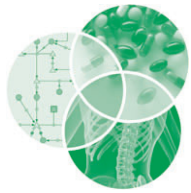
Opinion



Systems engineering meets quantitative systems pharmacology: from low-level targets to engaging the host defenses

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Quantitative systems pharmacology aims at systematizing, in a model-based manner, the integration of systems biology and pharmacology in an effort to rationalize the process of assessing the ability of a drug to enhance well-being by off-setting the effects of a disease. Systems engineering, on the other hand, has enabled us to develop principles and methodologies for designing and operating engineered networks of structures exploring the integration of the underlying governing (design) laws. Although the computational tools which have resulted in major advances in the design, analysis, and operation of complex engineered structures have had tremendous success in the analysis of systems pharmacology models, it is argued in this opinion paper, that exploring the underlying conceptual foundation of complex systems engineering will enable us to move toward integrated models at the host level to explore, and possibly, induce synergies between low-level drug targets and higher level, systemic, defense mechanisms. This is an approach which would require refocusing of the key activities; however, it is likely the more promising approach as we enter the new era of personalized and precision medicine. We finally argue for the development of an allostatic approach to quantitative systems pharmacology and the development of an integrated framework for considering drugs in their broader context, beyond their local site of action.

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INTRODUCTION

Broadly speaking systems engineering deals with the design and management of complex engineered systems (CoES). The analysis of a CoES is motivated by the realization that individual components comprising the system, as well as the system itself, exist in a *context*. Context is somewhat formally defined as 'the interrelated conditions in which something exists or occurs' (Merriam-Webster dictionary). Context, however extends beyond the interactions between the constitutive components to the interactions between the components and the environment the system resides in. 'By design' the dynamics of CoES are constrained by requirements of optimality, robustness, and flexibility. They have by judicious trial-and-error experimentation and/or computation, evolved to successfully perform specific functions (optimality) in a changing environment (flexibility) while maintaining responses within ranges in the face of uncertainties (robustness). The analysis, synthesis, and design of CoES aim to identify and explore the laws governing optimally integrated systems.

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As we improve our understanding of life's multi-scale nature and characteristics, we realize that living systems share many of the features of CoES, with much to be learned about biological complexity from engineered systems, and *vice versa*. If health reflects a dynamically stable integration of molecules, cell, tissues, and organs; disease indicates displacement compensated for and corrected by activation and combination of feedback mechanisms through interconnected networks.[1] Much like in CoES, the concept of *context* was precisely what drove the development of *Systems Biology* given the realization that cells, tissues, organs, and the entities associated with them (genes, proteins, and metabolites) do not exist in isolation but rather form a network of nested hierarchy and (horizontal and vertical) complexity.[2] *Systems Pharmacology* encompassed therefore the efforts to merge *systems biology, pharmacokinetics/pharmacodynamics*, *and pharmacology* in an attempt to understand how pharmacological treatments (i.e., *drugs*) aim at enhancing well-being by off-setting the implications of a disease through activation of appropriate defense mechanisms.[3] *Quantitative Systems Pharmacology* (QSP) attempts to further advance our understanding by exploring *integrative* and *model-based* approaches exploring our vast understanding and knowledge of computational tools based on the computational analysis of CoES.[3] In this article, however, we wish to move a step further thus we begin by drawing 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 the one hand and of the systemic intrinsic defense mechanisms on the other adding a new, and important, dimension to the development of QSP approaches.

A SYSTEMS VIEW OF LIVING ORGANISMS

It is beyond the scope of the present paper and likely redundant, to delve into exact, and rigorous definitions of terms such as systems, engineering, systems engineering, or complex systems. Appropriate textbooks provide precise, and alternative, definitions of all the above.[4,5] Furthermore, for the purpose of this discussion we will be using the fairly broad term 'Complex Biological System', CoBS, to describe a living host (*in vivo*), maintained in life via the proper and synergistic functioning of a compendium of biological and physiological functions. Therefore, the definition, as used herein, does not include *in vitro* or *ex vivo* systems. Admittedly, the acronym is also used throughout the text for consistency purposes (CoES vs. BioES) and it is not an attempt to introduce new terminology in this or any field.

