Under Determined Dynamical Systems, Discrete and Continuous

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Introduction

- "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."
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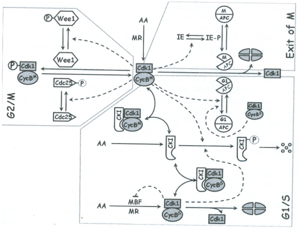
- J. J. Tyson, **Bringing cartoons to life**, Nature 445, 823, 2007

In other Words

- What is the relation (if any) between



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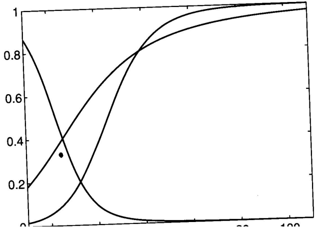
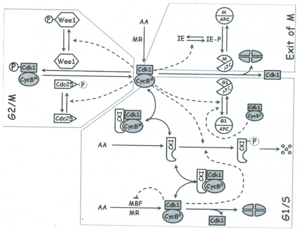
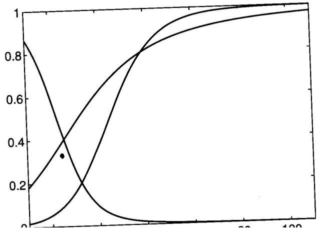


Systems and Behaviors





- Left object is supposed to correspond to a *model* of a *dynamical system* which explains the mechanism in question
- Right object is some *experimentally observed* behavior supposed to have some relation to the behaviors that the dynamical model generates
- What is this relation exactly?
- Current practice leaves a lot to be desired (at least for theoreticians)

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**
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- By the way what would a biologist say?

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- 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"

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

- To make progress in Systems Biology one needs to 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** (aka **Computer Science**) can help
- The whole systems thinking in CS is much more evolved and sophisticated than in physics and large parts of math
- This is true of other engineering disciplines such as circuit design or control systems

What "Is" Informatics ?

- Informatics is the study of **discrete-event dynamical systems** (automata, transition systems
- A natural point of view for for people working on modeling and verification of "**reactive systems**", less so for data-intensive software developers and users

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- This fact is sometimes **obscured** by fancy formalisms:
- Petri nets, process algebras, rewriting systems, temporal logics, Turing machines
- 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

Dynamical System Models in General

- Systems whose **state** evolves over **time** according to some **law**
- A state is a valuation to each of the **state variables**
- The **dynamic law** says how states evolve over time, possibly under the influence of external or unknown factors
- System behaviors are progressions of states in time
- Having such a model, knowing an initial state $x(0)$ one can **predict**, to some extent, the value of $x(t)$
- Classes of dynamical system models differ according to:
  1. The nature of state variables
  2. The nature of the time domain
  3. The form of the dynamic law (of course restricted by 1 and 2)
  4. Other features

Classical Dynamical Systems

- Those used today to explain, say, Newton laws
- 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: $\dot{x} = f(x)$ or
- Their discrete-time approximations: $x(t+1) = f(x(t))$
- Behaviors are **trajectories** in the continuous state space
- Presented typically as a collections of **waveforms** over time

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

Automata as Dynamical Systems

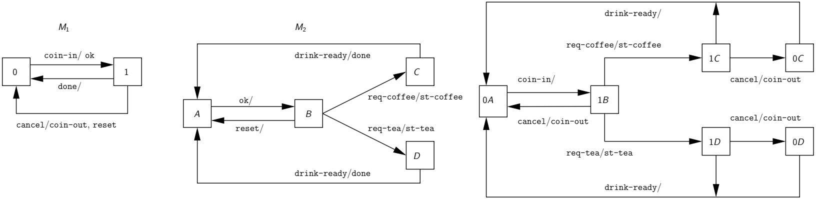
- **Abstract** discrete state space, state variables need **not** have a numerical meaning
- **Logical** time domain defined by the events
- Can express order: **a** before **b**, but not the quantitative temporal **distance** between the events
- Dynamics defined by **transition rules**: input event **a** takes the system from state **s** to state $\mathbf{s}'$
- The systems are inherently **open** to the external input (non autonomous in the math jargon)
- Behaviors are **sequences** of states and events
- Systems can be **composed** using various modes of interaction: synchronous / asynchronous, state-based / event-based; Hierarchical structuring; Syntax

Automata: Modeling and Analysis

- Automata model processes viewed as **sequences** of **steps**: software, hardware, ATMs, user interfaces administrative procedures, cooking recipes...
- Unlike continuous systems there are no simple analytical tools to determine 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**
- Verification of huge systems by sophisticated graph algorithms

