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RANDOM MATRIX THEORY APPLIED TO HEART DYNAMICS

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Abstract. *A representative and widespread sign of cardiac rhythm is the Electrocardiogram (ECG) that records the heart electrical activity in the form of waves. It represents the electrical current in different areas of heart allowing the identification of normal and pathological behaviors. This work deals with an uncertainty modeling on a mathematical model of cardiac system. The model is composed by three-coupled nonlinear oscillators with time-delayed connections. A nonparametric probabilistic modeling, that considers uncertainties for the mathematical model itself, is proposed by using Random Matrix Theory with matrix blocks. The advantage of this approach is to reduce of the analysis from eighteen to one parameter. In general, the model is able to capture the main behaviors of the cardiac system and results show that pathological behaviors can evolve from normal rhythms due to coupling variations.*

Keywords: *Nonlinear dynamics, chaos, cardiac rhythms, DDEs, random*

1. INTRODUCTION

Electrocardiogram (ECG) is one of the most popular measurement that records the heart electrical activity. The electrical impulses related to heart functioning are recorded waveforms, which represents the electrical current in different areas of heart. Several works deal with heart dynamics by using mathematical models: Grudzinski and Zebrowski (2004) proposed modifications on the original Van der Pol oscillator (an electronic circuit analogue to heartbeat signals) in order to present a more realistic description of the natural pacemaker; Santos *et al.* (2004) presented a simplified cardiac system model considering two asymmetrically coupled modified Van der Pol oscillators, representing the behavior of the two cardiac pacemakers, sinoatrial (SA) and atrioventricular (AV) nodules; and Gois and Savi (2009) proposed a three-coupled oscillator model in order to represent ECG signals. Besides, SA and AV nodules, His-Purkinje (HP) complex is considered in system modeling. Cheffer *et al.* (2021b) improved the model due to Gois and Savi (2009) by alterations on coupling terms. Besides, nonlinear dynamics tools are applied to assist rhythm identification and possible routes from normal functioning to pathologies. Cheffer and Savi (2020) and Cheffer *et al.* (2021a) introduced statistical aspects showing that combination of nonlinearities and randomness can provide a greater variety of response that properly represents the actual behavior of the cardiac system.

Uncertainties in heart dynamics are treated in recent researches by different approaches. Christini *et al*. (1995) investigated spectral uncertainties in experimental heart rate data and synthetic autoregressive time series by applying Monte Carlo analysis. Johnstone *et al*. (2016) discussed uncertainty quantification in cardiac action potential models and experimental canine action potential models. Pathmanathan *et al*. (2019) presented a novel action potential model that includes input variability for all parameters and performed uncertainty quantification and sensitivity analysis for a range of behaviors with physiological relevance.

The main objective of this work is describing uncertainties of the cardiac system model (Cheffer and Savi, 2020) by using a probabilistic approach that relies on Random Matrix Theory (RMT) (Mehta,1991) and Gaussian Orthogonal Ensemble (GOE) (Weaver, 1989; Ritto and Fabro, 2019). RMT have been used to represent model inadequacy, for example, in chemical kinetics (Morrison et al, 2018), and in voice signals with pathologies (Cataldo and Soize, 2016).

2. MATHEMATICAL MODELING

The model due to Cheffer *et al.* (2021a) is employed for mathematical modeling of the heart system considering that SA node, AV node and HP complex are described by three nonlinear oscillators (Grudzinski and Zebrowski, 2004) with asymmetrical and bidirectional connections. Time delays are considered to represent the time spent on impulse transmissions. This general model that is capable of reproducing the cardiac behavior, being described by the following governing equations:

$$\dot{\boldsymbol{x}} = \boldsymbol{H}(\boldsymbol{x}) + \boldsymbol{F}(t) + \boldsymbol{K}\boldsymbol{x} + \boldsymbol{K}^{\tau}\boldsymbol{x}^{\tau}, \tag{1}$$

where $\boldsymbol{x}$ is the state space vector; $\boldsymbol{x}^{\tau}$ is the delayed state space vector; $\boldsymbol{H}(\boldsymbol{x})$ is the system vector field; $\boldsymbol{F}(t)$ represents external stimulus; $\boldsymbol{K}$ is the coupling matrix; and $\boldsymbol{K}^{\tau}$ is the delayed coupling matrix. Follow the definition of each one of these terms,

