

REVIEW

Great future or greedy venture: Precision medicine needs philosophy

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Abstract

Introduction: Over the past decade, we have witnessed the initiation and implementation of precision medicine (PM), a discipline that promises to individualize and personalize medical management and treatment, rendering them ultimately more precise and effective. Despite of the continuing advances and numerous clinical applications, the potential of PM remains highly controversial, sparking heated debates about its future.

Method: The present article reviews the philosophical issues and practical challenges that are critical to the feasibility and implementation of PM.

Outcome: The explanation and argument about the relations between PM and computability, uncertainty as well as complexity, show that key foundational assumptions of PM might not be fully validated.

Conclusion: The present analysis suggests that our current understanding of PM is probably oversimplified and too superficial. More efforts are needed to realize the hope that PM has elicited, rather than make the term just as a hype.

KEYWORDS

biomarker, cancer, data, model, precision medicine, system

Science is not and will never be a finished book. Every great achievement brings new problems. Any development with the passage of time will be the emergence of new serious difficulties.—Albert Einstein

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1 | INTRODUCTION

In the last decade, the term “precision medicine” (PM) became abundant in the medical literature.^{1–3} It is often used interchangeably with various descriptions, such as personalized medicine, molecular medicine, genomic medicine, stratified medicine, individualized, or target therapy.^{4,5} Though the current concept of PM remains to date not

well-defined, its promises are expected to dramatically change patient care via individually tailored therapies and, as a result, to prevent and/or delay disease, improve survival, and extend health span.

While encouraging progresses have been made, the difficulties and challenges, which implementation of PM faces, have sparked intensive debates between its defenders and critics.⁶⁻⁸ For example, many people agree that although genes or genomes are pieces of the puzzle, which have already greatly contributed to scientific and medical successes, they are not golden tickets to fully understand health and disease.^{9,10} These debates remind us of the discussions held by the first World Science and Technology Development Forum (WSTDF), who identified unabated obstacles in the field of global health, notably, whether new techniques and methods can provide support for the prediction, prevention, and prognosis of cancer and other chronic noninfectious diseases. Considering the rapid and global rise of the current and unprecedented coronavirus disease 2019 (COVID-19) pandemic, these challenges should be further extended to infectious diseases.

As Hippocrates said, "Philosophy should be embedded in medicine, and medicine should be embedded in philosophy." Since the beginning of Western natural and experimental science, however, medical practice has gradually been transformed into an engineering and technical discipline. Excessive emphasis on modern technology in medicine has its limits, that is, when a living human being is not regarded as a whole person, but as a piece or set of organs or tissues, and when clinicians turn essentially into interpreters of reports.¹¹ The fact that modern medicine, including PM, has run up against a wall indicates that these challenges may not be solved only by technological advances and deserve to be discussed philosophically.¹² In this essay, we confront several philosophical issues pertinent to the complex concept and unprecedented practice of PM.

2 | COMPUTATION IS INDISPENSABLE BUT INSUFFICIENT FOR PRECISION MEDICINE

Today, computation and data have expanded into all aspects of society. While data are defined as facts and statistics collected together for reference or analysis, the essence of computation can be understood as the continuous transformation process of data based on special rules (algorithms or programs). With the advances of high-resolution, high-throughput technologies, the human body becomes akin to an extensive database, in which hundreds of kinds of data are included.¹³ Correspondingly, in the era of big data, it seems logical to expect that this ever-growing amount of data can and will progressively lead to a profound shift in healthcare, based on the assumption that larger volumes of medical information are more suitable to identify trends or associations that are not otherwise evident in smaller datasets and suggest effective interventions.¹⁴⁻¹⁷ This situation aroused heated debate whether computation is really a panacea or an universal methodology for modern medicine, including PM.

2.1 | Medical data: the more, the better?

