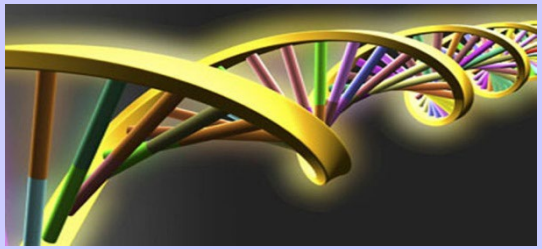
Introduction to Bioinformatics

Ulf Leser

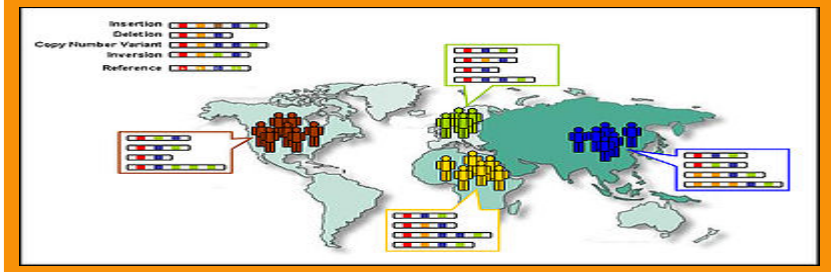
Bioinformatics



25.4.1953
Entdeckung der Doppelhelix durch
Watson/Crick + Wilkins/Franklin

14.4.2003
Humanes Genom zu ~95% sequenziert
mit ~99% Genauigkeit

2008
Genom of J. Watson finished
4 Months, 1.5 Million USD



2010
1000 Genomes Project

Example: Int. Cancer Genome Cons.

- Large-scale, international endeavor
- Planned for 50 different cancer types
- Cancer types are assigned to co
- Distribute
infrastruct
- First federat
to a large int.
project [HAA+08]

50 different cancer types, 500 samples per type, always control + cancer

> 50.000 genomes

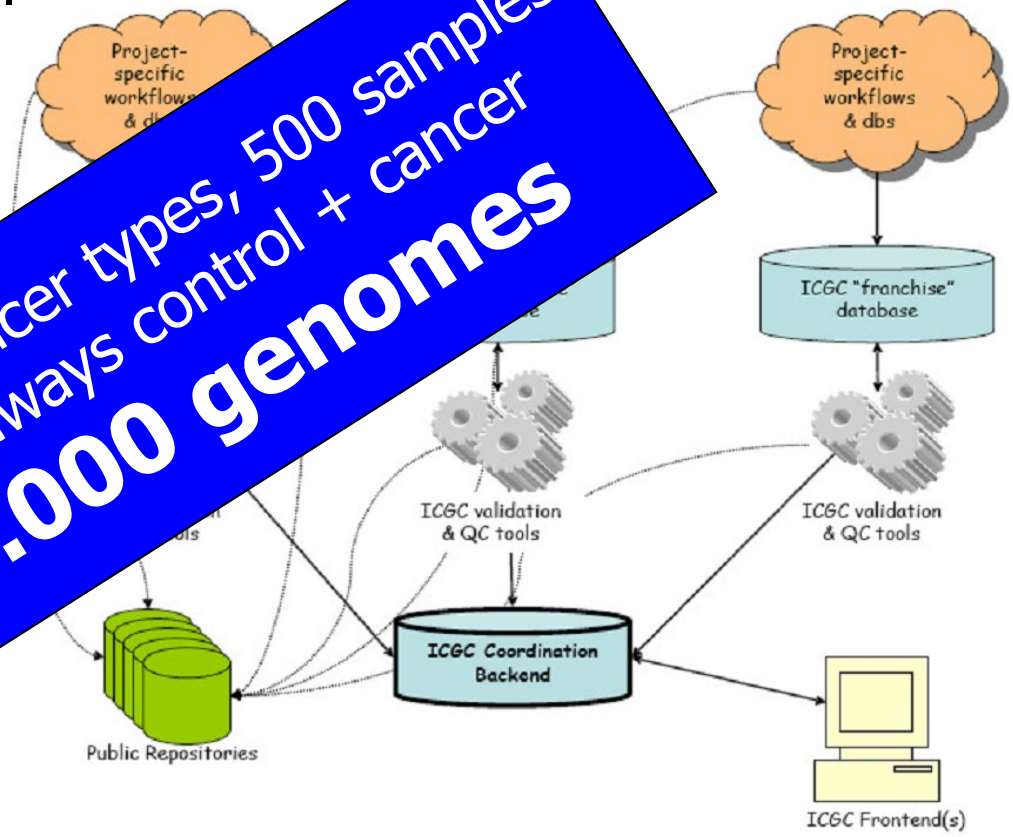
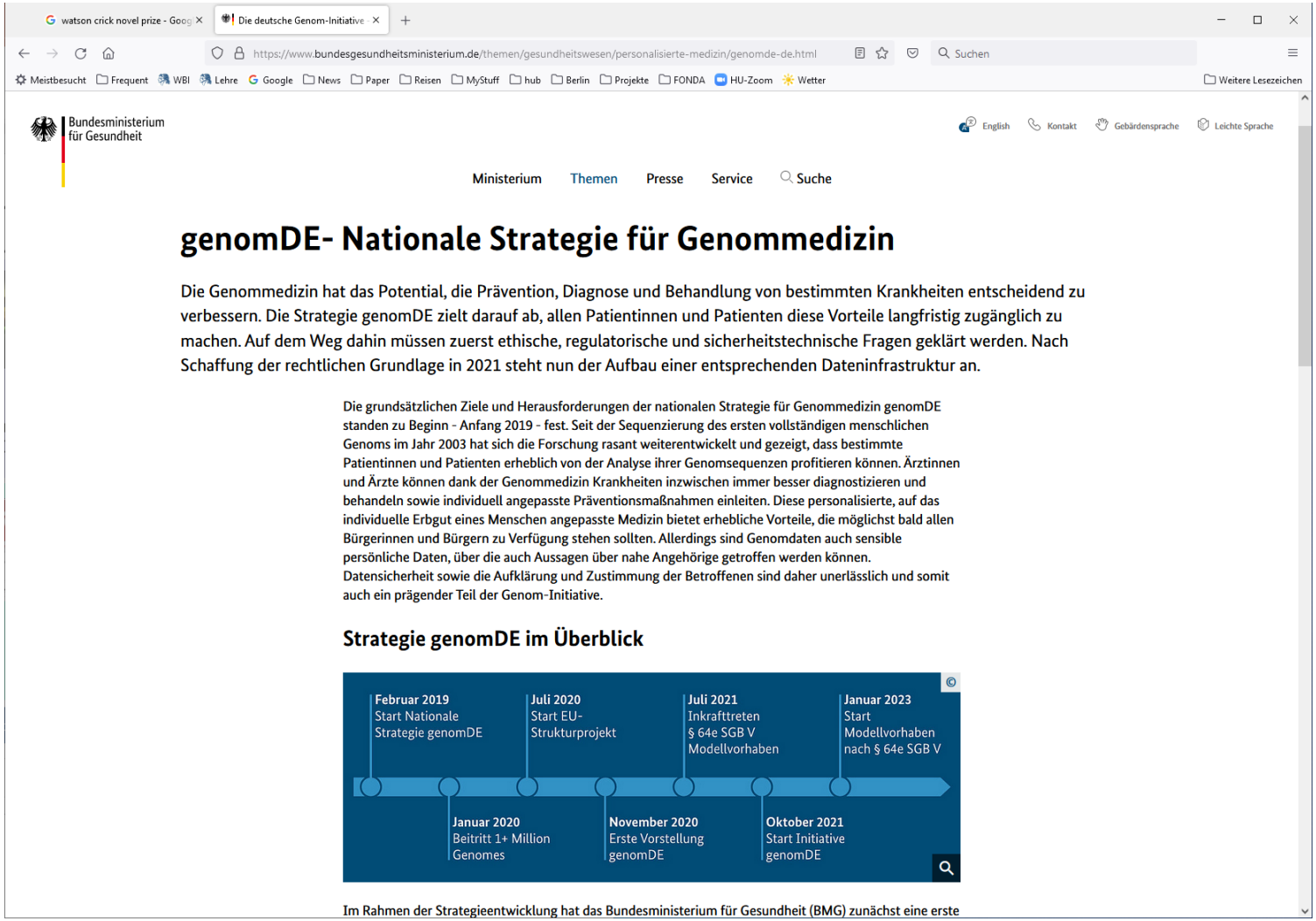
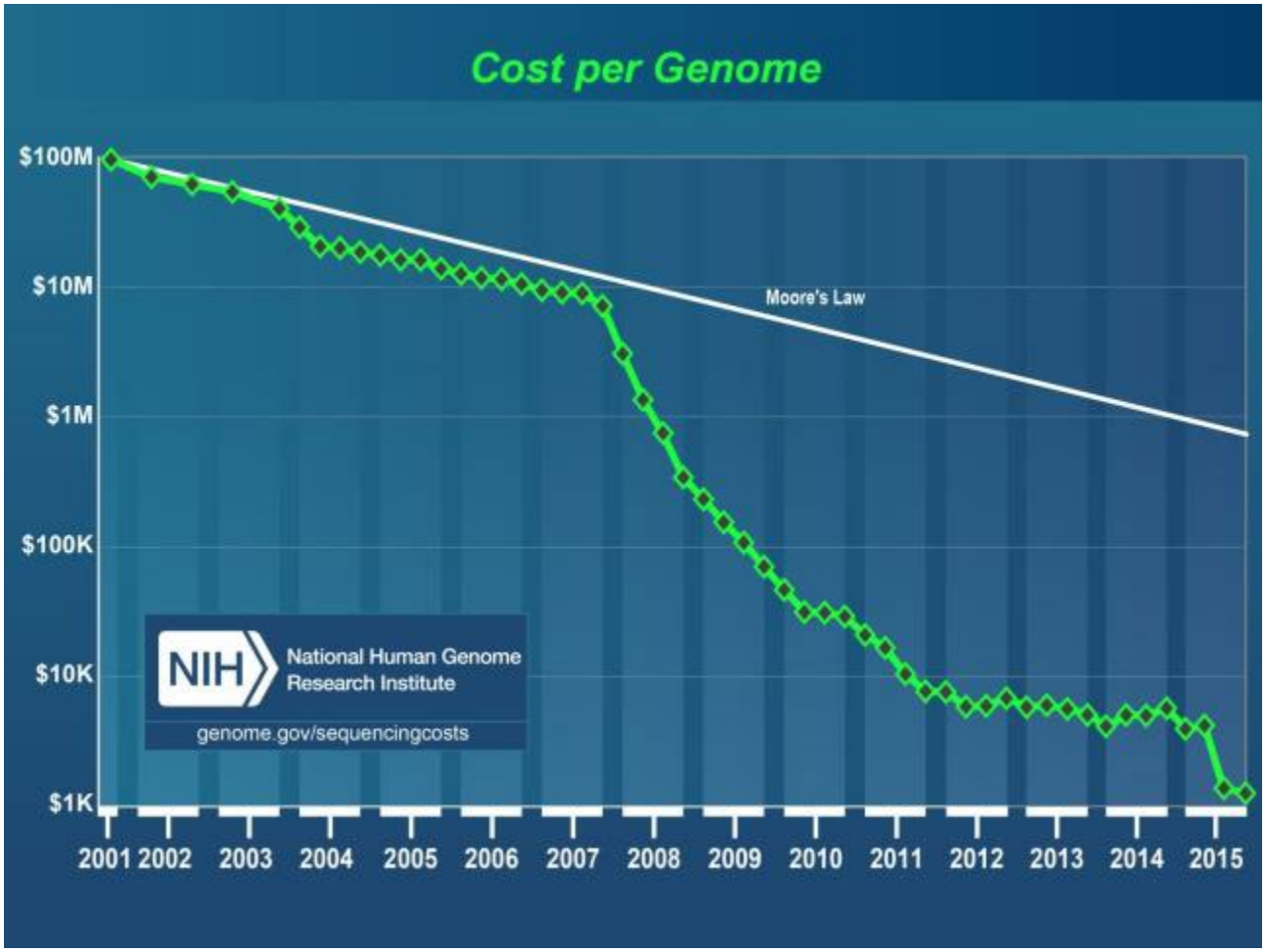


