Scientific Journal of Riga Technical University
Transport and Engineering. Mechanics.

2010

Volume 33

Research of Biomechanical Forces System with the Use of the Auto-Oscillatory Models

Igors Tipāns, *Riga Technical University*, Veronika Gržibovska, *Riga Technical University*

Abstract **- Present article investigates the application of auto-oscillatory models in the analysis of biomechanical force systems. To perform analysis, following tasks were accomplished: detailed description of used auto-oscillatory models, their properties and factors affecting their behaviour, analysis of the spread of excitation in a nerve fibre, analysis of mathematical models of cardiac and skeletal muscle fibres, analysis of behaviour of skeletal muscle cells from mechanical point of view.**

Keywords **- mathematical model, auto-oscillations, muscles, biomechanical forces, nerve fiber.**

I. Introduction

Auto-waves appear in wave processes where stable system parameters can be secured. Multiple auto-wave propagation is possible in so called active media, characterized by distributed external sources of energy. After passage of the auto-wave the medium needs to restore its properties by use of external energy in order to be ready for propagation of the new auto-wave. Time interval required for restitution is called as refraction period. During that period the active medium is not able to react on any new wave.

Mathematical modelling of biomechanical objects is idealized analytical description of corresponding biomechanical processes and systems corresponding to principal properties of real processes and systems. Physical modelling is based on representation of structure, function or processes of biological and biomechanical systems by physical methods. One of objectives of present article is the modelling of structures and physiological processes of different species which determine generation of mechanical work

Let us consider Hodgkin-Huxley model [3, 5], which is one of the first and still one of the principal models to investigate electric processes at the cell membrane level. Application of that model is not limited only by giant squid axon as it was originally described, but also allows investigate excitation processes of other species, including those in mammals.

Hodgkin-Huxley equations successfully described excitation processes in a nerve fibre. They served as a basis for many later modifications applied for mathematical description of excitation processes of cell membranes in a heart and other organs.

According to the Hodgkin-Huxley model during the excitation process a local response is generated in a cell membrane which depends on ionic current flows initiated by rather complex mechanism of opening of specific membrane channels, e.g. sodium channels.

During the influx of sodium ions through the cell membrane trans-membrane potential changes its sign.

During fast depolarization process due to sodium ion influx causes corresponding potassium ion activity and then subsequent restitution of initial trans-membrane potential value.

II. Description of Hodgkin-Huxley model

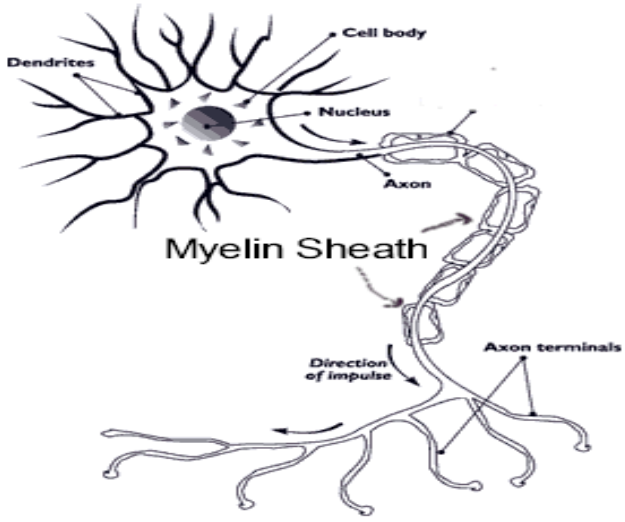

Fig. 1. Element of a nerve fibre

Trans-membrane potentials in different parts of the axon can vary. Axon itself may be described as a system with distributed parameters.

If there is an action to some part of an axon by sub-threshold positive external current, then trans-membrane potential in the area of an action and its closest vicinity will be shifted from equilibrium level to some positive values, producing so called local response. Excitation will disappear after some time.

There is a possibility to sum up excitations in different places. If repetitive external current stimulus is applied, the local response is added to a previous one. The response is depending from the stimulation time. In case if the local response due to strong single stimulus or as the result of summation of repetitive stimuli reaches threshold, single action potential is generated. Generated locally, action potential propagates along the axon.

