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A Framework and Mechanistically Focused, In Silico Method for Enabling Rational Translational Research

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Abstract

A precondition for understanding if-and-when observations on wet-lab research models can translate to patients (and vice versa) is to have a method that enables anticipating how each system at the mechanism level will respond to the same or similar new intervention. A new class of mechanistic, in silico analogues is described. We argue that, although abstract, they enable developing that method. Building an analogue of each system within a common framework allows exploration of how one analogue might undergo (automated) metamorphosis to become the other. When successful, a concrete mapping is achieved. We hypothesize that such a mapping is, itself, an analogue of a corresponding mapping between the two referent systems. The analogue mapping can help establish how targeted aspects of the two referent systems are similar and different, at the mechanistic level and, importantly, at the systemic, emergent property level. The vision is that the analogues along with the metamorphosis method can be improved iteratively as part of a rational approach to translational research.

Introduction

Complex problems often require well-designed, complex solutions. A pillar of the NIH Roadmap is the idea that scientific discoveries must be translated into practical applications. Translation means a rendering from one representational system into another; representation means a likeness, model, or other [analogue] reproduction. The phrase “from one representational system into another” is important for this report because it suggests a method within a common framework. There is a large and deep literature on biomedical ontologies serving as reality representations.¹ The focus here is somewhat different: it is to present a method of building flexible, *mechanistic* analogue representations of related model systems used for research, such as in vitro and in vivo, and then achieving an additional method for translating one analogue into the other, so that the embedded knowledge can leveraged for the benefit of patients.

In biomedical research, the representational systems typically include specific in vitro models, animal models, and abstract, “typical” patients exhibiting specific disease symptoms. The phrase translational research can imply that one seeks sufficient knowledge to propound mappings from observations made in vitro to those made in animals, and on to those made in patients (and/or the reverse). Often, the observations of interest are experimental outcomes following specific interventions. Because the systems are complex and at times possibly even non-intuitive, mappings between them have often proven difficult to establish.

Toward a Method

Because biomedical wet-lab research models are complex, we can expect most mappings between them to be nonlinear and rarely simple. A mapping requires selecting an aspect of each system on which to focus, and then selecting a perspective and means from which to view and measure phenotypic attributes. Identical aspects may not exist in the different models. It may not be clear which aspect in one model corresponds to the one of interest in another. Further, practical and ethical considerations may preclude observing and measuring the systems using the same means or even using the same observational perspective. Navigating these realities can be problematic and that has been one of the motivations for increased interest in mostly empirical biomarker discovery research².

The development of a new drug (a candidate therapeutic intervention) from early in vitro observations into a new, approved treatment, when successful, is a simple example of successful translational research. The extremely low rate of success of that process within the pharmaceutical and biotech industries³ is illustrative of our current limitations for translating information about one wet-lab model into useful insight about another, related model. To simplify the discussion that follows, we focus on development of new drug treatments as an example of translational research.

Occasionally, when translation is successful, it is because relationships that exist between the observable

and measurable phenotypic attributes of two or more model systems have been somewhat straightforward. That situation is illustrated in Fig. 1. Continuing the drug development example: in a few cases (e.g., the one marked *a* in Fig. 1A), following dosing with the compound being researched, the pharmacological attributes and their generative mechanisms may be within the area of overlap. More often (marked *b*), the pharmacological attributes and their generative mechanisms do not overlap because aspects of the generative mechanisms at the whole system level are fundamentally different. Such differences can occur even when specific details (within the generative mechanisms) are essentially the same. Because of the complexities involved, coupled with the limits of reductionism,⁴ only recently has effort been invested in trying specifically to develop and understand mappings between systems as in Fig. 1 at the mechanistic level. The expanding variety of measurements (omics, imaging, etc.) provides the mapping within the system's phenomenal manifold, commensurate with its environment. The phenomenal manifold has been the primary focus for biomedical informatics and ontologies research to date. It contains the intersection of bioinformatics and health informatics.⁵ Models and simulations can also provide mappings⁶ by virtue of the requirement that the model provide a phenomenal manifold (of its own) that is acceptably similar to its referent. Such mappings are essential elements of an anticipated ontology that would strive to account for how one system relates to another. Absent that, the research remains empirical, and the low translational success rate experienced by drug developers and basic researchers will most likely persist.

