DIGITAL TWINS AND VIRTUAL POPULATIONS: APPLICATIONS IN QUANTITATIVE SYSTEMS PHARMACOLOGY

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Quantitative Systems Pharmacology (QSP) models face challenges in estimating parameters from patient-specific data to obtain their digital counterparts. To this end, global and local fitting strategies involving optimization methods such as least squares and Bayesian inference are employed. In addition, identifiability and uncertainty quantification techniques can be instrumental in developing robust QSP models. Virtual populations generated by statistical approaches and Monte Carlo simulations can capture patient variability and incorporate genetic, demographic, and treatment factors. Digital patients (or twins) and virtual populations can help optimize dosing, inform clinical trials, and aid in understanding diseases. Here, we report two examples of their applications in studying neurofilament trafficking in spinal muscular atrophy patients and the rare Gaucher disease type 1, showing promising results. Overall, QSP combined with digital patients and virtual populations has the potential to push drug development toward personalized medicine.

Keywords: *QSP, mathematical modeling, virtual populations, neurodegenerative diseases, rare diseases*

1. Introduction

Quantitative systems pharmacology (QSP) is an approach that utilizes mathematical modeling to understand and predict the behavior of complex biological systems and their interactions with pharmacological treatments. It integrates data from multiple sources, from literature, *in-vitro*, preclinical and clinical experiments, and encompasses different biological levels [1]. Model-informed drug development (MIDD) is a framework that leverages pharmacokinetics, pharmacodynamics, and QSP models to facilitate decision-making throughout the drug development process [2]. The combination of QSP and MIDD has significantly accelerated the pace of introducing new drugs into clinical practice.

One of the primary challenges in QSP and MIDD lies in accounting for the variability and uncertainty in model parameters and outputs. Addressing this challenge involves employing individualized calibrations, which are techniques used to estimate model parameters for specific individuals based on observed data [3]. Additionally, digital twins and virtual populations are utilized to tackle this challenge. Digital twins are virtual replicas of individuals that can simulate their responses to various interventions or scenarios. On the other hand, virtual populations consist of collections of digital twins that represent the diversity and heterogeneity of a target population. By incorporating these methods, the accuracy, reliability, and applicability of QSP models can be enhanced, ultimately leading to more efficient and effective drug development processes.

In certain cases, such as rare or neurodegenerative diseases, virtual representations of patients can provide more comprehensive datasets that aid in understanding disease mechanisms and predicting treatment efficacy. This information is especially valuable when the number of patients is limited or when there are significant barriers to accessing the disease site. Furthermore, employing digital patients and virtual populations allows for the generalization of results to different populations, considering factors such as age or disease severity. This work exemplifies how digital patients and virtual populations were utilized within this context.

2. Digital patients and virtual populations in QSP modeling

One of the primary challenges in QSP modeling, which encompass multiple biological scales, is to estimate model parameters using patient-specific time series data, including biomarkers, pharmacokinetics data, and clinical manifestations or outcomes [1]. When sufficient data is available, this process enables the creation of digital patients, where specific model parameters are linked to the measured endpoints of individual patients. This approach helps to account for inter-individual variability and optimize dosing regimens. However, there are many adopted fitting strategies in QSP, and they may depend on various factors such as data availability and quality, model complexity, and computational resources. Different methods can be used to fit patient-specific time series data, such as least squares, heuristic evolutionary strategies, and Bayesian inference such as Markov Chain Monte Carlo. These methods have different advantages and disadvantages for both local and global optimization tasks, and they are essential for creating a digital representation of the patient [4].

Another key aspect of determining digital patients is the identifiability and uncertainty quantification of model parameters, which reflect the biological variability and measurement errors in the data. Parameter identifiability refers to the ability to estimate unique and precise values of model parameters from the available data, while uncertainty quantification measures the range and confidence of parameter estimates. Both are essential for ensuring the robustness, validity, and predictive power of QSP models and to assure that the model parameters can correctly identify a reliable digital twin. Several methods have been proposed and applied for parameter identifiability and uncertainty quantification in QSP, such as sensitivity analysis, Bayesian inference, profile likelihood, and bootstrap methods [3]. These methods have different advantages and limitations depending on the complexity and structure of the model, the quality and quantity of the data, and the available computational resources [3].

