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SPECIAL ISSUE: MATHEMATICS TO SUPPORT DRUG DISCOVERY AND DEVELOPMENT

Perspectives on the Role of Mathematics in Drug Discovery and Development

Richard Allen[1] · **Helen Moore**[2]

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Abstract
The goals of this article and special issue are to highlight the value of mathematical biology approaches in industry, help foster future interactions, and suggest ways for mathematics Ph.D. students and postdocs to move into industry careers. We include a candid examination of the advantages and challenges of doing mathematics in the biopharma industry, a broad overview of the types of mathematics being applied, information about academic collaborations, and career advice for those looking to move from academia to industry (including graduating Ph.D. students).

Keywords Pharmacometrics · Biotechnology and pharmaceutical (biopharma) · Industry careers

1 Introduction

The US Food and Drug Administration (FDA) defines *pharmacometrics* as "the science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions" (Pharmacometrics at FDA). According to that definition, this special issue, *The Mathematics of Discovering and Developing Therapies,* could have been titled *Pharmacometrics*. Meetings such as the American Conference on Pharmacometrics have participants from a range of quantitative back-

Richard Allen and Helen Moore have contributed equally to this work.

✉ Richard Allen
Richard.Allen@pfizer.com

[1] Internal Medicine Research Unit, Pfizer Inc, Cambridge, MA 02139, USA

[2] Oncology R&D, AstraZeneca, Waltham, MA 02451, USA

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grounds, including mathematics and engineering, with excellent representation from biotechnology/pharmaceutical (biopharma) companies.

Drug discovery and development requires many resources, particularly time, money, and ideas. Mathematics is being used more and more in the biopharma industry, and has been able to help with each of these resources. Mathematical approaches in this industry require both financial and practical investment. However, in our view, they provide extraordinarily good value given their potential impact and the comparative cost of running clinical trials. For example, if a modeler at a company makes just one insight in 1 year that leads to a clinical trial being run more efficiently (for example, testing fewer or better doses of a drug), then it is possible that they have returned the investment on their salary, *regardless of anything else they do that year!*

The biopharma industry invests large amounts of capital to gather data from both preclinical (animal) experiments and clinical (human) trials. Despite this effort, less than 14% of projects that initiate clinical trials end up being registered as drugs (Wong et al. 2018). The lowest probability of success in clinical development is in Phase II, when drugs are tested for efficacy (Wong et al. 2018). This high failure rate is partly reflective of the complexity and variability of human physiology, which increases the cost of successful therapies. To decrease costs and development time for patients and companies, it is important to do the right experiments, and to analyze them with appropriate quantitative tools. Cutting-edge mathematical techniques to address these points are of great benefit and interest to this industry.

In this special issue, a diverse selection of mathematical approaches is highlighted, along with their role in the drug development process. As the mathematical approaches applied routinely in industry increase in complexity and detail (mathematically or biologically), the benefit of closer collaboration with academics who can truly focus on challenging areas becomes ever greater. While there are numerous academic groups with close industry ties and/or working on problems highly pertinent to drug discovery applications, there are many others that are largely unaware that their work might be applied to critical problems involving real patients. This disconnect is reflected, for example, in the fact that the number of industry attendees at the Society of Mathematical Biology annual meeting is typically around 1%.

2 Applied Mathematics in the Biopharma Industry

In any application, the success of mathematical modeling depends on important factors, including getting the:

1) Right question,
2) Right model,
3) Right analysis.

Generally, items 1) and 2) depend on collaboration with domain-knowledge experts. In an industry setting, there is often a very specific set of questions we are pursuing. For example: “should we develop a drug for this molecular target?”; “what is the mechanism of this observed effect?”; “what should we measure to build confidence in our approach?”; or “which dose levels should we test?”. After agreeing on the ques-

tion(s) to be addressed, it is important to build a mathematical model that adequately captures the relevant biology and is suited for the available data. As with all mathematical modeling applications, the quality of the results depends on how well the model characterizes the system being modeled.

