Calibration of Human Cardiac Ion Current Models to Patch Clamp Measurement Data

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Abstract

Generally, models of cardiac electrophysiology describe physiologic conditions in detail. However, other conditions, such as drug interactions or mutations of ion channels are of interest for research. Therefore, the simulated ion currents have to be fitted to measured voltage or patch clamp data. In this work, three different methods for the model parametrization were compared: one based on Powell's algorithm implemented in a modular C++ framework and two optimization techniques realized in Matlab. The latter two approaches differed in solving the ordinary differential equations describing the channel gating. They can either be approximated numerically or solved analytically, since the transmembrane voltage is a piecewise constant function during the applied clamp protocol. All three methods were compared regarding computing time and quality of the fit using least squares. The modular C++ framework was slower than the numerical Matlab method, which took longer than the analytical one. The quality of the fit was similar for almost all analyzed methods. Therefore, the analytical method grants a fast and reliable solution for the calibration of ion current models for applications with constant membrane voltage, as e.g. in case of voltage or patch clamp data.

1. Introduction

Most of the current models of cardiac electrophysiology are based on the fundamental work of Hodgkin and Huxley published in 1952 [1]. Hodgkin and Huxley described ion currents in dependence of the transmembrane voltage of a giant squid axon mathematically by coupled ordinary differential equations. Nowadays, electrophysiological models are more complex and specialized by reflecting the behavior of only one certain type of myocytes and species. In 1998 for example, Courtemanche et al. [2] presented a model of human atrial electrophysiology and ten Tusscher et al. [3] published a mathematical model of human ventricular myocytes in 2004. Generally, these models offer a detailed description of cardiac myocytes under physiologic conditions. However, focus of research is on other conditions, such as drug interactions or mutations of ion channels. Furthermore, the models have to be adapted to new measurement data, e.g. of different regions of the heart to better describe tissue heterogeneities.

Normal and altered ion channel properties can be determined by voltage or patch clamp measurements, in which specific ion currents resulting from impressed voltage steps are recorded. The electrophysiological models have to be modified to reflect these conditions. For this purpose, the parameters of the ion channel models have to be adjusted in order to minimize the difference between simulation and experiment. However, the process of calibrating cardiac ion channel models can be very time-consuming depending on the number of adjustable parameters and the corresponding equations.

In this work, three different approaches for the calibration of the model parameters were investigated: the first method was based on Powell's algorithm implemented in a modular *C++* framework already presented in [4]. The two other methods were realized in *Matlab* (*R2012a, The MathWorks, Natick, MA*). They differed in the solution of the ordinary differential equations (ODEs) describing the ion channel gating. In general, these equations are approximated numerically in computational cardiology, which was used as the first method. The second option implemented in *Matlab* was the analytical solution of the ODEs. The computing time and quality of the fit using least squares were compared among all three methods. The aim was to improve the calibration of ion channel models to better investigate conditions like genetic defects or drug interactions *in silico*.

2. Methods & materials

2.1. Modeling rapid delayed rectifier potassium current

For the adaptation of the simulated rapid delayed rectifier potassium current I_{Kr} to measured voltage or patch clamp data, two different current formulations were chosen: the first one was published by Courtemanche, Ramirez and Nattel (CRN) [2] offering a description of human atrial myocytes:

$$I_{Kr} = \frac{g_{Kr} x_r (V_m - E_K)}{1 + exp\left(\frac{V_m+15}{22.4}\right)}, \quad (1)$$

where g_{Kr} is the maximal conductance of this channel, x_r is the activating gating variable, V_m the transmembrane voltage and E_K the potassium Nernst potential.

The second current formulation for human ventricular myocytes is that of ten Tusscher, Noble, Noble and Panfilov (TNNP) [3] originally published in 2004:

$$I_{Kr} = g_{Kr} \sqrt{\frac{K_o}{5.4}} x_{r1} x_{r2} (V_m - E_K). \quad (2)$$

Here, the extracellular potassium concentration K_o immediately influences the current. In contrast to the atrial model, the gating is described by an activating and additionally an inactivating gating variable x_{r1} and x_{r2}, respectively. In both models, E_K is assumed constant during the simulation of the clamp protocol, as the intracellular potassium concentration defined by the pipette solution remains nearly constant.

