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Applying Model Reduction to Lessen the Complexity of Quantitative Systems Pharmacology Models

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One of the greatest challenges in drug development is the high attrition rate obtained in Phase 2 clinical trials, resulting in significantly elevated R&D costs and time. In fact, approximately 80% of new drugs that move into Phase 2—the phase when a new drug is first tested in humans—fail to demonstrate safety and efficacy. This high failure rate is largely due to a lack of understanding of the complexity of biological systems, making it difficult to predict how a drug can perturb it.

What is systems biology and how has it helped enhance our understanding of biological systems and disease progression?

The explosion of high quality "omics" information—genomics, proteomics, transcriptomics, metabolomics and others—at the start of the 21st century fueled the development of systems biology. This field applies a nonlinear, integrative, quantitative, and holistic approach that uses biology, computational modeling, engineering, bioinformatics, and other sciences to understand complex biological systems and how perturbing them can cause disease.

Quantitative Systems Pharmacology

Bridging pharmacokinetics and systems biology to model drug disposition with detailed descriptions of target-scale dynamics

Quantitative Systems Pharmacology (QSP) is a relatively new discipline with enormous potential to improve pharma R&D productivity and inform decision-making across the drug development process from early discovery to Phase 3. QSP provides an *in silico* framework for constructing mechanistic, mathematical models of drug action. The discipline incorporates pharmacometric, pharmacokinetic/pharmacodynamic (PK/PD), and physiologically-based PK (PBPK) approaches with systems biology models of biological and biochemical processes. QSP models can inform the mechanisms of drug efficacy and safety and confirm drug target binding and expression.

This approach can be used to predict how drugs modify cellular networks and how drugs impact and are impacted by human pathophysiology. QSP can also facilitate evaluating complex, heterogeneous diseases such as cancer, immunological, metabolic, and CNS diseases that commonly require combination therapies to control disease progression.

The complexity of QSP models and its impact on clinical utilization

By seeking to describe target scale dynamics systematically, QSP models are inherently complex. Thus they are often too large to validate and use in a clinical setting, or fit in a traditional sense. The result is that they become difficult to interpret using standard methods of analysis or even the modeler's own intuition. As with any approach, QSP has its challenges, much of which is attributed to model complexity:

- Parameterization of very large models
- Model validation—what to include in a complex model in terms of target scale dynamics and what to leave out
- Model identifiability
- Model complexity

Model complexity is a recognized issue in QSP. These models are complex due to the following reasons:

- High dimensionality of the modeled species, reactions, or complexes
- Elements of the model are interconnected with a high degree of nonlinearity (with positive/negative feedback)
- Interactions are described by complex mathematical expressions
- The system is sensitive to particular components, and it evolves over a wide range of time scales, ie, stiffness

> "There is no unique definition of complexity—and the scientific notion has traditionally been conveyed using particular examples..."
>
> – Neil Johnson
> Professor of
> Complexity Science

Challenges with Model Complexity

There are several key challenges associated with model complexity that, when taken in combination, create difficulty in traditional modeling approaches. First, the "curse of dimensionality" is an exponential phenomenon where the number of features or dimensions, ie, states or variables in a system, results in data that becomes sparse relative to the volume of the space. For example, a model containing 40 dimensions will have 2^{40} or over 1 trillion levels, making it difficult to reliably know if you are capturing everything about a system where the data was captured. Such high-dimensional models make traditional application of data in modeling—model identification, validation, etc.—often untenable.

Other issues of model complexity include:

- Structural identifiability becomes compromised due to the complex model structure and the limited data
- Reduced computational speed and long modeling runs due to stiffness and dimensionality
- Unintuitive model structures hinder identifying critical physiological mechanisms

Types of model reduction and simplification and how they can be used to reduce complexity

