Many-body interactions determine the selectivity for Ca^{2+} vs. Mg^{2+} in proteins

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Metal ions in biology

- Calcium is a versatile messenger

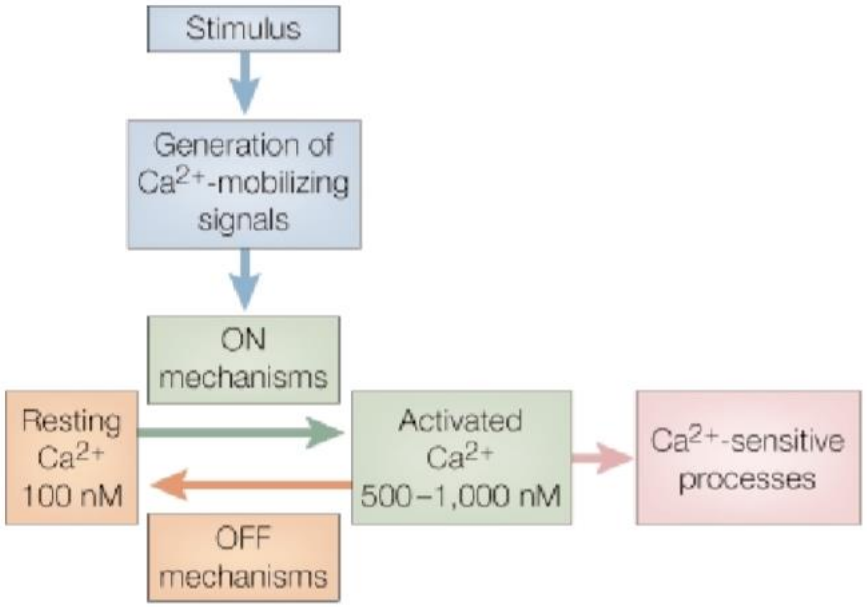
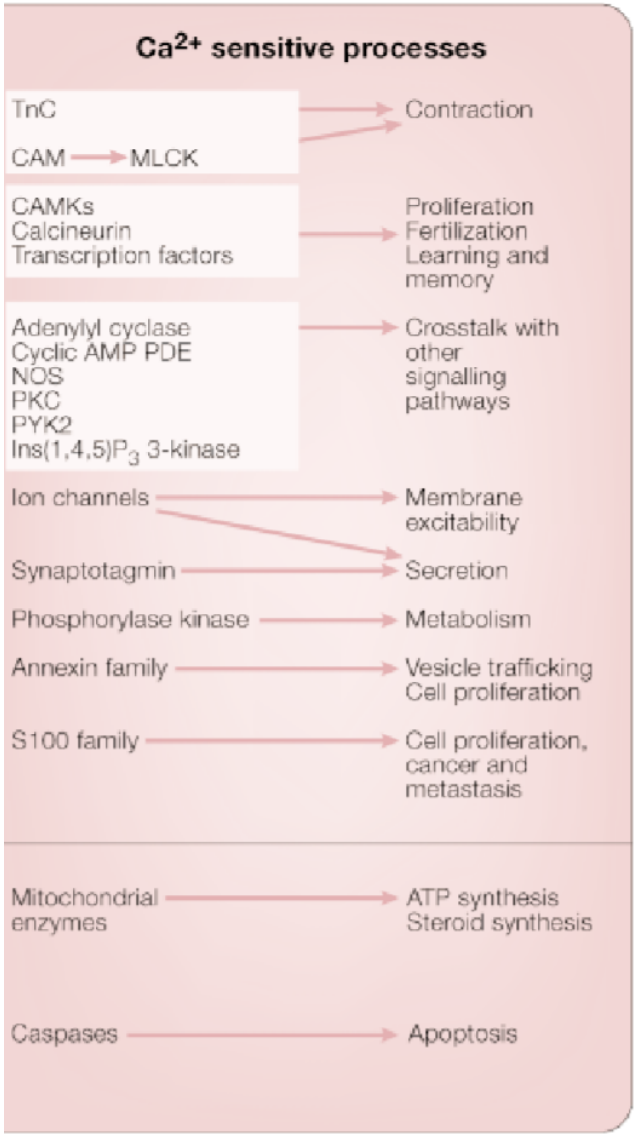


