

A Fixed Point Logic for Checking Properties of Biological Systems

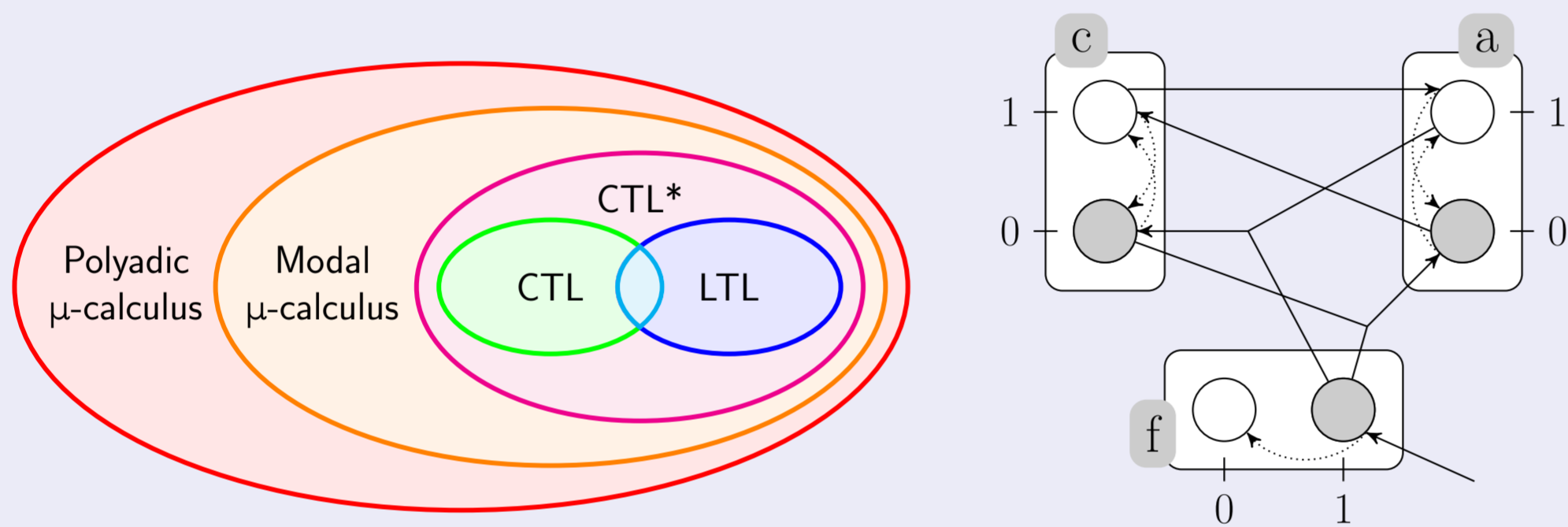
Maxime Folschette and Martin Lange

School of Electr. Eng. and Computer Science, University of Kassel, Germany

Motivations

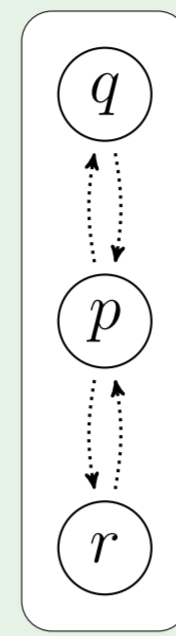
We use the **polyadic μ -calculus** [1], a generalization of modal μ -calculus and CTL*, in order to study biological models. The modal μ -calculus features atomic properties on nodes (p), the universal (\Box) and existential (\Diamond) modal operators to access immediate futures, and the least (μ) and greatest (ν) fixed point operators to express explicit iterative computations. Its polyadic extension introduces the notion of **tokens**, that are dynamic pointers to nodes in the considered model. Considering several tokens allows dynamical relations between nodes to be studied. Properties on nodes (p_i) as well as modal operators (\Box_i, \Diamond_i) get indexed by a token identifier i , specifying which token is being accessed by this operator.

Here, we apply the polyadic μ -calculus to **biological regulatory networks** in a way that does not require the computation of the state-transition graph beforehand. The logic is directly interpreted using the “compact” form that most biological models come into. We focus here on a range of models called **Asynchronous Automata Networks** (AANs) [4] that consist of Synchronous Automata Networks in which each transition changes the active local state of exactly one automaton. This class of models especially encompasses the widespread formalism of René Thomas. For this, the semantics of \Box_i and \Diamond_i is adapted to match the semantics of the considered class of models; in other words, a token can move along an edge only if the semantics of the model allows it.



