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REVIEW

# Computational methods and applications for quantitative systems pharmacology

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***Background*: Quantitative systems pharmacology (QSP) is an emerging discipline that integrates diverse data to quantitatively explore the interactions between drugs and multi-scale systems including small compounds, nucleic acids, proteins, pathways, cells, organs and disease processes.**
***Results*: Various computational methods such as ADME/T evaluation, molecular modeling, logical modeling, network modeling, pathway analysis, multi-scale systems pharmacology platforms and virtual patient for QSP have been developed. We reviewed the major progresses and broad applications in medical guidance, drug discovery and exploration of pharmacodynamic material basis and mechanism of traditional Chinese medicine.**
***Conclusion*: QSP has significant achievements in recent years and is a promising approach for quantitative evaluation of drug efficacy and systematic exploration of mechanisms of action of drugs.**

**Keywords:** quantitative systems pharmacology; network modeling; multi-scale platforms; traditional Chinese medicine

**Author summary:** Quantitative systems pharmacology (QSP) is an emerging discipline that integrates diverse data to quantitatively explore the interactions between drugs and multi-scale systems including small compounds, nucleic acids, proteins, pathways, cells, organs and disease processes. This review is an attempt to introduce the computational methods for QSP, including ADME/T (absorption, distribution, metabolism, excretion and toxicity) evaluation, molecular modeling, logical modeling, network modeling, pathway analysis, multi-scale systems pharmacology platforms and virtual patient as well as their applications in medical guidance, drug discovery and explorations of pharmacodynamics material basis and mechanism of traditional Chinese medicine.

## INTRODUCTION

Systems pharmacology (SP) combines systems biology approaches and computational methods to enable drug discovery for complex diseases and understand mechanisms of action (MoA) of drugs [1–4]. SP provides holistic approaches to facilitate the prediction of effectiveness and safety of molecules during the process of drug discovery. The human body is a complicated and integrated system, which can be regarded as biological networks [5]. Methods that can be applied to quantitative evaluation of the complex interactions between drugs and disease-related systems are urgently needed. The etiology and pathogenesis of complex diseases such as cancer, schizophrenia, and Alzheimer's disease concern lots of genes, gene products, small molecules and pathways, and there are still challenges in disease treatment [6–10]. Quantitative systems pharmacology (QSP), as a branch of SP, is an emerging approach to understand the interaction mechanism between drugs and the body and to predict the pharmacological effects of drugs [11–13]. QSP integrates diverse data, including preclinical and clinical information to analyze dynamic interactions between a drug or drug combination and multi-scale biological systems, that aims to understand the behavior of the systems as a whole [14,15]. It can also provide quantitative insights into biological and pharmacological processes [16]. QSP gets more and more attention in pharmacological research and

 

pharmaceutical industry [13,17,18].

QSP is usually described as three steps: gathering enough information such as disease-related targets, biomarkers, pathways, drug-target interactions and phenotypic characteristics; building a primary model based on the above information, calibrating and validating the model by comparing predictions with preclinical and clinical data [19,20]. QSP is a promising approach to quantitatively explore the interactions between drugs and the systems including targets, pathways, cells and organs and provides a comprehensive insight into the underlying mechanisms of drug action [21].

QSP has been becoming a discipline and the research in QSP involves describing pharmacokinetic/pharmacodynamic (PK/PD) characteristics of drugs, identifying the targets and drug-target interactions and investigating the factors that cause differences in the omics data of cells, tissues and patients [22,23]. Traditional drug discovery holds the thought "one drug, one target, one disease" and tries to treat the disease by adjustment of a single target which is responsible for the disease. This simple strategy pushes drug design to focus on selective drugs for specific targets. With the in-depth understanding of biological processes and pathogenesis, the disease phenotypes often represent a complex regulating network with multiple targets, pathways and cell signal transduction [1,24–29]. A single target can also be related directly or indirectly with many kinds of diseases [30,31]. QSP integrates the understanding of complex networks of diseases and adopts quantitative analytical and predictive methods, which provides a feasible approach for the development of new multi-target drugs and exploration of their MoAs. This review is an attempt to introduce the computational methods and applications for QSP, including ADME/T (absorption, distribution, metabolism, excretion and toxicity) prediction, network pharmacology and multi-scale systems pharmacology platforms (Table 1).