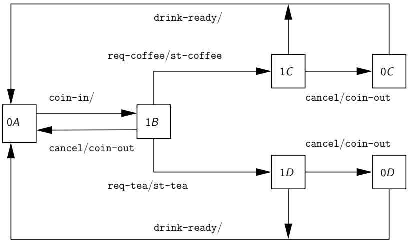
Illustration: The Coffee Machine

- Consider a machine that takes money and distributes drinks, built from two communicating subsystems:
- M_1 for money and M_2 for drinks;
- They are modeled as automata with transitions triggered by external (to the subsystem) events



- The complete system is the composition $M_1 \parallel M_2$: some transitions are independent and some are inter-dependent
- Behaviors are **paths** in this transition graph

Behaviors



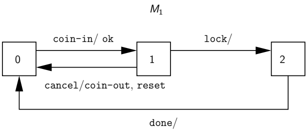
- Customer puts coin, then sees the bus arriving, cancels and gets the coin back $0A$ coin-in $1B$ cancel coin-out $0A$
- Customer inserts coin, requests coffee, gets it and the system returns to initial state

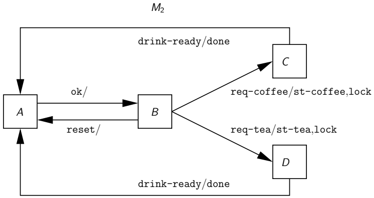
  $0A$ coin-in $1B$ req-coffee st-coffee $1C$ drink-ready $0A$
- Suppose the customer presses the cancel button **after** the coffee starts being prepared..

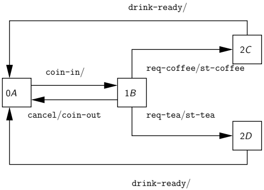
  $0A$ coin-in $1B$ req-coffee st-coffee $1C$ cancel coin-out $0C$ drink-ready $0A$

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



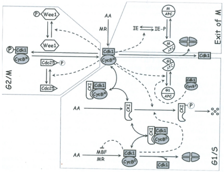


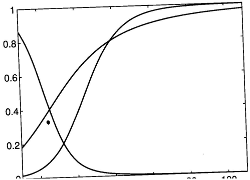


The Moral of the Story

- Complex systems can be modeled as a **composition** of interacting automata resulting in transition graph with size **exponential** in the number of components
- Behaviors correspond to **paths** in the the transition graph
- These paths are labeled by **input** events representing influences of the outside environment
- Each individual input **sequence** may induce a **different** behavior. We can **simulate** each but cannot do it exhaustively
- We need something stronger to make sure that a system responds correctly to all conceivable input stimuli...
- ...or to characterize the external environments that induce certain behaviors

Carrying the Insight to Continuous Systems





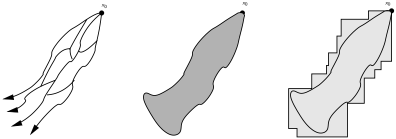
- A system admits a dynamics $\dot{x} = f(x, p, u)$ where:
  - p is a vector of **parameter** values; Experiments do not characterize their exact values (they may vary among cells)
  - $u(t)$ is an external disturbance signal indicating possible **dynamic** variations in the environment outside the model
- To generate a simulated behavior from an under-determined model you need to **fix** an **initial state** x_0, a **point** p in the parameter space, and a **disturbance profile** $u(t)$

So what is the Relation?

- A trajectory/waveform published in a respectable journal as a "proof of fit" between a proposed **model** and an observed **behavior** corresponds (at best) to..
- ..one point $(x_0, p, u(t))$ in the uncertainty space without any guarantee that a similar behavior will be manifested while choosing another point
- How do biologists get away with it?
- What is the meaning or usefulness of such statements?
- I had similar questions to control engineers who do only a **finite** number of simulations
- But they have other mathematical reasons and techniques that can justify the choice of **representative** simulations
- Do biologists have?

Our Modest Contribution

- We develop analysis methods and **tools** that take this under-determination seriously
- Either by exhaustive **set-based** simulation methods that compute "tubes" of trajectories the contain **all** the behaviors under **all** choices in the uncertainty space



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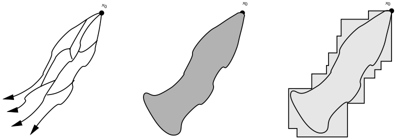

- Or by **systematic sampling** of the uncertainty space (easier to do with x_0 and p which are static) and..
- ..identifying the range of model parameters that lead to certain classes of behaviors
- Hopefully such tools will help increasing the meaningfulness of dynamic models and provide for their **composition**