Are 🧬 Genes Everything?!

Alireza Habibzadeh

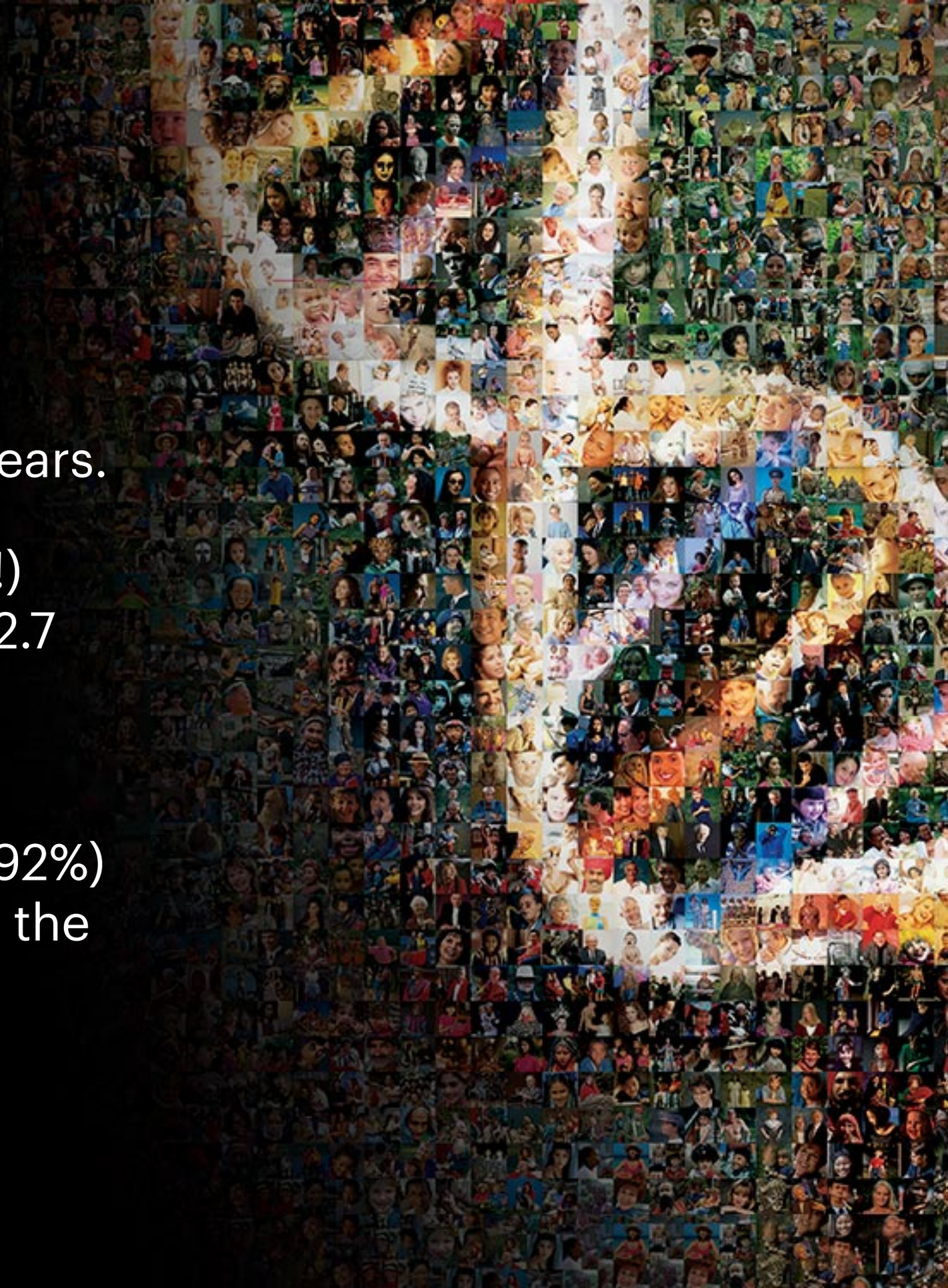
Biophysics Spring 2024 - Prof. Nader Reihani

The Human Genome Project

- 13 years from 1990 to 2003
  The initial estimate was 15 years.

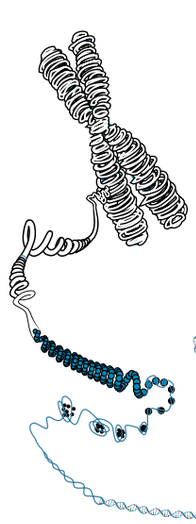
- $3 billion in 1990 (overfund!)
  In the end, approximately $2.7 billion was used.

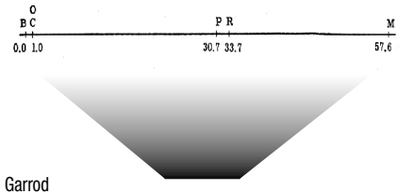
- The first (almost) complete human genome sequence (92%)
  The remaining 8% took until the year ———. (guess the year)

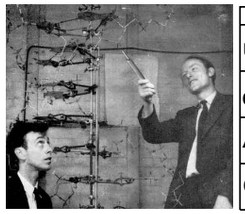


NIH National Human Genome Research Institute

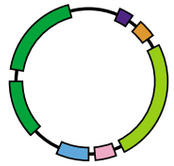
Landmarks in genetics and genomics







	U	C	A	G	
U	Phe Leu	Ser	Tyr stop stop	Cys stop Trp	U C A G
C	Leu	Pro	His Gln	Arg	U C A G
A	Ile Met	Thr	Asn Lys	Ser Arg	U C A G
G	Val	Ala	Asp Glu	Gly	U C A G



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Rediscovery of Mendel's work
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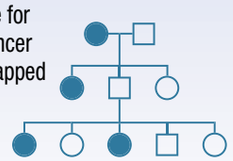
1990

The Human Genome Project (HGP) launched in the United States

Ethical, legal and social implications (ELSI) programmes founded at the US National Institutes of Health (NIH) and Department of Energy (DOE)

First gene for breast cancer (*BRCA1*) mapped



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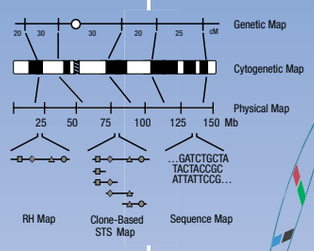
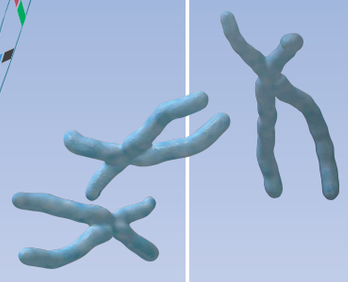
First US genome centres established



1992

Second-generation human genetic map developed



Rapid-data-release guidelines established by the NIH and DOE

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US Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace

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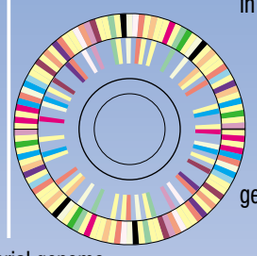
The HGP's human physical mapping goal achieved



First archaeal genome sequenced

First bacterial genome (*Haemophilus influenzae*) sequenced

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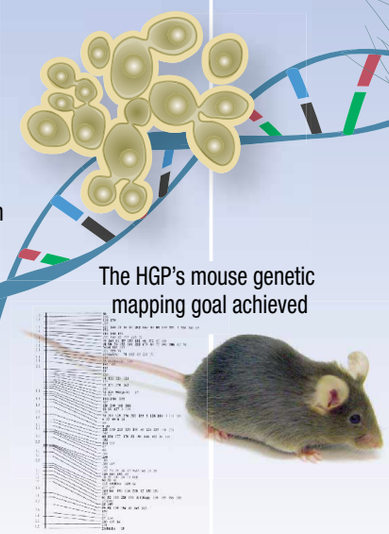
Yeast (*Saccharomyces cerevisiae*) genome sequenced



The HGP's mouse genetic mapping goal achieved

Bermuda principles for rapid and open data release established

1997

The DOE forms the Joint Genome Institute

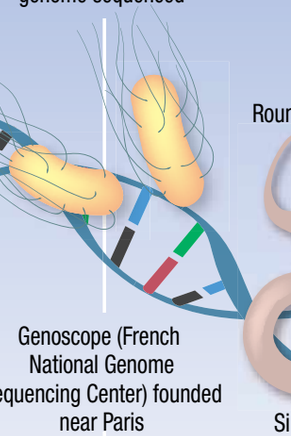
JGI
DOE JOINT GENOME INSTITUTE
US DEPARTMENT OF ENERGY
OFFICE OF SCIENCE

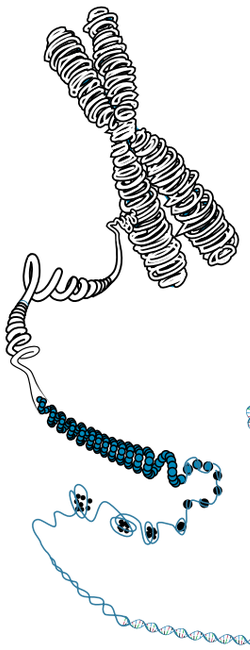
US National Center for Human Genome Research becomes the National Human Genome Research Institute (NHGRI)

National Human Genome Research Institute

Escherichia coli genome sequenced

Genoscope (French National Genome Sequencing Center) founded near Paris





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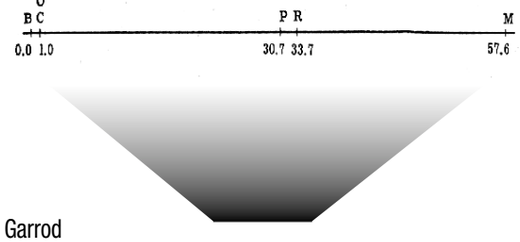

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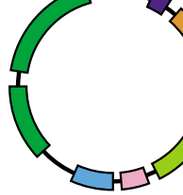

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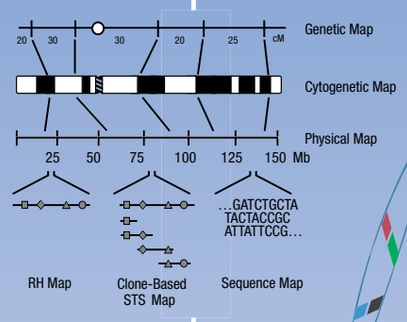

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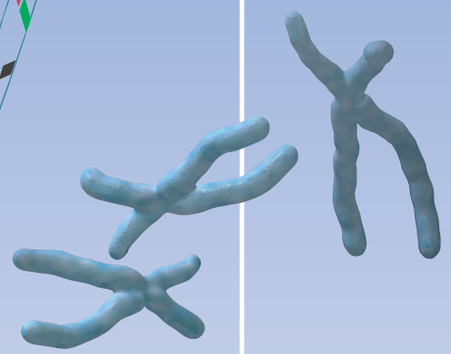

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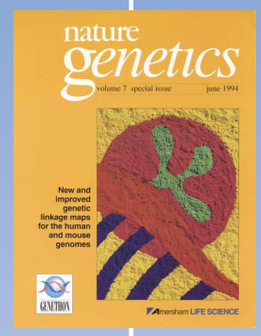

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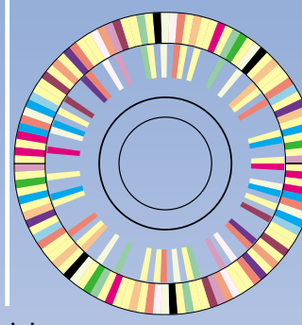

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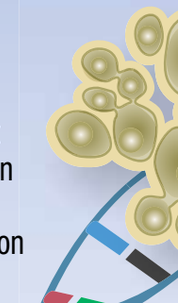

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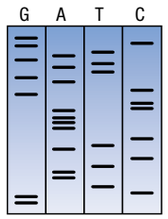

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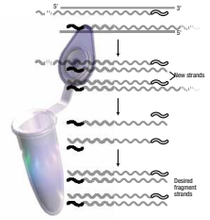
First human disease gene — for
Huntington's disease — is mapped
with DNA markers
1983

First public
discussion
of sequencing
the human
genome
1984

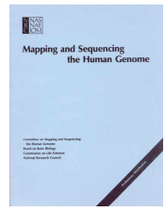


The polymerase
chain reaction (PCR) is invented
1985

International Nucleotide
Sequence Database
Consortium formed

Muscular-dystrophy
gene identified
by positional cloning

First automated
DNA-sequencing instrument
developed
1986

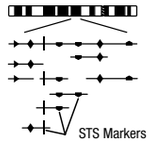


First-generation
human genetic
map developed
1987

US National Research
Council issues report on
*Mapping and Sequencing the
Human Genome*

Development
of yeast artificial
chromosome (YAC)
cloning

Human Genome
Organization (HUGO) formed
1988



Sequence-tagged
sites (STS) mapping
concept established

Cystic-fibrosis
gene identified by
positional cloning
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1990 — 2003

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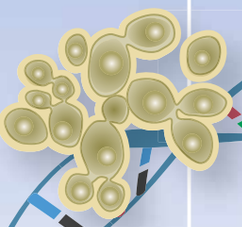

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Incorporation of 30,000
genes into human genome map

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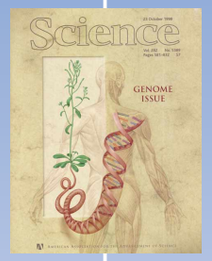
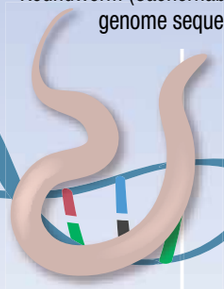


RIKEN Genomic Sciences
Center established in Japan

Roundworm (*Caenorhabditis elegans*)
genome sequenced



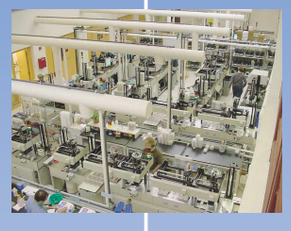
Single-nucleotide polymorphism
(SNP) initiative begins

GTGCT
GTCCT

Chinese National Human Genome Centers
established in Beijing and Shanghai

1999

Full-scale human genome
sequencing begins



Sequence of first human
chromosome
(chromosome 22)
completed

2000

Draft version of
human genome
sequence completed

US President Bill Clinton and
UK Prime Minister Tony Blair
support free access to
genome information

Fruitfly (*Drosophila melanogaster*)
genome sequenced

Mustard cress
(Arabidopsis thaliana)
genome sequenced

Executive order bans genetic
discrimination in US federal workplace

2001

Draft version of human
genome sequence published

10,000 full-length
human cDNAs sequenced

Mammalian
Gene
Collection

2002

Draft version of mouse genome
sequence completed and published

Draft version of rice genome
sequence completed and published

Draft version of
rat genome sequence completed

2003

Finished
version of
human
genome
sequence
completed

The HGP ends with
all goals achieved

To be
continued...

