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Voltage noise influences action potential duration in cardiac myocytes

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Abstract

Stochastic gating of ion channels introduces noise to membrane currents in cardiac muscle cells (myocytes). Since membrane currents drive membrane potential, noise thereby influences action potential duration (APD) in myocytes. To assess the influence of noise on APD, membrane potential is in this study formulated as a stochastic process known as a diffusion process, which describes both the current-voltage relationship and voltage noise. In this framework, the response of APD voltage noise and the dependence of response on the shape of the current-voltage relationship can be characterized analytically. We find that in response to an increase in noise level, action potential in a canine ventricular myocytes is typically prolonged and that distribution of APDs becomes more skewed towards long APDs, which may lead to an increased frequency of early after-depolarization formation. This is a novel mechanism by which voltage noise may influence APD. The results are in good agreement with those obtained from more biophysically-detailed mathematical models, and they suggest that increased voltage noise (due to gating noise) may partially underlie an increased incidence of early after-depolarizations in heart failure.

Keywords

Action potential duration; Voltage fluctuations; Cardiac left ventricular myocyte; Early after-depolarization; Mathematical modeling

1 Introduction

The cardiac action potential (AP; see Fig. 1A) is the characteristic electrical signal measured across the membrane of a heart muscle cell (known as a myocyte). Experimental measurements of guinea pig ventricular myocytes by Zaniboni et al.[1] have demonstrated that gating noise,

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arising from the random opening and closing of ion channels, may be the primary source of beat-to-beat variability in action potential duration (APD; see Fig. 1A). Nevertheless, the influence of noise on the statistical properties of a cardiac ventricular myocyte, such as average APD, has typically been ignored in mathematical models of a cardiac myocyte (e.g., Winslow et al.[2]).

The role of noise on AP shape and duration can be studied using a bio-physically detailed, stochastic mathematical model such as the nerve membrane model of Skaugen and Walløe [3], the sinoatrial node model of Wilders and Jongsma[4], and the canine ventricular myocyte model of Greenstein and Winslow[5] (henceforth referred to as the GW model). Of these three models, we will only consider the GW model which is the most appropriate model for the study of APD distribution in canine cardiac myocytes.

The GW model[5] is a mathematical model of the normal canine ventricular myocyte that conforms to local control theory[6]. The model formulation incorporates details of microscopic excitation-contraction coupling properties in the form of Ca^{2+} release units (CaRUs). In CaRUs, individual sarcolemmal L-type Ca^{2+} channels interact in a stochastic manner with nearby ryanodine receptors in localized regions where junctional SR membrane and transverse-tubular membrane are in close proximity. The CaRUs are embedded within and interact with the deterministic global systems of the myocyte describing ionic and membrane pump/exchanger currents, sarcoplasmic reticulum Ca^{2+} uptake, and time-varying cytosolic ion concentrations to form a model of the cardiac action potential. The model can reproduce both the detailed properties of excitation-contraction coupling, such as variable gain and graded sarcoplasmic reticulum Ca^{2+} release, and whole-cell phenomena, such as modulation of AP duration by sarcoplasmic reticulum Ca^{2+} release[5] and the experimentally observed beat-to-beat variation of APD accurately [7]. Beat-to-beat variability of APD in the GW model is largely mediated by stochastic behavior of Ca^{2+} transient and late sodium current [1]. While myoplasmic Ca^{2+} transient is modeled in detail, late sodium current has not been characterized completely and, consequently, was not incorporated in the GW model.

While an ionic model, such as the GW model, provides a good description of gating noise and can be used to study the role of gating noise on APD, such a model does not yield rigorous mathematical characterization on how noise influences statistical properties of APD. An analytically more tractable formulation of membrane potential is provided by a stochastic process known as a diffusion process[8–11]. Previously, the method has been employed by, e.g., Clay and DeHaan[9], who studied the role of fluctuations on interbeat interval (IBI) in chick heart-cell aggregates. By examining variation of IBI experimentally, they observed $1/\sqrt{N}$ relationship between coefficient of variation of IBI and the number N of cells in chick heart-cell aggregates. They also showed that the experimentally observed relationship can be accounted for by a model based on a diffusion process with constant drift. In this study, we will employ a diffusion process with general drift to analyze the noise response of APD analytically.

In addition to “graded modulation” of statistical properties of a biological system, noise may induce on-off type transitions, as is observed in a variety of biological systems [12,13]. For example, gating noise associated with fast sodium channels can induce spontaneous action potentials in neuronal cells by occasionally pushing membrane potential above the threshold for AP activation [3,14]. It has also been proposed that fluctuations of L-type calcium current arising from a high-activity gating mode (known as mode 2 [15]) of L-type calcium channels may generate secondary depolarizations[7]. These abnormal depolarizations of membrane potential are known as early after-depolarizations (EADs) in cardiac myocytes. EADs are thought to serve as a possible trigger for development of polymorphic ventricular tachycardia

[16,17]. In experiments, an increased occurrence of EADs is often associated with prolongation of APD [18,19].

Adair[20] argues that since the suppression of stochastic noise is biologically expensive, any organism operates at maximum noise level consistent with its survival and reproduction. Hence, stochastic noise added in any manner degrades the overall performance of an organism. Appropriate APD is important for proper myocyte function: when APDs are too short, heart muscle is more susceptible to reentrant electrical activity; when APD is excessive, potentially arrhythmogenic EADs may occur. This suggests that it is interesting to examine how noise influences APD.

In this study, we examine the statistical properties of APD in cardiac ventricular myocytes in the presence of voltage noise. To characterize the response of APD to a change in noise level, we employ two kinds of models: (1) the ionic GW model, and (2) models based on a stochastic process known as a diffusion process[11]. We derive rigorous results (section 2; proofs are presented in appendices A–D) on the characterization of noise response of APD using a more general diffusion process than previously[9]. As an application of the theoretical results, we consider the influence of voltage noise on APD and the occurrence of EADs in canine ventricular myocytes using a diffusion process approach (section 3), and compare results to those obtained with the GW model. In addition to an increase in variance of APD, we find that increased voltage noise level typically increases both average and skewness of APD distribution in canine ventricular myocytes.

2. Noise and APD in cardiac myocytes

2.1 Action potential duration

Action potential duration (APD; at 90 percent repolarization) measures the length of an AP. It is defined as the time required for membrane potential to decline from its peak value v_p to value $a = v_p - 0.9(v_p - v_r)$, where v_r is the diastolic membrane potential. In other words, APD is given by the hitting time of membrane potential V_t to voltage a , $\inf\{t \geq 0 : V_t = a; V_0 = v_p\}$, initially at the peak value v_p . In the following, we are mostly interested in three statistical measures of APD: (1) average APD; (2) coefficient of variation of APD (denoted by CV in the following) defined as the ratio of standard deviation of APD to average APD; and (3) relative skewness of APD distribution defined as $E[(APD/E[APD] - 1)^3]$, that is, the third central moment of APD distribution divided by the cube of its standard deviation.