Figure 1 | **The four units of the Ca^{2+} signalling network.** Stimuli act by generating Ca^{2+}-mobilizing signals that act on various ON mechanisms to trigger an increase in the intracellular concentration of Ca^{2+}. The increased level of Ca^{2+} stimulates various Ca^{2+}-sensitive processes to trigger many different cellular pathways. The response is terminated by OFF mechanisms that restore Ca^{2+} to its resting level. Details



Metal ions in biology

- Metabolism and apoptosis

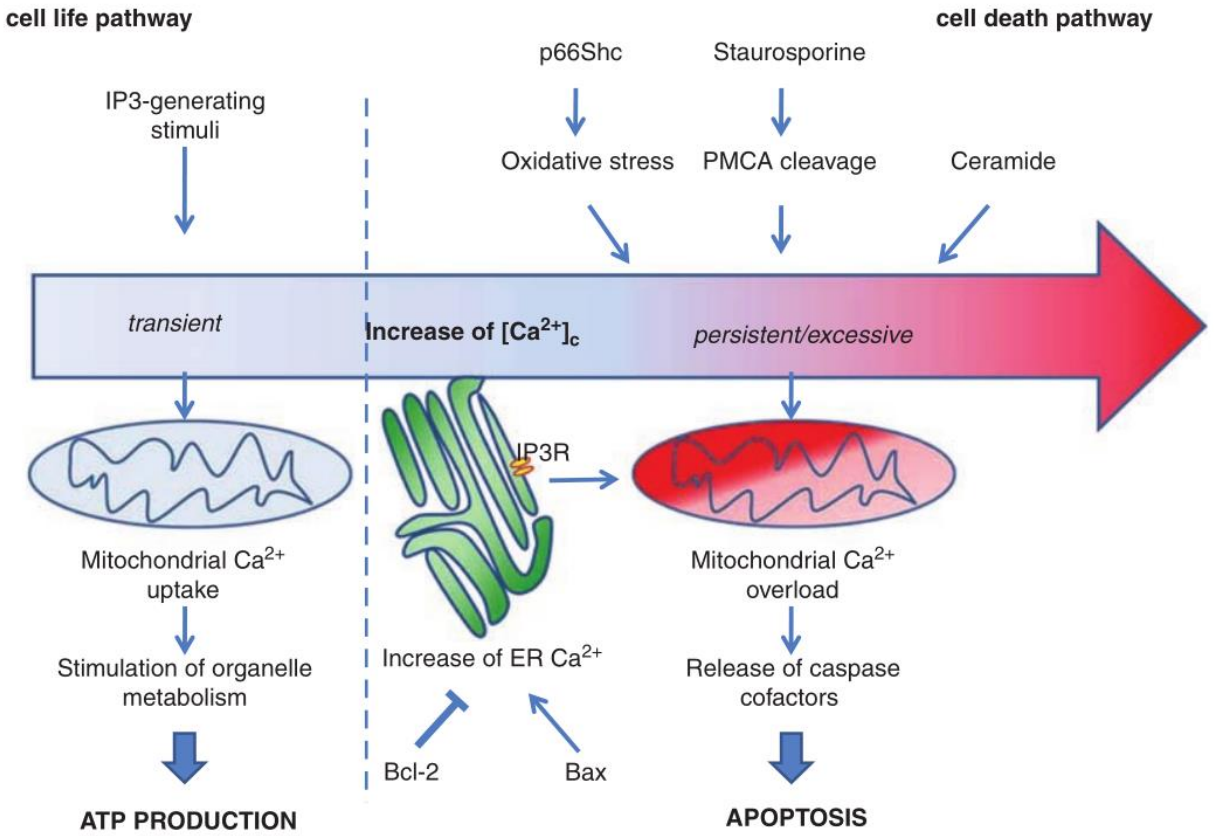
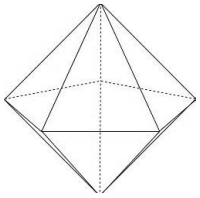


