SYSTEMS SCIENCE AND POPULATION HEALTH

edited by

Abdulrahman M. El-Sayed
Sandro Galea

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Abdulrahman M. El-Sayed

Executive Director and Health Officer,
Detroit Health Department, City of Detroit

Sandro Galea

Robert A. Knox Professor and Dean,
Boston University School of Public Health

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CONTRIBUTORS

Sanjay Basu, Stanford Prevention Research Center, Stanford University, Palo Alto, CA.

Hege Bøvelstad, Department of Community Medicine, University of Tromsø–The Arctic University of Norway, Tromsø, Norway.

Bobbi J. Carothers, Center for Public Health Systems Science, Washington University in St. Louis, St. Louis, MO.

Magdalena Cerdá, Department of Emergency Medicine, Violence Prevention Research Program, University of California, Davis, Sacramento, CA.

Daniel Chen, Social and Decision Analytics Laboratory, Biocomplexity Institute, Virginia Tech, Blacksburg, VA.

Helen de Pinho, Population and Family Health at the Columbia University Medical Center, Mailman School of Public Health, New York, NY.

Amar Dhand, Department of Neurology, Washington University School of Medicine in St. Louis, St. Louis, MO.

Abdulrahman M. El-Sayed, Detroit Health Department, City of Detroit, Detroit, MI.

James H. Faghmous, Arnhold Institute for Global Health, Icahn School of Medicine at Mount Sinai, New York, NY.

David S. Fink, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.

Sandro Galea, School of Public Health, Boston University, Boston, MA.

Kristin Heitman, Independent Scholar, Bethesda, MD.

Katherine M. Keyes, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.

Eric Lofgren, Paul G. Allen School for Global Animal Health, Washington State University, Pullman, WA.

David W. Lounsbury, Department of Epidemiology and Population Health, Department of Family and Social Medicine, Albert Einstein College of Medicine, New York, NY.

Douglas A. Luke, Center for Public Health Systems Science, George Warren Brown School of Social Work, Washington University in St. Louis, St. Louis, MO.

Eiliv Lund, Department of Community Medicine, University of Tromsø–The Arctic University of Norway, Tromsø, Norway.

Brandon D. L. Marshall, Department of Epidemiology, Brown University School of Public Health, Providence, RI.

Stephen J. Mooney, Harborview Injury Prevention & Research Center, University of Washington, Seattle, WA.

Karina Standahl Olsen, Department of Community Medicine, University of Tromsø–The Arctic University of Norway, Tromsø, Norway.

Mark G. Orr, Social and Decision Analytics Laboratory, Biocomplexity Institute, Virginia Tech, Blacksburg, VA.

Nathaniel Osgood, Department of Computer Science, Department of Community Health and Epidemiology, Bioengineering Division, University of Saskatchewan, SK, Canada.

Anton Palma, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.

Melissa Tracy, Department of Epidemiology and Biostatistics, University at Albany School of Public Health, Albany, NY.

Kathryn Ziemer, Social and Decision Analytics Laboratory, Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, VA.

1

Introduction

ABDULRAHMAN M. EL-SAYED

1. WHY SYSTEMS SCIENCE?

Population health is complex, involving dynamic interactions between cells, societies, and everything in between. Our modal approach to studying population health, however, remains oriented around a reductionist approach to conceptualizing, empirically analyzing, and intervening to improve population health.

Health scientists are concerned with identifying individual "risk factors" or "determinants" of disease in populations. This approach assumes that population health interventions can be designed by understanding each of these determinants individually, ultimately decreasing the risk of poor health outcomes they determine. Both population scientists and policymakers assume these interventions have direct, linear effects that do not extend beyond the outcomes they are meant to influence and that are consistent across different places in different times.

Sometimes these interventions work as expected. For this reason, population health science founded on simple understandings of the world can count many victories: germ theory, the health hazards of smoking, and a more nuanced understanding of the etiology of cardiovascular disease—all of which have vastly improved human health.

The trouble, however, is that interventions founded on simplifying a complex world often do not work, yielding failure, or worse, harm. The motivations for this book emerge from the truth that "silver bullet" health science often fails. And understanding why and how it fails can help us improve our approach to health science, and, ultimately, population health.

There are a number of examples from the population health science literature that illustrate the folly of oversimplification in population health. Many have had dramatic consequences for public health. Early evidence from observational studies

suggested that hormone replacement therapy (HRT) could reduce cardiovascular disease risk among post-menopausal women. This evidence ultimately informed clinical guidelines that recommended HRT to millions of women over several decades [1, 2]. However, it was only after a series of randomized trials were performed that HRT was actually shown to *increase* cardiovascular disease (as well as breast cancer risk) among women [3–5].

Yet randomized trials—the gold standard of population health science—have also led to policy failure. Consider the use of conditional cash transfer (CCT) to improve health. The *Progresa-Oportunidades* study showed improvements in the use of various health services and subsequent health outcomes in families that received cash transfers conditional on nutrition supplement, nutrition education, and health-care service use in Mexico [6, 7]. Several other randomized trials and literature reviews have shown that CCTs in low- and middle-income countries (LMICs) can improve the use of health services, nutritional status, and various health outcomes, including HIV and sexually transmitted infections [8–10]. This evidence has moved policy: CCT programs feature prominently in health policies in over 30 LMICs across South and Central America, Asia, and sub-Saharan Africa [11].

However, CCT programs have also failed. One CCT program to prevent HIV/AIDS in rural Malawi provides a telling example [12]. CCT did not prevent HIV status or diminish reported risky sexual behavior overall. Worse, men who received the benefit were actually more likely to engage in risky sexual behavior just after having received the cash. Another CCT program in New York City, which aimed to improve academic achievement among socioeconomically disadvantaged youth, provides an additional example. A program evaluation showed that the achievement benefits were concentrated among academically prepared teenagers, prompting the cancellation of the program. In each case, these programs were built from simplistic understandings of population health science that transported the evidence about CCTs from other contexts, without regard for how particular differences in context or time might influence the results.

Over the past 20 years, systems science has grown in influence and importance across several scientific disciplines. Across diverse disciplines, systems science has yielded insights that have illuminated our understanding of complex human systems. Complexity and systems science have often cogently and coherently explained why "silver bullet" policies have sometimes failed to produce desired outcomes, or created paradoxical outcomes on these parameters—or unexpected outcomes on seemingly unrelated parameters.

However, few population health scientists or policymakers understand the precepts of complexity or systems science, let alone how to apply them to their work. Conversely, few systems scientists understand the applications of their work to population health. This book aims to bridge the gap between systems

and population health sciences. We aim to unite contributions from leading authorities in the field to describe how complex systems science contributes to population health and to demonstrate how methodological approaches in systems science can sharpen population health science. Throughout, we rely on examples from the emerging literature at the nexus between complex systems and population health.

2. COMPLEXITY FOR POPULATION HEALTH

Systems science—a conceptual framework that emphasizes the relationships that connect constituent parts of a system rather than the parts themselves—has advanced a number of scientific disciplines over the past two decades. From economics to ecology to cancer biology, scientists and practitioners have embraced systems science, yielding profound insights that have improved our understanding of important phenomena, including financial markets, herd behavior, and the biology of metastasis. Population health, too, is a complex system, wherein individuals interact to produce collectives within varying environments, all of which feed back upon one another to shape the health and well-being of populations.

Systems science emphasizes relationships and scale. It is only appropriate that a book about systems science in population health should also emphasize relationships and scale between various concepts in epidemiology and population health. In that respect, we begin with a focus on simplicity, articulating why reductionism has formed the core of science and population health over the past century. The first section "Simplicity, Complexity, and Population Health" will walk the reader through the intellectual and conceptual history of systems science as it intersects with population health. It will begin with a discussion of the import of reductionism at the advent of epidemiology and public health. Next, it will explore challenges to reductionism in population health, considering both the intractability of a number of problems in the absence of systems approaches, as well as situations where a failure to appreciate complexity led to harm. The discussion will then follow the evolution and maturation of systems science. Finally, the authors will consider exemplar systems of population health to set the stage for the next several sections.

The second section, "Methods in Systems Population Health," will provide the reader with clear, concise overviews of several important and emerging systems science methodological tools, including systems dynamics, agent-based modeling, microsimulation, social network analysis, and machine learning with relevant examples drawn from the population health literature.

The third section, "Systems Science Toward a Consequential Population Health," synthesizes the previous two sections to explore the implications of systems science for our understanding of broad issue areas in population health.

Population health is ripe for systems science. We hope that this book will seed a future generation of population health scientists and thinkers with the conceptual tools and methodological understanding needed to frame population health through complexity and systems science. In an applied science such as ours, the responsibility for action is paramount and must guide our scientific efforts [13]. Therefore, answers to our most pressing scientific questions must be both correct and actionable. Our hope is that by incorporating complexity and systems thinking into population health, we might yield more correct and more actionable answers that ultimately improve the efficacy, efficiency, and equity of population health.

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SECTION 1

Simplicity, Complexity, and Population Health

2

Reductionism at the Dawn of Population Health

KRISTIN HEITMAN*

What we now think of as the field of population health emerged over the course of four and a half centuries. That transition from traditional understanding to modern science was less a triumph of rationality than an attempt to gain traction in a struggle with a host of complex problems, many of which are still with us. Near the turn of the 20th century, reductionists in medicine and public health managed to establish, as definitively scientific, their characteristic commitment to simple, unified, universal explanations of health and disease consistent with the standards and theories of chemistry and physics. Nonetheless, other camps with different practical and ontological concerns often put up legitimate resistance, in part because reductionist theories often simplified away phenomena with significant, observable, real-world consequences.

This chapter outlines the shifting concerns and constraints through that transition. Many of the most enduring insights arose from the combined efforts of several intellectual communities that wrestled simultaneously with the same phenomena. I begin by describing the conceptual tools, interests, and assumptions of classically educated intellectuals through the late 19th century. The second section reviews the initial emergence of population thinking via early attempts to collect and analyze quantitative data about populations and their health during

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the 16th, 17th, and early to mid-18th centuries, while the third traces the development of stable diagnostic categories over the same period. The fourth section looks at key developments during a "long" 19th century (approximately 1780 to 1920) to illustrate the shift toward the reductionist approach that yielded modern views about science, health, disease, and populations. To end, I discuss the uses and challenges of complexity in current efforts to construct a better understanding of human health and disease at the population level.

1. TRADITIONAL APPROACHES

Through the mid-19th century, most private intellectuals, physicians, and policymakers were grounded in a broadly Aristotelian view of nature and a broadly Hippocratic approach to healing and health. Indeed, even as late 19th-century advocates of new, scientifically-driven theories increasingly characterized both traditions as opaque clutter, many still found an inclusive, flexible, holistic approach much more reliable in their attempts to understand observed events, anticipate developments, and manage their everyday challenges.

1.1. Understanding Natural Phenomena

Aristotelianism lay at the heart of a classical education. Where the "new philosophy" of the early modern era aimed to generate consensus through shared experimental methods, shared or reproducible observations, and (sometimes) the rigor and precision of mathematics, the Aristotelians began with consensus in a much broader sense: what we might deem "common sense," and they often called "common opinion" [1]. They typically analyzed, critiqued, refined, shored up, and extended specific positions by invoking common experience, observation of individual cases, and their typically rigorous common training.

Aristotelian analysis relied on both formal logic and a powerful set of rhetorical techniques that included *post-hoc* inference, observation and selection biases, and confusions of part and whole [2]. However, even Aristotelian logic was driven less by an expectation of absolute universality than by a commitment to reflecting observed complexity. Aristotle himself had stipulated that universal statements should be expected to hold "usually or for the most part," and later Aristotelians cultivated a willingness to investigate and explain exceptions, especially in dramatic instances that they termed "monsters" or "miracles" [3, 4]. While the conceptual structures they developed were often normative, they embraced the idea that Nature itself included both deviation and complexity.

Aristotelian analysis was also explicitly qualitative. Aristotle had acknowledged the value of quantitative reasoning but set it aside because his logical

system was purely binary and, as he put it, "there is no single denial of fifteen" [3]. That decision became an essential element of formal education through most of the early modern era. While classical geometry and arithmetic were part of the Aristotelian *quadrivium* (advanced curriculum), even in the late 1800s only a small minority of Western students were trained as deeply in mathematical methods as they were in the logic, rhetoric, and grammar that had made up the basic *trivium* [1, 5, 6, 7].

1.2. Understanding Health and Healing

Hippocratic medicine likewise focused on individual instances organized into broad patterns that recognized significant variation. Its primary commitment was to keeping each individual patient's body in its own functional, dynamic balance with the environment in which it was embedded. Nearly all diseases were understood in terms of symptoms that signified that the body was somehow out of balance. But "balance" was not a simple concept. It was both individualized and essentially dynamic, although discernibly influenced by age, sex, and physiological type. An individual constitution, the Hippocratics taught, was best determined not via algorithms or abstract principles but through close observation of the individual's response to various influences, preferably over a long period of time and in good health as well as illness. Although the Hippocratics had a well-known interest in patterns and characteristics brought on by climate and environment, they were committed not to studying the health of populations but to using those broad, observable patterns in determining how best to help individual patients in the face of a huge array of unknowns, largely uncontrollable conditions, and the constant possibility of a therapeutic dead end [8–11].

Traditional medicine was usually more Galenic than simply Hippocratic. Galen (ca. 130 CE–ca. 200 CE), a Hippocratic revisionist, distilled the diversity of the Hippocratic tradition into a single, unified theory [8–9]. He kept the symptom-driven approach but devised a rigorously organized system of underlying principles, including an explanatory system of mechanisms drawn from his own extensive program of reading and animal dissection. The initial rich range of observation and opinion thus became a single, normative system of four humors (blood, phlegm, yellow bile ("choler") and black bile) and six "non-naturals" (diet, atmosphere, excretions, exercise, sleep, and stress). Galen had no more interest in population health than his ancestors had, but he did insist that all observed variations and complexities resulted from interactions of his simpler principles and mechanisms, which he laid down as universal in the Aristotelian sense [8, 11, 12].

Command of those principles was the distinguishing mark of learned Western medicine from the foundation of the first European universities in the 12th

century [12, 13]. Despite a series of significant additions and amendments, most Western medical faculties continued to find Galen's works eminently suitable for lectures and the examinable mastery of texts through the 1800s [12, 14, 15, 16]. The shift to modern medicine was more often transition than revolution. Medical practitioners and even many scientists typically retained Galen's architecture of humors, environment, and balance even as they replaced more specific content [12, 15]. Conversely, most new medical discoveries were quite focused and piecemeal. Even taken together, they could provide little integrated understanding of human physiology, health, or healing. Nor could the principles of medical science guide physicians in most of what they encountered in the course of their actual practice.

2. CONSTRUCTING POPULATIONS

Many view the Scientific Revolution as beginning with Francis Bacon (1561–1626), who proposed a "Great Instauration" to strip away all the old theoretical jargon and complications. For Bacon, genuine knowledge of natural phenomena consisted of singular, direct observations organized, via induction, to disclose an underlying structure of natural kinds and their relations. Further observation was supposed to organize those kinds and relations into ever-higher levels of generality until the whole of humanly possible natural knowledge had been realized. But for those conducting the investigations, the challenge was not just to "carve Nature at its joints," as Plato had put it [17]. They had to create their own tools and metrics even when the questions they sought to answer were not yet clearly formulated. The actual shift in scientific inquiry was thus less a unified, coordinated effort than a pattern of change seen most readily in retrospect.

2.1. Counting and Calculating

In Europe, organized disease surveillance began with the plague epidemics at the turn of the 15th century. Most cities identified each victim individually, typically by name, trade or social status, and location of death [18]. With few maps and measurements in hand, civic authorities interpreted their plague rolls in light of what they already knew or believed about local conditions.

Strictly numerical tracking seems to have begun in Tudor London, whose day-to-day management was run by its merchant-aldermen [19–21]. As early as 1532, London returned not socioeconomic information, nor even the names of the dead, but simply the number of burials in each parish each week, both from plague and in total [22]. More detailed mortality counts began in 1555, when London's aldermen ordered its Company of Parish Clerks (a city guild) to count

up every death every week, together with its cause, whether plague was present or not [21, 23]. Although we have no specific evidence about how the aldermen used those data, counts of deaths and their causes were useful metrics in an era when burial was controlled by the Established Church and living persons strongly resisted sharing their personal information. Counts of baptisms, divided into male and female, were added over the next two decades [21, 24].

From those weekly reports were born the London Bills of Mortality, which were in turn the basis for John Graunt's seminal *Natural and Political Observations on the Bills of Mortality* (1662) [25]. Graunt provided a master table constructed from several decades of published annual summaries and worked through a structured series of questions to show how to mine their data. He identified trends, exposed inexplicable outliers as likely errors, demonstrated divergence and covariance among causes of death, and suggested where additional data would help answer questions of clear civic value [26]. The newly founded Royal Society of London promptly elected Graunt a fellow (FRS) and others took up his suggestion of constructing mortality tables from parish records in cities such as Dublin, Amsterdam, Paris, and Norfolk (Britain's second-largest port) [27, 28]. However, retrospective data for locations outside of London could capture only counts of all baptisms (sometimes male and female) and all burials. Except in London, causes of death had never been tracked.

2.2. Local vs. Universal

The *Observations* also presented the first-ever life table. Graunt drew on the mortality counts for specific diseases and common knowledge about London life to develop techniques for estimating quantities for which he lacked data, particularly ages at death. It was an effective proof of concept despite its shortcomings: over the next two centuries, particularly as mathematics became an important element of university curricula, educated clergymen and interested gentlemen compiled life and mortality tables for parishes outside of London, sharing them via personal correspondence and intellectual organizations such as the Royal Society, both in Britain and on the Continent [29–32]. Some looked for ways to improve upon Graunt's methods, but many looked for connections between their results and the local climate, hoping to find Hippocratic implications about environment, longevity, and native constitutions.

The search for a universal Law of Mortality began when the astronomer Edmond Halley, FRS (1656–1742), published a life table[1] based on four years of data (1687–1691) compiled by a clergyman in the town of Breslau, in what

1. As Major Greenwood later pointed out [56], Halley had actually constructed a population table.

is now Poland [32–34]. Halley used an approach characteristic of the Royal Society's work in physics and chemistry [35, 36]. Where Graunt had looked for patterns in his data and developed techniques to clean up obvious errors without throwing out important clues about London's complexities, Halley sought to sidestep complexity entirely by identifying a standard case with no known confounding factors. That case was expected to establish an unadulterated universal mortality rate, as a norm against which variations could be identified and empirical explanations constructed. Halley's analysis relied upon the fact that whereas the populations of cities like London and Dublin were both notoriously varied and demonstrably subject to in-migration, Breslau was a small town with a stable, homogenous population engaged almost entirely in light manufacturing. Equally important, the Breslau data included ages at death, so Halley could use observations instead of relying on Graunt's estimation techniques.[2]

Halley used only arithmetic and tabulation to present his argument. Pierre Fermat (1601–1665), Blaise Pascal (1623–1662) and Christiaan Huygens (1629–1695) had all published their seminal works on probability. The proliferation of mortality tables had enticed many other eminent mathematicians, and Nicholas Bernoulli had even offered a probabilistic rendition of London tables [29, 37]. But Halley saw his work as both groundbreaking and empirical. Probability theory still turned on problems taken from games of chance, where rules were known a priori and outcomes stipulated by type and relation to each other [38]. By contrast, those interested in the social and environmental conditions of health acknowledged at least four major challenges. First, the information required to frame and answer questions was qualitative, patchy, and scarce. Until Sweden established the first universal census in the 1730s, no numerically significant programs collected causes of death outside of London—and even London had never attempted to count its entire living population. Second, disease categories were neither precise nor stable, even as used by MDs. That concern became increasingly important as attention shifted to diseases and more causes of death. Third, each set of records represented a mathematically self-contained population, and the search for local factors and variations kept that issue at the forefront. Finally, the significance of population-level results was not well understood. Both politicians and the demographically-inclined struggled to identify useful properties of a population as distinct from those of its members, and especially to identify the proper role of population thinking in debates about national policies, economics, and social changes [37]. These factors were

2. Graunt was exposed as a Catholic shortly before his death in 1674, which prompted the Royal Society's conservative Anglicans to reassign the whole of the *Observations* to Graunt's friend and sometime collaborator, Sir William Petty. . . Halley participated in that effort, as is apparent in the way he described the *Observations* in his own publications.

mutually reinforcing. The lack of data made it difficult to develop sound quantitative methods—or even appropriate categories and metrics—yet harnessing the social power needed to gather a significant range of reliable data required some promise of socially useful results.

3. METHODS AND STANDARDS

For at least the next 250 years, universalists and localists saw themselves less as engaged with different aspects of a single problem than as locked in battle over whose questions and methods were correct. It is crucial to recognize—as the warring proponents did not—that the two communities pursued significantly different projects. Mathematicians, particularly those who began in astronomy, tended to dominate universalist inquiry: they used selected empirical data but assumed a priori that an objective, univocal set of universal laws mostly awaited the discovery of appropriate mathematical techniques. Mucking about in dirty data, they held, would never advance their objectives. The localists, meanwhile, generally examined a broader range of data looking for patterns elicited via induction. While they might adopt the mathematicians' tools, they insisted that constructing allegedly universal laws based on artificially selected, simple cases failed to answer the questions that mattered. Both camps felt the constraints of limited quantitative data, but each fully expected that better methods and more of the right sort of data would prove them correct.

The scarcity of quantitative socioeconomic data set strict limits on the range of problems anyone could consider. Useful information could sometimes be gleaned from tax records, but until the mid-1800s no government institution was charged with collecting information beyond the usual requirements of taxation, inheritance, muster, and poor relief [29, 37]. Registries for births, marriages, and deaths established at the turn of the 18th century served not demography but legal concerns. Even those employed by a national government, including Britain's Gregory King (1648–1712) and William Farr (1807–1883), conducted their demographic and epidemiological work as private individuals or by extending their official duties without legal authorization [29, 37]. As long as Europeans continued to resist what they saw as intrusions into their private lives, reliable quantitative data could be gathered only about populations whose lives were already subject to external scrutiny and control: the military, commercial sailors, prisoners, orphans, and sometimes the urban poor.

3.1. Disease Categories

Finding consistent classification of diseases became increasingly important in the late 17th century, as diagnostic criteria were recognizably inconsistent even among

MDs [12, 29, 37, 39]. In the 1660s, the English physician Thomas Sydenham (1624–1689) began to revise traditional nosology by replacing Galenic constructs with characteristic patterns of observable symptoms, paying particular attention to the order and timing of their emergence [40–42]. Like Bacon, he argued for compiling a huge array of observations: individual cases were to be carefully described and shared by trained observers—in this case, experienced physicians. But like his Hippocratic forbearers, Sydenham viewed disease mostly in terms of an individual body's interaction with its local environment [12, 16, 40–43].

Encouraged by first the eminent medical professor Herman Boerhaave, MD (1668–1738) at the University of Leiden, and then by several distinguished medical faculty at universities in Scotland, Western physicians committed to Sydenham's program collected cases into the 1800s [15, 44]. Like the demographers, they drew upon their own records and experience, correspondence with colleagues, and local learned societies to compile relatively small sets of mostly local data. Such efforts became more frequent and better organized as the first Industrial Revolution (circa 1760–1890) created both conditions that made health concerns much more acute and a financial incentive to manage the health of workers. British industrialists and charitable elites opened dispensaries and small hospitals to care for the working poor in London, Edinburgh, Glasgow, and the new industrial cities of northern England [12, 16, 44]. Those institutions also served as training centers staffed by volunteer physicians and surgeons committed to the principles of Sydenham, Boerhaave, and the Scots: qualified practitioners conducted rounds with their students in order to demonstrate techniques in diagnosis and treatment. Some staff published monographs on their successes and on patterns they observed, but their reports admittedly amounted only to case series that might contribute to better clinical judgment.

Those looking for patterns accepted quantification only gradually. Boerhaave and the early Scottish medical faculty counted and calculated little more than Sydenham had [45]. But with the rising influence of physician-statisticians like Thomas Percival, MD, FRS (1740–1804), more hospitals and dispensaries kept systematic treatment records. The members of local statistical societies eagerly analyzed those records, looking for useful patterns. By the end of the century, a vocal contingent of physicians demanded the evidence of "mass" results instead of an author's clinical judgment or theoretical justifications. Yet as learned medical discussions increasingly used quantitative analyses, arguments about diagnosis and treatment increasingly came down to one man's numbers versus another's. The entire effort faced the clear challenge of analyzing several small series with no empirical reason for preferring one set of disease criteria over another.

3.2. A "calculus of observations"

Between 1750 and 1850, most significant developments in population thinking relied on an analogy between astronomy and demographics. As a series of prominent mathematician-astronomers developed and refined what became the method of least squares, the applications in demography were immediately obvious [29]. One can likewise treat a population as an objective, physical entity so extended in space and time that it is observable only in discrete samples by many individuals. The homogeneity of observations remained a stumbling block. But with the development of increasingly rigorous methods, many variations across observers could also be defensibly smoothed out in analysis.

The analogy came apart in the 1850s, as the European Enlightenment made more social intervention possible. Much like Graunt, the influential Belgian astronomer Adolphe Quetelet (1796–1874) found his interest piqued in looking through published records, in his case, late-Napoleonic crime reports, which exhibited stable regularities in population-level data about clearly independent human acts such as murders and suicides [29, 37]. The Scottish physician-mathematician John Arbuthnot (1677–1735) had noted stabilities in marriages and the mortality rates of men and women, but Quetelet was intrigued by regularities in socially disruptive human behavior.[3] Encouraged by the progressive regime of Napoleon III, he began a study of "moral statistics," hoping to identify environmental causes of crime that society could move to limit or eliminate [29].

Francis Galton (1822–1911), who also began as an astronomer, was equally interested in correlations and natural convergence. But he soon rejected the widespread practice of dismissing deviations as either trivial or signs of observational error [29, 37]. Instead, deeply influenced by the evolutionary theory of his cousin Charles Darwin, he argued that capturing the diversity evident in exceptions and variations was crucial to understanding a complex, evolving natural order, especially in matters such as human intelligence, psychology, and behavior. In emphasizing the advantages in valuing diversity and its potential as a tool for social progress, Galton advocated not a swing back to fascination with individual Aristotelian monsters and miracles but rather a move away from understanding diversity and natural variation purely as deviation from a set of humanly constructed norms.[4]

3. Like many of his time, Arbuthnot saw such stabilities as evidence that certain practices were favored by Nature, and thus intended by a Creator.

4. Unfortunately, Galton is now best remembered for his interest in eugenics. However, in line with the individualistic elitism of his time, he advocated not constraints on "substandard"

4. REDEFINING "HEALTH" AND "DISEASE"

The "long" 19th century (here, approximately 1780 to 1920) saw a profound transformation of the understanding of health and disease, even as the social programs of the Enlightenment brought yet another dimension to the battles over the nature and significance of health statistics. Class-based resistance to universal government censuses applied equally in medical care: those who could afford to pay for care expected to be treated as unique individuals in the Hippocratic manner, and their physicians were equally reluctant to use population-level results in their private practices [46, 47]. The growing use of statistics in deciding public policy sharpened that sense of division. As Western governments began to build social programs for their less powerful classes, statistical methods increasingly drove public debates about what government programs should offer the poor and the standards for effectiveness [12, 29, 37]. Then, toward the end of the 19th century, as interventional research began to yield an avalanche of powerful practical results, its successes reshaped the expectations of policymakers, statisticians, scientists, medical practitioners, and the public, both moneyed and otherwise. Public health efforts sensibly shifted to take advantage of them, towing population-level studies in their wake.

4.1. "Counting is not Easy" [48]

The Paris Hospitals and Schools, founded in the wake of the French Revolution, were designed to provide institutionalized support for high-quality medical research as well as the best patient care possible [12]. Their collective arrangements directly addressed the problem of small samples. From the French Republic forward, everyone was offered health care in a single, egalitarian system. French hospitals and their clinics likewise trained all physicians, surgeons, and midwives in a single program and established unified systems of records for the care of their patients. Thus, throughout the long 19th century, it was possible both to track thousands of individual patients from first visit to postmortem in hospital morgues and to compare patient outcomes across several different methods of diagnosis and treatment within a single system. The Paris approach emphasized not just observation but measurement, including unified, organized efforts to determine what measures were clinically significant and how best to interpret and use them.

individuals but rather efforts to enhance the overall creativity and intelligence of a population by encouraging creative, intelligent individuals to choose their mates in order to preserve and extend the benefits of both nature and nurture, including valuation of intelligent, educated, committed mothering.

The champion of the numerical method was Pierre-Charles-Alexandre Louis, MD (1787–1872), who reviewed thousands of patient records and performed hundreds of autopsies [12, 48, 49]. Using mathematical techniques developed by LaPlace, Gauss, and others, Louis identified stable categories for diseases such as tuberculosis, typhoid fever, and pneumonia; determined the relative effectiveness of therapies; and even identified non-disease similarities among patients that affected the course of their diseases and treatments. Although his numbers were still too small even for moral certainty, within the Paris system his findings could be incorporated into the new clinical methods and techniques of other faculty and students. Subsequent patient records and diagnostic or treatment innovations could then be assessed numerically to yield another round of numerical indications for diagnosis, prognosis, prevention, and treatment. Quantitative analyses outside the hospital setting were also undertaken, generally with the support of first the French Republic and then Napoleon I and III. Louis-René Villermé (1782–1863), for instance, mapped 1820s health outcomes for individual patients onto their Paris neighborhoods to expose socioeconomic patterns in health and recovery.

In Britain, relations were not so cordial. William Farr studied with Louis in Paris and then returned to London, where he eventually joined the newly founded General Register Office (GRO) as a compiler of mortality abstracts. He immediately saw two needs: (1) to standardize the categories used to identify cause of death and (2) to identify diseases in the context of a complex social environment. Farr's ideal was to construct mortality categories that would be exclusive, exhaustive, and disclose important empirical relations *à la* Louis [12, 29, 50, 51]. His efforts led to a very public clash with the reformer Edwin Chadwick (1800–1890), who was equally bent on implementing the policies of Britain's new poor laws, and conscious of the new power of statistics [52]. In 1839, Farr published a GRO report that included a conclusion that hunger was a significant contributing factor in both mortality and disease among the poor. Chadwick insisted that few in England or Wales starved—and those only by choice, since his new workhouses provided what he regarded a basic diet [50, 52, 53]. Political or not, the debate turned on what should be counted as death by starvation: Farr counted any sort of significant privation, including the long-term effects of poverty, whereas Chadwick would admit nothing except clear evidence that the person had eaten too little at the end of life.

4.2. From Induction to Reduction

Interventional physiology, in the tradition of Andreas Vesalius, MD (1514–1564) and William Harvey, MD (1578–1657) flourished across Europe, particularly in Italy, Germany, Britain, and France. The Paris faculty included interventional research from its foundation. Perhaps the most influential were the physiologist

François Magendie, MD (1783–1855) and his protégé and successor, Claude Bernard, MD (1813–1878). Bernard in particular advocated an a priori conviction that living things functioned via physical mechanisms governed entirely by the universal laws of physics and chemistry. He and his mentors trained as physicians but soon left patient care to focus on research. They employed a wide range of investigational techniques on a variety of non-human animals in order to understand diseases that they viewed as entities ontologically independent of who might be sick [9, 10]. Laboratory conditions were designed to provide scientific medicine with standards in Halley's sense: the interventionists constructed controlled conditions stripped of confounding factors in order to reveal the underlying universal laws. Universality was essential, Bernard held, for the mark of fully scientific medicine was the ability to cure every case of a disease, without exception [12, 54]. Even without a viable conceptual framework that did not draw on Galen's individualized, balance-based approach, the task of medical science was to discover universal physical mechanisms and their functions by framing and testing hypotheses and then deducing consequences from the results.

Much like Bacon, Bernard was a visionary whose strategies could never be fully realized. Until the turn of the 20th century, his approach was only rarely viable even as a means of improving standards of care. Interventionists typically produced only piecemeal results that medical practitioners found neither unified by coherent explanations nor useful in caring for humans in their self-evident diversity [12, 15]. Bernard had readily admitted that until scientific medicine was achieved, medical decisions grounded in population-level studies were a practical necessity. But he and his successors did not foresee that that this would then lead to encountering further complexities on every level they investigated. Instead, their successes deepened their faith that their methods would ultimately lead to complete success.

Initially, the pursuit of a unified, robust germ theory deepened the separation of medical research from medical practice. Much of that work was conducted in cutting-edge French and German laboratories of the late 1800s, which relied heavily on non-physician PhDs trained extensively in experimental medical science but not in medicine [12]. In the last years of the 19th century, the principles enunciated by Jakob Henle (1809–1885) and Robert Koch (1843–1910) ensured that isolated microbes and mechanisms could be confidently identified as causative. Given that knowledge, lab scientists began to develop new vaccines, discover antimicrobials, and refine the active ingredients in effective natural treatments even for non-infectious diseases such as diabetes and hypothyroidism. Medical practitioners then began to find that modern interventions, increasingly produced in industrial labs, had a consistency of effect that vastly outpaced both natural *materia medica* and patent medicines. With modern diagnosis and

treatment, people whom disease would have condemned to death a decade earlier could sometimes recover in a matter of days. At the population level, it suddenly became possible to limit the spread of the most devastating diseases and in some cases to deliver a cure.

Germ theory also led to aseptic surgical techniques that allowed surgeons to develop procedures to operate on regions of the body previously seen as too dangerous even to cut open. Greater surgical exploration and success produced better mechanistic explanations of human physiology and metabolism, with new definitions of metabolic and cardiovascular diseases based in structure and function based in biochemistry and modern physics. At the start of the 20th century, medical education began to incorporate courses in laboratory science and graduates increasingly sought hospital residencies where they learned to conduct laboratory tests as well as provide clinical care. Expanding public health services likewise incorporated the new science in investigating and addressing population-level challenges, particularly in contagious diseases. Even in studies of nutrition, exercise, sleep, and environment, mechanistic explanations of normalized physiology generally pushed aside any felt need to consider sleep, stress, or environmental factors [55].

5. SIMPLICITY AND COMPLEXITY

By the 1920s modern medicine could promise sweeping solutions to the challenges of health and disease. Its rapid, widespread success over the next half-century transformed the way that researchers, healthcare providers, policymakers, and the public all understood health and disease. Its promise, however, has faded in the face of more recent challenges such as AIDS, MRSA, autism, and Alzheimer's.

The difficulties arise in part because complexity comes in several forms. To be sure, the conditions of human health and disease have themselves become increasingly complex. More goods and people move more freely and rapidly about the world, spreading diseases in ways rarely imagined a century ago. New diseases emerge through processes that we sometimes struggle to identify. In Western countries, where infectious diseases are no longer the primary causes of death, biopsychosocial predictors of health and illness—including poor food choices, too little physical activity, and smoking—require attention to complexities of yet another sort. The causal influences of culture, gender, ethnicity, and socioeconomic status have proven to be significant factors in a heterogeneous host of health concerns, and even the study of genetics has turned out to require significant attention to environmental triggers and modifications.

How can the field of population health best handle such complexity? Much of the challenge stems from the way we conceive of simplicity itself. Even simple

laws and principles can act together to produce complex effects. Such phenomena are particularly evident in fields that must integrate many kinds of science, looking at indirect and nonlinear relations, mutual influences, and changes over time and across contexts. Indeed, the history of population-level investigations suggests that the differences among intellectual approaches can generate a rich range of new questions and results.

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3

Wrong Answers

When Simple Interpretations Create Complex Problems

DAVID S. FINK AND KATHERINE M. KEYES

1. INTRODUCTION

Information regarding the causes of health and illness influence nearly every part of our daily lives, from the foods we eat (or avoid) to the seatbelts we wear, and to the speed limits we observe while driving on our highways. Due to ethical and other concerns, such information often relies on observational studies of individuals who choose health behaviors, rather than randomized studies. The complexity of using observational data to inform public health initiatives is perhaps most often recognized after randomized controlled trials (RCTs) contradict observational studies [1, 2] or when simple interpretations of complex phenomena have led to ineffective, or even harmful, interventions [3]. The roots of these problems lie, in part, in basic processes of confounding and bias in observational studies. However, they also lie in the application of methodological reduction to better understand population health. While part of the process of scientific inquiry is often to reduce series of observations and hypotheses in order to describe more general processes, theories, or principles, such approaches can lead to inefficiency in building a knowledge base if complexity or context-specific effects are driving the data-generating process. Observational and experimental studies often abstract complex systems in order to understand the effects of changing discrete elements of that process. Underappreciating that societies form a complex adaptive system can result in wrong answers to arguably our most important research questions: those related to population health. In this chapter, we will discuss several examples of when simple interpretations have created complex problems in science. In particular, we will use the current reproducibility problems in science

to illustrate how ignoring complexity can create inferential errors, specifically within public health.

The scientific community has become increasingly concerned with the limited reproducibility of study findings [4–6]. Our preeminent scientific journals [1–4] have published several editorials highlighting these concerns and proposing strategies to improve reproducibility and replication. The United States (US) National Institutes of Health (NIH), in the wake of reports that only a fraction of landmark biomedical findings could be reproduced, issued a white paper titled "Principles and Guidelines for Reporting Preclinical Research" that focused on rigorous statistical analysis, transparency in reporting, data and material sharing, and consideration of refutations. Although much of this literature has focused on the reproducibility of preclinical research, the fields of psychology [5], ecology [7], and field biology [8] have also begun to grapple with reproducibility. Although there are many ways in which observational studies and RCTs can come to different conclusions, complexity of a system is one such process through which results that seem robust in observational studies, and valid to editors and referees of journals, do not stand the test of further studies [e.g., 9] or interventions [e.g., 3]. When should we expect reproducibility in population health studies? This is the question we will attempt to answer throughout this chapter.

The issue of reproducibility highlights a broader issue in population health science, which is how to consider the classical experimental paradigm simultaneously with the well-known contextual shifts and dynamic interactions among individuals in populations in which exposures occur. That is, experiments and reproducibility grew out of lab sciences. In population health studies, however, we are engaged outside of the lab and thus need to contend with the variables under which people function that are not laboratory defined. One way to confront this is to try to replicate the precision of the lab in the environment. Another way to confront this is to model the environment itself and examine how the variation in effect measures across it. This chapter will highlight both of these approaches and discuss their relation.

2. THE LIMITS OF RISK FACTOR ASSESSMENT AND ISOLATING CAUSES

Basic ideas of cause and effect fit well within human inquiry, and everyday causal inference is necessary for us to grow and function as humans (e.g., if I touch a stove when it is hot, I will get burned, therefore touching hot surfaces causes pain). The experimental paradigm, in turn, has carried on this tradition of isolating the effects of causes, which is a process that is certainly necessary for a robust science. However, the study of human populations, observed outside of the laboratory, makes such inference difficult unless there are substantially large effects

[10], such as those observed between smoking and lung cancer [11], diethylstilbestrol and cervical or vaginal cancer [12], or vaccine and immunity.

Epidemiological studies of health have focused on applying the ideas of the experimental paradigm, to the extent possible, in observational settings. This is done to tease out causes of human disease under conditions where humans cannot be randomized to potential exposures. Because that effort is fraught with potential confounding influences, the field has innovated substantially through the years with methods for confounder control, while simultaneously arriving at increasingly precise and elegant methods to estimate relatively small effect sizes of single exposures on a variety of outcomes. We do so partly because we think that if we just get it right, we will discover something about the natural process of disease and be able to reduce our observations to a general set of laws or theorems that govern the process of disease incidence. Yet as a field, epidemiology has been mired in small risk ratios with diffuse effects and methodological challenges regarding the assumptions we need to make in order to estimate such effects [13].

Reproducing effect measures is important to assuring that our science is strong, but the lack of reproducibility could indicate several different underlying processes. On the one hand, it could indicate that confounding, bias, and random error generated a set of findings. On the other hand, it could indicate that our effect estimates themselves are context and time specific, rather than general and unwavering. Indeed, even if the risk of disease among the exposed remains constant, a change in the base rate of disease can alter a relative effect measure.

Often, we study what happened to a particular sample over time, and use that information about what happened to make recommendations for future populations. This is a two-part process, consisting of causal description and causal explanation [14]. In this section, we will discuss the assumptions we need in order to estimate a valid causal effect within a study sample (i.e., causal description). Second, we will discuss whether a causal effect that is measured in one study should be expected to remain valid across various other populations, places, and times (i.e., causal explanation). Finally, we will examine the magnitude of effect measures that are necessary to predict future events.

2.1. Assumptions of a Valid Causal Effect

Causal description is the process of identifying a causal effect. An exposure is a cause if both the exposure and disease occurred and, all things being equal, the outcome would not have occurred if the exposure had not occurred, at least not when and how it did [15, 16]. A causal effect, then, is the hypothetical difference in the future health state of a person after that person is exposed versus what would have happened if that person had not been exposed [17, 18]. However,

because we can only observe a person under a single exposure state, we must make several strong assumptions to estimate causal effects from averaging across groups of exposed and unexposed individuals.

We estimate associations between exposed and unexposed in our data using group comparison; such effects will equal a causal effect when we have, among other assumptions, exchangeability between the exposure groups and stable unit treatment value assumption (SUTVA) [19]. Exchangeability assumes that the probability of disease in the unexposed group equals the counterfactual risk among the exposed (i.e., probability of disease in the exposed if they were unexposed). The likelihood of the validity of this assumption varies greatly between randomized and nonrandomized studies. In theory, randomized studies can control the exposure mechanism that determines which study participants are exposed and unexposed and, in expectation, people with different baseline probabilities of disease become balanced through randomization between the two groups. In nonrandomized studies, however, a researcher does not control the exposure mechanism that determines which study participants are exposed and unexposed. This loss of control over the exposure assignment mechanism can cause the baseline probability of disease in the unexposed group to vary from the counterfactual risk among the exposed, violating the exchangeability assumption.

A violation of the exchangeability assumption is typically referred to as "confounding," and residual confounding in observational studies is one of the main reasons why some findings from observational studies are later overturned by evidence from RCTs. Examples of such contradictory findings between nonrandomized and randomized studies are vitamin C for the treatment of advanced cancer [1] and the protective effect of hormone replacement therapy on coronary heart disease [2]. These examples provoked epidemiologists, and the public alike, to question how epidemiologic results can sometimes be so contradictory. The most likely reason for contradictory findings between randomized and nonrandomized studies is violation of the exchangeability assumption. A factor that is a common cause of both exposure and disease among those being studied can create differences in the probability of disease in the unexposed, thus creating nonexchangeability. Whereas randomization of exposure would balance, in expectation, the baseline risk in both exposure groups, nonrandomized studies must control or statistically adjust for any common antecedents of both the exposure and the outcome to reach the same balance. Such an approach is appropriate whenever a researcher can comfortably make the exchangeability assumption. However, there is more to observational studies versus experiments than exchangeability, which gets at the heart of why systems science methods are needed and why reproducibility is perhaps not optimal in all circumstances.

