Executable Biology

Tom Henzinger

IST Austria

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Modeling of biological objects (e.g. cells) and processes (e.g. pathways) as interacting computer programs.

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-complex natural systems	-complex engineered systems

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Computational Science

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The Essence of Computer Science

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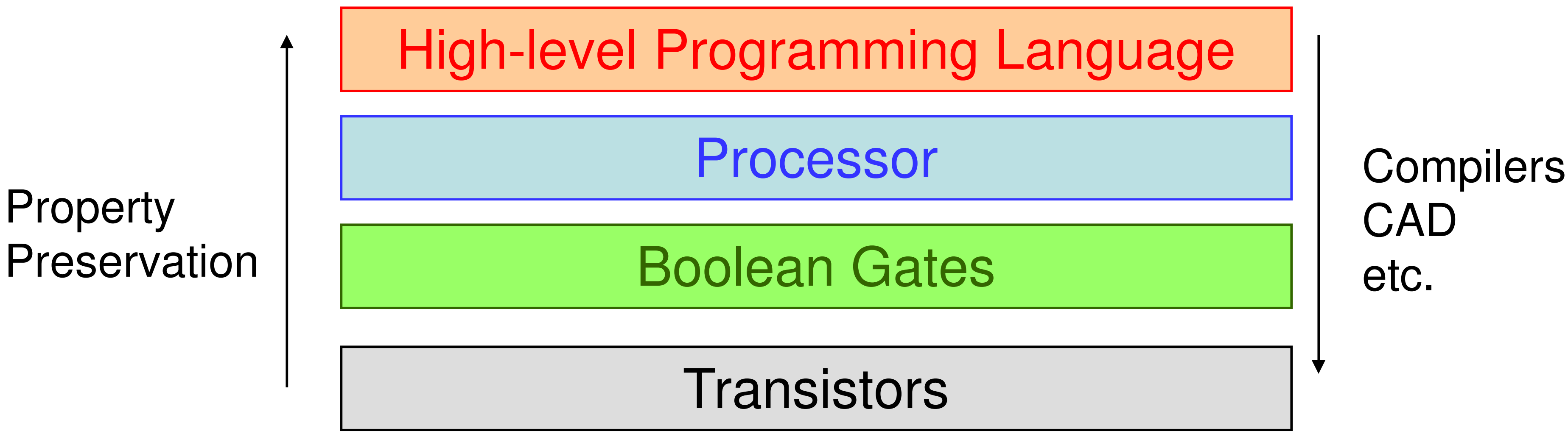
2. Towers of Abstraction



