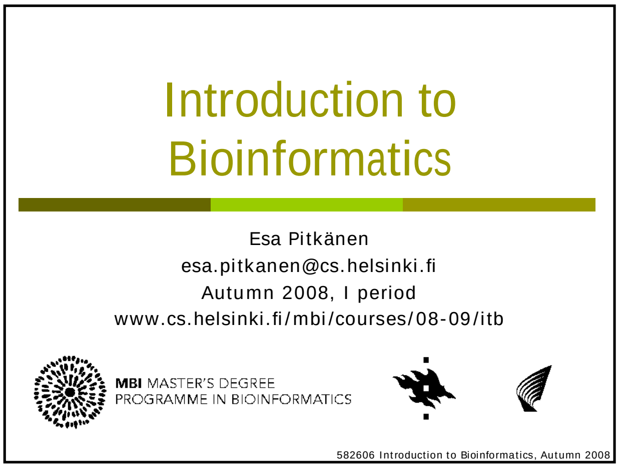
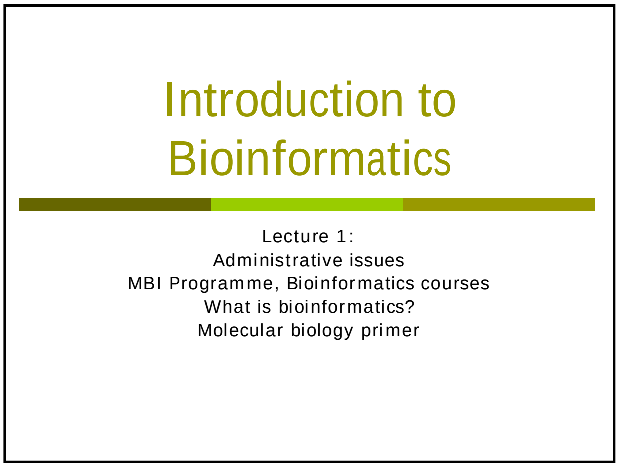


Introduction to Bioinformatics

Esa Pitkänen
esa.pitkanen@cs.helsinki.fi
Autumn 2008, I period
www.cs.helsinki.fi/mbi/courses/08-09/itb

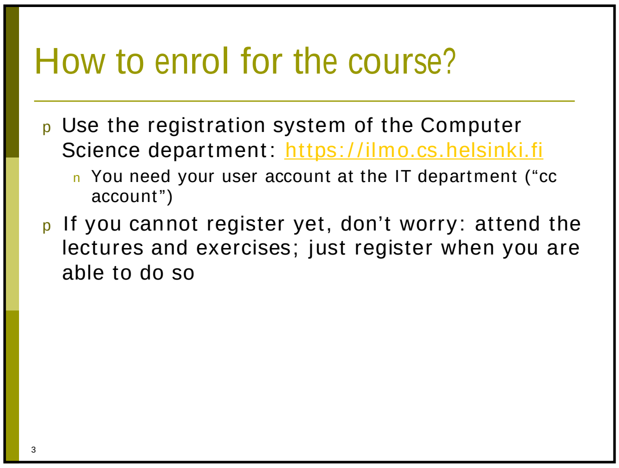
MBI MASTER'S DEGREE
PROGRAMME IN BIOINFORMATICS

582606 Introduction to Bioinformatics, Autumn 2008



Introduction to Bioinformatics

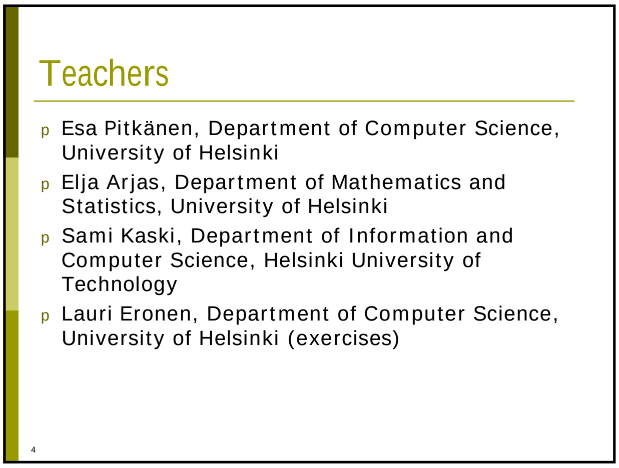
Lecture 1:
Administrative issues
MBI Programme, Bioinformatics courses
What is bioinformatics?
Molecular biology primer



How to enrol for the course?

- Use the registration system of the Computer Science department: https://ilmo.cs.helsinki.fi
  - You need your user account at the IT department ("cc account")
- If you cannot register yet, don't worry: attend the lectures and exercises; just register when you are able to do so

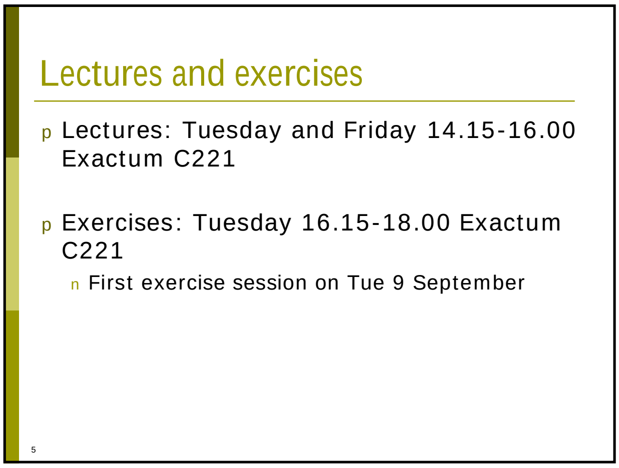
3



Teachers

- Esa Pitkänen, Department of Computer Science, University of Helsinki
- Elja Arjas, Department of Mathematics and Statistics, University of Helsinki
- Sami Kaski, Department of Information and Computer Science, Helsinki University of Technology
- Lauri Eronen, Department of Computer Science, University of Helsinki (exercises)

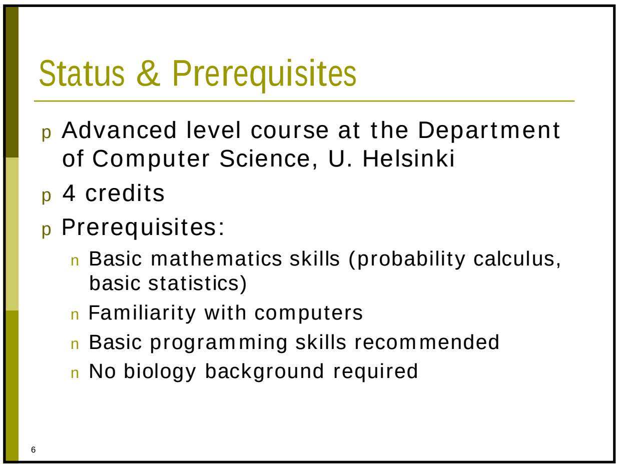
4



Lectures and exercises

- Lectures: Tuesday and Friday 14.15-16.00 Exactum C221
- Exercises: Tuesday 16.15-18.00 Exactum C221
  - First exercise session on Tue 9 September

5



Status & Prerequisites

- Advanced level course at the Department of Computer Science, U. Helsinki
- 4 credits
- Prerequisites:
  - Basic mathematics skills (probability calculus, basic statistics)
  - Familiarity with computers
  - Basic programming skills recommended
  - No biology background required

6

Course contents

- What is bioinformatics?
- Molecular biology primer
- Biological words
- Sequence assembly
- Sequence alignment
- Fast sequence alignment using FASTA and BLAST
- Genome rearrangements
- Motif finding (tentative)
- Phylogenetic trees
- Gene expression analysis

How to pass the course?

