

# A P System Description of the Sodium-Potassium Pump\* (Extended Abstract)

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## 1 Introduction

Cell membranes are crucial to the life of the cell. Defining the boundary of the living cells, membranes have various functions and participate in many essential cell activities including barrier functions, transmembrane signaling and intercellular recognition. In this paper we refer to the sodium-potassium exchange pump [8], a transmembrane transport protein in the plasma membrane that establishes and maintains the appropriate internal concentrations of sodium ( $\text{Na}^+$ ) and potassium ions ( $\text{K}^+$ ) in cells. It is an important physiologic process present in all animal cells. By using the energy from the hydrolysis of one molecule of ATP, the pump transports three  $\text{Na}^+$  outside the cell, in exchange for two  $\text{K}^+$  that are taken inside the cell, against their concentration gradients. This exchange is critical in maintaining the osmotic balance of the cell, the resting membrane potential of most tissues, and the excitable properties of muscle and nerve cells.

In [5], the Na-K pump was previously described by using the process algebra  $\pi$ -calculus. In [4], the changing conformations of the pump were described explicitly and the transfer mechanisms were described step by step.

In this paper we model the movement of ions and the conformational transformations of the sodium-potassium pump in the framework of P systems, hence using discrete mathematics instead of the usual partial differential equations. A similar approach was used, e.g., in [2, 3] to model the activity of mechanosensitive channels in prokaryotic cells, and in [7] to describe the phenomenon of leukocyte selective recruitment in immune system.

We assume the reader is familiar with basic notions of P systems (see the monograph [11]).

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## 2 Sodium-Potassium Exchange Pump

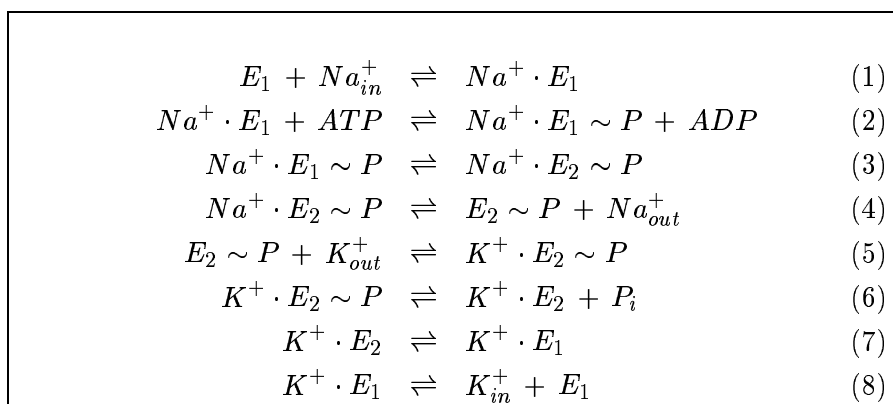
The sodium-potassium pump is a primary active transport system driven by a cell membrane ATPase carrying sodium ions out and potassium ions in. An animated representation of the pump is available on the web at

[http://arbl.cvmbs.colostate.edu/hbooks/molecules/sodium\\_pump.html](http://arbl.cvmbs.colostate.edu/hbooks/molecules/sodium_pump.html).

The description given in Table 1 is known as the Albers-Post model. According to the Albers-Post cycle, the sodium-potassium pump has essentially two conformations,  $E_1$  and  $E_2$ , which both may be phosphorylated or dephosphorylated. Ion transport is mediated by transitions between these conformations.

In the following table,  $A + B$  means that  $A$  and  $B$  are present together (e.g. in a test tube).  $A \cdot B$  means that  $A$  and  $B$  are bound to each other noncovalently.  $E_2 \sim P$  indicates that the phosphoryl group is covalently bound to  $E_2$ .  $P_i$  is the inorganic phosphate group ( $i$  means inorganic).  $\rightleftharpoons$  indicates that the process can go either way, i.e. it can proceed reversibly.