Figure 2: ICGC data coordination as a franchise system

2022: Deutschland



Possible Through Cost Reduction



What does this mean ?

http://www.genome.gov

Things you can do with it

- 2002
  - 2 companies
  - 32 Tests
  - Price: 100–1400€

Tabelle

Gentests, die im Internet in Deutschland bestellbar sind (Stand: Juli 2002)

Indikation*	Anbieter**	Untersuchungsgegenstand	Preis (inkl. MwSt.)
Alkoholverträglichkeit	2	keine Angaben (k. A.)	207,79 €
Alzheimer	2	k. A.	134,06 €
Alzhei	1	E4-Allel des Apolipoprotein-E-Gens auf Chromosom 10	650,00 €
Angelman-Syndrom [2]	1	Deletion auf dem Chromosom 15	850,00 €
Anti-Aging-Risikoprofil	2	k. A.	653,61 €
Arteriosklerose/Herzinfarkt/Schlaganf	2	k. A.	512,81 €
A	1	31 Mutationen einschließlich einer 5T-Variante auf dem CFTR-Gen auf dem Chromosom 7	850,00 €
Bluthochdruck	2	k. A.	127,40 € 439,24 €
hates Typ II	2	k. A.	127,40 € 194,39 €
Dickdarmkrebs [3]	1	MLH1- und MSH2-Mutationen	1600,00 €
Entgiftungsfähigkeit	2	k. A.	811,10 €
Faktor V Leiden-Mutation	1	Gerinnungsfaktor-V auf dem langen Arm von Chromosom 1	400,00 €
Familiäre Hypercholesterinämie	1	Mutationen im Low-Density-Lipoprotein-Rezeptor-Gen und im Exon 26 Apolipoprotein-B-Gen	850,00 €
Familiäre Hyperlipoproteinämie Typ III	1	E2-Allel des Apolipoprotein-E-Gens auf Chromosom 19	500,00 €
Familiärer Brustkrebs [3]	1	BCRA1- und BCRA2-Mutationen	1400,00 €
Fettgen/Adipositas	2	k. A.	241,35 € 576,44 €
Fettstoffwechsel/Cholesterin	2	k. A.	395,48 €
Fragiles X-Syndrom [4]	1	FMR1-(fragile X mental retardation-)Gen des X-Chromosoms (Region Xq27.3)	950,00 €
Hämochromatose	2	k. A.	207,84 €
Hämochromatose	1	Austausch der DNS-Basen Guanin zu Adenin an der Position 845 und von Cytosin zu Guanin an der Position 187 des HFE-Gens auf dem Chromosom 6	500,00 €
Hyperhomocysteinämie	1	k. A.	550,00 €
Mukoviszidose (Cystische Fibrose)	1	Mutation eines Gens auf Chromosom 7	850,00 €
Muskeldystrophie	1	Deletionen (Verlust von DNA-Teilsequenzen) im Dystrophin-Gen auf dem X-Chromosom	850,00 €
Osteoporose	2	k. A.	103,89 € 191,01 €
Osteoporose	1	Mutation (Basenaustausch von Guanin zu Thymin) im Intron 1 des Kollagen Typ I Alpha 1-Gens	650.00 €
Ovarialkarzinom [3]	1	BCRA1- und BCRA2-Mutationen	850,00 €
Persönliches Ernährungsprofil	2	k. A.	841,32 €
Prader-Willi-Syndrom	1	Deletion oder Translokation auf dem langen Arm des Chromosoms 15 (15q11)	850,00 €
Prothr	1	Austausch der DNS-Basen Guanin zu Adenin an der Position 20210 des Prothrombingens auf dem Chromosom 11	550,00 €
Risiko Alkohol- und Drogenabhängigkeit	2	k. A.	274,86 €
Thrombose	2	k. A.	134,06 € 281,52 €

Situation Today

- Precision oncology: Determine therapies depending on molecular characterization of an individual patient
- Tumors are driven by genomic variants ("mutations")
- Different variants – different prognosis & treatment
- Targeted therapies: Drugs whose applicability depend on the presence / absence of certain variants
  - 1/3 if all new anti-cancer drugs in 2019 (FDA)
  - 90% of all current late-stage anti-cancer drugs in developments

