Nonlinear identification of the total baroreflex arc

Mohsen Moslehpour,1 Toru Kawada,2 Kenji Sunagawa,3 Masaru Sugimachi,2 and Ramakrishna Mukkamala1

1Department of Electrical and Computer Engineering, Michigan State University, East Lansing, Michigan; 2Department of Cardiovascular Dynamics, National Cerebral and Cardiovascular Center, Osaka, Japan; and 3Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Submitted 18 June 2015; accepted in final form 5 September 2015

Nonlinear identification of the total baroreflex arc. Am J Physiol Regul Integr Comp Physiol 309: R1479–R1489, 2015. First published September 9, 2015; doi:10.1152/ajpregu.00278.2015.—The total baroreflex arc [the open-loop system relating carotid sinus pressure (CSP) to arterial pressure (AP)] is known to exhibit nonlinear behaviors. However, few studies have quantitatively characterized its nonlinear dynamics. The aim of this study was to develop a nonlinear model of the sympathetically mediated total arc without assuming any model form. Normal rats were studied under anesthesia. The vagal and aortic depressor nerves were sectioned, the carotid sinus regions were isolated and attached to a servo-controlled piston pump, and the AP and sympathetic nerve activity (SNA) were measured. CSP was perturbed using a Gaussian white noise signal. A second-order Volterra model was developed by applying nonparametric identification to the measurements. The second-order kernel was mainly diagonal, but the diagonal differed in shape from the first-order kernel. Hence, a reduced second-order model was similarly developed comprising a linear dynamic system in parallel with a squaring system in cascade with a slower linear dynamic system. This “Uryson” model predicted AP changes 12% better ($P < 0.01$) than a linear model in response to new Gaussian white noise CSP. The model also predicted nonlinear behaviors, including thresholding and mean responses to CSP changes about the mean. Models of the neural arc (the system relating CSP to SNA) and peripheral arc (the system relating SNA to AP) were likewise developed and tested. However, these models of subsystems of the total arc showed approximately linear behaviors. In conclusion, the validated nonlinear model of the total arc revealed that the system takes on an Uryson structure.

arterial baroreflex; Gaussian white noise; nonparametric system identification; sympathetic nervous system; Volterra model

THE TOTAL BAROREFLEX ARC—defined to be the open-loop system relating carotid sinus pressure (CSP) to arterial pressure (AP)—is a well-known contributor to cardiovascular regulation. When stimulated in a controlled manner, this system exhibits thresholding and saturation (i.e., maximal and minimal AP responses) (3, 4, 9), mean responses (i.e., direct current, or DC responses) to input changes about the mean (i.e., alternating current, or AC changes) (4, 13, 30, 31), as shown in Fig. 1, and other nonlinear behaviors (8, 20, 38). Interestingly, the system also displays DC responses to AC changes in Thrash-er’s chronic baroreceptor unloading model of hypertension (34). This model does not significantly alter mean CSP but does cause reductions in CS pulse pressure (i.e., a selective AC change), which, in turn, leads to a sustained, baroreflex-mediated increase in mean AP (i.e., a DC response). Hence, total arc nonlinearity could possibly play a role in the genesis of hypertension. Yet, most system identification studies of the total arc have been based on a linear dynamic model (7, 9–11, 17, 26, 29, 30). Further, the few studies that have represented the total arc with a nonlinear dynamic model assumed a particular form for the model (9, 20).

Our aim was to establish a second-order, nonlinear dynamic model of the total arc without making a priori assumptions about the model form. To achieve this aim, we employed the powerful Gaussian white noise approach for nonlinear system identification (24). In particular, we applied Gaussian white noise CSP stimulation, while measuring AP and sympathetic nerve activity (SNA), in an open-loop rat preparation followed by nonparametric identification to estimate first- and second-order kernels of a Volterra model of the total arc from the measurements. We also likewise identified two subsystems of the total arc, namely the neural arc, which relates CSP to SNA, and the peripheral arc, which relates SNA to AP. Since this approach requires long data records to yield accurate kernel estimates (15), our strategy for the obtained short data records was as follows. First, we examined the Volterra kernel estimates to define a reduced second-order, nonlinear dynamic model. Then, we applied nonparametric identification to estimate the kernels of this reduced, yet potentially more predictive, model. Finally, we assessed its output predictions. The nonlinear model of the total arc that we report here significantly improved upon AP predictions over a standard linear model and helped reveal the structure of the total arc.

