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1 A Hybrid Stimulation Strategy for Suppression of Spiral 2 Waves in Cardiac Tissue

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7 Abstract

8 Atrial fibrillation (AF) is the most common cardiac arrhythmia whose me-
9 chanisms are thought to be mainly due to the self perpetuation of spiral waves
10 (SW). To date, available treatment strategies (antiarrhythmic drugs, radiofre-
11 quency ablation of the substrate, electrical cardioversion) to restore and to
12 maintain a normal sinus rhythm have limitations and are associated with AF
13 recurrences. The aim of this study was to assess a way of suppressing SW by
14 applying multifocal electrical stimulations in a simulated cardiac tissue using
15 a 2D FitzHugh-Nagumo model specially convenient for AF investigations. We
16 identified stimulation parameters for successful termination of SW. However,
17 SW reinduction, following the electrical stimuli, leads us to develop a hybrid
18 strategy based on sodium channel modification for the simulated tissue.

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1. Introduction

Although human data support the idea that rotors are a crucial mechanism for fibrillation maintenance in both atria and ventricles, there are clear differences between the 2 chamber types. Ventricular fibrillation (VF), responsible for sudden cardiac death, can be considered as a lethal “three-dimensional” cardiac arrhythmia with multiple micro re-entries located deep inside the endocardial muscle [1]. VF has been widely studied [2, 3, 4], but because of electrophysiological characteristics, the only treatment available is indeed an electrical defibrillation via automated external defibrillators (AED), or via implantable cardiac defibrillators (ICD). Conversely, most of “two-dimensional” macro re-entry ventricular tachycardia (VT) can be stopped by rapid burst of stimulations delivered by an ICD via a single right ventricular lead [5].

As opposed to VF, atrial fibrillation (AF) is associated with a better outcome but it is by far the most frequently diagnosed cardiac arrhythmia affecting, for example, approximately 1% of the adult population of the United States. Recent clinical trial evidence suggests that the presence of AF is an independent predictor of morbidity and mortality. One of the primary goals of paroxysmal and persistent AF treatment is to relieve symptoms by a rhythm control strategy [6].

Endocardial walls of the atria are much thinner than their ventricular counterparts, therefore AF may be considered as a “two-dimensional” cardiac arrhythmia. Specifically, therapy for restoring and maintaining a normal sinus rhythm is multidimensional with treatment options spanning from pharmacologic therapy to electrical cardioversion and catheter-based radiofrequency ablation [7]. But even combined, these methods have limited efficacy as the AF recurrence rate is high, and are limited by numerous side effects [8]. To date, there are two known concepts to restore a normal sinus rhythm by using electrical stimulation. The first one is to “reset” the whole heart by applying high voltage via a dedicated defibrillation device (internal or external) in order to extinguish most of the fibrillatory wavefronts. External cardiac defibrillation cannot be rea-

1 lized very often as it has to be done under general anesthesia. Maintenance of
2 normal sinus rhythm using repeated internal cardioversion shocks via implan-
3 ted devices has also been shown to be effective and safe, however increase in
4 defibrillation thresholds and patient intolerance due to the pain were the main
5 reasons for discontinuation of this therapy [9]. The second way of suppressing
6 AF is based on Allessie's concept asserting that there is a critical number of
7 micro-reentries below which the cardiac arrhythmia can self terminate [10].

8 Micro-reentries can be observed experimentally or numerically as spiral waves
9 (SW). The rotors of SW, defined as rotating motors that give rise to the spiraling
10 wavefronts, gyrate at relatively high frequencies [11]. From such rotors, SW pro-
11 propagate throughout the myocardium in very complex ways [3], for example SW
12 meandering and drifting, whose dynamics have been well studied [12, 13, 14].
13 It is known that, under certain conditions, electrical stimuli can modify SW
14 dynamics [15, 16, 17]. Moreover, they can terminate SW either by preventing
15 rotor formation and maintenance, by re-driving / pacing SW [18] or by feedback
16 control [19]. This hypothesis could explain the global mechanism of defibrillation
17 by electrical stimulation. Namely, at cellular level, the propagation of action po-
18 tential in excitable medium is controlled by voltage-gated ion channels in cells.
19 These channels are shut when the membrane potential is near the resting po-
20 tential. They rapidly begin to open if the membrane potential increases to the
21 threshold value. However, as opposed to VT, AF can't be stopped by single site
22 burst stimulations via a pacing lead [7], but a multifocal and simultaneous sti-
23 mulation may help to extinguish most or all fibrillatory wavefronts in a selected
24 area by resetting cellular membrane potential under its threshold value.

