CS2220: Intro to Computational Biology
Course Briefing

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Recommended “pre-requisites”

- **Data Structures and Algorithms**

- **Basic statistics**
- **Biochemistry of Biomolecules**
- **Molecular Genetics**

You may also find the following to be a useful hands-on complement to CS2220:

- **LSM2241 Introductory Bioinformatics**

Objectives

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

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

Contents of course overview

- **Time table**
- **Course syllabus**
- **Course homepage**
- **Teaching style**
- **Project, assignments, exams**
- **Readings**
- **Assessment**

Time table

- **Lecture**
  - Thursday 2pm – 5pm, SR@LT19
- **Tutorial**
  - Integrated into each lecture
- **Email**
  - wongls@comp.nus.edu.sg
- **Consultations**
  - Any time; just make appt

Course syllabus

- **Intro to Bioinformatics**
  - molecular biology basics
  - tools and instruments for molecular biology
  - themes and applications of 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 Analysis**
  - Microarray basics
  - Gene expression profile normalization
  - Classification of gene expression 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
- **Seq Homology Interpretation**
  - protein function prediction by sequence alignment
  - protein function prediction by phylogenetic profiling
  - active site and domain prediction
  - key mutation sites prediction
- **Phylogenetic Trees**
  - Phylogeny reconstruction method basics
  - origin of Polynesians & Europeans
  - Large-scale sequencing basics
- **One or two other topics (drug-resistant mutation prediction, ortholog prediction, disease-causing mutations, etc.)**

Course homepage

- **LumiNUS**
  - https://luminus.nus.edu.sg/modules/0de7fd94-eb51-4eab-a422-846f88875af3

- **Lecture Slides & etc.**
  - http://www.comp.nus.edu.sg/~wongls/courses/cs2220/2021

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 (35% of marks)**
  - 3 assignments
  - Some simple programming required

- **Project (15% of marks)**
  - Based on material associated with self-learning
  - 8-10 pages of report / ppt slides expected

- **Exam (50% of marks)**
  - 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

Background readings

- **References are provided in the lecture slides; please look them up**

- **You can also read these or other books for background in general**
  - Limsoon Wong, *The Practical Bioinformatician*, WSPC, 2004
  - Wing-Kin Sung, *Algorithms in Bioinformatics: A Practical Introduction*, CRC, 2010

What comes after CS2220

- **CS2220 Introduction to Computational Biology**
  - Understand bioinformatics problems; interpretational skills
- **CS4330 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
- **Etc …**

Any questions?