$$\boldsymbol{x} = [x_1 \quad x_3 \quad x_5 \quad x_2 \quad x_4 \quad x_6]^{\boldsymbol{T}}; \ \boldsymbol{x}^{\tau} = \begin{bmatrix} x_5^{\tau HP-SA} & x_1^{\tau SA-} & x_3^{\tau AV-HP} & x_3^{\tau AV-} & x_5^{\tau HP-AV} & x_1^{\tau SA-HP} \end{bmatrix}^{\boldsymbol{T}};$$

$$\boldsymbol{H}(\boldsymbol{x}) = \begin{bmatrix} x_2 \\ x_4 \\ x_6 \\ -\alpha_{SA}x_2(x_1 - v_{SA1})(x_1 - v_{SA2}) - \frac{x_1(x_1+d_{SA})(x_1+e_{SA})}{d_{SA}+e_{SA}} \\ -\alpha_{AV}x_4(x_3 - v_{AV1})(x_3 - v_{AV2}) - \frac{x_3(x_3+d_{AV})(x_3+e_{AV})}{d_{AV}+e_{AV}} \\ -\alpha_{HP}x_6(x_5 - v_{HP1})(x_5 - v_{HP2}) - \frac{x_5(x_5+d_{HP})(x_5+e_{HP})}{d_{HP}+e_{HP}} \end{bmatrix}; \ \boldsymbol{F}(t) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ F_{SA}(t) \\ F_{AV}(t) \\ F_{HP}(t) \end{bmatrix};$$

$$\boldsymbol{K} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -(k_{AV-SA} + k_{HP-SA}) & 0 & 0 & 0 & 0 & 0 \\ 0 & -(k_{SA-AV} + k_{HP-AV}) & 0 & 0 & 0 & 0 \\ 0 & 0 & -(k_{SA-HP} + k_{AV-HP}) & 0 & 0 & 0 \end{bmatrix};$$

$$\boldsymbol{K}^{\tau} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ k_{HP-SA}^{\tau} & 0 & 0 & k_{AV-SA}^{\tau} & 0 & 0 \\ 0 & k_{SA-AV}^{\tau} & 0 & 0 & k_{HP-AV}^{\tau} & 0 \\ 0 & 0 & k_{AV-HP}^{\tau} & 0 & 0 & k_{SA-HP}^{\tau} \end{bmatrix}.$$

The indexes m and n represent SA, AV or HP, being $m \neq n$. Equation terms are now explained: k_{m-n} and k_{m-n}^{τ} are coupling coefficients between m and n nodes; and $x_i^{\tau m-n} = x_i(t - \tau_{m-n})$ are delayed terms where τ_{m-n} is the time delay. Thus, the system is governed by delayed differential equations (DDEs). Besides, the delayed coupling term, $\boldsymbol{K}^{\tau}$, can be split into matrix blocks as follows:

$$\boldsymbol{K}^{\tau} = \begin{bmatrix} \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{K}_{\boldsymbol{BD}} & \boldsymbol{K}_{\boldsymbol{BI}} \end{bmatrix}, \tag{2}$$

where $\boldsymbol{K}_{\boldsymbol{BD}}$ and $\boldsymbol{K}_{\boldsymbol{BI}}$ represent diagonal matrix blocks that can be interpreted, respectively, as direct and inverse directions of signal transmission between oscillators. Figure 1 show a scheme of conceptual model and highlight mentioned directions of signal transmission.

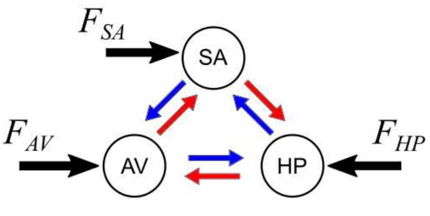

Figure 1. Conceptual model of the general cardiac functioning: direct (blue) and inverse (red) directions of signal transmission.