SUTVA is the a priori assumption that a person's potential outcome will be the same (i) no matter how that person was exposed and (ii) no matter what

exposures other people received [20]. Whereas the former explains treatment variation irrelevance, the latter defines interference. Interference, in most epidemiological contexts, refers to the process through which an individual's exposure status in the study influences another's outcome value; however, interference is also common among social exposures. Indeed, several studies have documented that peer networks contribute substantially to the effectiveness of interventions [21–24]. For example, the US Food and Drug Administration used a simulation study to show that raising the minimum legal age (MLA) from 18 to 21 to purchase tobacco increased the social distance between persons under age 18 and persons legally able to purchase tobacco, and it decreased initiation rates of smoking among persons under age 18 by over 25% [25]. Thus, modeling processes of inference—rather than assuming they do not exist—can give us greater insight not only into the mechanisms through which interventions can have an effect but also into the transportability of interventions across different settings and populations.

2.2. Assumptions of a Transportable Causal Effect

Causal explanation is about understanding how causal effects might vary as a function of time, space, or population (i.e., transportability, external validity), and the mechanisms through which particular causes influence outcomes. Transportability, or external validity, occurs when causal effects found in one population will hold in various other times, settings, and populations [26]. Because effect measures are as much an assessment of the prevalence of component causes (i.e., those causes that interact with the exposure of interest) as they are a measure of a causal effect of an exposure, any given effect measure between an exposure and an outcome will vary among populations as a function of each population's underlying distribution of component causes. For example, smokers in more recent cohorts have been documented to have a higher burden of psychopathology than in previous cohorts [27, 28], suggesting that, for example, the efficacy of smoking cessation programs may vary if such programs are less efficacious among those facing significant psychiatric morbidity. Previous studies have suggested that the association between smoking and psychopathology changed over time as a function of how deviant a behavior smoking was considered in a particular place and at a particular time [27]. Because social norms are ubiquitous exposures to a certain time and place, we must vary the time and place to identify both the causal partners for and the transportability of the causal effect between smoking and psychopathology.

Cross-population studies exploit differences in causal structures among populations to create variability in factors that are ubiquitous in any particular population [29]. As such, potential differences in causal structures can elucidate causes

that are otherwise hidden under a cloak of ubiquity. Through modeling the structures that underlie our constructs, we can further understand the complex interplay among person, place, and time. Through modeling systems, we are forced to confront the interactions among causes across levels that may be ignored when we reduce our vision to specific risk factors and causal effects that comprise the larger system.

2.3. Causal Effects and Prediction

Large odds ratios and other measures of association are required to overcome the differences in causal structures among populations and predict future disease. For example, Barker [30] recommended that a risk factor (e.g., biomarker) must correctly identify over 50% of cases and falsely identify no more than 2% of cases to have utility as a screening tool for prostate cancer. However, most of the "usual suspect" exposures that we measure (diet, substance use, toxins) render an increased odds or risk of about 2 to 3 fold. Pepe and colleagues [10] showed that an exposure with an odds ratio of 3, correctly detecting 50% of cases, must mislabel over 25% of controls as cases, which is far above the recommended 2% of false positives necessary to constitute a useful screening tool for prostate cancer. In fact, we would need an odds ratio that exceeds 171 to meet the recommendations for a useful screener (i.e., true positive ≥ 50% and false positive ≤ 2%) [30]. Therefore, a cause will produce a causal effect sufficient to predict future events only under rare circumstances.

However, we do not aim only to estimate causal effects for prediction but also to understand disease mechanisms and inform interventions. Unfortunately, it is well known that causal effects do not equal intervention effects [26, 31], because when isolating a causal effect we create a controlled world, absent of confounding factors, to isolate a single effect measure. In most cases, however, there is a complex interplay among different levels of exposures that bring about disorder over time. Therefore, we must again ask whether and when we should expect reproducibility in population health studies.

3. SYSTEMS THINKING IN A CONSEQUENTIALIST POPULATION HEALTH APPROACH

Over the second half of the 20th century, modern epidemiology consolidated a set of methods that often rendered a "risk factors" science focused on the behavioral and biological determinants of disease [32]. Although biological changes are likely to precipitate each individual's transition from a healthy state to a diseased state, the way in which biology becomes embedded to cause disease reflects

population-level patterns that span the lifecourse and social roles. As such, it is difficult to understand the dynamics of populations fully, in terms of both health and disease, from the biological changes that occur at the individual level.

A focus on individual- versus population-level influences on health makes the assumption that although social and environmental influences might originate upstream, they ultimately manifest as risk factors at the level of the individual. Although this process may be true for certain exposures, Link and Phelan [33] have documented another class of exposures (i.e., "fundamental causes") that "embody access to important resources, affect multiple disease outcomes through multiple mechanisms, and consequently maintain an association with disease even when intervening mechanisms change." Fundamental causes represent one class of exposures that are not amicable to a "risk factor" epidemiology, given the often long latency periods between exposure and outcome, the intervening mechanistic factors that need to be measured and conceptualized, and the network and dynamic processes through which these exposures are often embedded. This provided a blueprint for systems thinking to address a number of prevalent conceptual and analytical limitations that accompanied a science attempting to explain social phenomenon with an analytical armamentarium that was not equipped to investigate such phenomena.

Epidemiologic perspectives, such as ecosocial theory [34], eco-epidemiology [35], or social-ecological systems perspective [32], provide the framework to understand the causes and processes within a larger system of risks that drive variations in population health and disorder. What these perspectives share in common is an explicit multilevel, dynamic process, whereby population health is shaped by the social structures that contain it. Therefore, differences in disease burden represent the different health distributions of their respective populations. Under this paradigm, populations, like individuals, display observable manifestations of disorder in the mechanisms of a larger whole, the larger whole here being populations. Geoffrey Rose articulated this point when he stated that "[d]ifferences in the prevalence of 'mental illness' reflect the different states of mental health of the parent communities. The visible part of the iceberg [prevalence] is a function of its total mass (the population average)" [36, p. 72]. Population distributions of health emerge from the complex interplay of health-related factors at multiple levels.

Our goal in population health science is to understand the distribution and determinants of diseases in populations, so that we can intervene to improve health. A consequentialist approach reminds us to consider the public health implications of our science [37]; however, we must contend with the limitations of our current methods— specifically the fact that causal effects do not equal intervention effects. For example, people exposed to interventions that target a

single, proximal risk behavior have been found to change their behavior to compensate for the intervention and mitigate the intervention's effect. Intervention studies that have randomized smokers to either low-yield nicotine cigarettes or normal cigarettes have observed participants randomized to low-yield cigarettes smoke more cigarettes than participants randomized to normal cigarettes, compensating for the smaller amount of nicotine delivered in each cigarette [38]. Likewise, after several recent studies reported a link between sedentary behavior and mortality, sit-to-stand workstations have been implemented to reduce the long hours of sitting time that is common in some work environments. Whereas the early RCTs that focused only on sitting time during the work day found that sit-to-stand workstations decreased time spent sitting during work hours, a recent study observed that the reduction in sitting time during the work day is offset by increased time spent sitting and decreased light activity during nonworking hours [39]. These examples illustrate how some interventions that fail to consider a risk behavior within a larger system of risk can suggest wrong answers to important health problems.

4. CONCLUSION

Population health science has entered a new era. It is aware of the limits of reductionism in population health and is building tools that manifest what systems thinking can bring to understanding how exposure can cause disease. Although the application of methodological reductionism has been useful for answering certain causal questions about "downstream" exposures, our dominant methods remain best suited to identifying what the causal effect was in a particular study. Indeed, we can expect internally valid effect estimates when there is both exchangeability and SUTVA; however, variations in causal effects across populations are generated as much from the causal effect of the exposure as the population prevalence of other causes of disease. Therefore, we can expect reproducibility in population health studies when there is both internal validity (i.e., exchangeability and SUTVA) *and* when the prevalence of other causes of disease (other than the exposure) remains constant across populations. It is the latter case that is most often not met in populations, and methods beyond risk factor isolation can be informative tools to explain these causal processes. In sum, some causal effects are not reproducible because the original study got it wrong; however, other causal effects are not reproducible because there is variation in the causal effects across systems. Science that aims to understand causal variation is necessary to explain the context-specific ways in which exposures become embedded and vary across space and time.

The application of methodological reductionism has compelled population health scientists to prioritize individual-level causes over factors that drive the

dynamics of population health—as such dynamics are often not reproducible. The past few decades have seen several theoretical frameworks designed to generate population-level paradigms that integrate societal to biological processes that interact both between and within levels over time and area, explicitly linking social factors to biological processes of health and disorder. Systems adapt to compensate for interventions in ways that are often unpredictable at onset. Systems thinking is the process of understanding how the individual constituent parts of an entire system influence one another within a complete entity or larger system. The consequences of failing to consider the system will often lead to simple—and perhaps errant—interventions.

5. ACKNOWLEDGMENTS

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4

Complexity

The Evolution Toward 21st-Century Science

ANTON PALMA AND DAVID W. LOUNSBURY

Complexity is so common a characteristic in nature that ascribing it to any problem often feels trite. Ensuring national security, practicing equitable university admissions, and even parenting a child can all be considered complex problems. Hence, recognizing complexity must not simply mean conceding the difficulties in solving these problems but rather eliciting the means to *understand* and *address* the properties that make them complex. Though numerous in nature, these properties are largely unified by their dependency on context. Thus, we cannot reduce complex problems to simplistic relationships while ignoring the contexts they arise in.

Yet, reductionism is central to the scientific method and indeed to everyday life. Reducing causal mechanisms to small, decontextualized components has arguably many virtues: it enables generalizable inference, facilitates communication, and lends support for specific, implementable action. However, a narrow, prescriptive, problem-solving approach often fails to produce desired results. In *Developmental Evaluation*, Michael Quinn Patton invokes the example of parenting as a "highly variable and situational" problem and an intuitive metaphor for approaching other context-dependent problems [1]. A parent choosing from the myriad disciplinary techniques available recognizes that children learn and adapt, diminishing the effectiveness of previously successful techniques over time; prior failures take emotional tolls on the parent, affecting future implementation; and children's behavioral development requires coherent messages from their teachers and peers over time and across circumstances. Thus, behavior cannot be reduced to isolated causes. Accordingly, parenting requires "effective principles" tailored to the situation rather than "best practices" [1].

The failure of reductionism to address complex problems stems from ill-fitting assumptions about causal relationships in nature, inferences made on observations, and limited scope of action (see Table 4.1). Parents may not recognize their children's adaptive behavior if they assume linear effects across parenting circumstances and generalize one success to future occurrences, or if they infer success based on limited behavioral indicators (e.g., assessing compliance with chores vs. global behavior). These assumptions are often violated in practice, thus the

Table 4.1. Assumptions of Reductionism

Domain	**Assumption type and description**
Assumptions about causal relationships in nature (Ontological)	*Linear relationships*: Causal relationships are assumed to be linear for simplicity (e.g., to generate single slope parameters to estimate effects) *Independence*: Behaviors of individuals within a system are assumed to be unaffected by those of other entities *Unidirectional causality*: Causal relationships assume an absence of feedback *Single level of organization*: Higher-level phenomena are assumed to be simply aggregates of lower-level phenomena (absence of emergent properties)
Assumptions of measurement and inference methods (Epistemological)	*Indicator-specific*: Inferences are made on behaviors represented by summary indicators, rather than examinations of the relationships between the system and its parts *Time-specific*: Behavior is characterized by observations at one or more discrete time points, rather than examinations of behavior *patterns* over time
Assumptions of problem-solving approaches	*System as static*: Interventions assume absence of a system response to changes (e.g., homeostasis/equilibrium-seeking systems resist change by returning to the status quo) *Intervention scope*: Interventions assume a limited scope, focusing on changing behavior, rather than changing system structure and relationships that engender behavior

NOTE: Here, a system refers to the set of related parts that interact to produce behavior for a given question of interest, as per the ecological framework [2]. The constituents of a system depend on the question. For example, questions regarding the etiology of cancer could be concerned with behavioral norms around cancer-preventing lifestyle behaviors (system of individuals within a society) or on biological causes of cancer within the body (system of organs within an individual and their environment).

challenge is to determine when and how to account for complexity. Observing limited success, a parent could attribute their child's disobedience to fluctuations in disposition, or to permanent, learned responses to prior parenting. Either interpretation reasonably suggests different action. In this chapter, we present examples across three scientific disciplines where a complex problem ultimately proved to be insurmountable using reductionist approaches. In each example, scientists addressed complexity directly in order to better solve these problems.

1. ECONOMICS

For centuries, economists struggled to fully understand market behavior. They observed that markets generally followed large-scale trends but only understood the underlying processes and the role of constituent consumers and businesses in isolation [3]. Prevailing economic theories described individual behaviors predominantly as a function of personal preference and/or extrinsic society-level factors (e.g., market demands and the effects of political climates and scientific innovations on economic productivity). For example, neoclassical economists maintained free market views, theorizing that businesses selling products designed their products with characteristics that are in demand, such as durability or low price. However, this theory had trouble predicting behaviors under competitive conditions (e.g., when multiple businesses lose profits if they provide similar products [their outcomes are non-independent]). Purely free-market views disregarding non-independent decision making resulted in over-simplistic predictions [4].

Recognizing the fundamentally interactive nature of decision making, mathematicians worked separately to understand decision making in social settings more broadly. Drawing parallels from recreational games such as chess and poker, game theory posited that individuals predict how others' actions affect their own outcomes. This game concept readily extended to economics, where businesses predict their competitors' behaviors to maximize payoffs. Game theory was first applied to economic theory in *Theory of Games and Economic Behavior*, in which John Von Neumann and Oskar Morgenstern expanded established utility-based decision-making theories to incorporate interdependence explicitly [5]. To illustrate, classical marginal utility theory (MUT) states that businesses choose from a set of *alternatives* (product designs) by assigning each alternative an expected *utility* (say, end-of-year profits). While MUT allows for variation in personal preferences (e.g., prioritizing sustainable materials), it ignores interaction between decision makers. Utility is derived not only from consumer and personal preferences but also from competitors' designs and how they compete for demand. Game theory formalized this decision-making process by defining the *mixed strategy*

Nash equilibrium, the set of actions each player would choose under each possible set of circumstances, assuming other players' actions are held fixed—no business would change their design, assuming their competitors' designs are unchanged [6]. John Nash proved that there exists at least one Nash equilibrium in every finite game and devised a method for computing it, allowing economists to model business and consumer behaviors mathematically.

A well-known counterintuitive example is the Prisoner's Dilemma, where two prisoners, A and B, must choose between confessing or keeping silent, and their punishment depends on the unknown choice of the other prisoner [7]. If both keep silent, both receive minor punishment, and if both confess, both receive moderate punishment. If A confesses and B keeps silent, A goes free while B receives severe punishment. Assuming B's choice is fixed, A would always confess (likewise for B). Whereas the best outcome occurs when both prisoners keep silent, the Nash equilibrium predicts that both confess. This paradox arises partly because keeping silent requires trust in others to cooperate, and each prisoner possesses imperfect knowledge, fearing dire consequences if the other prisoner confesses. The paradox manifests in analogous problems across disciplines. Businesses choosing to split their consumer base by differentiating their products must trust their competitors to comply. In population health, health-service providers attempting to serve a community's unmet health needs risk overinvestment if other providers expand services into the same area [8].

Game theory also has implications for long-term decision making. Using simulation, Robert Axelrod examined how various strategies performed over consecutive Prisoner's Dilemma iterations, finding a "tit-for-tat" strategy was most successful. This strategy replicated an opponent's previous actions, thereby rewarding previous cooperators and punishing previous competitors [9]. In contrast, humans exhibited forgiving tendencies, favoring cooperation even after it backfired, possibly due to ethical considerations (morally valuing collaboration) or cognitive fallacy (presuming others must inevitably cooperate). Similarly, stock market investors often sell in direct response to sudden drops in stock values, causing collective harm when mass stock sales jeopardize the entire economy. As evinced by the mantra to avoid "market timing," investors often mutually benefit by holding falling stocks, yet holding requires that other investors will cooperate in the long term. These insights show the complexity of economic behavior owing to the fundamentally social nature of decision making. Economies cannot be understood by assuming independence among their constituent consumers and businesses, since their decisions involve personal factors (e.g., moral values and risk tolerance) and their anticipation of others' actions in the long term. These social interdependencies also exist between different species, as shown in the next example.

2. ECOLOGY

Ecologists are turning increasing attention toward human impacts on the natural environment, aiming to identify negative impacts early and minimize harm. Archetypal examples include carbon emissions, forestry, and energy use, for which understanding the complex interdependency of human populations and their ecosystems is essential [10]. One application tackled the problem of overfishing—specifically, the declining salmon harvest in the Pacific Northwest's Tucannon River region during the mid-twentieth century [11, 12]. Fisheries recognized the need to understand salmon populations to maintain sustainable harvesting practices, yet annual trends proved unpredictable. Despite efforts to restrict overfishing, salmon populations declined 90% by the 1980s.

Ecologists hypothesized why salmon populations were unresponsive to these efforts, attributing persistent declines to overinvestment in fishing gear and local agricultural development, which permanently impacted salmon spawning habitats [13, 14]. Further, they observed that salmon survival was dependent on sufficient species diversity, which helps salmon adapt to unexpected environmental changes (e.g., climate and predators). Prior theories of marine populations assumed a stable environment (neglecting human influences on the landscape) and a homogeneous marine population that poorly represented the region's five coexisting salmon species (underestimating the role diversity played in salmon survival). Lastly, given the four-year salmon lifespan and migration cycle, they speculated that observing annual changes in salmon populations was inadequate to detect effects.

Ecologists simulated salmon population trends over several decades in order to estimate the maximum sustainable yield (MSY), the largest annual harvesting fraction that would avoid permanent population declines [14, 15]. They applied known population growth rates, which reached a natural carrying capacity due to the limited number of feeding sites [13, 16]. They hypothesized that the MSY leveraged the salmon population's natural resilience but was sensitive to the river's carrying capacity, species diversity, and human impacts. Further, estimating the MSY would be possible only after observing at least four years.

Simulations showed a four-year cyclical pattern and S-shaped growth over a ten-year period, as predicted by the salmon lifecycle and the river's carrying capacity. A 95% harvesting policy showed little impact until four years out, where the population of returning adults dropped by 50% and exhibited marked drops every four years thereafter. The MSY ranged from 50% to 80% per year, accounting for uncertainty in model parameters, which was much lower than earlier predictions. The MSY was also affected by overfishing of any one species, such that species-naïve strategies caused greater long-term declines compared to diversity-maintaining strategies, even at the same harvesting fraction. Salmon populations

were resilient to species uniformity until sufficiently severe environmental shocks could no longer be sustained, thus the impacts remained unobserved until after several years. They also assessed the effects of agriculture and hydroelectric plant development on the salmon's habitat, hypothesizing that heavy erosion from dry cropland, cattle grazing, and runoff from new hydroelectric plants reduces water quality, further decreasing the carrying capacity [17]. Moreover, agricultural development increased demand for these resources, prompting further development. Simulating these impacts showed sharp population declines to less than 20% within a few generations, mediated by decreases in the carrying capacity, further compounding the effect of high-harvesting fractions.

The dynamics of overfishing and development gleaned from the Tucannon salmon fishing model generalize to other ecosystems around the world [18]. Animal populations naturally exhibit dramatic decline and recovery; however, co-mingling with humans reveals interdependent, co-evolutionary relationships that are insufficiently explained by reductionist approaches that assume static ecosystems and assess species survival by numbers alone. Ecologists' insights from complexity theory allowed fisheries to refine harvesting practices to ensure species diversity, balance human demand with the ecosystem's natural tendencies, and acknowledge the long delay in observing effects. Analogous examples exist in population health. A health clinic providing diverse medical care and supportive services to its patient population demands an equally diverse and competent team of providers, which can be frequently overburdened due to understaffing and frequent turnover. While temporary staffing shortages can be absorbed by sharing responsibilities among other providers, long-term strain can be physically and emotionally taxing and reduce the team's "carrying capacity" to provide future services. This type of worker fatigue will be explored in the next section.

3. PSYCHOLOGY

In the 1980s, burgeoning evidence in the psychology literature linked stress to poor psychological and behavioral outcomes. Work is a potentially major source of stress, but employers noted that some stressed workers suffered decaying job performance and economic productivity, while others benefited from stress as a motivator. The relationship between work stress and productivity was underexplored. Psychologists hypothesized that the negative effects of stress were mediated by worker burnout, states of severe exhaustion induced by prolonged, excessive work-related demands [19]. While variations in stress coping mechanisms influence the likelihood of developing burnout, it manifests when individuals become overcommitted to frustrating work and perceive a differential between work goals and performance, often unfolding slowly and remaining unrecognized until too late [20, 21, 22].

Strategies to prevent or remedy worker burnout had so far proved ineffective. Employers turned to reducing worker expectations or shifting tasks (actively diminishing sources of stress), training workers to manage stress (curbing its effects), or providing rewards and relaxation time (balancing stress with relief), yet no single strategy worked consistently [23]. Some workers also coped by engaging in addictive and damaging behaviors, such as drinking and gambling, which further undermined their physical health and exacerbated their intolerance for stress [24, 25]. Psychologists identified a need to understand the underlying psychological process causing burnout to uncover effective solutions.

Jack Homer explored the phenomenon of worker burnout, hypothesizing that the "workaholic syndrome" itself was sufficient to produce burnout, independent of extrinsic factors [26]. In other words, one's working conditions and individual skills may contribute to but are unnecessary to produce burnout. If so, workers could prevent burnout via managing the workaholic syndrome itself. Homer posited that when *work performance* equals or exceeds *expectations*, workaholics raise their expectations and increase their workload to meet these new expectations. However, a high workload undermines their *productivity*, which is further aggravated by the inevitable frustration from failing to meet their new goals. These discrepancies finally compel the worker to decrease their expectations [26]. This intuitive structure produces a dynamic cycle of stress buildup and burnout, illustrating how burnout may inevitably develop if effective stress-management strategies are not embraced.

Homer simulated the natural burnout cycle to identify leverage points for prevention. Glaringly familiar to psychologists for treating other disorders, he suggested controlling burnout by recognizing one's workaholic syndrome and maintaining realistic work expectations [26, 27]. He found that an essential component of the burnout cycle is the dynamic setting of work *expectations*, where workaholics increase their workload even when performance meets expectations—symbolic of the archetypal workaholic attitude that is perpetually dissatisfied. Such workaholics tend to delay the recovery process (resetting realistic work expectations) until catastrophic failure, which amplifies and prolongs burnout. Homer found that by restraining the tendency to increase *expectations* when meeting goals, and by setting a *maximum workload* even when failing to meet goals, the burnout cycle is blunted and overall productivity is improved over many burnout cycles [26]. Despite the model's simplicity, it provided a rational intuition for the failures of common stress-reduction techniques. If an unrecognized workaholic tendency exists, measures to reduce external sources of stress or provide relief would not address the intrinsic motivations that trigger the burnout cycle. Importantly, extended burnout periods with low productivity counterbalance temporary increases in productivity during stress buildup. Thus,

employers should promote supportive work environments, and workers should learn to recognize harmful workaholic tendencies.

Homer's model demonstrated the complexity of a pervasive psychological problem and its short-term and long-term solutions. In particular, Homer's application of causal feedback synthesized existing knowledge of burnout and recovery and affirmed a plausible underlying structure of burnout. Although there is no single way to control burnout, examining feedback facilitated the cultivation of solutions targeting its intrinsic source, a process that can be extended more broadly [28]. Conceptually, burnout could be applied to higher units of analysis, such as a family, team, organization, community, or entire society. For example, one could ascertain the interdependent effects of burnout risk between workers and their team members and upper management. When collective workload, available resources, and expectations are poorly aligned, and workers face impossible deadlines, burnout may lead to mass employee attrition or strikes.

Aside from the health consequences of burnout on the worker, these insights can be generalized to other health problems. For example, in population vaccination programs, inoculating sufficient proportions of a population achieves herd immunity, proffering protection to those who cannot be vaccinated (e.g., children and elderly). Yet, as shown by the resurgence of local outbreaks of vaccine-preventable illness in the mid-2010s, low risk perception due to prior vaccine success, and misinformation about the dangers of vaccines, triggered many individuals to opt out. Losses in herd immunity caused thousands of preventable cases of measles, pertussis, and other illnesses worldwide [29, 30]. After these outbreaks, epidemiologists pushed efforts to expel misconceptions and expand vaccine uptake. The cyclical pattern is caused by incongruent risk perception and reality, prompting the need to understand the process driving risk perception. Analogous to Homer's burnout study, characterizing the complex feedback between vaccine success and risk perception is crucial to interrupting the cycle to reduce vaccination loss and curb outbreaks.

4. CONCLUSION

As these examples illustrate, complexity is ubiquitous and inextricable from nature—yet ignoring complexity via reductionism remains the dominant method for scientific inquiry. However, while the simplicity of reductionism is attractive, its strict simplifying assumptions are mismatched to many problems in nature whose complexity cannot be ignored. It is not surprising then that many scientific disciplines have converged upon complexity theory. Unfettered by a simplistic focus on singular causative factors, these complex approaches permit scientists to explore the dynamics of context-driven causality, which has implications for both causal inference and intervention. Scientists across

disciplines have criticized reductionism's fixation on narrow causes, even calling for a paradigmatic revolution to address complexity [31, 32, 33, 34]. In population health, this is embodied in criticisms of randomized controlled trials as the gold standard for causal inference. These criticisms condemn the trials' reliance on strict inclusion criteria and narrow, manipulable causes as constraints to population health science—rendering them limited to studying "downstream" causes and too "politically conservative" to effect meaningful change [35, 36].

In response, population health scientists have advanced methods to incorporate contexts, including multilevel analysis to model influences from higher-level constructs, and simulation modeling to directly model complex systems. The latter gained popularity with the advent of increased computing capacity but has been fairly criticized for relying on data gleaned from reductionist techniques, thus suffering similar limitations [37]. Nonetheless, population health scientists who wish to disabuse themselves from the restrictions of reductionism may benefit from additional tools in their scientific toolbox that help them address complexity in complement with established reductionist approaches. These systems science approaches will be described in Part II of this book.

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5

Systems Thinking in Population Health Research and Policy

STEPHEN J. MOONEY

1. INTRODUCTION

This chapter illustrates how incorporating systems thinking into population health science helps to clarify key concepts, elaborate specific and testable hypotheses, and integrate findings from specific studies into policy decisions. We will discuss how policies designed to reduce environmental tobacco smoke have been more successful at preventing heart attacks than a naïve analysis might suggest, how eliminating endemic infectious disease through vaccination requires understanding the workings of social privilege, and the controversy surrounding whether liberalization of marijuana laws results in fewer traffic accidents.

2. SECOND-HAND SMOKE, SMOKING BANS, AND MYOCARDIAL INFARCTION

By the early 1980s, it was well understood that smoking tobacco causes heart disease [1]. Public health advocates became concerned that tobacco smoke exposure due to others' smoking (sometimes called "second-hand smoke" or "environmental tobacco smoke") might also cause heart disease [2, 3].

Epidemiologic studies showed a modestly (20%–30%) elevated lifetime risk of myocardial infarction among those whose spouses smoked [4]. Because environmental tobacco smoke was thought to result in much less inhalation of harmful components of tobacco smoke than active smoking [5, 6], even this modest elevation of risk was larger than had been expected. Working from this evidence,

public health advocates began to pursue "smoke-free" policies (a.k.a. smoking bans), limiting the locations where smoking tobacco was allowed [7].

Most of the evidence for the harms of environmental tobacco smoke was derived from the exposure of sharing a home with an active smoker [4], yet for pragmatic reasons, early smoking bans generally targeted public places and specifically excluded private homes [7]. Advocates thus relied on indications that exposure to environmental tobacco smoke in workplaces was roughly comparable or slightly greater than that of private homes [8].

Once passed, smoking bans were quite successful in reducing myocardial infarction rates [9–11], with one analysis indicating that hospitalizations for myocardial infarction dropped as much as 40% after a ban was implemented [12]. These substantially decreased hospitalization rates were more than might be expected due to the 20%–30% decrease in risk expected from removal of environmental tobacco smoke [10]. Indeed, early reports of decreased MI admissions after the implementation of smoking bans were sufficiently large that skeptics suggested they might be artifacts of incorrect analysis [13].

However, understanding the context in which smoking occurs helps to explain the bans' effectiveness. It is likely that policies that ban public smoking in the name of reducing environmental tobacco smoke also reduce active smoking, by decreasing smoking among current smokers [14], and by increasing cessation rates among smokers [15]. Figure 5.1 is a causal diagram illustrating this understanding of how smoking bans may prevent MI by reducing both active smoking and environmental tobacco smoke exposure.

This systems understanding helps to formulate effective anti-smoking policies and direct smoking research. For example, several case-control studies conducted in the wake of smoking bans confirmed that decreasing smoking prevalence was at least as much of a factor in the decrease in myocardial infarction admissions as decreases in environmental tobacco smoke [16, 17].

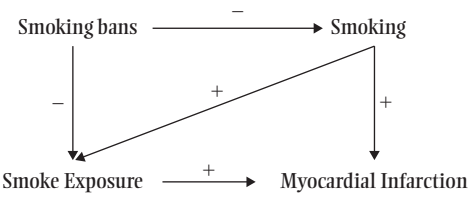

Figure 5.1 Smoking bans may prevent myocardial infarctions by removing smoke exposure among non-smokers, but they may also prevent myocardial infarctions by reducing smoking among smokers. Alternate laws, such as improving ventilation in bars, might prevent the smoke exposure among non-smokers but would not prevent smokers' myocardial infarctions that occurred due to smoking. Arrows represent causal links, where minus indicates a preventive link and plus indicates a causative link.

An analytic approach to smoking bans that failed to incorporate a systems perspective might incorrectly conflate the impact of reducing environmental smoke with the impact of removing smoking, leading to an overestimate of the risks of environmental tobacco smoke. By contrast, the systems approach incorporates the pathways through which smoking bans function and can identify why working to improve ventilation in bars, as proposed by the tobacco industry [18, 19], would be less effective from a public health standpoint.

3. THE DECISION TO VACCINATE

Widespread vaccination is among the most successful initiatives ever to improve population health [20]. Prior to the extensive deployment of vaccination in the mid-20th century, infectious disease caused about half of all deaths among US residents aged 5–44, and a substantial proportion at other ages as well [21]. After childhood vaccination became normative, the burden of infectious disease fell to about 4% of disability-adjusted life years, even accounting for the late 20th-century emergence of HIV [21]. For example, measles was common enough to infect 90% of American children before they were 15 years old [22].With the introduction of the measles vaccination program in 1963, measles was eventually eliminated as an endemic disease in the United States [23, 24].

Over much of the history of infectious disease control, the primary barrier to vaccination has been access to the vaccine itself [25]. However, in recent years, vaccination rates for common childhood diseases such as measles have fallen in the United States, particularly among privileged groups who typically do not lack access to the vaccine [26]. Indeed, one high-profile outbreak in late 2014 in which measles was transmitted at the Disneyland theme park [27] was likely vastly increased in scale due to substandard vaccination rates among relatively privileged children visiting the park [28]. A systems understanding of vaccination and socioeconomic privilege helps to explain this.

The reduction in disease risk conferred by any given vaccination is determined in part by the prevalence of vaccination among others. In particular, as a campaign successfully vaccinates more individuals, it decreases the probability that any given unvaccinated child will be exposed to and ultimately infected with the targeted disease [29].

One component of socioeconomic privilege is the capacity to leverage flexible resources such as money and social connections in pursuit of health [30]. Because vaccination carries risk, albeit minimal, of adverse events [31], in a context where measles is exceedingly rare and where clinical care can minimize harm in the event that a child does develop measles, scientifically informed parents may still feel the minimal risk outweighs the potential harms.

Indeed, opposing vaccination has been described as an expression of privilege [32]. Yet after the 2009–2010 emergence of the H1N1 strain of influenza, during which fears about the severity of symptoms reported among the infected stoked a general increase in interest in vaccination [33], vaccine uptake was much more common among upper socioeconomic status individuals than lower [34]. Considering how disease prevalence and access to care affect risk and risk perception, and taking a systems perspective, clarifies the rationale behind the decision to vaccinate.

In the absence of a systems perspective, public health officials might simply assume anti-vaccination sentiment was driven by distrust of authorities. While qualitative studies do indicate that distrust of authorities also plays a role in the decision [35], the systems perspective helps to illustrate the difference between uptake of measles and H1N1 vaccines. These differences may be vital in constructing messaging to maximize vaccine uptake [36].

4. MARIJUANA LIBERALIZATION AND TRAFFIC SAFETY

Starting with the 1996 passage of California's Compassionate Use Act, several states have liberalized regulations affecting marijuana, which was already North America's most widely used illegal drug [37]. By the end of 2014, 23 states and the District of Columbia (DC) had legalized the medical use of marijuana [38], and several had decriminalized or legalized non-medical use as well. Laboratory studies have established that intoxication with Tetrahydrocannabinol, the psychoactive component of marijuana, leads to slowed reaction times, distracted driving, and failure to react to challenging driving situations [39]. Epidemiologic studies confirm that driving in real-world conditions while intoxicated elevates risk of crashing [40]. Finally, a large proportion of college-age students have reported driving after consuming marijuana [41, 42]. Public health and traffic safety officials have therefore expressed concern that liberalizing marijuana laws may increase marijuana consumption and consequent traffic injuries and fatalities [43].

Yet in practice, states that have liberalized marijuana laws have not had substantial increases in traffic injuries and fatalities. Indeed, some early evidence suggests the opposite—that marijuana liberalization has led to decreased traffic fatalities [44]. This result may seem counterintuitive: can making it easier to access a substance that increases risk lead to decreased risk?

By considering the system in which marijuana is used, we can identify several factors that may explain this finding. First, while reported use of marijuana is higher in the states in which medical marijuana was legalized [45, 46], it remains unclear whether increases in marijuana use have followed liberalizations or an atmosphere of marijuana tolerance has encouraged public support

for liberalization. Indeed, several longitudinal analyses have suggested marijuana laws have no effect on consumption [47] or even that legal medical marijuana may prevent marijuana use among teens [48].

Second, while marijuana consumption increases crash risk when compared to not consuming marijuana [49, 50], in practice, liberalization of marijuana laws allows marijuana to substitute for other psychoactive substances that increase crash risk more than marijuana consumption does. For example, marijuana may substitute for opiates in pain management [51, 52], which may decrease crash risk because driving under the influence of opiates is even riskier than driving under the influence of marijuana [53]. Similarly, recreational marijuana use may substitute for alcohol use [44], which is associated with much greater risk of crashing at typical levels of intoxication [54].

Third, marijuana may elevate the risk of crashing while decreasing the severity of crashes, thereby preventing fatalities. Whereas alcohol users are often overconfident and drive at unsafe speeds, marijuana users frequently overestimate their impairment and drive more slowly [54]. Because the probability that a crash will result in a driver or pedestrian fatality increases greatly at high vehicle speeds [55, 56], decreasing the average speed of a collision should decrease fatality rates.

Fourth, while many young adults report driving under the influence of cannabis [41], it is possible that marijuana use may prevent crashes by deterring driving at a higher rate than the commensurate elevation of crash risk. Most estimates suggest that cannabis intoxication approximately doubles the risk of a crash [53]. Yet psychotropic effects of marijuana frequently include sluggishness and a feeling of detachment from surroundings [57]. If such effects decrease a marijuana consumer's desire to drive such that more than twice as much driving is avoided, then the total number of crashes may drop even if any given instance of driving is riskier.

Finally, because legal changes surrounding marijuana use have taken place in political climates aware of crash risks, it may be that the changes have led to more police awareness of driving under the influence of marijuana and to public service announcements oriented at deterring driving after ingesting marijuana [43]. These policies may be responsible for increased traffic safety.

Figure 5.2 illustrates the system in which marijuana laws may affect traffic safety, highlighting points in the system described here. We caution that the impact of marijuana laws is very much an area of active research [58].

An analytic approach to marijuana and traffic safety that failed to incorporate a systems perspective might incorrectly infer from consistent lab-based studies showing marijuana consumption decreasing driver safety that liberalized marijuana laws would necessarily elevate collision rates. Similarly, such an approach might commit the "ecologic fallacy," inferring from the preliminary evidence showing liberalization decreasing collision rates either that the finding was a

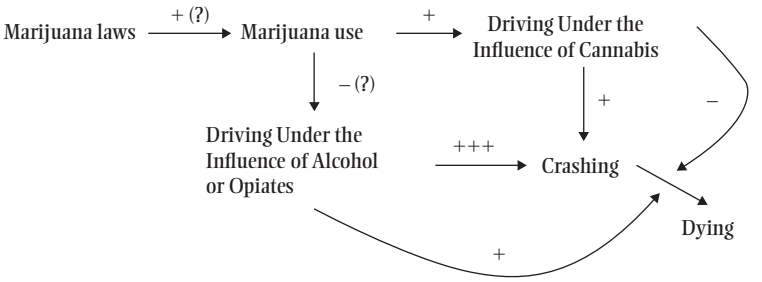

Figure 5.2 An illustration of the possible causal relationships linking marijuana laws to motor vehicle fatalities. Arrows represent causal links, where the number of pluses indicates the strength of the causal connection.

priori in error due to its contradiction of lab-based evidence or, equally falsely, that marijuana improves individual driver safety.

5. SUMMARY

Population health is a product of dynamic interrelated mechanisms. Most health researchers implicitly or explicitly consider this complexity in formulating specific study hypotheses. As these examples illustrate, holistic understanding of systems is a key component of identifying the optimal targets for study. Engaging with systems science principles can help investigators do the best science and identify the best interventions to protect population health.

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SECTION 2

Methods in Systems Population Health

6

Generation of Systems Maps

Mapping Complex Systems of Population Health

HELEN DE PINHO

1. INTRODUCTION

Population health problems are messy.[1] This "messiness" is characterized by interdependent factors, uncertainty as to how these factors will behave in relation to each other over time, and uncertainty as to how the problems should be resolved. Multiple and conflicting perspectives and assumptions about the problem situation abound. In other words, these are complex adaptive problems.

If our thinking fails to recognize the complexity of the problem situation, then we risk being caught up in two traps: the trap of reductionism, avoiding the interconnectivity between variables; and the trap of dogmatism, working on the basis of a single unquestioning and limited perspective [1]. Such reductionist and dogmatic thinking leads to inadequate formulation of the problems; hence solutions, no matter how well designed, fail to address the right population health problems—a situation all too familiar.

To address these type three errors (the right answer to the wrong question) [2], we need to move beyond simply "thinking about systems" (for example, health systems, political systems, financial systems, and legal and regulatory systems) and start using "systems thinking" approaches that regard systems as conceptual constructs that we select and use to inquire into, and engage with, situations of real-world complexity [3, 1]. A systems thinking approach requires that we use methods like systems diagrams to effectively organize thinking about problem situations so that action to bring about improvement can be taken [4].

1. The term "mess" in systems thinking is synonymous with Russell Ackoff [24].

Depending upon context, these actions may be to use these maps as the basis for further modeling, or to guide further data collection, discover new questions, illuminate core uncertainties, challenge the robustness of prevailing theories, and strengthen policy dialogue [5].

This chapter outlines an approach to creating these conceptual maps that facilitates systems thinking. It begins with a discussion of stakeholder participation in the mapping process, then puts forward frameworks for problem articulation and critiquing boundary judgments, and discusses the development of a dynamic hypothesis. The final part of the chapter outlines three systems thinking tools that specifically focus on exposing the relationships amongst factors in a problem situation (a focus on the forest so that we can see the trees in context), and serves to make explicit multiple perspectives and assumptions—necessary to manage the complex realities that characterize population health problems—avoiding reductionism and dogmatism.

2. STAKEHOLDERS AND PARTICIPATION

Collaboration among stakeholders in the co-creation and use of systems maps is essential to building a community of systems thinkers able to engage with complex issues [6]. Population health decisions often involve tradeoffs and are characterized by conflicting values, and these decisions, once taken, may be difficult to implement. Effective participation by stakeholders in systems thinking processes reduces conflict, builds trust and long-term relationships, and increases the legitimacy of decisions. Not only is the quality of decisions improved, but there is also an increased likelihood that the decisions will be implemented [7].

Who the stakeholders are and who should be involved in the mapping process is context specific, but there are generally three categories of stakeholders present [3, 6]. The first category, *issue owners*, are people who are affected by the situation and who would be affected by the outcomes of any interventions. While they may not have the power to implement change, issue owners are vital to informing the map-building process, and we should take care not to speak on their behalf. *Clients* are the second group of stakeholders. They are the driving force behind the map building process and are able to effect change based on the outcome of the mapping process. Clients may be issue owners, or they may come from outside organizations. It is important to know who they are and to understand their motivation and how they interact with the issue owners. The final category, *gatekeepers*, are stakeholders with the power to block or support map building and subsequent inquiry using the maps. They should be identified early in the process and brought on board, and they may also be issue owners or clients. Like all complex systems, stakeholder engagement should be viewed as a dynamic process, with stakeholders moving in and out of the process.

An additional group of people engaged in the process are of course the s*ystems practitioners, facilitators, and/or modelers.* The success of any participatory map building exercise relies on their skillful, reflective facilitation, and trust in and tolerance for the process. Systems practitioners must make sure that there is transparency of information, that assumptions and uncertainties are made explicit, and that the process is iterative to accommodate new information.

3. PROBLEM ARTICULATION

In a complex situation, there are multiple and competing perspectives on the "problem" and how this problem is changing over time. Establishing a clear articulation of the problem and overall purpose of the systems inquiry among stakeholders is therefore a vital step in the development of a systems map [8].

Peter Hovmand has identified a series of questions that systems thinking practitioners should ask at the beginning of any system mapping process in order to refine the problem [6]. The purpose of these questions are twofold: to establish a common understanding of the problem among all stakeholders, and to decide if a systems thinking approach is appropriate to address the problem. The questions begin by first asking stakeholders about their understanding of the problem to be addressed and the overall purpose of engaging in a systems thinking process. If, after discussion, a lack of clarity remains, this may well be reason to pause or stop the map building process.

Once a problem has been identified, the next question establishes whether the problem is dynamic. Is it possible to draw a graph with the desired and feared behavior over a defined period of time? These behaviors over time graphs form reference modes and serve to focus the systems thinking process. Additional questions focus on understanding the nature of the problem and how this understanding informs the kind of necessary systems analysis. For example, would a systems-rich picture suffice, or is the development of a simulation model needed in order to take action? Having decided upon the type of systems thinking analysis, the final question focuses on what would be the added value of this approach above existing tools [6].

