Published in final edited form as:

Proc IEEE Int Symp Comput Based Med Syst. 2017 June ; 2017: 379–384. doi:10.1109/CBMS.2017.161.

Simulation of Spiral Waves and Point Sources in Atrial Fibrillation with Application to Rotor Localization

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Abstract

Cardiac simulations play an important role in studies involving understanding and investigating the mechanisms of cardiac arrhythmias. Today, studies of arrhythmogenesis and maintenance are largely being performed by creating simulations of a particular arrhythmia with high accuracy comparable to the results of clinical experiments. Atrial fibrillation (AF), the most common arrhythmia in the United States and many other parts of the world, is one of the major field where simulation and modeling is largely used. AF simulations not only assist in understanding its mechanisms but also help to develop, evaluate and improve the computer algorithms used in electrophysiology (EP) systems for ablation therapies. In this paper, we begin with a brief overview of some common techniques used in simulations to simulate two major AF mechanisms – spiral waves (or rotors) and point (or focal) sources. We particularly focus on 2D simulations using Nygren *et al.*'s mathematical model of human atrial cell. Then, we elucidate an application of the developed AF simulation to an algorithm designed for localizing AF rotors for improving current AF ablation therapies. Our simulation methods and results, along with the other discussions presented in this paper is aimed to provide engineers and professionals with a working-knowledge of application-specific simulations of spirals and foci.

Keywords

atrial fibrillation; numerical simulation; spiral waves; focal sources; rotor localization; bayesian filtering

I. Introduction

Simulations have always been an invaluable tool to virtually create and analyze a desired phenomenon. They are widely used in various fields of science and engineering for research and development purposes. One of the major research applications of simulations is in understanding and analyzing biological phenomena. Cardiac electrophysiology (cardiac EP) is an inter-disciplinary field where investigations using simulations are ubiquitous. Cardiac simulations involve a significant contribution from applied mathematicians, and also incorporates experimental and theoretical knowledge from physicists, pharmacologists and engineers. Among cardiac arrhythmias, atrial fibrillation (AF) is the most common arrhythmia affecting over 2.7 million people in USA annually [1]. It is life-threatening and a major cause of stroke, thus making it a critical field of research. Initial era of investigations

on AF were only through in-vivo and in-vitro experiments of animal hearts. A revolutionary development in the field was made when computer simulations were introduced to perform the same or even better investigations. Since then, AF simulations were used for various purposes ranging from basic science applications such as understanding the properties of AF sources, to engineering applications such as designing and evaluating algorithms for localizing the AF sources.

Rotors and focal sources are believed to be two major non-pulmonary vein drivers of AF. Current ablation treatment for AF primarily involve pulmonary vein isolation (PVI) and do not consider the rotor and focal sources existing outside the PVs because of lack of reliable methods to locate them using conventional catheters. This results in a sub-optimal success rate of 40% to 60% for current AF ablation procedures. In order to improve the success rate, it is important to devise an algorithm for AF source localization. However, it is impossible to design and evaluate such algorithms entirely based on real atrial electrograms, hence simulations play a critical role for this purpose. In this paper, we discuss some techniques used in simulation for simulating AF rotors and focal sources, and we apply the simulation for testing a rotor localization algorithm designed by our group. We provide only an overview of the simulations in this paper, however, a detailed review of the basic principles of cardiac simulations can be found in these articles [2]–[4].

II. Simulation Methods

A. Overview

AF rotor and focal sources can be created on a simulated cardiac tissue made up of cells. These simulated cells should have the properties of real cardiac cells primarily the properties of excitability, conductivity and refractoriness. Excitability is the ability to produce a response for a specific duration when an external trigger is applied to it, and conductivity is the ability to conduct the potential difference or the voltage produced to the neighboring cells. After a cell is excited, a second external trigger can be given only after a certain duration of the completion of response to the first stimulus, and this duration in which no response occurs to an external stimulus is called refractory period, and the property is called refractoriness. This process of depolarization and repolarization continues as the stimuli are transferred from one or more cells to other neighboring cells, hence forming a wave propagation (eg. focal wave or rotor wave). The cells with these properties can be mathematically modeled generally by a network of conductances, capacitors and one or more voltage source using reaction-diffusion equations.

