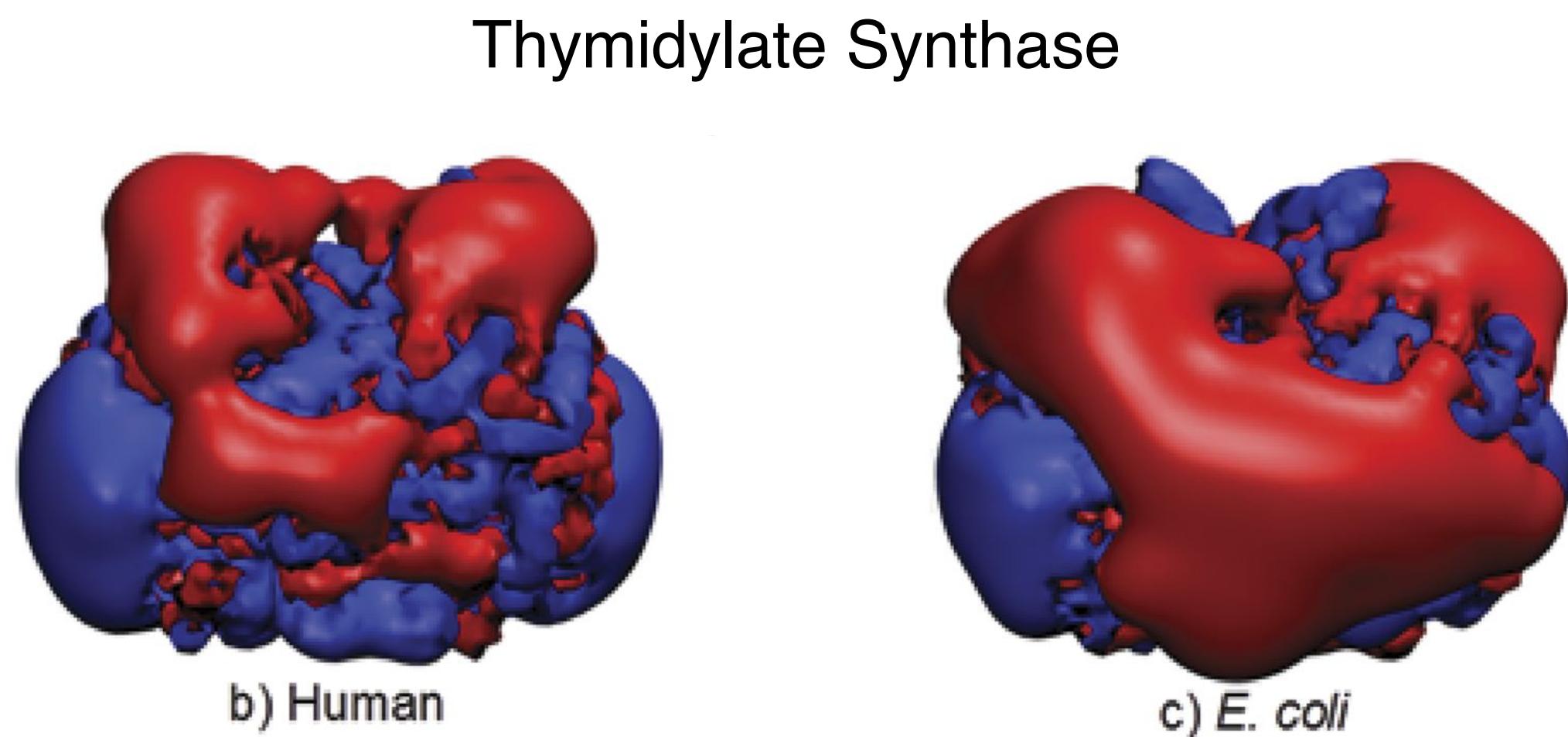


9/18 Biomolecular Electrostatics

- This week's lecture and lab are intended to help you achieve the following learning objectives:
 - Predict the pKa's of titratable amino acids on a protein and protonation at a given pH. Summarize the qualitative relationship between electrostatic potential and pKa.
 - Compute and visualize the electrostatic potential of a protein. Compare the advantages and disadvantages of several representations.
- At the end of this lecture, you should be able to explain, in a general sense, the
 - importance of electrostatics in biological macromolecules
 - origin of the Poisson-Boltzmann equation

Roles of Biomolecular Electrostatics

- Electrostatics important in (at least)
 - protonation, influencing side chain pKa
 - binding for
 - steering, facilitating approach of species
 - complexation, as complementarity means lower potential energy
 - enzyme catalysis, as electric potential stabilizes transition state
 - solvation
- Electrostatic potential usually conserved near functional sites



blue isocontours $+1 \text{ kT/e}$,
red isocontours -1 kT/e

From Fig 1 of Garg *et al.* (2015).

