

# Mathematical model of T-cell signaling

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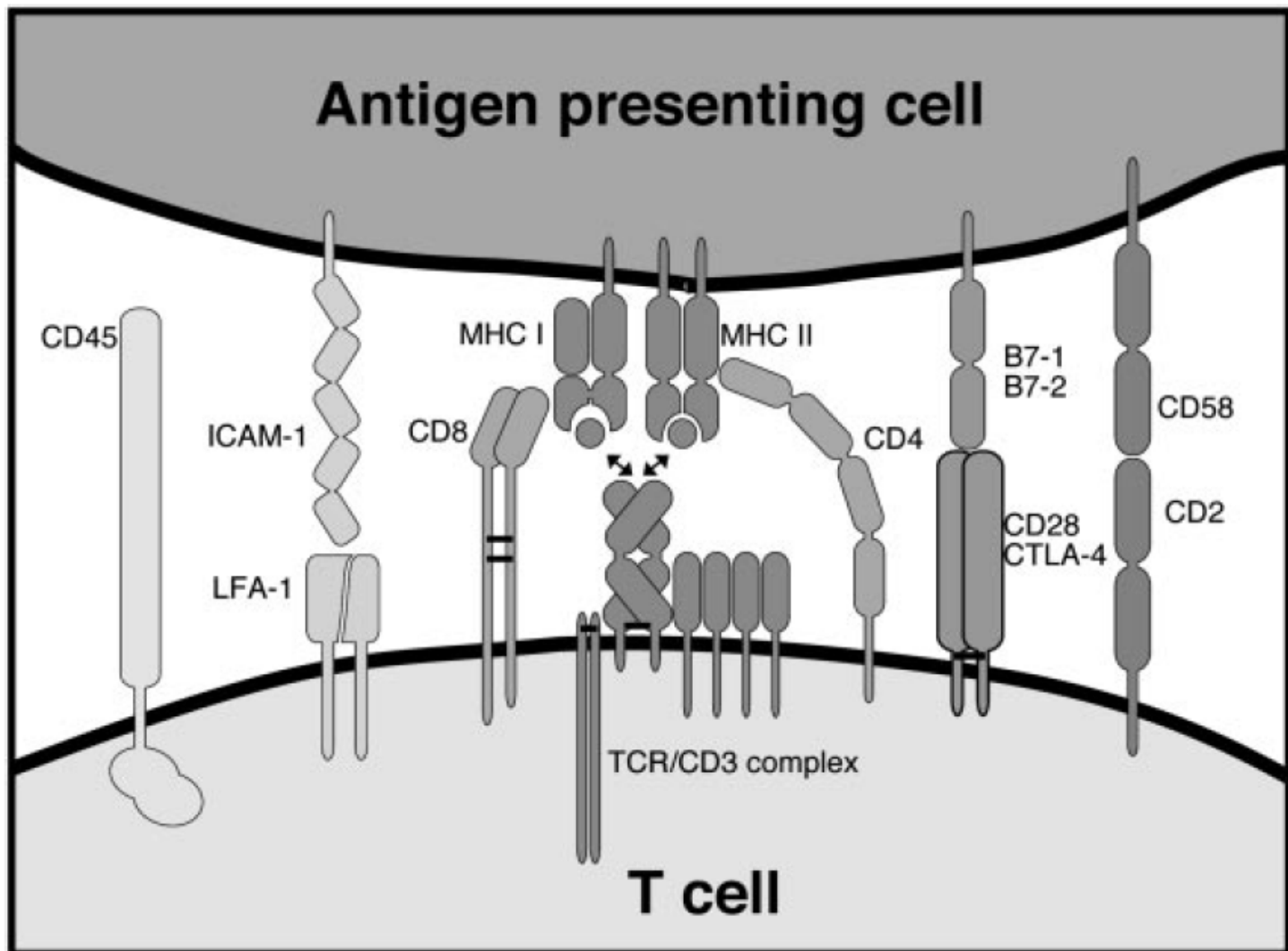
What are T-cells = T lymphocytes = thymocytes ?

T-cells govern the adaptive immune response in vertebrates.  
T-cells are activated by foreign antigens (peptides).

Two main types of T-cells: **helper** and **cytotoxic**.

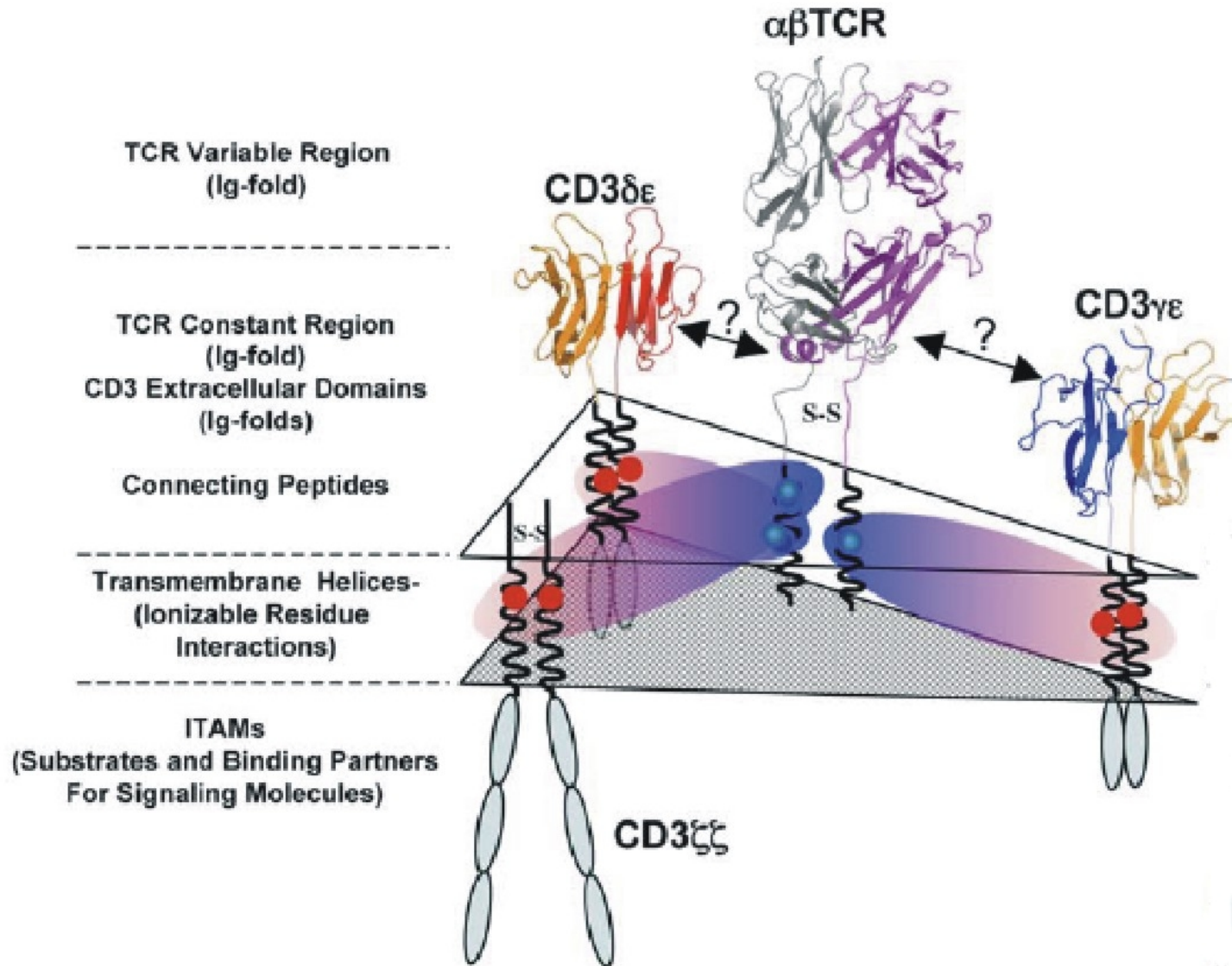
**Helper T-cells:** when activated secrete cytokines inducing B-cells to proliferate and mature into antibody secreting cells.

**Cytotoxic (killer) T-cells:** when activated induce apoptosis in cells on which they recognize foreign peptides. They act on fast scale of order of few minutes.



**Figure 1** Cell surface molecules involved in T cell recognition. Molecules thought to play key roles in T cell recognition, as discussed in the text.

# Helper and cytotoxic T-cells receptors ( $\alpha\beta$ TCRs)



# Two problems

Difficult: Why endogenous peptides bind to T-cell receptors for shorter time than foreign peptides?

Easy: How longer binding time of foreign peptides leads to discrimination between endogenous and foreign peptides ?

Only binding of foreign peptides leads to T-cell activation.