The model can be fit to data to obtain parameter estimates. Model predictions can be compared to additional data to evaluate the model. If additional data are not available, cross-validation can be used to evaluate the model. After rigorous model validation, modeling expertise is needed to decide appropriate analysis to be performed. If we have a validated model, then a full array of powerful mathematical and computational methods become available to us. In this issue, we highlight a few of these methods.

Some of the earliest applications of mathematics in drug development relate to pharmacokinetic (PK) and pharmacodynamic (PD) analysis. After a drug has been administered, we wish to know the concentration levels, C, at various times. By taking blood samples at multiple times after dosing, and fitting a mathematical model to the data, we can predict when the concentration may drop below a critical threshold and the drug needs to be re-dosed. For example, if a drug is dosed intravenously, we might model the concentration as $C(t) = C_0 e^{-kt}$, where t is time and C_0 and k are constants to be estimated by fitting the model to a set of concentration data. We call C_0 and k fixed effects in the mathematical model for concentration C (Gabrielsson and Weiner 2017).

When time series data are collected from each one of multiple individuals, we can fit them all simultaneously using a method called nonlinear mixed-effects (NLME) modeling. To do this, we include random effects on the parameters C_0 and k, usually so that an individual value of parameter P is represented by $P_i = \text{tvP*exp}(\text{eta}_{P,i})$, where tvP is the typical or population value of P and $\text{eta}_{P,i}$ is an individual's random effect, taken from a distribution usually assumed to be normal. This statistical structure leverages information from others when fitting the data for a given individual. Because we estimate both fixed effects (from the mathematical structure) and random effects (from the statistical structure), the modeling process is called mixed effects. It is nonlinear because the exponential decay function is not linear, hence "nonlinear mixed-effects modeling". We recommend a nice set of tutorials on this technique written by Diane Mould and Richard Upton (2012, 2013). The highly readable book by Peter Bonate (2011) covers these methods in more depth, and also includes topics such as mixture modeling, model averaging, and survival analysis.

Several software packages that perform NLME modeling are commonly used in the biopharma industry. ADAPT (D'Argenio et al. 2009) and the nlme package in R (Pinheiro et al. 2018) are freely available. Monolix (Lixoft) is free for academics. NONMEM (ICON) Beal et al. (2017), Phoenix NLME (Certara), and MATLAB (MathWorks) are proprietary packages that are available for a fee. Stan (Gelman et al. 2015) is a free, open-source C++ program that uses Bayesian methods to perform the maximization step in NLME modeling.

While linear mixed-effects modeling was developed by statisticians for a variety of applications to data modeling, applications in biopharma contributed significantly to the developments of NLME modeling (Lindstrom and Bates 1990; Davidian and Giltinan 1995). An area of interest currently is the development of numerical algorithms for estimating parameters in nonlinear mixed-effects models. Parameters in such models

are found by maximizing a likelihood function, and the maximization can be challenging. Current techniques include first-order conditional estimation, Laplacian methods, stochastic approximation expectation maximization (EM), and quasi-random parametric EM (Bonate 2011). Estimation of parameters and their uncertainty is important, as regulatory agencies expect drug applications to demonstrate understanding of variability, both within and between patients.

When and where a drug gets metabolized can greatly change its pharmacokinetic profile. For example, if the drug is transported in and out of multiple tissues, a multiple-compartment model may be required to fit the data. Starting from the simple example above, each additional compartment introduces another exponential term to the solution. Although this is a pragmatic approach, we often want to understand the physiological interpretation of these compartments. To provide greater prospective and retrospective insight into the tissue disposition of a drug, physiologically-based pharmacokinetic (PBPK) models can be employed (Sager et al. 2015). In this framework, the additional compartments represent organs or tissues. Parameters are either assumed to be directly related to the compound under consideration (e.g., tissue clearance rates) or to be physiological processes that are unaffected by the presence of compound (e.g., flow rates between compartments). In the former case, these parameters are experimentally measured for each specific compound (typically/initially in preclinical animal experiments); in the latter case, existing data are used to establish fundamental physiological parameters.

