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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

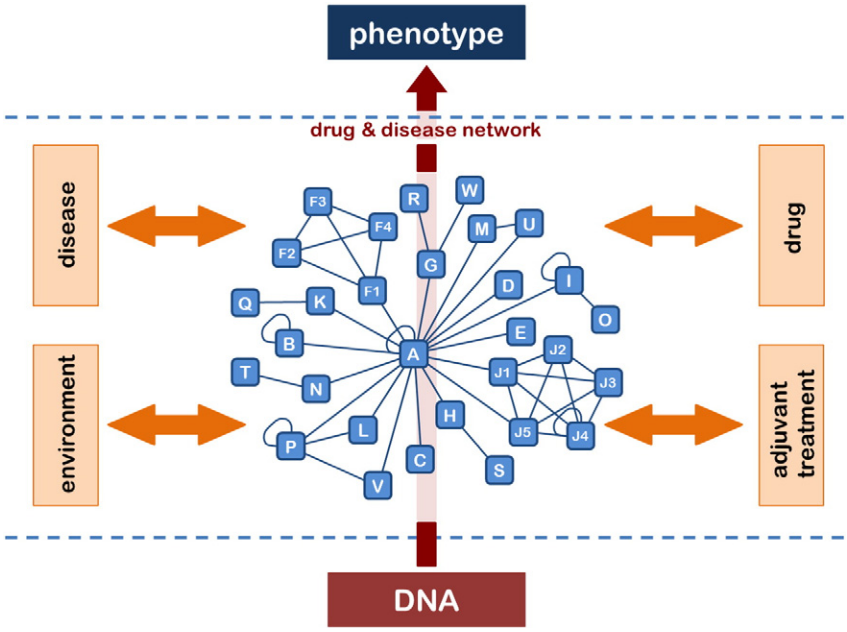

Fig. 1. Biological networks as the basis for the prediction of drug effects in complex biological systems. In this example, drug treatment, disease, environmental influences and adjuvant treatment all influence the biological network.
Modified from Kohl et al. (2010).

(De Cock et al., 2014; Strougo et al., 2011). In such a model structure, variability could be predicted by including expressions characterizing the interactions with specific environmental factors in a mechanistic manner.

Interdependency of compounds is the property that a compound that has no effect on its own, modifies the response to a second compound. This property is illustrated in the allosteric pharmacodynamic interactions and will be discussed in Section 3.1.

Convergence or redundancy is the phenomenon that multiple, distinctly different molecular defects, may cause a single disease with similar if not identical clinical features. In mechanistic terms convergence can be explained by the existence of multiple parallel pathways that converge into a single node of a biological network. This also explains individuality in the response to drug treatment. In a personalized treatment paradigm, information on the molecular mechanism of a disease is used in the selection of the drug for an individual patient. A well-known example is the genetic testing in the selection of drugs for the treatment of breast cancer (Ballinger et al., 2015; Paoletti and Hayes, 2014).

Resilience is the plasticity (i.e. relative insensitivity) of the functioning of biological systems to disease progression and to drug treatment effects. Prime examples of resilience are neurodegenerative disorders, where clinical symptoms only appear after an extensive loss of functional neurons. The lack of efficacy as a main cause of attrition in drug development (Schafer and Kolkhof, 2008) could be a reflection of the resilience of biological systems to drug effects. In mechanistic terms resilience can also be explained by multiple parallel pathways which converge in a single node. The implication is that interactions at multiple targets in a biological network may be required to obtain a robust treatment effect. The current practice of using rational drug combinations in the treatment of infectious diseases (e.g. HIV) is an example of this.

Multi-stationarity refers to the phenomenon that biological systems can exist in multiple, more or less stable states. The simplest way in which this can be the case is the distinction between the healthy and the disease state. A well-known example of multi-stationarity is paroxysmal supraventricular tachycardia, with atrial fibrillation and sinus rhythm as the two distinctly different states of the same system. For a variety of diseases multiple states may exist. Prime examples are neurological disorders such as migraine and epilepsy (Dahlem et al., 2015; Margineanu, 2014), and psychiatric disorders such as depression (Singh and Gotlib, 2014; Voytek and Knight, 2015). Hidden Markov models have been introduced to describe the transitions between different states in these disorders (Le Cam et al., 2013; Maas et al., 2006). However, hidden Markov models yield at best empiric descriptions of system behavior. In other areas of research the strength of rule-based modeling is clearly evident; for example in artificial intelligent systems that are based on empirical/historical data. Likewise, multi-stationarity is also a characteristic of chaos theory. These approaches could be readily utilized in systems pharmacological problems (Vicini, 2010). There is a clear need for more mechanistic dynamical systems analysis models for the prediction of multi-stationarity of biological systems.

The list of fundamental properties of biological system behavior in this paragraph is not complete. Additional fundamental properties of biological systems behavior are: emergence, robustness, self-organization, degeneracy (Holland, 1992, 2006; Whitacre, 2010). These properties are especially observed in adaptive dynamical systems, such as the immune system. Different approaches in mathematical modeling may be applied to understand or predict these special features of complex adaptive system behavior, such as rule-based modeling, pattern recognition (neural network, Bayesian, genetic algorithm) and agent-based modeling. In this paper the modeling of network interactions in non-adaptive systems is discussed.

