On the Roles of Informatics in Biology

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- Biophysics, Biomatics, Bioinformatics, Biostatistics...

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- The generic template:
  - I do X (for my pleasure, because I studied it, that's what I know) but... X can also be useful for Biology
- So Here I am, trying to sell my own X, a certain species of Informatics / Computer Science
- When you have a hammer, everything looks like a nail

Summary

- Computers are more than technology, it is also mathematics/physics
- Automata as dynamical systems
- Verification illustrated
- On hybrid discrete-continuous models and their verification
- Timed models and their applications
- Back to the big picture

Computer Technology

- Computers, Networks, Operating Systems
- Data-Bases, Web, Search Engines, Graphics,
- Embedded Systems, Sensors, Programming Languages
- Word Processing, Computer Control, Robotics, Security
- ..
- Influence on all domains of human activity

Including Biology

- String Processing for DNA
- Statistical Computations
- Simulation, Animation
- Date-Bases
- Micro-Arrays
- Ontologies and Description Languages
- Communication and Data Sharing
- Lab Management

In all those activities the computer is a useful *material tool* in the *service* of others

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- Biology seems to be trying to go through a kind of Newtonian revolution
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A More Noble Role, Perhaps

- Biology seems to be trying to go through a kind of Newtonian revolution
- The essence of such revolution is to upgrade (as much as possible) descriptive "models" by *dynamic* models with stronger predictive power and refutability
- Classical models of dynamical systems are clearly not sufficient for efficient modeling of biological phenomena
- Models, insights and computer-based tools developed within Informatics can help

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- Among other things informatics is:
- The (pure and applied) study of *discrete-event dynamical systems* (automata, transition systems)
- This point view is more natural for the "reactive systems" parts of informatics (hardware, protocols, real-time, stream processing)
- Especially for people working on modeling and verification of such systems

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- Remark: Variables in Biology can be of various natures and granularities (concentrations, states of individual molecules, stages in processes, etc.)

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- Achievements: Apples, Stars, Missiles, Electricity, Heat, Chemical processes
- Theorems, Papers, Simulation tools

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- Behaviors are sequences of states and events
- Composition of large systems from small ones
- Different modes of interaction: synchronous/asynchronous, state-based/event-based

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- ATMs, user interfaces
- Administrative procedures
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- Any process that can be viewed as a sequence of steps
- But what can we do with these models?
- There are no analytical tools as in continuous systems
- We can simulate and sometimes do formal verification

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  - Quantitative properties..

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  - Quantitative properties..
- Existing tools can do this type of analysis for huge systems by sophisticated graph algorithms

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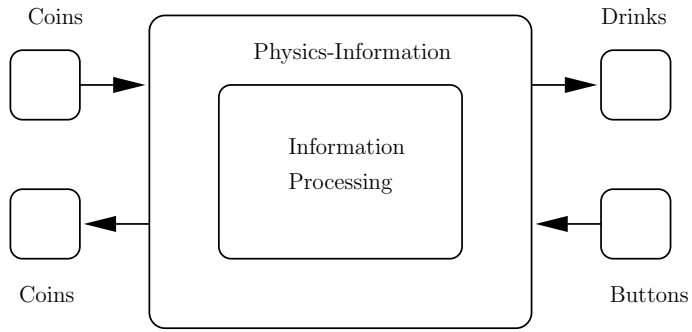
- For example, detect coin insertion or button pressing, initiate water heating



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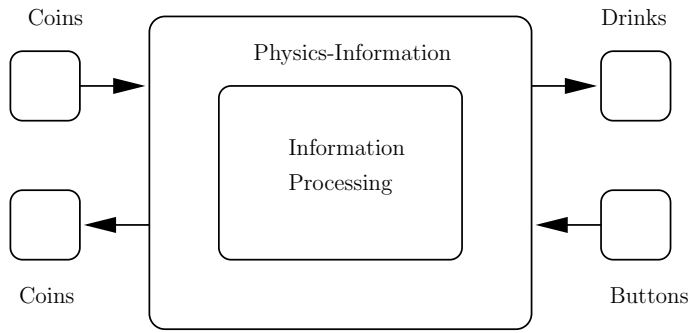
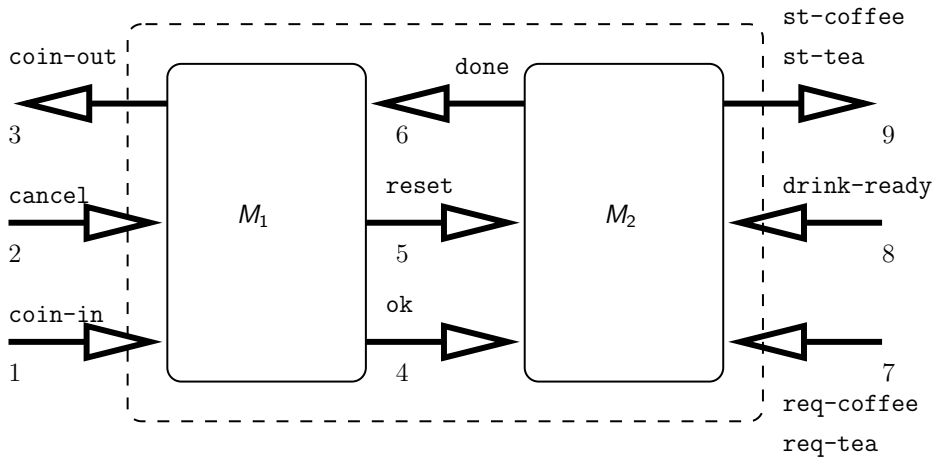


- In the information-processing system there are only events and reactions regardless of their physical origin

