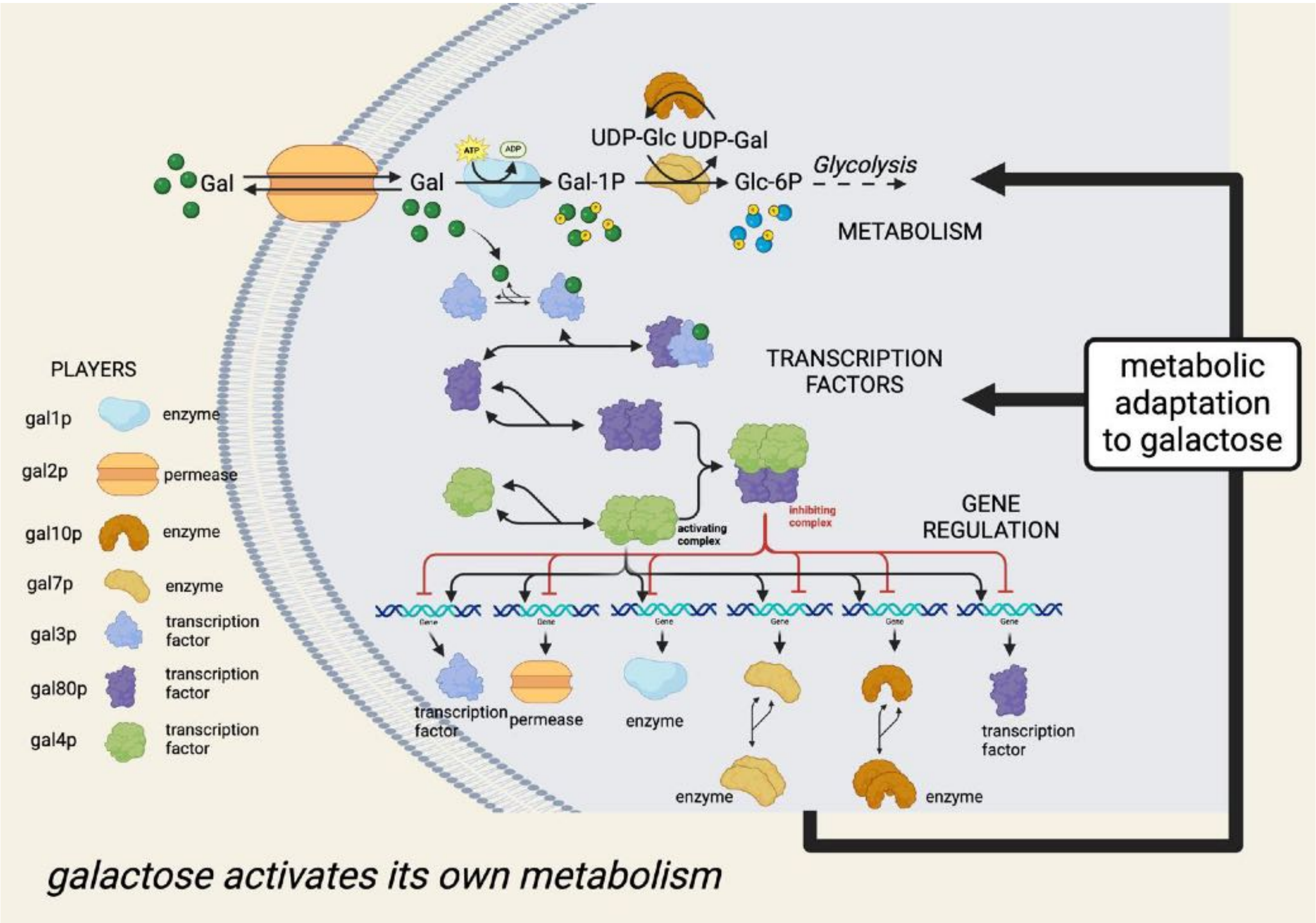
State transition diagrams

basic models of biological networks

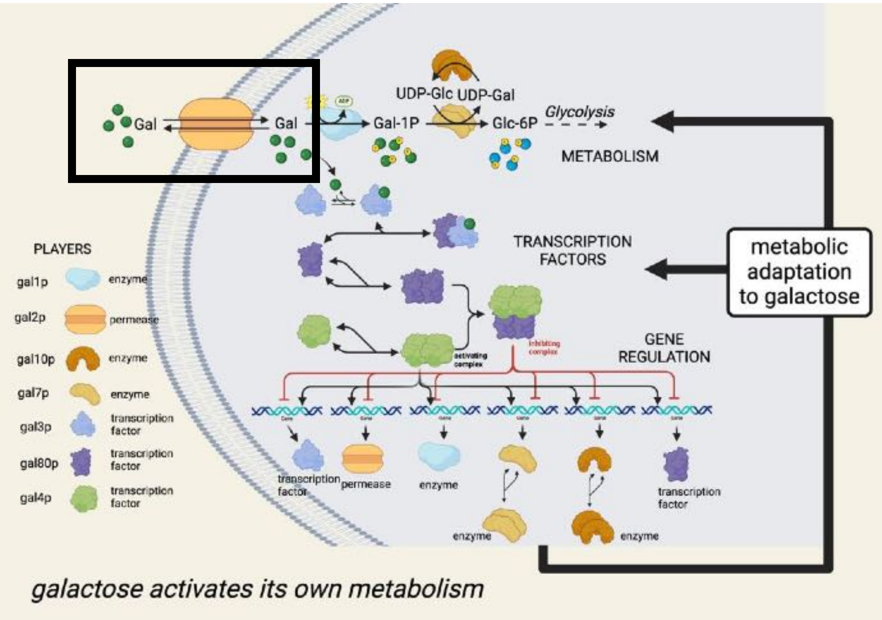
this network picture contains quite some biochemical complexity

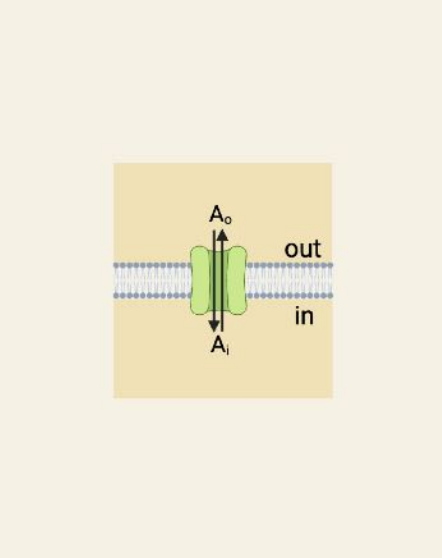


- transporter
- enzymes catalysing reactions
- small molecules as reactants
- small molecule – protein binding
- protein-protein complex formation
- DNA-protein complex formation
- transcription
- translation

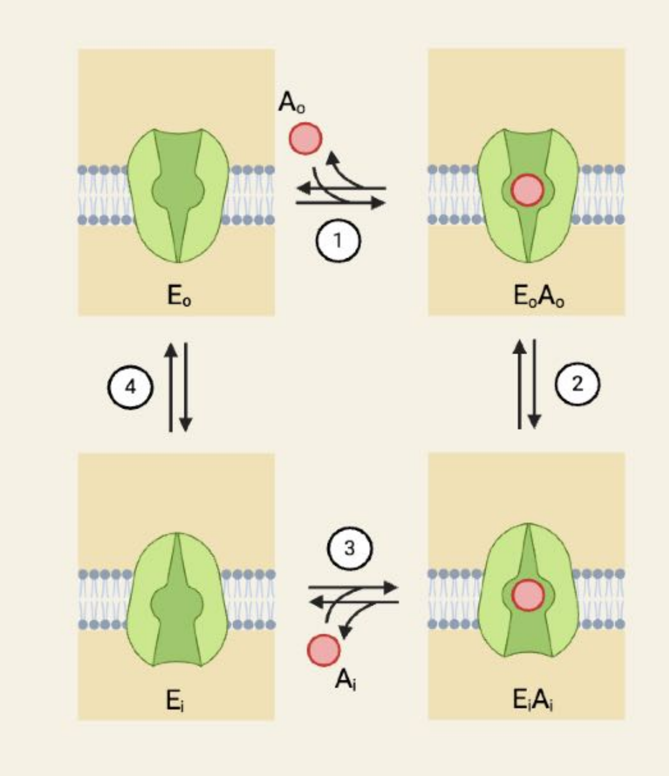
transporter (a protein, called a “permease”)

