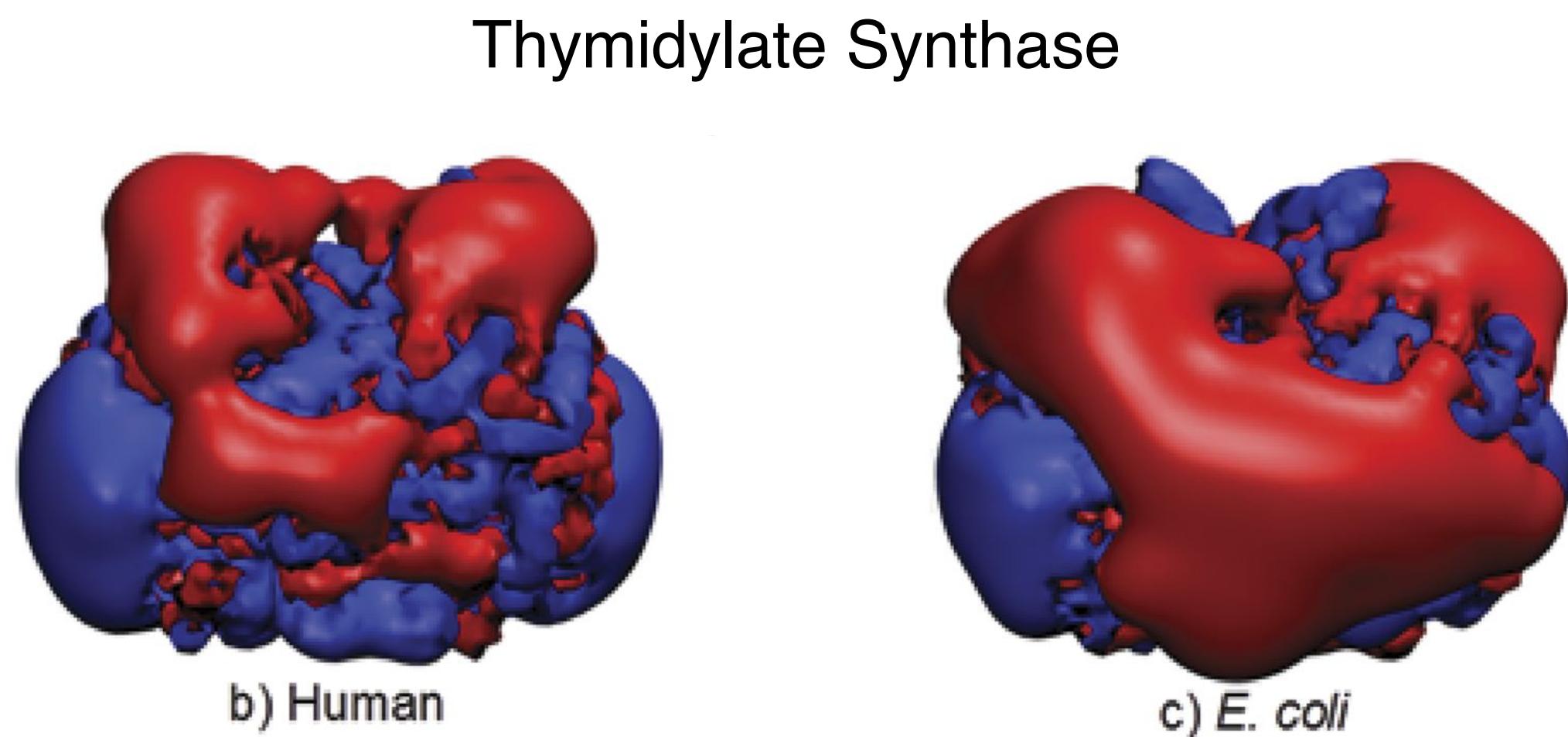


9/19 Biomolecular Electrostatics

- 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

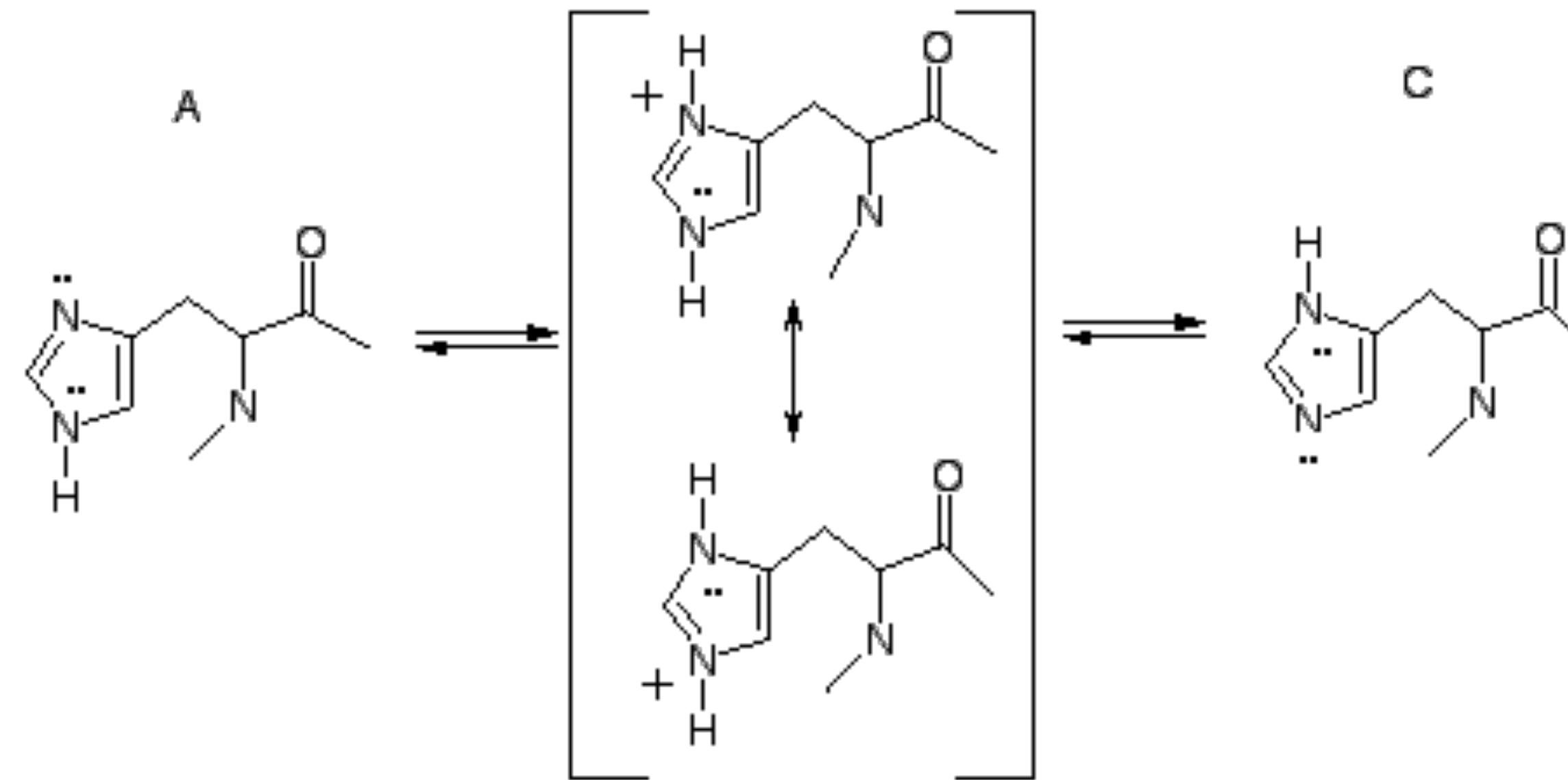
From Fig 1 of Garg *et al.* (2015).

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 $F = \frac{1}{4\pi\epsilon} \frac{Q_1 Q_2}{r^2}$.

