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Quantitative Systems Pharmacology: A Framework for Context

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Abstract

Quantitative Systems Pharmacology (QSP) is receiving increased attention. As the momentum builds and the expectations grow it is important to (re)assess and formalize the basic concepts and approaches. In this short review, I argue that QSP, in addition to enabling the rational integration of data and development of complex models, maybe more importantly, provides the foundations for developing an integrated framework for the assessment of drugs and their impact on disease within a broader context expanding the envelope to account in great detail for physiology, environment and prior history. I articulate some of the critical enablers, major obstacles and exciting opportunities manifesting themselves along the way. Charting such overarching themes will enable practitioners to identify major and defining factors as the field progressively moves towards personalized and precision health care delivery.

Keywords

quantitative systems pharmacology; inflammation; chronic disease; PKPD

Introduction

In recent year there have been numerous reports discussing opportunities, progress and successes of Quantitative Systems Pharmacology (Bai 2013; Leil, Bertz 2014; Sorger et al. 2011), referred to as QSP onwards. Multiple definitions have been provided in the literature and, as such, I will refrain from attempting yet another description of the term. It is by now, most likely, evident that the term QSP encompasses approaches related to the integrated analysis of complex (and simple) models in an attempt to rationalize drug action. The implications are expected to be many fold including, but 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 modeling approaches most often do not address discovery needs and most likely are developed during the later pre-clinical stages with the expectation to provide critical insight during the clinical stages of drug development (Kimko et al. 2011; Kimko, Duffull 2003; Ermakov et al. 2014).

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

While mathematical and computer modeling is at the core of QSP it is most likely not appropriate to focus exclusively on those aspects alone when talking about QSP. After all, in some shape or form, modeling in pharmacology has been around for decades, likely as far back as the 60's with *Gerhard Levy*'s pioneering work on the kinetics of pharmacologic effects (Levy 1964, 1966). Models have since increased substantially in complexity not only because of our increased fundamental understanding of biology, pharmacology and physiology and our improved ability to probe physiological systems and accumulate high-quality and high-dimension data, but also because of computational sciences and systems approaches that were formally adopted by traditional pharmacokineticists, thus rendering the process of developing and using complex models tractable, and the interpretation of the results more meaningful.

However, it would likely be rather shortsighted to limit the potential contributions of QSP strictly to the development of, however more complex, computational models. In fact, the purpose of this review is to argue that QSP's main contribution is not whether it could deliver “more of the same”, i.e, more complex models, but rather the fact that QSP can act as a framework within which we can begin to phrase a suite of questions of increasing complexity. QSP as a framework will enable us to place drugs and their pharmacologic actions within their proper broader context, which we realize extends beyond the site of action. This, I subsequently argue, will become a major and defining factor as we progressively move towards personalized and precision health care delivery.

Evolving role of modeling in pharmacology

Without delving into much technical detail, I will simply state that the term modeling, as used in the context of this paper, denotes the quantitative description of the dynamics of a system of interest using mathematical and computational approaches. I make use of the terms “mathematical” and “computational” broad at this point so as not to limit the discussion in any way in that respect. In that sense, mathematical models have been introduced in pharmacology over half a century ago, likely originating fromith the pioneering work of Gerhard Levy, recently published in a summary (Fung, Jusko 2015). From that point on, pharmacokinetic and pharmacodynamics models have been used to assess how much drug is available following a specific route of administration, whether it hits the target, whether it performs the actions it was designed to perform and, finally and more importantly, whether it generates the expected outcome (Wright et al. 2011). Along with these questions, it also becomes important to assess the extent to which the drug would also induce secondary, direct, indirect, synergistic or antagonistic effects – desirable or not. The value of modeling was realized early on as, likely, a critical enabler to assess critical questions such as identifying dose limits, dose effects and, of course, extrapolation (animals to humans, adult to pediatrics, etc) (Csajka, Verotta 2006; Maharaj, Edginton 2014).

