Cell-to-cell Mathematical Modeling of Arrhythmia Phenomena in the Heart

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Abstract

With an aperiodic, self-similar distribution of two-dimensional arrangement of atrial cells, it is possible to simulate such phenomena as Fibrillation, Fluttering, and a sequence of Fibrillation-Fluttering. The topology of a network of cells may facilitate the initiation and development of arrhythmias such as Fluttering and Fibrillation. Using a GPU parallel architecture, two basic cell topologies were considered in this simulation, an aperiodic, fractal distribution of connections among 462 cells, and a chessboard-like geometry of 60×60 and 600×600 cells. With a complex set of initial conditions, it is possible to produce tissue behavior that may be identified with arrhythmias. Finally, we found several sets of initial conditions that show how a mesh of cells may exhibit Fibrillation that evolves into Fluttering.

Keywords: Fibrillation, Fluttering, Arrhythmia, Pseudo-Electrogram, Mathematical modeling.

1. Introduction

For the sake of mathematical simplicity, we define only two types of arrhythmia in excitable media. One type is known as *Fluttering* and is related to reentrant waves of excitation, which remain in a self-perpetuating steady state. The second and more complex type of arrhythmia considered in this article is known as *Fibrillation*. Meanwhile, Fluttering is adequately described employing continuous or cell-to-cell modeling; the Fibrillation phenomenon is

more difficult to simulate with deterministic models. Since the first research papers, some authors, [5], [38], considered that Fibrillation could only be approached mathematically on a statistical basis, mainly due to the random distribution of anastomosis fibers in the heart. This standpoint is still in use [33], [34], [36], [42], but the primary mechanisms of flutter and Fibrillation are not fully understood. The researchers still have incomplete knowledge of how arrhythmias, such as ventricular Fibrillation, begin and develop. In opposition to the statistical basis thesis, we present a deterministic model in which we introduce complexity in the cellular network geometry as a factor for the generation of arrhythmias. In a network with simple topology, we produce Fibrillation by adding a set of complex initial conditions in a completely deterministic set of ordinary differential equations.

In this article, we study some of the consequences obtained by modeling weakly connected networks through different distributions of excitable cells within the mesh, what we call *the geometry of the network*. In this context, we argue in subsection 3 why cell-to-cell modeling fits better than the continuous model, at least to model the arrhythmia. We will illustrate in the Methods section 2, that neither the diffusivity provided by partial differential equations nor by the cell-to-cell coupling requires a complex dynamics in the cells to produce fibrillation and flutter phenomena. Elliptic-type operators give diffusivity in continuous mathematical modeling and also in cell-to-cell modeling using *weakly coupled variables* (see section 3.0.1). Nevertheless, we show *in silico* that fibrillation and Fluttering can be modeled even by using the simplest excitable cell models including only a few variables and “realistic models of heart cells” and compare the *silico* experiments of both realistic vs. few variables models [22], [24].

The main difference between flutter and Fibrillation, according to the classic definitions [38], is the randomness of Fibrillation as opposed to the regularity of flutter. Randomness precludes sharp, well-defined wavefronts. One contribution of our work is to introduce some degree of complexity (the tiling of Figure 5) instead of randomness to present an *in silico* phenomena, which can be identified with Fibrillation. We simulated Fibrillation in a simple Chessboard geometry in a mesh of 60×60 and a mesh of 600×600 cells by introducing a complex set of initial conditions. This Fibrillation is achieved with both models, two variables and Nygren model of the human heart. Another novelty in the present paper is that, contrary to the commonly established, Fluttering can be produced at a cellular level by a dynamic obstacle formed with a few cells and also by fixed non-dynamical obstacles

(for a definition see section 2.2.1). Finally, we found several sets of initial conditions that show how, even in the simplest mesh of cells, they may exhibit Fibrillation that evolves into Fluttering. This phenomenon that is well known in medical literature, for the best of our knowledge, is for the first time shown with human heart cell models.

2. Methods

2.1. Individual Cell models

In this work, we use two-variable models of excitable cells [1], [4], [12], [24], as well as a physiologically accurate model of Nygren and coworkers [27]. The idea of using two variables vs. many variables models is to extract the properties of a net of cells that depend only on the excitable media and do not depend on the limitations of individual cell models.

The models of excitable cells included here, as usual, go through four stages [40]: resting, exciting, excited, and refractory states; also, the models of coupled cells provide solitary waves flexible enough to flutter and fibrillate. In this way, the models represent observables in real tissue to some extent (for a mathematical definition of *observable* see section 3.0.1). The convenience and relevance of utilizing more complex models of individual cells is discussed in sections 5 and 6.

2.1.1. Realistic Models

There are many physiologically accurate models of excitable cells in the Heart, among them: Courtemanche et al., [8], Nygren et al., [27]; Lindblad et al., [21]. In this paper, we use Nygren et al. model (N), taking into account that the N model reconstructs action potential data that represent recordings from human atrial cells. In the N model, the sustained outward K^+ current determines the duration of the action potential (AP). On the other hand, the AP shape during the peak and plateau phases is determined by transient outward K^+ current, I_{sus} , and L-type Ca^{2+} current. The N model has 29 variables: 12 transmembrane currents, a two-compartment sarcoplasmic reticulum (SR), and restricted subsarcolemmal space for calcium dynamics handling and calcium buffering.