In general, the following ODE mathematically describes the time-dependent gating process:

$$\frac{dx_r}{dt} = \frac{x_{r\infty} - x_r}{\tau_{xr}}, \quad (3)$$

where $x_{r\infty}$ is the the steady-state value and τ_{xr} the time constant of this gating process.

In computational biology, the standard approach for the solution of these ODEs is to numerically approximate them using e.g. the simple forward Euler method or higher order methods. However, V_m is a piecewise constant function during the voltage clamp protocols. Therefore, the formulations of τ_{xr} and $x_{r\infty}$ are also piecewise constant functions except for the instant changes in voltage. As a consequence, equation 3 can be analytically solved as e.g. shown in [5]:

$$x_r(t - t_0) = x_{r\infty} + (x_{r0} - x_{r\infty}) exp\left(-\frac{(t - t_0)}{\tau}\right), \quad (4)$$

where x_{r0} is the initial value at the time t_0 of a voltage step.

2.2. Model parameter calibration frameworks

In this work, three frameworks for the calibration of model parameters, which differed in their implementation, the optimization algorithm and the solution of the ODEs, were investigated.

The first framework, implemented in *C++* and already presented in [4], is called CP in the following. This modular framework allows the usage and integration of different optimization algorithms and simulation software. In this work, Powell's algorithm was used for the minimization of the difference between measured and simulated I_{Kr}. This current was numerically computed by the above mentioned CRN and TNNP formulations also implemented in *C++*. The forward Euler scheme with a time step of 10 μs solved the ODEs.

The second and third model parameter calibration approaches were implemented in *Matlab*. Both frameworks used the *lsqnonlin* function, which offers a solution for nonlinear least squares problems, and the *trust-region-reflective* algorithm, which can be constrained by upper and lower bounds [6]. The difference between both *Matlab* frameworks was the solution of the ODEs. One framework solved these ion current equations using the numerical ODE solver *ode15s* and is therefore abbreviated MN. This solver has a variable time step with an error tolerance of 1e$-$9. The other approach (called MA) solved the ODEs analytically as described in equation 4.

All three methods used the least squares for the calculation of the difference between the measured and simulated currents in order to assess the quality of the fit:

$$\sum_{\mathrm{j}} \sum_{\mathrm{i}} \left(I_{Kr,meas}(t_{\mathrm{i}}, V_{\mathrm{j}}) - I_{Kr,sim}(t_{\mathrm{i}}, V_{\mathrm{j}})\right)^2, \quad (5)$$

where t_{i} is a discrete time of measurement and V_{j} the clamp voltage varied during the clamp protocol.

The search space was constrained by lower and upper bounds. Depending on the adjustable parameter, the upper limit was between the two- to ten-fold of the original parameter value and the lower limit was between one tenth and one half of the original value. Ten random initial parameter value sets with values within these boundaries were created. To better evaluate these different parameter sets, the results were summarized in boxplots (see Figures 1 and 2).

2.3. hERG measurement data

The exemplary hERG measurement data shown in this work was obtained using the double microelectrode voltage clamp technique. Nevertheless, similar data recorded during patch clamp measurements could be used instead.

Table 1. Original values of three exemplary adjustable model parameters.

Parameter	CRN	TNNP
g_{Kr} (nS/pF)	0.0294	0.096
$x_{r\infty(p_1)}$ / $x_{r1\infty(p_1)}$	14.1	6.5
$x_{r\infty(p_2)}$ / $x_{r1\infty(p_2)}$	26	7

Wild type (WT) hERG K^+ channels were heterologously expressed in Xenopus oocytes. Three to four days after the injection, voltage clamp measurements were performed. Tip resistances of the microelectrodes ranged from 1 to $5\,\mathrm{M}\Omega$. Measurements were recorded at room temperature (23 to 25°C). The bathing solution contained 5 mM KCl, 100 mM NaCl, 1.5 mM $CaCl_2$, 2 mM $MgCl_2$, and 10 mM HEPES (pH adjusted to 7.4 with NaOH) and the pipette solution 3 M KCl. The recorded currents of ten cells were low-pass filtered at 1 to 2 kHz, sampled at 5 to 10 kHz and averaged (see Figure 3, *dotted*).

