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A unified mapping framework of multifaceted pharmacodynamic responses to hypertension interventions

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Abstract

Increasing studies suggest that the best therapy for hypertension not only needs to control systolic (SBP) and diastolic blood pressure (DBP), but also requires the simultaneous control of the pulsatile component (pulse pressure, PP, defined as SBP minus DBP) and steady component (mean arterial pressure, MAP, defined as 1/3 SBP plus 2/3 DBP). However, the genetic basis of how these blood pressure measures respond singly or in combination to drug intervention is unclear, thus limiting the translation of personalized hypertension medicine. We propose a unified functional mapping framework for identifying specific quantitative trait loci (QTLs) that mediate multivariate response-dose curves of blood pressure. The mapping framework integrates the pharmacodynamic mechanisms of drug response into a genetic association study setting to characterize how QTLs govern PP and MAP through jointly regulating systolic and diastolic pressures. The framework can quantify the genetic effects of individual QTLs on maximal drug effect, the maximal rate of drug response, and the dose window of maximal drug response. In conclusion, the unified mapping framework provides a powerful tool for identifying pharmacological genes responsible for blood pressure and can potentially help to design the right medication and right dose for right patients based on their genetic makeup.

Keywords

Pulse pressure; mean arterial pressure; drug response; pharmacodynamics; QTL; association studies

Introduction

Systolic blood pressure (SBP) and diastolic blood pressure (DBP), reflecting roughly the peak and trough of blood pressure (BP), are commonly used as a criterion to diagnose and evaluate hypertension and its severity, and predict the possible-related comorbidities^{1,2}. A growing body of evidence shows that the association of BP with the risk of cardiovascular disease is determined not only by either SBP or DBP but also by the pulsatile component (described by pulse pressure, PP) and the steady component (described by mean arterial pressure, MAP)^{3–9}. Several studies have been conducted to characterize hemodynamic determinants of these two components and the physiological mechanisms of how they impact heart function and disease¹⁰. The pulsatile component is determined by ventricular ejection fraction, large-artery stiffness, early pulse-wave reduction, and heart rate¹¹, whereas the steady component is affected by left ventricular contractility, heart rate, and vascular resistance and elasticity averaged over time³. Current diagnostic protocols have used SBP and/or DBP, in conjunction with MAP and PP, to more comprehensively assess hypertension-related health risk⁶. For pharmacy sectors, a highly essential task is to develop and deliver specific medications for the simultaneous intervention for abnormal SBP and DBP as well as for PP and MAP according to patients' genetic makeups. Unfortunately, this is an extremely difficult process due to the inconsistent responses of different BP measures to drugs and to different patterns of how genes control these BP-related drug responses.

Previous studies through genetic mapping and genome-wide association mapping have identified important quantitative trait loci (QTLs) that affect MAP and PP in animal and human populations^{12–15}. In a meta-analysis of 150,134 individuals from 54 genome-wide association studies of European ancestry with 1000 Genomes Project-based imputation, Wain et al.¹⁶ identified a total of 48 genes that are involved in differences of SBP, DBP and PP among humans. Chauvet et al.¹⁷ found that QTLs affect the MAP of the inbred rat through modularity and epistasis. However, current studies of BP genetics are limited from a pharmacological perspective. First, these studies have not integrated the MAP- and/or PP-related drug response, limiting the discovery of genetic loci influencing BP improvement through drugs. Second, the MAP and PP responses to drugs are a dynamic process that follows pharmacodynamic (PD) and pharmacokinetic (PK) principles of drug effects and absorption in the body^{18,19}. The incorporation of PD and PK processes can enhance our understanding of the mechanistic basis of drug response.

Here, we propose and assess a genetic mapping framework of BP that incorporates PD principles into a pharmacogenetic trial. The advantages of PD modeling to study pharmacogenetics have been well recognized in previous studies. Wu and his group implemented a dynamic mapping, called functional mapping, to map pharmacogenetic loci for drug response^{20–23}. This model was then conceptualized as a theory for computational

pharmacogenetics and pharmacogenomics^{24–26}, which has been effectively used in practice. For example, Mustavich et al.²⁷ used it to detect loci that control susceptibility to alcohol dependence, and Wang et al.²⁸ applied it to identify important pharmacological genes for glucocorticoid intervention in asthma. This theory can be extended to model how SBP and DBP respond differently to drugs and how their derived variables, MAP and PP, are dynamically related with drug treatments. We review a statistical procedure for mapping and identifying specific QTLs that govern MAP and PP curves, and outline a number of clinically meaningful hypothesis tests used to address how a QTL determines the key events of PD and PK processes. We validate the model by analyzing a set of real data from dobutamine pharmacological studies.

