Algorithms for optimization of the transport system in living and artificial cells

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Abstract An optimization of the transport system in a cell has been considered from the viewpoint of the operations research. Algorithms for an optimization of the transport system of a cell in terms of both the efficiency and a weak sensitivity of a cell to environmental changes have been proposed. The switching of various systems of transport is considered as the mechanism of weak sensitivity of a cell to changes in environment. The use of the algorithms for an optimization of a cardiac cell has been considered by way of example. We received theoretically for a cell of a cardiac muscle that at the increase of potassium concentration in the environment switching of transport systems for this ion takes place. This conclusion qualitatively coincides with experiments. The problem of synthesizing an optimal system in an artificial cell has been stated.

Keywords Transport of ions · Systems biology · Game theory · Robustness · Efficiency · Synthetic biology

Introduction

Processes of the transport of substances in biomembranes of cells are important for vital cellular functions. For example, many cells (bacteria, archaebacteria, cyanobacteria, and yeasts) survive considerable variations in the concentration of ions in the environment. It is necessary to understand the mechanisms by which cells resist such changes. The transport of ions is controlled, to a certain

extent, by all cells. In terms of the systems biology, this property is called robustness (Kitano 2004; Stelling et al. 2004). Transport systems have one more important property, namely, their efficiency characterizing the ability of the cell to perform various kinds of useful work. However, these two properties practically have never been treated together. The robustness and the efficiency are mutually complementary in a certain sense. A large amount of consumption is required to achieve a high robustness (in this case, a cell will work inefficiently), and a 100% efficient system cannot be robust (Melkikh and Seleznev 2008). The problem is that the cell (living or artificial) is made maximally efficient at a preset robustness or is rendered maximally robust at an assigned efficiency.

The goal of systems biology is a comprehensive description of a cell (an organism) through mathematical methods by the use of computers. At present, systems biology is concerned mainly with gene and metabolic networks of cells. However, the transport subsystem of the cell has not been studied sufficiently in terms of systems biology.

On the other hand, advancing synthetic biology requires a general approach to simulating cell processes. In particular, it is necessary to understand the general principles according to which the transport subsystem of the cell is constructed. In the future, such understanding will help to answer why the transport subsystem of a cell is arranged exactly the way it is.

Despite a great number of papers devoted to application of control theory to biosystems, earlier in the literature, transport processes in cells from the point of view of optimization were practically not considered. It is possible to note, for example, papers (El-Shamad et al. 2002) in which the transport of ions of calcium in a cardiac muscle cell is modeled using control theory. One feature of such an

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approach is the obvious account of the time dependence of the regulation of the concentration of calcium ions in a cell. However, the regulation of potential and of other ions is not considered.

The aim of this work was to construct an algorithm which would allow calculating the optimal parameters of the transport subsystem of a cell at its maximum efficiency and, simultaneously, a minimum sensitivity to changes in the environment.

One transport system for one substance

The transport subsystem of a cell and other subsystems are the subject matter of systems biology [see, e.g., (Jamshidi and Palsson 2006; El-Shamad et al. 2002)]. However, optimization methods have been applied little to the system of the transport of substances in the cell. This is probably because the processes of the transport of substances in many respects are assumed to be secondary in relation to gene or metabolic processes.

Cell transport subsystem is connected with other subsystems. For example, the processes of transcription and translation are related to the transport of nucleotides or proteins through the nuclear membrane. The functioning of genetic and metabolic networks is related to the transport of proteins and metabolites within the cell and through the membranes of intracellular compartments (mitochondria, chloroplasts, nucleus, and others). On the one hand, transport processes in turn depend on metabolism, etc. In this sense, the separate consideration of the transport subsystem of a cell is an approximation. On the other hand, the consideration of transport subsystem allows a better understanding of the other subsystems with which it interacts. Ultimately, a separate description of the transport subsystem helps an understanding of the laws of cellular functioning as a whole.

In addition, the construction of models for optimization of the transport system is topical because at early stages of evolution, the transport of substances could be one of the few functions of a protocell. An understanding of the mechanisms by which transport is optimized in elementary cells would be helpful in the creation of artificial cells.

