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PERSPECTIVE

Methodologies for Quantitative Systems Pharmacology (QSP) Models: Design and Estimation

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With the increased interest in the application of quantitative systems pharmacology (QSP) models within medicine research and development, there is an increasing need to formalize model development and verification aspects. In February 2016, a workshop was held at Roche Pharma Research and Early Development to focus discussions on two critical methodological aspects of QSP model development: optimal structural granularity and parameter estimation. We here report in a perspective article a summary of presentations and discussions.

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OPTIMAL GRANULARITY AND DESIGN OF QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODELS

In the design of QSP models, finding the right granularity is notoriously difficult. Granularity is the level of detail in which biological and pharmacological processes are represented and is associated with higher expected predictive power. But granularity comes with a cost, which is the difficulty of building, running, communicating, and maintaining a model with a vast number of components and parameters which—for the purpose of this discussion—will be summarized as complexity. One particular aspect of this complexity is the difficulty in parameter estimation, potentially resulting in large uncertainty in parameter estimates.

In translational and clinical pharmacokinetic–pharmacodynamics (PKPD) modeling, the main aim is to predict response of a selected biomarker at different dosing regimens or in different patient populations with well-defined input (dose)-output (exposure/biomarker) relationships at tested dosing regimens. In the context of PKPD modeling, parsimony is one of the most powerful guiding principles in restricting model complexity. While controlling complexity is also important for QSP models, the principle of parsimony is not easily applicable for QSP models, since they are often developed to provide biological insights into unmeasured/unmeasurable biomarkers of interest.

Ultimately, the question of granularity can only be answered when comparing competing models with respect to their set objectives. As in every comparison, the rules for the evaluation need to be fixed in advance and be tailored to the research question, e.g., what metric to be applied; what data input to be used; and what pharmacological interventions to be compared?

Along with some examples of success (see, for instance, Refs. 1, 2), in our experience some early QSP initiatives were overambitious and lacked predefined specification of question(s) to be answered by the model, which would have determined the required model complexity and whether that was achievable. As a result, these modeling efforts, while scientifically sound, did not turn out to provide valuable return on investment (unfortunately, such "failures" do not tend to get published; see Ref. 3). In order to get the granularity-complexity balance of a QSP project right, the following five criteria were highlighted as being important:

Need: The need, in many cases, arises from a question that cannot be solved by other standard methods such as PKPD modeling. As an example, in Ref. 4 the question whether mechanistic understanding of changes in blood eosinophils (EOS) could provide insights into the pharmacology of anti-interleukin therapy could only have been addressed through a systems approach encompassing EOS and cytokine dynamics and regulations. In another case,[5] a QSP approach was also required to identify knowledge gaps on a pharmacological target for treating pain and generate hypotheses that would explain observed lack of efficacy of a tested target. A careful analysis of the need for QSP approach compared to a "simpler" approach can also serve to highlight the complementary value this approach brings to the table.

Prior knowledge: Biological, physiological, and pathophysiological knowledge is the *sine qua non* for QSP modeling. This should include quantitative data at each of the scales of interest, e.g., molecular, cellular, and/or organ levels, to calibrate the models. In many cases, useful QSP models can be developed with less complete data, provided that within a physiologically plausible range, the parameter

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uncertainties associated with these data gaps are shown to be insensitive to the question being asked of the model or when the purpose of the model is to generate hypotheses regarding missing data.

In addition to known data gaps, the data that are available may be prone to bias: e.g., the newer a drug target is, potentially the less is known about it. This implies also the necessity of a sound collaboration with experimental labs to fill the knowledge gaps in an iterative manner. In our experience, lack of such experimental support has been one of the main reasons for attrition of QSP projects.

Pharmacology: Pharmacological interventions "probe" the system in multiple ways; responses to these interventions offer some of the best ways to discriminate models and their granularity. To achieve this aim, interventions must target complementary parts of the system, similar to illuminating an object from various angles in order to get an understanding of its shape. Or in other words, compounds are needed that are as distinct as possible in their properties and their effects, while at the same time spanning a common pharmacological space, e.g., probing through both agonism and antagonism to a given system's target. Integrating and testing a series of compounds not only makes models more robust, but also builds credibility and quite often gives insights into mechanisms that were previously missing. Some authors and consortia have defined standardized "validation sets," i.e., sets of compounds that are available to anyone in order to gauge models against each other (see, for instance, Ref. 6). The number of compounds needed for validation is a matter of debate and typically constrained by availability of resources and time. Alternate methods used to provide pharmacological understanding are information on genetic mutations in animals and humans, and pathophysiological conditions leading to overexpression or suppression of some pathways.