This Lecture

- Formal stuff
- A very short introduction in Molecular Biology
- What is Bioinformatics?
  - And an example
- Topics of this course

This course

- Bachelor computer science, Wahlpflichtbereich
- 5 SP, lecture / exercises are 2+2
- We assume 4th semester knowledge in computer science
  - Programming, algorithms, complexity
- We do not assume knowledge in biology
- Introductory – many topics, often not much depth
  - Visit "Algorithmische Bioinformatik" afterwards …
- Ask questions! leser (a) informatik.hu … berlin…

Exercises

- Taught by Ulf Leser
- There will be 4-5 assignments
- We build teams
- System
  - First week: 2-3 presentations of results of previous assignment and discussion of new assignment
  - Next week: Questions
  - …
- Group needs to pass all assignments for exam admission

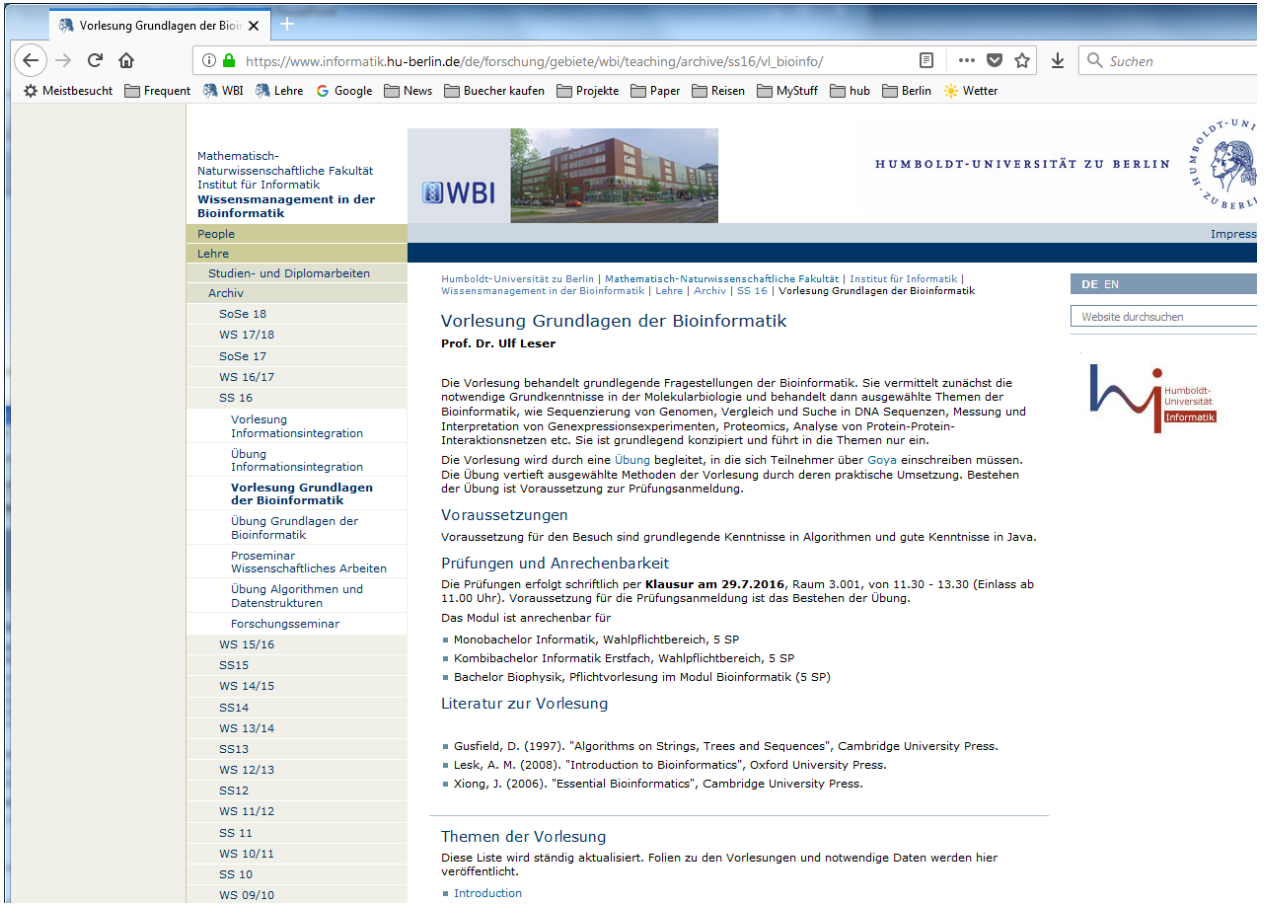
Exams

- Written examination
- Dates to be announced
  - July, October

Literature

- For algorithms and data structures
  - Gusfield (1997). „Algorithms on Strings, Trees, and Sequences“, Cambridge University Press
  - Böckenhauer, Bongartz (2003). „Algorithmische Grundlagen der Bioinformatik“, Teubner
- For other topics and overviews
  - Lesk (2005/2019). „Introduction to Bioinformatics“, Oxford Press
  - Cristianini, Hahn (2007). "Introduction to Computational Genomics - A Case Study Approach", Cambridge University Press
  - Merkl, Waack (2009). "Bioinformatik Interaktiv", Wiley-VCH Verlag.
  - Dandekar, Kunz (2017) „Bioinformatik: Ein einführendes Lehrbuch“, Springer
- For motivation and relaxation
  - Gibson, Muse (2001). "A Primer of Genome Science", Sinauer Associates.
  - Krane, Raymer (2003). "Fundamental Concepts of Bioinformatics", Benjamine Cummings.

Web Side


Vorlesung Grundlagen der Bioi
https://www.informatik.hu-berlin.de/de/forschung/gebiete/wbi/teaching/archive/ss16/vl_bioinfo/
Suchen
Meistbesucht
Frequent
WBI
Lehre
Google
News
Buecher kaufen
Projekte
Paper
Reisen
MyStuff
hub
Berlin
Wetter
Mathematisch-Naturwissenschaftliche Fakultät
Institut für Informatik
Wissensmanagement in der Bioinformatik
WBI
HUMBOLDT-UNIVERSITÄT ZU BERLIN
Impress
People
Lehre
Studien- und Diplomarbeiten
Archiv
SoSe 18
WS 17/18
SoSe 17
WS 16/17
SS 16
Vorlesung Informationsintegration
Übung Informationsintegration
Vorlesung Grundlagen der Bioinformatik
Übung Grundlagen der Bioinformatik
Proseminar Wissenschaftliches Arbeiten
Übung Algorithmen und Datenstrukturen
Forschungsseminar
WS 15/16
SS15
WS 14/15
SS14
WS 13/14
SS13
WS 12/13
SS12
WS 11/12
SS 11
WS 10/11
SS 10
WS 09/10
Humboldt-Universität zu Berlin | Mathematisch-Naturwissenschaftliche Fakultät | Institut für Informatik | Wissensmanagement in der Bioinformatik | Lehre | Archiv | SS 16 | Vorlesung Grundlagen der Bioinformatik
DE EN
Website durchsuchen
Humboldt-Universität Informatik
Vorlesung Grundlagen der Bioinformatik
Prof. Dr. Ulf Leser
Die Vorlesung behandelt grundlegende Fragestellungen der Bioinformatik. Sie vermittelt zunächst die notwendige Grundkenntnisse in der Molekularbiologie und behandelt dann ausgewählte Themen der Bioinformatik, wie Sequenzierung von Genomen, Vergleich und Suche in DNA Sequenzen, Messung und Interpretation von Genexpressionsexperimenten, Proteomics, Analyse von Protein-Protein-Interaktionsnetzen etc. Sie ist grundlegend konzipiert und führt in die Themen nur ein.
Die Vorlesung wird durch eine Übung begleitet, in die sich Teilnehmer über Goya einschreiben müssen. Die Übung vertieft ausgewählte Methoden der Vorlesung durch deren praktische Umsetzung. Bestehen der Übung ist Voraussetzung zur Prüfungsanmeldung.
Voraussetzungen
Voraussetzung für den Besuch sind grundlegende Kenntnisse in Algorithmen und gute Kenntnisse in Java.
Prüfungen und Anrechenbarkeit
Die Prüfungen erfolgt schriftlich per Klausur am 29.7.2016, Raum 3.001, von 11.30 - 13.30 (Einlass ab 11.00 Uhr). Voraussetzung für die Prüfungsanmeldung ist das Bestehen der Übung.
Das Modul ist anrechenbar für
Monobachelor Informatik, Wahlpflichtbereich, 5 SP
Kombibachelor Informatik Erstfach, Wahlpflichtbereich, 5 SP
Bachelor Biophysik, Pflichtvorlesung im Modul Bioinformatik (5 SP)
Literatur zur Vorlesung
Gusfield, D. (1997). "Algorithms on Strings, Trees and Sequences", Cambridge University Press.
Lesk, A. M. (2008). "Introduction to Bioinformatics", Oxford University Press.
Xiong, J. (2006). "Essential Bioinformatics", Cambridge University Press.
Themen der Vorlesung
Diese Liste wird ständig aktualisiert. Folien zu den Vorlesungen und notwendige Daten werden hier veröffentlicht.
Introduction

