Received: 9 August 2022 | Revised: 20 September 2022 | Accepted: 22 September 2022

DOI: 10.1002/psp4.12873

PERSPECTIVE

Conceptual and organizational barriers to quantitative systems pharmacology modeling of pathophysiological systemic drug hypotheses

Pharmaceutical research and development (R&D) relies on developing good systemic hypotheses about the effect of novel drug mechanisms on pathophysiology. Although quantitative systems pharmacology (QSP) has been advocated many times for this purpose,[1–3] there are still conceptual and organizational barriers hindering the strategic use of this type of computational modeling. In the next sections, we describe these barriers one by one and indicate how they could be overcome. Without loss of generality, we refer to central nervous system (CNS) drug research.

BARRIER 1: HESITANT APPROACH TO QSP COMPUTATIONAL MODELING

A fundamental barrier is evidenced by a hesitant, nearly anxious approach to QSP computational modeling by decision makers in the pharmaceutical industry. A common flow of events starts when an individual staff member seeks help with a complex issue around a pharmacological target or a clinical design question. Even if these isolated questions could be satisfactorily answered via QSP computational modeling, a broader application of the modeling to more general questions about the disease is not initiated, and single, isolated modeling attempts prevail. No attempt is made to build a disease model to address important questions much earlier in the process.

What is needed is a top-down, continuous approach, initiated by upper management setting a policy of ongoing disease modeling as suggested by Geerts et al.[1,3] This should be combined with broader education of decision-making managers about mathematical modeling approaches. Decision makers should be reminded of the disparity between the huge sums spent on gathering data and the pittance spent on understanding and synthesizing the data through modeling. These are the keys to the necessary and critically needed improvement in pharma productivity.

BARRIER 2: LACK OF EDUCATION ON QSP COMPUTATIONAL MODELING OF COMPLEX BIOLOGICAL SYSTEMS AND THE BENEFITS

Busy animal and molecular-oriented discovery biologists, as well as clinically oriented medical subject-matter experts, often strongly resist unfamiliar mathematical computer modeling of their systemic hypotheses. Mathematical biophysical modeling is a suspicious black box to discovery biologists trained on animals and cells and to clinicians trained on treating patients. Mathematics (except for perhaps some statistics) is not normally part of their training. The only remedy here is to foster education in computational modeling and to motivate these scientists to become modeling advocates.

Moreover, discussion in the discovery and development teams around the drug program assumptions and the systemic hypothesis (model) as it relates to key decisions; and computational simulation of that hypothesis, would enable scientists to develop a continuous train of thought about their systemic ideas. Furthermore, this process would enable them to see the simulated outcome, including the implications of any new data, rather than just drawing diagrams of their hypotheses. Thus the expensive intellectual capital of pharma (scientists, knowledge, and data) would be leveraged. Such embedded operational learning and collective memory would then become a strategic differentiation from competitors not easily reproduced.

BARRIER 3: QSP COMPUTATIONAL MODELING PLACED IN ISOLATION

Within an organization, there is sometimes the misconception that QSP computational modeling can be installed as an isolated department. However, it should be integrated with experimental and clinical disease experts, as subject matter knowledge and advice are of utmost importance for the creation of meaningful models. Moreover, these experts must participate in the model building, otherwise there will not be sufficient organizational buy-in.

BARRIER 4: THE QSP MODEL IS NOT COMPREHENSIBLE

Not including the organization's experimental and clinical experts in model building contributes to this issue, as well as does insufficient education (see Barriers 3 and 2). And models can also be made more comprehensible by the way they are communicated. A review on this topic, especially with regard to model acceptance and believability, is given in Bonate.[4] It is important to present models in a way that matches the background and expectations of the audience.

BARRIER 5: THE QSP MODEL IS NOT VALIDATED

Quite often it is said, without being specific, that the model in question lacks validation. What does this mean? Predictions (i.e., model outcomes) do not match expectations and/or predictions do not match observed outcomes? Major deviations from trustful observations in the past require a serious investigation of the whole model-building process. Often, the model can be revised to capture new observations.

However, with a model that explains past data, one cannot object that the model lacks validation for a future prediction. If one always waited until after the predicted future observation took place, there would never be any use for any model (computational or animal) as a predictor of the future. Supporting validative data of necessity must always be about the past from events that have already occured.

One can make blinded prospective predictions about the future and see how the predictions turn out. As an example, Nicholas et al.[5] adopted a QSP model that prospectively predicted a negative effect of a 5-hydroxytryptamine receptor 4 (5-HT_4) partial agonist in a scopolamine-reversal trial in healthy human subjects. This was in contradistinction to animal models which had predicted a positive effect.

The model comprised synaptic serotonergic transmission linked to 5-HT_4 activity (i.e., increase in the excitability of cortical pyramidal cells); both muscarinic and nicotinic cholinergic pharmacology; and a biophysically realistic neuronal network model composed of 80 pyramidal cells and 40 γ-aminobutyric acid (GABA) interneurons. Binding and functional activity data of the partial agonist were also included. The duration of network firing activity in response to external stimuli was the model output. This output had previously been stongly correlated with working memory and cognitive function.

The QSP model predicted an exacerbation of scopolamine impairment for the low intrinsic activity 5-HT_4 agonist, which prediction was born out by the subsequent human trial outcome. This was in complete contradistinction to the positive prediction of animal models. Moreover, the QSP model provided a complete mechanistic explanation of why this was true and offered a promising path forward.

The clinical prediction of the QSP disease model strongly suggested that 5-HT_4 agonists with high intrinsic activity might have a beneficial effect on cognition in patients with Alzheimer's disease. However, because of managerial barriers—in line with Barrier 1—the program was abandoned instead of following up on the promising new path suggested by the QSP modeling.