Working through these questions in collaboration with stakeholders serves to distill the description of the problem to be examined using a systems thinking approach and may even determine whether there is merit in proceeding with systems mapping, especially if there is no clarity on the problem definition.

4. BOUNDARY CRITIQUE

Even when there is clarity regarding the problem definition and purpose of the inquiry, the elements we select as relevant for consideration of the problem

situation implicitly set boundaries [9]. These boundary judgments are inevitable. No assessment, action, description or map can fully capture a situation and align it with everyone's perceptions [10]. What is included, excluded, and marginalized in the investigation of the complex problem reflects our values, mental models, and worldview.

How to bound or delineate a system for the problem situation under consideration is a subjective decision and does not have to correspond to any real-life barriers or limits of an organization. From a critical point of view, what matters is not the comprehensiveness of our boundary judgments but rather "how carefully we manage and reflect on the inevitable lack of comprehensiveness of our judgments" ([9] p. 15).

Critical systems heuristics (CSH) [11], provides a practical focus for assessing and discussing boundary judgments among stakeholders. It is a systematic framework of boundary categories, and twelve questions applied to problem situations in order to unfold multiple perspectives and promote reflective practice. We can use these questions, presented in Table 6.1, to understand the assumptions behind how boundaries are drawn and to explore the sources of values and motivation, power structures and control, knowledge, and legitimacy of the information used to determine boundaries.

Application of the CSH framework provides an opportunity to make judgments explicit, improve communication among stakeholders engaged in the mapping process, and promote a sense of mutual tolerance as we realize that "nobody has a monopoly for getting their facts, and values right" [11].

5. DEVELOPMENT OF DYNAMIC HYPOTHESIS

The end product of any systems thinking process when applied to a problem situation is not the map or model itself but rather an accumulation of insights gained through the mapping or modeling process. These insights, made explicit, are formulated into a dynamic hypothesis. In the context of systems modeling, the process of analysis leading to a dynamic hypothesis is not meant to enumerate "unlimited details of a 'system' " ([12] p. 348). Rather, the dynamic hypothesis provides a working theory of how the problem situation arose, postulating an initial explanation of the dynamics characterizing the observed system behavior in terms of the underlying causal relationships, feedback, delays, and structure of the system [13].

This explanation can be expressed verbally, but given the complexity of the interactions it is usefully communicated through systems maps such as causal loop diagrams (CLDs) and stock and flow diagrams. The dynamic hypothesis is refined, or at times abandoned, as these diagrams or maps are further explored

Table 6.1. The Boundary Categories and Questions of Critical Systems Heuristics (Reproduced From ([11] Page 244)

Sources of Influence	Boundary Judgments informing a system of interest (S)			
	Social roles (Stakeholders)	**Specific concerns (Stakes)**	**Key problems (Stakeholding issues)**	
Source of motivation	1. *Beneficiary* Who ought to be/ is the intended beneficiary of the systems (S)	2. *Purpose* What ought to be/is the purpose of S	3. *Measure of improvement* What ought to be/is S's measure of success	**The involved**
Source of control	4. *Decision maker* Who ought to be/is in control of the conditions of success of S?	5. *Resources* What condition of success ought to be/are under the control of S?	6. *Decision environment* What conditions of success ought to be/are outside the control of the decision maker?	
Sources of knowledge	7. *Expert* Who ought to be/is providing relevant knowledge and skills for S?	8. *Expertise* What ought to be/are relevant new knowledge and skills for S?	9. *Guarantor* What ought to be/are regarded as assurances of successful implementation?	
Sources of legitimacy	10. *Witness* Who ought to be/is representing the interest of those negatively affected by but not involved with S?	11. *Emancipation* What ought to be/are the opportunities for the interest of those negatively affected to have expression and freedom from the worldview of S?	12. *Worldview* What space ought to be/is available for reconciling differing worldviews regarding S among those involved and affected?	**The affected**

through the application of modeling techniques, or deeper engagement with key stakeholders in the real world.

6. GENERATION OF SYSTEMS MAPS

While much of the focus lies with the refinement of the dynamic hypotheses and subsequent models, there is limited attention paid to the actual creation of the initial systems maps. A scan of the literature focused on systems dynamic modeling and other simulation approaches provides limited insight into how the initial systems maps and dynamic models are developed, and the decisions taken regarding which elements are included in the maps. Instead, the focus lies on the refinement of the maps, models, and subsequent hypothesis once they are developed [14].

To avoid the two traps in thinking about problem situations, namely reductionism and dogmatism, we need a more systematic and transparent approach to building up a dynamic hypothesis for a given situation. This approach can be divided into three phases, and while there is variation among systems practitioners about how these three phases are labeled, there is agreement about what each phase sets out to achieve [15, 16]. The first phase, referred to as "searching" or "creativity," acts to sweep in multiple issues and perspectives—"to see the world through the eyes of another" [17]. During this phase there is an iterative examination of the problem situation, describing structural, functional, and behavioral aspects of the elements in the situation. The second phase, "connectivity" or "mapping," synthesizes the issues raised in the first phase, identifies relationships among these issues, and exposes existing assumptions. The third and final phase, "communication" or "telling the story," draws upon the first two phases to integrate insights into a map that facilitates systems thinking. This three-phased approach allows us to challenge mental models, include multiple perspectives, reflect critically upon boundary judgments, and ultimately develop a dynamic hypothesis that can be tested through a modeling process.

There are a number of systems thinking tools that can be used for each of these three phases. For the purposes of this chapter, three tools are described: rich pictures, interrelationship diagraphs, and causal loop diagrams. Each can be used on their own but are most effective when used as a sequence toward the development of a hypothesis to explain the structure and potential dynamics driving a problem issue.

7. RICH PICTURES

Rich pictures support the first phase of developing a dynamic hypothesis. The rich picture is a drawing that reflects a concern or problem situation identified by

key stakeholders, including the clients, gatekeepers, and issue owners. The pictures are ideally built through an iterative process of engagement: collaborative drawing and reflection with a group of key stakeholders. If working in a large group, it is sometimes helpful for smaller groups to develop their own rich picture and then have the group come together to discuss the different rich pictures.

Rich pictures serve to "sweep-in" multiple perspectives, expose existing mental models, and make tacit knowledge and assumptions explicit, as stakeholders work together to develop a more complex understanding of a situation. The picture should not be generic but clearly reflect contextual issues including existing resources and assets in the situation as well as problems.

The quality of the art is not important. Instead, what matters is that all elements, relationships, emotions, and interactions relevant to the issue at hand are included. This is detailed in Box 6.1. Symbols and images are used instead of words to facilitate exploration of thoughts not yet verbalized. The richness of the picture is based upon the experience of all the stakeholders engaged in the drawing process, and enhanced by additional quantitative and qualitative data from interviews and the literature.

The rich picture is particularly useful when working with a diverse stakeholder group with various power relationships. Not only is it an effective medium through which to communicate complex relationships, but the act of drawing has a leveling effect within a group. It is often easier for stakeholders to draw an issue rather than state it out loud.

Box 6.1

What Should Be Included in a Rich Picture?

- Issues and concerns–what are the motivations and perceptions of each of the key stakeholders in this situation? What values are driving stakeholder actions?
- Structure–this refers to both formal structures like organizational structure, geographic location, physical layout, and all the people who are affected by the situation, as well as informal hierarchies and networks that exist in the system.
- Process—this refers to flows or transformations that occur within the structures over time—such as flows of goods, information, resources, and communication patterns. It is also useful to include "behavior over time" graphs as tools to illustrate trends over time.
- Outcomes—include some of the outcomes of the system, both those that are intended and unintended. [18]

Box 6.2

Using Rich Pictures

A team looking to improve the availability of human resource for health data in a country developed the Rich Picture depicted in Figure 6.1. The group consisted of participants from the Ministry of Health as well as collaborating donor partners. It was only when they began drawing the flow of information from the ground up and from the Ministry of Health down that they realized that the two "routes" were quite separate from each other—accounting for the lack of coordination and poor quality of data. This was then used as the basis for developing a proposal to strengthen the overall system.

Figure 6.1 Rich Picture exploring a concern about the availability of human resources for health data.

While it is possible to use rich pictures as a standalone tool when working with a diverse group of stakeholders with widely different perspectives, they also provide a useful starting point to surface the different factors influencing a problem situation and to use these in the next phase of systems map development. Box 6.2 provides an example of using rich pictures.

8. INTERRELATIONSHIP DIGRAPH

The interrelationship digraph (IRD) is a visual tool that builds on the rich picture and is used to explore all possible interactions among the key variables in a situation. In the three-stage process of developing a dynamic hypothesis described earlier, the IRD supports the second stage, as it examines the relationships and connectivity among factors in the problem situation. The process of creating the IRD challenges existing mental models about the relationships among the variables and prevents coming to a quick conclusion about the structure of the system driving a particular problem situation. In the absence of hard data, it is a useful tool to explore complex relationships and surface key drivers and outcomes in a situation. The process of creating an IRD is summarized in Box 6.3.

IRDs can be used as a systems tool without going on to develop a causal loop diagram. When used as part of a group exercise, IRDs encourage team members to think in multiple directions rather than linearly and systematically explore the cause and effect relationships among all the key variables. This process will often surface basic assumptions and reasons for disagreements among team members, allowing key issues to emerge naturally rather than be forced by a dominant or powerful team member. Box 6.4 provides an example of using an IRD to explore a complex problem. The IRD also provides a useful starting point to begin the construction of the causal loop diagram.

9. CAUSAL LOOP DIAGRAMS

The third systems mapping tool is the causal loop diagram. Like the IRD, the CLD also aids in synthesizing issues and identifying the relationships among these issues and is then used by stakeholders and systems practitioners to communicate the hypothesized understanding of the system's structure driving the problem.

Transforming an IRD into a CLD is an iterative and collaborative process. Rather than rely on their mental models of what they think is happening in a system, the model developer(s)/systems practitioners work with stakeholders and use the IRD (and rich pictures) to surface the CLD. This process is summarized in Box 6.5.

Although there is no such thing as a "final" CLD, the completed map should tell a clear story about the structure of the problem situation without being overly complex (and not too simple!). The CLD is considered "done" when it

Box 6.3

How to Develop an Interrelationship Digraph

Before beginning an IRD, make sure that all involved in the process understand and agree on the problem statement (which would be the same statement that informed the rich picture). This done, step one is to identify ten to twelve key variables from the rich picture. These variables represent elements in the situation that may act or be acted upon, where their value can vary up or down over time, and should be measurable, at least in theory. They should be neutrally defined, distinguish between perceived and actual states, and should include the desired outcome(s) of interest. When working with a group of stakeholders, it is useful to develop a reference list of variable definitions capturing the key construct depicted by the variable name.

Arrange the selected variables in a circle, pick one of the variables to begin, and consider the relationship between this variable and each of the other variables in the circle. For each pair of variables, decide if there is an "influence" between the two variables and where there is a direct relationship, and use an "influence" arrow to connect the two related variables. The arrows should be drawn from the variable that influences to the one that is influenced. If two elements influence each other, the arrow should be drawn to reflect the stronger influence in the given context. Arrows can only be drawn in one direction.

Move on to the next variable in the circle and consider where there is a relationship between that variable and all others in the circle. Consider the relationships in pairs—a relationship need not exists between all variables. Continue until you have explored potential relationships amongst all variables.

The relationship should be a direct relationship and not via another variable. Where possible, base decisions on existing evidence, or consensus among experts. Always be aware of assumptions.

Once all possible relationships have been examined, the main drivers and outcome variables are determined by simply counting the number of arrows coming into and going out of a variable. Variables with more arrows coming in than going out are outcomes; those with more arrows going out are drivers.

reflects the problem situation as perceived by those affected by the situation, the issue owners, and those wanting to improve the situation—the clients [20]. It is also considered "done" when the CLD reflects a potentially plausible explanation (prior to systems dynamics modeling) for the reference modes identified during problem articulation and included in the rich pictures. Box 6.6. summarizes the process of identifying the feedback loops in a CLD.

Box 6.4

Using IRDs: Investigating Chronic Poor Maternal Health Outcomes in a District in South Africa

The IRD in Figure 6.2 was developed as part of a group model building process with key stakeholders in a district in South Africa. The clients were seeking to understand the drivers of poor maternal health outcomes in a context where financial resources were generally not limited, but health service delivery was consistently perceived to be poor. The IRD was developed through a participatory process using variables identified from a rich picture drawn by the participants. While the IRD produced some unanticipated insights, including the importance of data flows for management in this context, as well as the confidence of staff to perform certain functions, participants perceived that the greatest strength of the IRD was in the process of creating the diagram and the depth of discussions that ensued.

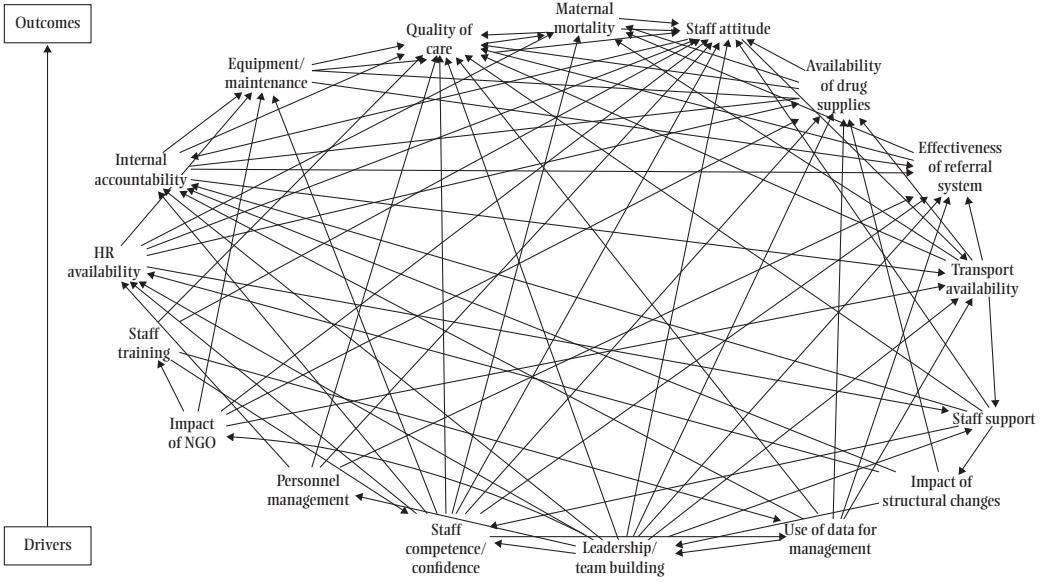


Figure 6.2 IRD developed to identify drivers of chronic maternal health outcomes in a district in South Africa.

Box 6.5

How to Develop a Causal Loop Diagram

The development and level of detail of the CLD should be informed by the following [19]:

- the problem statement or issue driving the creation of the CLD;
- boundary decisions including whose voices and issues are included or excluded; and
- an assessment of the stakeholders, issue owners, clients and gatekeepers, and their sphere of influence to affect change in the system.

A useful starting point for building a CLD is to surface a seed model from a related IRD. At least one key outcome of interest and driver of that outcome, and one or two variables that link the driver to the outcome, are identified from the IRD and transferred to a new sheet to begin the CLD.[1] The variables selected for the seed model should fall within the appropriate sphere of influence. For example, if the map is being built to effect change at a facility level, then beginning with a distal variable such as "socio-economic class" is not useful, as this is beyond the immediate sphere of influence. This is not to say that the distal variables cannot be included in the final CLD. The seed model is simply a useful starting place to begin surfacing the CLD.

Working between the IRD and seed model, start adding in the variables that are linked to the outcome and driver(s) in the seed model to build up the CLD. Through this process, smaller loops in the IRD may become redundant with respect to larger, more encompassing loops. It may also be necessary to add new links, including some that feedback between variables (not permitted during the creation of the IRD), as well as new variables to better explain the relationship between existing variables. It is not necessary to incorporate all possible variables in the CLD. In some cases there are external elements that do not change or change very slowly, or whose changes are irrelevant to the problem situation. Including these can unnecessarily complicate the map, particularly if there is no or little control over these variables [20]. Where appropriate, identify any links that have significant delays relative to the rest of the map. It is important to identify these delays, as they are often the source of imbalances that accumulate in the system.

There are some conventions to be followed when building a CLD [8]. Do not duplicate variable names, and avoid putting circles, boxes, or hexagons around the variables. Use curved lines to better reflect feedback loops, and as far as possible avoid crossed lines, although this is not always possible. The goal is to produce a map that effectively represents the structure and relationships among key factors giving rise to the outcome(s) of interest. The decision to include additional variables and causal links should be based on information received from stakeholder interviews and

discussions, rich pictures and existing literature and data available. When developing the CLD, it is good practice to keep a record of the data sources for each decision.

[1] The IRD and CLD can be drawn by hand, using sticky notes on a board, or using one of the existing modeling programs such as Vensim PLE.

Box 6.6

How to Surface the System's Feedback Loops

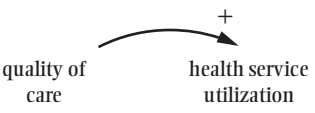
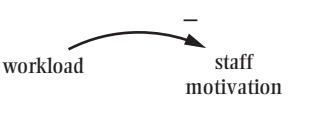
The next step in the development of the CLD is to identify the feedback loops underpinning the system's behavior. There are only two types of feedback loops—reinforcing loops and balancing loops.

To determine the nature of the feedback loop requires that every causal link in the CLD is assigned a polarity, either positive (+) or negative (−). The definitions of the link polarities are provided in Table 6.2. The polarity of a link should be unambiguous. Where there is a question about whether the polarity is positive or negative, consider whether there is more than one causal pathway between the two variables that acts in different directions, and include these in the CLD.

A reinforcing loop is one in which an action produces a result that influences more of the same action, thus resulting in growth or decline at an ever-increasing rate. Positive reinforcing loops produce virtuous cycles, and negative reinforcing loops produce vicious cycles. Identify a reinforcing loop when all the links in the loop are positive, or if there is an even number of negative links (irrespective of the number of positive links).

Balancing loops generate the forces of resistance, which eventually limit growth, maintain stability, and achieve equilibrium. These loops reduce the impact of a change and are generally goal seeking. A shortcut to determining a balancing loop is to count the number of minus signs in the loop: an odd number of minus signs

Table 6.2. Link Polarity: Definition and Example (Adapted From [8] pg. 139)

Symbol	Interpretation	Example
	All else equal, if X increases (decreases), then Y increases (decreases) above (below) what it would have been.	
	All else equal, if X increases (decreases), then Y decreases (increases) below (above) what it would have been.	

means it is a balancing loop. Note that not every link in a CLD is part of a feedback loop. For a loop to be a feedback loop, all the arrows must flow in the same direction.

To facilitate understanding and communication of the CLD, all feedback loops should be labeled, indicating the nature of the loop (reinforcing or balancing), and named. When using systems dynamic modeling software such as Vensim PLE, it is also possible to indicate whether the loop is clockwise or counterclockwise in the CLD

Box 6.7

CLDs: Investigating Chronic Poor Maternal Health Outcomes in a District in South Africa

Through a group model building process, the following CLD was developed (Figure 6.3), using the IRD depicted in Box 6.4 as the basis for identifying the seed model and exploring relationships. While it is not possible to estimate the strength of the linkages simply on the basis of this CLD, this systems map alerted participants to possible leverage points to intervene, and associated areas of policy resistance and unintended consequences.

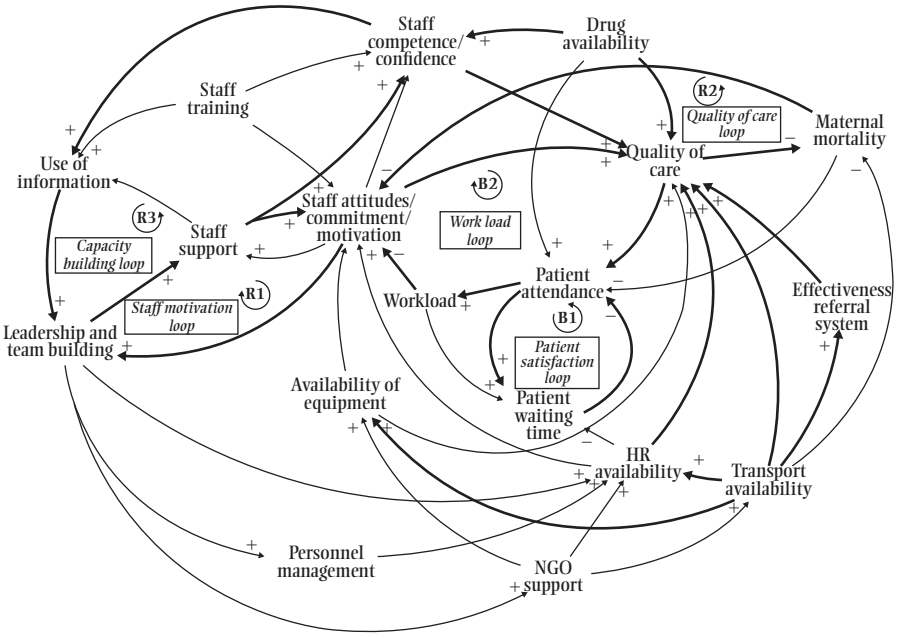


Figure 6.3 CLD investigating poor maternal health outcomes in a district in South Africa.

An examination of the complex systems structure and intersection of feedback loops and relationships among the variables in a CLD can reveal points of potential policy resistance, particularly in the presence of balancing feedback loops; identify possible leverage points where micro changes in the system could result in macro results; alert stakeholders to potential unintended consequences following an intervention; and through this elaboration of the problem situation, inform the formulation of appropriate research questions [5].

In recent years, a plethora of articles has appeared that utilize systems mapping and CLDs qualitatively, in addition to parameterizing the maps to develop systems dynamics models [14]. This has given rise to concerns that a failure to understand that a CLD does not provide an indication of the strength of the relationships between variables, nor any accumulations, could result in inappropriate application of CLDs to complex population health issues [21, 22]. For this reason, close attention must be paid to the process of systems mapping, including stakeholder engagement, approach to boundary decisions, the source of the data used to construct the CLD, and the interpretation of causality based on the CLD.

10. CONCLUSION

Systems mapping, through rich pictures, IRDs, or CLDs should not be regarded as the endpoint of the systems thinking process but rather the starting point for ongoing conversations, as well as systems dynamic modeling to facilitate policy experimentation not possible in the field. Each of these tools serves to make explicit and communicate an understanding of the structure of the complex web of factors driving a particular problem—in other words, the dynamic hypothesis.

Ultimately, if we are to avoid the traps of dogmatism and reductionism as we navigate a path through messy, complex population health issues, then we need both to expand and refine our practice of systems thinking. This will allow us to consistently challenge assumptions, test our understanding of the nature of these problems [23] and ultimately strengthen the models that we use to make sound population health decisions.

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7

Systems Dynamics Models

ERIC LOFGREN

1. INTRODUCTION

Systems dynamics models are representations of the real world made by dividing the population up into categories, with accompanying mathematical representations of how these categories interact with each other and how members of one category move to another. These models have a long history of use in epidemiology, appearing in rudimentary form in work by Bernoulli, before Ross, Kermack, and McKendrick refined them in the early 20th century [1, 2]. By virtue of their age and mathematical tractability, these models became the foundational tool of public health modeling and continue to be one of the main tools in the modeling of human health. Many other types of models, such as agent-based or network models, stem from trying to address the assumptions behind systems dynamics models, which are discussed below.

In this chapter, we first consider how to construct a systems dynamics model and how to solve these models computationally. Then we explore some of the key insights that come from these models and how these models can be combined with observational data. Finally, we explore a more complex example of a systems dynamics model, discuss some of the assumptions inherent to this model type, and touch on some basic extensions that aim to address these assumptions.

2. MODEL COMPOSITION AND THE SIR MODEL

The key to understanding a systems dynamics model lies in the equations that govern it. As such, understanding how these models are composed is an essential first step. The examples used in this chapter focus on infectious processes because

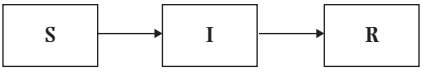

Figure 7.1 The population is divided up into three compartments: those susceptible to infection (S), those infected (I), and those who have recovered or died from the infection (R).

these models were initially intended to study infectious diseases, but they are by no means exclusively useful for infectious diseases. Systems dynamics models can be used for anything from chronic disease progression to estimating patient recruitment and retention in treatment programs.

Often called "compartmental models," these models are made of a series of compartments that represent distinct subpopulations. These can include health states, demographic characteristics, or other categories. Equations describe the flow between these compartments, including which transitions are allowed and at what rate. Graphically, this is represented as a flow diagram (Figure 7.1).

This model, known as the SIR model, is the most commonly used model in public health. Additional compartments and interactions between them can be added to give these models almost infinite variety. These schematics are helpful for providing a quick overview of the model, but just as the model itself is a simplified representation of reality, the flow diagram is a simplified version of the model. It does not say *how* one transitions from one compartment to another. In order to answer this, we need a precise way to describe the model: mathematical equations.

Differential equations are used for most of these models. Each is made up of *variables*, represented as italicized capital letters, and *parameters*, represented by lowercase Greek letters. Variables are the compartments (such as S) whose value will change. Parameters are constants used to connect these variables together—for example, the rate of movement from I to R. Working from the graphical representation of a model, each compartment needs one variable, and each arrow needs at least one parameter.

An equation is created for each variable. The left side of the equation, for the variable I, is written as dI/dt, or "the derivative of I with respect to t." This is the change seen in I with an infinitesimally small change in time, t. The right side of the equation describes this rate as a combination of parameters and variables. For example, if a proportion of individuals γ leave I per unit time, this would be expressed as $-\gamma I$, for a full equation $dI/dt = -\gamma I$.

The model begins to take shape when we link the equations together. For example, γ people leave I per unit time (subtracting γI people) and go to R (adding γI people). We now have the basis for two equations:

$$\frac{dI}{dt} = -\gamma I$$
$$\frac{dR}{dt} = \gamma I$$

The people leaving I are now accounted for in the equation for R.

Rather than occurring at a fixed rate, the transition from S to I is governed by the number of people currently in I. This makes intuitive sense for an infectious disease—with more people to transmit the infection, it is more likely that a susceptible person will come into contact with them. Risk of disease being a function of the current prevalence of disease is known as "dependent happenings." Modeling these dependent happenings is the primary use of systems dynamics models.

We use a contact rate, β, which takes into account the number of contacts an individual encounters per unit time, as well as the probability of contact between a susceptible and infectious individual resulting in the transmission of disease [3]. The full equations for the SIR model are:

$$\frac{dS}{dt} = -\beta S\frac{I}{N}$$
$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

Where the total number, $N = S + I + R$. The I/N term is often simplified to I when dealing with proportions of the population $(N = 1)$, rather than a number of individuals. For convenience, we use this formulation. Everyone is accounted for in the model and all the arrows in the flow diagram are represented in the equations—we have a fully formed model. But what do we do with it?

These models support a broad range of mathematical analysis, from determining the impact of parameter values on system dynamics to analytical proofs. For further information on these methods, readers are referred to more specialized texts [3, 4]. We focus on one particular type of analysis useful in public health research, known as numerical integration, which focuses on a set of parameters specific to a disease and setting. The behavior of the system is approximated by solving for the values of the variables over very small increments of time. Libraries

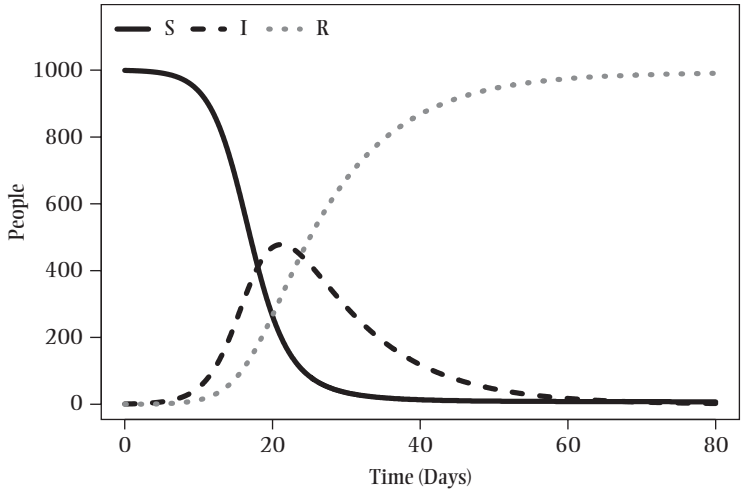

Figure 7.2 Thus we can see some of the key behaviors of the SIR model. The model produces a single, pronounced epidemic curve. How quickly this curve peaks, and how sharply, are a function of β and γ, but the outbreak will eventually exhaust itself, either by running out of new members of *S* to infect, or by all the members of *I* recovering or dying.

are available in most programming languages, and example code in R and Python is available at: http://www.github.com/elofgren/ssph. Using a numerical solver, we can obtain an estimate of the population within each compartment over time, revealing the dynamics of the system as a whole. This will reveal if the epidemic reaches a steady state, when it peaks, how severe that peak is, etc. In the example below, we visualize an epidemic in a population of 1,000 people, one of whom is infected, with $\beta = 0.5$ and $\gamma = 0.10$ (Figure 7.2).

3. THE BASIC REPRODUCTION NUMBER AND THRESHOLD EFFECTS

Beyond numerically simulating the results for a given set of parameters, analytical solutions may be obtained that describe the behavior of the system for *all possible* parameters. This is especially useful for discovering thresholds—where the behavior of the system will change based on which values the parameters take.

For example, there are some values of the parameters for an SIR model that will *not* cause an epidemic to occur, such as where $dI/dt \leq 0$. The most obvious is where $\beta = 0$. But there are others—diseases with swift recovery times or poor transmissibility. Understanding when this occurs brings us to another fundamental concept: the basic reproduction number, or R_0.

R_0 is defined as the average number of cases caused by a single infective individual in an entirely susceptible population. R_0 varies by both disease and setting, from 14-18 in the case of Measles, 3.5–6 for Smallpox, and 1.5–2.5 for the West African Ebola outbreak [6, 7, 8]. This number needs to be above one for an epidemic to occur—any lower and an infective person will not replace themselves before recovering or dying of the disease.

The methods to calculate R_0 are myriad and will vary with each model [5]. For the SIR model $R_0 = \beta/\gamma$. Additionally, other thresholds are related to R_0, such as the proportion of the population that must be vaccinated or immune in order for herd immunity to work, given as $1-(1/R_0)$.

R_0 is not without limitations. The foremost is the assumption of a fully susceptible population. For emerging pathogens, this may be justifiable, but for more established pathogens, it is problematic. This has lead to alternatives, such as the effective reproduction number, R_E, which is the average number of cases caused by an infective individual in the *current* population, or R_t, a measurement that varies with time over the course of the outbreak. Similarly, while R_0 is frequently viewed as an inherent property of a disease, this isn't the case. An estimate of R_0 is not necessarily portable between settings.

4. FITTING MODELS TO DATA

In an ideal world, the parameters needed for a model would be available in the literature, but this is rarely the case. In these circumstances, you must fit the model to data, statistically estimating the likely value of one or more parameters, in order to obtain a numerical solution. As with regression in observational epidemiology, there are a number of ways to fit models to data—from least squares to maximum likelihood and Markov Chain Monte Carlo (MCMC). The means to do so are available in most programming languages, though the details are beyond the scope of this chapter. Instead, this section will focus on some of the limitations and caveats behind model fitting.

The first, and most important, is the recognition of what a model fitting the data does—and does not—mean. Formulating a model and fitting it to a time series is often referred to as "validating" a model, which implies that it is "right." This is incorrect. The capability to fit a model to data only implies that that model *can* describe the observed data, not that it is the best or only description.

Second, the desirability of parsimony is less clear than it is for statistical models. There is no general agreement as to the desired level of complexity for a systems dynamics model. Simple models lend themselves to mathematical analysis

but may fail to represent the complexities of the real world. Complex models may be difficult to find parameter values for (and are often difficult to interpret) with combinations of parameters influencing the outcome of the model. Finding the balance between the two is one of the challenges of successfully modeling a disease system.

The availability of data places an additional constraint on complexity. Especially with emerging diseases, there is often scarce data, with few studies available to provide parameter estimates. In this circumstance, several variables must be estimated from the same data, and the model may become *non-identifiable*, meaning two or more possible sets of parameter values are equally likely, and estimating the true value of a parameter is impossible. This means that the model can give several (or many) different answers, all of which are equally supported by the available data. As with the balance between complexity and simplicity, it is challenging to balance the desire to model a system fully with the availability of data.

5. EXPANDING THE SIR MODEL: PERTUSSIS AND WANING IMMUNITY

To explore some of the concepts and problems outlined above, we turn to a previously published example. It is easy to build off the framework of the SIR model, adding new compartments and interactions to better represent a specific disease. In this case, we examine the impact of waning and naturally boosted immunity on the dynamics of pertussis [9]. The model is shown in Figure 7.3.

The model also includes a number of new interactions. Vaccination is modeled as the movement of people directly from *S* to *R*, and while *R* retains the same immunity to new infections as it did in the ordinary SIR model, individuals can now move out of R to a new class *W,* representing those whose immunity has begin to wane. Coming in contact with an infectious individual may challenge the immune systems of these individuals. Rather than developing an infection and moving to *I*, they move back to *R* as their immune system responds. In time, if not challenged, they move back to *S*. This model also incorporates births and

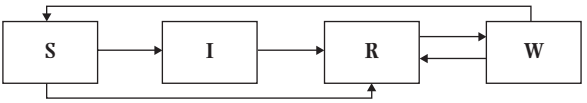

Figure 7.3 This schematic is a simplification of the model described in Lavine, King, and Bjørnstad, 2011, as there are *S, I, R* and *W* compartments for many age groups. Adding an age structure is a common extension of the SIR model, although it requires parameters for every age group.

deaths. Births replenish the population of *S*, allowing for multiple outbreaks (not shown). The full equations and parameters describing the model can be found in the referenced paper.

This model shows the flexibility and power that can be obtained with straightforward modifications of the SIR model. It captures the immune dynamics of pertussis, including the post-vaccine era shift in the incidence of pertussis towards teens, the reemergence of the disease even when the proportion of vaccinated individuals was above the $1-(1/R_0)$ threshold, and impermanent immunity, a shift from the type of dynamics one would expect in a SIR model sometimes called a "SIRS" model.

6. SYSTEMS DYNAMICS MODELS: ASSUMPTIONS AND EXTENSIONS

These models rely on two major assumptions: random mixing and large populations. The basic systems dynamics model assumes the entire population mixes at random. This is not the case—people assort non-randomly by demographics, social relationships, and geographic proximity. This assumption is often acceptable in large-scale models and can be addressed by creating different compartments for different groups of people, where the assumption that people mixing randomly *within their group* is more tenable. However, this modification requires parameters on how each group interacts. For some characteristics, such as age, well-conducted studies provide this information [10]. For others, the evidence will be far less strong.

It may be necessary to model different contact patterns entirely. For example, changing the transmission term from $\beta S(I/N)$ to simply βSI in a model with individuals changes the transmission from *frequency* dependent to *density* dependent—that is, it allows the contact rate to increase with population density, allowing progressively more contacts in larger populations. More complicated expressions exist to model more sophisticated forms of mixing [11].

The second assumption behind these models is that they are taking place in a large population, where the role of random chance is ignored. These models are known as *deterministic* models. Consider, for example, a disease with an R_0 of 2.0. In the models we have been discussing, this disease will invariably cause an epidemic. However, in the real world, the very first case may *not* cause two new cases. They may cause no new cases, or dozens. In small populations, these differences can matter quite a bit—the difference between no new cases and dozens could have profound implications for the fortunes of a village. In a large population (generally populations in the thousands), it may be safe to ignore this when studying the behavior of a system, but even larger populations are vulnerable to

randomness [12]. Models that take this randomness into account are called *stochastic* models.

A variety of tools are available when working with stochastic models. Similar to the numerical solutions obtained earlier in this chapter, a technique known as Gillespie's Direct Method can be used to simulate the model's dynamics [14]. This algorithm calculates the next time *an event* will take place, advances the simulation to that time step, randomly draws which event occurs (weighted by the frequency by which they occur) and moves a single individual from one compartment to another, before repeating the procedure. This method both takes into account random chance and allows only integer-numbers of individuals in compartments, useful for small models where deterministic models may result in fractions of people in a compartment, which is uninterpretable, at the cost of being considerably more computationally intensive.

Use of various techniques to mitigate aspects of the SIR model can add substantial complexity to the underlying system, but the core principles still apply. For example, the model found in Lofgren et al., 2014, is both stochastic and has a more complex mixing pattern. In this model of *Clostridium difficile* in a 12-patient intensive care unit, patients do not mix with one another [13]. Instead, their contact is indirect, through shared contact with healthcare workers. This type of indirect transmission is commonly used to model vector-borne diseases. While departing from a familiar form, and attempting to mitigate some of the assumptions of a deterministic SIR model, this model is still clearly a systems dynamics model, governed by equations that describe population compartments and the parameters that govern transitions between them.

Systems dynamics models combine flexibility, computational approachability, and an amenability to more advanced analytical techniques. While admittedly limited in the way they can represent the complexity of human interactions, they have proven remarkably powerful at providing insight into the dynamics of both infectious and non-infectious diseases. Understanding how these models work is a good first step in exploring modeling in public health.

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8

Agent-Based Modeling

BRANDON D. L. MARSHALL

1. INTRODUCTION

The objective of this chapter is to convey the key concepts, overarching methods, and common applications of agent-based modeling in population health science. I aim to provide the reader with a foundational understanding of how and why agent-based models (ABMs) are increasingly employed to address pressing public health challenges of the 21st century. I will demonstrate these concepts with an example from my own work using an ABM to simulate HIV transmission dynamics in high-risk populations. Readers interested in gaining a more in-depth appreciation for the design, construction, and validation of ABMs are referred to several excellent texts on the subject [4, 5]. I conclude this chapter with a discussion of two promising avenues for the continued adoption of agent-based modeling approaches to improve population health: the evaluation of policy experiments and evidence synthesis.

1.1. What are Agent-Based Models?

ABMs are individual-based microsimulations that simulate the behaviors and interactions of autonomous "agents." In most epidemiological applications, agents represent people who interact with each other to form an artificial society, thus simulating a hypothetical population of interest. However, an ABM can represent any discrete set of units that interact with each other (e.g., hospitals, schools, or governments).

The evolution of an ABM is determined by pre-programmed agent characteristics and by rules that regulate how agents behave, relate with each other, and interact with the simulated environment [7]. Even models with simple rules governing

agent behavior can result in complex, unanticipated population phenomena [8]. By comparing model output under different rule sets, hypothetical public health programs and policies can be implemented and tested. Interventions that change agent behavior, alter contact networks through which risk factors or diseases are transmitted, and/or modify environments in which health is produced can all be interrogated. Thus, ABMs serve as a highly flexible modeling laboratory in which a wide variety of interventions can be evaluated across populations and contexts. Although agent-based modeling within population health science has its roots in the study of infectious disease dynamics [9, 10], ABMs are increasingly used to explore the etiology and prevention of non-communicable diseases [11], social "contagions" (e.g., obesity, incarceration) [12–14], and the effects of place on health [15, 16].

1.2. Strengths and Challenges of Agent-Based Modeling

Like ant colonies, traffic jams, and stock markets, population health outcomes *emerge* from local interactions between autonomous units (i.e., people) and their environments [17]. Agent-based modeling, in which population-level phenomena arise as a result of micro-level interactions among the agents, is thus well suited to the study of many population health systems [18] (Box 8.1). In fact, the ability to simulate *emergence*—the appearance of larger entities and patterns from interactions among smaller or simpler entities that themselves do not exhibit such properties—is a key strength of agent-based modeling approaches [19]. In systems epidemiology, the unique contribution of ABMs and other "bottom up" simulation tools stems from their capacity to reproduce (and thus understand) the *processes* through which group-level phenomena are generated. For this reason, ABMs are commonly used to elucidate the origins and determinants of population-level protective factors (e.g., herd immunity) and harms (e.g., clustering of disease susceptibility) in human populations [20–22].

A second strength of agent-based modeling techniques arises from the fact that agent-level outcomes are, by definition, non-independent. In most ABMs, an agent's state is explicitly influenced by the status or behavior of other agents. Similarly, in infectious disease epidemiology and in many other health applications, an individual's health status is influenced by the outcome(s) and/or exposure(s) of other people in the population. In contrast, many standard causal inference methods assume that the effect of the exposure on an individual is independent of the exposure of other individuals [23]. This assumption has been extensively characterized and is widely known as the stable unit treatment value assumption (SUTVA) [24]. The paucity of methods to identify causal effects in circumstances when SUTVA is violated has led to challenges in identifying the individual- and population-level effect of vaccines [25], and neighborhood-level

Box 8.1

HIV Transmission in High-risk Populations: An Agent-Based Model

Agent-based modeling has several distinct advantages over other mathematical modeling approaches. First, agents can take on a multitude of time-varying characteristics, which permits the simulation of heterogeneous, adaptive, and complex behavior in human populations. Second, agents interact with one another to form dynamic networks. Modeling these "relationships" permits the simulation and analysis of network effects (e.g., partner concurrency, epidemiologic bridging) that are difficult to capture with compartmental models [1]. We constructed an ABM to examine HIV transmission dynamics and the effectiveness of combination HIV prevention programs to reduce HIV incidence among high-risk populations [2, 3]. In this model, agents form sexual and drug-using relationships, which results in an evolving "risk network" through which HIV is transmitted. The model simulates an artificial society of 100,000 agents, representative of the sociodemographic characteristics, epidemiological profile, and risk behavior patterns of the adult population of New York City. This setting was originally selected because of the rich demographic, HIV surveillance, drug-using behavior, and social network data available. The model is coded in Python™ and simulates the passage of time in discrete monthly time steps.

Over the course of the simulation, partnerships are formed, maintained or broken, resulting in a dynamic sexual and drug-injecting network. The number of partners at each time step for each class of agent was specified by random sampling procedures from negative binomial distributions, using parameters from previously published estimates. Assortative mixing is incorporated by weighting the formation of partnerships between agents with similar characteristics. A snapshot of the agent network is shown in Figure 8.1.

In the ABM, the probability of HIV transmission depends on the infected agent's HIV disease stage, HIV treatment status and adherence to therapy, the number of exposures (i.e., unprotected intercourse or syringe sharing) with an uninfected partner per time step, and the type of exposure (e.g., parenteral, sex between men, heterosexual). Moreover, interventions present in the agent environment modulate the likelihood of engaging in risk behavior and the probability that an HIV-diagnosed agent initiated antiretroviral therapy. For example, injection drug-using agents who are engaged with a needle and syringe program have fewer risk acts with their partners, compared with other agents.

