Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Dynamic Modeling of Renal Blood Flow in Dahl Hypertensive and Normotensive Rats

Knudsen, Torben; Elmer, H.; Knudsen, Morten; Holstein-Rathlou, N.H.; Stoustrup, Jakob

Dynamic Modeling of Renal Blood Flow in Dahl Hypertensive and Normotensive Rats

Torben Knudsen, Henrik Elmer, Morten H. Knudsen, Niels-Henrik Holstein-Rathlou, and Jakob Stoustrup*, *Senior Member, IEEE*

Abstract—A method is proposed in this paper which allows characterization of renal autoregulatory dynamics and efficiency using quantitative mathematical methods. Based on data from rat experiments, where arterial blood pressure and renal blood flow are measured, a quantitative model for renal blood flow dynamics is constructed. The mathematical structure for the dynamics is chosen as a "grey-box model," i.e. the model structure is inspired from physiology, but the actual parameters is found by numerical methods. Based on a number of experiments, features are extracted from the estimated parameters, which describe myogenic responses and tubuloglomerular feedback responses separately. The method is applied to data from normo- and hypertensive Dahl rats, and a discriminator that separates data from normotensive Dahl R rats and hypertensive Dahl S rats is constructed.

Index Terms—Discriminators, feature extraction, hypertension, myogenic response, normotension, system identification, tubuloglomerular feedback mechanism.

I. INTRODUCTION

THE KIDNEYS play an important role in regulating blood pressure and maintaining a proper internal environment for the cells of the body. Since the glomerular filtration rate (GFR) is highly sensitive to fluctuations in the blood pressure, an optimal regulation requires mechanisms that minimizes the effects of blood pressure fluctuations on GFR, and hence the renal excretion of salt and water. One such mechanism is renal blood flow autoregulation [1]. Autoregulation is the result of two physiological control mechanisms that operate at the level of the individual nephron: 1) the tubuloglomerular feedback mechanism (TGF) and 2) the myogenic mechanism. The TGF regulates the resistance of the afferent arteriole in response to changes in the tubular NaCl concentration at the *macula densa*. Experiments has demonstrated that this feedback regulation can become unstable and generate self-sustained oscillations with a typical period of 30–40 s [2], [3]. The myogenic mechanism is an intrinsic response of the preglomerular vessels where an increase in transmural pressure results in a vasoconstriction. Like the TGF, the myogenic mechanism also shows self-sustained oscillations albeit with a shorter period (4–8 s) [1].

There are many instances where it would be valuable both to quantify the individual efficiency and to characterize the dynamics of the two mechanisms. Recent experiments have shown a decreased efficiency of the myogenic component of autoregulation in Dahl salt sensitive hypertensive rats [4]. The decreased autoregulatory efficiency could contribute to the development of hypertension through its effects on salt and water balance, but it could also be a cause of the renal injuries seen in the hypertensive animals. Renal damage secondary to hypertension is one of the most common causes of end-stage renal failure in for example the United States of America [5]. A simple and efficient method for quantifying the efficiency of renal autoregulation could be a clinical tool to identify patients at risk for hypertensive kidney damage. Characterization of efficiency and dynamics could also be of value for monitoring kidney function in renal transplant recipients. By tracking autoregulatory efficiency or dynamics, it may be possible to detect rejection episodes or other conditions that require intervention to prevent loss of the graft. Screening transgenic animals for possible renal manifestations of the genetic trait, and monitoring for renal effects and possible side effects of pharmaceutical drugs are other potential applications for such a method. Preferably, such a method should be based on noninvasive techniques.

Various modeling approaches have been applied in the study of renal blood flow regulation. This includes techniques where the system is perturbed by a variable input, here defined to be the arterial pressure, like step changes [6], sinusoidal pressure variations [7], [8], the normally occurring spontaneous fluctuations in the arterial pressure [9] or a random input signal [10]–[12]. System identification can be performed both in the frequency and time domain. Nonlinear dynamical systems theory has also been applied, as in [13] where black-box Volterra and neural network approaches have been investigated. Although these approaches have yielded valuable insight into the dynamics of renal blood flow regulation, they do not produce a limited parameter set that is useful for diagnostic, prognostic, or screening purposes.

Other approaches have been to create white-box like models, or physiological models, where individual parts of the nephrons are included. Among those are [14] and [15], where a model of the tubuloglomerular feedback is made to describe spontaneous oscillations arising in this system. In [16], a myogenic response is added to the model. The latter models contain considerable physiological information (many parameters), and as such are unsuited for parameter estimation from experimental data.

The aim of the project was therefore to find a suitable model structure and a parameter estimation method which together models renal blood flow dynamics. It was an explicit goal that the model should have a limited number of parameters.
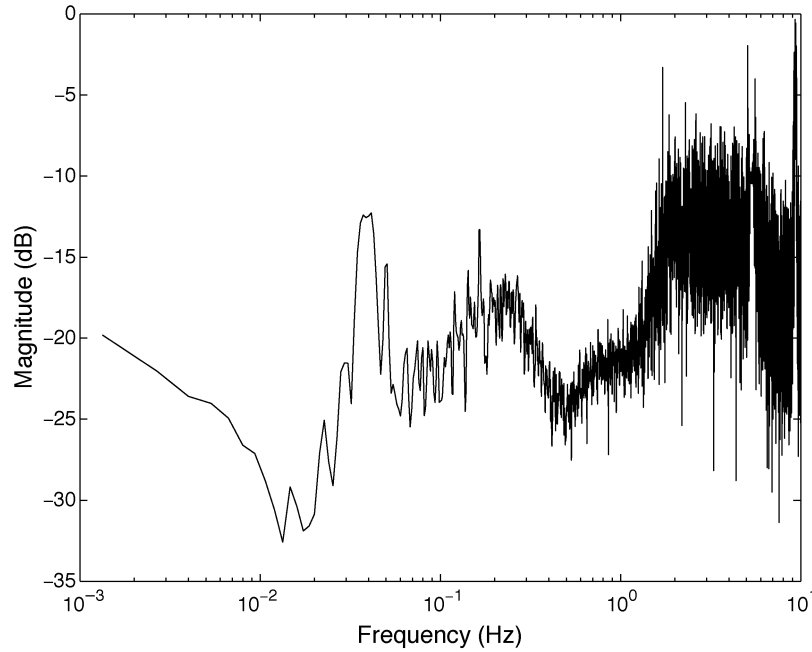
Fig. 1.   Estimated amplitude $[A(\omega)]$ of system transfer function for a Dahl salt resistant normotensive rat.

