Quantitative Methods in Systems Biology
Part I: Background

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Outline

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1. Background
2. The deterministic and stochastic approaches
3. Michaelis-Menten kinetics
   - Discrete state-space
   - Transient probability distribution
   - Probability distribution functions
   - Time series plots

Background

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- This deterministic approach has at its core the law of mass action, an empirical law giving a simple relation between reaction rates and molecular component concentrations.
- Given knowledge of initial molecular concentrations, the law of mass action provides a complete picture of the component concentrations at all future time points.

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- These are evidently simplifications, as it is well understood that chemical reactions involve discrete, random collisions between individual molecules.
- As we consider smaller and smaller systems, the validity of a continuous approach becomes ever more tenuous.
- As such, the adequacy of the law of mass action has been questioned for describing intracellular reactions.

Background: Application of Stochastic Models

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1. take into consideration the discrete character of the quantity of components and the inherently random character of the phenomena;
2. are in accordance with the theories of thermodynamics and stochastic processes; and
3. are appropriate to describe “small systems” and instability phenomena.

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Deterministic: The law of mass action

The fundamental empirical law governing reaction rates in biochemistry is the law of mass action.

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This states that for a reaction in a homogeneous, free medium, the reaction rate will be proportional to the concentrations of the individual reactants involved.

Deterministic: Michaelis-Menten kinetics

Consider the simple Michaelis-Menten reaction

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

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Hence, we can express any chemical system as a collection of coupled non-linear first order differential equations.

Deterministic: Michaelis-Menten kinetics

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

What is the differential equation for E?

$$\frac{\mathrm{d}E}{\mathrm{d}t} = ?$$

Deterministic: Michaelis-Menten kinetics

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

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$$\frac{\mathrm{d}E}{\mathrm{d}t} = -k_1 \times E \times S + (k_{-1} + k_2) \times ES$$

Deterministic: Michaelis-Menten kinetics

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

What is the differential equation for P?

$$\frac{\mathrm{d}P}{\mathrm{d}t} = ?$$

Deterministic: Michaelis-Menten kinetics

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

What is the differential equation for P?

$$\frac{\mathrm{d}P}{\mathrm{d}t} = k_2 \times ES$$

Stochastic: Random processes

- Whereas the deterministic approach outlined above is essentially an empirical law, derived from *in vitro* experiments, the stochastic approach is far more physically rigorous.
- Fundamental to the principle of stochastic modelling is the idea that molecular reactions are essentially random processes; it is impossible to say with complete certainty the time at which the next reaction within a volume will occur.

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Stochastic: Predictability of macroscopic states

- In macroscopic systems, with a large number of interacting molecules, the randomness of this behaviour averages out so that the overall macroscopic state of the system becomes highly predictable.
- It is this property of large scale random systems that enables a deterministic approach to be adopted; however, the validity of this assumption becomes strained in *in vivo* conditions as we examine small-scale cellular reaction environments with limited reactant populations.

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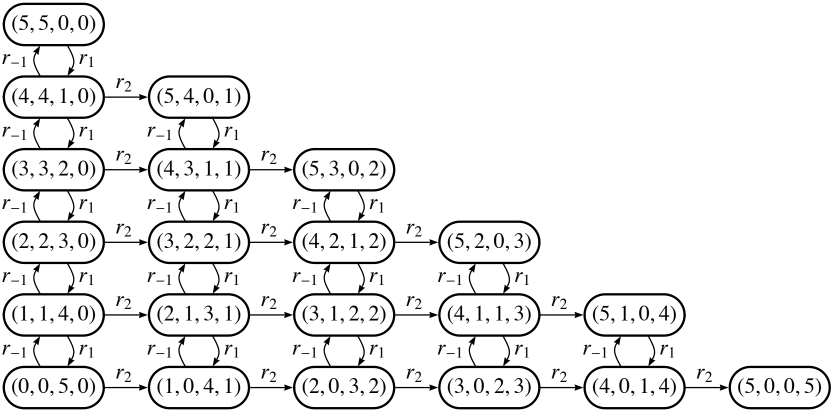
Discrete state-space of Michaelis-Menten example

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

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

Discrete state-space of Michaelis-Menten example

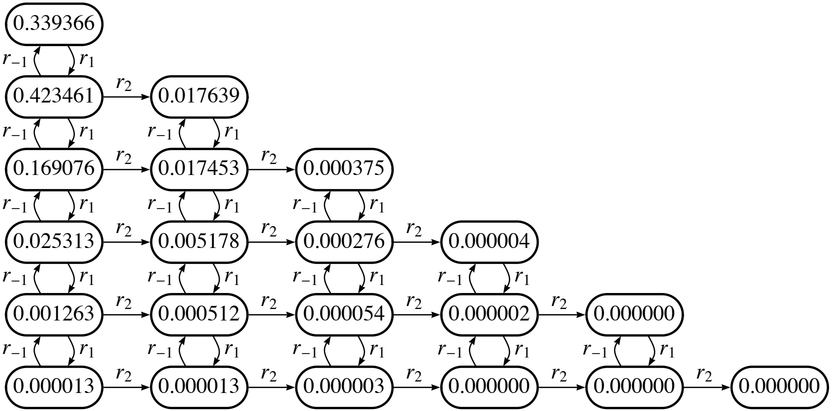


Probability distribution across the state-space

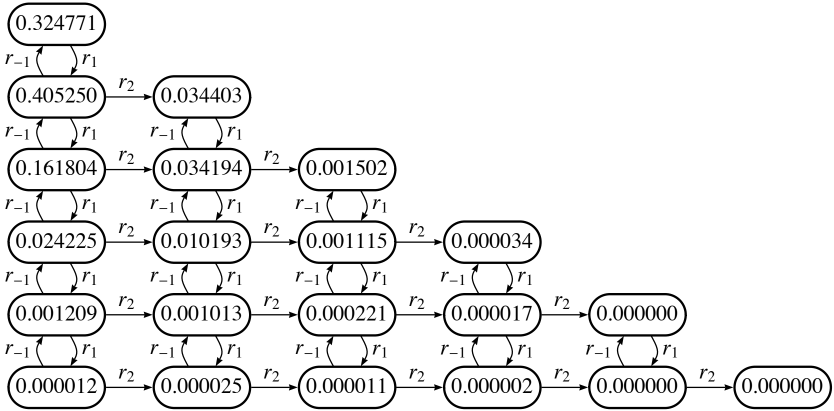
$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\longrightarrow} E + P$$

- 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 $\Pr(5, 5, 0, 0) = 1$.

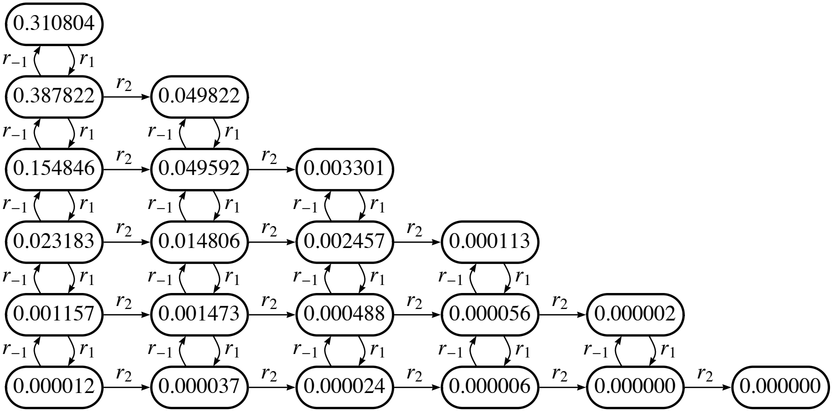
Transient probability distribution at $t = 1$



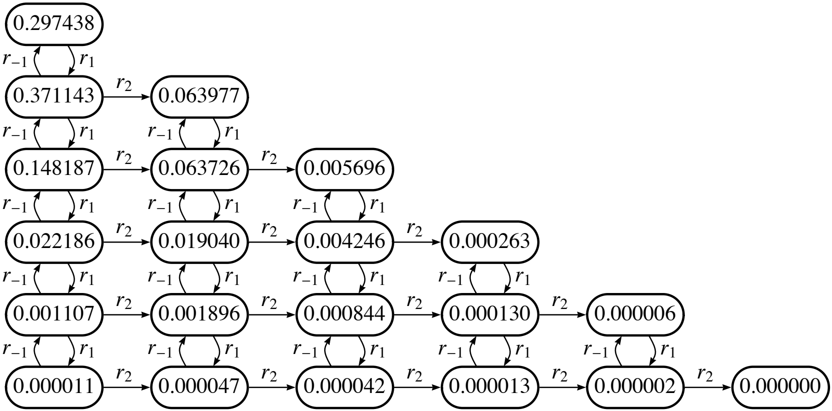
Transient probability distribution at $t = 2$



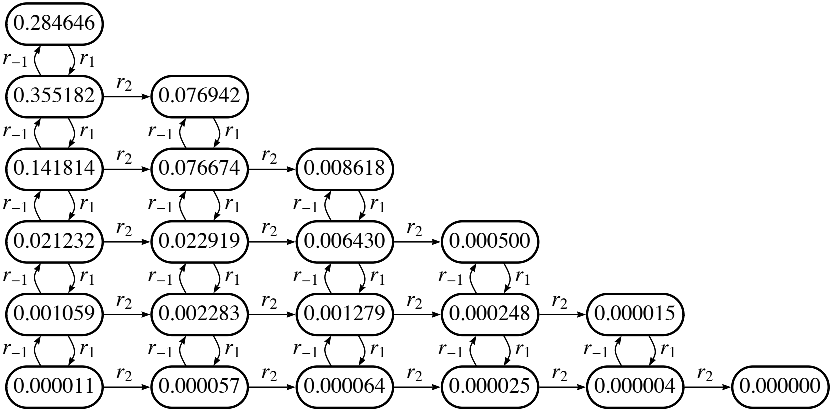
Transient probability distribution at $t = 3$



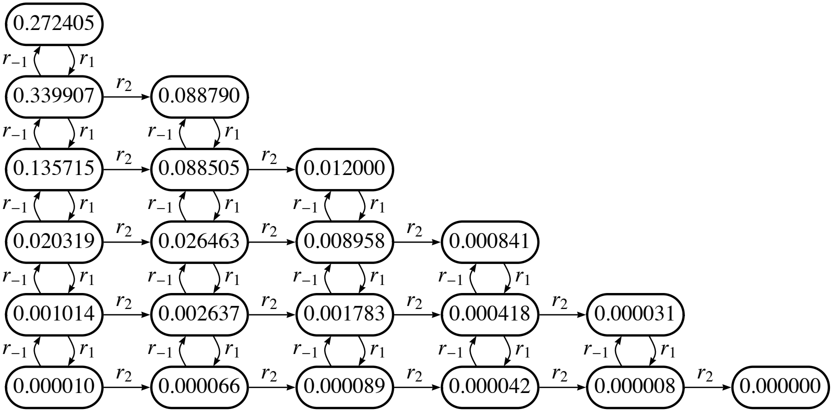
Transient probability distribution at $t = 4$



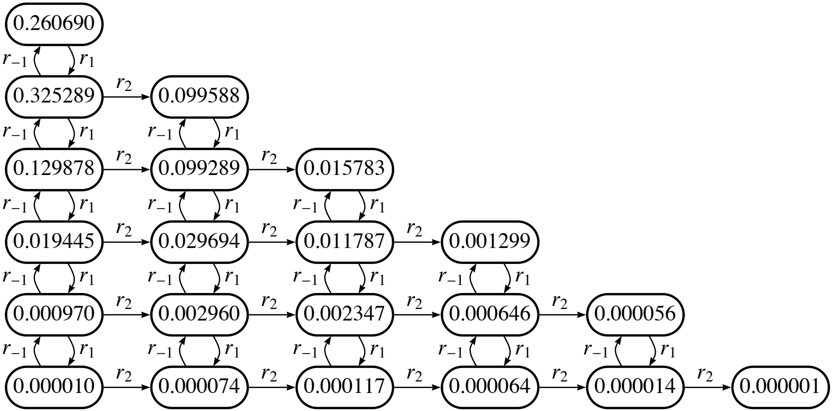
Transient probability distribution at $t = 5$



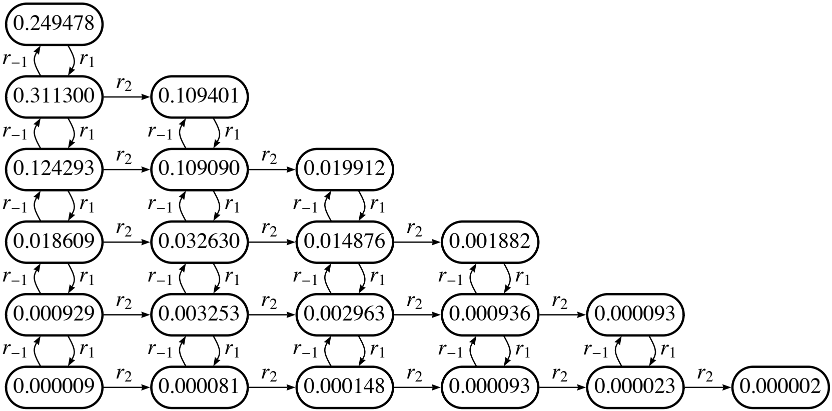
Transient probability distribution at $t = 6$



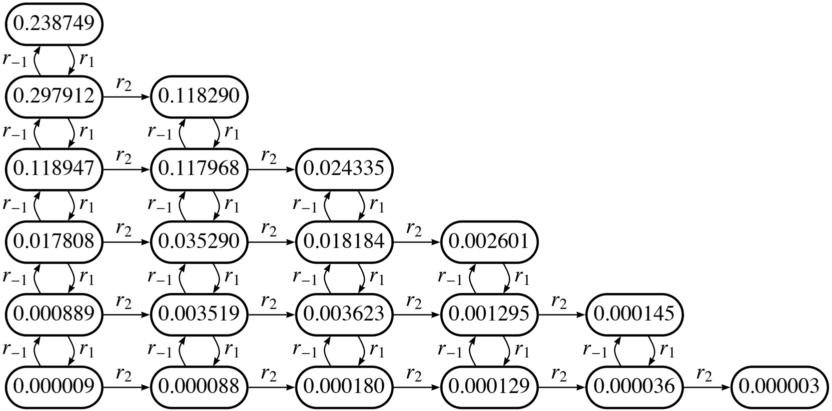
Transient probability distribution at $t = 7$



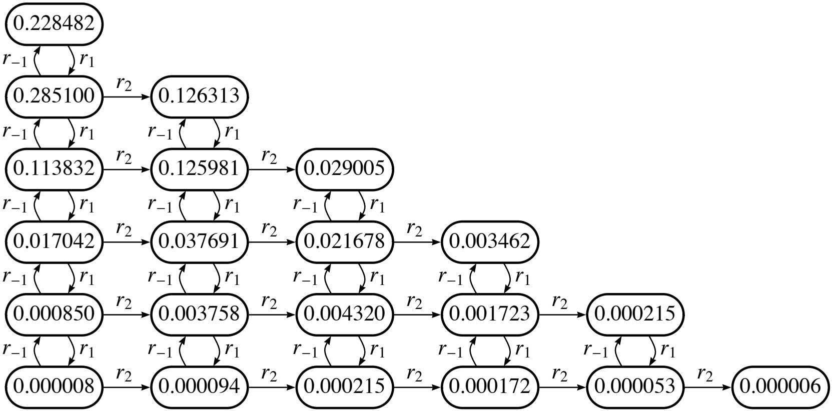
Transient probability distribution at $t = 8$



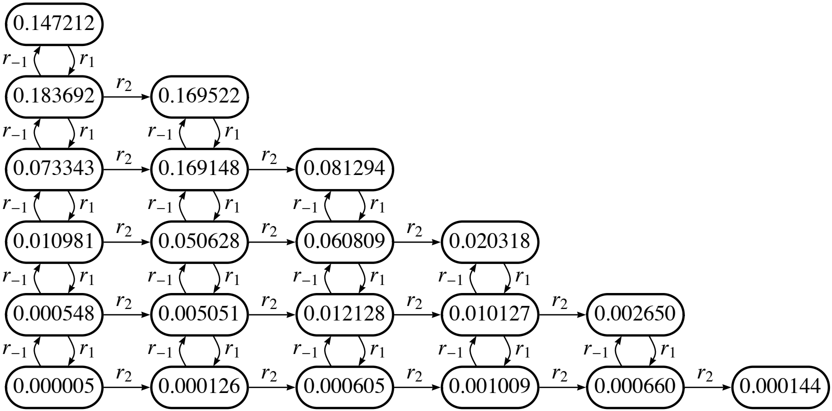
Transient probability distribution at $t = 9$



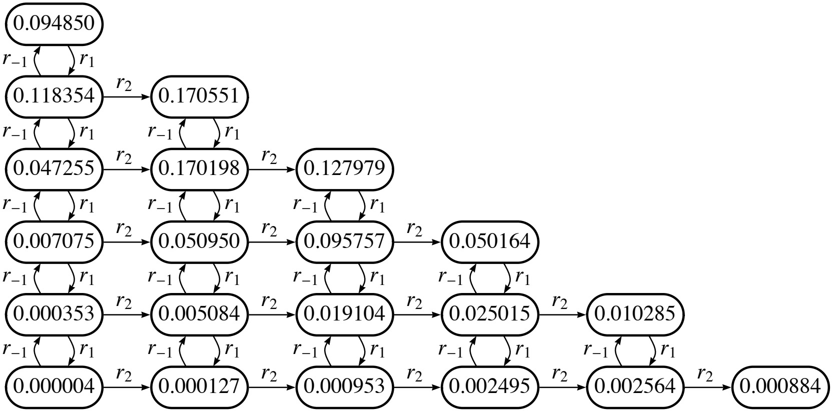
Transient probability distribution at $t = 10$