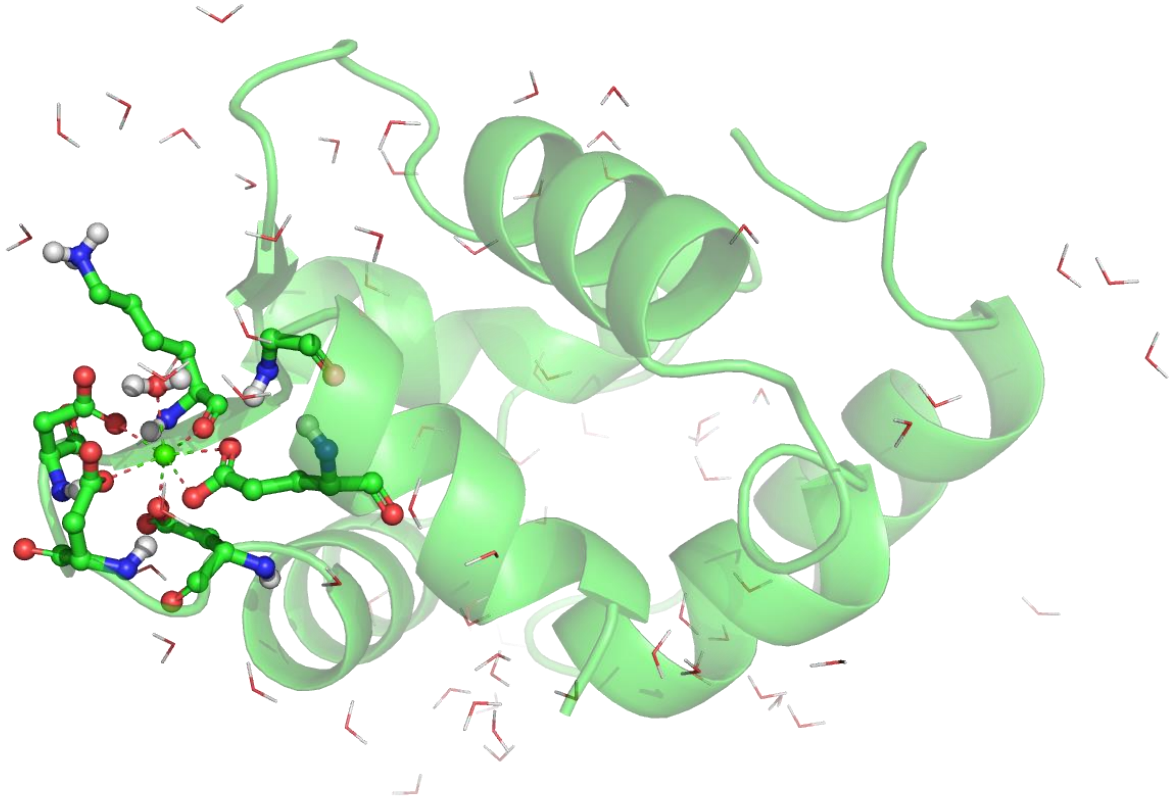
Figure 1 Differential decoding of Ca^{2+}-linked stimuli evoking the activation of cell metabolism or apoptosis.

Calcium and apoptosis. P. Pinton et al. Oncogene, 2008

Calcium binding protein

- EF hand
  - Pentagonal bipyramid coordination
  - 3-4 Asp/Glu side chains





Parvalbumin. PDB: 5CPV

Calcium binding protein

- Binding affinity can be tuned to achieve diverse functions

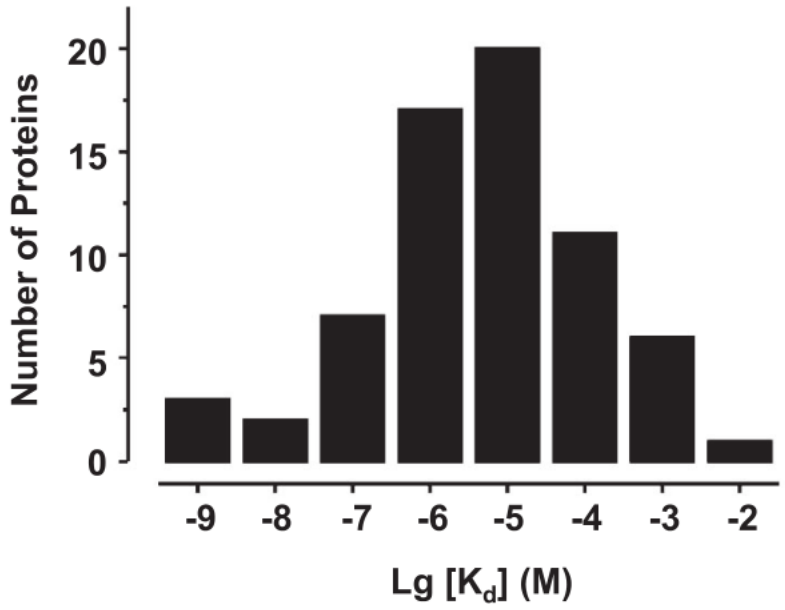
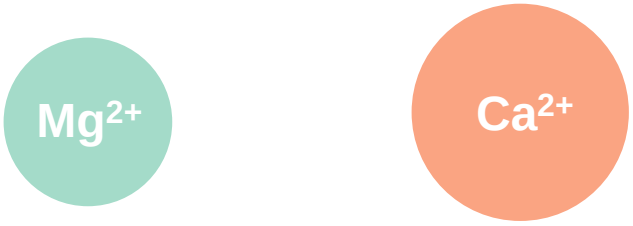