A unified framework of functional mapping

Clinical pharmacogenetic trial

Genome-wide association studies (GWAS) have been increasingly used to investigate the pharmacogenetic mediation of drug response. A particular GWAS includes n patients who differ in age, race, sex, body mass index (BMI), and other demographic factors, recruited from a general population. These demographic factors will be treated as covariates of drug response. Consider a drug that can control BP and PP. The drug is administered to each patient by a series of physiologically tolerable doses ($C_1, \dots, C_T$), at each of which both SBP and DBP are monitored. Let $\mathbf{x}_{1i} = [x_{1i}(C_1), \dots, x_{1i}(C_T)]$ and $\mathbf{x}_{2i} = [x_{2i}(C_1), \dots, x_{2i}(C_T)]$ denote the vectors of SBP and DBP values for subject i , respectively. MAP ($\mathbf{y}_i$) is approximated by one third of PP plus two thirds of DBP at normal resting heart rates, whereas PP ($\mathbf{z}_i$) of this subject is defined as the difference of DBP from SBP⁵. Then, we have

$$\mathbf{y}_i = [x_{1i}(C_1) + 2x_{2i}(C_1), \dots, x_{1i}(C_T) + 2x_{2i}(C_T)]/3 \quad (1a)$$

$$\mathbf{z}_i = [x_{1i}(C_1) - x_{2i}(C_1), \dots, x_{1i}(C_T) - x_{2i}(C_T)] \quad (1b)$$

These two derived variables are used to map BP-QTLs. All the patients who participated in this study are genome-wide genotyped for thousands of thousands of single nucleotide polymorphisms (SNPs), at each of which there are three different genotypes AA , Aa , and aa . Let n_1 , n_2 , and n_3 denote the observations of the three genotypes, respectively.

The drug-induced biochemical and distribution effects in the human body obey some basic kinetic rules that can be described by pharmacodynamic and pharmacokinetic equations. The Emax model is one of the most commonly used pharmacodynamic models to illustrate and quantify drug dose-effect relationships. The Emax model is written as

$$E = E_0 + \frac{E_{\max} C^H}{EC_{50}^H + C^H} \quad (2)$$

where E is the drug effect at dose C , E_0 is the baseline, $E_{\max}$ is the asymptotic (limiting) effect, EC_{50} is the drug concentration that results in 50% of the maximal effect, and H is the slope parameter that determines the slope of the dose-response curve. The larger H , the steeper the linear phase of the log-dose-effect curve. In practice, we can remove the baseline effect to increase the precision of curve fitting by normalizing the longitudinal data.

Likelihood and estimation

To map BP-QTLs, we formulate the likelihood of derived variables (1a) and (1b) at a given QTL as

$$L(\mathbf{y}, \mathbf{z}) = \prod_{i=1}^{n_1} f_1(\mathbf{y}_i, \mathbf{z}_i) \prod_{i=1}^{n_2} f_2(\mathbf{y}_i, \mathbf{z}_i) \prod_{i=1}^{n_3} f_3(\mathbf{y}_i, \mathbf{z}_i) \quad (3)$$

where $f_j(\mathbf{y}_i, \mathbf{z}_i)$ is a bivariate longitudinal normal distribution for genotype j ($j = 1$ for AA , 2 for Aa and 3 for aa). This distribution has a form of

$$f_j(\mathbf{y}_i, \mathbf{z}_i) = \frac{1}{(2\pi)^T |\Sigma|^{\frac{1}{2}}} \exp \left[-\frac{1}{2} (\mathbf{y}_i - \boldsymbol{\mu}_{j|i}^y) \Sigma^{-1} (\mathbf{z}_i - \boldsymbol{\mu}_{j|i}^z)' \right] \quad (4)$$

which is specified by the vectors of overall genotypic means for subject i who carries genotype j for two BP parameters, SBP and DBP, and the SBP and DBP covariance matrix. The overall genotypic mean vectors are defined as

