A personalized pharmaco-epistatic network model of precision medicine

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Precision medicine, the utilization of targeted treatments to address an individual's disease, relies on knowledge about the genetic cause of that individual's drug response. Here, we present a functional graph (FunGraph) theory to chart comprehensive pharmacogenetic architecture for each and every patient. FunGraph is the combination of functional mapping – a dynamic model for genetic mapping and evolutionary game theory guiding interactive strategies. It coalesces all pharmacogenetic factors into multilayer and multiplex networks that fully capture bidirectional, signed and weighted epistasis. It can visualize and interrogate how epistasis moves in the cell and how this movement leads to patient- and context-specific genetic architecture in response to organismic physiology. We discuss the future implementation of FunGraph to achieve precision medicine.

Keywords: Epistasis; genetic network; personalized medicine; association studies; functional mapping; functional graph theory

Introduction

Unlike traditional one-size-fits-all approaches, the goal of precision medicine is to tailor medical decisions, practices and interventions for individual patients based on their predicted response or risk of disease.[1] The more precise targeting of subgroups of disease with specific therapies makes precision medicine a powerful approach for maximizing therapeutic efficacies and minimizing toxic effects.[2–6] The cornerstone of precision medicine is pharmacogenomics – the study of how genes affect a person's response to drugs.[7,8] In modern medicine, pharmacogenetics, expanded to pharmacogenomics (studying a complete set of genes for drug response), has become a distinct discipline in life sciences.[9–13]

Despite tremendous efforts in pharmacogenetics research, our capacity to chart a complete portrait of pharmacogenetics architecture remains limited owing to challenges arising from pharmacological characteristics. First, the therapeutic effect of a drug involves a cascade of pharmacokinetic (PK) and pharmacodynamic (PD) interactions between the drug and body.[14,15] Mapping an endpoint phenotypic trait as drug response, as is the case in most pharmacogenetics research, fails to reveal the genetic machinery that shapes the PK and PD processes of drug–body interactions toward drug effects. Second, genetic associations

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using single markers ignore the nonlinear multifactorial characteristic of the drug response.[16,17] Epistasis (i.e., the masking of the effect of allelic substitution at one locus by the allelic state at a second locus)[18] plays a pivotal part in the drug response.[19–21] This definition of epistasis, as well as its extension to nonadditive interaction variance,[22] has a limited use because it cannot capture the full property of epistasis.

Third, drug response as a complex trait is polygenic but it might be better explained by omnigenic theory.[23] This theory proposes that all genes distributed throughout the genome can jointly affect a complex trait, including a small portion of core genes that are directly associated to key pathways that drive pharmacological etiology and vast numbers of peripheral genes whose function is transmitted to pharmacological pathways through interconnected networks. Although omnigenic theory can refresh our view about pharmacogenetics architecture, its implementation into practical genetic research is extremely difficult. To estimate the indirect effects of peripheral genes, which are small, an extremely huge sample size that cannot be met in practice is required.

Here, we present an emerging functional graph (FunGraph) theory that can address the three major challenges in pharmacogenetics studies. We review the basic principle of FunGraph construction, illustrate the merits and application of FunGraph to mapping pharmacogenomics and describe the statistical procedure of using FunGraph. We also discuss the prospect of FunGraph as a generic tool to unveil the regulatory mechanisms underlying drug response.

Conceptual construction of FunGraph

FunGraph is derived from the combination between functional mapping (FunMap) and evolutionary game theory into graph theory.[24–28] Treating drug response as a dynamic process, FunMap is a mechanistically driven statistical model[29,30] that integrates the mathematical principles of what the body does to the drug (PK) and what the drug does to the body (PD). It can characterize the PK/PD pattern of genetic control exerted by individual pharmacogenes. Because of its capacity to estimate genotype-dependent pharmacological parameters at each marker under consideration, FunMap can chart different genotypic curves at individual markers, from which to estimate the curves of single-locus genetic variances over time or drug concentration. FunMap has been instrumental for the identification of significant genes, known as quantitative trait loci (QTLs), which govern drug response.[31–34] These QTLs acting singly are a small set of the whole genes that form a complete picture of pharmacogenetic architecture. Some studies attempted to map epistatic QTLs[35] but they were often based on a marginal analysis, failing to take into account how all QTLs interact simultaneously with each other in a rock-paper-scissors network.