MATERIALS AND METHODS

Data Collection

Thirteen normotensive Wistar-Kyoto rats (weight 397.8 ± 18.5 g) were studied, according to a protocol that was approved by the Animal Subjects Committee at the National Cerebral and Cardiovascular Center of Japan. The procedures are described in detail elsewhere (11). Briefly, under general anesthesia (urethane and α-chloralose mixture) and mechanical ventilation, the bilateral vagal and aortic depressor nerves were sectioned to eliminate confounding reflexes from the aortic arch and cardiopulmonary region. (Hence, the model of the total arc developed herein precisely represents the sympathetically mediated carotid sinus baroreflex.) The carotid sinus regions were isolated from the systemic circulation to open the loop between CSP and AP/SNA. A servo-controlled piston pump was interfaced to the carotid sinus regions filled with warmed Ringer solution via catheters to control CSP. A femoral artery catheter was placed to measure AP. A pair of electrodes was positioned on a postganglionic branch of the splanchnic sympathetic nerve to measure SNA. The preamplified SNA was band-pass filtered with cutoff frequencies of 150 and 1,000 Hz. It was then full-wave rectified and low-pass filtered with cutoff frequency of 30 Hz. CSP was controlled for about 15 min...
using a Gaussian white noise signal with mean of 120 mmHg and standard deviation of 20 mmHg (with values more than three SDs from the mean being skipped). So, the signal ranged from about 90 to 150 mmHg for 90% of the stimulation. A different realization of this signal was used for each subject. The switching interval of the noise was 0.5 s to yield relatively flat input spectral power up to 1 Hz (see Fig. 2). To investigate static system behavior, CSP was also controlled using a staircase signal that started at 60 mmHg and then increased, step by step, in increments of 20 mmHg every 1 min up to 180 mmHg. So, for example, CSP was held flat at 100 mmHg in the third step of this signal. All measurements were recorded at a sampling rate of at least 200 Hz.

**Data Analysis**

**Data preprocessing.** The measurements during Gaussian white noise stimulation were first low-pass filtered using a high-order filter.

---

**Fig. 1.** The total baroreflex arc [open-loop system relating carotid sinus pressure (CSP) to arterial pressure (AP)] has been shown to exhibit nonlinear behaviors in previous studies, including mean responses to input changes about the mean (adapted from Ref. 13). CSP here was controlled using a binary white noise signal of the same mean but increasing amplitude. Mean AP and sympathetic nerve activity (SNA) both decreased with the increasing CSP amplitude.

---

**Fig. 2.** Gaussian white noise training data from one subject. **Left:** preprocessed CSP, AP, and calibrated SNA vs. time. **Right:** power spectrum and histogram of unprocessed CSP. CSP here was controlled using a Gaussian white noise signal of mean of 120 mmHg and standard deviation of 20 mmHg.
and then down-sampled to 2 Hz. For each subject, a 6-min segment of stationary data after linear detrending was selected for model development or training, while a separate 3-min segment of stationary data after linear detrending was selected for model testing. Data from three of the subjects were highly nonstationary and were, thus, excluded from further analysis. In some of the subjects, a peak in the AP power spectrum around 0.7 to 0.8 Hz was visible. This peak was likely caused by spontaneous respiratory effort rather than the CSP stimulation, so AP of all subjects was low-pass filtered again using a high-order filter but with a cutoff frequency of 0.7 Hz. This filtering had no significant impact on the kernel estimates of those subjects that did not reveal such a peak (results not shown). Finally, because the magnitude of the SNA measurement heavily depended on the electrode contact, SNA was calibrated per subject, so that the models of the neural and peripheral arcs could be meaningfully averaged over the subjects. In particular, SNA was calibrated per subject, such that the average gain of the linear kernel of the neural arc was unity for frequencies <0.03 Hz in the training data (11).

The measurements during the staircase stimulation were averaged over the last 10 s of each step. The average values of a system input and output were then plotted against each other.

Nonlinear model and identification. In general, a time-invariant system with fading memory can be written in the form of a Volterra series to within arbitrary precision (2). For such systems that are also causal and discrete-time, the Volterra series is given as follows:

$$y[n] = \sum_{k_1=0}^{M} \sum_{k_2=0}^{M} h[k_1, k_2] x[n-k_1] \cdots x[n-k_m],$$

where $n$ is discrete-time, $y[n]$ is the output, $x[n]$ is the input, $h[n_1, \ldots, n_l]$ is the first-order system kernel, $L$ is the order of nonlinearity, and $M$ is the system memory (which can be different for each kernel but is the same for all kernels here for convenience). In this model, the output is expanded in terms of the input samples and the interactions among input samples of different lags. These input terms affect the output through the kernels of the system.