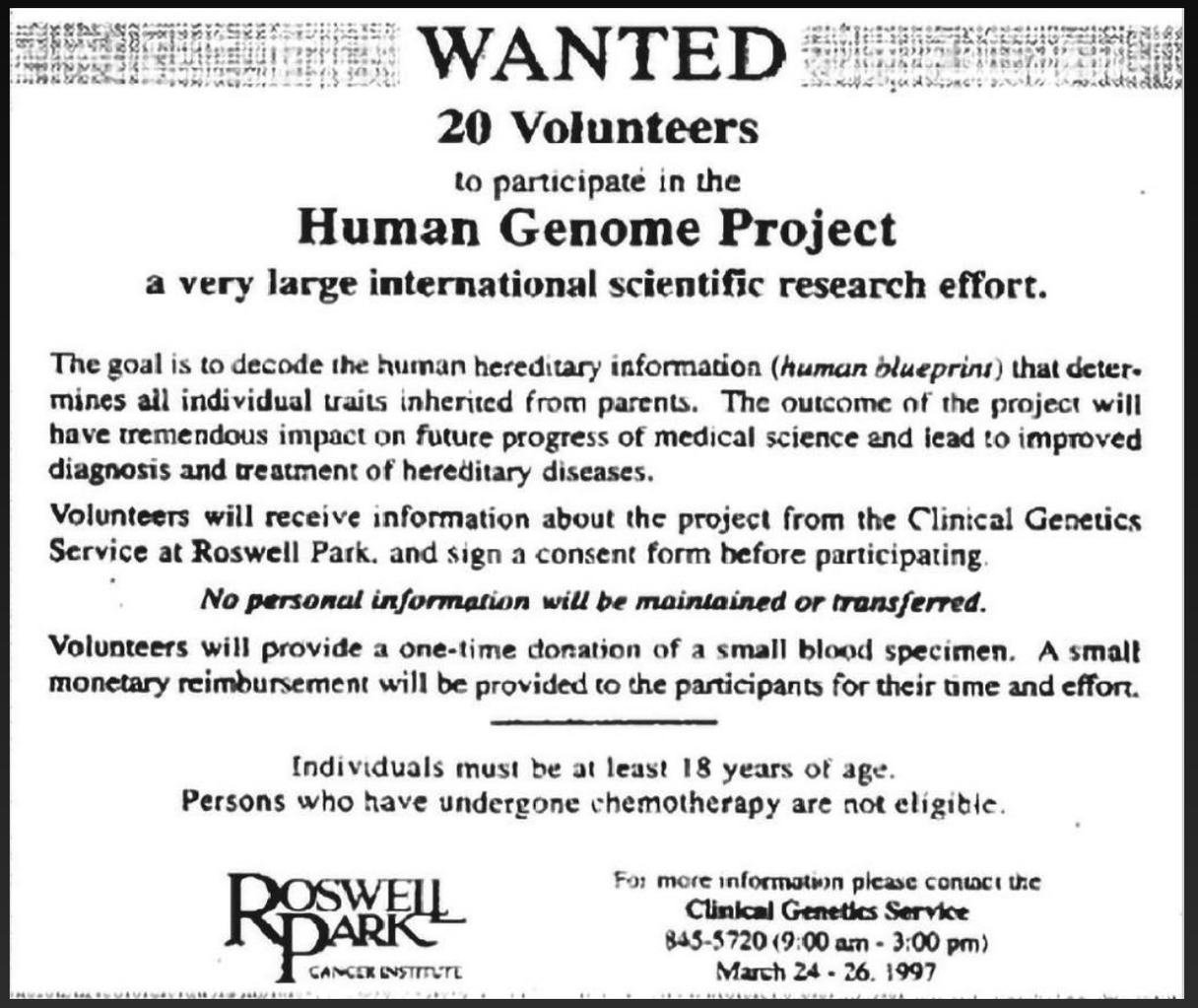
"Gene Therapy"

Lactose Intolerance

Mild Epilepsy

Whose gene is this?

- Some researchers suggested using a “normal” person. But who is really normal? :)
- 70% from one person of mixed race
- 30% from 19 people, mostly of European ancestry



WANTED

20 Volunteers

to participate in the

Human Genome Project

a very large international scientific research effort.

The goal is to decode the human hereditary information (*human blueprint*) that determines all individual traits inherited from parents. The outcome of the project will have tremendous impact on future progress of medical science and lead to improved diagnosis and treatment of hereditary diseases.

Volunteers will receive information about the project from the Clinical Genetics Service at Roswell Park, and sign a consent form before participating.

No personal information will be maintained or transferred.

Volunteers will provide a one-time donation of a small blood specimen. A small monetary reimbursement will be provided to the participants for their time and effort.

Individuals must be at least 18 years of age.
Persons who have undergone chemotherapy are not eligible.

ROSWELL PARK
CANCER INSTITUTE

For more information please contact the
Clinical Genetics Service
845-5720 (9:00 am - 3:00 pm)
March 24 - 26, 1997

~70%

1 individual of blended ancestry

~30%

19 individuals mostly from European ancestry

African

Admixed American

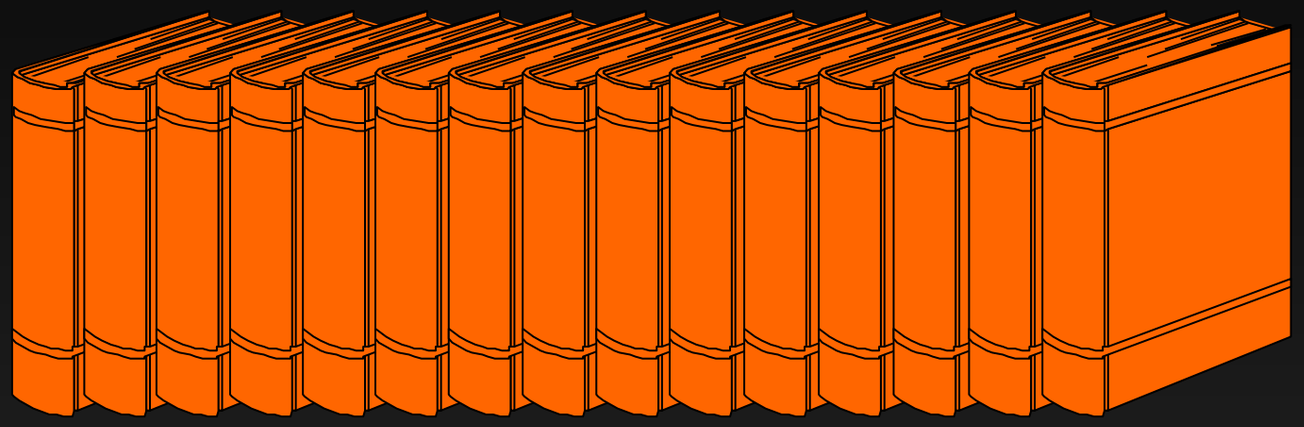
East Asian

European

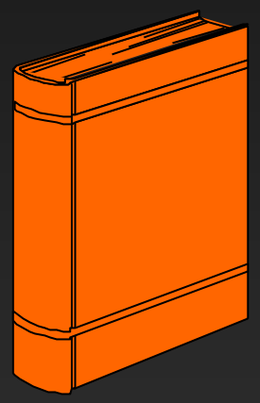
South Asian

Original reference human genome sequence

Scale of Genome, Chromosome, and Clone



Human Genome
(~3,000 Mb)



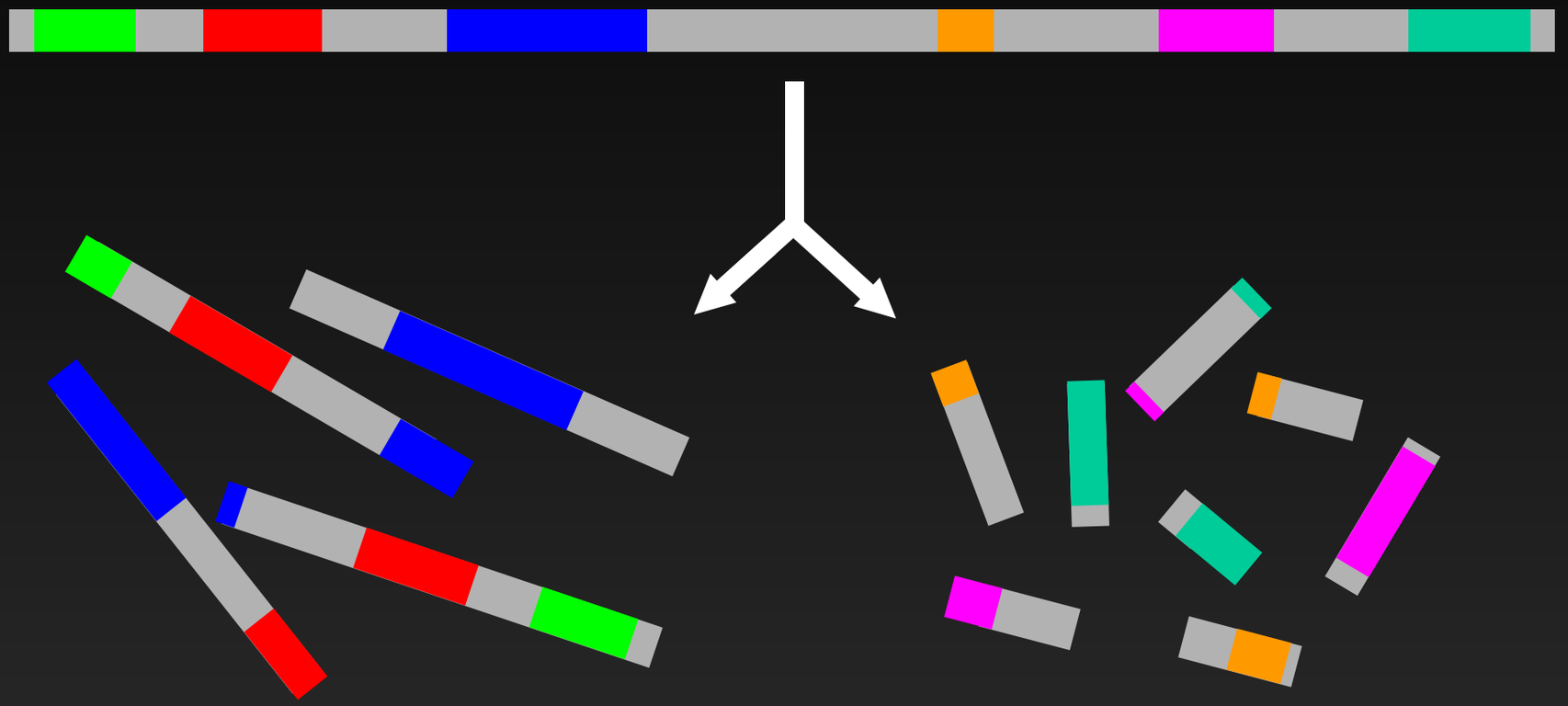
Human Chromosome
(~130 Mb)

Roughly size of entire fruit fly or nematode genome

Larger Clones
(~0.5-1.0 Mb)

Smaller Clones
(~0.1-0.2 Mb)

Mapping DNA by Physical Cloning

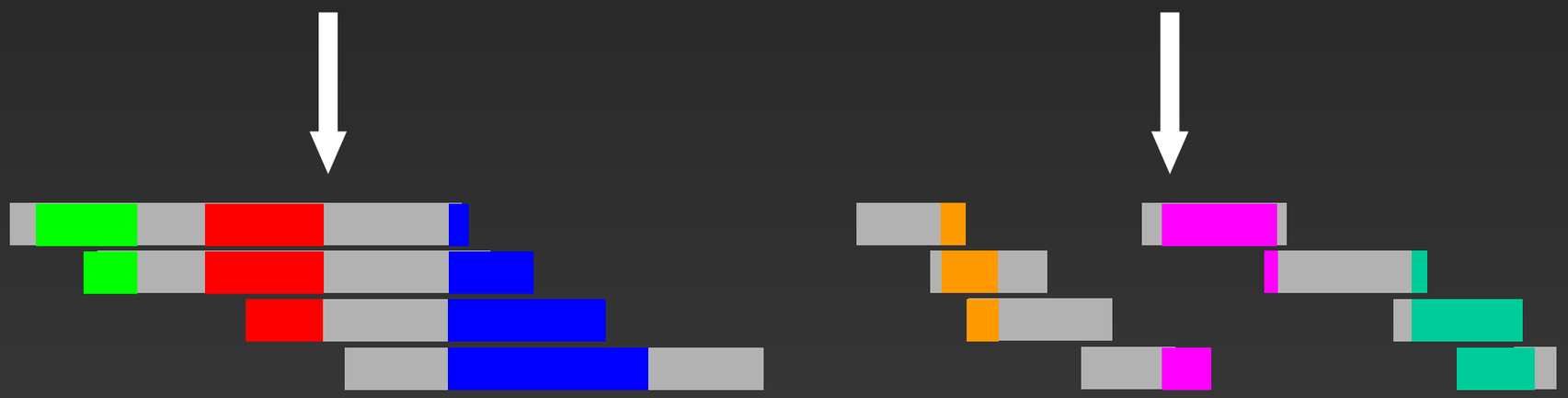


Chromosome

Clone

Large clones (like chapters of a book)

