

**MATHEMATICAL MODELING OF MAIN POTENTIAL
GENERATING IONS LOCALIZATION IN LIVING CELLS**

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Summary

The diagram of ions movement through the cell's membrane was offered and the mathematical model, which contains quantitative and qualitative dependences for the proper concentrations of the main electrogene ions and ions transport rate constants by the ion transport system, was built. The model has the ability to suggest changes of the kinetic parameters values of the ion transport systems (under action of metabolic factor, pharmacological, physical or chemical influences) be able essentially affect on homeostasis of the main potential generating ions.

KEYWORDS: Ions, Mathematical modeling, Transmembrane potential, Membrane associated processes

Introduction

Among inorganic components of cell the potential generating ions as K^+ , Na^+ , Cl^- and Ca^{2+} play key roles in cells metabolism. Ions can be specific regulators of different type of the metabolic systems.

The information exchanges between cells and environment is possible to add to the processes relate to the ions transition across the plasma membrane.

The dynamics of homeostasis of the potential generating ions is noted their complexity that based on great value of factors that act on ions localization inner and outer the cell. These factors are Na^+ , K^+ -ATPase, Ca^{2+} -ATPase, $\text{Na}^+/\text{Ca}^{2+}$ exchanger, K^+ , Na^+ , Ca^{2+} and Cl^- channels, Na^+ , 2Cl^- , K^+ cotransporter (NKCC) which are so powerful that result on the irregularity of the ion distributions on both side of the membrane [1-6]. Because of the ions “behavior” is insufficiently studied, the one of possible pathway is analyse of the model.

Materials and methods

Mathematical model of localization of K^+ , Na^+ , Cl^- , and Ca^{2+} ions is based on:

- 1) Assume existence of the independence flows of Na^+ , K^+ , Ca^{2+} and Cl^- ions on the base of the flow independence principle (few flows are independent if no one of theirs stoichiometric equations are not linear combinations of others) [7]. The diagram described direction of ions transfer is represented on Figure 1.
- 2) The kinetic model of ions concentration changes inner and outer the cell is proposed for theoretical investigation the ions “behavior”.

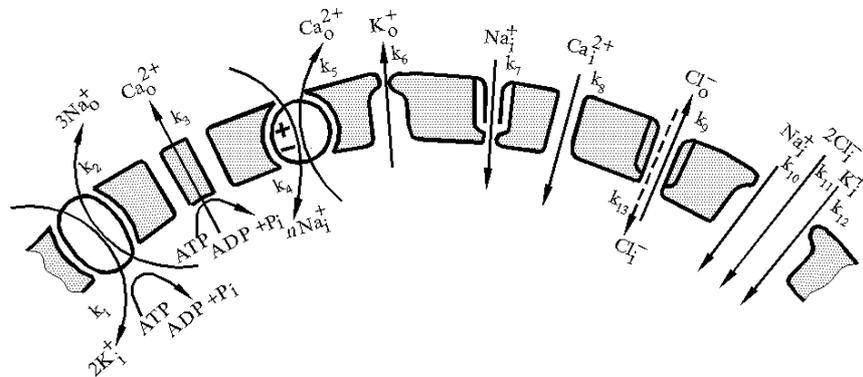


Figure 1. Diagram of ions transfer through the cellular membrane. The mechanism of ions transition through the cellular membrane includes 8 types of transport systems as Na^+ , K^+ -ATPase, Ca^{2+} -ATPase, $\text{Na}^+/\text{Ca}^{2+}$ exchanger (symbols +/- show effect: activatory or inhibitory), K^+ , Na^+ , Ca^{2+} , and Cl^- channels, NKCC. The flow directions of ions are presented by arrow.

