Coping with the noisy* nature of **life** in teaching & other philosophic ruminations.

*that is unpredictable

Mike Klymkowsky. - MCD Biology - UC Boulder

Intended take home messages:

→ biological systems (including us) are often inherently unpredictable; they are stochastic - a word we will define

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→ there are good reasons to embrace free will over determinism

Disclaimers + caveats

I am not …

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- a philosopher or philosophy professor

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How would Socrates teach science?


By Ann Riedl and Mike Klymkowsky

Aug. 4, 2022

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the challenge (to be comprehensible)….

“If you care about being thought credible and intelligent, do not use complex language where simpler language will do.”
— Daniel Kahneman

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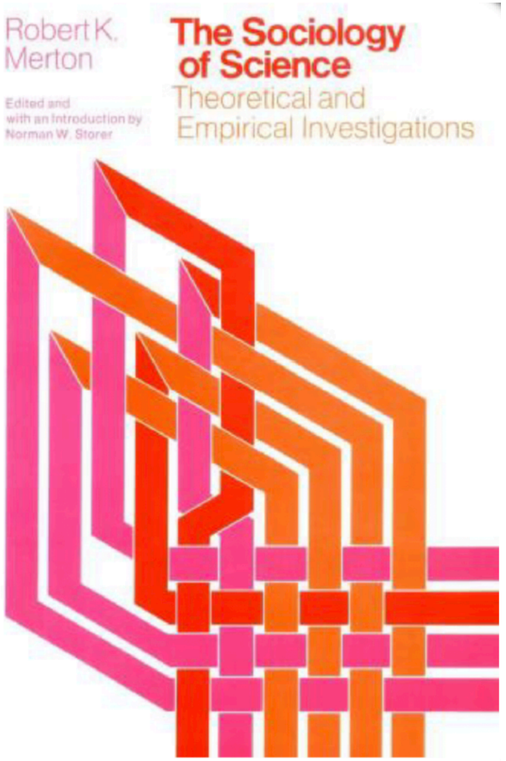
Basic (scientific) assumptions are …



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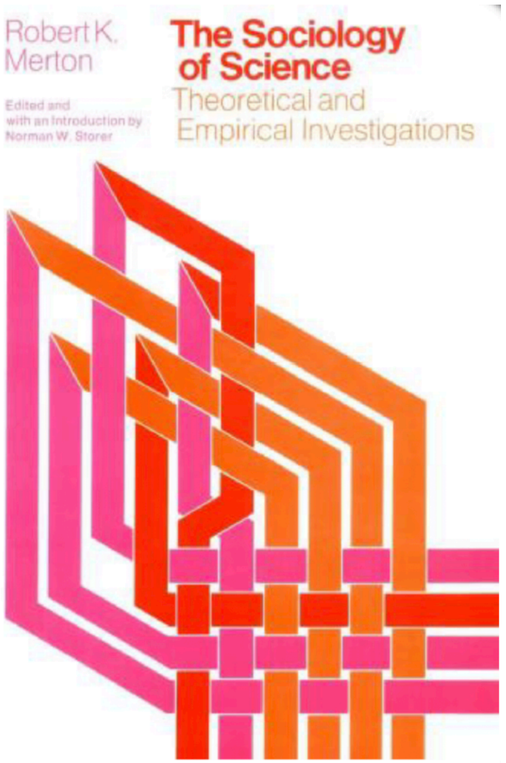

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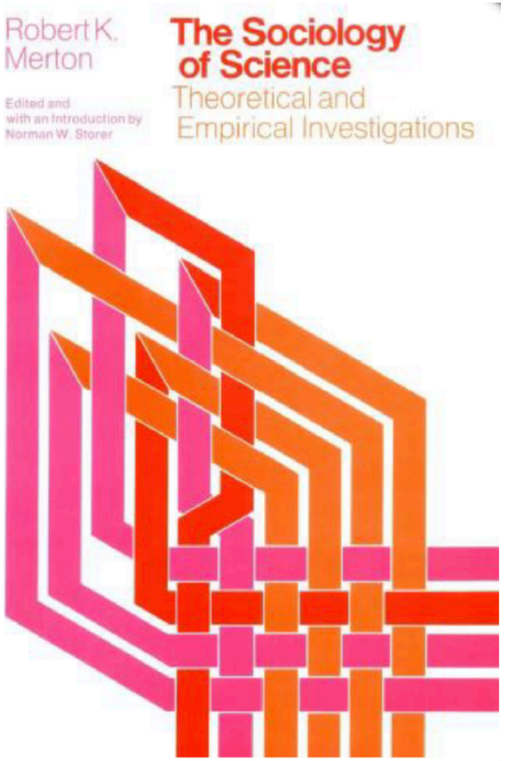

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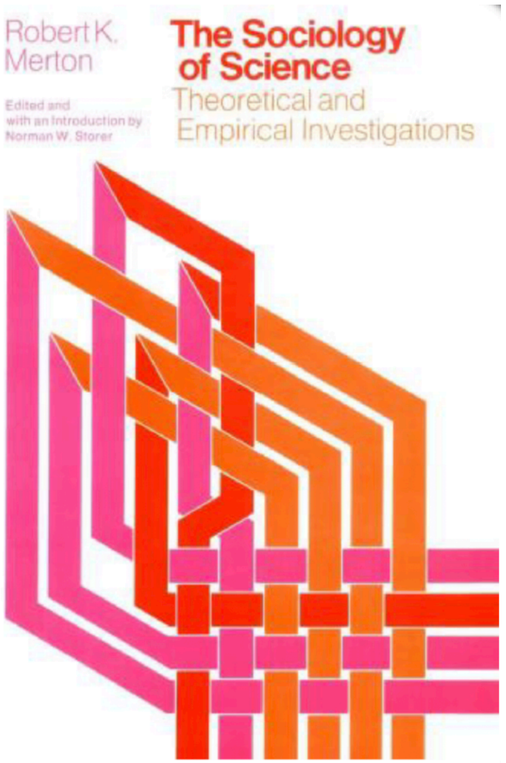

- posturing about the unknowable (multi-verses, quantum consciousness, the universe as simulation, angels on the head of a pin, and such) is anti-scientific

the story of a journey …

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– how to best **teach** developmental biology

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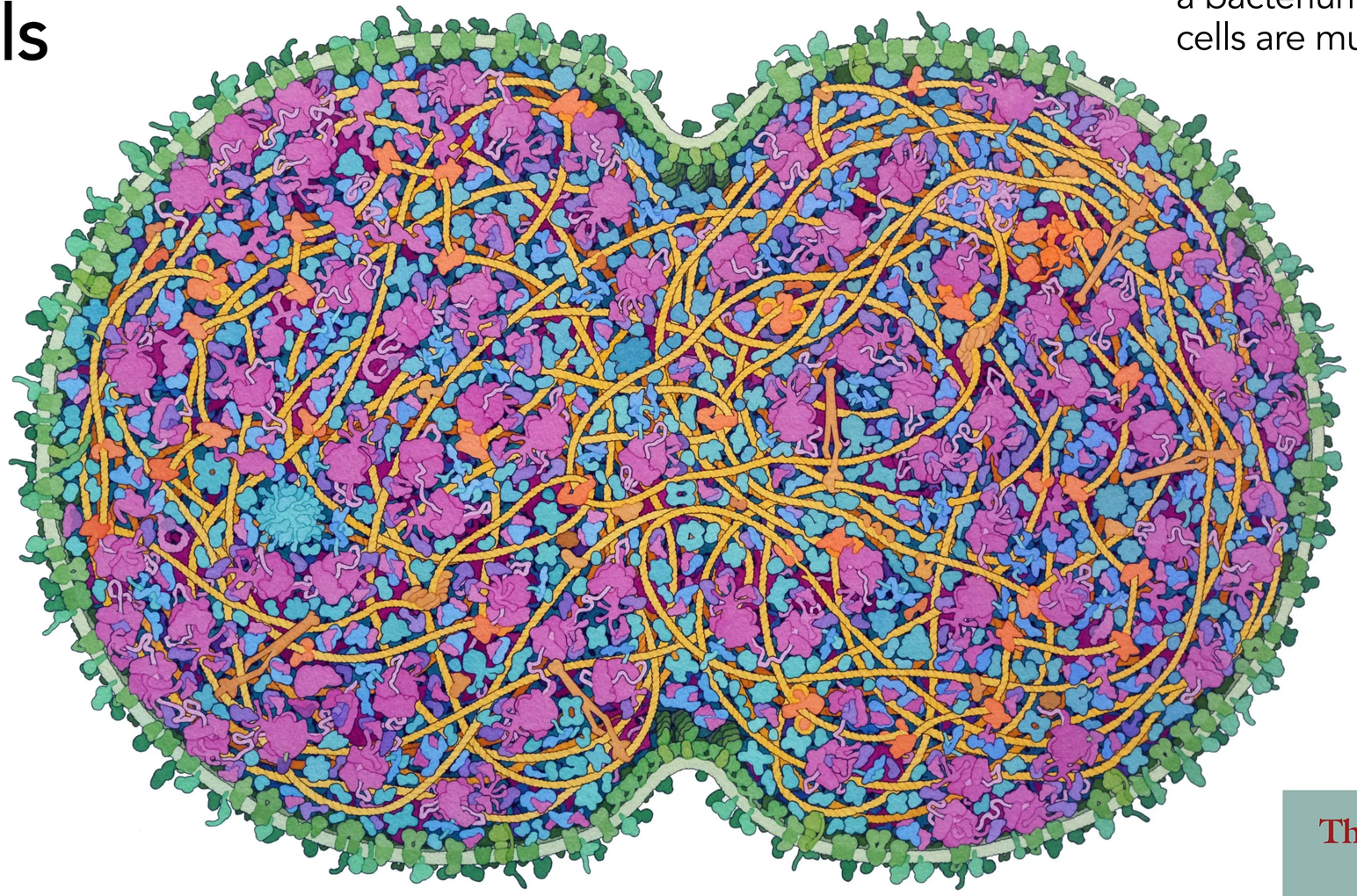
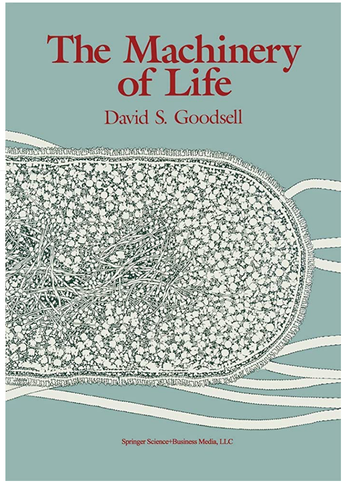
- but their ubiquity is being increasing recognized

