Modelovanie elektrickej aktivity srdca v prostredí COMSOL Multiphysics

(Modeling of the electrical activity of the heart in COMSOL Multiphysics environment)

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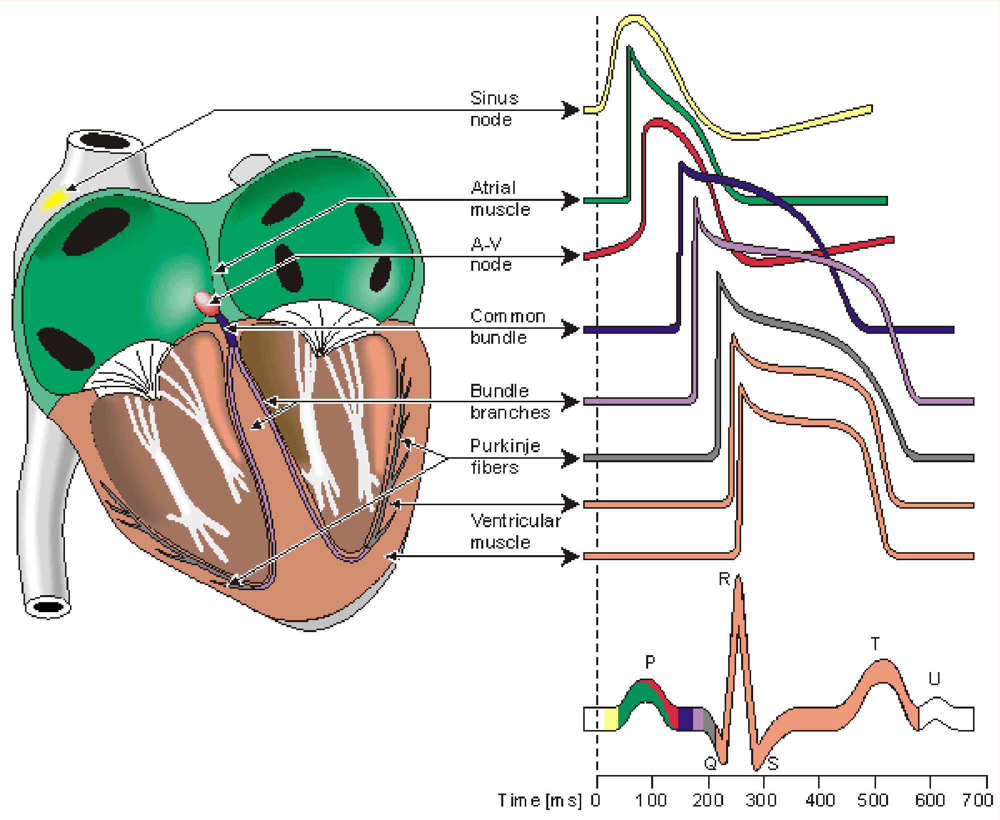
PRESENTATION OUTLINE

- **Electrical excitation - action potential (AP) in the heart**
- **Models of AP of atrial and ventricular heart cells**
- **Simplified model of heart cells (modified FitzHugh-Nagumo model) – in Matlab**
- **Modeling of AP propagation – monodomain model**
- **Modeling of AP propagation - in COMSOL Multiphysics**

Electrical excitation of the heart

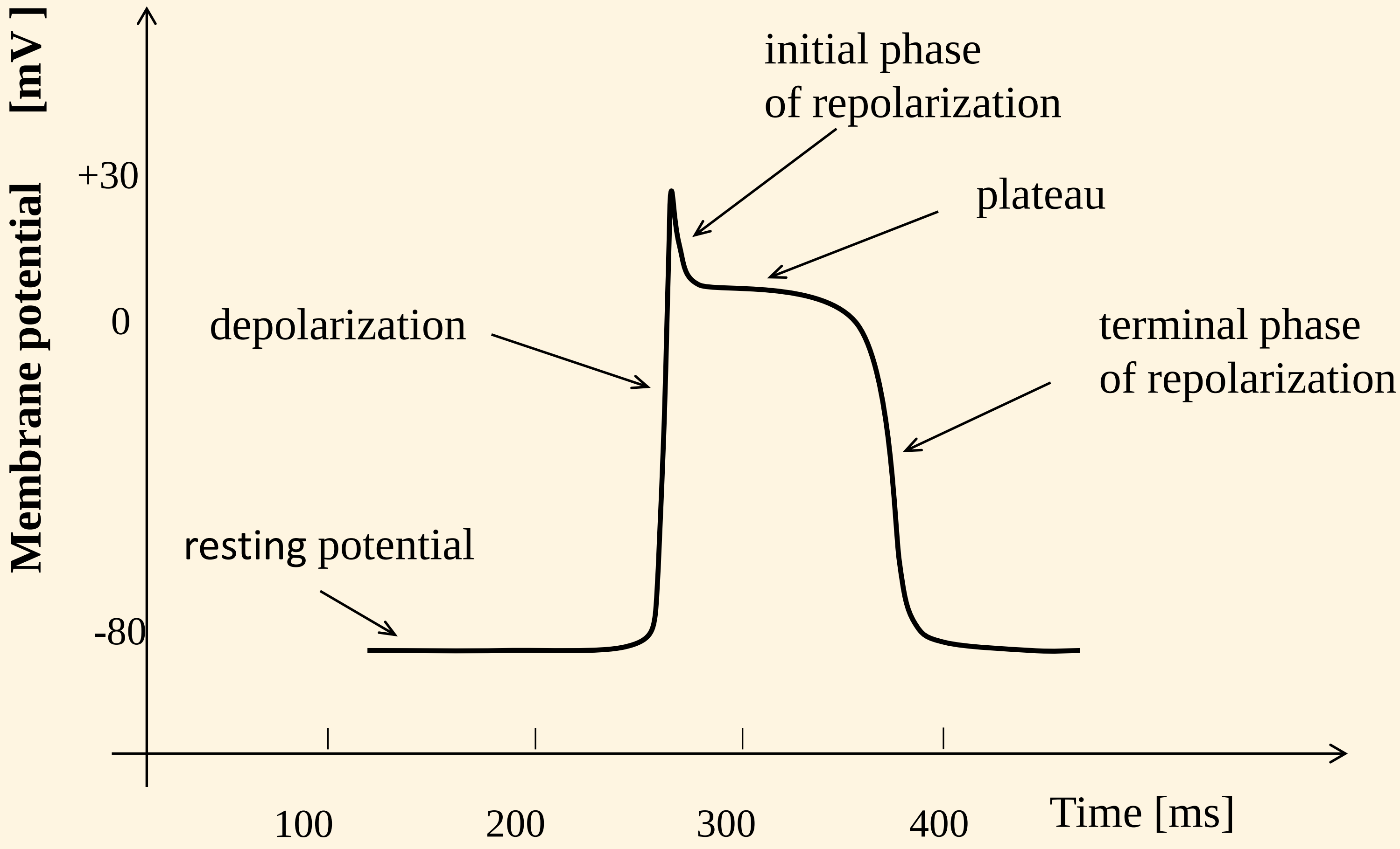
Electrical excitation (in form of action potential) is spreading in the heart through various types of heart cells [1] – [3]:

- **SA nodal** – origin of excitation
- **Atrial**
- **AV nodal**
- **Bundle of His**
- **Bundle branches**
- **Purkinje fibers**
- **Endocardial**
- **Mid-myocardial**
- **Epicardial**



