

## PERSPECTIVE

# The Mathematical and Computational Sciences Special Interest Group of the International Society of Pharmacometrics

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**This article is an introduction to the Mathematical and Computational Sciences (MCS) International Society of Pharmacometrics (ISoP) Special Interest Group (SIG) and recent and upcoming activities. The group was formed in 2016 and aims to bring more mathematical and computational techniques into drug development wherever they may be advantageous. This includes providing opportunities for ISoP members to learn from and collaborate with academic mathematicians and other researchers focused on quantitative methods, both theoretical and applied.**

If you know Wojciech Krzyzanski, you know that he is a mathematician who is passionate about using mathematical tools in drug development. In 2016, he initiated discussions among ISoP members with similar views for ways to better promote and support the use of mathematical techniques in drug development. We talked about bringing tools developed in academia into mainstream drug development modeling through tutorials, speakers from academia, web-based materials, and discussion boards. To support these activities in an organized and sustainable way and to tap into a cohort of talent and skills already existing in ISoP, we decided to form an ISoP SIG, the MCS SIG.

Although there are some quantitative techniques widely used in the biotechnology/pharmaceutical (biopharma) industry, such as pharmacokinetic/pharmacodynamic modeling, nonlinear mixed-effects modeling, covariate selection, and model selection, there are many more techniques that could be beneficial. These include dynamical systems analysis, global sensitivity and identifiability analysis, regimen optimization using optimal control, partial differential equations to incorporate spatial information, delay differential equations, stochastic methods, and machine learning and artificial intelligence for the selection of models, targets, or compounds. To help ISoP members learn about and apply such techniques, we provide opportunities for learning and collaboration. With most of our postdoctorate members in industry, we promote ties with academic departments such as mathematics and engineering that have traditionally been less well connected with the biopharma industry and yet are home to quantitative expertise and techniques that could benefit the industry.

Wojciech Krzyzanski agreed to serve as the first MCS chair. Helen Moore and Gilbert Koch took the roles of Vice Chair and Secretary, respectively. Frank Gibbons was elected as the next Secretary during the first election cycle, and the other roles rotated upward/onward. Approximately 45 ISoP members have joined the MCS SIG, with about one-third in academia. A steering committee to help determine goals and strategies and to suggest and help run activities was formed from interested ISoP members. This perspectives article describes some of our previous activities and our plans for the future.

## ACTIVITIES TO DATE

The MCS SIG was recently referred to as “the little SIG that could” by ISoP board member Peter Bonate. This is because despite having less than half the membership of any other ISoP SIG, the MCS SIG has sponsored a disproportionately large number of activities to benefit ISoP members. In our first year, we laid the ground work for future activities, starting with a “Meet the SIG” luncheon at the 2017 meeting of the American Conference on Pharmacometrics (ACoP) to discuss our goals and plans. We also sponsored a symposium titled “Mathematical Pharmacology: A Distinct Discipline of Pharmacometrics,” organized by Wojciech Krzyzanski and Coen van Hasselt and with speakers Johan Gabrielsson, Andy Stein, Gilbert Koch, and Fahima Nekka.

At the 2018 ACoP, we had even more activities to highlight MCS work. Peiyong Zuo wrote a summary of these activities; her article appeared in the February 2019 ISoP newsletter.<sup>1</sup> We selected three posters to feature during a poster walk, with each presenter speaking to a gathered crowd about her or his work for 5 to 10 minutes. The posters were on bifurcation analysis from dynamical systems to characterize the dynamics of monoclonal antibodies and tumor cells (by Hajihosseini *et al.*<sup>2</sup>), a machine learning/genetic algorithm for selecting a tumor growth model (by Liu *et al.*<sup>3</sup>), and a method to determine the best structure for a quantitative systems pharmacology model for drug metabolism (by Siripuram *et al.*<sup>4</sup>).

We endorsed a symposium titled “Pharmacometrics in the Big Data Era—Mission Possible to Find the Needle in a Haystack,” with mathematical and computational content likely to be of interest to our SIG members. We also hosted

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Received: January 3, 2019; accepted: March 25, 2019. doi:10.1002/psp4.12410

another Meet the SIG luncheon, with about 80 attendees, in which we discussed the objectives and plans of the MCS SIG, presented our poster award, and featured two speakers.