Despite great contributions in the understanding of cancer biology, precision oncology (PO), a major area of PM, whose implementation depends largely on the application of genetic or molecular data, appears more challenging and frustrating.¹⁸⁻²⁰ At the historic moment of the Human Genome Project (HGP) completion nearly two decades ago, Francis Collins suggested in 2000 that "over the longer term, perhaps in another 15 or 20 years, you will see a complete transformation in therapeutic medicine." Undoubtedly, the significance of HGP in biology was matched to the Apollo Project in astronautics and the Manhattan Project in physics. All these ventures received tremendous public attention and were hailed as epoch-making triumphs of science. Numerous impressive successes were achieved since completion of the HGP. Yet, most promises of the HGP are still elusive, and its effects on human diseases are far from what was anticipated initially.²¹

Thus, getting massive data is one thing; interpreting it accurately is another thing. In the oncology realm, interpreting the data is much harder than their collection. This is due to the fact that most cancers are caused by complex interactions between multiple genes and environmental factors.²² Therefore, the defenders of PO argue that it is unfair to expect immediate clinical applications as it takes time for the results of basic research to reach the patient's bedside. On the other hand, the critics claim that the promises of PO have been overblown and excessively optimistic. They state that it is only a "hypothesis that needs verification."^{23,24} These vivid controversies suggest that, in spite of its rationally conceptual foundation, essential issues may be missing, contributing to the current lack of breakthroughs.

2.2 | Is Life always computable?

In essence, these issues can be roughly classified into two categories: "scientific" and "philosophical and logistical" challenges.²⁵ The former about technical approaches have been systemically discussed previously in excellent reviews.²⁶⁻²⁸ Here, we focus on the philosophical nature of data and algorithms (or models) to tackle critical questions around the source of the epistemic value of data, as well as the relation between data and PM.

Philosophically, data are the results of interactions between researchers and the world, being construed and processed to function as available evidence for claims about phenomena.²⁹ Whether its material features consist of the numerical values obtained via measurement or the shapes captured by a photograph, it is the representational conceptualization of data epistemology, which has a vital role in understanding the empirical basis of scientific knowledge, since the properties instantiated by the data are the medium through which the world becomes amenable to scientific study. However, because data are "marks" or "traces" generated by the interactions between humans and a given target of investigation, there will inevitably be a certain degree of subjectivity in the data. In other words, data can only represent limited facts.³⁰ In medicine, data are often expressed in

terms of binary classifications (yes or no) concerning clinical endpoints of interest. This simplistic classification does not satisfy all requirements for clinical practice.³¹ In addition, the bio-psycho-social model of medicine tells us that patients are not merely individuals (ie, how classical medicine treated patients until now), but a dynamic constellation of a myriad of natural organisms granted that we also need to consider the inner ecosystem, for example, the microbiome, virome, etc. The latter are known to be akin to a moving target, changing constantly with some of these changes affecting wellness and disease.^{32,33} Moreover, human beings have their own emotional, personality, mental, psychological, cultural, and even economic factors, which can also impact health.³⁴⁻³⁶ A commonly seen example is that the patient who may be told that everything is normal after a series of pathological examinations even though he/she really feels obvious discomforts, where the realistic objective symptoms are distorted as a subjective illusion. Finally, it can be a dilemma for data collection that not all quantifiable features are important, and not all important features are quantifiable. For the treatment and control of COVID-19, this can be illustrated by many confounding factors, such as multiplicity of targets and effects, difference in the genetics of host susceptibility, asymptomatic carriers, hyper-spreaders, cultural and social behavior, interactions with other morbidities/diseases, or medication history. Can all these factors really be quantified exactly? Hence, it can be challenging to even collect most indicators needed to reflect accurately all these factors, not to mention to interpret them.

