Refining Dynamics of Gene Regulatory Networks in a Stochastic π-Calculus Framework

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Context

Hybrid modelling of Gene Regulatory Networks (GRN).

- Formal languages approaches:
  - κ language [Danos],
  - stochastic π-Calculus [Priami].
- Formal verification approaches:
  - Time(d) and Stochastic Petri Nets [Heiner],
  - Biocham [Fages],
  - Timed Automata [Siebert,Bockmayr],
  - Linear Hybrid Automata [Ahmad,Roux].

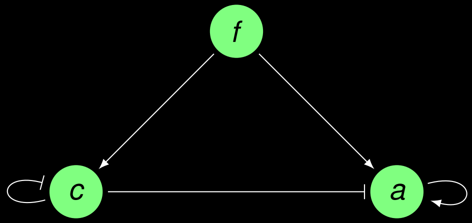
Goal: temporal parameters synthesis for hybrid models of GRN.

Contrib: introduction of temporal and stochastic parameters within π-calculus models of GRN.

Outline

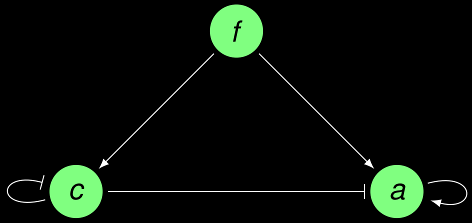
1. Generalized dynamics for Gene Regulatory Networks.
2. The Process Hitting framework.
3. Discrete (structural) refinements: cooperativity and stable states.
4. Temporal and stochastic parameters: temporal determinism.

Gene regulatory networks



- Activations and inhibitions between genes.
- Gene have a set of logical levels of expression.
- Regulation effect beyond a threshold, reverse effect below [Thomas].

Gene regulatory networks



- Established *in silico* by Francois et al.
- Generalizing segmentation processes (*Drosophila*,etc.).
- We consider only boolean levels (presence 1 / absence 0) but all presented methods work with any number of levels.

GRN dynamics

- c at level 0 activates a,
- c at level 1 inhibits a.

Generalized dynamics

- level may increase $\Leftrightarrow$ at least one activator is effective.
- level may decrease $\Leftrightarrow$ at least one inhibitor is effective.

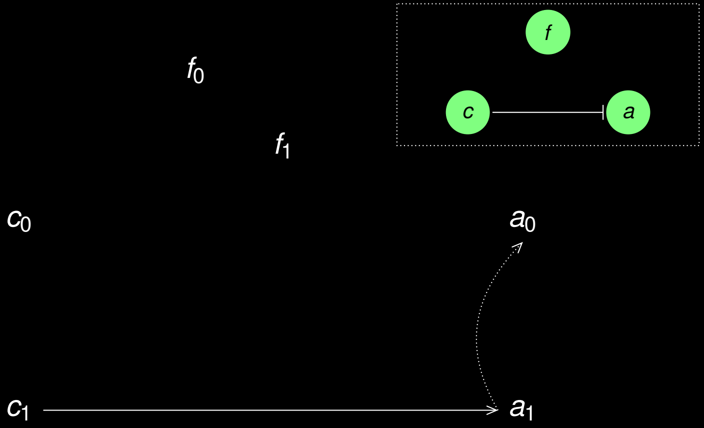
π-Calculus modelling

c at level 0 <u>activates</u> a.

- 3 processes: c_0, a_0 and a_1.
- Channel γ shared only by c_0 and a_0.
- c_0 outputs on channel γ.
- a_0 inputs on channel γ.
- If both a_0 and c_0 are present, a_0 may reduce to a_1.

$$c_0 ::= !\gamma.c_0 + <\text{other actions}>$$
$$a_0 ::= ?\gamma.a_1 + <\text{other actions}>$$

