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Model-Informed Drug Development:

Addressing the Critical Need for Training in the Promising New Field

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Abstract

The pharmaceutical industry faces a major challenge in drug discovery and development, with overall success rates of only 10–20%, often due to reductionist approaches that fail to account for complex biological networks. To address this challenge, industry and regulatory agencies, including the FDA, are increasingly adopting Model-Informed Drug Development (MIDD) and Quantitative Systems Pharmacology (QSP) to improve dose optimization, trial design, and decision-making throughout the drug development pipeline. At the same time, pharmaceutical investment in the United States, particularly in the greater Delaware region, is rapidly expanding, increasing the demand for a highly skilled workforce trained in advanced modeling and simulation. However, the widespread adoption of MIDD and QSP methodologies is hindered by a shortage of trained scientists, as traditional Biomedical Engineering curricula often lack the advanced mathematical and computational modeling preparation required by industry. To address this gap, the Biomedical Engineering department at the University of Delaware has integrated MIDD principles into its graduate curriculum and launched the nation's first Master's program dedicated to QSP, providing structured, industry-aligned training to prepare students for careers in the pharmaceutical and biotechnology industries.

Introduction

The pharmaceutical research landscape has long been constrained by reductionist methodologies that fail to capture the intricate, multi-dimensional nature of biological systems. Traditional drug discovery approaches typically isolate individual molecular targets, overlooking the complex, interconnected networks that govern biological responses. This fragmented approach explains the staggeringly low success rates in drug development.

Research indicates that the overall success rate for new drugs entering clinical trials is approximately 10-20%, depending on the phase of development. For instance, DiMasi et al.[1] reported that about one in six drugs entering clinical testing from 1993 to 2004 ultimately received marketing approval in the United States, suggesting a success rate of around 16%. However, this figure masks a more sobering reality when considering that the success rates for new molecular entities (NMEs) are significantly lower, particularly in later phases of clinical trials. Agrawal highlighted that while repurposed drugs have a success rate of about 25% from Phase II and 65% from Phase III, new NMEs only achieve success rates of 10% and 50%, respectively.[2] This stark contrast underscores the challenges faced by novel drug candidates.

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The high failure rates can be attributed to several factors, including inadequate efficacy, safety concerns, and issues related to pharmacokinetics and pharmacodynamics. For example, Mei et al. noted that the failure rate for drug candidates transitioning from animal testing to human trials exceeds 92%, with anticancer candidates facing even higher rates of failure, up to 97%.[3] This highlights the difficulties in predicting human responses based on preclinical animal models, which often do not accurately reflect human physiology.

The lack of an efficient pipeline to bring new drugs to market has important public health consequences. Perhaps most notably, only one small-molecule antibiotic based on a truly novel mechanism (and thus capable of overcoming existing resistance mechanisms) was approved between 2012 and 2022[4]; while recent approvals indicate some movement on this front, the threat of pan-resistant bacterial infections makes this a critical problem to address. Such inefficient drug discovery also means that rare conditions, as well as those with complex etiologies, are often treated using pharmaceuticals that are decades old, as there is not a solid business model to support development.

There are economic consequences as well, which are amplified in the greater Delaware region by the large number of pharmaceutical companies operating there. According to the New Castle County Chamber of Commerce, Biopharma in Delaware employs more than 5,700 highly skilled workers and generates more than $1.1 billion per year in economic activity.[5] Pharmaceutical investment in this area is growing dramatically, highlighted by the recent groundbreaking of a new $1 billion biopharmaceutical manufacturing facility by Merck[6] and a planned new $3.5 billion facility in nearby Lehigh Valley by Eli Lilly.[7] There is an opportunity for Delaware to take a leadership role in the future of pharmaceutical development.