My Questions

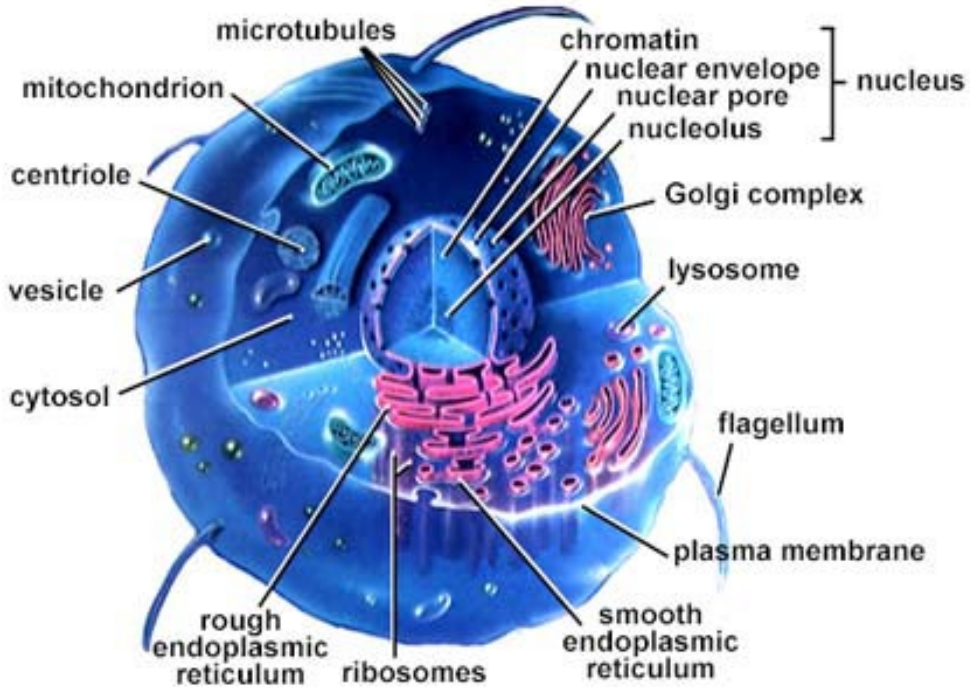
- Bachelor Informatik?
- Kombibachelor?
- Other?

- Semester?
- Prüfung?
- Spezielle Erwartungen?

This Lecture

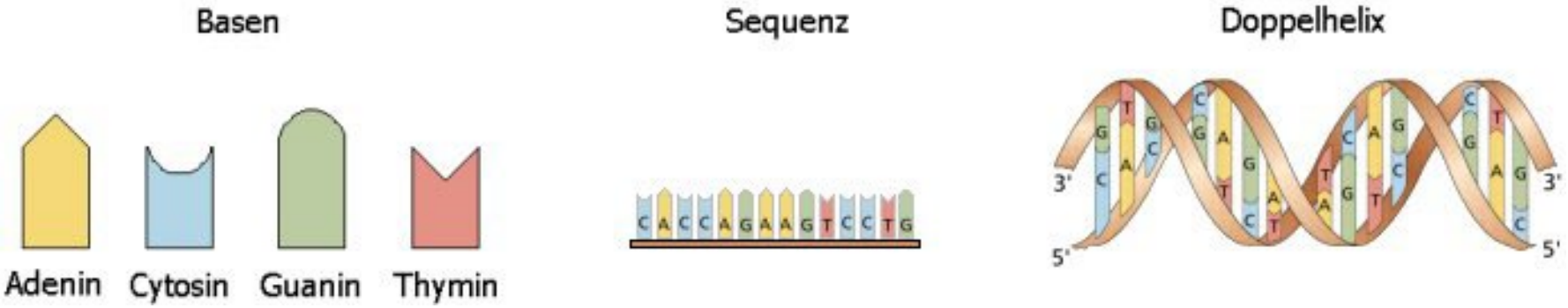
- Formal stuff on the course
- A very short introduction in Molecular Biology
- What is Bioinformatics?
- Topics of this course

Cells and Bodies



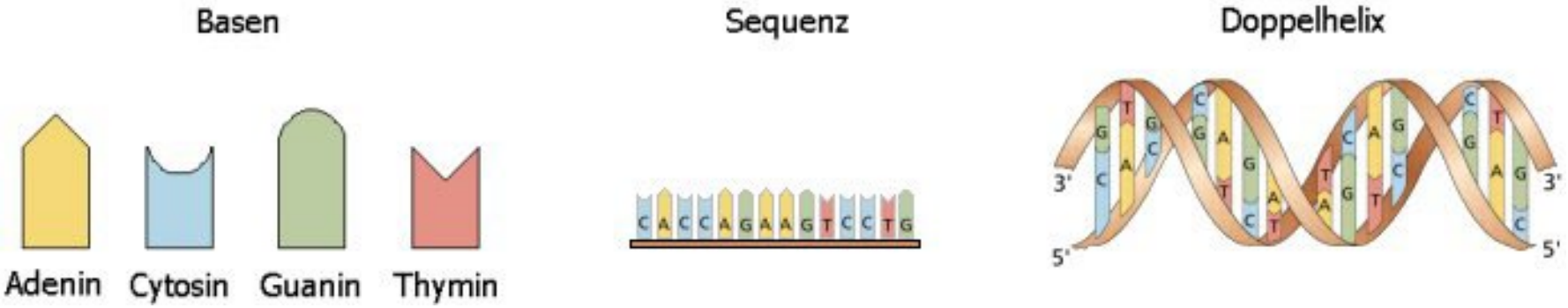
- App. 75 trillion cells in a human body
- App. 250 different types: nerve, muscle, skin, blood, …

DesoxyriboNucleicAcid



- DNA: Desoxyribonukleinsäure
  - Four different molecules
  - The DNA of all chromosomes in a cell forms its genome
  - All cells in a (human) body carry the same genome
  - All living beings are based on DNA for proliferation
  - There are always always always exceptions

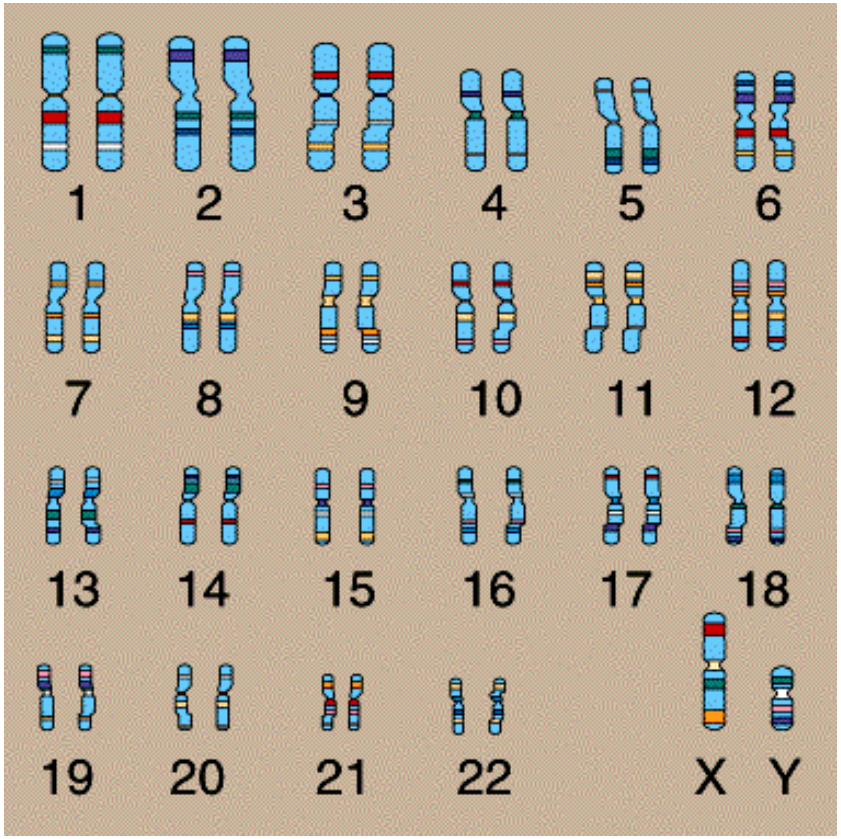
DesoxyriboNucleicAcid



- DNA: Desoxyribonukleinsäure
  - Four different molecules (one replaced in RNA)
  - The DNA of all chromosomes in a cell together with the mitochondria-DNA forms its genome
  - Almost all cells in a (human) body carry almost the same genome
  - All living beings are based on DNA or RNA for proliferation

