CS2220: Introduction to Computational Biology
2010

Course Briefing

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Co-teaching with Limsoon Wong

Recommended "Pre-requisites"

- **CS1102: Data Structures and Algorithms**
- **LSM1102: Molecular Genetics**

Objectives

- **Develop flexible and logical problem solving skill**
- **Understand bioinformatics problems**
- **Appreciate techniques and approaches to bioinformatics**

To achieve the goals above, we expose students to a series of case studies spanning gene feature recognition, gene expression and proteomic analysis, gene finding, sequence homology interpretation, phylogeny analysis, etc.

Contents of Course Overview

- **Time Table**
- **Course Syllabus**
- **Course Homepage**
- **Teaching Style**
- **Project, Assignments, Exams**
- **Readings**
- **Assessment**

- **Quick Overview of Themes and Applications of Bioinformatics**

Time Table

- **Lecture**
  - Thursday 2:00pm – 4:00pm, COM1-211
- **Tutorial**
  - Thursday 4:00pm – 5:00pm, COM1-207
- **Email**
  - wongls@comp.nus.edu.sg
  - tucker@comp.nus.edu.sg
- **Consultations**
  - Available for walk-in at COM1, Level 3.
    - Room 34 (Prof. Wong)
    - Room 24 (Dr. Lisa) -- Call 6516-2865 to see if I'm there.

Course Syllabus

- **Intro to Bioinformatics**
- **Essence of Knowledge Discovery**
  - Classification performance measures
  - Feature selection techniques
  - Supervised & unsupervised machine learning techniques
- **Gene Feature Recognition from Genomic DNA**
  - Feature generation, selection, & integration
  - Translation initiation site (TIS) recognition
  - Transcription start site (TSS) recognition
- **Gene Expression and Proteome Analysis**
  - Microarray and mass-spec basics
  - Classification of gene expression profiles
  - Classification of proteomic profiles
  - Clustering of gene expression profiles
  - Molecular network reconstruction
- **Essence of Seq Comparison**
  - Dynamic programming basics
  - Sequence comparison and alignment basics
  - Needleman-Wunsh global alignment algorithm
  - Smith-Waterman local alignment algorithm
- **Protein Seq, Structure, and Applications of Optimization**
  - Homology modeling and molecular modeling
  - Essence of optimization
  - Active site and domain prediction
- **Seq Interpretation**
  - Key mutation sites prediction
  - Protein function prediction by sequence alignment
  - Protein function prediction by phylogenetic profiling
- **Gene Finding**
  - Overview of gene finding
  - GRAIL
  - Handling of frame shifts and in-dels
- **Some hot current topics like PPI, miRNA, etc.**

Course Homepage

- **IVLE**
  - https://ivle.nus.edu.sg/lms/public/list_course_public.aspx?code=cs2220&acadyear=2009%2f2010
- **Lecture Slides & etc**
  - http://www.comp.nus.edu.sg/~wongls/courses/cs2220/2009 (From Last Year)
  - http://www.comp.nus.edu.sg/~wongls/courses/cs2220/2010

Teaching Style

- **Bioinformatics is a broad area**
- **Need to learn a lot of material by yourself**
  - Reading books
  - Reading papers
  - Practice on the web
- **Don't expect to be told everything**

Assignments, Project, & Exam

- **Assignments**
  - Probably 3-4 assignments
  - Some are simple programming assignments
- **Project**
  - Based on a case study in the class
  - 8-10 pages of report / ppt slides expected
- **Exam**
  - 1 final open-book exam

Be Honest

- **Exam**
  - Absence w/o good cause results in ZERO mark
  - Cheating results in ZERO mark
- **Discussion on assignments is allowed**
- **Blatant plagiarism is not allowed**
  - Offender gets ZERO mark for assignment or exam
  - Penalty applies to those who copied AND those who allowed their assignments to be copied
- **Other cultures are far more punitive about cheating**

Background Readings

- Limsoon Wong, *The Practical Bioinformatician*, WSPC, 2004
- Marketa Zvelebil and Jeremy Baum, *Understanding Bioinformatics*, Garland, 2007
- Rick Ng, *Drugs: From Discovery to Approval* 2009 **electronic**
- Peter Clote and Rolf Backofen, *Computational Molecular Biology: An Introduction*, John Wiley, 2000
- Pierre Baldi and Soren Brunak, *Bioinformatics: the Machine Learning Approach*, MIT Press, 1998
- Pavel Pevner, *Computational Molecular Biology: An Algorithmic Approach*, MIT Press, 2000
- Malcolm Campbell and Laurie Heyer, *Genomics, Proteomics, and Bioinformatics,* Pearson, 2007