In this connection, a “minimal cell”—a direction emerged recently at the turn of the systems and synthetic biology—seems to be topical (Murtas 2007; Forster and Church 2006; Munteanu and Sole 2006). The aim of this research is to establish the minimum necessary conditions for a system to be viewed as living. A systems simulation of the transport of ions in cells should contribute to the understanding of life.

The transport of substances through biomembranes is one of the most important functions of cells. The passive

(without energy consumption) and active (due to the ATP energy or the free energy of other ions) transports are distinguished among the basic types of the transports. To construct a model describing the control of a transport system in a cell, it is necessary to determine dependences of the internal concentrations of substances and the resting potential on their concentration in the environment. Such dependences have been obtained for some cells in (Melkikh and Seleznev 2005, 2006a, b, 2007a, b; Melkikh and Sutormina 2008). Notice that the Hodgkin-Katz formula, which is universally adopted for calculating the resting potential, requires the knowledge of both internal and external concentrations of ions.

Let us consider an abstract cell with several systems of the transport of basic substances in the context of the transport models proposed earlier (Melkikh and Seleznev 2005, 2006a, b, 2007a, b; Melkikh and Sutormina 2008). The main problem is how to make the internal medium of the cell insensitive to changes in the environmental composition and, at the same time, make the transport processes sufficiently effective.

We shall consider first the transport of one substance in the absence of a charge. This situation can take place either with neutral substances or when the concentration of ions of this type is small and influences little the resting potential. According to (Melkikh and Seleznev 2005, 2006a, b), the active flux of a substance J through the membrane can be written in the form

$$J = C_1(n_{\text{in}} \exp(\Delta\mu_A) - n_{\text{out}}), \quad (1)$$

where C_1 is a constant characterizing the operating speed of a pump, n_{in} is the internal concentration of the transferred substance, n_{out} is its concentration in the environment, and $\Delta\mu_A$ is the dimensionless difference of the chemical potentials for a nonequilibrium ATP-ADP system. For convenience, we shall use a dimensionless value:

$$\Delta\mu_A \equiv \frac{\Delta\mu_A}{kT},$$

where k is the Boltzman constant; T is the temperature.

In the stationary state, the flux (1) must be zero. In this paper, we consider the quasi-steady state, meaning that the changes in ion concentrations in the environment are rather slow in comparison with non-stationary processes in the cell (such as a nerve impulse).

From (1), it is possible to deduce the dependence of the internal concentration of a substance on its external concentration:

$$n_{\text{in}} = n_{\text{out}} \cdot \exp(-\Delta\mu_A).$$

As can be seen, this dependence is linear. Then, if only one transport system is available for each ion, a constancy

of the internal concentration of the ion with its varying external concentration cannot be ensured. However, the efficiency of such transport systems can be close to 100% (Melkikh and Seleznev 2006a, b). This approach (a hierarchical algorithm “one ion—one transport system”) was successfully used earlier for simulation of transport processes in various cells (Melkikh and Seleznev 2005, 2007a, b; Melkikh and Sutormina 2008). However, the task of simulating the regulation of the ion transport was not posed in these studies.

To estimate efficiency of transport of ions, it is necessary to include it in our model. This factor is determined, as the relation of useful capacity to the spent one. Useful capacity in our case is the work of active transport of ions, performed per unit of time. Similar ratio for thermodynamic processes in a cell was deduced earlier in papers (Oster et al. 1973). In our case, ATP energy is spent for producing a flux of ions through a membrane, i.e., in a denominator, there will be a product of ATP flux v' on its driving force—a difference of chemical potentials of ATP-ADP system $\Delta\mu_A$. Energy of ATP is spent only on active transport of ions, i.e., on a pure active flux of ions J' . To select an active flux of ions from a total one, it is necessary to expect that passive flux is zero, i.e., when concentration inside and outside of cell are equal (at $\Delta\mu = 0$). Useful capacity then calculated as product of a pure active flux and a difference of chemical potentials of the ions, produced by active transport ($\Delta\mu \neq 0$). Thus, it is possible to write down the formula for efficiency as:

$$\eta = \frac{J' \cdot \Delta\mu}{v' \cdot \Delta\mu_A}. \quad (2)$$

If the transferred substance has a charge, the dependence of the internal concentration on the external concentration will be nonlinear. However, a change in the resting potential more often than not is extremely unfavorable for a cell because in this case, the internal concentrations of all the ions will change.

capacity of these transport systems. The flux of a substance generated by the two systems can be written in the form

$$C_1(n_{\text{in}} \exp(\Delta\mu_A) - n_{\text{out}}) + C_2(n_{\text{in}} \exp(\Delta\mu_B) - n_{\text{out}}) = 0, \quad (3)$$

where $\Delta\mu_B$ is the motive force of the second transport system (dimensionless).