In this study, the total arc and its subsystems were assumed to be represented by a second-order Volterra series as follows:

$$y[n] = y_0 + \sum_{k_1=0}^{M} h_1[k_1] x[n-k_1] + \sum_{k_1=0}^{M} \sum_{k_2=0}^{M} h_2[k_1, k_2] x[n-k_1] x[n-k_2],$$

where $x[n]$ and $y[n]$ are the system input and output (i.e., CSP and AP for the total arc, CSP and SNA for the neural arc, and SNA and AP for the peripheral arc) with $x[n]$ precisely denoting the input after removing its mean value. The zeroth-order kernel $h_0$, which is the mean value of $y[n]$, along with the mean value of the input define the system operating point. The first-order or linear kernel $h_1[n_1]$ indicates how the present and past input samples affect the present output sample. The second-order kernel $h_2[n_1, n_2]$ indicates how the interaction or cross-talk between two input samples that are $n_1$ and $n_2$ samples in the past can affect the present output sample.

The kernels of the total, neural, and peripheral arcs were estimated from the Gaussian white noise training data using a nonparametric, frequency-domain method (37) (see APPENDIX). This method was more effective than other nonparametric methods (see DISCUSSION). The memory $M$ was set to 25 s, which is twice the length of the linear kernel of the total arc reported in previous studies (11). This value was able to capture the memory of all systems (see RESULTS). The second-order kernel estimates were then visually examined to ultimately arrive at reduced, yet potentially more predictive, nonlinear models (see RESULTS).

Note that nonparametric identification was employed, because it does not impose a particular form for the kernels. However, the trade-off is that long data records are needed to accurately estimate higher-order kernels. Since the training data here were relatively short, the Volterra series had to be limited to second-order. However, this limitation may not be too serious, as many physiological systems can well be represented with a second-order Volterra series (24).

Model evaluation. The merit of the resulting nonlinear models with the first- and second-order kernel estimates and linear models with only the first-order kernel estimates was evaluated as follows. First, the inputs from the Gaussian white noise training and testing data were applied to the models, and $R^2$ values between the predicted and measured outputs and squared coherence functions (the power spectrum of the predicted output divided by the power spectrum of the measured output) were computed. Then, the inputs from the staircase data were applied to the models, and the predicted and measured outputs were compared qualitatively. Finally, binary white noise CSP with mean of 95 mmHg but amplitudes of ±5, ±10, ±20, and ±40 mmHg and switching interval of 0.5 s were applied to the models of the total and neural arcs, and the predicted outputs were qualitatively compared with the corresponding measured data from a previous study shown in Fig. 1 (13).

Statistical comparison. The $R^2$ values from linear and nonlinear models were compared using paired t-tests. Before applying these tests, the $R^2$ values were log transformed for more normally distributed data (1). A $P < 0.0125$ was considered statistically significant on the basis of a Bonferroni correction for up to four pairwise comparisons.

RESULTS

Gaussian White Noise Data

Figure 2 shows the preprocessed CSP, AP, and calibrated SNA from the Gaussian white noise training data of one subject. Table 1 shows the group average (means ± SE) of the means and SD of these measurements and the pulse rate (PR). The mean of CSP, AP, and SNA were 120.3 ± 0.2 mmHg, 97.1 ± 4.4 mmHg, and 80.7 ± 11.8 AU, respectively. These values define the operating points of the models of the total arc and its subsystems developed herein. The standard deviation of CSP, AP, and SNA were 16.5 ± 0.3 mmHg, 6.6 ± 0.2 mmHg, and 20.7 ± 0.6 AU, respectively. These values indicate the range of validity of the models about their operating points. The mean of PR was 397 ± 11 bpm, which corresponds to 6–7 Hz. Hence, the systems were mainly stimulated at subpulsatile frequencies (i.e., frequencies beneath the PR).

Total Arc

Figure 3 shows the group average (means ± SE) of the first- and second-order kernels of a Volterra model of the total arc estimated from the Gaussian white noise training data. There are two points to note. First, the second-order kernel revealed small off-diagonal values. Indeed, none of the off-diagonal static gains (i.e., sums of $h_2[n_1, n_1 + 1], h_2[n_1, n_1 + 2], \ldots$) were significantly different from zero based on one-sample t-tests, except for the static gain of $h_2[n_1, n_1 + 4]$ ($P < 0.01$). However,
the static gain of this fourth off-diagonal was less than 25% of that of the main diagonal. Hence, the second-order kernel was approximately diagonal, thereby indicating that cross-talk between pairs of input samples of different lags (i.e., \( k_1 \neq k_2 \) in Eq. 2) hardly contributed to the output. Second, the diagonal of the second-order kernel appeared different in shape from the first-order kernel. Both of these findings were largely consistent for the individual subject kernel estimates (results not shown). The findings suggested to set \( k_1 = k_2 \) in Eq. 2 to arrive at the following reduced, yet potentially more predictive, second-order nonlinear model:

\[
y[n] = h_0 + \sum_{k_1=0}^{M} h_1[k_1] x[n - k_1] + \sum_{k_1=0}^{M} h_2[k_1] x^2[n - k_1]
\] (3)