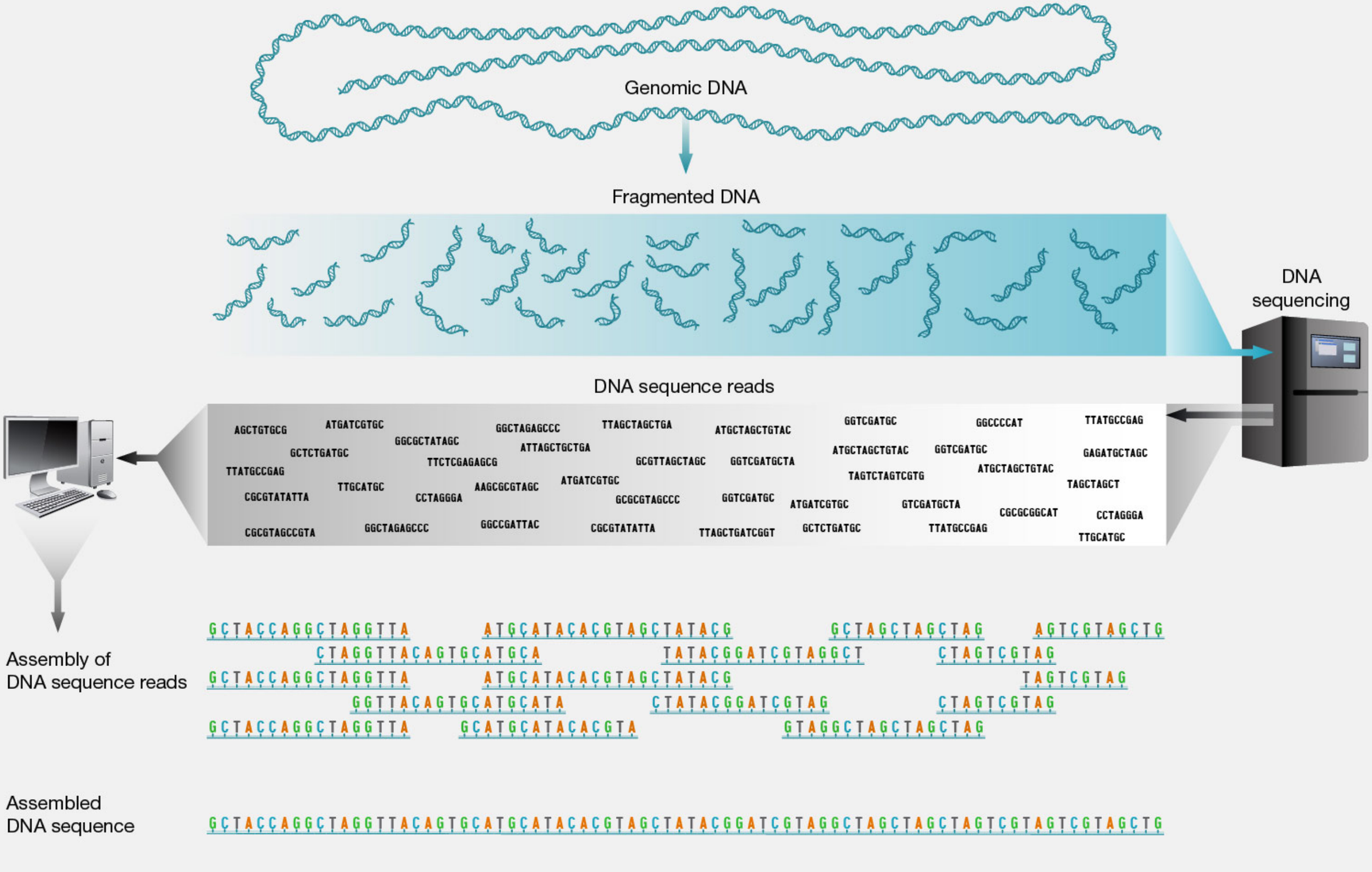
Small clones (like pages of a book)



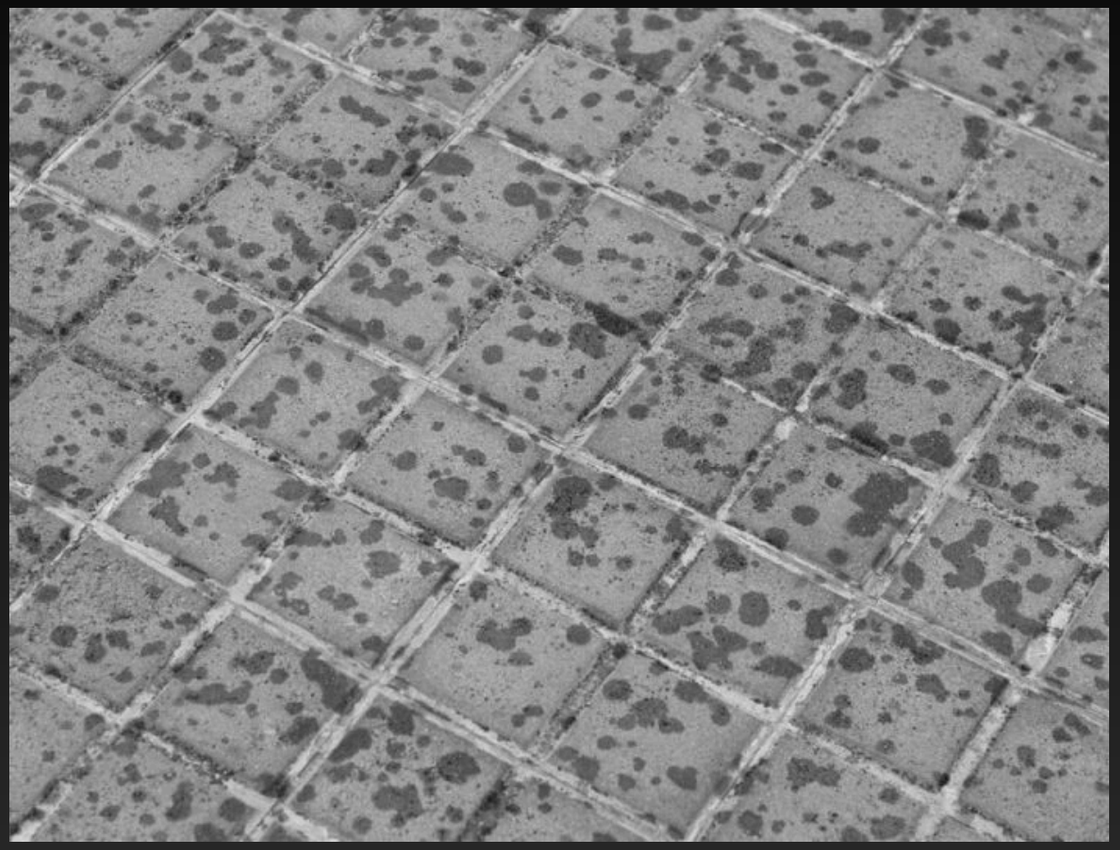
'Contig' of clones

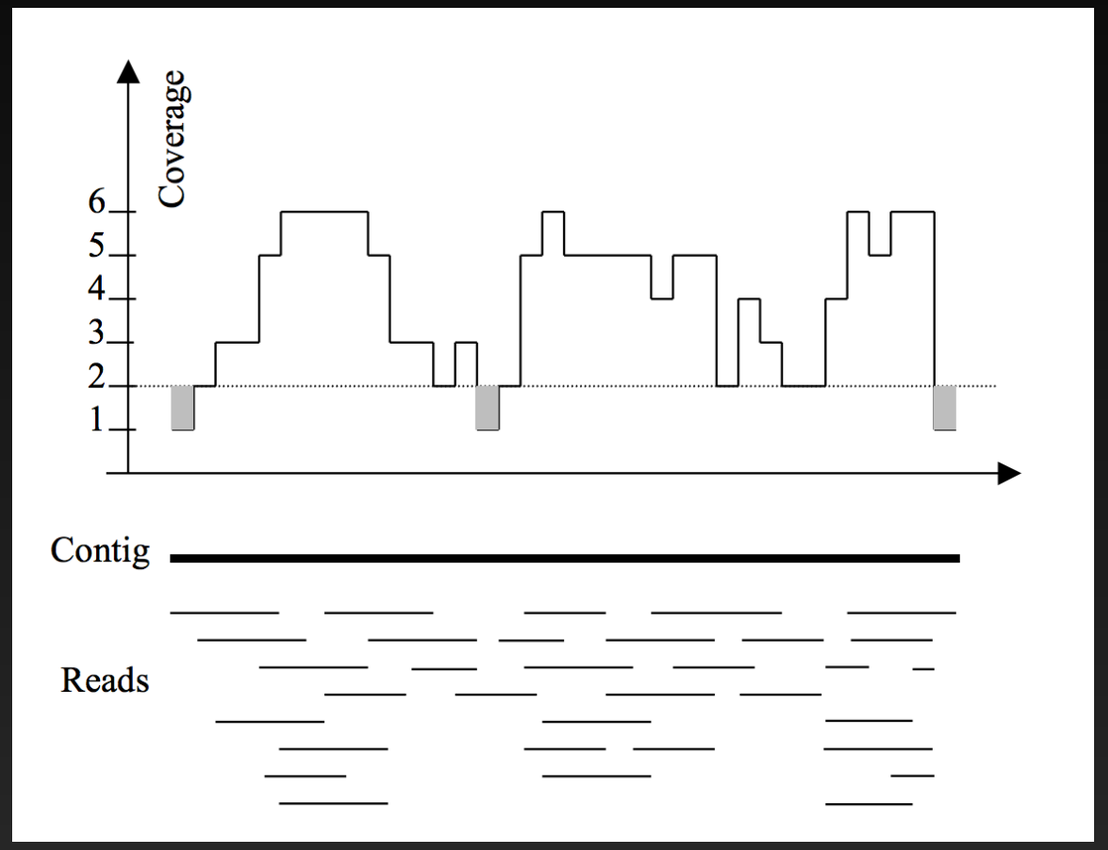
Shotgun sequencing

from genome.gov/genetics-glossary



Raindrops on a Sidewalk





- Because raindrops fall randomly in various places, some spots need to get extra drops for the entire sidewalk to get wet.
- Similarly, the final accuracy of sequencing depends on reading each part multiple times (for example, 30-50 times, which is called 'coverage').

Sequencing Saadi’s Gulistan (Persian Literature)

دو برادر یکی خدمت سلطان کردی و دیگر به زورِ بازو نان خوردی.

باری، این توانگر گفت درویش را که: چرا خدمت نکنی تا از مشقّتِ کار کردن برهی؟

گفت: تو چرا کار نکنی تا از مَذَلَّتِ خدمت رهایی یابی؟ که خردمندان گفته‌اند: نان خود خوردن و نشستن به که کمرشمشیرِ زرّین به‌خدمت بستن.

دو برادر یکی خدمت

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یکی خدمت سلطان

یکی خدمت سلطان

یکی خدمت سلطان

خدمت سلطان مشغولم و به خیرش امیدوار و از عقوبتش

خدمت سلطان کردی و دیگر به زور بازو نان خوردی

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خدمت سلطان کردی و دیگر به زور بازو نان خوردی

Coverage = 4

aligned reads

File Navigate Info Color Dim Misc Help

yg.fasta.screen.ace.3 | Contig32 | Some Tags | Pos:

Search for String | Compl Cont | Compare Cont | Find Main Win | Exp Err/10kb: 12.17