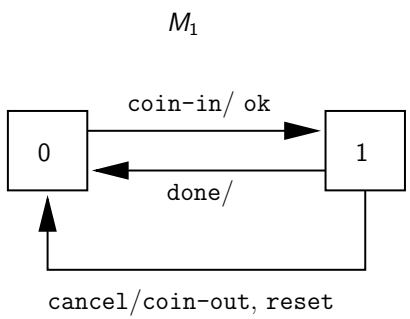
The Coffee Machine: Subsystems

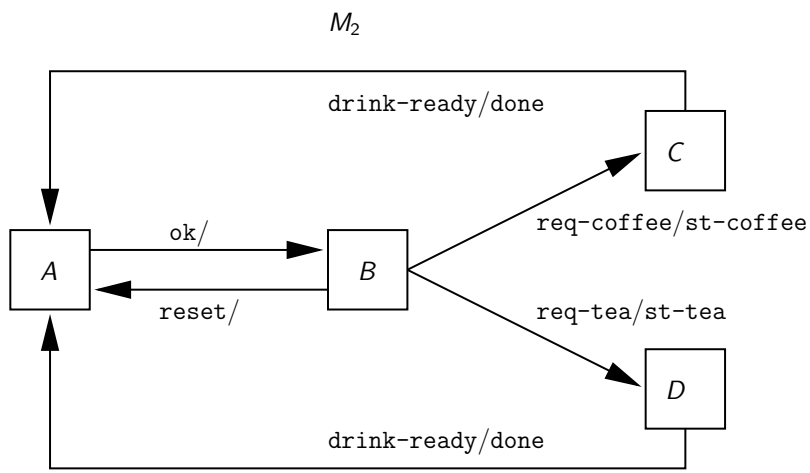
- The system is built from two subsystems, one that takes care of financial matters, and one which handles choice and preparation of drinks
- They communicate by sending messages



Automaton Models

- The two systems are models as automata (state-transition systems)
- transitions are triggered by external events and events coming from the other subsystem





The Global Model

- The behavior of the whole system is captured by a composition (product) $M_1 \parallel M_2$ of the components
- States are elements of the Cartesian product of the respective sets of states, indicating the state of each component

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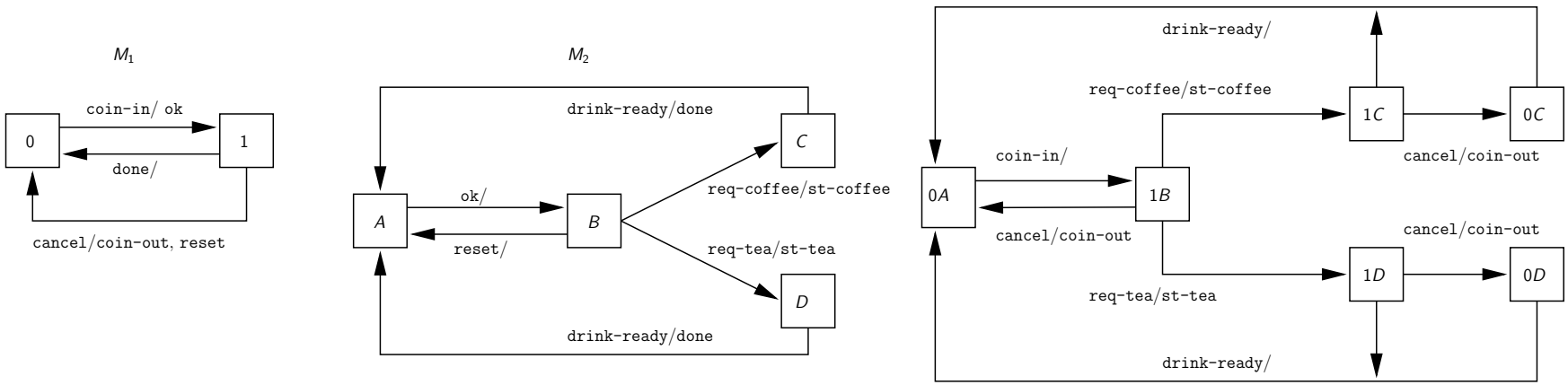
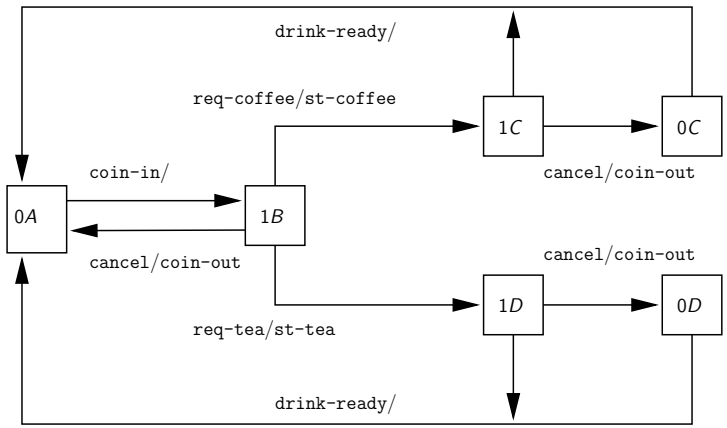
- The behavior of the whole system is captured by a composition (product) $M_1 \parallel M_2$ of the components
- States are elements of the Cartesian product of the respective sets of states, indicating the state of each component
- Some transitions are independent and some are synchronized, taken by the two components simultaneously



Normal Behaviors

- Behaviors of the systems are paths in this transition graph



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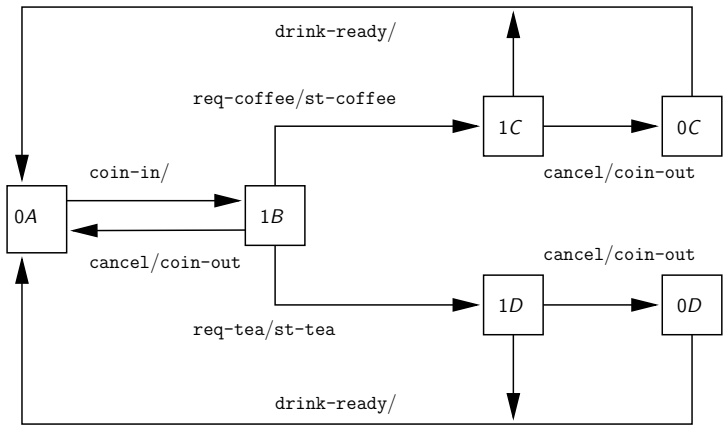

