EVOLUTION OF BIOLOGICAL SWITCHES

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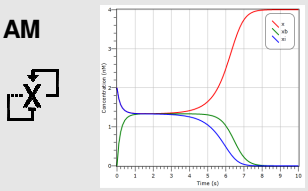
Introduction

The cell cycle transition between interphase and mitosis (G2/M) is a highly controlled step widely studied in biology. This transition is an irreversible process which behaves like an all-or-none switch. In the core of the switch (CC) are two positive feedback loops, where the Cyclin Dependent Kinase (CDK) activates its activator (CDC25), and inhibits its inhibitor (WEE1)[1].

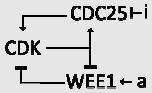
The efficiency of the switch relies on the complex interactions of its phosphatase and kinase components, leading to feedback loops. Although this core module the irreversible transition, it is not fully efficient in terms of speed and reaching the maxima. For being efficient, some other molecules are vital in the G2/M transition, like phosphatase PP1/PP2A, which inhibits CDC25 and activates WEE1, and the kinase GWL, the intermediary step to regulate PP1/PP2A (GWL)[3].

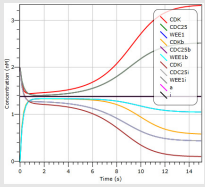
This complex system is fast, robust and reliable, but it has been shown that these properties can be achieved by a much simpler system based on the Approximate Majority algorithm (AM), used as a population protocol. This system is based on just one element that can exist in three states, two active states and one 'blank' state, which are connected by three positive feedback loops (two positive, one antagonistic)[1,2].

AM

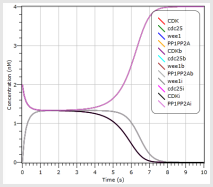


CC





GW

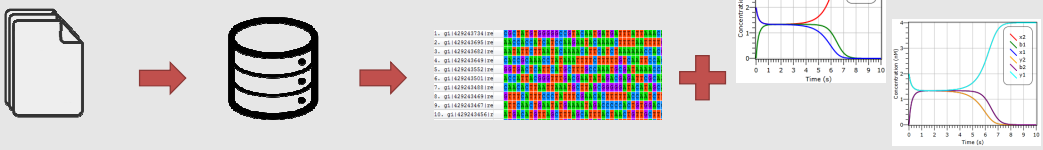


Objectives

Why do biological systems have evolved in complexity when simpler systems can lead to the same dynamical behaviour? What are the benefits of an increasing in complexity?

How phosphatases and kinases, the main players of the G2/M transition, have evolved?

Strategy



Looking for ancient eukaryotic protein kinases and phosphatases in the literature

Tracking their sequences across species looking for orthologous groups

Doing sequence alignments and structural alignments

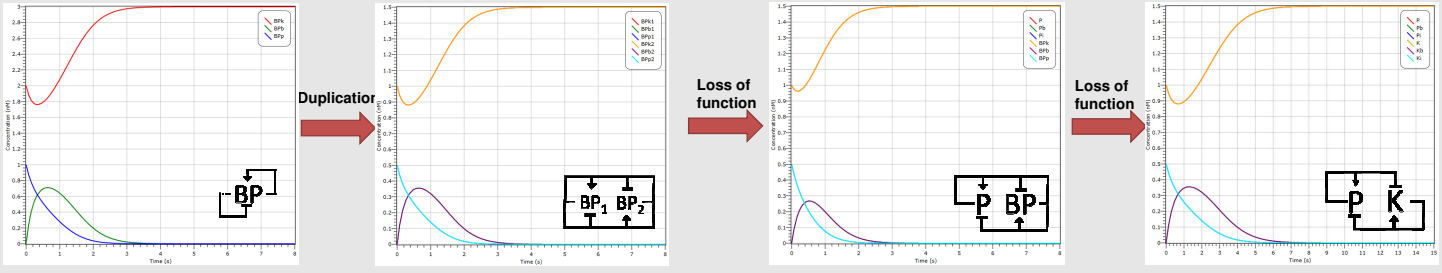
Comparing the dynamics of the regulatory networks at various complexity levels

Preliminary results

Events of (de)phosphorylation emerge at an early point in the evolution, probably before the division of the three kingdoms[4]. For kinases, piD261/Bud32 or RIO kinases could be the most ancient elements of the eukaryotic Protein Kinases (ePKs). Phosphatase families are more recent in the evolution, but it is possible that one of the most ancient molecules of this family belongs to the Low Molecular Weight PTP (LMW PTP)[5]. Interestingly, there is not evidence of a relationship between the number of phosphatases and ePKs (Archaea)[5].

Events like mutation and duplication increase the complexity of the networks. We have shown that a complex network like a mutual inhibition (MI) can arise from a simple one (AM) by duplication events and loss of function mutations.

AM **MI**



Significance of the project

Activation/Inhibition of molecules by (de)phosphorylation is one of the most extended mechanisms in biology for regulating molecular activity. Understanding the evolutionary process of phosphatases and kinases, the main players in the G2/M transition, is crucial to understand how cell cycle is regulated. Why are some elements more likely to be conserved than others? Why do networks increase their complexity during evolution if there are simple systems that are already efficient?

References

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