Semantics of the logic

Example 1



Atomic property (p, q, r)

$$\llbracket p_1 \wedge r_2 \rrbracket = \{(p, r)\}$$

$$\llbracket p_1 \rrbracket = \{(p, p); (p, q); (p, r)\}$$

Token affectation ($i \leftarrow j$)

$$\llbracket \{2 \leftarrow 1\} p_1 \wedge p_2 \rrbracket = \{(p, p); (p, q); (p, r)\}$$

Token comparison ($i = j$)

$$\llbracket 1 = 2 \rrbracket = \{(p, p); (q, q); (r, r)\}$$

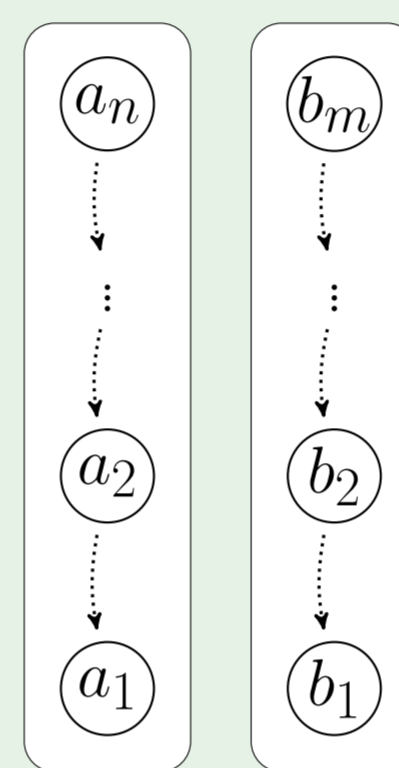
Possible future (“may”)

$$\llbracket \Diamond_1 q \rrbracket = \{(p, p); (p, q); (p, r)\}$$

Necessary future (“must”)

$$\llbracket \Box_1 q \rrbracket = \emptyset$$

Example 2



Least fixed point (μ)

$$\phi = \mu X. (\Box_1 \perp \wedge \Box_2 \perp) \vee \Diamond_1 \Diamond_2 X$$

Iterations:

$$\llbracket \phi \rrbracket_0 = \emptyset$$

$$\llbracket \phi \rrbracket_1 = \{(a_1, b_1)\}$$

$$\llbracket \phi \rrbracket_2 = \{(a_1, b_1); (a_2, b_2)\}$$

$$\llbracket \phi \rrbracket_3 = \{(a_1, b_1); (a_2, b_2); (a_3, b_3)\}$$

⋮

Generalization:

$$\llbracket \phi \rrbracket = \{(a_i, b_i) \mid i \in [1; \min(m, n)]\}$$

List the switches that prevent reaching a given state \mathbf{a} :

$$\varphi_s(\mathbf{a}) = (\mu X. (\mathbf{x} = \mathbf{a}) \vee (\bigvee_{i=1}^n \Diamond_{x_i} X)) \wedge \bigvee_{i=1}^n \Diamond_{x_i} \{1 \leftarrow 2\} (\nu Z. \neg(\mathbf{y} = \mathbf{a}) \wedge (\bigwedge_{j=1}^n \Box_{y_j} Z))$$

Computes all couples of successive states where a switch in the reachability of \mathbf{a} occurs.

$$\llbracket \varphi_s(\mathbf{a}) \rrbracket = \{(s; t) \in \mathcal{L} \times \mathcal{L} \mid s \rightarrow t \wedge s \rightarrow \mathbf{a} \wedge \neg t \rightarrow \mathbf{a}\}$$

Bisimulation of two models on observable components:

$$\varphi_b = \nu X. (\bigwedge_{p \in P} \bigwedge_{(i; j) \in C} p_i \Leftrightarrow p_j) \wedge (\Box_O^* \Box_{O'} \Diamond_{O'}^* \Diamond_O X)$$

