Reaction networks with delays applied to toxicity analysis

Joint work with Hanna Klaudel and Franck Delaplace

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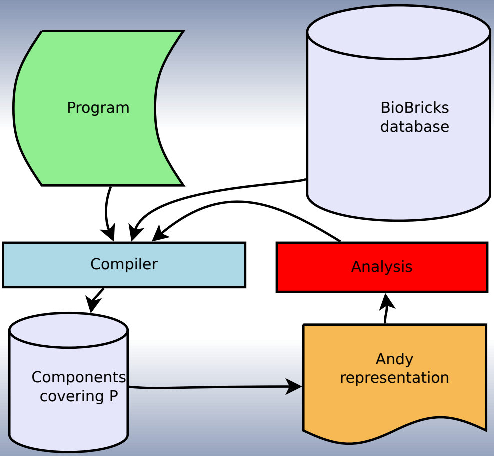
The SYNBIOTIC project



Motivation

- **Main goal**: design of artificial bio-systems
- **How**: development of computer-aided tools
- **What**: specification and analysis of cellular regulation networks (i.e., genetic and signalization networks and metabolic pathways)

Requirements

We want to build a model where:

- different regulatory networks can be expressed
- safety properties can be guaranteed

Safety

- in general $\Rightarrow$ nothing bad can happen
- in a bio-framework $\Rightarrow$ the system do not exhibit toxic behaviors

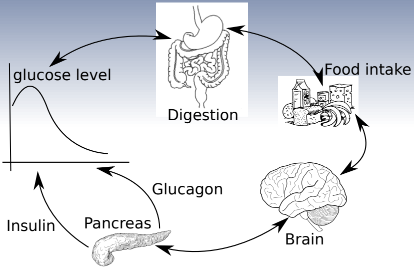
Toxicology

- The **toxicity process** is a sequence of physiological events that causes the abnormal behavior of a living organism with respect to its healthy state.
- Healthy physiological states generally correspond to **homeostasis**.
- Toxicity highly depends on the exposure time and the thresholds dosage delimiting the ranges of safe and hazardous effects.

Definition (Toxicity)

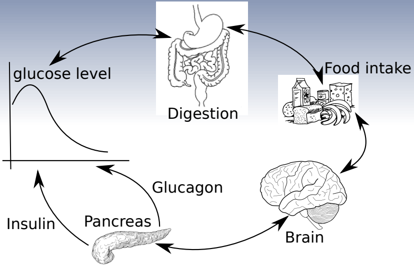
Toxicity is the deregulation of the homeostasis processes

Blood glucose regulation



- Glucose regulation is a homeostatic process.
- Glycemia is regulated by insulin and glucagon.
- Assimilation of sugars vs aspartame.

Blood glucose regulation



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Toxic!

Assimilation of food (even if it contains aspartame) should calm hunger and induce satiety, not the opposite!

Features

Our model features

- An explicit notion of discrete time
- Species with expression levels and decay
- Reactions with duration

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ANDy

An ANDy network is a set of species $\mathcal{S}$ governed by a set of reactions $\mathcal{R}$

Species

- Species have a finite number $\mathcal{L}_s$ of **expression** levels.
- Each species s is initialized at level η_s and it decays gradually as time passes by.
- Duration of decay vary among levels:

$$\delta_s : [0..\mathcal{L}_s - 1] \rightarrow \mathbb{N}^+ \cup \{\omega\}.$$

$\delta_s(0) = \omega.$

Reactions

- Reactions govern evolution of species

$$\rho ::= \; A_\rho \; ; \; I_\rho \xrightarrow{\Delta} R_\rho$$

- A_ρ, I_ρ are sets of pairs (s, η_s)
- R_ρ is a set of pairs $(s, \pm n)$
- Each reaction has a **response time**

$$\Delta : \mathcal{R} \rightarrow \mathbb{N}^+$$

Time required for yielding increase (+) and/or decrease (-) of levels of results.

Dynamics

A reaction of response time Δ can take place if

- each activator/reactant stays at least at a given level
- each involved inhibitor is at most at a given level

during the whole reaction time.

- **Outcome:** the level of results of the reaction can be increased or decreased.

Formalization

The dynamics of ANDy is formalized using high-level Petri nets.