G proteins have distinct fingerprints

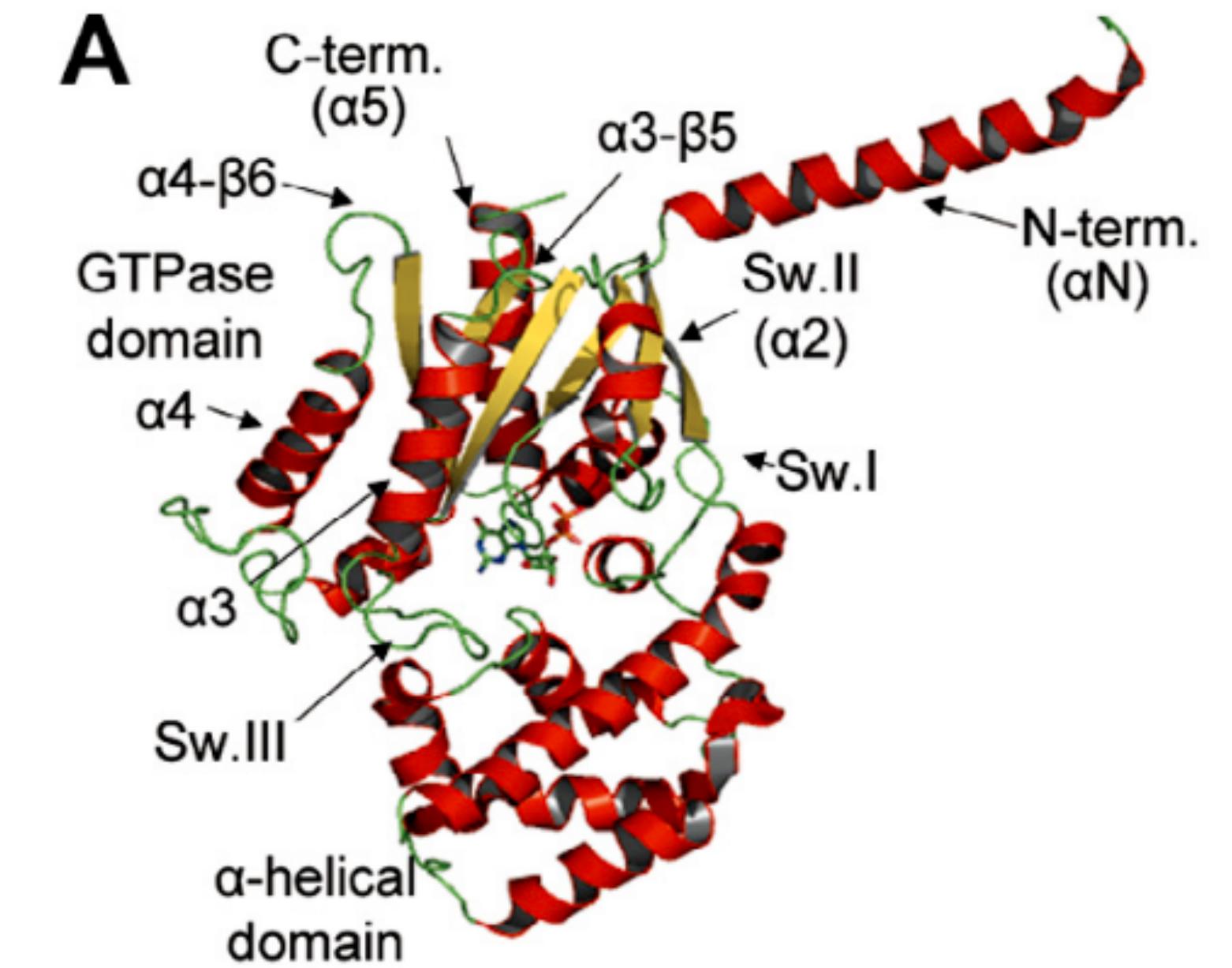
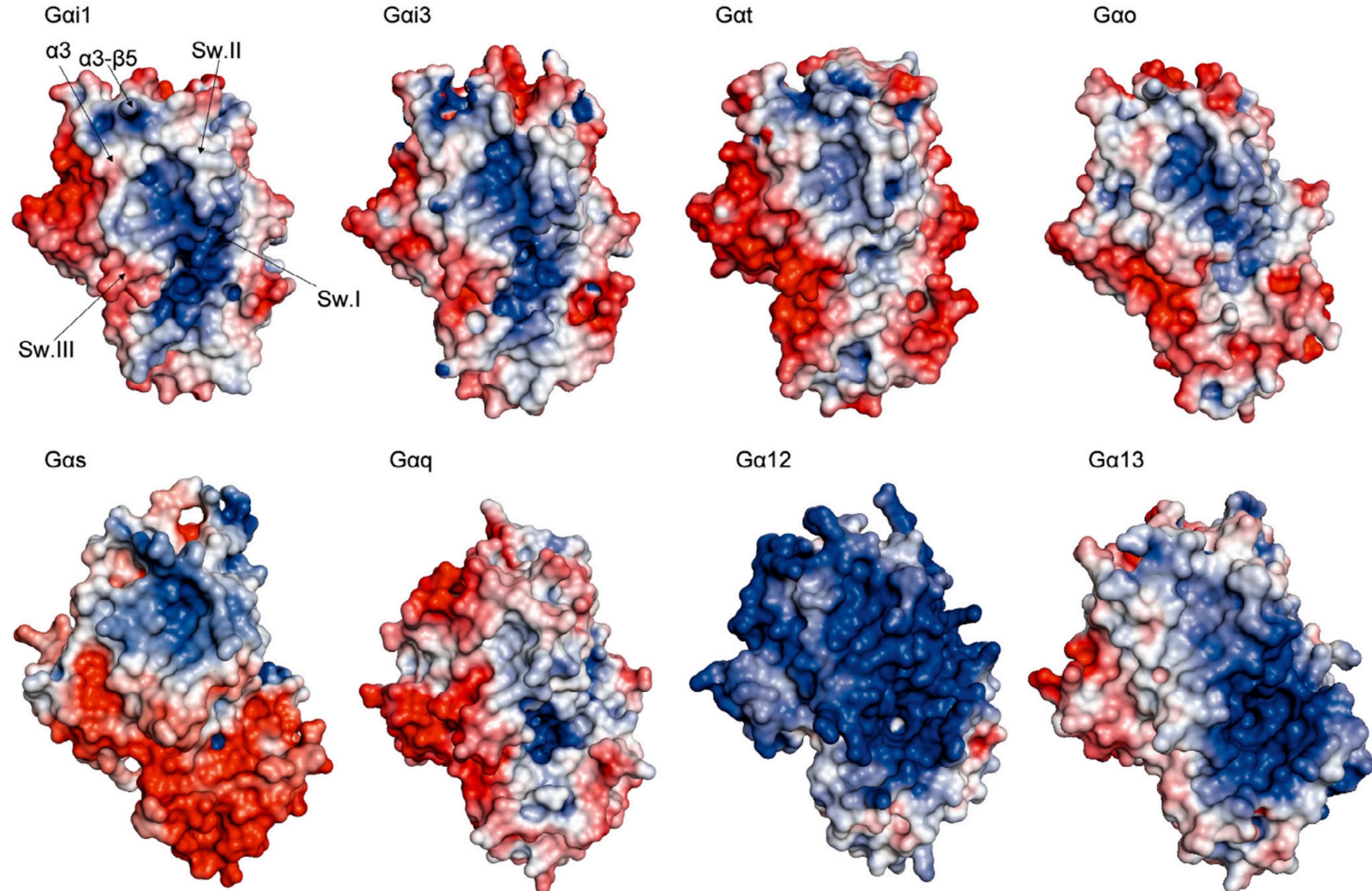


