A Probabilistic Model Checking Analysis of the Potassium Reactions with the Palytoxin and Na^+/K^+-ATPase Complex

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Abstract. In this paper, Probabilistic Model Checking (PMC) is used to model and analyze the effects of the palytoxin toxin (PTX) in cell transport systems, 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 pathologies. We have developed a model which focuses on potassium and cell energy related reactions, due to the known inhibitory effect of potassium on PTX action and the ATP role in its transportation. We have used PMC to estimate state probabilities and use the Goldman-Hodgkin-Katz equation to measure the induced current created by ion exchange. Our model suggests that as the concentration of external potassium increases, ion exchange occurs against its electrochemical gradient, despite the PTX effect. This suggests that potassium could be used to inhibit PTX action. PMC allowed us to further characterize the system dynamics.

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

1 Introduction

Probabilistic Model Checking (PMC) is a computational automated procedure to model and analyze complex systems that present non-deterministic and dynamic behavior. These stochastic characteristics are difficult to handle however frequently appear once we model real systems. The system description is modelled as a stochastic process such as Markov chains [14,20].

This procedure exhaustively and automatically explores the state space of a model, verifying if it satisfies properties given in probabilistic temporal logics, such as Continuous Stochastic Logic (CSL). Properties can be expressed as, for example, "the probability that a particular reaction occurs is at least 10%". Properties can offer valuable insight over model behavior [8,17].

J.C. Setubal and N.F. Almeida (Eds.): BSB 2013, LNBI 8213, pp. 181–193, 2013.

PMC can be directly applied to study biological systems which show probabilistic behavior, common at the cellular level. Chemical reactions and biological processes might occur, depending on the concentration of ligands (ions and molecules), and environmental and cellular conditions. PMC can be used to improve our understanding of these systems, complementary to others methods, such as stochastic and deterministic simulations, which present local minima problems that PMC avoids due to its exhaustive approach [16,15].

In this work, we present and evaluate a stochastic PMC model of the sodium-potassium pump (or Na^+/K^+-ATPase), an active cell transport system that exists in animal cells. The pump is important to several biological processes, such as cell volume control and heart muscle contraction. Its irregular behavior can be related to several diseases and syndromes, such as hypertension and Parkinson's disease, and it is one of the main targets of toxins and drugs [3].

In previous works, the pump has been exposed to a deadly toxin called palytoxin (PTX), which binds to the pump and disrupts its regular behavior. This has been done in order to understand the effects of PTX interactions with the pump. Our current model describes potassium (K) and cell energy related reactions since potassium has a known inhibitory effect on PTX and cell energy plays a major role on ion exchange [24].

We have used PMC to calculate state probabilities, which has allowed us to used the Goldman-Hodgkin-Katz (GHK) flux equation to measure the induced current created by ion exchange. Our model suggests that as the concentration of $[K^+]^o$ increases, the direction of ion exchange is reversed.

This suggests that $[K^+]^o$ could inhibit PTX action, which is a known inhibitory property of potassium on the PTX-pump complex [24]. The role of potassium could be further investigated in order to research novel methods to inhibit PTX action. PMC allowed us to further study the PTX-pump dynamics.

2 Background

This section describes the basic background on transmembrane ionic transport systems, namely ionic pumps and ion channels. Several aspects are discussed, such as their cycle, and associated diseases and syndromes.

2.1 Transmembrane Ionic Transport Systems

Animal cells contain structures called transmembrane ionic transport systems, which are responsible for ion exchange between the sides of the cell. The difference in charges and concentrations between ions creates an electrochemical gradient, which is essential for cells to perform their functions properly. Ionic transport systems are responsible for the maintenance of this gradient [2].

There are two types of transport systems: ion channels — a passive transport system which does not consume energy to promote ion exchange and ionic pumps — an active transport system that uses energy in the form of Adenosine Triphosphate (ATP) to perform ion exchange. Ion channels depend on the concentration