CoES compared to CoBS have one key, defining, difference: CoES are 'man-designed' and therefore the space of alternatives is effectively prescribed, well defined and implemented by the engineers who constructed the CoES. The various design alternatives are chosen such that they can be realized. Even though CoES are the result of a variant of evolution (i.e., optimization whether deterministic or stochastic) by and large the 'evolution rules' (gradient decent or mutations/random moves) are known and hard-coded by the designer, i.e., the engineer. By contrast, CoBS, are the result of an equivalent optimization process (natural evolution) however, even though the 'objective function' may be loosely defined (survival or adaptability[6,7]) the nature of the evolution of design improvements and versatility of alternative design components escapes, at least up until now, our capabilities, especially given the built-in redundancy to increase efficiency and robustness.[8] Therefore, precisely charting the design principles and components has been a daunting task in the context of CoBS.

The lack, or the *ill-posedness*, of the design principles becomes a key limiting factor, as well as exciting goal, as we aggressively enter the era of *in silico* approaches in their many renditions. Obviously, as we move along the complex hierarchy comprising CoBS from cells, to tissues, to organs, to the host, and eventually to the host interacting with its environment, be it whether the natural environment or one created by the use of a drug, it becomes harder to decipher and design operational rules of CoBS and, by extension, the means for modulating their dynamics.[9]

Our experience with CoES has taught us that functional description of the integration and interaction of the constitutive elements of such structures adds a critical element to the analysis. Namely, for a functional analysis to be relevant, components, and their networks, need to be placed within the appropriate *context*. The term functional analysis is used to describe the implications of a component within a particular context. In a (self-)similar vein the dynamics of the interconnected and networked sub-structures embedded within complex, engineered supply chains depends on their interactions as well as the environment within which the overall supply chain resides. The same is true for biological systems.