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CONSENSUS           AGGAAAAGACTATCACAGCGTATTCCTGAAAGAGATGAACTATGAATTGAGTGTAGGCTTCTCTGCAGAGGCAAA*GGTAGGATC
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yg03d09.y1          aggaAAAGACtatcAcagcgtaTtcctgaaAGAGAtgaaCTATGAattGAgtgtaggcttctctgcagaggcaaa*ggtaggatc
yg09g04.x1          aggaaaaagactatcacagcgtattcctgaaagagatgaactatgaattgagtgtaggcttctttgcagaggcaaa*ggtaggatc
yg13h04.x1          AGGAAAAGACTATCACAGCGTATTCCTGAAAGAGATGAACTATGAATTGAGTGTAGGCTTCTCTGCAGAGGCAAA*GGTAGGATC
yg01e03.y1          AGGAAAAGACTATCACAGCGTATTCCTGAAAGAGATGAACTATGAATTGAGTGTAGGCTTCTCTGCAGAGGCAAA*GGTAGGATC
yg08h10.x1          xxxxxxxxxxtatcAcagcgtattcctgaaagagatgaacTAtgatttGAgtgcaggctTCtctGcagaggcaaa*ggttgGATC
yg04f11.y1          xxxxxxxxxxxxxxxxxxxxcagctcgccca
yg01g01.y1          acatcgttcaaagttgaacatccgtatxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx*xxxxxxxx
yg01g07.y1          xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx*xxxxxxxx
yg02e04.y1          AGGAAAxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx*xxxxxxxx
yg02f10.y1          AgGAAAAGACTatcgcagCGTATTCCTGAAAGAGATGAACTATgaaTTGAGTGTAGGCTTCTCTGCAGAGGCAAA*GGTAGGATC
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yg03g10.y1          AGGAAAAGACTATCACAGCGTATTCCTGAAAGAGATGAACTATGAATTGAGTGTAGGCTTCTCTGCAGAGGCAAA*GGTAGGATC
yg18a10.y1          AGGAAAAGACTATCACAGCGTATTCCTGAAAGAGATGAACTxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx*xxxxxxxx
yg08f02.y1          aggaAAAGACTATCACAGCGTAttcctGaAaGAGATGAACTATGAATTGAGTGTAGGCTTCTCTGCAGAggCAAA*GGTAGGATC
yg02h10.y1          agaaaaatcctatcgcagcgtattcttaaaaaagatgaactatgaatcgagggtaggcttctctcaagag*cacagggtaggatc
yg18e09.y1          aggaAaAGACTAtcacagcgTAttcctGAAAGAGATGAACTATGAATTGAGTGTAGGCTTCTCTGCAGAGGCAAA*GGTAGGATC
yg13d05.x1                                                                ggtgccgcggtcactgtgccgcggtctgcgtcgccgca*tggcgcgcg
```

BamView v1.1.8

File | MAL1 | GoTo: | 101600 | - | + | Hide

101600 102000 102400 102800 103200 10360

Add BAM ...