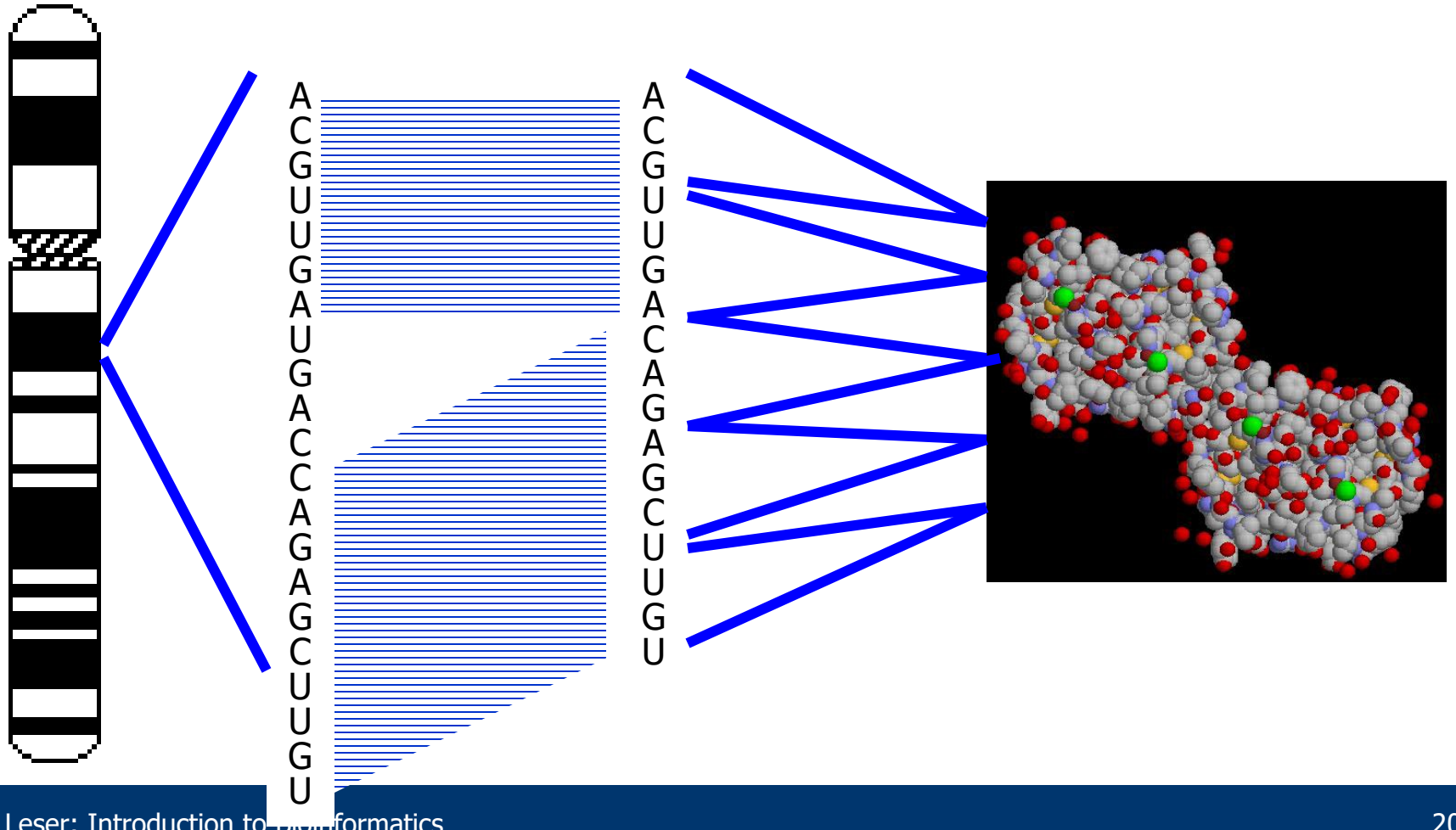
The Human Genome

- 23 chromosomes
  - 22 in pairs
- ~3.000.000.000 letters
- ~50% are repetitions of 4 identical subsequences
  - ~~~100.000 genes~~
  - ~~~56.000 genes~~
  - ~~~30.000 genes~~
  - ~~~24.000 genes~~
- ~22.000 genes



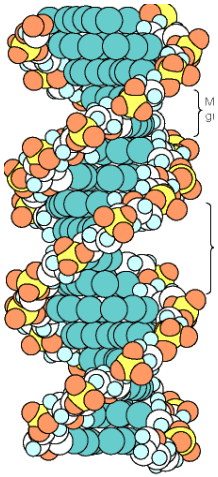
(Protein-Coding) Genes

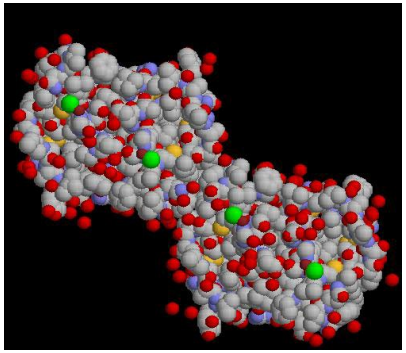
Chromosome RNA mRNA Proteine

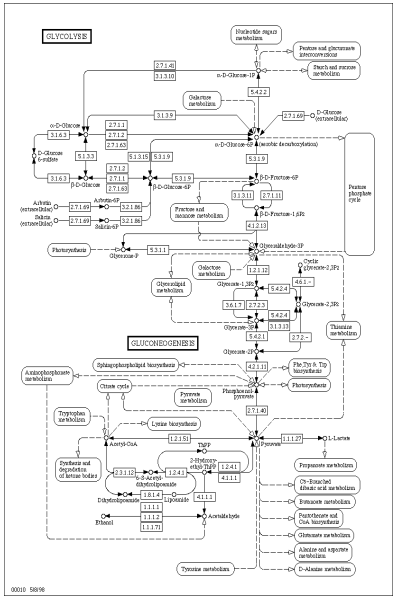


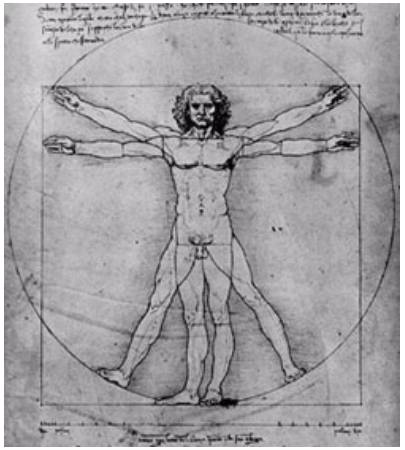
Proliferation

Sequence → Proteins → Networks → Organism









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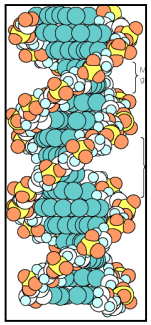

