Models and Languages for Computational Systems Biology
Lecture 9: Continuous Time

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Semester 2 Week 5
Outline

1 Symbolic Model Checking

2 Road Map

3 Continuous Time

4 Closing
How many states?

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.

Identify at which states the CTL formula $\text{AF}(\text{EX}(\text{AD}) \land \text{EX}(\text{BC}))$ holds.
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- 1000, 10,000 states — direct, but by machine.
- $10^6$, $10^{12}$, ... — 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 $State \rightarrow 2$ — 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 $\rightarrow \subseteq State \times State$
Binary Decision Diagrams

Randal E. Bryant.
Graph-based algorithms for boolean function manipulation.
Think big

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 $1.5 \times 10^{29}$ 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.

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1. Symbolic Model Checking
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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:

\[
\text{Petri nets} \leftrightarrow \text{transition systems} \leftrightarrow \text{LTL, CTL, CTL*, HML, } \ldots
\]

We can now repeat this:

- Continuous time, rates and probabilities;
- Continuous space, amounts and concentrations;
- Qualitative vs. quantitative;
- Markov chains, ODEs, process algebras, \ldots
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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.
If random variable $X$ has negative exponential distribution at rate $r$, then we have the following:

**Probability density**

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

**Cumulative distribution**

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

**Mean**

$$E(X) = \frac{1}{r}$$

**Variance**

$$\text{Var}(X) = \frac{1}{r^2}$$
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:

\[ X \sim \text{Exp}(r) \quad \& \quad Y \sim \text{Exp}(s) \quad \Rightarrow \quad \text{min}(X, Y) \sim \text{Exp}(r + s) \]

Suppose a repeating event happens at random, with \( \lambda t \) 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 \( \lambda \).

Similarly for space: the distance between mutations on a DNA strand has negative exponential distribution.
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When enabled, the transition fires at that rate (exponential distribution) until it is no longer enabled.
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Where more than one transition is enabled, we have a race.

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

$$\frac{r}{r + s} \quad \text{and} \quad \frac{s}{s + r}.$$
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We can explore this behaviour through simulation, or by model-checking using a probabilistic temporal logic such as PCTL.
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Homework

Read the following short articles.


Randal E. Bryant.  
Graph-based algorithms for boolean function manipulation.  
Reprinted in M. Yoeli, editor, *Formal Verification of Hardware Design*,  

Jerry R. Burch, Edmund M. Clarke, Kenneth L. McMillan, David L.  
Dill and L. J. Hwang  
Symbolic model checking: $10^{20}$ states and beyond.  
Falko Bause and Pieter S. Kritzinger. 
*Stochastic Petri Nets.*
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.