A Model for Multi-site Pacing of Fibrillation Using Nonlinear Dynamics Feedback

Victor D. Hosfeld · Steffan Puwal · Keith Jankowski ·
Bradley J. Roth

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Abstract Traditionally, cardiac defibrillation requires a strong electric shock. Many unwanted side effects of this shock could be eliminated if defibrillation were performed using weak stimuli applied to several locations throughout the heart. Such multi-site pacing algorithms have been shown to defibrillate both experimentally (Pak et al., *Am J Physiol* 285: H2704–H2711, 2003) and theoretically (Puwal and Roth, *J Biol Systems* 14:101–112, 2006). Gauthier et al. (*Chaos*, 12:952–961, 2002) proposed a method to pace the heart using an algorithm based on nonlinear dynamics feedback applied through a single electrode. Our study applies a related but simpler algorithm, which essentially configures each electrode as a demand pacemaker, to simulate the multi-site pacing of fibrillating cardiac tissue. We use the numerical model developed by Fenton et al. (*Chaos*, 12:852–892, 2002) as the reaction term in a reaction–diffusion equation that we solve over a two-dimensional sheet of tissue. The defibrillation rate after pacing for 3 s is about 30%, which is significantly higher than the spontaneous defibrillation rate and is higher than observed in previous experimental and theoretical studies. Tuning the algorithm period can increase this rate to 45%.

Keywords Defibrillation · Pacing · Feedback · Nonlinear dynamics · Numerical simulation · Heart

1 Introduction

Ventricular fibrillation (VF) renders the heart ineffective at pumping blood. If not corrected within minutes, the condition is fatal. Currently, the most effective treatment is defibrillation: the delivery of a high-energy shock to the heart. The large energy used to defibrillate is painful to the patient and possibly damaging to cardiac tissue. Our goal is to develop algorithms to control the nonlinear chaotic behavior of VF using weak enough

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V. D. Hosfeld · S. Puwal · K. Jankowski · B. J. Roth (✉)
Department of Physics, Oakland University, Rochester, MI 48309, USA
e-mail: roth@oakland.edu

stimuli to eliminate pain and other side effects, thereby reducing the problem of defibrillation to one of pacing [1].

Many researchers have studied electrical control techniques to suppress cardiac arrhythmias [1–7], particularly to control alternans (an alternating response to a periodic stimulus) [8–12]. Often, control can be maintained over a limited region surrounding the stimulating electrode (regional capture). In our study, we consider a multi-site electrode geometry, similar to that used by Pak et al. [6] in their attempt to stop VF in rabbit hearts by feedback pacing, and implement a nonlinear feedback algorithm motivated by the work of Gauthier et al. [7]. The Fenton-Karma model [13, 14], which characterizes the cardiac tissue, accounts for spiral wave breakup and the development of fibrillation. Our specific aim is to determine whether our algorithm – using low energy stimuli with a magnitude only modestly larger than the diastolic threshold – will increase the success rate of defibrillation compared to previous studies involving the multi-site application of low energy stimuli to terminate VF.

2 Methods

Except when stated otherwise, the mathematical model is the same as that used by Puwal and Roth [15]: an isotropic two dimensional tissue sheet, 5.25×5.25 cm, is discretized with a 350×350 array of nodes, implying a space step of 0.015 cm. Four stimulus electrodes form a square, 1.32 cm on each side, centered in the tissue sheet (Fig. 1). The electrodes themselves are 0.075×0.075 cm. Periodic boundary conditions determine the behavior of the tissue at the edge of the sheet and give the tissue a toroidal shape.

The transmembrane potential, V , obeys a reaction–diffusion equation

$$\frac{\partial V}{\partial t} = D \nabla^2 V - \frac{I_{\text{stim}} + I_{\text{fi}} + I_{\text{si}} + I_{\text{so}}}{C_m}, \quad (1)$$

where D is the diffusion constant ($1 \text{ cm}^2/\text{s}$) and C_m is the membrane capacitance ($1 \text{ } \mu\text{F}/\text{cm}^2$). The three ionic currents – I_{fi} , I_{si} , and I_{so} – are described by the Fenton et al. [14] and

Fig. 1 The geometry of the tissue sheet and four pacing electrodes

correspond approximately to the fast inward (sodium), slow inward (calcium), and slow outward (potassium) currents, respectively. The currents depend on two gate variables: w , which functions roughly like a calcium channel inactivation gate, and ν , which acts approximately like a sodium channel inactivation gate. We use the parameter set six of Fenton et al., which results in spiral wave breakup caused by the Doppler shift mechanism. The model is modified to behave properly in response to strong stimuli [15]. The stimulus is implemented as an additional contribution I_{stim} to the membrane current. We solve (1) using the explicit Euler method with a time step of 0.04 ms.

