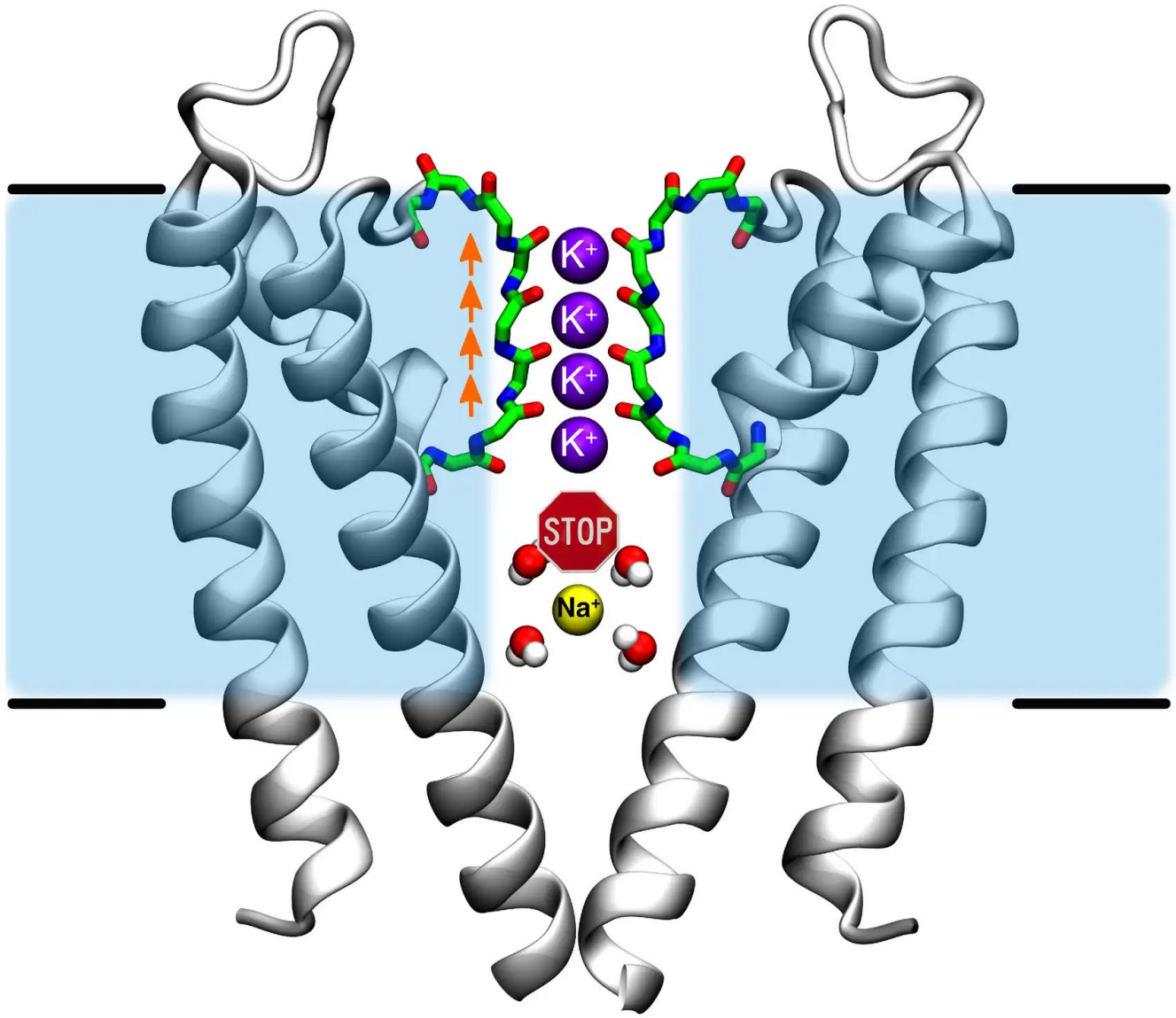
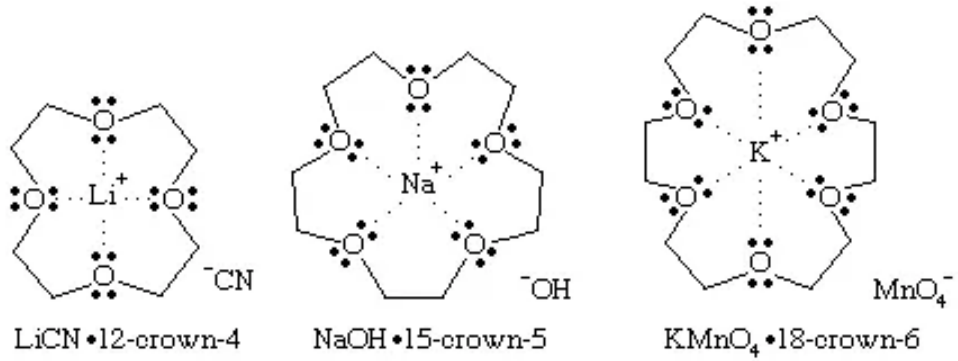