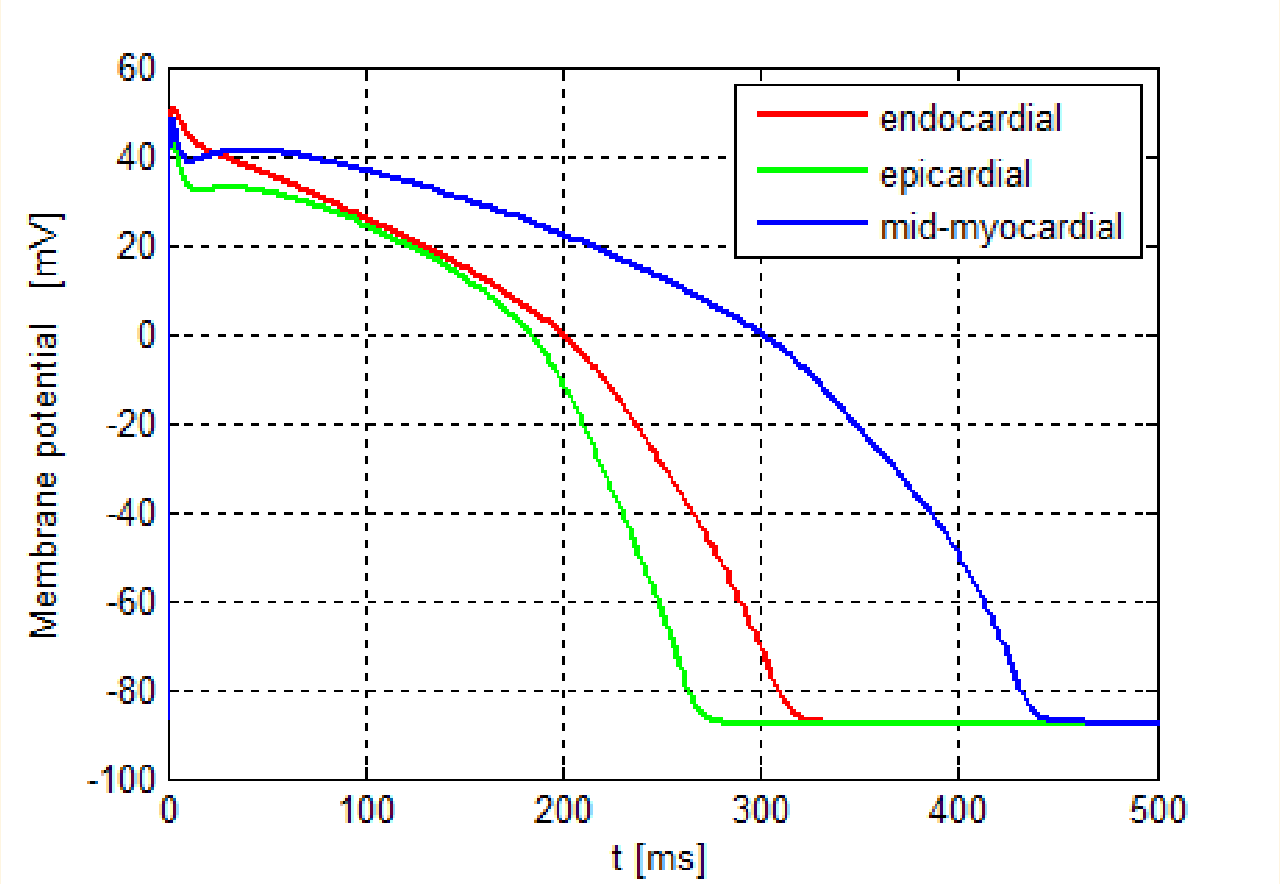
Action potential shape [2] is different for different types of heart cells

Action potential



Action potential phases in typical cardiomyocyte (cardiac muscle cell)

Various types of cardiomyocyte action potential shapes



Various types of action potential shapes in ventricular cardiomyocyte [4], [5]

Models of heart ventricular cells [4] – [11]

Luo – Rudy I model (1991) [6]

Luo – Rudy II model (1994) [7]

Winslow model (1999) [8]

Shannon-Bers model (2004) [9]

Hund-Rudy dynamic model (2004) [130]

O'Hara-Rudy model (2011) - enables to model [4], [5]:

- epicardial
- endocardial
- mid-myocardial cells

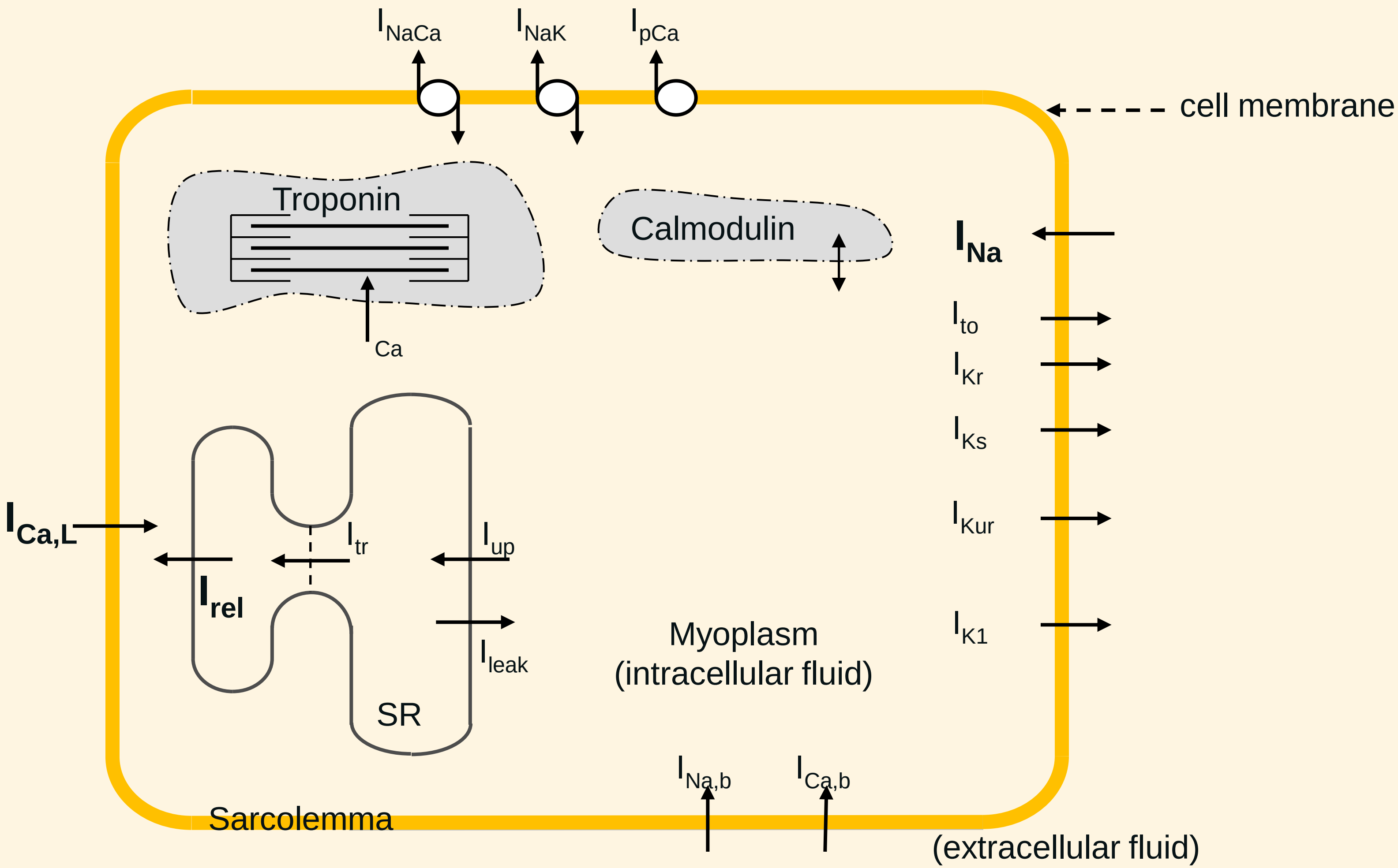
Model of heart atrial cells [12] - [15]

