

Chapter 2

Models of Ion Transport in Mammalian Cells

Cardiomyocytes, neurons, hepatocytes and erythrocytes are considered based on the algorithm “one ion—one transport system” models of some mammalian cells. Models of the compartments of mammalian cells, e.g., synaptic vesicles, sarco- and endoplasmic reticulum and mitochondria, are built; and models for the regulation of ion transport in mammalian cells and their compartments are presented. We find conditions under which a robust and effective strategy for the switching of transport systems of cells takes place.

2.1 Introduction

The basis of cellular forms of life lies in a process that involves continuous maintenance of the differential concentrations of ions inside the cell relative to that of the extracellular medium. Thus, most mammalian cells, when compared to the extracellular medium, have low concentrations of sodium and calcium and large concentrations of potassium ions. The constancy of these differences is critical for homeostasis and plays an important role in the regulation of metabolism, and this distribution is due to membrane permeability and ion pumps that are built into those membranes. Because of passive permeability, the cell has a tendency to equalize concentrations; however, pumps work to maintain a concentration gradient. Pump operation requires energy, in the form of ATP, which is generated by the combustion of the “fuel” of the cell, especially fats and carbohydrates, in the mitochondria. ATP has a large free energy (~ 150 kJ/mol) and is transported to the membrane pumps, which function constantly.

Molecules of transferred substances or ions can be transported by various manners: they can travel through the membrane, irrespective of the transfer of other compounds (uniport), their transfer can be carried out simultaneously and unidirectionally to other compounds (symport), or transport connections can be

simultaneously and oppositely directed (antiport). Symport and antiport are systems of co-transport for which the rate of the overall process is controlled by the availability and accessibility of transport systems for both ions. In turn, co-transport is a type active transport. Passive and active transport are provided with special structures such as channels, transporters, and enzymes that ensure the movement of specific ions against their concentration gradients, and this action is dependent upon the energy of ATP. This transfer is carried out by transport ATPases, which are also referred to as ion pumps.

In this chapter, we will build transport system models for some cells based on the proposed algorithm in [Chap. 1](#). To validate the algorithm, the model must be applied to cells—the representatives of the various kingdoms of nature, and we use the classification of the animal world, which was offered by Cavalier-Smith. In this work (Cavalier-Smith 2002; Cavalier-Smith 1998), all life was divided into two domains: eukaryotes and prokaryotes. Eukaryotes are divided into five kingdoms: animals, plants, fungi, protists and chromists. Prokaryotes were classified into archaea and eubacteria.

The considered mammalian cells possess a number of features that differentiate them from cells of other kingdoms. First, the ionic composition of their external environment is nearly constant, and second, the lack of flexibility of their cell walls and membranes require a minimum differential pressure across the membrane (i.e., the difference of internal and external pressures).

In addition to the four types of mammalian cells in this chapter, models of transport systems will be built for the mitochondria, synaptic vesicles, and the sarco- and endoplasmic reticula. By ignoring features of these compartments that are irrelevant for our algorithm, we consider these compartments as isolated systems that possess the ability to maintain intracellular concentrations at a given level.

2.2 Cardiac Cells

Functioning of a cardiac muscle cell considerably depends on the ion concentrations in the cell and its environment. These ions primarily include Na^+ , K^+ , Ca^{2+} , Mg^{2+} , HCO_3^- and Cl^- . For example, calcium ions participate in the contraction of muscles and signal processes, while magnesium ions specifically control the work of ATP-dependent exchangers. Intracellular magnesium is extremely important for intactness and the functioning of ribosomes, and it takes part in regulating the concentrations and transport of calcium, potassium, sodium and phosphate ions inside and outside the cell. As a cofactor, magnesium activates over 300 enzymatic reactions that are involved in metabolic processes in organisms. Magnesium interacts with cellular lipids, ensures the intactness of the cell membrane, and enters a competitive relationship with calcium for contraction elements. Furthermore, the concentrations of calcium, potassium and sodium ions largely determine the properties of the action potential in a cardiac muscle cell.

Table 2.1 Experimental data for ion concentrations and the resting potential for a cardiac cell

Ions	Internal concentrations, mM	External concentrations, mM
Na ⁺	12	145
K ⁺	155	4
Mg ²⁺	0.5 ÷ 1	1 ÷ 2
Ca ²⁺	10 ⁻³ ÷ 10 ⁻⁴	1
Bicarbonate	8	27
Cl ⁻	4	120
Others	155	7
Potential, mV	-(83 ÷ 100)	

All of the aforementioned processes are strongly sensitive to intracellular concentrations of Ca²⁺ and Mg²⁺ ions. These concentrations can change depending on the concentrations of the corresponding ions in the cellular environment. However, models for the independent prediction of ion concentrations in a cell and the membrane resting potential are unavailable in the current literature.

Details of the construction of the transport system for cardiomyocytes in the steady state have been established (Melkikh and Sutormina 2008). Here, we briefly present the main results, and based on the model of the transport system, we consider algorithms for the regulation of ion transport.

First, information on the values of the concentrations of internal and external ions are needed, and Table 2.1 gives the concentrations of the basic types of ions that are found inside and outside of a cell (Sperelakis 2000; Murphy 2000; Sperelakis and Gonzales-Serratos 2001).

The main and most well-studied pump in cardiac muscle cells is the Na⁺-K⁺-ATPase. This pump is ATP-dependent, and it transfers three sodium ions from the cell and exchanges them for two potassium ions. In addition to this pump, we will consider other sodium ion exchangers. For example, we will discuss the Ca²⁺-Na⁺ exchanger, which transports one calcium ion in exchange for three sodium ions, and the Mg²⁺-Na⁺ exchanger, which transports one magnesium ion in exchange for one sodium ion. Additionally, electrically neutral co-transport transports a sodium ion, potassium ion and two chlorine ions in one direction—K⁺-Na⁺-2Cl⁻. In turn, calcium ions are pumped out of the cell by the Ca²⁺-ATPase. Additionally, all ions can passively penetrate the through membrane, the magnitude of passive flow is determined by the membrane permeability coefficient P for each type of ion. Other mechanisms exist to transport chloride ions in addition to passive flow and the K⁺-Na⁺-2Cl⁻ co-transporter such as the K⁺-Cl⁻ and Na⁺-Cl⁻ symporters, which transfer potassium and chlorine or sodium and chlorine out of the cell, respectively, and the OH⁻-Cl⁻ antiporter, which transports chlorine through the membrane into the cell and the HCO⁻-Cl⁻-H⁺-Na⁺ co-transporter, which exchanges bicarbonate and sodium ions for a chloride ion and proton (Luo and Rudy 1991, 1994; Faber and Rudy 2000; Hume et al. 2000).

All of the described mechanisms are shown in Fig. 2.1.

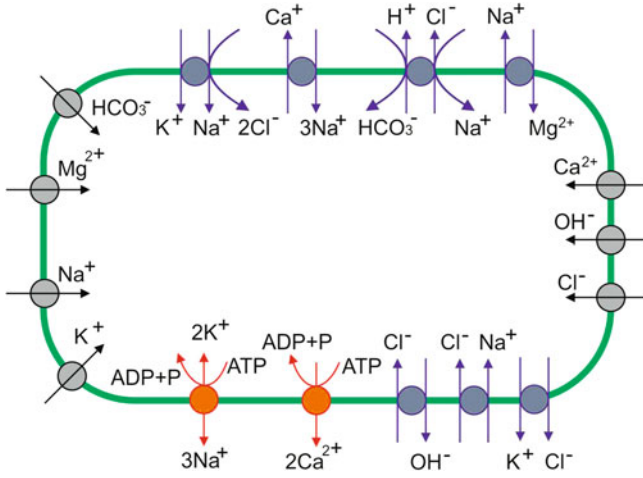


Fig. 2.1 Transport systems in a cardiac cell

2.2.1 Model of Transport Systems

Sodium ions are carried by several transport systems (Sperelakis 2000), but the main pump that transfers this ion to the external environment of the majority of animal cells is thought to be the $\text{Na}^+\text{-K}^+\text{-ATPase}$. Despite the fact that other transport mechanisms can provide a smaller deviation between the required and internal concentrations of sodium ions, the effect of ATPase activity is necessary to create a non-equilibrium state in the system. Thus, we chose this system as the basis for sodium ions. The $\text{Na}^+\text{-K}^+\text{-ATPase}$ carries three sodium ions out of the cell and two potassium ions into the cell. In accordance with the earlier proposed model, the equation for the sodium flow that is produced by this system has the following form:

$$J_{\text{Na-K-ATP}} = 3C_{\text{Na-K-ATP}} \left[\exp(\Delta\mu_A + \varphi) (n_{\text{Na}}^i)^3 (n_K^o)^2 - (n_{\text{Na}}^o)^3 (n_K^i)^2 \right], \quad (2.1)$$

where $C_{\text{Na-K-ATP}}$ is the constant of the active transport of sodium and potassium ions, and the remaining symbols have been given previously.

The analytical expression for the dependence of the internal concentrations of sodium ions on the values of the membrane potential and extracellular concentrations can be obtained after we determine the main transport system for potassium ions. The following systems transport potassium ions:

- $\text{Na}^+\text{-K}^+\text{-ATPase}$;
- $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ —co-transport;
- $\text{K}^+\text{-Cl}^-$ —co-transport;
- Potassium channels.

Because of the result from the calculation of the internal concentration of potassium ions that are produced by each of these systems and its comparison with the experimental data, it was concluded that the distribution of potassium ions is near the Boltzmann distribution because they can easily penetrate through the biomembrane.

We shall neglect the active flows of potassium ions relative to their passive flow; therefore, their concentration follows the Boltzmann distribution:

$$n_K^i = n_K^o \exp(-\varphi), \quad (2.2)$$

From (2.1) and (2.2), the expression that models the dependence of the internal parameters on the external parameters for sodium ions is as follows:

$$n_{Na}^i = n_{Na}^o \cdot \exp\left(-\varphi - \frac{\Delta\mu_A}{3}\right) \quad (2.3)$$

When considering chlorine transport as the third potential-forming type of ion transport, we found the minimal deviation from the actual values that were provided by the K–Cl, Na–Cl–HCO₃–H co-transporters and the passive penetration of chloride ions through their electrochemical gradient. Notably, the passive distribution of potassium ions, which is the dependence of the internal concentration of chlorine on the external concentration of K–Cl, is also described by the Boltzmann equation. The calculated value that is created by a complex mechanism of Na–Cl–HCO₃–H is near that of the calculated value of the K–Cl co-transporter and passive penetration of chloride ions, and it can be assumed that the analytical expression that depends on the internal concentration of the external parameters for this type of transport system will be similar. Therefore, the concentration of these anions in a cell approaches the Boltzmann distribution (although chlorine is also involved in several transport systems (Sperelakis 2000; Hume et al. 2000)):

$$n_{Cl}^i = n_{Cl}^o \exp(\varphi). \quad (2.4)$$

The focus of a work by Melkikh and Sutormina (2008) was given to the transport of divalent cations, which play a special role in carrying out vital functions in heart muscle cells.

In addition to passive transport across the cell membrane through the electrochemical potential, calcium in a cardiac muscle cell is transported by two systems: the Ca-ATPase and a Na⁺–Ca²⁺-exchanger.

It is known that a Na⁺–Ca²⁺-exchanger substitutes one calcium ion for three sodium ions in the absence of the consumption of ATP energy. Thus, in accordance with the model (Melkikh and Sutormina 2008), the equation has the following form:

$$J_{Ca-Na} = C_{Ca-Na} \cdot \left[n_{Ca}^i \cdot (n_{Na}^o)^3 - \exp(\varphi) n_{Ca}^o \cdot (n_{Na}^i)^3 \right], \quad (2.5)$$

The structure of the equation reflects the exchanger stoichiometry (i.e., one calcium ion is exchanged for three sodium ions) and the fact that sodium and calcium ions are transported in opposite directions.

Because one calcium ion is actively transported out of a cell during the hydrolysis of one ATP molecule, we obtain an equation for the active transport of calcium, which is in line with that of (Melkikh and Sutormina 2008):

$$J_{Ca-ATP} = C_{Ca-ATP} [\exp(\Delta\mu_A + 2\varphi)n_{Ca}^i - n_{Ca}^o], \quad (2.6)$$

The calculated values of the intracellular concentration of Ca ions for each system are the following:

- Ca-ATP: $n_{Ca}^i = 2.7 \cdot 10^{-6}$ mM;
- Na-Ca: $n_{Ca}^i = 1.5 \cdot 10^{-5}$ mM;
- Passive flux: $n_{Ca}^i = 1.3 \cdot 10^3$ mM.

When comparing these values with those from the experimental data ($10^{-3} \div 10^{-4}$), we see that the sodium exchanger produces the smallest deviation. However, the order of the values of the intracellular concentration of calcium ions is small when compared to the concentrations of other ions. In other words, in the first approximation in our algorithm, we can use an ATP-dependent calcium pump and exchanger. This situation is similar to the choice of the main system for sodium and we assume for the main ATP-dependent pump. Thus, the dependence of the internal concentration of calcium ions on the external concentrations (2.6) takes the following form:

$$n_{Ca}^i = n_{Ca}^o \cdot \exp(-2\varphi - \Delta\mu_A) \quad (2.7)$$

Transport of another divalent cation, magnesium, in cardiomyocytes is provided by the following mechanisms (Freudenrich et al. 1992; Murphy 2000):

- Na⁺-Mg²⁺-exchanger;
- Magnesium channels.

Expressions of fluxes that are generated by these transport systems can be written in the following form:

$$J_{Na-Mg} = C_{Na-Mg} \cdot [\exp(\varphi)n_{Mg}^{in} \cdot n_{Na}^{out} - n_{Mg}^{out} \cdot n_{Na}^{in}] \quad (2.8)$$

$$J_{Mgpas} = P_{Mg} \cdot [n_{Mg}^{in} \cdot \exp(2\varphi) - n_{Mg}^{out}] \quad (2.9)$$

Numerical calculations showed that passive flow creates an internal concentration of 2.7×10^3 mM, while the counter-transport of sodium and magnesium provides a value of 6 mM, which is in better agreement with the experimental data ($0.5 \div 1$ mM). Therefore, the expression for the intracellular concentration of magnesium ions, in view of (2.3), can be written as the following:

$$n_{Mg}^i = n_{Mg}^o \cdot \exp\left(-\frac{\Delta\mu_A}{3} - 2\varphi\right) \quad (2.10)$$

The next anion transport that will be considered to simulate ion transport in cardiomyocytes is the bicarbonate ion, HCO_3^- . The transfer of this ion is provided by work of the electroneutral complex $Na-Cl-HCO_3-H$, chlorine-bicarbonate exchanger and through special channels. The $Na^+ - HCO_3^- - Cl^- - H^+$ co-transporter operates as follows: a sodium and bicarbonate ion is exchanged for a chlorine anion and a proton, and this mechanism is electroneutral. Because the cell potential does not produce a barrier, the work of the exchanger depends on the concentration of ions and the probability that they will interact with the carrier. Considering the earlier proposed model, we can write the following equation:

$$J_{Na-HCO_3^- - Cl - H} = C_{Na-HCO_3^- - Cl - H} (n_{HCO_3^-}^i \cdot n_{Na}^i \cdot n_{Cl}^o \cdot n_H^o - n_{HCO_3^-}^o \cdot n_{Na}^o \cdot n_{Cl}^i \cdot n_H^i), \quad (2.11)$$

where $C_{Na-HCO_3^- - Cl - H}$ is the exchange constant for the HCO_3^- , Cl^- , Na^+ and H^+ anions.