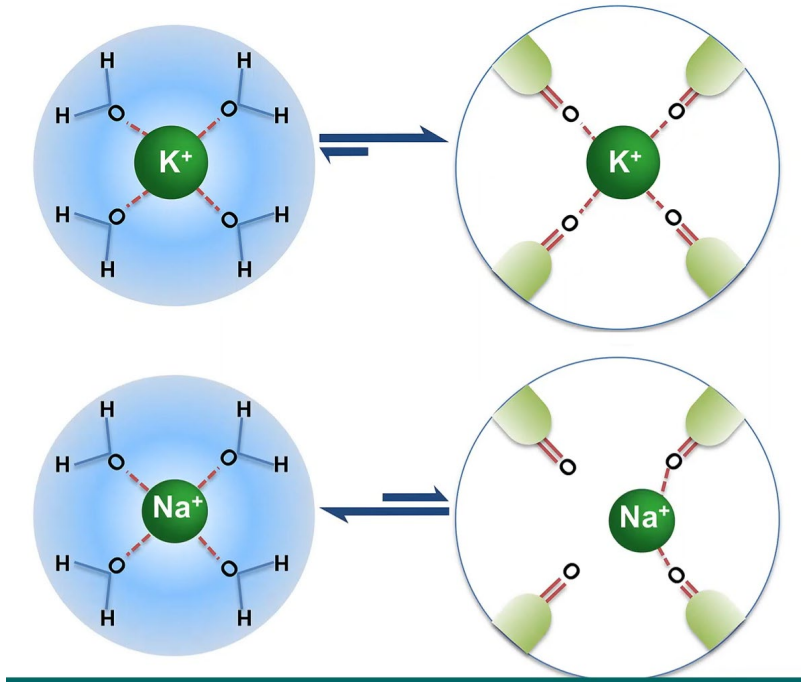
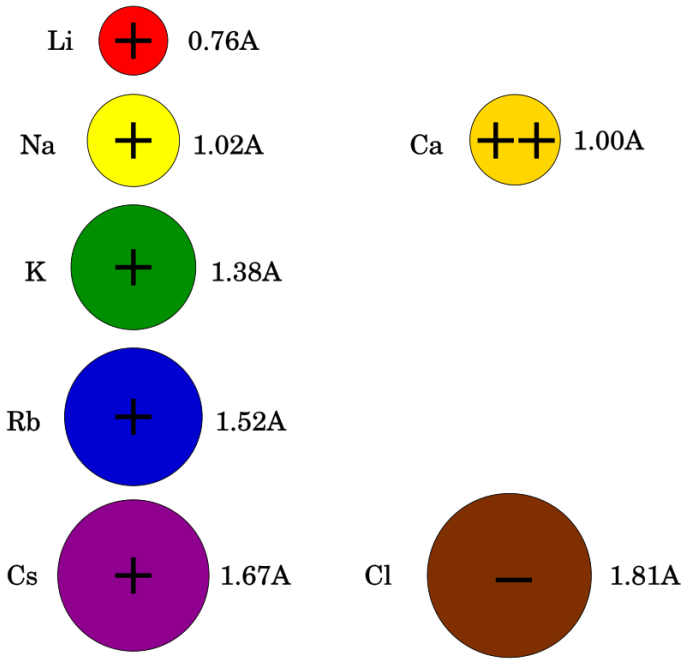


