Continuous-space analysis of Bio-PEPA models

Stephen Gilmore
LFCS, University of Edinburgh

PEPA Club

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Outline

1. Analysis with Bio-PEPA
2. Discrete-state analysis
   - Discrete state-space
   - Transient probability distribution
3. Continuous-space analysis
   - Differential equations and the Jacobian
   - Differential equation analysis

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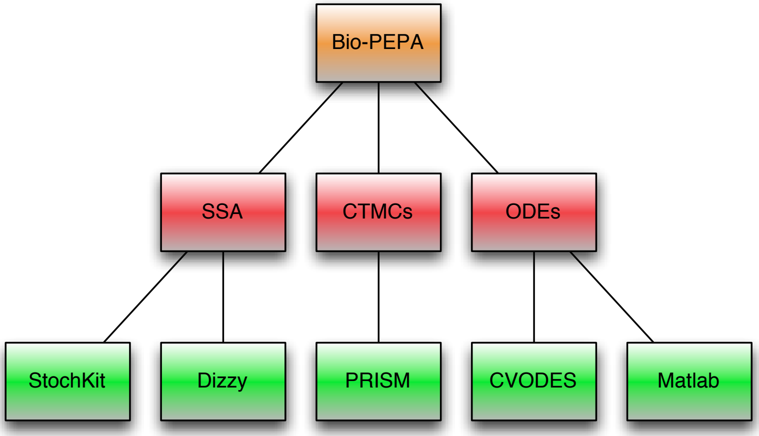
Analysis with Bio-PEPA



Enzyme-Substrate example

Consider the simple Enzyme-Substrate reaction

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{:}S \overset{k_2}{\longrightarrow} E + P$$

Formulation in Bio-PEPA

The kinetic functions

r_1	$k_1 \times E \times S$
r_{-1}	$k_{-1} \times E{:}S$
r_2	$k_2 \times E{:}S$

The Bio-PEPA model

E	$r_1 \downarrow$	$+$	$r_{-1} \uparrow$	$+$	$r_2 \uparrow$
S	$r_1 \downarrow$	$+$	$r_{-1} \uparrow$		
$E{:}S$	$r_1 \uparrow$	$+$	$r_{-1} \downarrow$	$+$	$r_2 \downarrow$
P					$r_2 \uparrow$

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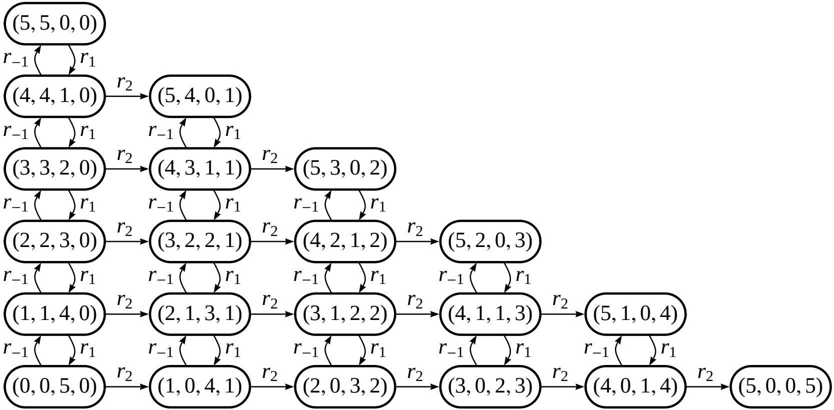
Discrete state-space of Enzyme-Substrate example

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{:}S \overset{k_2}{\longrightarrow} E + P$$

- In the discrete stochastic domain we can consider the state-space generated from initial numbers of molecules. E.g. $(E, S, E{:}S, P) = (5, 5, 0, 0)$.
- We consider the effect of each of the three reactions on the four molecule counts E, S, $E{:}S$, P.

Discrete state-space of Enzyme-Substrate example

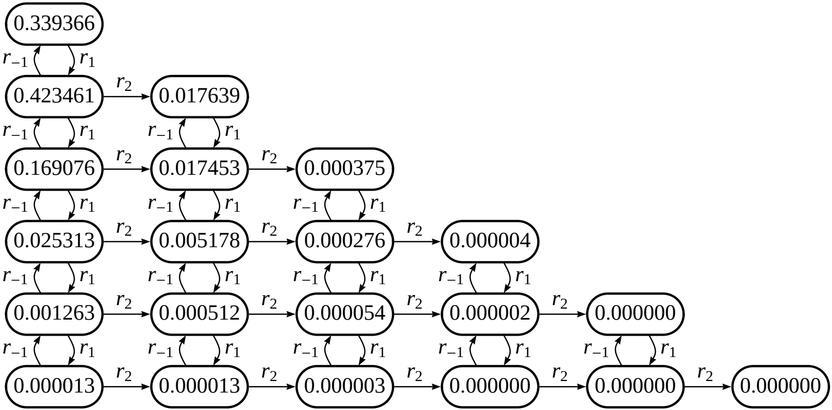


Probability distribution across the state-space

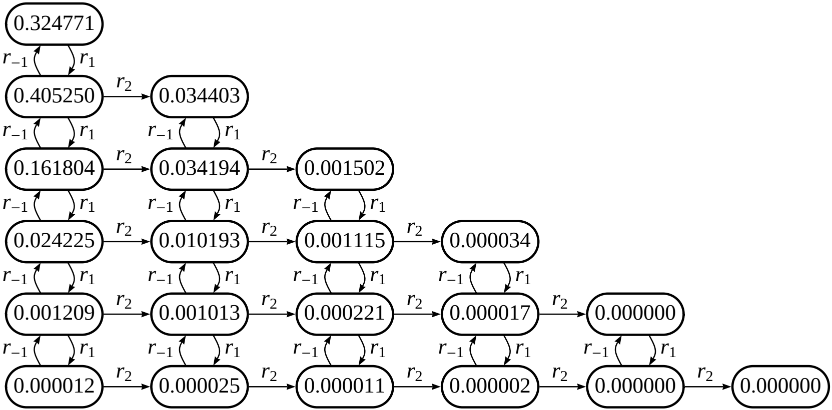
$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{:}S \overset{k_2}{\longrightarrow} E + P$$

- If we know the initial molecule counts and the values of the rate constants $k_1 = 1.0$, $k_{-1} = 20.0$ and $k_2 = 0.05$ we can compute the probability of being in each state of the state-space at all future time points.
- At time $t = 0$ we have $\Pr(5, 5, 0, 0) = 1$.

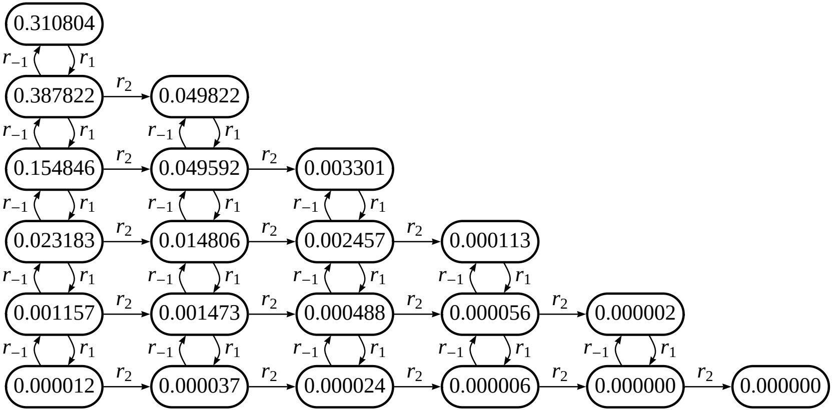
Transient probability distribution at $t = 1$