Once enough digital patients are collected, it is possible to define virtual populations (VPs) that can capture the inherent variability present in real patient populations. In addition, virtual populations are often created by incorporating various sources of variability, such as genetic factors, demographic characteristics, disease subtypes or severity, physiological parameters, or different treatments. Among the various methods used to generate virtual populations, statistical approaches are commonly used to infer distributions of model parameter estimates, while Monte Carlo simulation is employed to randomly sample parameter values from these distributions. This general framework inspired several effective methods, such as those in [5, 6], which incorporate biologically inspired constraints to generate more realistic virtual populations. Also in this case, the choice of the method depends on available data, model complexity, computational resources, and multiple methods that may be combined for comprehensive representation.

3. Applications in QSP modeling

Virtual populations in QSP modeling can be used to optimize dosing regimens in subpopulations, considering factors like age, gender, disease severity, and comorbidities. They provide insights into expected variability in clinical trials, allowing researchers to anticipate diverse patient responses and design robust trials. Here, we report two examples, studying rare or hard-to-reach populations, such as patients with rare and neurodegenerative diseases, and children. In these cases, virtual populations can help to understand the physiological processes and the effects of treatments.

In the works [7, 8], a quantitative systems pharmacology (QSP) model was developed to examine neurofilament trafficking in both healthy individuals and patients with spinal muscular atrophy (SMA). SMA is a rare genetic disorder affecting motor neurons and resulting in muscle weakness and atrophy, which is most impactful in pediatric ages, with high severity and lethality. Neurofilaments, which play a role in neuronal structure and transport, serve as biomarkers for disease progression in SMA and other neurodegenerative conditions.

The QSP model captures the dynamics of neurofilament production, transport, degradation, and release throughout the nervous system and periphery. It combines a previously established mathematical model of neurofilament trafficking in healthy adults [7] with detailed characterizations of pediatric physiological processes, such as organ volumes and postnatal nervous system development. The authors used data from clinical trials that enrolled SMA patients treated with nusinersen to build a virtual population of untreated subjects. The parameters related to the

treatment were estimated by fitting individual time series of SMA patients followed during the treatment. The combination of the estimated treatment parameters and the untreated virtual populations allowed the generation of virtual populations of treated patients with different ages and treatment protocols. The predicted neurofilament concentrations of these populations were compared to the time series of SMA patients reserved for model validation. This validation strategy confirmed the predictive performance of the model, making it a valuable tool for investigating neurofilament as a biomarker for disease progression and treatment response in SMA.

Another promising application is in Gaucher disease type 1 (GD1), a rare genetic disorder that can lead to significant morbidity and mortality through clinical manifestations such as splenomegaly, hematological complications, and bone disease. In [9], the authors developed a QSP model to represent the effects of eliglustat, a novel substrate reduction therapy for GD1, on treatment-naïve or enzyme replacement therapy (ERT) stabilized adult GD1. The model was informed by a data-driven genotype-phenotype relationship to represent a wide spectrum of patients with mild to severe GD1, even beyond the initial patients. The model was applied to predict ERT and eliglustat responses in virtual populations of adult patients with GD1, representing patients across a spectrum of disease severity as defined by genotype-phenotype relationships. The QSP model and the virtual populations provide a mechanistic platform for predicting different treatment responses within the heterogeneous GD1 patient population.

As shown, digital twins and virtual populations can play a crucial role in advancing QSP by addressing patient heterogeneity, optimizing treatment strategies, informing clinical trial design, and enhancing our understanding of complex biological systems. As more accurate methods emerge for characterizing virtual patients and digital twins, research is steadily moving toward the realm of *in-silico* modeling. This progress can change drug development, paving the way for increasingly personalized medicine approaches.

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