Modeling of *TRAIL*-Induced Receptor Clustering

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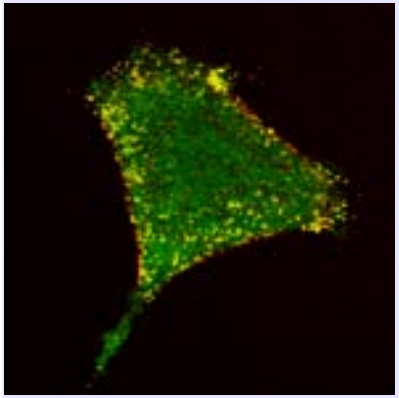
January, 12th

Single Cell Model

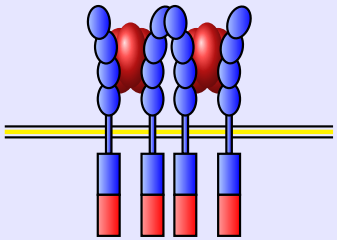
Modeling of cellular signaling

- to understand behavior of single cell
- to predict cell viability and growth rate in tissue during therapy
- to optimize therapy

Receptor clustering



- observed for:
  - many members of TNF family
  - medium and high ligand concentrations
- simplest signaling unit:
  2 ligands + 2 receptors



Outline

1. Modeling Framework
2. Receptor Clustering
3. Intracellular Signaling
4. Preliminary Results
5. Summary/Outlook

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General Modeling Framework

System

$$\dot{x} = S\, v(x, p), \quad x(0) = x_0$$

in which

- $x \in \mathbb{R}^n$ ... concentration vector
- $S \in \mathbb{R}^{n \times m}$ ... stoichiometric matrix
- $v \in \mathbb{R}^m$ ... reaction flux vector
- $p \in \mathbb{R}^q$ ... parameter vector

Questions

- Which concentrations are important?
- How can we model the system with a small number of parameters?

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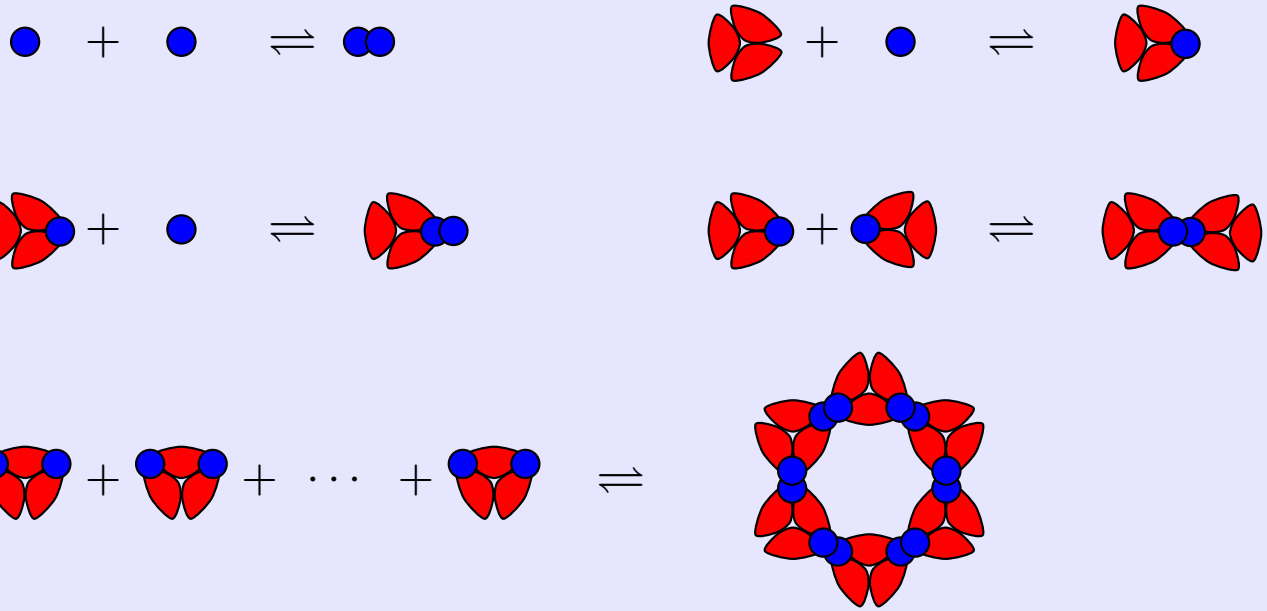
Ligand-Receptor Interaction

Elementary components

TRAIL trimer

receptor monomer (*TR*1, *TR*2)

Interactions



→ small number of interactions types

→ only number of stabilized receptor dimers of interest for signaling

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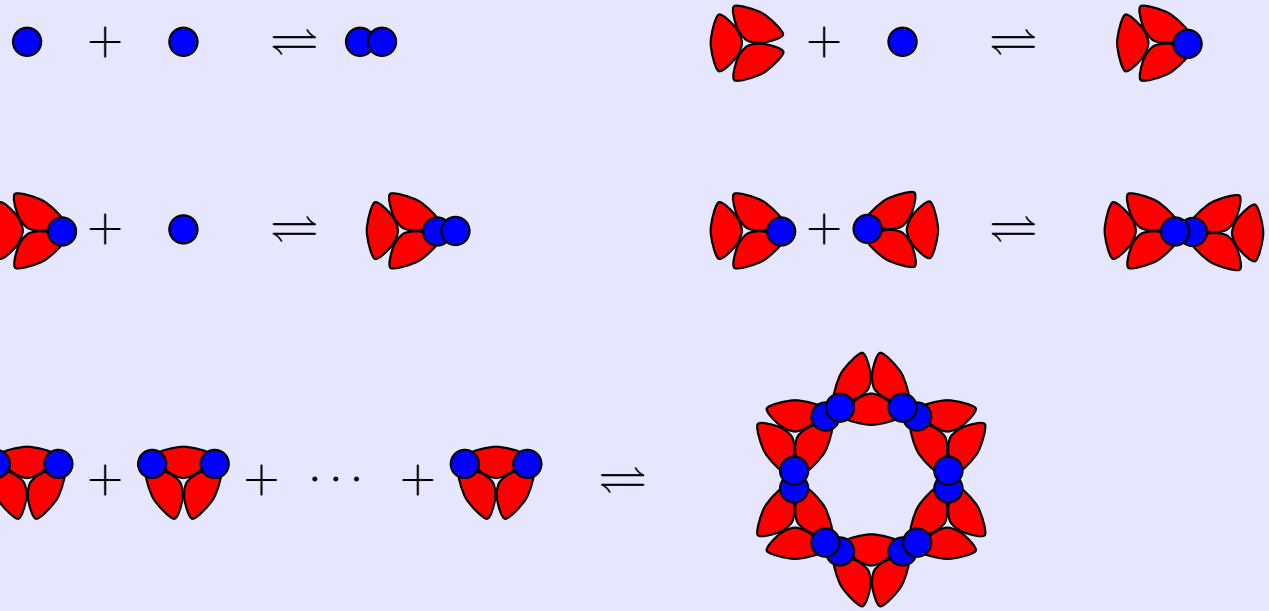