The ECG is formed by the signal of each one of the oscillators, being formed by a linear combination of the state variables given by (Gois & Savi, 2009),

$$X = ECG = \beta_0 + \beta_1 x_1 + \beta_2 x_3 + \beta_3 x_5\,, \tag{3}$$

where $\beta_0 = 1\,mV$, $\beta_1 = 0.06\,mV$, $\beta_2 = 0.1\,mV$ and $\beta_3 = 0.3\,mV$.

The probabilistic model is based on GOE (Ritto & Fabro, 2019) and in order to preserve the symmetry random germ matrix $\boldsymbol{G}_s = (\boldsymbol{G} + \boldsymbol{G}^T)/2$ is considered, where $\boldsymbol{G}$ is a random matrix with dimension $m \times m$, composed of independent and identically distributed normal random variables, with zero mean and standard deviation σ_M, algebraically $G_{ij} \sim N(0, \sigma_M^2)$.

The deterministic symmetric system matrix $\boldsymbol{X}_{det}$ is perturbed by the symmetric random matrix germ $\boldsymbol{G}_s$ yielding the symmetric random matrix $\boldsymbol{X}_S$:

$$\boldsymbol{X}_S = \boldsymbol{X}_{det} + \boldsymbol{G}_s, \tag{4}$$

Therefore $\boldsymbol{X}_S$ is symmetric by construction and its mean value is $\boldsymbol{X}_{det}$. The described stochastic modeling is applied to the system matrix $\boldsymbol{K}_{BD}$ and notice that uncertainties are introduced not only in the main diagonal, but also in the extra diagonal terms. Hence, it is possible to analyze effects of eighteen uncertainty elements of these matrices by varying just one parameter: the standard deviation σ_M.

3. NUMERICAL SIMULATIONS

The solution of system (1) is numerically obtained by using the fourth order Runge-Kutta method with linear interpolation of time-delayed variables to approximate their solutions in time instants before τ_j (Mensour & Longtin, 1998). Table 1 contains parameters for normal rhythm, which are used in all simulations, vanishing all other parameters that are not presented. Normal case has unidirectional couplings in such a way that the electrical impulse is conducted from SA to AV node and then, from AV node to HP complex. Also, does not present external stimuli. A convergence analysis reveals that time steps smaller than 10^{-3} presents error of the order of 10^{-6}, considered satisfactory.

Table 1. Cardiac system parameters for normal rhythm (Cheffer *et al.,* 2021a).

SA oscillator		AV oscillator		HP oscillator		Couplings		Time delays		Initial conditions	
α_{SA}	3	α_{AV}	3	α_{HP}	7	k_{SA-AV}	3	τ_{SA-AV}	0.8	$\boldsymbol{x_0}(1)$	-0.1
v_{SA_1}	1	v_{AV_1}	0.5	v_{HP_1}	1.65	k_{AV-HP}	55	τ_{AV-HP}	0.1	$\boldsymbol{x_0}(2)$	0.025
v_{SA_2}	-1.9	v_{AV_2}	-0.5	v_{HP_2}	-2	k^{τ}_{SA-AV}	3			$\boldsymbol{x_0}(3)$	-0.6
d_{SA}	1.9	d_{AV}	4	d_{HP}	7	k^{τ}_{AV-HP}	55			$\boldsymbol{x_0}(4)$	0.1
e_{SA}	0.55	e_{AV}	0.67	e_{HP}	0.67					$\boldsymbol{x_0}(5)$	-3.3
										$\boldsymbol{x_0}(6)$	2/3

The methodology consists in investigating generated responses (by varying only σ_M) and comparing them with experimental data found in PhysioBank ATM (physionet.org). In this work, only diagonal terms of $\boldsymbol{G}_S$ are summed to $\boldsymbol{K}_{BD}$. In order to analyze results, time series and phase plane $\{X, \dot{X}\}$ are presented. Monte Carlo simulations are employed: 100 simulations for each case and gray-shaded regions that defines the bounds of all responses are constructed. Similarly, RR histograms are constructed with Monte Carlo procedure, with 100 histograms and for each one is calculated mean μ_i. Mean μ, standard deviation, σ, and coefficient of variation ($CV = \sigma/\mu$) of this set of 100 μ_i are calculated. 100 simulations are enough to obtain converged behaviors of state spaces and RR histograms (including μ and σ).

