First-order differential-delay equation for the baroreflex predicts the 0.4-Hz blood pressure rhythm in rats

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Department of Chemistry and Physics, Asbury College, Wilmore 40390-1198; Department of Physiology, University of Kentucky College of Medicine, Lexington 40536-0084; and Center for Biomedical Engineering, University of Kentucky, Lexington, Kentucky 40506-0070

Burgess, Don E., Jon C. Hundley, Sheng-Gang Li, David C. Randall, and David R. Brown. First-order differential-delay equation for the baroreflex predicts the 0.4-Hz blood pressure rhythm in rats. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R1878–R1884, 1997.—We have described a 0.4-Hz rhythm in renal sympathetic nerve activity (SNA) that is tightly coupled to 0.4-Hz oscillations in blood pressure in the unanesthetized rat. In previous work, the relationship between SNA and fluctuations in mean arterial blood pressure (MAP) was described by a set of two first-order differential equations. We have now modified our earlier model to test the feasibility that the 0.4-Hz rhythm can be explained by the baroreflex without requiring a neural oscillator. In this baroreflex model, a linear feedback term replaces the sympathetic drive to the cardiovascular system. The time delay in the feedback loop is set equal to the time delay on the efferent side, ~0.5 s (as determined in the initial model), plus a time delay of 0.2 s on the afferent side for a total time delay of ~0.7 s. A stability analysis of this new model yields feedback resonant frequencies close to 0.4 Hz. Because of the time delay in the feedback loop, the proportional gain may not exceed a value on the order of 10 to maintain stability. The addition of a derivative feedback term increases the system's stability for a positive range of derivative gains. We conclude that the known physiological time delay for the sympathetic portion of the baroreflex can account for the observed 0.4-Hz rhythm in rat MAP and that the sensitivity of the baroreceptors to the rate of change in blood pressure, as well as average blood pressure, would enhance the natural stability of the baroreflex.

autonomic nervous system; stability; sympathetic drive

WE HAVE PREVIOUSLY DESCRIBED a low-frequency 0.4-Hz rhythm in renal sympathetic nerve activity (SNA) in the unanesthetized rat (2) that is strongly coupled to low-frequency oscillations in mean arterial blood pressure (MAP). The source of this periodicity is unknown because there is no other physiological system that is known to oscillate at 0.4 Hz. This rhythm could be due either to a central oscillator or to a resonant oscillator in the baroreflex control system. For example, the 2- to 6-Hz oscillation and the 10-Hz rhythm seen in the sympathetic nerve discharge of cats are thought to be generated by brain stem circuits (1, 18). Although these rhythms are seen in baroreceptor-denervated cats (1, 18), removal of the baroreflex eliminates the 0.4-Hz rhythm in rats (10). The goal of this study is to determine whether a feedback oscillation could explain the 0.4-Hz rhythm.

Previously, we developed a linear model that relates efferent renal SNA to fluctuations in MAP (4). This model uses a first-order differential equation to describe the response of MAP to sympathetic drive. The present differential equation for the baroreceptor reflex is built on top of this model. In place of sympathetic drive, we now use the baroreflex compensation as an input to the same first-order differential equation. We model the baroreflex compensation as a linear, proportional-plus-derivative feedback term with a time delay.

We analyze the stability of our baroreflex model to gain insight into how the stability of the baroreflex depends on its sympathetic limb. In general, a control system becomes unstable when the gain is too large or any time delays within the feedback loop become too long. When the system is perturbed, the perturbation dies away if the system is stable or grows if the system is unstable. As the perturbation dies away (or grows), the system oscillates with a resonant frequency determined by the feedback loop. By definition, a marginally stable system verges on becoming unstable. When a marginally stable system is perturbed, the perturbation neither grows nor decays; the system simply oscillates with its resonant (or marginal) frequency.

Based on time constants derived from earlier work, this new baroreflex model predicts a resonant feedback oscillation in the 0.4-Hz range. A Nyquist stability analysis (6) of our model yields stability criteria for the open-loop gain that depend on a dimensionless ratio of the model time constants. (A Nyquist analysis is a graphical method especially suited to problems with a time delay.) The stability analysis shows that the addition of a derivative feedback term enhances the stability of the baroreflex within a certain parameter range.

