Identification of the Time-Varying Ventricular Parameters During the Ejection Phase of the Cardiac Cycle: The Martingale Optimality Principle Approach

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Abstract: Physical parameters representing the energy components of the cardiac pump related to inertance, resistance, and compliance are developed. Stochastic calculus and the martingale optimality principle are used to estimate these time-varying parameters. The method is applied to the ejection phase of the cardiac cycle, using pressure and flow measured at the root of the aorta for the left ventricle. Another Malliavin-calculus-based approximate method is also reported. It is numerically tractable with higher accuracy.

Key words: Left ventricle, time-varying parameters, Ito calculus, Martingale Optimality Principle, Malliavin Calculus, Cardiac Cycle.

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1. Introduction

The ejection of blood from the heart is influenced by its filling, physiologic status, and the receiving arterial system (load), aspects recognized since [1]. Furthermore, the contractile properties of the ventricle represent good diagnostic tools for many heart diseases [2, 3]. Consequently, hemodynamic variables, such as ventricular pressure and flow, are outcomes of or represent the pump properties [4, 5 , 6]. Over the years several models were developed that describe the ventricular properties; this is described next.

1.1 Time Domain Models:

The Guyton, Coleman, and Granger model [7], is arguably the most popular and comprehensive circulatory-system model. Guyton's very extensive model has been in some sense the pioneer of the whole investigation into mathematical modelling of the circulation. It consists of many equations addressing most relevant aspects of total-body cardiocirculatory compensation by concentrating on specific subsystems (renal, haemopoietic, thirst, cardiac pump, etc.). In this report, the focus is on the modeling and estimation of the cardiac pump time-varying parameters.

Two compliances were utilized by [8] to model a simple ventricle: one compliance for diastole and a lesser value for systole. More recently, time-varying compliance was estimated from a parametric model [9]. Time-varying heart (myocardial) properties were also estimated using mechanical models [10]. These studies demonstrated that both a time-variant compliance and a time-variant resistance are manifested during the cardiac cycle. The theory proposed by [11] encompassing the concepts of 'time-varying elastance', 'pressure-volume area' and 'isoefficiency', has been widely applied in cardiac research. Recently it has been criticized from the point of view of metabolic balance.

Approximate, closed form relations between left ventricular time-varying resistance, compliance, and pressure and volume were derived using optimality principle [12]. Inertial properties as well as losses of both the blood and ventricle are often ignored on the assumption that at particular sites or conditions either may represent only small fractions of total energy. Although kinetic energy may constitute a small part of myocardium mechanical energy, flow and its derivative may achieve appreciable values particularly during systole where blood accelerated at the onset of ejection is appreciable. Consequently, a comprehensive study of myocardial behavior during ejection suggests inclusion of all time-varying parameters [12, 6]. These may be related as:

$$L(t)\frac{d^2Q}{dt^2}+R(t)\frac{dQ}{dt}+\frac{Q(t)}{C(t)}=p(t) \quad (1)$$

Where L(t), R(t), and C(t) denote time-varying inertance, resistance, and compliance, respectively, Q(t), p(t) are ventricular volume and pressure respectively at time t. In [6] a polynomial in time model was assumed for each unknown time-varying parameter. The coefficients of the polynomials were estimated using methods of the Ito calculus. The estimated time-varying parameters , L(t), R(t), and C(t), describing the cardiac properties seemed to be in line with what we know from Physiology. A problem with this approach is that we have assumed a shape (polynomial in time) for the time-varying parameters. One could argue that another polynomial shape such as Hermite or Laguerre polynomials might be more representative. In the current work we drop these assumptions about the shape and estimate the parameters as time-varying functions. The only constraint we impose are that the cardiac parameters, L(t), R(t), and C(t) are nonnegative and slowly varying over time. The technique we use is based on the martingale optimality principle [13]. The results are in agreement with that of [6].We use the martingale based method because it has proven its superior performance, with minimum assumptions, in the estimation of the time-varying shares of stock in financial engineering [14, 15].

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1.2 Estimation Methods of Time-Varying Parameters:

The problem of the estimation of time-varying parameters has, in general, four different ways of solving it:

(1) Assuming that the system coefficients are varying sufficiently slowly, they can be tracked using the localized (weighted or windowed) versions of the least squares or maximum likelihood estimators [16-18].
(2) Approximation of the time-varying coefficients by a weighted combination of a certain number of known functions (basis functions). If the unknown weights are assumed to be constants, a number of the well known identification techniques could be used [19, 20].
(3) Assumption that the time-varying coefficients evolve as Markov processes. In this case, the Kalman filter technique and its modifications could be used for the estimation of the time-varying parameters [21, 22].
(4) The time-varying coefficients could be treated as unknown controllers to be estimated to track the observed data. The method of Pontryagin maximum principle could be used to find the desired values [5, 23].

In this report we introduce another method that is based on the stochastic and the martingale optimality principle [13, 14, 24, 25]. A model is developed for each of the measured ventricular volume, cardiac flow, and the derivative of the cardiac flow. A polynomial in time model to describe each of the measured variables. The reason for using the polynomial models is numerical tractability and are also easy to manipulate. Assuming nonnegative and slowly time-varying cardiac parameters L(t), R(t), and C(t), we estimate their values using a method based on the Black-Scholes model used in financial engineering [26, 27, 28, 14]. The approach is to setup the problem such that the martingale optimality principle [13] could be used to estimate the unknown time-varying parameters. An approximate approach was also developed. It is based on the Malliavin calculus. It has the advantage of being numerically tractable and thus more accurate results were obtained.

The estimated time-varying parameters were compared to that estimated in [6]. It was found that the differences between both estimates lie within 20%. Thus, it is argued that assuming time polynomial shape for the cardiac parameters is not far from reality.

In section 2, existing methods are described for the estimation of time-varying parameters L(t), R(t), and C(t). In section 3, we introduce the proposed method that is based on the martingale optimality principle. In section 4, the equations for the estimates of the time-varying parameters L(t), R(t), and C(t) are described and a summary of the estimation algorithm is given. Also in section 4, results, summary and conclusions are presented. The derivations of the method are shown in the appendix.