Some of the mathematical techniques used in the biopharma industry were used for years in academia before being applied in industry. One example is the area of quantitative systems pharmacology (QSP). A QSP model provides a systems level description of a biological pathway, process, physiology, and/or disease. PBPK models are often considered to be QSP models due to their similar structures. In contrast to most PK/PD modeling which might be more abstract, a QSP model usually incorporates mathematical descriptions of biological mechanisms or their effects. However, components of PK/PD may be included in a QSP model. Another distinction is that a PK/PD model is often focused on a few goals, whereas a QSP model may have broader applications (Fig. 1). The cost of this breadth is both technical and practical: Model parameters may not be identifiable given the available data; and the time and investment required to build a comprehensive model are significant.

QSP models and systems biology models (common in mathematical biology research in academia) share many features. However, QSP models are specifically designed to support drug discovery and development questions. As such, they typically include a model of drug concentration and action. They could be constructed to simulate clinical trials—for example, by identifying parameter sets and collections of parameter sets as virtual patients and populations, respectively. Practically speaking, if you are currently a mathematical modeler building mechanistic models that describe biology, then you have the skills necessary to build a QSP model.

QSP models can be large systems of equations that aim to include all currently-known interactions (e.g., signal transduction pathways) involved in the dynamics of a disease. Or they can be smaller, fit-for-purpose models that capture “net effects”, and are sometimes called “disease models”. Often these models consist of systems of ordinary differential equations (ODEs), but they could consist of partial differen-

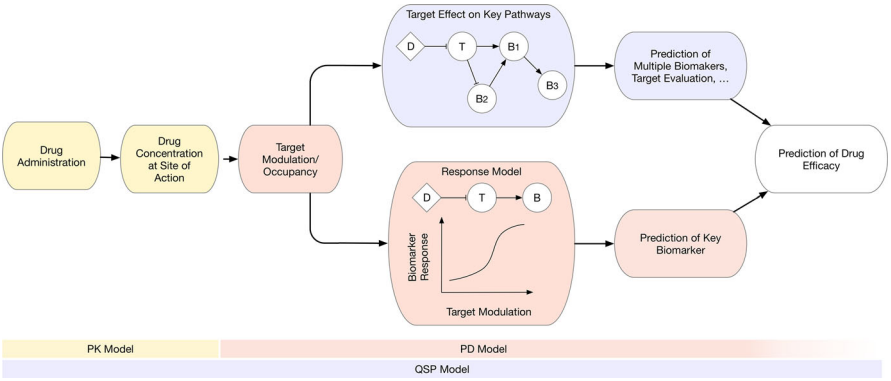

Fig. 1 Comparison and distinctions between PK, PD, and QSP models. PK models describe the concentration of the drug (D) in the relevant compartment (usually representing circulating blood). PD models link this concentration to a downstream gene or protein ("biomarker", B) that is hypothesized to be linked to disease state, often by direct consideration of the target (T) modulation. PD models can often be described by an Emax model that is stimulating or inhibiting (Gabrielsson and Weiner 2017). A QSP model typically replaces the response model component of a PK/PD model with a more-detailed mathematical representation of the biology (hence including multiple biological components: B1, B2, B3, etc). For prospective questions, such as "is T a good target?" the QSP model can be employed without coupling to a PK model by assuming optimal conditions (for example, 100% inhibition). Either model can ultimately be used to predict efficacy of a drug. Since QSP models attempt to be detailed representations of the pathophysiology, they may contain the necessary endpoints to assess efficacy (for example, HbA1c for a type 2 diabetes model). However, PK/PD models can also be directly linked to efficacy endpoints (for example, tumor size for cancer drugs)

tial equations (PDEs), or they could have stochastic components, or be agent-based models, or other types.