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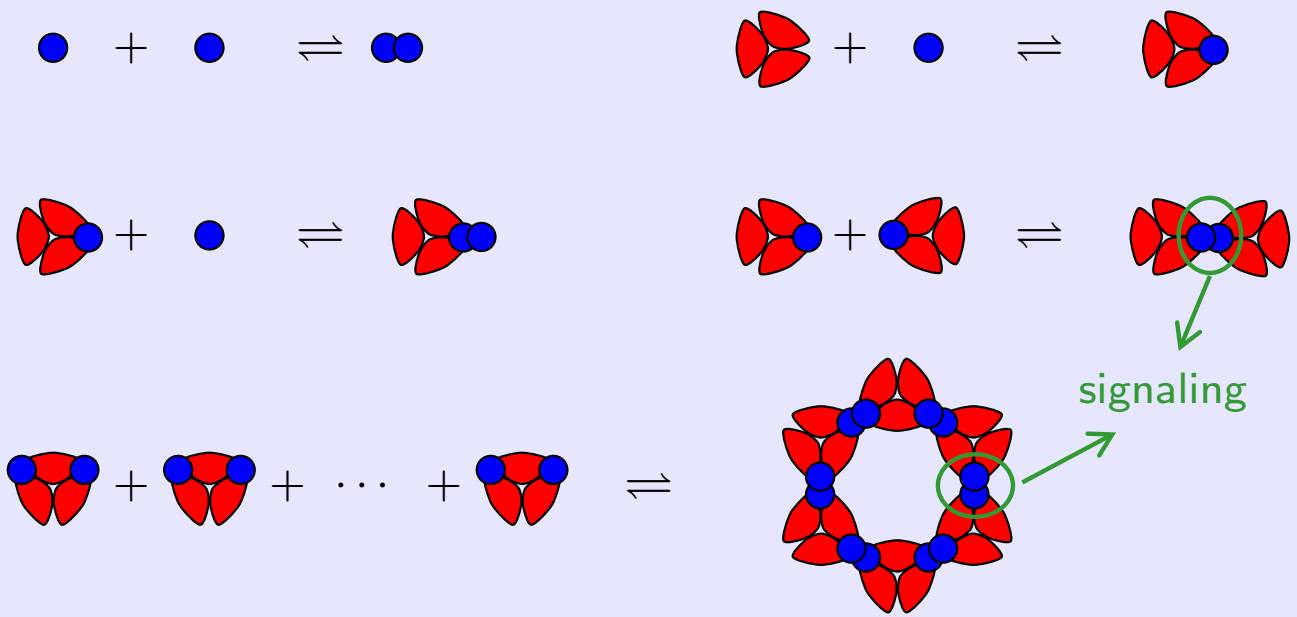

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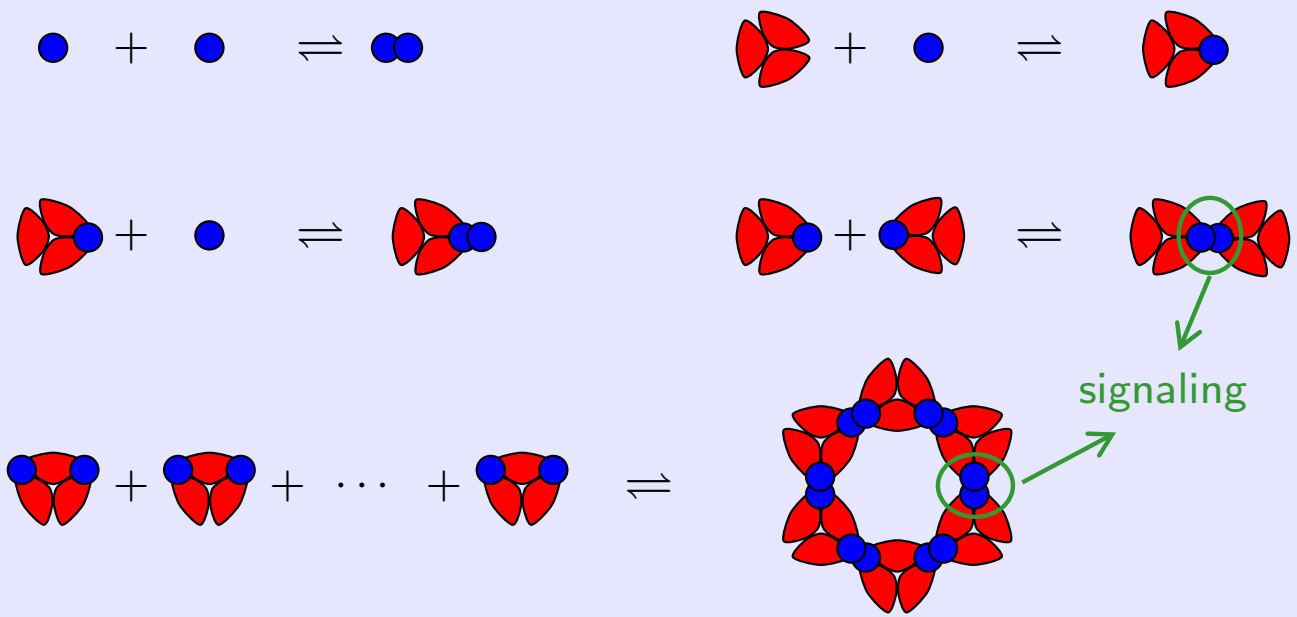

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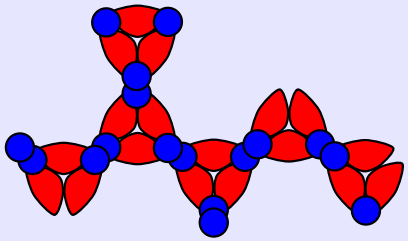
State Variables

Enormous number of different spatial structures



Two connected *TRAIL* trimers
$\Rightarrow$ more than 20 different spatial structures

Considered states

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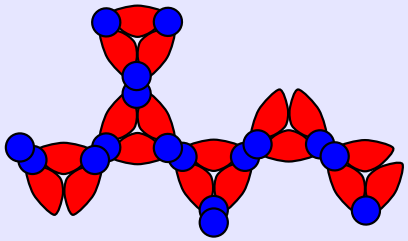

