A Novel Computational Model of the Human Sinoatrial Action Potential

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Abstract

The sinoatrial node (SAN) tissue is responsible for the heart rhythm in physiological conditions. SAN cells are self-oscillating and the phenomena underlying this feature are well-described through electrophysiological experiments carried out on animals. Recently, human SAN cell data were recorded, but a human SAN action potential (AP) mathematical model is still lacking.

Aim of this work is the formulation of a human SAN AP model that is able to reproduce the available experimental data. We started from the Severi-DiFrancesco SAN model (rabbit) and modified ion currents and calcium handling on the basis of available experimental data.

The AP waveform and calcium transient generated by the model were compared to experimental traces. We also studied the effect of I_f ('funny current') block on cycle length.

The model generates action potentials and calcium transients in line with experimental data. It can provide new insights into the phenomena that lead to the generation of SAN AP and allows us to study the effects of drugs that modulate the pacemaker activity.

1. Introduction

Pacemaker cells that constitute the sinoatrial node (SAN) of the heart are directly responsible for the cardiac electrical activity. They are self-oscillating, that is they are able to provide a rhythmic action potential (AP) without external stimuli. In experiments performed on animal cells, mainly isolated from rabbit hearts, the electrophysiological properties have been determined in depth, and principal currents underlying the pacemaker activity have been identified and characterized.

The plethora of experimental data and the ever increasing computing power allowed the formulation of progressively more complex and more reliable models [1-5].

Human adult SAN cell electrophysiology is still largely unexplored. Experimental data on small tissue samples or isolated cells are limited to studies by Drouin [6] and Verkerk et al. [7]. Recently, Danielsson et al. [8] collected patch-clamp data from spontaneously beating early embryonic human cardiomyocytes.

Chandler et al. [9] characterized human SAN tissue from the gene expression point of view. Then they built a mathematical human SAN AP model based on the Courtemanche et al. [10] human atrial single cell AP model. They assumed that the maximal conductance of a particular ionic current was roughly proportional to the mRNA expression level for the specific ion channel, neglecting possible non-linearities.

The modified model provided a self-oscillating AP, so Chandler et al. [9] highlighted that the SAN behaviour is the result of a specific gene expression.

Up to now a human SAN AP model based on electrophysiological data is still not present; therefore the aim of this work is the formulation of a human SAN AP model that includes the electrophysiological studies carried out on human SAN cells.

2. Methods

The rabbit SAN cell model by Severi et al. [5] was the starting point of our work.

The identification of currents, pumps and exchangers was led through different approaches: we included experimental data from electrophysiology [7,8] and gene expression [9] where these were available; otherwise we performed parameter tuning to reproduce as close as possible the experimental traces (AP and Ca^{2+} transient).

Cell capacitance and dimensions. We considered a membrane capacitance (C_m) of 57 pF, a cell length of 67 μm and a cell width of 7.8 μm according to Verkerk et al. [7] .

I_f. The funny current I_f was implemented splitting it in Na^+ and K^+ components with a g_{fNa}/g_{fK} conductance ratio of 0.5927, which yields a reversal potential of −22 mV, in accordance with Verkerk et al. [7].

Verkerk et al. [7] reported, for experiments performed on human SAN cells, a maximal conductance g_f of 75 pS/pF, so we assumed the maximal conductance g_f = 4.3 nS , with C_m = 57 pF.

I_{Kr}. The steady-state activation curve of I_{Kr} was fitted on data from embryonic human cardiomyocytes by Danielsson [8]. The conductance g_{Kr} was set to 4.2 nS (+10% compared to [5]) to hyperpolarize the maximum diastolic potential (MDP) towards more negative potentials as experimentally reported in human [6,7].

I_{Ks}. Similarly to I_{Kr} the steady state activation curve of I_{Ks} was fitted on data from embryonic human cardiomyocytes by Danielsson [8]. We assumed a conductance g_{Ks} of 0.65 nS, reducing it by 78% with respect the parent model.