transporter protein



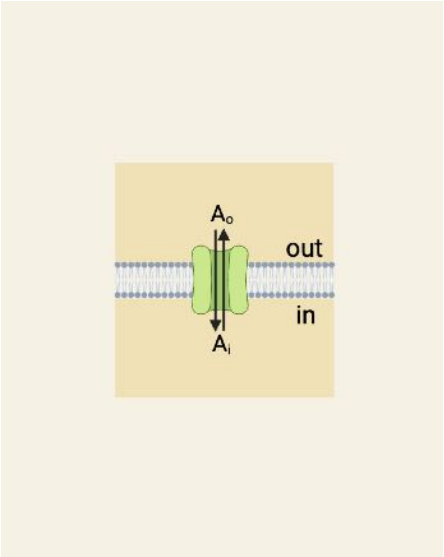


net process
(of membrane transport

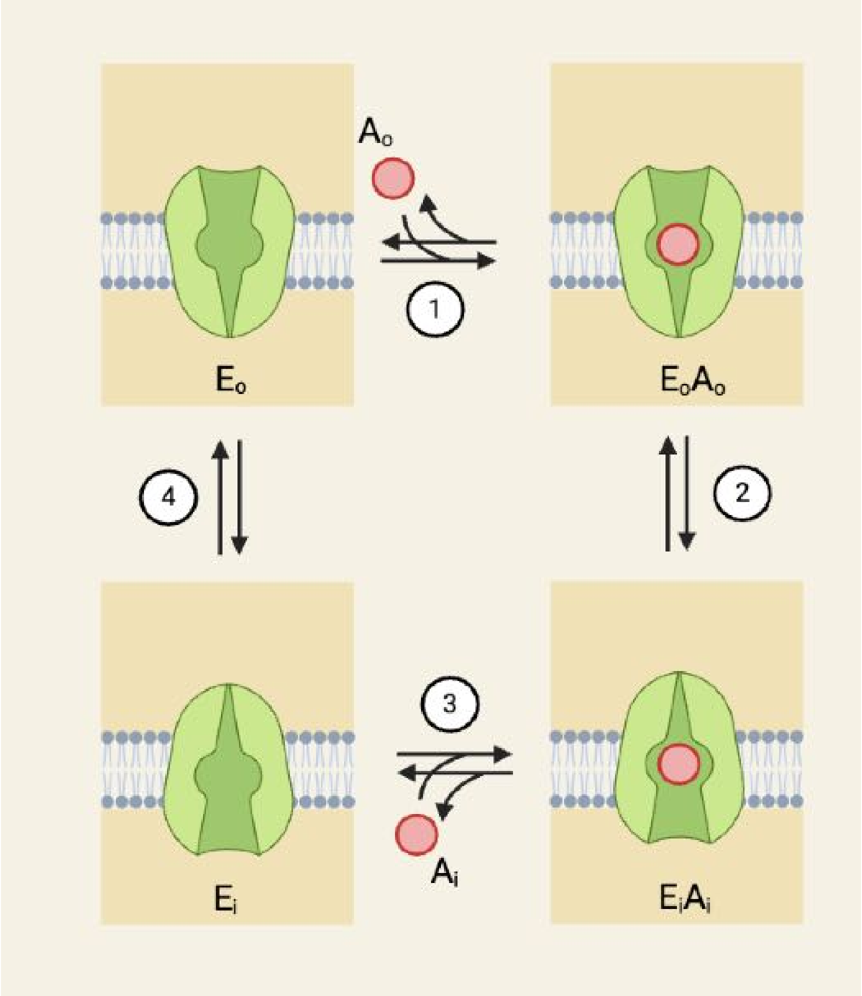


state transition diagram
(depicts the transport mechanism)

the state-transition diagram is the mechanism



net process

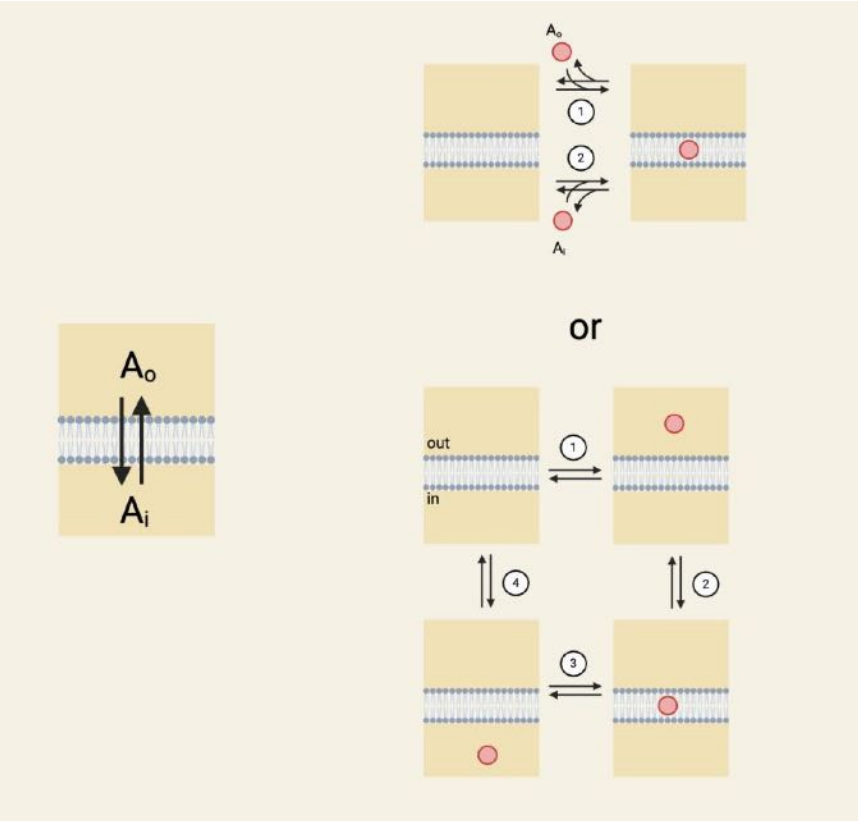


state transition diagram

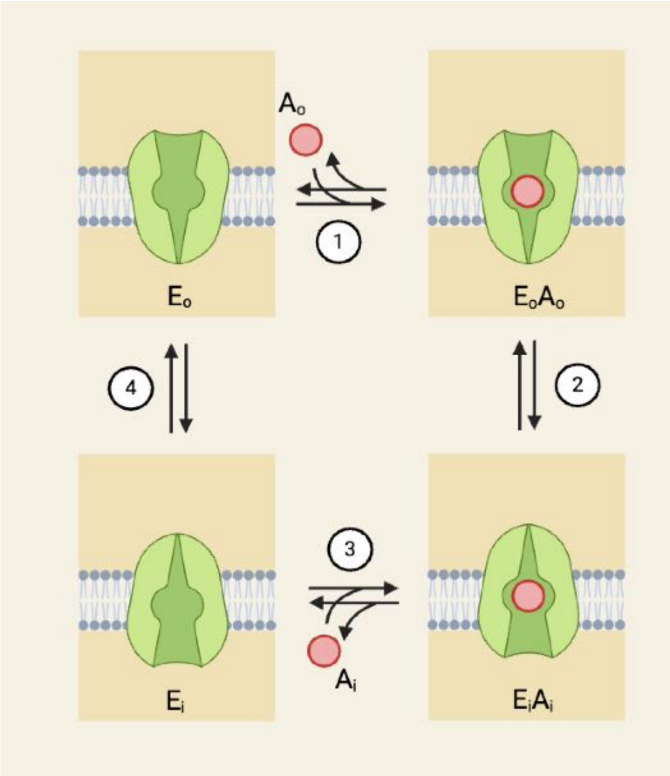
how many states?
how many transitions?

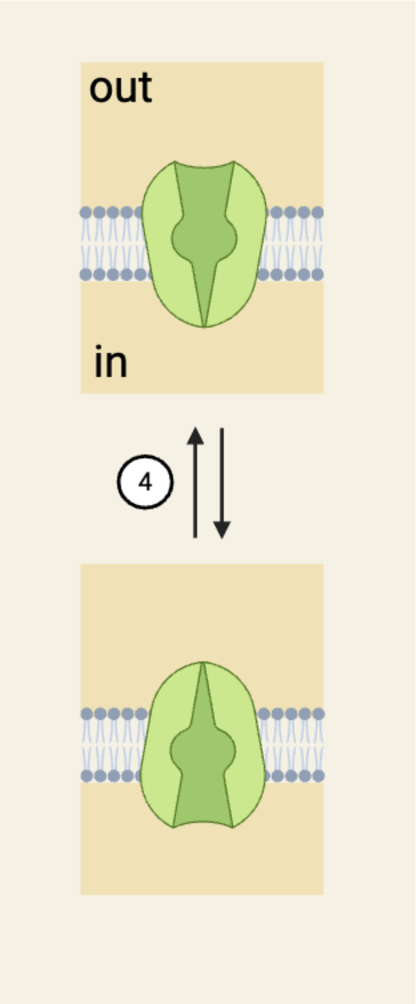
exercise

- make a state transition diagram of a protein independent membrane transport mechanism