Our method of initializing the simulation differs from that used by Puwal and Roth [15]. We induce fibrillation by initially setting the transmembrane potential V and the gate ν equal to zero or one throughout the tissue (w is everywhere equal to 0.5). The initial distribution V is determined by adding the eight lowest spatial frequency components, with random amplitude and phase, and then creating a binary representation determined by the sign of the sum. An independent initial distribution of ν is determined in a similar way. In almost every case, the contours of V and ν intersect to create several phase singularities, providing initial conditions resembling a state of fibrillation (Fig. 2). We perform 100 simulations with randomized initial conditions for each set of pacing parameters.

Each of the four pacing electrodes monitors and stimulates the tissue independently. We implemented an algorithm that was motivated by, but significantly simplified compared to, an algorithm presented by Gauthier et al. [7]. Starting with its “clock” at zero, if an electrode does not record a depolarization phase of an action potential wave front for 75 ms, we apply a 3-ms stimulus and reset the clock to zero. If, however, an action potential is detected before 75 ms, we do not stimulate and reset the clock to zero. Thus, the electrodes act much like a “demand pacemaker”, only stimulating when needed to maintain a minimum rate of 75 ms. We specify all stimuli as a particular multiple of diastolic threshold for resting tissue. The pacing algorithm is applied for 3 s, after which the tissue is monitored for an additional 2 s. We classify the state of the tissue at the end of the simulation (total time of 5 s) into one of three states: fibrillation (VF, multiple phase singularities), tachycardia (VT, a wave front propagating around the tissue but with no phase singularities present), or rest. For pacing to be effective, it should terminate fibrillation at a higher rate than the spontaneous defibrillation rate. We use sham pacing (stimulus strength of zero) to determine the spontaneous defibrillation rate.

3 Results

Sham pacing exhibits spontaneous termination (tissue returns to rest) in 7%, conversion to VT in 13%, and sustained fibrillation in 80% of simulations observed.

Figure 3 contains a plot of the success rate of defibrillation (% in resting state after 5 s) as a function of external stimulus strength ($\times$ threshold). For stimuli weaker than or equal to threshold, the defibrillation rate is low, in the range of 5–7%, consistent with spontaneous termination. Success increases rapidly for suprathreshold stimuli, and for strengths of three times threshold or greater, it plateaus at about 30%. The VF–VT conversion rate as a function of stimulus strength, shown in Fig. 4, is about 10%, and displays no obvious dependence on stimulus strength.

Figure 5 shows the wave front dynamics for a case in which defibrillation fails, for a stimulus strength of three times threshold. Although the stimuli clearly affected the wave front dynamics (for instance, see the 1,500-ms frame), they did not successfully eliminate all the phase singularities. This figure is typical of most unsuccessful simulations.

Fig. 2 The initial transmembrane potential distribution, V , and gate distribution, v (the gate w equals 0.5 everywhere). Black is 0 and white is 1. Intersections of the V and v contours are locations where phase singularities occur (dots in the lower frame). In this example, a total of eight phase singularities develop

The conversion of VF to VT is shown in Fig. 6. The stimulus (three times threshold) eliminates all phase singularities by 1,500 ms. However, a wave front remains that continues to propagate around the tissue, making use of the periodic boundary conditions to reenter the right side of the tissue after reaching the left edge. After the stimulus protocol ends at 3,000 ms, this wave front flattens until it appears as a planar wave front propagating right to left. In all simulations that result in VT, the wave front eventually flattens, but its direction can be left to right, right to left, top to bottom, or bottom to top. Once a planar wave front is established after the end of the pacing protocol, it continues to propagate indefinitely.