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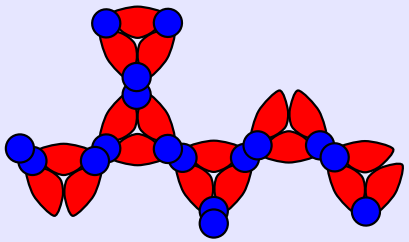

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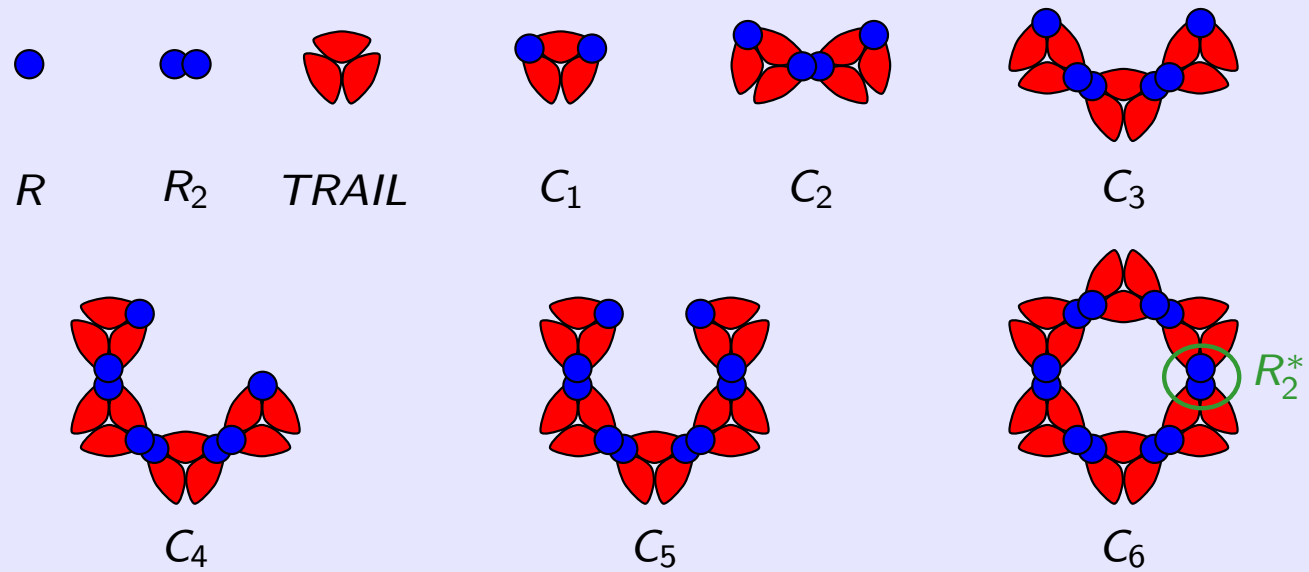

Model of Receptor Clustering

Reaction network

$$
\begin{aligned}
R + R &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2 \\
TRAIL + R_2 &\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C_1 \\
C_1 + C_1 &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \\
C_1 + C_2 &\underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} C_3 \\
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\end{aligned}
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Reaction rate constants

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\begin{aligned}
k_5 &= k_{5,0} \exp\left(-\frac{\Delta H_5}{RT}\right) \\
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Interrelation of the parameters

- $\Delta H_5 = \Delta H_{RR} = \Delta H_6$
- $\Delta E_5 = \Delta E_{RR} = \Delta E_6$
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$\Rightarrow$ 9 species, 10 parameter

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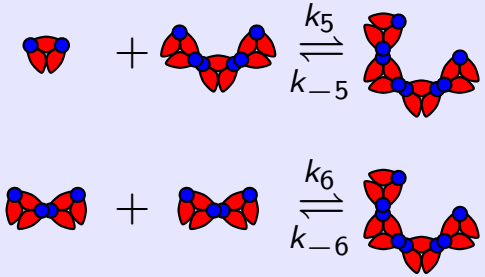

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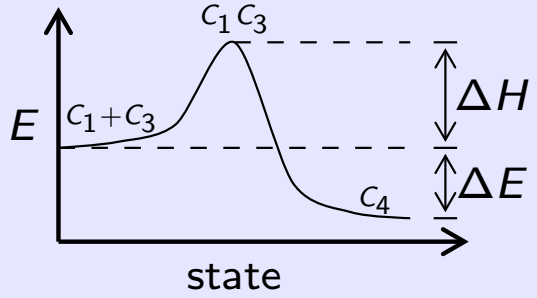

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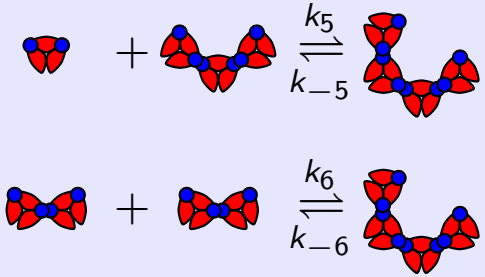

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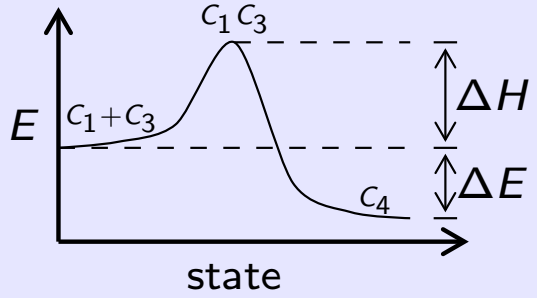

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Model Reduction

Applied simplifications:

- small number of considered *TRAIL*-receptor complexes
- homogene receptor distribution on membrane
- approximation of reaction rates

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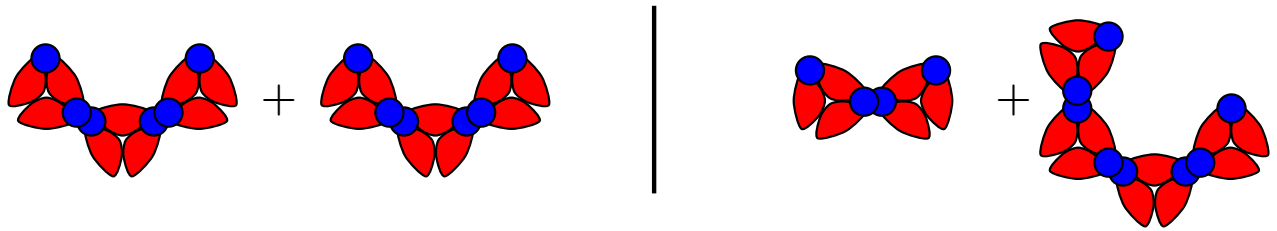