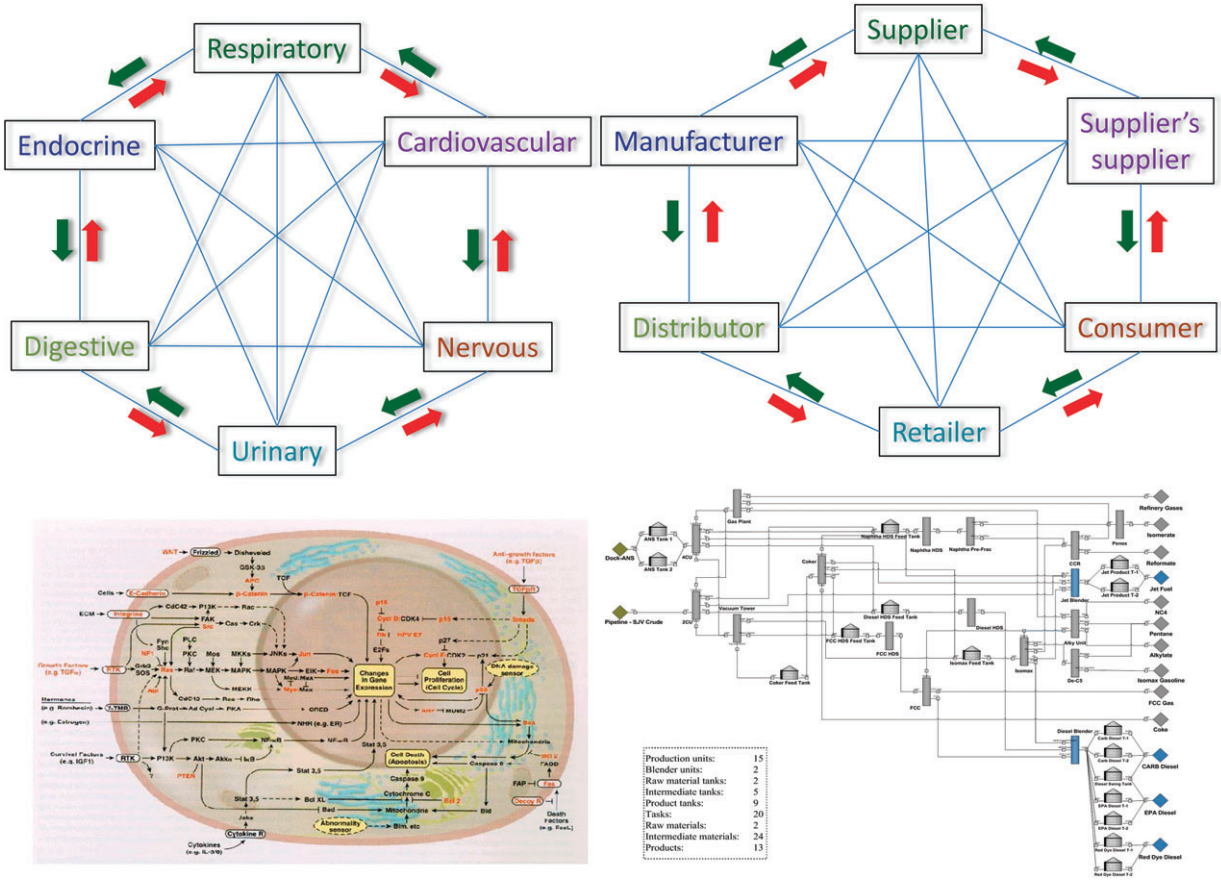

FIGURE 1 | (top) Notional equivalence between CoBS and CoES as 'horizontally'-integrated networked sub-structures interchanging information and communicating messages. (bottom) Equivalent network structures (cell signaling/metabolic network on the left: Reprinted with permission from Ref 10. Copyright 2000 Elsevier; chemical process network structure of the right: Reprinted with permission from Ref 11. Copyright 2011 John Wiley and Sons), extended vertically, underlie the higher level organization. High(er) level substructure communication is the result of 'messages' produced by low(er) level information. Communication exchanges are therefore explicit within a given level, but also implicit across levels.

So, the analysis of a biochemical reaction *per se* provides important information in terms of intrinsic rates however, the functional implications, such as conversion, of the reaction depend on a specific reactor embodiment (by regulating diffusion limitations, etc.) as well as on interactions of the reactor with its environment. Therefore CoES and CoBS share structural similarities in that they function as networked sub-structures with intense cross-communication of their components. Figure 1 depicts such network structures at a higher level of organization. However, it must be realized each level encapsulates a lower-level network structure, likely of a similar networked nature (organs → tissue → cells → pathways). This nested hierarchy of complexity has been earlier articulated and described, particular in the context of physiology.[12–15]

At a conceptual level we have previously elaborated on the likely equivalence between engineered and biological systems in the context of the fundamental issues guiding the flexibility, robustness and optimality of the operations of both.[16,17] For historical purposes the interested reader is highly recommended to explore the Fritz Kahn's rendition of the human body as an 'industrial palace' from the early 1900s (http://www.nlm.nih.gov/dreamanatomy/da_g_IV-A-01.html). Aside from identifying common underlying principles, systems engineering theory can potentially enable us toward efforts aiming at standardizing the modeling environment. In the process systems engineering arena, it has been suggested that one way toward enabling the systematic representation of complex engineering structures is via the definition of appropriate description of physicochemical phenomena rather than processes. A process can then be decomposed to its constitutive phenomena thus enabling the development of a generalized 'alphabet'.[18–20] At some future point, QSP scientists would benefit significantly by further expanding such concepts.

QUANTITATIVE SYSTEMS PHARMACOLOGY: A SYSTEMS ENGINEERING PERSPECTIVE

QSP adds a critical level of complexity to the picture. For completeness, we will briefly present broadly accepted definitions that have been suggested: The 2011 NIH-sponsored workshop on QSP defines the term to describe an approach to translational medicine that combines computational and experimental methods to elucidate, validate, and apply new pharmacological concepts to the development and use of drugs. The definition further places emphasis of the integrated systems-level approach to determine mechanisms of action of drugs.[21] Complementary definitions have also emerged articulating in great(er) detail the hierarchy of components and complexity that a QSP approach needs to account for and interpret.[22]

Independent of the definition one chooses to adopt, or propose, the heart of the issue remains the same: *QSP is the attempt to systematize the integration of information across multiple scales in the context of an autonomously living organism* (CoBS) *in order to assess the ability of a drug to enhance well-being by off-setting the implications of a disease through empowerment of appropriate defense mechanisms*. However, the above are not uniquely defined as hidden in the above mentioned statement are critical issues related to side effects, efficacy, toxicity, differential, and patient-dependent effects (and many more) of a drug.[23–26] Given the complexity of the task, QSP attempts to *adopt, adapt, develop, assess, amend, and deliver* ($[ADAD]^2$) computational and modeling methodologies to close the gap between the (limited) observations and the underlying (mechanism-based) driver of the observations, as they related to aforementioned characteristics of the action of a drug. The $[ADAD]^2$ framework begins by *adopting* a hypothesis, which is *adapted* accordingly based on the knowledge of (patho)physiology, mechanisms, and conditioned on data. It is further *developed* into an integrated *in silico* model replicating *in vivo* responses. Predictions are *assessed* and subsequently *amended* accordingly by further conditioning the model to possibly new data and/or model analyses. The iterative loop is repeated until a final model is *delivered*.

