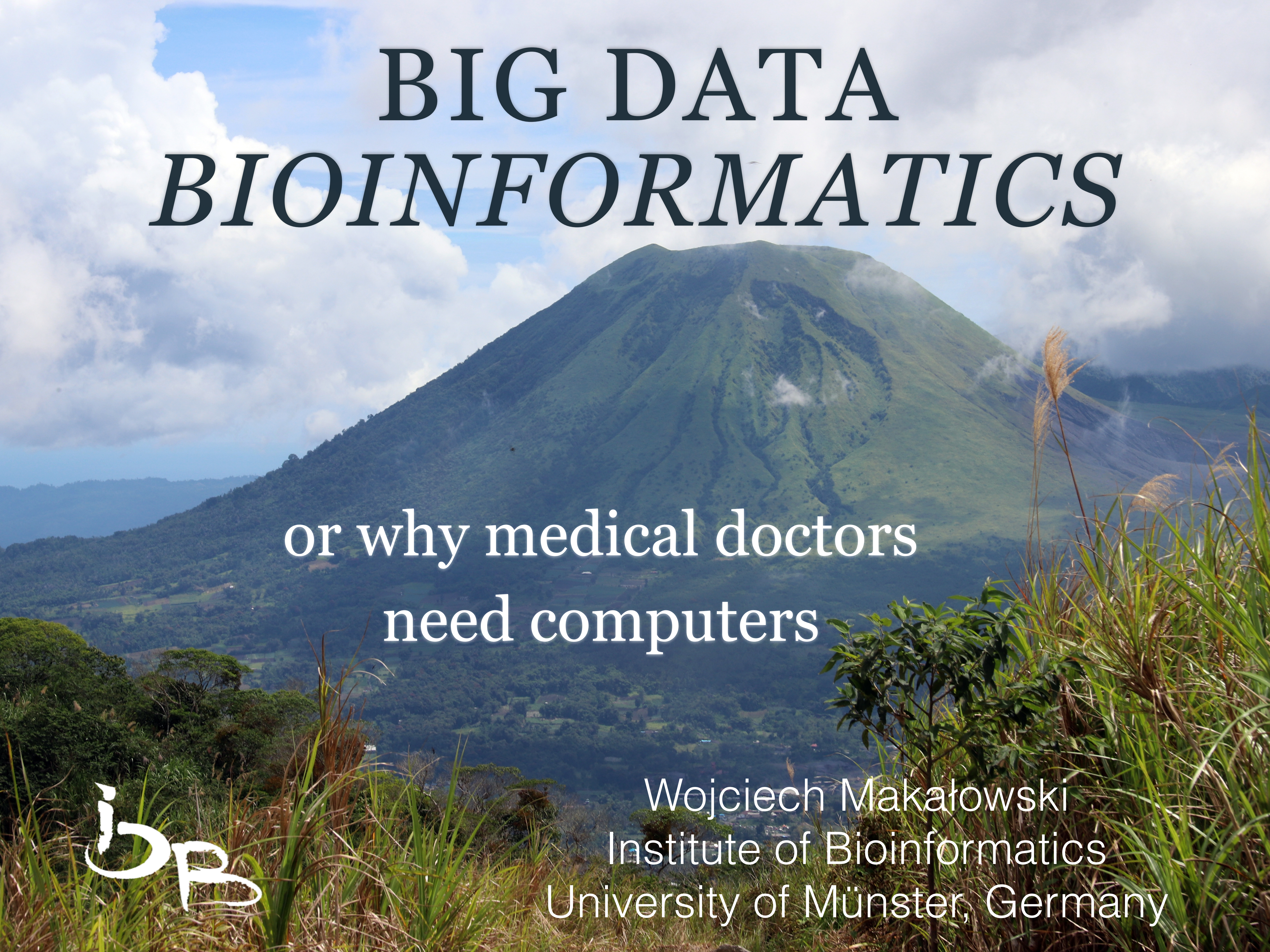


BIG DATA *BIOINFORMATICS*

or why medical doctors need computers

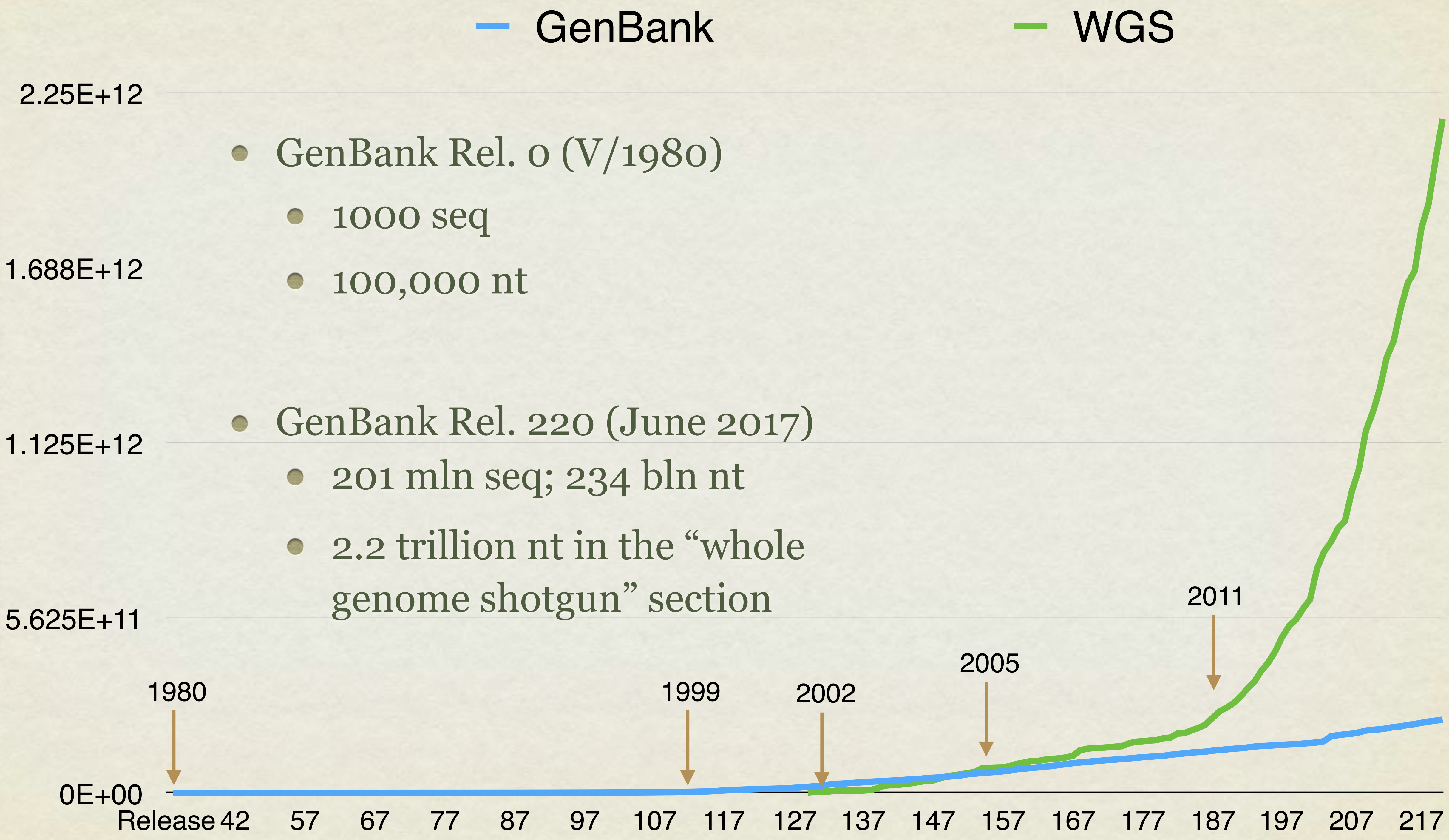
Wojciech Makałowski
Institute of Bioinformatics
University of Münster, Germany

It's sink or swim as a tidal wave of data approaches

Nature 399:517 10 June 1999

Unfortunately, it’s not a tidal wave,
it’s a tsunami!

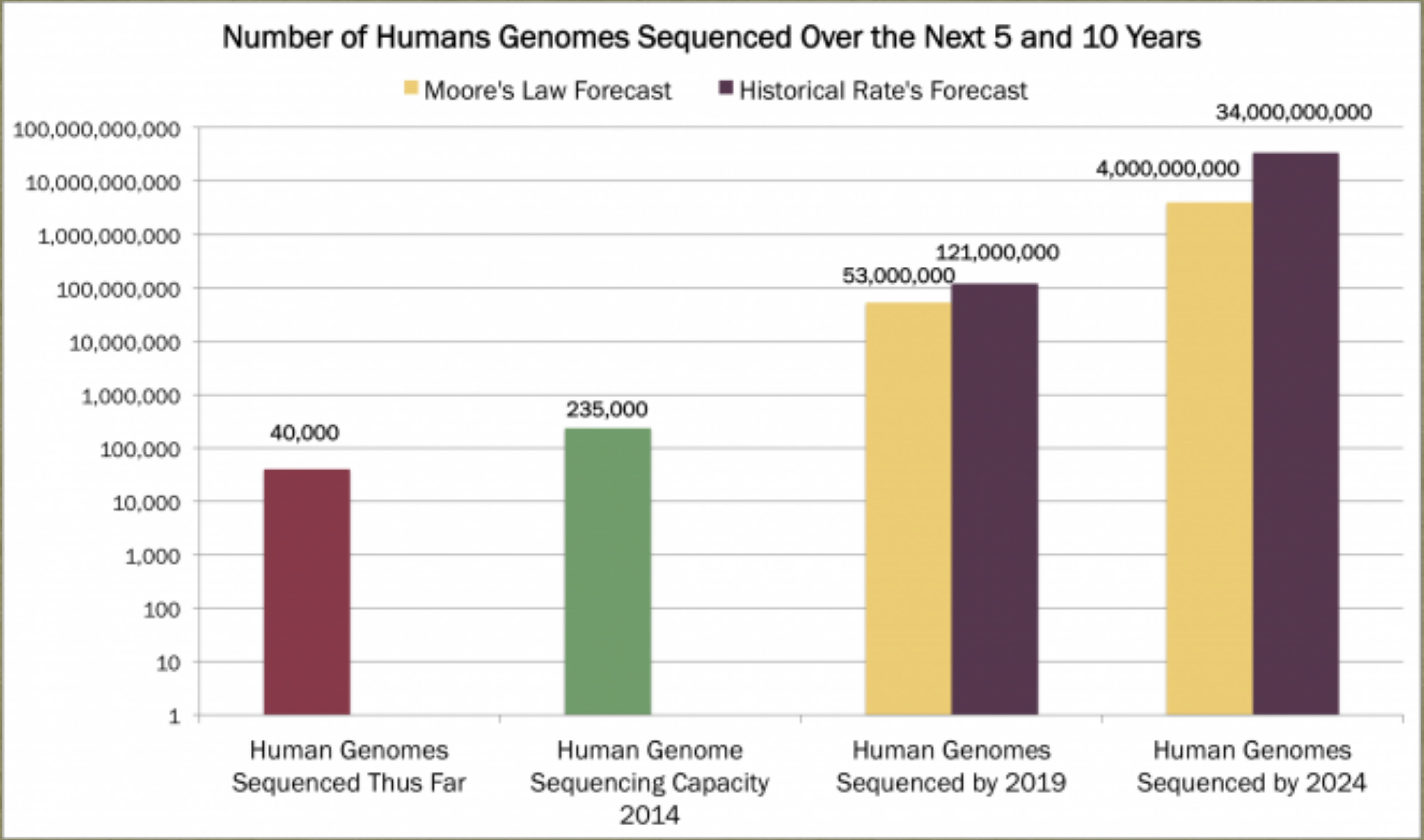
GROWTH OF BIOMEDICAL INFORMATION - GENBANK



- GenBank Rel. 0 (V/1980)
    - 1000 seq
    - 100,000 nt
- GenBank Rel. 220 (June 2017)
    - 201 mln seq; 234 bln nt
    - 2.2 trillion nt in the “whole genome shotgun” section

TECHNOLOGY MEETS BIOLOGY

IMPROVING TECHNOLOGY



http://ark-invest.com/genomic-revolution/declining-costs-of-genome-sequencing

CHALLENGE: HOW FROM THIS...

```
TGCATCGATCGTAGCTAGCTAGCGCATGCTAGCTAGCTAGCTAGCTACGATGCATCG
TGCATCGATCGATGCATGCTAGCTAGCTAGCTAGCATGCTAGCTAGCTAGCTATTGG
CGCTAGCTAGCATGCATGCATGCATCGATGCATCGATTATAAGCGCGATGACGTCAG
CGCGCGCATTATGCCGCGGCATGCTGCGCACACACAGTACTATAGCATTAGTAAAAA
GGCCGCGTATATTTTACACGATAGTGCGGCGCGGCGCGTAGCTAGTGCTAGCTAGTC
TCCGGTTACACAGGTAGCTAGCTAGCTGCTAGCTAGCTGCTGCATGCATGCATTAGT
AGCTAGTGTAGCTAGCTAGCATGCTGCTAGCATGCAGCATGCATCGGGCGCGATGCT
GCTAGCGCTGCTAGCTAGCTAGCTAGCTAGGCGCTAATTATTTATTTTGGGGGGTTA
AAAAAAAAATTTCGCTGCTTATACCCCCCCCCACATGATGATCGTTAGTAGCTACT
AGCTCTCATCGCGCGGGGGGATGCTTAGCGTGGTGTGTGTGTGTGGTGTGTGTGGTC
CTATAATTAGTGCATCGGCGCATCGATGGCTAGTCGATCGATCGATTTTATATATCT
AAAGACCCCATCTCTCTCTCTTTTCCCTTCTCTCGCTAGCGGGCGGTACGATTTACC
GGCCGCGTATATTTTACACGATAGTGCGGCGCGGCGCGTAGCTAGTGCTAGCTAGTC
AGCTCTCATCGCGCGGGGGGATGCTTAGCGTGGTGTGTGTGTGTGGTGTGTGTGGTC
TGCATCGATCGATGCATGCTAGCTAGCTAGCTAGCATGCTAGCTAGCTAGCTATTGG
CTATAATTAGTGCATCGGCGCATCGATGGCTAGTCGATCGATCGATTTTATATATCT
CGCTAGCTAGCATGCATGCATGCATCGATGCATCGATTATAAGCGCGATGACGTCAG
TCCGGTTACACAGGTAGCTAGCTAGCTGCTAGCTAGCTGCTGCATGCATGCATTAGT
```

Infer this

HOW TO SOLVE THE PROBLEM - A HUMAN OR A COMPUTER?