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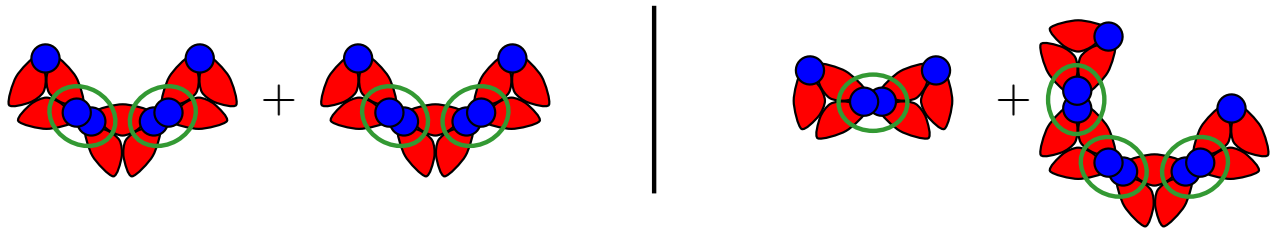

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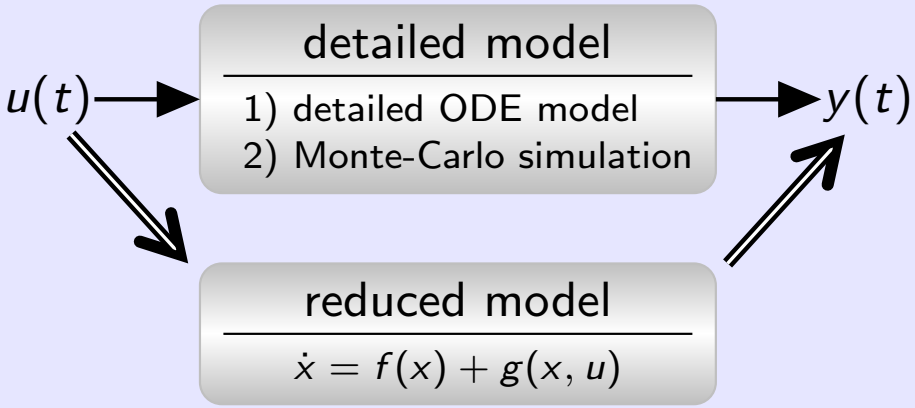
Simulation-based model reduction



- Input: $u(t) = [TRAIL](t)$
- Output: $y(t) = ([R_2^*](t), \ldots)$

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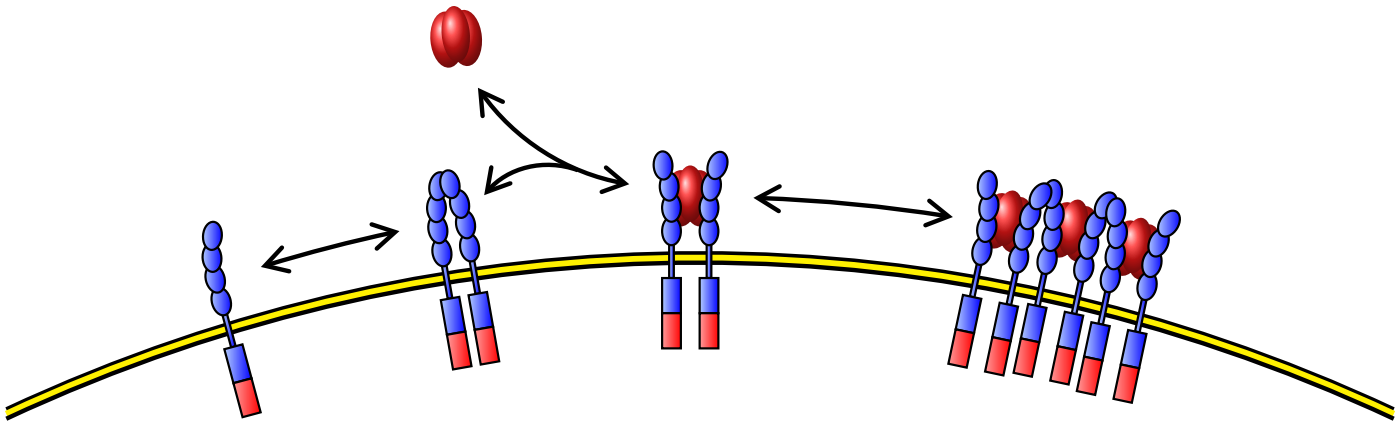
Receptor Production, Degradation and Internalisation



