Studying allosteric enzyme inhibition using simulated molecular dynamics

Ben Roberts
(ben.roberts@nesi.org.nz)

Outline

Houston, we have a problem.

Resistance to antibiotics is growing...

- Mid 1940s: Mass production of penicillin
- Late 1940s: Penicillin-resistant *Staphylococcus aureus*
- MRSA, gonorrhoea, etc.
- 70+ years of whack-a-mole...only worse.

The search for new antibiotics

- Try to block a bacterial enzyme
- We look for pathways not found in animals

Enzyme Inhibition

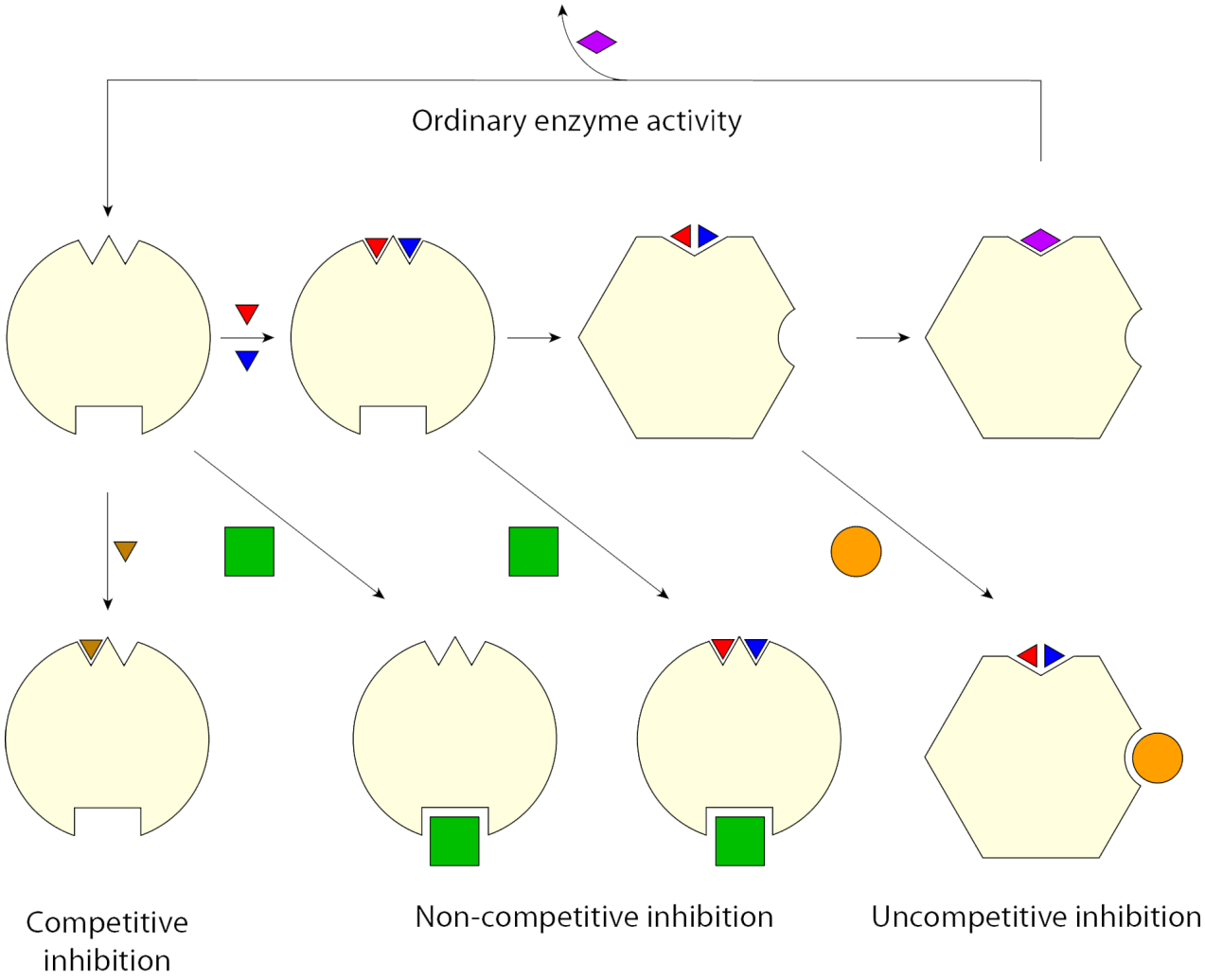
Competitive inhibition

- Binding in the active site
- Competes with substrate for room

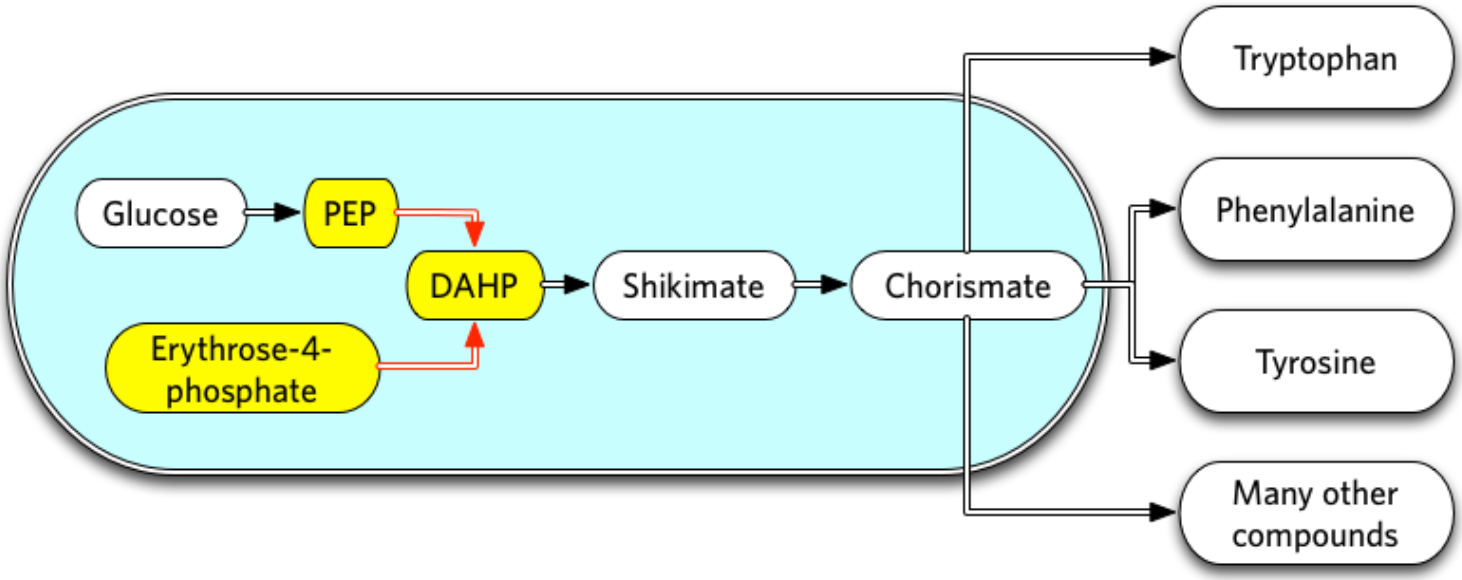
Uncompetitive, non-competitive, or mixed inhibition

- Does not compete with substrate for binding, but:
- Reduces affinity of enzyme for substrate, catalytic activity, or both
- Often involves binding at another site ("allosteric inhibition")