- Customer puts coin, then sees the bus arriving, cancels and gets the coin back

$$0A \texttt{ coin-in } 1B \texttt{ cancel coin-out } 0A$$

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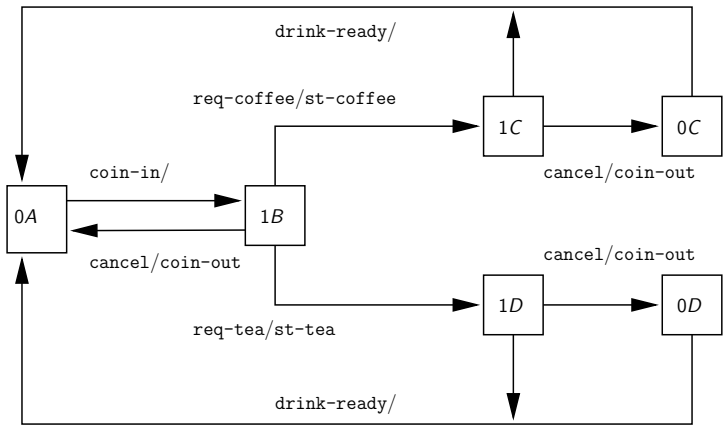

- Customer puts coin, then sees the bus arriving, cancels and gets the coin back

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- Customer inserts coin, requests coffee, gets it and the systems returns to initial state

$$0A \texttt{ coin-in } 1B \texttt{ req-coffee st-coffee } 1C \texttt{ drink-ready } 0A$$

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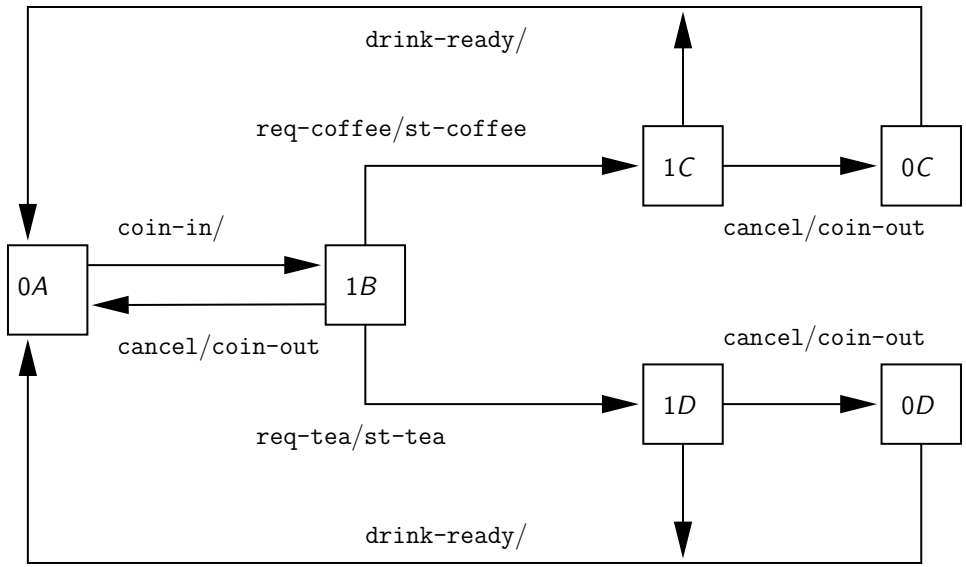

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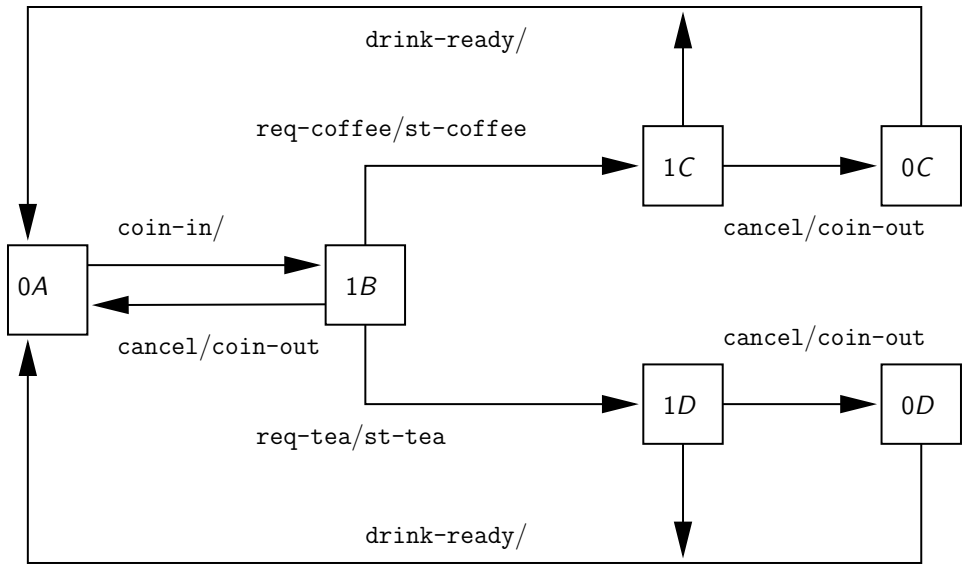

