Dynamical Systems Biology

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Executive Summary

- Systems Biology can be interpreted differently depending on where you **come from**, where you are **going to** and who **judges your research**
- **Dynamical systems** are important for Biology
- Those dynamical systems are **not** necessarily those that you learned about in school (in case you did)
- Some inspiration for dynamic biological models should come from **Informatics** and **Engineering**, not only from **Physics** and **Chemistry**
- In particular, methodologies for exploring the behavior of **under-determined** (open) dynamical systems, inspired by formal verification (my own research)

Organization

- **Some Provocative Views on Systems Biology**
- Dynamical Systems and Biology
- The Dynamical Systems of Informatics
- Verification for Dummies
- Exploring the Dynamics of Continuous Systems
- Conclusions

Towards Systems Biology

Towards a Paper without the word *Towards* in the Title

O. Maler and A. Pnueli

Abstract. With the advent of post-genomic buzzword-driven big science a need was felt to moderate the level of hype and optimistic false promises in scientific papers and research proposals. In this paper we do not provide a comprehensive and complete solution to the problem mentioned in the title but nevertheless make a promising step towards the fulfillment of the goal.

- The word **towards** indicates that we are not yet there
- But where is **there** ?
- Different people will interpret the term **systems biology** (especially when loaded with money) in their favor
- Arguments over the **meaning of words** are often the most fierce (and the most stupid in some sense)

Systems Biology: a Cynical View

- Systems Biology: the current **gold rush** for many **mathematical** and technical disciplines looking for **nutrition** (funding, self-esteem) in the **scientific food chain**
- Biophysics, Biomatics, Bioinformatics, Biostatistics...
- The story goes like this:
- I do X
- I do it for my pleasure, because I studied it, and anyway, this is the **only** thing I will do in my current incarnation...
- ...fortunately X is **very** useful for Biology
- When you have a **hammer**, everything looks like a **nail**
- Personally this is how I came to the domain ($X =$ **automata**, **verification** and **hybrid systems**)
- Fortunately, my hammer is **universal**

Systems Biology: an Arrogant View

- Biologists are essentially very **concrete** beings, spending most of their time in the **kitchen** doing manual work
- They were not selected (initially) based on ability to manipulate **imaginary concepts** or creativity and rigor in the abstract world of ideas but rather..
- ..based on their **rigor** and **efficiency** at the **bench**
- Now when they need to make a **real science** out of their details they need noble white collar brahmins, namely..
- ... physicists, mathematicians, computer scientists, as **spiritual guides**
- Like monotheists converting the pagans, these merchants of abstract methodologies try to impress the poor savage with their **logics** and **miracles**

Systems Biology: a Humble View

- Biologists are working with the most fascinating, complex and mysterious **real-life** phenomena
- Living systems are more complex than the **hydrogen atom** or the **electromagnetic field** (and are not effectively reducible to them)
- Living systems are more sophisticated than your **dumb terminal** or **smart phone** or mobile robot or car
- Living systems are more mysterious and primordial than the **prime numbers**, the **algebra of Boole** or the **free monoid**
- If some of our dry tricks can help them, even a bit, in their grand march toward..
- ..understanding something about **Life Itself** or helping doctors kill less patients
- We should be very happy and proud for doing, for once, something **meaningful**

Systems Biology: a (relatively) Sober View

- The dynamics of a scientific discipline may have different periods with various **trends** and **fashions**
- This dynamics is not always optimized towards **truth**
- Many aspects (politics, social dynamics, commercial interests, cognitive inertia, media distortion) play an important role
- Probably most of what is published today in top journals will go to the **garbage can of history**
- Few centuries ago, the science of this guy (**chemistry**, **medicine**, **metaphysics**) was debated extensively in prime time