$$\begin{aligned} \mu_{j|i}^y = & \left[\frac{E_{\max j}^S C_{\tau}^{H S j}}{3 \left(EC_{50 S j}^H + C_{\tau}^{H S j} \right)} + \sum_{r=1}^R \alpha_r^S u_{ir}^S + \sum_{h=1}^H \sum_{l=1}^{L_h} \xi_{ihl} v_{hl}^S + \frac{2 E_{\max j}^D C_{\tau}^{H D j}}{3 \left(EC_{50 D j}^H + C_{\tau}^{H D j} \right)} + \sum_{r=1}^R \alpha_r^D u_{ir}^D \right. \\ & \left. + \sum_{h=1}^H \sum_{l=1}^{L_h} \xi_{ihl} v_{hl}^D \right]_{\tau=1}^T \end{aligned} \quad (5a)$$

$$\mu_{j|i}^z = \left\{ \frac{E_{\max j}^S C_{\tau}^{H_{Sj}}}{EC_{50Sj}^{H_{Sj}} + C_{\tau}^{H_{Sj}}} + \sum_{r=1}^R \alpha_r^S u_{ir}^S + \sum_{h=1}^H \sum_{l=1}^{L_h} \xi_{ihl} v_{hl}^S - \frac{E_{\max j}^D C_{\tau}^{H_{Dj}}}{EC_{50Dj}^{H_{Dj}} + C_{\tau}^{H_{Dj}}} - \sum_{r=1}^R \alpha_r^D u_{ir}^D - \sum_{h=1}^H \sum_{l=1}^{L_h} \xi_{ihl} v_{hl}^D \right\}_{\tau=1}^T \quad (5b)$$

Equations (5a) and (5b) include two parts: the first is the genotypic expression specified by the Emax model and the second is the effect due to variate covariates. The Emax model is defined by the parameters $(E_{\max j}^S, E_{50Sj}, H_{Sj})$ for the SBP curve and $(E_{\max j}^D, E_{50Dj}, H_{Dj})$ for the DBP curve at genotype j . The covariate model specifies the effect of continuous and discrete covariates on SBP and DBP, respectively, including u_{ir} ($r = 1, \dots, R$), the value of the r th continuous covariate, such as age and BMI, for subject i ; α_r , the effect of the r th continuous covariate; v_{sl} ($l = 1, \dots, L_s$, $s = 1, \dots, S$), the effect of the l th level for the s th discrete covariate, such as race, gender, and treatment, with $\sum_{l=1}^{L_s} v_{sl} = 0$ where L_s is the number of levels for the s th discrete covariate; and ξ_{isl} is an indicator variable of subject i who receives the l th level of the s th discrete covariate.

The longitudinal covariance matrix Σ_i of probability function (4) contains covariance matrices within and between two BP parameters. A variety of statistical approaches have been proposed to model the covariance structure. These approaches can be parametric, such as autoregressive, antedependent, autoregressive moving average, Brownian motion, and Ornstein-Uhlenbeck process, and also nonparametric, such as B-spline and Legendre orthogonal polynomials. A model-selection procedure is implemented to determine an optimal order of each approach and then the most parsimonious approach for covariance modeling^{29–31}.

To obtain the maximum-likelihood estimates (MLEs) of the unknown parameters in likelihood (4), a hybrid of the Nelder-Mead Simplex and least squares methods can be implemented. The MLEs of the covariate effects are obtained by a least-square method, whereas the Emax parameters of three genotypes and covariance-structuring parameters are estimated by the Simplex method.

Hypothesis tests

We provide a platform to test a number of hypotheses regarding the genetic control of how BP parameters respond to drug intervention. To test whether a significant QTL for BP exists, the following hypotheses are formulated:

$$H_0: (E_{\max j}^S, E_{50Sj}, H_{Sj}) \equiv (E_{\max}^S, E_{50S}, H_S) \text{ and } (E_{\max j}^D, E_{50Dj}, H_{Dj}) \equiv (E_{\max}^D, E_{50D}, H_D) \quad (6)$$

H_1 : At least one of the equalities above does not hold

for any $j = 1, 2, 3$. By calculating the log-likelihood ratio of the H_0 and H_1 , we can claim whether or not a significant QTL has been detected. This can be done by comparing this ratio against the critical threshold determined by permutation tests.