The models have therefore, historically, evolved to describe drug levels in circulation, connect drug levels directly to outcome using phenomenological expressions, connect drug levels to cellular functions, and drug levels to outcome. Developments in pharmacology and the development of approaches integrating physiology with pharmacology with models evolving from simple pharmacokinetics, to compartment to comprehensive model

accounting for physiologic considerations(Aarons 2005) led to development of more complete models better accounting for drug liberation, absorption, disposition, metabolism and excretion (LADME) to describe drug release from formulation, pharmacokinetics, as well as signaling and regulation at the level of cell to capture the pharmacodynamics (Bouzom et al. 2012; Rein et al. 2013; Smith 2013). The incorporation of parameters reflecting physiology was a critical step in addressing the fundamental issue of extrapolating animal data to humans (Mager, Jusko 2008; Sager et al. 2015). The physiological basis of PBPK models easily allows to extend these to include PD considerations beyond simple receptor binding (Schaller et al. 2013).

The advances in systems biology and pharmacology, both conceptual in terms of network analysis as well as experimental in terms of readily generating *–omics* information, enabled researchers to increase the complexity of the analysis by simultaneously accounting for multiple complimentary, synergistic and antagonistic pathways, mostly intracellularly (Berger, Iyengar 2009; Boran, Iyengar 2010; Wist et al. 2009). As such, we recognized the importance of considering drug targets as part of a network of interacting elements (genes, proteins or metabolites) and recognized that information is not propagated in a strictly linear manner, but in rather convoluted ways as these emerge through complex networks (van der Graaf, Benson 2011).

Systems pharmacology approaches enabled us to increase the complexity of our models, by expanding the pathways and modes of action, accounting for multiple simultaneous interactions (Jusko 2013). Continued advances in high throughput *–omics* technologies facilitated the collection of information at the genomic, transcriptomic, metabolomic and proteomic levels, as well as regulatory and epigenomic levels. This wealth of information enabled us to further increase the complexity of our models by expanding the chain of events activated, or suppressed, as a result of a drug's action (Kamisoglu et al. 2015). High-throughput analysis enabled us to decipher differences related to, for example, dosing (Nguyen et al. 2010) or tissue-dependencies (Nguyen et al. 2014).

In the sections that follow, I wish to address broader issues related to challenges and opportunities in of QSP, and its potential to define the future.

QSP: The framework

QSP, as a framework, has emerged and morphed into an integrated and integrative approach, which relies heavily on exploring systems analysis and quantitative modeling approaches and methodologies for rationalizing the wealth of information generated by *in vivo* and *in vitro* systems and developing quantitative predictions. QSP capitalized, explored, and in some cases introduced novel computational methods formalizing the analysis and modeling approaches. The versatility of the available methods was critical in order to appreciate that different computational approaches are better suited for different types of pharmacological systems and questions. The phenomenal advances in computational and data sciences provide flexible and user-friendly computational environments making the use of sophisticated tools easily, and seamlessly adopted by a wide range of practitioners, addressing a multitude of problems across a broad spectrum of applications from disease

models to drug function, to the implications of drug formulation (Allan et al. 2008; Hamberg et al. 2015; Koch, Schropp 2013; Lunn et al. 2009; Wright, Duffull 2011; Verotta 2010; Sauro et al. 2003; Schmidt et al. 2013; Shoda et al. 2010; Einolf 2007; Rullmann et al. 2005; Kostewicz et al. 2014; Shono et al. 2010; Chetty et al. 2014; Mathias, Crison 2012).

From a computational point of view parameter estimation and model selection has, likely, been at the top of the list of critical challenges. However, the community has embraced systems approaches and has evolved them to a high level of standards (Ashyraliyev et al. 2009; Baker et al. 2015; Liepe et al. 2014).

It could be argued that a most critical roadblock towards the systematic development of QSP models is that apparent lack of standardization of models, and model components (Ghosh et al. 2013). This is a fundamental issue which, although receiving increased attention, underlies essential difficulties. In more mature science and engineering fields, so-called "modular process simulators" enable the automated development of complex structures in the form of networked elements, each characterized by its own dynamics. However, each component and element of the network is well annotated and described by appropriate constitutive equations. Each element of the network can be represented as an appropriate object in modular form (Chen, Adomaitis 2006), whereas the equation-oriented formalism enables the exact representation of each module by a set of detailed mathematical equations (Pattison, Baldea 2014). Assembling of individual models can easily be automated in a "drag-and-drop" manner and complex models can therefore be generated and analyzed in great detail. However, the so-called "*flow sheet optimization*" in the chemical process industries is an activity which has been in development for decades (Gaines, Gaddy 1976) and, furthermore, since it focuses on engineered constructs, the details of the dynamics of each constitutive module and element are well understood. As a result, modules are interchangeable and complex networks can be built by appropriately linking said modules in ways dictated by specific applications, regardless of the complexity or the module or the network.