Here, a linear system-identification method is used [17], [18]. Thus, the dynamic model is linear with the arterial pressures as input and the renal blood flow as output. Estimation of model parameters is done in the frequency domain using the tool called "Senstools" [19]. The model is constrained to the low-frequency range, where autoregulation is known to be active [1]. The method is tested by applying it to experimental data from normotensive (Dahl salt resistant) and genetically hypertensive (Dahl salt sensitive) rats [4].

II. METHODS

A. Input–Output Relation Between Arterial Pressure and Renal Blood Flow

In normal kidneys, both the tubuloglomerular feedback and the myogenic response contributes to autoregulation. Due to their intrinsic oscillations, both mechanisms are associated with characteristic resonances in the frequency domain [14]. This feature is used in creation of the dynamic model, by modeling both mechanisms as forced harmonic oscillators with a damping coefficient d and a resonance frequency ω. Two such models in series will then represent a dynamic model for the entire kidney input–output relation.

In general mathematical terms, the relation between arterial blood pressure and renal blood flow can be seen as a function H mapping the input, the arterial blood pressure $p(t)$, onto the output, the renal blood flow $f(t)$

$$f(t) = H\left\{p(t'), t' \le t\right\}. \tag{1}$$

If the function is linear, then a frequency-domain representation (2) can be found relating the cross-spectral density function $P_{pf}(\omega)$ and the power-spectral density $P_{pp}(\omega)$ [17]

$$P_{pf}(\omega) = H_{pf}(\omega) P_{pp}(\omega)$$
$$\Rightarrow H_{pf}(\omega) = \frac{P_{pf}(\omega)}{P_{pp}(\omega)}. \tag{2}$$
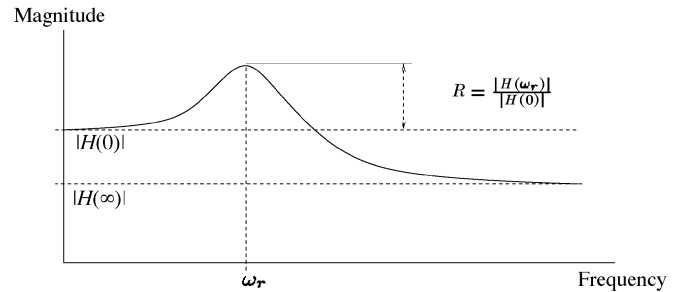
Fig. 2.   Sketch of a second-order system, having a resonance peak at the frequency ω_r, a low-pass gain $|H(0)|$, and a high-pass gain $|H(\infty)|$.

Both P_{pf} and P_{pp} are easily calculated from experimental data by a fast Fourier transform (FFT) algorithm [20]. $H_{pf}(\omega)$ is a complex function, thus containing an amplitude $A(\omega)$ and a phase $\phi(\omega)$

$$A(\omega) = |H_{pf}(\omega)|, \quad \phi(\omega) = \angle H_{pf}(\omega). \tag{3}$$

Fig. 1 shows a typical example of the amplitude $A(\omega)$ as estimated from experimental data. Characteristically, two peaks are found within the frequency range from 0.01 to 1 Hz.

B. Model Structure

The goal is to find a structure for parametric modeling of the input-output relation between arterial blood pressure and renal blood flow in the frequency domain. For simplicity, it will be constrained to the magnitude $A(\omega)$ of $H_{pf}(\omega)$ (3). To make parameter estimation feasible, the model should have a limited number of parameters. Consequently, it cannot be based on the detailed physiological properties of the system, but only represent its major dynamic features.

First, a model structure is sought that gives the magnitude plot seen in Fig. 2, with a resonance frequency ω_r, a low-pass gain $|H(0)|$, and a high-pass gain $|H(\infty)| \triangleq \lim_{\omega \to \infty} |H(\omega)|$. The
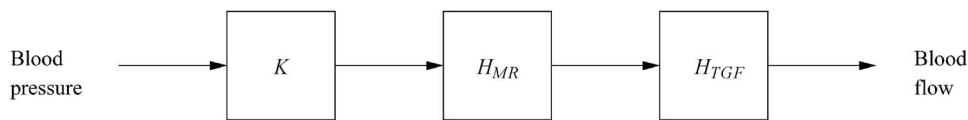
Fig. 3. Schematic drawing of the linear model consisting of the myogenic response H_{MR}, in series with the tubuloglomerular feedback H_{TGF}.

idea is to put two such structures in series to give peaks as in Fig. 1.

First, it is noted in Fig. 1 that the system may have a low-frequency gain different from one, so a gain constant K is introduced into the model. Furthermore, a high-pass gain larger than zero is present, so the number of zeros in the model must equal the number of poles.

A well-defined resonance peak can be obtained by a model for a forced damped oscillator which has the Laplace transformed transfer function given in (4) as follows:

$$H_{\mathrm{osc}}(s) \propto \left(\frac{1}{\frac{s^2}{\omega_0^2} + \frac{2ds}{\omega_0} + 1} \right) \tag{4}$$

where ω_0 is the natural frequency, d is the damping coefficient, and s is a complex variable. The transfer function contains two poles, so the same number of zeros has to be included in order to obtain a curve as in Fig. 2 with a nonzero high-frequency gain. Hence, the numerator must take the form given in

$$H_{\mathrm{inv}}(s) = \frac{s^2}{\omega'^2_0} + \frac{2d's}{\omega'_0} + 1. \tag{5}$$

Each component of autoregulation is modeled by a structure of the type in (6), where the index N is either MR for the transfer function modeling the myogenic response or TGF for the transfer function modeling the tubuloglomerular feedback

$$H_N(s) = \frac{f(s)}{p(s)} \propto H_{N,\mathrm{osc}}(s) H_{N,\mathrm{inv}}(s). \tag{6}$$

