Modelling of the eukariotic heat-shock response with probabilistic timed automata

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Motivation

Systems biology [1] aims at the analysis, modeling and simulation of biological systems and processes, through the supply of mathematical and computational models. The heat-shock response (HSR) is an ubiquitous and highly coordinate cellular process which is elicited by eukaryotic as well as prokaryotic cells primarily in response to protein damage [2]. The HSR, including exposure to environmental stresses (xenobiotics, heat shock, heavy metals), pathological states (viral, bacterial and parasitic infections, fever, inflammation, malignancy, ischemia), as well as physiological stimuli (growth factors, tissue development, hormonal stimulation), is characterized at molecular level, by the rapid and transient expression of a specific set of proteins belonging to the evolutionary conserved family of the heat shock proteins (HSPs). The HSPs primarily function as molecular chaperones contributing to protein homeostasis in cells under both normal and stressful conditions. The protective role of these chaperones (HSPs) is mainly exerted at the level of an active participation in the folding, assembly, translocation of proteins (under normal conditions) and in the repair or the degradation of non-native and damaged proteins (under stress conditions). Besides the well characterized roles of HSPs in cell survival and adaptation, to date there are increasing evidences of the importance of their chaperon function in a large numbers of human diseases. Critical roles in the regulation of the HSR are attributed to both the heat-shock transcription factor (HSF) and one of the major HSPs, the heat-shock protein 70 (Hsp70). Under normal conditions, the HSF is bound to Hsp70 in the cytoplasm of mammalian cells. Under stress conditions such as heat-shock and ischemia, HSF is separated from Hsp70, rapidly converted from a monomer to a trimer and inducibly phosphorylated and concentrated in the nucleus to activate heatshock gene transcription. The newly synthesized HSPs bind to HSFs to prevent further synthesis of HSPs via an auto-regulatory loop. The longterm aim of this study is to clarify the molecular mechanism(s) by which the eukaryotic cells sense and respond to stress. Although the same set of genes, known as heat shock genes are induced, different members of the HSF family are activated. All of them bind to conserved genetic elements known as heat-shock elements (HSE). We are currently developing a predictive model of the cytoplasmic and nuclear events of the eukaryotic HSR by means of probabilistic timed automata [3] trying to gain a better understanding of this universal cellular phenomenon.

Methods

We propose to model the structure and the dynamics of heat shock response of a cell as a probabilistic timed automata, a formal description mechanism in which both nondeterministic and probabilistic choices can be represented. In our model the compartments (cytoplasm and nucleous) of the cell are automata, and the actions are the interactions among components performing cellular processes. The initial stages of the modelling process employ the timed automata model checking tool UPPAAL [4] to automatically verify the soundness of several abstractions applied to our probabilistic timed automaton model. The use of nondeterminism allows us to model asynchronous behaviour of cell components. Moreover, the use of probabilities give us a chance to verify properties referring both to the likelihood of interaction with proteins, and to the probability that a cell component reacts to a certain environmental event.

Results

The model of eukariotic heat shock response has been created with probabilistic timed automata which allowed to clarify the molecular mechanism(s) by which eukaryotic cells sense and respond to stress. It is expected that the same set of genes (heat shock genes) are induced by different members of the HSF family; HSF1 becomes active in response to classical stress stimuli, whereas

HSF2 is active during differentiation-related processes.

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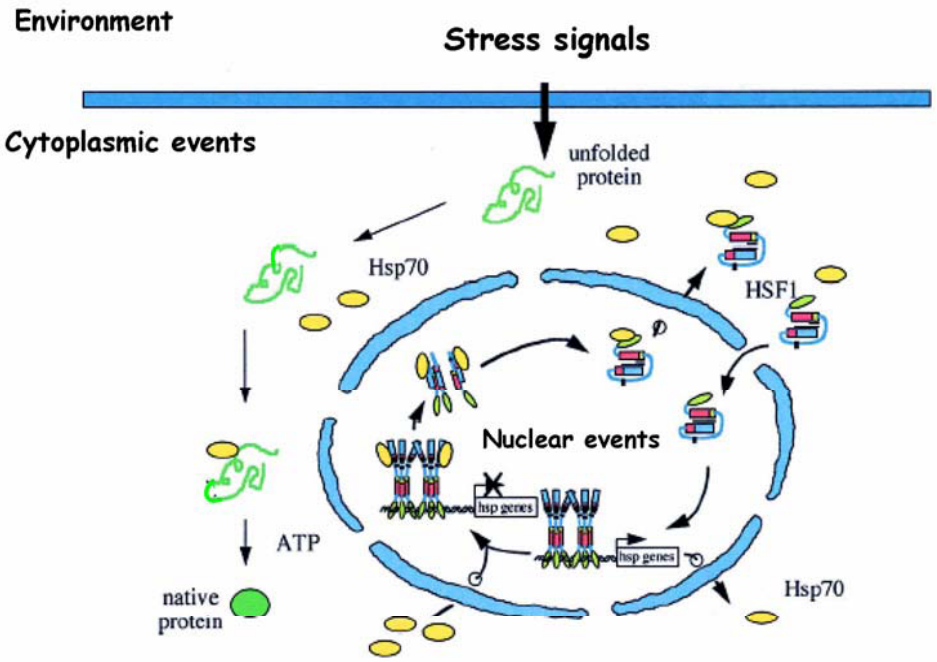
Supplementary informations

A multilayer architecture to support bioinformaticians of today and tomorrow, submitted to BITS 2006. The proposed study is being carried within the MIUR-FIRB LITBIO project (http://www.litbio.org/).



Regulation of the heat shock response (modified from Santoro MG, Biochem. Pharmacol., Vol.59, pp. 55-63, 2000