The experimental results of Zaniboni et al. [1] as well as the simulation studies of Wilders and Jongsma [4] suggest that stochastic variability of the major ionic currents operating during the plateau phase are responsible for the beat-to-beat variability in APD observed in isolated cardiac myocytes. Therefore, we concentrate on the influence of voltage fluctuations during plateau, where the balance of inward and outward currents is driven primarily by the inward L-type calcium current and outward potassium currents. For simplicity, the duration of AP before the plateau phase is treated as a constant.

Fig. 1 shows average APD and CV at four noise levels in the GW model¹. The noise in the GW model is due to stochastic gating of L-type calcium channels and ryanodine receptors in CaRUs. Comparison of average APDs at four noise levels shows that average APD decreases as a function of the number of simulated CaRUs, n_{CaRU} (Fig. 1B). Since noise in the total membrane current is proportional to $1/\sqrt{n_{\text{CaRU}}}$, this shows that increased noise level prolongs average APD in the GW model (Fig. 1C). This is counterintuitive, since one would assume

¹In the simulations, the aggregate current from the simulated CaRUs is in each simulation scaled to correspond to the number of CaRUs expected to exist in a real cell[5].

that increased noise level would more frequently push voltage to a range where I_{K1} takes over repolarizing membrane potential resulting in APD shortening. The counterintuitive influence of noise on average APD is supported by the observation that CV increases linearly with noise level $\sim 1/\sqrt{n_{CaRU}}$ (Fig. 1E), that is, average APD increases as a function of CV (Fig. 1F). These simulations demonstrate that noise level influences APD in a systematic manner in the GW model, however, it is not obvious why we should observe this kind of effect. Motivated by this computational study, we will now examine the response of APD to a variation in voltage noise level using the diffusion process framework.

2.2 Current-Voltage relationship

The time-evolution of membrane potential is determined by the total ionic current passing through the entire population of ion channels and active transporters. During an AP, membrane current $I(t, V)$ is a function of time and membrane potential. Assuming a 1-1 correspondence between voltage V and time t during the AP plateau, current I can be represented as a function of voltage alone. Membrane current can be approximated by a low-order polynomial

$I(V) = \sum_{k=0}^q c_k V^k$ of order q with coefficients $c_k \in \mathbb{R}$ (see, e.g., [21]). We will refer to this relationship of current to voltage as *the $I(V)$ function* in the following.

Since the sarcolemma can be treated as a capacitor[22], time-evolution of membrane potential V is related to the $I(V)$ function by

$$\frac{dV}{dt} = -\frac{1}{C_m} I(V), \quad (1)$$

where C_m is membrane capacitance[22]. Equation (1) shows that we assume current I is an instantaneous function of voltage. However, the $I(V)$ function is fitted to the I-V relationship in a full ionic model with time-dependent currents, and in this sense captures some time-dependent aspects of action potential.

2.3 Membrane potential as a diffusion process

The aim of this study is to examine how noise affects APD in canine myocytes, in particular during the plateau phase of the AP. Mathematically, we assume that membrane potential V_t is a regular, homogeneous diffusion process defined on a complete filtered probability space $(\Omega, \mathcal{P}, \{F_t\}, \mathcal{F})$ [23]. Its time-evolution in the presence of additive white noise B_t is described by the stochastic differential equation (see, e.g., [23,24]; with Itô interpretation)

$$dV_t = -\frac{1}{C_m} I(V_t) dt + \sigma(V_t) dB_t, \quad V_0 = x. \quad (2)$$

The $I(V)$ function $I: \mathbb{R} \rightarrow \mathbb{R}$ incorporates the influence of total membrane current on voltage as discussed above, and the diffusion coefficient $\sigma: \mathbb{R} \rightarrow \mathbb{R}^+$ describes the typical amplitude of noise, that is, the noise level. Both the $I(V)$ function I and diffusion coefficient σ are assumed to be continuously differentiable functions² of membrane potential. Diffusion process (2) enables analytical study of APD and its statistical properties in the presence of noise.

The assumption that noise has Gaussian shape is justified when fluctuations occur much faster than changes in membrane potential [10,25]. This is a reasonable assumption in the case of a cardiac myocyte: in the GW model, fluctuations in membrane current occur due to gating noise

²For notational convenience, we have also used σ to denote a constant diffusion coefficient, that is, $\sigma(V) = \sigma \in \mathbb{R}$.

of L-type calcium channels with typical open time 0.5 ms (in mode 1) [15], whereas the change in membrane potential is much slower during plateau.

In this study, we are interested in comparing how noise influences statistical properties of APD distribution. For this purpose, we need to compare different noise levels and, to be precise, we must define what is meant by “more noise” and “increased noise level” with respect to a diffusion process: When diffusion processes X and $\tilde{X}$ have identical $I(V)$ function but different diffusion coefficients σ and $\tilde{\sigma}$, we say that on range J process $\tilde{X}$ experiences higher noise level (or more noise) than process X if $\sigma(z) > \tilde{\sigma}(z)$ for all $z \in J$. This is a rather stringent definition that can likely be relaxed in many cases.

2.4 APD as a hitting time

When membrane potential is described as a diffusion process, APD is given by the hitting time $\tau(a) = \inf\{t \geq 0 : V_t = a\}$ to voltage a , that is, the first time membrane potential hits the predetermined voltage a . Initially at voltage x , expected hitting time $u(x) = E_x[\tau(a)]$ at a is given [11,26] by

$$u(x) = 2 \int_a^x \int_y^b \sigma^{-2}(z) e^{-2 \int_y^z I(s)/(C_m \sigma^2(s)) ds} dz dy, \quad (3)$$

when the lower boundary at a is absorbing (that is, $u(a) = 0$), and the upper boundary at b is reflecting³ (that is, $u'(b) = 0$). Total APD is given by the sum $d_0 + u(x)$, where d_0 is the duration of the AP before the start of plateau phase. The second moment $E_x[\tau(a)^2]$ can be computed from an ordinary differential equation [11]. Variance of τ , $w(x) = E_x[\tau^2(a)] - (E_x[\tau(a)])^2$, is given by

$$w(x) = 2 \int_a^x \int_y^b (u'(z))^2 e^{-2 \int_y^z I(q)/(\sigma^2(q) C_m) dq} dz dy. \quad (4)$$

Finally, CV is $\sqrt{w(x)/(d_0 + u(x))}$.

Distribution of APDs can be obtained by solving the Fokker-Planck equation [26], however, numerical methods come handy. We simulate a diffusion process using the Euler's method [27], that is, voltage is stepped according to $V_{t+\Delta t} = V_t - I(V_t)\Delta t/C_m + \xi n \sqrt{\Delta t}$, where n is $N(0,1)$ distributed random number, ξ is the diffusion coefficient, and Δt is time step.

2.5 How does noise influence average APD?

In the following, we will analytically characterize the noise response of average APD. Let us first work out the deterministic case $\sigma = 0$. Then APD (that is, hitting time) can be solved from equation (1) and is given by

$$T_x = \int_a^x \frac{C_m dz}{I(z)}, \quad (5)$$

where x is the initial voltage. Equation (5) gives duration of a journey from point a to x for an object moving at speed $I(z)/C_m$ at point $z \in [a, x]$.

