An analysis of the shock strength needed to achieve defibrillation in a simplified mathematical model of cardiac tissue

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Abstract

The pumping function of the heart is driven by an electrical wave traversing the cardiac muscle in a well-organized manner. Perturbations to the wave are referred to as arrhythmias. Such arrhythmias can, under unfortunate circumstances, turn into fibrillation. The only known therapy for fibrillation is to reset the heart using a strong electrical shock. This process is referred to as defibrillation and it is routinely used in clinical practice. Despite the importance of this procedure and the fact that it is used frequently, the success rate of defibrillation is not fully understood. For instance, theoretical estimates of the shock strength needed to reset the heart are much higher than what is used in practice. Several authors have pointed out that in theoretical models the strength of the shock can be decreased if the cardiac tissue is allowed to be heterogeneous. In this paper, we address this issue using the bidomain model combined with the Courtemanche model, and we also consider a linear approximation of the Courtemanche model. We present analytical considerations showing that for the linear model, the necessary shock strength needed to achieve defibrillation (defined in terms of a sufficiently strong change of the resting state) decreases as a function of an increasing perturbation of the intracellular conductivities. Qualitatively, these theoretical results compare well with computations based on the Courtemanche model.

1 Introduction

The beating of the human heart is a well-organized operation governed by an electrical wave which traverses the entire cardiac muscle to initiate contraction.

This is a robust process, as it continues for about 80 years on average without maintenance, and versatile in the sense that it adapts smoothly to strongly varying external conditions. However, the heartbeat is not infallible. The regular electrical signal controlling the synchronous contraction of the heart may be disturbed. Such rhythm disturbances are known as arrhythmias and may result in failure to adequately pump blood to the body. Ventricular fibrillation, an arrhythmia wherein the contraction of the heart muscle is completely asynchronous, is especially dangerous. If not treated within minutes, its ultimate consequence is sudden cardiac death [1].

Currently, the only effective means for prevention of sudden cardiac death is defibrillation of the heart by the timely application of a strong electric shock [2, 3, 4]. Significant advances have been made towards an improved understanding of the basic mechanisms by which a shock defibrillates the heart [5, 6, 7]. However, several key aspects of the interaction between an electric shock and the heart remain unclear. Hence, the mechanisms by which shocks terminate arrhythmias are far from fully understood. In recent years, mathematical modeling and simulation have had increasing importance in efforts to further understand the biophysical processes that underlie the generation of lethal arrhythmias and their termination via defibrillation [8, 9]. Simulations have offered not only increased understanding as to the mechanisms underlying defibrillation, but also valuable estimates of the amount of energy necessary to terminate fibrillation in a specific context [10, 11, 12].

Cardiac tissue, a functional syncytium, can be modeled mathematically via a continuum approximation, and fundamental ionic kinetics at the cell level by corresponding membrane models. However, when cardiac tissue is modeled via the bidomain approximation as a *homogenous* substrate having uniform conductivities controlling current flow, simulations may result in an overestimation of the shock strength required for defibrillation [11]. Indeed, the assumption of homogeneity represents a simplification, as heterogeneities (whether represented by alterations of conductivities or via another approach) are realistic in terms of actual tissue structure. Such a simplification may yield results which are of questionable physiological relevance and limited clinical utility. In contrast, the inclusion of heterogeneities provides more realistic and lower estimates of the energy necessary to successfully defibrillate a particular substrate [13].

In this paper, we analyze the problem initially presented by Plank et al [14, 13, 15] and Morgan et al [16]. These papers examine results obtained from simulations employing the bidomain model with cell membrane kinetics represented by the models of Courtemanche et al [17]. As outlined above, of particular interest is the result that the shock strength necessary to defibrillate decreases as tissue variability increases. Our aim is to contribute to a better understanding of this effect by providing theoretical estimates in addition to further numerical experiments.

The Courtemanche ionic model presents significant challenges to mathematical analysis. We have therefore introduced a linear approximation to the full model which we employ in its stead. In [18], it was demonstrated that this linear model provides fairly accurate solutions in the presence of strong shocks.

In this paper, we first present computational results examining the influence of random perturbations to the intracellular conductivities using both the linear and the full Courtemanche models. Secondly, we provide analytical estimates for the linear model, showing that an increase in the variability of the intracellular conductivities leads to a decrease in the necessary shock strength. This theoretical result is thus in agreement with the earlier numerical observations.