The data model is a simplified description of a system or process, especially a mathematical one, assisting calculations and predictions. Epistemologically, data models are considered as the ways of ordering data that are evaluated, manipulated, and modified with the explicit goal of representing a phenomenon, often meant to capture specific aspects of the world.³⁷ For PM, it is deeply connected to and dependent on data models, such as machine learning or artificial intelligence (AI), programs that learn to perform a task or make decisions automatically from data.³⁸⁻⁴⁰ In 2018, the overwhelming victory of AlphaGo (an AI developed by Google) against Lee Se-dol, a top Go player in South Korea, caused a tremendous sensation and made AI seem omnipotent. However, the current status of AI in medicine is confusing and unsatisfactory because only very few examples reached clinical practice so far. Moreover, it can be dangerous and erroneous to reduce biomedicine to an engineering discipline only given that patients are a mixture of objectivity and subjectivity with thought, emotion, mentality, will, and related roles in family and society, furthermore, subject to numerous additional external factors.⁴¹ For medical applications, therefore, the matter that AI has to face is, to some extent, about the infinite. For example, an attempt to apply nonlinear mathematics of complexity to understand the combinations of gene interactions needed for a single function in a genome of nearly 20 000 protein coding genes as well as unknown number of noncoding genes would yield a staggering number of possible combinations.^{22,26} Furthermore, as models derived from poor-quality input data can potentially amplify biases, big data and AI are not always infallible and can sometimes lead us astray, just like their human creators. Accordingly, it is necessary to evaluate and implement them with

a critical eye because of their inherent limitations.⁴²⁻⁴⁴ Collectively, more powerful computational tools, while helpful, cannot ensure that all problems can be resolved (Figure 1). These unabated limitations imply that computation is indispensable but insufficient to the implementation of PM. Eventually, it sends us back to the ontological topic under long-term debate: Is the world or life always computable? If life is theoretically computable, to what extent it is feasible in practice?

3 | INHERENT UNCERTAINTIES INTRODUCE IMPRECISION TO PRECISION MEDICINE

It is a common and fundamental misunderstanding that science is absolutely precise and definite. For a long time, the pursuit of certainty in scientific activities has become an inherent way of cognition and practice. However, people gradually find that the nature of the real world and of our expectations is quite different. The real world, which is objective and rooted in objects themselves, is uncertain.⁴⁵ Therefore, although scientific practice and exploration aim to pursue certainty, the essence is the exploration of the unknown and elimination of uncertainty.

Admittedly, the development of science provides new knowledge and insights, so that our understandings of life reach unprecedented breadth and depth. Regrettably, however, these new knowledge and advances, while providing answers to some questions, also produced more unsolved questions at a faster rate.⁴⁶ For instance, for infectious diseases, including COVID-19, four main factors determining the harm of disease (such as pathogens, transmission routes, transmission capacity, and mortality rate) can all be more or less uncertain. Conceivably, this inevitable uncertainty renders some factors in the management of infectious diseases uncontrollable. In our opinion, the different sources of uncertainties can be qualified as either extrinsic or inherent. While the former, such as the precision of the measures, the equipment, the observer collecting the data, will improve with new scientific and technical developments; the latter, internalized in the living systems, are unpredictable and therefore set up limits to inferable representations.⁴⁷

3.1 | Precision medicine needs embracing uncertainty

Uncertainty concepts are increasingly used in all fields of human endeavor, so their practical value is likely to be progressively appreciated nowadays.⁴⁸ Although the word “uncertainty” relates to the general concept of doubt, this situation indicates that uncertainty is a central feature of medicine, including PM.^{49,50} For instance, the previous commentary highlights the contradiction of the term “precision” in PM, stating that tailoring treatments to individuals will “demand greater tolerance of uncertainty by physicians and patients.”⁵¹ To some extent, it is the imperfection of formal logic and mathematization that contributes to the uncertainty and ambiguity in health decision-making, two prominent apparent characteristics in contemporary medical science. Regarding the formal logic, for example, one

