Biochemical Applications of Computational Chemistry

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Chemistry Today: A Different View

Old Way   **New Way**

Desired Properties — Correlate — Interpret — Simulate — Measure — Structural Design — Synthesize — Compounds — Build

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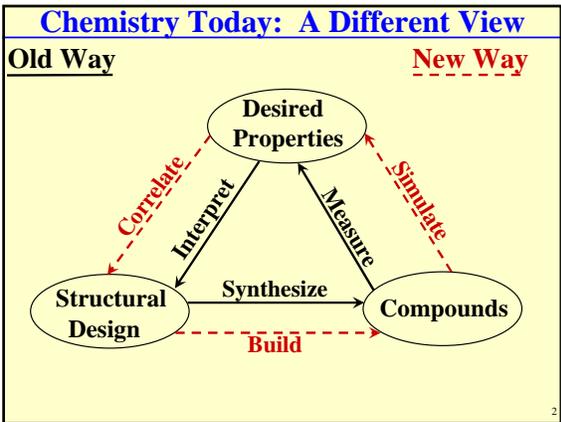
Why Computational Chemistry?

- Can rapidly focus attention on compounds most likely to have the desired properties
  - Save time and $$
  - Less "trial and error"

- Human Genome Project
  - Genes identified
  - Can get AA sequences of proteins that genes code for
  - 3-D protein structure prediction needed
  - Experimental protein structure determination is difficult
    - X-ray, NMR, and now computation

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Protein Data Bank

- PDB Content Growth: ~28,000 current proteins
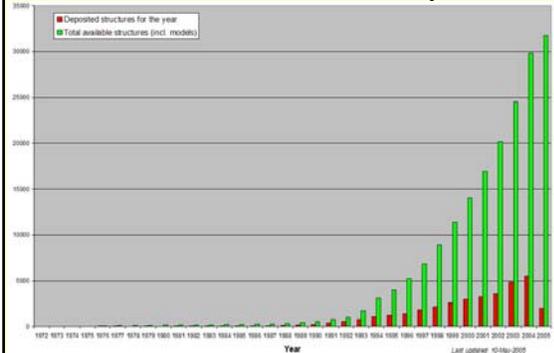
How Can We Use This Data?

- Visualization of structure
  - Possible insight into mechanism
  - Identify the active site

- Structure with ligand in place
  - Active site determination
  - Design new molecules to bind to active site

- Computation
  - Does new molecule bind more strongly than the natural occurring ligand?
    - MM or Semi-empirical calculation

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The Process

- Structure known?   http://www.rcsb.org
- Download the structural data
  - .pdb file
- Clean it up
  - Usually remove water molecules
- Find the ligand   (or find the receptor?)
- Remove the ligand   (or model the receptor site?)
- Insert our new ligand (drug candidate)
  - Nontrivial process, orientation is crucial
- Does it bind more strongly to the receptor?

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Example: Casodex and Prostate Cancer

- Most common type of cancer (excluding skin cancer) among American men

- Over 70% of all prostate cancer diagnosed is in men over 65 years old

- In 2003, approximately 221,000 new cases were diagnosed in the U.S.

- Overall survival rate ~97%

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Antiandrogen Therapy

- Most prostate cancers are driven by androgens (male hormones)

- Antiandrogen drugs block the body's ability to use androgens, such as testosterone
  - Eulexin, Casodex, and Nilandron are examples

- These drugs are also used following surgery to help prevent recurrence of the cancer
  - How do they work on the molecular level?
  - What protein do they interact with?

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Human Androgen Receptor Protein

- Antiandrogen drugs compete with testosterone for the binding site of this protein

- An affinity label (Metribolone) is used for the human androgen receptor in the prostate and in prostatic tumors
  - It binds strongly to the androgen receptor
 - Metribolone is a synthetic androgen and an anabolic steroid

Methyltrienolone

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Protein Data Bank

- Search for "human androgen receptor"
  - Get six hits, two of which include metribolone
  - Use 1E3G
- Download the file, "unzip", and rename with .pdb ending
- Open and view in CAChe Workspace
  - Try various "View / Backbone Ribbon" commands
    - Reveals ~26 associated water molecules
    - These were deleted to "clean up" the structure
    - Must also "Beautify / Valence" to add H atoms
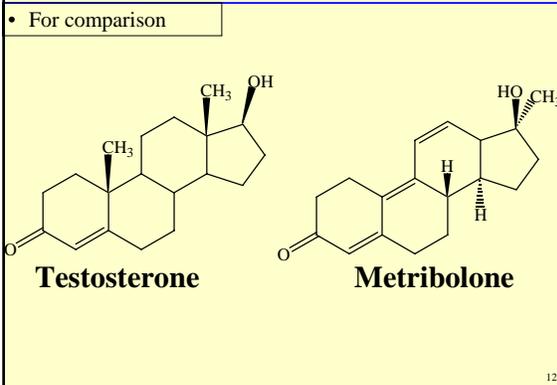 - Viewing as a "ribbon" structure clearly shows the position of the Metribolone

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Views of the Protein/Metribolone Complex

CAChe View (water deleted)

CHIME View from PDB site
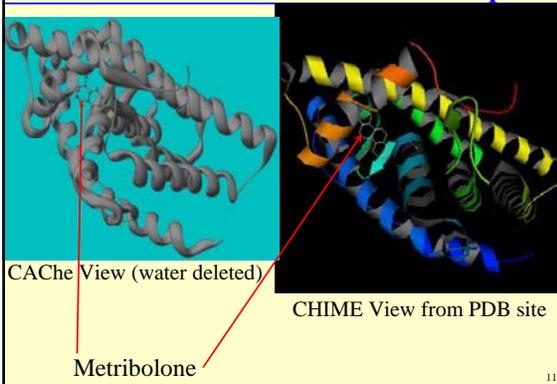
Metribolone

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Testosterone vs. Metribolone

- For comparison

**Testosterone**

Metribolone

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Steps For Insertion of a New Ligand

- Separate the old ligand
    - Leave protein structure unchanged
- Orient the new ligand
    - Can superimpose the new ligand onto the old ligand
- Insert the new ligand
    - See if the fit is sterically "reasonable"
- Minimize
    - Use MM or Semiempirical method
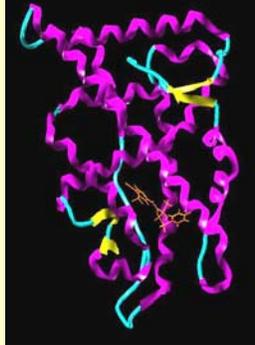   - Find the energy difference

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Structure of Casodex

- Antiandrogen drug
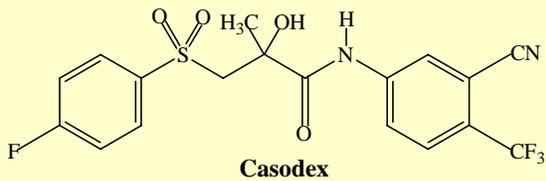
Casodex

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Casodex in the Receptor

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Where to Look

- Cache Users Guide 6.1
  - Chapter 19

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Further Tutorials and Credits

- http://www.ch.ic.ac.uk/local/organic/

- Department of Chemistry Local Teaching Pages: http://teaching.ch.ic.ac.uk/

- MedChem Homology Modelling: Designing an anti-TB drug. Copyright (c) H. S. Rzepa and ICSTM Chemistry Department, 2003 and Fujitsu/CAChe.

- Imperial College London

- Mr. James S. Giles, M.S. Student, North Carolina Central University

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