2. The evolution of physiology-based modeling of pharmacokinetics, pharmacodynamics and disease

Pharmacokinetic-pharmacodynamic (PKPD) modeling has long been recognized as a descriptive discipline, obtaining empirical evidence about the time course of the concentration and the effect of a drug in a biological system. By characterizing the processes on the causal path between plasma concentration and effect, PKPD modeling has become more mechanistic (Danhof et al., 2007, 2008). The pertinent processes on the causal path include 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 (Fig. 2). In addition, mechanistic disease system (DS) models can be used to characterize the interaction of drug effect with disease processes (Danhof, 2015; Danhof et al., 2008). As highlighted below, research in

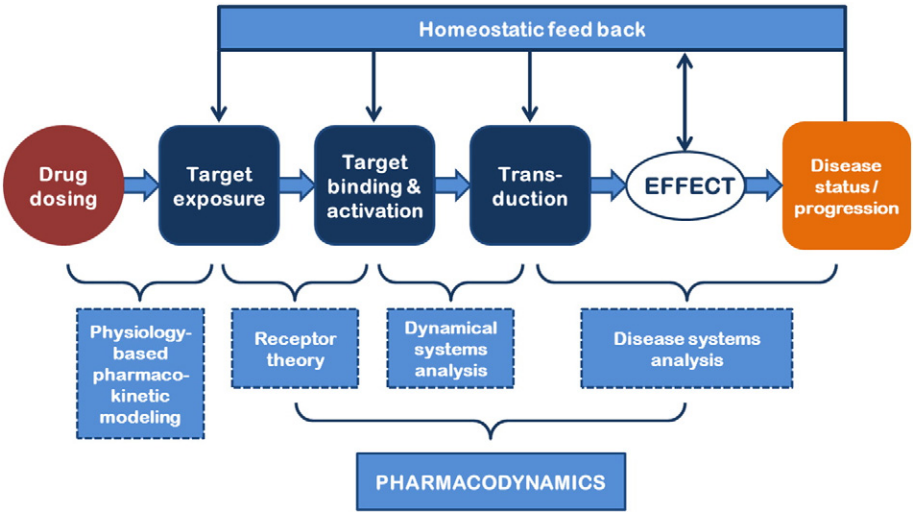

Fig. 2. Schematic representation of physiology-based pharmacodynamic (PB-PD) modeling. PB-PD models connect pharmacokinetics to the drug effects on disease progression, and contain expressions to describe the processes on the causal path between drug administration and effect (target site distribution, target binding and activation, and transduction and homeostatic feedback).
From: Danhof (2015).

the past years has been focused on the development of PB- PKPD modeling to further improve the predictive value of PKPD and DS models.

2.1. Physiology-based pharmacokinetic modeling

Traditionally, the time course of drug concentration in plasma is described by compartmental pharmacokinetic (PK) models. To take hysteresis between pharmacological effect and plasma concentration into account, an effect compartment is often included, which theoretically represents the distribution of the drug to the target site (Sheiner et al., 1979). In combination with non-linear mixed effects modeling for the description of variation in the individual plasma concentration time profiles, compartmental PK models provide a strong statistical framework for the individualization of drug treatment in the target population (Himebauch and Zuppa, 2014; Knibbe et al., 2011). However, compartmental PK modeling is much less useful for extrapolation of pharmacokinetics beyond the physiological ranges that have actually been studied (Strougo et al., 2012). Moreover compartmental modeling relies on steady-state assumptions and can therefore not predict the effect-time-varying changes in enzyme or transporter induction or inhibition nor the distribution kinetics of new drugs (Sager et al., 2015).

In recent years physiology-based pharmacokinetic (PB-PK) modeling is increasingly applied in drug development. PB-PK modeling uses physiologically realistic and species-specific data on tissue structure, volume and composition (Danhof et al., 2008; Jones et al., 2015; Sager et al., 2015). The structural model used for whole body PB-PK modeling is based on the anatomical arrangement of the tissues and organs of the body, linked by perfusing blood (Rowland et al., 2011) (Fig. 3). This structural model, in combination with a parameterization in drug-specific parameters (e.g. affinity to metabolizing enzymes, drug transporters) and biological system-specific parameters (e.g. blood flow, organ and tissue perfusion, expression and functioning of enzymes and transporters) constitutes the basis interspecies scaling and for the prediction of tissue and organ exposure (Danhof et al., 2008; Rowland et al., 2011). In its basic form, a PB-PK model is a network model in which the various compartments are the "nodes" and the transport between compartments and the elimination processes the "edges". Typically, for small molecules, the interactions in the network are described by relatively simple, linear functions. Meanwhile the utility of using PB-PK modeling for the characterization of the target site distribution kinetics as the first step towards mechanistic PKPD modeling is being explored (Danhof, 2015; Westerhout et al., 2012). For biologics, more complex "target-mediated" disposition models are used to describe time courses of the concentrations and the corresponding effects (Dua et al., 2015; Ferl et al., 2015).