The rate of change in ion concentrations ($d[Ca^{2+}]_o/dt$ and $d[Ca^{2+}]_i/dt$, $d[Na^+]_o/dt$ and $d[Na^+]_i/dt$, $d[K^+]_o/dt$ and $d[K^+]_i/dt$, $d[Cl^-]_i/dt$) are given by:

$$\begin{aligned} \frac{d[Ca^{2+}]_o}{dt} &= k_3[Ca^{2+}]_o + k_5[Ca^{2+}]_o; \\ \frac{d[Ca^{2+}]_i}{dt} &= k_8[Ca^{2+}]_i. \end{aligned} \quad (1)$$

$$\begin{aligned} \frac{d[Na^+]_o}{dt} &= 3k_2[Na^+]_o; \\ \frac{d[Na^+]_i}{dt} &= nk_4[Na^+]_i + k_7[Na^+]_i + k_{10}[Na^+]_i. \end{aligned} \quad (2)$$

$$\begin{aligned} \frac{d[K^+]_o}{dt} &= k_6[K^+]_o; \\ \frac{d[K^+]_i}{dt} &= 2k_1[K^+]_i + k_{12}[K^+]_i. \end{aligned} \quad (3)$$

$$\frac{d[Cl^-]_i}{dt} = 2k_{11}[Cl^-]_i. \quad (4)$$

Where k_3 , k_5 , k_8 are ion transport rate constants for Ca^{2+} ion transport systems, k_2 , k_4 , k_7 are ion transport rate constants for Na^+ ion transport systems, k_1 , k_6 , k_{12} are ion transport rate constants for K^+ ion transport systems, k_{11} is NKCC ion transport rate constant for Cl^- , extracellular concentrations of $[K^+]_o$, $[Na^+]_o$, $[Ca^{2+}]_o$, intracellular concentrations of $[K^+]_i$, $[Na^+]_i$, $[Ca^{2+}]_i$, and $[Cl^-]_i$.

Table 1. Numerical values of parameters

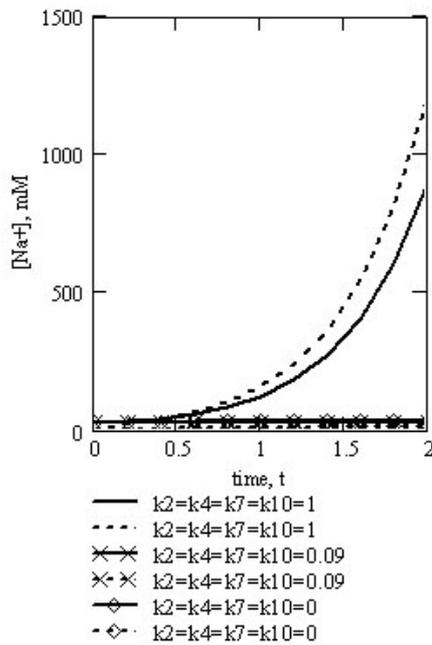
Parameter	Value
$[Ca^{2+}]_o$, $[Ca^{2+}]_i$	1 mM, 0,0001mM
$[Na^+]_o$, $[Na^+]_i$	31 mM, 2 mM
$[K^+]_o$, $[K^+]_i$	1 mM, 7,68 mM
$[Cl^-]_i$	0,5 mM
n	3,38

Results

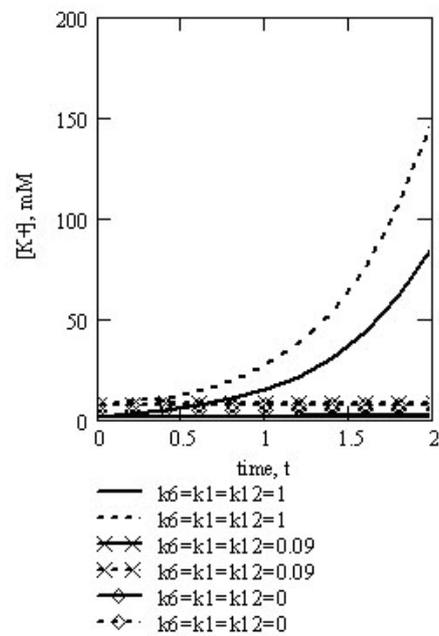
To perform the simulations Eqs. 1-4 were integrated numerically, employing the Runge-Kutta fourth-order method,

except for the determination of $[Ca^{2+}]_o$, $[Ca^{2+}]_i$, $[Na^+]_o$, $[Na^+]_i$, $[K^+]_o$, $[K^+]_i$, $[Cl^-]_i$. The values chosen for the ion transport rate constants are 1, 0,09 and 0. Such small value physical underscore slow work of the channel systems [6, 8,9].