Considering Eq. (2.11), the dependence of the intracellular concentration of the anions on their extracellular concentration and the membrane potential can be written as follows:

$$n_{HCO_3^-}^i = n_{HCO_3^-}^o \exp\left(\frac{\Delta\mu_A}{3} + 2\varphi\right). \quad (2.12)$$

Substituting the known values results in $n_{HCO_3^-}^i = 13.9$ mM,

The expression for the flow of ions that are produced by the $HCO_3^- - Cl^-$ exchanger can be written as follows:

$$J_{HCO_3^- - Cl^-} = C_{HCO_3^- - Cl^-} (n_{HCO_3^-}^i \cdot n_{Cl^-}^o - n_{HCO_3^-}^o \cdot n_{Cl^-}^i). \quad (2.13)$$

It is observed from this expression that the operation of this exchanger is equivalent to the passive transport of HCO_3^- ions. When the known values are substituted, $n_{HCO_3^-}^i = 0.7$ mM, and by equating the flow to zero, we obtain the following expression for the intracellular concentration of HCO_3^- ions when only this exchanger operates:

$$n_{HCO_3^-}^i = n_{HCO_3^-}^o \exp(\varphi).$$

Thus, we may conclude that the main transport system for HCO_3^- ions is the sodium-dependent exchanger because the intracellular concentration of HCO_3^- ions that are produced by this exchanger most closely approaches the experimental value.

However, this conclusion does not suggest that the role of the $HCO_3^- - Cl^-$ exchanger is insignificant in a cell. This exchanger can be significant in regulating the concentration of HCO_3^- ions and pH inside of the cell.

We decided on the main transport system for each type of ion. According to our algorithm and by using the equation of electrical neutrality, we derive the dependence of the membrane resting potential on the extracellular concentrations of ions that are under consideration:

$$2 \cdot n_{Ca}^o \cdot \exp(-\Delta\mu_A - 2\varphi) + n_{Na}^o \cdot \exp\left(-\frac{\Delta\mu_A}{3} - \varphi\right) + n_K^o \cdot \exp(-\varphi) + 2 \cdot n_{Mg}^o \cdot \exp\left(-\frac{\Delta\mu_A}{3} - 2\varphi\right) = n_{Cl}^o \cdot \exp(\varphi) + 0.89 \cdot n_{HCO}^o \exp\left(2\varphi + \frac{\Delta\mu_A}{3}\right) + Z_A \cdot n_A \quad (2.14)$$

Concentration $Z_A \cdot n_A$ of non-penetrating ions is known experimentally. By solving the equation numerically, it can be shown that the potential is equal to -3.7 (approximately -92.5 mV), which closely corresponds to the experimental data.

From Eq. (2.14), we can explicitly obtain an expression for the potential. Because the contributions of calcium, magnesium, and bicarbonate in the potential are small in comparison with other ions, they will be neglected; therefore, the dependence of the membrane potential on the extracellular concentrations has the following form:

$$\varphi = -\ln \left(\frac{\sqrt{\left(\frac{Z_A n_A}{2 n_{Cl}^{out}}\right)^2 + \left(\frac{n_{Na}^{out}}{n_{Cl}^{out}} \exp\left(\frac{-\Delta\mu_A}{3}\right) + \frac{n_K^{out}}{n_{Cl}^{out}}\right) + \frac{Z_A n_A}{2 n_{Cl}^{out}}}}{\left(\frac{n_{Na}^{out}}{n_{Cl}^{out}} \exp\left(\frac{-\Delta\mu_A}{3}\right) + \frac{n_K^{out}}{n_{Cl}^{out}}\right)} \right) \quad (2.15)$$

Graphically, the dependence of the membrane potential on changes in the extracellular medium is shown on Fig. 2.2.

Fig. 2.2 Dependence of the potential on the addition of potassium and chlorine ions to the environment

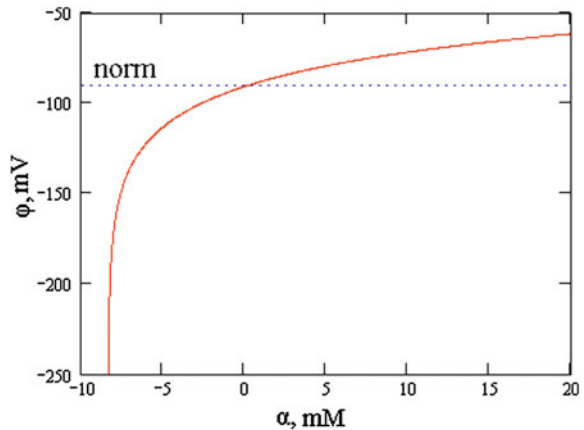


Table 2.2 Comparisons of the calculated values of the internal ion concentrations and membrane potential with the experimental data from cardiomyocytes

Ions	Experimental data, mM	Calculated data, mM
Sodium	12	6.9
Potassium	155	151.2
Magnesium	$0.5 \div 1$	3.6
Calcium	$10^{-3} \div 10^{-4}$	2.9×10^{-6}
Bicarbonate	8	13.2
Chlorine	4	3.1
Potential, mV	$-(83 \div 100)$	-90.8

In the Fig. 2.2, the solid line indicates the change in the resting membrane potential after adding a certain concentration of α (in mM) into the extracellular medium in an equal amount to that of potassium and sodium ions with chlorine. The points show the normal value of the membrane potential.

The value of the membrane potential without divalent cations is slightly smaller than the absolute value of approximately -90.8 mV, which is also consistent with the experimental data. By including (2.15), i.e., dependencies of the intracellular on the external concentration, we can calculate the values of the internal concentrations of ions, and detailed results of the calculation are given in (Melkikh and Sutormina 2008). The obtained results are tabulated in Table 2.2.

2.2.2 Regulation of Ion Transport

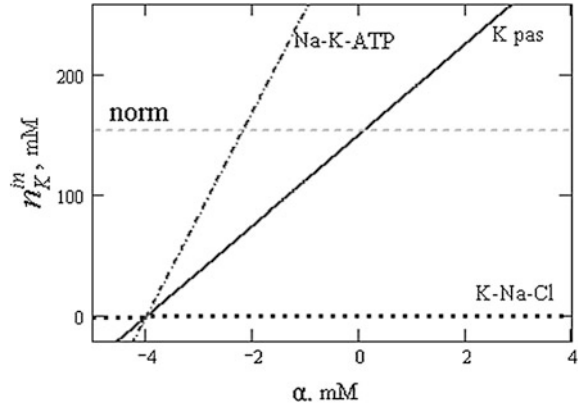
We have constructed a system of equations that describe the transport processes in the cell during the stationary state, and these equations can be used as a starting point for modeling the regulation of ion transport through the membrane under varying external conditions.

As mentioned earlier, potassium ion transport is carried out by four methods in cardiomyocytes: an ATP-dependent pump, two co-transporters and passive transport. According to our algorithm, we can construct the dependence of the intracellular on the extracellular concentration that is produced independently by each mechanism. We can then graphically determine an effective and robust strategy for regulation. The potential changes are taken into account when constructing strategies for the regulation of ions, which strongly affect the potential.

The work of the four transport systems are represented in the following graph (Fig. 2.3).

The figure displays the dependence of the intracellular concentration of potassium ions from the addition of α on the external environment of potassium ions with chlorine, in mM. The solid line indicates passive flow, points represent Na-K-Cl-co-transport, the dashed line denotes the actual concentration of potassium in the cell at steady state, and the dash-dot line represents the work of Na-K-ATP.

Fig. 2.3 Mechanisms for the transfer of potassium ions in cardiac cells



The figure shows that the dependence of the internal on external concentrations of ions is linear; however, this finding does not indicate that the potential depends weakly on the concentration of extracellular potassium. As shown in the figure, in the selected range, only a partial dependency is reflected, and the interval changes in the external concentration is limited to values that are approximately twice the normal value because strong deviations lead to cell death.

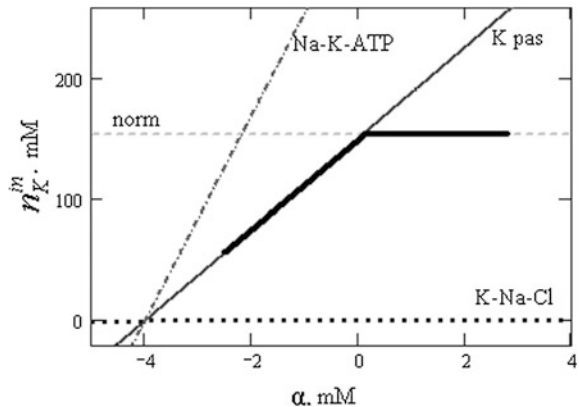
By using the algorithm for finding the optimal strategy for transport, the optimal strategy for the transport system of potassium ions can be determined graphically.

We show the selected, best strategy for transport systems of cardiac muscle cells in Fig. 2.4.

In the figure, the solid line indicates passive flow, the points refer to Na–K–Cl-co-transport, the dashed line denotes the actual concentration of potassium in the cell at steady state, the dash-dot line refers to the work of the Na–K–ATPase, and the bold solid line indicates the chosen strategy.

We utilize the optimal strategy to ensure the maximum efficiency of pumps and exchangers at any given time, i.e., only one transport mechanism is functional.

Fig. 2.4 Strategy for regulating potassium ion transport in cardiomyocytes



However, as observed in Fig. 2.4, a significant increase in the external concentration ensures that the robustness of cells that is required for simultaneous operation of at least two mechanisms occurs. From the literature, it is known that most potassium ions are transferred passively, but when the extracellular concentration of this ion is doubled, the electrically neutral Na–K–Cl co-transporter becomes functional.

To account for changes in two parameters, one can construct three-dimensional plots of the intracellular concentration of one ion in relation to changes in the external concentrations of the two types of ions. A change in potential will also affect the internal concentration of the desired value because it appears in the expression for determining the intrinsic value of the concentration, and it is an explicit function of external concentrations. When required to consider an effective strategy (i.e., at each moment, only one transport mechanism for each type of ion is present), the strategy will be a set of points on surfaces, which indicate the mechanisms of ion transport, and in this case, we introduce an objective function. Because changing variables (e.g., intracellular concentration and resting potential) differ substantially in value (sometimes by orders of magnitude) and have different dimensions (e.g., concentrations and potential), it is convenient to choose the following as the objective function:

$$\Delta = \sqrt{\sum_i \left(\frac{\Delta n_i}{n_i} \right)^2 + \left(\frac{\Delta \varphi}{\varphi} \right)^2} \rightarrow \min. \quad (2.16)$$

We will use such a criterion when changing the concentrations of two or more ions.

The following is a plot of the work of the transport systems in cardiomyocytes as a function of changes in the extracellular concentrations of potassium and sodium ions and taking into account the change in potential (Fig. 2.5).

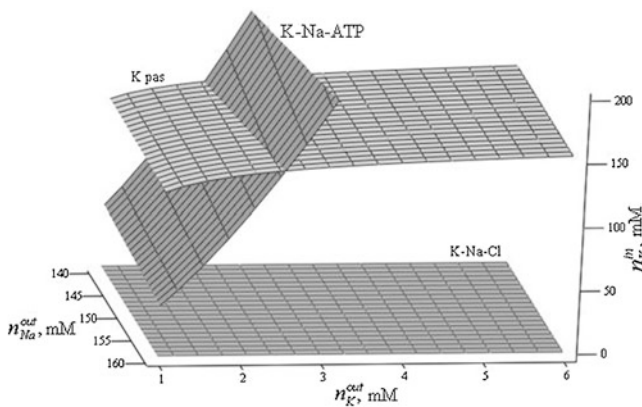


Fig. 2.5 Mechanisms of transport of potassium ions as functions of the external concentrations of two ions

It is evident from the figure that although the values deviate from those that are required for potassium ions, these ions remain passively transported. It may be noted that the ATP-dependent pump allows the required level of internal concentration values to be achieved for different values of the external concentration of sodium ions when the extracellular medium has a low content of potassium ions. However, it is only possible to maintain the normal value by passive transfer of ions through their electrochemical gradient. If a significant increase in the concentration of potassium ions outside the cell occurs, the internal concentration must exceed the normal value to maintain the desired value, and this process should include the K–Na–Cl-co-transporter. It should be noted that when simultaneously including several types of ions in the description and at a changing of two parameters, this picture could change.

2.3 Neurons

The electrical properties of neurons of different organisms that are at rest (i.e., in the absence of nerve impulses) are very similar. The main difference lies in that the external environment of neurons may differ in composition. We distinguish two different examples: mammalian neurons and neurons of marine organisms (e.g., a well-studied neuron of the squid). In the second case, the composition of the fluid surrounding the neuron is near the composition of sea water, which contains significantly more sodium, chloride and magnesium than in the blood of mammals.

Tables 2.3 and 2.4 list the ion concentrations in the neurons of squid and mammals (Raupach and Ballanyi 2004; El-Mallakh 2004; Barish 1991), correspondingly.

In addition to passive transport for all type of ions, neurons contain each of the following types of systems for ion transport (Craciun et al. 2005; Nicholls et al. 2001; Giffard et al. 2000; Chesler 2003):

- $\text{Na}^+ - \text{K}^+ - \text{ATPase}$, $\text{Ca}^{2+} - \text{ATPase}$;
- Co-transporters: $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$, $\text{Na}^+ - \text{Cl}^-$, $\text{Na}^+ - \text{HCO}_3^-$, $\text{K}^+ - \text{Cl}^-$;
- Exchangers: $\text{Na}^+ - \text{Mg}^{2+}$, $\text{Na}^+ - \text{H}^+$, $\text{Na}^+ - \text{Ca}^{2+}$, $\text{Cl}^- - \text{HCO}_3^-$.

