33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Heart Rate Variability Effect on the Myocyte Action Potential Duration Restitution: Insights from Switched Systems Theory

Hila Dvir and Sharon Zlochiver

Abstract— **The physiological heart rate presents a stochastic behavior known as heart rate variability (HRV). In this framework the influence of HRV on the action potential duration (APD) of the atrial myocyte is analyzed in a computer model. We have found that introducing HRV into the myocyte action potential model decreases the APD of the extra beat S2 in an S1-S2 protocol compared to constant heart rate. A possible theoretical explanation for this is also presented and is derived from switched systems theory. It is suggested to consider the myocyte action potential phase 4 and phase 2 as two operation modes of a switching system and analyze the stability of switching between them. Since random switching is known to have a stabilization effect on a switching system, this might explain why HRV has a stabilization effect on the myocyte APD restitution. Implications of this finding include reduced system stability for conditions with low HRV. A possible application for this phenomenon regards artificial pacemakers, where a preset added HRV is predicted to reduce susceptibility to arrhythmias.**

I. Introduction

At physiological conditions, the time intervals between heart beats vary, a phenomenon known as Heart Rate Variability (HRV) [1], [2]. Reduced HRV might indicate on pathological conditions. An example for the clinical importance of HRV is that reduced HRV was found to be an independent predictor of mortality following an acute myocardial infarction [2], [3]. A frequency-domain analysis of HRV reveals four main frequency ranges: ULF (≤0.003 Hz), VLF (0.003-0.04 Hz), LF (0.04-0.015 Hz) and HF (0.15–0.4 Hz) [2], [4]. The heart rate is controlled by the autonomic nerve system, and so does the HRV. The HF component is mainly mediated by the vagal activity, while the LF is influenced by both sympathetic and vagal activity [1]. Yet, the exact origin that mediates the HRV is not fully understood and may be in part related to feedback delays in baroreceptor control. Furthermore, HRV signal is modeled along with noise components [5], [6], [7]. This means that the heart rate is not deterministic but rather random. At the current paper we investigate how HRV affects the action potential duration (APD) of the myocyte.

It is accepted that rate-dependent modifications of the APD are an important risk factors for arrhythmias [8], [9]. Changes of heart rate that result in changes of APD, reflect dependence of APD on the preceding diastolic interval (DI) and are expressed by the APD restitution (APDR) curve [8]. The influence of the membrane potential noise on the APD in myocytes has been previously investigated by Tanskanen and Alvarez [10]. In their work it was found that membrane potential noise prolongs the APD by 5msec.

However, the influence of the irregular heart beat (HRV) on the APDR curve has not been investigated yet. We speculated that introducing HRV to the myocyte action potential may have the effect of shortening the APD in a standard S1-S2 protocol, thus acting as a protecting mechanism from arrhythmogenesis.

A possible theoretical explanation for this phenomenon is derived from switching system stability concepts. Many biological systems present a behavior which varies at different modes. For example switching mechanisms that control which genes exist in ‘on’ or ‘off’ states [11]. Although each mode may be simple to analyze, their combination in time and switching between the modes might present a complex and even an unstable behavior [12], [13].

Chatterjee and Liberzon [14], have provided sufficient conditions for almost sure stability of randomly switched nonlinear systems. When the switching is random, an almost sure stability was achieved under a particular condition on the random switching probability density [14]. When the switching is markovian random [14], [15], an almost sure stability is attained under a particular condition on the generator matrices of the underlying Markov chains parameters. But when the switching law is deterministic, for the same system, there is no guarantee that the system will maintain its stability when the switching rate elevates. Hence, for a nonlinear switched system, random switching has a stabilizing effect in compared to deterministic switching.

To the best of our knowledge, the switching behavior of the myocyte action potential has not been determined yet. In the present paper we suggest to view the myocyte action potential as a switching system with two switching modes: phase 2 and phase 4 of its action potential profile. As random switching has a stabilization effect on a switched system, we hypothesized that this may be a reason for the HRV to shorten the APD in compared to deterministic heart rates.

H. Dvir is with the Department of Biomedical Engineering, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel (phone: +972-3-640-7218; fax: +972-3-640-7939; e-mail: dvirhila@post.tau.ac.il).

S. Zlochiver is with the Department of Biomedical Engineering, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel (e-mail: sharonz@eng.tau.ac.il).