Systems Biology: a Sober (but subjective) View

- Today there is an **over emphasis** on doing something with data provided by new experimental machinery (omics)
- The main question about "knowing" all these details is whether this knowledge:
  - Is **sufficient** for understanding and learning something about underlying mechanisms ? (certainly not)
  - Is **necessary** for that ? (very hopefully not)
  - Is **helpful** or **counter-productive** ?
- Systems Biology is about seeking some clearer (conceptual and mathematical) models of **dynamical systems** at various **levels** of **abstraction**
- These models, if thoughtfully constructed, and carefully and **systematically analyzed/simulated** may help reducing the gap between cellular biochemistry and physiology

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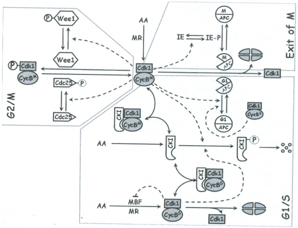
Dynamical Systems are Important

- Not news for biologists with a mathematical background
- J.J. Tyson, **Bringing cartoons to life**, Nature 445, 823, 2007:
-
- "Open any issue of *Nature* and you will find a diagram illustrating the **molecular interactions** purported to underlie some behavior of a living cell.
- The accompanying text explains how the **link** between **molecules** and **behavior** is thought to be made.
- For the simplest connections, such stories may be convincing, but as the **mechanisms** become more complex, **intuitive** explanations become more error prone and **harder to believe**."

In other Words

- What is the relation (if any) between



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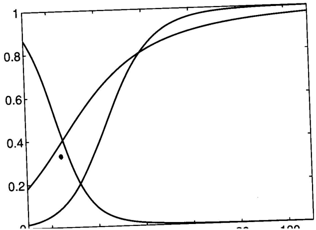
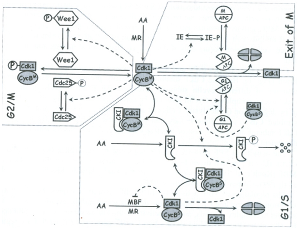
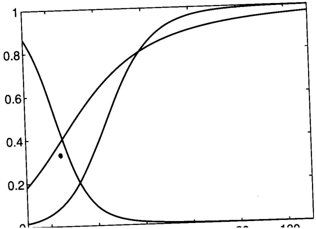


Systems and Behaviors





- Left: a **model** of a **dynamical system** which "explains" the mechanism in question
- Right: some **experimentally observed** behavior supposed to have some relation to the behaviors generated by model
- What is this relation exactly?
- Current practice leaves a lot to be desired, at least from a theoreticians' point of view

An Illustrative Joke

- An **engineer**, a **physicist** and a **mathematician** are traveling in a train in Scottland. Suddenly they see a **black** sheep
- Hmmm, says the engineer, I didn't know that sheeps in Scottland are **black**
- No my friend, corrects him the physicist, **some** sheeps in Scottland are **black**
- To be more precise, says the mathematician, **there is** a sheep in Scottland having **at least one black side**
- A discipline is roughly characterized by the number of logical quantifiers $\exists$ $\forall$ (and their alternations) its members feel comfortable with
- By the way what would a **biologist** say?
- In the Scottish sheep the agouti isoform is first expressed at E10.5 in neural crest-derived ventral cells of the second branchial arch

Dynamical Systems, a Good Idea

- The quote from Tyson goes on like this:
- “A better way to build bridges from **molecular biology** to **cell physiology** is to recognize that a network of interacting genes and proteins is ..
- .. a **dynamic** system evolving in **space** and **time** according to fundamental laws of **reaction**, **diffusion** and **transport**
- These **laws** govern how a **regulatory network**, confronted by any set of **stimuli**, determines the appropriate **response** of a cell
- This **information processing system** can be described in **precise** mathematical terms,
- .. and the resulting equations can be **analyzed** and **simulated** to provide **reliable**, **testable** accounts of the molecular control of cell behavior”
- No news for engineers..

Models in Engineering

- To build complex systems other than by **trial** and **error** you need **models**
- Regardless of the language or tool used to build a model, at the end there is some kind of **dynamical system**
- A mathematical entity that generates **behaviors** which are **progressions** of **states** and **events** in **time**
- Sometimes you can reason about such systems **analytically**
- But typically you **simulate** the model on the computer and generate behaviors
- If the model is related to **reality** you will learn **something** from the simulation about the **actual** behavior of the system
- Major difference: in engineering, the components are often **well-understood** and we need the simulation only because the outcome of their **interaction** is hard to predict

My Point: Systems Biology $\approx$ Dynamical Systems, but..