2.2. Physiology-based pharmacodynamic modeling

As early as 1966 it was recognized that the relations between pharmacokinetics and pharmacodynamics are highly non-linear and complex, with often significant hysteresis between the drug concentration and the effect (Levy, 1966; Nagashima et al., 1969). Furthermore, in a series of investigations, using experimental approaches which enabled a strict separation between variation in

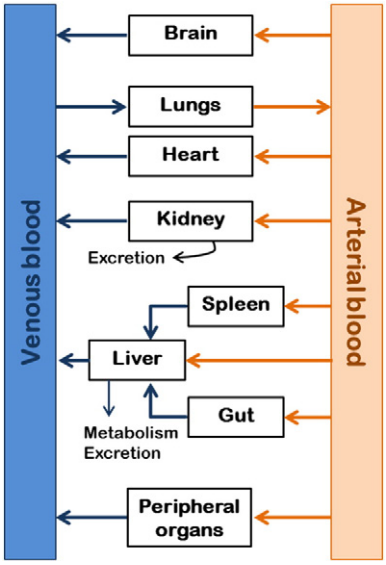

Fig. 3. A schematic whole-body physiologically-based pharmacokinetic model in which a selection of organs are depicted. The arrows indicate the blood flow. Drug administration (input) can be at any site of the body. Elimination is for simplicity depicted as occurring only from liver and kidneys, and the enterohepatic cycling is not included.
Modified from Rowland et al. (2011).

pharmacokinetics and pharmacodynamics (Danhof and Levy, 1984), it was shown that inter-individual variation in pharmacodynamics can be substantial (see for review: (Danhof, 2015)). Ultimately these developments have led to the concept of physiology-based pharmacodynamic (PB-PD) modeling for prediction of the time course of the drug effect. PB-PD models use separate expressions to describe i) steady-state drug concentration-effect relations and ii) the transduction mechanisms to describe hysteresis between concentration and effect.

2.2.1. Receptor theory to characterize steady-state concentration effect relations

To describe (variation in) steady-state in vivo drug concentration effect relationships, concepts from receptor theory are used (Ploeger et al., 2009). Target binding and activation are described by an agonist-dependent part: binding depends on the target affinity of the drug, while target activation depends on the intrinsic efficacy of the drug and the receptor density, respectively (Fig. 4). This is important since differences in receptor density may explain tissue selectivity of drug effect (Van der Graaf et al., 1999; van Schaick et al., 1997; Yassen et al., 2008, 2006) as well as functional adaptation and tolerance (Garrido et al., 2000). Next, a system-specific transducer function is used to characterize the translation of the target activation into the drug effect. While there is substantial evidence that the relation between drug concentration and target binding/activation can be described by a hyperbolic function, the transducer function can take any shape. The shape and the location of the transducer function, in terms of target activation, can differ between biological systems and thereby explain variation in drug effect. It has been shown that the system-specific transducer function can be identified by simultaneous analysis of the concentration-effect relationships of a training set of ligands at a given target (Cox et al., 1998a; Van der Graaf and Danhof, 1997; Visser et al., 2003; Zuideveld et al., 2004). In this manner receptor theory can be used to describe variation in drug concentration-effect relations (Danhof, 2015; Danhof et al., 2007; Ploeger et al., 2009; Van der Graaf et al., 1999). Receptor theory constitutes also the basis for the mechanistic characterization of drug interactions. In conceptual terms this turns the receptor model into a network model. The modeling of pharmacodynamic interactions is discussed below in Section 3.

2.2.2. Dynamical systems analysis to characterize transduction and homeostatic feedback

Modeling of transduction incorporates processes that link target activation to a response in vivo. Transduction is typically non-linear with large differences between biological systems in the rates at which transduction occurs. To take the time-dependency into account,

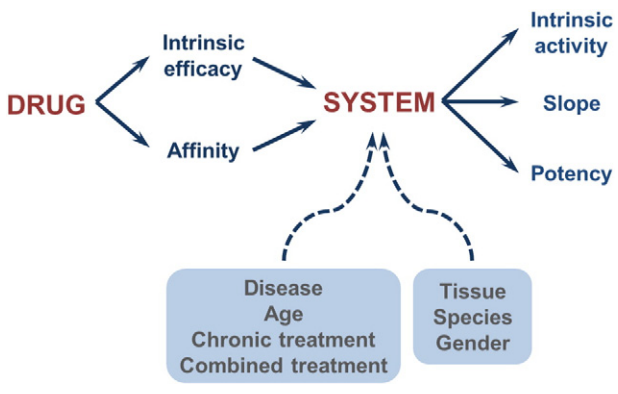

Fig. 4. The relationship between drug concentration and the intensity of the biological response depends on drug- and biological system specific factors. Drug specific properties are the target binding affinity and the intrinsic efficacy, which govern the target activation. A biological system-specific transducer function describes the relation between the target activation and the effect.
Reproduced from Van der Graaf and Danhof (1997).

PKPD modeling often uses concepts from linear dynamical systems analysis. In their most basic form these models are based on the concept of a physiological indirect response or turnover model as originally proposed by Levy to describe the time course of the anticoagulant effect of warfarin (Nagashima et al., 1969). Jusko et al. have subsequently formalized the concept of using various forms of a turnover model to characterize time-dependencies in the pharmacodynamics of a wide range of drugs (Dayneka et al., 1993; Jusko, 1995; Jusko and Ko, 1994; Sharma et al., 1998). Here, the drug effect is being characterized as an enhancing or inhibiting effect on either the zero order rate constant for input in the system or the first order rate constant for elimination from the system (Dayneka et al., 1993). Turnover models can be linked in a cascading manner, whereby the output of one turnover model serves as the input for a second turnover model; this makes it possible to characterize complex intermediary processes governing the time course of the drug response relative to the drug concentration, yielding a mechanistic model to describe transduction (Ramakrishnan et al., 2002). Turnover models also constitute a scientific basis for the modeling of homeostatic feedback, as is discussed below in Section 4. By definition, PKPD model structures which are based on the connection of two or more turnover models are network models.

