Shifting Focus from Fundamentals to Systems Pharmacodynamic Models

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ABSTRACT:
Several mechanistic pharmacokinetic-pharmacodynamic (PK/PD) models have developed, expanding upon several traditional pharmacology foundations, and are based on pharmacological action mechanisms and main physiological rate-limiting or turnover processes. Tolerance is only one of several complexity that may be added to a variety of basic models, which can then be used as building blocks to construct improved PK/PD or small system models. All of these ideas, together with aspects of both the vertical and horizontal integration of molecular to whole-body processes, are shown in our corticosteroid models. We outline the possible benefits and drawbacks of shifting PK/PD toward systems models.

KEYWORDS: Preclinical pharmacokinetics, Mathematical models, Dosage response, Indirect response models, pharmacodynamics etc.

INTRODUCTION

A lengthy tradition of appreciating fundamental pharmacological concepts, primarily as they pertain to static or in vitro systems, has given rise to the fields of pharmacokinetics and pharmacodynamics (PK/PD). Over the years, many basic PK/PD models for in vivo drug effects have developed into more complex ones, and small-to-large systems models have emerged to capture drug activities at different levels of biological organization. This review will discuss the different fields that have adopted PK/PD and pharmacometrics, will showcase prominent features and concepts of popular PK/PD models, will show how to build models that improve PK/PD and small systems models, and will indicate the challenges in developing better quantitative methods for larger systems models.

EvolutionofPK/PDandPharmacometrics

Realization that fundamental pharmacologic equations needed to be extended by including additional mathematical correlations.

The transition from static systems to in vivo time courses of drug effects started in 1965 with the Levy "k m" equation. This equation connected pharmacology (with the

mid-range slope of the Effect versus log drug concentration function) and pharmacokinetics (with the k reflecting the monoexponential elimination rate constant). Gerhard Levy's many subsequent contributions to PK/PD have earned him the title of "Father of Pharmacodynamics" due to this. Afterwards, simulation studies by Wagner [1, 2] made the Hill Function famous and proved that "signature profiles" (my word) were useful for representing the fundamental expectations of basic PK/PD functions.

Theoretical advances, multiple applications of PK/PD and pharmacometrics in the pharmaceutical business, government regulation, research institutions, and academia have all contributed to the widespread acceptance of these early contributions. In their recent study, Lalonde et al.[3] detail how the pharmaceutical industry makes use of modeling and simulation, highlighting the potential for quantitative pharmacology to be used at every stage of drug development. Pharmacometrics has influenced the quest for safer and more effective medications in a more efficient and timely fashion; the US Food and Drug Administration anticipated PK/PD in the early 1990s, and both the early and recent reviews conducted by Peck, Lesko, and Gobburu [4-7] offer perspectives on this. During a 2002 conference, the National Institutes of Health (NIH) evaluated the training requirements in thepharmaceutical research.

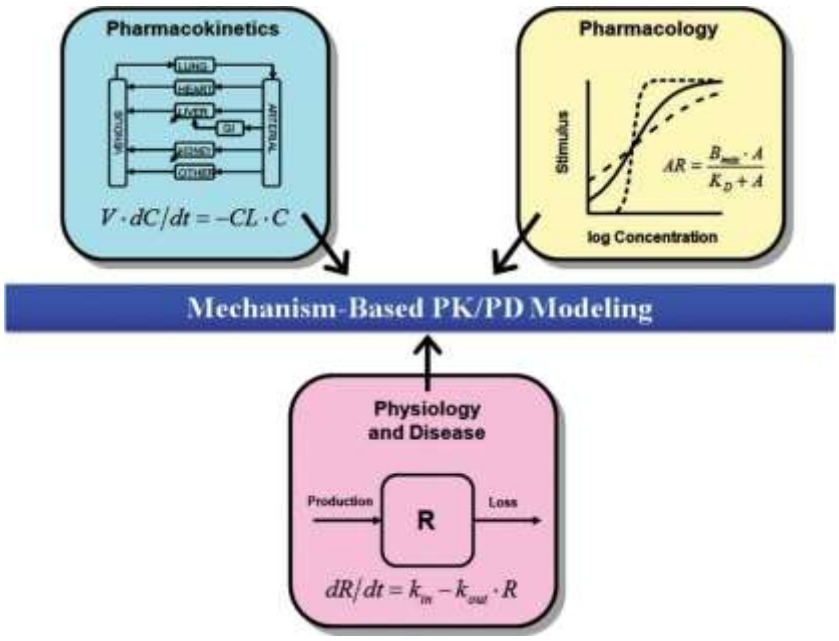

Figure1. Mechanism-basedpharmacokineticpharmacodynamic(PK/PD)modelstypicallyin tegrate the time course of drug concentrations (PK) including biophase distribution, the nature of drug–target interaction (Pharmacology), and turnover processes reflecting the relevantphysiologyanddisease.[12]

The authors came to the conclusion that "the principles of pharmacokinetics and pharmacodynamics" continue to be the fundamental focus of the field of pharmacology.

