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PERSPECTIVE

Perspectives on training quantitative systems pharmacologists

The rapidly evolving field of Quantitative Systems Pharmacology (QSP) calls for updated education curriculums and programs. QSP scientists need a wide variety of quantitative and soft skills, including "mechanistic modeling" skills, "data science" skills, and soft skills such as communication and influence. In this perspective, we share some aspects of how interdisciplinary educational programs can catch up and provide such needed skills. We hope that a mutually beneficial dialog between academia and industry will continue so that a growing number of well-trained QSP scientists will contribute to improved drug development and better clinical treatments.

Quantitative systems pharmacology has been rapidly adopted by industry and academia alike.[1–3] The potential benefit of QSP in de-risking drug development has led to an encouraging increase in demand from employers, from entry-level interns to mid- and senior-level group leaders. This quick expansion creates a challenge for educators: How should quantitative systems pharmacologists be trained?

Based on our own educational journeys and our experience of mentoring and teaching, we offer here some perspectives on the training of QSP scientists. This perspective aims to initiate a dialogue between industry and academia on this important topic so that we might in the future develop a best practice to train next-generation quantitative systems pharmacologists.

A QSP TOOLBOX

The ultimate goal of QSP in pharmaceutical development is to influence critical decisions. This goal is achieved by providing clear, actionable, and understandable quantitative data-driven conclusions and, importantly, communicating and advocating for the implications of those conclusions in the industry.

Starting from the need to generate conclusions, we first examine the practical toolbox of a QSP scientist (Figure 1). The most frequently used tool of a QSP scientist is mechanism-based, mathematical modeling. The developed models of systems physiology and systems pathology allow us to deeply understand how different parts of the body coordinate to properly function (physiology) as well as how the parts that dysfunction result in disease (pathology). In addition, a QSP scientist should also have a solid grasp in the principles of clinical pharmacology and pharmacokinetics (PK), including being able to understand and predict drug pharmacology using traditional, PK/pharmacodynamics-type modeling. At the end of the day, a QSP scientist should be able to integrate these different types of models together to interpret the efficacy and toxicity of drugs and provide insights on how treatments can be optimized.

Data, both preclinical and clinical, play an essential role in the daily work of a QSP scientist. Hence it is not surprising that a QSP scientist would need some data-handling tools in the toolbox. Mechanistic models need to be compared with observed data for parameter estimation, calibration, and validation. Furthermore, when the mechanism is not clear, or the data are too sparse to support the development of a mechanistic model, data-driven approaches such as machine learning[4,5] and time series analysis would be useful to extract the patterns from the data.

Mechanistic modeling and data-driven modeling study the systems from two different points of view. On one hand, mechanistic models derive the emergent behaviors of complex, dynamical systems with nonlinear interaction between their parts; hence they are also referred to as the bottom-up approach. On the other hand, data-driven models build models that relate a set of inputs to a set of outputs; these are also referred to as the top-down approach. We believe that a QSP scientist should have a good

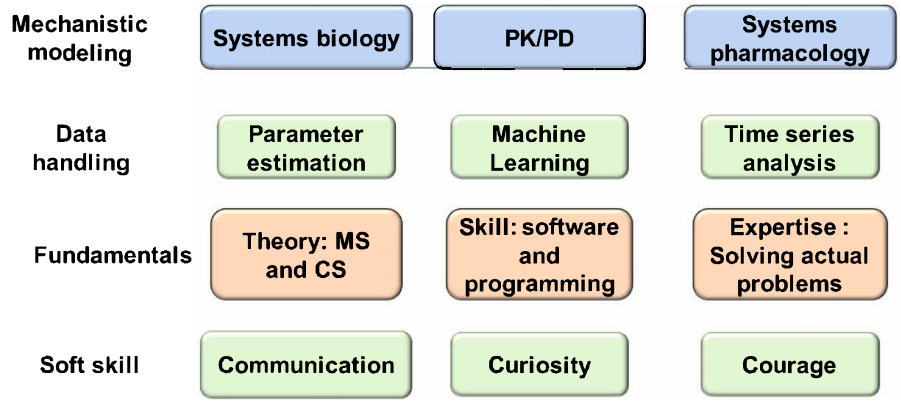

FIGURE 1 An example toolbox of a quantitative systems pharmacology scientist. In addition to the mechanistic modeling tools and data analysis tools, a quantitative systems pharmacology scientist would also need a solid theoretical foundation to be able to understand the strength and limitation of the available computational tools, know how to cope with the limitations, and choose or develop proper computational tools to get the jobs done. In addition, soft skills such as communication is essential for a quantitative systems pharmacology scientist to deliver impactful work. CS, Computer Science; MS, Mathematical Sciences; PD, pharmacodynamics; PK, pharmacokinetics