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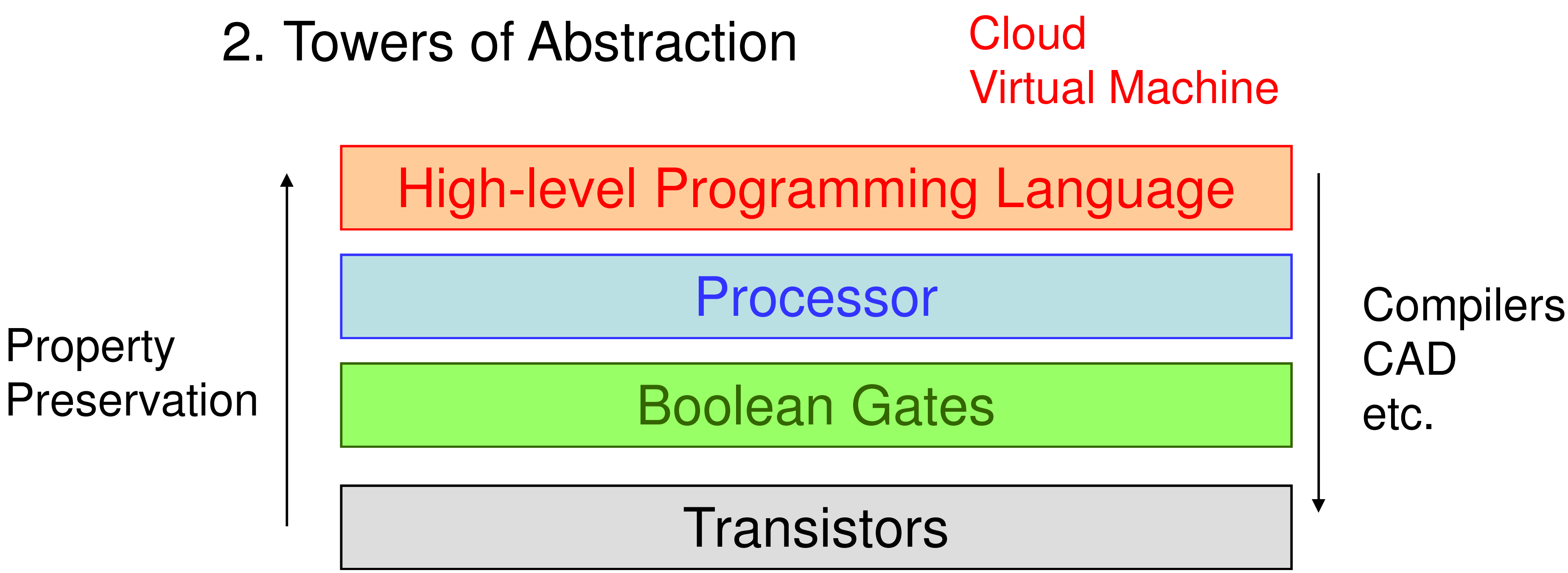
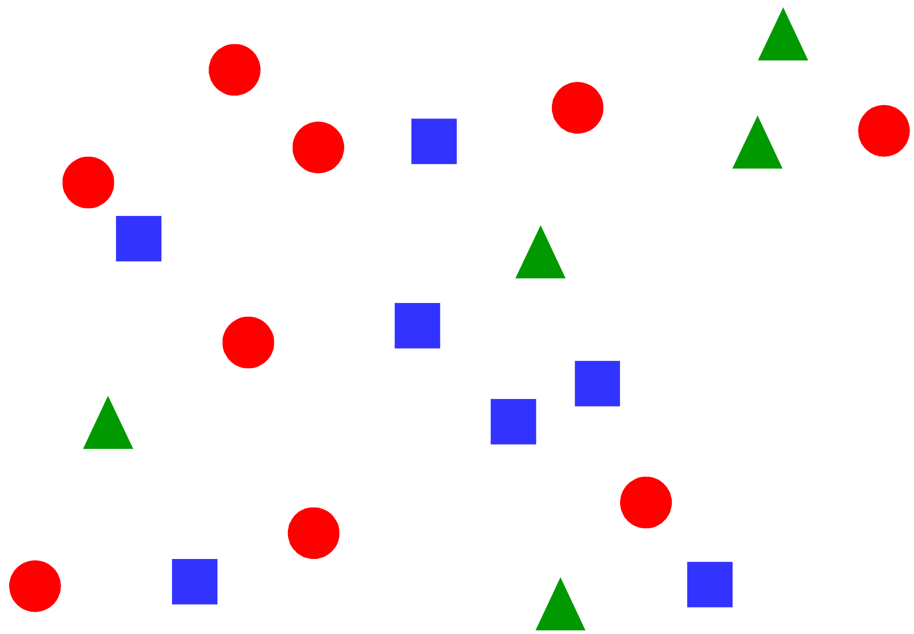