protein conformations: different 3D structures



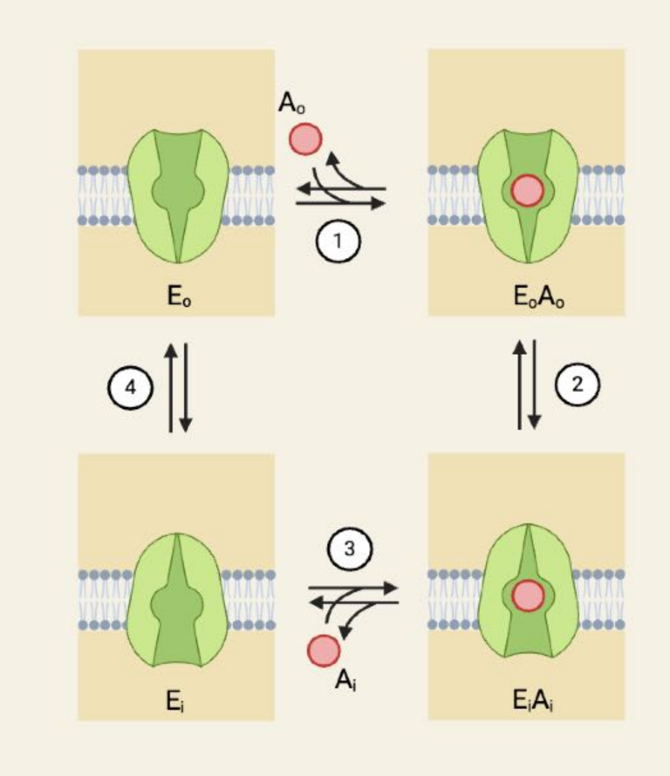


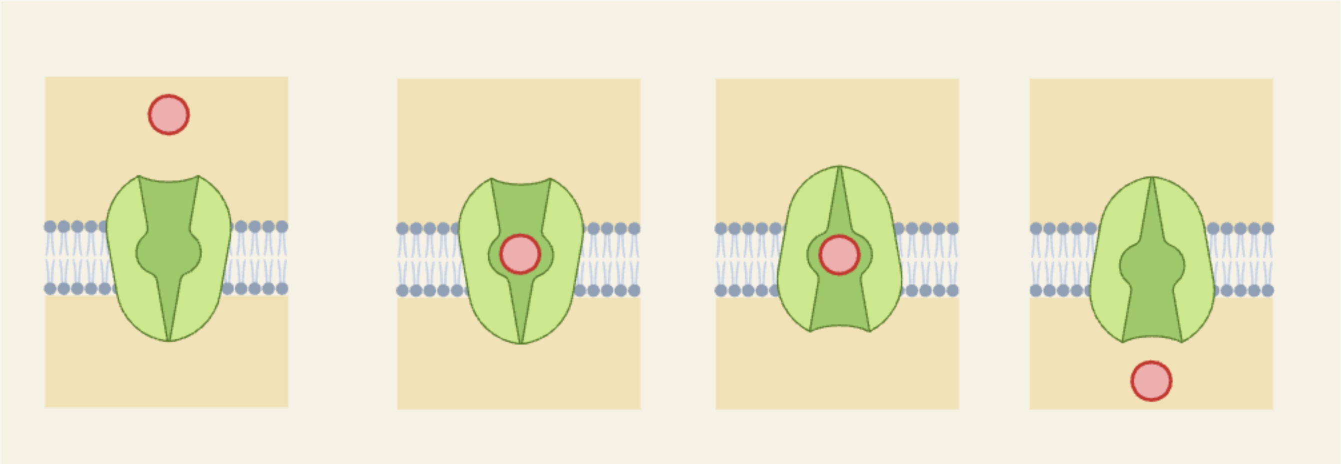
conformation 1

conformation 2

the protein switches between those 2 conformations continuously

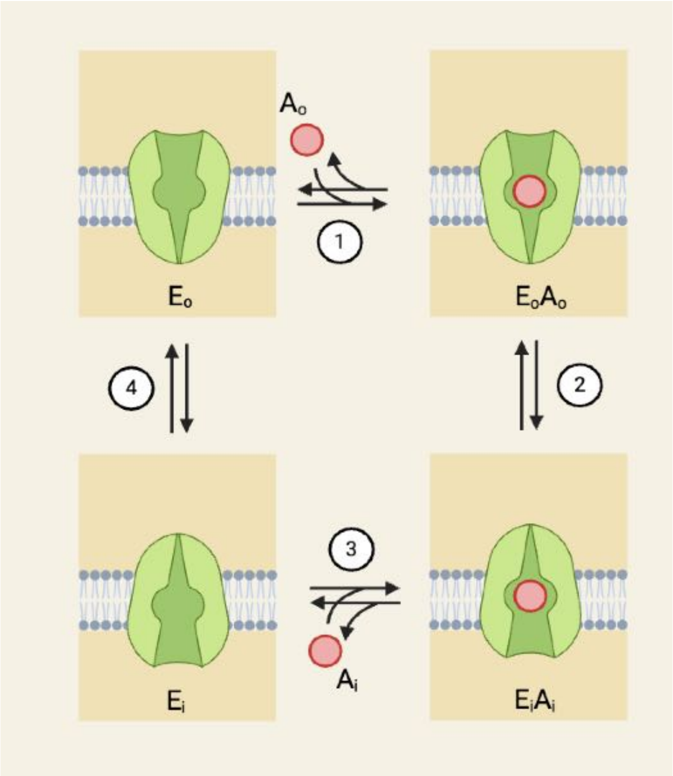
states





the 4 states of the system

state transitions are (bio)chemical reactions in this case



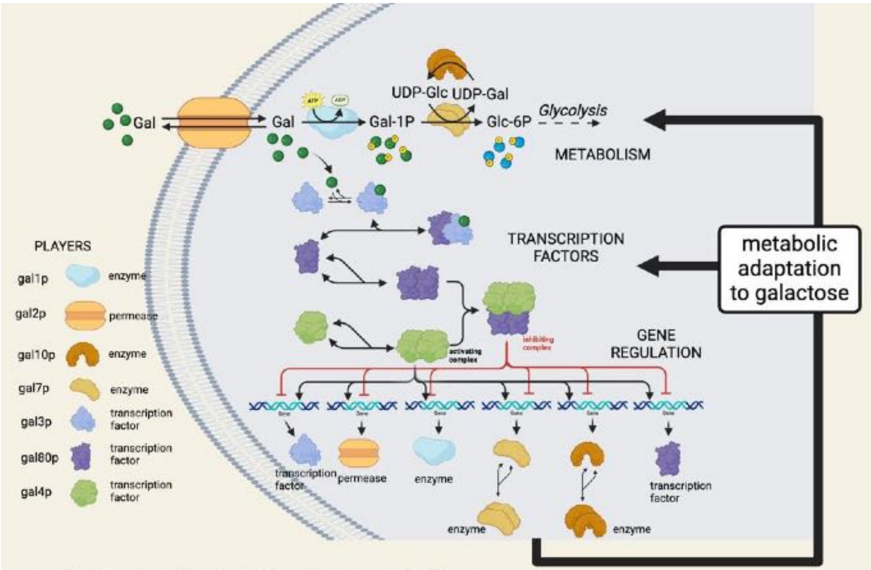
state transition diagram
in reaction form

1. Eo + Ao ⇄ EoAo
2. EoAo ⇄ EiAi
3. EiAi ⇄ Ei+Ai
4. Ei ⇄ Eo

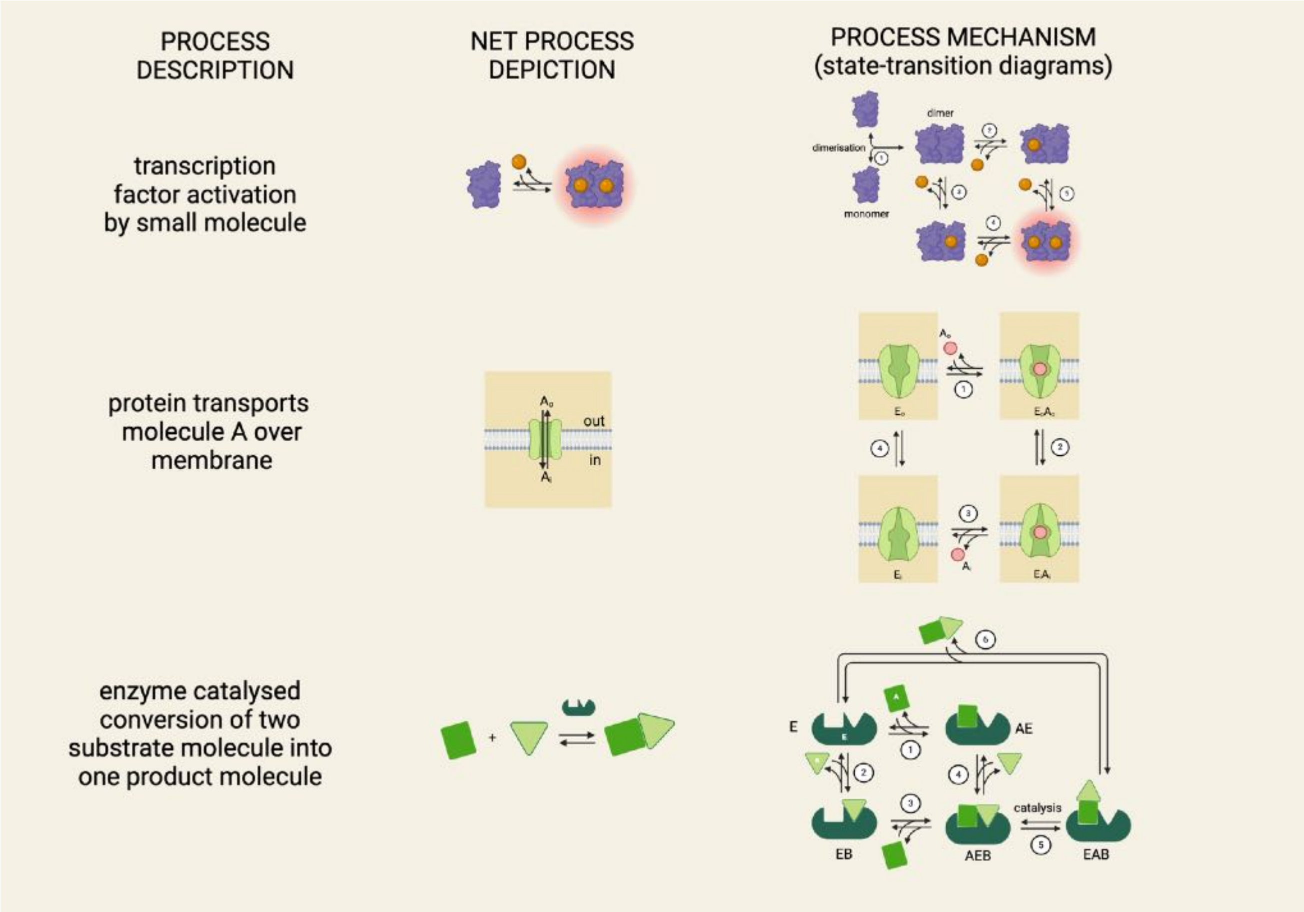
state transitions can in addition to (bio)chemical reactions be

- location transitions (diffusive movement)
- consumption (not necessarily of molecules; e.g. fox eats rabbit)
- production (fox makes baby fox)
- (dis)appearance, removal/addition