METHODS

Subjects. Previously, we simultaneously recorded MAP and renal SNA in conscious Sprague-Dawley rats during behavioral stress trials. These earlier data provide certain key values used in the current model. Data were measured on seven Sprague-Dawley rats (Harlan Industries, Indianapolis, IN), weighing between 375 and 450 g, whose SNA and MAP response to stressful and nonstressful tones has been described previously (12, 13).

Surgery. The rats were anesthetized with pentobarbital sodium (65 mg/kg) in preparation for implantation of the arterial catheter and renal nerve electrodes. A Teflon catheter (no. 30 LW, ID 0.012; Small Parts, Miami Lakes, FL) was inserted into the aorta by way of the caudal artery. A sympathetic nerve coursing over the aorta toward the kidney was identified through a flank incision. A small section of this nerve, usually from the cephalad angle formed by the renal artery and aorta, was dissected free of connective tissue and...
placed on fine, closely spaced (0.4–0.8 mm), bipolar gold electrodes (A-M Systems, Seattle, WA). The exposed nerve and electrode were encased in silicon gel (Wacker Chemie, Munich, Germany). The distal ends of the catheter and wires soldered to the end of the electrodes were tunneled under the skin, exited at the nape of the neck, and led through a flexible tether.

Experimental procedures and protocol. The rats were tested in the conditioning paradigm starting 1 day after surgery. The catheter was fitted to a pressure transducer (Cobe model CDX-III), and blood pressure was recorded on a Grass model 7 polygraph. The electrical signal from the renal sympathetic nerve was amplified (times 50) and band-pass filtered between 30 Hz and 3 kHz by a Grass P51K differential amplifier and displayed on a Tektronix 5111 oscilloscope. Blood pressure and renal SNA were recorded during presentation of five or more of each tone, after which the rat was returned to its cage.

Data acquisition and analysis. The blood pressure and SNA data were digitally sampled at 10,000 Hz. Sampling began 9 s before presentation of the tone and continued until 6 s after its termination. In subsequent analysis, blood pressure was reduced to a 1,000 samples/s signal by saving every 10th point. MAP was then calculated for each pulse. This began 9 s before presentation of the tone and continued until SNA data were digitally sampled at 10,000 Hz. Sampling returned to its cage.

We used the physiological responses to the behavioral tests to develop a model for sympathetic drive that took SNA data time series as its input and produced MAP fluctuations as its output (4). A key equation of that model is

\[ T \dot{p}(t) + p(t) = F(t) + u(t) \]  

where \( p \) is the fluctuation in MAP (the output) and \( \dot{p} \) is the rate of change of \( p \). The constant \( T \) is the characteristic time for the frequency-response function between the cardiovascular system and the effector elements controlled by sympathetic nerves, and \( F(t) \) represents the influence of sympathetic drive on MAP. The function \( F(t) \) was obtained from our input SNA at an earlier time \( \tau_e \), which represents the time delay on the efferent side of the baroreflex. We lump together the other factors that may affect arterial blood pressure into an unknown function \( u(t) \). For example, \( u(t) \) includes any vagal effects on heart rate and the autoregulatory function of the blood vessels themselves. Table 1 displays the time constants \( T \) and \( \tau_e \) for the model of sympathetic drive that were previously determined (4).

We now model the baroreflex by replacing \( F(t) \) in Eq. 1 with a linear-delay, proportional-plus-derivative feedback term to obtain

\[ T \dot{p}(t) + p(t) = -Gp(t - \tau) - G_d \dot{p}(t - \tau) + v(t) \]  

where \( G \) is the open-loop, proportional feedback gain, \( G_d \) is the derivative feedback gain, and \( \tau \) is the time delay in the feedback loop. Our analysis indicates how the baroreflex (as a closed loop) would respond to an external input \( v(t) \). The function \( v(t) \) represents inputs to the cardiovascular system outside of the baroreflex, such as respiration. Note that \( v(t) \) differs from \( u(t) \) (in the earlier model), which represented inputs to the cardiovascular system outside of sympathetic drive. We include a derivative feedback term because the baroreceptors respond not only to the magnitude of arterial pressure but also to the rate of change of arterial pressure (16).