The Evolution of Concepts in QSP

The relationships between a drug and its effects in a context of systems pharmacology has been broadly described in the context of Figure 2. The central idea, as adapted from Ref 27 is the delineation and quantification of ligand (drug)–receptor interactions, internalization, signaling, and cellular effects enables the rationalization of modes of action. Placing these key pharmacological concepts in their physiological context enabled the proper characterization of the physiological distribution (spatial and temporal) of key contributors along the chain of events.[28] Clearly, a number of challenges, and opportunities, emerged which relate to (1) the assembly and analysis of spatiotemporal-*omics* information characterizing events at the disparate, yet appropriate levels, across the continuum from circulating markers, to transcriptional, translational, posttranslational, epigenetic, and metabolic levels; and (2) the construction of large-scale computational model whose development and analysis has greatly benefited from years' worth of experience in computational sciences. The above are well established[3,29,30] and will not be discussed further in this paper. All these elements give rise to marvelous, from a systems analysis point of view questions and CoBS pose formidable challenges in terms of making useful predictions and/or reverse engineering responses to isolate and identify critical points of diversion and intervention.

The linear information flow perspective of Figure 2 (top) represents but one level of context: e.g., receptor binding turnover drives a complex signaling cascade which eventually induces or suppresses a cellular response. What QSP (and systems biology in general) enabled us to recognize and better characterize is that the information flow is not liner, rather feedback and feed forward loops, Figure 2 (bottom) emerge which endow biological systems with complex, emerging response characteristics. Once again, the 'self-similar' inherent nature of the problems remind us that even in a deceptively structure like the one depicted in Figure 2 each module is itself a complex network.

However, a critical observation needs to be made: QSP attempts to analyze such a dynamic system in the presence of two major perturbations: first, the basic dynamic response of the system has been perturbed because of the disease itself and second, the perturbed dynamics is furthered perturbed via the drug administration in an attempt to 'restore' the original steady state (i.e., homeostasis). The importance of these two perturbations is of paramount importance since these define the *context* within which the system operates.

HEALTH, DISEASE, AND DRUGS: RESTORING DELICATELY BALANCED DYNAMICS WITHIN THEIR CONTEXT

Conceptually, merging the representations of Figures 1 and 2 gives rises to a horizontally and vertically