BAM files ▶
Analyse ▶

Views ▶
Colour By ▶
Show ▶
Graph ▶

BamView Height ▶

Use Log Scale
Filter Reads ...

Clone window

Inferred Size
✓ Stack
Paired Stack
Strand Stack
Coverage

Coverage Options ▶

101600 102000 102400 102800 103200 10360

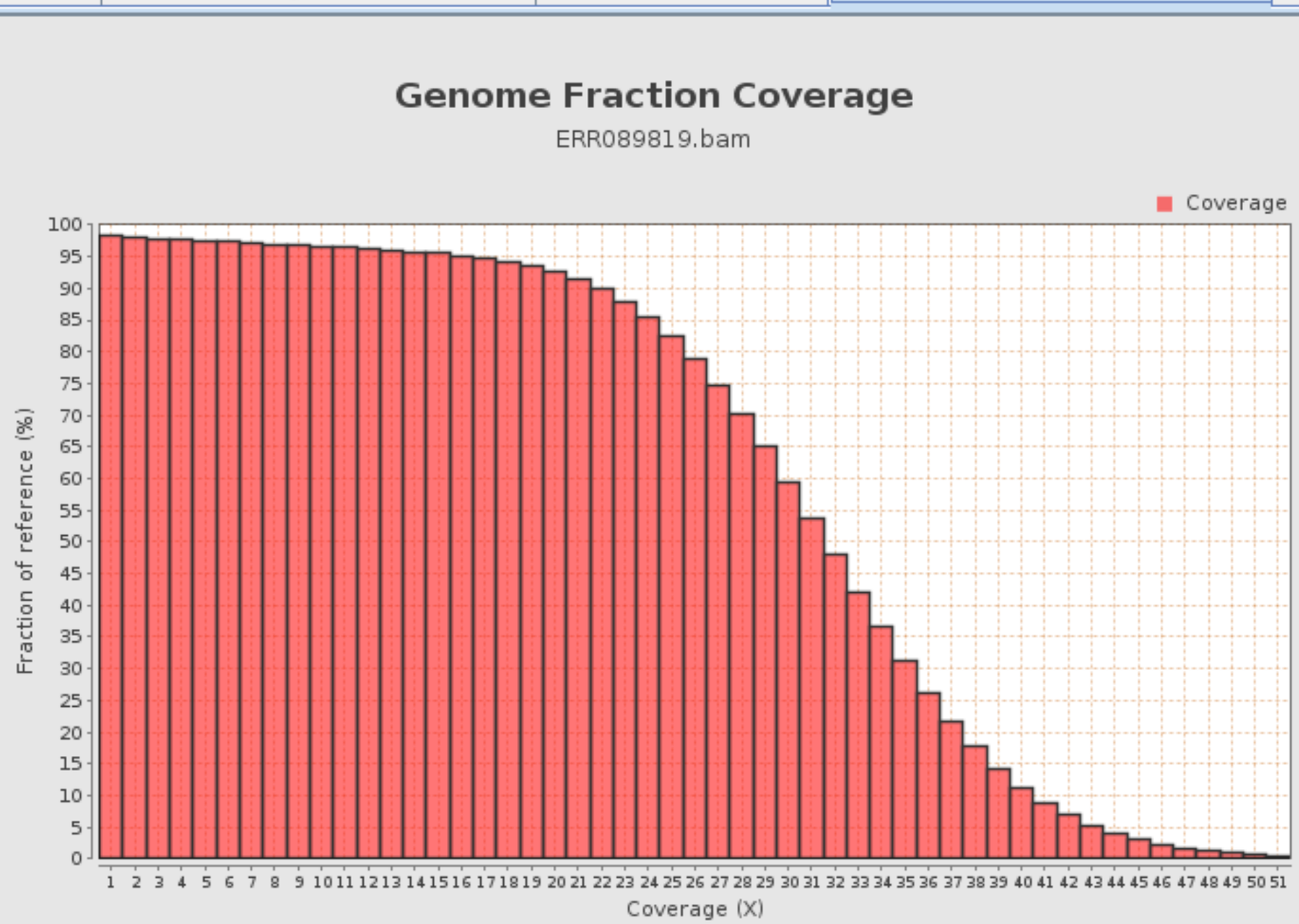
Qualimap v.2.0

File Tools Windows Help

RNA Seq QC: /home/kokonech/sampl... × | Multi-sample BAM QC: 4 × | Counts QC: 4 × | BAM QC: ERR089819.bam ×

Results

- Input data & parameters
- Summary
- Coverage across reference
- Coverage Histogram
- Coverage Histogram (0-50X)
- *Genome Fraction Coverage*
- Duplication Rate Histogram
- Mapped Reads Nucleotide Content
- Mapped Reads GC-content Distributi
- Mapping Quality Across Reference
- Mapping Quality Histogram
- Insert Size Across Reference
- Insert Size Histogram



Qualimap v.2.0

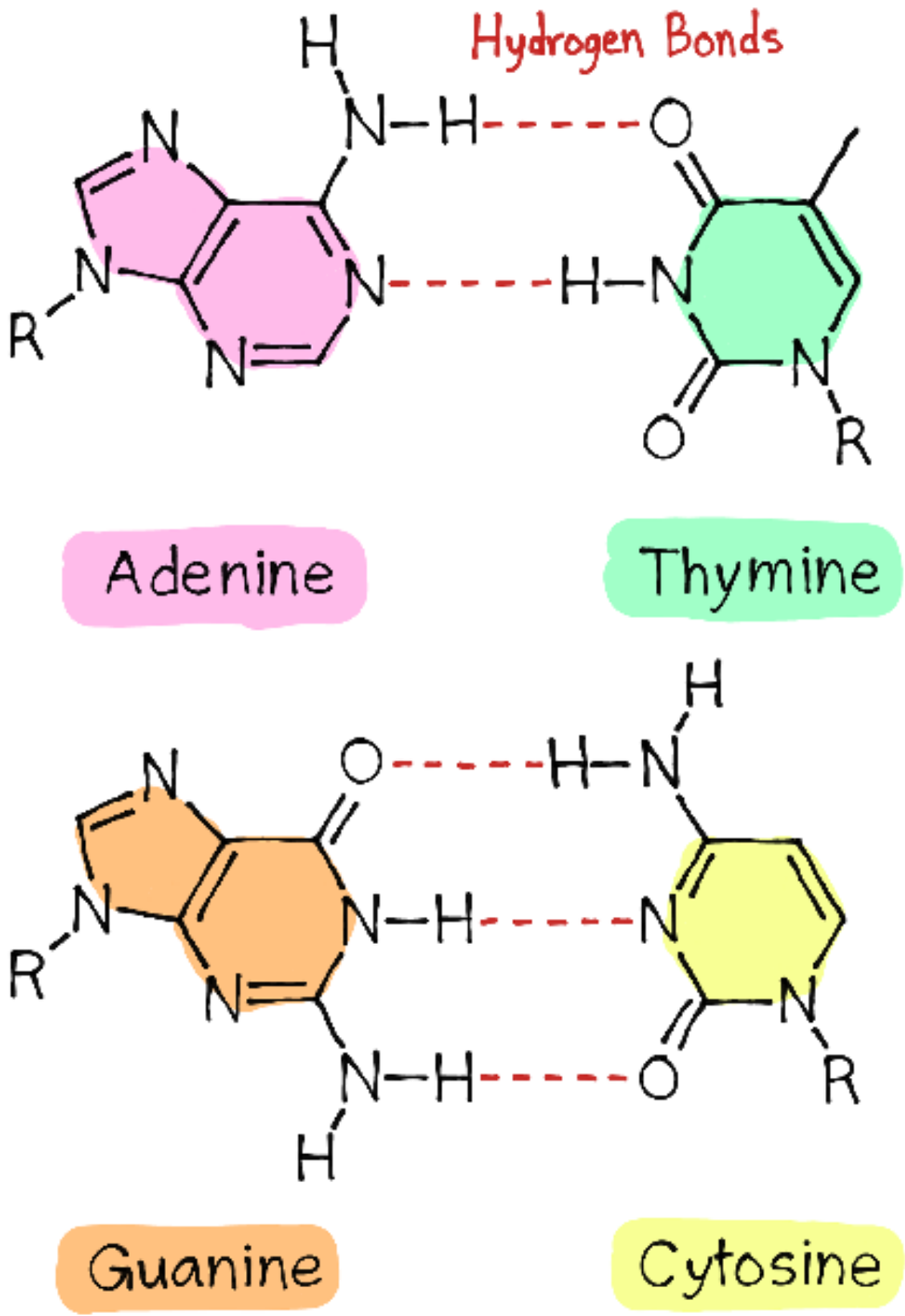
File Tools Windows Help

RNA Seq QC: /home/kokonec

M QC: ERR089819.bam ×

Results

- Input data & parameters
- Summary
- Coverage across reference
- Coverage Histogram
- Coverage Histogram (0-50X)
- Genome Fraction Coverage
- Duplication Rate Histogram
- Mapped Reads Nucleotide Conte
- Mapped Reads GC-content Distri
- Mapping Quality Across Referenc
- Mapping Quality Histogram
- Insert Size Across Reference
- Insert Size Histogram



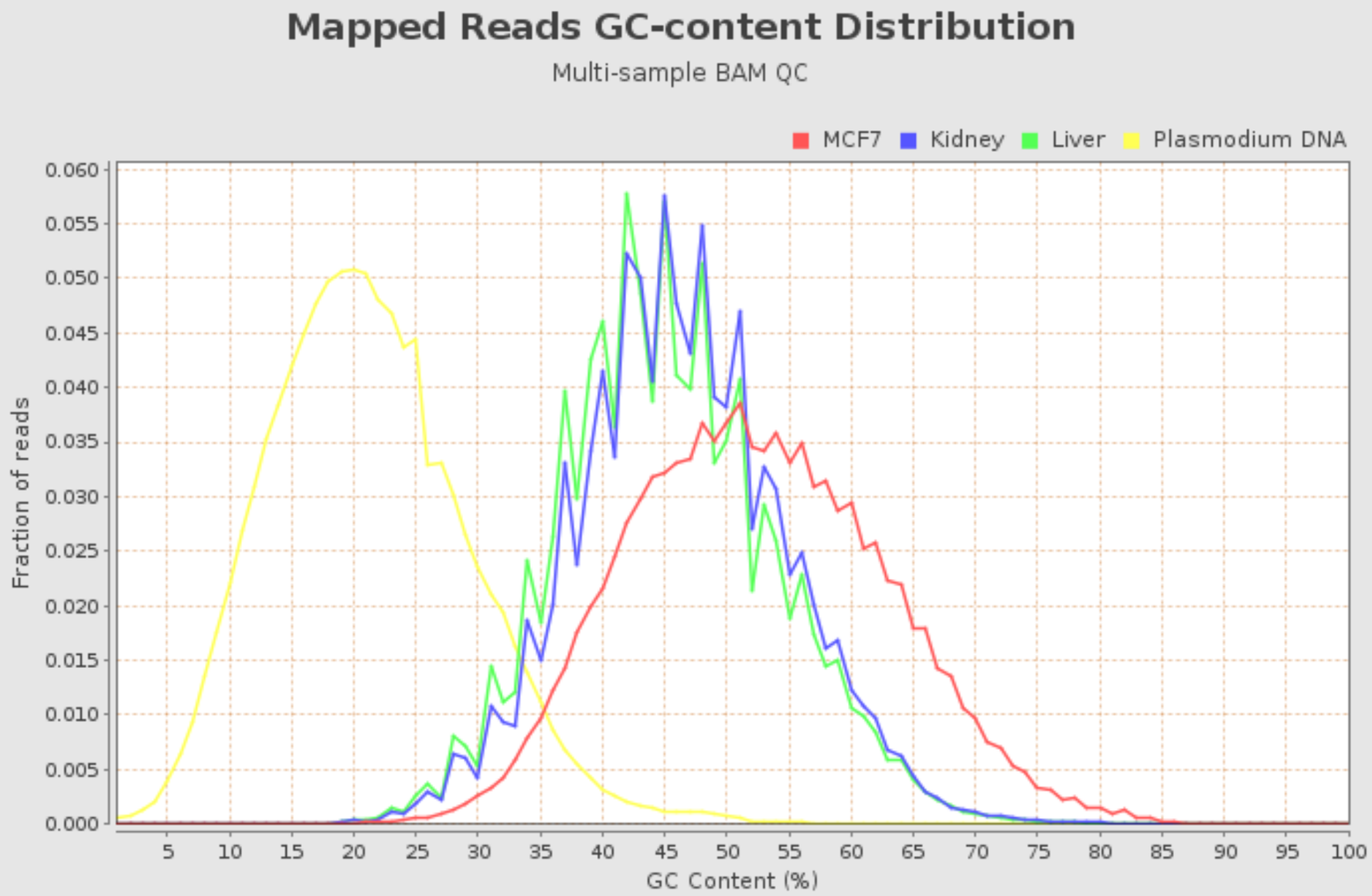
Qualimap v.2.0

File Tools Windows Help

RNA Seq QC: /home/kokonech/sampl... × | Multi-sample BAM QC: 4 × | Counts QC: 4 × | Counts QC: 4 ×

Results

- Input data & parameters
- Summary
- PCA
- Coverage Across Reference
- Coverage Histogram (0-50X)
- Genome Fraction Coverage
- Duplication Rate Histogram
- Mapped reads GC-content
- Mapped Reads Clipping Profile
- *Mapped Reads GC-content Distributi*
- Mapping Quality Across Reference
- Mapping Quality Histogram
- Insert Size Across Reference
- Insert Size Histogram

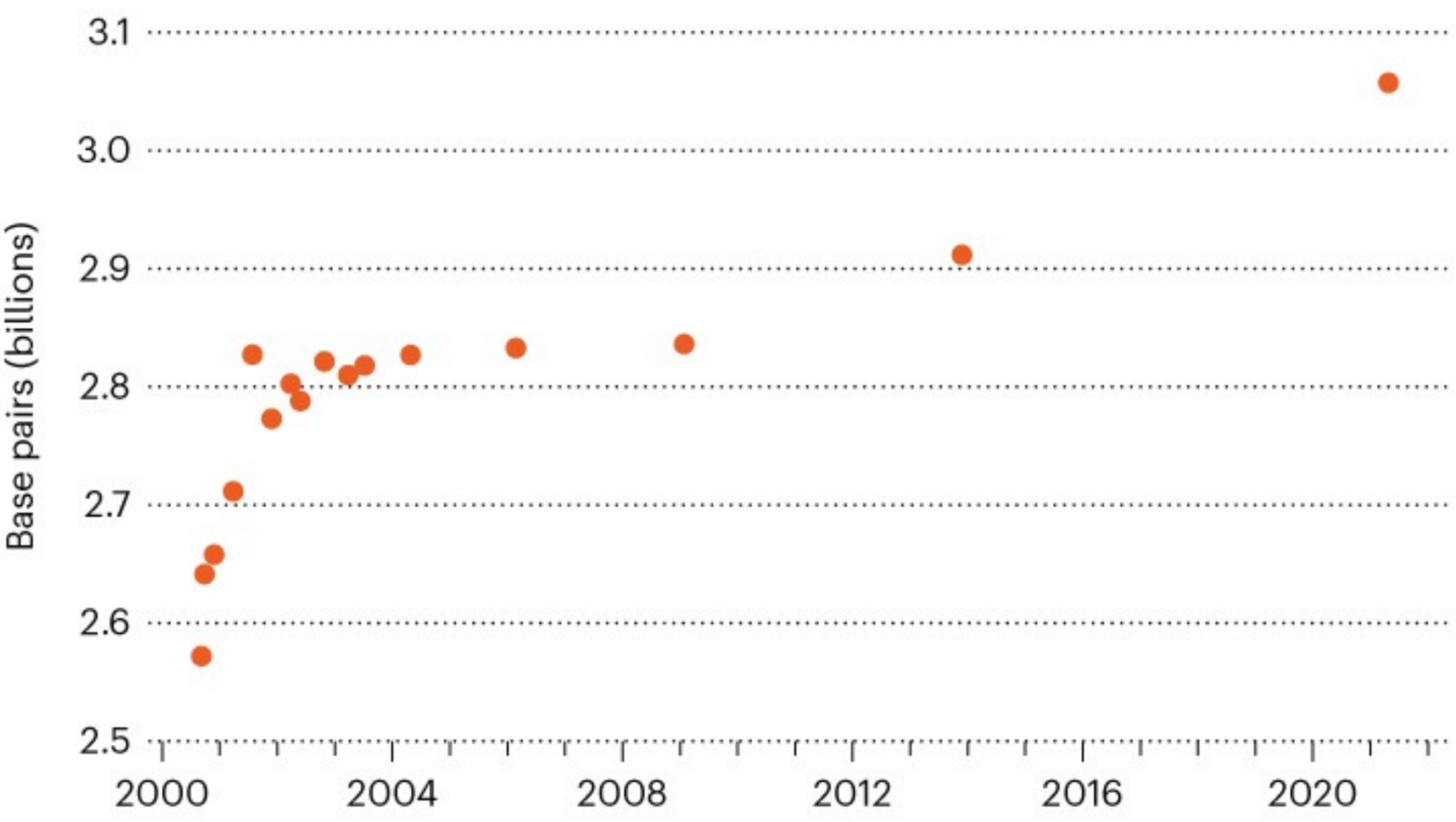


Reaching a Complete Genome

- The Human Genome Project (HGP) produced a high-quality sequence of the human genome, but it only covered 92% of the human genome.
