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Systems pharmacology – Towards the modeling of network interactions

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ABSTRACT

Mechanism-based pharmacokinetic and pharmacodynamics (PKPD) and disease system (DS) models have been introduced in drug discovery and development research, to predict in a quantitative manner the effect of drug treatment in vivo in health and disease. This requires consideration of several fundamental properties of biological systems behavior including: hysteresis, non-linearity, variability, interdependency, convergence, resilience, and multi-stationarity.

Classical physiology-based PKPD models consider linear transduction pathways, connecting processes on the causal path between drug administration and effect, as the basis of drug action. Depending on the drug and its biological target, such models may contain expressions to characterize i) the disposition and the target site distribution kinetics of the drug under investigation, ii) the kinetics of target binding and activation and iii) the kinetics of transduction. When connected to physiology-based DS models, PKPD models can characterize the effect on disease progression in a mechanistic manner. These models have been found useful to characterize hysteresis and non-linearity, yet they fail to explain the effects of the other fundamental properties of biological systems behavior.

Recently systems pharmacology has been introduced as novel approach to predict in vivo drug effects, in which biological networks rather than single transduction pathways are considered as the basis of drug action and disease progression. These models contain expressions to characterize the functional interactions within a biological network. Such interactions are relevant when drugs act at multiple targets in the network or when homeostatic feedback mechanisms are operative. As a result systems pharmacology models are particularly useful to describe complex patterns of drug action (i.e. synergy, oscillatory behavior) and disease progression (i.e. episodic disorders).

In this contribution it is shown how physiology-based PKPD and disease models can be extended to account for internal systems interactions. It is demonstrated how SP models can be used to predict the effects of multi-target interactions and of homeostatic feedback on the pharmacological response. In addition it is shown how DS models may be used to distinguish symptomatic from disease modifying effects and to predict the long term effects on disease progression, from short term biomarker responses. It is concluded that incorporation of expressions to describe the interactions in biological network analysis opens new avenues to the understanding of the effects of drug treatment on the fundamental aspects of biological systems behavior.

1. Networks as the basis for the prediction of drug action in complex biological systems: towards systems pharmacology

Modern drug discovery and development has been largely inspired by insights in pharmacological mechanisms and based on pharmacological concepts. Classical pharmacology considers a single transduction pathway, connecting the processes on the causal path between drug administration and response, as the basis of drug action. Pathway analysis has yielded many useful drugs which are often taken chronically to control symptoms of a disease. In many instances however these drugs do not modify the disease process. The focus on pharmacology on a single transduction pathway, as the basis of drug action is also reflected in the structure of physiology-based pharmacokinetic-pharmacodynamic (PB-PKPD) models, which are increasingly applied for prediction of drug effects in drug discovery and development (Danhof et al., 2007, 2008).

In recent years much progress has been made in the emerging field of systems biology. A system is defined as an entity which maintains its existence through the interactions between its parts (von Bertalanffy, 1968). In systems biology, a system is commonly described as a network of nodes (functional elements, vertixes) connected by "edges" describing the functional interactions. To date, research in systems biology has been mainly focusing on the structure (i.e. molecular level of organization) of the biological network, without consideration of the nature and the magnitude of the interactions between the nodes, and often also

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without incorporation of temporal or spatial information. In many cases this has led to doubtful translational or predictive value of systems biology towards higher levels of biological organization and dynamics or clinical endpoints, albeit that there are exceptions (Beard et al., 2002). Ultimately, for the prediction of drug effects in vivo, biological phenomena need to be described as dynamic processes across widely different time scales (Kohl et al., 2010).

In systems biology networks can sometimes be relatively simple, yet they can also become quite complex. This can turn the analysis of a network into a major challenge. Therefore, in practice a combination of reductionist and integrationist approaches is applied to understand biological systems behavior, crossing spatial scales of structural and functional integration. Meanwhile, steps have been taken towards the incorporation of network analysis in mechanism-based PKPD modeling. This concerns in particular the analysis of drug-drug interactions and of homeostatic feedback mechanisms as determinants of the effect (Fang et al., 2011; Lon et al., 2012; Ploeger et al., 2009; Stevens et al., 2012). The importance of the networks concept in pharmacology however, reaches much further. In conceptual terms a network structure may explain a number of the fundamental properties of biological systems behavior: i) hysteresis, ii) non-linearity, iii) variability, iv) interdependency, v) convergence, vi) resilience and vii) multi-stationarity (Table 1). Meanwhile, classical pharmacology concepts based on single transduction pathways have been found useful to understand the hysteresis and the non-linearity of biological system behavior and drug action, but have failed to explain the other aspects. I propose that incorporation of concepts from network analysis can be useful to describe complex patterns of pharmacodynamic responses (i.e. oscillatory behavior). In addition network analysis is particularly useful for the analysis of the dynamics of disease, where patterns of disease progression can be complex (Table 2).

