

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

Loïc Paulevé, Morgan Magnin, Olivier Roux

Moves team, IRCCyN, Nantes, France

Journée Réseaux, June 12, 2009

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].

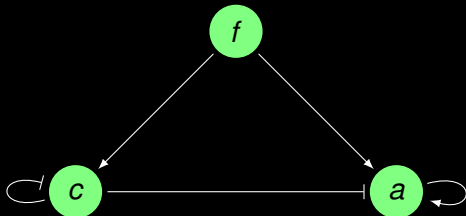
Goal: temporal parameters synthesis for hybrid models of GRN.

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

Outline

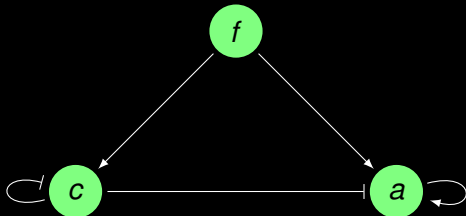
- 1 Generalized dynamics for Gene Regulatory Networks.
- 2 The Process Hitting framework.
- 3 Discrete (structural) refinements: cooperativity and stable states.
- 4 Temporal and stochastic parameters: temporal determinism.

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

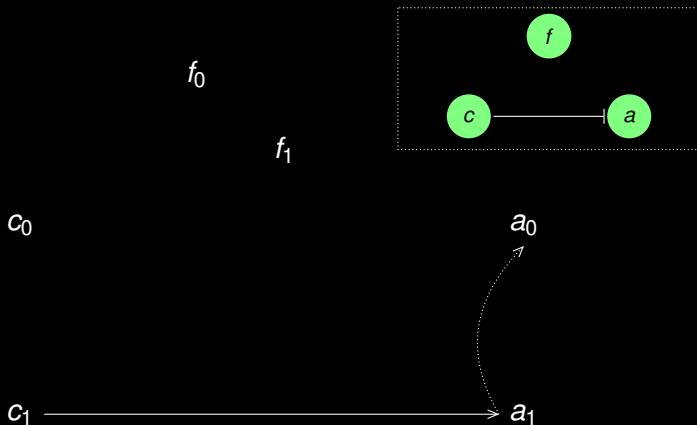
c at level 0 activates a .

- 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 .

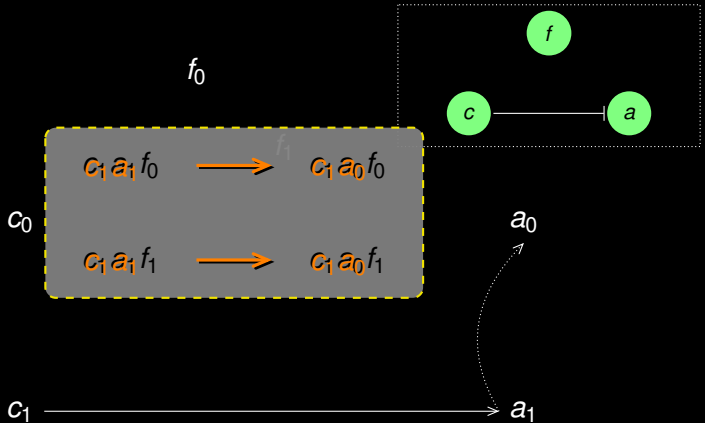
$$c_0 ::= !\gamma.c_0 + \langle \text{other actions} \rangle$$