Once we have an appropriate QSP model, it is important to evaluate its suitability for prediction or other planned uses (Friedrich 2016). We can perform global sensitivity analysis to determine key parameters that have the greatest impact on the system outcome. This information can be used to inform decisions about therapeutic targets. If we freeze all parameters except the key parameters, identifiability analysis tells us whether those key parameters can be estimated from the available data. This is important because numerical solvers may still provide estimates for parameters whose values cannot be identified correctly from available data.

In industry, where critical decisions are going to be made on novel (and perhaps unvalidated) models, there is an increased importance in characterizing parameter uncertainty and identifiability. In our view, it is crucial that this uncertainty or variability in parameters be propagated to quantify the uncertainty in those predictions. The most useful models therefore not only capture the mean response, but also the variability observed experimentally (typically via nonlinear mixed-effects modeling or a virtual population approach, Allen et al. 2016). Uncertainty quantification is an area of active research in academia (Smith 2014) which has not been used widely in the biopharma industry yet, though we believe it should be (Fig. 2).

Another example of a technique that has long been used in academia is the application of optimal control (Pontryagin 1959; Swan 1984; Martin and Teo 1994; Lenhart and Workman 2007). In this setting, we define an objective function that we can

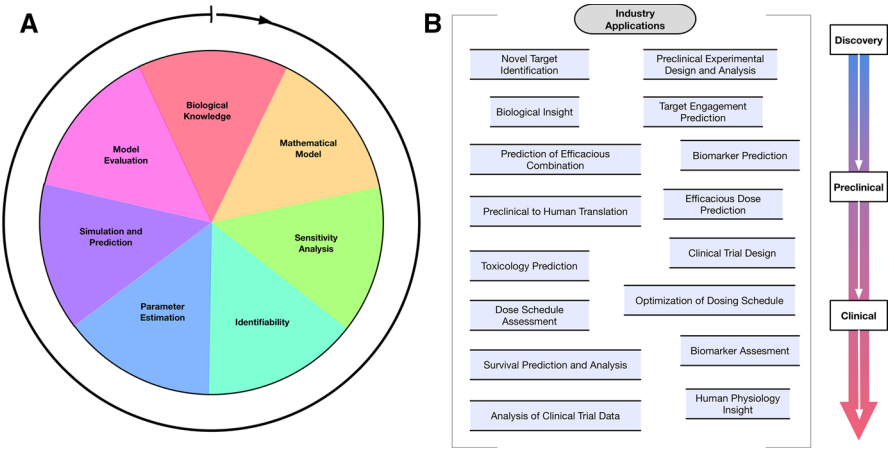

Fig. 2 Building a mathematical biology model to inform drug discovery and development. **a** Key steps in this process include: characterizing the biology in appropriate mathematics; understanding the parameters of the model and whether they can be estimated from data; and prediction, evaluation, and additional rounds as needed until validation is achieved. **b** There are many applications of systems biology models in the biopharma industry. These are some common ones

optimize, while having the disease dynamics and therapeutic effects governed by a QSP model. This allows us to build models that incorporate multiple therapies, and to optimize the regimens for greatest efficacy and least toxicity simultaneously. The technique has been used widely in other industries, but not as much in biopharma, as the mathematical models of biological systems were not as well validated in the past as models of other physical systems. A review article by one of us (Moore 2018) includes more background on the development of optimal control and on uses in other industry sectors.

Within the mathematical sciences more broadly, statistical methods have had great impact on the biopharma industry. The NLME modeling methods described earlier are based on statistics. Optimal design techniques optimize functions of the Fisher information matrix to determine experimental designs that allow for the most precise parameter estimation (Mentré et al. 1997). Additionally, the model selection process incorporates measures such as Akaike information criterion (AIC) and Bayesian information criterion (BIC) to determine relative goodness of fit while accounting for the number of parameters in a model (Burnham and Anderson 2002). And joint statistical modeling of longitudinal and time-to-event data (Rizopoulos 2012) provides the theoretical basis for predicting, for example, a relapse of prostate cancer based on prostate-specific antigen (PSA) levels over time (Desmée et al. 2017).