I hope you will enjoy this class ☺

Themes and Applications of Bioinformatics

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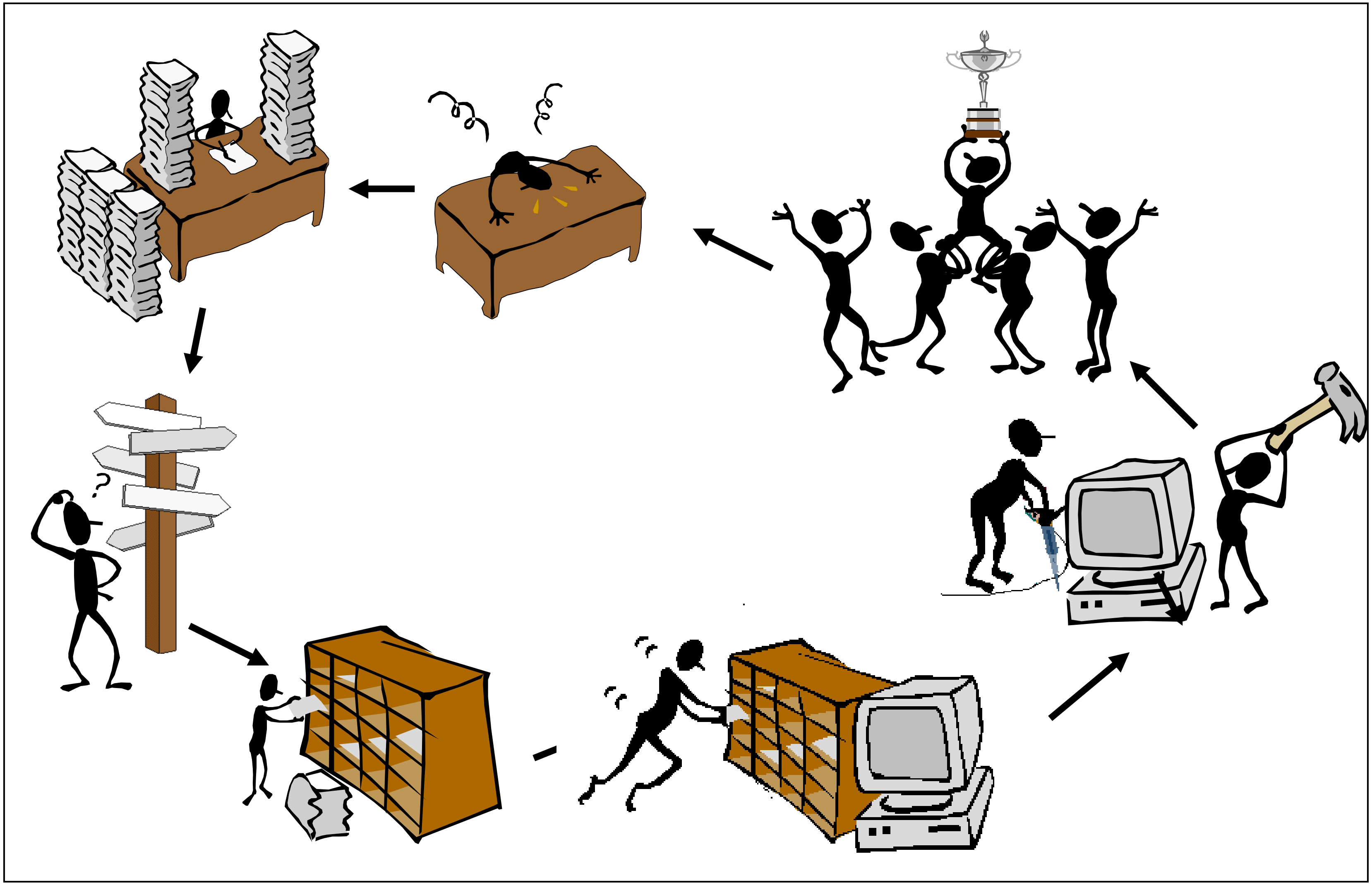
What is bioinformatics?