Next, it is important to test how the QTL affects MAP and PP. This can be done by formulating the following null hypotheses:

$$H_0: \frac{E_{\max j}^S C_{\tau}^{H_{Sj}}}{3(EC_{50Sj}^{H_{Sj}} + C_{\tau}^{H_{Sj}})} + \frac{2E_{\max j}^D C_{\tau}^{H_{Dj}}}{3(EC_{50Dj}^{H_{Dj}} + C_{\tau}^{H_{Dj}})} \equiv \frac{E_{\max}^S C_{\tau}^{H_S}}{3(EC_{50S}^{H_S} + C_{\tau}^{H_S})} + \frac{2E_{\max}^D C_{\tau}^{H_D}}{3(EC_{50D}^{H_D} + C_{\tau}^{H_D})} \quad (7)$$

$$H_0: \frac{E_{\max j}^S C_{\tau}^{H_{Sj}}}{EC_{50Sj}^{H_{Sj}} + C_{\tau}^{H_{Sj}}} - \frac{E_{\max j}^D C_{\tau}^{H_{Dj}}}{EC_{50Dj}^{H_{Dj}} + C_{\tau}^{H_{Dj}}} \equiv \frac{E_{\max}^S C_{\tau}^{H_S}}{EC_{50S}^{H_S} + C_{\tau}^{H_S}} - \frac{E_{\max}^D C_{\tau}^{H_D}}{EC_{50D}^{H_D} + C_{\tau}^{H_D}} \quad (8)$$

If both null hypotheses (7) and (8) are rejected, this means that this QTL pleiotropically determine MAP and PP. Otherwise, this QTL may be specific for one of the two traits.

We can also test how the QTL governs DBP and SBP. These tests can be based on the comparison of Hill coefficients among genotypes. Specifically, we have

$$H_0: (E_{\max j}^S, E_{50Sj}, H_{Sj}) \equiv (E_{\max}^S, E_{50S}, H_S) \quad (9)$$

$$H_0: (E_{\max j}^D, E_{50Dj}, H_{Dj}) \equiv (E_{\max}^D, E_{50D}, H_D) \quad (10)$$

If both null hypotheses (9) and (10) are rejected, this implies that the QTL is pleiotropic, triggering an effect on both DBP and SBP. Otherwise, it only affects one of the two BP parameters.

We can systematically characterize the genetic control of drug response as a dynamic process through BP parameters and their derived variables, which are physiologically meaningful. The additional advantages of this model lies in its capacity to detect the genetic basis of key events that play a central role in the outcome of drug efficacy. Based on the $E_{\max}$ model (1), this model can test how the QTL determines maximum drug effect ($E_{\max}$), the dose at which the drug effect achieves half of its maximal value (EC_{50}), the slope of drug response curve (H), and the dose at which drug-response change-rate is maximal (C_j), expressed as

$$C_I = \left[\frac{(H-1)EC_{50}^H}{H+1} \right]^{\frac{1}{H}}$$

We may be interested in testing genetic differences at any dose estimate, EC_p , which is the dose generating p -percentile of $E_{\max}$, as an estimate of the maximal effective dose. For example, EC_{90} is of interest in dose–response analysis. EC_p is calculated as

$$EC_p = EC_{50} \left(\frac{p}{1-p} \right)^{\frac{1}{H}}$$

All these tests can be established on both DBP and SBP parameters.

Model application

To validate the utility of our model, we analyze a pharmacogenetic data of cardiovascular disease²⁰. The study includes a group of 163 patients from age 32 to 86 years, treated by dobutamine, a medication able to control by intravenous administration acute congestive heart failure by increasing heart rate and cardiac contractility. The patients had a wide range of baseline (untreated) heart rates. The patients received increasing doses of dobutamine, from 0 (baseline) to 5, 10, 20, 30 and 40 mcg, at each of which their heart rates were recorded. The maximum doses vary among subjects due to different physiological limits (e.g., age, BMI, baseline heart rate). Dobutamine is a synthetic catecholamine playing an important role in enhancing cardiac inotropic function by primarily stimulating sympathomimetic β_1 -adrenergic receptors (β_1 AR), and thus increasing contractility and cardiac output. Dobutamine has also weak sympathomimetic β_2 -activity promoting target-organs artery vasodilation, and sympathomimetic α_1 -selective activity increasing BP. This study genotyped five SNPs, two located at codons 49 (Ser49Gly) and 389 (Arg389Gly) within the β_1 AR gene, two situated at codons 16 (Arg16Gly) and 27 (Gln27Glu) within the β_2 -adrenergic receptor (β_2 AR) gene, and one found at codon 492 (Arg492Cys) within the α_1 -adrenergic receptor (α_1 AR) gene. Here, we test whether these SNPs are associated with BP parameters.