Figure 4 shows a block diagram of the reduced model, which may be categorized as a Uryson model (28). This model is a linear dynamic system in parallel with a squarer in cascade with another linear dynamic system. The kernel of the former system is the linear kernel, whereas the kernel of the latter system is the second-order kernel. The kernels of this reduced model were reestimated using a nonparametric, frequency-domain method (see APPENDIX). Fig. 5 shows the resulting group average kernel estimates. Both kernels showed low-pass or integral characteristics and similar dynamics. That is, an impulsive increase in CSP at time zero would cause AP to initially decrease and then return to baseline. The static gain of the first-order kernel (i.e., change in steady-state output divided by change in steady-state input) was \(-0.70\) (unitless). The static gain of the second-order kernel, unlike the first-order kernel gain, depends on the size and sign of the input change due to the squaring operation. The static gain of this kernel was \(-0.22\) (unitless) for an average step CSP increase of 16 mmHg or \(+0.22\) for a CSP decrease of 16 mmHg. The dominant time constants [computed robustly via the kernel sum divided by the peak kernel amplitude (18)] of the first- and second-order kernels were about 4.1 and 6.2 s, respectively.

Table 2 shows the group average of the \( R^2 \) values between the AP predicted by the individual subject models when stimulated by the Gaussian white noise CSP in the training and
testing data and the measured AP. The training data results actually reflect model fitting rather than model prediction capabilities. The Volterra model achieved the best model fit, as indicated by the higher $R^2$ values, simply because it was a superset of the other models. For the testing data, which do indicate model prediction abilities, the linear model achieved a fairly high $R^2$ value of $0.64 \pm 0.03$. While the Volterra model did not improve upon this value, the Uryson model, which is simpler and may, thus, include more accurate kernel estimates, attained an $R^2$ value of $0.71 \pm 0.03$. So, the Uryson model improved AP prediction over the linear model by 12% ($P < 0.01$). Fig. 6 shows the group average of the squared coherence functions for the linear and Uryson models in the testing data. As can be seen, the improved AP prediction afforded by the Uryson model was in the low-frequency regime. Hence, the system nonlinearity was at low frequencies.

Figure 7 shows the group average of the static behavior of the total arc predicted by the individual subject Uryson models in response to the staircase CSP (wherein each CSP step or level was flat) and the measured static behavior. The model predicted thresholding (qualitatively) but not saturation. Figure 8 shows the AP predicted by the group average Uryson model when stimulated by the binary white noise CSP of increasing amplitude. Like the measured AP from a previous study (13) shown in Fig. 1, the model predicted significant mean AP reductions with increasing amplitude. But, unlike the measured AP, the model also predicted increases in AP variance as the amplitude increased. Note that the linear model cannot predict any of these nonlinear behaviors.

**Neural and Peripheral Arcs**

The first- and second-order kernels of a Volterra model of the neural arc estimated from the Gaussian white noise training data also suggested a reduced Uryson model (results not shown). Fig. 9 shows the group average of the first- and second-order kernels of the Uryson model of the neural arc

---

**Table 2. Group average of the $R^2$ values between AP predicted by three models of the total arc and measured AP during Gaussian white noise CSP stimulation**

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Second-Order Volterra</th>
<th>Second-Order Uryson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training data</td>
<td>$0.73 \pm 0.03$</td>
<td>$0.85 \pm 0.01^*$</td>
<td>$0.79 \pm 0.03^*$</td>
</tr>
<tr>
<td>Testing data</td>
<td>$0.64 \pm 0.03$</td>
<td>$0.64 \pm 0.04$</td>
<td>$0.71 \pm 0.03^*$</td>
</tr>
</tbody>
</table>

$^*$ Significant difference, $P < 0.01$ for paired t-test between indicated linear and nonlinear models after log transformation of the $R^2$ values.
estimated from these data. Both kernels showed high-pass or derivative characteristics and similar dynamics. The static gain of the first-order kernel was $-0.57$ (AU/mmHg), while the static gain for the second-order kernel was $-0.12$ (AU/mmHg) for an average step CSP increase of 16 mmHg or $+0.12$ for a CSP decrease of 16 mmHg. The dominant time constants of the first- and second-order kernels were about 0.3 and 0.6 s, respectively. While these small time constants may not have been accurately estimated due to the 2-Hz sampling rate, it is clear that the neural arc was much faster than the total arc.

Table 3 shows the group average of the $R^2$ values between the SNA predicted by the individual subject models when stimulated by the Gaussian white noise CSP in the training and testing data and the measured SNA. Again, as expected and indicated by the training data results, the Volterra model achieved the best model fit. However, the $R^2$ values were only modestly higher than those of the linear and Uryson models here. For the testing data, the linear model attained a high $R^2$ value of $0.77 \pm 0.02$. The nonlinear models did not significantly improve upon this value. Hence, the neural arc was approximately linear. Indeed, even though the neural arc exhibits the nonlinear behaviors of thresholding and saturation (9) and DC responses to AC changes, as indicated via SNA in Fig. 1, the nonlinear models of the neural arc showed predictions of these behaviors that were not that different from the linear model (results not shown).