How can we develop improved mechanistic mappings and thus begin putting in place the essential elements of quantitative methods of translational research? Consider the following five conditions.

1. A simple, abstract in silico system, containing active and passive components, is offered as a functioning analogue of a particular biological system used for experimentation.
2. A set of measurements of the analogue's behaviors under different conditions (phenotypic attributes) is judged by domain experts to be experimentally indistinguishable from (acceptably similar to) corresponding measurements of the referent system.
3. The analogue's components and their observable relationships have easily identified, logically consistent counterparts in the biological system.
4. The mechanisms underlying the analogue system's behaviors are a consequence exclusively of active (as opposed to merely reactive) component actions.

5. The analogue's active components function independently of one another (simulated autonomy): each uses axioms to determine the action to be taken based exclusively on its current state and the nature of its immediate, local environment.

When these five conditions are met, then we can state the following. 1) Understanding and predicting mechanisms in the referent is facilitated by studying the mechanisms in the analogue. 2) Studying the behavioral axioms of the analogue components facilitates exploration of their biological counterparts: a set of important principles of operation relied upon by the biological functional units.

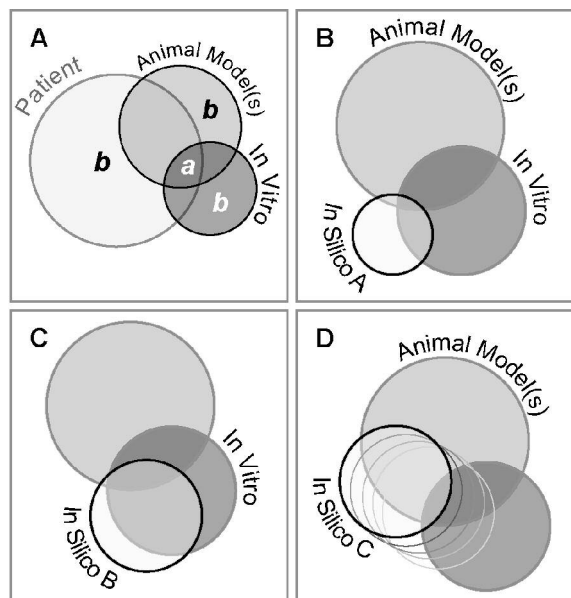


Figure 1: Relationships between the phenotypes of different model systems. Each circle represents a set of relevant, measurable phenotypic attributes, viewed from a common perspective, of three different systems (an in-vitro, wet-lab model, an animal model, and patients), along with their generative mechanisms. An example of attributes is measurable pharmacological properties following administration of the same drug. The in vitro system is a functioning analogue of targeted aspects of an animal model, which, in turn, is a model of certain aspects of a disease. **A:** The area of intersection among the three sets (marked *a*) represents a situation in which the pharmacological attributes and generative mechanisms in all three systems are similar. In such cases, extrapolation and thus translation from in vitro to patients is reasonably straightforward. However, the pharmacological attributes and/or their generative mechanisms can have fundamental differences (marked *b*); although aspects of each system are purposefully related, there is no logically consistent overlap in the full set of phenotypic

attributes of interest. **B:** A set of measurable phenotypic attributes of an in silico system are shown. Assume that it is a validated, abstract, but mechanistically realistic analogue (as in Fig. 2) of the in vitro system. Area of overlap: measurable properties of the analogue during execution (simulation) are experimentally indistinguishable from corresponding measures of the wet-lab system. **C:** After multiple rounds of revision and validation, “In Silico A” has evolved to become “In Silico B.” The larger area of overlap means that a larger set of the analogue’s relevant phenotypic attributes (and generative mechanisms) has been judged similar to wet-lab counterparts. Consequently, “In Silico B” embodies more of what we think we know about the in vitro system: it has become an informatics tool suitable for experimentation. **D:** Assume that a different in silico system—“In Silico C”—has been built using software components similar to those used by “In Silico B.” Further, it has been instantiated and validated within the same framework as “In Silico B”; the two analogues may use some of the same components but having different parameterizations. An automated method of *metamorphosis*, illustrated in Fig. 3, can be developed to change “In Silico B” into “In Silico C” and vice versa. The features lost and gained in that metamorphosis can stand as a hypothesis of what can and cannot be translated from in vitro to animal model.

