Models and Languages for Computational Systems Biology

Lecture 9: Continuous Time

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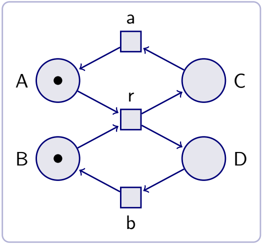
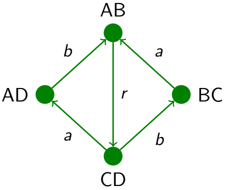
Semester 2 Week 5

http://www.inf.ed.ac.uk/teaching/courses/mlcsb

Outline

How many states?





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Model-checking allows us to evaluate high-level temporal queries about behaviour of structured processes.

However, this becomes more work as the number of possible states increases.

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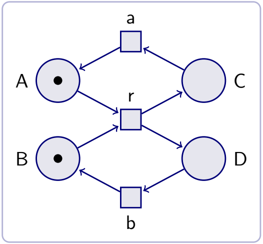

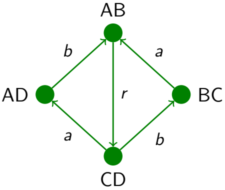

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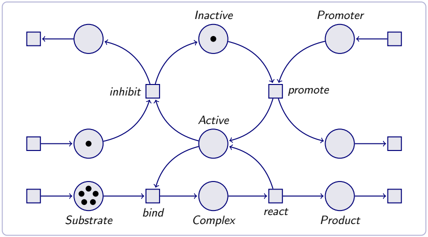

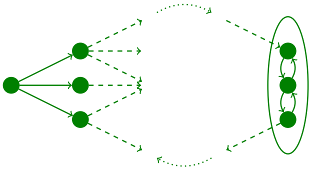

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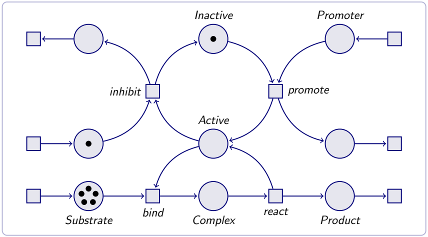

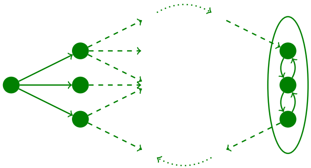

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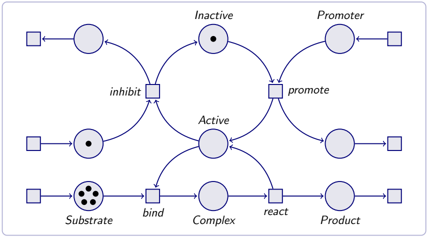

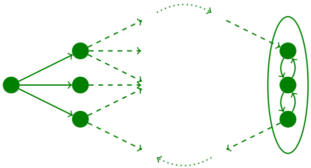

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- 10^6, 10^{12}, ... — explicit state exploration infeasible.

From individuals to sets

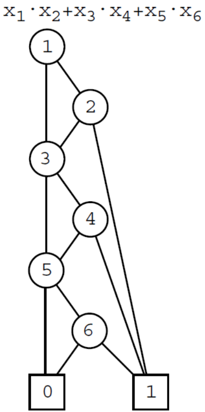
Working with individual states becomes infeasible. Instead, we can work with sets of states — which is anyway a better fit for branching-time assertions.

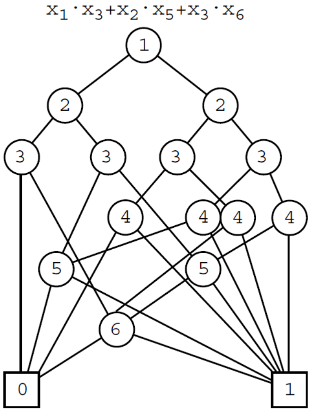
The key to success is choice of representation:

- Lists of states — no better.
- Bitmaps, trees — small improvement.
- Characteristic functions $\mathit{State} \to 2$ — very concise, limited manipulation (no comparison operation)
- Structured representation of characteristic functions: Binary Decision Diagrams — succinct, efficient operations, unique normal forms.

An efficient representation of sets can also express the transition relation $\to \subseteq \mathit{State} \times \mathit{State}$

Binary Decision Diagrams





Randal E. Bryant.
Graph-based algorithms for boolean function manipulation.
IEEE Transactions on Computers, C-35(8):677–691, 1986.

Think big

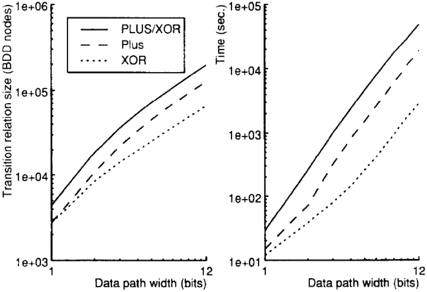


FIG. 4. Performance of BDD model checking algorithm on simple pipelines.

Figure 4 graphs the performance we obtained when checking formula 1 on a variety of pipelines of this type.

. . . The number of bits per register varied from 1 to 12. . . .

A pipeline with 12 bits has approximately 1.5×10^{29} reachable states.

Jerry R. Burch, Edmund M. Clarke, Kenneth L. McMillan, David L. Dill and L. J. Hwang
Symbolic model checking: 10^{20} states and beyond.
Information and Computation, 98(2):142–170, 1992.

