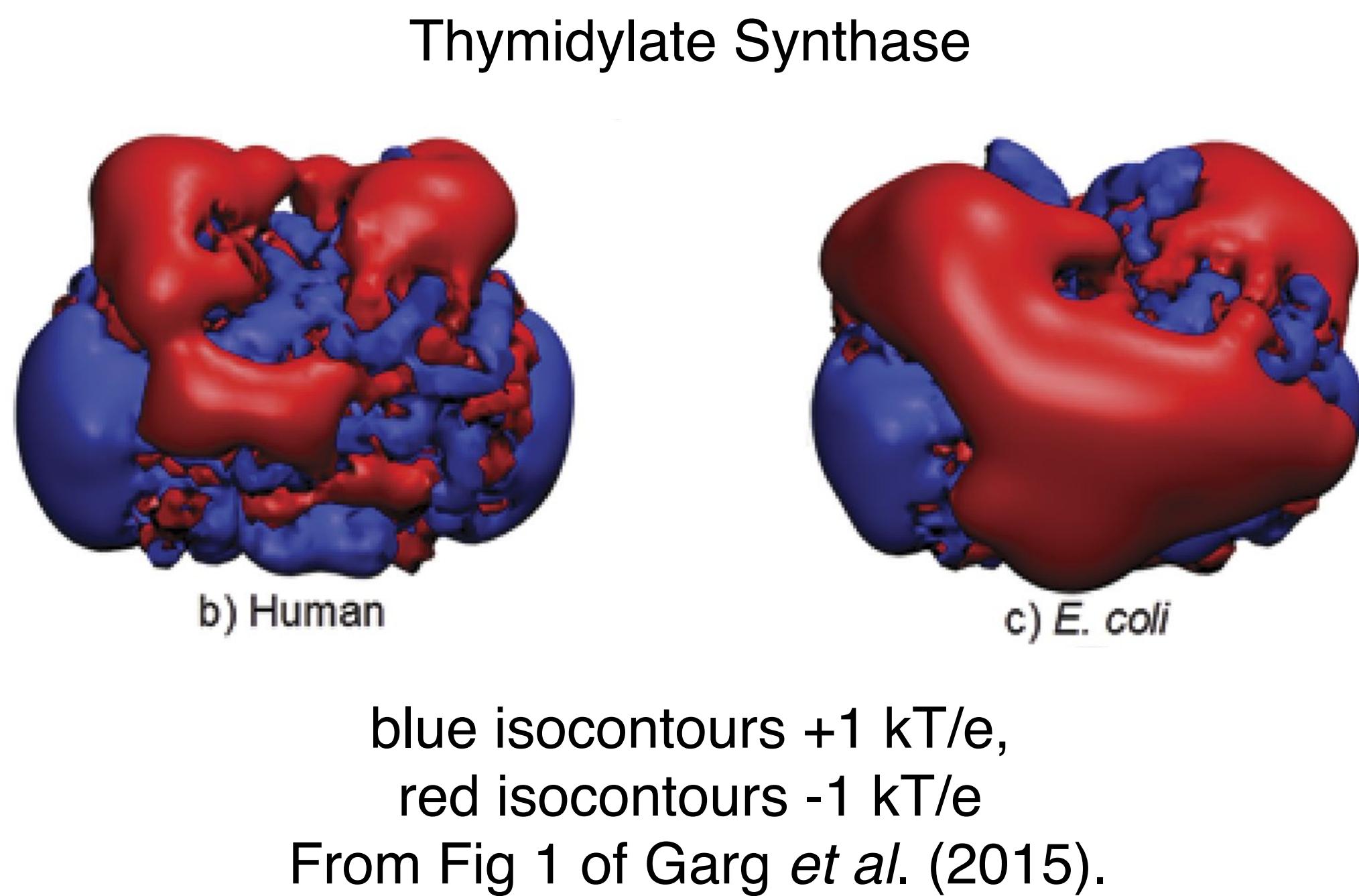


# Biomolecular Electrostatics

- This mini-lecture and lab will be about electrostatics calculations
- At the end of this mini-lecture, you should be able to
  - explain, in a general sense, the
    - importance of electrostatics in biological macromolecules
    - origin of the Poisson-Boltzmann equation
  - submit an electrostatics calculation to the APBS server

