

Illustrations of Credible Healthcare Focused Simulation Models

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Consider the diversity of the Committee's audience. We want an interested person to consider "buying into" (or not) and actively supporting the Committee's recommendations and pronouncements. I suggest that getting buy-in will be helped considerably by presenting a collection of clear, straightforward, instructive, plausible yet hypothetical examples, where each describes uses of a particular healthcare-focused, simulation model and, to a degree, illustrates how credibility is being garnered.

What follows is my initial attempt at four related examples.

The examples focus on asthma. Credible simulations are needed to select from competing options to improve and individualize treatment and prevention options along a path that is also reducing costs. A preamble for Examples 1-3 is that simulations aimed at humans will be preceded by credible simulations of animal models such as rat asthma models and humanized mouse model of severe asthma. Examples 1-3 describe simulations of those animal models.

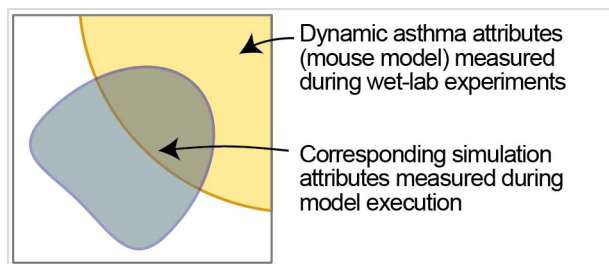


Figure 1. This sketch illustrates phenotype overlap for simulation Model-1. It has achieved degrees of credibility for use in support of new treatment research. A variety of mouse model attributes can be simulated at multiple scales. Quantitative in silico-to-wet-lab attribute similarity has been demonstrated for several previously completed experiments with and without different therapeutic interventions. When given prespecified, quantitative similarity targets, a small set of prospective simulation experiments successfully anticipated therapeutic intervention outcomes.

Example 1. *Model-1 is opaque.* It is analogous to the Archimedes Model (<http://archimedesmodel.com>), although much smaller. It is proprietary. Its short successful track record is a major factor behind the credibility already garnered. Insights provided by earlier prediction failures enabled model revisions, which reduced the frequency of subsequent prediction failures. Conceptual descriptions of the normal and asthma-altered physiology represented or accounted for in Model-1 are well documented. Some of the

mathematical implementations of those descriptions have been published. Others have not: they are valued intellectual property. Model-1's implementation in software is patented and has not been disclosed. However, records are available for many simulation experiments: from both current and earlier versions. Results from a battery of benchmark experiments are published following each significant revision. Model-1's credibility with users and domain experts is primarily a consequence of its track record and the abundant documentation of many simulation experiments.

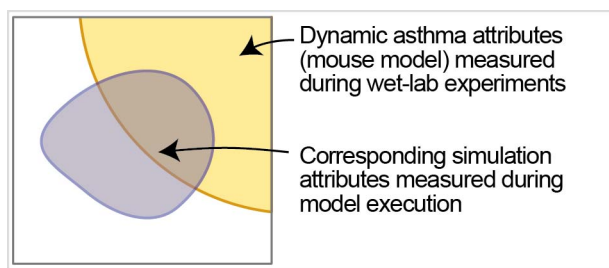


Figure 2. Same illustration as Fig. 1 but for simulation Model-2

Example 2. *Model-2 is translucent, open, but not biomimetic.* It is multiscale and multi-attribute. It is similar in several ways to the Virtual Physiological Rat [<http://virtualrat.org>] but simpler, with fewer fine grain features; it currently has a carefully circumscribed use case space. Validation evidence is available in five research articles. The physiological, mechanistic, explanatory theories on which Model-2 is based, along with explanations for levels of abstraction, are well documented. Particular details are easily traced to the literature. Justification arguments in support of the mathematical representation (primarily as ODEs) of those theories are provided. Parameterization protocols and sensitivity analyses are explained in an accessible version repository. A subset of parameter values is individually traced to source articles. However, Model-2's track record in predicting outcomes of experiments prospectively is still quite limited. Those experiments have been more narrowly focused than Model-1's because the scope and variety of simulated experiment designs for which Model-2 can provide predictions is smaller. Model-2's current (and past) code and execution instructions are available along with version records and verification documentation. A few independent labs have used Model-2 and published their results along with credibility-enhancing observations. However, requirements and specifications are not available. The degree of credibility enjoyed currently is a consequence primarily of the clarity of its biological and technical documentation coupled with the accumulating validation evidence.