FIG. 18. Diversity of Ca^{2+} binding affinity of Ca^{2+}-sensing proteins. The dissociation constants (K_d) of 68 Ca^{2+} binding proteins were obtained by text search and manual collection from the literature. [Modified from Cheng et al. (72).]

Calcium Sparks. Physiol Rev 88: 1491–1545, 2008;

Ca^{2+} vs. Mg^{2+}

- Should Mg2+ binding more tightly to calcium-binding proteins?
  - higher charge density
  - stronger ligand field
  - higher electron affinity
  - higher absolute/chemical hardness $\eta = \frac{1}{2}\frac{\partial^2 E}{\partial N^2} \approx \frac{1}{2}(I - A)$

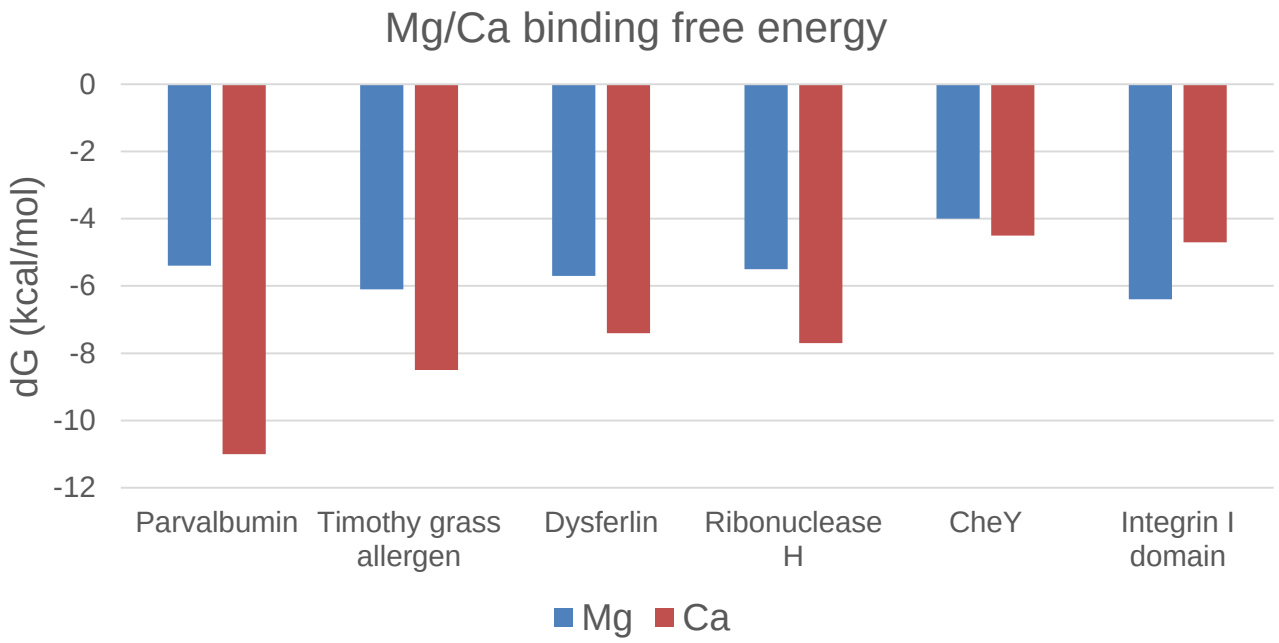


r = 0.76 Å r = 1.12 Å

R.G. Pearson. Chemical hardness, Wiley, 1997

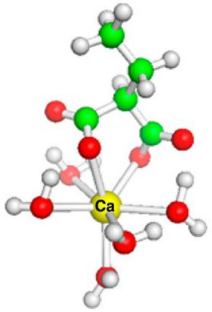
Metal ion selectivity

- Most proteins bind more favorably to Ca^{2+}



Previous studies on Mg/Ca selectivity

- Solvation penalty
  - Mg has larger solvation penalty
- Geometry
  - The pentagonal bipyramid geometry in EF hand binding site is favorable for Ca
- Geometric constraint
  - For specific proteins (Gla)