2.3. Disease systems analysis to characterize disease progression

In many instances PKPD analyses are based on data obtained at a single occasion and following the administration of a single dose of the drug under investigation. Thereby it is assumed that the biological system is stationary. Mechanism-based PKPD modeling however also requires consideration of non-stationarity of biological systems, which may occur at widely different time scales. Under physiological conditions non-stationarity may be the result of circadian variation, and/or maturation/degeneration of physiological function (e.g. in pediatrics, elderly). In addition non-stationarity may also result from drug treatment, both in terms of changes in pharmacokinetics (e.g. enzyme induction; up/down regulation of transporters) and in pharmacodynamics (e.g. tolerance development). Finally in disease, non-stationarity may be caused by disease progression. In this contribution we limit the discussion to the modeling of disease progression.

Characterization of the effect of drug treatment on disease progression represents a major challenge due to the complexity of this endeavor. Specifically, detailed data on the time course of the change in disease severity in patients receiving active treatment and placebo are needed. In addition, depending on the endpoint that is used, effects may occur at widely different time scales. Patterns of disease progression may relatively simple in the sense that the disease progresses as a continuous process, but they may also be quite complex (Table 2).To analyze complex patterns of disease progression, and to understand individual differences between patients, pattern recognition algorithms (e.g. on the basis of artificial networks) are increasingly used. These emerging methodologies may enable clustering, classification, and ultimately, prediction of disease progression in sub-populations of patients, for example by mining historic information (Zhang, 2007). These methodologies may contribute significantly to the developing area of systems pharmacology, where the emphasis is on personalized precision treatments.

As a first step towards a more mechanistic approach to the modeling of the interaction between drug action and disease progression, the concept of disease systems analysis has been introduced (Post et al., 2005). Disease systems analysis describes disease progression on the basis of a turn-over model, in which the disease status (S) is governed by a zero-order synthesis rate constant (*kin*) and a first-order elimination rate constant (*kout*). In a chronic progressive disorder, homeostasis is perturbed by either a time-dependent change in the synthesis or the elimination rate which is characterized by the rate constants *kin,D* or *kout,D, respectively*. In this model a symptomatic drug effect is characterized by an interaction with the rate constants *kin* or *kout* of the

turnover model. In contrast, a disease modifying drug effect is described by an interaction with the rate constants *kin*,*D* or *kout*,*D* respectively. In theory this allows characterization of the exposure-response relations for either the symptomatic effect, the disease modifying effect or the combined symptomatic/disease modifying effect. In a series of simulations it was demonstrated that the interactions at the various sites yield distinctly different signature profiles (Post et al., 2005). Therefore, these models constitute a scientific basis for distinction between symptomatic versus disease modifying effects. Another important feature of disease systems analysis is the ability to cope with the widely different time scales that are typically encountered when analyzing disease progression. In theory, disease progression can be observed at different levels of the biological system, which each operate at different time scales. When responses at different levels are characterized on the basis of a turn-over models, they can be connected in a cascading manner. This turns the disease progression model into a network model. The properties of such network models are discussed below in Section 3.

3. Systems pharmacology – towards the modeling of network interactions

In the previous paragraph it has been discussed that currently used PB-PKPD models are based on the assumption of a single transduction pathway, connecting processes on the causal path between drug administration and effect. It was also shown that, although such models may be useful to account for hysteresis and non-linearity in the pharmacodynamic response profile, they fail to describe other fundamental properties of biological system behavior. In this paragraph it is discussed how existing PB-PKPD model structures can be extended to account for interactions within a biological network.

3.1. Receptor theory – the modeling of multi-target interactions

Modeling of interactions is an integral part of PB-PKPD modeling, since drug molecules can interact with multiple targets in the biological system. Modeling of pharmacodynamic interactions concerns the prediction of combined drug effects. In this context, synergy occurs when the combined effect is larger than expected when assuming additivity or 'no interaction' of the two effects separately. In contrast, antagonism occurs when the combined drug effect is smaller.

The modeling of pharmacodynamic interactions is based on concepts of receptor theory (Mandema et al., 1992). A dual-pathway model serves to describe the interaction between drugs that exert their actions through the interactions with two separate receptor systems (Gottlieb et al., 2012; Imming et al., 2006; Jonker et al., 2005). By definition a dual pathway model is a network model (Fig. 5). In this model the two transduction pathways converge into a single transduction pathway. An important determinant of the synergy in this model is the point at which the transduction pathways converge and the degree of preamplification that occurs before convergence. As can be appreciated, pharmacodynamic drug interactions are highly dimensional and complex. For this reason pharmacodynamic interactions are evaluated on the basis of response-surface plots (Fig. 6) (Jonker et al., 2005). These three dimensional graphs depict the intensity of the effect versus two drug concentrations to fully characterize a drug-drug interaction at all concentration pairs; synergy is reflected in an increase while antagonism in a depression of the response surface.