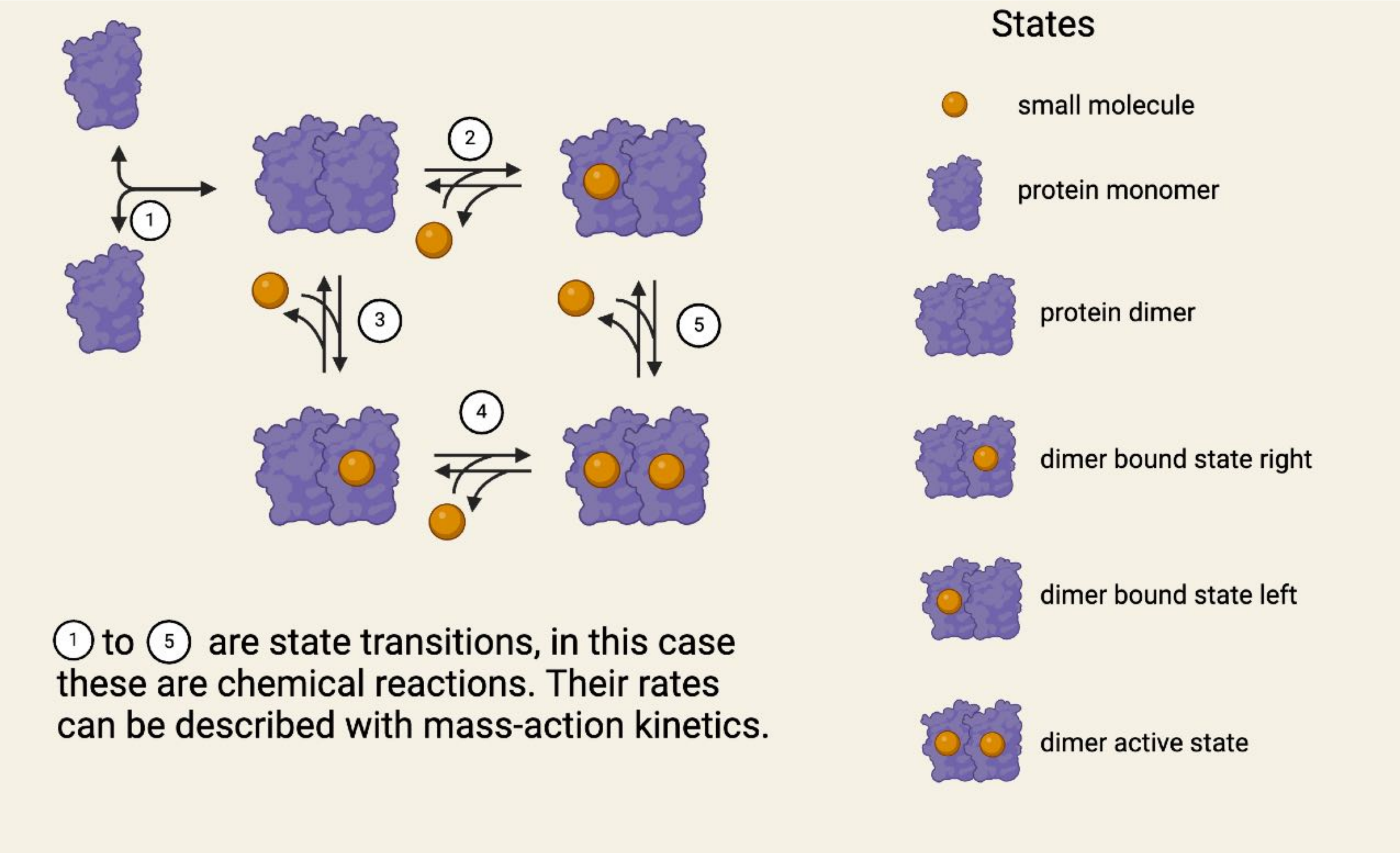
different net processes



galactose activates its own metabolism

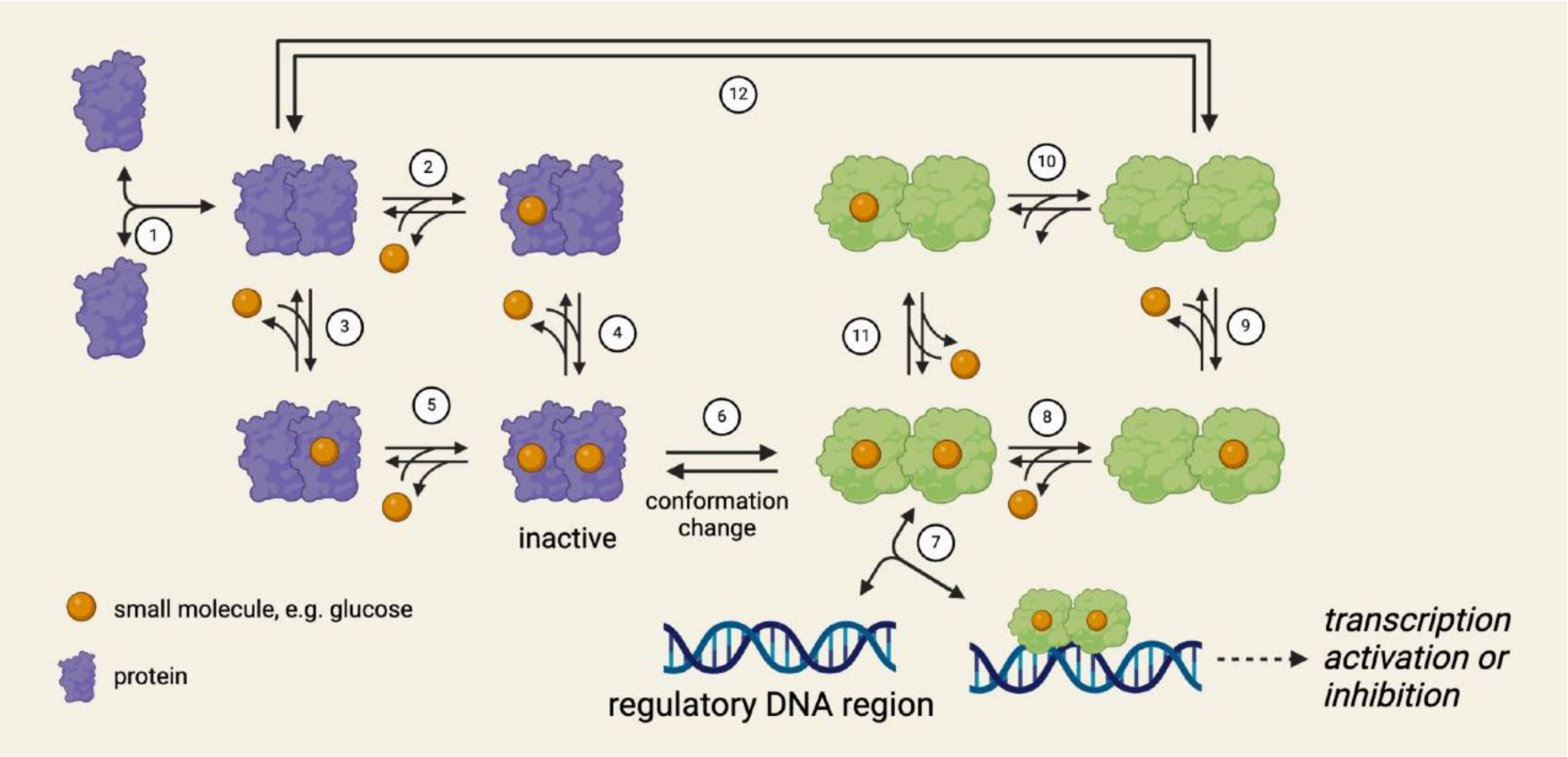


wrap up


States
small molecule
protein monomer
protein dimer
dimer bound state right
dimer bound state left
dimer active state
1
2
3
4
5
1 to 5 are state transitions, in this case these are chemical reactions. Their rates can be described with mass-action kinetics.

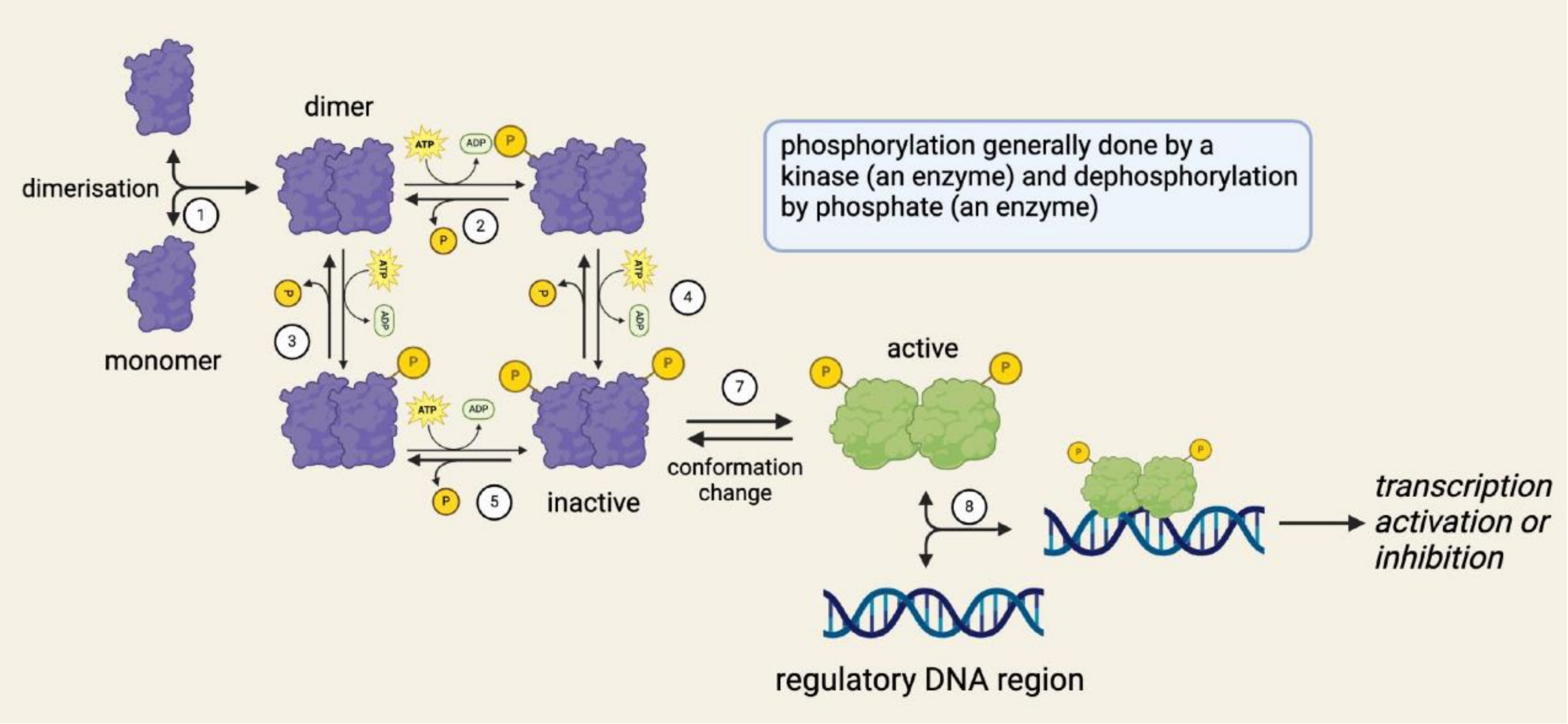
examples of state transition diagrams

transcription factor dimerisation, signal binding, conformational change, DNA binding