Bayesian methods provide powerful statistical techniques that allow clinical trials to be adaptive, adjusting the probability of enrolling new patients in a given study arm as new data become available. This is done without losing power in the study (Berry et al. 2010). In fact, it is Bayesian adaptive trial designs that allow for early stopping of clinical trials for reasons of efficacy, futility, or toxicity. As mentioned previously, Bayesian techniques can also be used to perform NLME modeling, using

priors and updates from sampling to determine the parameters that give the model the best possible fit to the data (Davidian and Giltinan 1995; Gelman et al. 2015).

The computational methods of machine learning have recently become widespread in the biopharma industry. With expanding experimental capabilities for data generation, data-rich methods have been able to aid in identifying patterns of importance. For example, with the new immunotherapies, an important question has been "Which patients will respond?" Some patients receive no or minimal benefit from immunotherapies. Others achieve unprecedented long-term responses. Machine learning applied to lymph node biopsies has been used to predict which patients may respond to immunotherapies (Dawood et al. 2018). Another important application of machine learning is the identification of tumors on patient's scans (Kadir and Gleeson 2018). Also, natural language processing is of great interest as a next-generation approach to extracting critical biological information from the literature and electronic health records (Gronsbell et al. 2018).

The examples above are active areas of research within the biopharma industry, but the plethora of mathematical techniques being employed in this industry is much broader than we can do justice to. For example, computational and mathematical analyses of metabolic flux and flux balance, clinical, preclinical, and in vitro image analysis, and biological networks are additional areas of research that have great potential for finding new medicines as efficiently as possible.

To be successful in applying and developing mathematical approaches, companies in the biopharma industry need to establish productive collaborations with the right academic groups and need to find talented modelers to work on these problems. So, how do you get a job in this industry and what can you expect?

3 Industry and Academic Collaborations

Attending conferences of the Society for Mathematical Biology (SMB) you would be forgiven for thinking that industry collaborations with academia are a rarity. In fact, this is only part of the story with many fruitful collaborations existing and producing key insights. Nevertheless, it is important to recognize that academia and industry can sometimes function as two parallel fields rather than one.

In areas such as PK/PD, PBPK, and NLME modeling, the academic leaders are well known to industry and results have been quickly assimilated into industry best practice. For systems-modeling approaches, there appears to be a bigger disconnect. First, academics in systems modeling tend to work in mathematics or engineering departments, which are not as well connected to the biopharma industry as academics in pharmaceutical sciences departments. Additionally, there is a clear division between industry and academic conferences. In our experience, industry attendance at SMB is very low—one of us (RJA) has attended SMB meetings in which there appeared to be no other attendees from industry. The Society for Industrial and Applied Mathematics (SIAM) and the SIAM Life Sciences group have more industry engagement, but still have disproportionately higher academic participation. On the other side, systems modelers from industry more likely to attend: American Conference on Pharmacometrics (ACoP), American Society for Clinical Pharmacology and Therapeutics Annual

Conference, or Population Approach Group in Europe Meeting. Academic attendance at these conferences is usually limited to academics in the pharmaceutical sciences with existing links to industry.

To foster additional collaborations, we encourage academics to attend industry-facing conferences, and drug development industry scientists to attend academic-focused conferences. There are also opportunities to publish in journals aimed primarily at one group or the other. We encourage academic groups working on understanding or treating disease, and industry groups who have clear technical and scientific challenges but not the expertise or resources to solve them, to publish in different journals than they might typically.

The main advantage of academic–industry collaborations is the complementary experience and expertise they bring together. An academic group can provide in-depth knowledge and scientific rigor, with a focus on particular areas. An industry group can provide insight into problems that have direct impact on patients.

Collaborations can sometimes be difficult to manage, but collaborations between academia and industry bring a unique set of challenges. In particular, the goals of the groups are not necessarily aligned. The goal of an industry team is to advance drugs more efficiently, or propose novel ones. An academic group is typically more focused on scientific insights that they can publish promptly. This gap can be narrowed by aligning along clear scientific goals and questions that are of interest to both groups.

