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## Manifold medicine: A schema that expands treatment dimensionality

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### Abstract

Drug discovery currently focuses on identifying new druggable targets and drug repurposing. Here, we illustrate a third domain of drug discovery: the dimensionality of treatment regimens. We formulate a new schema called ‘Manifold Medicine’, in which disease states are described by vectorial positions on several body-wide axes. Thus, pathological states are represented by multidimensional ‘vectors’ that traverse the body-wide axes. We then delineate the manifold nature of drug action to provide a strategy for designing manifold drug cocktails by design using state-of-the-art biomedical and technological innovations. Manifold Medicine offers a roadmap for translating knowledge gained from next-generation technologies into individualized clinical practice.

### Keywords

Manifold medicine; Systems pharmacology; Individualized medicine; Combinatorial therapeutics

### Introduction

Modern biomedicine is marked by innovations that allow us to understand biology in unparalleled detail. Technologies such as next-generation -omics, systems biology and deep-learning methods, genome editing, electronic biomedical wearables,<sup>1</sup> and organ-on-chip or human-on-chip,<sup>2</sup> have significantly expanded the depths to which biological states can be characterized. With the rapid progress of these technologies and our increased understanding of human disease complexity, more knowledge could be used to translate to the bedside. Clinically, this results in ‘simplistic’ and symptomatological-oriented treatment regimens. Translating such vast and innovative insights gained from these advanced technologies to the clinic will require a more data-driven and quantitative perspective on medicine.

Here, we adapt the concept of manifold from mathematics to describe multiscale-multifaceted aspects of health and disease and propose a schema called ‘Manifold Medicine’. Under this new concept, disease is defined in the context of multiple axes that

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Declaration of interests

The authors declare that they have no conflict of interests.

can be simultaneously impacted by pharmacological treatments (Box 1). We first define the body-wide axes as the areas in which the current biological state of an individual can be mapped. Next, we delineate the manifold nature of drug actions. Finally, we illustrate how the dimensionality (i.e., the multifaceted state space aspects of gene/protein/metabolic networks) of treatment regimens can be expanded to counter the vectorial nature of disease in the light of body-wide axes and manifold modes of drug actions.

## **A need for new medical thinking to redefine disease and expand treatment dimensionality**

Our understanding of ‘disease’ dictates our medical thinking, which in turn determines the principles of drug discovery and treatment design. Modern disease perception began during the 19th century, when Claude Bernard introduced the concept of the *milieu intérieur* (internal environment) of physiological processes; this was advanced by Walter Cannon during the 1920s, who used Bernard’s work to conceptualize homeostasis. Disease has since been deemed a homeostatic imbalance in physiological processes.<sup>3</sup> A subsequent paradigm shift occurred during the 1960s with the cracking of genetic code and the discovery of genetic circuits. These breakthroughs revealed how almost all biological processes are a consequence of the pathological action of genes.<sup>4,5</sup> For the remainder of the 20th century scientists furiously cataloged gene functions and their roles in disease. The rise of systems biology has since challenged this gene-centric dogma by uncovering the complexity of biological systems and revealing how a single aberrant gene is not sufficient to drive disease.<sup>6</sup> Systems-based network views of diseases,<sup>7</sup> as well as systems-based treatment paradigms,<sup>8</sup> have since been developed. However, systems biology primarily deals with genetic interaction networks in cellular contexts.

Thus, the expansion of dimensionality has not extended to the treatment domain despite a plethora of drugs and new targeting technologies. Therefore, a new conceptual framework is needed to redefine disease so that we can increase treatment dimensionality and account for whole-body disease phenotypes. As such, here we contextualize the human body as a set of coordinated multidimensional body-wide axes that define health and disease as well as the action of therapeutic interventions. This concept is framed under the schema of ‘Manifold Medicine’, which refers to the multiscale-multifaceted aspects of physiology, disease, and therapeutics.

### **The multidimensional body-wide axes**

The proper function of human body is sustained by millions of discrete processes carried out at different functional dimensionalities. These multidimensional functionalities can be encapsulated into the conceptual framework of the following series of body-wide axes: the genetic axis, the molecular network axis, the internal environment axis, the neural–immune–endocrine (NIE) axis, and the microbiota axis (Fig. 1a).