Experiments with different cells demonstrate that, as a rule, in normal conditions, each ion has one basic transport system, which provides a difference between the intra- and extracellular concentrations of this ion corresponding to the normal value. The other transport systems are regulatory. This means that they should operate when the environmental composition begins changing. Let us plot the relationships between the internal and external concentrations for each system so as to demonstrate the result of the concurrent operation of these systems. Let, for example, they have the shape shown in Fig. 1, where the circle denotes the concentration of an ion in the normal state.

It can be shown that the total efficiency of two or more different transport systems working concurrently will always be less than 100%, even if the efficiency of each individual system is 100%. Let us determine the efficiency when two transport systems work concurrently for one ion. Let one ion is transferred by two pumps with different values of the motive force. Then, the internal concentration of this ion can be found from the Eq. 3:

$$n_{\text{in}} = \frac{n_{\text{out}} \cdot (C_1 + C_2)}{C_1 \cdot \exp(\Delta\mu_A) + C_2 \cdot \exp(\Delta\mu_B)}.$$

If the motive forces ($\Delta\mu_A$ and $\Delta\mu_B$) are constant, the dependence $n_{\text{in}}(n_{\text{out}})$ is linear.

In this case (in the absence of a charge), the difference of the chemical potentials of an ion can be defined as

$$\Delta\mu = \ln \frac{n_{\text{out}}}{n_{\text{in}}} = \ln \frac{C_1 \cdot \exp(\Delta\mu_A) + C_2 \cdot \exp(\Delta\mu_B)}{C_1 + C_2}.$$

Therefore, for the efficiency we have

$$\eta = \frac{J' \cdot \Delta\mu}{v' \cdot \Delta\mu_A} = \frac{(C_1(\exp(\Delta\mu_A) - 1) + C_2(\exp(\Delta\mu_B) - 1)) \cdot \ln \frac{C_1 \exp(\Delta\mu_A) + C_2 \exp(\Delta\mu_B)}{C_1 + C_2}}{C_1(\exp(\Delta\mu_A) - 1) \cdot \Delta\mu_A + C_2(\exp(\Delta\mu_B) - 1) \cdot \Delta\mu_B}$$

Two transport systems for one substance

Consider now the case when two different transport systems are available for one substance. We shall show that the system can be rendered, to a large extent, insensitive to changes in the environmental concentrations by varying the

It is easy to see that if C_1 or C_2 is zero (only one transport system operates), the efficiency is 1 at any forces. On the other hand, if the forces are equal, the efficiency is 1 at any C_1 and C_2 . In all the other cases, the efficiency is $< 100\%$.

Fig. 1 Dependencies of internal concentrations on external concentrations

Figure 2 presents dependences of the efficiency on the ratio $C = C_2/C_1$ at different forces (from the top down $\Delta\mu_A = 2$, $\Delta\mu_B = 2.5$, $\Delta\mu_B = 2.9$, and $\Delta\mu_B = 3.9$).

When $C \rightarrow 0$ and $C \rightarrow \infty$, the efficiency tends to unity.

The formula retains its structure irrespectively of the number of fluxes and forces:

$$\eta_i = \frac{\sum_{i=1}^n C_i (\exp(\Delta\mu_{Ai}) - 1) \frac{\sum_{i=1}^n C_i \exp(\Delta\mu_{Ai})}{\sum_{i=1}^n C_i}}{\sum_{i=1}^n C_i (\exp(\Delta\mu_{Ai}) - 1) \Delta\mu_{Ai}}.$$

In this case, in numerator, the first multiplier represents the sum of pure active fluxes of the given ion produced by all forces $\Delta\mu_{Ai}$. The second multiplier is the chemical potential of ion produced as a result of active transport of this ion by different systems. Denominator is the total expenses of energy for all systems of active transport carrying the given ion.

