

# Mass-action kinetics and models of state-transition diagrams

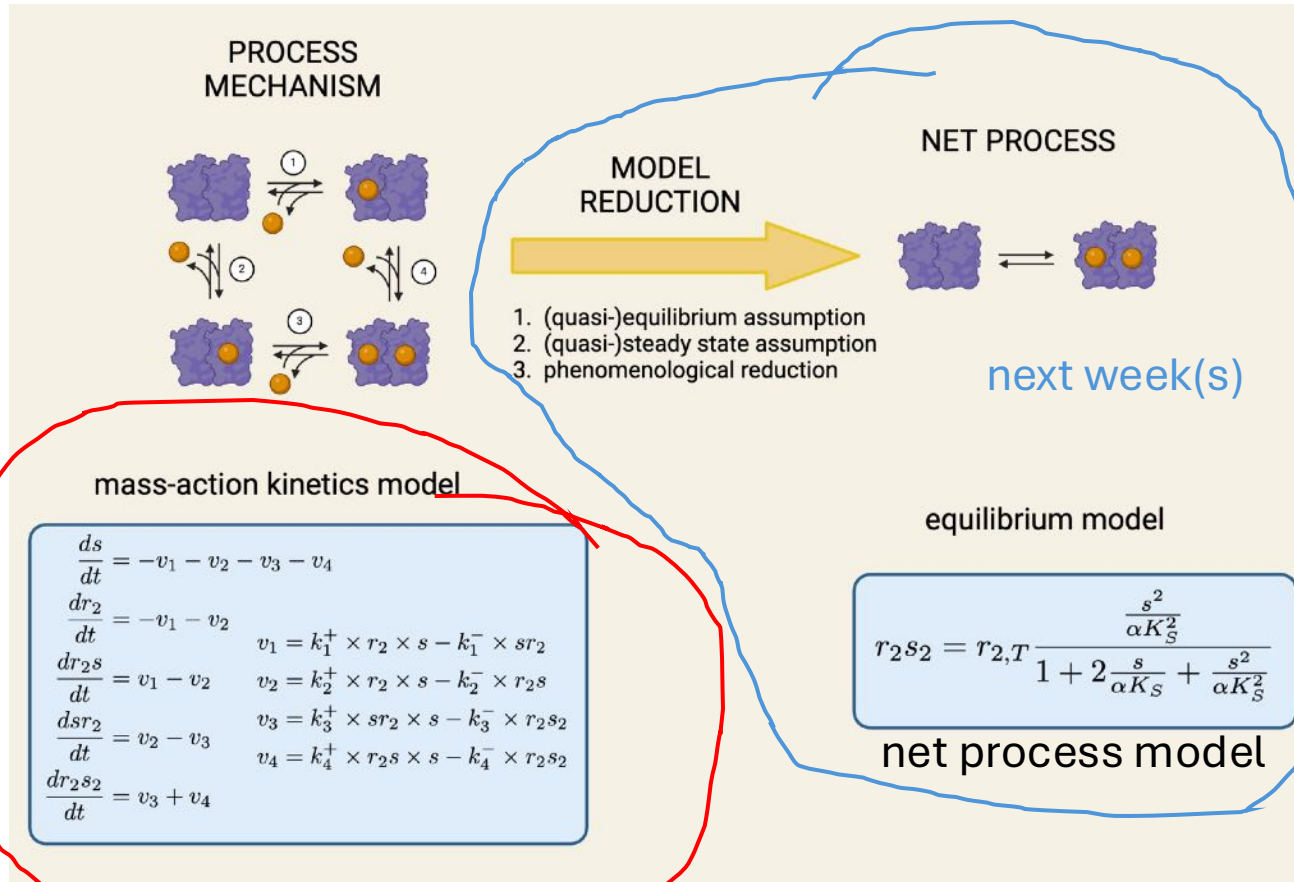
basic modelling of biological networks

# plan: make a mathematical model of a state-transition diagram

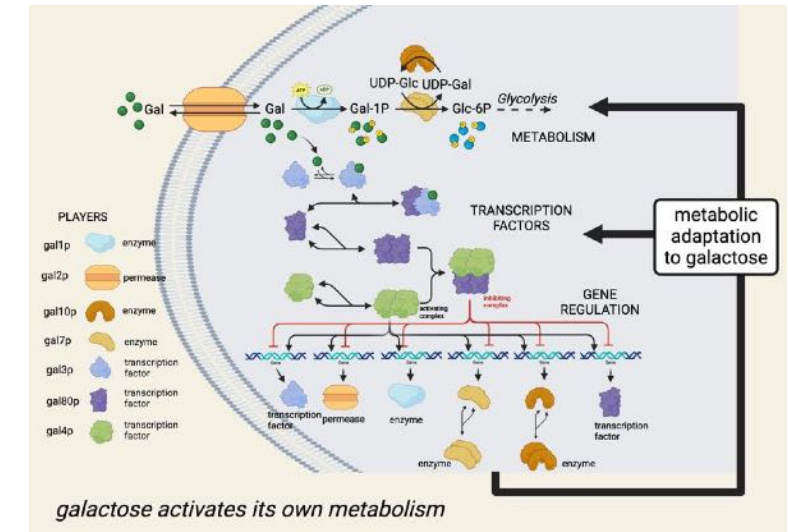
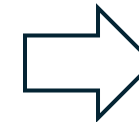
- We will model the rates of state-transitions in a state-transition diagram with *mass-action kinetics*. *This week I will show how this works.*
- for now, we will limit ourselves to state-transition diagrams of molecular processes, e.g. enzyme catalysis, transcription factor activation, membrane receptor activation, membrane transport etc.. What you learn is however more generally applicable, as you will see in the coming weeks.
- Due to reactions, the concentration of states occurring in the state-transition diagram will change, leading to dynamics. *This week I will show how this works.*
- Our model of a state transition diagram will be deterministic (for now) and predict the change in time of the concentrations of the states occurring in the diagram. *This week I will show how this works.*

# a model of a state transition diagram

following step (approx 2.5 weeks from now)