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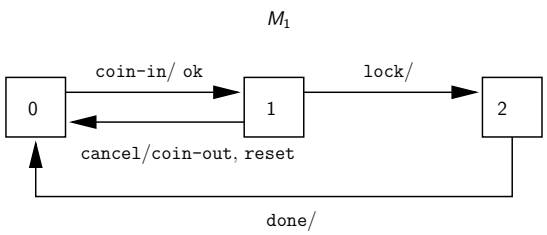
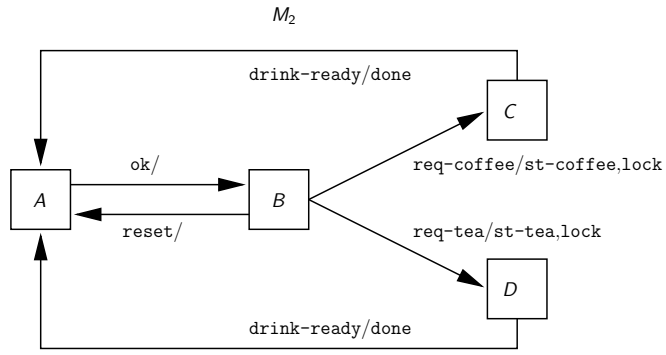
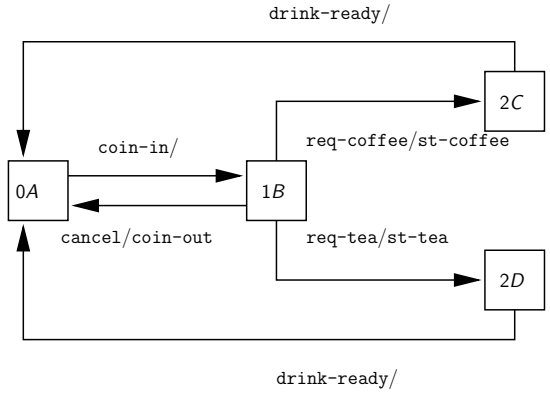
- Not so attractive for the owner of the machine

Fixing the Bug

- When M_2 starts preparing coffee it emits a `lock` signal
- When M_1 received this message it enters a new state where `cancel` is refused







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- Each input sequence may generate a different behavior
- We want to make sure that a system responds correctly to all conceivable inputs, that it behaves properly in any environment

The Moral of the Story

- We want to make sure that a system responds correctly to all conceivable inputs, that it behaves properly in any environment
- For every individual input sequence we can simulate the reaction of the system. But we cannot do it exhaustively
- Verification is a collection of automatic and semi-automatic methods to analyze all the paths in the graph
- This is hard for humans to do and even for computers

Hybrid Systems: Motivation

- Hybrid systems combine the discrete dynamics of automata with continuous dynamics defined by differential equations
- Each state may correspond to a mode of a system (a gene is on, a valve/heater is closed, the car is in a second gear)

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- Each state may correspond to a mode of a system (a gene is on, a valve/heater is closed, the car is in a second gear)
- In each state there is a different continuous dynamics
- The system may switch between modes according to the values of the continuous variables
- For example, the heater is turned off when temperature is high, a valve is opened when the water level crosses a threshold

Hybrid Systems Analysis is Difficult

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- Hybrid systems are much harder to analyze because switching breaks their nice mathematical properties
- New techniques inspired by discrete verification are being developed
- Combination of numerical analysis, graph algorithms and computational geometry

Verification for Continuous Systems

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Verification for Continuous Systems

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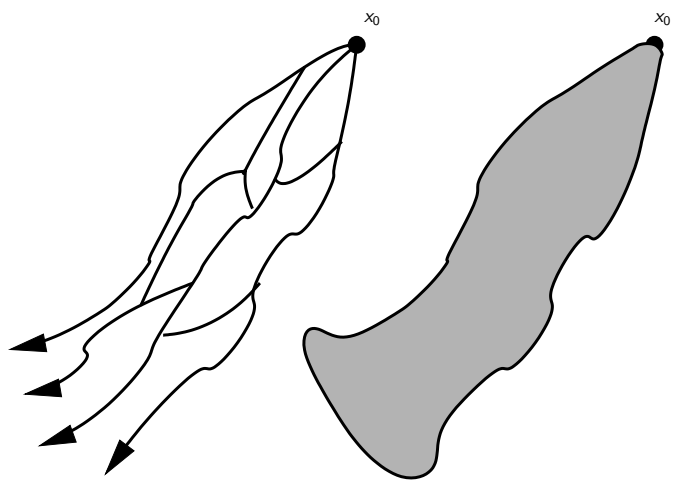
- Both u and p are not known exactly but are bounded
- Can something be said about all the possible behaviors of the system for all range of parameters and all external disturbances?



Verification for Continuous Systems

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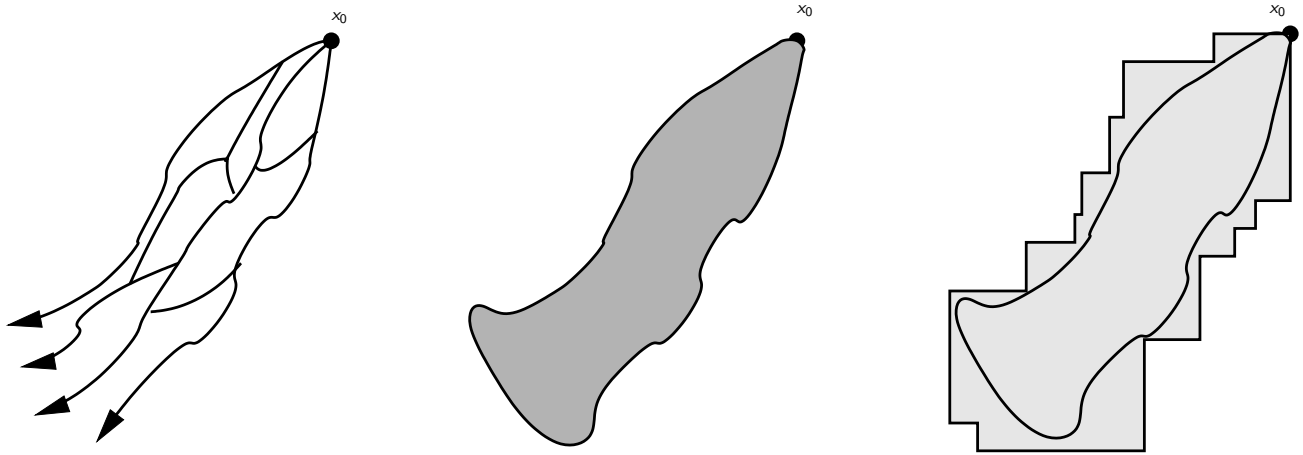

