Mapping Baroreceptor Function to Genome: A Mathematical Modeling Approach

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Manuscript received April 9, 2001
Accepted for publication January 11, 2002

ABSTRACT

To gain information about the genetic basis of a complex disease such as hypertension, blood pressure averages are often obtained and used as phenotypes in genetic mapping studies. In contrast, direct measurements of physiological regulatory mechanisms are not often obtained, due in large part to the time and expense required. As a result, little information about the genetic basis of physiological controlling mechanisms is available. Such information is important for disease diagnosis and treatment. In this article, we use a mathematical model of blood pressure to derive phenotypes related to the baroreceptor reflex, a short-term controller of blood pressure. The phenotypes are then used in a quantitative trait loci (QTL) mapping study to identify a potential genetic basis of this controller.

HUMAN diseases can be studied through the genetic dissection of quantitative traits in experimental models such as mouse and rat. Such studies have been carried out for diseases such as hypertension (Jacob *et al.* 1991; Deng and Rapp 1992, 1995; Schork *et al.* 1995), diabetes (Todd *et al.* 1991; Jacob *et al.* 1992; Gauguier *et al.* 1996), colon cancer (Dietrich *et al.* 1993), and breast cancer (Shepel *et al.* 1998; Lan *et al.* 2001). Studies of this type result in the association of a genome region with disease-defining measurements such as mean blood pressure, mean blood glucose level, or tumor number. Such associations have proven useful. For example, many quantitative trait loci (QTL) mapping studies have resulted in the identification of candidate genes that can give insights into these diseases or serve as therapeutic targets.

Although useful, the information provided by QTL mapping methods is limited by the data collected and the phenotypes defined. For example, data related to disease (end point data—*e.g.*, blood pressure recordings) are often collected and disease-defining measurements (phenotypes—*e.g.*, blood pressure recordings averaged over time) obtained and used in genetic mapping studies. As a result, any QTL region identified may contain genes affecting disease status, but no information about intermediate physiological controlling mechanisms is obtained. In addition, there is no information regarding the many physiological mechanisms that influence distinct characteristics of the end point data that is not summarized by the disease-defining measurements alone. Detailed knowledge of the genetic basis of a complex disease requires not only the identification of disease-causing genes, but also knowledge about the way in which these and other related genes act and interact to affect physiological mechanisms that in turn influence all aspects of the end point data dynamics. Such information is critical to the development of optimal methods of disease prevention, diagnosis, and control.

One possible approach to gain insight into the genetic basis of intermediate mechanisms that affect disease dynamics is to more closely combine physiological data with genetic studies. For example, data directly related to one or more physiological controlling mechanisms could be used as phenotypes in a genetic linkage analysis; then, any QTL identified would be directly related to the measured mechanism. The disadvantage to this approach is that collecting such data can be time consuming, expensive, and, in many cases, requires the development or implementation of protocols beyond the scope of most traditional genetics labs. In this work, we propose a method that provides information about the genetic basis of physiological controlling mechanisms using only end point data. The method utilizes a mathematical model to relate end point data with physiological mechanisms. By fitting the model to end point data, phenotypes that quantify the defined physiological mechanisms are derived. The derived phenotypes are then used in a genetic linkage analysis study to connect genome location with physiological mechanism.

The method is used in a study of mean arterial pres-

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sure control, but could be extended to studies of other physiological processes. Here, a mathematical model describing the direct effect of the baroreceptors on arterial pressure was constructed. By fitting the model to arterial pressure recordings from rat intercross populations, a quantification of the magnitude of the baroreceptor response for each member of the population is obtained. These quantifications are then used as quantitative traits in a genetic linkage analysis to identify regions of the rat genome that are correlated with baroreceptor activity. Since the parameters of the model (derived quantitative traits) capture detailed physiological information associated with the baroreceptor response, regions of the genome identified by mapping are considered to be involved in baroreceptor control. The article is organized as follows. First, the baroreceptor reflex is defined and open-loop experiments, designed to measure the strength of the baroreceptor reflex response, are discussed. Second, a mathematical model of arterial pressure, which defines the direct relationship between arterial pressure and the baroreceptor response, is introduced and validated. The model is then used to obtain a quantification of the baroreceptor reflex response from normotensive, hypertensive, and intercross rat populations. Finally, the quantifications for the intercross populations are used as quantitative traits in a genetic linkage analysis.

BARORECEPTORS

The baroreceptors are nerve terminals in the carotid sinus and aortic arch that stabilize moment to moment blood pressure variability, but are not involved in determination of the long-term level of arterial pressure (Cowley 1992). The baroreceptors monitor arterial pressure levels by sensing deviations from some baseline pressure and initiating a response that dampens such deviations. The response begins with impulses sent by the baroreceptors to the central nervous system, which in turn initiates a sequence of events resulting in both neural and humoral responses that ultimately result in a change in arterial pressure toward normal baseline levels. The baroreceptor reflex response can be thought of as a nonlinear controller whose efficacy can be calculated by conducting a series of experiments where the pressure sensed by the baroreceptors and the arterial pressure following baroreceptor response are maintained independently (open-loop experiments). To do this, the carotid sinus (which contains the baroreceptors) is isolated and the carotid sinus pressure, or baroreceptor sensing pressure, is maintained at some level independent from the pressure of the entire system. The conditioning pressure at which the carotid sinus is maintained before deviation is denoted by CSP^{cp} and is maintained in equilibrium with a level of pressure in the system, denoted X^{cp}. From this baseline, the carotid sinus pressure is deviated to CSP^{dp} and the resulting mean arterial pressure at steady state, X^{ss}, is recorded. Figure 1 reproduces the output from one such experiment (McKeown and Shoukas 1998).

