PERSPECTIVE

Perspective on the State of Pharmacometrics and Systems Pharmacology Integration

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Reliance on modeling and simulation in drug discovery and development has dramatically increased over the past decade. Two disciplines at the forefront of this activity, pharmacometrics and systems pharmacology (SP), emerged independently from different fields; consequently, a perception exists that only few examples integrate these approaches. Herein, we review the state of pharmacometrics and SP integration and describe benefits of combining these approaches in a model-informed drug discovery and development framework.

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The term "pharmacometrics" was conceived by the *Journal of Pharmacokinetics and Biopharmaceutics* in 1982, and more recently has been defined as "the science of developing and applying mathematical and statistical methods to characterize, understand, and predict a drug's pharmacokinetic (PK), pharmacodynamic (PD), and biomarker-outcomes behavior."[1] Individual or population PK and PD models and clinical trial simulations are typically considered "traditional" pharmacometric approaches; they may be empirical, semi-mechanistic, or mechanistic in nature.

To our knowledge (personal communication, Piet van der Graaf, August 5, 2017), the term "systems pharmacology" (SP) did not appear in a peer-reviewed publication until 2004.[2] The author states that, at the National Institute of General Medical Sciences, the new initiative of "integrative and organ systems pharmacology" is defined as "pharmacological research using *in vivo* animal models or substantially intact organ systems that are able to display the integrated response characteristic of the living organism that result from complex interactions between molecules, cells, and tissues." As described in the National Institutes of Health White Paper[3] published in 2011, the mathematical counterpart to SP, or "quantitative and systems pharmacology," aims to understand and predict how drugs modulate biological networks and impact human pathophysiology. The SP models are typically multiscale, multilevel, and physiologically based; that is, they incorporate data at multiple temporal and spatial scales and focus on interactions among multiple levels of biological organization (molecular targets, cells, tissues, organs, etc.) as a means to understand and predict therapeutic and adverse drug effects at the whole-organism level.[3]

Here, we propose to define a new type of model entitled "integrated pharmacometrics and SP (iPSP) model" as being a mathematical framework that uses a combination of pharmacometrics and SP approaches (**Figure 1**[4–7]): mechanistic/detailed biological components and relationships based on prior knowledge (SP); typical PK and PD biomarker observations/measurements or (clinical) outcomes in humans/animals (pharmacometrics); and, a focus on variability, such as between individuals (pharmacometrics).

Other publications have described the philosophical considerations of combining these approaches[8] and provided a mini review on the topic.[9] The purpose of this perspective is to evaluate the current state of pharmacometrics and SP integration by analyzing the number of iPSP models that have appeared as original research articles in *CPT: Pharmacometrics & Systems Pharmacology* (PSP; i.e., the only journal dedicated to these two fields).

METHODS

To assess the state of pharmacometrics and SP integration, we evaluated and reviewed original research articles published in this journal (*PSP*) from September 26, 2012, through March 22, 2017, which resulted in a total of 228 articles. Using the definitions above, we categorized each research article according to whether or not it utilized an iPSP modeling approach (**Figure 1**[4–7]). For articles categorized as iPSP, we evaluated the type of modeling approach that was used to represent each of three components: drug intervention, physiology, and study simulator/network analysis (i.e., whether these individual components were more representative of a traditional pharmacometrics or an SP approach). Importantly, we *a priori* elected to characterize physiologically based pharmacokinetic (PBPK) models as iPSP if they included at least a semimechanistic PD component from the SP part describing an organ level response.

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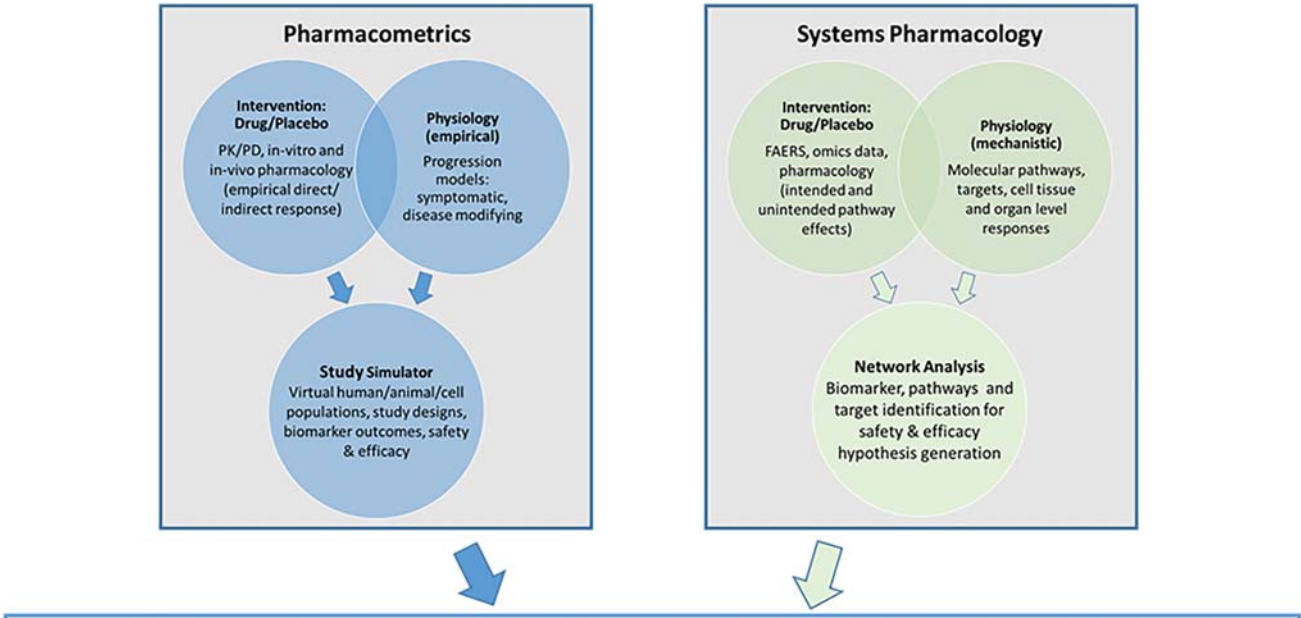