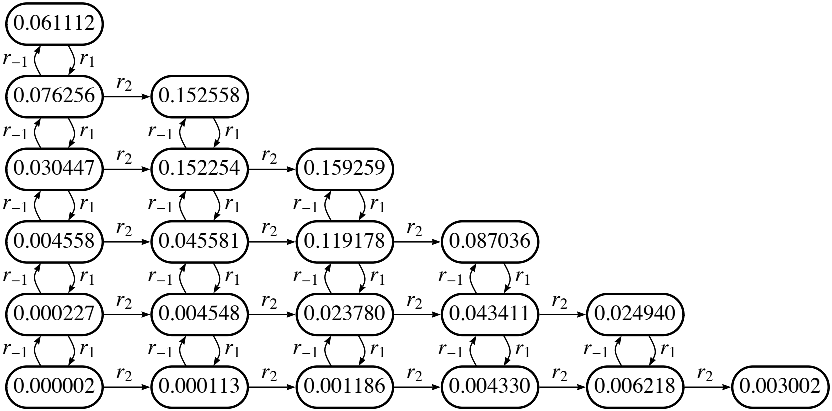
Transient probability distribution at $t = 20$



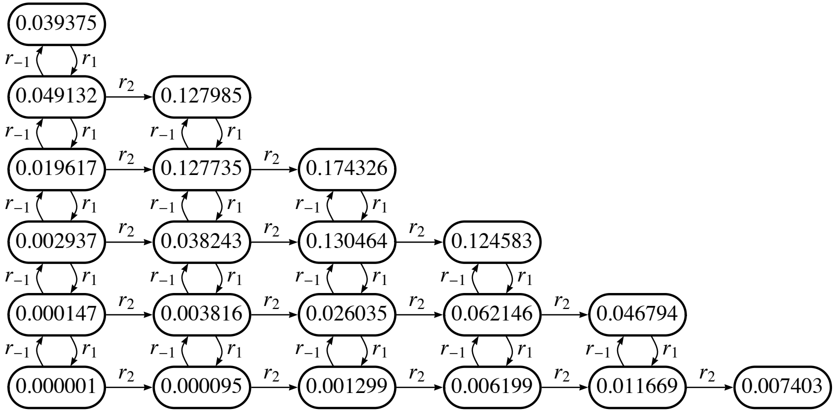
Transient probability distribution at $t = 30$



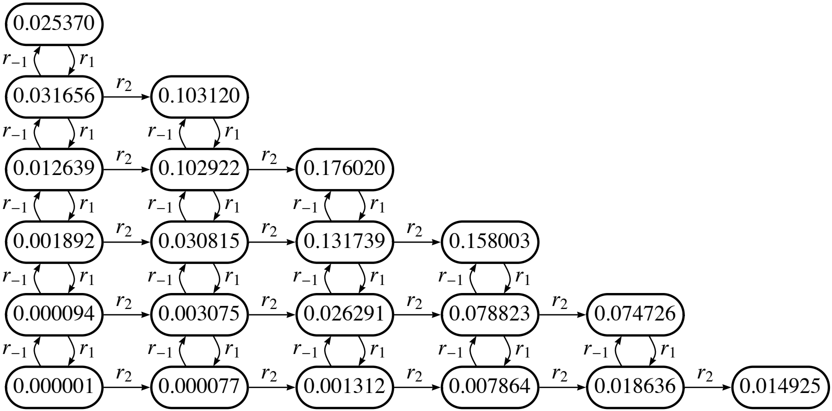
Transient probability distribution at $t = 40$



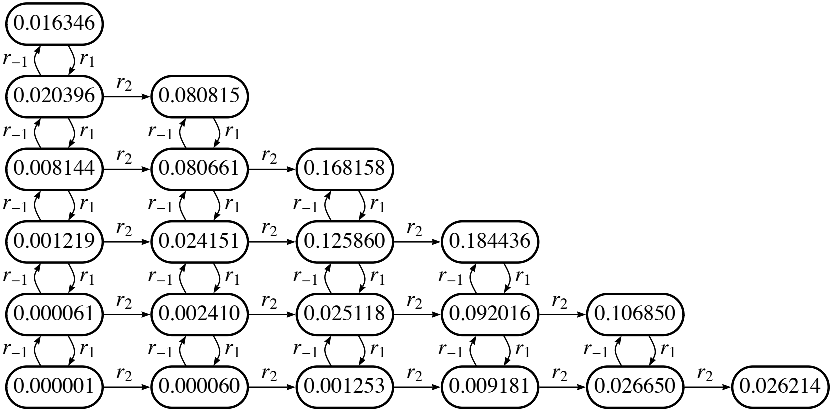
Transient probability distribution at $t = 50$



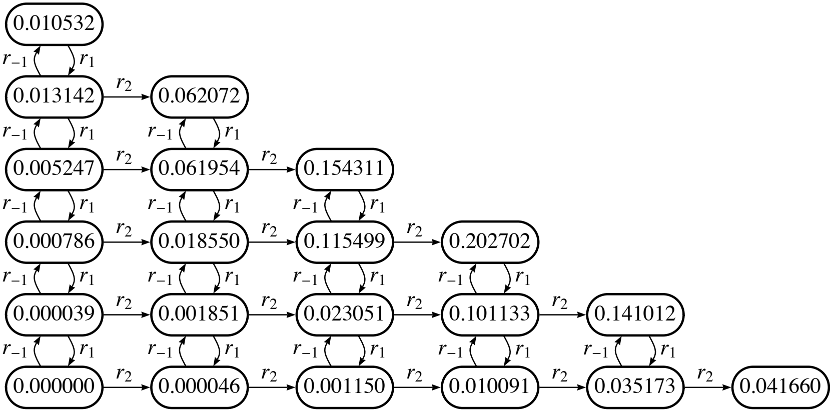
Transient probability distribution at $t = 60$



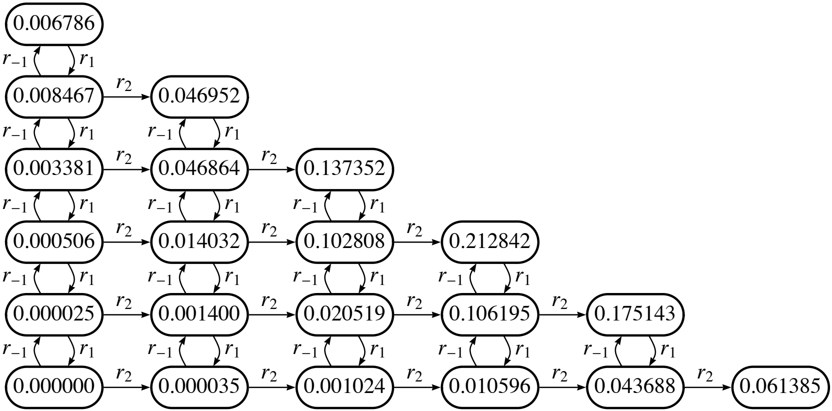
Transient probability distribution at $t = 70$



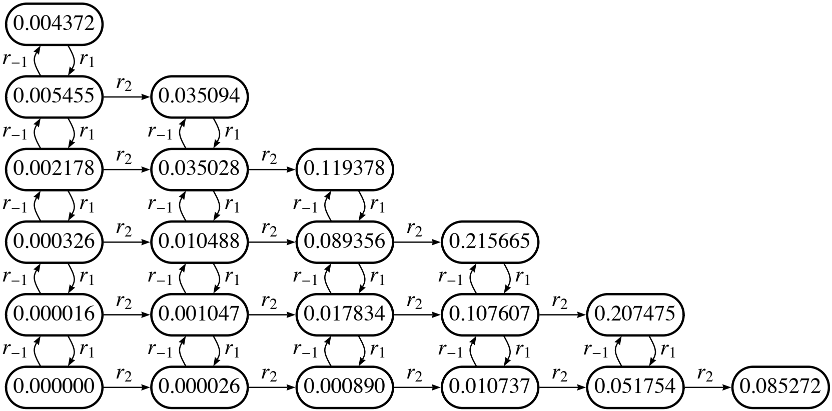
Transient probability distribution at $t = 80$



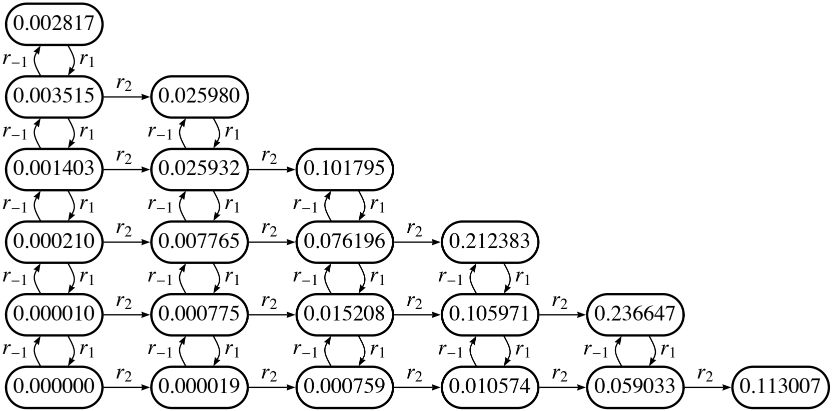
Transient probability distribution at $t = 90$



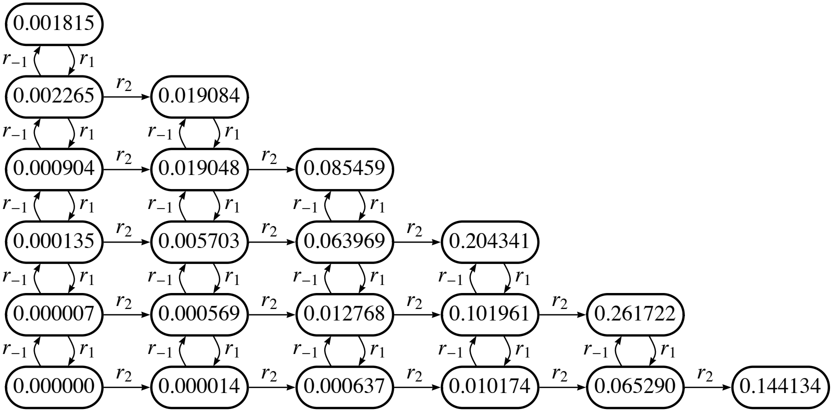
Transient probability distribution at $t = 100$



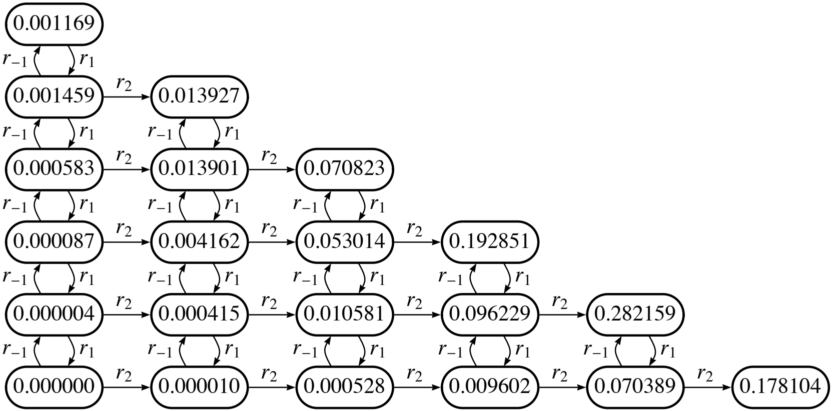
Transient probability distribution at $t = 110$



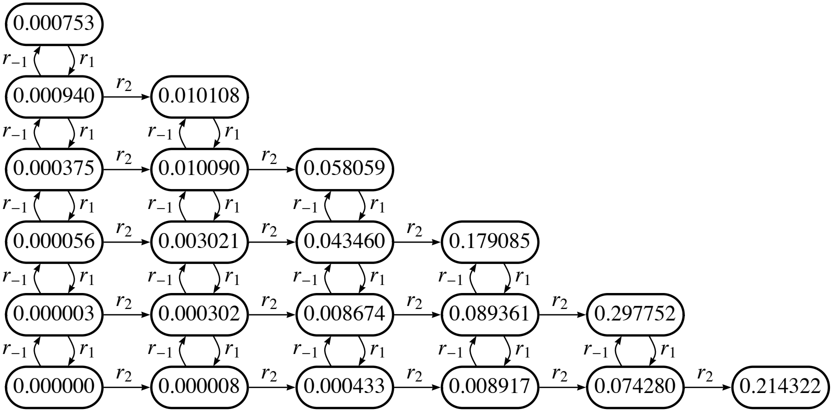
Transient probability distribution at $t = 120$



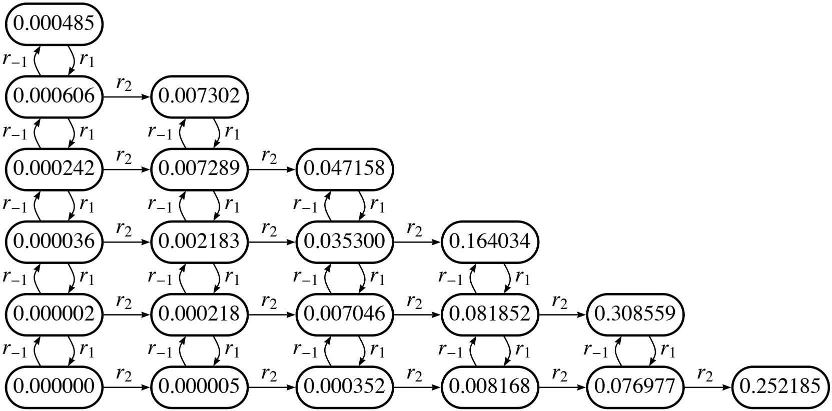
Transient probability distribution at $t = 130$



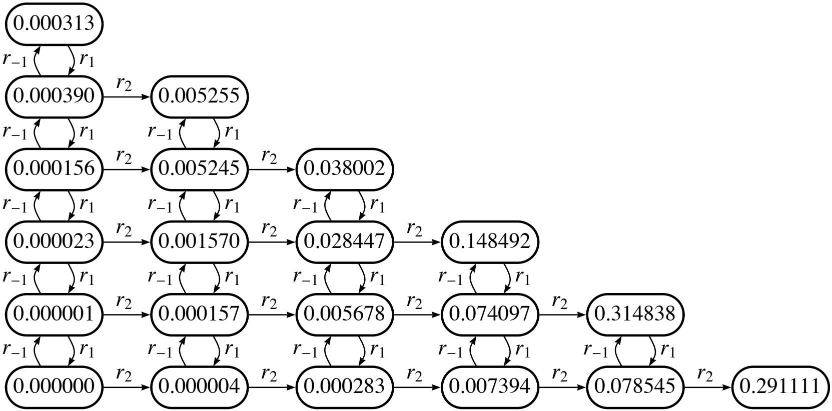
Transient probability distribution at $t = 140$



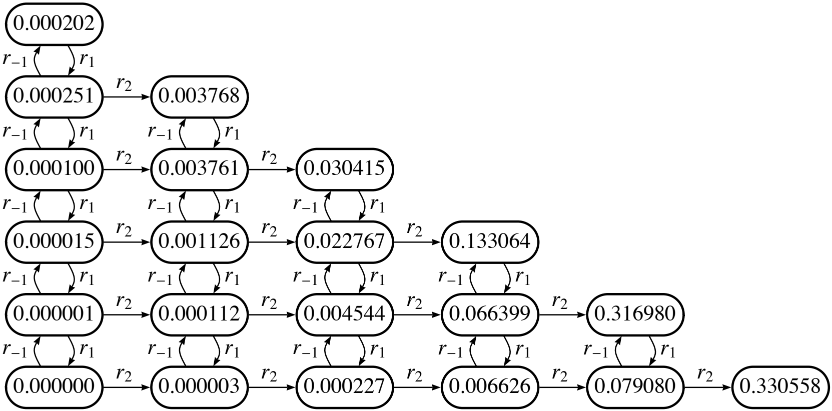
Transient probability distribution at $t = 150$



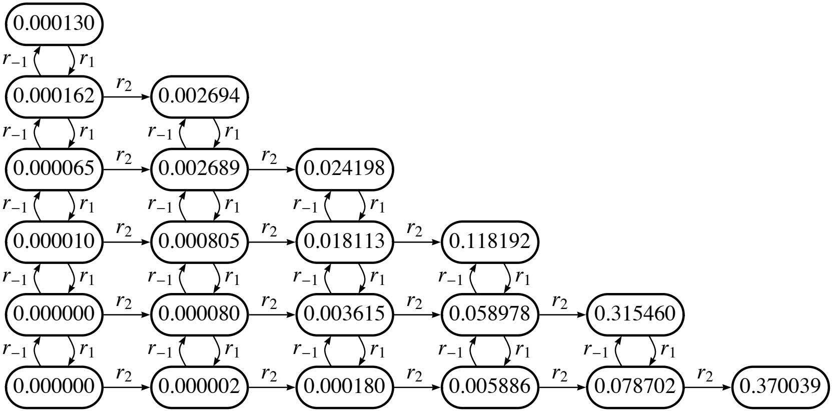
Transient probability distribution at $t = 160$



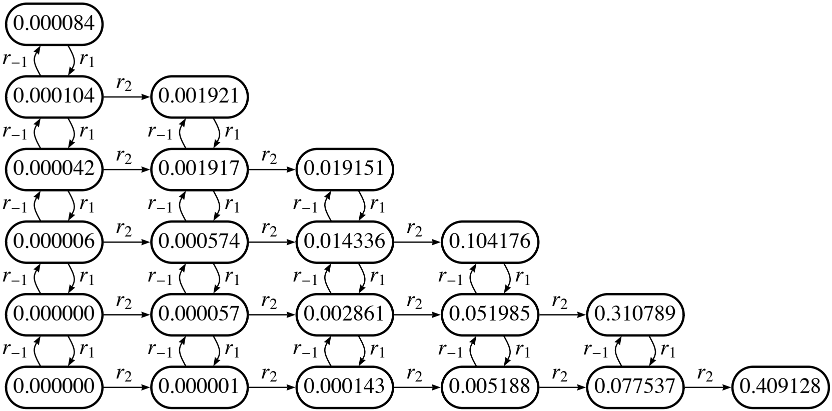
Transient probability distribution at $t = 170$