Table 1. Time constants for the sympathetic drive model parameters

<table>
<thead>
<tr>
<th>Rat</th>
<th>( T )</th>
<th>( \tau_e )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.0 ± 0.8</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>B</td>
<td>3.1 ± 1</td>
<td>0.58 ± 0.06</td>
</tr>
<tr>
<td>C</td>
<td>1.2 ± 0.4</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>D</td>
<td>3.3 ± 0.8</td>
<td>0.42 ± 0.08</td>
</tr>
<tr>
<td>E</td>
<td>1.3 ± 0.8</td>
<td>0.47 ± 0.09</td>
</tr>
<tr>
<td>F</td>
<td>0.6 ± 0.1</td>
<td>0.42 ± 0.09</td>
</tr>
<tr>
<td>G</td>
<td>1.2 ± 0.8</td>
<td>0.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE in s. For each rat, values are given for the time constant \( T \), which characterizes the frequency-response function between the effector elements controlled by the sympathetic nerves and the cardiovascular system and the efferent time delay \( \tau_e \) between a change in sympathetic nerve activity and a change in mean arterial blood pressure (MAP).

To illustrate how our model responds to a perturbation, we ran simulations that were initialized with a short segment of blood pressure data from our previous tests (12, 13). The initialization period was during the initial 2–3 s of the 9-s control before the onset of the behavioral tests. We approximated Eq. 2 with a finite difference equation and solved for \( p \) at discrete times \( t \), corresponding to a time step of 0.01 s. The resulting simulation shows how the system responds to a “kick.” The time constants \( T \) and \( \tau \) came from Table 2. The gains \( G \) and \( G_d \) were chosen to make the system marginally stable, with \( G_d \) set at its optimal value (defined in RESULTS).

Stability analysis. The stability of our model is determined by the roots of its characteristic equation, namely

\[ 1 + \lambda T + G \exp(-\lambda \tau) + G_d \lambda \exp(-\lambda \tau) = 0 \]  

where \( \lambda \) is a complex eigenvalue: \( \lambda = \mu + i \omega \). If the rate at which perturbations decay or grow \( (\mu > 0) \), the system is unstable. The letter \( i \) denotes \( \sqrt{-1} \). The complex part of \( \lambda \) (i.e., \( \omega \)) is the angular frequency of the system: \( \omega = 2\pi f \), where \( f \) is the natural frequency of the system. The presence of the time delay makes the system infinite-dimensional. Consequently, the characteristic equation has an infinite number of roots. In general, the behavior of the system is determined by the root with the most positive real part (the dominant root).

First we consider the solution to Eq. 3 corresponding to \( G_d = 0 \), which has been studied by Hayes (7, 9). One can find the frequency for marginal stability (the system is neither stable nor unstable) by setting the real part of \( \lambda(\mu) \) equal to zero. With \( G_d \) equal to zero, the marginal frequency \( \omega \) satisfies

\[ \tan(\omega \tau) = -\omega T \]  

where \( \tau \) indicates the time delay. Multiplying through by \( \sin(\omega \tau) \) gives

\[ \omega^2 T \sin(\omega \tau) + \omega \cos(\omega \tau) + 1 = 0 \]  

The function \( f(\omega) = \omega^2 T \sin(\omega \tau) + \omega \cos(\omega \tau) + 1 \) is a periodic function where \( f(\omega) = f(-\omega) \), so \( f(\omega) = 0 \) has finitely many solutions in \( \omega \). The solutions of Eq. 3 were obtained numerically by evaluating \( f(\omega) \) at a large number of equally spaced points in \( \omega \).
Fig. 1. Block diagram of our model for the baroreflex. \( H \) is the transfer function for response of mean arterial pressure (MAP) to sympathetic drive, and \( G \) is the transfer function for the feedback loop of the baroreflex. \( V \) and \( P \) are Laplace transforms of the input and the MAP fluctuations, respectively. The feedback loop includes the effect of both the carotid sinus reflex and the aortic reflex.

where

\[
\frac{\pi}{2} < \omega T < \pi
\]  

(5)

since \( \omega T > 0 \). The corresponding marginal gain is given by

\[
G = \frac{-1}{\cos(\omega T)}
\]  

(6)

When the gain is any larger than the marginal gain, the system is unstable (7). In the general case, given \( G \), \( G_d \), \( T \), and \( \tau \), we iteratively solve Eq. 3 for \( \lambda \) to determine the stability and natural frequency of the system. To find the dominant root, we start with \( G \) near the marginal gain and \( G_d \) = 0. We use the root from Eq. 4 as the initial guess. After we find the root for the new \( G \), we slightly modify \( G \) and/or \( G_d \) again and use the newly found root as the initial guess for the next root. In this way, we can find the dominant roots over a range of gains, with the roots varying in a continuous fashion as a function of the gains.