The open-loop gain of the baroreceptor reflex is defined to be the ratio of the pressure response (after steady state has been reached) to the change in carotid sinus pressure. The gain calculated in response to a carotid sinus pressure deviation to level CSP^{dp} is denoted by $g(CSP^{dp})$. Mathematically one can express this relationship as a relative change in response to sensed pressure deviation,

$$g(\mathrm{CSP}^{\mathrm{dp}}) = \frac{X^{\mathrm{ss}} - X^{\mathrm{cp}}}{\mathrm{CSP}^{\mathrm{dp}} - \mathrm{CSP}^{\mathrm{cp}}}. \quad (1)$$

In the example demonstrated in Figure 1, $g(CSP^{dp}) = (130 - 90)/(50 - 200) = -0.27$. Repeating such experiments for different values of CSP^{dp} gives a gain curve such as that shown in Figure 2. One can deduce from Figure 2 that the gain of a particular mechanism depends upon the distance between the carotid sinus pressure elevation (CSP^{dp}) and the baseline pressure, ($\overline{CSP}$), at which the mechanism has maximum gain. It is well known in physiological applications of control theory that the gain curve associated with the baroreceptor reflex can be approximated mathematically by the equation below (Riggs 1970):

$$g(\mathrm{CSP}^{\mathrm{dp}}) = Ce^{-\eta(\mathrm{CSP}^{\mathrm{dp}} - \overline{\mathrm{CSP}})^2}. \quad (2)$$

Equation 2 implies that the response to CSP^{dp} is summarized by three parameters: C, which gives the strength of the maximum gain; η, which is related to the range of sensed pressure to which the baroreceptors respond; and $\overline{CSP}$, the equilibrium pressure around which the baroreceptors maintain arterial pressure. The shape of the curve specified by Equation 2 (shown in Figure 2) shows that the farther the sensed pressure is from maximal gain, the smaller the relative effect of the baroreceptor response.

MEAN ARTERIAL PRESSURE MODEL

Data: Mean arterial pressure recordings were obtained from baroreceptor denervated and intact Wistar, normal BN/MCW, hypertensive SS/MCW, and F_2 (BN/MCW $\times$ SS/MCW) intercross rats. Recordings from Wistar rats differing only in their baroreceptor response were obtained as described in Fazan *et al.* (1997). In particular, recordings were taken at a rate of 1 Hz from 16 rats: 8 baroreceptor denervated and 8 baroreceptor intact. Mean arterial pressure recordings were also obtained from an F_2 population following a protocol described in Cowley *et al.* (2000). In short, male F_2 offspring were obtained from a cross between BN/MCW and SS/MCW rats. Four-hour measurements of mean arterial pressure were collected at 100 Hz and averaged to give 1-Hz recordings on two mornings (resting phase)

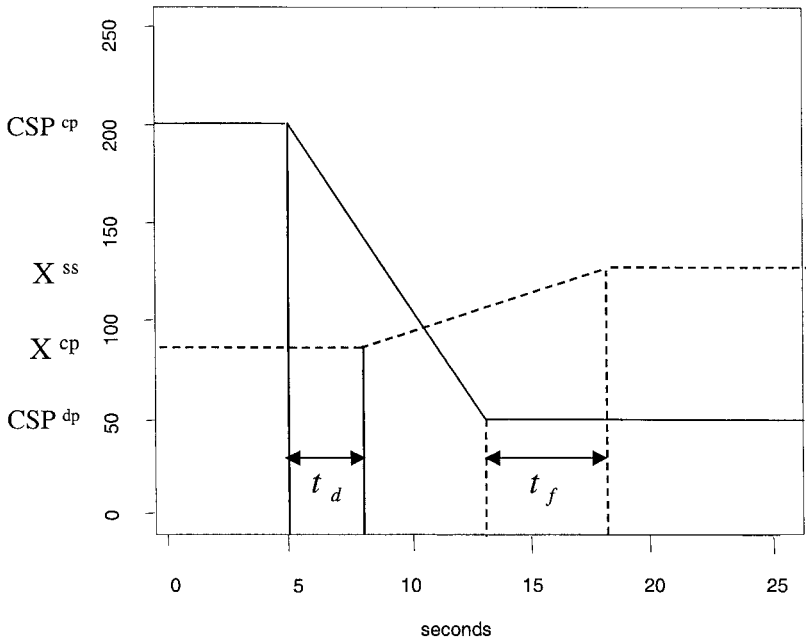

FIGURE 1.—Stylized open-loop experiment. Solid line gives pressure in the carotid sinus, which is deviated from 200 mmHg to 50 mmHg. The corresponding mean arterial pressure (dashed line) rises from 90 mmHg to 130 mmHg.

and one afternoon (active phase) for 58 BN, 44 SS, and 113 F_2 rats. Each of the F_2 rats was genotyped at 231 simple sequence length polymorphism (SSLP) genetic markers with an average spacing of 10 cM. Selective genotyping was done, resulting in 92% of the rats with some genotype information and 56% of the rats with at least 75% of the markers genotyped.

Development: A mathematical model was developed to concisely capture the direct effect of the baroreceptor reflex response on arterial pressure recordings. Unlike other models of baroreceptor control that require measurements from several experiments before quantitative information can be obtained, in this model, a measure of an animal's baroreceptor activity is obtained using only continuous recordings of arterial pressure. The mean arterial pressure at any discrete time t is denoted by X_t. Mean arterial pressure can be expressed as a two-compartment nonlinear difference equation: The linear term describes the pressure in the absence of baroreceptor control, while the other models the nonlinear effect of the baroreceptor response as measured by the gain. Mathematically, this model is expressed as

$$X_t = \overline{X} + \sum_{i=1}^{s} \alpha_i (X_{t-i} - \overline{X}) + g\left(\frac{1}{t_a}\sum_{k=t_d}^{t_f} X_{t-k}\right)\left(\frac{1}{t_a}\sum_{k=t_d}^{t_f} X_{t-k} - X^{bp}\right) + \varepsilon_t, \tag{3}$$

where $\varepsilon_t \sim N(0, \sigma^2)$. In the absence of baroreceptor control, the third term in Equation 3 is zero [zero gain gives $g(\cdot) \equiv 0$], and the expected value of X_t is $\overline{X}$. Thus, $\overline{X}$ represents the average pressure value in the absence of baroreceptor control. The delay of the baroreceptor response refers to the time lag between the change in sensing pressure and the resulting change in arterial pressure due to responses initiated by the baroreceptors. The delay is denoted by t_d and can be approximated from an open-loop experiment such as that shown in Figure 1. Specifically, t_d represents the time between the two solid lines of Figure 1 (here, $t_d = 3$). The length of time that one particular sensed pressure value continues to influence a response of the baroreceptor reflex on the pressure is denoted by t_a. In Figure 1, the length of time between the two dashed lines represents $t_f = t_a + t_d - 1$ (here, $t_f = 5$, which gives $t_a = 3$). The gain function, $g(\cdot)$, is given by Equation 2 with $\overline{CSP}$ replaced by X^{bp}; X^{bp} represents the baseline pressure around which the baroreceptor operates.