Enzyme Inhibition



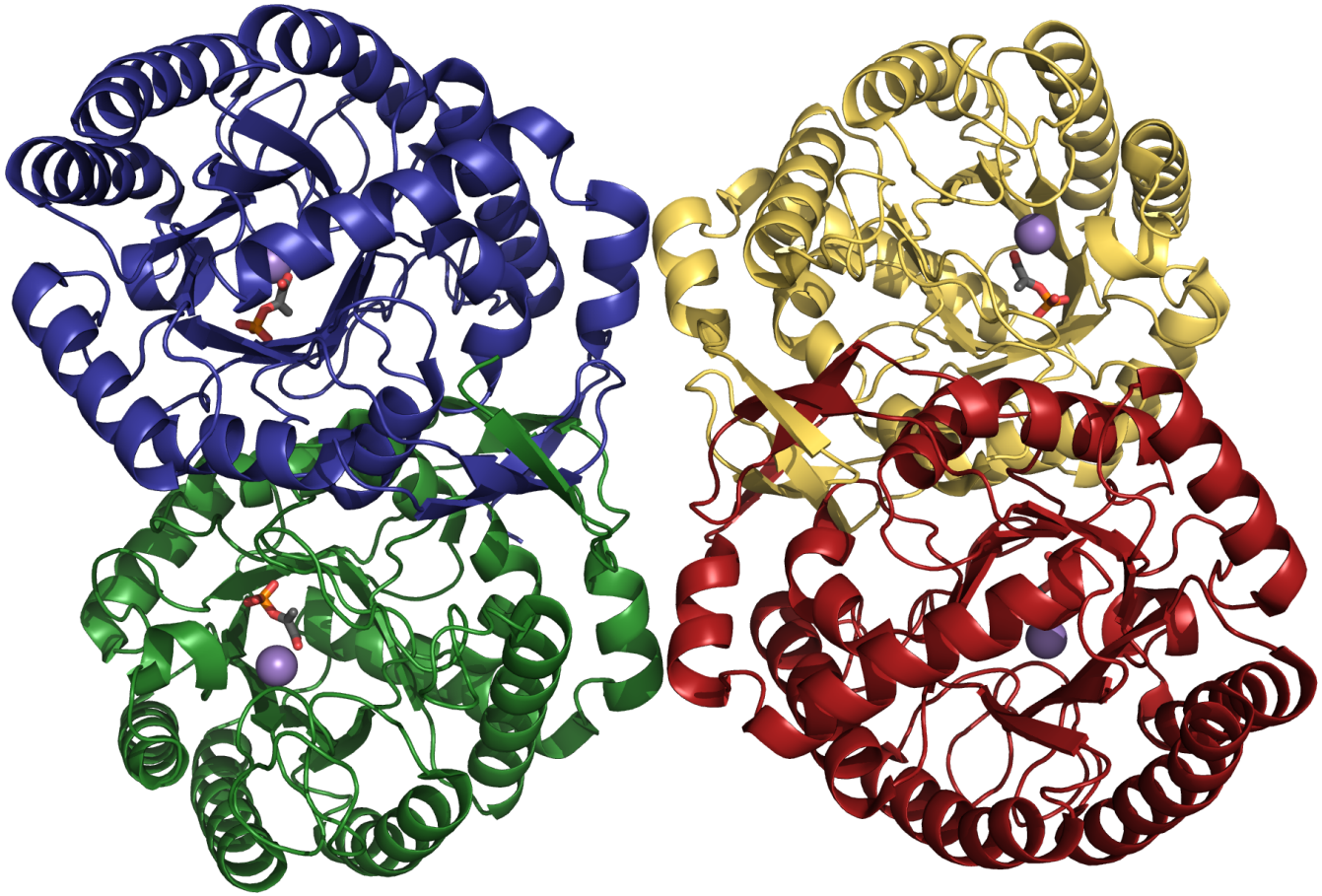
Aromatic Amino Acid Biosynthesis



The shikimate pathway

- Bacteria, fungi, plants, etc., but not humans or animals
- First enzyme: DAHP synthase (step in yellow and red)

DAHP Synthase



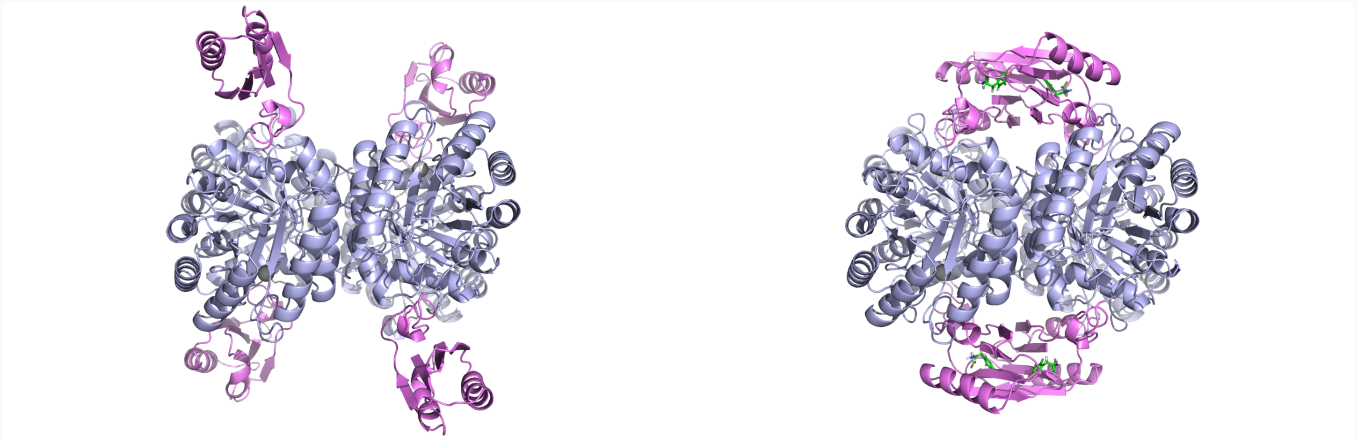
What can we study?

Molecular dynamics simulations of:

- Enzymes from different bacterial species
- Wild-type vs various mutants
- Open vs closed
- Presence vs absence of inhibitor

Simulations so far:

Open vs closed (*T. maritima*)



Presence vs absence of tyrosine

- Conformation and dynamics
- Free-energy changes

How NeSI has helped

Computers

1. Computing power on BlueGene/P and POWER 7
2. Software: NAMD (simulations), Amber (post-processing)

Expertise

1. Installing and configuring Amber
2. Expert MD advice
3. Avoiding the "waste-of-life" file

To Summarise...

- Hundreds of ns of time simulated
  - On BlueGene/P: approx 3,000 core hours per ns
  - On POWER 7: approx 400 core hours per ns
- Amber has been deployed on POWER 7
- Closed form is stable when simulated
- Open form is extremely dynamic
- Does tyrosine cause closure; if so, how?
- Next step: Free energy calculations

Acknowledgements

- Eric Lang
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Questions & Answers