## (Not as) Easy problem

I) 10 000 peptides/T-cell with dissociation time of 3s → **No** T-cell activity

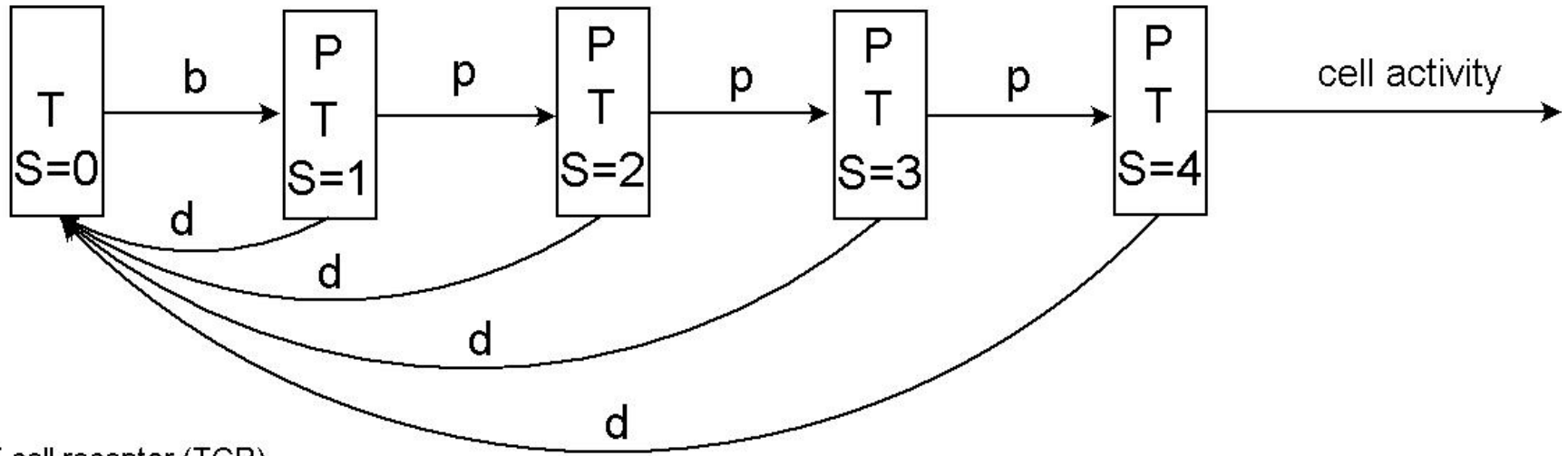
II) 3 peptides /T-cell with dissociation time of 20s → **High** T-cell activity

$$\frac{d TP}{dt} = b \times T \times P - d \times TP$$

$$TP = b \times T \times \frac{P}{d}$$

TP – number of bound T-cell receptors, T-number of free receptors,  
P- number of free peptides

# Kinetic proofreading



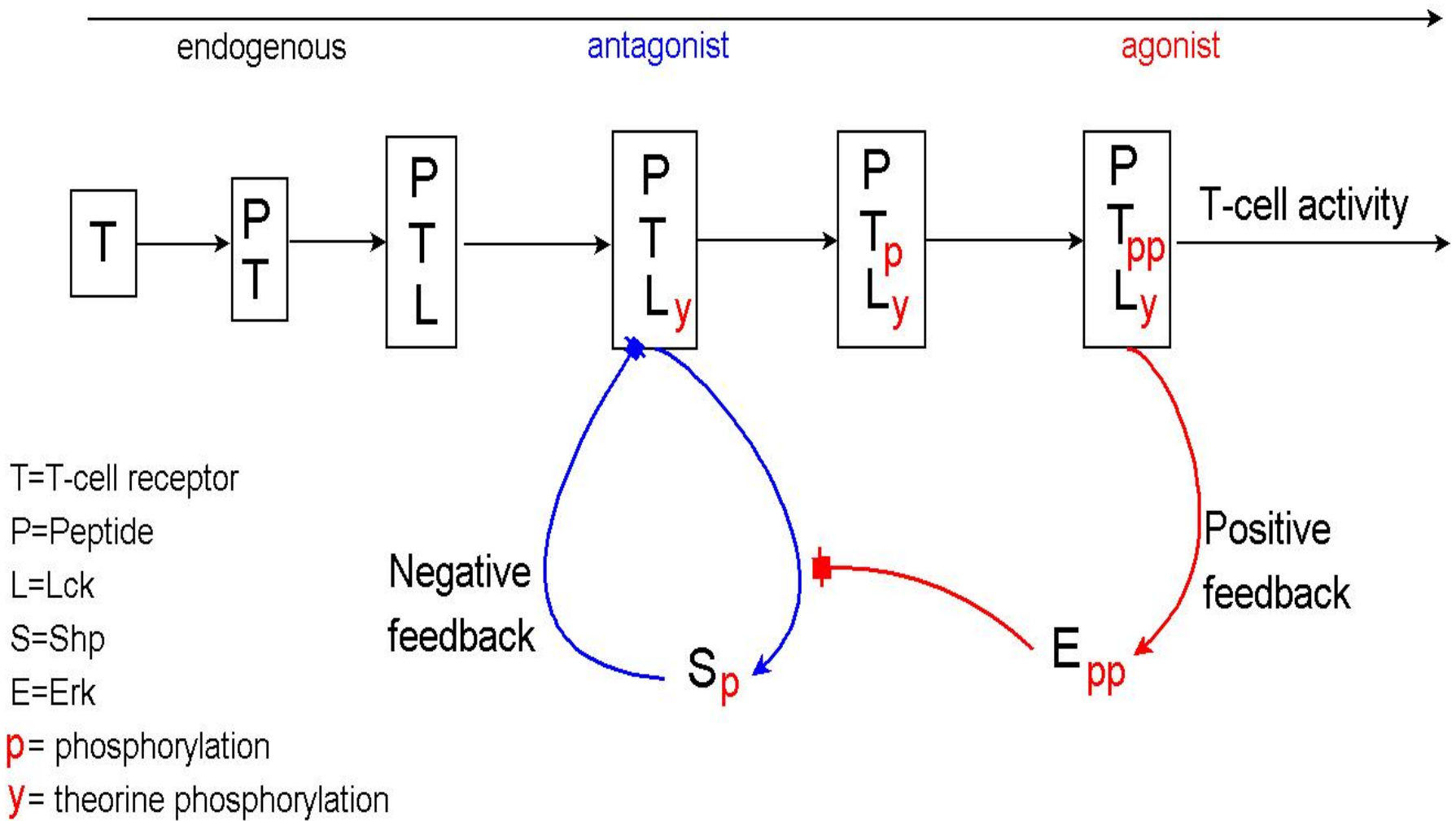
T=T cell receptor (TCR)  
P=Peptide  
S=state of receptor