## METHODS FOR QSP

### Molecular-level evaluation and simulation

At the molecular level, QSP focuses on the evaluation of molecular properties and identification of drug-target interactions. These methods such as ADME/T analysis, chemical space analysis, drug-likeness evaluation can provide information about the characteristics of metabolism of drugs or compounds. The widely used PK/PD models provide the most basic data about drug absorption, distribution, metabolism, excretion and toxic characteristics [32,69–71]. PK and PD data indicate how drugs change *in vivo* over time and the characteristics of targets to elucidate the mechanism of drug action [14,32–34,69]. For example, Rostami-Hodjegan took into account the knowledge of physiology and biology based PK to predict the effects of intrinsic and extrinsic factors of drugs [69].

There are several computational methods to simulate the drug-target interaction such as molecular docking, molecualr dynamics simulation, machine learning and similarity analysis. Molecular docking and molecular dynamics simulation are feasible approaches for drug discovery, which give insights into the conformation of drug-target interaction and provide theoretical basis for virtual screening of lead compounds [37,38,72,73]. Rational drug design can be carried out by simulating the characteristics of targets and interactions with drugs

**Table 1 Computational methods for QSP**

| | Method classification | Description | Refs. |
|---|---|---|---|
| Molecular level | Evaluation of molecular characteristics | Providing information about molecular properties of drugs (ADME/T, PK/PD model, chemical space analysis and drug-likeness evaluation) | [1–4,32–36] |
| | Identification of drug-target interaction | Predicting and evaluating drug/compound-target interaction (molecular docking, molecular dynamics simulation, machine learning and similarity analysis) | [37–42] |
| Network level | Drug-target network analysis | Analyzing the interactions between drugs and targets | [43–45] |
| | Protein-protein interaction network analysis | Analyzing topological structures of complicated protein–protein interaction network | [46] |
| | Pathway analysis | Investigating the connections between drug targets and regulatory networks of diseases, and evaluating drug efficacy in thecontext of pathway network | [47–50] |
| Systems level | Logical modeling | A mechanism-based mathematical method to endow the object with logical structure. | [51] |
| | Multiscale systems pharmacology platform | Evaluating the treatment effects of therapeutic regimens and exploring the MoA by integrating preclinical/clinical data of drugs and disease phenotypes (TCMSP, Virtual Tumour, CancerHSP, *etc*.) | [52–64] |
| | Virtual patient | A simplified model to translate complex biological processes into a series of intuitive equations | [65–68] |

 

and the high-throughput virtual screening is accomplished by analyzing the binding affinity between compound and target. For example, Omer discovered two novel antiviral molecules (Calanolide A and Chaetochromin B) and their target HRAS by molecular docking and molecular dynamics simulation [73]. In our recent work, a binding energy-weighted polypharmacological index was introduced to evaluate the importance of target-related pathways which had close correlation with the pathogenesis of psoriasis [74].

Machine learning and similarity analysis are another two important approaches to explore drug-target interactions and drug-drug interactions. Machine learning is a method used to improve the performance on a specific model with data, and plays an important role in systems pharmacology [39–42]. For example, Chiu and Xie integrated coarse-grained normal mode analysis with multi-target machine learning to predict protein-ligand binding/unbinding kinetics accurately [41]. Yang *et al*. constructed three best-performing model to screen inhibitors for P-glycoprotein (P-gp) by machine learning algorithm, and these models were employed as a virtual screening tool for identifying 875 potential P-gp inhibitors and 15 inhibitor-rich herbs from TCMSP [75]. Compounds that have similar structures would have similar functions. Predicting targets for a new molecule by comparing the similarity with active compounds whose targets are known is a traditional method. BindingDB [76] and BATMAN-TCM [77] are two famous web-server which can predict drug-target interaction by analyzing molecular similarity.

## Network modeling and pathway analysis

Network modeling integrates disease-related genes, pathways, targets and drugs into a complex network model and provides frameworks for understanding of how regulation arises from the interactions between cellular components [1,2,43–45]. The biological systems can be regarded as networks, where nodes represent molecular entities (DNA, RNA, protein and small compound) and processes, edges represent the relationships between nodes. Important nodes and edges in the network can be identified by network analysis. The change of global characteristics of network can be determined by network dynamics simulation. The network model can provide important information such as key targets in regulatory networks, the mechanism of interactions between drugs and targets. The results of network modeling can provide theoretical basis and guide for the development of multi-target drug, drug combination and credible options for personalized treatment as well as a feasible way to explore the pathogenesis of diseases. These network-based approaches are useful in understanding the basis for cancer combination therapy [3], discovering treatment regimens for optimal efficacy [78], identifying the origins of drug induced adverse events [79–81], and indicating how drug combinations can mitigate serious adverse events [82]. For example, Wu developed an integrated network and cheminformatics tool (SDTNBI) for systematic prediction of drug-target interactions and drug repositioning [83,84]. Wang applied network topologies and dynamics parameters to obtain two potential weak-binding drug candidates whose effects were validated by *in vitro* experiments so as to provide a feasible way for drug discovery [85].