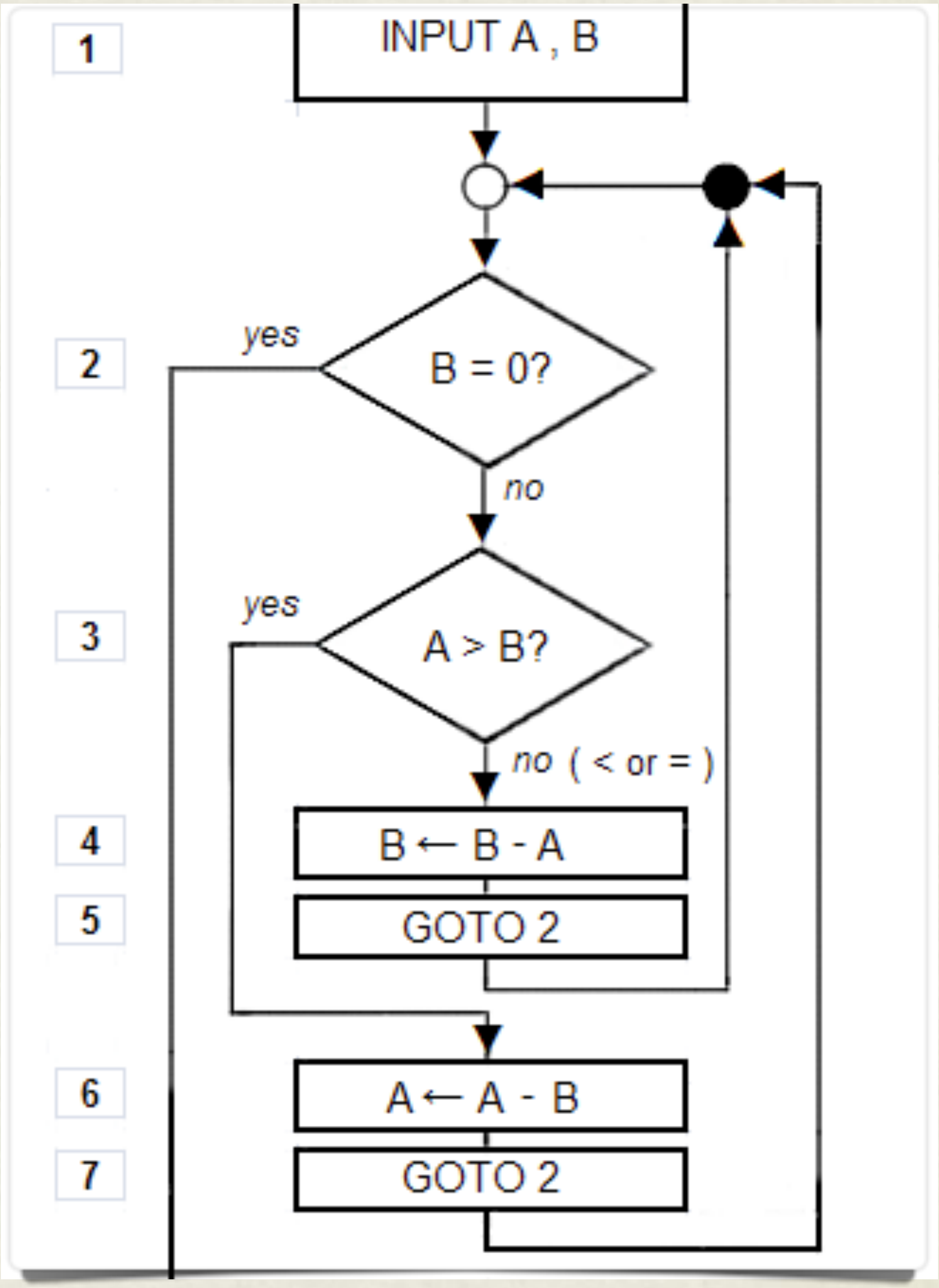
- very smart
- slow
- error prone
- doesn’t like repetitive tasks

- not so smart (stupid)
- extremely fast
- very accurate
- doesn’t understand human languages;

needs instruction provided in a special way

ALGORITHM

A step-by-step problem-solving procedure, especially an established, recursive computational procedure for solving a problem in a finite number of steps.



EXAMPLE TASK: PUT SHOES ON!

A human just understands an order and often executes it automatically even without thinking

A computer needs detailed instruction (an algorithm)

PUT SHOES ON! INSTRUCTION FOR A COMPUTER

1. Find two the same shoes
2. Check if you have left and right shoe
3. Check if they are of the same size
4. Check if this is the right size
5. Put the left shoe on
6. Put the right shoe on
7. Tie the laces

THE ORIGIN OF THE FIELD

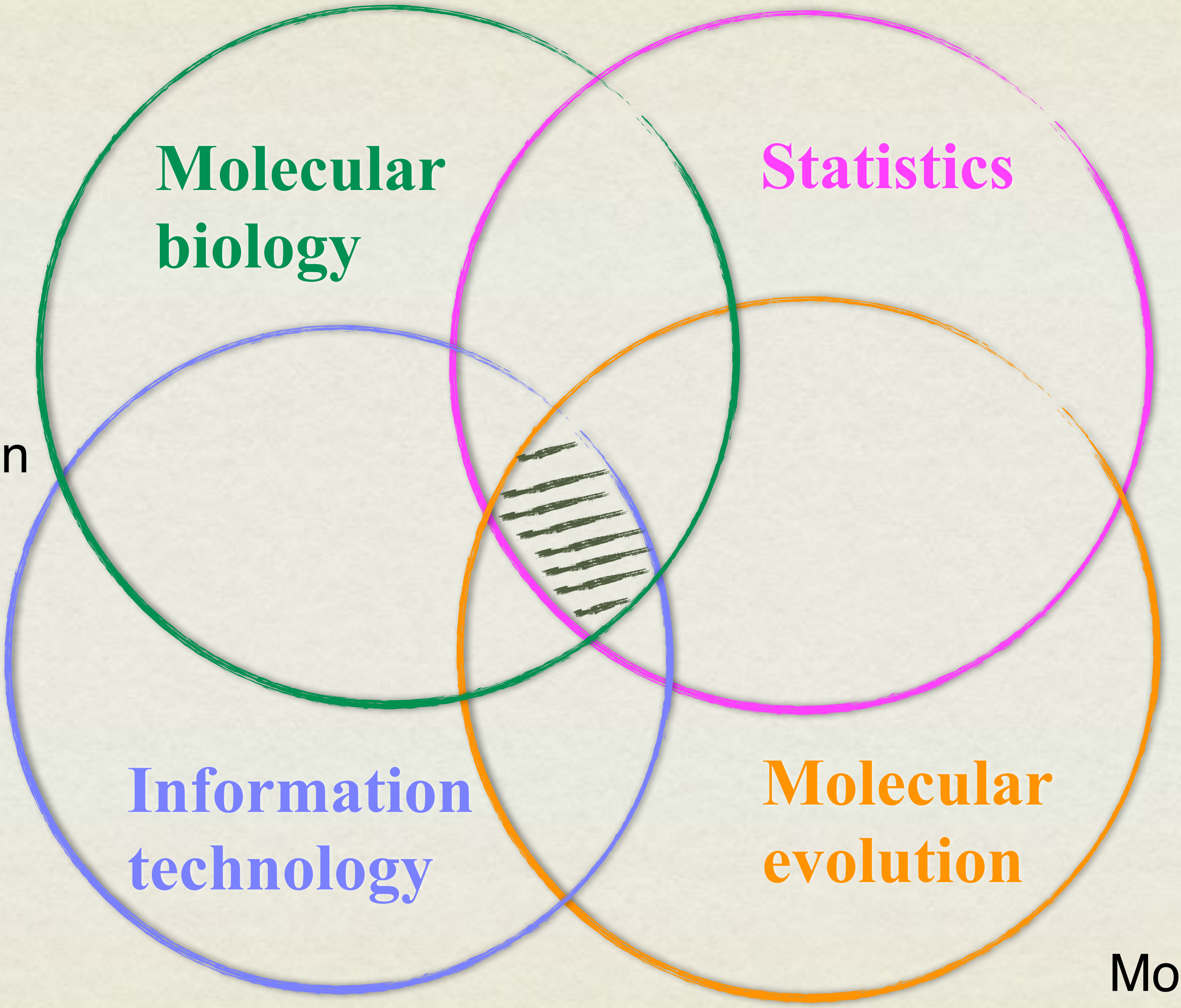
Paulien Hogeweg coined the term *bioinformatica* to define "the study of informatic processes in biotic systems". Hesper B, Hogeweg P (1970) Bioinformatica: een werkconcept. Kameleon 1(6): 28–29. (In Dutch.) Leiden: Leidse Biologen Club.

... but its origin can be tracked back many decades earlier.

BIOINFORMATICS EMERGED AS AN INTERSECTION BETWEEN DIFFERENT DISCIPLINES

James Watson

Alan Turing



Molecular biology

Statistics

Information technology

Molecular evolution

Thomas Bayes

Motoo Kimura

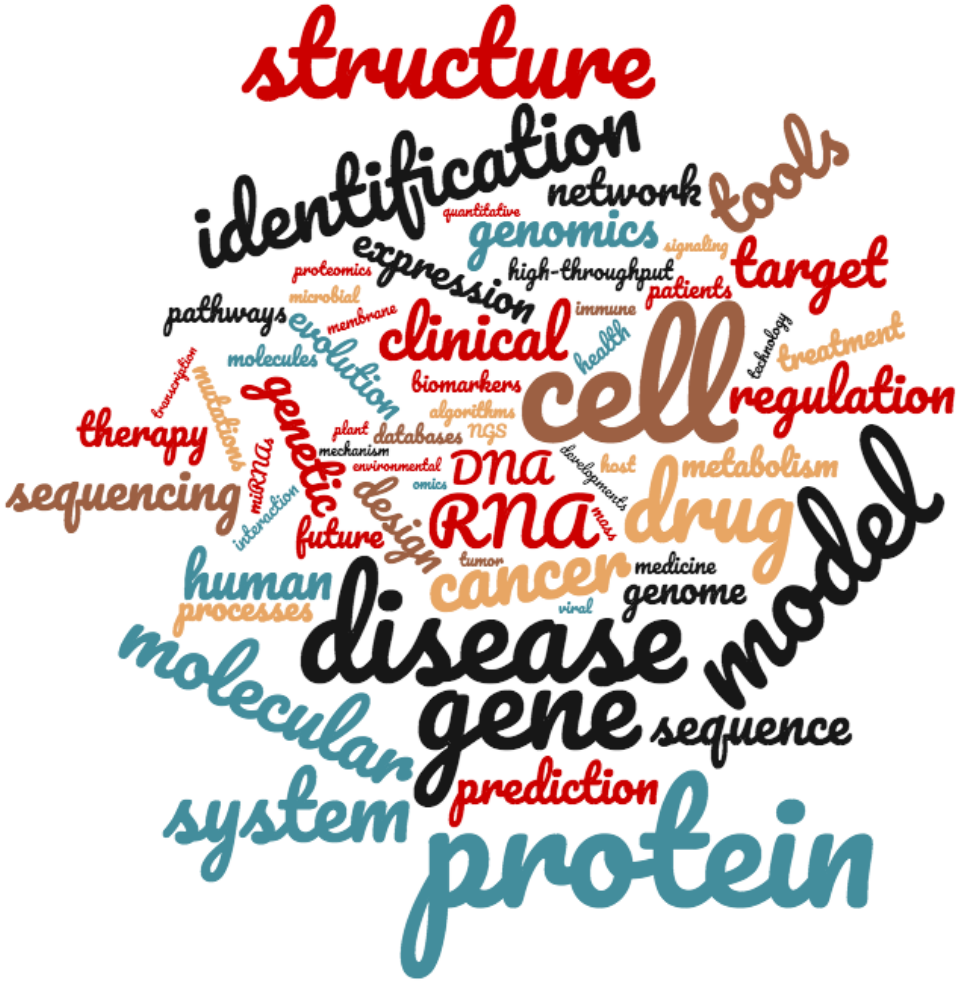
BIOINFORMATICS - DEFINITION

- Research, development, or application of computational tools and approaches for expanding the use of biological data, including those to acquire, store, organize, archive, analyze, or visualize such data.

- Its goal is to enable biological discovery based on existing information or in other words transform biological data into information and eventually into knowledge.

BIOINFORMATICS VERSUS COMPUTATIONAL BIOLOGY

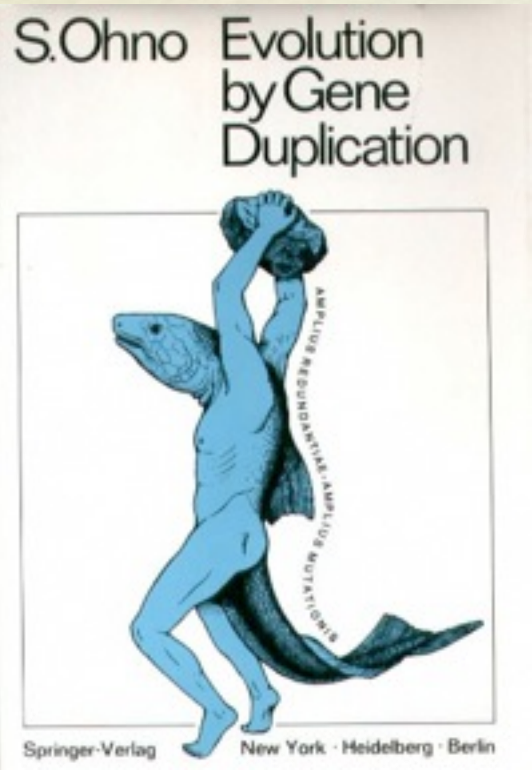
protein
disease
cell
gene
cancer
development
clinical
molecular
technology
therapeutic
pathway
expression
genomics
target
human
network
metabolism
sequence
health
plant
future
environment
tissue
microbiome
microorganisms
mutation
diagnosis
miRNA
database
transcription
RNA
DNA
NGS
virus
design
model
tool
drug
interactions
biomarker
bacteria
evolution
prediction
population
signaling
genetics
genome
treatment
molecules
immune
tumor
functions
individual
proteomic
structure
regulation
high-throughput
information
mechanisms
sequencing
potential
system
variants
targeted
patient
medicine
screening
host
lung
viral
diversity
detection
binding
stress
engineering
brain
algorithms
enzymes
life
food
stem
infection
pathogens
evolutionary
epigenetic
physiological
mitochondrial
modifications
variation
lncRNA
spectrometry



ROLE OF BIOINFORMATICS IN MODERN LIFE SCIENCES

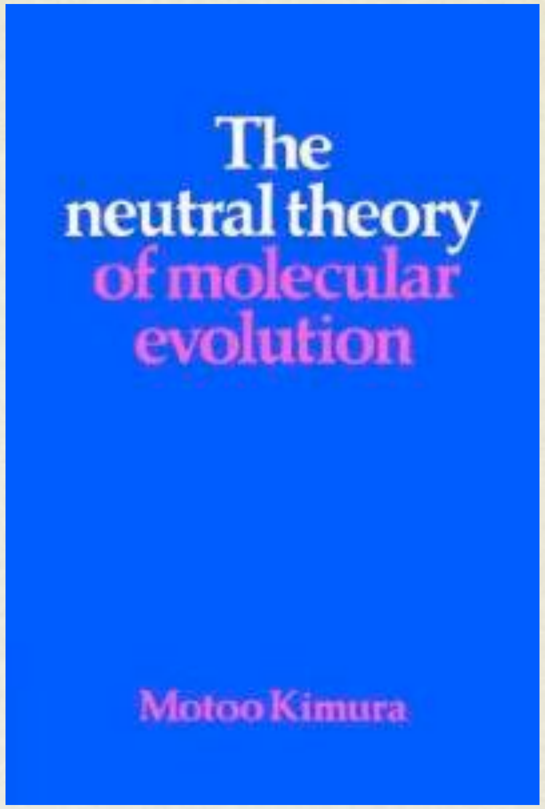
- molecular biology
- molecular evolution
- genomics
- system biology
- protein engineering
- drug design
- human genetics
- personalized medicine