Figure 10 shows the group average of the first-order kernel of a linear model of the peripheral arc estimated from the Gaussian white noise training data. A reliable second-order kernel

<table>
<thead>
<tr>
<th>Neural Arc</th>
<th>Peripheral Arc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>Second-Order</td>
</tr>
<tr>
<td>Training data</td>
<td>$0.80 \pm 0.01$</td>
</tr>
<tr>
<td>Testing data</td>
<td>$0.77 \pm 0.02$</td>
</tr>
</tbody>
</table>

*Significant difference, $P < 0.01$ for paired $t$-test between indicated linear and nonlinear models after log transformation of the $R^2$ values.
The peripheral arc was likely approximately linear anyhow. For both the training and testing data, the predicted AP by the individual subject linear model when stimulated by the SNA in the Gaussian white noise training and nonparametric identification was more sluggish than the neural arc. The kernel could not be estimated, since SNA, which is the input to the peripheral arc, was not Gaussian white noise. The linear kernel showed low-pass or integral characteristics and the expected, positive open-loop dynamics. That is, an impulsive increase in SNA at time zero would cause AP to initially increase and then return to baseline. The static gain was 1.6 mmHg/AU. Its dominant time constant was 5.8 s, so, as expected, the peripheral arc was more sluggish than the neural arc.

Table 3 shows the group average of the $R^2$ values between the AP predicted by the individual subject linear model when stimulated by the SNA in the Gaussian white noise training and testing data and the measured AP. For both the training and testing data, the $R^2$ value was high. In particular, for the more meaningful testing data, the $R^2$ value was $0.81 \pm 0.04$. Hence, the peripheral arc was likely approximately linear anyhow.

**DISCUSSION**

We developed a second-order, nonlinear dynamic model of the sympathetically mediated total baroreflex arc by employing Gaussian white noise stimulation and nonparametric identification. We validated the model by showing that it could predict 1) AP appreciably better than a standard linear model when stimulated by a new Gaussian white noise realization and 2) the important nonlinear behaviors of thresholding and DC re-stimulation. Hence, the inputs were not exactly Gaussian and white. We specifically applied a frequency-domain method to estimate the kernels without assuming any form (37) (see Appendix). Other nonparametric identification methods were available. The most popular is Lee and Schetzen’s cross-correlation method (19). This method assumes that the input is strictly Gaussian white noise and, thus, requires long data records (15). Korenberg’s method, which is also well known, efficiently solves the normal equations (14, 16). This method only assumes that the input is broadband. However, by not assuming a Gaussian input, it must compute higher-order correlations (to form the normal equations), which also requires long data records (15). Also note that this method can only produce an estimate, if the data length is at least equal to the number of kernel samples for estimation. The frequency-domain method for estimating the Volterra kernels assumes that the input is Gaussian but broadband and may, thus, be a good compromise between these methods. We actually applied all three methods. While the kernel estimates of the methods were similar on average, the frequency-domain method yielded the smoothest estimates (results not shown).

The frequency-domain method provides the optimal estimates of the linear and nonlinear kernels in the least squares sense without assuming a model form (6). The resulting kernels of this nonparametric identification method are, thus, the best unbiased estimates. In other words, the linear part of the nonlinear model and the best linear model are one in the same. Parametric identification methods could provide better estimates of both the linear and nonlinear kernels by trading off bias for precision. However, these methods assume a particular model form. Our purpose here was not to assume a model form but rather to discover the form. Nevertheless, we also applied standard autoregressive exogenous input identification to estimate the linear kernels (21). However, this parametric identification method did not yield more predictive linear kernels than the frequency-domain method (results not shown). Regardless of this finding, comparison between the linear and nonlinear models estimated by the frequency-domain method may be considered fair, since neither model assumes a particular form.

**Nonparametric Identification Method**

We estimated the first- and second-order kernels of the models using short periods (6 min) of Gaussian white noise stimulation. Hence, the inputs were not exactly Gaussian and white. We specifically applied a frequency-domain method to estimate the kernels without assuming any form (37) (see Appendix). Other nonparametric identification methods were available. The most popular is Lee and Schetzen’s cross-correlation method (19). This method assumes that the input is strictly Gaussian white noise and, thus, requires long data records (15). Korenberg’s method, which is also well known, efficiently solves the normal equations (14, 16). This method only assumes that the input is broadband. However, by not assuming a Gaussian input, it must compute higher-order correlations (to form the normal equations), which also requires long data records (15). Also note that this method can only produce an estimate, if the data length is at least equal to the number of kernel samples for estimation. The frequency-domain method for estimating the Volterra kernels assumes that the input is Gaussian but broadband and may, thus, be a good compromise between these methods. We actually applied all three methods. While the kernel estimates of the methods were similar on average, the frequency-domain method yielded the smoothest estimates (results not shown).