So one can make blinded prospective predictions about the future and see how the predictions turn out as in the aforementioned 5-HT_4 agonist example. However, for any future prediction, one can again argue that only past data are validative and doubt the new future prediction because the new circumstances are not identical. Therefore, the argument that the model lacks validation for future predictions relegates QSP computer modeling (or any modeling, including with cells and animals) to uselessness.

Moreover the argument fails to recognize that every prediction—every decision—about a new set of circumstances involves some inherent hypothesis, mental or otherwise, about an unknown future and is, hence, unvalidated. Not understanding that every decision about a novel therapeutic involves an unvalidated systemic hypothesis is a conceptual barrier to QSP computational modeling. The relevant question is whether the unvalidated systemic hypothesis should be computationally modeled and simulated using state of the art QSP.

BARRIER 6: THE QSP MODEL IS INCOMPLETE

Another common objection refers to the incompleteness of QSP computational models. The modeling process itself leads to a systematic identification of knowledge gaps, and sensitivity studies can prioritize them for further study.

However, all models are (and must be) simplifications of reality built from assumptions, facts, and mental models already being used in decision making. "Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful"[6] (relative to approaches without models).

An important guide is comparing QSP modeling with status quo approaches. The relevant question is not whether the modeling is 100% accurate and complete, but whether it is a material improvement over the status quo. It is important to understand that the decision maker is already using some kind of implicit mental model of the systemic hypothesis for the drug program. Not fully understanding that this implicit mental model is the status quo comparator is a conceptual barrier to the acceptance of QSP computational modeling. Making the implicit mental model of the systemic hypothesis explicit through the QSP modeling process and then simulating that hypothesis can only help the decision-making process (and we argue by a substantial margin).

Logically, one would want to see the predicted outcome of the drug program systemic hypothesis using the best available QSP computational model of that hypothesis. Indeed, one is better informed by computationally modeling the hypothesis (simulation) to see the results. This is because the systemic hypothesis may be wrong, but at least one can see if the hypothesis, as modeled with current knowledge, is predicting what one believed it would predict; and make adjustments to the hypothesis accordingly.

New hypotheses involving complex systems are virtually impossible to simulate without computation, and one is reduced to drawing diagrams and guessing what a systemic hypothesis predicts for the outcome of a myriad of complex interactions. An iterative dynamic between computational simulation and model building with informed intuition (modification of the model and interpretation of the simulation), that is to say, "augmented intelligence", is necessary for gains in pharma productivity in novel therapeutics.

EXPECTED BENEFITS

Continuous QSP modeling of the disease of interest will materially affect decisions around targets, compounds, and trial designs. If computational QSP modeling of the disease and the program systemic hypothesis cannot show a promising way forward for a compound or potential compound, one can argue not to engage further in development. Conversely, new opportunities for drug programs can be identified that would not otherwise be recognized.

This could be a game changer, especially in areas that present large systemic complexity such as the CNS, where researchers are blind to potential emergent properties that cannot be determined by examining individual parts of a whole system. QSP modeling, even with incomplete detailed information and low-resolution models, can reveal early on, for further exploration, unexpected systemically emergent large dangers and opportunities, not otherwise knowable. "In the land of the blind, the one-eyed man is king."[7]

More drug programs would be improved or saved, thereby fundamentally shifting CNS drug R&D economics relative to pharmaceutical companies that do not fully integrate QSP computational modeling. Highly profitable dominance of CNS therapeutics would be further enabled as more and more pharmaceutical companies pull out of CNS altogether for lack of adequate approaches.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

Ronald Gieschke[1,†]
Robert Carr[2]

[1]*Schopfheim, Germany*
[2]*In Silico Biosciences, Lexington, Massachusetts, USA*

Correspondence
Ronald Gieschke, Schillerstr. 19, Schopfheim 79650, Germany.
Email: ronald.gieschke@gmail.com

[†]Retired from F. Hoffmann-La Roche in 2017.

ORCID

Ronald Gieschke https://orcid.org/0000-0001-5688-8633

REFERENCES

1. Geerts H, Spiros A, Roberts P, Carr R. Has the time come for predictive computer modelling in CNS drug discovery and development? *CPT Pharmacometrics Syst Pharmacol*. 2012;1:e16. doi:10.1038/psp.2012.17
2. Vicini P, van der Graaf PH. Systems pharmacology for drug discovery and development: paradigm shift or flash in the pan? *Clin Pharmacol Ther*. 2012;93:379-381.
3. Geerts H, Wikswo J, van der Graaf PH, et al. Quantitative systems pharmacology for neuroscience drug discovery and development: current status, opportunities, and challenges. *CPT Pharmacometrics Syst Pharmacol*. 2020;9:5-20.

4. Bonate P. *Be a model communicator: and sell your models to anyone*. Peter Bonate; 2014.
5. Nicholas T, Duvvuri S, Leurent C, et al. Systems pharmacology modelling in neuroscience: prediction and outcome of PF-04995274, a 5-HT4 partial agonist, in a clinical scopolamine impairment trial. *Adv Alzheimer Dis*. 2013;2:83-98.
6. Box GEP, Draper NR. *Response Surfaces, Mixtures, and Ridge Analyses*. 2nd ed. John Wiley & Sons; 2007.
7. Bartlett J. *Bartlett's familiar quotations*. 17th ed. Little, Brown and Company; 2002.

How to cite this article: Gieschke R, Carr R. Conceptual and organizational barriers to quantitative systems pharmacology modeling of pathophysiological systemic drug hypotheses. *CPT Pharmacometrics Syst Pharmacol*. 2022;11:1556-1559. doi:10.1002/psp4.12873