Fig.2. Electrostatic molecular surfaces of G α subunits. All subunits are oriented in the same way as in Fig.1. Charged surfaces are colored in shades of blue for positive and red for negative charges, while uncharged surfaces are colored white. Subunit surfaces are contoured from -5 (red) to +5 (blue) kT/e⁻ based on the potential of the solvent-accessible surface. All subunits are in their activated state, with the exception of G α_{i3} and G α_o , which are in their RGS-bound state. There is a conserved, effector-binding pocket between Switch II and α_3 . A visualization of the potential of the opposite side of the G α subunits is shown in Supplementary Fig. S6. Crystal structures used are G α_{i1} (PDB: 1GIA), G α_{i3} (PDB: 2V4Z), G α_t (PDB: 1TND), G α_o (PDB: 3C7K), G α_s (PDB: 1AZT), G α_q (PDB: 3AH8), G α_{12} (PDB: 1ZCA) and G α_{13} (PDB: 3CX8).

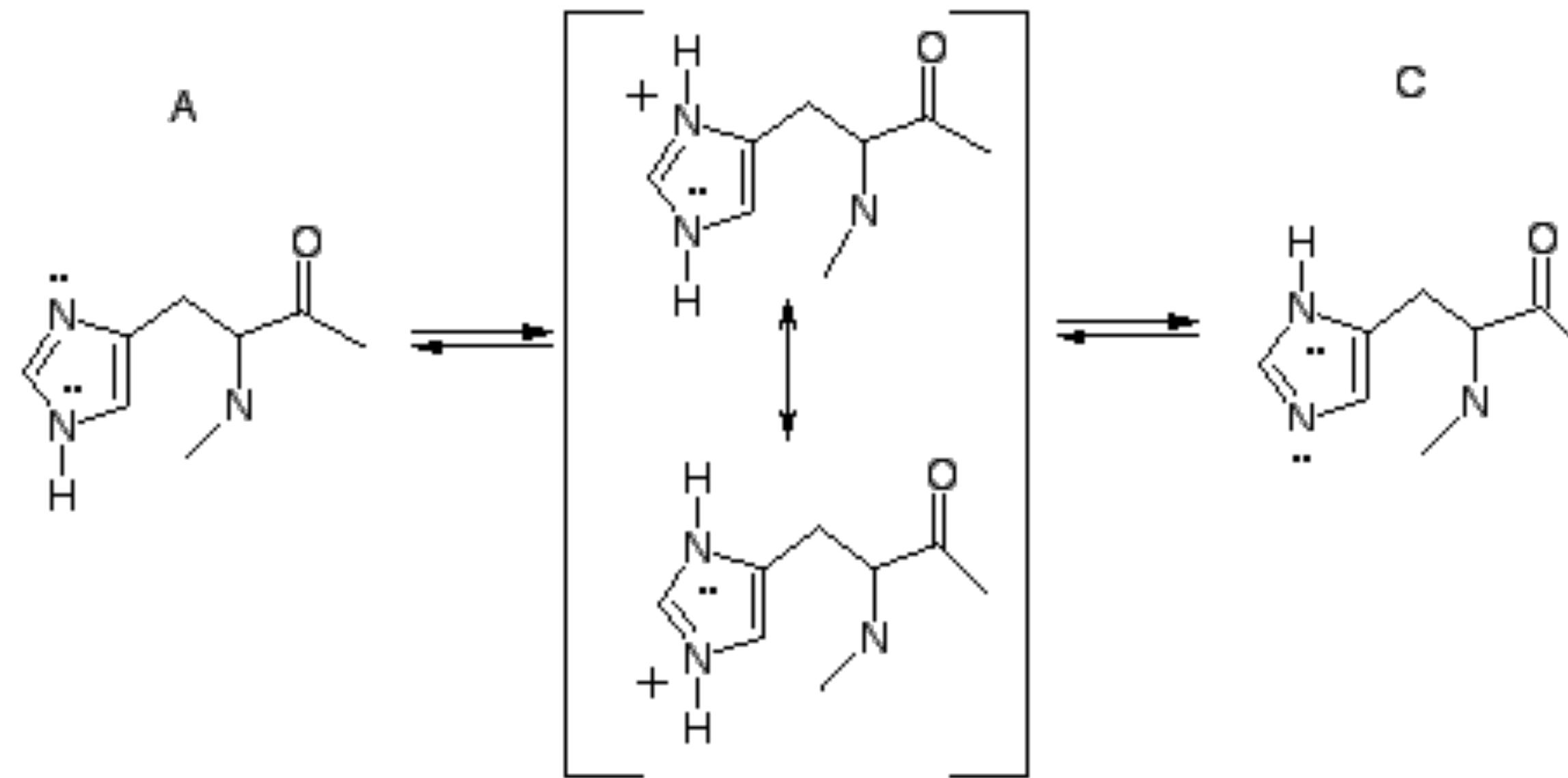
Baltoumas, F. A.; Theodoropoulou, M. C.; Hamodrakas, S. J. Interactions of the α -Subunits of Heterotrimeric G-Proteins with GPCRs, Effectors and RGS Proteins: A Critical Review and Analysis of Interacting Surfaces, Conformational Shifts, Structural Diversity and Electrostatic Potentials. *Journal of Structural Biology* 2013, 182 (3), 209–218. <https://doi.org/10.1016/j.jsb.2013.03.004>.