Table 1: The Albers-Post Model



$E_1$  binds  $Na^+$  to a high-affinity site available only from the inside (1). The binding of the sodium stimulates the enzyme to hydrolyze ATP (2), forming a phosphorylated enzyme intermediate. Then conformation  $E_1$  changes to  $E_2$  (3):  $Na^+$  is exposed to the outside surface, where  $Na^+$  binding is of a low-affinity type.  $Na^+$  is then released on the outside (4). On the outside surface is a potassium binding site exposed by the  $E_2$  phosphorylated enzyme. When  $K^+$  binds (5), the phosphoenzyme  $P$  is hydrolyzed (6). This stimulates the enzyme to expose the potassium binding site to the inside surface of the membrane, changing its conformation from  $E_2$  to  $E_1$  (7).  $K^+$  binding becomes of low affinity and we have the release of the potassium ions to the inside (8). The ATPase is now ready to bind  $Na^+$  once more. Inside and outside in this mechanism refer to the inside and the outside of the cell plasma membrane in which the  $Na^+/K^+$ -ATPase resides.

Regarding the relationship between the kinetic parameters of the transport process and the efficiency of the pump, we can mention that the rate constants of competing steps (that would decrease the efficiency) are small. This ensures that the

binding and the release of substrate occur at the proper point in the cycle. For example, the reaction  $E_1 + ATP \Leftrightarrow E_1 \sim P + ADP$  of equation (2) is slower than the reaction of equation (1). As a consequence,  $E_1$  has enough time to bind sodium ions before undergoing the transition to  $E_2$ . Similar relationships among rate constants ensure that ions are released from the enzyme before they come back to the side at which they were initially bound. In other words, the slow rate constants channel the enzyme along a reaction path in which the hydrolysis of ATP is tightly coupled to the transport process.

### 3 Modelling Na–K Pump with Membrane Systems

Since Na–K pump is a transmembrane protein associated with the phospholipid bilayer of the plasma membrane, we consider a membrane structure consisting of the skin membrane only. In order to formally describe the pump with a high resemblance to its biological structure and functioning, we also introduce a notation for the lipid bilayer by making use of symbols  $|$  which, placed next to the couple of square parentheses denoting a membrane, characterize a further intermediate region: the skin membrane with bilayer will be denoted as  $[| ]$ . Hence, the skin membrane with bilayer characterizes three distinct spaces:

$$Env [Bilayer | Reg | Bilayer] Env,$$

precisely the exoplasmic environment (in short,  $Env$ ), the lipid bilayer of the membrane ( $Bilayer$ ), the cytosolic space inside the plasma membrane ( $Reg$ ). In the following we will use only the semibracket notation for membranes, as introduced in [1], in order to simplify the global description.

The environment and the inner region are characterized by multisets of symbols over the alphabet  $V = \{Na, K, ATP, ADP, P\}$ , representing the substances floating inside them. We assume that, initially, the multiset inside the region consists of  $n$  sodium symbols,  $m$  potassium symbols and  $s$  molecules of  $ATP$ , that is  $M_{Reg} = \{Na^n, K^m, ATP^s\}$ , the multiset in the environment is  $M_{Env} = \{Na^{n'}, K^{m'}\}$ , while  $M_{Bilayer} = \emptyset$ .

We denote by  $R_{Na} = \frac{n'}{n}$ ,  $R_K = \frac{m'}{m}$  the ratios of occurrences of sodium and potassium ions outside and inside the membrane at any given step, respectively. These values are used to describe the starting time for the functioning of the pump. Indeed, in real cells it is known that the plasmatic concentration of sodium is very lower with respect to the external concentration, while the opposite holds for potassium concentration.<sup>1</sup> Whenever such natural conditions vary, the Na–K pumps in the plasma membrane try to re-establish the right physiological conditions. Hence, we assume that the activation of the pump is triggered by a change in the values of the ratios evaluated at the current step. Specifically, we define two conditions,  $k_1 \leq R_{Na}$  and  $k_2 \leq R_K$  (for some fixed  $k_1, k_2 \in \mathbf{R}$ ), such that the pump will not be activated if they are not satisfied. Otherwise, the pump starts its functioning. We call  $k_1, k_2$  *threshold values* and  $k_1 \leq R_{Na}, k_2 \leq R_K$  *threshold conditions*.

<sup>1</sup>For instance, a concentration of 145mM of sodium and 4mM of potassium can be found outside the cell, while 12mM of sodium and 139mM of potassium can be found inside (data taken from [9]).