### **The genetic axis: Genome-wide execution**

The instructions encoded within our genomes and chromatin modifications comprise the genetic axis, which is the most elementary axis in the body. This axis is responsible for executing developmental processes and daily bodily functions. Defects in this axis drive numerous types of disease, including inherited Mendelian disorders, polygenic disorders, and many types of cancer.

### **The molecular network axis: System-wide modulation**

The interaction between genes at the systems level gives rise to physiological properties and distinct pathological phenotypes. We encapsulate these emergent properties in the molecular network axis. Advances in systems biology have characterized the molecular network axis in specific disease contexts,<sup>9</sup> which in turn forms the basis of systems-based therapy.

### **The internal environment axis: Homeostatic regulation**

Our bodies primarily comprise aqueous solutions of ions and chemical metabolites. These solutions vary both temporally and spatially as our bodies dynamically traffic materials to compartments where they are needed and selectively transport chemical species. Maintaining consistent physiochemical parameters is crucial for ensuring optimal enzymatic activity and function. Serious deviations from these parameters are seen in many pathologies and can cause subsequent dysfunction in a domino effect.

### **The neural–immune–endocrine axis: Whole-body communication**

The nervous, immune, and endocrine systems monitor and alter bodily homeostasis. This NIE axis surveys the body for deviations in macroscopic homeostasis and attempts corrective actions. The autonomic nervous system regulates baseline organ function, and its dysfunction presents with serious symptoms, such as arrhythmias, hypertension, or fever, which can ultimately impact every organ. Meanwhile, the endocrine component integrates neurological signals and other stimuli to release hormones that coordinate whole-body state changes. Over or underproduction of any of these hormones can lead to widespread disease, including diabetes, hyper- or hypothyroidism, osteoporosis, and reproductive disorders. Finally, the immune component protects the host from disruption of homeostasis by pathogens. Hyperimmune activities can lead to autoimmune diseases and inflammatory complications, whereas hypoimmune activities can lead to repeated pathogen attacks.

### **The microbiota axis: The microecological interactions**

Our cells are outnumbered by commensal bacteria at a ratio of ~ 10:1,<sup>10</sup> and these inhabitants form the microbiota axis of the body. Commensal bacteria actively communicate with host cells and take part in normal bodily functions.<sup>11</sup> For instance, commensal bacteria can produce metabolites that mimic host ligands for GPCR signalling<sup>12</sup> and modulate host immunity.<sup>13</sup> The tight association between host–microbial interactions also implicates them in disease. For example, reduced ratios of *Bacteroidetes* to *Firmicutes* have been associated with obesity.<sup>14</sup>

## The manifold nature of drug actions

In pharmacology, drugs are assumed to act as ‘magic bullets’ with high target specificity and binding strength.<sup>15</sup> However, the modes of action of drugs are in practice ‘manifold’. To describe the manifold effects of drugs, we compare drug modes of action to the types of grammatical clause in sentences. Here, a drug mode of action is allocated as a target, regimen, or patient mode, which correspond to the ‘subject’, ‘predicate’, and ‘modifier’ clauses of sentences, respectively (Fig. 1b).

### Target modes

Target modes correspond to the ‘subject’ of a sentence, in that they describe what the drug is acting upon. Included in these modes are molecular target, multitarget, and pathogen modes.

The molecular target mode corresponds to the ‘lock-and-key’ properties of a drug, whereby it selectively binds to a target, altering its activity. Several first-in-class pharmaceuticals were discovered with this concept in mind.<sup>16</sup> One salient example is the tyrosine kinase inhibitor vemurafenib; which binds the mutant kinase B-Raf V600E to treat melanoma. However, single-target magic bullets rarely exist. Drugs frequently bind numerous proteins, giving rise to multitarget modes of action. Indeed, some drugs are designed with the purpose of interacting with multiple targets,<sup>17</sup> and this multitargeted polypharmacological mode of drugs can give rise to opportunities for drug repurposing.<sup>18</sup> For example;  $\beta$ -lactam antibiotics were found to be neuroprotective in regulating glutamate levels within the central nervous system (CNS).<sup>19</sup> By contrast; the multitarget mode can also describe incidental off-target effects, which are described colloquially as ‘dirty’ drugs. Incidental off-target effects cause substantial adverse effects, such as nausea and organ damage. For this reason, the multitarget mode of drugs must be considered carefully. Finally, in the case of infectious diseases, drugs act upon invading pathogens to cause damage to specific pathogen activities.