Propagation of an action potential can be explained as follows: cytoplasm is a good conductor. If between any two locations in cytoplasm potential difference exists, then currents will occur, flowing from locations with a higher

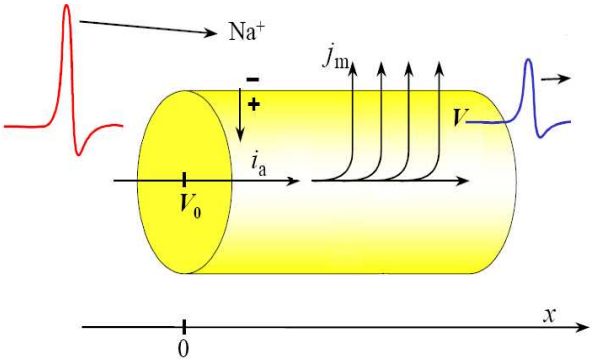

Fig. 2. Action potential propagation along the axon

potential to those with a lower potential. In locations close to the initial impulse surface potentials will grow and at some point will reach the threshold level, thus initiating the propagation of action potential. If two action potentials "collide", they may destroy further propagation. It is related to the membrane property that during the development of an action potential and after that for a definite time interval the membrane does not react to any next stimulus and the generation of a new action potential is impossible. Such membrane property is called as absolute refractory period. Gradually the absolute refractory period is replaced by relative refractory period when stronger stimulus is required to cause a new action potential [2, 6].

III. Description of Hodgkin-Huxley Model Equations

Based on experimental data on excitation of a gigant squid axon excitation process, Hodgkin and Huxley were able to set up a mathematical model of a nerve cell membrane. Differential equations are following:

$$\frac{dV}{dt} = -\frac{1}{C}\cdot(I_{Na} + I_K + I_L), \tag{1}$$

$$I_{Na} = \bar{g}_{Na}\cdot m^3\cdot h\cdot(V - V_{Na}), \tag{2}$$

$$I_K = \bar{g}_K\cdot n^4\cdot(V - V_K), \tag{3}$$

$$I_L = \bar{g}_L\cdot(V - V_L), \tag{4}$$

$$\frac{dm}{dt} = \alpha_m\cdot(1-m) - \beta_m\cdot m, \tag{5}$$

$$\frac{dn}{dt} = \alpha_n\cdot(1-n) - \beta_n\cdot n, \tag{6}$$

$$\frac{dh}{dt} = \alpha_h\cdot(1-h) - \beta_h\cdot h, \tag{7}$$

where V- trans-membrane potential,
V_{Na}, V_K, V_L – equilibrium potentials,
I_{Na} – sodium ionic current,
I_K – potassium ionic current,
I_L – leakage current,
C – membrane capacitance,
g_{Na} – sodium conductivity,
g_K – potassium conductivity,
g_L – leakage current conductivity,
m, n, h – kinetic variables, characterizing activation and inactivation processes of sodium and potassium ions,
α, β – rate constants of direct and reverse activation μ processes [5].

Variations of trans-membrane potential V in time are determined by values of sodium I_{Na} and potassium I_K ionic currents, membrane capacitance C and leakage current I. Correspondingly the rate of change of a ionic current I_i is depending from conductivity g_i value, trans-membrane potential and kinetic variables of activation and inactivation of corresponding ionic currents m, n, h. Kinetic variables can be determined as a probability that particles in membrane gates are in a position assisting ions to move across the cell membrane. Coefficient α characterizes the motion of a particle towards inside of the cell, β – the motion in opposite direction. With this model it is possible to imitate the generation of a single action potential, and also a propagation of excitation in a fibre. The model is able to reproduce action of different substances, e.g. pharmaceutical drugs to potential parameters.

Mathematical model by Hodgkin-Huxley was further transformed for MathCAD application.