The above issues can be overcome by introducing evolutionary game theory[36] – a strategic formulation of competition and cooperation, widely applied in various fields of social and life sciences.[37–39] Game theory suggests that the strategies with which individual players in a community act and interact to maximize their expression (fitness) are determined by their own intrinsic capacity and the will and resolution their counterparts have on them. The fundamental notion of game theory is Nash equilibrium[40] in which no player can gain any payoff by only changing its own strategy. This notation is generalized and refined as evolutionarily stable strategy in evolutionary game theory, which can be used to model strategic processes without the rationality assumption. Sun *et al.*[24] combine evolutionary game theory and predator–prey theory to derive a generalized Lotka–Volterra (LV) ordinary differential equation (gLVODE) used to distinguish and model the payoffs due to a player's own strategy and the strategies of other coexisting players. By solving a system of gLVODEs, these two types of payoff, each representing a different mechanism for a player to gain, can be estimated, tested and compared over time.

Taken together, FunMap estimates the genotypic curve of PK/PD at each locus in a mapping or association population. Each subject can be assigned such a genotypic curve based on the genotype carried by this subject. For a specific subject, gLVODEs decompose the genotypic value at a gene (estimated by marginally based FunMap) into the intrinsically driven independent 'payoff' of this gene (expressed in isolation) and the extrinsically induced dependent payoff (resulting from the influence of other genes on this gene). FunGraph codes the independent payoffs of individual genes as nodes and the dependent payoffs of individual gene pairs as edges into graphs. These graphs provide a chart for the roadmap of how each gene affects drug response, directly or through an indirect path.

A fully informative model of epistasis

Existing quantitative models in human genetics have two major limitations for epistasis estimation. First, they can only estimate aggregated epistasis from a large number of patients, failing to characterize interindividual variability. For example, genotype *Aa* at gene 1 promotes the expression of genotype *AA* at a different gene *s* to enhance subject 1's drug efficacy; but such a nonallelic interaction might cause drug toxicity for subject 2 (Figure 1). Also, it is possible that the genotype at gene 2 interacting with the same genotype *AA* at gene *s* is subject-dependent (i.e., *aa* for subject 1 and *Aa* for subject 2), which is expected to produce subject-typic drug effects. The lack of a systematic characterization of personalized interactions involving a complete set of genes has limited the effective translation of genetic information into precision medicine in clinical practice.

Second, current approaches can only estimate the overall strength of epistasis between a pair of loci. However, they can identify neither the causality of epistasis nor the sign or (bi)directionality of the causality. For example, positive epistasis detected from current quantitative genetic theory can derive from the mutual promotion of two loci, the unidirectional promotion of one locus for the second or the promotion of one locus for the second even although the second inhibits the first but to a lesser extent (Figure 2). Similarly, negative epistasis detected can arise from one of three possible types. Furthermore, current epistasis detection is based on a pairwise analysis but genes often co-occur in a community and, thus, co-act in a generalized rock-paper-scissors manner.[41]

Epistatic networks inferred by FunGraph are bidirectional, signed and weighted, leveraging Bateson's[18] and Fisher's[22] defini-