Figure 2 presents responses to $\sigma_M = 1.0$. Six rhythms can be identified: normal (black), incomplete branch block (bb) (red), complete bb (blue), ventricular flutter (purple), small QRS (yellow) and ventricular fibrillation (green). The last four are shown in Figure 3 and compared with respective experimental data. Complete bb (Figure 3-a) is characterized by the absence of R-waves, presenting small region loops on state space and a null-horizontal line on histogram. Ventricular flutter (Figure 3-b) is a tachycardia caused by a single ectopic focus, or peripheral reentry mechanisms, being usually caused by chronic processes (hypertensive, atherosclerotic, rheumatic), but can be induced by acute myocardial infarction. This rhythm presents state space with orbits around larger loop of normal case and one peak on RR histogram, indicating the presence of one frequency in response. The response with small QRS (Figure 3-c) exhibits state space with a closed curve with three loops: a smaller representing P and T waves, a larger referring to normal QRS and an intermediary generated by abnormal QRS. RR histogram presents a peak to the left of reference period, representing the interval between two normal QRS. Ventricular fibrillation (Figure 3-d) is a disordered myocardial contraction due to the chaotic activity of several ectopic foci located in the ventricles. This behavior results in total heart pumping inefficiency and, from the hemodynamic point of view, corresponds to cardiac arrest (Klein *et al.*, 1979). This rhythm presents a denser state space around the largest loop and a distribution of peaks in the interval [1, 1.7] in histogram. For this case RR statistics are $\mu = 2.8148$, $\sigma = 1.5964$ and $CV = 0.5671$.

4. CONCLUSIONS

Uncertainties in a cardiac dynamical model, composed by three-coupled nonlinear oscillators, are analyzed by introducing a probabilistic model based in random matrices. This strategy has the advantage of taking into account model uncertainties since it generates couplings that are not possible to obtain varying only the system parameters. Besides, just one parameter (standard deviation) is needed to control the level of uncertainty of the system. Monte Carlo simulations are carried out for different standard deviation values. It was observed that the uncertainty insertion tends to generate signals with pathologies and among them, the following cases are observed: incomplete and complete branch block, small QRS, ventricular flutter and ventricular fibrillation. In general, it is possible to conclude that the proposed stochastic model is consistent, being able to generate cardiac pathological dynamical responses that evolve from normal rhythm.