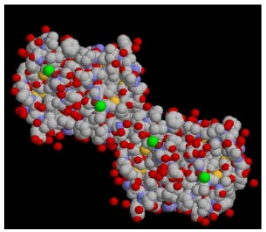

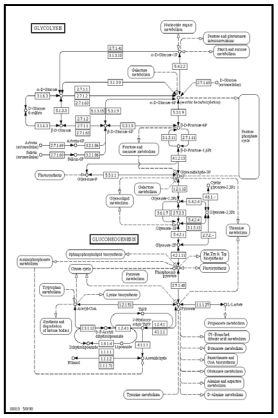

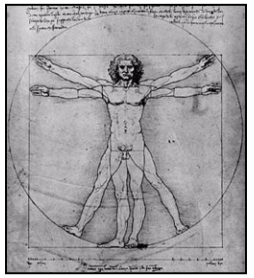

Genomics

Sequencing

Gene prediction

Evolutionary relationships

Motifs - TFBS

Transcriptomics

RNA folding

…

Proteomics

Structure prediction

… comparison

Motives, active sites

Docking

Protein-Protein Interaction

Proteomics

…

Systems Biology

Pathway analysis

Gene regulation

Signaling

Metabolism

Quantitative models

Integrative analysis

…

Medicine

Phenotype – genotype

Mutations and risk

Population genetics

Adverse effects

…

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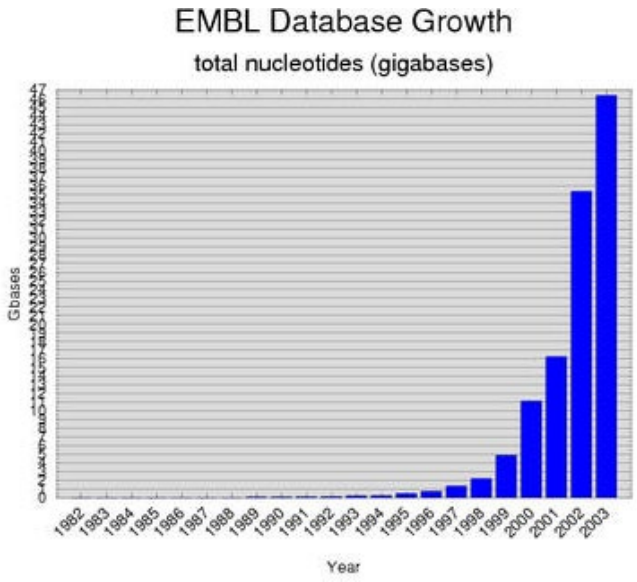
- Formal stuff on the course
- A very short introduction in Molecular Biology
- What is Bioinformatics?
  - And an example
- Topics of this course

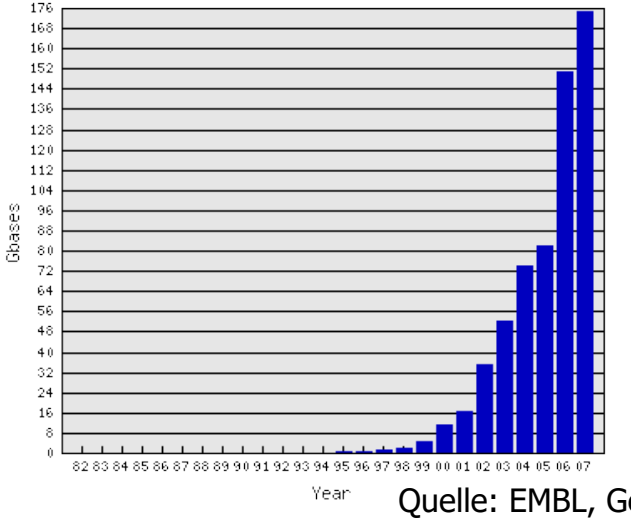
Bioinformatics / Computational Biology

- Computer Science methods for
  - Solving biologically relevant problems
  - Analyzing and managing experimental data sets
- Empirical: Data from high throughput experiments
- Focused on algorithms and statistics
- Problems are typically complex, data full of errors – importance of heuristics and approximate methods
- Strongly reductionist – Strings, graphs, sequences
- Interdisciplinary: Biology, Computer Science, Physics, Mathematics, Genetics, …

History

- First protein sequences: 1951
- Sanger sequencing: 1972
- Exponential growth of available data since end of 70th
  - Bioinformatics is largely data-driven – new methods yield new data requiring new algorithms





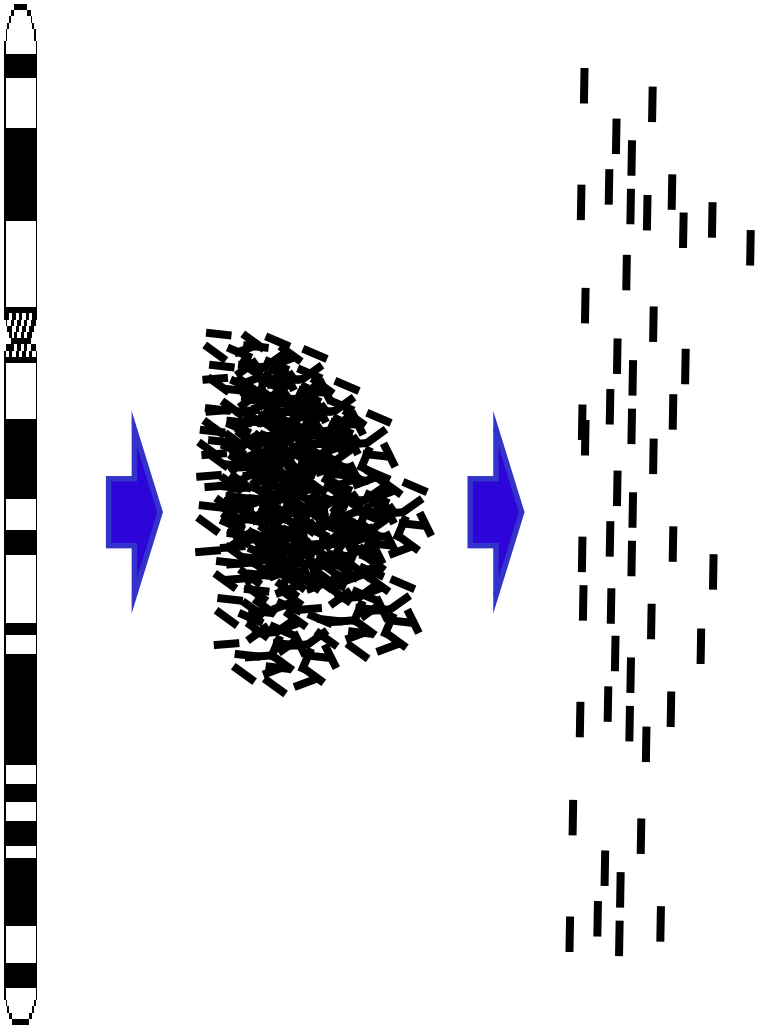
Quelle: EMBL, Genome Monitoring Tables

History 2

- First papers on sequence alignment
  - Needleman-Wunsch 1970, Gibbs 1970, Smith-Waterman 1981, Altschul et al. 1990
- Large impact of the Human Genome Projekt (~1990)
- Only 14 mentions of „Bioinformatics" before 1995
- „Journal of Computational Biology" since 1994
- First professorships in Germany: end of 90's
- First university programs: ~2000
- First German book: 2001
- Commercial hype: 1999 – 2004
- Indispensable for medical research: 2010 –
- Regular sequencing for some cases (cancer): 2016 -

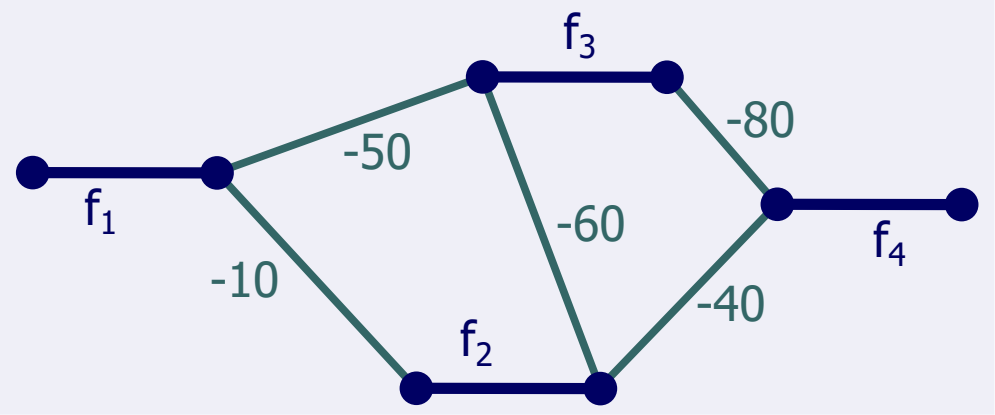
A Concrete Example: Sequencing a Genome

- Chromosomes (still) cannot be sequenced entirely
  - Instead: Only small fragments can be sequenced
- But: Chromosomes cannot be cut at position X, Y, …
  - Instead: Chromosomes only can be cut at certain subsequences
- But: We don't know where in a chromosome those subsequences are
  - Sequence assembly problem