$f(s)$ is the Laplace transform of the renal blood flow and $p(s)$ the Laplace transform of the arterial blood pressure. The combined action of the two components is modeled by placing them in series. This yields the transfer function in (7), which is shown graphically in Fig. 3

$$H(s) = K H_{\mathrm{MR}}(s) H_{\mathrm{TGF}}(s) \tag{7}$$

$$H_{\mathrm{MR}}(s) = \frac{\left(\frac{s}{\omega'_{\mathrm{MR}}}\right)^2 + \frac{2d'_{\mathrm{MR}}s}{\omega'_{\mathrm{MR}}} + 1}{\left(\frac{s}{\omega_{\mathrm{MR}}}\right)^2 + \frac{2d_{\mathrm{MR}}s}{\omega_{\mathrm{MR}}} + 1} \tag{8}$$

$$H_{\mathrm{TGF}}(s) = \frac{\left(\frac{s}{\omega'_{\mathrm{TGF}}}\right)^2 + \frac{2d'_{\mathrm{TGF}}s}{\omega'_{\mathrm{TGF}}} + 1}{\left(\frac{s}{\omega_{\mathrm{TGF}}}\right)^2 + \frac{2d_{\mathrm{TGF}}s}{\omega_{\mathrm{TGF}}} + 1} \tag{9}$$

$$\tag{10}$$

$$\theta = (K \ \ \omega'_{\mathrm{MR}} \ \ d'_{\mathrm{MR}} \ \ \omega_{\mathrm{MR}} \ \ d_{\mathrm{MR}} \ \ \omega'_{\mathrm{TGF}}$$
$$d'_{\mathrm{TGF}} \ \ \omega_{\mathrm{TGF}} \ \ d_{\mathrm{TGF}})^{\mathrm{T}}. \tag{11}$$

The result of this model structure is a parameter vector θ (11) containing nine parameters. This yields a model structure flexible enough to capture the basic dynamics seen in Fig. 1.

C. Parameter Estimation

Generally, the parameter estimate $\hat{\theta}$ is the parameter vector which minimizes a performance function $V(\theta)$ (12) that measures the difference between experimental data and a corresponding model prediction based on θ. Here, frequency-domain estimation is used where $V(\theta)$ (13) is the 2-norm based on frequency-domain errors $\varepsilon(\omega_k, \theta)$ (14) between nonparametric gain estimates $A(\omega_k)$ and corresponding predicted values $\widehat{A}(\omega_k, \theta)$ given by the model

$$\hat{\theta}_N = \arg\min_\theta V(\theta) \tag{12}$$

$$V(\theta) = \frac{1}{2N} \sum_{k=1}^N \varepsilon(\omega_k, \theta)^2 \tag{13}$$

$$\varepsilon(\omega_k, \theta) = A(\omega_k) - \widehat{A}(\omega_k, \theta). \tag{14}$$

Fig. 4 illustrates this by showing $A(\omega_k)$ and $\widehat{A}(\omega_k, \hat{\theta})$ in one plot.

The minimization can be done with several methods. Here, a Gauss–Newton algorithm is employed. This requires the Hessian matrix $\mathcal{H}$ (15), which can be approximated from the model gradient $\Psi(\omega_k, \theta)$

$$\mathcal{H} = \frac{\partial^2 V(\theta)}{\partial\theta \, \partial\theta^T}$$
$$= \frac{1}{N} \sum_{k=1}^N \Psi(\omega_k, \theta) \Psi^T(\omega_k, \theta) \tag{15}$$

$$\Psi(\omega_k, \theta) = \frac{\partial \widehat{A}(\omega_k, \theta)}{\partial\theta}. \tag{16}$$

The gradient $\Psi(\omega_k, \theta)$ can be determined analytically in some cases, but is always available through numerical differentiation.

An accurate estimate of a parameter θ_i requires that V is sensitive to θ_i. Furthermore, in general, the most sensitive parameters will be estimated most accurately. Consequently, characteristic sensitivity measures have been developed [18]. These measures are convenient for experiment design, assessment of parameter accuracy and choice of parameters to be identified.

D. Establishing a Discriminator

One of the goals of the present work is to establish a general method that can be used for allocating individuals to different groups based on differences in dynamic renal autoregulatory function as expressed by differences in the estimated model parameters. In the context of the present study, we use data from normo- and hypertensive rats (see below) to test whether the developed model can be used to detect a well established difference in renal autoregulatory function between two strains of rats. If f_h and f_n are the density functions for the parameters x from hypertensive Dahl S and normotensive Dahl R rats, re-
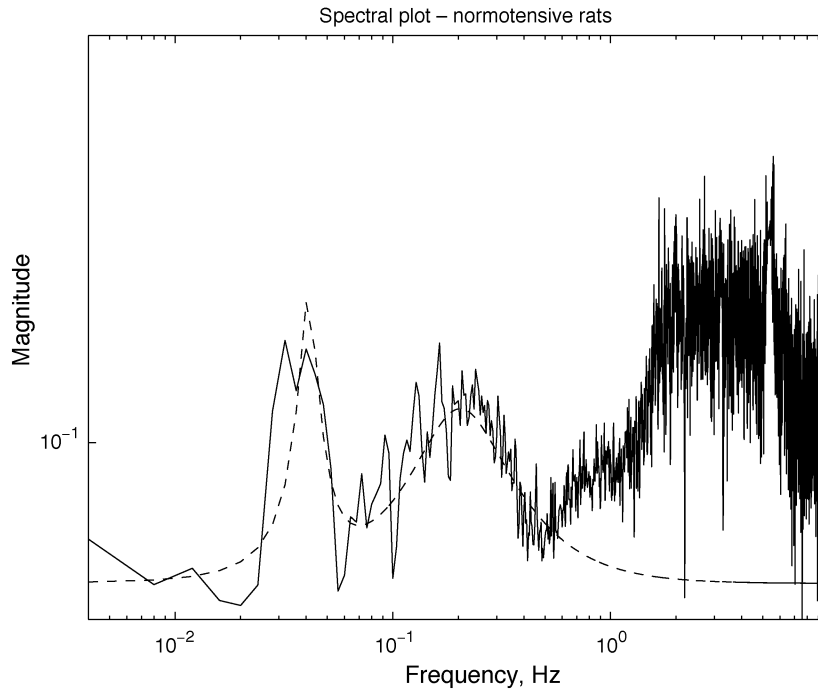
Fig. 4. The solid highly irregular curve is a nonparametric estimate of the transfer function for a Dahl R normotensive rat, calculated as the cross power spectrum of renal blood flow and renal arterial blood pressure divided by the auto power spectrum of the renal arterial blood pressure (2–3). The dashed line is a parametric model, based on two harmonic oscillators in series, fitted to the nonparametric one in the frequency range below 1 Hz.

spectively, the optimal rule for detecting hypertension ($x \in H$) is given by

$$H = \left\{ x : \frac{f_h(x)}{f_n(x)} \geq \frac{L_{h|n}}{L_{n|h}} \frac{p_n}{p_h} = c \right\}. \tag{17}$$

$L_{h|n}$ is the loss associated with the detection of hypertension when normotensive is the case and p_n is the a priori probability for normotension. Using equal losses and *a priori* probabilities gives $c = 1$.

