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On the analysis of complex biological supply chains: From Process Systems Engineering to Quantitative Systems Pharmacology

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Abstract

The use of models in biology has become particularly relevant as it enables investigators to develop a mechanistic framework for understanding the operating principles of living systems as well as in quantitatively predicting their response to both pathological perturbations and pharmacological interventions. This application has resulted in a synergistic convergence of systems biology and pharmacokinetic-pharmacodynamic modeling techniques that has led to the emergence of quantitative systems pharmacology (QSP). In this review, we discuss how the foundational principles of chemical process systems engineering inform the progressive development of more physiologically-based systems biology models.

Keywords

Pharmacokinetics; pharmacodynamics; multi-scale systems biology; quantitative systems pharmacology

1. Introduction

Mathematical modeling has played a key role in Chemical Engineering. *In lieu* of another definition of the term, we will borrow *Rutherford Aris*'s words and simply state that “*A mathematical model is a representation, in mathematical terms, of certain aspects of a nonmathematical system*” (Aris, 1999). Quite interestingly, the importance of mathematical representations of nonmathematical systems in physiology was identified and appreciated as

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Conflict of Interest
None

that field was slowly formalized. Worth mentioning is the 170 year old quote of *Claude Bernard*, a pioneer of the field, who stated “[...] *the application of mathematics to natural phenomena is the aim of all science, because natural phenomena should always be mathematically expressed*” (Bernard, 1949). A chemical engineer’s challenge of choosing a mathematical model of the correct spatial and temporal scale based on the desired granularity, complexity and the richness of available data to obtain a useful description of its nonmathematical counterpart, is in many ways, the same as that faced by a systems biologist (I. P. Androulakis, 2014). Due to the spatial and temporal complexity of biological systems and the incompleteness of experimental data, investigators must frequently take recourse to simplifying assumptions using phenomenological descriptions of biological processes in developing instructive mathematical counterparts.

The approach has necessitated a balance between the level of mechanistic detail that is included in the model and physiological scales at which the model can describe the behavior of the system. For instance, in cases where unknown mechanisms map regulatory inputs to output signals, black-box system modeling is often most instructive. Such black-box modeling approaches include logic-based, generalized linear models, Gaussian process models or neural networks (M. K. Morris et al., 2010; Saez-Rodriguez et al., 2011). Such methods have provided significant biological input in complex biological systems, such as revealing the component interactions that influence the timing of the *Arabidopsis* circadian clock (Dalchau, 2012), or in determining the relative importance of placental biochemical markers (such as IL-6, IGF-II and IGFBP-2 protein concentrations) on intra-uterine growth restriction (Street et al., 2013). While the mechanistic interpretations are limited, such approaches are advantageous when used in situations, as mentioned above, where the systems being modeled correlate variables at multiple temporal and special scales through non-trivial mechanisms. On the other hand, deep insights can often be drawn from models that incorporate even relatively simplistic mechanistic detail, as in the case of the Lewis model of the somatogenesis clock (Lewis, 2003). The inclusion of time delays representative of the times scales for transcription and translation to a model of negative feedback-based autoregulation of somatogenic genes allowed the Lewis model to make specific predictions regarding the functional dependency of the somatogenesis clock on the stability of the somatogenic proteins. These predictions have since been validated experimentally (Hirata et al., 2004).

Although simple mechanistic models can make accurate predictions, they are often limited to a narrow physiological scale (the cellular level in the case of the Lewis model), and cannot describe observed phenomena because of the molecular complexity within the cell. As alluded to in (Gunawardena, 2014) such a situation is analogous to the chemical engineer’s use of the ideal gas law, $PV = nRT$. While simple and extremely useful, the ideal gas law is restricted to describing macroscopic phenomena, but does not have the framework for connecting molecular phenomena to macroscopic phenomena.

At the same time, there have been concerted efforts to develop multi-scale, semi-mechanistic models that integrate mechanistic information from multiple temporal and physiological scales, gradually bridging the gap between models with physiological scale and (more) mechanistic detail. These models draw heavily from transport and reaction engineering

foundations by modeling the states of dynamic variables using principles of mass action, Michaelis-Menten kinetics and the properties of reaction networks. Early examples can be found in the chemical engineering literature (Lauffenburger & Kennedy, 1981, 1983).

As we add layers of complexity to a model or place a model in a multi-scale context, the iterative systems engineering approach to modeling, likely described as: *adopt, adapt, develop, assess, amend, and deliver* [(AAD)²] (I. P. Androulakis, 2015), proves quite powerful. First, a hypothesis is *adopted* and then *adapted* based on available knowledge. This hypothesis is the basis by which an *in silico* model is *developed*. Predictions by the model are *assessed* and then the modeling framework is *amended* accordingly in an iterative nature until the final model is *delivered*. We direct the readers to (I. P. Androulakis, 2015) for more detail on this iterative and integrative approach.

Of the many opportunities for developing and deploying mathematical models in relation to living systems, this review will focus on Quantitative Systems Pharmacology (QSP), defined as the intersection of Systems Biology and pharmacokinetic/pharmacodynamic modeling (I. P. Androulakis, 2015; I.P. Androulakis, 2016; Iyengar et al., 2012; Jusko, 2013; Sorger et al., 2011; van der Graaf & Benson, 2011). If one were to draw a simplified analogy between QSP and Process Systems Engineering (PSE), one can argue that much like PSE is concerned with understanding the ability and implications of a complex supply chain to respond to a disturbance, QSP considers a living host and its surrounding environment as the equivalent “supply chain” and the drug as the corresponding disturbance, asking in principle the same type of questions (I. P. Androulakis, 2014, 2015; I.P. Androulakis, 2016). Given the intricacy and diversity of drug responses, many of the challenges faced in the development of integrated pharmacokinetics/pharmacodynamics (PKPD) models are the same as those faced in systems biology (Rosenbaum, 2011). Combining these progressing fields into quantitative systems pharmacology as shown in Figure 1 offers interesting insight into the entire drug-body system, from pharmaceutical properties, formulation, and delivery to the role played by the body’s inherent mechanisms in response to a xenobiotic compound (van der Graaf & Benson, 2011; Vicini & van der Graaf, 2013).