### Regimen modes

Regimen modes are ‘predicates’ that define the effects resulting from drug targeting. Regimen modes can be categorized as symptom-relieving, protective, replacement, activity-modulating, and evolutionary modes.

The symptom-relieving mode describes a large proportion of currently prescribed drugs, such as pain relievers, sleep aids, and decongestants. Although they do not address the root cause of disease, they can offer substantial benefits to a patient’s quality of life. They can be used to alleviate symptoms caused by the disease itself or by other therapies. For example, the antiemetic aprepitant acts on neurokinin receptors to prevent nausea caused by chemotherapies, and the antihistamine promethazine is used to treat excess vomiting during pregnancy.

In some situations, disease progression reflects a build-up of toxic materials. The protective mode aims to dispose of these harmful substances. A classic example is the use of antitoxins to prevent damage from venoms or *N*-acetylcysteine to prevent hepatic toxicity after acetaminophen overdose.

Under certain circumstances, damage from disease can prevent the body from carrying out normal functions. The drug replacement mode uses pharmacotherapies to replace impaired function caused by disease. For instance, in type 1 diabetes mellitus, autoimmune damage can destroy the pancreas so that it can no longer produce insulin. By contrast, patients with type 2 diabetes mellitus can no longer produce or respond to insulin because of significant deviations in the molecular network and endocrine signaling. Both kinds of diabetes often require insulin replacement.

The activity modulation mode aims to modulate certain physiological parameters to facilitate recovery to a healthy baseline. For example, GM-CSF is used to restore patient neutrophil levels during states of hypoproduction to re-establish a healthy homeostasis. Likewise, patients with heart failure struggle to effectively excrete excess fluid because of the loss of an effective circulation, but diuretics can modulate the kidney to increase fluid excretion beyond normal physiological levels, which can alleviate fluid build-up.

The evolutionary mode expresses the adaptation of a patient's disease state in response to therapeutic regimens. This mode has an important role during regimen selection, and its manipulation can help devise the highest level of patient benefit. During treatment, diseases or pathogens often morph to maintain the disease state and survival. This evolution needs to be anticipated and treatments adjusted. For example, high doses of chemotherapy can select for aggressive drug-resistant cancer subclones and, in some cases, clinicians have pivoted toward using smaller doses over longer periods of time to prevent drug resistance.<sup>20</sup>

### Patient modes

Patient modes 'modify' drug efficacy and action with patient-specific variables. It is important to take these factors into account as we chart a path toward individualized precision medicine. The modifying effects of drugs in individualized patients can be divided into personalized genetic, body-clock, and delivery modes.

Drug metabolism and uptake depend heavily on the genetic background of the patient. The personalized genetic mode looks at the pharmacological properties of administered drugs and how those will be shifted by specific patient genetic backgrounds. For instance, the normal dosage of 5-fluorouracil, a standard agent used to treat colon cancer, can cause toxicity and death in slow metabolizers. In addition, the underlying genetics of a specific patient's disease often affects the efficacy of a treatment. For example, poly(ADP-ribose) polymerase inhibitors are particularly effective against tumors with mutations in the homologous recombination DNA repair pathway (e.g., *BRCA1* and *BRCA2*).

Patients additionally have cyclical body rhythms that can modulate drug effects. The body-clock mode seeks to account for these cycles by incorporating insights from chronomedicine and circadian biology.<sup>21</sup> Given these cyclical activities, drugs administered at different hours of the day exhibit different effectiveness. For instance, the common COX inhibitor, aspirin, is most effective in the evening,<sup>22</sup> whereas corticosteroids have maximum efficacy in the morning.<sup>23</sup>

The delivery mode encapsulates with a patient's vascular health and, in the case of oral drugs, gastrointestinal health. Older patients with poor vascular health experience less effective drug delivery compared with younger patients. Likewise, absorption of oral drugs can be reduced for patients who do not have optimal gastrointestinal health. Dosage and drug selection must take these factors into account to ensure that patients receive adequate drug quantity to target organs.