Regarding the number of variables, simulating a system of 360 000 cells, as we do in this work, is somehow onerous in computational terms. For example, 360 000 times 29 gives a system of ODE of 104 400 variables. For instance, simulating 15 seconds with step-size of the order of milliseconds may

Figure (1) Color code of the AP corresponding to Nygren's model. In the video captures and videos, the deep blue color corresponds to a rest state and deep red to a maximum of the action potential in the Nygren et al. cell model.

81 illustrate what we mean by “onerous computationally”. To accomplish this
 82 task, we employed parallel architecture using Nvidia GPU (RTX 2080 Ti),
 83 and we developed it with C-CUDA libraries. The Procedures and Algorithms
 84 that we used are described in Nicolás and coworkers [25]. To solve the ODE
 85 systems, we implemented a Runge-Kutta numerical method of order four
 86 with absolute error tolerances of 10^{-6} .

87 2.1.2. Modeling Atrial fibrillation

88 For the Nygren model, we used the data in Cherry et al. [7] and refer-
 89 ences therein to simulate electrophysiological changes that occur as a result of
 90 sustained Atrial Fibrillation. Specifically, $I_{Ca,L}$ is decreased 30 percent of its
 91 original value, and I_{to} and I_{Kur} are both decreased to 50 percent of their orig-
 92 inal values. As mentioned in Cherry et al., APs are triangular in morphology
 93 at all cycle lengths and are shorter under these conditions. Additionally, rate
 94 adaptation is largely abolished. The reduction in rate adaptation shown by
 95 the model is in agreement with some experimental studies of chronic Atrial
 96 Fibrillation (AF) and tissues obtained from right atrial appendage tissue of
 97 patients with chronic AF (see references therein [7]). Low conductivity of
 98 cells in the heart is associated with ischemia [18], and in experiments, con-
 99 ductivity may be lowered pharmacologically by heptanol [5].

100 Finally, to simulate Fibrillation as those in Figure 15, we found sets of
 101 initial conditions by implementing a random search in both models N and

102 B. In generating in the net the initial conditions, we alternate stimulated
 103 cells with refractory state cells. These complex sets of initial conditions
 104 in continuous media modeled with partial differential equations represent
 105 a discontinuous function and, therefore, highly improbable sets. However,
 106 modeling cell-to-cell such complex sets of initial conditions is not improbable
 107 since its discontinuity is inherent to the heart tissue structure. Discontinuity
 108 in the real tissue is another argument that favors ODE modeling over PDE
 109 modeling. Summarizing, we consider two types of initial conditions: (a) One
 110 small connected set of exciting cells surrounded by refractory cells; (b) Many
 111 small islands of exciting cells scattered throughout the entire net mixed with
 112 refractory cells. The interested reader may obtain our data on the sets of
 113 initial conditions under request to the corresponding author.

114 A vast difference exists among two-variable models and realistic ones,
 115 regarding, for instance, the number of observable phenomena. Nevertheless,
 116 all ordinary differential equations models we used have four states. A rest
 117 state corresponding to a minimum value of the AP variable; an exciting state,
 118 which corresponds to a negative derivative of the AP profile; an excited state,
 119 corresponding to the maximum of the AP profile; and a refractory state,
 120 associated to a positive derivative of the AP profile. In figures 1 and 2(b),
 121 the rest state is represented in the deepest blue color, and the excited state
 122 is represented in the darkest red.

123 2.1.3. Simple ordinary differential equations models

124 For this part, although only the experiments with the Barkley [4] model
 125 are reported, the Fitzhugh-Nagumo model and the Aliev-Panfilov model
 126 whose description is elsewhere [12], [24], [1] were also subject of experimenta-
 127 tion. Since results obtained for Fluttering and Fibrillation are similar to those
 128 obtained with the Barkley model, Fitzhugh-Nagumo, and Aliev-Panfilov, we
 129 do not include plots of the last two, and from now on we will only refer to
 130 the Barkley model when we talk about two-variable models. If a suitable
 131 geometry of the cell system is introduced (see section 2.2), it is possible to
 132 represent Fibrillation and flutter phenomena with all these models. They
 133 are two-variable models, as is well known, and they are dynamical bi-stable
 134 systems. For these systems, the existence of limit cycles is well established
 135 in the mathematical theory, and even *analytical* approximations of physio-
 136 logically relevant limit cycles in a region between heteroclinic trajectories are
 137 possible to calculate [17].

Figure (2) The AP corresponding to the Barkley model of equation (1), recall that x and t are adimensional for this model. Each value of x of the plot in the left corresponds a color to each height. The color bar corresponds to the Barkley model's states in the videos and two-dimensional plots shown in this paper. Deep blue corresponds to rest state $x(t) = 0$ and the darkest red corresponds to $x(t) = 1$.

138 The Barkley model used in this paper is the following

$$\begin{aligned} \frac{dx}{dt} &= \frac{1}{\varepsilon} x (1 - x) \left(x - \frac{y + b}{a} \right) \\ \frac{dy}{dt} &= gx - y, \end{aligned} \quad (1)$$

139 where a, b, g, ε are fixed parameters. Figure 2 shows an AP of Barkley model
 140 with initial conditions $x(0) = 0.4$, $y(0) = 0$. The variable x in this arti-
 141 cle corresponds to an adimensional voltage, and may be identified with the
 142 variable V of the Nygren model.