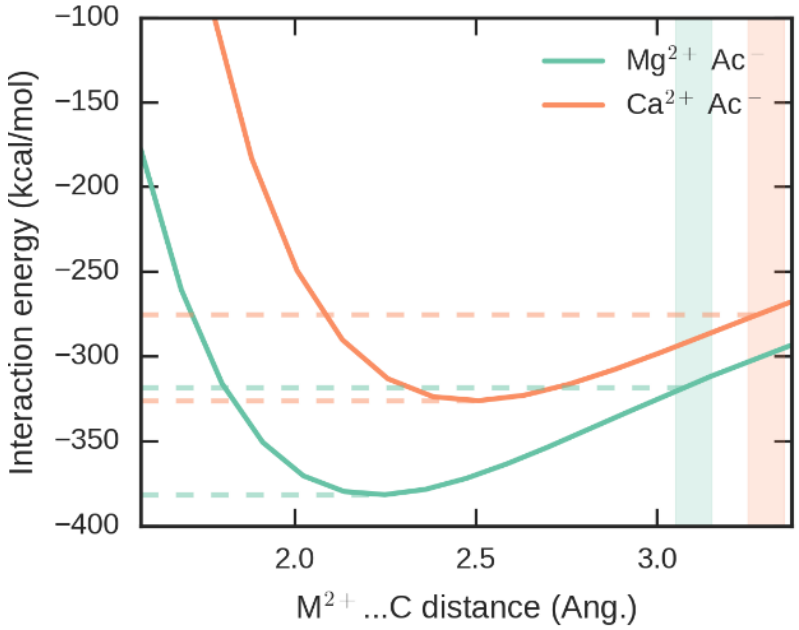
Gla-Ca binding

The general selectivity of many proteins for Ca is still unexplained

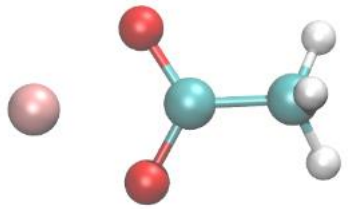
Biochemical Journal **2007**, 405 (2), 199-221.
Chem Rev **2014,** *114* (1), 538-56

Dimer interaction in vacuum

- Mg/Ca acetate interaction



Interaction energy calculated by MP2/def2-QZVPPD



~40 kcal/mol
difference between Mg and Ca for one pair

3-4 COO-
in typical EF hand binding pockets

~80 kcal/mol
difference between Mg and Ca hydration free energies

Many-body interactions in model compounds

PDB	$\Delta\Delta E_{2B}$	$\Delta\Delta E_{MB}$	$\Delta\Delta E_{int}$	$\Delta\Delta G_{bind}^{calc}$	$\Delta\Delta G_{bind}^{expt}$
1IG5/4ICB	232.6	-165.6	67.0	-10.8	-6.2
2LVJ/K	144.3	-73.1	71.1	-6.7	-2.4
1B8L/C	180.3	-103.4	77.0	-0.8	-1.6

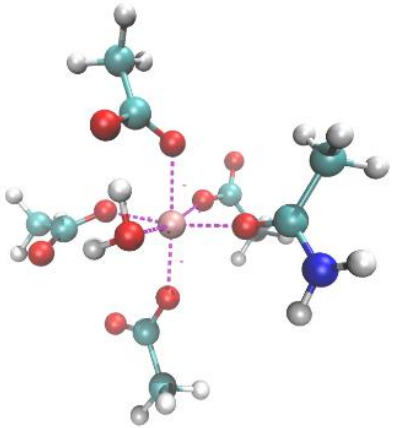
$$\Delta\Delta E = \Delta\Delta E(\mathrm{Mg} \rightarrow \mathrm{Ca}) = \Delta E(\mathrm{Ca}) - \Delta E(\mathrm{Mg})$$
$$\Delta\Delta G_{\mathrm{bind}} = \Delta\Delta G_{\mathrm{bind}}(\mathrm{Mg} \rightarrow \mathrm{Ca}) = \Delta G_{\mathrm{bind}}(\mathrm{Ca}) - \Delta G_{\mathrm{bind}}(\mathrm{Mg})$$