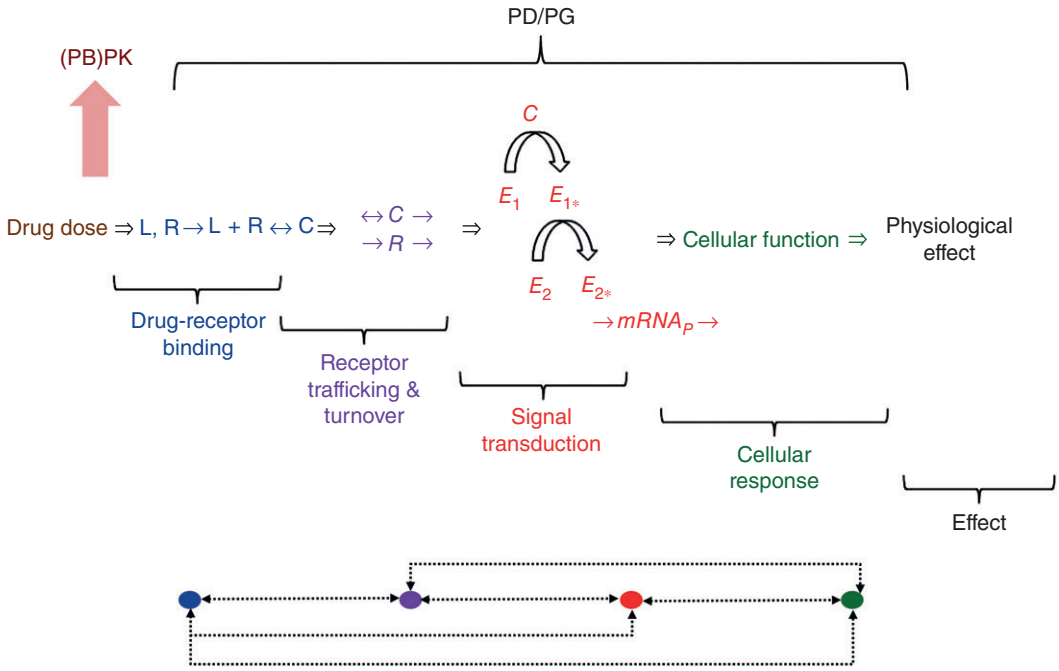

FIGURE 2 | (top) Simplified representation of the systems pharmacology 'supply chain'. Often drugs are considered as 'ligands' (L) binding on appropriate 'receptors' (R). Drug bioavailability, i.e., concentration of L, is often determined by the drug's pharmacokinetics PK (obtained via appropriate physiologically based PK—PBPK—models). Binding of the drug on its receptor will induce a 'signal' (C) which will induce an appropriate cascade of 'signals' eventually inducing a cellular response, likely mediated by alteration of transcription/translation events. Cellular responses induce physiological effects by appropriate modulation of the release of various mediators. Responses are represented by appropriate pharmacodynamics/pharmacogenomics models (PD/PG) (bottom) The information flow is the aforementioned 'chain' of events is rarely linear and feed-forward. Signals emanating from each event feedback to upstream nodes either within the same level of organization (e.g., within a same signaling pathway) or across levels of organization (e.g., the product of cellular metabolism in one tissue type may act as a signal to a different tissue type)

integrated hierarchy with implications in QSP: although a drug will act on the receptor of the target cell/tissue/organ, its metabolic products and/or the targeted tissue cellular output will interact with horizontally integrated cells/tissues/organs. Therefore, the action of a drug by means of the networked nature of the host will have, eventually, systemic implications. Furthermore, and likely more important: *a drug is a means of restoring perturbed homeostasis due to a disease doing so by either inducing suppressed defense mechanisms or producing novel defense actions*. However, innate defense mechanisms are an integral part of the nested, dynamic network which maintains homeostasis. Therefore drug actions need to be coordinated with the innate mechanisms or else critical conflicts will arise due to the loss of balance between the proper alignment of the multiple objectives pursued by the alternative innate mechanisms.[31] Therefore, *from a systems analysis point of view, a drug constitutes a (localized at first, yet possibly systemic) perturbation to an already (localized at first, yet possibly systemically) perturbed system*.

Systems engineering approaches applied to QSP in the context of CoBS differ conceptually from equivalent approaches applied to the analysis of CoES in two important aspects:

a In CoES the logical sequence of the $[ADAD]^2$ computational analysis starts with the detailed description of the *normal* operation of the system. Subsequently, perturbations are introduced to target specific elements, thus inducing deviations from normal operation, and then control actions are activated to reestablished nominal operational dynamics. Simply put, a flight simulator is designed to model take-off and landing before evaluating the aircraft's ability to withstand high turbulence. Interestingly, in developing QSP models we often perform the analysis in a very different way: the study begin with the 'perturbed' system, be it either the analysis of the response of a patient cohort or the analysis of the responses to a drug. However, we most often, bypass the analysis of the dynamics of the *normal* (homeostatic) function. But there is a

reason from that: it needs to be emphasized that 'normality' is not easily defined in a living organism. It is really a challenge to properly characterize the steady state, deviations from which characterizes the disease. This observation naturally leads to an important question: can we define normality (i.e., health) in a CoBS and how this can become part of QSP?

b By virtue of the fact that CoES are 'engineered' and therefore all the details of the system (or at very least the overwhelming majority of it) is known and available during $[ADAD]^2$, any perturbation, either external or manipulation, engages the totality of the dynamic elements and their responses. Therefore, the complete set of intrinsic dynamics is engaged and explored. Given that in CoBS we are still trying to chart the compendium of intrinsic dynamic elements, we focus the analysis on the control action potentially aiming at restoring the deviation while we do not properly engage and characterize the innate dynamics of the defense mechanisms. This observation leads to another important question: should the intrinsic defense mechanisms, at the systemic level, be part of QSP?