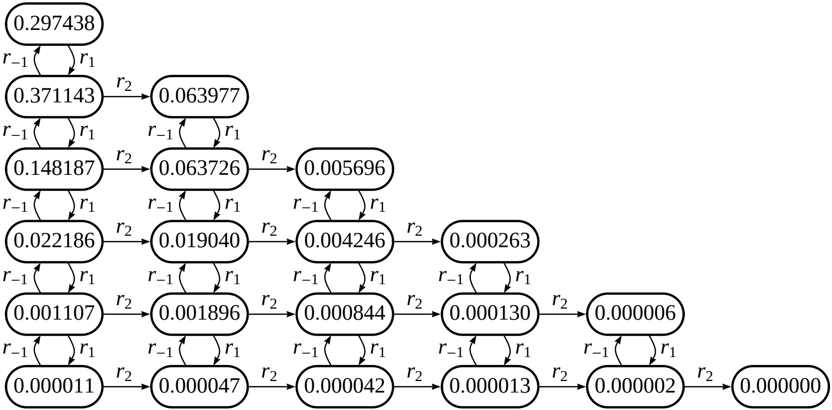
Transient probability distribution at $t = 2$



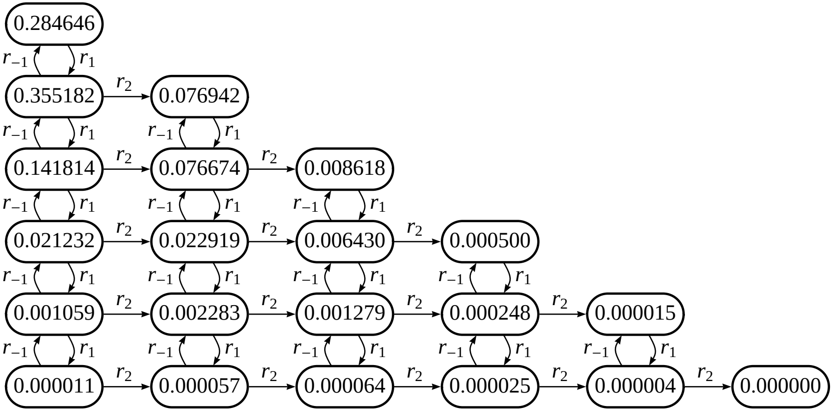
Transient probability distribution at $t = 3$



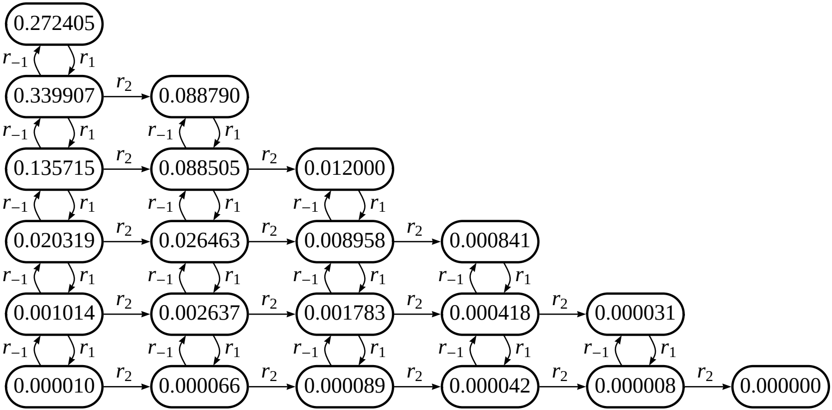
Transient probability distribution at $t = 4$



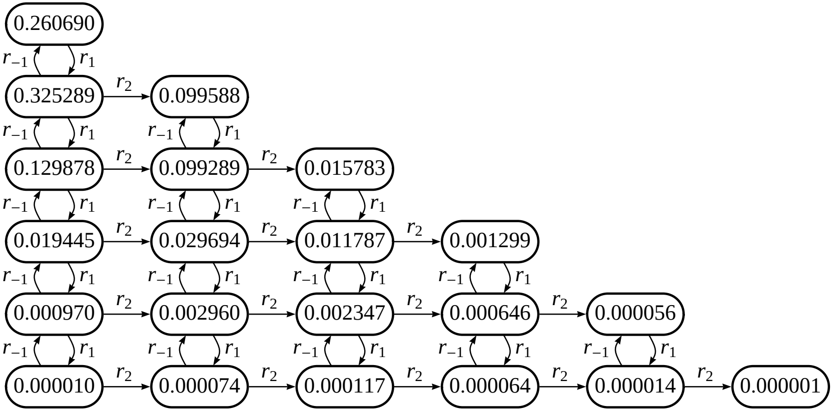
Transient probability distribution at $t = 5$



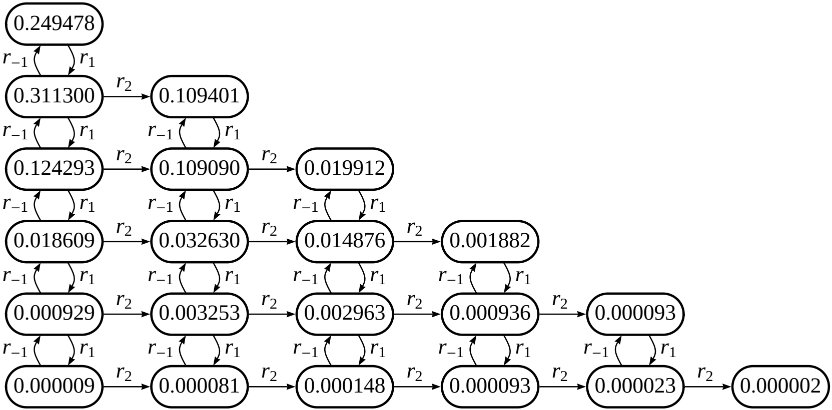
Transient probability distribution at $t = 6$



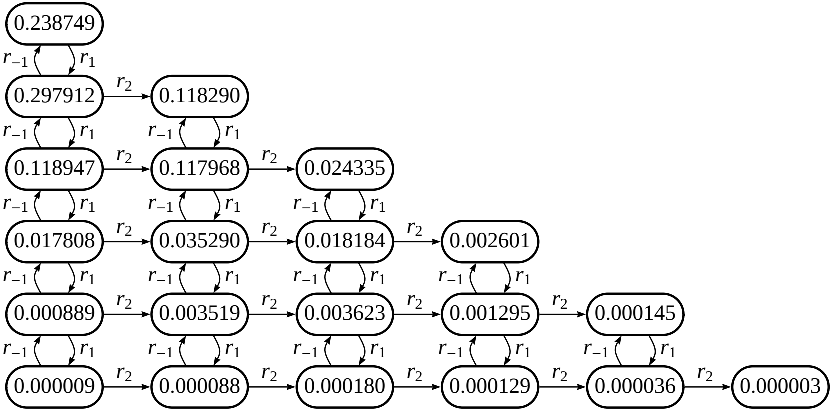
Transient probability distribution at $t = 7$



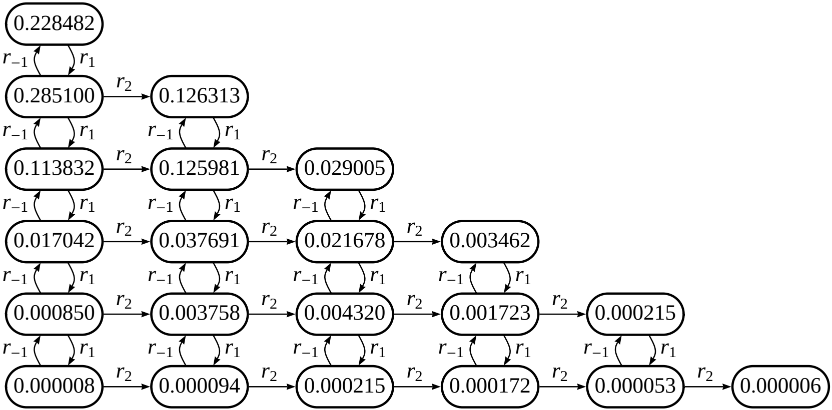
Transient probability distribution at $t = 8$



