STRETCH ACTIVATED ION CHANNELS IN MYOCYTES: PARAMETER ESTIMATION, SIMULATIONS AND PHENOMENA

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Abstract— **Mechanosensitive ion channels influence the electrophysiological state of cardiac myocytes. An examination of the mechanisms of mechano-electrical coupling on cellular level by the mechanosensitive ion channels was performed. Simulations with a detailed electrophysiological model were carried out. Static stretch leaded to an increase of the resting potential and a decrease of the duration of the action potential with increasing sarcomere length. Dynamic stretch delivered a variety of phenomena depending on the duration and amplitude of the stretch. An arrhythmogenic single cell phenomenon, early afterdepolarisation, was observed.**

I. Introduction

Mechanosensitive ion channels were observed in a variety of cells, including bacteria, plant and animal cells. The channels show changes in their probability to be in the open state dependent on mechanical quantities like strain and stress. The behavior of the channels influences the cellular electrophysiological state, e. g. the resting potential and the course of action potentials, as well as the initiation of excitation [1][2]. Potential pathophysiological consequences, i. e. arrhythmogenic effects, of the resulting mechano-electrical coupling are subject of recent examinations [3][4][5][6][7].

This work is focussed on the examination of the mechanisms of mechano-electrical coupling on cellular level by the mechanosensitive ion channels. Therefore, stretch currents in a detailed electrophysiological model of ventricular myocytes were parameterized. Simulations with the resulting model by applying static and dynamic stretch were performed and their results discussed.

II. Models of stretch activated channels

Different models were proposed to calculate mechanosensitive conductances and to reconstruct the associated currents. The models differ concerning the weighting of the ion conductances by functions of the mechanical quantities like strain and stress effecting the sarcolemma. Furthermore, the models differ in their inclusion of ionic currents and the ion specificity of the channels.

This work is focused on stretch activated channels of cardiac myocytes. Hereby, weighting functions can be derived from the strain using the change of sarcomere length [8][9][10], and the cell volume V_{cell} [11][12]. A weighting function derived from the stress is the isometric tension [10].

An exemplary weighting function s dependent on the sarcomere length SL is determined by:

$$s(SL) = \frac{1}{1 + \alpha e^{-\beta(SL - SL_0)}}$$

with the parameters α and β, and SL_0 [8][10]. Similar weighting functions are used with the parameters isometric tension and cell volume.

A model without differentation of ion types proposed in [8][9] describes the stretch current I_{str} by

$$I_{str} = s(SL)\ g_{str}\ (V_m - E_{str})$$

with the maximal conductivities g_{str}, the transmembrane voltage V_m, and the equilibrium voltages E_{str}.

A second model [10] describes the summary stretch current I_{str} with a non-specific $I_{Ns,str}$ and an anion stretch current $I_{An,str}$:

$$I_{str} = I_{Ns,str} + I_{An,str}$$

The currents $I_{Ns,str}$ and $I_{An,str}$ are determined by the stretch function s dependent on the sarcomere length SL, the maximal conductivities $g_{Ns,str}$ and $g_{An,str}$, resp., and the equilibrium voltages $E_{Ns,str}$ and $E_{An,str}$, resp.:

$$\begin{aligned} I_{Ns,str} &= s(SL)\ g_{Ns,str}\ (V_m - E_{Ns,str}) \\ I_{An,str} &= s(SL)\ g_{An,str}\ (V_m - E_{An,str}) \end{aligned}$$

A third model [13] dissipates the summary stretch current I_{str} in a sodium current $I_{Na,str}$, a potassium current $I_{K,str}$, a calcium current $I_{Ca,str}$, and an anion stretch current $I_{An,str}$:

$$I_{str} = I_{Na,str} + I_{K,str} + I_{Ca,str} + I_{An,str}$$

Hereby, the stretch currents are calculated as described in the simple model with the stretch function s, the maximal conductivities and the equilibrium voltages:

$$\begin{aligned} I_{Na,str} &= s(SL)\ g_{Na,str}\ (V_m - E_{Na}) \\ I_{K,str} &= s(SL)\ g_{K,str}\ (V_m - E_K) \\ I_{Ca,str} &= s(SL)\ g_{Ca,str}\ (V_m - E_{Ca}) \\ I_{An,str} &= s(SL)\ g_{An,str}\ (V_m - E_{An,str}) \end{aligned}$$

The latter model describes the stretch current obviously more detailed regarding the different types of ions and herewith offers the advantage to update quantitatively the sodium, potassium and calcium concentrations. This model is used in the following simulations.