EVOLUTIONARY BASIS OF BIOINFORMATICS



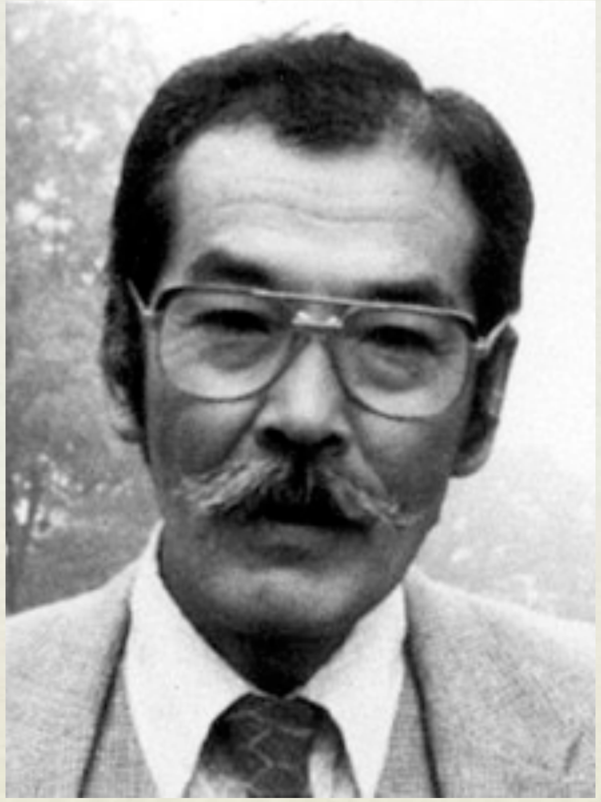
S.Ohno Evolution by Gene Duplication

Springer-Verlag New York · Heidelberg · Berlin

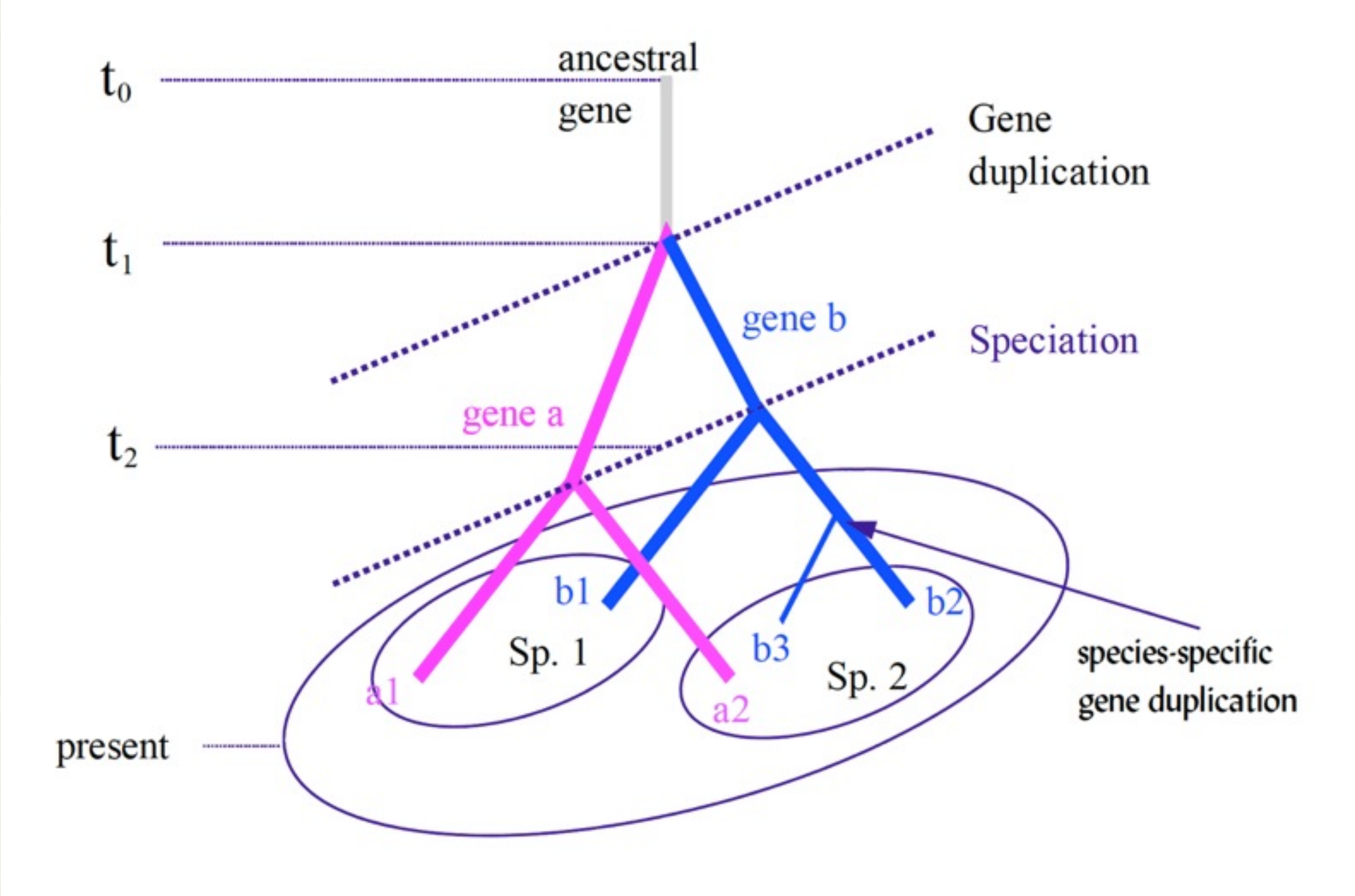


The neutral theory of molecular evolution

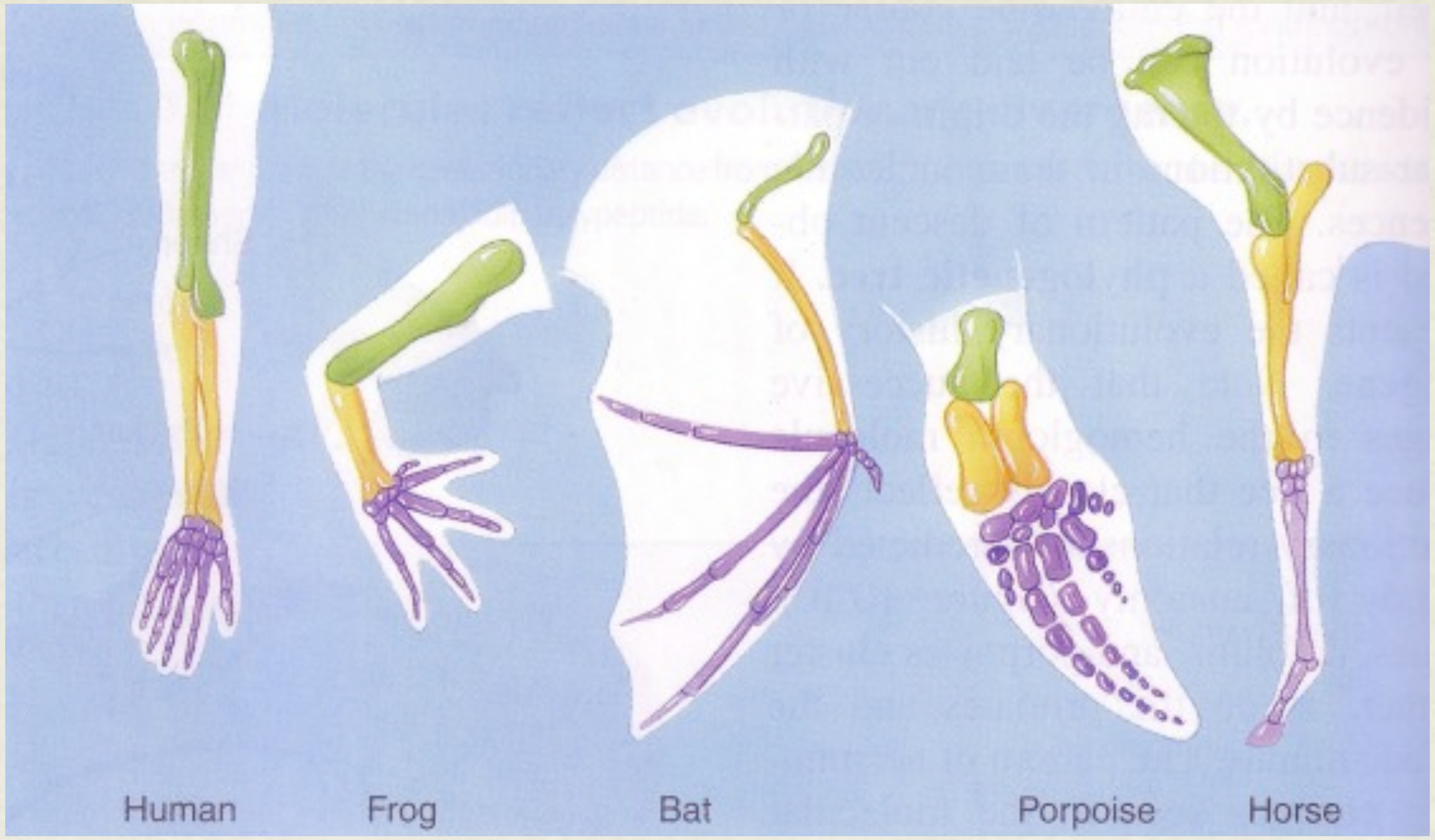
Motoo Kimura



EVOLUTIONARY BASIS OF BIOINFORMATICS



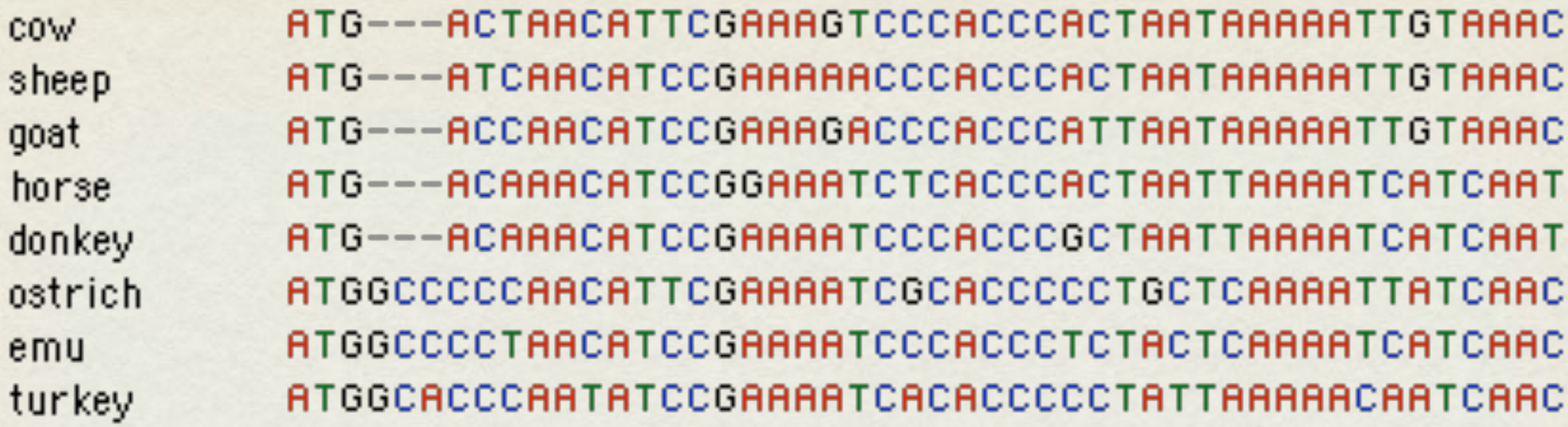
HOMOLOGS



Two anatomical structures or behavioral traits within different organisms which originated from a structure or trait of their common ancestral organism. The structures or traits in their current forms may not necessarily perform the same functions in each organism, nor perform the functions it did in the common ancestor. An example: the wing of a bat, the fin of a whale and the arm of a man are homologous structures.

http://www.everythingbio.com/glos/definition.php?ID=3385

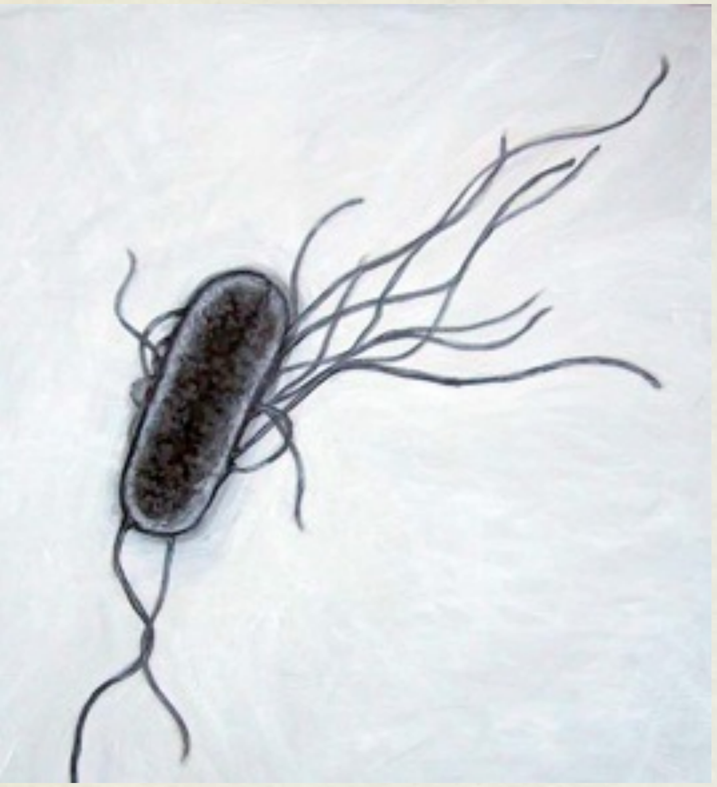
HOMOLOGS AT THE MOLECULAR LEVEL



```
cow        ATG---ACTAACATTCGAAAGTCCCACCCACTAATAAAAATTGTAAAC
sheep      ATG---ATCAACATCCGAAAAACCCACCCACTAATAAAAATTGTAAAC
goat       ATG---ACCAACATCCGAAAGACCCACCCATTAATAAAAATTGTAAAC
horse      ATG---ACAAACATCCGGAAATCTCACCCACTAATTAAAATCATCAAT
donkey     ATG---ACAAACATCCGAAAATCCCACCCGCTAATTAAAATCATCAAT
ostrich    ATGGCCCCCAACATTCGAAAATCGCACCCCCTGCTCAAAATTATCAAC
emu        ATGGCCCCTAACATCCGAAAATCCCACCCTCTACTCAAAATCATCAAC
turkey     ATGGCACCCAATATCCGAAAATCACACCCCCTATTAAAAACAATCAAC
```

Two sequences that share common ancestry. Significant sequence similarity usually suggests homology, however sequence similarity may occur also by chance and some homologous sequences may diverge beyond detectable similarity.

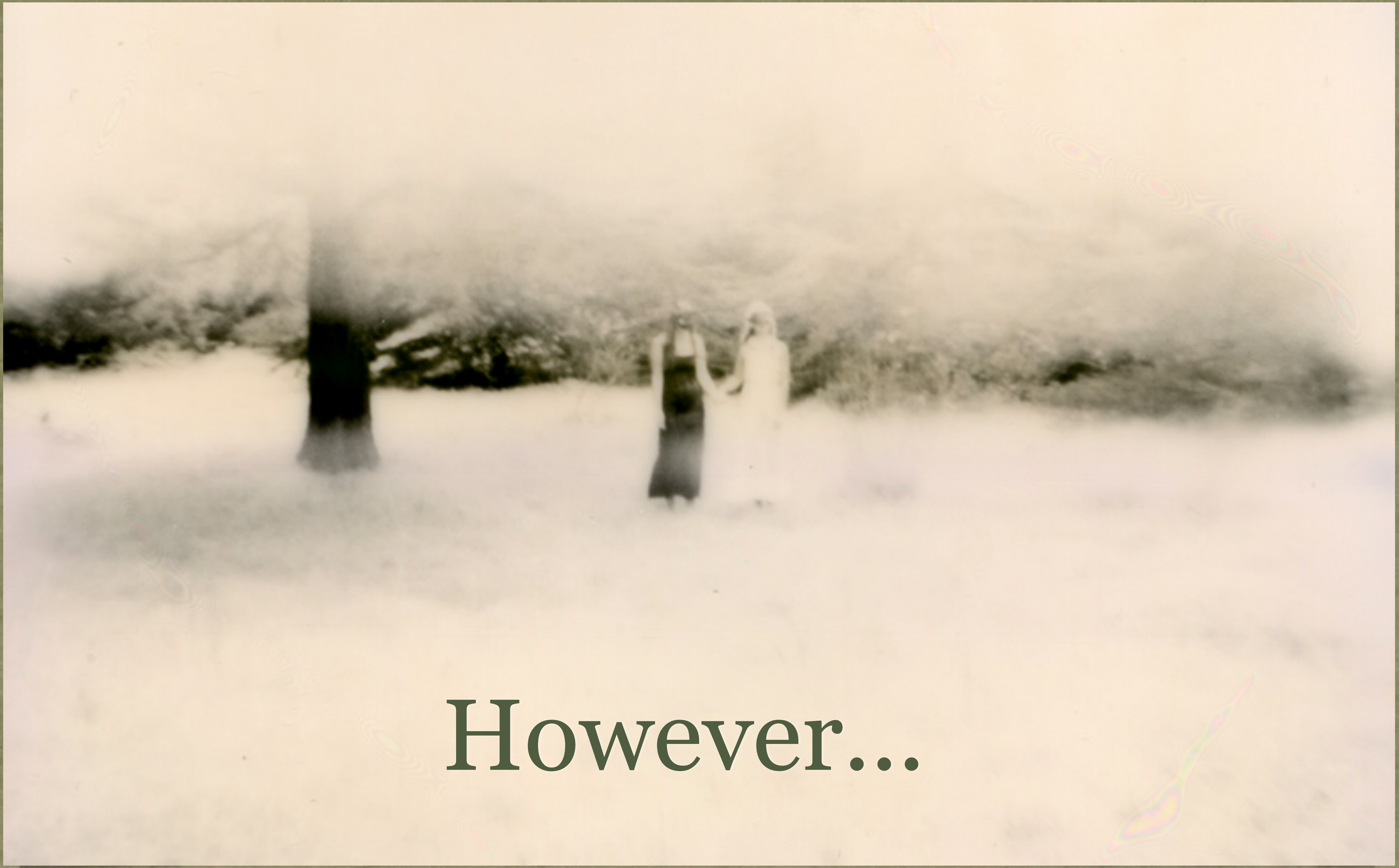
COMPARATIVE GENOMICS



What is true for *E. coli* is also true for elephant.