2. Problem Formulation:

The measured pressure at the root of the Aorta, p(t), is composed of the weighted sum of (d-1), where d=4, stochastic processes where the weights are the unknown parameters L(t), R(t), and C(t). The objective is to estimate, from p(t), the unknowns L(t), R(t), and C(t). To solve the problem, we embed the sum of the processes (the observations) into another signal; $p(t)$, termed the augmented observations. The augmented observations consist of the original observations plus a deterministic component. The addition of the known deterministic component is needed to facilitate the analysis as shown in the appendix.

The augmented observed signal, $p(t)$, with (d=4) components, could be modeled as follows:

$$p(t) = \eta_1(t)S_1(t) + \sum_{i=2}^{d} \eta_i(t)S_i(t) \quad (2)$$

$\eta_i(t)$, i>1, is the ith unknown time-varying coefficients they are defined as:

$\eta_2(t) = 1/C(t)$, $\eta_3(t) = R(t)$, $\eta_4(t) = L(t)$

We also define the stochastic processes or signals as: ventricular volume = $S_2(t) = Q(t)$, ventricular flow $= S_3(t) = dQ(t)/dt$, and $S_4(t) = d^2Q(t)/dt^2$

with

$\eta_1(t)$ = known constant

$$dS_1(t) = \alpha_1 S_1(t)dt \quad (3)$$

where $S_1(t)$ is a reference signal and both α_1 and $S_1(t)$ are known. Usually we set α_1 close to zero such that it has minor or no effect on the results.

2.1 Commonly Used Models of the Signals:

Several models are commonly used that represent different physical situations [29].

The signal $S_i(t)$ could be modeled as an OU process with no trend:

(1) $dS_i(t) = c_i S_i(t)dt + e_i dW_i(t)$ i>1 (4)

i.e. $$S_i(t) = S_i(0)e^{c_i t} + e_i e^{c_i t}\int_0^t e^{-c_i s} dW_i(s)$$

where c_i, and e_i are unknown constants.

Or an OU form that has a stochastic differential equation (SDE):

(2) $dS_i(t) = c_i[a_i(t) - S_i(t)]dt + e_i dW_i(t)$, i>1 (5)

i.e.

$$S_i(t) = e^{-c_i t}\left[S_i(0) + c_i\int_0^t e^{c_i s}a_i(s)ds\right] + e_i e^{-c_i t}\int_0^t e^{c_i s} dW_i(s)$$

where $a_i(t)$ is a polynomial in time that represents the trend or the base data, and $S_i(t)$ bounces around $a_i(t)$.

Or as the form that has a stochastic differential equation (SDE) [30]:

(3)

$$dS_i(t) = da_i(t) + c_i\left[a_i(t) - S_i(t)\right]dt + e_i(t)dW_i(t)$$

, i>1 (6)

where the trend, $a_i(t)$, and the diffusion parameter $e_i(t)$ could be modeled as a sum of frequencies i.e.

$$a_i(t) = \alpha_0 + \alpha_1 t + \sum_j \beta_{ij}\sin(2\pi f_{ij}t + \phi_{ij}) \quad (7)$$

and

$$e_i^2(t) = \delta_{i0} + \sum_j \sigma_{ij}\sin(2\pi g_{ij}t + \varphi_{ij}) \quad (8)$$

Using the Ito formula [31], the explicit solution is given as:

$$S_i(t) = a_i(t) + e^{-c_i t}\left[S_i(0) - a_i(0)\right] + e^{-c_i t}\int_0^t e_i(s)e^{c_i s}dW_i(s) \quad (9)$$

Or as Geometric Brownian motion which has the stochastic differential equation (SDE):

(4) $dS_i(t) = c_i S_i(t)dt + e_i S_i(t)dW_i(t)$ (10)

which has a solution:

$$S_i(t) = S_i(0)\exp\left[\left(c_i - \frac{1}{2}e_i^2\right)t + e_i W_i(t)\right]$$

In this paper each signal (the ventricular volume and its derivatives) is modeled as a Brownian process with a time-varying trend. We will consider the circumstances where each unknown time-varying parameter $\eta_1(t)$, $L_v(t)$, $R_v(t)$, and $1/C_v(t)$, changes slowly over time i.e.

$$dp(t) \approx \eta_1(t)dS_1(t) + \sum_{i=2}^{d}\eta_i(t)dS_i(t) \quad (11)$$

One could find, via the martingale optimality principle, a closed form expression for the SDE of p(t) and for each time-varying parameter as clarified in section 3. First we describe the conventional methods for the estimation of the unknown time-varying parameters $\eta_i(t) \quad i > 1$.

2.2 Conventional Method for Time-Varying Parameter Estimation:

2.2.1 Chow's Method:

The familiar scalar regression format with time-varying coefficients is:

$$p(k) = \underline{S}^T(k)\underline{\eta}(k) + \varepsilon(k) \quad (12)$$

Where T represents transpose, the mx1 vector $\underline{S}(k)$ could have the lagged values of p(k), the exogenous variables and their lagged values. $\underline{\eta}(k)$ is an mx1 vector of the unknown time-varying coefficients.

The most common method to estimate the coefficients $\underline{\eta}(k)$ is Chow's method, which is based on a maximum likelihood approach.

The key is to assume a Markov model for the time-varying parameters. That is, the set of unknown parameters, $\underline{\eta}(k)$, could be modeled as a vector autoregressive (VAR) process as follows [21]:

$$\underline{\eta}(k) = M\underline{\eta}(k-1) + \underline{\xi}(k) \quad (13)$$

Where $\underline{\eta}(k)$ is a column vector of m unknown values, M is an unknown matrix of dimensions m x m, and $\underline{\xi}(k)$ is an m-variate column vector normally distributed with zero mean and covariance matrix $\Xi = \sigma_\varepsilon^2 I$, and I is the unity matrix.

Note that when M=I and Ξ=0, this model is reduced to the standard constant coefficient model. When M=0 and $\Xi \neq 0$, we have a pure random model. When M=I, and $\Xi \neq 0$, we have the random walk model.