$$\Delta E_{2\mathrm{B}} = \sum_{i,j} \left(E_{ij} - E_i - E_j\right),$$

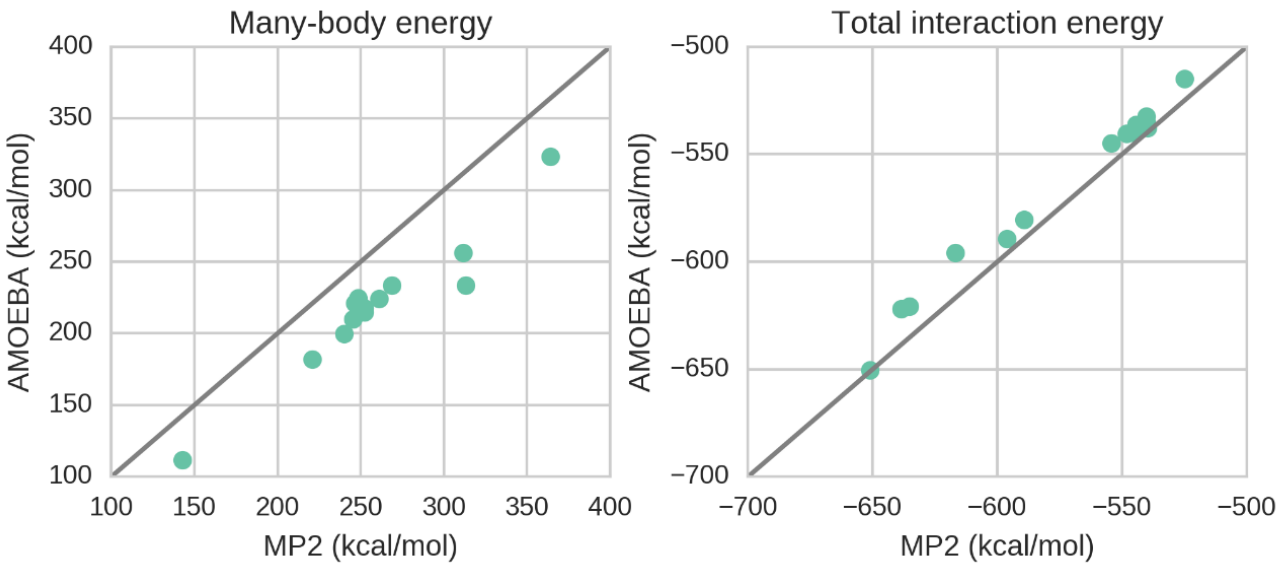
i, j are indices of molecules in the system

$$\Delta E_{\mathrm{int}} = E_{\mathrm{total}} - \sum_i E_i$$
$$\Delta E_{\mathrm{MB}} = \Delta E_{\mathrm{int}} - \Delta E_{2\mathrm{B}}$$

$$\Delta\Delta G_{\mathrm{bind}}^{\mathrm{calc}} = \Delta\Delta E_{\mathrm{int}} - \Delta\Delta G_{\mathrm{solv}}$$