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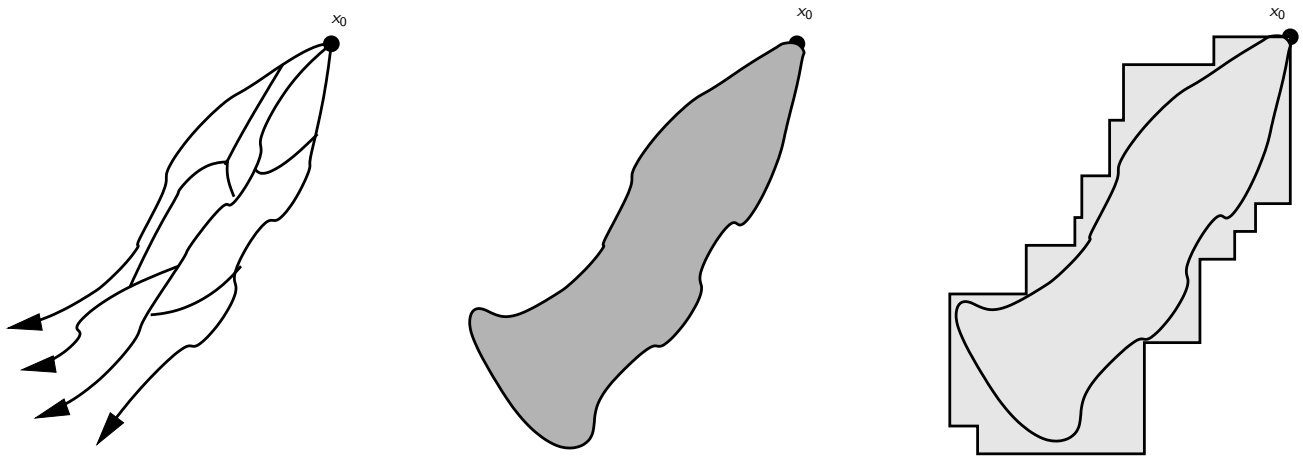

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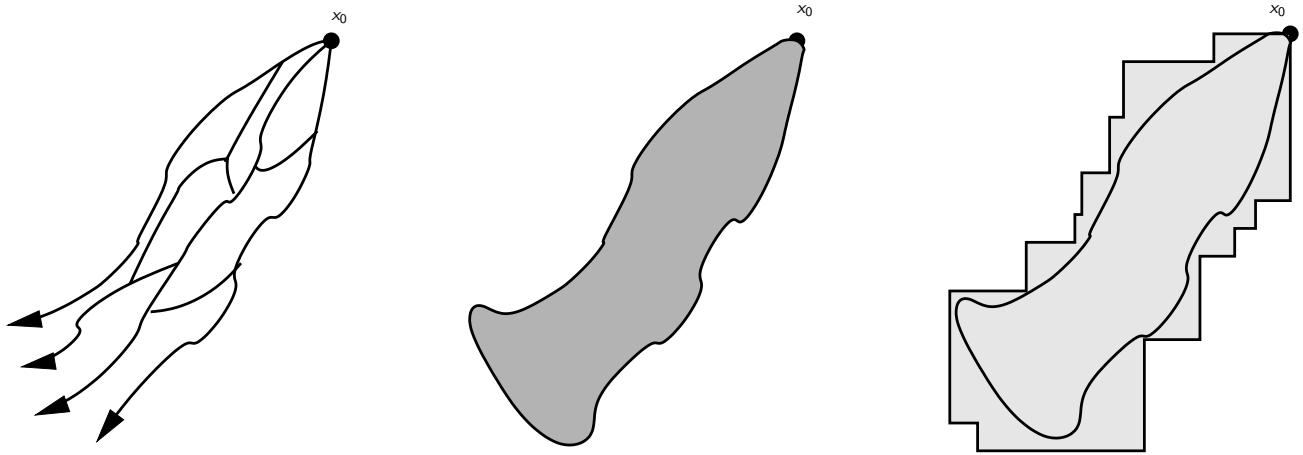

- Can replace an infinite number of simulations
- Useful for Biological models where exact parameters are hard or impossible to obtain
- State-of the-art: tools at various levels of sophistication and maturity can analyze linear systems with hundreds of state variables, as well as small nonlinear ones

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- Continuous description: how the concentration of some product evolves over time
- Discrete description: the product levels moves from low to high
- Timed description: the product levels moves from low to high and this process takes between 3 and 5 hours to complete
- At this level the dynamical models are timed automata, automata with auxiliary clock variables
- Illustration: adding time to the discrete models of R. Thomas (see also Siebert and Bockmayr)

Genetic Regulatory Networks for (and by) Dummies

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- Feedback from products concentrations to genes: when the quantity of a product is below/above some threshold it may set one or more genes on or off

Continuous and Discrete Models

- Product quantities can be viewed as integer (quantity) or real (concentration of molecules in the cell) numbers
- The system can be viewed as a hybrid automaton with discrete states corresponding to combinations of gene activations states
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- Alternatively, the domain of these concentrations can be discretized into a finite (and small) number of ranges
- The most extreme of these discretizations is to to consider a Boolean domain $\{0, 1\}$ indicating *present* or *absent*

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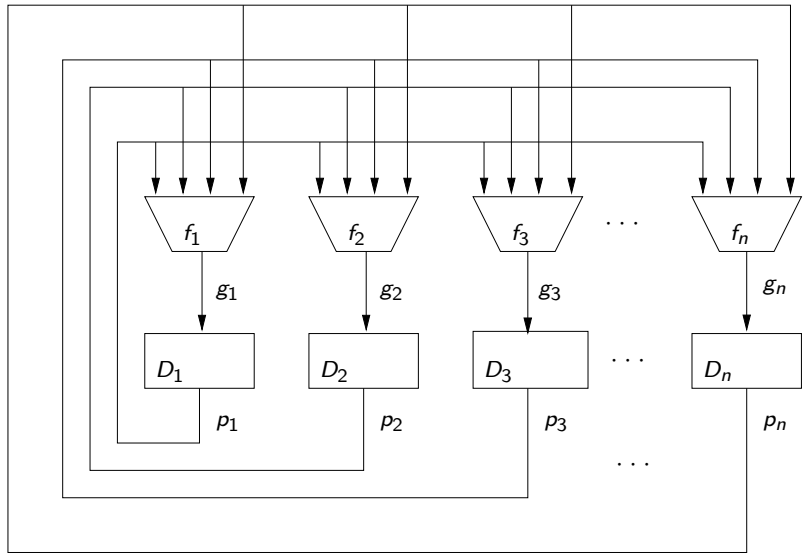
- We want to add this timing information in a systematic manner as we did in the past for asynchronous digital circuits [Maler and Pnueli 95]