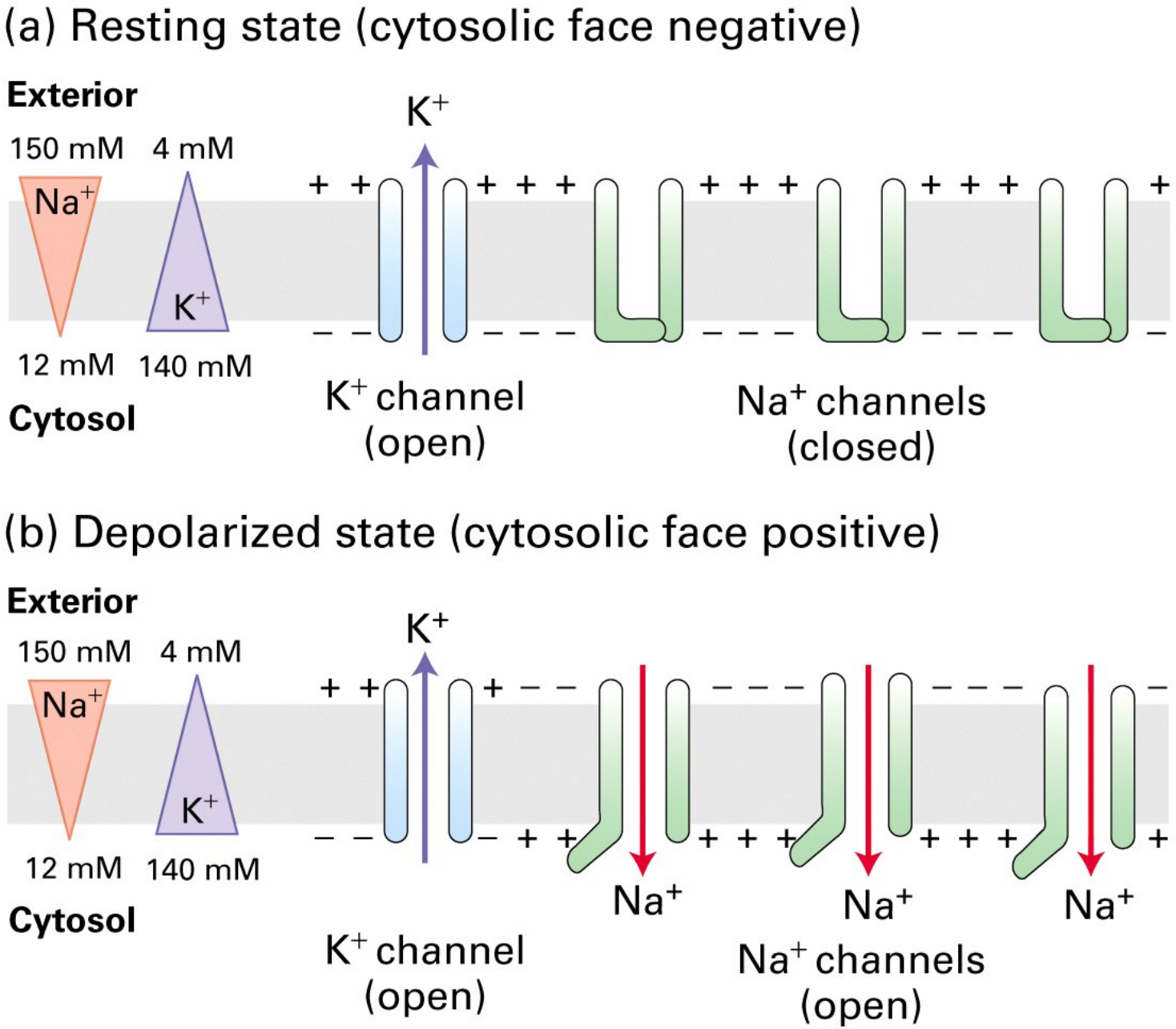
Computer simulations show why potassium channels select potassium ions so effectively while blocking sodium. Potassium ions shed their water shell to pass through the narrow pore, making them small enough to fit the filter. Sodium ions, however, hold on to their water shell more tightly because their compact charge binds water molecules more strongly. This makes them effectively larger than potassium and unable to pass through the narrow channel. Understanding these differences is crucial, as ion channels are key targets for many drugs, including those for cardiac arrhythmia.