With a small number of observations as, e.g. 2×10, there is usually reason to assume normal distributions and equal covariances for f_h and f_n. These assumptions (18) are therefore accepted, as they simplify the detection rule to one that is linear in x (21). Notice the notation $z \in a(b,c)$ meaning z has the distribution a with parameters b and c

$$x|h \in \mathrm{N}(\mu_h, \Sigma), \quad x|n \in \mathrm{N}(\mu_n, \Sigma) \tag{18}$$

$$\frac{f_h(x)}{f_n(x)} \geq \frac{L_{h|n}}{L_{n|h}} \frac{p_n}{p_h} = c \Rightarrow \tag{19}$$

$$(\mu_h - \mu_n)^{\mathrm{T}} \Sigma^{-1} x - \frac{1}{2} \mu_h^{\mathrm{T}} \Sigma^{-1} \mu_h$$
$$+ \frac{1}{2} \mu_n^{\mathrm{T}} \Sigma^{-1} \mu_n \geq \log(c) \Rightarrow \tag{20}$$

$$v^{\mathrm{T}} x \geq l, \quad v = \Sigma^{-1}(\mu_h - \mu_n) \tag{21}$$

$$l = \frac{1}{2} \mu_h^{\mathrm{T}} \Sigma^{-1} \mu_h - \frac{1}{2} \mu_n^{\mathrm{T}} \Sigma^{-1} \mu_n + \log(c). \tag{22}$$

Here, μ_h and μ_n are means and Σ is the common covariance. All of these can be estimated. Inserting these estimates in (21) gives the application specific constants v and l.

Among the initial number of parameters p there could be some q parameters which do not contribute to the discrimination. This makes a reduction to $r = p - q$ parameters possible. A test for this possibility is based on (26), where D^2 and D_r^2 (23) is Mahalanobi's distance for all parameters and the reduced set, respectively, n_h and n_n are the number of samples in each population

$$D^2 = (\mu_h - \mu_n)^{\mathrm{T}} \Sigma^{-1} (\mu_h - \mu_n) \tag{23}$$

$$D_r^2 = (\mu_{rh} - \mu_{rn})^{\mathrm{T}} \Sigma_r^{-1} (\mu_{rh} - \mu_{rn}) \tag{24}$$

$$k_Z = \frac{n_h + n_n - p - 1}{q} \tag{25}$$

$$Z = k_Z \times \frac{n_h n_n \left(D^2 - D_r^2 \right)}{(n_h + n_n)(n_h + n_n - 2) + n_h n_n D_r^2}$$
$$\in \mathbf{F}(q, n_h + n_n - p - 1). \tag{26}$$

E. Experimental Preparation and Data Collection

The data are taken from a previous study where simultaneous recordings of arterial blood pressure and renal blood flow were performed in ten hypertensive and ten normotensive rats form the inbreed Dahl rat strains [4]. The experimental conditions are briefly described below. For details, see [4].

Experiments were performed on hypertensive male Dahl salt sensitive rats (S) weighing 220–430 g, and normotensive male Dahl salt resistant rats (R) weighing 200–300 g. The experimental protocol had been approved in advance by the institutional animal care committee.

The normotensive Dahl R rats were fed a low salt diet (0.4% NaCl) from the time of weaning at four weeks of age and for the following seven weeks prior to the experiments. The hypertensive Dahl S rats were fed a low-salt diet (0.4% NaCl) during the

first week after weaning, then switched to a high-salt diet (8% NaCl) for the next four weeks, and were finally put on a low-salt diet for the last two weeks prior to experiments.

Anesthesia was induced by placing the rats in a chamber containing 5% halothane administered in a mixture of 35% oxygen and 65% nitrogen. Catheters were inserted into the left jugular vein for infusions and into the right carotid artery for continuous recording of the arterial blood pressure. A tracheostomy was performed, and the rats were placed on a servo-controlled operating table that maintained their body temperature at 37°C. The rats were connected to a small animal ventilator that was adjusted to maintain arterial plasma pH between 7.35 and 7.45 with a mixture of 35% oxygen and 65% nitrogen, tidal volume 1.9–2.1 ml, and a frequency of 55–57 breaths/min. The final halothane concentration needed to maintain sufficient anesthesia was 1%.

The abdomen was opened through a midline incision extended to the left flank. The distal aorta was cannulated at the bifurcation with a polyethylene tube (PE-90), filled with blood freshly obtained from a donor animal, which had been on the same diet. The blood-filled tube led to a small Plexiglas chamber where low-viscosity silicone oil made an interface with the blood. Another polyethylene tube filled with silicone oil connected the chamber to a stainless steel bellows. The bellows was connected to a linear motor (Ling Dynamic Systems, Royston, U.K.) controlled by a computer.

The left kidney was denervated by stripping away all visible nerves, and wiping the artery with a solution of 5% phenol dissolved in ethanol. The ureter was cannulated to ensure free flow of urine. 6% bovine serum albumin (BSA) (Sigma, St. Louis, MO) in saline was infused at a rate of 20 μl/min for the duration of the surgery, and 1% BSA was continued throughout the experiment at the same infusion rate. The left kidney was superfused with saline preheated to 37 °C.

A catheter (PE-50) was inserted into the superior mesenteric artery. It was connected to a Statham P23-dB pressure transducer (Gould, Oxnard, CA). Renal blood flow was measured continuously with an electromagnetic blood flowmeter (Scalar Medical, model 1402, Delft, The Netherlands) with the probe placed around the left renal artery.

Arterial blood pressure and renal blood flow were recorded while broad-band fluctuations were induced in the arterial blood pressure. The fluctuations were generated by the bellows pump, and resulted in blood pressure fluctuations with the spectral properties of band-limited white noise. The duration of the forcing was 30 min.

Data acquisition has previously been described in detail [4]. Briefly, the two signals were passed through an antialiasing filter, and sampled simultaneously (off-line), each at a frequency of 20 Hz for 25 min.

III. RESULTS

A. Initial Parameter Values

Because the two subparts of (9) are identical, there is no *a priori* information about which of the two peaks they are meant to represent. Any difference between the MR part and the TGF part is only to be found in the parameters. Hence, the knowledge that the resonance frequencies should be found within different frequency ranges is used to separate the model

	Mean (NT)	Std. dev. (NT)	Mean (HT)	Std. dev. (HT)
d_{TGF}	0.2805	0.2639	0.3417	0.3142
ω_{TGF}	0.2433	0.1374	0.1937	0.0545
d'_{TGF}	0.1078	0.2477	0.3838	0.3643
k_{TGF}	0.7890	0.2388	1.2301	0.4607
d_{MR}	0.3018	0.0967	0.5812	0.4465
ω_{MR}	1.4070	0.2445	0.7028	0.1894
d'_{MR}	0.6071	0.3138	0.8046	0.3696
k_{MR}	1.2955	0.2929	1.3888	0.4425
$gain$	0.0790	0.0505	0.1630	0.1019

parts in the estimation. This is done by choosing the initial values of ω_{TGF} and ω_{MR} to be, respectively, substantially lower and higher than their expected values. The rest of the initial parameters are chosen so that the model starts with a "correct" shape with two peaks, each having a height comparable to the one found in most data sets.