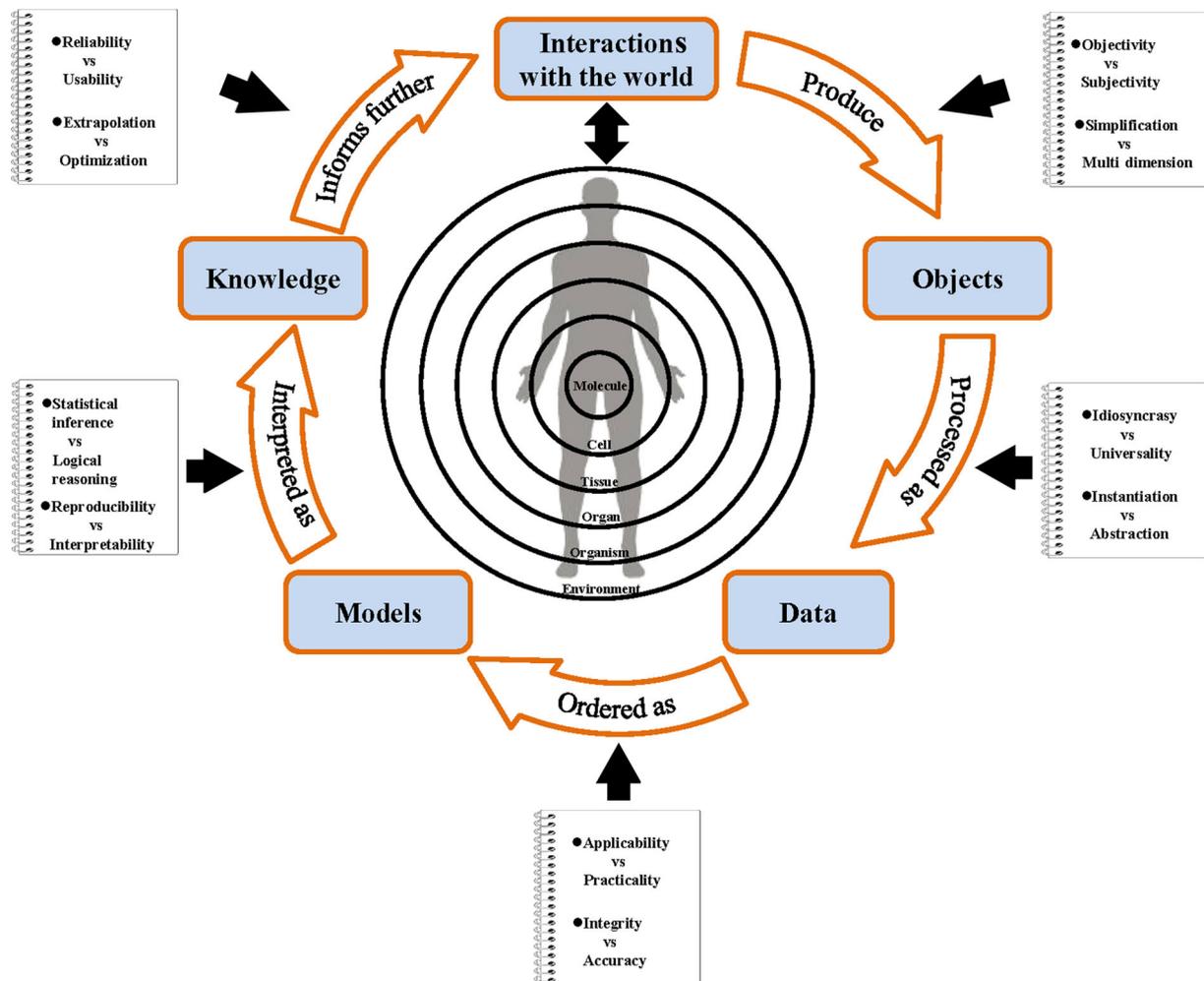


FIGURE 1 A cyclical representation of the process of empirical inquiry grounded on the relational approach to data, models, and knowledge. The hierarchically ordered subsystems in human body have been shown. As the multilayered, multidimensional resources of data, some foundational trade-offs should be emphasized during each stage of the epistemological cycle

