A KALMAN FILTERING BASED APPROACH FOR THE MODELING OF THE CARDIOVASCULAR REGULATION SYSTEM

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ABSTRACT
Short-term cardiovascular responses to orthostatic stress involve complex interactions among various mechanisms of short-term cardiovascular and respiratory blood flow and blood pressure control. Clinical procedures such as sit-to-stand and head-up-tilt (HUT) are often used to assess a patient's ability to regulate blood pressure. In this paper, we present a cardiovascular regulation model capable of predicting blood flow, volumes, and pressures in the systemic circulation during HUT. The cardiovascular regulation model adjusts cardiac contractility, vascular resistance and arterial compliance in response to changes in blood pressure. In previous studies, these control variables were modeled using a piecewise linear function parameterization. In this paper, we present an on-line estimation procedure based on the ensemble transform Kalman filter (ETKF) to estimate these dynamic control variables.

Keywords: cardiovascular regulation system, head-up-tilt, ensemble transform Kalman filter, parameter estimation

1. INTRODUCTION
The main role of the cardiovascular system is to maintain a set level of oxygen and nutrients in tissues as well as to ensure continuous removal of carbon dioxide and other metabolites. This is accomplished through tightly regulated control mechanisms. One of the main control systems promoting this regulation is the baroreflex system, which is part of the autonomic nervous system. Quantities being controlled by baroreflex regulation include blood flow and blood pressure. These quantities are kept close to their reference levels by a complex feedback control system regulating heart rate and vascular tone. Failure of this system has clinically significant consequences including dizziness, falls and reflex mediated syncope (Zaqqa and Massuni 2000), in particular for the elderly and for patients with hypertension and diabetes. The underlying pathophysiology lead to regulatory failure, which can be difficult to analyze since the detailed physiology involved with blood flow and pressure control is not well understood, and it is difficult to study the complex regulatory responses experimentally. These facts suggest that there is a need for development of more advanced methodologies to predict blood flow and pressure regulation.

Sit-to-stand as well as the more commonly used head-up-tilt (HUT) (Lanier, Mote and Clay 2011) tests are often used to assess patient's ability to regulate blood pressure, in particular for patients who suffer from frequent episodes of syncope, lightheadedness, or dizziness (Miller and Kruse 2005). During HUT test, the patient rests on a tilt-table in supine position. After steady values for pressure and heart rate are achieved the table is tilted to angle of 60-70 degrees. Upon tilting, gravity causes pooling of 500-1000 ml of blood in the lower extremities reducing venous return, which induces a reduction in cardiac filling, pressure and volume. As a response blood pressure in the upper body decreases, while blood pressure in the lower body increases. Baroreceptors located in the carotid sinuses sense the drop in blood pressure causing sympathetic activation and parasympathetic withdrawal, which in turn lead to an increase in heart rate, cardiac contractility, vascular resistance, and vessel tone (Robertson, Low and Polinsky 2004).

In this paper we consider the development of a cardiovascular model capable of predicting blood flow, volumes, and pressures in the systemic circulation during HUT. In essence, the mathematical model consists of three principle components: a lumped cardiovascular model predicting dynamics while the subject is resting in supine position; a model predicting dynamic changes in response to HUT; and a model predicting the impact of the baroreflex and other regulating systems on heart rate, cardiac contractility, arterial compliance, and vessel resistance. In this model, heart rate is used as an input, thus the parasympathetic heart rate regulation is implicitly accounted for in the model. For the other three control variables; cardiac contractility, arterial compliance and vascular resistance, we modeled them in our previous studies by a piecewise linear function parameterization approach (Olufsen, et al. 2005). However, since these control variables, in general, do not vary significantly around some baseline values, an alternative and very promising approach to model them is by using the nonlinear Kalman filtering. The Kalman filter, which was introduced in the 1960's, is a recursive algorithm that calculates the optimal state of the system by taking a weighted average of the probability distribution from the model and the probability distribution from the measurement (Kalman 1960). It is deterministic in nature and characterizes the entire optimal estimate through the propagation of the mean and covariance of the estimate at each step. The filter is very powerful in several aspects: it takes explicitly into account the measurement errors, it takes measurement data into account incrementally, and it is an efficient and simple to implement computational tool. It is recursive in the sense that at each step, the updated estimate is found through the previously estimated state and the observation data at that step. The Kalman filter is useful for estimating both system dynamics and time-varying or constant parameters.