³The reflecting upper boundary limits the admissible voltages and can be interpreted as a point above which a strong outward current reduces voltage rapidly (so strongly that voltages above the reflection point are not admissible). A biophysical justification for the use of reflecting boundary condition is that membrane potential cannot obtain extremely high values due to, e.g., finite reversal potentials of the major ionic currents.

Let us next compute the average influence of a symmetric fluctuation $x \pm \varepsilon$ in the initial voltage on APD using equation (5). The average noise response of APD, denoted by ΔT_x , to this fluctuation is

$$\Delta T_x = \frac{1}{2}(T_{x+\varepsilon} + T_{x-\varepsilon}) - T_x = \int_x^{x+\varepsilon} \frac{C_m dz}{2I(z)} - \int_{x-\varepsilon}^x \frac{C_m dz}{2I(z)}. \quad (6)$$

If the $I(V)$ function is positive and *increasing* (which corresponds to repolarization of voltage at a rate that is increasing with time), the second integral dominates over the first one, that is $\Delta T_x < 0$. Under these conditions, APD is on average reduced in response to these fluctuations. Similarly, if the $I(V)$ function is positive and *decreasing* (which corresponds to repolarization of voltage at a rate that is decreasing with time), the first integral in equation (6) dominates over the second integral, that is $\Delta T_x > 0$, and on average APD is increased in response to these fluctuations. Hence, the sign of I' influences the noise response of APD asymmetrically, even when the fluctuation in the initial voltage is symmetric. The following will consider the full stochastic case, which can be expected to behave in a similar fashion.

2.5.1 Noise response of APD—General noise response of APD can be examined using the Laplace transform $E[\exp(-r\tau(y))]$ of hitting time τ , where $r > 0$. The Laplace transform provides an invertible transformation of probability density of τ , and it contains all information on moments of τ , that is, $(-1)^n \frac{d^n}{dr^n} \big|_{r=0} E[e^{-r\tau(y)}] = E[(\tau(y))^n]$. When the initial membrane potential x is higher than membrane potential a , that is $x > a$, the Laplace transform can be expressed [28] as

$$E_x[e^{-r\tau(y)}] = \phi(x)/\phi(y), \quad (7)$$

where ϕ is the decreasing fundamental solution (unique up to a multiplicative constant) of the second order ordinary differential equation

$$\frac{1}{2}\sigma^2(z)v''(z) - \frac{I(z)}{C_m}v'(z) - rv(z) = 0 \quad (8)$$

with reflecting upper and absorbing lower boundary conditions, $z \in \mathbb{R}$. By studying the properties of ϕ , we can describe how noise influences APD. In the following, we will separately consider concavity and convexity of ϕ .

2.5.2 Convexity—As shown by equation (7) and by Theorem 1 (appendix A), the decreasing fundamental solution ϕ of equation (8) has a special connection to statistical properties of APD. The second derivative of ϕ is given (Theorem 2 in appendix B by

$$\frac{1}{2}\sigma^2(x)\frac{\phi''(x)}{s(x)} = \frac{r\phi(b)}{s(b)} - \int_x^b [I'(y)/C_m + r] \frac{\phi'(y)}{s(y)} dy, \quad (9)$$

where $s(y) = \exp(2 \int_a^y I(z)/(\sigma^2(z)C_m) dz)$. Equation (9) shows that convexity/concavity of ϕ depends on the sign of I' and the position b of the reflecting upper boundary. On range where the $I(V)$ function is non-decreasing (note that $\phi' \leq 0$), the decreasing fundamental solution ϕ is always convex. Theorem 1 (appendix A) proves that when ϕ is convex on finite interval $(a, b) \subset \mathbb{R}$, more noise increases the Laplace transform $E[\exp(-r\tau)]$. Under these conditions, more noise decreases the expected APD $E_x[\tau]$ (Theorem 3 in appendix C), regardless of position b of the upper boundary.

When the $I(V)$ function is increasing, the upper reflecting boundary does not alter the sign of ϕ'' , and ϕ is always convex. For a linear $I(V)$ function, we should expect no response from APD to voltage noise [30,31], however, the boundary conditions may introduce response. This is a consequence of the presence of term $r\phi(b)/s(b)$ in equation (9), which forces ϕ convex near the upper boundary at b . Thus, the average APD may decrease in response to more noise when the $I(V)$ function is decreasing as a result of the reflecting upper boundary condition.

2.5.3 Concavity—A similar result on the noise response of APD can be proven for the case where ϕ is concave, however, it is slightly more complex. If ϕ is concave on a finite interval $J \subset (a, b]$, it contributes to the Laplace transform $E[\exp(-r\tau)]$ by decreasing it in response to more noise (Theorem 1 in appendix A). Consequently, the concavity on interval J contributes to the expected APD $E[\tau]$ by increasing it in response to more noise (Theorem 3 in appendix C).

The decreasing fundamental solution ϕ cannot be concave everywhere on $(a, b]$ due to the assumption that the upper boundary is reflecting, and we must consider concavity locally. The reflecting upper boundary imposes a positive term $r\phi(b)/s(b)$ to ϕ'' (equation (9)) and, consequently, the decreasing fundamental solution ϕ is always convex near the upper boundary. Assuming the $I(V)$ function is positive and that the upper boundary at b is far, the contribution of the upper boundary is typically negligible to the overall noise response of APD. Assuming the $I(V)$ function is *strictly decreasing*⁴ on interval $[a, b]$, and that the influence of the reflecting upper boundary at b is small, ϕ is concave on subinterval $(a, d) \subset [a, b]$ according to equation (9). In this case, $E_x[\tau]$ increases in response to more noise on interval (a, d) .

In general, the $I(V)$ function is both decreasing and increasing on interval $(a, b]$. A partition of $(a, b]$ into components on which the $I(V)$ function is monotonic separates the different influences of noise on $E[e^{-r\tau}]$. The total noise response of APD depends on the relative strengths of individual components.

In conclusion, we prove that the response of average APD to more noise can be reduced to a question of concavity/convexity of the fundamental solutions of equation (8). This has the consequence that when the $I(V)$ function is increasing, the average APD $E_x[\tau(y)]$ decreases in response to more noise (regardless of the boundaries); and when the $I(V)$ function is decreasing, the average APD $E_x[\tau(y)]$ increases in response to more noise (the reflecting upper boundary may influence this).

2.6 Distribution of APDs

Until here, we have studied the impact of noise on average APD. Clay and DeHaan [9] observed that IBI distribution in clusters of chick heart-cells is skewed towards long intervals. They reproduced the experimentally observed IBI distribution as a hitting time to boundary of a diffusion process with a constant drift, that is, a constant $I(V)$ function. Here we consider the impact of noise on the shape of distribution of APDs for an arbitrary positive monotonic $I(V)$ function. In the following, we will restrict the consideration to specific forms of the diffusion coefficient σ . For completeness, we will first derive APD distribution of cardiac myocytes under conditions corresponding to the situation studied previously [9].