of the major primary aims in PO is to discover and validate the genes driving pathogenesis, given that one or more molecular aberrations can be considered as either etiologic or sustaining a malignancy.^{52,53} Although major drivers have been identified in certain tumors, such as *BRCA*, *ESR1*, *ERBB2*, *PIK3CA*, and *AKT1* in breast cancer, in most cases, cancer etiology can be highly complex, involving large numbers of gene variants with small or limited effect sizes.⁵⁴⁻⁵⁶ In addition, the finding of latent mutations indicated that so-called driver and passenger status are not absolute.⁵⁷ In this situation, passenger mutations whose individual effects appear insignificant may transform into driver mutations when acting in certain combinations. Thus, it is not always possible to know a priori what the best biomarkers are. Besides these, the widespread heterogeneity of tumors further complicates the situation. The failure of hundreds of GWAS to find actionable relationships between exposure and disease shows that the common disease-common variant assumption in PO is, at least in part, unfounded.⁵⁸ These biomarkers were chosen based on the best knowledge and understanding we have nowadays

and were identified only according to inferences drawn from selected populations.

3.2 | From statistical noise to clinical relevance: the balance between probability estimate and clinical reasoning

At present, medicine is a science of uncertainty and an art of probability. Reasonably, different mathematical models are created to design tools for diagnosis, prognosis, and therapy. However, it must be recognized that the mathematical or statistical models typically only capture statistical dependencies, such as correlations, from data. It should also be emphasized that correlation does not imply causation. This scenario is exemplified by the knowledge on biomarkers, which does not focus on the causes of diseases, but uses statistical methods to calculate susceptibilities, that is, the statistical association between a biological indicator and a health outcome.⁵⁹ Consequently, the

mathematical or statistical significance often does not necessarily imply biological relevance leading to the adage “statistically significant but biologically/clinically irrelevant.”^{60,61} This is further reflected by the fact that a multitude of biomarker signatures yielding similar prediction performances can be constructed to disentangle the same patient groups. As a result, it is not so surprising that some suggestions consider biomarkers as one of the wagers of PM because of their unwanted effects in clinical decision-making.^{62,63} An outstanding example is that even marked successes with targeted therapies in cancer are likely to be discounted because of increased incidence driven by obesity.⁶⁴ Therefore, in contrast with the hidden underlying assumption of PM that the host genome is the driver of every cellular event, we prefer to believe that it is often the interplay between genetic and nongenetic factors (eg, environmental stimulus), not always the genes or genes only. Integrated approaches of molecular pathological epidemiology (MPE) may provide novel insights into interactions among environment, disease, and host and open new research frontiers.^{65,66} Thus, full collaboration of statisticians and clinical experts is crucial to make important decisions (such as which variables to include in a model) and mitigate the cliché of “garbage in, garbage out.”⁶⁷

Finally, it should be stressed that, in consideration of the enormous complexity of the disease processes, informed decision-making is not possible without estimates of probabilities.⁶⁸⁻⁷⁰ Meanwhile, we should also be aware that, in biology and medicine, approaches based solely on mathematization or computation forsaking a conceptual account may fail because probabilities are at best reasonable betting odds constructed from available knowledge and information. To avoid axiological bias, it is necessary to declare “approximate certainty in uncertainty” rather than “approximate uncertainty in certainty,” which

is dialectics (Figure 2). Therefore, we need to be careful not to throw out the bath water and baby together.