Themes of bioinformatics
Themes of this course

Bioinformatics involves

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

Knowledge Discovery =

Statistics + Algorithms + Databases

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

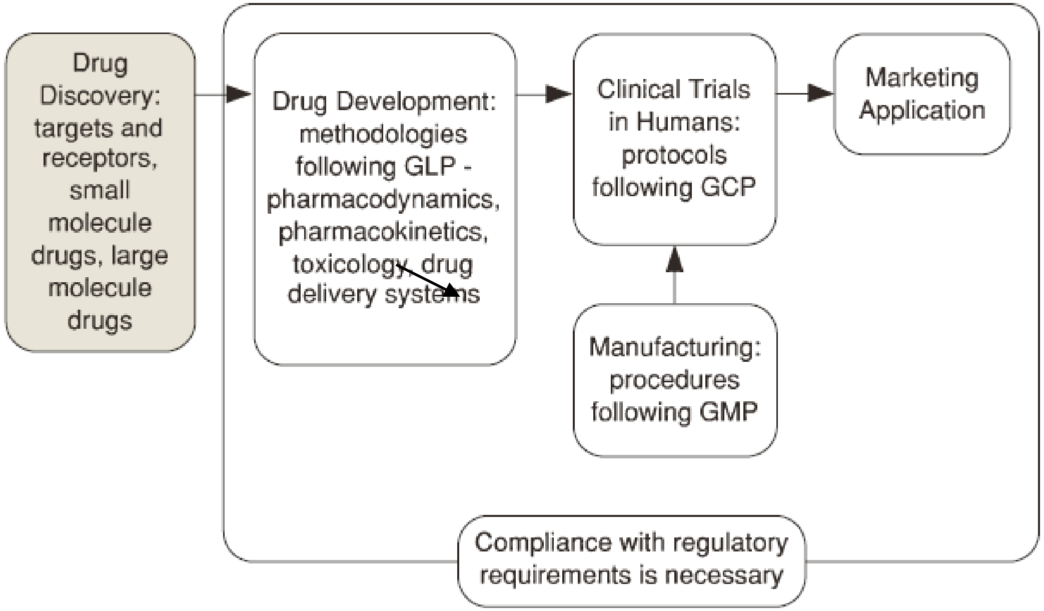

Drug Discovery: targets and receptors, small molecule drugs, large molecule drugs
Drug Development: methodologies following GLP - pharmacodynamics, pharmacokinetics, toxicology, drug delivery systems
Clinical Trials in Humans: protocols following GCP
Marketing Application
Manufacturing: procedures following GMP
Compliance with regulatory requirements is necessary

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

- **Bioinformatics is applicable to drug development**
- **Drug discovery: Design small molecules that bind target proteins**
  – Which proteins?
  – What should binding accomplish?
- **Biomarkers**

Pervasiveness of bioinformatics

- **Bioinformatics is mandatory for large-scale biology**
  - e.g., High-throughput, massively-parallel measurements, or “lab on a chip” miniaturization

- **Computational data analysis is mandatory for indirect experimental methods**
  - e.g., protein identification from mass-spectra

- **What about the rest of biology (and medicine) ?**
- **Limitless opportunities!**

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**
- **Protein function prediction**
- **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.

