# Concluding Remarks

This book has treated the fundamental problems of mathematical modeling of electrophysiological processes responsible for generation of AP in cardiomyocytes and their propagation through myocardium. These processes, together with cells' ability to contract, are responsible for providing the primary heart function of pumping blood through whole organism.

From a structural point of view, the myocardium represents a system of discrete excitable and contractile elements, myocytes. Gap junctions provide one of the key interconnects between these elements. The size of a myocyte is on the order 10 nanometers while the scale of cardiac tissue is incomparably bigger. Thus the average cell properties of AP generation, concentrated at each point of the myocardium and connected through intra- and extra-cellular liquid resistance are usually assumed for investigation the wave processes in myocardium. The spatially distributed intra-cellular properties are typically neglected. Under normal conditions, the resistance of a gap junction is much smaller than the resistance of intra- cellular liquid and it is possible to consider all cardiac tissue as syncytium, a continuous system, where AP propagates according to diffusion properties.

Mathematical modeling of these systems is reduced to the solution of a special type of nonlinear reaction-diffusion equations. Obtaining these solutions in analytical form is very difficult, even for simplified cases, and is impossible for more realistic cases. Moreover, some relationships are not known and are introduced into models as analytical expressions obtained by fitting to results of particular physiological experiments (semi-phenomenological models).

Therefore computer simulations are required to obtain qualitative and quantitative results. Due to the enormous computational complexity, massively parallel supercomputers are needed, even today, for most 2D and all 3D problems. Special numerical algorithms, which include the application of adaptive time and space steps for a given grid representation of tissue, are required to obtain computationally tractable results.

When stimulus is applied to the extracellular domain of tissue (e.g. in a case of defibrillation), it is necessary to introduce the bi-domain tissue representation. Except for the case of fully uniform tissue, this representation requires an additional, simultaneously, solution of an elliptic PDE for the same tissue grid. Experience shows that an advanced multigrid sequential algorithm approximately doubles computation time (R. Samade personal communication). Thus development of an efficient version of the multigrid algorithm suitable for parallel execution remains an outstanding problem.

Mathematical modeling and computer simulation of complex problems are a powerful method for scientific investigation not only in physics, engineering, but in biology and medicine as well. In order to obtain successful results the subject and major goals of investigation must be precisely formulated. At the same time all assumptions and restrictions must be mentioned, including the conditions under which the experimental data used for the simulation were obtained. A good mathematical model can predict new phenomena but this does not mean that the results of simulation can be extrapolated to the cases not covered by the used model.

For example, it is impossible to judge about results of Ca dynamics using models where it is not represented or is represented in rudimentary form.

Validation of the modeling results is one of the important subjects. Even today, direct comparison with physiological experiments is difficult if not impossible for some cases because the shape and heterogeneity of a real heart are very different from that using in simulation. For example, small blood vessels anchor the spiral waves; cells change their directions and so on. Physiological experiments, especially with a tissue, cannot measure the all internal variables of a mathematical model and accuracy of measured values is not high enough. It is worthwhile to remember that almost all mathematical models were developed to reproduce the heart functions under normal conditions when all the processes are close to stationary or quasi-stationary. These relate to obtaining the gated channel currents using constant clamp voltages and use of stationary expression for $C_aIC_aR$ processes from JSR (LRd and Chudin models). New phenomena appeared during tachycardia and fibrillation connected with Ca accumulation in SR and sarcoplasma, which lead to appearance of EADs and DADs clusters on the pattern of cells, occurring under high pacing rate. The latter also lead to changing the character of $C_aIC_aR$ process in SR from static to dynamic and under some conditions may cause Ca and AP alternance (see [22] in chapter 4). Thus many questions are left unanswered about the correctness of applying an AP model developed for normal conditions to pathological cases. Here appropriately to compare at least the results obtain for membrane channel gates controlled by AP under different pacing rates. Very little information is available about mechanisms of Ca release from SR, especially, about spontaneous release caused by overloading of SR and intracellular domain with Ca.

Results from physiological experiments for AP and wave propagation under normal conditions were used to validate the mathematical model. Instead of discarding and disregarding new phenomena observed using the model under abnormal conditions (see chapter 4 and [28] where spontaneous release is not presented) it is worthwhile to create a plausible hypothesis about the unknown mechanism and continue the investigation further. As new experimental data becomes available, the hypothesis may have to be reconsidered. It may be recognized to be incorrect or to have restricted application. This approach is widely used in physics and other branches of sciences connected with real world.

Application of mathematical models and computer simulations produced many fruitful predictions. Spiral waves, discovered in the author's lab (see [3] in chapter 8), in 2D cardiac tissue, were later observed in real tissue. Simulations results found and explained the appearance of EAD and DAD clusters in 2D tissue during spiral wave propagation, proved that EAD and DAD can appear in single cell not only in case of long but also under short period of stimulation.