4 | EXTREME COMPLEXITY IS THE FUNDAMENTAL OBSTACLE TO PRECISION MEDICINE

The idea that human biology and disease are composed of complex networks of interconnected systems is not new. For a long time, two distinct and even antagonistic stances co-existed in biology, termed reductionism and holism. Methodological reductionism claims that the best way to explain a complex system is to access its lowest possible level, such as the molecular and biochemical ones.⁷¹ Objectively, the methodological aspect of reductionist approaches had positive outcomes and should absolutely not be downplayed. By providing the elements required for the understanding of the components of the larger system, reductionist approaches paved the way to our present scientific and medical knowledge.⁷² However, because there are few systems more complex than those encountered in medicine, the current strategy of medicine based on the overuse of reductionist approaches is somewhat akin to the parable of the blind men and the elephant. COVID-19 is the latest illustration of such complexities. These include, among others, issues associated with host and virus characteristics, its transmission route, the wide diversity of clinical symptoms, prevention and treatment methods, environmental conditions, etc. This elaborate multisystemic and multiorgan complexity, which we have only begun to uncover, needs to be addressed in both medical research and clinical practice.

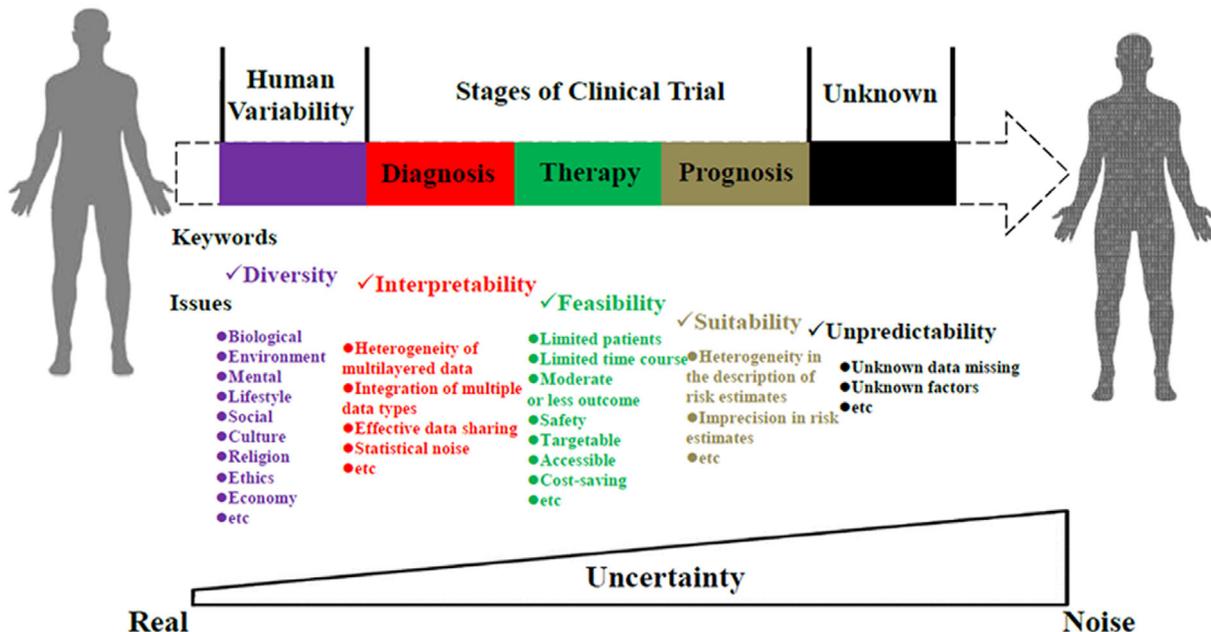


FIGURE 2 The range of sources of uncertainty during medical practice. It has been shown that the sources of uncertainty in medicine are generally stemmed from the underlying variability in human beings, the process of clinical trials, and unknown events

4.1 | Medical view: more zoom in or more zoom out?