- To make progress in Systems Biology we should upgrade descriptive "models" by **dynamic models** with stronger **predictive power** and **refutability**
- Classical models of dynamical systems and classical analysis techniques tailored for them are **not** sufficient for **effective modeling** and **analysis** of biological phenomena
- Models, insights and **computer-based** analysis **tools** developed within **Informatics** (**Computer Science**) can help
- The whole **systems thinking** in CS is more evolved and sophisticated in some aspects than in Physics and Mathematics
- This is true of other **information-oriented engineering** disciplines such as the design of **circuits** or **control systems**

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What "Is" Informatics ?

- Informatics is the study of **discrete-event dynamical systems** (automata, transition systems)
- A natural point of view for those working on modeling and verification of "**reactive systems**"
- Less natural for data-intensive software developers and users
- This fact is sometimes **obscured** by fancy formalisms:
- Petri nets, process algebras, rewriting systems, temporal logics, Turing machines, programs
- All honorable topics with intrinsic beauty, sometimes even applications and deep insights
- But in an inter-disciplinary context they should be distilled to their **essence** to make sense to potential users.. rather than **intimidate** them
- In fact, the need to impress one's **own community** is a **serious impediment** in **inter-disciplinary** research

Dynamical Systems in General

- The following abstract features of dynamical systems are common to both **continuous** and **discrete** systems:
- **State variables** whose set of **valuations** determine the **state space**
- A **time domain** along which these values evolve
- A **dynamic law**: how state variables evolve over time, possibly under the influence of **external** factors
- System **behaviors** are **progressions** of **states** in **time** produced according to the dynamic law
- Knowing an initial state $x[0]$ the model can **predict**, to some extent, the value of $x[t]$

Types of Dynamical Systems

- Dynamic system models differ from each other according to their concrete details:
- State variables: **numbers** or more **abstract** domains that do not have a quantitative meaning
- Time domain: **metric** (dense or discrete) or **logical**
- The form of the dynamical law, constrained, of course, by the state variables and time domain
- The type of available analysis (analytic, simulation)
- Other features (open/closed, type of non-determinism, spatial extension)

Classical Dynamical Systems

- State variables: **real numbers** (location, velocity, energy, voltage, concentration)
- Time domain: the **real time axis** $\mathbb{R}$ or a discretization of it
- Dynamic law: **differential equations**

$$\dot{x} = f(x, u)$$

  or their **discrete-time** approximations

$$x[t+1] = f(x[t], u[t])$$

- Behaviors: **trajectories** in the continuous state space
- Typically presented in the form of a collection of **waveforms** or **time-series**, mappings from time to the state-space
- What you would construct using tools like Matlab Simulink, Modelica, SPICE simulators, etc.

Discrete-Event Dynamical Systems (Automata)

- An **abstract discrete state space**
- State variables need **not** have a numerical meaning
- A **logical time domain** defined by the **events** (order but not metric)
- Dynamics defined by **transition rules**: input event **a** takes the system from state **s** to state **s**′
- Behaviors are **sequences** of **states** and/or **events**
- **Composition** of large systems from small ones using different modes of **interaction**: synchronous/asynchronous, state-based/event-based
- What you will build using tools like Raphsody or Stateflow (or even C programs or digital hardware simulators)

Preview: Timed and Hybrid Systems

- Mixing **discrete** and **continuous** dynamics
- **Hybrid automata**: automata with a different continuous dynamics in each state
- Transitions = **mode switchings** (valves, thermostats, gears, genes, walking)
- **Timed systems**: an intermediate level of abstraction
- Timed Behaviors = **discrete events** embedded in **metric** time, Boolean signals, Gantt charts
- Used implicitly by **everybody** doing real-time, scheduling, embedded, planning in professional **and** real life
- Formally: **timed automata** (automata with clock variables)