Figure 7 shows successful defibrillation. The pacing protocol captures the tissue response, so that, by 2,500 ms, no phase singularities remain. However, the electrodes continue to excite wave fronts every 75 ms, launching a series of outwardly propagating, closed wave fronts. When the pacing protocol ends at 3,000 ms, the tissue goes to rest within a few hundred milliseconds and remains at rest throughout the remainder of the

Fig. 3 The defibrillation rate as a function of stimulus strength. The length of the error bars are determined by $\pm$ the square root of the number of cases of successful defibrillation, which is the standard deviation if the process obeys Poisson statistics

simulation. The time at which capture occurs varies between simulations and can be quite early during the pacing protocol.

Online movies of the simulations in Figs. 5, 6, and 7 (see [Supplementary Material](#)) show the tissue behavior with better temporal resolution (frame rate = 10 ms). These simulations are representative of the types of behavior in most simulations. Of course, the details are different in each case. In addition, a few simulations do not fit these categories. For instance, spontaneous defibrillation occurs occasionally, even with no stimulus, but it does not happen by regional capture as in Fig. 7.

We examined the effect of the pacing period in our algorithm by varying it between 25 and 175 ms (Fig. 8). A pronounced peak in the defibrillation rate occurred at 75–95 ms (compared to the VF cycle length of 116 ms), at which point the defibrillation rate reached 40–45%. The VF–VT rate varied widely and was not a simple function of period.

Finally, we examined the effect of tissue size on our results. When the tissue size was reduced to 250×250 nodes (14 cm^2 , or about half the area of our standard tissue size) with all other parameters held constant, the success rate increased to 100% (100 out of 100 simulations), but the spontaneous defibrillation rate increased to 73%, implying that, in

Fig. 4 The rate of conversion of VF to VT, as a function of stimulus strength. The length of the error bars are determined by $\pm$ the square root of the number of cases of VF to VT conversion, which is the standard deviation if the process obeys Poisson statistics

Fig. 5 The transmembrane potential distribution at various time points (in ms). The pacing protocol is on from 0 to 3,000 ms. In this case, defibrillation failed. *White* is 1 (depolarized) and *black* is 0 (rest). The stimulus strength is three times the threshold

nearly three fourths of the simulations, the tissue could not support VF for 5 s. When the tissue size was increased to 450×450 nodes (46 cm^2 , about 65% larger area compared to our standard tissue size), the spontaneous defibrillation rate dropped to zero (0 out of 100 simulations), but our success rate dropped to 1%. Thus, we were not able to capture a large tissue size using our four-electrode algorithm.

4 Discussion

A defibrillation rate on the order of 30% is quite good compared to the peak rate of 16% we found previously with another feedback algorithm [15] and compared to the peak rate of 16% observed in the experiment by Pak et al. [6]. The primary difference between our previous study and our present results is the implementation of the pacing algorithm motivated by the work of Gauthier et al. [7]. Furthermore, we have found that we can

Fig. 6 The transmembrane potential distribution at various time points (in ms). The pacing protocol is on from 0 to 3,000 ms. In this case, VF converted to VT. *White* is 1 (depolarized) and *black* is 0 (rest). The stimulus strength is three times the threshold

Fig. 7 The transmembrane potential distribution at various time points (in ms). The pacing protocol is on from 0 to 3,000 ms. In this case, the tissue is defibrillated by pacing. *White* is 1 (depolarized) and *black* is 0 (rest). The stimulus strength is three times the threshold

improve the success rate through a simple variation of pacing parameters (such as tuning the stimulation period, resulting in a peak success rate on the order of 45%).

The conversion of fibrillation into a tachycardia is possible because of the periodic boundary conditions, which makes our model topologically similar to propagation on the surface of a toroid. VT occurs when the wave front propagates around the toroid. In our previous study [15], cases of VT may have been present but misclassified as persistent VF. In that study, the criterion for successful defibrillation was that the entire tissue returned to rest, which is clearly not the case for VT. Thus, a few of the persistent VF cases in our previous study may actually have been VT.