Can (should?) Health Be Defined and Modeled?

This is a neither a rhetorical nor a contrived question. The definition of what constitutes health is far from trivial.[32,33] In the context of QSP this may sound as a likely nonsensical concern. After all, drug discovery is driven by defined and specific symptoms. i.e., subjective evidence, associated with a disease. However, from a systems point of view, the definition of health and more precisely of the dynamic interactions of the CoBS components giving rise to health is of paramount importance, the key reason being that disease is the manifestation of improperly functioning defense mechanisms which have either been compromised or confronted with unknown disturbances. It has been argued that 'Good health, which reflects the harmonious integration of molecules, cells, tissues, and organs, is dynamically stable: when displaced by disease, compensation and correction are common, even without medical care. Physiology and computational biology now suggest that healthy dynamic stability arises through the combination of specific feedback mechanisms and spontaneous properties of interconnected networks.'[1] Therefore, health is maintained through the proper interactions of homeostatic defense, i.e., control, mechanisms. It is in fact fascinating to recognize that the idea of dynamic equilibration of defense mechanisms was established as early as 1929 by Walter Cannon when he introduced the concept of homeostasis in relation to the surrounding environment by stating that 'The highly developed living being is an open system having many relations to its surroundings—in the respiratory and alimentary tracts and through surface receptors, neuromuscular organs, and bony levers. Changes in the surroundings excite reactions in this system, or affect it directly, so that internal disturbances of the system are produced. Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby oscillations are prevented and the internal conditions are held fairly constant.'[34] It is therefore important to realize that health is maintained via means of dynamically interacting defense mechanisms which require appropriate levels of coordination and collaboration. Therefore, 'modeling health' is not a goal in and of itself, but rather the attempt to understand the dynamics, and trade-off, of processes whose delicate balance gives rise to 'health' and whose dysregulation and off-balance predisposes, or initiates, a disease condition.

The $[ADAD]^2$ analysis of a CoES begins with a clear definition and quantitative description of the 'normal operating' range and the definition of the control structures and dynamics preserving optimality, not only in the context of characteristic outputs, but also and more importantly in the context of the dynamics that give rise to the observed normal operating conditions. Abnormal events and faults, therefore, have meaning and substance only in the context of an underlying normal operating regime and the interactions and dynamics that define it. What likely complicates matters in CoBS is that deviations from 'normal' levels may actually indicate an appropriate response (such as raising temperature of heart rate transiently), whereas deviation from steady state in a CoES is usually a red flag. The prototypical example of a transient deviation from 'normal' levels of response is the *acute inflammatory response*, whereby a number of mediators are transiently elevated until the danger has been eliminated.[35–37] Given that health is likely better characterized as an emerging property of the host, it further complicates the functional implications of a drug target which, independent of the context of the network of defense mechanisms, attempts to alter localized cellular responses which are bound to eventually produce broader, if not systemic, diffusion of signals. However, it is fairly well established that these defense mechanisms function in a dynamic, rather anticipatory, manner and not as simple on-off switches activated on need basis.

The inherent dynamic regulation of the defense mechanisms is usually expressed in the form of recurring patterns of activity, most notably—but not limited to—those of approximately 24-h (circadian) period.[38,39] However, although it is well accepted that biological rhythmicity of defense mechanisms is likely an evolutionary trait to prepare the host to predictable environmental changes (*predictive homeostasis*) it is also recognized that this rhythmic dynamic of defense mechanisms improves the host response to unpredictable changes (*reactive homeostasis*).[40] Furthermore, evidence, experimental and theoretical, has indicated that oscillatory dynamics of defense mediators enhance efficiency, specificity and reactivity of the host.[41–45] Therefore, the concept of health reflects the dynamic interactions of complex innate defense mechanisms which are engaged, altered or emerging as a result of a drug.