- Recommended method:
  - Attend the lectures (not obligatory though)
  - Do the exercises
  - Take the course exam
- Or:
  - Take a separate exam

How to pass the course?

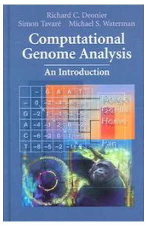
- Exercises give you max. 12 points
  - 0% completed assignments gives you 0 points, 80% gives 12 points, the rest by linear interpolation
  - “A completed assignment” means that
    - You are willing to present your solution in the exercise session and
    - You return notes by e-mail to Lauri Eronen (see course web page for contact info) describing the main phases you took to solve the assignment
  - Return notes at latest on Tuesdays 16.15
- Course exam gives you max. 48 points

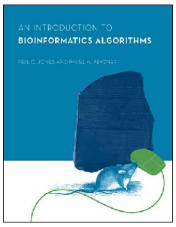
How to pass the course?

- Grading: on the scale 0-5
  - To get the lowest passing grade 1, you need to get at least 30 points out of 60 maximum
- Course exam: Wed 15 October 16.00-19.00 Exactum A111
- See course web page for separate exams
- Note: if you take the first separate exam, the best of the following options will be considered:
  - Exam gives you 48 points, exercises 12 points
  - Exam gives you 60 points
- In second and subsequent separate exams, only the 60 point option is in use

Literature

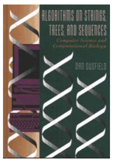
- Deonier, Tavaré, Waterman: Computational Genome Analysis, an Introduction. Springer, 2005
- Jones, Pevzner: An Introduction to Bioinformatics Algorithms. MIT Press, 2004
- Slides for some lectures will be available on the course web page

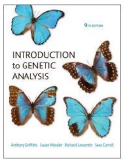

Richard C. Deonier
Simon Tavaré Michael S. Waterman
Computational Genome Analysis
An Introduction

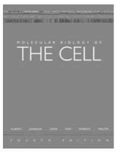


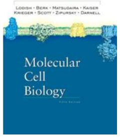
Additional literature

- Gusfield: Algorithms on strings, trees and sequences
- Griffiths et al: Introduction to genetic analysis
- Alberts et al.: Molecular biology of the cell
- Lodish et al.: Molecular cell biology
- Check the course web site









Questions about administrative & practical stuff?

13

Master's Degree Programme in Bioinformatics (MBI)

- Two-year MSc programme
- Admission for 2009-2010 in January 2009
  - You need to have your Bachelor's degree ready by August 2009

MBI MASTER'S DEGREE PROGRAMME IN BIOINFORMATICS

www.cs.helsinki.fi/mbi

News and Events

MBI programme organizers

Department of Computer Science,
Department of Mathematics and Statistics
Faculty of Science, Kumpula Campus, HY

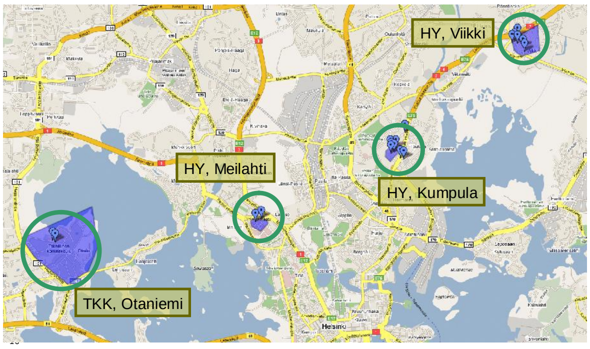
Laboratory of Computer and
Information Science, Laboratory of
CS and Engineering,TKK

Faculty of Biosciences
Faculty of Agriculture and Forestry
Viikki Campus, HY

Faculty of Medicine, Meilahti Campus, HY

15

Four MBI campuses



MBI highlights

- You can take courses from both HY and TKK
- Two biology courses tailored specifically for MBI
- Bioinformatics is a new exciting field, with a high demand for experts in job market

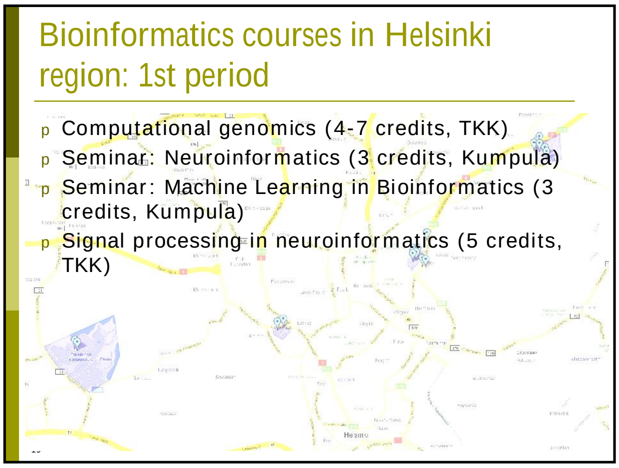
- Go to www.cs.helsinki.fi/mbi/careers to find out what a bioinformatician could do for living

17

Admission

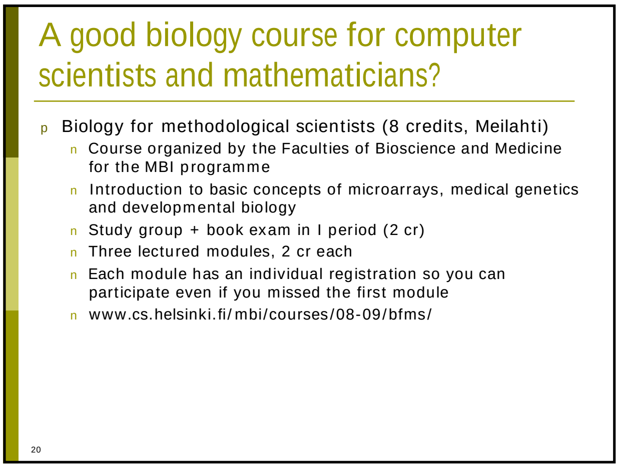
- Admission requirements
  - Bachelor's degree in a suitable field (e.g., computer science, mathematics, statistics, biology or medicine)
  - At least 60 ECTS credits in total in computer science, mathematics and statistics
  - Proficiency in English (standardized language test: TOEFL, IELTS)
- Admission period opens in late Autumn 2009 and closes in 2 February 2009
- Details on admission will be posted in www.cs.helsinki.fi/mbi during this autumn