[8] Particularly in Pharmacy Schools, this field is being taught extensively. In order to discuss the current and future of quantitative and systems pharmacology (QSP), the National Institutes of Health (NIH) funded two symposia that brought together pharmacologists, system biologists, and PK/PD modelers. As a consequence, a comprehensive "white paper" [9] was produced, which should pave the way for further financing and future studies.[10] Alongside these developments in PK/PD, computational power and software applications like Adapt, WinNon-lin, and NonMem have progressed. For the pharmaceutical and generic industries, a plethora of small businesses provide consulting, data analysis, modeling, and pharmacometric reports. The quantity of journals and articles published in quantitative pharmacology has skyrocketed over the past half-century, spearheaded by the 1973 debut of the Journal of Pharmacokinetics and Bio-pharmaceutics (now Pharmacodynamics), edited by Sidney Riegelman, Leslie Benet, and Malcom Row-land (of whom I am the current editor-in-chief). From 1963 to 1972, there were 153 articles in MEDLINE11 with the title "Pharmacodynamics." From 1973 to 1982, there were 255 articles. From 1983 to 1992, there were 970 publications. From 1993 to 2012, there were 1564 papers. And from 2003 to 2012, there were 1772 articles. Symposiums and themes related to PK/PD and QSP are included in a plethora of scientific gatherings. A number of PK/PD specialized conference series, such as those organized byThe American Conference on Pharmacometrics, the Population Approach Group Europe (PAGE) meetings, David D'Argenio of Biomedical Simulation Resources in Los Angeles, MeindertDan of the Netherlands, and others. Go-Isop! is the website of the newly formed International Society of Pharmacometrics.

BasicMechanism-BasedPK/PDModels

A common feature of "mechanism-based" PK/PD models is the acknowledgement that physiology, including homeostatic and disease mechanisms, as well as PK, receptor, or target binding mechanisms, control one or more important steps in the drug action. This recognition allows for the determination of solvable parameters for the main rate-limiting process or processes. Figure 2 shows these three primary parts. Applying such models is like taking a "top-down" strategy; before assigning a general model, planning research, and analyzing experimental data, the modeler should have a good grasp of the underlying physiology, pharmacology, and pharmacology. In general, the models aim for simplicity. Underlying processes (such as the production or clearance of endogenous chemicals) should be represented by model parameters, which should have high statistical reliability. When it comes to simulation, nevertheless, systems models are "bottom up" in configuration and require a plethora of equations and assumed parameters. for exploratory purposes and with the goal of matching expectations with experimental data profiles.

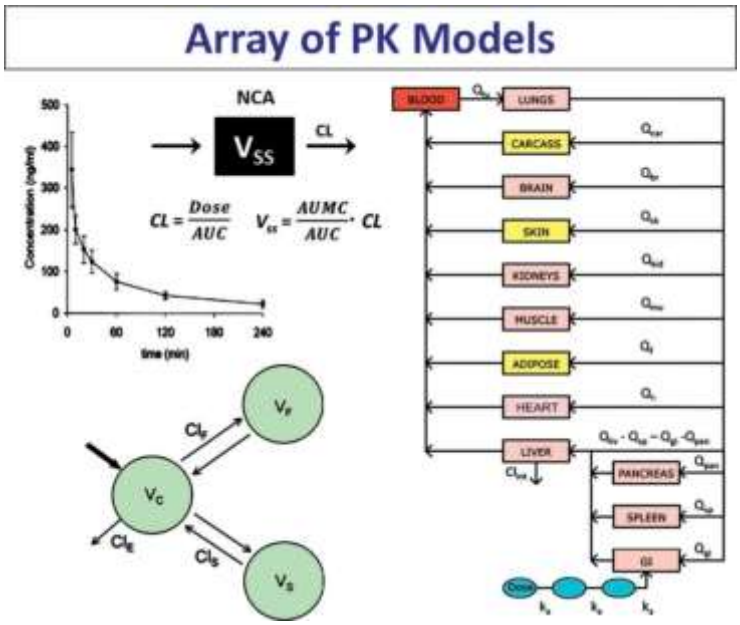

Figure 2.
Variousmodelingapproachestoassessmentofpharmacokineticdata including oncompartmental(NCA),compartmental,andphysiologicallybasedPK.