Fig. 2 Dependences of the efficiency of two simultaneously working transport systems on the ratio of speeds of their work

Since the difference of the denominator and the numerator in this formula is the entropy production in the system, which is the product of fluxes and thermodynamic forces, the inequality $\eta < 1$ is a natural consequence of the second law of thermodynamics.

The deduced formulas are easily generalized to the presence of a charge by introducing the chemical potentials of ions as the basic variables.

Then two strategies, which correspond to the limiting cases of the pump operation, can be distinguished in the regulation of the ion transport.

In the first case, we shall require that the efficiency of two concurrently operating systems is always 100% (an absolutely efficient system). This is possible if only one of the transport systems for one ion is working at each moment of time. Then, it is easy to see that in this case the relative robustness can be achieved by following the curve that approaches the most the normal concentration (the heavy line in Fig. 3). Here in term « relative robustness » we understand ability of cell to maintain the value of internal concentrations required for normal life within an acceptable deviation δ from the norm $[\tilde{n}_{in} \pm \delta]$, where $\tilde{n}_{in}$ being a value equal to the normal concentration of an ion for a cell in a physiologically normal state. Therewith the robustness will knowingly be larger than the robustness ensured with one transport system only.

Notice that this piecewise dependence of the internal concentrations on the external ones ensures the robustness as it is defined in (Kitano 2004, 2007). In other words, it is not only that some cell parameter is maintained at a constant level in the system, but some function of the cell is switched to another function so as to ensure such constancy. Such switching of transport systems is known for many cells [see, for example, for hepatocytes (Haussinger 1996; Fossat et al. 1997), neurons (Nicholls et al. 2003), fungi (Rodrigues-Navarro 1987; Rodriguez-Navarro et al. 1994; Silva-Graca and Lucas 2003), and bacteria (Maguire

Fig. 3 Effective strategy of regulation. On increasing the external concentration at point A, the switching from one transport system (1) to another (2) takes place

2006)]. Switching can be due to a considerably nonlinear dependence of the pump operation frequency on the concentrations $C = C(n_{in}, n_{out})$.

In the second case, we shall require that at least in some region the internal concentrations are fully independent of the external concentrations. This requirement is fulfilled by selecting an appropriate concentration dependence of the operation frequency of one of the transport systems. Assuming that the frequency of the transport system depends on concentration external ions, we can derive from (3) the explicit form of this function. For example, for C_2 we get:

$$C_2(n_{out}) = C_1 \frac{\tilde{n}_{in} \cdot \exp(\Delta\mu_A) - n_{out}}{n_{out} - \tilde{n}_{in} \cdot \exp(\Delta\mu_B)}. \quad (4)$$

For this case, the strategy has the form shown in the Fig. 4.

Since the pump capacity can only be a positive value (in this case, the direction of the pump operation is fixed), the equality (4) only holds within the range (the range G-F in Fig. 4):

$$\tilde{n}_{in} \cdot \exp(\Delta\mu_B) < n_{out} < \tilde{n}_{in} \cdot \exp(\Delta\mu_A).$$

Beyond this range,

$$n_{out} > \tilde{n}_{in} \cdot \exp(\Delta\mu_A), \quad C_2(n_{out}) = 0$$

and the internal concentration will be defined by the formula

$$n_{in} = n_{out} \cdot \exp(-\Delta\mu_A)$$

that is, a linear dependence.

In the other range,

$$n_{out} < \tilde{n}_{in} \cdot \exp(\Delta\mu_B),$$

and we have correspondingly

$$n_{in} = n_{out} \cdot \exp(-\Delta\mu_B).$$

Thus, it is seen from Fig. 4 that in the range G-F the system is fully robust, but the efficiency is less than 100%.

Fig. 4 Robust strategy of regulation. In the interval of concentrations between points G and F, both transport systems work simultaneously, and the internal concentration of ions remains constant and equal to $\tilde{n}_{in}$

In the other ranges, the efficiency is 100%, but the robustness is partial. It is easy to show that the larger the absolute difference between $\Delta\mu_A$ and $\Delta\mu_B$, the wider the robustness range. But the efficiency is still less.

