The role of the hyperpolarization-activated inward current $I_f$ in arrhythmogenesis: a computer model study

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Abstract—Atrial fibrillation is the most common cardiac arrhythmia. Structural cardiac defects such as fibrosis and gap junction remodeling lead to a reduced cellular electrical coupling and are known to promote atrial fibrillation. It has been observed that the expression of the hyperpolarization-activated current $I_f$ is increased under pathological conditions. Recent experimental data indicate a possible contribution of $I_f$ to arrhythmogenesis. In this study, the role of $I_f$ in action potential propagation in normal and in pathological tissue is investigated by means of computer simulations. The effect of diffuse fibrosis and gap junction remodeling is simulated by reducing cellular coupling non-uniformly. As expected, the conduction velocity decreases when cellular coupling is reduced. In the presence of $I_f$, the conduction velocity increases both in normal and in pathological tissue. In our simulations, ectopic activity is present in regions with high expression of $I_f$ and is facilitated by cellular uncoupling. We conclude that an increased $I_f$ may facilitate propagation of the action potential. Hence, $I_f$ may prevent conduction slowing and block. Overexpression of $I_f$ may lead to ectopic activity, especially when cellular coupling is reduced under pathological conditions.

Index Terms—Atrial Fibrillation, Ectopic Activity, Bidomain Model, Hyperpolarization-activated Inward Current, Fibrosis, Gap Junction Remodeling

I. INTRODUCTION

ATRIAL FIBRILLATION (AF) is the most common cardiac arrhythmia [1]. The prevalence of AF increases with age from 0.5 percent of people under the age of 60 to almost 10 percent of people over the age of 80 [2]. Related to the occurrence of AF is structural remodeling of the tissue, including increase of cell size, interstitial fibrosis and gap junction remodeling [3]. These effects lead to the loss of electrical coupling between cardiac cells and are known to promote recurrence of AF episodes [4], [5]. Changes in gap junction distribution may be involved in the initiation and persistence of atrial fibrillation [6], [7], [8], [9].

Besides structural remodeling, electrophysiological remodeling is related to AF, including shorter atrial effective refractory periods (AERP), greater dispersion of atrial refractoriness, and atrial conduction delay [10]. However, even if AF initiation and AF perpetuation are facilitated by electrophysiological remodeling, the initiation of AF still requires a trigger [11]. Such a trigger may come from ectopic foci. Especially in the case of paroxysmal AF, episodes of atrial fibrillation are often triggered by ectopic foci that are located in the pulmonary veins [12]. The mechanism of focal activity leading to AF is, however, still unknown [12]. Two possible mechanisms are micro-reentry within the pulmonary veins [13] and spontaneous depolarization of cells located in the pulmonary veins [14].

The ionic current responsible for pacemaker activity of sino-atrial node cells and Purkinje fibers is the hyperpolarization-activated inward current $I_f$ [15]. $I_f$ channels are believed to be complexes of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [16]. $I_f$ channels in atrial myocardium are most likely heteromeric complexes composed of HCN4 and/or HCN2 [17], [18]. $I_f$ conducts both K$^+$ and Na$^+$, with about a 3:1 preference for K$^+$ [15]. It has some unusual features and is thereby known as the “funny” current [15], [16]. The first unusual feature is that $I_f$ is activated by hyperpolarization with a threshold of approximately $-40$ to $-50$ mV in the sinus node [16] and about $-65$ mV in other myocardial cells [19]. The second unusual feature is that the fully activated current/voltage relation reverses near $-10$ to $-20$ mV in physiological solutions as a consequence of the channel’s mixed permeability to Na$^+$ and K$^+$ [16]. The activation by hyperpolarization and permeability to Na$^+$ and K$^+$ are important properties with respect to the role of $I_f$ in diastolic depolarization and spontaneous activity [16]. As opposed to earlier results [20], [21], [22], [23], it was recently observed by Michels et al. [18] that half-maximum activation of single-channel $I_f$ is within the diastolic range of human atrial myocardium. These observations support a possible contribution of HCN-gated channels and $I_f$ to arrhythmogenesis under pathological conditions [18].

$I_f$ has been identified in cardiac tissue that is normally not capable of pacemaking, including human left ventricular myocytes [20], [21] and human atrial myocytes [19], [22], [24]. Interestingly, the expression of $I_f$ in left ventricular myocytes of the rat increases with age [25]. Also in ventricular myocytes of hypertrophied and failing hearts of the rat, the expression of $I_f$ is increased and leads to diastolic depolarization in isolated myocytes [25], [26], [27]. Sartiani et al. [28] observed two action potentials of different HL-1 cells derived from the atria of a transgenic mouse. One of the action potentials showed spontaneous diastolic depolarization and the other a
flat diastolic potential. A hyperpolarization-activated inward current was observed in the cell with a spontaneous diastolic depolarization phase, but not in the other cell [28]. Besides, they observed spontaneously beating cells in some regions of HL-1 cell cultures with a frequency varying between 1.3 and 5 Hz [28]. Since the beating stopped in the presence of I_f-blocker Cs^+ , it is suggested that the spontaneous activity is caused by I_f [28]. However, whether I_f may favor spontaneous diastolic depolarization in individual human atrial myocytes remains to be determined [22].

Previous simulation studies to investigate conduction velocity and arrhythmia in structurally remodeled tissue did not include I_f. Fast and Kléber showed that conduction slowing and block may occur at an abrupt tissue expansion [29]. Shaw and Rudy applied a multicellular monodomain fiber model to investigate conduction slowing and block in relation to reduced membrane excitability and decreased gap junction coupling [30], [31]. Street and Plonsey applied a multi-fiber bidomain model to investigate conduction slowing and block in regions of passive, connective tissue representing infarcted regions [32]. Recent large-scale simulation studies to atrial arrhythmia apply detailed models of the ionic membrane currents, electrophysiological remodeling, anisotropy and 3D geometry [33], [34], [35], [36], [37], [38], [39].

The aim of the present simulation study is to investigate the influence of I_f on the conduction velocity and ectopic activity under normal and pathological conditions. We apply a discrete bidomain model with active membrane behavior to represent the cardiac tissue. Diffuse fibrosis and gap junction remodeling are modeled by decreasing intracellular coupling at random throughout the tissue. The amount of I_f current and of cellular uncoupling are varied to investigate their respective influence on the conduction velocity and ectopic activity.

II. METHODS

We have developed a new discrete bidomain model, the Cellular Bidomain Model, which we previously applied to investigate virtual electrode polarization during external field stimulation under normal and pathological conditions [40]. Active membrane behavior as well as intracellular coupling and interstitial currents are described by this model. Similar to the volume averaging approach of the continuous bidomain model, each point in the tissue is assigned both an intracellular and an extracellular potential [32], [41]. In our model, the bidomain is subdivided in segments and the same state is assumed everywhere within a single segment, which is why we call it a discrete bidomain model, or Cellular Bidomain Model [40]. Although a segment may represent a single myocyte, we usually apply somewhat larger segments such that less computational power is required to simulate sheets of cardiac tissue. The segment sizes may vary as well as the electrical coupling between adjacent segments. Pathology such as fibrosis and gap junction remodeling can be modeled by reducing the intracellular coupling between the segments. Furthermore, active membrane behavior can be varied throughout the tissue by assigning different membrane properties to individual segments.

