Gens, Ordinadors i Malalties

Biologia i Ordinadors al segle XXI

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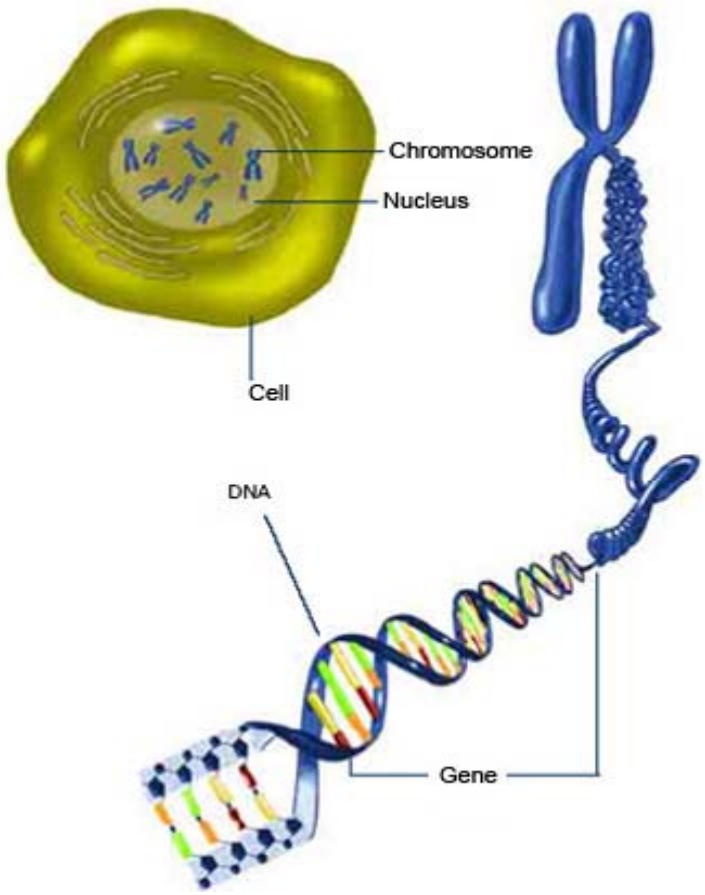
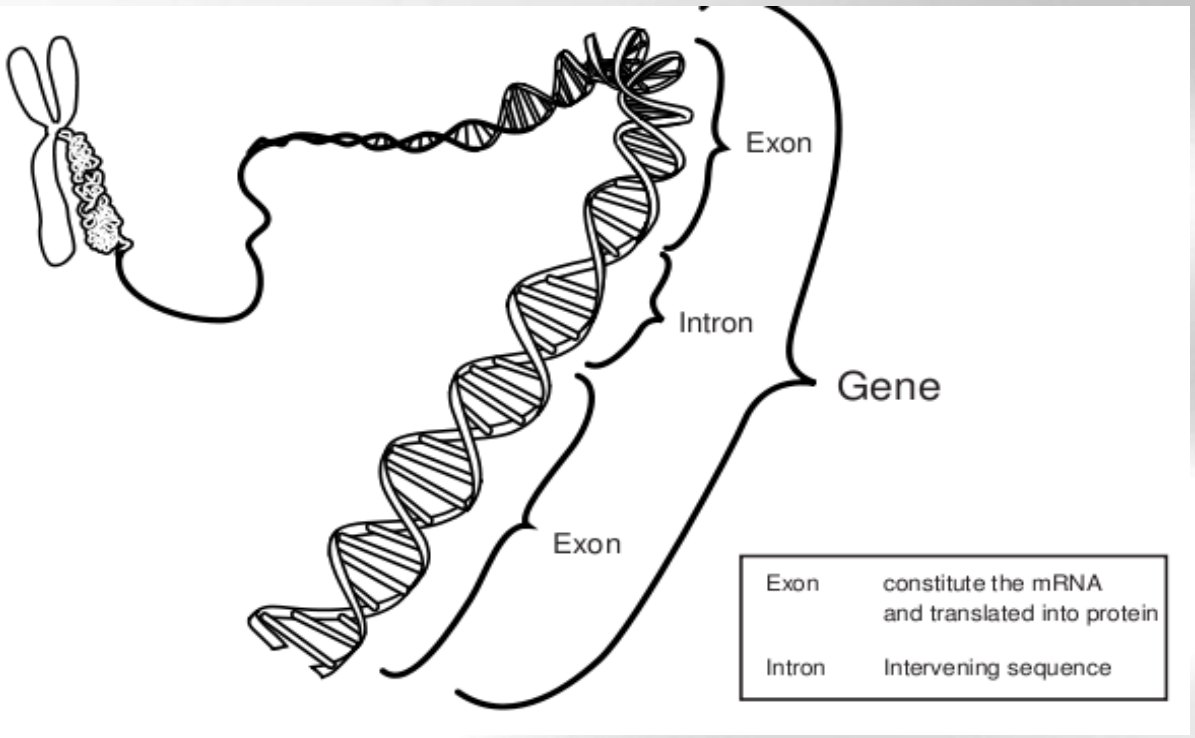
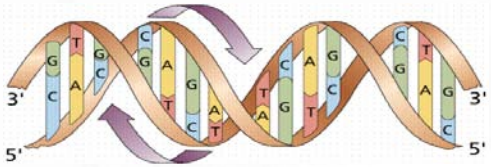
Genes are made of DNA





The Central Dogma of Molecular Biology



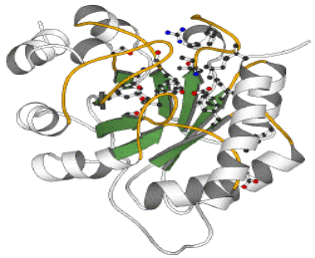
DNA

transcription

mRNA

translation

Protein



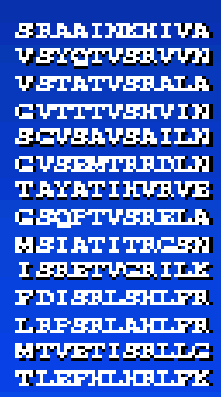
CCTGAGCCAACTATTGATGAA

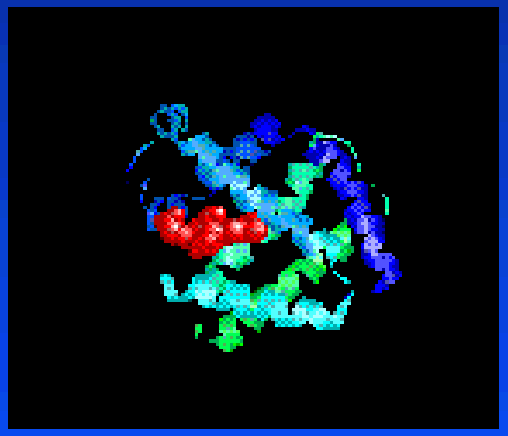
CCUGAGCCAACUAUUGAUGAA

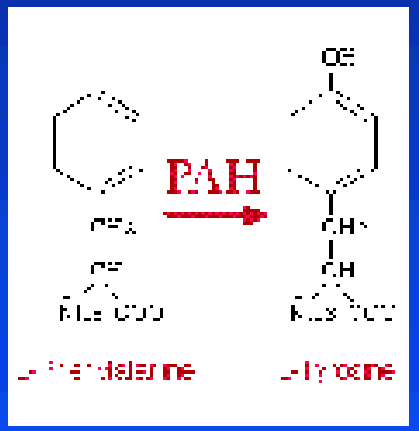
PEPTIDE

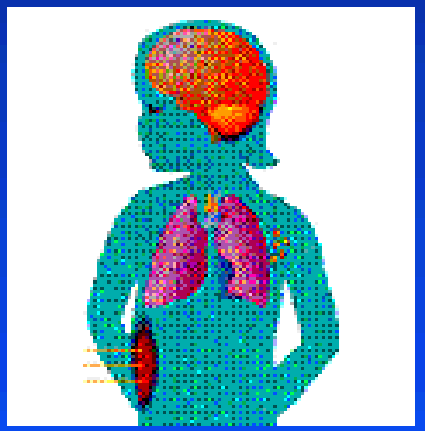
Central Paradigm of Bioinformatics

Genetic Information → Molecular Structure → Biochemical Function → Symptoms (Phenotype)