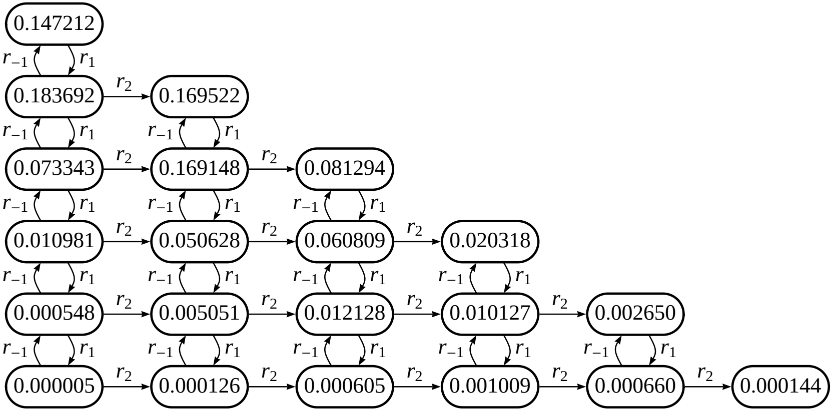
Transient probability distribution at $t = 9$



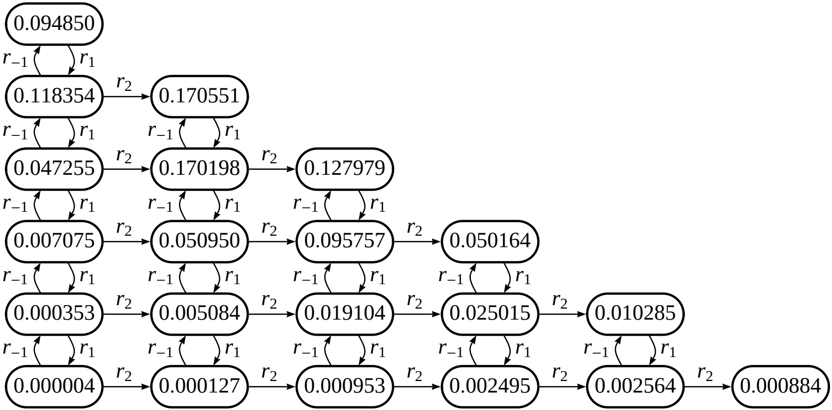
Transient probability distribution at $t = 10$



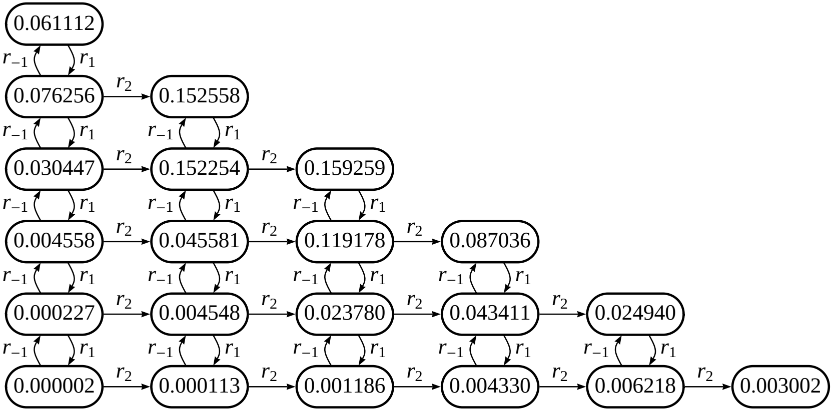
Transient probability distribution at $t = 20$



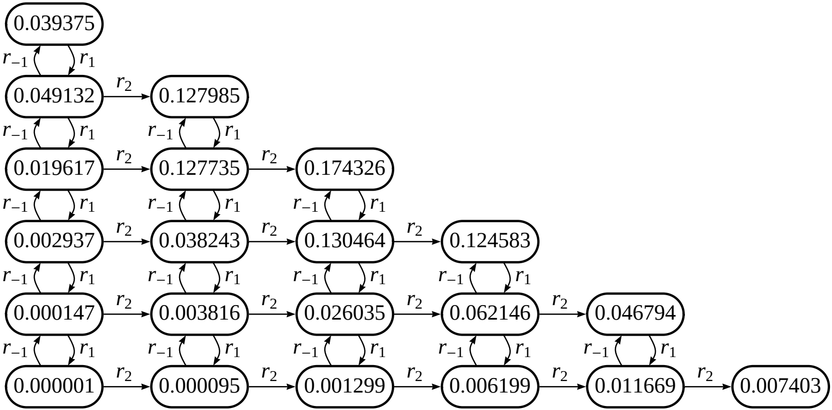
Transient probability distribution at $t = 30$



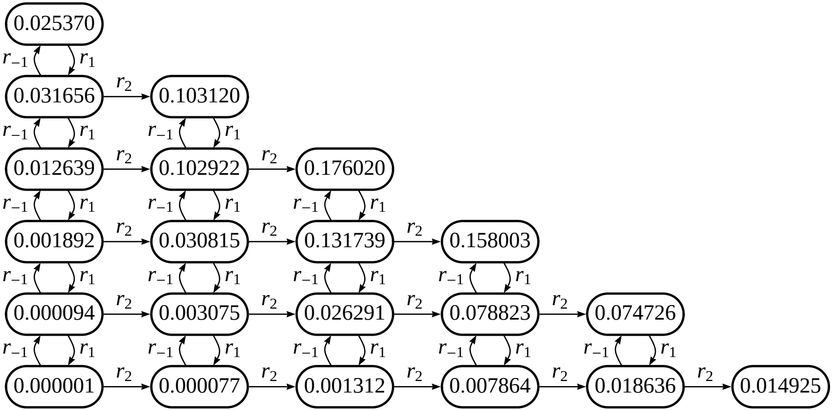
Transient probability distribution at $t = 40$



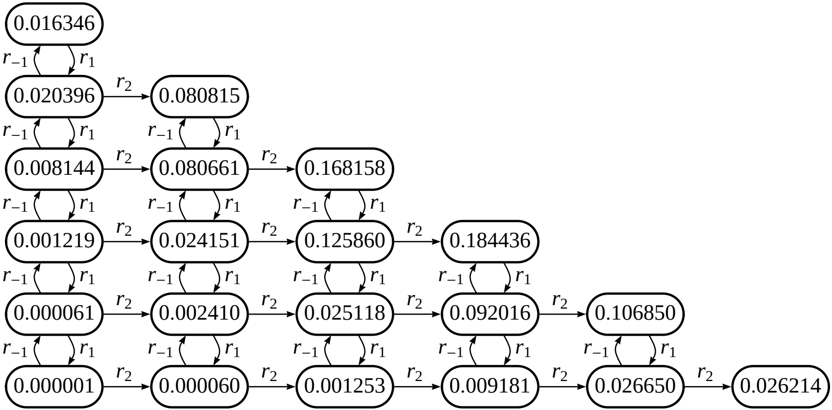
Transient probability distribution at $t = 50$



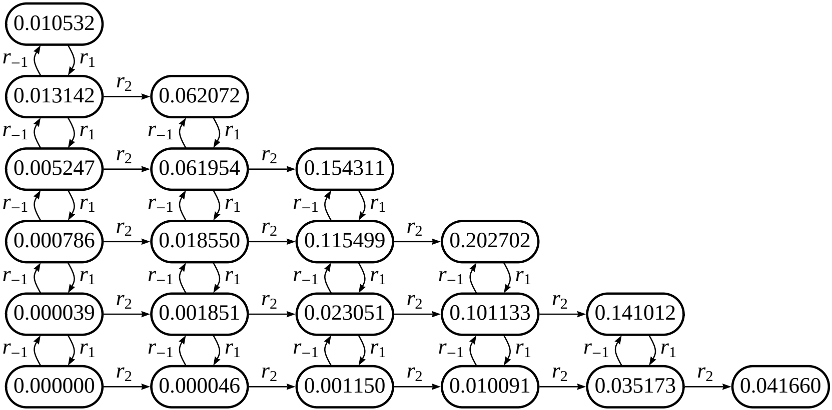
Transient probability distribution at $t = 60$