it all starts with cells

a bacterium, eukaryotic cells are much bigger





Thinking about the Conceptual Foundations of the Biological Sciences

M. W. Klymkowsky

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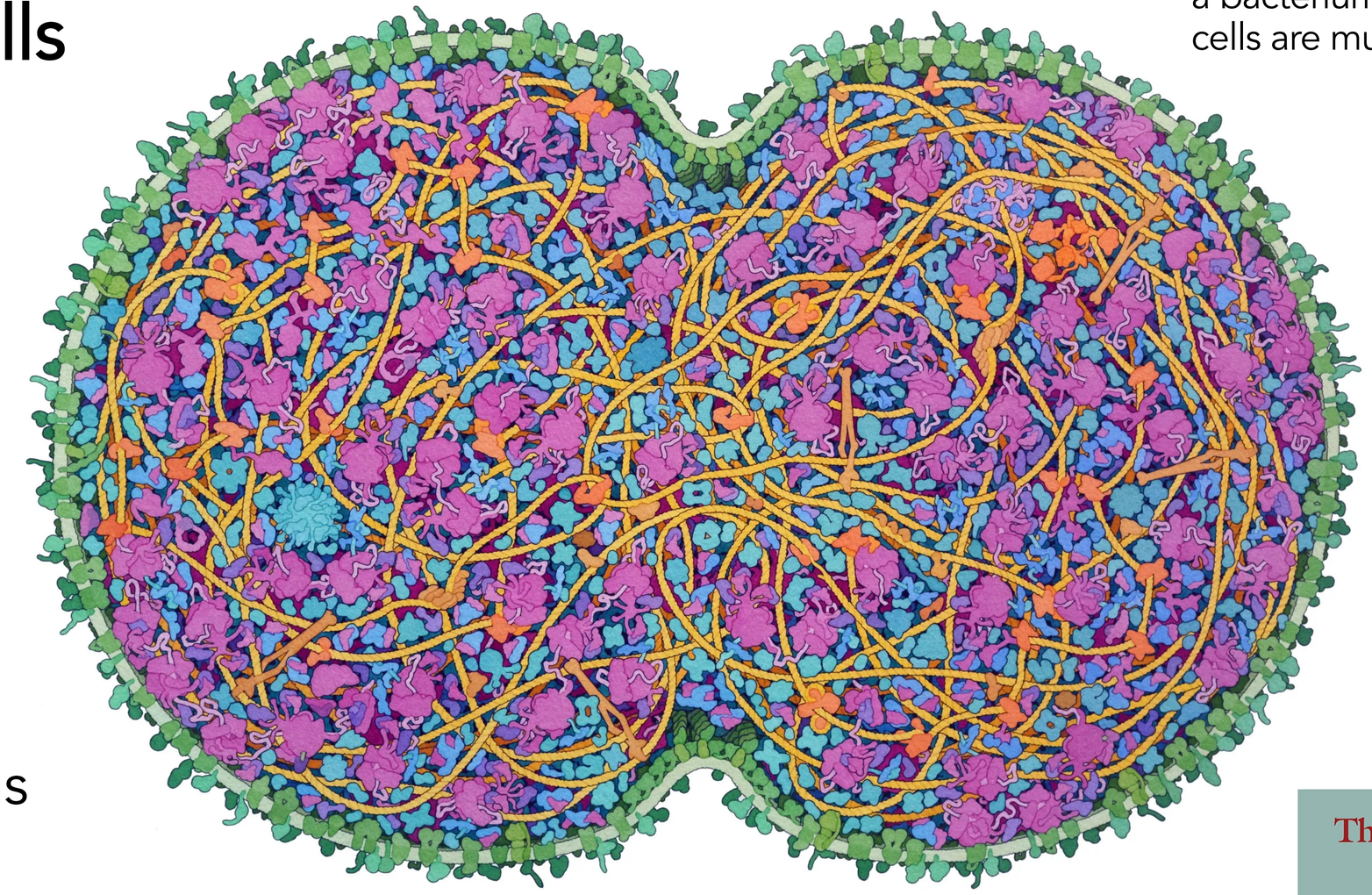
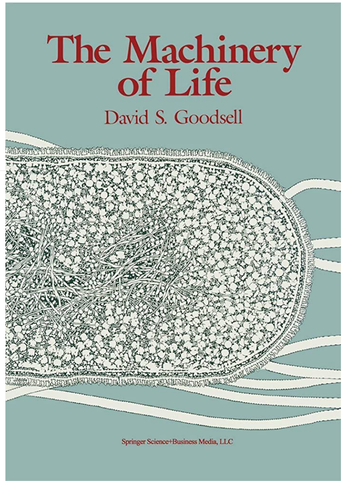


- bounded, continuous



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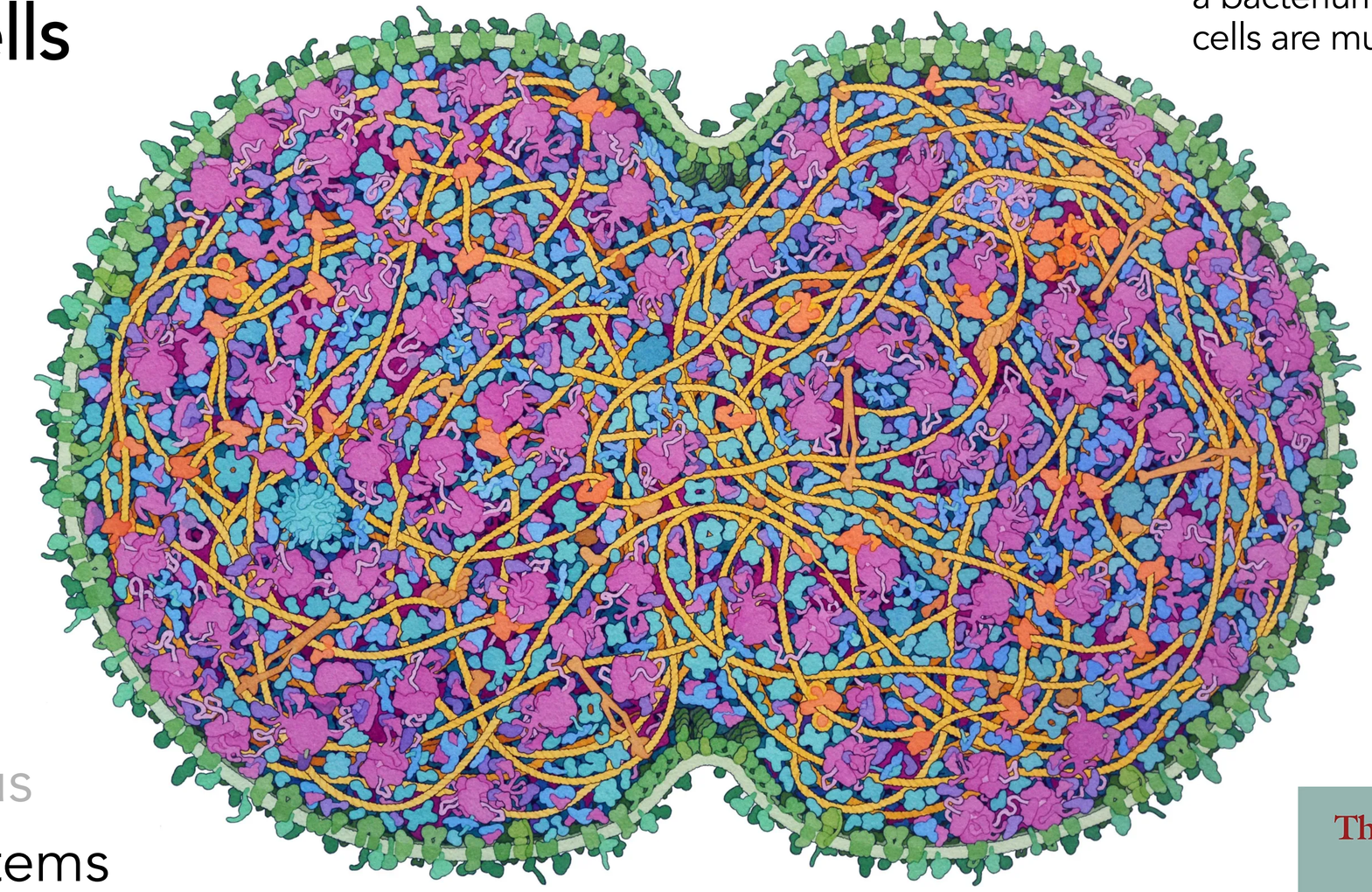