- The remaining 8% was not sequenced due to the inability of the available DNA sequencing methods at the time, but these regions are important for structural (centromeres and telomeres) and medical reasons. (Previously, it was thought that these regions were useless.)
- In the past 20 years or so, several new and revolutionary methods for DNA sequencing have been developed.
- These new methods, along with better computational techniques, enabled a new group of researchers to finally produce a complete sequence of the human genome in 2022.

COMPLETING THE HUMAN GENOME

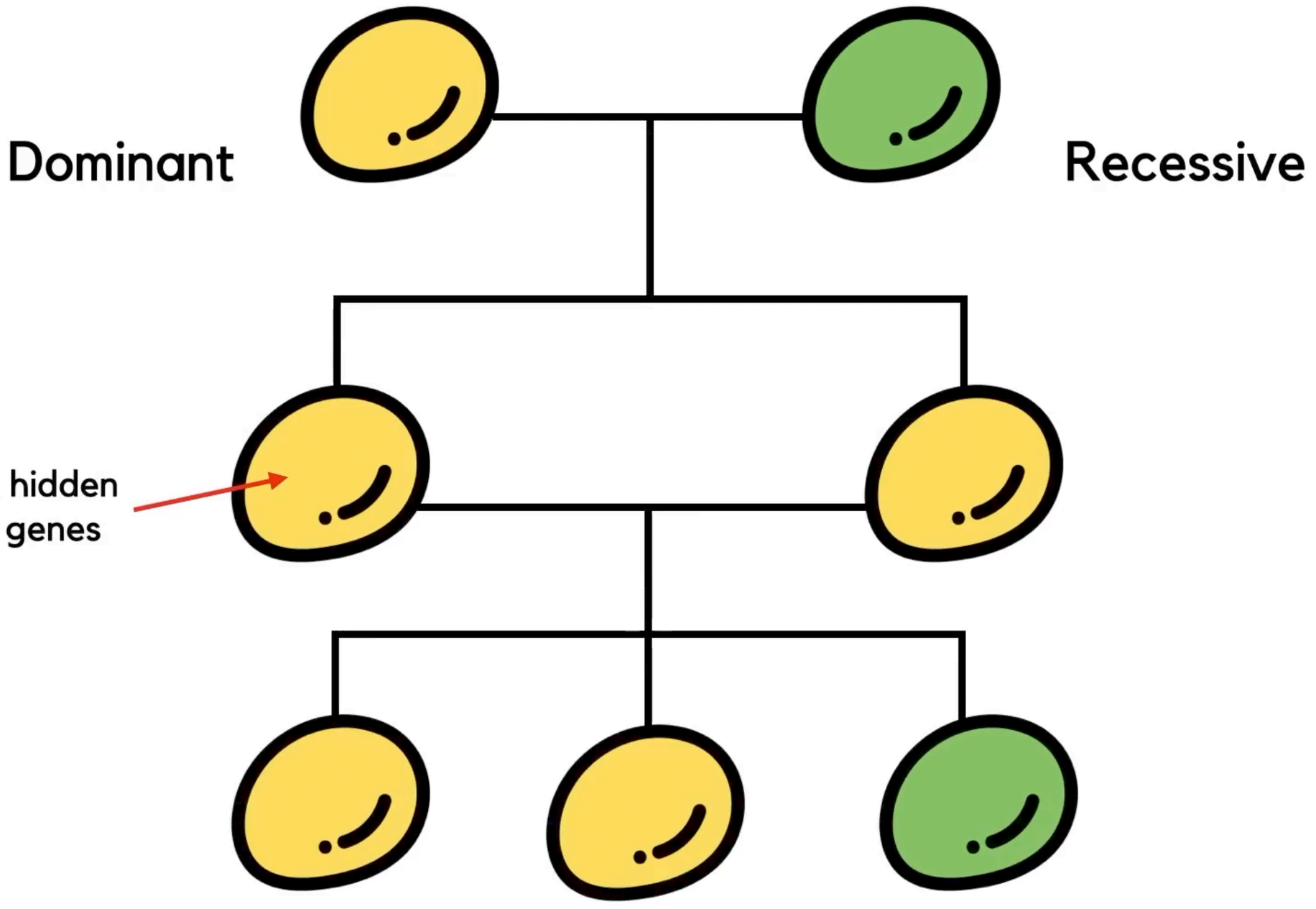
Researchers have been filling in incompletely sequenced parts of the human reference genome for 20 years, and have now almost finished it, with 3.05 billion DNA base pairs.



0.3% of sequence might still have errors. Includes X but not Y chromosome. Count excludes mitochondrial DNA.

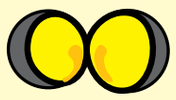
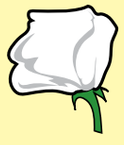
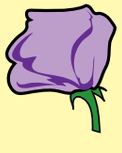
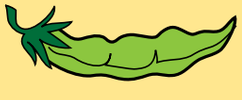
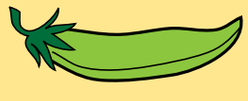
Does DNA explain everything?

Mendel's model (1865)

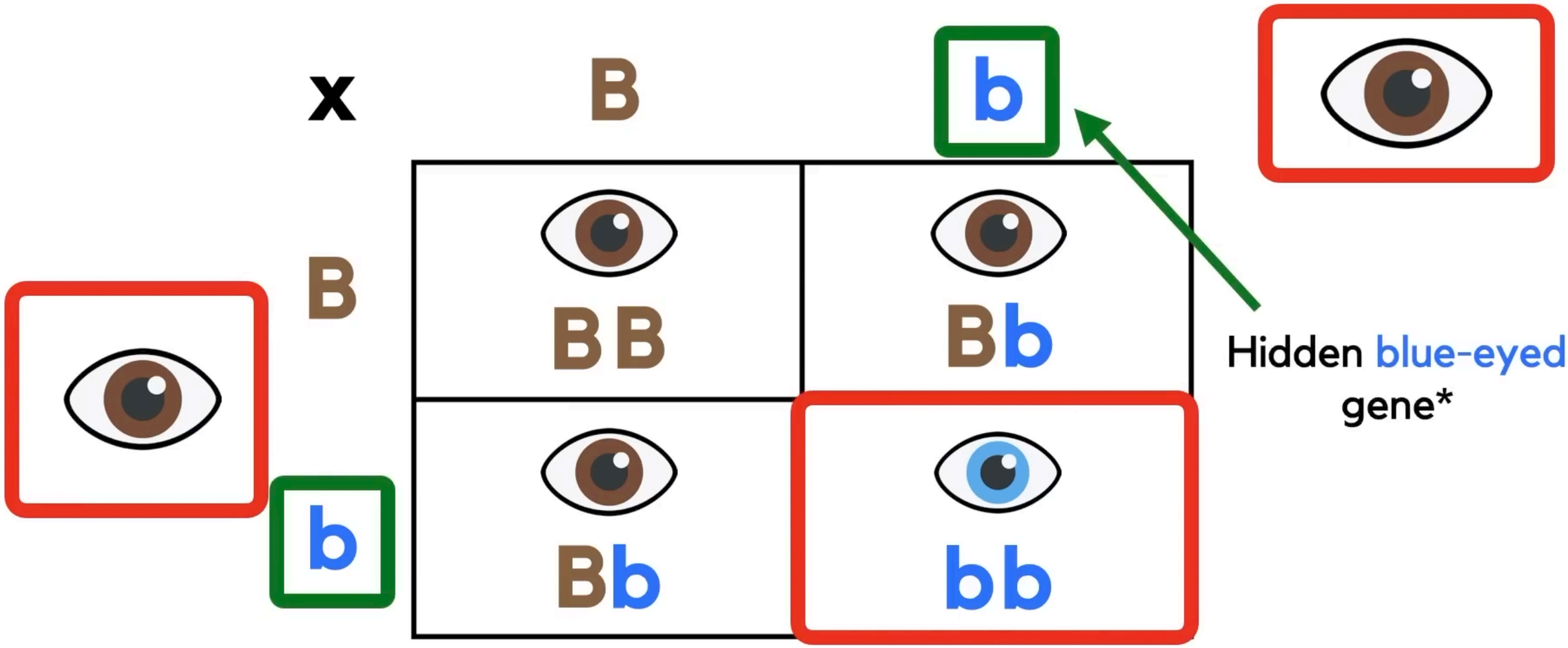


Mendel's model

- Every organism has two alleles for each trait, one received from the father and the other from the mother.
- Of the two alleles for a trait, one may completely express itself (dominant allele), while the other may show no observable effect (recessive allele).
- The two alleles for a trait may be identical or different.
- The two alleles for a trait separate from each other during gamete formation, and each gamete receives only one of them. During the formation of the zygote, one allele from the male gamete and one from the female gamete combine.

Seed		Flower	Pod		Stem	
Form	Cotyledons	Color	Form	Color	Place	Size
						
Grey & Round	Yellow	White	Full	Yellow	Axial pods, Flowers along	Long (6-7ft)
						
White & Wrinkled	Green	Violet	Constricted	Green	Terminal pods, Flowers top	Short (¾1ft)