Mechanistically 6 different types of interactions can be distinguished: a) interdependency, b) allosterism, c) modulation, d) summation, e) Bliss independency and f) competition (Jonker et al., 2005). In this context interdependency refers to the situation were a drug does not have an effect, unless co-administered with a second drug which also doesn't have an effect on its own. Allosterism refers to the situation where a drug, which does not have an effect on its own, modulates the effect of a second drug by shifting the concentration-effect relation to a lower or a higher concentration. Modulation is the situation where a second drug, which again has no effect when administered alone, affects the concentration-effect relation of a second drug leading to a change in the maximum effect. A more common situation is where both drugs elicit a response when given alone. When signal transduction of both agents is very inefficient this mechanism is equivalent to summation of the individual pharmacologic responses. However, when signal transduction is efficient, summation of the two pharmacologic responses may not apply. Bliss independence is the situation where the combined response is restricted through saturation at the transduction (Bliss, 1939; Koizumi and Iwami, 2014). Finally stimulus competition can arise if two receptor stimuli are interdependent in the sense of a competitive interaction.

The described mechanism-based analysis of interactions between two drugs in a biological network is generally applicable and not limited to drug-drug interactions. Examples of other applications include the modeling of homeostatic feedback mechanisms and the modeling interactions with environmental factors to predict inter-individual variation.

3.2. Dynamical systems analysis – the modeling of homeostatic feedback

In vivo homeostatic mechanisms can have a major impact on the time course of drug effect. Counter regulatory mechanisms not only attenuate the primary response to a drug, they may also be the cause of complex pharmacological effect versus time profiles such as the profiles that have been observed for serotonin 5-HT_{1a} receptor agonists (Zuideveld et al., 2001, 2004). In addition, changes in drug effect depending on the rate of administration have been observed for vasodilators (Francheteau et al., 1993; Kleinbloesem et al., 1987) and the development of tolerance upon continued and repeated drug administration (Bauer and Fung, 1994; Cox et al., 1998b). In conceptual terms, modeling of homeostatic feedback concerns the modeling of internal interactions in the biological system. Typically model structures based on turnover models are used to characterize the effects of counter regulatory mechanisms on the drug response.

A recent example of a model to describe attenuation of the primary drug effect is the systems model for drug effects on the cardiovascular system (Snelder et al., 2014, 2013). Here a cascade of 2 turnover models describing the changes in cardiac output (CO), total peripheral resistance (TPR), with homeostatic feedback between mean arterial pressure (MAP) and CO and between MAP and TPR respectively, successfully described attenuation of the hypotensive effects of 8 cardiovascular drugs with different mechanisms of action. In mechanistic terms the influence of physiological counter regulation was incorporated in the model on the basis of a relatively simple "modulation" interaction term connected to MAP (see Section 3.1). By application of sensitivity analysis it was

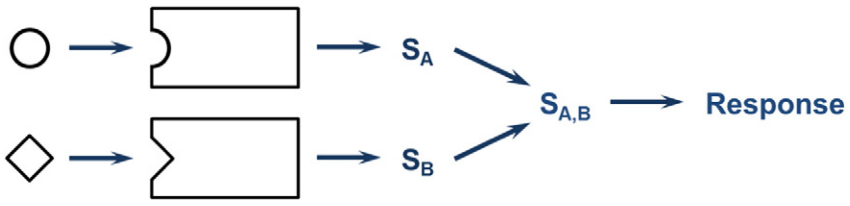

Fig. 5. A dual pathway model to describe pharmacodynamic drug interactions. In this example, independent receptors activate two signal transduction pathways that converge to produce a common response (Jonker et al., 2005).