Protein Protonation

- Which structure determination technique(s) have been used to identify the protonation of amino acid side chains?
 - A. X-ray crystallography
 - B. X-ray crystallography, at very high resolution
 - C. Nuclear magnetic resonance
 - D. Cryo-electron microscopy
 - E. None of the above

Histidine

B



<https://spdbv.unil.ch/TheMolecularLevel/Goodies/Get2NoHistidine.html>

- As the side chain has a $\text{pK}_a \sim 7.0$, imidazolium ion (B) and imidazole (A or C) are all present in physiological conditions
- Which state(s) are stabilized by a negative electrostatic potential?
- What can stabilize a specific form of imidazole?

Electrostatics is important in solvation

- It is an *implicit solvent* model that does not account for specific water positions
- Solvent is assumed to modify the dielectric constant

- Coulomb's law is $F = \frac{1}{4\pi\epsilon} \frac{Q_1 Q_2}{r^2}$.

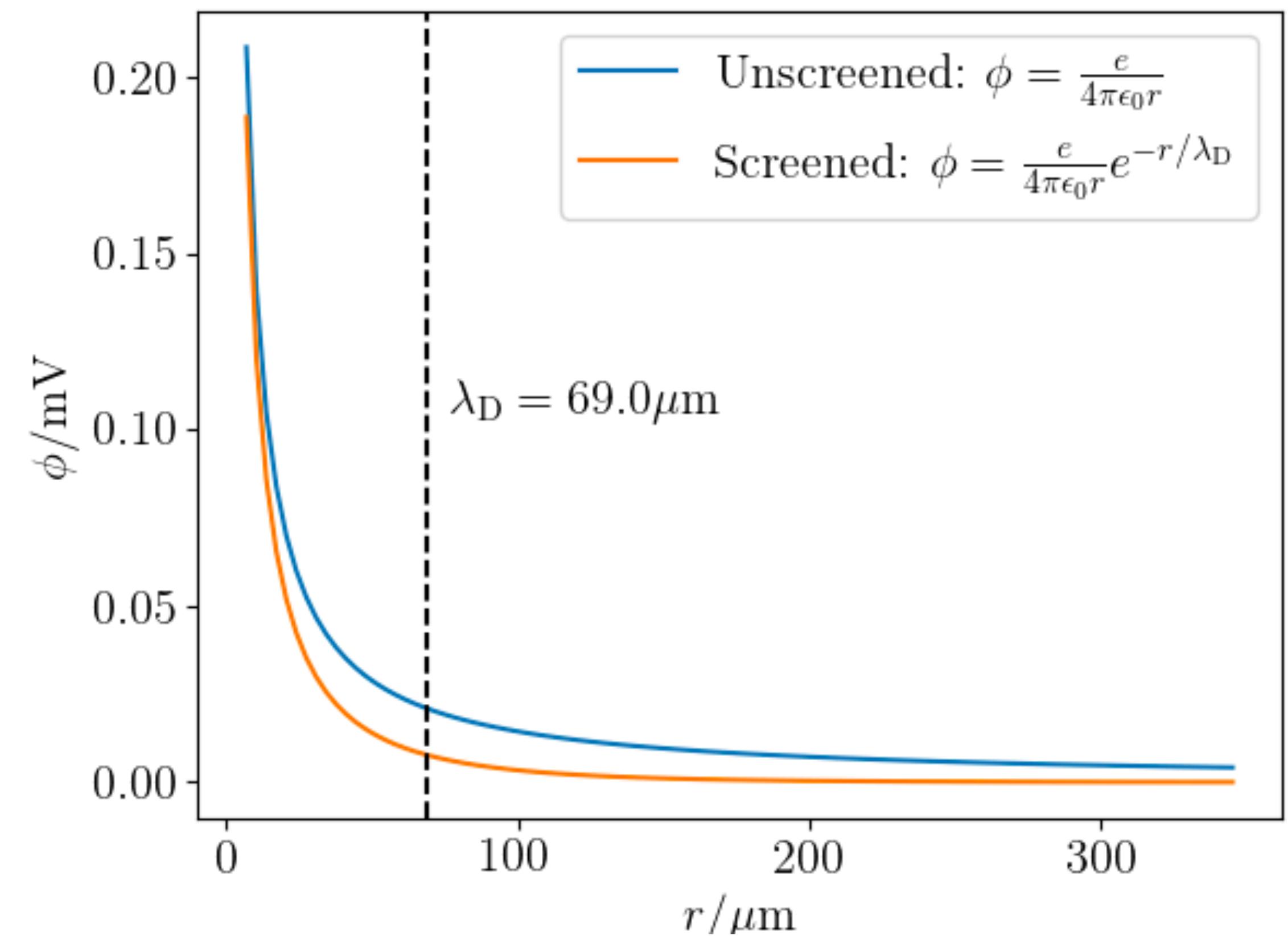
- The permittivity ϵ is related to the permittivity of free space ϵ_0 by the dielectric constant κ , $\epsilon = \kappa\epsilon_0$.
 - ~80 for water
 - ~1 for the protein interior
- The electrostatic component of the solvation energy is modeled as the difference between the energy in water and in vacuum