The estimation are separated into two parts. First, only the resonance frequencies, ω_{TGF} and ω_{MR}, and the damping coefficients, d_{TGF} and d_{MR}, are estimated given the initial values of the rest of the parameters. The hope is that the two resonances each will find a peak in the data, and settle there. Second, these estimated parameters are used as new initial parameters in an estimation were all parameters are free to change.

B. Parameter Estimation in Dahl R Normotensive Rats

In Fig. 4, the estimated amplitude of the nonparametric transfer function is shown as the solid irregular line. The dashed line represents the parametric model where the parameters in (9) are estimated to fit the amplitude $A(\omega)$ of the nonparametric transfer function. The parametric model identifies the two peaks with good fits for both the frequencies and the amplitudes. For the system shown the frequencies are found to be $\omega_{TGF} \sim 0.04$ Hz and $\omega_{MR} \sim 0.2$ Hz. The two damping coefficients were found to be $d_{TGF} = 0.07$ and $d_{MR} = 0.44$, respectively.

Fig. 6 shows all nine estimated parameters from ten different data sets, measured on ten Dahl R normotensive rats and represented as circles.

The standard deviation for the estimated d_{TGF} are 0.26, being substantially higher than for the d_{MR} being 0.1. This is probably because the number of points in the TGF range is much less than in the MR range. The mean values of the two parameters are much closer, being 0.28 and 0.3, respectively. In the case of the resonance frequencies ω_{TGF} and ω_{MR}, the standard deviations are found to be 0.022 and 0.04, respectively, and the mean values are found to be 0.039 and 0.22. For the estimated low-frequency gain (K), the mean is found to be 0.08 with a standard deviation of 0.05.

A comparison of means and standard deviations for both normotensive and hypertensive animals are shown in Table I.

C. Parameter Estimation in Dahl S Hypertensive Rats

The solid irregular line in Fig. 5 is the estimated amplitude of the nonparametric transfer function in a Dahl S hypertensive rat. In contrast to the normotensive rats where two distinct peaks were present, only one broad based peak is detectable in the hypertensive rats. The estimated frequency of the MR part of
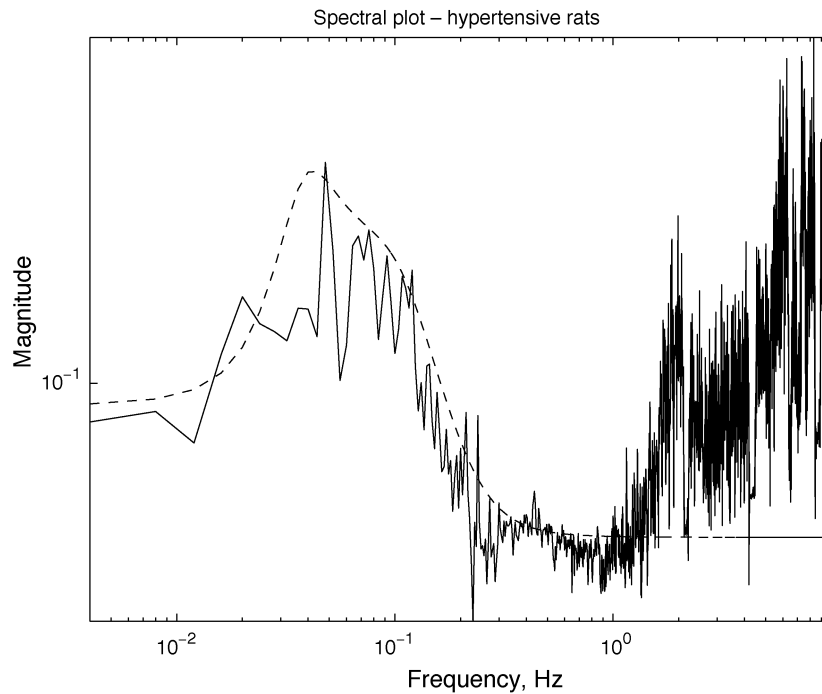
Fig. 5.   The figure is similar to Fig. 4, but data is from a Dahl S hypertensive rat.
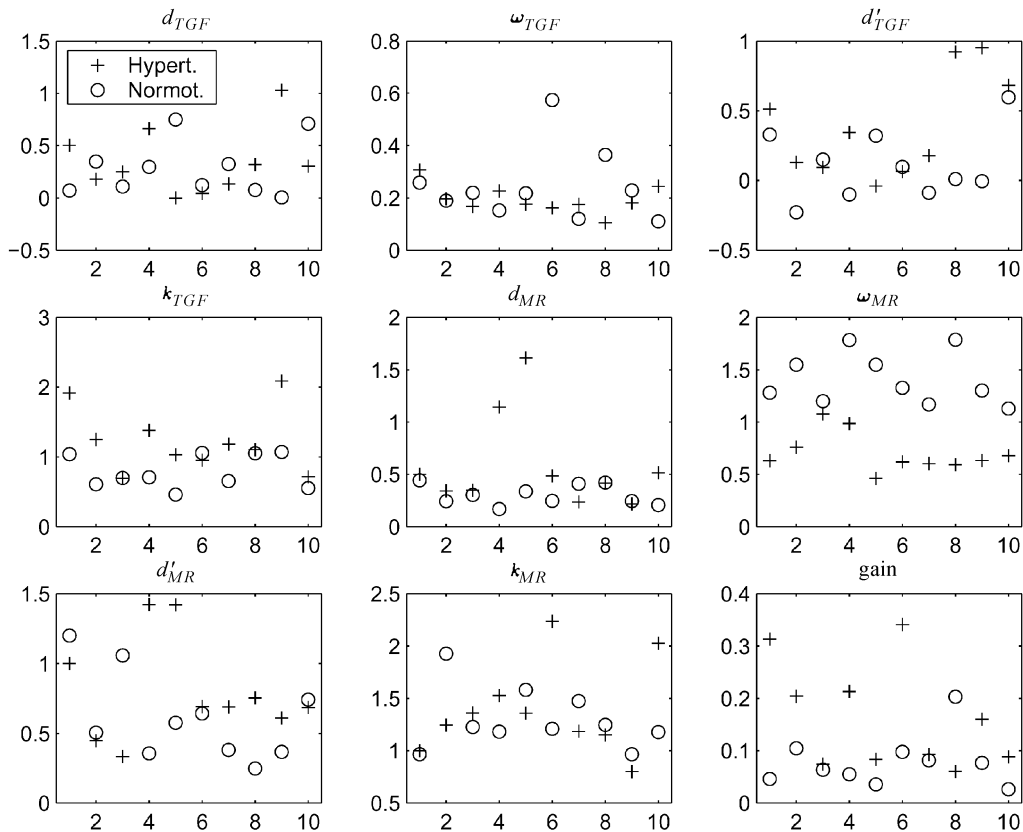