Indeed, the enormous mass of information on cellular and molecular structures, characteristics, behavior, and interactions generated from the reductionistic paradigm revealed the immense complexity of modern biology. "It seems like we're climbing a mountain that keeps getting higher and higher," says Jennifer Doudna, "The more we know, the more we realize there is to know." Similarly, at the tenth anniversary of the completion of the Human Genome Project, Hayden EC wrote that the more biologists look, the more complexity there seems to be.^{73,74} Soon after, Weinberg RA also appreciated that, over the past four decades, oncology scientists have witnessed wild fluctuations from times where endless inexplicable phenomenology reigned supreme to periods of reductionist triumphalism and, in recent years, to a move back to confronting the endless complexity of cancer.⁷⁵ These statements indicate that mainstream biomedical researchers began to realize that what hinders their research could be due to their philosophical stance, in spite of impressive new technological wonders.

Since the mid-1980s, technoscientific innovations lead to the molecularization of medicine.⁷⁶⁻⁷⁸ The latter involves viewing and understanding the body at its molecular level and providing mechanistic explanations for higher biological functions in terms of the "parts" of the biomedical machine uncovered through molecule-centered approaches referred to as -omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics, ...). For the past decade, the reductionist program resulted in the identification of innumerable metabolic products and communicating molecules. However, many biologists were frustrated by the lack of success of reductionism in tackling problems posed by complex biomedical systems. Gradually, they became aware that it would be impossible to fully understand the functioning of biological organisms using only physicochemical principles. Sarewitz, a regular columnist for *Nature*, pointed out that some big-data projects trying to tackle complex problems, including the PM Initiative, just look like they are making great progress when in fact they are just adding to noise.⁷⁹ In this context, it would be idle that shortcomings and paradoxes uncovered by research findings can be addressed only