Problem

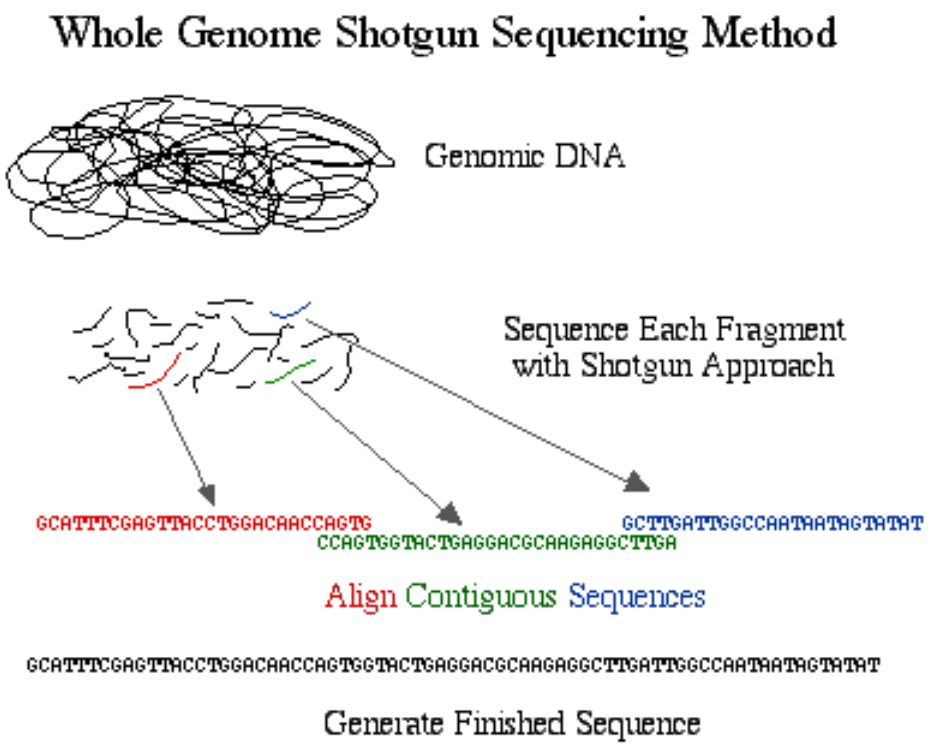
- Given a large set of (sub)sequences from randomly chosen positions from a given chromosome of unknown sequence
- Assembly: Determine sequence of the original chromosome
  - Everything may overlap with everything to varying degrees
  - Let‘s forget about orientation and sequencing errors



Abstract Formulation

- SUPERSTRING
  - Given a set S of strings
  - Find string t such that
    - (a) $\forall s \in S: s \in t$ (all s are substrings of t)
    - (b) $\forall t'$ for which (a) holds: : $|t| \leq |t'|$ (t ist minimal)
- Problem is NP-complete
  - Very likely, there is no algorithm that solves the problem in less than $k_1 * k_2 2^n$ operations, where k_1, k_2 are constants and n=|S|
- Bioinformatics: Find clever heuristics
  - Solve the problem "good enough"
  - Finish in reasonable time

Dimension



- Whole genome shotgun
  - Fragment an entire chromosome in pieces of 1KB-100KB
- Sequence start and end of all fragments
  - Homo sap.: 28 million reads
  - Drosophila: 3.2 million reads
- Eukaryotes are very difficult to assemble because of repeats
  - A random sequence is easy

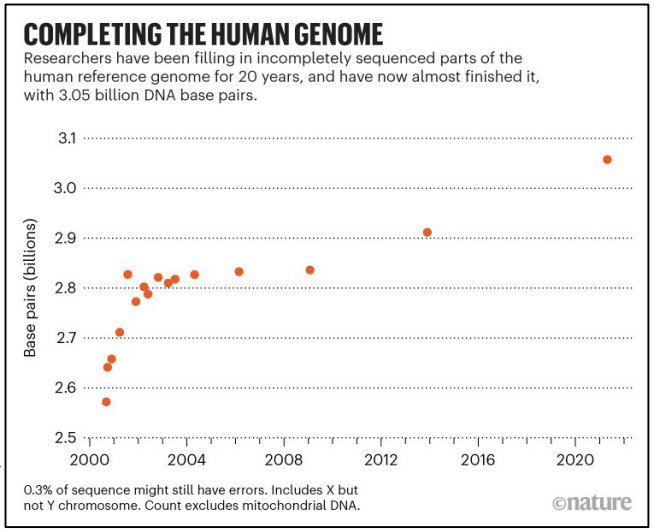
Why is this "reductionist"?

- Real alphabet is larger: N, AorT, …
- Errors need not be errors: Humans have two alleles
- Errors are not equally distributed but accumulate at begin / end of read
- Paired-end sequencing
- Substantial parts of a genome cannot be sequenced – wholes in the genome
- Why sequence everything when only genes count?
  - Whole genome, whole exome, RNASeq, …

Sequencing Today

A month ago!

- 2003: 1st human reference sequence
  - Continuously refined since then
- Two human genomes are >99% identical
  - And ~98% identical to a mouse genome
- Today: Sequencing by "read mapping"
  - Create reads as before
    - 2nd generation: Many more yet shorter reads (~100bp)
    - 3rd generation: Much larger reads (15K bp); still highly error prone
  - "Mapping": Find position of reads in reference genome
    - String matching with few errors
  - Much faster and cheaper
  - Cannot detect larger ("structural") variations



Nature, 6/2022

This Lecture

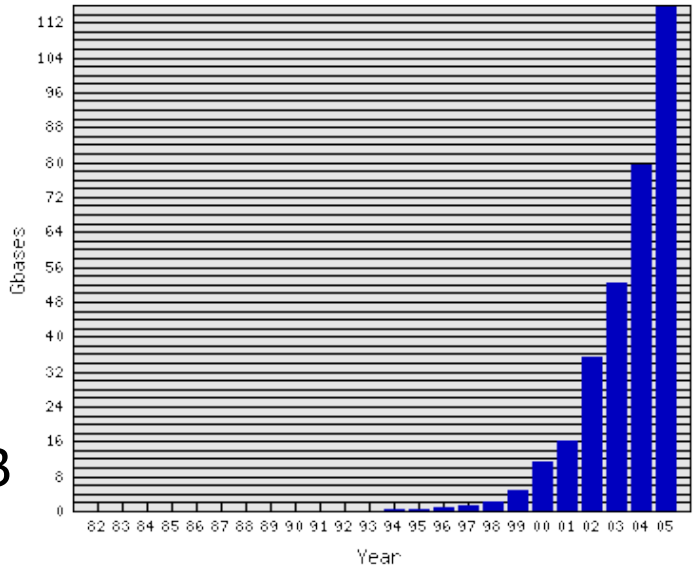
- Formal stuff on the course
- A very short introduction in Molecular Biology
- What is Bioinformatics?
  - And an example
- Topics of this course

Searching Sequences (Strings)

- A chromosome is a string
- Substrings may represent biologically important areas
  - Genes on a chromosome
  - Transcription factor binding sites
  - Similar gene in a different species
  - …
- Exact or approximate string search