A. Cellular Bidomain Model

In the Cellular Bidomain Model, the structure of the cardiac tissue is represented by a graph consisting of nodes and edges, where a node represents a segment and an edge the electrical coupling between the segments. Let \( \mathcal{N} \) represent the set of nodes and \( \mathcal{E} \) the set of edges connecting the nodes. Each node has its own membrane model describing the ionic membrane currents. The state of each node \( n \in \mathcal{N} \) is defined by the internal potential \( V_{\text{int}}^n \) and the external potential \( V_{\text{ext}}^n \). The membrane potential \( V_{\text{mem}} \) for node \( n \) is defined as \( V_{\text{mem}}^n = V_{\text{int}}^n - V_{\text{ext}}^n \). Edges define the conductance for intracellular and extracellular currents between two adjacent nodes. We distinguish the internal and external conductance, which are denoted by \( \sigma_{\text{int}} \) and \( \sigma_{\text{ext}} \), respectively, see Fig. 1.

It is assumed that for each edge \( (n,m) \in \mathcal{E} \) it holds \( \sigma_{\text{int}}^{(n,m)} > 0 \) and \( \sigma_{\text{ext}}^{(n,m)} > 0 \). The internal and external currents flowing from node \( n \) to node \( m \) are denoted by \( I_{\text{int}}^{n \rightarrow m} \) and \( I_{\text{ext}}^{n \rightarrow m} \), and are given by Ohm’s law:

\[
I_{\text{int}}^{n \rightarrow m} = (V_{\text{int}}^n - V_{\text{int}}^m) \sigma_{\text{int}}^{(n,m)},
\]

\[
I_{\text{ext}}^{n \rightarrow m} = (V_{\text{ext}}^n - V_{\text{ext}}^m) \sigma_{\text{ext}}^{(n,m)}.
\]

The intracellular current entering node \( n \) coming from all adjacent nodes \( a \), \((a,n) \in \mathcal{E} \), is denoted by \( I_{\text{int}}^n \) and the extracellular current by \( I_{\text{ext}}^n \). These currents are defined by

\[
I_{\text{int}}^n = \sum_{(a,n) \in \mathcal{E}} I_{\text{int}}^{a \rightarrow n},
\]

\[
I_{\text{ext}}^n = \sum_{(a,n) \in \mathcal{E}} I_{\text{ext}}^{a \rightarrow n}.
\]

According to Kirchhoff’s law, current entering a node as intracellular current must flow to the interstitial space as transmembrane current and leave the node as extracellular current. By choosing the transmembrane current, denoted by

![Fig. 1. Graphical representation of a simulation graph. Each node represents a rectangular segment of cardiac tissue. The state of each node is represented by the internal potential \( V_{\text{int}} \), the external potential \( V_{\text{ext}} \), and the membrane potential \( V_{\text{mem}} \). Electrical coupling between the nodes is indicated by the intracellular and extracellular conductances, denoted by \( \sigma_{\text{int}} \) and \( \sigma_{\text{ext}} \). The intracellular and interstitial current flowing between the nodes are represented by the arrows labeled \( I_{\text{int}} \) and \( I_{\text{ext}} \).](#)
\( I_{\text{man}} \), flowing from the intracellular space to the interstitial space, we obtain for node \( n \)
\[
I_{\text{man}}^n = I_{\text{m}}^n = -I_{\text{int}}^n.
\] (5)
The transmembrane current is the sum of capacitive and ionic currents, i.e.,
\[
I_{\text{man}}^n = C_{\text{m}}^n \frac{dV_{\text{man}}^n}{dt} + S_{\text{m}}^n I_{\text{man}}(V_{\text{man}}^n, q^n),
\] (6)
where \( C_{\text{m}}^n \) represents the membrane capacitance of node \( n \) in \( \mu \text{F} \) and \( S_{\text{m}}^n \) the membrane surface in \( \text{cm}^2 \). The ionic membrane current of node \( n \), denoted by \( I_{\text{man}}(V_{\text{man}}^n, q^n) \), is expressed in \( \mu \text{A} \) per \( \text{cm}^2 \) membrane surface and depends on the membrane potential \( V_{\text{man}}^n \) as well as gating variables and ionic concentrations denoted by the vector \( q^n \).

In the present study, we apply a modified version of the Human Atrial Action Potential Model of Courtemanche et al. [42] to model the ionic currents. We extended this model with the hyperpolarization-activated current \( I_f \) and adapted the \( I_{\text{man}} \) kinetics as described below. The total ionic current is given by
\[
I_{\text{man}} = I_{\text{Na}} + I_{\text{Ca}} + I_{\text{leak}} + I_{\text{Na,L}} + I_{\text{Ca,L}} + I_{\text{K,I}} + I_{\text{K,T}} + I_{\text{NaK}} + I_{\text{Na,LK}} + I_{\text{Na,LK}},
\] (7)
The ionic and pump currents, including the handling of the intracellular \( \text{Ca}^{2+} \) concentration ([\( \text{Ca}^{2+} \)]) by the sarcoplasmic reticulum (SR), are described in Ref. [42]. The model keeps track of [\( \text{Ca}^{2+} \)], as well as \([\text{Na}^+]\), and \([\text{K}^+]\), while the extracellular concentrations \([\text{Ca}^{2+}]_\text{e}\), \([\text{Na}^+]_\text{e}\), and \([\text{K}^+]_\text{e}\) are constant [42].

When solving the equations of the Cellular Bidomain Model, no-flux boundary conditions are assumed for both the intracellular and the interstitial domain. The numerical integration scheme is described in the appendix. Below, we describe how the pacemaker current \( I_f \) is modeled and the inward \( \text{Na}^+ \) current \( I_{\text{Na}} \) is modified. Next, it is described how normal and pathological atrial tissue is modeled. Furthermore, the simulation protocol for the present study is described.