Automata: Modeling and Analysis

- Automata model processes viewed as **sequences** of **steps**: software, hardware, ATMs, user interfaces administrative procedures, cooking recipes, smart phones...
- Unlike continuous systems there are **no simple analytical** tools to predict their long-term behavior
- We can **simulate** and sometimes do **formal verification**:
- Check whether **all behaviors** of a system, exposed to some uncontrolled inputs, exhibit some **qualitative behavior**:
- *Never reach some part of the state space; Always follow some sequential pattern of behavior...*
- These **temporal properties** include **transients** and are much richer than classical **steady states** or **limit cycles**
- There are **tools** for the verification of huge systems by sophisticated graph algorithms and powerful SAT solvers

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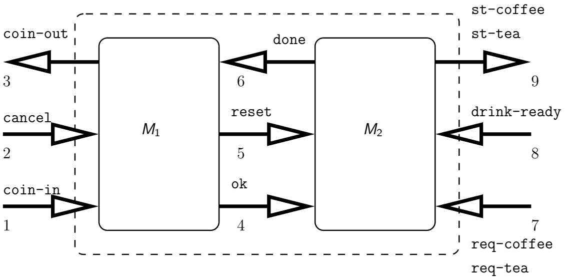
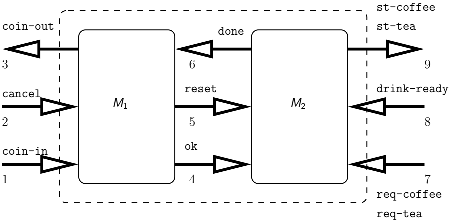
Illustration: The Coffee Machine

- Consider a machine that takes **money** and distributes **drinks**
- The system is built from two subsystems: one takes care of **payment** and one handles **choice** and **preparation** of drinks
- They communicate by sending **messages**



Remark: Signalling

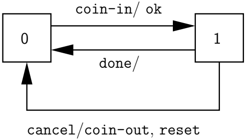
- Modern systems separate **information-processing** from the **physical interface**
- An inserted coin, a pushed button or a full cup are **physical events** translated by sensors into **uniform low-energy signals**
- These signals are treated as **information**, without thinking too much about their material realization
- Unless you are an engineer specialized in such mechanisms



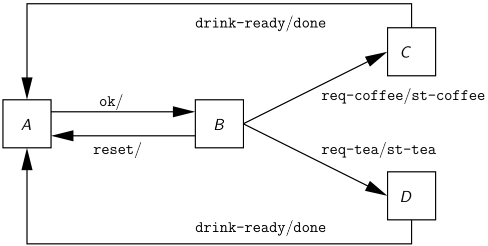
Automaton Models

- The two systems are modeled as automata
- transitions are triggered by **external events** and by events coming from the **other** subsystem

M_1



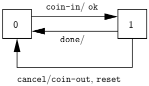
M_2



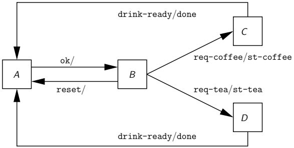
The Global Model

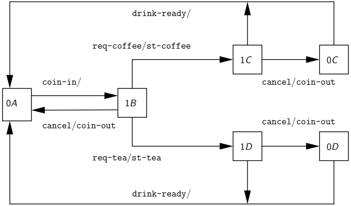
- The behavior of the whole system is captured by a **composition** (product) $M_1 \parallel M_2$ of the components
- States are elements of the **Cartesian product** of the respective sets of states, indicating the state of each component
- Some transitions are **independent** and some are **synchronized**,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