Fig. 6.   Scatter plots of estimated parameters for the ten Dahl R normotensive rats ($\circ$) and the ten Dahl S hypertensive rats ($+$). The x-axis is rat number.

the dynamic model has moved into the lower frequency range, and it can be seen as a knee in the curve at $\omega_{\mathrm{MR}} \sim 0.1$ Hz. The low-frequency part (TGF) is in the same range as found for the normotensive rats, being at $\omega_{\mathrm{TGF}} \sim 0.039$ Hz. The two damping coefficients are found to be $d_{\mathrm{TGF}} = 0.3$ and $d_{\mathrm{MR}} = 0.5$, respectively.

Fig. 6 shows the estimated parameters from ten different data sets from the Dahl S hypertensive rats. The individual values are represented as pluses.

The standard deviation for the estimated d_{TGF} is 0.31, almost the same as found in the normotensive case. However, there is a substantially higher variability for the d_{MR}-parame-
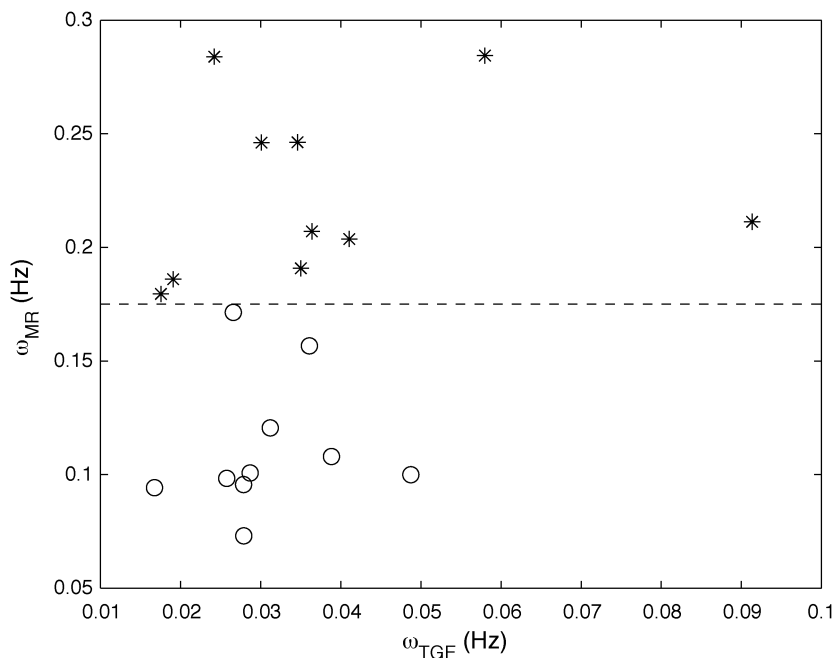
Fig. 7.   Estimated resonance frequencies related to the myogenic response. The stars are estimated for normotensive Dahl R rats and the circles for hypertensive Dahl S rats. The resonances are in hertz.
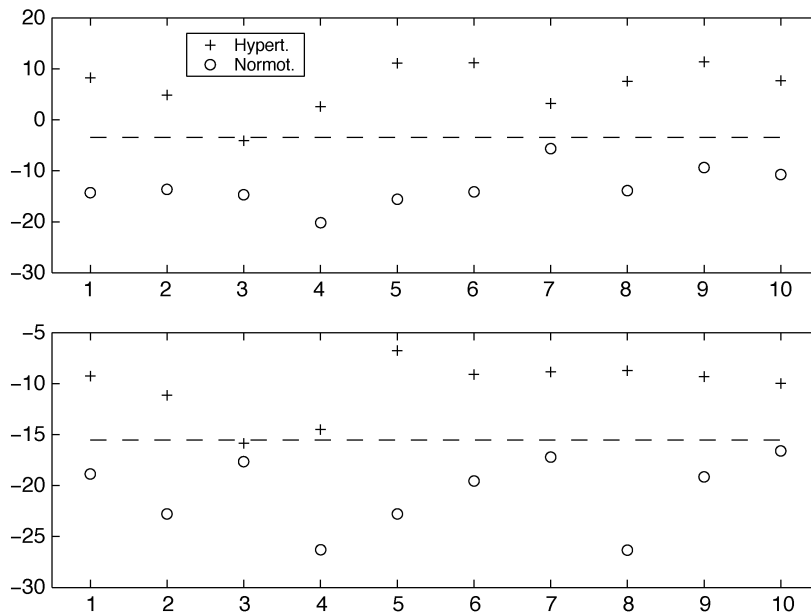

Fig. 8.   Values for all rats using the optimal discriminator with all parameters in the top plot and only ω_{MR} in the bottom plot. The x-axis is rat number.

ters, the standard deviation being 0.44. The mean values of the two damping coefficients are 0.34 and 0.58, respectively. In the case of the resonance frequencies ω_{TGF} and ω_{MR}, the standard deviations are 0.03 and 0.009 respectively and the mean values are found to be 0.03 and 0.11.

An overview of means and standard deviations for all nine parameters both in the normotensive and the hypertensive cases is shown in Table I.

D. Discrimination Between the Two Populations

Inspection of Fig. 6 reveals that ω_{MR} is useful to discriminate data from the two strains of rats. This parameter is plotted on

Fig. 7 against the corresponding values for ω_{TGF} with asterisks for the normotensive rats and circles for the hypertensive rats. The line separating the two rats strains are chosen by inspection to be at 0.175 Hz.

However, the other eight parameters could also hold useful information for the discrimination even though it is not evident when considering one parameter at a time. To test this possibility, we applied the test described in Section II-D.

The result is shown in Fig. 8. The plotted points are the values of the optimal discriminators $v^{\mathrm{T}}x$ for all 2×10 rats, the dashed line is the level l (21). In the top plot, all nine parameters are used while in the bottom plot only ω_{MR} is included. The contribution from parameters other than ω_{MR} are insignificant as

Mahalanobi's distance drops from 19.6 to 10.4, corresponding to a p-value of 0.61.