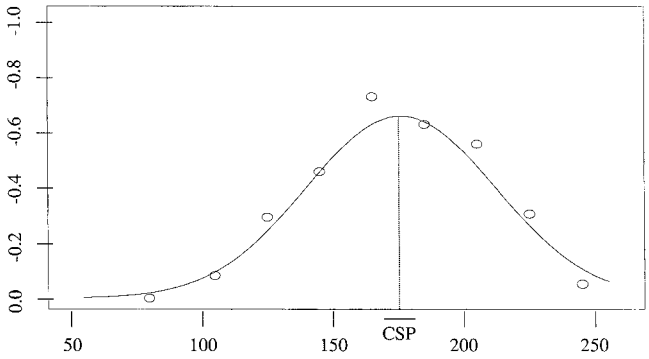

FIGURE 2.—Results of a gain calculating experiment (STEPHENSON and DONALD 1980) and approximation given by Equation 2. Note that it is standard to plot the gain curve on a scale from 0.0 to −1.0. Parameters were obtained using the nonlinear least-squares algorithm (nls) in S-PLUS.

Parameter estimation and validation: Estimates of t_a and t_d were obtained from open-loop experiments in the rat (MCKEOWN and SHOUKAS 1998). They are in agreement with estimates obtained in other studies (ALLISON *et al.* 1969; JACOB *et al.* 1995). The order, $s = 3$, of the linear autoregressive (AR) component describing

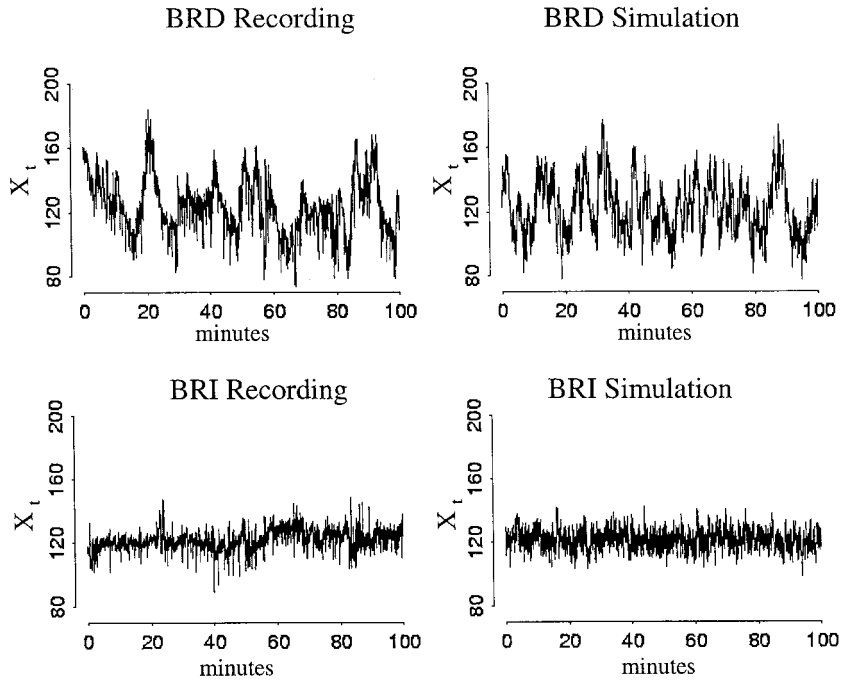

FIGURE 3.—Mean arterial pressure recordings with baroreceptor denervated (BRD) and intact (BRI) are given at top left and bottom left, respectively. Model (Equation 3) output is given on the right.

uncontrolled pressure was obtained from standard time series analysis techniques (BOX and JENKINS 1970) applied to mean arterial pressure recordings from baroreceptor denervated rats and through simulations of various order models. In particular, for each data set, estimated autocorrelation and partial autocorrelation functions (ACFs and PACFs) were generated and compared with theoretical ACFs and PACFs from AR processes of various orders. It can be shown that the ACF of an AR process of order s tails off slowly whereas the PACF drops to zero beyond order s. The Akaike information criterion (AIC) was also used to compare models of varying orders (AKAIKE 1974). The AIC provides a balance between goodness of fit of a model to data and the number of model parameters. The nonlinear regression algorithm nls in S-plus (MATHSOFT 1997) was used to obtain estimates for all remaining unknown parameters ($\{\alpha_i\}_{i=1}^{s}$, $\overline{X}$, C, X^{bp}, and η).

The model given by Equation 3 was fit to mean arterial pressure recordings from baroreceptor denervated and intact rats, the parental populations, and the derived F_2 population. Using the estimated parameters, simulations of the model were generated for each recording and compared with the original. Comparisons were done in the time, correlation, and frequency domains by considering time plots, antocorrelation functions, and spectra (BOX and JENKINS 1970). Residuals were checked for time dependence and normality.