143 2.2. Cell-to-cell Nets Geometry

144 The geometry in cellular systems can be determined by considering the
 145 geometry of the individual cells and how they are connected. For example,
 146 the working cells in the auricula in the heart are mostly cylindrical and are
 147 connected in a way that favors the longitudinal transmission of Action Po-
 148 tentials [35]. By comparison, brain cells have extremely branched forms, and
 149 their connections can reach a complexity that is far from being understood
 150 in its entirety [31]. In the following system,

$$\dot{\alpha}_i = G_i(\alpha_i) + \varepsilon_{ij} \sum_{j \neq i} (\alpha_j - \alpha_i), \quad \alpha_i \in \mathbb{R}^n, \quad (2)$$

where n represents the number of variables of each cell. The geometry of the network (and hence the diffusivity) is determined by the values of ε_{ij} different from zero. So, equation (2) can be written as a vectorial equation with $\alpha = (\alpha_1, \dots, \alpha_n)$, $G(\alpha) = (G_1(\alpha), \dots, G_n(\alpha))$. So, as an illustration, for two variables with the Barkley model in equation (1), the system (2) has the form

$$\begin{aligned} \frac{dx_i}{dt} &= \frac{1}{\varepsilon} x_i (1 - x_i) \left(x_i - \frac{y_i + b}{a} \right) + \varepsilon_{ij} \sum_{i \neq j} (x_j - x_i), \\ \frac{dy_i}{dt} &= gx_i - y_i, \quad i = 1, \dots, N, \end{aligned} \quad (3)$$

where N is the number of cells in the system and $\varepsilon_{ij} = 0$ for unconnected cells. Notice that only the x_i variables are coupled to each other as corresponds to variables related to the Action Potential in the heart's cells. Similarly, for the N model of atrial cells of 28 variables, only the voltage is coupled.

In practice, the use of rectangular and cubic matrices are the most commonly used [9], [13], [28], [41], without considering the complex geometry of the cytoarchitecture of the network that exists in the tissues of living beings. Systems made of systems of equations of the form (2) are known as *weakly connected networks* (WCN) and have a vast number of applications in neurophysiology [14]; cardiology [41], [9], [28]; and many other sciences. In general, WCN have applications in every system of cells connected through gap junctions, such as those in atrial tissue in the human heart.

2.2.1. Obstacles

There are two types of obstacles to be considered: dynamical and static. Dynamical obstacles are formed by individuals or groups of cells in a refractory or excitable or excited state. Static obstacles are formed by objects that do not change in time. They may correspond to fibroblast, adiposity in real tissue, or dead tissue due to heart attacks. In this article, we consider only dynamic obstacles.

2.2.2. Tiling

One of the central thesis of this work is that, under certain circumstances, an intricate connection between cells is essential in the generation of flutter

Figure (3) The procedure presented in the Figure is repeated several times to produce the tiling of Figure 5. Note the fractal structure obtained.

Figure (4) Here is shown one of many possible representations of working cells in the heart. They are not distributed randomly but following the distribution described in Figure 5, where the reader can find the color's code. The arrangement here presented corresponds to the up and left corner of Figure 5.

179 and Fibrillation. We take as a paradigm of cell connections, hence the in-
 180 trinsic geometry of the cells, those of the working cells in the auricula, and
 181 the ventricle in the heart. In the literature, histological studies of heart's
 182 cells are available [35]. Nevertheless, mathematical models, including the
 183 real geometry of the cells, are more scarce. Spach and Heidlage [36, Fig. 1]
 184 give a schematic representation myocardial architecture of 33 cells in a two-
 185 dimensional array. Following their representation, Figure 4 depicts a two
 186 dimensional model of cells, but our model is not based in real cells as in [36]
 187 but in a distribution generated by an aperiodic tiling called "Table" which
 188 we describe below. After the cells' connectivity is fixed, it is possible to estab-
 189 lish a correspondent cell geometry, as in Figure 4. Note that the random-like
 190 distribution of the cells is not for real; in Figure 4 are represented in the up
 191 and left corner in Figure 5. This distribution can be verified, noting that the
 192 code of colors corresponds to the same cells, meaning green for cells with six
 193 connections, pink for cells with five connections, and so on. Observe that in
 194 our figure, cell connections occur only in the vertical edges where most of the
 195 standard electrical coupling between cells have place [35].