25 This approach has already been investigated in previous studies. Allessie
26 has shown that, during electrically induced AF in chronically instrumented
27 conscious dogs, it was possible to control the local fibrillatory process by ra-
28 pid focal pacing through a grid of electrodes at the left atrial appendage [20].
29 However, this method failed to terminate AF as the area under control was
30 very limited. Other authors have used an array of control points in order to
31 terminate spatiotemporal chaos in excitable media and focused mainly on the

1 stimulation amplitude [21]. However, we strongly believe that there are many
2 other parameters to be taken into account.

3 Other methods to suppress SW based on boundaries conditions or spatial
4 inhomogeneity [22, 23] are either difficult in controlling the inhomogeneity of a
5 real cardiac tissue, or are associated with the generation of new waves. In [24],
6 a spatially extended mesh which could be more successful in the elimination
7 of spiral turbulence has been mentioned. But the optimal parameters of the
8 controlling signals have not been defined. Moreover, these techniques have strong
9 limitations as they not only eliminate SW, but also reinduce new ones.

10 In fact, the ideal atrial stimulation/defibrillation method should suppress
11 enough SW in a dedicated region for the whole heart to stop fibrillating, but
12 without generating new ones.

13 In order to address this major concern, we studied two different options by
14 using 2D numerical simulations of the model, as described in section 2. Then,
15 we optimized the stimulation parameters (section 3). For example, we defined
16 the number of required stimulated sites via an electrode array; we optimized
17 the frequency and duty cycle of the stimulation, and the output amplitude
18 which has to be set as low as possible to prevent from new SW and to protect
19 the whole heart from arrhythmia re-introduction. But this minimal amplitude
20 being still too large, we investigated then a second option, in developing a hybrid
21 strategy based on a sodium channel modification of the simulated tissue. By
22 increasing the threshold of new SW generation, we showed that it is possible to
23 protect the tissue from arrhythmia re-induction. We sought to identify the best
24 balance between cells number needed to be stimulated compared to the number
25 of total cells simulated and the SW generation threshold. In the last section 4,
26 we concluded this paper and gave some future prospects of this work.

27 2. Model and methods

28 In literature, there are many cardiac excitation models, for example, Luo-
29 Rudy 1 and 2 models [25, 26], Ten Tusscher-Noble-Panfilov model [27]. These

models represent an interesting way to investigate the heart activity at cellular level, but the control of their parameters is quite complex. The FitzHugh-Nagumo (FHN) model [28, 29] remains simple and keeps the essential mathematical properties of excitation and propagation from the electrochemical properties of sodium and potassium ion flows. FHN model is then used to study the ionic current of nerve or cardiac membrane [30, 31], completed by adding terms to a non-linear “relaxation oscillators” dimensionless equation. We start from the generic ionic equation of excitable medium with realistic units,

$$C_m \frac{\partial V}{\partial t} = C_m d \Delta V(x, y, t) - i_{Na} - i_{other} + i_{stim}, \quad (1)$$

where C_m is the membrane capacitance; $V(x, y, t)$ is the transmembrane potential at location (x, y) at time t ; d is the diffusion parameter; Δ is the continuous Laplace operator; i_{Na} is the sodium current; i_{other} is the sum of other ionic currents and i_{stim} is the stimulus current.

The dynamics of the currents in FHN model are characterized as Fast-Slow ones, where the sodium one is the fast part and is expressed as

$$i_{Na} = k \cdot g_{Na} \cdot V(V - V_a)(V - V_b). \quad (2)$$

Biologically, k intervenes in the control of the sodium current dynamics and kinetics of sodium channels. In this model, changing k results in modifying the dynamics of sodium current, then the value and the position of nullclines in the phase space. g_{Na} is the maximum sodium conductance; V_a and V_b are respectively the activation and inactivation potential;

Substituting Eq.(2) into Eq.(1), we obtain :

$$C_m \frac{\partial V}{\partial t} = C_m d \Delta V - k \cdot g_{Na} \cdot V(V - V_a)(V - V_b) - i_{other} + i_{stim}. \quad (3)$$