For the purposes of mathematical analysis, we make certain assumptions regarding initial conditions. We assume that the tissue is at rest, and then analyze what shock strength is necessary to effect a sufficiently large change in the transmembrane potential as compared to a predefined threshold. This starting-point is motivated by the assumption that the resting state is the most stable state the system can assume, and therefore the hardest state to significantly perturb. It follows that an estimate for the necessary energy to defibrillate; that is, initiate sufficient perturbation of the tissue, based on the resting state should also apply for any other initial, less stable state.

2 The mathematical models

We consider a 2D version of a problem presented by Morgan et al [16] (see also [13, 14]). Let the domain be given by $\Omega = (0,4) \times (0,2)\,\mathrm{cm}^2$ with boundary $\partial\Omega$, $t \in (0,T]$, and consider the bidomain model

$$v_t = \nabla\cdot(m_i \nabla v) + \nabla\cdot(m_i \nabla u) - I(v,s), \tag{1}$$

$$I_e = \nabla\cdot(m_i \nabla v) + \nabla\cdot(m_{i+e} \nabla u), \tag{2}$$

$$s_t = F(v,s), \tag{3}$$

with the boundary conditions

$$(m_i \nabla v + m_i \nabla u)\cdot n = 0, \quad (m_i \nabla v + m_{i+e} \nabla u)\cdot n = 0 \quad \text{on } \partial\Omega, \tag{4}$$

and the initial condition

$$v(\cdot,\cdot,0) = v_0.$$

In the system above $v = v(x,y,t)$ is the transmembrane potential, $u = u(x,y,t)$ is the extracellular potential, $I_e = I_e(x,y)$ is a prescribed extracellular current (the defibrillation shock, scaled by $(C_m\chi)^{-1}$), $m_i = m_i(x,y)$ and $m_e = m_e(x,y)$ are the intra– and extra–cellular conductivities and $m_{i+e} = m_i + m_e$. The conductivities are given by:

$$m_i = \begin{pmatrix} \sigma_{ix} & 0 \\ 0 & \sigma_i \end{pmatrix} = \frac{1}{C_m\chi}\begin{pmatrix} \hat{\sigma}_{ix} & 0 \\ 0 & \hat{\sigma}_{iy} \end{pmatrix},$$

$$m_e = \begin{pmatrix} \sigma_{ex} & 0 \\ 0 & \sigma_{ey} \end{pmatrix} = \frac{1}{C_m\chi}\begin{pmatrix} \hat{\sigma}_{ex} & 0 \\ 0 & \hat{\sigma}_{ey} \end{pmatrix},$$

where C_m is the membrane capacitance per unit area and χ is the membrane surface to volume ratio. Furthermore, I denotes the total ionic current density,

and F represents the electrochemical processes underpinning each action potential. From a physiological point of view, the natural boundary conditions are given by no-flow conditions on both the intra- and extracellular potential. The form given in (4) above is derived from these conditions.

In the present paper, we will use the Courtemanche model [17] as modified by [13] (we employ $B = 0$ in their model), and a linear model introduced in [18]. We will assume that (see [16])

$$\chi = 1400 \text{ cm}^{-1}, \; C_m = 1.0\,\mu\text{F/cm}^2,$$

and

$$\hat{\sigma}_{ex} = 6.25, \quad \hat{\sigma}_{ey} = 2.36, \quad \hat{\sigma}_{ix} = 1.46N(x,y), \quad \hat{\sigma}_{iy} = 0.19N(x,y),$$

all in mS/cm. Here N is given by

$$N = 1 + \varphi\eta.$$

where η is a random number uniformly distributed between -0.9 and 0.9, and φ is a control parameter ranging from 0 to 1.

The full bidomain model coupled to complex and realistic models of cell electrophysiology is hard to approach via analytical tools. However, we have established in [18] that a linear model of the total ionic current density provides good approximations in the context of analyzing defibrillation.

To this end, assume that the initial state v_0 is a resting state. The linear model invokes the approximation

$$I(v,s) = \alpha(v - v_0)$$

where α will be specified below. Introducing $v := v - v_0$, we then obtain the system

$$v_t = \nabla\cdot(m_i \nabla v) + \nabla\cdot(m_i \nabla u) - \alpha v, \tag{5}$$

$$I_e = \nabla\cdot(m_i \nabla v) + \nabla\cdot(m_{i+e} \nabla u). \tag{6}$$

We equip the system defined by (5) and (6) with the boundary conditions given by (4) and the initial condition $v(0,\cdot) = 0$.