18



Bioinformatics courses in Helsinki region: 1st period

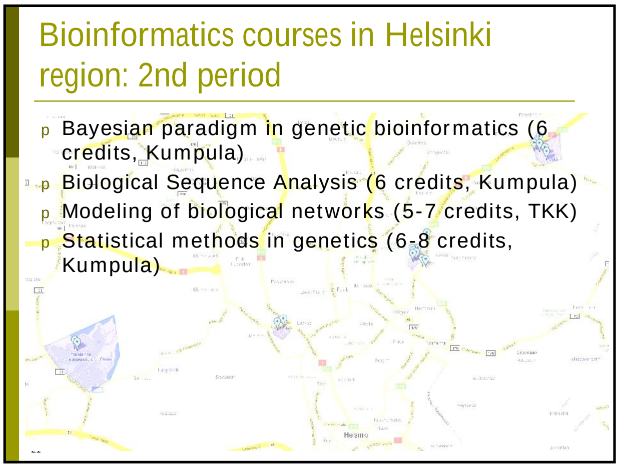
- Computational genomics (4-7 credits, TKK)
- Seminar: Neuroinformatics (3 credits, Kumpula)
- Seminar: Machine Learning in Bioinformatics (3 credits, Kumpula)
- Signal processing in neuroinformatics (5 credits, TKK)



A good biology course for computer scientists and mathematicians?

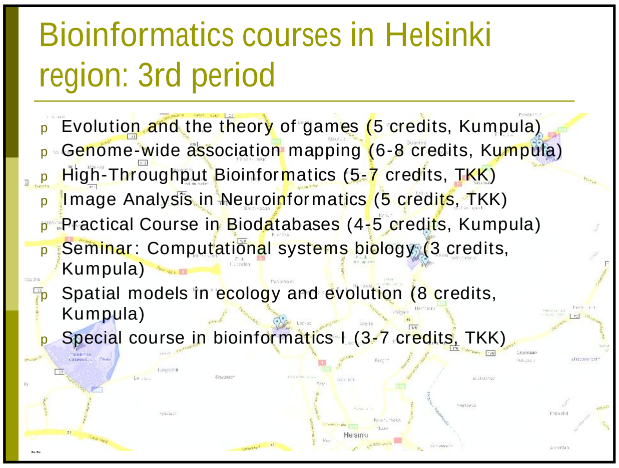
- Biology for methodological scientists (8 credits, Meilahti)
  - Course organized by the Faculties of Bioscience and Medicine for the MBI programme
  - Introduction to basic concepts of microarrays, medical genetics and developmental biology
  - Study group + book exam in I period (2 cr)
  - Three lectured modules, 2 cr each
  - Each module has an individual registration so you can participate even if you missed the first module
  - www.cs.helsinki.fi/mbi/courses/08-09/bfms/

20



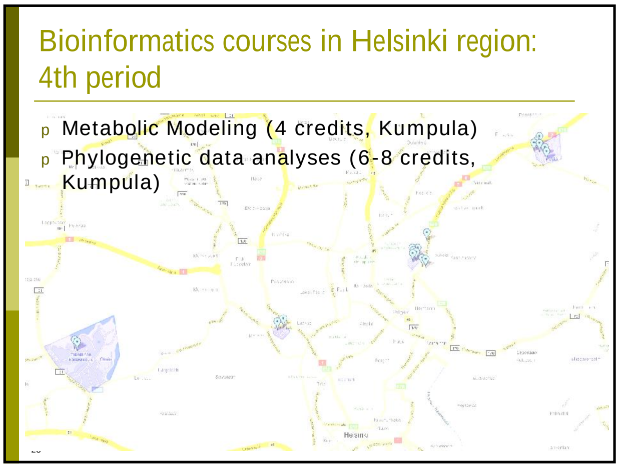
Bioinformatics courses in Helsinki region: 2nd period

- Bayesian paradigm in genetic bioinformatics (6 credits, Kumpula)
- Biological Sequence Analysis (6 credits, Kumpula)
- Modeling of biological networks (5-7 credits, TKK)
- Statistical methods in genetics (6-8 credits, Kumpula)



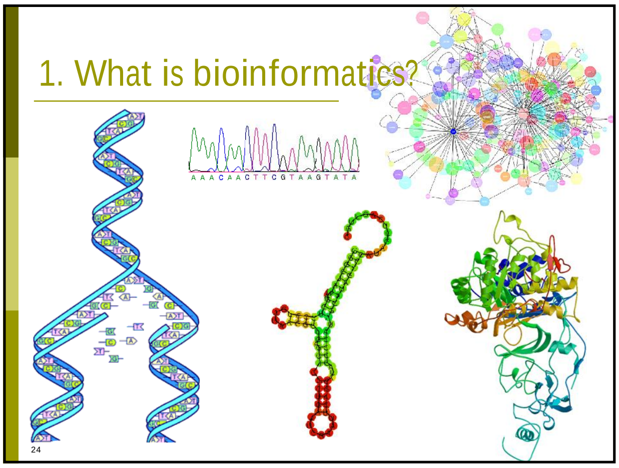
Bioinformatics courses in Helsinki region: 3rd period

- Evolution and the theory of games (5 credits, Kumpula)
- Genome-wide association mapping (6-8 credits, Kumpula)
- High-Throughput Bioinformatics (5-7 credits, TKK)
- Image Analysis in Neuroinformatics (5 credits, TKK)
- Practical Course in Biodatabases (4-5 credits, Kumpula)
- Seminar: Computational systems biology (3 credits, Kumpula)
- Spatial models in ecology and evolution (8 credits, Kumpula)
- Special course in bioinformatics I (3-7 credits, TKK)



Bioinformatics courses in Helsinki region: 4th period

- Metabolic Modeling (4 credits, Kumpula)
- Phylogenetic data analyses (6-8 credits, Kumpula)



1. What is bioinformatics?

24

What is bioinformatics?

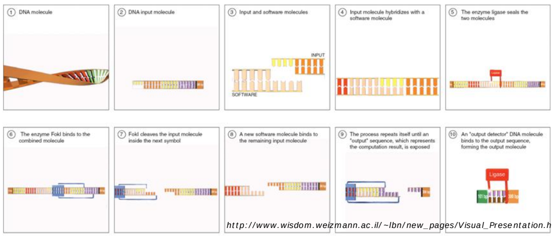
- Bioinformatics, *n.* The science of information and information flow in biological systems, esp. of the use of computational methods in genetics and genomics. (Oxford English Dictionary)
- "The mathematical, statistical and computing methods that aim to solve biological problems using DNA and amino acid sequences and related information." -- Fredj Tekaia

What is bioinformatics?

