Supplementary Material

V241F KCNQ1 Mutation Shortens Electrical Wavelength and Reduces Ventricular Pumping Capabilities: A Simulation Study with an Electro-Mechanical Model

Aulia Khamas Heikhmakhtiar, Fakhmi Adi Rasyidin, Ki Moo Lim\*

**\* Correspondence:** Ki Moo Lim: kmlim@kumoh.ac.kr

# Mathematical equation for the electrophysiological model

We used the mathematical equation of human ventricular cell model based on ten Tusscher *et al*. [22] to simulate the cardiac electrophysiological activities. To simulate the electrophysiological propagation in a 3D ventricular model, the Eq. (1) of the single-cell can be expanded by the following partial differential equation (PDE):

$\frac{dV}{dt}=\frac{-I\_{ion}+I\_{stim}}{C\_{m}}+\frac{1}{ρ\_{x}S\_{x}C\_{m}}\frac{∂^{2}V}{∂x^{2}}+\frac{1}{ρ\_{y}S\_{y}C\_{m}}\frac{∂^{2}V}{∂y^{2}}+\frac{1}{ρ\_{z}S\_{z}C\_{m}}\frac{∂^{2}V}{∂z^{2}}$

where *ρ* is cellular resistivity and *S* is surface to volume ratio in *x*, *y*, and *z* directions.

To implement the WT, intermediate V241F, and pure V241F mutation conditions, we modified the *IKs* equation of ten Tusscher (equation 24 in ref [22]) based on Ki *et al*. [14] as follows:

WT,

$$I\_{Ks}=G\_{Ks}⋅x\_{s}^{2}(V- E\_{Ks})$$

$$x\_{s\infty }= \frac{1}{1+e^{(-5-V)/14}}$$

$$α\_{xs}= \frac{1400}{\sqrt{1+e^{(5-V)/6}}}$$

$$β\_{xs}= \frac{1}{1+e^{(V-35)/15}}$$

$$τ\_{xs}=α\_{xs}β\_{xs}+80$$

Intermediate V241F,

$$\overline{n}\_{fast}= \frac{1}{1+e^{-(V+11.0344)/19.13835}}$$

$$\overline{n}\_{slow}= \overline{n}\_{fast}$$

$$τ\_{\overline{n}\_{fast}}= 603.72722+\frac{1}{ 1.47338⋅10^{-4}⋅e^{-\frac{V}{10.75311}}+3.99874⋅10^{-4}⋅e^{-V/27.38942}}$$

$$τ\_{\overline{n}\_{slow}}= 5.59215⋅10^{-14}+\frac{1}{ 3.38684⋅10^{-5}⋅e^{-\frac{V}{28.06848}}+3.51093⋅10^{-4}⋅e^{-V/45.58635}}$$

$τ\_{\overline{n}\_{fast}}=603.72722+ \frac{1}{1.47338. 10^{-4}.e^{-V/10.75311}+3.99874.10^{-4}.e^{-V/27.38942}}$V241F,

$$\overline{n}\_{fast}= 0.25+\frac{0.75}{1+e^{-(V+34.83766)/19.48842}}$$

$$\overline{n}\_{slow}= \overline{n}\_{fast}$$

$$τ\_{n\_{fast}}= \frac{1}{1.8075⋅10^{13}⋅e^{-\frac{V}{4.62}}+0.02238⋅e^{-\frac{V}{9.82608}}}+\frac{1}{ 2.02983⋅10^{-4}⋅e^{-\frac{V}{76.68}}+8.4305⋅10^{-4}⋅e^{-V/51.66998}}$$

$$τ\_{n\_{slow}}= \frac{1}{7.58278⋅10^{11}⋅e^{-\frac{V}{6.81641}}+0.07943⋅e^{-\frac{V}{7.86159}}}+\frac{1}{ 2.02983⋅10^{-4}⋅e^{-\frac{V}{76.68926}}+8.4305⋅10^{-4}⋅e^{-V/51.56998}}$$

$$\frac{dn\_{fast}}{dt}= \frac{\overline{n}\_{fast}-n\_{fast}}{τ\_{n\_{fast}}}$$

$$\frac{d\overline{n}\_{slow}}{dt}= \frac{\overline{n}\_{slow}-n\_{slow}}{τ\_{n\_{slow}}}$$