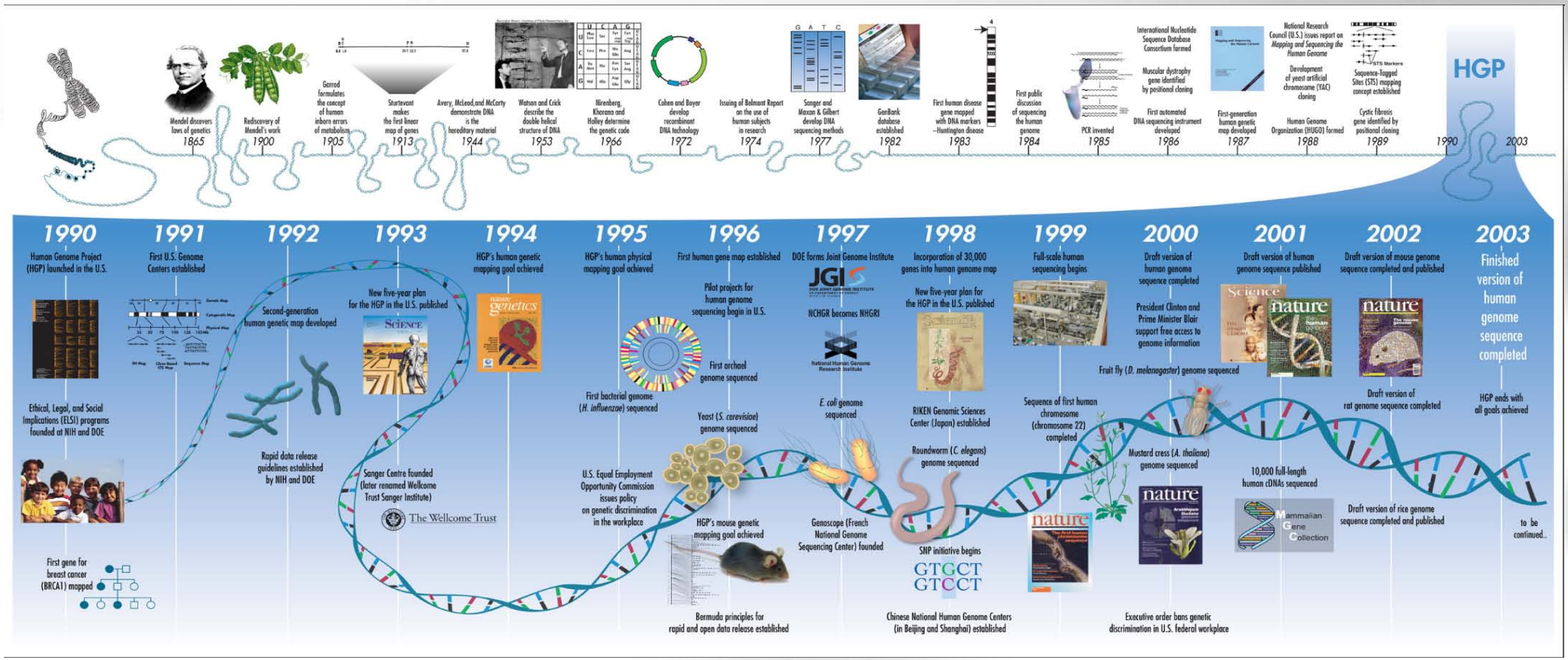








The human genome project



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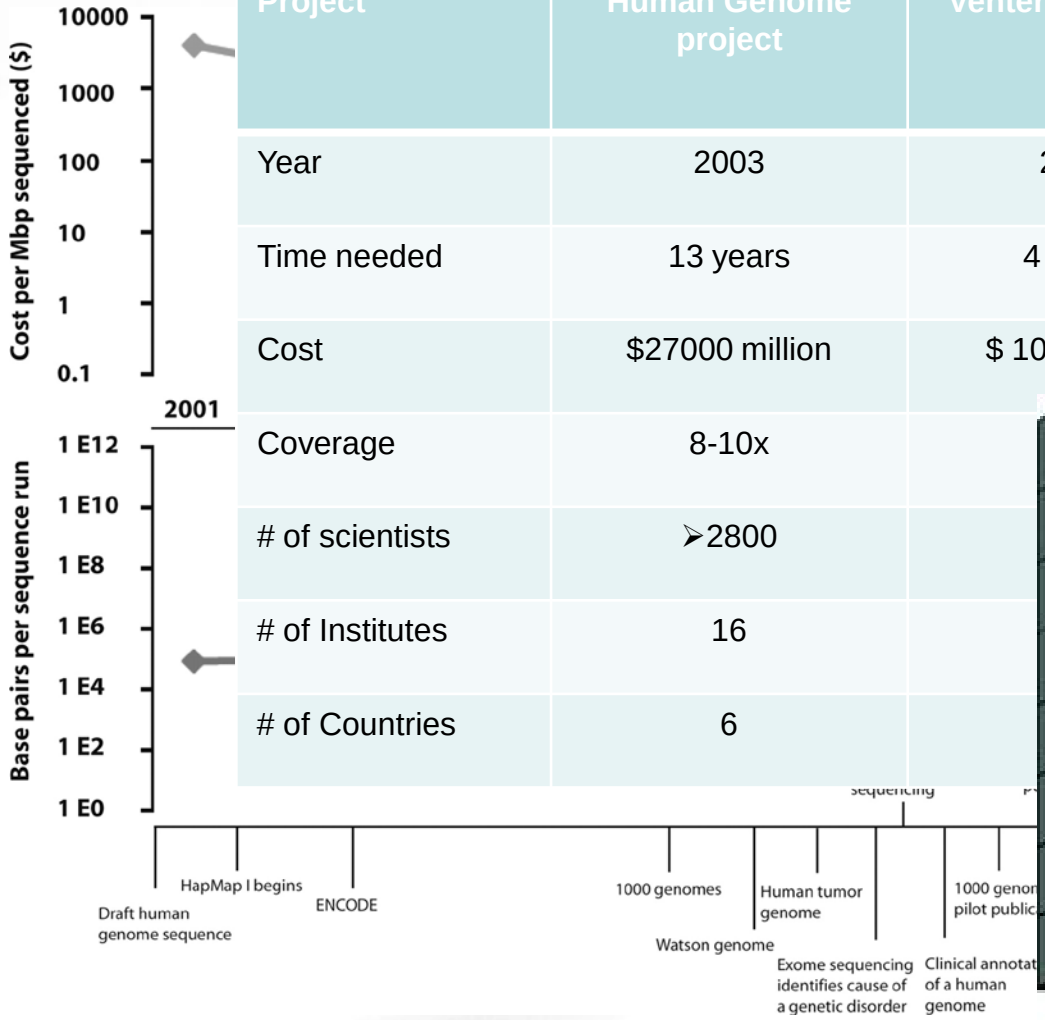
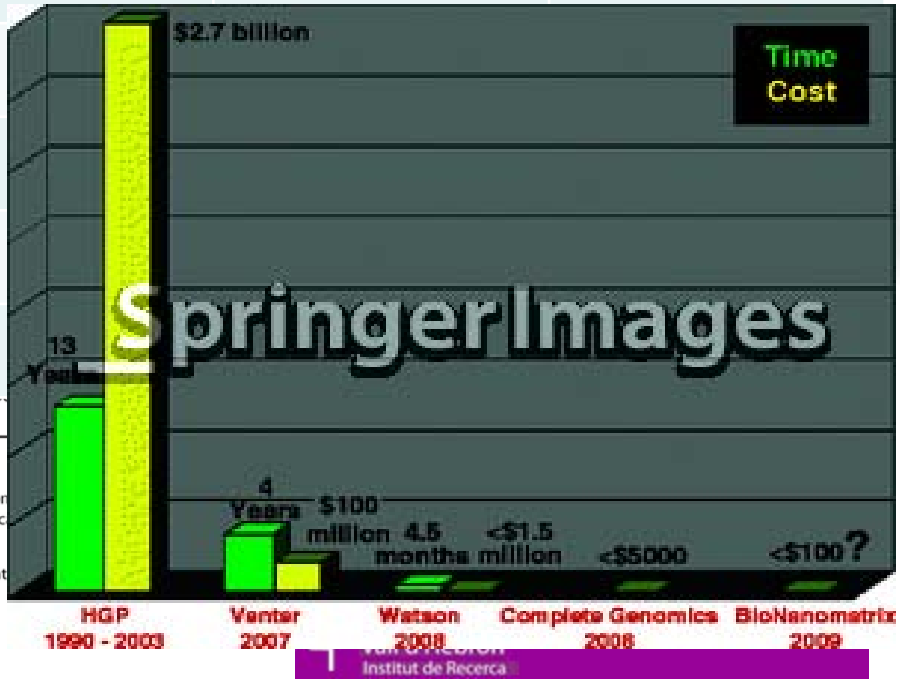
Decreasing costs & Increasing capabilities of genome sequencing