For a constant function $I(V) = vC_m$, $v \in \mathbb{R}$, and a constant diffusion coefficient $\sigma \in \mathbb{R}$, hitting time from v_0 to a can be solved from probability density $p(V, t)$, where $p: \mathbb{R} \times [a, \infty) \rightarrow \mathbb{R}$, describing the probability that membrane potential is V at time t . Probability density p can be solved from the Fokker-Planck equation[26]

⁴It suffices to study arbitrarily small $r > 0$ (Theorem 3 in appendix C). Hence, condition $I'(y) \leq -rC_m$ is essentially the same as the condition that the $I(V)$ function is strictly decreasing on a compact subset of $\mathbb{R}$.

$$\frac{\partial p(V,t)}{\partial t} = \frac{1}{2}\sigma^2 \frac{\partial^2 p(V,t)}{\partial V^2} + v \frac{\partial p(V,t)}{\partial V}, \quad (10)$$

with absorbing boundary at a (that is, $p(a, t) = 0$) and natural boundary at ∞ [11] and the initial condition $p(V, 0) = \delta(V - v_0)$, that is, voltage is initially at v_0 . The method of images yields solution [10,29]

$$p(V,t) = (2\pi\sigma^2 t)^{-1/2} [e^{-(V-v_0+vt)^2/2\sigma^2 t} - e^{2v(a-v_0)/\sigma^2 - (V+v_0-2a+vt)^2/2\sigma^2 t}]. \quad (11)$$

When position b of a reflecting upper boundary is finite, the solution is significantly more complex [10], however, similar methods apply. Equation (11) enables [29] computation of probability density p_{APD} of APDs (that is, probability density of hitting times to voltage a),

$$p_{APD}(t) = \frac{1}{2}\sigma^2 \frac{\partial}{\partial V} \bigg|_{V=a} p(V,t) = \frac{v_0 - a}{\sqrt{2\sigma^2 \pi t^3}} e^{-(v_0 - a - vt)^2/2\sigma^2 t}, \quad (12)$$

where the partial derivative is evaluated at voltage a . The average of probability density (12) is independent of the diffusion coefficient σ [30], however, increase in the diffusion coefficient σ will increase skewness of (12). Clay and DeHaan[9] derive a slightly different result

$p_{CD}(t) = \frac{v}{\sqrt{2\sigma^2 \pi t^3}} e^{-(v_0 - a - vt)^2/2\sigma^2 t}$ (in our notation; note the power of t). However, they estimate that $v = (v_0 - a)/\bar{\tau}$, where $\bar{\tau}$ is the average APD, which yields $p_{CD}(t) = t p_{APD}(t)/\bar{\tau} \approx p_{APD}$. Hence, equation (5) of [9] is a good approximation of the exact result (12), and we believe that their other analysis is valid.

Next we generalize our considerations to an arbitrary monotonic $I(V)$ function in the presence of a specific form of diffusion coefficient. This is enabled by the observation that we can transform a diffusion process Z_t of form

$$dZ_t = -I(Z_t)/C_m dt + \sqrt{\alpha I(Z_t)/C_m} dB_t, \quad (13)$$

where $\alpha \in \mathbb{R}^+$, to the standard Brownian motion with constant drift: Process Z_t induces through an infinitesimal generator a local martingale (p. 313 in [32])

$$M_t = f(Z_t) - f(z_0) - \frac{1}{C_m} \int_0^t \left(\frac{1}{2} \alpha f''(Z_s) - f'(Z_s) \right) I(Z_s) ds, \quad Z_0 = z_0. \quad (14)$$

Define the stochastic time transform $T(t) = \int_0^t I(Z_s)/C_m ds$ that is continuous and monotonically increasing (and thus injective and invertible), $T(0) = 0$ and $T(\infty) = \infty$. In particular, for T^{-1} equation (14) yields

$$\begin{aligned} M_{T^{-1}(t)} &= f(Z_{T^{-1}(t)}) - f(z_0) - \frac{1}{C_m} \int_0^{T^{-1}(t)} \left(\frac{\alpha}{2} f''(Z_s) - f'(Z_s) \right) I(Z_s) ds \\ &= f(Z_{T^{-1}(t)}) - f(z_0) + \int_0^t \left(\frac{\alpha}{2} f''(Z_{T^{-1}(s)}) - f'(Z_{T^{-1}(s)}) \right) ds. \end{aligned} \quad (15)$$

Equation (15) shows that diffusion process (13) is a random time transform of Brownian motion with constant drift, defined by $dY_t = -dt + \sqrt{\alpha} dB_t$. Hence, the stochastic time transform T maps process Y_t to process Z_t with non-constant drift $-I(Z_t)/C_m$, that is, $Z_{T^{-1}(t)}$ equals Y_t in law.

Transform T enables the mapping of APD distribution of process Y_t (given by equation (12)) to APD distribution of process Z_t . The form of transform T shows that the $I(V)$ function modulates APD distribution. When the $I(V)$ function is positive and decreasing, T maps APD

distribution of process Y_t so that APD distribution of process Z_t becomes more skewed towards long intervals (note that Z_t is decreasing on average). When the $I(V)$ function is positive and increasing, T maps APD distribution of process Y_t so that APD distribution of process Z_t becomes more skewed towards short intervals. Hence, the $I(V)$ function modulates the shape of APD distribution for a general $I(V)$ function. This result also shows that skewness of APD distribution increases with more noise for most monotonic $I(V)$ functions with this particular form of the diffusion coefficient. This leads us to expect that APD distribution is skewed in general.

3 Application to ventricular myocytes

3.1 Canine ventricular myocytes

As an application of the above considerations, we examine the response of APD to voltage noise in a canine ventricular myocyte. In the following, we assume (as a simplification) that the duration of an AP prior to the plateau is constant. We constrain the diffusion process (2) describing membrane potential V to interval $(-80, 200]$ mV. Reflecting upper boundary at 200 mV is set above the typical reversal potential of L-type Ca^{2+} current around 125 mV [33], and it has essentially no influence on the noise response of APD.

First, we need to estimate the $I(V)$ function and diffusion coefficient of diffusion process (2). To obtain a realistic $I(V)$ function, a low-order polynomial is fitted to simulated total membrane current in the GW model during an AP at 1 Hz pacing. A minimal form of the $I(V)$ function (Fig. 2B) is given by a second order polynomial $I(V) = 0.0004854V^2 - 0.01086V + 0.10953$, which reproduces the shape of the AP well (Fig. 2). However, it does not have a fixed point corresponding to diastolic membrane potential. A better fit is obtained by a fifth order polynomial (Fig. 2), however, the results on noise response of APD are not significantly different and we will employ the second order model.