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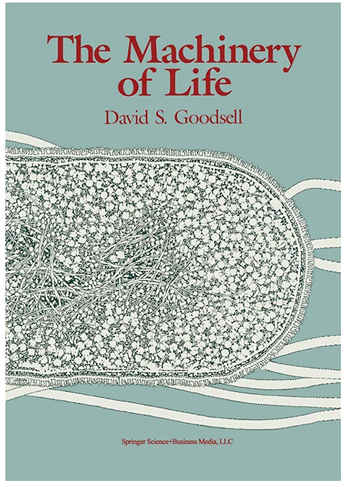

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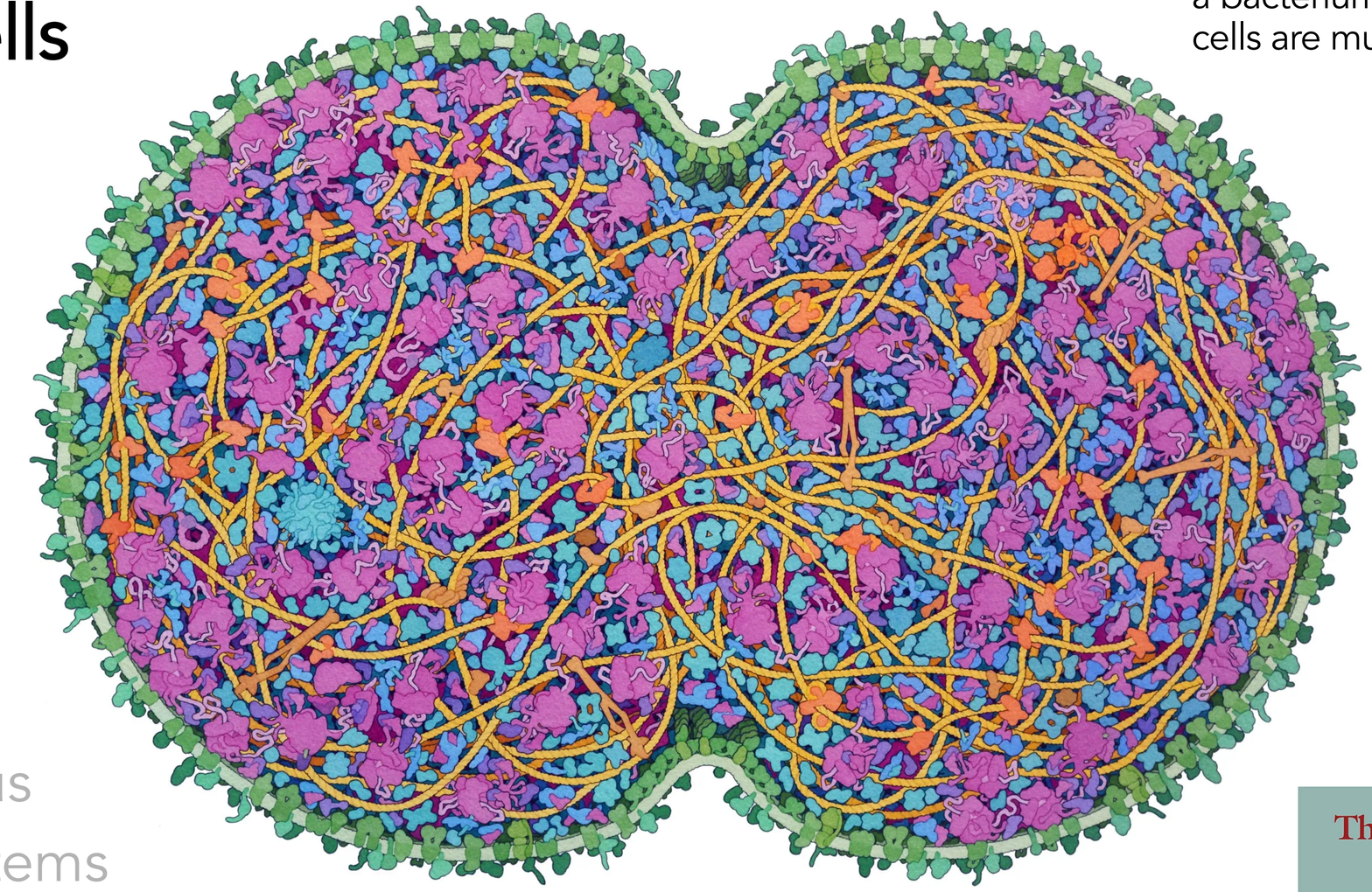

- bounded, continuous
- non-equilibrium systems
- controlled by selection-derived information stored in DNA & cell structure

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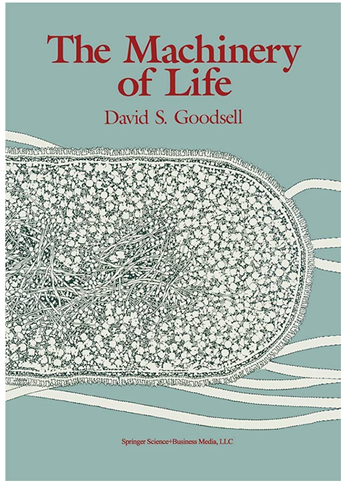
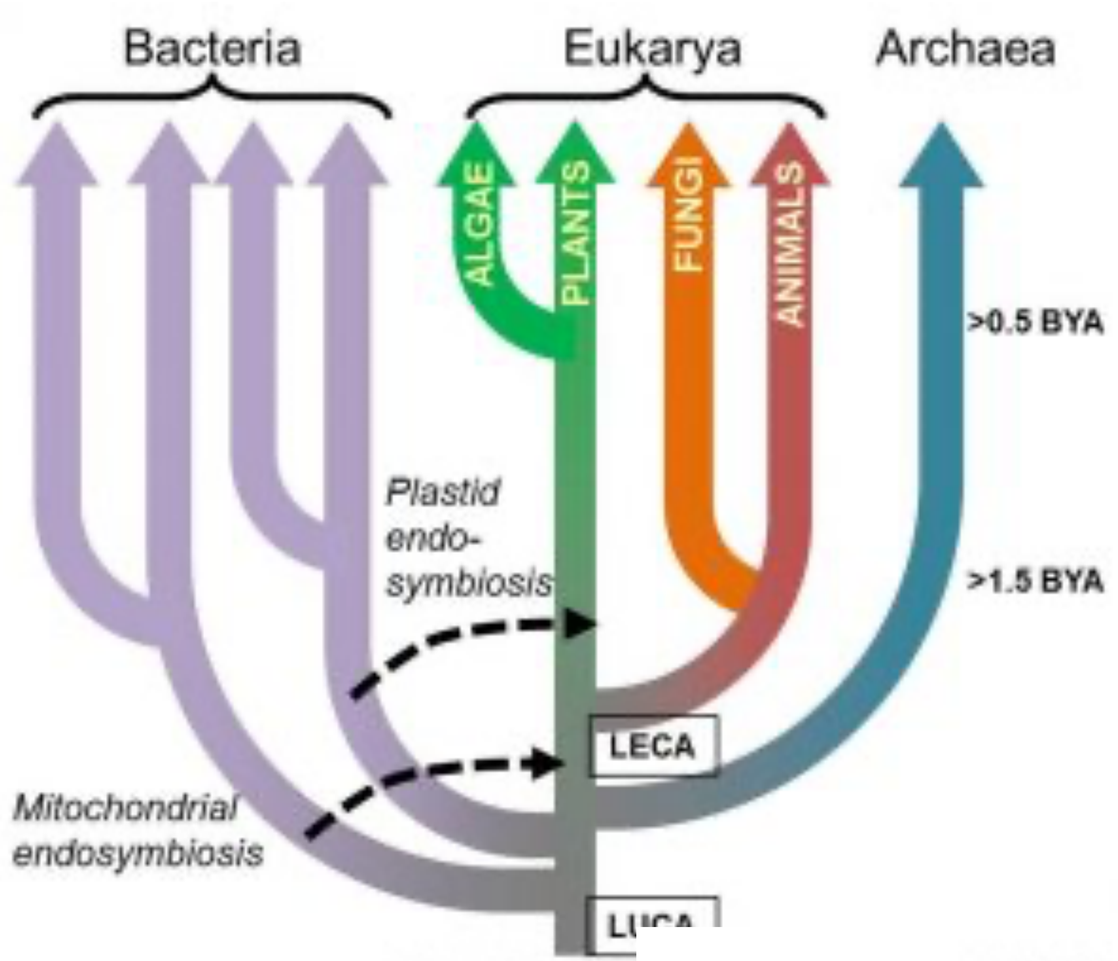