Project	Human Genome project	Venter's genome	Watson's genome	Anybody's
Year	2003	2007	2008	20012
Time needed	13 years	4 years	4.5 months	2 weeks
Cost	$27000 million	$ 100 million	< $1.5 million	<$10000
Coverage	8-10x			
# of scientists	➢2800			
# of Institutes	16			
# of Countries	6			





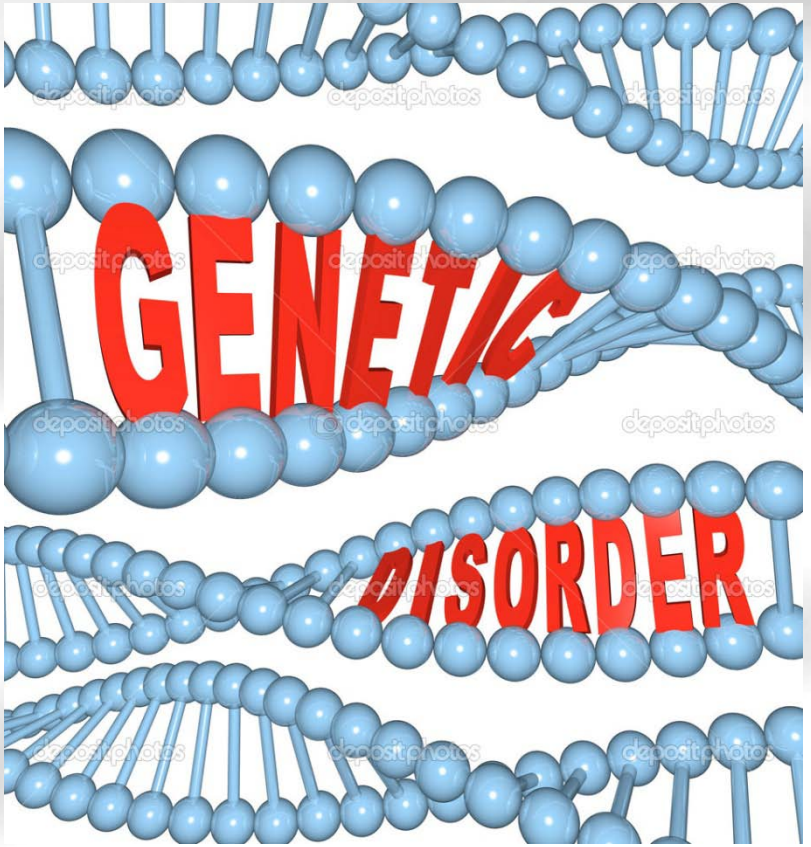
Diseases and genetic diseases

- Traditionally : 3 types of diseases
  - 1. genetically determined
  - 2. environmentally determined
  - 3. 1. + 2.

- Today : distinctions are blurred
  - up to 20% of pediatric in-patients have genetic abnormality
  - about 50% of spontaneous abortuses have chromosomal aberration
  - only mutations that are not lethal are reservoir of genetic diseases

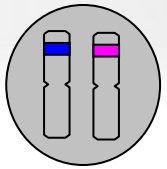
Genetic disease

- Genetic disorders are caused by abnormalities in the genetic material.
- Abnormalities can range from a small mutation in a single gene to the addition or subtraction of an entire chromosome or set of chromosomes.

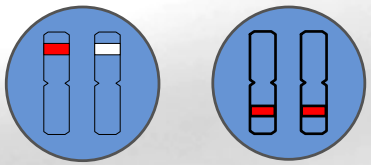


Classification of genetic disorders

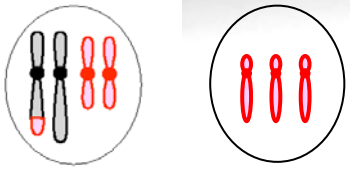
- Multifactorial
- Single gene
- Chromosomal
- Mitochondrial
- Somatic mutations (cancer)



+ environment



Male



Gene identification of inherited disease

- Every gene has a specific task
- Disease genes carry mutations,
  which change the protein, which
  alters the way the task is usually performed.
- The mutation may be
  - within a gene/protein or
  - within a regulatory part of the genome that, e.g., affects the amount of protein being produced.