IV. MathCAD Application of Hodgkin-Huxley Equations

As a result of action potential modelling in case of external current I = 15 $\mu A/cm^2$ is applied to a cell membrane following graphic images of single action potential in time and current – potential diagrams were produced, see Fig. 3, 4.

Having small values of external current, the reaction of a model is not significant. After that external current was increased till $I = 25\ \mu A/cm^2$, we got small oscillations on the action potential during its repolarization phase, Fig. 5, 6.

After further increase of external current up to I = 50 $\mu A/cm^2$ further increase in oscillation amplitudes can be notified, see Fig. 7, 8.

In figures 3 - 8 we can imitate action potential generation under external stimulation, and by using the model we can determine critical values of such stimulations being able to initiate action potential, caused by massive influx of sodium ions due to opening of voltage sensitive ionic channels. Positively charged sodium ions penetrate inside the cell due to concentration gradient. As a result transmembrane potential

rapidly reaches positive values. After that slow and fast repolarization phases follow as a result of efflux of positively charged potassium ions, and trans-membrane potential is reaching its initial values.

In the starting phase intensity of potassium current is high, and repolarization process is fast, after both potassium current intensity and repolarization rate is slower. After that we the model imitates hyperpolarization phase developed due to residual potassium current and activity of sodium-potassium pump. Presence of depolarizing external current leads to auto-oscillations.

As it was mentioned, Hodgkin-Huxley model is the main action potential model, and it serves as the basis for all further developments of action potentials of other specific cells with more complicated ionic current mechanisms. We use cardiac pacemaker cell action potential model to investigate cell auto-oscillating processes.

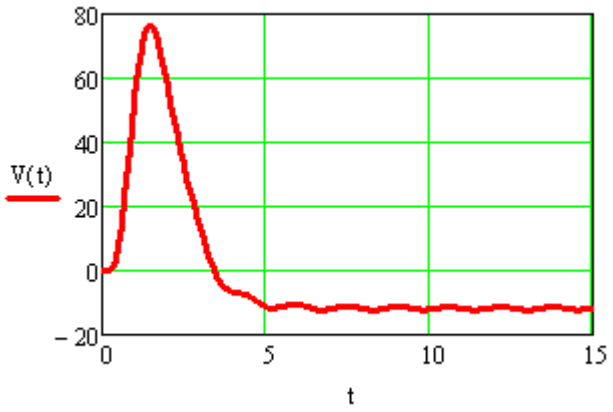

Fig. 3. Action potential in time (t –ms, V- mV)