Setting that $v = \frac{V - V_b}{V_a - V_b}$, $\alpha = \frac{V_a}{V_a - V_b}$ and converting the continuous Laplace operator to discrete Laplace operator with spatial step δh , yields :

$$\frac{\partial v}{\partial \tau} = D \Delta v - k \cdot g_{Na} \cdot v(v - \alpha)(v - 1) - I_{other} + I_{stim}, \quad (4)$$

with :

$$\tau = \frac{g_{Na} \cdot V_b^2}{C_m} \cdot t \quad (5)$$

$$D = C_m \frac{1}{g_{Na} \cdot V_b^2 \cdot \delta h^2} \cdot d \quad (6)$$

$$I_{stim} = \frac{1}{g_{Na} \cdot V_b^3} \cdot i_{stim} \quad (7)$$

1 where I_{stim} , the normalized stimulus current, is defined by :

$$\left\{ \begin{array}{l} I_{stim}(x, y, \tau) = A(x, y) \text{rect}\left(\frac{F}{\theta}\tau\right) * \sum_{n=0}^N \delta\left(\tau - \frac{n}{F}\right) \\ A(x, y) = \begin{cases} A, & \text{if cell } (x, y) \text{ is stimulated;} \\ 0, & \text{otherwise.} \end{cases} \end{array} \right. \quad (8)$$

2 $A(x, y) \cdot \text{rect}\left(\frac{F}{\theta}\tau\right)$ is a rectangular pulse with amplitude $A(x, y)$, frequency F ,
3 duty cycle θ , duration $\frac{\theta}{F}$, and centered in time $\tau = 0$. The function $\sum_{n=0}^N \delta\left(t - \frac{n}{F}\right)$
4 is a Dirac comb corresponding to a series of Dirac delta functions spaced at
5 intervals of $\frac{n}{F}$.

6 The current I_{other} in FHN model is introduced by a recovery variable w
7 which indicates the capacity of the medium to revert to its resting state after
8 the propagation of impulsions :

$$\frac{\partial w}{\partial \tau} = \varepsilon(v - \gamma w) \quad (9)$$

9 where ε and γ are dimensionless constant parameters.

10 The above equations allow us to obtain the realistic values from numerical
11 ones and vice versa. Some typical values for the realistic parameters are used
12 here : $C_m = 10^{-6} \text{ F cm}^{-2}$, $g_{Na} = 23 \text{ mS V}^{-2} \text{ cm}^{-2}$, $V_b = 122 \text{ mV}$ ([30, 32]),
13 $d = 0.026 \text{ cm}^2 \text{ s}^{-1}$. However, considering the difference of action potentials (AP)
14 lengths¹ and the different properties of cell models, this conversion can only
15 provide some qualitative features.

1. Sodium-based AP lasts for less than 1 ms, calcium-based AP lasts for 100 ms or longer and normal human atrial AP lasts usually for $383 \pm 103 \text{ ms}$ [33].

1 The method used to suppress SW is obtained by sending a train of monopha-
2 sic stimuli from external electrodes distributed periodically in the system. The
3 cardiac tissue is covered by an electrodes network. The size of each electrode is
4 set to be the same as a cardiac cell's. The electrodes network has a square grid
5 form but other patterns and sizes could be considered.

6 3. Optimization of parameters and Results

7 Simulations were performed with an isotropic cardiac tissue of 200×200 cells
8 grid ($\delta h = 280 \mu\text{m}$, $\varepsilon = 0.005$, $\gamma = 0$ and $\alpha = 0.1$) and implanted with a Runge-
9 Kutta scheme including Neumann boundary conditions. For the readability of
10 our results, we call Stimulation Rate (SR) the ratio between the number of cells
11 under stimulation and the total cell number in the cardiac tissue. $\text{SR} = 100\%$
12 corresponds to the case where all cardiac cells are stimulated. An illustration of
13 the suppression process of SW corresponding to a case $\text{SR} = 2.1\%$, is shown in
14 Fig. 1 with the parameter $k = 1$.

15 Three categories of simulations have been carried out to optimize the sup-
16 pression of SW : global stimulation, wave generation threshold by stimulation
17 and hybrid stimulation.