The conformations of the pump are described by means of labels attached to the membrane, that is  $[[l]$ , with  $l \in L, L = \{E_1, E_2, E_1^P, E_2^P\}$ . The labels  $E_1, E_2$  correspond to the dephosphorylated conformations of the pump, while  $E_1^P, E_2^P$  correspond to the phosphorylated conformations, as already described in Section 2. Note the appearance of the common symbol  $P$  in both the alphabet  $V$  and in the label set  $L$ ; the meaning of this aspect will be explained in the sequel.

In this model, a generic evolution rule has the form

$$M_{Env} [M_{Bilayer}|_l M_{Reg} \xrightarrow{C} M'_{Env} [M'_{Bilayer}|_{l'} M'_{Reg},$$

where  $C$  is a threshold condition associated to the rule.  $C$  can be empty or expressed as a combination of other conditions, joined by logic connectives.

We also define two new types of evolution rules.

1. A *binding rule* has the form

$$b_{out,within} : x [[l \rightarrow [x|l'$$

$$b_{in,within} : [[l x \rightarrow [x|l'$$

for some  $x \in V^+$  and  $l, l' \in L$  (not necessarily distinct).

The application of a binding rule of the type  $b_{out,within}$  ( $b_{in,within}$ ) causes the movement of a multiset  $x$  from the environment (region) into the bilayer, without producing any modification for the communicated objects. Though, the label of the membrane can change.

2. An *unbinding rule* has the form

$$u_{within,in} : [x|l \rightarrow [[l' x$$

$$u_{within,out} : [x|l \rightarrow x [[l'$$

for some  $x \in V^+$  and  $l, l' \in L$  (not necessarily distinct).

The application of an unbinding rule of the type  $u_{within,in}$  ( $u_{within,out}$ ) causes the movement of a multiset  $x$  from the bilayer into the region (environment), without producing any modification for the communicated objects. Though, the label of the membrane can change.

A communication step can be described as the coupling of a binding and an unbinding rule: a couple of the type  $(b_{out,within}, u_{within,in})$  causes the passage of some objects from the outer environment into the internal region, while a couple  $(b_{in,within}, u_{within,out})$  causes the passage of some objects from the internal region to the outer environment, without modifying the nature of the objects. In contrast to the usual and direct communication with target indication in P systems, here the passage of objects happens by means of the interplay of two rules and this corresponds to the presence of an intermediate region.

**Remark 1** We stress here the fact that this kind of communication could be defined in another analogous way, namely using classical evolution rules with a new target indication of the type *within*, which would cause an object to pass from the environment or from the internal region directly into the bilayer. Anyway, this kind of mechanism would not be enough to model the Na–K pump, since in this case it is important to consider also the current label of the membrane and let the rule (possibly) modify also the label. Indeed, in this system the membrane plays a fundamental role, since it represents (a part of) the cellular pump we are modelling and not only a separator for different regions.

Given all the necessary definitions, the functioning of the Na–K pump can be now described by means of the following rules:

$$\begin{aligned}
r_1 &: [ ]_{E_1} Na^3 \xrightarrow{(R_{Na} > k_1) \wedge (R_K > k_2)} [Na^3]_{E_1} \\
r_2 &: [Na^3]_{E_1} ATP \longrightarrow [Na^3]_{E_1^P} ADP \\
r_3 &: [Na^3]_{E_1^P} \longrightarrow Na^3 [ ]_{E_2^P} \\
r_4 &: K^2 [ ]_{E_2^P} \longrightarrow [K^2]_{E_2^P} \\
r_5 &: [K^2]_{E_2^P} \longrightarrow [K^2]_{E_1} P \\
r_6 &: [K^2]_{E_1} \longrightarrow [ ]_{E_1} K^2
\end{aligned}$$

The application and meaning of rules is as follows. If threshold conditions are both satisfied, the pump is in conformation  $E_1$  and (at least) three sodium symbols are present inside the internal region, then the pump is activated (rule  $r_1$ ), it remains in conformation  $E_1$  and three sodium ions are bound to the bilayer.