Drug distribution

Both the amount of time a drug is exposed to and, in many cases, how long it takes for a medication to take effect are controlled by the input rates and elimination processes, which are in turn driven by the PK. Figure 2 depicts the three main categories of PK models: physiological, non-compartmental, and compartmental. Diagnostic objectives, preliminary assessment of properties like linearity and stationarity, and evaluation of clearance (CL) and steady-state volume of distribution (Vss) may all benefit from noncompartmental analysis (NCA), which provides a helpful "black-box" baseline. The semimechanistic nature of compartmental models provides valuable insights into the distribution features of medications and organisms. Direct investigation of plasma concentrations and tissue transport, binding, and metabolic characteristics are used to resolve parameters in physiologically based pharmacokinetic (PBPK) models, which are systems models. These parameters are allocated using physiological measures, such as blood flow and organ sizes. Promising pharmacokinetic (PBPK) models have been around for a while, first for small compounds and, more recently, for biologics.[14] The translation of preclinical data to humans, the prediction of changes in the physicochemical properties of medications, and the evaluation of the effects of changing physiology, such as that seen in newborns and children, are all areas where they excel. Our new work shows that minimum PBPK models, also known as highly "lumped" models, are superior to conventional compartment models for evaluating drug PK characteristics.[15] The time course and parameters affecting medication availability to target locations is an important aim of pharmacokinetics

(PK). This phenomenon is referred to as "bio-phase distribution."[16] Given identified target locations and the absence of complications caused by local binding, metabolism, and transporters, such insights may be provided by the PBPK models. It is challenging to assess or confirm the amounts of free or unbound drugs in interstitial fluids and tissue cells. Proof of target exposure and proof of target activity are two important PK/PD concepts that are often followed throughout the early stages of drug development. As part of the preclinical development of PK/PD models, the medication should be evaluated at target locations. When working with human data, it's important to simulate all potential biophases, not only plasma. A few examples of such possibilities are arterial rather than venous blood or plasma, free drug at different locations, cerebrospinal fluid, drug in urine (for diuretics), and, of course, particular organs or tissues as measured, analyzed using PBPK models, or examined with imaging techniques.

Delays or gradual start of observed effects are common when medicines are distributed to peripheral sites of action. Drug entry via rate constant k_{eo} to a hypothetical biophase compartment (concentration Ce) was popularized by Sheineret al.17 in 1979 using a diffusion-like equation.

$$\frac{dC_e}{dt} = k_{eo}C_p - C_e \quad (1)$$

If the biophase is not known or measured and the rate-limiting step for a delayed medication effect is really the rate of peripheral access, then this equation is useful for evaluating clinical PD data. It is important to check the values of k_{eo} to make sure they are compatible with PBPK principles, which often include rather fast distribution rates. The delayed onset of pharmacological effects may be explained by a variety of different causes. Many systems have had this bio-phase model applied incorrectly, when other reasons for delayed effects are more likely.[18]

Receptor Attachment

Receptor theory was founded on the recognition by Ehrlich [19] that "Corpora non agunt nisi fixita" (Substances do not act un-less bound.), although the nature and time course of drug effects on the body have been observed and reported for many centuries. For a long time, pharmacologists have used the term "receptor occupancy" to describe the relationship between drug (A) and receptor (R) concentrations, using formulas based on the law of mass action, first developed by Clark [20].

$$A + R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} A\text{-}R \quad (2)$$

Thiscanbeviewedasarateequation

$$dAR/dt = k_{on} \cdot A \cdot R - k_{off} \cdot AR \quad (3)$$orequilibriumbinding

The need for textbooks to provide a more comprehensive analysis of target interactions has increased.[21] The identification of the relationships between linking Bmax to Emax, KD to EC50, and in vitro (A) to plasma or biophase drug concentrations (Cp), is one of the fundamental aims of PK/PD modeling, which is a translational objective from in vitro and preclinical to clinical. Various quantitative pharmacology tools, ranging from simple to complex systems PK/PD models, might be useful in this context.