B. Hyperpolarization-activated inward current \( I_f \)
The \( I_f \) current is expressed in \( \text{pA/\mu F} \) and is defined by
\[
I_f = G_f p_f(V_{\text{man}} - E_f),
\] (8)
where \( G_f \) is the maximum membrane conductance for \( I_f \) in \( \text{nS/\mu F} \), \( p_f \) the fraction of channels in the open state, and \( E_f \) the reversal potential. The dynamics of \( p_f \) is defined by
\[
\frac{dp_f}{dt} = \alpha_{p_f}(1 - p_f) - \beta_{p_f} p_f,
\] (9)
where \( \alpha_{p_f} \) and \( \beta_{p_f} \) are defined as in DiFrancesco [43]:
\[
\alpha_{p_f} = 2.83 \times 10^{-7} \exp\left(-\frac{V_{\text{man}}}{15.08}\right)
\] (10)
\[
\beta_{p_f} = 8.31 \times 10^{-2} \exp\left(-\frac{V_{\text{man}}}{15.08}\right).
\] (11)
Moroni et al. [44] describe human \( I_f \) kinetics based on HCN2 only. Ludwig et al. [17] concluded that pacemaker activity in the human heart is a combined effect of HCN2 and HCN4 channels. Michels et al. [18] observed that single-channel characteristics of \( I_f \) in human atrial myocytes resemble those of HCN4 or HCN2 + HCN4. Since HCN4 kinetics are slower than HCN2 kinetics [17], [44], and the kinetics obtained by DiFrancesco [43] for rabbit sino-atrial nodal \( I_f \) are slower than the HCN2 kinetics obtained by Moroni et al. [44], we decided to model activation parameter \( p_f \) as described by DiFrancesco [43]. Using these parameters, the half activation potential is \(-95 \text{ mV} \) and only a small fraction of \( I_f \) channels will be open in diastolic range (above \(-81 \text{ mV} \)) [43].

The reversal potential \( E_f \) is defined as in Moroni et al. [44]:
\[
E_f = \frac{RT}{F} \ln \frac{([\text{K}^+]_e + (P_{f_0}/P_{f_1})[\text{Na}^+]_e)}{([\text{K}^+]_e + (P_{f_0}/P_{f_1})[\text{Na}^+]_e)},
\] (12)
where \( P_{f_0} \) and \( P_{f_1} \) are permeabilities to \( \text{Na}^+ \) and \( K^+ \), \( R \) the universal gas constant, \( T \) the temperature (310 K [42]), and \( F \) Faraday’s constant. The ratio \((P_{f_0}/P_{f_1})\) is 0.41 [44]. In the Courtemanche model, the extracellular ion concentrations are constant \( ([\text{K}^+]_e = 5.4 \text{ mM}, [\text{Na}^+]_e = 140 \text{ mM}) \), while the intracellular concentrations are dynamic \( ([\text{K}^+]_i = 139 \text{ mM} \) and \([\text{Na}^+]_i = 11.2 \text{ mM} \) when \( V_{\text{man}} = -81.2 \text{ mV} \)). We have adapted the Courtemanche model to take the influence of \( I_f \) on the intracellular concentrations into account as described by DiFrancesco and Noble [45]. With the parameters defined in the Courtemanche model, the reversal potential \( E_f \) is approximately \(-22 \text{ mV} \).

C. Fast inward \( \text{Na}^+ \) current \( I_{\text{Na}} \)
\( I_{\text{Na}} \) is modeled in the Courtemanche model as in the Luo-Rudy phase-2 model [46], and is given by
\[
I_{\text{Na}} = G_{\text{Na}} m^3 h j(V_{\text{man}} - E_{\text{Na}}),
\] (13)
Here, \( G_{\text{Na}} \) is the maximum \( I_{\text{Na}} \) conductance \( (7.8 \text{ nS/\mu F}) \) and \( E_{\text{Na}} \) the equilibrium potential for \( \text{Na}^+ \) [42]. Further, \( m \) is the fast activation variable, and \( h \) and \( j \) are the fast and slow inactivation variables [42], [46]. To obtain diastolic action potentials, we adapted the \( I_{\text{Na}} \) kinetics by doubling the forward rates \( \alpha_m \) and \( \alpha_h \) of the fast gating variables \( m \) and \( h \) (see equations (30), (31) and (34) of the Courtemanche model [42]). With this change, the \( I_{\text{Na}} \) channels open and diastolic action potentials occur with a basic cycle length (BCL) of 1.5 seconds for \( G_f = 0.27 \text{ nS/\mu F} \). The action potential morphology and duration remain unchanged when a stimulation current of 20 \text{ pA/\mu F} \) is applied during 2 ms as in Ref. [42].

D. Modeling normal atrial tissue
The modifications of the \( I_{\text{Na}} \) kinetics have effect on the maximum upstroke velocity \((dV_{\text{man}}/dt)_{\text{max}}\) and thus on the conduction velocity. In our simulations, \((dV_{\text{man}}/dt)_{\text{max}}\) increased from 167 V/s to 288 V/s. To obtain conduction velocities similar to those reported by Spach and Boineau (0.48 m/s longitudinal and 0.15 m/s transverse [47]), we have scaled the conductivity parameters as reported by Clerc [41], [48] with a factor 0.6. The bidomain parameters used in the present study for normal atrial tissue are listed in Table I.

To obtain criteria for the size of individual segments, we apply cable theory and consider subthreshold behavior along
TABLE I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{\text{mL}}$</td>
<td>longitudinal internal conductivity</td>
<td>1.0440 mS/cm</td>
</tr>
<tr>
<td>$g_{\text{mT}}$</td>
<td>transverse internal conductivity</td>
<td>0.1158 mS/cm</td>
</tr>
<tr>
<td>$g_{\text{elL}}$</td>
<td>longitudinal external conductivity</td>
<td>3.7500 mS/cm</td>
</tr>
<tr>
<td>$g_{\text{elT}}$</td>
<td>transverse external conductivity</td>
<td>1.4160 mS/cm</td>
</tr>
<tr>
<td>$C_{\text{m}}$</td>
<td>membrane capacitance</td>
<td>1.0 μF/cm²</td>
</tr>
<tr>
<td>$\chi$</td>
<td>surface-to-volume ratio</td>
<td>2000/cm</td>
</tr>
</tbody>
</table>

remodeling are simulated by varying the internal conductivities non-uniformly throughout the tissue. A normal distribution with parameters $(\mu, \sigma)$ is applied to determine a factor by which the initial values for the internal conductivities ($\sigma_{\text{m}}$) are multiplied for each edge. Negative factors and factors larger than one are replaced by zero and one, respectively. The average and standard deviation of the gap junction remodeling factor in longitudinal direction are denoted by $\mu_l$ and $\sigma_l$, respectively, and the average and standard deviation in transverse direction by $\mu_t$ and $\sigma_t$, respectively.

Fibrosis causes the loss of side-to-side cell coupling which can result in a disturbed wavefront propagation and may isolate groups of myocytes [49]. Since side-to-side coupling is affected, the main effect of fibrosis is a reduction of the transverse conduction velocity [47]. We model the effect of diffuse fibrosis [50] by randomly removing some of the internal conductivities in transverse direction, i.e., $\sigma_{\text{m}}$ becomes zero for a fraction of the edges in transverse direction. This fraction is called fibrosis fraction and is abbreviated by $FF$.

F. Simulation protocol

1) Single cell simulations: A series of single cell simulations over a period of four seconds was performed with varying expression of $I_r$ ($G_i = 0.08, 0.16, 0.31$ and $0.55$ nS/pF). Initially, the membrane state was equal to the resting state of a human atrial cell without $I_r$ ($V_{\text{mem}} = -81$ mV [42]). No stimulation current was applied in these simulations.