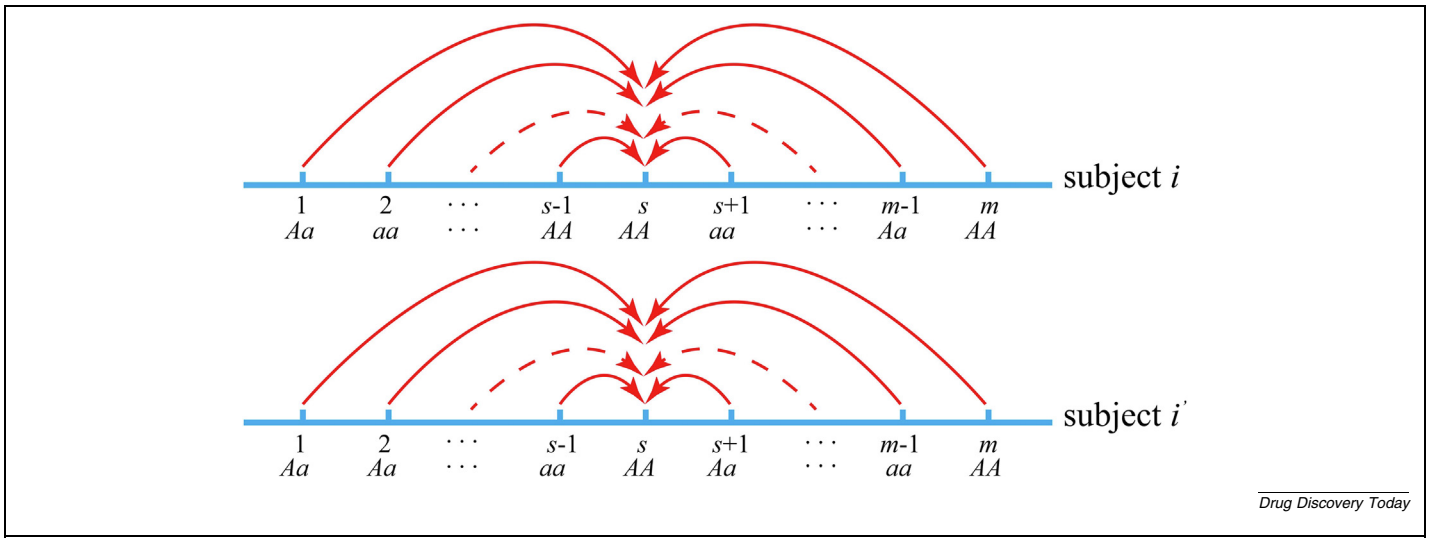


FIGURE 1

Diagram showing how epistasis changes from subject to subject. Subjects i and i' have the same genotype *AA* at a typical SNP *s*; but the influence this genotype receives from other loci varies between two subjects. For example, genotype *AA* at SNP s is affected by genotype *AA* in subject i but *aa* in subject i' at SNP $s-1$, by genotype *aa* in subject i but *Aa* in subject $i\prime$ at SNP $s+1$, etc. We argue that the difference of subject i from subject i' is not only due to genotypic differences at different loci but also due to epistasis expressed at the genotype level, both causes of which can be characterized by functional graph theory.

tions of epistasis by capturing the full information. Comparing reciprocal dependent payoffs between two genes in terms of their sign and magnitude estimated from gLVODE allows us to classify epistasis into different types: symmetrical positive epistasis – two genes promote each other at the same strength; asymmetrical positive epistasis – two genes promote each other but to different extents; directional positive epistasis – one gene promotes the other but the second has no effect on the first; altruistic/parasitic epistasis – one gene promotes the other but the second inhibits the first; symmetrical negative epistasis – two genes inhibit each other at the same strength; asymmetrical negative epistasis – two genes inhibit each other but to different extents; and directional negative epistasis – one gene inhibits the other but the second is neutral to the first.

FunGraph shows its practical utility to map the genetic architecture of drug response for individual subjects from an association population (Figure 3). FunMap incorporates the Hill equation to estimate genotypic curves of heart rate for each subject in response to different dosages of dobutamine at each single nucleotide polymorphism (SNP).[31,35] A system of gLVODEs is implemented to estimate the independent and dependent components of genotypic values that are coded into personalized epistatic networks. We find that five randomly chosen subjects vary in the strength, sign and causality of genetic interactions within five-node SNP–SNP networks (Figure 3a). These topological discrepancies are related to different genetic mechanisms that each subject uses to respond to dobutamine. By comparing the independent and dependent dose–response curves, one can better characterize the role of how each SNP mediates drug response for a specific subject (Figure 3b). For subject 1, genotype *AA* at codon49 is inhibited by genotypes at other SNPs, its net genotypic value becomes less responsive to dobutamine compared with its independent value. This finding suggests that manipulating the interactive relationship of codon49 with its regulators can better improve the heart rate of subject 1 by dobutamine than targeting codon49 alone.

Stratification-specific networks: A shift from personalized medicine to precision medicine

Personalized medicine aims to tailor unique disease treatments and preventions for each patient by reconstructing his or her individualized networks. In clinical practice, precision medicine is more feasible by focusing on subgroups of disease risk via population stratification rather than the individual.[42] Precision medicine relies on the general rule that governs the network structure of patients from the same stratification. FunGraph implements functional clustering[43,44] to classify all patients into distinct categories based on the similarity of genotypic curves for drug response.