Even in the most basic PD cases, drug effects are proportional to plasma drug concentrations according to the Hill Function, and biophase distribution and receptor binding are lightning fast. In the case of the succinylcholine-induced muscular relaxation that Levy modeled, this was crucially the case.1 When measuring enzyme activity in blood, such straightforward direct effects are most often found. With benazeprilat's angiotensin converting enzyme inhibitory actions, for instance, the medication and target are both present in the blood at the same time.[22] Here is the one case when the correlation between effects and plasma drug concentrations does not exhibit hysteresis due to the absence of temporal delays. Even for apparently straightforward pharmacological effects, equations other than the Hill Function could be used. The electroencephalogram effects of several benzodiazepines in rats were found to be identical when using plasma concentrations and KD values to compute receptor occupancy (Eq. 4), as shown in an early application of Black and Leff principles by Mandemaetal.[23].

For example, Bmax could regulate Emax, although the effectiveness of drugs is frequently dictated by the degree (capacity) of receptor binding and/or physiological signaling pathways. Rates of binding and k_{off} may sometimes determinewere expanded to include the intricacies of interferon-beta PD by the use of the drug-receptor complex

WhereE_{max} is the maximum achievable effect, EC_{50}isthe drug concentration associated with half of E_{max},and $\gamma$is the Hill percentage. In subsequent work, Black and Leff [22] made a significant discovery: receptor binding might serve as a gateway for signaling cascades that can be modeled using a coupled second-order nonlinear function, which is known as the operational model of antennas. This compound's delayed effects are controlled by a complex array of ideas and relationships between different drugs and receptors.[24]

Stability and Rotation

There are two fundamental principles of PD: first, that there is a limit to how much a medication may bind to its target or activate it, and second, that all physiological and disease-related processes are subject to turnover and homeostasis.

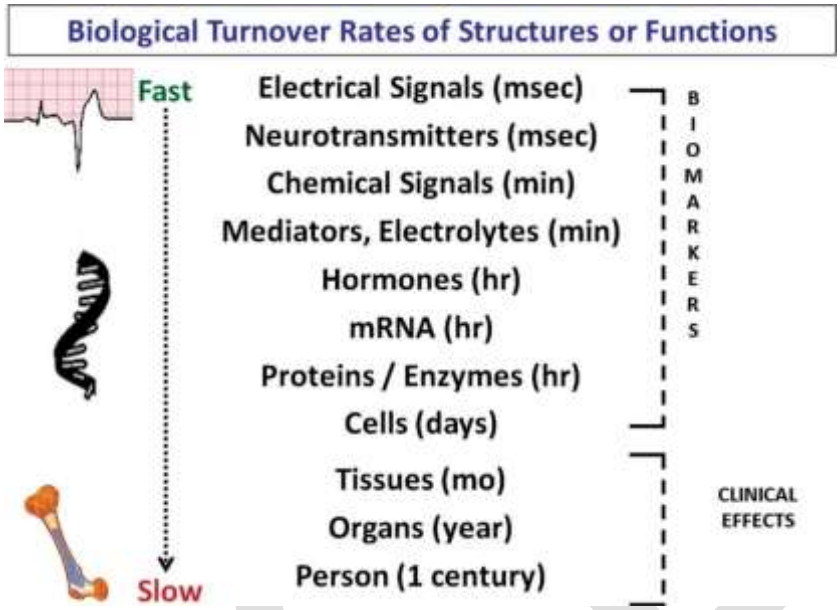

Figure 3.
Selectedphysiologicalstructuresandfunctionsandtheirapproximateturnoverrates.

Figure 3 shows a variety of biological structures and functions along with an approximation of their lifetimes or turnover rates. An essential characteristic of the vast majority of living things is the constant production and degradation, or turnover, of their constituent parts. Although these systems are susceptible to changes brought on by the circadian rhythm, development, aging, illness, and other disturbances, the homeostatic element is that they remain relatively stable. Homeostasis is maintained by tolerance or functional adaption mechanisms. The PD of a medicine might be determined by measuring any one of the aforementioned components. The duration of PD assessments may be better assessed with the use of turnover rates. Unlike extremely slow rates, such changes in bone structure, which need years of monitoring, rapid rates, like electroencephalograms and electrocardiograms, may be caught in a matter of seconds. Biomarkers that may indicate changes in more substantial bodily processes are often found around the top to middle of the list. Clinical consequences, including patient survival, are shown in the lowest portion of the list. These effects are often substantial bodily symptoms.