Table 2.3 Experimental data on the concentrations of ions for the neurons of squid

Ions	Internal concentrations, mM	External concentrations, mM
Potassium	360	10
Sodium	69	425
Chlorine	157	496
Calcium	0.0001	10
Magnesium	10	50
Bicarbonate	8	25

Table 2.4 Experimental data on the concentrations of ions for the neurons of mammals

Ions	Internal concentrations, mM	External concentrations, mM
Potassium	150	5.5
Sodium	15	150
Chlorine	9	125
Calcium	0.0001	2.5
Magnesium	0.7	1
Bicarbonate	8	25

Value of the membrane potential: (65 ÷ 70) mV

Figure 2.6 shows the major ion transport systems in neurons:

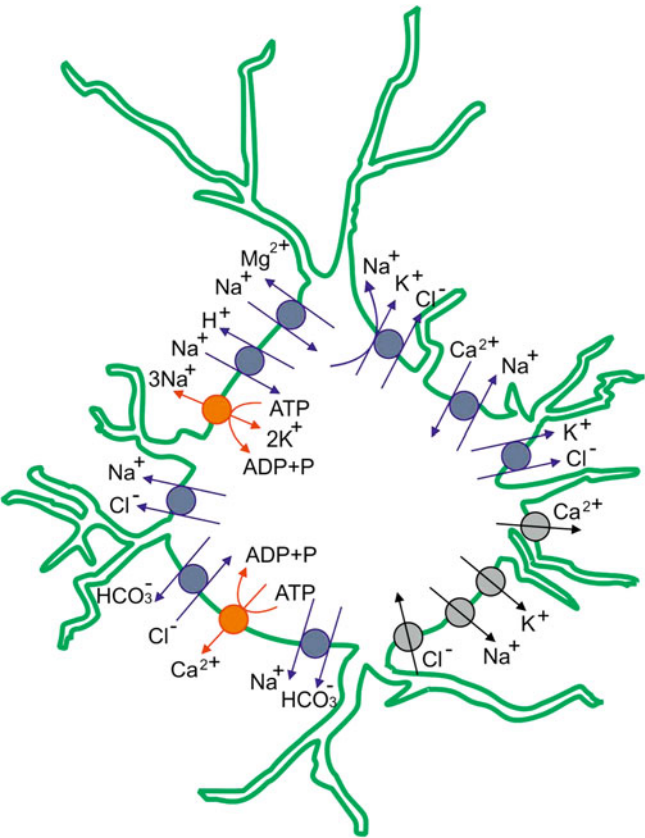


Fig. 2.6 Transport systems in neurons

2.3.1 Model of Transport Systems

Based on the model of active transport of ions that was proposed in the first chapter, the different transport systems for all types of ions are analyzed, the basic system is determined, and the flow of ions is recorded.

The transport of potential-forming ions is first modeled. According to the algorithm, we assume that the sodium ions are transported mainly by the Na–K–ATPase. Potassium is transported by a number of systems: passive transport, the sodium–potassium–chlorine co-transporter, the sodium–potassium pump, or the potassium–chlorine co-transporter. The expressions for the flows that are generated by these systems are similar to what was recorded for cardiomyocytes. Using the known value for the membrane potential and extracellular ion concentrations, the intracellular concentrations of potassium ions are calculated to be the following:

- for the neurons of squid:
 - Na–K–ATP: $n_K^i = 3.9 \cdot 10^3 \text{ mM}$;
 - K–Na–Cl: $n_K^i = 615 \text{ mM}$;
 - K–Cl: $n_K^i = 31.6 \text{ mM}$;
 - Passive flux: $n_K^i = 134.6 \text{ mM}$.
- for the neurons of mammals:
 - Na–K–ATP: $n_K^i = 1.01 \cdot 10^3 \text{ mM}$;
 - K–Na–Cl: $n_K^i = 1.1 \cdot 10^4 \text{ mM}$;
 - K–Cl: $n_K^i = 76.4 \text{ mM}$;
 - Passive flux: $n_K^i = 74.1 \text{ mM}$.

By comparing the calculated values with the known experimental data for the squid neuron, which was 360 mM, and mammalian neurons, which was 150 mM, we note that the minimum deviation results in a passive flow of ions through the membrane. We find that the dependence of the internal concentration of potassium ions and potential on external concentrations will be similar to that which was described for cardiac muscle cells. Therefore, the expression that models the dependence of the internal concentration of sodium ions of neurons will also be analogous to that for the cardiac cell.

Chlorine ions are transferred by the following systems: sodium–chlorine co-transporter, sodium–potassium–chlorine co-transporter, chlorine–bicarbonate exchanger, potassium–chlorine co-transporter, and passive flow of ions through the membrane. The expressions for the flow of chlorine ions that is produced by these systems are similar to those that are recorded in item 2.1. By using the known value of the membrane potential and ion concentrations, the intracellular concentration of chlorine is calculated as the following:

- for neurons of squid (the experimental value for the concentration of chlorine ions is 157 mM):

- K–Na–Cl: $n_{Cl}^i = 205.1 \text{ mM}$;
 - Na–Cl: $n_{Cl}^i = 3.1 \cdot 10^3 \text{ mM}$;
 - K–Cl: $n_{Cl}^i = 13.8 \text{ mM}$;
 - Cl–HCO₃: $n_{Cl}^i = 158.7 \text{ mM}$;
 - Passive flux: $n_{Cl}^i = 36.8 \text{ mM}$.
- for neurons of mammals (the experimental value for the concentration of chlorine ions is 9 mM):
 - K–Na–Cl: $n_{Cl}^i = 75.7 \text{ mM}$;
 - Na–Cl: $n_{Cl}^i = 1.2 \cdot 10^3 \text{ mM}$;
 - K–Cl: $n_{Cl}^i = 4.6 \text{ mM}$;
 - Cl–HCO₃: $n_{Cl}^i = 40 \text{ mM}$;
 - Passive flux: $n_{Cl}^i = 9.3 \text{ mM}$.

For the squid neuron, the minimum deviation from the experimental values provides the electro-neutral exchanger with bicarbonate ions. For mammalian neurons, passive penetration of chloride ions through their electrochemical gradient occurs, thus, the dependence of the internal values of this type of ion on the external values will have the form (2.14). The expression for the squid neuron can be written after the main transport system for HCO₃ is found.

In the literature, the transport of bicarbonate by a chlorine-bicarbonate exchanger, passive transport and sodium-bicarbonate co-transporter (Craciun et al. 2005) has been verified in neurons. Expressions of the fluxes that are created by the first two transport systems are shown above, and the formula for the flow that is generated by the third co-transporter is the following:

$$J_{Na-HCO_3} = C_{Na-HCO_3} \cdot [(n_{HCO_3}^i)^3 n_{Na}^i - \exp(2\varphi)(n_{HCO_3}^o)^3 n_{Na}^o] \quad (2.17)$$

The values for the internal concentrations of HCO₃, which are provided by each mechanism, can be calculated as follows:

- for the neurons of squid:
 - Cl–HCO₃: $n_{HCO_3}^i = 7.9 \text{ mM}$;
 - Na–HCO₃: $n_{HCO_3}^i = 8.1 \text{ mM}$;
 - Passive flux: $n_{HCO_3}^i = 1.9 \text{ mM}$.
- for mammalian neurons:
 - Cl–HCO₃: $n_{HCO_3}^i = 1.8 \text{ mM}$;
 - Na–HCO₃: $n_{HCO_3}^i = 9.5 \text{ mM}$;
 - Passive flux: $n_{HCO_3}^i = 1.9 \text{ mM}$.

The experimental data (8 mM for both neurons) best fits the value that is created by the sodium-bicarbonate co-transporter, in which case, the expression for the intracellular concentration will be the following:

$$n_{HCO_3}^i = n_{HCO_3}^o \exp\left(\varphi + \frac{\Delta\mu_A}{9}\right). \quad (2.18)$$

Subsequently, the dependence of the intracellular concentration of chlorine anions for the neurons of squid can be written as follows:

$$n_{Cl}^i = n_{Cl}^{out} \cdot \frac{n_{HCO}^i}{n_{HCO}^{out}} = n_{Cl}^{out} \exp\left(\varphi + \frac{\Delta\mu_A}{9}\right) \quad (2.19)$$

Two systems exist in neurons for the transport of calcium: the Ca^{2+} -ATPase and the Na^+ - Ca^{2+} -exchanger. Furthermore, the cell membrane is permeable to these ions; therefore, passive penetration of ions occurs. The expressions for the fluxes will be similar to those that were recorded for cardiomyocytes, and the calculated values for the internal concentrations of this ion will be the following:

- for the neurons of squid:
 - Ca-ATP: $n_{Ca}^i = 3.7 \cdot 10^{-6}$ mM;
 - Na-Ca: $n_{Ca}^i = 3.2 \cdot 10^{-3}$ mM;
 - Passive flux: $n_{Ca}^i = 1.8 \cdot 10^3$ mM.
- for the neurons of mammals:
 - Ca-ATP: $n_{Ca}^i = 9.3 \cdot 10^{-7}$ mM;
 - Na-Ca: $n_{Ca}^i = 1.9 \cdot 10^{-4}$ mM;
 - Passive flux: $n_{Ca}^i = 453.2$ mM.

The minimum deviation from the experimental data (for both types of neurons, this value is equal to 0.0001 mM) is provided by the calcium-sodium exchanger; therefore, the expression for calcium ions is the following:

$$n_{Ca}^i = n_{Ca}^o \cdot \left(\frac{n_{Na}^i}{n_{Na}^o}\right)^3 \cdot \exp(\varphi) = n_{Ca}^o \cdot \exp(-2\varphi - \Delta\mu_A). \quad (2.20)$$

The resulting expression is identical to that of the dependence of the internal on external parameters for Ca-ATPase.

No information exists in the literature about the systems of active transport for magnesium in neurons. However, such a system should exist. If it is assumed that magnesium is transported in neurons only by a passive mechanism due to the doubly charged ion of Mg^{2+} , a very large concentration of magnesium ions within the cell will occur. Equation (2.9) can be used to determine the distribution of the passive transfer of magnesium:

$$n_{Mg}^i = n_{Mg}^o \exp(-2\varphi). \quad (2.21)$$

By substituting the values of the experimental data for the values of the potential and extracellular concentration of magnesium ions, we obtain the values

of the internal concentration of magnesium ions: 9.1×10^3 mM for the squid neuron and 181.2 mM for mammalian neurons. This value indicates a clear discrepancy between the experimental data, which is 10 and 0.7 mM, respectively. A similar situation was considered previously for cardiac muscle cells (Melkikh and Sutormina 2008), and it was shown that passive transport of magnesium ions into the cell results in a high concentration of these ions inside the cell and a considerable reduction in the potential across the membrane. In heart muscle cells, a $\text{Na}^+ - \text{Mg}^{2+}$ exchanger is the primary method of transport of magnesium. In view of the above data and based on the considerable similarity of the transport systems in cardiac muscle cells and neurons, we assume that the same exchanger exists in neurons. The ion concentrations that are produced by this exchanger can be calculated by substituting the known experimental data for the neurons in (2.8):

$$n_{Mg}^i = n_{Mg}^o \exp(-\varphi) \frac{n_{Na}^i}{n_{Na}^o} = 109.3 \text{ mM for the neurons of squid, and}$$

$$n_{Mg}^i = n_{Mg}^o \exp(-\varphi) \frac{n_{Na}^o}{n_{Na}^i} = 1.3 \text{ mM for the neurons of mammals,}$$

which is in qualitative agreement with the experimental data. Thus, we can assume that the $\text{Na}^+ - \text{Mg}^{2+}$ exchanger is essential for the transport of magnesium. When the expression for the concentration of sodium ions is taken into account, the dependence on magnesium ions will take the form of (2.10).

By choosing the main transport system, we can derive an equation for the membrane potential of a neuron, which will depend only on the external concentrations of the main potential-forming ions. Note that for both types of neurons, we chose the same main transport systems except for chlorine anions. By substituting the expressions that are obtained for the ions, the condition of electro-neutrality for the squid neuron can be written as follows:

$$\begin{aligned} n_{Ca}^o \cdot \exp(-2\varphi - \Delta\mu_A) + n_{Mg}^o \cdot \exp\left(-2\varphi - \frac{\Delta\mu_A}{3}\right) + n_{Na}^o \exp\left(-\frac{\Delta\mu_A}{3} - \varphi\right) \\ + n_K^o \exp(-\varphi) = (n_{Cl}^o + n_{HCO_3}^o) \exp\left(\varphi + \frac{\Delta\mu_A}{9}\right) + Z_A n_A; \end{aligned} \quad (2.22)$$

and the condition for mammalian neurons can be written as follows:

$$\begin{aligned} n_{Ca}^o \cdot \exp(-2\varphi - \Delta\mu_A) + n_{Mg}^o \cdot \exp\left(-2\varphi - \frac{\Delta\mu_A}{3}\right) + n_{Na}^o \exp\left(-\frac{\Delta\mu_A}{3} - \varphi\right) \\ + n_K^o \exp(-\varphi) = \left(n_{Cl}^o + n_{HCO_3}^o \cdot \exp\left(\frac{\Delta\mu_A}{9}\right)\right) \exp(\varphi) + Z_A n_A. \end{aligned} \quad (2.23)$$

When neglecting the divalent cations because of their small effect on the membrane potential, solutions of these equations can be written as the following:

- for the neurons of squid:

$$\varphi = -\ln \left(\sqrt{\left(\frac{Z_A n_A}{2(n_{Na}^o \cdot \exp(-\frac{\Delta\mu_A}{3}) + n_K^o)} \right)^2 + \frac{(n_{Cl}^o + n_{HCO_3}^o) \cdot \exp(\frac{\Delta\mu_A}{9})}{2(n_{Na}^o \cdot \exp(-\frac{\Delta\mu_A}{3}) + n_K^o)}} + \frac{Z_A n_A}{2(n_{Na}^o \cdot \exp(-\frac{\Delta\mu_A}{3}) + n_K^o)} \right). \quad (2.24)$$

- for mammalian neurons:

$$\varphi = -\ln \left(\sqrt{\left(\frac{Z_A n_A}{2(n_{Na}^o \cdot \exp(-\frac{\Delta\mu_A}{3}) + n_K^o)} \right)^2 + \frac{n_{Cl}^o + n_{HCO_3}^o \cdot \exp(\frac{\Delta\mu_A}{9})}{2(n_{Na}^o \cdot \exp(-\frac{\Delta\mu_A}{3}) + n_K^o)}} + \frac{Z_A n_A}{2(n_{Na}^o \cdot \exp(-\frac{\Delta\mu_A}{3}) + n_K^o)} \right). \quad (2.25)$$

Currently, the intracellular concentration of non-penetrative anions is unknown, but we can calculate this value by using the electro-neutrality condition of the internal environment:

$$n_A = n_{Na}^i + n_K^i - n_{Cl}^i - n_{HCO_3}^i.$$

When substituting the concentrations of sodium, potassium, bicarbonate and chloride ions outside of cells and the intracellular concentrations of non-penetrative ions, we obtain a value for the resting potential of a mammalian neuron of approximately—86.7 mV, and the potential value for the squid neuron would be approximately—85.1 mV. The obtained results from the calculations for the concentrations and potentials for squid and mammalian neurons are shown in Tables 2.5 and 2.6, respectively.