However, QSP models/modules do not have a quality yet comparable to their engineering counterparts. In QSP the constitutive modules are often the purpose of the analysis, reflective of the fundamental differences between Complex Engineered and Complex Biological Systems (Androulakis 2015). Unlike engineered systems, in complex biological (and pharmacological) systems, the constitutive elements of the network modules need to be identified through perturbations, which will uncover different aspect of their dynamics, which need to be quantified depending on the perturbation. At a higher level, indirect response modeling replicates this formalism, in the sense that the certain structures (such as indirect activation or inhibition of production/synthesis of a mediator, receptor mediated processes, transit compartments to name a few) can be made interchangeable with appropriately adjusted parameters (Krzyzanski, Jusko 1998; Hazra et al. 2006; Yao et al. 2006). However, the question is whether the mathematical description of a signaling pathway targeted by a drug, for example, can be easily rendered ubiquitous and interchangeable as the analysis moves from one drug molecule, or disease, to another. Consider for example a critical, and rather pervasive, signaling pathway such as Nfκ B. Even though it represents a relatively common player in model development, numerous alternative

representations have emerged (Cheong et al. 2008; Williams et al. 2014). These reflect not only differences in the level of complexity that is required, or desired, but also differences in the way the elements of the signaling pathway present themselves, depending on the perturbation employed to reveal the wiring of the pathway (Androulakis et al. 2013; Kyrmizi et al. 2006; Nguyen et al. 2011; Nguyen et al. 2014).

Interestingly, the practitioners have expressed the need for standards as well as the concerns outlined above. An insightful discussion based on practitioners' input was presented in (Klipp et al. 2007) where the challenges were nicely articulated: "[…] *80% of the respondents consider the creation of* [modeling] standards necessary or desirable: standards are expected to improve model reuse, expandability and integration, and allow for more productive collaboration […] standards improve communication between software tools, free exchange of information and comparison between different studies […] reimplementation of models becomes easier or dispensable, which reduces the duplication of work and the possibility of implementation errors. Theoreticians and software developers need benchmark data as experimentally verified gold standards to apply and to improve their methods […] respondents also expressed the concern that standards should be flexible, not become too restrictive and not prevent alternatives or new developments. Those respondents who were against standards argued that biology is too complex to be standardized and obeying standards may cause practical difficulties." However, a number of efforts are currently under way aiming at developing model standardization frameworks (Drager, Palsson 2014; Friedrich 2016; Hucka et al. 2003; Hucka et al. 2004; Klipp et al. 2007; Kohl 2011; Shapiro et al. 2004; Ermakov et al. 2014).

QSP: The context

Modeling and computation in the context of upgrading the information content of biological information defined, in late '70s, what eventually came to be known as "bioinformatics", namely the collective efforts aiming at studying the "informatics processes of biotic systems" (Hogeweg 2011). The power of the collective methods that have since emerged, and now encompass not only bioinformatics but also systems biology approaches, is that it did not simply enable the faster, and more accurate, interpretation of complex data, i.e., defining the framework, but really enabled us to approach biological questions (or drug actions) from a different, more integrative, perspective, i.e., defining the context (Kidd et al. 2015). As such, I wish to argue that QSP offers such an opportunity and needs to be evaluated and developed along the same lines, in other words the framework that enables us to place drug action in its broader context. In fact, this is not a methodology issue (see "framework" in preceding section) but it is rather driven by the critical health challenges of the future where the systems (host) view will be required to play a major role.

Despite the promise and potential of systems biology, "friendly", yet constructive, criticism has indicated that for it to progress to the next level, physiology (i.e., the broader network of defense mechanisms) and environment (socio-economic, life style), in other words the system, need to become part of the analysis (Joyner, Pedersen 2011). The idea of extending the operating envelope beyond the cell, which by and large has been the focus of most

systems biology/pharmacology models focusing on complex signaling pathways and/or modes of action has gained momentum.