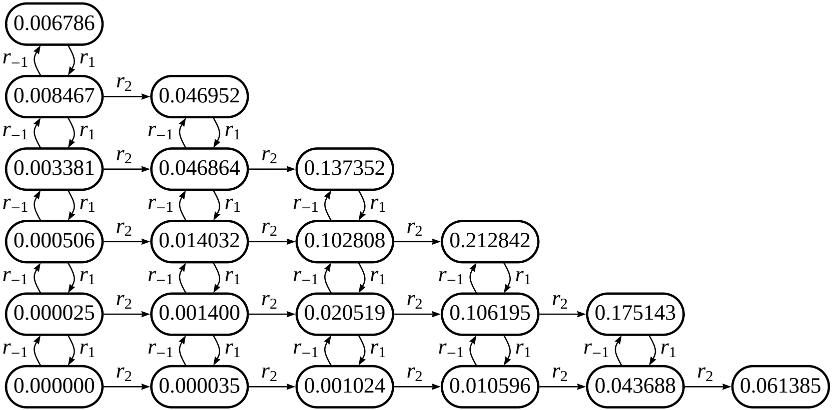
Transient probability distribution at $t = 70$



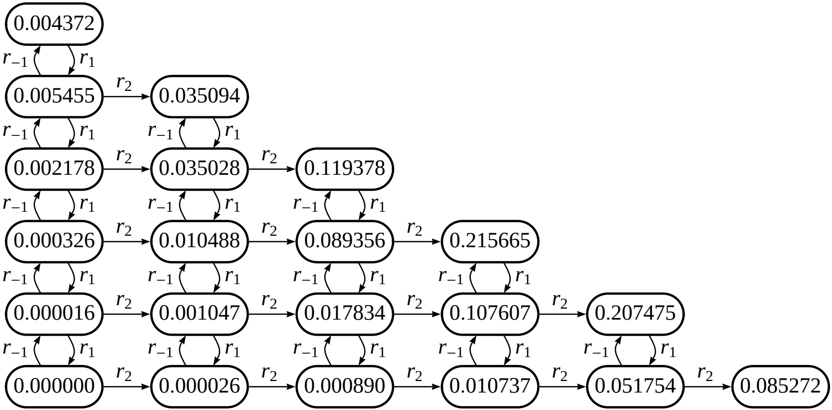
Transient probability distribution at $t = 80$



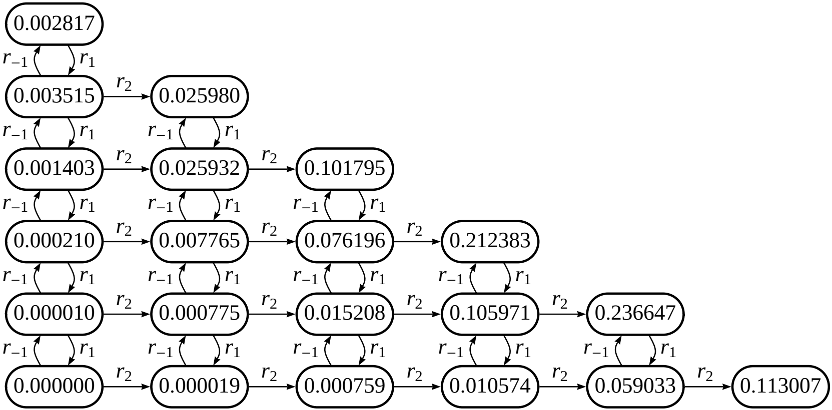
Transient probability distribution at $t = 90$



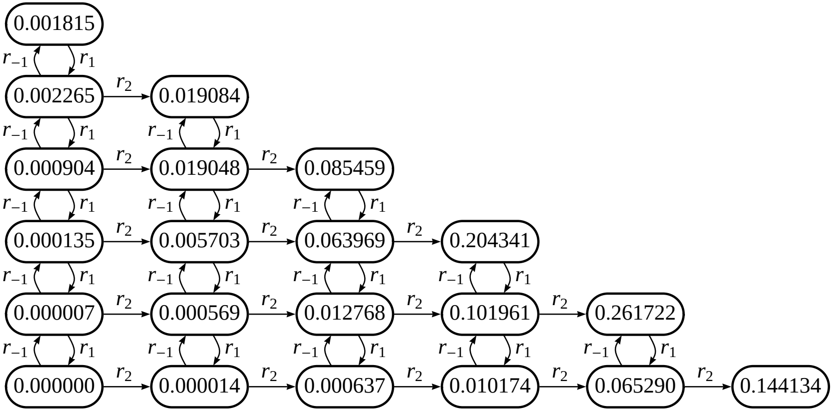
Transient probability distribution at $t = 100$



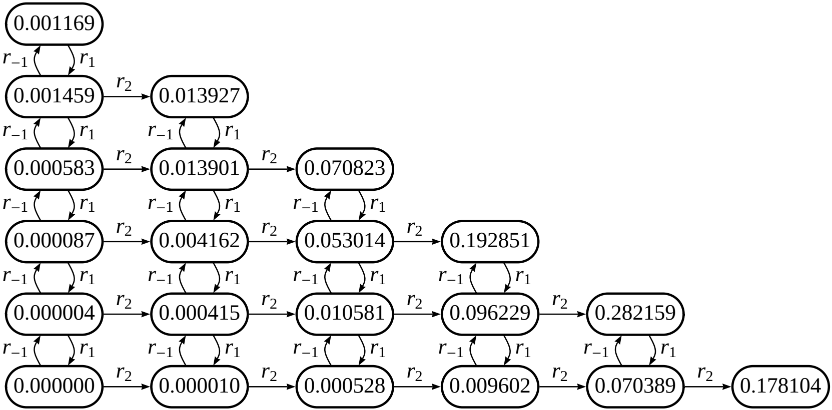
Transient probability distribution at $t = 110$



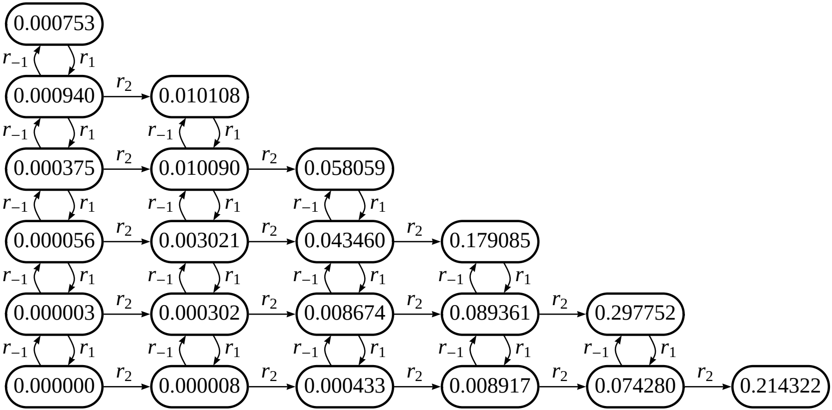
Transient probability distribution at $t = 120$



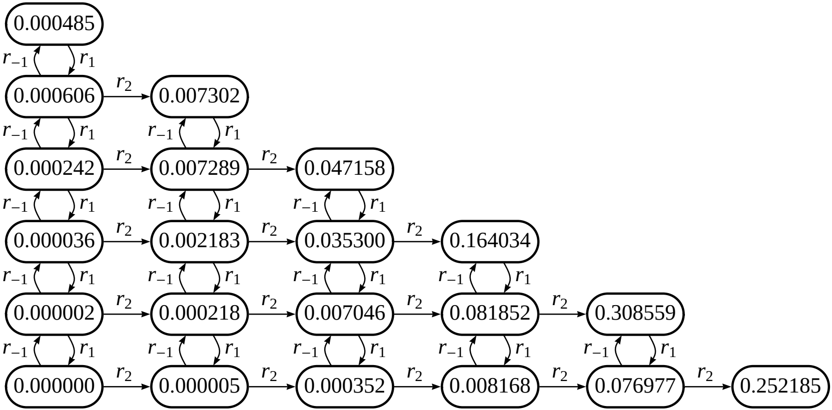
Transient probability distribution at $t = 130$