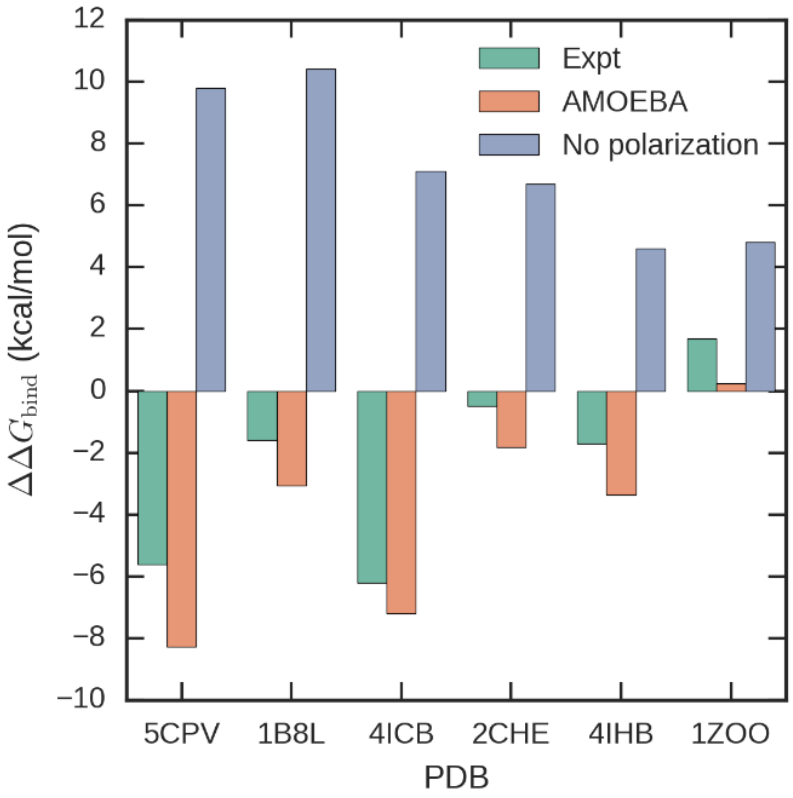


QM and AMOEBA many-body interactions



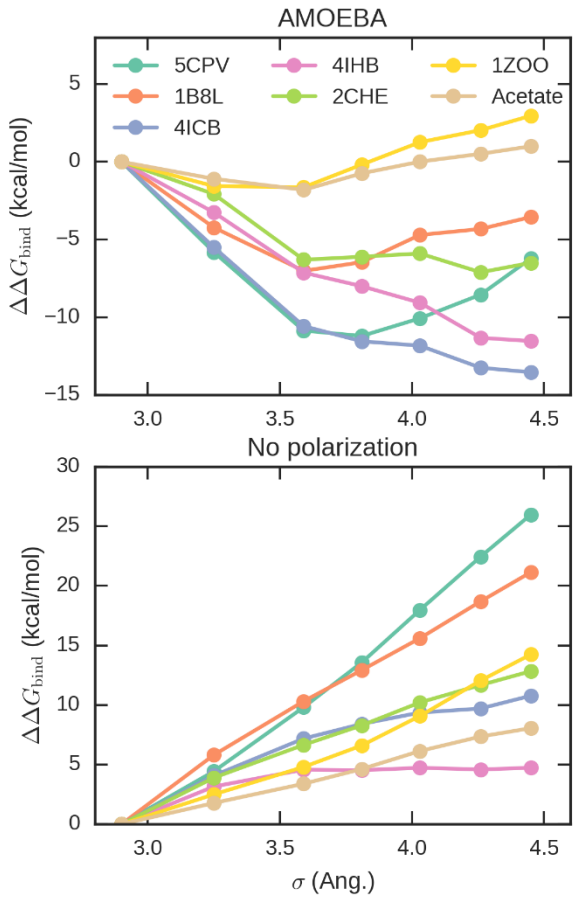
Comparison between MP2 and AMOEBA many-body energies and total interaction energies between the molecules in the model compounds. define

Binding free energy



Comparison between experimental and calculated relative binding free energies $\Delta\Delta G_{\mathrm{bind}}(\mathrm{Mg}\rightarrow\mathrm{Ca})$ of proteins.
5CPV, 1B8L, 4ICB, 2CHE, 4IHB, 1ZOO have 4, 4, 3, 2, 2, 1-2 first-shell Asp/Glu groups, respectively.