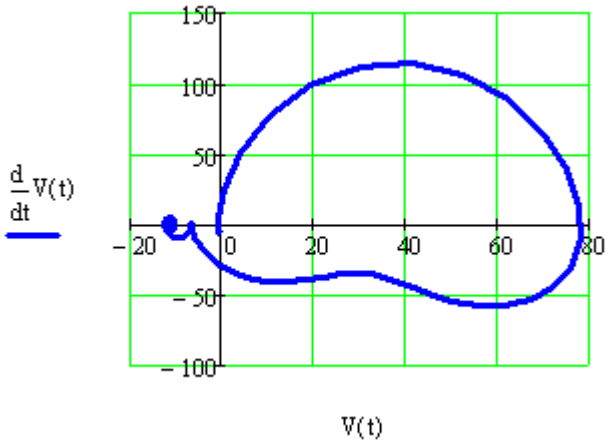

Fig. 6. Phase diagram of the action potential

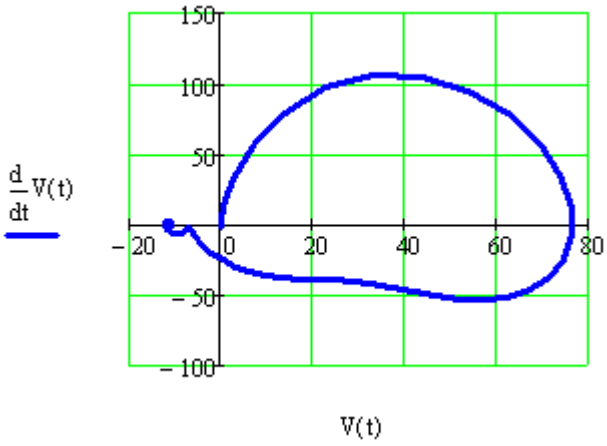

Fig. 4. Current – voltage (phase) diagram

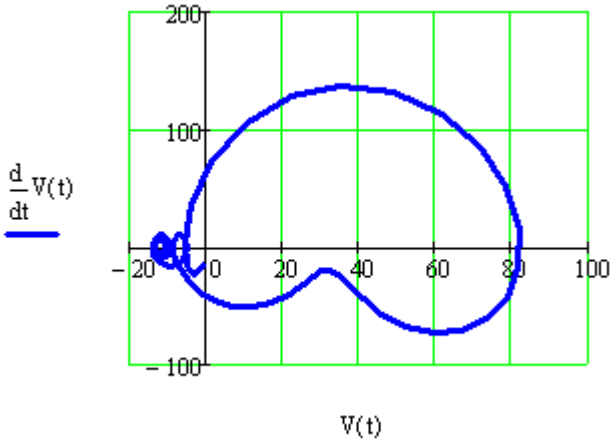

Fig. 7. Phase diagram of the action potential

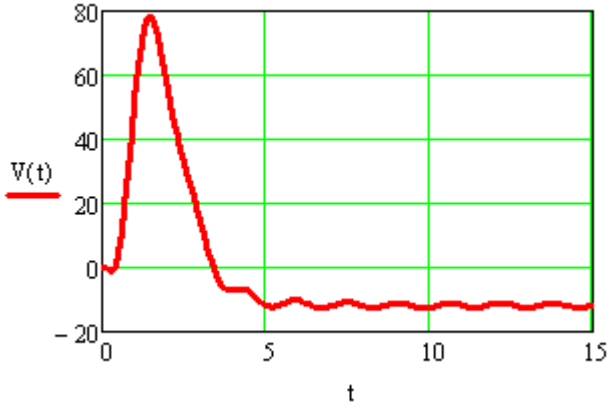

Fig. 5. Small oscillations of action potential when external current is increased

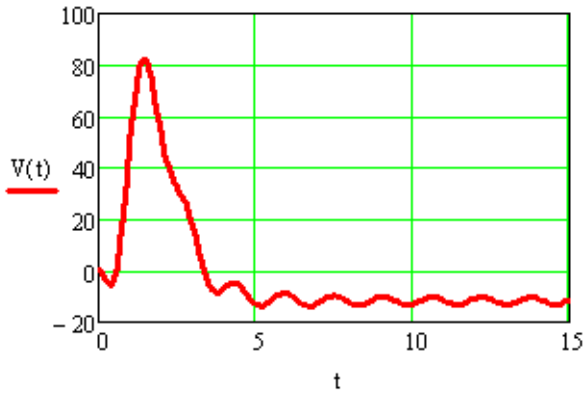

Fig. 8. Phase diagram for action potential with increased external current

V. Description of Noma - Irisawa model

Cardiac muscle is a complex multi-level system with two components to characterize its mechanical behaviour. First is determined by passive elastic and viscous properties of a muscle as a composite material.

The second is active which determines execution of main cardiac function – generation of the blood flow. Mechanical activity of a muscle is determined by a contraction process and its regulation. As it is known, the force generation is determined by periodic attachment and detachment of acto-myosin cross-bridges during ATP hydrolization process. During attachment of cross-bridges actin and myosin filaments are displaced and force is generated. The regulation of comtraction is realized through access of the binding sites for cross-bridges, determined by variations of calcium concentration in the cell initiated by action potential.

Action potential is generated as a respose to external stimulus by different kinetics of several ionic currents representing ion flow through cell membrane, including, sodium potassium and calcium currents [4].