The frequency-domain method provides the optimal estimates of the linear and nonlinear kernels in the least squares sense without assuming a model form (6). The resulting kernels of this nonparametric identification method are, thus, the best unbiased estimates. In other words, the linear part of the nonlinear model and the best linear model are one in the same. Parametric identification methods could provide better estimates of both the linear and nonlinear kernels by trading off bias for precision. However, these methods assume a particular model form. Our purpose here was not to assume a model form but rather to discover the form. Nevertheless, we also applied standard autoregressive exogenous input identification to estimate the linear kernels (21). However, this parametric identification method did not yield more predictive linear kernels than the frequency-domain method (results not shown). Regardless of this finding, comparison between the linear and nonlinear models estimated by the frequency-domain method may be considered fair, since neither model assumes a particular form.
**Total Arc Model**

We arrived at the second-order, nonlinear dynamic model of the total arc shown in Figs. 4 and 5 in two steps. First, we applied the frequency-domain method to estimate the kernels of a Volterra model. The resulting second-order kernel shown in Fig. 3 was approximately diagonal. Hence, only the past values of the square of the input, rather than the product of input samples of different lags, contributed to the output. Further, this diagonal differed in shape from the first-order kernel (see Fig. 3). So, the Volterra model may be reduced to an Uryson model (see Fig. 4). Second, we again applied the frequency-domain method with the aim of more accurately estimating the kernels of the reduced model (see Fig. 5). The resulting model is a linear system in parallel with a squarer in cascade with another linear system. The kernel of the former system \( h_1[n] \) is the linear kernel, while the kernel of the latter system \( h_2[n] \) is the second-order kernel, which was more sluggish. We tried to further simplify the total arc model by assuming that \( h_1[n] = h_2[n] \). However, the resulting Hammerstein model did not improve AP predictions over a linear model (results not shown). We also tried to derive a more accurate total arc model by estimating the second-order kernel with a non-zero diagonal and a non-zero fourth off-diagonal (whose gain was statistically different from zero in the Volterra model). However, this model did not improve AP predictions over the Uryson model (results not shown).

We assessed the validity of the Uryson model of the total arc. In particular, we applied three different CSP inputs to the model and compared the predicted AP to the measured AP. First, we applied a Gaussian white noise input that was not utilized to develop the model. As shown in Table 2, the linear model with only the first-order kernel was able to predict 64% of the measured AP variance, while the Uryson model with both kernels predicted 71% of the variance. Although the linear model was quite explanatory, the nonlinear model significantly improved the AP prediction by 12% \( (P < 0.01) \). The squared coherence function of Fig. 6 indicated that this AP improvement was at low frequencies. Hence, the system nonlinearity was in the low-frequency regime. While the Uryson model did improve the prediction, 29% of the measured AP variance remained unexplained. These variations were not white (results not shown) and could be due to higher-order nonlinearity, nonstationarity, SNA from higher brain centers, and fast-acting hormonal loops. Note that measurement noise may not have been a factor, as AP was invasively measured and then low-pass filtered and down-sampled all the way to 2 Hz. Also, note that low-frequency AP may be similar regardless of the site of measurement (27).

Second, we applied a staircase input to predict static system behavior. As shown in Fig. 7, the model was able to predict thresholding. The mechanism for this prediction is as follows. When CSP increases relative to its mean value, the second-order kernel enhances the magnitude of the AP drop. However, when CSP decreases relative to its mean value, the second-order kernel blunts the AP increase. On the other hand, the model did not predict saturation. One reason is that the Gaussian white noise stimulation used to develop it (mean and SD of 120 and 16.5 mmHg) hardly excited the saturation regime (CSP > 160 mmHg). Quantitative differences between predicted and measured thresholding may have been due to differences in the operating points of the data used to develop the model (mean CSP and AP of 120 and 97 mmHg as shown in Table 1) and test the model (mean CSP and AP of 120 and 120 mmHg as shown in Fig. 7).

Third, we applied binary white noise of increasing amplitude. As illustrated in Fig. 8, the model predicted reductions in mean AP, but increases in AP variance, with increasing amplitude. While a previous study also indicated mean AP reductions (see Fig. 1; Ref. 13), it revealed little change in AP variance. Higher-order nonlinearity may be needed to blunt the AP variance. Another possible reason for the difference between the prediction and measurement may be variations in the range of CSP input used to develop and test the model.

As implied above, the Uryson model developed herein can only be expected to be valid over the range of data utilized in its development. This range is defined by a CSP of 120 ± 16.5 mmHg (mean ± SD) and mostly <1 Hz and an AP of 97 ± 6.6 mmHg. The model should be considered only over this range.