At the beginning of the era of modeling, simple mathematical models of cardiac cells were formulated based on a popular nerve axon model that was introduced by Hodgkin and Huxley in 1952 [5]. The first cardiac cell model was derived from Hodgkin-Huxley (HH) model and was developed by Noble in 1962 [6]. It consists of four variables that model three different currents and it represents a single Purkinje cell model [7]. Another mathematical model for computer simulation was developed by Moe *et al.*, in 1964 which was significantly different from other models – it is based on cellular automata as opposed to a reaction-diffusion system. Many other people introduced models based on cellular automata

but the technique eventually faded since it was not possible to realize action potentials (AP, change of transmembrane voltage over time) from the system.

Later, many models for specific cardiac cells of specific organisms were developed. For example, there are models for ventricular cells, atrial cells *etc.*, each for organisms such as human, rabbit, canine, rodent *etc.* A detailed description of some most popular cell models present in the literature is provided in this article [7]. One of the most popular human atrial cell model was developed by Nygren *et al.*, published in 1998 [8]. The Nygren *et al.*'s model was developed based on Luo-Rudy ionic model [9]. In this paper, we use the Nygren *et al.*'s model for all our simulations.

B. Cell and Tissue Modeling

A cardiac cell model is a mathematical representation of the structure and function of a cardiac cell, and its membrane kinetics. Using a cell model, any excitation phenomenon such as AF rotor and focal source can be simulated. There are different types of cell models categorized based on dimensions, domain kind, electrical characteristics, and the organism. The reaction-diffusion equations of all these models give the relationship between the current, voltage and the components used to represent the cell such as resistors, conductors, capacitors *etc.* These formulations are based on the fundamental Ohm's law:

$$V = IR \Rightarrow I = \frac{1}{R}V \Rightarrow I = gV \quad (1)$$

where, V is voltage, I is current, R is resistance, g is conductance. The primary equation of all mathematical models is in the form specified by the Equation 1.

The general representation of transmembrane current in a cardiac cell model is:

$$I_Y = g_Y(V_m - E_Y) \quad (2)$$

where I_Y is transmembrane current corresponding to ion Y, g_Y is the conductance of ion Y, V_m is the transmembrane voltage and E_Y is the Nernst potential for ion Y. Note that this equation is similar to Ohm's equation given in Equation 1.

In this paper, we create our simulations using the Nygren *et al.*, atrial cell model and we confine our discussions to 2D simulations although 3D tissue simulations are possible. All our simulations discussed were programmed in Fortran and the visualization was obtained in Matlab. The Nygren model has the following properties:

- Domain: Mono and Bidomain
- Organism: Human
- Anatomy: Atrium
- Core stability: Stable compared to Courtemanche model [10].

Designing an AF rotor or focal simulation using the Nygren model can be elucidated in two steps:

- Modeling the tissue using Nygren *et al.* atrial cell model
- Modeling the AF phenomenon (rotor or focal source)

The Nygren model consists of 12 transmembrane currents represented by a total of 29 variables which includes 12 voltage gates, intracellular calcium and potassium concentrations, extracellular calcium, potassium and sodium ion concentrations, Cytoplasmic calcium concentration, two sarcoplasmic reticulum, two variables that control the release of calcium ions from the sarcoplasmic reticulum, one for subsarcolemmal space, five variables for calcium buffering, and a voltage variable. The equations connecting these ionic currents to the final transmembrane voltage output can be found in the original publication of the Nygren *et al.*'s model [8]. We programmed all the variables, parameters and the equations of the model with some of the minor variations that are mentioned in [11].

Once the cell model is implemented, the next step is to couple everything together to form the tissue. The following are some important aspects of modeling the tissue from the cell model:

- Initial Conditions
- Boundary Conditions
- Laplacian Computation
- Coupling Parameters

1) Initial Conditions—The simulated tissue before getting activated by a stimulus, should always be initialized with some initial conditions. All 29 variables of the Nygren model should be initialized to an appropriate value. In most cases, the initial conditions are given by the cell model itself. In all our simulations, we use a standard set of initial conditions specified by the Nygren *et al.* model, for example, the voltage is set to -74.2525 mv (see Table 19 in [8]).

