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Toward Online, Noninvasive, Nonlinear Assessment of Cerebral Autoregulation

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Abstract— **Online estimation of cerebral autoregulation (CA) may be advantageous in neurosurgical and neurointensive care units. Data from transcranial Doppler, and continuous arterial blood pressure are readily available at high temporal resolution and may be used to assess CA. There are currently no methods for nonlinear, noninvasive, online assessment of CA. We frame the assessment of CA as a parameter estimation problem, in which we estimate the parameters of a nonlinear mathematical model of CA using the ensemble Kalman filter (EnKF).**

In this simulation study, we use the EnKF to estimate the parameters of a model of cerebral hemodynamics which predicts intracranial pressure and cerebral blood flow velocity, generated from real patient arterial blood pressure measurements. We examine the flexibility and appropriateness of the EnKF for CA assessment.

I. INTRODUCTION

Cerebral autoregulation (CA) is a compensatory mechanism which adjusts cerebral arterial diameters to accommodate cerebral blood flow (CBF) demands of brain tissue in spite of fluctuations in arterial blood pressure (ABP). Dynamic cerebral autoregulation (dCA) refers to the transient response of cerebral blood vessels to rapid changes in ABP [1]. Alternatively, static cerebral autoregulation (sCA) refers to the quasi steady-state values of CBF for sustained ABP.

Disrupted dCA function is associated with poor outcomes in stroke [2], [3] and traumatic brain injury (TBI) [4], [5]. Therefore, continuous dCA monitoring is a potentially important tool to guide anesthesiologists, and neurosurgical intensive care units treating these conditions. While a variety of measurement techniques have been developed to assess dCA, continuous, noninvasive monitoring of cerebrovascular function remains a relatively unexplored field.

Some of the difficulty with the development of continuous dCA monitoring technologies is the lack a gold standard metric of dCA function[15]. Many metrics utilize invasive measurements, require the participation of the patient (such as vasalva maneuver), or require restrictive apparatuses (such as for lower body negative pressure). Fortunately, assessment of dCA function can be achieved by analysis of spontaneous fluctuations in noninvasive measurements of ABP and BFV [7], [8], [13], [16].

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Czosnyka used a moving-window method analyzing the correlation between ABP and intracranial pressure (ICP) signals, termed PRx, over a 20 second period [5]. However, the method appears to track vasomotor reserve, where PRx=1 when vasomotor reserve is exhausted, not at failure of dCA function *per se*, and therefore cannot give an impression of autoregulatory function until autoregulatory vasodilation is already exhausted. Furthermore, the PRx utilizes ICP measurements, which necessitates the invasive insertion of an pressure transducer within the cranium, placing the patient at risk for infection. While the PRx may be a useful clinical tool to assess the state of cerebral hemodynamics, a measure of autoregulatory function prior to exhaustion of autoregulatory reserve, and prior to the necessity of ICP measurement, may be an important early warning sign to guide the clinician in appropriate interventions. A similar metric, the Mx index, a measure of sCA, is strongly correlated with dCA and measurements of sCA and dCA may be redundant [9].

Kashif et al. [12] utilized a perturbation solution of a mathematical model of ICP dynamics [11] to obtain continuous, noninvasive estimates of cerebrovascular resistance, compliance, or intracranial pressure. It should be pointed out that the concept of cerebrovascular compliance is not one that is well developed and should be interpreted with caution. While the method seems to provide reasonable estimates of intracranial pressure, it does little to determine autoregulatory function.

The autoregulatory index (ARI) [10] is a widely used method used for assessment of dCA. Panerai et al. have used this method to obtain continuous measurements of dCA function [14], however, this method assumes a linear relationship between ABP and BFV. The nature of ARI as an inverse problem, makes the interpretation of ARI difficult. Parameter estimates, particularly, those that are estimated suboptimally, retain uncertainties associated with residual errors in the model fit. These errors are further propagated into the estimation of the final ARI metric. Thus, in order to gain a realistic idea of how ARI varies between populations, uncertainty within subjects, between measurements, and within populations must be accounted for. In previous studies, only between measurement, and between subject, variability has been accounted for [6]. An honest assessment of uncertainty in the ARI due to propagated errors is lacking.