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Abstract

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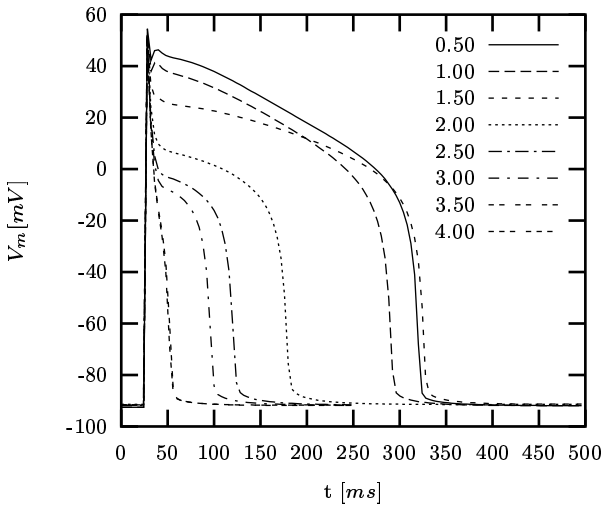

Fig. 1. Simulations with the Noble-Varghese-Kohl-Noble model. Transmembrane voltage V_m is dependent on the stimulus frequency ranging from 0.5 to 4 Hz. For each frequency a single action potential is visualized.

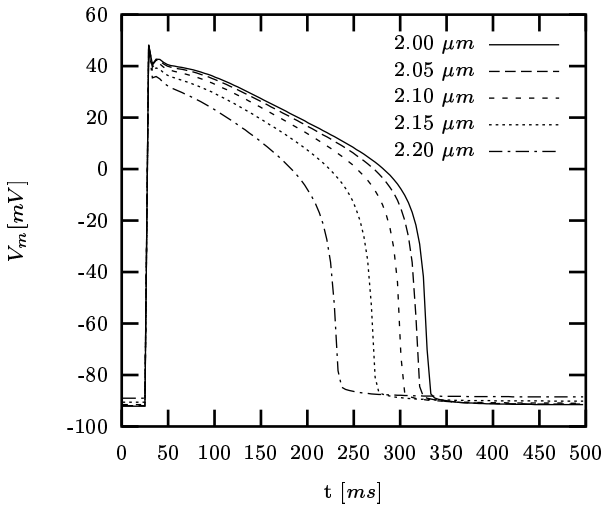

Fig. 2. Transmembrane voltage dependent on length of sarcomere calculated with Noble-Varghese-Kohl-Noble model. The cell is excited by applying a stimulus current at $t = 25\ ms$ with a length of 3 ms. The sarcomere length ranges from 2.0 to 2.2 μm. The default length of the sarcomere is 2 μm. The stimulus frequency was set to 1 Hz.

III. Electrophysiological Model and Parameterization

The Noble-Varghese-Kohl-Noble model forms the framework for the simulations of the cellular electrophysiology. The model describes a ventricular cell including effects on ionic channels by the concentration of ATP and ACh as well as by stretching (fig. 1). A description of the diadic space is incorporated. Different variants and configurations of the model exist. The following description is based on [13] [10] [14].

Hereby, the transmembrane currents are described by:

$$\begin{aligned} I_m \;=\; & I_{Na} + I_{Na,b} + I_{Na,p} \\ & + I_{K1} + I_{Kr} + I_{Ks} + I_{K,ATP} + I_{K,ACh} \\ & + I_{Ca,b} + I_{Ca,L,K} + I_{Ca,L,Na} + I_{Ca,L,Ca} \\ & + I_{Ca,L,K,ds} + I_{Ca,L,Na,ds} + I_{Ca,L,Ca,ds} \\ & + I_{NaK} + I_{NaCa} + I_{NaCa,ds} \\ & + I_{stretch} \end{aligned}$$

with the fast sodium current I_{Na}, the background sodium current $I_{Na,b}$, the voltage dependent sodium current $I_{Na,p}$. the time-independent potassium current I_{K1}, the time-dependent, delayed potassium currents I_{Kr} and I_{Ks}, the sodium dependent potassium current $I_{K,Na}$, the ATP-dependent potassium current $I_{K,ATP}$, the ACh-dependent potassium current $I_{K,ACh}$, the background calcium current $I_{Ca,b}$, the currents through L-type calcium channels $I_{Ca,L,X}$, the L-type calcium current into the diadic space $I_{Ca,L,Ca,ds}$, the Na-K exchanger current I_{NaK}, the Na-Ca exchanger current I_{NaCa}, the Na-Ca exchanger current for diadic space $I_{NaCa,ds}$, and the stretch activated currents $I_{stretch}$.

In this work the stretch activated current was reparameterized by fitting data measured in single guinea-pig ventricular myocytes [1] with methods similar to those presented in [8]. The parameters are $\alpha = 1$, $\beta = 14$, $SL_0 = 2.4\ \mu m$, $g_{Na-str} = 15\ nS$, $g_{K-str} = 30\ nS$, $g_{Ca-str} = 0.1\ nS$, $g_{An-str} = 15\ nS$, and $E_{An-str} = -20\ mV$.