In order to have a unique solution of the extracellular potential u, we impose the additional requirement

$$\int_\Omega u = 0, \tag{7}$$

and the corresponding compatibility condition for the extracellular current I_e:

$$\int_\Omega I_e = 0.$$

Moreover, it follows from (4), (5), and the fact that $\int v(0) = 0$ that

$$\int_\Omega v = 0. \tag{8}$$

Note that this observation does not hold in the nonlinear case.

We introduce the standard $L^2(\Omega;\mathbb{R}^n)$ inner product and norm:

$$\langle u, v\rangle = \int_\Omega u \cdot v \,\mathrm{d}x, \quad \|u\|^2 = \langle u, u\rangle.$$

A natural variational form of the system defined by (5) and (6) reads: find $v(t) \in V$ and $u(t) \in V$ such that

$$\langle v_t, w\rangle + \langle m_i \nabla v, \nabla w\rangle + \langle m_i \nabla u, \nabla w\rangle + \langle \alpha v, w\rangle = 0 \qquad \forall\, w \in V, \quad (9)$$

$$\langle m_i \nabla v, \nabla q\rangle + \langle m_{i+e} \nabla u, \nabla q\rangle = -\langle I_e, q\rangle \qquad \forall\, q \in V. \quad (10)$$

In Figure 1 we have compared the solution at time $t = 5$ms using the Courtemanche model and the linear model with $\alpha = 0.05$. In the computations, we have used a uniform mesh with $\Delta x = \Delta y = 2$mm and $\Delta t = 0.01$ms. We have used a common random field η, and then varied the strength of the variations in conductivity by choosing $\varphi = 0, 0.3, 0.6, 0.9$. Furthermore, we have applied the electrical shock (scaled by $1/C_m\chi$) given by:

$$I_e = \left\{ \begin{array}{cc} 10^4\mathrm{mV/ms} & (x,y) \in [0, 0.95] \times [0.1, 1.05], \\ -10^4\mathrm{mV/ms} & (x,y) \in [3.9, 0.95] \times [4, 1.05], \\ 0 & \text{for all other } (x,y). \end{array} \right\}$$

We observe that for all choices of φ, the results of the linear model and the Courtemanche model are quite similar. Further comparison of these models are provided in [18]. The numerical method used to solve the problem is presented in Section 4.

3 A theoretical requirement on the necessary strength of I_e

We *assume* that defibrillation is achieved at time $t = t^*$ provided that the norm of v exceeds a certain threshold v^*; i.e. provided that

$$\|v(t^*)\| \geqslant v^*.$$

The aim of this section is to provide an upper bound of the norm of v solving (9) and (10), in terms of the strength of the defibrillation shock I_e. The bound will take the form

$$\|v(t)\| \leqslant c(t)\, \|I_e\|$$

where the function $c(t)$ is to be estimated. Combining the bound and the threshold, we can conclude that a necessary condition for defibrillation is given by