To obtain a general picture of the stability of our model, we performed a Nyquist stability analysis in the complex plane (6). Nyquist stability analysis is a powerful method for determining whether all the roots of the characteristic equation (Eq. 3) lie to the left of zero in the complex plane. We performed a Nyquist stability analysis in the complex plane on the Laplace transform of the MAP fluctuations and \( V \) transform of the MAP fluctuations and \( V \) transform of the external input. Figure 2 illustrates how our model responds to a perturbation. In particular, it shows a simulation for 8 s as compared with an actual data time series during the control period of a trial with rat E. After the point indicated by the asterisk, the system is free running in response to the initial perturbation. The response is an oscillation that is not due to any "inertia" in the system. Rather, the oscillation is the result of the time delay in the feedback loop. Notice the good agreement between the simulation and the data time series while the system is freely running. For this simulation, \( T = 1.3 \) s; this value is the mean characteristic time for rat E (4). The time delay \( \tau = 0.8 \) s; this value equals \( \tau_e \) reported in Ref. 4 plus 0.2 s for \( \tau_e \). The gains were set to \( G = 3.6 \), \( G_d = 0.37 \) so that the system was marginally stable. For these parameters, the system's natural frequency is 0.44 Hz.

In Table 2, we show the results of calculations for each of the seven rats. For the characteristic time \( T \), we used the mean value reported for each rat (4). For the time delay \( \tau \), we used the mean value of \( \tau_e \) plus 0.2 s (8). For these time constants, we calculated the marginal gains and the marginal frequencies from Eqs. 4 and 6, with the derivative gain set to zero. The marginal frequencies are close to 0.4 Hz, and the marginal gains are reasonable physiological values for open-loop gains of the baroreflex (16). The uncertainty in the time delay due to the low-pass filter. Our transfer function is composed of both the carotid sinus reflex and the aortic reflex because our measurements were done on whole animals (14). Note that \( G \) is the open-loop direct current feedback gain.

In a Nyquist stability analysis, one determines whether or not the open-loop transfer function \( GH \) evaluated on the Nyquist contour encircles the point \((-1, 0)\) on the negative real axis in the complex plane. Because of the time delay, a Nyquist plot of our open-loop transfer function looks like a spiral. So, stability is determined by the magnitude of \( GH \) when the spiral curve first crosses the real axis at the crossover frequency. If the magnitude of \( GH \) is larger than the marginal gain, then the spiral curve encircles \((-1, 0)\) and the model is unstable. By considering the crossover frequency, we determine stability constraints on the gains \( G \) and \( G_d \) as a function of the dimensionless ratio \( \pi T \).

RESULTS

For these parameters, the system's natural frequency is 0.44 Hz.

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Table 2. Marginal frequencies and gains

<table>
<thead>
<tr>
<th>Rat</th>
<th>T, s</th>
<th>τ, s</th>
<th>f, Hz</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.0 ± 0.0</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>B</td>
<td>3 ± 1</td>
<td>0.8 ± 0.1</td>
<td>0.35 ± 0.05</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>C</td>
<td>1.2 ± 0.4</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>D</td>
<td>3.3 ± 0.6</td>
<td>0.6 ± 0.1</td>
<td>0.43 ± 0.07</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>E</td>
<td>1.3 ± 0.4</td>
<td>0.8 ± 0.1</td>
<td>0.38 ± 0.06</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>F</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.49 ± 0.08</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>G</td>
<td>1.2 ± 0.8</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>4 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. For each rat, values are given for the time constant T, which describes the MAP response to the effectors on the sympathetic limb of the baroreflex, the time delay τ in the feedback loop, the oscillation frequency f, and the proportional feedback gain G.

τ is related to the uncertainties in τa and τb via

$$\Delta \tau = \sqrt{(\Delta \tau_a)^2 + (\Delta \tau_b)^2}$$

because τa and τb were determined by independent methods. The uncertainties in f and G were obtained from the range of results produced when T and τ were set equal to their extreme values.