2) Gap junction remodeling and fibrosis: To investigate the effect of gap junction remodeling and fibrosis on the longitudinal conduction velocity $\theta_l$ and the transverse conduction velocity $\theta_t$, three series of simulations were performed on a $1 \times 0.4$ cm sheet of atrial tissue composed of uniform $200 \mu$m $\times$ $80 \mu$m segments. An action potential front was initiated by stimulating the left-most segments of each row (first series) or the upper row of segments (second and third series). The segments were stimulated by adding a stimulus current of $100$ pA/pF to theionic membrane currents until the membrane was depolarized. In the first series, $\mu_l$ ranged from 0.1 through 1, $\mu_t = 1$, $\sigma_l = 0$, $\sigma_t = 0$ and 0.5 and 1. In the second series, $\mu_l = 1$, $\mu_t$ ranged from 0.1 through 1, $\sigma_l = 0$, and $\sigma_t = 0, 0.5$ and 1. In the third series, fibrosis fraction $FF$ ranged from 0 through 0.9. No gap junction remodeling was applied in the third series. $\theta_l$ and $\theta_t$ were determined by averaging the velocity of the action potential front along nine parallel tracks of length $0.8$ cm in longitudinal direction and $0.32$ cm in transverse direction.

3) Uniform expression of $I_r$: To investigate the influence of a uniform expression of $I_r$ on $\theta_l$ in normal, remodeled and fibrotic tissue, five series of simulations were performed on a $2 \times 0.5$ cm sheet of atrial tissue with segment lengths varied randomly between 150 and $250 \mu$m and width $80 \mu$m. Two types of remodeled tissue were simulated by applying gap junction remodeling ($\mu_l = \mu_t = 0.75$ and $\sigma_l = \sigma_t = 0.25$), and $\mu_l = \mu_t = 0.5$ and $\sigma_l = \sigma_t = 1$). Two types of fibrotic tissue were simulated by applying both gap junction remodeling and fibrosis ($FF = 0.35$). The expression of $I_r$ ranged from 0.0 through 0.6 nS/pF. The left-most segments of the center fibers

a fiber as described in Ref. [41]. The application of a stimulus current produces a spatial change in the membrane potential along the fiber. For subthreshold behavior, the transmembrane current $I_{\text{mem}}$ can be described by

$$I_{\text{mem}} = C_{\text{mem}} \frac{dV_{\text{mem}}}{dt} + \frac{V_{\text{mem}}}{R_{\text{mem}}},$$

(14)

where $R_{\text{mem}}$ is the membrane resistance in $\Omega$ cm$^2$ and $C_{\text{mem}}$ the membrane capacitance in $\mu$F/cm$^2$ [41]. The steady-state response of $V_{\text{mem}}$ along the fiber to a subthreshold current at position $x = 0$ is exponential and can be described by

$$V_{\text{mem}}(x) = V_{\text{mem}}(0) \exp(-\frac{x}{\lambda}),$$

(15)

where $V_{\text{mem}}(x)$ is the membrane potential on position $x$ from the stimulus site, $V_{\text{mem}}(0)$ the membrane potential at the stimulus site ($x = 0$), and $\lambda$ the length constant [41]. Using the bidomain parameters listed in Table I, the length constants in longitudinal and transverse direction, denoted by $\lambda_x$ and $\lambda_y$, can be expressed as

$$\lambda_x = \frac{R_{\text{mem}} g_{\text{mL}}^2 g_{\text{mL}}^y}{\chi (g_{\text{mL}}^2 + g_{\text{mL}}^y)},$$

(16)

and

$$\lambda_y = \frac{R_{\text{mem}} g_{\text{mT}}^2 g_{\text{mT}}^y}{\chi (g_{\text{mT}}^2 + g_{\text{mT}}^y)},$$

(17)

where, as before, $R_{\text{mem}}$ is the membrane resistance in $\Omega$ cm$^2$ [32], [41]. We estimated $R_{\text{mem}}$ for the modified Courtemanche model by applying a subthreshold simulation current of 0.3 pA/pF during 300 ms. $R_{\text{mem}}$ was estimated using

$$V_{\text{mem}} - V_{\text{rest}} = \frac{I_{\text{mem}}}{R_{\text{mem}}}$$

(18)

for $V_{\text{mem}} = -81$ mV and $V_{\text{rest}}$ ranging from $-80$ mV to $-70$ mV. We found values for $R_{\text{mem}}$ between 22 and 38 $\Omega$ cm$^2$. For these values of $R_{\text{mem}}$, $\lambda_x$ is in between 0.095 and 0.125 cm, and $\lambda_y$ is in between 0.034 cm and 0.045 cm. To obtain accurate simulation results, the tissue is modeled as a brickwall with segments of length 200 $\mu$m and width 80 $\mu$m. Hence, the segment sizes are approximately one fifth of the length constant in both directions.

E. Modeling pathological tissue

In the Cellular Bidomain Model a distinction is made between longitudinal coupling (along the fiber direction) and transverse coupling (side-to-side). The effects of gap junction coupling (side-to-side). The effects of gap junction
were stimulated at the start of the simulation. Stimulation was repeated after 800 ms. Four independent measurements of $\theta_e$ were obtained by measuring over four consecutive tracks of length 0.4 cm along the central fiber.

4) Regional expression of $I_f$: To investigate the critical size of an ectopic pacemaker in relation to cellular coupling, a series of simulations was performed on a 1 cm × 0.4 cm strip of tissue. $I_f$ was present in the right part of the strip ($G_f = 0.3$ nS/pF), but not in the left part. The size of the region in which $I_f$ was present varied between 10% and 50% of the tissue. Uniform, reduced cellular coupling was simulated ($\mu = \mu_r$ ranged from 0.1 through 1, and $\sigma = \sigma_f = 0$). Each simulation lasted 5 seconds. No stimulation current was applied. In case ectopic activity occurred, the basic cycle length (BCL) was determined for each segment by averaging the interval times between consecutive depolarizations.

5) Non-uniform expression of $I_f$: To compare ectopic activity in normal and remodeled atrial tissue when the expression of $I_f$ is non-uniform, two series, A and B, of 12 simulations were performed on a 1 cm × 0.4 cm sheet of tissue composed of uniform 200 μm × 80 μm segments. In series A, $G_f$ was uniformly increased from 0.27 nS/pF (BCL 1.5 seconds) on the left to 0.58 nS/pF (BCL 0.75 seconds) on the right. In series B, $G_f$ was randomly distributed throughout the tissue with average 0.42 nS/pF and standard deviation 0.19 nS/pF. $G_f$ was bound by a minimum of 0.27 nS/pF (BCL 1.5 seconds) and a maximum of 0.58 nS/pF (BCL 0.75 seconds). Besides normal tissue, various types of remodeled tissue were simulated ($\mu = \mu_r = 0.5$ and 0.3, and $\sigma = \sigma_f = 0.0, 0.5, 1.0, 1.5$, and 2.0) as well as totally uncoupled tissue ($\mu = \mu_r = 0.0$ and $\sigma = \sigma_f = 0.0$). The distribution of $G_f$ was exactly the same for all simulations of a series, thus the simulations of one series only differ in cellular coupling. Each simulation lasted 5 seconds. No stimulation current was applied. The basic cycle length (BCL) was determined for each segment by averaging the interval times between consecutive depolarizations.