We found that the defibrillation rate is about equal to the spontaneous rate for stimulus strengths below diastolic threshold. For suprathreshold stimuli, the defibrillation rate increases with stimulus strength up to about three times threshold and is nearly independent

Fig. 8 The defibrillation rate as a function of the period in the stimulation algorithm. The stimulation strength was three times the threshold. The length of the error bars are determined by $\pm$ the square root of the number of cases of successful defibrillation, which is the standard deviation if the process obeys Poisson statistics

of stimulus strength above three times threshold (Fig. 3). This saturation of the response for high strengths is similar to the experimental results of Newton et al. [16]. The rate of conversion of VF to VT depended only weakly on stimulus strength.

Clinically, pacing stimuli are dramatically weaker than defibrillation shocks. If feedback pacing is effective at stimulus strengths on the order of three times the threshold strength, then the pacing stimuli will be orders of magnitude weaker than typical defibrillation shocks used clinically, reducing side effects.

Because defibrillation is inherently a probabilistic event, for each set of pacing parameters we performed 100 simulations. We assume that the number of successful cases obeys Poisson statistics, so that the standard deviation is simply the square root of the number. The error bars in Figs. 3, 4, and 8 indicate this standard deviation.

The original experiment by Pak et al. [6] monitored the tissue by optical mapping. They decided if they should stimulate or not using information about the actual value of the transmembrane potential. One advantage of the technique we propose is that it only requires detection of propagating wave fronts. Extracellular electrodes do not record the transmembrane potential but are useful in detecting wave fronts. Thus, one could imagine performing this protocol with extracellular electrodes. Such a method would be much easier to implement clinically than a method that required optical mapping to record transmembrane potential. One other advantage of our technique compared to the technique of Pak et al. is that a reference electrode is not required.

Our model contains several assumptions that limit its ability to accurately model experiments and its clinical relevance. The details of the heart shape and its complex fiber geometry are not accounted for in our simple model. The model is two-dimensional, but cardiac tissue is three-dimensional. Therefore, we cannot say if our simulations represent endocardial or epicardial pacing because these three-dimensional concepts are not represented in our two-dimensional model. We assume isotropic tissue, whereas cardiac tissue is anisotropic. We use a monodomain model, whereas cardiac tissue would be better represented as a bidomain. However, most of the unique effects of an anisotropic bidomain occur for strong stimuli. For stimuli with strengths of only a few times diastolic threshold, bidomain effects should be unimportant. The Fenton-Karma model [13, 14] is not based on detailed experimental measurements of specific ion channels. However, it is a well-studied model that reproduces several key features of cardiac muscle, such as the restitution properties and the decay of VT into VF. These features are critical for our simulations, whereas accurate kinetics of specific channels is of secondary importance.

Another limitation of our model is the tissue size. Previous studies have observed regional capture of cardiac tissue but limited success controlling the entire heart. For instance, Echebarria and Karma [11] concluded that “spatiotemporal control of alternans in paced cardiac tissue...is only effective up to a maximum tissue size that drops sharply beyond the threshold for alternans in large tissue.” Our results also are sensitive to tissue size. For a tissue area half as large as our standard size, the spontaneous defibrillation rate increases high enough that the tissue essentially does not support VF. For a tissue area about 65% larger than our standard size, our success rate drops to almost zero, indicating only regional capture of VF at best. However, three considerations suggest that our study is valuable, nevertheless. First, the area of our simulations (28 mm^2) is similar to the surface area of the ventricles in a rabbit heart as studied by Pak et al. [6], which is the study that motivated our analysis. Second, for a fixed tissue size, we can compare different pacing algorithms and stimulation scenarios to determine which are most effective. Although we have not proven it, we expect that the relative effectiveness of different algorithms is much less dependent on tissue size than is the actual defibrillation rate. Third, our method

provides a testbed from which we can examine different electrode numbers and spacings to determine in what situations larger tissue areas can be controlled. Our initial electrode geometry and spacing were motivated by the experiment of Pak et al. [6], but different electrode geometries might better enable us to control tissue areas similar to the size of the human heart.

In conclusion, we find that configuring each electrode in the mode of a demand pacemaker increases significantly the defibrillation rate during multi-site pacing. If this result is confirmed experimentally, it will bring us one step closer to a defibrillation method that does not require a strong shock.

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