Derivation of qualitative dynamical models from biochemical networks

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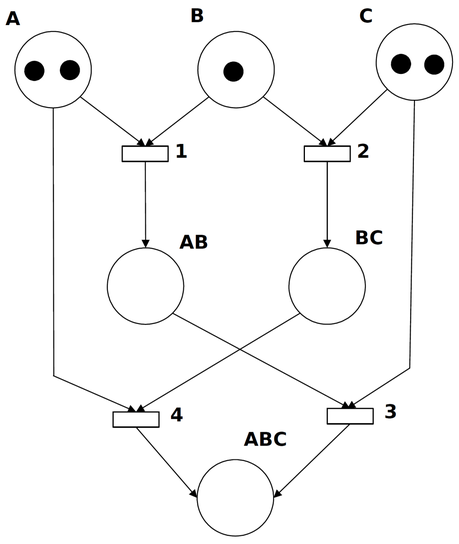
1 Introduction

- As technological advances allow a better identification of cellular networks, more and more data are produced allowing the construction of large scale and detailed molecular interaction maps[1].
- One approach to unravel the dynamical properties of such complex systems relies on the derivation of qualitative dynamical models from these maps in order to ease their analysis.
- Existing automatic methods for such model derivation still lack convenient trade-off between complexity and accuracy.

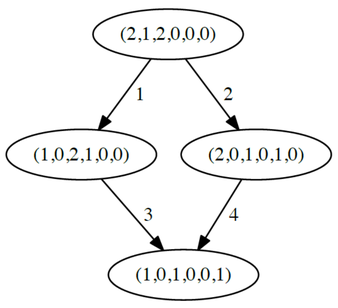
2 Aim and methods

- Design of an automatic tool to derive accurate qualitative dynamical models.
- Clarification of the underlying assumptions made in the process of qualitative modelling.
- Abstract interpretation framework to formally relate model behavior at different levels of abstraction[2].
- Using of relevant case studies to assess the accuracy of our approach on properties of interest.

3 Concrete semantics



a) Petri Net

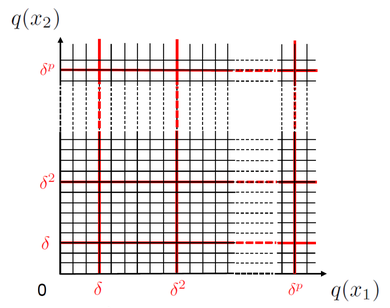


b) Transition system

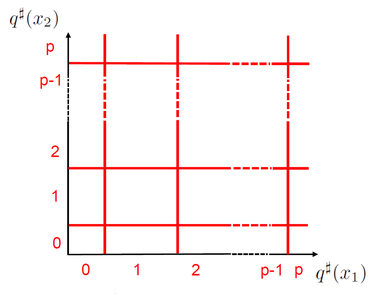
Fig.1. (a) Petri Net representation of a model with a protein adaptor (protein B), in the initial state (q(A)=2, q(B)=1, q(C)=2, q(AB)=0, q(BC)=0, q(ABC)=0). Placeholders denote the chemical species, tokens represent the number of instances of each chemical species, rectangular nodes denote the reactions. (b) Induced transition system. Nodes denote concrete states, while arcs represent transitions triggered by the reactions labeling the arcs.

4 Abstract semantics

- Abstraction of values



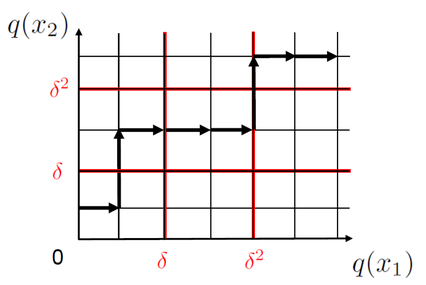
a) Concrete states



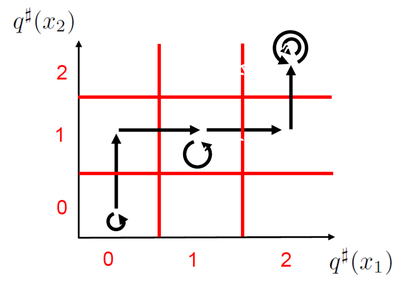
b) Abstract states

The domain of states is sampled within intervals (red lines). The number of instances (black lines) in each interval is then abstracted away and the intervals are mapped to their corresponding abstract values.