The means and standard deviations averaged over each of the eight recordings from the denervated and intact rat populations, along with standard errors, are (123.72 ± 5.73) and (18.52 ± 1.58) for the denervated and (117.36 ± 3.10) and (8.06 ± 1.21) for the intact, respectively. As an illustration of the model's ability to reproduce the data, the time plots of one baroreceptor denervated and one baroreceptor intact rat are shown in Figure 3 next to model simulations. The mean and standard deviation of the baroreceptor denervated experimental data are $\mu = 124.07$ and $\sigma = 17.39$, while the corresponding mean and standard deviation of the simulated data are $\mu = 122.16$ and $\sigma = 16.88$. In the baroreceptor intact experimental data, the mean and standard deviation are $\mu = 121.99$ and $\sigma = 5.95$, compared with $\mu = 121.38$ and $\sigma = 5.90$ in the simulated data. These simulations indicate that the model is capable of reproducing the dynamics of blood pressure in both baroreceptor denervated as well as baroreceptor intact animals.

For the parental strains, the means and standard deviations averaged over each of the recordings, along with standard errors, are (117.73 ± 2.29) and (8.65 ± 0.45) for the BN and (180.40 ± 5.46) and (10.13 ± 0.54) for the SS strains, respectively. The time plots of pressure recordings from two parentals, their correlation functions, and their spectra (log-log scale) are shown in Figure 4 next to model simulations. As Figure 4 indicates, the physiologically based model captures distinct features between the normal and hypertensive populations. The first two moments for the BN and SS recordings are $(\mu, \sigma)_{BN} = (101.70, 5.21)$ and $(\mu, \sigma)_{SS} = (198.03, 11.16)$; for the corresponding simulations, $(\mu, \sigma)_{BNsim} = (101.53, 5.32)$ and $(\mu, \sigma)_{SSsim} = (198.16, 11.49)$. Qualitative characteristics in the time plots, as well as the mean and standard deviation, are preserved in the model simulations. There is significant estimated autocorrelation at large lags in the autocorrelation functions

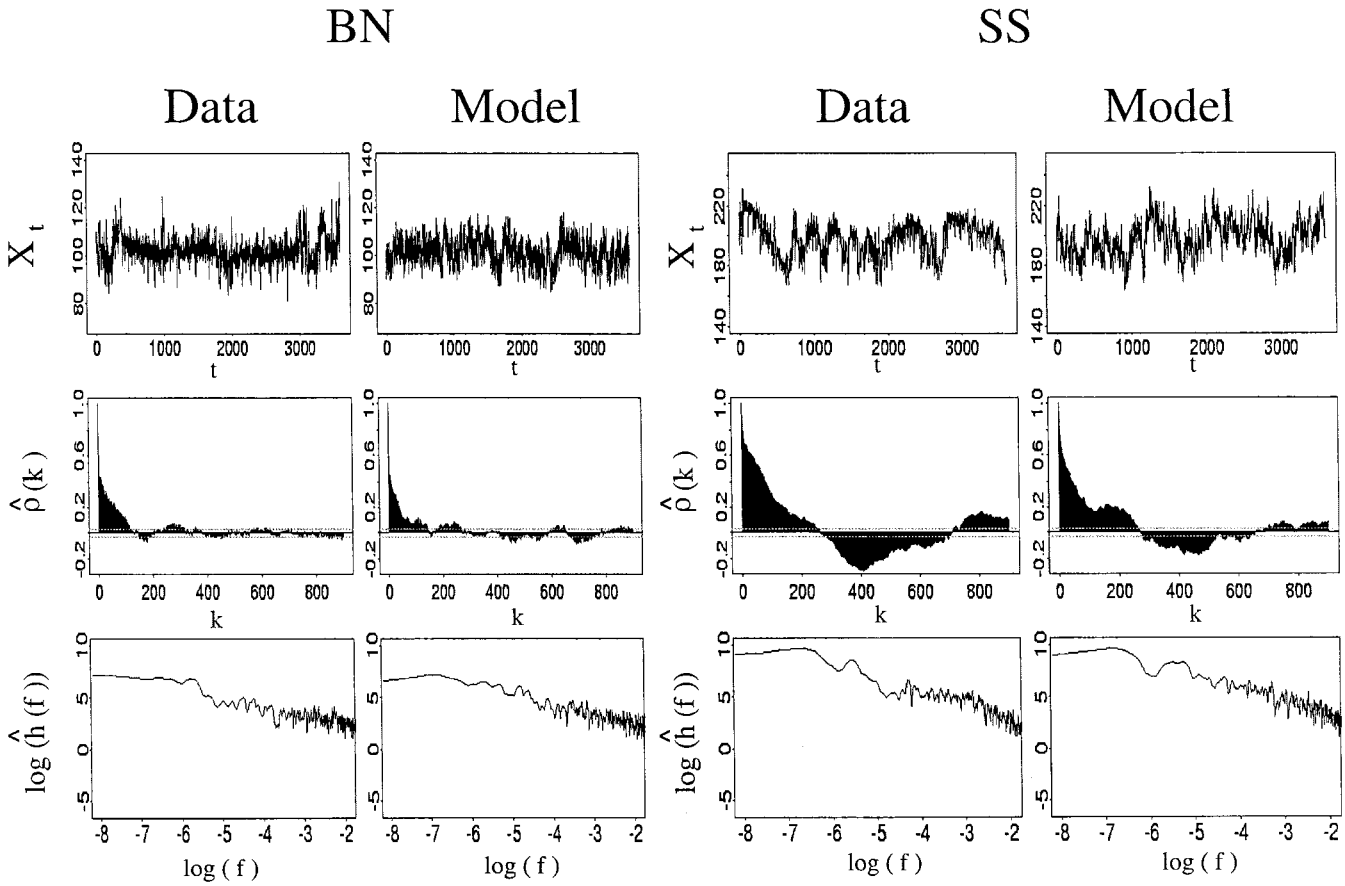

FIGURE 4.—Mean arterial pressure recordings from a respective BN and SS rat. Time plots (top), autocorrelation functions (middle), and spectra (log-log scale, bottom) are shown.

and power concentration near the origin in the spectra of the arterial pressure recordings. These properties are also evident in the corresponding model simulations. For the F_2 population, the averaged means and standard deviations, along with standard errors, are (133.79 ± 1.26) and (10.10 ± 0.23). Characteristics of the F_2 recordings resembled those present in the parental populations and model reproducibility for any given recording was similar to that shown in Figure 4.

