

s-block elements:

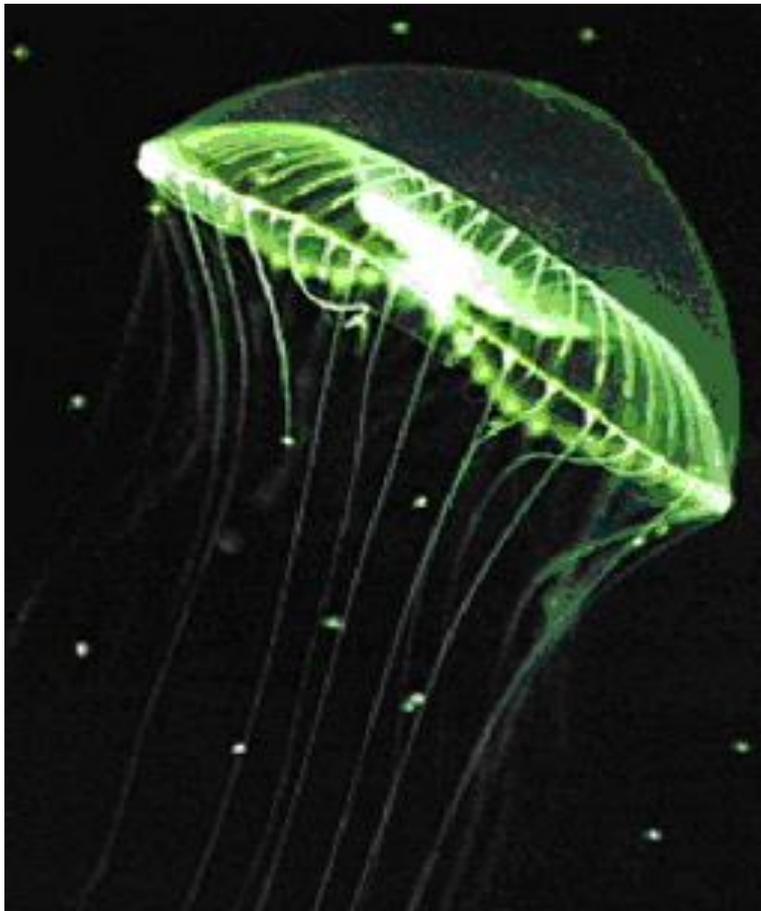


Together with the anions Cl^- and HPO_4^- they represent the **electrolytes** of living systems.

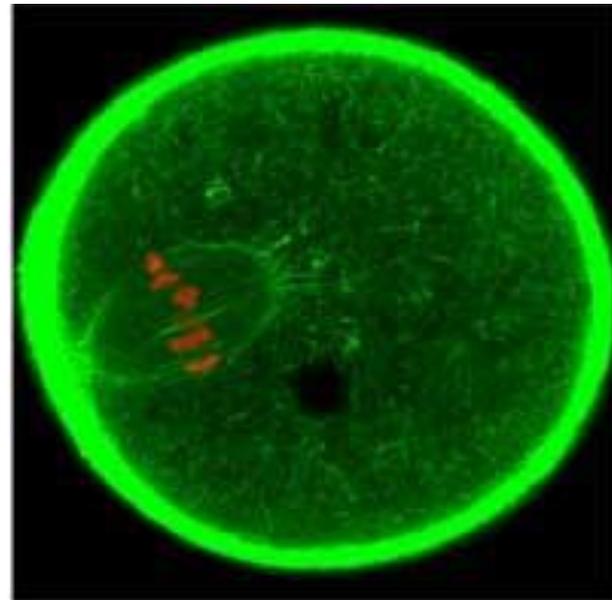
By virtue of their high mobility, they are used as **charge transporters** and to create **charge gradients** across membranes

Ion	Radius (Å)	Ion	Radius (Å)
Na ⁺	1.02	Mg ²⁺	0.72
K ⁺	1.38	Ca ²⁺	1.00

Mg²⁺ is the least labile ion, with water exchange kinetic constant ca. 10^5 s^{-1} (vs 10^8 s^{-1} for the others)

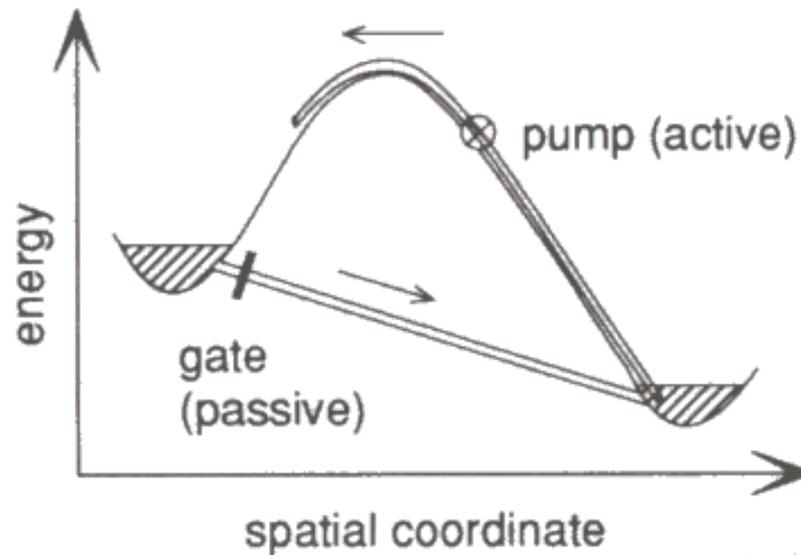


Green Fluorescent Protein (GFP) =
fluorescent sensor for Ca²⁺

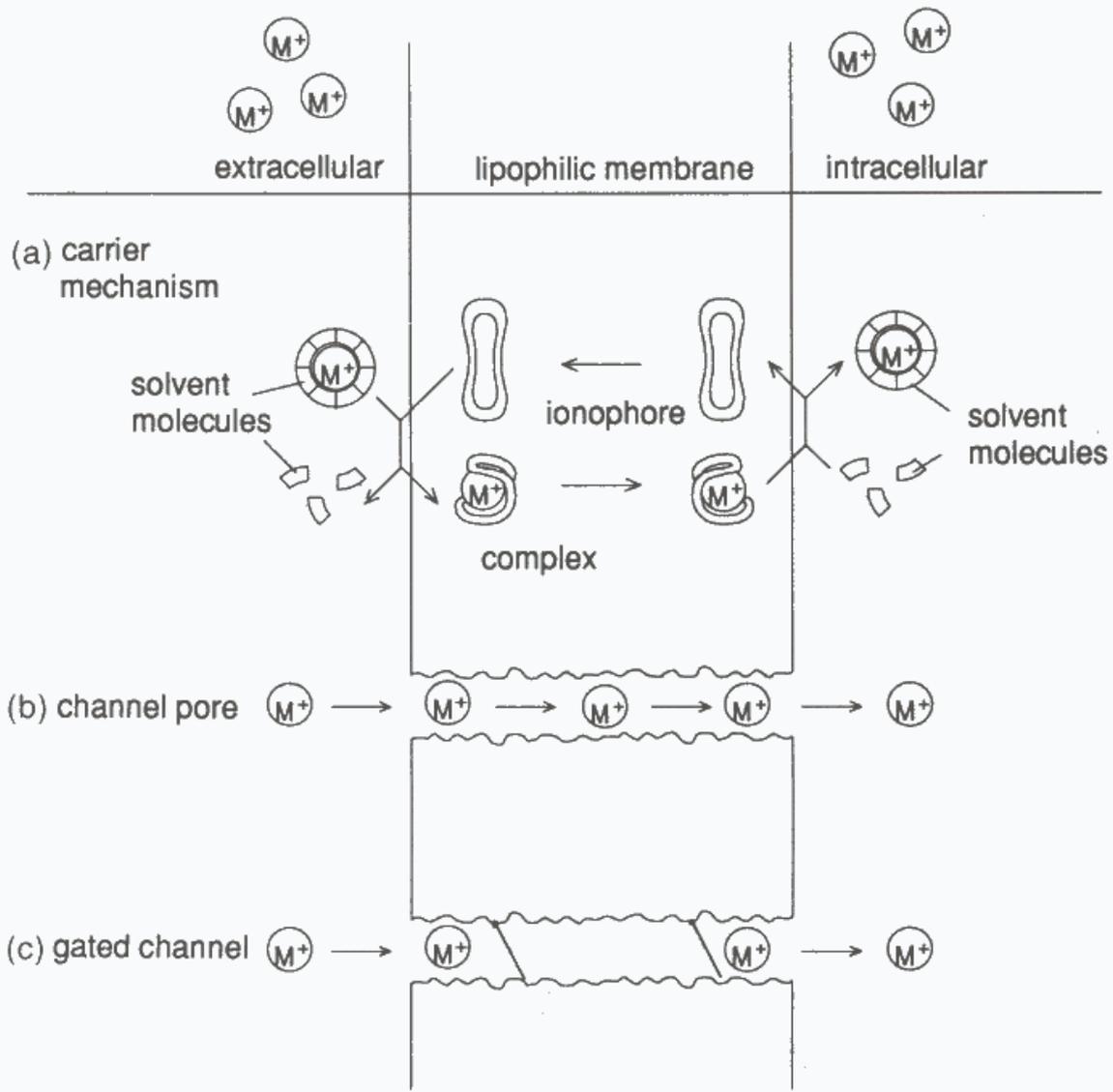


Ion	Intracellular (mM)	Extracellular (mM)
Na ⁺	10	150
K ⁺	100	5
Mg ²⁺	2.5	1.5
Ca ²⁺	0.1 ^a	2.5
Cl ⁻	4	100

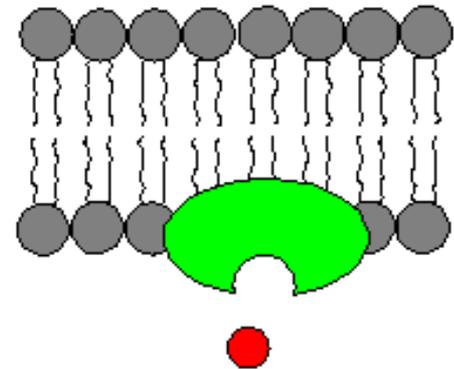
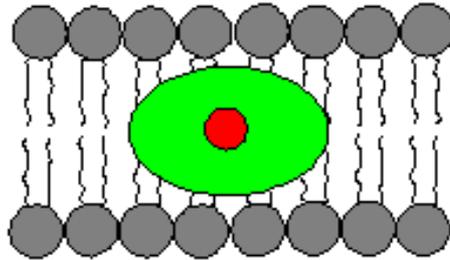
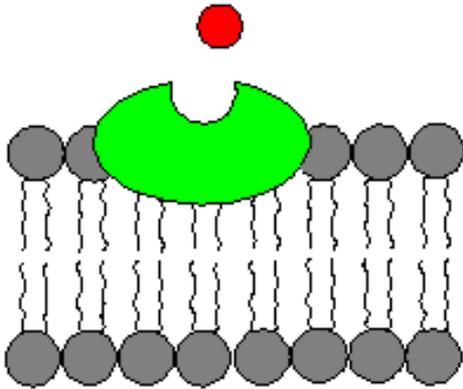
^a0.1 μM inside the cytoplasm of resting cell, i.e. 10⁴ times less than outside



ion-transport mechanisms



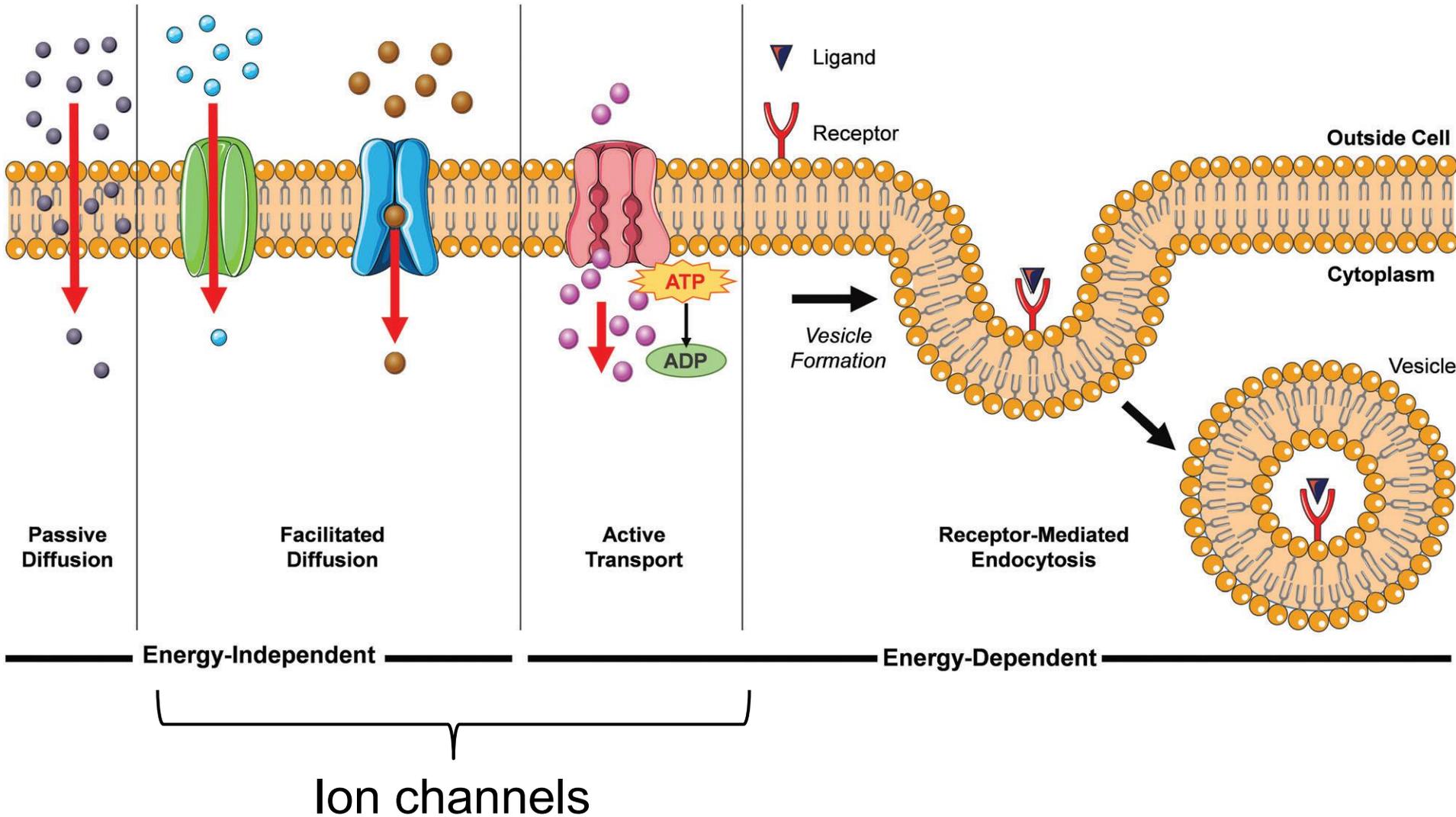
Ionophores



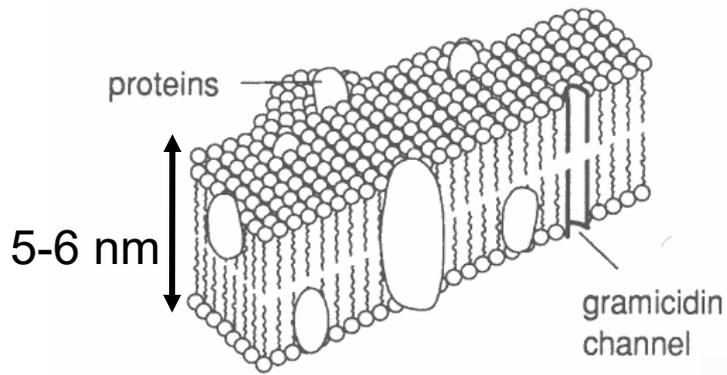
Valinomycin transports through the mitochondrial membrane $10^3 - 10^4$ K^+ ions per second without affecting the concentration of Na^+ ions.

