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PERSPECTIVE

Approaching Pharmacometrics as a Paleontologist Would: Recovering the Links Between Drugs and the Body Through Reconstruction

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Our knowledge of dinosaurs comes primarily from the fossil record. Notwithstanding the condition of these vestiges, paleontologists reconstruct early reptilian life by comparison to previously discovered specimens. When relics are missing, reasonable deductions are used to fill in the gaps.
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As outlined above, one can draw parallels to systems of pharmacology/mechanistic modeling (the explicit depiction of the causality between drug exposure and response),[1] which gives a more complete picture of drugs in the human body.

MODELING AND THE SYSTEMS OF PHARMACOLOGY

Mathematical modeling in pharmacokinetics (PKs) and pharmacodynamics (PDs) continues to become increasingly refined, in step with improvements to both computational and mathematical analytical techniques and our understanding of human physiology. In that vein, mechanistic models, which offer phenomenological insights absent from traditional empirical data-driven modeling techniques, are useful tools for subsequent pharmacometric research.[2] The parameters involved in the system models bear a direct correspondence to the physiological system of interest and have a "fundamental basis in our understanding of the biological/pharmacological system."[3] In practice, these models are constructed in consortium with clinicians and other scientists to ensure a rational and realistic construction to improve their reliability. Generally, given the specificity of each of the model's parameters and the paucity of available datasets, parameters are identified through established sources (deemed the prior method[4]). Models are then evaluated and refined by comparison to published experiments and can be used to predict the behavior of the system in a variety of scenarios. As a result of the generic nature of the model's construction, their application to a diverse range of patients and pathologies is possible. It is well-recognized that drug concentrations act as surrogates for their action in the body and that the plasma concentrations are only proxies for drug effect sites that are located outside the blood.[2] Physiological modeling replies directly to this issue by taking the whole system into account. With the aim to recreate the processes underlying drug effects as faithfully as possible, physiological models are able to better represent the true action of xenobiotics and are therefore well-positioned for hypothesis generation and verification.[3]

Despite the increasing use of physiological modeling in the systems of pharmacology, the approach is underrepresented in the literature when compared with traditional approaches in which the main goal is to successfully mimic the data. This can be attributed to the relative mathematical complexity of the techniques involved in physiological modeling, which require time to understand the system, construct the model, and determine parameters. Further, as is the case with the more common physiologically based pharmacokinetic model, the role of PK and PD variability upon system-level models has not been fully addressed.[3] In response, using a physiological model of granulopoiesis that we developed for the optimization of chemotherapy,[5] we have recently shown that when the physiology is sufficiently detailed, the model inherently explains and reduces the previously estimated population PK variability.[6] This is likely attributable to its bottom-up construction because development from first principles suggests that variability is explicated and incorporated into the minute details of the resulting models and their parameters.[2] Incertitude, included by design, is thereby progressively reduced throughout the model's construction.[7] Nevertheless, we maintain that an ideology-free methodology should be adopted when addressing the quantification of drug-effects to best balance the feasibility and benefits of any given approach.

Calls for the integration of quantitative systems pharmacology (QSP) along the drug discovery pathway have come from scientific bodies, as the recognition of the indispensability of translational models increases.[2,7] Several authors have previously highlighted numerous applications of QSP from early discovery to late stage drug development.[2,8] Publishing such case studies is important to both situate QSP in the current scientific environment and to highlight their essentiality to the future of translational drug discovery.

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A physiological model of granulopoiesis applied to chemotherapeutic dose optimization

An illustrative example of the use of mechanistic modeling in systems pharmacology is in applications to hematology in which there is a need to predict the neutrophil response to chemotherapeutic treatment (ref. 5 and references therein). In a PK/PD setting, the most common strategy to study myelosuppression-related neutropenia is to relate dose or concentrations to neutrophil numbers using mixed effects modeling techniques and transit compartment modeling.[9] These semimechanistic models estimate the transit time from progenitor neutrophil cells to circulating neutrophils from clinical data and mimic the developmental stages of neutrophils in the bone marrow. Because the underlying model structure is fairly straightforward, parameter estimates from data are available in a reasonable timeframe and can be used early in the drug development pipeline. Crucially, a downside to using data to estimate the model structure and its parameters is the disconnect from the physiology. Indeed, although we can easily register patient blood counts, measuring the proliferation, the cytokine-dependent rate of maturation, and reservation within the marrow is more complicated and rarely performed. As in the case of mixed effects modeling applied to PKs, blood counts (concentrations) reflect the upstream marrow processes and the interaction of the regulatory cytokines with the blood system.[2] To advance our understanding of granulopoiesis for applications to both different pathologies and to different experimental conditions, physiological models developed with systems biology approaches are warranted.[3]