Processes listed above are highly non-linear with several feedbacks, e.g. calcium activation and corresponding calcium current parameters will affect binding and unbinding processes of acto-myosin cross-bridges and general mechanical properties of contraction. Cardiac muscle may be considered as cotractile mechanism which can be efficiently analysed by mathematical modelling There are several mathematical models created and further improved which already now allow to investigate different properties of a cardiac muscle. Since significant attention is to be paid to propagating excitation waves and conditions to create spiral waves – source for arrhythmias, rather simple models were created such as FitzHue-Nagumo or Wiener-Rosenbluth models and their modifications. For single cell or single fiber, or simple spatial structures more sophisticated models such as Hudgkin-Huxley model were used [7, 9].

Model proposed by Noma Irisawa is one of the most complete models to investigate auto-oscillatory activitiy in heart cells. Initially it was set up for sino-atrial node cell membrane, but mechanisms underlying auto-oscillating activity may have more common mechanisms.

VI. Description of equations of Noma – Irisawa model

Noma – Irisawa's model includes five currents [1]:

I_{si} – slow outgoing current, carried by calcium and sodium ions;

I_K – slow outgoing potassium current;

I_f – hyperpolarization activated current;

I_{Na} – fast inward sodium current;

I_b – total background current.

Those currents are dependent from kinetic variables described later. Equations for trans-membrane potential change are following:

$$\frac{dV}{dt} = -\frac{I_{tot}}{C},$$
$$I_{tot} = I_{b,Ca} + I_{b,K} + I_{b,Na} +$$
$$+ I_{Ca,L} + I_{Ca,T} + I_f + I_K +$$
$$+ I_{Na} + I_{NaCa} + I_{NaK}, \quad (8)$$

where V – trans-membrane potential;

C – membrane capacitance;

I_{tot} – total ionic current;

$I_{b,Ca}$ – calcium background current;

$I_{b,K}$ – potassium background current;

$I_{b,Na}$ – sodium background current;

$I_{Ca,L}$ – L – type calcium (slow) current;

$I_{Ca,T}$ – T – type calcium (fast) current;

I_{NaCa} – sodium – calcium exchange current;

I_{NaK} – sodium – potassium exchange current.

L – type calcium channels („slow"channels) are mainly located in cardiomyocites and in blood vessel walls. In cardiovascular system they participate in the support of electrical and mechanical activity of cardiomyocites and smooth muscle cells

T – calcium channels ("fast" channels) mainly are located in the heart control system and in neurons.

Calcium ionic current plays principal role in the control of excitation and contraction processes, generation of pacemaker potentials. Under normal physiological conditions calcium current varies due to neurotransmitters: adrenaline leads to an increase, acetylcholine – to a decrease of the current [8].

Fast inward sodium current I_{Na} and slow outgoing potassium current I_K start to increase almost simultaneously, but I_{Na} grows faster and faster reaches its maximal value.

VII. Application of Noma – Irisawa's model by MathCAD

Similarly to application using Hodgkin – Huxley model, also is applying Noma – Irisawa's model.

We investigated action potential and ionic currents in time in presence of external current I = 50 $\mu A/cm^2$, as a result following graphical results were obtained, see Fig. 9 – 19.