Recent evidence emerges which clearly implicates broader mechanisms, likely independent of obvious low-level targets and instigators of the disease, as modulators of the systemic response and therefore affecting outcome. These include, but clearly are not limited to: physiological stress and disease,[46,47] social/psychological stress and glucocorticoid resistance.[48,49] The study reported in Ref 50 is particularly interesting in that respect since it demonstrated that burn wound healing effects pursuant drug administration were equivalent to those induced via environmental enrichment, likely mediated via central mechanisms (CNS) demonstrating that targeting of underlying enablers (such as stress component) non-pharmacologically has, potentially, a major impact. In that respect latest evidence offers fascinating opportunities: engagement of peripheral clocks, a means to explore the circadian–immune interactions, improves symptoms in a model of Huntington disease[51]; tumor growth is inhibited by rhythmic metabolic cues[52]; resetting peripheral clocks diminished implications of high-fat diet. Aside from the interest in the circadian modulation of host response, what is important to emphasize in the context of QSP models, is that engagement (positive) of peripheral defense mechanisms induced improved host response. It is important to clarify that this engagement is not along the lines of chronotherapeutic interventions which also focus on drug delivery, metabolism, disposition, and toxicity,[53] rather the reflect the engagement of the broader defense machinery which indirectly affects the host's ability to mount an improved response. The question therefore, from a QSP point of view, is whether drugs interfere (how and to what extent) with such mechanisms and whether concurrent activation would improve (or better target) therapeutics. Clearly the aforementioned refocus again the discussion around the concept of *context*. Namely, the drug functions in a context which is defined by the disease and the indirect defense machinery. In a CoES analysis framework it has been recognized that neglecting context is often a critical limitation.[4]

Therefore an improved understanding of what constitutes health and how the mechanisms maintaining heath could be integrated within QSP models is not a theoretical exercise but would shed light into the ways innate, systemic defense mechanisms (1) participate in the manifestation of a disease; (2) contribute to the causes of the disease; (3) interact with and are affected by the localized action of a drug; (4) contribute to positive and negative direct/side effects of the drug; and (5) engage and activate systemic responses which could further suppress, induce or enhance disease symptoms. Therefore, *the key question is how to place the low-level pharmacological targets in their systemic context*. We will revisit this question shortly in discussing the *allostatic* context of QSP.

Disease Progression Models: Engaging and Interacting with Innate Defense Mechanisms

A disease can be defined as any pathological condition affecting the organism whereas a drug is a substance which aims at impacting the organism in ways that ameliorate the implications of the condition. However, it is well known that diseases interfere with the basic functional characteristics of drugs.[54–56] Therefore, coupling within a QSP disease progression model alongside PK/PD will likely open up avenues for improved understanding of broader implications and will likely play a key role in chronic diseases,[57,58] particularly in the context of developing tolerance to treatments.[59] However, the key issue that was raised in the previous section remains: disease models integrated with pharmacokinetic/pharmacodynamics (PK/PD) models often center on the mode of action of the drug and do not significantly engage peripheral defense pathways. Engagement of such mechanisms generates fascinating questions once we realize that it is not simply a question of activating a mechanism but rather a question of properly engaging their innate dynamics.

Sex-Dependence of QSP Models

Intrinsic defense mechanisms play central role in considering a critical aspect of the immune host response: dependence on sex. For completeness we note that sex

is defined as the *genetic, biological and physiological characteristics and processes that generally distinguish males and females*. The notable differences in response to treatment and disease type and severity have prompted the NIH to lunch a initiative on Studying *Sex to Strengthen Science* (S4, http://orwh.od.nih.gov/sexinscience/overview/index.asp). Significant sex-dependent differences are known in the context of immune response,[60–63] PKPD,[64] in basic housekeeping functions and life cycles[65–67]; disease predisposition and outcome[68]; and tissue-specific metabolizing enzymes and receptors[69,70]; while the potential role of intrinsic (circadian) rhythms has been implicated.[71] Therefore, the recent refocusing on the role of sex in disease will have to be extended to QSP as it critically affects the underlying implications of innate defense mechanisms as well as the interactions between the host and the drug.

QSP: NEED FOR AN ALLOSTATIC PERSPECTIVE?