Assessment

- **Continuous Assessment: 50%**
- **Final Exam: 50%**

What comes after CS2220

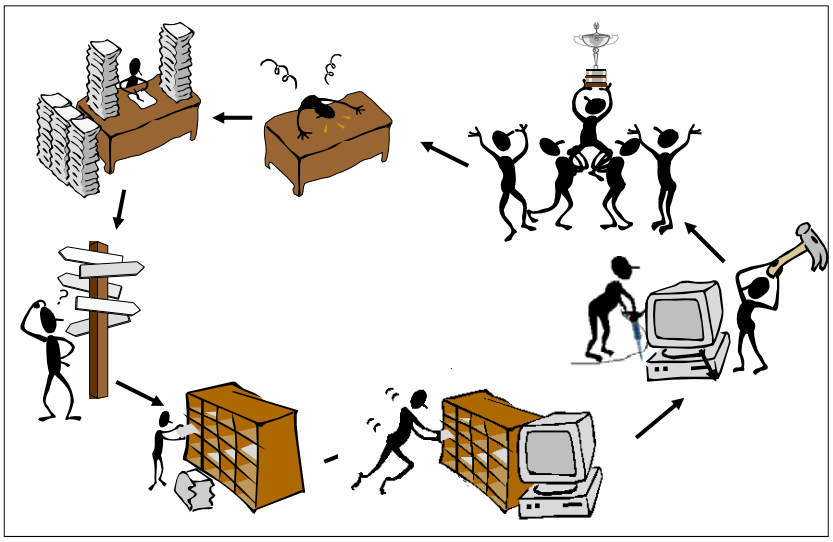
- **CS2220 Introduction to Computational Biology**
  - Understand bioinformatics problems; interpretational skills
- **CS3225 Combinatorial Methods in Bioinformatics**
- **CS4220 Knowledge Discovery Methods in Bioinformatics**
  - Clustering; classification; association rules; SVM; HMM; Mining of seq, trees, & graphs
- **CS5238 Advanced Combinatorial Methods in Bioinformatics**
  - Seq alignment, whole-genome alignment, suffix tree, seq indexing, motif finding, RNA sec struct prediction, phylogeny reconstruction
- **CS6280 Computational Systems Biology**
  - Dynamics of biochemical and signaling networks; modeling, simulating, & analyzing them
- **Etc …**

Any questions?

I hope you will enjoy this class ☺

Themes and Applications of Bioinformatics

What is Bioinformatics?



Themes of Bioinformatics
Themes of This Course

Bioinformatics involves

Data Mgmt +
Knowledge Discovery +
Sequence Analysis +
Physical Modeling + ...

Knowledge Discovery =

Statistics + Algorithms + Databases

The Promises of Bioinformatics

To the patient:

Better drug, better treatment

To the pharma:

Save time, save cost, make more $

To the scientist:

Better science

Fulfilling the Promise via Drugs

- **Bioinformatics is applicable to many phases of drug development**
- **Drug discovery: Design small molecules that bind target proteins.**
  - Which proteins? What should binding accomplish?
- **Biomarkers**
- **Personalized Medicine (future)**
- *There have been some disappointments too.*

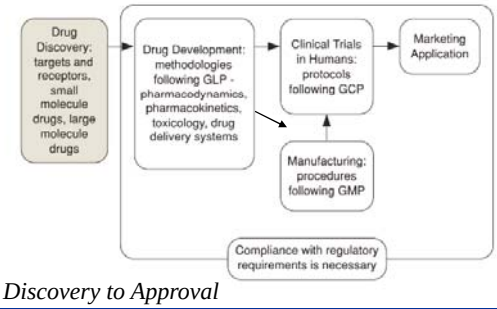


Figure from Rick Ng, *Drugs: From Discovery to Approval*

Pervasiveness of Bioinformatics

For large-scale biology
e.g., High-throughput, massively-parallel measurements, or "lab on a chip" miniaturization.
Bioinformatics is mandatory

For indirect experimental methods
e.g., reconstruction based on phase contrast or wave diffraction.
Computational data analysis is mandatory

What about the rest of biology (and medicine) ?
Limitless opportunities exist, but computational methods are in competition with non-computational methods, such as human intuition.

Some Bioinformatics Problems

- **Biological Data Searching**
- **Biological Data Integration**
- **Gene/Promoter finding**
- **Cis-regulatory DNA**
- **Gene/Protein Network**
- **Protein/RNA Structure Prediction**
- **Evolutionary Tree reconstruction**

- **Infer Protein Function**
- **Disease Diagnosis**
- **Disease Prognosis**
- **Disease Treatment Optimization, ...**

Biological Data Searching

- **Biological Data is increasing rapidly**
- **Biologists need to locate required info**
- **Difficulties:**
  - Too much
  - Too heterogeneous
  - Too distributed
  - Too many errors
  - Need approximate searches because of errors, mutations, etc.