"A single principle governs high conductance as well as strict ion selectivity in K^+ channels", **Nature Chemistry, 2018**


K+
K+
Na+
Na+


Li
0.76A
Na
1.02A
Ca
1.00A
K
1.38A
Rb
1.52A
Cs
1.67A
Cl
1.81A


(a) Resting state (cytosolic face negative)
Exterior
150 mM
4 mM
Na+
K+
12 mM
140 mM
Cytosol
K+
K+ channel (open)
Na+ channels (closed)
(b) Depolarized state (cytosolic face positive)
Exterior
150 mM
4 mM
Na+
K+
12 mM
140 mM
Cytosol
K+
Na+
Na+
Na+
K+ channel (open)
Na+ channels (open)

Narrowest part of the pore plays a key role in selectivity

Magnitude of ion–protein interactions e.g. electronic effects dictated by the cation that is a better electron acceptor, that is, divalent Ca^{2+} over monovalent Na^+ and K^+.

In contrast, diminishing electronic effects enhances the relative contribution of solvation effects and increases the competitiveness of the ion with the smaller dehydration penalty, that is, K^+ over Na^+ .

Metal Coordination Number (CN): Decreasing the metal Coordination Number favours Na^+ binding to the pore more than K^+ or Ca^{2+} binding, mainly because K^+ and Ca^{2+} generally prefer larger Coordination Numbers in both protein and aqueous solution compared to Na^+.

The smaller Coordination Number in **trimeric selectivity Filters** enhances Na^+/K^+ selectivity, as it reduces the steric repulsion among the bulky protein ligands around Na^+ more than that around the larger K^+.

Ligand Ligating Strength

Increasing the charge and charge-donating ability (i.e., ligating strength) of a protein ligand favors the ion with the better electron-accepting ability.

The ligand's charge-donating ability increases in going from the Ser/Thr hydroxyl group to the Asn/Gln/backbone amide group to the Asp/Glu carboxylate, whereas the electron-accepting ability increases as $K^+ < Na^+ < Ca^{2+}$.

Hence, Asp^-/Glu^- interacts more favorably with Na^+ than with K^+, helping to offset the larger dehydration penalty of Na^+ (−98 kcal/mol) compared to that of K^+ (−81 kcal/mol)

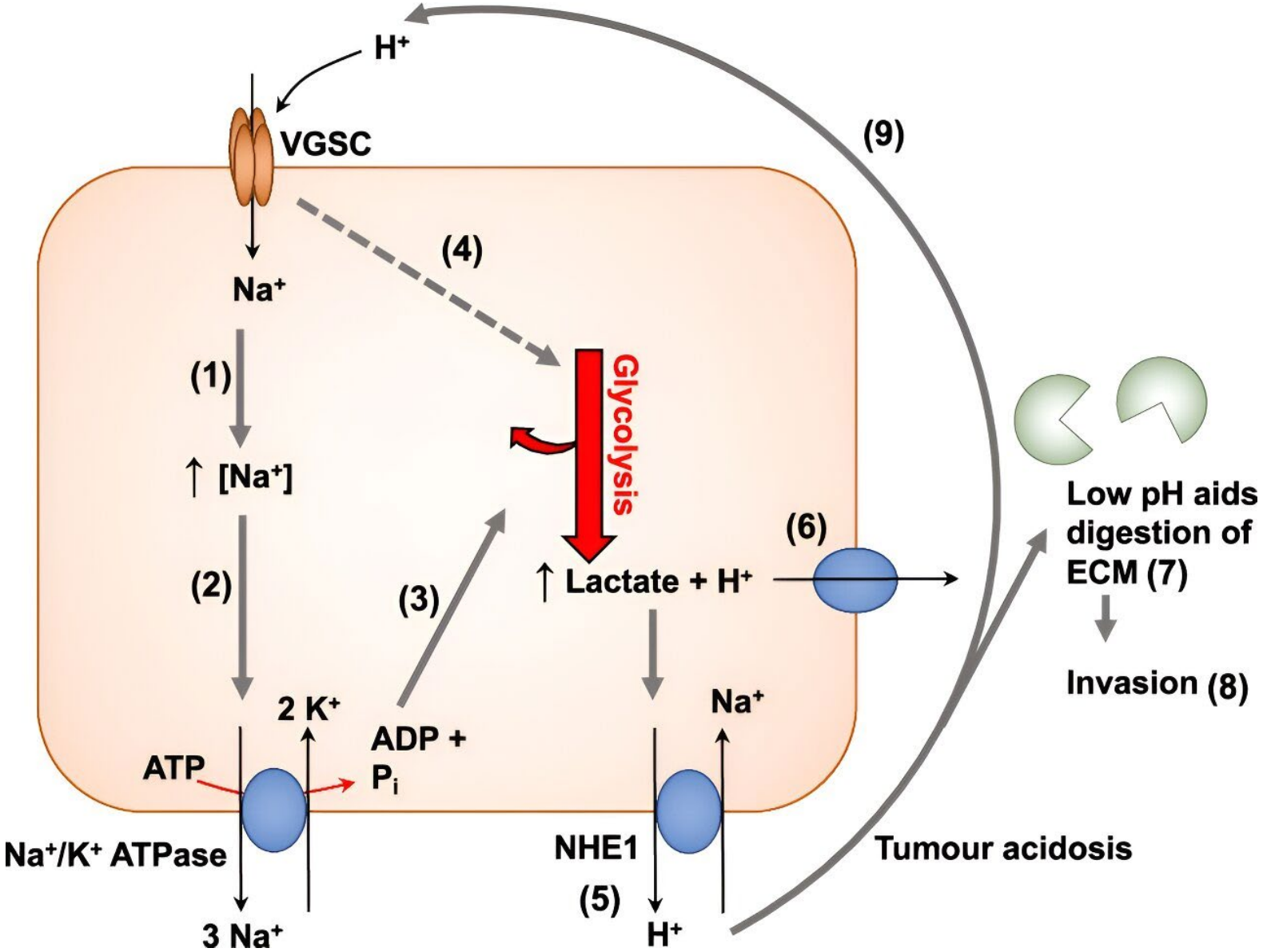
SF Pore Size, Rigidity, and Solvent Exposure