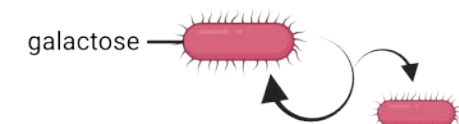
this week



use net process model to make larger model



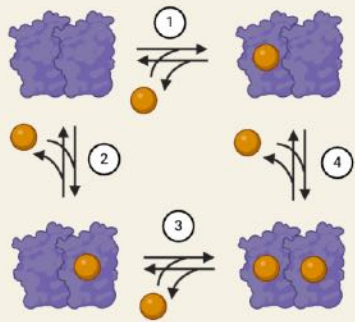
final step



make phenomenological model

# to do

## PROCESS MECHANISM

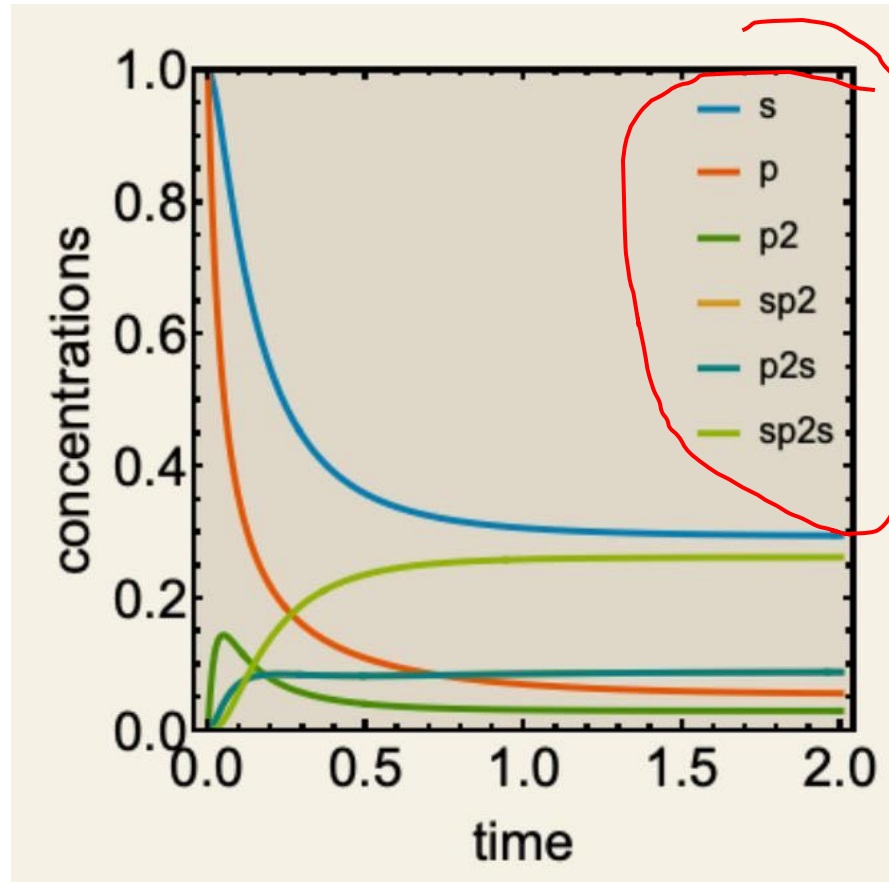


mass-action kinetics model

$$\begin{aligned} \frac{ds}{dt} &= -v_1 - v_2 - v_3 - v_4 \\ \frac{dr_2}{dt} &= -v_1 - v_2 & v_1 &= k_1^+ \times r_2 \times s - k_1^- \times sr_2 \\ \frac{dr_2s}{dt} &= v_1 - v_2 & v_2 &= k_2^+ \times r_2 \times s - k_2^- \times r_2s \\ \frac{dsr_2}{dt} &= v_2 - v_3 & v_3 &= k_3^+ \times sr_2 \times s - k_3^- \times r_2s2 \\ \frac{dr_2s2}{dt} &= v_3 + v_4 & v_4 &= k_4^+ \times r_2s \times s - k_4^- \times r_2s2 \end{aligned}$$

- become familiar with mass action kinetics (chemical kinetics) describing the rate of state transition in terms of kinetic parameters and concentrations
- become familiar with rate of concentration change equations (differential equations) expressed in terms of mass action kinetics
- numerically solve the resulting differential equation, given initial concentrations and parameter values to obtain a time series

time series: concentration of states as function of time, outcome of numerical simulation of our model



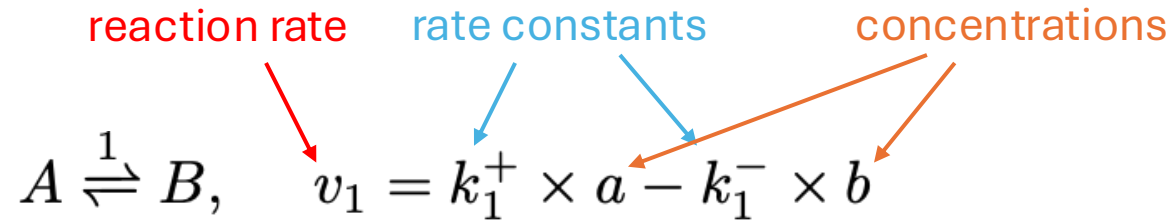
name of states

let's start

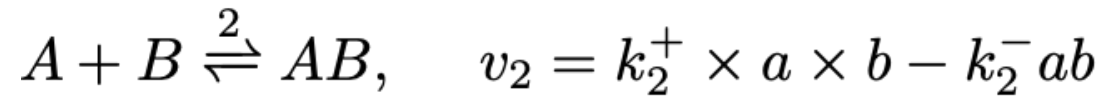
# mass action kinetics express the rate of reactions in terms of parameters and concentration of reactants

- examples:

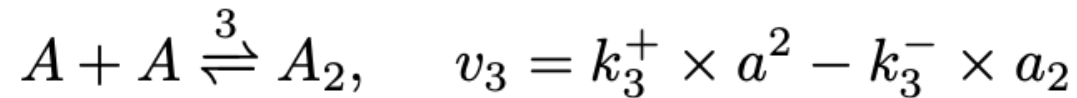
isomerisation reaction



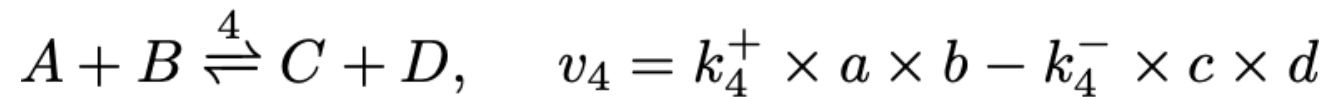
complex formation reaction



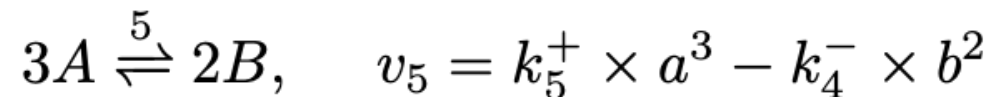
dimer formation reaction



conversion reaction



conversion reaction



↑  
reactions

↑  
reaction rate equations,

according to principles of *mass-action kinetics*

convention: name A, concentration a.