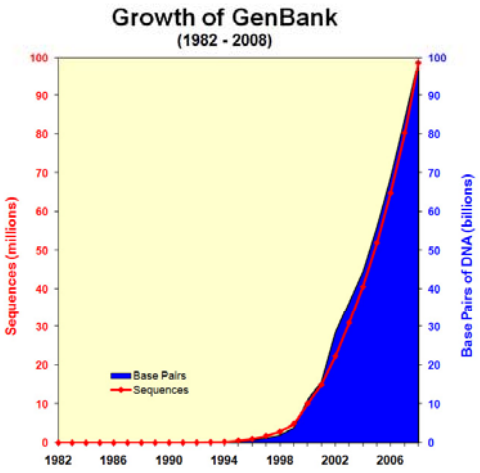


Image credit: NCBI

Biological Data Integration

- In the "post-Genbank" era, most bioinformatics data is about experiments.
  - Some datasets are useless without reference points. (Measurements relative to control, or requiring normalization.)
  - Some datasets have little meaning without their biological context (Cell type, disease state, treatment conditions, what was selected and what was discarded.)
  - To benefit from data often requires a huge amount of "meta-data" about the samples and methods.

METADATA becomes mandatory

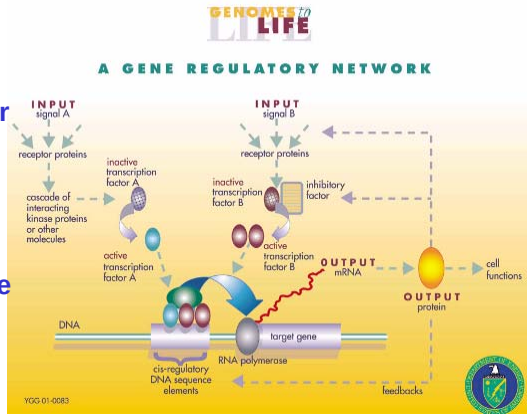
→ **Semantics & Ontologies**

→ **"Artificial Intelligence meets Databases"**

Cis-Regulatory DNAs

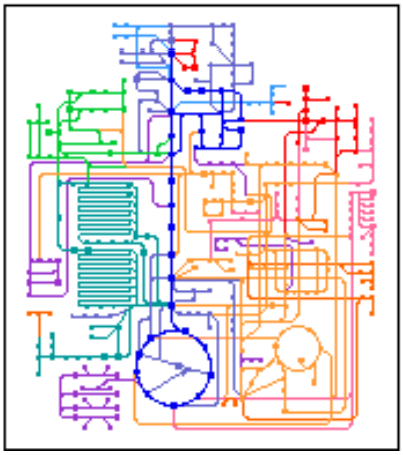
- **Cis-regulatory DNAs control whether genes should express or not**
- **Cis-regulatory DNAs may locate in promoter region, intron, or exon**
- **Finding and understanding cis-regulatory DNAs is one of the key problem in coming years**

Image credit: US DOE



Gene Networks

- Inside a cell is a complex system
- Expression of one gene depends on expression of another gene
- Such interactions can be represented using gene network
- Understanding such networks helps identify association betw genes & diseases



Protein/RNA structure prediction

- Structure of Protein/RNA is essential to its functionality
- Important to have some ways to predict the structure of a protein/RNA given its sequence
- This problem is important & it is always considered as a "grand challenge" problem in bioinformatics

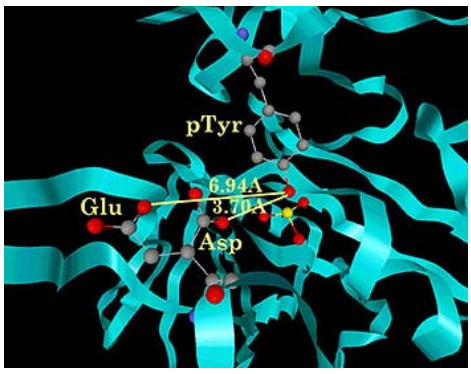
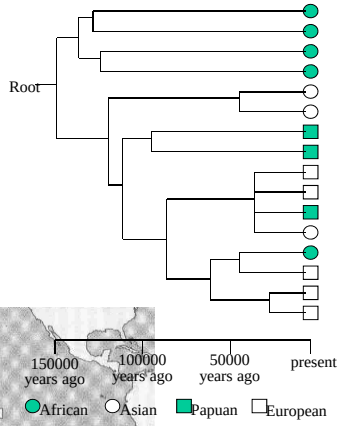


Image credit: Kolatkar

Evolutionary Tree Reconstruction

- **Protein/RNA/DNA mutates**
- **Evolutionary Tree studies evolutionary relationship among set of protein/RNA/DNAs**
- **Figures out origin of species**