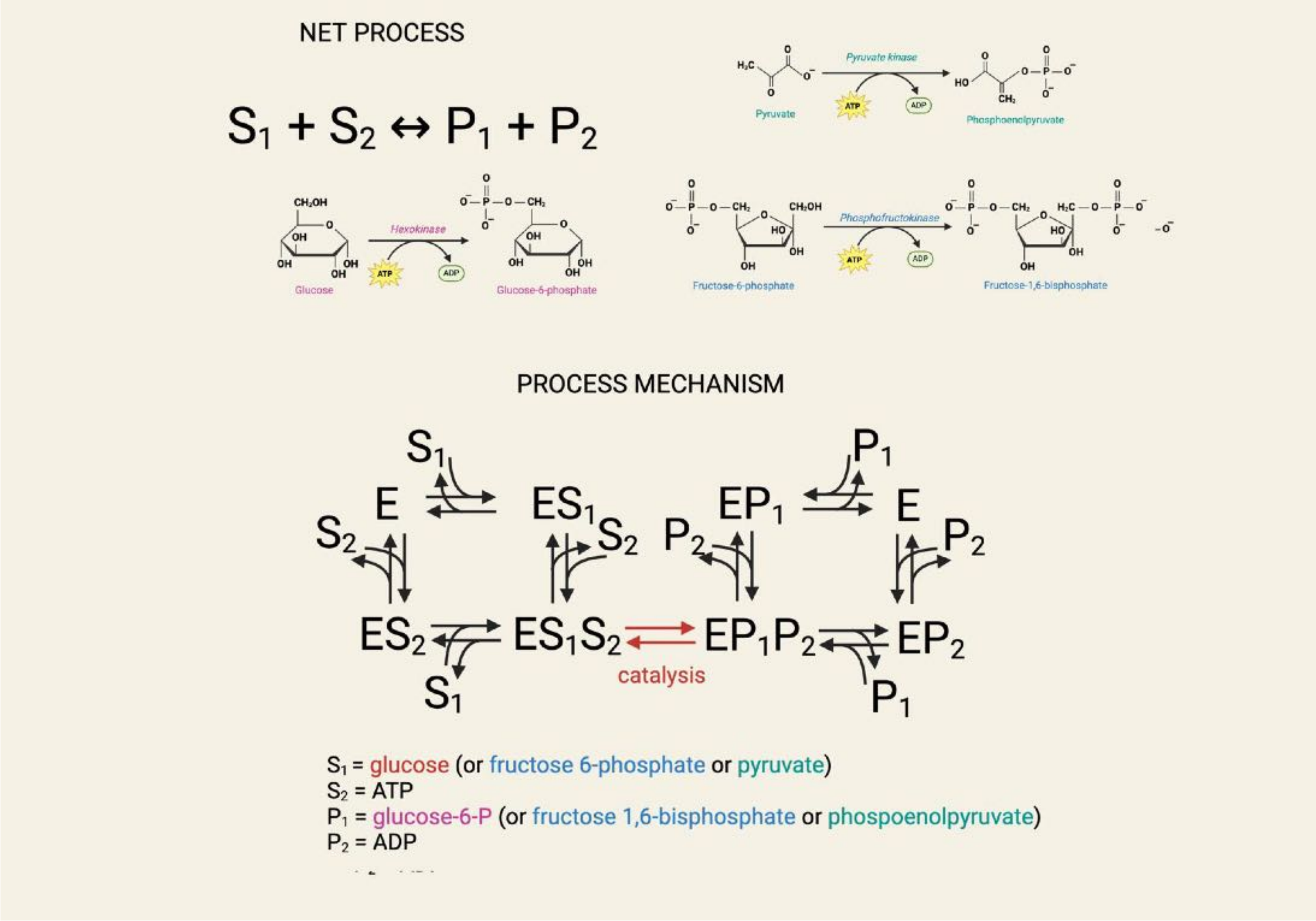
examples of state transition diagrams

transcription factor dimerisation, phosphorylation and dephoshorylation by dedicated enzymes, conformational change, DNA binding

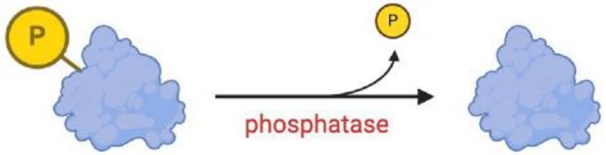


examples of state transition diagrams

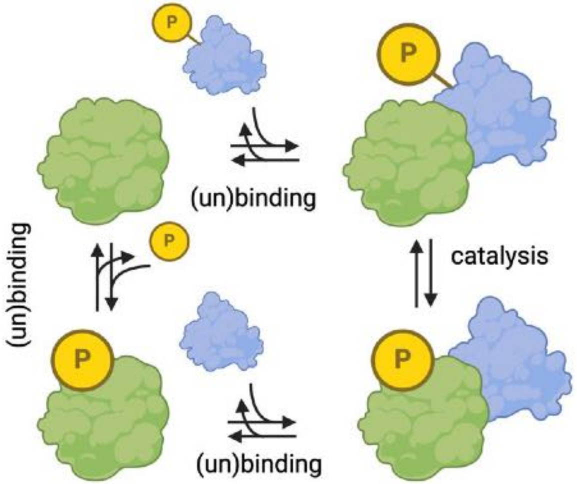
two substrate and two product enzyme mechanism; e.g. protein phosphorylation



exercise: make an enzyme-catalysed protein dephosphorylation state-transition diagram