Pathway analysis is an approach to investigate the therapeutic mechanism by analyzing the connections between drug targets and regulatory networks of diseases [47]. It is a universal way that provides various information as the basis of many models in QSP [86]. Topological analysis is usually used to measure the importance of genes to simplify the complex pathway network into a structured collection of related genes. It can effectively reduce the difficulty of modeling and analyzing the pathway network which is responsible for the disease phenotype. But it may reduce the accuracy of the results as it ignores some potentially valuable information such as the connections of genes that belong to different pathways and potential pathogenic genes [87]. Nie *et al*. studied the regulation mechanism of Toutongning capsule by analyzing the signaling pathway of the migraine and the results showed that 19 active compounds and 8 targets played a crucial role in the treatment of migraine through TNF pathway [88].

We have developed a pathway network-based method by combining network modeling and molecular docking to evaluate drug efficacy. Network efficiency (*NE*) and network flux (*NF*) are both global measures of the network connectivity. We used *NE* and *NF* to quantitatively evaluate the inhibitory effects of compounds. The edge values of the pathway network were reset according to the Michaelis-Menten equation, which used the binding constant and drug concentration to determine the degree of inhibition of the target protein in the pathway. The dose-response curve was sigmoid and the predicted effects of compounds were in good agreement with experimental results [5,48–50]. Moreover, This approach can be used for predictions of drug combination and drug repositioning [5,89].

## Systems-level methods

### Logical modeling

Logical modeling is a kind of mathematical method based on the mechanism which can endow the object with logical structure. It can provide insights into a variety of

 

phenomics profiles through the analysis of the logical relationship between phenotype and mechanism [51,90–92]. This modeling method can be established according to the known information of the biological process and optimized by calibrating the modeling results with experimental data. Then altering parameters of the model to simulate the changes of biosystems to obtain various outcomes which can provide useful information and meaningful predictions to the process. This approach can provide reasonable way to build enormous biological network models in lack of various preclinical and clinical data by predicting the logical relationship. However, it is important to be aware of the simplification in this mechanism-based simulation which would cause the impossibility of representing the complexity and diversity of biological systems [51]. Poltz *et al.* built a discrete logical model of signal transduction of DNA damage response to screen target proteins for DNA-damaging agents that could be suitable for radio- and chemotherapy, and contributed to the design of more effective therapies [90].

## Multi-scale systems pharmacology platforms

QSP takes the whole body as the starting point of research to seek the relationship between drug administration and disease to speculate the underlying mechanisms. It is also used to guide personalized medicine by integrating genomics knowledges. Multi-scale systems pharmacology focuses on disease-related multiple drugs, targets, pathways, biomarkers and phenomics. Several multi-scale systems pharmacology platforms have been developed such as TCMSP [52], Virtual Tumour [53], CancerHSP [54], $C^2$Maps [55], VisANT 4.0 [56], PDTCM [57], CVDHD [58], Lipoprotein Metabolism and Kinetics (LMK) Platform [59], Rheumatoid Arthritis PhysioLab platform [60], and others [61–64].

TCMSP is a unique systems pharmacology platform of Chinese herbal medicines and sparks a new interest in the search of candidate drugs from TCM [52]. TCMSP contains chemicals and their pharmacokinetic properties, targets and drug-target networks, drug-target-disease networks to capture the relationships between drugs, targets and diseases. Virtual Tumour Preclinical platform integrates available PK and cell cycle PD measurements for chemotherapeutic and targeted cancer treatment agents into a model of cell cycle and xenograft tumor growth [53]. Musante *et al*. reported an Immuno-Oncology (I-O) platform to investigate the effects of two kinds of regimens for cancer and suggest possible applications based on clinical data and analysis of mechanism [59]. Kirouac *et al*. developed a multi-scale systems model of ErbB signaling to support the preclinical investigation of a bispecific antibody targeting HER2 and HER3 in cancer [93]. Another important QSP modeling platform is the DILIsym® which is developed by the non-profit Hamner Institutes of Health Sciences. It can be used for drug development [94], explaining the mechanisms of hepatotoxicity [95] and liver toxicities [96]. PDTCM [57] and CVDHD [58] are two online servers that developed for psoriasis and cardiovascular disease, respectively. PDTCM and CVDHD integrated medicinal herbs, natural products, disease-related proteins, docking results and clinical biomarkers. By using virtual screening and network pharmacological methods, PDTCM and CVDHD streamline drug/lead discovery from natural products and explore the action mechanism of medicinal herbs and formulae [57,58].