M_1

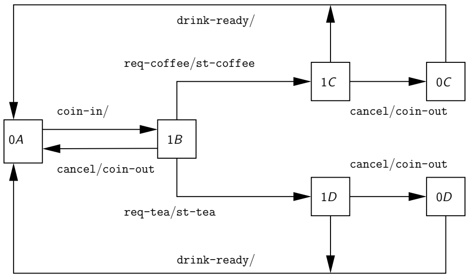


M_2





Normal Behaviors



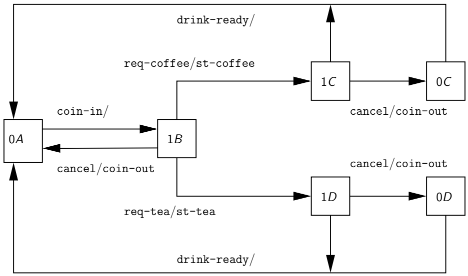
- Customer inserts a coin, then sees the bus arriving, cancels and gets the coin back

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

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

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

An Abnormal Behavior



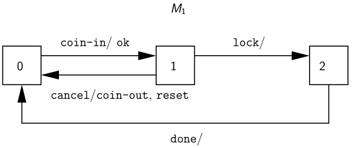
- Suppose the customer presses the **cancel** button **after** the coffee starts being prepared..

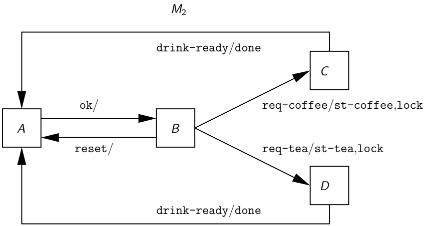
  $0A$ `coin-in` $1B$ `req-coffee` `st-coffee` $1C$ `cancel` `coin-out` $0C$ `drink-ready` $0A$

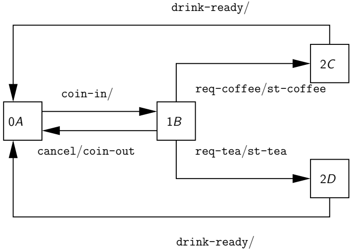
- Not so attractive for the owner of the machine

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 ignored







The Moral of the Story I

- Many complex systems can be modeled as a **composition** of **interacting** automata
- Behaviors of the system correspond to **paths** in the **global** transition graph of the system
- The size of this graph is **exponential** in the number of components (state explosion, curse of dimensionality)
- So if you have an interaction diagram which covers the **wall**, its state-space can cover the **universe**
- These paths are labeled by **input** events representing influences of the **external** environment
- Each input sequence may induce a **different behavior**, a **different scenario**

The Moral of the Story II

- We want to ensure that the system responds correctly to **all** conceivable inputs
- That it is **robust** and behaves properly in many contexts, not only where users **never** push the **cancel** button inappropriately
- We can choose an **individual input sequence** and **simulate** the behavior it induces, 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 type of analysis we **export** to the assessment of biological models and hypotheses

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Under-Determined Continuous Dynamical Systems

- We study open dynamical systems of the form

$$x[t+1] = f(x[t], p, u[t])$$

- Such systems are incomplete, **under-determined** in the following sense:
- The **initial state** $x[0]$ is not precisely known, only that it is in some set X_0
- The system has a vector of **parameters** p whose value is not precisely known, only that it is in some **parameter-space** P
- The exact form of the dynamic disturbance $u[t]$ is not known, only that it is constrained to be in some U for every t
- In order to **produce** a **simulation trace** $x[0], x[1], x[2], \cdots$ you need to **fix** values for those

Static/Punctual Under-Determination

- Let us ignore dynamic inputs and focus on the first two types of under-determination that we call **punctual**
- In both cases, in order to **simulate** your model and produce a trace $x[0], x[1], x[2], \cdots$ you need to fix **one** point/vector:
- $x[0]$ in the state space
- p in the parameter space
- Technically their treatment is similar and I will use **parameters** as **motivation** and **initial states** for graphical **illustration**

Models, Reality and Parameters

- Whenever models are supposed to represent something non-trivial they are just **approximations**
- This is evident for anybody working in modeling concrete **physical** systems
- It is less evident for those working on the functionality of **digital hardware** or **software**
- In these domains you have powerful **deterministic** abstractions (logical gates, program instructions) that work
- A common way to pack our ignorance in a compact way is to introduce **parameters** ranging in some **parameter space**