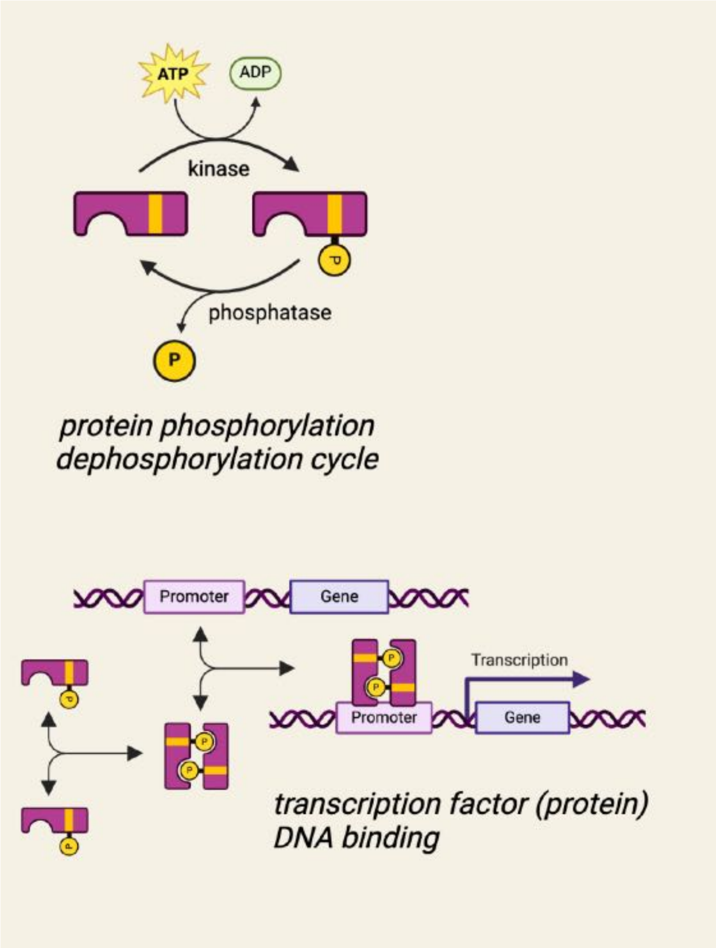


net process



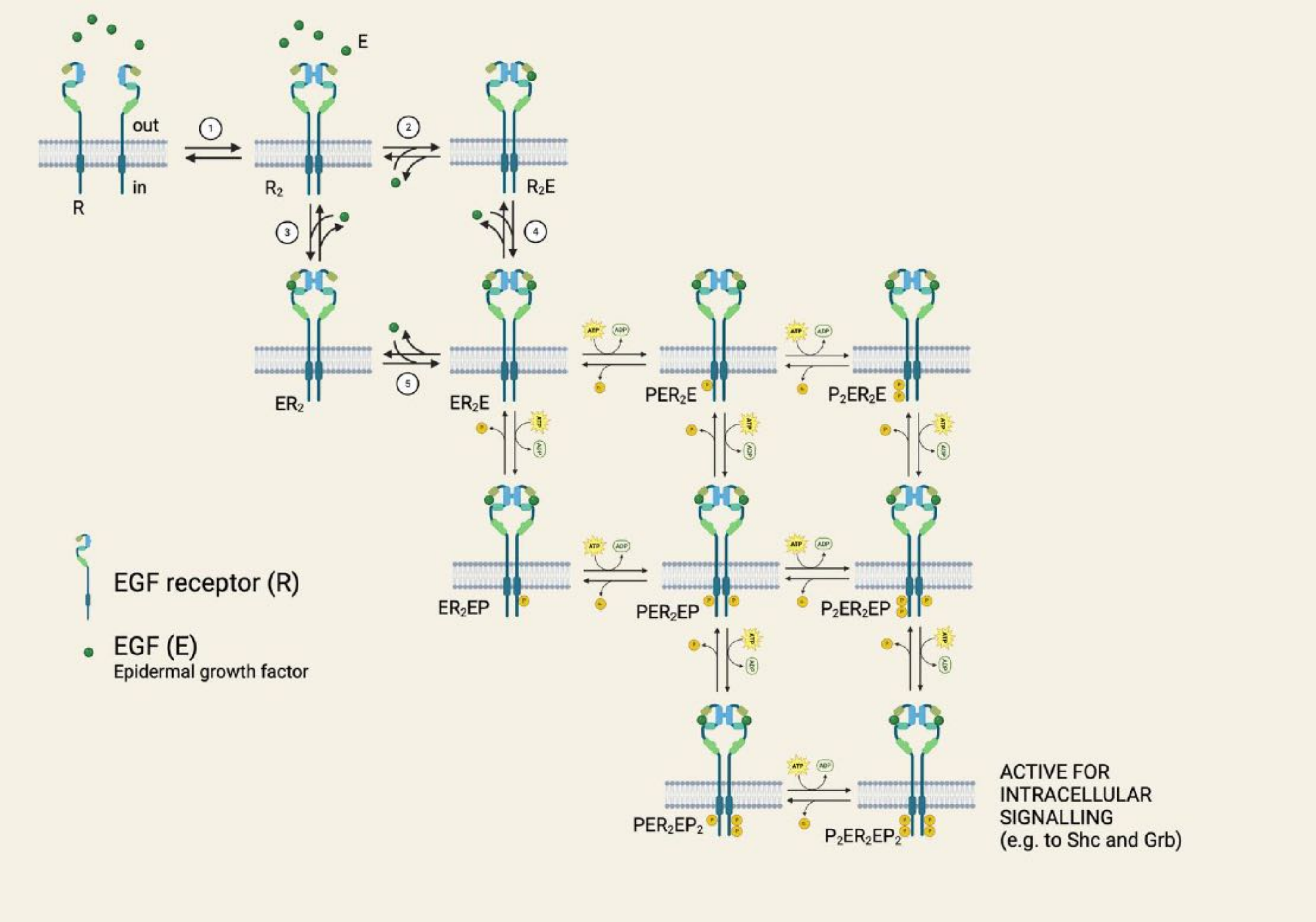
state
transition
diagram

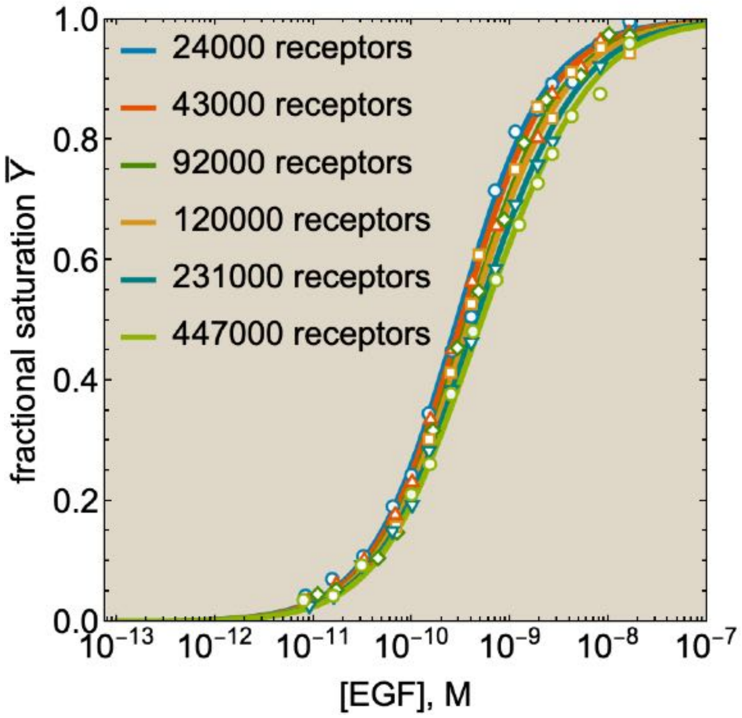
Transcription factor phosphorylation and DNA binding



examples of state transition diagrams

membrane receptor dimerisation, ligand (growth factor) binding, autophosphorylation





SEE CORRECTION FOR THIS ARTICLE

Heterogeneity in EGF-binding affinities arises from negative cooperativity in an aggregating system

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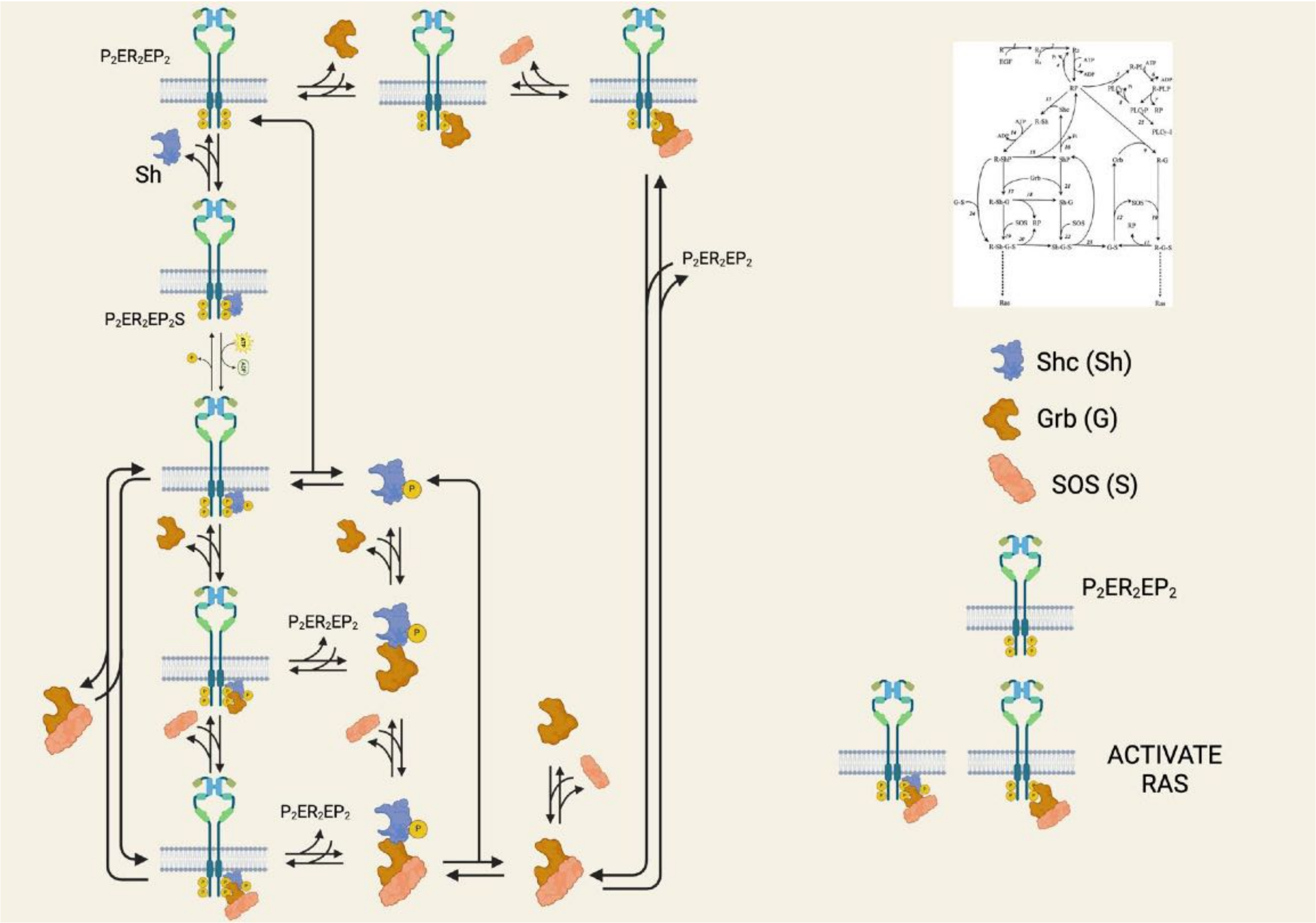
Edited by Philip W. Majerus, Washington University School of Medicine, St. Louis, MO, and approved November 6, 2007 (received for review July 27, 2007)