II. METHODS

A. The Myocyte Action Potential Switched System

Without loss of generality, let us consider the classical Hodgkin–Huxley (HH) equations [16]:

$$\begin{cases} \dfrac{dv}{dt} = \dfrac{1}{C_M}\left[I - \bar{g}_{Na} m^3 h (v - V_{Na}) - \bar{g}_k n^4 (v - V_k) - \bar{g}_l (v - V_l)\right] \\ \dfrac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v) m \\ \dfrac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v) h \\ \dfrac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v) n \end{cases} \quad (1)$$

Where v is the trans-membrane potential, and I is the external stimulus current. $\bar{g}_{Na}$, $\bar{g}_k$ and $\bar{g}_l$ are the maximum conductance of the sodium, potassium and the leak channels, respectively. V_{Na}, V_k and V_l are the reversal potentials of the relevant channels. m, h and n, represent the sodium activation, the sodium inactivation, and the potassium activation, respectively. C_M is the membrane capacitance. α and β are the rate constants of the ion channel state transitions, which depend on the trans-membrane potential v [16].

Equation (1) may be rewritten as:

$$\begin{cases} \dot{\underline{x}} = \underline{f}(\underline{x}) \\ \underline{x} = \begin{bmatrix} v \\ m \\ h \\ n \end{bmatrix} \end{cases} \quad (2)$$

Where f is a nonlinear function. The action potential may be approximated as a two-mode switching system, where the switching is between the two quasi-stable phases 2 and 4. Phases 0,1, and 3 are referred as transitional zones of the switching. Since the trans-membrane potential values are different for phase 2 and phase 4 (see Fig. 1), α and β that are relatively stable within each mode take distinct values during each one of those phases, so that f(x) is also different for each phase:

$$\dot{\underline{x}} = \underline{f}_\sigma(\underline{x}), \qquad \sigma \in \{\text{phase2}, \text{phase4}\} \quad (3)$$

Equation (3) yields the nonlinear switched system [12], [13]. Furthermore, since in general ion-channels can be accurately modeled using markov chains, the transition from phase 2 to phase 4 can be considered markovian. Therefore, the myocyte action potential system along with HRV switching rate can be described as randomly switched nonlinear markovian system.

B. The Stability of the Myocyte Switched System

Randomly markovian switched nonlinear systems have been investigated at the literature and were found to be stable almost surely for every mean switching rate if its generator matrix applies to certain condition [14], [15].

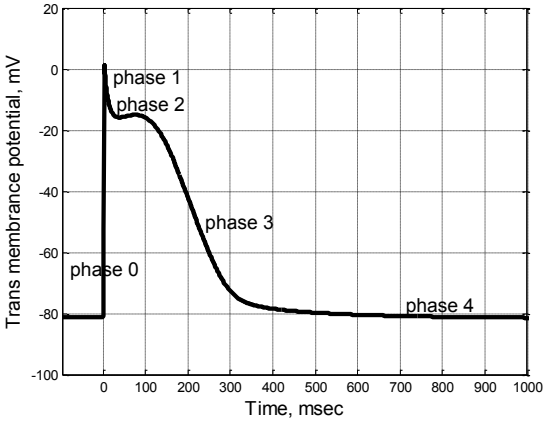

Fig. 1. The five phases of the atrial myocyte action potential. Phases 2 and 4 are considered as a two-mode switched system, phases 0,1,3 are considered as transitional zones.

Nevertheless, if the switching is deterministic, there is no assurance that the system will maintain stability when the switching rate elevates. This means that random switching has a stabilizing effect on the switched system.

The myocyte action potential under constant low heart rate is assumed to be stable. But we hypothesized that adding variability to the heart rate will have an additional stabilizing effect on its system that will be expressed at the APD restitution curve measurements, in particularly at high heart rates.

C. APD restitution curve

For the myocyte action potential duration, its restitution (APDR) curve is an indicator for stability [8]. When the heart rate raises, the recovery of the slow rate gates are not totally completed, which enables a compensatory APD length that adjusts to the fast heart rate. This mechanism prevents overlap between two consecutive beets. A stable action potential system is less susceptible to those overlaps and to the interruption of an extra beat S2 as in S1-S2 protocol.

Since random switching contributes to the stability of a switched system, non-deterministic heart rate is assumed to present a more stable behavior of the myocyte switched system. Hence, we would like to test the APDR of deterministic heart rate versus varying heart rate.