Modeling Electrostatics

- In biological macromolecules, the electrostatic potential is usually calculated based on the Poisson-Boltzmann equation
 - The Poisson equation $\nabla \cdot \epsilon(r) \nabla \phi(r) + 4\pi\rho(r) = 0$ describes the potential $\phi(r)$ due to a given charge density $\rho(r)$ and dielectric $\epsilon(r)$. Atoms in the biomolecule are assumed to have a fixed charge.
 - The Poisson-Boltzmann equation assumes that (infinitely small) ions surround a biomolecule in accordance with the Boltzmann distribution
 - The PB equation is a partial differential equation that is solved numerically
 - The equation is often linearized to be more numerically stable

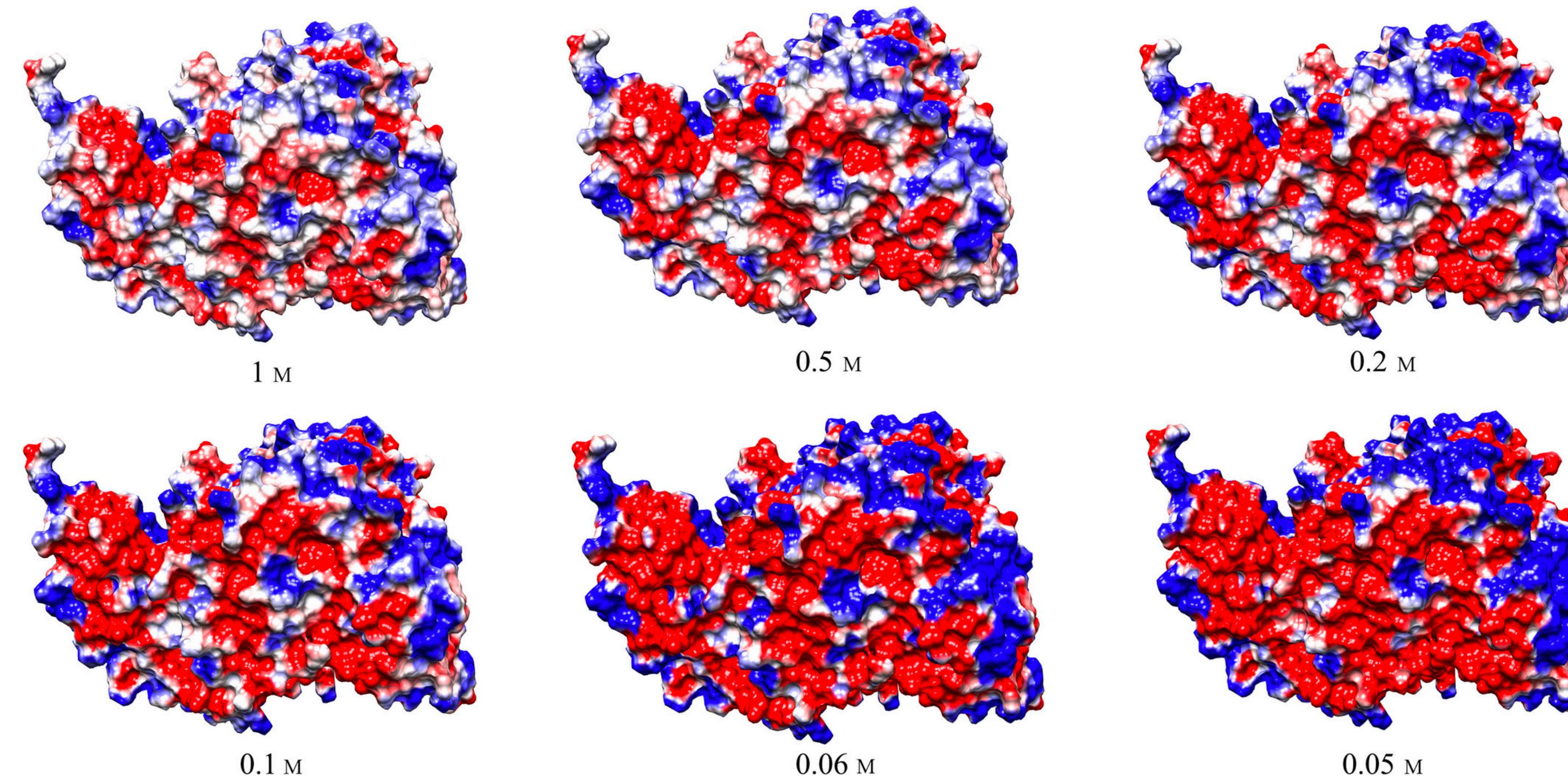
Electrostatic Screening

- Ions “screen” the electrostatics between two charges



<https://scipython.com/blog/the-debye-length/>

Ion concentration effects



Potential contours (-0.5 (red) and $+0.5$ (blue) kT/e) around AGT-Ma at pH 7.4, 37°C , at the indicated ionic strength.
from Dindo et al (2017) <https://febs.onlinelibrary.wiley.com/doi/full/10.1111/febs.14269>

- What happens to the electrostatic potential as the ionic concentration is increased.
Why?

Influences on biomolecular electrostatics

- Which are influences on biomolecular electrostatics?
 - A. pH
 - B. Concentration of ions
 - C. Valency of ions (+1 vs. +2)
 - D. Identity and size of ions (Ca^{2+} vs Mg^{2+})
- Which are accounted for by the Poisson-Boltzmann equation?
 - A. pH
 - B. Concentration of ions
 - C. Valency of ions (+1 vs. +2)
 - D. Identity and size of ions (Ca^{2+} vs Mg^{2+})

Review Questions

- Discuss some of the ways in which electrostatics is important for the function of biological macromolecules
- An equation often used to model the electrostatics of biological macromolecules is the Poisson-Boltzmann equation. Why does the equation have this name?
- How can the Poisson-Boltzmann equation be used to calculate the electrostatic component of the solvation free energy?

The PDB2PQR-APBS web server

<https://server.poissonboltzmann.org/>



APBS

Welcome to the new home for running the APBS-PDB2PQR software suite

Please [register](#) to ensure continued support for this software.

Getting Started:

PDB2PQR

APBS



Go to Project
Homepage



Register to help
support PDB2PQR &
APBS



See Examples



1 PDB2PQR Configuration

2 PDB2PQR Job Status

3 APBS Configuration

4 APBS Job Status

5 Visualization

PDB Selection

* PDB Source

* Please upload a PDB file

 7t2gABC.pdb

For continued support of this server, please register your use of this software:

pKa Options

pH: No pKa calculation Use PROPKA to assign protonation states at provided pH

Forcefield Options

Please choose a forcefield to use

Please choose an output naming scheme to use

Additional Options

- Ensure that new atoms are not rebuilt too close to existing atoms