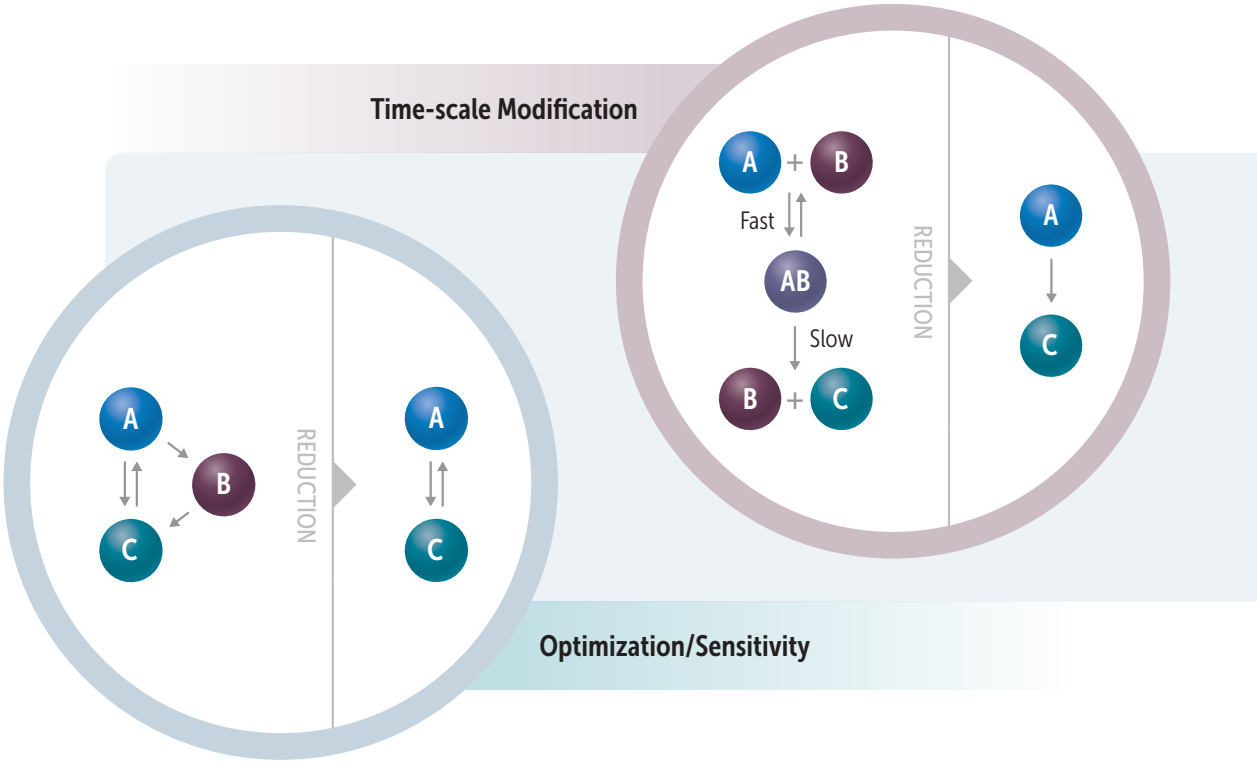
A range of methods used for model reduction exist in the literature which can be used to alleviate complexity and make models easier to manage.

Time-scale Modification refers to any method that exploits the often large differences in reaction rates that can occur within a biochemical system to create a reduced model that is accurate at a given time-scale of interest. Quasi steady state approximation (QSSA), used in enzyme kinetics, is the most well-known example of this type of reduction approach.

Optimization/Sensitivity refers to methods that evaluate the relative importance of model components and eliminate uninfluential ones, especially on the end points, to give a reduced system. Sensitivity differs from optimization analysis by looking at the system *a priori* and asks: How sensitive are each of the components to the network? Which are the least sensitive? Can these be eliminated? Optimization involves trying different reductions on many reduced systems and works out which reduced system is giving the best result. A typical optimization procedure might sequentially "switch off" reactions or species.

Lumping is a method that constructs a reduced system with new state-variables corresponding to sums of subsets of the original species. Proper lumping is where each of the original species corresponds to, at most, one of the lumped states. In improper lumping, each of the original states can correspond to one or more of the lumped states.

Balanced Truncation provides a way to approximate a matrix via one of the lower rank. The reduced dynamical description focuses on maintaining the input-output behavior of the original system. Typically this method is only applicable to linear systems, but it can be generalized to nonlinear models via empirical balanced truncation.