For example, it has been increasingly recognized that large portion of the health challenges of the 21st century will be non-communicable conditions with one common, underlying, characteristic: persistent, low-grade, systemic inflammation, also known as *meta-inflammation* (Egger, Dixon 2014; Libby 2007; Egger 2012; Bauer et al. 2014; Tabas, Glass 2013). However, inflammation and inflammation related diseases have been difficult to control and regulate due to complexity and intertwined character of the response (Laroux 2004). Inflammation characterizes a reaction critical for survival which evolved to balance redundancy, compensation and necessity (Tabas, Glass 2013). The balancing of seemingly conflicting objectives is really at the core of what characterizes biological complexity (Csete, Doyle 2002). Because the mechanisms orchestrating the inflammatory response are redundant, targeting one pathway may, and most likely will, not be enough; inhibiting one mechanism may, and most likely will, induce activation of alternatives to compensate; and finally inflammation is necessary for defense and survival, therefore the risk/benefit balance may, and most likely will, not be easily achieved. Obesity-associated inflammation, for example, appears to help to maintain insulin sensitivity, therefore it has also been postulated that anti-inflammatory therapies have failed in the treatment of insulin resistance (Gao, Ye 2012) since inflammation promotes energy expenditure in a feedback manner to counteract an energy surplus to regulate energy balance (Ye, Keller 2010) whereas in peripheral tissues induces fat mobilization and oxidation to promote energy expenditure. In fact this broader (dys)regulation of energy in the context of chronic inflammatory diseases (such as rheumatoid arthritis) has been beautifully articulated by Straub in a series of papers exploring the systemic implications of chronic inflammation (Straub 2011; Spies et al. 2012; Straub et al. 2010; Straub 2012; Straub, Besedovsky 2003).

Considering the major challenges of the future, it has already been recognized that diseases such as Alzeihmer's and cancer have strong systemic components acting as either pre-disposing factor or contributing to the development of the disease (Morris et al. 2014; Krstic, Knuesel 2013; Krstic et al. 2012; Redig, McAllister 2013). The systemic nature of cancer is not a recent realization (Meyer 1931), 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.

Although the aforementioned analyses point largely to disease etiology, a number of recent studies have also identified the potential of “non-obvious (non-targeted) interventions”. The “systemic” view is not simply an abstraction to enable the discussion, but it is rather a major factor in disease etiology and treatment justifying the role and potential of said interventions. Here is a short list of characteristic examples where non-specific “stressors” and “interventions” lead to disease and enable treatment:

- **social interactions** when absent can induce chronic-inflammation phenotype, leading to related diseases and all-causes mortality (Cole et al. 2015); while when present, induce enhanced host's response (wound

healing) and in fact mimic a drug's effect (Vitalo et al. 2009). What is particularly intriguing, besides the fact that environmental enrichment, or lack of it, can impact specific cellular pathways, is that “mood” modification, either pharmacologically or behaviorally modified (through nest making), has the ability to induce fundamental changes at the cellular level of peripheral tissues given the intimate relations between brain and the immune system (Quan, Banks 2007) – a concept further explored by allostatic approaches (Karatsoreos, McEwen 2011).

- **circadian rhythms** (central and peripheral) coordinate and integrate a number of functional responses and metabolic cues (Asher, Schibler 2011). The links between reprogramming of peripheral circadian clocks and physiological responses (Schibler et al. 2003) were beautifully exemplified in series of experiments which aimed at circadian reprogramming via time restricted feeding (controlling access to food without calorie restriction). It has been shown that timing of access to food, effectively setting metabolic rhythms, impacts tumor growth (Li et al. 2010), reverses the liver-specific abnormalities in a model of Huntington's disease (Maywood et al. 2010), alters high-fat diet metabolism impacting obesity factors (Hatori et al. 2012). On the other end, shift-work, often associated with disrupted feeding patterns, is a known disease pre-disposition factor (Yoon et al. 2012; Barclay et al. 2012). Similarly well-established are the links between sleep disruption and immunity (Besedovsky et al. 2012) whereas the daily (Smolensky et al. 2015) and seasonal patterns of inflammation and chronic inflammatory diseases (Dopico et al. 2015; Iikuni et al. 2007; Kumar et al. 2007) are well established. Well characterized as well are 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.
- voluntary regulation of the autonomic nervous system (ANS) often achieved by means of modulating breathing patterns (biofeedback) has clear impact on the inflammatory response (Lehrer et al. 2010). The links between “relaxation” activities, such as yoga, and impact on ANS-related disease (such as epilepsy, depression, post-traumatic stress disorder) is becoming more clear (Streeter et al. 2012), while ANS-engagement (yoga training) improved response to pharmaceutical treatment in a pulmonary tuberculosis study (Visweswaraiah, Telles 2004). Therefore, a seemingly, non-specific systemic modulation has clearly identifiable impact on cellular, disease-related, pathways affecting outcome.
- **expectation** of a positive outcome was found to induce dopamine release likely impacting manifestation of placebo effect (de la Fuente-Fernandez et al. 2001). Interestingly, genomic studies confirmed genetic pre-disposition of likely activation of up-/down-stream dopamine pathway