Chow's method begins by assuming that M is diagonal and with initial estimated entries $\hat{M}$. The initial estimate of $\underline{\eta}(0)$ is taken to be the time-invariant estimate. Thus, an estimate for the sequence $\{\underline{\eta}(1), \underline{\eta}(2), ..., \underline{\eta}(k)\}$, and consequently an estimate for the sequence {p(0), p(1), …, p(k)} are obtained via the equations:

$$\hat{\underline{\eta}}(k) = \hat{M}\hat{\underline{\eta}}(k-1) \quad (14)$$

$$\hat{p}(k) = \underline{S}^T(k)\hat{\underline{\eta}}(k) \quad (15)$$

The values of $\hat{M}$ are updated, for example by means of the gradient method, where one seeks to minimize the squared difference between the estimated observations, $\hat{p}(k)$, and the measured observations *p*(k).

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2.2.2 Polynomial Model for the Time-Varying Coefficients/Amplitudes [6]:

Each of the unknown time-varying parameters can also be modeled as a polynomial in time. For example:

$$\eta_1(k) = \alpha_{10} + \alpha_{11}(k\Delta) + \alpha_{12}(k\Delta)^2 + ... = \sum_i \alpha_{1i}(k\Delta)^i \quad (16)$$

Thus, the estimated time-varying coefficients become:

$$\hat{\eta}_j(k) = \sum_i \hat{\alpha}_{ji}(k\Delta)^i \quad (17)$$

where $\hat{\alpha}_{ji}$ is the estimate of α_{ji}.

An SDE is developed for the pump equation (I. 1) and the values of $\hat{\alpha}_{ji}$ are found through the maximum likelihood method and the stochastic calculus techniques.

3. The Martingale Optimality Principle for the Estimation of the Unknown Time-Varying Coefficients/Amplitudes:

In this section we introduce the martingale optimality principle and use it to determine the estimates of the time-varying parameters $L_v(t)$, $R_v(t)$, and $1/C_v(t)$. We first consider the general case of the sum of several signals without restrictions on the shape of the stochastic differential equation (SDE) that generates each signal. The only requirement is that the time-varying parameters vary slowly with time. The martingale optimality principle is used to find the unknown quantities. A derived SDE for the observed signal p(t) is obtained. A closed form expression is then obtained for each of the unknown time-varying parameters/amplitudes.

3.1 The Martingale Optimality Principle:

In this report we use the martingale optimality principle [13, 24] to find the optimal value of the cardiac parameters. The main idea of the martingale approach is to decompose the optimization problem into a static optimization (determination of the optimal pressure) and a representation problem (find the time-varying cardiac parameters that lead to this optimal pressure). The steps involve finding two equations for the pressure p(t). The first is obtained from the system dynamics. The second equation is obtained through the optimization process. Equating both formulae will yield the unknown cardiac parameters.

3.2 Sum of Signals with slowly time varying parameters; the General Case:

We shall first consider the estimation of time-varying parameters for a general model of the observations. We then specialize the results to the cardiac parameters. Let the augmented signal $p(t)$ be defined as:

$$p(t) = \sum_{i=1}^{d} \eta_i(t) S_i(t) \quad (18)$$

It is assumed that the unknown coefficients $\eta_i(t)$ vary slowly with time i.e. :

$$d\eta_i(t) \to 0 \quad (19)$$

or more precisely $d\eta_i(t) << dS_i(t)$

The signals, $S_i(t)$, each has an SDE of the general form:

$$dS_i(t) = c_i(t, S_i(t))dt + e_i(t, S_i(t))dW_i(t) \qquad i > 1 \quad (20)$$

Where $c_i(t, S_i(t))$ and $e_i(t, S_i(t))$ are to be determined according to the signal model and the physical situation under study [see Section 3]. $S_i(t)$ has the solution:

$$S_i(t) = S_i(0) + \int_0^t c_i(u, S_i(u))du + \int_0^t e_i(u, S_i(u))dW_i(u) \qquad i > 1 \quad (21)$$

and $$dS_1(t) = a_1(t, S_1(t))dt = \alpha_1 S_1(t)dt \quad (22)$$

In such an analysis, the presence of a deterministic component makes it easier for the analysis. In this case the component is $S_1(t)$ and it is known. This component acts as a reference signal or numeraire. Thus, the original problem is embedded into a larger problem. The observed signal does not usually come with a known deterministic component but in this case we add a known deterministic component and proceed to the analysis. We now attempt to find an expression for the SDE that describes the evolution of $p(t)$. This expression will be a function of the unknown stochastic time-varying parameters $\eta_i(t)$. Using the martingale optimality principle, we will be able to find a closed form expression for the time-varying parameters, $\eta_i(t)$, as function of the observations p(t) [see the Appendix].

Following the derivations shown in the appendix we find the closed form expression for the estimates of the unknown time-varying parameters as:

$$d\eta_i(t) \approx \eta_i(t)\left(\frac{e_i^2}{c_i(t,S_i(t))}\right)$$

$$\left[\sum_j\left(\frac{c_j(t,S_j(t))}{e_j}\right)^2 + \left(\frac{1}{e_i^2}\right)\left(\frac{dc_i(t,S_i(t))}{dt}\right)\right]dt \text{ ,i>}$$

$$+\eta_i(t)\left(\sum_j \frac{c_j(t,S_j(t))}{e_j}dW_j(t)\right)$$

1 (A.39)

3.2 Estimation Equations for the Cardiac Parameters :

We now specialize the previous general results to the case under study; the estimation of the ventricular parameters. We shall use a polynomial for the drift of the Brownian motion model as a model for the ventricular volume and its derivatives. Specifically we have:

$$dS_i(t) = c_i(t,S_i(t))dt + e_i dW_i(t) \qquad i>1 \qquad (23)$$

Where $c_i(t,S_i(t)) = c_i(t)$ is a polynomial in time and e_i is a constant estimated value. Recall that: ventricular volume = $S_2(t) = Q(t)$, ventricular flow $= S_3(t) = dQ(t)/dt$, and $S_4(t) = d^2Q(t)/dt^2$.