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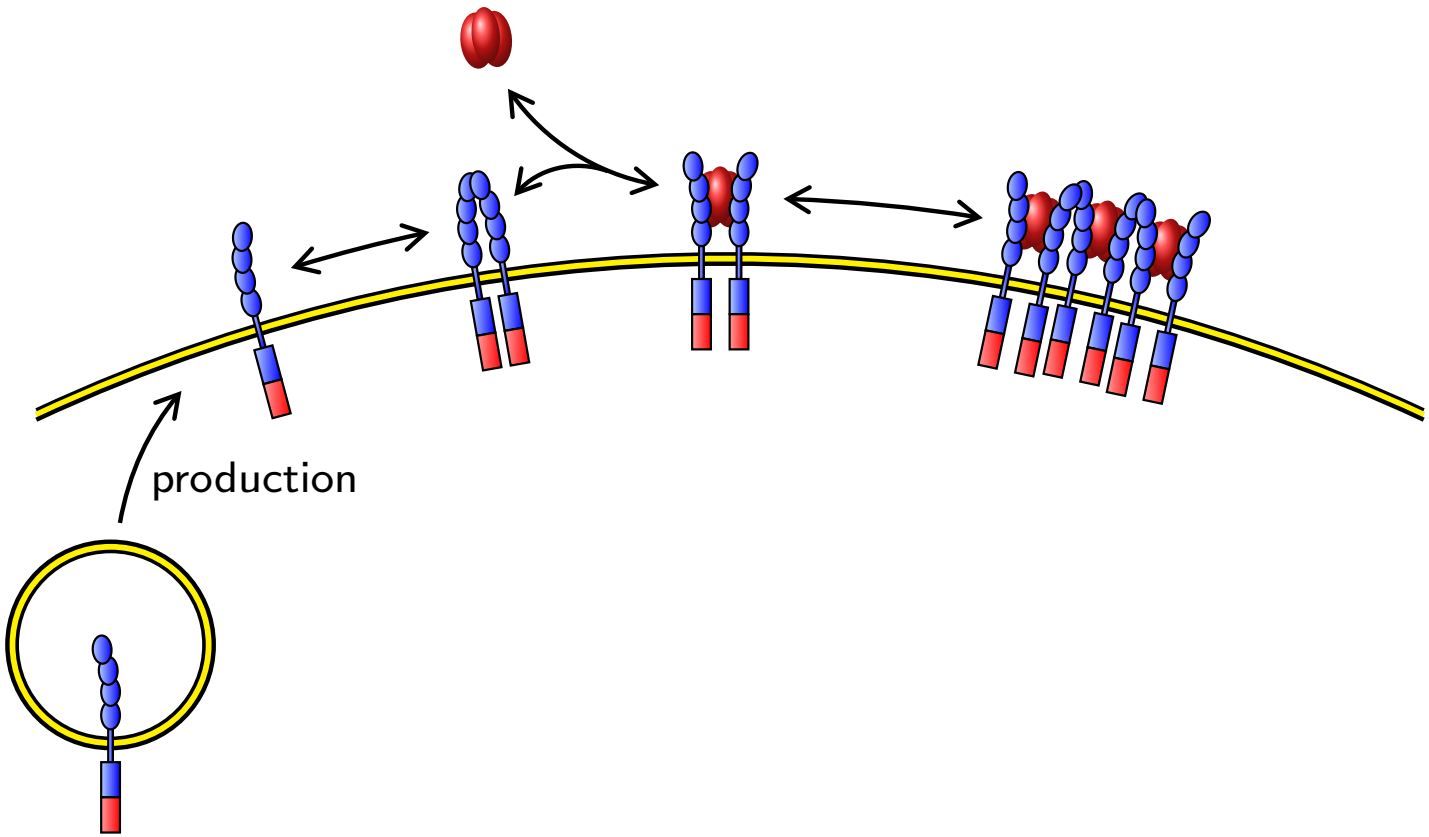
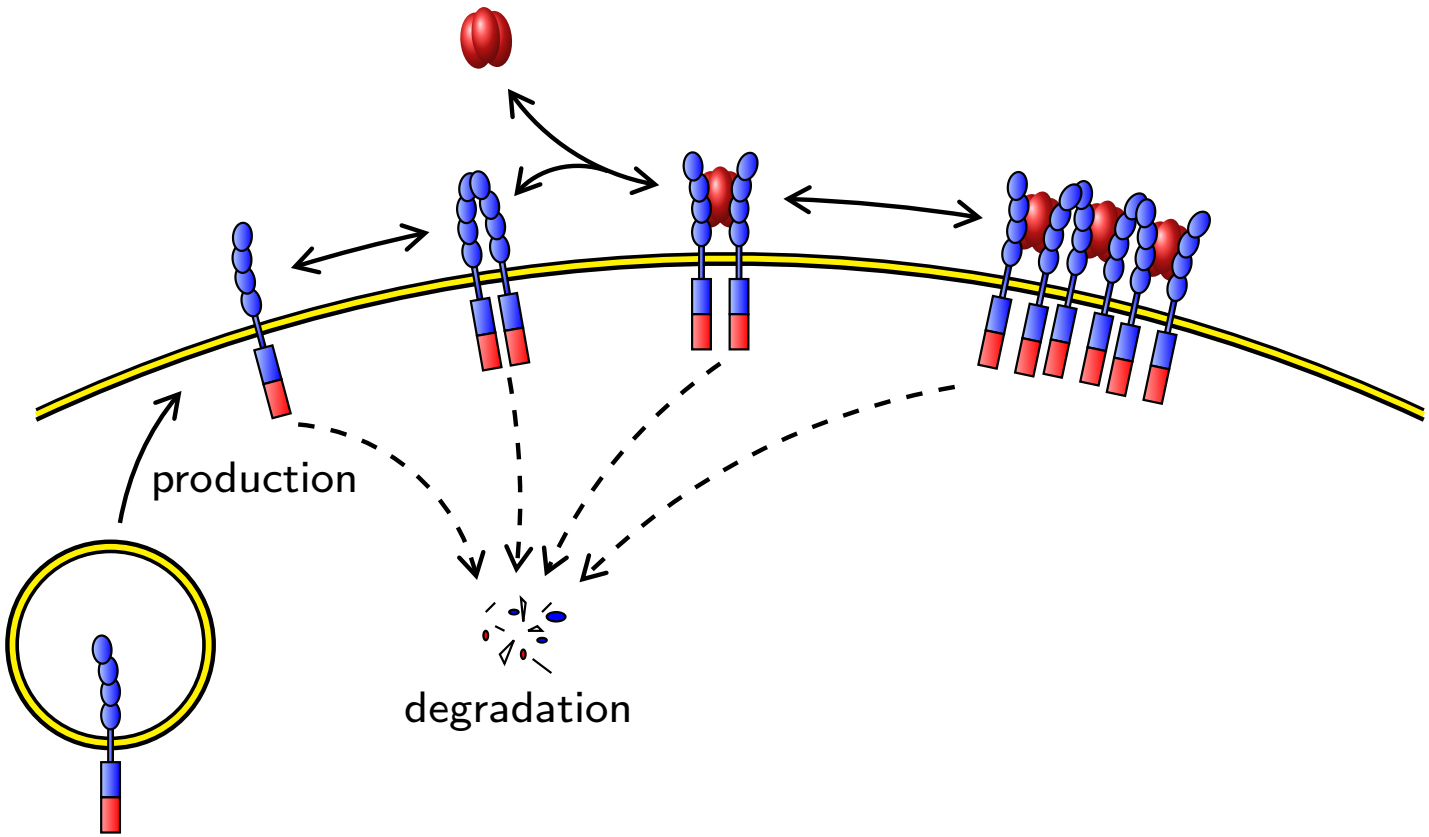