Mckeithan 1995

**Discuss antagonisms**

# Feedbacks

## Kinetic proofreading

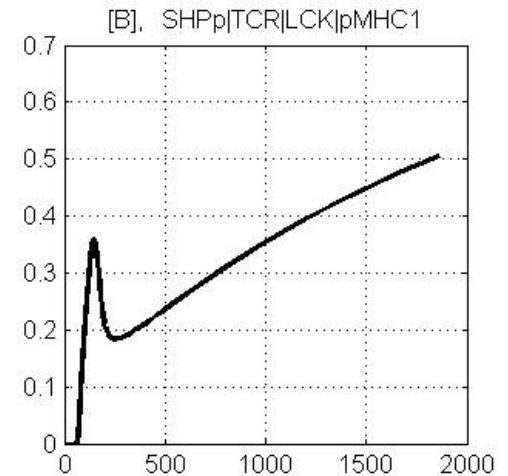
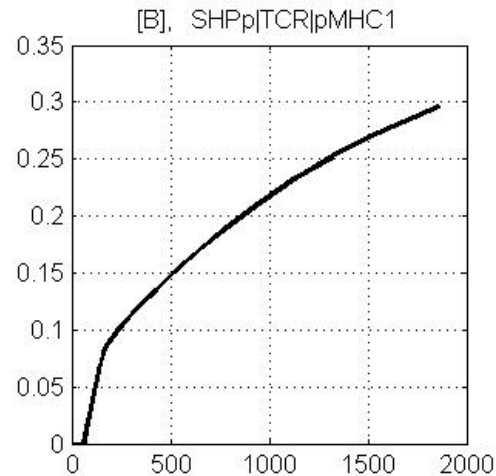
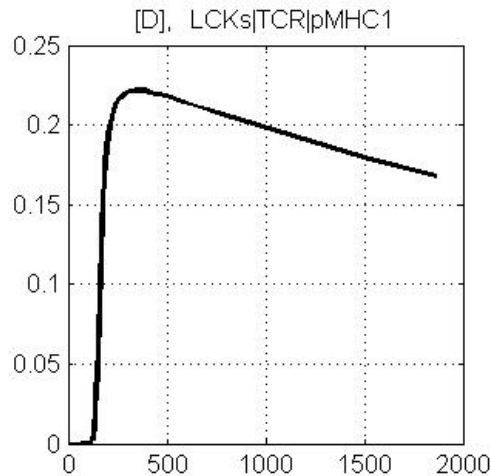
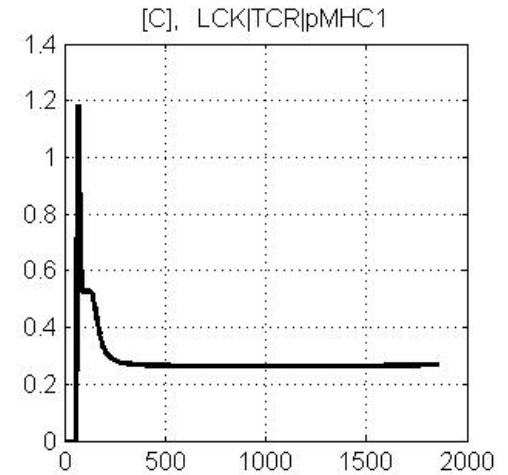
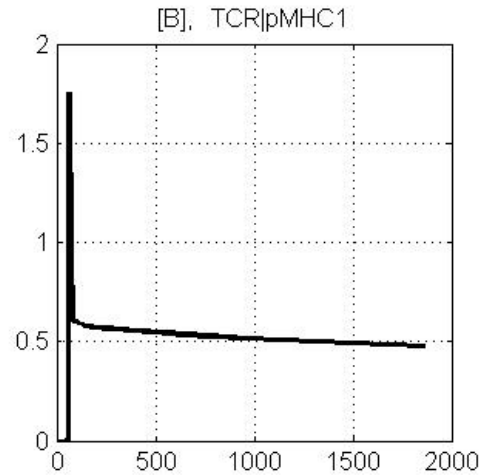
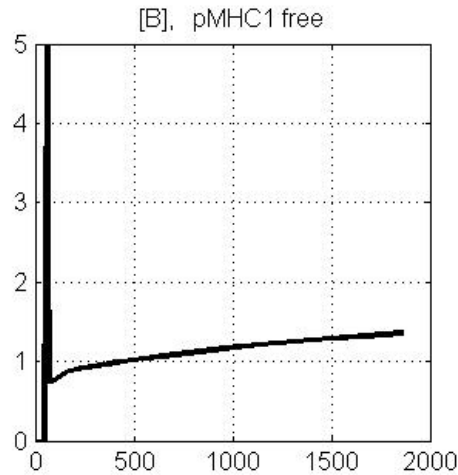




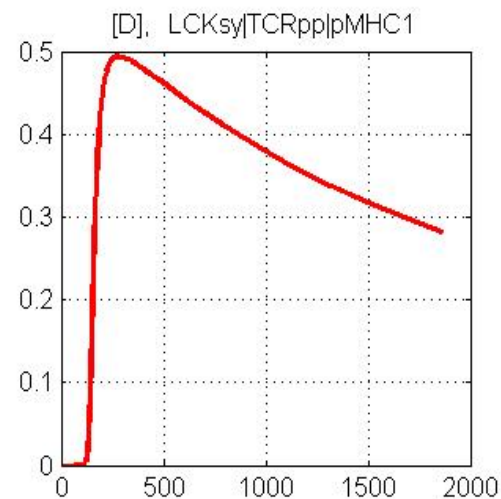
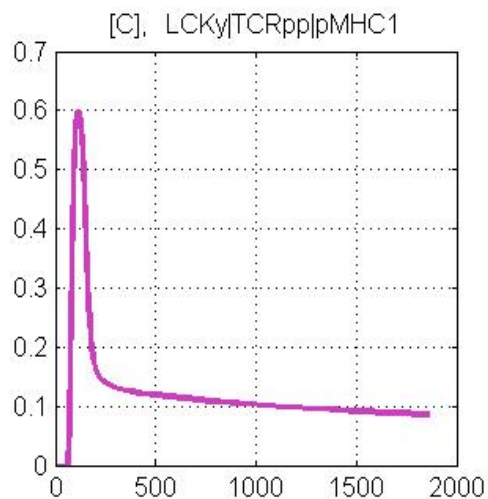
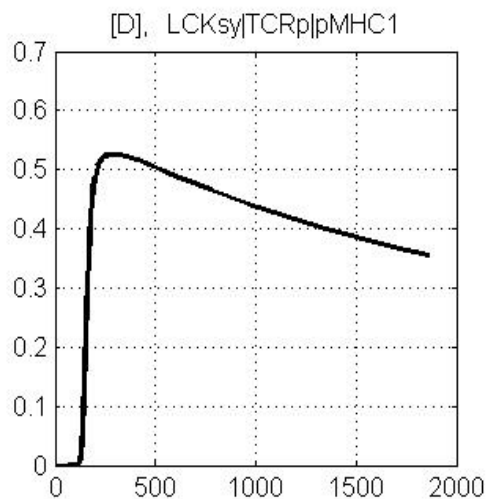
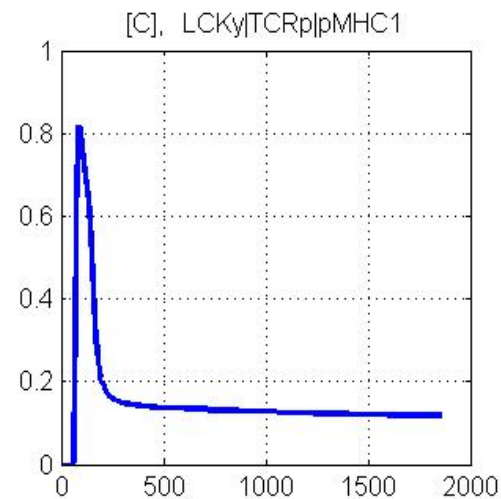
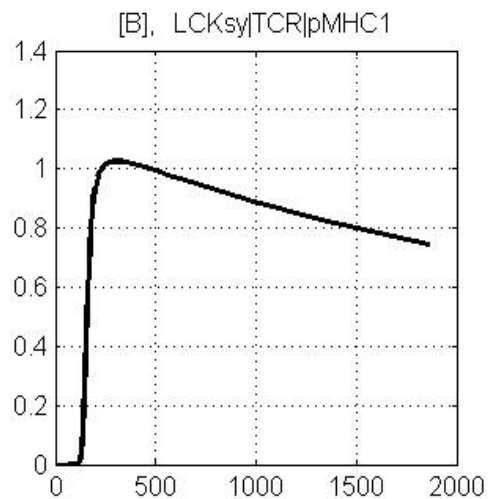
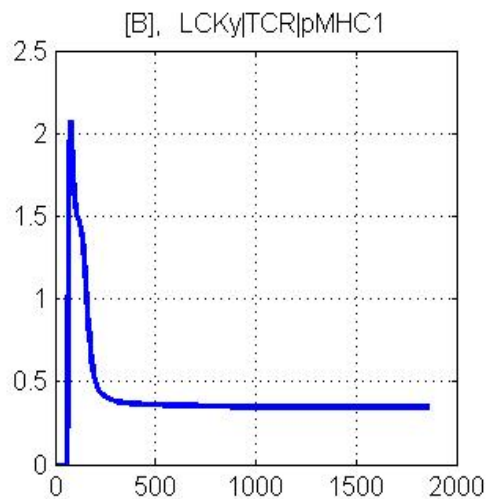
# Mathematical representation

1. Deterministic: 34 ordinary differential equations.
- 2.
- 3.
4. Stochastic: 87 reactions simulated using direct stochastic simulation algorithm SSN, Gillespie 1977.