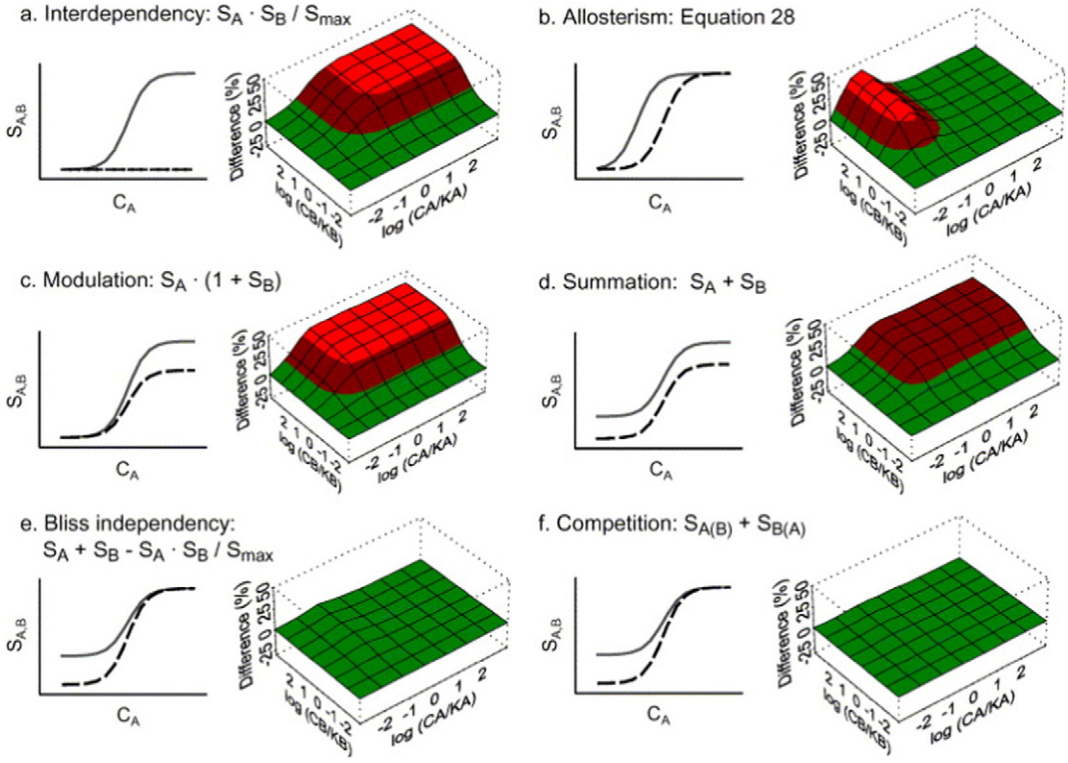

Fig. 6. Simulated response surface area (RSA) plots for 6 different interaction models for responses that are mediated through two converging signal transduction pathways. For full explanation of the parameters that were used during the simulations please see the original reference (Jonker et al., 2005).

shown that estimates of the parameters describing the homeostatic feedback interaction were independent of the drug, indicating that they were true systems parameters. An interesting property of this systems model is that hysteresis is observed between the effects on CO and TPR, for a drug with a direct effect on TPR but not for drugs with a direct effect on CO. In theory, this enables identification of the site of action of novel blood pressure lowering drugs. The development of the systems model for drug effects on the cardiovascular system is a prime example illustrating how biological insight in combination with smart study designs contribute to the identification of a relatively complex systems model.

The modeling of 5-HT_{1A} receptor agonists induced hypothermia is an example of the use of dynamical systems analysis to predict complex effect versus time profiles. To characterize serotonin 5-HT_{1A}-agonist-induced hypothermia in a mechanistic manner, a model was proposed which is based on the concept of a set-point thermostat model connected to a physiological indirect response model (Fig. 7) (Zuideveld et al., 2001). In the physiological indirect response part of the model, the change in body temperature is described as a response to either the inhibition of the production of body heat or the stimulation of its loss. The thermostat-like regulation of body temperature is implemented in the model as a continuous process in which the body temperature is compared with a reference or set point temperature (T_{SP}). Serotonin 5-HT_{1A} agonists elicit hypothermia by decreasing the value of the set point temperature T_{SP} in a concentration dependent manner. In the model the interaction between body temperature and set point temperature was described as "interdependence" (see Section 3.1); this creates a feedback loop that can give rise to oscillatory behavior. It has been shown that the proposed model is able to reproduce the complex effect versus time profiles, which are typically observed upon the administration of serotonin 5-HT_{1A} receptor agonists in rats (Zuideveld et al., 2001). The identification of such a model in terms of drug-specific and system-specific parameters constitutes a major challenge, given the complexity of the model. To achieve this, a mathematical approach based on redefinition of variables was applied to reduce the model. The reduced model was successfully applied to experimental data for 6 distinctly different serotonin 5-HT_{1a} receptor agonists, partial agonists and antagonist, upon widely different modes of administration (Zuideveld et al., 2004). This yielded physiologically relevant estimates of drug- and system-specific parameters. Specifically, significant correlations were observed between the drug-specific parameters characterizing the target binding and activation in the mechanism PKPD model and corresponding parameters in in vitro bio-assays (Zuideveld et al., 2004). Finally, on the basis of allometric scaling it was shown that such an effect does not occur in humans (Zuideveld et al., 2007).

The modeling of counter-regulatory mechanisms also constitutes a basis to the modeling of multi-stationarity of biological systems, as was recently demonstrated for the prolactin response following the

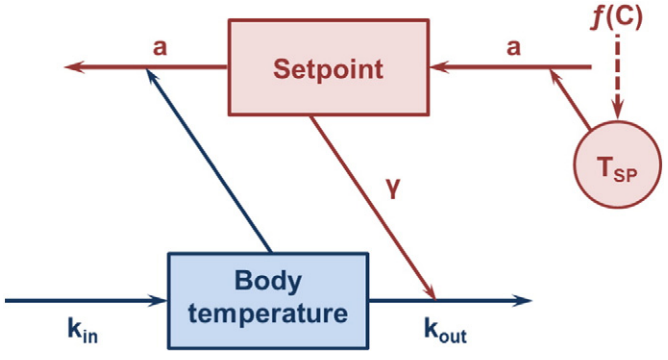

Fig. 7. Systems pharmacology model to characterize 5-HT_{1A} receptor mediated hypothermia. The model is based on the concepts of the indirect physiological response model and takes into account rate constants associated with the warming of the body (k in) and cooling of the body (k out). The indirect physiological response model is combined with the thermostat-like regulation of body temperature, in which body temperature (T) is compared with a fixed reference or set-point temperature (T_{SP}) at rate a, generating a set-point signal X. The extent to which the set-point value decreases is a function of drug concentration f(C), which decreases X by the amplification factor γ. From: Zuideveld et al. (2001).