# principle of mass action kinetics

$$\sum_{j=1}^{N_S} n_j^+ S_j \rightleftharpoons \sum_{j=1}^{N_P} n_j^+ P_j$$
$$v = k^+ \prod_j s_j^{n_j^+} - k^- \prod_j p_j^{n_j^-}$$

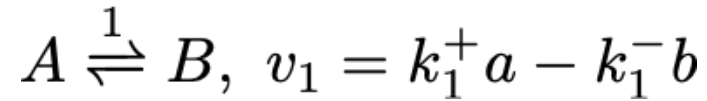
note:

1. holds for spontaneous reactions, so not for those that are catalysed by an enzyme!  
That requires enzyme kinetics (next week).
2. (non-enzyme catalysed) reactions with more than three substrates or products are rare



# rate of change in concentrations due to reactions

- example



Consider:

1.  $b=0$  then  $v_1 > 0$ ,  $A \Rightarrow B$  and B rises in concentration and A goes down in concentration
2.  $a=0$  then  $v_1 < 0$ ,  $B \Rightarrow A$  and A rises in concentration and B goes down in concentration
3. Note that  $a$  and  $b$  cannot become smaller than zero (a negative concentration is not possible)

Accordingly,

$$\frac{da}{dt} = -v_1, \quad \frac{db}{dt} = v_1$$



rate of concentration change  
(ordinary) differential equation  
slope in plot of  $a$  as function of time

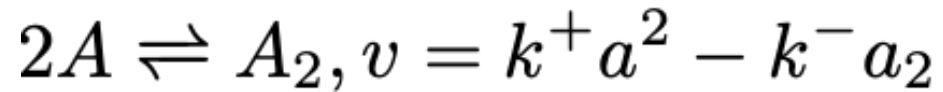
Question:

Why is  $da/dt + db/dt = 0$ ?

Because 1 A is converted into 1 B and vice versa  
the total number of molecules of A and B is therefore  
conserved

# rate of change in concentrations due to reactions

- example



Now:

$$\frac{da}{dt} = -2v, \quad \frac{da_2}{dt} = 1v$$

per reaction 2 A consumed to make 1 A<sub>2</sub>



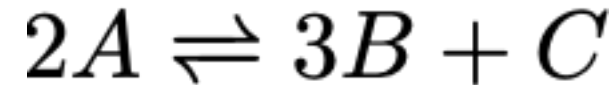
Question:

$da/dt + 2da_2/dt = 0$ , why?

Now total amount of A is conserved and A<sub>2</sub> consists of 2 A's.

# Exercise

Give the rate of concentration change equation for all reactants of the reaction



Express the reaction rate in terms of mass action kinetics and the differential equations describing the rate of change of the concentrations

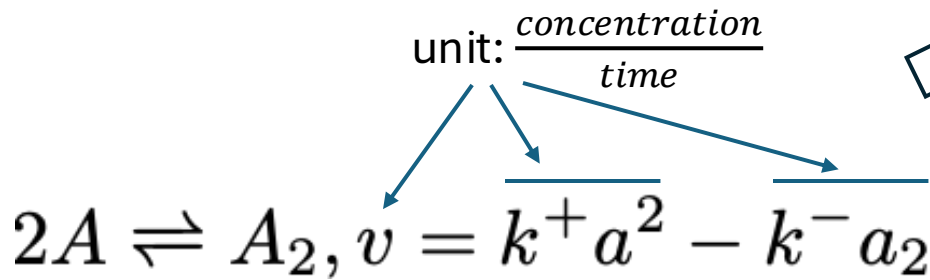
$$\frac{da}{dt} = -2v$$

$$\frac{db}{dt} = 3v$$

$$\frac{dc}{dt} = v$$

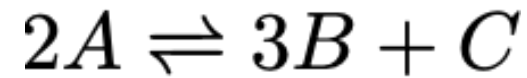
$$v = k^+ a^2 - k^- b^3 c$$

# Units



Question is the unit of  $k^+$  and  $k^-$ ?

$$k^+ \text{ in } \frac{1}{\text{conc} \times \text{time}} \text{ and } k^- \text{ in } \frac{1}{\text{time}}$$



$$\frac{da}{dt} = -2v, \frac{da_2}{dt} = 1v$$

unit:  $\frac{\text{concentration}}{\text{time}}$

$$\begin{aligned} \frac{da}{dt} &= -2v \\ \frac{db}{dt} &= 3v \\ \frac{dc}{dt} &= v \end{aligned}$$

$$v = k^+ a^2 - k^- b^3 c$$

unit:  $\frac{\text{concentration}}{\text{time}}$

unit rules:

1. left and right hand side of an equation have the same unit
2. all terms in a sum or subtraction have the same unit

Question is the unit of  $k^+$  and  $k^-$ ?

$$k^+ \text{ in } \frac{1}{\text{conc} \times \text{time}} \text{ and } k^- \text{ in } \frac{1}{\text{conc}^3 \times \text{time}}$$

# Summarising

due to unit of left hand side of

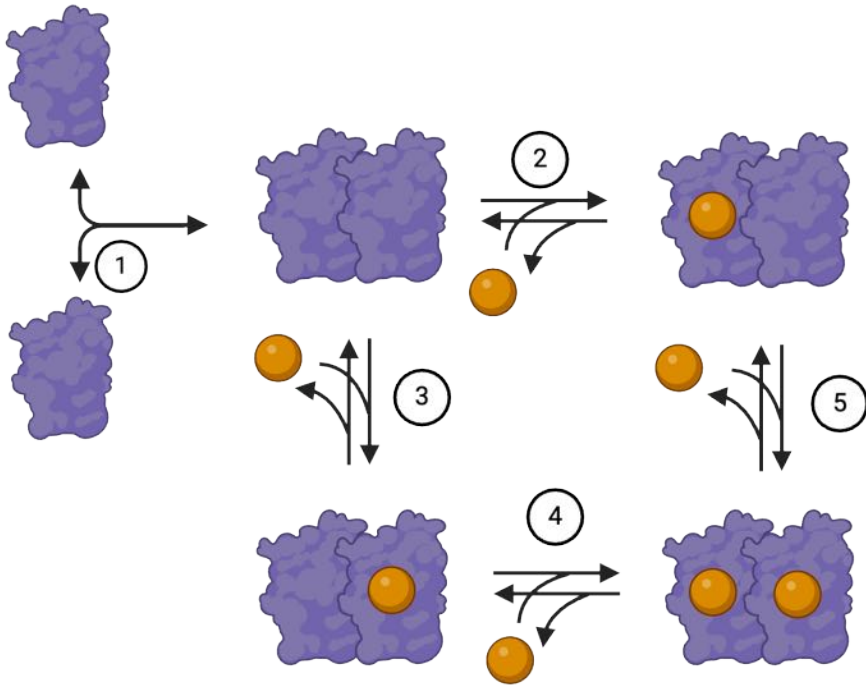
$$\frac{d \text{ concentration}}{dt} = \text{sum or subtraction of rates}$$