The K^+/Na^+ selectivity is ca. 10^4 .

trans-membrane transport mechanisms



Ion channels

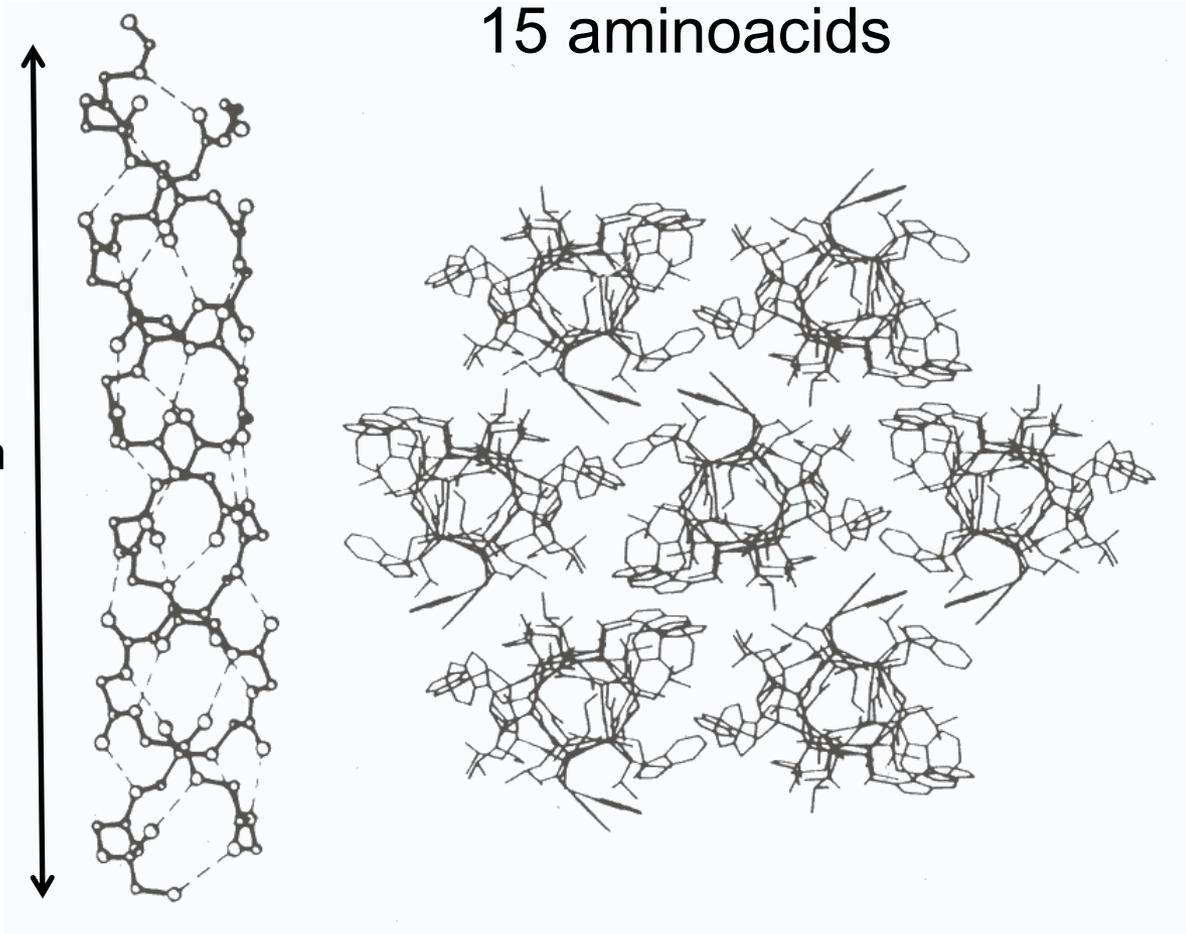


fluid double layer

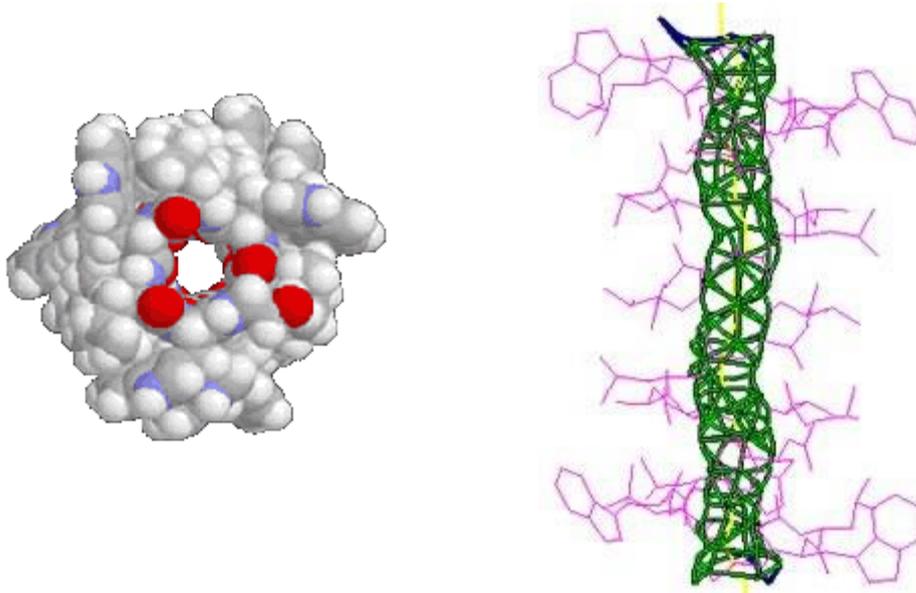
0.4 nm

3 nm

Gramicidin A
15 aminoacids

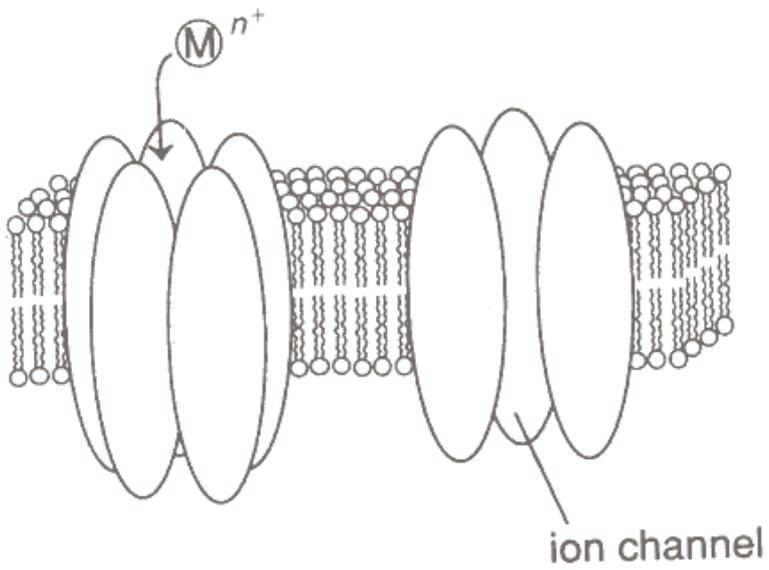


Gramicidin A

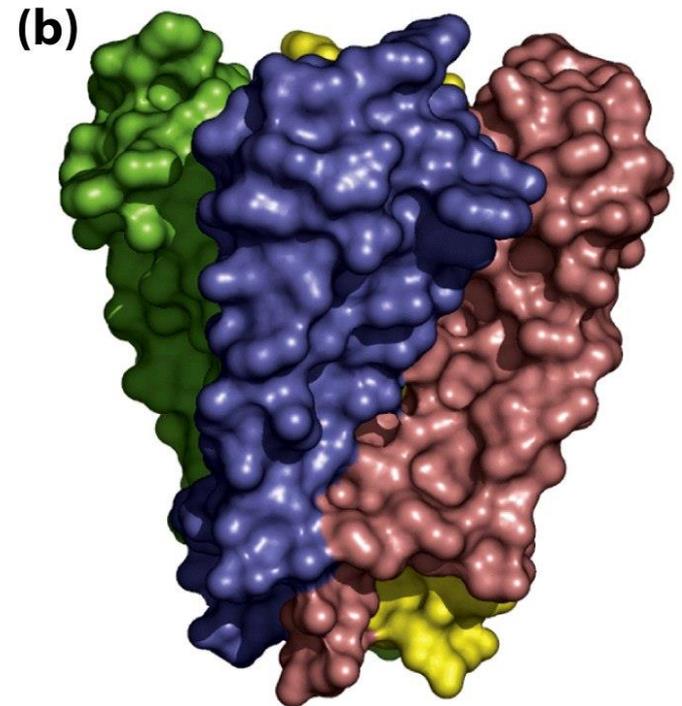
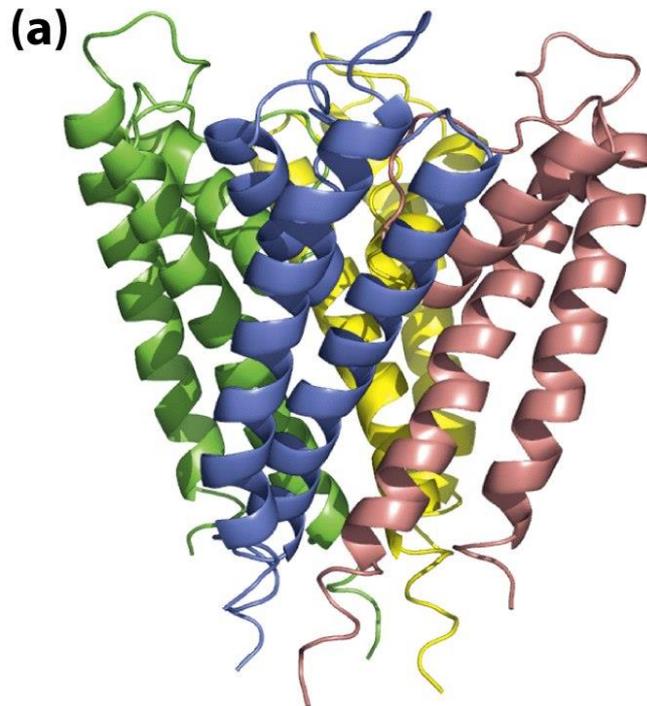


Gramicidin A transports through the cell membrane 10^7 K^+ or Na^+ ions per second. The divalent cations block the pore.

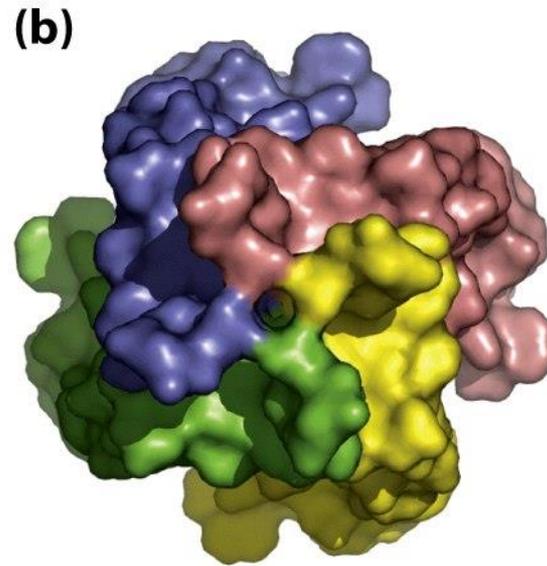
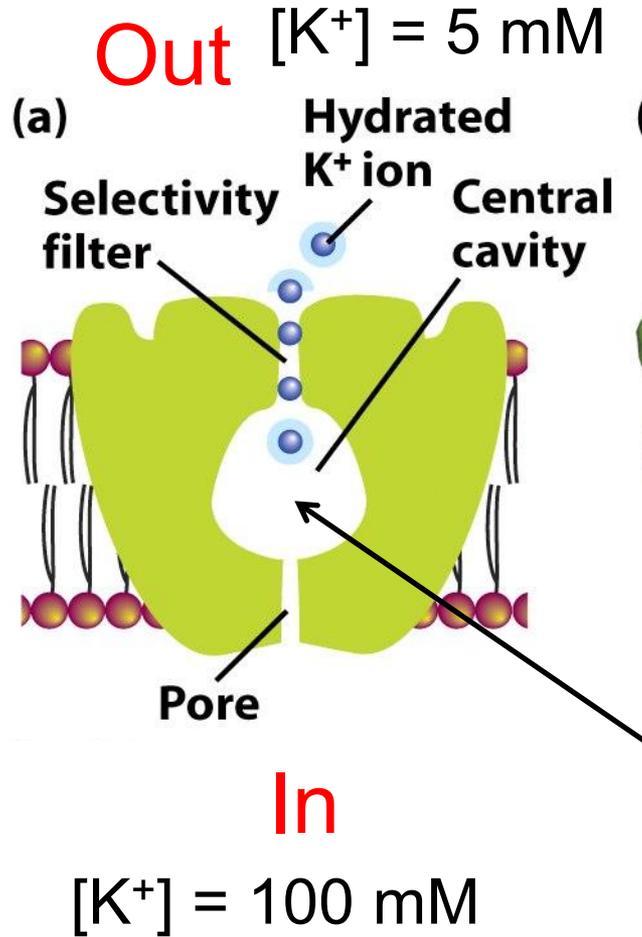
trans-membrane proteins