A narrow, rigid pore optimized to fit a bare Na^+ is Na^+-selective, as it cannot optimally fit a bulkier cation. A wide, rigid pore that fits a partially/fully hydrated permeable ion with a CN > 3 can also be Na^+-selective

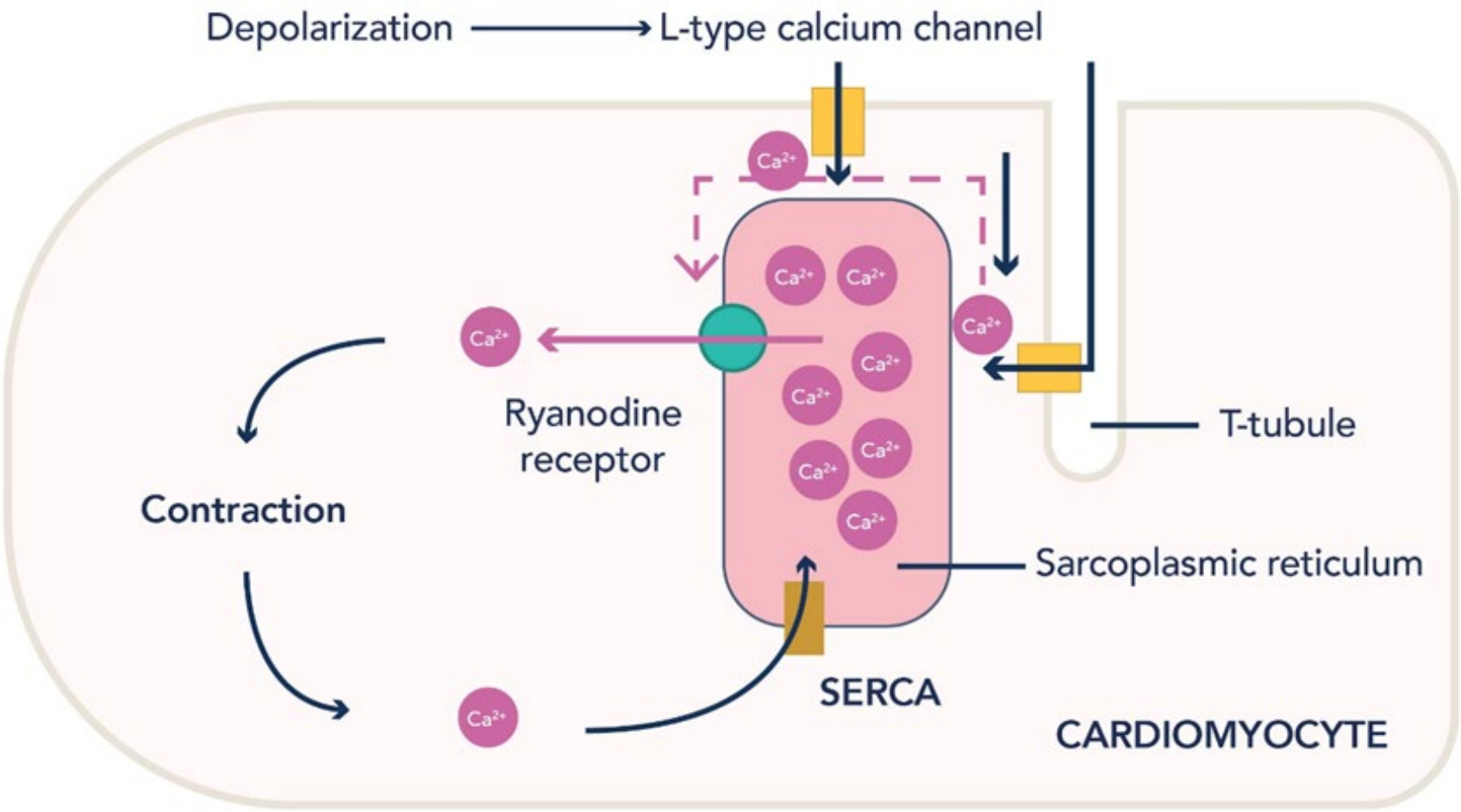
Ion hydration favors Na^+/Ca^{2+} selectivity, as the metal ion indirectly binds the SF ligands via its first-shell water molecules, resulting in longer metal–ligand distances, which disfavors Ca^{2+} binding more than Na^+ binding