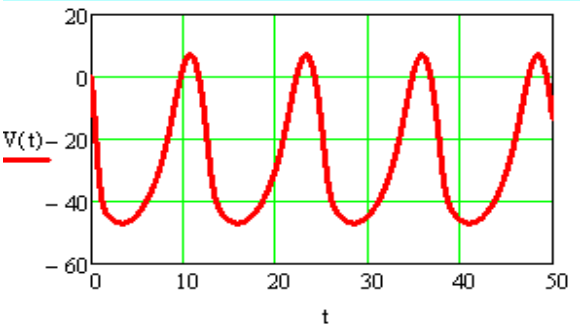

Fig. 9 Action potential in time

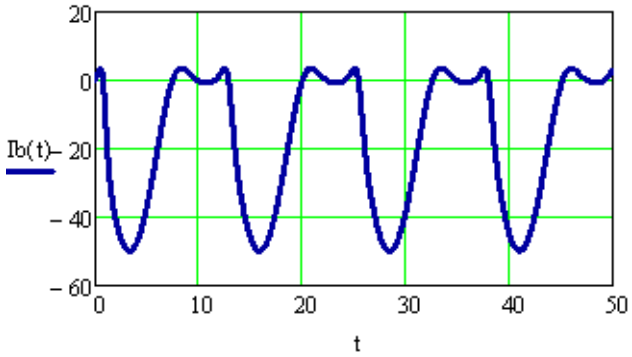

Fig. 10 Total background current in time

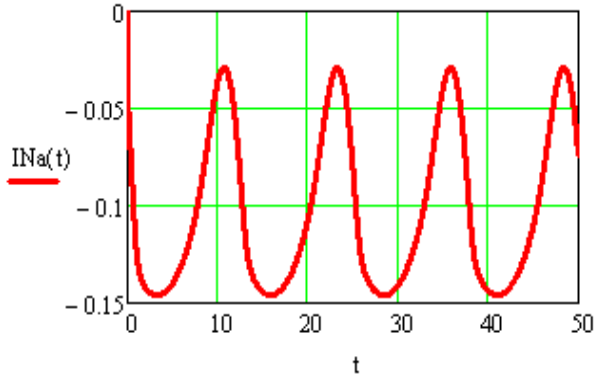

Fig. 11. Dependence of fast inward sodium current from time

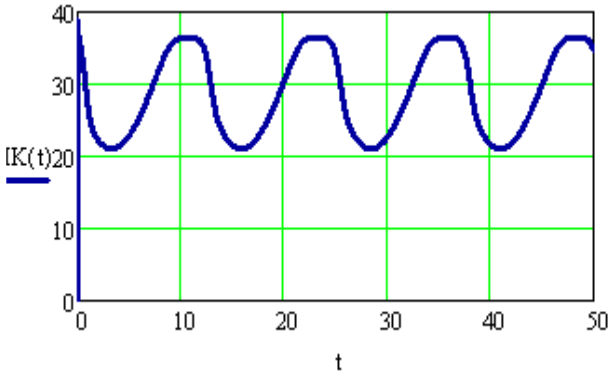

Fig. 12. Dependence of slow outward potassium current from time

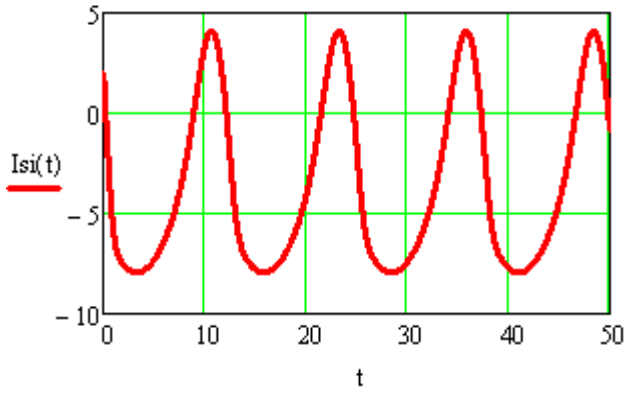

Fig. 13. Dependence of slow inward current from time

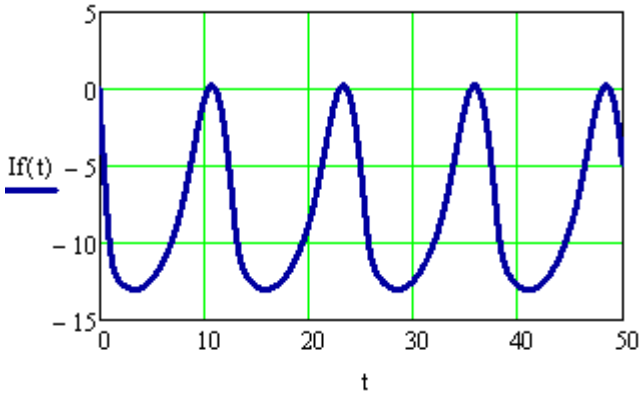

Fig. 14. Dependence of hyperpolarizing current from the time

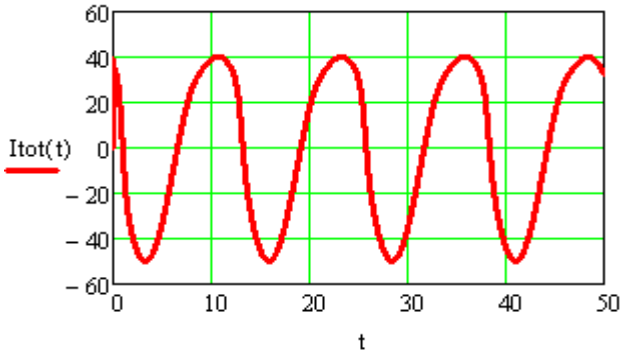

Fig. 15. Variations of total current in time

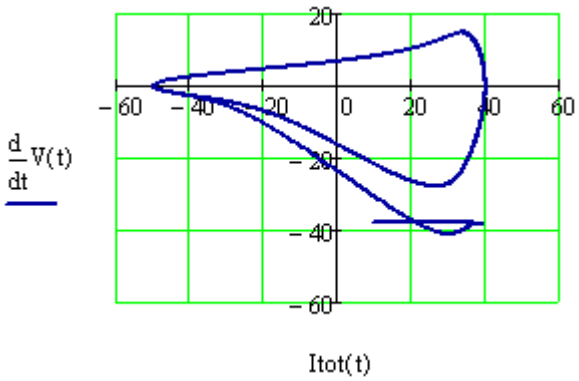