Our approach to the online estimation problem differs from others in thee fundamental ways; 1) we propose using a nonlinear mathematical model of cerebral autoregulation which has parameters that are more physiologically interpretable; 2) we do not summarize the values of the

parameters into a single metric; 3) parameter estimation can be achieved simultaneously with estimates of parameter uncertainty.

The purpose of this study was to determine the feasibility of online CA estimation by parameter estimation using the ensemble Kalman filter (EnKF) and simulated patient data.

II. Methods

A. Data

Measurement of ABP were recored continuously from the finger using the Finapres device (Finapres, Ohmeda Monitoring Systems, Englewood CO). Transcranial Doppler ultrasound (TCD) was used to record BFV from the temporal window. A transient drop in ABP, and a corresponding drop in BFV was induced by a postural transition from sitting to standing (sit-to-stand). Measurements were recorded at a sampling rate of 1000Hz. A 80 second segment of the recordings, which includes the drop and return of ABP and BFV were preprocessed by filtering with a FIR filter at .5 Hz and down-sampled to 10Hz.

B. Model of cerebral autoregulation

A complete description of the model used in this study, can be found in [11]. Specific modifications that we made to the model are described below.

The model [11] was modified in order to better correspond with the experimental conditions used in this study. For this study, the time scale of the ABP-BFV dynamics was much shorter than the dynamics of cerebrospinal fluid circulation. We therefore discarded terms corresponding to the flow of cerebrospinal fluid. Particular to our BFV data, we have observed from a number of subjects that, following a sit-to-stand, BFV does not always return to pre-standing levels. We did not find this to be due to a corresponding decreased ABP. Therefore, assuming volumetric blood flow q to be proportional to BFV, we modeled baseline blood flow, q_n as

$$q_n(t) = \frac{q_{n,init} - q_{n,fin}}{1 + \exp(t - \delta_q)} + q_{n,fin}$$

where $q_{n,init}$ and $q_{n,fin}$ are the initial and final estimated blood flows, respectively, and δ_q corresponds to the time of the transition of q_n.

C. The ensemble Kalman filter

The EnKF is a Monte Carlo method for online state estimation [17]. The EnKF is a stochastic filter which has been shown to provide robust results compared to other ensemble filters [18]. The generalized state-space description of the model is given by

$$\begin{aligned} x_j &= f(x_{j-1}, \theta) + \epsilon_{p,j} \\ x(t_0) &= x_0 + \epsilon_0 \\ y_j &= h(x_j, \theta) + \epsilon_{m,j} \end{aligned} \tag{1}$$

where x_j is the model state at time t_j, θ are the model parameters, x_0 is the model initial condition, y_j is the data generated by the nonlinear observation function $h(\cdot)$, and ϵ_{p_j}, ϵ_m are process and measurement noise, respectively, at time t_j, and ϵ_0 is initial measurement uncertainty. For the analysis shown here, we assume evenly-spaced measurements in time. Here, we are primarily concerned with the estimation of the model parameters, θ. However, if we let the augmented state vector be $\mathbf{x} = (x_j^T, y_j^T, \theta_j^T)^T$, then we may estimate $\mathbf{x}$ at each time step, and model the parameters with the dynamics $\theta_j = \theta_{j-1}$.

D. Simulation experiments

Initial parameter values θ_0 were determined from a combination of values taken from [11] and functional relations between parameters and mean ABP and BFV values given there. Improved parameters were obtained by least squares fitting to real BFV data. In order to eliminate problems due to "modeling errors", these improved parameters were taken to be the true parameter values θ^* and were used to simulate BFV data y^* . Gaussian noise, $\epsilon_m \sim \mathcal{N}(0, \sigma_m^2)$, was added to y^* in order to simulate measurement errors with $\sigma_m^2 = 2$. The EnKF was used to estimate θ^* using this simulated data.

III. Results

A. Filter Performance

Mean squared error of BFV was found to be 3.2897, which is slightly larger than $\sigma_m^2 = 2$, indicating that the filter performed worse than measurements alone for estimation of BFV. However, estimation of BFV was not the goal of this analysis and we find the estimation error is within reasonable limits. The filter estimate of BFV, data and the true solution y^* are plotted in Fig. 1.