The Process Hitting framework



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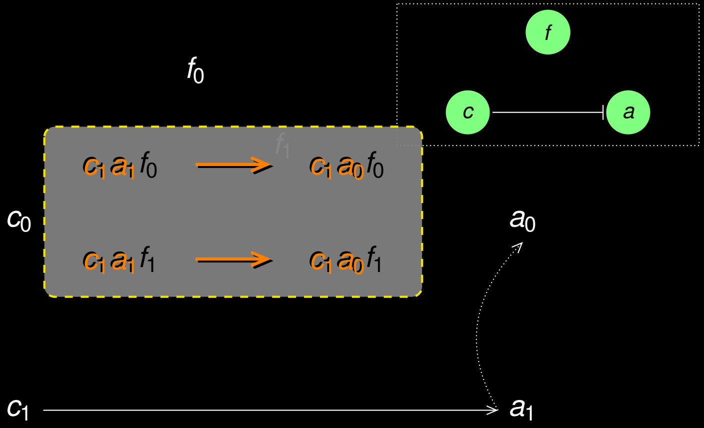

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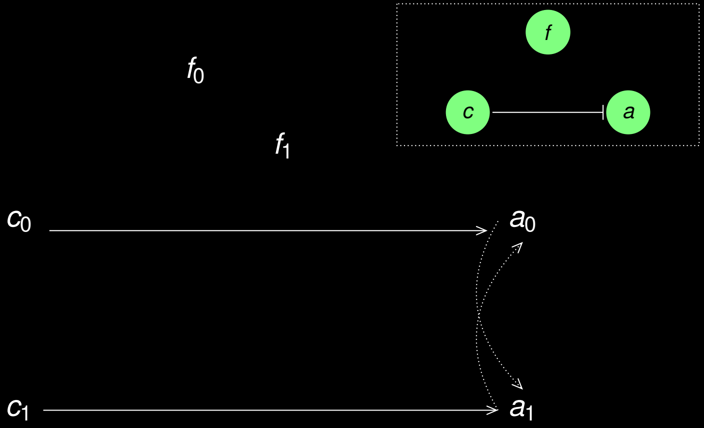

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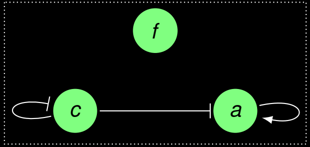

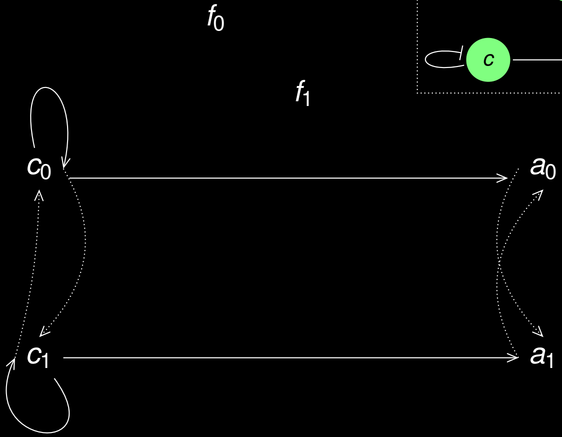

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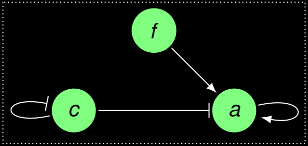

