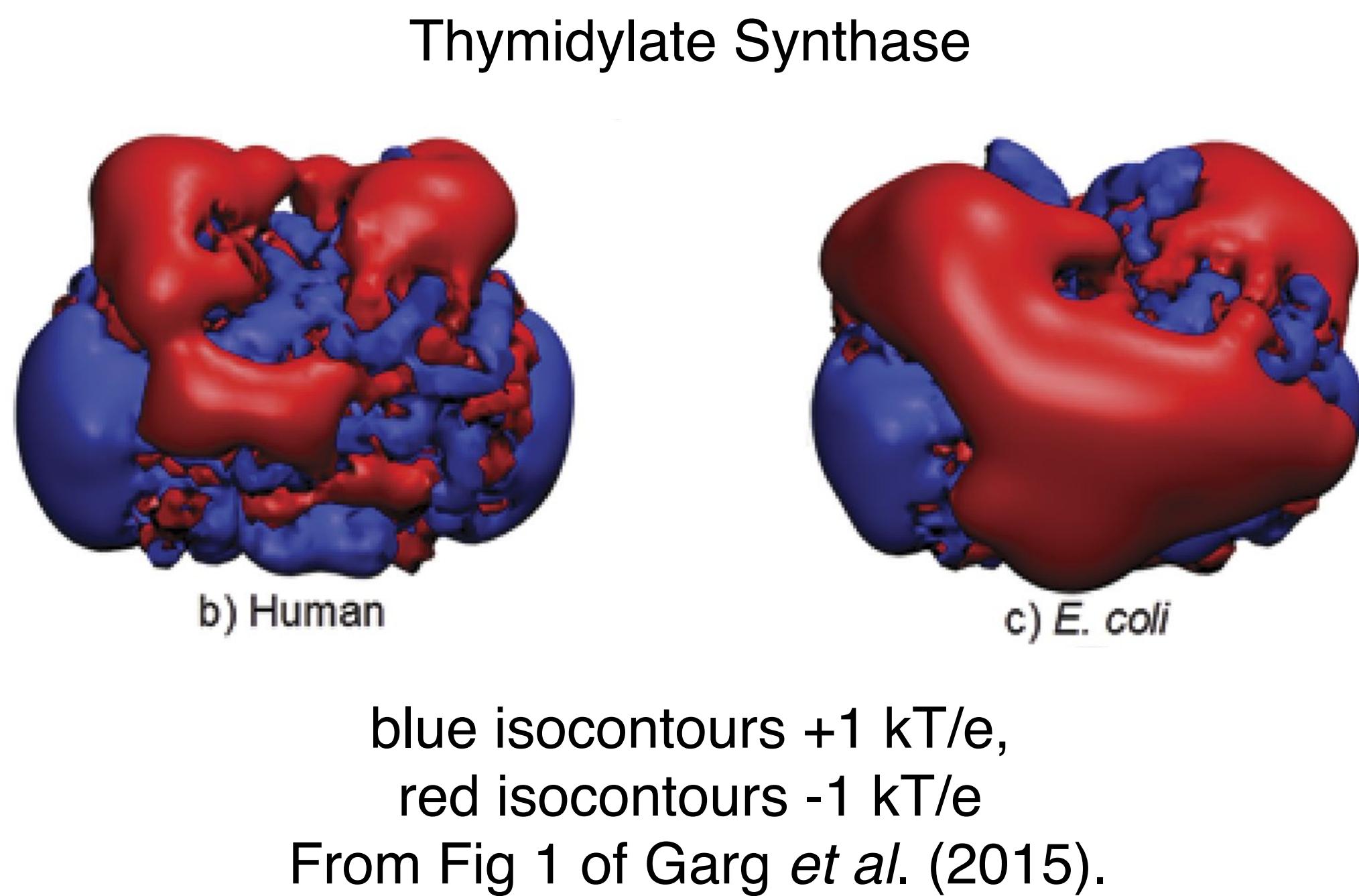


# 9/19 Biomolecular Electrostatics

- 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

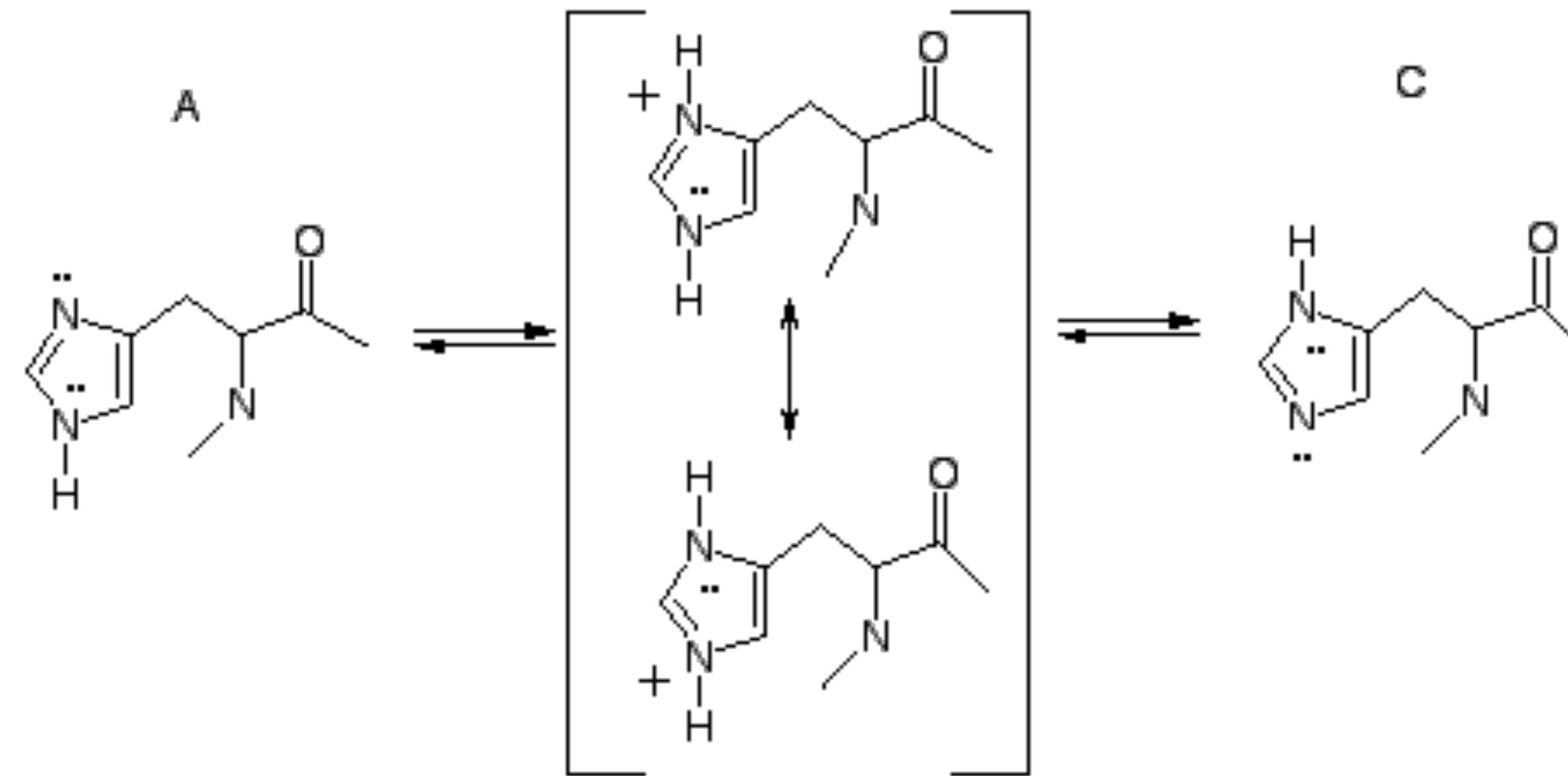


# Protein Protonation

- 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

