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Network-based discovery through systems biology

Towards integrative systems pharmacology models in oncology drug development

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Quantitative systems pharmacology (QSP) modeling represents an emerging area of value to further streamline knowledge integration and to better inform decision making processes in drug development. QSP models reside at the interface between systems biology models and pharmacological models, yet their concrete implementation still needs to be established further. This review outlines key modeling techniques in both of these areas and to subsequently discuss challenges and opportunities for further integration, in oncology drug development.

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Introduction

Attrition rates in the therapeutic area of oncology are among the highest, mostly due to unforeseen toxicities or lack of efficacy [1]. To reduce attrition, the use of modeling and simulation is widely accepted as important technology to inform decision making processes [2]. Nonetheless, various complex challenges persist in oncology drug development (ODD) and treatment optimization (Box 1). Quantitative systems pharmacology (QSP) [3] is an emerging scientific area which may address some of these challenges in ODD [4]. Conceptually, QSP models can be considered to reside at the interface of mechanistic systems biology modeling, and more parsimonious pharmacokinetic-pharmacodynamic (PKPD) modeling. Approaches for the concrete and relevant implementation of QSP modeling still need to be explored and consolidated further. In this review we firstly provide a brief overview of key modeling technologies in systems biology and pharmacology. Secondly, we discuss challenges and opportunities for integration of these technologies into effective QSP approaches for ODD.

Modeling technologies: systems biology

Systems biology models comprise a diverse range of cellular, multi-cellular or multi-scale models [5]. This section briefly discusses some key modeling technologies relevant to QSP and ODD. We focus mostly on systems biology modeling of multivariate biochemical datasets using either statistical data mining and network modeling approaches. A comprehensive on these type of modeling approaches in oncology is described elsewhere [6]. In our discussion, we distinguish between statistical data mining and network modeling approaches.

Statistical mining approaches

Statistical (data) mining approaches (or machine learning) employ methods such as clustering, regression and dimensionality reduction to derive abstracted insights in often large multivariate datasets. Examples of such approaches include principal component analysis, partial least squares (PLS) regression, and random forest models.

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Box 1. Key challenges in ODD.

Efficacy prediction and rational treatment design
Robust prediction of expected efficacy during early stages of drug development in oncology remains highly challenging. Either because there is insufficient understanding or inadequate consideration of the complexity of the disease, when scaling between translate across model systems. At the same time, wide variation in disease phenotypes further complicates translation. In addition, treatment resistance development related to the intrinsic redundancy and robustness of biological networks still prevents long-term disease control or cure in many cases. Poly-pharmacological treatment strategies could potentially address this issue. However, development of such combination therapies that take into account both dynamical characteristics of exposure–response and relevant signaling networks still represents a major challenge.

Off-target drug effects
Anti-cancer agents, including targeted therapeutics, are typically associated with off-target effects, which potentially induces severe dose-limiting toxicity, limiting or preventing treatment. Thus, a mechanistic understanding of such toxicities is crucial to optimize therapies and dosing strategies in oncology.

Optimizing clinical development & personalized treatments
Dose selection, identification of optimal (combination) dosing regimens, prediction of clinical outcome, and selection of responsive patients remain major challenges in the clinical development of cancer agents. The paradigm of personalized drug treatment in oncology based on gene expression signatures has been strongly established and could potentially be extended further by considering biological network topology and knowledge on exposure–response relationships.

One area where direct use of statistical mining approaches have demonstrated direct relevance is in the field of quantitative structure activity prediction [8]. Another major application relevant to oncology is the identification of predictive signatures for toxicity or efficacy in patients. Gene expression profiling-based signatures are already used in clinical settings [9], and increasingly methods are also being developed for toxicity risk prediction [10].

In other cases, statistical mining approaches may represent a starting point to guide further experiments and/or more focused network modeling approaches. For instance, the value of PLS to identify potential biomarkers from a panel of breast cancer cell lines was described recently [11].

Compared to network models, statistical data mining approaches have a relatively high abstraction level [7]. These approaches are particularly useful when more detailed and mechanistic inference is not relevant, or not possible based on the available data. However, various of these models have a linear nature whereas biology is inherently nonlinear, and in addition mechanistic interpretation of these empirical models can be difficult. Awareness of underlying model assumptions and their implications is therefore important. When considering the integration of statistical mining, these models may be helpful to identify predictors that can be included in empirical PK models, and as such provide increased mechanistic value to these models.

Network modeling

Network modeling approaches provide insight into topological relationships, and are mostly used to model biochemical intracellular networks. Frequently used network modeling approaches include graph models, logic-based models, and ordinary differential equation (ODE) models. Graph models (including Bayesian networks) are probabilistic models that provide insights into dependence structures of variables. As such they are still relatively abstract, similar to statistical data mining approaches. Nonetheless, they can be useful to obtain initial insights in relationships that can be explored and modeled further using more specified modeling approaches. Boolean- and fuzzy logic models use a rule-based approach to associate activation of nodes in a network and are increasingly used to model biological networks [12]. Lastly, ODE models may be considered the 'golden standard' with full description of the dynamics between biological nodes using rate constants. However, in order to identify parameters in ODE models, vast amounts of data may be required, which cannot always be feasibly generated. Overall, moving from graph models to ODE models, there exists an increasing level of specificity [7]. A comprehensive overview of the use of network models in cancer biology is described elsewhere [6].

The potential value of network-modeling approaches to design rational (combination) treatments for targeted anticancer therapeutics is high, yet their application in ODD still appears limited. Conceptual examples have demonstrated their potential value for rational design of optimal dosing regimens for drugs targeted at the EGFR [13] and VEGF [14] pathways. However, data to support development of a full ODE model will be available, and only lower lever network models can be established. To address this challenge, Kirouac *et al.* proposed that fuzzy logic approaches might be of special relevance for bridging between network biology and pharmacological modeling [15], in ODD. Others have suggested this approach might not be the optimal way forwards [16].

Network modeling has also been demonstrated to be useful to analyze the increasing availability of 'big data' in order to make association between for instance biochemical '-omics' datasets and clinical datasets, in order to obtain mechanistic insights into toxicity or efficacy mechanisms. One recently published motivating example studied the U.S. Food and Drug Administration adverse event reporting system (FAERS) database, which contains adverse events reporting for approved drugs. In this analysis, bipartite graph modeling was used to derive insights into biological networks associated toxicity and its mitigation [17]. The potential to apply such approaches to obtain increased understanding in the risk for toxicities is recognized [18]. Also in case of efficacy prediction signatures, the added value of including network topology rather than pure statistical mining approaches, is of increasing interest [19].