196 The values $\varepsilon_{i,j}$ different from zero in equation (2) give an adjacency ma-

Figure (5) Example of a “Table” tiling showing the number of connections of each cell. Cells in green are connected with six cells, cells in pink are connected with five cells, and so on, as indicated in the figure’s left-hand side.

trix between cells which represents the geometry of the entire net. In this paper, we use a “Table” distribution of connections among cells. A *Table* is a polygon belonging to the class that can be tiled by a finite number of smaller, congruent copies of itself (see [32], where the properties of the “Table” as tiling-dynamical-system are studied). We used this tiling for the following reasons. a) It is an aperiodic tiling of the plane so that some degree of complexity is intrinsic in the adjacency matrix. b) The tiling is self-similar, so it does possess a fractal structure. c) Each cell is connected to an average of 4.86 cells, which is a good 2D approximation compared with an average of 9.1 reported from experimental data measures by Hoyt et al. [15] for three-dimensional structures. Besides, the connectivity approaches that of the cells in the Spach diagrams of Figure 1 in [36], which represents a sample of two-dimensional tissue cells with average two-dimensional connectivity of 4.66 cells. d) The “Table” aperiodic setting provides the more simple arrangement in the authors’ opinion, which satisfies the mentioned properties.

Figure 5 shows a tiling (see Figure 5) used in our in silico experiments. This arrangement is only one sample of an infinite number of such aperiodic tilings. It is necessary to assign each cell a number to set a matrix corre-

sponding to the tiling in Figure 5. Then, once the assignment is completed, the adjacency matrix can be settled down. Algorithms to construct the *Table* and other aperiodic tilings are well known, but finding algorithms to set the associated adjacency matrix of such tilings is still an open problem, to the best of the authors' knowledge. The recursive procedure for the self-similar aperiodic tiling is shown in Figure 3.

2.3. Flutter, Fibrillation, and pseudo-EG mathematical definitions

In this paper, we depart from the classical definitions of Flutter and Fibrillation in use to formulate the following definition that applies to the rest of the article.

Definition. Flutter and Fibrillation are reentrant waves of excitation which remain in a self-perpetuating steady-state; flutter having a periodic (or nearly periodic) pseudo-electrogram (pseudo-EG), and Fibrillation having a non-periodic pseudo-electrogram. Alternatively, we call Fibrillation a steady-state, self-perpetuating pattern of systems of cells without a defined front or back wave.

2.3.1. Mathematical Pseudo-EG

Following the classical definitions, we consider flutter and Fibrillation as self-generating phenomena. Flutter is considered a periodic wave of waves contrary to Fibrillation, which is considered a highly complex non-periodic wave or waves. A precise difference between flutter and Fibrillation is provided by the pseudo-EG which is calculated by the following formula:

$$EG(t) = \sum_{i \neq j} g_{i,j} (V_j(t) - V_i(t)), \quad (4)$$

which is a non-weighted, two-dimensional version of the formula of Kazbanov et al. in [16]. Observe that the distance between cells may be taken into account handling specific weights; however, in this work this parameter is neglected since the size of the modeled tissue is small and, more importantly, the geometry and thus the real distance between cells is not modeled in our study, so that weight due to the distance may not be considered.

2.3.2. Electrogram analysis

One of the most widely used techniques for analyzing fluctuations in the cardiac cycle period is the detrended fluctuation analysis (DFA). This technique has the advantage that it prevents the detection of inexistent long

term correlations produced by the non-stationarity of the time series. Given the complexity of the electrograms analyzed, in this work, we used the DFA technique to determine if they present either a random behavior or a temporal structure with long term correlations, which gave us information about the propagation of the electrical signal obtained from the in silico experiments. The scaling exponents α obtained from the DFA analyses were evaluated as previously described by Peng et al. [29]. In short, a scaling exponent α near or equal to 0.5 indicates a random or uncorrelated behavior, whereas a value near or equal to 1 indicates long-term correlations in the time series; that is, current data are statistically correlated with previous data, which reflects a non-random behavior.

3. Theory

The concept of observable has been used through the article; next, we provide a mathematical definition. We also discuss a comparison between PDE and cell-to-cell models, which is relevant for the understanding of our results.

3.0.1. Observables

In mathematical modeling, the dynamics of the cells that form living beings (or that represent other excitable means) are represented by dynamic systems of form,

$$\dot{y} = G(y), \quad y \in \mathcal{Y} \subset \mathbb{R}^N, \quad (5)$$

where the dot denotes the time's derivative. So, cells are thought of as not wholly known (so far) dynamical systems, let us say

$$\dot{x} = F(x), \quad x \in \mathcal{X} \subset \mathbb{R}^M, N < M, \quad (6)$$

of which (5) is a representation, and scientists expect that the model G in some sense approaches F , which remains partially unknown. More formally, (5) is a model of (6) if there exists a continuous function (called observation [14]) $h : \mathcal{X} \rightarrow \mathcal{Y}$ such that if $x(t)$ is a solution of (6), then $y(t) = h(x(t))$ is a solution of (5). In practice, many information of system (6) is unknown, for instance, the dimension of the space (i. e., in this instance, the actual number of variables of the system). In many cases, a model could be a rough representation of the real system. As mentioned by Hoppenstead and

276 Izhikevich [14], for example when (6) has a periodic solution and the model
 277 (5) is one dimensional, the observation $h(x(t))$ cannot be a solution of (5)
 278 unless h maps the limit cycle to a point. The existence of the function h and
 279 its properties are purely theoretic but allow us to speak about the relations
 280 of the real system (6) with the model in a mathematical fashion. As an
 281 example the variable $y(t) = h(x(t))$ is called an *observable*. In this article,
 282 the dimension of $\mathcal{Y}$ is bigger or equal than 2 so, we call *observable* to each of
 283 the y 's component functions.