The idea that a broader picture, i.e., one which considers the host and goes beyond the local site of action of a drug, was formalized through the introduction of the concept of *allostasis* and *allostatic load*[72,73] suggesting the role of the living organism is to improve higher-level functions aiming at restoring *predictive fluctuations* and broader defense mechanisms. The model departs from a more standard definition invoking homeostasis in that it argues that regulation of life is based on the ability of the host to anticipate needs and constantly adjusts defenses to maximize efficiency. As a result, the allostatic view argues that the brain coordinates both low-level peripheral mechanisms but also higher level behaviors. The concept of allostasis enabled us to realize that pharmacologic restoration of low-level parameter values to 'appropriate' levels can potentially have dire implications: (1) clamping physiological parameters makes them insensitive to future needs; (2) suppressed signals induce compensatory actions to contribute to deficient responses; and (3) the network structure of the living host will induce lateral changes due to blocking specific low-level mechanisms. Underlying these effects, is the fact that pharmacological treatment of low-level targets may preclude, prevent or hamper the engagement of broader mechanisms (at the systemic level) whose disruption accompanies the disease, or act as predisposition factors.[74] Unexpected results, such placebo effect can likely be explained by recognizing the beneficial effects of activating peripheral (higher-level and non-specific) defense mechanisms.[73] A number of fascinating finding indicate that non-targeted, systemic interventions, induce drug-like behaviors such as nest-making replicating the effects of oxycontin in a burn wound healing model[50]; desynchronization produced by meal timing during the rest period slowed down tumor progression[75]; temporally scheduled feeding during the rest period reverses some of the liver-specific metabolic abnormalities in a mouse model of *Huntington's* disease[51]; Yoga as complementary pulmonary tuberculosis therapy[76] and driver of ANS-related effects in epilepsy, depression and PTSD[77]; biofeedback modulation of hear rate variability modulates autonomic effects in inflammation[78]; Fear of terror contributes to heart rate increases, inflammation and affects cholinergic control[79] to name a few. The insightful paper by Joyner and Pedersen has in fact further argued using interesting population data that broader factors such as culture, environment, social class, education, and life-style choices (diet and exercise) greatly influence health[80] rendering factors modulated by drugs less sensitive and reactive.

In light of the discussion above we would raise the possibility of adopting an allostatic approach to QSP by acknowledging that drugs impact a broader network of peripheral, and indirect, mechanisms. The concept of allostasis and the likelihood of extending/incorporating such concepts within a QSP framework becomes particularly pertinent as it is increasingly been speculated that a number of pathophysiologies are likely the result of extended, low grade stress over-activity (*allostatic load*) and the physiologic 'price' the host needs to pay to adapt to such long term stressful conditions.[81] Thus pathologies need not have originated at the speculated site of action of a drug molecule but may have resulted from loss of equilibrium among competing trade-offs.

Interestingly it should be pointed out that the integrated, systems-based, approaches would be better suited for confronting disease challenges of the future. It has already been that diseases such as Alzheimer's and cancer have strong systemic components be either predisposing factor or contributing to the development of the disease.[82–85] Needless to point out that the systemic nature of cancer is not a recent realization,[86] however, we may now have the opportunity to materialize such ideas for the benefit of drug discovery, disease treatment and improvement of health, by understanding the systemic aspect of the response mechanisms, their interactions with low-level targets and their reciprocal engagement and activation. Finally, in Ref 87 we argued in support of the health-promoting roles of regulating (i.e., restoring) circadian rhythms, thus suppressing harmful effects of circadian dysregulation as a systemic means of enhancing immune defenses.

CONCLUSIONS

Complex and integrative modeling approaches have greatly assisted in the identification and evaluation of drug targets by computationally enabling systems pharmacology.[88,89] As our ability to collect, annotate, and mine high-throughput, genome-wide data is expected to continuously increase, advanced statistical, and data analyses methodologies as also expected to improve our capabilities within a QSP framework.[90] It has been extensively argue that QSP has enabled the proper integration of model-driven decision across the entire supply chain of drug discovery.[91,92] The present opinion paper, however, addresses a different perspective. Drawing from analogies to CoES, we argue that a likely approach for the future development of QSP should begin to place low-level, molecular targets within the broader context of systemic defense mechanisms as we move toward the development of response models for complex biological systems. We have argued that low-level drug targets reside in the context of a nested hierarchy of horizontally and vertically integrated components all of which *in tandem* contribute to the well-being of the host. As a result, it is the concerted effort of both low-level and systemic mechanisms that drive the host response to disease and treatment. The concepts, we feel, will become more important as we move toward more complex diseases as well as we attempt to engage the host in a holistic manner, as opposed to targeting individually likely instigating events. Augmenting the scope of such models would necessitate the seamless integration of larger teams and would require that we engage systems approaches at their conceptual level and not just as means of addressing specific, well defined computational questions.

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