First, the ABM was calibrated to reproduce empirically observed HIV epidemic trends observed in New York between 1992 and 2002. Then, HIV incidence trajectories from a "status quo" scenario (in which 2012 intervention coverage remains stable) were compared to those under hypothetical scenarios

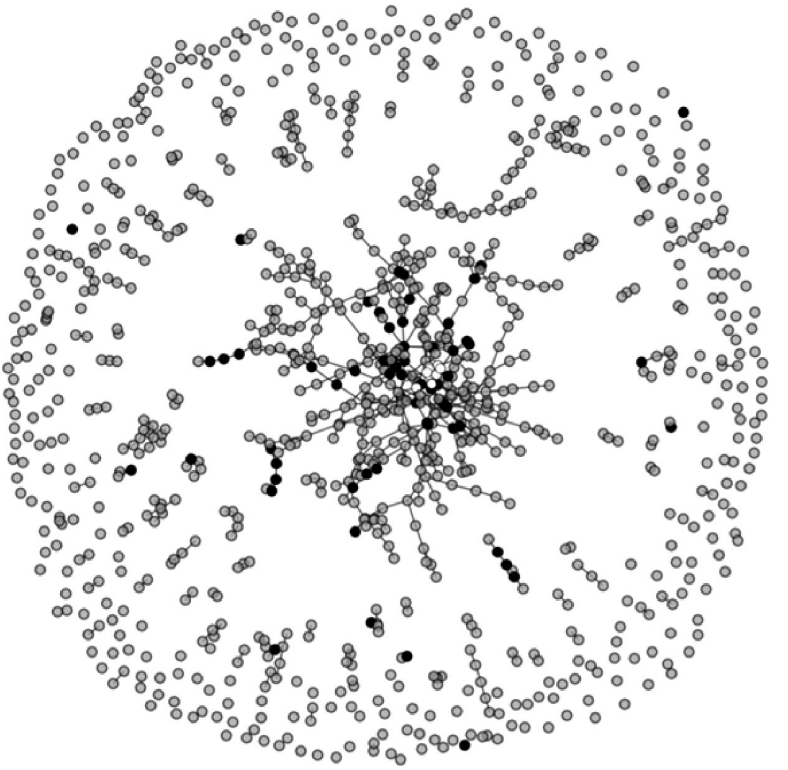

Figure 8.1 Network agent-based HIV transmission model.
White: Agents acutely infected with HIV; Black: chronically infected agents;
Gray: HIV-negative agent. Edges linking nodes represent past-month sexual and/or injecting risk behavior. Note the cluster of acutely-infected agents forming a "core" high-risk transmission group.

in which various HIV prevention interventions are scaled up. A "high-impact" combination prevention approach, in which coverage for all interventions was increased by 50% from 2012 levels, not only produced the lowest HIV incidence in 2040 but also resulted in a more immediate and sustained drop in new HIV cases. Importantly, HIV transmission was not eliminated under any scenario tested, demonstrating the importance of comprehensive, high-coverage interventions. More recent work has sought to determine whether HIV transmission occurring during early and acute HIV infection stages will hamper the success of antiretroviral-based prevention efforts [6].

effects on health [26], among other areas. Agent-based models are not so constrained; disaggregating the influence of non-independence between units (i.e., "spillover effects") from individual exposures (i.e., "direct effects") is a useful and practical application of agent-based modeling in epidemiology [27].

Like all simulation models, the validity of ABMs depends on the strength and validity of assumptions made during the model development process. The availability (and accuracy) of empirical data with which to parameterize the model is also critical in many population health studies employing ABMs. The number of frameworks upon which to base the construction, calibration, and validation of ABMs continues to grow [28, 29]. Guidelines for reporting ABMs, including their key assumptions and more detailed elements, are also available [30, 31]. Nonetheless, agent-based modeling rests on the fundamental assumption that, for any given research question, people and their relevant health states, interactions, and environments can be credibly modeled at a reasonable level of abstraction [28]. Meeting this assumption carries at least two important challenges. First, the researcher must decide which minimal set of characteristics defining the agents, their relationships, and their environments are needed to accurately capture the processes being modeled. Second, data or prior knowledge must exist to inform the specific structure and parameterization of the model processes. In the sections that follow, we describe the most commonly employed methods to help ensure that an ABM has internal validity, and that the model's results have relevance to solving real-world problems.

2. AGENT-BASED MODELING METHODOLOGIES

2.1. Implementation of agent-based models

For an ABM to run, the model developer must identify, define, and program agent behaviors, agent-agent interactions, and the relationship between agents and their environments. The first step in this process is to specify a "target"—the phenomena the model is intended to represent, reproduce, and simulate [4]. Since no model can capture all possible characteristics, behaviors, and environments that may influence a health outcome of interest, building a model for the target requires a theoretically motivated and conceptually grounded process of abstraction [29]. The goal is not to construct an all-encompassing representation of reality, but a highly simplified depiction that nonetheless provides valid insights into real-world phenomena and improves scientific understanding [32]. Commonly employed conceptual frameworks in population health, including the social-ecological model of health behavior and the syndemic theory of disease production [33, 34], can be helpful in identifying the core components of an ABM as employed in epidemiology. Given that simplification is a necessary step in all

models used in epidemiology, existing tools, including causal diagraming [35], may also be helpful in determining the key processes to be modeled in an ABM.

An ABM requires a set of code and a computational engine to be executed. Many ABMs are designed from scratch using all-purpose programming languages such as Python™, Java™ and C++. A number of modeling services (with preloaded libraries of commonly employed routines and functions) are also available. Among the most common programs are NetLogo (https://ccl.northwestern.edu/netlogo) and Repast (http://repast.sourceforge.net); other software has been reviewed elsewhere [28]. Once the model has been developed, the simulation is run by having agents repeatedly execute their behaviors and interactions according to pre-programmed rules. Most ABMs simulate the passage of time in steps that are either discrete or activity based.

In an ABM, agents are endowed with static or dynamic behaviors that can depend on everything from simple "if-then" rules to complex adaptive processes. The model developer must also define which agents are (or could be) connected to whom and the dynamics of these interactions. The way in which agents are connected is referred to as an ABM *topology*. Common typologies include a spatial grid, a more complicated spatial geography (e.g., agents can only interact with other agents who are nearby), or a social network. The typology of an ABM can also evolve over time. For example, in one study that used an ABM to evaluate policies to reduce influenza transmission in the workplace, agents were assigned to and moved between specific geographic locations representing schools or workplaces [36]. During each simulated day, agents could only interact with other agents who shared the same social activity location.

Agents can be entirely passive (i.e., purely responsive to exogenous stimuli) or seek to actively alter other agent characteristics or the environment. Therefore, unlike many socio-ecological models of health production which assume that health outcomes are determined by immutable upstream forces, ABMs allow individuals to not only interact with, but change, their environment(s). The environment may represent a set of geographic characteristics (e.g., pollutants, crime, or other aspects of the physical or built environment), venues (e.g., homes, bars, workplaces), or institutions (e.g., hospitals, prisons). An agent's location in the simulated landscape is usually recorded as a dynamic attribute as they move in space. Different types of environments may promote, facilitate, or constrain agent behaviors. For example, in one ABM that simulated walking behaviors within a city, the agent environment was composed of 400 equal-sized neighborhoods, each with two properties: safety and aesthetics [37]. A walking index (representing each person's walking experience) was a function of both individual agents' characteristics (e.g., age, walking ability) and the safety and aesthetic quality of

all neighborhoods along a walking route. Each agent's walking index in turn affected how much she/he would walk in the subsequent day.

2.2. Verification and Validation of Agent-Based Models

Model verification and validation are essential components of the ABM design process. Model verification asks the question, "Does the ABM work as intended?" while model validation seeks to determine whether the "right" model has been built. While there is no universal approach or consensus on how to conduct verification and validation in agent-based modeling, a number of principles and overall techniques are available [38–40].

The goal of verification is to determine whether the programming implementation of the conceptual model is correct. This process includes debugging, verification of all model calculations, and determining whether equations in the model are solved correctly. Some common verification methods include debugging procedures, code "walk-throughs" (a form of software peer review), and boundary testing (i.e., determining whether the model performs as expected at the parameter boundaries).

Broadly, model validation is a process through which the research team assesses the extent to which the model is a credible representation of the real world. Several techniques are available to demonstrate a model's validity. For example, a model is said to have *face validity* if content experts believe the model behaves reasonably well by making subjective judgments about its performance. Most ABMs also go through a procedure known as *empirical validation*. Here, the developer determines whether the model is a good representation of the target by comparing whether model output is consistent with observed data. Model calibration refers to an iterative process through which unmeasured or poorly measured parameters are adjusted until the model output is in agreement with empirical data. A number of different approaches to conduct calibration and empirical validation have been developed and are reviewed elsewhere [41]. A variety of statistical tests can be used to determine if the model's behavior has an acceptable level of consistency with observed data [42].

2.3. Interpretation of Results from Agent-Based Models

Interpreting the output of an ABM has distinct challenges from other mathematical modeling approaches. First, isolating the causal mechanisms and effects of one parameter can be difficult in models with a high degree of agent heterogeneity and many interdependent processes. For this reason, conducting parameter

sweeps over multiple variables (frequently simultaneously) to understand model behavior is recommended.

Second, ABMs can be highly sensitive to initial conditions. In complex and chaotic systems, even small perturbations in initial conditions can lead to large differences in model output. We have previously shown that the identification of causal effects is only possible in models that meet a regularity assumption called "ergodicity" (for any given set of initial conditions, the model output can be represented by an ensemble average as the number of model iterations increases) [27]. If non-ergodic behavior is present, the mean of model output across runs is not well defined, and casual effects comparing two counterfactual scenarios cannot be estimated.

Third, precise prediction of real-world phenomena under different inputs can be problematic when many assumptions are made regarding agent behavior and interactions. Given the complexity of many ABMs, the objective should not necessarily be to predict specific population outcomes under different scenarios per se, but to conduct a robust policy analysis, such that recommendations consist of an ensemble of policy options which perform well under plausible model specifications and are robust to model assumptions.

3. AGENT-BASED MODELS AND THE FUTURE OF EPIDEMIOLOGY

Epidemiology is, at its heart, a pragmatic discipline that identifies opportunities to control and prevent disease [43]. As such, epidemiologists must concern themselves not only with the isolation of causal effects but also with the identification of effective ways to intervene. Doing so necessitates more than an understanding of the causal mechanics that link an exposure with a health outcome. One must also consider the population context (i.e., the underlying prevalence of the health condition and related risk factors) and how multifactorial causal structures interact to produce disease [44].

Agent-based modeling represents one (but not the only) method to synthesize prior knowledge of a population—and the causal structures that act on this population—to understand how an intervention could affect the public's health. In this manner, agent-based modeling is a science of evidence synthesis. Specifically, ABMs (and other simulation approaches) represent a platform for the integration of diverse evidence sources, including inconsistent or inconclusive scientific information, to support decision making for complex public health problems. Formalized methods and frameworks for the integration of diverse data streams into simulation models (and their implications for evidence-based

policy analysis) have recently been proposed for population health sciences [45, 46]. Continued adoption of these methods is warranted.

I wish to conclude this chapter by noting that, although systems science in epidemiology and public health has clearly "arrived," more work is needed. Agent-based modeling of population health systems and the impact of hypothetical policy changes on health have led to novel scientific insights. However, the actual uptake of programs and policies informed by ABMs, and their subsequent evaluation in real-world settings, are lacking. A multidisciplinary and iterative science, in which model developers work collaboratively with interventionists and policymakers to implement, evaluate, and improve public health programs, is needed. Further stymieing the uptake of agent-based modeling is the fact that systems science methods are not currently featured in much public health curricula or training [7]. Thus, the capacity for agent-based modeling to enhance the health of populations requires understanding and appreciation of the method among not just epidemiologists, but also public health practitioners and population health scientists broadly.

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9

Microsimulation

SANJAY BASU

A microsimulation is a model that simulates individuals within a population. The goal of microsimulation is to understand how variations in disease-relevant characteristics among individuals produce a population distribution of health outcomes. Microsimulation models therefore differ from models that simulate a *population average* rate of disease; microsimulation models, by focusing on *individual* risks of disease, enable modelers to pay particular attention to the tail ends of population distributions: for example, identifying those individuals at unusually high risk of illness.

In this chapter, we discuss how to determine if a microsimulation modeling approach may be relevant in terms of addressing a given problem in population health. We detail the microsimulation modeling process through a series of examples, which reveal common applications of the method, pitfalls, and solutions adopted by researchers constructing and utilizing microsimulation models, as well as scenarios that may be amenable to microsimulation to address population health dilemmas. We identify key opportunities for the application of microsimulation methods to population health research.

1. AN ILLUSTRATIVE EXAMPLE

Suppose we wish to study strategies to reduce the incidence of cardiovascular disease events (myocardial infarctions and strokes) in a population of patients treated at a local medical clinic. A new initiative focuses on finding individuals at the highest risk for cardiovascular disease and providing them with a home-based health intervention: visits from a nurse to help the patients take complex medications to lower their risk of cardiovascular disease events. The risk of cardiovascular

disease events is related to many underlying risk factors such as high blood pressure, high cholesterol, type II diabetes, tobacco smoking, age, and sex [1]. These underlying risk factors are correlated; for instance, if an individual has high blood pressure, they are likely to also have high cholesterol [2]. As a result of these correlations, some individuals in the population are at much greater risk for cardiovascular disease events than others, and the population "average" rate of risk may be less important for targeting an intervention to the most needy group than the question of which people are at highest risk. Furthermore, the individuals who have multiple risk factors for cardiovascular disease are also known to experience the greatest relative benefits from treatment [3]. Hence, the clinic hopes that providing a home-based nursing intervention will help the individuals at greatest risk for disease avoid a future myocardial infarction or stroke. Prior randomized studies have indicated that this intervention improves adherence to medications significantly, such that the full benefits of the medications should accrue over time [4].

The physicians in the program choose which patients to enroll into the program using Framingham "risk equations," which are equations that estimate the risk of myocardial infarction and stroke over the next 10 years for a given individual [1]. The risk equations take into account a person's age, sex, his or her history of tobacco smoking, and whether the patient has type 2 diabetes, high blood pressure, and/or high cholesterol, among other factors. The equations use regression coefficients derived from a longitudinal study of cardiovascular disease to estimate how different values of these risk factors would be expected to increase or decrease the overall risk of cardiovascular disease events over the next decade.

Suppose the physicians who perform this calculation assign nurses to visit the homes of patients who have at least a 10% risk of myocardial infarction or stroke over the next decade, per the Framingham risk calculator. We wish to estimate the potential impact and cost-effectiveness of the nursing program over the next decade; over this period of time, we would expect the long-term benefits of the medication treatment program to manifest as a significant reduction in the rate of cardiovascular disease events. Because the time course of observing benefits is typically long [5], a randomized trial may be costly to perform, and several decisions for the clinic (such as whether to expand the program to individuals at slightly lower risk than 10%) are of great interest to the staff. Hence, the clinic officials elect to employ a modeling strategy to study their program. If they construct a typical cohort model (e.g., the model illustrated in Figure 1A), they might substantially misestimate the impact and cost-effectiveness of the nursing program. In particular, a cohort-level model simulates a population by examining the average rate of disease within the population. In this case, a cohort model might estimate the average rate of

events predicted by the Framingham equation among the treated population receiving home nursing and compare that rate to the average rate of events predicted by the Framingham equation among the same population not receiving home nursing. The model would specifically apply the Framingham equations to the average blood pressure, cholesterol level, and average values of other risk factors among the treated population, and calculate the difference in predicted event rates between the simulated population receiving nursing visits and the simulated population not receiving nursing visits. A problem with this approach to studying the intervention is that the rate of disease among the extremely high-risk subgroup of the population may drive the real-world outcomes from the program. Even if we repeatedly sampled from the probability distributions of each risk factor to capture uncertainty around the average values (Figure 9.1A), we would arrive at a Gaussian (normal) distribution of estimated risk. If we constructed the cohort model by dividing the treated population into smaller subpopulations—say, a higher-risk and a lower-risk subpopulation of the treated group—the cohort model would still not accurately estimate the benefits of the program, as the model would generate an estimate of the average risk among the two subgroups and not account for the very skewed nature of the cardiovascular disease risk distribution. The extreme high-risk subgroup of the higher-risk population will accrue more benefits than the average subgroup in the higher-risk group, and therefore more and more subgroups would be needed to accurately estimate the benefits of the program.

In breaking down the cohort model into smaller and more specific subgroups, we arrive at a natural limit: defining the model to the individual level, which produces a microsimulation. A microsimulation model, depicted in Figure 9.1B, simulates each individual to account fully for the skewed nature of the probability distributions of cardiovascular disease events and treatment benefits among individuals. As illustrated in Figure 9.1B, a microsimulation model departs from a traditional cohort model because it does not simply take into account the average blood pressure, average cholesterol, and average values of risk factors among each subpopulation. Rather, each individual in the model is provided with a specific value for their blood pressure, cholesterol level, and so on—by sampling from *correlated* probability distributions of these factors, which captures the truly skewed nature of the risk distribution. By applying the Framingham equations to each individual in the model with and without the nursing intervention, the full benefits of the intervention (driven by the very high-risk individuals who benefit the most) can be captured. Furthermore, the model can be utilized to identify how changes to the criteria for intervention—for example, enrolling those with a 5% risk of cardiovascular events over a decade, or 15% risk, instead of the original 10% risk threshold—could change the outcomes of the program.

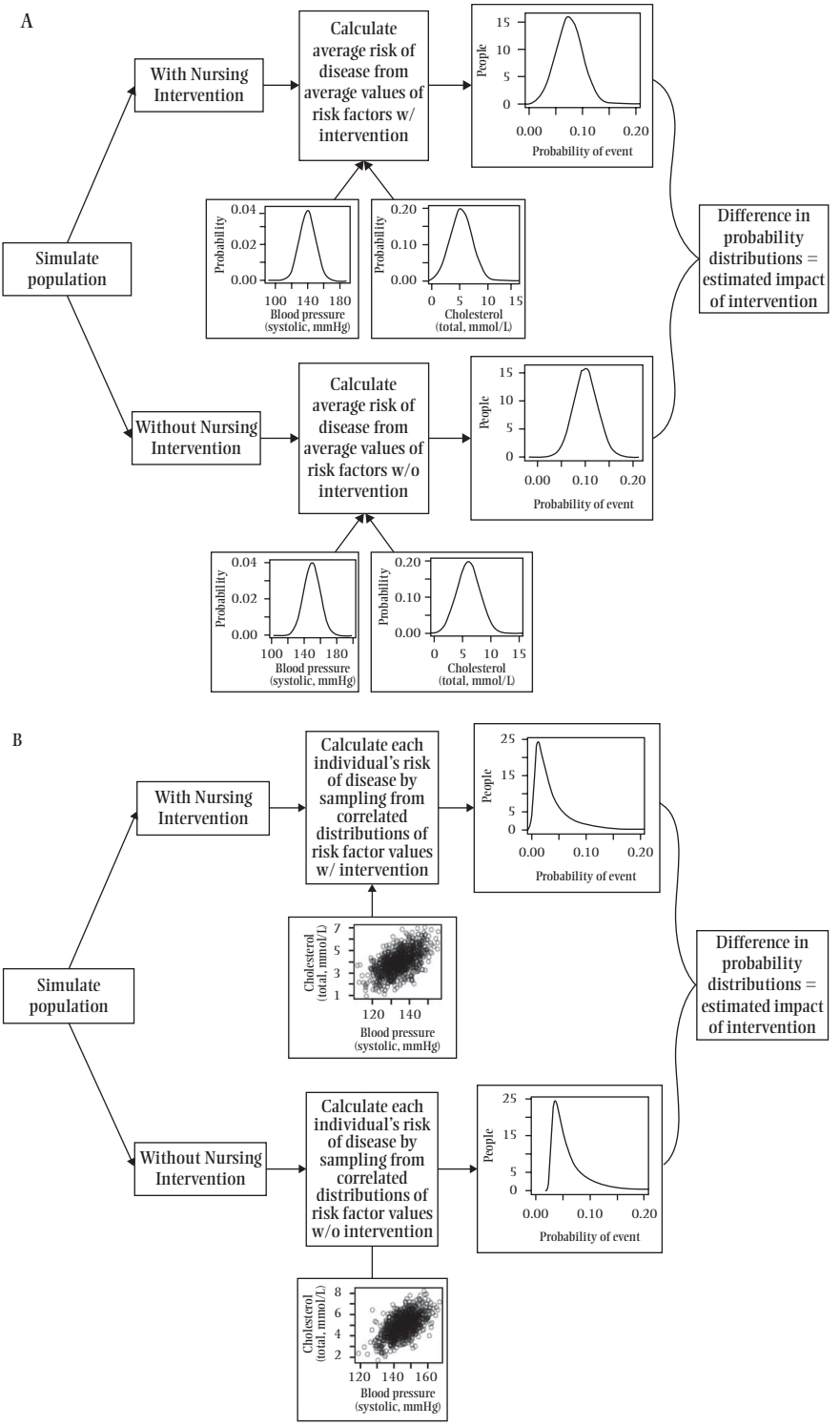
A
Simulate population
With Nursing Intervention
Without Nursing Intervention
Calculate average risk of disease from average values of risk factors w/ intervention
Calculate average risk of disease from average values of risk factors w/o intervention
Probability
Blood pressure (systolic, mmHg)
Cholesterol (total, mmol/L)
People
Probability of event
Difference in probability distributions = estimated impact of intervention
B
Simulate population
With Nursing Intervention
Without Nursing Intervention
Calculate each individual's risk of disease by sampling from correlated distributions of risk factor values w/ intervention
Calculate each individual's risk of disease by sampling from correlated distributions of risk factor values w/o intervention
Cholesterol (total, mmol/L)
Blood pressure (systolic, mmHg)
People
Probability of event
Difference in probability distributions = estimated impact of intervention

Figure 9.1 Conceptual diagram of microsimulation modeling Differences when constructing (A) a standard cohort model, versus (B) a microsimulation model of a nursing intervention to lower the risk of cardiovascular disease events. A cohort model is typically run by sampling independently from estimates of the average value of each input parameter. Hence, it fails to capture the skewed distribution of outcomes, as repeated sampling from the independent distributions of input parameters produces a Gaussian, or normal, distribution. The cohort approach would therefore underestimate the benefit of the intervention by failing to take into account the benefits of the program for high-risk individuals among whom the distribution of risk factors is correlated. Note that most risk calculation approaches take into account several risk factors, but only systolic blood pressure and total cholesterol are illustrated here for simplicity.

2. METHODOLOGICAL FRAMEWORKS

As illustrated by the above example of cardiovascular disease microsimulation, the scientific questions that may be appropriate for microsimulation modeling are those that require us to consider differential risks among individuals within a complex, heterogeneous population. In the public health context, microsimulation models are increasingly used for two common tasks: the optimization of screening or treatment strategies for chronic diseases, and the study of population-wide health policies that may differentially affect individuals within a population. We consider each of these two cases in turn.

Microsimulation modeling is particularly helpful for optimizing screening or treatment strategies for chronic diseases, because it allows a modeler to identify how including or excluding different individuals in a screening or treatment program can alter the expected population-level effectiveness of the program. For example, suppose we wish to develop an optimal strategy to screen people who may have a high risk for cardiovascular disease events, by posting community health-care workers at local supermarket parking lots to ask shoppers screening questions and refer "high risk" shoppers to a local health clinic for further evaluation. We could choose from many different questions that could be administered verbally by community health-care workers to identify who might be at high risk: whether a person has a family history of myocardial infarctions or strokes, whether they have been previously diagnosed with high blood pressure or high cholesterol or type 2 diabetes, or whether they currently smoke tobacco, for instance. These screening questions are non-invasive but attempt to identify individuals who likely have biomarkers predisposing them to cardiovascular disease, which cannot be assessed without a further examination or laboratory assessment.

A microsimulation model could help identify the links between the factors that can be assessed through non-invasive screening questions and the underlying biomarkers for cardiovascular disease. Specifically, as shown in Figure 9.2, a

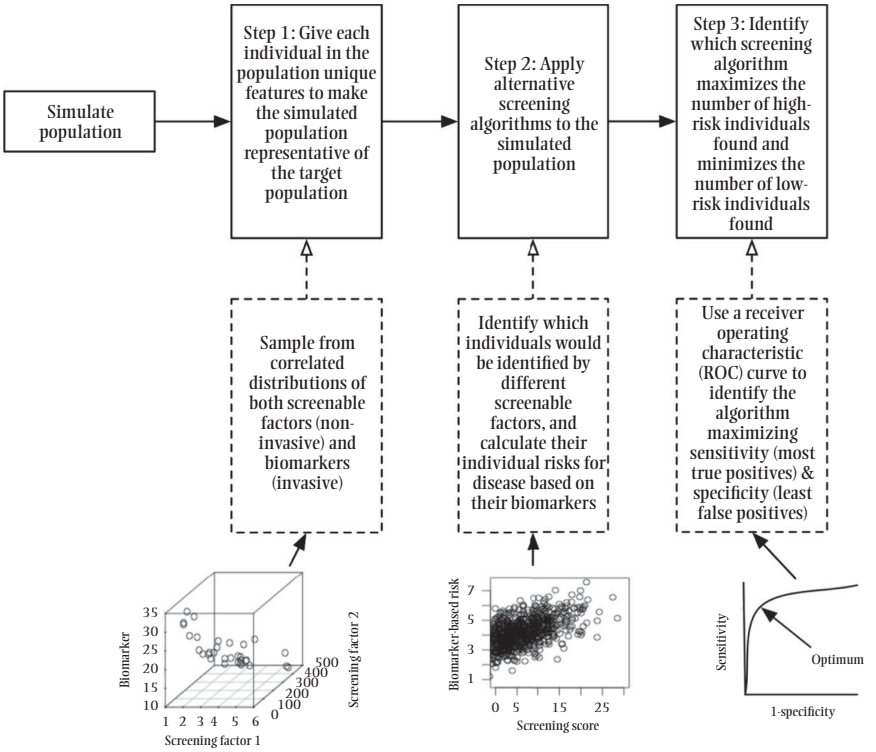

Figure 9.2 Application of microsimulation modeling to screening or treatment questions A microsimulation model can be applied to compare alternative disease screening or treatment algorithms. Suppose we wish to develop non-invasive questionnaires to screen individuals at high risk of disease and send those screening positive to a local clinic for more invasive testing. The questionnaire items are intended to probe factors like family history, diagnosed risk factors, and risk behaviors (e.g., nutrition), to help identify individuals who may have high levels of underlying biomarkers (e.g., cholesterol) that are predictive of disease risk (e.g., risk of cardiovascular disease). A microsimulation model can be constructed by sampling from population-representative data to assemble a simulated population in which each individual has both screen-able factors (e.g., self-reported nutrition) and underlying biomarkers of disease (e.g., cholesterol level). By sampling from correlated distributions, the relationships between screen-able factors and underlying biomarkers are captured. Second, alternative screening algorithms (combinations of screening questions) are administered to the simulated population, to determine which individuals would screen positive when using different combinations of the screening questions to construct an overall screening score. Finally, the alternative screening algorithms are compared by using the biomarkers in the simulated population to calculate disease risk for each simulated individual and identify which screening algorithm maximizes the chances of finding individuals at truly high risk while minimizing the number of individuals at low risk that are found.

microsimulation of the population could be constructed by sampling from the correlated distributions of both factors assessed through non-invasive screening and underlying biological risk factors for disease (both of which are found in population-representative data sets such as the National Health and Nutrition Examination Survey in the United States [6]). Hence, individuals in the simulated population could be assigned both screening question responses (what the community health-care workers would be able to assess in a supermarket parking lot) and biomarkers of disease (what the community health-care workers would not be able to assess in a supermarket parking lot) by repeatedly sampling from the correlated distributions among these factors (illustrated graphically in Figure 9.2). The microsimulation could then be used to identify which subset of the population would be found through alternative combinations of screening questions administered via the health-care workers. The optimal combination of questions could be found through simulations in which alternative combinations of screening questions would be compared, to identify which screening question combinations maximize the chances of finding high-risk individuals (true positives) and minimize the risks of subjecting low-risk individuals to further evaluation (false positives) [7].

A second use of microsimulation modeling is to study population-wide health policies that may differentially affect individuals. Continuing with the theme of applying microsimulation to cardiovascular disease, suppose we wish to study the impact of a national program to reduce the sodium content in processed foods, under the premise that sodium is related to elevated blood pressures and subsequent cardiovascular disease. Most sodium intake in the United States is from processed foods (i.e., added by a manufacturer) rather than from table salt (i.e., added by the consumer) [8]. A large-scale program to reduce sodium in the food supply may affect people in different ways: some individuals may have high blood pressure that becomes lower, which decreases the risk of cardiovascular disease events and associated deaths; conversely, some individuals with low blood pressure could experience extremely low blood pressure, which can perversely increase their risk of death [9]. A microsimulation could help inform whether the program would be expected to benefit the population overall and among whom potential perversities might occur. Such a microsimulation model would first simulate the pre-intervention levels of sodium intake and blood pressure among individuals in the population (i.e., sampling from the sodium intake and blood pressure data in the National Health and Nutrition Examination Survey, if studying a US population [6]). The model would then estimate how much less sodium would be consumed after the intervention, given the amount of sodium that is withdrawn from the food supply and the amount added back in table salt by consumers. The model would finally use the results of major trials that related lower sodium intake to lower blood pressure to estimate how each

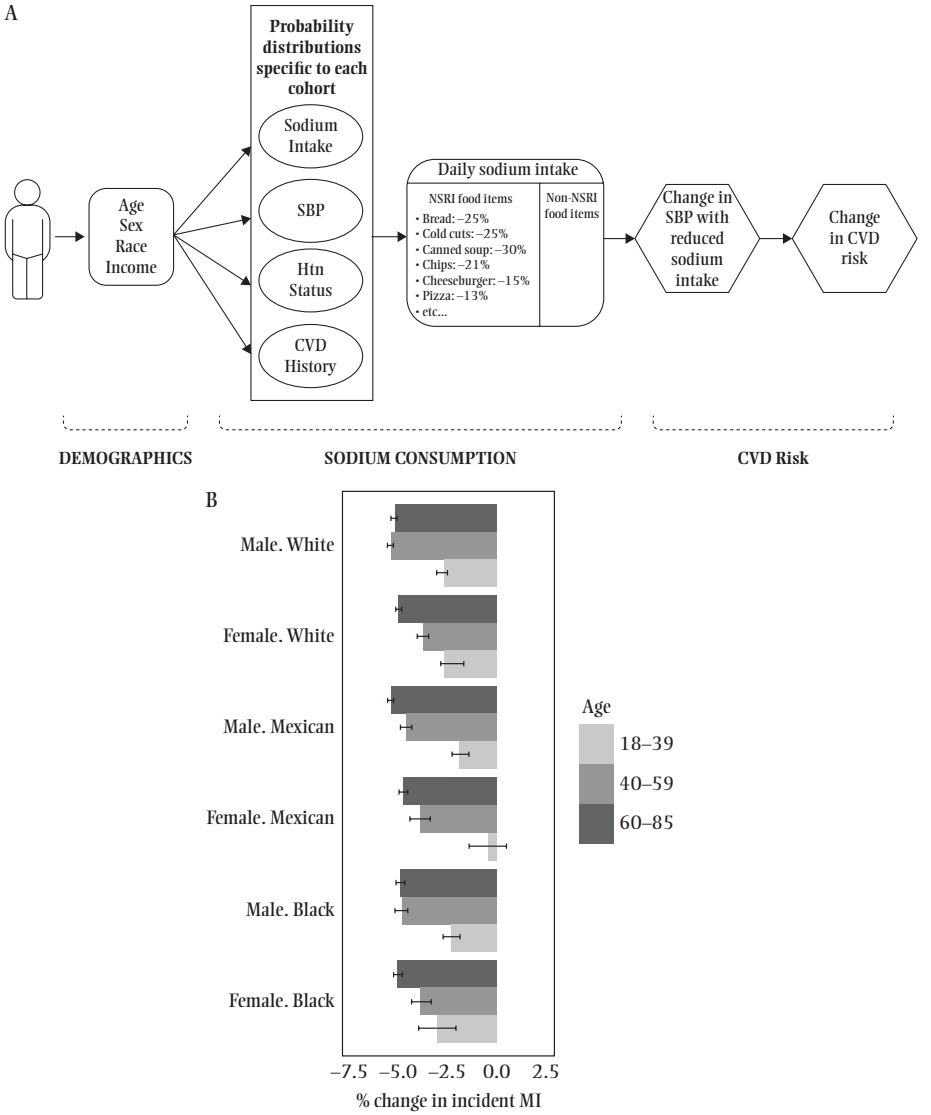

Figure 9.3 Exploring potential benefits and perversities of a population health measure using microsimulation Simulation results from a microsimulation of the National Salt Reduction Initiative (NSRI) in the United States (11). The microsimulation involved (A) simulating the sodium intake, systolic blood pressure (SBP) levels of the US population and associated hypertension (Htn) and cardiovascular disease (CVD) history using data from the National Health and Nutrition Examination Survey, then estimating the reduction in blood pressure given the reduction in daily sodium intake among each person given the sodium reduction in foods published by the NSRI and data relating sodium reduction to blood pressure reduction from randomized trials of low sodium diets (10). The blood pressure levels were then related to CVD risk given observational data revealing a J-shaped relationship between sodium intake and mortality (9). As shown in (B), young Mexican women might experience a perverse increase in incident myocardial infarction (MI) risk due to excessively low blood pressure following the sodium reduction program.

individual in the model would experience a blood pressure change based on their change in sodium intake, and estimate the change in risk of mortality given the J-shaped relationship between blood pressure and mortality gleaned from prior observational studies [10, 9]. As shown in Figures 9.3A and B., a microsimulation model performing these tasks to simulate the National Salt Reduction Initiative in the United States (which reduced sodium content in many processed food products) observed that most populations could benefit from the sodium reduction, while young Mexican females might be at risk for perversely low blood pressures following the initiative. The model was then used to identify which foods might be best to target, given the vast differences in consumption patterns and types of foods consumed by young Mexican women as compared to other populations [11].

3. PRACTICAL DETAILS FOR MICROSIMULATION MODELING

To construct a microsimulation model, three steps are generally required: (i) constructing a simulated population; (ii) sampling from correlated input data to assign relevant risk factors and other relevant attributes to each simulated individual in the population; and (iii) estimating the incidence of disease among the population using the assigned risk factors and attributes.

A simple way to conceptualize a microsimulation model is to imagine the model as a large table. Each row is an individual. Each column is a property of that individual—for example, their age, sex, race/ethnicity, blood pressure, cholesterol, diabetes status (a 0/1 dummy variable), and so on. To "fill in" the table, we populate the columns by constructing a multidimensional joint probability distribution that can be defined by two features: a copula (the correlation among properties), and a marginal distribution for each individual property (the population distribution of that property) [12]. Figure 9.4 illustrates the copulas and marginal distributions between cardiovascular risk factor data for a microsimulation model of myocardial infarctions and strokes. We construct the copula and marginal distributions from population data on the distributions of each property and the correlation matrix between the properties; if such data are unavailable, a microsimulation is essentially impossible to construct, and without the correlation matrix, a microsimulation would collapse into the same structure as a traditional cohort model.

Using these individual properties, we calculate a hazard of disease—which is specific to the disease process being simulated. In our cardiovascular disease examples, a Framingham risk score is employed, which involves multiplying each risk factor (e.g., systolic blood pressure) by coefficients estimated through logistic regression from a longitudinal cohort study of cardiovascular disease (e.g.,

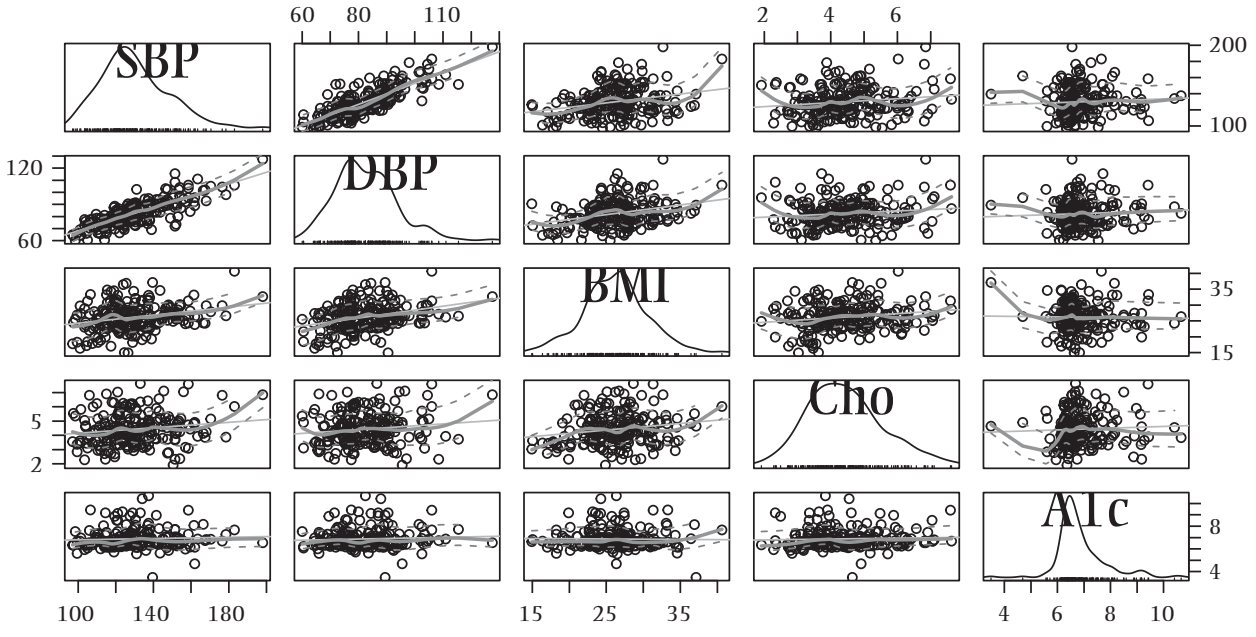

Figure 9.4 Illustration of copulas and marginal distributions Multidimensional copulas and marginal distributions among cardiovascular risk factor data for a microsimulation model of myocardial infarctions and strokes. The copulas are illustrated on the non-diagonal graphs while the marginal distributions for each risk factor are provided on the diagonal. Curved lines and dashed lines correspond to locally weighted non-linear regressions and 95% confidence intervals, while straight lines correspond to linear regressions for reference. As shown, the copulas capture population heterogeneity beyond that captured from standard regression. Data used for this plot are from a prior study in India conducted by the author (7). Legend: SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), BMI = body mass index (kg/m2), Cho = total cholesterol (mmol/L), A1c = glycosylated hemoglobin (%, an index of diabetes).

each 1 mmHg increase in systolic blood pressure relates to a particular increase in the risk of myocardial infarction or stroke). In the case of other diseases, longitudinal data from observed cohorts with a given disease will be necessary to define how the properties of a simulated person would be combined to define the risk of the specific disease being studied. If studying the potential impact or cost-effectiveness of an intervention is the purpose of the simulation, then the microsimulation will be run twice: once using estimated distributions of input parameters from individuals who receive the intervention, and a second time (a counterfactual case) using estimated distributions of input parameters from individuals who do not receive the intervention.

There are at least three major challenges faced by modelers who attempt to implement such a microsimulation model. First, the question arises as to how many times to sample from input probability distributions to produce a reasonable estimate of outcomes from the model. At the present time, there is no "rule" for how many times the sampling should be repeated; greater sampling typically produces a more stable estimate of the mean outcome and an overall sense of the distribution of the outcome around the mean. Just as in a randomized trial, however, one can use a power calculation to estimate what minimum amount of sampling is necessary to detect a certain degree of effect size between the counterfactual and intervention cases; one essentially treats the intervention and counterfactual simulation as matched pairs, such that the power calculation is the same as performing a *t*-test to detect the difference between two dependent means [13].

A second challenge is the question of how to validate a microsimulation model. External validation can be performed if we have data from a longitudinal cohort study that is independent from our input data. We can enter the risk factor values for every individual in the independent cohort and compare the individual's simulated outcomes to their actually observed outcomes over the period of the study duration, providing a sense of how well the microsimulation performs among people at varied levels of risk. When such an external data set is unavailable, microsimulation modelers will frequently resort to out-of-sample internal validation: input data for two-thirds of an input sample are used to produce the input probability distributions, then the model is applied to the other one-third of the sample to estimate the degree of error between the modeled outcomes and observed outcomes [14].

4. IMPLICATIONS FOR POPULATION HEALTH

Overall, the microsimulation approach offers an opportunity to bridge the philosophical divide between "precision medicine" and population health. Precision medicine aims to identify how individual features may result in tailored

interventions for individuals [15]. The precision approach, however, appears fundamentally at odds with public health evidence suggesting that most population health disparities and avoidable causes of premature mortality are not due to individual features but misdistribution of health opportunities and resources, as well as disparities in adverse exposures [16]. Yet the population critique may need to address the circumstances of individuals who may be unassisted or even harmed if public health interventions do not consider the variations in risk within a population, as suggested by the sodium reduction example discussed above.

We may meld the two perspectives of precision medicine and population health with microsimulation: identifying how unequal exposures and risk factors lead to differential risk among individuals within populations, permitting a public health approach that attempts to maximize population benefits while minimizing individual-level risks. Hence, microsimulation may bring large-scale analytic tools to users who require direct policy comparisons of alternative policy strategies that are intended for deployment across complex, heterogeneous populations of people. As the field of microsimulation remains in its early stages, the next step for modelers is to share their experiences applying microsimulation models to new population health questions, both to identify what challenges remain to ensuring the usefulness of the technique to emerging public health problems of interest, and to detail strategies to enhance the approach as it becomes increasingly used to provide insights into complex problems that are not easily addressed through traditional study designs.

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10

Social Network Analysis

DOUGLAS A. LUKE, AMAR DHAND, AND BOBBI J. CAROTHERS

Network science has been developed over the last century as a scientific paradigm that explores human and other types of complex systems as socially structured. Network analysis is the set of analytic tools that allow this exploration. Population health is driven in part by network characteristics and dynamics. This chapter attempts to answer the following five questions: (1) What is network science and social network analysis? (2) Why are networks important for studying, understanding, and influencing population health? (3) What do we know about how social networks influence population health, especially infectious and chronic diseases and their associated risk factors? (4) What are the primary methods used by network scientists when studying health? (5) What are some important challenges and opportunities for social network analysis and population health?