284 As science advances, mathematical models of cells include an increasing
 285 number of observables and each observable with an increasing refinement
 286 following experimental data. In this way, we obtain systems of complex
 287 differential equations that include an increasing number of equations. A
 288 typical example of this phenomena is the development in the study of the
 289 sinoatrial node cells in the heart (SAN) [6], [26], (for a detailed review of the
 290 SAN mathematical models see [19]).

However, this is just the first step on the way to modeling the actual cell
 tissue. A second step consists of forming a system of systems of equations by
 coupling variables among different systems, let say n different systems like
 the following

$$\dot{y}_i = G_i(y_i) + C_i(y_1, y_2, \dots, y_n), \quad i = 1, \dots, n. \quad (7)$$

291 A very used example of a coupling functions C_i are linear functions of the form
 292 $\varepsilon_{ij} \sum_{j \neq i} (y_j - y_i)$ where ε_{ij} are small (experimentally obtained) parameters
 293 and the values assigned to j depend on the geometry of the net. There are
 294 at least two ways of modeling excitable media. One is by utilizing partial
 295 differential equations (PDE) to represent the diffusive nature of the media.
 296 Another is by establishing a system of cells, each cell, in turn, is a system
 297 of ordinary differential equations (ODE). In ordinary differential equations,
 298 diffusion of the excitatory wave is modeled by coupling appropriate variables,
 299 for instance, the Action Potential (AP) in excitable biological cells. In this
 300 paper, we call *continuous* mathematical modeling to the first form (PDE),
 301 and the last form (ODE) is what we call *cell-to-cell modeling*.

302 3.0.2. Continuous vs. cell-to-cell modeling

303 Continuous mathematical modeling of anisotropic media such as ventric-
 304 ular tissue, normally includes fiber patterns and the continuous rotation of

the fiber axis [11], so that the equations have the form:

$$\frac{\partial V}{\partial t} = \nabla \cdot (D \nabla V) - I(V, y), \quad (8)$$

$$\frac{\partial y}{\partial t} = g(V, y) \quad (9)$$

$$\hat{n} \cdot (D \nabla V) = 0. \quad (10)$$

Where $V = V(t, x_1, x_2, x_3)$ is the membrane potential, (x_1, x_2, x_3) in $\Omega \subset \mathbb{R}^3$, I is the total current through the membrane, y is a vector of gate variables describing the dynamics of the various currents that constitute I , ∇V denotes the gradient operator, and D is a conductivity tensor divided cell surface to volume ratio times the membrane capacitance of the cell. We will show that a system of equations (3) is equivalent to the system (8), (9). Note that equation (10) represents Neumann boundary conditions where $\hat{n}$ is the normal to $\partial\Omega$. To begin with, observe that the tensor D is of the form

$$D = \begin{pmatrix} D_{11} & D_{12} & 0 \\ D_{21} & D_{22} & 0 \\ 0 & 0 & D_{33} \end{pmatrix},$$

where D_{ij} are functions of diffusivities parallel and perpendicular to the fiber, and $\theta(x_3)$, the angle between the fiber to the axis of each plane. In the setting of [11], is easily shown that for a two-dimensional model, since $\theta(x_3) \equiv 0$, then D becomes

$$D = \begin{pmatrix} D_{11} & 0 & 0 \\ 0 & D_{22} & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

where now D_{11}, D_{22} are constants, so that the elliptic operator $\nabla \cdot (D \nabla V)$ in equation (8) becomes simply

$$\nabla \cdot (D \nabla V) = D_{11} \frac{\partial^2 V}{\partial x_1^2} + D_{22} \frac{\partial^2 V}{\partial x_2^2}.$$

After discretization of the second partial derivatives we obtain

$$\nabla \cdot (D \nabla V) = \left\{ \frac{D_{11}}{\Delta^2} (V_{i+1,j}^n - 2V_{i,j}^n + V_{i-1,j}^n) + \frac{D_{22}}{\Delta^2} (V_{i,j+1}^n - 2V_{i,j}^n + V_{i,j-1}^n) \right\}_{i,j}, \quad (11)$$

321 a formula which is valid for interior cells in the grid. Since in many articles
 322 including [11] the grid spacing is about $\Delta \approx 200 - 300 \mu\text{m}$ which is bigger
 323 than the length of the cell, $\approx 80 \mu\text{m}$ [35], is worth to mention that PDE
 324 continuous approach is, in this case, not better than cell-to-cell modeling
 325 whatsoever. Moreover, note that equation (11) corresponds to a rectangu-
 326 lar grid of square cells (of much bigger dimensions than actual heart cells),
 327 meaning a chessboard-like geometry of the cells. In this way, a complex
 328 geometry, such as that depicted in Figure 4, cannot be represented by the
 329 elliptic operator in equation (8) since such an arrangement can not at all be
 330 represented by tridiagonal matrices such as those in equation (11).