Fig. 16. Dependence of action potential from total current

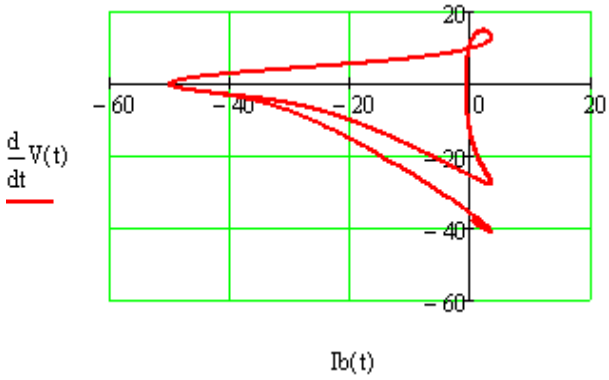

Fig. 17. Dependence of action potential from total background current

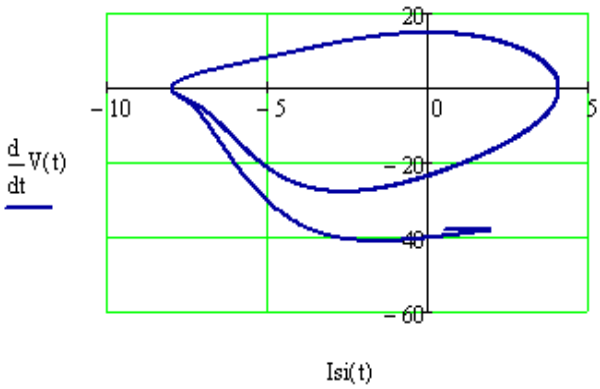

Fig. 18 Dependence of action potential from slow inward current

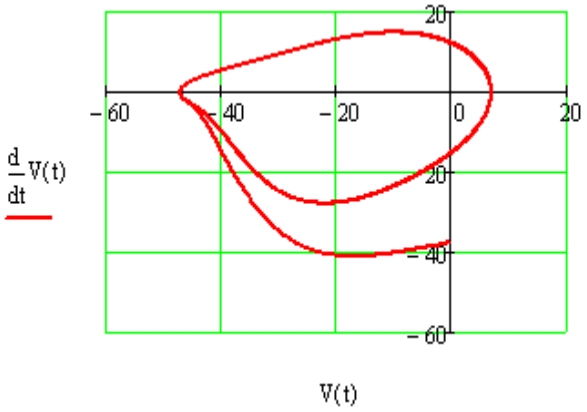

Fig. 19. Phase diagram of action potential

Here we have described ionic currents and their influence to action potential. By using MathCAD we were able to reproduce appearance of auto-oscillations if external current is applied. From graphic relationships (see Fig.9) we can see that main action potential characteristics are adequately reproduced by MathCAD model.