which may help predict predisposition to positive response to placebo (Hall et al. 2015). On the other end, expectation of negative outcome was found to be a strong inducer of low-grade, chronic inflammation resulting in heart health decline (von Kanel 2015)

The aforementioned list, certainly partial and incomplete, points to a significant realization: response to treatment and development of disease is the result of the orchestrated coordination, and convolution, of a vertically and horizontally integrated network of pathways and function working *in tandem*. This realization becomes particularly important as we begin to delve deeper into the etiology of chronic disease which is not necessarily the result of a single genetic modification or initiating factor. Thus, this is clearly a major opportunity for QSP to adjust the context of the broader analysis. The implications could be significant not only because the integrated -systemic - approaches will shed light on the pathology, as the result of multiple low-level failures, but will also point to alternative pharmacological interventions supporting peripheral (causative) mechanisms leading to the symptoms and not only treating the symptoms.

QSP: Towards a framework for context

At the core of personalized medicine lies our ability to control the factors influencing disease processes and therapy. Simply put "*steering* [the right] patients to the right drug at the right dose at the right time"(Hamburg, Collins 2010). Key contributors in assessing and predicting drug effects are the drug's properties; the physiological characteristics guiding the processes of liberation, absorption, distribution, metabolism, and excretion (LADME) (Kostewicz et al. 2014) and; the way the drug interacts, affects, and is affected by systemic defense mechanisms maintaining overall health aside from disease state. Among the most critical factors are the patient's sex (male vs. female) and age. Major breakthroughs will result not only from our ability to forecast such physiological implications during the early stages of the development of a drug (Kambayashi et al. 2013) but also how these would interact beyond the local site of action. The consequences are twofold: to streamline the drug development process by increasing the likelihood of success and reducing time to market through optimal design of formulations; and to enable the development of patient-specific formulations increasing the likelihood of treatment success targeting specific patient sub-populations (Dickschen et al. 2014).

Earlier QSP efforts enabled us to extend and expand the concept of context in two ways: extending the "simpler" receptor-ligand effect model toward detailed signaling networks – with the help of pharmacogenomics (Jin et al. 2003; Yao et al. 2008); whereas PBPK enabled us to better understand the mechanisms and processes that enable the drug to reach its target PBPK (Sager et al. 2015; Berlin et al. 2015). Both conceptual approaches have proven extremely successful and systems models are gaining ever increased acceptance, slowly getting to the point where model predictions are emerging in the regulatory arena (Peterson, Riggs 2015).

The multifactorial and complex nature of the disease challenges of the future will require innovative therapeutic paradigms integrating pathology with therapeutic intervention. QSP

can form the foundation of such an approach (Leil, Bertz 2014). I previously argued (Androulakis 2015), and wish to re-emphasize in this review that the integrated approach, allowing us to move beyond the local site of action of a drug, would likely define the way forward for QSP. The concept of allostasis (McEwen 2000; Sterling 2012, 2003) enabled us to realize that pharmacologic restoration of low-level parameter targets, such a cytokine levels, to rather ill defined, “appropriate” levels can potentially have dire implications, since clamping such physiological parameters makes them insensitive to their systemic role. Furthermore, suppressed signals may induce compensatory actions and contribute to deficient responses while the network nature of the defense mechanisms 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) leading to associate comorbidities, or act as predisposition factors (Brame, Singer 2010). As discussed earlier, unexpected results, such as placebo effects, can likely be explained by recognizing the beneficial implications of activating peripheral (higher-level and non-specific) indirect defense mechanisms (Sterling 2003).

Moving forward, QSP can not only provide the framework for model development, but also, more importantly, help us define the context within which a drug is expected to function. Given the health challenges of the future, I expect that a more integrated understanding of disease etiology and drug function would be required to approach the health challenges of the future. I propose therefore, that QSP can help define the context as the intellectual tools needed to advance the field.

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