3. Results

3.1. Adaptation of model parameters

For the calibration of simulated I_{Kr} to measured voltage clamp data, 11 parameters of the CRN current formulation and 15 parameters of the TNNP formulation were adapted. Of those parameters, three exemplary parameters, g_{Kr}, $x_{r\infty(p_1)}$ and $x_{r\infty(p_2)}$, were taken to visualize their changes in the following. The CRN formulation for $x_{r\infty}$ with the two adjustable parameters $x_{r\infty(p_1)}$ and $x_{r\infty(p_2)}$ is:

$$x_{r\infty} = \left[1 + exp\left(-\frac{V_m + x_{r\infty(p_1)}}{x_{r\infty(p_2)}}\right)\right]^{-1}. \qquad (6)$$

The same formulation was also used in the TNNP model for $x_{r1\infty}$ and $x_{r2\infty}$. Table 1 shows the original values of the adjustable parameters published by CRN for $x_{r\infty}$ and TNNP for $x_{r1\infty}$. In Figure 1, changes of the three exemplary parameters in relation to the original values are presented. The boxplots show the resulting parameter changes after the calibration of simulated to measured current data. For this purpose, ten different random initial values for each parameter served as an input for the calibration using the analytical and numerical *Matlab* (MA and MN, respectively) and the *C++* (CP) frameworks. The MA and MN frameworks revealed similar changes of the parameters independent from the initial value, whereas the parameter changes obtained by the CP framework show a larger variation and they differ from those of both other frameworks. Depending on the initial value, the relative changes of most parameters of the TNNP model varied more than those of the CRN model.

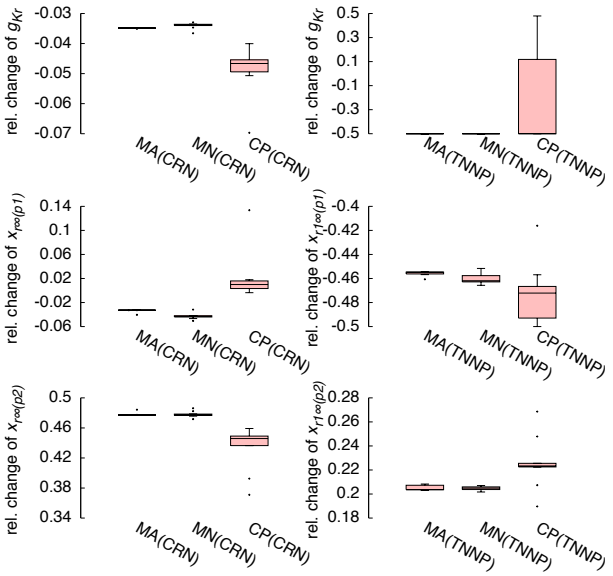

Figure 1. Changes of exemplary adapted model parameters in relation to original values published by CRN (*left*) and TNNP (*right*).

3.2. Quality of the fit and computing time

Prior to the parameter adaptation, the least squares were on average 163.6 in case of the CRN model and 611.6 in case of the TNNP model using the random initial parameter values. These values were significantly reduced after the calibration of both models using the different frameworks. The resulting least squares are visualized in Figure 2, *top*. The resulting least squares of the different frameworks were in the same range of around 4.3 with very small variance, except for the TNNP model using the CP framework. In this case, some parameter adaptations caused values of up to 7.9.