6) Large-scale simulations: To investigate the effect of a non-uniform expression of $I_f$ under normal and pathological conditions, three large-scale simulations were performed on an 8 cm × 3 cm sheet of atrial tissue with non-uniform expression of $I_f$. The width of the segments was 80 μm, while the length was varied using a normal distribution with average 200 μm and standard deviation 50 μm. The segment lengths were bound by a minimum of 150 μm and a maximum of 250 μm. $G_f$ was 0.27 nS/pF in the leftmost 6.4 cm of tissue and $G_f$ was varied in the rightmost 1.6 cm of the tissue with average 0.42 nS/pF and standard deviation 0.19 nS/pF. $G_f$ was bound by a minimum of 0.27 nS/pF (BCL 1.5 seconds) and a maximum of 0.58 nS/pF (BCL 0.75 seconds). The left-most segments of the center fibers were stimulated at the start of the simulation. Stimulation was repeated each 800 ms.

To simulate pathological tissue, two simulations were performed on the same 8 cm × 3 cm sheet of atrial tissue with the same distribution of $I_f$. The fibrosis fraction $FF$ was 0.35. After the first stimulation, the action potential propagated from left to right such that the entire tissue was depolarized after approximately 250 ms. Just before the second stimulation at simulation time 800 ms, the conductivity properties of the tissue were changed to simulate gap junction remodeling with average $\mu = \mu_r$ equal to 0.5 and 0.3, and standard deviation $\sigma = \sigma_f$ equal to 1 and 2, respectively. The second simulation of pathological tissue lasted 15 seconds of simulation time.

III. RESULTS

A. Single cell simulations

The membrane potential $V_{mem}$, the hyperpolarization-activated inward current $I_f$ (pA/pF), the time-independent rectifier $K^+$ current $I_{K1}$ (pA/pF), and conductance $g_i = G_i p_i$ (nS/pF) for single cell simulations with different $G_i$ values: dotted $G_i = 0.08$ nS/pF, short dash $G_i = 0.16$ nS/pF, long dash $G_i = 0.31$ nS/pF, solid $G_i = 0.55$ nS/pF. No external stimulation current was applied. Initially, the membrane state was equal to the resting state of a human atrial cell without $I_f$ ($V_{mem} = -81$ mV).

B. Gap junction remodeling and fibrosis

In Fig. 3 the longitudinal and transverse conduction velocities $\theta_l$ and $\theta_t$ are presented for varying $\mu$ and $\mu_r$ = 1 (top), $\mu_l$ = 1 and varying $\mu_t$ (center) and varying $FF$ (bottom). For
larger values of $\sigma_L$ and $\sigma_T$, the conduction velocities are smaller for large $\mu_L$ and $\mu_T$, while larger conduction velocities are obtained for small $\mu_L$ and $\mu_T$. This is caused by the requirement that the factors by which $\sigma_m$ is multiplied must lie between 0 and 1. The average of these factors is thus smaller than $\mu_L$ or $\mu_T$ for $\mu_L, \mu_T > 0.5$ and larger than $\mu_L$ or $\mu_T$ for $\mu_L, \mu_T < 0.5$.

The solid lines indicate $\theta_L$ and $\theta_T$ predicted by cable theory. For non-curved action potential fronts, $\theta_L$ and $\theta_T$ are proportional to the length constants $\lambda_x$ and $\lambda_y$ (see equations (16) and (17)) [32], [41]. The prediction of $\theta_T$ using cable theory is accurate for $\sigma_T = 0$ and $\mu_T \geq 0.3$. Cable theory overestimates $\theta_T$ for both transverse gap junction remodeling and fibrosis. As indicated by the dashed line, the effect of fibrosis is better estimated assuming a linear descent of $\theta_T$.

A reduction of 30% in $\theta_T$ due to gap junction remodeling in rat ventricular tissue was reported by Uzzaman et al. [51]. A similar reduction of $\theta_T$ in our model is obtained for $\mu_L = 0.5$ and $\sigma_L = 0.5$. Spach and Dolber observed transverse conduction velocities related to uncoupling of side-to-side connections as low as 0.085 m/s in human cardiac tissue of adults over age 50 [49]. From Fig. 3 it can be observed that such low values for $\theta_T$ in our model can be obtained for fibrosis fraction $FF$ between 0.3 and 0.4.

### C. Uniform expression of $I_e$

The longitudinal conduction velocity $\theta_T$ versus $G_t$ after the second stimulation is presented for five different types of tissue in Fig. 4. The standard deviation is indicated by the error bars. A similar increase in $\theta_T$ is obtained for normal, remodeled and fibrotic tissue. For $G_t$ above 0.3 nS/Pf, the increase in $\theta_T$ is approximately 0.04 m/s for all types of tissue. Compared to the conduction velocity in tissue without $I_e$, this increase is about 20% for remodeled tissue ($\mu_r = \mu_T = 0.5$ and $\sigma_T = \sigma_T = 0.05$, see Fig. 4). Note that although for $G_t$ above 0.27 nS/Pf spontaneous diastolic action potentials can occur, the increase in conduction velocity for $G_t$ below 0.5 nS/Pf is caused by a higher (more depolarized) diastolic membrane potential. For values of $G_t$ above 0.5 nS/Pf ectopic pacemaking with BCL less than 800 ms occurred and the pacemaker at the stimulation site was captured (results not shown).

### D. Regional expression of $I_e$

Average BCLs for various $\mu_r = \mu_L$ and size of region with expression of $I_e$ are presented in Table II. Region size is indicated as a percentage of the total tissue. A dash means no ectopic activity occurred. In these simulations, the current generated by the $I_e$ channels was spread over the entire tissue such that the threshold was not reached in any of the segments. For comparison, $G_t = 0.3$ nS/Pf in single cell simulations leads to an average BCL of 1331.9 ms. From Table II it can be observed that when $I_e$ is present in 50% of the tissue, ectopic activity occurs in normal atrial tissue. In tissue with reduced cellular coupling, smaller regions with expression of $I_e$ lead to ectopic activity. Furthermore, the BCL decreases when cellular coupling decreases.