In this review article, we first introduce the evolution of pharmacokinetic/pharmacodynamic models from simple, empirically-derived models towards integrated, mechanistic frameworks. While drawing from our experiences over the years, we will attempt to present how PSE concepts enabled us to pursue the continued development of complex systems biology models, with emphasis on the inflammatory response.

2. Pharmacokinetic Models

Mathematical modeling in pharmacology, using basic principles of mass action, dates back over half a century, originating with the pioneering work of Gerhard Levy, recently reviewed in (Fung & Jusko, 2015). Pharmacokinetics (PK) loosely describes “what the body does to the drug”, or put differently as describing the kinetics of drug movement within the human body. The level of scrutiny to which transport is characterized in bodily tissues depends on the desired, required or achievable level of detail, and by extension the complexity of the model structure. As a drug candidate goes through development, more *in vitro* and clinical

data become available. New understanding is translated into the corresponding model by refining its structure and input parameters in an iterative manner per the (AAD)² methodology to better describe the behavior and transport of the drug. In the context of pharmacokinetic models, three approaches can be taken to enhance model complexity: (1) incorporating additional compartments to represent additional biological processes, (2) dividing existing compartments into sub-compartments based on available knowledge, and (3) increasing the level of detail and thus precision within each existing compartment to describe drug behavior more specifically. The degree of complexity of the model is often limited either by a lack of necessary input data or by incomplete knowledge of the physiology or the drug compound itself. To parallel traditional chemical process simulations, these compartments would be comparable to unit operations in a multi-step process to describe the absorption, distribution, metabolism, and elimination of a drug. These compartments, or unit operations, are inherently connected through a system of mass balances that ultimately explain time-dependent drug exposure. As model complexity increases, the compartments better describe the movement of drug throughout the body using first principles, such as transport or reaction kinetics. Clearly, this methodology is rather reminiscent to decomposition approaches in PSE, where a system is broken up to sub-systems and each of the components is approximated at an appropriate level of detail.

In the simplest form, pharmacokinetic models are empirical. The model structure is determined from existing experimental data without any biological considerations. Thus, model development requires little knowledge of the system itself, only known input such as the drug administered and patient body weight as well as a measured output (drug concentration in blood, saliva, urine, etc). The number of exponential terms (or compartments) needed to describe the resulting drug concentration profile is identified and the modeling framework is established as a basic compartment model (Bonate, 2011). Often times the simplest model structure that describes the clinical data is selected and used to estimate the associated pharmacokinetic parameters (Rosenbaum, 2011). The resulting model requires only a limited number of parameters to describe the bidirectional transport of drug between these arbitrary compartments. Thus, the physicochemical properties of the drug, *in vivo* behavior, associated biological processes and all other considerations affecting drug transport are ultimately lumped into these few parameters. Empirical PK model development follows a methodology referred to as “top down”, where the model is strictly limited to the clinical data from which it was built with minimal predictive power (Tylutki et al., 2016).

As an extension of the simple models, which arbitrarily represent the body as central and peripheral compartments, the modeling framework may more specifically define these compartments by incorporating some basic knowledge of drug behavior and biology. Physiologically-based pharmacokinetic models have a wide range of mechanistic detail, ranging from minimal PBPK in which major physiological features of the body are grouped together based on defining characteristics (blood flow, tissue/blood partitioning, volume, etc) to whole body PBPK which has the ability to describe drug partitioning in specific tissues (Cao & Jusko, 2012). The simplest form of a PBPK model exists as a single-organ, described by the well-stirred tank model (DiStefano, 2014). Of increasing detail is a three compartment model developed by Ibarra *et al.* for valproic acid that considered the impact of

enterohepatic recycling by including a central, peripheral and gall bladder compartment into the modeling structure (Ibarra et al., 2013). Further increasing in mechanistic complexity is a model developed to describe the exposure of rats to perfluorooctanoate (PFOA) by incorporating three additional compartments to describe the role of transporters in renal reabsorption and secretion in the kidney (Loccisano et al., 2012; Worley & Fisher, 2015). Each of these examples provides an insight into drug behavior mechanistically, but to varying scales of physiological scrutiny. Numerous applications have also appeared in the PSE and Chemical Engineering literature (Abbiati et al., 2016; Abbiati & Manca, 2016; Heitzig et al., 2014; Mořat' et al., 2013).

PBPK models, although still highly complex compared to their empirical compartment model counterparts, include several assumptions to simplify the bodily functions into a series of differential equations that describe the transport of drug between tissues and within systemic circulation. These models combine compartment models with the tank and flow concepts of chemical engineering and fluid dynamics, leveraging knowledge of physiology to describe blood flow between compartments (DiStefano, 2014). As more knowledge regarding a drug's mechanism is gained, the model can be expanded to account for transporter activity and metabolic enzyme kinetics, leading to physiologically-relevant estimates of the extent and rate of drug transport (Abuasal et al., 2012). An example of such expansion is the PBPK model that Yang *et al.* coupled to a Biochemical Reaction Network (BRN) model to account for drug metabolism to better understand possible reaction pathways and the effect of metabolite concentration in the body (Yang et al., 2005). To model drug distribution in tissues and organs, additional information is needed to describe the transport and reaction kinetics down to this level, including organ volumes, lipid partitioning, ionization, plasma protein binding, and blood perfusion data (Suenderhauf & Parrott, 2013). In all cases, physiologically-based pharmacokinetic models can be developed according to the (AAD)² methodology introduced previously (I. P. Androulakis, 2015). Under this context, the model structure or parameter estimates are refined to better match predicted exposure profiles with experimental data.