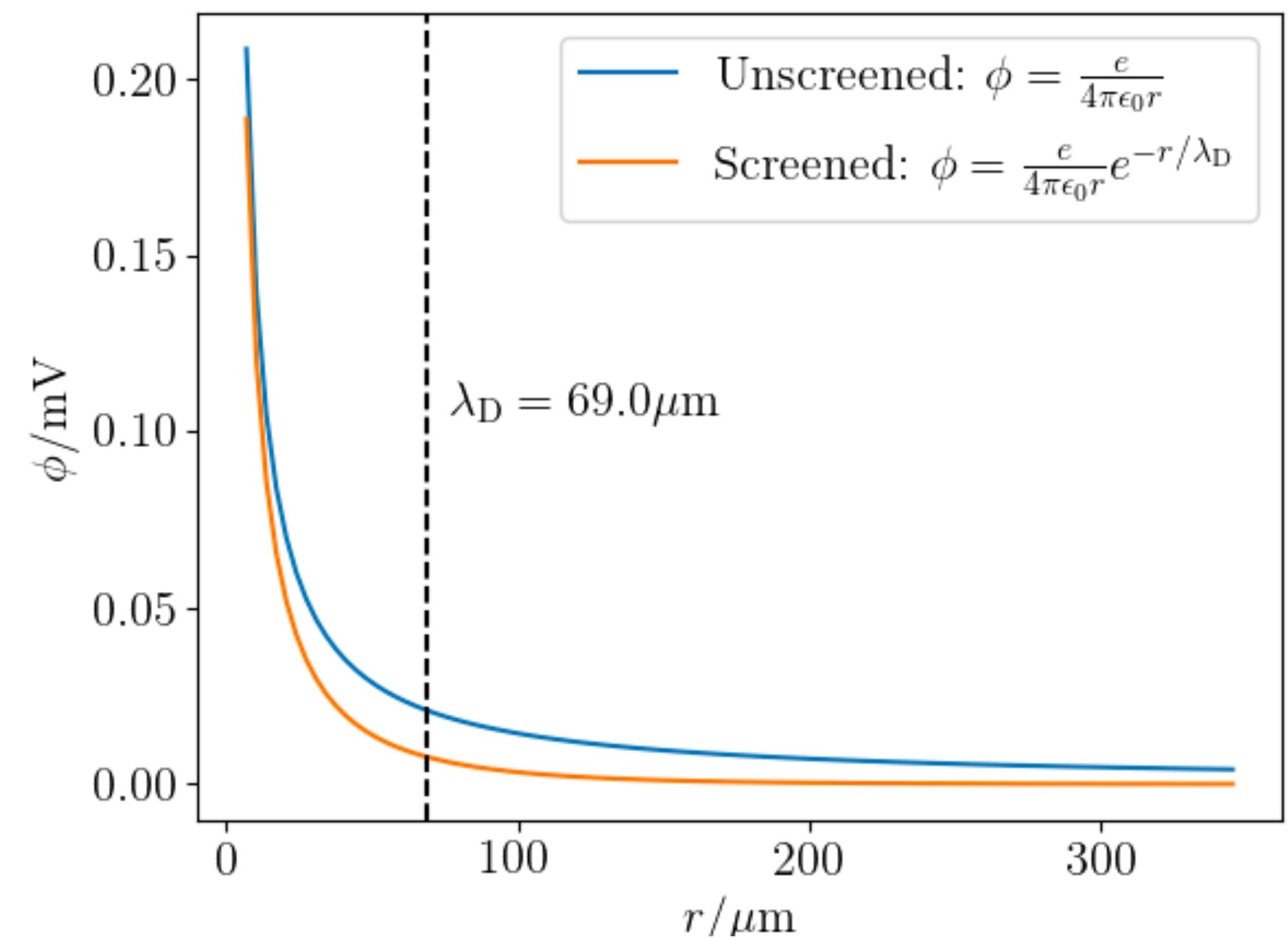
- The permittivity ϵ is related to the permittivity of free space ϵ_0 by the dielectric constant κ , $\epsilon = \kappa\epsilon_0$.
 - ~80 for water
 - ~1 for the protein interior
- The electrostatic component of the solvation energy is modeled as the difference between the energy in water and in vacuum

