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Modeling and Simulation: Synthetic Models and Methods

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Definition

A synthetic (biomimetic) model (SM) is constructed from extant, autonomous software components whose existence and purpose are independent of the underlying model they comprise. It combines these elements in a systematic manner to form a coherent whole. A simulation, which is an executed instance of an SM, generates the model's behavior according to a pre-specified computational design. Synthetic methods (Hunt et al. 2006) were invented to tease apart the underlying dynamics of complex systems, in contrast to inductive models and related methods, which target prediction of the average behavior of systems in a continuous manner and are less concerned with the dynamics of individual model components.

Characteristics

Fundamentally different models

Successful development of new, safe and effective drugs and treatment protocols requires deeper insight into the mechanisms involved, at all biological levels. Because the systems are complex and dynamic, we need new classes of simulation models, calibrated to current mechanistic knowledge, to facilitate experimentation to discover plausible treatment outcomes and enable exploration of the origins of emergent phenomena as they unfold.

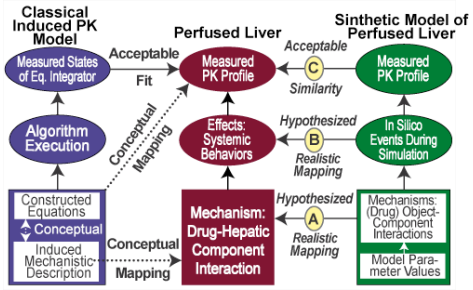

Figure 1. Contrasting synthetic, wet-lab, and familiar inductive pharmacokinetic models.

As an example in describing differences in model types, we consider hepatic drug disposition. Relationships between three different model types are illustrated in Fig. 1. Measures of drug loss from perfusate during liver perfusion (center) provide a classical pharmacokinetic (PK) profile. During perfusion, hepatic components interact with transiting drug changing the drug's concentration-time profile. The leftmost diagram illustrates creating and fitting a PK model to the profile data. The researcher identifies patterns in the data in both an exploratory and a statistical fashion. An abstract, albeit idealized, mechanistic description of what is thought to have occurred is formulated, thus establishing a conceptual mapping between this abstract description and hepatic cellular mechanisms. One or more PK equation models are selected to describe data patterns. There is also a conceptual mapping from description to

equations. Software is executed to simulate equation output, enabling a quantitative mapping from simulation output to PK data. Metrics specify the goodness of fit.

In contrast, in the rightmost model, a mechanistic description is specified; it is similar, but not identical, to the one on the left side. Software components are designed, coded, verified, and connected, guided by the mechanistic specifications. The product is a collection of micro-mechanisms rendered in software. A concretizable mapping (A) exists between in silico components and how they fit together, and 1) hepatic physiological and micro-anatomical details, and 2) drug interactions between components. Dynamics observed during simulations map to (B) corresponding dynamics (believed to occur) within the liver. Simulation measures provide a PK profile that is intended to mimic the liver perfusion PK profile. Quantitative measures establish similarity between the two outflow profiles (C).

The rightmost model of Fig. 1 is an extant hypothesis: the components (objects) will illuminate a traceable mechanism upon simulation execution, a consequence of which will be the emergence of phenomena, such as response following xenobiotic exposure. If similarities between the resulting simulated system and the referent system meet some prespecified criterion, the simulation stands as an abstract, plausible, mechanistic theory about events that may have occurred during the wet-lab experiments.

Agent-based methods

The mechanisms that generate pharmacological phenomena are consequences of components at multiple levels of detail interacting in a complex manner with drug compounds. Simulation of such behavior may be achieved by adopting discrete-event modeling and simulation (M&S) methods (Fishman 2001) in which component interactions can proceed according to stochastically-defined rules (Ullah and Wolkenhauer 2010).

Some biological components subject to wet-lab analysis possess a degree of spatial organization, are semi-modular, and quasi-autonomous. Synthetic models must be capable of exhibiting these same attributes. Component quasi-autonomy coupled with realistic, spatially organized, biomimetic mechanisms can be achieved using agent-based and agent-oriented methods (An et al. 2009; Hunt et al. 2009). Quasi-autonomous, decision-making entities called agents can map to an organism, an organ, a tissue subsection, a cell, and/or a subcellular process. Other components, such as compounds (biologics or xenobiotics), may themselves be represented as objects or environments. Reactive objects (agents) follow sets of rules that govern their actions and interactions. A biomimetic agent will have its own agenda, can schedule its own actions, and can dynamically change its operating logic. Agent-based SMs have advantages when attempting to understand and simulate phenomena produced by systems of interacting components, and that makes them useful in gaining deeper insight into pharmacological phenomena within different individuals. An important use is in understanding the mechanisms that generate disease-related phenomena and how compounds and treatment protocols influence those mechanisms and alter pharmacological phenomena.

Objects and agents can be either atomic or composite. Organizational levels define the system's granularity, or the extent to which the system is subdivided, and in which the smallest components are considered “atomic” (an atomic object contains no components of its own). Indeed, the more finely-grained the system, the greater level of biological detail the model wishes to examine. Objects, both atomic and complex, are designed to be inherently modular, and can be replaced (as distinct from being subdivided) with more fine-grained components that exhibit the same behaviors. Components can be hierarchically nested, allowing the use of SMs to discover plausible upward and downward relations

necessary for hypothesizing, instantiating, and in silico testing of multiscale genotype-phenotype relationships. Though in practice, a greater degree of nesting implies more components and interactions, SMs should be just fine-grained enough to produce targeted phenomena and achieve the analogue's specified uses.