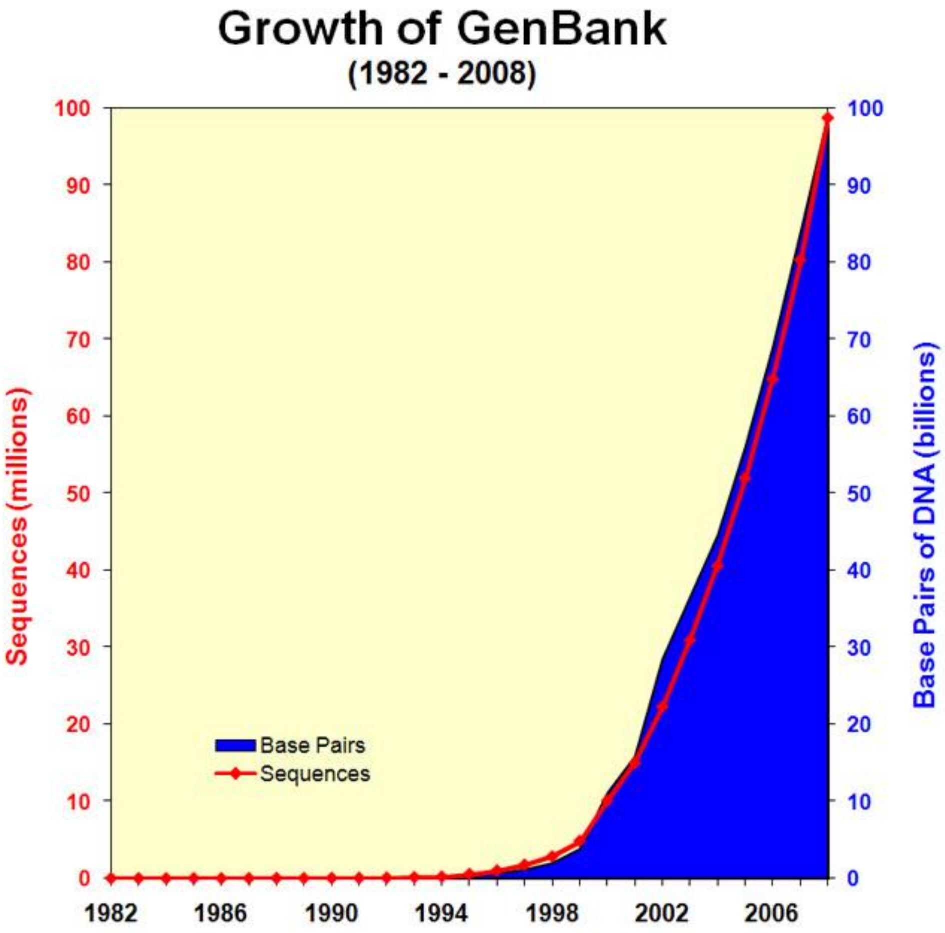


Image credit: NCBI

Cis-regulatory DNAs

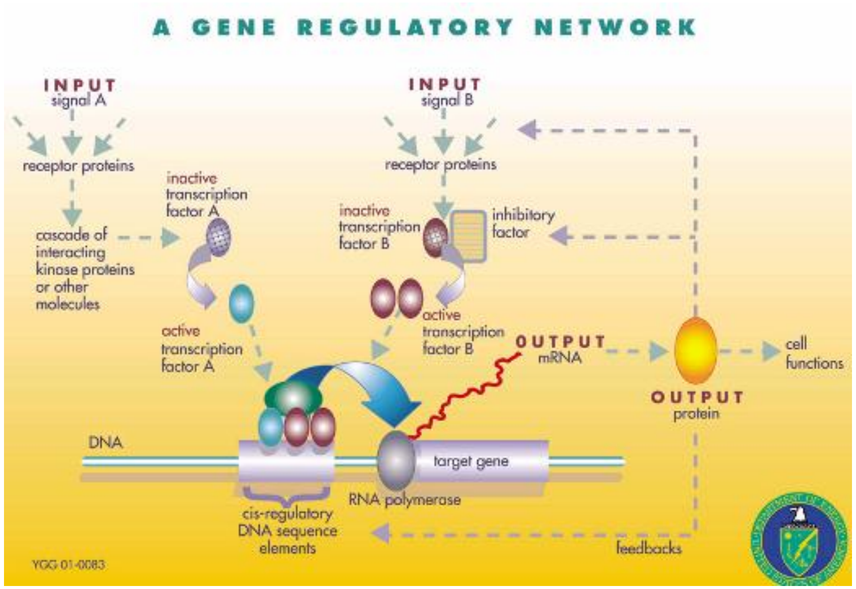
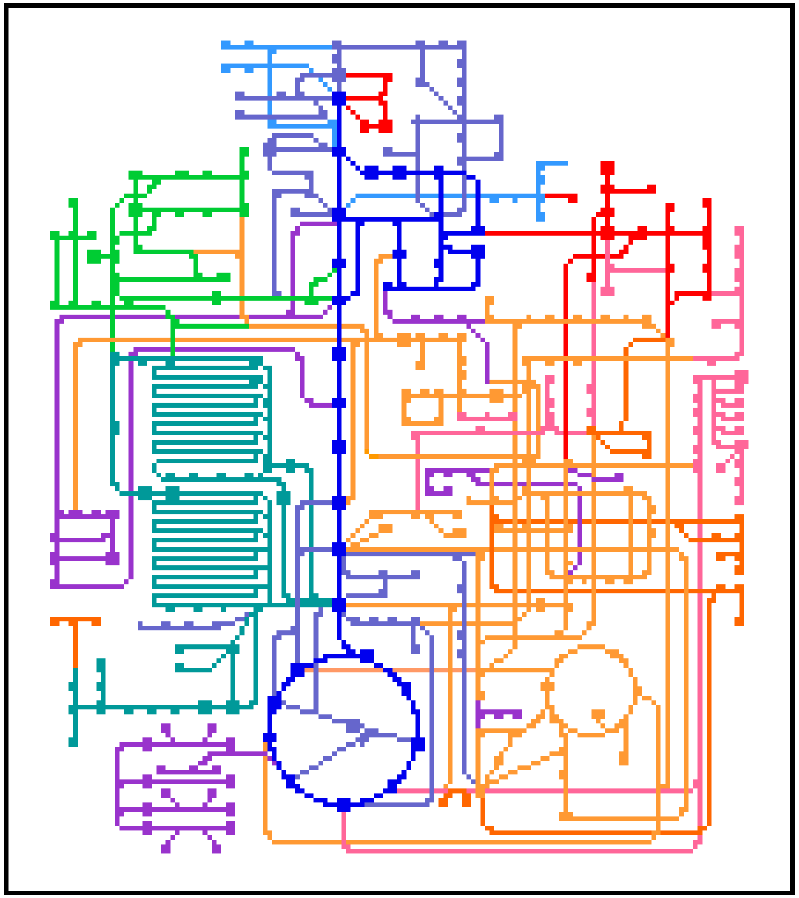