Although the least squares of the CRN and TNNP model coming from the calibration with the MA framework were almost equal, the simulated current traces presented in Figure 3 differ. As the variation of the resulting parameter sets could be neglected, only one exemplary current trace for each model is shown here. In general, the simulated currents look quite similar to the measured ones. However, both models could not fit well all parts of the curves. The CRN model e.g. failed to reproduce the steep upstroke at the beginning of the high voltage steps, whereas the TNNP model did not fit well the tail currents at high voltages.

Regarding the computing time, which was measured with a 2.66 GHz Intel Core i5 and 16 GB RAM under Mac OSX 10.6 (*Apple Inc., Cupertino, CA*), pronounced differences between the three frameworks and two models could be observed (see Figure 2, *bottom*). The calibration of the parameters of the TNNP model was on average much

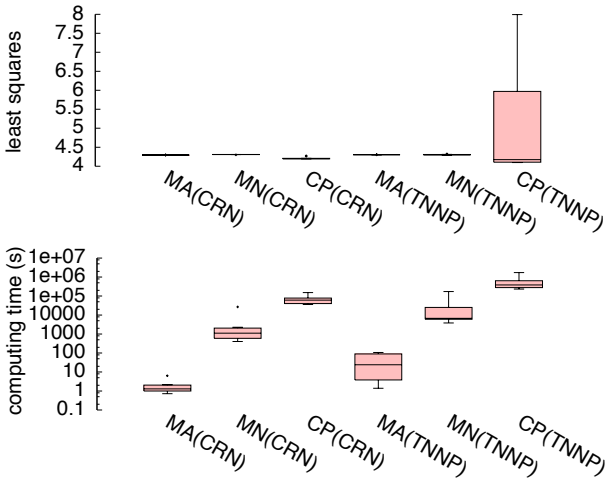

Figure 2. Least squares (*top*) and computing times (*bottom*) resulting from the fit of simulated to measured I_{Kr} using different electrophysiological models and parameter calibration frameworks.

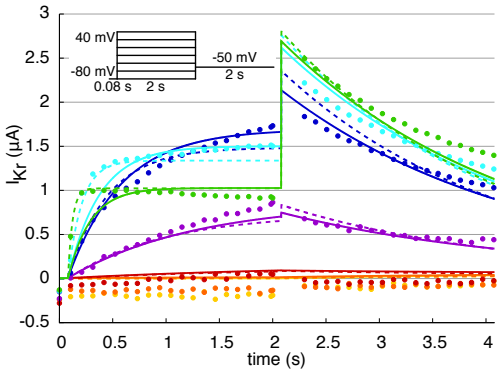

Figure 3. Measured (*dotted*) and exemplary adapted simulated (*solid*: CRN model, *dashed*: TNNP model) hERG / I_{Kr} current resulting from the voltage clamp protocol.

slower than that of the CRN model (MA: 21.6 times, MN: 9.7 times, CP: 7.9 times). Furthermore, the CP framework took longer than the MN framework (CRN: 18.7 times, TNNP: 15.2 times), which was much slower than the MA framework (CRN: 1988.0 times, TNNP: 889.4 times).

4. Conclusion and discussion

The analytical method grants a fast and reliable solution for the calibration of ion current models for applications with constant transmembrane voltage, as e.g. in case of voltage or patch clamp data. The differences between the MN and the CP framework regarding computing time might be caused by the different optimization algorithm as well as the implementation, which is a disadvantage of the modularity of the CP framework. Depending on the complexity of the model and the number of parameters, the computing time also differed. The quality of the fit measured by the least squares was similar in almost all cases except for the TNNP model using the CP framework. Since this model offers more adaptable parameters, which varied more than those of the CRN model, Powell's algorithm probably ended in different local minima depending on the set of initial parameters. Therefore, a proper choice of parameter boundaries is required or a genetic algorithm finding a global minimum as in [7] should be used in future work. Furthermore, both the CRN and TNNP models could not reproduce all parts of the voltage clamp protocol well, due to the different current formulations of the models. Consequently, an ion channel model using e.g. multi-state Markov chains has to be chosen to fit the measurement data best.

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