331 A further consideration regarding the mathematics in this article must
 332 be considered. Flutter and arrhythmia will appear as solutions to systems
 333 of ODEs for a particular set of initial conditions. However, somehow the
 334 solutions appear in some fashion unpredictable since they occur after global
 335 bifurcations of the parameters given by the conductivity and of the distribu-
 336 tion of conductivity. Hence, only after integrating the systems will emerge
 337 more of the most striking patterns of the next section in an unexpected form.
 338 Although the spirals formed by the Barkley model [2], [3], [4], and other mod-
 339 els [10] have been extensively studied, the study of the combination of spirals,
 340 collisions of spirals, and spirals emerging after a massive dynamic blocking
 341 is still of interest regarding Fibrillation.

342 4. Results

343 In this paper, the waves mentioned in the definitions above are travel-
 344 ing waves with a defined front and back given by the ordinary differential
 345 equations of the different bistable ODE systems. As mentioned in section
 346 2, systems with no apparent wave's fronts and backs are noticeable. Never-
 347 theless, a periodic pseudo-EG may appear after time in some of the systems
 348 formed with a small number of cells. While flutter is produced by the collision
 349 of traveling waves with dynamical or static obstacles at a macroscopic level
 350 as in the classic definition, there is a difference in this document with the
 351 standard definitions since microscopic (cell-to-cell) collisions are considered,
 352 and very intricate patterns may happen as, for instance, these in Figures 13
 353 and 14.

354 In both types of models, two-variables and realistic Nygren model, we
 355 found that by using the tiling distribution described in Figure 5 the propa-
 356 gation of voltage is allowed in a very efficient way under normal conditions.

Table (1) Detrended Fluctuation Analysis for N model (atrial cells)

Network	Initial Conditions	Figure	pseudo-EG	α
aperiodic tiling	(a)	Figure 8	quasi periodic	1.0515
aperiodic tiling	(b)	Figure 7(b)	quasi periodic	1.0130
60×60	(a)	Figure 10	quasi periodic	0.7790
60×60	(b)	Figure 11	non-periodic	0.5445
600×600	(a)	Figure 12 (d)	non-periodic	0.4192
600×600	(b)	Figure 13	non-periodic	0.4413
600×600	(b)	Figure 14 (d)	non-periodic	0.5620
600×600	(b)	Figure 15 (b)	non-periodic	0.5246

Paradoxically under certain circumstances, the same topology facilitates the generation of Fluttering.

Moreover, in a chessboard arrange of 600×600 cells, we found that the generation of some Fibrillation generated by a randomly stimulated number of cells evolves to a stable multi-spiral which resembles Fluttering at least in the generation of pseudo-EG with some periodic resemblance as, for instance, in Figure 7.

We recall that we presented the description of the 29-variable model N in section 2.1.1 and a two variable model B in section 2.1.3. Given that only the Nygren model corresponds to real atrial cells in the heart, we used the DFA technique only with this model. In Table 1 we present the α values obtained for each in silico experiment. From subsection 2.1.2, recall that there are two types of initial conditions: (a) One small connected set of exciting cells surrounded by refractory cells; (b) Many islands of exciting cells scattered throughout the entire net mixed with refractory cells. We recall that a scaling exponent α near or equal to 0.5 indicates a random or uncorrelated behavior, whereas a value near or equal to 1 indicates long term correlations in the time series.

Given the coincidences between non-realistic vs. realistic models, we conclude that the generation of Fluttering and fibrillations does depend strongly on the nature of the diffusive media, more than in the variables involved in the modeling. Nevertheless, realistic models facilitate the reduction of parameter values according to experimental data that occur during arrhythmias.

Figure (6) Massive blocking produces Fibrillation and evolves to Fluttering here in the tiling of Figure 5. The link to the video of the complete sequence is <http://pacifico.izt.uam.mx/aurelio/>.

380 4.1. Fibrillation at a microscopic level case Nygren Model

381 In Figure 6 after a massive blocking with dynamical obstacles (initial
382 conditions type (a)) in the aperiodic distribution of cells of Figure 5, an
383 apparent Fibrillation becomes a Fluttering, i. e., a self-perpetuating spiral.
384 This event is well known in the literature, but as far as we know, it is for the
385 first time reproduced in silico.

386 This coincidence in the formation of spirals of the two models, one cari-
387 cature (Barkley) and the other realistic (Nygren), provides us with evidence
388 that the Fibrillation that becomes Fluttering occurs naturally in any diffusive
389 media under appropriate initial conditions. Notice that the pseudo-EG after
390 a non-periodic behavior from $t = 0$ to $t < 2500$ (recall that t is adimensional
391 for Barkley model) resembles a periodic plot. See Figure 7.

392 Another interesting kind of Fluttering is produced by stimulating a small
393 number of connected cells and blocking them with neighboring cells in a
394 refractory state. Here, the array of cells facilitates the propagation due to its

(a) Steady state of the Nygren system.

(b) Pseudo-EG For Nygren Model

(c) Steady state of Barkley system.

(d) Pseudo-EG for Barkley model.

Figure (7) In both Nygren and Barkley models, massive blocking produces Fibrillation, which becomes Fluttering. Noticeable differences do appear in the wavelength as a consequence of intrinsic dynamics in each model, but in both of the models under certain sets of initial conditions, a periodic self-perpetuating spiral emerges. The pseudo-EG in both Figure 7(b) and 7(d) show certain periodicity.