Examples:

- **Voltage level** modeling and simulation of circuits:
- A lot of variability in transistor characteristics depending on production batch, place in the chip, temperature, etc.
- **Timing performance analysis** of a new application (task graph) on a new multi-core architecture:
- Precise execution times of tasks are not known before the application is written and the architecture is built
- **Biochemical reactions** in cells following the **mass action** law:
- Many parameters related to the affinity between molecules cannot be deduced from first principles
- They are measured via isolated experiments under different conditions and only wide bounds on their values can be known

So What is the Problem?

- So you have a model which is under-determined, or equivalently an **infinite** number of models
- For **simulation** you **need** to determine, to make a **choice** to pick a point p in the parameter space
- The simulation shows you something about **one** possible behavior of the system, or a behavior of **one** possible model
- But **another choice** of parameter values could have produced a **completely different** behavior
- Ho do you live with that?

Possible Attitudes

- The answer depends on many factors
- One is the **responsibility** of the modeler/simulator
- What are the consequences of not taking under-determination seriously
- Is there a **penalty** for jumping into conclusions based on one or few simulations?
- Another factor is the **mathematical** and **real natures** of the system you are dealing with
- And as usual, it may depend on culture, background and tradition in the industrial or academic community

Non Responsibility: a Caricature

- Suppose you are a **scientist** not engineer, say **biologist**
- You conduct **experiments** and observe **traces**
- You propose a model and **tune** the parameters until you obtain a trace **similar** to the one observed experimentally
- These are **nominal** values of the parameters
- Then you can **publish** a paper about your model
- Except for picky reviewers there are **no real consequences** for neglecting under-determination
- The situation is different if some engineering is involved (pharmacokinetics, synthetic biology)
- Or if you want others to **compose** their models with yours

Justified Nominal Value

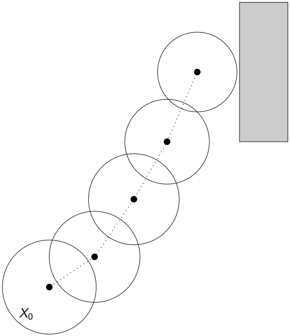
- You can get away with using a nominal value if your system is very **smooth** and **well-behaving**
- Points in the **neighborhood** of p generate **similar** traces
- There are also mathematical techniques (bifurcation diagrams, etc.) that can tell you sometimes what happens when you vary parameters
- This smoothness is easily broken by mode switching
- Another justification for ignoring parameter variability:
- When the system is anyway **adaptive** to deviations from nominal behavior (**control**, **feedback**)

Taking Under-Determination More Seriously: Sampling

- One can **sample** the parameter space with or without probabilistic assumptions
- Make a **grid** in the parameter space (exponential in the number of parameters)
- Or pick parameter values at **random** according to some **distribution**
- In the sequel I illustrate a technique (due to **A. Donze**) for **adaptive search** in the parameter space
- Local **sensitivity** information from the numerical simulator tells you where to **refine** the coverage
- Arbitrary dimensionality of the state space, but no miracles against the dimensionality of the parameter space

Sensitivity-based Exploration I

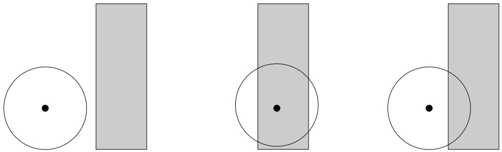
- We want to prove **all** trajectories from X_0 do not reach a bad set of states
- Take $x_0 \in X_0$ and build a ball B_0 around it that covers X_0



- Simulate from x_0 and generate a sequence of balls $B_0, B_1, \ldots$
- B_i **contains** all points reachable from B_0 in i steps

Sensitivity-based Exploration II

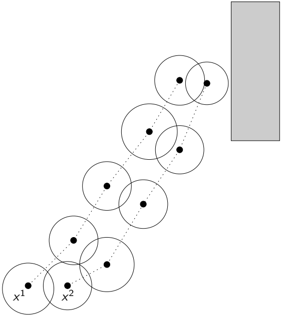
- After k steps, three things may happen:



- 1. No ball intersects bad set and the system is **safe** (due to over-approximation)
- 2. The **concrete trajectory** intersects the bad set and the system is **unsafe**
- 3. Ball B_k intersects the bad set but we do not know if it is a **real** or **spurious** behavior

Sensitivity-based Exploration III

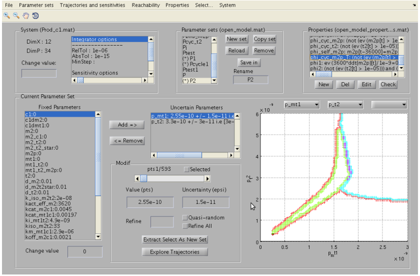
- In the latter case we refine the coverage and repeat the process for two **smaller** balls

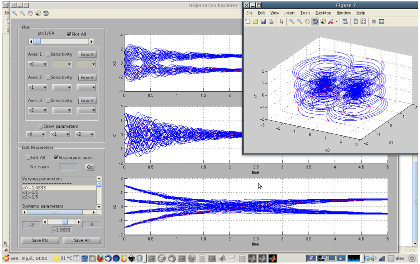


- Can prove correctness using a **finite** number of simulations, focusing on the **interesting** values
- Can approximate the **boundary** between parameter values that yield some qualitative behaviors and values that do not

The Breach Toolboox

- Parameter-space exploration for arbitrary continuous dynamical systems relative to **quantitative temporal properties** expressed in STL (**signal temporal logic**)
- Applied to embedded control systems, analog circuits, biochemical reactions (haematopoiesis, angiogenesis, apoptosis) and anasthesia.





Dynamic Under-Determination

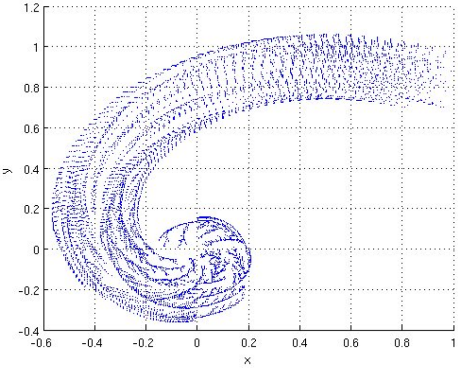
- The system is modeled as **open**, exposed to **external disturbances**
- Dynamics of the form

$$x[i+1] = f(x[i], v[i])$$

- The natural way to represent the influence of other unmodeled subsystems and external environment
- Under-determination is dynamic: to produce a trace you need to give the value of v at every time step, a signal/sequence $v[1], \ldots, v[k]$
- A priory a much larger space to sample from: dimension mk compared to m for static
- One can use a nominal value: **constant**, **step**, **sinusoid**, **random noise**, etc.

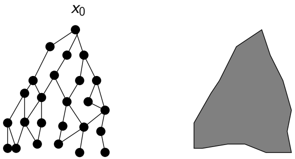
Taking Under-Determination Seriously: Guided Sampling

- A method due to **T. Dang**:
- Use ideas from robotic motion planning (RRT) to generate inputs that yield a good **coverage** of the reachable state space
- Applied to analog circuits



Taking Under-Determination More Seriously: Verification

- Paranoid **worst-case** formal **verification** attitude:
- If we say something about the system it should be provably true for **all** choices of p, $x[0]$ and $v[1], \ldots, v[k]$
- Instead of doing a simple simulation you do **set-based** simulation, computing **tubes of trajectories** covering everything
- Breadth-first rather than depth-first exploration