Boolean Delay Networks



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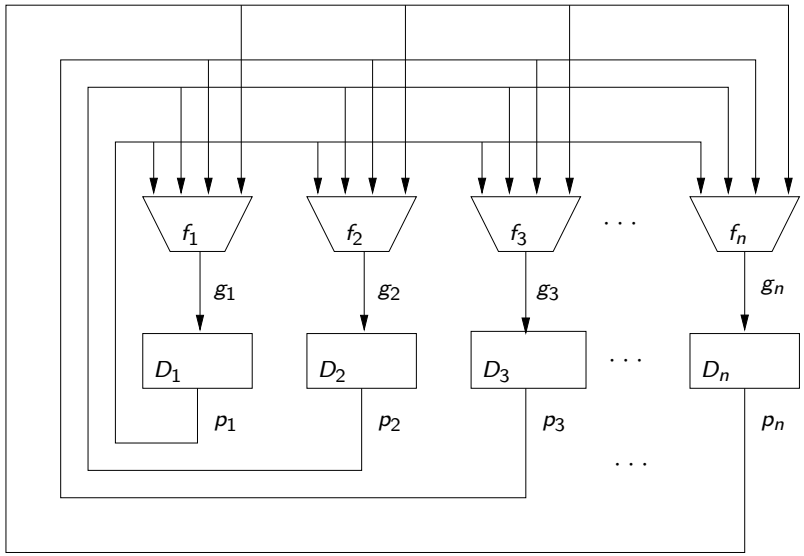

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- This change is propagated to the product within a non-deterministic but bi-bounded delay specified by an interval

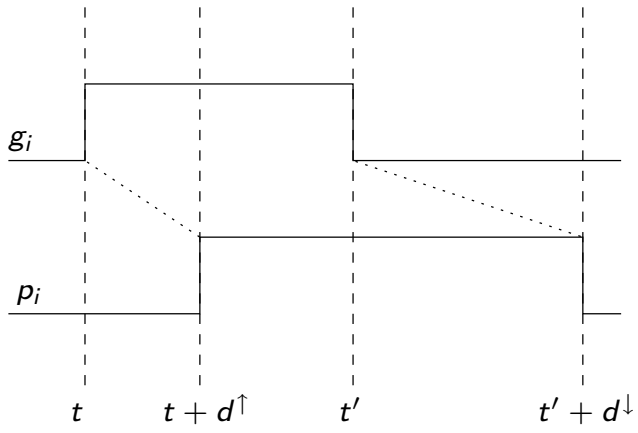
The Delay Operator

- For each i we define a delay operator D_i, a function from Boolean signals to Boolean signals characterized by 4 parameters

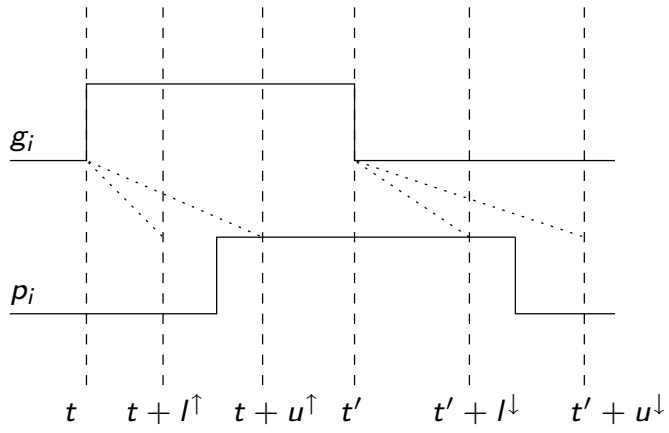
p_i	g_i	p_i'	Δ
0	0	0	–
0	1	1	$[l^{\uparrow}, u^{\uparrow}]$
1	0	0	$[l^{\downarrow}, u^{\downarrow}]$
1	1	1	–

- When $p_i \neq g_i$, p_i will catch up with g_i within $t \in [l^{\uparrow}, u^{\uparrow}]$ (rising) or $t \in [l^{\downarrow}, u^{\downarrow}]$ (falling)

The Delay Operator

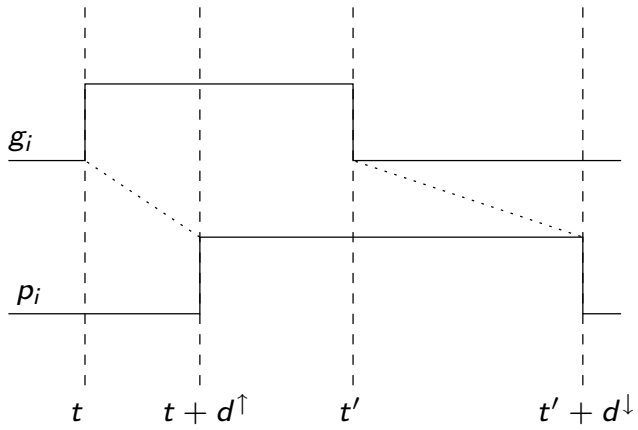


Determinisitc



Nondeterministic

The Delay Operator



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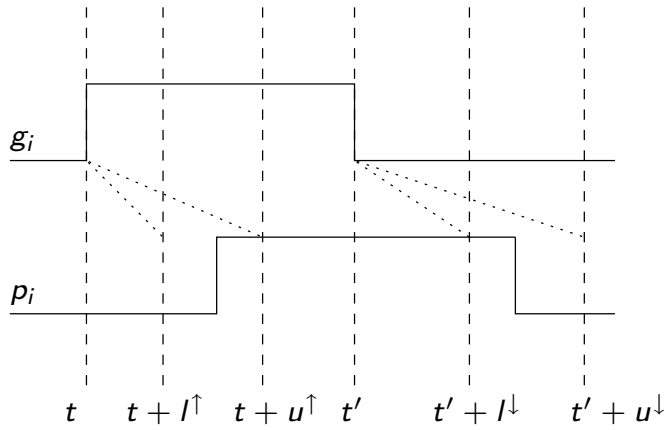