For simplicity, we assume that voltage noise present on the membrane current is constant during an AP, that is, the diffusion coefficient is constant. In Fit 1, the diffusion coefficient σ is measured as standard deviation of total membrane current in the GW model during plateau, which yields values [0.0245; 0.0475; 0.1068; 0.2008] corresponding to [125;500;2,000;12,500] CaRUs. The diffusion coefficient σ can also be estimated by fitting simulated APD distributions to those obtained from the GW model. Values of σ estimated employing this method (Fit 2) are [0.035; 0.085; 0.19; 0.32]. Based on these estimated diffusion coefficients, equations (3) and (4) yield average and CV of APD.

APD distribution shapes from the GW model and from the diffusion processes are compared in Fig. 3. The general shape of APD distribution is determined by the $I(V)$ function, however, the diffusion coefficient modulates the characteristics of the distribution. Fig. 3A–B shows that the shape of APD distribution in the GW model is accurately reproduced by a diffusion process based on Fit 2, while the diffusion process based on Fit 1 underestimates the width of APD distribution. At a low noise level, the shape of APD distribution is nearly Gaussian, while at a high noise level, APD distribution is skewed towards long APDs (Fig. 3C–D). While the highest frequency of APDs shifts towards short intervals, average APD increases. This is consistent with the expectation that increased noise level would typically shorten APD, however, increased skewness of APD distribution towards long intervals results in an increase in average APD.

Fig. 4 compares the APD statistics in the GW model to those in the two diffusion processes, Fits 1 and 2. In all three models, average APD is increased with increased noise level (Fig. 4A). While average APD saturates at high noise level in the GW model, in the diffusion process models it always increases with noise level. Fig. 4B shows that the diffusion process based on

Fit 2 reproduces CV of the GW model almost exactly, while the diffusion process based on Fit 1 underestimates CV. In each case, CV increases linearly with the noise level. In a similar way, relative skewness of APD distribution increases with noise level in all three models (Fig. 4C–D). Figures 3 and 4 show that both qualitative and quantitative statistical properties of the APD distribution in the GW model are reproduced by a diffusion process to a significant degree.

The noise response of average APD can be explained by our theoretical considerations: In the second order model, the $I(V)$ function is strictly decreasing for $V \in [-80, 11]$ mV and increasing for $V > 11$ mV. Hence, at voltages below 11 mV, APD increases with more noise; whereas at voltages above 11 mV, APD decreases with more noise. Initially at 6 mV, voltage spends most of the time in range $[-80, 11]$ mV and, consequently, average APD increases.

3.2 Early after-depolarizations

An EAD is an abnormal depolarization of membrane potential occurring during phase 2 (plateau) or phase 3 (rapid repolarization) of the cardiac AP [33]. In experiments, an increased occurrence of EADs is often associated with prolongation of APD [18,19]. In particular, increased beat-to-beat variability coupled with prolonged APD has been connected with arrhythmogenesis [34,35]. Both in the GW model and in the diffusion process models, increased noise level skews the APD distribution towards long APDs (Fig. 4D). Thus, long APDs predisposing a myocyte to EADs become more frequent with increased noise level.

In the diffusion process framework, relation of the frequency of EADs to the noise can be examined analytically. Theorem 4 (appendix D) proves that the probability of hitting a voltage higher than the present voltage is increased in response to more noise if the $I(V)$ function is positive. That is, more noise increases the probability of a second depolarization when the total membrane current is outward. This is not an obvious result, as is demonstrated by the fact that the opposite is true for a negative $I(V)$ function [30].

Fig. 5A shows the steady state AP shapes at four pacing rates in a deterministic canine ventricular myocyte model [36] (based on [2], which is modified to have a steady state and appropriate APD pacing rate dependence). A corresponding diffusion process can be formulated by fitting the $I(V)$ function to the current-voltage relationship during a steady state AP in the model of [36]. Fig. 5B shows CVs computed using the diffusion process. At a constant noise level (the same diffusion coefficient at all pacing rates), CV increases slightly as the pacing rate is slowed from 2 Hz to 0.5 Hz, even though APD increases due to increased pacing rate (Fig. 5B). At 0.25 Hz pacing, CV increases significantly, which suggests that the AP shape is more sensitive to noise and that the presence of stochastic fluctuations in membrane current occasionally induces EADs at low pacing rates. In conclusion, our study suggests that increased voltage noise will increase the frequency of EADs.

4 Discussion

4.1 Response to noise

Traditionally, electrophysiological properties of a cardiac myocyte have been described by deterministic mathematical models based on ordinary differential equations [37,38]. While this approach has yielded many insightful results, it cannot be used to study the influence of noise on average properties of a myocyte. To examine the influence of noise on, e.g., APD distribution, the two main methods are: (1) a fully stochastic model describing stochastic gating of individual ion channels; or (2) an approximative model containing certain degree of stochasticity. The GW model has a fully stochastic dyadic calcium subsystem [5], otherwise it is a deterministic model. The diffusion processes based on the GW model are approximative models in which membrane potential is influenced by Gaussian voltage noise.

In this study, we employ the GW model to examine the response of APD distribution to noise in an ionic model. We also develop a method based on a diffusion process to examine the statistical properties of APD analytically in the presence of voltage noise. The noise response of APD in the GW model is to a significant degree reproduced using a diffusion process. The main finding of this study is that average and skewness of APD distribution are influenced in a systematic way by a variation in the noise level. The results suggest a novel mechanism by which the voltage noise may influence APD.

In the GW model[5], average APD increases with increased noise level. Using the diffusion process framework, we provide a possible explanation (section 2.5; note the role of boundary condition) for the behavior observed in the GW model simulations: when the $I(V)$ function is a strictly decreasing function of voltage, more noise increases APD; whereas when the current is an increasing function of voltage, more noise will decrease APD. Thus, the shape of the $I(V)$ function modulates the response of APD to voltage noise. While voltage fluctuations are symmetric about the mean, the response to fluctuations is not symmetric due to non-linear $I(V)$ function (Sec. 2.5).

Example on Section 2.5 shows that the presence of stochastic independent, identically and symmetrically distributed shocks in voltage will on average influence APD in the same way as the presence of voltage noise with Gaussian distribution. This suggests the conjecture that the presence of voltage noise with a symmetric distribution influences the statistical properties of APD distribution as is described in Sec. 2.5. Hence, noise response of APD to a symmetric voltage noise may depend more on the shape of the $I(V)$ function than on the specifics of voltage noise.

The influence of noise on average APD is systematic but rather modest: Our results (Fig. 4) suggest that at the experimentally observed physiological noise level (CV $2.3\% \pm 0.4\%$ [1]), APD is increased by 2.3 ms compared to APD in a noiseless model. A higher noise level is observed when I_{K_r} is blocked. Under these conditions, CV increases to 10% due to gating noise in other ion channels[1]. According to our study, increase of roughly 8 ms in average APD, that is 2.4% of APD, takes place in response to a noise level corresponding to 10% CV level. In addition, APD distribution becomes significantly skewed towards long intervals at this noise level.