### E. Non-uniform expression of $I_e$

The tissue properties, average BCLs and standard deviation of BCLs for the gradual increase of $I_e$ (series A) and random distribution of $I_e$ (series B) are presented in Table III. In both series, the average BCL decreases when coupling is reduced. In case coupling is non-uniformly reduced, the BCLs are even more decreased. The standard deviation of the BCLs is smaller for coupled tissue compared to totally uncoupled tissue ($\mu_L = \mu_T = 0.0$). Due to coupling, the segments fire with similar frequencies (frequency entrainment [52]). By inspecting the times of activation we found that when coupling is increased,
the segments not only fire with similar frequencies, but also at similar times (waveform entrainment [52]). The larger standard deviation of BCL in less coupled tissue is mainly caused by a few non-synchronized segments that fire at their own basic cycle length.

F. Large-scale simulations

The membrane potentials after the second stimulation are presented for normal atrial tissue in the left column of Fig. 5. Note that although the cardiac tissue is modeled as an irregular brickwall, the curvature of the wavefront is smooth and ellipsoidal, confirming that the segments are small enough to represent normal atrial tissue. The conduction velocities of the wavefront are similar to the results reported by Spach and Boineau, within the range of 0.5 m/s and 1.5 m/s as well as the anisotropy ratio f = 0.5 m/s and 0.7 m/s, respectively. These conduction velocities are similar to the results reported by Spach and Boineau [52].

In the present study, we investigate the influence of atrial tissue on the conduction velocity and ectopic activity triggered by structural remodeling. One of the key factors is the role of the pulmonary veins in atrial fibrillation [59], [60]. In the present study, we investigate the influence of atrial tissue on the conduction velocity and ectopic activity triggered by diastolic action potentials.

B. Hyperpolarization-activated inward currents

The membrane potentials after the second stimulation for pathological tissue are presented in the center and right column of Fig. 5. Ectopic activity occurs on the right side of the tissue approximately 1000 ms after the start of the simulation. In this region, the depolarizing current is compensated by the sodium current i_{Na}, which may lead to a decrease in fibrillation. In our simulations, we observe that for G_C smaller than 0.27 nS/pF, a steady-state membrane potential is reached at which the depolarizing current is compensated by the sodium current i_{Na}.

C. The role of I_f in structurally remodeled tissue

Based on our simulation results, we conclude that ectopic activity in regions with an increased expression of I_f is
enhanced by a reduced cellular coupling. Similar observations are reported by Wilders et al. [64] in a study on focal activity related to anisotropy. Cai et al. [52], Winslow et al. [65] and Cloherty et al. [66] observed in simulation studies that little cellular coupling is required for frequency entrainment of sino-atrial node cells. Frequency entrainment was also observed in our simulations of regional and distributed focal activity. However, we also observed that non-uniform uncoupling due to fibrosis and gap junction remodeling leads to lower basic cycle lengths of ectopic activity. We conclude that the combination of a distributed expression of $I_I$ and uncoupling due to fibrosis and gap junction remodeling might lead to ectopic activity, contributing to arrhythmogenesis in diseases characterized by $I_I$ overexpression such as heart failure, hypertrophy, and atrial fibrillation [18], [20], [21], [22].

From our simulation results we also conclude that an increased expression of $I_I$ leads to an increased conduction velocity. Due to the presence of $I_I$, the diastolic membrane potential rises, such that less current load is needed to reach the threshold. Especially in cases where few cells need to load a larger number of cells (current-to-load mismatch) this mechanism may prevent drastic slowing or even a total block of action potential propagation. We observed that the increase in conduction velocity is similar in normal, remodeled and fibrotic tissue. Compared to the conduction velocity in tissue without $I_I$ we observed an increase of up to 20% in remodeled and fibrotic tissue. Based on these findings, we propose that an increased expression of $I_I$ in early stages of cellular uncoupling due to aging or pathology may be a mechanism to prevent conduction slowing and block. Michels et al. [18] hypothesize a therapeutic role for $I_I$ blockers to modify pathological automaticity. Based on our simulation results, we conclude that blocking of $I_I$ under pathological conditions might lead to slowing or block of action potential propagation.

<table>
<thead>
<tr>
<th>time (ms)</th>
<th>$\mu_e = \mu_r = 1$</th>
<th>$\mu_e = \mu_r = 0.5$</th>
<th>$\mu_e = \mu_r = 0.3$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>$\sigma_e = \sigma_r = 1$</td>
<td>$\sigma_e = \sigma_r = 2$</td>
<td></td>
</tr>
<tr>
<td>$FF = 0$</td>
<td>$FF = 0.35$</td>
<td>$FF = 0.35$</td>
<td></td>
</tr>
<tr>
<td>$\theta_I = 0.42 , m/s$</td>
<td>$\theta_I = 0.19 , m/s$</td>
<td>$\theta_I = 0.12 , m/s$</td>
<td></td>
</tr>
<tr>
<td>$\theta_I = 0.13 , m/s$</td>
<td>$\theta_I = 0.05 , m/s$</td>
<td>$\theta_I = 0.03 , m/s$</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 5. Simulation of normal (left column) and pathological (center and right column) atrial tissue with non-uniform expression of $I_I$. The membrane potential is shown for different simulation times after the second stimulation. Just excited tissue is colored red, depolarized tissue is yellow or green, and repolarized tissue is blue.
D. Model validity and limitations

In the present study, structural remodeling and active membrane behavior extended with a hyperpolarization-activated inward current are brought together into one model. The aim of the model is to study action potential propagation and ectopic activity in normal and in structurally remodeled tissue. Although similar results would have been obtained by a monodomain formulation of the model, we think that, in order to model reduced intracellular coupling caused by pathology, the interstitial space should explicitly be modeled as a possible conduction pathway. The validity of the model with respect to the cardiac tissue is discussed in Methods (see also Ref. [40]). Below, we discuss the validity of our model of \( f \), the modified \( Na \) kinetics, the ionic concentrations, and the distribution of \( f \) expression.

1) \( f \) kinetics: We use large, non-physiological, values for the maximum membrane conductance \( G_f \) to obtain significant diastolic depolarization and diastolic action potentials. \( I_f \) conductances of this size have not been observed experimentally [20], [21], [22], [23]. However, Michels et al. [18] recently observed that half-maximum activation of single-channel \( I_f \) is in fact within diastolic range of human atrial myocardium. These recent observations are most likely because cell dialysis was omitted in the new study [18]. The \( I_f \) channel availability in human atrial myocytes \( (p_f) \) in our model reported by Michels et al. [18] in diastolic range is much larger than the measurements reported by DiFrancesco [43] on which \( p_f \) in our model is based. For example, \( G_f = 0.16 \text{nS/pF} \) in our model leads to a steady-state membrane potential \( V_{\text{mem}} = -70.8 \text{mV} \), a conductance \( g_f = G_f p_f = 0.006 \text{nS/pF} \) and \( p_f = 0.0375 \) (see Fig. 2). However, the channel availability reported by Michels et al. [18] would lead to \( p_f = 0.26 \) for \( V_{\text{mem}} = -70.8 \), giving a maximum conductance \( G_f = g_f / p_f = 0.006/0.26 = 0.023 \text{nS/pF} \). Porciatti et al. [19] reported a current density of \(-3.77 \text{pA/pF} \) at \( V_{\text{mem}} = -120 \text{mV} \) for human atrial myocytes. For reversal potential \( E_f = -13 \text{mV} \) [19], the conductance \( g_f = I_f / (V_{\text{mem}} - E_f) = 0.035 \text{nS/pF} \). Since \( p_f = 1 \) for \( V_{\text{mem}} = -120 \text{mV} \) [19], the maximum conductance \( G_f \) equals \( g_f = 0.035 \text{nS/pF} \) in that case. Although the values we have used for \( G_f \) are somewhat larger than the experimentally obtained values, the \( I_f \) current size in diastolic range is similar to the recent findings by Michels et al. [18]. The major findings of our study, namely the facilitation of action potential propagation and possible ectopic activity in