Although deviations from the experimental data are high, we have achieved satisfactory agreement between theory and experiment.

Table 2.5 Comparison of the experimental and calculated values of the internal ion concentrations and potential for squid neurons

Ions	Experimental data, mM	Calculated data, mM
Potassium	360	135
Sodium	69	7.3
Chlorine	157	158.7
Calcium	10^{-4}	3.7×10^{-6}
Magnesium	10	11.5
Bicarbonate	8	17.1
Potential, mV	$-(65 \div 70)$	−86.7

Table 2.6 Comparison of experimental and calculated values for the internal ion concentrations and potentials of mammalian neurons

Ions	Experimental data, mM	Calculated data, mM
Potassium	150	74
Sodium	15	2.6
Chlorine	9	9,3
Calcium	10^{-4}	9.3×10^{-7}
Magnesium	0.7	0.2
Bicarbonate	8	17.1
Potential, mV	$-(65 \div 70)$	-85.1

2.3.2 Model of Ion Transport with a Restriction of Deviation from the Experimental Data

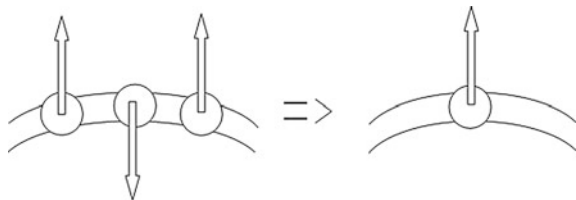
In some cases, the accuracy of calculating the internal concentrations of ions and resting potential based on the algorithm “one ion—one transport system” may not be sufficient. In this case, we use a special method to find dependencies of the intracellular on the external concentrations; and this method is referred to as “equivalent transporter”. In a situation where it is not possible to choose a main mechanism of ion transport, we assume that two transporters work simultaneously and that when both work together, they give the most significant contribution to the overall result. In other words, two or more transport systems are replaced by one whose action is equivalent to their combined actions, as is schematically shown in Fig. 2.7:

The flux that is produced by an “equivalent mechanism” for the j th type of ion will be the following:

$$J = C_j(n^i \exp(\Delta\mu_j - A\varphi) - n^o) \quad (2.26)$$

where A is the charge of the transported ions, and $\Delta\mu_j$ is the EMF (electromotive force) of the equivalent mechanism. To find the parameter $\Delta\mu_j$, we can use the concentrations inside and outside of the cell that were obtained experimentally. The desired relationship is used to find the potential as a function of the extracellular concentration.

One type of ion, such as potassium ions, being simultaneously transported by several systems is much more difficult to solve analytically. In this case, unknown

Fig. 2.7 Equivalent transport mechanism

constants, which take into account the speed of the pumps, appear in the equations. We make the following assumption, which can significantly improve the accuracy of the algorithm: combine several active transport mechanisms for potassium ions in an “equivalent pump.” The result of such a pump would be the distribution of potassium ions inside the cell, which would differ from its passive distribution. The expression for the intracellular concentration, which takes into account active and passive transport, can be written as follows:

$$n_K^i = n_K^o \exp(\Delta\mu_K - \varphi) \quad (2.27)$$

where $\Delta\mu_K$ —is the effective potassium EMF. From this expression and by using known ion concentrations inside and outside the cell, we can find the value of the EMF of potassium ions and further to use this expression to calculate the potential and the intracellular concentrations of other ions. For the squid neuron, $\Delta\mu_K = 0.984$, and for mammalian neurons, $\Delta\mu_K = 0.706$.

The expression for calculating the intracellular concentration of sodium ions, which is generated by the Na–K-ATPase, takes into account the equivalent transport system for potassium ions and takes the following form:

$$n_{Na}^{in} = n_{Na}^{out} \exp\left(\frac{2 \cdot \Delta\mu_K}{3} - \varphi - \frac{\Delta\mu_A}{3}\right). \quad (2.28)$$

By substituting the known values and the calculated EMF, we obtain the following values for the intracellular concentrations of sodium ions: 14 mM for the neurons of squid and 4.1 mM for mammalian neurons. The obtained values correspond better to the experimental data (69 and 15 mM, respectively) than those that were calculated in the previous section.

The values of the concentrations of calcium ions, which were generated by the sodium-calcium exchanger, can be recalculated by altering the expression for sodium ions:

$$n_{Ca}^i = \exp(\varphi) \cdot n_{Ca}^o \cdot \left(\frac{n_{Na}^i}{n_{Na}^o}\right)^3 = n_{Ca}^o \exp(-2 \cdot \varphi - \Delta\mu_A + 2 \cdot \Delta\mu_K) \quad (2.29)$$

By substituting the known data, it is evident that the intracellular concentration of calcium ions in the neurons of squid will be equal to 2.7×10^{-5} mM, and in mammalian neurons, this concentration would be equal to 3.8×10^{-6} mM (0.0001 mM is the experimental value in both neurons).

Similarly, the dependence of intracellular on external concentrations of magnesium ions will change as follows:

$$n_{Mg}^i = n_{Mg}^o \cdot \exp(-\varphi) \cdot \frac{n_{Na}^i}{n_{Na}^o} = n_{Mg}^o \cdot \exp\left(\frac{2}{3} \cdot \Delta\mu_K - 2\varphi - \frac{\Delta\mu_A}{3}\right) \quad (2.30)$$

As a result, for these ions, we find that in squid neurons, the intracellular concentration is equal to 22.2 mM, and in mammalian neurons, this value is 0.4 mM (the experimental data is 10 and 0.7 mM, respectively).

The condition of electro-neutrality can be written as follows:

- for the neurons of squid:

$$\begin{aligned} n_{Na}^{\circ} \exp\left(\frac{2 \cdot \Delta\mu_K}{3} - \frac{\Delta\mu_A}{3} - \varphi\right) + n_K^{\circ} \exp(\Delta\mu_K - \varphi) \\ = \left(n_{Cl}^{\circ} + n_{HCO_3}^{\circ}\right) \exp\left(\varphi + \frac{\Delta\mu_A}{9}\right) + Z_A n_A \end{aligned} \quad (2.31)$$

- for the neurons of mammals:

$$\begin{aligned} n_{Na}^{\circ} \exp\left(\frac{2 \cdot \Delta\mu_K}{3} - \frac{\Delta\mu_A}{3} - \varphi\right) + n_K^{\circ} \exp(\Delta\mu_K - \varphi) \\ = \left(n_{Cl}^{\circ} + n_{HCO_3}^{\circ} \cdot \exp\left(\frac{\Delta\mu_A}{9}\right)\right) \cdot \exp(\varphi) + Z_A n_A \end{aligned} \quad (2.32)$$

The explicit expressions for the potential will be written as follows:

- for the neurons of squid:

$$\varphi = -\ln \left(\sqrt{\left(\frac{Z_A n_A}{2 \left(n_{Na}^{\circ} \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right) + n_K^{\circ} \cdot \exp(\Delta\mu_K) \right)} \right)^2 + \frac{(n_{Cl}^{\circ} + n_{HCO_3}^{\circ}) \cdot \exp(\Delta\mu_A/9)}{2 \left(n_{Na}^{\circ} \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right) + n_K^{\circ} \cdot \exp(\Delta\mu_K) \right)} + \frac{Z_A n_A}{2 \left(n_{Na}^{\circ} \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right) + n_K^{\circ} \cdot \exp(\Delta\mu_K) \right)}} \right) \quad (2.33)$$

- for the neurons of mammals:

$$\varphi = -\ln \left(\sqrt{\left(\frac{Z_A n_A}{2 \left(n_{Na}^{\circ} \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right) + n_K^{\circ} \cdot \exp(\Delta\mu_K) \right)} \right)^2 + \frac{n_{Cl}^{\circ} + n_{HCO_3}^{\circ} \cdot \exp(\Delta\mu_A/9)}{2 \left(n_{Na}^{\circ} \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right) + n_K^{\circ} \cdot \exp(\Delta\mu_K) \right)} + \frac{Z_A n_A}{2 \left(n_{Na}^{\circ} \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right) + n_K^{\circ} \cdot \exp(\Delta\mu_K) \right)}} \right) \quad (2.34)$$

By substituting the external concentrations of the main ions and the calculated EMF for potassium, we obtain the following values of the potential: -68.7 mV for

Table 2.7 Comparison of the experimental and calculated values of the internal ion concentrations and potential for squid neurons

Ions	Experimental data, mM	Calculated data, mM
Sodium	69	14
Calcium	10^{-4}	2.7×10^{-5}
Magnesium	10	22.2
Potential, mV	$-(65 \div 70)$	-68.7

Table 2.8 Comparison of the experimental and calculated values for the internal ion concentrations and potential for mammalian neurons

Ions	Experimental data, mM	Calculated data, mM
Potassium	15	4.1
Calcium	10^{-4}	3.8×10^{-6}
Magnesium	0.7	0.4
Potential, mV	$-(65 \div 70)$	-70.7

squid neurons and -70.7 mV for mammalian neurons. These results are in good agreement with the experimental data.

The results from calculating the concentrations and potential when using an “equivalent potassium pump” for squid and mammalian neurons are shown in Tables 2.7 and 2.8, respectively. The tables show only those ions with altered concentrations by using the algorithm for the potassium EMF.

2.3.3 Regulation of Ion Transport

According to our algorithm, we can construct a model for the regulation of ion transport in the neurons of mammals. Transport systems in neurons, such as the sodium ion transport system, were identified earlier, and graphs of this ion transport mechanism are shown on Fig. 2.8.

The figure shows the intracellular concentration after change α of sodium ions in the external medium. Symbols in the figure are as follows: the solid red line indicates the required value of the intracellular concentration, blue dots represent the work of the K-Na-ATPase, the green dotted line represents the work of the co-transporter for Na-HCO₃; and the purple dash-dot line refers to the Na-Ca-exchanger.

When switching transport systems, it is advantageous for a cell to maintain only one active mechanism to be effective in energy consumption. In this case, a strategy of switching must be constructed that gives the smallest deviation from the desired value, assuming that one transport system works (Fig. 2.9).

The graph shows that when the external sodium ion concentration is reduced by about approximately 30 % of the normal level the calcium ion exchanger works.

Fig. 2.8 Mechanisms of sodium transfer in neurons

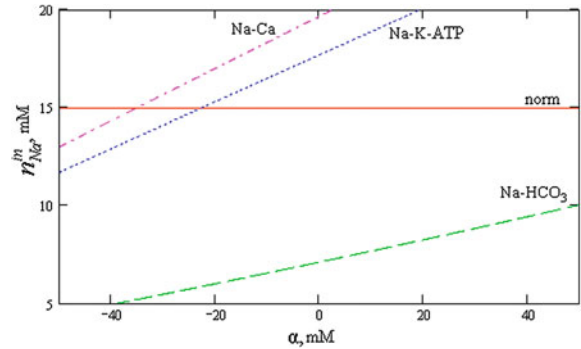
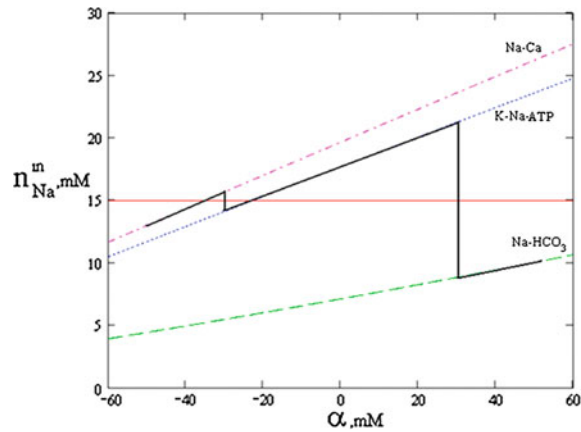


Fig. 2.9 Strategy of sodium ion transport in neuron regulation



Furthermore, the ATP-dependent pump effectively works in a sufficiently large range of extracellular concentrations of sodium but only when in excess of the normal value. When the external sodium concentration is large, the Na–HCO₃ symporter works.

However, during such a strategy, a significant change in the intracellular concentration of sodium takes place, which results in a deviation from the normal value by nearly 50 % and may be detrimental to vital cells. If the tolerance of the internal concentration of sodium is limited to an interval of 30 % in both directions, then it needs to perform ion transport by two mechanisms in a range of external concentrations (Fig. 2.10).

In the figure, the dotted line separates the region of tolerance values for the intracellular concentrations of sodium. It is observed when the external sodium ion concentration increases by 20 mM or more to maintain the desired value of the internal concentration is only possible by the simultaneous operation of the ATP-dependent pump and Na–HCO₃ co-transporter. Additionally, when this increase (more than 55 mM $\approx$ 40 % of the normal value) exceeds the external concentration of sodium ions, the sodium-bicarbonate co-transporter can maintain the necessary internal concentration in the absence of other transport systems.

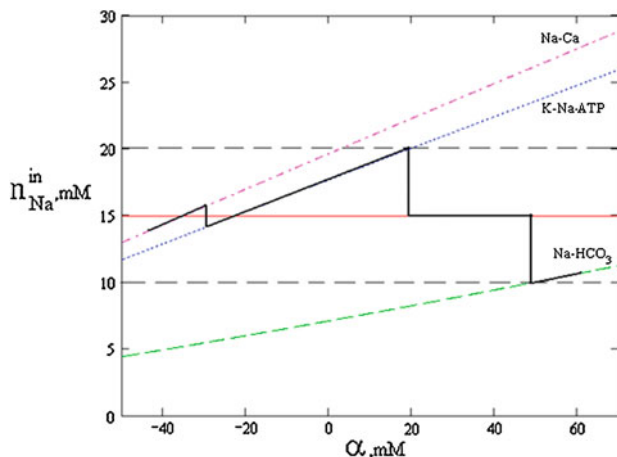


Fig. 2.10 Strategy of sodium ion regulation with a restriction of maximum deviations from the normal values

Graphs show how transport systems work at the changes in the extracellular concentrations (Fig. 2.11).

From the figure and by taking into account (2.17), it is evident that in a certain range of external low concentrations of sodium, the $\text{Na}^+ - \text{Ca}^{2+}$ -exchanger is sufficient. When the ion content in the external environment increases, the ATP-dependent pump requires for maintaining ion balance; co-transport is able to maintain the necessary intracellular concentration only after a greater increase in the extracellular concentration of sodium ions.