Markovian Population Models



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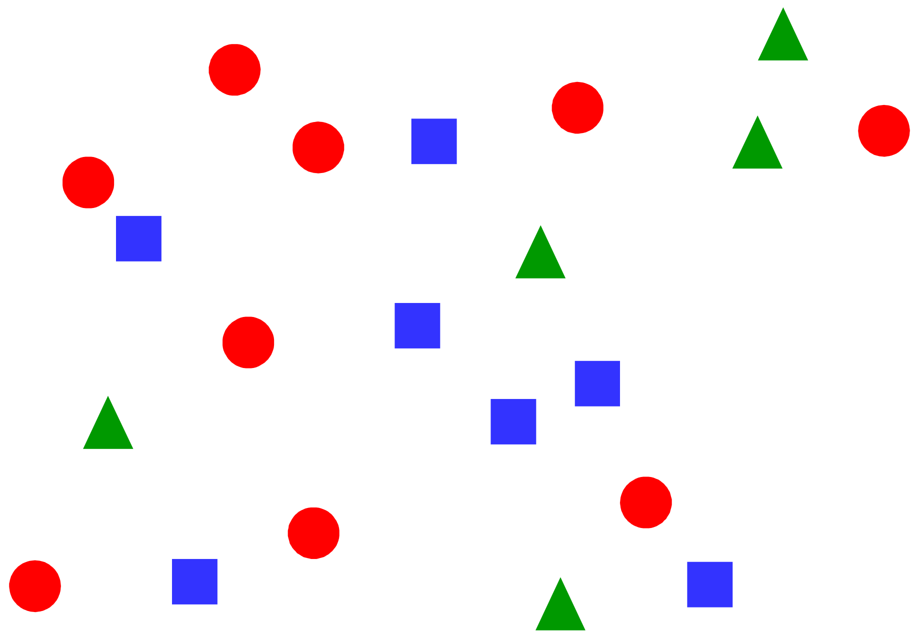

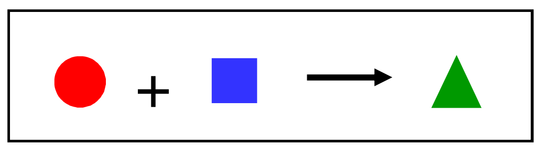

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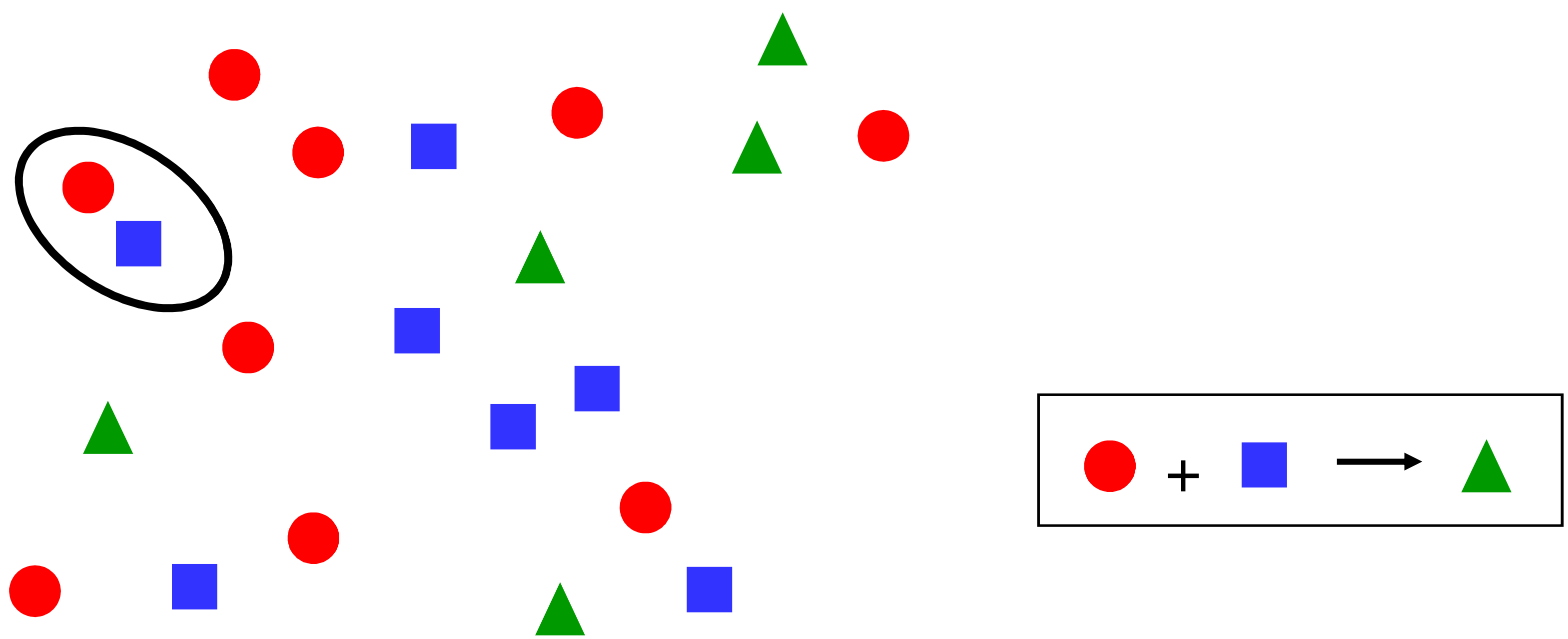