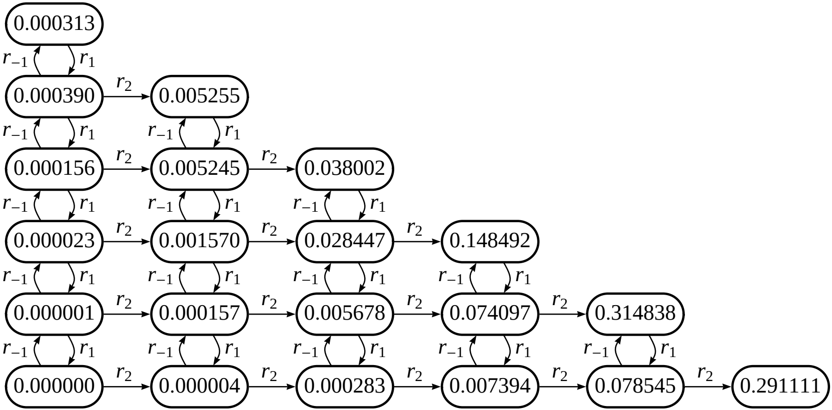
Transient probability distribution at $t = 140$



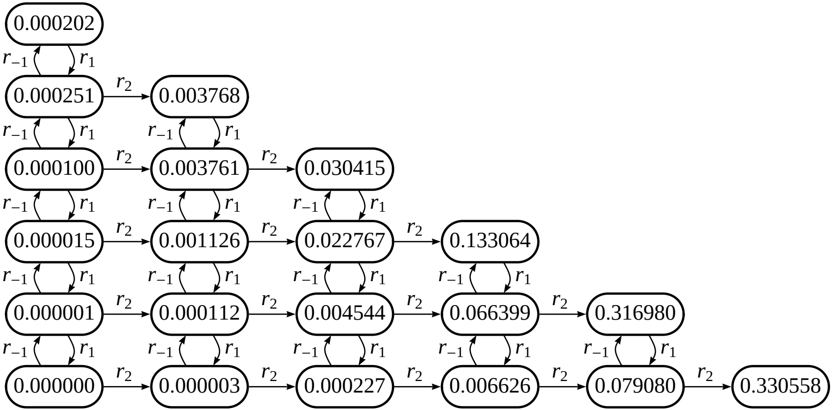
Transient probability distribution at $t = 150$



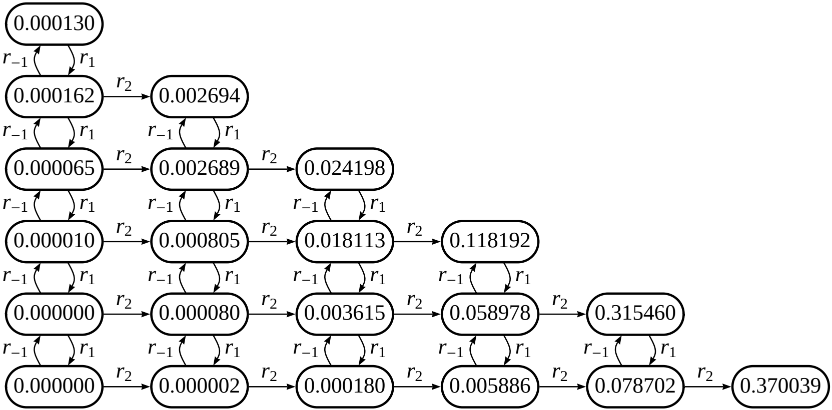
Transient probability distribution at $t = 160$



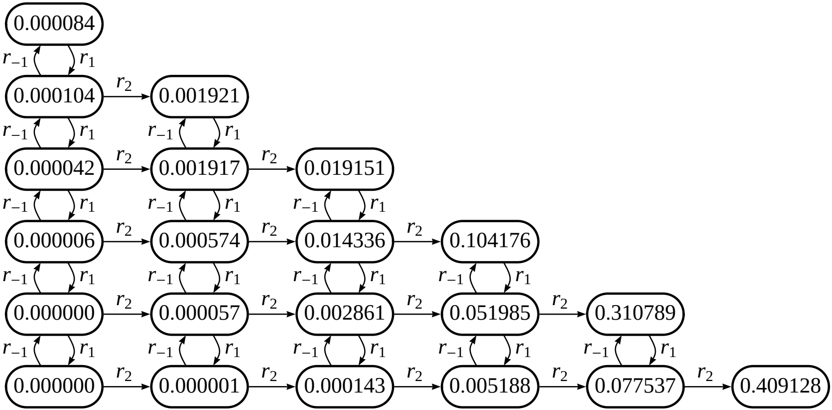
Transient probability distribution at $t = 170$



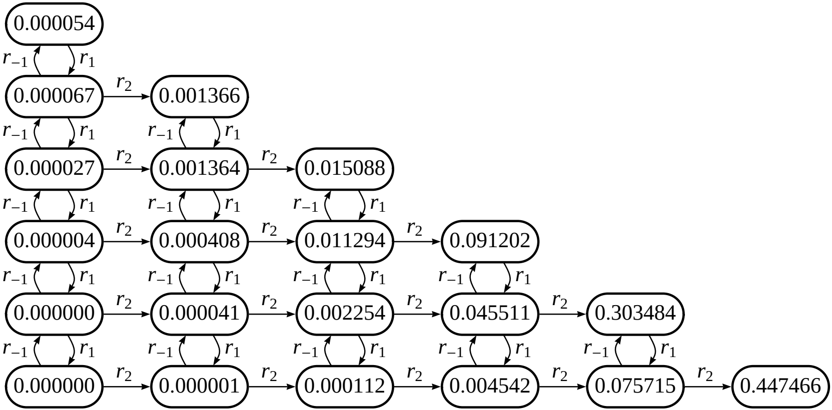
Transient probability distribution at $t = 180$



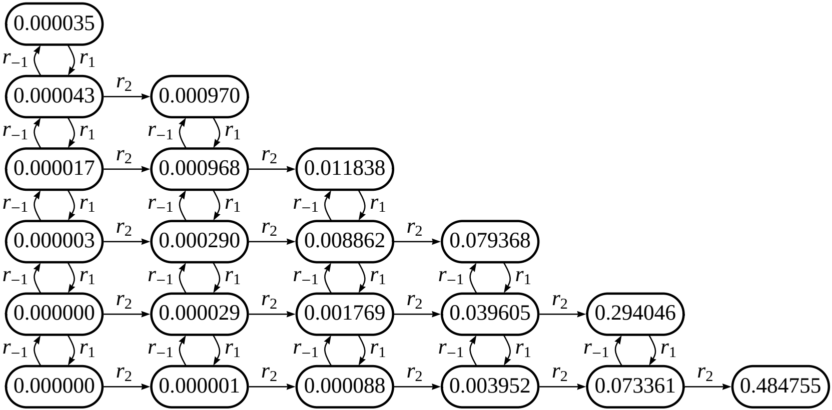
Transient probability distribution at $t = 190$



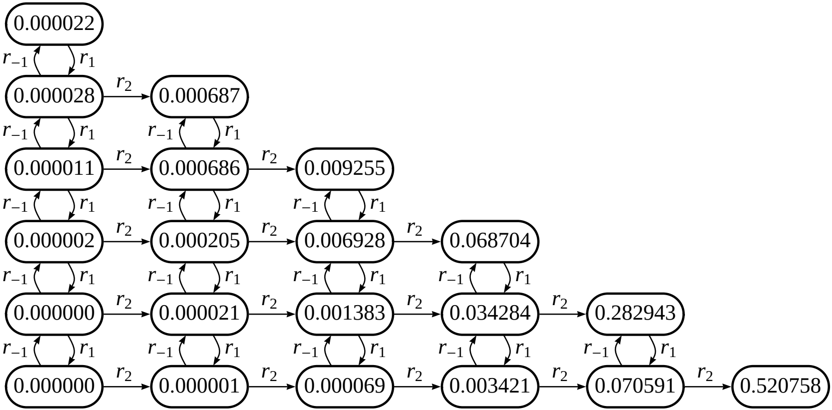
Transient probability distribution at $t = 200$



