Hex Demo – Basic Operations

- Hex web site: http://hex.loria.fr/dist800/

- Loading structures into Hex
- Basic concepts: "receptor", "ligand", "complex" (reference)
- Graphical viewing modes
- Editing the scene (moving structures around)
- Setting docking parameters
- Launching a docking calculation
- Viewing the results
- Saving structures
- ...
- Ask me!

- Disclaimer: please remember, Hex is not "commercial" software!

Practical: CAPRI Target 40 – API-A/Trypsin

R Bao *at al.* (2009), J Biol Chem, 284, 26676–26684

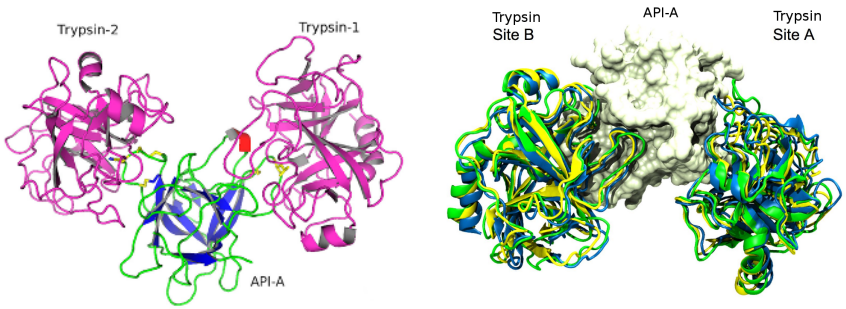
"The Ternary Structure of the Double-headed Arrowhead Protease Inhibitor API-A Complexed with Two Trypsins Reveals a Novel Reactive Site Conformation"

The double-headed arrowhead protease inhibitors API-A and -B from the tubers of *Sagittaria sagittifolia* (Linn) feature two distinct reactive sites, unlike other members of their family. Although the two inhibitors have been extensively characterized, the identities of the two P1 residues in both API-A and -B remain controversial. The crystal structure of a ternary complex at 2.84 Å resolution revealed that **the two trypsins bind on opposite sides of API-A and are 34 Å apart.** The overall fold of API-A site sides of API-A belongs to the β-trefoil fold and resembles that of the soybean Kunitz-type trypsin inhibitors. The two P1 residues [on API-A] were unambiguously assigned as **Leu87** and **Lys145**, and their identities were further confirmed by site-directed mutagenesis...

- The CAPRI challenge: **blind prediction of the two binding modes...**

CAPRI T40 Results

X-ray solution **Our predictions**



- Using Hex + MD refinement gave NINE "acceptable" solutions

Practical Activities

- Download the structures from: http://hex.loria.fr/emmsb/t40.tgz
  - t40_a.pdb (Trypsin 1)
  - t40_b.pdb (Trypsin 2)
  - t40_c.pdb (API-A)
  - t40_abc.pdb (solution)
  - t40.col (Hex colour file)
- Load the structures C+A or C+B as "receptor" and "ligand"
- Experiment with different graphical viewing options
- Use the "edit mode" to try docking by hand
- Load the solution structure as "complex" and try again by hand
- Load the color file to highlight the key residues
- Does this help?
- Finally, place the API-A key residue near the trypsin site
- Set up and run a focused docking calculation (45 deg on each)
- View and analyse by eye the solutions generated