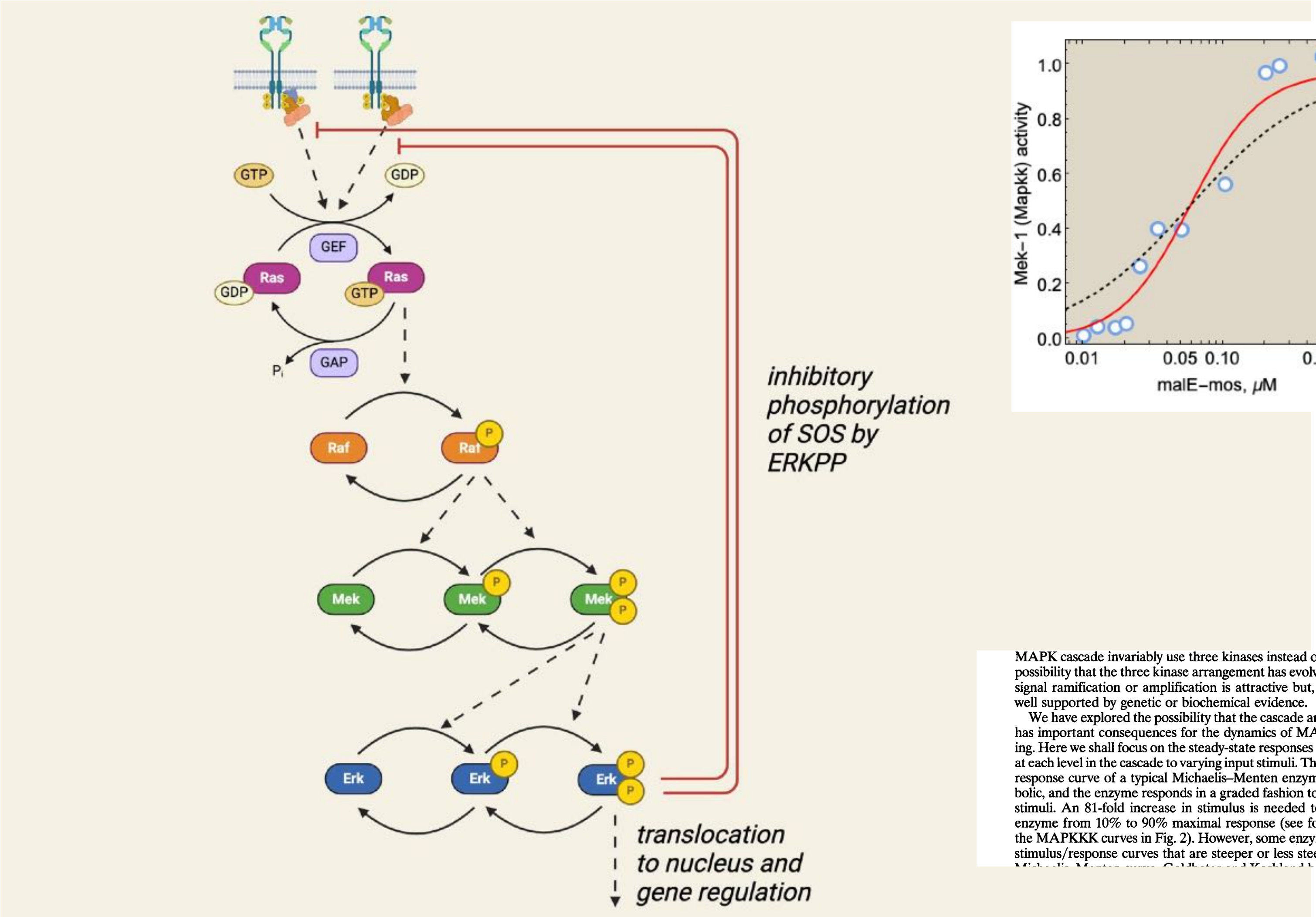
examples of state transition diagrams

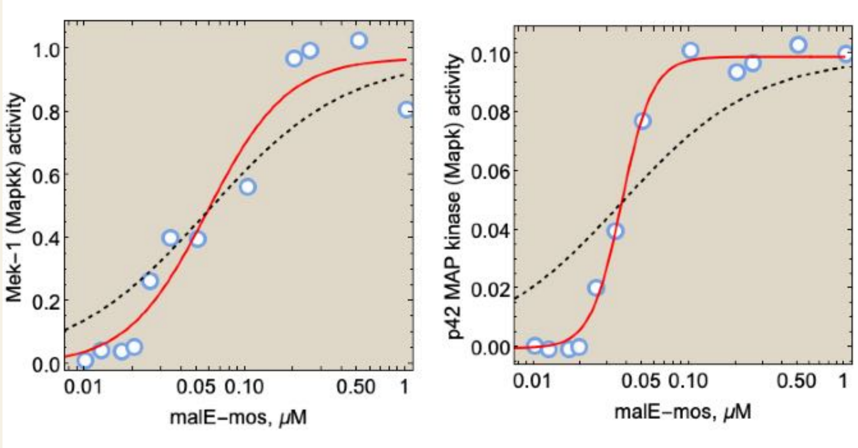
downstream signalling from EFG receptor, binding of adaptor proteins



examples of state transition diagrams

downstream signalling from EFG receptor continued, activation of MAPK pathway





MAPK cascade invariably use three kinases instead of one? The possibility that the three kinase arrangement has evolved to allow signal ramification or amplification is attractive but, as yet, not well supported by genetic or biochemical evidence.

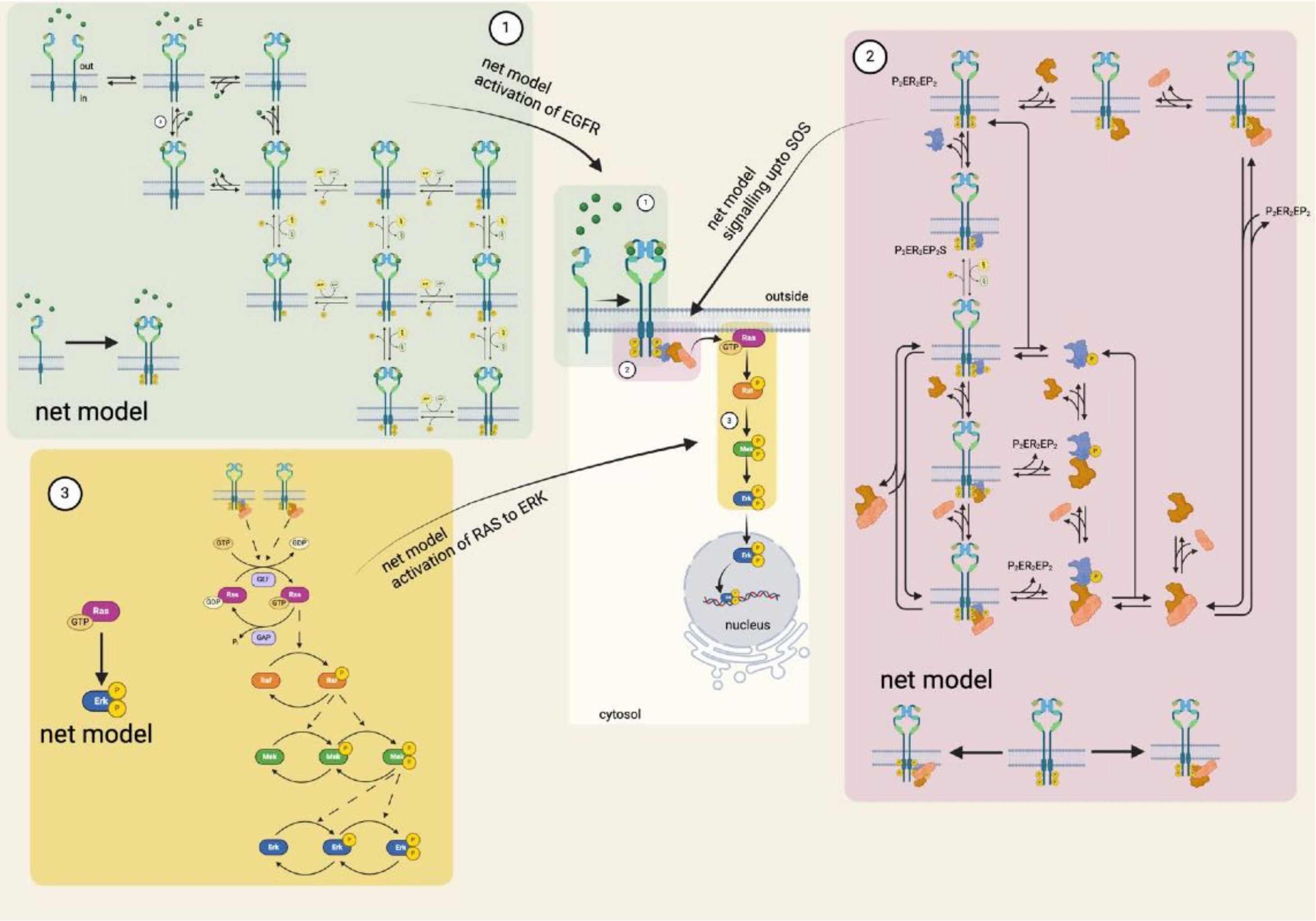
We have explored the possibility that the cascade arrangement has important consequences for the dynamics of MAPK signaling. Here we shall focus on the steady-state responses of enzymes at each level in the cascade to varying input stimuli. The stimulus/response curve of a typical Michaelis–Menten enzyme is hyperbolic, and the enzyme responds in a graded fashion to increasing stimuli. An 81-fold increase in stimulus is needed to drive the enzyme from 10% to 90% maximal response (see for example, the MAPKKK curves in Fig. 2). However, some enzymes exhibit stimulus/response curves that are steeper or less steep than the

enzymes tend toward all-or-none, switch-like responses.

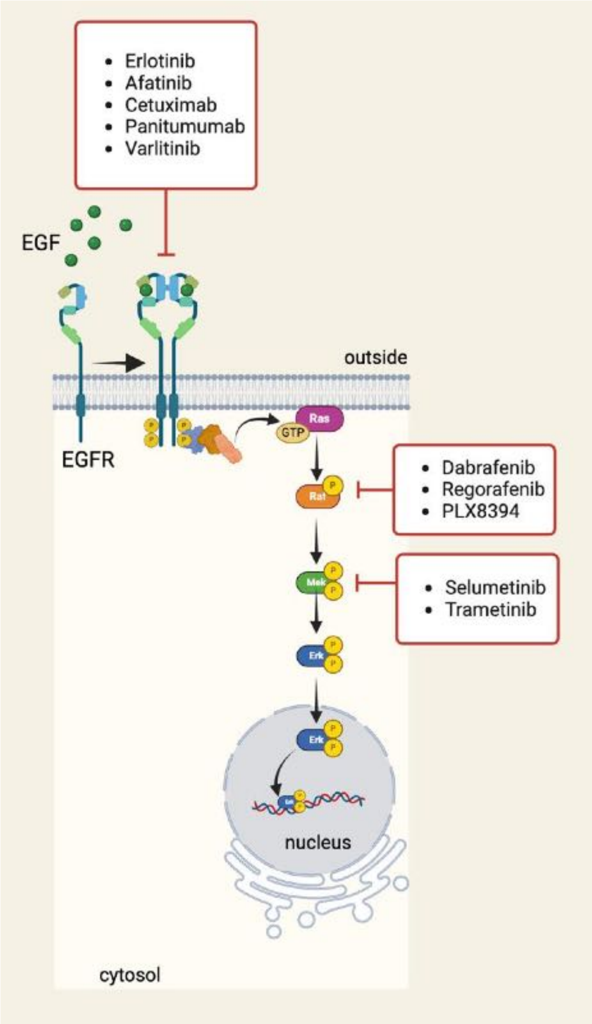
The most widely appreciated mechanism for genera ultrasensitive responses is cooperativity. Positively cooper enzymes have sigmoidal stimulus/response curves, and rec less than an 81-fold stimulus to drive them from 10% to maximal response. However, cooperativity is not the mechanism through which ultrasensitive responses car generated. Ultrasensitivity also arises when enzyme c operate near saturation ["zero-order ultrasensitivity" (and when stimuli impinge upon multiple steps of an enz cascade ["multistep ultrasensitivity" (12–14)].