The augmented observations, *p*(*t*), are given by the equation:

$$p(t) = \sum_{i=1}^{d}\eta_i(t)S_i(t) \qquad (24)$$

and we need to find an estimate for each $\eta_i(t)$. Remember that $\eta_2(t) = 1/C(t)$, $\eta_3(t) = R(t)$, $\eta_4(t) = L(t)$.

Define $\theta_i(u) = \dfrac{c_i(t,S_i(t)) - \alpha_1 S_i(u)}{e_i}$

$$\approx \frac{c_i(t,S_i(t))}{e_i} \qquad |\alpha_1| << |\mathrm{c_i}| \quad \forall i$$

After some manipulations [see the appendix], an estimate for the unknowns is obtained as:

$$d\eta_i(t) = \mathcal{U}(t)\left[d\left(\frac{c_i(t)}{e_i^2}\right) + \left(\frac{c_i(t)}{e_i^2}\right)\sum_j\left(\frac{c_j(t)}{e_j^2}\right)^2 dt\right]$$

$$+\left(\frac{c_i(t)}{e_i^2}\right)\left(\mathcal{U}(t)\sum_j \theta_j(t)dW_j(t)\right)$$

, i>1

Where $d\left(\frac{c_i(t)}{e_i^2}\right)$ is the change in $\left(\frac{c_i(t)}{e_i^2}\right)$.

This is a closed loop estimate of the cardiac parameters and yields good estimates. Recall that $\mathcal{U}(t) \approx (p(t) - p_o(t))$ where $p_o(t)$ is the observed pressure and $p(t) \approx \sum_{i=2}^{d}\eta_i(t)S_i(t)$.

Another open loop estimate is obtained by substituting for the SDE of $\mathcal{U}(t)$; Viz:

$$\frac{d\eta_i(t)}{\eta_i(t)} \approx \left[\begin{array}{c}\left(\frac{c_i(t)}{e_i^2}\right)\left(\frac{1}{e_i^2}\right)\left(\frac{dc_i(t)}{dt}\right) \\ +\sum_j\left(\frac{c_j(t)}{e_j^2}\right)^2\end{array}\right]dt \text{ ,i>1} \qquad (A.39)$$

$$+\left(\sum_j \frac{c_j(t)}{e_j^2}dW_j(t)\right)$$

Where $\eta_2(t) = 1/C(t)$, $\eta_3(t) = R(t)$, $\eta_4(t) = L(t)$.

Equation (A.39) is a closed form expression for the estimate of the ith time-varying cardiac parameter $\eta_i(t)$. Equation (A.39), however, is not easy to solve and one must resort to numerical methods or to some mathematical approximations.

3.3 Summary of the Algorithm:

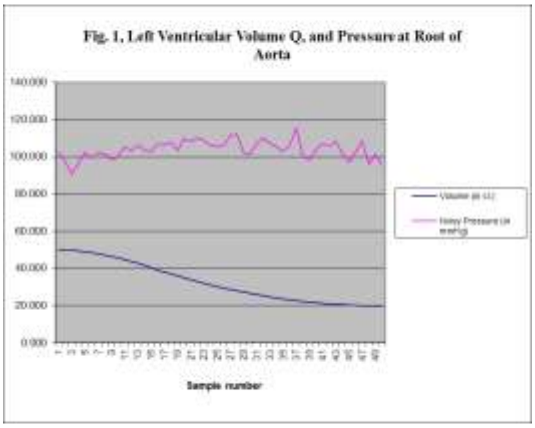
(1) Find the parameters of the time polynomials describing the SDE for each of the observed values: ventricular volume = $S_2(t) = Q(t)$, ventricular flow $= S_3(t) = dQ(t)/dt$, and $S_4(t) = d^2Q(t)/dt^2$.

(2) Equation (A.37) is utilized as a parametric model for each unknown time-varying cardiac parameter $\eta_i(t)$, where $\eta_2(t) = 1/C(t)$, $\eta_3(t) = R(t)$, $\eta_4(t) = L(t)$.

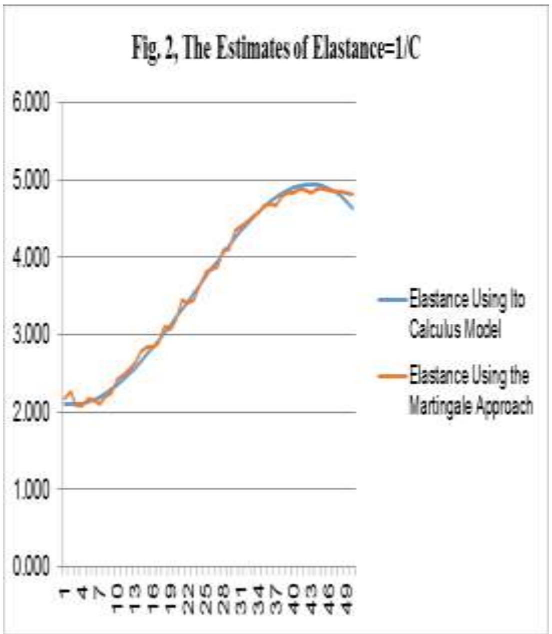
(3) Minimize sum of squared error, $\int_0^T \left(p(t) - p_o(t)\right)^2 dt$ with respect to the initial conditions of the cardiac parameters (L(0), R(0), and C(0)). Where $p_o(t)$ is the observed ventricular pressure at the root of the Aorta. The estimated pressure, p(t), is obtained from eqn. (IV.2) and by numerically solving eqn. (A.37). Eqn. (A.37) is used to find each of the unknown time-varying coefficients, $\eta_i(t)$.