Integration using parts from Pharmacometrics and SP ➡ **iPSP**

Examples	Pharmacometrics			SP			Integration of PMX & SP
	Intervention	Physiology	Study Simulator	Intervention	Physiology	Network Analysis	Integration Type
Bone Model (Peterson and Riggs)[4]	x		x		x		iPSP
Bone Model (Berkhout et al.)[5]	x	x	x		x (reduced)		reduced iPSP
Bone Model (Lisberg et al.)[6]	x		x		x		PBPK-PD
Anticoagulation Model (Hartmann et al.)[7]	x		x		x	x	iPSP

Figure 1 Components of pharmacometrics and systems pharmacology approaches that may be included in an integrated model (integrated pharmacometrics and systems pharmacology (iPSP)). As indicated in **Supplementary Table S1**, iPSP models often include representations of drug intervention and study simulators based on a pharmacometric approach, whereas the representations of physiology (or pathophysiology) typically utilize a systems pharmacology (SP) approach. The models of Peterson & Riggs[4] and Berkout *et al.*[5] are described in the text. The physiologically based pharmacokinetic-pharmacodynamic (PBPK-PD) model by Lisberg *et al.*[6] highlights a case in which modeling the differential drug distribution in the system, leading to quantification of organ level and tissue-specific drug concentrations, can improve our understanding of drug responses at those specific sites of action. Given that the PD part in this specific example comes from the SP site, it falls under the integration type as iPSP according to our definition. The model developed by Hartman *et al.*[7] was highlighted because it provides an example of an iPSP model wherein drug PK was linked with an underlying systems biology network, which allows the model to be used as study simulator assessing efficacy and safety of antithrombotic therapies on the molecular and pathway level. FAERS, US Food and Drug Administration Adverse Event Reporting System.

RESULTS AND EXAMPLES

Of the 228 articles evaluated, 43 (~19%) were classified as iPSP according to the descriptors in **Figure 1,**[4–7] including a subset of 5 PBPK-PD examples (see **Supplementary Table S1**). One observation from this review is that an iPSP model typically utilizes a pharmacometric approach to represent the drug intervention and interindividual variability, which allows the model to be used as study simulator, whereas the biological or physiological part within an iPSP model is informed by an SP approach. Furthermore, an iPSP model contains physiological, systems-level parameters that can be repurposed for application to other targets or compounds; this feature is inherited from SP.

To further illustrate these concepts, we describe two examples highlighted in **Figure 1**[4–7] that incorporate different approaches to integration.

Example 1. Multiscale iPSP

With the first example by Peterson & Riggs,[4] we highlight one of iPSP's greatest attributes: the extensibility for re-use and repurposing. The authors' original iPSP model was developed to relate denosumab (a treatment for osteoporosis) exposure (pharmacometrics) with functional (SP) effects. Physiologically based representations were included in the model to describe bone mineral homeostasis and, simultaneously, the inter-related effects on calcium, phosphate,

parathyroid hormone, vitamin D, and bone formation. Subsequently, PK/PD models describing the pharmacologic effects of a parathyroid hormone analogue (teriparatide), calcium sensing receptor modulators, exogenous vitamin D, and sclerostin inhibition were added into the iPSP model. Many of these extended applications have led to, or taken advantage of, "middle-out" extensions of the model that were added to describe, for example, bone mineral density (BMD) changes associated with bone marker changes and fracture risk associated with BMD. These, along with disease progression effects, such as kidney failure and estrogen depletion, enabled a range of drug development evaluations, including proof of mechanism and concept, dose ranging, disease-state implications, and off-treatment effects. For example, predicted BMD change combined with proportional odds modeling for efficacy was used to evaluate the benefit-risk ratio of GnRH-modulating therapies. In addition, and notably, external validation and use of the model by the US Food and Drug Administration (FDA) during regulatory review of a parathyroid hormone therapy stands as one of the first known regulatory decisions informed by an iPSP model.[4]

