Special Section on Quantitative Systems Pharmacology: A Foundation to Establish Precision Medicine

Quantitative Systems Pharmacology: A Foundation To Establish Precision Medicine–Editorial

In this issue, the “Special Section on Quantitative Systems Pharmacology” highlights the evolution of the field that has merged a number of disciplines into its own. The roots of quantitative systems pharmacology (QSP) can be traced to systems biology, biochemistry, and pharmacodynamics (PDs), which have their underpinnings in multiple basic fields such as chemistry, physics, and math (Gallo, 2022). Its goal is to provide a mechanistic foundation for drug action. Thus, there are two branches of inquiry related to QSP, which are 1) applied: drug development and therapy and 2) basic: utilizing multiomic data to construct network models of drug action. These branches are not mutually exclusive, and one might consider branch 2 to be a prerequisite to branch 1.

Pharmacokinetics (PKs) and PDs have a significant place in the drug discovery and development pipeline and offer quantitative metrics to evaluate new drug candidates, as well as translate pharmacological measurements into drug dosing guidelines and regimens. However, at times, relying on biomarker-driven PD data such as target inhibition is inadequate to explain why drugs may fail or even succeed in the clinic. Iyengar et al. (2012) illustrated how a QSP, also referred to as an enhanced PD (ePD), model for an EGFR inhibitor was needed to understand why 80% target inhibition did not yield the same degree of tumor growth suppression. Moreover, it is known that many drugs have multiple targets, some considered off targets, and relying on a potpourri of biomarkers could be limiting compared with integrating multiple cell signaling pathways into a single cohesive QSP model that would likely be more pharmacologically accurate and also serve as a platform to design drug therapy.

Formulation and Integral Approaches to QSP Models

There are a number of reviews on QSP model building, evaluation, and applications (Azeloglu and Iyengar, 2015; Bouhaddou and Birtwistle, 2016; Friedrich 2016; Gadkar et al., 2016; Azer et al., 2021; Aghamiri et al., 2022; Chelliah and van der Graaf, 2022), and our intent here is not to provide another review but rather to offer a synopsis of QSP and the contributed papers to this Special Section.

The nature of QSP is diverse with the mathematical formulations most often based on ordinary or partial differential equations, stochastic processes, and hybrids of these. Biochemical reaction kinetics—first-order, zero-order and Michaelis-Menten—are the standard currency to model cell signaling pathways, whereas certain biologic processes such as gene transcription are stochastic in nature and thus set the basis of the standard mathematical approaches. A feature of the mechanistic models is to include feedback and cross-talk processes to try to capture the inherent system dynamics (Kholodenko, 2006; Novák and Tyson, 2008; Ferrell and Ha, 2014).

Model building is often a stepwise approach combining literature information and experimental data. Literature data provides protein-protein interactions or edges into signaling pathways (see, for example, https://www.genome.jp/kegg/). Specific articles related to your project of interest can provide initial conditions and estimates of kinetic parameters. The BioModels website (https://www.ebi.ac.uk/biomiodels/) is a very useful repository of systems-based model that includes documentation and computer code. New experimental data might serve to perform model-fitting algorithms and validation; perhaps training and test datasets. There is a growing role for incorporating machine learning approaches into QSP model development, and to such an extent it was a subject of a recent white paper (Zhang et al., 2022). Global sensitivity analyses are often used in the model development plan to depict sources of model uncertainty and focus experiments to reduce high degrees of uncertainty (Zhang et al., 2015). There have been interesting analyses and discussions concerning sloppiness that underlie large-scale
systems biology models that indicate that even though some parameters may be highly uncertain, the model simulations produced by the whole or collective system are valuable (Gutenkunst et al., 2007; Daniels et al., 2008).

Boolean network modeling has a role in QSP, as it reduces the complexity of identifying unique parameter values characterizing reaction rates between protein nodes by casting reactions as logic gates (AND, OR, NOT operators) (Albert and Barabasi, 2000, Bloomingdale et al., 2018). Although limitations of Boolean models are recognized (Birtwistle et al., 2013), new simulation tools can provide insight into the system behavior and generate hypothesis for further evaluation (Stoll et al., 2017; Montagud et al., 2022).

**Challenges to QSP**

Given the larger scale—number of protein nodes and connections—of QSP models, there are questions on how to determine unique parameter values (mentioned above) and how to validate model predictions, not to mention the prerequisite data to generate an initial model. There are mathematical approaches, possibly most intriguing is modular response analyses (MRA) and newer iterations (Klinger et al., 2013; Halasz et al., 2016; Klinger and Blüthgen, 2018; Sarmah et al., 2022) to assist in the experimental design; how many proteins need to be measured and at what times? Not to discount the challenges of QSP model building and validation, there is a place for theoretically grounded model simulations that may forge new paths of inquiry. For example, epigenetic modulation within the guise of QSP modeling has been shown via simulations to be a means to combat drug resistance, at least theoretically (Saini and Gallo, 2021; Saini et al., 2023). Naturally, such predictions seek data confirmation to embrace the drug therapy strategy.

**Synopsis of Contributed Papers**

This Special Section comprised five original research papers presenting QSP approaches for optimizing cancer treatment and one review focusing on the interface between QSP and machine learning (ML).