It also favors Na^+/K^+ selectivity partly because Na^+, being a stronger Lewis acid, polarizes the first-shell water molecules more than K^+, resulting in stronger metal–water–ligand interactions in the Na^+ complexes than in the respective K^+ clusters.

$Na_v1.5$ V GSC subtype strongly correlates with increased metastasis and shortened cancer-specific survival in breast cancer patients



Oncogene (**2024**). DOI: 10.1038/s41388-024-03098-x



Cardiomyocytes are the *cells responsible for generating contractile force in the intact heart*.

Inside cardiomyocytes Ryanodine receptors (RyRs) are linked to voltage-gated calcium channels, or Dihydropyridine receptors (DHPRs), through physical coupling in skeletal muscle and calcium-induced calcium release (CICR) in cardiac muscle.

In skeletal muscle, a physical link between the DHPR and RyR triggers calcium release from the sarcoplasmic reticulum when an electrical signal activates the DHPR.

In cardiac muscle, DHPRs allow a small influx of calcium, which then triggers the RyRs to release a much larger amount of calcium from the sarcoplasmic reticulum, a process known as CICR. This large increase in cytosolic calcium causes the muscle to contract.

FYI: T-tubules are inward extensions of the muscle cell membrane (sarcolemma) that conduct electrical signals (action potentials) deep into skeletal and cardiac muscle cells