The rule  $r_2$  can be applied if one occurrence of the object  $ATP$  is available inside the region:  $ATP$  is transformed into  $ADP$  with the production of one copy of the object  $P$  and, accordingly, the conformation of the pump is changed from  $E_1$  into its phosphorylated form  $E_1^P$ . Note an important aspect of this system: the object  $P$  now “becomes part” of the membrane label, hence it undergoes a “structural modification” by passing from being an element of the alphabet  $V$  to being a component of the membrane labels in the set  $L$ . We believe that, instead of considering  $P$  as a free object, it is more appropriate to use such a formal description (rather than using, for instance, the couple of rules  $[Na^3]_{E_1} ATP \longrightarrow [Na^3]_{E_1} ADP P$  and then  $[Na^3]_{E_1} P \longrightarrow [Na^3]_{E_1^P}$  instead of rule  $r_2$ ) since, actually, the phosphate directly intervene in the structural conformation of the pump (which is formally described here by means of membrane labels).

Now, in the system configuration  $[Na^3]_{E_1^P}$  rule  $r_3$  can be applied, the conformation of the pump changes from  $E_1^P$  to  $E_2^P$  and three sodium ions are left free in the environment. This is exactly an unbinding rule of the form  $u_{within,out}$  which, applied after the binding rule  $r_1$  (of the form  $b_{in,within}$ ) allows the communication of objects from the region to the environment.

When the system configuration is  $[[E_2^P]$  and at least two copies of the object  $K$  are present in the environment, then rule  $r_4$  can be applied: two potassium ions are bound within the bilayer and the pump conformation remains unchanged. By releasing the phosphate attached to the pump into the region, we obtain a conformation transition from  $E_2^P$  to the initial conformation  $E_1$  (rule  $r_5$ ) and, consequently, the unbinding of two objects  $K$  into the region (rule  $r_6$ ).

An activation cycle of the pump is thus finished. The thresholds conditions must be evaluated again according to the current multisets and subsequent activation cycles might occur.

The reader can easily check that the proposed P model for the sodium-potassium pump correspond to the biological description given by Albers and Post.

## 4 Conclusions and Future Work

In the following sections we briefly present future investigations and some possible extensions of the previous model.

Here we only mention that, as said in the Introduction, in [4] a description of the Na-K pump was given by using  $\pi$ -calculus, and software tools of verification were also applied. This means that it would be possible to verify properties of the described systems by using a computer program, and the use of the verification software as a substitute for expensive lab experiments. A similar development for P systems would be a very useful achievement.

### 4.1 An Analysis of the Pump with P Automata

In a P automaton (see [6], the seminal paper about the topic) the membranes are only allowed to communicate with each other, that is objects are never modified during a computation but only exchanged among regions, or consumed from the environment through the skin membrane.

Since the P system proposed in this paper present similar features with P automata, as a future extension of this work we intend to translate the model of the sodium-potassium pump into its corresponding P automaton (with the appropriate type of objects communication), and then to investigate its computational power. In this way, we think we could establish a theoretical link between the theory of Formal Languages and the (present description of) biological transmembrane protein.

### 4.2 Towards a stochastic approach

It would be interesting to extend P systems with some stochastic features able to characterize the molecular interactions involving the dynamic efficiency of the pump and other quantitative aspects (e.g., kinetics rates, energy, pump failures). Regarding the sodium-potassium pump, the whole transport process can have failures, and the pump can fail to transport  $\text{Na}^+$  out in exchange for  $\text{K}^+$  that are taken in.

There are some competing steps that may decrease the efficiency of the pump. For example, as already mentioned in Section 2, due to the lower rate constant for the reaction  $E_1 + ATP \Leftrightarrow E_1 \sim P + ADP$ ,  $E_1$  has enough time to bind sodium before

undergoing the transition to  $E_2$ . However, the reaction  $E_1 + ATP \Leftrightarrow E_1 \sim P + ADP$  can work sometime before the sodium ions bind to the pump; this occurs quite rarely compared to the usual activity of the pump. Mainly, ATP is working faster than the sodium ions, and the pump changes its conformation (from open inside to open outside) without the sodium ions.

This simple biological example motivates the study of stochastic aspects related to the P system proposed here. Therefore, in order to have a more realistic description of the pump, we could give a probabilistic model of the pump and even add some probability distributions to the actions of the pump. In this way, we could also model the quantitative behavior of the system.

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