A GENE REGULATORY NETWORK
INPUT signal A
INPUT signal B
receptor proteins
receptor proteins
inactive transcription factor A
cascade of interacting kinase proteins or other molecules
inactive transcription factor B
inhibitory factor
active transcription factor A
active transcription factor B
OUTPUT mRNA
cell functions
OUTPUT protein
DNA
target gene
RNA polymerase
cis-regulatory DNA sequence elements
feedbacks
YGG 01-0083

Image credit: US DOE

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

Gene networks

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



Protein/RNA structure prediction

- **Structure of protein / RNA is essential to its functionality**
- **Impt to predict structure of a protein / RNA given its seq**
- **Problem is considered a “grand challenge” problem in bioinformatics**

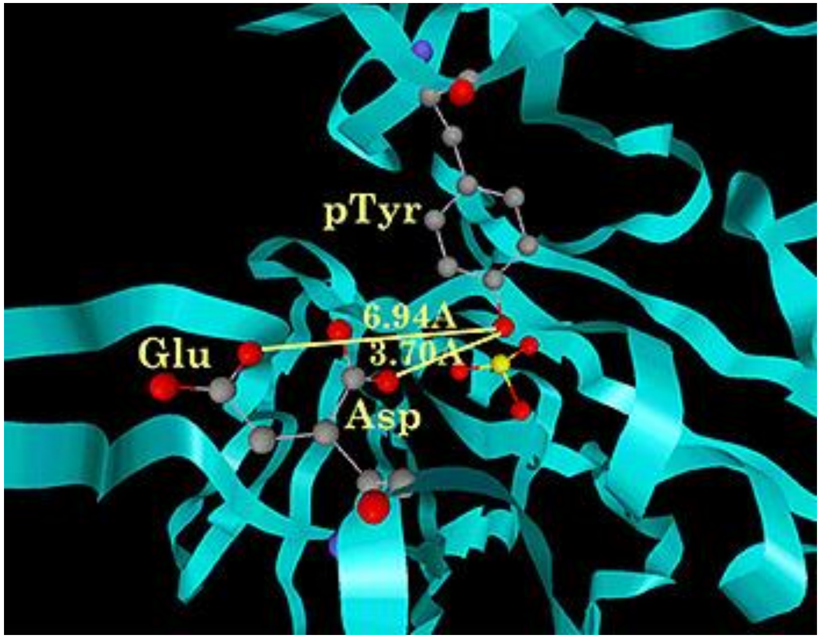


Image credit: Kolatkar

Evolutionary tree reconstruction

- Protein /RNA / DNA mutates
- Evolutionary tree studies evolutionary relationship among set of protein / RNA / DNAs
- Origin of species