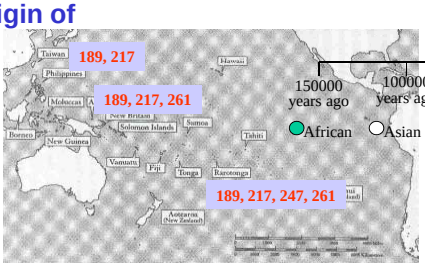


Image credit: Sykes

Breast Cancer Outcome Prediction

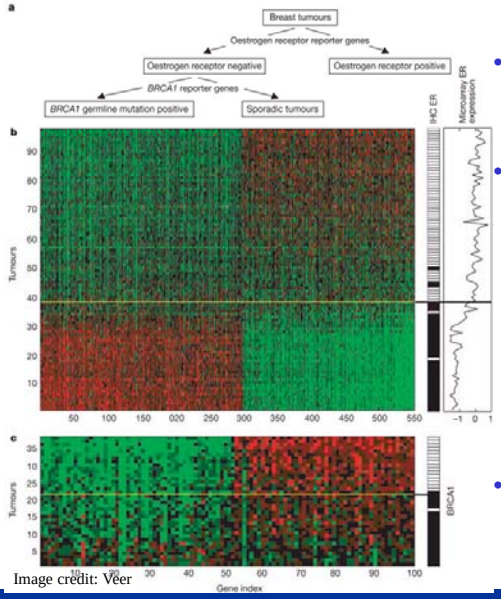


Image credit: Veer

- **Van't Veer et al., *Nature* 415:530-536, 2002**
- **Training set contains 78 patient samples**
  - 34 patients develop dist-ance metastases in 5 yrs
  - 44 patients remain healthy from the disease after initial diagnosis for >5 yrs
- **Testing set contains 12 relapse & 7 non-relapse samples**

Commonly Used Data Sources

Type of Biological Databases

- **Micro Level**
  - Contain info on the composition of DNA, RNA, Protein Sequences
- **Macro Level**
  - Contain info on interactions
    - **Gene Expression**
    - **Metabolites**
    - **Protein-Protein Interaction**
    - **Biological Network**
- **Metadata**
  - Ontology
  - Literature

Exercise: Name a protein seq db and a DNA seq db

Transcriptome Database

- **Complete collection of all possible mRNAs (including splice variants) of an organism**
- **Regions of an organism's genome that get transcribed into messenger RNA**
- **Transcriptome can be extended to include all transcribed elements, including non-coding RNAs used for structural and regulatory purposes**

Exercise: Name a transcriptome database

Gene Expression Databases

- **Detect what genes are being expressed or found in a cell of a tissue sample**
- **Single-gene analysis**
  - Northern Blot
  - In Situ Hybridization
  - RT-PCR
- **Many Genes: High Throughput Arrays**
  - cDNA Microarray
  - Affymetrix GeneChip® Microarray

Exercise: Name a gene expression database

Metabolites Database

- **A metabolite is an organic compound that is a starting material in, an intermediate in, or an end product of metabolism**
- **Metabolites dataset are also generated from mass spectrometry which measure the mass the these simple molecules, thus allowing us to estimate what are the metabolites in a tissue**

- **Starting metabolites:**
  - Small, of simple structure, absorbed by the organism as food
  - E.g., vitamins and amino acids
- **Intermediary metabolites:**
  - The most common metabolites
  - May be synthesized from other metabolites, or broken down into simpler compounds, often with the release of chemical energy
  - E.g., glucose
- **End products of metabolism**
  - Final result of the breakdown of other metabolites
  - Excreted from the organism without further change
  - E.g., urea, carbon dioxide

Protein-Protein Interaction Databases

- **Proteins are true workhorses**
  - Lots of the cell's activities are performed thru PPI including message passing, gene regulation, etc.
- **Function of a protein also depends on proteins it interact with**

- **Methods for generating PPI database include:**
  - biochemical purifications, yeast-two hydrid, synthetic lethals, in silico predictions, mRNA-co-expression
- **Contain many false positives & false negatives**

Exercise: Name a PPI database

Any Question?

Acknowledgements

- **Most of the slides used in this lecture are based on original slides created by**
  - Ken Sung
  - Anthony Tung
  - Limsoon Wong
- **But you should blame me for any errors**

References

- **S.K. Ng, "Molecular Biology for the Practical Bioinformatician", *The Practical Bioinformatician*, Chapter 1, pages 1—30, WSPC, 2004**
- **DOE HGP Primer, http://www.ornl.gov/sci/techresources/Human_Genome/publicat/primer/index.shtml**
- **Lots of useful videos, http://www.as.wvu.edu/~dray/Bio_219.html**