To date, such principles have arrived piecemeal by induction following experimentation. Achieving and refining analogues like that described above offers a scientific, experimental approach to discovering cohesive sets of principles. A cohesive set operating principles (as distinct from isolated principles) can provide a framework into which more detailed, multilevel (cellular, subcellular, molecular, etc.) information can be connected directly to system level phenotype.

The above conditions suggest an approach⁷. We can begin by using available tools and semi-autonomous components⁸⁻¹⁰ to build a functioning in silico system that is an analogue, a non-deterministic representation, that exhibits a narrowly circumscribed set of phenotypic attributes. Such a model will have a phenotype of its own, one that overlaps somewhat with that of the referent in vitro system, as shown in Fig. 1B (condition 2). The in silico white blood cells (ISWBC)¹¹ and agent-based inflammatory cells¹² are early examples.

The best way to understand how particular system behaviors emerge is to build a separate, independent, simpler system that exhibits some of those same behaviors (condition 1). Note: that idea, motivated by the reductionist paradigm, has in turn motivated the crea-

tion and development of many of the in vitro systems currently used in biomedical research today. However, reductionist research methods may not succeed in describing system-level properties of living organisms¹³. The envisioned, in silico analogue in Fig. 2 is conceptually different from the precise mathematical descriptions of hypothesized mechanisms and the behaviors that characterize the majority of current, inductive, computational biomedical models.

Once we have an in silico analogue comprised of locally interacting semi-autonomous components (mechanisms) that cause systemic events and behaviors, we can hypothesize mappings to a referent biological system at two or more levels, as illustrated in Fig. 2.

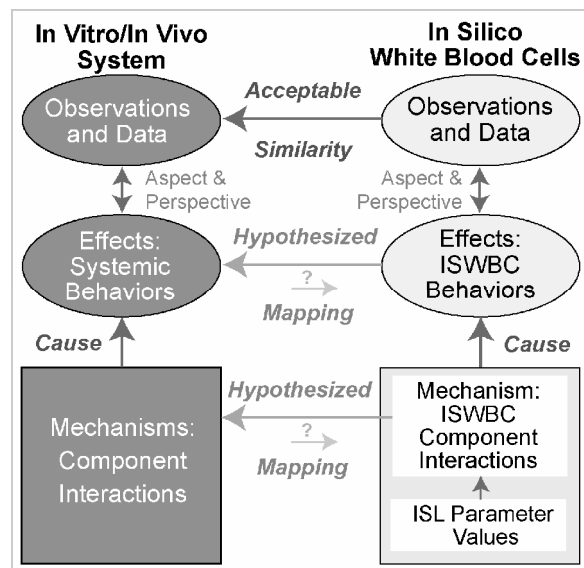


Figure 2. Illustration of relationships between the mechanisms and components within an in silico analogue (example: in silico white blood cells¹¹: ISWBC) and the referent in vitro or in vivo counterparts. When there is acceptable, temporal and dynamic similarity at the observational level (in silico observations and data validate against referent observations and data), then we can hypothesize that the in silico behaviors have biological counterparts (an iteratively concretizable mapping exists). Because those behaviors are caused by in silico mechanisms, we can also hypothesize that they too have biological counterparts. The in silico analogue stands as an instantiated, temporal, dynamic, and adaptive theory for how the biological system works.

Driven by coordinated, iterative, wet-lab and in silico experimental observations, the foundational analogue can be iteratively revised and validated with the aim of improving its mapping to the in vitro system, as

illustrated in Fig. 1C. In this way, more realistic in silico components can map to biological components, and at the systems level, in silico behaviors can map to in vitro behaviors. The ultimate goal of this process is to develop methods and hypotheses that support a metamorphosis of one validated in silico analogue into another (Figs. 1D and 3). A validated in silico analogue of an in vitro model that can change into a validated in silico analogue of a related, in vivo model stands as an instantiated hypotheses for corresponding mappings between the in vitro and in vivo systems. In silico, the method is extensible to patients, because some experimental in vitro systems serve as analogues of aspects of disease, e.g., when material form a patient becomes a component of the in vitro system¹⁴.