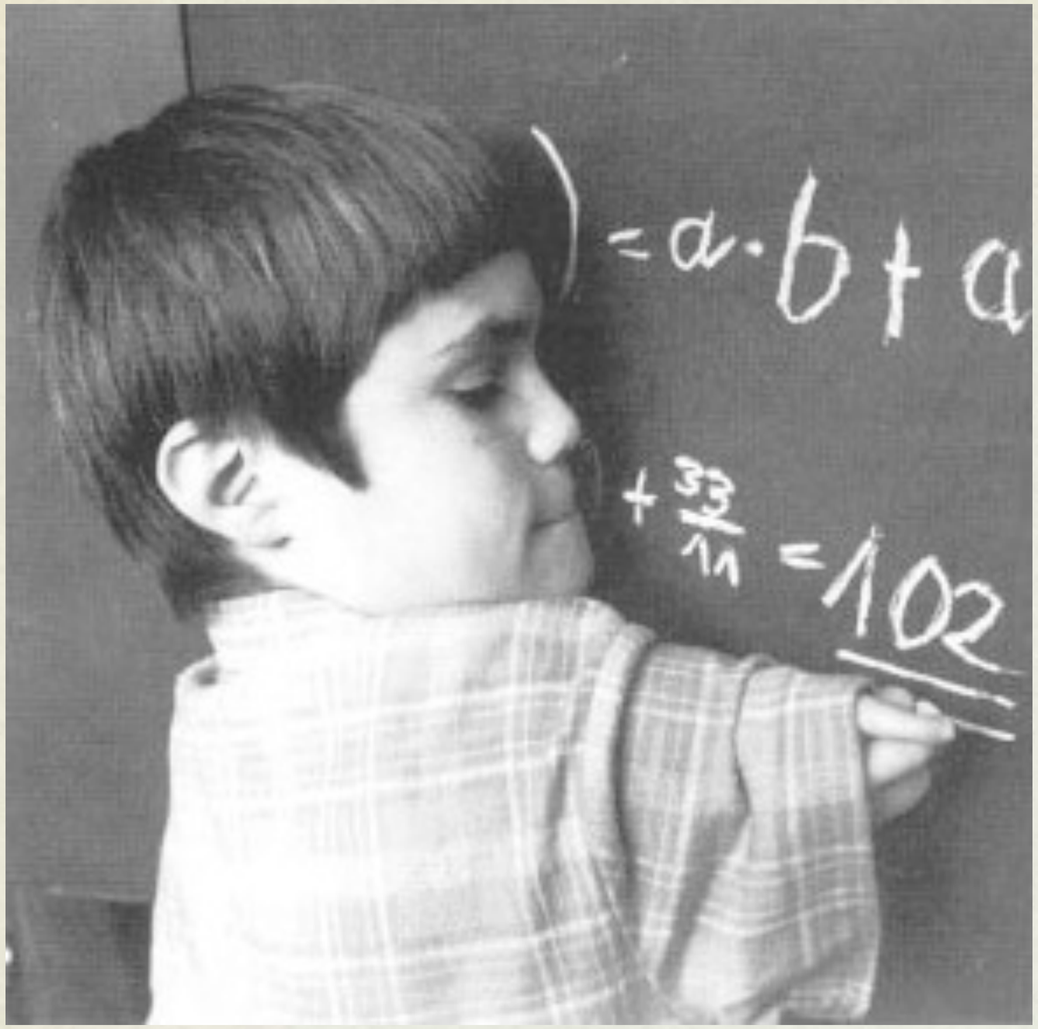
J. Monod, c. 1961

COMPARATIVE GENOMICS



However...

COMPARATIVE GENOMICS

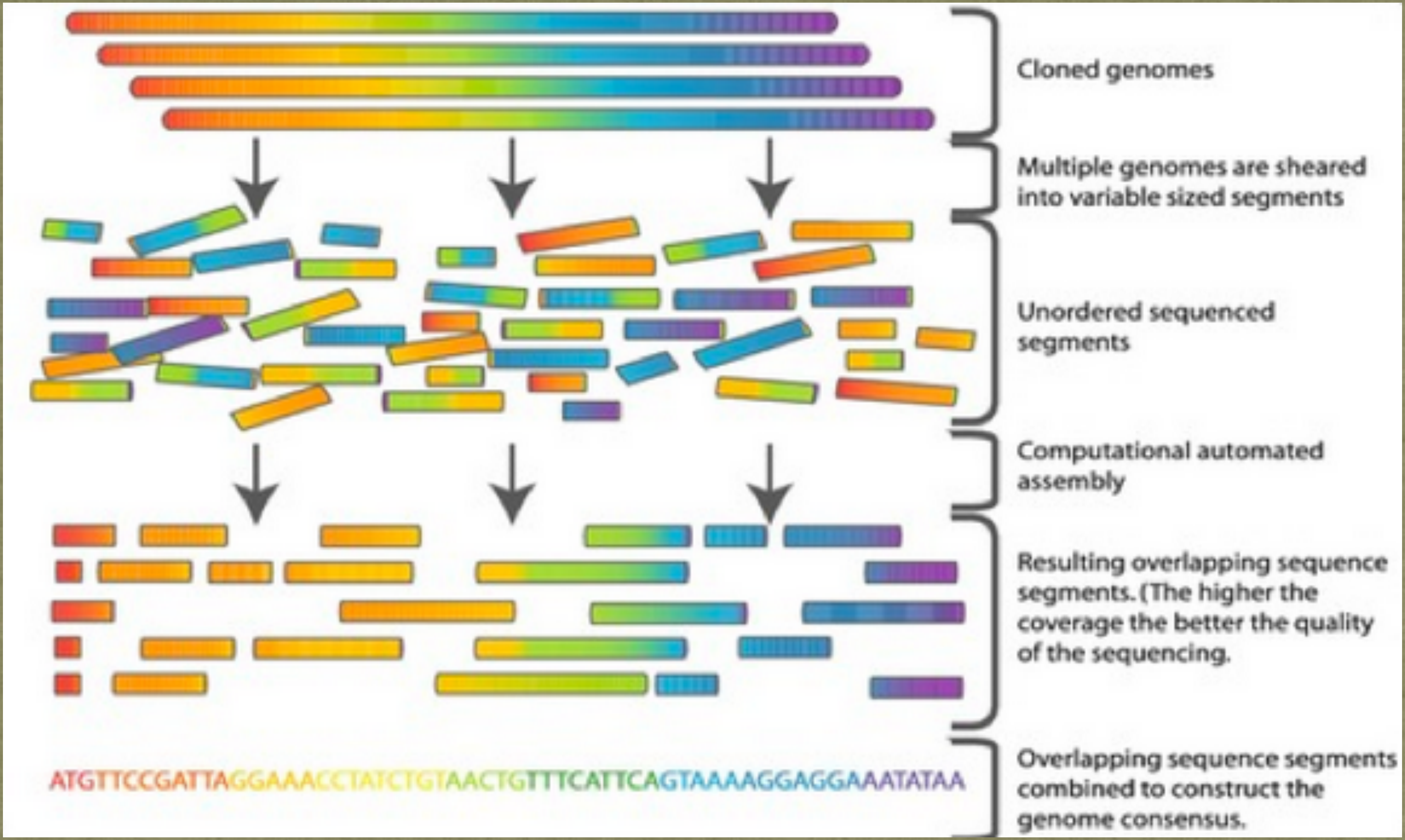


15 000 victims of thalidomide

What is true for mouse is not necessarily true for human…

Nucleotide Sequence Assembly

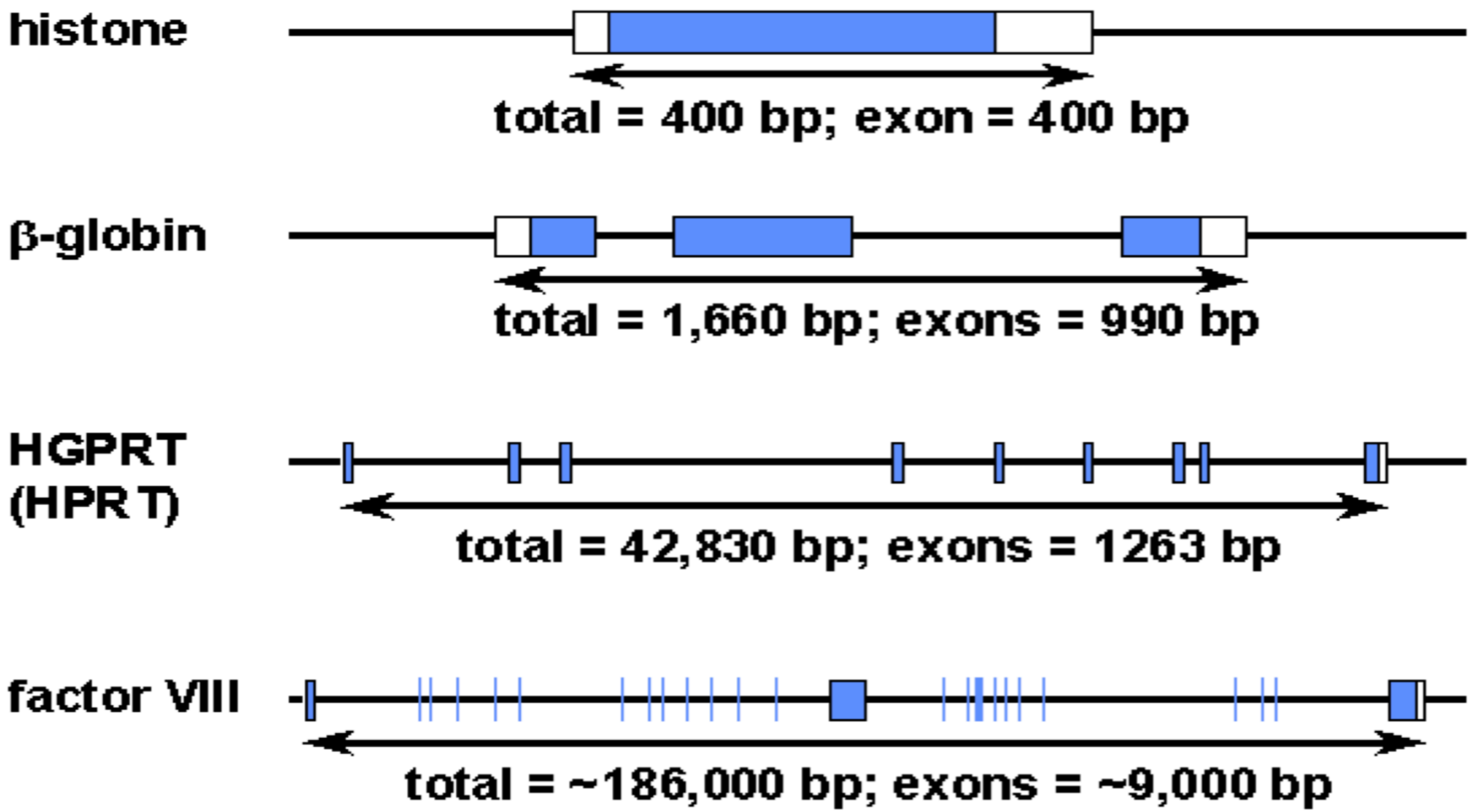
NUCLEOTIDE SEQUENCE ASSEMBLY


Cloned genomes
Multiple genomes are sheared into variable sized segments
Unordered sequenced segments
Computational automated assembly
Resulting overlapping sequence segments. (The higher the coverage the better the quality of the sequencing.
ATGTTCCGATTAGGAAACCTATCTGTAACTGTTTCATTCAGTAAAAGGAGGAAATATAA
Overlapping sequence segments combined to construct the genome consensus.

Similarity Search

Gene Prediction

(exon-intron-exon)$_n$ structure of various genes



histone

total = 400 bp; exon = 400 bp

β-globin

total = 1,660 bp; exons = 990 bp

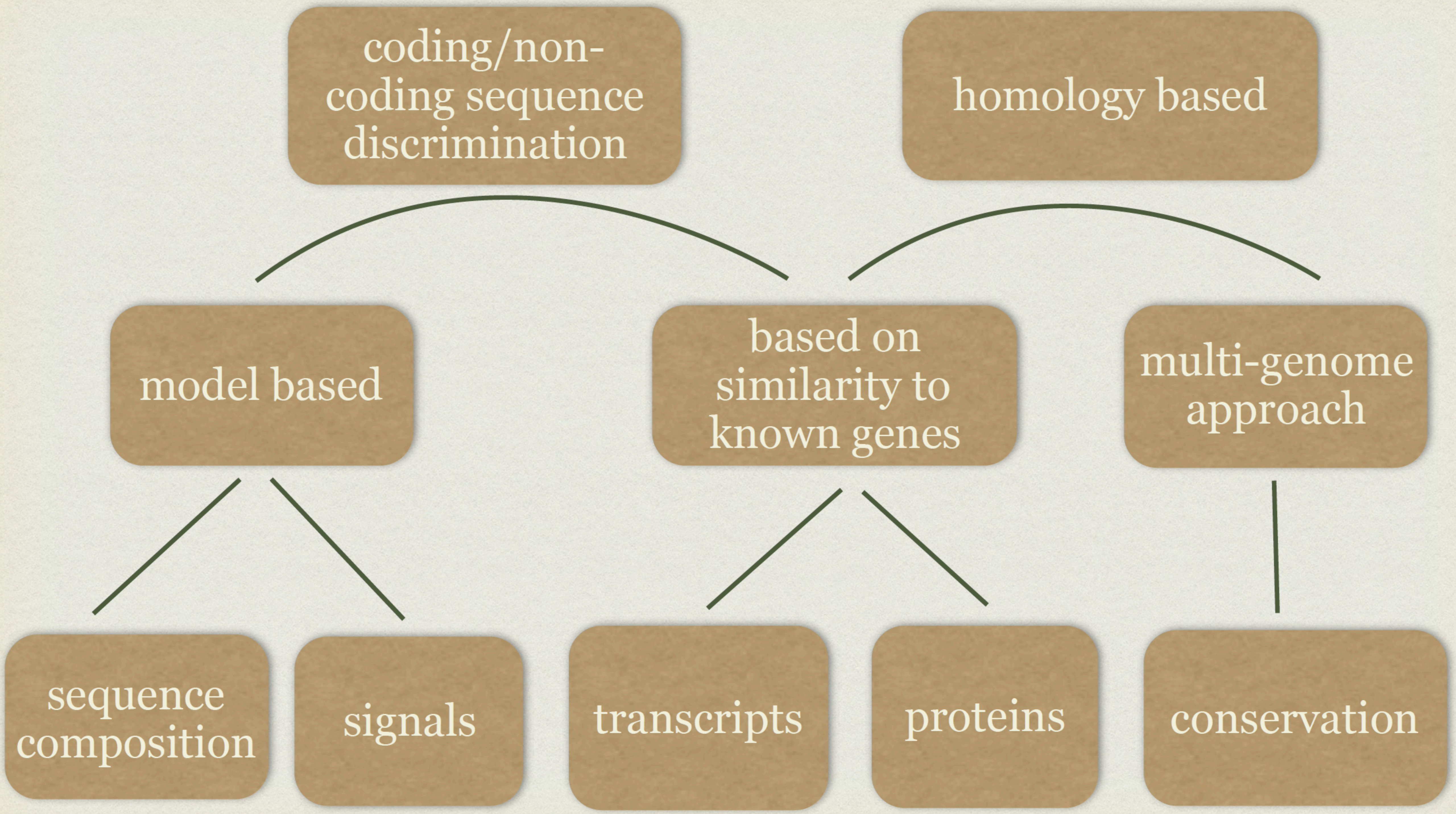
HGPRT (HPRT)