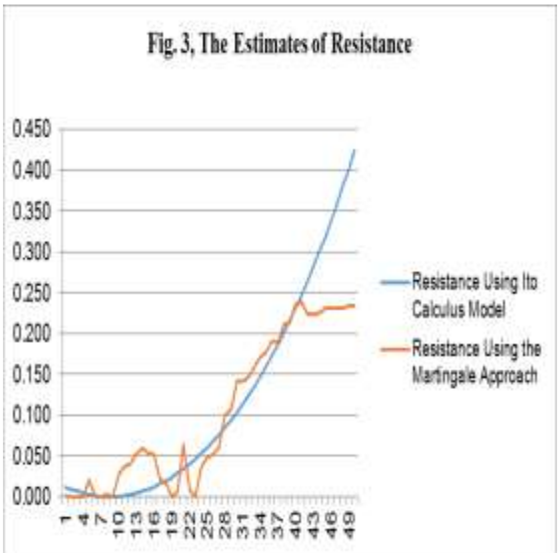
4. Conclusions

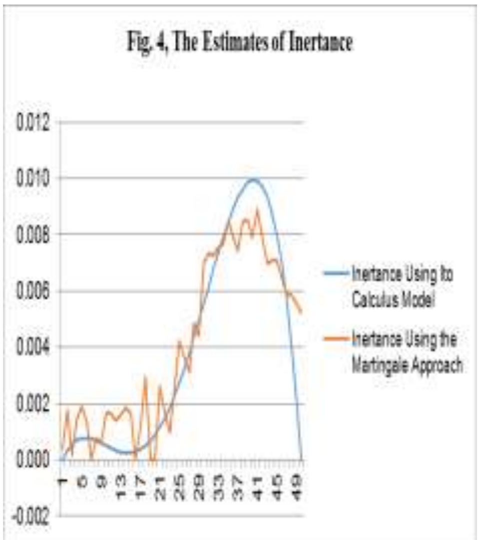
Figure 1 shows the raw data with duration 0.2 seconds and the sampling interval is 0.004 second.



Using the proposed martingale based method we were able to find estimates for the cardiac parameters. The estimates using the martingale optimality principle and the stochastic calculus-based approach [6] are shown in Figs. 2-4. The jaggedness in the estimates using the martingale approach is due to the presence of the Wiener process in the estimation equations.







The advantage of the proposed approach is that no initial shape (polynomial in time or Hermite polynomial or other polynomials) was assumed for the cardiac parameters. The only assumptions used were that the cardiac parameters are nonnegative and slowly varying over time. The resultant estimates were within 20% from the estimates obtained in [6]. The following comments are applicable:

1) The Left Ventricle $C(t)$ as estimated for the ejection period agrees, both in magnitude and in its general time course, with compliance derived by other methods, specifically, with instantaneous $Q(t)/p(t)$.

2) Similar to $C(t)$, the resistive parameter, $R(t)$, agrees with the lower values reported elsewhere [32, 33, 34]. [35] reported higher values for the resistance parameter, but concludes that the resistance values agree with those reported previously, a conclusion based on differences of ventricular chamber volumes between dogs (lower $R(t)$ values) and rabbits (higher $R(t)$ values.

3) The jaggedness in the estimates of the time-varying parameters is due to the noisy data. We expect the estimates to be smoother.

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Appendix A: Derivation of the Estimates

Let the signal p(t) be defined as:

$$p(t) = \sum_{i=1}^{d} \eta_i(t) S_i(t) \approx \sum_{i=2}^{d} \eta_i(t) S_i(t) \qquad \text{(A. 1)}$$

Where $\eta_1(t) << 1$, $\eta_2(t) = 1/C(t)$, $\eta_3(t) = R(t)$, $\eta_4(t) = L(t)$,

$S_2(t) = Q(t)$, $S_3(t) = dQ(t)/dt$, and $S_4(t) = d^2Q(t)/dt^2$

It is assumed that the coefficients $\eta_i(t)$ vary slowly over time i.e. :

$$d\eta_i(t) \to 0 \qquad \text{(A. 2)}$$

or more precisely $d\eta_i(t) << dS_i(t)$

The signals, $S_i(t)$, each has the general form of the SDE as:

$$dS_i(t) = c_i(t, S_i(t))dt + e_i(t, S_i(t))dW_i(t) \qquad i > 1 \qquad \text{(A. 3)}$$

which has a solution:

$$S_i(t) = S_i(0) + \int_0^t c_i(u, S_i(u))du + \int_0^t e_i(u, S_i(u))dW_i(u) \quad i > 1 \qquad \text{(A. 4)}$$

also $\eta_1(t)$ = known constant

$$dS_1(t) = a_1(t, S_1(t))dt = \alpha_1 S_1(t)dt, \ \alpha_1 << 1 \qquad \text{(A. 5)}$$

With the assumption of slowly varying parameters we have:

$$dp(t) = \sum_i \eta_i(t) dS_i(t) \qquad \text{(A.6)}$$

Substituting for $dS_i(t)$ we obtain an expression for the SDE of $p(t)$ as:

$$dp(t) = \sum_i \eta_i(t) c_i(t, S_i(t))\,dt + \sum_i \eta_i(t) e_i(t, S_i(t))dW_i(t) \qquad \text{(A. 7)}$$

and since $\eta_1(t) = \dfrac{p(t) - \sum_{i>1} \eta_i(t) S_i(t)}{S_1(t)}$

(A. 8)

then

$$dp(t) = \sum_{i>1} \eta_i(t) \left\{ c_i(t, S_i(t)) - \frac{a_1(t, S_1(t))}{S_1(t)} S_i(t) \right\} dt + \frac{p(t) a_1(t, S_1(t))}{S_1(t)} dt + \sum_{i>1} \eta_i(t) e_i(t, S_i(t)) dW_i(t) \qquad \text{(A. 9)}$$

We need to find an SDE for $p(t)$ that is function only of $p(t)$ and the parameters of $S_i(t)$. First we find $\eta_i(t)$ as function of $p(t)$ and $S_i(t)$ or $W_i(t)$. For this we do some mathematical manipulations such as a change of the probability measure. This will enable us to find an expression for $\eta_i(t)$ as function of $p(t)$ and $S_i(t)$.