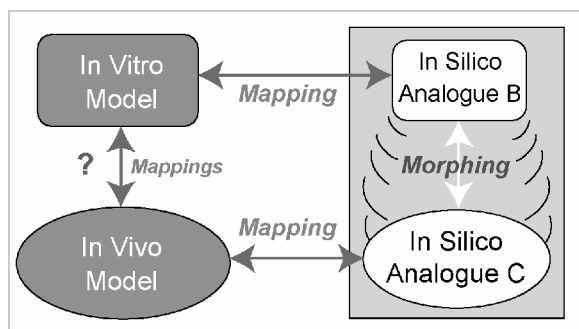


Figure 3. Mapping between in vitro and in vivo model systems. An in vitro model serves as an abstract analogue of an in vivo model, as in Fig. 1B. There is uncertainty about the degree to which observable consequences of interventions made in vitro can be used to predict the consequences of comparable interventions in vivo, because knowledge of how the in vitro model maps to the in vivo model is too vague. Assume that a validated analogue (B) exists, as in Fig. 2, of the in vitro system, and that a validated analogue (C) also exists of the in vivo system. Both analogues exist within the same framework. A method is developed to structurally change analogue B into analogue C, and vice versa. That metamorphosis stands as a working, testable hypothesis of how an experimental intervention on the in vitro system translates to expected consequences in the in vivo system. In silico, we know what is gained and lost in translation (during the metamorphosis), including translational heterogeneity. Additionally, we can acknowledge (and in some cases simulate) translation error and ambiguity. We can use the representation of that insight to anticipate counterparts for the biological systems. Further, we can imagine extending the relationship to patients. When that is done, the silico analogues become the current best ontology for what does and does not *translate*.

The plan for achieving translation mappings as depicted in Figs. 2 and 3 cannot be achieved using traditional, inductive models as analogues: although that class of models works well for precise prediction in a well-defined context, inductive models lack the conditions listed above that we argue are essential for achieving analogues of the type illustrated in Fig. 2. Merging lessons from the literature with those learned during the evolution of three projects^{11, 15-17}, along with identifiable requirements that must be met in order to achieve analogues that can be extended to include the temporal features implied in Fig. 3, we identify five capabilities that the envisioned analogues should exhibit.

1. *Transparency*: in silico analogues must be transparent. Component details and their interactions need to be visualizable, measurable, and accessible to intervention as the simulation progresses.
2. *Articulation*: It must be easy to join, disconnect, and replace in silico components within and between levels, and within the simulated experimental context: i.e., the components articulate.
3. *Granularity*: it should be relatively simple to change usage and assumptions, or increase or decrease detail (unplug a component and replace it with one that is more or less complicated, having finer or coarser granularity) in order to meet the particular needs of an in silico experiment, without requiring significant re-engineering of the in silico system.
4. *Reusability*: The analogue and its components need to be designed to be reusable for simulating behaviors in different experimental conditions.
5. *Discrete interactions*: to enable the above capabilities, the analogues in Fig. 3 and their framework must include discrete interactions that explicitly show relations between components.

A simulation system that exhibits these five capabilities has three advantages. First, the quantifiable set of rules or axioms^{11, 15-17} that govern their behavior are the in silico counterpart of a biological systems principles of operation. The operating principles followed are based on local information rather than central control. Validation of plausible principles of operation is an essential step in building mappings between laboratory models and from those models to patients. Second, agent based modeling methods take advantage of the principle of emergence. The temporal interaction of adaptive agents allows the resultant dynamics to develop within the context of the system as a whole, thus preserving aspects of the complexity inherent to living systems. This conservation of complexity is thought to be vital in studying the behavior of complex systems and understanding what may be vital to

successful translational research. Third, agent based modeling is intuitive. For researchers who are non-mathematicians, the agent-based paradigm has demonstrated its ability to allow easier transfer of their domain-specific knowledge into simulations. As a result, analogue engineering is more transparent, and it is potentially easier to identify artifacts arising during construction.

Summary

In summary, we have argued that in order to achieve a much higher frequency of successful translation of basic, biomedical research (bench) findings into applications that improve health (bedside), new, in silico methods are needed to facilitate the rendering from representational systems that live in the research domain (in vitro, animals, etc.) into that of patients. These methods, we argue, will need to include the use of analogue systems capable of producing emergent properties analogous to those characteristic of living organisms. With the described class of analogues, we can begin to identify if and how observations in a wet-lab research model may map to expected observations in patients. Without that critical component, potential benefits of research will continue to be at risk of getting lost in translation from bench to bedside.

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