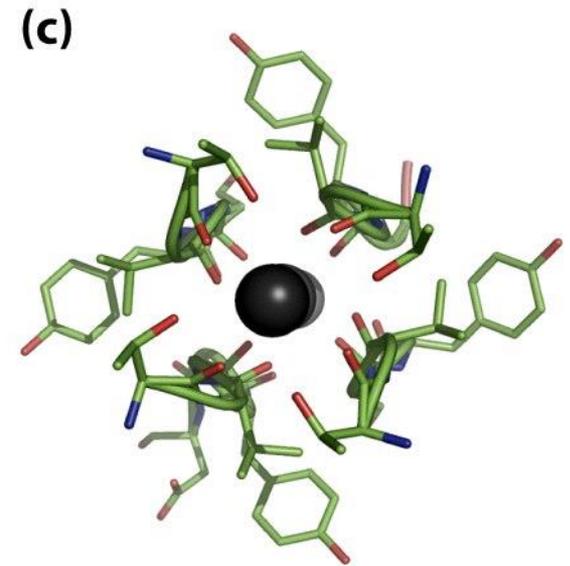
K^+ Channel

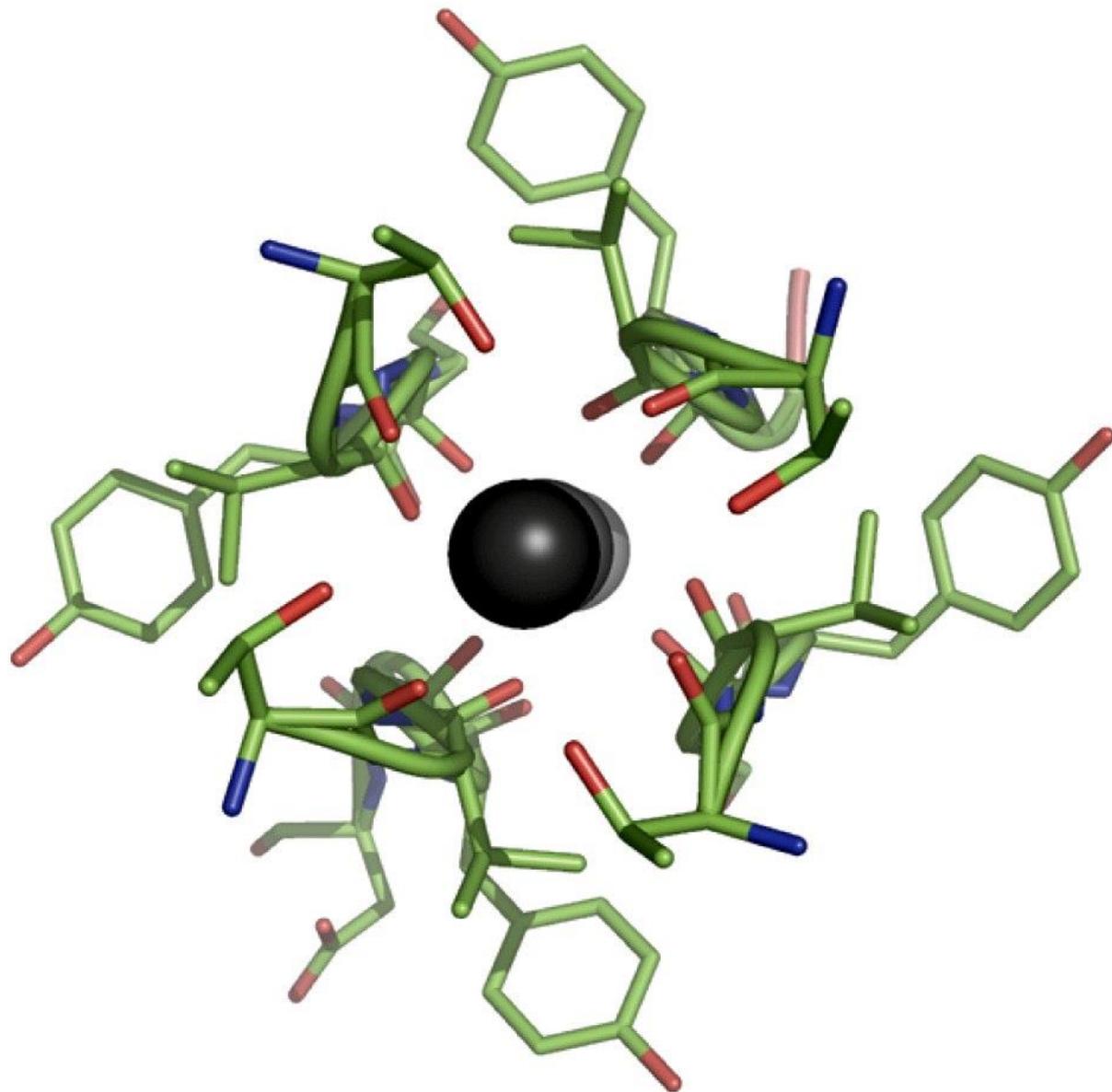


potential gated K^+ channel

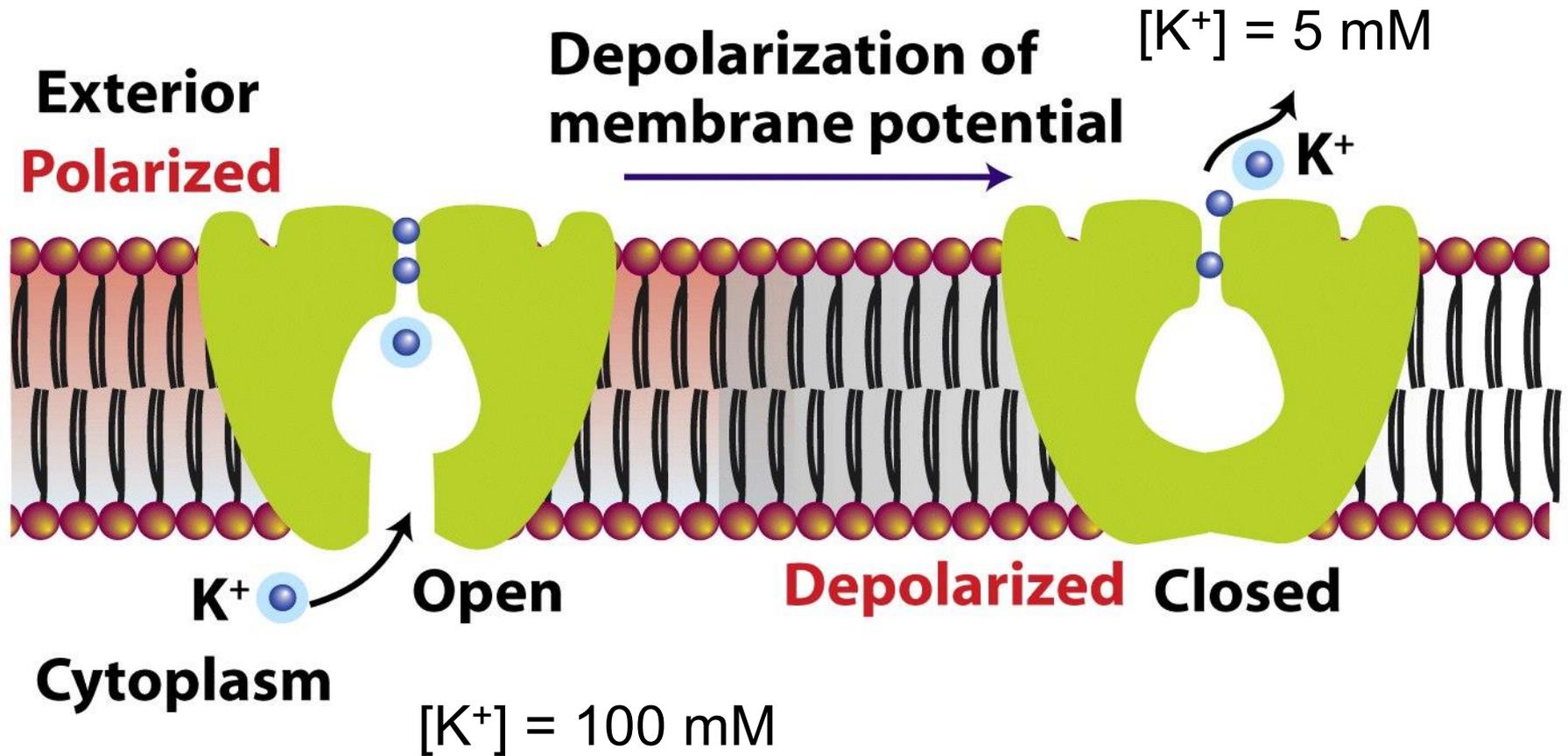


$\text{\AA} = 1 \text{ nm}$
 $[K^+] = 2 \text{ M}$



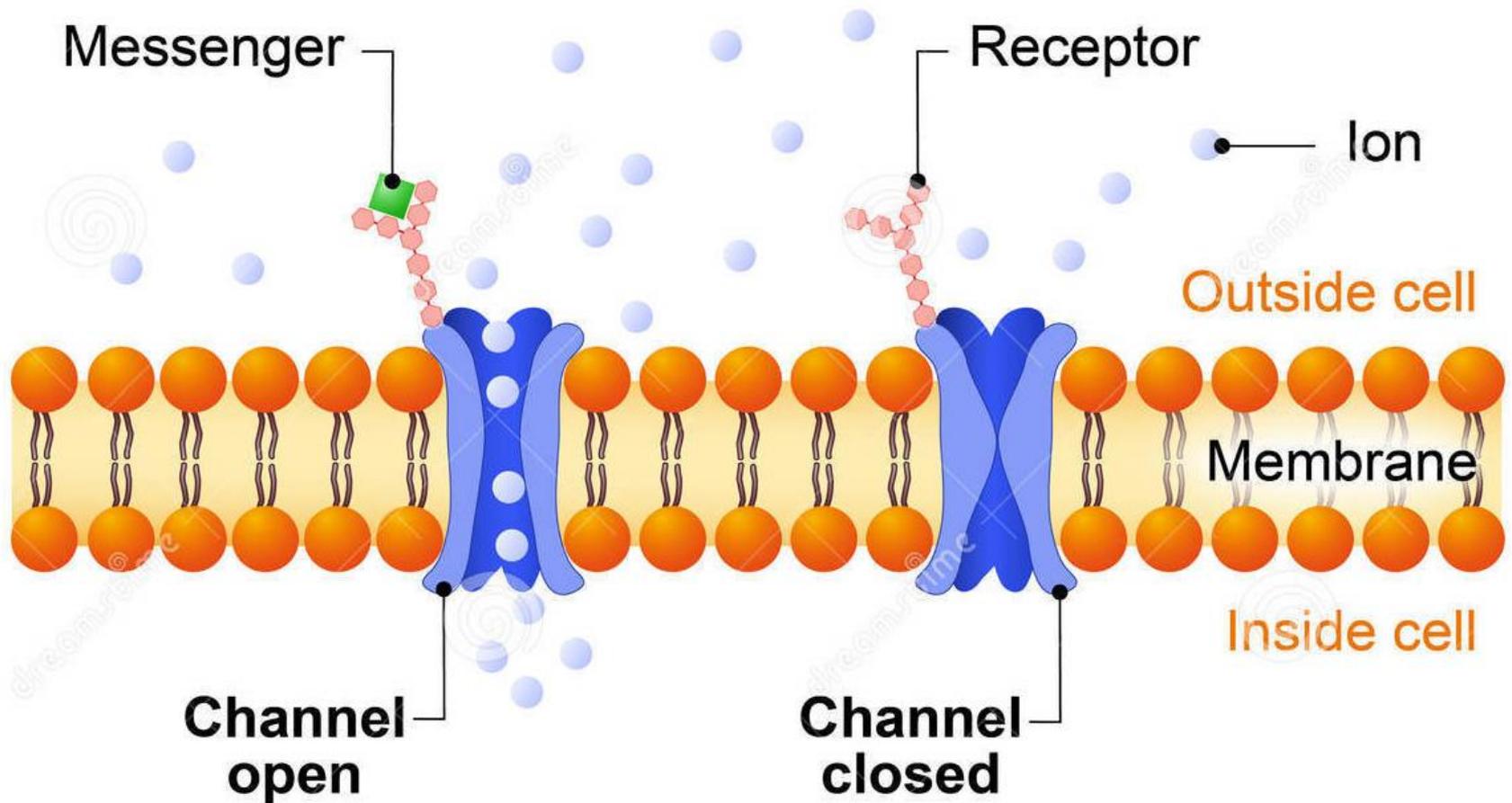


potential gated K^+ channel

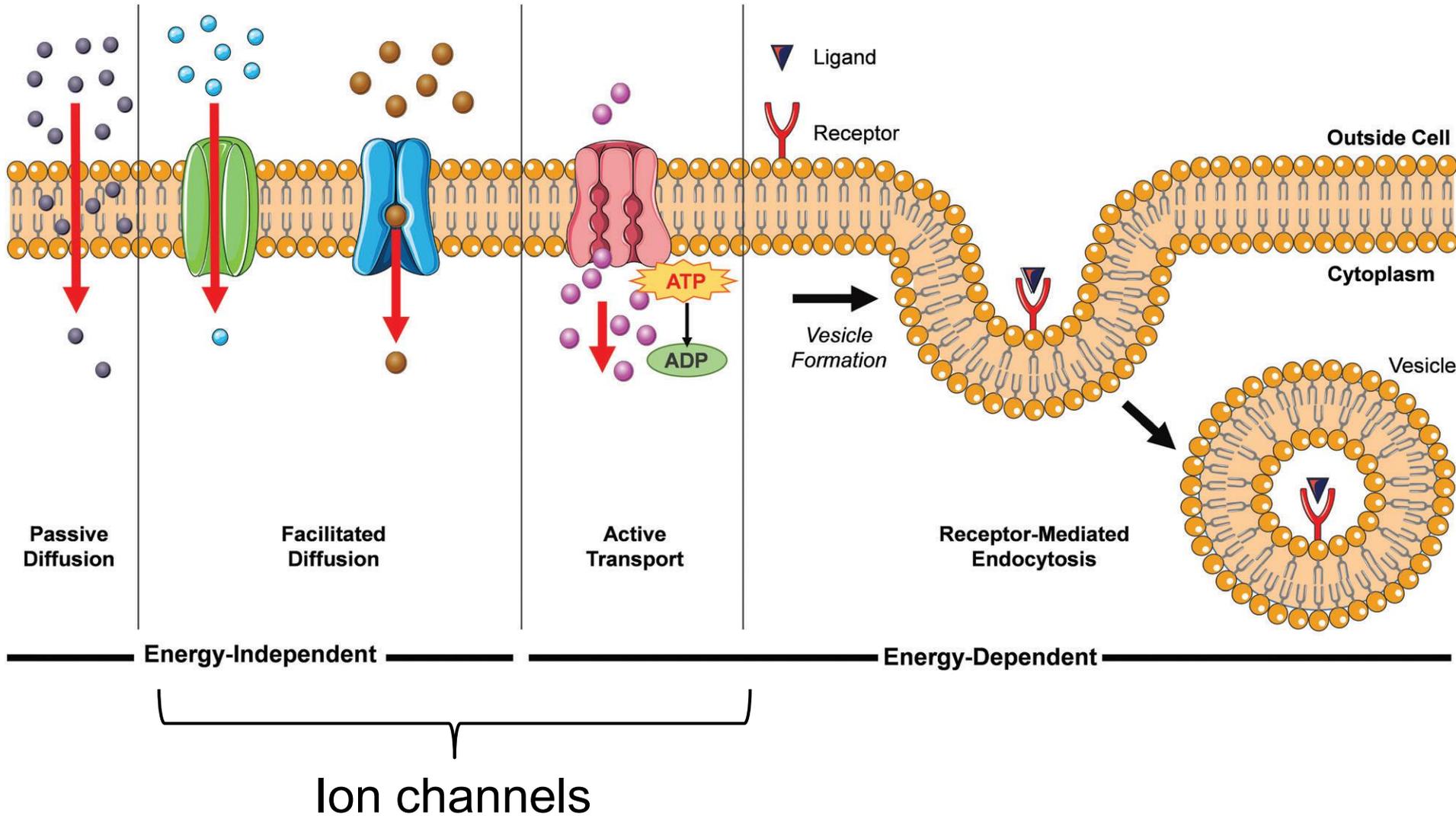


The K^+/Na^+ selectivity is ca. 10^4

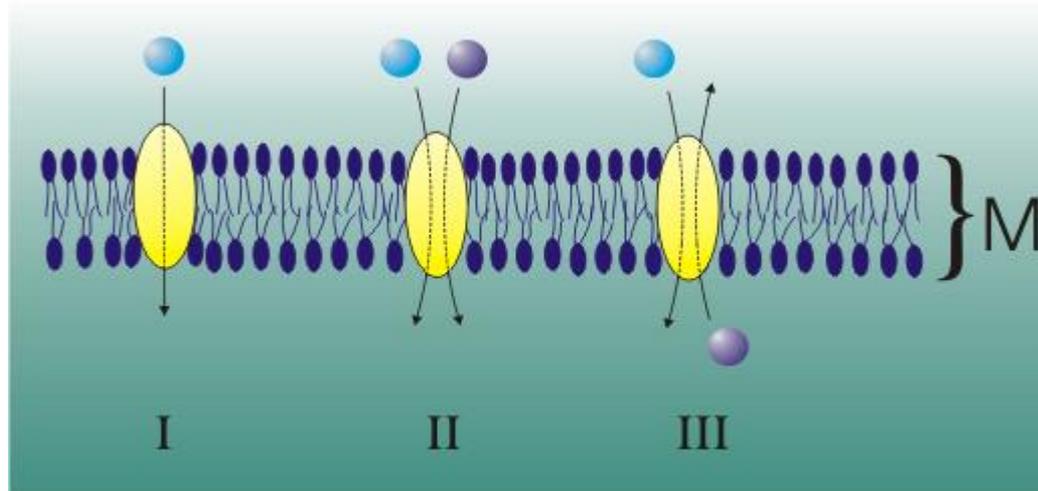
Ligand-gated ion channel



trans-membrane transport mechanisms

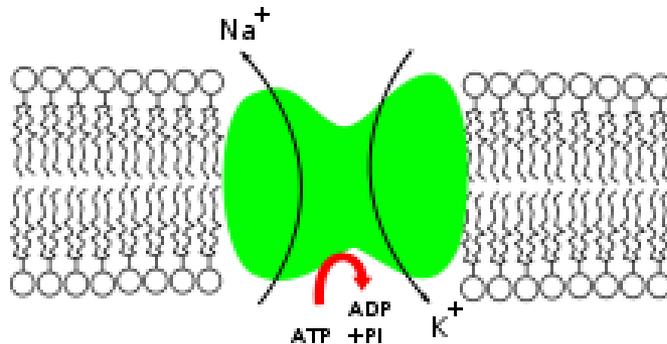


Ionic pumps (ATPases)



Uniporter Symporter Antiporter

Na^+/K^+ -ATPase *antiporter* ionic pump

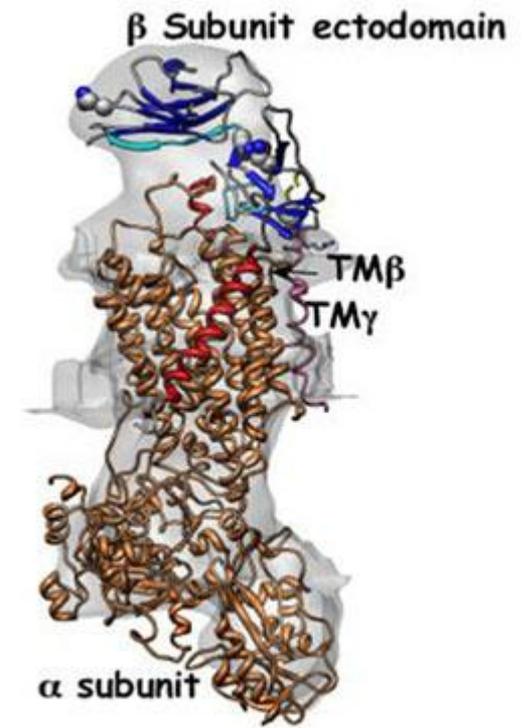
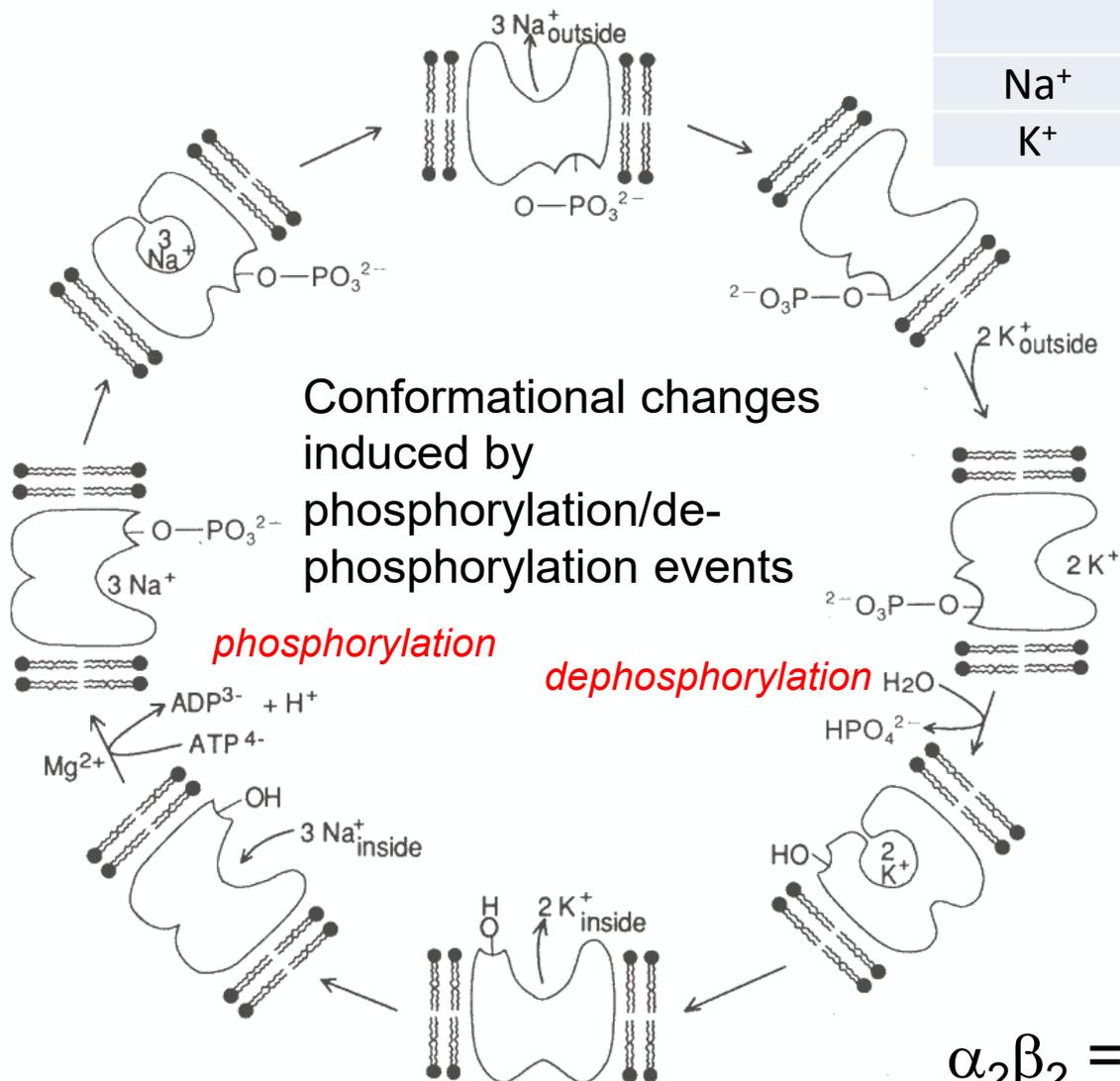