- Optimize the hydrogen bonding network
- Assign charges to the ligand specified in a MOL2 file
- Create an APBS input file
- Add/keep chain IDs in the PQR file
- Insert whitespaces between atom name and residue name, between x and y, and between y and z
- Make the protein's N-terminus neutral (requires PARSE forcefield)
- Make the protein's C-terminus neutral (requires PARSE forcefield)
- Remove the waters from the output file



1 PDB2PQR Configuration

2 PDB2PQR Job Status

3 APBS Configuration

4 APBS Job Status

To return to your results after leaving, **save this page.**

Job ID:
nrzz8189gt_20240918

Job Type:
PDB2PQR

Time Elapsed:
00:00:19

✓ Submitted

✓ Pending Job Start

✓ Running

✓ Complete

Next:

[Use results with APBS >](#)**PDB2PQR Input Files**

7t2gABC.pdb

357.7 KB | [Download](#)**PDB2PQR Output Files**

nrzz8189gt.log

198.78 KB | [Download](#)

pdb2pqr-metrics.json

624 Bytes | [Download](#)

pdb2pqr.stderr.txt

136.75 KB | [Download](#)

pdb2pqr.stdout.txt

0 Bytes | [Download](#)

nrzz8189gt.in

436 Bytes | [Download](#)

nrzz8189gt.pqr

646.15 KB | [Download](#)

If you haven't already, please remember to **register your use of this software:**

[Register Here](#)**Log Preview** Show line numbers

> Log (nrzz8189gt.log)

[↓](#)

> Stdout (pdb2pqr.stdout.txt)

[↓](#)

> Stderr (pdb2pqr.stderr.txt)

[↓](#)

Data Retention
Files for the job nrzz8189gt_20240918 will be retained for 14 DAYS following job creation.
Please download the files you wish to keep in the meantime.



1 PDB2PQR Configuration

2 PDB2PQR Job Status

3 APBS Configuration

4 APBS Job Status

For continued support of this server, please register your use of this software:

[Register Here](#)[Input](#)[mg-auto Options](#)[Misc Options](#)[Output Settings](#)

Scalar data output

▼ OUTPUT OF SCALAR DATA CALCULATED DURING THE PB RUN:

- Write out the biomolecular charge distribution in units of ec (multigrid only)
 - Write out the electrostatic potential in units of kbT/ec (multigrid and finite element)
 - Write out the solvent accessibility defined by the molecular surface definition
 - Write out the spline-based solvent accessibility
 - Write out the van der Waals-based solvent accessibility
 - Write out the inflated van der Waals-based ion accessibility
 - Write out the Laplacian of the potential in units of kBT/ec/A² (multigrid only)
 - Write out the "energy density" in units of kBT/ec/A² (multigrid only)
 - Write out the mobile ion number density for m ion species in units of M (multigrid only)
 - Write out the mobile charge density for m ion species in units of e_t c M (multigrid only)
 - Write out the dielectric map shifted by 1/2 grid spacing in the x-direction
 - Write out the dielectric map shifted by 1/2 grid spacing in the y-direction
 - Write out the dielectric map shifted by 1/2 grid spacing in the z-direction
- Write out the ion-accessibility kappa map

