In silico model of Molecular Interaction Maps: c-Myc and cell cycle control

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Introduction

Cell behaviour is largely determined by protein:protein interactions. In particular, it has become increasingly evident that cell cycle control, differentiation and death are governed by networks of molecular interactions involving both proteins and DNA. The concomitant rapid increase of data concerning gene expression as measured in large scale experiments, has made evident the need to represent biochemical effectors (proteins and DNA) and their mutual interaction in an integrated way, in the form of a Molecular Interaction Map (MIM). To describe MIMs in a coherent graphical notation, the use of "wiring diagrams" similar to those adopted in electronics is proposed. In this work we describe the main features of a MIM focused on the oncogene c-Myc and on its role in cell cycle control.

c-Myc Molecular Interaction Map

Regulatory networks include a variety of interactions, such as formation of multi-protein complexes, covalent protein modification (e.g. phosphorylation), inhibitory or triggering actions. MIMs employ a system of symbols and syntactic conventions capable of describing the distinct interactions which have been proposed in several recent seminal studies [e.g. 1,2]. In its original form, a MIM is identified as a two-dimensional network representing both proteins/DNA and their mutual interaction. Among the advantages of this representation is a portray of competing interactions, which are common in bio-regulatory networks [1].

From a biological point of view, regulatory networks control whether cells of particular tissues may divide, depending on factors such as differentiation state, hormone or growth factor stimuli, and metabolic or genotoxic stress. They not only control cell proliferation, but also many other cellular behaviors. Additional controls impose checkpoints at transitions from one cell cycle phase to the next, in order to assure that each cell cycle phase is completed before the next phase is initiated. Notably, cell cycle control deregulation is associated to cancer onset, and the control of the state of the regulatory network is a promising approach to find new therapies for neoplastic diseases. In particular, c-Myc is a multifunctional protein whose expression, when deregulated, is one of the most important inducers of cancer. Many human cancers have altered c-Myc expression. In the first stages of this study we assembled the molecular interaction map centered on c-Myc protein and focused on cell cycle, based on available (and published) experimental information [3]. In the present version of c-Myc MIM, proteins and interactions are clickable and hyperlinked to the major biological databases (e.g., EMBL DataLibrary, Swissprot, OMIM, PFAM, LocusLink)

Part of the present work is aimed at building an *in silico* representation of the c-Myc MIM described in [3], by using an extended version of the System Biology Markup Language [2]. The map will be represented in five logical layers, each representing specific characteristics of either proteins/DNA or interactions (e.g. protein:protein complex formation, inhibition/activation, covalent modification, multidomain proteins). Further activity is focused on digital simulation carried out using a simplified (Boolean) representation of the map. The import of data derived from large scale gene expression experiments (DNA microarrays) is also implemented, and should provide a first step to integrate and interpret these data.

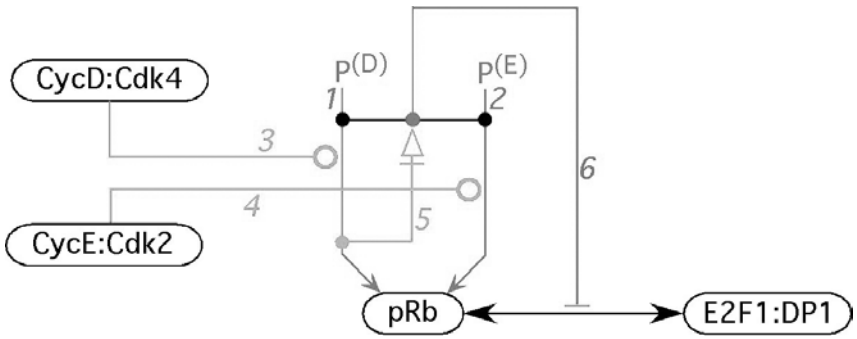

Fig. 1 Example of molecular interaction map: pRb phosphorylation.

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