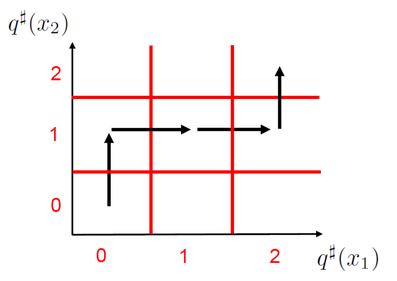
- Abstraction of traces



a) A concrete trace



b) Sampling values



c) Omitting silent transitions

5 Refinements

- Introduction of three refinements in our abstraction

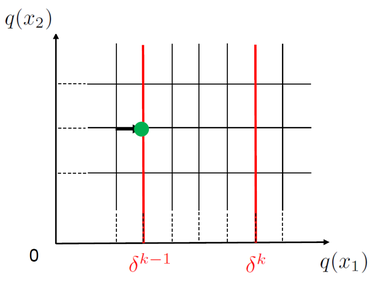
1) Mass invariants

The overall number of instances of the chemical units composing the chemical species remains constant:

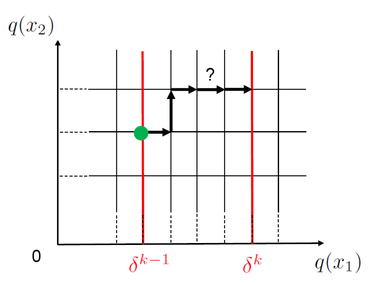
$$\sum \alpha_x q(x) = b$$

2) Constraints on the crossing of intervals

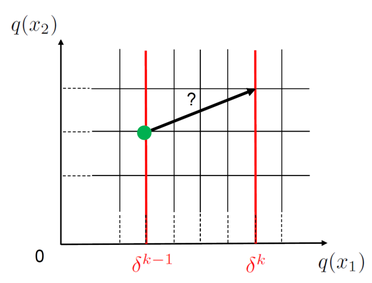
When the number of instances of a chemical species enters a new sampling interval, there may not be enough resources so that it may reach the next interval.



a) A value enters a new interval



b) Is there a trace to reach the next one ?



c) Is there a flux vector to reach the next one ?

3) Time scale separation

Enrichment of the model behavior with information on reaction kinetics.

Taking into account the separation between time scales: slow reactions are preempted by fast ones.

- Combination of the refinements using a reduced product.
- Soundness of our approach: no behavior is lost during the abstraction[3,4].

6 Application to a case study

- Case study: a model with a protein adaptor (see Fig.1).
- Property of interest: sequestration effect appearing when the initial level of the protein adaptor (protein B) is high compared to the ones of its binding proteins (proteins B and C).

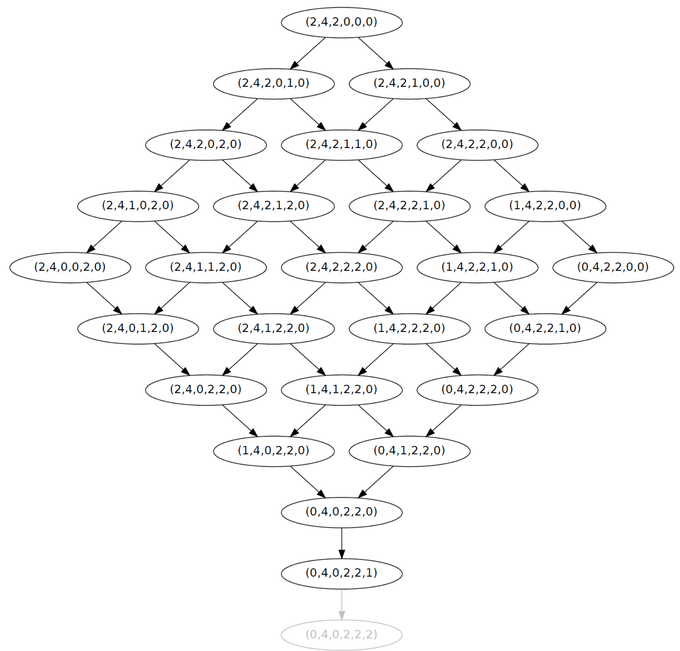


Fig. 2. Set of abstract transitions refined with our three properties for the case study of a model with an adaptor (see Fig. 1), starting from the initial state ($q^\sharp$(A)=2, $q^\sharp$(B)=4, $q^\sharp$(C)=2, $q^\sharp$(AB)=0, $q^\sharp$(BC)=0, $q^\sharp$(ABC)=0). A node denotes an abstract state, while an arrow represents single or multiple transitions. The reactions associated with the transitions are omitted. The grey arrow denotes a transition which is discarded by the refinement on the constraint on interval crossing.
Our refined abstraction is able to capture the sequestration effect by the adaptor protein B: we can prove, from the abstract semantics, that the number of instances of ABC always remain very low starting from an initial state for which the number of instances of B is higher that those of its binding proteins A and C[4].

7 Prospects

- Scaling up of the methodology: extension of the framework to reduced reaction networks obtained by the fragmentation of the models written in kappa language[5].
- Analysis of other case studies showing properties of interest, and identification of modeling refinements allowing to capture these properties.

References

[1] Grieco *et al.*, *PloS Comput Biol* 9 (2013); [2] Cousot P., Cousot R., *POPL'77, ACM* (1977);
[3] Abou-Jaoudé *et al., CMSB 2015* (2015); [4] Abou-Jaoudé *et al., submitted to BioSystems*;
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