- "I do not think all biological computing is bioinformatics, e.g. mathematical modelling is not bioinformatics, even when connected with biology-related problems. In my opinion, bioinformatics has to do with management and the subsequent use of biological information, particular genetic information."
  -- Richard Durbin

What is *not* bioinformatics?

- Biologically-inspired computation, e.g., genetic algorithms and neural networks
- However, application of neural networks to solve some biological problem, could be called bioinformatics
- What about DNA computing?



① DNA molecule
② DNA input molecule
③ Input and software molecules
INPUT
SOFTWARE
④ Input molecule hybridizes with a software molecule
⑤ The enzyme ligase seals the two molecules
⑥ The enzyme FokI binds to the combined molecule
⑦ FokI cleaves the input molecule inside the next symbol
⑧ A new software molecule binds to the remaining input molecule
⑨ The process repeats itself until an "output" sequence, which represents the computation result, is exposed
⑩ An "output detector" DNA molecule binds to the output sequence, forming the output molecule
Ligase

http://www.wisdom.weizmann.ac.il/~lbn/new_pages/Visual_Presentation.html

Computational biology

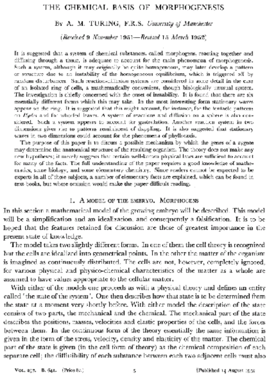
- Application of computing to biology (broad definition)
- Often used interchangeably with bioinformatics
- Or: *Biology* that is done with computational means

Biometry & biophysics

- Biometry: the statistical analysis of biological data
  - Sometimes also the field of identification of individuals using biological traits (a more recent definition)
- Biophysics: "an interdisciplinary field which applies techniques from the physical sciences to understanding biological structure and function" -- British Biophysical Society

Mathematical biology

- Mathematical biology "tackles biological problems, but the methods it uses to tackle them need not be numerical and need not be implemented in software or hardware."
  -- Damian Counsell



THE CHEMICAL BASIS OF MORPHOGENESIS

BY A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

The purpose of this paper is to discuss a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism. The theory does not make any new hypotheses; it merely suggests that certain well-known physical laws are sufficient to account for many of the facts. The full understanding of the paper requires a good knowledge of mathematics, some biology, and some elementary chemistry. Since readers cannot be expected to be experts in all of these subjects, a number of elementary facts are explained, which can be found in text-books, but whose omission would make the paper difficult reading.

1. A MODEL OF THE EMBRYO. MORPHOGENS

In this section a mathematical model of the growing embryo will be described. This model will be a simplification and an idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge.

The model takes two slightly different forms. In one of them the cell theory is recognized but the cells are idealized into geometrical points. In the other the matter of the organism is imagined as continuously distributed. The cells are not, however, completely ignored, for various physical and physico-chemical characteristics of the matter as a whole are assumed to have values appropriate to the cellular matter.

With either of the models one proceeds as with a physical theory and defines an entity called 'the state of the system'. One then describes how that state is to be determined from the state at a moment very shortly before. With either model the description of the state consists of two parts, the mechanical and the chemical. The mechanical part of the state describes the positions, masses, velocities and elastic properties of the cells, and the forces between them. In the continuous form of the theory essentially the same information is given in the form of the stress, velocity, density and elasticity of the matter. The chemical part of the state is given (in the cell form of theory) as the chemical composition of each separate cell; the diffusibility of each substance between each two adjacent cells must also

Vol. 237. B. 641. (Price 8s.) 5 [Published 14 August 1952

Alan Turing

Turing on biological complexity

- "It must be admitted that the biological examples which it has been possible to give in the present paper are very limited.

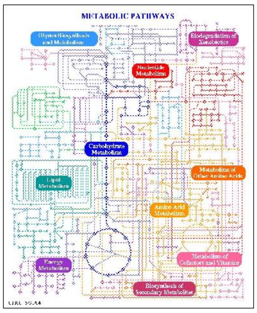
  This can be ascribed quite simply to the fact that biological phenomena are usually very complicated. Taking this in combination with the relatively elementary mathematics used in this paper one could hardly expect to find that many observed biological phenomena would be covered.

  It is thought, however, that the imaginary biological systems which have been treated, and the principles which have been discussed, should be of some help in interpreting real biological forms."

  – Alan Turing, The Chemical Basis of Morphogenesis, 1952

Related concepts

- Systems biology
  - "Biology of networks"
  - Integrating different levels of information to understand how biological systems work
- Computational systems biology



Overview of metabolic pathways in KEGG database, www.genome.jp/kegg/

Why is bioinformatics important?

- New measurement techniques produce huge quantities of biological data
  - Advanced data analysis methods are needed to make sense of the data
  - Typical data sources produce noisy data with a lot of missing values
- Paradigm shift in biology to utilise bioinformatics in research

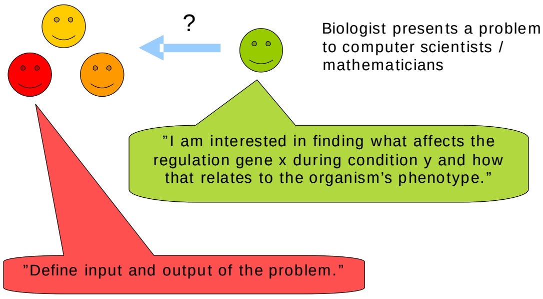
Bioinformatician's skill set

- Statistics, data analysis methods
  - Lots of data
  - High noise levels, missing values
  - #attributes >> #data points
- Programming languages
  - Scripting languages: Python, Perl, Ruby, …
  - Extensive use of text file formats: need parsers
  - Integration of both data and tools
- Data structures, databases

Bioinformatician's skill set

- Modelling
  - Discrete vs continuous domains
  - -> Systems biology
- Scientific computation packages
  - R, Matlab/Octave, …
- Communication skills!

Communication skills: case 1



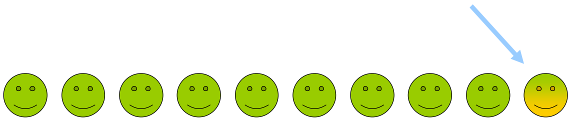
Biologist presents a problem to computer scientists / mathematicians

"I am interested in finding what affects the regulation gene x during condition y and how that relates to the organism's phenotype."

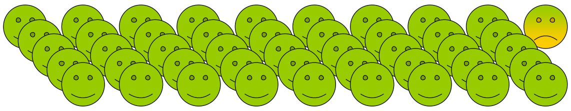
"Define input and output of the problem."

Communication skills: case 2

Bioinformatician is a part of a group that consists mostly of biologists.