18 3.1. Global stimulation

19 In the global stimulation case, the effects of the parameters of the stimu-
20 lation signal on the suppression of SW are investigated. Under the hypothesis
21 that there are SW evolving on the tissue, the whole tissue is stimulated. The
22 results are presented by the relationship between the SR and I_{stim} parameters
23 (amplitude, frequency and duty cycle), as shown in Figs. 2, 3 and 4.

24 There is a decreasing relationship between SR and each of these stimulation
25 parameters. Indeed, the larger the applied energy is, the smaller the number
26 of stimulated cells can be. However, there exists asymptotically a minimal sti-
27 mulated cells number needed in the SW suppression process, whatever are the
28 amplitude, frequency or duty cycle of the stimulus, which is in agreement with
29 [20]. The slope is very important for smaller amplitudes, lower frequencies and

1 smaller duty cycles. This means that in these regions, small variations of ampli-
 2 tude or frequency could greatly change the result of suppression process of SW.
 3 Furthermore, decreasing too much both parameters would increase SR which
 4 is contradictory to our main goal : stimulating less cells. As a consequence,
 5 a reasonable compromise should be taken. In following simulations, we take
 6 $A = 83.53 \mu\text{A cm}^{-2}$, $F = 21.40 \text{ Hz}$, $\theta = 50\%$ as our benchmark parameters.

7 Observing these results, it seems possible to suppress SW by choosing the
 8 appropriate parameters, but this is valuable only if the stimulation grid covers
 9 the whole tissue. **This global stimulation is not possible in the clinical case,**
 10 **because it is difficult to stimulate the whole cardiac tissue.** If this grid covers
 11 just a localized area of the tissue, SW can actually be suppressed in this area,
 12 but outside this area the stimulation provokes other waves (see wave fronts in
 13 Fig. 5c and 5d, propagating with a growing rough square shape outwards the

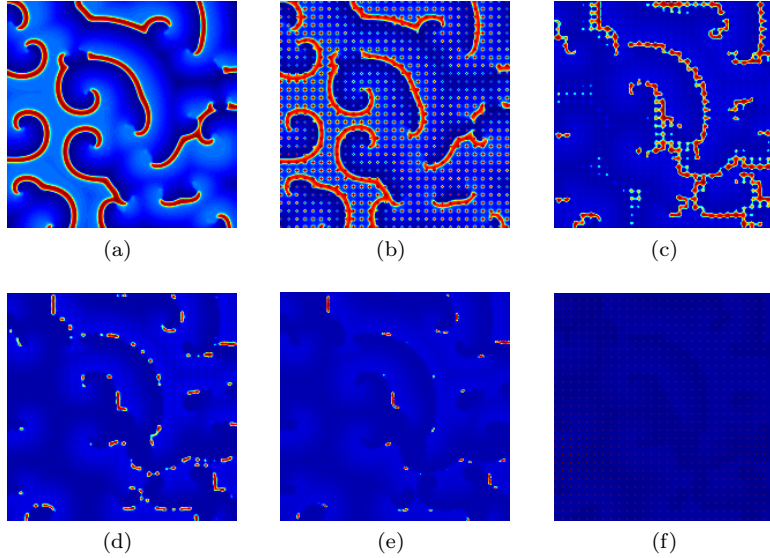


FIGURE 1: Suppression of SW at different times : (a) $t = 0 \text{ ms}$; (b) $t = 26.29 \text{ ms}$; (c) $t = 181.11 \text{ ms}$; (d) $t = 219.09 \text{ ms}$; (e) $t = 265.82 \text{ ms}$; (f) $t = 391.43 \text{ ms}$. (Tissue size 200×200 cells grid, $k = 1$, $A = 375.88 \mu\text{A cm}^{-2}$, $F = 21.40 \text{ Hz}$, $\theta = 50\%$, $\text{SR} = 2.1\%$).