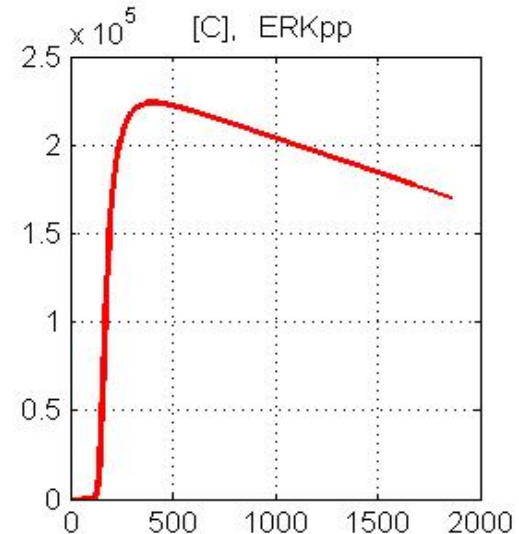
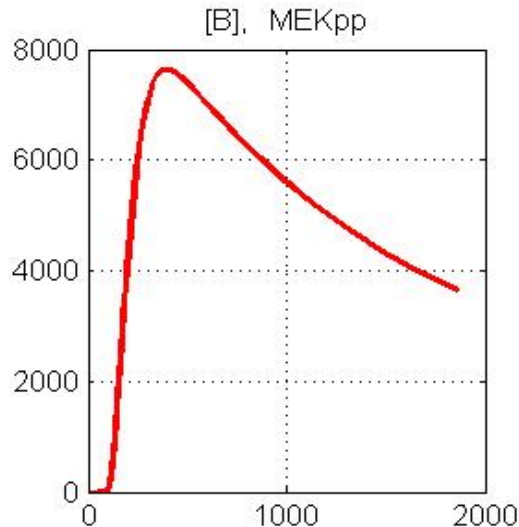
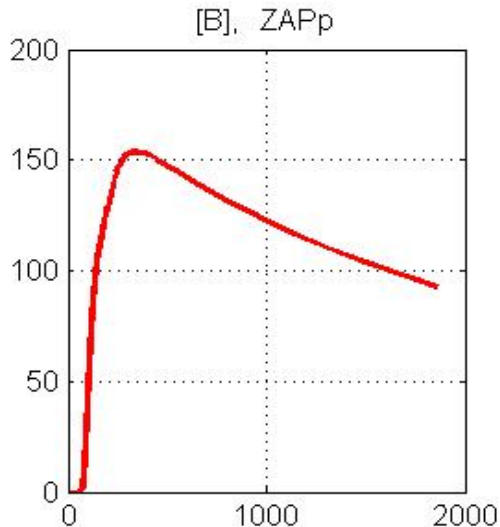
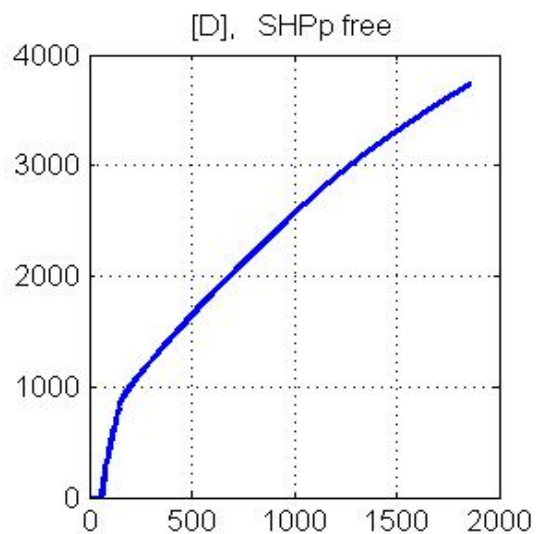
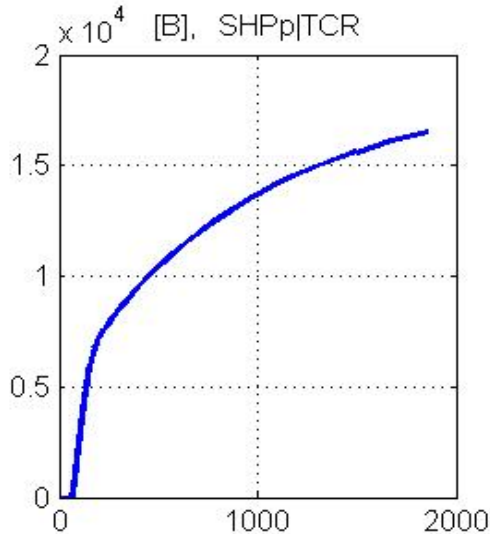
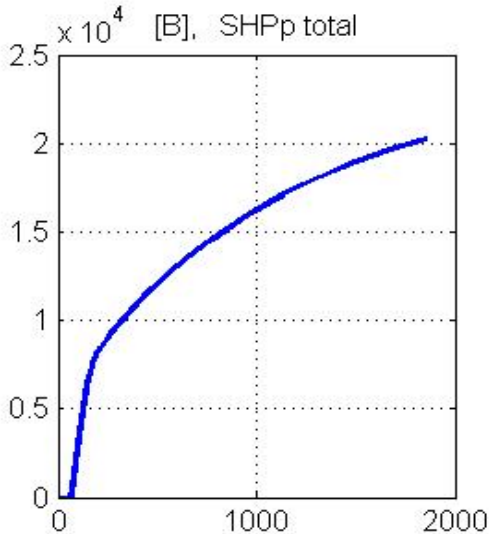
# Deterministic simulation (less than 1s)