These platforms that combine the preclinical/clinical data of many aspects and a variety of disease phenotypes are able to evaluate the treatment effects of therapeutic regimens and explore the MoA. These models are also applicable to different diseases after appropriate adjustment. However, the development of these platforms requires a certain depth of clinical research on the diseases and a wider range of preclinical and clinical data [59].

## Virtual patient

Using QSP model to translate complex biological processes into a series of intuitive equations is a promising way to get insights into curative effects in drug discovery and disease treatment. However, the preclinical and clinical data for the establishment of models is lacking in some aspects. Many scientists simplified the models by alternative parameterization to reduce the need for data, and this method is also called “virtual patient” [65–68,97]. Moreover, a mechanistically-based weighting method to match clinical trial statistics at population level was introduced in a comprehensive analysis (virtual population) [60]. Geerts *et al*. used a mechanism-based QSP platform, virtual human patient, to simulate the biological processes of Alzheimer’s disease and to build a tool to realize personalized drug treatment [66]. Allen *et al*. [68] developed a new approach to generate virtual population without the step of weighting. This approach includes following steps: define plausible ranges for model parameters and initialize parameters; calibrate the model by comparing the prediction with database, then repeat the selection and optimization steps until the available model patients are plentiful enough. Finally, a credible virtual population model is constructed after calculating probability of inclusion into virtual population and optimizing the inclusion rate.

 

## APPLICATIONS

### Drug discovery

The strategy of drug discovery has been shifting from searching selective drug for single target that aimed to decrease side effects into looking for drugs that can rebalance the biological processes and regulatory networks [1,25,98–104]. The *in vivo* dynamics and kinetics of drug-target interactions can be simulated and evaluated by establishing QSP models to reduce the cost of money and time in a certain extent comparing with the traditional *in vivo* experiments [78,105]. QSP models integrate multiple regulatory networks of disease-related biological processes and build platforms for screening. The applications of these platforms can increase the efficiency of high-throughput screening of candidate compounds and reduce the time required to study the links between drugs and complex networks. Unwanted side effects and toxicity of candidate drugs can be evaluated by adverse drug reactions [82,106–109] and toxicity models [70,110]. Liu *et al*. [111] applied a comprehensive systems approach to identify 73 bioactive components from licorice and 91 potential targets for this herb. The mechanism of this herbal medicine by mapping drug-target and drug-target-disease networks was further elucidated. Luo used a network-based multi-target computational approach to screen potential anticancer drugs from natural products and predict the interactions between anticancer drugs and cancer-related targets [112]. Archimedes model is a human physiology-based statistical disease progression model to simulate the effect of treatments for cardiometabolic diseases [113,114]. These works all make it easier and cheaper to find new effective drugs.

### Medical guidance

QSP models are utilized to inform different questions in pharmacology, such as MoA exploration, efficacy evaluation, translational medicine and drug discovery. The QSP modeling of drug metabolizing process usually uses a time dependent equation. QSP models can be built on a time scale while the time of reaction can be as short as action process of quick-acting drugs and as long as the generation and deterioration of chronic diseases. QSP modeling approaches can address challenges in the translation of preclinical findings to the clinical applications [115–117]. Instead of analyzing the instantaneous outputs of models, researchers usually use frequency-domain response analysis in mathematics to explore the process of change under perturbation (treatment of disease) at the systems level [118]. Taylor *et al.* analyzed 14 distinct PD models of four class (indirect response, auto regulation, precursor-pool and moderator-mediated feedback) to evaluate the practicability of frequency-domain response analysis method [118].