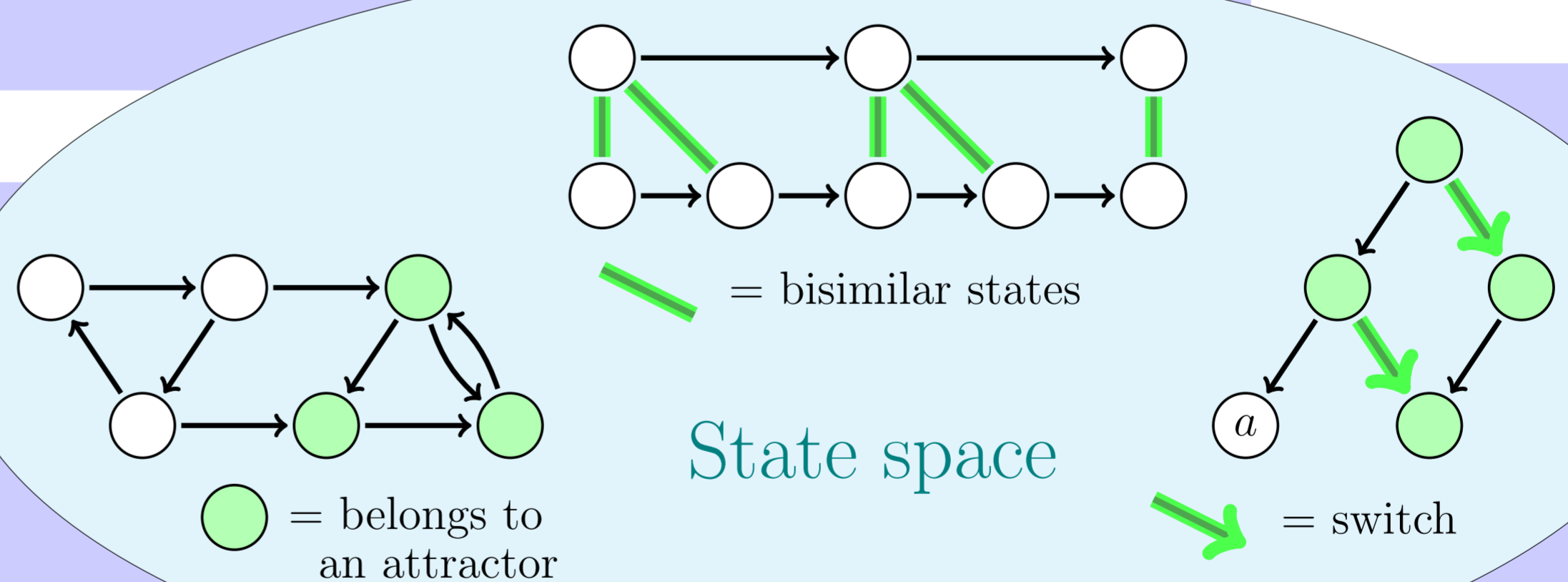
for two given sets of observables O and O' and a correspondence relation C . Ensures that the two models are bisimilar when considering only observables.

List all states belonging to an attractor:

$$\varphi_a = \{\mathbf{y} \leftarrow \mathbf{x}\} \nu W. (\bigwedge_{i=1}^n \Box_{x_i} W) \wedge \mu Z. (\mathbf{x} = \mathbf{y}) \vee (\bigvee_{j=1}^n \Diamond_{x_j} Z)$$

All finite paths starting from \mathbf{x} never prevent to loop back to \mathbf{x} .

$$\llbracket \varphi_a \rrbracket = \{(s; s) \mid \forall t, s \rightarrow t \Rightarrow t \rightarrow s\}$$



$$\text{AAN} \stackrel{?}{\models} \varphi$$

Model checking the polyadic μ -calculus

The problem of checking whether an AAN with n components, each of size at most k , satisfies a formula φ is **decidable** in time $\mathcal{O}((k^{cn} \cdot |\varphi|)^{ad(\varphi)+1})$ where c is the number of tokens used in each component and $ad(\varphi)$ is the nesting depth of alternating fixed point operators in φ . This is low for typical properties of interest: reachability properties for instance can be formalized with depth 0, some properties of repeated reachability require alternation depth 1. Equally, c will also be low, typically at most 3, and k often equals 2 in biological networks.

Conceptually, the **model checking problem** is reduced to that of the modal μ -calculus over the state-transition graph of the AAN [5]. **On-the-fly techniques** [3] then avoid the construction of the whole graph in general.

Symbolic model checking using BDDs [2] is also possible.

Conclusion

A model-checking tool is currently under development. Finding optimizations for specific formulas or models may help reduce the complexity of the model checking in some cases.

Further work also includes the formalization of more interesting properties on biological systems into polyadic μ -calculus.

References

- [1] H. R. Andersen. A Polyadic Modal μ -Calculus. Technical Report ID-TR: 1994-145, DTU, 1994.
- [2] J. Burch, E. Clarke, K. McMillan, D. Dill, and L. Hwang. Symbolic model checking: 10^{20} states and beyond. *Information and Computation*, 98(2):142–170, 1992.
- [3] C. Courcoubetis, M. Y. Vardi, P. Wolper, and M. Yannakakis. Memory-efficient algorithms for the verification of temporal properties. *Formal Methods in System Design*, 1(2/3):275–288, 1992.
- [4] Maxime Folschette, Loïc Paulevé, Morgan Magnin, and Olivier Roux. Sufficient conditions for reachability in automata networks with priorities. *Theoretical Computer Science*, in press, 2015.
- [5] M. Lange and E. Lozes. Model checking the higher-dimensional modal μ -calculus. In *FICS'12*, volume 77 of *EPTCS*, pages 39–46, 2012.