If the transport systems are assigned, it can be shown that the requirements of a 100% efficiency and a full robustness cannot be fulfilled simultaneously in either range.

An optimization of the transport system of a cell as a game problem

It can be seen that with this statement the problem is similar to a game problem. In the theory of games, some problems involve only one player, while the nature acts as the second player. That is, answers are determined by known laws of the physics. In our case, the first player is a cell, which can select different strategies; that is, it can switch on and off ion transport systems. Therefore, some internal concentrations of ions are established following the laws of transport phenomena. A gain (a loss) is decrements in the cell as its internal parameters deviate from the normal value. The operation of one transport system for one ion corresponds to a pure strategy, while the operation of two transport systems corresponds to a mixed strategy in terms of the theory of games.

Considering what has been said above, it is possible to propose an algorithm for solving the problem of the regulation of ion concentrations in a cell:

1. Determine the basic transport system for a given ion (it provides the best fit to experiment with respect to the normal value).
2. Determine regulatory systems from experimental data.
3. Plot the internal versus external concentration dependence for the basic system (taking into account a possible variation of the potential).
4. Plot the internal versus external concentration dependence for the regulatory systems (taking into account a possible variation of the potential).
5. Use a graphical method and select the curve that approaches mostly the normal value as the external concentration changes.
6. Determine the point where it is beneficial to switch from the basic system to a regulatory system.

A model for regulation of the transport of ions in a cardiac muscle cell

Let us consider the problem of the optimization of transport systems taking the transport of potassium ions in a cardiac muscle cell as an example.

Fig. 6 Dependence of internal concentration of potassium ions on changing this ion in the external environment in the case of different transport mechanisms

Fig. 7 Optimal strategy at changing concentrations of potassium ions in the external environment

designates the real concentration of potassium in a cell under steady-state conditions; the dash-and-dot line shows the Na-K-ATPase operation; and the heavy solid line designates the chosen strategy.

We shall assume that an optimal strategy is the one that provides a maximum efficiency of the pumps and the exchangers, i.e., only one transport mechanism operates at any moment of time. However, as can be seen from the curve, if the external concentration increases considerably, at least two mechanisms should operate concurrently to ensure the robustness of the model. It is known from the literature that potassium ions are carried passively for the most part. However, as the extracellular concentration increases approximately twice, a Na-K-Cl co-transporter, which carries simultaneously one cation of each species and two anions, comes into play (see, for example, Alvarez-Leefmans 2001; Payne et al. 1995). Thus, the strategy found for switching the transport systems for cardiac muscle cell is in qualitative agreement with experimental.

However, most frequently, a change in one parameter of a cell inevitably entails changes in many other parameters. Hence, to find an optimal strategy, changes in the external concentrations of all the ions and the potential variation need be considered.

To take into account at least two parameters, one can construct three-dimensional graphs showing the dependences of the intracellular concentration of some ion on the potential (or the internal concentration of another ion) and the environmental changes. In this case, the required strategy is assumed to be the maximum efficient strategy; that is, when only one transport mechanism operates at each moment of time. Then, the required strategy will be a set of points on the surfaces denoting the mechanisms by which the ions are transported, with a minimum deviation from the norm in relative units. That is, the condition of a minimum will be fulfilled for some criterion function described by a squared deviation from the normal. Thus, for each quantity, e.g., the extracellular concentration of an ion, a point, which approaches mostly the preset parameters, will be found on one of the planes responsible for the operation of the transport mechanisms. The criterion functions will have the form

$$\Delta = \sqrt{\left(\frac{\Delta n_1}{n_1}\right)^2 + \left(\frac{\Delta n_2}{n_2}\right)^2} \rightarrow \min;$$

$$\Delta = \sqrt{\left(\frac{\Delta n_1}{n_1}\right)^2 + \left(\frac{\Delta \varphi}{\varphi}\right)^2} \rightarrow \min.$$

The relative units have been introduced so as to compare the contributions of the additions of each ion despite considerably different (sometimes on one order of magnitude) values and, also, for comparison with the variation of the potential.

