

## PERSPECTIVE

## Quantitative Systems Pharmacology and Empirical Models: Friends or Foes?

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**Recently, it has been proposed that more complex models should routinely be compared to empirical or simpler models<sup>1</sup>; often, simple models can predict specific emergent properties of complex systems as well as more complex models, hence questioning the added value of the latter. This perspective discusses this important point in the context of the purpose of modeling.**

## DISCUSSION

Arguably, pharmaceutical industry productivity continues to decline, and some suggest it will cross the zero net return on investment threshold soon.<sup>2</sup> The conclusion of analyses of this is that phase II failure is the key event, showing we did not understand the consequences of perturbing a biological system with a xenobiotic. Although it can be advocated that novel technology will help,<sup>2</sup> precedent indicates this can only achieve so much. Thus, the requirement for improved understanding of human disease biology complexity remains. Quantitative Systems Pharmacology (QSP) is gaining traction as a tool to tackle this problem. However, one reasonable criticism of this approach is that the confidence in such highly complex models is hard to quantify. Biology data are incomplete, constantly evolving and potentially incorrect; thus, how can we be confident in models built upon this foundation, what is the added value, and how can the effort be resourced to deliver insight in a timely way?

To answer these questions, we need to think about the purpose of building models.

Simple models have been in use for decades in pharmaceutical research, typically as pharmacokinetic/pharmacodynamic (PK/PD) models. These have been successful in improving phase II/phase III efficiency but had a limited effect on Translational efficiency.<sup>3</sup> One reason for this may be that empirical models parameterized with significant population data are good for extrapolating to the next clinical phase or patient cohort. Mechanistic insight is not necessarily required, as the empirical and probabilistic suffices. In contrast, extrapolating from a preclinical observation in an animal model or *in vitro* dataset is an entirely different proposition; a type of “far extrapolation” vs. the “near extrapolation” of interpatient prediction. Thus, questions arise as to whether we clearly understand how to extrapolate preclinical PK/PD or indeed whether the data themselves lack

translational validity. Put simply, is the biology in the animal model similar enough to human disease to inform a useful prediction or not? Attrition data alone would indicate not.

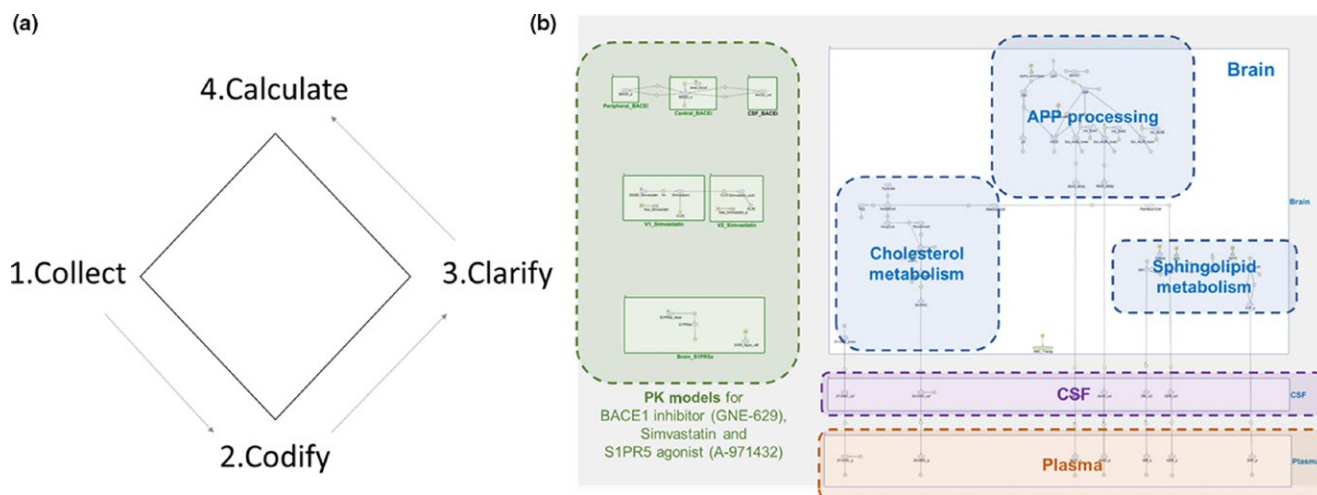
Thus, a clear need exists for another methodology to extrapolate from the preclinical data and hypothesis. A logical step would be to explore the utility of more complex mathematical (e.g., QSP) models. In contrast to the empirical, the aim of QSP models is typically to generate mechanistic insight that can aid decision making. However, what can we do with a more complex model that we cannot do with a simple model?