Recognizing turnover rates helps in determining the sort of mechanism-based PKPD model that may be required, in addition to the mechanism of action. Since the rate-controlling factor in rapid turnover processes is the time course of drug concentrations, simple direct effect and biophase models are adequate. When production (k_{in}) or loss (k_{out}) controls the observed responses in a process with intermediate turnover rates, indirect response models (IRM) will represent such processes. Some bodily parts with slower turnover rates may have severalprocesses that may be modeled more intricately or via transduction and hence represented as production or loss. In the lack of a more comprehensive set of metrics that would allow for the use of small systems models or enhanced PD (ePD), they may be

enough.

Varied Fundamental Models of Employee Attrition

When looking at the progression of drug reactions over time, Figure 4 shows the seven main mechanism-based PKPD models that are often used as a foundation. You can see the previously mentioned receptor-binding (top left), biophase (top right), and direct effect (center right) models in the picture. The subsequent models are all subject to PK regulation and include a turnover process in addition to a pharmacologic function representing the drug's mechanism of action. Each of these models may have varying degrees of complexity applied to it as needed.

Cell self-replication (ks) and drug-induced loss (k_L) are shown in the schematic in the middle-left. Although this model was first developed to explain the effects of cytotoxic anticancer medications, it has now been extended to include some antibiotics and antimalarial medications. [25] In the middle picture, we can see a basic model that includes k_{in}=0, k_{out}=1, and kCp=2, which are the order of the response parameter's irreversible activation and first and second orders, respectively. This model has been used to explain the effects of pantoprazole and other proton pump inhibitors on gastric acidity reduction, as well as the antiplatelet in-activation of COX-1 by aspirin [25]

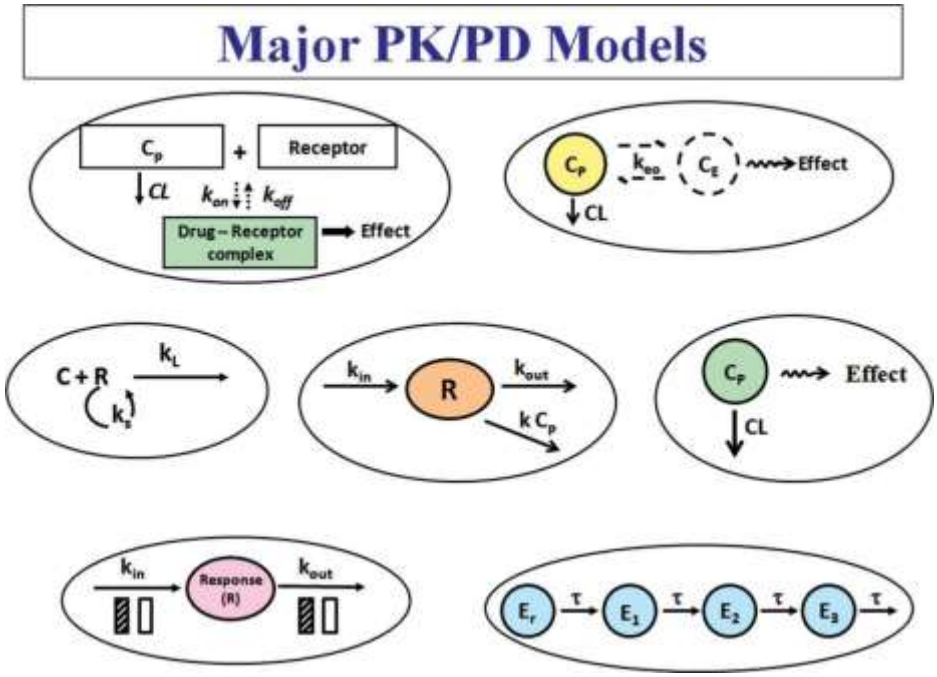

Figure 4. Based on the drug's action mechanism and the main rate-limiting phases in the kinetic, target-binding, or physiological process, seven broad kinds of basic PK/PD models are routinely used.

The four basic IRM that measure the impact of drugs on k_{in} inhibition or

k_{out}stimulation are shown in the diagram on the bottom left. Several antidiabetic medications are among those that have benefited from these models' extensive use to pharmacological responses.[18] One of the first uses of population PKPD modeling was to determine the analgesic effects of six different doses of tolmetin in a rat inflammatory model.[26] Each step or compartment in the bottom-right model represents a transduction model, and its turnover time is represented by τ.[26] Assuming the medication acts in the first compartment (e.g., receptor binding), the observable response is considered to occur in the final compartment after some time has passed. One of the many reported uses of this model is the capture of chemotherapeutic effects on tumor xenografts.Tolerance and functional adaptability in PD may be described by extending some of these concepts. As an illustration, a biophase-like compartment can stand in for receptor desensitization; a step before an IRM can capture tolerance and rebound; an additional step after an IRM can give feedback on changes to production or loss; and counter-regulation can be depicted as a series of compartments with an intervening transduction step.[27] More complicated and mechanistic systems pharmacology models will face problems and opportunities in understanding the body's homeostatic and signaling processes, which are characterized by a wide array of feedback loops and regulatory mechanisms.[28]