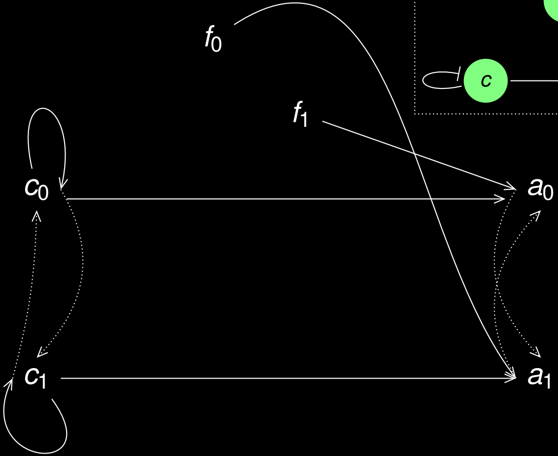

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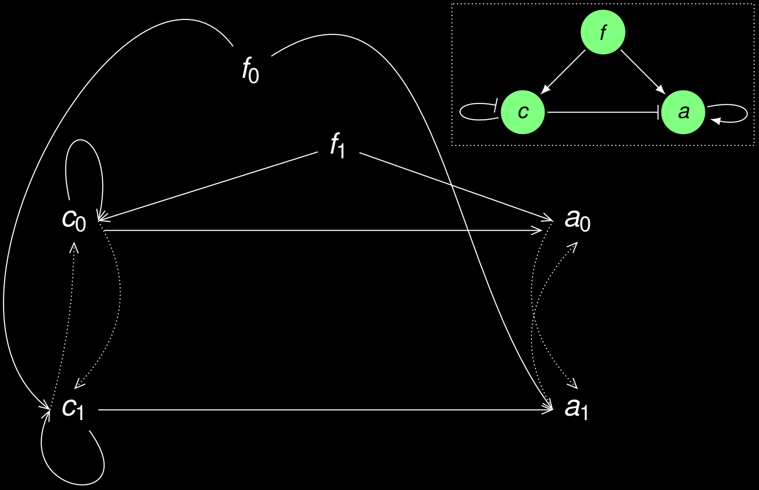

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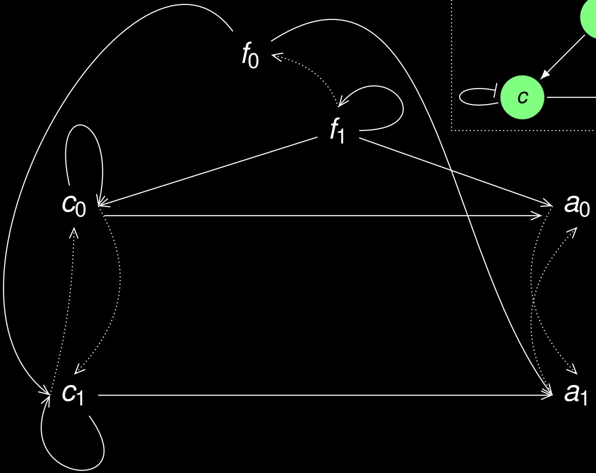
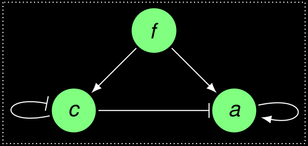
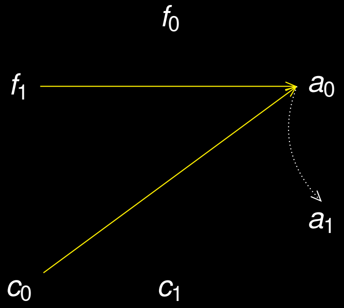




Generalized dynamics for the GRN

Refining: cooperativity

a_0 increases only if f_1 and c_0 are present:



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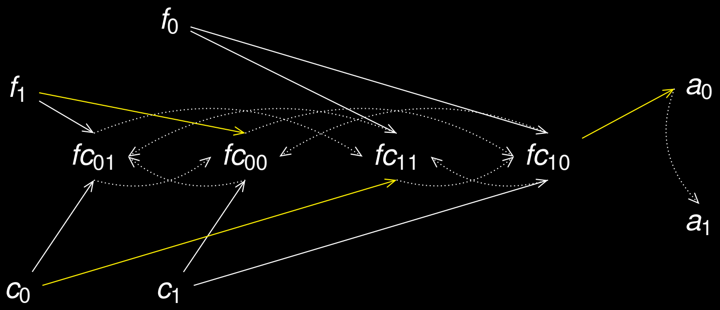
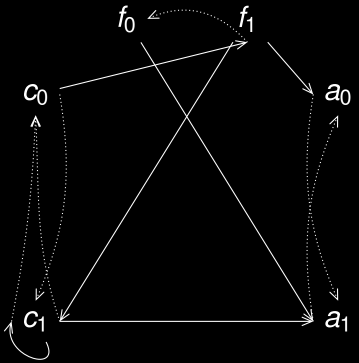
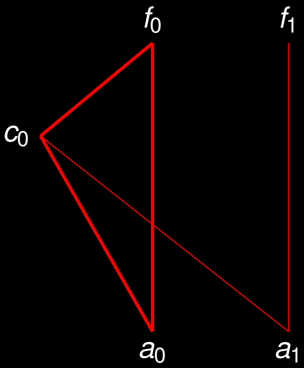