Ion	Intracellular (mM)	Extracellular (mM)
Na ⁺	10	150
K ⁺	100	5

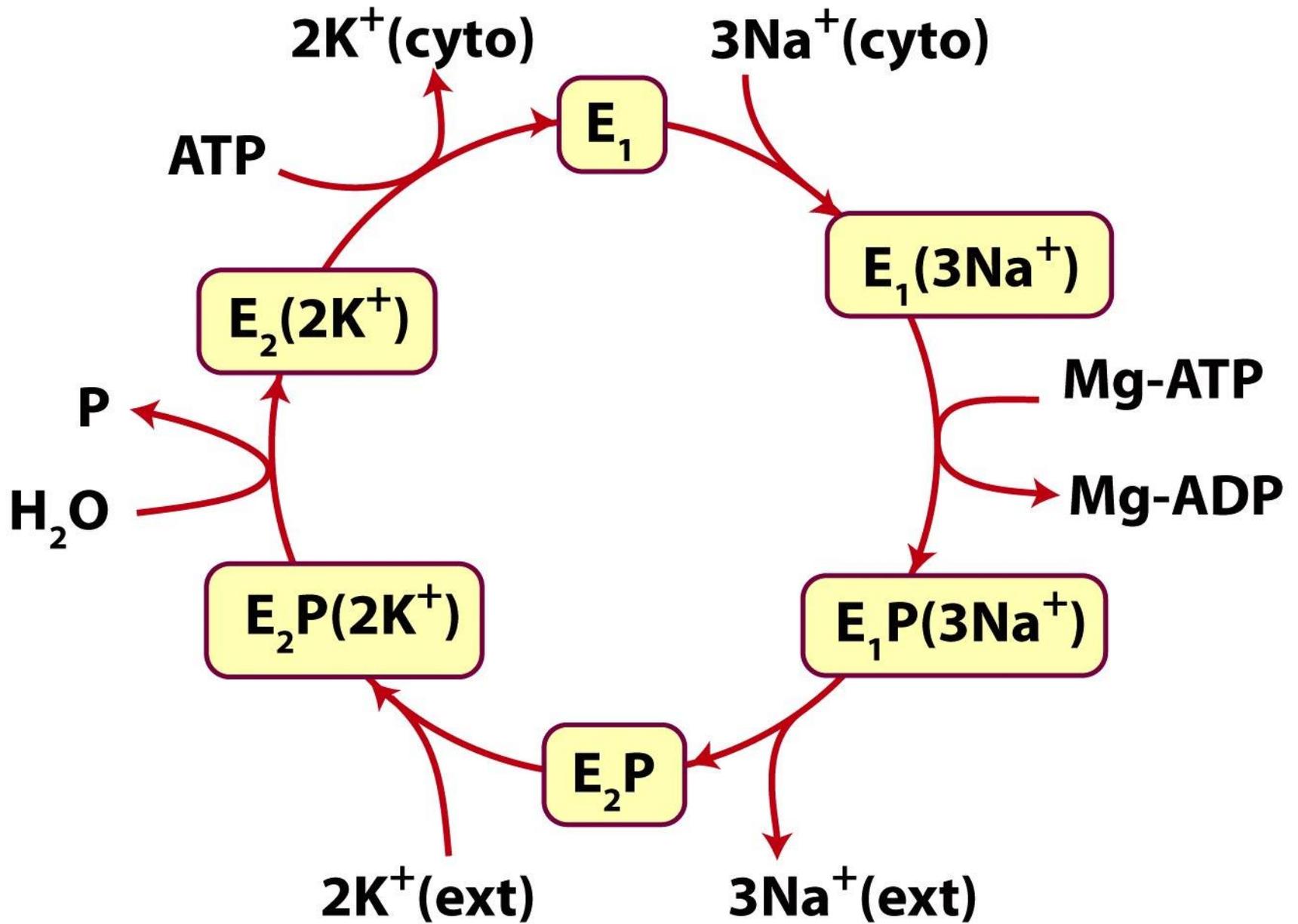
antiporter Na⁺/K⁺-ATPase ionic pump

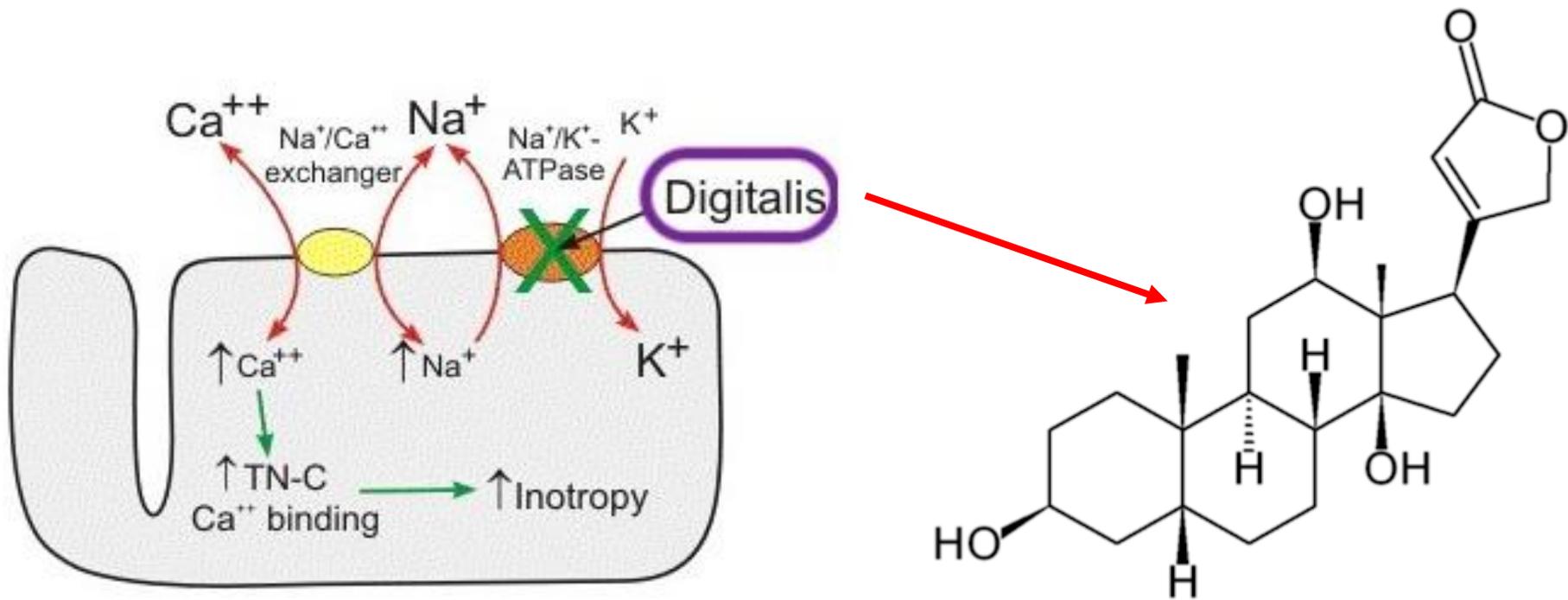


Ion	Intracellular (mM)	Extracellular (mM)
Na ⁺	10	150
K ⁺	100	5



$$\alpha_2\beta_2 = 2 \times 112(\alpha) + 2 \times 35(\beta)$$



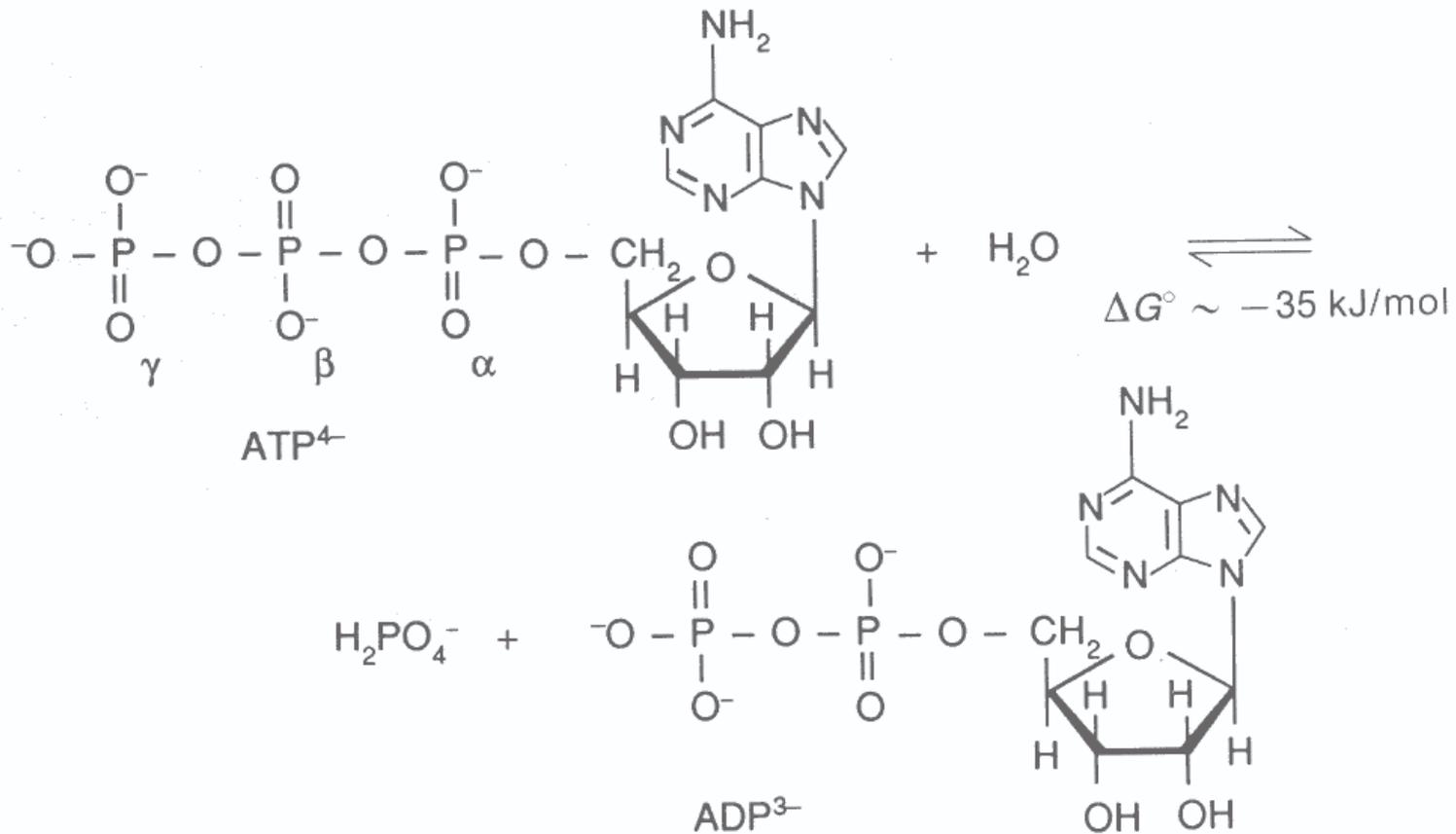


At the level of cardiac muscle, inhibition of the Na^+/K^+ pump by **digitalis** (an alkaloid) increases $[\text{Na}^+]$ within the cell, leading to activation of the **$\text{Na}^+/\text{Ca}^{2+}$ antiport pump**, and thus to an increase in intracellular $[\text{Ca}^{2+}]$ that – by binding to troponin-C – results in intensification of muscle contraction (cardiotonic effect).



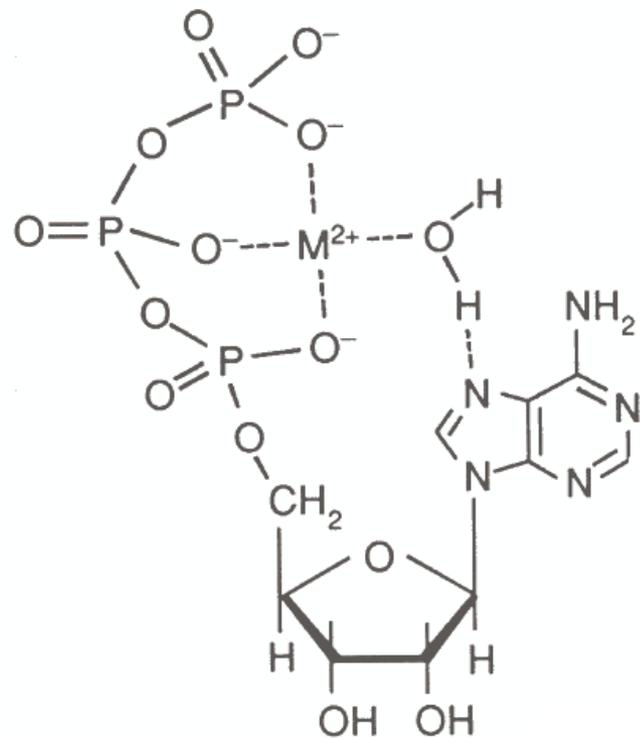
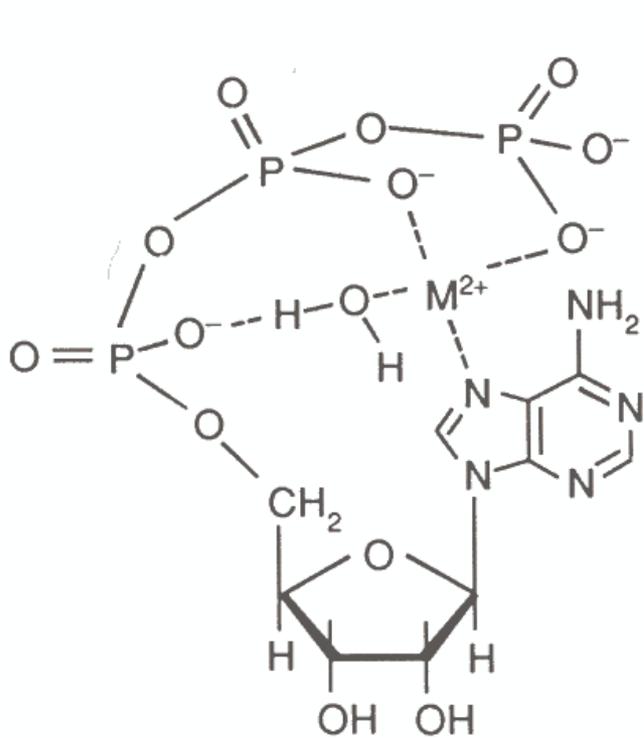
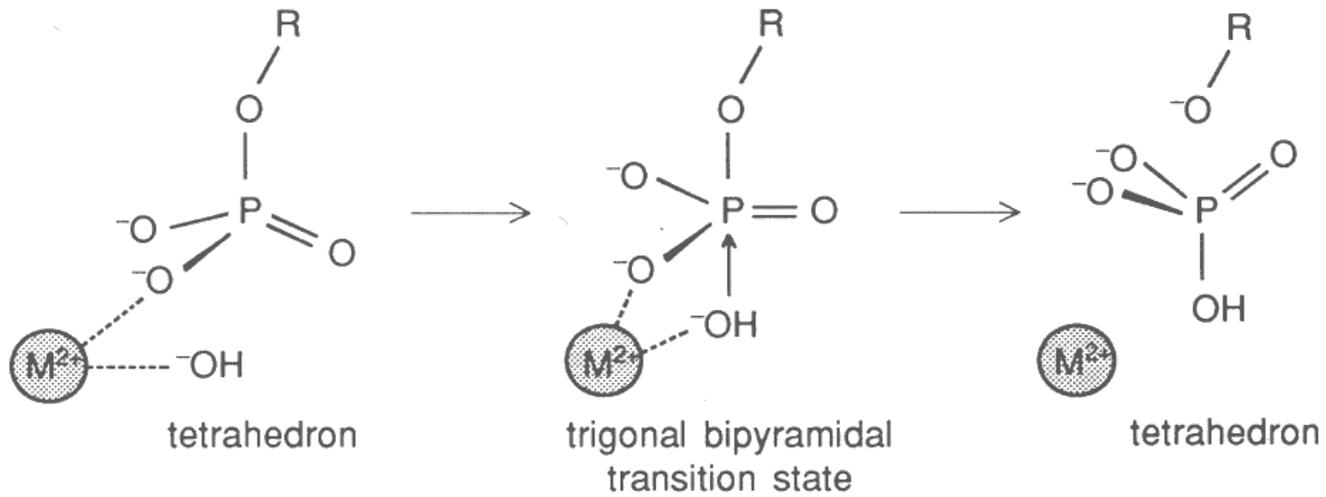
Very hard cation, strong preference for 6-coordination (octahedral) with negatively-charged O donor atoms, mainly phosphates (with remarkable exceptions, e.g. RuBisCo, chlorophyll).
Its roles are both structural (RNA and DNA *folding*) and functional (Lewis acid catalyst).