have all the rates the unit  $\frac{\text{concentration}}{\text{time}}$

the unit of the rate constants then follows from how many reactant concentrations it is multiplied with, e.g. given  $k a^3 b$ , unit of  $k$  equals

$$\frac{1}{\text{conc}^3 \times \text{time}}$$

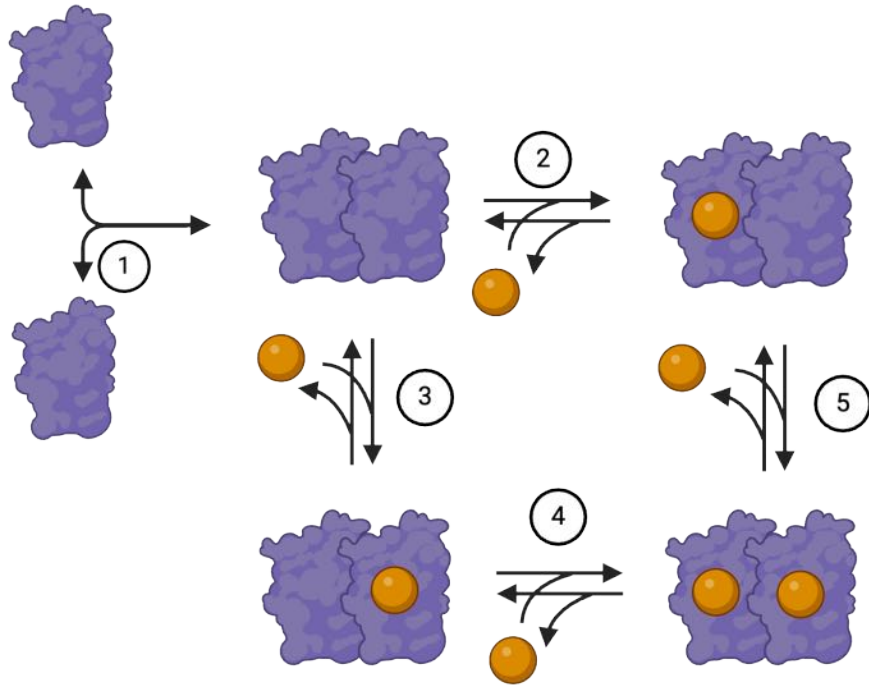
# Exercise: make a model of



Give the:

1. Reactions
2. Their rate equations
3. The rate of concentration change equations (differential equations) of all molecular species.

# Sketch the dynamics of the system without small molecule



Question:

Without the small molecule, model reduces too:

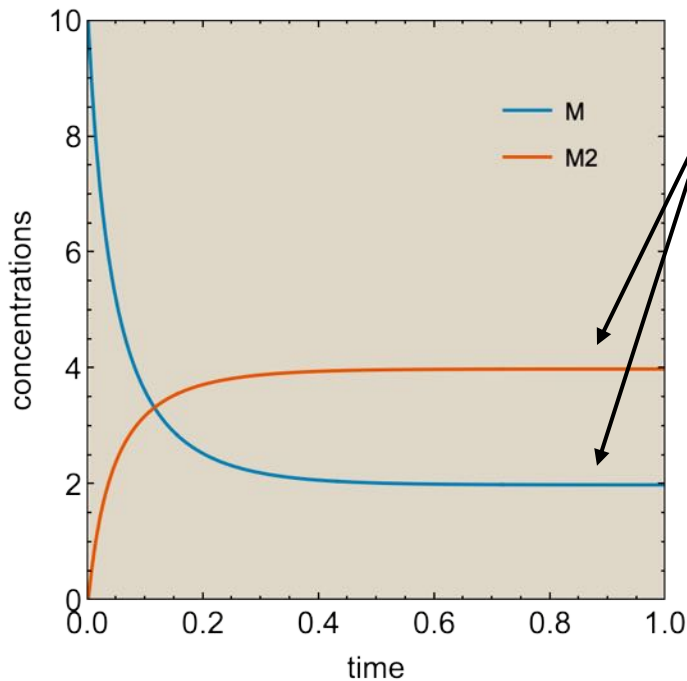
.....

Say you add only monomers to a test tube what happens as function of time?

.....

# Dynamics of $2M \leftrightarrow M_2$

Initial conditions  $M(t) = 10$  and  $M_2(0) = 0$



the system moves to a stationary state  
with all concentrations constant  
the reaction is then 0

$m_{\text{tot}}$  is the concentration of monomer added to the test tube.  
Thus,  $m_{\text{tot}}$  bounds the allowable concentrations of  $m$  and  $m_2$ .  
Hence,  $m_{\text{tot}} = m + 2m_2$