I_{Kur}. We added the formulation for I_{Kur} current in accordance with Chandler et al. [9], who reported the expression level of Kv1.5 channels in human SAN tissue. Current equations were formulated as in the Maleckar et al. [11] human atrial cell model. We set the conductance g_{Kur} to 0.23 nS, 8% of the corresponding atrial value.

In order to mimic the experimental $[Ca^{2+}]_i$ data recorded by Verkerk et al. [12] (transient range and amplitude) the following changes have been applied:

I_{NaCa}. We reduced the maximal I_{NaCa} activity by 60% to increase diastolic Ca^{2+} level.

J_{rel}. We tuned parameters of Ca^{2+} release by RyR channels to control $[Ca^{2+}]_i$ transient amplitude, maintaining a release flux of hundreds of mM/s.

J_{up}. The uptake flux was formulated through a sigmoidal curve, leaving the Michaelis-Menten (MM) formulation adopted by the parent model. The sigmoidal formulation allows a higher control on Ca^{2+} uptake, in particular during the diastolic phase.

Finally, we modified Ca^{2+} diffusion rate from subsarcolemmal space to cytosol (+27%) and Ca^{2+} sequestration by calmodulin and calsequestrin.

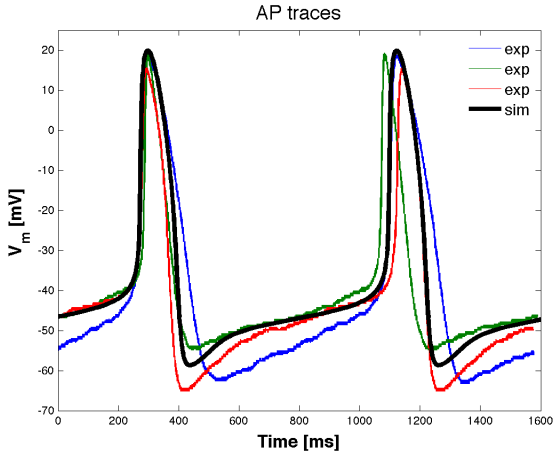

Figure 1. Comparison between AP waveform generated by the model and experimental traces from Verkerk & Wilders [13].

Table 1. AP features

AP features	Units	Experimental Values [7]	Present Model
APA	mV	78.0 ± 4.5	78.6
MDP	mV	-61.7 ± 4.3	-58.7
CL	ms	828 ± 15	825
V_{max}	V/s	4.6 ± 1.2	5.8
APD_{20}	ms	64.9 ± 16.9	86.0
APD_{50}	ms	101.5 ± 27.0	120.0
APD_{90}	ms	143.5 ± 34.9	145.0
OS	mV	16.4 ± 0.7	19.9
DDR_{100}	mV/s	48.9 ± 18	56.9

APA: action potential amplitude; MDP: maximum diastolic potential; CL: cycle length; V_{max}: maximum upstroke velocity; $APD_{20,50,90}$: action potential duration at 20, 50, and 90% repolarization; OS: overshoot; DDR_{100}: diastolic depolarization rate in the first 100 ms of DD.

3. Results

The model generates AP waveforms that are close to those recorded from human single SAN cells by Verkerk et al. [13], as shown in Figure 1.

All the AP features are quite close to experimental data (see Table 1).

Figures 2 and 3 show AP, current densities ($I_{tot,}$ I_{CaL}, $I_{Kr,}$ I_{CaT}, I_f, I_{Na}, $I_{Ks,}$ I_{NaCa}, $I_{NaK,}$, I_{to}, I_{Kur}), Ca^{2+} fluxes (J_{up} and J_{rel}) and Ca^{2+} concentrations (Ca_i, Ca_{sub}, Ca_{jsr}, Ca_{nsr}) of the model relative to the action potential of a human SAN single cell in physiological conditions, with $[Na^+]$ clamped at 5 mM according to Verkerk et al. [7]

Ca_i transient measurements on human SAN refer to a unique SAN single cell [12]. The Ca_i transient generated by the model is close to experimental traces. The model shows a slightly lower Ca_i range (98 vs 115 nM). Diastolic and systolic $[Ca^{2+}]_i$ were both slightly lower (98 vs 105 nM MDC, 197 nM vs 235 MC), than experimental data (Figure 4).