Figure 8 (a) A group of cells surrounded by cells in a refractory state is stimulated. (b), (c), (d), (e) A self-generating spiral which may be identified with Fluttering is apparent. (f) A quasiperiodic pseudo-EG is produced after a small, turbulent interval of time similar to that in Figure 7d.

395 fractal nature paradoxically when a dynamic obstacle (a group of cells out
396 of phase) prevents the wave from propagating. See Figure 8.

397 A similar phenomenon occurs with the Barkley model, but in this case,
398 by blocking only one cell. A single excited cell surrounded by refractory cells
399 produces (when the network has critical connectivity) an intricate pattern
400 of diffusion. In this way, some spirals arise due to variable cellular connec-
401 tivity and low conductivity. It is worth mentioning that spirals broke into
402 scrolls, which, according to the electrogram obtained, may be identified with
403 Fibrillation of the system (see Figure 9).

404 After studying the Table array, we proceed to study a more significant
405 number of cells but scattered in simpler arrangements. For both the Nygren
406 and Barkley models, we started with a square of 60 by 60 cells. Furthermore,
407 we continue with a 600 by 600 with the Nygren model. We present two types
408 of in silico experiments. One type we block a large number of cells and

Figure (9) Barkley model produces several self-generating spirals by blocking one cell, with neighboring cells in a refractory state. The electrogram produces a noise-like signal which may be identified with Fibrillation.

409 scattered throughout the network, another group is stimulated. The second
 410 type, only a few connected cells, is stimulated and blocked by neighbors.
 411 We obtained the same phenomenon produced with the array. Hence a self-
 412 generating spiral is produced, see Figure 10.

413 In Figure 11 the same phenomenon illustrated in Figure 9 is represented
 414 in a 60×60 array of cells. A set of initial conditions alternating refractory
 415 state cells with stimulated cells produces a pattern that may be identified
 416 with Fibrillation due to the complex pattern of the pseudo-EG.

417 With a 600×600 cell array, a spiral is produced with a small group
 418 of stimulated cells surrounded by cells in a refractory state. See Figure 12.
 419 Observe that assuming that a cell has $100 \mu\text{m}$ of length, a square of 360 000
 420 cells is equivalent to 36 mm^2 of tissue.

421 A fascinating phenomenon occurs in a 600×600 array when a large
 422 group of stimulated, scattered cells through the entire net is surrounded by
 423 refractory cells. Fibrillation occurs during several seconds, and under certain
 424 initial conditions, it becomes Fluttering, which persists in a stationary and
 425 complex spiral. See Figure 13.

426 Moreover, in the 600×600 array, we can produce with a set of initial
 427 conditions a more complex pattern than in Figure 13 f). Many self-generating
 428 spirals resembling a micro-reentry associated with Fibrillation emerges after
 429 the collision presented with a massive blocking. See Figure 14.

430 A comparison of the patterns produced by the Nygren cell model and

Figure (10) Nygren model in a 60×60 net of cells produces a self-generating spiral by dynamic blocking. a) At $t = 0$, a group of cells is stimulated. b) A wavefront is produced. c) A self-generating spiral appears. d) Spiral collides with the border. e) Steady-state. f) Quasiperiodic pseudo-EG.

Figure (11) a) At $t = 0$ a massive group of scattered cells through the entire 60×60 net is stimulated randomly. b) Waves propagate at $t = 0.001s$. c) A couple of fronts emerge. d) Spiral after colliding produces a complex pattern e) Steady-state. f) A couple of self-generating spirals leads to a complex pseudo-EG, which may be identified with Fibrillation.

Figure (12) Nygren model in a 600×600 net of cells produces a self-generating spiral by dynamic blocking. (a) Notice the small group of stimulated cells in the left bottom corner. (b) A series of spirals emerge. (c) Steady-state. (d) Pseudo-EG of the entire simulation.

Figure (13) a) At $t = 0$ a massive group of scattered cells through the entire net is stimulated, but each cell is surrounded by refractory cells. b) Waves propagate at $t = 0.08s$. c) After the collisions, only two fronts survive in this particular setting. d) Spirals are formed with the remanent waves. e) A complex pattern emerges of self-generating spirals. f) Pseudo-EG of the entire simulation.

Figure (14) Under a different set of initial conditions than those in Figure 13, an intricate pattern of several self-generated spirals surges. (a) A large number of collisions of wavefronts after the massive blocking are apparent. (b) Some curved wavefronts survive after collisions. (c) Several spirals are generated with the curved wavefronts in (b) and persist in a steady complex state. (d) Pseudo-EG of the entire series.

the Barkley model is shown in Figure 15. Such is the pattern produced by massive blocking in a 60×60 net.