Let us demonstrate the algorithm for the mechanisms by which potassium ions are transported in a cardiac muscle cell.

In Fig. 8, the a is the addition to the extracellular environment of potassium ions; φ is the value of the potential (in dimensionless units); and n_{in}^K is the intracellular concentration of potassium ions. The solid line shows the normal values of the intracellular concentration and the potential at the membrane. The ruled surface reflects the operation of a K-Na-Cl co-transporter; the checked surface is the passive distribution of potassium ions. The points in the Fig. 8 show the effective strategy selected.

Regulation of the transport of many ions

The proposed algorithm ensures the robustness or the efficiency for one ion only. However, a multitude of ions are transferred in a cell at a time. Then, a drawback of the proposed algorithm reveals itself immediately. That is, if

Fig. 8 Dependence of potential and internal concentration of potassium ions on the addition of potassium ions in external environment

the concentration of one ion is regulated at the expense of another ion, the concentration of the latter will obviously change dramatically in the opposite direction. This optimization problem is typical of systems where several alternative strategies of behavior are possible. For example, classical methods for business systems are those of the operations research. Optimization methods were also applied to some processes (expression of genes, etc.) in biological systems (Yilmaz et al. 2004; Ben-Dor et al. 1999), but transport problems were not considered from this viewpoint.

Let us discuss a mathematical problem statement for optimization of the transport system of a cell in terms of the operations research. Here too, several variants are possible since at present we do not have full information about the “price” to be paid for changes in a specific parameter of a cell.

Let us consider the problem of *optimizing a system*. We shall assume that the ion transport systems are known, and our task is to choose an optimal (in a sense) strategy and compare it with the strategy adopted in the nature.

The first variant. The efficiency is a maximum,

$$\eta \rightarrow \max. \quad (7)$$

The internal concentrations are limited to preset intervals,

$$n_{in}^{i1} \leq n_{in}^i \leq n_{in}^{i2}. \quad (8)$$

The flows are zero in the stationary state,

$$\sum_{i=1}^n J_i = 0. \quad (9)$$

The electroneutrality condition (the total charges of positive and negative ions are equal) is fulfilled,

$$\sum_{i=1}^n Z_i \cdot n_{in}^{i+} = \sum_{i=1}^n Z_i \cdot n_{in}^{i-}, \quad (10)$$

where Z_i is the charge of the i -th ion.

The second variant. The deviation of the internal concentrations from their normal values is a minimum,

$$\sum_{k=1}^n b_k \cdot (n_{in}^k - \tilde{n}_{in}^k)^2 \rightarrow \min, \quad (11)$$

where $\tilde{n}$ is the normal concentration of an ion, and the coefficients b_k are assigned and represent the weight (the significance for a cell) of each ion.

The system is fully efficient,

$$\eta = 1. \quad (12)$$

The flows are zero in the stationary state, and the electroneutrality condition is fulfilled.

From the viewpoint of the operations research, these two variants are dual problems (Hillier and Lieberman 2005). In both cases, it is necessary to determine operation frequencies of transport systems (pump capacities), C_{ik} , which determine both all the ion flows and the efficiency.

In a more general problem statement, these values can depend on both the internal and all external concentrations $C_{ik}(n_{in}, n_{out})$ (where n_{in} and n_{out} denote vectors). Then, the dependences $C_{ik}(n_{in}, n_{out})$ are to be determined.

For the algorithm to be implemented for a cell in an uncertain environment, it is necessary to define more clearly the concept of the “distance” (11) in this case. The point in question is the distance to the norm from some strategy described by a broken line. This distance can be determined if we have some aprioristic information about the intervals and the distributions of the concentrations of substances in the environment. In the simplest case, we shall assume that the intervals of the external concentrations of substances have been preset and the concentration distributions within an interval have been equiprobable. Then, the distance from each strategy to the norm can be defined as an average value determined from the formula (11), but averaged over a preset interval n_{out} . In a more general case, averaging is performed taking into account the probability that a particular value of n_{out} occurs.