Periodic Table of the Elements

1 IA 1A	2 IIA 2A	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8	9 VIII 8	10	11 IB 1B	12 IIB 2B	13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A
1 H Hydrogen 1.008																	2 He Helium 4.003
3 Li Lithium 6.941	4 Be Beryllium 9.012											5 B Boron 10.811	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180
11 Na Sodium 22.990	12 Mg Magnesium 24.305											13 Al Aluminum 26.982	14 Si Silicon 28.086	15 P Phosphorus 30.974	16 S Sulfur 32.066	17 Cl Chlorine 35.453	18 Ar Argon 39.948
19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.867	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.845	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.631	33 As Arsenic 74.922	34 Se Selenium 78.971	35 Br Bromine 79.904	36 Kr Krypton 83.798
37 Rb Rubidium 85.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868	48 Cd Cadmium 112.414	49 In Indium 114.818	50 Sn Tin 118.711	51 Sb Antimony 121.760	52 Te Tellurium 127.6	53 I Iodine 126.904	54 Xe Xenon 131.294
55 Cs Cesium 132.905	56 Ba Barium 137.328	57-71	72 Hf Hafnium 178.49	73 Ta Tantalum 180.948	74 W Tungsten 183.84	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.217	78 Pt Platinum 195.085	79 Au Gold 196.967	80 Hg Mercury 200.592	81 Tl Thallium 204.383	82 Pb Lead 207.2	83 Bi Bismuth 208.980	84 Po Polonium [208.982]	85 At Astatine 209.987	86 Rn Radon 222.018
87 Fr Francium 223.020	88 Ra Radium 226.025	89-103	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [266]	107 Bh Bohrium [264]	108 Hs Hassium [269]	109 Mt Meitnerium [278]	110 Ds Darmstadtium [281]	111 Rg Roentgenium [280]	112 Cn Copernicium [285]	113 Nh Nihonium [286]	114 Fl Flerovium [289]	115 Mc Moscovium [289]	116 Lv Livermorium [293]	117 Ts Tennessine [294]	118 Og Oganesson [294]

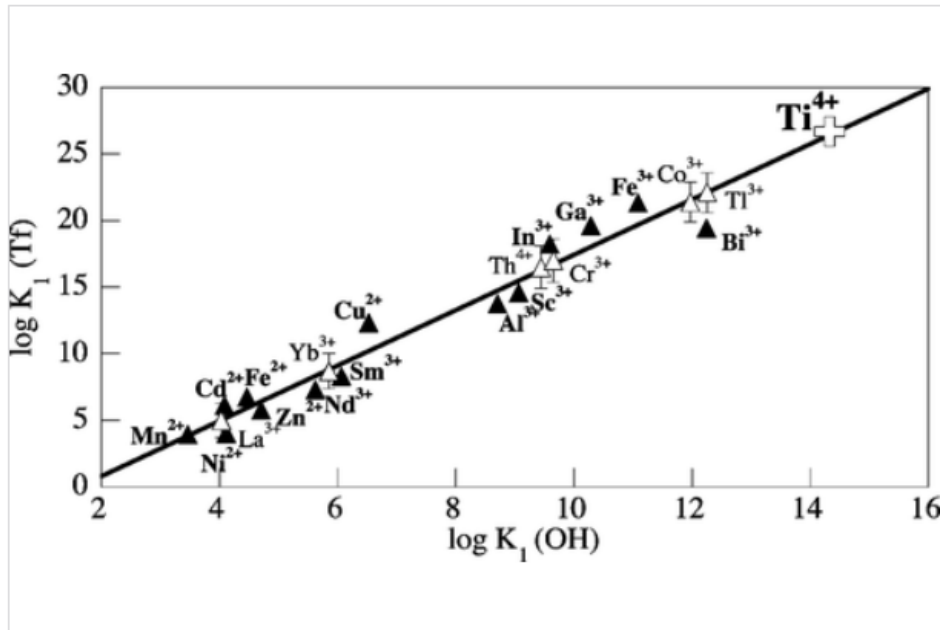
Lanthanide Series	57 La Lanthanum 138.905	58 Ce Cerium 140.116	59 Pr Praseodymium 140.908	60 Nd Neodymium 144.243	61 Pm Promethium 144.913	62 Sm Samarium 150.36	63 Eu Europium 151.964	64 Gd Gadolinium 157.25	65 Tb Terbium 158.925	66 Dy Dysprosium 162.500	67 Ho Holmium 164.930	68 Er Erbium 167.259	69 Tm Thulium 168.934	70 Yb Ytterbium 173.055	71 Lu Lutetium 174.967
Actinide Series	89 Ac Actinium 227.028	90 Th Thorium 232.038	91 Pa Protactinium 231.036	92 U Uranium 238.029	93 Np Neptunium 237.048	94 Pu Plutonium 244.064	95 Am Americium 243.061	96 Cm Curium 247.070	97 Bk Berkelium 247.070	98 Cf Californium 251.080	99 Es Einsteinium [254]	100 Fm Fermium 257.095	101 Md Mendelevium 258.1	102 No Nobelium 259.101	103 Lr Lawrencium [262]

COMMUNICATION | July 23, 2005

Ti(IV) Binds to Human Serum Transferrin More Tightly Than Does Fe(III)