In order to assess the stability of the myocyte action potential system, APDR curves were obtained with the use of a standard S1-S2 protocol [8], [17]. The APD restitution curve was calculated from the 80th cell from a simulation of a one-dimensional cable with 100 cells, in order to avoid boundary artifacts [17]. The APD was measured at 90% repolarization [18], while the rest of the RR interval was defined as the Diastolic Interval (DI). The APDR curves were generated by decreasing the S1-S2 coupling interval and plotting the APD generated by the S2 stimulus against its preceding DI [18]. Three values of mean S1 RR intervals were tested: 500msec, 600msec, and 700msec. For each mean RR interval, 7 random pulse series were delivered in the following way: 140 S1 pulses were first delivered with a mean RR interval of 500msec, 600msec or 700msec and

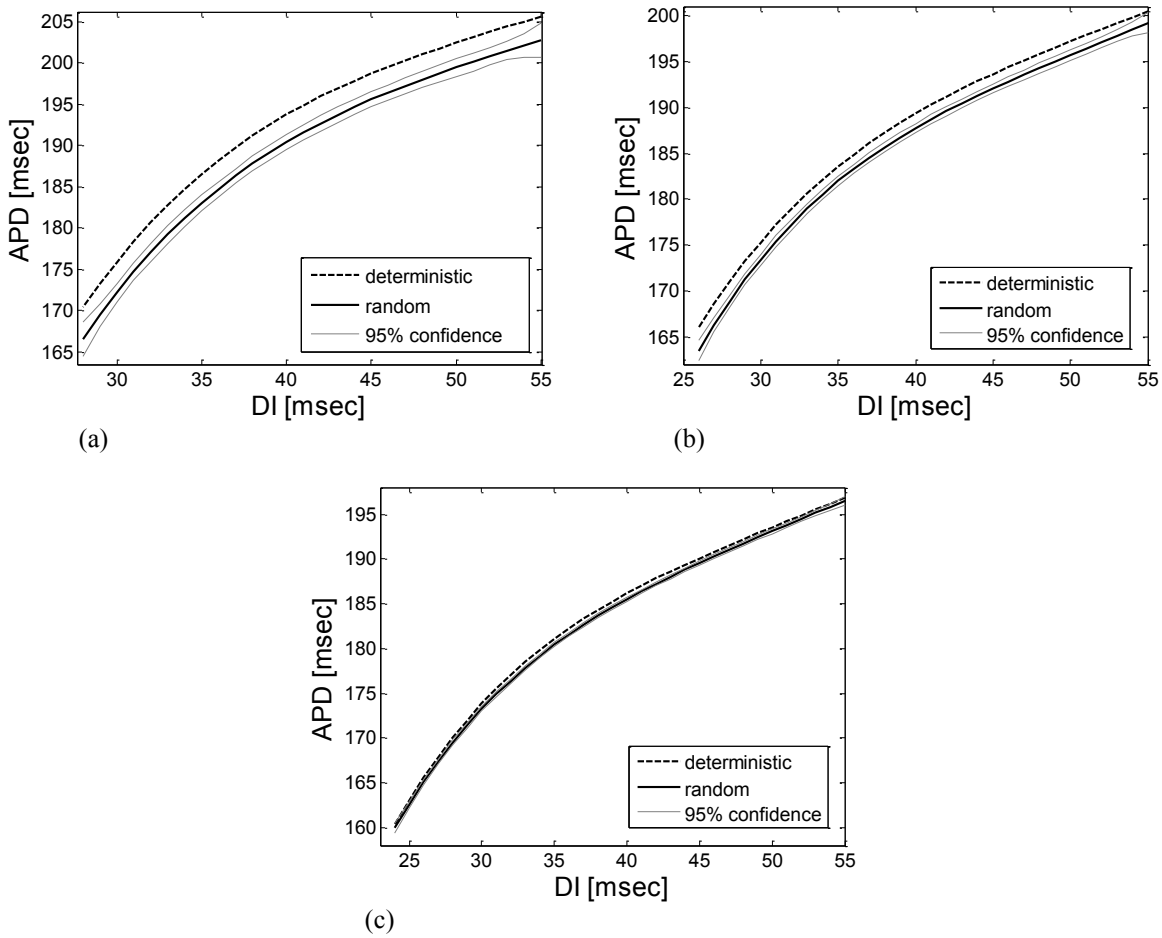

Fig. 2. APDR curves using S1-S2 protocol, for deterministic heart rate and for random Uniform distribution with ±100msec range around the mean. Random RR intervals were obtained with the same mean RR as the deterministic.(a) mean RR=500msec. (b) mean RR=600msec. (c) mean RR=700msec.