$$a_0 ::= ?\gamma.a_1 + \langle \text{other actions} \rangle$$

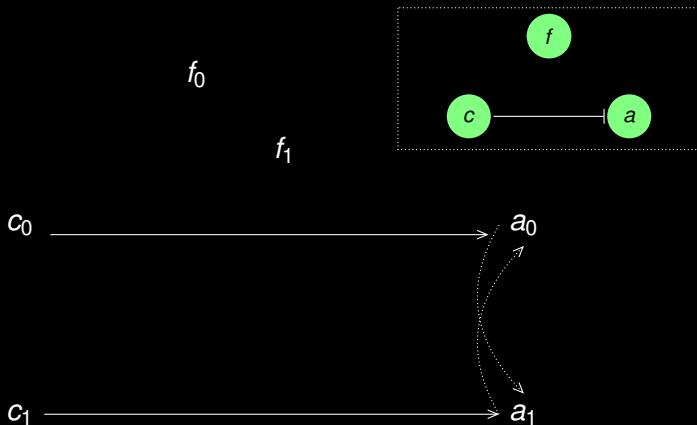
The Process Hitting framework



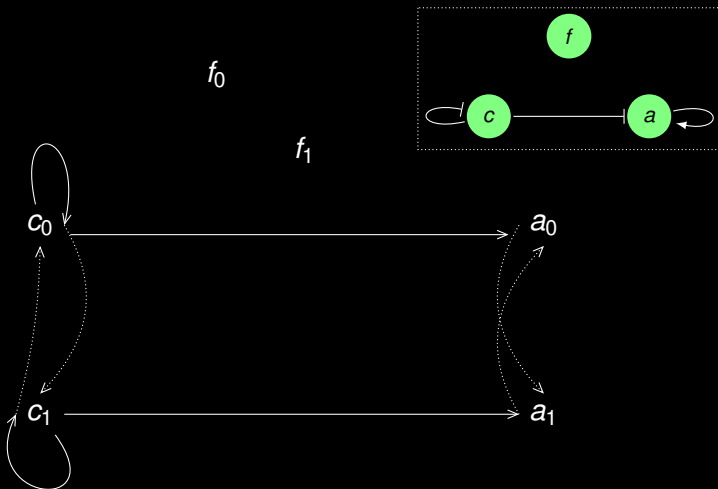
The Process Hitting framework



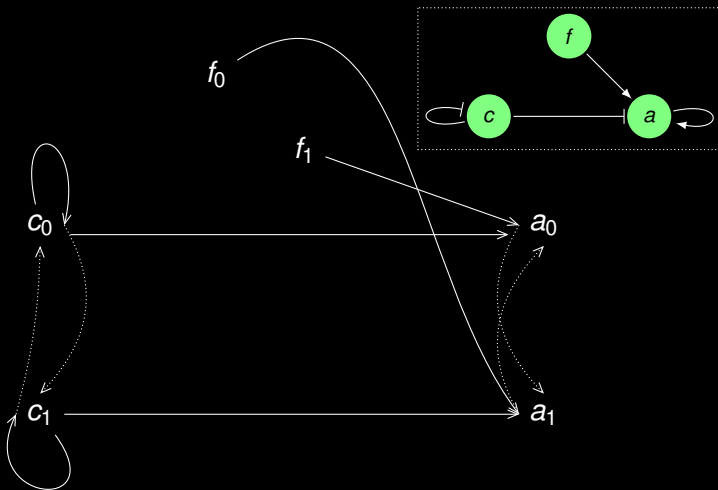
The Process Hitting framework



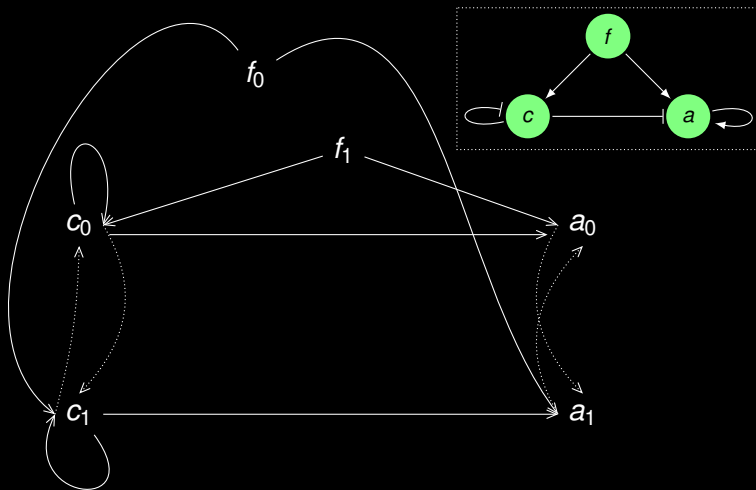
The Process Hitting framework



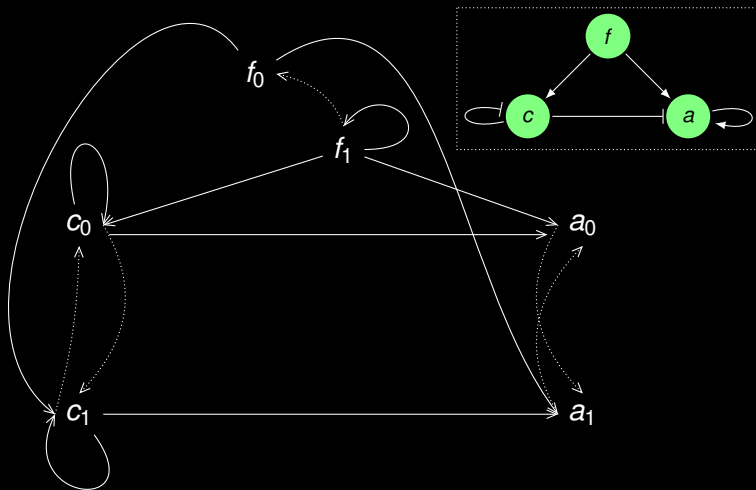
The Process Hitting framework



The Process Hitting framework



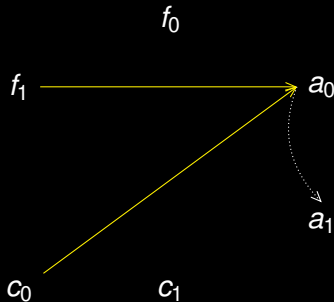
The Process Hitting framework



Generalized dynamics for the GRN

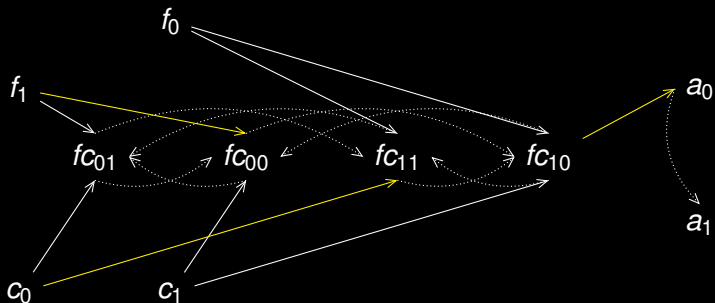
