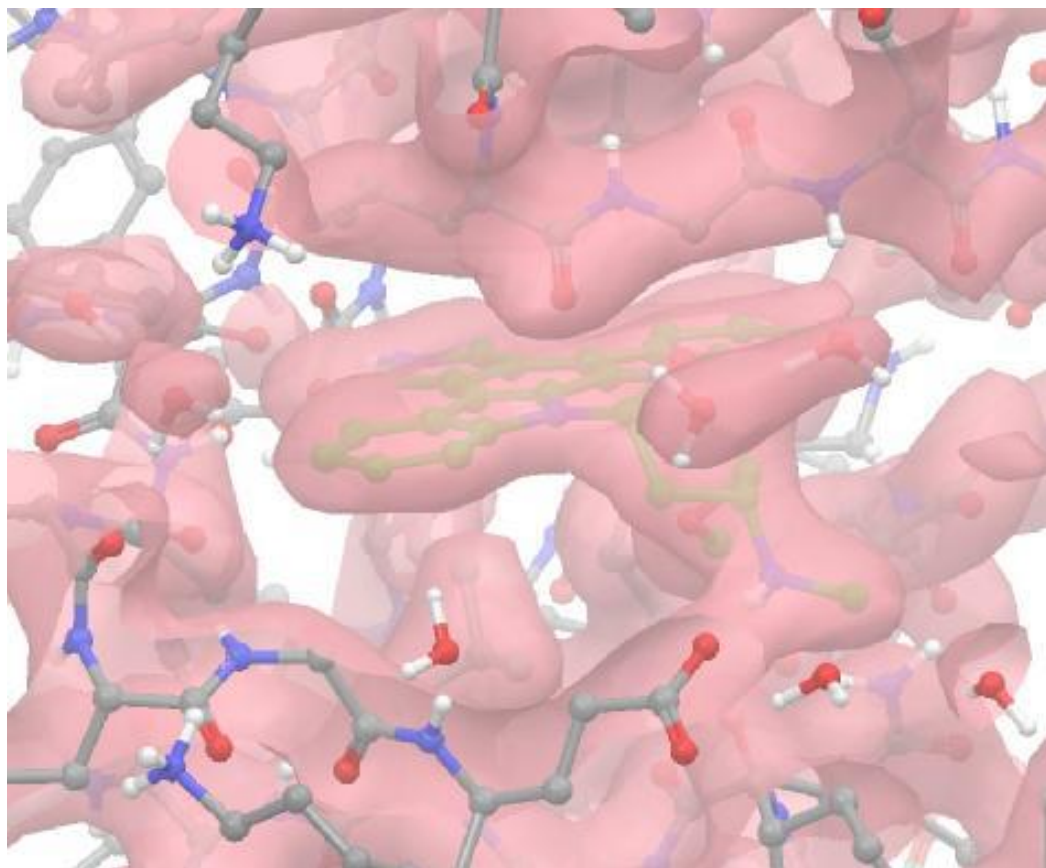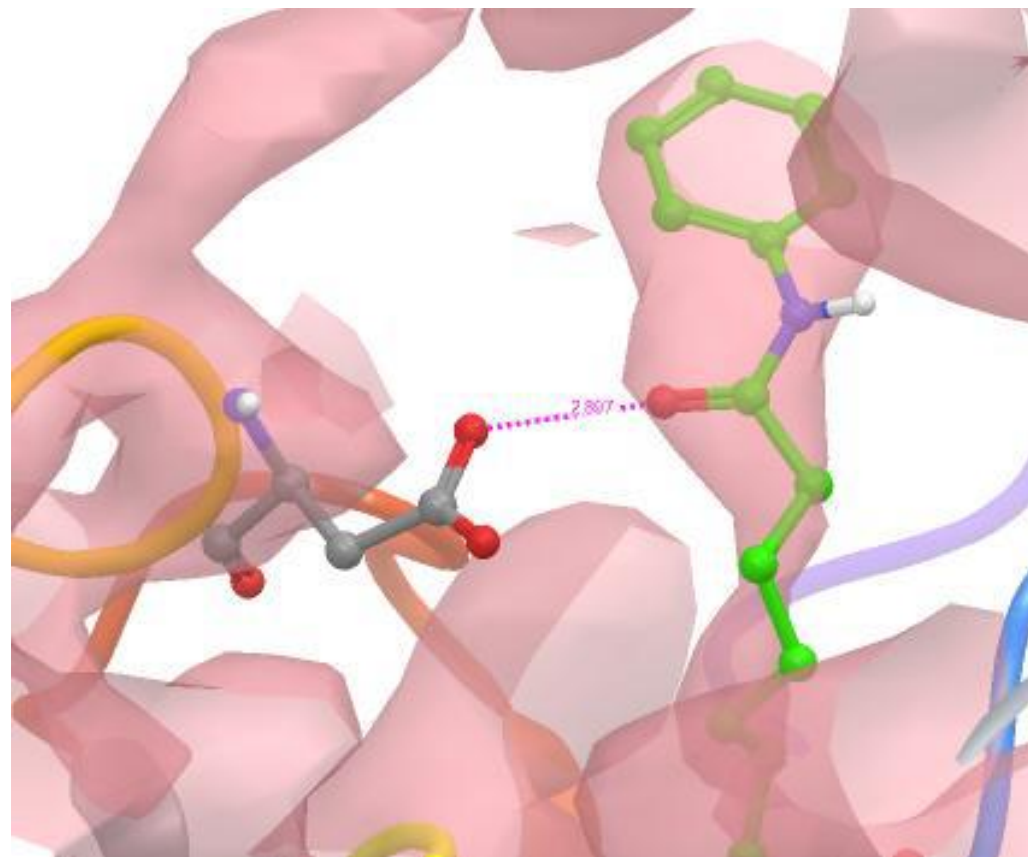# Introduction to Protein Preparation