In the Kalman filter, the model dynamics are assumed to be linear and that the errors in both the model and the observations are Gaussian. However, if these restrictive assumptions do not hold, the Kalman filter fails and adjustments have to be made to account for them (Grewal and Andrews 2008). One approach to deal with the nonlinear model dynamics is by using sampling techniques to characterize the probability distributions of the state. In this paper, we consider the ensemble transform Kalman filter (ETKF) (Evensen 2009a, Evensen 2009b), which belongs to a broader category of filters known as particle filters, for both state and parameter estimation.

2. A CARDIOVASCULAR REGULATION MODEL

In essence, the cardiovascular regulation model consists of three principle components: a lumped cardiovascular model predicting dynamics while the subject is resting in supine position; a model predicting dynamic changes in response to HUT; and a model predicting the effects of cardiovascular regulation.

2.1. A lumped cardiovascular model

The basic cardiovascular model comprises 5 compartments (see Fig. 1) representing arteries and veins in the upper and lower body of the systemic circulation, respectively, and the left ventricle. Here, the upper body compartments represent arteries and veins in the head, thorax, and abdomen, while the lower body compartments represent all vessels in the legs. The model mimics an electrical RC-circuit with voltage analogous to pressure, current analogous to flow, charge analogous to volume, compliance analogous to capacitance, while resistance is the same in both formulations. Note that with this model, it can predict blood pressure and flow in the various compartments, while it cannot predict the actual wave-propagation in the arterial network. Therefore, the model is well suited for predicting systolic and diastolic pressure values. Abbreviations (subscripts) in Fig. 1 are given in Table 1.

For each compartment, a pressure-volume relation is defined as

$$V - V_{un} = C(p - p_{ext}), \tag{1}$$

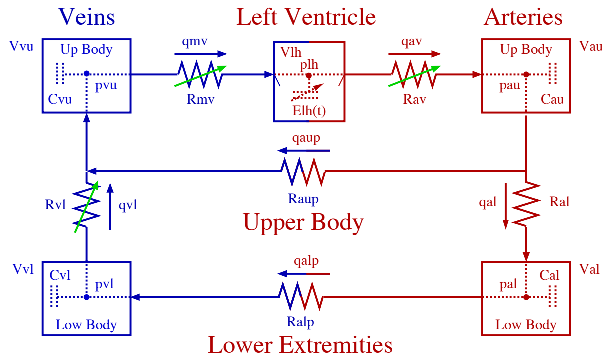

Figure 1: Compartmental model of systemic circulation. The model consists of 5 compartments with resistances in between compartments. The two heart valves, the mitral valve and the aortic valve, are modeled as time-varying resistors R_{mv} and R_{av}, respectively. In addition, the resistance between the lower and upper body veins V_{vl} is also modeled as time-varying function to prevent retrograde flow into the lower-body during the HUT

Abbreviation	Name
av	aortic valve
au	upper body arteries
al	lower body arteries
aup	upper body "peripheral" vascular bed
alp	lower body "peripheral" vascular bed
vu	upper body veins
vl	lower body veins
lh	left ventricle

Table 1: Abbreviations (subscripts) used in the cardiovascular regulation model

where V is the compartment volume, V_{un} is the unstressed volume, C is compartment compliance, p is instantaneous pressure, and p_{ext} is the pressure in the surrounding tissue. Using Ohm's law, the volumetric flow q and the pressure p are related by the relation

$$q = \frac{p_{in} - p_{out}}{R}, \tag{2}$$

where p_{in} and p_{out} are the pressure in and out of the resistor R, respectively. Differentiating (1) and using Ohm's law (2) yields the following system of differential equations for the pressure in the four arterial and venous compartments

$$\frac{dp_i}{dt} = \frac{1}{C}\frac{dV}{dt} = \frac{p_{i-1} - p_i}{R_{i-1}} - \frac{p_i - p_{i+1}}{R_i}. \tag{3}$$