1	2	3	4	5	6	7

Punnett squares



*Technically allele, not gene.

Criticisms of Mendel's theory

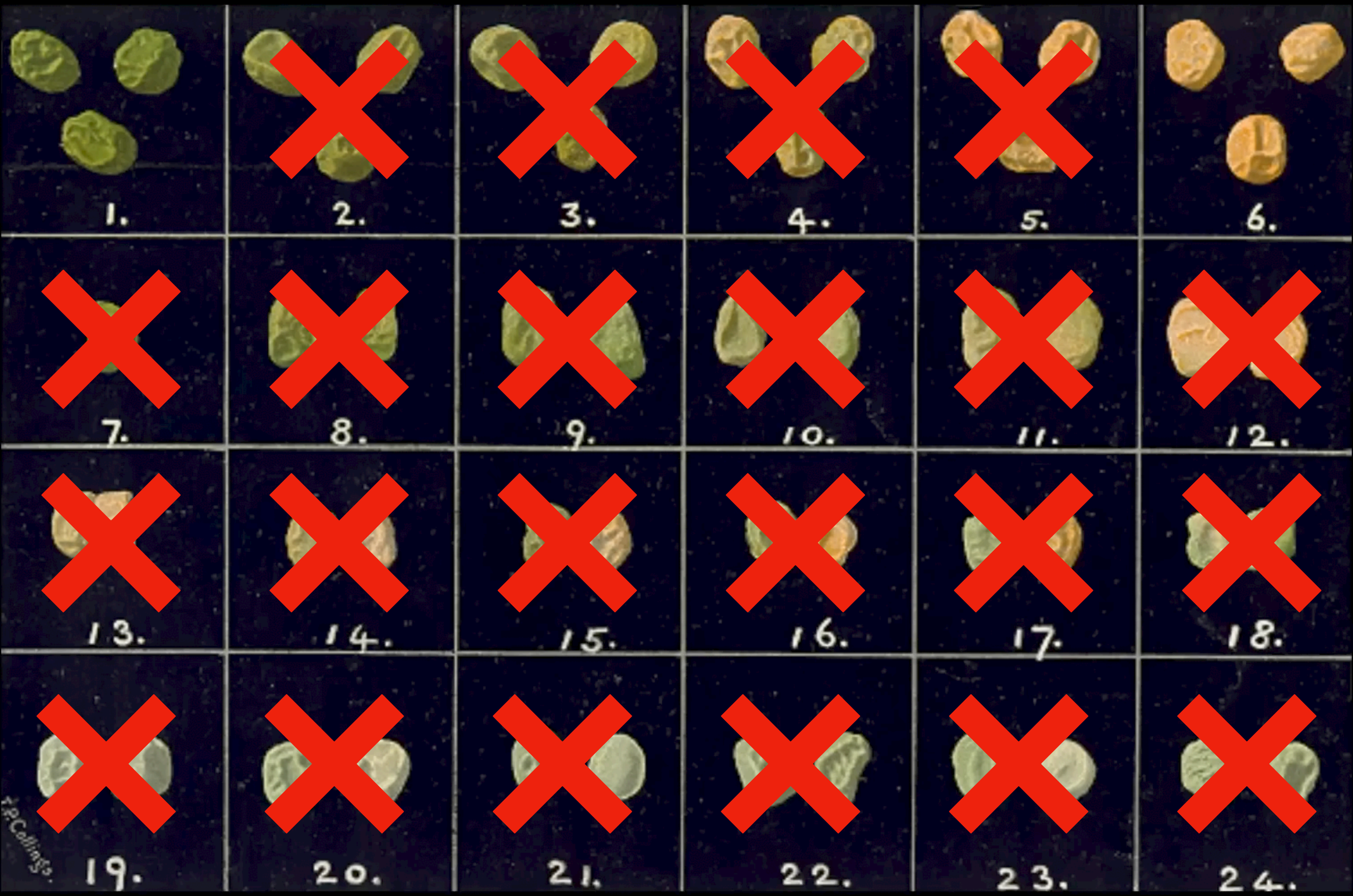
Weldon organized his findings into table form and sent them to Pearson in late November 1901. About Mendel, Weldon wrote: "He is either a black liar, or a wonderful man" – "wonderful" in the older, literal sense of "wonder-making." For the most part, Weldon was inclined to think neither that Mendel was lying nor that he was miraculously lucky, but that he had reported truthfully on what he had observed in the particular varieties he worked with, under the conditions that he observed them in:

> [I]f you take all Mendel's figures together, they are wonderfully good approximations to his hypothetically probable results. ~~Remembering his shaven crown, I can't help wondering if they are not too good?~~ I do not see that the results are so good as to be suspicious, so that I can see no alternative to the belief that Mendel's "laws" are absolutely true for his peas, and absolutely false for Laxton's, while those of Tschermak are intermediate …. But the fear of Mendel is before my eyes. Really one has never seen such perfectly devised observations, lasting over 8 years, give a result so absolutely untrustworthy. It seems to me to

…

Weldon, 1901

TLDR; Mendel's results are too good to be true!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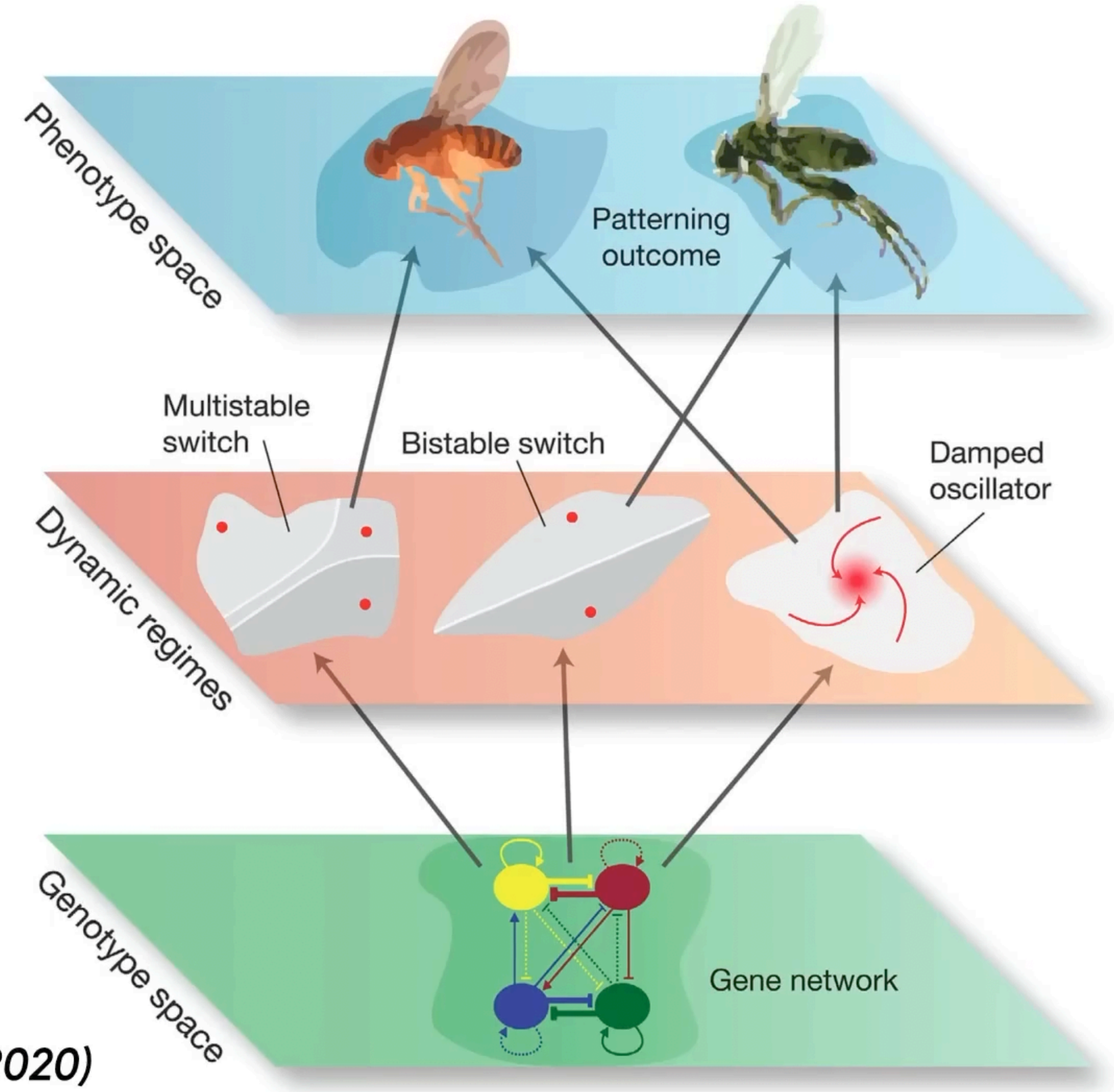
T.P. Collings.



DiFrisco & Jaeger (2020)

Nothing works all the time

Environmental conditions change things

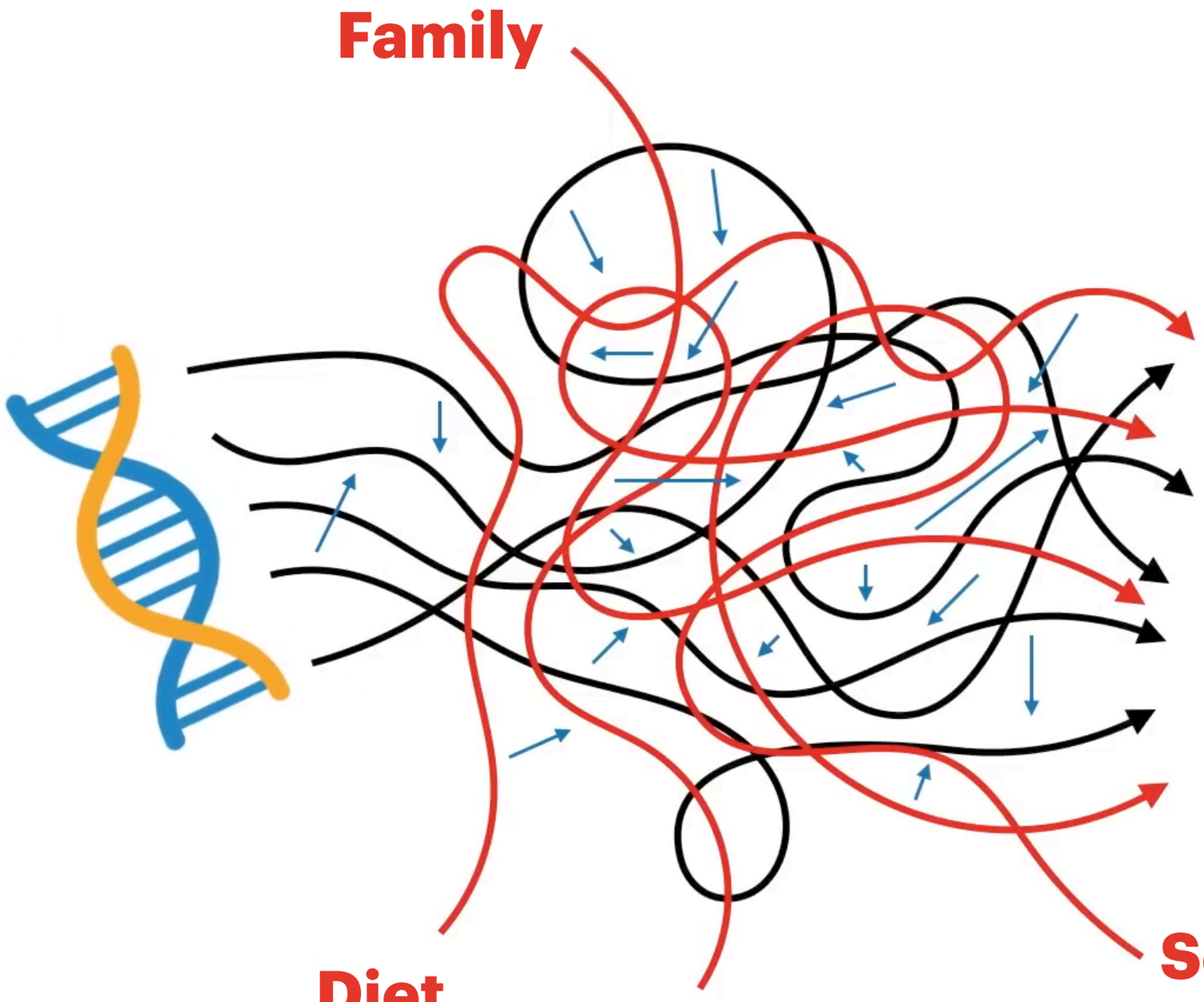
Table 5. Changes in Iris Color in Twin Pairs by Zygosity*

Age	Identical Twins			Fraternal Twins		
	No. of Subjects	Same,† %	Different, %	No. of Subjects	Same, %	Different, %
3 mo-6y‡	101	92.1	7.9	94	62.8	37.2
6-9 y	128	89.1	10.9	123	87.8	12.2
9-15 y‡	87	88.5	11.5	79	74.7	25.3
15 y-adult‡	40	85.0	15.0	27	59.3	40.7
6 y-adult	48	83.3	16.7	37	73.0	27.0

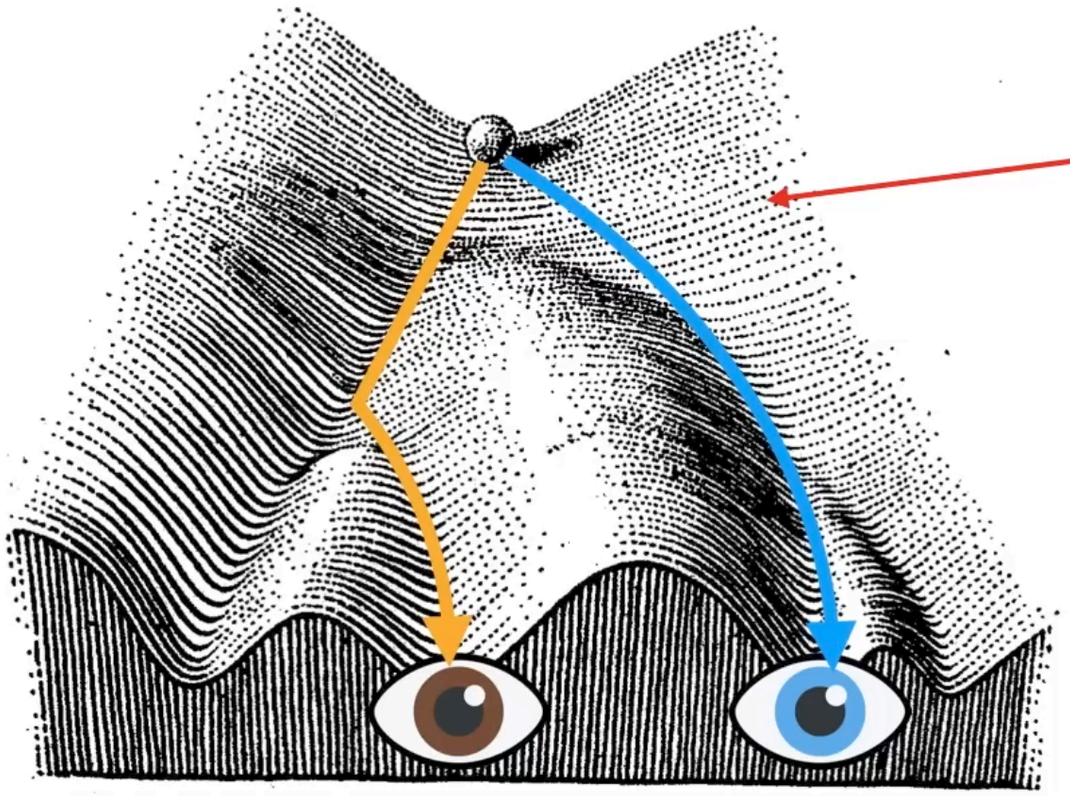