Refining: cooperativity

a_0 increases only if f_1 and c_0 are present:

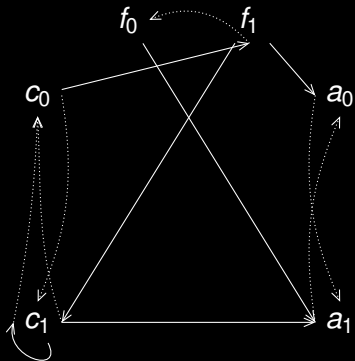


Refining: cooperativity

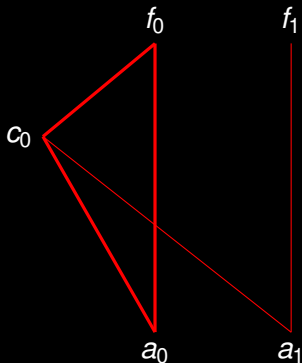
a_0 increases only if f_1 and c_0 are present:



Refining: stable states



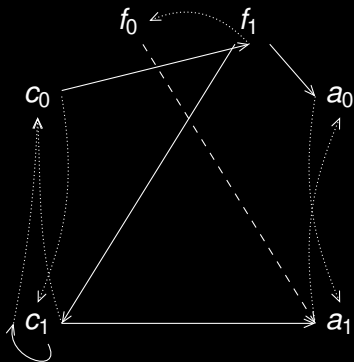
Process Hitting Hypergraph



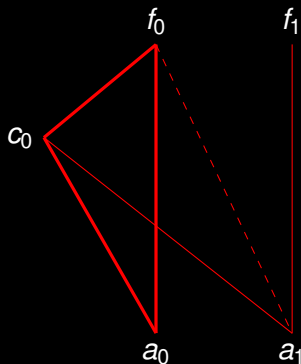
Hitless Graph

n -cliques are stable states.

Refining: stable states



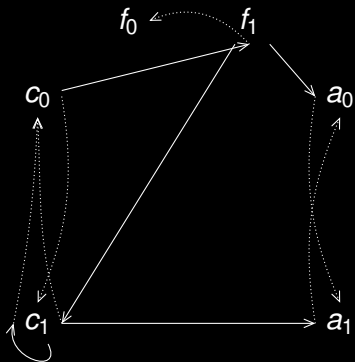
Process Hitting Hypergraph



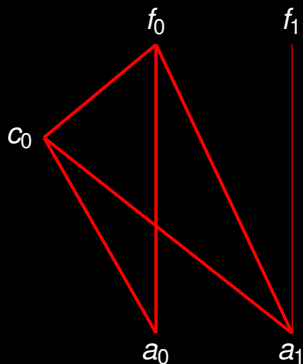
Hitless Graph

n -cliques are stable states.