There are also many other kinds of medical guidance provided by QSP models. Visser *et al.* simulated and optimized *in vivo* dosing regimens by informing both preclinical and translational evaluation of single drug and combination therapy [119]. Geerts *et al*. contributed a lot in development of schizophrenia treatment such as predicting the effect of existing drugs and developed a mechanism-based QSP model of a relevant key cortical brain network with schizophrenia pathology to gain insights of cognitive deficits in schizophrenia [97,120–122]. Vega-Villa *et al*. developed a QSP model to characterize metabolome of nitric oxide after a long-term infusion of sodium nitrite that would be valuable for nitrite dosing selection in clinic [123]. John *et al*. investigated the mechanisms of anxiolytic drugs on hippocampal electric patterns and interpreted the stimulus-frequency relationship of hippocampal theta [124]. Rostami-Hodjegan developed a physiologically based pharmacokinetic model to guide administration of oseltamivir in pediatric patients [69,125]. Recently, Kaddi *et al*. presented a multiscale and mechanistic QSP modeling of acid sphingomyelinase deficiency and the enzyme replacement therapy that quantitatively assessed systemic pharmacological effects in adult and pediatric patients at molecular-level, cellular-level, and organ-level effects [126]. Other works contributed to expand knowledge of disease processes by phenotypic screening and developing personalized medicine [47,127–129].

### QSP in TCM

Systems pharmacology methods are frequently used in exploration of pharmacodynamic material basis and MoA of traditional Chinese medicine (TCM) [130–139]. The recent applications of these QSP methods in TCM are summarized in Table 2. For example, Li *et al*. dissected the mechanism of the addition and subtraction theory of traditional Chinese medicine by building a SP platform to contrast and analyze the variation of kinetic parameters and targets of active compounds in Xiao-Chaihu-Decoction and Da-Chaihu-Decoction [180]. Yao *et al*. investigated the different pharmacological effects of herbs in Ma-huang decoction to elucidate the combination principles of TCM [158]. Zhou *et al*. investigated the underlying mechanisms of efficacy of herbs for eliminating blood stasis and tonifying Qi by linking the drugs, targets and diseases to obtain compound-target-disease associations for reconstructing the biologically-meaningful networks based on systems pharmacology methods [181]. Zhao *et al*. built a pharmacological system model of Bufei Jianpi formula by absorption filtering, network targeting,

 

**Table 2 Selected applications of QSP methods in TCM**

| TCM | Computational method | Refs. |
|---|---|---|
| Acori Tatarinowii Rhizoma and Curcumae Radix | Data mining, pathway enrichment, network analysis | [140] |
| *Erigeron breviscapus* | ADME pharmacokinetic screening, target fishing, protein-protein interaction network analysis and *in vitro* experiments verification | [141] |
| *Eucommia ulmoides* Oliv. | Drug-likeness evaluation, oral bioavailability prediction, multiple drug targets prediction and network pharmacology techniques | [142] |
| *Hedyotis diffusa* Willd. | Active component gathering, target prediction, related gene collection, gene enrichment analysis and network analysis | [143] |
| Licorice | Oral bioavailability screening, drug-likeness evaluation, blood-brain barrier permeation, target identification and network analysis | [111] |
| *Semen strychni* and *Tripterygium wilfordii* Hook F. | Data mining, target prediction, network analysis | [144] |
| *Sinomenium acutum* | Pathway, network and function analyses, data mining | [145] |
| Anti-Thrombosis Drug from TCMs | Data mining, molecular docking, *in silico* screening | [146] |
| Qi-enriching herbs and blood-tonifying herbs | ADME prediction, target fishing and network analysis | [147] |
| Baihe Dihuang Tang | ADME/T calculation, target prediction, network analysis | [148] |
| Bufei Jianpi formula | Systems pharmacology modeling based on absorption filtering, network targeting and systems analyses | [132,149] |
| Bushenhuoxue formula | Target screening, molecular docking, network analysis, literature mining | [150] |
| Bushen-Yizhi prescription | ADME/T filter analysis, target prediction, network analysis | [151] |
| Danlu Capsules | Oral bioavailability and drug-likeness evaluation, gene enrichment analysis | [152] |
| Danggui-shaoyao-san | Oral bioavailability screening, drug-likeness assessment, target identification and network analysis | [153] |
| Diesun Miaofang | Cluster ligands, human intestinal absorption and aqueous solution prediction, chemical space mapping, molecular docking and network pharmacology techniques | [154] |
| Dragon's blood tablets | Chemical analysis, prediction of ADME, and network analysis | [155] |
| Ge-Gen-Qin-Lian decoction | Target profile clustering, network target analysis | [156] |
| Liu-Wei-Di-Huang pill | Chemical and therapeutic properties, network analysis | [157] |
| Ma-huang decoction | Pharmacokinetic analysis, drug targeting, and drug-target-disease network analysis | [158] |
| Mahuang Fuzi Xixin decoction | Drug-likeness evaluation, oral bioavailability prediction, multiple drug target prediction, and network analysis | [159] |
| MaZiRenWan | UPLC-QTOF-MS/MS identification, hierarchical clustering analysis, *in vitro* experiment verification, network analysis | [160] |
| NiaoDuQing granules | ADME modelling and target prediction, topology analysis, pathway enrichment analysis, rat test | [161] |
| Qigui Tongfeng tablet | Molecular similarity analysis, network analysis | [162] |
| Radix Curcumae formula | Chemical predictors based on chemical structure and chemogenomics data linking compounds, pharmacological information, a system biology functional data analysis and network reconstruction method | [163] |
| Reduning injection | ADME filtering, network targeting, pathways integrating, target selection, reverse drug targeting and network analysis | [164–166] |
| Shenmai injection | Network construction, network recovery index evaluation | [167] |
| SiNiSan formula | ADME screening, targets prediction, and DAVID enrichment analysis, | [168,169] |
| Taohong Siwu decoction | Chemical space analysis, virtual screening, chemical distribution and potential compound prediction | [170] |
| Tian-Ma-Gou-Teng-Yin fomula | Network link prediction and statistical analysis | [171] |
| Tianshu formula | Pharmacokinetic filtering, target fishing and network analysis | [172] |
| Xiaoyaosan | Reversed pharmacophore matching method, network analysis | [173] |
| Xijiao Dihuang decoction | ADME screening, drug targeting, network and pathway analysis | [174] |