VIII. Conclusions

In present paper we explored possibility to apply MathCAD software for investigation of auto-oscillations in biological systems. Several mathematical models were introduced for specificē applications of different cell membranes. It is essential to say that existing biological systems provide examples of self-organizing and control to be further used in biomechanical technologies.

At the moment rather detailed models exist to investigate structures and processes in production of biomechanical force. Further development of such models will enable to apply quantitative approach to description of different biomechanicasl functions, determination of critical situations, onset of different pathologies, investigate action mechanisms of different drugs. Application of methods of non-linear oscillations - rather well developed for mechanical systems, to oscillations in biological systems can significantly contribute to better understanding of their behaviour.

References

1. **Noma, A., Irisawa, H.** Pacemaker activity of the rabbit sinoatrial node. A comparison of mathematical models. *Japanese Journal of Physiology*, 1980, vol. 30, N 6, p. 841 – 857.
2. **Gennis, P.** *Biomembranes. Mollecular structure and function.* (in Russian.) Moscow: Mir Publishers, 1997. – 624 p.
3. **Ivanitsky, G.R., Krinsky, V.I., Selkov, Y.Y.** *Mathematical Biophysics of a Cell.* (in Russian) Moscow: Nauka Publishers, 1978. –308 p.
4. **Lakhno, V.D., Ustinina, M.N.** *Computers and Supercomputers.* (in Russian.) Moscow – Izhevsk: Institute of Computer Research, 2002. 528 p.
5. **Plonsey, R., Barr, R**. *Bioelectricity: Quantitaitve Approach.* (in Russian.) Moscow: Mir Publishers.1992. 366 p.
6. **Evans, R.M.., Moore, D.D.** *Biological Membranes.* (in Russian.) Moscow: Mir Publishers. 1990. 424 p.
7. *Mathematical cell: Models.* Available: http://www.mathcell.ru/ru/obzors/obzor_Elkin2.shtml
8. Journal. Articles. Available: http://www.vestar.ru/article.jsp?id=2660&marker
9. Encyclopaedia. Articles. Available: http://ru.wikipedia.org

Igors Tipans, Dr.sc.ing., asoc. Professor, Riga Technical university. Scientific direction: Biomechanics of muscles. Address: 6, Ezermalas Street, Riga, LV-1006, Latvia. Phone: +37167089473. E-mail: igors.tipans@rtu.lv

Veronika Grzibovska, M.sc.ing., postgraduate student, Riga Technical University. Address: 6, Ezermalas Street, Riga, LV-1006, Latvia. Phone +371 29921864. E-mail: rutja@inbox.lv

Igors Tipāns, Veronika Gržibovska. Autosvārstību modeļu pielietojums biomehānisku spēku sistēmu analīzē
Rakstā ir izpētīts autosvārstību modeļu pielietojumu biomehānisko spēku sistēmu analīzē. Mērķa sasniegšanai tika izpildīti sekojoši uzdevumi: dots iespējamo autosvārstību modeļu, īpašību un to uzvedību ietekmējošo faktoru sīks apraksts, tika veikta ierosas modelēšana nervu šķiedrā, veikta skeleta muskuļu un sirds šūnas elektriskās aktivitātes matemātisko modeļu analīze, kā arī tika analizēta kalcija strāvas loma elektrisko un biomehānisko svārstību ģenerēšanā.

Игорс Типанс, Вероника Гржибовская. Применение автоколебательных моделей в анализе систем биомеханических сил
Целью данной статьи является изучение использования автоколебательных моделей в анализе систем биомеханических сил. Для достижения цели были выполнены следующие задачи: дано подробное описание возможных автоколебательных моделей, свойств и влияющих на их поведение факторов. Произведён анализ математических моделей распространения возбуждения в нервном волокне и в клетках сердца. Исследования проводились с помощью программы MathCad.