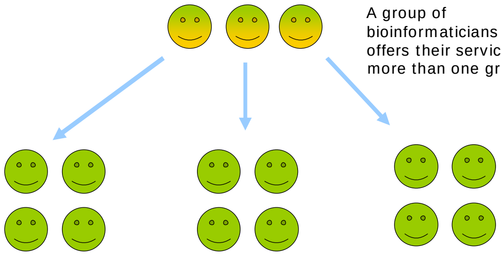


Communication skills: case 2



...biologist/bioinformatician ratio is important!

Communication skills: case 3

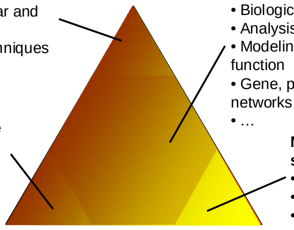


A group of bioinformaticians offers their services to more than one group

Bioinformatician's skill set

- How much biology you should know?

Bioinformatician's skill set



Biology & Medicine
- Basics in molecular and cell biology
- Measurement techniques

Computer Science
- Programming
- Databases
- Algorithmics

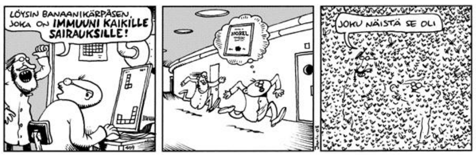
Bioinformatics
- Biological sequence analysis
- Biological databases
- Analysis of gene expression
- Modeling protein structure and function
- Gene, protein and metabolic networks
- ...

Mathematics and statistics
- Calculus
- Probability calculus
- Linear algebra

Where would you be in this triangle?

Prof. Juho Rousu, 2006

A problem involving bioinformatics?

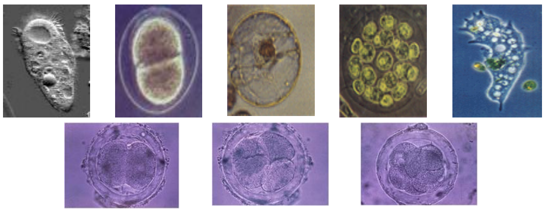

LÖYSIN BANAANIKÄRPÄSEN, JOKA ON IMMUUNI KAIKILLE SAIRAUKSILLE!
NOBEL
JOKU NÄISTÄ SE OLI

- "I found a fruit fly that is immune to all diseases!"

- "It was one of these"

Pertti Jarla, http://www.hs.fi/fingerpori/

Molecular biology primer

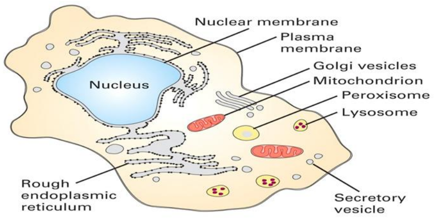


Molecular Biology Primer by Angela Brooks, Raymond Brown, Calvin Chen, Mike Daly, Hoa Dinh, Erinn Hama, Robert Hinman, Julio Ng, Michael Sneddon, Hoa Troung, Jerry Wang, Che Fung Yung
Edited for Introduction to Bioinformatics (Autumn 2007, Summer 2008, Autumn 2008) by Esa Pitkänen

Molecular biology primer

- Part 1: What is life made of?
- Part 2: Where does the variation in genomes come from?

Life begins with Cell

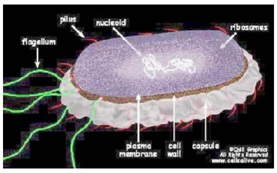


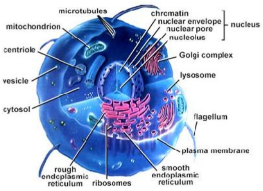
- A cell is a smallest structural unit of an organism that is capable of independent functioning
- All cells have some common features

Cells

- Fundamental working units of every living system.
- Every organism is composed of one of two radically different types of cells:
  - prokaryotic cells or
  - eukaryotic cells.
- Prokaryotes and Eukaryotes are descended from the same primitive cell.
  - All prokaryotic and eukaryotic cells are the result of a total of 3.5 billion years of evolution.

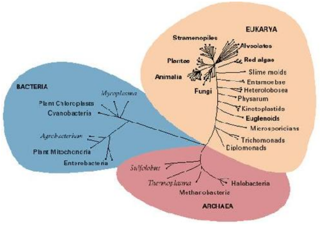
Two types of cells: Prokaryotes and Eukaryotes





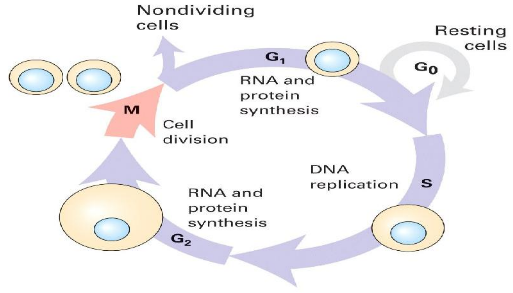
Prokaryotes and Eukaryotes

- According to the most recent evidence, there are three main branches to the tree of life
- Prokaryotes include Archaea (“ancient ones”) and bacteria
- Eukaryotes are kingdom Eukarya and includes plants, animals, fungi and certain algae



► Lecture: Phylogenetic trees

All Cells have common Cycles



- Born, eat, replicate, and die

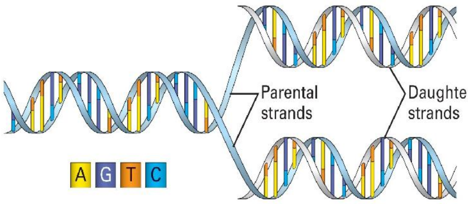
Common features of organisms

- Chemical energy is stored in ATP
- Genetic information is encoded by DNA
- Information is transcribed into RNA
- There is a common triplet genetic code
- Translation into proteins involves ribosomes
- Shared metabolic pathways
- Similar proteins among diverse groups of organisms

All Life depends on 3 critical molecules

- DNAs (Deoxyribonucleic acid)
  - Hold information on how cell works
- RNAs (Ribonucleic acid)
  - Act to transfer short pieces of information to different parts of cell
  - Provide templates to synthesize into protein
- Proteins
  - Form enzymes that send signals to other cells and regulate gene activity
  - Form body’s major components (e.g. hair, skin, etc.)
  - “Workhorses” of the cell

DNA: The Code of Life

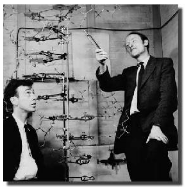


- The structure and the four genomic letters code for all living organisms
- Adenine, Guanine, Thymine, and Cytosine which pair A-T and C-G on complimentary strands.