Courtemanche-Ramirez-Nattel model (1998) [12], [13]
enables to control AP morphology (three main morphological types)
- 21 ordinary differential equations (ODE)

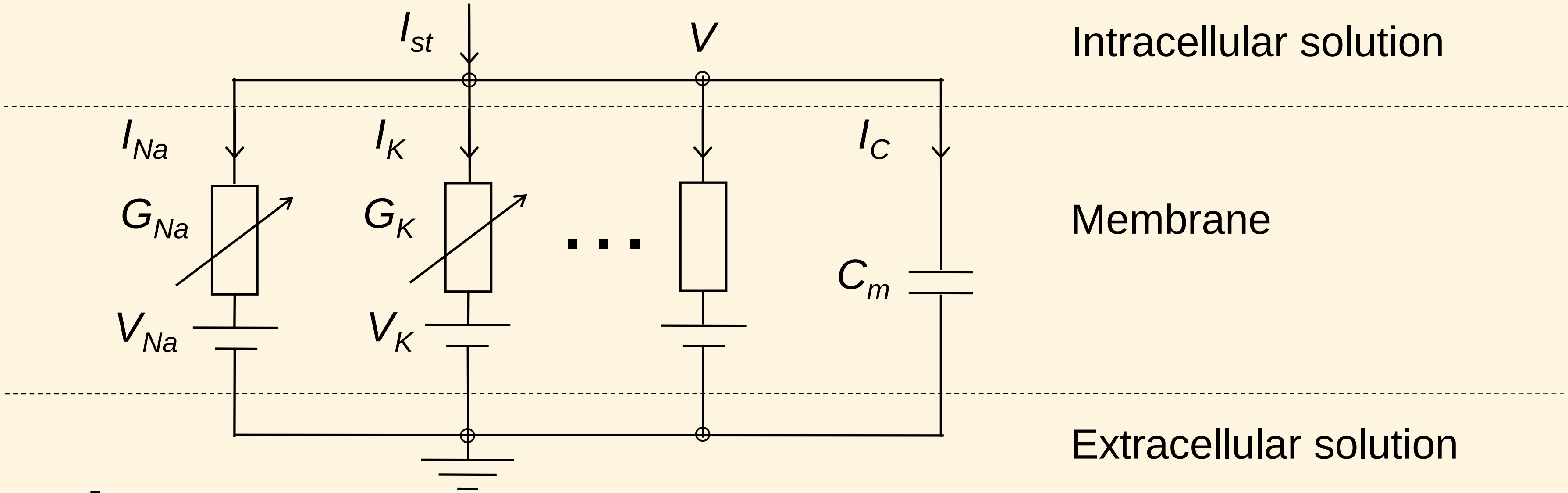
Simplified model of heart cells

modified FitzHugh-Nagumo model [16] – [20]
enables to control AP shape
- 2 ordinary differential equations

Courtemanche-Ramirez-Nattel model of human atrial cell [12]



Courtemanche-Ramirez-Nattel membrane model of the human atrial cell



$$\frac{dV}{dt} \cdot C_m + I_{ion} = I_{st} \quad \Rightarrow \quad dV/dt = \left(-I_{ion} + I_{st}\right)/C_m$$

$$I_{ion} = I_{Na} + I_{Ca,L} + I_{to} + I_{Kr} + I_{Ks} + I_{K1} + I_{Kur} + I_{NaK} + I_{NaCa} + I_{Ca,p} + I_{Ca,b} + I_{Na,b}$$

where e. g.:

$$I_{Na} = G_{Na}\ m^3\ h\ \left(V - V_{Na}\right)$$

21 ordinary differential equations (ODE)
75 algebraic equations

Modified FitzHugh-Nagumo model of the cardiac cell

- using **modified FitzHugh-Nagumo** equations [16] – [20]

$$\frac{dV}{dt} = -k\,c_1 (V_m - B)\left(-\frac{(V_m - B)}{A} + a\right)\left(-\frac{(V_m - B)}{A} + 1\right) - k\,c_2 R (V_m - B)$$

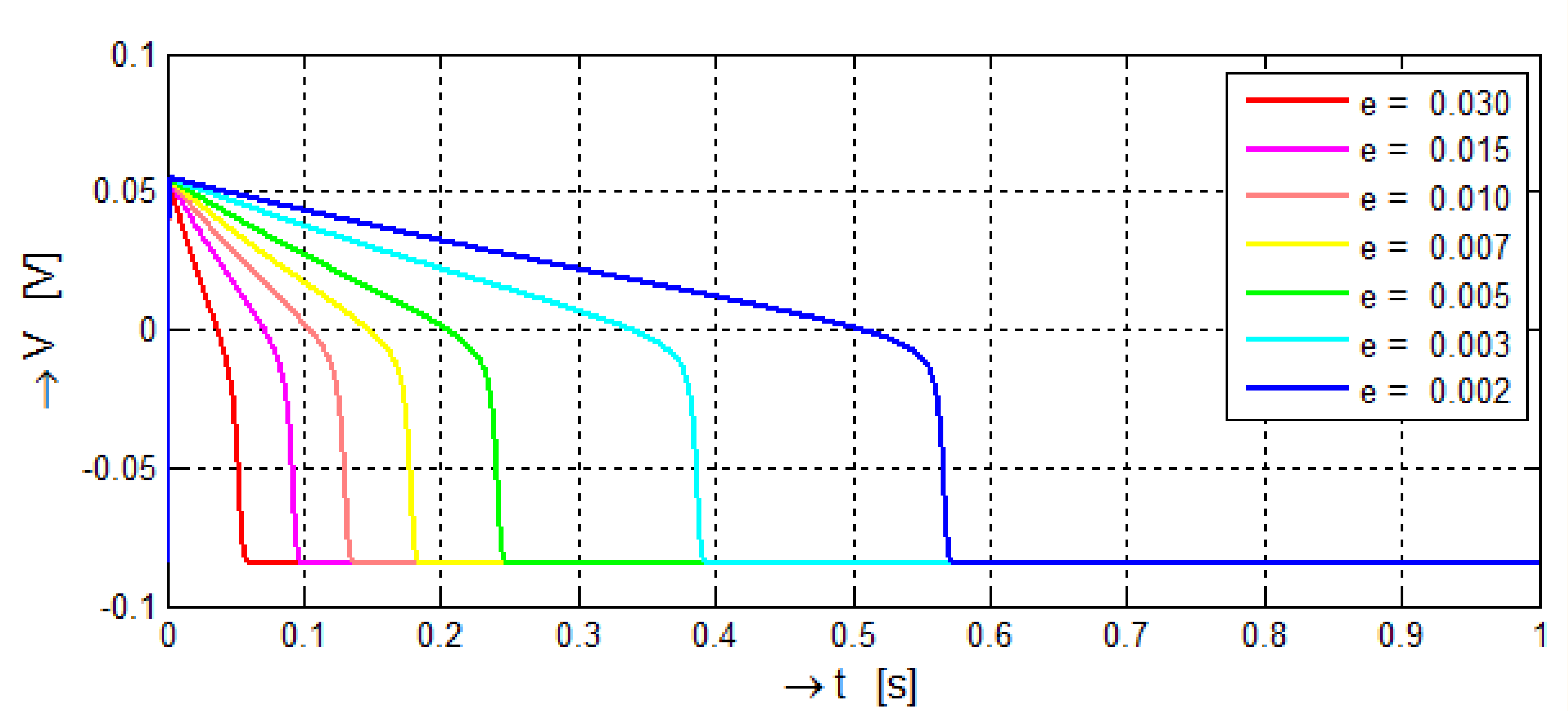
$$\frac{d\,R}{d\,t} = k\,e\left(\frac{(V_m - B)}{A} - R\right)$$

where V_{m} is the membrane potential,
R is the recovery variable
a is relating to the excitation threshold
e is relating to the excitability
A is the action potential amplitude
B is the resting membrane potential and
c_1, c_2, and k are membrane-specific parameters.