As an example, we identify three categories of subjects in five-SNP genotypic dose–response curves from 142 subjects (Figure 4). There are very few subjects in category 2, whose drug response is under genetic control in a way that is different from the majority of the association panel. In general, the joint mean dose–response curve of five SNPs differs dramatically among three categories (Figure 4); but such a difference is SNP-dependent. FunGraph reconstructs five-node pharmacogenetic networks for each category using its mean genotypic curves (Figure 4a). We find that interaction architecture differs dramatically among categories, suggesting that the genetic mechanisms underlying drug response are category-dependent. Subjects from the same category initiate a similar genetic mechanism to mediate their response to dobutamine, whereas those from different categories use different mechanisms. For subjects from categories 1 and 3, codon49 from the β_1AR gene promotes codon16 from the β_2AR gene, whereas the latter inhibits the former; but this altruistic

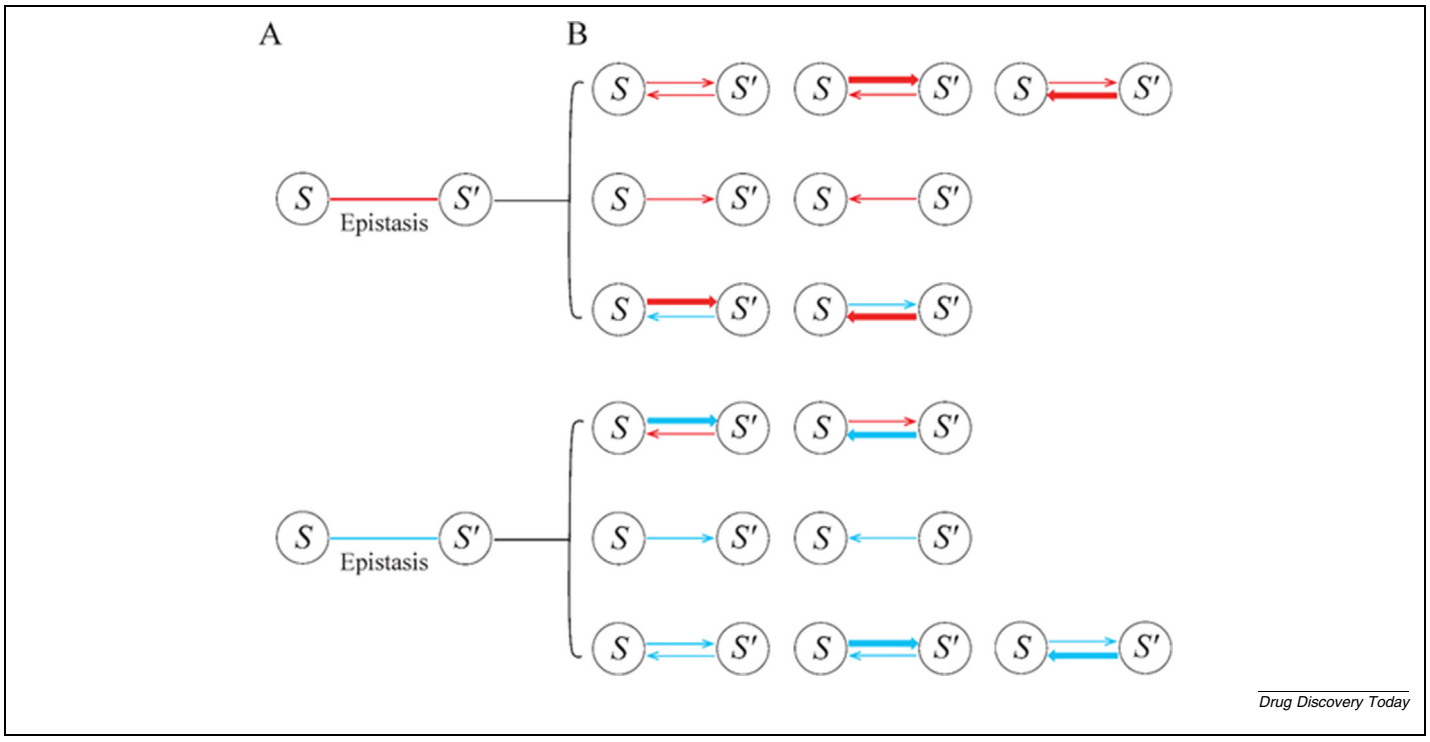


FIGURE 2

Observed epistasis attributed to different types of SNP–SNP interactions**.** Non-arrowed lines between SNP s and s' denote their non-causal epistasis, whereas arrowed lines stand for the casualty of epistasis, with the thickness of lines proportional to the strength of epistasis. Red and blue lines represent promotion and inhibition, respectively.

parasitic relationship does not take place in category 2. In category 1, codon49 inhibits codon492 from the α_1A gene but this asymmetrical antagonism does not occur in categories 2 and 3. Codon389 from the β_1AR gene establishes symmetric antagonism with codon16 from the β_2AR gene in category 3 but with codon492 from the α_1A gene in category 2.