model:  $\frac{dm_2}{dt} = v$

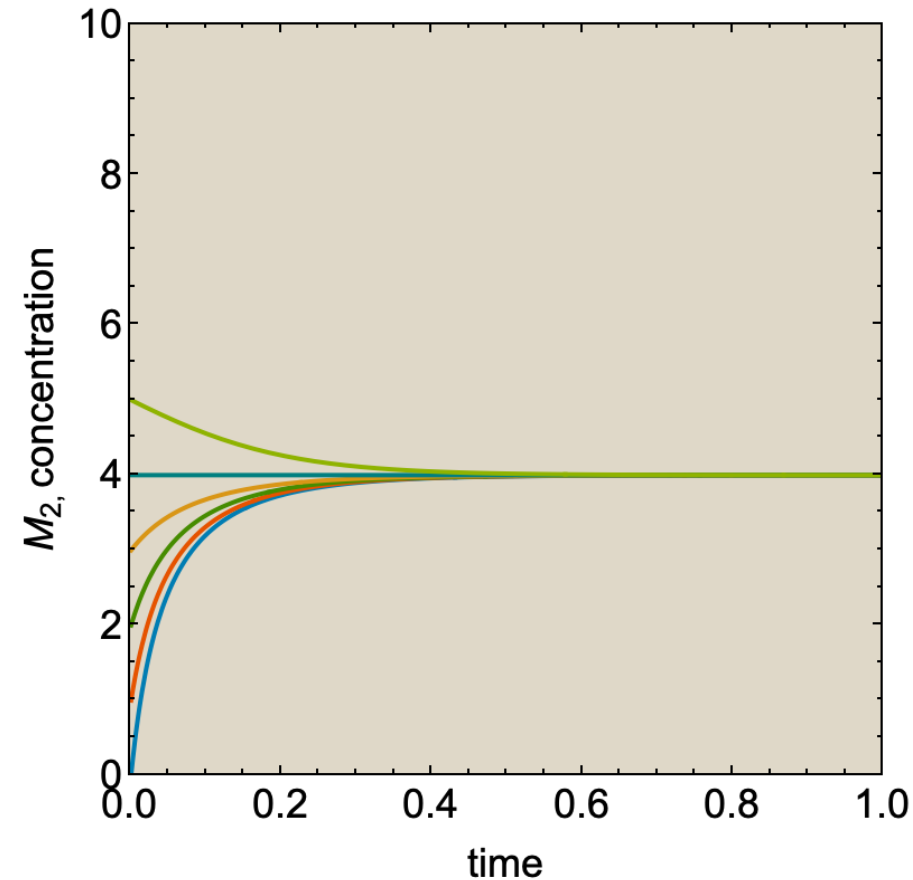
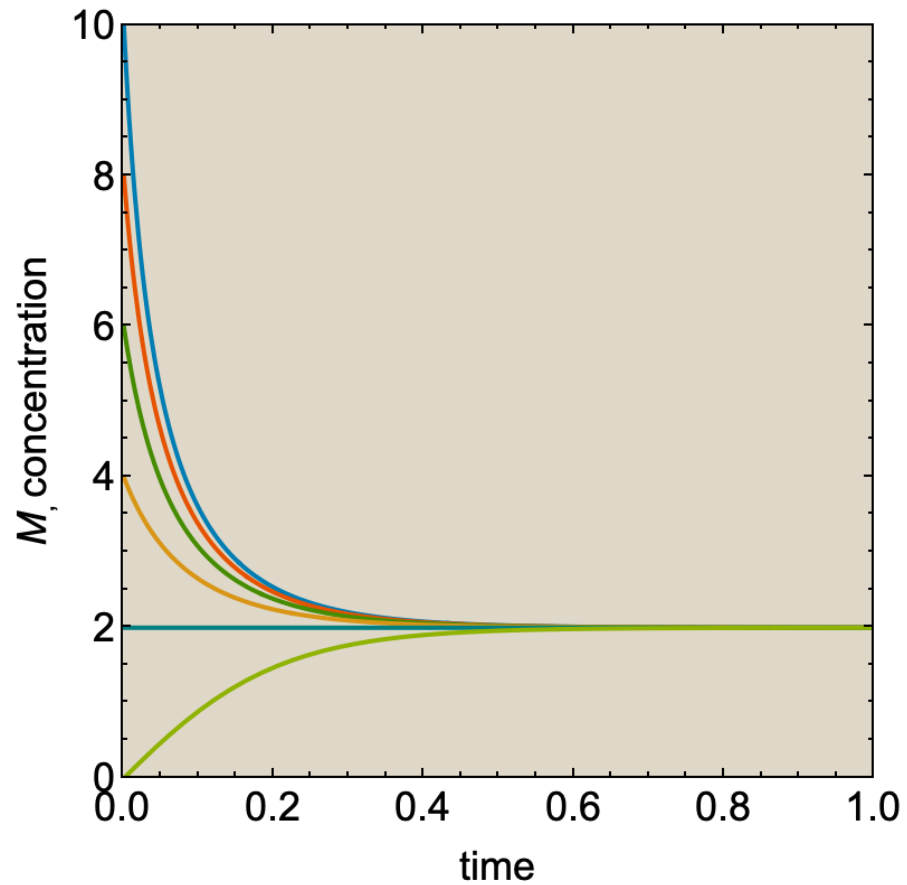
$$v = k^+ m^2 - k^- m_2$$

$$m_{\text{tot}} = m + 2m_2$$

$$m_{\text{tot}} = 10 \mu\text{M}, k^+ = 1 \mu\text{M}^{-1} \text{s}^{-1}, k^- = 1 \text{s}^{-1}$$



Dynamics of  $2M \leftrightarrow M_2$   
Varying the initial conditions, always same stationary state



# Conservation of total monomers simplifies the model to 1 differential equation

model:

$$\frac{dm_2}{dt} = v, \quad \frac{dm}{dt} = -2v$$
$$v = k^+ m^2 - k^- m_2$$

conservation of total monomers:

$$\frac{dm}{dt} + 2\frac{dm_2}{dt} = -2v + 2v = 0$$

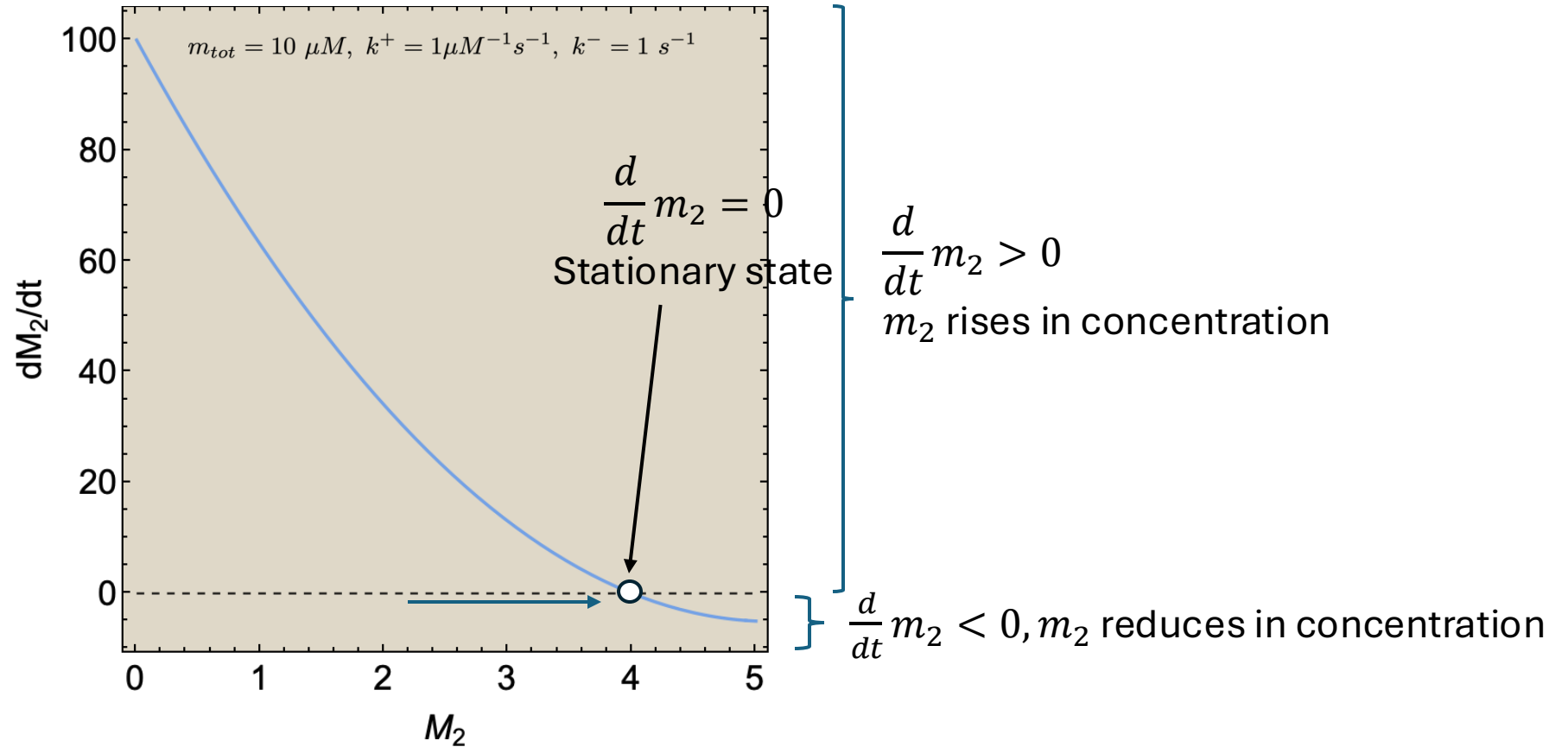
$$\text{Hence, } \frac{d}{dt}(m + 2m_2) = 0$$