The scenario studied in this study - in which increased voltage noise level increases average and more importantly skewness of APD distribution - may be relevant to the cellular basis of heart failure. It is known that EAD frequency is increased in ventricular myocytes isolated from the failing heart[39] and that AP shapes are more variable in heart failure than in normal myocytes [40,41]. Failing human left ventricular myocytes show unchanged average L-type calcium current density compared to normal, while the number of L-type calcium channels is reduced [42,43]. Under these conditions, the current through a single channel is increased and current fluctuations due to a single ion channel are larger, that is, level of gating noise is increased. Our results suggest that this increased noise level leads to an increase in average and skewness of APD distribution, which predispose a myocyte to EADs. In particular, skewness of APD distribution may become significant at high noise levels (Fig. 4). While electrotonic interactions between neighboring myocytes may suppress the propagation of EADs[1], it is important to describe the mechanisms of EAD induction as completely as possible at single myocyte level.

4.2 Comparison with previous studies

Previous studies[1,9,3,4] have examined the beat-to-beat variation in APD and IBI employing experiments and mathematical modeling. In the following, we will compare our results with those from these studies.

Zaniboni et al.[1] experimentally studied beat-to-beat variation of APD in guinea pig cardiac ventricular myocytes. In a statistic of 132 myocytes, the average steady state APD increased with increased standard deviation of APD[1]. This agrees with our finding that APD increases in response to more noise. However, in experiments of [1] CV was almost independent of average APD, which suggests that different myocytes had similar internal noise levels. Zaniboni et al.[1] fit the normal distribution to the observed APD distribution, which is consistent with our result that at low noise level normal distribution approximates the skewed distribution (Fig. 3). Nevertheless, supported by the results of [9] we believe that a skewed distribution is more appropriate than the normal distribution in the description of APD distribution.

Clay and DeHaan [9] studied mean IBI in clusters of chick cardiac ventricular cells experimentally. They observed that IBI is influenced by membrane noise and that IBI in small cell clusters is more skewed towards long IBIs than in large clusters. A small cell cluster has higher internal noise level than a large cluster, which suggests that current noise skews IBI distribution towards long intervals. In addition, Clay and DeHaan [9] reproduced the experimentally-observed IBI mathematically using a diffusion process with a constant $I(V)$ function. Here we find that APD distribution in the normal canine cardiac myocytes becomes more skewed at higher noise levels in the GW model and in the diffusion process models, generalize the results of [9] to an arbitrary monotonic $I(V)$ function, and correct a slight error in [9].

Skaugen and Walløe [3] formulated a stochastic, mathematical ionic model of neural membrane and observed a stochastic resonance like phenomenon in spontaneous firing frequency. In [3], at large number of sodium channels (>200) and at all potassium channels numbers, spontaneous firing frequency decreases as noise level increases (the number of channels decreases; Figures 3 and 4 in [3]). The situation in [3] is mirror symmetric to the one we consider: Assuming that the I-V relationship in [3] is such that membrane current initially decreases (inward current increases) with voltage (as suggested by Fig. 1 of [3]), we can apply our results in the initial phase of the AP. In particular, our results suggest that the increased noise level should decrease the time until the next firing, which is consistent with behavior in Fig. 2 (at >200 channels) and in Fig. 3 in [3]. However, this conclusion only applies to the initial stage of the AP, and cannot explain the firing frequency completely.

Wilders and Jongsma [4] test the hypothesis that random fluctuations in IBI in pacemaker cells arise from the stochastic behavior of the membrane ionic channels in an experimental and simulation study. In their ionic, mathematical model of a pacemaker cell, the stochastic open-close kinetics of the individual membrane ionic channels were incorporated. Based on the model simulations, they concluded that fluctuations in IBI of single sinoatrial node pacemaker cells are due to the stochastic open-close kinetics of ion channels. Furthermore, IBI in [4] is approximately normally distributed, which is consistent with our observation that APD distribution is nearly normal in the limit of small noise. Nevertheless, Fig. 4C of [4] showing experimental distribution of IBIs suggests that the distribution is skewed towards long IBIs.

In a simulation study, Tanskanen et al.[7] proposed that current fluctuations, especially those of L-type calcium channels gating in mode 2, can induce EADs under β -adrenergic stimulation. Here we prove that when the $I(V)$ function is positive, more noise will make EADs more frequent (appendix B), and that increased noise level skews the APD distribution towards long APDs when the $I(V)$ function is decreasing. While both the EAD mechanism discussed here and the mechanism described in [7] are based on current fluctuations, the sources of noise are partially different. Here, we assume that channel gating is fast, whereas in the study of [7] the main component of gating noise was due to the slow gating of L-type calcium channels in mode 2. Nevertheless, the method developed here can be applied to L-type calcium channels gating

in mode 1, and it may in part explain the EAD generation observed in [7]. In the presence of relatively high noise level, induction of occasional prolonged APs may be a contributing mechanism in addition to the standard mechanism of deterministically prolonged plateau phase leading to recovery of L-type Ca^{2+} channels[44].

While a stochastic, biophysically detailed model, such as models of [3,5], can represent gating noise more accurately than the diffusion process studied here, simulations of such models do not provide general characterization of the noise response of APD. Contrary to this, complete characterization of noise response in a diffusion process is possible and it provides a basis for analysis in more biophysically-detailed models. In particular, the diffusion process models suggest that null hypothesis should be that APD is distributed according to a skewed distribution instead of the normal distribution.

4.3 Shortcomings

The GW model only incorporates stochastic calcium subsystem, the other components of the model are deterministic. However, we are not aware of any fully stochastic model of a cardiac myocyte. The diffusion process framework on the other hand enables rigorous proofs on the statistical properties of the system studied, but the method does not describe the detailed mechanisms of ion channel gating. The method works best when applied to a regime, in which a 1-1 mapping between time and voltage exists, which is typically the case during the plateau phase. A more realistic diffusion process would include recovery of L-type calcium current from inactivation, which likely increases the dispersion of APD due to strong feedback on membrane potential through L-type calcium current. An issue related to this is the time evolution in input resistance of sarcolemma, which may influence the noise response.

4.4 Conclusions

In this manuscript, we present both simulation and rigorous theoretical results on the impact of noise on statistical properties of APD distribution in cardiac myocytes. The major findings are: (1) increased voltage noise typically increases average and skewness of APD distribution in a canine ventricular myocyte, which may predispose the myocyte to EADs at high noise levels; (2) a simple diffusion process reproduces the distribution of APDs in the biophysically-detailed ionic model of AP in cardiac ventricular myocyte[5]. Comparison of our results with those from experimental studies shows a high level of agreement. The results suggest that fluctuations of ionic currents may have a significant influence on the statistical properties of APD in cardiac myocytes.