QUANTIFICATION AND MAPPING OF BARORECEPTOR RESPONSE

By fitting the model to each arterial pressure recording, a characterization of mean arterial pressure ($\overline{X}$) and a quantification of baroreceptor response (C, X^{bp}, η) is obtained. Averages of the estimates of C, X^{bp}, and η calculated over the parental populations (BN, $N = 58$; SS, $N = 44$) are $\overline{C}_{BN} = -0.53$ (0.27), $\overline{X^{bp}_{BN}} = 114.48$ (4.52), $\overline{\eta}_{BN} = 1.54$ (0.70), and $\overline{C}_{SS} = -0.29$ (0.18), $\overline{X^{bp}_{SS}} = 175.43$ (6.29), $\overline{\eta}_{SS} = 1.32$ (0.43); standard errors are shown in parentheses. Thus, compared with the hypertensive SS population, the average maximum gain is stronger in the BN population and the average value around which the baroreceptors maintain the pressure is lower. These results are clearly shown in experimental studies that measure the baroreceptor reflex response directly (STEPHENSON and DONALD 1980; ANGELL-JAMES and GEORGE 1980; BRUNNER and KLIGMAN 1992). In addition, the estimated averages of arterial pressure without baroreceptor control [$\overline{\overline{X}_{BN}} = 124.22$ (3.32), $\overline{\overline{X}_{SS}} = 179.93$ (6.78)] are slightly greater than the corresponding averages with control [$\overline{X^{bp}_{BN}} = 114.48$ (4.52), $\overline{X^{bp}_{SS}} = 175.43$ (6.29)]. This is consistent with a number of studies that have demonstrated that mean arterial pressure increases only slightly following baroreceptor denervation (for a review, see COWLEY 1992).

Since recordings are taken on 3 different days, each of the four quantifications for each F_2 was averaged over the 3 days to give four average phenotypes: $\overline{X}$, C, X^{bp}, and η (average not denoted). The distributions of $\overline{X}$ and X^{bp} were well approximated by Gaussian distributions and did not require transformation. The phenotype C was scaled (multiplication by negative one and addition of a constant) so that all values were positive. The resulting distribution and the distribution of η were Poisson like, and thus square roots were taken to stabilize the variance and approximate Gaussian-distributed phenotypes (MCCULLAGH and NELDER 1989). C_{trans} and η_{trans} refer to these transformed phenotypes. Linkage

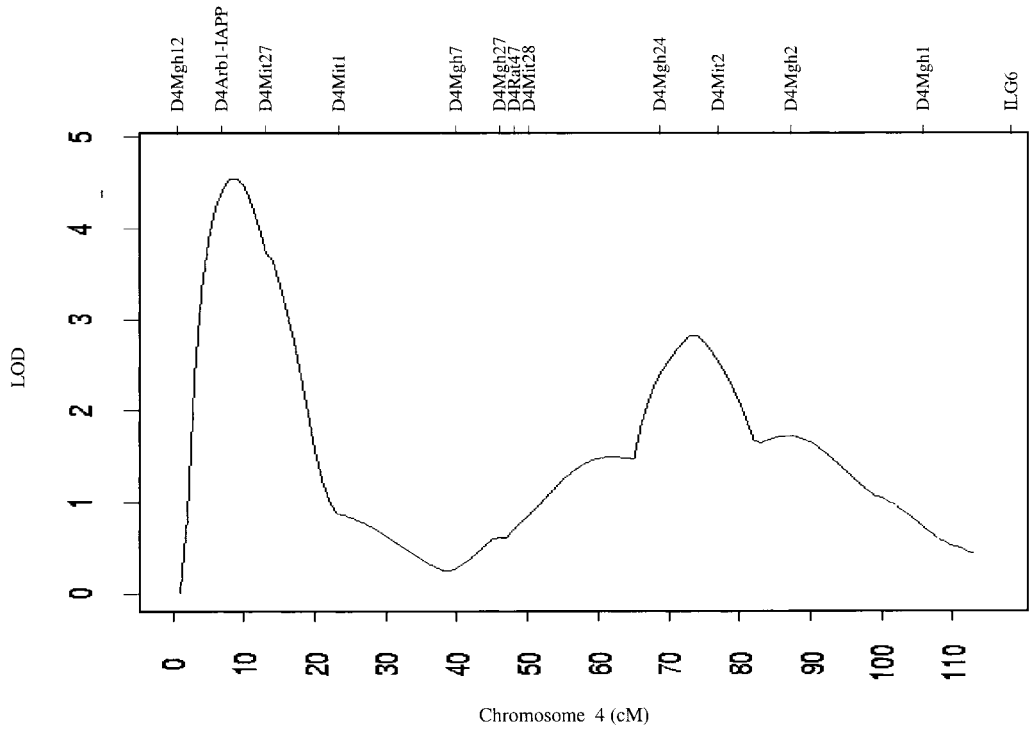

FIGURE 5.—LOD profile for C_{trans}.

analysis was conducted (Mapmaker/EXP 3.0b, LANDER *et al.* 1987; LINCOLN *et al.* 1993a; and Mapmaker/QTL 1.1, LINCOLN *et al.* 1993b) on $\overline{X}$, X^{bp}, C_{trans}, and η_{trans} to determine if the physiologically based traits are genetically informative. To ensure that the transformations themselves did not result in spurious LODs, nonparametric scans (KRUGLYAK and LANDER 1995) were also done on the untransformed phenotypes C and η. Analysis of C_{trans} linked it to chromosome 4 (*D4Arb1* region) with a LOD of 4.6 (Figure 5); the nonparametric scan of C was very similar and identified the same peak region. Permutation tests as described in CHURCHILL and DOERGE (1994) were used to verify that this LOD is in fact statistically significant. Specifically, phenotypes were randomly reassigned to the marker genotype vectors by permutation and LOD profiles were recomputed. This was repeated 1000 times. The 95th (99th) percentile of the permutation distribution of maximum LOD scores was 3.8 (4.3).