$$\text{Thus, } m_{tot} = m + 2m_2$$

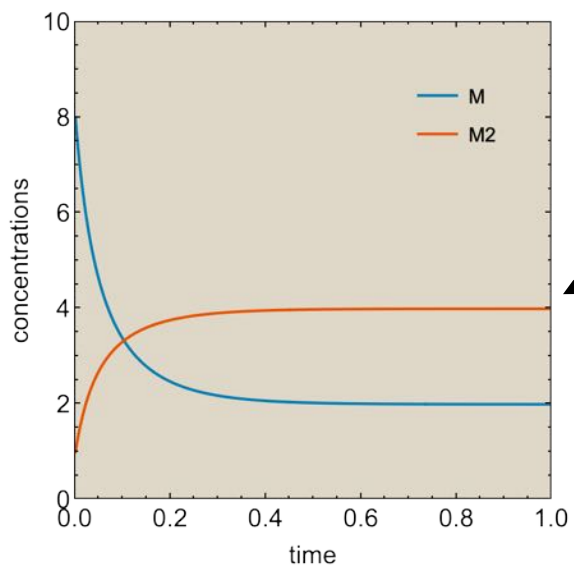
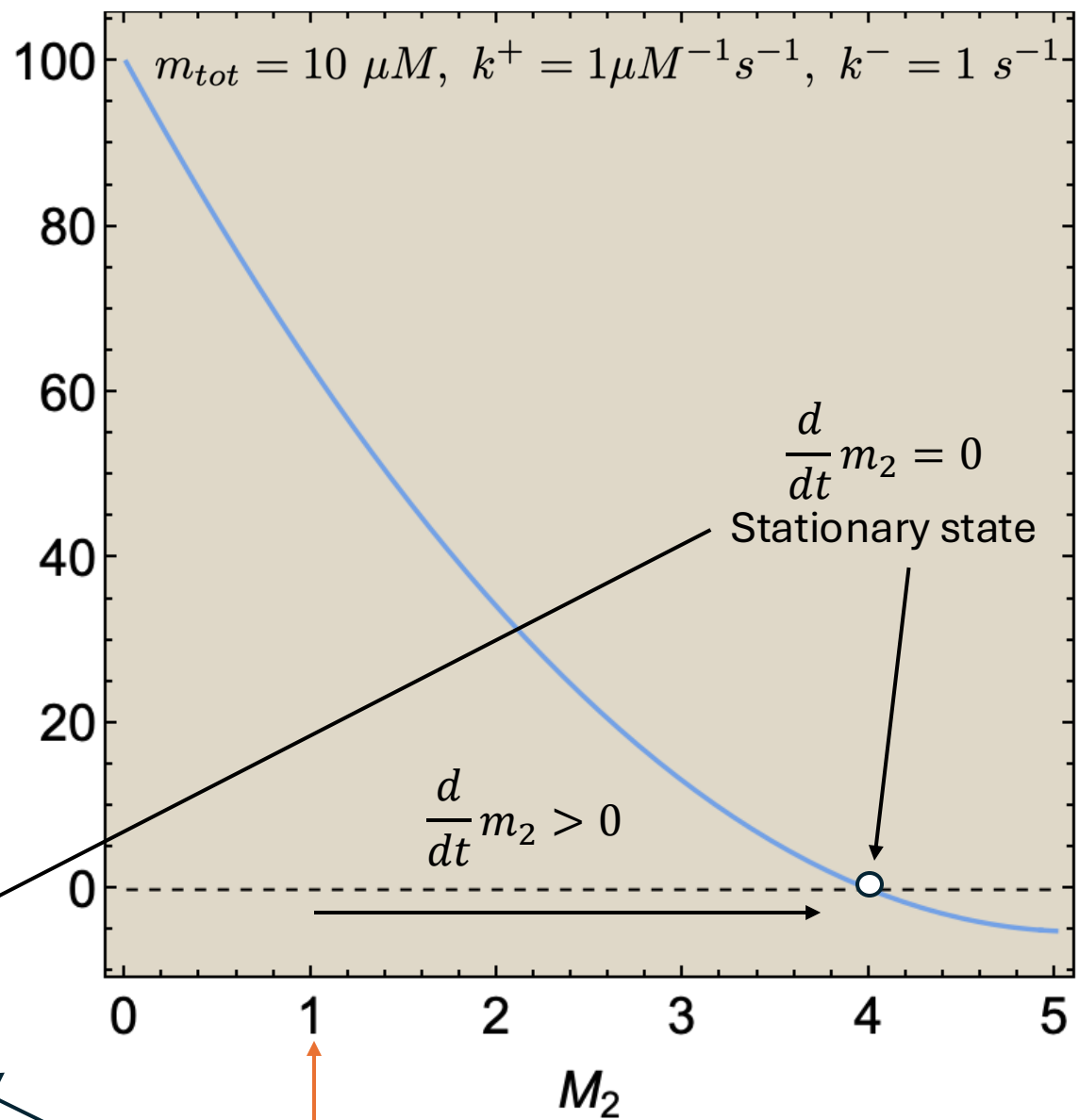
this simplifies the model, we can eliminate  $m$  as variable:

$$\frac{dm_2}{dt} = k^+ m^2 - k^- m_2$$
$$= k^+ (m_{tot} - 2m_2)^2 - k^- m_2$$

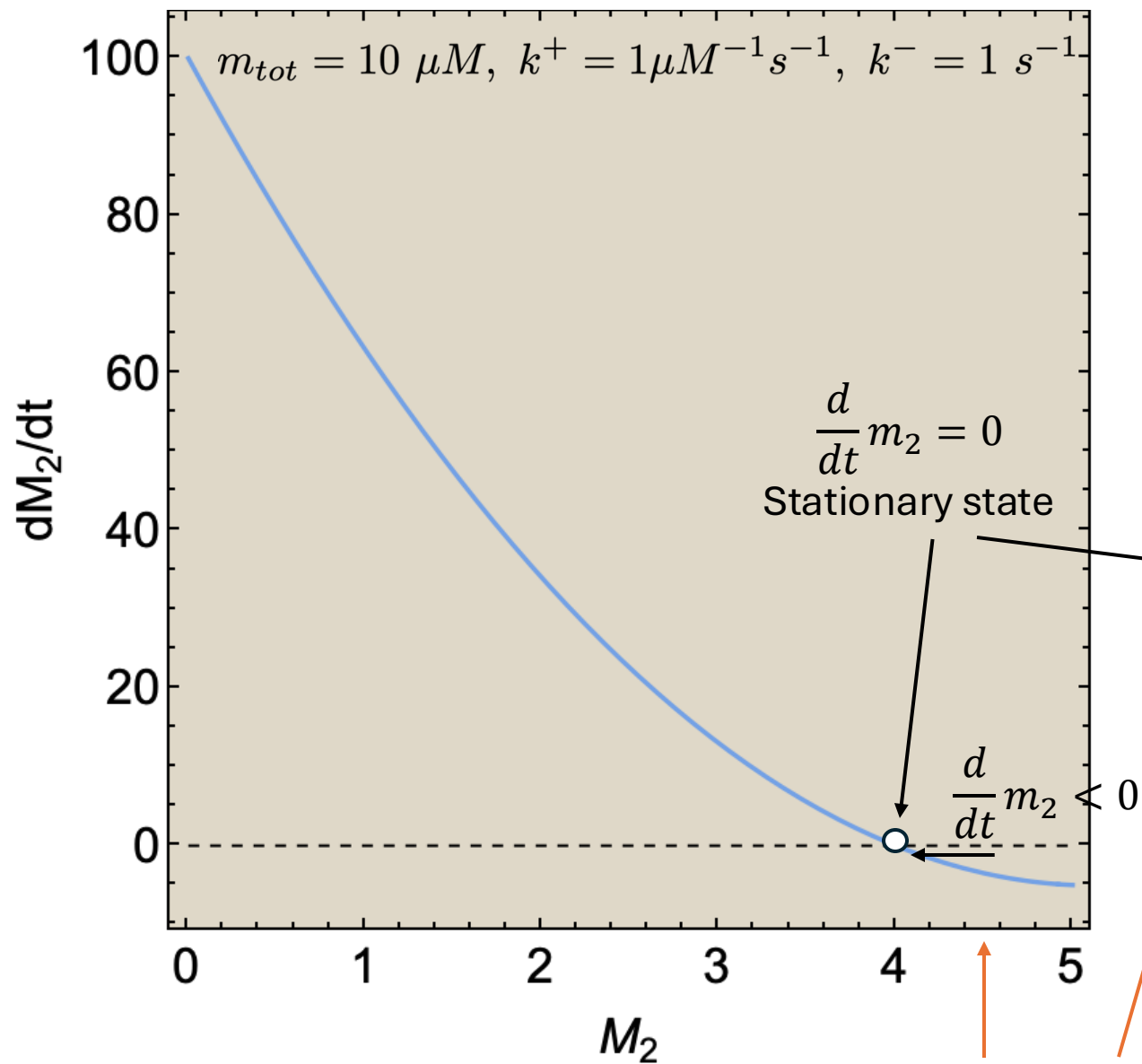
the model always went to the same stationary state because....



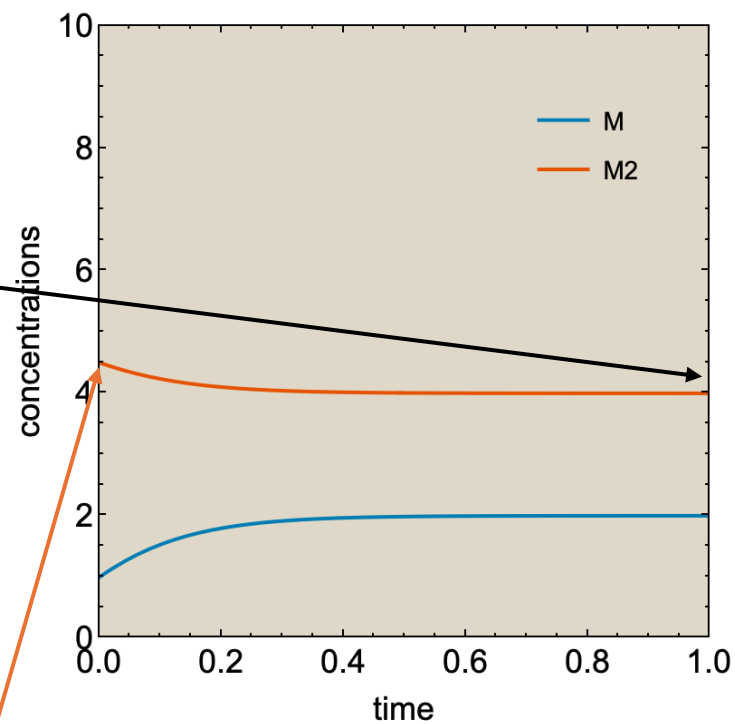
... it is determined by the parameters ( $k^+$ ,  $k^-$  and  $m_{tot}$ )



