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Bridging Pharmacology and Pathophysiology via Systems Modeling

David Z. D'Argenio, PhD, and Donald E. Mager, PharmD, PhD

From its inception, the multidisciplinary field of pharmacometrics and its precursors have applied principles and methods from other fields, including engineering, physics, and applied mathematics, in an effort to better understand and quantify the processes involved with drug kinetics and drug action. A few notable examples of this transfer of intellectual technology include the following:

- Transform theory from mathematics enabled the solution of the linear compartmental models that were the mainstay of pharmacokinetics in its formative years.
- Transport phenomena from engineering and physics motivated the physiologically based pharmacokinetic modeling approach; it continues to guide an understanding of cellular transport processes.
- Linear systems analysis from engineering systems theory provided a formal basis for noncompartmental analysis in pharmacokinetics.
- Control theory from electrical engineering served as a unifying framework for the use of therapeutic drug monitoring in drug therapy.
- Estimation theory from statistics provided the principles for solving individual and population estimation problems in pharmacometrics.
- Image processing and computation have contributed powerful algorithms for the new generation of robust population modeling approaches.

The application and, in some cases, further development of these and many other ideas by the pharmacometrics community have greatly advantaged the process of drug development and drug therapy.

A recent challenge in pharmacometrics and drug development, the need for physiologically based disease progression (PBDP) models, may also benefit

from a thoughtful assimilation of models and approaches developed in pharmacology's sister field of physiology. During the latter half of the 20th century, some of the same principles and methods from engineering, physics, and mathematics cited above were also being applied to understand and model physiological processes in health and disease, under the rubric of systems physiology. During that time, this active area of research was promoted and funded in the United States by the largely disease-oriented institutes of the National Institutes of Health (NIH) and focused on the application of systems modeling at the level of organs and whole-body pathophysiological processes. Some of the models resulting from this work (and some more recent similarly inspired efforts) may be especially relevant as they incorporate physiologically meaningful properties that characterize the disease process and thus provide a rational basis for reflecting disease progression. A few examples include the following:

- Models of respiratory mechanics incorporating nonlinear airway resistance and compliance terms can predict pulmonary function test results (eg, FEV₁, FVC) and therefore have application for modeling the disease progression of these underlying properties. They have application to the treatment of chronic asthma and allergic rhinitis.
- Lumped cardiac-circulatory models that incorporate inotropy and the mechanical self-regulation of the circulatory system can predict measures of cardiac function (eg, ejection fraction) and thus have application to modeling progression of chronic heart disease during drug treatment with cardiostimulatory/cardioinhibitory drugs.
- Models of viral dynamics that incorporate the natural production and loss of virions and their interplay with endogenous target cells (eg, T cells, hepatocytes) are capable of predicting a range of phenotypic behavior (eg, partial and sustained responses, breakthrough, relapse). These models have application in understanding disease progression and treatment of chronic infections such as hepatitis C and human immunodeficiency virus.

From the Department of Biomedical Engineering, University of Southern California, Los Angeles (Dr D'Argenio) and Department of Pharmaceutical Sciences, University at Buffalo, Buffalo, New York (Dr Mager). Submitted for publication May 26, 2010; revised version accepted June 9, 2010. Address for correspondence: David Z. D'Argenio, PhD, Department of Biomedical Engineering, University of Southern California, 1042 Downey Way, DRB 154, Los Angeles, CA 90089; e-mail: dargenio@bmsr.usc.edu. DOI:10.1177/0091270010377505

Even though these and other modeling efforts arising from systems physiology were not motivated by drug development applications, because of their mechanistic focus, many of them can be modified to incorporate drug action. These models also will need to be distilled to their essence to yield the more compact descriptions of the disease process that can be useful in drug development.

A recent review article by Landersdorfer and Jusko on modeling in diabetes mellitus lights the way forward by providing an example of the type of analysis and synthesis that is needed to advance PBDP modeling.¹ The article thoroughly reviews modeling efforts in diabetes mellitus, including those from systems physiology and more recent efforts aimed at describing drug action; critically evaluates these contributions; and provides a blueprint for the use and further development of PBDP models in diabetes mellitus and other metabolic diseases. We need similar review articles in other

therapeutic areas, along with the type of systems thinking espoused by the Danhoff group (eg, Post et al²). Such articles will help motivate and direct others who might take up the challenge of developing physiologically based disease progression models for drug development. A concerted and coordinated effort to this end is needed; after all, it is already 2010!

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