IV. Simulations

The electrophysiological model is described by a set of ordinary differential equations. The integration of these equations was performed using the Euler method [15] with a time step of 20 μs.

For all simulations in this work the initial values of the model variables, e. g. the transmembrane voltage V_m, the ion concentrations, and the activation and inactivation parameters, were set to those, which result from a stationary stimulus frequency of 1 Hz.

Two sets of simulations were performed to examine the influence of static and dynamic stretch. The influence of static stretch of different strength was tested by initiation of excitation via injection of a convenient current with a duration of 3 ms. The phenomena of dynamic stretch were examined with different stretch impulses and durations. The application of stretch starts in the diastolic phase. In both sets of simulations the calculated model variables were stored and processed.

V. Results

The influence of static stretch on the course of the transmembrane voltage is illustrated in fig. 2. Hereby, the stretch amplitude is specified by the length of the sarcomere with a default of 2 μm. The resting potential as well as the course of the action potential are dependent on the length of the sarcomere ranging from 2.0 to 2.2 μm. The resting potential increases and the duration of the action potential decreases

with larger sarcomere length. Both effects can be attributed to the raise of the sarcolemmal conductances. The maxima of the transmembrane voltage are independent of stretch.

The influence of mechanical stretch impulses is depicted in fig. 3 and 4. In the presented simulations the stretch amplitude and duration were varied. Once again, the stretch amplitude was specified by the length of the sarcomere with a default of 2 μm. Depending on the amplitudes and length an effect ranging from a small change of the resting potential to an excitation of the cell was achieved.

The simulation presented in fig. 3 (a) shows the initiation of an action impulse by a relatively small stretch duration only for large sarcomere length or stretch amplitude. The simulations with sarcomere length 2.5 μm show an increase in the duration of the action impulse with the exception of the results with a relatively long stretch duration depicted in fig. 4 (b) and (c).

The initiation of an early afterdepolarisations (EAD) is apparent in fig. 4 (a) and (b) for sarcomere lengths 2.4 and 2.5 μm, and for length 2.4 μm, resp.. The classification of the EADs was performed using the description of [16] by examination of the activation and inactivation gates of the L-type calcium channels during the plateau phase.

VI. Discussion and Conclusions

The presented simulations with the electrophysiological cell model deliver information of the mechanisms of cellular mechano-electric feedback by stretch activated ion channels. Therefore, a model of stretch activated ion channels was parameterized based on measurements.

The effects resulting from static stretch can be attributed directly to the change of the conductivity of the sarcolemma. While the increase of the resting potential seems to be a common phenomenon of sustained stretch, the stated decrease of the duration of the action potential is controversial [9]. Nevertheless, crossover effects delivering an increasing duration by increasing stretch can be found with the presented model for larger sarcomere lengths, i. e. $SL > 2.35\ \mu m$.

The phenomena visible in simulations with dynamic stretch were multifaceted. Depending on the duration and amplitude of stretch different mechanisms can be assigned, e. g. the sarcolemmal conductivity is changed in different phases of the action potential.

The observation of EADs in the simulations is to our knowledge not confirmed by measurements. Nevertheless, the observation deserves further attention, because EADs are regarded as arrhythmogenic single cell phenomena.

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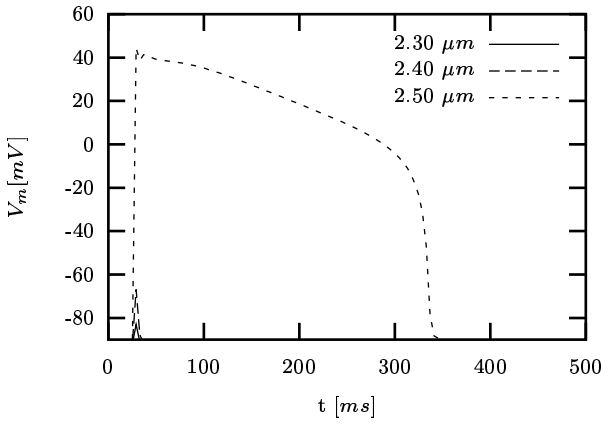
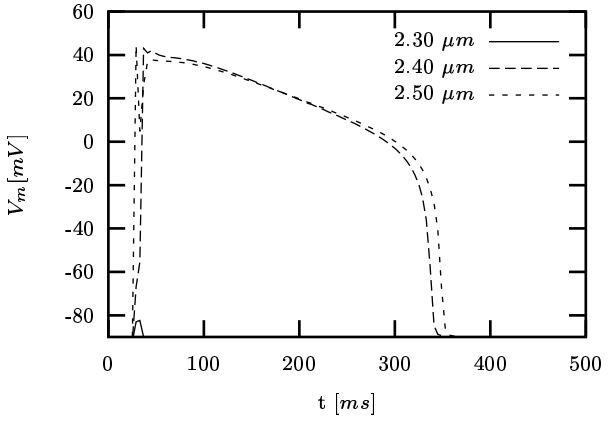