initial condition:  
M2=1 then M=8

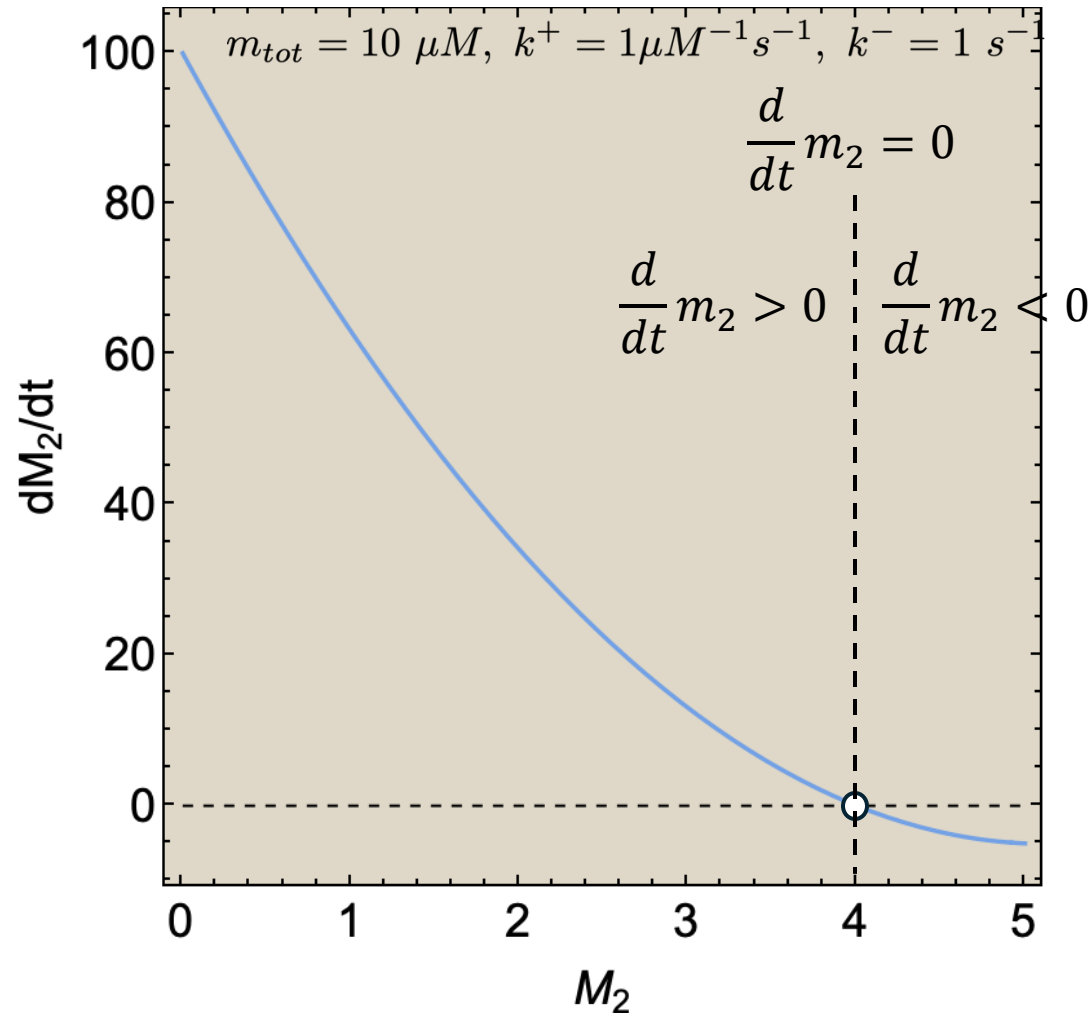


initial condition:  
 $M_2 = 4.5$  then  $M = 1$



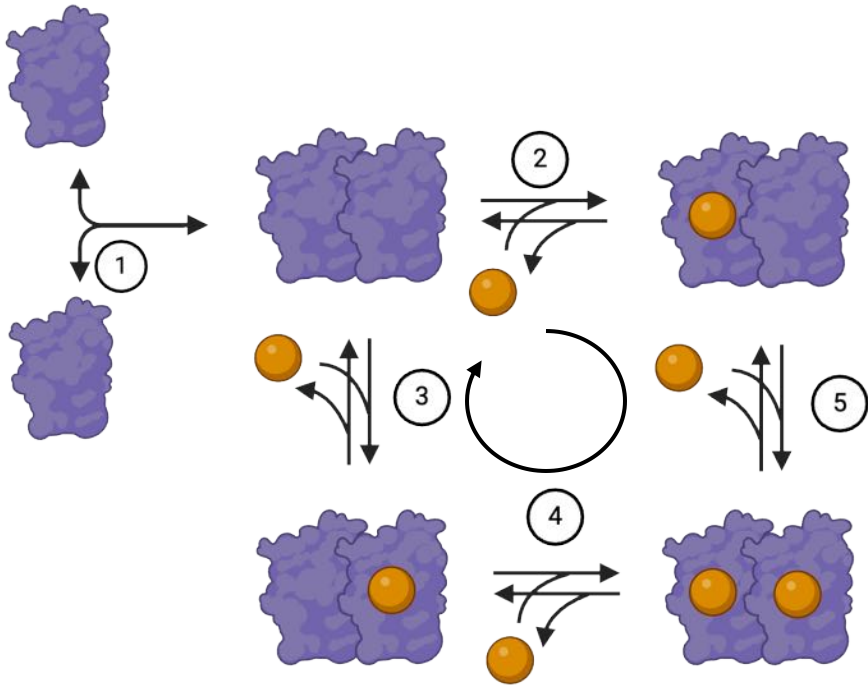
# Dynamics of $2M \leftrightarrow M_2$

## The stationary state is attracting



Thus, the stationary state is attracting.  
All initial conditions eventually move towards it.

# Entire model, small molecule added



$$\frac{dm}{dt} = -2v_1$$

$$\frac{dm_2}{dt} = v_1 - v_2 + v_3$$

$$\frac{dsm_2}{dt} = v_2 - v_5$$

$$\frac{dm_2s}{dt} = v_4 - v_3$$

$$\frac{dsm_2s}{dt} = v_5 - v_4$$

$$v_1 = k_1^+ \cdot m^2 - k_1^- \cdot m_2$$

$$v_2 = k_2^+ \cdot m_2 \cdot s - k_2^- \cdot sm_2$$

$$v_3 = k_3^+ \cdot m_2s - k_3^- \cdot m_2 \cdot s$$

$$v_4 = k_4^+ \cdot sm_2s - k_4^- \cdot m_2s \cdot s$$

$$v_5 = k_5^+ \cdot sm_2 \cdot s - k_5^- \cdot sm_2s$$

# Entire model, dynamics, convergence to stationary state