$$\|I_e\| \geqslant \frac{v^*}{c(t^*)}. \quad (11)$$

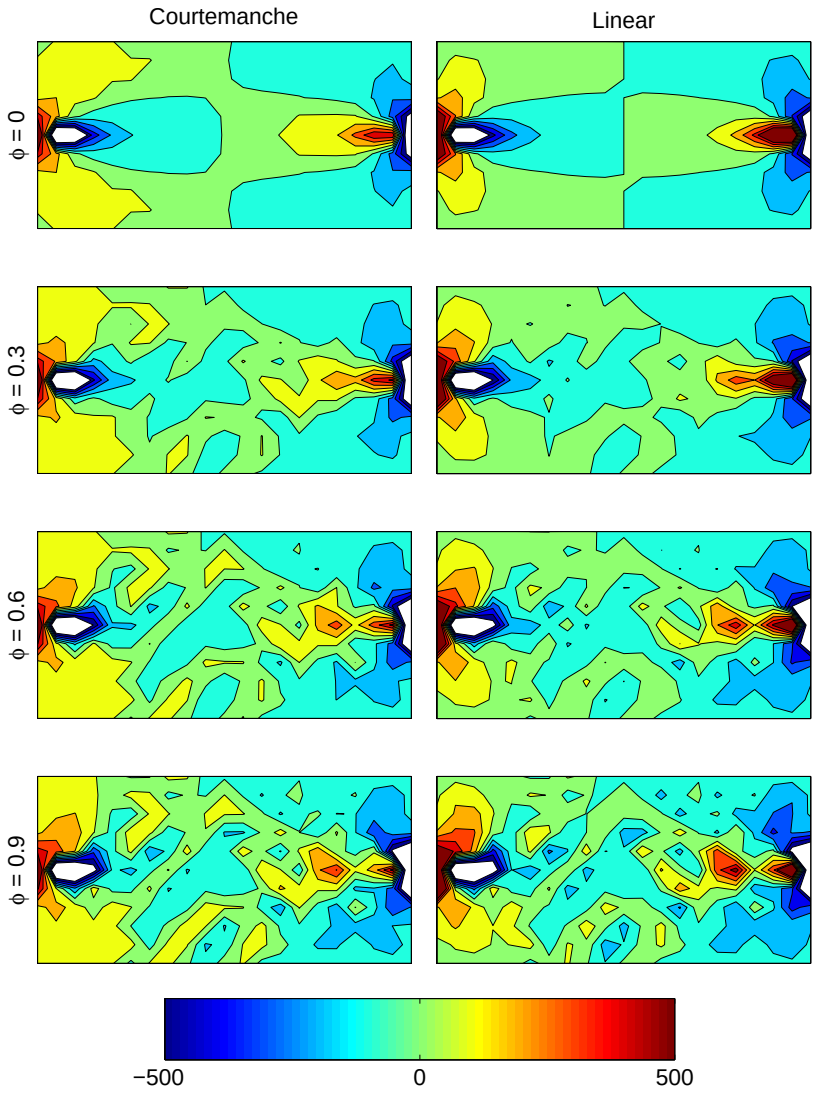

Figure 1: The transmembrane potential at $t = 5$ms of bidomain computations using a Courtemanche cell model (left) and linear model (right). (The random field η was generated using the `rand` function in Matlab.) The variability of the medium is increased for $\varphi = 0$ (upper row) to $\varphi = 0.9$ (lower row). We observe that in all cases the linear model provides reasonable approximations.

Moreover, we want to assess the consequences of this estimate in terms of the current needed to bring about a successful defibrillation. In particular, we want to analyze how the necessary strength of the defibrillation current depends on the variability φ of the medium.

We begin by making some observations. From the definitions of m_i and m_e, there are positive constants $a_i^-, a_i^+, a_e^-, a_e^+$ such that

$$a_i^- \langle \nabla w, \nabla w \rangle \leqslant \langle m_i \nabla w, \nabla w \rangle \leqslant a_i^+ \langle \nabla w, \nabla w \rangle \tag{12}$$

$$a_e^- \langle \nabla w, \nabla w \rangle \leqslant \langle m_e \nabla w, \nabla w \rangle \leqslant a_e^+ \langle \nabla w, \nabla w \rangle \tag{13}$$

for all $w \in V = H^1(\Omega; \mathbb{R}^2)$. In particular, we have

$$a_e^- \leqslant \sigma_{ex}, \sigma_{ey} \leqslant a_e^+, \quad a_i^- \leqslant \sigma_{ix}, \sigma_{iy} \leqslant a_i^+$$

with

$$a_e^- = 2.36/1400, \quad a_e^+ = 6.25/1400,$$
$$a_i^- = a_i^-(\varphi) = \frac{0.19}{1400}(1-\varphi), \quad a_i^+ = a_i^+(\varphi) = \frac{1.46}{1400}(1+\varphi).$$

It follows in particular that for all $w \in V$

$$\langle m_i \nabla w, \nabla w \rangle \leq \beta \langle m_{i+e} \nabla w, \nabla w \rangle \quad \text{where } \beta = \frac{a_i^+}{a_e^- + a_i^+} < 1. \tag{14}$$

Also observe that because of (7) and (8), Poincaré's inequality states that there exists a $C > 0$ such that for u and v solving (9) and (10),

$$\|w\| \leq C \| \nabla w \| \quad \text{for } w \in \{u, v\}. \tag{15}$$

The following lemma gives an upper bound for v and hence an estimate for the function c in (11).

Lemma 1 *Let $v(t)$ and $u(t)$ solve (9) and (10) with $v(0) = 0$ and prescribed α. Then*

$$\|v(t)\| \leq c(t) \|I_e\|$$

where

$$c(t)^2 = c_1 c_0^{-1} \left(1 - e^{-c_0 t}\right), \quad c_0 = 2(\alpha + \gamma a_i^- C^2), \quad c_1 = \frac{C^2}{2\gamma a_{i+e}^-}, \tag{16}$$

Here, C is given by (15), $a_{i+e}^- = a_i^- + a_e^-$, a_i^- and a_e^- are given by (12), $\gamma = 1 - \beta^{1/2}$, and β is defined by (14).