Searching a Database of Strings

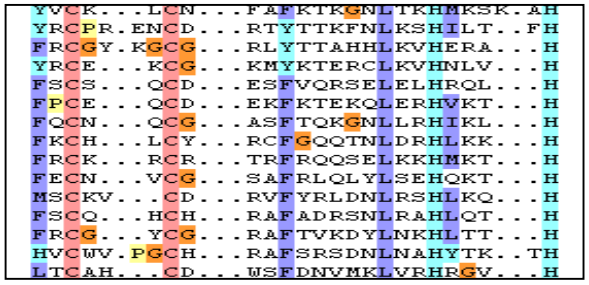
- Comparing two sequences is costly
- Given s, assume we want to find the most similar s' in a database of all known sequences
  - Naïve: Compare s with all strings in DB
  - Will take years and years

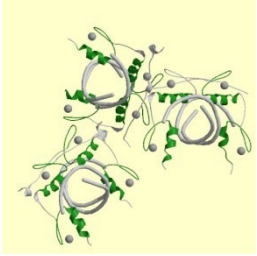


- BLAST: Basic local alignment search tool
  - Ranks all strings in DB according to similarity to s
  - Similarity: High is s, s' contain substrings that are highly similar
  - Heuristic: Might miss certain similar sequences
  - Extremely popular: You can "blast a sequence"

Multiple Sequence Alignment

- Given a set S of sequences: Find an arrangement of all strings in S in columns such that there are (a) few columns and (b) columns are maximally homogeneous
  - Additional spaces allowed



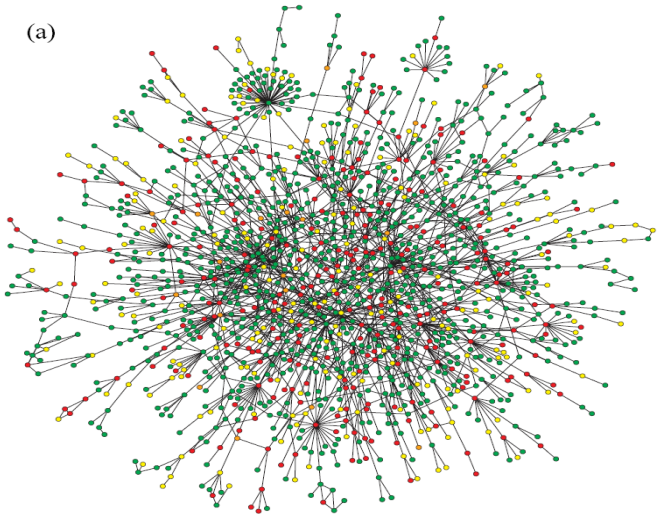


Source: Pfam, Zinc finger domain

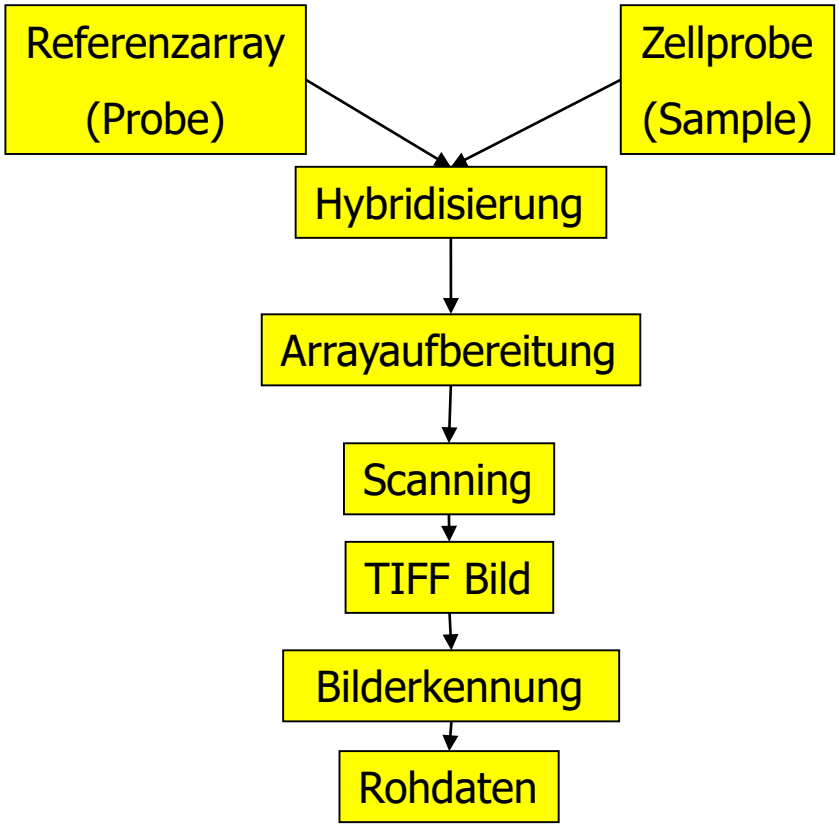
- Goal: Find commonality between a set of functionally related sequences
  - Proteins are composed of different functional domains
  - Which domain performs a certain function?

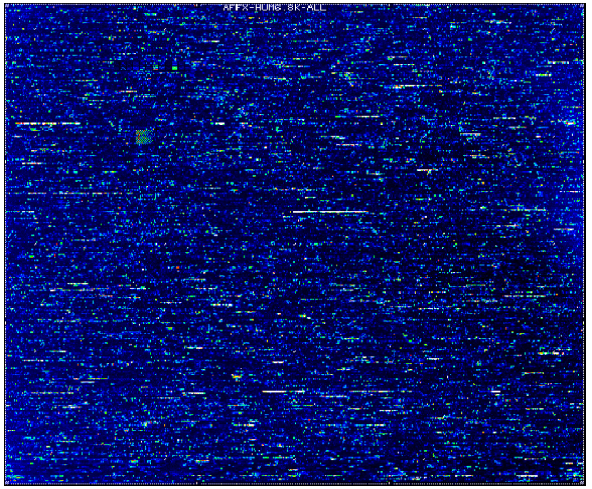
Protein-Protein-Interactions

- Proteins do not work in isolation but interact with each other
  - Metabolism, complex formation, signal transduction, transport, …
- PPI networks
  - Neighbors tend to have similar functior
  - Interactions tend to be evolutionary conserved
  - Dense subgraphs (cliques) tend to perform distinct functions
  - Are not random at all



Transcriptomics

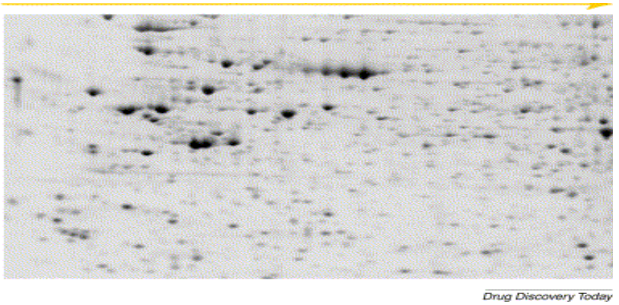




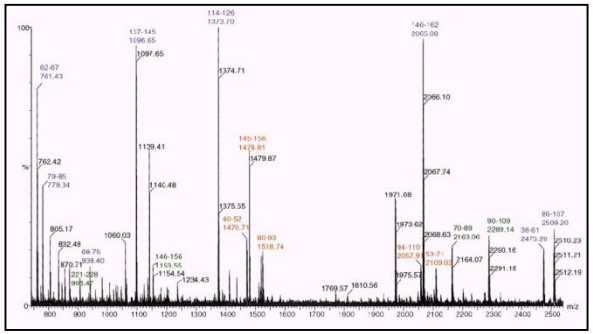
Proteomics

- The real workhorses in a cell are proteins
  - Differential splicing, post-translational modifications, degradation rates, various levels of regulation, …
- But: Much more difficult to study (compared to mRNA)

- Separation of proteins
  - 2D page, GC / LC

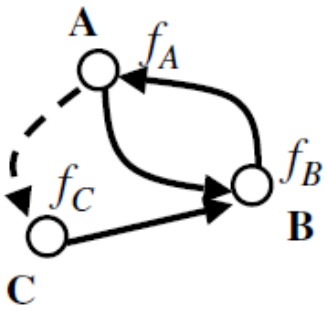


- Identification of proteins
  - Mass-spectrometry



Network Reconstruction

- Molecules perform functions by means of interactions
- Regulation: Networks of genes regulating each other
- Reconstruction: Which gene regulates which other genes in which ways?
- One approach: Boolean networks



$f_A(B) = B$

$f_B(A, C) = A \text{ and } C$

$f_C(A) = \text{not } A$

Boolean Network