- Time is explicitly represented.
- Places: Species + 1 place for time
- Transition: Reaction + 1 transition for time

Places

- We assume a unique discrete global clock that starts at zero and always shows the current date (timestamp).
- Each species is represented by a place
- The state of a species s is a tuple $\langle l_s, u_s, \lambda_s \rangle$
  - l_s stores the current level;
  - u_s is a timestamp recording the last date when the level has been updated;
  - λ_s is a tuple of timestamps with $\mathcal{L}_s$ fields;

Transitions – 1

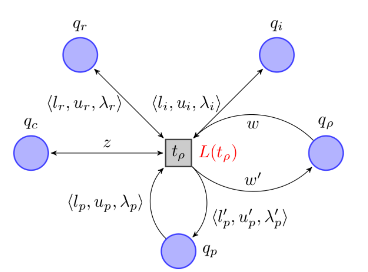
ANDy networks can evolve in two ways:

1. as effect of an enabled reaction ρ
2. as an effect of the clock:

Transition: reaction

Transition guard:

$$
\begin{aligned}
& w < z \wedge w' = z \quad \wedge \\
& \textstyle\bigwedge_{(a,\eta_a)\in A_\rho} (l_a \geq \eta_a \wedge z - \lambda[\eta_a] \geq \Delta(\rho)) \\
& \textstyle\bigwedge_{(i,\eta_i)\in I_\rho} (l_i < \eta_i \wedge z - \lambda[\eta_i] \geq \Delta(\rho))
\end{aligned}
$$



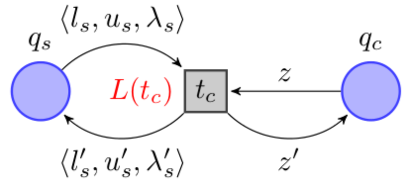
Result: a result r at level l_r and the clock at time t

$$
\begin{aligned}
& (r, +1) \\
& \langle l_r, u_r, \lambda_r\rangle \rightarrow \langle l_r + 1, t, \lambda_r\{{}^t/l_r + 1\}\rangle \\
& (r, -1) \\
& \langle l_r, u_r, \lambda_r\rangle \rightarrow \langle l_r - 1, t, \lambda_r\{{}^t/l_r\}\rangle
\end{aligned}
$$

Transitions – Clock

2. as an effect of the clock:
   - The timestamp t stored in the clock is incremented by one ($t+1$).
   - A species may stay at level l for $\delta(l)$ time units. Decay happens as soon as the interval $\delta(l)$ is elapsed ,

$$\langle l, u, \lambda \rangle \rightarrow \langle l-1, t+1, \lambda\{^{t+1}/_{l}\} \rangle$$

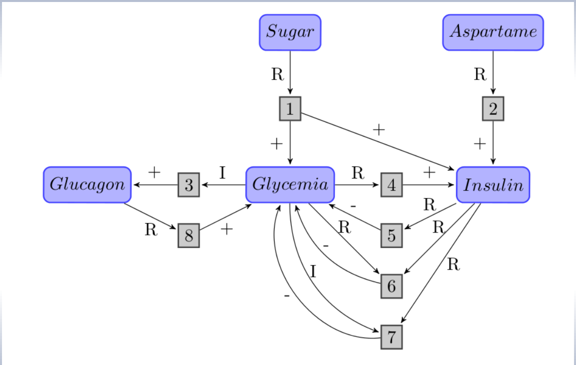


Glucose regulation – 1

The set of species involved:

Sugar	$\mathcal{L}_{sugar} = \{0, 1\}$	$\delta_{sugar}(1) = 2$
Aspartame	$\mathcal{L}_{aspartame} = \{0, 1\}$	$\delta_{aspartame}(1) = 2$
Glycemia	$\mathcal{L}_{glycemia} = \{0, 1, 2, 3\}$	$\delta_{glycemia}(1) = 8$
		$\delta_{glycemia}(2) = 8$
		$\delta_{glycemia}(3) = 8$
Glucagon	$\mathcal{L}_{glucagon} = \{0, 1\}$	$\delta_{glucagon}(1) = 3$
Insulin	$\mathcal{L}_{insulin} = \{0, 1, 2\}$	$\delta_{insulin}(1) = 3$
		$\delta_{insulin}(2) = 3$