We first corrected dobutamine dose-dependent heart-rate data by removing the effects due to age, sex, race, and BMI. By plotting all subjects' SBP and DBP values against different doses of dobutamine, we found different patterns of change between these two BP measures. In general, SBP increased with dose (Fig. 1A), whereas DBP decreased with dose (Fig. 1B). The average curves of both SBP and DBP can be fitted by the Hill equation (Adjusted $R^2 > 0.098$). By incorporating the Hill equation into expressions (1a) and (1b), we estimated the average curves of MAP (Fig. 1C) and PP (Fig. 1D). Both MAP and PP increased with dose; while the PP dose-related increase was expected given the dose-dependent SBP augmentation and DBP reduction. PP also had a much greater rate of change than MAP. Comparisons among SBP, DBP, MAP and PP suggest divergent patterns by which these four types of BP measures respond to dobutamine. Also, dramatic differences noted among

subjects in each type of BP parameter may imply the existence of genetic variants that affect specific inter-individual drug response.

Previous mapping studies with these data suggest that haplotype variants are a better determinant of pharmacological response to dobutamine than individual SNPs. As such, we incorporated the haplotype model into the likelihood (2). Consider a pair of SNPs with alleles A versus a , and B versus b , respectively, which form four possible haplotypes AB , Ab , aB , and ab with frequencies estimated from the EM algorithm²⁰. The haplotype model states that differences among these haplotypes is one of the causes for the phenotypic variation of a complex trait³². We used a risk haplotype to define a haplotype that is different from the remaining haplotypes. If AB is a risk haplotype and $\overline{AB}$ is the collective set of all remaining haplotypes, we can expect that diplotypes $AB|AB$, $AB|\overline{AB}$, and $\overline{AB}|\overline{AB}$ perform differently. It is possible to distinguish $AB|AB$, $\overline{AB}|\overline{AB}$, and most types of $AB|\overline{AB}$ directly from the genotype data. However, an individual carrying double heterozygote genotype $AaBb$ can be either diplotype $AB|ab$ or diplotype $Ab|aB$, which cannot be directly distinguished from each other. Lin et al. (2005) implemented the EM algorithm to distinguish these two diploypes so that their effect on drug response can be estimated. By assuming each haplotype as a risk haplotype, we estimated the likelihood value from (2). The optimal risk haplotype can be inferred from information criteria AIC.

By testing each pair of SNPs from the same gene, the haplotype model identified a significant risk haplotype AC within the β_1AR gene for BP parameters in response to dobutamine (Fig. 2). This haplotype affects MAP and PP in two fashions. First, diploypes ($AC|AC$, $AC|\overline{AC}$) that contain at least one copy of the risk haplotype are dramatically different from the haplotypes ($\overline{AC}|\overline{AC}$), which do not contain the risk haplotype ($P < 0.01$; Fig. 2A, B). Second, and yet more interestingly, diplotype ($AC|AC$) with two copies of the risk haplotype differs at an even higher significance level ($P < 0.001$) from diplotype ($AC|\overline{AC}$) with one copy of the risk haplotype. These results indicate that risk haplotype AC mediates MAP and PP not only through its existence but also through its frequency and interaction with non-risk haplotypes. Over the whole dobutamine-dose levels considered, diplotype $AC|AC$ correlates consistently with a larger MAP value than the other two diploypes, whereas the diplotype $\overline{AC}|\overline{AC}$ correlates consistently with a larger MAP than $AC|\overline{AC}$. This suggests that the risk haplotype AC , by its interaction effect with the other haplotypes, can reduce MAP more effectively than the dobutamine dose can increase it (Fig. 2A).

Compared with MAP, PP was found to be more sensitive to dobutamine (Fig. 2B). Starting at a lower BP increment level (about 50 mmHg), among three diploypes, $AC|AC$ reaches the largest PP (> 100 mmHg) increment at a medium to high dose of dobutamine due to its highest slope of PP response to dobutamine. Among three diploypes, diplotype $AC|\overline{AC}$ has the lowest slope, suggesting that the interaction between risk haplotype AC and any of the other haplotypes can inhibit the response of PP to dobutamine. Using the diplotype-dependent estimates of Hill coefficients from the likelihood estimate (2), We draw the curves of SBP and DBP (Fig. 2C, 2D) from which we found that, among three diploypes, diplotype $AC|AC$ exhibits the highest SBP and DBP over the entire range of dobutamine doses.

Diplotype $AC|AC$ has the lowest SBP and DBP, suggesting again the interaction between the risk haplotype AC and the other haplotypes as a critical determinant of BP parameters.