understanding of the power and limitation of both tools so that suitable tools can be chosen, modified, and combined to best solve the biomedical challenges at hand.

To deeply understand how these tools work and where their boundaries are, a QSP scientist would need a solid theoretical foundation in applied mathematics (e.g., mathematical sciences, physics, theoretical chemistry, computer science). This ensures that the scientist understands how different biological and physiological process should be described using proper mathematical formalism and how correct numerical analysis should be applied to analyze the system. For example, a good understanding of differential equations and numerical integration would help avoid numerical errors when integrating stiff dynamical systems, experience with nonlinear dynamical system theory would help with grasping the qualitative boundaries of complex biological models, and experience with various optimization algorithms allow the QSP scientist to increase the computational efficiency without impairing the solidness of the results.

Proficiency with coding and the relevant software packages[6] is essential for the practical work of a QSP scientist. In addition, the ability to develop code empowers a QSP scientist with more flexibility to develop novel tools and should be encouraged. In lieu of such expertise, many excellent QSP scientists have been well trained in domain expertise with critical mechanistic thinking and focus on key, disease-specific questions, coupled with training on at least one computational platform. Deep familiarity with one platform can often be leveraged to more easily use new tools. The ability to work with several different tools and programming languages allows a QSP scientist to cross-check the computational results across different platforms so that the risk of computational errors can be minimized.

The toolbox is by no means universal or standard, and different QSP researchers would likely add personalized tools based on training background and working experience. A QSP scientist often must update or modify the computational toolbox to fit the need of biomedical teams and to effectively use the available knowledge and data so that the delivered work could add value of risk reduction and efficacy increase. Given this, the ability to adapt quickly and learn fast is essential for a QSP scientist at work.

In this regard, we should also train the QSP scientists to master useful soft skills in addition to computational skills. Pharmacometrics departments reflect considerable diversity of educational backgrounds,[7] so a QSP scientist often needs to work with experts from very different backgrounds, and it is furthermore essential for a QSP scientist to communicate well with experts from diverse areas.[8] Successful communication often requires the QSP scientist to demonstrate both technical excellence (i.e., why a certain algorithm was used and how it is implemented to eliminate potential computational error) and biomedical impact. For instance, rather than elaborating on the technical details, the QSP scientist should communicate something such as "compared with the current practice, incorporation of the modeling and analysis could help reduce the needed time by 21%~25%" for nonmodeling decision makers. Trainees should be provided with experience in developing research relationships with a variety of scientists from disparate fields.

To effectively communicate impact, a QSP scientist often needs to learn more than modeling and its analysis. For example, to compute the time reduction, it is essential to understand what the current process is and how the time is distributed. In this regard, a healthy amount of curiosity on how the data were collected, what the current solutions are, and how the computational results would be used in the overall pipeline would help the QSP scientist to deliver impactful results.

There is considerable debate surrounding the degree to which QSP scientists need to be a subject matter expert in the therapeutic area they are in. Certainly, understanding both the modeling and the biology gives the

QSP scientists more credibility on the teams to which they are assigned. However, given the rapid changing rate of technology and the complexity of real-world needs, a QSP scientist can expect to dive into new areas frequently and cope with novel challenges routinely. Hence, a QSP scientist could be working in immunology one moment and then diabetes the next. The argument can be made that QSP scientists need a basic understanding of biology so that they can effectively interact with other team members who are indeed subject matter experts to develop their models. Most QSP scientists often gain knowledge from different disciplines and should be familiar with the practice of stepping out their comfort zones. Interdisciplinary programs should nurture such courage and open mindedness so that the trainees continue to grow during their career.

