A Probabilistic Model Checking Approach to Investigate the Palytoxin Effects on the Na^+/K^+-ATPase

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Abstract. Probabilistic Model Checking (PMC) is a technique that is used for the specification and analysis of unpredictable and complex systems. It can be applied directly to biological systems that show these characteristics. In this paper, PMC is used to model and analyze the effects of the palytoxin toxin (PTX) in transmembrane ionic transport systems, cellular structures responsible for exchanging ions through the plasma membrane. The correct behavior of these systems is necessary for all animal cells, otherwise the individual could present diseases and syndromes. We have discovered that high concentrations of ATP could inhibit PTX action, therefore individuals with ATP insufficiency, such as brain disorders (i.e. stroke), are more susceptible to the toxin. This type of analysis can provide a better understanding of how cell transport systems behave, give a better comprehension of these systems, and can lead to the discovery and development of new drugs.

Keywords: Probabilistic Model Checking, Systems Biology, Sodium-Potassium Pump, Palytoxin, Ion Channels Blockers and Openers.

1 Introduction

Probabilistic Model Checking (PMC) is a technique to model and analyze unpredictable and complex systems. PMC explores a stochastic model exhaustively and automatically, verifying if it satisfies properties given in special types of logics. Properties can be expressed, for example, as "What is the probability of an event happening?", offering valuable insight over the model [6,18,15].

PMC can be applied directly to biological systems to obtain a better understanding than others methods, such as simulations, which present local minima problems that PMC avoids [8,14,13,7].

We present and evaluate a PMC model of the sodium-potassium pump (or Na^+/K^+-ATPase), a transmembrane ionic transport system that exists in all

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animal cells and important to several biological processes i.e. cell volume control and heart muscle contraction. Its irregular behavior is related to numerous diseases and syndromes, and it is one of the main targets of toxins and drugs [3].

In our model we have exposed the pump to a deadly toxin called palytoxin (PTX) that essentially disrupts the behavior of the pump. This was done to better understand the effect of PTX interactions with the pump [19].

We have found that high doses of Adenosine Triphosphate (ATP), the cellular energy unit, could inhibit the action of PTX. For example, when the concentration of ATP is changed from 10 mM to 100 mM, the probability of being in PTX related sub-states is reduced by 38.37%. This suggests that individuals with ATP insufficiency are more susceptible to the toxin. This ATP deficiency appears in different forms, such as brain disorders, for example, stroke. Since ATP production cannot be stimulated directly, the study of its role and capability to change our Na^+/K^+-ATPase model behavior is even more important.

PMC can improve our understanding of cell transport systems and its behavior, and can lead to the discovery and development of new drugs.

Outline. This paper describes transmembrane ionic transport systems in Section 2. The related work to the analysis of these systems and PMC usage are discussed in Section 3. Our model is introduced in Section 4 and 5, and our experiments, properties and results are shown in Section 6. Finally, our conclusions and future works are presented in Section 7.

2 Preliminaries

2.1 Transmembrane Ionic Transport Systems

Transmembrane ionic transport systems are structures present in all animal cells. They are responsible for ion exchange from the extra to the intracellular medium. The difference in charges and concentrations between ions in these sides creates an electrochemical gradient. Ionic transport systems are responsible for the gradient maintenance, which is necessary for cells to perform their functions [2].

There are two types of transmembrane transport systems: ion channels, a passive transport that does not consume energy; and ionic pumps, an active transport that consumes energy in the form of Adenosine Triphosphate (ATP, or $[ATP]^i$ for intracellular ATP concentration). Ion channels depend on the concentration gradient of ions to be transported, moving in favor of that gradient. Ionic pumps move ions against the concentration gradient, electrical charge or both [16]. Once open, ion channels diffuse ions rapidly, allowing abrupt changes in ions concentrations. Ionic pumps, on the other hand, move ions very slowly, permitting only subtle changes in ions concentrations.

A generic ion channel is shown in Figure 1. The ion channel is initially closed, and there is a high concentration of ions in the extracellular medium. A signaling molecule binds to the ion channel. This opens the ion channel and allows the ions to diffuse rapidly from the extra to the intracellular side (low concentration of ions). The change in the ion concentration in the intracellular medium triggers