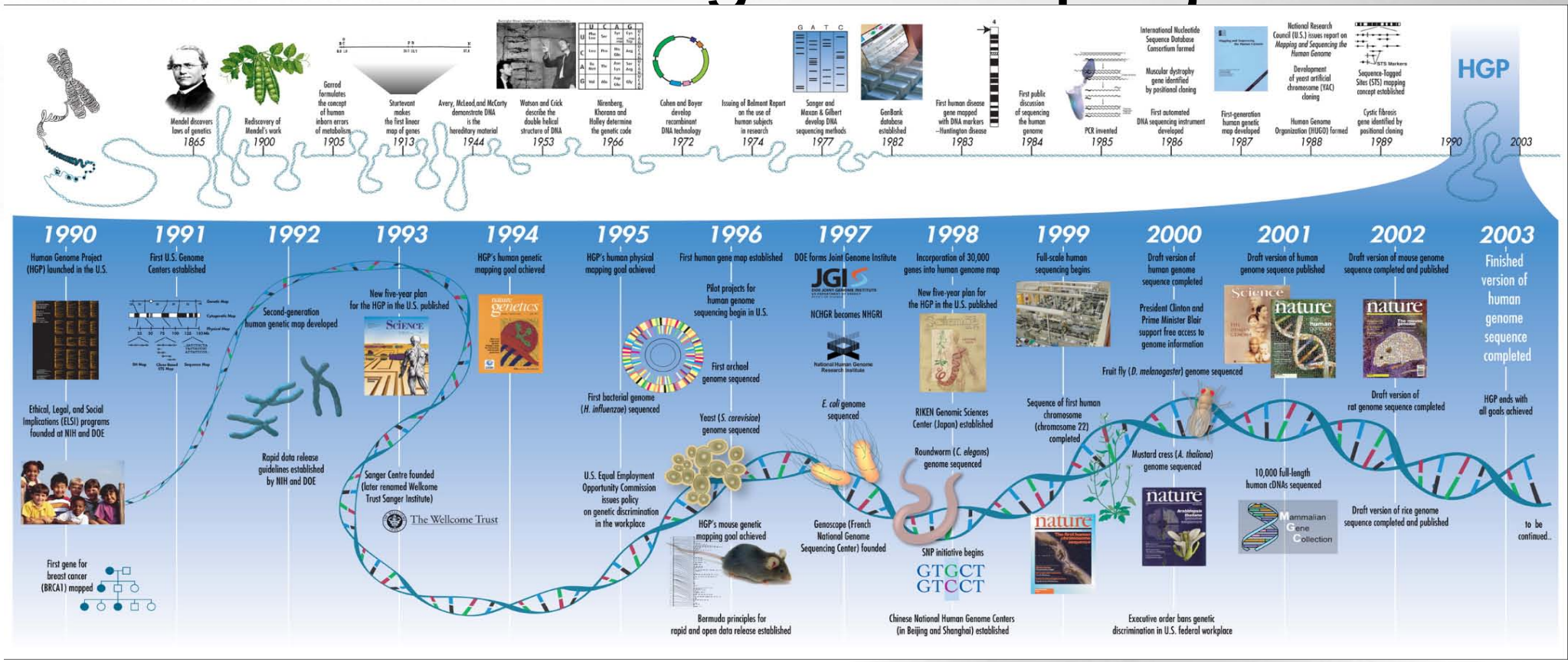
Modern approaches to disease gene identification and analysis

- The release of genomic sequences, full-lenght cDNA sequences, of human and model organisms offer invaluable resources for studying genetic diseases.
- It is not possible, however, to access such an impressive quantity of biological information without the use of powerful informatics resources
- ***That is where bioinformatics enters the scene***

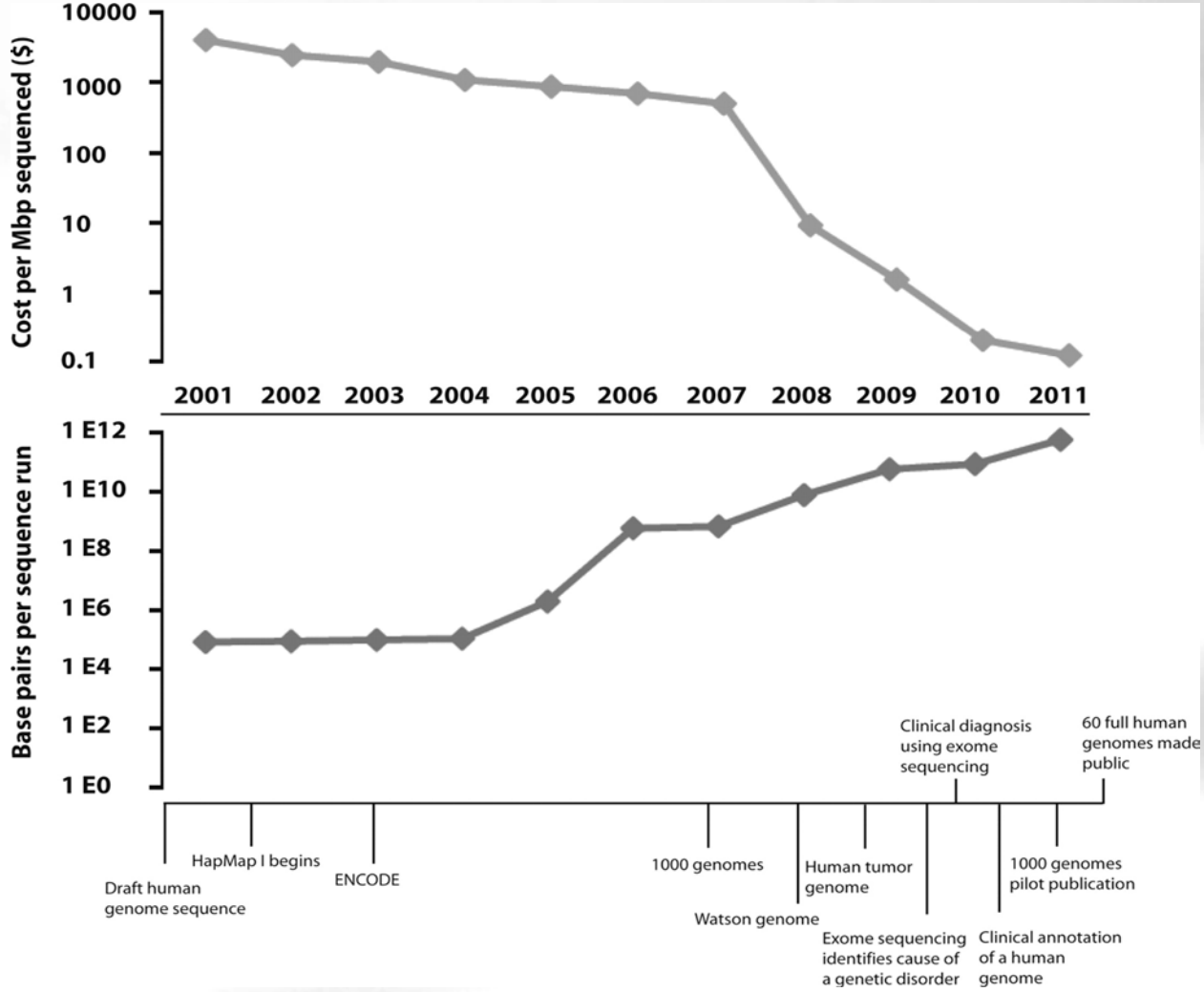
The data explossion(s)

- Bioinformatics has evolved in parallel with
  - The increase in biological data available
  - The ability to generate (and *manage*) them.
- We distinguish (up to now) …
  - Pre-genomic age
  - Early post-genome age
  - Late post-genome age