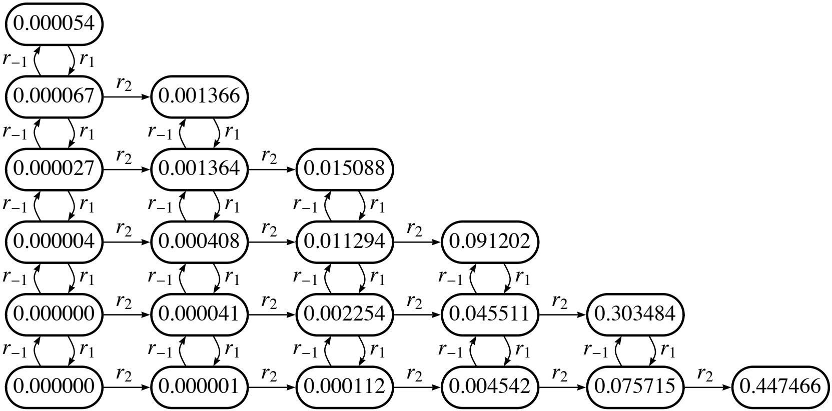
Transient probability distribution at $t = 180$



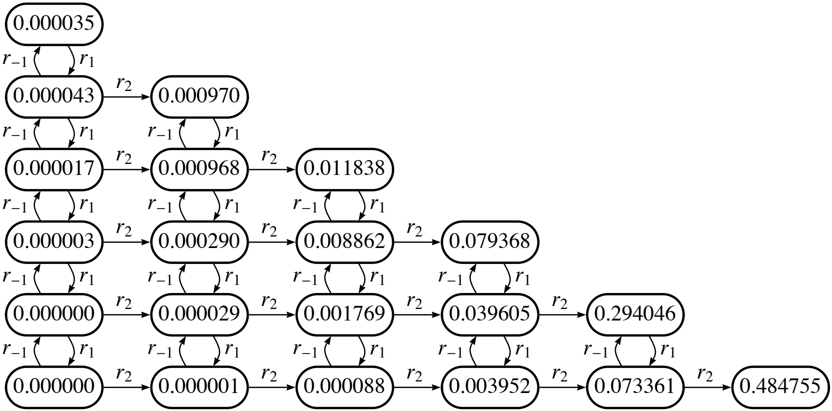
Transient probability distribution at $t = 190$



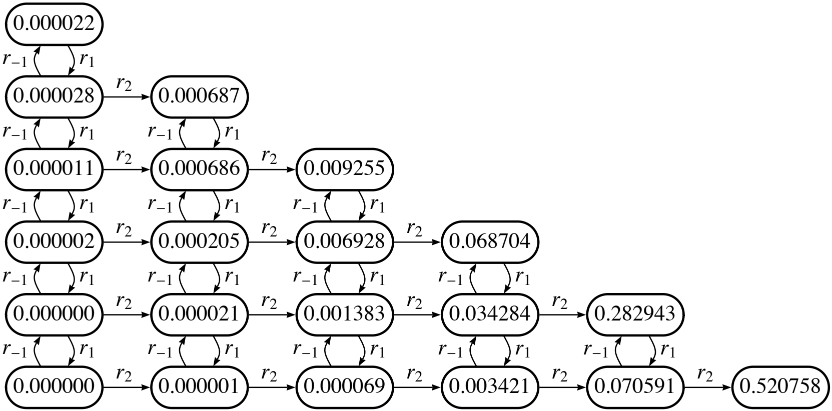
Transient probability distribution at $t = 200$



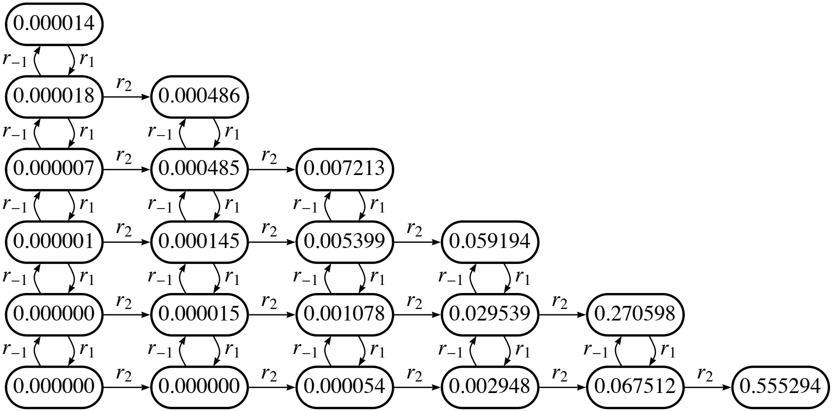
Transient probability distribution at $t = 210$



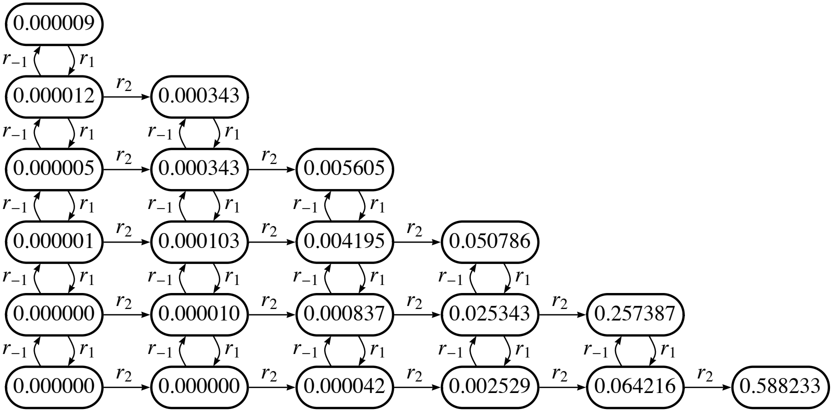
Transient probability distribution at $t = 220$



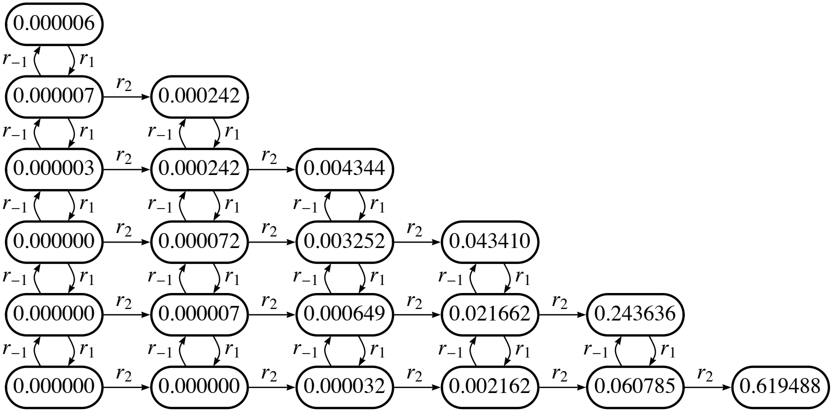
Transient probability distribution at $t = 230$



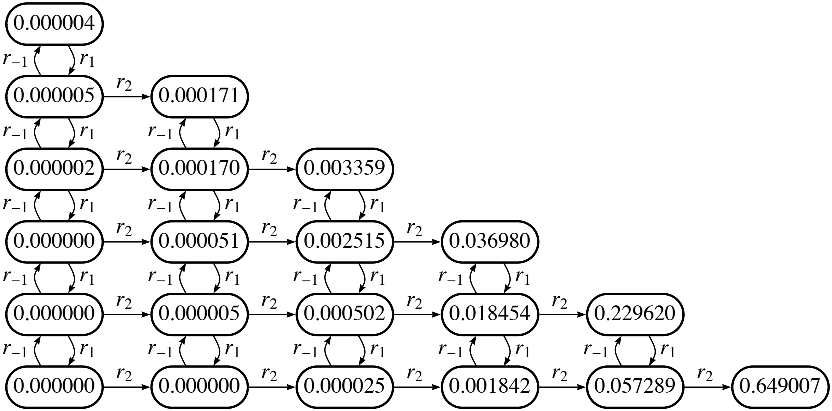
Transient probability distribution at $t = 240$



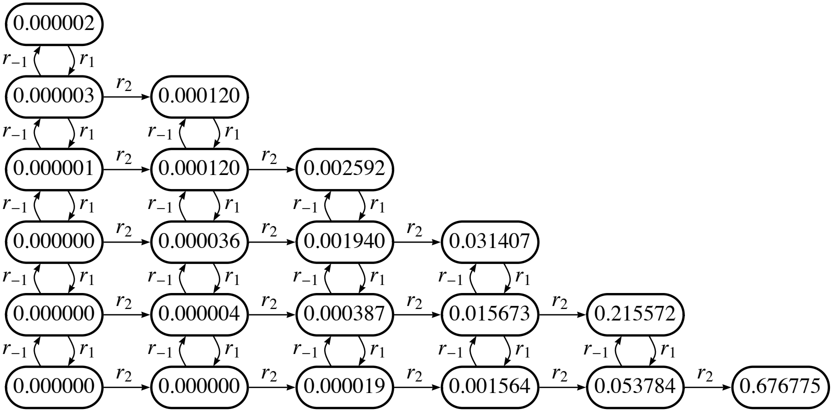
Transient probability distribution at $t = 250$



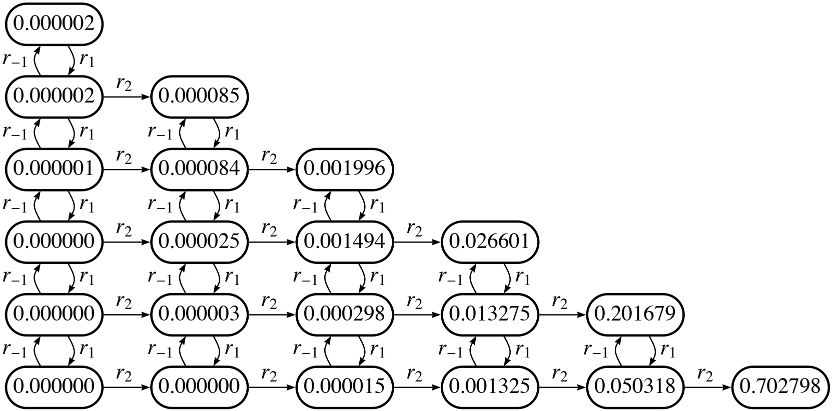
Transient probability distribution at $t = 260$



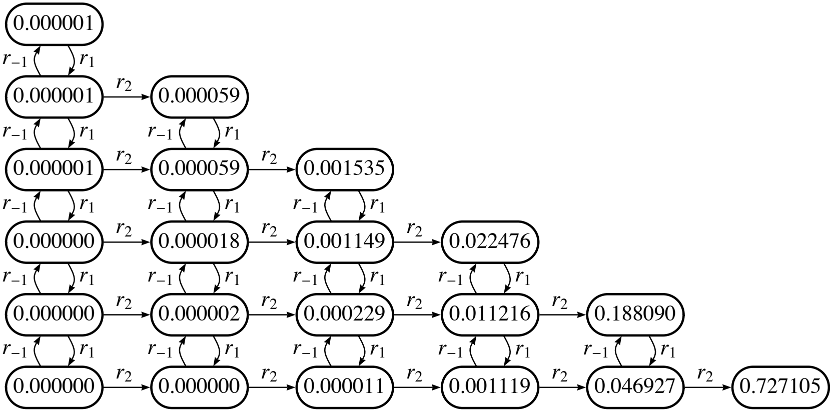
Transient probability distribution at $t = 270$



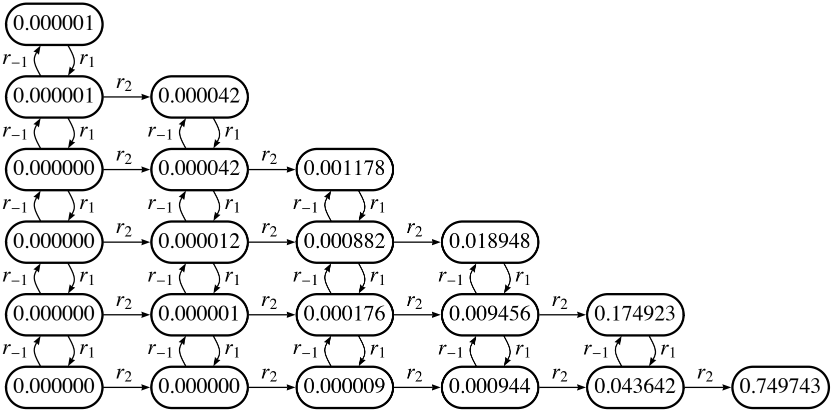
Transient probability distribution at $t = 280$



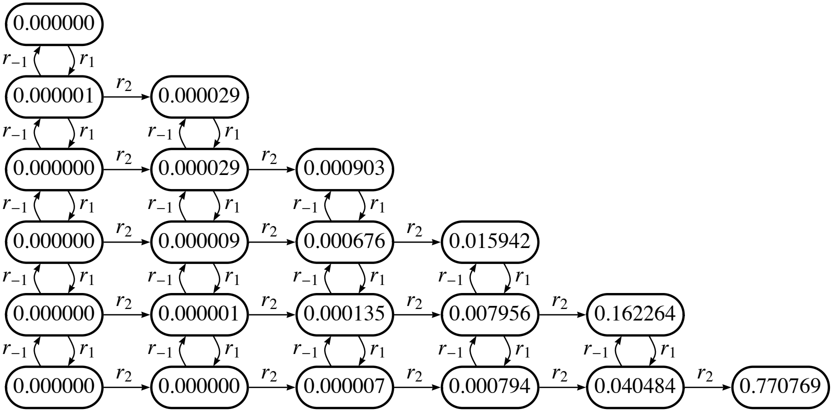
Transient probability distribution at $t = 290$



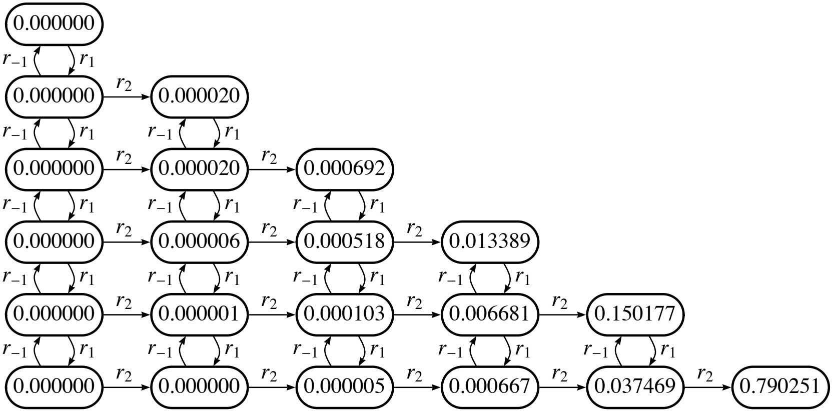
Transient probability distribution at $t = 300$



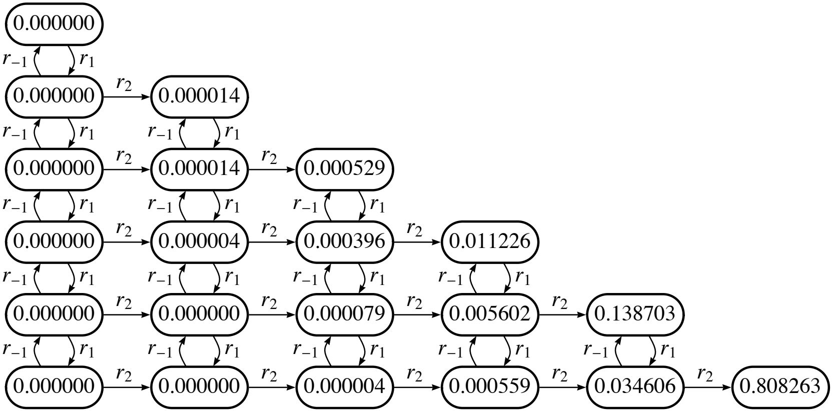
Transient probability distribution at $t = 310$



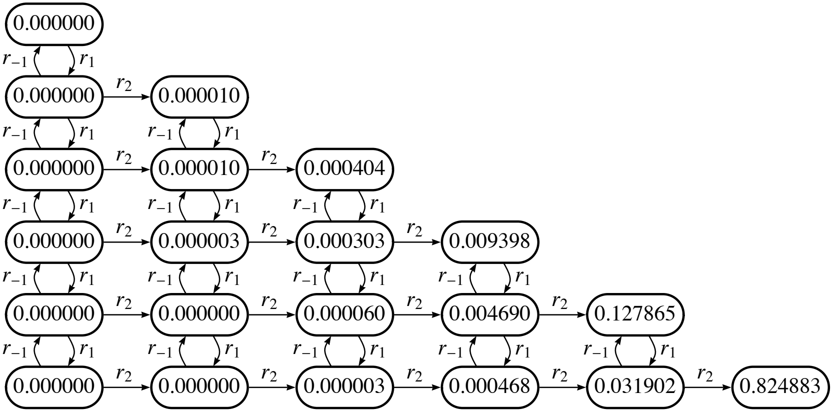
Transient probability distribution at $t = 320$