Arthur D. Tinoco, and Ann M. Valentine

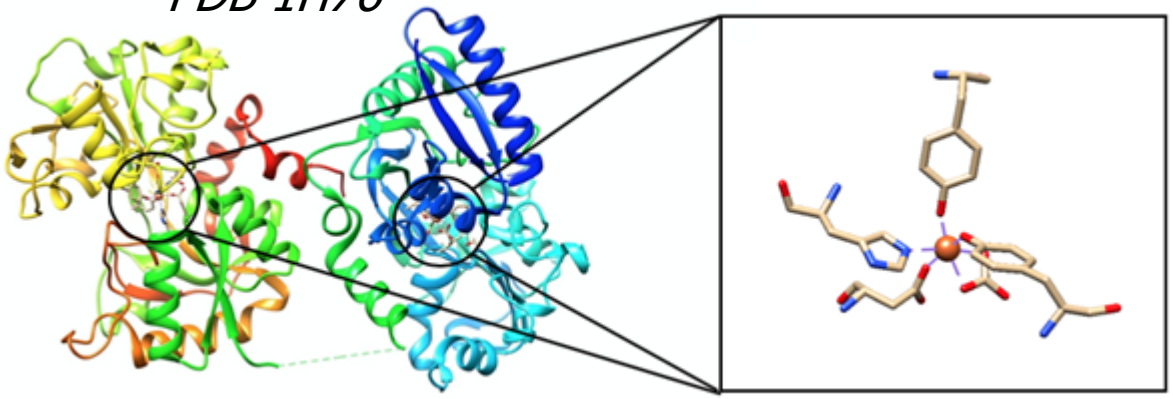
Abstract

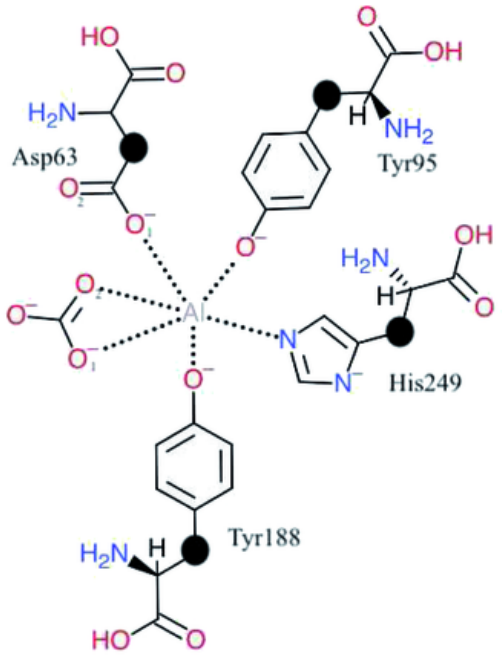


The binding of titanium(IV) to human serum transferrin in 50 mM Tris with 20 mM bicarbonate and 10 mM citrate at pH 7.4 was studied by UV/vis kinetics and by isothermal titration calorimetry. Ti(IV) citrate, $[Ti(C_6H_4O_7)_3]^{8-}$, employed in this study was previously characterized and delivers the metal to transferrin rapidly, allowing the quantification of the intrinsic binding constants for Ti(IV) to the C- and N-sites of transferrin. The results after correcting for blood plasma conditions (pH 7.4, $[HCO_3^-]$ = 27 mM) reveal that Ti(IV) binds with greater affinity (log K = 26.8 and 25.7) than Fe(III) (log K = 22.5 and 21.4) to transferrin, a finding not previously observed for other examined metal ions. The strength of metal binding to transferrin correlates with the Lewis acidity of the metal. Ti(IV) is more Lewis acidic than Fe(III) and is nearly the same size. The study also reveals that Ti(IV) binds more tightly to one site than the other, and this difference is due to both entropic and enthalpic contributions. The study has implications for the role of transferrin in the cancer activity of Ti(IV) drugs and the serum binding of Ti(IV) ions released from implants or imaging reagents.

Human Serum transferrin: a dimeric Fe(III) transport protein → A protein that carries almost any metal to various sites from blood. Mostly around 60% of the protein is always free and roaming around in blood

PDB 1H76





Binds Al(III) too! Which can lead to aluminium toxicity in brain which is thought to be one of the causes of Alzheimer's