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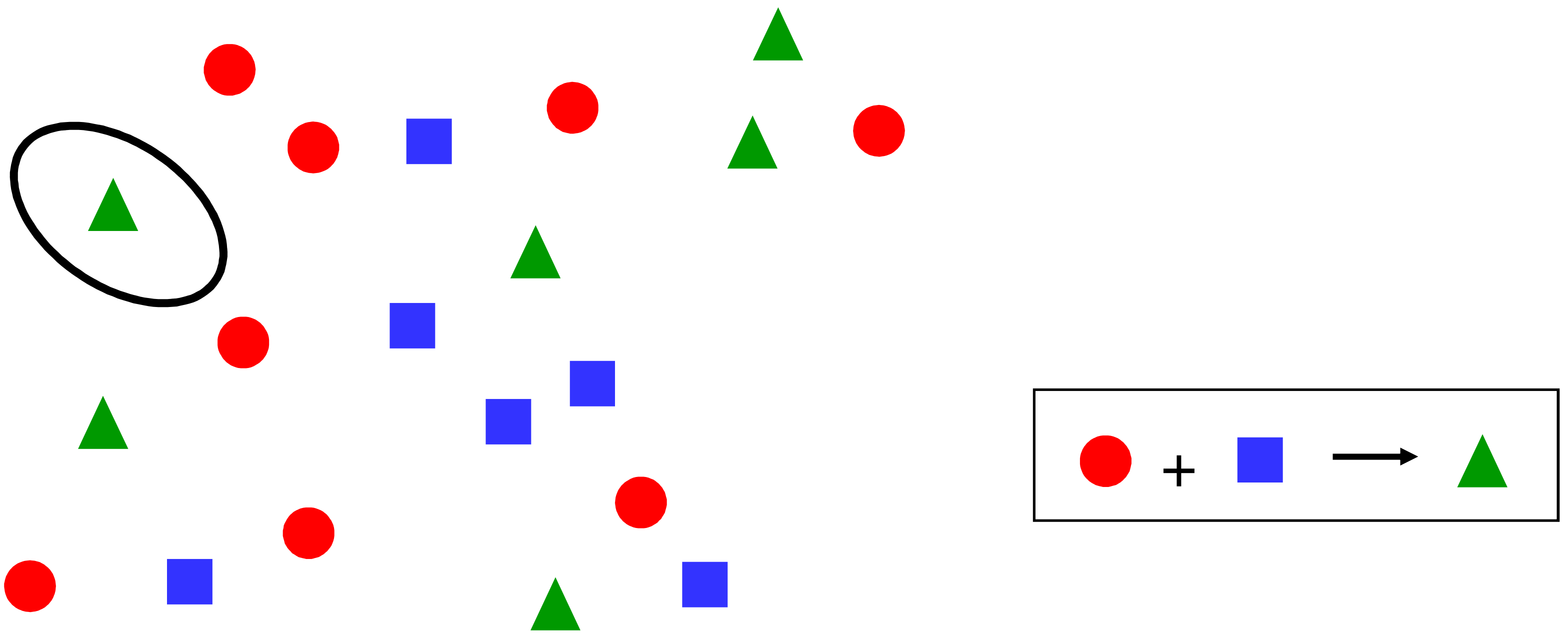