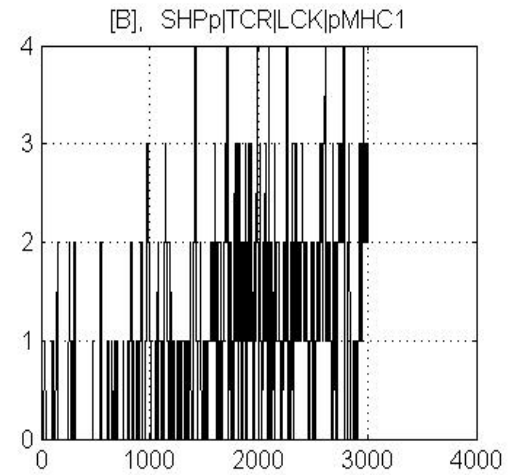
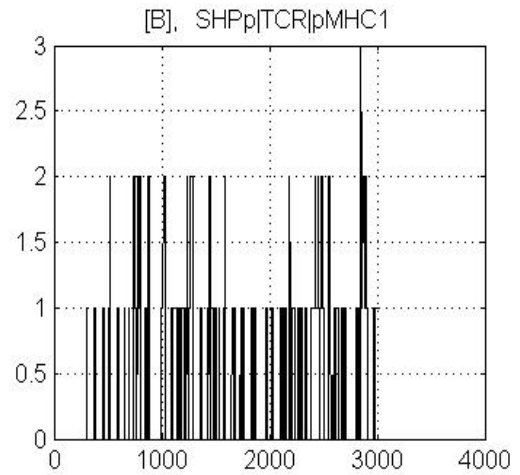
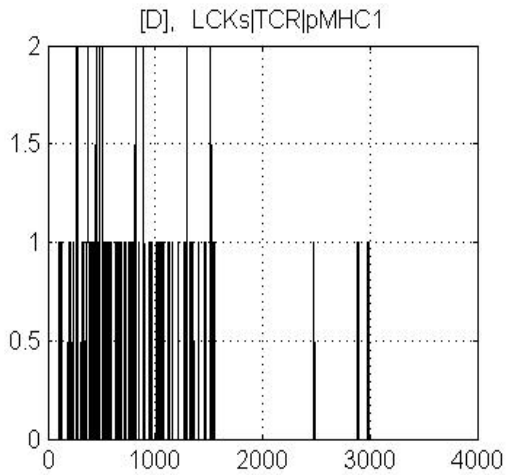
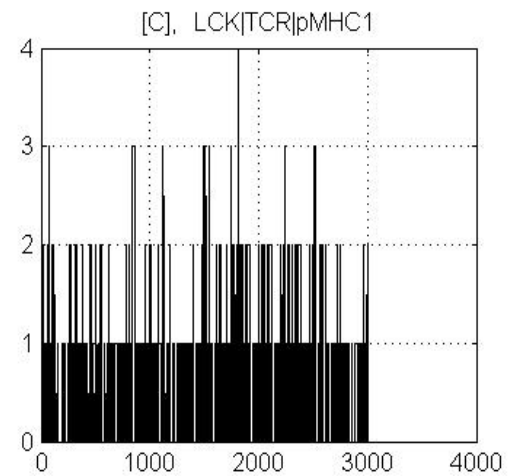
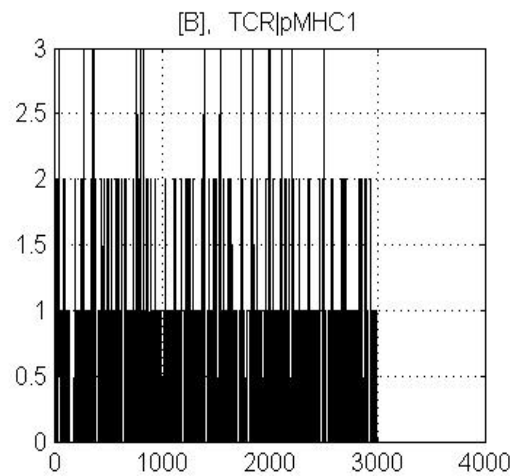
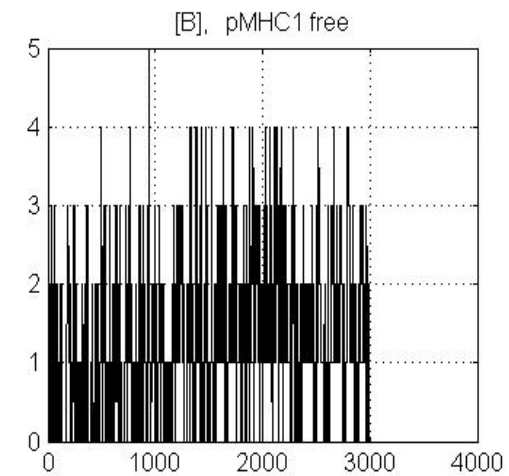
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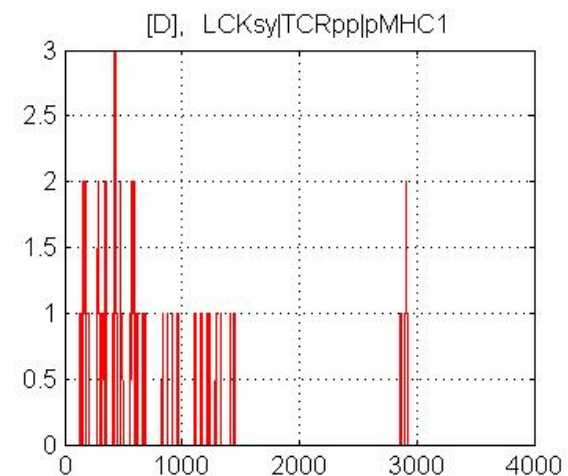
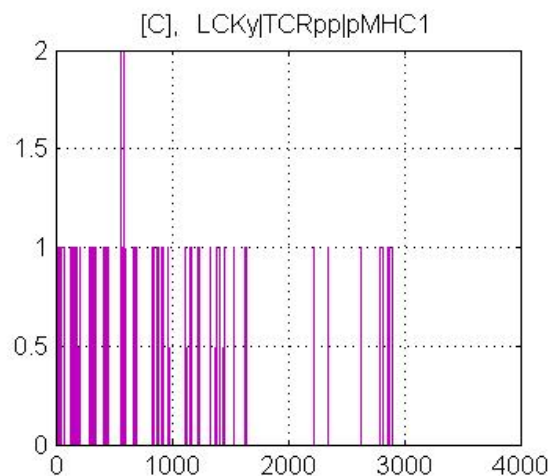
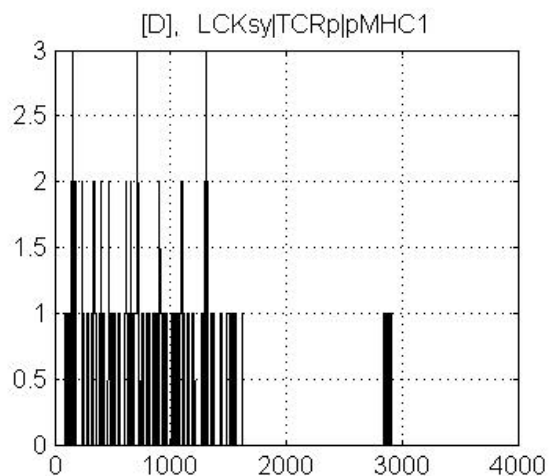
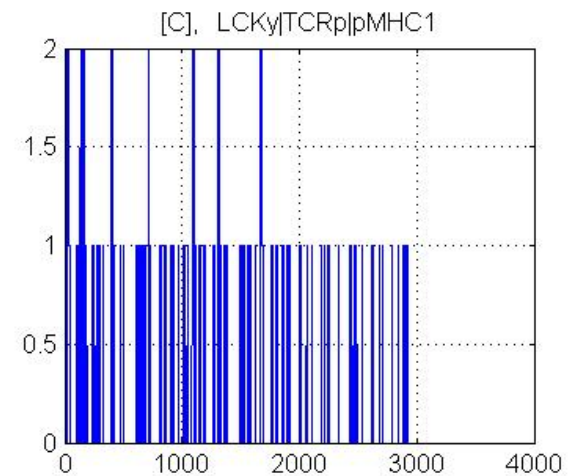
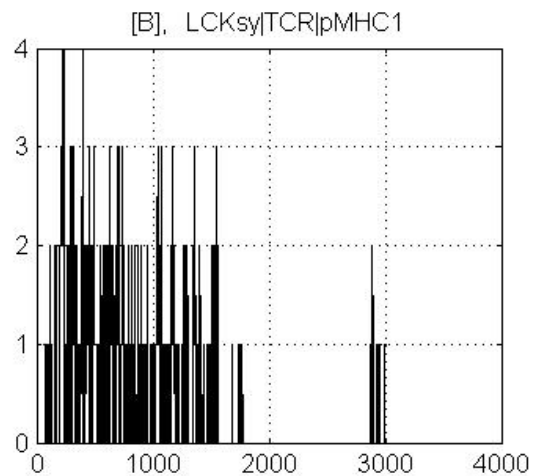
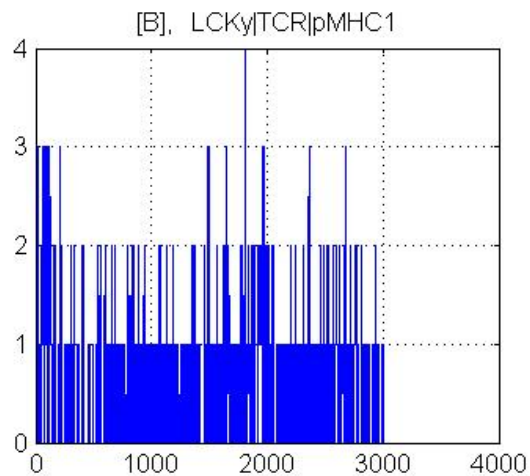
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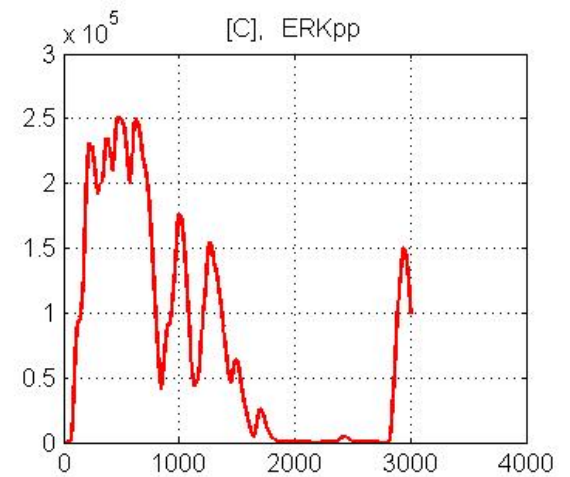
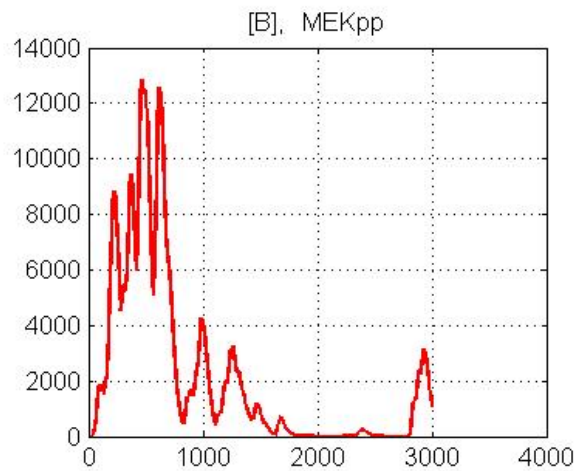
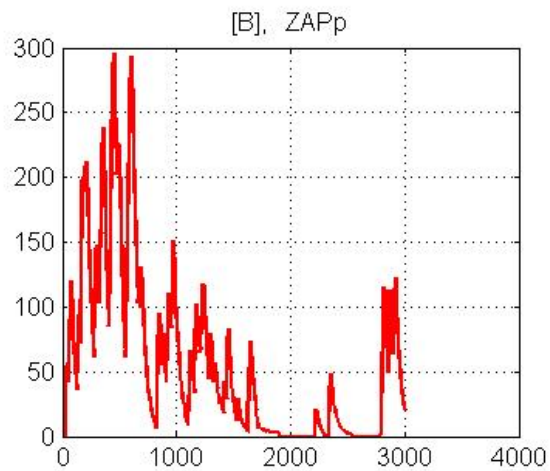
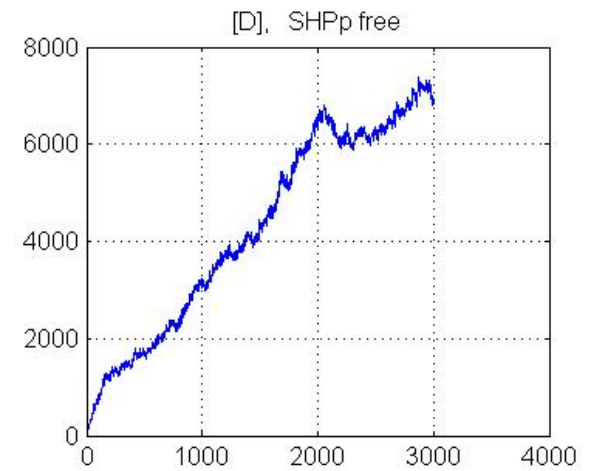
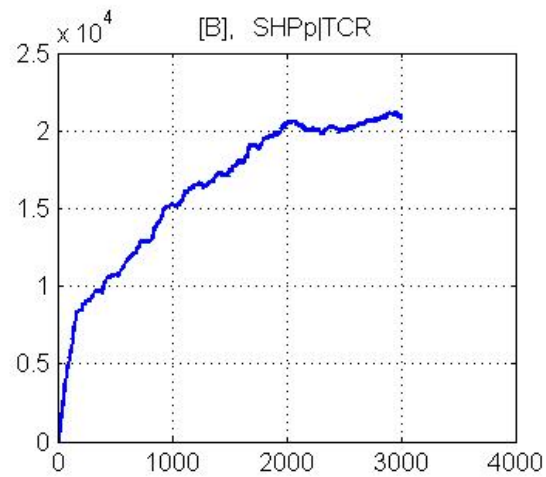
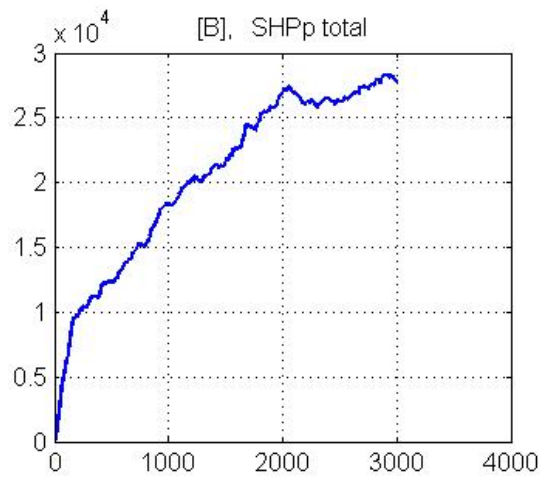
# Stochastic simulations, Gillespie algorithm (10min)