For the heart compartment, the change in the volume is given by

$$\frac{dV_{lh}}{dt} = q_{in} - q_{out}. \tag{4}$$

Here, the heart pressure is predicted from the volume using the pressure-volume relation

$$p_{lh} = \frac{1}{C_{lh}}(V_{lh} - V_{un}) = E_{lh}(V_{lh} - V_{un}), \quad (5)$$

where E_{lh} is the elastance (the reciprocal of the compliance). Pumping is modeled by introducing a variable elastance function of the form (Ellwein 2008)

$$E_{lh}(\tilde{t}) = \begin{cases} \frac{E_{\max} - E_{\min}}{2}\left[1 - \cos\left(\frac{\pi \tilde{t}}{T_M}\right)\right] + E_{\min}, \tilde{t} \in [0, T_M] \\ \frac{E_{\max} - E_{\min}}{2}\left[1 + \cos\left(\frac{\pi(\tilde{t} - T_M)}{T_R}\right)\right] + E_{\min}, \tilde{t} \in [T_M, T_M + T_R] \\ E_{\min}, \tilde{t} \in [T_M + T_R, T], \end{cases}$$

where $\tilde{t}$ is the time within a cardiac cycle, $E_{\min}$ and $E_{\max}$ denote the maximum and minimum elastance, respectively. Values for the cardiac cycle T (which is the reciprocal of the heart rate) and T_M are obtained from data, while T_R is a model parameter. Finally, heart valves are modeled using time-varying resistors for which a large resistance R_{cl} represents a closed valve and a small resistance R_{op} represents an open valve. These time-varying resistors have the forms

$$R_v = R_{cl} - \frac{R_{cl} - R_{op}}{1 + e^{-\beta(p_{in} - p_{out})}},$$

where p_{in} and p_{out} denote the pressure in and out of the valve, respectively.

In summary, the five differential equations representing the five compartments are given by

$$\frac{dp_{au}}{dt} = (q_{av} - q_{al} - q_{aup}) / C_{au},$$
$$\frac{dp_{al}}{dt} = (q_{al} - q_{alp}) / C_{al},$$
$$\frac{dp_{vl}}{dt} = (q_{alp} - q_{vl}) / C_{vl},$$
$$\frac{dp_{vu}}{dt} = (q_{aup} + q_{vl} - q_{mv}) / C_{vu},$$
$$\frac{dV_{lh}}{dt} = q_{mv} - q_{av},$$

where the volumetric flow q_i is written in terms of the pressure and resistance as in equation (2) (e.g., $q_{av} = (p_{lh} - p_{au}) / R_{av}$).

2.2. Modeling HUT

The response to HUT is modeled by accounting for hydrostatic pressure acting on the affected compartment. During supine position, gravity does not influence the system. Upon HUT, blood is pooled in the lower extremities leading to an increase in pressure in the lower body, while pressure in the upper body decreases. To account for gravity, the pressure at the level of the carotid arteries were used as a reference pressure, so an extra term is added to the flows to (q_{al}) and from (q_{vl}) the lower body compartments. In particular, the modified flow equations are calculated as follows (Olufsen, et al. 2005)

$$q = \frac{\rho g h \sin(\theta(t)) + p_{in} - p_{out}}{R},$$

where

$$\theta(t) = \frac{\pi}{180}\begin{cases} 0, \ t < t_{st} \\ v_t(t - t_{st}), \ t_{st} \le t \le t_{st} + t_{ed} \\ 60, \ t > t_{st} + t_{ed}. \end{cases}$$

Here, ρ is the blood density, g is the gravitational constant, h is the distance between the lower and upper compartments, $\theta = 60^0$ is the tilt angle, $v_t = 15$ is the tilt speed, and t_{st} and t_{ed} are the starting and ending times of the tilt, respectively.