2) Boundary Conditions—Since the simulation is a 2D tissue, the wave propagation must be restricted to a specific 2D plane. Hence, first, the tissue dimensions are defined. In all our simulations, we use a dimension of 400×400 discrete points with a spatial resolution of 0.025 cm, resulting in a 10×10 cm atrial tissue. After defining the tissue dimensions, we must define the boundary voltage conditions since the wave should not be allowed to propagate further than the boundaries. A commonly used boundary condition is the no-flux condition or the Neumann conditions. According to homogeneous Neumann conditions, the derivative at the boundaries of the tissue is simply zero. However, we use Dirichlet boundary conditions, which can be achieved simply by assigning a value of zero to the voltage variable in the Nygren *et al.* model when the simulation solver encounters the boundaries.

3) Laplacian Computation—The next step is to define a differential equation solver to sequentially solve for the voltage at every point of the tissue. The solution is obtained by

computing the laplacian of the transmembrane voltage which could be numerically solved for using well-known methods. We use the forward Euler's method to solve for it.

The following equation gives the monodomain (for each of the bidomain space) formulation that we solved in the tissue:

$$\frac{\partial V}{\partial t} = \nabla(D \nabla V) - \frac{I_{ion}}{C_m} \quad (3)$$

where V is the transmembrane voltage, ∇ is the gradient operator, D is diffusion tensor that is a constant ($0.001 \text{ cm}^2/\text{s}$ [12]), C_m is the membrane capacitance and I_{ion} ionic current specified by the model formulation.

There are several mathematical variations of laplacian stencils of 5-point, 9-point or others. For isotropic simulations, more visually pleasing wave propagation morphology can be obtained by using appropriate laplacian. A five point stencil in an isotropic simulation produces different curvatures at the corners of the wave compared to the edges, and a 9-point produces relatively more curved corners since the discretization error is rotationally symmetric to first order. Figure 2A shows an isotropic focal source with 9-point laplacian stencil which appears to be visually more circular because of less error at the corners.

4) Coupling Parameters—Once the cell and its kinetics are defined using the Nygren *et al.*'s equations, and the laplacian solver is set up, the cells have to be coupled to form a tissue. Although there are many other functions for a coupling matrix, one of the important function is that it describes the connection of the cells in both longitudinal and transverse directions. This matrix is a binary matrix where, '1' represents the presence of a connection and a '0' represents the absence of a connection. Hence, a matrix with all ones will create a homogeneous tissue, and a matrix with zeros in one of the direction will create heterogeneity for propagation in that direction, and hence a matrix with randomly placed zeros (defines randomly missing connections) introduces heterogeneity in the tissue. An example of a homogeneous rotor is shown in Figure 1A, and a rotor with 20% randomly (based on poisson distribution) introduced septa with mean length $2500 \mu\text{m}$ is shown in Figure 1B.

Another major parameter that defines the wave propagation on the tissue is diffusion coefficient. The diffusion coefficient provides the nature of voltage transmission between the coupled cells. If the diffusion coefficient is small, then the propagation is slow, and if it is large, then the propagation is fast. On the other hand, we could also have different diffusion coefficients for transverse and longitudinal directions (as given by Eqn 4 which is a modified version of Eqn 3) resulting in a wave with different speeds in two directions. The simulation shown in Figure 2A is a focal with diffusion coefficient value of $0.001 \text{ cm}^2/\text{s}$ in both directions. The simulation of a focal source shown in Figure 2B has a diffusion coefficient of 0.001 in longitudinal direction and one fifth of that in transverse direction, hence, the slow propagation in the vertical direction can be clearly seen in B.

The equation for different diffusion coefficients in the horizontal and vertical directions is given by:

$$\frac{\partial V}{\partial t} = D_{\parallel} \frac{\partial^2 V}{\partial x^2} + D_{\perp} \frac{\partial^2 V}{\partial y^2} - \frac{I_{ion}}{C_m} \quad (4)$$

where V is the transmembrane voltage, $D_{\parallel}$ and $D_{\perp}$ are the diffusion coefficients in horizontal and vertical directions, C_m is the membrane capacitance and I_{ion} ionic current specified by the model formulation.

This completes the modeling of the substrate for the wave to be simulated. The next and the final step is to simulate the desired wave (rotor or focal) on the substrate.

C. Modeling the AF Phenomenon

There are several theories for how an AF rotor or focal is initiated based on experiments with explanted animal hearts. According to the experimental results, some simulation protocols for rotor and focal sources were established.