The calcium dynamics generated by the model had an upstoke steeper than the experimental one. Moreover, TD_{20} and TD_{50} predicted by the model are close to the experimental trace. TD_{90} is higher then experimental one highlighting a slower $[Ca^{2+}]_i$ decay. Experimental data and predicted values are collected in Table 2.

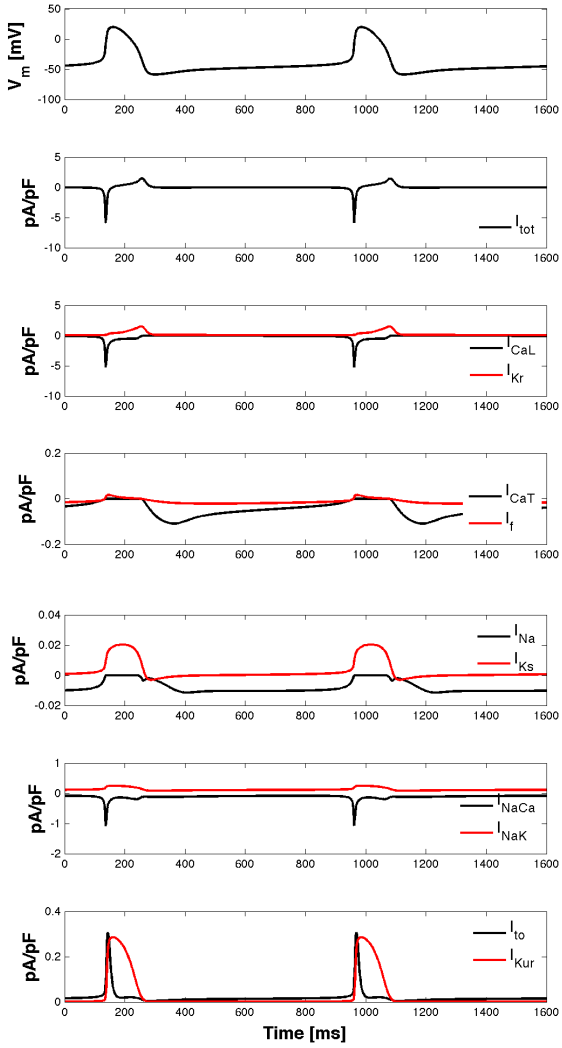

Figure 2. Simulation of 1600 ms of spontaneous electrical activity in a human SAN cell. AP, total ionic current and individual currents are plotted.

Table 2. Intracellular Ca^{2+} transient

Ca_i Transient	Units	Experimental Values [12]	Present Model
Ca_i range	nM	105 - 220	97 - 195
TA	nM	115	98
TD_{20}	ms	138.9	131.0
TD_{50}	ms	217.4	209.0
TD_{90}	ms	394.0	565.0

TA: transient amplitude; $TD_{20,50,90}$: transient duration at 20, 50 and 90% decay.

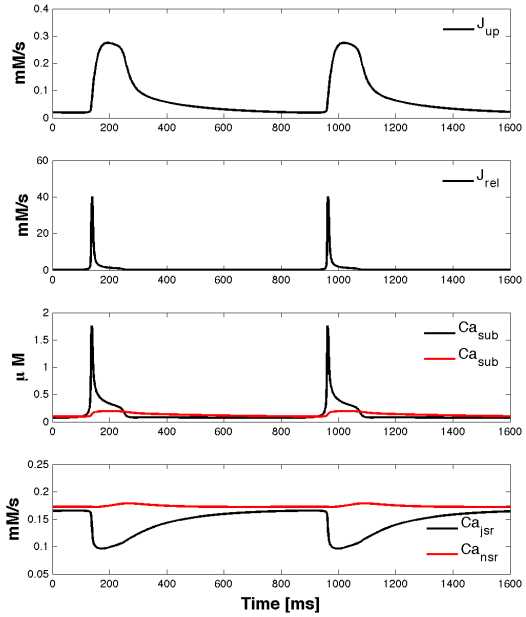

Figure 3. *Upper panels:* Ca^{2+} flux from cytosol to sarcoplasmic reticulum (SR), J_{up}, and from SR to subspace by ryanodine receptors (RyRs), J_{rel}. *Lower panels:* Ca^{2+} concentration in the four cellular compartments, i.e. subspace (Ca_{sub}), intracellular (Ca_i), junctional SR (Ca_{jsr}), and network SR (Ca_{nsr}).