Cellular systems are ancient …
an unbroken (~3.5 billion year long) lineage



LUCA

origin of "living" systems

exact details are unknowable

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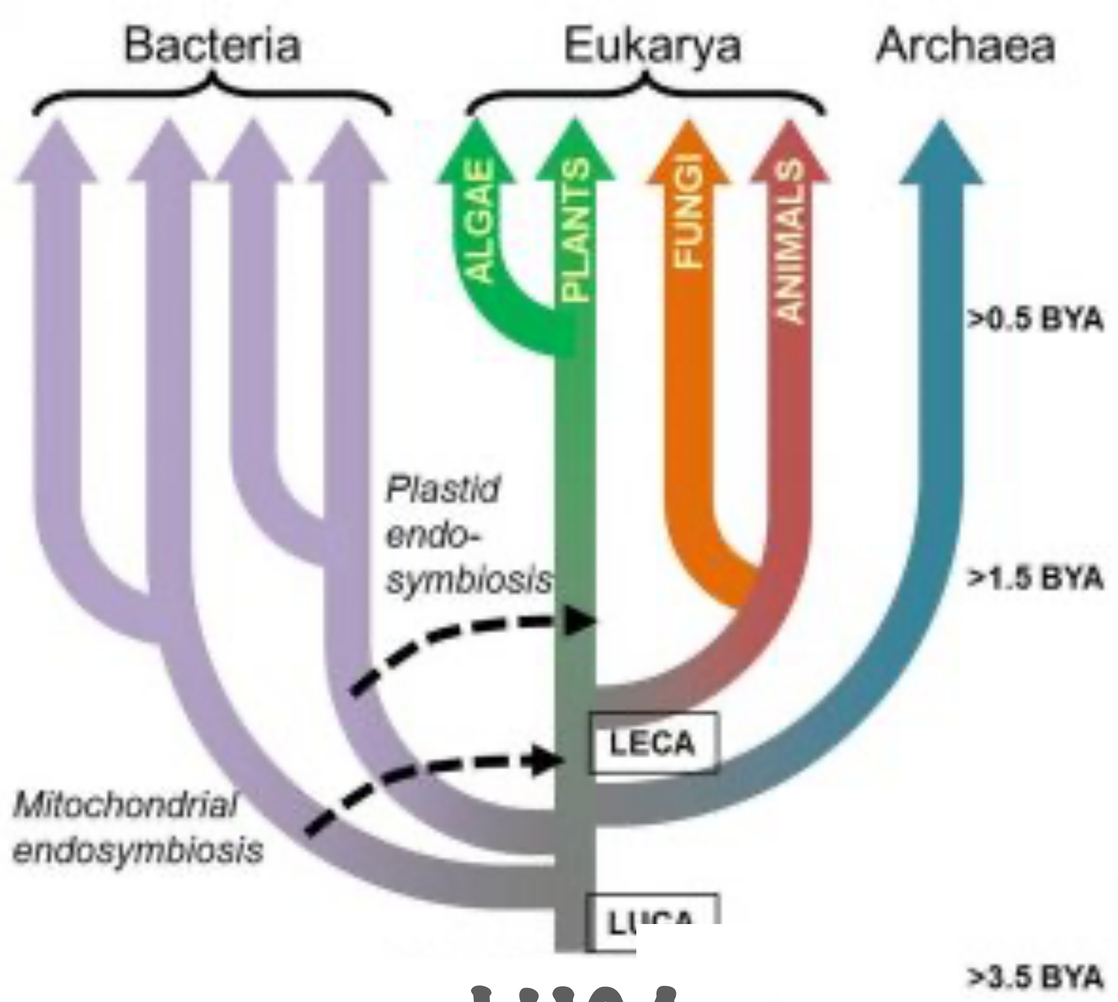

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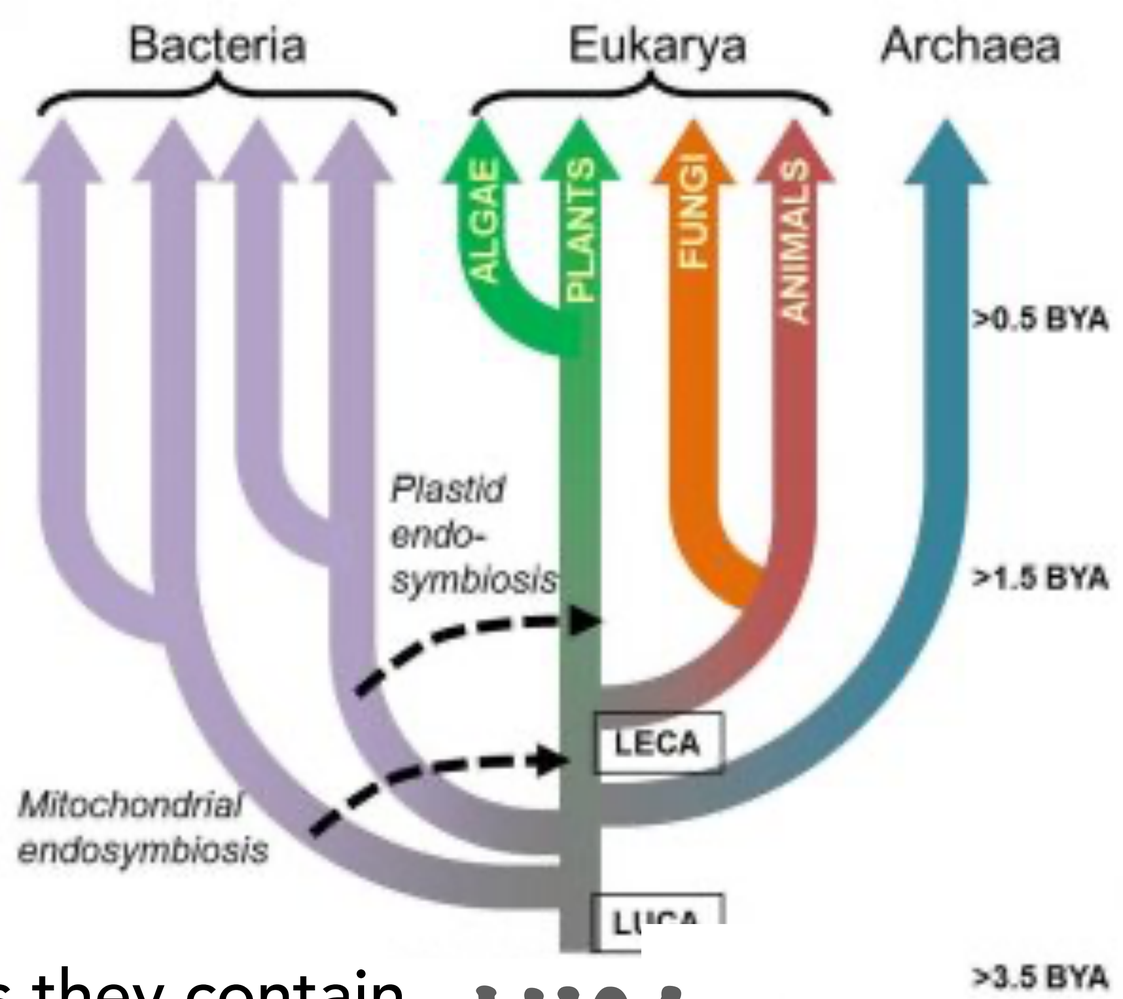

Cells differ in terms of the genes they contain and the structures and processes then make possible