Naturally as PBPK models transition from empirical to predictive, the complexity of the model structure required to do so increases significantly. In the "bottom up approach" to PK modeling, the models are now based primarily on first principles to describe the movement of drug through the body (Bonate, 2011). Human physiology is defined through a larger set of parameters that are estimated from *in vivo* and *in vitro* data as the biological processes needed to describe transport and kinetics of the drug are de-lumped. These models no longer consider only the model input (dose) and output (plasma concentration profiles), but attempt to describe the transport in more detail, enabling the prediction of both the rate of appearance as well as disappearance from systemic circulation. In the case of an orally administered drug, these models predict the movement from the stomach to the colon while simultaneously considering absorption through the gastrointestinal wall, and transfer to the liver before ending up in systemic circulation. A well-known example of such a mechanistic and detailed absorption model is the Advanced Compartmental Absorption and Transit model (ACAT) (Suenderhauf & Parrott, 2013). This model is capable of predicting passive absorption of the drug from the gastrointestinal tract which occurs according to Fick's laws of diffusion (Tubic et al., 2006) as well as the existence of the drug in several states

(unreleased, undissolved, and dissolved). The ACAT model may then be linked to a PK model which describes the distribution of drug after reaching the liver and ultimately the elimination of the drug from the body (Almukainzi et al., 2016).

3. Pharmacodynamic Models

While systemic drug exposure, also referred to as bioavailability, is a key piece of information in the drug development process, the effect of the drug on the body is not explained by this parameter. Thus, a pharmacodynamic (PD) element is often required to describe the mechanism of the compound and its interactions with biological targets, to establish an exposure-response relationship, and to ultimately understand the potency and efficacy of the compound. While the pharmacokinetic component describes how much of the drug reaches systemic circulation, the pharmacodynamic component considers the concentration-dependent biological effect of the drug. As such, simulated PK/PBPK data can be considered as an input to PD models and so it may be argued that PD models rely on the accuracy of PK models. A PD model requires drug-specific parameters, such as affinity for the target or extent of activation, which can typically be identified from bioassays. The challenging part of PD modeling lies in identifying the function and structure of the biological system or process that drives a drug response as this information can often be estimated at best from *in vivo* analyses (Danhof et al., 2008). Thus, the predictive power of the pharmacodynamic model depends heavily on knowledge of biological systems involved.

Integrated pharmacokinetic and pharmacodynamic modeling enable evaluation of the drug dose-concentration-response relationships in the body (Meibohm & Derendorf, 1997). Several studies have shown how PKPD models leverage the link between dose, exposure, and response (Asin-Prieto et al., 2015; Girard et al., 2005; Nielsen et al., 2011). Integrated PKPD models aim to predict the response associated with a drug “at any time, after any dose, administered by any route”. However, the biological processes underlying drug response are more complex and varied than the first order kinetics that are often used to describe drug transport (Danhof et al., 2007; Rosenbaum, 2011). Before the response can be modeled, the level of drug in systemic circulation must be known, the site of action must be understood, and the interactions between the drug and receptor signaling pathways must be elucidated (Rosenbaum, 2011). For receptor targets, the effect of the drug is either caused by direct modulation of cellular or physiological function or through receptor binding, triggering a cascade of responses (Raffa, 2010). Kinetic principles such as Michaelis-Menten enzyme kinetics and the Hill function are often used to describe such interactions (Goutelle et al., 2008). At the most basic level, PD model rely on drug-receptor theory to explain how a drug interacts with a receptor to induce a response (Rosenbaum, 2011). A natural extension of pharmacodynamic modeling is to consider incorporating disease process and progression since many drugs are targeted at altered and transient physiologies that differ from the healthy homeostatic baseline. Disease progression models add significant complexity in that the baseline of the biological system is now time variant compared to conventional pharmacodynamic modeling in which biological processes remain constant in the absence of a drug (Danhof et al., 2007). As the complexity of a pharmacodynamic model increases and becomes mechanistically-based, many parallels can be drawn from the methodology and concepts associated with systems biology models

(Danhof et al., 2008). In that context, the examples of indirect effect, transduction and transit models, tolerance models, and feedback mechanisms (Fang et al., 2013; Hazra et al., 2007; Jin et al., 2003; Jin & Jusko, 2009; Sukumaran et al., 2011) adapt basic elements of reaction kinetics towards revealing the exposure-response relationship of a drug.