2.3. Modeling effects of cardiovascular regulation

Upon HUT blood pressure decreases, leading to sympathetic activation and parasympathetic withdrawal. Parasympathetic withdrawal elicits increase in heart rate and cardiac contractility, while the sympathetic response elicits increase in vascular resistance and compliance. The model developed in this paper does not describe in detail sympathetic and parasympathetic afferents, but predicts the impact of the baroreflex and other systems regulating heart rate, cardiac contractility, arterial compliance, and vessel resistance. Heart rate is used as an input, thus the parasympathetic heart rate regulation is implicitly accounted for in the model. Increase of cardiac contractility is modeled by controlling the minimum elastance function of the left heart ($E_{\min}$), while the decrease of arterial compliance was incorporated in the upper body through regulation of (C_{au}). Finally, regulation of vascular resistance is included in both the upper and lower body. The upper body compartment includes abdominal and intestinal vessels, while the lower body compartment lumps vessels in the lower extremities. Consequently, both R_{aup} and R_{alp} are regulated. However, the compartments representing the upper and lower body arteries appear in parallel; hence, both resistances are not identifiable. In this paper, we controlled R_{aup} directly and let $R_{alp} = kR_{aup}$ with k denotes the ratio of the optimized rest values of R_{aup} and R_{alp}.

As discussed above, three quantities $(E_{\min}, C_{au}, R_{aup})$ are controlled to counteract the effect of the tilt. However, since the development of an accurate physiologically based model for these control variables is a rather nontrivial task, we utilize ensemble transform Kalman filter to estimate these time varying control functions by treating them as unknown parameters in the model.

3. THE ENSEMBLE TRANSFORM KALMAN FILTER

To begin the discussion on the ETKF, we consider a state space model of the form

$$x_{i+1} = f(i, x_i, \theta) + w_i,$$
$$y_{i+1} = h(i+1, x_{i+1}, \theta) + v_{i+1}$$

where f is a nonlinear function of the state $x_{i+1} \in \Re^{n_x}$, and h is a nonlinear function relating the observation, $y_{i+1} \in \Re^{n_y}$, to the state. w_i and v_{i+1} are independent and identically distributed (i.i.d.) noise processes, and θ are the model parameters. The problem is to find the optimal parameter estimates to give the state the best fit to the data. Classically, parameter estimation is carried out by using an optimization technique to minimize a cost functional, which, in general, is the sum of the squares of the difference between the model observation and the data. Utilizing the filtering technique to estimate parameters, there are multiple methods in which we can achieve our goal. First, and most direct, is to modify the state space representation to accommodate our objective. Since we are assuming the observations are coming from our model and the parameters are our main focus, we can proceed by assuming that the parameters have zero dynamics

$$\theta_{i+1} = \theta_i + r_i$$
$$y_{i+1} = h(i+1, x_{i+1}, \theta_{i+1}) + v_{i+1},$$

where r_i is i.i.d. noise process for the model parameter. However, our goal is to not only estimate the parameters, but also to fit the states as accurately as possible. This methodology is known as dual estimation. There are two methodologies that directly achieve this. First is joint estimation. This is achieved by concatenating the parameters into the state-space as follows

$$z = [x; \theta]$$
$$z_{i+1} = f(i, z_i) + w_i$$
$$\theta_{i+1} = \theta_i + r_i.$$

A second approach is called the dual filter. This is done by concurrently running a state filter and parameter filter in parallel. The state filter estimates the state, x_i, using the parameter value from the parameter filter at time, $i-1$. While, the parameter filter estimates the parameter, θ_i, using the state estimate at time, $i-1$. These both propagate forward in time and obtain estimates at each time step.