Precise stoichiometric knowledge of component-compound interactions is rarely if ever available. An advantage of discrete-event methods is that both knowledge and ignorance (uncertainties) can be represented concurrently and simulated across a wide spectrum. The effective stoichiometry of interactions involving compounds can be represented at almost any convenient granularity level below that of the targeted phenomena, but the mappings from objects representing compounds to their referent molecules are not one-to-one. The presence of a compound can be represented as a property of a space or as mobile objects (Hunt et al. 2009). Mobile objects representing compounds can map to an arbitrary number of molecules. An important feature of the synthetic approach, from a pharmaceutical sciences perspective, is that each mobile object carries a list of physicochemical properties (PCPs) along with bioactivity attributes (the chemical entity is a CYP 2C9 substrate, etc.). In that way, SMs can accommodate any number of different compounds concurrently, which of course is ideal for studying and exploring drug-drug interactions (Lam et al. 2009). A component empowered to interact can use PCP information to adjust how it interacts.

Parameterizations

Early in SM development, micro-mechanistic knowledge is insufficient to parameterize component-compound interactions a priori using PCPs. Micro-mechanism logic must be tuned for the first several compounds. As the set of compounds enlarges, inductive modeling methods (e.g., multiple regressions, ODEs, PDEs) can be used to establish quantitative mappings from patterns in PCPs to patterns in parameter values of tuned component-compound interactions. Such mappings will be the synthetic model’s counterpart to a structure-activity relationship. In subsequent rounds of SM refinement, the new knowledge contained in that relationship can be used, in some cases automatically, to provide an initial SM parameterization for the next chemical entity to be studied. Simulations using those parameterizations will stand as crude predictions of the new compound's attributes (Yan et al. 2008).

Iterative Refinement

The stages in scientific M&S are illustrated on the right side of Fig. 2. The micro-mechanisms form a hypothesis to be executed in silico and to yield output data. When the data fails to achieve a pre-specified measure of similarity with referent data, the mechanisms are rejected as being plausible representations of wet-lab counterpart (Lam et al. 2010), and the cycle begins anew.

The iterative refinement protocol in Fig. 2 facilitates parsimony, which is important when building SMs that are expected to become increasingly complex. The protocol facilitates generating multiple mechanistic hypotheses and then eliminating the least plausible through experimentation.

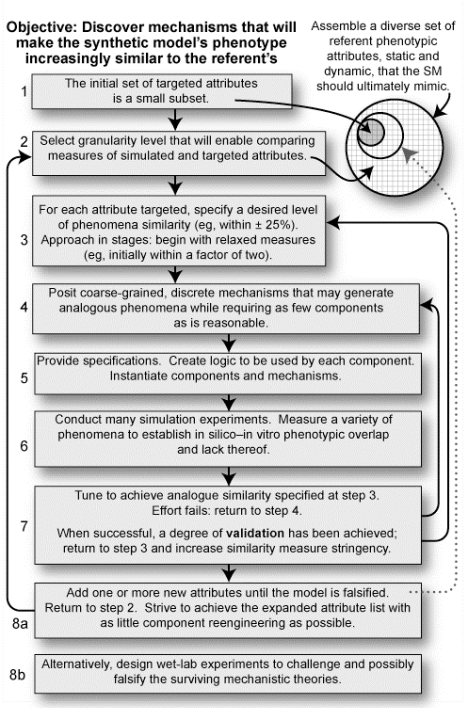

Figure 2. An iterative refinement protocol used to improve synthetic models.

The iterative refinement protocol in Fig. 2 is core to the scientific use of SMs. When faced with the task of building a scientifically relevant, multi-attribute SM in the face of significant gaps in knowledge, parameterizations and model components must strike a balance between too many and too few. Doing so can be complicated by the fact that a validated, parsimonious, multi-attribute SM will be over-mechanized ("over-parameterized") *for any one attribute*. Too many components and parameters can imply redundancy or a lack of generality; too few can make the SM useless for researching multi-attribute pharmacological phenomena. SMs are ideal for discovering mechanistic explanations in the form of relationships between components. However, because of the uncertainties reflected in poorly resolved model parameters and mappings to referent, they lack the precise predictive power of mathematical models. A SM such as that on the right side of Fig. 1 can be used to make predictions (quantitative or qualitative), for example, about where and how multiple "compounds" administered together may effectively interact.

Knowledge embodiments

SMs have the potential to evolve into executable representations of what we know (or think we know) about biological systems during pharmacological exposure: they become executable biological (Fisher and Henzinger 2007) knowledge embodiments that provide concrete instances of that knowledge (right side of Fig. 1) rather than computational descriptions of conceptual representations (left side of Fig. 1). During simulation, a synthetic model demonstrates when, how, and where our knowledge matches or fails to match details of the referent system.

Such systems will represent the current best theory for how different pharmacological phenomena emerge within different individuals (Hunt and Ropella 2011). Adjusting (tuning) a SM to represent (for example) a normal rat liver in one in silico experiment, a diseased rat liver in another (as in (Park et al. 2010)), and a human liver in another will be relatively straightforward because uncertainty can be

preserved. Automatable cross-validation of component functions can specify which features to tune and by how much. One may take copies of the same model and tune each separately to reflect differences in measured, patient-specific attributes.

Cross-references

ODEs,
PDEs

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