*IKs* current amplitude is given by:

$$I\_{Ks}=P\_{Ks}⋅(0.67⋅n\_{fast}^{2}+0.33⋅n\_{slow}^{2})⋅(K\_{i}⋅e^{δ⋅\frac{FV}{RT}}-K\_{i}⋅e^{-\left(1-δ\right)⋅⋅\frac{FV}{RT}})$$

Where $\overline{n}\_{fast}$ and $\overline{n}\_{slow} $are the steady state for the fast and slow component of *IKs*, respectively, *V* is the membrane voltage, and $τ\_{n\_{fast}}$ and $τ\_{n\_{slow}}$ are the activation time constant for the fast and slow component of *IKs*, respectively. *PKs* is a conversion factor (picoampere/millimolar), and $n\_{fast}$ and $n\_{slow}$ are the activation gating variable for a fast and slow component, respectively.

Table 1. Parameters used to simulate the 3D electrophysiological activation of WT, intermediate V241F, and pure V241F mutation conditions.

|  |  |  |
| --- | --- | --- |
| Variable  | description | Values and units |
| *Cm* | Cell capacitance per unit surface area | 2 µF/cm2 |
| *ρx, ρy, and ρz*  | cellular resistivity in *x*, *y*, and *z* | 162 Ω·cm |
| S | Surface-to-volume ratio | 0.2 µm-1 |
| R | Gas constant | 8.3143 J·K-1·mol-1 |
| T | Temperature | 310 K |
| F | Faraday constant | 96.4867 C/mmol |
| dtw | Time step of the simulation | 10 ms |
| *GNa* | Maximal *INa* conductance | 14.838 nS/pF |
| *GK1* | Maximal *IK1* conductance | 5.405 nS/pF |
| *Gto epi, M* | Maximal epi and M *Ito* conductance | 0.294 nS/pF |
| *Gto endo* | Maximal *Ito* conductance | 0.073 nS/pF |
| *GKr* | Maximal *IKr* conductance | 0.153 nS/pF |
| *GKs, epi, endo* | Maximal epi and endocardial *IKs* conductance | 0.392 nS/pF |
| *GKs, M* | Maximal M cell *IKs* conductance | 0.098 nS/pF |
| *GCaL* | Maximal *ICaL* conductance | 3.980-5 cm·mc-1·µF-1 |
| *GpK* | Maximal *IpK* conductance | 0.0146 nS/pF |
| *GpCa* | Maximal *IpCa* conductance | 0.1238 nS/pF |
| *GbNa* | Maximal *IbNa* conductance | 0.000290 nS/pF |
| *GbCa* | Maximal *IbCa* conductance | 0.000592 nS/pF |

# Key equation to couple the electrical simulation with the mechanical simulation

After we run the electrical simulation for WT, intermediate, and V241F pure mutation, we extract the calcium concentration from the electrical simulation results. The calcium information can be obtained from the equation (39) of the ten Tusscher et al. [22]. The calcium dynamic is then used as input to the mechanical compartment. We used Gaussian points to interpolate the scalar from the electrical simulation result to the mechanical finite element mesh. The calcium concentration was inputted to the myofilament dynamic model of Rice et al. [24] in the eq. (1) and eq. (2) which represented the regulatory calcium-binding to troponin of high or low strongly-bound crossbridges.

# Key equation to couple the electrical simulation with the mechanical simulation

To couple the circulatory model with the finite element (FE) model, we followed the method of Kerckhoffs *et al*. [26] in which synchronizing the LV and RV pressures in the FE and circulatory model. The pressures served as the boundary condition in both FE and circulatory model. When the cavity volume of FE and circulatory model has small differences, then the time was increased (Kerckhoffs et al. in eq. B16 and B26). We implemented the pressure updating algorithm that they provided in order to ensure the continuity flow between the two models.