We further dissect the pattern of how the risk haplotype governs BP. Three diplotypes start from slightly different baselines of SBP and display small differences in the dose reaching a half of maximum drug effect (EC_{50}), but they diverge dramatically in the persistence to response to dobutamine (Fig. 2C). In spite of a smaller slope ($H = 2.77$), $AC|AC$ reaches 90% of maximum drug effect at a much larger dose (EC_{90}), compared to diplotypes and $AC|AC$ ($H = 3.17$). Unlike SBP, DBP exhibit remarkable differences among three diplotypes over an entire range of dobutamine doses (Fig. 2D). Starting from a larger DBP baseline, diplotype $AC|AC$ is more responsive to dobutamine, at a greater steepness ($H = 2.69$), than diplotypes $AC|AC$ ($H = 0.98$) and $AC|AC$ ($H = 0.89$). The three diplotypes strikingly differ in the dose reaching a half of the maximum drug effect, whereas the difference in the dose at 90% of maximum drug effect is even more pronounced.

Concluding remarks

Increasing evidence from large-scale epidemiological cohort studies has shown that the difference of SBP from DBP, defined as PP reflecting arterial stiffness, and two thirds of DBP plus one third of SBP, defined as MAP reflecting left ventricular contractility and heart rate, are highly associated with heart function, disease, and aging^{7–10,15}. Genetic studies have demonstrated the genetic variation of PP and MAP^{12–14}, suggesting that the influences of these two BP traits on heart dysfunction may vary inter-individually. As such, it is essential to investigate the genetic basis of these BP-parameters responses to drug interventions, which should be based on personalized medicine, to best prevent and treat cardiovascular disease, thereby improving quality of life and prolonging life expectancy.

We argue that a unified functional mapping framework is powerful for identifying, visualizing, and quantifying the genetic architecture of PP- and MAP-related drug responses. This framework integrates the pharmacodynamic principle of drug response into a mapping or association setting through mathematical equations. It is characterized by three features. First, by taking advantages of pharmacodynamics, hemodynamics, genetics, and statistics, the framework can map individual QTLs for the pharmacological response of PP and MAP. Second, the framework can demonstrate and test whether and how PP and MAP are governed jointly by the same set of QTLs. Results from this testing are important for stratifying patients and tailoring therapy based on how the patients respond to PP and MAP treatments. Third, the framework enables testing a number of clinically meaningful hypotheses regarding pharmacological reactions and metabolism. It can identify and quantify how some key events of drug response affect drug-effect outcome.

The mapping framework focuses on the genetic effect of DNA sequence variants on drug response, but many other sources, such as genetic imprinting and epigenetic modifications, may play an important role in moderating drug efficacy. Genetic imprinting can be incorporated into the model by recruiting the DNA information of patients' parents. Li and Wu³³ developed a model that can jointly analyze genetic data from parents and their offspring. This model is able to estimate in a case-control³⁴ and population-based cohort

study³⁵ the genetic influences and the genetic imprinting effects at the same QTLs. These extensions can be readily implemented into our model, allowing joint testing of genetic influences as well as genetic imprinting effects. Second, as a demonstration, we assumed a single marker analysis, which per se cannot estimate epistatic effects. Multi-locus models can be developed, allowing the genetic architecture of drug responses to be dissected in terms of genetic interactions¹⁷. Third, marginal single marker genetic analysis may be limited in charting an overall picture of genetic control mechanisms among all loci. Variable selection has been implemented to analyze all possible markers at the same time and further select and estimate a sparse set of loci for complex traits in genetic mapping or association studies of dynamic traits^{36–38}. This statistical procedure can be readily merged with our model, which will certainly help to systematically illustrate and characterize the pharmacogenetic control over PP and MAP.

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Figure 1.

Response curves for systolic (SBP) (A) and diastolic blood pressure (DBP) (B) to dobutamine in a pharmacogenomic study composed of 107 patients. From SBP and DBP, we obtained the curves of mean arterial pressure (MAP) (C) and pulse pressure (PP) (D). Thin green lines are response curves of individual subjects, and thick black lines are the mean curves fitted by the Hill equation. Dots are the doses of dobutamine at which SBP and SBP were measured.

Figure 2. Genetic curves of MAP (A) and BP (B) in terms of three diplotypes AC/AC , $AC|AC$, and $AC|AC$ between two SNPs within the β_1AR gene, estimated from the likelihood (2). The estimated Hill coefficients were used to draw SBP (A) and DBP curves (B) for each diplotype. The doses at which drug response reaches half of the maximum effect (EC_{50} , solid circles) and 90% of maximum effect (EC_{90} , solid triangles) are indicated.