The human genome project



NGS: (much) More per (much) less



http://www.genome.gov/sequencingcosts

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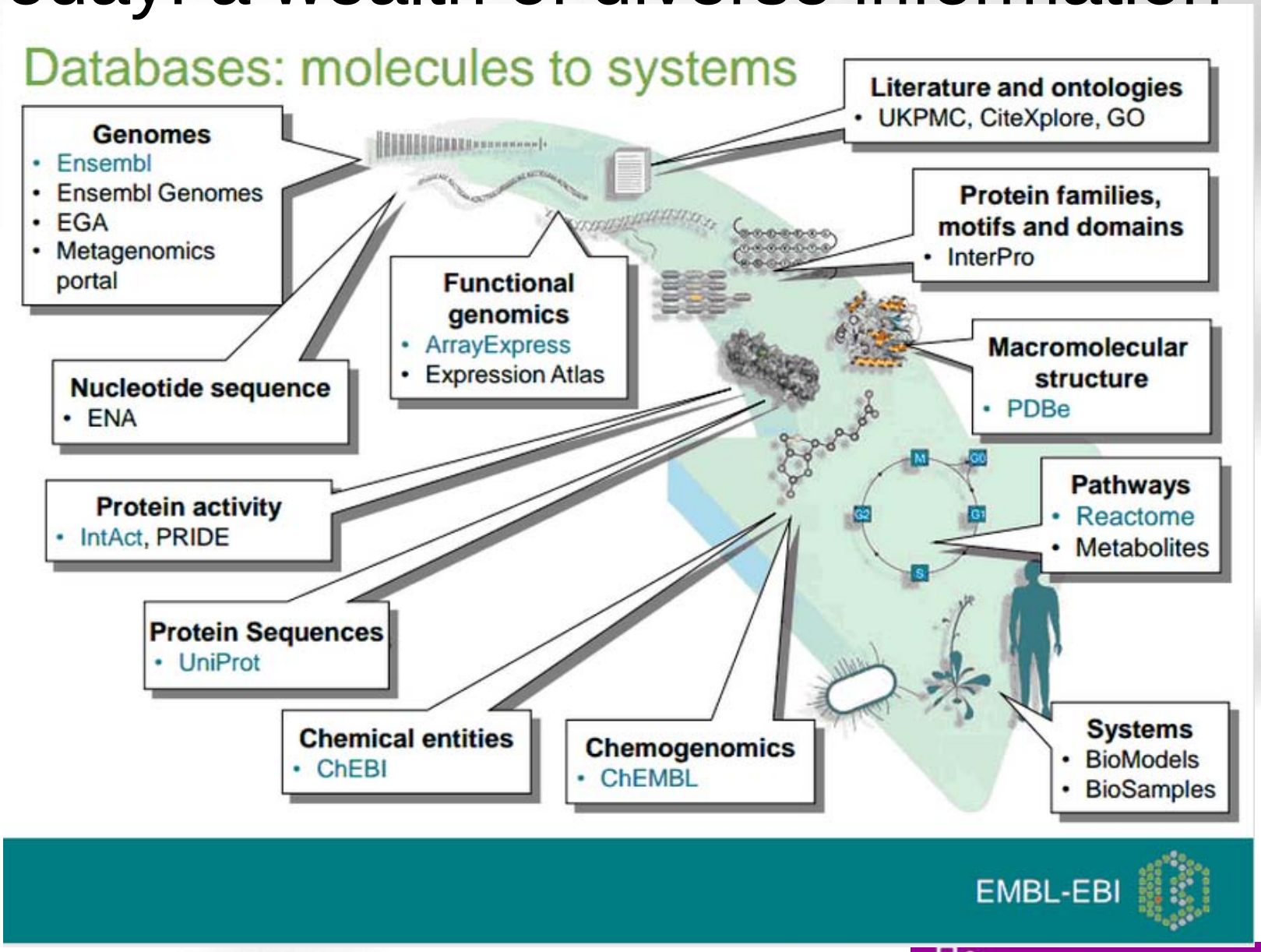
Today: a wealth of diverse information

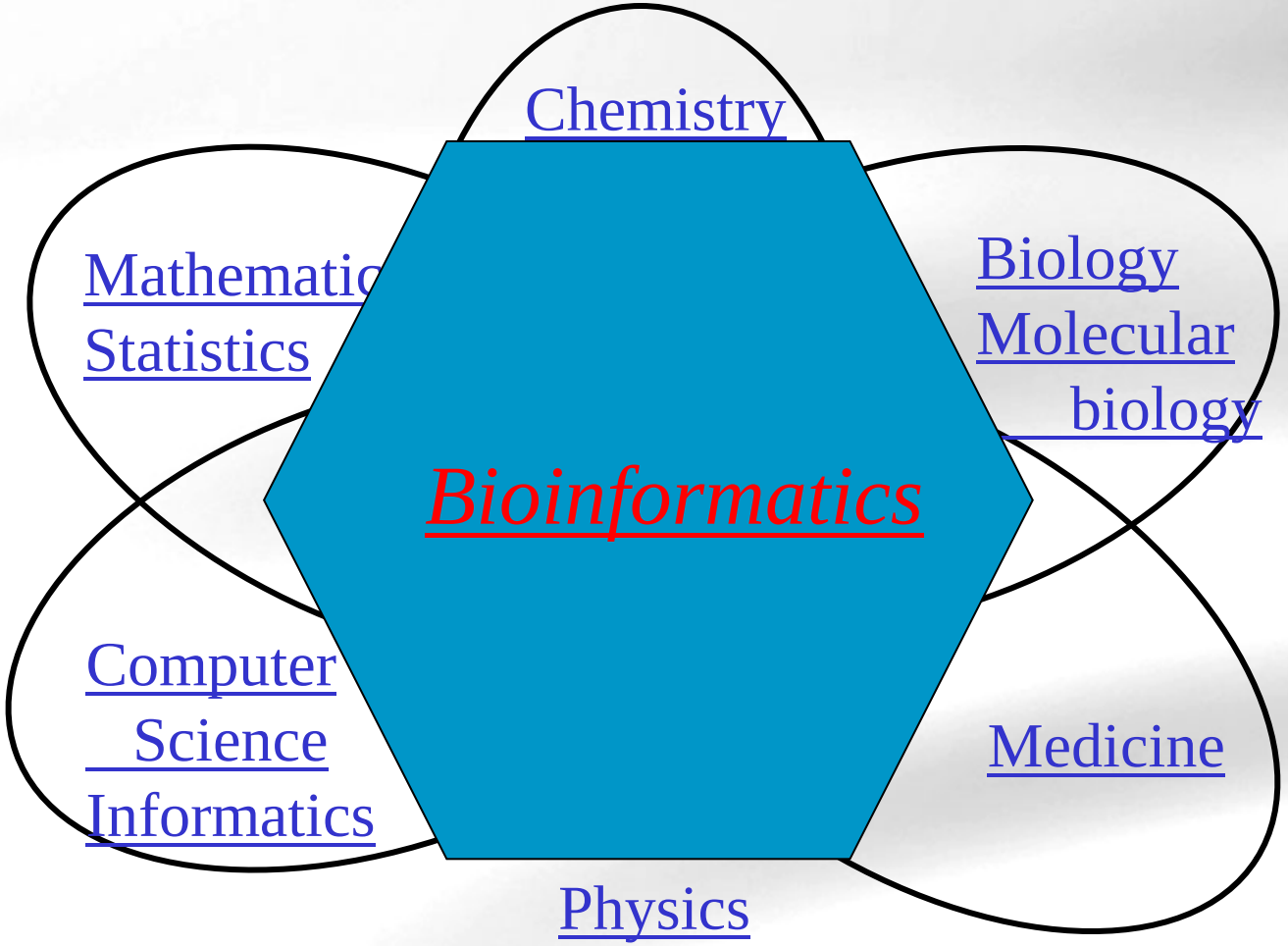


BIOINFORMATICS

- Born on the lookout for
  - –the development of new technologies and
  - –its application in the generation of huge amounts of data.