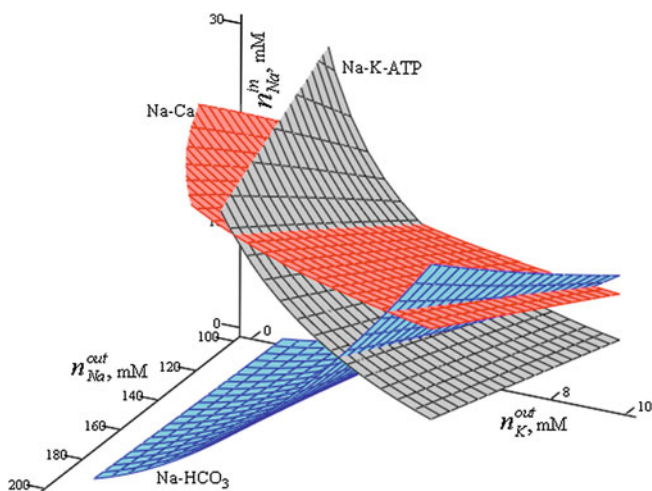


Fig. 2.11 Systems of sodium transport in neurons as a function of the external concentrations of two ions

2.4 Erythrocytes

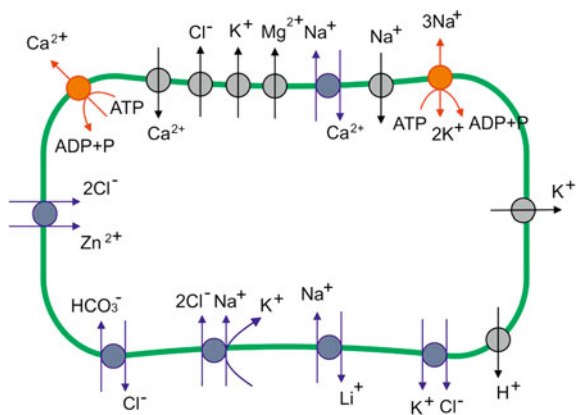
The current red blood cell model includes (see, for example, (Jamshidi et al. 2001)) 36 independent variables that are described in the main biochemical pathways in the human erythrocyte. Transport of ions through the red blood cell (RBC) membrane is also included in this system of equations (Werner and Heinrich 1985; Joshi and Palsson 1989; Jamshidi et al. 2002; Mulquiney et al. 1999; Lew and Bookchin 1986). The goal of systems biology is a comprehensive description of a cell (or an organism) through mathematical methods by the use of computers. Currently, systems biology of RBCs is concerned mainly with gene and metabolic networks of cells; however, the transport subsystem of RBCs has not been studied sufficiently.

2.4.1 Model of Ion Transport

In red blood cells, ion transport includes the following transport systems (Freedman 2001; El-Mallakh 2004; Freedman and Hoffman 1979): ATP-dependent pumps (Ca^{2+} -ATP-pump; Na^{+} - K^{+} -ATP-pump), exchangers (K^{+} - Cl^{-} -symporter; Na^{+} - Ca^{2+} -antiporter; K^{+} - Na^{+} - Cl^{-} -symporter; Cl^{-} - Zn^{2+} -symporter; HCO_3^{-} - Cl^{-} -antiporter; and Na^{+} - Li^{+} -antiporter), and passive transportation for all types of ions (Fig. 2.12).

Based on the proposed algorithm, we shall discuss the transport systems that transfer potential-generating ions in a red blood cell. Because the nonequilibrium state in a cell is provided by the consumption of energy in the form of ATP, it is necessary to choose an ATP-dependent pump as one of the main methods of transport. Therefore, the expression for the flux of sodium ions that is created by the pump may be written as the following equation:

Fig. 2.12 Ion transport systems in RBCs



$$J_{Na-K-ATP} = C_{Na-K-ATP} \left[\exp(\Delta\mu_A + \varphi) (n_{Na}^i)^3 (n_K^o)^2 - (n_{Na}^o)^3 (n_K^i)^2 \right], \quad (2.35)$$

where $C_{Na-K-ATP}$ is the constant of the active transport of sodium and potassium ions.

This system may be the main method of transport for sodium or potassium ions. By setting the flux (2.35) equal to zero and using the experimental data on the potassium ions inside and outside of a cell and the extracellular sodium ion concentration, we calculate the concentration of internal sodium to be $n_{Na}^i = 6.1$ mM. Similarly, we calculate the concentration of potassium ions, which is created by this transport system when in equilibrium, as $n_K^i = 279$ mM. After comparing both calculated quantities with the experimental data ($n_{Na}^i = 10$ mM, $n_K^i = 135$ mM), we chose the ATP-dependent pump as the main method of transport of sodium ions.

Three systems exist that transport potassium ions: $Na^+-K^+-ATPase$, and K^+-Cl^- and $K^+-Na^+-Cl^-$ —co-transporters, and the permeability of the membrane provides a passive flux of ions along the electrochemical gradient. The expressions for the fluxes that are created by other mechanisms (except ATPase) can be written separately.

$$J_{K-Cl} = C_{K-Cl} \cdot [n_K^i \cdot n_{Cl}^i - n_K^o \cdot n_{Cl}^o], \quad (2.36)$$

$$J_{K-Na-Cl} = C_{K-Na-Cl} \cdot [n_{Na}^i \cdot n_K^i \cdot (n_{Cl}^i)^2 - n_{Na}^o \cdot n_K^o \cdot (n_{Cl}^o)^2], \quad (2.37)$$

$$J_{Kpas} = P_K \cdot [n_K^i \cdot \exp(\varphi) - n_K^o], \quad (2.38)$$

here and elsewhere, P_i is the constant of passive transport for the i th type of ions along their electrochemical gradient. The values of the internal concentrations of potassium ions that are created by each mechanism are as follows:

- K-Cl: $n_K^i = 5.1$ mM;
- K-Na-Cl: $n_K^i = 97.5$ mM;
- passive flow: $n_K^i = 5.7$ mM.

After comparing the results with the experimental data (135 mM), we determine that the $K^+-Na^+-Cl^-$ —co-transporter is the main transport system for potassium. We can obtain the explicit form of the dependencies of the internal on the external concentrations and the membrane potential for Na^+ and K^+ by solving the system of two equations that describe the work of the mechanisms that were chosen: the ATPase and co-transporter. However, doing so requires the explicit form of the dependence of the internal on the external parameters for chlorine ions.

Similarly, we shall consider chlorine ion transport, which is provided by the following co-transporters: K^+-Cl^- , $K^+-Na^+-Cl^-$, and $Cl^- - Zn^{2+}$, the anti-porter $HCO_3^- Cl^-$ and passive flux through a membrane. By comparing those types of transport with the experimental data, we can conclude that the largest contribution to the required concentration of chlorine ions is made by its passive flux or their

exchange for bicarbonate ions. In this case, chlorine ions are transported passively, and the dependence of the internal on the external concentration will be represented by the following equation:

$$n_{Cl}^i = n_{Cl}^o \exp(\varphi). \quad (2.39)$$

The explicit forms of the dependencies of the internal concentrations of sodium and potassium ions can be written as the following equations:

$$n_{Na}^i = n_{Na}^o \exp\left(-\frac{3}{5}\varphi - \frac{\Delta\mu_A}{5}\right), \quad (2.40)$$

$$n_K^i = n_K^o \exp\left(-\frac{2}{5}\varphi + \frac{\Delta\mu_A}{5}\right). \quad (2.41)$$

The transport of bicarbonate ions across the red blood cell membrane, apart from passive penetration, is implemented by their exchange with chlorine ions. Calculations showed that the required concentration is created by passive flux, and the expression for the internal concentration of HCO_3 will be the following:

$$n_{\text{HCO}_3}^i = n_{\text{HCO}_3}^o \exp(\varphi). \quad (2.42)$$

There is currently no published information concerning the systems of active magnesium ion transport. By considering the transport of these ions as passive, we determine the value of the internal magnesium ion concentration to be 3.5 mM. These results satisfactorily coincide with the experimental data (2.5 mM) for magnesium ions; therefore, we may consider passive flux as the main transport system for this type of ion.

The transport of lithium ions into a cell is provided by its exchange with sodium; however, passive flux of these ions also exists. After comparing the internal concentration of lithium ions ($0.7 \div 1.0$ mM) that is created separately (0.007 mM and 0.06 mM, respectively), we determined that the passive flow of these ions along their electrochemical gradient is the main transport system for such ions.

Similar reasoning for protons gives the value of their internal concentration as 0.061 mM, and these results satisfactorily coincide with the experimental data ($n_H^i = 0.062$ mM). Therefore, we may consider passive flux as the main transport system for protons.

The flux of zinc ions is provided by the work of a co-transporter that also transports chlorine and passive membrane permeability. However, the calculated value of the internal concentration that is created by the co-transporter better coincides with the experiment results.

Three ways to transport doubly charged calcium cations in a red blood cell exist: active transport with ATP energy consumption, passive transport, and transport in exchange for sodium ions.

- Ca-ATP: $n_{Ca}^i = 9.8 \cdot 10^{-8}$ mM;
- Na–Ca: $n_{Ca}^i = 2.4 \cdot 10^{-4}$ mM;
- passive flow: $n_{Ca}^i = 2.4$ mM.

The best coincidence with the experimental data (i.e., the Ca^{2+} concentration in a red blood cell ranges from $(30 \div 60) \times 10^{-6}$ mM) is provided by the $\text{Na}^+ - \text{Ca}^{2+}$ exchanger. Thus, the expression for the dependence of the internal concentration of sodium ions on the membrane potential and external concentration of sodium ions will be the following:

$$n_{Ca}^i = \exp(\varphi) \cdot n_{Ca}^o \left(\frac{n_{Na}^i}{n_{Na}^o} \right)^3 = n_{Ca}^o \cdot \exp \left(-\frac{4}{5} \cdot \varphi - \frac{3 \cdot \Delta\mu_A}{5} \right) \quad (2.43)$$

Thus, we can calculate the intracellular concentrations of the main ions that are transported through the RBC membrane (Freedman 2001; El-Mallakh 2004; Freedman and Hoffman 1979), and these obtained values have been tabulated (Table 2.9).

When taking into account all the ion types that are present in a cell, the electro-neutrality condition for the internal environment of a cell can be written as the following equation:

$$n_{Na}^{in} + n_K^{in} + 2n_{Ca}^{in} + 2n_{Mg}^{in} - n_{Cl}^{in} - n_{HCO}^{in} + n_{Li}^{in} + n_H^{in} + 2n_{Zn}^{in} - Z_A n_A = 0, \quad (2.44)$$

where $Z_A n_A$ is the product of the charge and the concentration of non-penetrating, intracellular anions. From this expression, we can obtain the analytical dependency of the resting potential of the cell membrane as a function of the external concentration; however, the conclusion for analytical dependency seems to be complex if we do not neglect bivalent cations.

After numerically solving the expression, we calculate the potential of the red blood cell membrane to be -10.88 mV (Freedman 2001), which is in good agreement with the experimental data.

Table 2.9 Comparison of the experimental and calculated values of the internal concentrations of ions in RBCs

Ions	Experimental data, mM	Calculated* data, mM
Sodium	10	6.1
Potassium	135	97.5
Chlorine	78	69.6
Bicarbonate	16	16.3
Magnesium	2.5	3.5
Lithium	$0.7 \div 1.0$	0.06
Protons	0.062	0.061
Zink	0.024	0.028
Calcium	$(30 \div 60) \times 10^{-6}$	53×10^{-6}

*The membrane potential value (-11 mV) that was obtained experimentally was used

The calculations were made using $\Delta\mu_A = 17$, which is based on the best agreement of the concentrations and potential with the experimental data; however, this value is somewhat less than the conventional value of $\Delta\mu_A = 20$ for different types of cells. It is necessary to take into consideration that RBCs do not have mitochondria; therefore, ATP molecules should be transported inside this organelle by specific proteins. Hence, we can conclude that in a red blood cells, the $\Delta\mu_A$ should be less than in other cells.

2.4.2 Model of Regulation of Ion Transport: Efficiency or Robustness?

To simulate the processes of regulation, we shall consider the two extremities and realize that the actual cell behavior strategies are a combination of these behaviors.

The model that was constructed in Sect. 2.3.1 largely coincides with the experimental data; however, we cannot affirm that when environmental changes occur, this model will give reliable results.

According to the proposed algorithm, all of the transport systems for potassium ions in a red blood cell are considered, and the internal concentrations of potassium ions form dependencies on the external ions for each transport system. In doing so, we shall also take into consideration the potential change (Fig. 2.13).

The figure shows the dependencies of the internal concentration of potassium ions on an α change of K ion concentration in the environment. The figure legend is as follows: the required value of the intracellular concentration is shown by a solid red line; the work of the K–Na–ATPase is represented by blue dots; and K–Na–Cl-co-transport is represented by a green, dashed line.

For energy-effective work, it is profitable for a cell to keep only one transport mechanism functional. A strategy of switching for this case supposes that an ion transport system works that gives the least deviation from the required value (Fig. 2.14).

Fig. 2.13 The dependencies of the internal concentration of potassium ions on K–Cl α , which are additive in the external environment when two different transport systems are functional

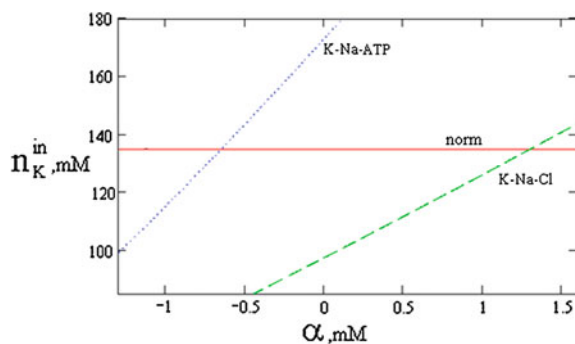
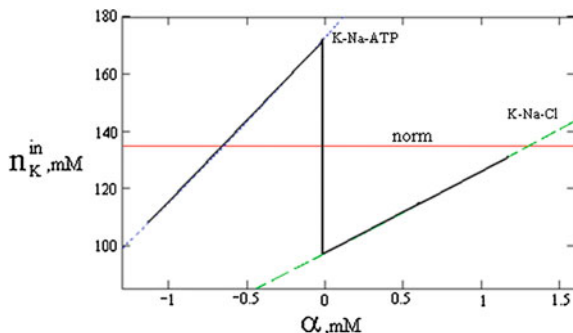


Fig. 2.14 The strategy of regulation of potassium ion transport. α is the change of the external concentration of potassium ions



The dotted and dashed lines show the changes in the internal concentration that are conditioned by the work of the K–Na–ATPase and K–Na–Cl-co-transporters.

The graph shows that when the extracellular concentration of potassium ions is reduced, the ATP dependent pump works, but when this concentration increases, the K–Na–Cl-co-transporter is switched on. We make this conclusion because, at a deviation of 35 %, only one transport system is required to maintain the internal concentration.