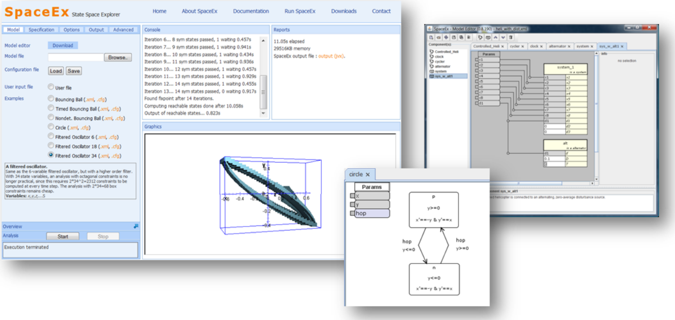


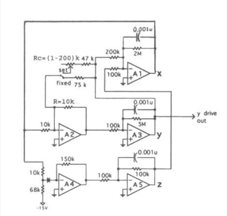
- Advantages: works also for hybrid (switched) systems
- Limitations: manipulates geometric objects in high dimension

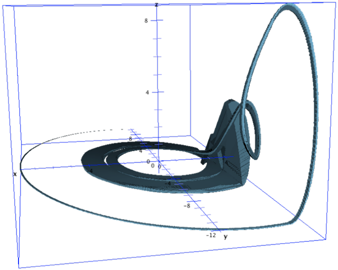
State of the Art

- Linear and piecewise-linear dynamics ~ 200 variables using algorithms of **C. Le Guernic and A. Girard**
- Nonlinear dynamics with $10 - 20$ variables - an ongoing research activity
- Implemented into the **SpaceEx** tool developed under the direction of **G. Frehse**
- Available on `http://spaceex.imag.fr` with model editor, visualization and more
- Waiting for more beta testers

The State-Space Explorer (SpaceEx)

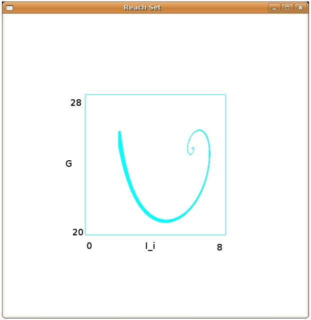


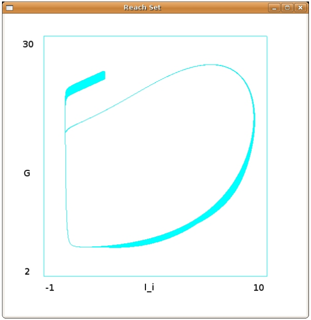




Example: Lac Operon (T. Dang)

$$
\begin{aligned}
\dot{R}_a &= \tau - \mu * R_a - k_2 R_a O_f + k_{-2}(\chi - O_f) - k_3 R_a I_i^2 + k_8 R_i G^2 \\
\dot{O}_f &= -k_2 r_a O_f + k_{-2}(\chi - O_f) \\
\dot{E} &= \nu k_4 O_f - k_7 E \\
\dot{M} &= \nu k_4 O_f - k_6 M \\
\dot{I}_i &= -2k_3 R_a I_i^2 + 2k_{-3} F_1 + k_5 I_r M - k_{-5} I_i M - k_9 I_i E \\
\dot{G} &= -2k_8 R_i G^2 + 2k_{-8} R_a + k_9 I_i E
\end{aligned}
$$





Organization

- Some Provocative Views on Systems Biology
- Dynamical Systems and Biology
- The Dynamical Systems of Informatics
- Verification for Dummies
- Exploring the Dynamics of Continuous Systems
- **Conclusions**

Back to the Big Picture

- Biology needs (among other things) more **dynamic models** to form **verifiable predictions**
- These models can benefit from the accumulated understanding of **dynamical system** within **informatics** and cannot rely only on **19th century mathematics**
- The views of dynamical system developed within informatics are, sometimes, more adapted to the **complexity** and **heterogeneity** of Biological phenomena
- 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

Back to the Big Picture

- Systems Biology should combine insights from:
- Engineering disciplines: modeling and analysis of very **complex man-made systems** (chips, control systems, software, networks, cars, airplanes, chemical plants)
- Physics, Chemistry: experience in mathematical modeling of natural systems with measurement constraints
- Mathematics and Informatics as a unifying theoretical framework

Thank You