Better Models

More extensive experiments, measurements, and data assembly will allow for the merging of the proposed fundamental processes and models into more complex PKPD models. Our "giant rat" studies have evaluated the receptor-gene mediated effects of corticosteroids by exposing animals to different doses of methylprednisolone and then sampling their blood and various tissues at sacrifice to evaluate pharmacokinetics (PK), tissue receptor content, tissue gene expression (both specific and with gene arrays), tissue enzymes or proteins, different biomarkers in the blood, and occasionally observable structures or functions. Aside from the standard fare of PK, receptor-binding, and transduction, our fifth-generation model also included two kinds of IRM: one to stimulate the synthesis of biomarker genes and another to feedback inhibit the production of receptor genes.[29] The effects of dexamethasone (Dex) on suppression of proinflammatory cytokine genes in inflamed rat paws were studied, and the disease progression in a rat model of rheumatoid arthritis (RA; paw edema) was described using this improved PKPD model, which was then integrated into a broader small systems model.[30] A portion of our experimental data is shown in Figure 5. This data includes the pharmacokinetics (PK) of Dex, the ease of development of paw edema as recorded by trans-sit compartments, and the reduction in cytokine expression caused by Dex, which results in reduced paw edema as an inhibitory IRM. Figure 6 shows the PK/PD/DIS model that was utilized to capture this data.

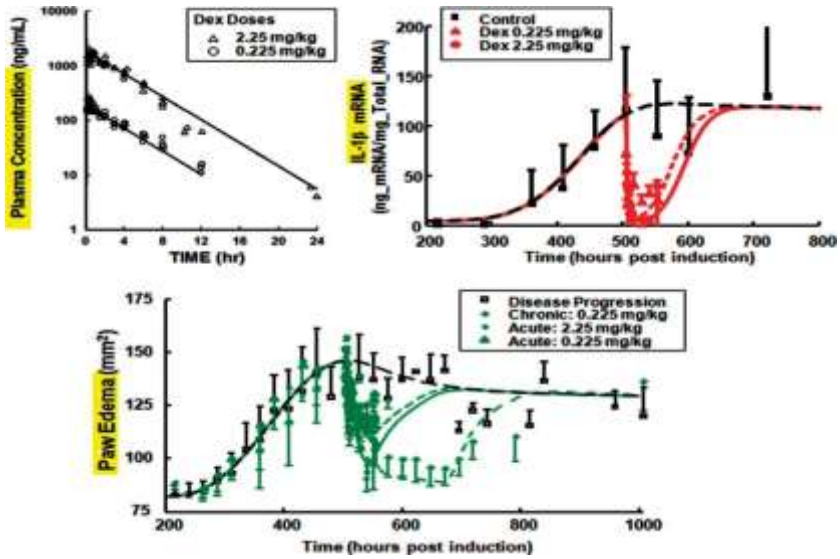

Figure 5. A multi-level analysis of dexamethasone (Dex) pharmacokinetics, IL-1$ production in rat paws and its inhibition by Dex, and the temporal pattern of paw edema following collagen injection in rats illustrating the natural progression of RA disease and the inhibitory effects of different Dex dosage regimens.

Our fifth-generation corticosteroid model [29] is used in the systems model for receptor kinetics of Dex and corticosterone binding (top left section), and for the slower unmeasured immune responses that cause inflammation and bone loss (right side and bottom), mostly via transit compartments. It is theorized that other approaches or experiments may be used to detect normal or pathological occurrences in trans-sit compartments. According to systems modeling, these endeavors constitute a combination of horizontal and vertical integration.[9] When evaluating hundreds of genes (and, more recently, proteins) at the molecular level, our tissue measurements are horizontal.[28] Drug molecule, gene, protein, and inferred cellular event data are all vertically linked in the models. The end-organ responses, such as those in the paw and bone, are also included. Like human clinical trials, some RA animal research use a symptom score to represent the extent to which the complete body is dysfunctional.[29] Simulations allow for the optimal design of new experiments to seek the next-generation advanced PKPD model, and these models have provided a foundation for general understanding of the major determinants of corticosteroid action. They have also allowed us to assess conceptual limitations when the models do not fit.