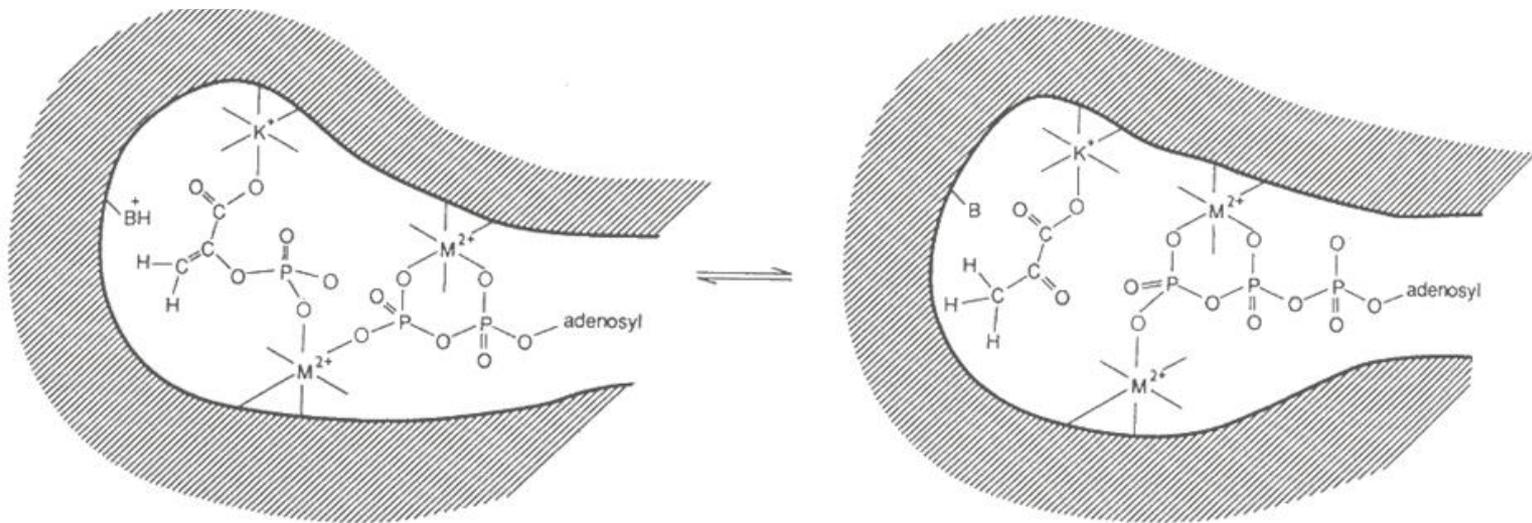
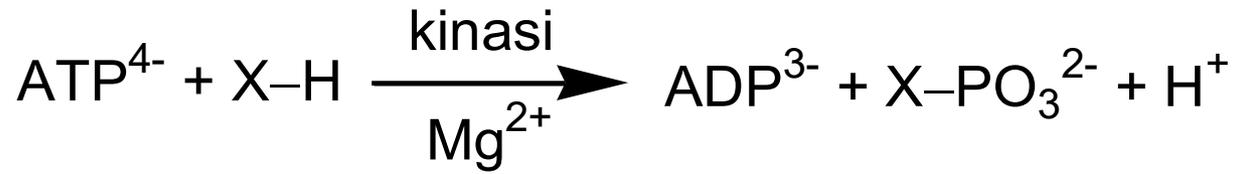
Magnesium



On average, every single day an adult synthesizes and uses an amount of ATP corresponding to its own body weight

S_N2



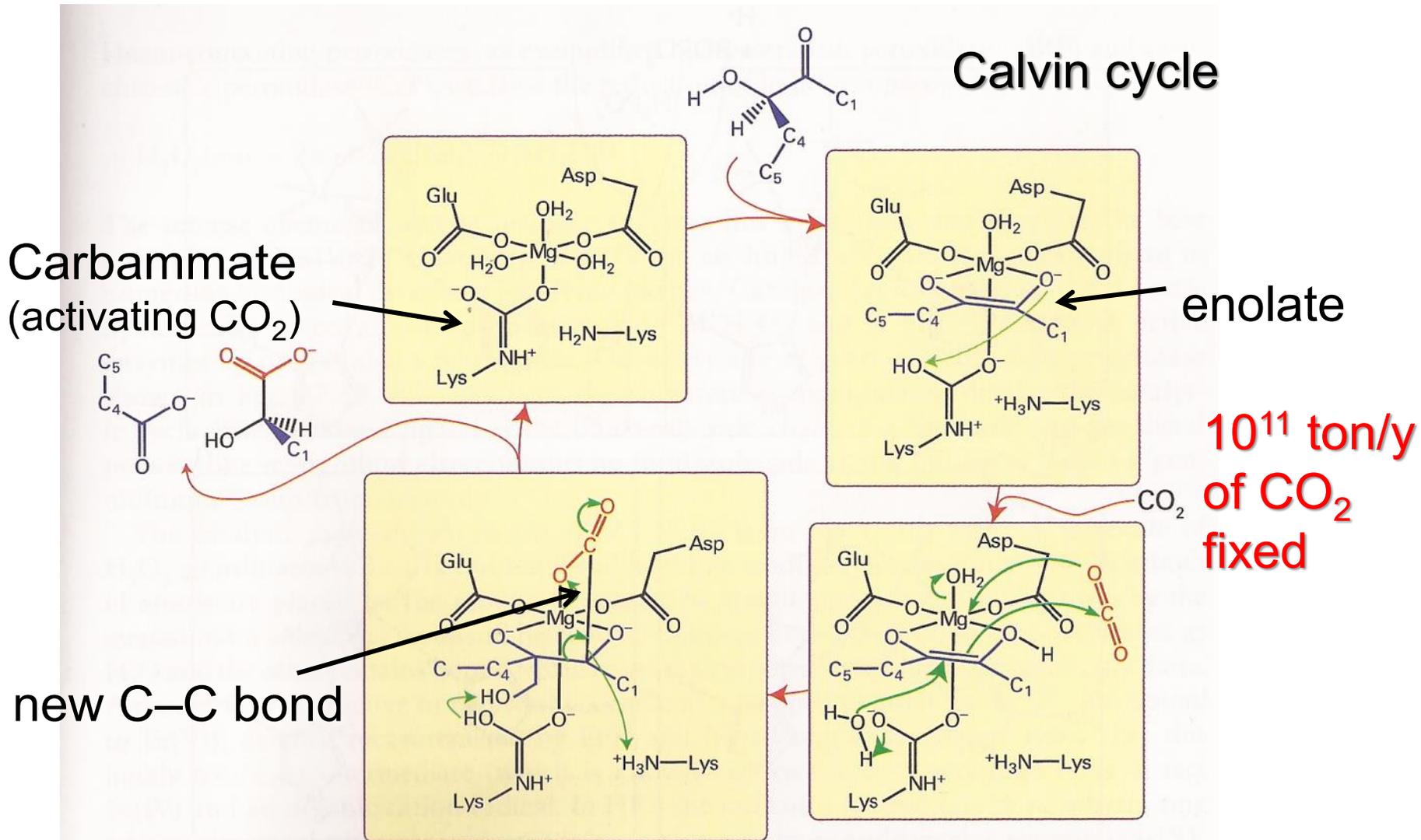


Pyruvate-kinase

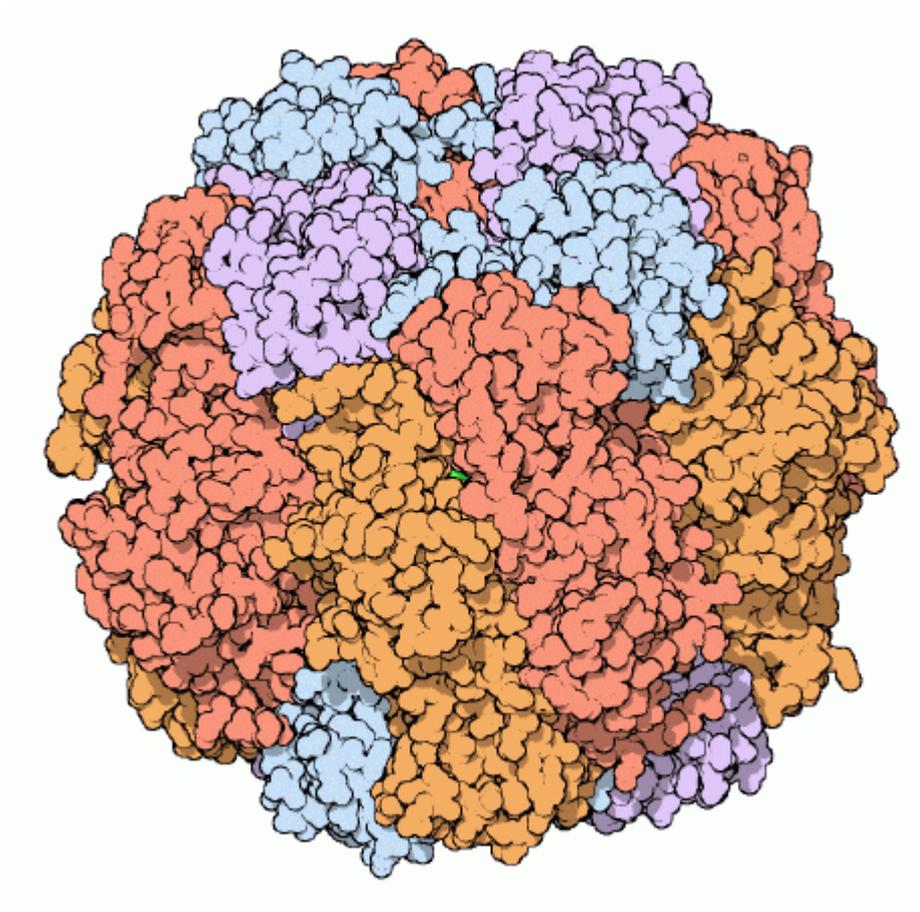
Ribulose 5-bisphosphate carboxylase (*RuBisCo*)