FitzHugh-Nagumo model – simulation in Matlab

Influence of membrane parameters on :

- action potential duration (APD)

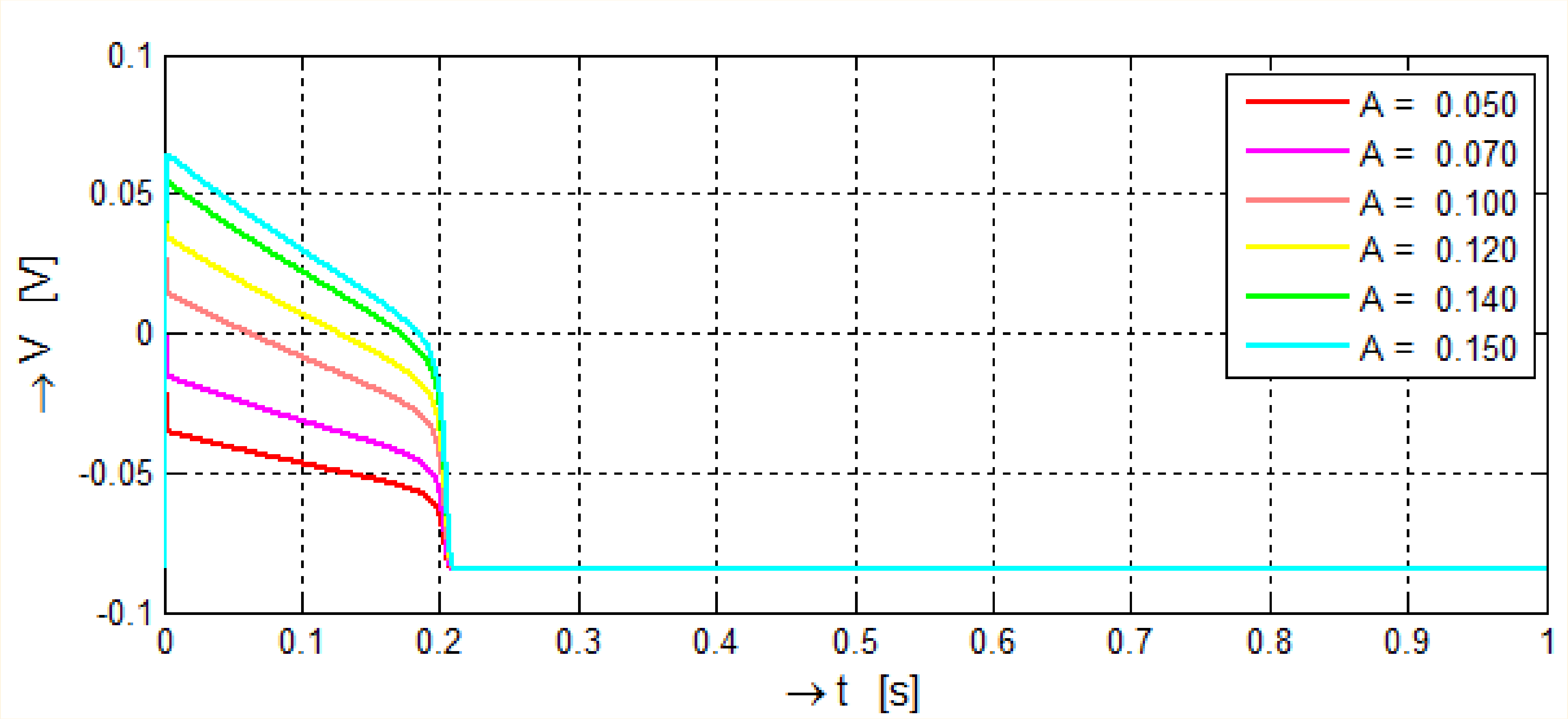


Influence of membrane parameter "e" on APD [20].

FitzHugh-Nagumo model – simulation in Matlab

Iinfluence of membrane parameters on :

- action potential amplitude (APA)



Influence of membrane parameter “A” on AP amplitude [20].

Modeling of **propagation** of electrical activation using monodomain model

- monodomain model [21], [22] with incorporated modified FitzHugh-Nagumo equations [18] – [20], [23]

$$\frac{\partial V_m}{\partial t} = \frac{1}{\beta C_m}\left\{\nabla \cdot \left(\sigma \nabla V_m\right) - \beta\left(I_{ion} - I_s\right)\right\}$$

$$D = \frac{\sigma}{\beta C_m}$$

where

V_m	is the membrane potential,
β	is the membrane surface-to-volume ratio,
C_m	is the membrane capacitance per unit area,
σ	is the tissue conductivity,
I_ion	is the ionic transmembrane current density per unit area and
I_s	is the stimulation current density per unit area.

Simulation parameters

- of monodomain model with modified FitzHugh-Nagumo equations:

$a = 0.13$ - relating to the excitation threshold
$e = 0.0132$ - relating to the excitability
$A = 0.120$ V - the action potential amplitude
$B = -0.085$ V - the resting membrane potential
$c_1 = 2.6$ - membrane-specific parameter
$c_2 = 1$ - membrane-specific parameter
$k = 1000\ s^{-1}$ - membrane-specific parameter
$D = 0.0005\ m^2/s$ - diffusivity

.

Modeling of **propagation** of electrical activation in COMSOL Multiphysics

- monodomain model for AP propagation in the heart is:

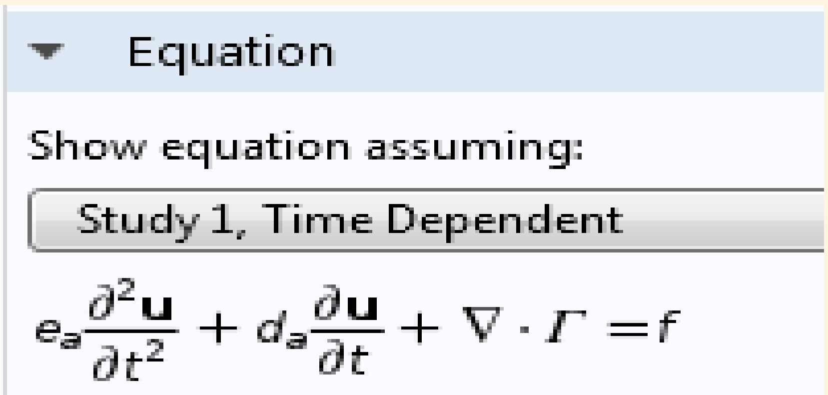
$$\frac{\partial V_m}{\partial t} = \frac{1}{\beta C_m}\left\{\nabla\cdot\left(\sigma\nabla V_m\right) - \beta\left(I_{ion} - I_s\right)\right\}$$