The Special Section opens with an article by Hermange et al. (2023) focusing on the treatment of myeloproliferative neoplasms (MPNs), which are blood cancers that occur due to the acquisition of driver mutations in hematopoietic stem cells, with JAK2 mutations being the most common. Although interferon alpha (IFNα) is an effective treatment, there are unknowns related to achieving long-term remissions without drug-induced toxicity. The team of Hermange, Cournède, and Plo develop a model-based approach to optimize IFNα therapy. The model can simulate cell population dynamics but when combined with patient data enables a hierarchical Bayesian inference approach that can be keyed to molecular endpoints such as variant allele frequency (VAF) to evaluate IFNα treatment regimens. The IFNα treatments can be designed to avoid drug toxicity and early relapses (see Fig. 5 in Hermange et al. (2023)). The authors also investigate experimental designs to provide guidelines to clinicians as to when individual patients should be sampled for VAF, which can then be used in the model-based dosing procedure to optimize IFNα therapy.

Next, Hodson and coworkers (Hodson et al., 2023) used nonlinear mixed effects modeling applied to mouse datasets to optimize the combination of radiotherapy (RT), DNA damage response pathway inhibitors (DDRi, here inhibitors of either DNA protein kinase or poly ADP ribose polymerase) and immune checkpoint blockade. A mathematical model was developed to capture the impacts of combination treatments on tumor growth and immune interactions. Model simulations allowed the authors to identify optimal dosage regimens in preclinical tumor models, which could hold translational potential.

Pugh et al. (2023) further proposed a mathematical model based on ordinary differential equations to optimize concomitant administration and scheduling of several DDRi, namely the ataxia-telangiectasia and Rad3-related (ATR) inhibitor ceralasertib and the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib. Building on in vitro data in the FaDu ATM-KO cell line, the authors explored different possible drug mechanisms and designed a model of cell cycle-specific interactions of olaparib and ceralasertib that faithfully reproduced experimental findings. Simulations concluded that combining both drugs with lower doses and for shorter treatment periods induced greater or equal cytotoxicity in cancer cells than using either as a single agent.

The next study by Surendran et al. (2023) proposed a computational model for investigating new approaches to the treatment of glioblastoma: immune checkpoint blockade and oncolytic viruses. Glioblastoma is the most frequent brain tumor in adults and is associated with a 15-month average survival time despite intensive treatments involving maximum-safe surgery, radiotherapy, and temozolomide (TMZ)-based chemotherapy. Clinical trials testing the combination of this standard of care with therapies aiming to reactivate the immune response against the tumor have shown limited success. Here, Surendran et al. (2023) developed a computational model that describes the interplay between glioblastoma, immune, and stromal cells under combination therapies and investigated the cellular and molecular mechanisms driving treatment outcomes. The authors initialized their model with spatial imaging mass cytometry visualization.
of patient samples and concluded on the importance of localization of glioblastoma cells and of CD8+ T cell infiltration for predicting treatment responses.

Next, Khera et al. (2023) investigated the dynamics of antibody-receptor occupancy using spatiotemporal mechanistic modeling. Determination of antibody drug doses using receptor occupancy approaches is challenging, in part due to the heterogeneous distribution of the antibody in tissues, such as tumor tissue. Khera and coworkers (2023) expand on the average free target tissue to initial target ratio (AFTIR) concept and derive a mechanistically weighted global average free target tissue to initial target ratio (gAFTIR) that improves dosing guidelines for antibody therapeutics by accounting for subsaturating doses that are clinically relevant. The underlying foundations to gAFTIR are the Krogh cylinder—a partial differential equation model—to simulate spatiotemporal receptor occupancy, nondimensional terms, and use of the relevant intratumoral antibody concentrations. The authors provide a systematic means (supplemented with Excel worksheets) to calculate receptor occupancy from gAFTIR from the aforementioned variables [see Fig. 6 in Khera et al. (2023)], which leads to an antibody targeting regimen.

The last article of this Special Section reviewed the combined application of ML and QSP in the context of drug development (Tindall et al., 2023). QSP offers a detailed mechanistic view of the system and of the molecular mechanisms of drug pharmacology but cannot recapitulate gene networks of size larger than ≈100 species without a loss in model reliability due to the presence of too many parameters or degrees of freedom. However, multitype and multiscale quantitative data and qualitative prior knowledge are nowadays available and call for the individual and combined application of ML and QSP to ultimately inform drug development. Tindall and coauthors (2023) reviewed how ML approaches may be undertaken to inform mechanistic model design and conversely, how sensitivity and structural identifiability analyses of QSP models may guide the design of experimental datasets to which ML may be applied.

Conclusions and Future
The papers contributed to the Special Section on QSP describe a range of approaches to conduct computational models to understand human biology and to quantitatively design drug therapy for complex diseases. QSP is a rich and growing discipline that offers insights into biologic and pharmacological processes from the molecular to whole organism scales and in so doing embodies many preceding quantitative modeling areas such as systems biology, pharmacokinetics, and pharmacodynamics. The further development of QSP, including combined approaches with ML, seems essential to tackle complex diseases and to provide opportunities for drug discovery and a framework for precision medicine.

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