The modeling results were given by family of integral curves, form and position of which t . Result shows exponential increase of ion concentration at $k = 0,09$ and $k = 1$ and steady state at $k = 0$. The modeling results were given by family of integral curves, form and position of which depended on ions transport rate constants of the proper transport systems. This model provide independent “behavior” of ions concentrations in a cell. Figure 2, A, B, C, and D shows dynamics in ion concentration at different values of the ion transport rate constants of t . Result shows exponential increase of ion concentration at $k = 0,09$ and $k = 1$ and steady state at $k = 0$.



A)



B)

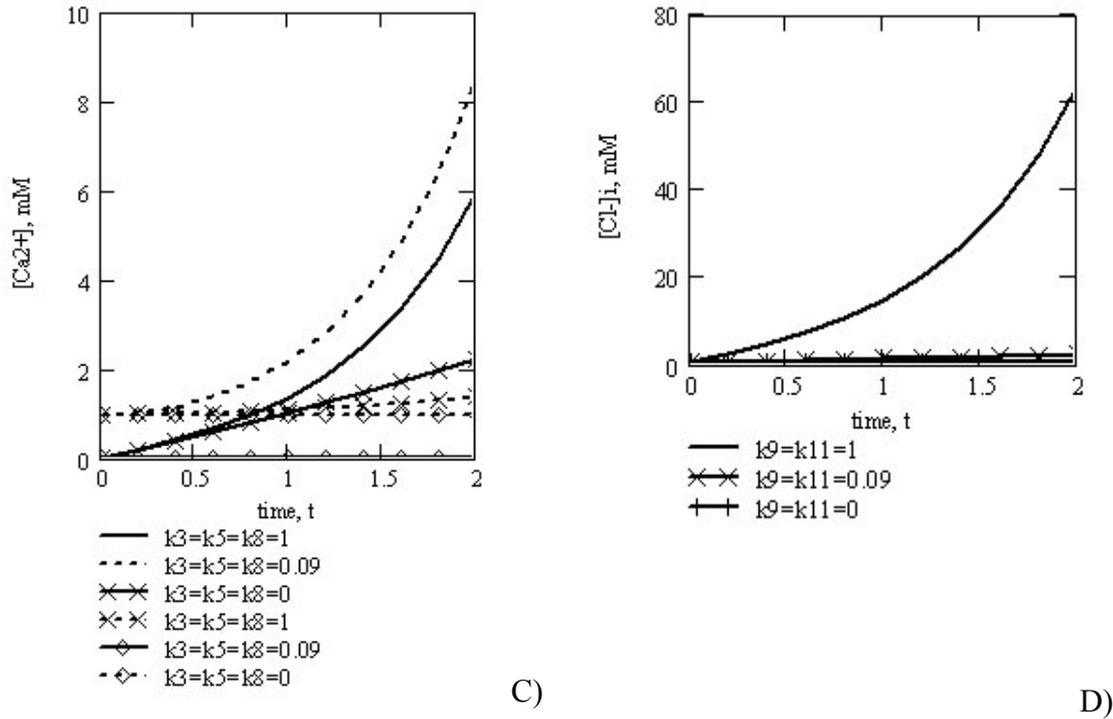


Figure 2. Dynamics of ion concentrations changes.

Discussions

The present study shows that the model based on the principles (see Materials and Methods) can qualitatively described changes in ion location those experimentally observed in a variety of cells. Because ions transitions appear to behave differently in various cell types, it is of interest to try to understand the origin of these features.

Apparently, cases with the ion transport rate constants $k = 0,09$ and $k = 1$ characterise cells during division and growth, case with $k = 0$ characterises cell with low action of transport systems that state shown for unfertilized oocytes [6]. The model has the ability to suggest changes of the kinetic parameters values of the ion transport systems (under action of metabolic factor, pharmacological, physical or chemical influences) be able essentially affect on homeostasis of K^+ , Na^+ , Cl^- and Ca^{2+} ions.

The proposed models were compared with experimental data. Calculated values of ion concentrations were in good qualitative agreement with experimental data.

As a result of numeral integration the dynamics of ions accumulation in the cell and external environment gotten. Showed that potential generation concentration grow gradually. Determined that influence of the parameter on the state of system the can be different. The resulted material is illustration of important mechanism for the analysis of ions transition and distribution between the cell and external environment.

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