- *It is the interdisciplinary scientific field that develops methods for storing, retrieving, organizing and analyzing biological data.*

BIOINFORMATICS AND INTERDISCIPLINARITY



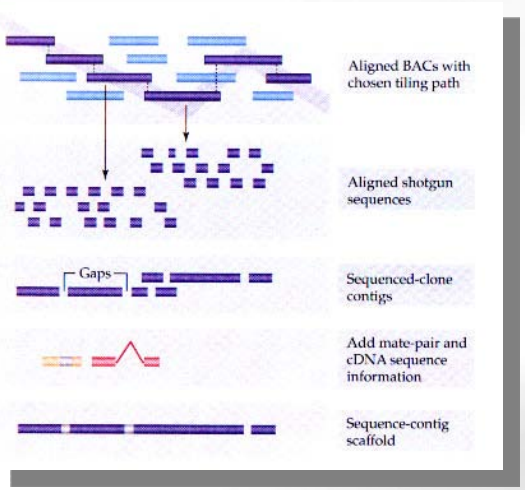
THE SCOPES OF BIOINFORMATICS

- Information organization
  - Databanks and databases
  - Algorithms and exploitation tools
- Analysis and interpretation of experimental results
  - Genome analysis and sequencing
  - Comparative genomics
  - Gene expression and transcription
  - Proteomics, protein-protein interaction
- Systems biology modeling

INFORMATION ORGANIZATION

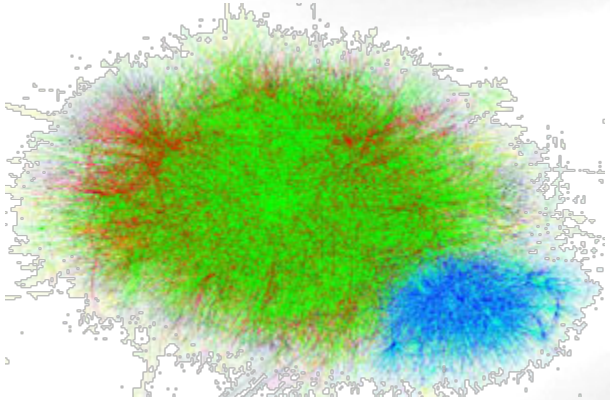

UniProt
Universal Protein Resource
prosite
Fasta
Similarity and Homology Searching
WU-Blast2
Basic Local Alignment Search Tool
IntEnz
SeqVISTA
Pfam
PRINTS
Protein Fingerprints Database
InterPro
GENOMES
ClustalW
Multiple Sequence Alignment Tool
emboss
CAST
ProDom
SMART
Alternative Splicing Database
CSA
Catalytic Site Atlas
PDBj
Protein Data Bank Japan
TIGR
tigr fams
PANTHER
Cassification System
caBIG
SeqHound
PIRSF
Gene3D
BioLayout
NCBI
LION
caBIO
Superfamily
SCOP
BALI
GeneQuiz
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health
MOUNT SINAI HOSPITAL
CATH
Protein Structure Classification
MSD
Ensembl
Parasite Blast
DDBJ
DNA Data Bank of Japan
wellcome trust
sanger
institute
SWISS-MODEL
MODBASE
GENOME REVIEWS
iUPHAR
KEGG
Kyoto Encyclopedia of Genes and Genomes
PathPort
The Pathogen Portal Web Project