The most abundant protein (enzyme) on Earth

It catalyzes the carboxylation of ribulose 1,5-disphosphate



Rubisco



L = large
S = small

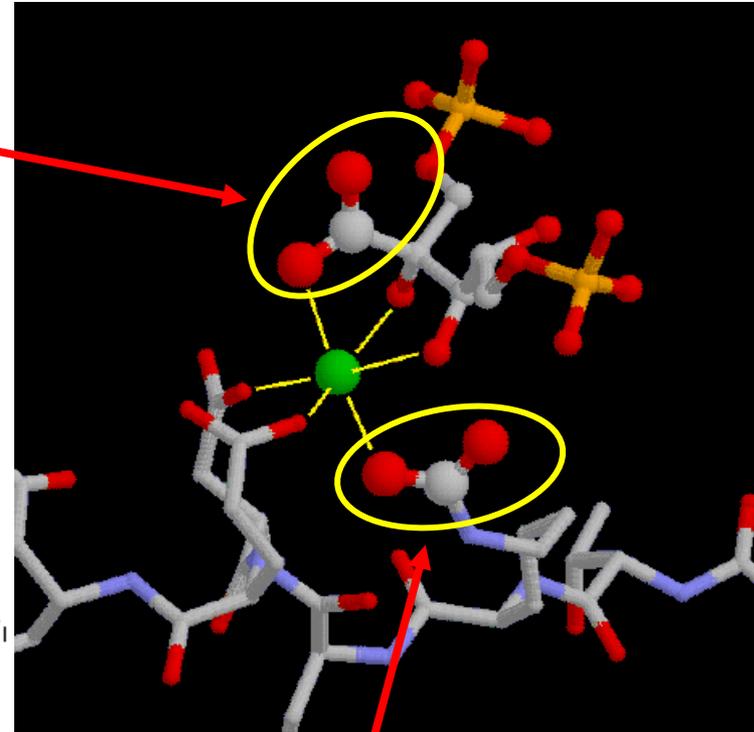
16 subunits L_8S_8

Two Mg active sites at the interface of each L_2 pair

Rubisco

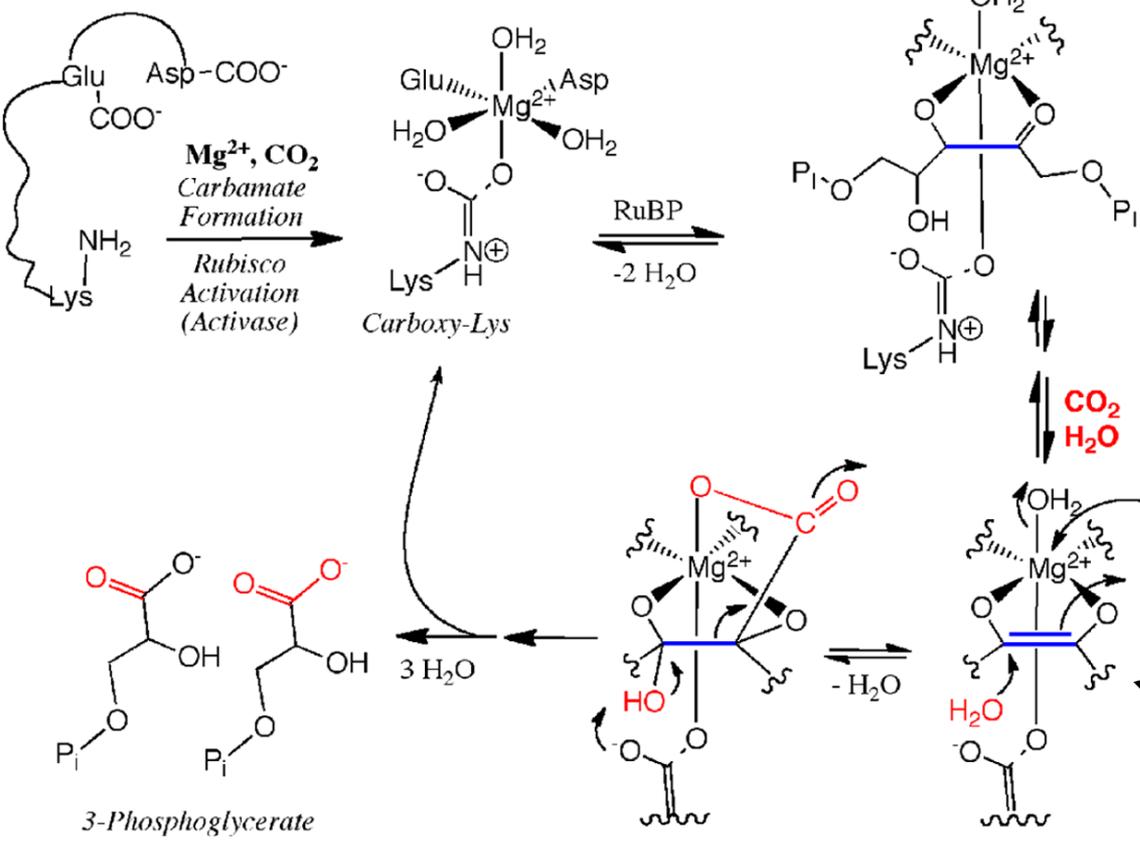
only 3 cycles/second

Substrate CO_2



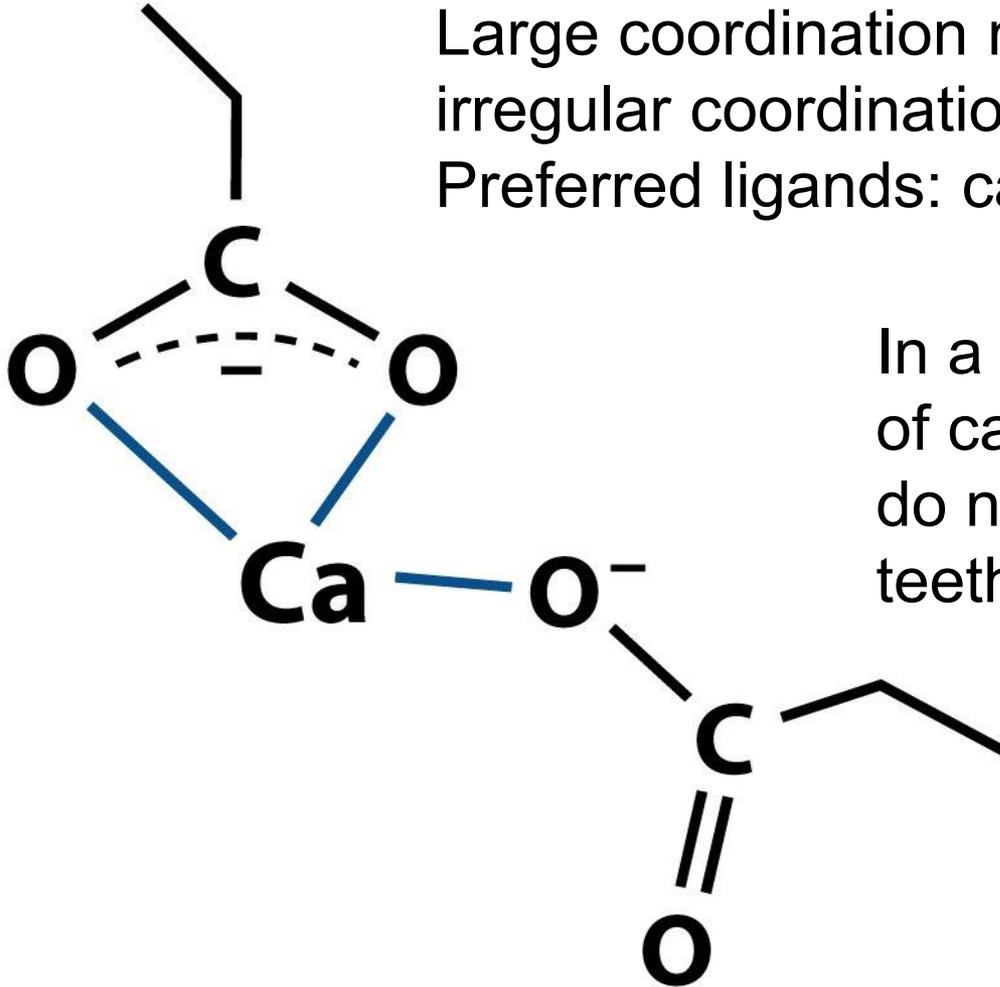
Activating CO_2

enolate



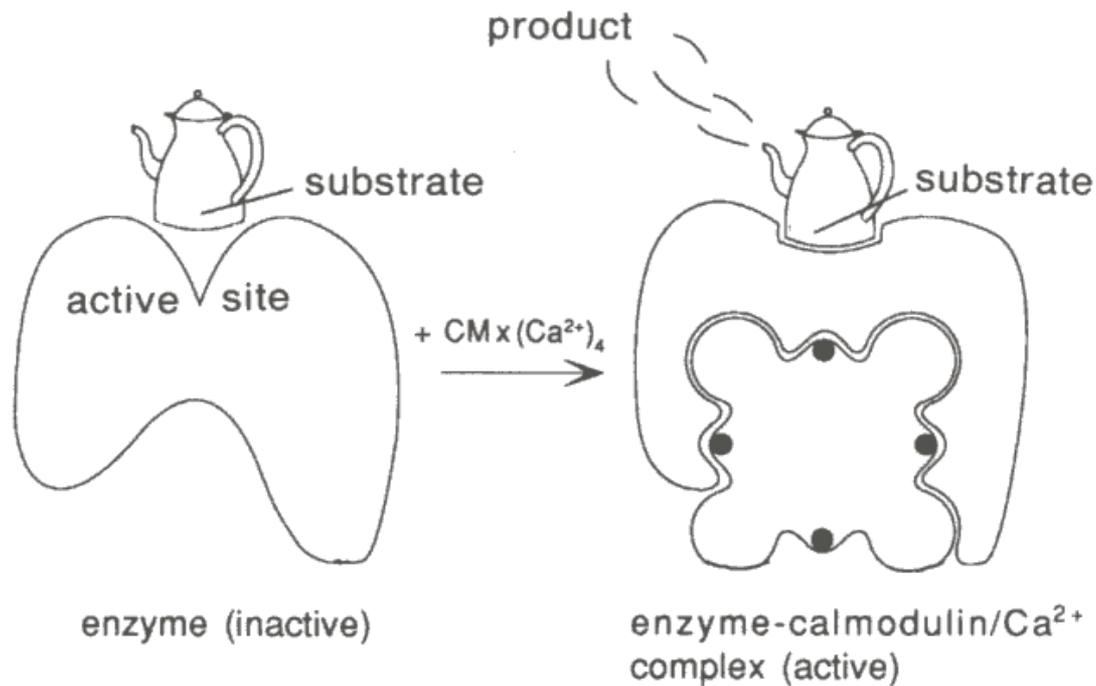
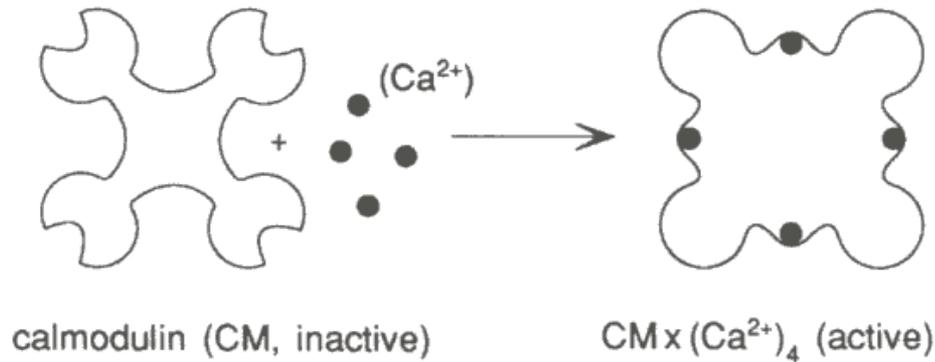
Calcium

Large coordination numbers, 7 – 8, with irregular coordination geometry
Preferred ligands: carboxylates



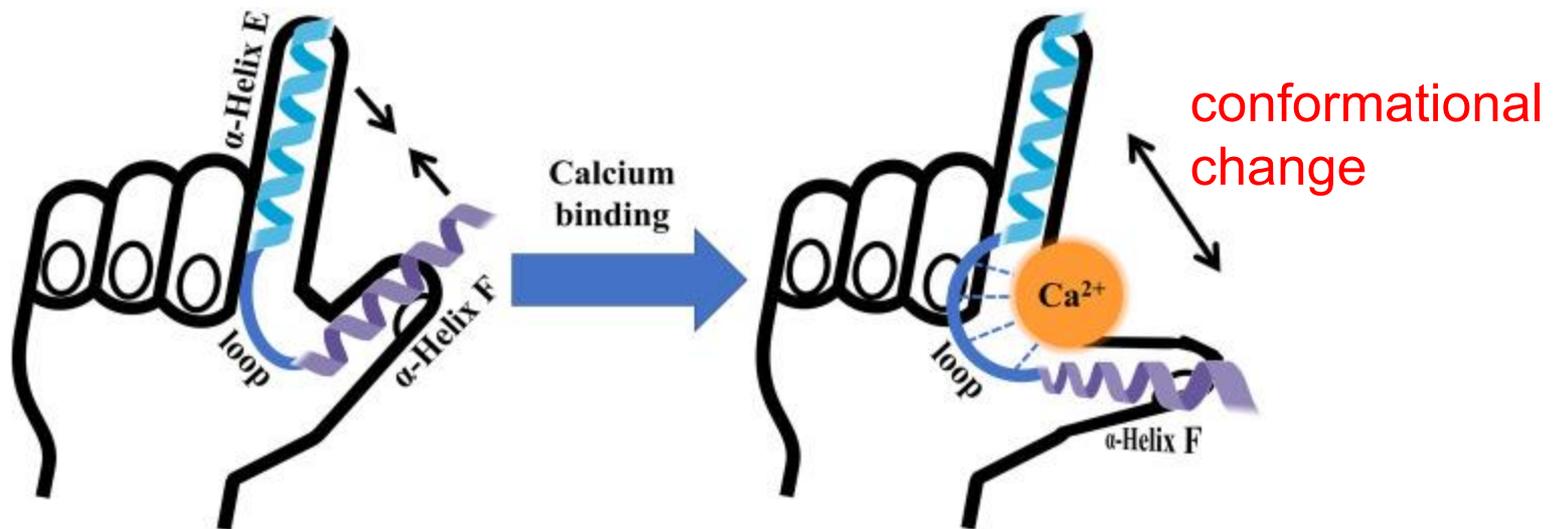
In a human being, ca. 10 g of calcium (out of 1200 g) do not belong to bones and teeth

Ca²⁺: a secondary messenger inside cells



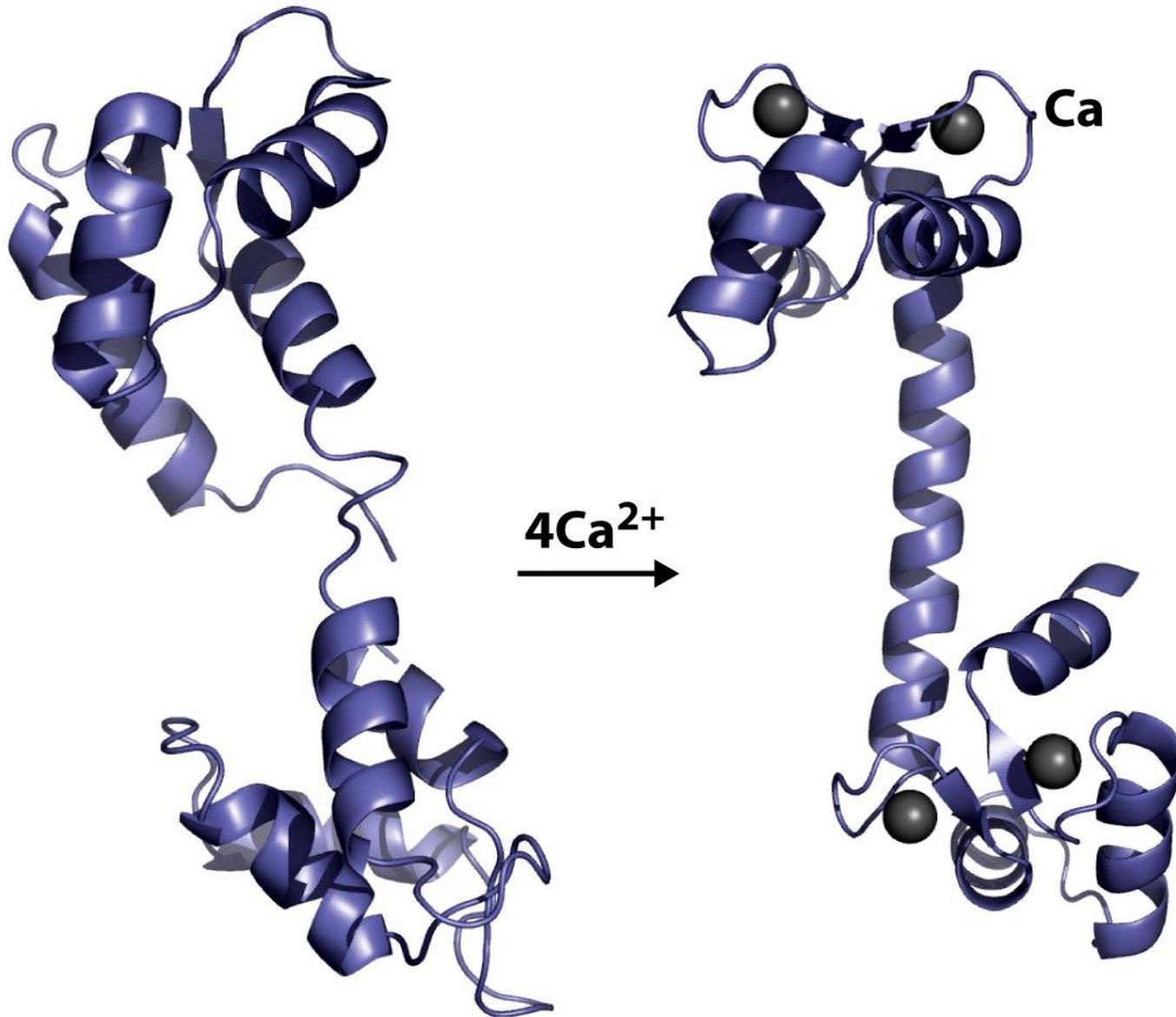
e.g.: NO synthase (NO), adenylate and guanylate cyclase (cAMP, cGMP), NAD kinase (NADP)