Proof. Let $w = v$ in (9) and $q = u$ in (10) and add the equations to obtain

$$\begin{aligned} \langle v_t, v \rangle + \langle m_i \nabla v, \nabla v \rangle + \langle \alpha v, v \rangle + \langle m_{i+e} \nabla u, \nabla u \rangle \\ = -\langle I_e, u \rangle - 2 \langle m_i \nabla u, \nabla v \rangle. \end{aligned} \tag{17}$$

Recall Cauchy's inequality with ϵ, stating that for any inner product a

$$|a(u,v)| \leq \epsilon a(u,u) + \frac{1}{4\epsilon} a(v,v) \quad \forall\, u, v, \epsilon > 0. \tag{18}$$

Using (18) for (the absolute value of) the right-hand sides of (17), we have

$$\begin{aligned} &\langle v_t, v\rangle + \langle m_i \nabla v, \nabla v\rangle + \langle \alpha v, v\rangle + \langle m_{i+e} \nabla u, \nabla u\rangle \\ &\qquad \leq \epsilon\langle u, u\rangle + \frac{1}{4\epsilon}\langle I_e, I_e\rangle + \delta\langle m_i \nabla v, \nabla v\rangle + \frac{1}{\delta}\langle m_i \nabla u, \nabla u\rangle \end{aligned} \tag{19}$$

for any $\epsilon, \delta > 0$. Applying (14) to the right-most term of (19) and moving the terms involving δ across the inequality, we obtain

$$\langle v_t, v\rangle + (1-\delta)\langle m_i \nabla v, \nabla v\rangle + \langle \alpha v, v\rangle + (1 - \frac{\beta}{\delta})\langle m_{i+e} \nabla u, \nabla u\rangle \leq \epsilon\langle u, u\rangle + \frac{1}{4\epsilon}\langle I_e, I_e\rangle.$$

We can now choose δ and ϵ. First, let $\delta = \beta^{1/2}$ and define $\gamma = 1 - \beta^{1/2} > 0$. This choice yields

$$\langle v_t, v\rangle + \gamma\langle m_i \nabla v, \nabla v\rangle + \langle \alpha v, v\rangle + \gamma\langle m_{i+e} \nabla u, \nabla u\rangle \leq \epsilon\langle u, u\rangle + \frac{1}{4\epsilon}\langle I_e, I_e\rangle.$$

Second, using (15) for u, (12), and (13), we find that

$$\langle u, u\rangle \leq C^2\langle \nabla u, \nabla u\rangle \leq \frac{C^2}{a^-_{i+e}}\langle m_{i+e} \nabla u, \nabla u\rangle,$$

and thus

$$\langle v_t, v\rangle + \gamma\langle m_i \nabla v, \nabla v\rangle + \langle \alpha v, v\rangle + (\gamma - \epsilon\frac{C^2}{a^-_{i+e}})\langle m_{i+e} \nabla u, \nabla u\rangle \leq \frac{1}{4\epsilon}\langle I_e, I_e\rangle.$$

Taking $\epsilon = \gamma a^-_{i+e} C^{-2}$ and using (15) for v, we find that

$$\langle v_t, v\rangle + \left(\alpha + \gamma a^-_i C^2\right)\langle v, v\rangle \leq \frac{C^2}{4\gamma a^-_{i+e}}\langle I_e, I_e\rangle.$$

Since $2\langle v_t, v\rangle = \frac{d}{dt}||v||^2$, Grönwall gives the stated result. ■

Remark 2 *The same argument holds for the case of homogeneous Dirichlet boundary conditions.*

Remark 3 *The same argument holds for spatially discrete solutions $v_h(t)$ and $u_h(t)$ solving* (9) *and* (10) *for all $w \in V_h$ and $q \in V_h$ when $V_h \subseteq V$.*