Define $$\theta_i(t) = \frac{c_i(t, S_i(t)) - \alpha_1 S_i(t)}{e_i(t, S_i(t))} \approx \frac{c_i(t, S_i(t))}{e_i(t, S_i(t))} \qquad |\alpha_1| << |\mathrm{c_i}| \qquad \text{(A. 10)}$$

Let $v_i(\eta_i, S_i, t) = \eta_i(t) e_i(t, S_i(t))$,

$\underline{S}(t) = [S_2(t), ..., S_d(t)]^T$,

$\underline{\eta}(t) = [\eta_2(t), ..., \eta_d(t)]^T$,

$\underline{v}(t) = [v_2(t), ..., v_d(t)]^T$,

$\underline{W}(t) = [W_2(t), ..., W_d(t)]^T$, a (d-1)-dimensional Brownian motion, $\underline{\theta}(t) = [\theta_2(t), ..., \theta_d(t)]^T$ is a (d-1)-dimensional adapted process and $0 \le t \le T$

(A.11)

Define:

$$W_{Qj}(t) = \int_0^t \theta_j(u)du + W_j(t) \qquad \text{(A.12)}$$

i. e. $dW_{Qj}(t)(t) = \theta_j(t)dt + dW_j(t)$, j=2,…, d

$$Z(t) = \exp\left\{ -\int_0^t \underline{\theta}^T(u) d\underline{W}(u) - \frac{1}{2}\int_0^t \underline{\theta}^T(u)\underline{\theta}(u) du \right\}$$
(A. 13)

With $dZ(t) = -Z(t)\underline{\theta}^T(t) d\underline{W}(t)$
and define the new probability measure:
$dQ = Z(T)dP$ (A. 14)
where P is the old probability measure and Q is the new probability measure.
Using Ito lemma we get an SDE for 1/Z(t) as:

$$d\left(\frac{1}{Z(t)}\right) = \frac{-1}{Z^2(t)} dZ + \frac{1}{Z^3(t)}\left(dZ(t)\right)^2$$

$$= \frac{-1}{Z^2(t)}\left(-Z(t)\underline{\theta}^T(t)d\underline{W}(t)\right) + \frac{1}{Z^3(t)}\left(-Z(t)\underline{\theta}^T(t)d\underline{W}(t)\right)^2$$

$$= \frac{1}{Z(t)}\underline{\theta}^T(t)\underline{\theta}(t)dt + \frac{1}{Z(t)}\underline{\theta}^T(t)d\underline{W}(t)$$

$$= \frac{1}{Z(t)}\underline{\theta}^T(t)\left[\underline{\theta}(t)dt + d\underline{W}(t)\right] \quad \text{(A.15)}$$

Substitute $d\underline{W}_Q(t) = \underline{\theta}(t)dt + d\underline{W}(t)$, we obtain:

$$d\left(\frac{1}{Z(t)}\right) = \frac{1}{Z(t)}\underline{\theta}^T(t)d\underline{W}_Q(t) \quad \text{(A.16)}$$

Thus 1/Z(t) is a martingale under the measure Q when $dZ(t) = -Z(t)\underline{\theta}^T(t)d\underline{W}(t)$

Girsanov's theorem states that $W_{Qj}(t)$ is a Wiener process with respect to the probability measure Q. In addition $W_{Qj}(t)$ is an $\mathfrak{F}_t$ martingale with respect to Q [Oksendal; 1998]. Substitute equations (A. 13) into equation (A. 12) we get:

$$dp(t) = \frac{p(t)a_1(t, S_1(t))}{S_1(t)} dt + \underline{v}^T(t) d\underline{W}_Q(t)$$
(A. 17)

this has the form

$$dp(t) = \rho(t)p(t)dt + \underline{v}^T(t)d\underline{W}_Q(t)$$
(A. 18)

where $\rho(t) = \frac{a_1(t, S_1(t))}{S_1(t)} = \frac{\alpha_1 S_1(t)}{S_1(t)} = \alpha_1$
(A. 19)

<u>The Estimates for the Stochastic time-varying coefficients; $\eta_i(t)$:</u>

The martingale optimality principle [13] is now used to find an estimate for the unknown time-varying coefficients $\eta_i(t)$ as function of $p(t)$ and $S_i(t)$.

Let $U(t) = e^{-\int_0^t \rho(s)ds} p(t) = e^{-\alpha_1 t} p(t)$,
i.e. $dU(t) = e^{-\alpha_1 t}\underline{v}^T(t)d\underline{W}_Q(t)$
(A. 20)

Or equivalently

$$e^{-\alpha_1 T}p(T) = p(0) + \int_0^T e^{-\alpha_1 t}\underline{v}^T(t)d\underline{W}_Q(t)$$
(A. 21a)
Or

$$U(T) = U(0) + \int_0^T e^{-\alpha_1 t}\underline{v}^T(t)d\underline{W}_Q(t)$$
(A.21b)
Or

$$U(t) = U(0) + \int_0^t e^{-\alpha_1 s}\underline{v}^T(s)d\underline{W}_Q(s)$$
(A.21c)

Since U(t) is a martingale under the measure Q, we get:

$$E_Q\{U(T)/\mathfrak{F}_t\} = U(0) + \int_0^t e^{-\alpha_1 s}\underline{v}^T(s)d\underline{W}_Q(s)$$
(A.22)

This is the first equation in the unknowns $\eta_i(t)$. The second equation is obtained through the optimization process.
Using eqns. (A.21) we get:
$E_Q\{U(T)\} = U(0)$ (A.23a)
Or $E_Q\{U(t)\} = U(0)$ (A.23b)
and $\int_0^T E_Q\{U(t)\}dt = \int_0^T U(0)dt$
This is a constraint on the final value U(T) or U(t).

<u>The Optimization Problem:</u>

The objective is to minimize the log of the squared difference between the pressure p(t) and the observed pressure $p_o(t)$ subject to the constraint $E_Q\{U(t)\} = U(0), \forall t$. The reason we used the log function is mathematical tractability and to ensure concave objective function [Bjork; 2009]. Recall that:

$$U(t) = e^{-\int_0^t \rho(s)ds} p(t) = e^{-\alpha_1 t} p(t) \approx p(t)$$

For constrained optimization, we use the method of the Lagrange multipliers. Thus,

Find $\inf_{U(t)} E\left\{\int_0^T \log\left([U(t)-U_o(t)]^2\right)dt\right\} - \lambda\left[\int_0^T E_Q\{U(t)-U(0)\}dt\right]$ where λ is the Lagrange multiplier. In terms of the probability measure P, we need:

$$\inf_{U(t)} E\left\{\int_0^T \log\left([U(t)-U_o(t)]^2\right)dt\right\} - \lambda\left[\int_0^T E\{Z(t)[U(t)-U(0)]\}dt\right] \quad \text{(A.24)}$$

Taking the derivative w.r.t. U(t) we get:

$$2\frac{[U^*(t)-U_o(t)]}{[U^*(t)-U_o(t)]^2} - \lambda Z(t) = 0$$

i.e. $\frac{2}{[U^*(t)-U_o(t)]} = \lambda Z(t)$

or $[U^*(t)-U_o(t)] = \frac{2}{\lambda Z(t)}$ (A.25)

where $U^*(t)$ is the optimal value of U(t).