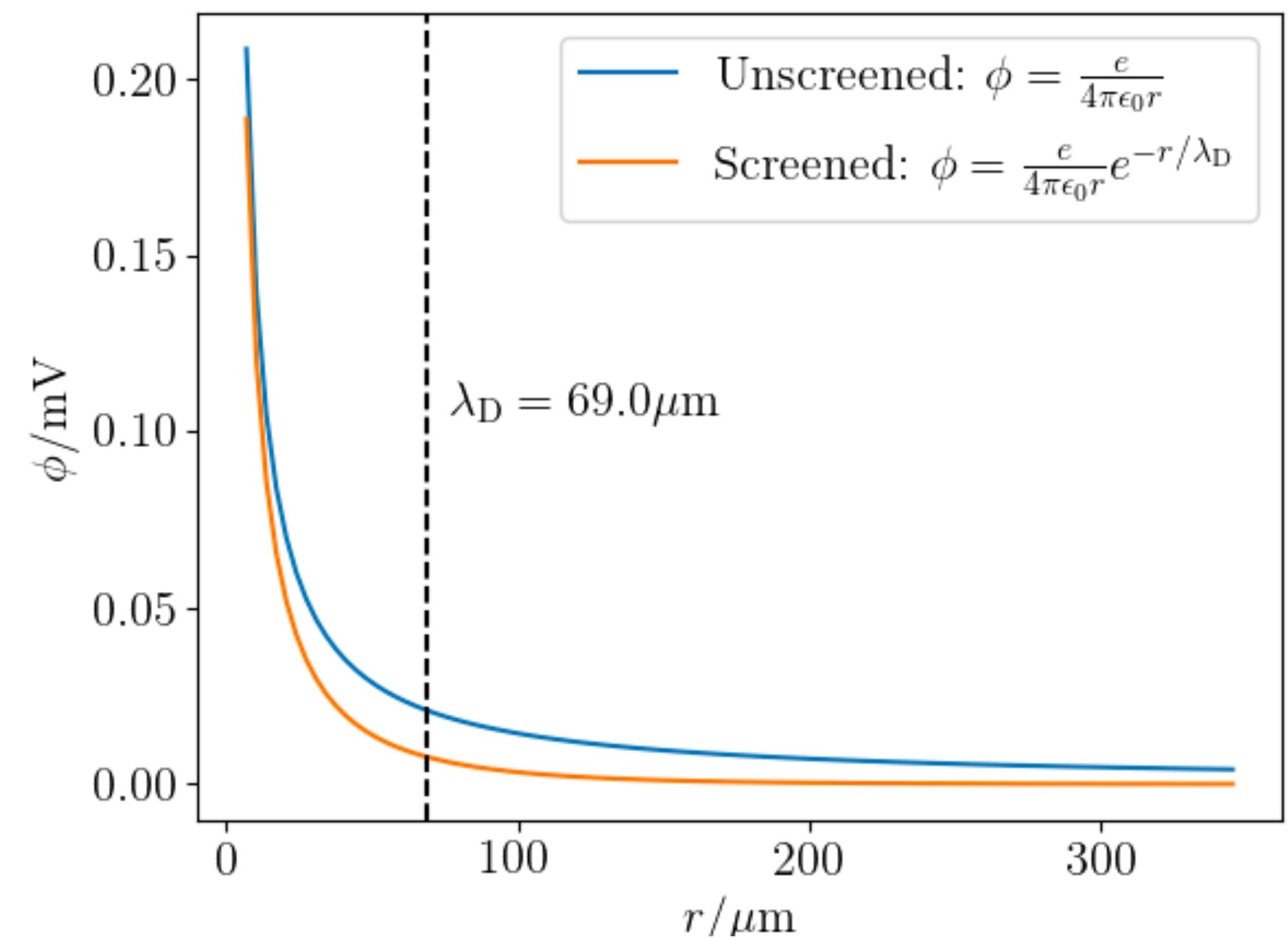
- It is an *implicit solvent* model that does not account for specific water positions
- Solvent is assumed to modify the dielectric constant
  - Coulomb's law is  $F = \frac{1}{4\pi\epsilon} \frac{Q_1 Q_2}{r^2}$ .
  - The permittivity  $\epsilon$  is related to the permittivity of free space  $\epsilon_0$  by the dielectric constant  $\kappa$ ,  $\epsilon = \kappa\epsilon_0$ .
    - ~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