administration dopamine D_2 receptor antagonists. Previously, a precursor pool depletion model has been proposed to describe tachyphylaxis of the prolactin response following repeated administration of the dopamine D_2 receptor antagonist remoxipride in humans (Movin-Osswald and Hammarlund-Udenaes, 1995). Recently, in a study in rats, where the effects of remoxipride were studied at multiple dose levels, this model was extended with an extra homeostatic feedback loop to characterize positive feedback between the serum prolactin concentration and the prolactin synthesis rate in the lactotrophs (Stevens et al., 2012). In a series of simulations it was shown that this system can exist in multiple, more or less stable, states (Bakshi, S, Danhof, M, et al., unpublished observations). The model structure constitutes therefore a basis for the modeling of multi-stationarity in biological systems. This model structure could be of considerable interest as the basis for the modeling of complex patterns of disease progression (e.g. episodic disorders). Ultimately this might constitute the basis for the design of pre-emptive treatment modalities, aimed at "resetting" of the biological system from the diseased to the healthy state.

3.3. Disease systems analysis – the modeling of disease progression

Disease systems analysis has been introduced as novel approach to characterize the effect of drug treatment on disease progression. Modeling of disease progression is particularly important for drugs which aim to modify disease progression or when an adverse effect of drug treatment on disease progression needs to be excluded. The modeling of drug effects on disease progression can be challenging, due to the inherent complexity of disease models. This concerns in particular the distinction between a symptomatic and a true disease modifying effect in situations where there may be a combination of a placebo effect, a symptomatic effect and a disease modifying effect. The prediction of the long term treatment effect on the basis of the data from a short term treatment intervention constitutes a significant challenge.

In theory disease progression can be observed at different levels of the biological system. As a result disease progression is increasingly modeled on the basis of biomarker responses in addition to, or instead of, clinical parameters, using a model structure in which multiple turnover models are connected in a cascading fashion. Typically rather simple "modulation" interaction terms are used to characterize the interactions between the turnover components of the model.

The first application of disease systems analysis has been to analyze the effects of pioglitazone, metformin, and glyclazide on disease progression in type 2 diabetes mellitus (de Winter et al., 2006). The mechanism-based model to characterize disease progression contained expressions to characterize: i) the homeostatic feedback relationship between fasting serum insulin (FSI) and fasting plasma glucose (FPG) concentrations and ii) the feed-forward relationship between FPG and glycosylated hemoglobin A_{1c} (HbA_{1c}). A unique feature of the model is that it contains also expressions to describe changes in beta cell function and insulin sensitivity. In addition, the model contains physiologically relevant expressions to characterize the interaction with drug treatment (Fig. 8) (de Winter et al., 2006). This model allowed the identification of the long-term effects of different treatments on loss of β cell function and insulin sensitivity in treatment-naïve type-2 diabetes mellitus patients. This model constitutes a promising conceptual advance in the study of drug effects on type 2 diabetes mellitus disease progression.

Disease systems analysis has also been applied successfully to analyze the effect of drug treatment on disease progression in osteoporosis (Post et al., 2013; Schmidt et al., 2011). Disease progression models in osteoporosis are based on the mechanistic bone cell interaction model proposed by Lemaire et al. (2004). Briefly, this model describes bone remodeling on the basis of the interactions between three distinctly different cell types, not yet active osteoblasts (R), active osteoblasts (B), and active osteoclasts (C). Due to its inherent complexity this model is not readily identifiable. It has been shown however that the model can be mathematically reduced without compromising its dynamic properties (Schmidt et al., 2011). The reduced model contains expressions describing the activities of two cell types: active osteoblasts and active osteoclasts (Fig. 9). The reduced model has been applied to data on plasma bone specific alkaline phosphatase (BSAP) and urinary N-telopeptide (NTX) as biomarkers for the activity of osteoblasts and osteoclasts, respectively, and the plasma concentration of osteocalcin (OST) as a biomarker reflecting the combined action of osteoblasts and osteoclasts. In addition, bone mineral density (BMD) in lumbar spine and total hip were included as the primary clinical biomarkers in the model (Post et al., 2013). Wide differences in the dynamics of the turnover of the biomarkers were observed. While the dynamics of bone turnover markers changes rapidly, closely following changes in the activity of bone cells, changes in BMD were slower. Application of the reduced mechanism-based disease systems model to the clinical data allowed for an adequate description of the data and yielded parameter estimates that are consistent with physiological values reported in the literature (Lemaire et al., 2004). The used model enabled