4. Towards integrative models in Systems Biology and Systems Pharmacology: A PSE Perspective

Quantitative Systems Pharmacology (QSP) advances our understanding of pharmacological treatment by exploring *integrative* and *model-based* approaches exploring our vast understanding and knowledge of computational tools integrating systems biology, pharmacokinetics/pharmacodynamics and pharmacology (Berger & Iyengar, 2011). In recent years, there have been numerous reports discussing opportunities, progress and successes of QSP (Bai, 2013; Leil & Bertz, 2014; Sorger et al., 2011). Broadly speaking, QSP encompasses approaches related to the integrated analysis of complex models in an attempt to rationalize drug action. Implications include, but are not limited to, predicting an individual's response to treatment, assessing efficacy and safety and enabling the rational design, and rationalization of results of clinical trials. QSP models most likely developed during the later pre-clinical stages and are expected to provide critical insight during the clinical development (Ermakov et al., 2014; Kimko & Duffull, 2003; Kimko et al., 2011). Mathematical and computer modeling is at the core of QSP, however, it is not appropriate to focus exclusively on those aspects when talking about QSP. Modeling in pharmacology can be found as far back as the 1960's with *Gerhard Levy*'s work on the dynamics of pharmacologic effects (Levy, 1964, 1966). Since then, mathematical and computational model have substantially increased in complexity due to advances in biology, pharmacology and physiology as well as our ability to accumulate high-quality and high-dimension data. In the meantime, pharmacologists adopted advanced computational approaches. Nevertheless, it would be shortsighted to reduce QSP strictly to the process of developing complex computational models. In fact, one could argue that QSP is not simply delivering "more of the same", but instead providing a framework by which drugs are placed in an appropriate and broader context (I.P. Androulakis, 2016).

The PSE perspective

One of the main contributions of PSE was that it enabled analyses that take an integrated look at networked responses, as opposed to considering isolated components (Klatt & Marquardt, 2009). The PSE tools and concepts allowed researchers to work on operating envelopes which were gradually expanded and extended based on the questions that require further analysis. In a manner analogous to that, we wish to demonstrate how the operating envelope of a biological system can be gradually expanded and the corresponding analyses can begin to shade light as we attempt to rationalize a living system's function within a dynamic environment. Previously, we articulated that PSE principles are instrumental in advancing modeling in biological and medical applications (I. P. Androulakis, 2014). Four basic concepts were mirrored onto the analysis of biological and pharmacological systems: (i) *flexibility, trade-offs and design through evolution*; (ii) *abnormal event detection and management*; (iii) *perturbations and optimal strategies*; and (iv) *distributed and*

decentralized control. These four concepts constituting the pillars of PSE have direct analogues in the context of QSP, as further elaborated in (I. P. Androulakis, 2014, 2015; I.P. Androulakis, 2016). To this point, we wish to draw analogies between concepts in systems engineering and conceptual models of health and disease; establish connections between these concepts and physiologic modeling; and more importantly suggest that QSP models need to be developed in a proper context in order to appropriately engage, and synergize with the dynamics of the disease on one hand and of the systemic intrinsic defense mechanisms on the other. The latter concept adding a new, and important, dimension to the development of QSP approaches.

Any, voluntary or involuntary, disturbance in a complex supply chain will initially manifest itself at the level of a “process”. The latter is loosely defined as a well characterized (unit or other) operation which senses the disturbance and adapts its response and dynamics. The effects will eventually be global and systemic as the output of the unit forces the system to move away from its steady state, of which the initiating event can often be associated with the run-away operation of an individual unit. The overall chain will then attempt to re-normalize its operation and appropriate control actions will attempt to diminish the implications of the disturbance and absorb any deviations. Therefore, anticipatory control mechanisms, negative feedback, specialized control actions, distributed control, and networks are some of the key ideas that have been imbedded and analyzed within complex PSE constructs to accommodate and mitigate the implication of disturbances (I. P. Androulakis, 2014). The aforementioned concepts have found their direct analogues within biological systems, going all the way back to the pioneers of human physiology when *Walter B. Cannon* was beginning to lay the foundations of physiology, based on the earlier work of French physiologist *Claude Bernard* who introduced the concept of *homeostasis* (Cannon, 1929; Gross, 1998). Homeostasis, a word of Greek origin: ὁμοιος, *hómoios*, similar, and στάσις, *stásis*, standing still, is nowadays defined as the “*relatively stable condition of extracellular fluids that results from regulatory systems actions* (Windmaier et al., 2004)”. The argument was that humans are composed of an intricate web of living parts which exist in an internal environment that surrounds them. The fixity, or constancy, of this *milieu intérieur* (internal environment referring to the extra-cellular fluids which provide stability to the organs) becomes, therefore, the condition of free and independent life. Physiological functions in the face of the ever changing environment in which the living organisms exists, are aimed at preserving the constancy of conditions of life and by extension the constancy of the internal environment. As early as the 19th century, German gynaecologist and world-renowned popular science writer *Fritz Kahn* presented his view of a human, and its functions, in the form of what was referred to as the *industriepalast (industrial palace)*, strongly reminiscent of a chemical plant (Debschitz et al., 2009). Such representations convey a strong message: the human body is a collection of networked processing units (reactors), organized in the form of a plant, with individual units exchanging mass and energy in an open system setting, and maintaining stability through mass and energy transformations. The idea of “mapping” a physiological system onto a “connected network” eventually motivated the basic principles of physiologically-based pharmacokinetic models (Sung et al., 2014) – a concept we further elaborated on in previous sections.

In a living system, and depending on the granularity of the approach, the role of the (process) unit is expressed by an idealized “cell”. When mathematically describing a cell, one is left to decide on the appropriate level of details (i.e., mathematical complexity) that will be required to describe a “nonmathematical” entity. The mathematical granularity will be dependent on the knowledge of the system, data availability, purpose and complexity that can be realistically handled.

The curious case of inflammation

Much of the work to be discussed, centers around inflammation, inflammatory components and anti-inflammatory drugs. Inflammation is, loosely, defined as the response of a living organism to stress. It is an evolutionarily conserved response, simple to describe, yet very complex to understand and more difficult to control: you need to know the right amount, at the right time and for the right duration (Dick et al., 2012; Laroux, 2004; Namas et al., 2012). The inflammatory response is a key component of the host’s reaction to acute stress, acting as a major contributor to the recovery from trauma and injury (S. F. Lowry, 2009). In addition, low-grade, chronic inflammation has been shown to play a critical role in a wide variety of pathophysiological conditions such as obesity, diabetes, and cancer (Coussens & Werb, 2002; Haffner, 2006; Luft et al., 2013; Southerland et al., 2006). Managing, modulating, and eventually controlling the progression of the inflammatory response, either acute or chronic, has faced numerous obstacles.