Glucose regulation – 2



Glucose regulation – 3

The set of reactions:

ρ_k	Activators A_k	Inhibitors I_k	Results R_k	Δ_k
ρ_1	$\{(Sugar, 1)\}$	$\emptyset$	$\{(Insulin, +), (Glycemia, +)\}$	1
ρ_2	$\{(Aspartame, 1)\}$	$\emptyset$	$\{(Insulin, +)\}$	1
ρ_3	$\emptyset$	$\{(Glycemia, 1)\}$	$\{(Glucagon, +)\}$	1
ρ_4	$\{(Glycemia, 3)\}$	$\emptyset$	$\{(Insulin, +)\}$	1
ρ_5	$\{(Insulin, 2)\}$	$\emptyset$	$\{(Glycemia, -)\}$	2
ρ_6	$\{(Insulin, 1), (Glycemia, 3)\}$	$\emptyset$	$\{(Glycemia, -)\}$	2
ρ_7	$\{(Insulin, 1)\}$	$\{(Glycemia, 2)\}$	$\{(Glycemia, -)\}$	2
ρ_8	$\{(Glucagon, 1)\}$	$\emptyset$	$\{(Glycemia, +)\}$	2

Observation

- Decay and reactions are different types of behaviors
- Decay is synchronous
  it corresponds to an abstraction of the action of the environment
- Reactions are asynchronous
  their duration corresponds to the time required to observe an effect
- Execution time vs Simulation time
  More reactions are enabled less probable is the execution of time

Toxicity analysis

- ANDy can be used to detect and predict toxic behaviors related to the dynamics of bio-molecular networks.
- We resort to temporal logics and model checking techniques.
- We use computation tree logic (CTL)
- We provide an abstraction of ANDy into Kripke structures

Examples of questions

We are interested in checking whether the inner equilibrium of an organism is maintained when administrating drugs or applying stressors.

Toxicology properties can be classified into:

1. properties checking for the appearance of **symptoms**,
2. properties characterizing **causal relations** between events.

Glucose regulation

Causality:

Does assimilation of sweeteners cause hypoglycemia?

$$\mathbf{EF}[((Sugar, 1) \vee (Aspartame, 1)) \wedge (Glycemia, 1)] \rightarrow \mathbf{AF}(Glycemia, 2)$$

Paths for glucose regulation

$$\mathbf{EF}[((\mathit{Sugar},1)\vee(\mathit{Aspartame},1))\wedge(\mathit{Glycemia},1)]\rightarrow \mathbf{AF}(\mathit{Glycemia},2)$$

- Path that satisfies

$$(\mathit{Sugar},1),(\mathit{Aspartame},0),(\mathit{Glycemia},1),(\mathit{Insulin},0),(\mathit{Glucagon},0)\xrightarrow{\rho_1}$$
$$(\mathit{Sugar},1),(\mathit{Aspartame},0),(\mathbf{Glycemia},\mathbf{2}),(\mathit{Insulin},1),(\mathit{Glucagon},0)$$

- Path that contradicts

$$(\mathit{Sugar},0),(\mathit{Aspartame},1),(\mathit{Glycemia},1),(\mathit{Insulin},0),(\mathit{Glucagon},0)\xrightarrow{\rho_2}$$
$$(\mathit{Sugar},0),(\mathit{Aspartame},1),(\mathit{Glycemia},1),(\mathit{Insulin},1),(\mathit{Glucagon},0)\xrightarrow{\rho_7}$$
$$(\mathit{Sugar},0),(\mathit{Aspartame},0),(\mathbf{Glycemia},\mathbf{0}),(\mathit{Insulin},1),(\mathit{Glucagon},0)$$

Sound and completeness

Theorem

Given an ANDy *network* $(\mathcal{S}, \mathcal{R})$*, its encoding into*

- *Kripke structures*
- *Timed Automata*

is sound and complete.

Summing up

- ANDy, a high-level Petri net framework for cellular regulation networks.
- Species that can degrade as time passes by governed by a set of reactions.
- Toxicity properties can be expressed via a temporal logic.
- Properties can be verified thanks to a sound and complete abstraction.

Final remarks

- Comparison with stochastic models à la Gillespie
- Refinement of the abstraction
- Implementation: Snakes, Snoopy + Marcie

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