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Glossary

a	Lower boundary for admissible voltages
AP	Action potential
APD	

	Action potential duration at 90% repolarization
b	Upper boundary for admissible voltages
B_t	Brownian motion
CaRU	Calcium Release Unit
C_m	Specific conductance of membrane
CV	Coefficient of Variation
d_0	Duration of APD before plateau
EAD	Early After-Depolarization
EC coupling	Excitation-Contraction coupling
$E_x[\cdot]$	Expectation for a process starting from value x
ϕ	The decreasing fundamental solution of equation (8)
The GW model	Canine ventricular myocyte model of [5]
IBI	Interbeat interval
$I(V)$	The $I(V)$ function describing current at voltage V
n_{CaRU}	Number of CaRUs
p	Probability density
P_x	Probability for a process starting from value x
p_{APD}	Probability density of APDs
σ	The diffusion coefficient
$\tau(a)$	Hitting time to voltage a

T_x	Deterministic hitting time to voltage x
ΔT_X	Noise response of hitting time T_x
V_t	Membrane potential at time t
x	Initial voltage

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A Average APD is influenced by noise level

In the following appendices, we assume that X and $\tilde{X}$ are Itô-processes denned on $J = [a, b]$ by $dX_t = \mu(X_t)dt + \sigma(X_t)dB_t$, and by $d\tilde{X}_t = \mu(\tilde{X}_t)dt + \tilde{\sigma}(\tilde{X}_t)d\tilde{B}_t$. Drift $\mu : \mathbb{R} \rightarrow \mathbb{R}$, and diffusion coefficients $\sigma : \mathbb{R} \rightarrow \mathbb{R}^+$ and $\tilde{\sigma} : \mathbb{R} \rightarrow \mathbb{R}^+$ are assumed to be continuously differentiable. Here

drift μ corresponds to the $I(V)$ function in the main text by equation $\mu(z) = -I(z)/C_m$. Hitting times τ for process X and $\tilde{\tau}$ for process $\tilde{X}$ to $y \in J$ are defined by $\tau(y) = \inf\{t \geq 0 : X_t = y\}$, and $\tilde{\tau}(y) = \inf\{t \geq 0 : \tilde{X}_t = y\}$, where $y \in \mathbb{R}$. Differential operators $\mathcal{A}$ and $\tilde{\mathcal{A}}$ are defined on $C^2(\mathbb{R})$ by

$$(\mathcal{A}f)(z) = \mu(z) \frac{\partial}{\partial z} f(z) + \frac{1}{2} \sigma^2(z) \frac{\partial^2}{\partial z^2} f(z),$$

$$(\tilde{\mathcal{A}}f)(z) = \mu(z) \frac{\partial}{\partial z} f(z) + \frac{1}{2} \tilde{\sigma}^2(z) \frac{\partial^2}{\partial z^2} f(z),$$

where $z \in J$. We denote by ϕ the decreasing fundamental solution of equation (8) subject to the boundary condition $\phi'(b)/s(b) = 0$, where $s(y) = \exp(-\int_a^y 2\mu(z)/\sigma^2(z) dz)$ and $y \in J$. Function $\tilde{\phi}$ denotes the fundamental solution of the corresponding equation with $\tilde{\sigma}$. We are ready to state the first theorem, which proves that more noise decreases Laplace transform of hitting time τ .

Theorem 1

Assume drift $\mu(z) < 0$ and $0 < \sigma(z) < \tilde{\sigma}(z)$ for all $z \in J$. If the decreasing fundamental solution ϕ is concave in interval J ,

$$E_x[e^{-r\tilde{\tau}(y)}] \leq E_x[e^{-r\tau(y)}] \quad (\text{A.1})$$

for all $x, y \in J$, where τ and $\tilde{\tau}$ are hitting times defined above. If the decreasing fundamental solution ϕ is convex in interval J ,

$$E_x[e^{-r\tilde{\tau}(y)}] \geq E_x[e^{-r\tau(y)}] \quad (\text{A.2})$$

for all $x, y \in J$, where τ and $\tilde{\tau}$ are hitting times defined above.

Proof

First, observe that since $\tilde{\phi}$ is concave and $\tilde{\sigma}(z) > \sigma(z)$,

$$((\mathcal{A} - r)\tilde{\phi})(z) = ((\mathcal{A} - \tilde{\mathcal{A}})\tilde{\phi})(z) = \frac{1}{2}(\sigma^2(z) - \tilde{\sigma}^2(z))\tilde{\phi}''(z) \geq 0$$

for all $z \in J$. Dynkin's formula and Itô's theorem (e.g. [23]) state that

$$E_x[e^{-r\tau(y)} \tilde{\phi}(X(\tau(y)))] = \tilde{\phi}(x) + E_x\left[\int_0^{\tau(y)} e^{-rs} \mathcal{A}\tilde{\phi}(X_s) ds\right] \geq \tilde{\phi}(x).$$

On the other hand, $E_x[e^{-r\tilde{\tau}(y)} \tilde{\phi}(X(\tilde{\tau}(y)))] = \tilde{\phi}(y) E_x[e^{-r\tau(y)}] = \tilde{\phi}(y) \frac{\phi(x)}{\phi(y)}$, hence

$$\frac{\phi(x)}{\phi(y)} \geq \frac{\tilde{\phi}(x)}{\tilde{\phi}(y)},$$

which together with equation (7) proves (A.1). Proof of (A.2) is similar.

B Convexity and concavity of the decreasing fundamental solution

Theorem 2

The second derivative of the fundamental decreasing solution ϕ is given by

$$\frac{1}{2}\sigma^2(x)\frac{\phi''(x)}{s(x)} = \frac{r\phi(b)}{s(b)} + \int_x^b \theta'(y)\frac{\phi'(y)}{s(y)}dy, \quad (\text{B.1})$$

where $\theta(z) = \mu(z) - rz$ and $x, z \in J$.

Proof

Subtracting and adding a term to equation (8), we obtain

$$\frac{1}{2}\sigma^2(x)\frac{\phi''(x)}{s(x)} = r\left(\frac{\phi(x)}{s(x)} - x\frac{\phi'(x)}{s(x)}\right) - \theta(x)\frac{\phi'(x)}{s(x)},$$

where $\theta(x) = \mu(x) - rx$. Denoting $m'(x) = 1/(s(x)\sigma^2(x))$ and by differentiating,

$$\frac{d}{dx}\left[\frac{\phi(x)}{s(x)} - x\frac{\phi'(x)}{s(x)}\right] = \theta(x)\phi(x)m'(x).$$

Integration over (x, b) and applying the boundary condition yields

$$r\left[\frac{\phi(x)}{s(x)} - x\frac{\phi'(x)}{s(x)}\right] = \frac{r\phi(b)}{s(b)} - r\int_x^b \theta(y)\phi(y)m'(y)dy,$$

and we obtain

$$\frac{1}{2}\sigma^2(x)\frac{\phi''(x)}{s(x)} = \frac{r\phi(b)}{s(b)} - r\int_x^b \theta(y)\phi(y)m'(y)dy - \theta(x)\frac{\phi'(x)}{s(x)}.$$

According to the canonical representation [11] of the differential equation (8), we get

$$r\int_x^b \phi(y)m'(y)dy = -\frac{\phi'(x)}{s(x)}, \text{ and finally}$$

$$\frac{1}{2}\sigma^2(x)\frac{\phi''(x)}{s(x)} = \frac{r\phi(b)}{s(b)} + r\int_x^b (\theta(x) - \theta(y))\phi(y)m'(y)dy,$$

from which Fubini's theorem yields equation (B.1).