At the heart of this conundrum is the fact that the inflammatory response, under normal circumstances, engages an intricate web of interacting protective mechanisms aiming at restoring homeostasis following a stressful challenge. However, when the response does not resolve appropriately, or is initiated inappropriately, it can lead to detrimental results (Laroux, 2004). The delicate balance of the forces that induce and maintain a proper response is critical in re-establishing homeostasis under conditions of stress (Bone, 1996) as well as performing the balancing act of maintaining homeostasis (Chrousos, 2009). Challenges in understanding how to modulate inflammation ultimately stem from the underlying complexity of the inflammatory response itself, a homeostatic mechanism which has served as a major component during our evolutionary development (S. F. Lowry & Calvano, 2008). Cytokines, hormones, and autonomic signaling all convey immunomodulatory signals that are typically redundant and pleiotropic, making it difficult to infer how perturbing individual components will impact the overall systemic response in a specific context. The intrinsic complexity of the immune response to stress (Segel & Cohen, 2001) naturally triggered interest in systems-based approaches to rationalize the evolution of the dynamic interactions of the constitutive components (Vodovotz & An, 2010, 2013; Yoram Vodovotz et al., 2013). Model-based approaches attempt to quantify the causal relationships between the components manifesting and driving the onset, maintenance, and resolution of the inflammatory response. These representations can vary from statistical and correlational (Clermont et al., 2004) to mechanistic (Foteinou, Calvano, et al., 2009c); from deterministic and continuous (J. D. Scheff et al., 2011) to discrete and stochastic (An et al., 2009; Dong et al., 2010; Nguyen et al., 2013). As we increasingly understand and appreciate the systems characteristics of the inflammatory response and the inflammation-related pathophysiological conditions (Carre & Singer, 2008; Yoram Vodovotz et al., 2013), the

need for establishing appropriate mathematical and computational frameworks becomes more apparent (Zenker, Clermont, et al., 2007; Zenker, Rubin, et al., 2007)

Inflammation is initiated by local events, yet quickly progresses to engage to system with consequences above and beyond the initial site of the initiating event (Dick et al., 2012; Namas et al., 2012; Jeremy D. Scheff et al., 2013; Y. Vodovotz et al., 2013; Vodovotz et al., 2010). Surrogates of the host's response to stress have been developed which could isolate specific components of the response and thus rendering the analysis more manageable. Once such model is endotoxemia (Stephen F. Lowry, 2005) where a specific agent will act as the "disturbance". However, that agent has (relatively) well-defined pathways through which it is sensed, and its implication are propagated through the system (Foteinou, Calvano, et al., 2009c). In this section, we wish to describe efforts of increasing complexity in an "inside-out"-type of approach which have been enabling us to construct models that enable us to, using PSE parlance, move the operating boundary from the process to the integrated open supply chain.

The process: A cell

To describe the quantitative relationships between the multiple components of the acute inflammatory response, we have developed a suite of physicochemical model of human endotoxemia of increased complexity by focusing on an idealized fundamental process unit which represents a prototypical "immune" cell over the years (Dong et al., 2010; Foteinou, Calvano, et al., 2009b, 2009c; Nguyen et al., 2011; J. D. Scheff et al., 2012). An important simplification made in the development of these models is that the endotoxemic challenge activates only inflammation-specific signaling cascades within immune cells – the basic defense unit. Furthermore, even though many regulatory elements are known to be involved in the inflammatory response, most computational models focus on NF- κ B (nuclear factor kappa-light-chain-enhancer) as the central module responsible for the activation of the proinflammatory cytokines, which are the primary mediators of the inflammatory response. Therefore, the acute inflammatory agent (lipopolysaccharide, LPS in our case), is "sensed" by the unit or cell following its binding to a signaling receptor (TLR4) to induce a cascade of events that ultimately activates the proinflammatory cytokines via NF- κ B (Foteinou, Yang, et al., 2009). The proinflammatory cytokines further activate the anti-inflammatory response in the form of the steroid hormone, cortisol, which constitutes the primary physiological stress response mechanism. Semi-mechanistic models of this signaling cascade using indirect response models likely relate network structures to the experimentally measured cellular transcriptional response to LPS. Indirect-response (IDR) models have been widely used in the development of PKPD models while simulating time delay in the response of a physiological system to external signals, by assuming that the external signal influences either the synthesis or degradation rates of the system (Jusko & Ko, 1994; Krzyzanski & Jusko, 1997). The adoption of IDR models in this case serves to illustrate the AAD² principle. Thus, this model can semi-mechanistically describe both cellular transcriptional response to LPS, as well as the dynamics between two interacting arms of the immune physiological subsystem i.e. systemic responses of the proinflammatory cytokines and the anti-inflammatory cortisol. With this level of mechanistic detail, the model can qualitatively describe several behaviors of the typical human inflammatory response to

endotoxemia. These include the model's ability to capture a self-limiting inflammatory response with elimination of the inflammatory stimulus within 2h and resolution of the response within 24h; the progression of an unconstrained inflammatory response by increasing the host susceptibility to endotoxemia challenge, and dysregulation of the NF- κ B signaling dynamics; and finally, the pre-exposure of the system to LPS resulting in hypercortisolemia, which "reprograms" the system in favor of a balanced immune response. Furthermore, this model also has the potential to evaluate the outcomes of corticosteroid based intervention strategies on the evolution of the inflammatory response (Foteinou, Calvano, et al., 2009a). This serves to highlight the convergence of putative goals of systems pharmacology (i.e. modeling the dynamics of healthy and pathological states of the host system) with those of PKPD; predicting and evaluating the effect of pharmacological interventions on disease pathology.