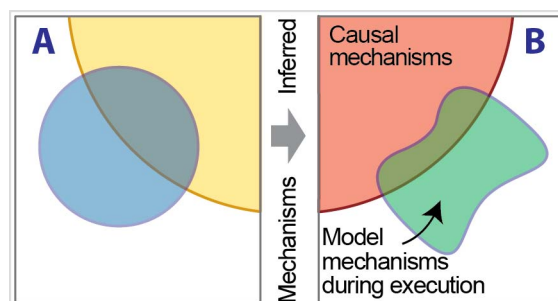


Figure 3. Frame **A** is the same illustration as Fig. 1 but for simulation Model-3. **B**: Different discrete event abstractions of dynamic mechanisms inferred by domain experts are implemented in software to be biomimetic during execution. Mechanisms within the region of overlap are hypothesized to have actual counterparts in mice.

Example 3. *Model-3 is transparent.* Its simulated multiscale, multi-attribute phenomena are similar in several ways to those of Model-2. However, Model-3 uses object-oriented, discrete event simulation methods. Development of Model-3 & Model-2 was both guided by the same body of evidence and physiological, mechanistic, explanatory theories. Model-3 has achieved some of the same quantitative validation targets as Model-2. Model-3's current and envisioned use cases are specified. They are concerned more with improving and challenging explanatory, multiscale, mechanistic insight (in the search for improved intervention and normalization strategies) and less with precise prediction. For that reason, differences in unfolding of Model-3's causal cascades during execution, in response to simulated interventions (Fig. 3B), are designed to be biomimetic and observable. Because those mechanistic features as well as simulated phenomena can be quantitative validation targets, Model-3 has available additional means to build credibility. Further, Model-3's requirements and specifications have been published. That enabled another group to build an independent implementation of the model, which cross-validated with the original, a process that is infeasible with Model-1. Independent reproduction provides an additional means to build credibility.

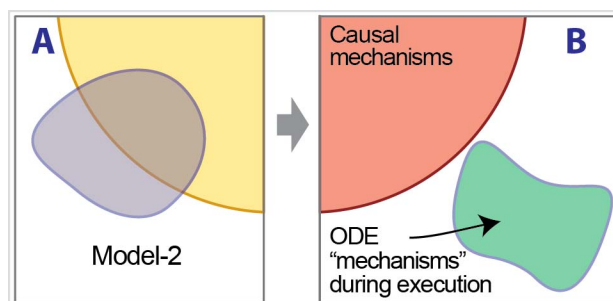


Figure 4. Frame **A** is a copy of Fig. 2. The builders of Model 2 describe conceptual mapping from the ODEs to idealized versions of the physiological, mechanistic, explanatory theories. The ODEs have been implemented using Matlab tools with a priority given to execution speed. Making execution mechanistically biomimetic was not a requirement, so

there are no similarities (no hypothesized overlap as in Fig. 3B) to mouse model causal mechanisms.

Example 4. *Model-4 is extant, tacit.* Its simulation focus is severe asthma in hospitalized patients, not a rodent model. The model is a proprietary mannequin used in training healthcare providers to deal effectively and individually with hospitalized severe asthmatics. The mannequin contains a variety of hardware and software. It can be connected to standard monitors. Trainees have access to instructor-selected “patient records.” Trainees respond (e.g., altering or changing treatments) to changes in monitor readings. Mannequin responses emerge from simulations based on detailed normal and asthmatic physiology models similar to those used by Model-1 and the Archimedes Model. Hardware, software, and simulation model details remain confidential. The company, following each significant revision, posts results from a battery of benchmark experiments. Both positive and negative unedited testimonials from recognized domain experts and a variety of instructors, trainees, and trainee supervisors are available on a user-group-maintained website. The degree credibility enjoyed by the mannequin’s simulation model component derives primarily from is those testimonials, supported by the available technical documentation.