Stephan Ehrlich

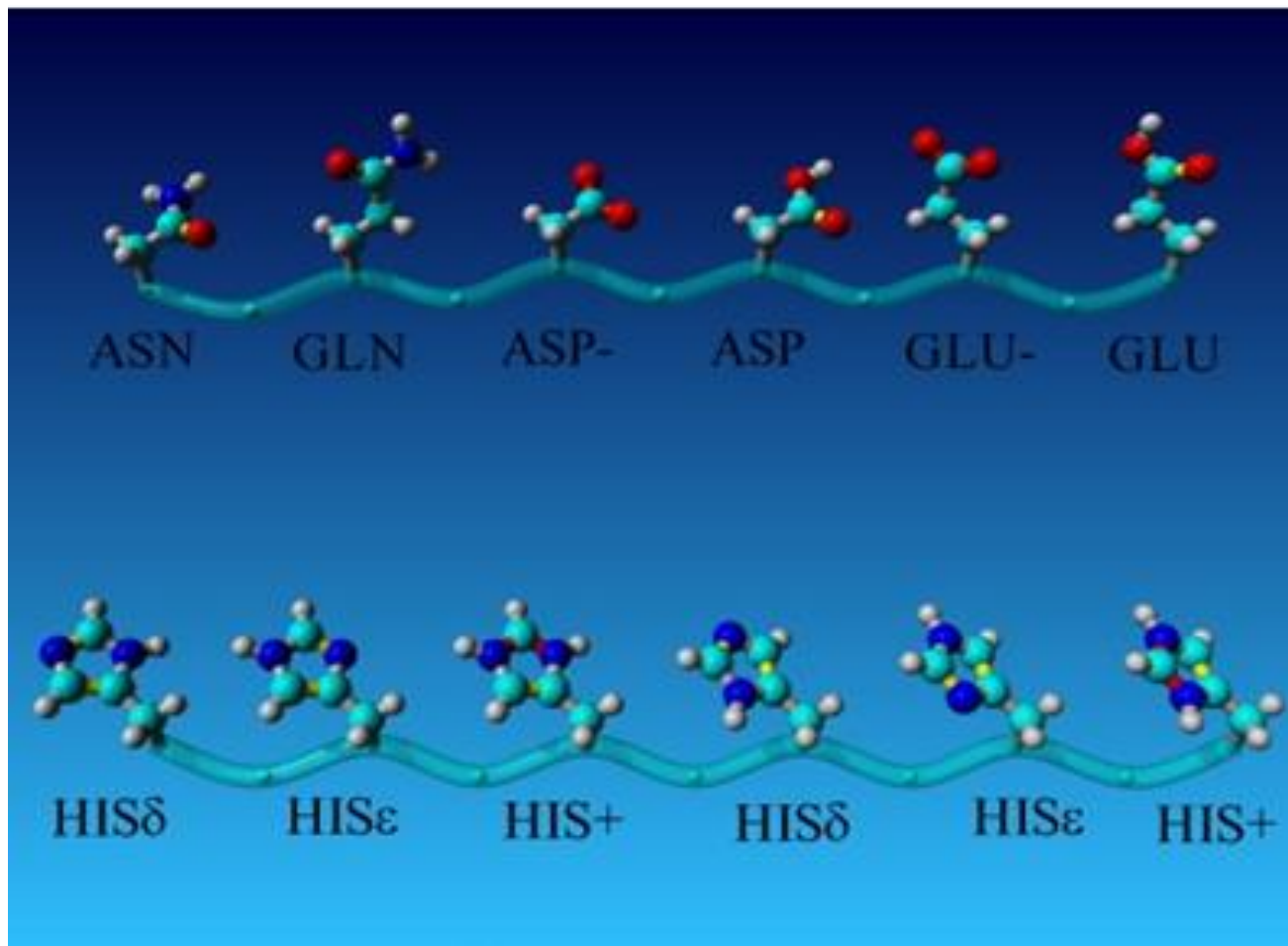# Not all Crystal Structures are High Quality Structures