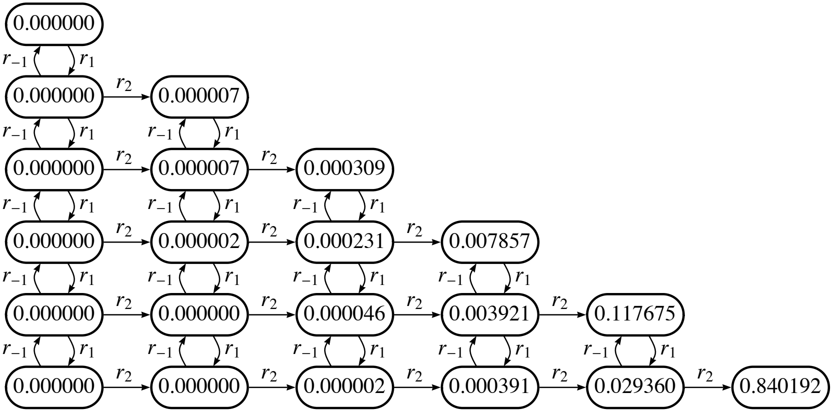
Transient probability distribution at $t = 330$



Transient probability distribution at $t = 340$



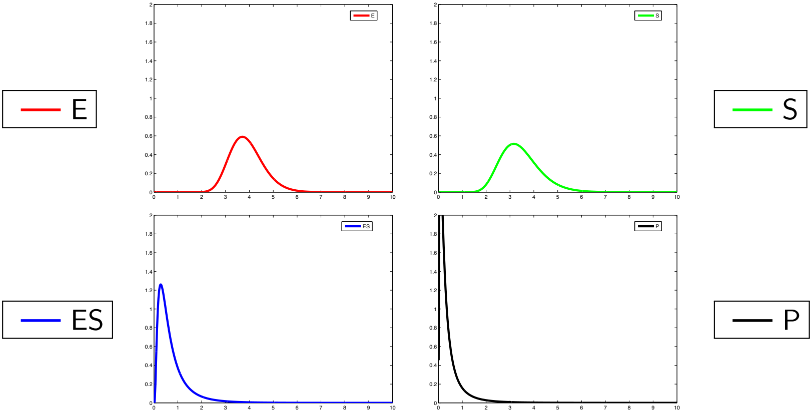
Transient probability distribution at $t = 350$



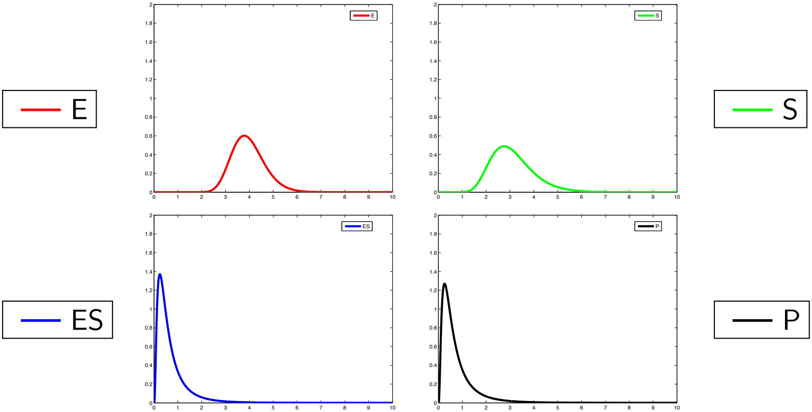
Probability distribution functions

- It is rarely the case that we wish to see the probability distribution across all of the reachable states of the model. Rather we wish to see more meaningful results which can be computed from the probability distribution.
- We might find it easier to visualise the probability distribution associated with each species E, S, ES and P.

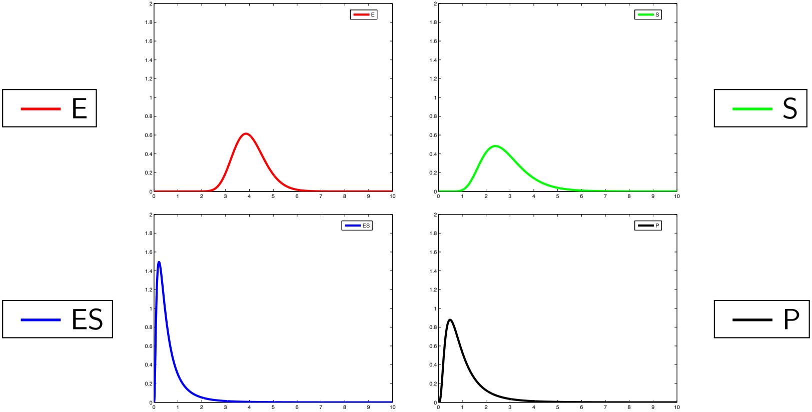
Michaelis-Menten PDFs ($t = 10$)



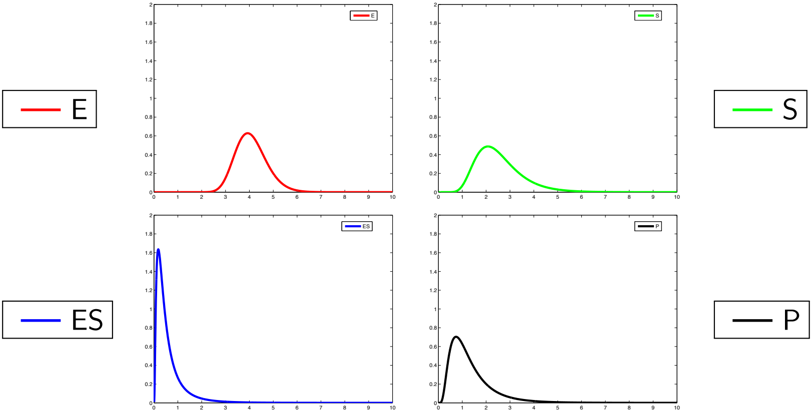
Michaelis-Menten PDFs ($t = 20$)



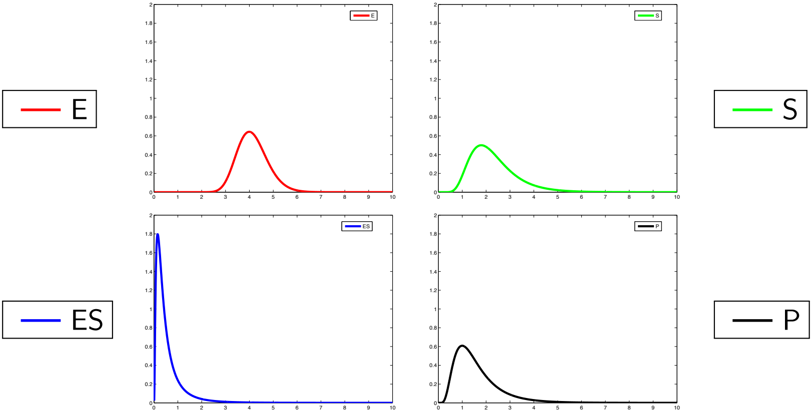
Michaelis-Menten PDFs ($t = 30$)



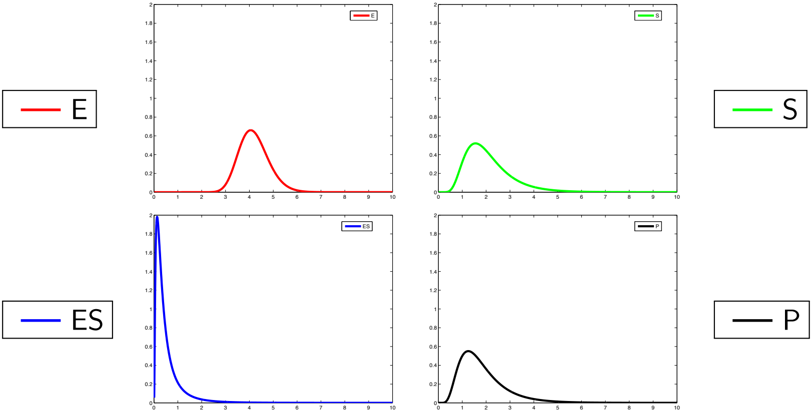
Michaelis-Menten PDFs ($t = 40$)



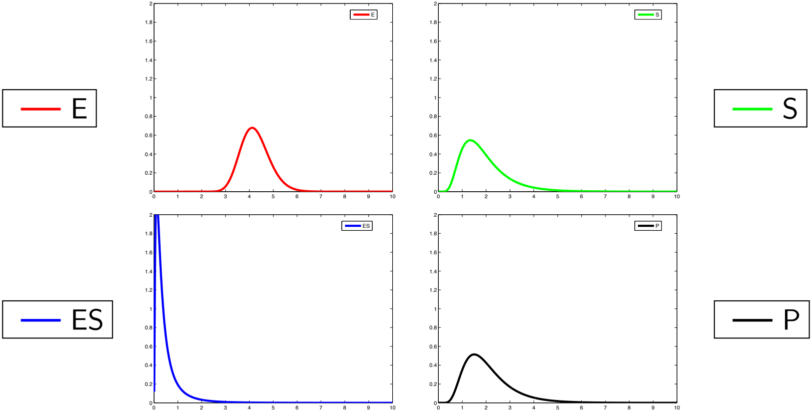
Michaelis-Menten PDFs ($t = 50$)



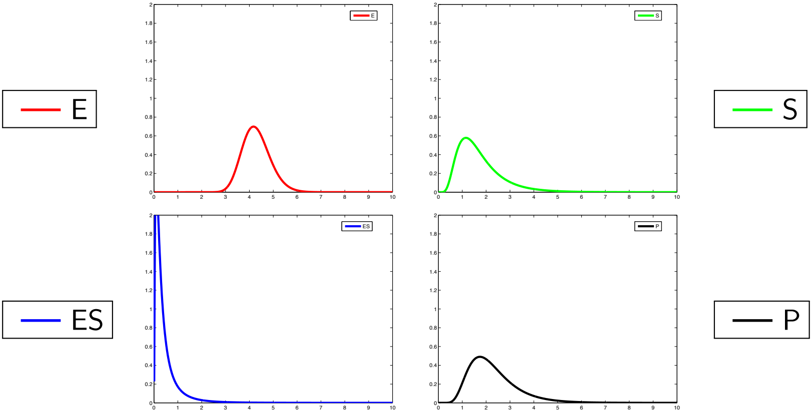
Michaelis-Menten PDFs ($t = 60$)



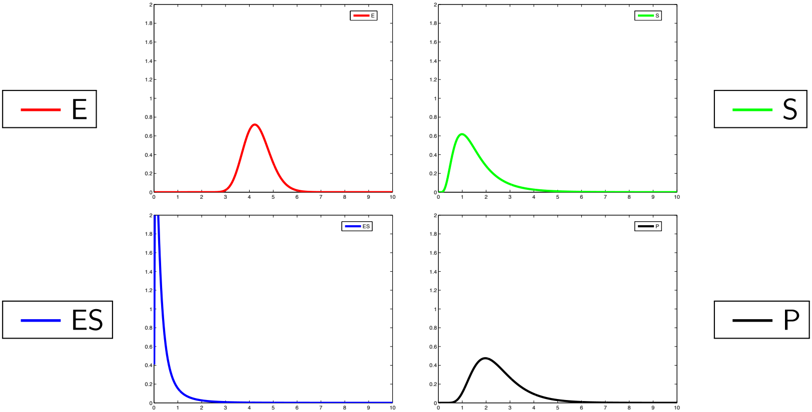
Michaelis-Menten PDFs ($t = 70$)



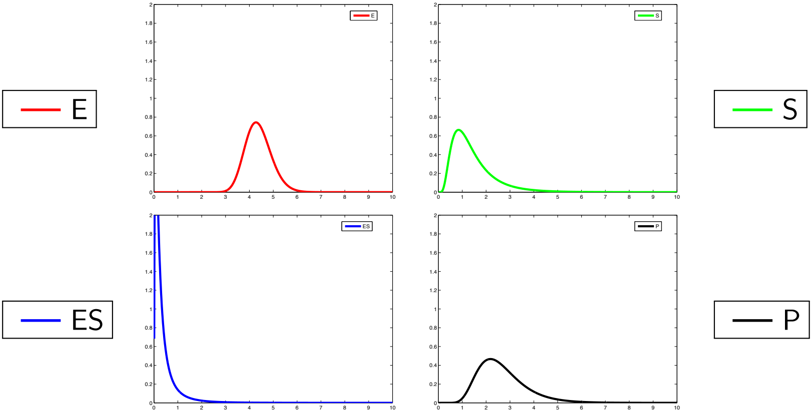
Michaelis-Menten PDFs ($t = 80$)



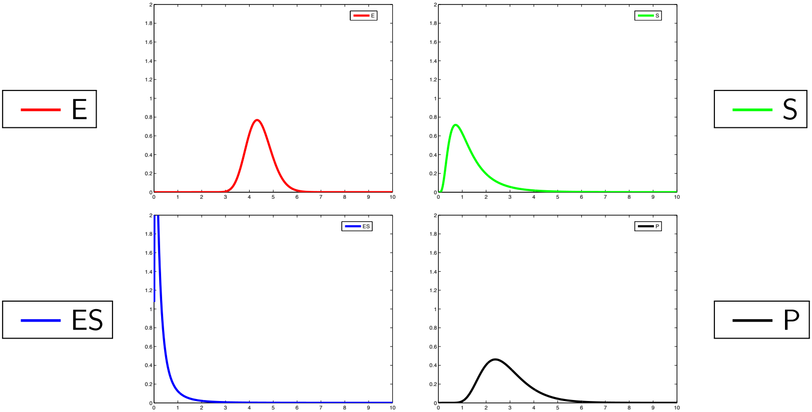
Michaelis-Menten PDFs ($t = 90$)



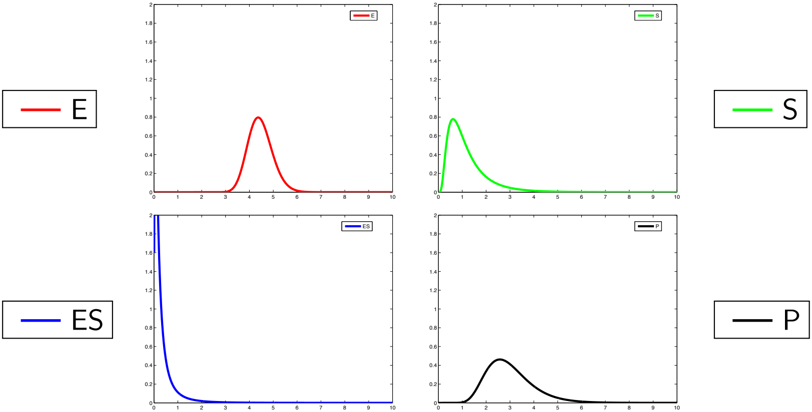
Michaelis-Menten PDFs ($t = 100$)



Michaelis-Menten PDFs ($t = 110$)



Michaelis-Menten PDFs ($t = 120$)



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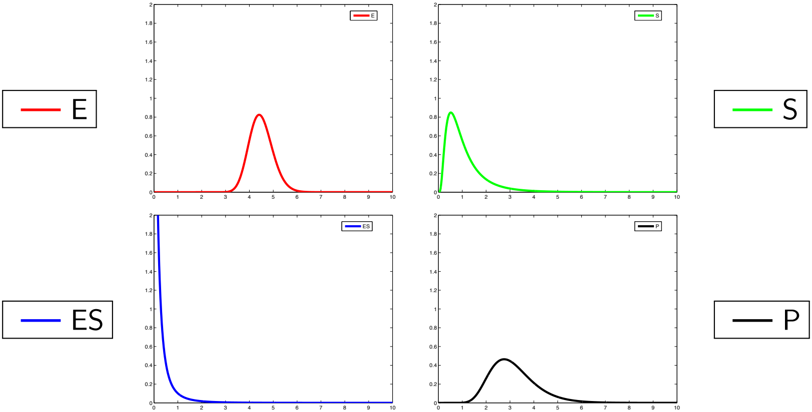
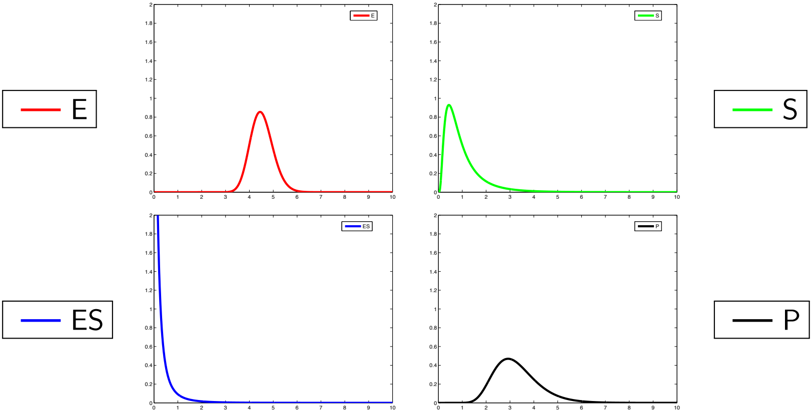


Michaelis-Menten PDFs ($t = 140$)