A few other nonlinear dynamic models of the total arc have been previously conceived. After finding that neither a Hammerstein model (a static nonlinearity followed by a linear dynamic system) nor a Wiener model (a linear dynamic system followed by a static nonlinearity) could explain data, a sandwich model—a Wiener model (to represent the neural arc) in cascade with a linear model (to represent the peripheral arc)—was proposed to represent the total arc (9). A more complicated nonlinear model, which may also be viewed as a sandwich model, was developed earlier (20). The main difference between these previous efforts and the present study is that we did not assume a certain model form. Rather, we let the data dictate the form via Gaussian white noise stimulation and nonparametric identification. Indeed, we found that the total arc could be represented with an Uryson model, which contradicts a sandwich, Hammerstein, and Wiener model. That is, a sandwich model with a static nonlinearity that is odd about the operating point (similar to a thresholding and saturation curve) would show an identically zero second-order kernel; a Hammerstein model would reveal identical first- and second-order kernels; and a Wiener model would show a second-order kernel with non-zero off-diagonal values (25).

**Neural Arc and Peripheral Arc Models**

We arrived at the second-order Uryson model of the neural arc shown in Fig. 9 using a similar two-step approach and, likewise, assessed the model. However, this model (and a Volterra model) displayed approximately linear behavior. In particular, when stimulated by a new realization of Gaussian white noise, it could not predict SNA better than a linear model, as shown in Table 3. Indeed, the linear model could already explain much (77%) of the SNA variance. The unexplained variations could be due to the aforesaid factors, as well as measurement noise. In addition, while the neural arc shows thresholding and saturation (9) and DC responses to AC changes (see SNA response in Fig. 1), the Uryson model of the neural arc could not well predict these behaviors. We could not develop a reliable nonlinear model of the peripheral arc, because the SNA input was not Gaussian white noise. Thus, we settled upon the linear model shown in Fig. 10. When stimulated by new Gaussian white noise, this model was also able to predict much (81%) of the AP variance, as shown in Table 3.
In summary, while the total arc exhibited appreciable nonlinear behaviors, its two subsystems displayed approximately linear behavior. Hence, identification of the neural and peripheral arcs did not shed light on the sources of total arc nonlinearity. One possible explanation for this seemingly contradictory finding is that splanchic SNA, which was used to construct the subsystem models, did not represent whole body SNA, which actually determined total arc behavior. However, we performed pilot experiments and found similar cardiac and splanchic SNA responses to controlled CSP stimulation (results not shown). So, these experiments did not support this explanation. Another explanation may be that the neural arc is actually nonlinear, but its nonlinearity was not well identified. In particular, as indicated in Fig. 6, the nonlinearity was in the low-frequency regime. However, SNA power was predominantly in the high-frequency band due to the derivative characteristics of the neural arc. Hence, the little SNA power at low frequencies may have been dominated by SNA from higher brain centers rather than from the baroreflex. As described in Ref. 24, this “physiologic noise” may have had a linearizing effect in the identification process, such that neural arc nonlinearity was masked over the low-frequency regime. Note that afferent C-fibers could be responsible for neural arc nonlinearity. These fibers are slow-acting nerves (32, 33) that are highly nonlinear with respect to stretch (33). Such behaviors are congruent with the findings here that the nonlinear behavior of the total arc was in the low-frequency regime.

As indicated above, a Wiener model of the neural arc was previously proposed (9, 13). We also tried to represent this system with Wiener and Hammerstein models. But, neither model appreciably improved SNA predictions over a linear model (at most 4% when stimulated by new Gaussian white noise). The reason for the difference between this and past studies could possibly be variations in the amplitude of the CSP stimulation employed.

**Study Limitations**

Our study has several limitations. First, the use of anesthesia and open-loop conditions surely impacted the models. However, closed-loop identification has its own challenges (12). Second, CSP excitation was limited to an amplitude range that hardly reached the saturation regime, a short time period, and frequencies mainly within 1 Hz. Hence, saturation and DC responses to long-term, pulsatile changes could not be modeled. However, note that increasing the amplitude, time period, and switching rate of CSP stimulation could damage the baroreceptors and cause major nonstationarity. Third, the vagal arm of the total arc was abolished. However, inclusion of this arm would also bring in the confounding effects of the cardiopulmonary baroreflex. Finally, the model was restricted to second-order nonlinearity due to the short data records. However, parametric identification methods, which assume a particular model form, may be required to estimate higher-order kernels from short data records (25).