## The vectorial nature of diseases and manifold interventions across body-wide axes

In both multifactorial and monogenic diseases, changes in one axis can ripple to other axes or cause another axis to attempt to compensate for deviations. Hence, the nature of a disease can be represented by multidimensional 'vectors' that aggregate across all body-wide axes (Fig. 2a). Indeed, the vectorial nature of disease resulting from collective deviations of multidimensional body-wide axes implies what is called 'arrow of time' in physics,<sup>24</sup> indicating that diseases progress in a specific direction over time. Furthermore, these vectors have both magnitude (severity of deviation) and direction (a tendency for morphing disease or regression states) that result from the actions occurring in each axis (Fig. 2b). For example, in schizophrenia, deviations in the molecular network and genetic axes cause significant severe symptoms, but these deviations can be reduced in magnitude by correcting the activity modulation mode of atypical antipsychotics.

Unfortunately, atypical antipsychotics also impact metabolic targets and exemplify the multitarget mode; new deviations within the internal environmental axis can lead to metabolic syndrome<sup>25</sup> and many of these patients will need additional corrective therapies. When a 'manifold' treatment is applied, the patient's vectorial tendencies will be countered by the aggregative drug action (Fig. 2c). This is analogous to the superposition of vectorial forces.

Multifactorial disorders are complex diseases, such as metabolic syndrome and neurodegenerative disorders, which are initiated through layers of genetic and environmental stimuli. Given that both internal and external causes combine, we postulate that the most important axes for therapeutic intervention in these diseases are the NIE and internal environment axes (Fig. 2di). Furthermore, the microbiota axis interacts with the NIE axis to produce unique commensal bacterial states, making it additionally important. In considering drug modes for multifactorial disorders, we postulate that the regimen and patient modes of the treatment are more important for countering the biased vectorial tendencies resulting from multifactorial disorders (Fig. 2dii).

By contrast, in monogenic diseases, the genetic axis is the predominant causal axis and repercussions are felt across the remaining axes. The immediate effect of genetic changes is the rewiring of the molecular network axis. The internal environment, NIE, and microbiota axes are then disturbed because of perturbations in the more fundamental axes (Fig. 2di). Thus, molecular and multitarget modes are hypothesized to be key for designing manifold interventions in monogenic diseases (Fig. 2dii).

## Principles for formulating manifold drug cocktails by design

We connect the above frameworks by proposing that vectorial tendencies require high-dimensional treatment and, thus, the manifold nature of drugs regimens must be considered. Drug cocktails with this expanded dimensionality are termed ‘manifold drug cocktails by design’ (M-CODE). Given the patient modifiers of drug action and each patient’s unique biased vectorial position on the body-wide axes, M-CODE regimens are formulated for each individual patient (Fig. 3). Here, three tasks must be accomplished to formulate a patient’s treatment: (i) prioritization of therapeutics; (ii) assessment of appropriate dosage; and (iii) timing of each medication. Here, we summarize the current feasibility of accomplishing these tasks.

Systems biology algorithms and machine-learning approaches have begun to approximate personalized drug discovery.<sup>26</sup> Some of these algorithms integrate multi-omic data to identify molecular targets, including previously unsuspected targets, which could have potential therapeutic value.<sup>27</sup> In addition, several computational models had been developed to predict side effects by examining drug chemical structures, drug phenotypes, and -omic signatures. In the M-CODE pipeline, combinatorial drug efficacy and side effects are prioritized because M-CODE emphasizes the combinatorial use of existing drugs. Nonetheless, drug-drug interactions can be difficult to access. Computational approaches, including artificial intelligence and drug interaction networks, have proven to be a fruitful strategy for exploring pharmacological interactions.<sup>28</sup> In addition, a patient’s ability to metabolize certain drugs can now be predicted by examining their specific variants of drug-metabolizing enzymes, which is key when formulating individualized drug dosages.<sup>29</sup> The final task of M-CODE requires further innovation and study. No computational tool for the optimal timing of treatment administration is currently available. Databases of rhythmically expressed genes across multiple species and tissues<sup>30,31</sup> and available oscillatory networks reverse-engineered from single cell data<sup>32</sup> provide a strong starting point for future development of such tools.