LUCA

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still has a way to go
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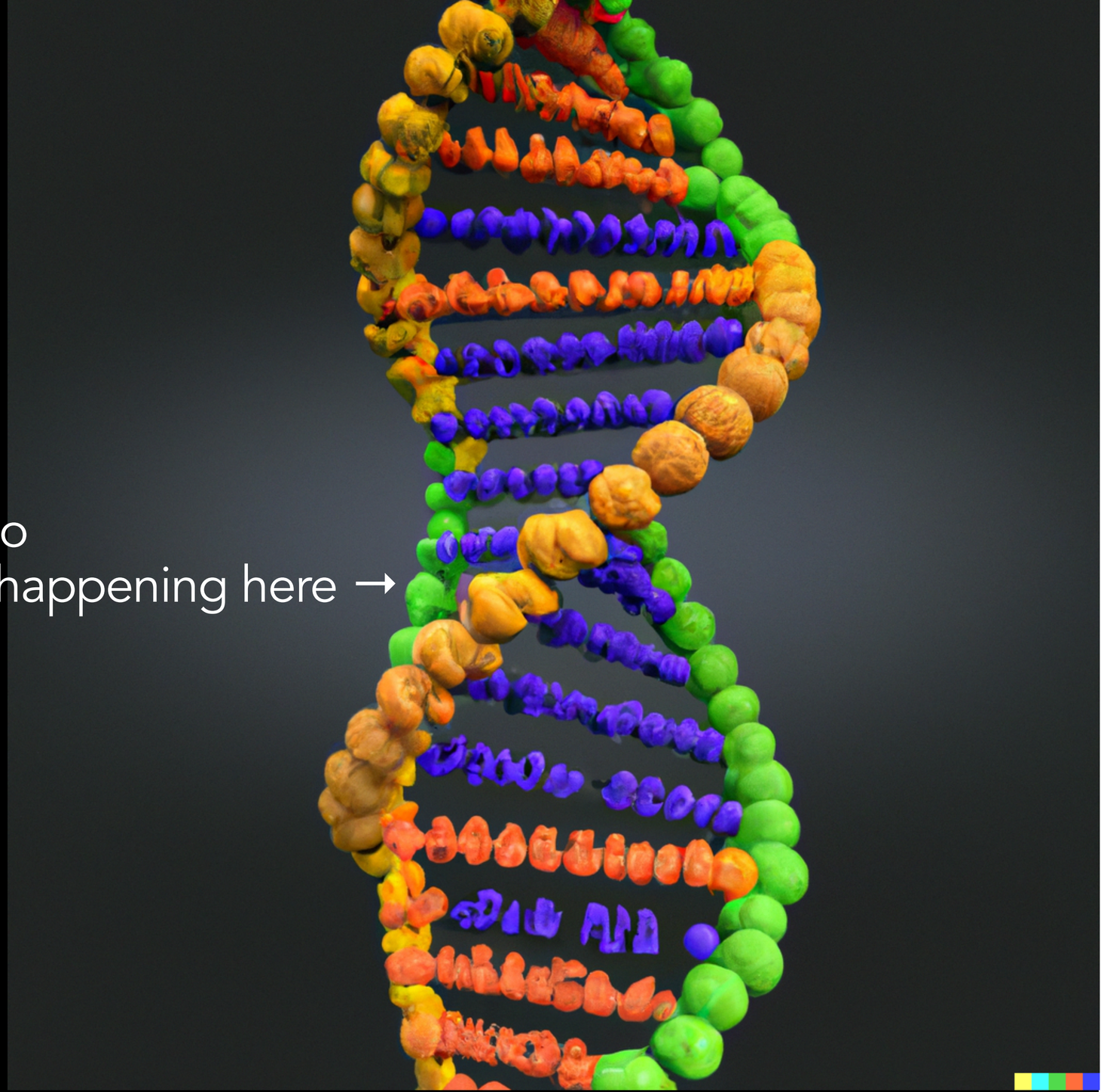

Cells “obey” the law …

one reason to take chemistry

Using Catalysis to Drive Chemistry Away from Equilibrium: Relating Kinetic Asymmetry, Power Strokes, and the Curtin–Hammett Principle in Brownian Ratchets

Shuntaro Amano, Massimiliano Esposito, Elisabeth Kreidt, David A. Leigh,* Emanuele Penocchio,* and Benjamin M. W. Roberts

High and stable ATP levels prevent aberrant intracellular protein aggregation in yeast

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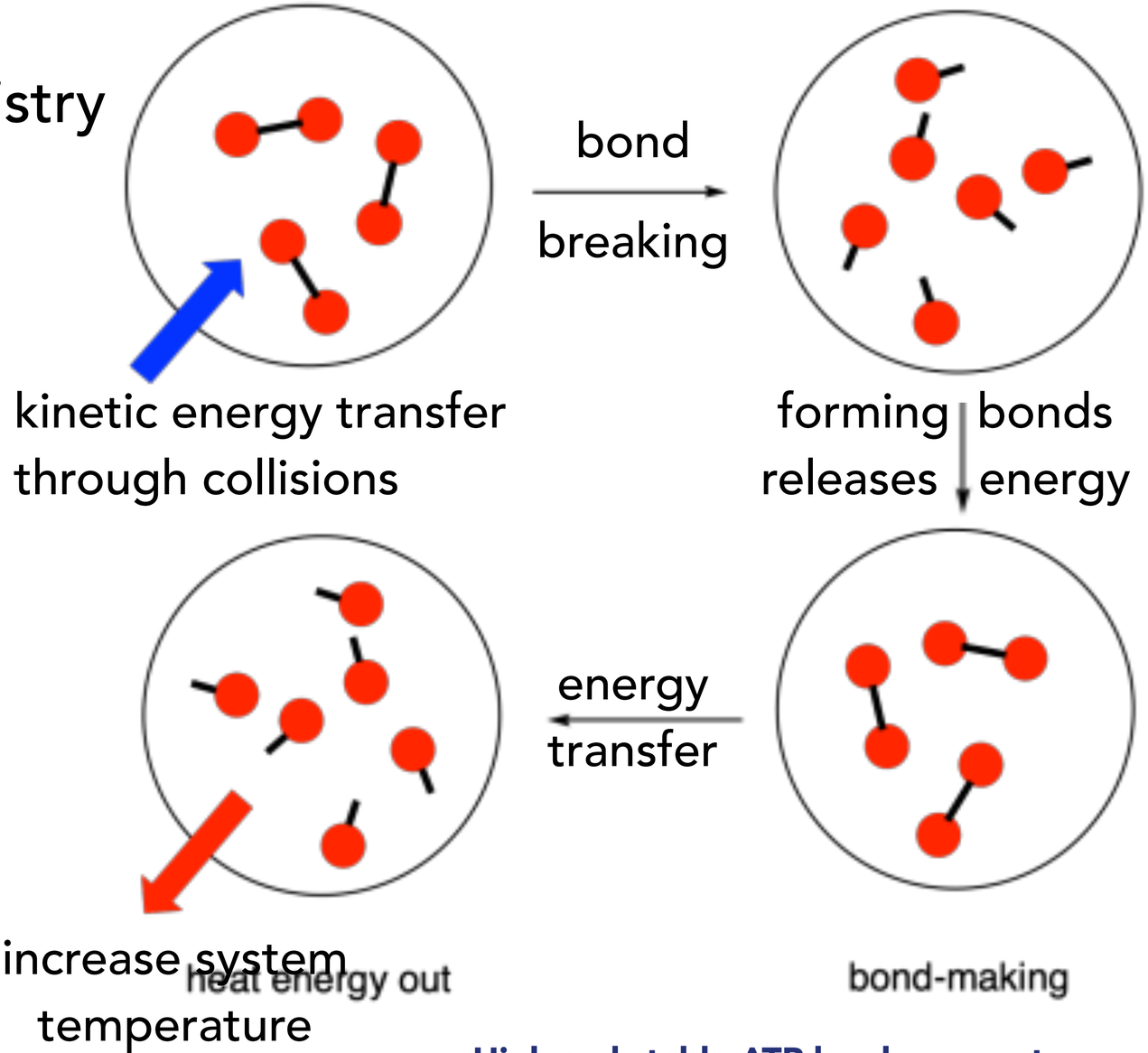