# 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

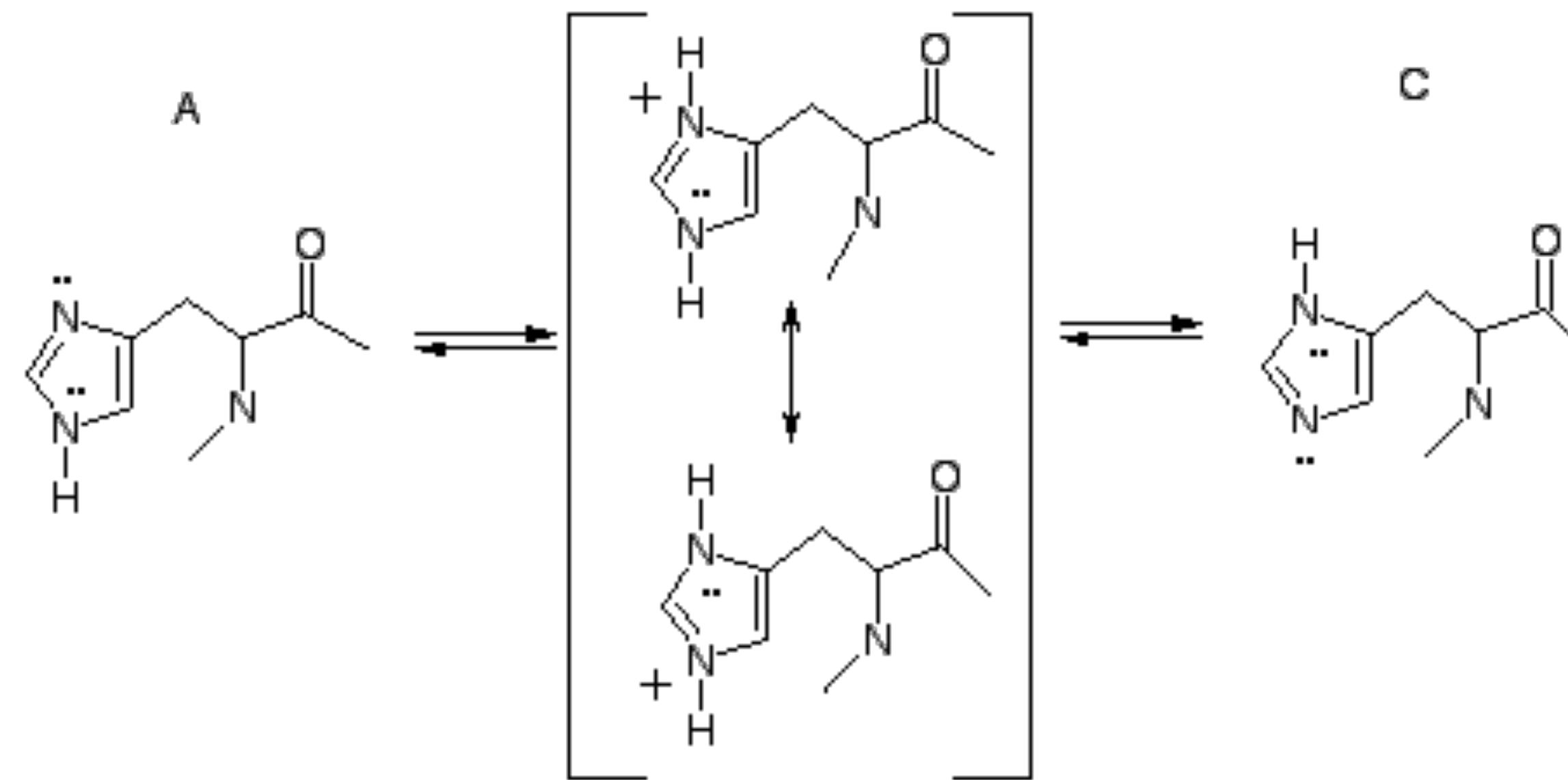


# Protein Protonation

- Which structure determination technique(s) identify the position of hydrogen atoms?
  - A. X-ray crystallography
  - B. X-ray crystallography, at very high resolution
  - C. Nuclear magnetic resonance
  - D. Cryo-electron microscopy
  - E. All of the above
  - F. 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

# 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>

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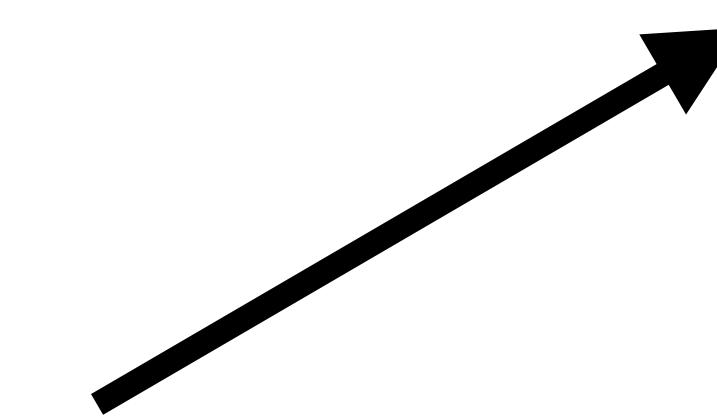
Home

# APBS

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

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

Getting Started:

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\* PDB Source

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\* Please upload a PDB file

[Select File](#)[bestmodel\\_aligned.pdb](#)

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



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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

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**PDB2PQR**

Time Elapsed:

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Running

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# 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.