Figure 6 shows gain curves averaged over animals grouped by genotype at marker *D4Arb1*. The set point pressure in the homozygous SS group is higher than the BN group and the average maximum of the gain curve is lower. This indicates that the baroreceptor reflex operates around a higher pressure in the homozygous SS rats, with a diminished response. As discussed above, this qualitative behavior is consistent with experimental studies of the baroreceptor reflex in normotensive and hypertensive animals and further validates the model. The gain curves for the heterozygous animals were similar to the SS group, indicating that the effect of the SS allele is dominant. In addition to higher set point pressures and diminished responses, animals with deficient baroreceptors show an increase in blood pressure variability (see Figure 2 and COWLEY *et al.* 1973). This region of the genome linked to baroreceptor response seems to be related to blood pressure variation. With zero, one, and two copies of the SS allele at *D4Arb1*, the average standard deviations of the blood pressure recordings are 8.76, 9.92, and 10.89, respectively. The differences between groups are not statistically significant, indicating that the baroreceptor response affects, but is not completely characterized by, blood pressure variation. Finally, this region has not been previously linked with any blood pressure-related phenotypes. This is not surprising considering the fact that most studies have focused on average arterial pressure, and the baroreceptor response does not set the long-term level of mean pressure, but rather affects short-term dynamics (COWLEY *et al.* 1973).

Since the baroreceptor does not determine the long-term level of average arterial pressure, the average arterial pressure is expected to be similar in animals with and without baroreceptor control. In terms of the model parameters, X^{bp} (the set point or average pressure around which the baroreceptor reflex controls pressure) and $\overline{X}$ (the average pressure in the absence of baroreceptor control) should be similar. This is the case numerically, and both phenotypes map to the same genome region. Specifically, X^{bp} was linked to chromosome 10, in a region associated with average arterial pressure and the angiotensinogen converting enzyme (JACOB *et al.* 1991; DENG and RAPP 1992, 1995; KOVACS *et al.* 1997; GARRETT *et al.* 1998), with a LOD of 3.1.

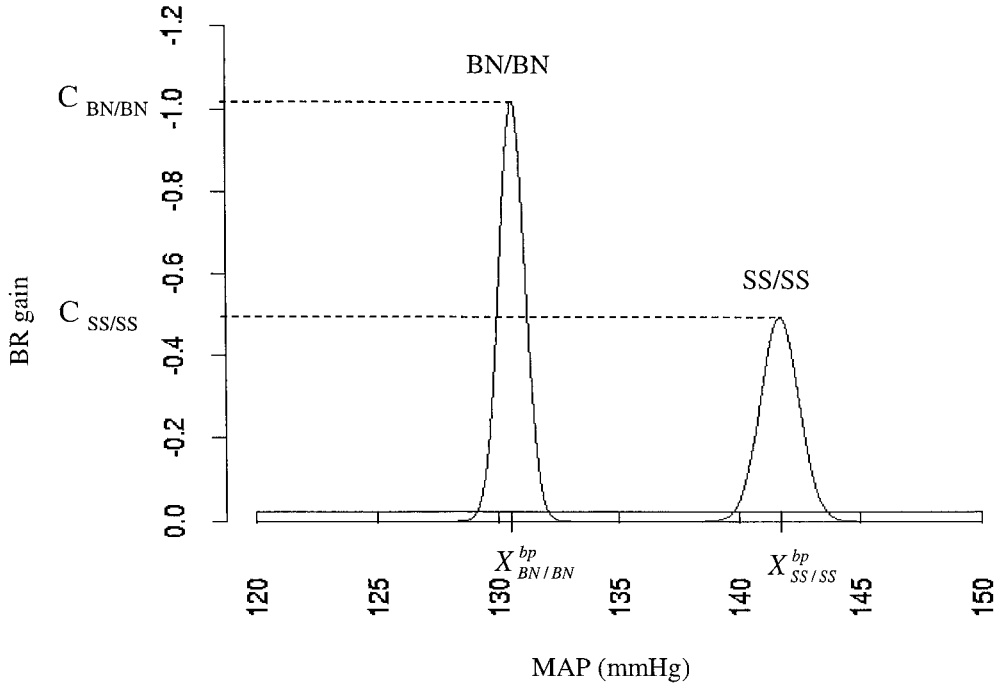

FIGURE 6.—Gain curves averaged over subsets of rats with genotypes BN/BN and SS/SS at marker D4Arb1.

$\bar{X}$ was also linked to this region with a suggestive LOD of 2.74. This is further indication that the model parameters are accurately quantifying the components they were defined to quantify.

DISCUSSION

This study has shown how a mathematical model of arterial pressure can be used to obtain genetically informative quantitative traits related to the baroreceptor reflex, a physiological mechanism that affects arterial pressure. A mathematical model is certainly not required to obtain such information. For example, one could perform a series of experiments to directly calculate the gain of the baroreceptor reflex response and use the gain of each animal as a phenotype in a similar study. However, such experiments are time consuming and expensive. In addition, when phenotyping an animal, one often wants to collect as many phenotypes as possible, and conducting an extensive series of experiments to obtain a single phenotype can reduce the number of additional phenotypes that can be collected. Furthermore, in other populations such as human, directly obtaining such information is not feasible. In such cases, where it is difficult or impossible to measure particular phenotypes, a mathematical model can be used.

The model of mean arterial pressure presented here was developed to measure the effect of the baroreceptor reflex response on the pressure. Simulations indicated that the model was capable of capturing the dynamics of arterial pressure under varying physiological conditions. In addition, model simulations and the model-based quantifications were compared with laboratory data obtained from related experiments and proved to be consistent. For these reasons, it seems that the model is capable of quantifying baroreceptor dynamics. However, it should be noted that open-loop experiments on each animal were not conducted to directly quantify the baroreceptor reflex. As a result, the exact connection between the derived traits and the baroreceptor reflex was not definitively confirmed.