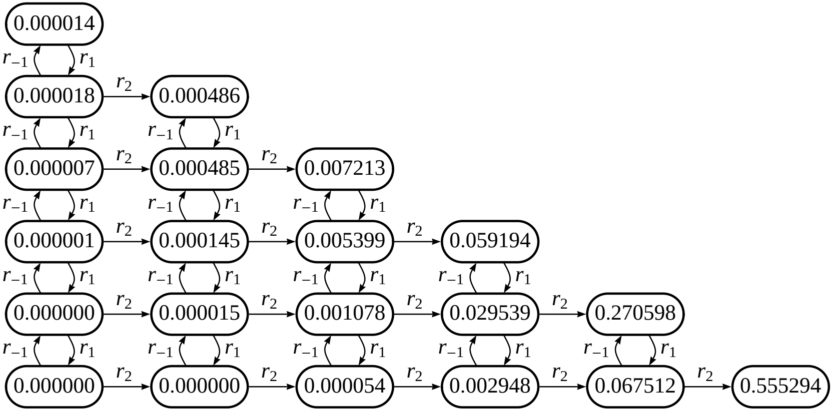
Transient probability distribution at $t = 210$



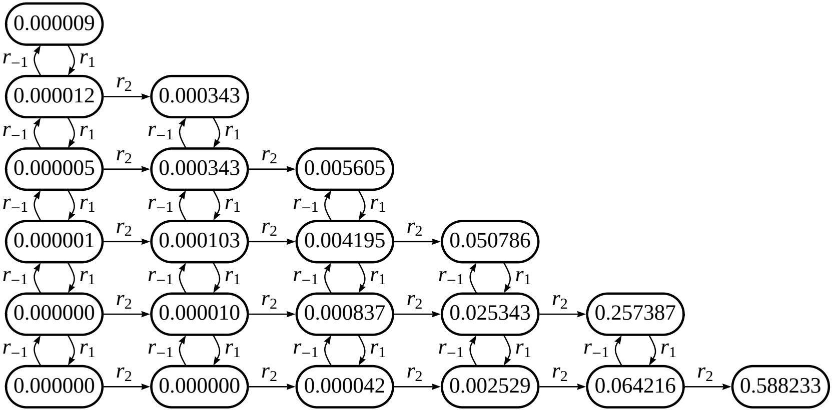
Transient probability distribution at $t = 220$



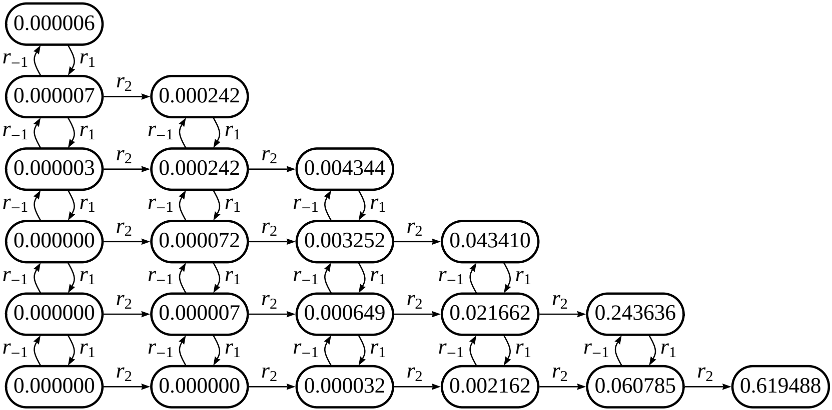
Transient probability distribution at $t = 230$



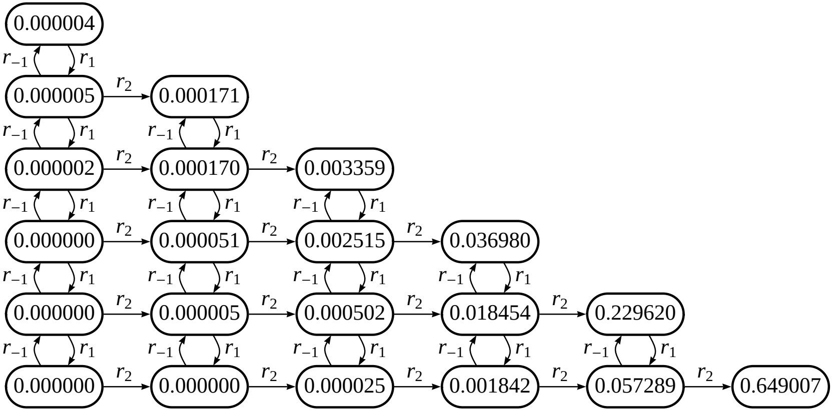
Transient probability distribution at $t = 240$



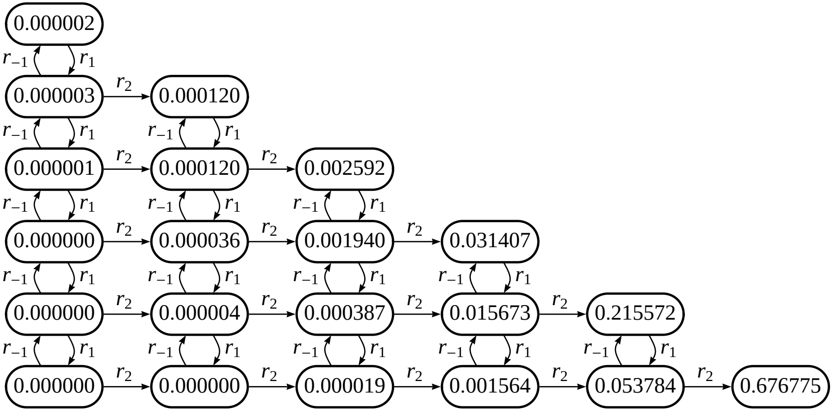
Transient probability distribution at $t = 250$



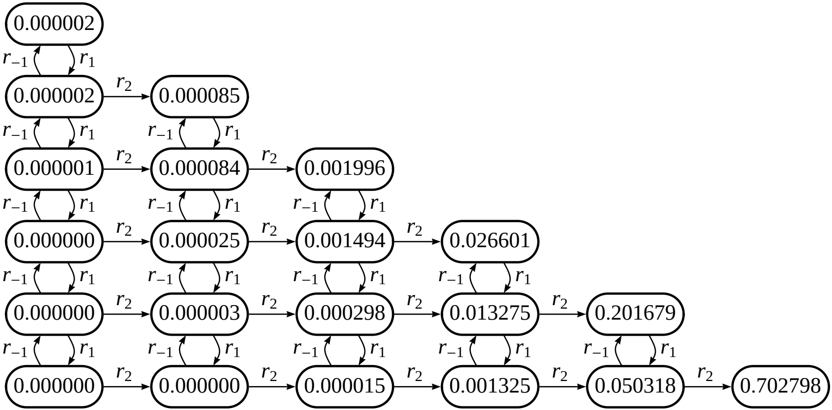
Transient probability distribution at $t = 260$



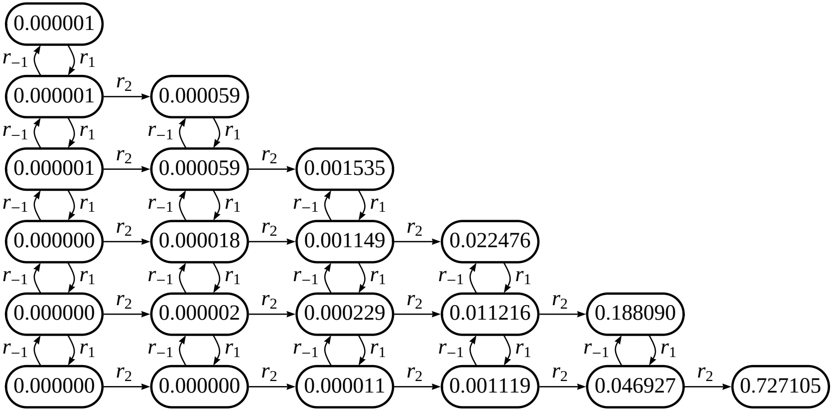
Transient probability distribution at $t = 270$