The ion transport system of a cell can be displayed as a graph whose nodes will be transport systems of individual ions and arcs will be their bonds determined by the stoichiometry (see, for example, graph for cardiac cell at the Fig. 9). Therefore, it is topical to develop algorithms for solution of optimization problems on graphs.

These two strategies of regulating the transport in a cell can be compared with efficient and fast motor vehicles. Similarly to motor vehicles, artificial cells need be

Fig. 9 Representation of the transport system in the cardiac muscle cell as a *graph*

different. Some of them will be efficient in one environment, while others in another environment.

It is not improbable that different strategies of regulating the intracellular composition correspond to different environmental states in natural conditions. This is especially topical for early stages of the evolution (Melkikh and Seleznev 2008) as the transport of substances in simplest cells probably was one of the few functions. “Efficient” cells will win in a relatively constant environment; and “robust” cells, in a variable environment.

From the above consideration, it is possible to construct the following algorithm for optimizing the transport system in a cell:

- Plot the internal versus external concentration dependence for each ion.
- Find an optimal trajectory for each ion from the condition it is close to the norm.
- Rank the trajectories; that is, find such a trajectory, for which the distance to the norm is minimum. Fix this trajectory taking into account exchangers of other ions.
- Rank all the remaining trajectories considering the trajectory that has been fixed first. That is, find a trajectory with a minimum distance to the norm.
- Continue until all the ions have been enumerated.

The algorithm can be easily modified allowing for the weight factors of different ions.

The problem of synthesizing the transport system of an artificial cell

In the problem of optimizing the transport system, all systems of the transport of substances in a cell have been assumed to be known. However, in a more general case, one can pose himself the task to create efficient systems of

transport for a specific substance. This problem can be especially topical for artificial cells. Thus, the problem of *synthesizing* an efficient transport system is that among the multitude of permissible transport systems we chose systems, which offer the highest efficiency at a minimum sensitivity of the internal medium to variations in the environment. In this case, two limiting problem statements similar to those considered in section “[Regulation of the transport of many ions](#)” are possible.

The complexity of such a problem obviously depends on the aprioristic information about a cell and its environment. For example, if all systems of the transport of ions, except sodium ions, in a cell are known, the problem can be solved using the algorithms described in section “[Regulation of the transport of many ions](#)”, with the enumeration of possible systems of the transport of sodium ions. If no restrictions are imposed on systems of the transport of sodium ions, these systems can be large in number. The complexity of the problem will increase with an uncertainty in the environmental concentration of an ion (e.g., sodium).

Thus, since possible transport systems are many, calculation of an artificial cell is a more complicated problem. In this case, the unknowns also include the types of transport systems, each being characterized by the stoichiometry of ions transferred by the system. The number of transferred ions can only be an integer, and, therefore, the problem can be referred to integer problems of the operations research (Hillier and Lieberman 2005; Nemhauser and Wolsey 1988). This problem can be reasonably solved by statistical or approximate methods, because it can prove to be NP-complete, leading, if the transport systems are numerous, to enumeration of an exponentially large number of variants.

The proposed algorithm has an advantage over modeling the regulation of intracellular ion concentrations, based on control theory: rapid switching on (off) transport systems of the cell can be considered quasi-stationary. In this case, internal ion concentration do not explicitly depend on time, which allows for the calculation of the effective regulation of ion transport analytically. In this case, a minimum number of adjustable parameters must be determined from experiment. In addition, the analytical solution allows for a better understanding of optimal regulation laws of ion transport in cells.

Conclusion

Applying optimization methods to the transport system of a cell can help us understand the principles of its organization and the laws it obeys. This approach seems to be promising since the basic concept of biology—an

efficiency of all biological processes—is also one of the most significant concepts of cybernetics. In future, it will be possible to construct a full transport model for protozoa whose genome has been fully decoded.

A game problem statement of this study allowed constructing simple algorithms for optimization of the transport system of a cell. The problem of synthesizing an optimal system for an artificial cell has been considered, too.

The offered model was considered on an example of transport of potassium ions through a membrane of cardiac cell. Considered effective strategy of cell behavior is in a qualitative agreement with experimental data (simultaneous work of active transport systems during variation of external concentrations of ions was observed in experiments). It allows us to predict strategies of different cells behavior under various external conditions.

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