5. Discussion

In many articles, one and two-dimensional arrangements (for instance, in [9] and references therein, and [41]) are considered disregarding that the actual geometry of tissue is three dimensional. This reduction in modeling is a generalized attitude that can be understood under the dynamic of building models that go from the simple to the more complicated. Nevertheless, as Fenton et al., claim [10], in models of cardiac electrical activity “simulations in 3D have shown that the existence of purely three-dimensional breakup mechanisms”. So that arrhythmias are, in this sense, three-dimensional phenomena virtually. Hence, to obtain more accurate models of arrhythmias, it is necessary to work in 3D frameworks, but utilizing 2D layers makes sense for the following reasons. In modeling auricular heart tissue, it is known that rotational anisotropy of fibers of ventricular muscle can be model by superposing and rotating two-dimensional layers of cells [11]. To this aim, two ways to incorporate connectivity parameters in the cells are available: experimental histological data or stochastic or complex connectivity provided by mathematical models ad hoc. In this article, we used an aperiodic tiling model, which is possible to extend to 3D nets of cells. Anyhow, the extension to 3D of the aperiodic tiling model presented here is not straightforward. Creating an adjacency matrix corresponding to aperiodic, fractal arrangements is a complex task and constitutes an open problem, although algorithms to produce many of such patterns are known (see, for instance, Rangel-Mondragon article [30]).

Although simplified models in one or two dimensions may reflect certain experimental data [13], it may be that such simplifications do not represent the actual behavior of big groups of cells, for instance, in the transmission of the action potential of the system formed by mixing pacemaker and atrial cells. For example, in [21] for specific mathematical models of atrial and sinus cells, the activation of the complex depends on the number of cells involved and the geometric distribution of the cells in the network. Modeling diffusive media with cells, including many observables, may not be a trivial task, since even the stability of the numerical methods involved may be challenged. Moreover, since the real geometry of the cells must be considered, real data of local topology of diffusive tissue must be incorporated, when available, to

Figure (15) (a)Nygren model in a Fibrillation pattern. (b) Pseudo-EG of the Nygren model. (c) Barkley mode in a Fibrillation. (d) A massive blocking of individual cells with low conductivity produces an intricate pattern that, according to the pseudo-EG in the figure, can be identified with Fibrillation. Here we show systems of 60×60 cells.

model big groups of cells. As mentioned in section 4 our representation of groups of cells in Figure 4 may not correspond to any real biological tissue, but only constitute the first approach of statistical data of a mean of the number of observed connections in the atrial heart tissue. A refinement of this data is required for the two-dimensional layers forming atrial and ventricular tissue in the heart.

On the other hand, many interesting works such as [36] study the stochastic distribution of inhomogeneities at the cellular level that can cause cardiac propagation to be stochastic. In contrast, in this article, without considering the stochastic setting, we obtained a complex propagation in the diffusive tissue, despite the simplicity of the included models, only by varying the local topology of the network. Nevertheless, variable conductance may be included in future work either employing stochastic distributions or, as was done in this article, introducing some aperiodic pattern of the distributions of the different conductances referred to in [36] of the individual cell membranes.

As a final remark, a note about our analysis of pseudo-EG. Electrograms were statistically analyzed using the DFA technique to associate the visual behavior of the propagation of the electrical signal with a quantitative indicator of the propagation dynamics. When a scaling exponent near to 0.5 was obtained, the simulated electrical signal showed a random behavior, which corresponds to what we denominated Fibrillation (Figures 11). In the electrograms where it was possible to observe a “noisy” periodic behavior, the value of the scaling exponent α was near to 1, indicating long term correlations (i.e., a non-random behavior), which corresponds to the wave-like propagation observed in images and videos from the simulated experiments (Figures 8). From these results, we can conclude that images and videos of the propagation of the simulated electrical signals give us valuable information about their dynamics and factors affecting it, which is a crucial aspect to consider when analyzing structural and functional mechanisms triggering the different types of arrhythmias, such as atrial Fibrillation and Flutter.

6. Conclusions

In modeling cell-to-cell in this document, we found that very complex self-perpetuating diffusion patterns arise utilizing a massive blocking of cells in an excited state. This complexity emerges even in utilizing an elementary chessboard-like distribution of cells. One remarkable property of nets of diffusive cells in this document is that reentrant waves are formed in a

wide variety of initial conditions contradicting the intuitive folk thinking that arrhythmia phenomena are exceptional in diffusive media, especially in considering Fibrillation.

We introduced a net with a tiling distribution in which Fibrillation, Fluttering, and a sequence of Fluttering-Fibrillation phenomena emerged. In this way, the two basic types of arrhythmia were modeled in two-dimensional tissue with a degree of complexity given by the non-periodic, fractal distribution connections in the tiling. The interesting fact is that it is possible to model a complex-like Fibrillation phenomenon by introducing a certain degree of complexity in the distribution of neighbor cells (for example, with tiles similar to those in Figure 4), instead of using any random distribution whatsoever. To the best of the knowledge of the authors of this paper, this is a novelty. Moreover, in this study, the authors found a critical value of conductivity among the cells integrating the ODE's systems. Such critical value emerges with an adjacency matrix given by the arrangement in Figure 5. In this way, modeling Fluttering by lowering conductivity in our model of simple two-variable ODE or the state of the art ODE model by adding only specified complexity in the distribution of cells could be relevant in mathematical modeling and computational simulation.

Micro-reentry can be simulated with Barkley and Nygren models. In some in silico experiments emerged several self-perpetuating waves that collide, leading to a complex pseudo-EG, which anyhow may be identified with Fibrillation of the system. An example of this EG for such arrhythmia is shown in Figure 15(b) for the Nygren model and Figure 15(d) for Barkley model.

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Videos

To access all the simulation videos in this document, the reader can use the following link: <http://pacifico.izt.uam.mx/aurelio/>

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