FunGraph further decomposes the net genotypic curve of each category at each SNP into its independent and dependent components (Figure 4b), from which a clearer picture of the role of genetic interactions in modulating drug response can be charted. Codon49 from the β_1AR gene has a greater genotypic independent value of drug effect, with a greater slope of drug response, than its net genotypic value in categories 1 and 3, which is due to negative regulation from codon16 from the β_2AR gene. Because of small positive regulation received from codon492 of the α_1A gene, the net genotypic value of codon49 from the β_1AR gene is not much different from its independent value. For categories 1 and 3, heart rate can be improved through codon49 from the β_1AR gene by altering the activity of codon16 from the β_2AR gene. Taken together, we can design an optimal strategy to improve the heart rate of patients from specific categories.

Sparsity theory and modularity theory: from pharmacogenetic networks to pharmacogenomic networks

Pharmacogenetics is the study of genetic variability in drug response due to key genes, whereas pharmacogenomics is the study of the role of the genome in drug response. In general, pharmacogenetic networks deal with a limited number of interactive genes but pharmacogenomic networks cover all genes throughout the genome. The complexity of network reconstruction increases exponentially with the increasing number of genes. It is computationally impossible to reconstruct fully interconnected networks among thousands of thousands of genes as genotyped in a typical pharmacogenomic study.

To infer pharmacogenomics networks, we implement sparsity theory and modularity theory into FunGraph. Sparsity theory states that the stability of a living system is positively associated with its sparsity in certain domains; a dense system is usually vulnerable to stochastic perturbations.[45–47] Network sparsity theory has been proposed to interpret system stability, according to which the percentage of the active interactions is inversely proportional to the system size.[48–51] Through statistical variable selection, we introduce this theory to choose a subset of the most significant genes that are linked to a given gene, because we believe that not all other genes are linked with the focal gene. This process shifts a fully interconnected network to a sparsely connected network.

In a big living system, different entities display functional similarities and differences and, therefore, are organized into distinct modules within each of which entities are more functionally correlated with each other than with those from other modules.[52,53] In pharmacogenomics, some SNPs can change their genetic effects in a similar pattern, which are thus coalesced into the same communities of networks. SNPs with different pat-