ANALYSIS AND INTERPRETATION

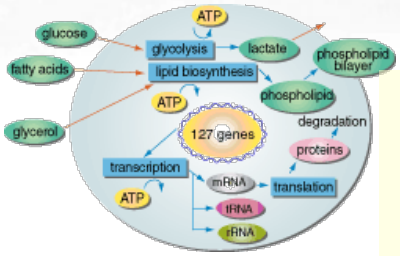


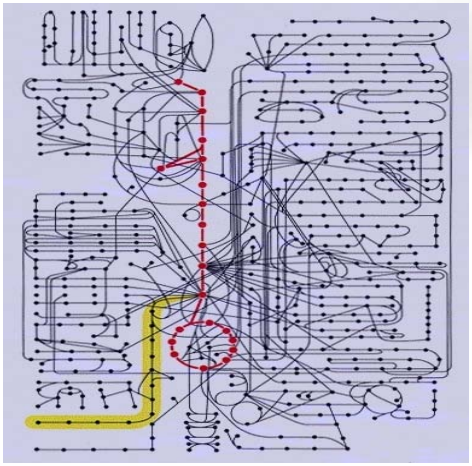
AGAGTTCTGCTCG

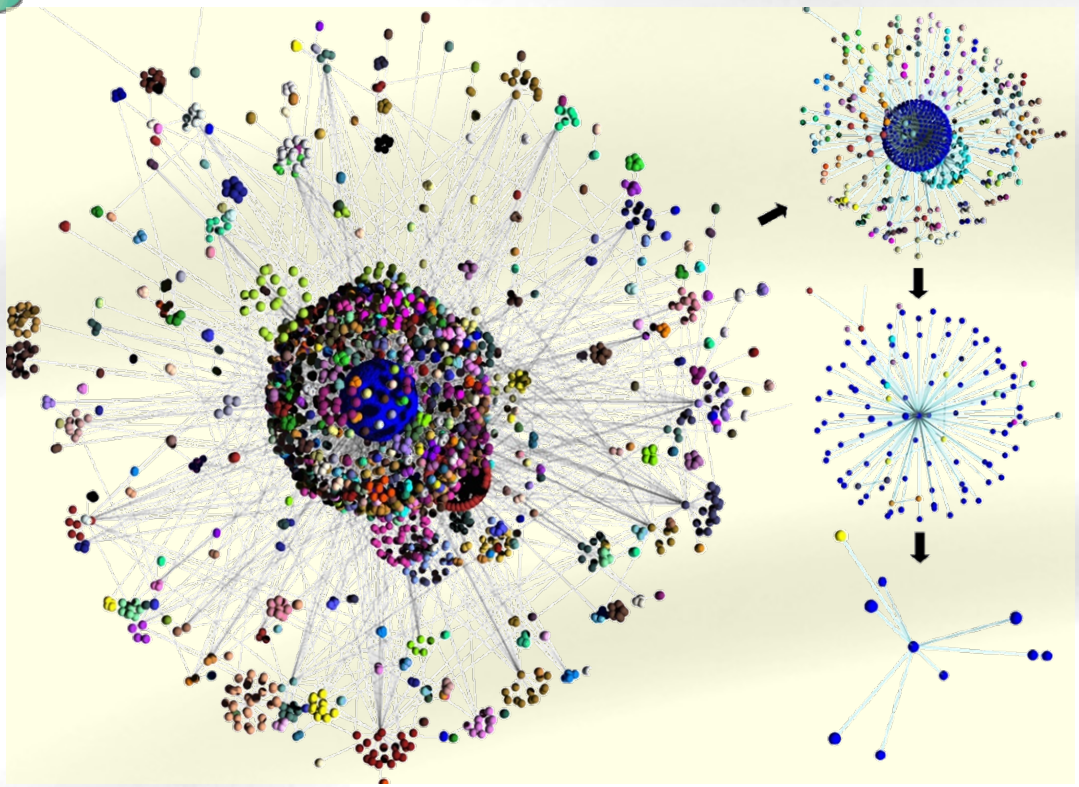
AGGGTTATGCGCG



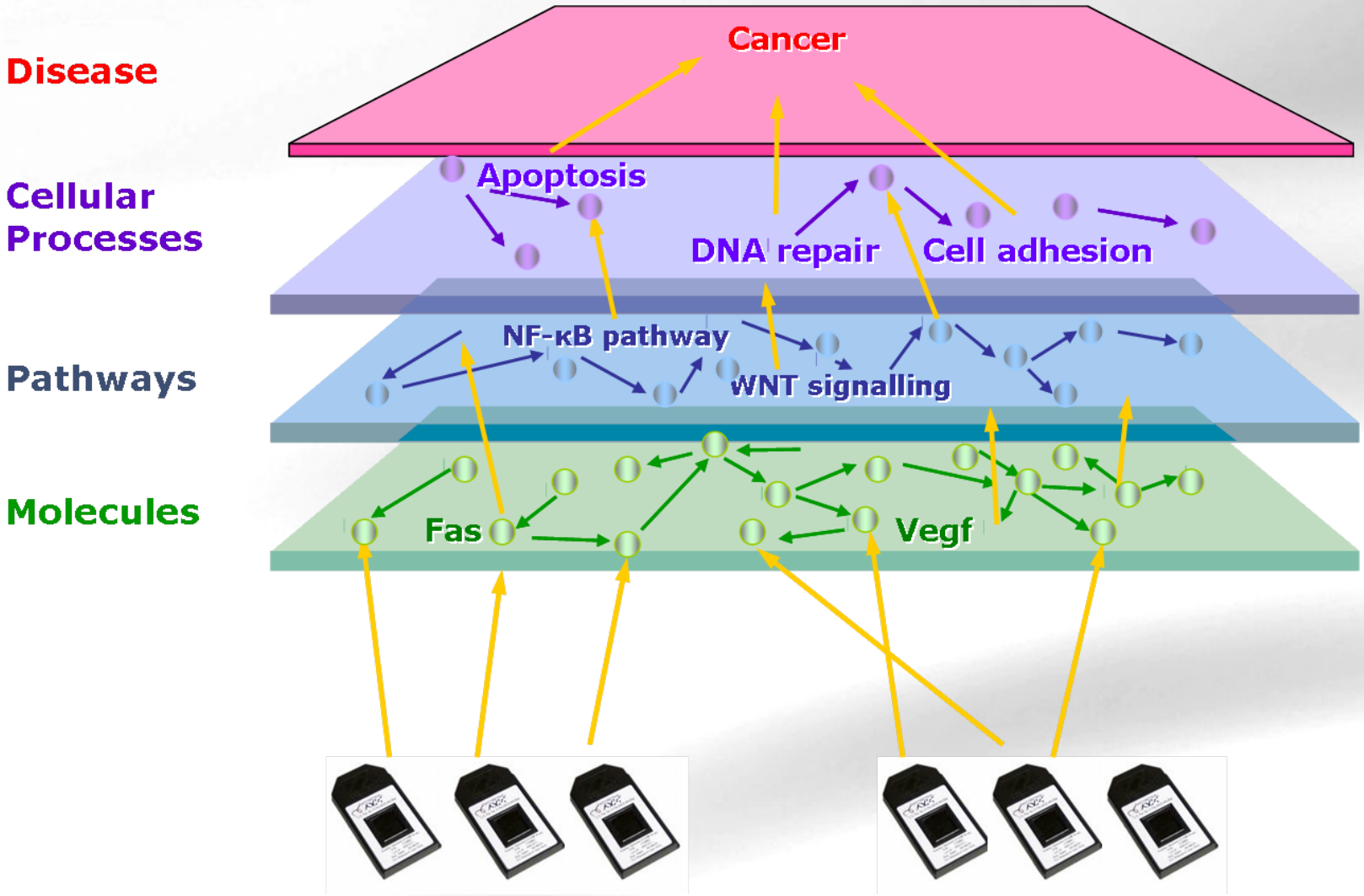
SYSTEMS BIOLOGY MODELING





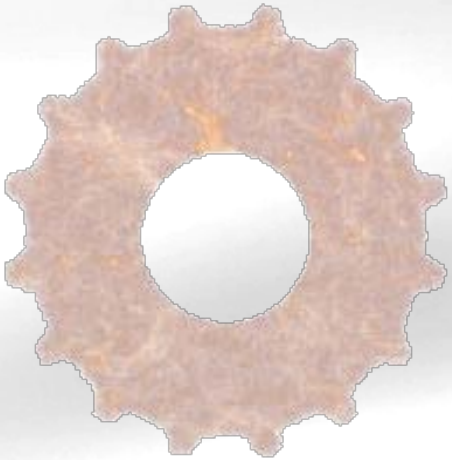


INTEGRATIVE BIOINFORMATICS

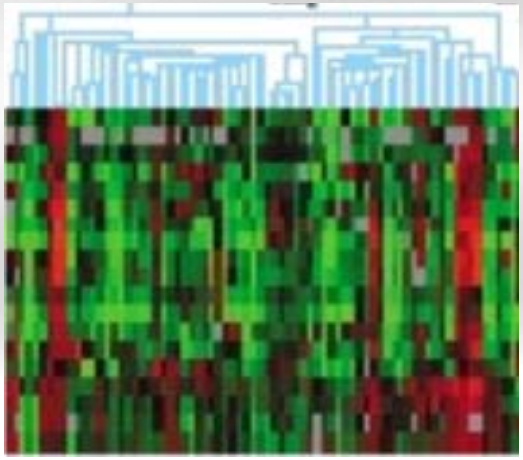


IN SUMMARY…

Data



Bioinformatics tools and resources



Knowledge

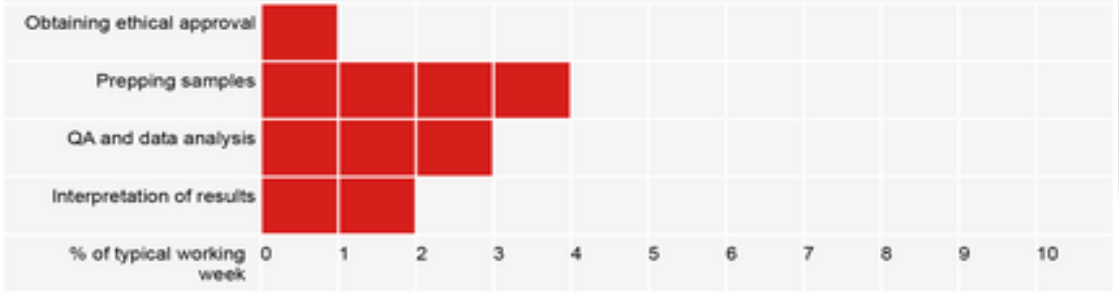
How does one do bioinformatics?