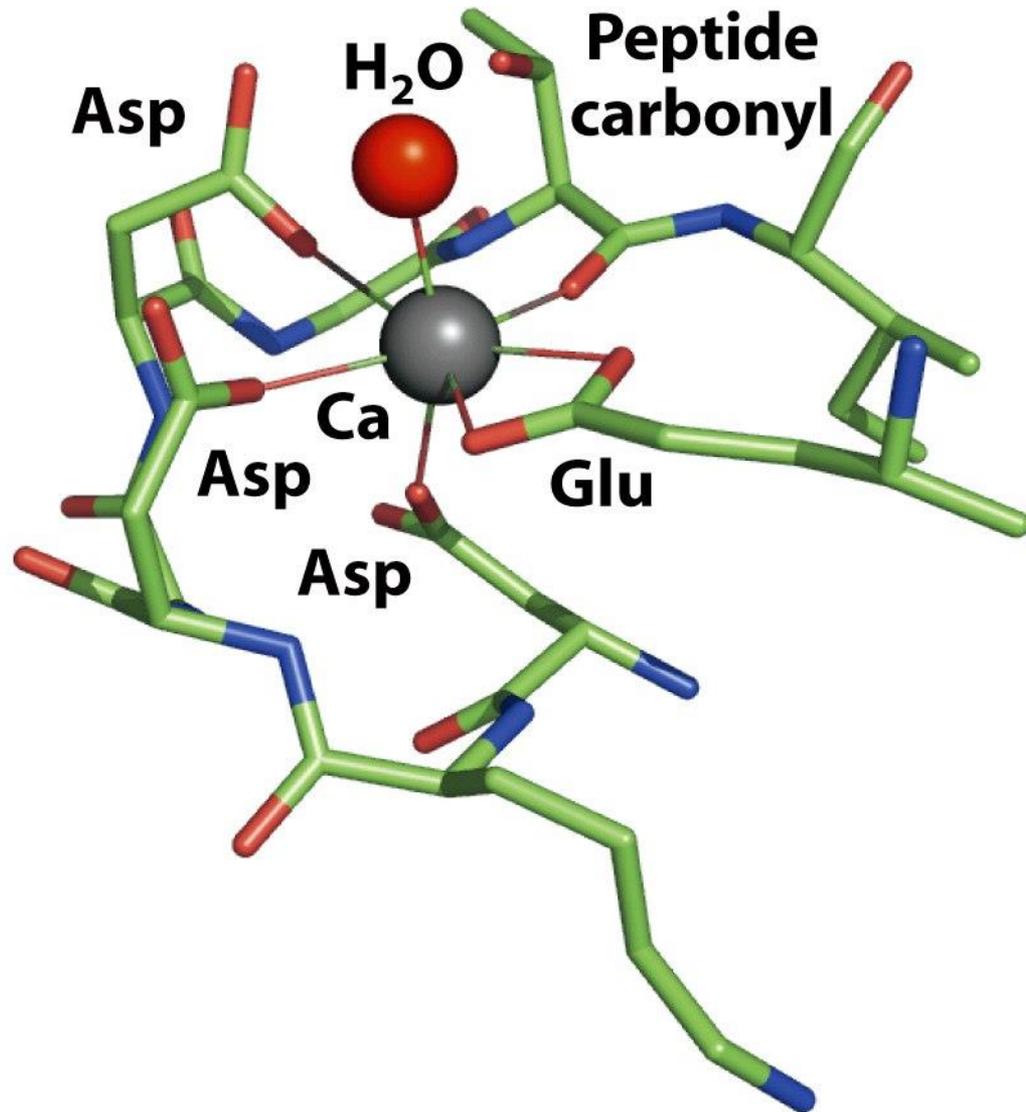
The *EF hand* calcium binding motif



Ca^{2+} ions are coordinated by ligands within the loop

Conformational change in a calmodulin

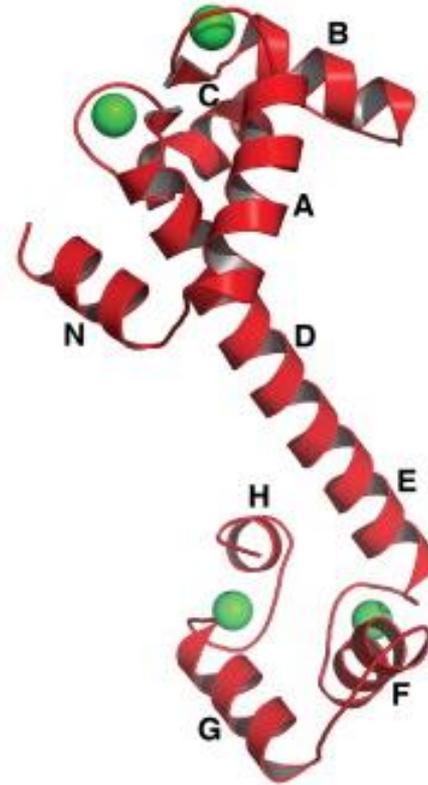
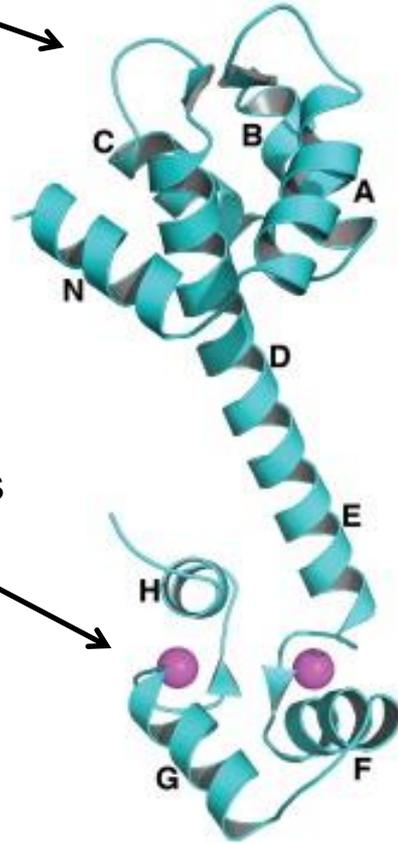




One of the Ca^{2+} coordination sites of a calmodulin

Troponin-C

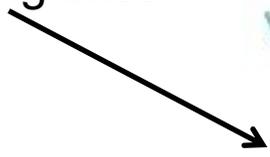
Lower affinity binding sites



actin
myosin

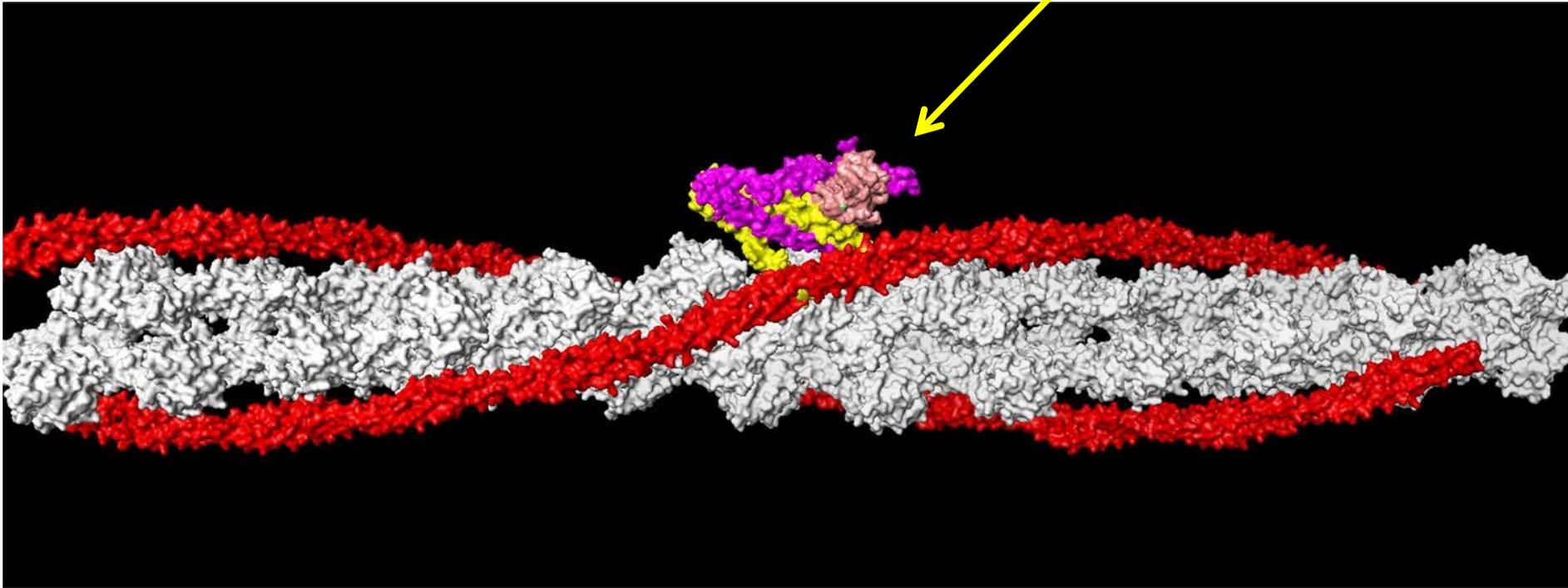
(protein
components of
muscular
filaments)

High affinity binding sites
($K > 10^6$)



Model of a muscular filament

Troponin



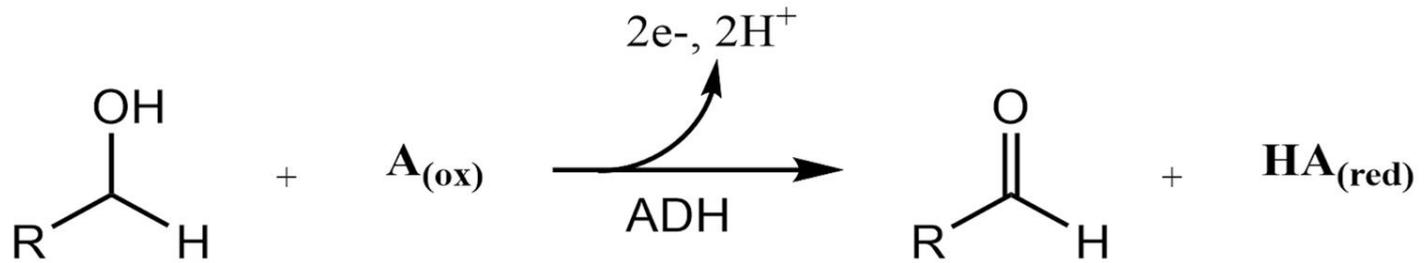
Actin = white

Tropomyosin = red

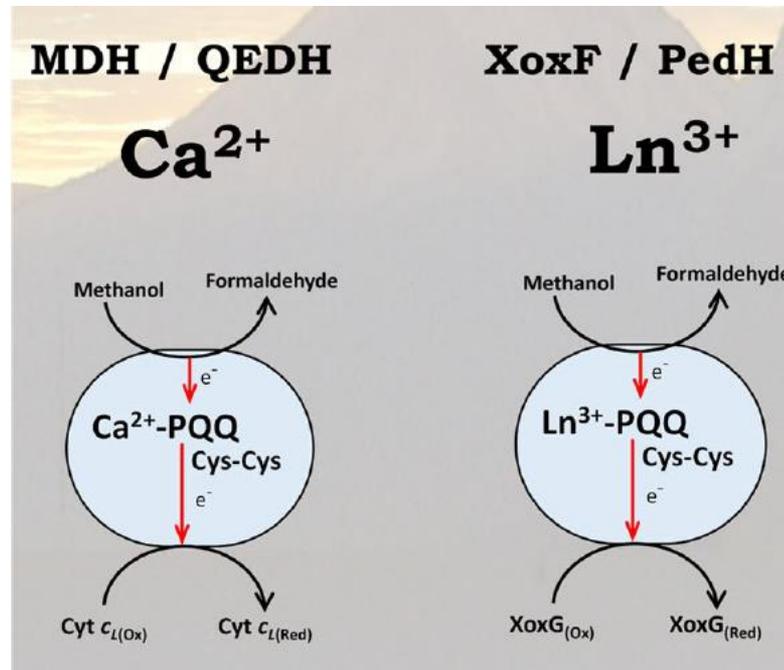
Lanmodulins and co.

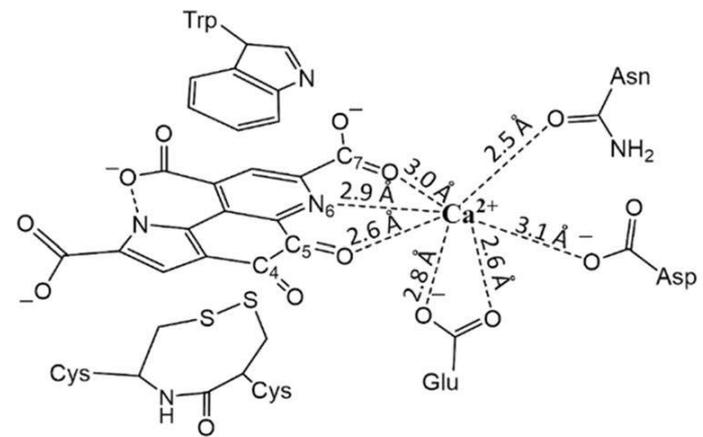
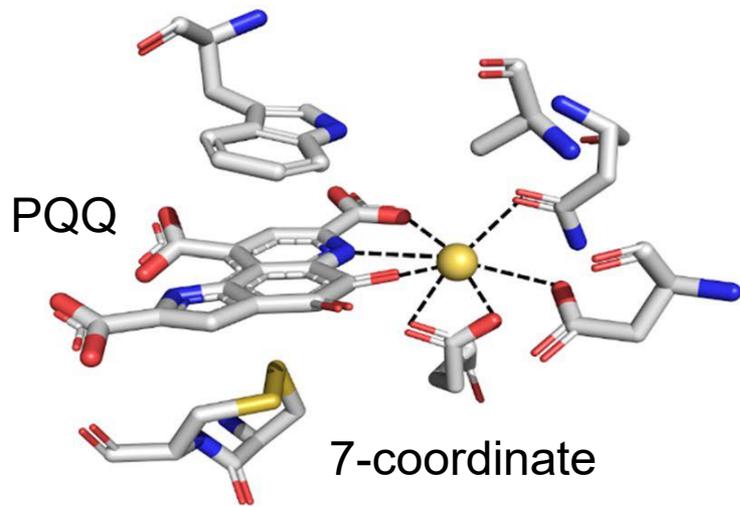
Ln^{3+} vs Ca^{2+}

PQQ-dependant alcohol dehydrogenases (ADHs) (PQQ = Pyrroloquinoline quinone)