Generally, a concentration change of at least one ion outside of a cell results in a change in the concentrations of all of the internal ions due to a change in potential. Therefore, it is important to study the dependence of the concentration of one ion in a cell on the change in the concentrations of two ions outside of the cell. The dependence of the intracellular concentration of potassium ions on the change of the external concentrations of potassium and sodium ions was plotted. In this case, the sought-for strategy will be the one that is maximally effective at each moment when only one transport mechanism is functional and will consist of a set of dots on planes that designate the mechanisms of ion transport that differ minimally from the normal value in relative units. Thus, for each value of extracellular concentration of an ion, a point on one plane will represent the work of the transport mechanisms, which is as close as possible to the specified parameters.

The algorithm for simulation of the ion transport regulation processes in a cell for a three-dimensional case is similar to that for a two-dimensional case.

From the Fig. 2.15, we can conclude that when the concentration of potassium ions is low in the extracellular environment, it is necessary to spend energy to provide the required intracellular concentration for any amount of sodium ions. In other words, the difference in Na^+ concentrations is not sufficient to maintain the normal level of potassium ions in a cell. When K^+ levels are sufficient in the cellular environment, a switch takes place from an ATPase-dependent system to a co-transporter-dependent system, and the energy consumption for maintaining the intracellular balance of K^+ concentrations decreases, which indirectly confirms our supposition concerning “selection” by a cell for the most effective systems of ion transport. Furthermore, the co-transporter switches on when the external concentration of potassium ions increases.

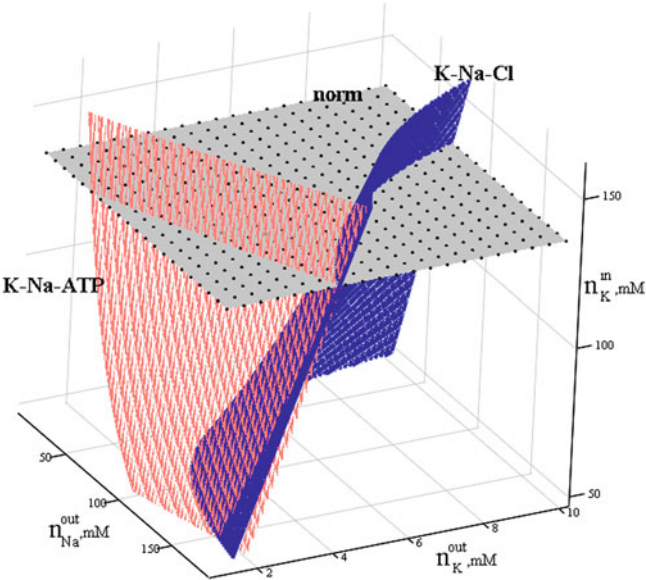
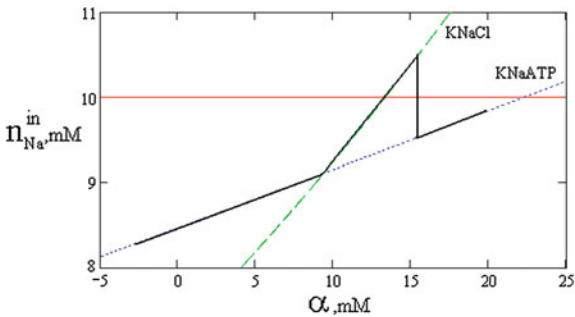


Fig. 2.15 The dependence of the internal concentrations of potassium and sodium ions in the environment for different transport mechanisms

Fig. 2.16 The strategies for Na^+ transport regulation



Similarly, the transportation of Na^+ will be discussed with the supposition that sodium is added with chlorine. Two systems for Na^+ transport are capable of creating concentrations of this ion that are similar to the experimental value: the K-Na-ATPases and the K-Na-Cl-co-transporter.

In Fig. 2.16 α is the change in the Na^+ external concentration; and the dotted and dashed lines indicate the changes in the internal concentration that are conditioned by the work of the K-Na-ATPases and K-Na-Cl-co-transporter, respectively.

As follows from Fig. 2.16, the use of the K-Na-ATPase is the optimal mechanism for a defined concentration, but the K-Na-Cl-co-transporter functions when the external concentration of sodium ions increases to above 10 % of the normal value. Afterward, the ATP dependent pump switches on again.

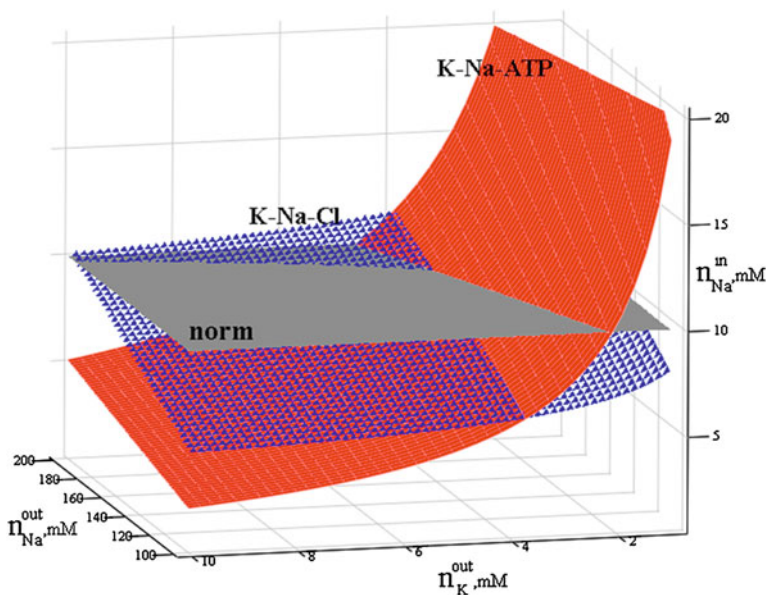


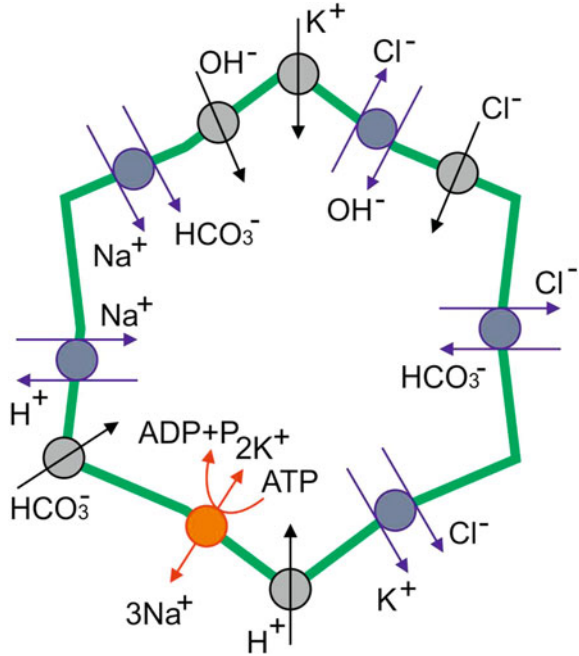
Fig. 2.17 The Na^+ transport systems as functions of the extracellular concentrations of two ions

The three-dimensional model in the figure shows that the main transport system for sodium ions is the ATP-dependent pump. In the short range of small values of K^+ external concentrations and when the external concentrations of both cations increase considerably (by approximately 30 % or more), K–Na–Cl-co-transport is sufficient to provide the required concentration of external Na^+ ions.

As is clear from Figs. 2.15 and 2.17, when there is an excessive amount of both cations in the environment, their homeostasis in a cell can be provided without energy consumption. But when the values of their external concentrations are small, ATP energy is required.

According to the experimental data, the speed of the different transport systems (including red blood cells) depends significantly on the ionic composition of their cells and their environment. For example, according to previous work (Freedman 2001, Lluch et al. 1996, Sriboonlue et al. 2005), the rate of the Na^+ – K^+ -pump and Na^+ – K^+ – Cl^- -cotransporter in erythrocytes significantly changes when the environmental NaCl concentration is altered, i.e., switching from one transport system to another takes place. In addition, the cell volume depends on the concentration of NaCl or KCl in the environment. For example, regulation of the volume that occurs due to an increase (or decrease) in the speed of the various transport systems is well known for a variety of cells (see Alvarez-Leefmans 2001; Garcia-Romeu et al. 1991; Hoffman and Dunham 1995; Swietach et al. 2010; MacManus et al. 1995; Yachie-Kinoshita et al. 2010) and in particular, for red blood cells (Freedman 2001, Baumgarten and Feher 2001; Sarkadi and Parker 1991; Gusev et al. 1996).

Fig. 2.18 Mechanisms of ion transport in hepatocytes



2.5 Hepatocytes

A model for active transport of ions across the membrane of hepatocytes has been published previously (Melkikh and Sutormina 2010). Here, we only present the main results that are needed to analyze the possible strategies for regulation.

Several transport systems exist in hepatocytes (Fossat et al. 1997; Murphy et al. 1980; Furimsky et al. 2000) such as the Na–K–ATP pump, the Na–H, Cl–HCO₃ and OH–Cl exchangers, and the Na–HCO₃ and K–Cl co-transporters. All of these systems are shown schematically in Fig. 2.18.

We will consider only the transport of ions that play a major role in the formation of the resting potential on the cell membrane. Furthermore, we will consider only K⁺, Na⁺, Cl[–] and HCO₃[–] as the main ions for this cell type. Other ions will be neglected because their contributions to the potential are negligible. In Table 2.10, the values of the concentrations of the major ions and the resting potential for rat liver cells according to Sillau et al. (1996) are listed.

2.5.1 Model for Ion Transport

Four transport systems are known to carry sodium ions in hepatocytes: the Na–K–ATPase, the Na–H exchanger, the Na–HCO₃ co-transporter and passive flow. The

Table 2.10 Experimental data for ion concentrations and potential in hepatocytes

Ions	Internal concentrations, mM	External concentrations, mM
Sodium	29	143
Potassium	166	4
Chlorine	20	120
Bicarbonate	25	27
Potential, mV		−49.8

contribution of the ATP-dependent pump in the formation of the internal sodium ion concentration will be considered as the most significant, and the pump itself is the main transport mechanism for this type of ion.

When selecting the main transport system for potassium ions, we assumed that hepatocytes act similar to neurons and introduced an “equivalent transporter”, which is an expression that is similar to (2.28). Using the experimental value of the concentration of potassium ions on both sides of membrane we calculated that the value of the potassium EMF must be 1.73.

The dependence of the internal concentration of sodium ions on the external concentration, when an “equivalent transporter” is used, of potassium ions will be similar to that shown for the neuron (2.29).

The transport of chloride ions is provided by the Cl-HCO_3 and OH-Cl exchangers, the K-Cl co-transporter and passive transport through the membrane. The experimental data best fit the concentration that is created due to passive penetration of chloride ions through the membrane on the electrochemical gradient.

Transport of bicarbonate is provided by addition to the passive flow by the Cl-HCO_3 exchanger and Na-HCO_3 co-transporter, and the Cl-HCO_3 exchanger provided the minimum deviation from the experimental data.

For further calculations, the concentrations of non-penetrating anions must be determined. To calculate these concentrations, it is assumed that the pressure difference inside and outside of a mammalian cell can be neglected. Therefore, the condition of pressure equality on the membrane is written as follows:

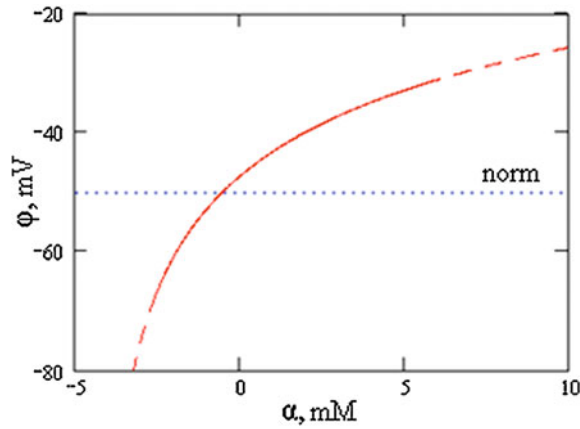
$$n_{Na}^i + n_K^i + n_{Cl}^i + n_{HCO_3}^i + n_A = n_{Na}^o + n_K^o + n_{Cl}^o + n_{HCO_3}^o \quad (2.45)$$

From this equation, the concentration of non-penetrating ions can be calculated. Additionally, if the expressions that are obtained for the intracellular concentration of chloride ions, sodium, potassium, and bicarbonate are substituted, we obtain the following expression for the potential:

$$n_K^o \exp(\Delta\mu_K - \varphi) + n_{Na}^o \exp\left(2\frac{\Delta\mu_K}{3} - \varphi - \frac{\Delta\mu_A}{3}\right) - n_{Cl}^o \cdot \exp(\varphi) - n_{HCO_3}^o \cdot \exp(\varphi) - Z_A n_A = 0 \quad (2.46)$$

Then, the analytic dependence of the resting potential of cells on the external concentration is represented by the following equation:

Fig. 2.19 Changing of potential in hepatocytes is dependent on the addition of potassium ions into the environment



$$\phi = \ln \left[\sqrt{\left(\frac{-Z_A n_A}{2 \cdot (n_{Cl}^o + n_{HCO_3}^o)} \right)^2 + \frac{n_K^o \cdot \exp(\Delta\mu_K) + n_{Na}^o \cdot \exp\left(\frac{2\Delta\mu_K}{3} - \frac{\Delta\mu_A}{3}\right)}{2 \cdot (n_{Cl}^o + n_{HCO_3}^o)}} - \frac{Z_A n_A}{2 \cdot (n_{Cl}^o + n_{HCO_3}^o)} \right] \tag{2.47}$$

By numerically solving this equation, we obtain the potential value of -47.4 mV, which agrees well with the experimental data (Fig. 2.19).

The Fig. 2.20 shows the dependence of the resting membrane potential (solid line) on the addition of α (in mM) into the environment by potassium ions with chlorine. The experimental value of the potential for hepatocyte cells is shown by dotted lines.

Table 2.11 summarizes the calculated values in comparison with the experimental data.

Table 2.11 clearly shows that the expressions that are obtained for the resting potential of the cells and those of the concentrations of chloride ions are in good agreement with the experimental data. However, a discrepancy exists between the calculated results and the experimental data for sodium and bicarbonate, which is possibly due to the lack of completeness of the information on systems of transport in hepatocytes.