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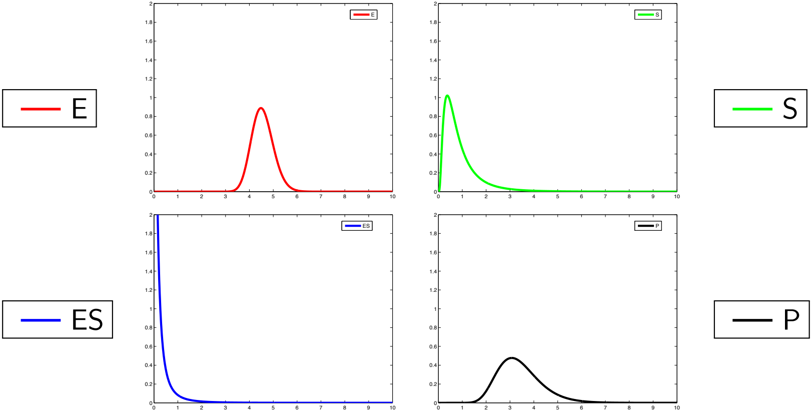
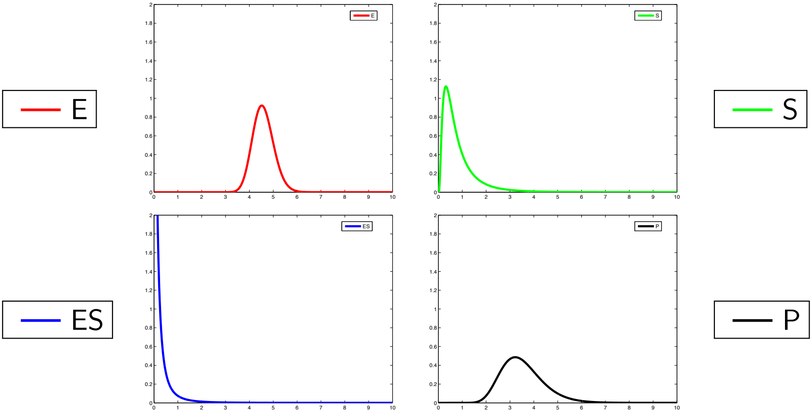
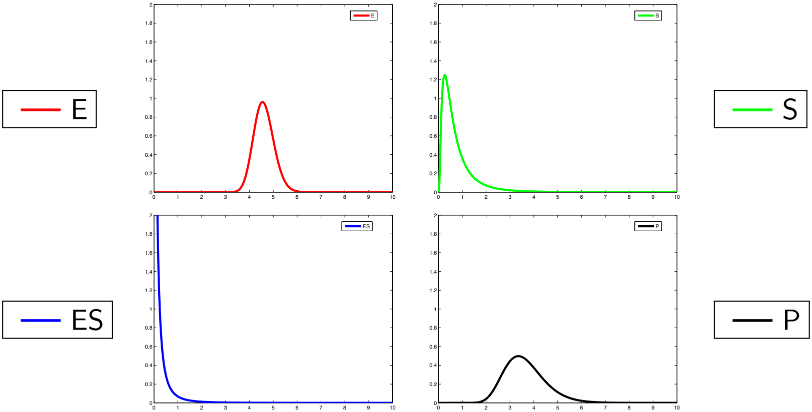


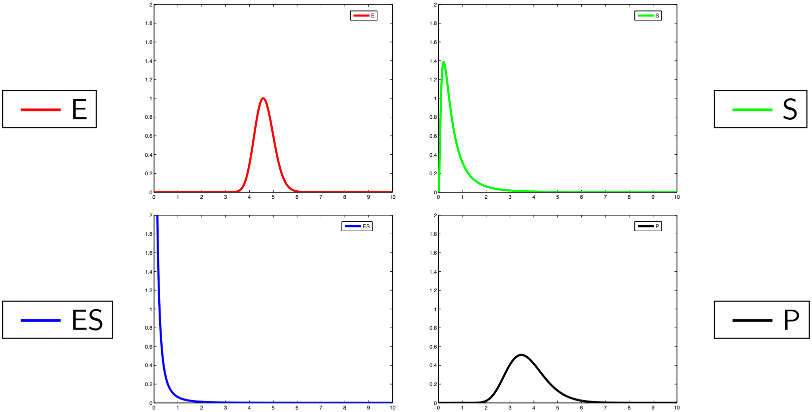
Michaelis-Menten PDFs ($t = 160$)



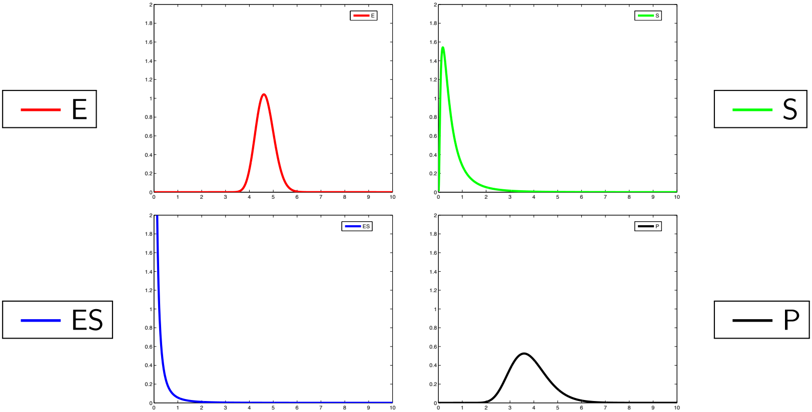
Michaelis-Menten PDFs ($t = 170$)



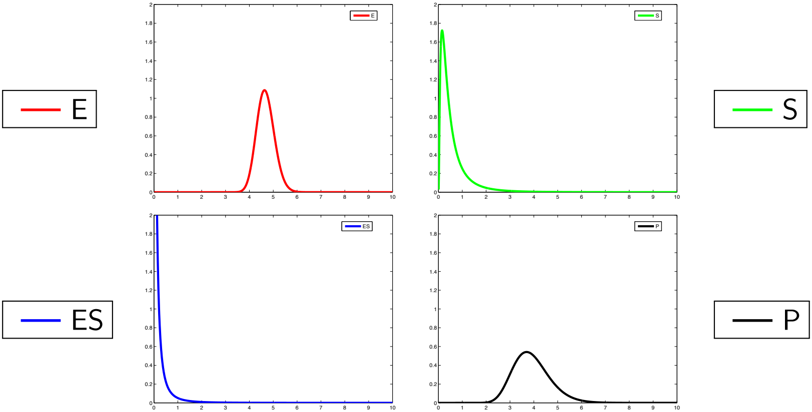
Michaelis-Menten PDFs ($t = 180$)



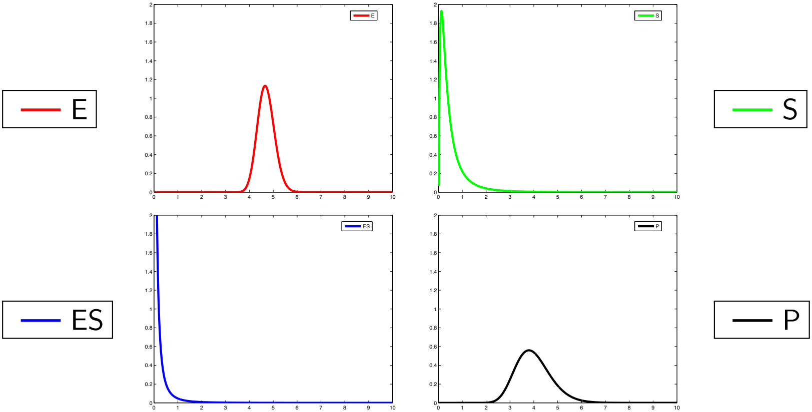
Michaelis-Menten PDFs ($t = 190$)



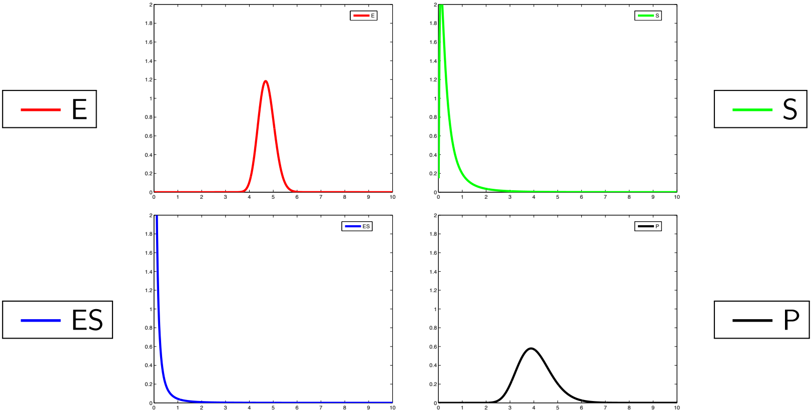
Michaelis-Menten PDFs ($t = 200$)



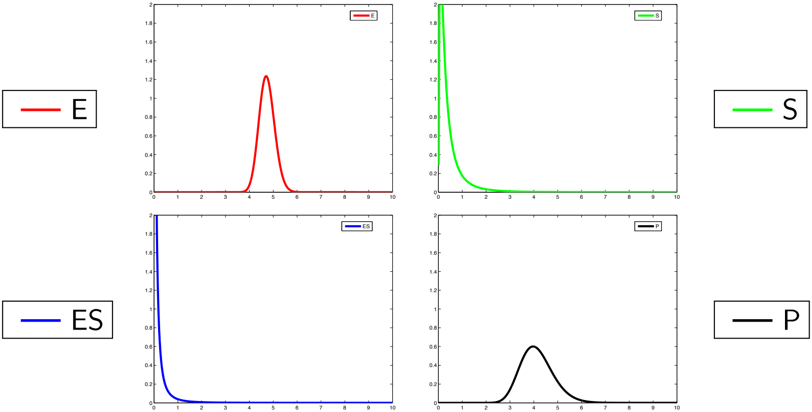
Michaelis-Menten PDFs ($t = 210$)



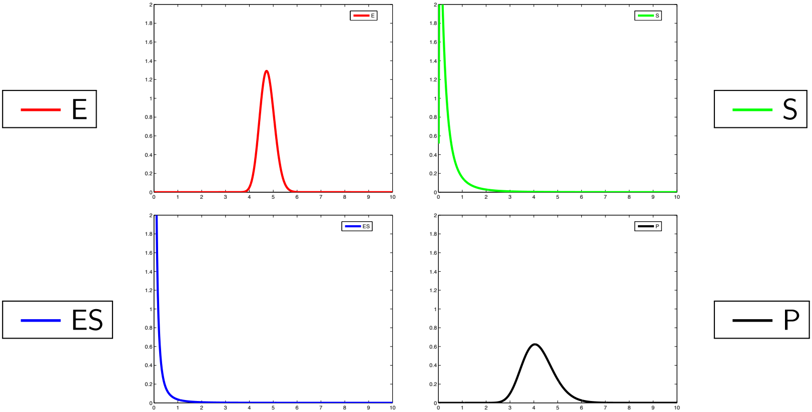
Michaelis-Menten PDFs ($t = 220$)



Michaelis-Menten PDFs ($t = 230$)



Michaelis-Menten PDFs ($t = 240$)



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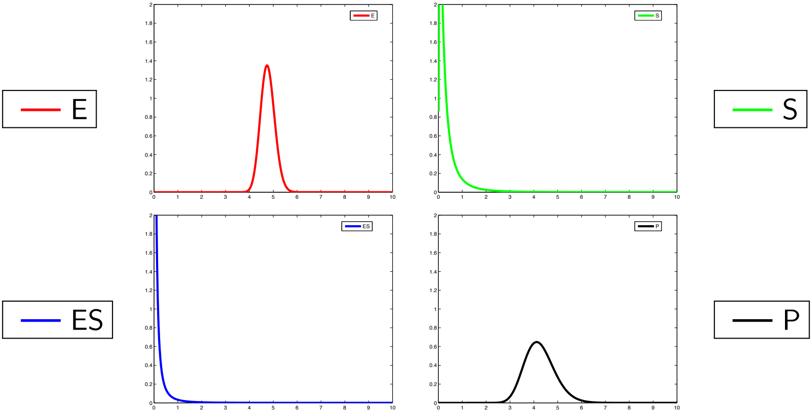
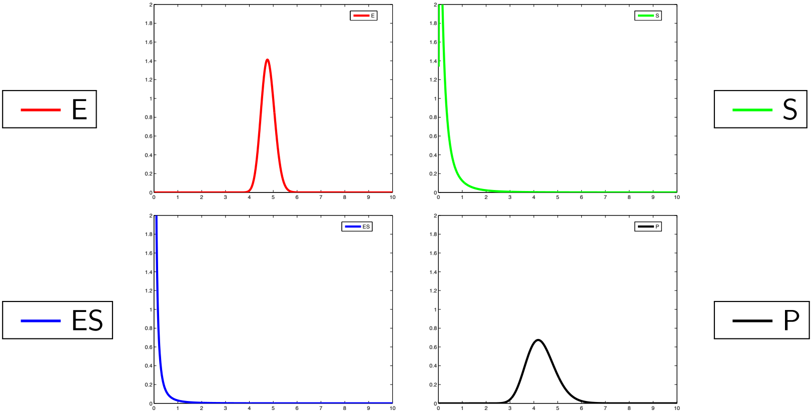
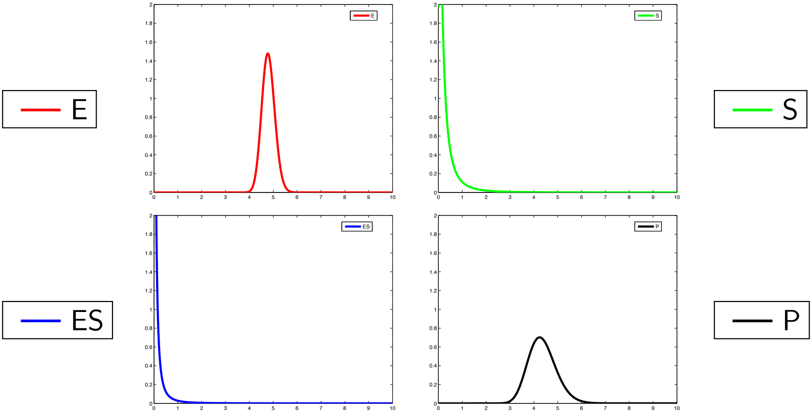


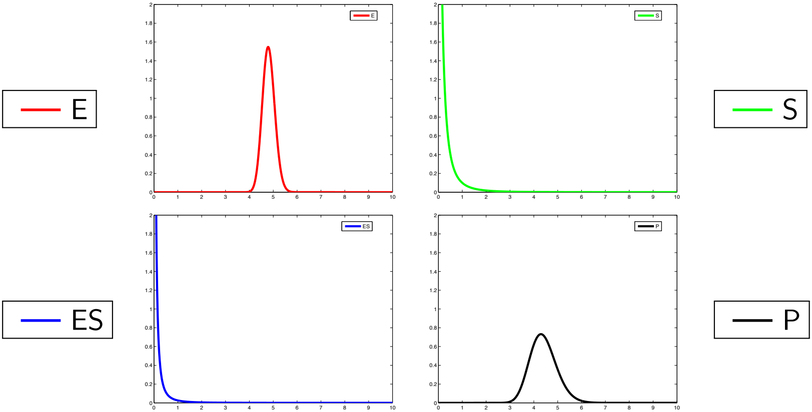
Michaelis-Menten PDFs ($t = 260$)



Michaelis-Menten PDFs ($t = 270$)



Michaelis-Menten PDFs ($t = 280$)



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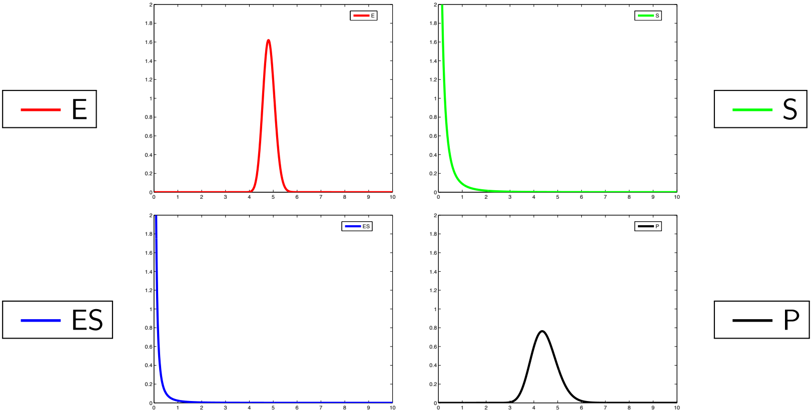

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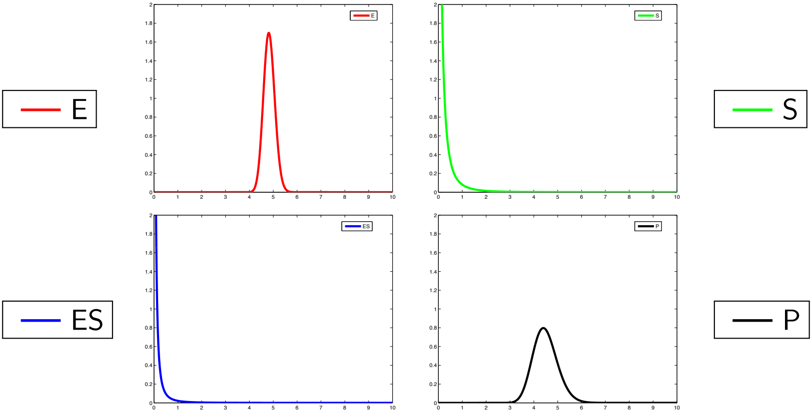
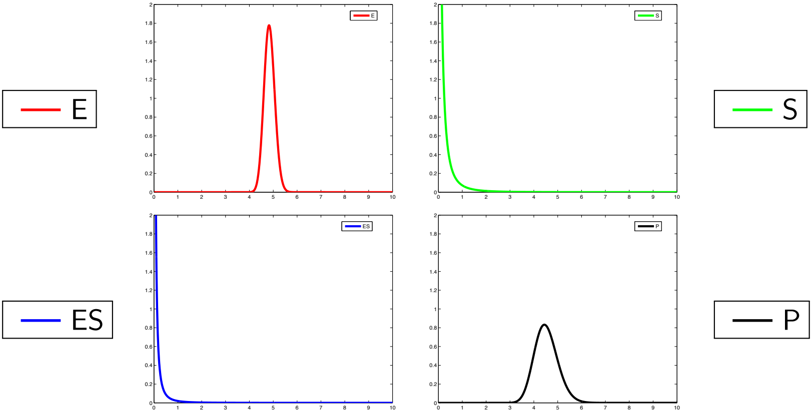


Michaelis-Menten PDFs ($t = 310$)