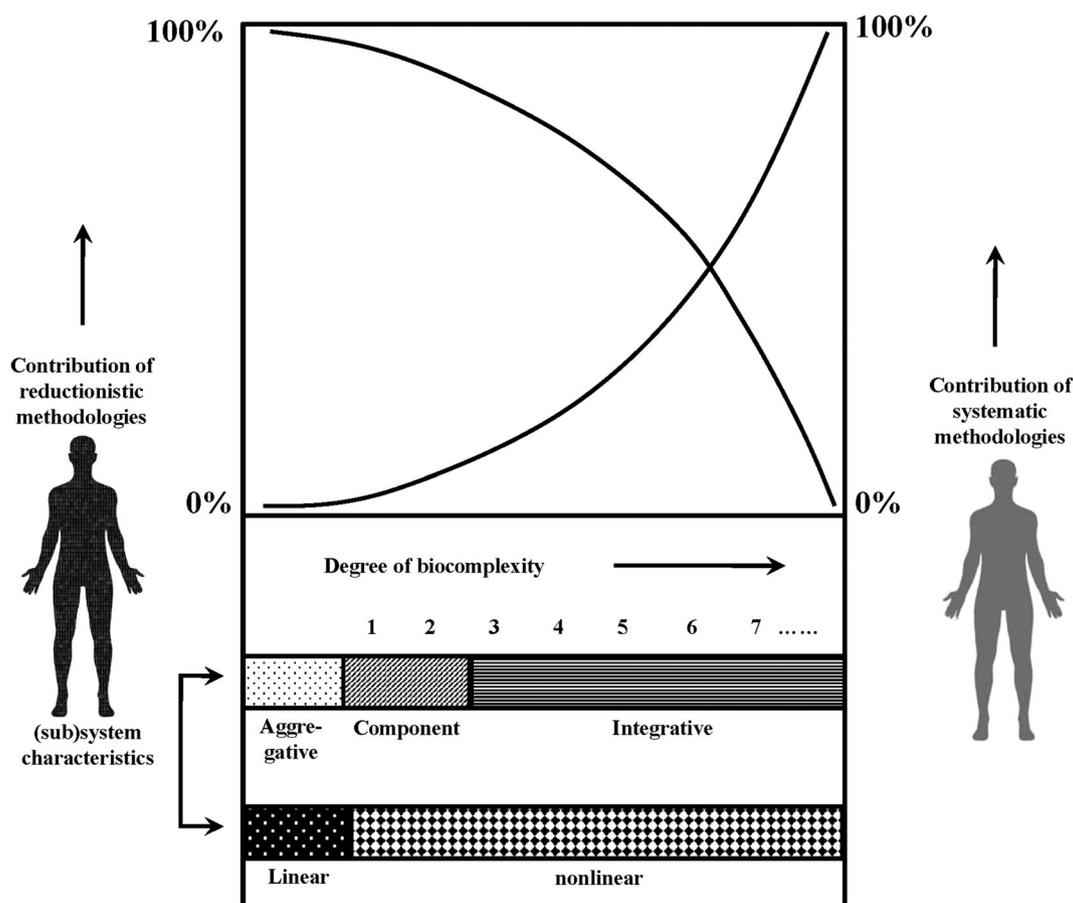


FIGURE 3 The contribution of reductionist and systematic methodologies to the mechanistic explanation of increasing complex biological phenomena. The kind (linear or nonlinear) of process is illustrated in the lower x-axis. The kind of system the processes are part of (aggregative, component, or integrative) is indicated in the middle x-axis. The degree of biocomplexity of biological phenomena is ranked in the upper x-axis (number 1-7). The left and right y-axis portray the contribution (in percentages) of reductionist and holistic methodologies, respectively, to a research program aiming to mechanistically explain a biological phenomenon exhibiting a given degree of complexity. (The re-use of the figure with some revisions from Reference 84 has been authorized. Copyright 2002 Taylor and Francis Ltd., <http://www.tandfonline.com>)

through increasing data volume or modifying the models, rather than questioning the fundamentals.⁸⁰

4.2 | Implementation of PM should consider complexity and simplification simultaneously

A maxim said that when you change the way you look at things, the things you look at change. While new techniques offer new roads of discovery, the theories should be central to scientific practice, including medicine. In this context, systems theory is one such additional framework, a focus on the whole to determine overlying principles that then guide the individual components rather than the reductionist bottom-up approach to understanding. Originating at the intersection of many disciplines, systems biology, a holistic approach or strategy, represents the application of systems theory to biological issues. At present, system biology is a relatively young field of research, and its advancement in methods and successful applications is far from over. For instance, it has been discussed that most of today's system biologists belong to the "pragmatic" stream, who tend to view systems as mere collections of parts not as emergent realities.^{81,82} Although system biology has not yet revealed when and how the vast number of molecular networks produce highly organized and functional single cells, not to mention a whole organism, it can be anticipated that further development may allow to approximate how biological hierarchies function.⁸³

Finally, it is worth emphasizing that reductionist and holistic sciences are not mutually exclusive. Instead, the technological advances that have enabled us to "zoom in" should be complemented by methodologies that allow us to "zoom out": the microscope of molecular and cell biology should be complemented by the "macroscope" of systems theory. Thus, the complete understanding of a complex system will best be achieved by merging the two philosophies (Figure 3).⁸⁴ Or, as Waddington pointed out, "to explain the complex by the simple, but also to discover more about the simple by studying the complex."⁸⁵

5 | CONCLUSION

It should be emphasized that all the points made do not mean that we must go to complete skepticism and even agnosticism. At the meanwhile, we have to realize that current understanding of PM is probably too simplistic and superficial. The war on the disease will be ever-lasting. In a broad sense, medicine is not as much a strictly pure science as an evolving elusive system of knowledge, technique, consciousness, and, of course, philosophy. Perhaps, medicine in the molecular era might be no more "precise" than in prior eras. At present, the problem for PM is more absence of evidence than evidence of absence, indicating the present foundation and framework of PM is not sufficiently sound. For this reason, open discussion and debate, bridging the dream and the reality of PM and ensuring the transition of PM from hype to hope, are urgently needed. We must be careful not to claim success in the absence of robust proof, just as what Alan Turing told us: "We can only see a short distance ahead, but we can see plenty there that needs to be done."

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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All authors have read and approved the final version of the manuscript.

Shuyang Xie had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY DECLARATION

The lead author Shuyang Xie affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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