1) Rotor Simulation—A rotor is a spiral shaped wave that consists of a wavefront and a wavetail that meet at a center point (called the core) and continuously propagates in clockwise or anticlockwise direction (see Figure 7 in [14]). A popular method to initiate a rotor wave is the S1-S2 protocol, in which a plane wave is first initiated, and then at an appropriate timing another plane wave is initiated perpendicular to the previous wave. When these two mutually perpendicular waves collide at the right time, a core is formed at the edge of collision and a spiral is initiated. We simulated spiral waves using a similar technique but instead of applying a second wave, we change the transient properties of the tissue to divert the wave direction to form a spiral. Our method of spiral initiation is shown in Figure 3. First, a plane wave is initiated from the left boundary of the tissue (Figure 3A and B). Then at an appropriate timing ($t = 190ms$), we revert a part of the tissue to its initial conditions thus making the region quiescent (Figure 3C). Now a part of the wave continues in the same direction, but the upper edge of the wave start to enter the excitable region created because of the quiescent update (Figure 3D). The tail of the wave is refractory and hence the wavefront has to go around and make a rotation thus creating a spiral wave (Figure 3E).

The simulation offers the flexibility of modifying certain properties of the rotor wave according to the desired application. Some common modifications include:

Cycle Length: Cycle length of a rotor is the time taken by a rotor wave to complete one full rotation. We can increase or decrease the cycle length in order to speed up or slow down the wave. As a result of increase in cycle length, multiple arms of the spiral may be created along with the increase in velocity. One way of increasing the cycle length is by increasing the conductance of inward potassium channel in the Nygren *et al.* model and it can be decreased by decreasing the same. However, there are multiple ways to perform the same.

Core Stability: Some applications of AF simulations require the spirals to meander as opposed to having a fixed core position. The meandering can be controlled by modifying the cleft space concentrations of sodium, potassium and calcium ions, and intracellular concentrations of sodium and potassium ions. There could be multiple patterns of meandering in a Nygren model, article [11] discusses some meander patterns.

Multiple Rotors: As opposed to creating a single spiral, we could also create multiple spirals by modifying the method of initiation. An example of creating double spirals on one single tissue is shown in Figure 4. The quiescent region in Figure 4C is modified in such a way that two rotors are formed instead of one. In addition, the direction (clockwise or counterclockwise) of the each of the two rotors can also be controlled by using appropriate technique of initiation.

2) Focal Source Simulation—A focal source is simply a circular wave periodically propagating from a single point. The method of initiating a focal source is completely different from that of rotors and also, the procedure is relatively simple. As opposed to initiating a plane wave (as performed for rotors), we have to provide an external stimulus at a point (or group of points) on the tissue where the focal source have to be initiated at (Figure 5A). The amplitude and the duration of the stimulus must be sufficiently high to excite the tissue. The same stimulus must be applied at regular intervals which is determined by the cycle length that we set. This will hence result in a periodic focal source (Figure 5B,C,D). We used a stimulus amplitude of 20 mV and a stimulus duration of 3 ms, and a cycle length of 150 ms for the focal source.

Similar to rotors, we have two major control parameters in focal source: cycle length and the number of foci. The cycle length is an explicit parameter in focal simulation since it is the period of the external stimulus. Hence by simply changing the stimulus period value, the cycle length can be changed. Creating multiple foci is also only a matter of applying multiple stimulus on the tissue. An example of creating double focal source is illustrated in Figure 6, where two stimulus is applied at the same time to create two waves.

Such simulations of rotors and focal sources can be used for a wide variety of applications including engineering applications. Because of the flexibility to create multiple varieties of wave simulations and change many properties of the rotor and focal waves, AF simulations are widely used by engineers to evaluate their algorithms.

III. Application of AF Simulation to a Rotor Localization Algorithm

Catheter ablation is a commonly preferred non-pharmacological therapy for treatment of AF. Current ablation procedures utilize a multi-polar diagnostic catheter (MPDC) to construct the electroanatomy map of the left atrium and then perform PVI and other standard ablation procedures. However, the success rate of current ablation procedures is only 40% to 60%, one of the reason is because of not ablating the non-PV sources. Rotors are considered to be one of the dominant non-PV AF drivers existing in the left atrium, and there are no reliable EP systems to locate rotors using a conventional MPDC. Hence, we developed a preliminary method to locate the core of the rotor using MPDC electrograms.