## Concluding remarks

Although multiscale models of disease have existed for years,<sup>33,34</sup> they remain primarily as mathematical models and lack an integrated conceptual framework to guide clinical translation. However, knowledge gained from next-generation technological advancements has the potential to revolutionize future clinical practice. To facilitate translation of medical knowledge into the clinic, we propose a schema called Manifold Medicine, which expands the dimensionality of treatment regimens by examining and manipulating the body-wide axes and manifold nature of drugs. Here, the biased body-wide vectorial tendencies of diseases can be countered by M-CODE. This conceptual formulation offers new opportunities to integrate biomedical and technological innovations into multidimensional personalized medicine (Fig. 3). Ultimately, we envision that Manifold Medicine and M-CODE regimens will evolve into automated artificial intelligence platforms that assist physicians in addressing disease with personalized therapies. In the meantime, Manifold Medicine not only provides a new perspective on the nature of disease, but, more importantly, also stimulates new ways of thinking about the design and administration of



new treatments, thus initiating new lines of inquiry in individualized medicine and drug discovery.

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**Box 1****Definitions and terminology use.****Dimensionality:**

multifaceted aspects of a state space in biology, such as nested and interacting gene/protein/metabolic network configurations.

**Manifold Medicine:**

conceptual schema that considers the multiscale-multifaceted contributory modes of disease etiology and treatment design.

**Manifold:**

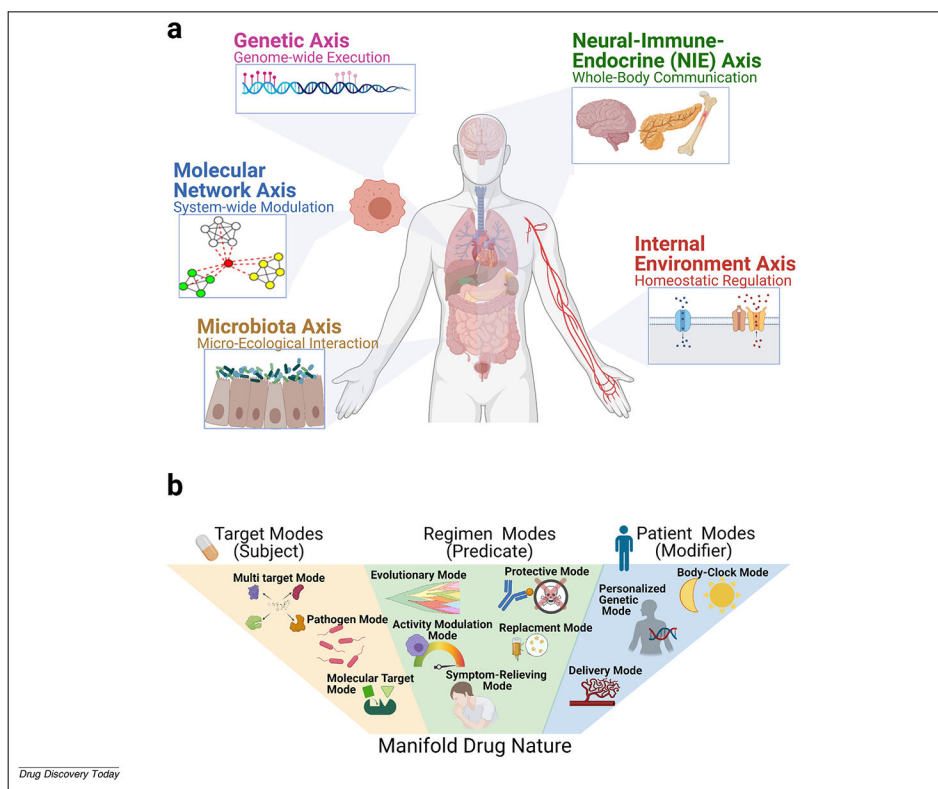
‘borrowed from the field of topology, in which it refers to  $n$ -dimensional space, which resembles an Euclidean space. Here, the term ‘manifold’ describes the multiscale-multifaceted features of bodily processes at the molecular, cellular, tissue, organ, and systemic levels that comprise the human body. The usage of ‘manifold’ in this way invites the abstraction of biological processes into a high-dimensional biological state space.