The main idea around the ensemble Kalman filter is to approximate the error statistics of our estimate by a set of particles sampled from the probability distribution. That is, we calculate the prior and posterior error covariances by the ensemble covariance matrices around the corresponding ensemble mean

$$\begin{aligned} P_{x_{i+1|i}} &= \frac{1}{K-1} U_{i+1|i} U_{i+1|i}^T \\ P_{x_{i+1|i+1}} &= \frac{1}{K-1} U_{i+1|i+1} U_{i+1|i+1}^T, \end{aligned} \quad (6)$$

where

$$U_{i+1|i} = [x_{i+1|i}^1 - \hat{x}_{i+1|i}; x_{i+1|i}^2 - \hat{x}_{i+1|i}; \ldots; x_{i+1|i}^K - \hat{x}_{i+1|i}]$$
$$U_{i+1|i+1} = [x_{i+1|i+1}^1 - \hat{x}_{i+1|i+1}; x_{i+1|i+1}^2 - \hat{x}_{i+1|i+1}; \ldots; x_{i+1|i+1}^K - \hat{x}_{i+1|i+1}]$$

with $x_{i+1|i}^j$ being the j^{th} particle being propagated through the model, and $x_{i+1|i+1}^j$ is the update of each particle. With this, we define K to be the number of particles in which to approximate the distribution and $\hat{x} = K^{-1} \sum_{j=1}^{K} x^j$. From now on, we shall define U to be the ensemble perturbation matrix as it gives us the deviation of each particle from the mean. The essence of this methodology is that we just integrate each ensemble member in time through our dynamical model.

To obtain the update equations, we first compute the Kalman gain as follows

$$\begin{aligned} K_{i+1} &= P_{x_{i+1|i}} H^T (H P_{x_{i+1|i}} H^T + R)^{-1} \\ &= (K-1)^{-1} U U^T H^T (H (K-1)^{-1} U U^T H^T + R)^{-1} \\ &= (K-1)^{-1} U (HU)^T ((K-1)^{-1} (HU)(HU)^T + R)^{-1}. \end{aligned}$$

From the above equation, it is noted that anywhere the linear operator H appears, it is coupled to the ensemble perturbation matrix, U. Due to this consequence, given a nonlinear observation function h, we can take advantage by replacing HU with the following approximation

$$V = \left[h(x_{i+1}^1) - \hat{y}_{i+1}; h(x_{i+1}^2) - \hat{y}_{i+1}; \ldots; h(x_{i+1}^K) - \hat{y}_{i+1} \right],$$

where $\hat{y}_{i+1}$ is the mean of the observation function given each sample, $\hat{y}_{i+1} = \sum_{j=1}^{K} h(x_{i+1}^j)$.

To obtain our final estimates, we apply the classical Kalman filter update equations to each ensemble member

$$x_{i+1|i+1}^j = x_{i+1|i}^j + K_{i+1}(y_{i+1}^k - h(x_{i+1|i}^j)),$$

where K_{i+1} is the Kalman gain defined as above, and the observation, y_{i+1}, is perturbed accordingly

$$y_{i+1}^k = y_{i+1} + \psi_{i+1}^k,$$

where ψ_{i+1}^k is a Gaussian random variable with mean zero and covariance R. This perturbation is a Monte Carlo method applied to the Kalman filter formula that yields an asymptotically correct analysis error covariance estimate for large ensemble sizes (Majda and Harlim 2012). In practice, to keep these perturbations unbiased, we generate these random perturbations by first randomly drawing a $M \times K$ matrix A, where K is the number of particles and M is dimension of the data, and take the singular value decomposition of $(K-1)^{-1} A A^T = F \Sigma F^T$. Therefore, we have unbiased random vectors of y_{t+1}^k, which are just the column vectors of the matrix (Majda and Harlim 2012) $T = ((K-1)R)^{1/2} F \Sigma^{-1/2} F^T A$. Since we are perturbing the measurements, we can define the measurement error covariance matrix to be

$$R = (K-1)^{-1} EE^T,$$

where $E = [e_1, e_2, ..., e_K]$ are the ensemble measurement perturbations, with mean zero. Other alternative implementation of the ensemble Kalman filter also exists (Evensen 2009b).