**White subjects only.*

†Same indicates both twins changed in the same direction or both had no change; different, the pattern of change differed between twins.

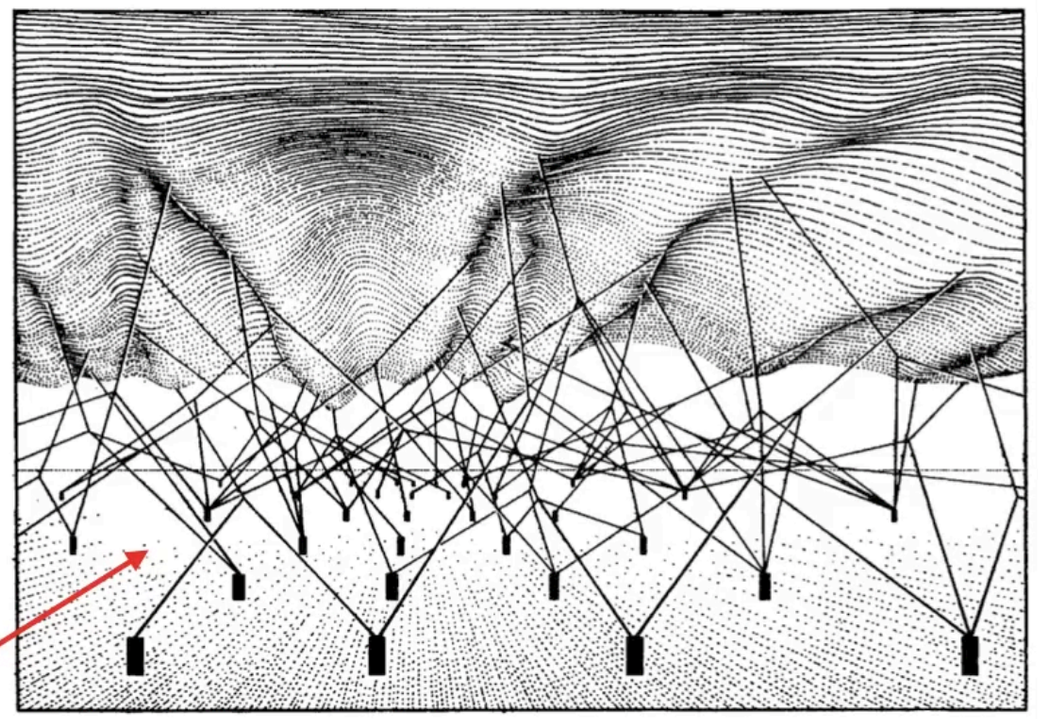
‡χ^2 Test (P<.05).



Social interactions and friends



View from above

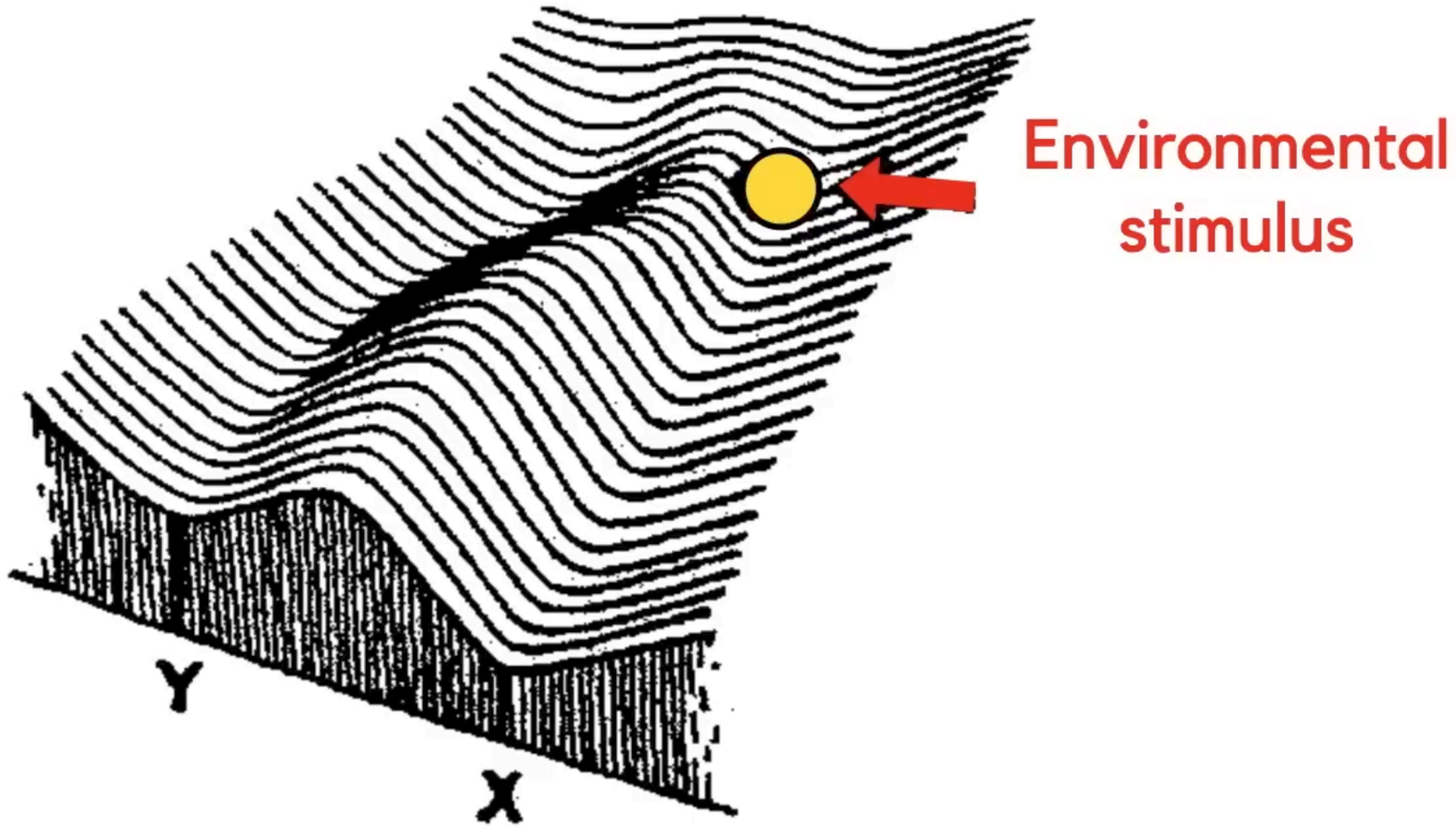


Guy-ropes underneath the surface

(View from below the surface)

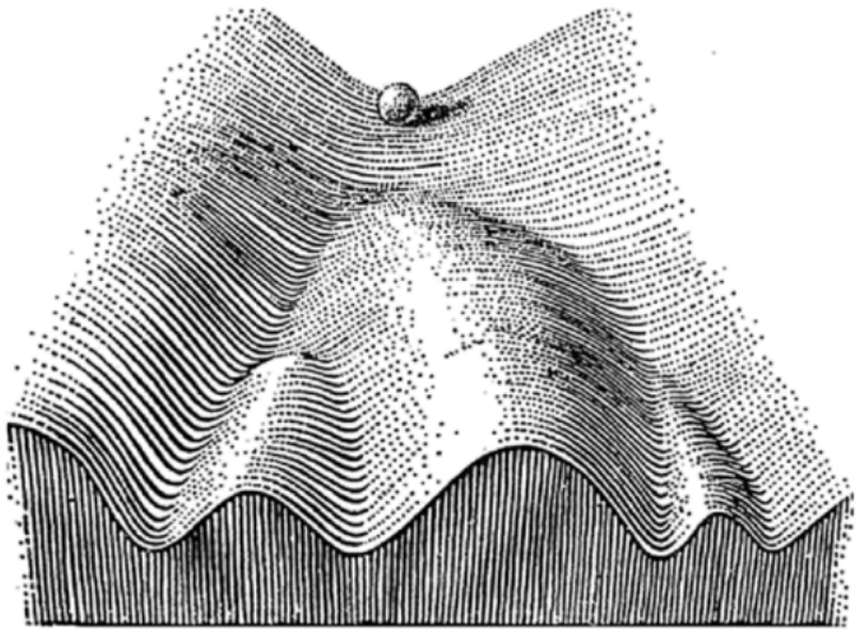
Waddington (1957)

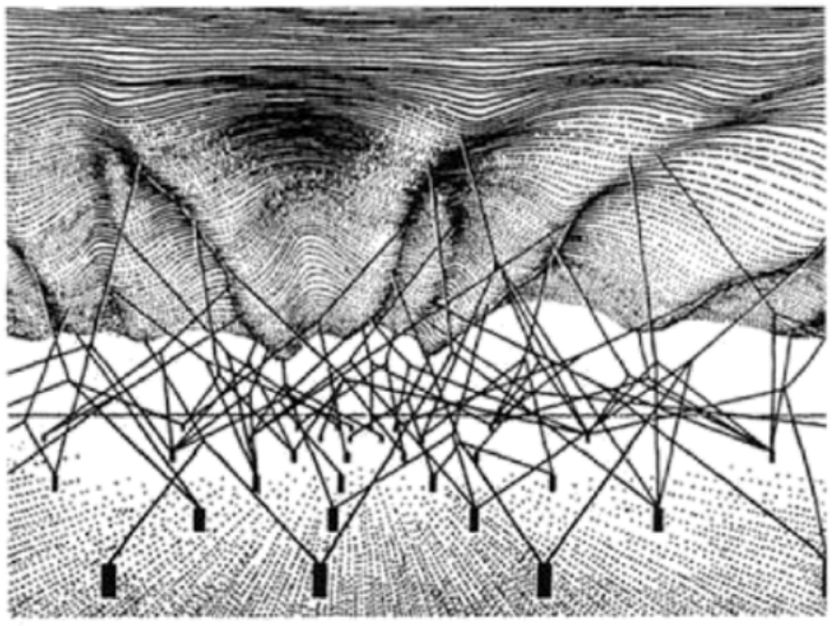
From the book The Strategy of the Genes, written by Waddington in 1957



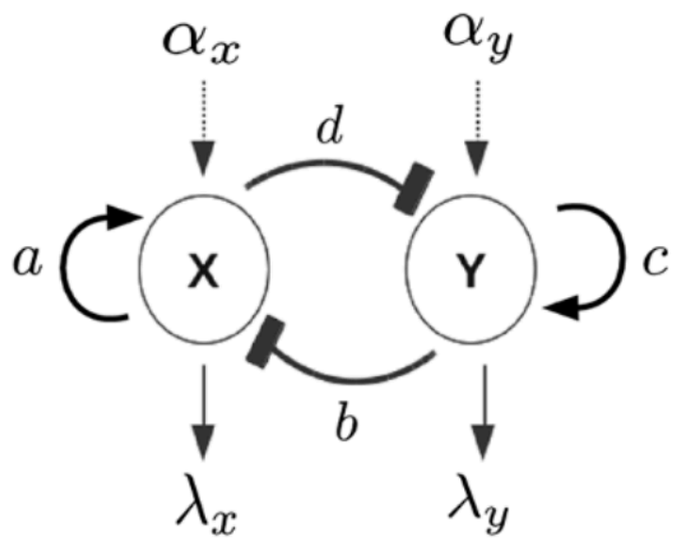
Waddington (1957)

A Waddington's epigenetic landscape





B 1 Toggle switch model

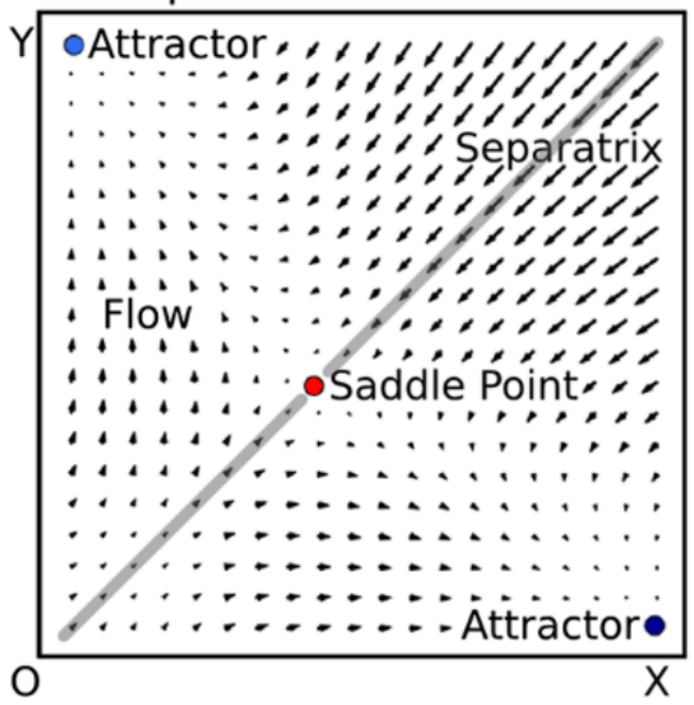


2 Equations

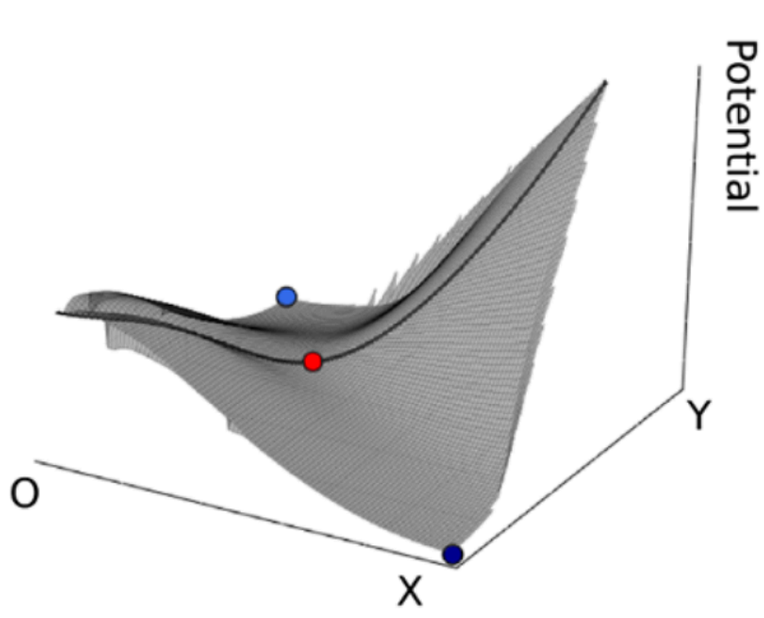
$$\frac{dx}{dt} = \left[\alpha_x + \frac{x^4}{a^4 + x^4}\right]\left[\frac{b^4}{b^4 + y^4}\right] - \lambda_x x$$

$$\frac{dy}{dt} = \left[\alpha_y + \frac{y^4}{c^4 + y^4}\right]\left[\frac{d^4}{d^4 + x^4}\right] - \lambda_y y$$

3 Phase portrait



4 (Quasi) potential landscape



2 Equations

Ratio in the final protein

External gene activation rate

Decay rate

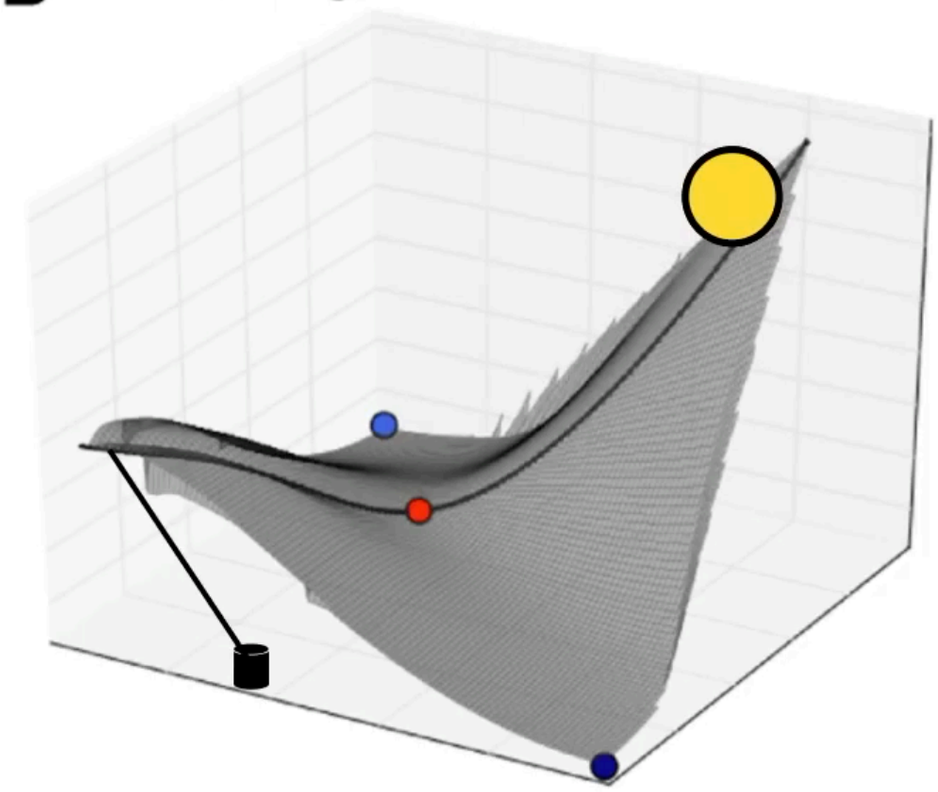
$$\frac{dx}{dt} = \left[\alpha_x + \frac{x^4}{a^4 + x^4}\right]\left[\frac{b^4}{b^4 + y^4}\right] - \lambda_x x$$

$$\frac{dy}{dt} = \left[\alpha_y + \frac{y^4}{c^4 + y^4}\right]\left[\frac{d^4}{d^4 + x^4}\right] - \lambda_y y$$

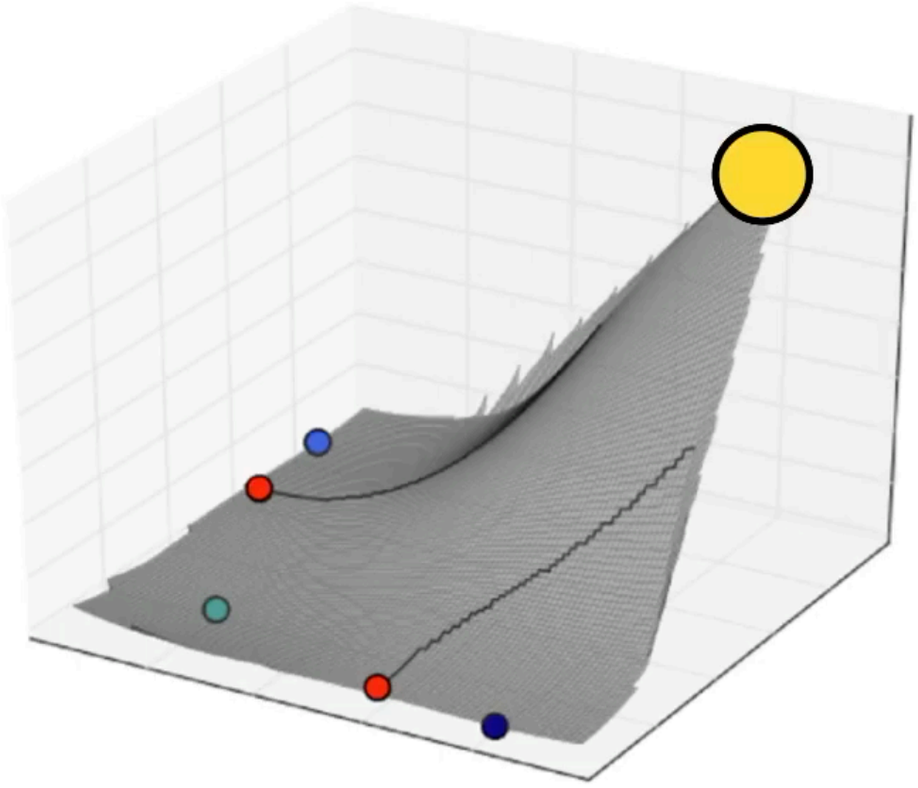
c

4 (Quasi) potential landscape

B Bistable regime

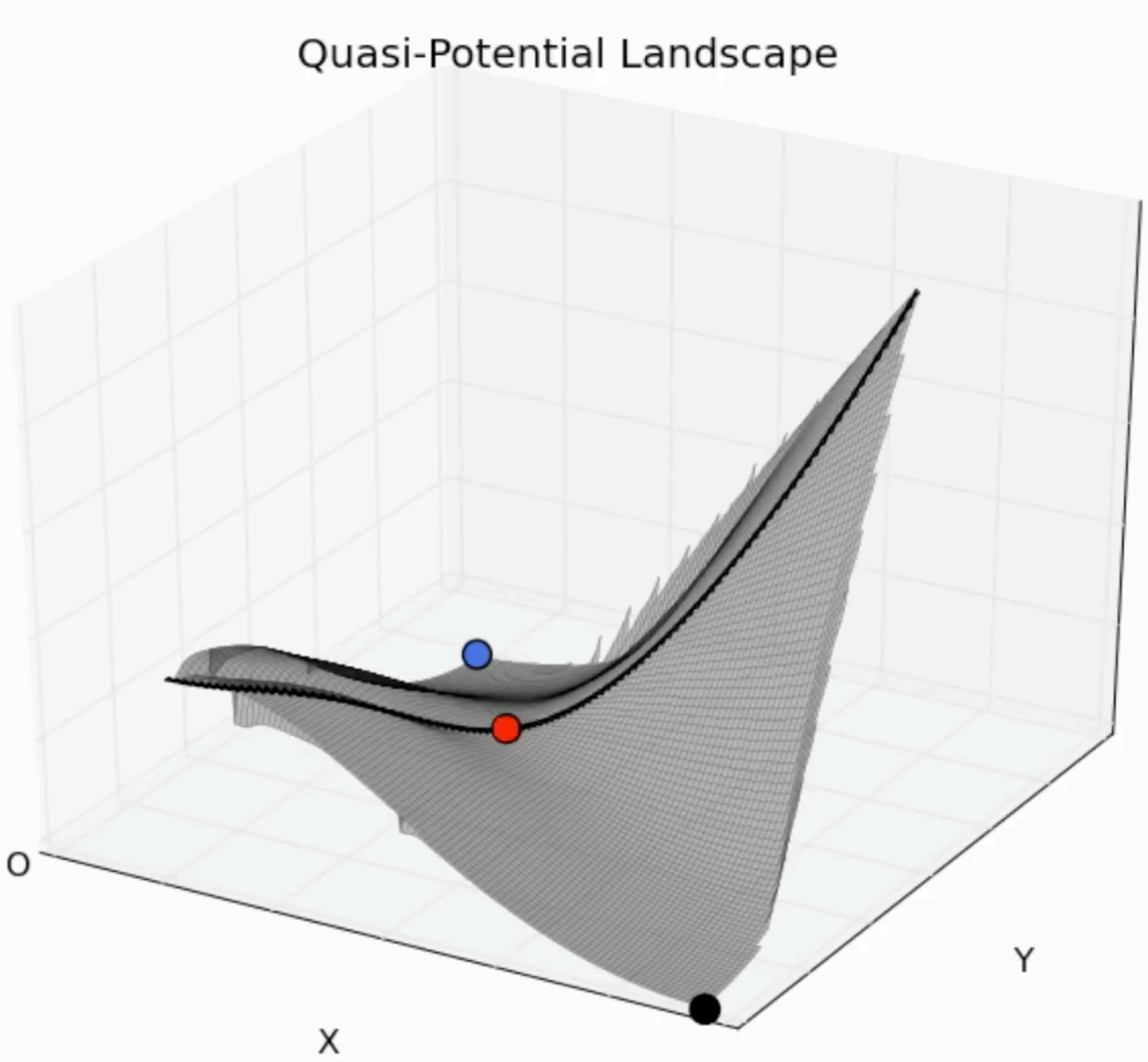


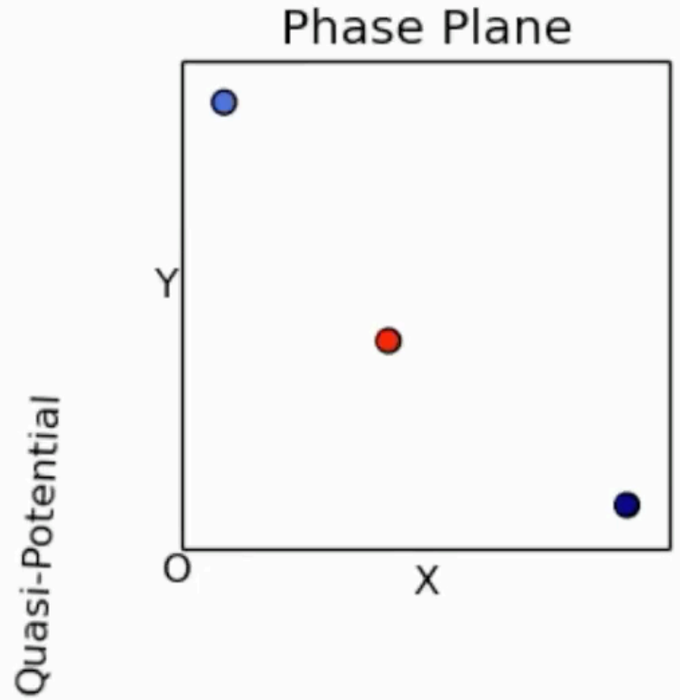
C Tristable regime



Verd et al. (2014)

1.00





Parameter Values .

X autoactivation = 0.28
Y autoactivation = 0.28

X repression on Y = 0.4
Y repression on X = 0.4

X external activation = 0.25
Y external activation = 0.25

X degradation = 1.25
Y degradation = 1.25

Verd et al. (2014)

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- Waddington, C. H. (1957). **The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology.** Kiribati: Allen & Unwin.

Thank you! 🫛🌸