Refining: stable states



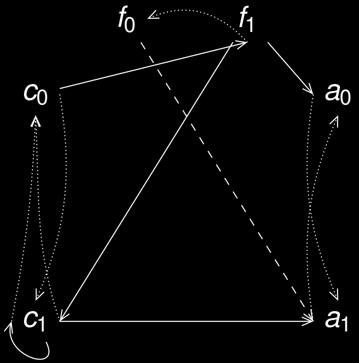
Process Hitting Hypergraph



Hitless Graph

n-cliques <u>are</u> stable states.

Refining: stable states



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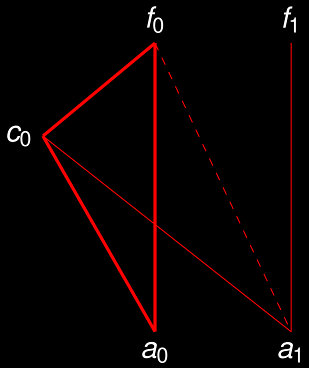

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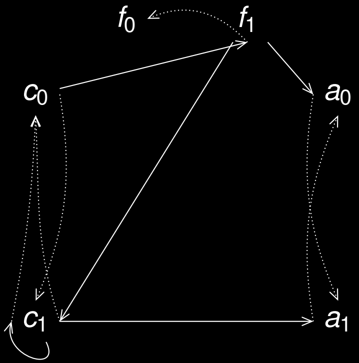
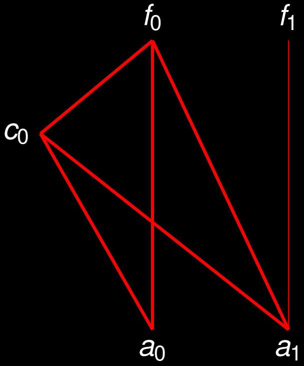
Refining: stable states



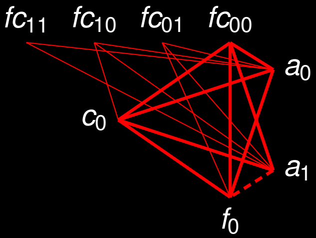
Process Hitting Hypergraph

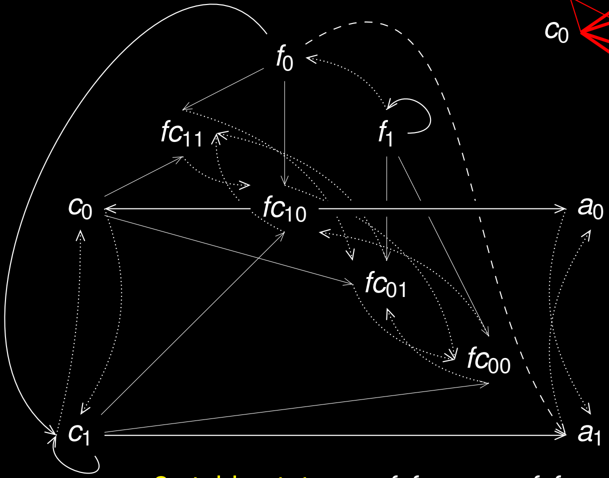


Hitless Graph

n-cliques are stable states.

GRN refinements

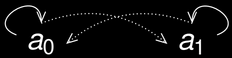




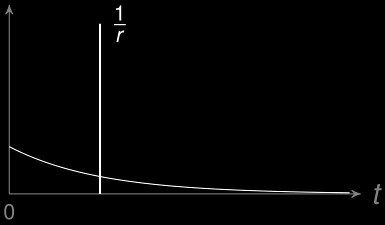
2 stable states: $c_0 f_0 fc_{00} a_0$, $c_0 f_0 fc_{00} a_1$.