Two definitions are particularly useful for this chapter. First, *network science* is the use of relational and structural theories to study network representations of complex physical, biological, and social systems. Network science is inherently multidisciplinary, spread across many disciplines including genetics, biology, psychology, sociology, political science, public health, engineering, and computer science. Second, s*ocial network analysis* is the set of analytic tools used to explore and model network data, made up of network members (nodes) related to one another via some type of social relationship (tie).

1. WHAT IS NETWORK SCIENCE AND SOCIAL NETWORK ANALYSIS?

Networks are all around us. Networked systems can be found at every level of organization, from genes, proteins, and cells at the lower end, to networks of

organizations, nations, and cultures at the higher end. "Below-the-skin" networks of genes, protein interactions, and intercellular communication account for much of human development, physiology, and human disease. The human brain is now viewed as a complex network, or *connectome* [1]. Similarly, human diseases and their underlying genetic roots are connected as a *diseasome* [2]. Humans naturally organize themselves in "above-the-skin" networked systems. Families, broader kinship ties, neighborhoods, and communities organize themselves in networked systems of relationships. Businesses and other social institutions operate via complex interorganizational systems of trade, influence, and partnerships [3]. Networks are a fundamental means by which the universe is organized and humans function and thrive.

Exploring and influencing human networks requires alternative scientific theories, methods, and data. Network science is a multidisciplinary set of biological, social, and health theories that view human behavior, health, and disease through relational and structural lenses. Moreover, traditional data collection and analytic approaches are inadequate for studying networked systems. Network data are comprised of information about the relationships (ties) that connect the members (e.g., people, organizations, proteins, etc.) of the network. This implies that networked data are inherently non-independent. Customary statistical assumptions of independence of observations mean that traditional statistical modeling (e.g., general and generalized linear models) cannot be used to analyze network data. Instead, analytic approaches that are appropriate to study dyads, local network structures, network subgroups, and entire networks must be developed and used.

2. WHY ARE NETWORKS IMPORTANT FOR STUDYING, UNDERSTANDING, AND INFLUENCING POPULATION HEALTH?

Social networks mediate and moderate the influence of broader cultural, socioeconomic, and physical contexts—and in turn shape a wide variety of psychosocial mechanisms and psychophysical pathways leading to health conditions and outcomes. This can be seen in Figure 10.1, which has been adapted from Berkman's original model [4, 5]. More specifically, social networks influence their members in two broad ways [6]. First, the networks serve to shape the flow of some resource to the individual members. The resource could be money, health information, social support, etc. Second, the structural position of a person within a social network is important. For example, persons who are in more isolated positions in a network are at greater risk for certain types of health outcomes (e.g., earlier death after a cancer diagnosis). In the rest of this chapter, we will review the

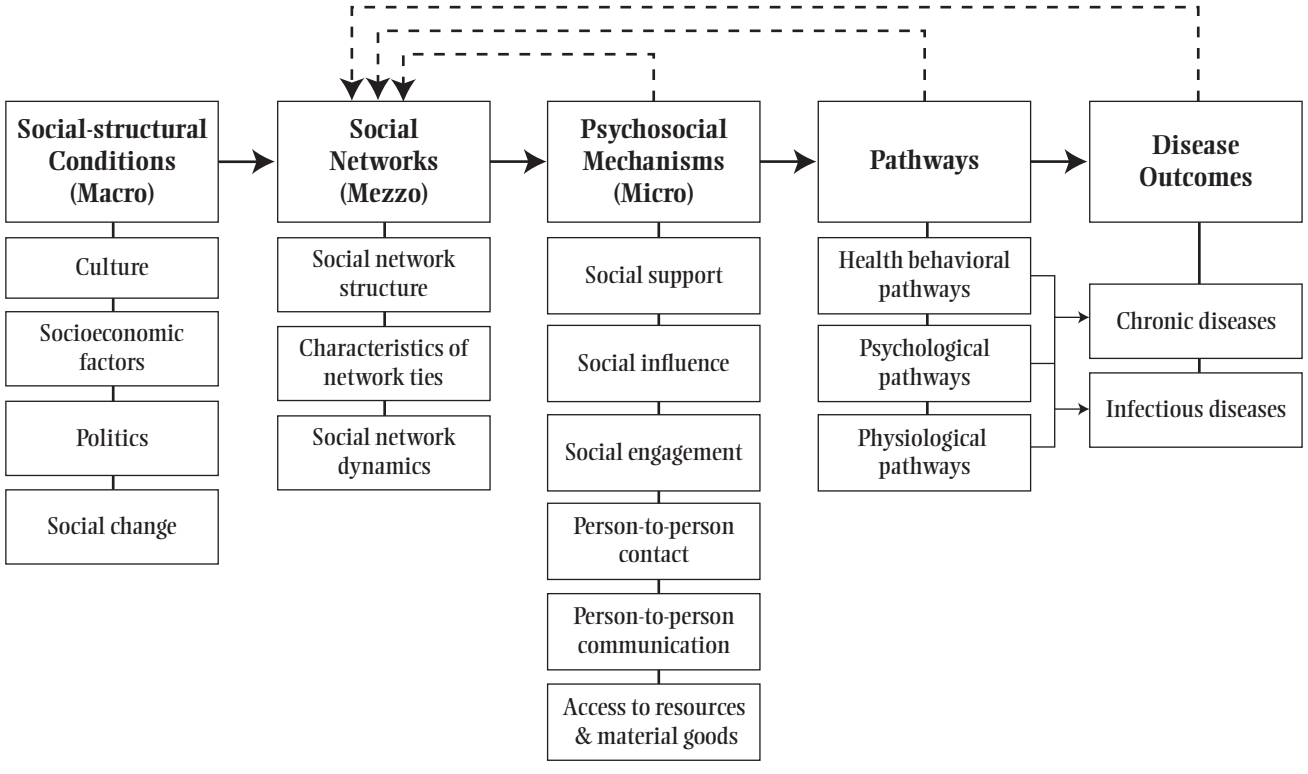

Figure 10.1 Conceptual model linking social networks to population health (adapted from [4]).

relationship between social networks, human disease, and population health, and present an overview of important network analytic approaches and tools.

Network analysis grew out of many disciplines, including anthropology, sociology, psychology, political science, computer science, and mathematics. What we now recognize as network analysis started in the 1930s, with Jacob Moreno's invention of sociometry and sociograms (network diagrams) [7]. From the beginning, network analytic methods were applied to study human behavior and health. Early applications examined family and genealogical systems, friendship and peer-support networks, and the role of social support on health. Over the last several decades, health, public health, and public policy researchers have increasingly used network approaches to study structural and systemic factors related to population health, with special emphasis on infectious and chronic diseases.

3. WHAT DO WE KNOW ABOUT HOW SOCIAL NETWORKS INFLUENCE POPULATION HEALTH?

3.1. Networks and Infectious Disease

Human relationships are essential to the spread of disease. Social aspects of disease transmission have been well studied in infectious diseases because of the relative ease of defining affected and unaffected individuals in a population. Traditional epidemic models of infectious disease such as the S-I-R (Susceptible, Infected, Removed) model and others function well when there are relatively clear mechanisms of transmission, infectivity, and outcomes [8]. These models are particularly useful for predicting the life course of an epidemic: when it started, how long it will last, and how many people will be affected by it. However, most of the research using S-I-R models assumes random mixing within a population; i.e., social structure is ignored. Starting in the 1970s, epidemiologists began adding structural and relational concepts into both their models and methods (e.g., contact tracing). More recent empirical and computational modeling studies have begun to demonstrate the need for—and advantages of—incorporating network information into epidemiologic models [9]. Instead of a traditional epidemic outbreak curve, diagramming the network growth of the spread of infection is more revealing of the underlying disease process [10].

The HIV/AIDS epidemic in the 1980s accelerated the adoption of network methods into infectious disease research and control. These methods were adapted and extended to study other types of STDs, including syphilis [11], as well as IV drug use and other risky behavior [12]. These studies identified how various structural aspects of the networks were related to disease incidence,

propagation, and maintenance, as well as suggesting effective new ways to intervene and treat infectious and behavioral diseases [13].

This work extends to understanding and controlling large-scale global pandemics. In recent years, network information derived from global airline transportation data, as well as intra- and international commuting patterns, have been used to develop accurate models of infectious disease outbreaks [14]. These network models allow for accurate real-time forecasting of global infectious diseases such as H1N, as well as helping to design surveillance systems for foodborne illnesses [15, 16, 17]. It is no longer a radical idea to understand infectious diseases as being driven by social and relational processes; network analysis is a primary tool for understanding those relationships.

3.2. Networks and Chronic Disease and Disease Prevention

At first glance, the mechanisms underlying the connection between social networks and chronic disease (and hence, population health) are a little harder to elucidate than those for infectious diseases. In a highly visible and influential set of studies, Christakis and Fowler have suggested that chronic diseases such as obesity and smoking may be "contagious" and influenced through peer and family social network processes [18, 19]. Referring back to the earlier conceptual model (Figure 10.1), we can see that networks can shape a variety of social support, social influence, and social engagement processes that can in turn influence behavioral, psychological, and physical pathways that are implicated in chronic diseases.

Starting as early as the Alameda County study in the 1970s, a number of studies have identified social isolation as a predictor of poorer morbidity and mortality outcomes from a wide variety of chronic conditions, including heart disease, cancer, and respiratory diseases [20]. Social support and larger social networks have been linked to longer survival times after cancer diagnosis [21]. Most of these and similar studies have used fairly general or crude measures of network characteristics. One exception is a recent study by Villingshoj and colleagues that included actual measures of social network contact frequency and related them to colorectal cancer survival [22].

Of all chronic diseases, smoking and tobacco use has received the most attention from network scientists. Smoking behavior, especially smoking initiation, is inherently relational and has a network aspect. Almost all people who start smoking do so before they are 18, and when they start they typically get their first cigarettes from another person, usually a friend or family member [23]. Ennett and Bauman were among the first to study smoking with a network framework, showing that adolescents who were most isolated

from their peers were more likely to smoke [24]. More recent network studies of tobacco use have started to use more sophisticated methods, which allow testing of richer structural and causal hypotheses. For example, Alexander and colleagues conducted an important study that demonstrated an interaction between social network characteristics and school context on the likelihood of smoking. Specifically, they found that popular students (defined in network terms) were more likely to smoke in schools with high smoking prevalence and less likely to smoke in schools with low smoking prevalence [25]. This body of work has started to elucidate more precisely the mechanisms by which networks influence smoking initiation and cessation, including isolation and risk accumulation, diffusion of cultural norms, and structuring flows of emotional support [26, 27, 28]. Finally, using innovative new network modeling techniques (exponential random graph models, see below), Mercken and colleagues have shown that both social selection and social influence are important processes that shape adolescent smoking behavior [29].

There are relatively fewer network analytic studies of obesity and physical activity than for smoking. However, there is a growing body of research that suggests obesity and its related risk factors are in part socially determined. Valente and colleagues found that friendship ties were significantly more likely to occur between teenagers who were of the same weight, compared to those with different weights [30]. In a similar vein, but using more sophisticated stochastic network modeling techniques, Schaefer and colleagues analyzed the network data in the National Longitudinal Study of Adolescent to Adult Health and found that non-overweight adolescents (as measured by BMI) tended to avoid forming friendship ties with overweight peers [31].

Although it is challenging to study network effects *on* obesity, it is somewhat easier to assess how networks influence the behavioral risk factors *for* obesity, viz., physical activity and diet. For example, adolescents who report spending more time with friends in physical activity are more likely themselves to be physically active [32]. At the other end of the age spectrum, adults in their seventies who have more social ties show less functional decline and greater physical activity [33]. In general, physical activity and exercise to reduce obesity can be enhanced via social networks—for example, participating in a carpool social network has been shown to predict exercise adherence [34].

4. WHAT ARE THE PRIMARY METHODS USED BY NETWORK SCIENTISTS WHEN STUDYING HEALTH?

Network analysis comprises a wide variety of analytic techniques. Like any other rich analytic tradition, these network analytic tools can be used for exploratory

data analysis, hypothesis building and testing, and more formal model development. Most network analysis techniques fall into one of three broad categories: visualization, network description, and network modeling.

4.1. Visualization

A primary product of network analysis, and often the first step of network exploration, is the network diagram. Network diagrams are information graphics that depict the network members (often called "nodes") and the relationships that connect them to one another (called "ties"). Network diagrams are not just pretty pictures; they are analytic tools that can convey important structural properties of a system. For example, consider Figure 10.2, which depicts the sexual transmission network in the early days of the HIV/AIDS epidemic [35, 36]. The pattern of ties displays the transmission route of the outbreak, and judicious use of node labeling and coloring tells a rich story of biology, sexuality, disease, and transportation. These types of disease transmission network

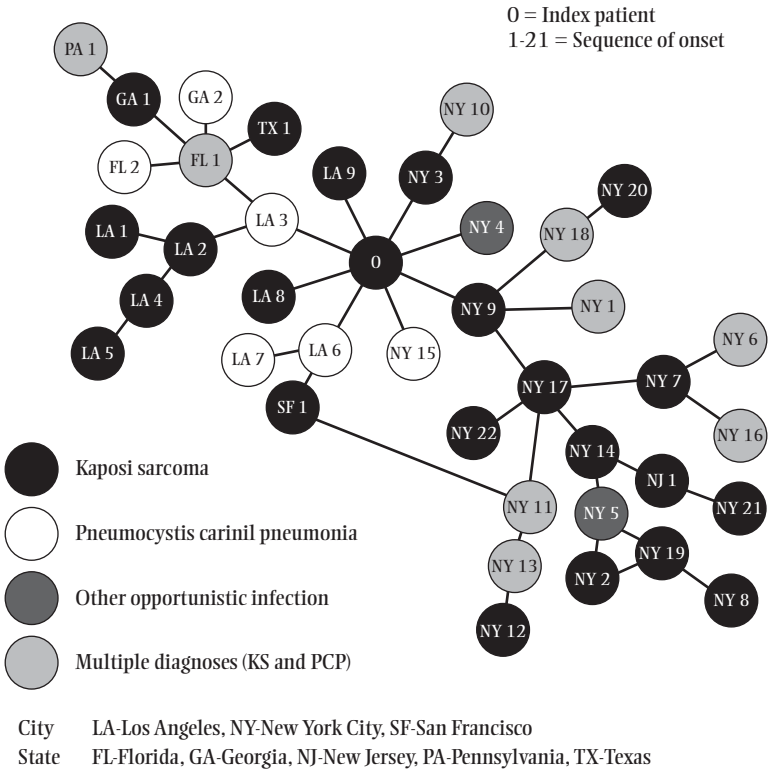

Figure 10.2 HIV/AIDS sexual transmission network.

visualizations revolutionized how epidemiologists both modeled and observed disease outbreaks, starting in the mid-1980s.

4.2. Network Description

Network scientists have developed a multitude of network descriptive statistics that are used to summarize important characteristics and aspects of social networks. These characteristics fall into a few broad categories, including network position (e.g., centrality), local network structure (e.g., transitivity), network subgroups and communities (e.g., modularity), and overall network structure (e.g., density) [37].

Figure 10.3 is a schematic that illustrates the rich diversity of descriptive methods that can be used by network scientists. In addition to the more basic network descriptions of node location, local structure, subgroups, and overall network characteristics, network analysts can use more advanced techniques to study multiple networks, multiple types of network ties within the same network (e.g., examining trust, friendship, and sexual contact ties within a school), multilevel networks, and how networks change over time.

4.3. Network Modeling

Until recently, network analysis was restricted to visualization and simple description, due to limitation in statistical network theory and computational power. However, in the past few decades there has been rapid development and application of mathematical, statistical, and dynamic network modeling techniques. Theoretical and mathematical models have been developed that help explain fundamental structural properties of real-world social networks, as well as how those networks form. A particularly important theoretical development is the discovery that many real-world networks have heavy-tailed degree distributions that approximately follow a power law. These are typically called *scale-free* networks. Scale-free networks have a distinctive pattern where most nodes have small degree (number of connections), while a few nodes have much larger degrees. For example, sexual contacts in human social networks are scale-free [38]. Figure 10.4 is a good illustration of the distinctive "hub-and-spoke" structure in a scale-free network [39]. This shows the large connected component of a high-school romantic contact network; while most members are connected to just one or two other students, a small number of students have dramatically more romantic partners.

New advances in statistical modeling of social networks have been one of the most important aids to empirical network research. Exponential random graph

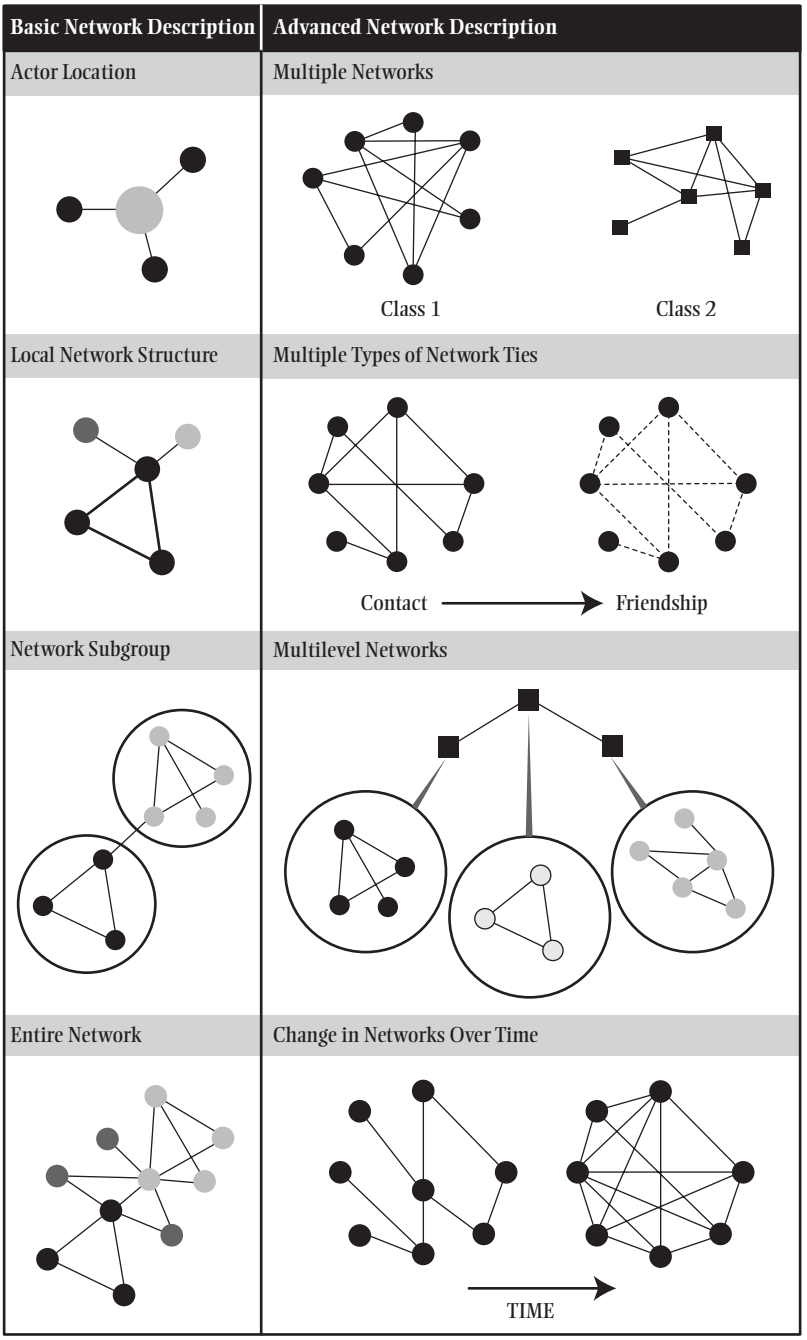

Figure 10.3 Schematic of potential network analysis approaches.

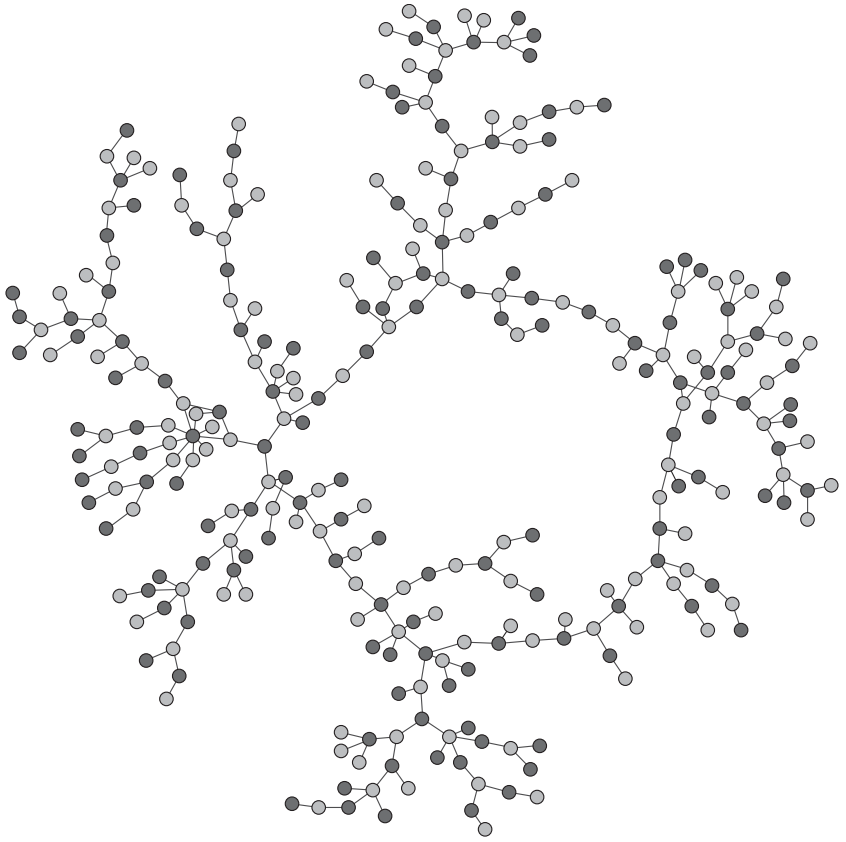

Figure 10.4 Large component of a high school romance network [39].

models (ERGMs) can be used to develop and test hypotheses about the likelihood of tie formation in cross-sectional social networks [40, 41]. This means that we can build predictive models that allow us to examine how characteristics of network members, characteristics of pairs of members (dyads), and local structural properties (such as transitivity) affect characteristics of the overall social network. These modeling approaches have started to be used more widely in the social sciences and public health, such as in examining the predictors of collaboration among tobacco control networks [42].

Valid techniques for modeling network dynamics have also been developed that allow for predictive models of network changes over time [43]. These models have important implications for studying social processes, social networks, and health. For example, these types of models have been used to disentangle for the first time the effects of social selection from social influence in how friendship networks and health behavior co-evolve [44].

5. WHAT ARE SOME IMPORTANT CHALLENGES AND OPPORTUNITIES FOR SOCIAL NETWORK ANALYSIS AND POPULATION HEALTH?

In early 2000 Stephen Hawking called the next century "the century of complexity." If his prediction proves true, then we will need new theories, methods, and types of data to study these complex social systems. Network science and network analysis provides some of these new approaches and tools. If network science, however, is to benefit our understanding and enhance population health fully, there is one important challenge to address. Unlike some of the other methods covered in this book (e.g., system dynamics, agent-based modeling), network analysis is predominately an empirical analysis approach. Population health network models need high-quality health-relevant network data. There are no large-scale health surveillance systems that currently collect health-relevant complete network data. Add Health (The National Longitudinal Study of Adolescent to Adult Health) is one important source of whole network data, but that ended new data collection in 2008.

One important opportunity to consider is greater integration of network data and network methods into other types of computational models. In particular, agent-based models of health-related complex systems often incorporate social network data and information. However, these ABMs tend to use simple network structures or data, and there is an opportunity to integrate ABMs with richer and more sophisticated social network data [45].

In summary, it is helpful here to remind ourselves of a call to action from sociologist Allen Barton in 1968:

> *If our aim is to understand people's behavior rather than simply to record it, we want to know about primary groups, neighborhoods, organizations, social circles, and communities; about interaction, communication, role expectations, and social control* [46].

With the rapid integration of network science theories and the widespread use of network data, we are making good progress toward Barton's vision, thus leading to a more evidence-based population health science.

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SECTION 3

Systems Science Toward a Consequential Population Health

11

Machine Learning

JAMES H. FAGHMOUS

1. INTRODUCTION

Machine learning has become one of the fastest growing technical fields of the last few decades, aided by an unprecedented ability to create and store data at massive scales, as well as increased computational capabilities such as distributed and cloud computing. Machine learning has shown great promise in domains where data are abundant and the problems lend themselves to classification or regression, and as a result, an increasing number of scientific fields are interested in adopting machine learning techniques to take advantage of their own data deluge. This chapter introduces non-computational scientists to the general field of machine learning and its methods. We begin by outlining the common structure of machine learning applications. We will then discuss a case study at the intersection of machine learning and epidemiology: Google Flu Tends. We conclude the chapter with steps on how to begin creating practical machine learning algorithms for population health.

2. OVERVIEW

In his classic text, Tom Mitchell defines machine learning as "the study of algorithms that improve automatically through experience" [1]. More concretely, the field of machine learning develops algorithms that improve their performance at a predefined task as more data are observed. There are three parts to this definition. First, machine learning focuses on *algorithms* and not necessarily explanatory models. Second, these algorithms have a clear task whose *performance* is measurable. Third, performance is associated mainly with more data.

Table 11.1 The Difference Between the Modeling and Algorithmic Approaches to "Learning from Data"

	Modeling approach	**Algorithmic approach**
Focus	Understanding	Prediction
Goal	Understand phenomena	Statistical accuracy
Priority	Interpretability	Flexibility (black-box)

An example of a learning problem is predicting hospital re-admissions. The task is to assign a label of re-admission or no re-admission to any given hospital visit record. The performance metric to be improved might be the accuracy of this re-admission classifier, and the training experience might consist of a collection of historical hospital admission records, each labeled in retrospect as leading to a re-admission or not. Alternatively, we might define a different performance metric that assigns a higher penalty when a "re-admission" case is labeled "no re-admission" by the algorithm, compared to when a "no re-admission" is incorrectly labeled as "re-admission."

This algorithmic focus is a fundamental departure from statistics, arguably the first science to formalize learning from data. In the statistical sciences, we are interested in descriptive models that can explain the observed data. These models tend to be interpretable especially on reasonable sample sizes. The algorithmic approach in machine learning assumes no knowledge about the data generation process and is not concerned with understanding what information leads to statistical skill. Instead, the focus is on maximizing predictive accuracy by optimizing a performance metric (Table 11.1).[1]

Generally speaking, a learning algorithm searches through a large space of hypotheses, guided by the data, to find a hypothesis that optimizes the performance metric the task is evaluated on. In practice, a learning algorithm is concerned with first selecting the family of hypotheses to search (e.g., mathematical functions, trees, etc.) and then choosing an approach to search through the selected set of hypotheses (e.g., optimization, simulations, etc.).

The rise of machine learning coincided with three major trends. First, the Internet democratized the production, storage, and distribution of data on unprecedented scales, which gave anyone with an Internet connection access to more data than most statisticians ever had in the 1990s. The data explosion enabled learning by examples on a scale that was not possible before the Internet and made the algorithmic approach a valid alternative to mainstream statistical modeling. The second trend was that the Internet not only created new data,

1. The late Leo Breiman has a great discussion of the modeling and algorithmic approaches to learning from data in [2].

it also created a host of problems to be addressed; chief among them was how we manage, annotate, and study the massive amounts of data created on a daily basis (of course, there are other problems such as spam filtering, product recommendations, and image annotation, etc.). Finally, the focus on general objective, yet abstract, performance metrics greatly facilitated comparing new methods, which accelerated innovation. This was further aided with the launch of the UCI Machine Learning Repository [3], which hosts various benchmark data sets that researchers can use to objectively compare algorithm performance. While these focused developments led to rapid growth of machine learning, they also narrowed the types of problems it tackled. The algorithmic and learning by example approaches lead machines to focus mainly on classification, regression, and ranking problems, as opposed to traditional artificial intelligence tasks such as reasoning or semantics [4]. Similarly, machine learning does not focus on inference as much as other sciences.

To summarize, machine learning is a field that seeks to learn from large-scale data sets with a large number of observations and numerous dimensions in each observation. The focus of learning algorithms is to produce a formula that maps new data (input) to a correct output based on input-output examples used to train the model. More recently, thanks to advances in cloud and distributed computing, we are able to learn from these large data sets and deploy algorithms in real-world settings, such as self-driving cars. As a result, there has been an increasing focus on scalability and operational performance of such methods, as opposed to understanding the formal properties of the resulting input-to-output formula. It is important to note the differences between problems traditionally tackled in machine learning and those that emerge in population health. Not every data-driven investigation within population science will warrant a machine learning approach. Instead, we must focus on problems where relevant and abundant data are available, where the goal is to forecast an outcome as opposed to estimating the effect of an intervention, and where there is a premium on creating a real-world working system as opposed to a traditional research study.

3. MACHINE LEARNING PRINCIPLES

3.1. Anatomy of a machine learning application

We begin by broadly defining a machine learning problem and the steps that are commonly taken to produce a machine learning application. Given a data set, we need to split it into *training* and *testing* data sets. The training data set is used to build the model independent of the testing data. The testing data is used to objectively evaluate the quality of the learned model. It is important

that the training and testing data sets be independent but representative of the overall data distribution. Next, the researcher chooses a family of models to fit (e.g., linear regression). Each model is governed by a set of parameters (e.g., slope and intercept for linear regression), and a model is *fit* to the data, by estimating its parameters using the training data set. Model parameters are fit through an iterative process where the parameters are slightly modified until a parameter choice that minimizes an objective function is identified (optimization [5] is an active field of research dedicated to this iterative process). The trained or fit model is then tested using the independent training data set to see how well the model generalizes to unseen data. If the model performs well on the training data, but poorly on the testing data, the model is said to have *overfit* the data. Overfitting is similar to brute force memorization instead of learning the general concepts of a problem. The final model and parameters are often referred to as a *hypothesis*.

It is important to note that machine learning can only *estimate* a function from observations. This is because it is assumed that any observation used to train the model is obtained using the true function we wish to estimate and an independent error that is unrelated to the observation (e.g., measurement error in an instrument; this is also known as *irreducible error*). The exact way that an algorithm executes the above-mentioned procedure depends on a few factors we discuss below.

3.2. Learning

One aspect that is unique to machine learning is the notion of *learning*. A broad view of learning is the assumption that given enough observations, we can learn an underlying process behind the data. Depending on the data we have, there are several variations of this learning process. *Supervised learning* refers to settings where we have access to both the data and target labels and the data come in explicit input-output pairs. This can be thought of as learning by example. *Unsupervised learning* refers to the setting when no labels are given to the user (e.g., in the hospital example, we do not know who got readmitted in the past). In this setting, exploratory tasks are usually favored. *Active learning* refers to the setting where there is a small set of training examples, but the algorithm has the opportunity to get new examples at a cost (e.g., ask an expert to create a new input-output pair). Finally, in *reinforcement learning*, instead of having input-output pairs, the algorithm only knows for a given input whether the output is correct or not. If the output is incorrect, the algorithm still needs to identify the correct output. This approach is commonly used in the autonomous solving of puzzles and adversarial games [6].

3.3. Model Evaluation

For much of this chapter we will focus on *supervised learning* problems, where we assume we are given input-output pairs to learn a mapping between inputs and outputs. As mentioned earlier, a learning algorithm will search for a set of hypotheses that maximizes an evaluation metric or minimizes the error of a task. How do we know if the algorithm has learned? The concept of learning comes from the *theory of generalization*, where we measure the error on unseen (out-of-sample) data and compare it to the error on the examples used to train the model. Specifically, an algorithm is said to have learned if the difference between the in-sample and out-of-sample errors is small (known as *Hoeffding's Inequality*).

3.4. Flexibility Versus Interpretability

We introduced the notions of in-sample and out-of-sample errors because they are critical in practical design decisions. Specifically, as we train a model to learn from (in-sample) data, we seek to minimize the error within this sample. However, solely focusing on minimizing the in-sample error will lead us to choose increasingly complex hypotheses that will indeed minimize the in-sample error by "fitting" the data very well. However, fitting the training too well usually means that the model is learning about the peculiarities of the training data (e.g., noise, or what we referred to earlier as *irreducible error*) as opposed to the underlying process. This results in poorly generalizable hypotheses, where the difference between the out-of-sample error and the in-sample error are too large. On the other hand, a less complex hypothesis set would give a better chance of generalizing to unseen data. As a result, a central concept in machine learning is that of maximizing model complexity while minimizing out-of-sample error, known as *the bias-variance tradeoff*. This notion is also important from a population health (and interdisciplinary) perspective. As algorithms are able to model increasingly complex functions (i.e., they are more flexible to fit the data), they become harder and harder to interpret from a domain perspective. Hence, in practice, a model might be statistically accurate but scientifically uninterpretable. In these settings, we would seek to maximize statistical accuracy while maintaining a minimum level of scientific interpretability.

3.5. Challenges in Machine Learning Applications

While machine learning offers a wide range of methods and approaches that are appropriate for numerous settings, including regression methods, artificial neural network approaches, and decision tree methods, there are notable challenges

that we must be aware of before embarking on a machine learning project in population health.

3.6. Data Empathy

A fundamental assumption in machine learning is that there is a process generating observations on hand and that the data are representative of such a process. These assumptions usually hold for when the data are large and observations are independent of each other. However, in practical settings we cannot take these assumptions for granted. Thus, a level of *data empathy* [7] is needed to understand why and how the data were collected. Recently, we have seen efforts in open science to create "data descriptors" to afford users a more nuanced understanding of data they are about to analyze. In addition to lack of familiarity with the data, another challenge is that numerous data sets are collected without any consultation with machine learning experts to advise on the types of data required to perform the needed analysis. As a result, a large number of data sets that currently exist in the sciences are ill-suited to tackle traditional machine learning problems. This design flaw of thinking about the machine learning steps only after data collection are common across disciplines and industries. However, the biggest disadvantage science faces is that data collection tends to be a time-consuming and expensive process. This is in contrast to Internet applications, where if a design flaw is identified, we could deploy a new data collection initiative and begin collecting samples within minutes.

3.7. Multiple Hypothesis Testing

One of the challenges we face in complex high dimensional settings is the ability of our model to generalize to unseen data and other settings. A common challenge in exploratory research is to ensure that, as we adaptively design our model (by repetitively training and testing it), our test data remain independent from the training data. This iterative approach to model tuning based on repetitive testing is known as *adaptability*, or "the garden of forking paths" [8], and is an implicit multiple hypothesis testing problem that is not easily captured in traditional significance tests or techniques that control for false discovery rate [9]. The most appropriate way to address this challenge is to list in advance the hypotheses and experiments that will be undertaken; once the experiments are run, the data should no longer be used. This is not feasible in exploratory settings or where new data are not readily available. Thus, we need more robust mechanisms to partition the data into training and testing sets that are independent but also representative. Recent work has suggested new approaches to safely reuse a

holdout data set without affecting the generalizability of the resulting model [10]. However, in other instances we will need to ensure that the training and testing data maintain the overall context of the data. For example, it has been shown that certain adverse health outcomes cluster over distinct spatial locations. There is a high likelihood that a uninformed split of the data may cause the training data to only have the spatial bias and not the test data set (or vice versa) that would lead to a poorly generalizable model.

3.8. Beyond Accurate Models

Based on the survey of the machine learning methods available to population health researchers, there remains a question of the utility of such methods for core population health research tasks. In order to create intervenable insights, more work is needed beyond the world of data and algorithms. Issues of communication, persuasion, and mobilization become nearly as critical as the science itself. There are some avenues for intervention (or at least suggesting interventions) by creating interpretable models where we can understand the impact of covariates and their interactions on a target outcome. Furthermore, we can leverage advances in *microsimulations*, so that once the model is fit we can impose changes to a covariate and simulate the output's response to such change. Finally, as more complex questions beyond "understanding" are sought in Internet domains, new research efforts are emerging on how to identify causal effects from observational data [11].

4. CASE STUDY: GOOGLE FLU TRENDS

Machine learning has rapidly become a valuable tool in the toolkit of most data-driven researchers. Its recent success has even pushed some to call for the "End of Theory" [12], where one could forgo scientific theory if there are sufficient data available.

A good example at the intersection of machine learning and epidemiology is Google Flu Trends. In 2009, a team of Google researchers reported being able to predict the incidence of flu outbreaks by analyzing the millions of flu-related search queries that are input into the Google search engine. The model worked so well that it accurately detected outbreaks much quicker than the Centers for Disease Control and Prevention [13]. More recently [14, 15], however, it has been shown that for consecutive years Google made more bad predictions than good ones. This raises questions about the usefulness of big data in population health and other settings. It is important to point out that there is nothing fundamentally wrong about what the Google team did—thousands of machine

learning teams take the same prediction-based approach. Because of the high visibility of Google as well as that of the initial publication (*Nature*), what we witnessed was the messy iterative process of machine learning unfolding in the public eye. There were, however, some problems with the approach taken. First, as is the case with any machine learning algorithm, its success hinges on the quality of the data available. This is why *data empathy* is so important. However, in Google's case, the algorithm had no control over the data or search queries, and there might have been significant sampling biases. Furthermore, the relationship between the inputs and the outputs is not obvious. For instance, while it is perfectly plausible that people might search for flu symptoms because they are feeling ill, it is also possible that populations search for flu symptoms because of timely media coverage. Finally, it seemed like there was no scientific hypothesis as to why the algorithm worked well in practice—were there other metrics beyond statistical accuracy that would provide additional evidence to the power of this approach? Could the authors verify the accuracy of their model by comparing the predicted spatio-temporal spread of the disease to more traditional epidemiological models?

In hindsight, the Google Flu Trends approach suffers, like many data-driven scientific endeavors, from the siloed approach to data collection, scientific enquiry, and algorithmic techniques—all of which are developed almost independently of one another. Instead, what we must see in the future are diverse teams coming together to form a homogeneous unit of data collection, algorithmic design, and scientific hypothesis generation/verification. Interestingly, Google recently announced that it will provide its model to various scientific institutions, including the Centers for Disease Control and Prevention. This is a more prudent approach, more in line with the collaborative spirit, that we believe is necessary to make machine learning actionable in the sciences.

5. THE ROAD AHEAD

In this chapter, we introduced the main principles of machine learning and highlighted unique aspects of the field compared to statistics and other quantitative fields of study. It is important to remember that machine learning is a relatively new field. Many new advances will emerge in the near future, some of which will have transformational impact across disciplines. However, in order to fully take advantage of the state-of-the-art in machine learning, population health researchers must develop a basic understanding of the discipline and create deep bonds with practitioners. The platonic collaborations (consultancies) between scientists and machine learning experts are not conducive to the level of integration necessary to fully leverage the deep insights developed over decades of scientific research and the multiplicative potential of machine

learning. In the near future, we hope to see a seamless integration of machine learning advances with deep population health knowledge, where the product of the two would be an inseparable process of data-driven scientific discovery.

6. ACKNOWLEDGMENTS

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12

Systems Science and the Social Determinants of Population Health

DAVID S. FINK, KATHERINE M. KEYES, AND MAGDALENA CERDÁ

1. INTRODUCTION

The distribution of health, both within and between populations, is often described with three statistics that communicate a measure of the central tendency, spread, and shape of that distribution. Mean life expectancy at birth, to take one measure of the central tendency, averaged 71 years worldwide in 2013 [1]. However, the mean can conceal the distribution's spread: while the average worldwide life expectancy at birth is 70 years, the spread between countries is 38 years, from 46 years in Sierra Leone to 84 years in Japan. Finally, the shape of a distribution communicates the symmetry of the distribution. For example, mean life expectancy at birth is left skewed among the World Health Organization regions, such that the African region's mean life expectancy is 58 years, which is 10 years below the next lowest regions (i.e., Southeast Asia and Eastern Mediterranean) and nearly 13 years below the worldwide mean of 71 years. The global distribution of life expectancy reveals that lower life expectancy is found among people who are born into poverty, afflicted by political upheaval, or marginalized within their own countries [2]. Both within and between populations, the differences in the distribution of health reveal what Paul Farmer called the "biological reflections of social fault lines" [3].

The distribution of health within and across populations is driven by a combination of factors that lie above the individual and shape their actions and interactions within societies. Examples of these factors include the social structure, the economy and corporate practices, and political factors (e.g., taxation, environmental regulation). These macrosocial factors create differential access

to resources and opportunities and influence the level and the distribution of health and disease across and within populations. In population health, we aim to identify the upstream factors that shape health and to understand how we might intervene in effective ways both to improve population health overall and to reduce health inequality. The health inequalities that arise from an unequal distribution of such macrosocial factors are of particular interest to population health sciences.

The drive to understand the processes that shape population health, and to identify the pathways that connect macrosocial factors to patterns of health and to health inequalities, has traditionally relied on a range of archival and survey data on social factors and health conditions at multiple levels—and on the use of analytic approaches such as multilevel models for the investigation of linear relationships between these factors and individual health states. Yet the relation between macrosocial factors and population health often arises from the collective actions of individuals, social structures, and population dynamics, in addition to the influence of individuals who comprise populations, requiring analytic strategies that take account of such a complex system of non-linear dynamics.

Systems science approaches have provided the methodological armamentarium to examine the complex processes that drive population health and produce inequalities in health. In this chapter, we will review three critical contributions that systems science approaches have made to population health science. First, a systems science approach has helped us model how health inequalities shape population health. Second, it has elucidated how feedback cycles between micro- and macro-level processes produce population health. Third, it has been used to identify targets for intervention in order to reduce inequalities in health. These contributions are not exclusive to systems science but rather steps that can be taken by population health scientists who employ systems science approaches to identify health inequalities, determine what causes them, and provide informed prevention strategies to ameliorate such health inequalities.

Systems science approaches are varied and include agent-based models, systems dynamic models, and network models, among others. In this chapter, we focus on agent-based models (ABM) but include other systems science approaches as relevant in order to complement the discussion. In brief, ABMs consist of simulations that follow prescribed rules about the characteristics of agents, their networks, contexts, and behaviors. By running simulations, we can observe how rules specified at the individual level produce population-level patterns. ABMs allow us to specify interdependence between agents and the spread of agent behaviors. Agent interactions can be a function of spatial proximity to other agents or based on a social network structure. Agents can also be placed within larger contexts such as workplaces, neighborhoods, and cities.