In this case, the ligand density is relatively unambiguous

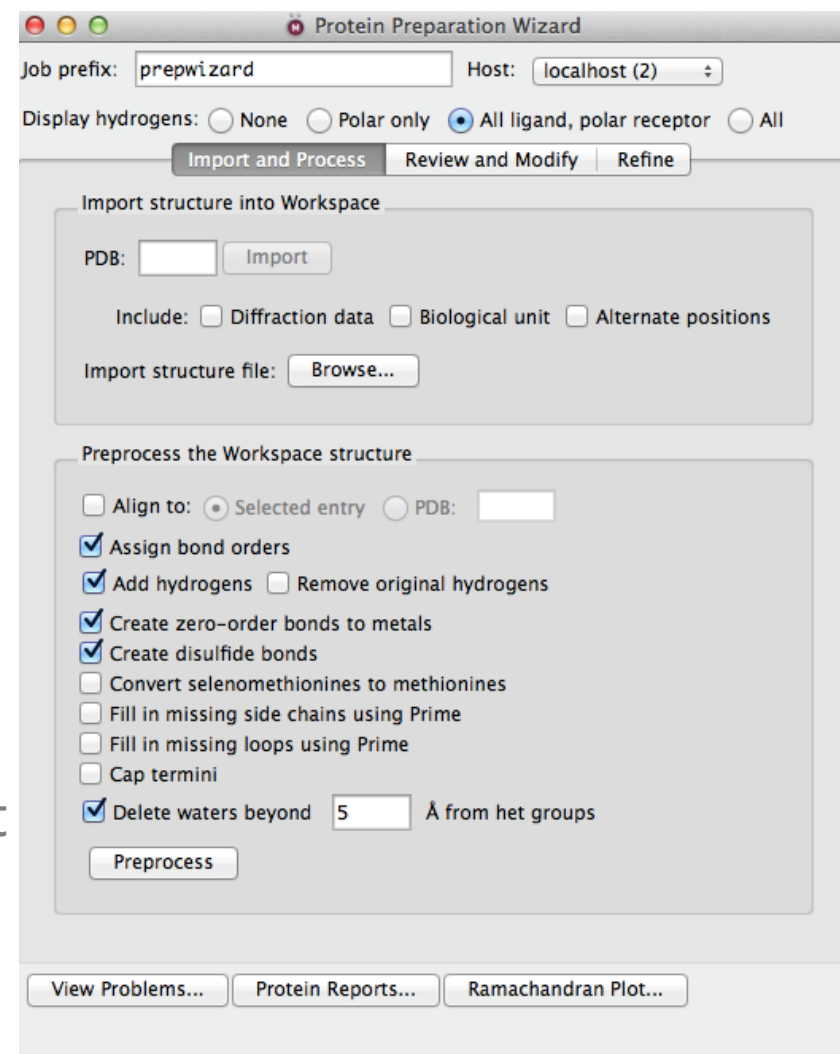But in this case the density is missing, leading to potentially misleading information

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And the details matter

pH-dependent tautomeric and protonation states for His, Glu, and Asp

The Protein Preparation Wizard is useful!

- **It fixes common problems**
  - Protonation
  - Missing side chains
  - Missing loops
- **It removes unwanted molecules**
  - Counterions, random small molecules, waters
  - But be be careful not to remove important things!
- **And it optimizes your structure**
  - Hydrogen-bond optimization (via assigning correct Asn/Gln/His flipping)
  - Restrained minimization

Also keep in mind that a crystal structure is a snapshot

- Proteins are constantly in motion

  – This motion is essential for function

- Traditionally, CADD has modeled proteins as rigid bodies with the "lock and key" analogy as a guide

  – But this is changing

- **It is imperative to choose the appropriate conformational state to use as a starting point for SBDD.**

  – For example, in the case of kinases, ensure you are using a structure with the DFG conformation relevant to your studies.

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