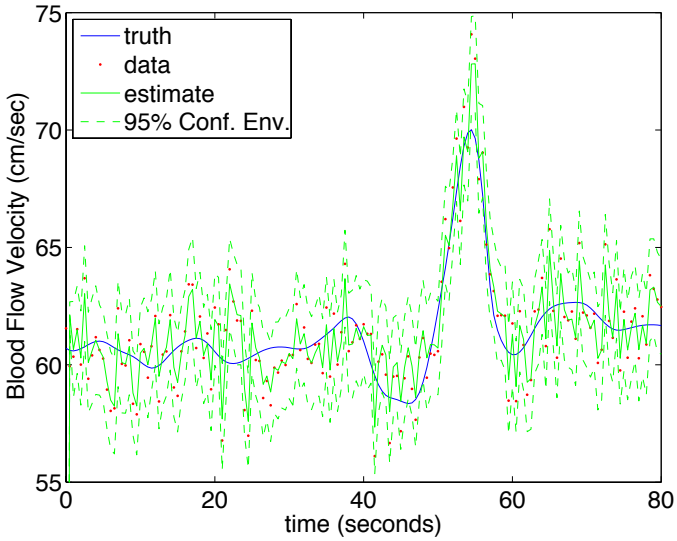

Fig. 1. Simulated blood flow velocity (BFV) (blue), BFV data (red dots), and BFV estimate (green) generated from real arterial blood pressure recording. Dashed lines represent 95% confidence interval of BFV estimate.

B. Parameter estimation performance

Initial parameter values, true parameter values, and 95% confidence interval for parameter estimates are given in Table I. Table I shows that although θ_0 were far from the true parameter values θ^*, θ^* where within the 95% confidence

TABLE I

NUMERICAL RESULTS OF PARAMETER ESTIMATION FOR SIMULATED DATA. A DESCRIPTION OF THE PARAMETERS LISTED IS GIVEN IN [11]. TRUE θ^*, INITIAL θ_0, AND ESTIMATED $\hat{\theta}$ PARAMETERS ARE GIVEN IN $\log_{10}$ SCALE.

	θ^*	θ_0	$\hat{\theta}$	95% CI	
k_E	-1.9212	-3.5650	-1.89155	-2.0766	-1.7065
τ	0.9588	2.6021	1.78045	1.2234	1.5792
G	1.1393	2.0000	0.98465	0.8190	1.1503
k_R	4.6299	9.2658	4.6714	4.5116	4.8312

interval for three of the four estimated parameters. These results clearly indicate an accurate estimation of the model parameters by the EnKF following a sit-to-stand.

IV. CONCLUSIONS AND FUTURE WORKS

The results of this study suggest that parameter estimation for a model of CA can be achieved by the EnKF using measurements of ABP and BFV. More work must be done in order to determine the optimal set of parameters to be estimated, as well as the optimal filtering strategy.

Although parameter estimates were reasonable for this study, in general, parameter estimates obtained through the EnKF tend to be biased toward initial values. The degree of bias is reciprocally related to the magnitude of the process noise covariance. Thus, a larger process noise may have resulted in a more accurate estimate of τ, present in Table I, but only at the expense of estimation precision. It is possible that this problem may be mitigated by adjusting the process noise adaptively [19], [20].

While the filter methods used here have shown to be appropriate, better results for patient-specific dCA assessment should account for variation in CO_2. Both linear [21] and nonlinear [22] systems identification methods have shown that CO_2 significantly improves dynamic BFV prediction compared to prediction by ABP alone. Therefore, future iterations of this method should utilize a mathematical model of intracranial dynamics that includes the contribution of CO_2 to dCA.

For real BFV data, the sampling rate is far higher than the time scale of the dominant dynamics described by the model. Therefore, the assumption of white noise may be erroneous. This possibility could result in under-estimating the parameter uncertainty [23]. Future iterations of this method will account for colored noise by augmenting the state vector with the time-correlated error terms, as described by Jazwinski [19].

V. ACKNOWLEDGMENTS

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