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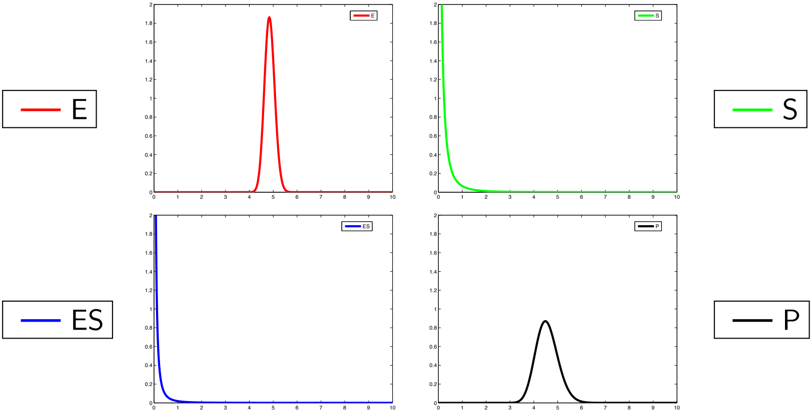
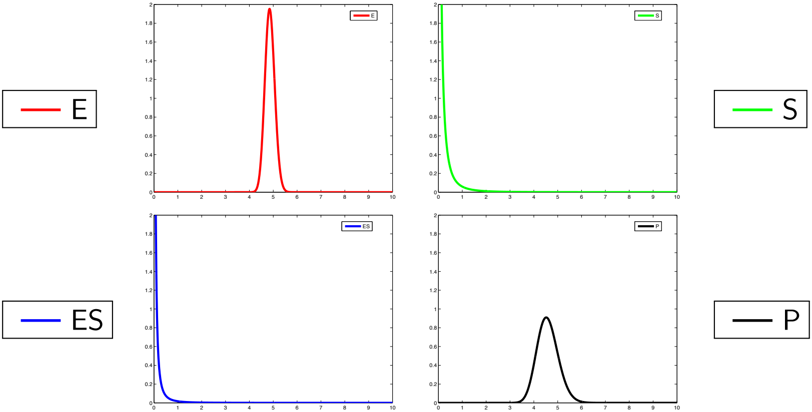
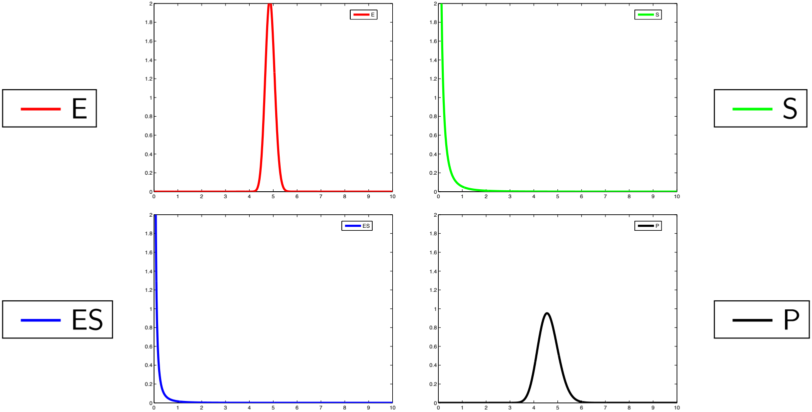


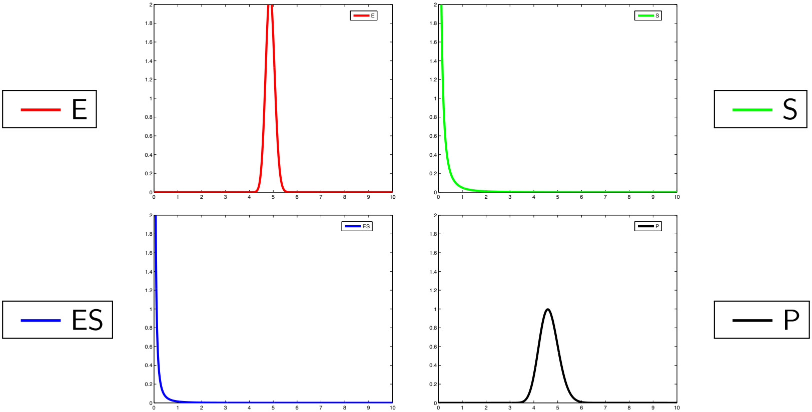
Michaelis-Menten PDFs ($t = 330$)



Michaelis-Menten PDFs ($t = 340$)



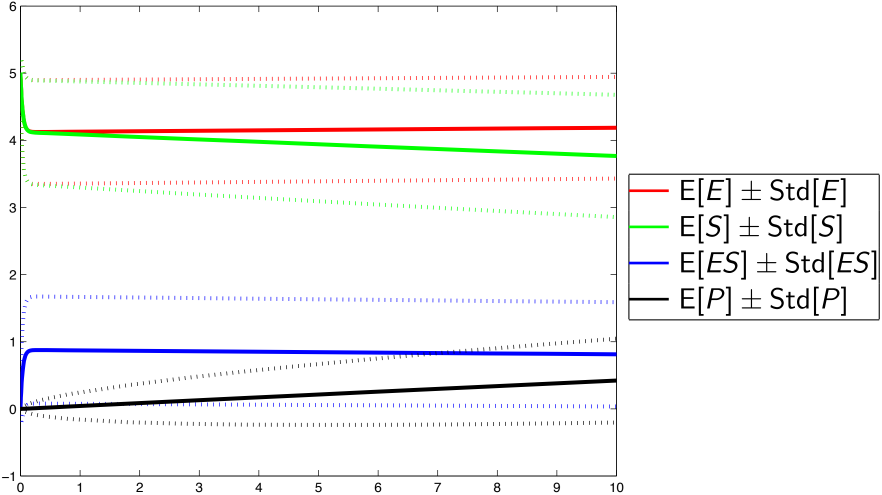
Michaelis-Menten PDFs ($t = 350$)



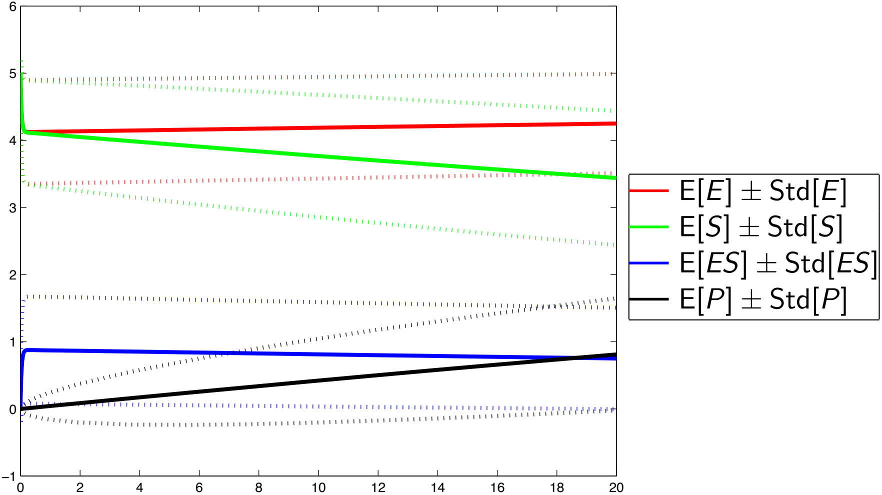
Time series

- An alternative way to view the system dynamics is to plot the expected values of the species as a function of time.
- This view has the advantage that it is easily obtained by solving the initial value problem for the ODEs and that it is easier to compare against time course data obtained from wet lab experiments.

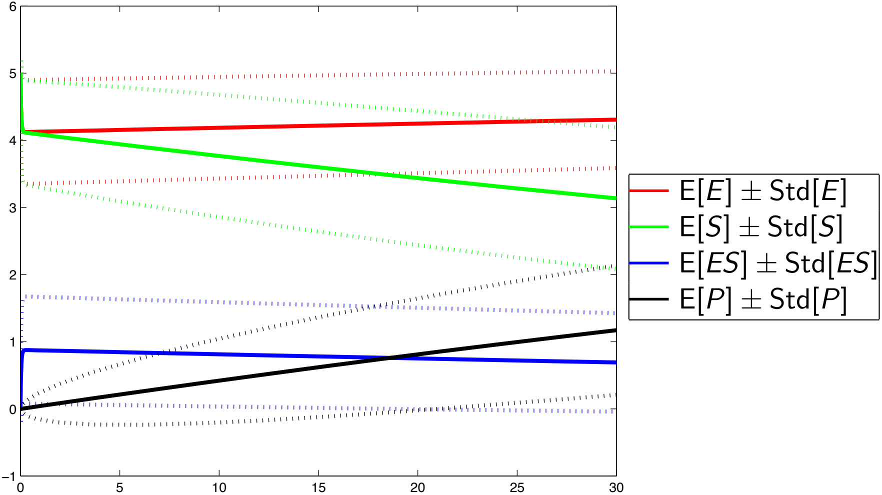
Michaelis-Menten Time series ($t = 10$)



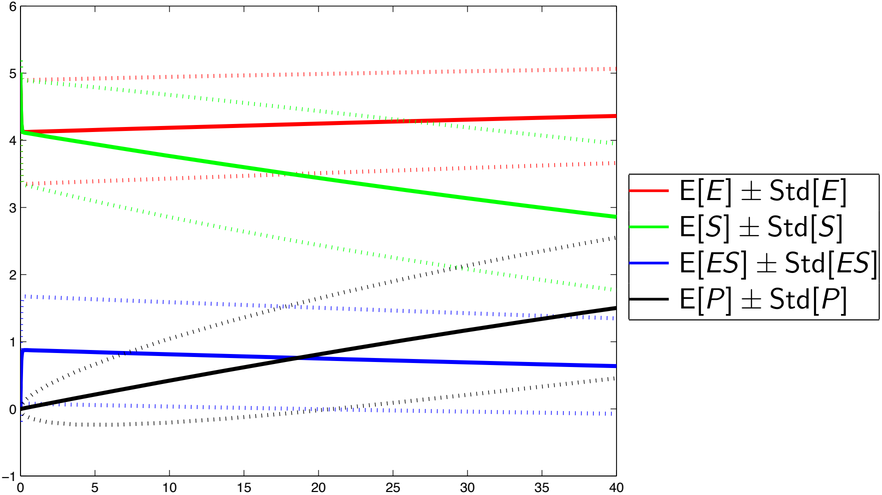
Michaelis-Menten Time series ($t = 20$)



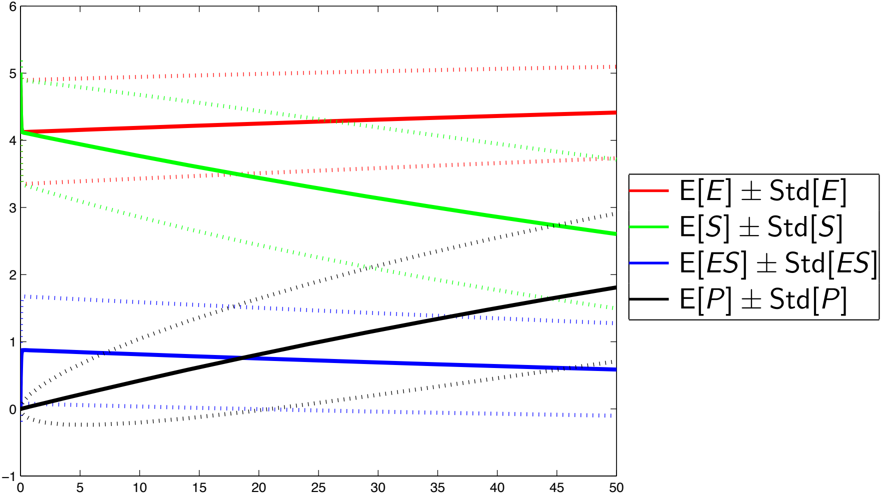
Michaelis-Menten Time series ($t = 30$)



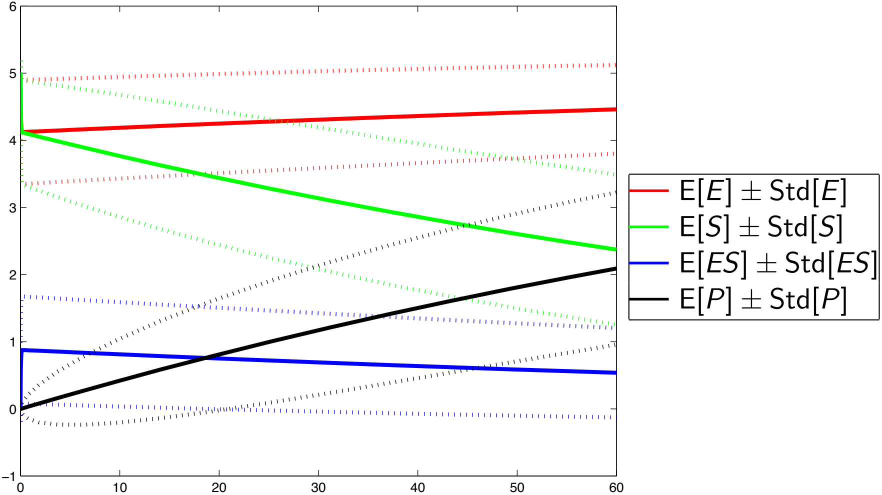
Michaelis-Menten Time series ($t = 40$)



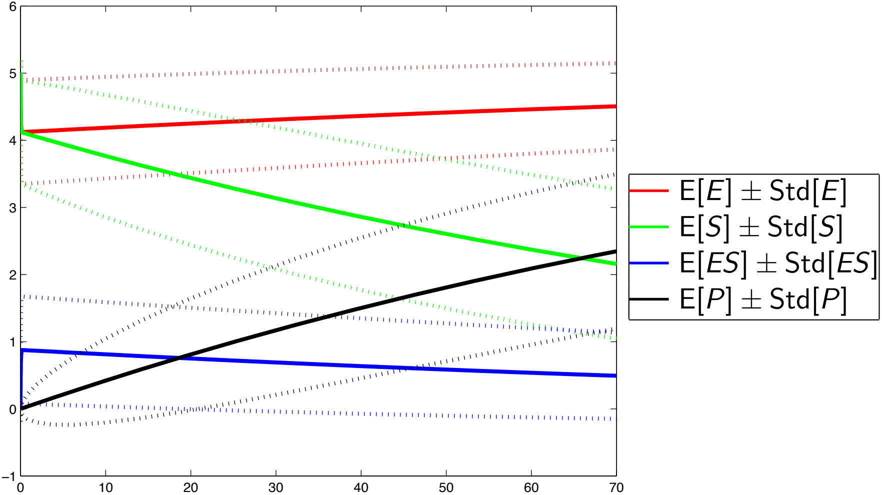
Michaelis-Menten Time series ($t = 50$)



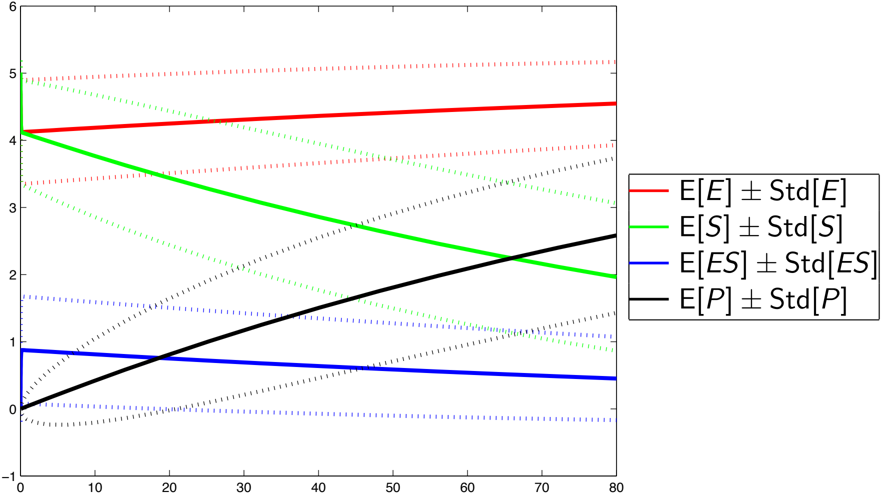
Michaelis-Menten Time series ($t = 60$)



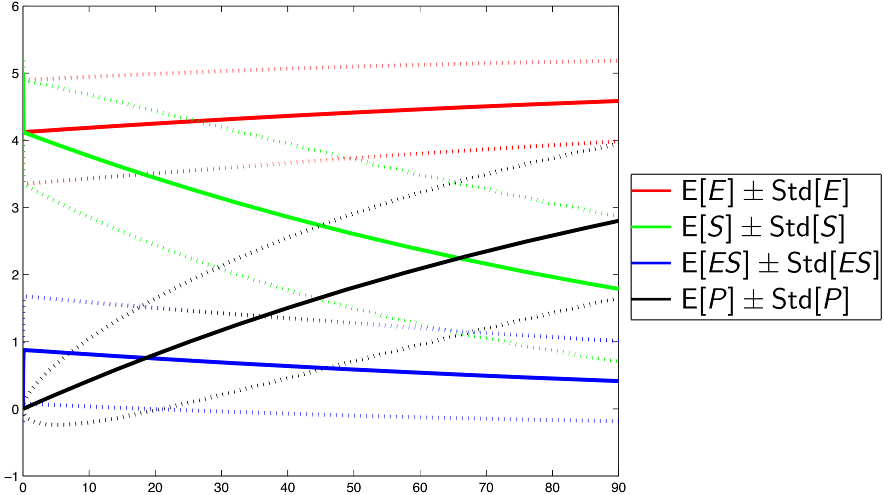
Michaelis-Menten Time series ($t = 70$)