Production

$$0 \xrightarrow{k_{12}} R$$

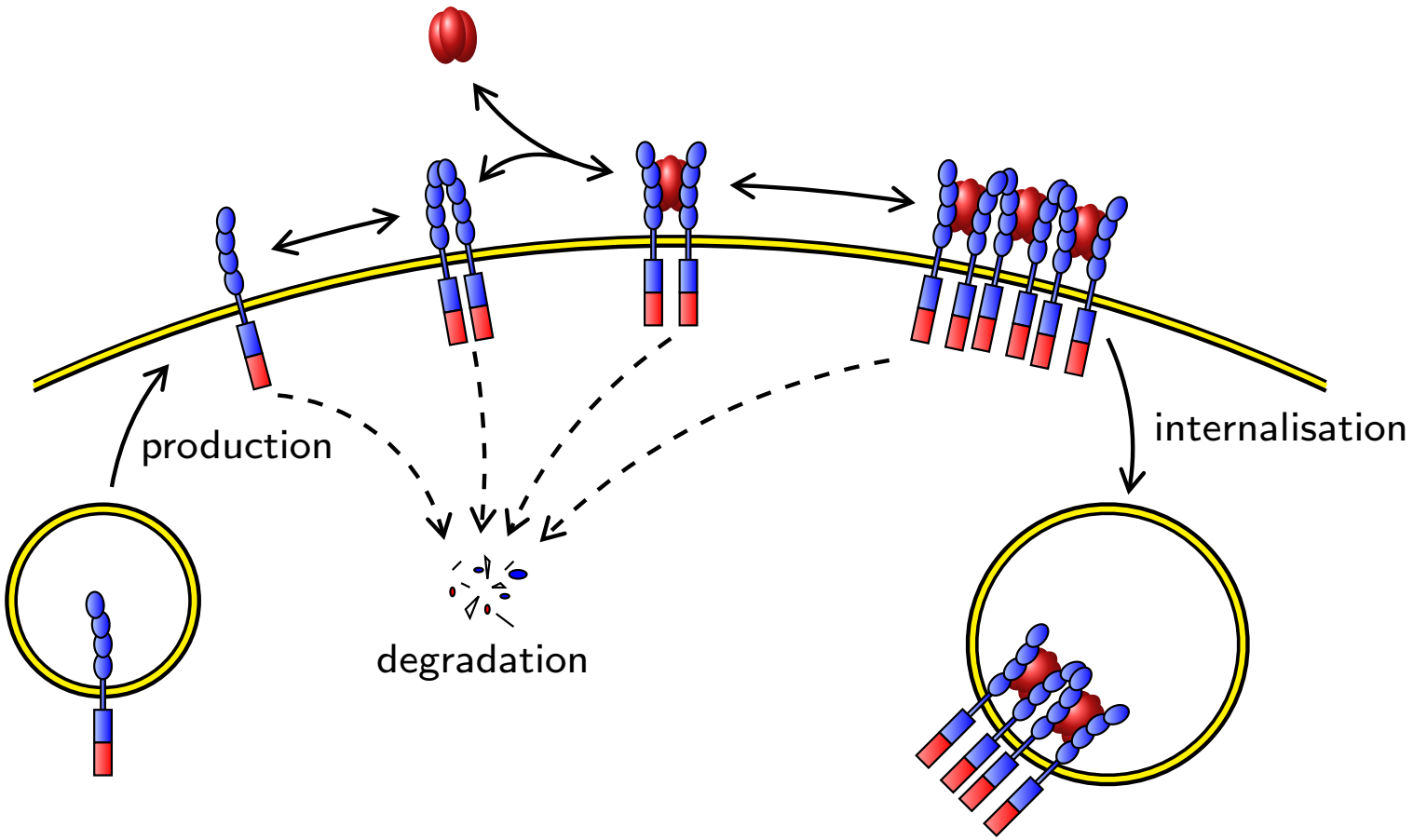
Receptor Production, Degradation and Internalisation



Degradation

$$R \xrightarrow{k_{-12}} 0 \qquad R_2 \xrightarrow{k_{-12}} 0 \qquad C_i \xrightarrow{k_{-12}} 0 \text{ with } i = \{1, \ldots, 6\}$$

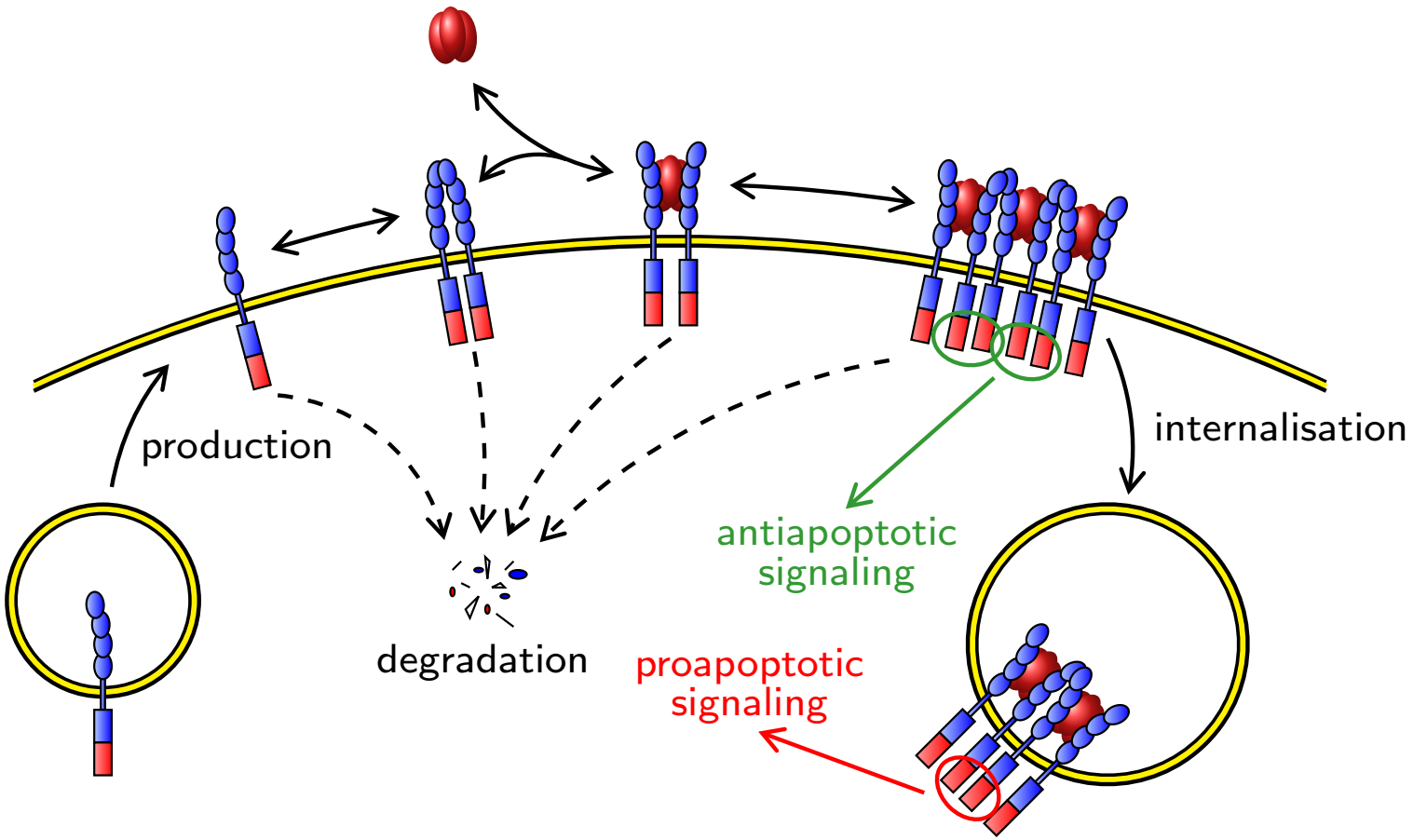
Receptor Production, Degradation and Internalisation