**Multidimensional body-wide axes:**

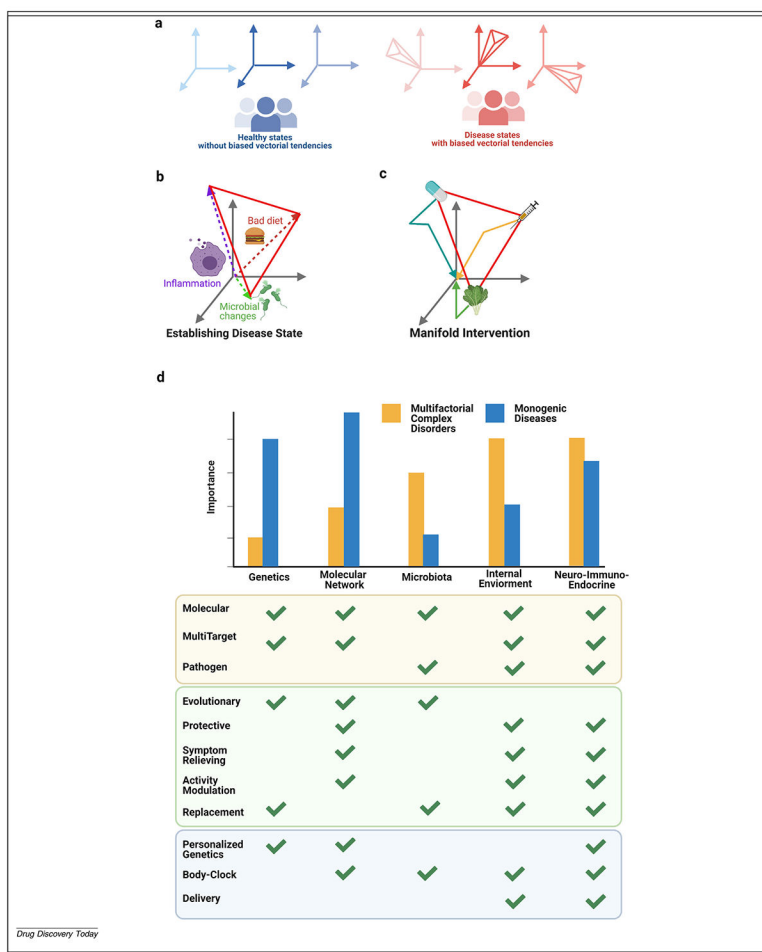
conceptual model that maps the manifold nature of the human body. The multidimensional body-wide axes comprise a genetic axis that describes genome-wide execution, a molecular network axis that describes systems-wide modulation, an internal environment axis that describes homeostatic regulation, a microbiota axis that describes microecological interactions, and a neural–immune–endocrine axis that describes whole-body communication. ‘Body-wide axes’ are distinct from the axes commonly used in anatomy and developmental biology that describe bodily position.

**Vectorial nature of biological processes:**

‘vectorial’ is borrowed from mathematics to refer to the directionality and magnitude of biological processes. This means that biological processes proceed in a specific direction over time, depending on the context within the examined cells and tissues. ‘Vectorial’ in this article is distinct from its definition in epidemiology, in which it is used to describe a disease-spreading entity.