2. IDENTIFYING HEALTH INEQUALITIES

Systems science approaches have made two important contributions to understanding the drivers of health inequalities. First, in systems thinking, macro-level patterns of health emerge from the characteristics and behaviors of individuals embedded in different contexts and defined by their relations to each other. In this way, systems approaches force us to identify the processes at multiple levels that generate observed patterns of inequality. For example, in the United States, black men are over 6 times more likely to be incarcerated than their white counterparts. Kristian Lum and colleagues [4] have argued that the process of incarceration can be conceptualized similarly to a virus, one that is spread through social networks, and highlight several potential mechanisms for this process, including that an individual's incarceration can expose his or her family to a network of criminals [5] and expose both their friends and family to closer police scrutiny [6, 7]. Furthermore, blacks are significantly more likely to be both sentenced [8] and receive longer sentences [9] than whites, even after controlling for legal factors and social context. Therefore, Lum and colleagues [4] employed an ABM to show how the social spread of incarceration through social networks, combined with modest racial differences in sentencing (i.e., blacks sentenced on average 3 months more than whites over a period of 25 years for the same crime), could produce the racial disparities that are currently observed in the United States. This study illustrated how small disturbances (i.e., likelihood and length of incarceration) in one part of a system can generate substantial changes in another part of the system (i.e., blacks are 6 times more likely to be incarcerated than whites), replicating the mechanisms whereby social inequalities can generate health inequalities.

Second, in systems science analytics (e.g., ABMs), we can change either one aspect of the initial conditions or multiple aspects of the initial conditions to identify causal effects and causal mechanisms, respectively [10]. By doing so, we can identify contextual factors that have the potential to modify an intervention's effect on population health, amplifying or reducing inequalities in health. A recent study we conducted on the impact of universal versus targeted interventions on health inequalities illustrated how fundamental causes of population health, such as residential segregation, might modify the effectiveness of interventions in reducing inequalities [11]. As a test case to investigate this point, we created an ABM that simulated whether a universal (citywide) or targeted (to the most violent neighborhoods) increase in collective efficacy could reduce racial/ethnic inequalities in homicides in New York City (see Figure 12.1). From 2009 through 2013, the annual rate of homicide in the United States among blacks was over five times higher than whites [12]. Robert J. Sampson and colleagues [13] have argued that lower levels of collective efficacy (defined as "social cohesion

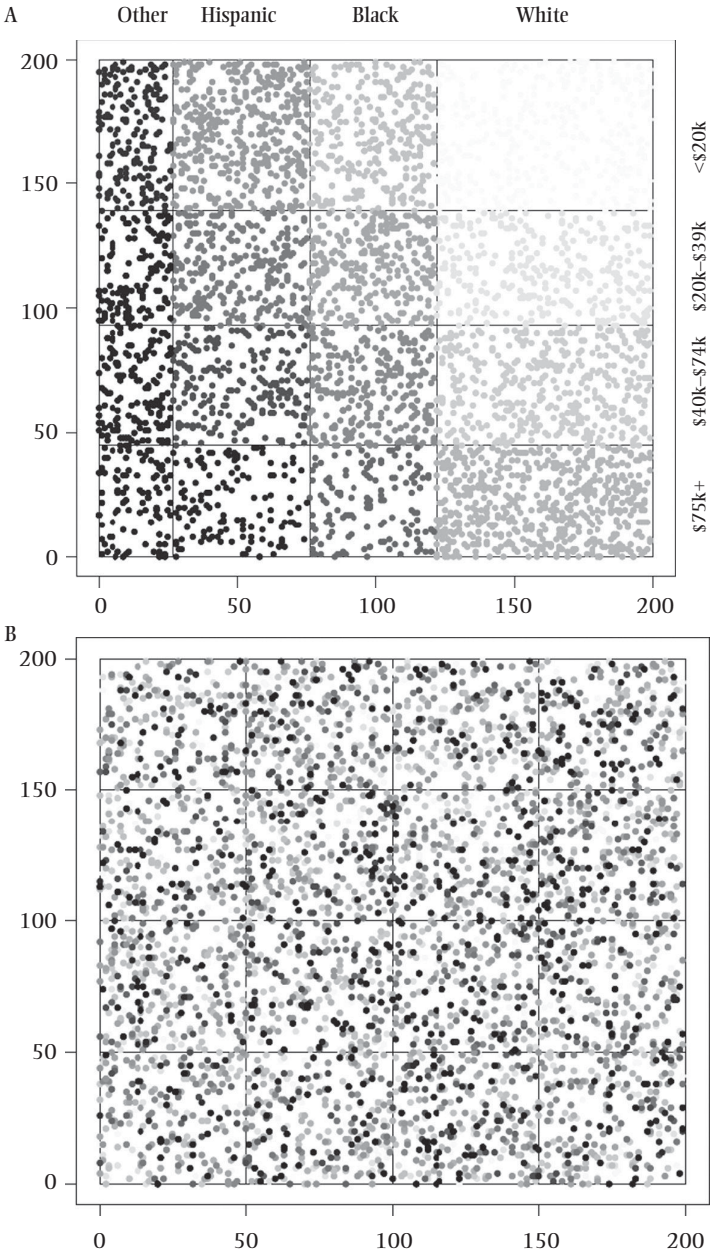

Figure 12.1 Agent locations in a grid of neighborhoods, with agents (a) segregated in neighborhoods by race and income, or (b) assigned random locations [11].
NOTE. Each racial/ethnic group is represented by a different shade of gray (black: other non-Hispanic; medium gray: Hispanic; light gray: black non-Hispanic; lightest gray: white non-Hispanic). Darker circles reflect higher income levels within each racial/ethnic group.

among neighbors combined with their willingness to intervene on behalf of the common good") present in economically disadvantaged neighborhoods place residents at higher risk of violence. Using this ABM, we observed that a universal strategy lowered overall rates of violent victimization; however, neither the universal nor the targeted prevention strategy reduced racial/ethnic inequalities in victimization. We were concerned that this failure to reduce inequalities in homicides may be due to segregation of blacks into low-income neighborhoods, which would, in the long term, reduce collective efficacy and continue to drive higher rates of homicide. We thus simulated the same interventions under three alternative scenarios: (1) complete racial/ethnic residential segregation across the city; (2) intermediate segregation; and (3) no segregation. Racial/ethnic inequalities in victimization were only reduced through the elimination of residential segregation (i.e., scenario 3). This study illustrates how, by using a system science approach to simulate a series of different interventions under a range of counterfactual scenarios of segregation (something impossible to observe in the real world), we were able to visualize how targeting proximal risk factors such as collective efficacy could fail to reduce health inequalities if we do not address the fundamental drivers of health inequalities [14].

3. UNDERSTANDING FEEDBACK

Systems science analytics are particularly well suited to help us understand the influence of feedback between micro- and macro-level processes that drive population health and health inequalities. James Ladyman and colleagues [15] explain that "(a) part of a system receives feedback when the way its neighbors interact with it at a later time depends on how it interacts with them at an earlier time." Consider a series of neighborhoods, comprising heterogeneous households, where each household prefers to live near neighbors that share a recognizable characteristic (e.g., race/ethnicity). Each household's decision either to stay in their current neighborhood or relocate to a new neighborhood depends on the characteristics of their current neighbors, but after the household makes their decision to stay or relocate, each neighbor will make a similar decision in response to their neighbors' movements. An early example of the application of systems science approaches to the generation of residential segregation dynamics illustrated this process [16], showing how household preferences about location can give rise collectively to population segregation and neighborhood tipping points. In this model, every unit was assigned membership into one of two permanent and recognizable groups (i.e., black and white ethnicity). Through a series of discrete intervals each unit evaluated their current situation and decided whether to stay in their current location or relocate to a new area based on whether the color mixture in their current space was acceptable (i.e., half or more of the eight

adjacent neighbors were of a similar color). This study contributed two important findings about the drivers of residential segregation. First, each unit is constantly affected by the decisions of others; irrespective of a unit's decision to stay or relocate, everybody else's movements will affect each unit's location prior to the next interval, precipitating future movement. This chain of cause-and-effect between movement at the individual level and neighborhood composition at the group level produces a feedback loop. Second, it is through this feedback that the behavior of micro-level units give rise to macro-level phenomena (segregation).

More advanced ABMs have considered multiple contemporaneous feedback processes to understand the influence of place-related factors on creating health inequalities [17–19]. An illustrative example relates to the influence of place-related factors on food preferences. It has been proposed that reduced access to healthy and affordable foods in low-income neighborhoods likely helps shape differences in food preferences between low- and high-income households [17, 18], forming a feedback loop between individual behavior and neighborhood markets whereby availability drives preferences, which then affect availability. To identify the drivers of income inequalities in diet, Amy H. Auchincloss and colleagues [19] employed an ABM that assigned households and stores behaviors based on their access to healthy foods and customers, respectively. In this model, each household's decision to shop at a store was driven by food price, distance, and preferences for healthy foods, whereas stores decided to change location and food type in response to their customer base. Through these feedback processes, Auchincloss and colleagues found that the currently observed patterns of income differentials in access to healthy foods arise from the total segregation of high-income households and health food venues from low-income and unhealthy food venues. This finding refuted the hypothesis that inequalities in diet reflect difference in food preferences between low- and high-income households. Next, using the segregation scenario where income differentials in diet emerged (i.e., total segregation), Auchincloss and colleagues examined under what conditions healthy food prices and preferences could overcome or exacerbate the effects of segregation on healthy diet. In this series of experiments, the currently patterned segregation of healthy food stores to high-income areas could be reversed by simultaneously changing food preferences among low-income households and reducing food prices. Although these models do not require the explicit specification of interventions that can simultaneously shift both food preferences and prices, they provide evidence that synergistic interventions will be required to ameliorate the currently patterned health inequalities.

This *in silico* experiment by Auchincloss and colleagues [19] examined the interdependencies between household choices and business decisions, and how dynamic feedback over time between the changes in household choices and business decisions gave rise to either salubrious or deleterious household health

behaviors. In addition, studies have documented that these reenforcing feedback cycles produce and maintain contextual factors that influence violent victimization and racial/ethnic segregation [11], physical activity and built environment [20, 21], and alcohol consumption and density of alcohol retailers [22]. As these examples illustrate, systems science methods can be used to ask questions about the dynamic mechanisms through which macrosocial determinants of population health produce health inequalities.

4. IMPROVING INTERVENTIONS

Finally, systems science approaches have helped us identify targets for intervention to reduce health inequalities. While many of the previous examples have tested manipulable factors that could inform policy interventions to target health inequalities, the following models were explicitly built to optimize interventions and inform future policy decisions. Although several models have been built to represent a very specific population or geographic area [23], this specificity comes at a cost to generalizability—that is, the closer a model is built to represent a specific population or location, the less likely its findings will be generalizable to other societies with different mobility patterns, structural factors, and distributions of individual-level risk factors. As such, some studies aim to examine more fundamental processes to increase their generalizability.

Systems science approaches can be used to identify hypothetical points of intervention that will obtain optimum improvement in population health. Previous models have compared individual- versus structural-level interventions [23–25], active versus passive interventions [26], and primary versus tertiary prevention [27–29]. In one study, we investigated whether a population-level violence prevention intervention (i.e., hot-spot policing) or an individual-level treatment intervention (i.e., cognitive behavioral therapy [CBT]) could produce a greater reduction in the burden of violence-related posttraumatic stress disorder in urban areas [27]. In this model, we observed an equally slight reduction in the annual prevalence of violent victimization from implementing either hot-spot policing for 10 years or increasing CBT by 100% for 30 years; however, the joint implementation of hot-spot policing and a 50% increase in CBT resulted in a similar reduction in just five years. Much systems science literature has replicated our observation that interventions can work synergistically to obtain optimum improvement in population health [19, 20, 28]. Because the development, implementation, and long-term evaluation of community health interventions can be costly, ABMs have provided a particularly attractive opportunity to sequentially evaluate several competing intervention approaches to determine those most likely to provide population health benefits.

Systems science approaches can also be used to simulate the effect of interventions within a context of social transmission of health-related behaviors and interference. Interference refers to the process through which an individual's exposure status in the study influences another's outcome. Because the decision to consume tobacco is partly social [30], and because an intervention on tobacco use affects not only the smoker but also others around the smoker, issues of interference [30, 31] influence the effect of tobacco control interventions on smoking. In 2003 the National Cancer Institute (NCI) began the Initiative on the Study and Implementation of Systems (ISIS) project that aimed "to use systems thinking approaches and theory to address previously intractable issues, to improve the health outcomes associated with tobacco control and, by corollary, to improve all of public health" [32]. Furthermore, the Center for Tobacco Products (CTP) at the US Food and Drug Administration (FDA) employed two population models, SimSmoke and the Cancer Intervention and Surveillance Modeling Network (CISNET), to examine whether increasing the minimum legal age (MLA) to purchase tobacco from 18 to 19, 21, or 25 decreased initiation rates among persons under 18 [33]. As the majority of underage persons rely on social contacts (e.g., acquaintances, friends, family) to get tobacco, the study hypothesized that raising the MLA to age 21 or above, compared to 19 years, would produce the greatest social distance between underage persons and potential sources that could legally purchase tobacco. Indeed, in these models, raising the MLA from 18 to 19, 21, or 25 would result in respectively about a 10%, 25%, or 30% decrease in initiation rates of smoking among 15–17 year olds. Further, this study found that raising the MLA to 21 or above reduced the likelihood that persons under age 18 would be in the same social networks as those who can legally obtain tobacco and, consequently, reduce tobacco initiation rates among persons under 18. By applying the intervention to persons aged 19 or older and measuring the outcome in those under 18, this study showed how modeling interference among agents can be exploited to both identify and maximize intervention effects.

The utility of systems science methods to evaluate a broad range of public health interventions is clear. Policymaking is difficult, but system science approaches can be used to weigh the costs and benefits paid and accrued by different groups under multiple counterfactual interventions [10], while simultaneously considering intervention effects on both the entire population and the sub-groups that comprise that population. Indeed, much research has documented that individual-based medical interventions disproportionately favor the health of people occupying higher socioeconomic positions within societies, acting to perpetuate and exacerbate extant health inequalities. As such, taking an equity-focused approach to policymaking is particularly important to reduce the growing health inequalities that exist within our societies.

5. CONCLUSIONS

Traditionally in public health and other sciences we have looked to behavioral risk factors that vary within populations as potential manipulable exposures that cause poor health, and there have been calls to move even further "downstream" to examine individual differences in biological factors. Yet such approaches make it more difficult to grapple with the macrosocial determinants and processes that create and maintain health inequalities. Systems science approaches provide both the theory and the tools to examine structural and macrosocial factors, allowing us to hypothesize about the fundamental drivers that shape health and how we might intervene on them in effective ways both to improve population health overall and to reduce health inequality. The years to come will be an exciting time for complex systems modeling in population health science, as more scholars are trained in these methods and technical and methodological innovation continues to push the field forward. Increasing recognition that the systems that underlie the generation of our data are critical to answer questions regarding how to improve population health will benefit our science and our ability to intervene for a healthier society.

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13

Systems Approaches to Understanding How the Environment Influences Population Health and Population Health Interventions

MELISSA TRACY

Population health is determined through a multitude of interrelated factors, including features of the social and physical environment. Although a large body of research has examined relations between aspects of the environment and population health, it is only more recently that attempts have been made to understand the dynamic interrelations between the environment and population health using systems science approaches.

In this chapter, I describe the utility of systems approaches for furthering our understanding of how the physical and social environment influences population health, as well as the effectiveness of population health interventions. This includes a brief review of some of the evidence for the complex and reciprocal relations between environmental features and health, and the influence of environmental characteristics on the outcomes of population health interventions. I then discuss the advantages of systems approaches over traditional analytic methods for capturing the complex influences of the environment on health. Finally, I use several examples from the public health literature to illustrate best practices for developing and applying systems science models to the study of environmental influences on health and on the effectiveness of population health interventions.

1. THE ENVIRONMENT AND POPULATION HEALTH

The increase in multilevel research over the past few decades has demonstrated the influence of a variety of characteristics of the social and physical environment

on mental and physical health [1]. Under the multilevel framework, this research has attempted to quantify the influence of a particular environmental characteristic on health, independent of individual-level characteristics and in isolation from other environmental features, at least in theory. However, given the connections between diverse environmental features and the patterning of individual behaviors and experiences by environmental characteristics, estimating independent effects may not be possible, or even desirable, as an approach to understanding population health [2].

An alternative approach seeks to understand the whole system in which population health develops, including representations of individual behaviors, social networks, health-related resources, and environmental influences. Rather than attempting to isolate the effects of a particular environmental characteristic on health, this approach aims to characterize the pathways through which the environment influences health and the dynamic relations between the components of the system that give rise to healthy and unhealthy states of being. Understanding the complex and diverse ways in which the environment may shape population health becomes of central importance in this paradigm, along with recognizing that the environment may also be influenced by population health, both directly and indirectly.

1.1. Complex and Reciprocal Relations Between the Environment and Health

The environment may shape population health in a variety of ways, including serving as a direct threat to health, influencing health behaviors, shaping interactions between individuals, and determining the availability of resources like health care. Individual aspects of these relations have been studied in depth, though appraising their joint effect on health has proved challenging. In addition, the potential for population health to influence the environment as well, and the implications of that reciprocity, have not been fully explored. Below are some examples of the relations between different environmental characteristics and health that have been established.

A large body of literature has assessed the negative effects of direct environmental threats to health. These environmental exposures include pollutants and other toxic contaminants in the air, water, and soil, as well as natural disasters like tornadoes and hurricanes. They have been linked to a variety of outcomes—from mental health problems to cancer to respiratory problems and asthma—using a range of observational study designs, natural experiments, and study populations. Prevalent health conditions and perceived health risks may also directly impact environmental features, highlighting the reciprocal nature of these relationships.

For example, health concerns have influenced building design and acceptable materials for use in residential dwellings (e.g., see the eradication of lead paint and asbestos). High rates of prescription drug use among the population, including antidepressants, have also begun to alter aquatic life in creeks and rivers [3].

In addition to direct associations between environmental features and health, the environment in which one lives, works, goes to school, or otherwise spends time may influence one's health behaviors, including physical activity, healthy or unhealthy eating, moderate or immoderate alcohol or drug use, and participation in or exposure to violence. A number of studies have examined aspects of the environment in relation to health behaviors, including residence in a "food desert" in relation to eating habits and neighborhood educational inequality in relation to alcohol consumption, for example [4, 5]. These health behaviors in turn have important influences on health outcomes, including the development of chronic conditions like cardiovascular disease, thus providing an indirect pathway between the environment and health. Furthermore, health behaviors may also shape environmental features; for example, increased walking and physical activity among area residents may encourage relocation of businesses to high-trafficked areas and the development of safer and better-cared-for public spaces [6].

Besides influencing health outcomes and health behaviors, the environment also shapes the social network structures and interactions through which health behaviors and disease risks may be transmitted. The most straightforward example of this relates to infectious disease, in which the patterning of social contacts is directly relevant to the spread of disease throughout the population. Models of infection transmission dynamics have analyzed these social network influences in order to identify the optimal infection control strategies under different scenarios [7]. Recent studies have also emphasized the "contagious" nature of other health conditions, like obesity and violence, extending the importance of social network interactions to health outcomes not traditionally thought of as infectious [8, 9]. However, the role of the environment in shaping social contacts has received less attention, as has the influence of social interactions on changes in the environment.

These are just a few illustrations of the complex pathways between different features of the environment and population health. Many other examples can be found, including the spatial patterning of health-related resources, including hospitals, clinics, doctors' offices, and businesses or facilities that promote or discourage healthy living, with more positive resources generally found in more affluent areas with greater proportions of white residents, with important implications for access to needed services [10]. In addition, the effectiveness of population health interventions may be strongly influenced by environmental characteristics.

1.2. Population Health Interventions in a Complex Environment

The outcomes of population health interventions are notoriously difficult to predict. Interventions that address environmental features (e.g., housing conditions) often exhibit inconsistent improvements in health outcomes because of the interplay of other factors that also influence health to different degrees and are present to different extents in different settings [11]. Structural and social features that aggregate risk factors in certain groups or areas may influence the effectiveness of health interventions or policies focused on one particular risk [12]. The underlying level of risk in the population also determines the choice of optimal health interventions, including whether interventions should be applied broadly or targeted more specifically to certain subgroups [13]. Rigorous evaluations of community-level interventions are difficult to conduct, with financial and time costs being prohibitive for randomized controlled trials and methodologic issues inhibiting inferences from observational studies.

Systems approaches have been touted as one possible way to compare intervention strategies in a simulated environment in order to gain insight into what approaches may be most effective in reality [14, 13]. The challenges of identifying the effects of population health interventions across varying environments, together with the complex and reciprocal pathways between environmental features and health, emphasize the need for a systems approach to fully understand the processes through which the environment influences health and how best to design and implement population health interventions.

2. SYSTEMS APPROACHES TO UNDERSTANDING THE INFLUENCE OF THE ENVIRONMENT ON HEALTH

Complex systems approaches include a variety of computational models that use computer-based algorithms to simulate dynamic processes, including interactions between individuals and between individuals and their environment [15, 16]. Two types of systems approaches are agent-based models and system dynamics models. In agent-based models, heterogeneous agents with specified characteristics interact with each other over time according to predefined rules, updating their behaviors based on their past experiences and influences from other agents and their spatial environment [14]. By contrast, system dynamics models use a series of differential equations to reflect stock variables (e.g., population subgroups) and flows into and out of stocks, including bidirectional relationships [17, 18]. In both approaches, population-level patterns can be compared under different scenarios.

2.1. Advantages of Systems Approaches for Studying Environmental Influences on Health

There are several advantages of using systems science approaches to understand relations between the social and physical environment and health. First, conceptualizing population health as arising from a complex system with explicit interrelations between different environmental features, social network characteristics, and individual behaviors allows for a more comprehensive assessment of the dynamic effects of environmental conditions on health. This approach allows for the possibility of joint environmental influences on multiple outcomes, reciprocal relations between the environment and health, and unintended health consequences of environmental changes. This is a clear advantage over traditional analytic approaches, which essentially attempt to isolate the health effect of one among many highly correlated area-level characteristics.

Second, systems approaches can compare the results of simulated interventions, policies, and changes in environmental features, keeping other aspects of the model constant in a way that is exceedingly challenging to accomplish with observational studies in real life. One particular advantage of systems approaches is the removal of issues related to constraints on where individuals can live given their circumstances (e.g., household income), which can make it hard to untangle health effects of the environmental context vs. attributes of area residents [6, 19]. In agent-based or system dynamics models, the health effects of environmental features themselves can thus be identified more clearly.

Third, the model can be calibrated to a variety of different initial scenarios, including simulations of different geographic locations and social groups, allowing for tests of health interventions and policies across diverse settings. Finally, the process of developing an agent-based or system dynamics model often helps bring together stakeholders in the community with academic researchers, and assists in the identification of empirical information needed to specify the relevant system fully.

Of course, a number of assumptions must be made to draw inferences from these simulated models about the real-life systems they are made to represent. Simulation models are also reliant on past, existing data, which may not allow for accurate prediction of future trends. Given the very real possibility of model misspecification, these models should not necessarily be treated as quantifying intervention effects precisely [2, 17]. However, these models do have much to offer in the study of environmental influences on health, as illustrated by the following examples demonstrating best practices for a systems science approach.

2.2. Best Practices for Systems Approaches to Understanding the Environment and Health

I now use four examples from the public health literature to illustrate systems approaches incorporating the complex associations between the environment and health. Each example is described briefly, with additional information provided in Table 13.1. Together, these examples highlight best practices in applying systems approaches to the study of environmental influences on health.

The first example, a system dynamics model of land use, transport, and health developed by Roderick J. McClure and colleagues, highlights the direct health consequences of environmental conditions [20]. Rather than using traditional methods to quantify relations between different features of the environment (e.g., length of road networks) and particular outcomes (e.g., traffic injuries or fatalities) in different settings, McClure et al. used this system dynamics model to gain a better understanding of the dynamics and interrelations between economic development, population wealth, car ownership, land-use patterns, and transport norms and how those dynamics influence population health in six major cities. In particular, while increased mobility may exacerbate certain health risks like transport-related injuries, increased access to transportation may also have positive health consequences through improved access to health-related resources, improved health through the use of active transport modalities, and improved quality of life as a result of the increased economic development and wealth that often goes along with increased mobility. The authors simulated a series of transport policies aimed at reducing risk of injuries and encouraging modes of active transport as well as public transportation in order to maximize the health of the population.

In the second example, which focuses on environmental influences on walking behaviors, Yong Yang and colleagues described an agent-based model in which individuals with heterogeneous characteristics were embedded in social networks and neighborhood environments that influenced their actions [6]. Agents could choose to walk to work, for leisure, or for basic needs like shopping in a simulated city; walking ability was a function of age, while walking preferences were influenced by previous walking experiences, seeing others walking, and the walking attitudes of friends and family members. In this way, the model incorporated multiple levels of influence on individual behaviors, including feedback from past experiences. Walking behaviors, including inequalities in walking behaviors across socioeconomic status (SES), were then observed under different distributions of land use and safety throughout the environment.

The study by Bruce V. Lee and colleagues used an agent-based model simulating the actions of every resident of Norfolk, Virginia, over a one-year period to observe outcomes of a theoretical influenza epidemic [21]. One strength of

Table 13.1. Representative Examples from the Population Health Literature Illustrating Systems Science Approaches to Understanding the Influence of the Environment on Health

Example	Citation	Study Objective(s)	Methods	Experimental Condition(s)	Outcome(s) of Interest	Main Findings	Conclusions
Environment as a direct threat to health	[20]	Identify land use and transport policies that would optimize population health in alternate settings.	Develop a qualitative conceptual model illustrating the relations between land use, transport, economic development, and population health. Convert this representation into a quantitative system dynamics model incorporating population wealth, population mobility and modes of transport, transport-related health risks and other measures of population health. Adjust the base model to represent 6 cities: London, Copenhagen, Beijing, Delhi, New York, and Melbourne.	*Policy 1*: Reduce the risk of crashes per kilometer and the risk of serious injury per crash. *Policy 2*: Change the distribution of transport modes from individual motorized transport to mass transport and individual active transport. *Policy 3*: Combine polices 1 and 2.	Transport crash deaths and all-cause disability-adjusted life years (DALYs).	Combining transport risk reduction policies with policies that reduced personal motorized transport provided the greatest reduction in transport-related health risks, though model results varied according to initial levels of development and distributions of modes of transport.	Optimal land use and transport policies need to be considered in the context of an integrated system of environmental, economic, and health influences. Increasing availability of mass transport and active transport options, improving safety of existing road infrastructure, and encouraging land use changes that increase urban density are likely to optimize population health.

(*continued*)

Table 13.1. Continued

Example	Citation	Study Objective(s)	Methods	Experimental Condition(s)	Outcome(s) of Interest	Main Findings	Conclusions
Environment as a determinant of health behaviors	[6]	Evaluate how the built and social environments influence social inequalities in walking.	Develop an agent-based model simulating walking behavior in a hypothetical city, including walking to work, for basic needs, and for leisure. Walking ability is a function of age and attitude toward walking is influenced by walking experiences as well as the walking behaviors of friends and family. Residential segregation was represented by the location of lower socioeconomic status (SES) households in the center of the city, with higher SES households located on the periphery.	Four scenarios were compared, with different combinations of the spatial distribution of non-household locations and of safety: (1) randomly distributed non-household locations and random safety level; (2) randomly distributed non-household locations and lower safety level in the city center; (3) more non-household locations in the city center and random safety level; and (4) more non-household locations and lower safety level in the city center.	Average number of walking trips per day per person, by SES.	Known SES gradients in walking behaviors, with lower-income individuals more likely to walk to work and higher-income individuals more likely to walk for leisure, were replicated by the model.	Patterning of walking behaviors by SES is a function of the co-location of residential segregation, land use, and safety.

Environment as a determinant of social interactions	[21]	Simulate a theoretical influenza epidemic in Norfolk, Virginia.	Develop an agent-based model that simulates every resident of Norfolk, VA and includes detailed city-level features including geographic characteristics, weather, and locations of homes, schools, and workplaces. Agent movements and interactions are also simulated, including health-care-seeking behaviors, including after 200 cases of influenza are introduced into the population.	The model was repeated multiple times, varying key parameters: the influenza transmission rate (i.e., the probability an infected agent transmits influenza to a non-infected agent with whom it interacts); the incubation period; the contagious period; and the percent of the population who were immune to influenza.	Epidemic curves, overall and by age and race; reproductive rates (R_0); and number of health-care visits.	Cyclical variations in influenza incidence were observed, with increases on weekdays and decreases on weekends. The number of influenza cases peaked earlier and the prevalence of influenza remained high for longer among individuals aged 65 years and older than among other age groups.	Social distancing measures like school and workplace closures may be critical to reducing the spread of an influenza epidemic; the elderly may act as a "reservoir" for influenza during an epidemic and thus may be an important target of vaccination campaigns.

(*continued*)

Table 13.1. Continued

Example	Citation	Study Objective(s)	Methods	Experimental Condition(s)	Outcome(s) of Interest	Main Findings	Conclusions
Environment as a determinant of population health interventions	[13]	Compare population levels of violent victimization and racial/ethnic inequalities in victimization under universal and targeted interventions increasing collective efficacy.	Develop an agent-based model that simulates violent victimization and perpetration in a population representing adults in New York City, including the prevention of violent incidents through high neighborhood collective efficacy. Adjust the base model to reflect extreme scenarios of racial and economic segregation in the environment: complete segregation by race/ethnicity and income vs. no segregation at all (i.e., random locations of individuals, irrespective of race/ethnicity and income.)	In the *universal* experiment, neighborhood collective efficacy was increased by different increments across all neighborhoods. In the *targeted* experiment, neighborhood collective efficacy was increased only in neighborhoods with above-average levels of violence. Experiments with durations of 1 and 30 years were also compared.	Average percent violently victimized in the past year, overall and among blacks and whites separately.	Universal experiments increasing collective efficacy reduced the overall percentage who were violently victimized each year more than the targeted experiments. However, racial/ethnic inequalities in violence were not reduced by universal nor targeted experiments when the population was segregated by race and income.	Residential segregation is a fundamental cause of health that influences the effectiveness of interventions aimed at reducing racial/ethnic inequalities in health outcomes and experiences like violent victimization.

this model was its detailed social network (including family members, neighbors, coworkers, classmates, and friends) and explicit opportunities for interactions between agents. Importantly, the model environment included simulated weather conditions and geographic features that restricted or promoted social interactions throughout the model run. In this way, environmental features contributed to the spread of disease through their influence on social networks and interactions. Influenza incidence was then observed under scenarios with varying transmission probabilities, incubation periods, contagious periods, and level of immunity in the population.

The final example, using a systems science approach to anticipate environmental influences on the effectiveness of a population health intervention, comes from Magdalena Cerdá and colleagues, who developed an agent-based model of violent victimization among adults in New York City [13]. The objective of this model was to compare universal vs. targeted experiments increasing neighborhood collective efficacy in order to reduce experiences of violence, as well as racial/ethnic inequalities in violent victimization, where the universal experiment was characterized by a small increase in collective efficacy across the whole city and the targeted experiment comprised a more concerted effort to increase collective efficacy but only in high-violence neighborhoods. As in previous models ([6, 20]) the experimental conditions were compared under different hypothetical scenarios, in this case contrasting complete racial and economic residential segregation with a complete lack of segregation in the city. The authors found that the universal experiment led to greater reductions in violent victimization across all groups, but racial/ethnic inequalities in violence persisted in the presence of racial and economic residential segregation. Only by reducing residential segregation through an artificial random distribution of individuals across the spatial environment were racial/ethnic inequalities in violence eliminated through increased neighborhood collective efficacy.

What can we learn from these examples? These models share a number of features that are critically important to any assessment of environmental influences on health, including detailed representations of a variety of environmental characteristics; consideration of multiple outcomes and unintended consequences of experimental manipulations; examination of results under alternate scenarios; and caution against treating model results as inviolate predictions of reality.

The influenza epidemic model by Lee et al. best illustrates the importance of detailed empirical representations of multiple features of the environment, including population characteristics, geographic boundaries, businesses and workplaces that operate at expected times of day, social networks linking individuals, and behaviors that mimic daily experiences [21]. Although simple models also have their advantages, the social interactions simulated in this model, which were realistically constrained by geography, weather, and individual routines, allowed

epidemic patterns to emerge in a way that hadn't been captured by less detailed models. Of course, including this level of detail required empirical information to parameterize individual behaviors as well as geographic and other environmental features; however, detailed data sources are available, including synthetic populations and the General Social Survey and Environmental Protection Agency Time Usage Survey, and geographic information systems (GIS) data can be incorporated into systems science programs as a matter of routine [22, 21, 23]. The models by Yang et al. and Cerdá et al. reflect a more modest reliance on empiric data, with populations simulated to represent a particular city and agent behaviors based on available data but without quite the level of detail and fine-tuned daily experiences of Lee et al.'s model (2008) [6, 13, 21]. Importantly, however, interactions between individuals were still of central importance to individual behaviors in these models, with interactions constrained by the spatial environment (e.g., walking behaviors were influenced by observing others walking in Yang et al. and violence exposures were determined by spatial contact between victims and perpetrators in Cerdá et al. [6, 13]).

McClure et al.'s land-use model and Cerdá et al.'s model of violence best demonstrate the utility of systems science approaches in considering unintended consequences, as well as opposing outcomes of health policies and interventions [20, 13]. By explicitly including both positive (increased active transport) and negative (increased transport injuries and fatalities) potential effects of land-use and transport policies, McClure et al. were able to assess the overall benefits of different policies for population health [20]. By considering both overall levels of violent victimization as well as racial/ethnic inequalities in violence, Cerdá et al. recognized that experimental manipulations of neighborhood collective efficacy were not able to reduce inequalities in violence when residential segregation was high, even though overall levels of violence declined [13]. These examples highlight the importance of considering multiple outcomes in systems science models in order to detect any unintended consequences or areas not benefitting from public health efforts and thus identify optimal policies to maximize population health.

All four models demonstrate the usefulness of observing model results under a variety of scenarios. In Yang et al., four different spatial patterns of safety and land use were generated, reflecting combinations of non-household locations clustered in the center of the spatial environment vs. randomly spatially distributed, and lower safety levels in the center of the spatial environment vs. random safety levels throughout the environment [6]. These alternate scenarios had important implications for socioeconomic disparities in walking behaviors under the assumption that lower SES individuals tend to live in the city center [6]. Similarly, in their study of the effects of alternate transport policies, McClure and colleagues applied their model to representations of six major cities: London,

Copenhagen, Beijing, Delhi, New York, and Melbourne [20]. This approach acknowledged that different settings are starting with different distributions of land use, road infrastructure, and risks of traffic injuries and thus stand to benefit from land-use and transport policies in different ways. Lee et al. examined patterns of influenza incidence assuming different levels of population immunity, different transmission rates, and different incubation and contagious periods, in order to characterize the full range of potential public health consequences of plausible influenza epidemics [21]. Cerdá et al. contrasted two extreme scenarios of racial and economic segregation to show that inequalities in violent victimization persist despite effective violence prevention interventions because, in unequal societies, the benefits of population health interventions accrue to those with more resources [13]. Being able to repeat experimental scenarios under alternate environmental conditions is a major strength of systems science models with the potential for important insight into fundamental causes of health and appropriate targets of interventions.

Finally, the authors of all four models were transparent about the assumptions and limitations underlying their approaches and were careful to caution against using model results as predictions of quantifiable reductions or improvements to be expected, a caution that has been repeated by many public health researchers using these approaches [2, 17]. Rather than replacing real-world evaluations of interventions, these models are meant to serve as a sort of "virtual laboratory," enabling a better understanding of the system as a whole, including the relations between different aspects of the environment that may be disturbed through interventions, and thus the potential system-wide implications of those disturbances [21, 2].

3. CONCLUSIONS

As discussed throughout this chapter, a variety of mechanisms link environmental features to health outcomes and behaviors, both directly and indirectly. Systems science approaches that incorporate dynamic relations between the physical and social environment in producing and modifying health-related risks, behaviors, and resources hold great promise for advancing our understanding of the many environmental influences on population health. Although systems science models have numerous limitations and require strong assumptions, by following best practices, they allow testing of alternate intervention strategies for improving health, including consideration of how environmental features may impede or facilitate intervention effectiveness. Using these systems science approaches in concert with other research strategies represents an integrated approach that can be applied to a variety of population health problems.

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14

Systems of Behavior and Population Health

MARK G. ORR, KATHRYN ZIEMER, AND DANIEL CHEN

1. INTRODUCTION

The purpose of this chapter is to bring meaning to the idea of systems of behavior in the context of population health. Systems of behavior are the mental apparatus (thoughts, beliefs, memory, emotion, motivation, etc.) that drive behavior. The emphasis on systems is decisive because it bounds the nature of explanations, mechanisms, and factors under consideration to dynamic processing models of behavior. Furthermore, we consider systems of behavior in the service of systems of populations, a topic that is rarely covered within either population health or the behavioral and neural sciences. Thus, ultimately, this chapter aims to provoke thinking about how to embed systems in systems, where behavior is nested within populations.

One approach to building systems of behavior might be to co-opt the mental apparatus from related fields such as behavioral medicine, health behavior, and health education—fields that have adopted theories of behavior to drive intervention and prevention approaches. However, this is not fully satisfactory because the theoretical approaches are less oriented toward a systems approach of behavior (we will describe what we mean by systems of behavior in detail below) than toward serving as frameworks for choosing measures of interest (for intervention) and capturing risk factors (for study). In a similar way, the addiction literature is limited in what it offers for building systems of behavior.

In what follows, we start with defining what we mean by systems of behavior and put forth a set of minimal criteria to help define it. Our approach reflects our training in cognitive science, a field that has specialized in building systems of

human behavior since the 1950s [1], and is thus ultimately constrained by what is known about humans (as opposed to any computation that solves a particular task). Then we provide an example from our recent work of a systems model of health behavior along with a critique of the model and some preliminary attempts to embed this system into a system of a population. Finally, we provide some thoughts and suggestions on the practicalities of embedding behavioral systems within population systems, thus addressing to some extent how to move forward.

We cannot emphasize strongly enough that what is presented below is about systems of populations, not developing systems of behavior for the purpose of informing intervention or prevention needs at the level of the individual. We will save the latter topic, an important one, for another discussion.

2. SYSTEMS OF BEHAVIOR

Figure 14.1 is a schematic of a well-known and influential system of behavior—a model of an individual human's memory—whereby the circles represent mental constructs and the solid lines represent interactions among them [2]. Underlying this schematic is a set of detailed, formal assumptions, some capturing learning and some dictating the processing of information—all of which were implemented in a computer program. The conceptual development of this model was in response to a large body of experimental evidence on the nature of human memory. Equally important, the criteria for judging confidence in the model was determined by virtue of the matching between experimental data and data generated by the model during simulations. The similarities to agent-based modeling are obvious; the differences are only of scale—the interacting parts are mental constructs in place of people.

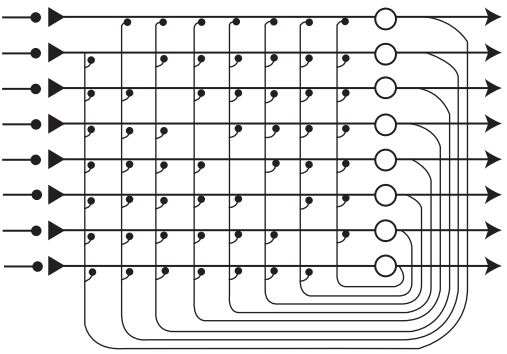

Figure 14.1 A classic system of behavior (from [2]; adapted with permission). See the text for a description of its components and operations.

We will not venture to rigorously define what is and is not a system of behavior but will instead explore three broad classes of criteria for gauging the extent to which a model of behavior represents a system. Table 14.1 describes these classes in detail. Operations is a class referring to the parts of a system: how they interact internally, the potential interactions external to the system, and how the system adapts over time via learning mechanisms. Variation captures the notion of differences in behavior across implementations of the system as a function of values of the parameters that define the operations of the system. A simple example would be the speed at which new information is learned—the operation of learning is not changed, just its rate. Development focuses on how the model was conceptualized, how it is compared to empirical findings, and the degree to which the system is implemented in a usable computational formalism. Ideally, this last criterion satisfies the need for embedding the system of behavior into a system of the population.

An issue that is not represented in Table 14.1 is how to define what counts as behavior. For the purposes of this discussion, overt behavior is not required for a

Table 14.1. Criteria for Qualifying as a System of Behavior

Criterion	**Description**	**Class**
Process-Oriented/ Mechanistic	Postulates mental constructs and their interactions	Operations
Dynamic	Representation of change over time and, potentially, interfaces dynamically with social contexts and environment	
Learning	Aspects of the model can change permanently over time	
Individual Differences	Has the capacity to represents systematic and theoretically important variation in behavior across individuals	Variation
Theoretical Grounding	Processes and constructs are grounded and constrained by neuroscientific, psychological, or behavior economic theory	Development
Empirical Grounding	Proper comparison to empirical (most likely experimental) data to include testing of novel predictions. Ideally, a wide variety of experimental conditions would be considered	
Computational Implementation	A formal model of the operations and drivers of variation that also represents its theoretical basis in a way that is empirically comparable to human experiment and observation	

model of behavior (e.g., picking up a cup of coffee). Thoughts and other mental processes alone qualify as behavior (e.g., recognizing that one wants coffee and planning to get it are both behaviors).

3. A SYSTEM OF HEALTH BEHAVIOR

We now show a system of health behavior—derived from some of our recent work [3, 4]—based on a well-understood formalism used extensively in cognitive science called "artificial neural networks" (henceforth "neural networks"). This formalism has been used repeatedly to represent important perceptual, cognitive, and social phenomena (see [5] for a review; [6] for more recent work). The import for population health is the natural analogy between the socio-cognitive aspects of health behavior (e.g., beliefs, attitudes, intention, and social learning) and the kinds of mental processes that neural networks are good at representing (see [7] for a review). Specifically, neural networks are able to capture social processes that can be conceptualized as a dynamic human memory process, both taking into account what has been learned from past experience and the potential for more immediate influences such as current social and environmental contexts [2, 8–10].

It is precisely these features that make neural networks useful for modeling health behavior—to capture the simultaneous influence of prior learning from past social contexts and the more current (or immediate) social context. For illustration, Figure 14.2 shows one of our systems models of the Theory of Reasoned Action [11] using the neural network formalization [4]. This model conceptualizes intention toward a behavior as driven by a dynamic, on-the-fly memory process called "constraint satisfaction"—the set of beliefs, cued by the social context external to the model, become activated, and then the system settles into a state (the intention state in this case) that has maximized how well it has satisfied the many constraints in the model. The constraints are the positive and negative relations between beliefs that encode belief structures from past experience via learning (e.g., exposure to peers' beliefs over the past year).

