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Modelling genetic regulatory networks from specified behaviours

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Introduction

Modelling and simulation are needed to understand genetic regulatory networks. But parameters of the models are usually difficult to determine. To deal with this problem we propose a methodology in which the qualitative approach developed by R. Thomas [1] is used. The parameters of the model, which are related to the kinetic parameters of a differential description, may be unknown. We translate the set of possible models into one Symbolic Transition System, and the known behaviours into temporal logic formulas; then the constraints on the parameters corresponding to all models having the specified behaviours can be determined.

Models

In the asynchronous discrete modelling of regulatory networks [1], each variable x represents the concentration of a constituent of the network. In each state, the value of x is an integer bounded by the number of variables that x can regulate. Each state and each variable is associated with a parameter that has an integer value. This parameter is the value toward which the variable tends in the associated state.

Examples

Pseudomonas aeruginosa are bacteria that secrete mucus in lungs affected by cystic fibrosis, but not in common environment. As it increases respiratory deficiency, this is a major cause of mortality in this disease. The regulatory network proposed in [2], contains the protein AlgU, and an inhibitor complex anti-AlgU (Fig. 1A). Bacteriophage lambda is a virus whose DNA can integrate into bacterial chromosome. After infection, most of the bacteria display a lytic response, but some display a lysogenic response, i.e. survive and carry lambda genome, becoming immune to infection. The graph of interactions described in [3] involves four genes, cI, cro, cII and N (Fig. 1B). The lytic (resp. lysogenic) response leads to the states where cro (resp. cI) is fully expressed. In these two cases the parameters are unknown.

Methods

The set of all discrete models associated with a graph of interactions are translated into a Symbolic Transition System. Then we apply symbolic execution techniques [4], to construct a tree of states sequences, such that each path is associated with the constraint on parameters necessary to its existence: this constraint is called *path condition*. To search a specific path in the symbolic execution tree, we have adapted model-checking techniques for Linear Temporal Logic (LTL): all paths verifying the LTL formula are selected, and the disjunction of the associated path conditions is synthesised. The resulting constraint represents all parameters compatible with the specified behaviour.

Results

It has been observed that mucoid *P. aeruginosa* can continue to produce mucus isolated from infected lungs. It is commonly thought that the mucoidy is due to a mutation which cancels the inhibition of algU gene; an alternative

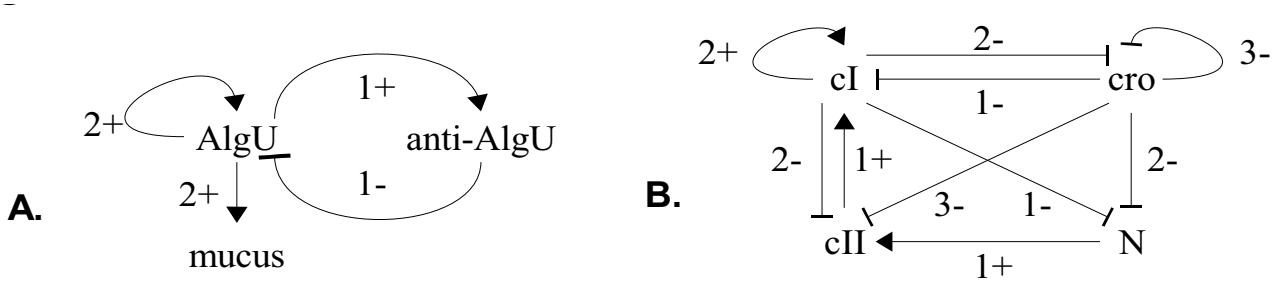

Figure 1
Graphs of interactions: **A**. Mucus production in *P. aeruginosa*. **B**. Immunity control in lambda-phage. Each arrow indicates an interaction; the sign indicates a positive or negative effect, and the integer is the threshold of the interaction; when the regulator is greater than or equal to the threshold, the interaction is effective.

hypothesis is that it is an epigenetic modification, occurring without mutation [2]. With the method described here it is possible to find the constraints such that the resulting models have two stable behaviours, one mucoid and one non-mucoid: the 8 selected models are compatible with the epigenetic hypothesis. In the case of lambda-phage, there are 2156 coherent models with pathways from initial state to lysis and to lysogeny. But in all these models, there is a common path to lysis, and at least one of two precise paths to lysogeny.

Conclusion

Because of the partial knowledge of systems, even with a qualitative formalism, different models can fit with experimental results. Our method allows manipulating not only one model, but a set of coherent models. Then we can efficiently respond to two kinds of questions: is there any selected model coherent with a hypothetic behaviour (as the epigenetic modification in *P. aeruginosa*)? Are there common behaviours in selected models (as pathways to lysis or lysogeny in lambda-phage)? Moreover, by keeping this set, new experimental results can be added incrementally to restrict and refine the models.

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