The plant: A cell within the host

Process units do not reside in a vacuum, but rather are organic elements and components of broader (sub)systems. Therefore, a unit's response is driven and constrained, if not defined, by the likely interactions of the unit with its immediate, and eventually distant, surroundings. Since information flow in a complex supply chain is rarely linear, feedback loops, however long and extended they might be, eventually self-regulate individual units. In a very analogous manner, the idealized "cell" of the previous section resides within the confines of the "surrounding environment". The surrounding environment is defined by physiological and biological signals emanating by proximal and distal cells, tissues and organs, defining in turn the context of which a cell operates. Therefore, the ability of the cell to respond and adapt by enacting the regulatory mechanisms just discussed, is defined by the status of its surrounding environment. Of importance to our work are the intrinsic dynamics of numerous regulatory components acting on, and impacted by, cells. Most notably those components which possess their own intrinsic dynamic which is dependent of exogenous factors and, in particular, components with identifiable intrinsic dynamics.

To make inflammation models more physiologically relevant, one can begin to explore the relationship between human endotoxemia and the circadian rhythms (Jeremy D. Scheff et al., 2010; J. D. Scheff et al., 2012). This consideration is important as it allows us to place the living host within the broader environment – as defined by the light/dark cycles of night/day – within which it functions and operates. Furthermore, several key mediators of the immune response, including the ones considered above (plasma cortisol and the proinflammatory cytokines), are known to exhibit pronounced circadian rhythmicity (Scheiermann et al., 2013). The effects of having a system with a dynamic steady state rather than a stationary steady state is an important consideration, with the aim of developing a more nuanced description of the system in the context of inflammation. Eventually, molecular level markers will result in changes affecting systemic components and manifest as systemic markers as observed, for example, in heart rate variability (HRV), (Dick et al., 2012; Foteinou et al., 2011; Namas et al., 2012; J. D. Scheff et al., 2011; Jeremy D. Scheff et al., 2013; J. D. Scheff et al., 2012). HRV, simply put, quantifies the distribution of time interval between successive heart beats. It is a clinically informative, non-invasive parameter that has the potential to reveal the inflammatory state of the host as often correlates with the

severity of the disease state in inflammatory disorders. Increased regularity and loss of “variability” in the time intervals is indicative of the system entering a state of systemic distress. The loss of variability is seriously considered as predictive warning signals for imminent systemic failure (Lake et al., 2014; Moss et al., 2015). While there are numerous accounts of reduced HRV in response to a variety of inflammatory stressors, as in the case of sepsis; a conceptual framework linking the molecular-level inflammatory process to the physiologically manifest response in HRV is still lacking. Modeling efforts exploring how the changes in the immune response at the cellular level are transduced through the autonomic nervous system, rendering local disturbances to global and are eventually manifested as HRV, would be quite impactful (J. D. Scheff et al., 2013). While the physiological implications of changes in HRV are yet to be clarified, we believe that adopting such a modeling approach, when appropriate, can provide a more complete description of why a correlation between a regulatory input and a physiological outcome might exist.

The analysis can be extended to study the importance of the circadian characteristics of cortisol on the cellular responses with physiological implications (Mavroudis et al., 2013). The relay of circadian inputs from the hypothalamic circadian clock in the suprachiasmatic nucleus (SCN) to peripheral circadian clocks in tissues such as the liver, adipose tissue and heart by cortisol is well known. By incorporating network models of the peripheral clocks, we were able to highlight the importance of the entrainer (cortisol) circadian characteristics in modulating the synchronization of circadian clocks in peripheral tissues (Mavroudis et al., 2012). We have also extended our model of circadian rhythms of cortisol to elucidate the observed time-of-day dependence in host susceptibility to inflammatory stimuli by incorporating a more detailed description of glucocorticoid modulation of the inflammatory response; whereby depending on its dynamic state, cortisol can both support and inhibit the inflammatory response (Mavroudis et al., 2014, 2015).

In simulating the circadian rhythms of the mediators of the inflammatory response in the above models, oscillations were imposed on these mediators through the use of oscillatory functions without considering the fact that oscillations in physiological systems are often a property of the network dynamics between the various regulatory components and are thus dependent on the states of the individual components. Therefore, subsequent efforts adopted and developed a more biochemically realistic depiction of cortisol oscillations based on the Goodwin oscillator for negative feedback (Goodwin, 1965; Sriram et al., 2012). This approach allows one to then study the impact of stressors on the network components, and how the influence of these perturbations might manifest as disruptions in the circadian rhythm of cortisol. Such a model was developed to explain observed dampening of the cortisol amplitude in chronic inflammatory diseases, such as rheumatoid arthritis. The model was developed as an extension of a model of collagen induced arthritis and was thus adapted to describe the disease dynamics in rats with the inclusion of physiological parameters describing disease severity such as the extent and circadian variability in paw edema (Rao et al., 2016). The latter was one of the first models to have accounted for the intimate interplay between the loss of systemic characteristics in conditions of disease-induced stress.

The host and its environment

Much like a unit operation resides within the constraints imposed by the network of its immediate surroundings of the plant it belongs to (a process within a chemical plant, for example), the plant itself resides within the open global environment of its supply chain, often also impacted by loose connections with other supply chains.