- this PDE (partial differential equation) is numerically solved in COMSOL Multiphysics
- detailed description how realize similar example for heart of ellipsoidal shape in COMSOL Multiphysics is in [23]:

Select Physics:
→ Δu Mathematics
→ Δu PDE Interfaces
→ Δu General Form PDE (g)

Modeling in COMSOL Multiphysics

General Form PDE (g)
in COMSOL Multiphysics:



where: $u \rightarrow V_\mathrm{m}$

$e_\mathrm{a} = 0$

$d_\mathrm{a} = 1$

Mathematical description of monodomain model:

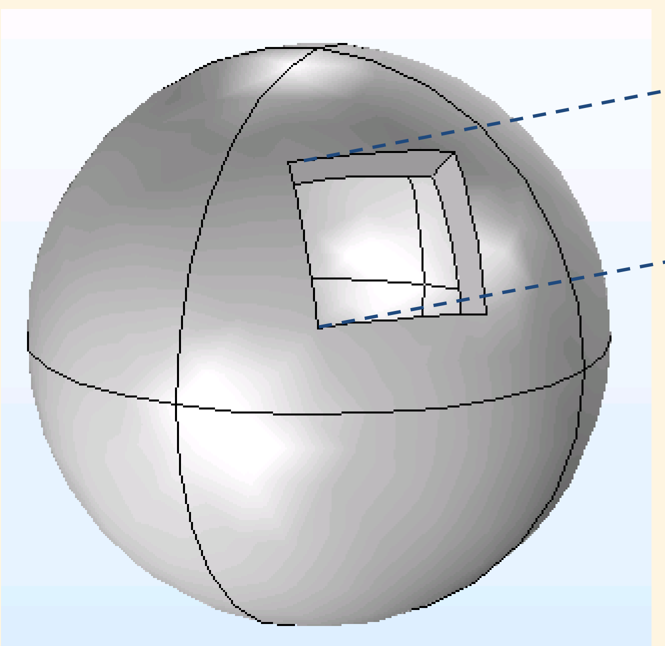
$$\frac{\partial V_m}{\partial t} = \nabla \cdot \left(\frac{1}{\beta C_m} \sigma \nabla V_m \right) - \frac{1}{C_m} \left(I_{ion} - I_s \right)$$

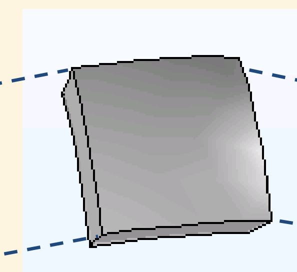
$-\Gamma$ $\qquad$ f

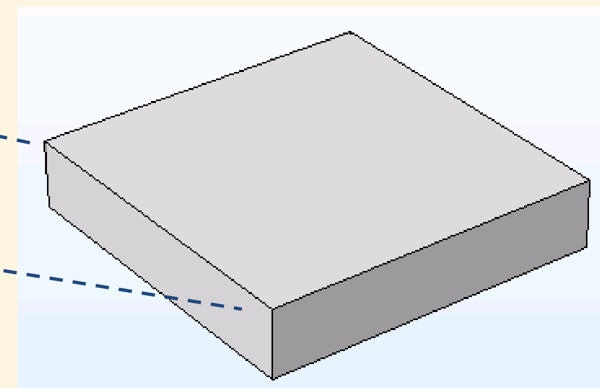
$$i_{ion} = \frac{I_{ion}}{C_m}$$

Modeling geometry of heart wall

whole heart as a hollow sphere: → part of heart wall: → approximate part of heart wall of box (“SLAB”) shape:

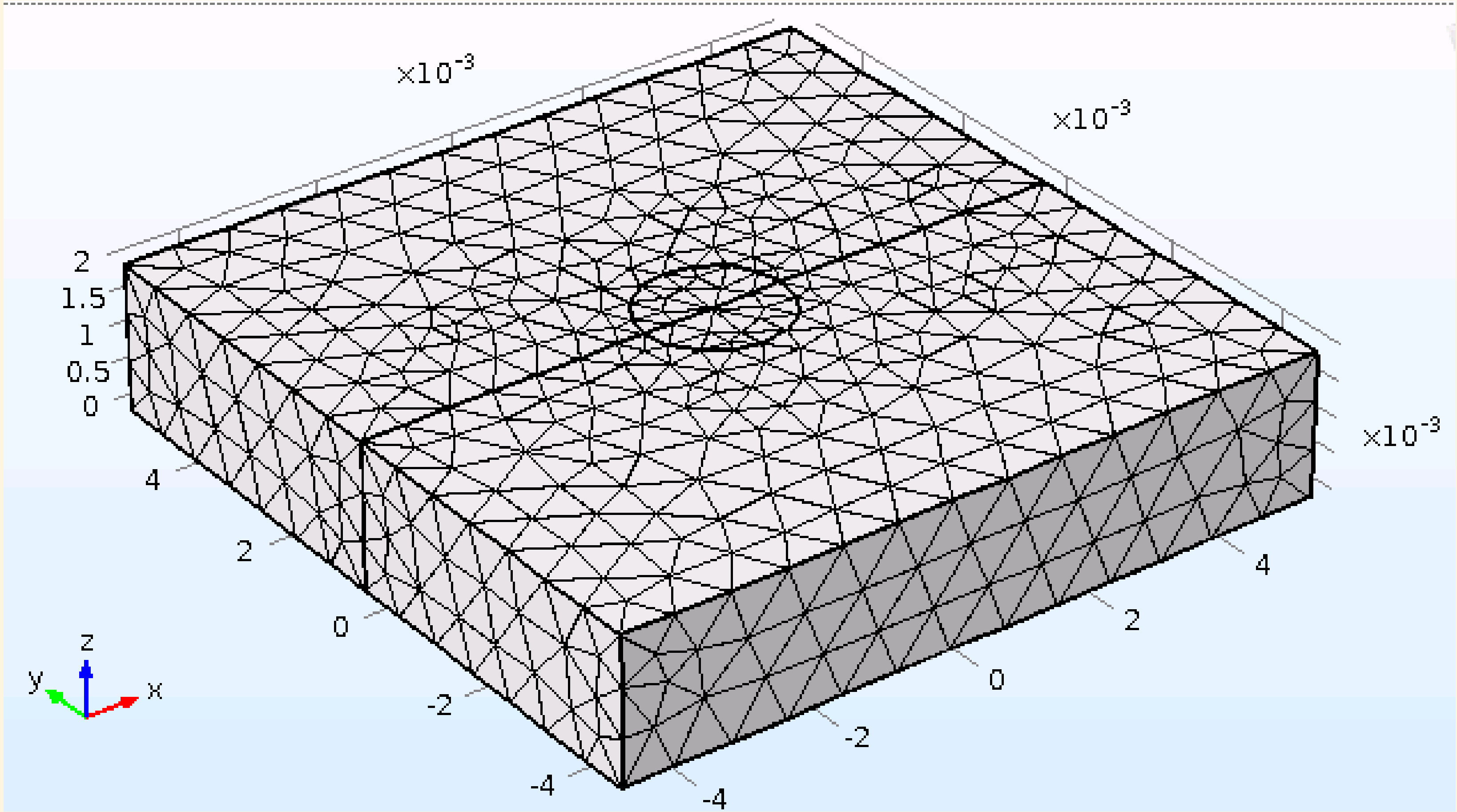






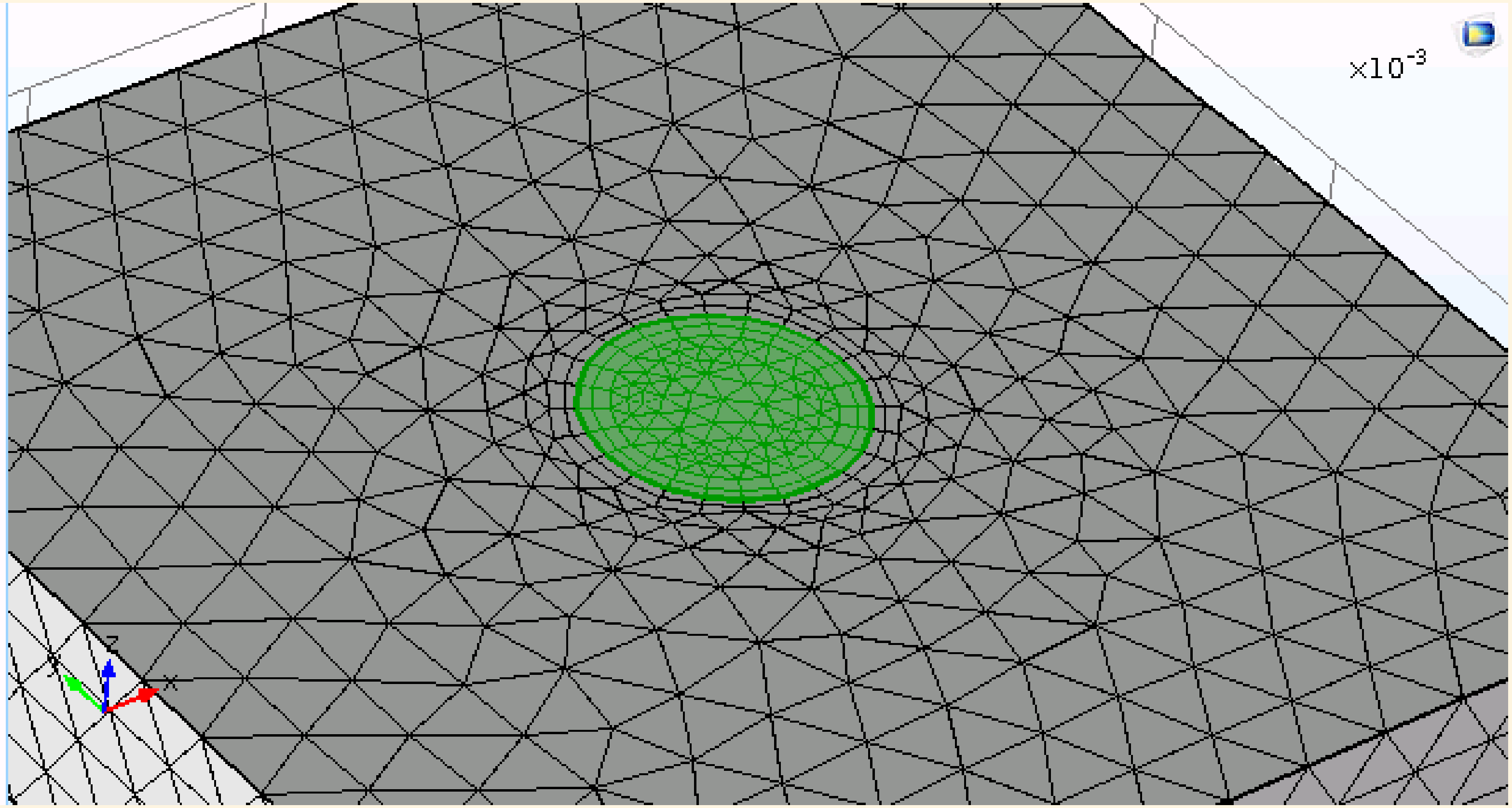
the SLAB model of wall that is used for the following simulation

Meshing of the model



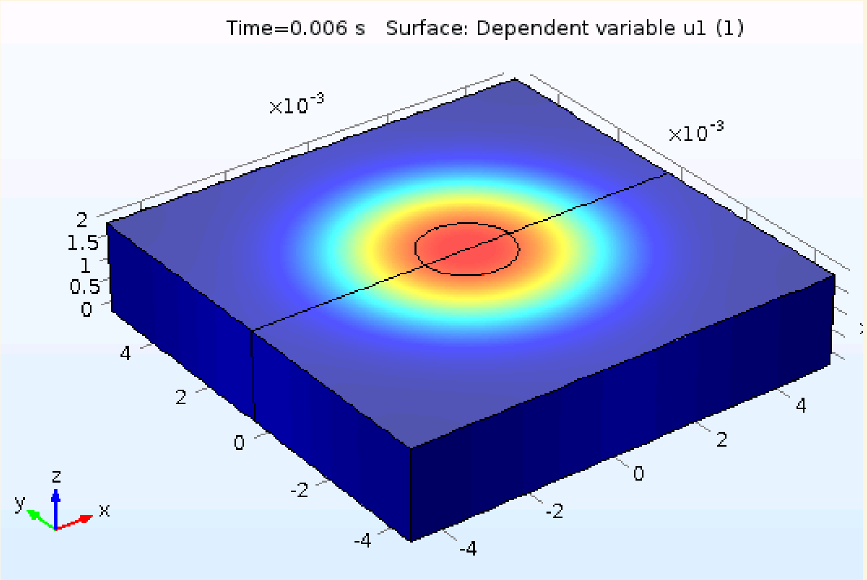
The SLAB model of the heart wall covered with mesh (predefined „Fine“ mesh). The stimulated area is a cylinder with r = 1 mm radius situated in the middle of the slab model.

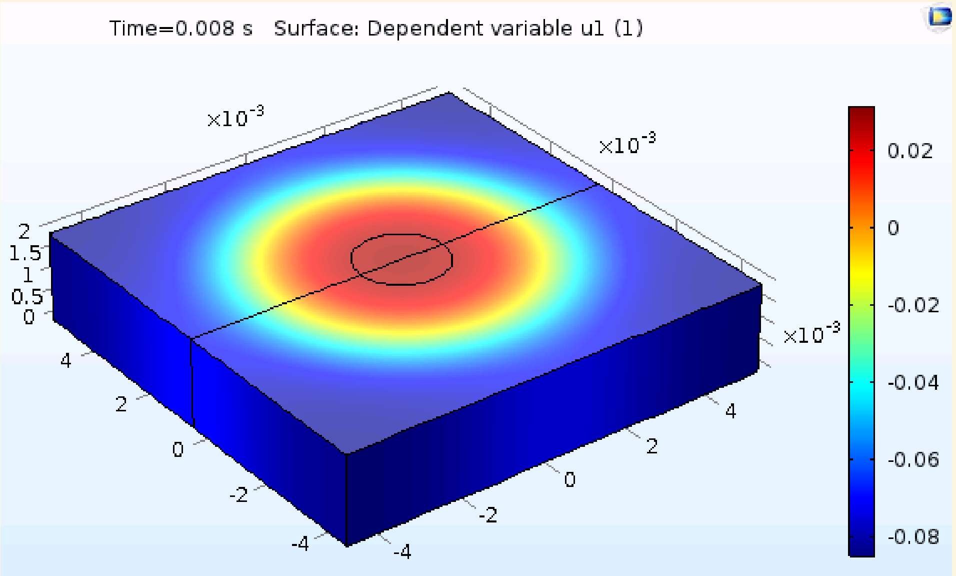
Meshing of the model



More dense meshing of the SLAB near the boundary of stimulated area of *r* = 1 mm radius (green) is performed with two manually added boundary mesh layers from both sides.