In Table 3 we show the solution of Eq. 3 for rat B over a range of gains for the general case (Gd ≠ 0). For Table 3, we used the following values for the time constants: T = 3 s, τ = 0.8 s. This value of T for rat B was reported in Ref. 4. The time delay τ is equal to the value of τa for rat B plus 0.2 s for τb. For these time constants, the marginal frequency is 0.35 Hz and the marginal gain is G = 6.6. For the range of gains shown in Table 3, the oscillation frequencies remain within 10% of the marginal frequency. As μ becomes more negative, perturbations will decay away more rapidly. Note especially that for a given G the presence of the derivative feedback term enhances the stability of the system for small positive values of Gd.

A general picture of our model for the baroreflex can be obtained by doing a Nyquist stability analysis. Figure 3A shows a Nyquist plot for an unstable system (T = 3 s, τ = 0.8 s, G = 7, Gd = 0.0). The time constants are for rat B, and Fig. 3A corresponds to line 7 of Table 3. Figure 3B shows a Nyquist plot for a stable system (T = 3 s, τ = 0.8 s, G = 7, Gd = 0.4). The addition of the derivative feedback term has made the system stable. For Gd = 0, the radius of the spiral approaches zero, as seen in Fig. 3A, whereas for nonzero Gd, the radius of the spiral approaches a limit equal to Gd, as seen in Fig. 3B.

In the limit of large ω, the open-loop transfer function reduces to GH → Gdeωt, which has a magnitude equal to Gd. Thus, according to the Nyquist stability criteria, we must have |Gd| < 1 so that the curve GH(ω) does not enclose (−1, 0). Further analysis shows that we must also have |G| < 1, or, to ensure stability for |G| > 1

$$C(G, G_d) = \sqrt{\frac{G^2 - 1}{1 - G_d^2}} \frac{\tau}{T} \cos^{-1} \left( -\frac{1 + GG_d}{G + G_d} \right) < 0 \quad (8)$$

For further details refer to APPENDIX. For G > 1 (which is the case of physiological interest), the stability criteria are summarized in the value of the function C(G, Gd). If C > 0 the system is unstable and if C < 0 the system is stable. In accordance with our first stability constraint, C can be negative only when |Gd| < 1 because of the singularity under the square root. Referring to Table 3, for G = 7.0 and Gd = 0.0 or 0.1 (i.e., lines 7 and 8) the stability criterion function, C, is positive and the system is unstable, as indicated by the positive value of μ. On all other lines, C < 0 and the
system is stable, as indicated by the negative values of $\mu$.

In Figure 4, we show a family of curves for $C(G, G_d)$ as a function of $G_d$ for $G = 5, 6, 7,$ and $7.34$. In this plot, we used the same time constants (appropriate for rat B) as we used in Table 3 to give a dimensionless ratio $\tau/T \approx 0.26$. Each entry from Table 3 is marked by an “x” on the appropriate curve. For a given proportional gain $G$, the addition of a derivative feedback term enhances the stability of the system for $G_d > 0$ but decreases the stability of the system for $G_d < 0$. Figure 3A corresponds to the point on the curve labeled by “$G = 7$” at $G_d = 0.0$. Figure 3B corresponds to the point at $G_d = 0.4$ on the same curve. Along a curve for a fixed proportional gain $G$, there is an optimal derivative gain $G_d$ at the minimum of the curve, where the system is most stable. The top curve represents the maximum possible gain ($G_{\text{max}}$) the system can have without being unstable at the optimal value of $G_d$. The addition of a derivative feedback term has increased the maximum possible gain $G$ from a marginal gain of 6.6 to a value of $\sim 7.34$.

If $G_d$ is set at its optimal value while $G$ is varied, the natural frequency of the system remains about constant (invariant), as shown in Table 4. For the simulation shown in Fig. 2, $G = G_{\text{max}}$ and $G_d$ is equal to its optimal value so that the simulation frequency is the invariant frequency of rat E. If the system remains near the optimal value of $G_d$, small changes in the system parameters will leave the frequency of the system unchanged.