Internalisation (considering the dead time)

$$C_i \xrightarrow{k_{13}} (i-1) \cdot R_2^* \text{ with } i = \{1, \ldots, 5\} \qquad C_6 \xrightarrow{k_{13}} 6 \cdot R_2^*$$

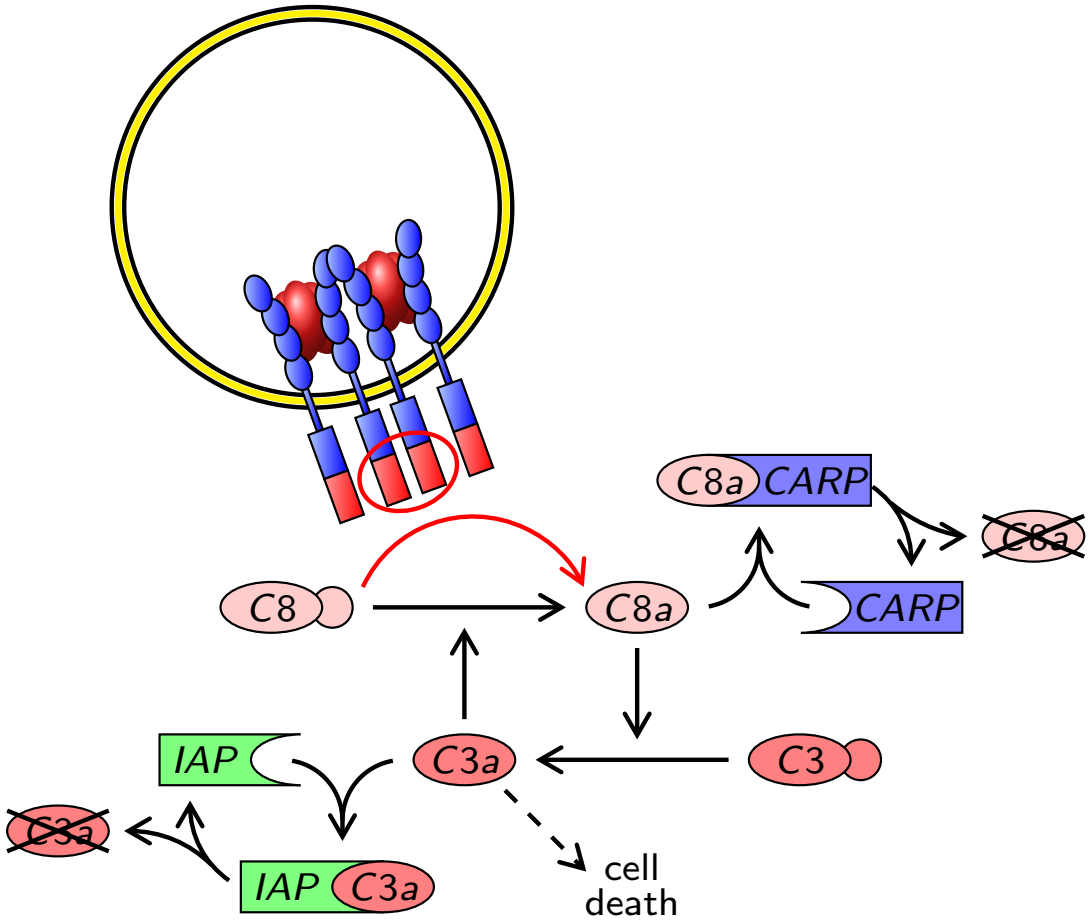
Receptor Production, Degradation and Internalisation



Adaptor protein binding

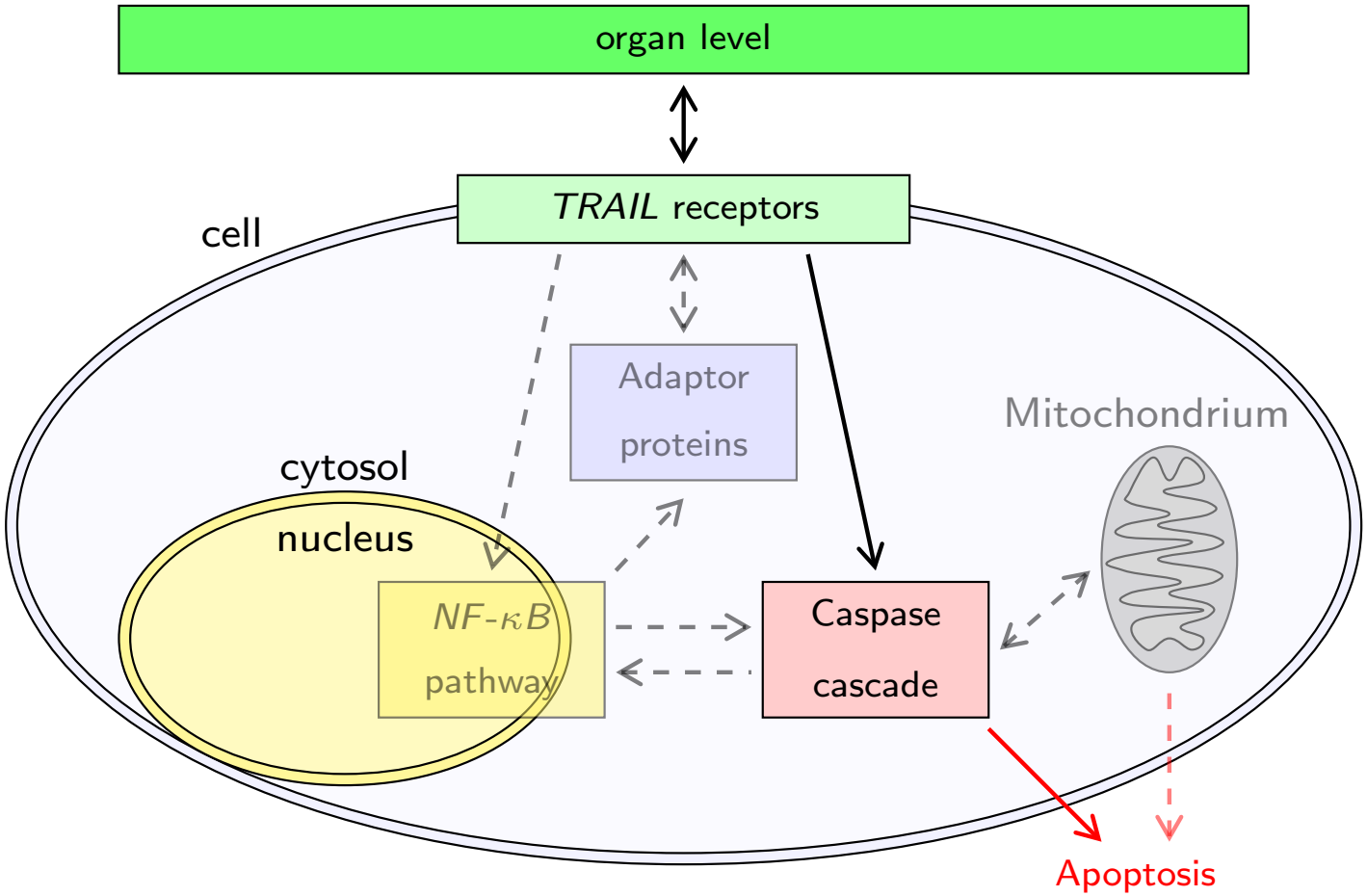
relatively fast $\Rightarrow$ neglected so far!