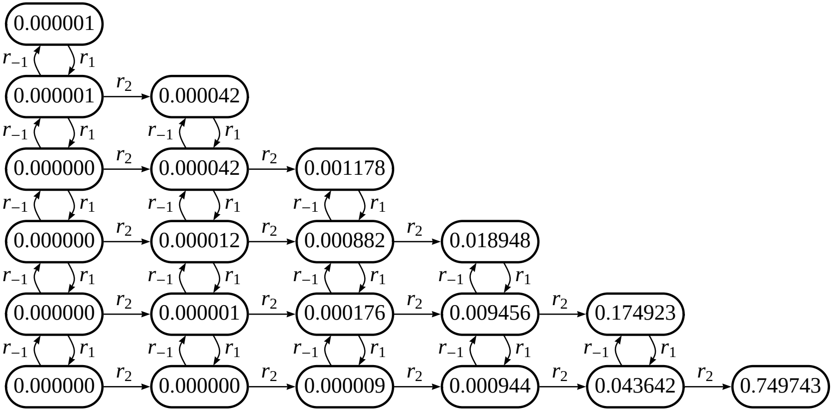
Transient probability distribution at $t = 280$



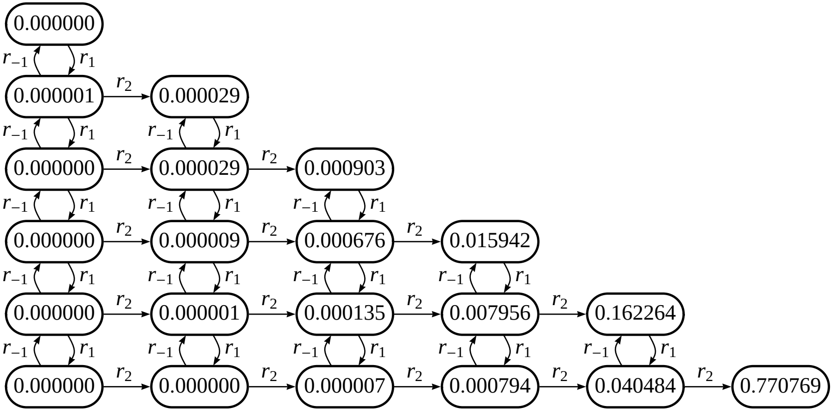
Transient probability distribution at $t = 290$



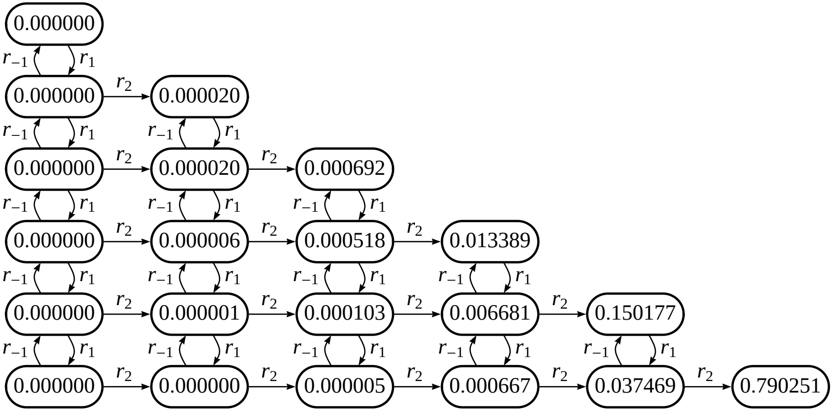
Transient probability distribution at $t = 300$



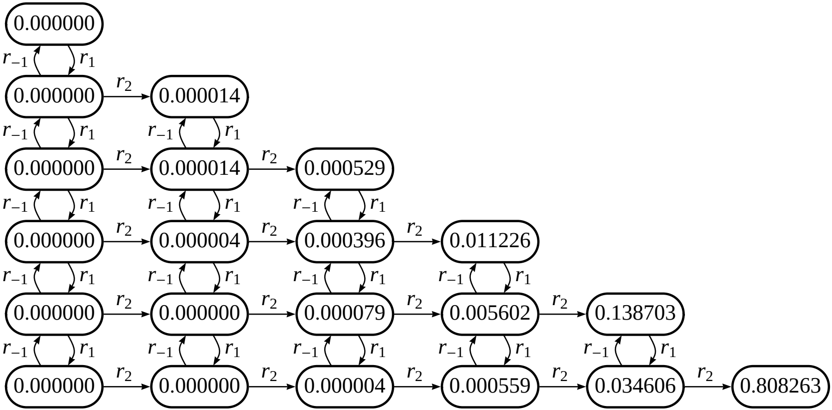
Transient probability distribution at $t = 310$



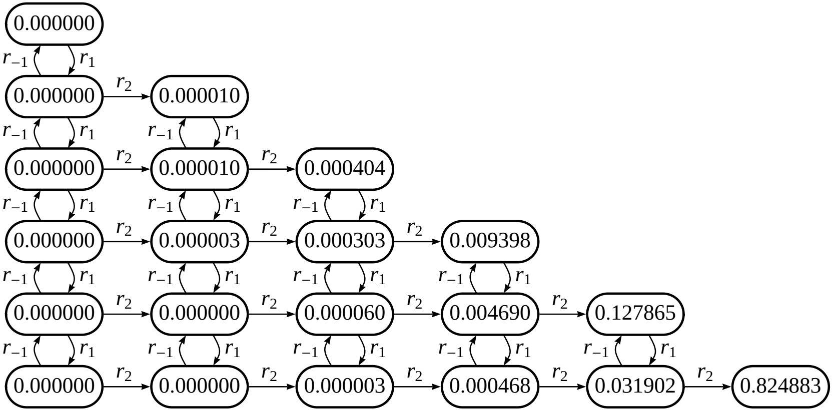
Transient probability distribution at $t = 320$



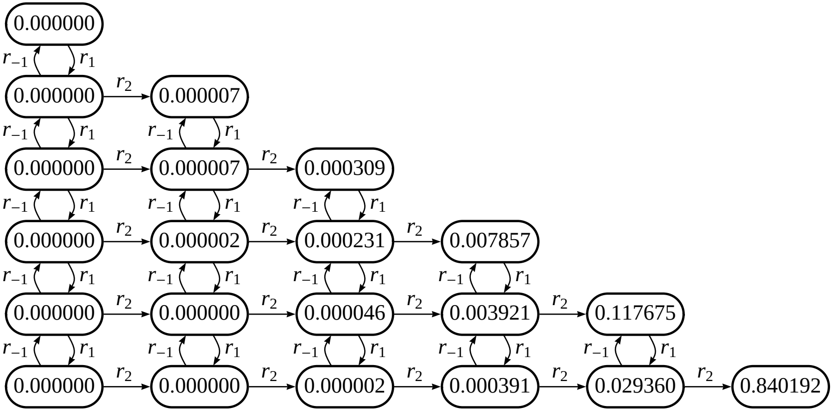
Transient probability distribution at $t = 330$



Transient probability distribution at $t = 340$



Transient probability distribution at $t = 350$



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The kinetic functions and the Bio-PEPA model

The kinetic functions

r_1	$k_1 \times E \times S$
r_{-1}	$k_{-1} \times E{:}S$
r_2	$k_2 \times E{:}S$

The Bio-PEPA model

E	$r_1 \downarrow$	$+$	$r_{-1} \uparrow$	$+$	$r_2 \uparrow$
S	$r_1 \downarrow$	$+$	$r_{-1} \uparrow$		
$E{:}S$	$r_1 \uparrow$	$+$	$r_{-1} \downarrow$	$+$	$r_2 \downarrow$
P					$r_2 \uparrow$

The Bio-PEPA model and the differential equations

The Bio-PEPA model

E	$r_1 \downarrow$	$+$	$r_{-1} \uparrow$	$+$	$r_2 \uparrow$
S	$r_1 \downarrow$	$+$	$r_{-1} \uparrow$		
$E{:}S$	$r_1 \uparrow$	$+$	$r_{-1} \downarrow$	$+$	$r_2 \downarrow$
P					$r_2 \uparrow$

The differential equations

dE/dt	$-r_1$	$+$	r_{-1}	$+$	r_2
dS/dt	$-r_1$	$+$	r_{-1}		
$dE{:}S/dt$	r_1	$-$	r_{-1}	$-$	r_2
dP/dt					r_2