IV. DISCUSSION AND CONCLUSION

The long term perspective of this project is to develop a method for assessing possible changes in renal blood flow regulation from noninvasive measurements of arterial blood pressure and renal blood flow. Steady state measurements of these variables can detect changes in autoregulatory efficiency, but they cannot discriminate between changes due to alterations in either the TGF mechanism or the myogenic mechanism. The present approach takes advantage of the fact that the two autoregulatory mechanisms operates on slightly different timescales [1]. The hypothesis is that by combining dynamic measurements with dynamic modeling, it will be possible to separate the contributions of the two mechanisms to renal autoregulation, and thus, to determine whether a possible dysfunction is present in one or both the autoregulatory mechanisms.

This hypothesis has been tested with success as the method developed in the present paper successfully separated dynamic recordings of arterial blood pressure and renal blood flow from normo- and hypertensive Dahl rats. It is especially promising that the parameter that was most efficient for discriminating between the two data sets was the resonance frequency associated with the myogenic response. The data were obtained in a previous study where it was shown, using micropuncture techniques, that the hypertensive Dahl S rats had a severely reduced efficiency of the myogenic mechanism, whereas the TGF response was normal [4], [21]. The latter is also in excellent agreement with the present results, since there was no discriminatory information in the parameters associated with the TGF response.

It is important to stress that the results do not allow the conclusion that the method can be used to discriminate between normo- and hypertensive rats from other genetically hypertensive strains. Hypertension is a multifactorial disease, and there are important pathophysiological differences between the different experimental models. It is, of course, a prerequisite that the underlying disease process should involve the relevant control systems, i.e., the myogenic and/or the TGF mechanism, and lead to changes in renal autoregulatory dynamics. In the latter case, the present results show that by using a simple dynamic model it is possible to extract a parameter set that discriminates between renal function in normo- and hypertensive rats.

A method for assessing detailed information on renal function based on simple, noninvasive measurements is highly desirable. Using finger-cuff based methods, it is possible to obtain continuous measurements of the arterial blood pressure in humans. Furthermore, the improvement of ultrasound Doppler systems has now made it possible to continuously measure renal blood flow noninvasively. One of the next goals is therefore to apply the present method to human data.

Such a method could be useful in several clinically relevant situations. For example, it is well known that a subgroup of hypertensive patients are at high risk for developing kidney failure as a consequence of the high blood pressure [5]. Based on experimental data, it has been suggested that one reason for this propensity could be a reduced autoregulatory efficiency [22]. However, at present it is not possible to predict which patients will develop renal failure due to hypertension. If it was possible, using the present method, to detect a subgroup of patients at high risk for developing hypertensive renal damage, these patients could be subjected to a more aggressive antihypertensive therapy with the goal of preventing future renal damage. We speculate that the method could also be of use in monitoring kidney function in for example renal transplant recipients. Early detection of organ rejection is vital for securing both graft and patient survival. It is possible that alterations in dynamic autoregulatory efficiency could be an early sign of rejection. Clearly, the potential clinical applications are highly speculative at present, and additional experiments, including prospective trials, are needed in order to decide the clinical utility of the method.

The model was fitted to renal blood flow data obtained using a broadband forcing of the arterial blood pressure. We do not, however, expect this to be a major limitation. Results from other laboratories have shown that similar transfer functions can be obtained in both dogs and rats using only the spontaneously occurring fluctuations in the blood pressure [23], [24].

The parameter estimation task proved to be difficult and required the application of specially designed methods. Also, the model was only fitted to the frequency gains, i.e. all phase information was left unused. These subjects calls for further research so as to optimize model identification, and possibly the discriminatory efficiency.

In conclusion, we have developed a parsimonious dynamic model that can be used for characterising the efficiency and dynamics of the two most important renal autoregulatory mechanisms. The model could be clinically useful by, for example, allowing tracking of kidney function in individual patients, or for identifying subgroups of patients having an increased risk of renal disease.

REFERENCES

[1] N.-H. Holstein-Rathlou and D. J. Marsh, "Renal blood flow regulation and arterial pressure fluctuations: A case study in nonlinear dynamics," *Physiol. Rev.*, vol. 74, no. 637–681, 1994.
[2] N.-H. Holstein-Rathlou and P. P. Leyssac, "TGF-mediated oscillations in the proximal intratubular pressure: differences between spontaneously hypertensive rats and Wistar-Kyoto rats," *Acta Physiol. Scand.*, vol. 126, pp. 333–339, 1986.
[3] P. P. Leyssac and N.-H. Holstein-Rathlou, "Effects of various transport inhibitors on oscillating TGF pressure response in the rat," *Eur. J. Physiol. (Pflügers Arch.)*, vol. 407, pp. 295–291, 1986.
[4] F. M. Karlsen, P. P. Leyssac, and N.-H. Holstein-Rathlou, "Dynamic autoregulation and renal injury in Dahl rats," *Hypertension*, vol. 30, pp. 975–983, 1997.
[5] J. M. Flack and W. H. Wiist, "Epidemiology of hypertension and hypertensive target-organ damage in the United States," *J. Assoc. Acad. Minor. Phys.*, vol. 2, pp. 143–150, 1991.
[6] E. Basar and C. Weiss, "Analyze des frequenzganges druckinduzierter änderungen des strömungswiderstandes isolierter rattennieren," *Pflügers Arch.*, vol. 304, pp. 121–135, 1968.
[7] E. Basar, H. Tischner, and C. Weiss, "Untersuchungen zur dynamik druckinduzierter änderungen des strömungswiederstandes des autoregulierenden, isolierten rattenniere," *Pflügers Arch.*, vol. 299, pp. 191–213, 1968.
[8] T. Kenner and K. Ono, "The low frequency impedance of the renal artery," *Pflügers Arch.*, vol. 324, pp. 155–164, 1971.
[9] J. He and D. J. Marsh, "Effects on captopril on fluctuations of blood pressure and renal blood flow in rats," *Amer. J. Physiol.*, vol. 264, pp. F37–F44, 1993.
[10] P. Eggert, V. Thieman, and C. Weiss, "Periodic changes of blood flow in the in vivo rat kidney," *Pflügers Arch.*, vol. 382, pp. 63–66, 1979.

[11] K. H. Chon, Y.-M. Chen, N.-H. Holstein-Rathlou, D. J. Marsh, and V. Z. Marmarelis, "On the efficacy of linear system analysis of renal autoregulation in rats," *IEEE Trans. Biomed. Eng.*, vol. 40, pp. 8–20, Jan. 1993.