(a)



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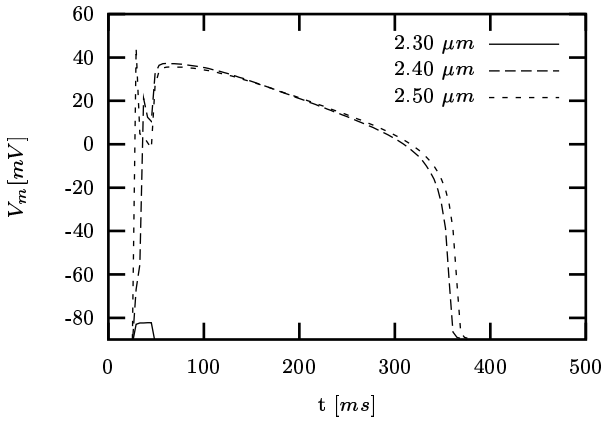
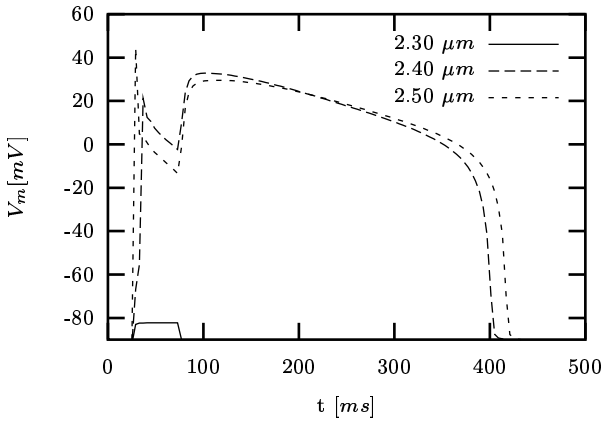
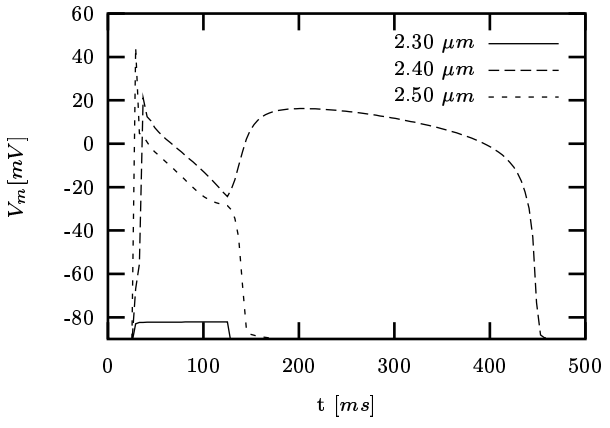


(c)

Fig. 3. Initiation of action impulse by stretch simulated with Noble-Varghese-Kohl-Noble model. At $t = 25\ ms$ a mechanical stretch of (a) 5 ms, (b) 10 ms, and (c) 20 ms was performed delivering a sarcomere length from 2.3 to 2.5 μm. The default length of the sarcomere is 2 μm.



(a)



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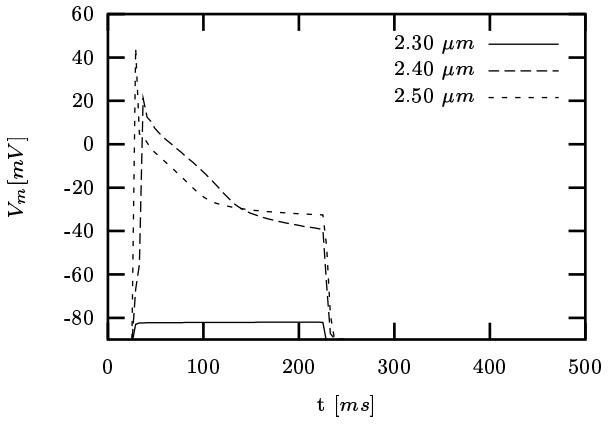

(c)

Fig. 4. Initiation of action impulse by stretch simulated with Noble-Varghese-Kohl-Noble model. At $t = 25\ ms$ a mechanical stretch of (a) 50 ms, (b) 100 ms, and (c) 200 ms was performed delivering a sarcomere length from 2.3 to 2.5 μm. The default length of the sarcomere is 2 μm.

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