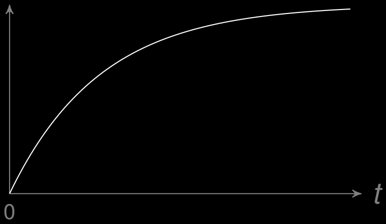
Stochastic parameters

Example: *self-hitting* process:

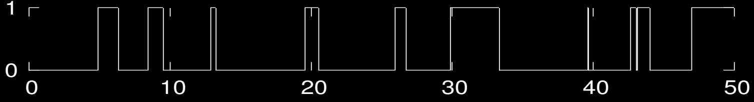


Use rate r of exponential distribution (average duration: $\frac{1}{r}$).





Simulation through SPIM [Phillips]:



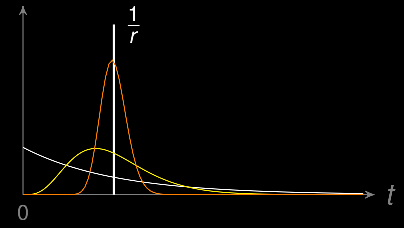
Stochasticity absorption factor

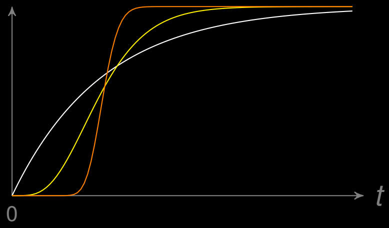
“Duration follows one exponential random variable of rate *r*”

becomes

“Duration follows the sum of *sa* exponential random variables of rate $r.sa$“

Aka Erlang distribution (particular Gamma) of shape *sa* and rate $r.sa$.

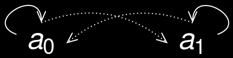




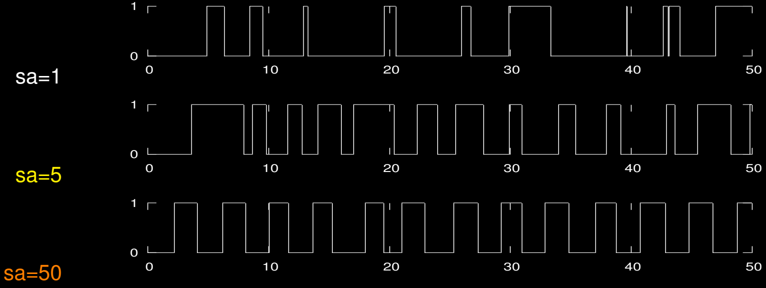
sa=1, sa=5, sa=50

Temporal and stochastic parameters

Example: *self-hitting* process:



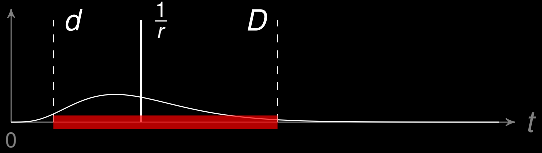
Use rate r + stochasticity absorption factor *sa*
(average duration: $\frac{1}{r}$ unchanged).



Firing intervals

Given a confidence $1 - \alpha$:

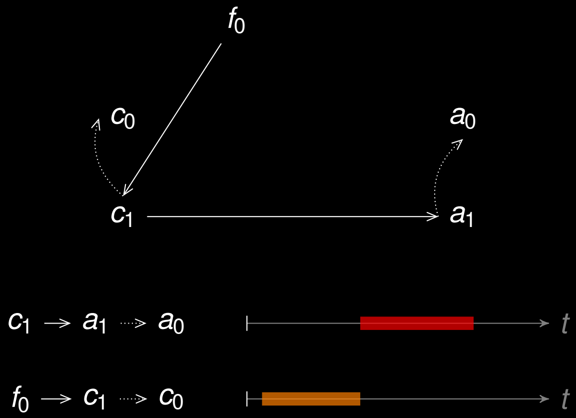
$(r, sa) \rightleftarrows$



lower sa

higher sa

Towards parameters synthesis



Conclusion

Contrib

- Stochastic π-Calculus framework to model GRN dynamics.
- Introduction of the stochasticity absorption factor
  $\Rightarrow$ temporal features tuning.
- Structural pattern for stable state presence.
- No state space exploration.
- Model checking using PRISM.