Caspase-Cascade Activation



→ Not only internalised receptor pairs can catalyse Caspase 8 activation!

Overview over Intracellular Signaling



- How do *TRAIL*-receptors activate *NF-κB*?
- How important is the mitochondrial pathway?

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Differences: *TRAIL*-receptor 1 and *TRAIL*-receptor 2

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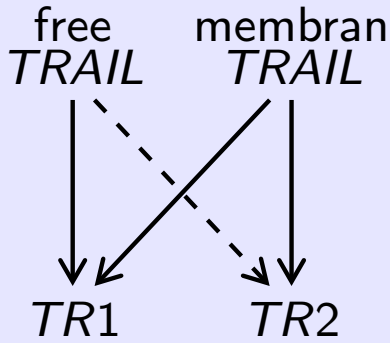
- *TR*1: apoptotic signal for free and membran *TRAIL*
- *TR*2: apoptotic signal only for membran *TRAIL*



Hypothesis

Different signaling strength is due to differences in the receptor-receptor interaction which leads to altered clustering properties.

Can our model reproduce this?

Yes! Comparatively minor changes in three of the ten parameter which describe the clustering dynamics can lead to a dramatic change in the outcome.

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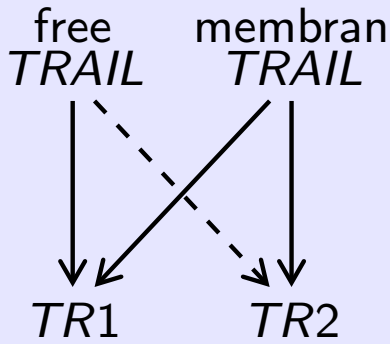

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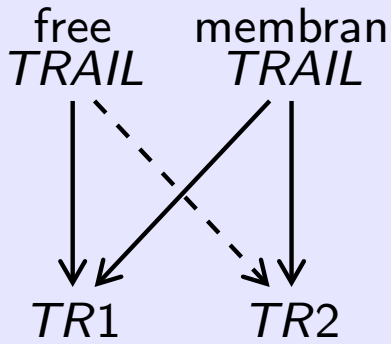

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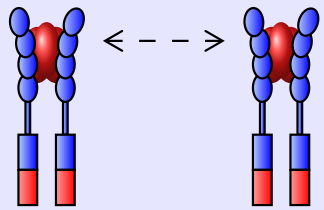

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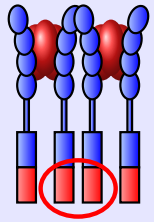
Summary

Q1: Which concentrations are important?

A1: For the intracellular signaling mainly the concentration of stable receptor-receptor complexes.

Q2: How can we model the system with a small number of parameters?

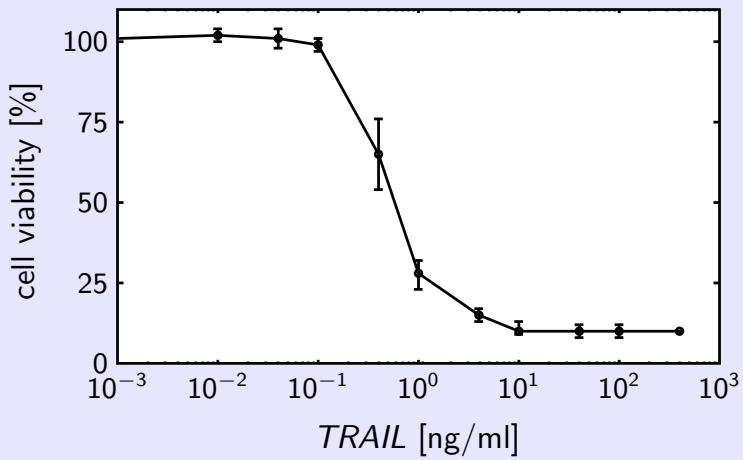
A2: By considering the relation between the different types of reactions.



$\Rightarrow$ preliminary model of receptor clustering and intracellular network which reproduces the qualitative data!

Outlook (1): Single Cell Model

- *NF-κB* activation
- mitochondrial pathway
- cell cycle
- parameter estimation
  (single cell and cell population)
- model validation
- experimental design
- model reduction



Cooperations

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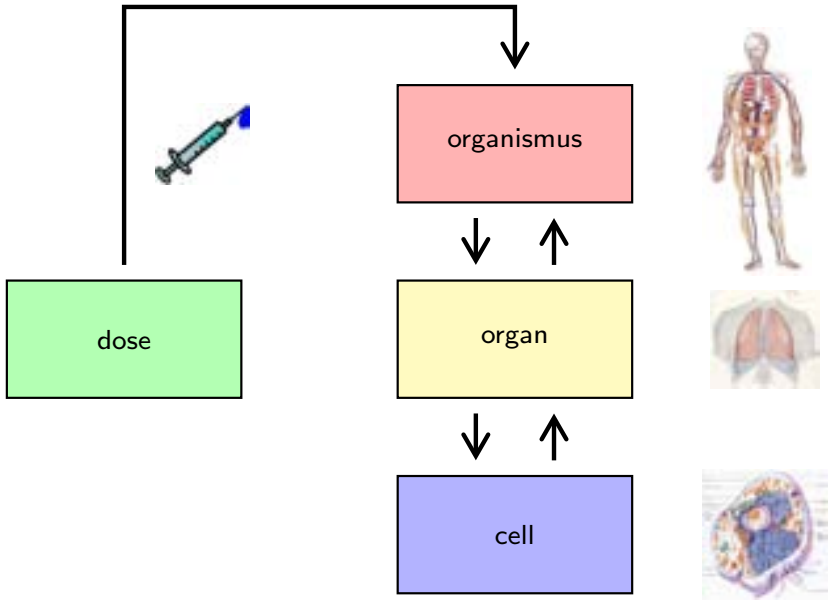
→ Rolf Findeisen, Steffen Borchers (FORSYS Magdeburg)

Outlook (2): Multi-Scale Model

- coupling of single cell, organ and organisum level
- development of a common simulation plattform
- comparision of simulation results with measurements
- development of offline and online optimisation strategies



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Thank you!