Output

> FORMAT TO WRITE DATA:

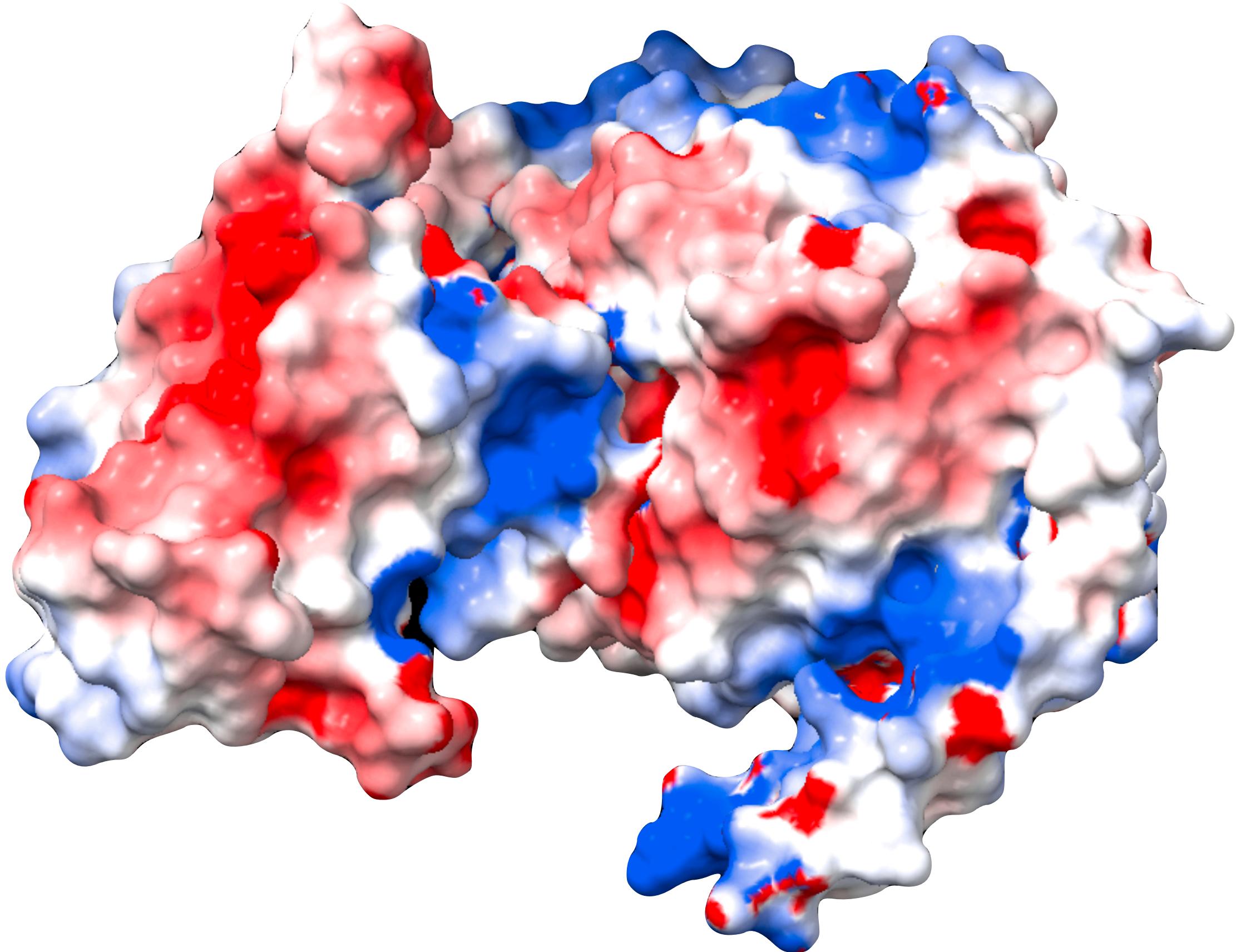
! Data Retention

Files for the job nrzz8189gt_20240918 will be retained for 14 DAYS following job creation.
Please download the files you wish to keep in the meantime.

[Start Job](#)

Visualization

- Google Colab can show isosurfaces
- The APBS web server shows the electrostatic potential at the protein surface.
- UCSF Chimera X
 - can visualize volumetric data
 - or show the potential at surface (as on the right)
- Visual Molecular Dynamics (VMD) has different representations for electrostatics
 - VolumeSlice
 - Isosurface





To return to your results after leaving, [save this page.](#)

Job ID:
nrzz8189gt_20240918

Job Type:
APBS

Time Elapsed:
00:00:29

Next:
[View in 3Dmol >](#)

Submitted

Pending Job Start

Running

Complete

APBS Input Files

nrzz8189gt.pqr	646.15 KB	Download
apbsinput.in	339 Bytes	Download

APBS Output Files

io.mc	13.29 KB	Download
apbs-metrics.json	631 Bytes	Download
nrzz8189gt-pot.dx	95.15 MB	Download
apbs.stderr.txt	0 Bytes	Download
apbs.stdout.txt	6.08 KB	Download

