Model-Informed Drug Discovery and Quantitative Systems Pharmacology: Key Applications, Opportunities and Challenges (24w2017)

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Drug design and development are costly and lengthy. Mathematical and computational modelling anchored in model-informed drug development (MIDD) and quantitative systems pharmacology (QSP) methodologies are integral to accelerating the R&D pipeline. In parallel, MIDD and QSP can be used to better understand the biological basis of drug responses and fuel new biomedical research paths. Formally recognized in the Prescription Drug User Fee Act (PDUFA) VI of the Food and Drug Administration in the United States in 2017, MIDD continues to be increasingly relied upon within drug discovery programs and submissions[5]. This workshop brought together experts in the fields of MIDD and QSP with the goal of strengthening ties between industrial and academic researchers and advancing these exciting fields.

To ensure high productivity, the scope of the workshop was limited to application of QSP and MIDD in a select therapeutic area. Specifically, an area of infectious diseases, which represents an important global health burden (e.g. amongst top 10 in low and middle-income countries [2]), was chosen, with a particular focus on vaccines. Overall, the workshop facilitated discussions, collaborations between academic institutions and between pharmaceutical industry and academia as well as produced outputs such as white papers (in preparation) to educate on and promote mechanistic mathematical modelling for application in vaccine development within both mathematical, biological and clinical communities across academia, industry and regulatory bodies.

1 Overview of the Field

Vaccine development is one of the more conservatives areas in drug discovery and development to incorporate mechanistic mathematical modeling as part of its tool. For example, the duration of Paxlovid's treatment of COVID-19 was informed by a mathematical model of the viral dynamics of SARS-CoV-2 [3]. However, unfortunately, such modelling approaches are largely absent in vaccine regulatory submissions. In 2024 Desikan et al. published a paper introducing the framework of model-informed vaccine development [4]. Additionally, numerous publications over the past decade have come out with vaccine modelling applications in drug development.

QSP models are mathematical models that describe physiological, pathophysiological and drug mechanisms. A key aspect of such models is that they require an understanding of the underlying biological mechanisms of the system being studied. This knowledge is then translated into a series of mathematical equations to describe the system's behavior under various conditions. This sets these types of models apart

from statistical approaches such as artificial intelligence and/or machine learning that largely use data to drive the creation of the model without requiring a prior understanding of the underlying physiology. Accomplishing model-informed vaccine development requires a close partnership/productive collaboration between modellers, immunologists, clinicians, statisticians, and pharmaceutical scientists, among others.

Additionally, discussions about calibration, validation and required assessment of mechanistic models to ensure their robustness has been a recent active topic in the community, with general MIDD guidance (including on QSP and QST models) being established as part of International Council for Harmonisation (ICH) M15 [5]. Therefore it have been timely to host the workshop in August 2024 to bring up and align on challenges and future perspectives in model-informed vaccine development field driven by mechanistic modelling.

2 Presentation Highlights

At the workshop each participant presented a quick overview of their research and expertise, which facilitated insightful questions and discussions on what are the key open questions and key needs within model-informed vaccine development as perceived from academic, pharmaceutical and regulatory perspectives and from earlier career scientists and later career scientists perspectives. Through chaired discussions (both in person and with colleagues joining remotely), we were able to set clear goals for the 2 day meeting, organize productive small working group discussions, and output a clear plan on the next steps including an agreement to write a positional paper aimed at virologists and healthcare practitioners, potentially to be followed by a more technical manuscript on the methodologies used and best practices technical recommendations. We discussed positional paper and technical paper outlines and assigned colleagues for work on each of the sections.

3 Recent Developments and Open Problems

During recent Covid-19 pandemic in 2020-2023 mechanistic mathematical modeling received high visibility, especially around the role of modeling in informing dosing regimens and optimal sub-populations and the choice key biomarkers to measure. With the vision of combining digital twin QSP and machine learning to enable the development of personalized vaccines, a number of challenges and open problems still exist. Today's key challenges include:

- limited availability and limited quality of longitudinal data
- multi-modal nature of data going into the model, hence challenges around parameter identifiability, uncertainty quantification, parameter estimation as well as around linking quantitative data and mechanistic knowledge across multiple scales and sources
- high computational cost of running virtual populations of virtual patients and virtual twins
- conservative nature of traditional vaccine development paths, and hence a significant delay before embracing mathematical modelling as part of vaccine development
- the speed of changes is fast, yet processes and guidance for model credibility assessment are still being developed and aligned on by experts, which makes it challenging to readily adopt new technology by non-modellers, who traditionally have not used mathematical approaches
- another imminent challenge includes ethical questions around digital twin technologies, including whether open-source models may end up raising issues around accessibility, privacy and ownership of data including by insurance companies, pharmaceutical companies, government, etc.

Through active discussions, a number of distinct perspectives emerged making it more challenging, yet more fruitful due to facilitating the need to align on and to organize what key topics and messages are to be included into joint manuscripts (e.g., perspective (aka white paper) manuscript).

4 Outcome of the Meeting

This workshop [1] facilitated engaging and eye opening discussions where different representatives from academia, pharmaceutical industry and regulatory bodies openly shared key excitements and key challenges in model-informed vaccine development. A number of controversial areas have been brought up and addressed, including model robustness evaluation and model validation, modeling application impact and influence, as well the role of AIML in MIDD and MIVD at present (given release evolvement of Chat GPT and evolving role of AIML in research and in QSP modelling specifically) and its anticipated impact in future.

In summary, at workshop the scientific progress was made through sharing knowledge about QSP modelling methodologies, applications and potential impact. The workshop laid foundation to new collaborations across academic and industrial partners. Through the white paper that is being drafted, as a result of this meeting, workshop will facilitate education and promotion of mathematical modeling to the traditionally conservative vaccine community, which will pave way to more collaborations and application of MIVD tools to help accelerate and de-risk vaccine discovery and development. The white paper both overviews the field and proposes education and training steps required to move MIVD field forward.

A follow up BANFF workshop meeting has been planned to take place in 2026 to continue on the progress of this workshop to strengthen and grow the community of MIVD, and start addressing the question of best practices and guidance in MIVD modeling including development, evaluation (calibration and validation, and application.

References

[1] BANFF workshop *https://www.birs.ca/events/2024/2-day-workshops/24w2017*

[2] World Health Organization *https://www.who.int/data/global-health-estimates*

[3] *https://www.fda.gov/media/166197/download*

[4] Desikan et al. 2024. A Quantitative Clinical Pharmacology-Based Framework For Model-Informed Vaccine Development. J Pharm Sci. 113(1):22-32. doi: 10.1016/j.xphs.2023.10.043 *https://pubmed.ncbi.nlm.nih.gov/37924975/*

[5] Marshall, Scott, et al. 2023. Model-informed drug development: steps toward harmonized guidance. Clinical Pharmacology and Therapeutics. 114.5 954-959.

[6] https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-assessment-reporting-mechanistic-models-used-context-model-informed-drug-development_en.pdf