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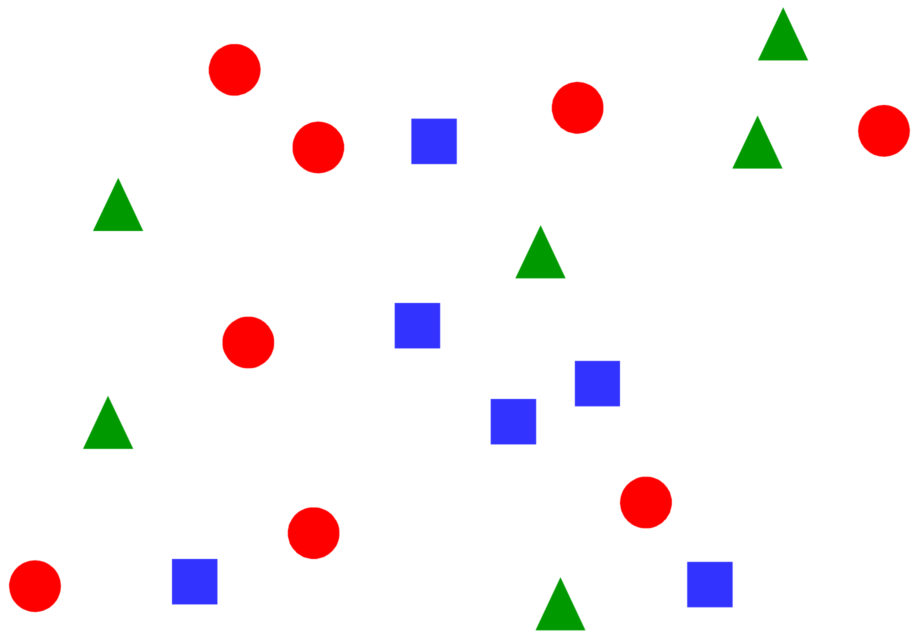
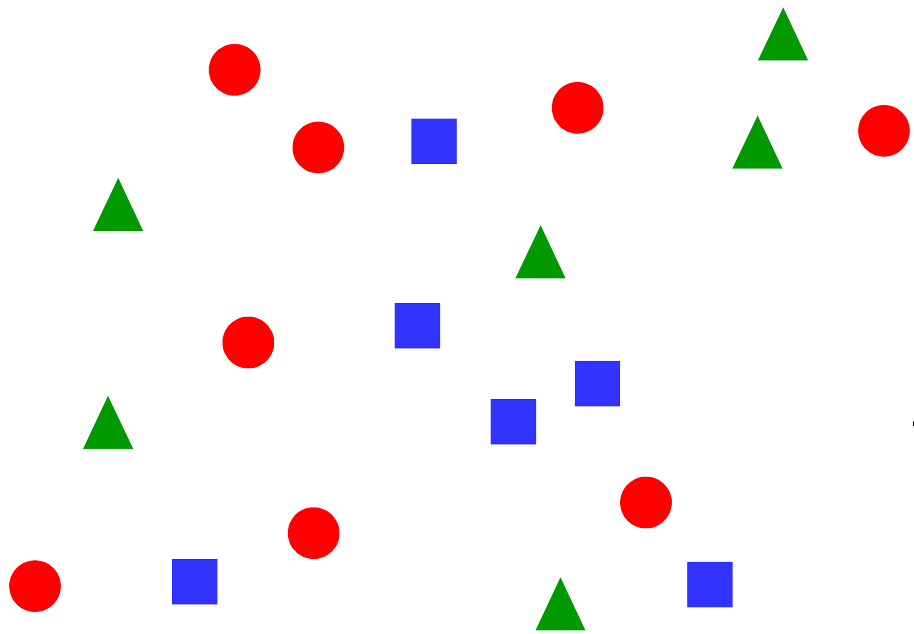


State: (8 , 6 , 6)