(*Continued*)

| TCM | Computational method | Refs. |
|---|---|---|
| Xin-Sheng-Hua granule | Plasma metabolomics profiling with UHPLC-QTOF/MS and multivariate data method, network analysis | [175] |
| Xing-Nao-Jing | Drug-likeness and brain-blood-barrier evaluation, biological process and pathway enrichment analyses | [130] |
| Yangxinshi tablet | Molecular docking, network analysis | [176] |
| Yinchenhao decoction | Oral bioavailability screening, drug-likeness and intestinal epithelial permeability evaluation, target prediction, pathway identification and network construction | [177] |
| Zhi-Zi-Da-Huang decoction | Molecular docking and network analysis | [178] |
| Ginsenoside Rb1, ginsenoside Rg1, schizandrin and DT-13 (effective compounds from ShengMai preparations) | Target-pathway network analysis | [179] |

and systems analysis and identified 145 bioactive ingredients and 175 potential targets [149]. The model also provides insights of potential synergistic effects between herbs which links with similar targets. Wang *et al*. used a systems pharmacology method to provide new insights into the pharmacological interactions of *Ophiocordyceps sinensis* so as to find new adjuvant for hepatitis B vaccine [182]. Yang *et al*. built an *in silico* model to predict potential P-Glycoprotein inhibitors and select out 875 potential P-Glycoprotein inhibitors and 15 inhibitor-rich herbs from TCMSP [75]. These results make TCM more reasonable and promote the modernization of TCM.

## FUTURE PROSPECT

QSP integrates various types of *in vivo* and *in vitro* results from different research areas. QSP methods can simulate a series of biological processes and diseases for multiple-scale and systematic exploration of MoA of drugs. The biological responses and changes in disease treatments from the molecular and genetic level to systems level provide a deep insight into these processes. It can also make up quantitative and credible predictions for complex disease while the pathogenesis is not yet fully understood. There are still many challenges in both developing QSP methods and applications. The lack of biological and pharmacological details for complex disease leads to deviations in simulations. Analytical and comprehensive multi-level evaluation methods are urgently needed to construct the appropriate models. Complex associations between factors involved in MoA of drugs further increase the difficulty to obtain meaningful results by analyzing the predictions of modeling. With the development of omics technologies and mathematical techniques such as network dynamics, ordinary differential equations, logic-based approaches, statistical regression and finite element methods, QSP will help to understand the MoA of drugs and TCM, and to improve the efficiency of drug discovery.

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Fuda Xie and Jiangyong Gu declare that they have no conflict of interests.

This article is a review article and does not contain any studies with human or animal subjects performed by any of the authors.

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