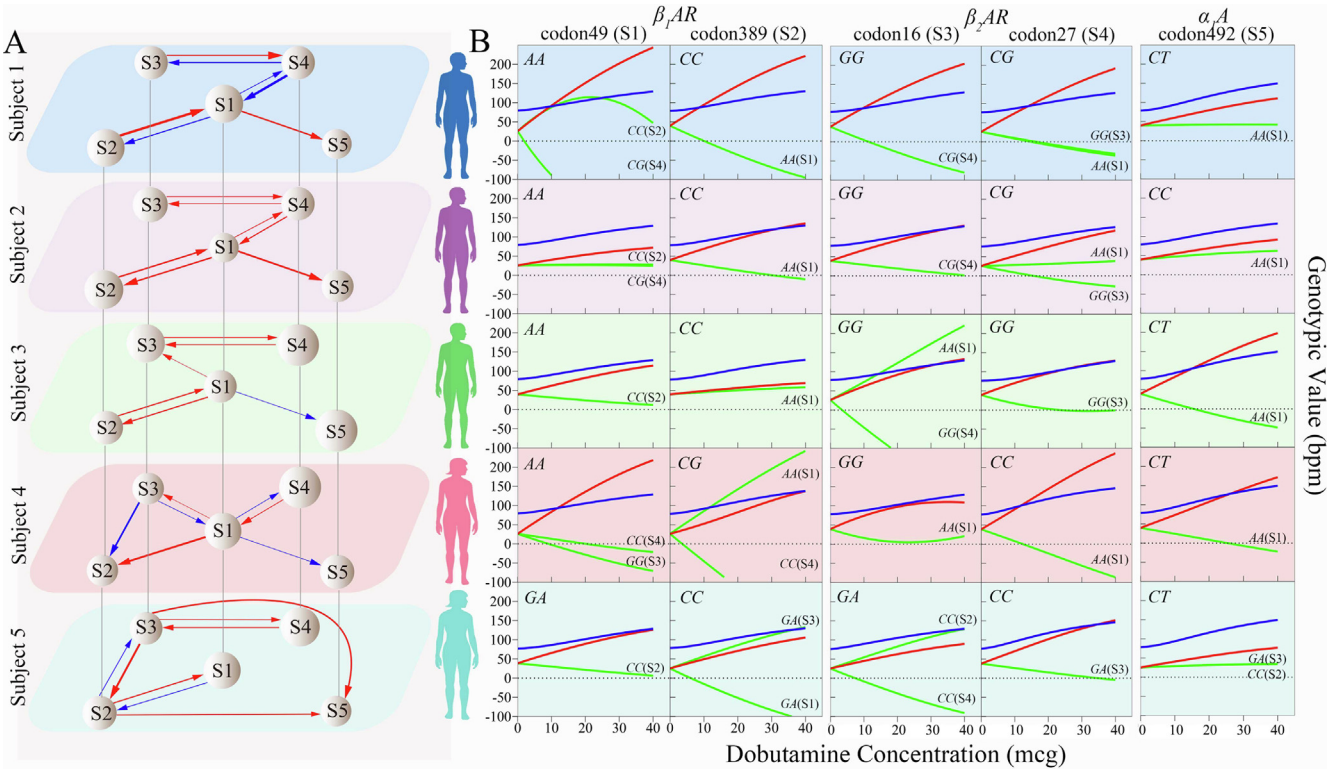


FIGURE 3

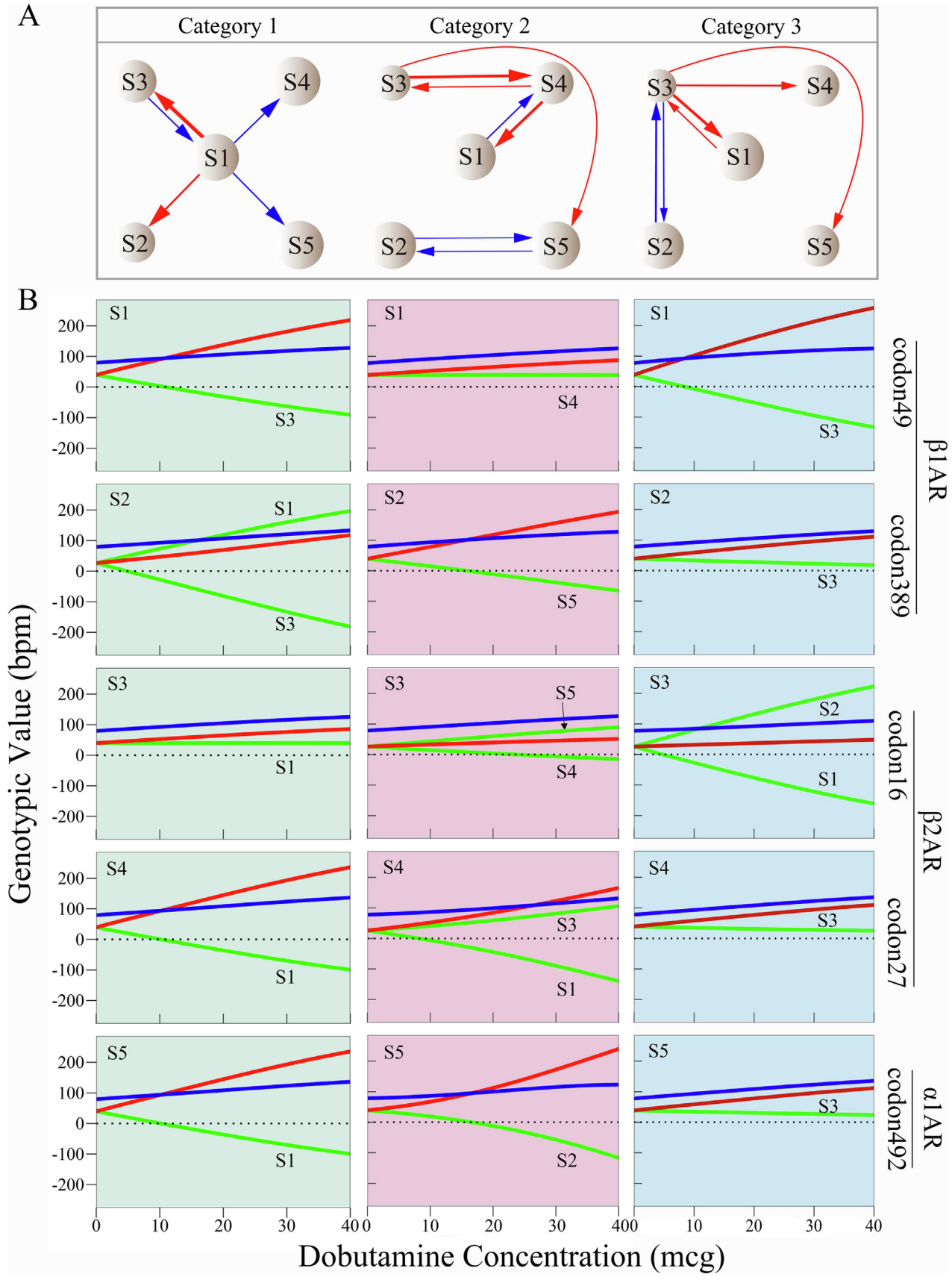
Subject-specific genetic networks reconstructed by functional graph theory. (a) Five-node interaction networks underlying heart rate response to dobutamine for five randomly chosen subjects from a panel of candidate gene association study population, in which nodes represent the independent genotypic values of each SNP, with circle size proportional to the value, and edges represent directed epistasis from one SNP to next, with line thickness proportional to the strength of epistasis. Red and blue arrowed lines denote promotion and inhibition, respectively. (b) Decomposition of net genotypic dose–response curve at each SNP (blue line) into its independent genotypic curve (red line) and dependent genotypic curve (green line) for five randomly chosen subjects. Five SNPs: codon49, codon389, codon16, codon27 and codon492, are denoted as S1–S5 in order. Adapted, with permission, from 64 with the data used, with permission, from 31.