C Connection of $E_x[\tau]$ to $E_x[e^{-r\tau}]$

Theorem 3

Assume that $0 < \sigma(z) < \tilde{\sigma}(z)$ for all $z \in [a, b]$ and that both $E_x[\tau]$ and $E_x[\tilde{\tau}]$ are finite. Further assume that for a given x , such $\alpha > 0$ exists that $E_x[e^{-r\tau}] \leq E_x[e^{-r\tilde{\tau}}]$ for each $r \in (0, \alpha)$. Then,

$$E_x[\tau] \geq E_x[\tilde{\tau}] \quad (\text{C.1})$$

If for a given x such $\alpha > 0$ exists that $E_x[e^{-r\tau}] \geq E_x[e^{-r\tilde{\tau}}]$ for each $r \in (0, \alpha)$, inequality

$$E_x[\tau] \leq E_x[\tilde{\tau}], \quad (\text{C.2})$$

holds.

Proof

Since $E_x[e^{-r\tau}] \leq E_x[e^{-r\tilde{\tau}}]$ for every $r \in (0, \alpha)$, inequality $(E_x[e^{-\varepsilon\tau}] - 1)/\varepsilon \leq (E_x[e^{-\varepsilon\tilde{\tau}}] - 1)/\varepsilon$ holds for any $\varepsilon \in (0, \alpha)$. When ε is taken to zero, the inequality holds, and the definition of derivative gives $-E_x[\tau] \leq -E_x[\tilde{\tau}]$, from which the inequality (C.1) follows. Inequality (C.2) is proven in a similar way.

D Increased noise level increases EAD likelihood

The next theorem proves that increased noise influences the future membrane potential asymmetrically, by decreasing the probability of repolarization. Proof is a modification of Theorem 2 of [30] to the case $\mu(x) < 0$.

Theorem 4

Assume that drift $\mu(x) < 0$ and $0 < \sigma(x) \leq \tilde{\sigma}(x)$ for all $x \in [a, b]$. Given $y \in \mathbb{R}$ such that $a \leq y < b$, probabilities of hitting times τ and $\tilde{\tau}$ satisfy inequalities

$$P_x[\tilde{\tau}(b) < \tilde{\tau}(y)] \geq P_x[\tau(b) < \tau(y)], \quad (\text{D.1})$$

$$P_x[\tilde{\tau}(b) > \tilde{\tau}(y)] \leq P_x[\tau(b) > \tau(y)] \quad (\text{D.2})$$

for all initial values $x \in (y, b]$.

Proof

According to [11], $P_x[\tau(b) < \tau(y)] = (S(x) - S(y))/(S(b) - S(y))$, where

$S(z) - S(y) = \int_y^z s(t)dt$, and $s(t) = \exp(-\int_t^b \frac{2\mu(\iota)}{\sigma^2(\iota)} d\iota)$, $t \in \mathbb{R}$. Defining $u(x) = P_x[\tau(b) < \tau(y)]$, we observe that

$$\frac{d^2}{dx^2} u(x) = \frac{d^2}{dx^2} P_x[\tau(b) < \tau(y)] = -\frac{2\mu(x)}{\sigma^2(x)} \frac{s(x)}{S(b) - S(y)} \geq 0,$$

since $\mu(y) \geq 0$ on $y \in (a, b)$. Since $(\mathcal{A}u)(x) = 0$, we obtain

$$(\tilde{\mathcal{A}}u)(x) = ((\tilde{\mathcal{A}} - \mathcal{A})u)(x) = \frac{1}{2}(\tilde{\sigma}^2(x) - \sigma^2(x))u''(x) \geq 0$$

for all $x \in (a, b)$. Applying Dynkin's formula (Øksendal, 2003) yields

$$E_x[u(\tilde{X}(\min\{\tilde{\tau}(b), \tilde{\tau}(y)\}))] = u(x) + E_x \int_0^{\min\{\tilde{\tau}(b), \tilde{\tau}(y)\}} \tilde{\mathcal{A}}u(\tilde{X}_s) ds \geq u(x).$$

Therefore $u(x) \leq E_x[u(\tilde{X}(\min\{\tilde{\tau}(b), \tilde{\tau}(y)\}))] = P_x[\tilde{\tau}(b) < \tilde{\tau}(y)]$, proving (D.1). Equation (D.2) is a consequence of (D.1).

Figure 1.

Statistical properties of APD in the GW model [5] at four noise levels, of which 12,500 CaRU case corresponds to the physiological number of CaRUs in a myocyte. The average properties are computed from a data set of 200 APs. (A) A typical, simulated canine left ventricular action potential. Horizontal arrow depicts APD; (B) Average APD (ordinate; ms) as a function of the number of CaRUs n_{CaRU} simulated (abscissa); (C) Average APD (ordinate; ms) as a function of noise level $\sim 1/\sqrt{n_{CaRU}}$ (abscissa); (D) CV (ordinate; %) as a function of noise level $\sim 1/\sqrt{n_{CaRU}}$ (abscissa); (E) CV (ordinate; %) plotted against the number of CaRUs simulated (abscissa); (F) Average APD (ordinate; ms) as a function of CV (abscissa).

Figure 2.

Polynomial approximation of the GW model's $I(V)$ function: (A) Shapes of APs in the GW model (dark gray dots), in the fifth order approximation (dashed light gray line), and in the second order approximation (solid black line); (B) Current densities (ordinate; A/F) in the GW model (dark gray dots), in the fifth order approximation (dashed light gray line), and in the second order approximation (solid black line) plotted against voltage (abscissa; mV).

Figure 3.

Comparison of APD (ordinate; ms) distributions in the GW model and in the diffusion process models at four noise levels: (A) APD distributions in the diffusion processes Fit 1 (solid gray line) and Fit 2 (solid dark gray line) compared with the GW model (bars), each corresponding to 2,500 CaRUs; (B) APD distributions in Panel A scaled by peak height and shifted to the same average; (C) APD distributions in Fit 2 at four noise levels corresponding to 12,500 (solid black line), 2,500 (solid gray line), 500 (solid dark gray line) and 125 CaRUs (solid light gray line); (D) APD distributions in Panel C scaled by peak height (marked in an identical way).

Figure 4. Increased noise level increases average, CV and skewness of APD distribution both in the diffusion processes and in the GW model: (A) Dependence of the average APD (ordinate; ms) on noise level $\sim 1/\sqrt{n_{CaRU}}$ (abscissa); (B) CV (ordinate; %) as a function of noise level $\sim 1/\sqrt{n_{CaRU}}$ (abscissa); (C) APD (ordinate; ms) as a function of CV (abscissa; %); (D) Relative skewness (ordinate) of APD as a function of noise level $\sim 1/\sqrt{n_{CaRU}}$ (abscissa).

Figure 5.

Dependence of CV on pacing rate in a diffusion model. (A) Steady state APs in the modified Winslow model [2,36] at 2.0, 1.0, 0.5, and 0.25 Hz pacing rates; (B) CV (ordinate) in the corresponding diffusion process models as a function of pacing rate (abscissa; Hz) at a constant noise level.