Underlying the physiological model of neutrophil development is a particular attention to first principles modeling and the translation of the current knowledge of the system's inner workings mathematically.[10] These physiological models are flexible in that they do not rely on empirical data for their construction and can be applied to various experimental models.[3] Their development can take longer than the data-driven approaches because in-depth mathematical and physiological knowledge is required. Accordingly, in the present study, we do not make the case for the abolishment of empirical methods. Instead, we caution against discounting the power of mechanistic modeling in pharmacology altogether in favor of quicker or more direct methods. We recently refined a physiological model for granulopoiesis and applied it to the problem of dose optimization in oncological settings.[5] The basis of our approach was a physiological model of marrow neutrophil development that accounts for hematopoietic stem cells, proliferating and maturing neutrophils, the marrow neutrophil reservoir, circulating neutrophils, and the marginal pool. The complete model is comprised of three delay differential equations with state-dependent delays and a variable aging rate (see the model schematic in Figure 1 of ref. 5). Together with the physiological model, we incorporated validated PK models of a chemotherapeutic drug (PM00104) and filgrastim, a recombinant-human form of granulocyte colony-stimulating factor and predicted clinical data of 172 patients undergoing the CHOP14 protocol, a 14-day periodic chemotherapeutic treatment. In the original protocol, filgrastim was administered 10 times, from day 4 to day 13 of each chemotherapy cycle. We were able to demonstrate that delaying the first dose of filgrastim postchemotherapy administration to day 7 reduced the number of doses of filgrastim necessary to mitigate neutropenia from 10 to 4 or even 3. These results are supported by the physiology of neutrophil marrow development because the delayed response to chemotherapeutic drugs and to granulocyte colony-stimulating factor are directly related to the time it takes for cells to reach and subsequently be released from the marrow reservoir. In this model, parameters were estimated from a broad swath of the literature for an individual patient and no data fitting was undertaken. Additionally, the myelosuppression model was shown to be generalizable across different chemotherapy regimens (PM00104 vs, combination chemotherapy in the CHOP14 protocol), highlighting the flexibility presented by QSP modeling developed using first-principles. The robustness of the model's prediction was demonstrated by incorporating the full PK variability profiles of both drugs and checking for statistical differences in the model's output.[6] Despite the presence of variability in the PKs, we found no statistically significant change in the model's prediction with reference to three critical clinical endpoints.

PERSPECTIVES

The debates and advances of the naturalists in the early 19th century subsequently reimagined our understanding of the species that walked our planet. These early scientists' capacities for abstraction and their appeal to a system-level organizational structure filled in the gaps in not only the knowledge of the day, but the missing pieces in the records left behind. QSP, which exists at the confluence of systems biology and pharmacometrics, provides a return to this macroscopic examination of drugs and their interactions with the body. System pharmacology is increasingly recognized for its dual impact on drug development and patient care and models of adverse drug reactions have been identified as a crucial goal of QSP.[7] The field does and will play an increasingly important role as drug targets become progressively complex and elusive and as we seek to not just explain data, but to understand the fundamentals of physiology that drive the response to drugs. The model discussed in this article serves as an example of the application of system-level modeling to translational medicine and is demonstrative of the influence of system modeling on both drug development and on the means with which we respond to patient needs. Broadly, it is important to recognize that physiological modeling is not applicable in all settings or for all problems because of the more complex nature of model construction and the difficulty of estimating and identifying parameters. Nevertheless, there is room within the pharmacometrics community to develop both empirical and mechanistic models in concert as they respond to different philosophical questions: how do we explain our data (traditional PK/PD) and what response drives the observed response observed (systems pharmacology)? Acknowledging and making use of approaches outside of those traditionally used in PK/PD modeling will allow pharmacometricians to answer elemental questions

about drugs and improve patient care, which remains the ultimate task of our discipline.

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Conflicts of Interest. The authors have no conflict of interest to declare.

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