Understanding the translation: While most drug development is focused on human application, a wealth of data is available in animals at early stages of discovery, and hence understanding how a given intervention manifests in different organisms is precious. As far as possible, the understanding of biological, physiological, and metabolic differences between model organisms (e.g., cell cultures, organs on a chip, or animal models) should be used to characterize the multifaceted effects of pharmacological interventions. Adequate representation of human pathophysiology and pharmacology in a single model organism is notoriously difficult and often impossible, especially with highly specific treatment modalities and with targets that have a low degree of evolutionary conservation. Most often, several model organisms are used in parallel, each representing specific aspects of the pharmacology such as biodistribution, target engagement, and cell-level effects. A synthesis of this knowledge should be aspired by building QSP models around the relevant model organisms and to finally assemble these pieces in a QSP model embodying the physiology of the patient.

Collaboration: The cost and time of QSP models is most easily justified if they can serve various projects, and can build on strong collaboration across various groups and institutions. Only long-term integration with wet-labs and drug development project teams can ensure that the circle is closed between model predictions, new experiments, and model refinement. Complex models need a scientific network across groups and companies to survive and to evolve. This implies minimal standards on modeling language, validation sets and metrics for model comparison.

In summary, the granularity of a QSP model can be gauged based on the need, the amount of biological and pharmacological knowledge on the system, the understanding of the translational aspects, and the strength of the collaborative network.

MODEL IDENTIFIABILITY AND PARAMETER ESTIMATION OF QSP MODELS

An obvious consequence of granularity is parameter uncertainty. In PKPD modeling, parameter estimation techniques have been well documented and packaged in softwares such as NONMEM (ICON Development Solutions, Ellicott City, MD) or Monolix (Lixoft, Antony, France) that incorporate state-of-the-art techniques. For highly granular structural models and heterogeneous data sources, methodology around parameter identification is an open field of research and new approaches to apply these techniques will need to be developed in the future.

Several authors have successfully used model reduction techniques through variable lumping to reduce large network models to more manageable PKPD models (see Refs. 7,8, as examples). Development of robust techniques for addressing parameter identifiability is critical for QSP model development, in particular to prevent modelers to conclude on some results that data cannot support. In this respect, these methods can be viewed as powerful allies for communication of modeling results because they help to clarify uncertainties associated with a modeling or simulation outcome and help to fix boundaries of what can be or should not be communicated given a tolerable degree of uncertainty. Herein, our aim is not to provide an in-depth overview but mainly to encourage more work in this area.

Among the different methodological topics related to parameter estimation or uncertainty, the topic of structural (*a priori*) and practical (*a posteriori*) identifiability is certainly a fundamental one. Structural identifiability (SI) is about which variables need to be observed in order to identify a unique set of parameters and practical identifiability (PI) is about how frequently observations of a given set of variables needs to be to constrain parameter estimates within reasonable and finite bounds.

SI is often addressed with the use of algebraic methods (the reader can refer to Ref. 9 as an example). To evaluate PI, several approaches can be used such as data bootstrapping followed by reestimation of parameters to find different sets of parameter values, thus designing an estimation interval. The covariance matrix is the most straightforward way to assess identifiability. Lower and upper bounds of prediction interval can be obtained with this matrix as well as the correlation coefficient between parameters. If this correlation coefficient is high, then the model is not identifiable. Exploring

the *a posteriori* distribution of parameters can be also approached by Markov Chain Monte Carlo approaches to explore the distribution of individual parameters following a Bayesian formulation of the optimization problem. A wide distribution will indicate identifiability issues.

Recently, it has been suggested to address PI through the concept of likelihood profiling.[10] Raue *et al*. defined practical nonidentifiability of the likelihood-based confidence region is infinitely extended in increasing and/or decreasing the direction of a given parameter, although the likelihood has a unique minimum for this parameter value. Profile likelihood (PL) approaches rely on minimizing each likelihood function for each parameter, but not the parameter in question. The PL of a practically nonidentifiable parameter has a minimum, but does not exceed a threshold for increasing and/or decreasing the values of the given parameter. In contrast, for an identifiable parameter, the likelihood will go over a threshold when increasing/decreasing the parameter value.

In conclusion, selection of the right level of granularity is challenging because, as discussed, several factors must be considered. Guided by examples, more work should be performed to better define these factors and to propose methods to help modelers understand when and how to apply available tools to rationally guide the design and the granularity of a model.

The more granular and complex a model is, the less defined and validated are the methods to handle parameter estimation and uncertainty. In consequence, the model's granularity and the parameter's uncertainty are two themes closely interlinked and deserve dedicated research to enhance the value of QSP models in medicine research and development.

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