Outlook

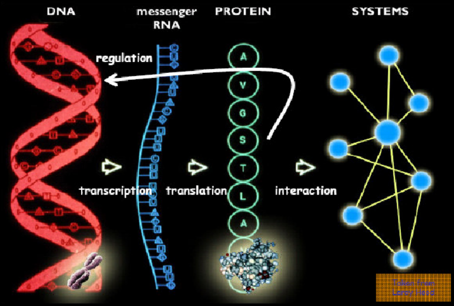
- More structural patterns (oscillations, reachability, etc.).
- Tools around Erlang distribution.
- Automate parameters synthesis.

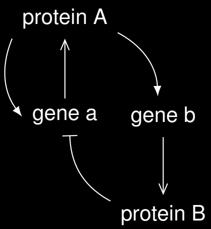
Questions ?

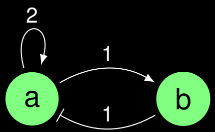
Thank you for your attention !

Bonus

Gene regulatory networks

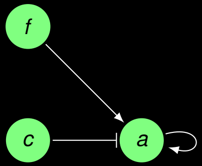


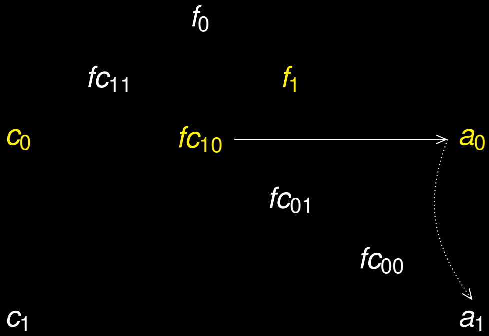




René Thomas' parameters inference

- Full set of K is an essential input for many GRN analysis tools.
- $K_{a,\{f,c\},\{a\}}$: level toward which a will tend when f, c effectively activate it and a effectively inhibits it.





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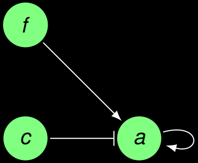

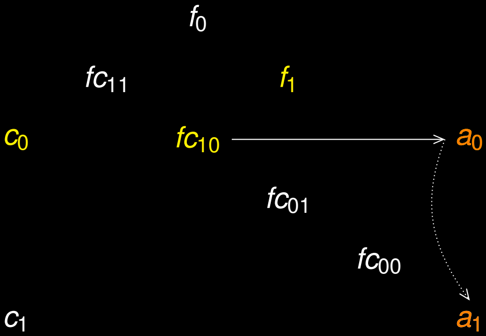

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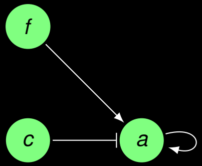

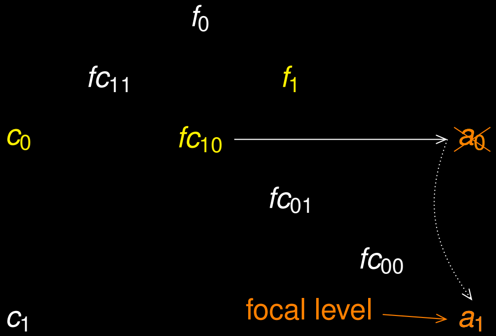

A Stochastic π-Calculus framework

$$\begin{tikzcd} h = c_0 \arrow[r] & a_0 \arrow[d, dotted] \\ & a_1 \end{tikzcd} \equiv \begin{cases} C_0 ::= \cdots + !\gamma_h.C_0 \\ A_0 ::= \cdots + ?\gamma_h.A_1 \end{cases}$$

- Straightforward translation to the Stochastic π-Calculus.
- To each channel γ_h we attach a use rate r_h.
- Average duration of an action with use rate r: $\frac{1}{r}$.
- Natural introduction of stochastic parameters into the Process Hitting framework.
- Gillespie: reaction duration follows an exponential law.