We awarded a poster prize to the first author of a group that had applied optimal control to predict the best anti-hormonal therapy for prostate cancer patients. The prize winner, Itziar Irurzun-Arana, PhD student at the University of Navarra, gave a 10-minute presentation at the Meet the SIG luncheon. She presented the main ideas in her poster, which was based on a publication.<sup>5</sup>

Linda Petzold, Mehrabian Distinguished Professor in Mechanical Engineering and Computer Science at the University of California Santa Barbara, also spoke at the luncheon. Her work on numerical algorithms for solving differential equation systems, especially DASSL and LSODA, is widely known. In particular, LSODA is an algorithm she came up with to detect stiff and nonstiff regions in differential equation systems and to switch between solvers accordingly.<sup>6</sup> LSODA is used in ADAPT, Monolix, NONMEM, Phoenix, R, Stan, and other software used in the biopharma industry. Dr Petzold spoke about her latest open-source software package, StochSS, which can simulate discrete stochastic systems. As few as 10 transcription factors in a cell can determine its fate, but this low number of molecules cannot be modeled accurately with ordinary differential equations; hence the need for a stochastic approach. To help explain the relevance of Dr Petzold's work to the ISoP community and encourage attendance at her talk, we published an interview with her in the September 2018 ISoP newsletter.<sup>7</sup>

Outside of the annual ACoP meetings, the MCS SIG has initiated some activities to build stronger ties between the biopharma industry and academic math and engineering departments. These include efforts around web-based materials, conferences, and journals. The MCS Steering Committee is gathering materials to post on our web pages as resources for our members interested in learning more about quantitative techniques that can be used in drug development. Our web pages can be accessed starting at our ISoP MCS SIG page: <https://insp.memberclicks.net/mcs-sig>. The link at the bottom of that page can be used to join the MCS SIG to receive information about upcoming events and opportunities.

The MCS SIG has made efforts to coordinate activities at conferences outside of biopharma. We aim to submit proposals for symposia at the Society for Industrial and Applied Mathematics (SIAM) annual meeting, the SIAM Life Sciences conference, and at the Society for Mathematical Biology annual meeting. These conferences are well attended by academics developing new methods for use in mathematical modeling. We are also reaching out to academic communities and encouraging their participation in conferences such as ACoP and the Population Approach Group in Europe (PAGE), which are well attended by those working in drug development.

As with conferences, journals provide both a means to build ties between our communities and an opportunity to share knowledge. The *Bulletin of Mathematical Biology*, a journal with articles primarily written and read by academics in math departments, recently put together a special

issue titled "Mathematics to Support Drug Discovery and Development" to appear in early 2019. Richard Allen and I edited this special issue to highlight research areas of interest to the biopharma industry.<sup>8</sup> There are several other journals that publish articles by academics that are often relevant to the biopharma industry. These include the *Journal of Mathematical Biology*, the *Journal of Theoretical Biology*, *Mathematical Biosciences and Engineering*, and *Mathematical Biosciences*. In the other direction, Wojciech Krzyzanski and J.G. Coen van Hasselt edited a special issue of the *Journal of Pharmacokinetics and Pharmacodynamics* titled "Mathematical Pharmacology."<sup>9</sup> Their issue contains papers with strong MCS content in a journal often read by modelers working in the biopharma industry.<sup>10</sup>

## FUTURE PLANS

We have a full slate of activities planned once again for ACoP in 2019. Some of our members proposed sessions at ACoP with mathematical or computational topics. Others reviewed session proposals with MCS content and provided recommendations to the programming committee.

We are offering another poster prize for the best poster abstract that applies mathematical and/or computational techniques to drug development. We will select additional posters with mathematical content to highlight in a poster walk. We will host a Meet the SIG luncheon in 2019, and we plan to bring another researcher from outside the ISoP community to be the featured speaker.

Our steering committee has recently added a liaison from the student community group to help us plan and implement activities to help students who want to learn more about the quantitative methods they will need for their future in the biopharma industry. Most of these students are working toward doctorate degrees in departments of pharmaceutical sciences and may not have much exposure to mathematical and computational techniques.

There are currently the following three other SIGs in the ISoP organization: Quantitative Systems Pharmacology, Statistics and Pharmacometrics, and Clinical Pharmacometrics. As there are overlapping interests between the SIGs both in content focus and logistics, we are coordinating activities and sharing experiences and ideas among the leadership of the four SIGs. One example of a topic of interest to members of several of the SIGs is the question of how to evaluate a mathematical model of disease/drug dynamics and its appropriateness for answering a given question.

The MCS SIG is working to bring relevant cutting-edge quantitative research to members. We seek to decrease the lag time between the development of techniques and their application to problems in the biopharma industry. Membership in the MCS SIG is open to all ISoP members, and we invite you to join us in ISoP and in the MCS SIG!

**Acknowledgments.** The author is grateful to past and present leadership of the MCS SIG as well as the anonymous reviewers for comments that led to improvements in this article.

**Funding.** No funding was received for this work.

**Conflict of Interest.** H.M. is an employee of AstraZeneca and owns stock in Bristol-Myers Squibb.

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