The main idea of the ensemble transform Kalman filter (ETKF) is to take the square root of the covariance matrix, and transform it to a space where it is more robust and well conditioned (Evensen 2009a). There are multiple methods for taking the square root, the one we utilized in this paper is the ETKF as derived in (Bishop 2001). The basic idea is to find a transformation matrix T so that

$$U_{i+1|i+1} U_{i+1|i} T = UT$$

and

$$UT(UT)^T = (K-1) R_{i+1|i+1},$$

where $R_{i+1|i+1}$ is the sample posterior covariance matrix as previously defined. The posterior ensemble is then generated by taking the posterior mean and adding each column vector from U. Using the identity

$$A^T (AA^T + R)^{-1} = (I + A^T (R^{-1}) A)^{-1} A^T R^{-1},$$

and letting $V = A$, we apply this to the Kalman gain and arrive at the following expression

$$K_{i+1} = (K-1)^{-1} U (I + (K-1)^{-1} V^T R^{-1} V)^{-1} V^T R^{-1}.$$

Substituting the above expression and (6) into the posterior covariance formula, we obtain

$$P_{x_{i+1|i+1}} = (I - \frac{U}{K-1}(I + (K-1)^{-1} V^T R^{-1} V)^{-1} V^T R^{-1} H) \frac{UU^T}{K-1}.$$

Factoring out $U/(K-1)$ yields

$$P_{x_{i+1|i+1}} = \frac{U}{K-1}\Big(I - \Big(I + \frac{V^T R^{-1} V}{K-1}\Big)^{-1} \frac{V^T R^{-1} V}{K-1}\Big) U^T.$$

Therefore, we finally obtain

$$P_{x_{i+1|i+1}} = \frac{1}{K-1} U (I - (I+B)^{-1} B) U^T,$$

where $B = V^T R^{-1} V / (K-1)$. Using the identity

$$I - (I+B)^{-1} B = (I+B)^{-1}$$

we obtain

$$P_{x_{i+1|i+1}} = U\Big((K-1)I + V^T R^{-1} V\Big)^{-1} U^T$$
$$= U \Sigma U^T = U \frac{TT^T}{K-1} U^T.$$

Applying this to the above analysis for the ensemble Kalman filter, we obtain the algorithm for the ensemble transform Kalman filter.

4. APPLICATIONS OF ETKF

The performance and feasibility of using the ensemble transform Kalman filtering based approach for modeling the cardiovascular regulation system will be illustrated using HUT data collected from a healthy young male volunteer age 37 who was fit and had no known heart or vascular diseases at the Coordinating Research Center (Frederiksberg Hospital, Copenhagen, Denmark). After resting for 10 minutes in supine position, the subject was tilted to an angle of 60 degrees at a speed of 15 degrees per second measured by way of an electronic marker. The subject remained tilted for five minutes, and was then returned to supine position at the same tilt speed. For the model based analysis, we extracted a total of 690 seconds of data: including a 180 seconds segment recorded while the subject was resting in supine position and a 180 second segment recorded during HUT.

Literature values and subject specific information were integrated to identify nominal values for all model parameters (resistances, capacitors, heart, and tilt parameters) as well as to predict initial conditions for all state variables. Nominal parameter values were obtained by considering mean values for all pressures, flows, and volumes in the system obtained while the subject was in supine position (before the tilt). Then, using heart rate as an input, we estimate the three unknown model parameters $(E_{\min}, C_{au}, R_{aup})$ from measurements of arterial blood pressure in supine position and during HUT. The parameter estimation is carried out using the ensemble transform Kalman filter methodology discussed in Section 3. It should be noted that the cardiovascular regulation model presented in Section 2 predicts blood pressure and flow as pulsatile quantities, but since the model is analogous to an RC-circuit it does not allow for prediction of wave-propagation, consequently direct comparison of computed and measured values of blood pressure is not valid. To obtain adequate pulsatility, we identify model parameters that allow prediction of systolic and diastolic values of blood pressure. These values can be obtained from computing the maximum and minimum pressure within each cardiac cycle.

In the following, we picked noise covariances w_i and v_i to be $Q = 0.01I$ and $V = 0.01$, respectively. The noise covariance r_i for the parameter model is $R = 1.0 \times 10^{-8} I$. The estimated blood pressure obtained from the ETKF using 50 ensemble members is depicted in Fig. 2 against the actual data. The figure shows very good agreement between the state estimate and the data.