[12] V. Z. Marmarelis, K. H. Chon, Y.-M. Chen, D. J. Marsh, and N.-H. Holstein-Rathlou, "Nonlinear analysis of renal autoregulation under broadband forcing conditions," *Ann. Biomed. Eng.*, vol. 21, pp. 591–603, 1993.

[13] K. H. Chon, N.-H. Holstein-Rathlou, D. J. Marsh, and V. Z. Marmarelis, "Comparative nonlinear modeling of renal autoregulation in rats: Volterra approach versus artificial neural networks," *IEEE Trans. Neutral Networks*, vol. 9, pp. 430–435, May 1998.

[14] N.-H. Holstein-Rathlou and D. J. Marsh, "A dynamical model of the tubuloglomerular fedback mechanism," *Amer. J. Physiol.*, vol. 258, pp. F411–F428, 1990.

[15] K. S. Jensen, "Nonlinear dynamical phenomena in renal physiology," Ph.D. dissertation, Technical Univ. of Denmark, Denmark, 1987.

[16] N.-H. Holstein-Rathlou and D. J. Marsh, "A dynamic model of renal blood flow autoregulation," *Bull. Math. Biol.*, vol. 56, no. 3, pp. 411–429, 1994.

[17] L. Ljung, *System Identification, Theory for the User*, 2nd ed, ser. Information and System Sciences. Englewood Cliffs, NJ: Prentice-Hall, 1999.

[18] M. Knudsen, "A sensitivity approach for estimation of physical parameters," in *Proc. 10th IFAC Symp. System Identification*, vol. 2, Copenhagen, Denmark, 1994, p. 231.

[19] ——, *SENSTOOLS—A Matlab Toolkit for Parameter Estimation in Linear and Nonlinear Systems Using a Sensitivity Approach*, 1st ed. Aalborg, Denmark: Dept. Control Eng., Aalborg University, Sept. 1996.

[20] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, *Numerical Recipes*. Cambridge, U.K.: Cambridge Univ. Press, 1992.

[21] F. M. Karlsen, P. P. Leyssac, and N.-H. Holstein-Rathlou, "Tubuloglomerular feedback in Dahl rats," *Amer. J. Physiol.*, vol. 274, pp. R1469–R1561, 1998.

[22] K. A. Griffin, M. A. Picken, and A. K. Bidani, "Deleterious effects of calcium channel blockade on pressure transmission and glomerular injury in rat remnant kidneys," *J. Clin. Invest.*, vol. 96, pp. 793–800, 1995.

[23] A. Just, U. Wittmann, H. Ehmke, and H. R. Kirchheim, "Autoregulation of renal blood flow in the conscious dog and the contribution of the tubuloglomerular feedback," *J. Physiol.*, vol. 506, pp. 275–290, 1998.

[24] W. Cupples, P. Novak, V. Novak, and F. C. Salevsky, "Spontaneous blood pressure fluctuations and renal blood flow dynamics," *Amer. J. Physiol.*, vol. 270, pp. F82–F89, 1996.

Henrik Elmer received the M.Sc. degree in physics and mathematics Odense University, Odense, Denmark, in 1998.

He was with the Center for Physiological Processes, Aalborg University, Aalborg, Denmark, involved in a project which models changes in blood flow and pressure related to the action of regulating mechanisms in the kidneys. He is currently a Patent Agent at Danfoss A/S, Nordborg, Denmark. His areas of special interest include medical engineering and micro-fluid systems, either physiological or on chips.

Morten H. Knudsen received the M.Sc. degree in electrical engineering from the Technical University of Denmark, Lyngby, in 1963, and the Ph.D. degree from Aalborg University, Aalborg, Denmark, in 1993.

He was with the Technical University of Denmark (1965–1968), General Dynamics, Rochester, NY (1968–1969), and Measurex Corporation, Santa Clara, CA (1969 to 1971).

Since 1971, he has been an Associate Professor, and since 1990 a Reading Professor (Docent) in control engineering, at the Institute for Electronic Systems, Aalborg University. His main interests are modeling, system identification, and control, e.g. in relation to cancer hyperthermia systems, loudspeakers, and ac motors. He has developed a method for direct estimation of physical parameters in linear and nonlinear dynamic systems, which is implemented in a Matlab Toolbox, SENSTOOLS. In recent years, a considerable part of his time has been spent on IT-based learning.

Niels-Henrik Holstein-Rathlou received the M.D. degree in 1983 and the Ph.D. degree in physiology in 1992, both from the University of Copenhagen, Copenhagen, Denmark.

He was an Associate Professor of Physiology and Biophysics at the University of Southern California, Los Angeles, from 1988 to 1993. Since 1993, he has been a Professor of Medical Physiology at the University of Copenhagen. His current research interests are within the field of renal physiology and hypertension, and include the application of the theory of nonlinear dynamical systems to physiological problems.

Torben Knudsen was born in Aarhus, Denmark, in 1958. He received the M.S. degree in 1983 and the Ph.D. degree in 1990 from the Institute for Mathematical Modeling, both at the Technical University of Denmark, Lyngby.

In 1986, he was with the Wind Energy and Atmospheric Physics Department, Risø National Laboratory, Roskilde, Denmark, as a Research Assistant. Since 1987, he has been at Department of Control Engineering, Aalborg University, Aalborg, Denmark, where he is now an Associate Professor. His main research areas are stochastic systems, state estimation, system identification, and control. He has been working on wind turbines and, more recently, with physiological systems.

Jakob Stoustrup (S'87–M'91–SM'99) was born in Aalborg, Denmark, in 1963. He received the M.Sc. degree in electrical engineering and the Ph.D. degree in applied mathematics from the Technical University of Denmark, Lyngby, in 1987 and 1991, respectively.

He was a Teaching Assistant at the Technical University of Denmark and a Visiting Researcher at Eindhoven University of Technology, Eindhoven, The Netherlands, in 1988. During 1991, he was a Senior Researcher, sponsored by the Danish Technical Research Council. He was then an Assistant Professor (1991–1995) then Associate Professor (1995–1996), both at the Department of Mathematics, Technical University of Denmark. During 1996, he was a Visiting Professor at the University of Strathclyde, Glasgow, U.K. Since 1997, he has been a Full Professor at the Department of Control Engineering, Aalborg University, Aalborg, Denmark. He is the author of more than 100 papers and four international patents. His areas of research include control theory, fault detection and isolation, intelligent sensors based on Rudin-Shapiro theory and wavelets, and grey box modeling.

Dr. Stoustrup received the Statoil Prize in 1997.