Outline

Road map

- High-level model
  - Intuitive, human-readable; Modular, succinct, descriptive, ...
  - Precise, well-defined, compositional.
  - E.g. Petri Nets; later we shall also see process algebras in this rôle.
- Low-level semantic model
  - Describes system behaviour.
  - Can be mechanically generated from a high-level model.
  - E.g. labelled transition systems; later Markov chains and ODEs.
- Analysis
  - Pose questions about the model.
  - Questions and answers phrased on high-level model.
  - Mechanically evaluated on low-level semantics.
  - E.g. model checking temporal logic; but will also see simulation,

Let's do it again

So far we have seen this with qualitative, discrete models:

Petri nets $\longleftrightarrow$ transition systems $\longleftrightarrow$ LTL, CTL, CTL*, HML,. . .

We can now repeat this:

- Continuous time, rates and probabilities;
- Continuous space, amounts and concentrations;
- Qualitative vs. quantitative;
- Markov chains, ODEs, process algebras,. . .

Outline

Introducing time

All models so far have been qualitative: a behaviour is possible, or not.

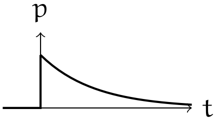
We introduce quantitative information about the relative probabilities of behaviours with stochastic actions: events that happen at a random time.

We qualify "random" by concentrating on events whose behaviour is stochastic, but time-invariant. This gives rise to a *negative exponential* probability distribution over time, with a single parameter, the *rate* at which the event happens.

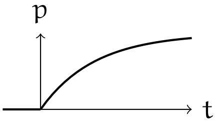
Negative exponential distribution

If random variable X has negative exponential distribution at rate r, then we have the following:

Probability density $\quad f(X,r) = \begin{cases} re^{-rt} & t \geqslant 0 \\ 0 & t < 0 \end{cases}$



Cumulative distribution $\quad F(X,r) = \begin{cases} 1 - e^{-rt} & t \geqslant 0 \\ 0 & t < 0 \end{cases}$



Mean $\quad E(X) = \dfrac{1}{r}$

Variance $\quad \mathrm{Var}(X) = \dfrac{1}{r^2}$

Properties of the negative exponential

- Memoryless:

$$\forall t, u > 0 \,.\, P(t < X < t + u \mid X > t) = P(0 < X < u)$$

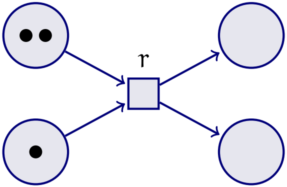
- Minimum of independent negative exponentials:

$$X \sim \mathrm{Exp}(r) \quad \& \quad Y \sim \mathrm{Exp}(s) \quad \Longrightarrow \quad \min(X, Y) \sim \mathrm{Exp}(r + s)$$

Suppose a repeating event happens at random, with λt occurrences expected within any time interval of length t (a *Poisson* process). Then the time until it next occurs, and the time between occurrences, are both random variables with negative exponential distribution, rate λ.

Similarly for space: the distance between mutations on a DNA strand has negative exponential distribution.

Stochastic Petri Nets



To introduce continuous time into a Petri nets, we label each transition with a rate.

When enabled, the transition fires at that rate (exponential distribution) until it is no longer enabled.

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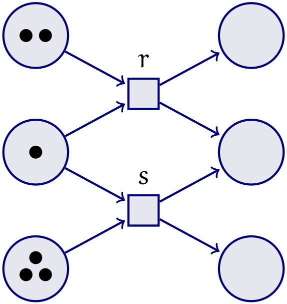

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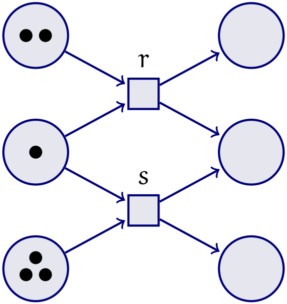

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The combined rate of firing is $r + s$, with respective probabilities

$$\frac{r}{r+s} \qquad \text{and} \qquad \frac{s}{s+r} \;.$$

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We can explore this behaviour through simulation, or by model-checking using a probabilistic temporal logic such as PCTL.

Outline

Reading

Homework

Read the following short articles.

- Lucas Laursen.
  Computational biology: Biological logic.
  Nature 462:408–410, 2009.

- Jasmin Fisher and Thomas A Henzinger.
  Executable cell biology.
  Nature Biotechnology 25:1239–1249, 2007.

- Nathalie Chabrier and Fran cois Fages.
  Symbolic model checking of biochemical networks.
  In *Computational Methods in Systems Biology, Proceedings of the First International Workshop, CMSB 2003.* Lecture Notes in Computer Science 2602, pages 149–162. Springer-Verlag, 2003

References (1/2)

Randal E. Bryant.
Graph-based algorithms for boolean function manipulation.
IEEE Transactions on Computers, C-35(8):677–691, 1986.
Reprinted in M. Yoeli, editor, *Formal Verification of Hardware Design*, IEEE Computer Society Press, 1990, pages 253–267. Electronic version with annotations available at http://www.cs.cmu.edu/~bryant/pubdir.

Jerry R. Burch, Edmund M. Clarke, Kenneth L. McMillan, David L. Dill and L. J. Hwang
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- Falko Bause and Pieter S. Kritzinger.
  Stochastic Petri Nets.
  Vieweg Verlag, 2nd edition, 2002.
  Out of print, but electronic version available at
  http://www4.cs.uni-dortmund.de/~Bause/spnbook2.html

- M. Ajmone Marsan.
  Stochastic Petri nets: An elementary introduction.
  In *Advances in Petri Nets 1989*, Lecture Notes in Computer Science 424, pages 1–29. Springer-Verlag, 1990.