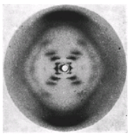
► Lecture: Genome sequencing and assembly

Discovery of the structure of DNA

- 1952-1953 James D. Watson and Francis H. C. Crick deduced the double helical structure of DNA from X-ray diffraction images by Rosalind Franklin and data on amounts of nucleotides in DNA



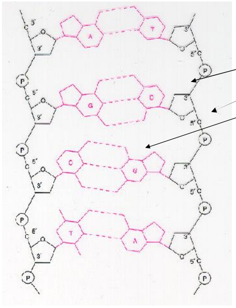
James Watson and Francis Crick



”Photo 51”

Rosalind Franklin

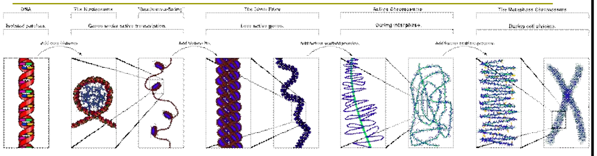
DNA, continued



- DNA has a double helix structure which is composed of
  - sugar molecule
  - phosphate group
  - and a base (A,C,G,T)
- By convention, we read DNA strings in direction of transcription: from 5’ end to 3’ end

5’ ATTTAGGCC 3’
3’ TAAATCCGG 5’

DNA is contained in chromosomes

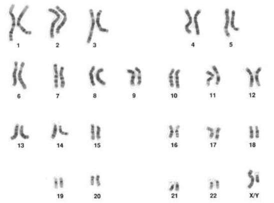


- In eukaryotes, DNA is packed into *chromatids*
  - In metaphase, the "X" structure consists of two identical chromatids
- In prokaryotes, DNA is usually contained in a single, circular chromosome

http://en.wikipedia.org/wiki/Image:Chromatin_Structures.png

Human chromosomes

- Somatic cells in humans have 2 pairs of 22 chromosomes + XX (female) or XY (male) = total of 46 chromosomes
- Germline cells have 22 chromosomes + either X or Y = total of 23 chromosomes



Karyogram of human male using Giemsa staining
(http://en.wikipedia.org/wiki/Karyotype)

Length of DNA and number of chromosomes

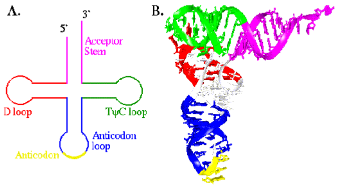
Organism	#base pairs	#chromosomes (germline)
Prokaryotic		
Escherichia coli (bacterium)	4×10^6	1
Eukaryotic		
Saccharomyces cerevisia (yeast)	1.35×10^7	17
Drosophila melanogaster (insect)	1.65×10^8	4
Homo sapiens (human)	2.9×10^9	23
Zea mays (corn / maize)	5.0×10^9	10

Hepatitis delta virus, complete genome

```
   1 atgagccaag ttccgaacaa ggattcgcgg ggaggataga tcagcgcccg agaggggtga
  61 gtcggtaaag agcattggaa cgtcggagat acaactccca agaaggaaaa aagagaaagc
 121 aagaagcgga tgaatttccc cataacgcca gtgaaactct aggaagggga aagagggaag
 181 gtggaagaga aggaggcggg cctcccgatc cgaggggccc ggcggccaag tttggaggac
 241 actccggccc gaagggttga gagtacccca gagggaggaa gccacacgga gtagaacaga
 301 gaaatcacct ccagaggacc ccttcagcga acagagagcg catcgcgaga gggagtagac
 361 catagcgata ggaggggatg ctaggagttg ggggagaccg aagcgaggag gaaagcaaag
 421 agagcagcgg ggctagcagg tgggtgttcc gcccccgag aggggacgag tgaggcttat
 481 cccggggaac tcgacttatc gtccccacat agcagactcc cggacccct ttcaaagtga
 541 ccgaggggg tgactttgaa cattggggac cagtggagcc atgggatgct cctcccgatt
 601 ccgcccaagc tccttccccc caagggtcgc ccaggaatgg cgggacccca ctctgcaggg
 661 tccgcgttcc atcctttctt acctgatggc cggcatggtc ccagcctcct cgctggcgcc
 721 ggctgggcaa cattccgagg ggaccgtccc ctcggtaatg gcgaatggga cccacaaatc
 781 tctctagctt cccagagaga agcgagagaa aagtggctct cccttagcca tccgagtgga
 841 cgtgcgtcct ccttcggatg cccaggtcgg accgcgagga ggtggagatg ccatgccgac
 901 ccgaagagga aagaaggacg cgagacgcaa acctgcgagt ggaaacccgc tttattcact
 961 ggggtcgaca actctgggga gaggagggag ggtcggctgg gaagagtata tcctatggga
1021 atccctggct tccccttatg tccagtccct ccccggtccg agtaaagggg gactccggga
1081 ctccttgcat gctggggacg aagccgcccc cgggcgctcc cctcgttcca ccttcgaggg
1141 ggttcacacc cccaacctgc gggccggcta ttcttctttc ccttctctcg tcttcctcgg
1201 tcaacctcct aagttcctct tcctcctcct tgctgaggtt ctttcccccc gccgatagct
1261 gctttctctt gttctcgagg gccttccttc gtcggtgatc ctgcctctcc ttgtcggtga
1321 atcctcccct ggaaggcctc ttcctaggtc cggagtctac ttccatctgg tccgttcggg
1381 ccctcttcgc cgggggagcc ccctctccat ccttatcttt ctttccgaga attcctttga
1441 tgtttcccag ccagggatgt tcatcctcaa gtttcttgat tttcttctta accttccgga
1501 ggtctctctc gagttcctct aacttctttc ttccgctcac ccactgctcg agaacctctt
1561 ctctcccccc gcggttttc cttccttcgg gccggctcat cttcgactag aggcgacggt
1621 cctcagtact cttactcttt tctgtaaaga ggagactgct ggccctgtcg cccaagttcg
1681 ag
```

RNA

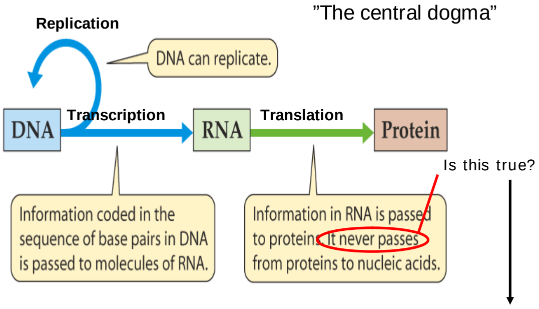
- RNA is similar to DNA chemically. It is usually only a single strand. T(hyamine) is replaced by U(racil)
- Several types of RNA exist for different functions in the cell.



tRNA linear and 3D view: http://www.cgl.ucsf.edu/home/glasfeld/tutorial/trna/trna.gif

DNA, RNA, and the Flow of Information

"The central dogma"



Replication

DNA can replicate.

DNA

Transcription

RNA

Translation

Protein

Information coded in the sequence of base pairs in DNA is passed to molecules of RNA.

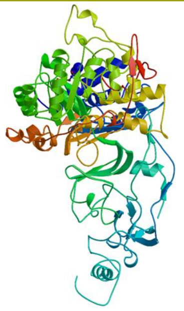
Information in RNA is passed to proteins. It never passes from proteins to nucleic acids.