The pharmaceutical industry has responded to these challenges by increasing the role that theoretical and computational modeling plays in the drug development pipeline, and the FDA has responded by initiating a pilot program to increase the integration of modeling in drug development and regulatory review. The recent shifts in FDA regulations, coupled with the low success rate of new drugs entering clinical trials (approximately 10–20%), highlight the growing need for specialized training in Model-Informed Drug Development (MIDD).[8] MIDD applies quantitative modeling and simulation to combine clinical and nonclinical data with existing knowledge, guiding decisions in drug development and regulatory processes. The FDA's MIDD Pilot Program recognizes Quantitative Systems Pharmacology (QSP) as a tool to improve dose optimization and trial design, marking its emergence as an effective MIDD approach with visible impact across the pharmaceutical industry.[9]

Quantitative Systems Pharmacology: A Comprehensive Computational Framework

Quantitative systems pharmacology (QSP) represents a transformative approach in the field of drug discovery and development, integrating computational modeling with experimental data to elucidate the complex interactions between drugs and biological systems. This interdisciplinary field draws from various domains, including systems biology, pharmacokinetics, pharmacodynamics, and engineering, to create predictive models that can inform therapeutic strategies and optimize drug efficacy. The evolution of QSP has been driven by the need to address the intricacies of biological systems and the challenges associated with traditional pharmacological approaches, which often rely on reductionist methodologies that fail to capture the holistic nature of drug action.[10–12]

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One of the key aspects of QSP is its ability to create mechanistic models that simulate the dynamic interactions between drugs and their biological targets (Figure 1). These models can incorporate a wide range of data, including chemical and biochemical knowledge, pharmacokinetic and pharmacodynamic information, genomic and metabolomic data, and medical informatics, to predict how drugs will behave in vivo and across populations. For instance, Fang et al. demonstrated the utility of QSP in identifying new drug targets for natural products, showcasing how computational frameworks can facilitate the discovery of novel therapeutic agents.[11] Similarly, the work by Derbalah et al.[10] emphasize the importance of simplifying QSP models to enhance their applicability in clinical pharmacology, thereby making them more accessible for practical use in drug development.

Figure 1: Examples of Engineering Tools Used in QSP Modeling, with Examples From the Literature.

The prominent methods used in each study are color-coded corresponding to the bolded method.

Methodology and Foundations

The application of QSP spans various stages of the drug development process, from target identification to clinical trial design, thereby facilitating a more informed and efficient pathway to new therapeutics. One of the foundational aspects of QSP is its ability to combine mechanistic insights with pharmacokinetic and pharmacodynamic (PK/PD) modeling. This integration allows researchers to simulate the dynamic responses of biological systems to drug interventions, thereby predicting the efficacy and safety of drug candidates. For instance, the work by Fang et al.[11] highlight the use of in silico models to predict drug-target interactions, which is crucial for identifying new therapeutic targets, particularly in cancer therapy. Similarly, Ramakrishnan et al.[13] provide insights into the amyloid pathway in Alzheimer's disease, demonstrating how QSP models can elucidate the therapeutic mechanisms of clinical candidates. These examples

underscore the versatility of QSP in addressing complex biological questions and guiding drug development decisions.

Moreover, QSP modeling facilitates the exploration of multi-scale interactions within biological systems. As noted by Meng and Tao, the discipline merges computational systems biology with pharmacology, enabling researchers to leverage high-throughput omics data to understand disease progression and drug action.[14] The ability to incorporate diverse data sources, including in vitro, animal, and clinical data, enhances the robustness of QSP models, making them invaluable in the early stages of drug discovery.[15]

The application of QSP is not limited to understanding drug mechanisms; it also plays a critical role in optimizing clinical trial designs. As highlighted by Marshall et al., model-informed drug discovery and development (MID3) strategies utilize quantitative modeling to streamline the drug development process, thereby reducing costs and improving the likelihood of success.[16] This approach is particularly beneficial in pediatric drug development, where Kaddi et al.[17] emphasize the importance of mechanistic modeling to extrapolate findings from adult populations to children. By employing QSP models, researchers can better tailor clinical trials to specific populations, ensuring that therapeutic interventions are both safe and effective.

Furthermore, the use of QSP models extends to the evaluation of combination therapies and the identification of synergistic effects among drug candidates. Wang et al. discuss the role of QSP in understanding exosome-mediated drug efflux, which is critical for developing strategies to enhance drug delivery and efficacy.[18] This is particularly relevant in oncology, where combination therapies are often employed to overcome resistance mechanisms. The ability to model these interactions quantitatively allows for the identification of optimal dosing regimens and treatment sequences, thereby improving patient outcomes.