To see the full advantage of the derivative feedback term, one should consider dynamic effects such as the rate at which perturbations decay (which is given by the real part of the eigenvalue $\mu$). For example, from Tables 3 and 4, for a proportional gain of $G = 5.0$, the rate at which perturbations decay doubles in going from no derivative feedback term to the optimal derivative gain $G_d = 0.38$. For a proportional gain of $G = 6.0$, making $G_d = 0.40$ triples the rate at which perturbations decay compared with only proportional feedback. The faster the cardiovascular system brings blood pressure fluctuations under control, the smaller the stress on cardiovascular organs.

From Eq. 8, we obtain an estimate of the maximum possible gain $G_{\text{max}}$ for stability

$$G_{\text{max}} = \frac{T}{\tau} \sqrt{1 - G_d^2 \cos^{-1}(-G_d)}$$

when $G \gg 1$. The larger the ratio $T/\tau$, the larger $G_{\text{max}}$ can be. The right-hand side of Eq. 9 has a maximum at $G_d = 0.44$, which is an approximation for the optimal value of $G_d$. For this value of $G_d$, $G_{\text{max}}$ is $\sim 1.82 T/\tau$. Our largest value of $T/\tau$ is 8.8 for rat A, making $G_{\text{max}} < 16$ for the time constants that we measured in rats.

### DISCUSSION

The major finding of this study is that the 0.4-Hz periodicity in MAP observed in rats (2) can be explained by the time delay obtained from the known parameters of the baroreflex. The calculation of the marginal frequency (for $G_d = 0$) depends solely on the known time constants $T$ and $\tau$. As shown in Table 3, the frequencies of the system remain near the marginal frequency over a range of gains. Our analysis also indicates that our measured time constants for the sympathetic limb of the baroreflex are sufficient to explain the 0.4-Hz MAP rhythm. Other feedback loops such as vagal effects and the renin-angiotensin system are not necessary for the generation of the 0.4-Hz rhythm.

We find that the time delay associated with the sympathetic limb of the baroreflex is $\sim 0.7$ s and that most of this time delay is associated with the efferent side of the baroreflex. The afferent time delay of $\sim 0.2$ s reported by Green and Heffron for cats (8) is consistent with our observations during behavioral conditioning trials for rats, where we reported an $\sim 0.2$-s delay between the start of a tone and the onset of a “sudden burst” of SNA (12).

To produce the coherence between MAP and SNA near 0.4 Hz observed by Brown et al. (2), the 0.4-Hz rhythm must be persistent across the data segments that are averaged together during the analysis. A strong coherence was not seen for respiratory interactions at $\sim 1.5$ Hz in the conscious rat because of the variability of respiration. Conversely, respiratory inter-
actions were evident after anesthesia, which removed respiratory variability. A conceivable explanation for the relative invariance of the 0.4-Hz rhythm is that the baroreflex feedback loop remained in the "valley" associated with the optimal value of the derivative gain $G_d$, where the resonant frequency remains constant while the proportional gain $G$ is varied (refer to Table 4). In this situation, the resonant frequency of the baroreflex would remain invariant even if the system's gain $G$ changed as a result of a change in operating conditions.

Limitations. Our model only captures the sympathetic limb of the baroreflex and says nothing about how the numerous other feedback systems (e.g., vagal effects, the renin-angiotensin system, autoregulation) work together to regulate MAP. In addition, our model is linear and does not predict whether nonlinear effects could stabilize the baroreflex for gains that do not satisfy the stability criteria given here.

Though our model only captures the sympathetic side of the baroreflex, we believe for rats that the parasympathetic side is generally not critical in the generation of the 0.4-Hz rhythm. The vagal portion of the baroreflex acts on a faster time scale than the sympathetic portion. Consequently, vagal effects have the wrong time constants to generate the 0.4-Hz rhythm. Moreover, we were able to predict fluctuations in MAP using only sympathetic nerve traffic as our input (and ignoring parasympathetic activity) (4).

The idea that a time delay in the baroreflex can be responsible for oscillations in MAP has been proposed for humans (5, 17) and for dogs (11). Our model for the baroreflex for rats is consistent with these earlier works. Our open-loop transfer function consists of a time delay in series with a low-pass filter, which is how the feedback loops are modeled in (17) and in (11). These earlier works are different from our model in that they contain both parasympathetic and sympathetic sides of the baroreflex acting on a beat-to-beat model of the circulation. However, our model is the only one to include a derivative term in the feedback loop and to show that a derivative term enhances the stability of the baroreflex. The simplicity of our model allows us to analyze the stability in detail and to understand the physiological limitations on the maximum value of the feedback gain $G$. The frequency response of our model is qualitatively similar to the response function of the deBoer model (5).