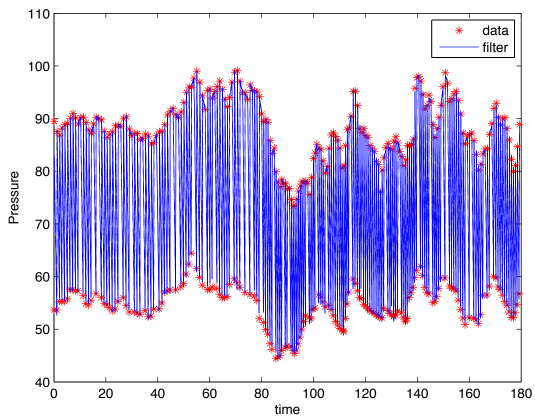

Figure 2: Blood pressure from the state estimates obtained using the ensemble transformed Kalman filter and the actual systolic and diastolic values of blood pressure are shown

Using the joint estimation, the estimates for the regulating parameters $(E_{\min}, C_{au}, R_{aup})$ are depicted in Figures 3, 4 and 5, respectively.

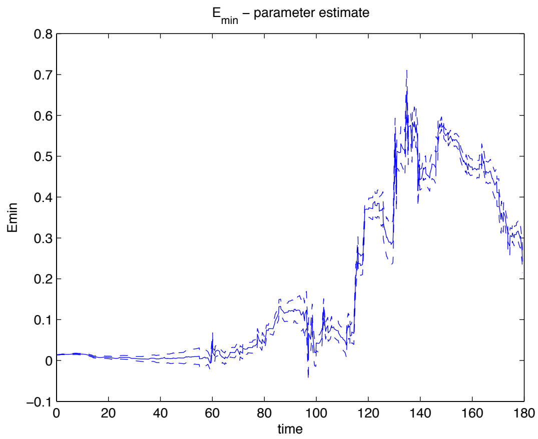

Figure 3: Profile of the time varying parameter $E_{\min}$ obtained from the ETKF with 3 standard deviations (dashed)

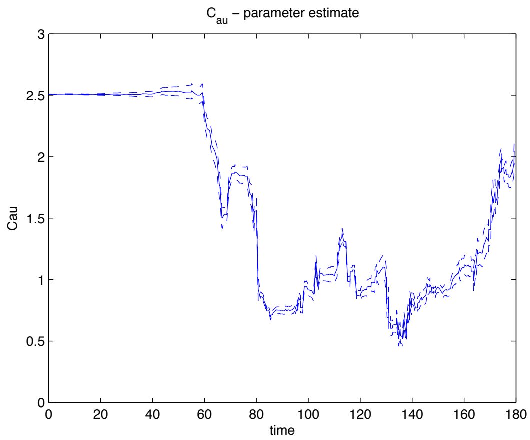

Figure 4: Profile of the time varying parameter C_{au} obtained from the ETKF with 3 standard deviations (dashed)

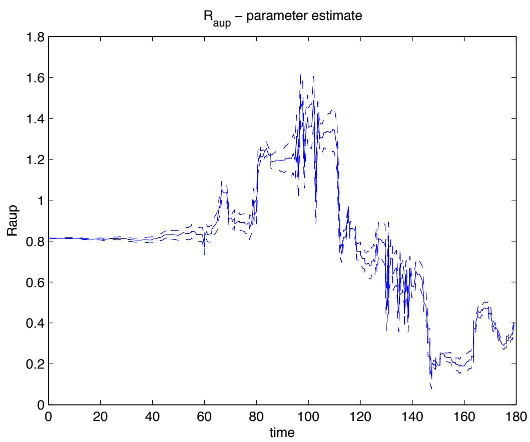

Figure 5: Profile of the time varying parameter R_{aup} obtained from the ETKF with 3 standard deviations (dashed)

5. CONCLUSION

In this paper we illustrate the feasibility of using the ensemble transform Kalman filter algorithm for the dual estimation problem of estimating both the state and unknown time-varying parameters in a cardiovascular regulation model. The ETKF is widely used in weather forecasting applications. Our initial efforts to apply the ETKF to biological applications such as the cardiovascular problem considered in this paper are very promising.

6. ACKNOWLEDGEMENTS

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