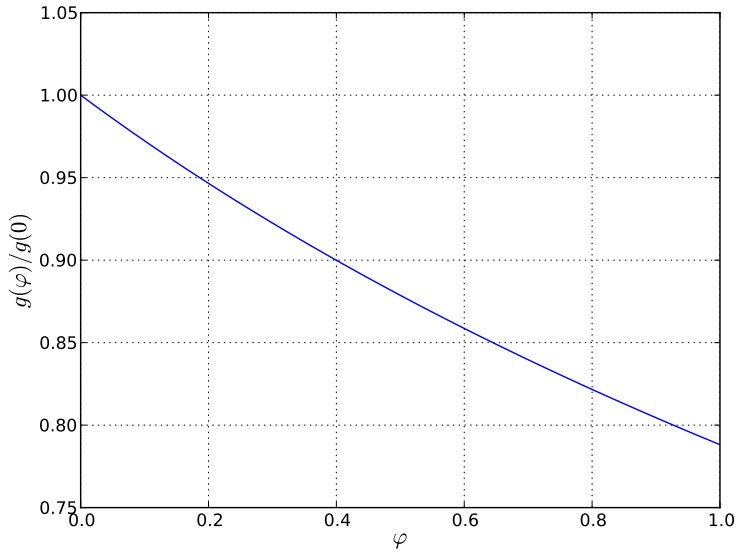

Figure 2: The figure shows $g(\varphi)/g(0)$, and we observe that the minimal shock strength decreases as the intracellular variability increases.

3.1 Physiological interpretation of the theoretical estimate

We have proved that

$$\|v(t)\| \leqslant c(t,\varphi)\,\|I_e\| \tag{20}$$

where $c(t,\varphi)$ is given by (16). By assuming that defibrillation is achived at time $t = t^*$ if $\|v(t)\| \geqslant v^*$, we see, as above, that we need the strength to satisfy $\|I_e\| \geqslant v^*/c(t^*,\varphi)$. Let us define this to be the minimum shock strength at time $t = t^*$; i.e.

$$g(\varphi) = \frac{v^*}{c(t^*,\varphi)}. \tag{21}$$

In Figure 2 we plot the function $g(\varphi)/g(0)$ as a function of the variability φ in the case of $\alpha = 0.05$ and $t^* = 5$. Here, we have used the Poincaré constant $C = \frac{4}{\pi}$; it is explained in e.g. [19] how this constant can be computed for rectangular domains. We observe that the minimal shock strength based on this theoretical estimate is a decreasing function of the variability φ of the intracellular conductivity. This result is in accordance with the numerical experiments provided by Plank et al [13, 14].

4 Numerical experiments

4.1 Numerical method

Many numerical methods have been developed for solving the bidomain system $(1, 2, 3)$; see e.g. [20, 21]. In the present paper we are primarily interested in the qualitative properties of the solution of the system for the geometry described above. Since the geometry is simple, we use a finite difference approach to solve the system. Given a uniform mesh with spacing Δx and Δy in the $x-$ and $y-$ direction respectively, we use standard finite difference approximations of the form

$$\frac{\partial}{\partial x}\left(m(x,y)\frac{\partial v(x_j,y_k)}{\partial x}\right) \approx \frac{m_{j+1/2,k}(v_{j+1,k}-v_{j,k}) - m_{j-1/2,k}(v_{j,k}-v_{j-1,k})}{(\Delta x)^2} \tag{22}$$

where $v_{j,k}$ denotes an approximation of $v(x_j, y_k)$ and where (x_j, y_k) denote nodes in the computational mesh. Similarly, we have $m_{j+1/2,k} = m(x_{j+1/2}, y_k)$. Using these approximations for the spatial derivatives in the bidomain system, we obtain the following system of differential-algebraic equations

$$v' = A_i v + A_i u - I(v,s), \tag{23}$$

$$I_e = A_i v + A_{i+e} u, \tag{24}$$

$$s' = F(v,s). \tag{25}$$

Here u, v and s carry the nodal approximations of the associated continuous variables, I_e carries nodal values of the electrical shock and the matrices A_i, A_e represent terms involving spatial derivatives in the system, with $A_{i+e} = A_i + A_e$. It follows from the system $(1, 2, 3)$ that if (v, u, s) is a solution of the the system, then also $(v, u + \alpha, s)$ is a solution for any constant α. Hence the matrix A_{i+e} is singular. Using an iterative method as described in e.g. [22], the singularity is not a problem, but here we want to eliminate the extracellular potential u from the system, and thus we need A_{i+e} to be non-singular. Theoretically, this can be achieved by imposing the condition (7), but in computations we achieve this by adding a small regularization term of the form $-\varepsilon u$ to the right-hand side of (2) and introduce the matrix

$$A_{i+e,\varepsilon} = A_{i+e} - \varepsilon J \tag{26}$$

where J is the identity matrix and $\varepsilon > 0$ is small number. In the computations we have used $\varepsilon = 10^{-6}$. Numerical experiments show that the results are robust with respect to small changes of this parameter.