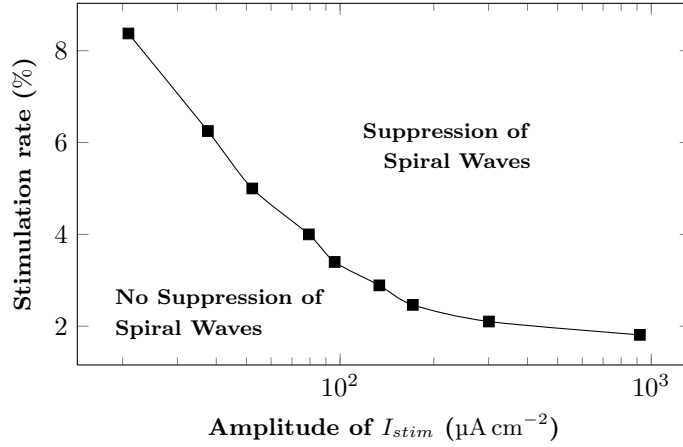


FIGURE 2: SR vs. amplitude of stimulus ($F = 21.40$ Hz, $\theta = 50\%$, $k = 1$).

1 stimulated area). In certain conditions, for instance : with local inhomogeneity,
 2 presence of obstacles or collision of waves, the new generated wave could be
 3 transformed into spiral waves. This implies that the amplitude of I_{stim} is above
 4 the threshold of new wave generation. Consequently this kind of stimulation
 5 cannot be considered as a real suppression of SW. As a result, it is necessary to
 6 determine this threshold as described in the following subsection.

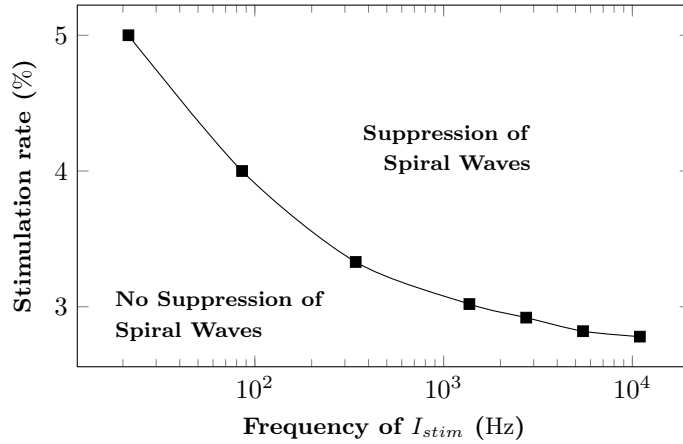


FIGURE 3: SR vs. frequency of stimulus ($A = 83.53 \mu\text{A cm}^{-2}$, $\theta = 50\%$, $k = 1$).

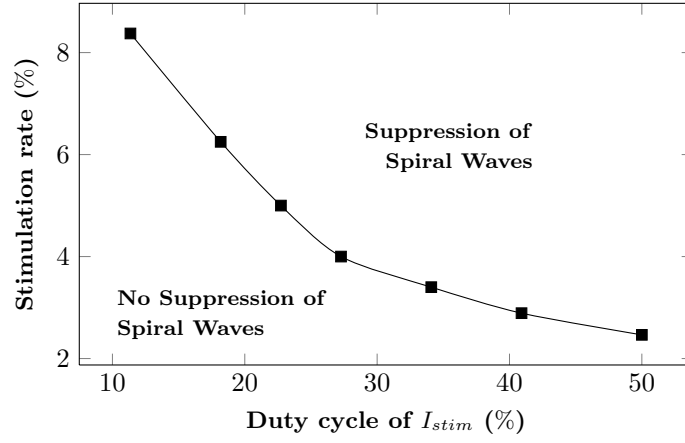


FIGURE 4: SR vs. duty cycle of stimulus ($A = 83.53 \mu\text{A cm}^{-2}$, $F = 21.40 \text{ Hz}$, $k = 1$).