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

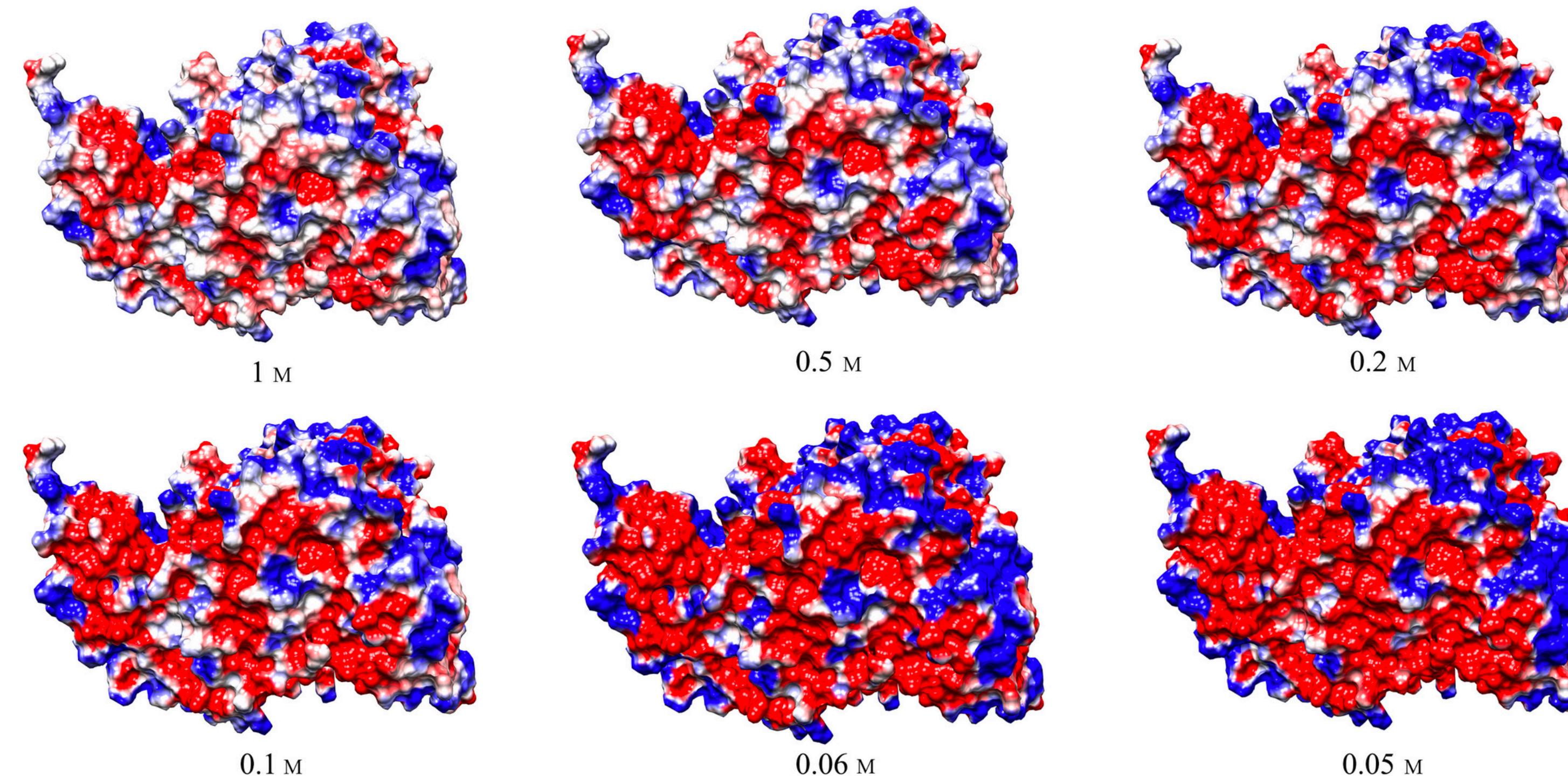
Electrostatic Screening

- 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?
 - pH
 - Concentration of ions
 - Valency of ions (+1 vs. +2)
 - Identity and size of ions (Ca^{2+} vs Mg^{2+})
- Which are accounted for by the Poisson-Boltzmann equation?
 - pH
 - Concentration of ions
 - Valency of ions (+1 vs. +2)
 - 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/pdb2pqr>

[Home](#)[Tools](#)[About](#)[Documentation](#)[Announcements](#)