The two traits defined to measure mean arterial pressure ($\bar{X}$ and X^{bp}) map to chromosome 10 in a region (ACE) known to be associated with blood pressure. The derived phenotype C mapped to chromosome 4 between markers D4Mgh12 and D4Mit1. Recall that C quantifies the magnitude of the baroreceptor reflex response. No pressure-related phenotypes have been mapped to this region previously. This is not surprising considering the fact that the baroreceptor response does not set the long-term level of pressure, but rather affects short-term dynamics. This region of chromosome 4 is homologous to mouse chromosome 6 and human chromosome 12 (12p12–2p14), which contain two genes of interest: IAPP and CCHL1A1 (also symbolized as CACNL1A1 and CACNA1C). The IAPP gene is known to encode islet amyloid polypeptide (IAPP), a polypeptide secreted by the pancreas. It is deposited as pancreatic islet amyloid in 90% of patients with noninsulin-dependent diabetes mellitus (NIDDM; CLARK *et al.* 1996) and has also been associated with insulin dependent diabetes (IDDM; KARLSSON *et al.* 1996). Interestingly, there are numerous studies demonstrating a decline in baroreceptor reflex activity in subjects with IDDM (WESTON *et al.* 1996a,b, 1998; JENSEN-URSTAD *et al.* 1999) or NIDDM (PAMIDIMUKKALA and JANDHYALA 1996). CCHL1A1 is a gene involved in activation of calcium channels from cardiac muscle (POWERS *et al.* 1991). It

has been shown that certain calcium channel blockers can reduce the gain of the baroreceptor reflex response (Gurtu *et al.* 2000), and calcium channel promoters can restore baroreceptor reflex sensitivity (Uechi *et al.* 1998).

This approach confirms the establishment of previously identified blood pressure QTL and provides the first evidence of candidate genes that may be contributing to the baroreceptor reflex. More generally, this study has shown how a mathematical model describing end point data (such as arterial pressure recordings) can be used to quantify physiological reflexes that affect or determine the end point when directly obtaining such information is not feasible. By using the quantifications as derived phenotypes, one can obtain information about the genetic basis of physiological controlling mechanisms affecting end points of interest. Such an approach can help to increase our understanding of intermediate phenotypes and the basic biology underlying disease pathogenesis.

We are grateful for the contributions from the laboratories of A. W. Cowley, Jr., and H. J. Jacob at the Medical College of Wisconsin. In particular, Mary Kaldunski (Cowley) coordinated all blood pressure time series collection and Monika Stoll (Jacob) was instrumental in building the linkage map.

LITERATURE CITED

Akaike, H., 1974 A new look at statistical model identification. IEEE Trans. Automat. Control **AU-19:** 716–722.

Allison, J. L., K. Sagawa and M. Kumada, 1969 An open-loop analysis of the aortic arch barostatic reflex. Am. J. Physiol. **217**(6): 1576–1584.

Angell-James, J. E., and M. J. George, 1980 Carotid sinus baroreceptor reflex control of the circulation in medial sclerotic and renal hypertensive rabbits and its modification by the aortic baroreceptors. Circ. Res. **47**(6): 890–901.

Box, G. P., and G. Jenkins, 1970 *Time Series Analysis: Forecasting and Control.* Holden-Day, San Francisco.

Brunner, M. J., and M. Kligman, 1992 Rapid resetting of baroreflexes in hypertensive dogs. Am. J. Physiol. **262:** H1508–H1514.

Churchill, G. A., and R. W. Doerge, 1994 Empirical threshold values for quantitative trait mapping. Genetics **138:** 963–971.

Clark, A., S. B. Charge, M. K. Badman and E. J. deKoning, 1996 Islet amyloid in type-2 (NIDDM) diabetes. APMIS **104**(1): 12–18.

Cowley, A. W., Jr., 1992 Long-term control of arterial blood pressure. Physiol. Rev. **72**(1): 231–300.

Cowley, A. W., Jr., J. F. Laird, Jr. and A. C. Guyton, 1973 Role of the baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ. Res. **32:** 564–576.

Cowley, A. W., Jr., M. Stoll, A. S. Greene, M. L. Kaldunski, R. J. Roman *et al.*, 2000 Genetically defined risk of salt sensitivity in an intercross of Brown Norway and Dahl S rats. Physiol. Genomics **2:** 107–115.

Deng, Y., and J. P. Rapp, 1992 Cosegregation of blood pressure with angiotensin converting enzyme and atrial natriuretic peptide receptor genes using Dahl salt-sensitive rats. Nat. Genet. **1:** 267–272.

Deng, Y., and J. P. Rapp, 1995 Locus for the inducible, but not a constitutive, nitric oxide synthase cosegregates with blood pressure in Dahl Salt sensitive rat. J. Clin. Invest. **95:** 2170–2177.

Dietrich, W. F., E. S. Lander, J. S. Smith, A. R. Moser, K. A. Gould *et al.*, 1993 Genetic identification of Mom-1, a major modifier locus affecting Min-induced intestinal neoplasia in the mouse. Cell **75:** 631–639.

Fazan, R., Jr., J. A. Castania, G. Ballejo, M. C. Salgado and H. C. Salgado, 1997 Influence of sympathetic blockade on the acute hypertensive response to aortic constriction. Am. J. Physiol. **273:** H2648–H2651.

Garrett, M. R., H. Dene, R. Walder, Q. Y. Zhang, G. T. Cicila *et al.*, 1998 Genome scan and congenic strains for blood pressure QTL using Dahl salt-sensitive rats. Genome Res. **8:** 711–723.

Gauguier, D., P. Froguel, V. Parent, C. Bernard, M. Bihoreau *et al.*, 1996 Chromosomal mapping of genetic loci associated with non-insulin dependent diabetes in the GK rat. Nat. Genet. **12:** 38–43.