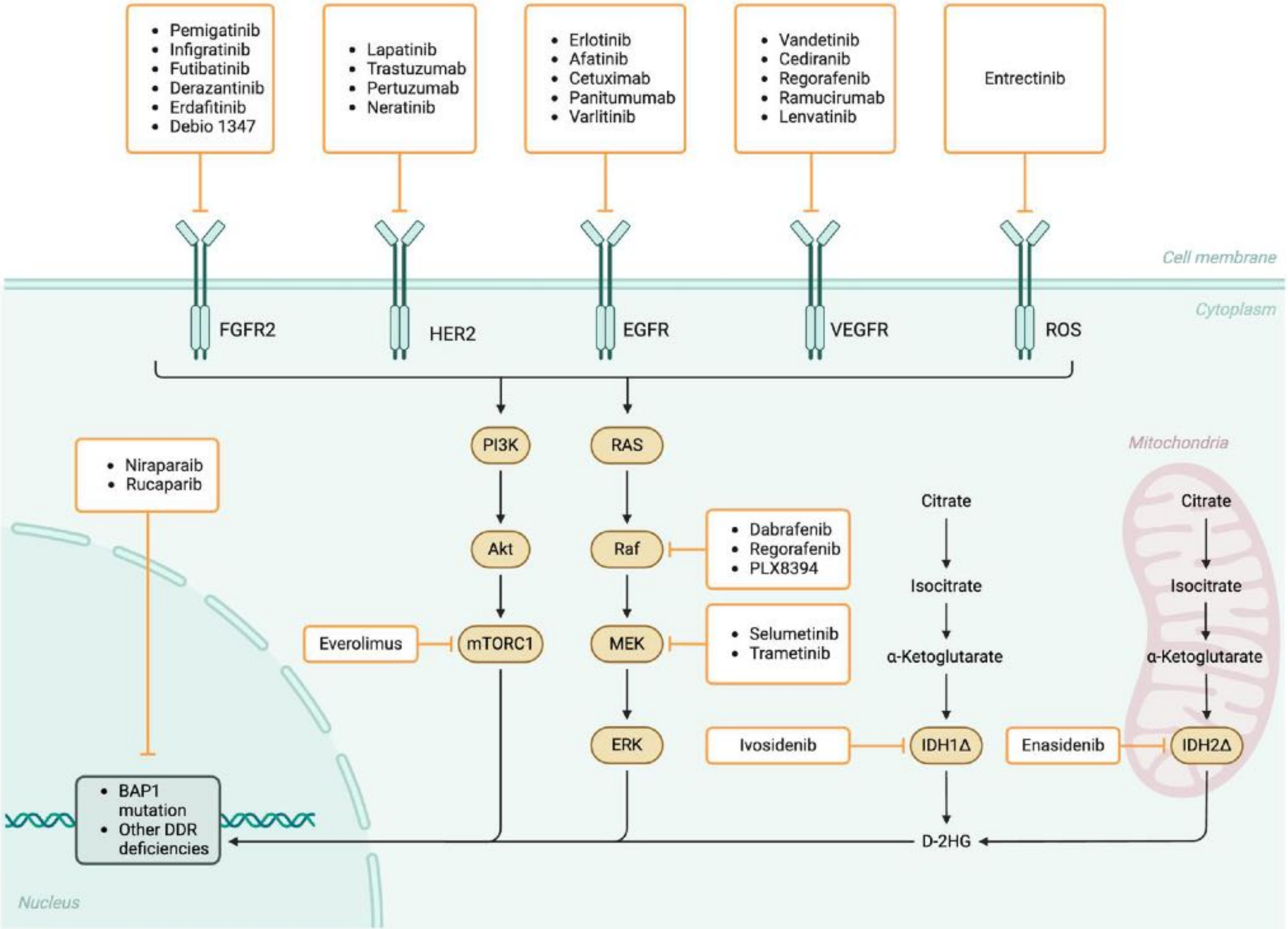
We have investigated whether an ultrasensitive, switch response would be expected of the vertebrate Erk1/ MAPK cascade, given what is known about the abundance

net models and state transition diagrams



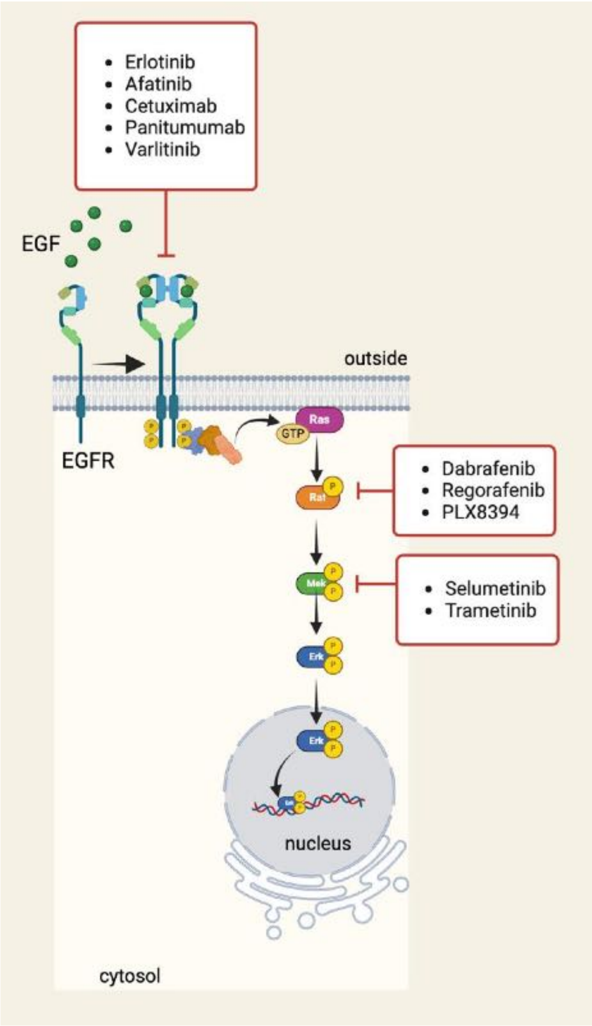
drug targets cancer treatment often in this signaling network





net process of last four slides

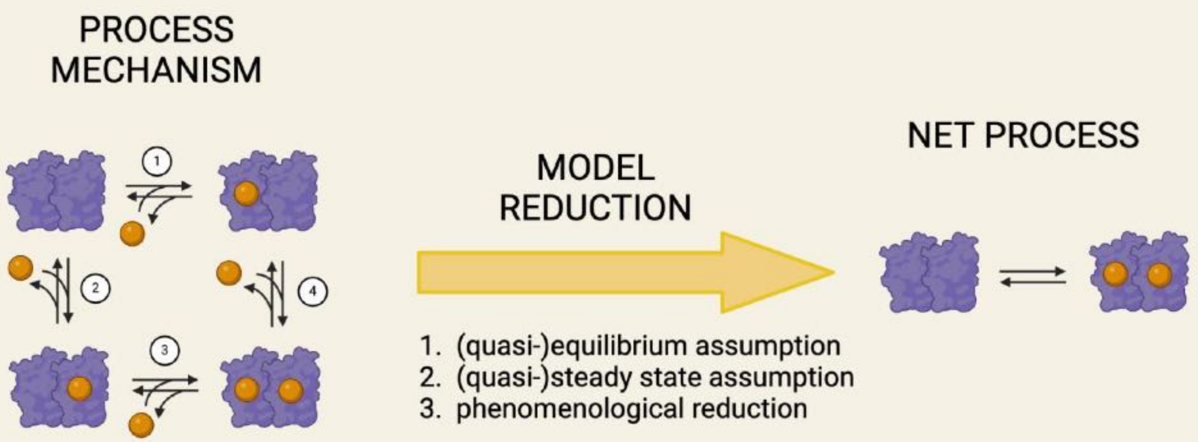
exercise



- give three mechanisms for the inhibitory effect of trametinib on MEKPP.

- why do we make state-transition diagrams?

Next steps, coming weeks



mass-action kinetics model

$$\frac{ds}{dt} = -v_1 - v_2 - v_3 - v_4$$
$$\frac{dr_2}{dt} = -v_1 - v_2$$
$$\frac{dr_2s}{dt} = v_1 - v_2$$
$$\frac{dsr_2}{dt} = v_2 - v_3$$
$$\frac{dr_2s_2}{dt} = v_3 + v_4$$

$$v_1 = k_1^+ \times r_2 \times s - k_1^- \times sr_2$$
$$v_2 = k_2^+ \times r_2 \times s - k_2^- \times r_2s$$
$$v_3 = k_3^+ \times sr_2 \times s - k_3^- \times r_2s_2$$
$$v_4 = k_4^+ \times r_2s \times s - k_4^- \times r_2s_2$$

equilibrium model

$$r_2s_2 = r_{2,T}\frac{\frac{s^2}{\alpha K_S^2}}{1 + 2\frac{s}{\alpha K_S} + \frac{s^2}{\alpha K_S^2}}$$

Make a few state transition models of net processes occurring in this diagram