**Things we can do with a big model that we cannot with a simple/empirical model**

**Tools to investigate the drug targets in a specific pathway.** As an example, consider the nerve growth factor (NGF) pathway currently of interest in drug discovery. QSP models of the NGF pathway have been developed using preclinical data.<sup>4</sup> Thus, a sensitivity analysis identified NGF, TrkA kinase, and Ras as the optimal drug targets in the pathway and suggested efficacious doses for NGF and TrkA inhibitors. These predictions differed significantly from standard empirical predictions but have subsequently been supported by clinical data. The clinically efficacious dose for an NGF-binding monoclonal antibody tanezumab was predicted by the QSP model to be ~10 mg, as was subsequently established via phase II clinical trials.<sup>5</sup> The model predicted TrkA kinase is also a target, but > 99% maintained inhibition would be required to achieve efficacy on par with anti-NGF monoclonal antibodies. This conclusion was recently supported by clinical trial data for PF-06273340.<sup>6</sup> Finally, the model predicted that the Ras/Gap in the pathway is one of the most important control points. Human genetic evidence shows that patients bearing a loss of function mutation in neuronal Ras/Gap exhibit a chronic pain phenotype.<sup>7</sup> Thus, the information content of the QSP model has led to targets and associated dose predictions that have been verified by clinical data. In this respect, the complex model “wins.” Simple PK/PD models have also been used to assist decision making for the clinical development of tanezumab.<sup>8</sup> Sufficient understanding to extrapolate across patient groups can be achieved with a simple model and, thus, the simple “wins.” This does not show that a simple model is better than a more complex one but, rather, that they are different tools addressing different questions; one

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**Figure 1** Added value of more complex models. (a) The “four C” value diamond of typical complex Quantitative Systems Pharmacology (QSP) models. In stage 1, input data are collected. These can come from text mining of literature corpuses (both automated and manual). In addition, domain expert opinion should also be utilized. In stage 2, these data are captured and codified in the model structure. Parameter and reactant values are hyperlinked to sources, thus preventing drain away of institutional data. To ensure scalability ontologies may be used. In stage 3, a graphical user interface (GUI) of the model is presented to domain experts to initiate a dialogue and clarify the accuracy of the model. Finally, in stage 4, the model can be used for calculations, such as calibration simulation and sensitivity analysis exercises. The diamond can be reinitiated as new data emerges. Gray arrows indicate typical order of execution of the stages. (b) An example representation of a QSP model for AD. (Image reprinted from ref. 10, *CPT: Pharmacometrics & Systems Pharmacology* <https://doi.org/10.1002/psp4.12351>, image is licensed under CC BY-NC-ND 4.0. ©2018 The authors.) The visual representation of compartments, reactions, and reactants allows cross-discipline dialogue concerning the model. The GUI can be examined as shown at the level of the holistic model or specific areas can be visualized. APP, amyloid beta precursor protein; BACE1, Beta-secretase 1; CSF, cerebrospinal fluid; PK, pharmacokinetic; S1PR5, Sphingosine-1-phosphate receptor 5.

is focused on our understanding of the pathway biology. In contrast, the other relates population PK/PD to a pain score and to extrapolate dose response to the next patient cohort.

#### Store mixed data on structure, components, and process.

A unique property of QSP models is that they enable the collection of a summary of mixed multiscale data types. This can be subdivided into the tasks of capturing data, codifying data, clarifying data, and ultimately calculating or quantifying the implications (**Figure 1a**). This enables a concise summary of all of the information a given project team believes is the relevant biology. The pathways and interactions can be displayed graphically (**Figure 1b**), facilitating discussions with domain experts. Pathways and parameters can be linked to sources that allow rapid interrogation of the underlying data. Thus, such models act as a single repository of institutional information that is simple to access and easily updated and can prevent the drain away of institutional know-how. Empirical models cannot enable this type of mixed-data capture in this way and, hence, the complex “wins.”

**Model reduction: large models can be reduced but simple/empirical models cannot necessarily describe new data.** There are several examples of successful model reduction; the complex pathway (full) NGF model was reduced from 99 to 11 state variables.<sup>9</sup> In terms of simulating a given response to NGF pathway stimulation, the models perform equally well and, in this case, the simpler model “wins.” However, some information content of the full model is lost. At a simple level, the known biological pathway information is replaced by a series of input/output boxes.

This has pros and cons; a pro may be that the complexity is rendered simpler to view. A con is that the known true pathway connections are lost and parameters that are linked to external data sources are lumped. At a quantitative level, the individual key controlling elements cannot be identified in the reduced model. From a drug discovery perspective, this is valuable information content, as discussed earlier.

It is also important to note that this reduction is a closed process, in the sense that details can be lumped and expanded, but those that were not in the model originally cannot necessarily be inferred (**Figure 2**). Following on from this, an advantage of multispecies QSP models is that they can be calibrated to and can simulate multiple end points (**Figure 2**). In contrast, an empirical model is typically restricted to a limited number of emergent properties. In addition, if complex models can be lumped efficiently, then simple empirical models can be produced as required from more complex models (e.g., during clinical trials to fit clinical emergent property data and to simulate clinical trial designs).

**Enable an enquiry into biological complexity.** There are now many pathways in which the structure and reactions are in part agreed (e.g., NGF pathway). A logical step is, therefore, to build models that most closely reflect this, rather than an abstraction. We may not currently understand what this is telling us, but this approach gives the best possible capture of the biology and, hence, an optimal chance of extracting useful knowledge. The example of model reduction for the NGF pathway model mentioned previously illustrates the point; nature has evolved a pathway for the NGF pain response containing multiple steps. Model