The constraint satisfaction process used in the model is a hill-climbing algorithm. That is, the final state of the model, once cued by a social context, is the end path of a trajectory on a goodness surface that seeks increased goodness (larger goodness means more constraints were satisfied). Figure 14.3 is an idealized representation of the goodness surfaces for two instantiations of the model (given a cue from the social context). Panel A suggests that the model will settle in a separate state compared to Panel B (the highest point on the goodness surface is the settling point).

The differences between the two panels in Figure 14.3 represent three distinct scenarios: (1) the difference between two people given an identical social

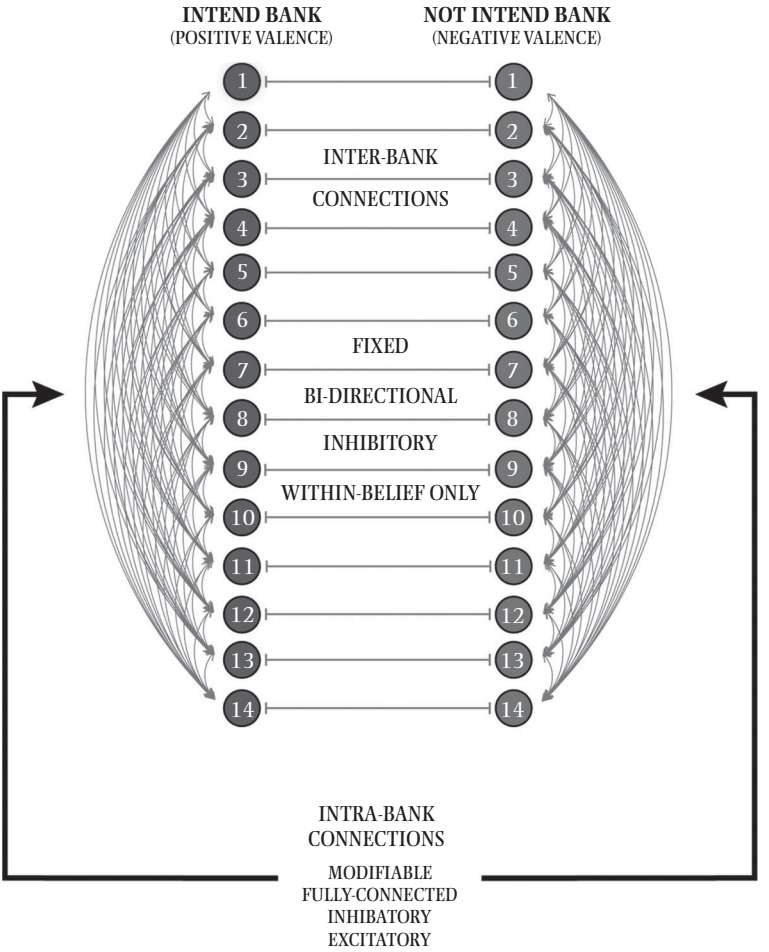

Figure 14.2 A schematic of an artificial-neural network implementation of the Theory of Reasoned Action [11] (borrowed from [4]; adapted with permission). Each belief is constructed from two processing units, one of which represents positive valence and the other negative valence (see the numbered circles; number indexes the belief). Within bank constraints (shown as curved arrows on the left and right of the belief units) capture the relations among beliefs and are modifiable via learning. Between bank constraints are fixed and represent the theoretical construct that beliefs are unidimensional, and thus valence units should be mutually inhibitory. The operation of the model proceeds from an exposure to beliefs in its external social context and results in a stable intention state via a constraint satisfaction process.

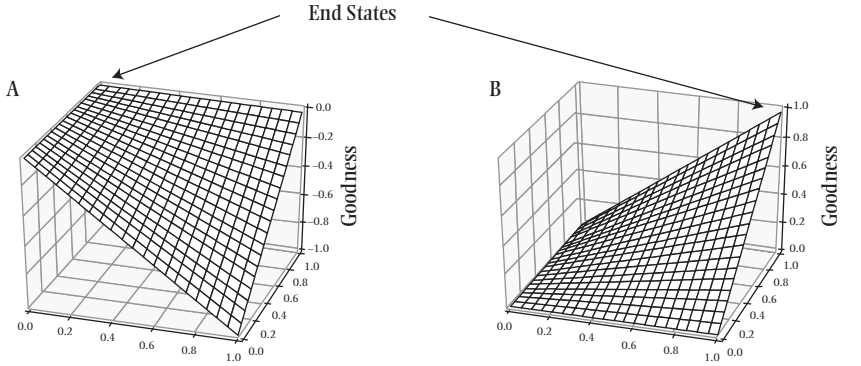

Figure 14.3 A stylized goodness surface across possible states of a hypothesized neural network that uses constraint satisfaction as a settling mechanism. The x- and y-axes represent the full range of values for two units in the neural network (the full goodness surface for the model in Figure 2 is 28 dimensions, one per network node). See text for interpretation and comparison of Panels A & B and for additional details.

context, where the differences are driven by variable social histories or different past exposures to social context features, or (2) the difference between two social contexts for the same person, or (3) the same context, the same person, but before and after the model had significant time to learn from past contexts. In short, end states, driven by hill climbing, vary because of learning (changes in the constraints) or differences in current social context.

Our prior work with this model, some of it using human data, illustrated the following via a series of simulations: (1) its predictive power with respect to intentions toward behavior and (2) a formalization that accounts, simultaneously, for both past experience via learning and a person's more immediate social contexts [3, 4].

How does this example model fair against the criteria presented in Table 14.1? Is it a system of behavior? The operations of the model are clearly mechanistic (beliefs and their attendant constraints serve as the mental constructs and their interactions), dynamic (through the constraint satisfaction process), and enable learning over time from exposure to social contexts. Although variation in the model across individuals was not explicitly explored to date, it is something that the model could easily afford. For example, the rate of learning in the system (slower, faster) and the degree to which positive and negative valences inhibit one another (see [12, 13] regarding ambivalence in attitudes) might serve as explanations of variation across individuals. Finally, the development of the model was grounded in the Theory of Reasoned Action [11] (a highly influential theory both in health behavior and in social psychology), was tested against empirical data, and was formalized using a well-understood computational formalism. Thus, all of the criteria in Table 14.1 were met.

4. SYSTEMS OF BEHAVIOR IN A SYSTEM OF A POPULATION

A fundamental goal for population health is to have a clear understanding of the relation between models of individuals and models of populations, both in the service of scientific understanding and intervention/prevention needs. Under the i.i.d. (independent and identically distributed) assumption, statistical models offer an appropriate realization of this goal, especially when data are longitudinal in nature. Multilevel hierarchical modeling can accommodate non–i.i.d. conditions within a statistical framework but do not capture bi-directional feedback across levels of a system. Agent-based modeling addresses the question of bi-directional feedback in a flexible dynamic way, but has yet to incorporate systems of behavior, instead relying on extra-simple assumptions regarding individuals' behavior [14–17]. Little, if any, work approaches this goal in the context of systems of behavior.

Next, we will present new preliminary work of our own that begins to explore questions about the relation between individuals and populations using a systems of behavior approach. Specifically, we address the following question: to what degree do the parameters of a model of intention within individuals affect the diffusion of intention across a population? This question aligns with work over the past decade on the diffusion of health behaviors on social networks [18–25] in that it is primarily concerned with diffusion dynamics of behavior. The difference lies in how the individual is represented.

Using our newly developed modeling platform called MANN (Multi-Agent Neural Networks, see https://github.com/chendaniely/multi-agent-neural-network accessed 3/25/16) we explored the diffusion of intention toward a behavior on a social network as a function of two parameters related to how intention operates within the individual. That is, over a large set of simulations, we varied the parameters of a neural network representing the Theory of Reasoned Action [11] while fixing the social network parameters, thus providing an experimental test, in-silico, of whether variation in the neural network parameters affected the diffusion dynamics of intention on the social network.

Specifically, the parameterization of the neural network focused on two competing aspects, illustrated in Figure 14.2, that are dictated by the nature of the constraints built into the model. The within-bank constraints represent the degree of excitation within intention units (or not intention units) such that as these constraints become stronger in magnitude, the likelihood is increased that a small degree of activation within each bank will lead to amplification within the same bank. The between-bank constraints are similar but inverse, so as these increase in magnitude, each bank inhibits more the degree to which the other

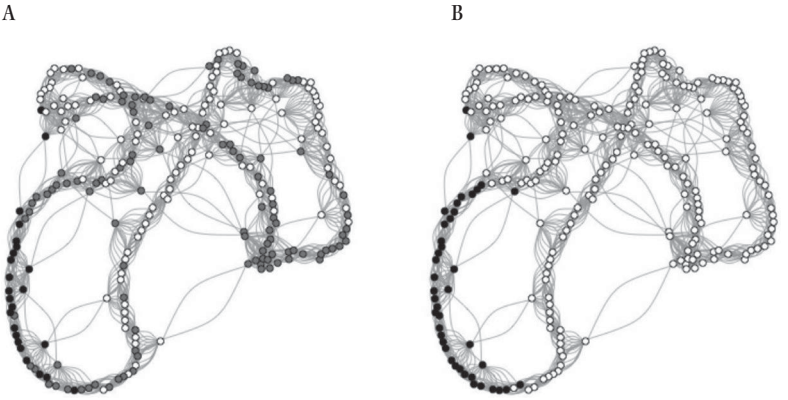

Figure 14.4 Example of the time course of the diffusion of intention on a small-world graph with 250 vertices. Each vertex represents a recurrent neural network instantiation of the Theory of Reasoned Action [11]. The black vertices represent a state of not intending, the white intending, and the gray, ambivalent. Panels A & B illustrate the state of the network early and late in the diffusion process, respectively.

bank will become activated. Both of these constraints are reflected in the hill-climbing procedure that is described above and illustrated in Figure 14.3.

A single simulation consisted of instantiating a small world network (specified in [26]; our parameter values for the social network were 250 vertices, 10 nearest neighbors and a 0.02 probability of rewiring per each network edge, using bidirectional edges) in which each vertex was represented as a neural network (similar to Figure 14.2) that had the within-bank and between-bank constraints set to a value dictated by the experimental design (described below). A simulation was initialized so that all vertices were identical in terms of the value of the within and between bank constraints (with some purposeful random noise added). After initialization, five of the vertices were exposed randomly to one of three social contexts (high intention, high not intend, or ambivalence). Then, the simulation ran for 100 time steps. During each time step all vertices were updated in a random sequential order. A vertex was updated by using one of its neighbors' last intention states, a portion of which was directly accessible to the updating vertex and thus served as a constraint on the updating vertex. In this way, intention states had the chance to propagate through the social network. Figure 14.4 compares an early to later state of a single simulation.

Figure 14.5, a heat map, presents the full results of the simulations across the neural network parameter space (there were 25 levels of the between bank constraints and 31 levels of the within-bank constraints totaling 775 points in parameter space). Each cell in the heat map, representing one point in parameter space, is the average over approximately 10 simulations. (Figure 14.5, thus, captures

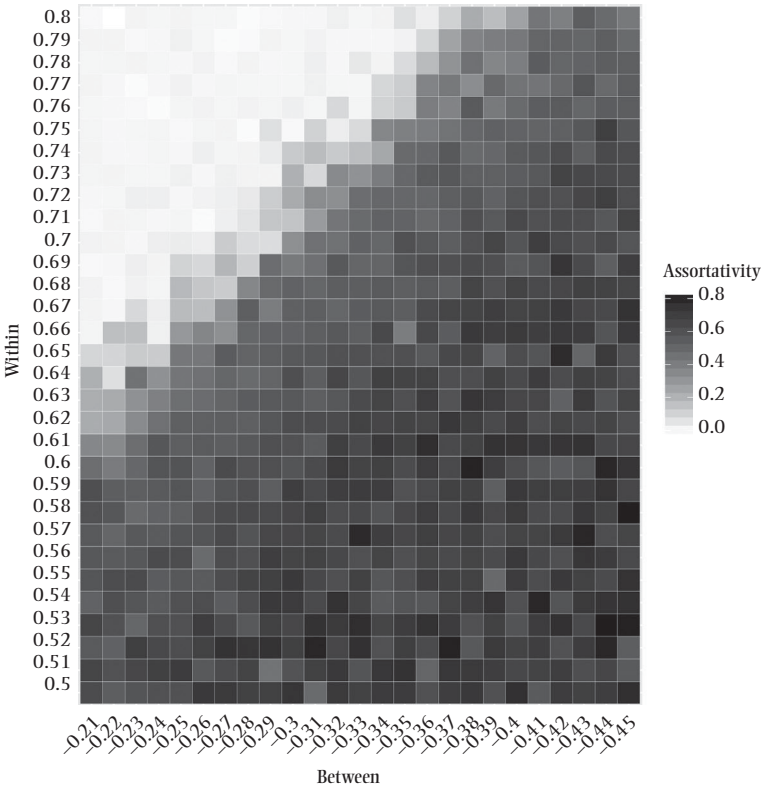

Figure 14.5 A heat map representing 7750 diffusion of intention simulations (Figure 4 represents one of these). The axes represent two parameters of the recurrent neural network instantiation of the Theory of Reasoned Action [11]. The value of each cell in the heat map represents the average network assortativity (on the small-world graph) on intention of approximately 10 simulations for one point in the parameter space. See text for further details.

approximately 7750 simulations.) The metric represented in Figure 14.5 is the average amount of assortativity with respect to intention state at the final time step (t = 100) of each simulation. That is, roughly, it captures how much clustering of intention is present on the social network at the end of the simulation. As a point of reference, Figure 14.4, Panel B shows a high degree of clustering on intention.

The pattern shown in Figure 14.5 suggests that, although there are two regions of the parameter space in which changes in the neural network parameters have little consequence, the two regions are very distinct—one exhibits a large degree of assortativity with respect to the intention state; the other does not. This type of phase transition is characteristic of complex systems.

In sum, by constructing a simulation environment in which systems of behavior were nested within a population, we illustrated, experimentally, that the

parameters of the system of behavior affected the population dynamics, even when holding the social network parameters constant.

5. LOOKING FORWARD

Thus far we have (1) suggested criteria for a system of behavior, coming largely from work in cognitive science and computational psychology (see Table 14.1), and (2) provided an example of a system of health behavior and a glimpse of what insights might be gleaned when implementing said system into a system of a population. We will now focus on some core issues to consider as we move forward with further development of the systems of behavior approach in the domain of population health.

The most basic consideration is to recognize the conditions under which a system of behavior model is desirable, while appreciating that much work using systems science has yielded useful insights into population health phenomena without implementing systems of behavior [15–18, 27]. In some cases, the research question itself will require a systems of behavior approach, like the work shown above in which we explored the effect of variation in the parameters of a system of behavior on the diffusion dynamics in a population. Beyond such obvious cases, however, the need for a systems of behavior model will be less clear.

One unmistakable situation in which systems of behavior will be desirable is when intervention/prevention levers under question implicate a set of complex mental processes such as those described in Table 14.1 (e.g., changes in dietary habits). By implementing a system of behavior in a model of a population, the insights will be in terms of the actual mental processes that should be targeted in order to see changes in the population. To date, however, there is a dearth of work, if any, that addresses interventions using a system of behavior (as outlined in Table 14.1) embedded in a system of a population. Although Figure 14.5 represents this notion directly, it is only in the abstract as proof-of-concept.

Another core consideration is feasibility. Although there exist many systems of behavior already in computational form, covering many aspects of human behavior [28], it is uncertain to what extent these are directly applicable to population health needs. To gauge this will require both exploration of existing models and, most likely, extension of existing theory (computational or not) to include processes that are yet postulated but relevant for population health. Consider the system of behavior for the Theory of Reasoned Action [11] presented in Figure 14.2. We co-opted a general model used for attitude formation and reconceptualized the Theory of Reasoned Action to fit. In the process, we extended the Theory of Reasoned Action by implementing

additional mechanisms (e.g., how beliefs of one person are communicated to another, learning, and constraint satisfaction), none of which were empirically grounded. Only now are we in the process of developing social experiments to provide empirical grounding.

One intriguing idea is to leverage the extensive work on what are called architectures in cognitive science [29–31]. Architectures attempt to capture several core aspects of human behavior that are general across tasks and can account for individual differences. This might serve as a useful approach for understanding difficult issues such as behavioral comorbidity (e.g., smoking and unhealthy diet behavior) and could incorporate a general set of individual difference mechanisms that are directly related to health behaviors (e.g., delayed discounting [32]; self-regulation [33]).

A final consideration is the appreciation that common risk factors (e.g., gender, age, race/ethnicity, geography, socioeconomic status) cannot be represented in a direct way in a system of behavior. It is not that these factors are negligible, only that they are placeholders for the direct processes represented in Table 14.1—e.g., differences in attitudes between two genders/racial ethnic groups can only be explained by the operations and individual difference parameters of a system of attitude formation. A useful heuristic is this: to the extent that a risk factor can be conceptualized in terms of Table 14.1, it can be considered as a system of behavior or a part thereof.

6. CONCLUSION

The main point of this work was to introduce the feasibility of integrating systems of behavior with systems of populations for further understanding, practice, and policy in population health. Paradoxically, this notion is not only foreign to those in population health but also to those who focus on human behavior. In part, the latter group doesn't see the purpose; studying individuals is sufficient. However, it is the former group for whom this chapter is targeted.

In any event, it is clear that much work is to be done in such a novel enterprise. Mostly, this work will require highly interdisciplinary teams, the generation of novel theory for application, and mostly, evidence and buy-in that this effort will, in fact, help to drive improvements in population health. We are hopeful that the work in this chapter begins a fruitful discussion.

7. ACKNOWLEDGMENTS

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15

Systems Under Your Skin

KARINA STANDAHL OLSEN, HEGE BØVELSTAD, AND EILIV LUND

1. INTRODUCTION

Due to the differing focus of medical researchers, the question of what causes a certain disease can receive distinct and diverse answers. For example, when asked what causes cancer, an epidemiologist will focus on exposures to harmful substances or lifestyle factors, but a molecular biologist may focus on mutational processes and alterations of cellular pathways. Even though the methods and explanatory models may differ, both epidemiologists and molecular biologists are searching for causes of disease. Hence, they are conceptually, albeit not methodologically, related. In a systems medicine approach, this relatedness becomes clear—and it holds promise of greater insights into disease processes at many levels [1].

The research field of molecular epidemiology evolved in the 1980s as an attempt to combine epidemiology and molecular biology. In 1982 Perera and Weinstein described molecular epidemiology as "the use of advanced laboratory methods in combination with analytic epidemiology to identify at the biochemical or molecular level, specific factors that play a role in human disease causation" [2]. With these advances, the traditional epidemiologist had to look inside "the black box," and the molecular biologists had to look outside of the box. During the 1970s, 1980s, and 1990s, the topic of "genes versus environment," or nature versus nurture, was heavily debated by geneticists, biologists, psychologists, and social scientists, but it is only recently that technologies have been developed to enable explorative investigations of molecular mechanisms of disease in an epidemiological scale and framework. The revolution of molecular

epidemiology came with the sequencing of the human genome published in 2001 [3, 4], and the concurrent development of –omics technologies for the efficient study of the total genome and other –omes like the transcriptome, metabolome, proteome, etc. Technology paved the way for new study designs searching for associations between genetic variability and diseases at the population level, the genome-wide association studies (GWAS). In some cases, this new approach resulted in great insight and identified potential for public health benefits: DNA from the human papilloma virus was found in virtually all cervical cancers, and certain variants of the BRCA genes lead to highly increased risk of breast cancer. However, findings of such magnitude have been rare: there are very few genes with big effects [5].

This chapter will discuss, with some brief historical background, how –omics analyses in population research help to bring us closer to a more functional view of causal associations and how systems science is an essential tool in our armamentarium toward this understanding. We will discuss some prerequisites of this new emerging field: aspects of study design, human sample material, data analysis, and biological interpretation of –omics data in population research. In conclusion, we discuss challenges for the future and emerging directions in the field.

2. CAUSALITY IN EPIDEMIOLOGY

The epidemiological research tradition studies statistical associations between lifestyle factors and disease and aims to identify causal associations in the face of any confounding factors. Originally, studies were based on questionnaires to gain information about exposures, and diagnostic information about outcomes, diseases, or deaths. To improve the precision of the exposure estimates, biological tissue like blood began to be collected to allow measurements of biomarkers: biochemical substances that reflect either the exposure itself, or a biological/biochemical event during absorption, metabolism, or interaction with target tissues [6]. In addition to improved exposure information, more detailed classification of diseases using molecular markers enables stratified analyses in molecular subgroups and revelations of previously un-detectable differences of statistical associations.

Even though the use of biomarkers improves assessment of exposures, and new technology enables more detailed classification of disease, the statistical analyses of associations between exposure and disease have been straightforward, using well-known statistical methods. A set of nine guidelines published by Bradford Hill in 1965 is the most frequently used tool to evaluate the causality of statistical associations between exposures and outcomes in epidemiological studies [7]. Briefly, the guidelines address nine aspects, known collectively as

"Hill's criteria of causality": strength of the association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experiment, and analogy. At the time of Hill's publication, the biological mechanisms of many diseases were unknown: this was only 12 years after the description of the DNA double-helix, and 35 years before the sequencing of the human genome [8]. Among Hill's criteria is that of biological plausibility, which refers to the use of existing knowledge of biological mechanisms to lend strength to a statistical association between exposure and outcome. At any given time, this criterion thus rests on the current state of knowledge. It follows from this that as long as the current knowledge of disease mechanisms is derived mainly from cell line or animal studies, the true causal mechanisms that are at play in humans may remain obscure. It is increasingly evident that mice studies have limited transferability to human conditions and that they fail to capture the complexity of human disease etiologies and mechanisms [9, 10]. Systems medicine holds the promise of improving causal thinking by adding mechanistic information derived from human studies to the statistical associations found in epidemiological studies. Ultimately, advances in the field may enable disease models based on human observational data.

3. THE –OMICS IN POPULATION RESEARCH: TOWARD FUNCTIONAL UNDERSTANDING AND SYSTEMS MEDICINE

The first applications of –omics studies at the population level were the GWAS, large-scale studies searching for gene variants associated with increased risk of diseases. One example is a multicenter study of lung cancer patients and controls that identified two genetic variants (single nucleotide polymorphisms, SNP) associated with increased risk [11]. One of the SNP loci was situated in the gene coding for nicotinic acetylcholine receptor subunit 5, a gene that binds nicotine and nicotine derivatives. The finding raised the question of how the genetic variant affected the biological mechanisms that led to increased disease risk. However, this type of static genetic data is only marginally helpful in elucidating functional chains of events. On the other hand, –omics data like DNA methylation and gene expression provide an opportunity to understand, from a systems dynamics point of view, the functional, dynamic mechanisms that explain the observed phenomena. For example, it has been shown that smoking induces methylation changes in the DNA of blood cells, and that some of these changes remain even 30 years after smoking cessation [12]. The persistent smoking-dependent change is in line with the fact that smoking may still increase lung cancer risk up to 20 years after cessation [13]. Furthermore, DNA methylation changes have now been linked to future lung cancer risk independently of

smoking status [14]. The same study showed that the smoking-induced hypomethylation was significantly inversely correlated with expression levels of the corresponding genes and that these genes were relevant to lung cancer etiology [14]. This illustrates how functional genomics may help to elucidate the causal pathways between exposure and disease.

Importantly, several enabling factors are prerequisites for exploring the functional aspects of disease-related molecular mechanisms that are at play at the population level. The following enabling factors are further discussed below: access to human sample material, adequate study design, preferably with repeated measurements, and advanced data analysis and management.

4. SAMPLE MATERIAL FOR FUNCTIONAL GENOMICS

Two practical and ethical constraints limit the nature of the human sample material that is available to researchers: the tissue of interest may not be easily accessible, and it is not ethically acceptable to impose harm on study participants in order to investigate the molecular chains of events in the etiology of a disease that may be associated with exposure to a harmful substance. As an example, collection of blood samples from healthy individuals in a prospective cohort design is relatively non-invasive and feasible in epidemiological studies, and provides access to analysis of systemic processes [1]. However, adequate sample handling at all stages is paramount to preserving the biological information of interest. In combination with exposure information (questionnaires or biomarkers), functional genomics analysis of human sample material may provide snap shots of etiological disease mechanisms.

5. STUDY DESIGN OPPORTUNITIES

Functional genomics analyses in combination with prospective studies enable more sophisticated study designs and analytical approaches. As an example, the prospective globolomic study design has been developed to describe the systems epidemiology approach to disease causation [1]. The many aspects of this design are illustrated in Figure 15.1. The design incorporates multi-omics data sets collected repeatedly from different tissues of healthy persons and incorporates questionnaire information to enable stratified analyses. In a nested case-control study, a change in status from healthy to diseased enables analyses of functional disease mechanisms that may be present before any clinical manifestation of disease. Knowledge of these mechanisms holds promise of improved disease prevention, early detection of disease, and may provide new targets for treatment.

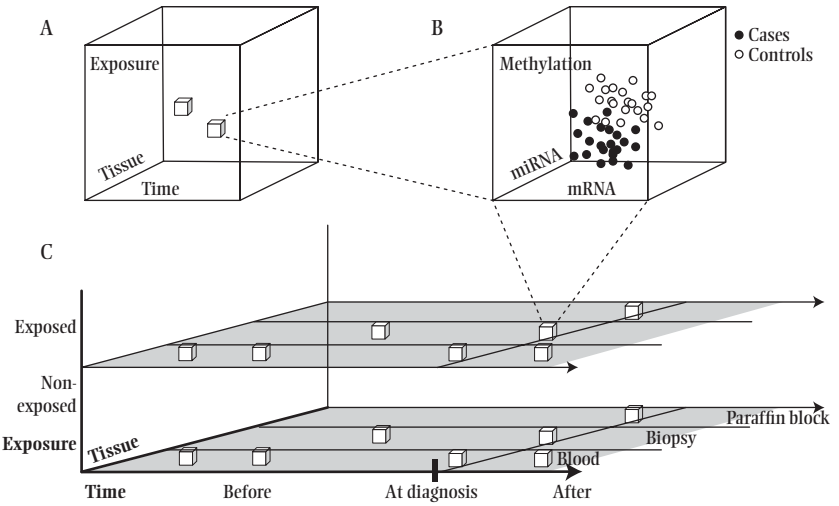

Figure 15.1 The multidimensionality of the globolomic study design. (A) The three dimensions of the study design cube, including time, tissues, and exposures; (B) the three dimensions of the functional genomics data cube, including mRNA, microRNA, methylation; and (C) the combination of the functional genomics cube within the study design cube.

6. DATA ANALYSIS AND INTERPRETATION—THE EXAMPLE OF TRANSCRIPTOMICS

6.1. Differential gene expression analysis

Statistical methods for differential gene expression analysis may be divided into two broad levels: single gene analyses and gene set (or pathway) analyses. However, it must be mentioned that adequate pre-processing of data sets must be carried out to account for possible systematic biases. Pre-processing steps include annotation, data filtering and outlier removal, background adjustment, normalization, adjustment of batch effects, etc. For differential gene expression analysis at the single-gene level, methods based on t-test and linear models are popular. When comparing two groups (e.g., cases versus controls), these methods result in lists of differentially expressed genes and a measure of statistical significance. All such methods require adjustment for multiple testing (e.g., by using the false discovery rate) [15]. Extracting biological meaning from a list of differentially expressed genes may be time consuming and extremely challenging, because a list does not provide any mechanistic insight into the biological processes that may be altered in cases compared to controls. Furthermore, there is a risk of introducing bias in the presentation of results: researchers are likely to

focus on genes and processes that are familiar to them, even though other processes may be more pronounced. The risk of researcher bias contrasts the very nature of transcriptomic analyses: it offers the opportunity to let the results speak for themselves in a non-hypothesis driven approach, whereas relying solely on the researcher's previous knowledge may greatly reduce the degree to which the results are exploited.

6.2. Extracting Biological Information Using Pathway Analysis

To avoid the pitfalls mentioned above, several methods for gene set- or pathway-level analyses have been developed [16]. Their overall aim is to reduce the biological complexity by analyzing genes in groups (gene sets or pathways), thereby reaching a higher explanatory power and reducing researcher bias in the interpretation of results. How the groups of genes are defined will have great impact on the information that such analyses provide. The groups of genes (gene sets) may be any list of genes with some relation to each other. Examples include biological pathways derived from comprehensive databases like KEGG [17] or Gene Ontology [18]. Another example is gene sets (lists of genes) derived from experimental literature. A biological pathway may be characterized as one of the following: (1) a metabolic pathway, which involves the enzyme-catalyzed step-by-step modification of an initial chemical or molecule to form another product; (2) a protein interaction pathway, which describes the interaction of proteins that may work alone or together in large complexes to perform cellular and physiological processes; (3) a gene regulatory pathway, which describes how external cellular stimuli are sensed, then transduced through the cellular interior into the DNA in the cell nucleus, where gene transcription into mRNA takes place; (4) the term signaling pathways, which may describe the same processes as the previous example but might also be used to describe similar pathways that do not lead to the transcription of a gene but to some other cellular alteration. Finally, the term "molecular pathway" is defined as a series of actions among molecules in a cell that leads to a certain end point or cell function (National Cancer institute).

A comprehensive overview of statistical methods to identify significantly differentially expressed pathways is beyond the scope of this chapter, but we will provide an introduction to the main approaches. All methods are based on the general scheme depicted in Figure 15.2 (modified from [19]). The first generation of methods, over-representation analysis [20], starts with a list of differentially expressed genes after running single-gene level analysis to compare cases and controls. Then, the number of differentially expressed genes that are present in each pathway is counted, and finally, that number is compared to what you would expect to find by chance. The first generation methods rely on the

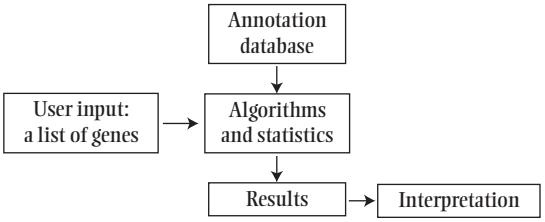

Figure 15.2 General scheme of pathway analysis methods.

assumptions that genes and pathways are independent of each other, which is highly questionable. Furthermore, the significance cutoff value for defining the input list of differentially expressed genes is arbitrary. If you use an FDR threshold of 0.05 and fold change cutoff of 2, all genes with a fold change of 1.95 or FDR 0.051 will be disregarded. These genes are arguably just as biologically important as the genes just under the arbitrary significance cutoff. Finally, the methods ignore how strongly the genes are associated with the phenotype (case/control status). In spite of these limitations, first generation resources like MSigDB and GenMAPP provide an easily accessible first glimpse of gene set-level insights.

Second generation methods (e.g., Gene Set Enrichment Analysis [21] and Global Test [22]) are based on the hypothesis that weaker but coordinated changes in sets of functionally related genes (i.e., pathways) can also have significant effects [16, 23]. The general approach is to first calculate the differential expression and significance level. Then, for genes in Pathway A, the gene-level statistic is combined using univariate or multivariate approaches. Lastly, the pathway-level significance is assessed. Second generation methods consider the proportion of differentially expressed genes in the pathway, the size of the pathway, and the degree of correlation between genes in the pathway. Also, accessory biochemical measurements or clinical information may be included. An important difference from first generation methods is that all genes are considered, not just the most significant ones.

Methods that consider pathway topology are not easily generalizable, but collectively they may be considered a third generation of gene set-level analysis methods. With these methods, pathways are viewed as graphs and/or networks with nodes (genes) and edges (interactions) [16]. The same main steps as second generation methods may be employed, but the key difference is that information on pathway topology—the type of interaction and position of the gene in the pathway—is combined with the gene expression change in order to compute a gene-level statistic. These are further combined into a pathway-level statistic. A main limitation to these methods is the fact that biological pathways are not static—they are cell-type specific, condition-dependent, and dynamic.

Currently, no database holds comprehensive information regarding the conditional interactions between any two genes. Still untackled by method developers is the fact that not only are genes dependent, but pathways are also mutually dependent on each other.

7. CHALLENGES

Advances in technology for functional genomics analyses, as well as computing and statistics, have allowed researchers to approach the true complexity of human disease etiology. However, numerous challenges remain, often related to design of studies and availability of human sample material. A review of nutrigenomics studies revealed generally small sample sizes, which hinders generalizability of the results and increases the chance of false positive findings [24]. The problem of false positive results can be reduced by increasing the number of participants in each study, by applying a test-retest design, or by using repeated measurements from each individual. Statistical analysis of multi-omics data sets face challenges related to mass significance testing and functional interpretation, and there are few established methods available for analysis of time-dependent changes.

In addition, despite the great progress in the biological interpretation of gene expression data sets, there are also still challenges in the process of extracting meaningful information from –omics data. There is a lack of human-derived *in vivo* data describing gene function dependent on regulatory mechanisms like DNA methylation. Furthermore, comprehensive information on functional effects of splicing variants and SNP variations, as well as information on condition- and tissue-specific mechanisms is scarce. Importantly, modeling dynamic systems remains difficult, and there is not enough information on dependency between multiple molecular pathways.

8. EMERGING DIRECTIONS

Over the last two decades, the introduction of –omics technologies has changed epidemiology. Traditional epidemiology was focused on single-disciplinary interpretation of statistical associations, but now the focus has shifted toward more challenging multidisciplinary approaches to causality. This multidisciplinary work demands a mutual understanding of many research traditions and methods and depends on collaborative efforts. There is a strong momentum to form larger groups or research centers for the exploration of functional genomics as part of systems medicine.

Equally important is the challenge of building new studies with biobanks containing material eligible for functional genomics analyses, with a particular focus

on gene expression or other responsive molecules that are present in both blood and other tissues. The complexity of multilevel analyses is directly transferable to a need for increased size of studies, in order to handle statistical power and enable retest studies.

By using blood samples, results from –omics analyses will provide insight into immunological processes of the body. In recent years, the ubiquitous relevance of these processes has become clearer, and the immune system is no longer regarded only as the body's defense system. Rather, immunological processes are major regulators of homeostasis, and the importance for etiology and causation of chronic diseases is increasingly apparent. For example, in cancer research, the systemic, immunological regulation of cancer progression includes all steps from primary tumor growth to metastasis [25].

This insight is likely to be relevant for many other diseases and highlights the need for prospective, preclinical studies with the collection of high-quality biological material. When available, such studies will provide ample opportunity to investigate and establish causal chains of events, and as such they hold promise of discovering new targets for disease prevention, detection, and treatment.

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16

Frontiers in Health Modeling

NATHANIEL OSGOOD

1. INTRODUCTION

A rapid evolution is taking place in the character of health applications of system science. Much of this change reflects its embedding of such applications within a rapidly changing scientific and technology landscape but also a growing appreciation for how systems science methods fit into the policy and health science milieu and the emergence of practitioners trained in several modeling approaches. While such nascent trends are just starting to exert notable departures from past practice, they seem likely to thoroughly reshape the field in coming decades. In this chapter, we briefly survey six such trends and discuss their implications for health modeling.

2. HYBRID VIGOR: THE RISE OF HYBRID SYSTEMS SCIENCE

Systems science techniques in general—and dynamic modeling techniques in particular—have long been fragmented into distinct and largely independently pursued traditions dating back many decades, with their origins in, and focus on, different types of questions. The community of practitioners in each of these traditions have generally pursued their work with little interaction with—and often little awareness of—the techniques and communities of the other traditions. On occasion, however, practitioners have bridged those communities of practice and advanced models that fall on the boundaries between two different traditions. For example, System Dynamics models have since the inception of the approach been articulated at the level of individual actors (e.g., firms) [1], an approach that has included some of the most widely known such models, such as the Beer

Game [5]. In recent years, this has been expanded to consider the interaction of large numbers of such actors [3, 4]. Methodologists have also advanced research frameworks combining the approaches [52, 2]. However, it has not been until the past decade that adequate support has been available for the interweaving of several system science approaches within a given model [59]. With the resulting awareness of the potential of hybrid modeling, support for hybrid modeling has been incorporated in platforms with their origins in the agent-based modeling [59, 6], System Dynamics [60] and Discrete Event [61] traditions.

2.1. Motivations for Hybrid Modeling

There are a number of distinct motivations for application of hybrid modeling in general, with some of those motivations enjoying particular relevance to the health context. We discuss some of the most compelling here.

2.2. Competitive Advantages

Each type of modeling offers distinct competitive advantages. The most broadly recognized such advantages relate to ease of characterization of certain types of system behavior—for example, the fact that agent-based modeling exhibits pronounced advantages when it comes to capturing agent-agent interactions involving heterogeneous actors, or that Discrete Event Modeling provides an exceptional economy in specification of resource-constrained workflows, or System Dynamics in depicting the dynamics of regulatory systems involving continuous variables. The capacity to weave together formalisms offering differing natural domains of expressiveness permits exploitation of metalinguistic abstraction [8]—the capacity to choose the appropriate language (and associated analytic lens) for particular areas of the system or problem of interest. For example, in a model of chronic disease and health-care processes in a demographically diverse aging population, the representation of agent characteristics and the natural history of disease for various comorbid conditions could be expressed using agent-based modeling, while progression of such agents through various primary and specialist care pathways could be best captured using Discrete Event Modeling. It bears emphasizing that such advantages are not reflective of inherent capacity. Each such modeling technique is computationally universal, meaning that models built with each such tradition could in principle be represented into the other traditions. However, it will often be far more economical, transparent, and convenient to represent such logic in one particular domain.

A second area of comparative advantage relates to ease of stakeholder understanding for and appreciation of modeling using different approaches. For

example, clinicians often find it far easier to relate to a depiction of a system at an individual level. Those involved in health service delivery may find a representation that offers a visualization and supports ready reporting of resource use far more important for enhancing confidence in a model. By contrast, demographers can often find an aggregate-level representation of a system familiar and intuitive. When we seek to build models that actually get used and are persuasive to decision makers, such stakeholder-centric considerations can be important for the success of a project.

Like the second, the third area of competitive advantage is pragmatic: computational burden and latency. Models built in the different modeling traditions covered in this volume—and particularly individual-based models when compared to aggregate models—can exhibit profoundly different levels of computational effort to simulation. While heavier computational burdens can currently take exploration with certain types of models (e.g., those with large synthetic populations) out of the hands of many researchers, this problem is decreasing with the advent of cloud-based computational engines. However, what is likely to remain a major differentiator in future years is the latency associated with the latency of model operation—the time between starting a model run and when practically useful results are at hand. Although techniques such as large-scale parallel computation and preexecution of model scenarios are likely to ameliorate this significantly, such latency is likely to remain far higher for complex individual-based models with larger populations for at least a decade. This difference in latency imposes, in turn, a considerable opportunity cost, particularly in terms of shortchanging the prospects for learning through interactive exploration of model behavior.

2.3. Flexibility in Response to Model-Based Learning

The effects of the competitive advantages are enhanced by a second fundamental motivation for use of hybrid approaches: the flexibility they provide to nimbly evolve the model design and level of detail captured in response to learning during the modeling process. Specifically, hybrid modeling provides the capacity to reshape which sections of the model are captured using what modeling approach. This advantage reflects the status of models as "learning tools," as living artifacts that help make a team's learning faster, deeper, and more robust and evolve in response to that learning. As modeling continues, sensitivity analyses, observations of inconsistencies between model results and empirical data, demonstration of model results to stakeholders, and other experiences coming through simulation-based model exploration commonly identify needs for refining areas of the model. Often these recognized needs

involve elaboration or disaggregation of areas of the model—for example, adding representation of social support networks, changing the model to consider educational level or to distinguish rural vs. suburban vs. urban contexts, incorporation of resource dependencies in a health-care process, etc. As a result of these changes, an area of the model that was originally couched using one modeling approach may benefit from respecification using an alternate approach. When a modeler is using a software platform supporting just a single type of simulation formalism, the need to undertake such changes would typically entail an entire rewrite of the model in a new formalism—and a correspondingly different modeling package. Even in those comparatively rare cases where available skill sets make such a rewrite feasible, it is nevertheless likely to impose a high opportunity cost. By contrast, in the context of hybrid modeling, such a change can be supported by simply altering the boundaries between regions of the model that employ different approaches. Because of the central value attached to learning in many modeling projects, this flexibility to change direction confers great value.

2.4. Additional Motivations for Hybrid Modeling

Two other motivations for hybrid modeling include the capacity to subject certain areas of the model to methodology-specific analyses (such as the analysis of the location and stability of long-term equilibria possible with System Dynamics models) and the capacity to employ multiscale models. In the context of hybrid modeling, the latter involves the potential for articulating behavior at different scales using different modeling approaches.

2.5. Hybrid Modeling Patterns

While a previous contribution has enumerated a large and combinatorial array of different hybrid modeling schemes with applications across them that span diverse domains [44], our health modeling applications work has identified specific hybrid schemes that offer particularly compelling value in the arena of health and health care. One example is an agent-based population interacting with a discrete event simulation-based service network, in which individual agents representing persons evolve in the population and seek care from resource-limited service facilities represented using Discrete Event Simulation (Figure 16.1, drawn from [12, 54]). In the individuated focal population [ABM] in a broader aggregate population [SD] pattern, System Dynamics is used to provide a coarse view of an aggregate upstream population (often the lion's share of the population), while agent-based modeling provides a "zoomed in" view of

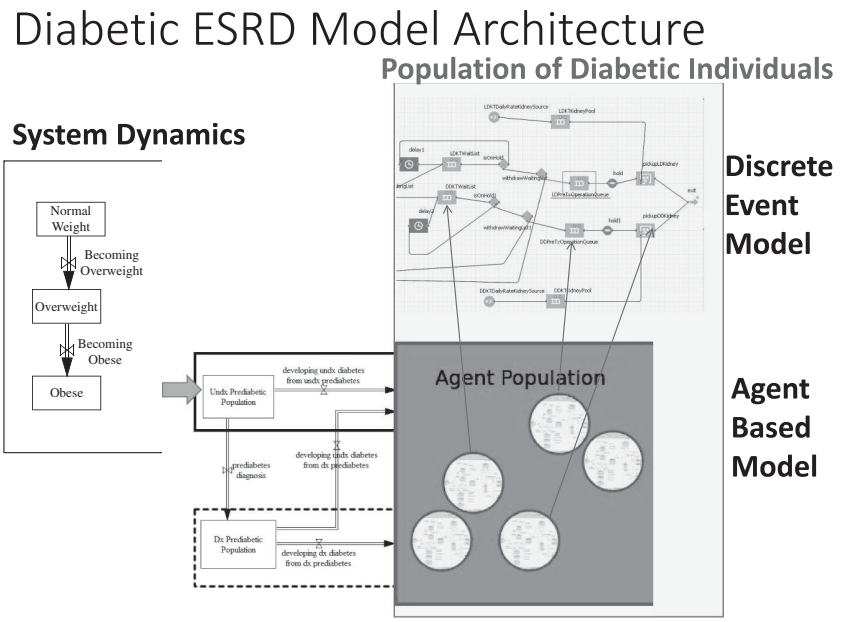

Figure 16.1 A hybrid model incorporating three modeling schemes: agents presenting in a discrete-event process, and a population in an aggregate system dynamics model individuating into agents at a point in the risk continuum.

those of greatest interest—high-risk and potentially at-risk subpopulations for which the model captures agent trajectories, aspects of agent spatial and network context, pronounced agent heterogeneity (including dynamic elements, such as progression of co-morbidities), rich individual decision making, and targeted interventions [12]. The System Dynamics driven agent evolution patterns offers a very different means of combining System Dynamics and agent-based modeling; System Dynamics is used within agents to capture aspects of continuous health dynamics and regulatory feedbacks [52, 53]. Agents [ABM] driving or driven by aggregate System Dynamics allows agents to drive, or be driven by, high-level continuous dynamics characterized using System Dynamics [31]. In many cases, such higher-level dynamics consist of agent-driven flows and accumulations, such as QALYs, costs, sizes of environmental pathogen reservoirs, emissions and levels of atmospheric carbon dioxide, etc. These combinations support highly flexible, powerful, and responsive models, and seem likely to become a mainstay of modeling in coming years, With several modeling packages now offering support for hybrid modeling, the greatest barrier to the use of hybrid models is likely to be the requisite understanding of several different modeling approaches.