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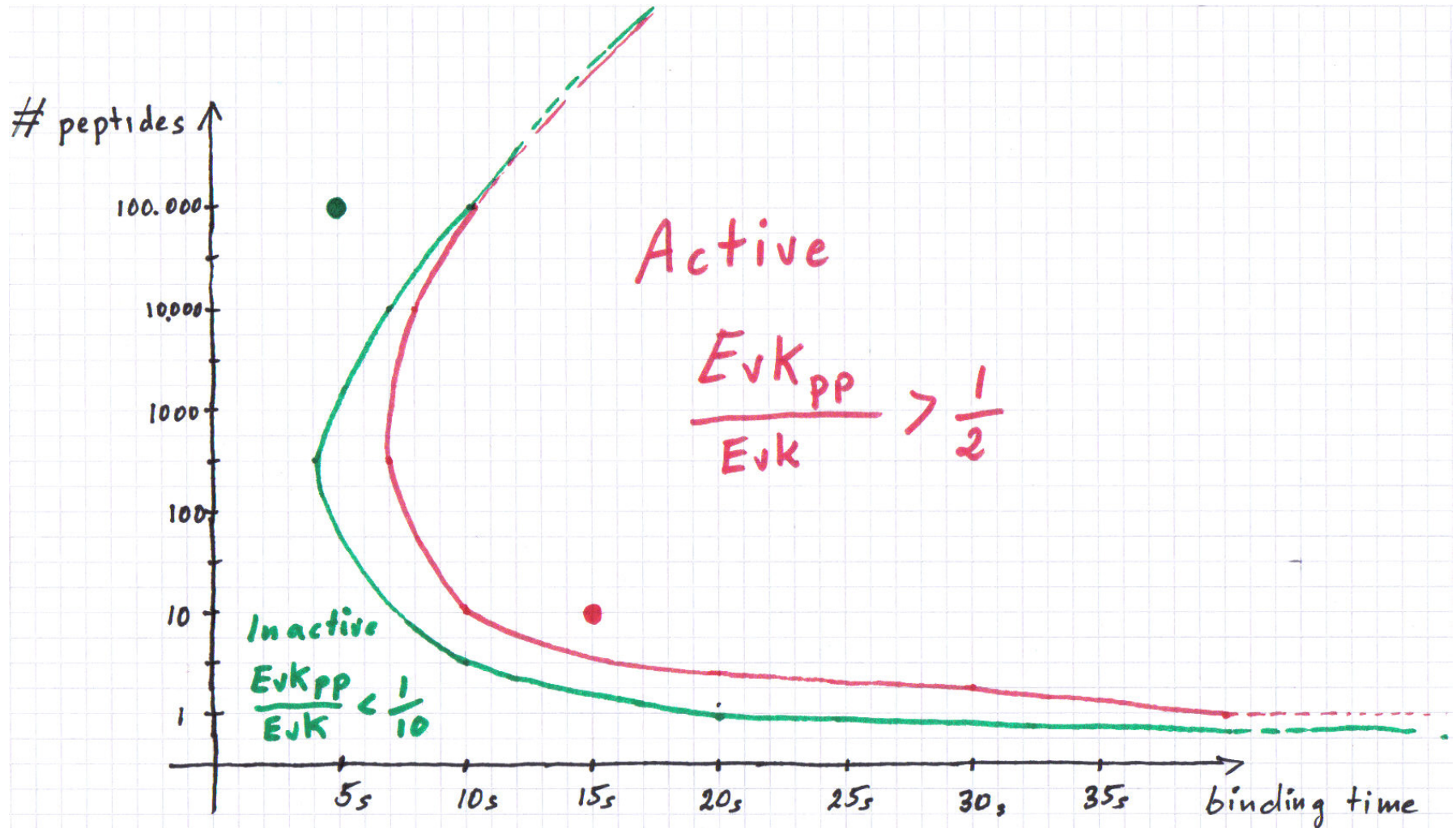


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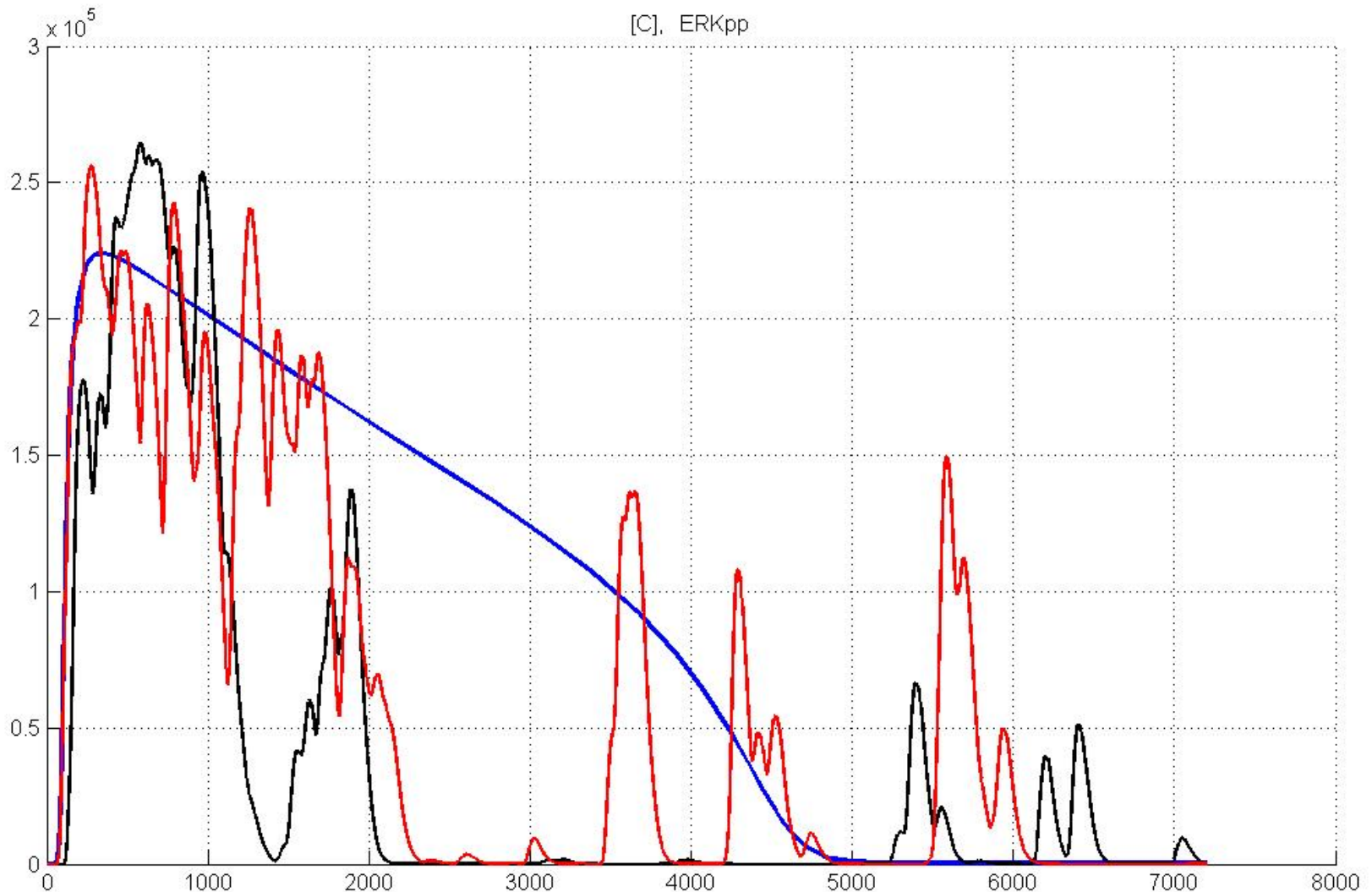
# Discrimination of endogenous and foreign peptides