<table>
<thead>
<tr>
<th>time (ms)</th>
<th>( \mu_x = \mu_y = 0.3 )</th>
<th>time (ms)</th>
<th>( \mu_x = \mu_y = 0.3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1120</td>
<td>( \sigma_x = \sigma_y = 2 )</td>
<td>6810</td>
<td>( FF = 0.35 )</td>
</tr>
<tr>
<td>1950</td>
<td>( FF = 0.35 )</td>
<td>8440</td>
<td>( FF = 0.35 )</td>
</tr>
<tr>
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<td>( FF = 0.35 )</td>
<td>10060</td>
<td>( FF = 0.35 )</td>
</tr>
<tr>
<td>3580</td>
<td>( FF = 0.35 )</td>
<td>11690</td>
<td>( FF = 0.35 )</td>
</tr>
<tr>
<td>4390</td>
<td>( FF = 0.35 )</td>
<td>14980</td>
<td>( FF = 0.35 )</td>
</tr>
</tbody>
</table>

Fig. 6. Capturing ectopic rhythm. An 8 cm \( \times \) 3 cm sheet of atrial tissue is represented by an irregular brickwall structure. The membrane potential is shown for different simulation times. The two black lines indicate how the collision front moves to the right. After approximately 15 seconds of simulation, the wavefront generated by ectopic activity vanishes. Just excited tissue is colored red, depolarized tissue is yellow or green, and repolarized tissue is blue.
uncoupled tissue, also hold for physiological $G_i$ when the $I_i$ kinetics are based on these recent findings.

2) $I_{sa}$ kinetics: To obtain diastolic action potentials for large values of $G_{sa}$, we adapted the kinetics of $I_{sa}$ such that the $I_{sa}$ channels open faster when the membrane depolarizes. In single cell simulations with the Courtemanche model, action potentials are generated by applying a stimulation current of 20 pA/pF for 2 ms [42]. When slowly depolarizing the membrane by applying a small stimulation current for a longer period of time, a minimum current of 0.5 pA/pF is required to generate an action potential. When smaller stimulation currents are applied, the threshold for the opening of the $I_{sa}$ channels is never reached due to the increasing voltage dependent $I_{sa}$ current. $I_{sa}$ reaches a maximum of approximately 0.5 pA/pF for membrane potential $-67$ mV [42]. By adapting the $I_{sa}$ kinetics as described in Methods, action potentials can be generated when applying a stimulation current above 0.4 pA/pF. The changes of the $I_{sa}$ kinetics have no effect on the action potential morphology and duration when the usual stimulation current is applied.

3) Ionic concentrations: The ionic currents of the Courtemanche model interact with intracellular Na$^+$, K$^+$ and Ca$^{2+}$ concentrations [42]. We adapted the model to take the influence of $I_i$ on [Na$^+$], and [K$^+$], into account as described by DiFrancesco and Noble [45]. However, the effect on ionic concentrations of the stimulus current and the intracellular currents responsible for loading of the cells are not taken into account. This may lead to a drift in ionic balance when simulating a longer period of time [42], [67]. Indeed, we observed some deviation in the ionic balance after several seconds of simulation time (not shown). However, the drift was marginal and since the longest simulation run lasted only 15 seconds, we do not expect any noticeable influence on our simulation results.

4) Distribution of $I_i$ expression: An important aspect of our model is the non-uniform expression of $I_i$, Porciatti et al. [19] observed expression of $I_i$ in 82% of human atrial cells. Hoppe and Beuckelmann found $I_i$ in 95 to 100% of human atrial myocytes [22]. They report a considerable variability of $I_i$ size from cell to cell [22]. Sartiani et al. [28] detected $I_i$ in about 30% of cultured HL-1 cells (adult mouse atrial myocytes). Since little quantitative information is available on the distribution of $I_i$ expression, we decided to model variability in the expression of $I_i$ using a normal distribution of $G_i$.

V. CONCLUSION

In our model, an increased expression of $I_i$ leads to a larger conduction velocity in normal, remodeled and fibrotic tissue. The nominal increase in conduction velocity is similar for all types of tissue. Compared to tissue without $I_i$, the relative increase in conduction velocity is up to 20% in remodeled and fibrotic tissue. Based on these results, we propose that an increased expression of $I_i$ in early stages of cellular uncoupling, due to aging or pathology, may be a mechanism to facilitate action potential propagation. Hence, $I_i$ may prevent conduction slowing and block. We also found that in tissue with a non-uniform expression of $I_i$, the basic cycle length of an ectopic pacemaker decreases due to cellular uncoupling. Thus, overexpression of $I_i$ may lead to ectopic activity, especially in regions with reduced cellular coupling.

APPENDIX

NUMERICAL INTEGRATION SCHEME

A numerical integration scheme to solve the equations (1) through (6) is obtained by introducing the connectivity matrices $D_{m}$ and $D_{ext}$ and rewriting the equations as a combination of a system of differential equations and a system of linear equations. For a tissue represented by $N$ nodes, the $N \times N$ matrices $D_{m}$ and $D_{ext}$ are defined by

$$D_{m}^{n,m} = \begin{cases} \sigma_{m}^{n,m}, & \text{if } (n,m) \in \mathcal{E} \\ 0, & \text{otherwise} \end{cases} \quad (19)$$

$$D_{ext}^{n,m} = \begin{cases} \sigma_{ext}^{n,m}, & \text{if } (n,m) \in \mathcal{E} \\ 0, & \text{otherwise} \end{cases} \quad (20)$$

Observe that the number of non-zero elements on each row of these matrices equals the number of adjacent nodes for the corresponding node plus one. Since this number is in general small compared to the total number of nodes, $N$, $D_{m}$ and $D_{ext}$ are sparse matrices. Also note that $D_{m}$ and $D_{ext}$ are constructed such that the sum of all elements in each row equals zero, which makes them singular matrices. The matrix $D_{m}$ is defined such that for node $n$ it holds

$$T_{n} = \sum_{m \in N} D_{m}^{n,m} V_{m}. \quad (21)$$

Using (21) to rewrite equations (1) through (6) of the Cellular Bidomain Model we obtain the system of equations

$$C_{mem} \frac{dV_{mem}}{dt} + S_{mem} I_{mem} = D_{m} V_{int} \quad (22)$$

$$D_{m} V_{int} + D_{ext} V_{ext} = 0, \quad (23)$$

$$V_{mem} = V_{int} - V_{ext}, \quad (24)$$

where $V_{int}$, $V_{ext}$ and $V_{mem}$ are vectors of length $N$ representing the internal, external and membrane potential of all nodes, and vector $I_{mem}$ of length $N$ represents the ionic membrane current of all nodes. Furthermore, $C_{mem}$ and $S_{mem}$ are diagonal matrices with elements $C_{mem}^{n,n}$ and $S_{mem}^{n,n}$, respectively, on the diagonal.