terns of genetic effect change are located in different network communities. Thus, by clustering all SNPs into different modules, FunGraph can determine the number and size of network communities. Ultimately, we dissolve a big network into a set of multiple communities, each representing a subnetwork, which form multilayer and multiplex networks. This process has two advantages: first, this is a sparse network that could be more stable than a full network; second, the number of SNPs within a community reduces so that computational efficiency increases.

In summary, one significant merit of FunGraph is to reconstruct an omnigenic network from a complete set of genome-wide genes by implementing developmental modularity theory. According to this theory, all genes, no matter how many, can be classified into distinct modules of smaller size. If a module is still too big, FunGraph classifies it into its distinct submodules. This procedure is repeated until the number of genes within a unit reduces to a tractable level. At the end, FunGraph can coalesce all genes into multilayer and multiplex interactome networks. Because FunGraph is constructed as a system of ordinary differential equations expressed as a function of dose, it does not rely on an extremely big sample size that is crucial for reconstructing large-scale genome-wide networks according to a usual thinking. FunGraph capitalizes on the result from functional mapping, thus relying on the precision of functional mapping. Because functional mapping is based on a single marker analysis, however, its requirement for sample size is not as strong as required by network reconstruction.

Concluding remarks and future perspectives

Networks are central features of complex systems. The genetic architecture of drug response can be viewed as a system in which several genes, perhaps all genome-wide distributed genes, as predicted by omnigenic theory,[23] act and interact with each other in a complicated way.[54–57] As such, reconstructing pharmacogenetic networks to disentangle the genetic machineries of how patients respond to medications opens up a new gateway to pharmacogenomic research standing in the core of precision medicine. There have been several attempts to identify genetic networks for drug response[58,59] but these attempts can be limited when they are applied in practice. Their main disadvantages



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include that the networks reconstructed by existing approaches are not informative in terms of network architecture.

FunGraph can overcome the limitations of existing network models.[24–28] In statistical genetics, FunMap has been proposed to map the developmental pattern of genetic effects exerted by individual genes.[29–35] FunGraph integrates FunMap, evolutionary game theory and the Lotka–Volterra prey–predator model into mathematical graphs, in which nodes represent the independent genetic effects of genes assumed to be expressed in isolation and the edges denote directional, signed and weighted interactions between pairs of genes. FunGraph has been applied to reconstruct genetic interactome networks mediating growth traits in Euphrates poplar[26,27] and microbial resistance to antibiotics[28] from a number of samples, and it can be generalized to characterize subject-specific genetic networks, which are sorely needed for precision medicine.

FunGraph uses a system of gLVODEs for genotypic decomposition at each SNP to characterize how each SNP regulates, and also is regulated by, every other SNP in a community of genes. Such a rock-paper-scissors loop of genetic interactions circumvents the limitation of traditional approaches that can only analyze a pair of SNPs at a time.[41] Beyond this, FunGraph reconstructs fully informative networks that capture all fundamental features of epistatic interactions. Epistasis is traditionally defined as a population concept[54,58] but FunGraph leverages epistasis to describe individual members in the population. It can discern which genotype at one locus epistatically promotes or inhibits the expression of the genotype at the other locus for each subject, rather than measuring epistasis as a genetic variance.[22] Such individualized informative networks are expected to have an immediate implication for designing personalized medicine. From genetic networks of a specific subject, we can more precisely alter the activity of certain genotypes toward maximizing drug efficacy.