total = 42,830 bp; exons = 1263 bp

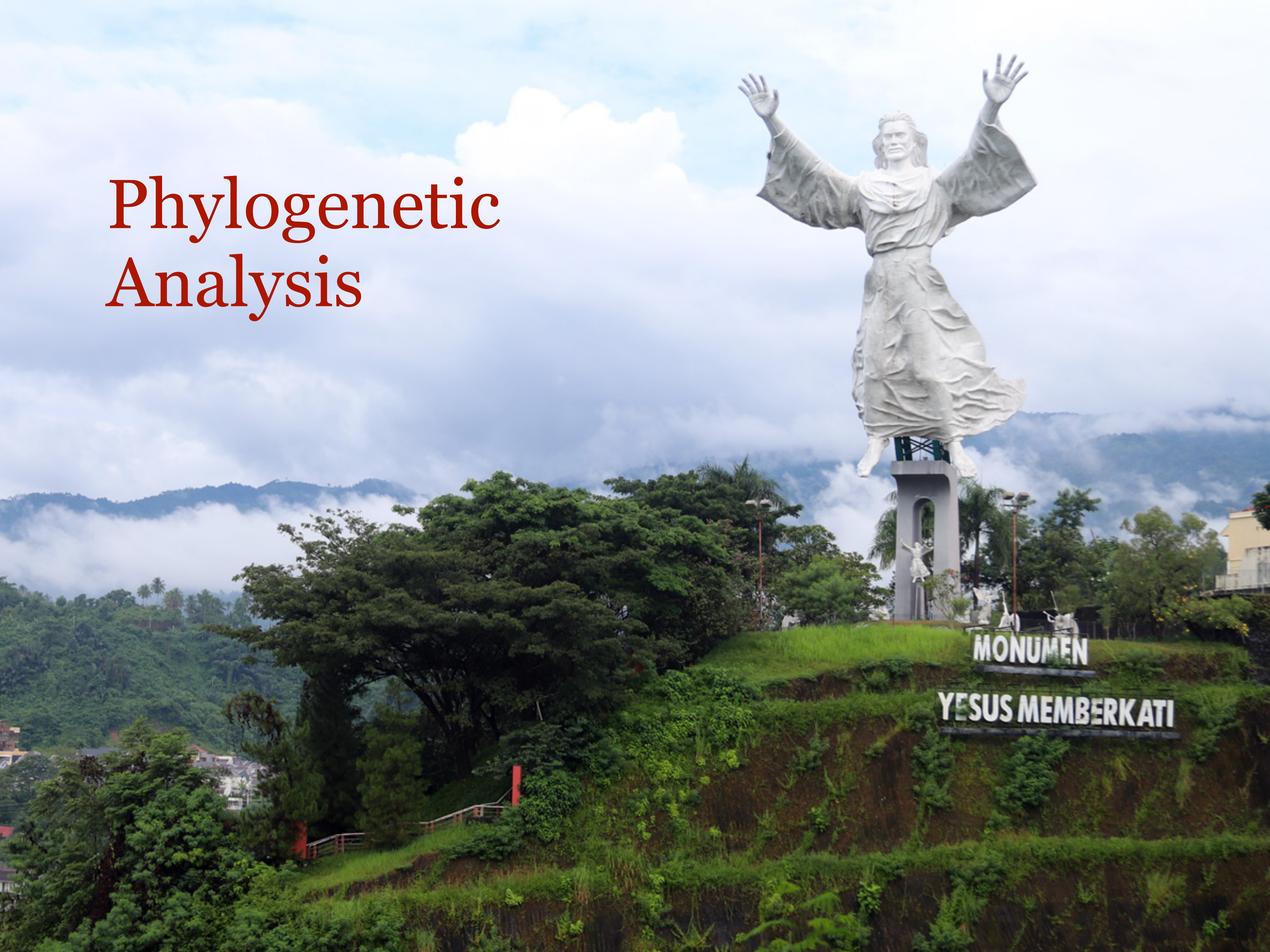
factor VIII

total = ~186,000 bp; exons = ~9,000 bp

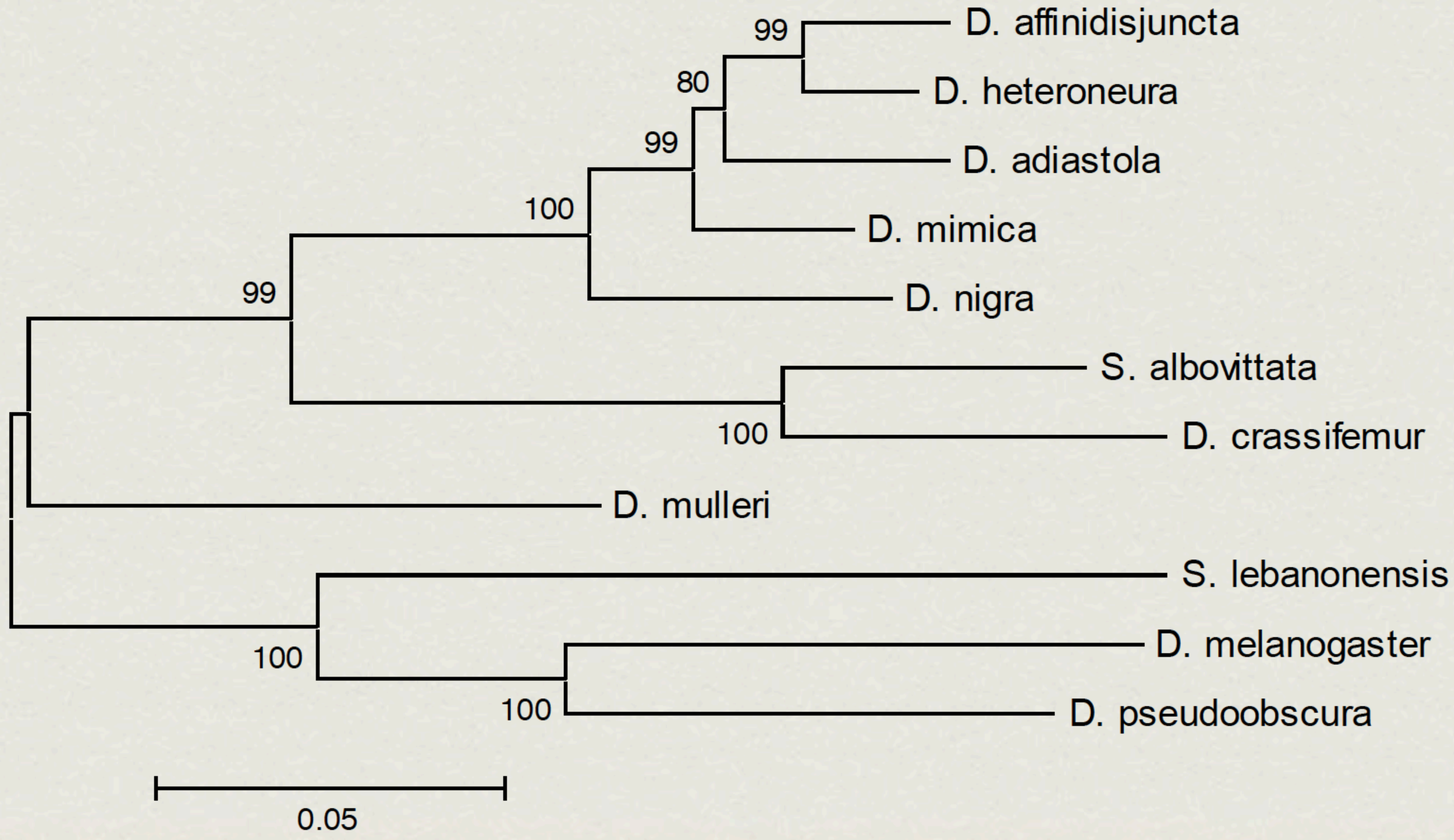
GENE FINDING METHODS



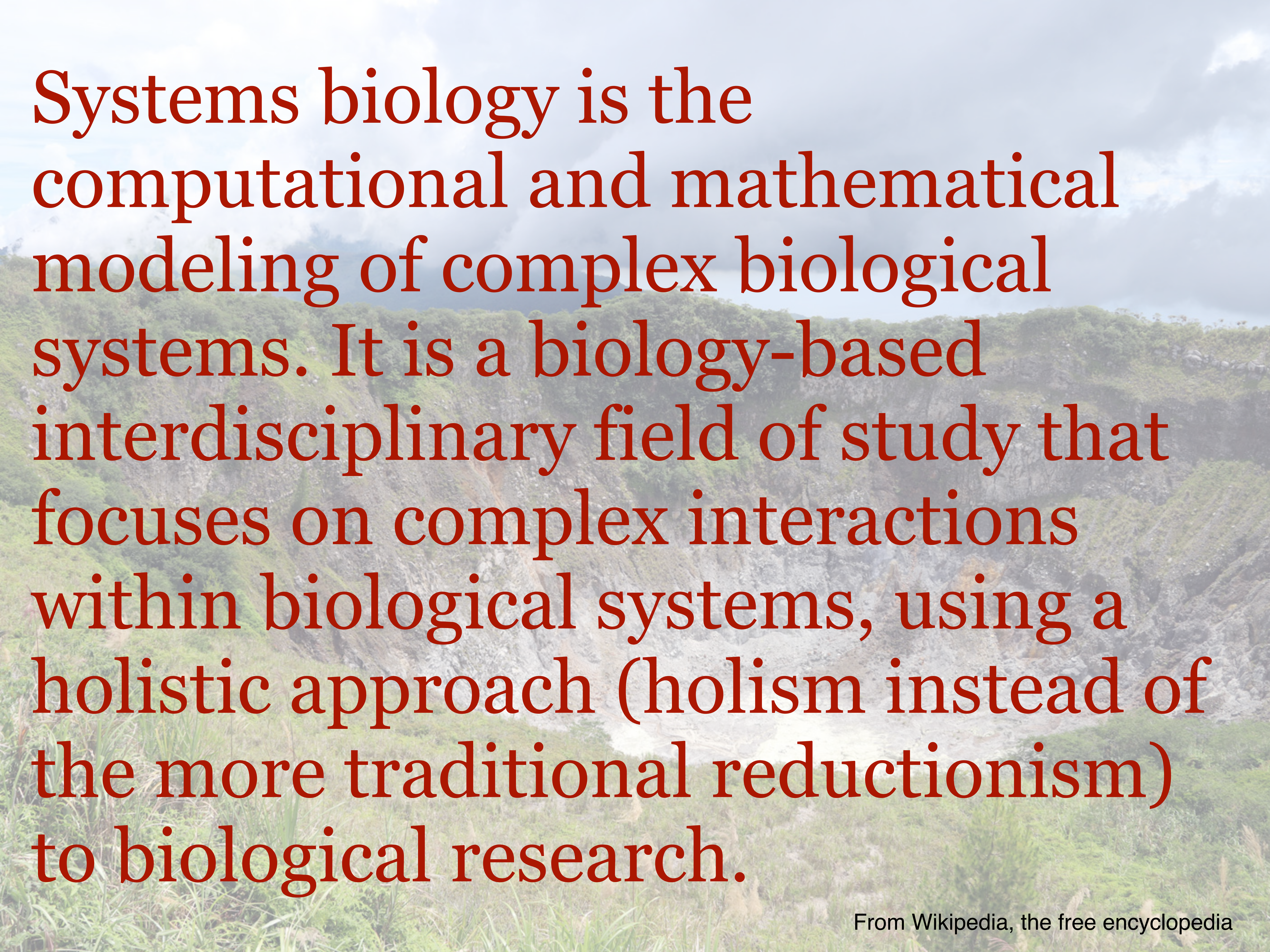
Phylogenetic Analysis



Phylogenetic Analysis



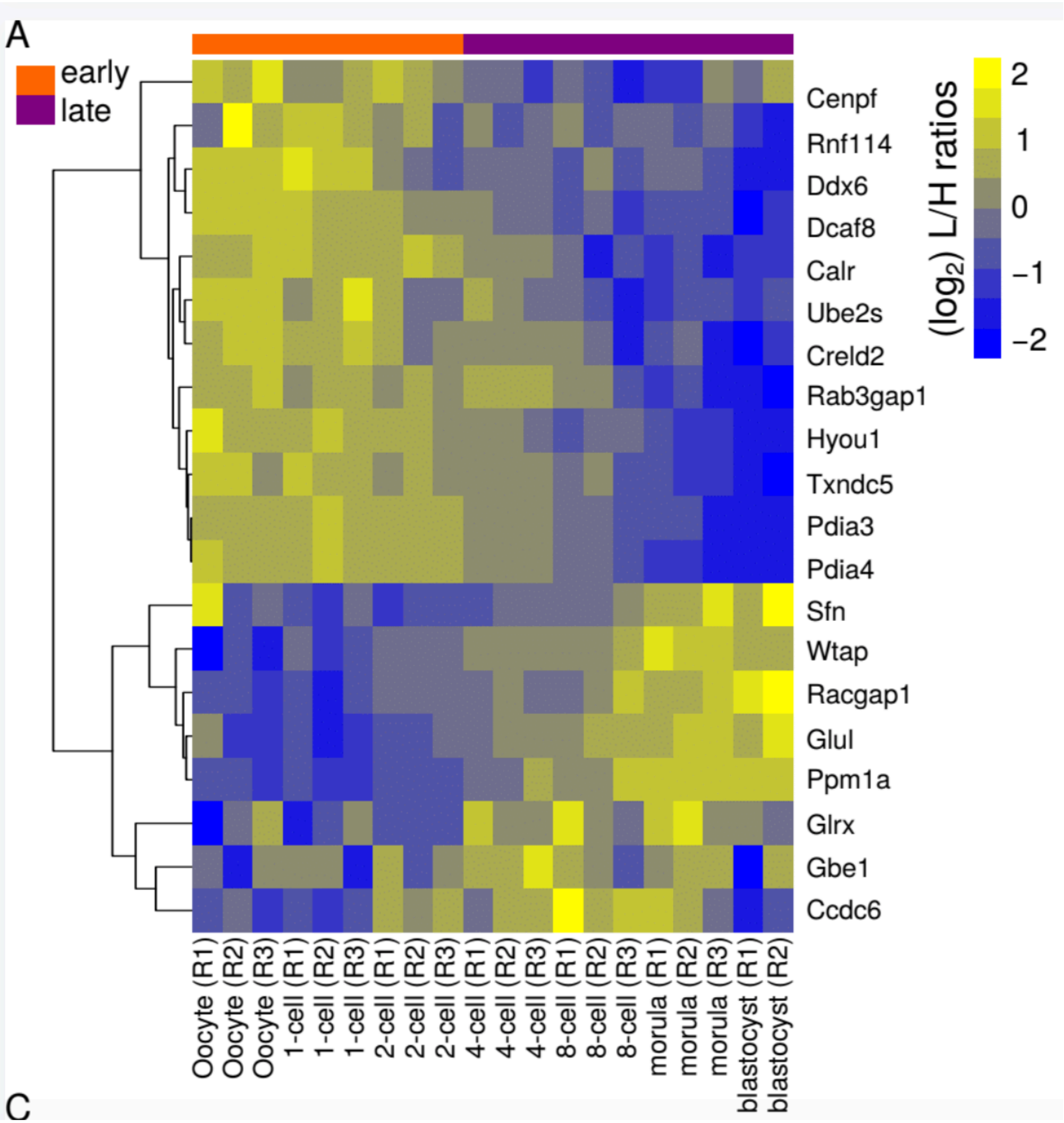
Systems Biology



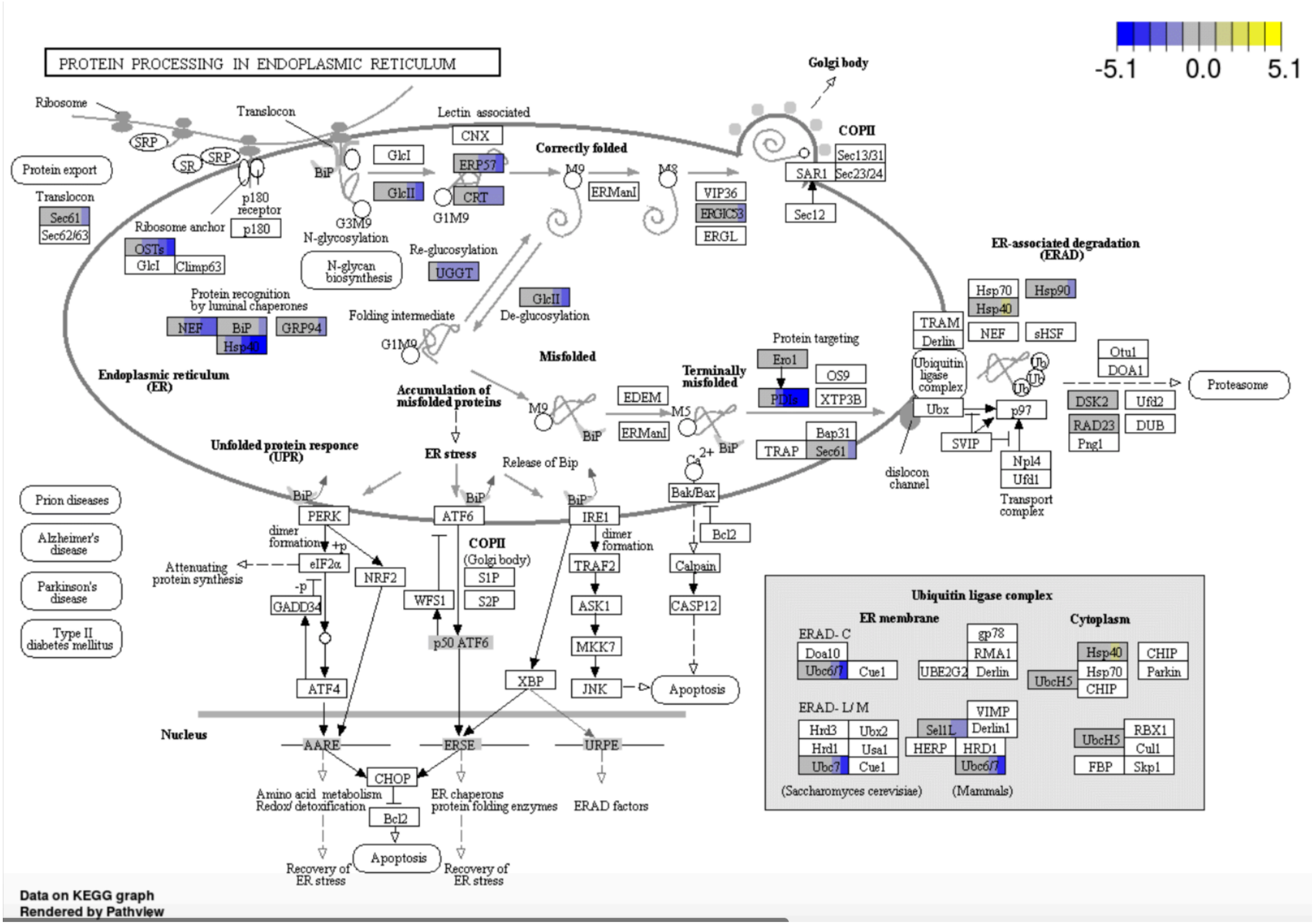
Systems biology is the computational and mathematical modeling of complex biological systems. It is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach (holism instead of the more traditional reductionism) to biological research.

From Wikipedia, the free encyclopedia

Differential gene expression during mouse early embryogenesis

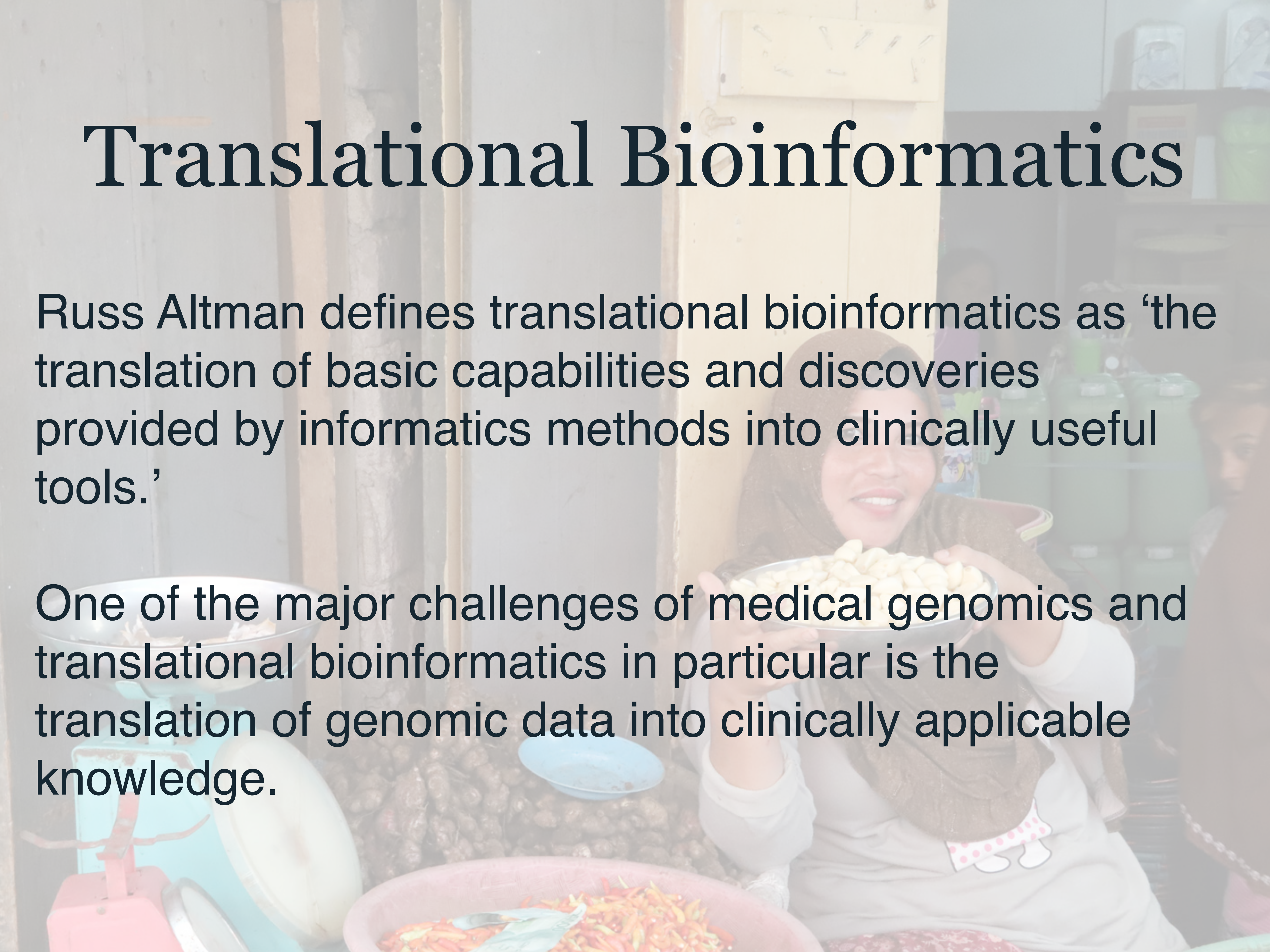


Israel et al. *Genome Research,* under revision



Israel et al. *Genome Research,* under revision

Translational Bioinformatics