Markovian Population Models

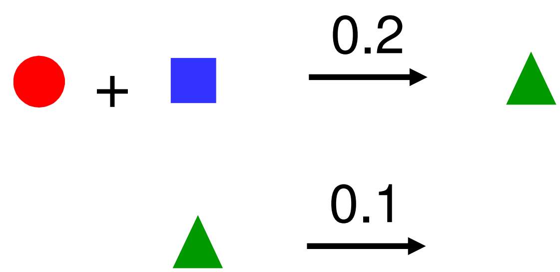


(9 , 7 , 5)

Transition: $\downarrow$

(8 , 6 , 6)

Markovian Population Models



Syntax: stoichiometric equations (finite object)

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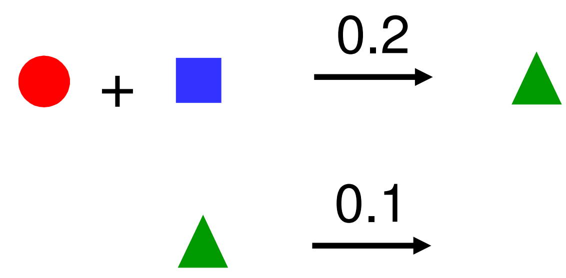

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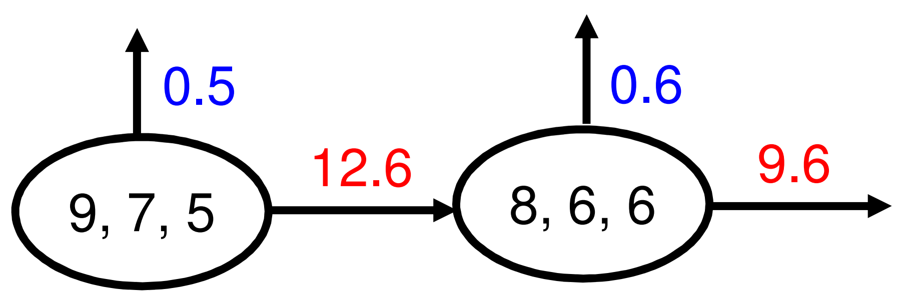


Semantics: CTMC (infinite object)

Syntax: Guarded Commands

Dimension n: state $(x_1, ..., x_n)$ 2 S
state space $S = N^n$

$n = 3$

Finite set of guarded commands:

each consists of
1. guard G µ S
2. update function u: G ! S
3. rate function α: G ! R^+

G_1: x_1 ¸ 1 Æ x_2 ¸ 1
$u_1(x_1,x_2,x_3) = (x_1-1,\ x_2-1,\ x_3+1)$
$\alpha_1(x_1,x_2,x_3) = 0.2$ ¢ x_1 ¢ x_2

G_3: x_3 ¸ 1
$u_1(x_1,x_2,x_3) = (x_1,\ x_2,\ x_3-1)$
$\alpha_1(x_1,x_2,x_3) = 0.1$ ¢ x_3

Syntax matters!

1. Composition and compositionality
2. Expressiveness and succinctness
3. Executability
4. Encapsulation and abstraction

e.g. Petri nets: not compositional
Stoichometric equations: not expressive
Rate matrices: not succinct
Differential equations: not executable