FunGraph is powerful for inferring multilayer and multiplex pharmacogenomic SNP–SNP interactome networks from a classical genome-wide association study. However, there is much room to improve FunGraph, making it a more practically useful tool. First, the process from SNP to drug response includes gene regulatory networks composed of transcriptional genes, proteins, metabolites and even microbes. Genetic variants modulate the expression of causal genes under the regulatory mechanisms shaped by the functional elements. FunGraph should integrate intermediate molecular traits, such as gene expression, protein expression and metabolite abundance, to deduct possible molecular mechanisms underlying drug response. Second, FunGraph relies on the mathematical solving of ODEs. Current AI approaches can provide a more powerful and more general solution of nonlinear dynamic equations. Third, more-robust dynamic equations, such as stochastic differential equations, should be implemented into FunGraph, capturing the random effect of genes and their interactions on drug response (Box 1).

Box 1 A statistical procedure of FunGraph

The original formulation of FunGraph was systematically given in previous articles[25–28,60] and summarized in by Wu and colleagues.[61] For this article to be self-contained, we briefly describe its procedure as below. Suppose we sample n subjects from a natural population to build a pharmacogenetic association study. To investigate drug response, these subjects are administered by a drug at a series of dosages, deigned to improve a physiological parameter of patients. Considering differences in administration schedule, let (c_{i0}, c_{i1}, . . ., c_{iT_i}) denote different dosages for a specific subject i (where $c_{i0} = 0$) ($i = 1, \ldots, n$) and ($y_i(c_{i0})$, $y_i(c_{i1})$, . . ., $y_i(c_{iT_i})$) denote the observed values of drug response parameter of this subject. All these subjects are genotyped at a panel of m genome-wide distributed SNP loci. In the subsequent analysis, we use adjusted phenotypic data of drug response that are corrected for all possible covariates including demographic factors, lifestyle and population structure detected from all m SNPs. Data structure for association studies is illustrated in Figure S1a (see Supplementary material online).

The genotypic curve of a subject at a SNP is decomposed into two components: the independent component that is expressed when this SNP is assumed to be in isolation; and the dependent component that results from the influence of other SNPs on this SNP.[24–28] This argument can be formulated by a system of gLVODEs, by which the $z_s(c)$ value at SNP s is expressed as shown in Eq. (1):

$$\dot{z}_s(c) = Q_s(z_s(c)) + \sum_{s'=1, s' \neq s}^{m=5} Q_{ss'}(z_{s'}(c)) + \epsilon_s(c) \quad (1)$$

where $Q_s(\cdot)$ is the independent component, determined by SNP s' own genotypic value $z_s(c)$, $Q_{ss'}(\cdot)$ is the dependent component, determined by the genotypic value $z_{s'}(c)$ of SNP s', and $\epsilon_s(c)$ is the residual error, distributed as $N(0, \sigma_s^2(c))$. Because there is no explicit form for $Q_s(\cdot)$ and $Q_{ss'}(\cdot)$, FunGraph implements a nonparametric smoothing approach, such as Legendre Orthogonal Polynomials (LOP), to model their dynamic changes.[62,63] The residual error might be antedependent (i.e., the error at a drug dose is influenced by those at its previous dose). Thus, FunGraph implements an autoregressive approach, such as the first-order structured antedependent model (SAD (1)),[60,64] to fit the residual covariance structure.

FIGURE 4

Category-specific genetic networks by functional graph theory. (a) Five-node interaction networks underlying heart rate response to dobutamine for three categories, in which nodes represent the independent genotypic values of each SNP, with circle size proportional to the value, and edges representing directed epistasis from one SNP to the next, with line thickness proportional to the strength of epistasis. Red and blue arrowed lines denote promotion and inhibition, respectively. (b) Decomposition of net genotypic dose–response curve at each SNP (blue line) into its independent genotypic curve (red line) and dependent genotypic curve (green line) for three categories. Five SNPs: codon49, codon389, codon16, codon27 and codon492, are denoted as S1–S5 in order. Adapted, with permission, from 64 with the data used, with permission, from 31.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.drudis.2023.103608.

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