By now, we realized that the pressing health challenges of the 21st century will be non-communicable conditions with one common, underlying, characteristic: persistent, low-grade, systemic inflammation, (Bauer et al., 2014; Egger, 2012; Egger & Dixon, 2014; Libby, 2007; Tabas & Glass, 2013), leading to realizing the importance of “context” (I.P. Androulakis, 2016). Inflammation and inflammation-related diseases have been difficult to control and regulate due to complexity and intertwined character of the response (Laroux, 2004). Inflammation is critical for survival (Tabas & Glass, 2013) expressing a balance of conflicting objectives (Csete & Doyle, 2002). The mechanisms orchestrating the inflammatory response are redundant: targeting one is likely not enough; inhibiting another will, induce an alternative. Obesity-associated inflammation, for example, appears to help to maintain insulin sensitivity, thus anti-inflammatory therapies have failed in the treatment of insulin resistance (Gao & Ye, 2012). Diseases, such as Alzheimer’s and cancer, have systemic components acting as either a pre-disposing factor or contributing to the development of the disease (Krstic & Knuesel, 2013; Krstic et al., 2012; J. K. Morris et al., 2014; Redig & McAllister, 2013). The systemic nature of cancer is not a recent realization (Meyer, 1931); however, we now realize that the “systemic” view is not simply an abstraction, but rather a major factor in disease etiology and treatment. The realization of the importance of the systemic component of disease lends naturally to considering the broader context in the environment of the host. A series of interesting experiments demonstrated that circadian reprogramming via time restricted feeding (controlling access to food without calorie restriction) led to re-setting of metabolic rhythms, and impacted tumor growth (Li et al., 2010), reversed liver-specific abnormalities (Maywood et al., 2010), or impacted obesity onset (Hatori et al., 2012). Shift-work, also associated with disrupted sleep and feeding patterns, is now widely accepted as a disease pre-disposition factor (Barclay et al., 2012; Yoon et al., 2012). Well-established are also the links between sleep disruption and immunity (Besedovsky et al., 2012) as well as the daily (Smolensky et al., 2015) and seasonal patterns of inflammation and chronic inflammatory diseases (Dopico et al., 2015; Iikuni et al., 2007; V. Kumar et al., 2007), and finally the links between circadian disruption, inflammation and mood disorders (Alesci et al., 2005; Geoffroy et al., 2015; Quera Salva et al., 2011). In (Sunderram et al., 2014), the metabolic engagement of circadian rhythms in support of their health-promoting role was further argued. Expectation of a positive outcome is now known to positively impact health (de la Fuente-Fernandez et al., 2001) and detailed studies shed light into possible predisposition to positive response to placebo (Hall et al., 2015). On the other end, expectation of a negative outcome has been shown to induce low-grade, chronic inflammation leading to health deterioration (von Kanel, 2015). In a similar vein, absence of social interactions when absent can induce the chronic-inflammation phenotype (Cole et al., 2015); while their presence enhanced the host’s response to physical stress, often as much as a xenogenous drug (Vitalo et al., 2009). “Mood” changes, induced

either pharmacologically or behaviorally, drive changes at the cellular level (Karatsoreos & McEwen, 2011; Quan & Banks, 2007).

What these observations help us realize and appreciate is that the “global” supply chain plays a significant role. In all the examples just mentioned, even though the eventual dysregulation will manifest itself at the cellular level, the initiating event (sleep deprivation, meal patterns, social stress, etc) was non-specific. An important focus of systems pharmacology is extending the scope of biological process modeling beyond the cell level and integrating it with physiology and environment (I.P. Androulakis, 2016), as biological subsystems rarely function in isolation but rather as part of the larger organ or organism under the influence of its surroundings. Among the multitude of factors defining a host’s environment, two leading influences emanate from seasonal and longitudinal variations in photoperiod and nutritional input patterns.

As our abilities to model the host’s defense mechanism in relation to an immune stressor improve, we can begin to investigate, and mathematically model, the dynamics under the broader influence of environmental and/or behavioral cues. Along those lines, we have demonstrated the implications of accounting for seasonal variations on the immune response (Pierre et al., 2016) eventually in the context of inflammatory diseases. Immune function and inflammatory components vary significantly throughout seasons (Dopico et al., 2015; Maes et al., 1994; Nelson, 2004). Seasonal variations in inflammatory components are risk biomarkers for cardiovascular (Douglas et al., 1995; Rocco et al., 1987) and inflammatory diseases (Haus et al., 2012; Schlesinger & Schlesinger, 2005) exhibiting seasonality with higher prevalence and aggravated symptoms occurring during the winter and spring months, as well diurnal activity fluctuations with symptom intensity aggravated in transition from the inactive to the active period. Our modeling work enabled us to recognize the importance of the “dynamics” of the regulatory elements since response to a disturbance (stress) is not only dependent on the level of the control (regulatory) elements, but also – and most likely even more so – on the dynamics of the element itself (Mavroudis et al., 2015). Undoubtedly, seasonality affects a number of critical factors, including temperature and rainfall, however, photoperiod is most widely considered as the environmental signal that synchronizes physiological changes due to seasonality (Hazlerigg & Wagner, 2006). Motivated by these observations, the role of photoperiod-driven cortisol level change in circadian modulation of immune responses was recently discussed in (Pierre et al., 2016). Interestingly, and as explored in (Pierre et al., 2016), neurons in the hypothalamus show a more synchronized firing activity during the short winter days, resulting in increased ensemble amplitude (Meijer et al., 2010; Rohling et al., 2006). The issue of periodic signals increasing synchronization and entrainment, and by extension acting as an implicit signal strengthening mechanism, is a concept also explored in our earlier work discussing the importance of maintaining robust rhythmic (circadian) patterns in circulating hormones (Mavroudis et al., 2012). In all cases, the intrinsic dynamics of the control elements, greatly impacted by exogenous factors, eliminates the ability of the system to respond to a disturbance.