Guarded Commands

-compositional

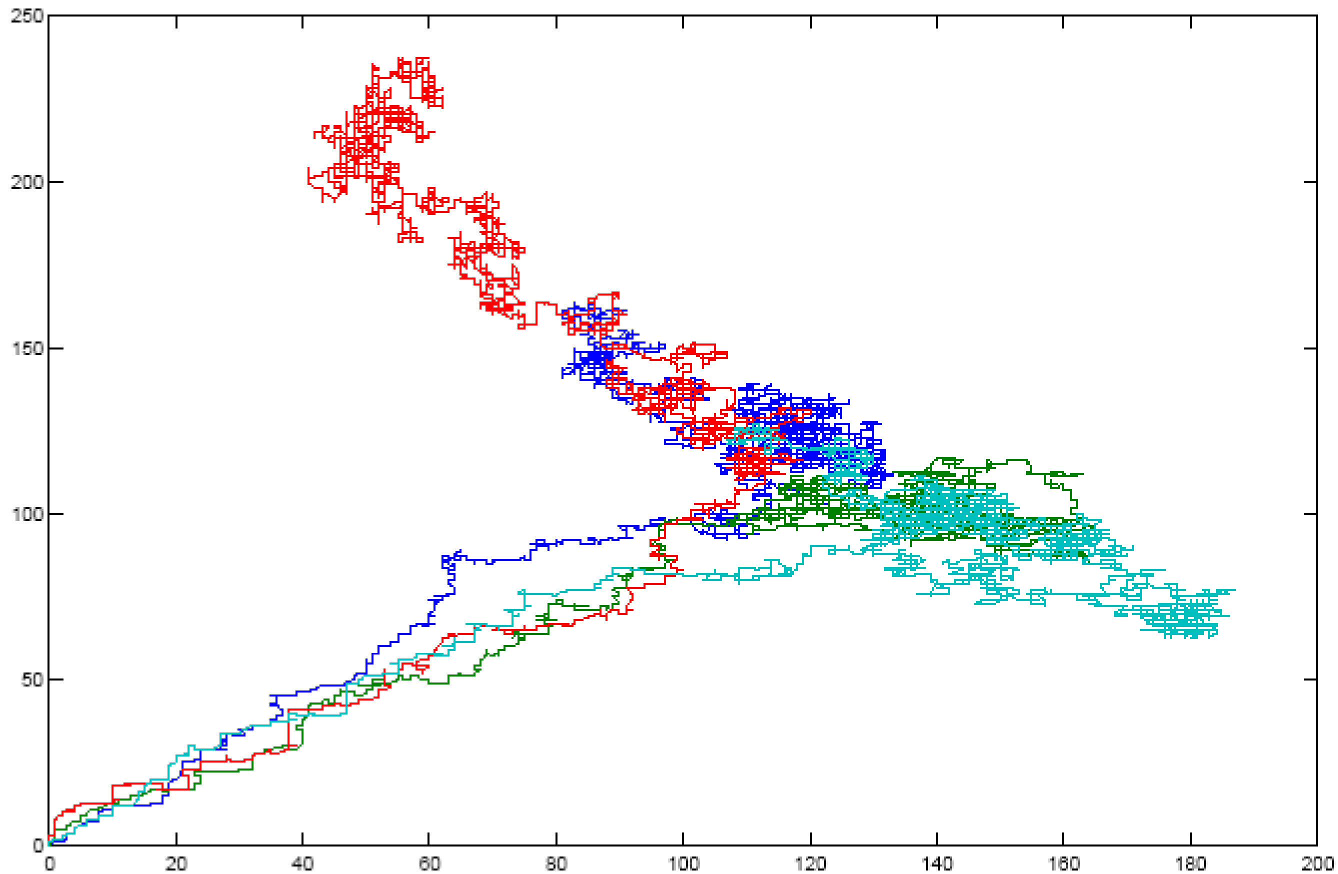
-expressive and succinct

-executable

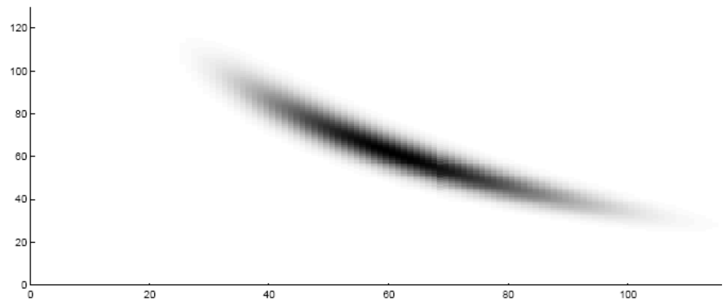
-counterexample-guided abstraction refinement