Leon (bioinformatics user)

Leon is on his second postdoctoral fellowship, working on quorum sensing in bacteria. "I'm using a combination of transcriptomics, proteomics and metabolomics to understand these pathogenic changes better" he explains. "I end up with big spreadsheets of protein or gene IDs and I'm trying to piece together which signaling pathways are involved in flipping to the pathogenic state". He has been on an introductory Unix course but is much more comfortable with GUIs than with the command line. "I just have a visual brain", he says.

Career timeline

Typical activities



Distribution of time between bench-work and computational work

Preference for using GUI vs command line

Drivers

- Understanding what makes a usually harmless bacterium pathogenic in the lungs of people with cystic fibrosis

Goals

- QA of -omics data
- Statistical analysis of data
- Data integration and pathway analysis

Pain points

- Lack of access to departmental compute farm
- Sporadic to non-existent access to bioinformatics support

•A typical "bioinformatics user."

Welch L, Lewitter F, Schwartz R, Brooksbank C, et al. (2014) Bioinformatics Curriculum Guidelines: Toward a Definition of Core Competencies. PLoS Comput Biol 10(3): e1003496. doi:10.1371/journal.pcbi.1003496 http://www.ploscompbiol.org/article/info:doi/10.1371/journal.pcbi.1003496

PLOS | COMPUTATIONAL BIOLOGY

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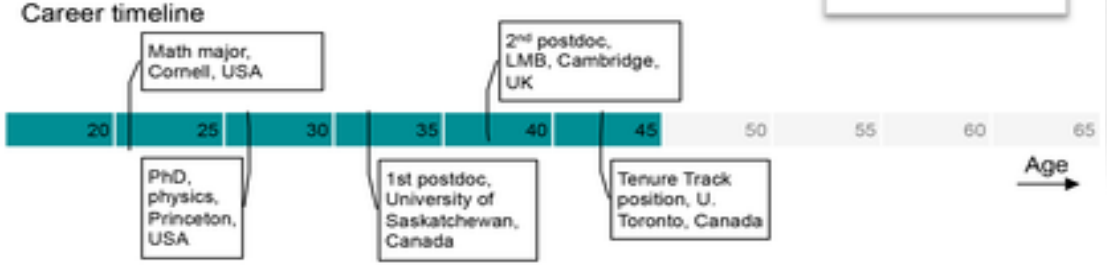
Martha (bioinformatics scientist)

Martha is a senior bioinformatician in an international structural genomics consortium. Her biggest project is on predicting the functions of proteins whose structures have just been solved; she's building a structure-to-function prediction pipeline for the project. This is funded partly by the NIH and partly through industrial funding. She also has a fascination for predicting structure and usually has a student or two working on structural prediction projects.

Career timeline



Typical activities

Distribution of time between bench work and computational work

Preference using for GUI vs command line

Drivers

- Understanding the relationship between sequence, structure and function
- Application to target discovery and validation

Goals

- Create a structure-to-function pipeline for molecular biologists
- Predict structures de novo from models of similar, solved structures

Pain points

- Sometimes the guys in the lab expect her to fix their computers for them
- Finding students and more senior staff with adequate math

•A typical "bioinformatics scientist."

Welch L, Lewitter F, Schwartz R, Brooksbank C, et al. (2014) Bioinformatics Curriculum Guidelines: Toward a Definition of Core Competencies. PLoS Comput Biol 10(3): e1003496. doi:10.1371/journal.pcbi.1003496 http://www.ploscompbiol.org/article/info:doi/10.1371/journal.pcbi.1003496

PLOS | COMPUTATIONAL BIOLOGY

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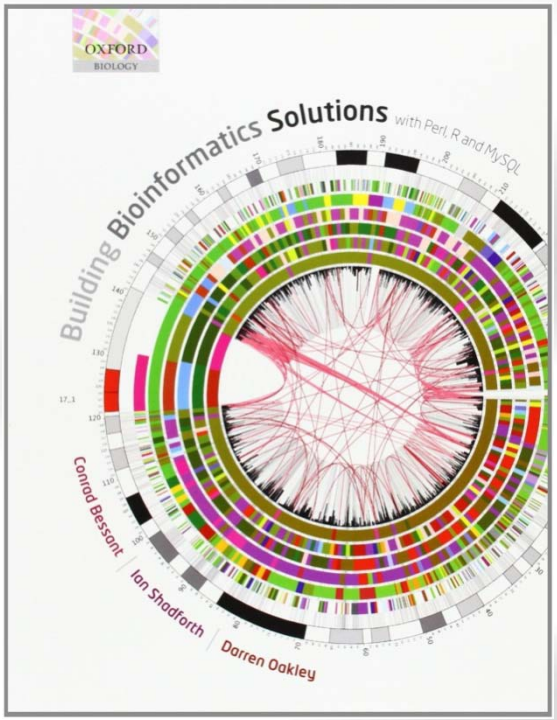
Computer systems for Bioinformatics

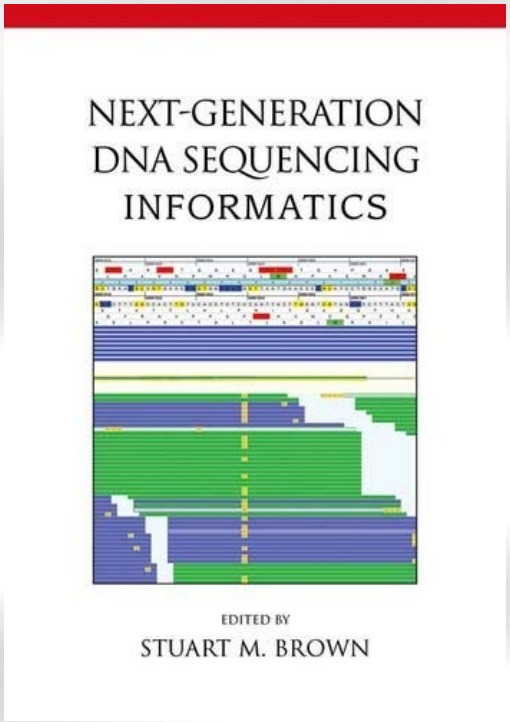
- Bioinformatics has been developped in environment which required …
  - Creating and accessing databases in the web
  - Creating and executing programs in the web
  - Installing and Managing web servers.
  - Ability of file text parsing and batch processing.
  - The need of developping and sharing tools between diverse systems and users.
- Windows was not an option of choice
  - No console (or almost). Difficult to share with non-windows systems. Difficult to scale-up applications.
- Unix/Linux best suited for this purpose

Bioinformatics “computer skills”

- Some consensus on that these include:
  - SQL and knowledge of databases.
  - Perl or Python.
  - basic Linux.
  - basic bash shell scripting.
  - Some experience with Java or other “traditional languages”.
  - R + Bioconductor.

Some references





TO KNOW MORE

- There are a lot of free courses and training activities:
  - EBI's Online training and courses
  - NCBI's tutorials
  - Local training courses
    - Introducción a la Bioinformática (Alex Sánchez, UEB/UB)
    - Invitació a la Bioinformàtica (Plataforma BioinfoUAB)
- A great variety of rerefence books:
    - List of books on bioinformatics
- Scientific Societies and Publications:
  - Bioinformatics, Briefings in Bioinformatics
  - International Society for Computational Biology