**Perspectives and Significance**

The baroreflex was long believed to regulate AP only on the time scales of seconds to minutes (5). However, chronic baroreceptor stimulation and other studies have now indicated that this system could contribute to long-term AP regulation (22, 23, 34–36). Hence, the baroreflex could play a causative or protective role in hypertension and heart failure. As indicated by Thrasher’s chronic baroreceptor unloading model of hypertension (34), nonlinearity of the baroreflex, in particular, could induce sustained increases in AP. However, baroreflex nonlinearity is not well understood. We developed a second-order, nonlinear dynamic model of the sympathetically mediated total baroreflex arc by employing Gaussian white noise stimulation and nonparametric identification. We validated the model by showing that it is able to predict AP appreciably better than a conventional linear model and some important nonlinear behaviors, including thresholding and DC responses to AC changes. A key advantage of nonlinear identification over linear identification is that it can indicate the structure of the system under study. For example, consider a system that is composed of a static nonlinearity in cascade with a linear dynamic system. Nonlinear identification of the overall system cannot only yield a more accurate model than linear identification but also reveal whether the static nonlinearity precedes or follows the linear dynamic system. The validated nonlinear model likewise provides information about the structure of the internal components of the total arc. In particular, the model illustrates that the structure is not a previously proposed cascade connection of systems (e.g., Hammerstein, Wiener, or sandwich model) but rather a parallel connection of a linear system and Hammerstein system. In addition to providing information about the structure of the total arc, the model also indicates that the second-order nonlinear dynamics are slower than the linear dynamics and not insignificant in magnitude of effect compared with these dynamics. While system identification cannot reveal the physical basis of the nonlinearity, it is interesting to speculate that the parallel connection of a fast linear system and a slower nonlinear system corresponds to the structure of anatomical components. In particular, the linear system may correspond to the fast, afferent A-fiber pathway, whereas the nonlinear system could correspond to slower, afferent C-fiber pathway. However, the model is only valid over the CSP range covered by the Gaussian white noise. This range essentially did not include the saturation regime or pulsatile frequencies. In the future, the model may be improved by estimating higher-order kernels using parametric identification and, if possible, broadening the Gaussian white noise to cover saturation, thresholding, and pulsatile frequencies. Subsequent investigation of the nonlinear model in disease would also be worthwhile. Such modeling efforts may improve our understanding of the baroreflex as a dynamic system.

**APPENDIX**

The kernels of the Volterra model in Eq. 2, \( h_0, h_1[n_1] \) and \( h_2[n_1, n_2] \), were estimated from the measured zero-mean input \( x[n] \) and measured output \( y[n] \) using a frequency-domain method. This method is described in detail elsewhere (37). Briefly, the kernels were estimated in succession. First, the zeroth-order kernel was estimated as the mean of the output as follows:

\[
h_0 = \frac{E(y[n])}{E(x[n])},
\]

where \( E() \) is the expectation operator. Next, the first-order kernel was estimated by first subtracting the contribution of the zeroth-order kernel from the output and then computing the cross-spectrum divided by the input spectrum (i.e., Wiener filter) as follows:
where $R(\cdot)$ is the autocorrelation or cross-correlation function between the indicated signals, $\mathcal{F}(\cdot)$ is the convolution operator, and $\mathcal{F}(\cdot)$ is the Fourier Transform operator. Finally, the second-order kernel was estimated by first subtracting the contribution of the zeroth- and first-order kernels from the output and then computing a two-dimensional generalization of the Wiener filter as follows:

$$y[n] - h_0 = h_1(\lambda) \otimes R_\alpha(\lambda) \rightarrow \mathcal{F}\{h_1(\lambda)\} = \mathcal{F}\{R_\alpha(\lambda)\} \mathcal{F}\{h_\alpha(\lambda)\},$$

where $R(\cdot)$ is again the correlation function among the indicated signals, $\otimes$ is the two-dimensional convolution operator, and $\mathcal{F}(\cdot)$ and $\mathcal{F}(\cdot)$ are one- and two-dimensional Fourier transform operators, respectively. Note that $E(\cdot)$ and $R(\cdot)$ above were computed via the standard sample mean and unbiased correlation function estimates. The kernels of the Uryson model of Fig. 4, $h_0$, $h_1[n]$, and $h_2[n]$, were estimated analogously. First, the zeroth- and first-order kernels were estimated, as described above. Then, the contribution of these kernels was subtracted from the output, also as described above. Finally, the second-order kernel was estimated by first squaring the input and then computing the Wiener filter as follows:

$$y[n]^2 = x[n] \otimes h_2(\lambda) \otimes 2R_\alpha(\lambda) \rightarrow \mathcal{F}\{h_2(\lambda)\} = \mathcal{F}\{2R_\alpha(\lambda)\} \mathcal{F}\{h_\alpha(\lambda)\},$$


Lohmeier TE, Biescu R. Chronic lowering of blood pressure by cardiac baroreflex activation: mechanisms and potential for hypertension therapy. Hypertension 57: 880–886, 2011.