A SYNERGISTIC CYCLE FOR EDUCATING FUTURE QSP SCIENTISTS

The pharmaceutical industry has well recognized the need for better education of QSP scientists.[9] As educators working in academic and industrial institutions, we believe that updated education strategies and their continuous improvement are essential to meet such needs. In the Supplementary Text S1, we elaborate currently available resource and methods for training. Because it would be impossible for either the academic or industrial field to carry out the education tasks alone, we hope that more academic and industrial educators can join forces in training our next-generation quantitative systems pharmacologists (Figure 2): the academic community integrates both hard skills (computation, math, programming, etc.) and soft skills (communication, team work, etc.) in the training curriculum, and the industrial community contributes by providing internship opportunities as well as feedback on what skills are most used in the actual work.

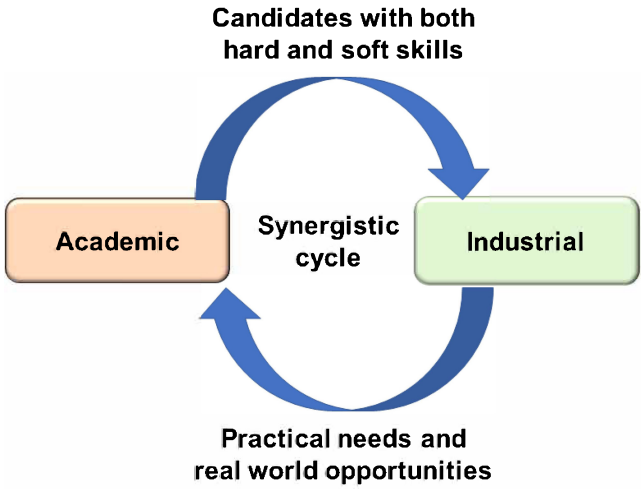

FIGURE 2 A synergistic cycle for educating future quantitative systems pharmacology scientists. In the long run, a synergistic cycle between academic and industrial fields would be able to nurture quantitative systems pharmacology scientists and promote the growth in the field of quantitative systems pharmacology

We envision that a synergistic cycle will help fulfill the tremendous potential of QSP modeling by expanding the pool of next-generation QSP scientists who are proficient with different tools and are able to deliver impactful results. We hope this perspective is a call to the QSP community for an intentional approach to developing this synergistic cycle and the relevant best practices.

CONFLICT OF INTEREST

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REFERENCES

1. Azer K, Kaddi CD, Barrett JS, et al. History and future perspectives on the discipline of quantitative systems pharmacology modeling and its applications. *Front Physiol*. 2021;12:637999. doi:10.3389/fphys.2021.637999
2. Bai JP. Quantitative systems pharmacology for shifting the drug discovery and development paradigm. *Biopharm Drug Dispos*. 2013;34(9):475-476. doi:10.1002/bdd.1870

3. Musante CJ, Ramanujan S, Schmidt BJ, Ghobrial OG, Lu J, Heatherington AC. quantitative systems pharmacology: a case for disease models. *Clin Pharmacol Ther*. 2017;101(1):24-27. doi:10.1002/cpt.528
4. Benzekry S. Artificial intelligence and mechanistic modeling for clinical decision making in oncology. *Clin Pharmacol Ther*. 2020;108(3):471-486. doi:10.1002/cpt.1951
5. Hutchinson L, Steiert B, Soubret A, et al. Models and machines: how deep learning will take clinical pharmacology to the next level. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(3):131-134. doi:10.1002/psp4.12377
6. Ermakov S, Schmidt BJ, Musante CJ, Thalhauser CJ. A survey of software tool utilization and capabilities for quantitative systems pharmacology: what we have and what we need. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(2):62-76. doi:10.1002/psp4.12373
7. Stone JA, Banfield C, Pfister M, et al. Model-based drug development survey finds pharmacometrics impacting decision making in the pharmaceutical industry. *J Clin Pharmacol*. 2010;50(9 Suppl):20S-30S. doi:10.1177/0091270010377628
8. Bonate PL. Be a Model Communicator: And Sell Your Models to Anyone. Amazon.com: Books; 2014. ISBN: 9780692323816
9. Nijsen M, Wu F, Bansal L, et al. Preclinical QSP modeling in the pharmaceutical industry: an IQ consortium survey examining the current landscape. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(3):135-146. doi:10.1002/psp4.12282

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