Is this true?

Denis Noble: The principles of Systems Biology illustrated using the virtual heart
http://velblod.videolectures.net/2007/pascal/eccs07_dresden/noble_denis/eccs07_noble_psb_01.ppt

Proteins

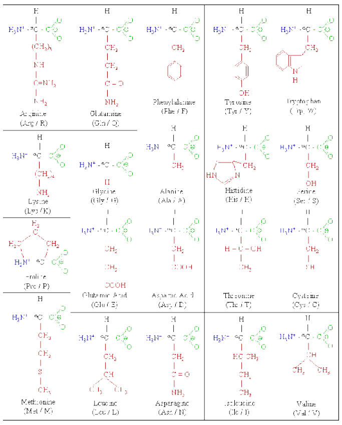
- Proteins are polypeptides (strings of amino acid residues)
- Represented using strings of letters from an alphabet of 20: AEGLV…WKKLAG
- Typical length 50…1000 residues



Urease enzyme from Helicobacter pylori

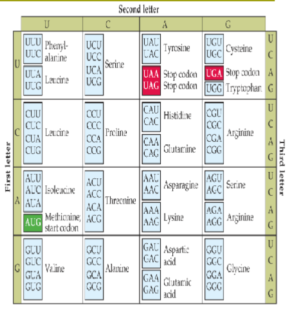
Amino acids

http://upload.wikimedia.org/wikipedia/commons/c/c5/Amino_acids_2.png



How DNA/RNA codes for protein?

- DNA alphabet contains four letters but must specify protein, or polypeptide sequence of 20 letters.
- Dinucleotides are not enough: $4^2 = 16$ possible dinucleotides
- Trinucleotides (triplets) allow $4^3 = 64$ possible trinucleotides
- Triplets are also called *codons*

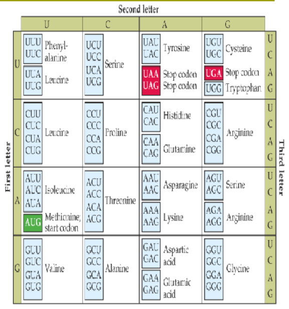


Second letter

First letter	U	C	A	G	Third letter
U	UUU Phenylalanine	UCU Serine	UAU Tyrosine	UGU Cysteine	U
	UUC	UCC	UAC	UGC	C
	UUA Leucine	UCA	UAA Stop codon	UGA Stop codon	A
	UUG	UCG	UAG Stop codon	UGG Tryptophan	G
C	CUU Leucine	CCU Proline	CAU Histidine	CGU Arginine	U
	CUC	CCC	CAC	CGC	C
	CUA	CCA	CAA Glutamine	CGA	A
	CUG	CCG	CAG	CGG	G
A	AUU Isoleucine	ACU Threonine	AAU Asparagine	AGU Serine	U
	AUC	ACC	AAC	AGC	C
	AUA	ACA	AAA Lysine	AGA Arginine	A
	AUG Methionine; start codon	ACG	AAG	AGG	G
G	GUU Valine	GCU Alanine	GAU Aspartic acid	GGU Glycine	U
	GUC	GCC	GAC	GGC	C
	GUA	GCA	GAA Glutamic acid	GGA	A
	GUG	GCG	GAG	GGG	G

How DNA/RNA codes for protein?

- Three of the possible triplets specify ”stop translation”
- Translation usually starts at triplet AUG (this codes for methionine)
- Most amino acids may be specified by more than triplet
- How to find a gene? Look for start and stop codons (not that easy though)



Second letter

First letter	U	C	A	G	Third letter
U	UUU Phenylalanine	UCU Serine	UAU Tyrosine	UGU Cysteine	U
	UUC	UCC	UAC	UGC	C
	UUA Leucine	UCA	UAA Stop codon	UGA Stop codon	A
	UUG	UCG	UAG Stop codon	UGG Tryptophan	G
C	CUU Leucine	CCU Proline	CAU Histidine	CGU Arginine	U
	CUC	CCC	CAC	CGC	C
	CUA	CCA	CAA Glutamine	CGA	A
	CUG	CCG	CAG	CGG	G
A	AUU Isoleucine	ACU Threonine	AAU Asparagine	AGU Serine	U
	AUC	ACC	AAC	AGC	C
	AUA	ACA	AAA Lysine	AGA Arginine	A
	AUG Methionine; start codon	ACG	AAG	AGG	G
G	GUU Valine	GCU Alanine	GAU Aspartic acid	GGU Glycine	U
	GUC	GCC	GAC	GGC	C
	GUA	GCA	GAA Glutamic acid	GGA	A
	GUG	GCG	GAG	GGG	G

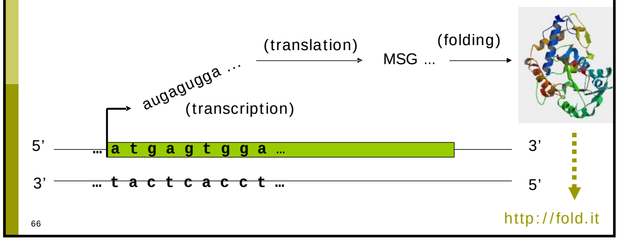
Proteins: Workhorses of the Cell

- 20 different amino acids
  - different chemical properties cause the protein chains to fold up into specific three-dimensional structures that define their particular functions in the cell.
- Proteins do all essential work for the cell
  - build cellular structures
  - digest nutrients
  - execute metabolic functions
  - mediate information flow within a cell and among cellular communities.
- Proteins work together with other proteins or nucleic acids as "molecular machines"
  - structures that fit together and function in highly specific, lock-and-key ways.

► Lecture 8: Proteomics

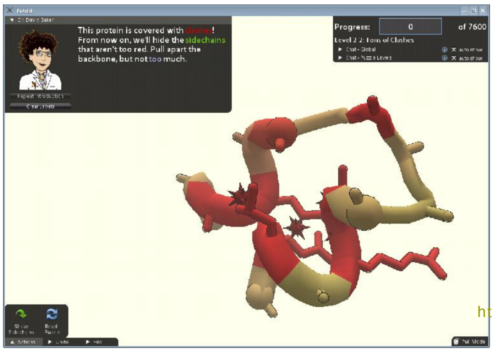
Genes

- “A gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products” --Gerstein et al.
- A DNA segment whose information is expressed either as an RNA molecule or protein



http://fold.it

FoldIt: Protein folding game



This protein is covered with clashes! From now on, we'll hide the sidechains that aren't too red. Pull apart the backbone, but not too much.