In addition to its applications in drug discovery and development, QSP also serves as a framework for understanding disease mechanisms at a systems level. The work by Bloomingdale et al.[19] illustrate how QSP can be utilized to explore the hallmarks of neurodegenerative diseases, providing insights into potential therapeutic targets and treatment strategies. By adopting a holistic approach, QSP models can capture the complexity of disease processes, enabling researchers to identify critical pathways and biomarkers that may be targeted in therapeutic interventions.

The integration of QSP with emerging technologies, such as artificial intelligence and machine learning, further enhances its potential in drug design. As noted by Lazarou et al.,[20] the incorporation of omics data into QSP models allows for more accurate predictions of drug responses and patient outcomes. This convergence of technologies not only accelerates the drug development process but also facilitates the identification of novel therapeutic candidates that may have been overlooked using traditional methods.

Despite the numerous advantages of QSP, challenges remain in its widespread adoption across the pharmaceutical industry. The complexity of biological systems and the need for high-quality data can hinder the development of robust QSP models. However, as highlighted by Trame et al., the integration of pharmacometrics and systems pharmacology offers a pathway to overcome these challenges, fostering a more comprehensive understanding of drug action and disease mechanisms.[21] By leveraging advances in computational biology and systems engineering, researchers can develop more sophisticated models that accurately reflect the intricacies of biological systems.

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An Educational Framework for Quantitative Systems Pharmacology

A 2011 NIH White Paper highlighted the growing need to train more individuals in QSP and proposed concrete solutions to address this gap.[22] It emphasized that graduate training should combine didactic coursework with hands-on laboratory and computational experiences, fostering the integration of structural biology, biomedical sciences, applied mathematics, and engineering principles. The report also underscored the importance of industry and academic collaboration to better prepare trainees for real-world applications.

Gallo[23] emphasized that graduate programs in QSP are critical for closing the gap between industry demand and the shortage of trained QSP scientists. Such programs should include 2 to 3 dedicated courses, totaling at least six credits, covering core areas like mechanistic modeling, Pharmacokinetics and Pharmacodynamics (PK/PD), and computational methods. In addition, Hendrick and Tilbury[24] highlighted the importance of applied mathematics in biomedical engineering education to build critical thinking and problem-solving skills. Their approach connects differential equations to real-world biomedical challenges and promotes interdisciplinary problem-solving across physiology, drug kinetics, instrumentation, and organ systems. Similarly, Pennell et al.[25] emphasized that integrating project-based engineering problems with mathematical modeling and numerical solutions using tools like MATLAB significantly strengthens students' analytical and engineering competencies.

Although Biomedical Engineering (BME) programs provide a strong foundational background, they often lack advanced mathematical modeling that links complex biological and pharmacological interactions into computational frameworks.[26] Such models enable predictions of drug behavior before clinical trials, reducing risk and improving efficiency. Therefore, current BME curricula can incorporate MIDD techniques to meet the expectations of potential employers in both industry and academia and ensure successful student transitions into the workforce.

To address the identified gap in MIDD training, we have integrated relevant topics into the University of Delaware graduate BME curricula and launched the nation's first Master's program focused on Quantitative Systems Pharmacology. The curriculum begins with core principles of mathematical modeling in biomedicine, including PK/PD for linear and nonlinear systems, and progresses to advanced, industry-focused techniques. Students gain hands-on experience with industry-standard tools such as MATLAB and SimBiology, building a foundation for computational modeling. The courses emphasize mechanistic modeling and systems pharmacology, and students engage in literature-based projects that translate theoretical knowledge into real-world applications. To strengthen industry alignment, guest lectures from pharmaceutical and regulatory professionals will provide real-world perspectives and discuss essential soft skills for success in the QSP field. This structured approach ensures that the depth and complexity of topics are tailored to industry needs, preparing students for successful careers in model-informed drug development.

Conclusions

Quantitative Systems Pharmacology represents more than a methodological innovation—it is a fundamental reimagining of how we understand and develop therapeutic interventions. By embracing computational complexity, we can transform drug discovery from a high-risk endeavor to a precise, predictable scientific process. The growth of this field will aid in the

development of effective pharmaceutical therapies for rare diseases and those with complicated etiologies, with important public health benefits. The high density of pharmaceutical companies, as well as novel and targeted educational programs, uniquely place the greater Delaware area for leadership in this promising area of growth.

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