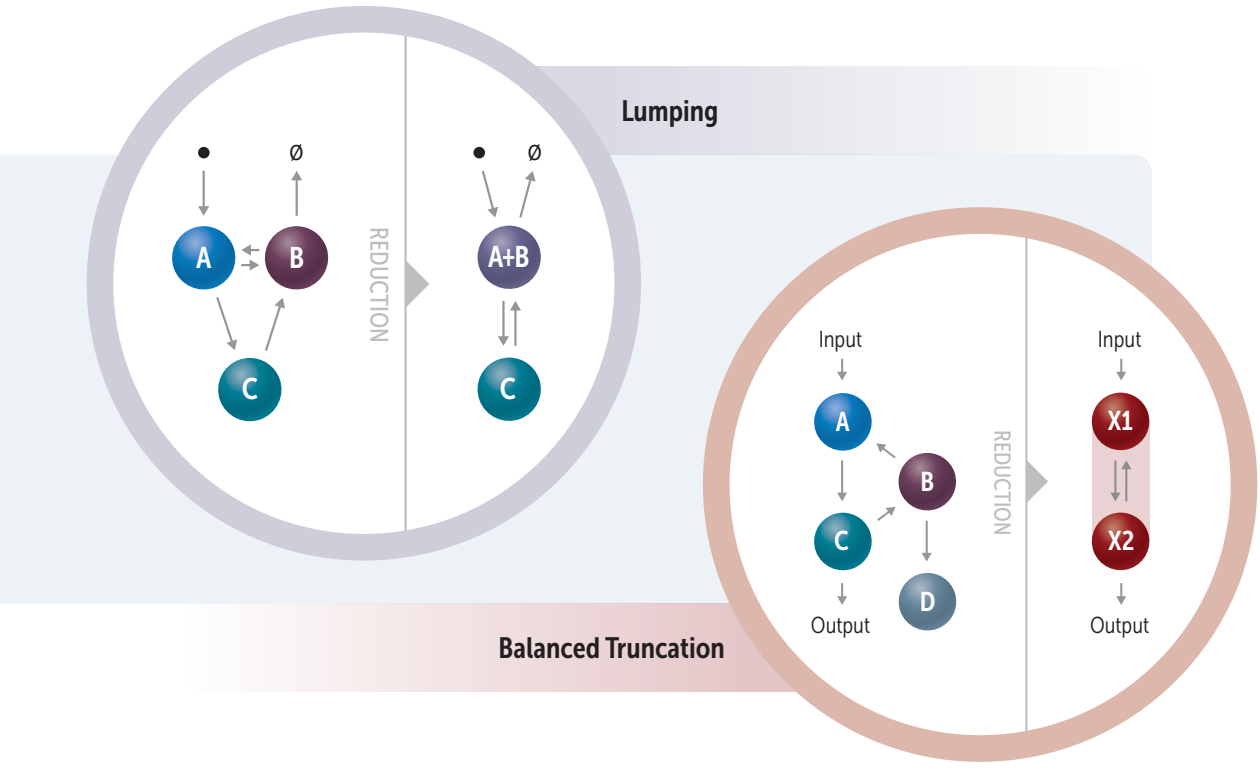
Along with reduction there are other methods of simplification that can be used to simplify the description of a biological system. These include:

- **Conservation Analysis**, which can reduce the number of differential equations by recasting the model as a system of differential-algebraic equations
- **Nondimensionalization**, which exposes ratios of parameters key to the dynamics, potentially reducing the number of parameters explicitly represented
- **Model Decomposition**, which exposes key division points in a system

Model reduction as an approach to alleviate QSP model complexity

The beauty of QSP is that by combining modeling frameworks it can potentially provide one modeling framework that continues along the entire drug development pipeline. However, QSP models are too complicated to typically use in the clinic, and in some respects, may be excessive for a systems biology model. Model reduction can simplify QSP models and get them to the scale of pharmacometric models.

Developing methodologies that address model complexity will result in better utilization of QSP models to predict safety and efficacy throughout the drug development continuum. The goal of model reduction is to reproduce the behavior of the original model—within reasonable error—while reducing the number of species, reactions, or complexes. Model reduction can be used to "zoom in" and "zoom out" of QSP-type models relative to the application being explored at the time. The benefit of this is ending up with one model. Thus, every experiment that is done contributes to the learning and validation of the single overall model because it is contributing to the validation of the overall reduced model. This information can be fed back up into the learning of the overall QSP model.



Other examples of model reduction

Model reduction can be used to significantly reduce PBPK models, over a range of drug parameterizations, down to classical compartmental PK models. These simpler PBPK models maintain a relatively accurate prediction of the dynamics as observed in the more complex PBPK models, demonstrating that values in reduced models can be fed back to the overall PBPK models.

A recent article by Snowden et al., illustrates how a combined model reduction algorithm using lumping and empirical balanced truncation was used to simplify two complex "controlled" systems biology models and still maintain predictive accuracy. The systems used were an 11 dimensional *E. coli* chemotaxis model reduced to 2 state variables, and a 99 dimensional 150-reaction extracellular regulatory kinase activation (ERK), mediated via the epidermal growth factor (EGF) and nerve growth factor (NGF) pathways, reduced to 7 state-variables. The method centered on the complementary natures of the two reduction methods and how they relate to model stiffness. Combining the methods produced more accurate reductions than using each method independently, significantly accelerated simulation rates, and lended itself to automation.

Model reduction—consider the gains to QSP

Model reduction is not a magic bullet. Like any set of tools, model reduction requires care and asking clear questions to be best utilized. The highly technical methods require a good grasp of mathematics. The relationship between reduction accuracy and model parameterization is complex, which may have implication for identifiability. Also, there may be a compromise between accuracy and practicality, as information is lost with model reduction.

However, model reduction can provide valuable gains. This rigorous method can extract a practical, usable model from biological understandings, which can be used to bolster QSP. It also can improve numerical difficulties and parameter identifiability properties and expose the most influential components of a model on the behaviors of interest. Fewer parameters and species leads to less validation and fewer experiments. Model reduction can enable creating modeling frameworks that last through the duration of the pipeline and across compounds, potentially allowing us to learn more from failure, thus increasing R&D productivity.

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