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Logical modelling and analysis of the budding yeast cell cycle

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Biological background

The budding yeast cell cycle core engine has been modelled in great detail, most notably by the groups of Béla Novak and John Tyson, using a differential formalism. Several models focusing on different regulatory modules have been developed. In this respect, the use of a logical formalism facilitates the development of more integrated models, through the articulation of control modules to the core engine. Such integrated models are difficult to build with the differential formalism due to the lack of quantitative data, as well as to numerical instabilities inherent to large non linear systems.

Logical modelling of cell cycle regulatory modules

Relying on the logical framework defined by Thomas and Kaufman [1], we use GINsim, the modelling software developed in our team [2] to integrate the morphogenesis checkpoint module to the core model of the yeast cell cycle published by Chen *et al*. [3] (see also [4] for an application on the Mammalian cell cycle).

Our current logical model recapitulates the wild type succession of events as presently characterised. We are now adjusting the model parameters to account for all mutant phenotypes described together with the original differential model [3]. At this point we focus on Knock Out (KO) mutants and on strong gene over-expressions.

Our logical simulations provide consistent results for two thirds of the 90 mutants already tested. The remaining problematic cases involve regulatory genes such as Sic1 and Cdh1, whose parameterisation is very complex. We are currently implementing in GINsim the possibility to define the parameters in the form of logical formulas to overcome this problem.

In parallel with our model of the budding yeast cycling core, we are developing a logical model of the morphogenesis checkpoint, inspired by the work of Ciliberto *et al*. [5]. This module is expected to produce a stable state with active Clb2 when the checkpoint is off, and when the checkpoint is on, Clb2 activation should be delayed, to prevent the formation of dinucleate cells. Still, the arrest is not complete, and after a while the checkpoint can be overcome. In our model, this relates to an increase of mass. Clb2 is then activated and the cell can complete nuclear division, becoming dinucleate.

This module has been designed to fit the wild-type behaviour, as well as that of the swe1Δ, mih1Δ and hsl1Δ mutants. Interestingly, the double mutants mih1Δ hsl1Δ and mih1Δ swe1Δ also exhibit the expected behaviour. Other mutant phenotypes listed or predicted in [3,5] have still to be tested.

Conclusions and prospects

The two models have then been connected together. Preliminary stable state analysis shows that the coupled model retains the properties of the two modules. A more thorough analysis should confirm this result. At the present time, we still have to tune these models to fit all

the mutant phenotypes. In the longer term, we plan to model other checkpoints and connect the resulting modules to our cell cycle core model. Finally, we also plan to systematically apply regulatory circuit analysis and model-checking approach to the resulting model.

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