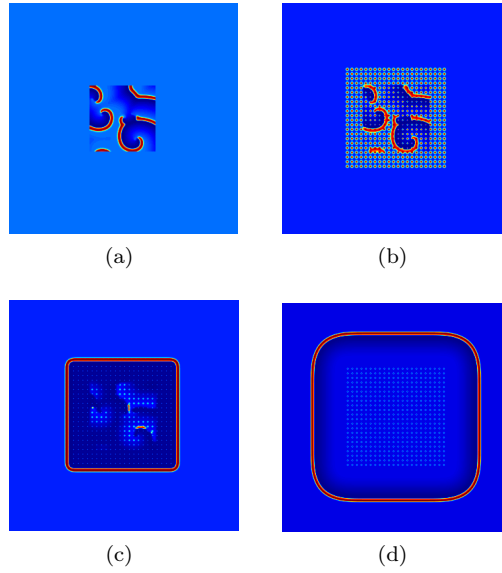


FIGURE 5: New waves generated outside the stimulated region in the SW suppression process. Tissue size : 350×350 , stimulated region 150×150 , spiral waves in the center 100×100 . (a) $t = 0 \text{ ms}$; (b) $t = 27.00 \text{ ms}$; (c) $t = 261.73 \text{ ms}$; (d) $t = 1123.80 \text{ ms}$. ($k = 1$, $A = 83.53 \mu\text{A cm}^{-2}$, $F = 21.40 \text{ Hz}$, $\theta = 50\%$, SR = 1.96% in spiral waves region).

3.2. Wave generation threshold

Let us consider a tissue initially in a resting state and stimulated by an electrodes grid with fixed frequency and duty cycle values and let us investigate the influence of the variation of k on the generation of waves. Fig. 6 shows the minimum values of SR above which waves are generated ($k = 1$ and $k = 0.75$) versus the amplitude of I_{stim} . Compared to Fig. 2, when $k = 1$, the threshold allowing to generate waves is therefore much smaller than the necessary amplitude to suppress SW. It is thus impossible to eliminate SW without generating new waves in this case. When $k = 0.75$, the threshold of wave generation is shifted and the amplitude of I_{stim} is increased considerably. Thus, decreasing the value of k may provide a potential way to suppress SW without generating new ones.

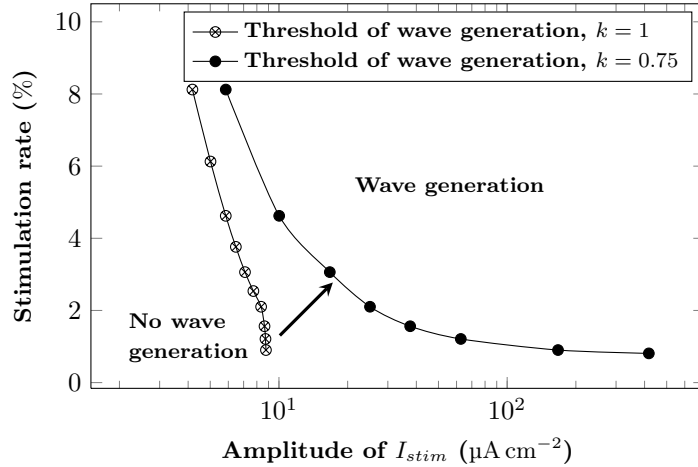


FIGURE 6: Comparison of thresholds of wave generation for $k = 1$ and $k = 0.75$. ($F = 21.40$ Hz, $\theta = 50\%$).

In order to investigate the influence of k on wave generation, stimulations with a single electrode injected to the tissue initially in resting state have been performed. As shown in Fig. 7, the minimum amplitude of I_{stim} leading to wave generation can reach $A = 2.09 mA cm^{-2}$ when $k = 0.75$, which is 238 times larger than what is needed for $k = 1$ ($A = 8.77 \mu A cm^{-2}$). So, in the next

1 subsection, the effect of the modification of the parameter k combined to the
2 SW suppression is studied.

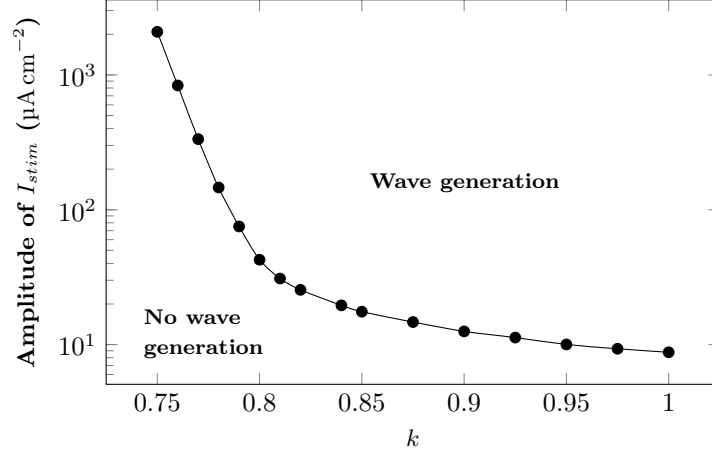


FIGURE 7: Amplitude of stimulus vs. Parameter k characterizing the threshold of waves generation using one stimulating electrode. ($F = 21.40$ Hz, $\theta = 50\%$).