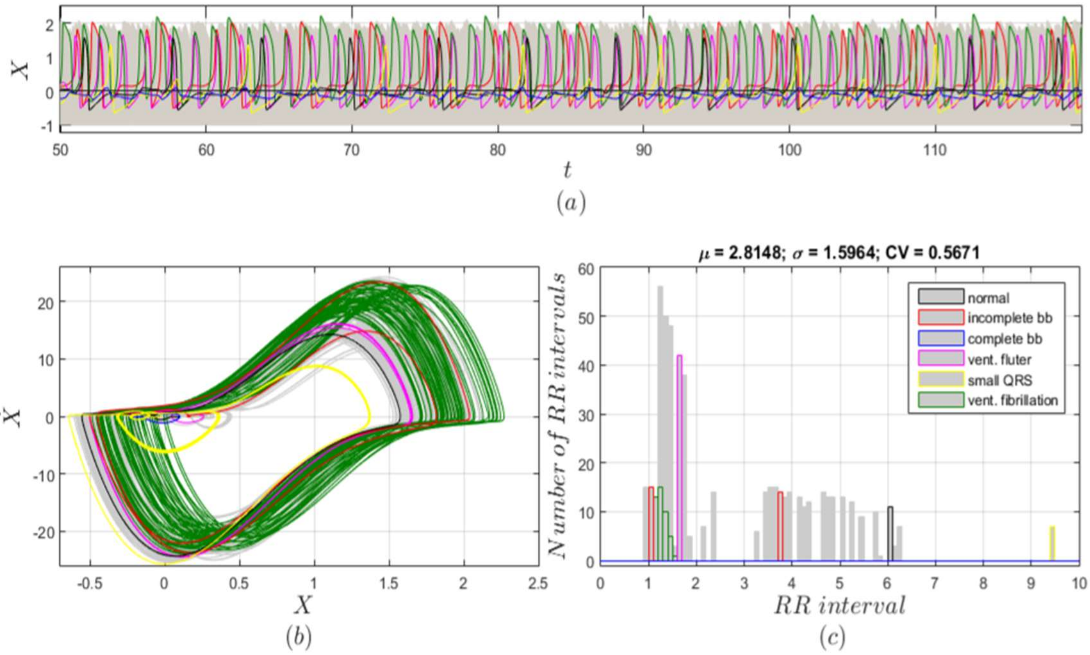

Figure 2. Stochastic analysis of $\boldsymbol{K}_{BD}$ with $\sigma_M = 1.0$: (a) ECG Monte Carlo response samples; (b) respective state spaces and (c) RR histograms. (d) Complete bb, (e) ventricular flutter, (f) low-voltage QRS and (g) ventricular fibrillation.

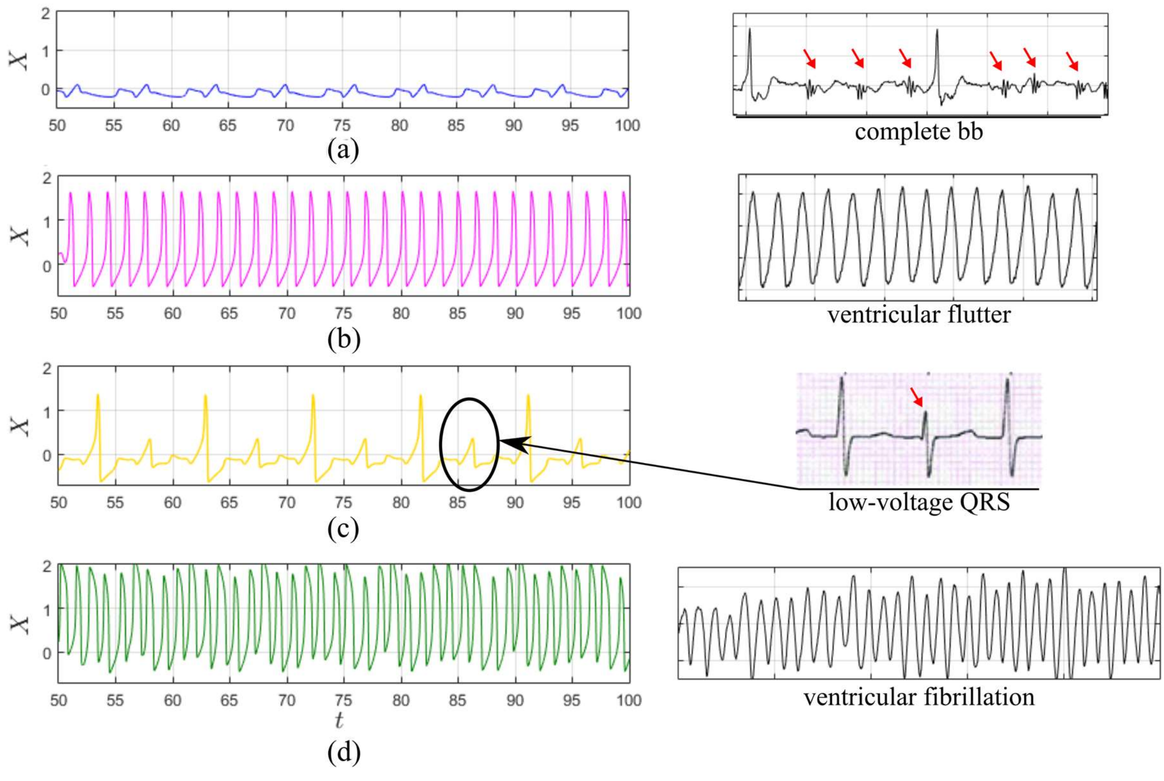

Figure 3. Clinically relevant rhythms in analysis for $\boldsymbol{K}_{BD}$ with $\sigma_M = 1.0$: (a) Complete bb, (b) ventricular flutter, (c) low-voltage QRS and (d) ventricular fibrillation.

5. ACKNOWLEDGEMENTS

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