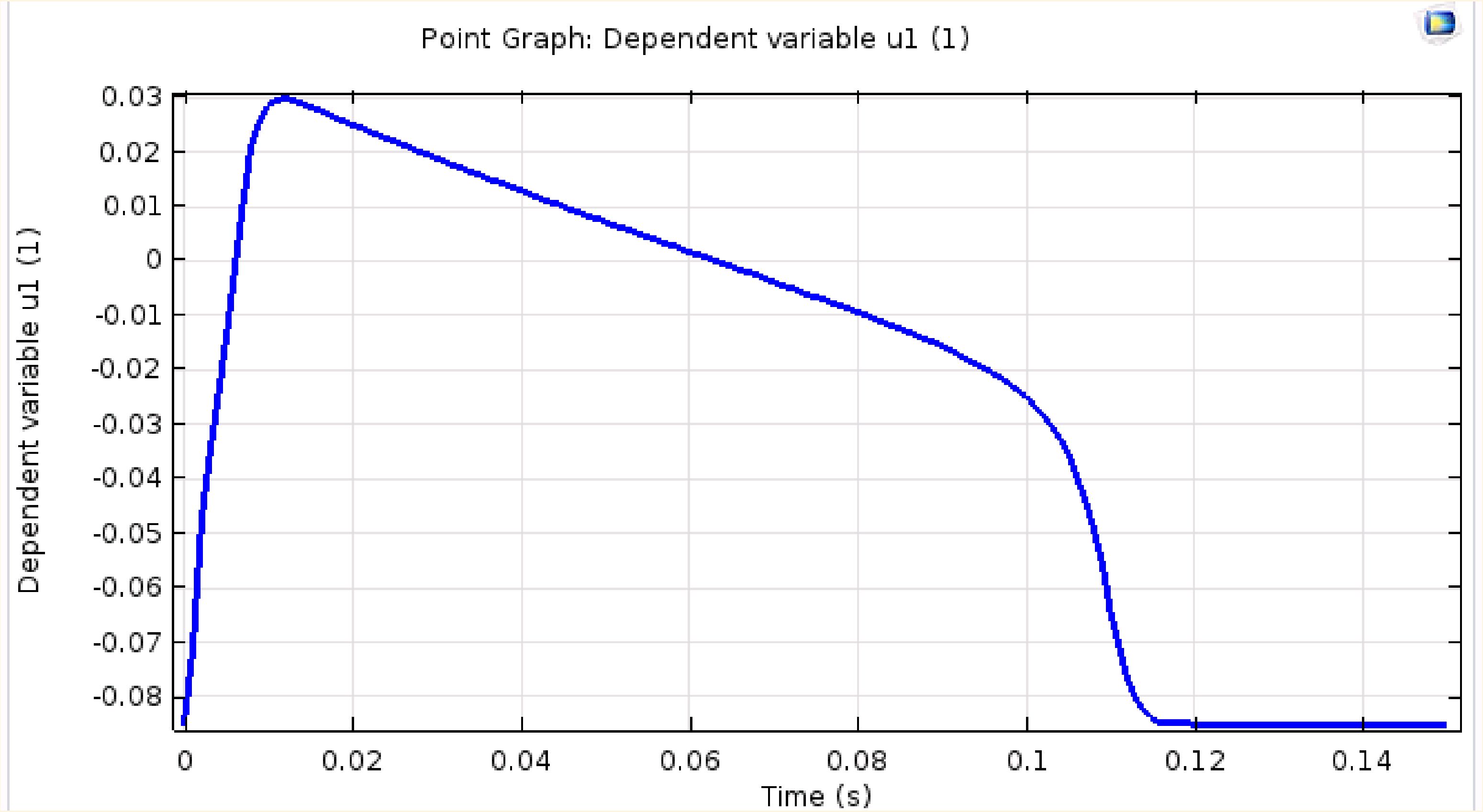
Propagation of AP – simulation results





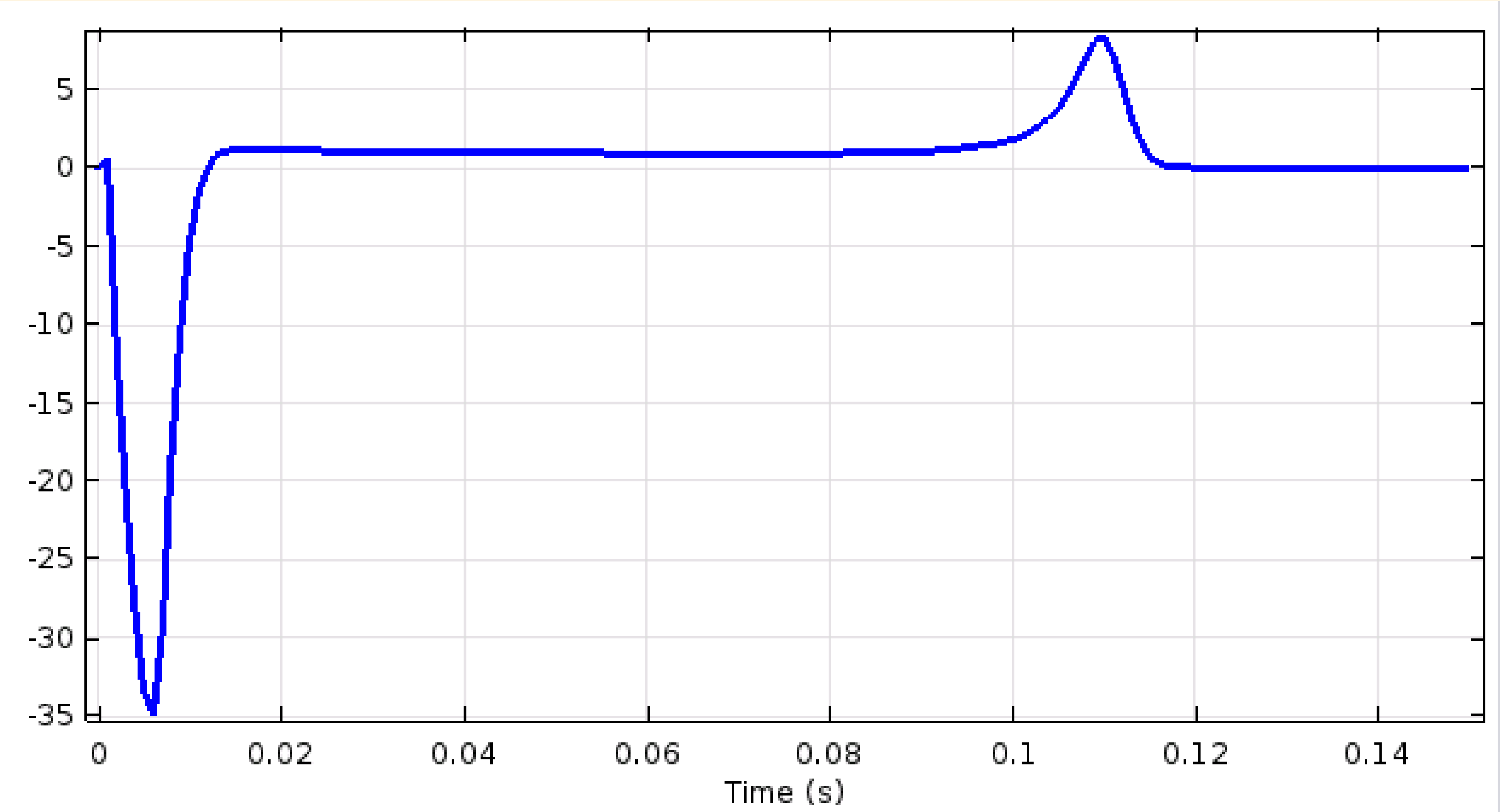
Distribution of membrane potential [V] in the SLAB model at 0.006 s and 0.008 s after stimulation onset (r = 1 mm, stimulation duration T_s = 0.002 s, amplitude of stimulation current i_s = 100 A/F). Activated area is shown in red, resting area in blue.