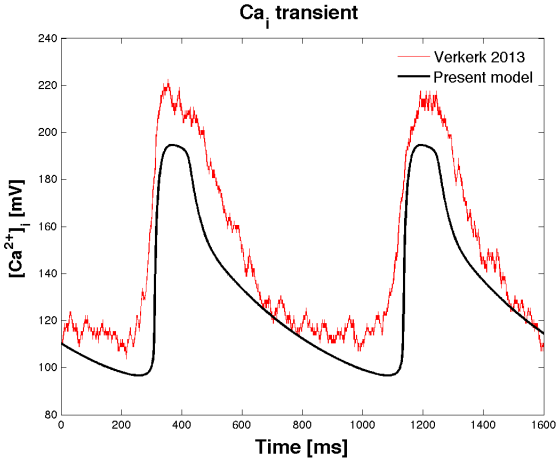

Figure 4. Comparison between intracellular Ca^{2+} transient generated by the model (black line) and experimental data (red line) recorded by Verkerk et al. [12].

We performed the funny current block implementing the administration of Cs^+ 5mM and through a progressive block (30%, 70%, 90%, 100%). Cs^+ administration induced a CL of 1050 ms (+27.2% compared to CTRL) in line with the experimental observation by Verkerk [7], who observed a 26% increase upon block of I_f by 2 mM Cs^+. The progressive block of I_f induced a CL of 917 ms (+11.1%), 1136 ms (+37.7%), 1269 ms (+52.7.2%) and

1275 ms (+54.5%), respectively. The effects on I_f block are shown in Figure 5.

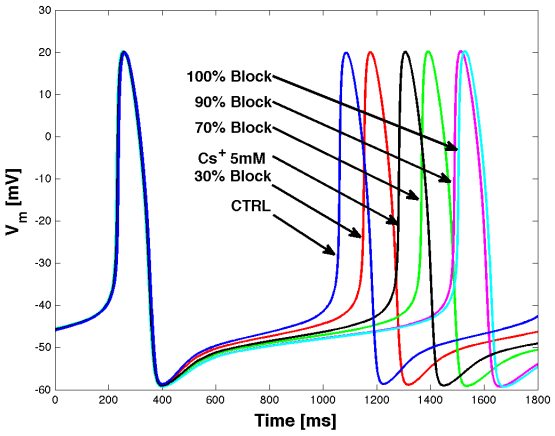

Figure 5. Simulation of the effects of progressive I_f block (30%, 70%, 90%, 100%) and Cs^+ 5 mM on CL.

4. Discussion and Conclusions

Aim of this work was the formulation of a human SAN single cell mathematical AP model based on the available electrophysiological data on human SAN cell.

AP waveforms and Ca_i transient are close to experimental traces reported by Verkerk et al. [7,12]. In particular the model well describes AP morphology, both during the upstroke and during the diastolic depolarization phase. The progressive I_f block led to an increasing of CL. This is caused by a lower DDR_{100}, as in the experimental observations [7]. Increasing progressively the I_f block (30%, 70%, 90%, 100%) led to a DDR_{100} of 51.7 mV/s (-9.1%), 40.9 mV/s (-28.1%), 35.9 mV/s (-36.9%), 35.9 mV/s (-37.4%), respectively.

The full block of I_f led to a CL increase of 54.5% but it didn't stop the self-oscillations in the simulated SAN cell. This can suggest that funny current is capable of a continuous regulation of CL in the physiological range.

This work represents a first step to achieve a reliable description of human SAN single cell behaviour.

The model will allow us to investigate in depth the phenomena underlying the human pacemaker activity; it will provide guidelines for further experiments and it will allow us to study the effects of drugs that modulate pacemaking activity.

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