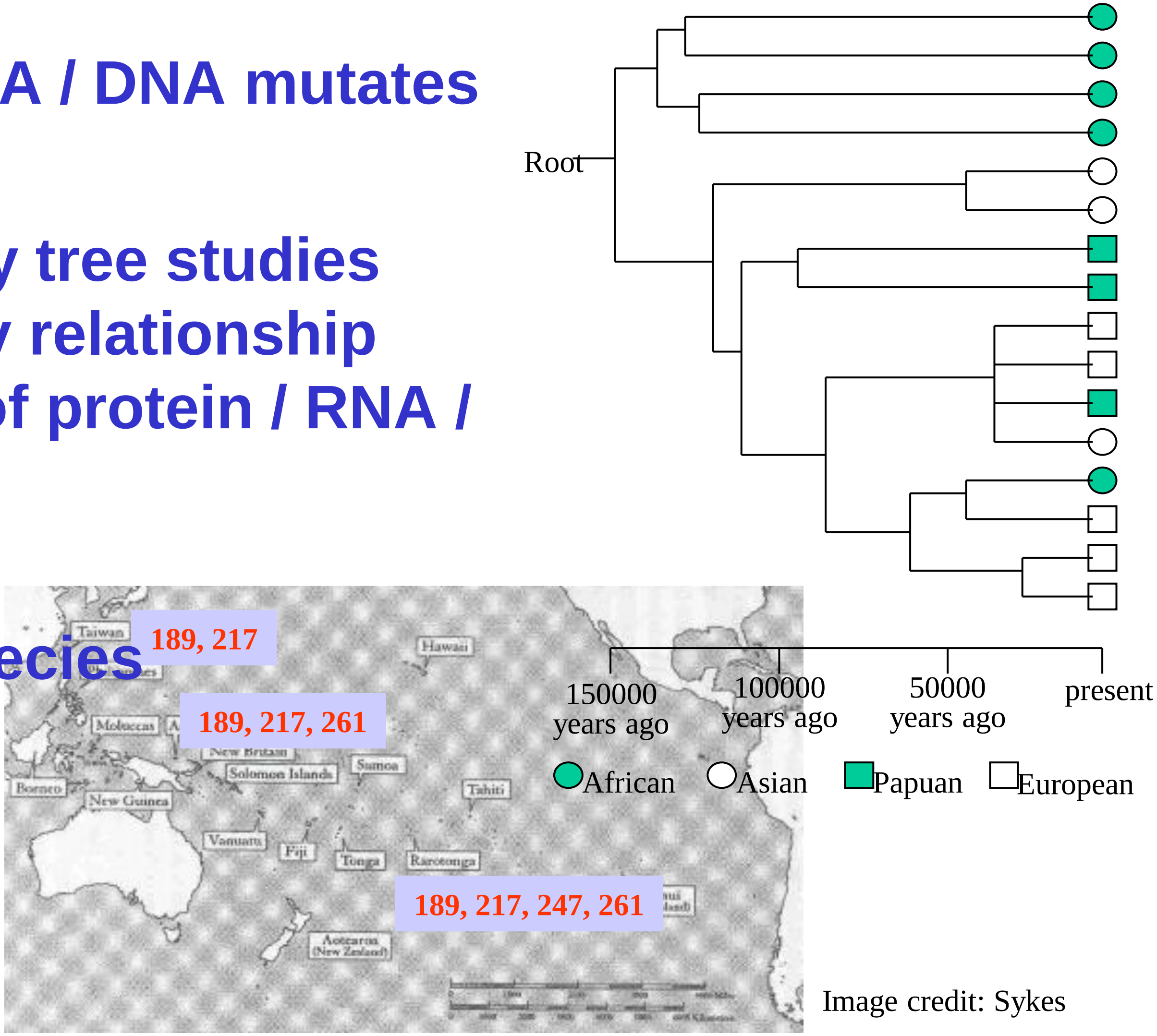


Image credit: Sykes

Breast cancer outcome prediction

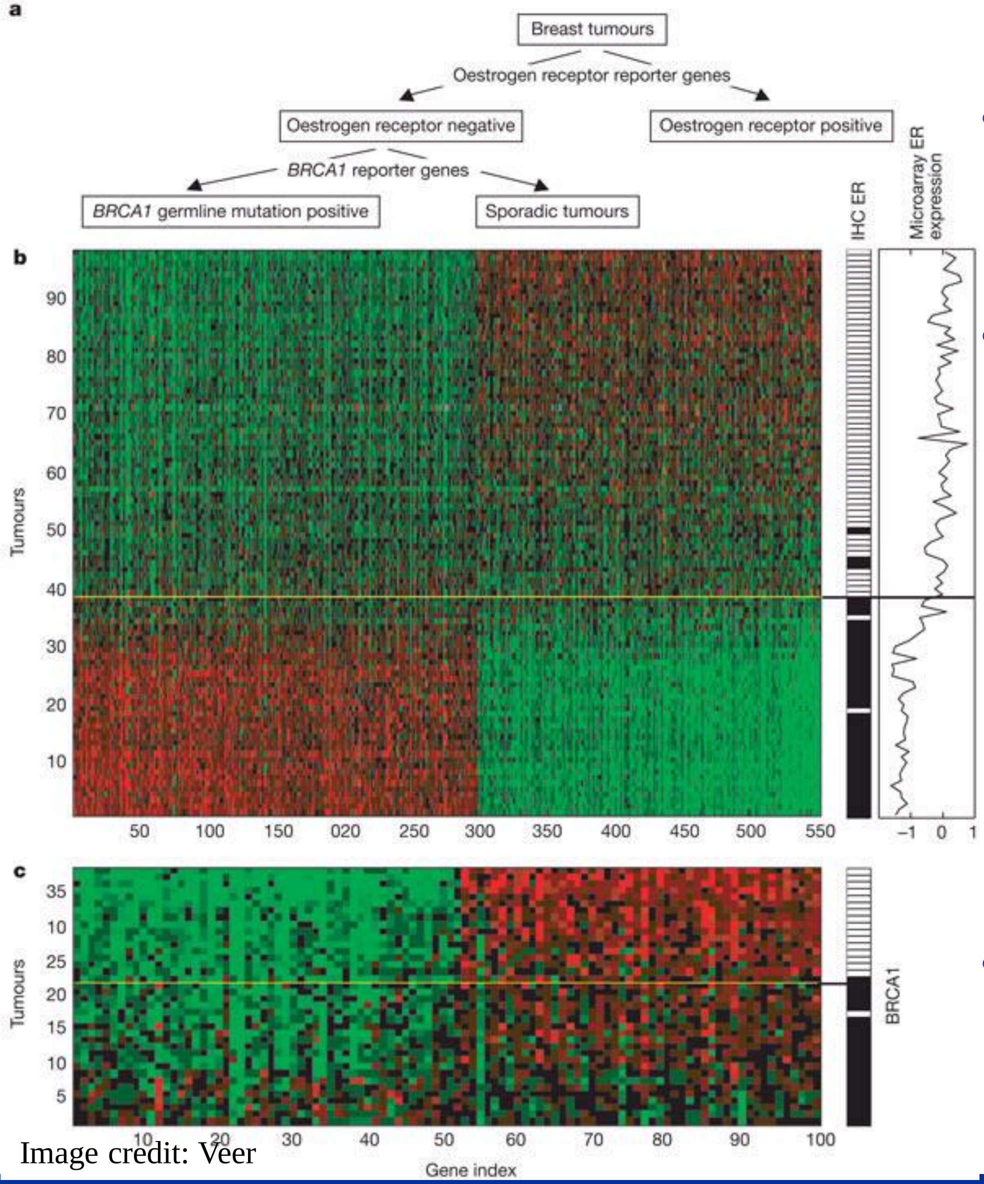


Image credit: Veer

- **Van't Veer et al., *Nature* 415:530-536, 2002**
- **Training set contains 78 patient samples**
  - 34 patients develop distance 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
- **Metadata**
  - Ontology
  - Literature
- **Macro Level**
  - Contain info on interactions
    - **Gene Expression**
    - **Metabolites**
    - **Protein-Protein Interaction**
    - **Biological Network**

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 cell's activities are performed thru PPI, e.g., message passing, gene regulation, etc.
- **Function of a protein depends on proteins it interacts with**
- **Methods for generating PPI db**
  - biochemical purifications, Y2H, synthetic lethals, in silico predictions, mRNA-co-expression
- **Contain many false positives & false negatives**

Exercise: Name a PPI database

Any Question?

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Acknowledgements

- **Most of the slides used in this lecture are based on original slides created by**
  - Ken Sung
  - Anthony Tung

- **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**

- **Lots of useful videos, http://www.as.wvu.edu/~dray/Bio_219.html**