Gurtu, S., S. Shukla, D. Mukerjee and S. Khattri, 2000 Effect of calcium channel blockers on baroreceptor reflex in anaesthetized cats. Pharmacol. Res. **42**(1): 101–105.

Jacob, H. J., K. Lindpaintner, S. E. Lincoln, K. Kusumi, R. K. Bunker *et al.*, 1991 Genetic mapping of a gene causing hypertension in the stroke-prone spontaneously hypertensive rat. Cell **67:** 213–224.

Jacob, H. J., A. Pettersson, D. Wilson, Y. Mao, A. Lernmark *et al.*, 1992 Genetic dissection of autoimmune type I diabetes in the BB rat. Nat. Genet. **2:** 56–60.

Jacob, H. J., A. Ramanathan, S. G. Pan, M. J. Brody and G. A. Myers, 1995 Spectral analysis of arterial pressure lability in rats with sinoaortic deafferentation. Am. J. Physiol. **269:** 1481–1488.

Jensen-Urstad, K., P. Reichard and M. Jensen-Urstad, 1999 Decreased heart rate variability in patients with type 1 diabetes mellitus is related to arterial wall stiffness. J. Intern. Med. **245**(1): 57–61.

Karlsson, E., M. Stridsberg and S. Sandler, 1996 Islet amyloid polypeptide secretion from pancreatic islets isolated from non-obese diabetic (NOD) mice. Regul. Pept. **63**(1): 39–45.

Kovacs, P., B. Voight and I. Klöting, 1997 Novel quantitative trait loci for blood pressure and related traits on rat chromosome 1, 10, and 18. Biochem. Biophys. Res. Commun. **235:** 343–348.

Kruglyak, L., and E. S. Lander, 1995 A nonparametric approach for mapping quantitative trait loci. Genetics **139:** 1421–1428.

Lan, H., C. M. Kendziorski, J. D. Haag, L. A. Shepel, M. A. Newton *et al.*, 2001 Genetic loci controlling breast cancer susceptibility in the Wistar-Kyoto rat. Genetics **157:** 331–339.

Lander, E., P. Green, J. Abrahamson, A. Barlow, M. J. Daly *et al.*, 1987 MAPMAKER: an interactive computer package for constructing primary genetic linkage maps of experimental and natural populations. Genomics **1:** 174–181.

Lincoln, S., M. Daly and E. Lander, 1993a Constructing genetic linkage maps with MAPMAKER/EXP 3.0b, Ed. 3. Whitehead Institute Technical Report. Whitehead Institute for Biomedical Research/MIT Center for Genome Research, Cambridge, MA.

Lincoln, S., M. Daly and E. Lander, 1993b Mapping genes controlling quantitative traits using MAPMAKER/QTL 1.1b, Ed. 2. Whitehead Institute Technical Report. Whitehead Institute for Biomedical Research/MIT Center for Genome Research, Cambridge, MA.

MathSoft, 1997 *S-PLUS Guide to Statistical and Mathematical Analysis.*

McCullagh, P., and J. A. Nelder, 1989 *Generalized Linear Models.* Chapman & Hall, New York.

McKeown, K. P., and A. A. Shoukas, 1998 Chronic isolation of carotid sinus baroreceptor region in conscious normotensive and hypertensive rats. Am. J. Physiol. **275:** H322–H329.

Pamidimukkala, J., and B. S. Jandhyala, 1996 Evaluation of hemodynamics, vascular reactivity and baroreceptor compensation in the insulin resistant Zucker obese rats. Clin. Exp. Hypertens. **18**(8): 1089–1094.

Powers, P. A., R. G. Gregg, P. A. Lalley, M. Liao and K. Hogan, 1991 Assignment of the human gene for the alpha-1 subunit of the cardiac DHP-sensitive Ca(2+) channel (CCHL1A1) to chromosome 12p12-pter. Genomics **10:** 835–839.

Riggs, D. S., 1970 *Control Theory and Physiological Feedback Mechanisms.* Waverly Press, Baltimore.

Schork, N. J., J. E. Krieger, M. R. Trolliet, K. G. Franchini, G. Koike *et al.*, 1995 A biometrical genome search in rats reveals the multigenic basis of blood pressure variation. Genome Res. **5:** 164–172.

Shepel, L. A., H. Lan, J. D. Haag, G. M. Brasic, M. E. Gheen *et al.*, 1998 Genetic identification of multiple loci that control breast cancer susceptibility in the rat. Genetics **149:** 289–299.

Stephenson, R. B., and D. E. Donald, 1980 Reflexes from isolated carotid sinuses of intact and vagotomized conscious dogs. Am. J. Physiol. **238:** H815–H822.

Todd, J. A., T. J. Aitman, R. J. Cornall, S. Ghosh, J. R. Hall *et al.*,

1991 Genetic analysis of autoimmune type I diabetes mellitus in mice. Nature **351:** 542–547.

Uechi, M., K. Asai, N. Sato and S. Vatner, 1998 Voltage-dependent calcium channel promoter restores baroreflex sensitivity in conscious dogs with heart failure. Circulation **98**(13): 1342–1347.

Weston, P. J., M. A. James, R. B. Panerai, P. G. McNally, J. F. Potter *et al.*, 1996a Abnormal baroreceptor-cardiac reflex sensitivity is not detected by conventional tests of autonomic function in patients with IDDM. Clin. Sci. **91**(1): 59–64.

Weston, P. J., R. B. Panerai, A. McCullough, P. G. McNally, M. A. James *et al.*, 1996b Assessment of baroreceptor-cardiac reflex sensitivity using time domain analysis in patients with IDDM and the relation to left ventricular mass index. Diabetologia **39**(11): 1385–1391.

Weston, P. J., M. A. James, R. B. Panerai, P. G. McNally, J. F. Potter *et al.*, 1998 Evidence of defective cardiovascular regulation in insulin-dependent diabetic patients without clinical autonomic dysfunction. Diabetes Res. Clin. Pract. **42**(3): 141–148.

Communicating editor: G. A. Churchill