I hope that publication of this book will attract new researchers to the application of mathematical modeling and computer simulation of biological system and, in particular, generate more attention to cardiology problems.

# Exercises

1. Prove that linear second order oscillator
   $$\frac{d^2u}{dt^2} + 2\alpha\frac{du}{dt} + \omega_0^2 u = 0$$
   with initial conditions: $u(0) = 7$, $\dot{u}(0) = 0$ and parameters $\alpha = -1$, $\omega = 10$ produces oscillations with amplitude increasing over time. Explain why the amplitude of oscillations will be finite in real systems.

2. Ionic currents through a membrane can be expressed using two formulations:
   a. the Hodgkin-Huxley (HH) formulation
   b. and the Goldman-Hodgkin-Katz (GHK) formulation.

   What formulation would you choose if the extracellular and intracellular concentration of the considered ions are variable?
   Show that both current formulations give the same results when $V_m = V_{m,S}$.

3. Calculate the rest potential using the GHK equations if $Na^+$, $K^+$, and $Cl^-$ ions participate in the ionic currents. Use the data about ionic concentrations and ion channel permeability ratios given in the previous chapter.

4. Derive the relationship between $I_{st}$ and $T_{st}$ for a given $V_{m,th}$. Explain the restrictions applied to the values of $T_{st}$.

5. Given the definition of the length constant $\lambda$. Write the relationship between the length constant and the cardiac cell's parameters. Calculate the length constant for local propagation in a 1D fiber if the cardiac cell is considered to be a cylinder with a radius $a$ = 8 μm, $R_i$ = 200 Ω-cm, and $R_m$ = 6.25 kΩ-cm$^2$.

6. Calculate the diffusion coefficient using the values of $\lambda$ and $R_m$ from the previous question. Assume that $C_m$ = 1 μF/cm$^2$.

7. To what category of mathematical models is it possible to relate action potential (AP) models? Explain your reasoning.

8. Find the value of the length constant, λ, for passive propagation in tissue with the following parameters. (See chapter 7, page 128)
   $a = 8 - 10\mu M$
   $R_i$ = 0. 2 [kΩ cm]
   $R_m$= 6.25 [kΩ cm$^2$]

9. Which case is excitation conduction velocity larger: for the monodomain or bidomain approach?

10. FitzHugh and Nagumo derived their simplified model from the van der Pol equation.
    a. Show on a phase-plane plot ($w$, $v$) the changes introduced by FitzHugh in order to reproduce the nerve AP.
    b. Investigate the stability of the steady state point on the phase-plane plot.

11. The computational solution of mathematical models requires the selection of effective numerical algorithms, adequate computer architectures, and programming tools for visualizing data and calculating complex inherent characteristics of the model, such as the conduction velocity, relaxation coefficient, the AP duration restitution curve, etc.
    a. Explain the rationale for using the operator splitting algorithm in the numerical solution of parabolic partial differential equations.
    b. Describe the hybrid method and compare it with the Euler method for solving ordinary differential equations.
    c. Explain the computer simulation approach for calculating conduction velocity on a given point of a two-dimensional (2D) wavefront.
    d. Using the Noble AP model for propagation in 2D myocardium, show that it is possible to reduce this model into dimensionless form.

12. Stationary propagation of a spiral wave is considered to correspond to ventricular tachycardia, the precursor to ventricular fibrillation.
    a. Given the definitions of the points $q$ and $Q$ on the front of wave exhibiting stationary propagation.
    b. Define the area that is termed the *core* of a spiral wave. What geometric form does the core of the spiral wave have?
    c. Explain why stationary propagation of a spiral wave is impossible in a square-shaped section of myocardium with a restricted size.

13. Excitation-propagation through narrow passes are frequently observed in myocardium following an episode of myocardial infarction, when surviving regions of tissue are surrounded by damaged or dead regions.
    a. What are the three types of boundary conditions characteristic of narrow passes? Give their mathematical formulations and physical meanings.
    b. What geometrical configurations in narrow passes facilitate the appearance of reentrant propagation? What are the necessary conditions for reentry?
    c. How does wavefront curvature inside a narrow path and at its openings depend on the geometry, boundary conditions, and properties of surviving regions of myocardium.

14. According to Courtemanche and associates, the membrane capacitance for an atrial cell with dimensions $L = 100$ μm and $D = 16$ μm is equal to $C_m = 100$ pF. What is the specific capacitance, expressed in μF/cm$^2$, corresponding to this value of $C_m$? Note that 1 μm = $10^{-4}$ cm and 1 pF = $10^{-6}$ μF.

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