The hybrid approach of small systems and focused PD models is further shown by other instances of ePD models provided by Iyengaretal.[31]. Important characteristics and applications of ePD models are detailed in their study. It lays out the steps to take when developing an ePD model, begins with existing genomic and epigenomic data, incorporates drug-centered regulatory networks, and incorporates drug-target information for use in designing and evaluating appropriate PK/PD trials.

Models for Systems

It is common practice in systems biology and pharmacology to use a large number of differential equations, with parameters chosen based on the best results from a variety of experiments reported in the literature or obtained via actual experimentation, in order to determine the known biological mechanisms that regulate physiological occurrences.[9] The models in these extensive networks run in simulation mode until they can be evaluated with experimental data, at which point they undergo relatively subjective changes. This is the standard operating procedure for PBPK models, but, with the help of modern computing power and software, we can now simulate comprehensive and population-type PBPK investigations including several animal groups.[31] Inflammation, calcium homeostasis, and bone remodeling may all be described using complex systems models [32, 33] At least three companies—Entelos, Archimedes, and Rosa—have used commercial system model assemblies to simulatediabetes and make it feasible to theoretically evaluate the impact of potential antidiabetic drugs.Systems models have shown great promise as registries for biologic, pharmacologic, and clinical data (Vodovotz et al., 1953; Iyengar et al.,)cal understanding. Figure 7 shows a more generalized view of the systems model that might be used to several areas of illness and pharmacology. Collaborative efforts with specialists from other fields would be necessary to construct such models and data repositories.

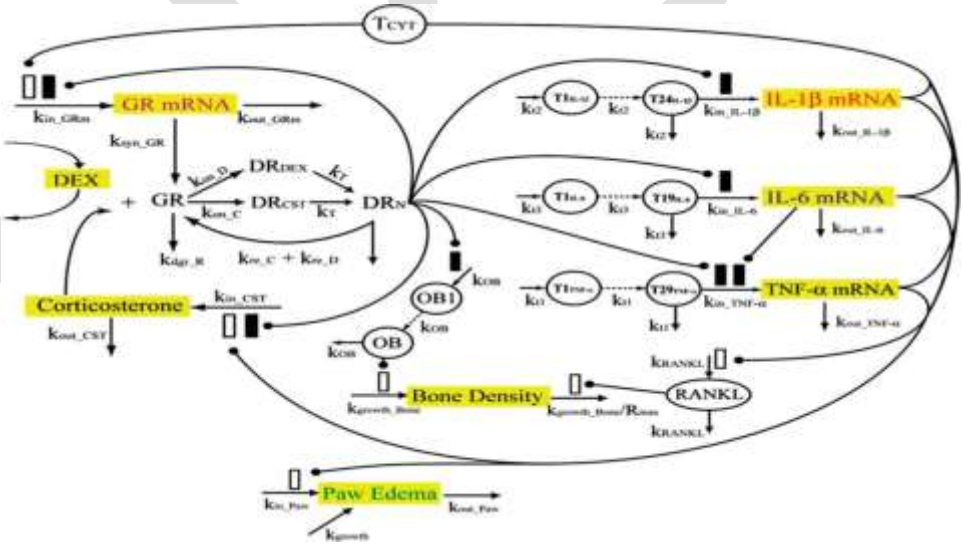

Figure 6. Pharmacokinetic/pharmacodynamic/disease (PK/PD/DIS) model used to characterize the PK, receptor binding, disease progression, and Dex alteration of geneexpressionresultinginameliorationofpawedemainratswit hRA.Measuredentities aremarkedinyellow.