If you haven't already, please remember to [register your use of this software:](#)

[Register Here](#)

Log Preview

Show line numbers

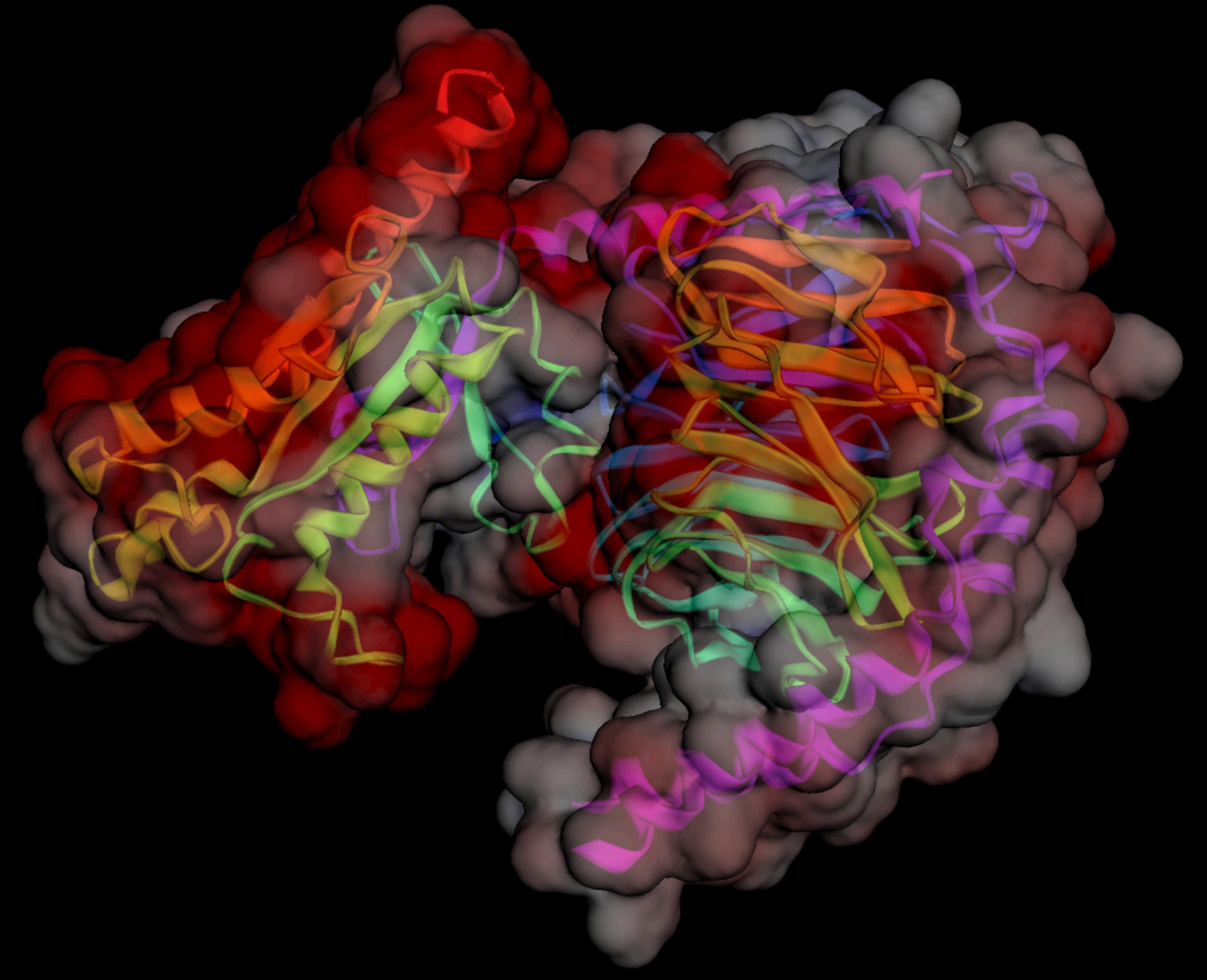
> Stdout (apbs.stdout.txt)

[Download](#)

> Stderr (apbs.stderr.txt)

To view within 14 days of 9/17/2024:

<https://server.poissonboltzmann.org/jobstatus?jobtype=apbs&jobid=nrzz8189gt&date=2024-09-18>



Surface:

Solvent Accessible

Show Translucent

Surface Potential:

Min -5 kT/e

Max 5 kT/e

Reset

Model: Cartoon

Scheme: Red-White-Blue

Labels: Remove

Recenter

Background Transparency:

0

Export as: PNG

Export

References

- Garg, D.; Skouloubris, S.; Briffotaux, J.; Myllykallio, H.; Wade, R. C. Conservation and Role of Electrostatics in Thymidylate Synthase. *Sci Rep* 2015, 5 (1), 17356. <https://doi.org/10.1038/srep17356>, adapted under the CC BY 4.0 license.
- Dindo et al (2017) <https://febs.onlinelibrary.wiley.com/doi/full/10.1111/febs.14269>
- Baltoumas, F. A.; Theodoropoulou, M. C.; Hamodrakas, S. J. Interactions of the α -Subunits of Heterotrimeric G-Proteins with GPCRs, Effectors and RGS Proteins: A Critical Review and Analysis of Interacting Surfaces, Conformational Shifts, Structural Diversity and Electrostatic Potentials. *Journal of Structural Biology* 2013, 182 (3), 209–218. <https://doi.org/10.1016/j.jsb.2013.03.004>.