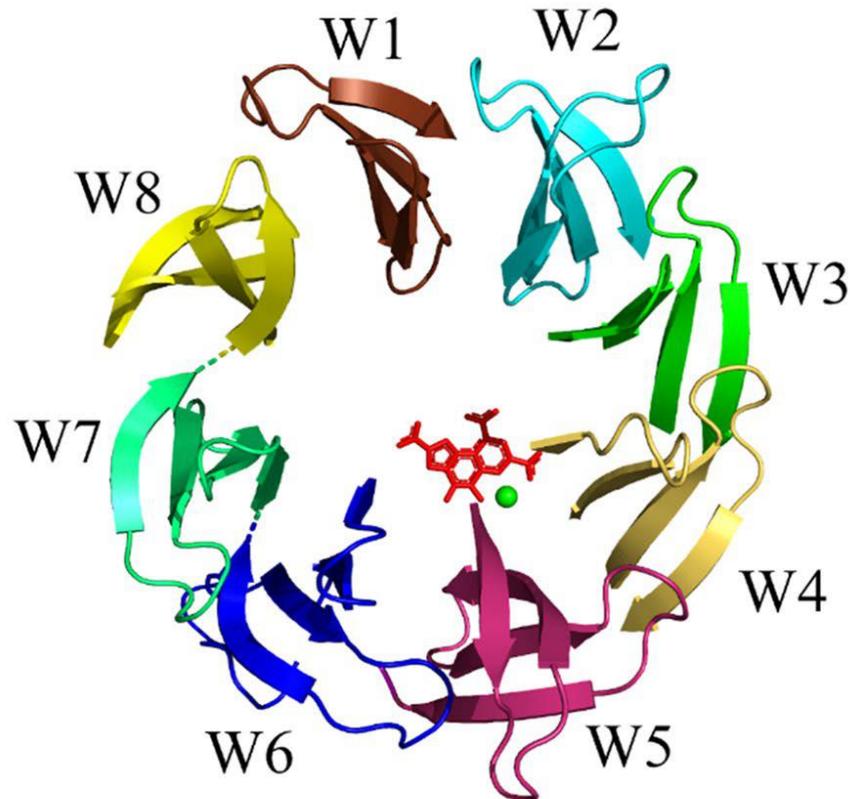


R, usually: CH₃, CH₂CH₃, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃

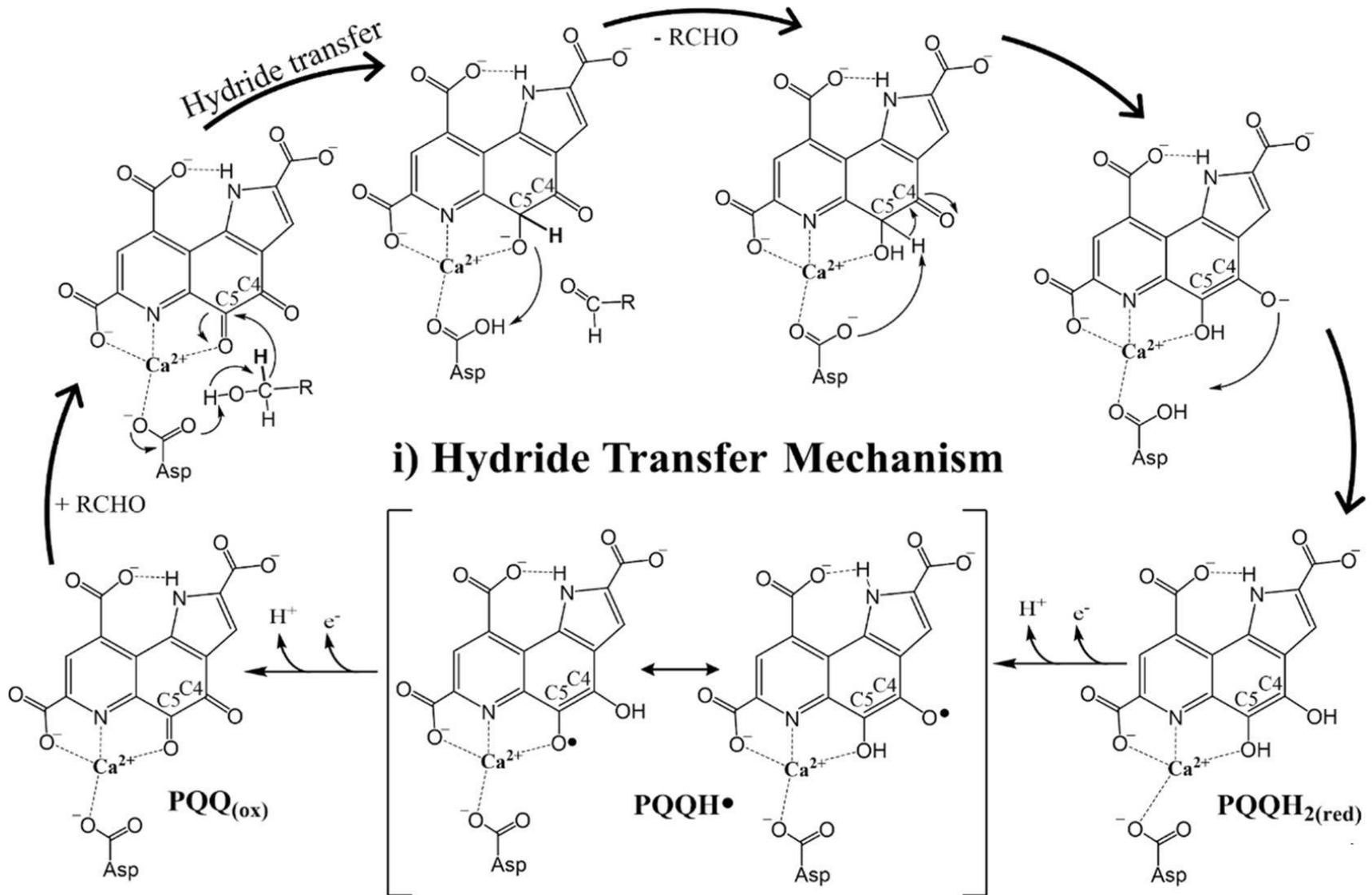


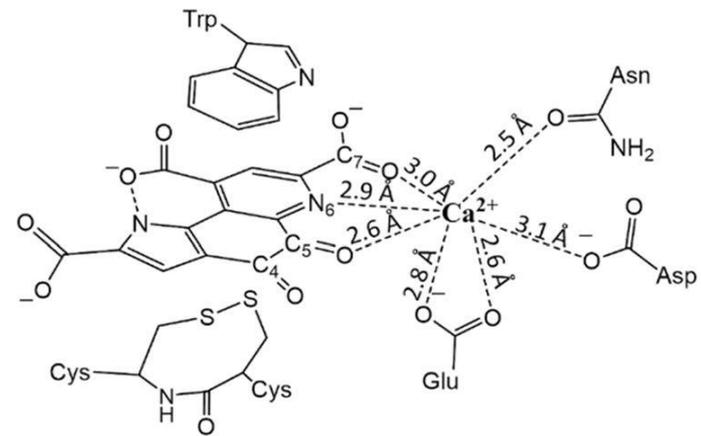
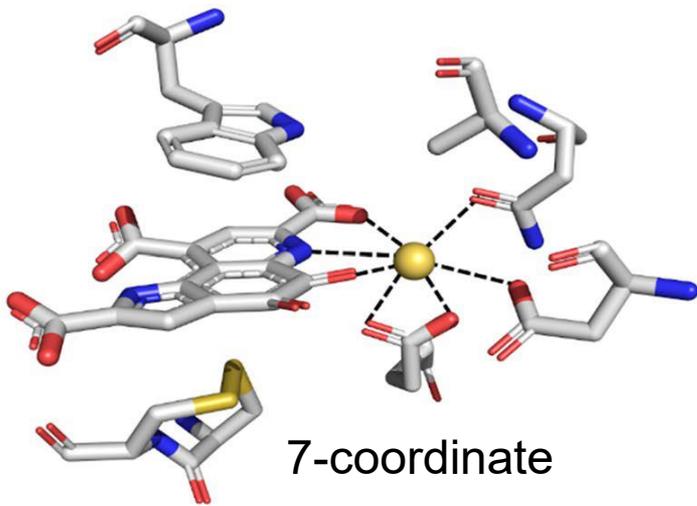


Ca²⁺-PQQ active site of *methanol dehydrogenase*, MDH

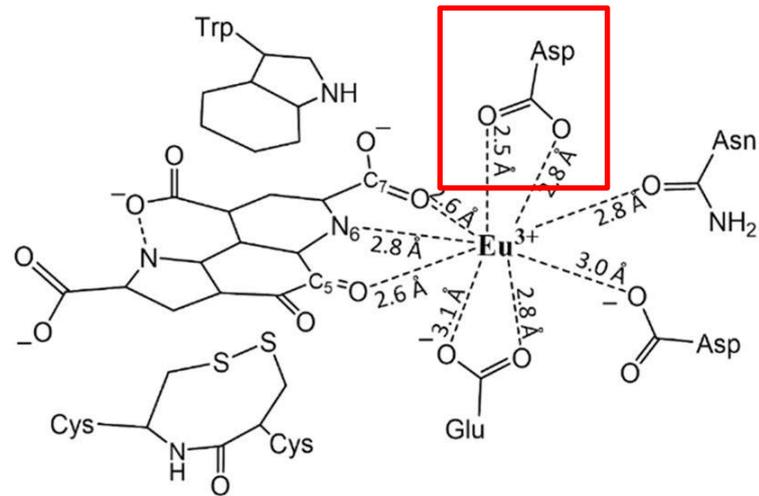
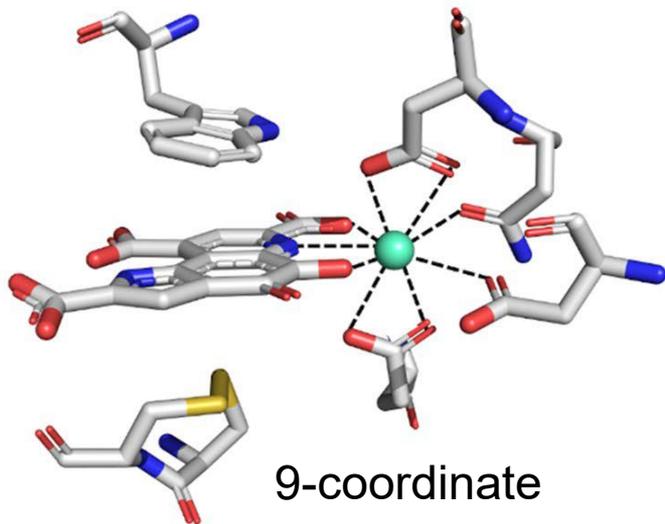


Hypothetical mechanism



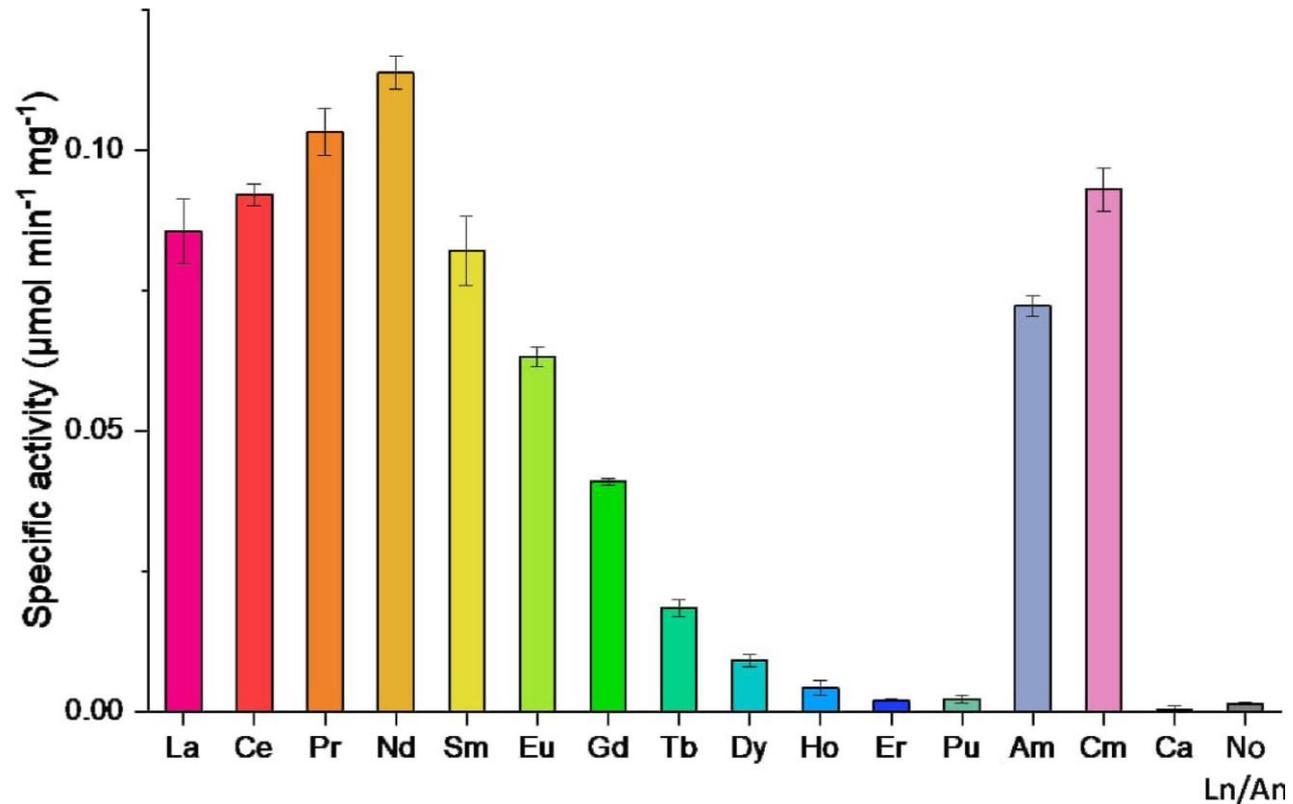


Ca^{2+} -PQQ active site of *methanol dehydrogenase*, MDH



Ln^{3+} -PQQ active site of *methanol dehydrogenase*, MDH

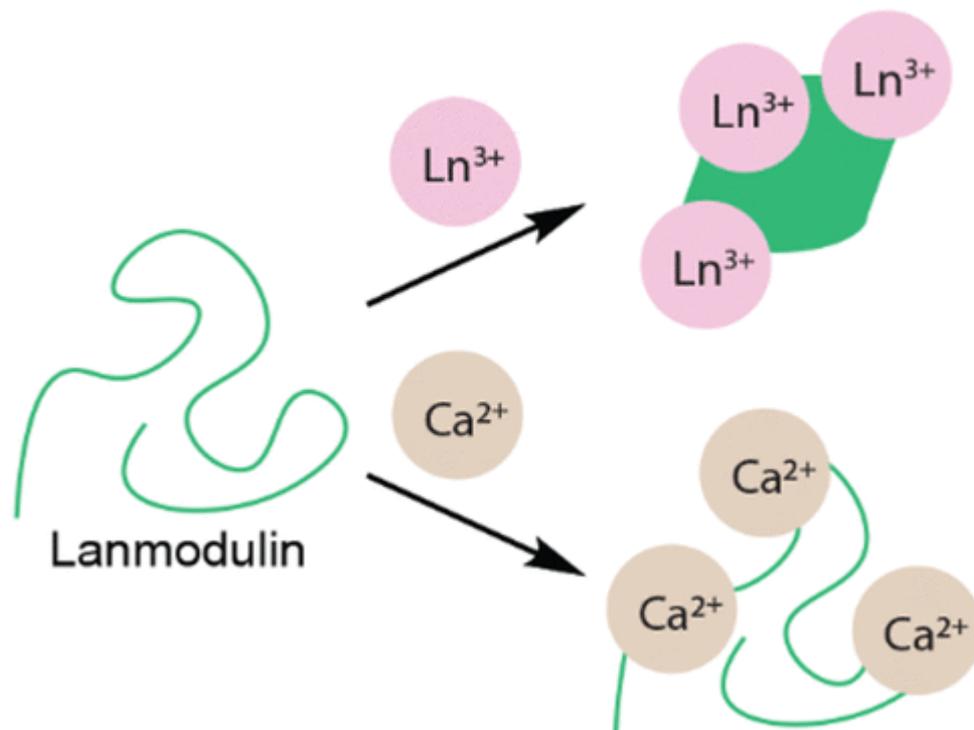
enzymatic activity depends on the nature of Ln^{3+}



2018: the discovery of Lanmodulin

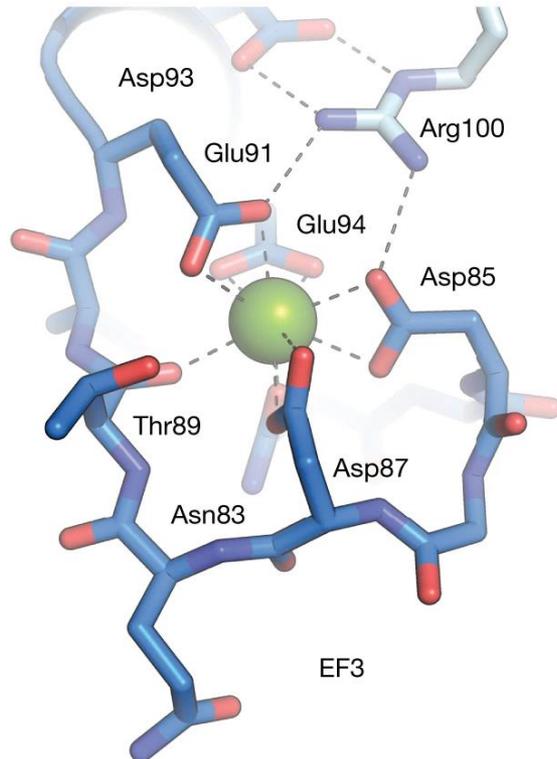
LanM possesses four metal-binding *EF hand* motifs, commonly associated with Ca^{II} -binding proteins

100 million-fold selectivity for Ln^{3+} over Ca^{2+} !

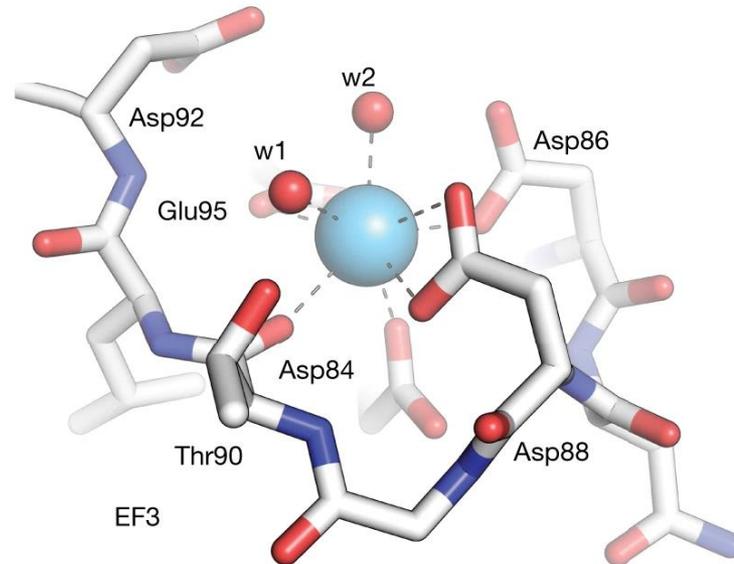


X-ray structures

La^{III} -*Hans*-LanM

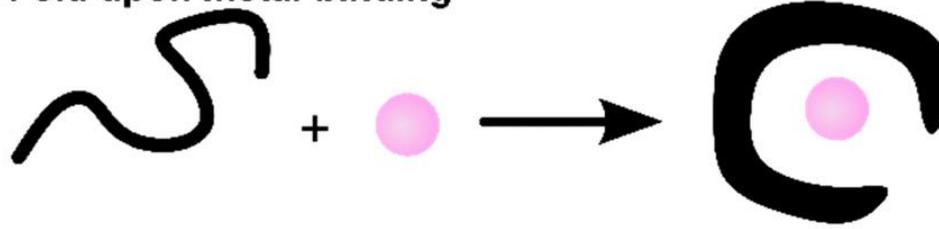


Nd^{III} -*Mex*-LanM

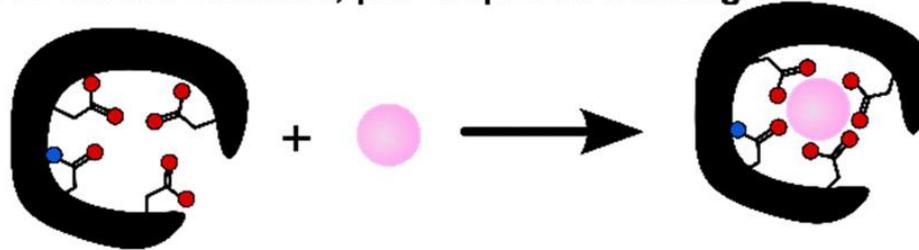


The $\text{Ln}^{\text{3+}}$ coordination spheres in LanMs feature **high CN** (9 or 10) that depend on the type of LanM. In addition, *Hans*-LanM binds 3 Ln ions, whereas *Mex*-LanM binds 4.

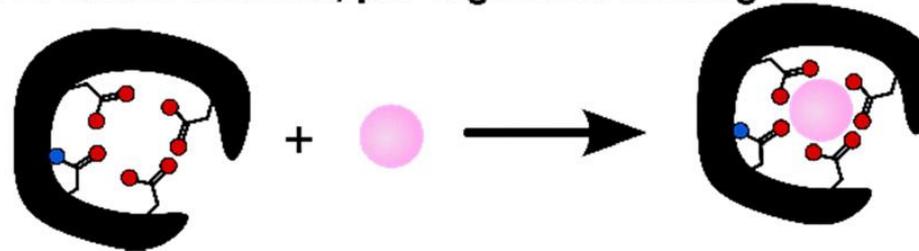
A. Fold upon metal-binding



B. Pre-folded scaffold, pre-disposed binding site



C. Pre-folded scaffold, pre-organised binding site



Whereas CaM is already folded in the apo-state and undergoes a conformational change upon metal-binding, LanM is disordered and only upon binding four Ln^{3+} ions, it forms a compact three-helix bundle fold