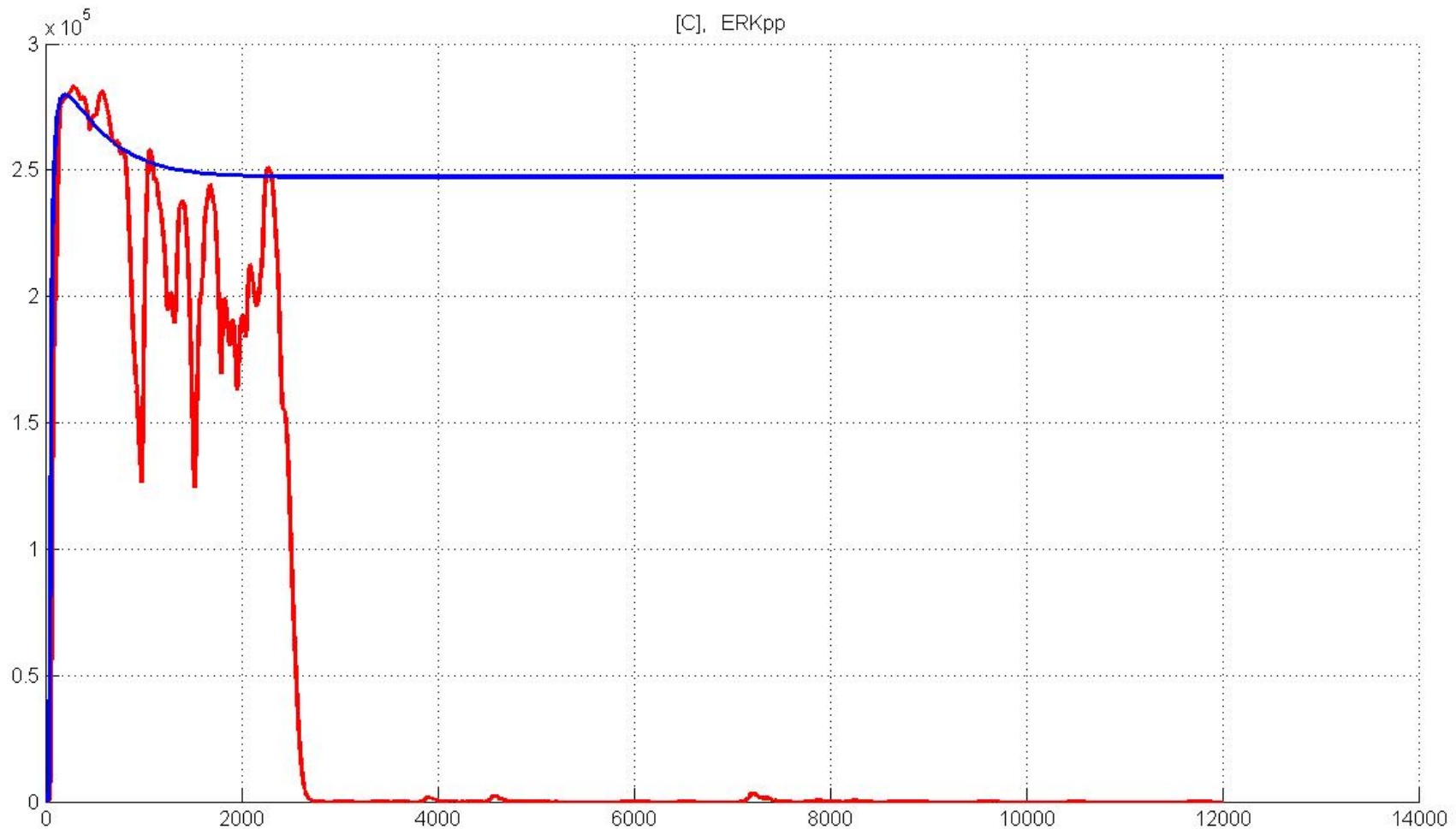
# Erk<sub>pp</sub> for stimulation with 5 foreign peptides

Deterministic (blue) versus Stochastic (red & black)



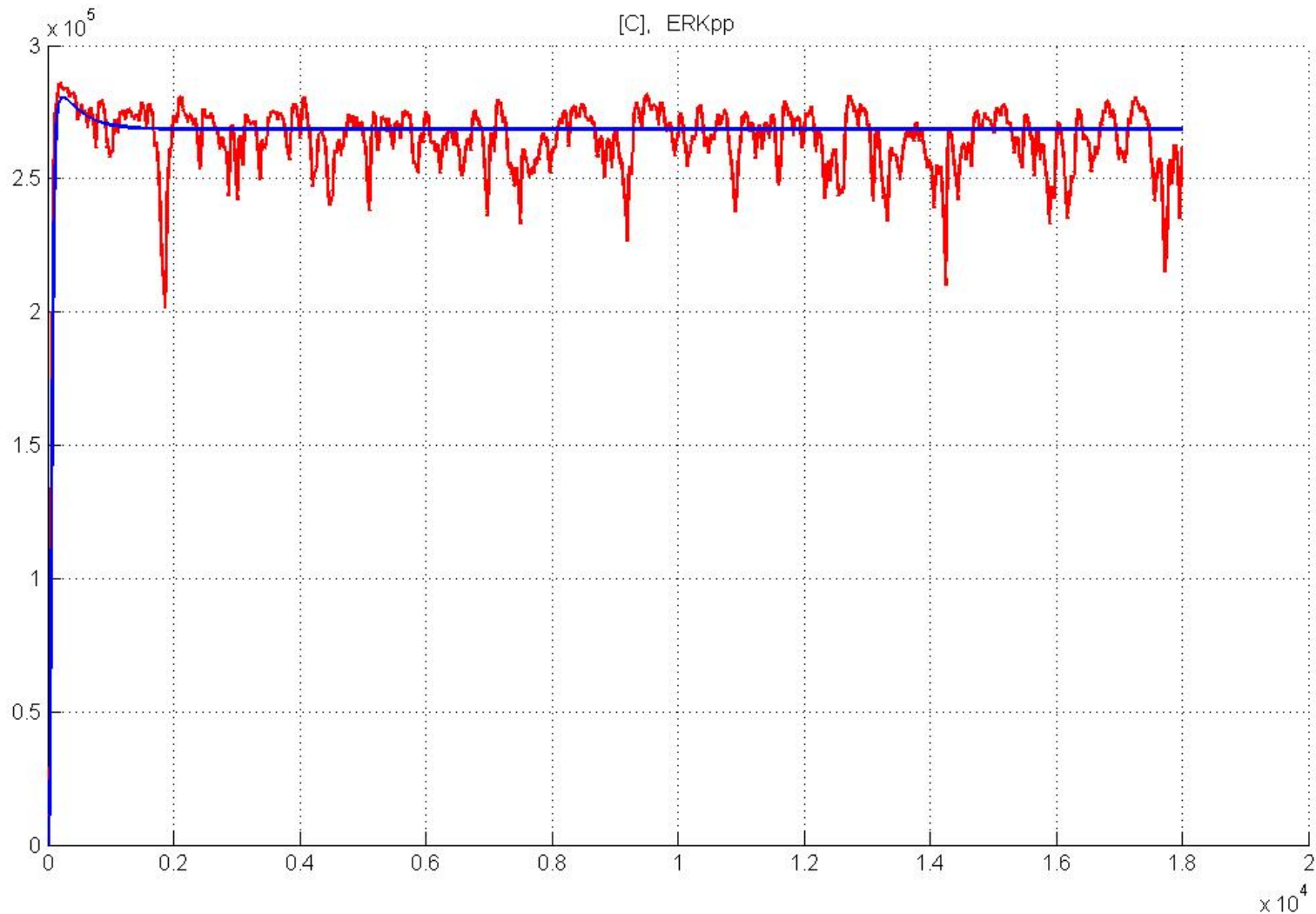
# Erk<sub>pp</sub> for stimulation with 100 foreign peptides