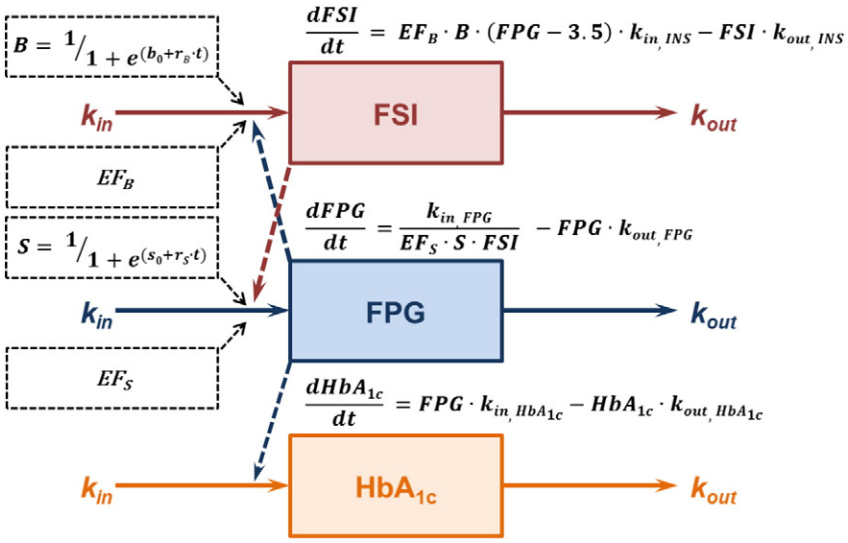

Fig. 8. Schematic representation of a disease systems analysis to analyze the effect of drug treatment on disease progression in type 2 diabetes mellitus. This model contains homeostatic feedback between fasting serum insulin (FSI) and fasting plasma glucose (FPG) as well as feed-forward between FPG and glycosylated hemoglobin A_{1c} (HbA_{1c}).
From: de Winter et al. (2006).

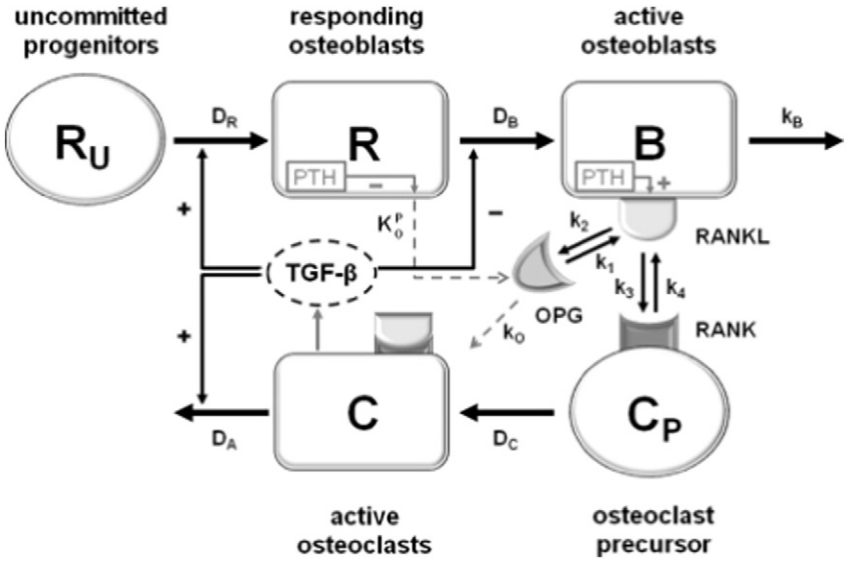

Fig. 9. Schematic illustration of the bone-cell interaction model to analyze the effect of drug treatment on disease progression in osteoporosis. The original model by Lemaire et al. (2004)) was mathematically reduced without compromising its dynamic properties.
From: Schmidt et al. (2011).

characterization of (i) the critical time scales involved in disease progression, (ii) the dynamics of the system during onset and offset of the therapeutic intervention, and (iii) the distinction between responders and low-responders to tibolone treatment.

4. Summary and conclusions

In this contribution the concept of systems pharmacology modeling is introduced as an approach to predict the effect of drug treatment on biological systems behavior. Systems pharmacology considers a biological network structure, rather than a single transduction pathway as the basis of drug action. As a result systems pharmacology models are extensions of traditional mechanism-based PKPD models, which contain expressions to characterize the pharmacodynamic interactions in biological networks. Receptor theory constitutes the scientific basis for modeling of pharmacodynamic interactions and mathematical expressions have been developed to account for different mechanisms of interaction: interdependence, allosterism, modulation, summation, bliss independence and competition. The application of these models is not limited to the analysis of drug-drug interactions per se. They also constitute a basis for the modeling of the interactions in cascading turnover models which are increasingly used to describe complex patterns of pharmacological responses and disease progression.

The identification of systems pharmacology models constitutes a significant challenge, given the complexity of the models structure. Through the application of advanced mathematical principles, based on redefinition of variables, the number of parameters in a model may be reduced without affecting the dynamic behavior (Post et al., 2013; Schmidt et al., 2011; Zuideveld et al., 2001). This has enabled the identification of complex pharmacodynamic and disease progression models.

Progress in the field of systems biology will lead to novel insights in the mechanisms of disease and the identification of novel drugs targets. This will lead to the development of novel "systems therapeutic" interventions. Such interventions will be 'precision treatments', which differ in many ways from traditional drugs. Systems therapeutic interventions will be: i) personalized, both with respect to the selection of the drug (or the combination of drugs) and the dose, ii) disease modifying, leading to preventive and pre-emptive treatment modalities and iii) complex, based on a rational combinations of multiple drugs, drugs combined with intelligent drug delivery systems. Given their complexity, systems therapeutic interventions cannot be developed nor be applied in clinical practice by trial and error. Instead, model-based approaches will be paramount.

It is concluded that on the basis of biological insight, the use of smart study designs, and the application of advanced mathematical and statistical techniques, meaningful systems pharmacology models can be developed and identified, which constitute a scientific basis for the development and clinical implementation of novel systems therapeutic interventions.

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