3. AGILE MODELING FOR LEARNING ACROSS TEAMS AND COMMUNITIES

A second major modeling trend is a reflection less of the technical artifacts delivered by a modeling endeavor than of the modeling processes and practices. For many modelers, the goal is not only to build a useful model but also to see that model be put into actual use—in shaping policy, in informing understanding of and learning from incoming epidemiological data on the part of stakeholders, in shaping intervention implementation and scale-up plans, thinking through care system redesign, prioritizing data collection, and operational decision making. A central factor in determining the degree to which models get used in practice is the degree to and capacity in which modeling projects engage stakeholders. A discussion of the issue of stakeholder engagement in modeling projects looking forward bears consideration of some historic context. From the perspective of modeler-end user interaction, it is broadly fair to view dynamic modeling as having witnessed two historic eras, with a third era just starting to emerge. In the first era ("Bring us your problem, and we'll tell you what decision is best") [13], modeling projects were overwhelmingly conducted inside academic or specialist organizations, with the primary deliverable to the knowledge users being findings from model explorations conducted by such specialists. Elements of that first era of modeling remain widespread, but increasingly it was replaced by a second era in which models are commonly delivered to the knowledge users and stakeholder team for use—but often in a fairly "black box" fashion. Within this context, the team of stakeholders may interact with the model (for example, through a web-based or desktop interface), but only for prespecified scenarios, and only by viewing certain tightly circumscribed outputs. More importantly, within this second era of modeling, the internals of that model, including the assumptions made, typically remain opaque to end users, and cannot be modified by them. Even in those cases in which the modeler is embedded within the end user team, requests to evolve the model—even for modest changes to the assumptions, or to add certain outputs or new types of scenarios—must be referred to the modeler(s). The inaccessibility of the model to the end users and the bottleneck around the modeler not only inhibit the speed of model evolution but also leave that evolution and those model assumptions notably vulnerable to misunderstandings. More critically, the model opacity and bottleneck around the modeler slows down the learning process and the speed of iteration toward improved understanding.

A combination of factors—evolution of modeling technologies to include more transparent and declarative model specifications (Figure 16.2), participatory modeling efforts, understanding of contemporary software development best practices and processes—are beginning to reshape how modeling is pursued

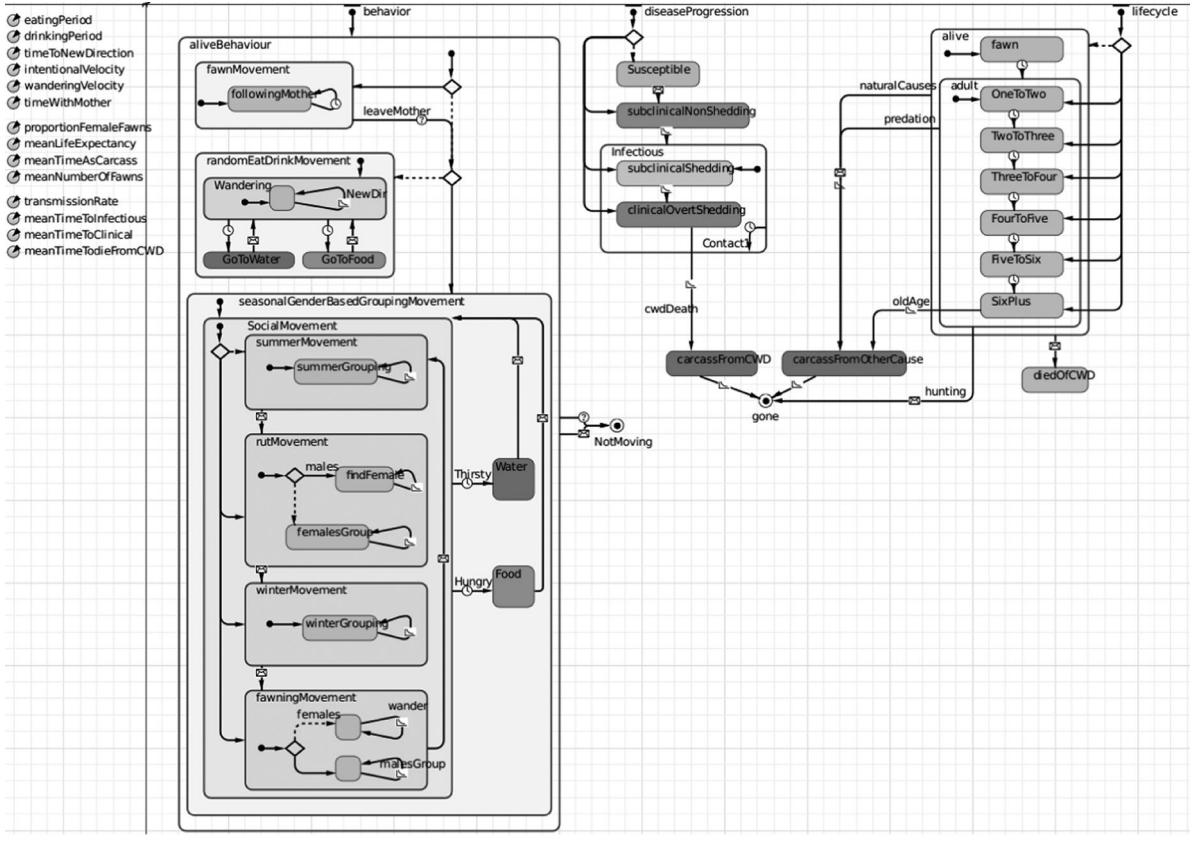

Figure 16.2 Example of a visual declarative modeling language used in agent-based modeling.

and to usher in a third modeling era. In this emerging era of "Agile Modeling," such modeling is increasingly embedded within interdisciplinary teams. Although modeling experts are still required, modeling is no longer purely the domain of such experts; models within such Agile Modeling contexts are designed in a fashion to be broadly accessible across team members. This environment supports team members in being able to proactively inspect—and thereby critique—the assumptions of a model, locally modify those assumptions, run the model, and increasingly to supplement previously defined model outputs with those of their own devising. Such broader access to the model will support faster model evolution and learning, particularly in identifying discrepancies between model results and empirical observations or knowledge concerning the world and in helping to refine mental models [5] across the team.

More significantly, this emergence of "Agile Modeling" aids in realizing the potential for models to serve as learning tools. Rather than being viewed as "crystal balls" that are either accurate and successful or flawed and a failure, models are increasingly realizing their potential to *enhance the rapidness, depth, and robustness of organizational learning*. Although dynamic models most certainly do not directly confer reliable understanding of processes in the world, they can help us more quickly identify inconsistencies between our best understanding of that world and empirical evidence. The importance of models as "learning prostheses" reflects the fact that unaided humans are notoriously poor at perceiving the implications of their understanding concerning underlying processes of a system on systems behavior as a whole [7]; by contrast, given an unambiguous model specified on a computer, computers are extremely effective at playing out the logical implications of the assumptions captured within that model. From this perspective, the discovery of an inconsistency between what the model suggests in simulation results (often the logical but previously unrecognized consequence of erstwhile tacit organizational assumptions) and empirical knowledge is not a failure of the model, but a success of the modeling process—and a success of organizational learning, in that it helps refine that understanding, and render it more robust. Within this third and "Agile" era of modeling, embedded transparent models within teams help harness knowledge across the breadth of the team and greatly accelerates the team's ability to identify areas where that knowledge falls short, and contribute to making it more robust. Such modeling can further aid in identification of key uncertainties that will make that knowledge more firm and in planning interventions that will use that knowledge to offer high-leverage and cost-effective improvements for the health of the population. The results of such evidence gathering and from interventions can then further serve to help test the model and to refine the understanding captured therein, thereby refining the team's knowledge. Like Agile software development processes [9, 10, 11], such modeling will take place incrementally and embedded among stakeholders.

This is a process in which ongoing learning and observation takes place—and in which the plan adapts to such learning and to evolving stakeholder prioritizations of possible model extensions. Fully appreciating the benefits of Agile modeling requires appreciation for the implications of stakeholder involvement in modeling projects, a topic about which the space constraints only allow for a few words. Benefits of rich stakeholder involvement include *informing and grounding the understanding going into and captured in the model, the potential for shaping stakeholder cooperation and capacity, to enhance a sense of buy-in—and sometimes ownership—over the model.* Within this area, and particularly in the practice of "group model building" and "participatory modeling" [15, 14, 16, 17, 18, 19, 20], there has been a widespread recognition of the value of models as "boundary objects" [14]—that is, to serve as mutually understood concrete focal points for discussion concerning the underlying system by parties who otherwise speak very different languages. By concretizing the discussion around commonly understood elements that can be literally pointed at, the models not only help bring diverse parties to the table, but can further help foster communication between parties who lack the common abstract language to communicate readily about the system being structured.

Success in this area will benefit much from the ongoing strengthening of the visual, declarative specification of models (Figure 16.2) such that they are transparent to stakeholders not trained in modeling, as well as support for interactive, collaborative software for geographically disparate stakeholders to interact with a model. While the transition is in its nascent phase [46, 45], coming years are likely to see simulation follow the trend in many other areas of information technology toward collaboratively oriented cloud-based support, similar to what is seen in Google Docs and Microsoft Office 365.

4. SYSTEMS SCIENCE IN THE AGE OF BIG DATA

A third major trend affecting health applications of systems science relates to the emerging synergies between electronically sourced health data and dynamic modeling. While large components of health information have long been stored and manipulated electronically, many such representations were largely undertaken for day-to-day operational purposes (e.g., billing, clinical workflow, to enable mandated reporting formats, etc.); when data was retained for research, planning, and administrative decision making purposes, such data was commonly fragmented between information silos, including separate databases, spreadsheets, and separate files for tools such as SAS, SPSS, STATA, etc.

The past half-decade has witnessed a sea change within the health field in terms of the emergence of new data collection modalities, of interlinking previously balkanized data sets, and in terms of processes and infrastructure to make

such electronically sourced data available for decision-making purposes. This data comes in diverse forms, and relates to different areas of health behavior, contexts, status, and exposures. Several classes and types of such widely available health-related information are discussed below.

4.1. Important Classes of "Big Data" in Health

A first major class of health-related "big data" consists of *physical measures of health behavior and status* via sensor data from wearable devices and consumer electronics—for example, smartwatch-collected accelerometry, heart rate and heart rate variability, electrodermal activity, similar information and orientation from smartphones, and measures from devices supporting wireless data transport such as weight scales (potentially with adiposity measurement), glucometers, and blood pressure cuffs. This information can be of exceptional value in areas where self-reported data is often unreliable—such as with respect to nutritional intake, physical activity, contact, and mobility patterns.

The second major class of health-related "big data" captures aspects of *context. Geospatial environmental information* can lend an understanding of mobility, location, duration and occurrence of exposure to particular indoor and outdoor environments. Such information can particularly be gleaned from the strength of WiFi, GPS, Bluetooth, RFID, cellphone tower signals and certain sensors, which are commonly available on smartphones and some other consumer electronic devices. *Environmental information* concerning those contexts—such as are present in GIS systems, databases collected from environmental sensors, or from building control systems—can provide an understanding of the character of these exposures. Some of such environmental information comes directly via wearables and consumer electronic devices carried by the subject (e.g., humidity, temperature, barometric pressure, magnetometers). Other information comes from cross-linking data on location with other data sources. Some of this data can be linked in real time—for example, measurements from proximate environmental sensors associated with infrastructure, such as in building control systems, municipal infrastructure, and weather stations. Other such linkages are reliant on retrospective databases, including GIS databases and historical databases compiled from monitoring infrastructure (e.g., weather records). *Network context* can be information used to detect dynamic interpersonal contact patterns and degree of proximity between participants can be derived from technologies such as Bluetooth and RFID.

A third broad class of health-related "big data" information consists of information shared with others, or self-reported by participants to surveillance initiatives, research studies, or other health or health-care actors, as facilitated

by use of electronic technologies. A first such type of information has older roots but has been substantially enhanced by synergy with other types of collected information: *Responses to on-device questionnaires and ecological momentary assessments (EMAs)*. Tools such as the EpiCollect [21], mEMA [62] and DREAM [57] systems provide easy ways of gathering health information via personal mobile devices (and soon via wearables), with the iEpi system [32, 33] additionally supporting triggering of such ecological momentary assessments, based on sensed aspects of context or participant history (e.g., questionnaire triggering at recreational locations, fast food restaurants, or following periods of sedentary behavior, in certain social contexts [47], or other aspects of sensed data). Such triggering can elicit place- or exposure-specific information and enhance likelihood of participant response. A second major type of self-reported information is the growing volume of electronically mediated *crowdsourced information*. A growing amount of public online health data is volunteered by individuals, either as part of community efforts, as a side effect of operational needs, or for personal insight. Examples include information submitted by parties using services such as Endomondo, Google Fit, and those using Apple Health, fitness-oriented apps such as FindSports, via FitBit sharing, etc.—interactions which also fall into the class of health-related communicational behavior covered below. Tools such as iEpi/Ethica Health [32, 33] further support easy collection of study-specifc participantreported information on exposures, subclinical symptomology, etc., in a way that can be adapted without programming (Figure 16.3).

An overlapping class of information consists of *health-related communicational behavior*, which is key for informing understanding of health-related beliefs, cognitions and decision making. Such information includes information shared via social media, such as Facebook status updates, twitter feeds, blogs, chatrooms, etc. In a surveillance and research context, there can also be monitoring of additional communicational browsing behavior (including URLs visited and page contents—particularly to health-related information and community sites), use of health-related apps, text messages occurrence and content, and phone calls.

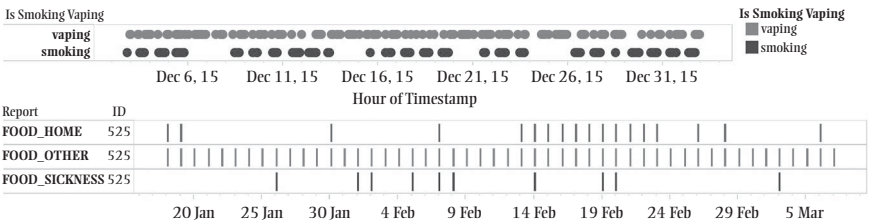

Figure 16.3 High temporal density longitudinal data of the sort that could be used for model calibration.

The growing use of technologies to identify affect and stress from voice communicational behavior can enhance the data available.

Beyond the above classes of health information, there are a variety of important additional types of information. For example, electronic information on *purchasing behavior* can provide insight into health-related personal protective behaviors, risk behaviors, and concerns. Sources for such data include point of sale data from stores, online purchase transaction data, data preserved through use of purchase functionality (increasingly integrated with smartphones, etc.). *Electronic clinical data* is of great interest in the clinical and health-care management sphere but can also offer great value in terms of understanding the interaction between care-seeking and underlying population health concerns. Such clinical data is present in electronic health records, providing information on care-seeking, laboratory test outcomes, diagnoses, imaging results, physical measurements concerning diverse quantities such as patient height, weight, blood pressure, reflexes, etc.

Collectively, the "Four Vs" characteristic of "big data" [22] offer much to enhance the prospect of building dynamic models. The volume offers much evidence, the velocity (Figure 16.1) can help parameterize and calibrate fine-grained dynamic models, as well as aid in theory building. Given that dynamic models commonly characterize many aspects of human behavior, the variety can help simultaneously ground many elements of individual state and behavior (including location and obility, social network context, and diverse health behaviors), and the veracity can often considerably elevate accuracy in grounding certain elements more so than would be possible with self-reporting (particularly when compared to self-reporting in areas such as nutritional intake, physical activity, weight dynamics, contact patterns, and spatial mobility; see Figure 16.4).

4.2. Hierarchy of Data Science Models

Absent models to make sense of them, the electronic data discussed above offers simply a cacophony of numbers. Models to secure insight from such data come in a variety of forms and serve different purposes—for example, to classify, infer, estimate, filter, or smooth. Before incorporating elements of "big data" into dynamic models, it is frequently necessary to apply several such models in a successive fashion. For example, we often first need to screen out patently spurious sensor values (e.g., recognizable GPS artifacts), aggregate to lessen the effects of noise, and then analyze the underlying data in order to identify features in the empirical data that correspond to elements of the simulation model—high-level elements that are merely implicit in the "raw" data, such as "visit to park," "contact between a child and their mother," "visit to convenience store," "period of sedentary behavior," "use of a sidewalk." After passing through several layers of

Figure 16.4 Example of variety of information often received in big data, combining temporal and geographic context plus survey answers, and audio recordings (from Ethica iEpi/Ethica Health system).

model-based filtering and classification methods, the data may be suitable for use with a dynamic model. We discuss that combination below.

4.3. Combining Big Data and Dynamic Models

Dynamic models can be informed by the big data discussed above in several ways. Perhaps the most notable and direct way that "big data" can work with dynamic models is by serving as a source for model parameter estimates. In some cases, this estimate is more direct—for example, emerging from analysis of the frequency of some event clearly marked by the previous classifiers (e.g., visits to a convenience store or a park, contact with another participant, uses of an e-cigarette). Another more direct case is seen in [34, 35, 36], where measured proximity data directly drives network connectivity in the model. In other cases, derivation of this parameter estimate may require further statistical analysis, such as for hazard rates derived through survival, recurrent event or competing risk analysis. In another more indirect estimation example, the empirical data could function as revealed preference data for estimating preferences in discrete choice theory models [23].

In an alternative set of cases—of nearly equal significance to the above—"big data" informs the model in another way: through calibration. In this process, rather than being used directly to derive estimates for particular parameters, the empirical data is systematically compared against emergent behavior from the model as certain little-known parameter values in the model are tuned. We then assume as the value of those underinformed parameters the parameter value vector that minimizes the discrepancy between dynamic model output and empirical data.

Another important case focuses on the handling of incoming temporal sequences of data. Within this "filtering" case, rather than simply being used by the dynamic model, the incoming data is combined with model estimates of states derived from the simulation, forming a single or distribution of consensus values. For example, [37] demonstrated the use of the venerable Kalman Filtering technique for combining model estimates with incoming data, including sensor-based data from dynamic networks. Additional elements of this approach are discussed in the section below on sequential Monte Carlo approaches.

In other cases, the data flow between machine learning and dynamic models is reversed, and dynamic models serve as a source for "synthetic ground truth" to test machine learning models or study designs involving big data. These approaches take key advantage of the fact that a dynamic modeler has complete access to information concerning the state of the simulation at any given time. Recourse to this true state of the model allows it to be compared with estimates

or classifications of that state derived from machine learning methods, or from other analytics being evaluated as elements of the planned study design. For example, [56, 35] used synthetic ground truth from an agent-based model to identify contact network sampling rates (at different levels of specificity) required for reliable inferences to be drawn concerning the spread of information across those contact networks.

Another key way in which "big data" and modeling fit together lies in support of validation and learning. Here, electronically sourced empirical data is compared with corresponding items from a simulation model in a particular context—for example, following an intervention. Frequently, the different elements and subsets of such "big data" can help elucidate dynamics of distinct pathways hypothesized to drive outcomes of interest. For example, Figure 16.5 depicts hypothesized pathways by which a move of a low-income family to a mixed neighborhood might affect health and social outcomes (such as obesity) in that family. The "variety" component of "big data" can help shed light on the operation of such pathways, and the degree to which they are affected by the intervention. For example, GPS- and WiFi-based location sensors over time could pick up the degree to which significant changes in the use of recreational space occur before and after the move, the degree to which there is a change in the use of grocery stores (as compared to convenience stores) pre- and post-intervention, and changes in the amount of time that children are spending

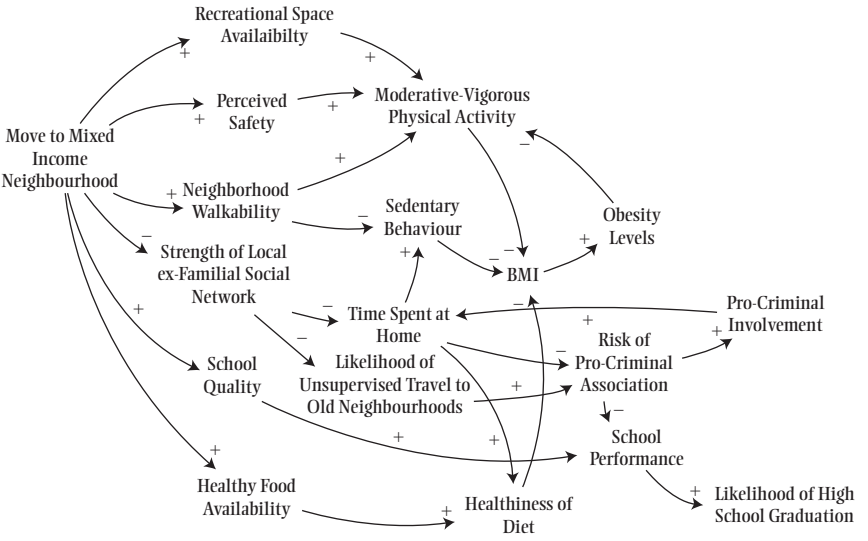

Figure 16.5 Hypothesized pathways by which an intervention might affect outcomes of interest. Dynamics associated with such different pathways can often be measured by different subsets of sensor information.

at time or are returning to their old neighborhood. Such location-based sensors together with accelerometers could help quantify the degree to which changes in walking intensity, the level of sedentary behavior, and moderate-vigorous physical activity that apply between old and new neighborhoods. On integrated sensor-crowdsourcing-EMA smartphone platforms such as Ethica iEpi [32, 33], EMAs could moreover be used to elicit attitudes and perceptions (such as perception of safety, of walkability, etc.), shedding light on their dynamics pre- and post-intervention. While such sensor-based mechanisms provide an admirably multifaceted view of the effects of intervention, often they are well matched in richness by a corresponding simulation model. Such a simulation model will also include a diversity of such causal pathways within its representation, with the parallel character of these representations raising the opportunity for great insight via side-to-side comparison. Specifically, in the event of an intervention being put into place, empirical data collected from such smartphone-based mechanisms over time can be compared against the model's expectations concerning the dynamics of corresponding pathways. Discrepancies can be used to refine the model or data collection strategies, and—even more importantly—to sharpen the research team's understanding of the effects of such interventions.

5. COMBINING BAYESIAN MONTE CARLO APPROACHES AND DYNAMIC MODELS

The section on big data above briefly noted the joint roles played by dynamic models and their machine learning/computational statistical and dynamic cousins in the specific context of big data, with dynamic models being informed and grounded by findings from machine learning models, and dynamic models being used to evaluate and refine machine learning models.

While the combinations of models drawn separately from each domain is of great value, the modes of cooperation of the *methods* of machine learning/computational statistics (henceforth "machine learning") and dynamic modeling are not limited to their use in distinct models. Although traditionally pursued by distinct communities, each with a depth of methodological knowledge, we can use machine learning methods with a given dynamic model in several ways. We focus here on the powerful prospects extending from combining dynamic modeling approaches with one specific class of machine learning approaches—Bayesian Monte Carlo methods. This combination provides for modeling approaches supporting a capacity to readily incorporate new information as it becomes available and that is more robust by virtue of not only complex system behavior but also statistical variability and probabilistic model structure. In this section, we sketch

the combination of two specific Bayesian Monte Carlo methods with dynamic models: Markov Chain Monte Carlo methods and Sequential Monte Carlo Methods (in the form of the particle filter) and note their combination in the form of Particle Markov Chain Monte Carlo methods.

While the three types of Bayesian Monte Carlo methods covered here differ in their specifics, when combined with dynamic models they share several important features of relevance: (1) explicit probabilistic models relating observations and other quantities (e.g., parameters), (2) the incorporation of dynamic model results to be incorporated into the likelihood functions employed, (3) the capacity to readily deal with estimation of *latent* quantities—quantities for which direct observations are not available, (4) a shared (Monte Carlo) goal of repeatedly *sampling* (drawing) from posterior distributions associated with model quantities—once such samples are drawn, they can be used in many powerful ways, and (5) as Bayesian approaches, these methods support specification of *prior* distributions over the model quantities being sampled—distributions that allow characterizing prior beliefs about such parameters (beliefs possibly drawn as posterior distributions emerging from earlier data).

We now briefly characterize the role of such methods when combined with dynamic modeling.

5.1. Markov Chain Monte Carlo Methods

Dynamic modelers have long relied heavily on model calibration to estimate model parameters by matching simulation model data against empirical observations. While valuable, calibration exhibits some notable shortcomings: it frequently yields just point estimates with unclear uncertainty. Even when such uncertainty is estimated by a covariance matrix, it fails to account for multimodal distributions and cannot be translated into similar bounds for model outputs, and differences between outputs for model scenarios, etc. A rapidly growing literature [24, 25, 38, 40, 41] has applied Markov Chain Monte Carlo (MCMC) methods to deterministic dynamic models, particularly in the methodologically sophisticated area of mathematical epidemiology of infectious disease, and a handbook chapter by Osgood and Liu [40] provides a systematic introduction to the use of such models, while [26] provides a video tutorial designed to introduce viewers to the use of such models at a very elementary level. Given a prior distribution over a (vector of) model parameters θ, one or more observations y, and a likelihood function $p(y|\theta)$, MCMC methods seek to sample (i.e., draw particular parameter vectors in turn) from the joint posterior distribution $p(\theta|y)$ of those parameters. When combining MCMC methods with dynamic models, some of the θ parameters are typically associated with the dynamic model,

others are associated instead with the probabilistic model. Within this context, the dynamic model typically plays a central role in calculating the likelihood function $p(y|\theta)$—particularly in translating one or more parameters within θ into dynamic model outputs that can be compared directly or indirectly to the empirical observations y. The capacity to compute this likelihood function and the prior likelihood function allows for (jointly) sampling parameters θ from the posterior distribution. Once each parameter is sampled, it can then be used for a variety of types of analyses, including sampling from the posterior distributions of model states, of future trajectories of the system under different intervention scenarios, of differences in outcome between two scenarios (e.g., between baseline scenario and an intervention), from a cost effectiveness ratio, or estimating the probability of a given occurrence, etc.

5.2. Sequential Monte Carlo Methods

A second and more recent approach to combining of machine learning and dynamic modeling methods can be found in the use of sequential Monte Carlo methods, specifically in the form of particle filtering. In contrast to MCMC approaches—which sample from the joint distribution of parameter values of the dynamic and probabilistic models—particle filtering samples from joint distributions of *latent states* of the dynamic model. This approach is specifically well suited to "online" planning that takes into account incoming data streams while balancing the fact that both the simulation model and the data are error-prone. As a result of performing particle filtering with a dynamic and probabilistic model, we can sample from the distribution of model state over time, both during the period when new data is recurrently available as well as looking forward. This distribution reflects both uncertainty concerning how the underlying state of the model evolves forward over time (reflecting model stochastics) and uncertainty with regard to the measurements.

Reflecting its focus on stochastic models, Sequential Monte Carlo methods secure great computational efficiency by virtue of an incremental and recursive approach with use or arrival of each new observation updating the samples drawn on the basis of earlier observations. As with MCMC, particle filtering using a given (stochastic) dynamic model requires that the modeler specify a prior distribution—here, over initial latent states x_0 of the dynamic model—and a likelihood function $p(y_t|x_t)$, which specifies the likelihood that empirical observation y_t would be obtained given some posited state x_t of the model at time t. Based on this, the system samples from the posterior distribution $p(x_t|y_t)$ for all t. Moreover, far from being limited to sampling from the state vector at each time point in isolation, particle filtering allows for sampling from the distribution of latent state trajectories over the timeframe of the model, as well as dynamically

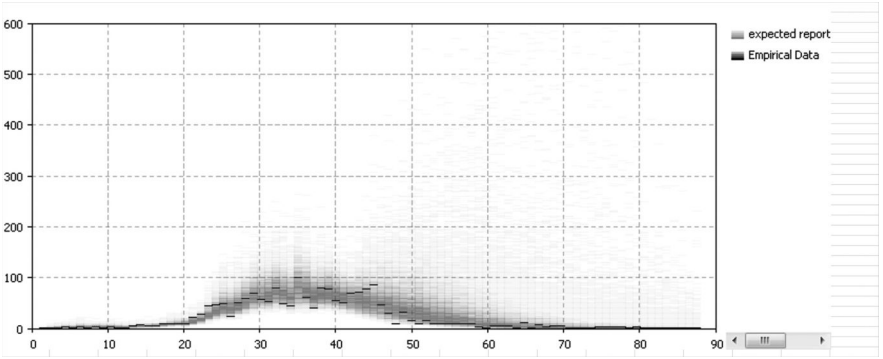

Figure 16.6 Particle filtering for an aggregate transmission model applied to incoming data until day 35, with projection forward following that time. Empirical data on incident cases shown in darker horizontal markers, samples from the distribution of model predictions over incident cases shown in lighter color.

evolving parameter values. Sampling jointly from both the latent state over time and the values of θ, by contrast, requires Particle MCMC (see Figure 16.6).

As a technique, particle filtering raises the extraordinary prospects of "learning" models—modeling in a fashion that limits model uncertainty by recurrently regrounding a model's estimate of its current state (including any evolving dynamic values) by reference to (recognizably noisy) external observations. This technique fits the needs of modeling emergent situations, such as outbreaks of new pathogens when many epidemiological parameters—and potentially some aspects of the natural history of infection or transmission pathways—remain uncertain. Indeed, particle filtering has been applied notably to H1N1 [27, 41] and for TB [41], and has demonstrated its effectiveness in correcting model state estimates for diverse networks using synthetic ground truth data [42]. By virtue of its ability to balance uncertainty about a model with uncertainty regarding empirical observations, its close support for automatic handling of incoming data streams, and the capacity to "learn" (in terms of state and evolving parameters) from repeated observations even in the context of an uncertain model, it seems likely that particle filtering will constitute a prominent staple of real-time decision making using dynamic models in coming years, despite acutely limited current software support [43].

The Particle Markov Chain Monte Carlo (PMCMC) technique represents a recent contribution in the literature that combines the essential elements of Markov Chain Monte Carlo techniques and particle filtering within a single algorithm. When used in conjunction with a dynamic model, PMCMC can be used to sample from a joint distribution over both parameter values and latent states of that dynamic model. Despite tremendous potential, the technique is encumbered by high computational load and complexity and has yet to see widespread application to dynamic models.

6. REPRESENTATIONS OF COGNITIVELY PLAUSIBLE SITUATED HUMAN BEHAVIOR

In systems science models in the health area, representation of human health behaviors and decision making has long been of interest. Since the inception of dynamic modeling of vector-borne diseases with Ross [28, 29] and person-to-person spread of communicable diseases by Kermack and McKendrick in the 1920s [30], dynamic models have sought to represent aspects of human health behavior. Recent decades have seen increasing use of individual-based models (and particularly agent-based models) depicting situated decision making by actors based on aspects of local context in geographic space and within networks. However, traditional representations of behavior in such models have often been highly stylized—for example, positing utility maximization, fixed responses to the external stimuli, or even behavior dictated by fixed probabilities.

Similarly, when examining the impacts of interventions on population health outcomes, modelers have often made the simplifying assumption that parameter values would change in a defined fashion, for example by lowering the hazard rate associated with relapsing to smoking by 10%, or the probability of electing to take a convenience store meal by 20%. Models and model scenarios making use of these simple representations can contribute much insight—for example, in understanding the distal impacts of an intervention or other scenario on downstream health outcomes, such as incidence of diabetes or heart disease—but often beg the question as to exactly how and how quickly such behavior change can be realized. For many purposes, use of more evolved behavioral representations can open notable opportunities. Rather than representing behavior as occurring with fixed probabilities, consisting of a fixed rule in response to observed external circumstance, or positing fixed changes to such behavior in response to interventions, for the sake of model-based learning, it is advantageous to see how changes to behavior emerge endogenously in response to a novel choice environment, or in the context of changed incentives, including those brought about by policies.

In addition to the desire for enhanced flexibility in examining behavioral assumptions, there is often a sense of a yawning gap between the types of behavioral representations commonly depicted in today's models and what is suggested by evidence from empirical choice theories and cognitive science. One example concerns scientific recognition of widespread use of heuristic strategies in place of rational deliberation for many decisions in day-to-day life, which has been well documented by Kahneman, Tversky and others [49]. Several lines of evidence also suggest a tiered process in which strikingly different decision strategies are employed to perform a rough shakedown of possible choices (on the one hand) and to select among the strategies so chosen (on the other). Failure to adequately capture the impact of such heuristics on decision making in the

context of changed choice environments may yield to systematic mis-estimates of the relative gains to be expected through different interventions [55].

Based on these gaps between traditional approaches and research findings, some leading researchers have advanced strategies to incorporate more cognitively plausible decision strategies within agent behavior, based on modern discrete choice theory [48, 31] or on connectionist approaches drawn from cognitive science [50, 51]. Models embracing such strategies can capture agents' decision behavior that is simultaneously more cognitively realistic and also capable of generating far more endogenized behavioral response to interventions than is possible with most of today's modeling (in which such behavioral responses are often presupposed, or are more directly implied by the rules obtained). By virtue of such endogenization, models investing in more realistic representations of behavior, the door is opened to a greater ability to examine concerns regarding the intervention science. In contrast to traditional models in which behavior change is directly posited, the dynamics of intervention implementation can be simulated within the model, better capturing the delays associated with securing intervention effects on both behavior and on distal outcomes.

In the context of the emerging "big data" milieu discussed above, discrete choice theory is notable in its association with techniques for eliciting preference information from both stated and revealed preference data. For the former, the approach offers refined strategies for crafting instruments that will lower both the number of required respondents and the burden of questions on those respondents; the growing proliferation of wearables and mechanisms for smartphone-based EMAs can ease delivery of such questionnaires. While revealed preference data has most traditionally been associated with analyzing point of sale data, within the health area it is notable for being positioned to make use of the high-velocity longitudinal sensor data discussed above. While stated preference data will remain important for understanding certain types of counterfactuals, the prospects are strong for using revealed preference methods to exploit evidence collected via the growing number of low-burden, automatically collected electronic data sources within the health area.

7. AN EMERGING TRANSFORMATION OF SYSTEMS SCIENCE

The trends discussed above are working to make the insights extending from health applications of systems science more widespread and accessible, deeper, more grounded, more impactful, less siloed, more easily conducted and shared, and more robust in light of the uncertainties present. The trends above and others not covered here—such as the growth of cloud-based computing—will draw systems science closer to computational statistics, the

behavioral sciences, and policymakers, while allowing for a broader appreciation and dissemination of its findings. The coming decades are likely to significantly reshape for the better the practice of health systems science in terms of project goals, technologies, social environment and team composition, and day-to-day operation. At the same time, some factors will remain invariant: key challenges in the education and training area, the need to embrace both rigor and relevance, and to break down barriers both within systems science communities and between systems science and cognate areas. If those challenges can be overcome, the contributions of health systems science are likely to multiply greatly.

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Systems Science and Population Health

ABDULRAHMAN M. EL-SAYED AND SANDRO GALEA

This book is mainly concerned with the health of populations and with understanding the determinants of the distribution of health within and between populations. Our concern with the health of populations extends beyond academic considerations. We are interested in understanding the health of populations so that we may intervene and identify solutions that shift population curves and that produce healthier populations both in the present and over time. We came to systems science because of a recognition that our dominant approaches to understanding population health frequently fall short. This is because populations are the quintessential complex system, and understanding the production of health in populations must, almost by definition, lean on methods that can grapple with this complexity to illuminate levers of action that can serve to improve population health.

In this book we have presented sixteen chapters that trace the evolution of systems thinking in population health, articulate methods that hold promise for systems analysis of population health, and consider how specific approaches can guide our thinking toward a population health science of consequence. We conclude the book by tackling one specific question: what is the role of systems science approaches in population health science? In closing, we offer three thoughts on this, building on the chapters that have preceded this conclusion, with an eye toward the field's evolution and emergence.

First, we suggest that populations are, inevitably, complex systems, and any approach to understanding populations must adopt a systems science approach. Specifically, this means the adoption of a systems science framework and perspective, recognizing that there are a multitude of factors that influence a given population's health and also recognizing that these factors interrelate—and

further, these interrelations are spatially and temporally dependent, characterized by feedback, reciprocity, non-linearity, and stochasticity. At some level there is nothing surprising about this statement; that populations of heterogeneous, networked, unpredictable individuals represent complex systems should surprise no one. However, at another level, saying that all population health thinking must rest on complex systems thinking upends how we currently do the business of population health science. Systems science has had to elbow its way into the mainstream of population health science thinking, and is far from accepted as a dominant paradigm. This relative marginalization simply reflects the evolution of the field, and an embrace of deterministic methods that aim to isolate causes, encouraging us to focus on the identification of single "silver bullets" whereby we can intervene to effect change. An understanding that population health is the product of a set of complex interrelations positions systems science and population health as twinned approaches. The former is a mechanistic representation of the latter, and systems science is an indispensable approach if we are to understand population health. This provides us with a lens through which to understand the health of populations and a frame through which many other observations may be viewed. It suggests that we are better served not by looking for isolated causes but by understanding the causal architecture that shapes the health of populations and potential levers within that architecture that can be manipulated toward improving health.

This is not a trivial distinction: it gets us down the path of understanding causal interrelations and away from causal isolation. It also suggests that several of the methods discussed in this book may have utility to the population health analyst, providing an organizing frame for our approaches as much as they may provide particular analytic approaches to tackle specific questions.

Centrally, though, this suggests that adopting a systems science lens toward population health sets up our approaches differently, asks different questions, and accepts different answers than would a more reductionist approach. This does not make for easier answers, and it demands perhaps greater tolerance of complicated answers that call for creative solutions. But they can be solutions that can inflect the trajectory of population health toward fulfilling the central goal of the population health enterprise.

Second, perhaps one of the sentinel challenges of a systems science approach to population health is the temptation to always think "big" and to embrace approaches that aim to be everything for all problems. This runs the risk of embracing everything at all times, making it difficult to understand anything. After all, the health of populations in the present is produced by influences across generations, combining forces that extend from the pre-, peri- and postnatal period through to adulthood, that include behaviors of individuals, characteristics of their social networks, features of their neighborhood physical and

social environments, municipal policies, and overriding national forces including but certainly not limited to politics, laws, and policies. It would be hard not to articulate mechanisms that link any of these factors to any given health indicator and not to articulate mechanisms that link these factors to one another. This centrally reinforces that what matters for population health is the product of a very complex system. It also, however, runs the risk of expanding our universe to thousands of analytic options and approaches, where we recognize that everything matters; in so doing we set ourselves up for failure if we are to identify any tractable approaches that can make a difference.

In the face of complexity, the population health scientist must be disciplined. She must take a hardheaded analytic approach that focuses on what matters most, even as we recognize that, yes, everything might matter at some level. Such an approach therefore builds on the point we are making above (i.e., starting from a recognition that all populations are complex systems and that a systems lens can help articulate the core drivers of health in populations), and then using the conceptual and analytic tools of systems science to focus on the aspects of the system that may be most important for the health indicators under consideration. It is this balance between complexity and reduction of that complexity to its digestible elements that is, to our mind, the most promising approach to population health thinking and analysis. It is a balance that requires a conceptual frame that is consistent with a complex systems perspective, facility with the armamentarium of systems science analytic methods, and confidence to use the simplest methods possible, but not simpler ones.

Third, recognizing that systems science approaches are an inevitable lens for population health science nudges our frame for communicating and teaching population health science, for the identification of questions and the articulation of answers in the field. The field of population health is bedeviled by competing narratives that emerge as study after study produces conflicting results. These results often emerge from internally valid state-of-the-science studies that fall short only insofar as they are producing answers that are valid within a particular narrow definition of the system factors of interest. Other studies, similarly well conducted, but similarly concerned with narrow (but different) definitions of underlying complex systems, then inevitably yield different answers. This challenge is not new. It is a challenge to the external validity of any study that cites its identification of factors of interest narrowly. A systems science approach to population health aims to do away with this problem by carefully and systematically situating our studies within the full complex system that produces a particular health indicator and articulating the answers we identify within the constraints of the system elements studied. This approach, however, requires both discipline and humility on the part of the population health analyst. It requires us to teach our students how to ground all observations within the broader complex system

of interest, to communicate our findings as such, and to have the humility to recognize that what we do discover is limited by the frame we adopt—and subject to reconsideration if we can grapple with more underlying complexity than any particular analysis takes into consideration. This may be a particular challenge to health communication, accustomed as we are to communicating health information as the sum of many individual "risk factors" (more blueberries, more steps walked a day) that dominate both the news cycle and countless sources of health information that characterize the health and medical landscape.

When we consider these three roles for systems science: its provision of an overall frame for our thinking about population health, the clarity of balance about the fullness of the systems at hand and the specific system aspects that we must take into consideration to identify tractable solutions, and the implications of both these perspectives for how we teach and communicate the science, one cannot help but feel that the task ahead is formidable. In some respects, it is nothing short of a rethink of how we approach population health, and the integration of systems science approaches into population health education, practice, and communication in all aspects of our work in the field.

And yet we remain optimistic. The field has come far in a relatively short period of time. Systems science and population health were strangers a decade ago but are now featured regularly in scientific meetings, in academic papers, and now in books. A new generation of population health scientists are embracing systems science, and a new generation of systems scientists are learning about the potential to make a contribution to population health. It is our aspiration that this book be one part of that emerging conversation between these fields and that subsequent books and scholarly contributions improve on what we have done. Then we can continue to move the field forward, toward a more consequential population health scholarship.

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