Since 1/Z(t) is a martingale under the measure Q, then $[U^*(t)-U_o(t)]$ is also a martingale under Q. Thus,

$$E_Q\{[U^*(T)-U_o(T)]/\mathcal{F}_t\} = [U^*(t)-U_o(t)] = \left(\frac{2}{\lambda}\right)\frac{1}{Z(t)} \quad \text{(A.26)}$$

This is the second equation in the unknowns.

Recall from (eqn.A.22) that:

$$E_Q\{U(T)/\mathcal{F}_t\} = U(0) + \int_0^t e^{-\alpha_1 s} \underline{v}^T(s) d\underline{W}_Q(s)$$

which could be written as:

$$E_Q\{U(T)-U_o(T)/\mathcal{F}_t\} + E_Q\{U_o(T)/\mathcal{F}_t\} = U(0) + \int_0^t e^{-\alpha_1 s} \underline{v}^T(s) d\underline{W}_Q(s)$$

i.e.

$$E_Q\{U(T)-U_o(T)/\mathcal{F}_t\} = U(0) - E_Q\{U_o(T)/\mathcal{F}_t\} + \int_0^t e^{-\alpha_1 s} \underline{v}^T(s) d\underline{W}_Q(s) \quad \text{(A.27)}$$

Equating equations (A.26) and (A.27), we get:

$$U(0) - E_Q\{U_o(T)/\mathcal{F}_t\} + \int_0^t e^{-\alpha_1 s} \underline{v}^T(s) d\underline{W}_Q(s) = \left(\frac{2}{\lambda}\right)\frac{1}{Z(t)} \quad \text{(A.28)}$$

Then $\frac{1}{Z(t)} = \left(\frac{\lambda}{2}\right)\left(U(0) - E_Q\{U_o(T)/\mathcal{F}_t\}\right) + \left(\frac{\lambda}{2}\right)\int_0^t e^{-\alpha_1 s} \underline{v}^T(s) d\underline{W}_Q(s)$

i.e. $d\left(\frac{1}{Z(t)}\right) = \left(\frac{\lambda}{2}\right) e^{-\alpha_1 t} \underline{v}^T(t) d\underline{W}_Q(t)$

From eqn. (A. 16), we know that: $d\left(\frac{1}{Z(t)}\right) = \frac{1}{Z(t)} \underline{\theta}^T(t) d\underline{W}_Q(t)$

and $[U^*(t)-U_o(t)] = \left(\frac{2}{\lambda}\right)\frac{1}{Z(t)}$, i.e. $\frac{1}{Z(t)} = \left(\frac{\lambda}{2}\right)[U^*(t)-U_o(t)]$

Thus, $d\left(\frac{1}{Z(t)}\right) = \frac{1}{Z(t)} \underline{\theta}^T(t) d\underline{W}_Q(t) = \left(\frac{\lambda}{2}\right)[U^*(t)-U_o(t)]\underline{\theta}^T(t) d\underline{W}_Q(t)$ (A.30)

Comparing eqns. (A.29) and A(30), we get:

$$\left(\frac{\lambda}{2}\right) e^{-\alpha_1 t} \underline{v}^T(t) = \left(\frac{\lambda}{2}\right)[U^*(t)-U_o(t)]\underline{\theta}^T(t) \quad \text{(A.31)}$$

For small values of α_1 we get:

$$\underline{v}^T(t) \approx [U^*(t)-U_o(t)]\underline{\theta}^T(t)$$

This is an equation in the unknowns $\underline{v}^T(t)$ as function of the observations and the unknown quantity $U^*(t)$. Recall that $v_i(\eta_i, S_i, t) = \eta_i(t) e_i(t, S_i(t))$, and $\theta_i(t) \approx \frac{c_i(t, S_i(t))}{e_i(t, S_i(t))}$. Thus

$$e^{-\alpha_1 t} e_i(t, S_i(t)) \eta_i(t) = \left[U^*(t) - U_o(t)\right] \frac{c_i(t, S_i(t))}{e_i(t, S_i(t))}$$

which is reduced to:

$$\eta_i(t) = e^{\alpha_1 t} \left[U^*(t) - U_o(t)\right] \frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}$$

$$\approx \left[U^*(t) - U_o(t)\right] \frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}, \ \alpha_1 \approx 0$$

In order to find and SDE for $\eta_i(t)$, we need to find an SDE for $\left[U^*(t) - U_o(t)\right]$

<u>An SDE for the estimated $\eta_i(t)$:</u>

Define $\mathcal{U}(t) = \left[U^*(t) - U_o(t)\right]$, then from eqn. (A.25) $\mathcal{U}(t) = \left(\frac{2}{\lambda}\right) \frac{1}{Z(t)}$, and

$$\eta_i(t) \approx \mathcal{U}(t) \frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))} = \left(\frac{2}{\lambda}\right) \frac{1}{Z(t)} \frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}$$

and from eqn. (A.32),

$$\mathcal{U}(t) \approx \eta_i(t) \frac{e_i^2(t, S_i(t))}{c_i(t, S_i(t))}$$

The SDE of $\mathcal{U}(t) = \left[U^*(t) - U_o(t)\right] = \left(\frac{2}{\lambda}\right) \frac{1}{Z(t)}$ is obtained as:

$$d\mathcal{U}(t) = \left(\frac{2}{\lambda}\right) d\left(\frac{1}{Z(t)}\right) = \left(\frac{2}{\lambda}\right) \frac{1}{Z(t)} \underline{\theta}^T(t) d\underline{W}_Q(t)$$

$$= \mathcal{U}(t) \underline{\theta}^T(t) d\underline{W}_Q(t)$$

$$= \mathcal{U}(t) \underline{\theta}^T(t) \underline{\theta}(t) dt + \mathcal{U}(t) \underline{\theta}^T(t) d\underline{W}(t)$$

$$= \mathcal{U}(t) \underline{\theta}^T(t) \underline{\theta}(t) dt + \mathcal{U}(t) \sum_j \theta_j(t) dW_j(t)$$