with a uniform distribution with a range of ±100msec around the mean. Following these pulses, an additional S1 pulse (number 141) was given, but rather than using a random RR-interval as before, the last RR interval was always constant (the same as the known mean RR interval) in order to be consistent and to avoid dependence on the last S1 beat. Finally, an S2 pulse was delivered with varying coupling intervals. For comparison, a similar protocol of 141 S1 pulses but with constant RR intervals of either 500msec, 600msec or 700msec was tested as the deterministic reference case. Since almost sure stability of the switched system implies stability in probability [14], [19], for each one of the 3 mean RR value, we measured the mean and standard deviation values of APD and of DI across the 7 different simulation experiments.

D. The Action Potential Model

The action potential was simulated using a human atrial cell model [20]. This model includes 12 currents and 21 state variables and is more comprehensive than the simplification in equation (1). Nevertheless, although the simulated model is more complex, equations (2) and (3) remain similar, since $\dot{x}$ is nonlinear with voltage dependent parameters.

III. RESULTS

Fig. 2 presents the APDR curves for the deterministic RR interval values (in dashed line) and for the uniformly distributed random RR intervals (in solid black line, mean curve for the 7 experiments). Three APDR curves are shown for the 3 cases of mean RR intervals: (a) 500msec, (b) 600msec and (c) 700msec. The thin gray lines mark the 95% confidence level zone around the mean plot. For each one of the mean RR interval, the random curve was obtained by first employing a 4 degree polynomial curve fitting for each of the 7 simulations (this fit was necessary for averaging purposes in order to have all 7 curves with the same DI values), and then averaging the 7 polynomials.

As can be observed from Fig. 2, the APDR curves were consistently lower for the random RR intervals case than for the deterministic RR intervals reference. This conclusion applies to all 3 values of mean RR interval. For example, referring to the left-most value on the curves, the differences between the APDs of the deterministic and the random S1 series were: 4msec for a mean RR of 500msec (p-value=0.03), 2.6msec for a mean RR interval of 600msec (p-value=0.02) and 0.4msec for a mean RR interval of 700msec (p-value =0.1). In addition, the 95% confidence area is

narrow, which is another indication that the results are significant statistically.

IV. Discussion

The APD restitution curves shown in Fig. 2 point out that random RR interval values lower the restitution curve in compared to deterministic RR values. Moreover, the more random the RR values are (relatively to the mean RR value), the lower the restitution curve is. This phenomenon is suggested to be attributed to the theory that random switching has a stabilizing effect on the switched system. Therefore, the myocyte action potential system, that presents a switching behavior, acts upon this theory and is less susceptible to S2 interruptions.

Obtaining shorter APDs as the heart rate increases is an important compensating mechanism which can prevent arrhythmias. A prolonged APD is often associated with increased occurrence of early after depolarization (EAD) arrhythmias [21] and wave breaks. As random RR values shorten the APD of an S2 beat, this mechanism might be important in preventing arrhythmias. Clinically, several conditions have been found to reduce HRV, for example smoking [22], aging [23] and heart failure [24]. Considering our simulation results, it is possible that such low HRV conditions present a less compensating APD restitution curve, which possibly expresses as susceptibility to arrhythmias in particular during high heart rate.

Several limitations in this study should be noted. At the present model, HRV was simply modeled as a uniform noise with a constant noise range for all 3 simulated heart rates. A more complete model should be tested in a further research to simulate a more characteristic HRV with specific spectral properties along with an additive random noise. During exercise HRV alters in compared to rest, there are differences at HRV even between dynamic and static category of exercise [1]. In addition the action potential model parameters are different for pathologies such as heart failure. At the current scope of the paper we did not take those factors into account, and used a general model behavior of healthy cells. In the future, we will extend this analysis for ischemic cells model as well.

V. Conclusion

An important clinical conclusion of this paper is that HRV may be an important mechanism to prevent arhytmias, and low HRV (during diseases) can be the origin for arhytmias. One application of the current findings refers to the artificial pacemaker. It is suggested that adding noise to the artificial pacemaker's beat intervals may obtain a more compensating myocyte action potential system and have an anti-fibrillatory effect.

References

[1] M. Malik and A. J. Camm, *Heart Rate Variability*. Armonk, NY: Futura Publishing Co, 1995.

[2] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology**, "**Heart rate variability, standards of measurements, physiological interpretation, and clinical use," Circulation vol. 93, pp. 1043–1065, 1996.