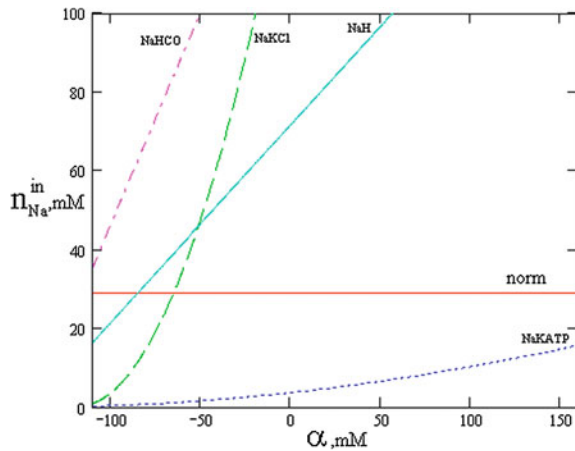
Table 2.11 Comparison of experimental and calculated values for the internal ion concentrations and potential for hepatocytes

Ions	Experimental data, mM	Calculated data, mM
Sodium	29	4.3
Chlorine	20	16.2
Bicarbonate	25	4.5
Potential, mV	-49.8	-47.4

2.5.2 Regulation of Ion Transport

A model for the Regulation of Ion Transport in liver cells using all of the transport mechanisms that were introduced in the previous section can be constructed based on the model for sodium ions. Graphically, the work of each transport system when the external concentration of sodium ions change by the value of α (in mM) is shown in Fig. 2.20.

Fig. 2.20 Dependences of the internal concentrations of potassium on the external concentrations when different transport systems are functioning



The figure shows that none of the transport systems are in good agreement with the required value for the internal concentration of sodium ions. Additionally, in the previous section, calculations were carried out to support this finding. It can be concluded that to maintain the required concentration of intracellular sodium ions in hepatocytes, two transport mechanisms are required to function at the same time (Fig. 2.21).

Three-dimensional modeling confirms our conclusions on the basic functions of the ATP-dependent pump in forming the desired concentration of sodium ions and on the activation of the K–Na–Cl and Na–HCO₃ co-transporters with decreasing sodium content in the extracellular medium. However, the assumption that the Na–H-antiporter functions independently at low concentrations of sodium ions outside the cell is not confirmed. Therefore, we can conclude that the role of the antiporter is only regulatory, and this transporter switches only in addition to the co-transporter of sodium ions with bicarbonate. Importantly, experiments have shown that these transporters are activated together.

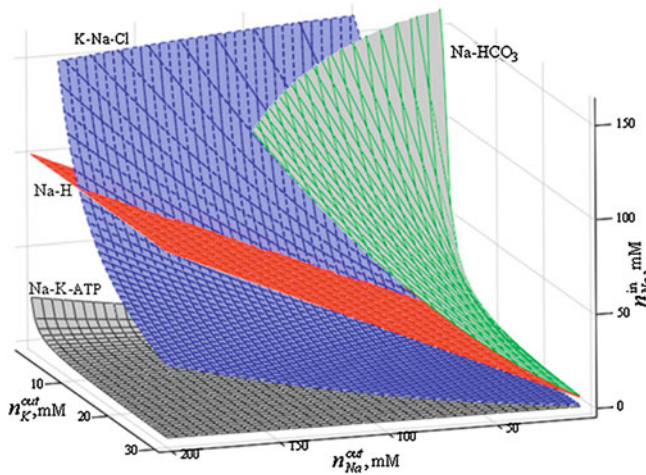


Fig. 2.21 Systems of transport for sodium ions as the function of the external concentrations of two ions

2.6 Regulation of Ion Transport in Compartments of a Mammalian Cell

Cells of living organisms contain a large number of compartments that are surrounded by membranes and are the basis of cell activity. In these compartments, the main processes for life function in the exchange of matter, energy and entropy between the organism and the environment. These compartments also divide the totality of the vital processes of cells into separate stages. The rough endoplasmic reticulum and ribosomes provide protein synthesis in accordance with the structure of RNA. In the Golgi apparatus, the conversion of tertiary and quaternary protein structures and the formation of markers that govern their directional transport occurs, and synaptic vesicles store neurotransmitters that are necessary for the transmission of nerve impulses. The mitochondria convert energy from the oxidation of food to the free energy of ATP, and ATP hydrolysis is a universal source of free energy at all stages of life.

Each of these stages of life, and many other processes, requires special conditions (concentrations of substances, osmotic pressure, electric potential) for their implementation.

In this regard, the maintenance of the concentrations of certain types of ions in cellular compartments plays an important role in the functioning of the cell as a whole. Transport systems have many different compartments that match the structure and properties of elements (specialized proteins), and the general ideology of constructing models of transport for substances in these compartments is described by Melkikh and Seleznev (2012). The model of active transport in some compartments of mammalian cells will be considered, and the possible

mechanisms for regulating the concentrations of substances in these compartments will be discussed. Several models of these compartments will be considered in Chap. 3.

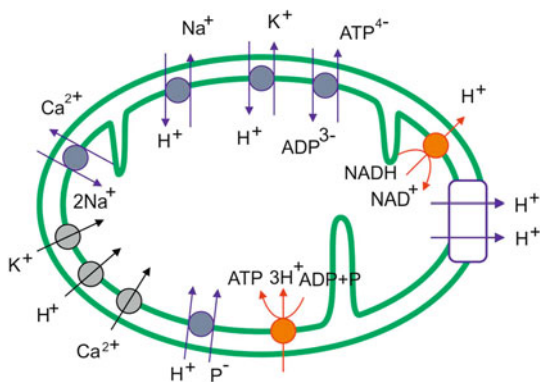
2.6.1 Mitochondria

The mitochondrion is one of the most complex cellular compartments that plays an important role in the life of a cell. First, the importance of a mitochondrion is determined by the fact that it transforms free energy from nutrients and oxygen into ATP, which is a universal energy carrier and is convenient to use in any part of a living organism. Because the work that is performed by animals in the environment is frequently accompanied by peak loads, ATP production should be controlled so that it is possible to change the ATP synthesis rate by many orders of magnitude during a short period. Therefore, the structure and functions of a mitochondrion possess a complex system of regulation, which is linked to the variation in Ca^{2+} concentration between the matrix of a mitochondrion and the cytoplasm. In particular, a change in Ca^{2+} concentration initiates the mechanisms of programmable death of a cell, and this change can lead to a change in the matrix volume.

A mitochondrion is covered by two membranes. The inner membrane consists of folds (cristae) that provide a maximum surface area. This membrane contains principal enzymes that provide a selective exchange of substances between the cellular plasma and the matrix. Furthermore, the matrix contains enzymes that participate in the Krebs cycle and fatty acid oxidation.

It is believed that during the early stages of evolution, mitochondria were likely to be an independent organism because its matrix contains ribosomes and DNA. Moreover, enzymes that are built into the inner membrane play a significant role in the processes that occur at this membrane (Beard and Qian 2008, Melkikh and Seleznev 2012). The scheme of the mitochondrion is shown in Fig. 2.22.

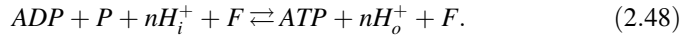
Fig. 2.22 Simplified scheme of the ion transporters in the inner mitochondrial membrane



Details of the reactions that occur through the mitochondria enzymes are discussed in Melkikh and Seleznev (2012), and this section will present the main results from modeling ion transport through the membrane of the mitochondria.

We will consider the systems of the ion transport membrane of the mitochondria, which function independently of the respiratory chain and are not affiliated with the respiratory chain by stoichiometry integer coefficients because the respiratory chain was analyzed and shown previously (Melkikh and Seleznev 2012).

The ATPase enzyme maintains the ATP synthesis reaction at the expense of the free energy of protons $\Delta\mu_H^e$.



Therefore, the flux of the reaction is represented by the following equation:

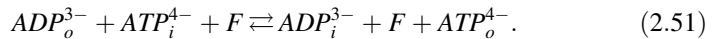
$$J_A = k_{ATP} n_F n_A^i n_H^o (\exp(n\Delta\mu_H^e - \Delta\mu_A) - 1). \quad (2.49)$$

where k_{ATP} is the reaction rate constant,

$$\Delta\mu_H^e = \ln \frac{n_H^o}{n_H^i} - e\varphi, \quad \Delta\mu_A = \ln \frac{n_A^i n_{D0}^i n_{P0}^i}{n_D^i n_P^i n_{A0}^i} \quad (2.50)$$

where $n_A^i, n_D^i, n_P^i, n_{A0}^i, n_{D0}^i, n_{P0}^i$ are the concentrations of ATP, ADP, and P inside a mitochondrion and their corresponding concentrations at equilibrium, respectively.

The next enzyme of the mitochondrion membrane is adenosine nucleotide translocase. This enzyme supplies the substrate for ADP^{3-} synthesis from the cytoplasm into the mitochondrion, and the reaction product, ATP^{4-} , travels through the membrane and into the cellular plasma. The equation for the ion exchange reaction through the antiporter under consideration is as follows:



The ion flow through the antiporter will take the following form:

$$J_{TD} = \frac{n_F k_{D\uparrow} k_{T\uparrow} (k_{T\downarrow} + k_{D\downarrow})}{2 k_{T\downarrow} k_{D\downarrow}} [n_D^o n_T^i \exp(\varphi) - n_D^i n_T^o], \quad (2.52)$$

where $k_{D\uparrow}, k_{T\uparrow}, k_{D\downarrow}, k_{T\downarrow}$ are the constants of ADP^{3-} and ATP^{4-} binding and release rate, respectively.

The K^+-H^+ and Na^+-H^+ antiporters are described by the following formulas:

$$J_{NaH} = \frac{n_F^{NaH}}{2} \frac{k_{Na\uparrow} k_{H\uparrow} (k_{Na\downarrow} + k_{H\downarrow})}{k_{H\downarrow} k_{Na\downarrow}} [n_{Na}^o n_H^i - n_{Na}^i n_H^o], \quad (2.53)$$

$$J_{KH} = \frac{n_F^{KH}}{2} \frac{k_{K\uparrow} k_{H\uparrow} (k_{K\downarrow} + k_{H\downarrow})}{k_{H\downarrow} k_{K\downarrow}} [n_K^o n_H^i - n_K^i n_H^o]. \quad (2.54)$$

A similar expression for the flow characterizes the $\text{Ca}^{2+}\text{-}2\text{Na}^+$ exchanger:

$$J_{\text{CaNa}} = \frac{n_{\text{CaNa}}}{2} \frac{k_{\text{Na}\uparrow} k_{\text{Ca}\uparrow} (k_{\text{Na}\downarrow} + k_{\text{Ca}\downarrow})}{k_{\text{Ca}\downarrow} k_{\text{Na}\downarrow}} \left[n_{\text{Ca}}^o (n_{\text{Na}}^i)^2 - n_{\text{Ca}}^i (n_{\text{Na}}^o)^2 \right]. \quad (2.55)$$

The flow through the P-H^+ symporter is described by the following formula:

$$J_{\text{PH}} = \frac{n_{\text{F}}^{\text{PH}} k_{\uparrow}^i k_{\downarrow}^o}{k_{\downarrow}^o + k_{\uparrow}^i} \left[n_{\text{P}}^o n_{\text{H}}^o - n_{\text{P}}^i n_{\text{H}}^i \right]. \quad (2.56)$$

The ion flows through the electrogenic H^+ , K^+ , Ca^{2+} , Cl^- uniporters:

$$J_{\text{H}} = \frac{n_{\text{F}}^{\text{H}} k_{\text{H}\uparrow}^i k_{\text{H}\downarrow}^o}{k_{\text{H}\downarrow}^i} \left[n_{\text{H}}^o - \exp(\varphi) n_{\text{H}}^i \right], \quad (2.57)$$

$$J_{\text{K}} = \frac{n_{\text{F}}^{\text{K}} k_{\text{K}\uparrow}^i k_{\text{K}\downarrow}^o}{k_{\text{K}\downarrow}^i} \left[n_{\text{K}}^o - \exp(\varphi) n_{\text{K}}^i \right], \quad (2.58)$$

$$J_{\text{Ca}} = \frac{n_{\text{F}}^{\text{Ca}} k_{\text{Ca}\uparrow}^i k_{\text{Ca}\downarrow}^o}{k_{\text{Ca}\downarrow}^i} \left[n_{\text{Ca}}^o - \exp(2\varphi) n_{\text{Ca}}^i \right], \quad (2.59)$$

$$J_{\text{Cl}} = \frac{n_{\text{F}}^{\text{Cl}} k_{\text{Cl}\uparrow}^i k_{\text{Cl}\downarrow}^o}{k_{\text{Cl}\downarrow}^i} \left[n_{\text{Cl}}^o \exp(\varphi) - n_{\text{Cl}}^i \right]. \quad (2.60)$$

By using the flow of ions that was published previously (Melkikh and Seleznev 2012), the system of equations for the conservation of particles of each component and charge were recorded. This system allows the determination of the internal concentration and electrical potential of mitochondria as a function of the concentration in the solution and time.

Due to the complexity of the system of equations, the solution is possible only with the use of numerical methods. To accomplish the task of restoring the characteristics of the flow of ions through the mitochondrial membrane, must be utilized a special program of experimental work to the duplicate samples of mitochondrial suspensions from the cell body of a particular species to restore the features of the investigated organelles.

Melkikh and Seleznev (2012) undertook a simpler alternative approach, which allowed for the derivation of analytical formulas for the potential and internal concentrations of ions as functions of their external concentrations. It is suggested that through evolution, living organisms have selected structures and physiological processes that optimally control vital functions and provide the necessary adaptability and robustness of that control.

Based on this principal and assuming that the system has reached steady state, we can obtain the following system of equations:

$$mJ_r + nJ_A =$$

$$= mA^*(\exp(\Delta\mu_r - m\Delta\mu_H^e) - 1) + n(\exp(n\Delta\mu_H^e - \Delta\mu_A) - 1) = 0 \quad (2.61)$$

$$n_T^i + n_D^i = n_T^o + n_D^o, \quad (2.62)$$

$$n_T^i n_D^o \exp(e\varphi) - n_D^i n_T^o = 0, \quad (2.63)$$

$$n_P^o n_H^o - n_P^i n_H^i = 0, \quad (2.64)$$

$$n_K^i n_H^o - n_K^o n_H^i = 0, \quad (2.65)$$

$$n_{Cl}^o \exp(\varphi) - n_{Cl}^i = 0, \quad (2.66)$$

$$n_n^i + n_{Cl}^i + 2n_T^i + n_D^i + n_P^i = n_K^i + n_H^i. \quad (2.67)$$

Here, A^* is a constant that relates to the ratio of the numbers of F-ATPases and respiratory chains. In the obtained system, the following values are unknown: μ_H^e , n_T^i , n_D^i , n_P^i , n_K^i , n_{Cl}^i , φ , and all of these variables should be determined by the seven Eq. (2.61–2.67).