In eqn. (A.34) we used $d\underline{W}_Q(t) = \underline{\theta}(t) dt + d\underline{W}(t)$

Thus, $\mathcal{U}(t)$ has the solution:

$$\mathcal{U}(t) = \mathcal{U}(0) \exp\left\{\int_0^t \underline{\theta}^T(u) d\underline{W}_Q(u) - \frac{1}{2} \int_0^t \underline{\theta}^T(u) \underline{\theta}(u) du\right\} \quad \text{(A.35)}$$

From eqn. (A.33) and using Ito lemma we get an SDE for $\eta_i(t)$ as:

$$d\eta_i(t) \approx \mathcal{U}(t) d\left(\frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}\right) + \left(\frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}\right) d\mathcal{U}(t) \quad \text{(A.32)}$$

$$+ d\left(\frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}\right) d\mathcal{U}(t) \quad \text{(A.36)}$$

Where $d\left(\frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}\right)$ is the change in $\left(\frac{c_i(t, S_i(t))}{e_i^2(t, S_i(t))}\right)$.

Since the mathematical models for the signals are all having a polynomial in time drift term and constant diffusion coefficient, then eqn. (A.36) is reduced to:

(A.33a)

$$d\eta_i(t) \approx \mathcal{U}(t) d\left(\frac{c_i(t)}{e_i^2}\right) + \left(\frac{c_i(t)}{e_i^2}\right) d\mathcal{U}(t)$$

$$= \mathcal{U}(t) d\left(\frac{c_i(t)}{e_i^2}\right)$$

(A.33b)

$$+ \left(\frac{c_i(t)}{e_i^2}\right) \left(\mathcal{U}(t) \underline{\theta}^T(t) \underline{\theta}(t) dt + \mathcal{U}(t) \sum_j \theta_j(t) dW_j(t)\right)$$

Collecting terms and substituting for $\theta_i(t) \approx \left(\frac{c_i(t)}{e_i^2}\right)$, we get:

$$d\eta_i(t) = \mathcal{U}(t)\left[d\left(\frac{c_i(t)}{e_i^2}\right) + \left(\frac{c_i(t)}{e_i^2}\right) \sum_j \left(\frac{c_j(t)}{e_j^2}\right)^2 dt \right] + \left(\frac{c_i(t)}{e_i^2}\right)\left(\mathcal{U}(t)\sum_j \theta_j(t) dW_j(t)\right) \quad \text{(A.37)}$$

This is a closed loop estimate i.e. the cardiac parameters are estimated as function of the observed pressure, the estimated pressure, and the flow models.

Substitute eqn. (A.33b) into eqn. (A.37), we get:

$$d\eta_i(t) \approx \eta_i(t)\left(\frac{e_i^2}{c_i(t)}\right) \left[d\left(\frac{c_i(t)}{e_i^2}\right) + \left(\frac{c_i(t)}{e_i^2}\right) \underline{\theta}^T(t)\underline{\theta}(t) dt \right] + \eta_i(t)\left(\sum_j \theta_j(t) dW_j(t)\right) \quad \text{(A.38a)}$$

Which is reduced to:

$$d\eta_i(t) \approx \eta_i(t)\left[\left(\frac{c_i(t)}{e_i^2}\right) d\left(\frac{c_i(t)}{e_i^2}\right) + \underline{\theta}^T(t)\underline{\theta}(t) dt \right] \quad \text{(A.38b)}$$

$$+ \eta_i(t)\left(\sum_j \theta_j(t) dW_j(t)\right)$$

Substitute $\theta_i(t) \approx \left(\frac{c_i(t)}{e_i^2}\right)$ of eqn. (A.10) into eqn. (A.38b), we get:

$$d\eta_i(t) \approx \eta_i(t)\left[\left(\frac{c_i(t)}{e_i^2}\right)\left(\frac{1}{e_i^2}\right)\left(\frac{dc_i(t)}{dt}\right) + \sum_j \left(\frac{c_j(t)}{e_j^2}\right)^2 \right] dt \quad ,\text{i>1}$$

$$+ \eta_i(t)\left(\sum_j \frac{c_j(t)}{e_j^2} dW_j(t)\right)$$

Which is reduced to:

$$\frac{d\eta_i(t)}{\eta_i(t)} \approx \left[\left(\frac{c_i(t)}{e_i^2}\right)\left(\frac{1}{e_i^2}\right)\left(\frac{dc_i(t)}{dt}\right) + \sum_j \left(\frac{c_j(t)}{e_j^2}\right)^2 \right] dt + \left(\sum_j \frac{c_j(t)}{e_j^2} dW_j(t)\right) \quad \text{, i>1 (A.39)}$$

This the desired SDE for the unknown parameters but the initial conditions, $\eta_i(0)$, i>1, are unknown. They are next estimated. Equation (A.39) is an open loop estimate of the cardiac parameters. The accuracy of the resulting estimates are less than that of the closed loop equation (A.37).

Recall that:

$\eta_2(t) = 1/C(t)$, $\eta_3(t) = R(t)$, $\eta_4(t) = L(t)$

Since $$p(t) = \sum_{i=1}^{d} \eta_i(t) S_i(t) \approx \sum_{i=2}^{d} \eta_i(t) S_i(t) \quad \text{(A. 1)}$$

We numerically solve eqn. (A.39) and find the initial values , $\eta_i(0)$, i>1, that minimize the sum of squared error , $\int_0^T (p(t) - p_o(t))^2 dt$, where $p_o(t)$ is the observed pressure and T is the observation period.

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