We now have the system $(23, 24, 25)$ where A_{i+e} is replaced by $A_{i+e,\varepsilon}$. From (24) , we get

$$u = A_{i+e,\varepsilon}^{-1}\left(I_e - A_i v\right) \tag{27}$$

and thus we have the system,

$$v' = (J - A_i A_{i+e,\varepsilon}^{-1})A_i v + A_i A_{i+e,\varepsilon}^{-1} I_e - I(v,s), \tag{28}$$

$$s' = F(v,s). \tag{29}$$

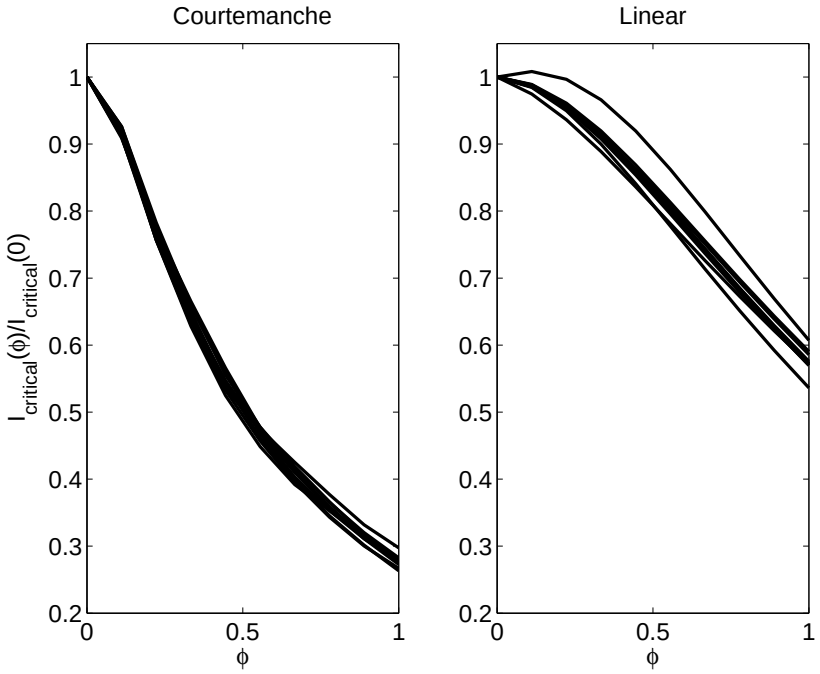

Figure 3: Figures represent shock strength necessary to defibrillate as the variability φ of the intracellular conductivities increases when using the modified Courtemanche (left) and the linear (right) model. Each line in the computation corresponds to one realization of the random field $\eta = \eta(x, y)$.

This is a system of ordinary differential equations and we solve it using ODE15s in Matlab.

4.2 Computations

The theoretical estimates presented above indicate that the necessary shock strength needed to achieve defibrillation decreases as the variability of the intracellular conductivities increases. This effect has also been observed in computations by several authors (see e.g. Plank et al [14, 13]). In Figure 3, we address this issue computationally using the bidomain model combined with the modified Courtemanche model and the linear model described above. Each line in the graphs of Figure 3 corresponds to one realization of the random field $\eta = \eta(x, y)$. We have used the finite difference method described above in the computations. The mesh parameters are the same as the ones used for Figure 1. We observe that for both ionic models, the necessary shock strength decreases as the control parameter φ increases. In addition we note that the linear models provide reasonable approximations of the shock strength needed for the modified Courtemanche model. The graphs have a form similar to the one obtained

by our theoretical analysis, but theoretical analysis underestimates the needed shock strength. It is important to keep in mind that the theoretical analysis provides a necessary but not sufficient condition for obtaining defibrillation.

5 Conclusion

It has been observed previously that the shock strength needed to achieve defibrillation decreases when the variability of the intracellular conductivities increases. In this paper, we have analyzed a linear model and derived a necessary condition for defibrillation for that model. The theoretical estimate states that the necessary shock strength decreases as the variability of the medium increases. This effect is also clearly confirmed by computations presented here.

References

[1] Heart Rhythm Foundation. Sudden cardiac arrest key facts, January 2010. http://www.heartrhythmfoundation.org/facts/scd.asp.

[2] Craig Pratt. Clinical implications of the survival with oral d-sotalol (sword) trial: An investigation of patients with left ventricular dysfunction after myocardial infarction. *Cardiac Electrophysiology Review*, 2:28–29, 1998.

[3] American Heart Association. Sudden death from cardiac arrest: statistics, 2004. http://www.americanheart.org.