[3] P. Libby, R.O. Bonow, D.L. Mann, and D.P. Zipes, *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA, USA: Saunders, 2007.

[4] S. Akselrod, D. Gordon, F.A. Ubel, D.C. Shannon, A.C. Barger, and R.J. Cohen, "Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control," Science vol. 213, pp. 220-222, 1981.

[5] R. Silipo, G. Deco, and R. Vergassola, "Markov models and heart rate variability hidden dynamic," Computers in Cardiology, vol. 25, pp. 337- 340, 1998.

[6] M.R. Guevara, and T.J. Lewis, "A minimal single-channel model for the regularity of beating in the sinoatrial node," Chaos, vol.5, pp. 174-183, 1995.

[7] R. Wilders, and H. J. Jongsma, "Beating irregularity of single pacemaker cells isolated from the rabbit sinoatrial node," Biophys. J., vol. 65, pp. 2601–2613, 1993.

[8] M.L. Koller, M.L. Riccio, and R.F. Gilmour Jr," Dynamic restitution of action potential duration during electrical alternans and ventricular fibrillation," Am J Physiol Heart Circ Physiol vol. 275, pp. H1635–H1642, 1998.

[9] M. Watanabe, N. F. Otani, and R. F. Gilmour Jr, "Biphasic restitution of action potential duration and complex dynamics in ventricular myocardium," Circ. Res. Vol. 76, pp. 915–921, 1995.

[10] A. J. Tanskanen, and L. H.R. Alvarez "Voltage noise influences action potential duration in cardiac myocytes," Mathematical Biosciences, vol. 208, pp. 125–146, 2007.

[11] C.A. Hazzalin, and L.C. Mahadevan, "MAPK-regulated transcription: a continuously variable gene switch?" Nat. Rev. Mol. Cell. Biol. vol. 3, pp. 30–40, 2002.

[12] M. Margaliot, "Stability analysis of switched systems using variational principles: An introduction," Automatica, vol. 42, pp. 2059–2077, 2006.

[13] D. Liberzon, *Switching in Systems and Control*. Boston, MA: Birkhauser, 2003.

[14] D. Chatterjee, and D. Liberzon, "On stability of randomly switched nonlinear systems," IEEE Trans. Autom. Control, vol. 52, no. 12, pp. 2390–2394, Dec. 2007.

[15] C. Yuan and X. Mao, "Asymptotic stability in distribution of stochastic differential equations with markovian switching," Stochastic Process. Appl., vol. 103, pp. 277–291, 2003.

[16] T. F. Weiss, *Cellular Biophysics*. Volume 2. MIT Press, Cambridge, MA, 1996, ch. 4.

[17] E.M. Cherry and S.J. Evans, "Properties of two human atrial cell models in tissue: restitution, memory, propagation, and reentry," Journal of Theoretical Biology, vol. 254, pp. 674–690, 2008.

[18] K.H.W.J. ten Tusscher, D. Noble, P.J. Noble, and A.V. Panfilov, "A model for human ventricular tissue," Am J Physiol Heart Circ Physiol. vol. 286, pp. H1573–H1589, 2004.

[19] R. Z. Khas'minskii, *Stochastic Stability of Differential Equations*, Sijthoff & Noordhoff, Netherlands, 1980.

[20] M. Courtemanche, R.J. Ramirez, and S. Nattel, "Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model," Am J Physiol Heart Circ Physiol, vol. 275, pp. H301–H321, 1998.

[21] V. Fuster, R.A. O'Rourke, R.A. Walsh, and P. Poole-Wilson, *Hurst's The Heart*, 12th ed., New York, NY: McGraw-Hill Medical, 2008, ch. 35.

[22] I. Barutcu, A.M. Esen, D. Kaya, M. Turkmen, O. Karakaya, M. Melek, O.B. Esen, and Y. Basaran, "Cigarette smoking and heart rate variability: dynamic influence of parasympathetic and sympathetic maneuvers," Ann Noninvas Electrocardiol, vol.10, no.3, pp. 324–329, 2005.

[23] J. Zhang, "Effect of age and sex on heart rate variability in healthy subjects," J. Manipulative Physiol. Ther. vol. 30, pp. 374–379, 2007.

[24] P.K. Stein, M.S. Bosner, R.E. Kleiger, and B.M. Conger, "Heart rate variability: a measure of cardiac autonomic tone," Am Heart J, vol. 127, pp. 1376–1381, 1994.