Translational Bioinformatics

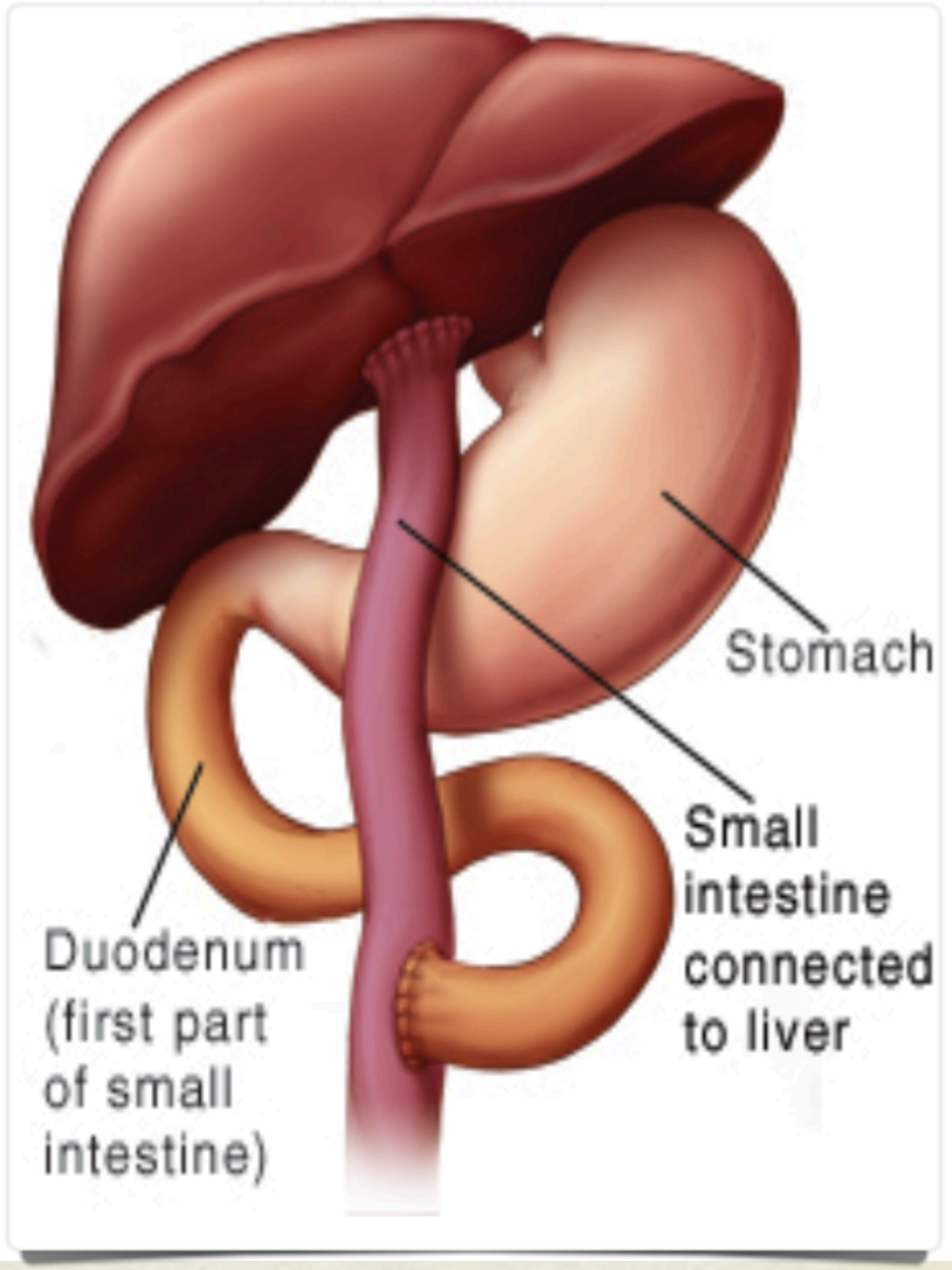
Russ Altman defines translational bioinformatics as ‘the translation of basic capabilities and discoveries provided by informatics methods into clinically useful tools.’

One of the major challenges of medical genomics and translational bioinformatics in particular is the translation of genomic data into clinically applicable knowledge.

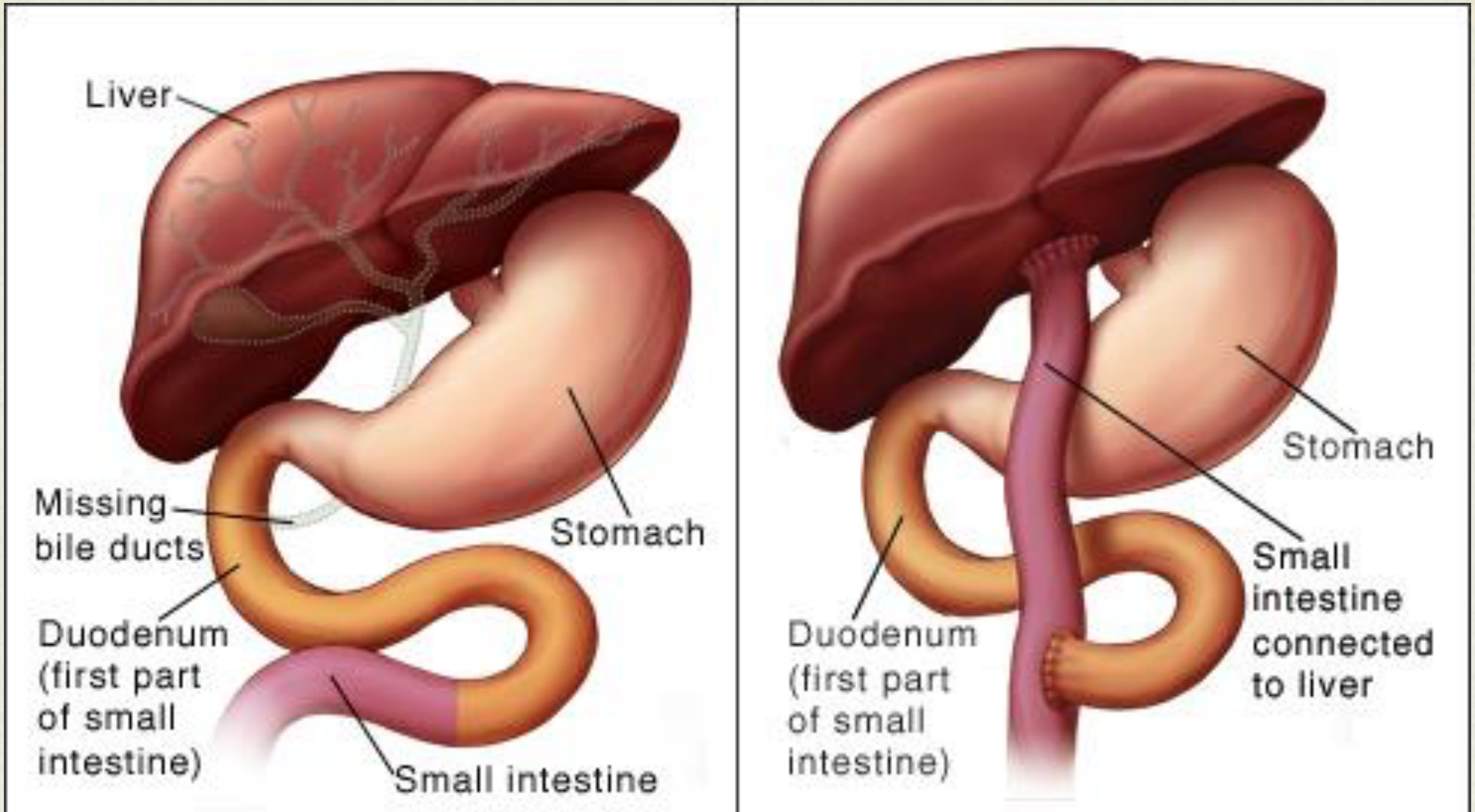
CLINICAL SUCCESS STORY

RADY CHILDREN'S HOSPITAL BABY 6026

- Two month old child admitted to PICU with severe jaundice & poor weight gain for one month
- Echo: Congenital heart disease, underdeveloped pulmonary arteries
- Clinical diagnosis: biliary atresia
  - one incidence in ten thousand
- Empiric treatment: Kasai procedure


Stomach
Small intestine connected to liver
Duodenum (first part of small intestine)