Action potential in Point Probe



Distribution of membrane potential [V] (action potential) in the slab model in point x = 1.5 mm, y = 0 mm, z = 2 mm (T_s = 0.002 s, i_s = 100 A/F).

Ion current in Point Probe



Distribution of I_{ion} normalized current [A/F] in the slab model in point x = 1.5 mm, y = 0 mm, z = 2 mm (T_s = 0.002 s, i_s = 100 A/F). First negative current causes depolarization of membrane (AP onset), positive peak of current causes membrane repolarization (terminal phase of repolarization).

Conclusion

Simulation of electrical activity (AP) of heart cell using FitzHugh-Nagumo equations

- ordinary differential equations (ODE)
  - in Matlab.

Simulation of **AP propagation** in heart tissue using monodomain model with FitzHugh-Nagumo equations

- partial differential equations (PDE)
  - in **Comsol Multiphysics**.

THANK YOU FOR YOUR ATTENTION!

References

[1] MACFARLANE, P. W. - OOSTEROM, A. - PAHLM, O. - KLIGFIELD, P. - JANSE, M. - CAMM, J.: Comprehensive Electrocardiology. 2nd ed. London: Springer-Verlag, 2011.

[2] MALMIVUO, J. - PLONSEY, R.: Bioelectromagnetism. Principles and Applications of Bioelectric and Biomagnetic Fields. Oxford University Press, Oxford, 1995, ISBN 0-19-505823-2, < http://www.bem.fi/book/> .

[3] PULLAN, A.J. - CHENG, L.K. - BUIST, L.: Mathematically Modelling the Electrical Activity of the Heart: From Cell to Body Surface and Back Again. Singapore : World Scientific, 2005. ISBN 981-256-373-3.

[4] O'HARA, T. - VIRÁG, L. - VARRÓ, A. - RUDY, Y.: Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. PLoS Computational Biology, 2011, Vol.7, N. 5.

[5] RUDY, Y.: List of Models for Ion Channels, Myocytes and Regulatory Pathways: ORd orginal human ventricular model, 2011. Matlab code, Rudy Laboratory, < http://rudylab.wustl.edu/research/cell/code/AllCodes.html >.

[6] LUO, CH. - RUDY, Y.: A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction, Circulation Research, 1991, Vol. 68, pp.1501-1526.

[7] LUO, CH. - RUDY, Y.: A dynamic model of the cardiac entricular action potential: I. Simulations of ionic currents and concentration changes, Circulation Research, 1994, Vol. 74, pp.1071-1096.

[8] WINSLOW, R. L. – RICE, J. – JAFRI, S.- MARBAN, E.- O'ROURKE, B.: Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, II: model studies. Circ. Res., 1999, Vol. 84, pp. 571-586.

[9] SHANNON, T. R. - WANG, F. - PUGLISI, J. - WEBER, C. - BERS. D. M.: A mathematical treatment of integrated Ca dynamics within the ventricular myocyte. Biophys.J. , 2004, Vol. 87, pp.3351-3371.

[10] HUND, T. J. - RUDY, Y.: Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. *Circulation, vol. 110, no. 20, pp. 3168-3174, Nov, 2004.*

[11] TEN TUSSCHER, K. H. - BERNUS, O. - HREN, R. - PANFILOV, A. V.: Comparison of electrophysiological models for human ventricular cells and tissues. *Prog Biophys Mol Biol, vol. 90, no. 1-3, pp. 326-45, Jan-Apr, 2006.*

[12] COURTEMANCHE, M. - RAMIREZ, R. J. - NATTEL, S.: Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. American Journal of Physiology-Heart and Circulatory Physiology, 1998, vol. 275, no. 1, p. 301 - 321.

[13] FENG, J.- YUE, L. - WANG, Z. - NATTEL, S.: Ionic mechanisms of regional action potential heterogeneity in the canine right atrium. Circulation Research, 1998, vol. 83, no. 5, p. 541-551.

[14] NATTEL, S. - MAGUY, A. - LE BOUTER, S. - YEH, Y.-H.: Arrhythmogenic ion-channel remodeling in the heart: Heart failure, myocardial infarction, and atrial fibrillation. Physiological Reviews, 2007, vol. 87, no. 2, p. 425 - 456.

[15] WILHELMS, M. - HETTMANN, H. - MALECKAR, M. M. - KOIVUMAKI, J. T. - DOSSEL, O. - SEEMANN, G.: Benchmarking electrophysiological models of human atrial myocytes. *Front Physiol, vol. 3, pp. 487, 2012.*

[16] FITZHUGH, R.: Impulses and physiological states in theoretical models of nerve membrane. Biophysical J., 1: 445-466, 1961.

[17] NAGUMO, J. – ARIMOTO, S. – YOSHIZAWA, S.: An active pulse transmission line simulating nerve axon. Proc. IRE., 50: 2061-2070, 1962.

[18] SOVILJ, S. – MAGJAREVIĆ. R. – LOVELL, N. H. – DOKOS, S.: A simplified 3D model of whole heart electrical activity and 12-lead ECG generation. *Computational and Mathematical Methods in Medicine*, 2013, doi:10.1155/2013/134208.

[19] SOVILJ, S. - MAGJAREVIC, R. - LOVELL, N. - DOKOS, S.: Realistic 3D Bidomain Model of Whole Heart Electrical Activity and ECG Generation. *2013 Computing in Cardiology Conference, Computing in Cardiology Conference, pp. 377-380, New York: IEEE, 2013.*

[20] COCHEROVÁ, E.: Modeling of electrophysiological properties of heart cells. In Technical Computing Bratislava 2014, 22nd Annual Conference Proceedings. Bratislava, SR, 4. 11. 2014. Prague : Institute of Chemical Technology, 2014,

< http://www2.humusoft.cz/www/papers/tcb2014/014_cocherova.pdf >.

[21] POTSE, M. – DUBÉ, B. – RICHER, J. – VINET, A. – GULRAJANI, R.M.A.: Comparison of Monodomain and Bidomain Reaction-Diffusion Models for Action Potential Propagation in the Human Heart. IEEE Transactions on Biomedical Engineering, 53 (12): 2425-2435, 2006.

[22] CLAYTON, R. H. - BERNUS, O. - CHERRY, E. M. - DIERCKX, H. - FENTON, F. H. - MIRABELLA, L. - PANFILOV, A. V. - SACHSE, F. B. - SEEMANN, G. - ZHANG, H.: Models of cardiac tissue electrophysiology: Progress, challenges and open questions. *Progress in Biophysics & Molecular Biology, vol. 104, no. 1-3, pp. 22-48, Jan, 2011*

[23] FILIPPI , S. – CHERUBINI, C.: Electrical Signals in a Heart. Application ID: 981, University Campus Biomedico di Roma, Italy. < https://www.comsol.com/model/electrical-signals-in-a-heart-981 >