Analysis of Gene Regulatory Networks – An Overview –

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Discrete Models of GRN

- State transition graph;
- Vertexes are **genes** and arcs encode the **activation/inhibition**;
- **Time** occurs in synchronous **discrete** steps.

Thomas' formalism

– Multi-valued concentration values with discrete variables.

Boolean networks

– Genes are either active or inactive.

Discrete Models of GRN

Probabilistic boolean networks

– Expresses the possible regulatory functions for an entity.

Petri Nets

– Non-deterministic models;

– Can express Boolean networks as well as uncertainty in regulatory functions.

Discrete Models of GRN

- Less detailed model - good for small nets when only qualitative information is available;
- Allow the use of model checking techniques (but state explosion problem);
- Neglects the time delay in the change between genes levels of expression.

Continuous Models of GRN - ODE

- Description of the change in each entity as a function of other entities;
- Detailed information about the dynamics but requires **data on kinetic parameters**.

Piecewise Affine (PWA) Systems

- Continuous evolution + boolean-valued regulation;
- $\dot{x}_i = f_i(x) - \gamma_i x_i$;
- $f_i(x)$ is the production rate regulated by a boolean value;
- $\gamma_i x_i$ is the loss/transformation rate.

Continuous Models of GRN

- Pure analytical approaches represent a more realistic model;
- Allow simulations but no verifications (only with abstractions like Thomas' model);
- Needs parameter values which there are not always available.

Modeling considerations

- Some continuous models allow parameter uncertainty;
- Best of both worlds: Hybrid Systems!

BUT...

- Model checking approaches require linear dynamics in the discrete transitions and various forms of **linear approximations** in the continuous dynamics;
- Even in the simpler timed automata, in which clocks are the only source of continuous dynamics, parameters immediately make the **model checking problem undecidable**;

Available tools

System/Work	Model(s)	Logic(s)	Model Checker(s)
SMBioNet	Thomas	CTL	NuSMV
Biocham	ODEs, stochastic, discrete	CTL,LTL+ constraints, PLTL	NuSMV, PLTL
GNA	pw-linear eq., Bool	CTL, $\mu-$calculus, CTRL	NuSMV, CADP, CTRL
Pathway logic	rewrite rules, Petri, Bool	LTL	LoLA
Antelope	Boolean	Hybrid CTL	Antelope's
Simpathica, XSSYS	ODEs	variant LTL	XSSYS
Fisher et al. (2007)	reactive modules	Altern.-time temp. logic	Mocha
Ahmad et al. (2006)	Linear Hybrid Automata	"while" language	HyTech
Calder et al. (2006)	cont.-time Markov chains	CSL	PRISM
Heath et al. (2006)	cont.-time Markov chains	CSL	PRISM
Ciocchetta et al. (2006)	cont.-time Markov chains	CSL	PRISM

Table: Summary of modeling tools using model checking [5].

Formal reasoning in biological queries

Advantages of reasoning capabilities

- Info about open problems (possible behaviours, refutation of hypotheses, missing variables, missing interactions..) that may help improve the model;
- Suggestion of new bio experiments when proving previously unknown properties.

Biological queries

About reachability

- Given an initial state, is there a series of reactions that will produce some compound P?
- Which are the states from which a series of products P1,...,Pn can be produced simultaneously?

About pathways

- Given an initial state, can the cell reach a state s while passing by another state s2?
- Is state s2 a necessary checkpoint for reaching s?
- Is it possible to produce P without creating nor using some Q?
- More generally, is a state s reachable under a certain constraint c from a set of initial states?

Biological queries

About stability properties

- Is a certain state s of the system a stable state?
- Can/Must a system reach a given stable state s from the initial state?
- What are the stable states?
- Can the system exhibit a cyclic behaviour w.r.t the presence of a product P?

About durations

- How long does it take for a molecule to become activated?
- In a given time, how many Cyclins A can be accumulated?
- What is the duration of a given cell-cycle's phase?

Biological queries

About correctness of the model

- Can we detect the inaccuracies of the model and correct them?

The previous queries were taken from [6].

New approach - Logical Analysis of Hybrid Systems

Differential dynamic logic d$\mathscr{L}$

- Supports dynamical evolution + discrete control;
- Accounts for delayed controller reactions to bridge the gap of continuous-time models and discrete control;
- Parametric extraction techniques allow the identification of the requirement for verifying a certain property.

Differential Algebraic Logic (DAL)

- Complements dl in a way that allows systems with **disturbances and non linear constraints**;
- DAL programs can be verified by exploiting their differential constraints algebraically without having to solve them.

New tool - KeYmaera

KeYmaera is a hybrid verification tool for hybrid systems that **combines deductive, real algebraic, and computer algebraic** prover technologies.

- Supports d$\mathscr{L}$, nonlinear discrete jumps, nonlinear differential equations, differential-algebraic equations, differential inequalities, and systems with non-deterministic discrete or continuous input;
- Has a **compositional verification** principle helps scaling up verification;
- Implements procedures for automatically generating invariants and differential invariants.

Next

- Formulation of **case studies in KeYmaera** and proof of useful properties;
- Extension of the **biological queries list** for the case of differential analysis;
- Documentation of the developments.


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