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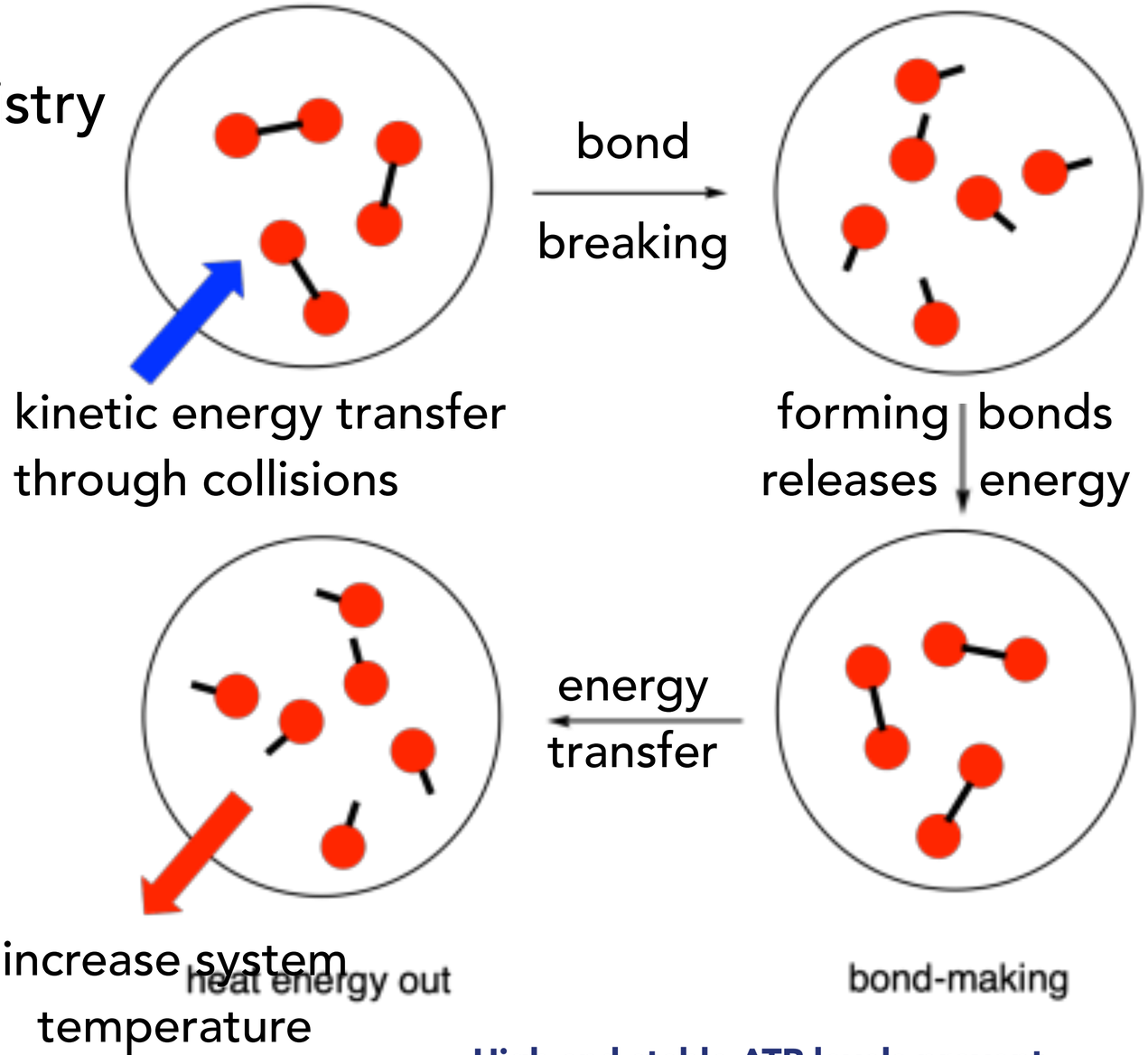

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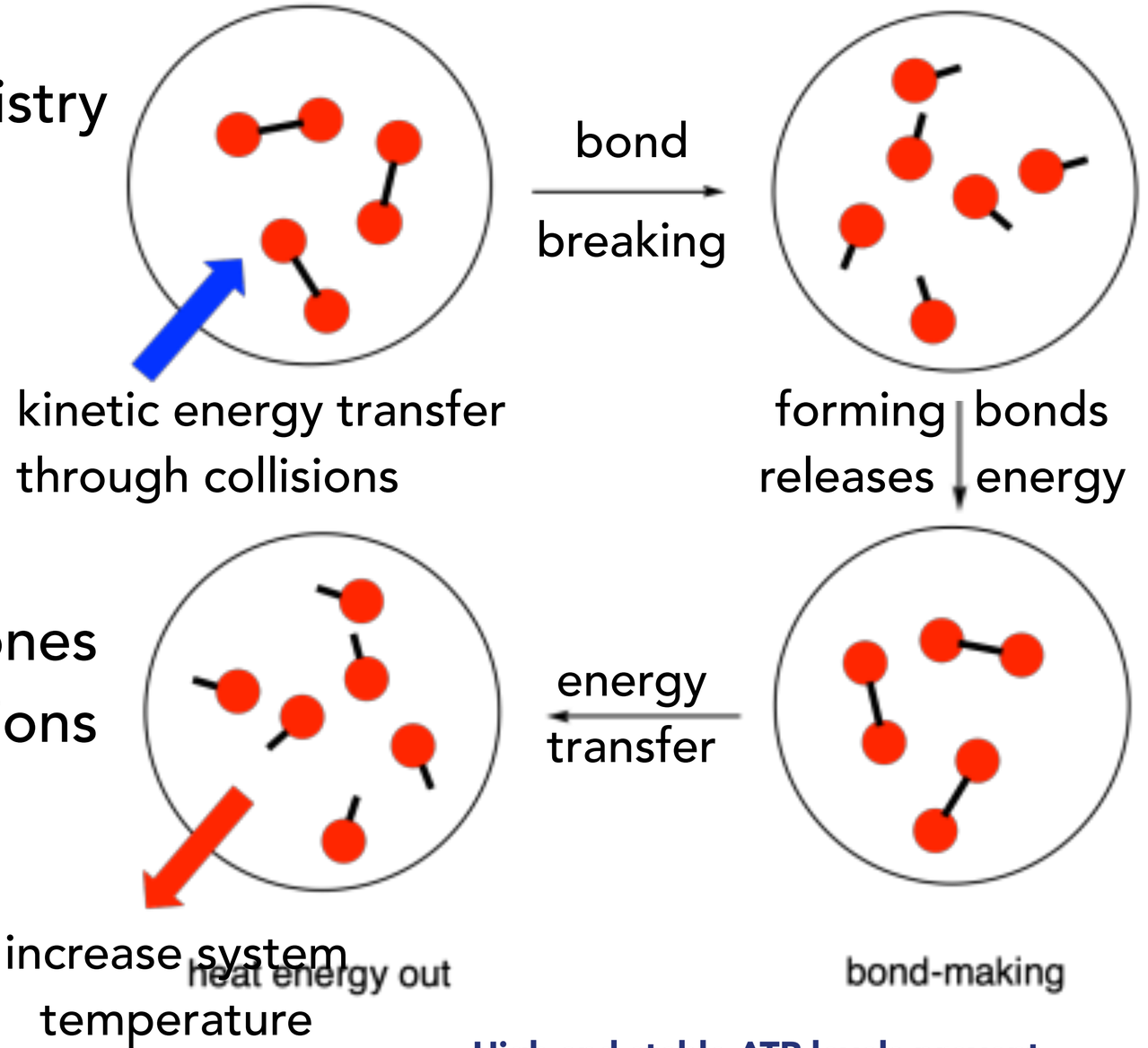