4 Careers for Modelers in Biopharma

The biopharma industry employs hundreds of modelers with various backgrounds. Companies look for candidates with experience in mathematical and computational techniques. Knowledge of one or more disease areas is beneficial, but general knowledge of biology is more important. Industry experience is a plus, which makes internships and industry postdoctoral opportunities important. Most students receiving a Ph.D. in pure or applied mathematics need additional experience before getting a job in the biopharma industry. One key skill that employers in this field look for, beyond technical expertise, is communication. In particular, you need evidence that you have successfully worked with colleagues from different disciplines. In industry, modelers work with clinicians, biologists, chemists, statisticians and more. Hence, any experience that you can gain working in an interdisciplinary environment will be valuable.

Academic faculty spend a lot of their time teaching classes or writing grant proposals. However, they have relative independence in choosing their research direction and problems to work on. In industry, you often work on a project proposed by someone else, although there are times when you can work on projects you propose. Most projects in a biopharma company have multiple groups of people contributing to them. Modelers can easily access experts in the disease being studied, and are an integral part of the experimental data collection planning.

Some companies have restrictions on publishing, which is a factor to consider if you would like to work in academia later in your career. This can vary even between groups in the same company. If this is important to you, you can ask at your interviews about

the policies and expectations around publishing. You can also check the publication history of the group you are applying to. Exceptions to this are postdoctoral programs in industry for which publication and dissemination of results are key goals. Any publications on work done at a company will usually need to be approved by more than one level of management before they can be submitted externally. Instead of publishing a manuscript in a journal, you may be permitted to present a poster at a conference. However, some companies encourage publication and engagement with the external scientific community. Many companies pay the expenses for employees to attend one or more conferences per year.

If you are interested further in a career in industry what should you do next?

- Network at local events and conferences (for example, the International Society for Pharmacometrics has an annual meeting in the USA each fall, and has regional chapters that meet more frequently).
- Hand out business cards with your name, title, affiliation, and contact information.
- "Link In" with anyone you do meet—recruiters can find you through their connections, and people will often share job postings this way. When you send your link request, include a brief statement of how you met. People are much more likely to accept a link request if you remind them that you actually met in person.
- Consider industry postdoctoral and summer intern positions—look on company web sites for openings of these types (in addition to regular full-time positions).

5 Frequently Asked Questions

- How different is industry from academia?

  There are some key differences such as resource levels, job security, timelines, and focus on applications. However, they are probably more similar than you expect—remember a large percentage of industry colleagues trained and worked in academia for over 10 years!

- Will I be able to go to conferences and to publish manuscripts?

  Yes, and usually!

- Will I discover a drug that gets to patients?

  If you are in industry for 30 years, then as part of a team…maybe. Be prepared to be a part of projects that could fall apart very quickly.

- What is an industry postdoctoral position like?

  Industry postdoc positions are usually for 2 or 3 years, with an expectation of publications. We aim to provide the same support and opportunities that academic postdocs have.

- What courses outside of mathematics would help me get a job in industry?

  Statistics, computer programming, biology, and communication.

- Where do I have to live in order to work in biopharma?

  The main hubs of biopharma industry in the USA are near Boston and San Francisco, with additional clusters near San Diego, Chicago, and in New Jersey. Outside the USA, there are active industry/consulting groups doing modeling and research in Switzerland, Sweden, France, the Netherlands, and the UK.

- Do people ever leave the biopharma industry and go into academia, and vice versa?

  Yes, though it is not as common as people moving from one company to another. Industry employees who keep up their publication record and have time for the longer job search have been able to transition to academia. And successful academics who are good at prioritizing project or patient outcomes are attractive candidates to industry.

- Do I really have to post a profile on LinkedIn?

  Yes. Really.

- What should I include in my LinkedIn profile?

  A photo of yourself and a description of your research with keywords. It's also nice if you can post short descriptions of your papers with links to them online.

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