Refining: stable states



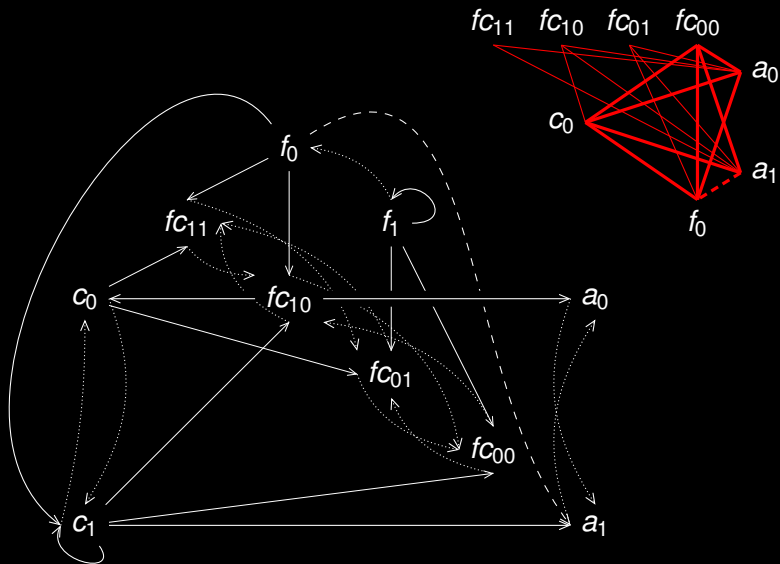
Process Hitting Hypergraph



Hitless Graph

n -cliques are stable states.

GRN refinements



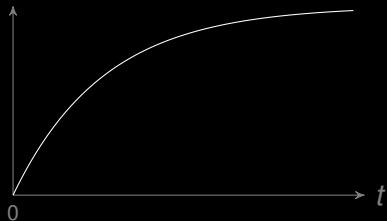
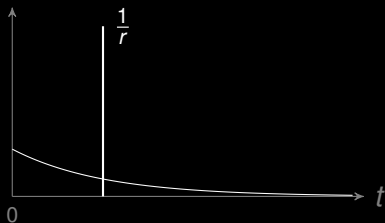
2 stable states: $c_0 f_0 fc_{00} a_0$, $c_0 f_0 fc_{00} a_1$.

Stochastic parameters

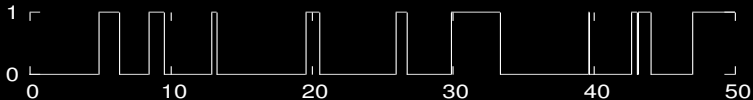
Example: *self-hitting* process:



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



Simulation through **SPIM** [Phillips]:



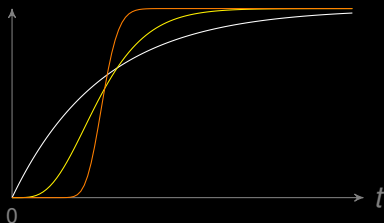
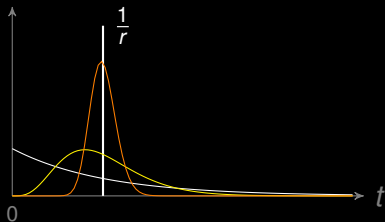
Stochasticity absorption factor

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

becomes

“Duration follows the **sum** of **sa** exponential random variables of rate $r \cdot sa$ ”

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



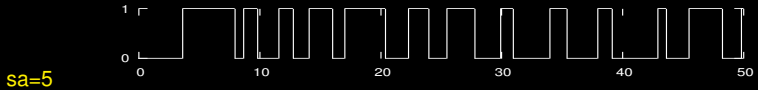
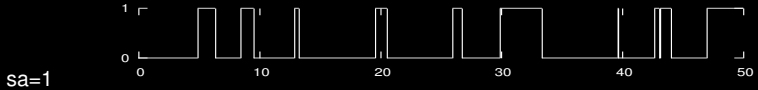
$sa=1$, $sa=5$, $sa=50$

Temporal and stochastic parameters

Example: *self-hitting* process:

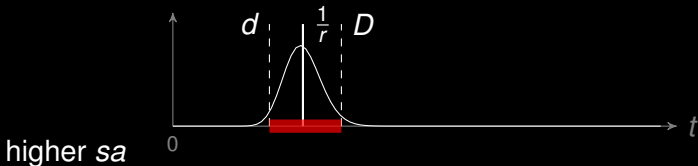
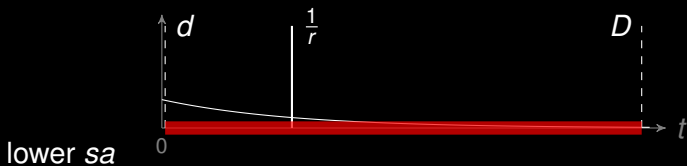
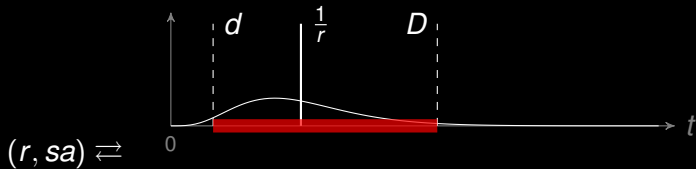


Use rate r + **stochasticity absorption factor sa**
(average duration: $\frac{1}{r}$ unchanged).



Firing intervals

Given a confidence $1 - \alpha$:



Conclusion

Contrib

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

Outlook

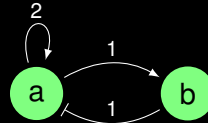
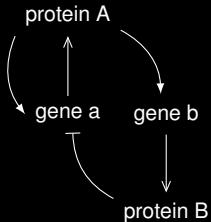
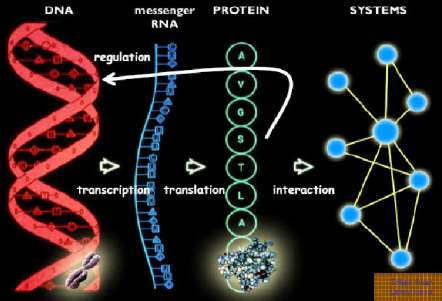
- More structural patterns (oscillations, reachability, etc.).
- Tools around Erlang distribution.
- Automate parameters synthesis.

Questions ?

Thank you for your attention !

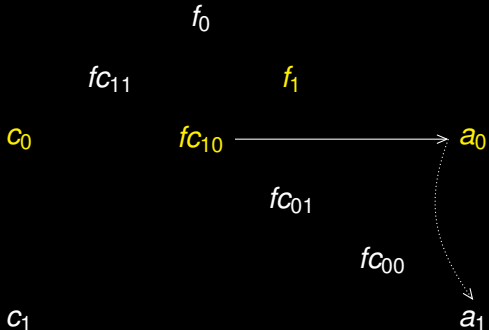
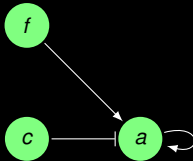
Bonus

Gene regulatory networks



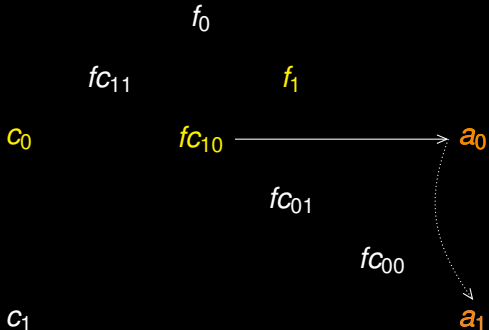
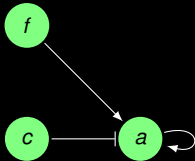
René Thomas' parameters inference

- 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.



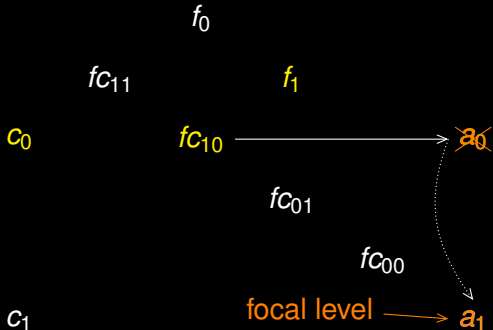
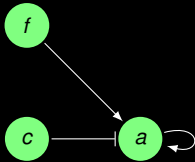
René Thomas' parameters inference

- 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.



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.



A Stochastic π -Calculus framework

$$h = c_0 \longrightarrow a_0 \equiv \begin{cases} C_0 ::= \dots + !\gamma_h \cdot C_0 \\ A_0 ::= \dots + ?\gamma_h \cdot A_1 \end{cases}$$

The diagram shows a transition from $h = c_0$ to a_0 via a solid arrow. To the right of a_0 is an equivalence symbol \equiv followed by a large curly brace containing two lines of text: $C_0 ::= \dots + !\gamma_h \cdot C_0$ and $A_0 ::= \dots + ?\gamma_h \cdot A_1$. A dashed arrow points from a_0 down to a_1 .

- 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**.