3 3.3. Hybrid stimulation

4 From precedent results, we know that suppressing locally SW by electrical
5 stimuli without generating new waves may be obtained by modifying the value
6 of the parameter k . Biologically, it could correspond to use pharmacological
7 agents in order to reduce the conductance of the sodium channels. This yields a
8 hybrid method. First, our simulation results show that when $k < 0.73$, it is even
9 not possible to excite the tissue. The cells have only sub-threshold oscillations
10 even if the stimulation strength becomes substantial. Namely, considering the
11 fact that FHN model is a fast-slow dynamical system, the velocity of traveling
12 wave depends mainly on the fast dynamics *i.e* on the depolarization phase of the
13 action potential. In this case, the front velocity value is mainly a function of the
14 nonlinear threshold α of the sodium conductance and the diffusion parameter
15 D [34, 35] and depends also on the value of k . There exists a velocity threshold,
16 below which the system is unstable and waves fail to propagate through the
17 tissue [30]. Since k controls the dynamics of sodium current, it is clear that a

- 1 relatively small value of k will result in a too low excitability of stimulated tissue
2 and the collapse of the waves.

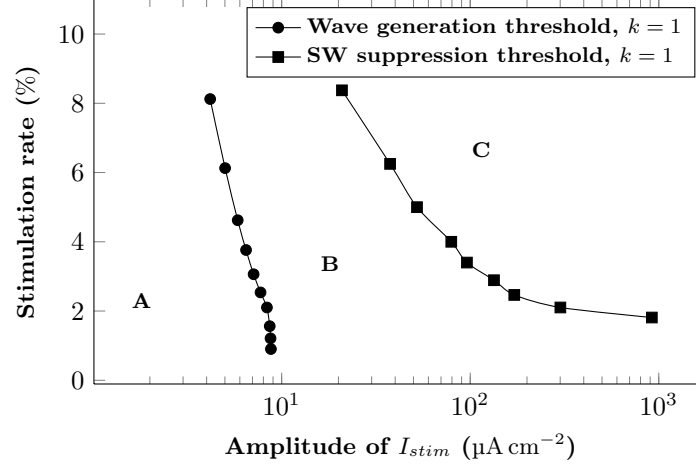


FIGURE 8: Comparison of the waves generation threshold and the SW suppression threshold with $F = 21.40$ Hz, $\theta = 50\%$. $k = 1$.

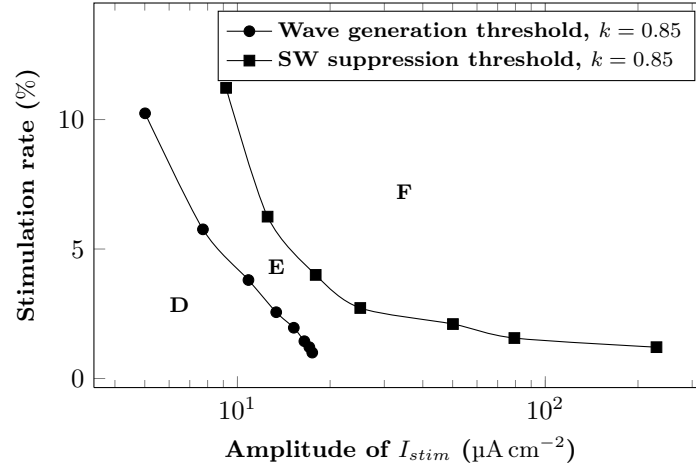


FIGURE 9: Comparison of the waves generation threshold and the SW suppression threshold with $F = 21.40$ Hz, $\theta = 50\%$. $k = 0.85$.

- 3 The results of the hybrid stimulation are shown in Figs. 8, 9, 10. As k
4 decreases, two curves are getting nearer to each other : the wave generation

1 threshold increases and the spiral wave suppression threshold decreases. When
 2 $k = 0.75$ (Fig. 10), they are totally reversed compared to those when $k = 1$ (Fig.
 3 8). It can be observed that in the regions B and E , SW cannot be suppressed
 4 and propagate as other new waves provoked by the stimulation in the tissue. The
 5 suppression can be performed in C , F and I regions, but the stimuli generate
 6 also new waves. Nothing happens (no suppression of SW and no generation of
 7 waves) in A , D and G , the stimulation process does not influence the dynamics
 8 of the tissue. In the last region H , SW can be suppressed without yielding new
 9 waves and the tissue is still excitable after the suppression of SW. This region
 10 is interesting in the optimization of the stimulation process.

