Pharmaceutical Molecular Biology with Bioinformatics
Lecture 1: Introduction to pharmaceutical bioinformatics

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The central dogma of molecular biology
Structure determines function

The genetic code

Pharmacology
"The study of the interactions that occur between a living organism and exogenous chemicals"

Drug discovery
"The process by which new drugs are discovered and/or designed."

Personalized Medicine
"Application of genomic and molecular data to provide better health care."

Bioinformatics
- IT applied to molecular biology
- Storage and provisioning of biological data (e.g., sequences, proteins, pathways etc)
- Development of algorithms, methods, and tools for analyses
- Application of tools to solve biological problems
Experiment types

- **In vivo** - experiments performed in living animals
- **In vitro** - experiments performed in the laboratory
- **In silico** - experiments performed in computers

Why should you learn basic bioinformatics?

- Computers are increasingly being used in bioscience
  - Store and analyze data and results
  - Use public resources (tools and databases)

  You need to have a basic understanding of how bioscience data is stored and processed in computers, and a notion of the publicly available tools.
Sequence analysis

Sequence bioinformatics
- Nucleotide and protein primary sequences

Typical bioinformatics problems
- Compare sequences, search databases
- Analyze sequences
  - Identify coding regions (ORF)
  - Mutations, indels, SNPs
  - Translate to proteins
  - Functional assignment
  - Much more…

Phylogeny: Evolutionary relationships

Structural bioinformatics

Simulations

This movie shows the translocation of a 58-nucleotide DNA strand through the transmembrane pore of alpha-hemolysin.
Systems biology

- Systems biology is the study of an organism, viewed as an *integrated and interacting network* of genes, proteins and biochemical reactions which give rise to life.
  - For example, the immune system isn’t made up of one single component but instead a multitude of genes, proteins and external influences.

So how can we meaningfully integrate the data?

Cheminformatics

- Management of chemical data (drugs and other compounds)
- Calculation of chemical properties
- Virtual screening
- Predictive modeling
  - E.g. predict toxicity *in silico*

High throughput screening and virtual screening

- Biochemical target
- Test many compounds
- Compounds with desired effect on target = Hit

Virtual screening

- Computational or *in silico* analog of biological screening
  - Score, rank, and/or filter a set of structures using one or more computational procedures
- Can be 2D (ligand based) or 3D (structure based)
Pharmacophore searches

Molecular features which are necessary for activity

- E.S.A
- G.S.P
- T.G.A

Pharmacophore

Saquinavir (most active compound) fitted to pharmacophore

Integrate data

Protein sequences
Nucleotide sequences
Chemical structures

Web pages and services

Applications
Local data

Integration of cheminformatics and bioinformatics

The phases of drug discovery

- **TI**: Target Identification
- **LI**: Lead Identification
- **LO**: Lead Optimization
- **PCD**: Preclinical development

**Preclinical phase**

- TI
- LI
- LO
- PCD

**Clinical phase**

- 1
- 2
- 3

Drug Development: Overview

- Choose a disease
- Choose a drug target
- Identify a “bioassay”

bioassay = A test used to determine biological activity.
• Find a “lead compound” ("drug lead")
  = structure that has some activity against
the chosen target, but not yet good enough to be the drug itself.

• Optimize the lead in vitro/in silico
  – Maximize efficacy
  – ADME (absorption, distribution, metabolism, excretion)
  – Minimize toxicity and other problems (e.g. solubility)
  – Limit secondary effects

• Determine toxicity and efficacy in animal models.

Clinical trials
• Phase 1: Drug tested on healthy volunteers to
determine toxicity relative to dose and to screen
for unexpected side effects
• Phase 2: Drug tested on small group of patients
to see if drug has any beneficial effect and to
determine the dose level needed for this effect.
• Phase 3: Drug tested on much larger group of
patients and compared with existing treatments
and placebo
• Phase 4: Drug placed on the market and
patients monitored for side effects

Pharmacogenomics
• Can patients/virus/bacteria genetic properties affect medication?
  – Improve or worsen drug effect?
  – Is drug toxic or non-toxic?
• Example: Herceptin (Trastuzumab)
  – Important treatment for the 15-20 percent of
patients with breast cancer whose tumors
overexpress HER2
• Example 2: HIV treatment
  – Choose drug based on HIV strain

Computational drug discovery
• Use of computers to aid drug discovery
  and development
• Examples
  – Target identification (e.g. bioinformatics)
  – Lead finding (e.g. cheminformatics)
  – Lead optimization (e.g. chembioinformatics)
Chemical liabilities (drug safety)
Can we, based on existing experimental studies, IT, and statistical models, predict the outcome for new compounds?
Adverse effects?
Is it toxic? ⚠
How is the compound metabolized?
Are any of its metabolites reactive/toxic?

Predict site-of-metabolism

Personalized HIV medication predictions
Based on HIV infection genomics, predict susceptibility to anti-HIV drugs

Robotized Drug Screening

What is research?
- Discover new scientific findings
- Publish papers in high-impact scientific journals, cite other papers
- (Hopefully) get citations

Thank you
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