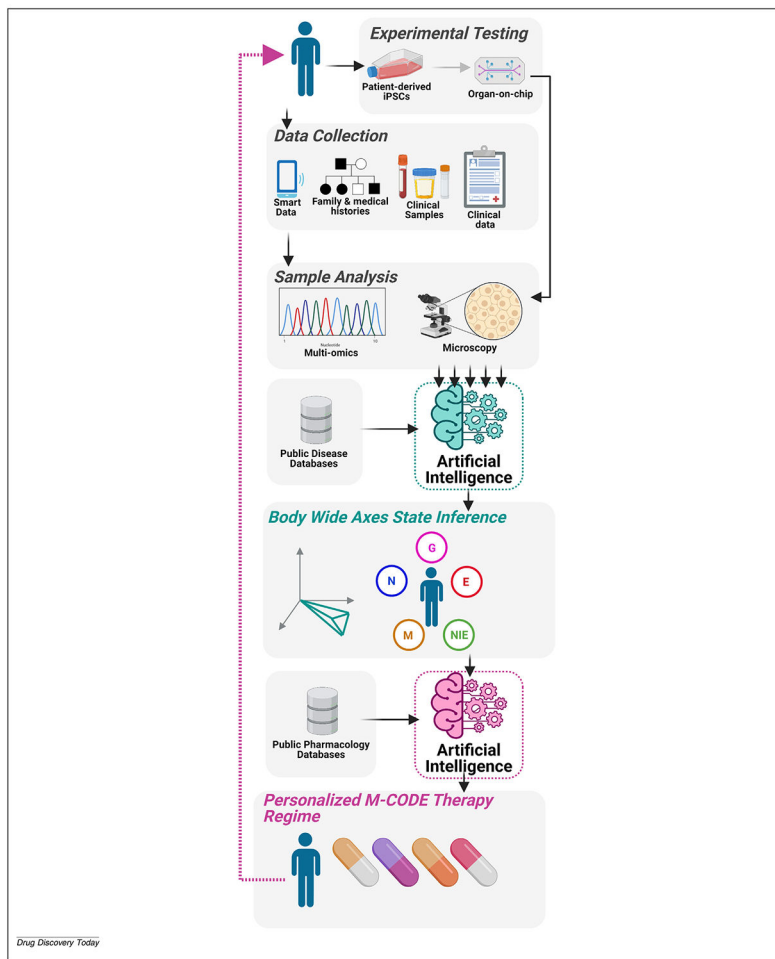
**FIGURE 1.**

The multidimensional body-wide axes and the manifold nature of drug actions. **(a)** Five body-wide axes characterize the structure and function of a patient’s health state. Each axis has a corresponding role that describes its purpose. Harmonious coordination between these axes gives rise to a healthy state, whereas their incoordination generates disease. **(b)** The ‘target–regimen–patient’ modes of the manifold nature of drug actions. The target modes are the ‘subject’ that pertain to the targeting of different drugs. The regimen modes are the ‘predicates’ describing the results of drug actions. The patient mode encapsulates the ‘modifiers’ of individual patients that interact with drugs to produce varied effects.



**FIGURE 2.**

The body-wide vectorial tendencies of diseases and the use of the manifold nature of drugs to counter them. **(a)** Incoordination between body-wide axes generates biases in each axis that combine to form body-wide ‘vectorial tendencies’ that are specific to individual patients. These vectorial tendencies are not generated in healthy individuals, in whom the activities of body-wide axes are harmoniously coordinated (axis origin). **(b)** Generation of biased body-wide vectorial tendencies arise from multiple pathological factors, such as inflammatory reactions, poor diet, and shifts of resident microbial community in the gut. **(c)** Manifold interventions counter disease vectorial tendencies and reset a patient back to a healthy state. **(d)** The histogram shows the relative importance of body-wide axes in multifactorial complex disorders *versus* monogenic diseases (i), whereas the check board indicates which drug modes of action to consider when a given body-wide axis is altered (ii).



**FIGURE 3.** Translation of medical discoveries into the clinic by integrating state-of-the-art biomedical technologies to formulate individualized ‘manifold drug cocktails by design’ (M–CODE). Patient-specific data will be compiled from sample collection, wearable monitors, and medical records. Multi-omics sequencing data (genomics, epigenomics, transcriptomics, and metabolomics) can be generated from collected samples (blood, urine, and tissues). In parallel, patient-derived induced pluripotent stem cells (iPSCs) can also be generated and reprogrammed into desired tissues for the study of their disease phenotypes using organ-on-chip technology. All data will be integrated and subjected to artificial intelligence models trained using existing repositories of healthy and disease data. These models will be deployed to chart the patient’s state on the body-wide axes. M–CODE drug recipes will be formulated to rectify any biased vectorial tendencies found in the previous step. The M–CODE regimen will be further ‘tuned’ by artificial intelligence models trained on pharmacokinetic, pharmacogenomics, and drug–drug interaction data. The final customized M–CODE will be administered to the patient with the goal to re-establish harmonious coordination across body-wide axes. Abbreviations: E, internal environment axis; G, genetic axis; M, microbiota axis; N, molecular network axis; NIE, neural–immune–endocrine axis.