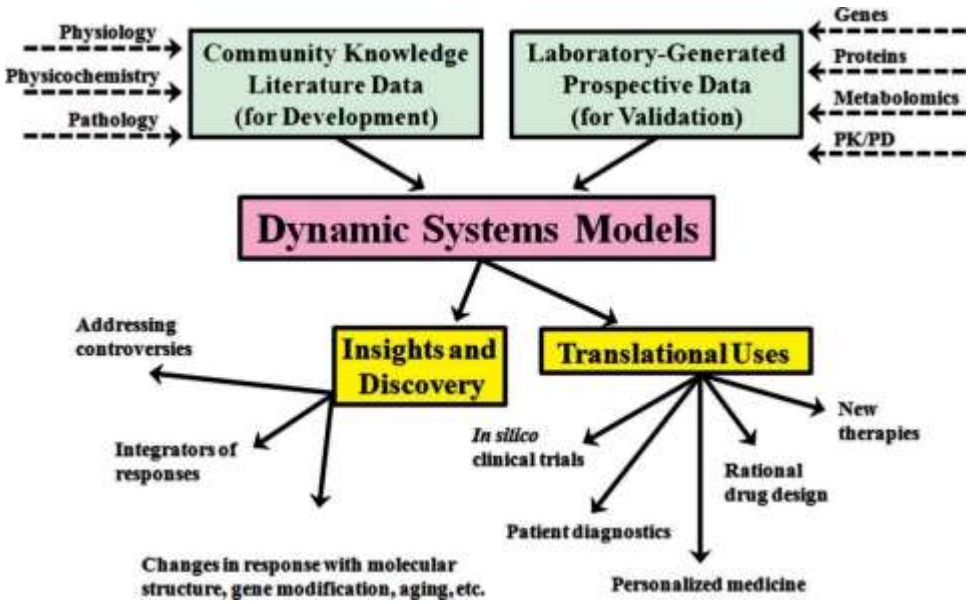

Figure7.
Conceptualizationoftheinformationflow,integrationofknowledge,andpotentialapplicationsofsystemspharmacologydatabasesandmodels.

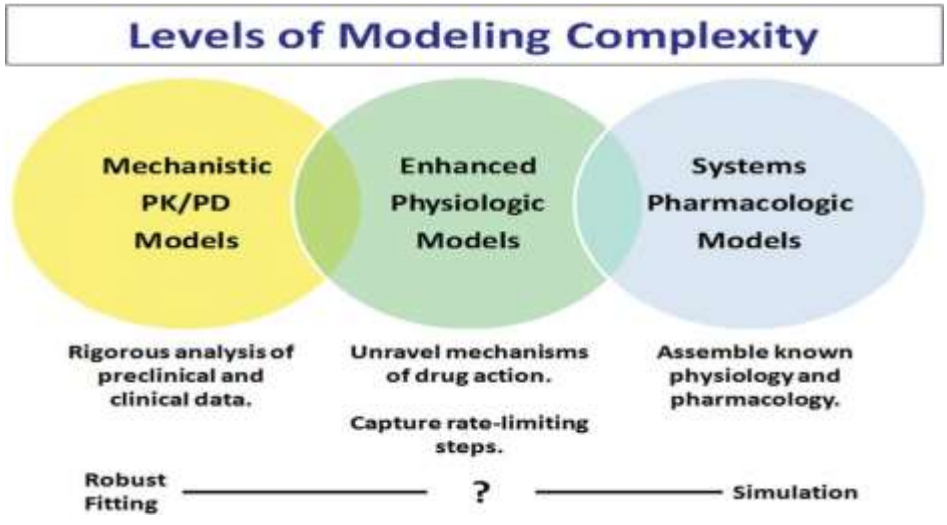

Figure8. Rangeandtypesofmodelingcomplexityat threemodelinglevelsofquantitativeandsystemspharmacology(QSP).subject areas.

They provide a forum for shared knowledge, insightful debate, productive experimentation, and the ongoing development of better quantitative models.

Moving Beyond the Fundamentals to Modeling Systems

In their pursuit of focused or improved PKPD models, the NIH QSP Workshops[9] uncovered both a fundamental tension and potential. Figure 8 shows that the computational, statistical, and bioinformatic requirements change as the modeling work becomes more sophisticated. Even with mixed-effect population assessments, it is easy to use current software to fit basic and improved PKPD models. Although they are always changing, the modeling metrics are rather solid. Visual predictive checks and other widely used diagnostic plots are on the rise, standardization is taking shape, metrics shown are becoming more complex, and there are established methods for determining how well model functions match the data. You may find both different fitting algorithms and equivalent ones on a lot of software platforms. There is a large number of equations in a systems model, the parameters are not always known, the assumptions are not always obvious or accurate, and the models are run via simulation with minor adjustments when compared to experimental results. Primordial PKPD modeling is progressing to-Strive for a middle ground when dealing with increasingly complex models; in such cases, many components should be assigned according to the best available experimental or theoretical evidence; missing elements may require approximation with empirical components (such as transit components); and more conventional fitting procedures can capture the major rate-limiting steps. Our RA PK/PD/DIS model mostly used this strategy (Fig. 6). Our next big computational problem as we go from basic to systems models is to determine the optimal methods between robust model fitting and simulation.

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Conflict of Interest

The Author declares that there is no conflict of interest.

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