In accordance with Melkikh and Seleznev (2012), we shall now consider the normal physiological condition. For ATP synthesis ($J_A > 0$), the difference between chemical potentials of the synthesis reaction $\Delta\mu_A^i$ was less than $n\Delta\mu_H^e$. When utilizing the experimental value of $\Delta\mu_A^i = 25.6$, it is easy to determine the stoichiometric number n :

$$n \geq \frac{25.6}{8.2} \approx 3.$$

Taking into consideration that

$$\mu_H^e = \ln \frac{n_H^o}{n_H^i} - \varphi, \quad (2.68)$$

the following expression for the ratio of proton concentrations inside and outside a mitochondrion can be easily derived:

$$\frac{n_H^o}{n_H^i} = \exp\left(\frac{\mu_A^i}{3} + \varphi\right). \quad (2.69)$$

$$n_T^i = \frac{(n_T^o + n_D^o)n_T^o \exp(-\varphi)}{n_T^o + n_D^o \exp(-\varphi)}. \quad (2.70)$$

$$n_D^i = n_T^o + n_D^o - \frac{(n_T^o + n_D^o)n_T^o \exp(-\varphi)}{n_T^o + n_D^o \exp(-\varphi)} = \frac{n_D^o(n_T^o + n_D^o)}{n_T^o + n_D^o \exp(-\varphi)}. \quad (2.71)$$

Phosphate ion concentration:

$$n_p^i = \frac{n_p^o n_H^o}{n_H^i} = n_p^o \exp\left(\frac{\Delta\mu_A^i}{3} + \varphi\right). \quad (2.72)$$

Potassium ion concentration:

$$n_K^i = \frac{n_K^o n_H^i}{n_H^o} = n_K^o \exp\left(-\frac{\Delta\mu_A^i}{3} - \varphi\right). \quad (2.73)$$

By using the neutrality equation, we shall obtain the approximate equation for determining the resting potential:

$$\exp(-\varphi) = \frac{2(n_T^o + n_D^o) + n_n^i}{(n_K^o + n_H^o)} \exp\left(\frac{\Delta\mu_A^i}{3}\right), \text{ or} \quad (2.74)$$

$$\varphi = \ln \frac{(n_K^o + n_H^o)}{2(n_T^o + n_D^o) + n_n^i} - \frac{\Delta\mu_A^i}{3}. \quad (2.75)$$

A simplified system of equations allows us to understand the basic mechanisms that are responsible for the reaction in the mitochondria after an environmental change.

Another area of mitochondrion physiology investigation is related to the study of regulatory functions of calcium transport systems. As shown by studies from the last 30 years, the cell utilizes a large sum of energy in maintaining a low concentration of calcium ions. Calcium ions are universal intracellular regulators, they transmit incoming signals to the cell through enzymatic systems. In the resting cell, the concentration of calcium is low, but when the cell receives the appropriate signal, it responds with an avalanche-like increase in the concentration of calcium ions.

It is necessary that cellular systems control the concentration of calcium in the cytoplasm and are able to rapidly lower these levels, and these systems are built into the cell membrane. In the outer membrane, the Ca-ATPase is a pump that acts against the Ca^{2+} gradient from the cell and into the intercellular medium. An additional system, the Ca^{2+} - Na^+ exchanger, is responsible for lowering the concentration of calcium in the cytoplasm by exchanging intracellular Ca^{2+} for extracellular Na^+ .

The Ca-ATPase is located on the membrane of the endoplasmic reticulum. This enzyme pumps Ca^{2+} ions from the cytoplasm into the endoplasmic reticulum cisterns by way of ATP hydrolysis. In addition, in the mitochondria, a special transport system can pump calcium from the cytoplasm to the matrix.

Increased intracellular Ca^{2+} is a type of alarm. In response to an increase in the concentration of calcium ions, the cell mobilizes all its systems, which removes calcium. Furthermore, the elevated concentration of calcium in the cell occurs only for a short period, which allows for transmission of the stimulus.

The above scheme of signal transduction through calcium ions is at the base of many systems, especially of muscle contraction.

2.6.2 Sarcoplasmic and Endoplasmic Reticulum

The sarcoplasmic reticulum (SR) is a depot for calcium ions. To provide this function, the SP membrane contains an ATP-dependent calcium pump that transports two calcium ions from the cellular plasma into the SP for one event of ATP hydrolysis.

The SR membrane is connected to the tubes of the T-system, which are directly linked to the membrane of a muscular cell, by special membrane bridges (Fig. 2.23). The signal for necessary muscle contraction travels through this system to the SR membrane, Ca^{+2} channels open, and Ca^{+2} ions are injected into the cytoplasm of the muscle cell where they excite muscle fiber contraction. During the rest period, Ca^{+2} channels close, and Ca^{+2} ions are pumped into cisterns by an ATP-dependent pump. For the described system to function, potential-dependent, passive channels with variable permeability and an active calcium pump should be present in the SP membrane.

The results of previous investigations (Meissner 2001; Shannon et al. 2000, 2001) show that no electric potential exists on the SP membrane or that this potential is very low. Moreover, when the channels are closed, Ca^{+2} pumps maintain the ratio of the concentration of Ca^{+2} ions inside and outside the SP at approximately 7,000. It is reported that the Ca^{+2} pump also works as the mode of ATP synthesis.

Functions of the endoplasmic reticulum (ER) consist of accumulation and transport of substances that are important for a cell, and the ER, like the SR, is a depot for Ca^{+2} . The resting potential on the ER membrane is obtained within the framework of the model for ion transport in the ER that was developed in a previous paper (Marhl et al. 1998), and the balance of Ca^{+2} concentration in the cytosol is carried out within this model. In particular, the passive and active flows of Ca^{+2} ions through the ER membrane contribute substantially to this balance.

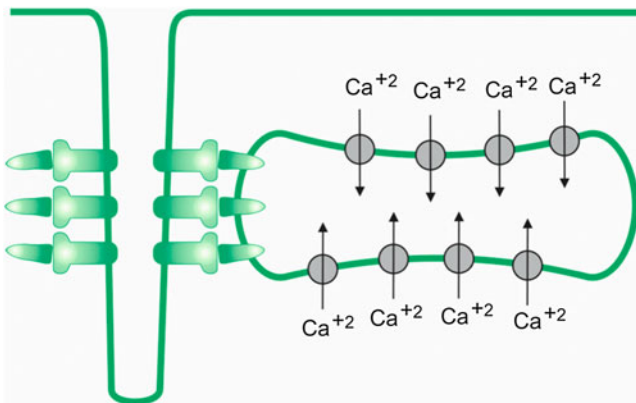
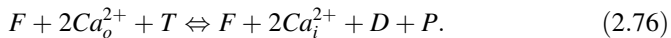


Fig. 2.23 Simplified scheme of the ion transporters in sarcoplasmic reticulum

Thermodynamically correct expressions for the ratio of the concentrations of calcium ions on the membranes of the SR and ER were obtained previously (Melkikh and Seleznev 2012) on the basis of the proposed algorithm. From experimental data on the stoichiometry of the ATP-dependent calcium pump (two Ca^{2+} ions for the hydrolysis of one molecule of ATP), the following reaction can be written:



In accordance with (6.6), we write the expression for the calcium flux with a small calcium concentration as:

$$J_{Ca}^{ATP} = k_{\downarrow}^{Ca} n_F n_D n_P (n_{Ca}^i)^2 \exp(4\varphi) [\exp(\Delta\mu_A - 4e\varphi - 2\Delta\mu_{Ca}) - 1] \quad (2.77)$$

Because the calcium concentration is much smaller than the concentrations of potassium, sodium and other ions, and because there are no pumps other than calcium pump, in the SR, the potential will be close to zero. This result is in agreement with the experimental data. Then, following from (2.77), the ratio of the concentrations of calcium ions across the membrane in the case ($J_{Ca}^{ATP} = 0$) can be determined by the relation:

$$\Delta\mu_{Ca} = \ln \frac{n_{Ca}^i}{n_{Ca}^o} = \frac{\Delta\mu_A}{2}. \quad (2.78)$$

With $\Delta\mu_A = 20$, we have:

$$\frac{n_{Ca}^i}{n_{Ca}^o} = \exp(10) \approx 22000,$$

which is in qualitative agreement with the experimental value of this ratio. The reason for the difference, in all likelihood, is that we have neglected passive transport of Ca^{2+} ions in (2.78).

2.6.3 Synaptic Vesicles

A model of active ion transport in synaptic vesicles has been discussed in detail in Melkikh and Seleznev (2007, 2012). Here, we consider the model's basic results.

Neurotransmitters are molecules that open channels and control the generation of nerve impulses in neurons (for example, see Nicholls et al. 2001). At rest, neurotransmitters are kept in synaptic vesicles (or in large, dense-core vesicles and synaptic-like microvesicles (Harada et al. 2010)). During impulse propagation, neurotransmitters leave the vesicles and open neighboring cellular channels in the place of synaptic contacts.

According to some publications (Nicholls et al. 2001), a proton gradient, which is created by H-ATPase as it transports protons into synaptic vesicles, is used to transport neurotransmitters into synaptic vesicles.

Experiments have shown that proton flow into a synaptic vesicle is provided by energy from ATP. An expression for the flux of protons through an H-ATPase has the following form:

$$J_H = \tilde{C}_H [\exp(\Delta\mu_A)(n_H^o) - \exp(4\varphi)(n_H^i)] \quad (2.79)$$

From this equation, we can calculate the steady-state proton concentration within a synaptic vesicle as:

$$\exp\left(\frac{\Delta\mu_A}{4} - \varphi\right) n_H^o = n_H^i. \quad (2.80)$$

Neurotransmitters accumulate in various synaptic vesicles with individual active transport systems. The schemes of select neurotransmitter transport systems are shown in Figs. 2.24, 2.25, 2.26 (Nicholls et al. 2001).

The passive flow of all neurotransmitters was neglected based on the need for the maximum effectiveness of ATP hydrolysis in energy utilization.

The active flow of neutral neurotransmitters into a vesicle has the following form for monoamines and acetylcholine:

$$J_T = C_1 \left(n_T^o \exp(\varphi) (n_H^i)^2 - n_T^i (n_H^o)^2 \right). \quad (2.81)$$

Expressing this equation as the internal concentration of positive neurotransmitters with an electroneutrality condition, the resting potential can be expressed as:

Fig. 2.24 The transport scheme of monoamines and acetylcholine

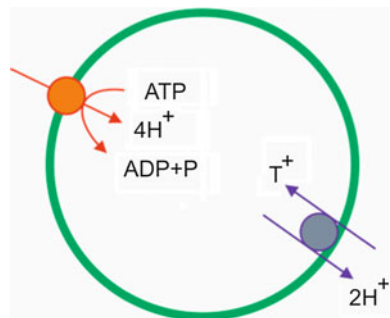


Fig. 2.25 The transport scheme of GABA and glycine

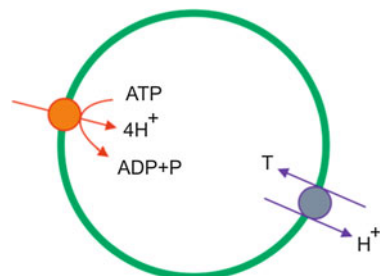
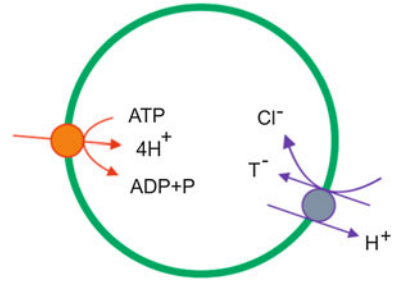


Fig. 2.26 The transport scheme of glutamate



$$\varphi = \ln \left(\frac{n_T^i + \sqrt{(n_T^i)^2 + 4n_-^o n_+^o}}{2n_-^o} \right). \quad (2.82)$$

The concentrations of passive negative ion and positive ions are roughly equal on the outside of the vesicle and are on the order of 0.1 M. The concentration of the mediator on the inside of the synaptic vesicle is approximately 0.5 M. Considering that $\Delta\mu_A$ has a magnitude of 20, the calculated potential is approximately 41 mV.

The proton concentration within the vesicle is equal to 0.0011 mM, which corresponds to a ΔpH of 1.46 across the vesicle membrane. This value coincides with the experimental data, which reports a $\Delta\text{pH} < 2$ (Gidon and Sihra 1989; Tabb et al. 1992).

The mediator concentration outside of the vesicle is approximately 0.1 mM.

Similarly, we can derive an expression for the potential of GABA and glycine as follows:

$$\varphi = \frac{1}{2} \ln \frac{n_H^o \exp\left(\frac{\Delta\mu_A}{4}\right) + n_K^o}{n_{Cl}^o} \approx \frac{n_H^o \exp\left(\frac{\Delta\mu_A}{4}\right)}{2n_{Cl}^o} \approx 2.97 \times 10^{-5}. \quad (2.83)$$

In dimensional units, the potential is 7.4×10^{-4} mV. This value is very small in comparison to the characteristic potentials of a cellular membrane. In this case we can consider the potential on the membrane of a synaptic vesicle to be absent.

The cellular mediator concentration is 3.4 mM in this case. This value qualitatively agrees with the experimental data.

For glutamate transport in a stationary case, the expression for potential will take the form:

$$\varphi = \ln \left(\frac{-n_T^i + \sqrt{(n_T^i)^2 + 4n_-^o n_+^o}}{2n_-^o} \right), \quad (2.84)$$

which results in a negative potential of approximately—41 mV in dimensional units. The cellular neurotransmitter concentration is 18 mM. This result is also on the same order of magnitude as the experimental data.

Neurotransmitters play an extremely significant role in ensuring the normal functioning of the nervous system. At the same time, maintaining the concentration of neurotransmitters in the intercellular space and regulating the transport of synaptic vesicles within the cell are also important. However, models of these processes are absent from the literature.

2.7 Conclusions

By constructing models of transport systems in four cell types and compartments, we were able to verify some of the proposed algorithms in [Chap. 1](#). A comparison with experimental data suggested that the proposed algorithms can qualitatively describe ion transport processes across cellular membranes and compartments. A transport system model was constructed for steady-state, allowing us to offer algorithms for the regulation of ion transport. Ion concentrations could be maintained at level required by the cells, which may correspond to conditions with insufficient experimental data.

Good agreement between the numerical modeling results and the mammalian cell data supports the validity of our previous hypotheses to simplify the model. In particular, this result supports the electroneutrality of the internal environment and the minimum osmotic pressure difference across the membrane. Thus, within the framework of our algorithm, it can be argued that animal cells have sufficient commonality and that their structural and functional differences can be ignored. In the future, the proposed algorithm can be used for building regulatory transport systems in any animal cell, even in the absence of experimental data. Also justified is the assumption that, in the framework of our model, compartments can be considered isolated systems for modeling transport across the membrane.

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