**Perspectives**

Because of the difficulty of defining and measuring the open-loop baroreflex gain (14), we do not think there is a good value for the open-loop gain of the baroreflex for the rat reported in the literature. In particular, the sensitivity of the baroreflex control of heart rate is not a good measure of the ability of the baroreflex to control MAP (14). So, we can only speak in terms of the order of magnitude of the baroreflex gain. Roughly speaking, the open-loop gain for animal models seems to be small (i.e., $\approx 10$) compared with the gains in engineering control systems (16). Consistent with these experimental results, our model also indicates small gains for the baroreflex on the order of 10. As explained by our stability analysis in Eq. 9, the baroreflex gain $G$ is small because of the presence of a considerable time delay in the feedback loop.

In addition, our model gives an explanation of the physiological benefit of including rate information in the baroreflex. The addition of a derivative term in the feedback loop enhances the stability of the baroreflex for a positive range of derivative gains, with an optimal derivative gain $G_d$ of $\approx 0.44$. Thus, with the presence of a derivative term, the baroreflex gain $G$ can be larger, which leads to more precise regulation of MAP. The full advantage of the derivative feedback term is seen in its effect on the rate at which perturbations decay. From Tables 3 and 4, the addition of a derivative feedback term can enhance the rate of decay by a factor of two or three.

**APPENDIX**

We will give an argument for the validity of Eq. 8 based on the concept of continuity. Consider the stability criterion function

$$C(G, G_d) = \sqrt{\frac{G^2 - 1}{1 - G_d^2}} \cos\left(-\frac{G G_d}{G + G_d}\right)$$

defined in Eq. 8. We treat $G$ and the time constants as fixed parameters and vary $G_d$. According to Eq. 8, when $C < 0$ the system is stable and vice versa. Figure 4 shows a family of curves for $C(G, G_d)$ for several values of $G$.

First, we know that Eq. 8 is true in the limit as $G_d \to 0$. In this limit, our model Eq. 2 reduces to the linear delay equation studied by Hayes (9). Setting $G_d$ equal to zero in Eq. 8 gives

$$\sqrt{G^2 - 1} \cos\left(-\frac{1}{G}\right) < 0$$

which is one of Hayes' stability conditions (7). So, we know the curves in Fig. 4 are valid when they intersect the $G_d = 0$ axis.

Secondly, $C = 0$ when the system is marginally stable as we now show. Referring to the Nyquist stability plots in Fig. 3, stability is determined at the crossover frequency $\omega_c$ where the contour first crosses the real axis (6). When the system is marginally stable, the contour passes through the point $(-1, 0)$ so that

$$\frac{G + iG_d \omega_c T}{1 + i \omega_c T} e^{i\pi} = -1$$

Solving for $\omega_c$, we obtain

$$\omega_c = \frac{\sqrt{G^2 - 1}}{\sqrt{1 - G_d^2}}$$

when the system is marginally stable. We can also write Eq. 10 as

$$G + iG_d \omega_c T \left[\cos(\omega_c T) - i \sin(\omega_c T)\right] = -1$$

by using Euler's theorem to expand the exponential. Equat-
ing the real and imaginary parts of Eq. 12, we obtain
\[
\frac{GG_d + 1}{G + G_d} = -\cos (\omega_n \tau)
\]  
(13)

Then, solving Eq. 13 for \( \omega_n \) and setting the result equal to Eq. 11, we find
\[
\sqrt{\frac{G^2 - 1}{1 - G_d^2}} \frac{\tau}{T} = \cos^{-1} \left( -\frac{1 + GG_d}{G + G_d} \right)
\]  
(14)

Thus the plot shown in Fig. 4 is valid when the curves cross the zero axis.

In summary, Eq. 8 is true for \( G_d = 0 \) (when the curves cross the \( G_d = 0 \) axis in Fig. 4) and when \( C = 0 \) (when the curves cross the zero axis). Because the stability of the system can only change when \( C = 0 \), Eq. 8 must be true for all other points in Fig. 4 by continuity.

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