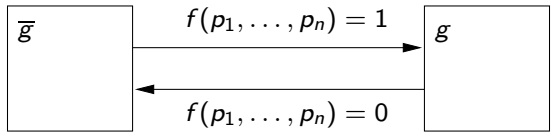
Nondeterministic

- The semantics of the network is the set of all Boolean signals satisfying the following set of signal inclusions

$$g_i = f_i(p_1, \ldots, p_n)$$
$$p_i \in D_i(g_i)$$

Modeling with Timed Automata

- For each equation $g_i = f_i(p_1, \ldots, p_n)$ we build the automaton



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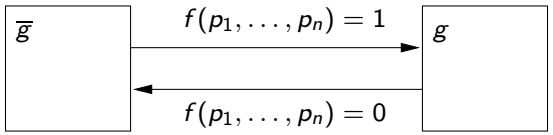

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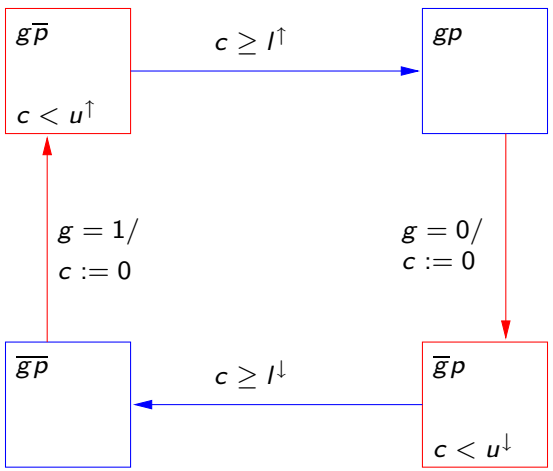

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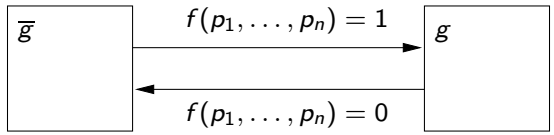

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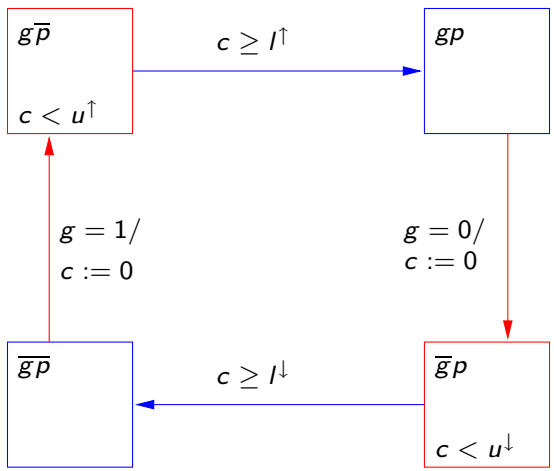
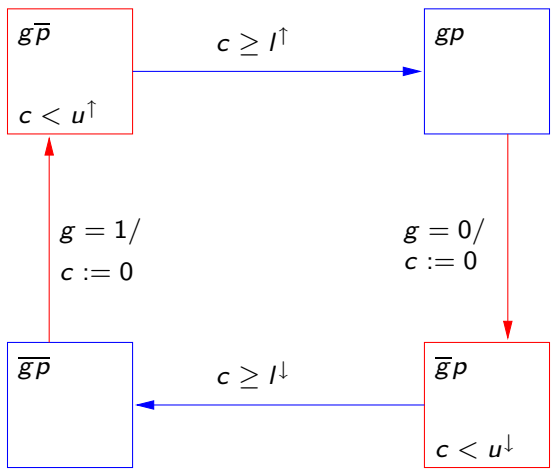


- Composing these automata together we obtain a timed automaton whose semantics coincides with that of the system of signal inclusions

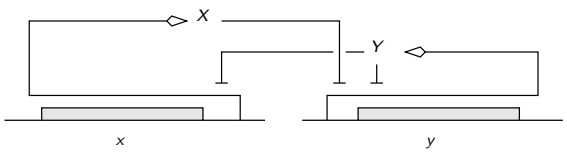
The Delay Automaton

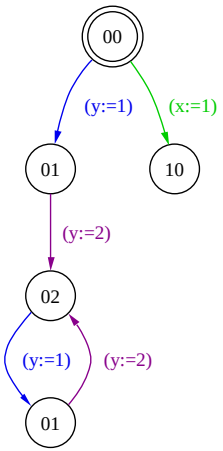
- The automaton has two stable states gp and $\overline{gp}$ where the gene and the product agree
- When g changes (excitation) it moves to the unstable state and reset a clock to zero
- It can stay in an unstable state as long as $c < u$ and can stabilize as soon as $c > l$.