The differential equations and the Jacobian

The differential equations

dE/dt	$-k_1 \times E \times S + k_{-1} \times E{:}S + k_2 \times E{:}S$
dS/dt	$-k_1 \times E \times S + k_{-1} \times E{:}S$
$dE{:}S/dt$	$k_1 \times E \times S - k_{-1} \times E{:}S - k_2 \times E{:}S$
dP/dt	$k_2 \times E{:}S$

The Jacobian

	E	S	$E{:}S$	P
E	$\partial f_E/\partial E$	$\partial f_E/\partial S$	$\partial f_E/\partial E{:}S$	$\partial f_E/\partial P$
S	$\partial f_S/\partial E$	$\partial f_S/\partial S$	$\partial f_S/\partial E{:}S$	$\partial f_S/\partial P$
$E{:}S$	$\partial f_{E:S}/\partial E$	$\partial f_{E:S}/\partial S$	$\partial f_{E:S}/\partial E{:}S$	$\partial f_{E:S}/\partial P$
P	$\partial f_P/\partial E$	$\partial f_P/\partial S$	$\partial f_P/\partial E{:}S$	$\partial f_P/\partial P$

The differential equations and the Jacobian

The differential equations

dE/dt	$-k_1 \times E \times S + k_{-1} \times E{:}S + k_2 \times E{:}S$
dS/dt	$-k_1 \times E \times S + k_{-1} \times E{:}S$
$dE{:}S/dt$	$k_1 \times E \times S - k_{-1} \times E{:}S - k_2 \times E{:}S$
dP/dt	$k_2 \times E{:}S$

The Jacobian

	E	S	$E{:}S$	P
E	$-k_1 \times S$	$-k_1 \times E$	$k_{-1} + k_2$	
S	$-k_1 \times S$	$-k_1 \times E$	k_{-1}	
$E{:}S$	$k_1 \times S$	$k_1 \times E$	$-k_{-1} - k_2$	
P			k_2	

Obtaining and using the Jacobian

- The Jacobian (and Hessian and higher derivatives) are computed automatically from the differential equations using *symbolic differentiation*.

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- The Jacobian (and Hessian and higher derivatives) are computed automatically from the differential equations using *symbolic differentiation*.
- ODE solvers generally use *finite differences* to approximate the Jacobian matrix if it is not supplied, but an implementation of the analytically derived Jacobian can improve the speed, accuracy and reliability of the program.
- Programs that compute *bifurcations* will use the Hessian and higher derivatives.

Differential equation analysis

Several different differential equation solvers exist.

- SUNDIALS — ODE integrators in C

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Different formats and languages for problem description.

VFGEN: A Vector Field File Generator

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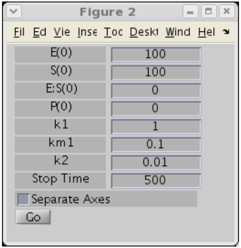
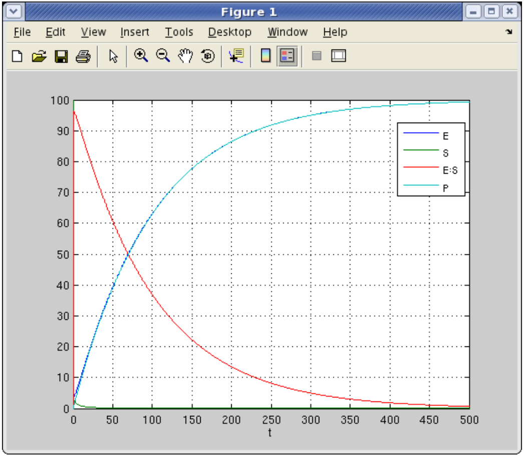
Warren Weckesser.
VFGEN: A Code Generation Tool.
Journal of Numerical Analysis, Industrial and Applied Mathematics, Volume 3(1-2):151–165, 2008.

VFgen representation of the Enzyme-Substrate model

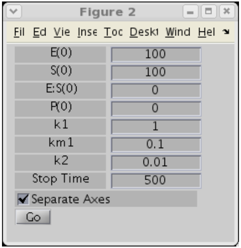
```
<?xml version="1.0"?>
<!-- VFgen model compiled from Bio-PEPA input file "mm" by
 Bio-PEPA Workbench Version 0.9.8 "Hillel Slovak" [20-June-2008] -->
<VectorField Name="mm001">

<Parameter Name="k1_" Description="k1" Latex="k_1" DefaultValue="1"/>
<Parameter Name="km1_" Description="km1" Latex="k_{-1}" DefaultValue="0.1"/>
<Parameter Name="k2_" Description="k2" Latex="k_2" DefaultValue="0.01"/>

<Expression Name="r1_" Description="r1" Latex="r_1" Formula=" k1_ * E_ * S_ "/>
<Expression Name="rm1_" Description="rm1" Latex="r_{-1}" Formula=" km1_ * E_colon_S_ "/>
<Expression Name="r2_" Description="r2" Latex="r_2" Formula=" k2_ * E_colon_S_ "/>

<StateVariable Name="E_" Description="E" Latex="E" DefaultInitialCondition="100"
   Formula=" - r1_ + rm1_ + r2_"/>

<StateVariable Name="S_" Description="S" Latex="S" DefaultInitialCondition="100"
   Formula=" - r1_ + rm1_"/>

<StateVariable Name="E_colon_S_" Description="E:S" Latex="\hbox{\textit{E:S}}" DefaultInitialCondition="0"
   Formula="r1_ - rm1_ - r2_"/>

<StateVariable Name="P_" Description="P" Latex="P" DefaultInitialCondition="0"
   Formula="r2_"/>

<!-- End VFgen model compiled from mm -->
</VectorField>
```

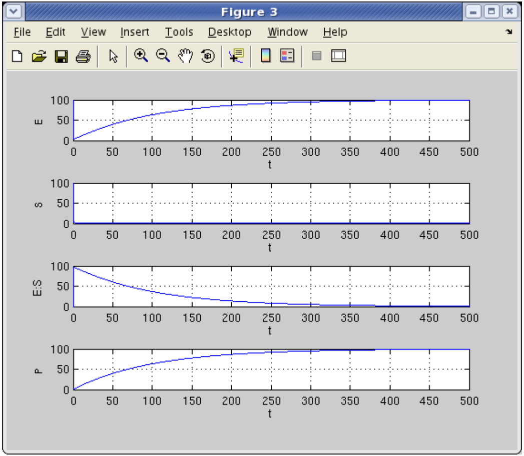
Analysing Bio-PEPA models with Matlab





Analysing Bio-PEPA models with Matlab





Conclusions

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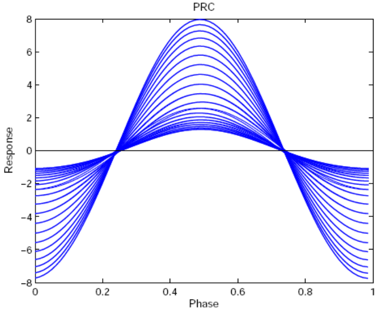
  - Useful for studying systems which oscillate.
- Can compute *phase response curves* ▸ Defn

Phase response curve

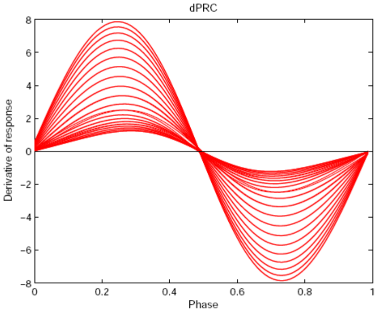


A. Dhooge, W. Govaerts, Yu.A. Kuznetsov, W. Mestrom, A.M. Riet and B. Sautois

MATCONT and CL_MATCONT: Continuation toolboxes in Matlab

December 2006.

Derivative of the phase response curve



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Phase response curve

The phase response curve of a limit cycle, or PRC, is a curve, defined over the period of the cycle, that expresses, at each time of that period, the effect of a small input vector on the cycle. In experimental circumstances, this may correspond to injected current, to the addition of more chemical agents, etc. A positive value means that the current cycle is shortened in time, a negative value means that the period is prolonged.

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