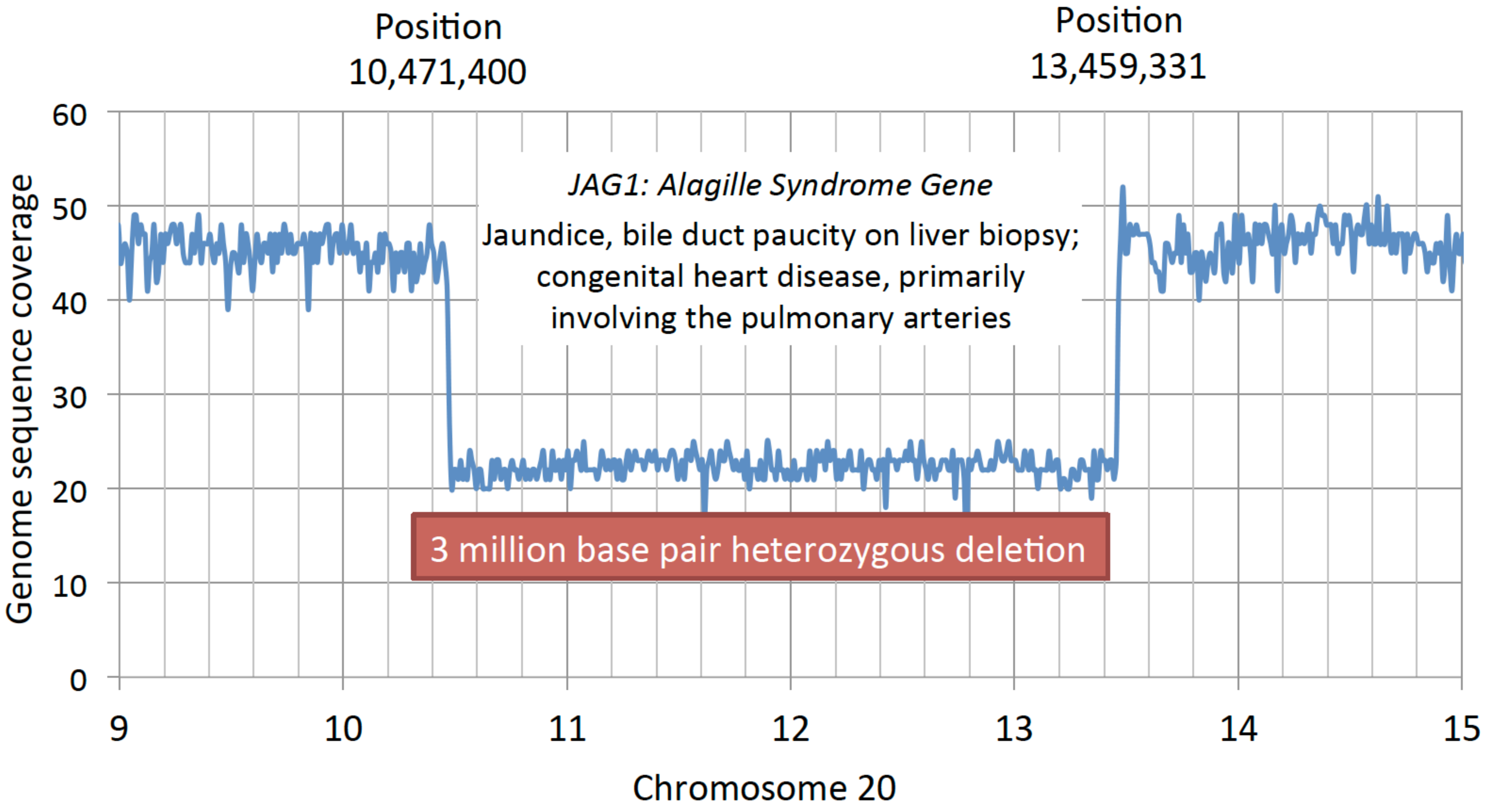
KASAI PROCEDURE


Liver
Missing bile ducts
Stomach
Duodenum (first part of small intestine)
Small intestine
Stomach
Small intestine connected to liver
Duodenum (first part of small intestine)

The dotted lines show areas that can be affected by biliary atresia.

During the Kasai procedure, the intestine is attached to the liver. This allows bile to drain.

43 HOURS LATER: PROVISIONAL DIAGNOSIS



JAG1: Alagille Syndrome Gene

Jaundice, bile duct paucity on liver biopsy; congenital heart disease, primarily involving the pulmonary arteries

3 million base pair heterozygous deletion

CLINICAL IMPACT & OUTCOME

- Kasai procedure scheduled for 11:00 am
- Genetic diagnosis communicated to clinical team just before surgery – procedure cancelled
- Infants with Alagille syndrome are occasionally misdiagnosed as biliary atresia and subsequently undergo Kasai operation during infancy
- Among 15 children with Alagille syndrome, mortality was 60% after Kasai procedure, and only 10% among those without Kasai procedure. Liver transplantation was performed in 100% of the Kasai group, and 20% of the non-Kasai group.

Dr. Narayanan Veeraraghavan, personal communication

BIOINFORMATICS IN MEDICINE CHALLENGES

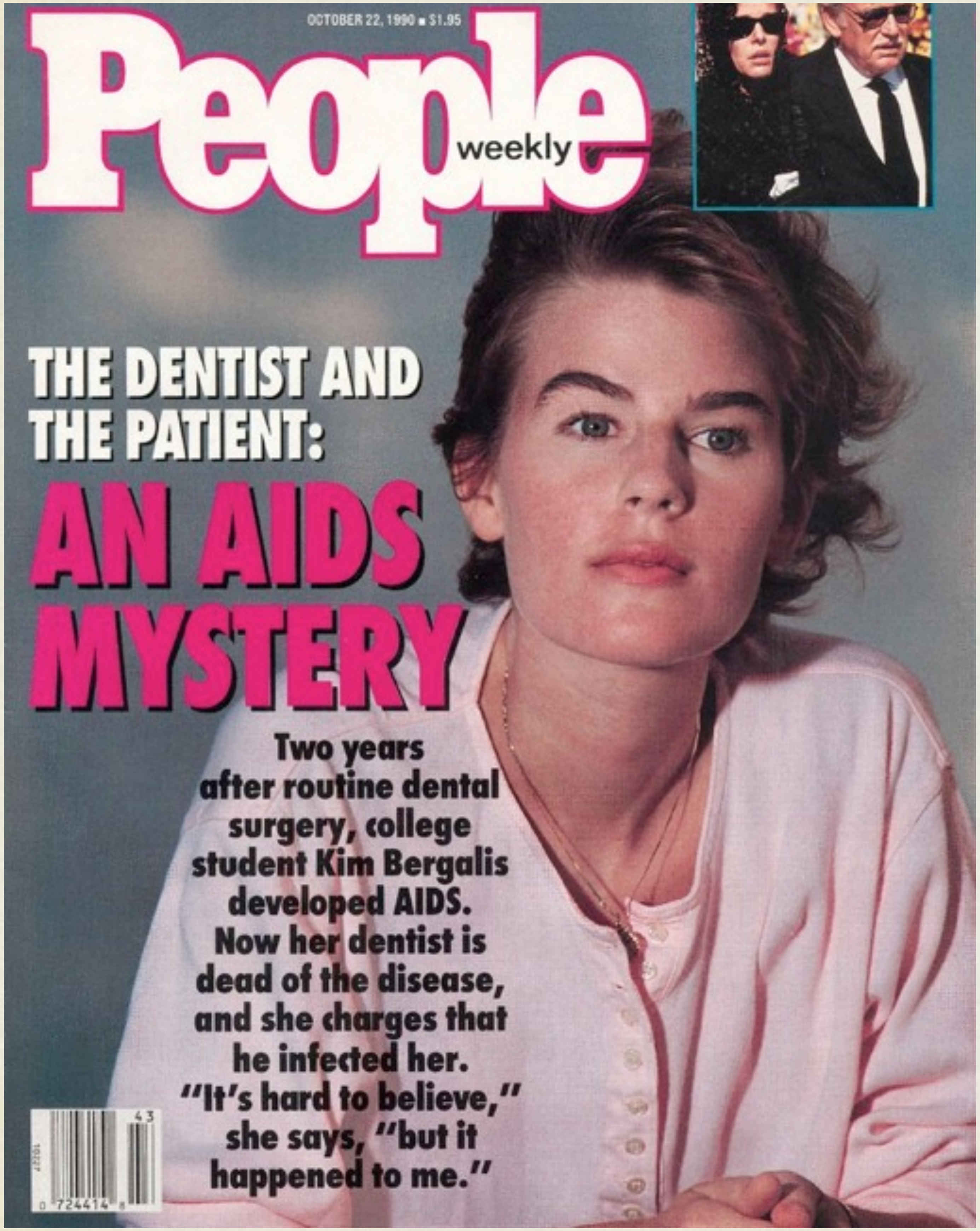
- Data volume
- Computational skills for in-depth analyses
- Data interpretation
- Research translation
- Data volume!!!

Data Volume Problem

Type of cancer	Number of whole genome	Number of whole exome	Data volume (Tb)	Time to download
Colon Adenocarcinoma (COAD)	302	443	33.04	24 days
Lung	134	582	40.95	30 days
Breast	248	1050	69.82	50 days
Prostate Adenocarcinoma (PRAD)	272	1049	26.53	10 days

http://bioinformatics.uni-muenster.de

Did the Florida Dentist infect his patients with HIV?



OCTOBER 22, 1990 ■ $1.95

People weekly

THE DENTIST AND THE PATIENT:

AN AIDS MYSTERY

Two years after routine dental surgery, college student Kim Bergalis developed AIDS. Now her dentist is dead of the disease, and she charges that he infected her. "It's hard to believe," she says, "but it happened to me."

Kimberly Bergalis

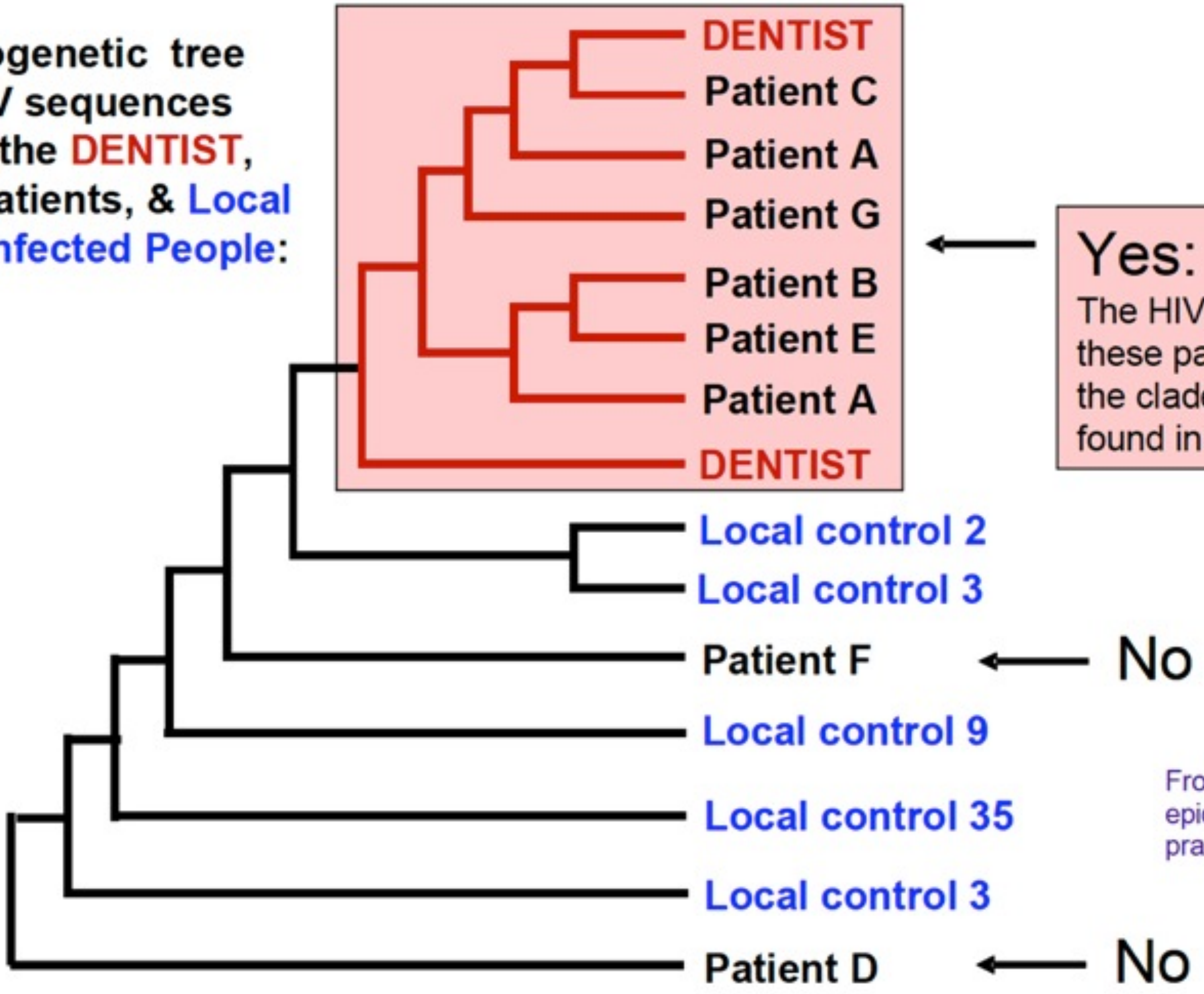
(1968-1991)

David J. Acer

(1940-1990)

DID THE FLORIDA DENTIST INFECT HIS PATIENTS WITH HIV?

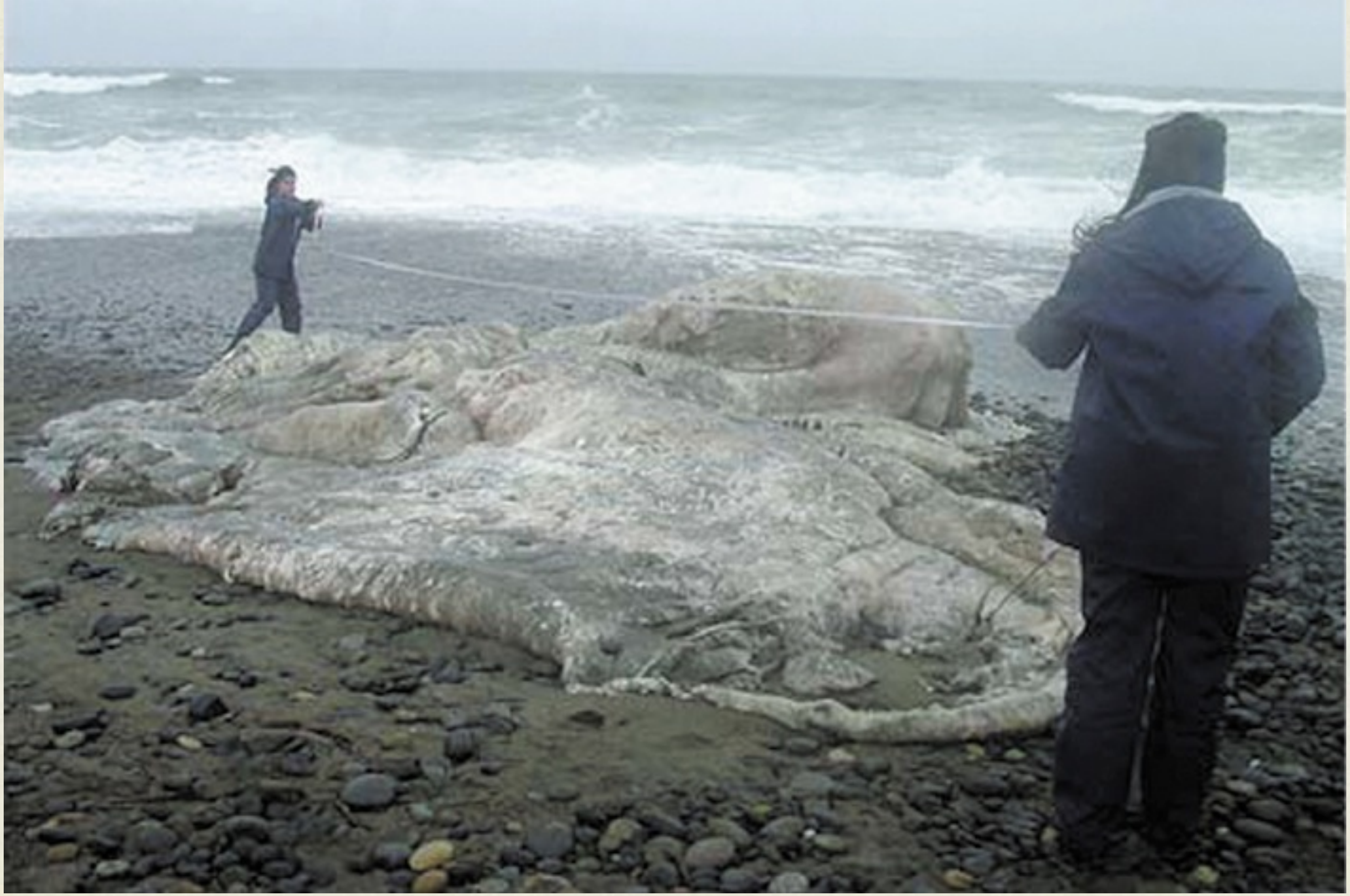
Phylogenetic tree of HIV sequences from the DENTIST, his Patients, & Local HIV-infected People:



Yes:
The HIV sequences from these patients fall within the clade of HIV sequences found in the dentist.

From Ou et al. (1992) Molecular epidemiology of HIV transmission in a dental practice. Science. 256:1165-71.