11 4. Conclusion and Discussion

12 It is well known that atrial fibrillation (AF) begets AF [36]. However, accor-
 13 ding to Allessie's concept, AF can also self terminate if the spiral waves (SW)
 14 number is not enough to self maintain this cardiac arrhythmia [10]. In fact, the
 15 ideal atrial stimulation/defibrillation method should be able to suppress enough
 16 SW in a dedicated region to stop fibrillating for the whole heart, but without

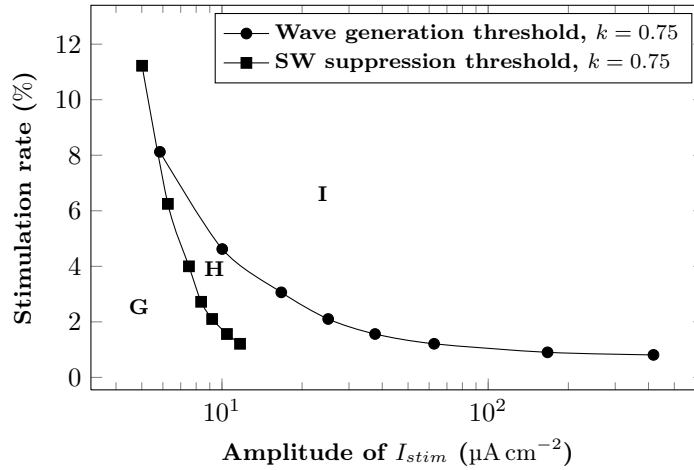


FIGURE 10: Comparison of the waves generation threshold and the SW suppression threshold with $F = 21.40$ Hz, $\theta = 50\%$. $k = 0.75$.

1 generating new ones. In this intend, we studied here a simulated tissue of car-
2 diac cells using FHN model. Compared to other some realistic ionic models,
3 the FHN model is usually considered as a simple one and has its shortcomings.
4 However, we adopted it because it seems to be well adapted for modeling the
5 main dynamics of ion channels we needed in our study.

6 In this numerical model study, we showed that it may be possible to sup-
7 press spiral waves (SW) inside a local area by using a hybrid strategy. This
8 strategy combined the optimization of multifocal stimulations delivered via a
9 grid of electrodes, and simulated sodium channel modification of the cardiac
10 tissue. Although this strategy may only be a local and temporary solution (the
11 confined area may be colonized by outside wandering SW), we believe that it
12 could be of interest to restore the normal sinus rhythm under certain conditions
13 considering for example Allessie’s concept. In our study, we took into account
14 physical parameters like the size and geometry of the electrode network as well
15 as the number of the stimulating electrodes needed. We also identified some
16 ideal pacing parameters in order to prevent from SW reinduction. However, in
17 order to address this last issue, one of the options available is to modify the
18 action potential dynamics (we choose here the sodium channel modification) in
19 a simulated cardiac tissue.

20 In clinical practice, it is well known that antiarrhythmic drugs can optimize
21 atrial defibrillation success rate. Na^+ channel blockers are commonly used to
22 control the cardiac rhythm, and especially during AF [7, 37, 38, 39]. Whereas,
23 their use can be limited by potentially serious side effects like other antiarrhyth-
24 mic drugs, they remain at the first line therapy in AF treatment [40].

25 In summary, we showed that a hybrid strategy applied to the FitzHugh-
26 Nagumo model helped to identify specific regions where it was possible to sup-
27 press SW without provoking new reentries. In order to confirm these encouraging
28 results, it would be of interest to apply the same strategy to more realistic ionic
29 models. The next step could also be to use in vitro culture of cardiomyocytes
30 [41, 42, 43] . The MEA (Microelectrode Array) technology could be a useful
31 tool in testing the role of multifocal stimulation strategies on induced SW. As a

1 clinical perspective, we may infer that resetting one or more local regions of the
2 left atrium via implanted array of electrodes connected to a dedicated pacing
3 device may help to eradicate enough SW to get back to normal sinus rhythm.

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