1.1. Fundamental aspects of complex biological systems behavior

The prediction of drug effect on biological system behavior constitutes a major challenge, given the complexity of the underlying systems and the multitude of system properties that need to be accounted for. In principle, two types of dynamical systems can be distinguished: "non-adaptive" versus "adaptive" systems. Here "non-adaptive" systems are stable systems in the sense that their functional properties remain constant over time. In these models time dependencies are described on the basis of changes in the values of the model parameters. "Non-adaptive" models are increasingly used to account for the effects of e.g. developmental changes or disease progression. In contrast, in "adaptive" systems the functional behavior may change, in the sense that new, previously absent properties emerge. Pertinent properties of the functioning of "adaptive" systems include: emergence, self-organization, degeneracy. "Adaptive" models are for example needed to describe the functioning of the immune system (Germain et al., 2011; Subramanian et al., 2015). In this contribution I will restrict the discussion to the fundamental properties and the modeling of "non-adaptive" complex biological systems.

Table 1
Fundamental properties of therapeutic interventions on biological systems behavior.

Feature	Description
Non-linearity	Non-linear relations between dose, exposure and response
Individuality	Effectiveness limited to patients with a distinct molecular mechanism of the disease
Variability	Variation in concentration and/or effect between and within individuals
Interdependency	A compound that does not have an effect on its own modifies the response to a second compound (e.g. allosteric modulation)
Convergence	Multiple molecular defects cause diseases with similar or identical clinical features
Resilience	The plasticity of biological systems with regard to disease progression and drug effects
Multi-stationarity	A biological system may exist in multiple, stable conditions

Table 2
Examples of diseases with their progression pattern.

Pattern	Examples
Stationary	Hormone insufficiency
Linear	Neurodegenerative disorders: Alzheimer's disease, Parkinson's disease
Asymptotic	Neurodegenerative disorders
Exponential	Infectious disease, cancer
Burnt out	Common cold
Episodic	Neurological disorders (epilepsy, migraine, multiple sclerosis) Psychiatric disorders (bipolar disease)

Hysteresis in the time course of the pharmacological effect relative to the plasma concentration is common. In mechanistic terms hysteresis can be explained by slow target site distribution, slow target association/dissociation kinetics and slow transduction mechanisms. For each of these mechanisms relevant PKPD modeling concepts have been developed (Danhof et al., 2007, 2008).

The non-linearity of pharmacodynamics is also well appreciated. This is partly caused by non-linearities at the level of the pharmacokinetics (i.e. the absorption, distribution and elimination). The main causes of non-linearity, however, are the intrinsic non-linearities at the level of the pharmacodynamics (i.e. the target binding/activation, transduction and homeostatic feedback mechanisms). PB-PKPD modeling concepts have been successfully developed to characterize these non-linearities in a strictly quantitative manner (Danhof, 2015; Danhof et al., 2007, 2008). A pertinent feature of these models is that they are based on physiological reality, with a strict distinction between drug-specific and system-specific parameters. It is believed that in particular the distinction between drug- and system-specific parameters constitutes a scientific basis for the extrapolation between different biological systems (i.e. in vitro–in vivo correlations, scaling between tissues, species etc.). The utility of PB-PKPD models for these extrapolations has been illustrated for adenosine receptor agonists, mu opioid receptor agonists, and serotonin 5-HT1a receptor agonists (Garrido et al., 2000; Van der Graaf et al., 1999; Yassen et al., 2008; Zuideveld et al., 2004). PB-PKPD models constitute a scientific basis for the development of increasingly complex systems pharmacology models.

In addition to non-linearity, variability in drug effect is well appreciated. This variability results from the complex interactions of genetic factors, environmental factors, disease, drug treatment and adjunctive therapy with the biological system (Fig. 1). At present, advanced statistical techniques based on non-linear mixed effect modeling (NONMEM) are widely applied to describe intra- and inter-individual variation. This enables the identification of co-variates which explain part of the observed inter-individual variation and which can serve as the basis for dose adjustment in clinical practice (Admiraal et al., 2014; Sime et al., 2015). Population approaches typically express variation in normal distributions. While the prediction of such variation may be relatively straightforward, the prediction of outliers constitutes the real challenge. The identification of outliers and unexpected events may require the application of even further advanced statistical approaches, such as by including randomness in parameter values or by using stochastic rather than deterministic modeling. For reasons of parsimony these advanced statistical techniques are usually applied in combination with relatively simple structural pharmacokinetic and/or pharmacodynamic models (e.g. compartmental models). As was outlined above, a model structure based on physiological reality, combined with a strict distinction between drug-specific and system-specific properties, constitutes a scientific basis for extrapolation and prediction of the variation outside the range that has actually been studied. There is clearly a need for approaches in which non-linear mixed effects modeling is combined with more mechanistic physiology-based pharmacokinetic and pharmacodynamic models. Here the challenge is to design semi-physiological models with sufficient mechanistic detail to allow meaningful extrapolation, while at the same time being sufficiently simple to allow estimation of the parameter values