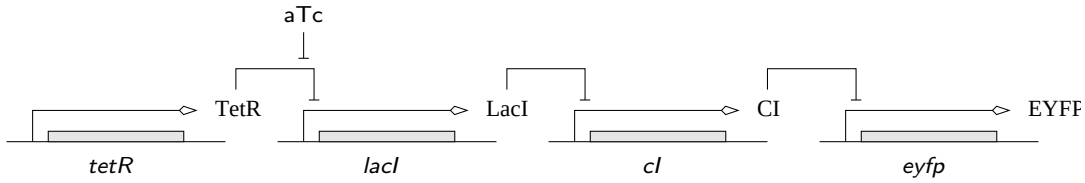
Implementation and Experiments

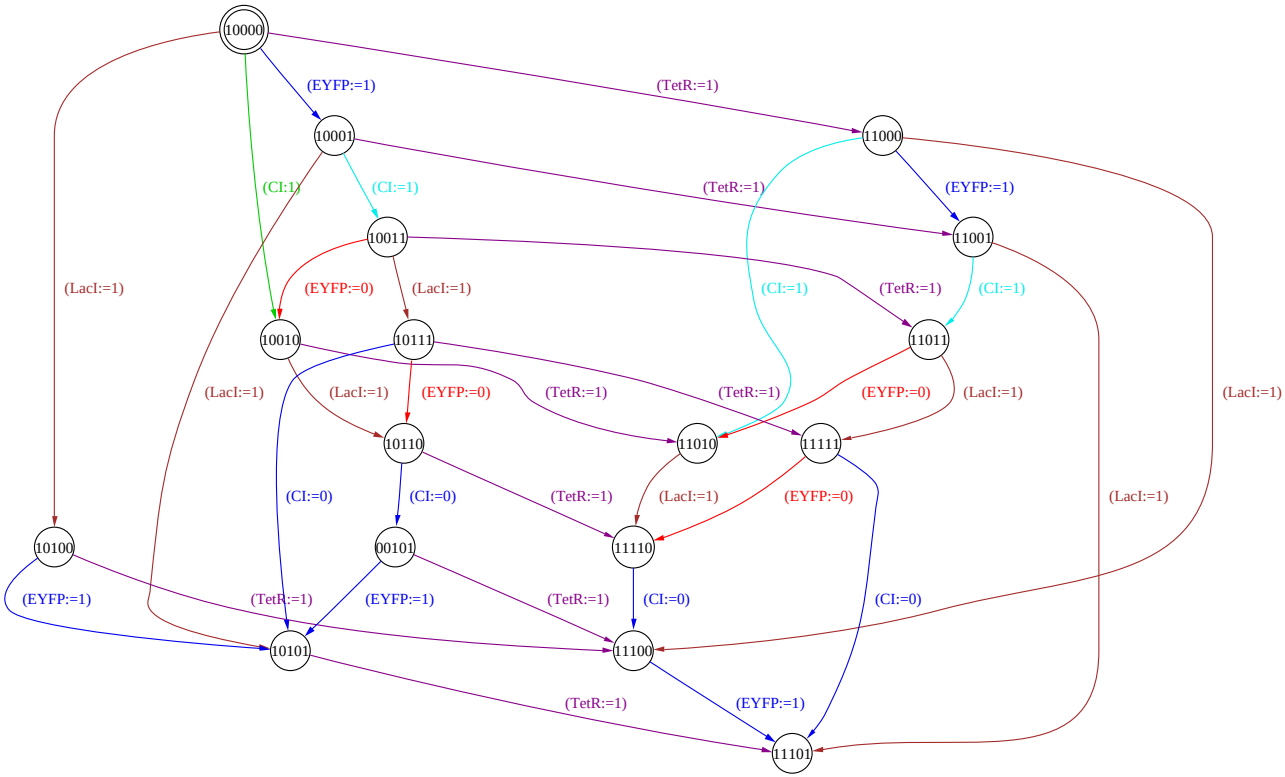
- Existing tools can take a description of such a timed automaton and compute all the possible behaviors under all choices of delays
- We use our IF toolbox and demonstrate its capabilities on several examples (not much biological significance at this point)
- Example 1: a cross inhibition network (also modeled by [Siebert and Bockmayr 06])





Transcription Cascade for E. Coli





Nutritional Stress Response for E. Coli

- Six genes, six proteins and one additional variable encoding the presence or absence of nutrition
- Arbitrarily chosen delays, cyclic behaviors
- Reachability graph with 69 states and 209 transitions, computed in less than one second

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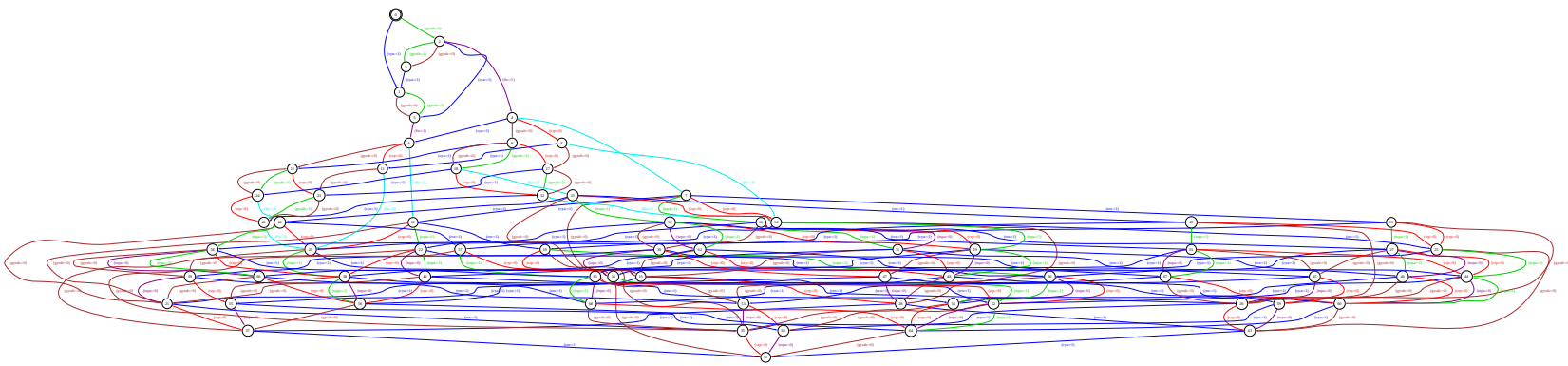

Back to the Big Picture

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- Biological modeling should be founded on various types of dynamical models: continuous, discrete, hybrid and timed
- These models should be strongly supported by computerized analysis tools offering a range of capabilities from simulation to verification and synthesis

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- Mathematics and Informatics as a unifying theoretical framework

Thank You