## Deterministic (blue) versus Stochastic (red)

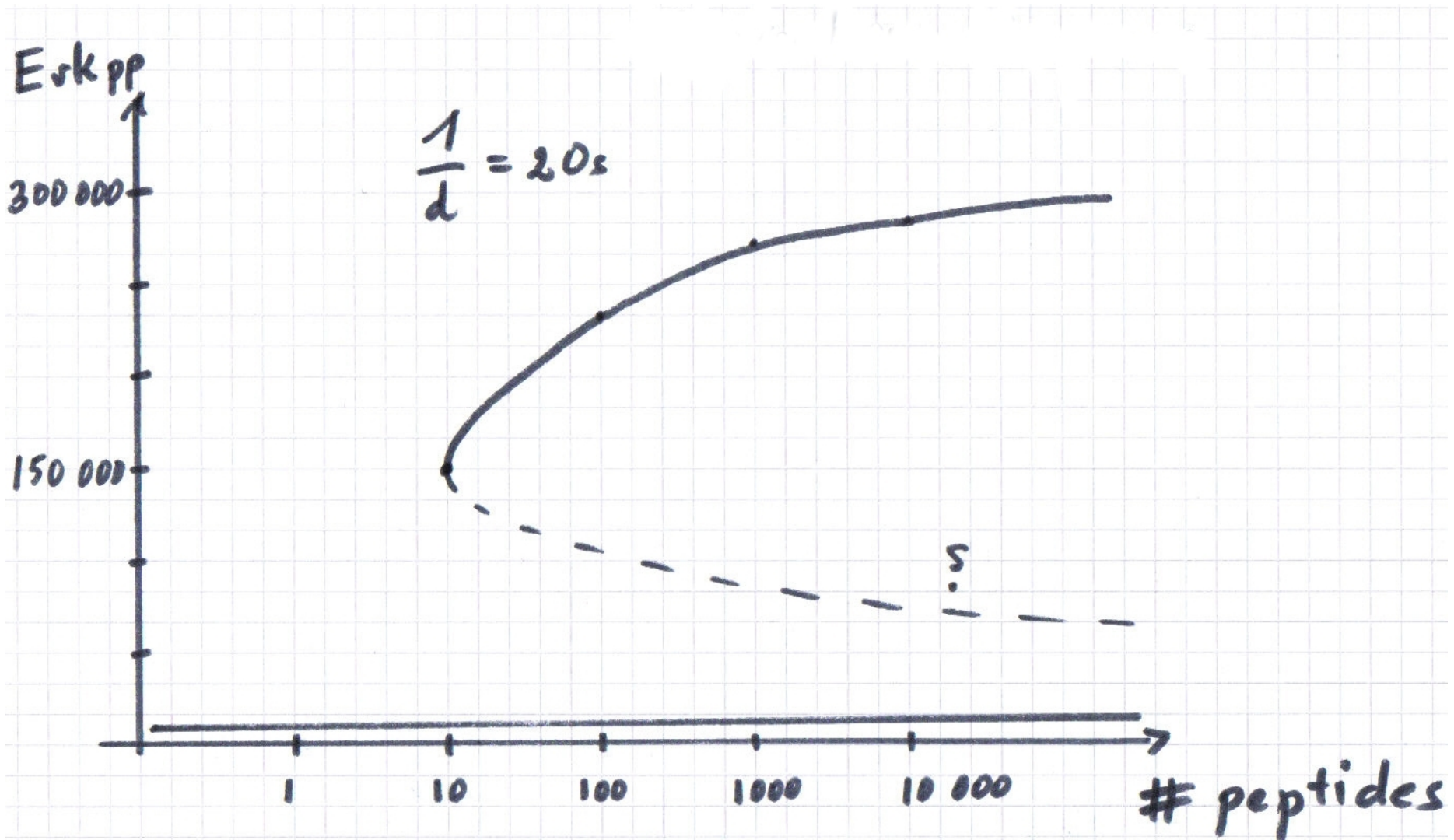


# Erk<sub>pp</sub> for stimulation with 500 foreign peptides

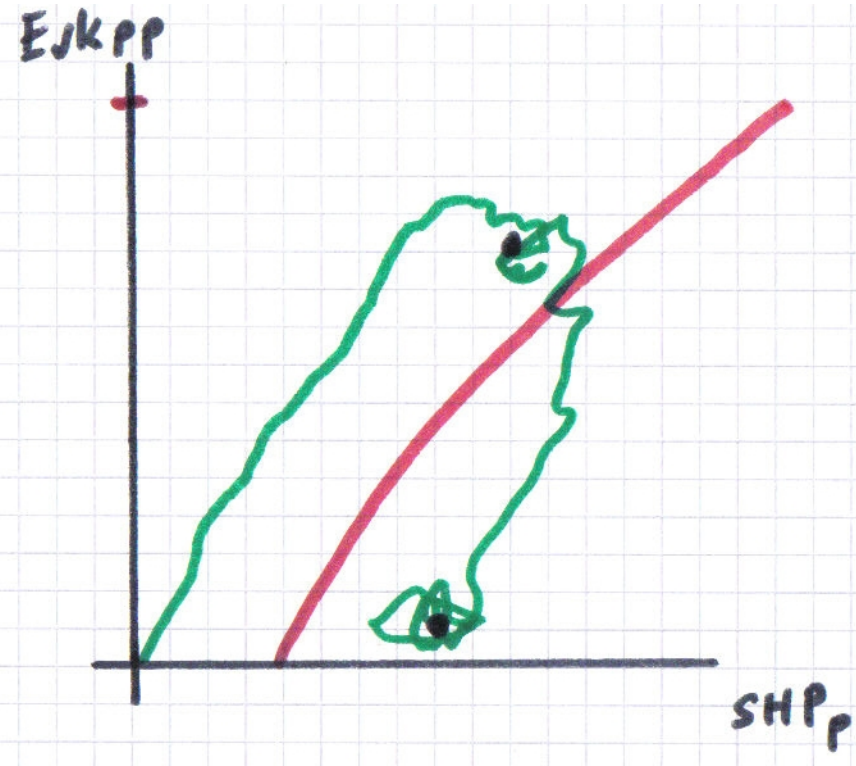
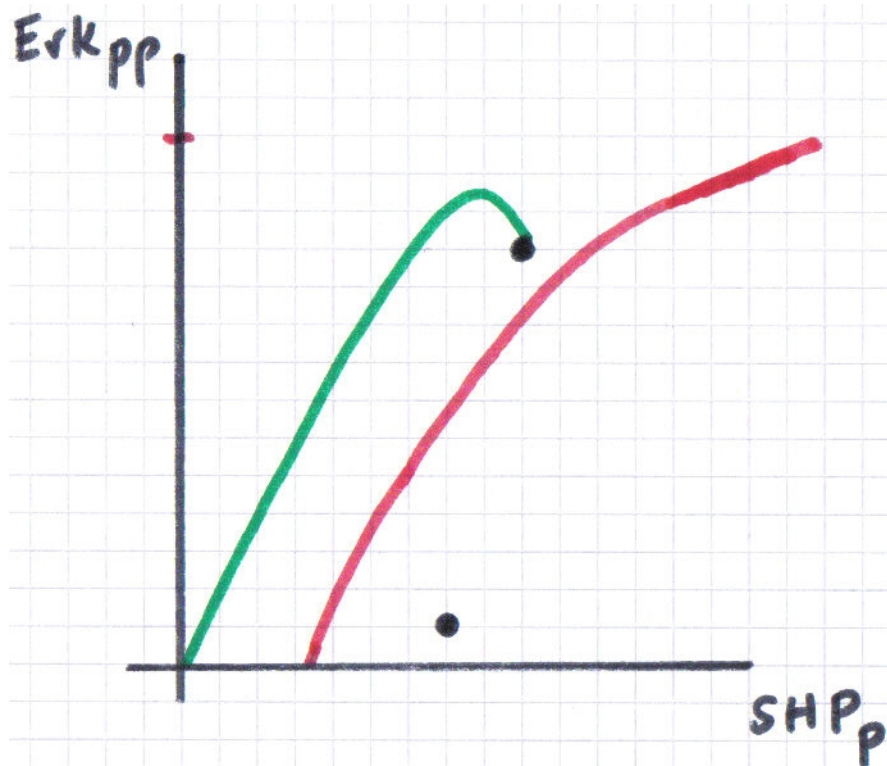
## Deterministic (blue) versus Stochastic (red)



# Bifurcation diagram



# Deterministic and stochastic trajectories



# Summary of the current model

Kinetic proofreading, positive and negative feedbacks

+

1) Bistability

2) Stochastic versus deterministic modeling