Example 2. iPSP with reduced mechanistic detail

The example by Berkhout *et al.*[5] is a disease system analysis in osteoporosis that represents an iPSP model with reduced mechanistic detail, which we term "reduced iPSP." It integrates a physiologically based bone cell (SP) model with pharmacometric components, including empirical drug effects and disease functions. The model captures the effect of 4 years of treatment with placebo and alendronate on multiple bone strength biomarkers in 1,379 women. Originally, the modeling framework was derived using data from tibolone and placebo treatment. The SP model was reduced to its core rate-limiting components while maintaining the inter-related bone cell dynamics of the osteoblasts and osteoclasts. This core was linked to available biomarker data, which are the observable, integrated output of the underlying system, disease processes, and treatment effects. Leveraging information on these components that was embedded in the data enabled the estimation of the model parameters and had the added benefit describing the individual subject level data. This iPSP approach utilized the physiological bone cell dynamics to inform the dynamics of the biomarkers, thereby making it more than just an empirical description of the markers. The treatment effects are included at their site of action and disease progression (although an empirical representation of estrogen decline) is represented from disease onset onward (i.e., disease timescale instead of study timescale). Moreover, the trajectory of the BMD (which is a reflection of the system's history) is driven by the ratio of the bone cell dynamics.

DISCUSSION AND FUTURE DIRECTIONS

Recently, the MID3 Good Practices article[10] highlighted various modeling approaches as quantitative tools to answer the pertinent research and development questions that arise in the development of new medicines. These modeling approaches range from empirical to semimechanistic PK/PD, model-based meta-analyses, systems pharmacology, and PBPK.

As demonstrated in the examples above, an iPSP approach provides value in supporting drug development by combining strengths of each field, including: relevant timescales of various interacting biological networks and physiological responses to drug intervention; a description of rate-limiting pathways and inclusion of system-level parameters; representation of site(s) and mechanism(s) of action; inclusion of disease processes as reflected by the measured disease status; population and individual-subject level predictions; a description of the relationship between biomarkers and primary outcomes; an accounting for study differences (e.g., assays, covariates, populations, dropout expectations, recruitment criteria and rates, etc.); and simulations of clinical trials for decision-making purposes. Thus, an iPSP model becomes a valuable tool to simulate and predict individual subject-level and population-level responses for efficacy and safety assessments, at the molecular and target levels, of novel therapeutic interventions.

Although there remains opportunity to develop and apply new models that integrate pharmacometrics and SP approaches, by our definition, ~19% of the articles published in this journal between September 2012 and March 2017 implemented an iPSP approach. Importantly, although this represents a moderate percentage of research articles, we think it is a reasonable proportion based on the relative newness of the SP field and the diversity of pharmacometric applications in drug discovery and development. What is important to any modeling effort is that the chosen approach is tailored to pragmatically and robustly address the research question(s) under consideration; that is, that the relative simplicity or complexity of the model should be considered in the context of the question(s) to be answered. We encourage active engagement in our community to continue toward these goals.

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1. Williams, P.J. & Ette, E.I. Pharmacometrics: Impacting Drug Development and Pharmacotherapy. 1–21. Pharmacometrics. (John Wiley & Sons, Hoboken, NJ, 2006).

2. Preusch, P.C. Integrative and organ systems pharmacology: a new initiative from the National Institute of General Medical Sciences. *Mol. Interv.* **4**, 72–73 (2004).
3. National Institutes of Health (NIH) QSP Workshop Group *et al.* Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms – An NIH White Paper by the QSP Workshop Group – October, 2011. In: Ward R, ed. 2011.
4. Peterson, M.C. & Riggs, M.M. FDA Advisory Meeting Clinical Pharmacology Review utilizes a quantitative systems pharmacology (QSP) model: a watershed moment? *CPT Pharmacometrics Syst. Pharmacol.* **4**, e00020 (2015).
5. Berkhout, J., Stone, J.A., Verhamme, K.M., Danhof, M. & Post, T.M. Disease systems analysis of bone mineral density and bone turnover markers in response to alendronate, placebo, and washout in postmenopausal women. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 656–664 (2016).
6. Lisberg, A. *et al.* Mathematical modeling of the effects of CK2.3 on mineralization in osteoporotic bone. *CPT Pharmacometrics Syst. Pharmacol.* **6**, 208–215 (2017).
7. Hartmann, S., Biliouris, K., Lesko, L.J., Nowak-Göttl, U. & Trame, M.N. Quantitative systems pharmacology model to predict the effects of commonly used anticoagulants on the Human Coagulation Network. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 554–564 (2016).
8. Duffull, S.B. A philosophical framework for integrating systems pharmacology models into pharmacometrics. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 649–655 (2016).
9. Helmlinger, G. *et al.* Drug-disease modeling in the pharmaceutical industry – where mechanistic systems pharmacology and statistical pharmacometrics meet. *Eur. J. Pharm. Sci.* **109S**, S39–S46 (2017).
10. EFPIA MID3 Workgroup *et al.* Good practices in model-informed drug discovery and development (MID3): practice, application and documentation. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 93–122 (2016).

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (http://psp-journal.com)