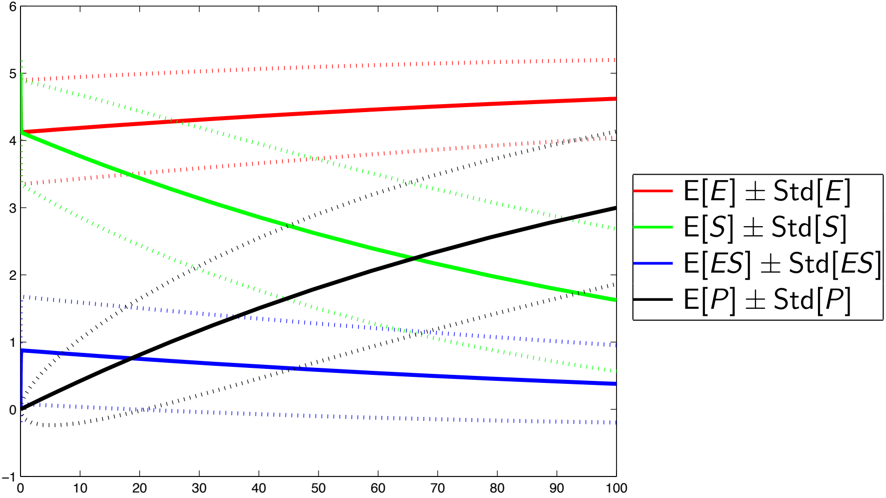
Michaelis-Menten Time series ($t = 80$)



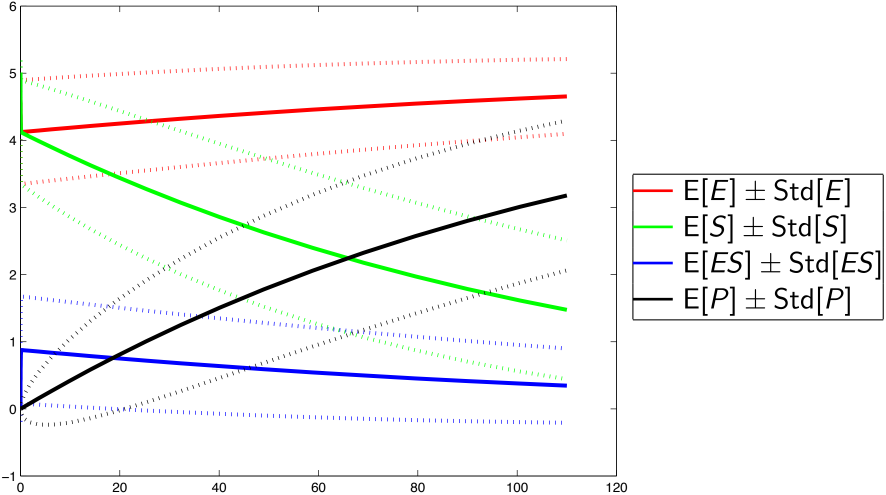
Michaelis-Menten Time series ($t = 90$)



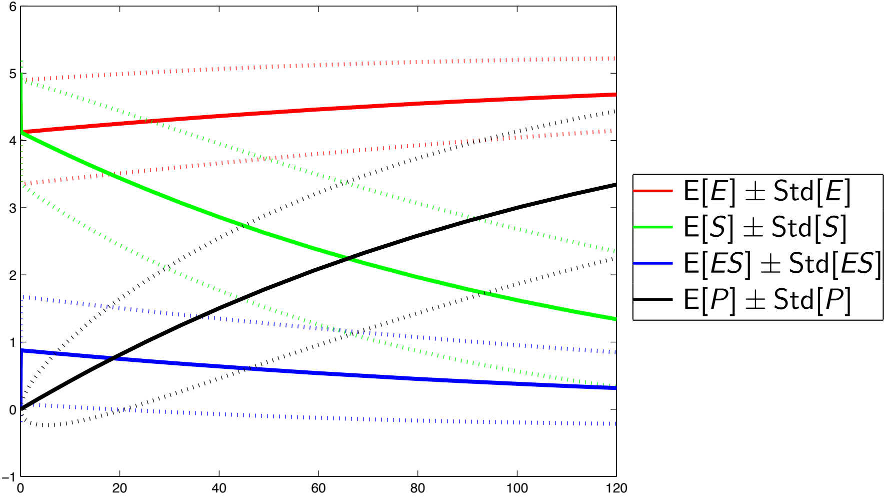
Michaelis-Menten Time series ($t = 100$)



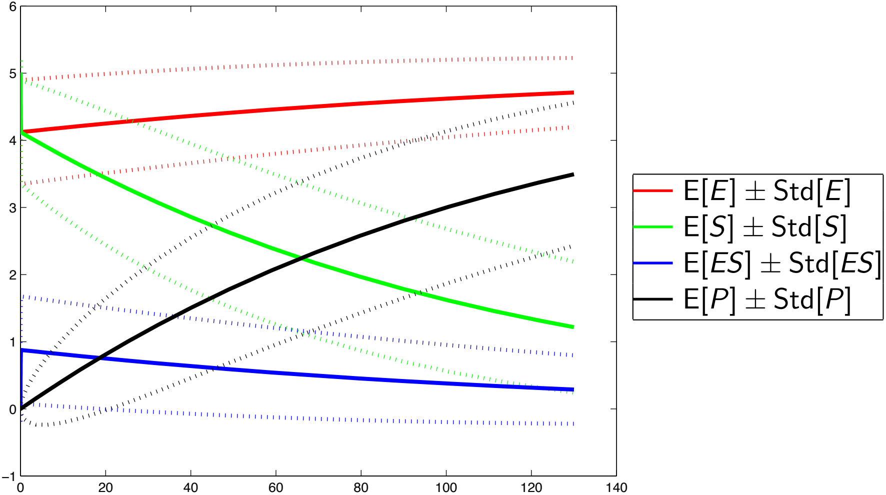
Michaelis-Menten Time series ($t = 110$)



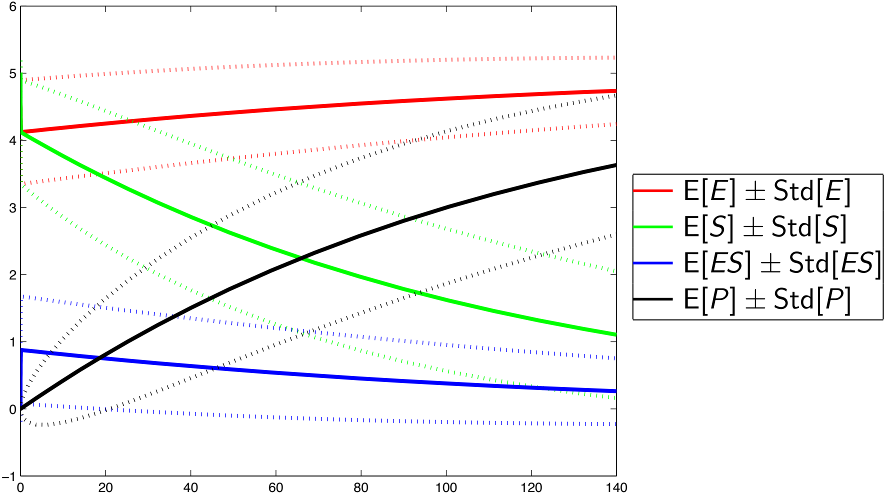
Michaelis-Menten Time series ($t = 120$)



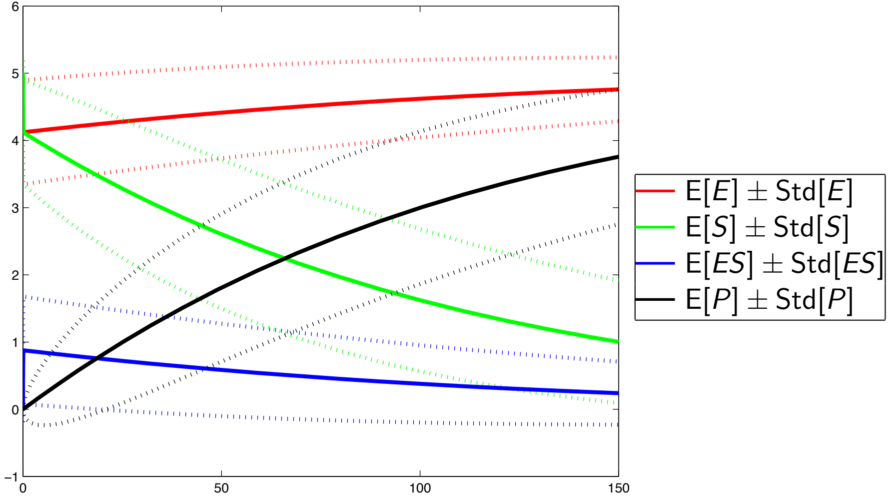
Michaelis-Menten Time series ($t = 130$)



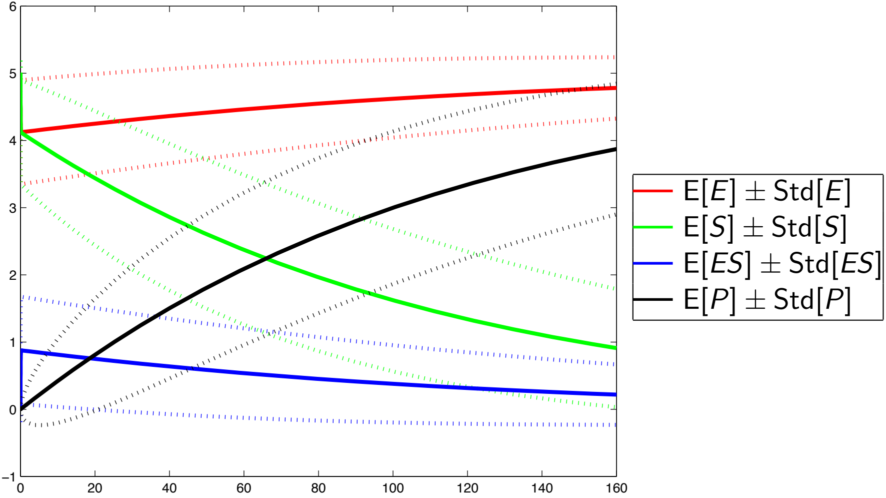
Michaelis-Menten Time series ($t = 140$)



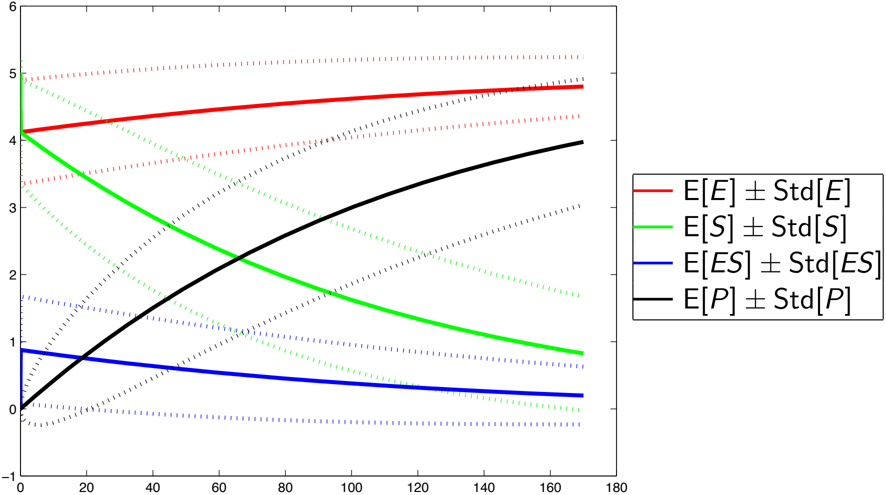
Michaelis-Menten Time series ($t = 150$)



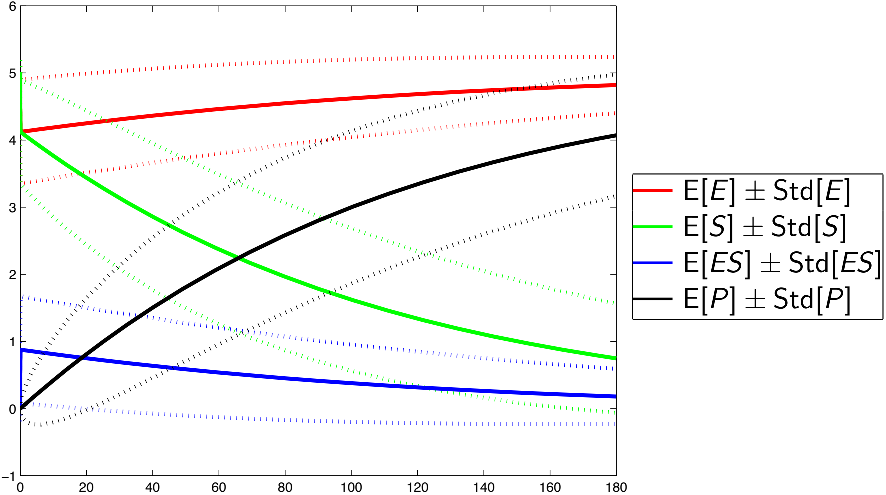
Michaelis-Menten Time series ($t = 160$)



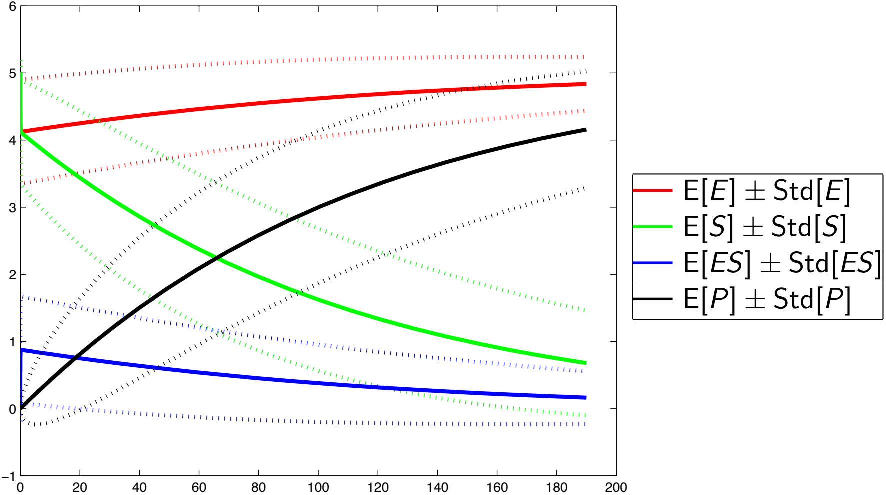
Michaelis-Menten Time series ($t = 170$)



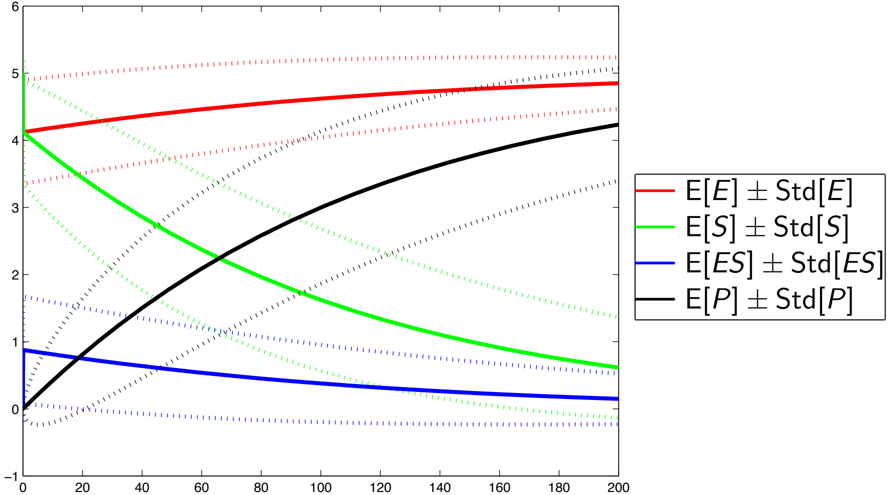
Michaelis-Menten Time series ($t = 180$)



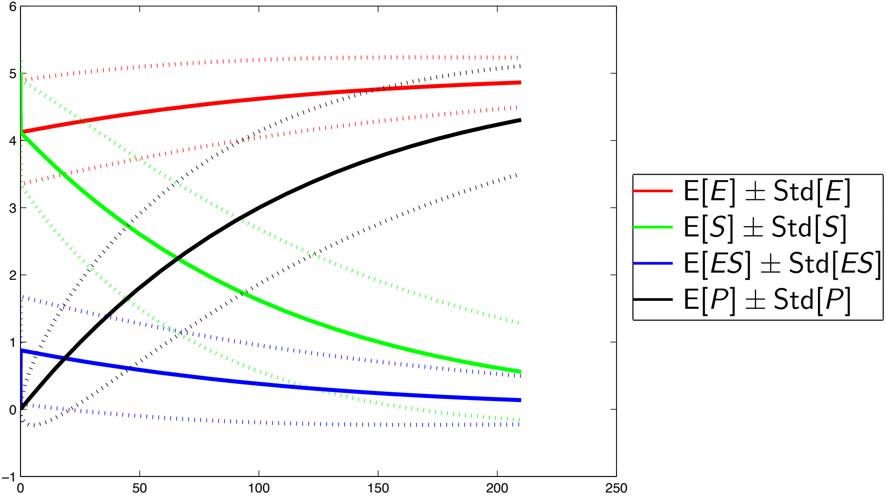
Michaelis-Menten Time series ($t = 190$)



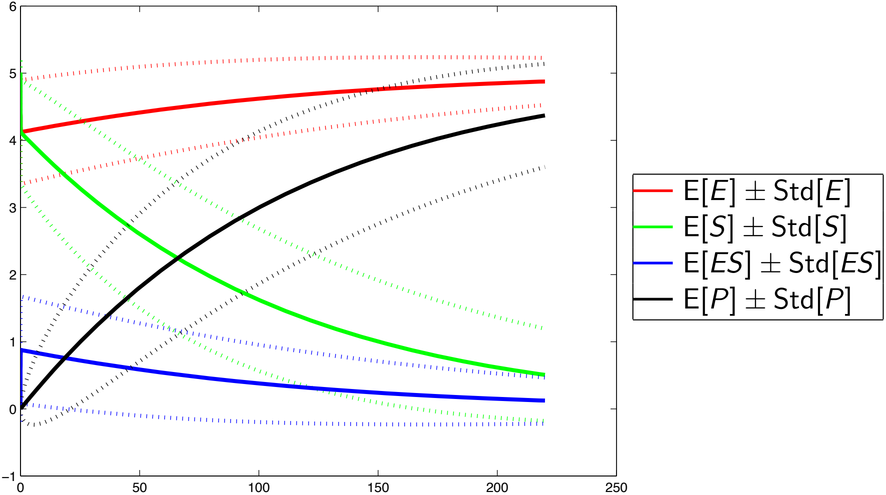
Michaelis-Menten Time series ($t = 200$)