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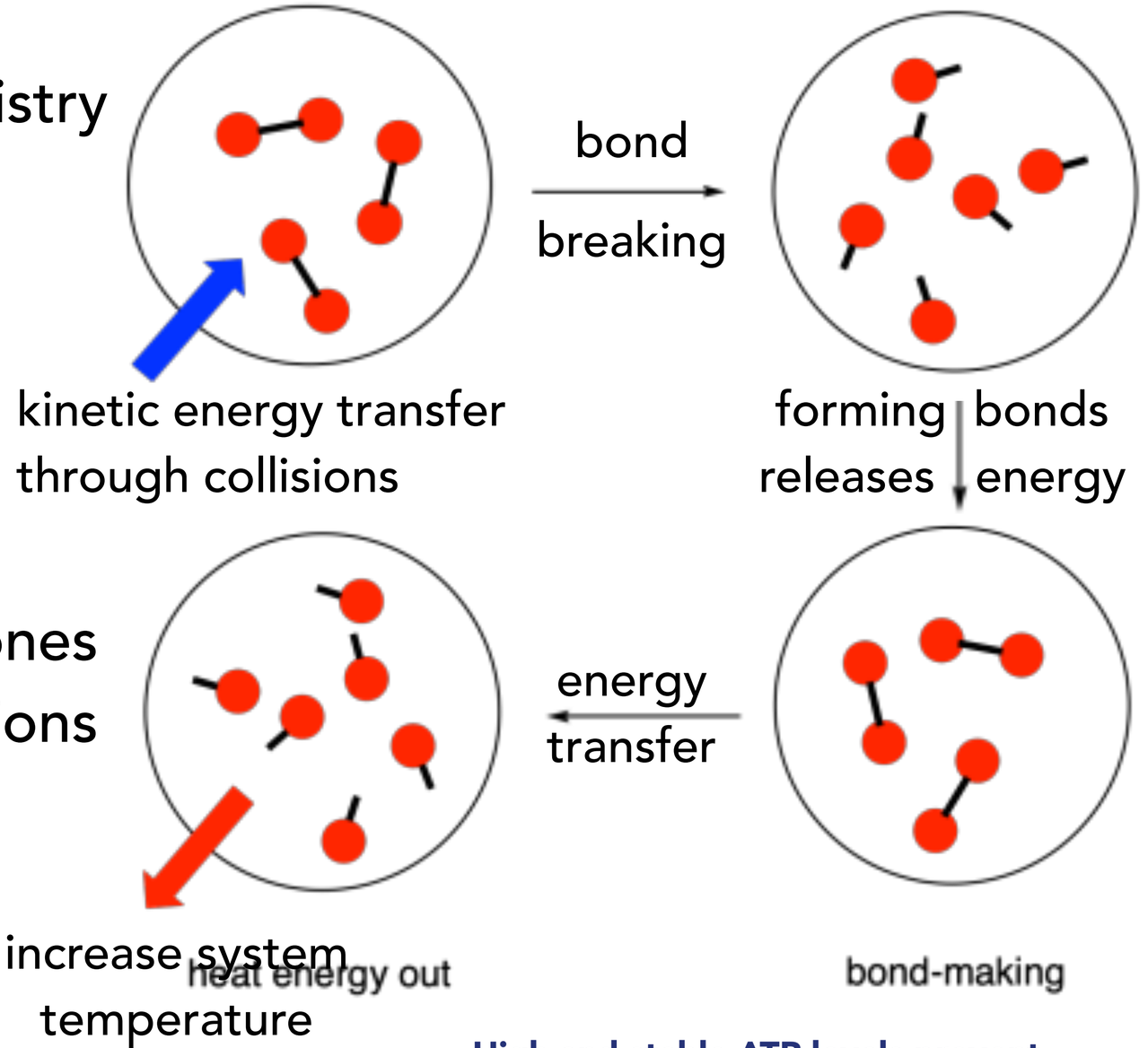
BUT cellular processes are inherently noisy



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Why noisy?

Size-dependent studies of macromolecular crowding on the thermodynamic stability, structure and functional activity of proteins: *in vitro* and *in silico* approaches

Sumra Shahid, Md. Imtaiyaz Hassan, Asimul Islam *, Faizan Ahmad

Why noisy? – because cells are small

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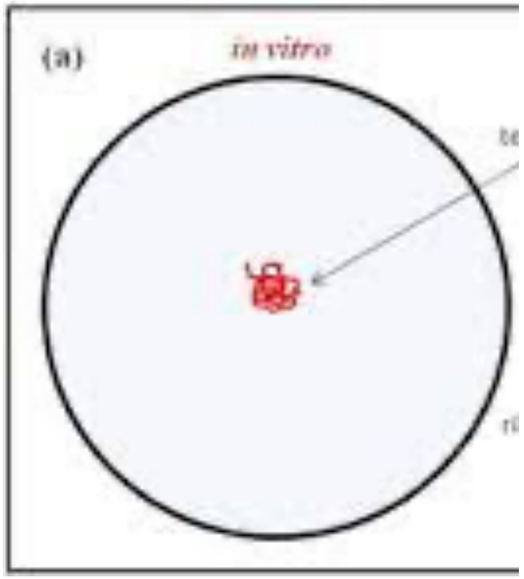

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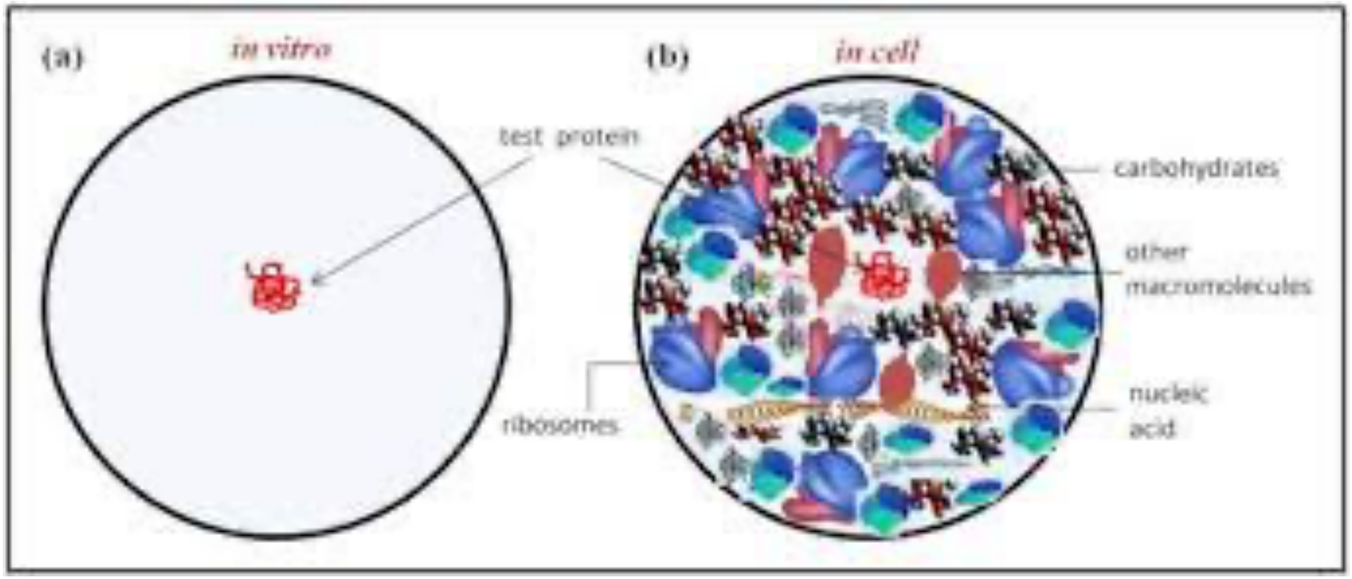

each cell contains (relatively) small numbers of many different types of interacting molecules and one or two copies of each gene

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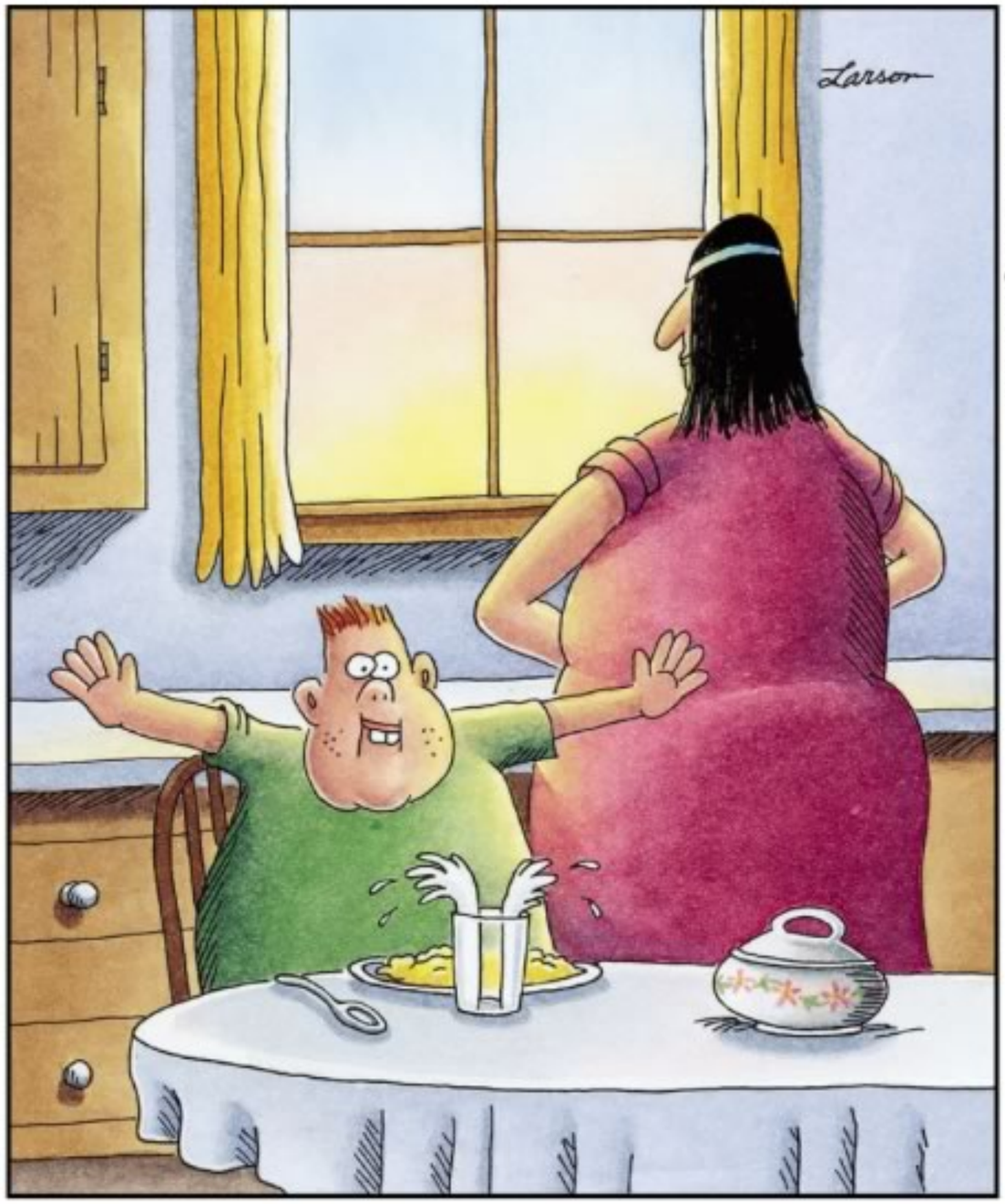
  - while the behavior of a large (enough) population is predictable