[4] Gust H. Bardy, Kerry L. Lee, Daniel B. Mark, Jeanne E. Poole, Douglas L. Packer, Robin Boineau, Michael Domanski, Charles Troutman, Jill Anderson, George Johnson, Steven E. McNulty, Nancy Clapp-Channing, Linda D. Davidson-Ray, Elizabeth S. Fraulo, Daniel P. Fishbein, Richard M. Luceri, and John H. Ip. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *New England Journal of Medicine*, 352(3):225–237, 01 2005.

[5] T. Ashihara, J. Constantino, and N. A. Trayanova. Tunnel propagation of postshock activations as a hypothesis for fibrillation induction and isoelectric window. *Circ Res*, 102(6):737–45, 2008.

[6] N. Trayanova and Ed. J. Jalife G. Plank. *Modeling cardiac defibrillation, In: Cardiac Electrophysiology: From Cell to Bedside*, page 361372. WB Saunders, Philadelphia, 2009.

[7] D. J. Dosdall, V. G. Fast, and R. E. Ideker. Mechanisms of defibrillation. *Annu Rev Biomed Eng*, 12:233–58, 2010.

[8] G. I. Fishman, S. S. Chugh, J. P. Dimarco, C. M. Albert, M. E. Anderson, R. O. Bonow, A. E. Buxton, P. S. Chen, M. Estes, X. Jouven, R. Kwong, D. A. Lathrop, A. M. Mascette, J. M. Nerbonne, B. O'Rourke, R. L. Page,

D. M. Roden, D. S. Rosenbaum, N. Sotoodehnia, N. A. Trayanova, and Z. J. Zheng. Sudden cardiac death prediction and prevention: report from a national heart, lung, and blood institute and heart rhythm society workshop. *Circulation*, 122(22):2335–48, 2010.

[9] N. A. Trayanova. Whole-heart modeling: applications to cardiac electrophysiology and electromechanics. *Circ Res*, 108(1):113–28, 2011.

[10] J. L. Jones and O. H. Tovar. Threshold reduction with biphasic defibrillator waveforms. role of charge balance. *J Electrocardiol*, 28 Suppl:25–30, 1995.

[11] J. P. Keener. Direct activation and defibrillation of cardiac tissue. *J Theor Biol*, 178(3):313–24, 1996.

[12] A. L. de Jongh, E. G. Entcheva, J. A. Replogle, 3rd Booker, R. S., B. H. Kenknight, and F. J. Claydon. Defibrillation efficacy of different electrode placements in a human thorax model. *Pacing Clin Electrophysiol*, 22(1 Pt 2):152–7, 1999.

[13] G. Plank, L. J. Leon, S. Kimber, and E.J. Vigmond. Defibrillation depends on conductivity fluctuations and the degree of disorganization in reentry patterns. *J Electrophysiol*, 16:205–216, 2005.

[14] G. Plank, E. J. Vigmond, and L. J. Leon. Shock energy for successful defibrillation of atrial tissue during vagal stimulation. *Proceedings of the 25th annual International Conference of the IEEE EMBS*, pages 167–170, 2003.

[15] G. Plank, A. Prassl, E. Hofer, and N. A. Trayanovay. Evaluating intramural virtual electrodes in the myocardial wedge preparation: Simulations of experimental conditions. *Biophysical Journal*, 94:1904–1915, 2008.

[16] S. W. Morgan, G. Plank, I. V. Biktasheva, and V. N. Biktashev. Low energy defibrillation in human cardiac tissue: A simulation study. *Biophysical Journal*, 96:1364–1373, 2009.

[17] M. Courtemanche, R. J. Ramirez, and S. Nattel. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *Am J Physiol*, 275(1):H301–21, 1998.

[18] A. Tveito, G. T. Lines, M.M. Maleckar, and O. Skavhaug. Simplified mathematical models of defibrillation. *preprint*, 2010.

[19] A. Tveito and R. Winther. *Introduction to Partial Differential Equations*, volume 29 of *Texts in Applied Mathematics*. Springer, 1998.

[20] Joakim Sundnes, Glenn Terje Lines, Xing Cai, Bjørn Fredrik Nielsen, Kent-Andre Mardal, and Aslak Tveito. *Computing the electrical activity in the heart*. Springer-Verlag, 2006.

[21] Svein Linge, Joakim Sundnes, Monica Hanslien, Glenn Terje Lines, and Aslak Tveito. Numerical solution of the bidomain equations. *Philosophical Transactions of the Royal Society A*, 367(1895):1931–1951, 2009.

[22] K.-A. Mardal, B.F. Nielsen, X. Cai, and A. Tveito. An order optimal solver for the discretized bidomain equations. *Numer. Linear Algebra Appl.*, 14:83–98, 2007.