A numerical integration scheme for the equations (22), (23) and (24) is obtained as follows. Let vectors $V_{mem}^{k}$, $V_{int}^{k}$ and $V_{ext}^{k}$ denote the membrane, internal and external potential of all nodes at time $k\Delta t$, where $\Delta t$ represents the simulation time step size. Vector $I_{mem}^{k}$ denotes the ionic membrane current of all nodes at time $k\Delta t$. $I_{mem}^{k+1}$ is obtained from $I_{mem}^{k}$ and $V_{mem}^{k}$ using a modified Euler method as described in Ref. [42]. The values of the potentials on time $(k+1)\Delta t$ can be computed by the following explicit numerical scheme:

$$V_{mem}^{k+1} = V_{mem}^{k} + \Delta t C_{mem}^{-1} (D_{m} V_{int}^{k} - S_{mem} I_{mem}^{k+1}), \quad (25)$$

$$(D_{m} + D_{ext}) V_{int}^{k+1} = -D_{int} V_{mem}^{k+1}, \quad (26)$$
\[
V_{\text{int}}^{k+1} = V_{\text{mem}}^{k+1} + V_{\text{ext}}^{k+1}.
\]

Hence, first the membrane potential on time \((k + 1)\Delta t\) is computed using a forward Euler step. Next, the external potential on time \((k + 1)\Delta t\) is found by solving the system of linear equations (26). Finally, the new internal potential is obtained by adding the new membrane and external potentials.

Since \(G_{\text{mem}}\) is a diagonal matrix, the computation of \(V_{\text{mem}}^{k+1}\) from Equation (25) requires only one matrix-vector multiplication with sparse matrix \(D_{\text{int}}\). Solving \(V_{\text{int}}^{k+1}\) from Equation (26) is, however, more complicated. Due to the singularity of the matrix \(D_{\text{int}} + D_{\text{ext}}\), no unique solution of this system of equations exists. However, it can be shown that if the tissue is connected, the various solutions of (26) differ only by a constant shift of all external potentials. To obtain a unique solution for Equation (26) we introduce one extra equation stating that on each time the sum of external potentials equals zero, i.e.,

\[
\sum_{n \in N} V_{\text{ext}}^{n,k} = 0,
\]

(28)

where \(V_{\text{ext}}^{n,k}\) denotes the external potential of node \(n\) at time \(k\Delta t\). Initially, this extra requirement can be satisfied by choosing \(V_{\text{ext}}^{n,0} = 0\), for all nodes \(n \in N\).

The system of differential equations is solved using a forward Euler scheme with time step 0.010 ms. The system of linear equations is then solved with an iterative method. Let \(D = D_{\text{int}} + D_{\text{ext}}\) and let \(P\) be the diagonal part of \(D\), with reversed sign. Hence, the elements of \(P\) are given by \(P_{n,n} = \sum_{(n,\alpha) \in E} (\sigma_{\alpha}^{\text{int}} + \sigma_{\alpha}^{\text{ext}})\). Since the tissue is connected, each node \(n\) is connected to at least one other node, which implies that all elements \(P_{n,n}\) are positive. Hence, the matrix \(P\) is not singular. Equation (26) can now be reformulated as

\[
P V^{k+1}_{\text{ext}} = (D + P)V^{k+1}_{\text{ext}} + D_{\text{int}} V_{\text{mem}}^{k+1}.
\]

(29)

The solution of (29) can be approximated by iterating

\[
V^{k+1,i+1}_{\text{ext}} = P^{-1} (D + P)V^{k+1,i}_{\text{ext}} + P^{-1} D_{\text{int}} V_{\text{mem}}^{k+1},
\]

(30)

where \(V^{k+1,i}_{\text{ext}}\) denotes the approximation of \(V^{k+1}_{\text{ext}}\) after \(i\) iterations. This is in fact Jacobi’s method for solving systems of linear equations. As a first approximation of \(V^{\text{int}}_{\text{ext}}\) at time \((k + 1)\Delta t\), the value of \(V^{\text{int}}_{\text{ext}}\) at time \(k\Delta t\) is chosen, i.e.,

\[
V^{k+1,0}_{\text{ext}} = V^{k}_{\text{ext}}.
\]

(31)

The stop criterion is based on Equation (5), and defined by

\[
(\mathcal{L}_{\text{int}}^{n} + \mathcal{L}_{\text{int}}^{\alpha})^{2} < \epsilon,
\]

(32)

for all nodes \(n \in N\).

The system of linear equations (26) is often solved by the Conjugate Gradient Method (CGM). Although CGM converges faster than Jacobi’s method, one iteration of CGM requires more computational effort than one iteration of Jacobi’s method. We now compare the computation time spent by our method to the computation time spent by the Conjugate Gradient Method. For both methods we used the solution of the former time step as a first approximation and Equation (32) as stop criterion. We measured the computation time spent by both methods for \(\epsilon\) ranging from \(10^{-3}\) through \(10^{-10}\) on a sample tissue of \(1\) cm \(\times\) \(0.4\) cm with varying segment sizes and varying internal conductances (\(\mu_{\text{r}} = \mu_{\text{s}} = 0.5\) and \(\sigma_{\text{r}} = \sigma_{\text{s}} = 0.5\)). As expected, the number of iterations per time step increases faster for Jacobi’s method compared to CGM for decreasing \(\epsilon\). However, for \(\epsilon > 10^{-5}\), the number of iterations used by Jacobi’s method is smaller than the number of iterations used by CGM. Jacobi’s method uses less computation time per time step for \(\epsilon > 10^{-7}\). To measure the conduction velocities and basic cycle times, we use the moment of depolarization of individual segments. For both methods, the moment of depolarization for all segments differed at most one time step between \(\epsilon = 10^{-4}\) and the most accurate solution found by CGM with \(\epsilon = 10^{-10}\). We decided to apply Jacobi’s method with \(\epsilon = 10^{-5}\) to perform the simulations for the present study. All simulations were performed on a single processor machine, except for the large-scale simulations. These were performed on a cluster of eight processors using a parallel implementation of our in-house developed program.

REFERENCES


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