The developed algorithm is a probabilistic method that is based on Bayesian filtering. The algorithm utilizes the MPDC electrograms and the 2D atrial tissue boundaries as the input. The algorithm calculates certain characteristics of the electrograms and uses the bayesian formulation to find the probability of the presence of rotor in the 2D atrial tissue. The electrogram characteristics used in this algorithm are based on our previous studies [15]. The developed algorithm iteratively guides the MPDC from any random location that we start from, to converge at the core of the rotor. This iterative probabilistic approach is an improvement of our non-probabilistic MPDC guidance algorithm published previously [13].

The Bayesian formulation of the algorithm is described below:

$$P(R = S_n | \Phi, \tau) = \frac{P(R = S_n)P(\Phi, \tau | R)}{P(\Phi, \tau)} \quad (5)$$

where,

$$P(\Phi, \tau) \triangleq \sum_{n=1}^N P(R = S_n)P(\Phi, \tau | R)$$

In Equation 5, $P(R = S_n | \Phi, \tau)$ is the posterior probability distribution over the search grid, which indicates the probability of rotor convergence at every S_n given the observed EGM characteristics (*i.e.*, Φ and τ); $P(R = S_n)$ is the prior probability distribution; $P(\Phi, \tau | R)$ is the likelihood function of the EGM characteristics and $P(\Phi, \tau)$ is the normalization function for the probability distribution $P(R)$.

A detailed description of the algorithm can be found in [16]. The algorithm was evaluated using 2D single and double rotor simulations developed using Nygren *et al.*'s model.

A. Results of the Localization Algorithm

Two cases of homogeneous rotors were simulated using Nygren *et al.*'s model for the evaluation of the algorithm: single rotor and double rotor case. In both the cases, the MPDC was placed on all possible locations of the simulated atrial tissue and the algorithm was executed. The results of the algorithm for a single rotor case is shown in Figure 7A, and that of double rotor is shown in Figure 7B.

From the figure, it is clear that the algorithm adaptively guides the MPDC to the core within a few number of jumps. For example, in Figure 7, s_1 to s_2 is a large jump compared to s_2 to s_3 , which indicates that the algorithm makes bigger jumps when the MPDC is far from the center of the rotor and makes smaller jumps as the MPDC get closer to the rotor. The direction of the jump also changes adaptively based on the MPDC location. This verifies the potential of the algorithm to successfully locate the center of the rotor. This algorithm should be extended to locate more complicated scenarios of rotors in the future.

IV. Conclusion

We reviewed some important concepts and techniques of AF rotor and focal simulation with the help of Nygren *et al.*'s human atrial cell model. This overview was aimed to provide engineers and other professionals to understand and gain a working-knowledge of numerical AF simulations. Finally, we demonstrated the importance of computer simulation for engineering applications by discussing a rotor localization algorithm that was evaluated using a homogeneous Nygren simulation. The evaluation of the algorithm successfully verified its robustness and can thus be potentially improved using more complex simulations of 2D and 3D AF rotors and focal sources, in order to implement it in clinical EP labs in the future.

Acknowledgments

This work was supported by the National Institutes of Health, R15HL127663.

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Fig. 1. Example of homogeneous and heterogeneous rotor simulations – A. Rotor on a perfectly homogeneous tissue, B. Rotor on a heterogeneous tissue [13].

Fig. 2.
Example of focal source simulations with two types of diffusion coefficients – A. Same diffusion coefficient in both directions, B. Higher diffusion coefficient in longitudinal direction than the transverse.

Fig. 3. Simulation of a rotor wave on the 2D tissue – A – E shows the step by step method for initiating a spiral wave using the Nygren model at times of 10ms, 140ms, 196ms, 208ms, and 400ms, respectively.

Fig. 4. Simulation of two rotors on the same 2D tissue – A – E shows the step by step method for initiating two spiral waves using the Nygren model at times of 20ms, 120ms, 196ms, 210ms, and 386ms, respectively.

Fig. 5. Simulation of a focal wave on the same 2D tissue – A – D shows the step by step method for initiating a focal wave using the Nygren model at times of 2ms, 40ms, and 50ms, respectively.

Fig. 6. Simulation of two foci on the same 2D tissue – A – C shows the step by step method for initiating two foci using the Nygren model at times of 2ms, 40ms, 120ms, and 180ms, respectively.

Fig. 7.

Some examples of the paths of finding rotor using the localization algorithm – Each path is indicated from the first step, s_1 , to the rotor core location in s_3 for A. Single rotor case, B. Double rotor case.