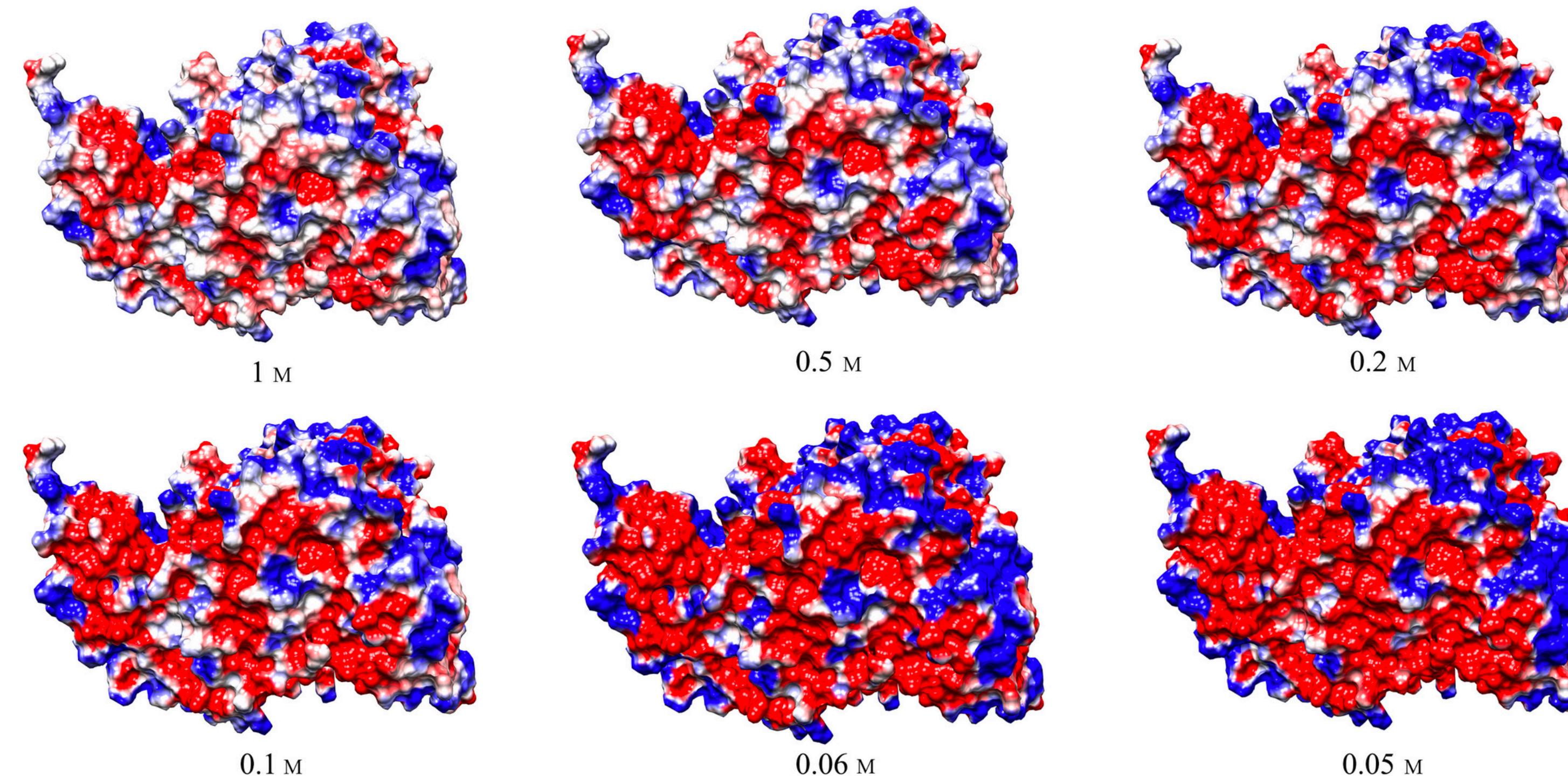
# Electrostatic Screening

- 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,  $37^\circ\text{C}$ , 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 ( $\text{Ca}^{2+}$  vs  $\text{Mg}^{2+}$ )
- Which are accounted for by the Poisson-Boltzmann equation?
  - pH
  - Concentration of ions
  - Valency of ions (+1 vs. +2)
  - Identity and size of ions ( $\text{Ca}^{2+}$  vs  $\text{Mg}^{2+}$ )

# 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](#)

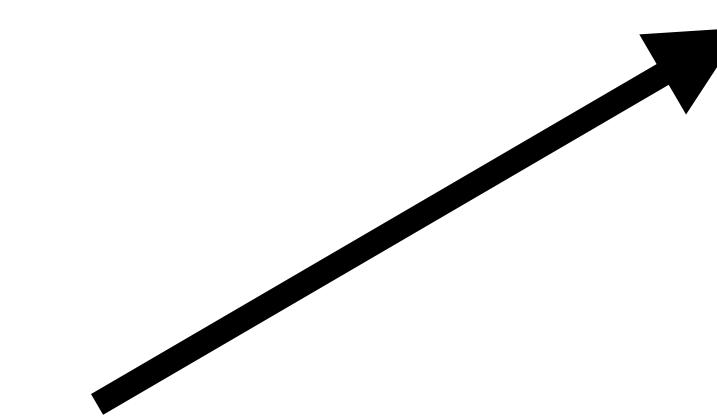
Home

# 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](#)



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: 7.0

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

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:

**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

- Lab 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>