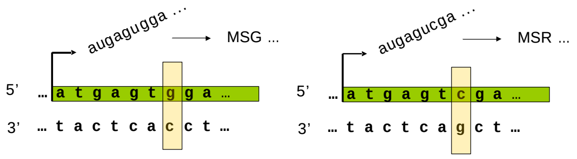
Progress: 0 of 7600

Level 2-2: Tons of Clashes

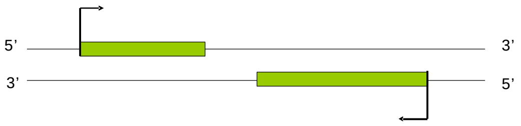
http://fold.it

Genes & alleles

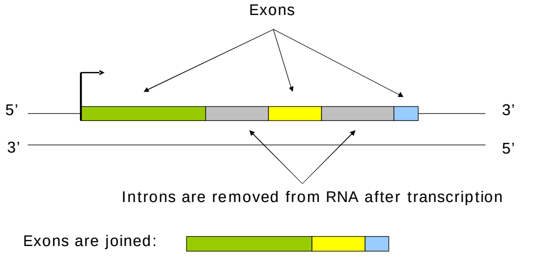
- A gene can have different variants
- The variants of the same gene are called *alleles*



Genes can be found on both strands



Exons and introns & splicing



Exons

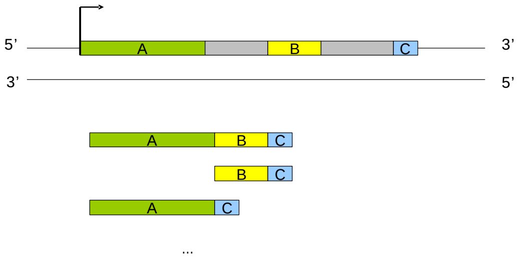
Introns are removed from RNA after transcription

Exons are joined:

This process is called *splicing*

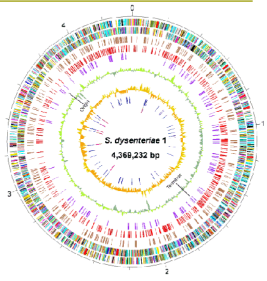
Alternative splicing

Different *splice variants* may be generated



Where does the variation in genomes come from?

- Prokaryotes are typically haploid: they have a single (circular) chromosome
- DNA is usually inherited vertically (parent to daughter)
- Inheritance is clonal
  - Descendants are faithful copies of an ancestral DNA
  - Variation is introduced via mutations, transposable elements, and horizontal transfer of DNA



Chromosome map of *S. dysenteriae*, the nine rings describe different properties of the genome
http://www.mgc.ac.cn/ShiBASE/circular_Sd197.htm

Causes of variation

- Mistakes in DNA replication
- Environmental agents (radiation, chemical agents)
- Transposable elements (transposons)
  - A part of DNA is moved or copied to another location in genome
- Horizontal transfer of DNA
  - Organism obtains genetic material from another organism that is not its parent
  - Utilized in genetic engineering

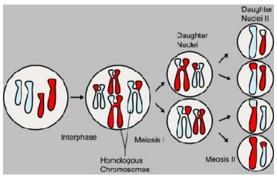
Biological string manipulation

- Point mutation: substitution of a base
  - ...ACGGCT... => ...ACGCCT...
- Deletion: removal of one or more contiguous bases (substring)
  - ...TTGATCA... => ...TTTCA...
- Insertion: insertion of a substring
  - ...GGCTAG... => ...GGTCAACTAG...

► Lecture: Sequence alignment
Lecture: Genome rearrangements

Meiosis

- Sexual organisms are usually diploid
  - Germline cells (gametes) contain N chromosomes
  - Somatic (body) cells have 2N chromosomes
- Meiosis: reduction of chromosome number from 2N to N during reproductive cycle
  - One chromosome doubling is followed by two cell divisions



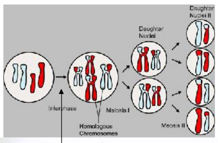
Major events in meiosis

http://en.wikipedia.org/wiki/Meiosis

http://www.ncbi.nlm.nih.gov/About/Primer

Recombination and variation

- Recap: Allele is a viable DNA coding occupying a given locus (position in the genome)
- In recombination, alleles from parents become suffled in offspring individuals via chromosomal crossover over
- Allele combinations in offspring are usually different from combinations found in parents
- Recombination errors lead into additional variations



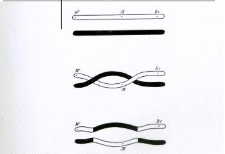
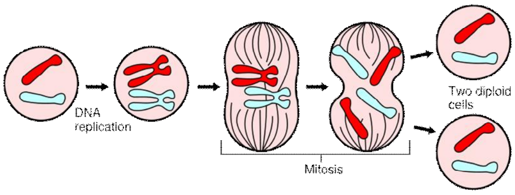


FIG. 63. Scheme to illustrate double crossing over.

Chromosomal crossover as described by T. H. Morgan in 1916

Mitosis



- Mitosis: growth and development of the organism
  - One chromosome doubling is followed by one cell division

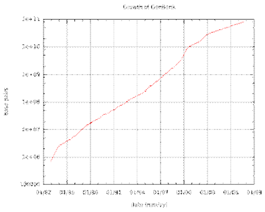
http://en.wikipedia.org/wiki/Image:Major_events_in_mitosis.svg

Recombination frequency and linked genes

- Genetic marker: some DNA sequence of interest (e.g., gene or a part of a gene)
- Recombination is more likely to separate two distant markers than two close ones
- Linked markers: "tend" to be inherited together
- Marker distances measured in centimorgans: 1 centimorgan corresponds to 1% chance that two markers are separated in recombination

Biological databases

- Exponential growth of biological data
  - New measurement techniques
  - Before we are able to use the data, we need to store it efficiently -> biological databases
  - Published data is submitted to databases
- General vs specialised databases
- This topic is discussed extensively in *Practical course in biodatabases* (III period)



10 most important biodatabases… according to ”Bioinformatics for dummies”

GenBank/DDJB/EMBL	www.ncbi.nlm.nih.gov	Nucleotide sequences
Ensembl	www.ensembl.org	Human/mouse genome
PubMed	www.ncbi.nlm.nih.gov	Literature references
NR	www.ncbi.nlm.nih.gov	Protein sequences
UniProt	www.expasy.org	Protein sequences
InterPro	www.ebi.ac.uk	Protein domains
OMIM	www.ncbi.nlm.nih.gov	Genetic diseases
Enzymes	www.expasy.org	Enzymes
PDB	www.rcsb.org/pdb/	Protein structures
KEGG	www.genome.ad.jp	Metabolic pathways

FASTA format

- A simple format for DNA and protein sequence data is FASTA

Header line, begins with >

```
>Hepatitis delta virus, complete genome
atgagccaagttccgaacaaggattcgcggggaggatagatcagcgcccgagaggggtga
gtcggtaaagagcattggaacgtcggagatacaactcccaagaaggaaaaaagagaaagc
aagaagcggatgaatttccccataacgccagtgaaactctaggaaggggaaagagggaag
gtggaagagaaggaggcgggcctcccgatccgaggggcccggcggccaagtttggaggac
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