However, the external environment of the “global” supply chain, is rarely under the influence of a single factor. As such, the assessment of multiple factors with distinct dynamic characteristics, exerting – via convolution – their regulatory control on

(sub)systems is quite intriguing. Behavioral patterns, most notably associated with nutritional supplementation, interacting with environmental patterns, such as light/dark sequences, are prime targets for assessing global impact on the inflammatory response. Work in this context was motivated by observations that circadian disruption leads to metabolic abnormalities while restricted feeding restores lost rhythms, suggesting a bi-directional influence between biological clocks and metabolism. At a clinical level, shift-work and sleep deprivation dampens the circadian rhythms and causes obesity (Spiegel et al., 2009). At a molecular level, clock gene mutant mice show a decreased metabolic rate (Turek et al., 2005), and liver-specific Bmal1 (one of the core clock components and a transcription factor) knock-out mice exhibit a disruption in glucose homeostasis (Lamia et al., 2008). At the other end, restricted feeding schedule restored oscillations of some peripheral clock components in clock-deficient mouse livers (Vollmers et al., 2009). Extension of the scale for studying the circadian rhythms to include the influence of feeding patterns could elucidate the mechanism of metabolic abnormalities due to circadian disruption. Along those lines, our recent work aimed at integrating feeding and light patterns to assess the interplay between multiple external periodic signals (Bae & Androulakis, 2017).

Building and executing the model

As the complexity of the mathematical model is expected to increase, the fundamental issues associated with building and executing the model will dominate. QSP model cover a wide range of representation including: *Statistical*: aiming at exploring correlational relationships based on experimental observations; *Lumped & phenomenological*: aiming at describing broad and coarse characteristic responses as proxies of state variables of which such models tend to be less complex or at least their complexity can be controlled (R. Kumar et al., 2004); and *[quasi] mechanistic*: capturing and expressing increased level of details by introducing tangible cause-effect relationships. More involved renditions engage multiple cell types, tissues, organs, and eventually integrated host systems interacting with their environment. The physiologically-based pharmacokinetic models (Rowland, 2013) can be considered as the prototypical example of such an approach. Despite their advantages, the complexity of such models can easily escalate such that critical assumptions and simplifications are often required. Once the nature of the representation has been indentified, the execution of the model will reflect the nature of that representation. As such, multiple approaches can be identified, including mathematical vs. rule-based; stochastic vs. deterministic; and discrete vs. continuous representations. *Mathematical approaches describe the physical reality through mathematical equations while rule-based models describe the physical reality through logical statements and execution rules.* The underlying hypotheses are the same, but the expression of the outcome of an interaction differs. Often times, rule-based descriptions aim at addressing issues related to the discrete nature of the dynamics of the underlying processes. While stochastic approaches recognize variability exists in both biological and physiological systems (Ullah & Wolkenhauer, 2010) and aim to capture its effects, deterministic approaches represent an exact condition. Whether the increased complexity of stochastic models translates to improved insight has yet to be evaluated. A final consideration is the choice of discrete and continuous representations of physiological phenomenon. Although the continuum approximations simplify the model, a

multitude of cell-level events take place in a discrete manner. This representation constitutes a design decision endowing the modeling approach with specific characteristics depending on whether the modeler wishes to emphasize events which evolve continuously or in discrete fashion (Bortolussi & Policriti, 2008). Selection of the appropriate model formalism and model execution depends on the aims and targets of the study. Therefore, general and generic guidelines are very difficult to identify.

6. Perspective/Outlook

Over the years, Process Systems Engineering has enabled us to develop concepts, methodologies, approaches and tools to synthesize, analyze, control and optimize complex, engineered, supply chains (Klatt & Marquardt, 2009). In this short review, we attempted to share our perspective and understanding of how PSE concepts pave the way towards developed approaches to analyze complex, biological, supply chains (I. P. Androulakis, 2014, 2015). Our understanding can, and will, be significantly enhanced through the development of multi-scale models that link semi-mechanistic descriptions of biological processes across different physiological scales. There has recently been renewed interest in developing multi-scale models in a variety of chemical engineering settings, including in the study of multi-phase flow, and the development of nano-biological devices (Stephanopoulos & Reklaitis, 2011). Such an approach borrows heavily from a variety of disciplines, not least from foundational PSE concepts, as illustrated through examples within this review.

As we enter the era of personalized and precision medicine aiming at “*steering [the right] patients to the right drug at the right dose at the right time*” (Hamburg & Collins, 2010), it becomes imperative to truly address the integrated “supply chain” of delivering appropriate treatment. This framework should encompass all steps from discovery to formulation, manufacturing, delivery, *in vivo* assessment and response at the individual level. We recently articulated how we envision these type of “global” modeling structures enable the development and delivery of precision and personalized health delivery, eventually bridging the gap across all scales of QSP (Hartmanshenn et al., 2016). There is significant work that remains to be accomplished in many areas. However, the framework enabled by systems approaches is paving the way for a rational integration of such components.

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Highlights

- Overview of quantitative systems pharmacology and its relations to PSE
- Overview of models of increasing complexity of the inflammatory response
- Challenges and opportunities in bridging PSE and QSP ideas

Figure 1.
Systems Biology and Pharmacokinetics as the building blocks for Quantitative Systems Pharmacology modeling framework