-model checking

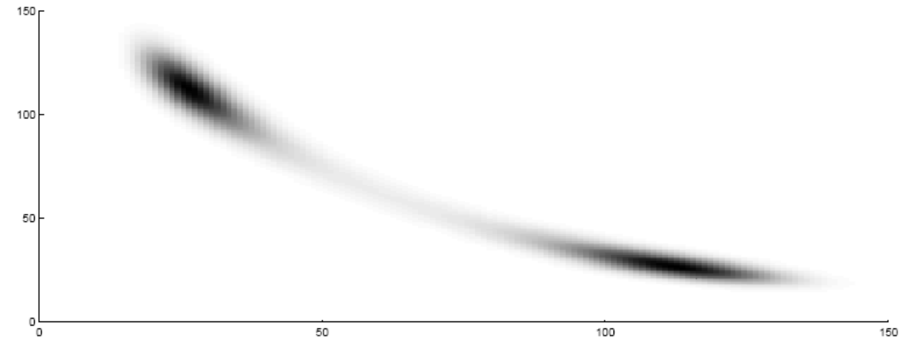
Genetic Toggle Switch: Four Simulation Runs



Genetic Toggle Switch: Model Checking [DHMW09]



t = 5000



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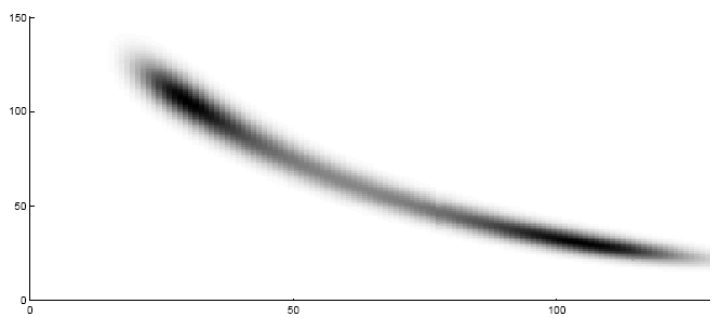

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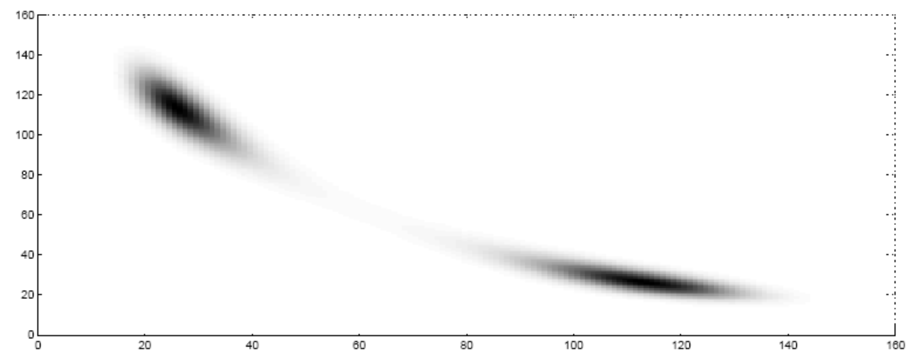

t = 50000

Bacteriophage λ Model [DHMW09]

Desired precision:	3×10^{-6}
Model checking:	55 min runtime
Gillespie simulation ($\beta = 0.95$):	67 h runtime (3×10^{8} runs)

Model Checking CTMCs [DHMW09]

Transient distributions can be efficiently approximated by combining adaptive uniformization with ideas from Computer Science:

1. on-the-fly state space exploration
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Executable Syntax

Sliding Window Abstraction

Opportunity and Challenges

1. Computer Science can contribute to biology far more than *algorithms* and *tools*, e.g. modeling principles such as

   reactivity, *compositionality*, *executability*, *hybrid systems*, *property preserving abstraction*, and *model checking*.

Example: bounded asynchrony [FHMP08]

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2. Computer Science needs to develop more *quantitative* models.

B versus R

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2. Computer Science needs to develop more *quantitative* models.

3. Training of scientists!!!

IST Austria

8 biologists, 4 computer scientists, 1 PhD program