Binding free energy



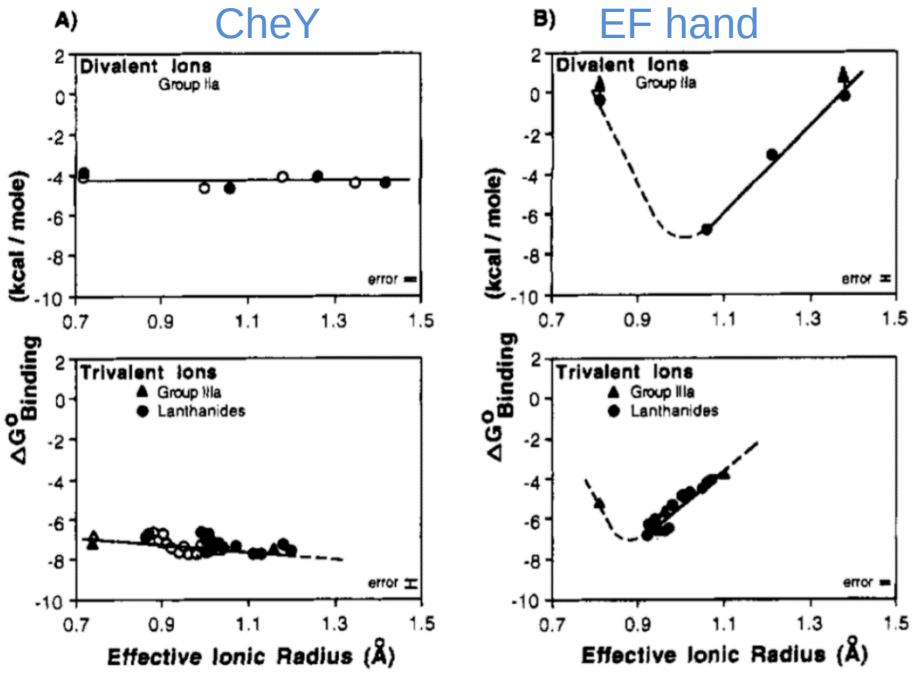
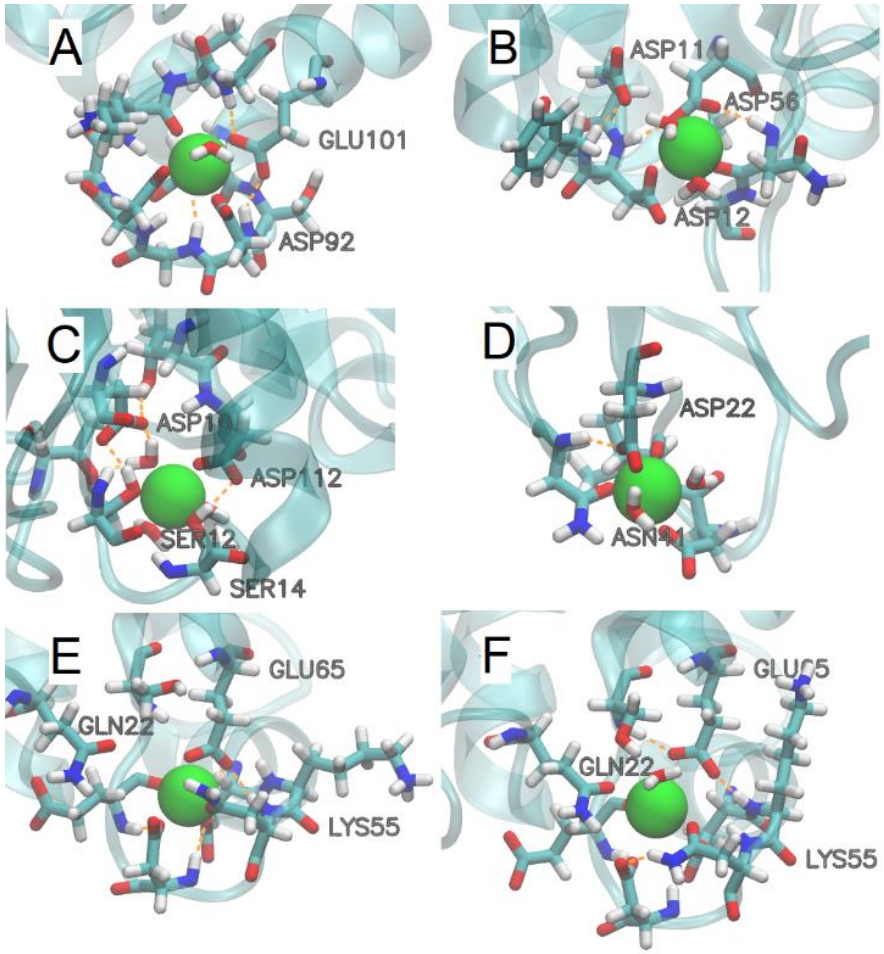


FIGURE 2: Free energies of metal ion binding to (A) the CheY Mg-(II) site and (B) the D-galactose chemoreceptor Ca(II) site, as a function of effective ionic radius. Binding free energies were measured by fluorescence titrations carried out as in (A) Materials and Methods

$\Delta\Delta G_{\mathrm{bind}}$(Mg→Ca) as a function of vdW size.
5CPV, 1B8L and 4ICB are EF hands;
2CHE is CheY.

Biochemistry, **1993**, *32* (13), pp 3363–3367

Structures of binding pockets



(A-D) 5CPV, 2CHE, 1ZOO and 4IHB bound with Mg2+, respectively. (E-F) 4ICB bound with Mg2+ (σ = 2.90 Å) and an artificial ion with σ = 4.45 Å.

Summary

- The selectivity of many proteins for Ca2+ vs. Mg2+ is mainly driven by the many-body interaction; Ca2+ has weaker repulsive many-body interactions and thus higher binding affinities.

- Without many-body polarization, the smaller Mg2+ will be favored

- Polarization is sensitive to spatial arrangement of ligands, and offers a way to fine tune the selectivity