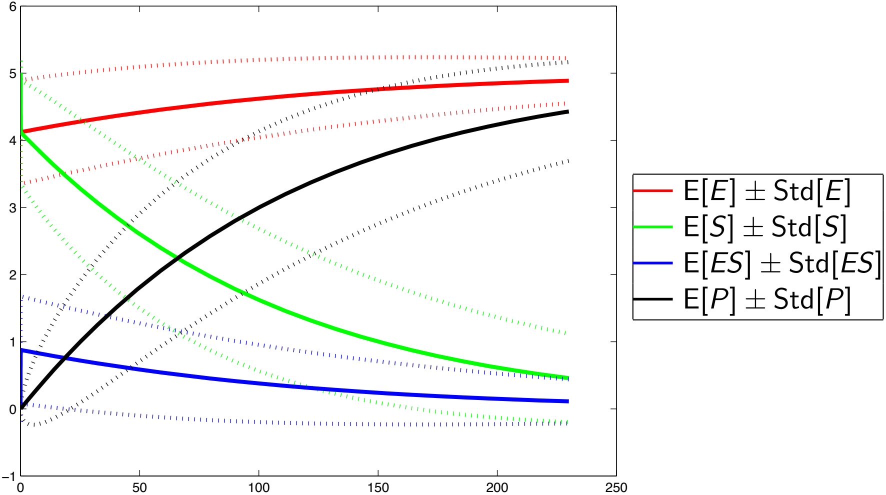
Michaelis-Menten Time series ($t = 210$)



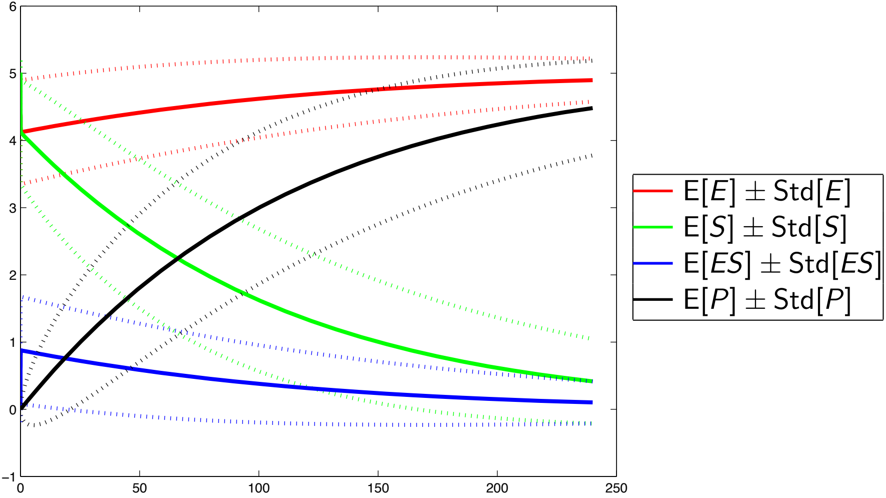
Michaelis-Menten Time series ($t = 220$)



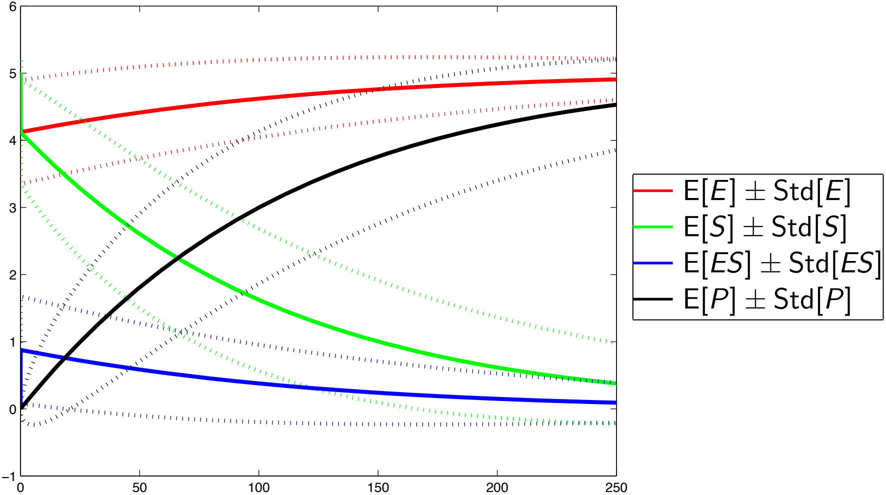
Michaelis-Menten Time series ($t = 230$)



Michaelis-Menten Time series ($t = 240$)



Michaelis-Menten Time series ($t = 250$)



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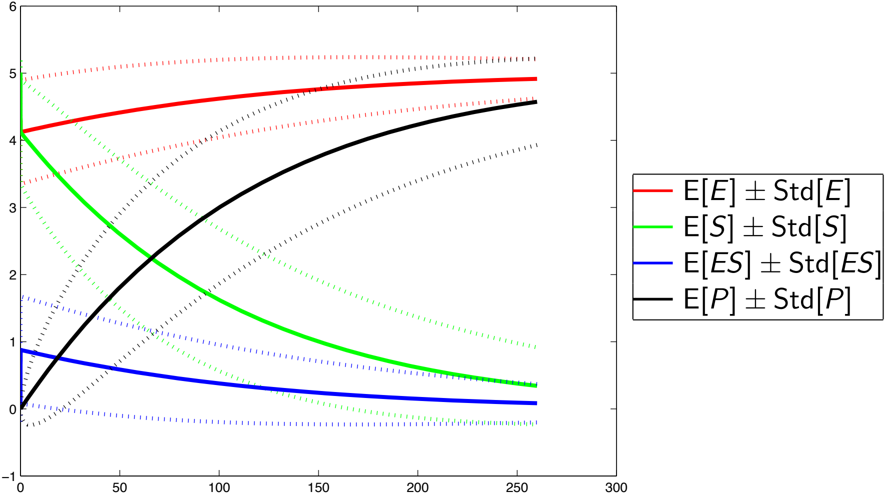
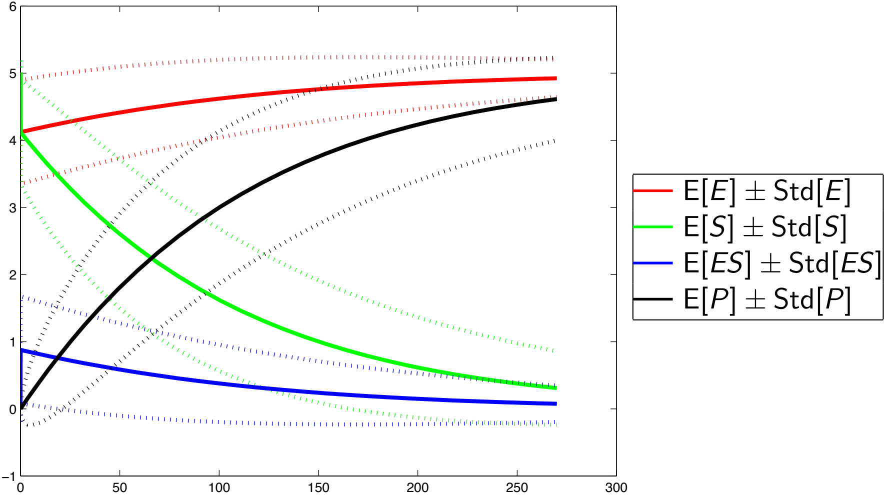


Michaelis-Menten Time series ($t = 270$)



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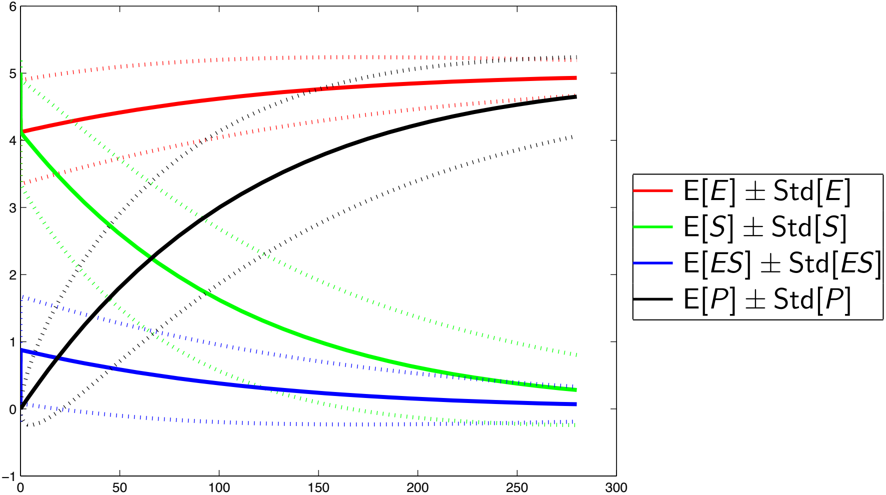
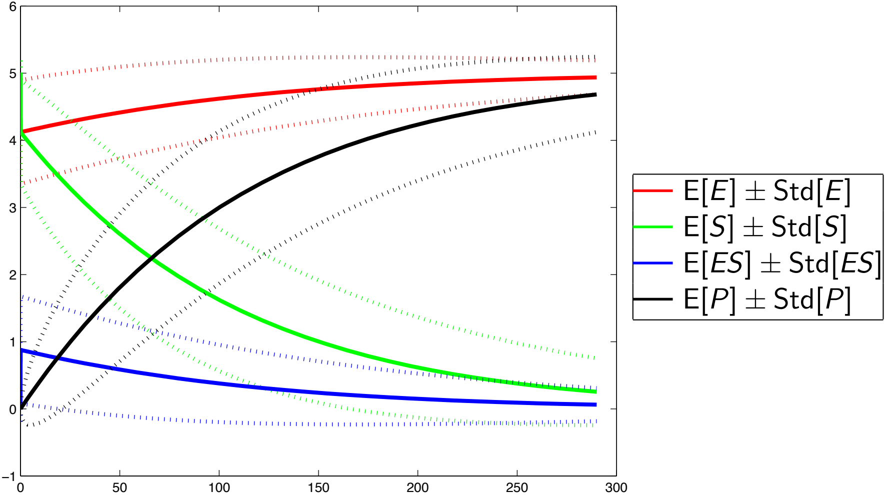
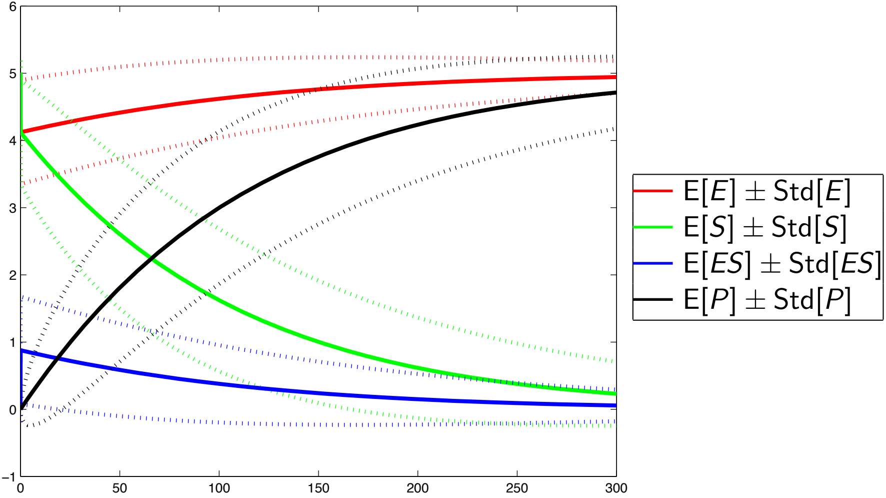


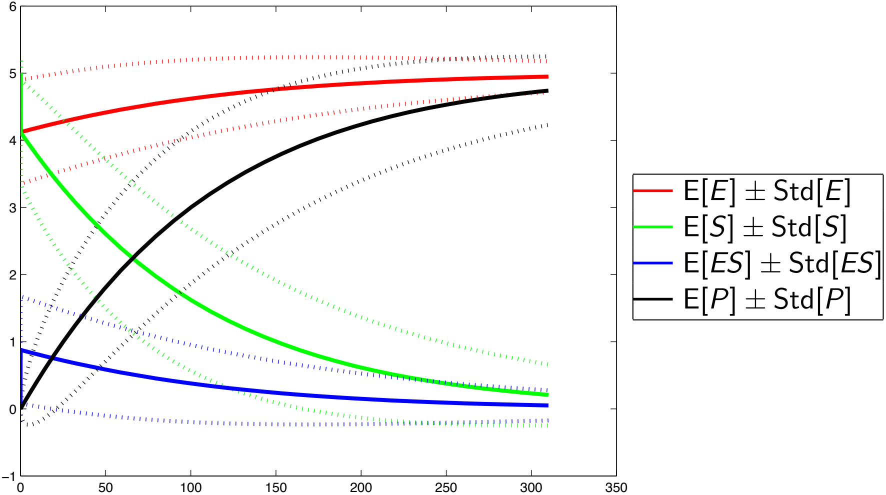
Michaelis-Menten Time series ($t = 290$)



Michaelis-Menten Time series ($t = 300$)



Michaelis-Menten Time series ($t = 310$)



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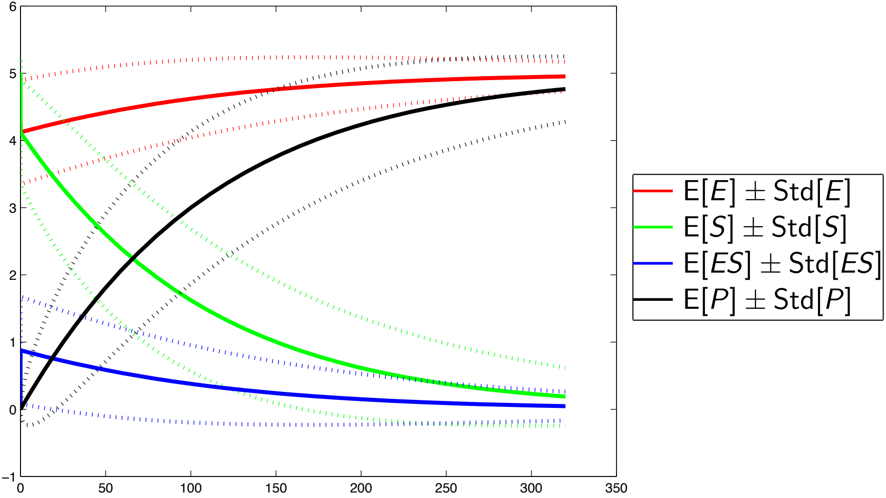
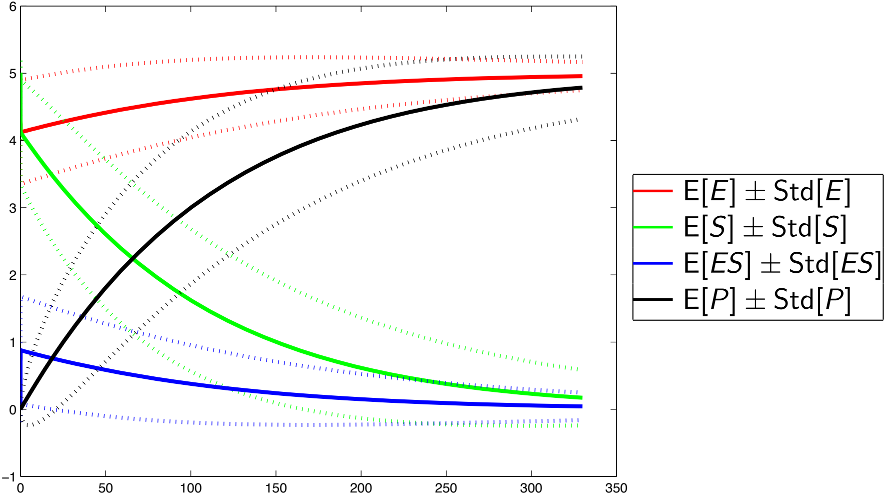
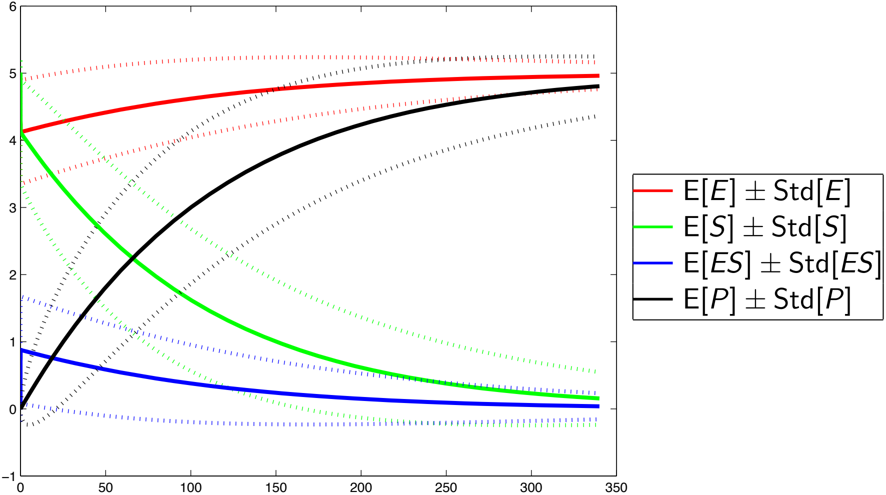


Michaelis-Menten Time series ($t = 330$)



Michaelis-Menten Time series ($t = 340$)



Michaelis-Menten Time series ($t = 350$)