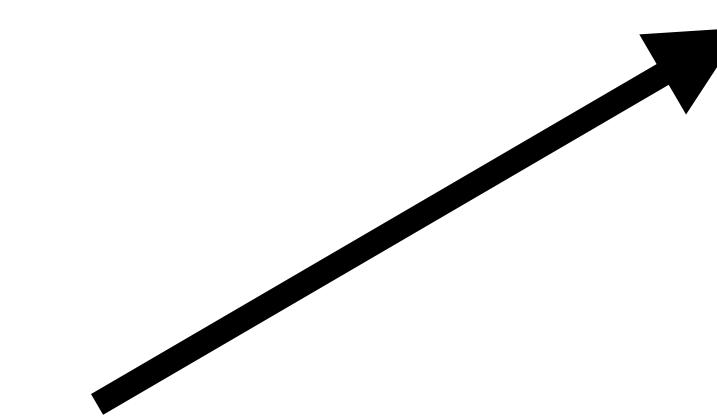
Home

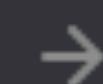
APBS

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](#)



Apps

Productivity

IIT

Teaching

Research

Funding

Bookmarks Menu

[Home](#)[Tools](#)[About](#)[Documentation](#)[Announcements](#)**1 PDB2PQR Configuration****2 PDB2PQR Job Status****3 APBS Configuration****PDB Selection**

* PDB Source

[PDB ID](#)[Upload a PDB file](#)

* Please upload a PDB file

[Select File](#)[bestmodel_aligned.pdb](#)

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

[Register Here](#)**pKa Options**pH: No pKa calculation Use PROPKA to assign protonation states at provided pH



Home

Tools

About

Documentation

Announcements

pH: 7.0

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

Forcefield Options

Please choose a forcefield to use

AMBER

CHARMM

PEOEPB

PARSE

SWANSON

TYL06

User-defined Forcefield

CLI

ning scheme to use

--ff=AMBER

AMBER

CHARMM

PARSE

PEOEPB

SWANSON

TYL06

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

[PDB2PQR Configuration](#)[2 PDB2PQR Job Status](#)[3 APBS Configuration](#)[4 APBS Job Status](#)

Data Retention

Files for the job k5f10lg2t7_20220306 retained for 14 DAYS following job completion.
Please download the files you wish to keep during this time.

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

Job ID:

k5f10lg2t7_20220306

Job Type:

PDB2PQR

Time Elapsed:

00:00:13

Next:

[Use results with APBS >](#)

Submitted

Pending Job Start

Running

Complete

PDB2PQR Input Files

bestmodel_aligned.pdb

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

pdb2pqr-metrics.json

621 Bytes | [Download](#)

pdb2pqr.stderr.txt

60.85 KB | [Download](#)

k5f10lg2t7.pqr

642.66 KB | [Download](#)

pdb2pqr.stdout.txt

0 Bytes | [Download](#)

k5f10lg2t7.in

435 Bytes | [Download](#)

k5f10lg2t7.log

63.43 KB | [Download](#)

[PDB2PQR Configuration](#)[PDB2PQR Job Status](#)[APBS Configuration](#)[APBS Job Status](#)

Data Retention

Files for the job k5f10lg2t7_20220306 retained for 14 DAYS following job completion. Please download the files you wish to keep during this time.

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

Job ID:

k5f10lg2t7_20220306

Job Type:

APBS

Time Elapsed:

00:00:33

Next:

[View in 3Dmol >](#)[Submitted](#)[Pending Job Start](#)[Running](#)[Complete](#)**APBS Input Files**

k5f10lg2t7.pqr

642.66 KB | [Download](#)

apbsinput.in

336 Bytes | [Download](#)**APBS Output Files**

io.mc

13.59 KB | [Download](#)

apbs-metrics.json

632 Bytes | [Download](#)

k5f10lg2t7-pot.dx

97.93 MB | [Download](#)

apbs.stderr.txt

0 Bytes | [Download](#)

apbs.stdout.txt

6.07 KB | [Download](#)

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

Visualization

- Exercise 4 describes how to use Google Colab to show isosurfaces.
- The APBS web server shows the electrostatic potential at the protein surface.
- Visual Molecular Dynamics (VMD) has different representations for electrostatics. See <https://dasher.wustl.edu/chem478/labs/lab-08/tutorial-vmd.pdf>.
- VolumeSlice <https://www.ks.uiuc.edu/Research/vmd/vmd-1.8.3/ug/node66.html>
- Isosurface <https://www.ks.uiuc.edu/Research/vmd/vmd-1.8.3/ug/node67.html>
- UCSF Chimera also can visualize volumetric data

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>