THE MYSTERY OF THE CHILEAN BLOB



THE MYSTERY OF THE CHILEAN BLOB

```
>Chilean_Blob
TAATACTAACTATATCCCTACTCTCCATTCTCATCGGGG
GTTGAGGAGGACTAAACCAGACTCAACTCCGAAAAATTA
TAGCTTACTCATCAATCGCCCACATAGGATGAATAACCA
CAATCCTACCCTACAATACAACCATAACCCTACTAAACC
TACTAATCTATGTCACAATAACCTTCACCATATTCATAC
TATTTATCCAAAACTCAACCACAACCACACTATCTCTGT
CCCAGACATGAAACAAAACACCCATTACCACAACCCTTA
CCATACTTACCCTACTTTCCATAGGGGGCCTCCCACCAC
TCTCGGGCTTTATCCCCAAATGAATAATTATTCAAGAAC
TAACAAAAAACGAAACCCTCATCATACCAACCTTCATAG
CCACCACAGCATTACTCAACCTCTACTTCTATATACGCC
TCACCTACTCAACAGCACTAACCCTATTCCCCTCCACAA
ATAACATAAAAATAAAATGACAATTCTACCCCACAAAAC
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AG
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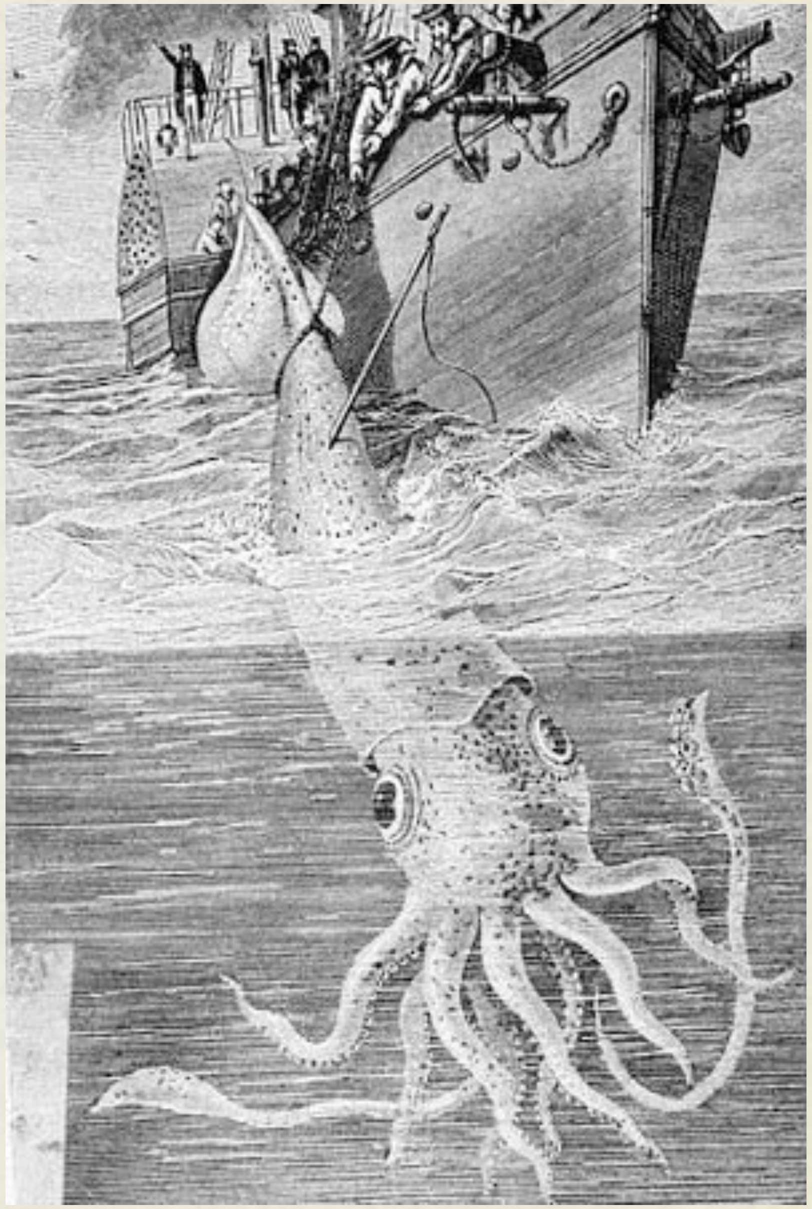
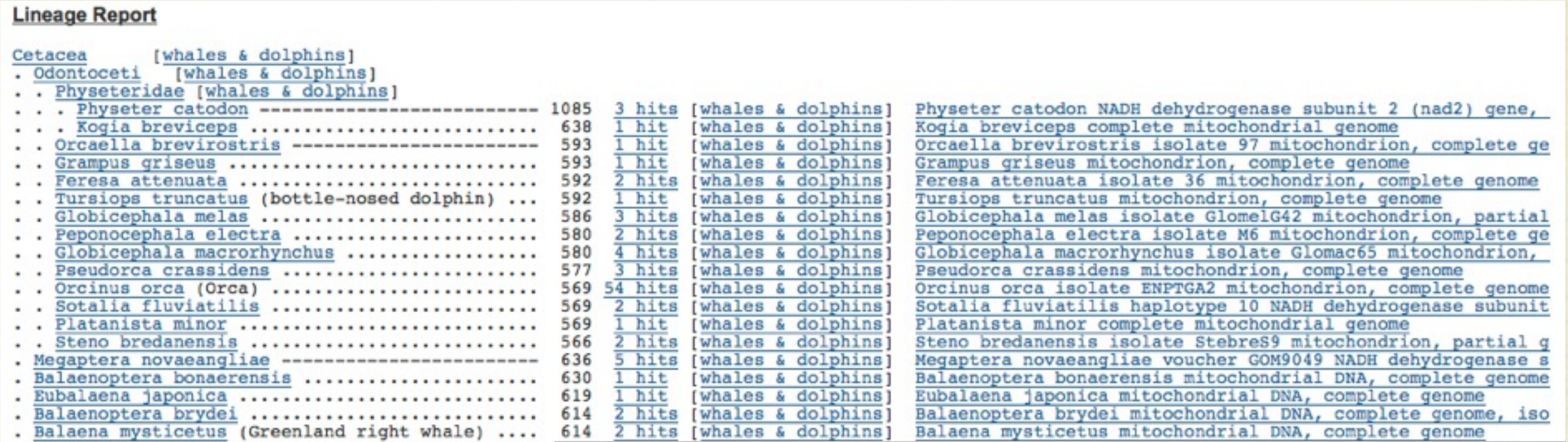


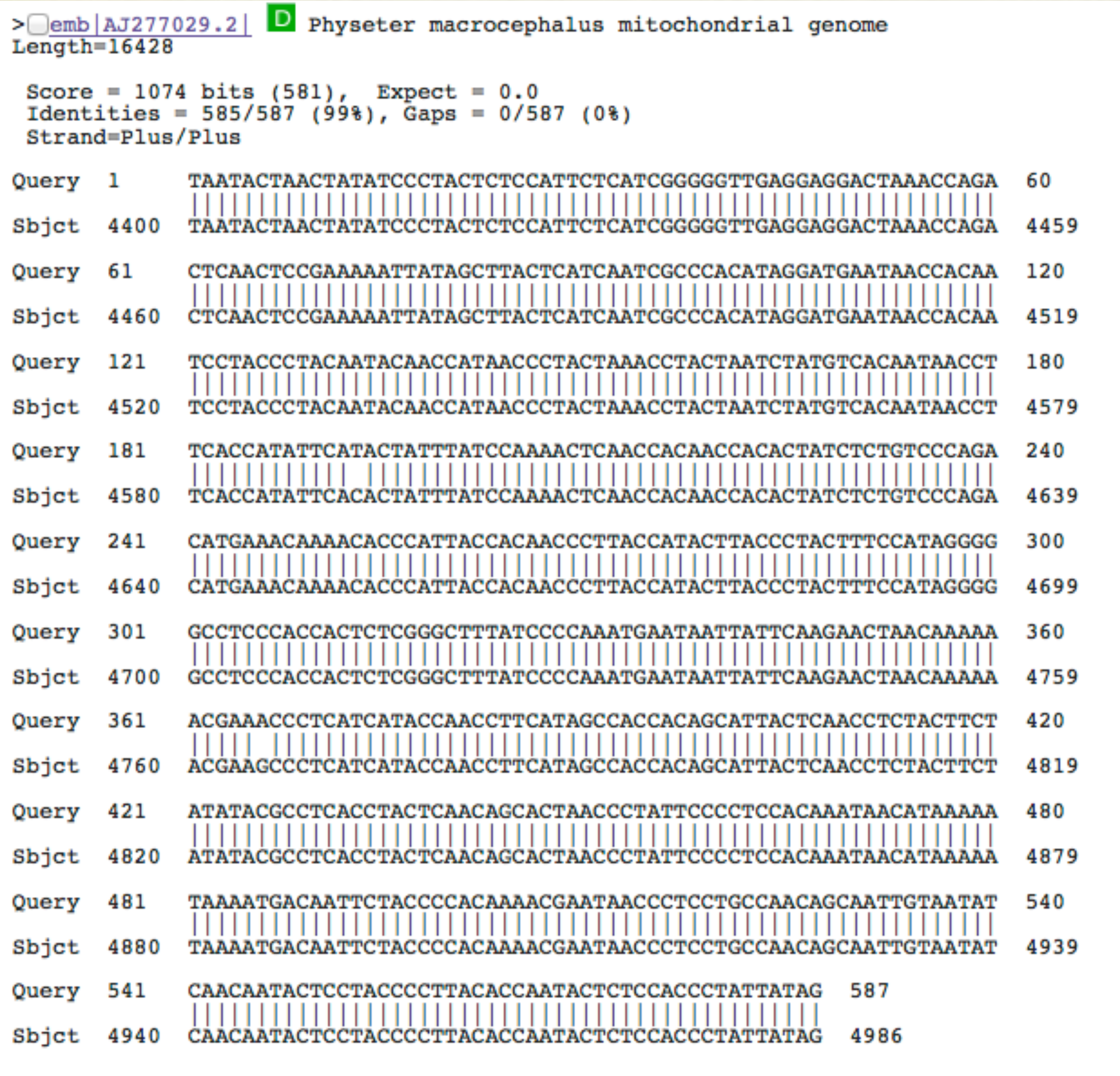
THE MYSTERY OF THE CHILEAN BLOB



Lineage Report

```
Cetacea      [whales & dolphins]
. Odontoceti    [whales & dolphins]
. . Physeteridae [whales & dolphins]
. . . . Physeter catodon --------------------------- 1085   3 hits [whales & dolphins]   Physeter catodon NADH dehydrogenase subunit 2 (nad2) gene,
. . . . Kogia breviceps ............................  638   1 hit  [whales & dolphins]   Kogia breviceps complete mitochondrial genome
. . Orcaella brevirostris ----------------------  593   1 hit  [whales & dolphins]   Orcaella brevirostris isolate 97 mitochondrion, complete ge
. . Grampus griseus ............................  593   1 hit  [whales & dolphins]   Grampus griseus mitochondrion, complete genome
. . Feresa attenuata ...........................  592   2 hits [whales & dolphins]   Feresa attenuata isolate 36 mitochondrion, complete genome
. . Tursiops truncatus (bottle-nosed dolphin) ...  592   1 hit  [whales & dolphins]   Tursiops truncatus mitochondrion, complete genome
. . Globicephala melas .........................  586   3 hits [whales & dolphins]   Globicephala melas isolate GlomelG42 mitochondrion, partial
. . Peponocephala electra ......................  580   2 hits [whales & dolphins]   Peponocephala electra isolate M6 mitochondrion, complete ge
. . Globicephala macrorhynchus .................  580   4 hits [whales & dolphins]   Globicephala macrorhynchus isolate Glomac65 mitochondrion,
. . Pseudorca crassidens .......................  577   3 hits [whales & dolphins]   Pseudorca crassidens mitochondrion, complete genome
. . Orcinus orca (Orca) ........................  569  54 hits [whales & dolphins]   Orcinus orca isolate ENPTGA2 mitochondrion, complete genome
. . Sotalia fluviatilis ........................  569   2 hits [whales & dolphins]   Sotalia fluviatilis haplotype 10 NADH dehydrogenase subunit
. . Platanista minor ...........................  569   1 hit  [whales & dolphins]   Platanista minor complete mitochondrial genome
. . Steno bredanensis ..........................  566   2 hits [whales & dolphins]   Steno bredanensis isolate StebreS9 mitochondrion, partial g
. Megaptera novaeangliae ----------------------  636   5 hits [whales & dolphins]   Megaptera novaeangliae voucher GOM9049 NADH dehydrogenase s
. Balaenoptera bonaerensis .....................  630   1 hit  [whales & dolphins]   Balaenoptera bonaerensis mitochondrial DNA, complete genome
. Eubalaena japonica ...........................  619   1 hit  [whales & dolphins]   Eubalaena japonica mitochondrial DNA, complete genome
. Balaenoptera brydei ..........................  614   2 hits [whales & dolphins]   Balaenoptera brydei mitochondrial DNA, complete genome, iso
. Balaena mysticetus (Greenland right whale) ....  614   2 hits [whales & dolphins]   Balaena mysticetus mitochondrial DNA, complete genome
. Balaenoptera musculus ........................
. Balaenoptera edeni ...........................
. Balaenoptera omurai ..........................
. Eschrichtius robustus (California gray whale) .
. Balaenoptera borealis ........................
. Caperea marginata ............................
. Balaenoptera physalus (finback whale) .........
```

THE MYSTERY OF THE CHILEAN BLOB



```
>emb|AJ277029.2| D Physeter macrocephalus mitochondrial genome
Length=16428

 Score = 1074 bits (581),  Expect = 0.0
 Identities = 585/587 (99%), Gaps = 0/587 (0%)
 Strand=Plus/Plus

Query  1     TAATACTAACTATATCCCTACTCTCCATTCTCATCGGGGGTTGAGGAGGACTAAACCAGA  60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4400  TAATACTAACTATATCCCTACTCTCCATTCTCATCGGGGGTTGAGGAGGACTAAACCAGA  4459

Query  61    CTCAACTCCGAAAAATTATAGCTTACTCATCAATCGCCCACATAGGATGAATAACCACAA  120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4460  CTCAACTCCGAAAAATTATAGCTTACTCATCAATCGCCCACATAGGATGAATAACCACAA  4519

Query  121   TCCTACCCTACAATACAACCATAACCCTACTAAACCTACTAATCTATGTCACAATAACCT  180
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4520  TCCTACCCTACAATACAACCATAACCCTACTAAACCTACTAATCTATGTCACAATAACCT  4579

Query  181   TCACCATATTCATACTATTTATCCAAAACTCAACCACAACCACACTATCTCTGTCCCAGA  240
             |||||||||||| |||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4580  TCACCATATTCACACTATTTATCCAAAACTCAACCACAACCACACTATCTCTGTCCCAGA  4639

Query  241   CATGAAACAAAACACCCATTACCACAACCCTTACCATACTTACCCTACTTTCCATAGGGG  300
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4640  CATGAAACAAAACACCCATTACCACAACCCTTACCATACTTACCCTACTTTCCATAGGGG  4699

Query  301   GCCTCCCACCACTCTCGGGCTTTATCCCCAAATGAATAATTATTCAAGAACTAACAAAAA  360
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4700  GCCTCCCACCACTCTCGGGCTTTATCCCCAAATGAATAATTATTCAAGAACTAACAAAAA  4759

Query  361   ACGAAACCCTCATCATACCAACCTTCATAGCCACCACAGCATTACTCAACCTCTACTTCT  420
             ||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4760  ACGAAGCCCTCATCATACCAACCTTCATAGCCACCACAGCATTACTCAACCTCTACTTCT  4819

Query  421   ATATACGCCTCACCTACTCAACAGCACTAACCCTATTCCCCTCCACAAATAACATAAAAA  480
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4820  ATATACGCCTCACCTACTCAACAGCACTAACCCTATTCCCCTCCACAAATAACATAAAAA  4879

Query  481   TAAAATGACAATTCTACCCCACAAAACGAATAACCCTCCTGCCAACAGCAATTGTAATAT  540
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4880  TAAAATGACAATTCTACCCCACAAAACGAATAACCCTCCTGCCAACAGCAATTGTAATAT  4939

Query  541   CAACAATACTCCTACCCCTTACACCAATACTCTCCACCCTATTATAG  587
             |||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4940  CAACAATACTCCTACCCCTTACACCAATACTCTCCACCCTATTATAG  4986
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