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Throwing (fair) dice - a stochastic process

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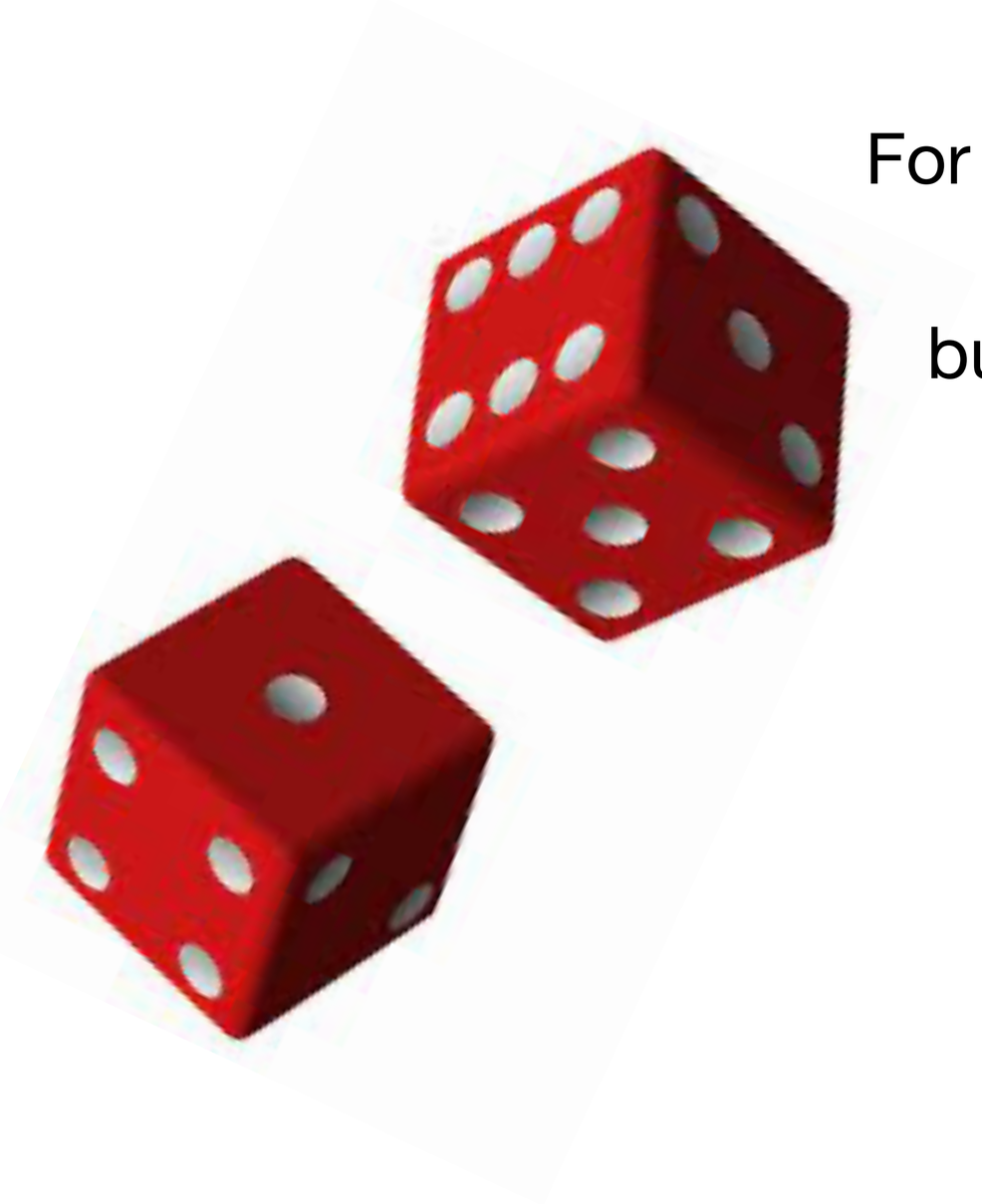

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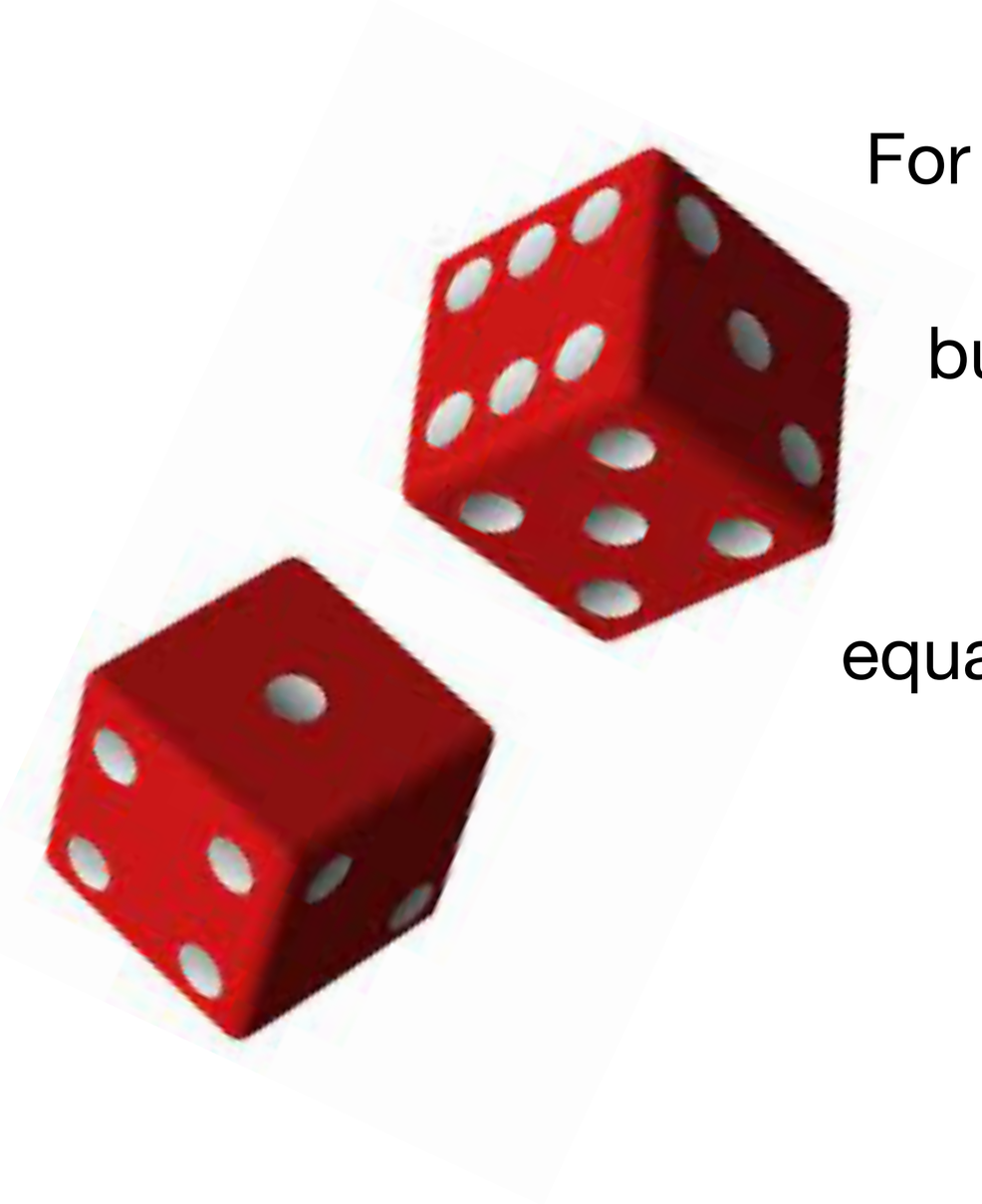

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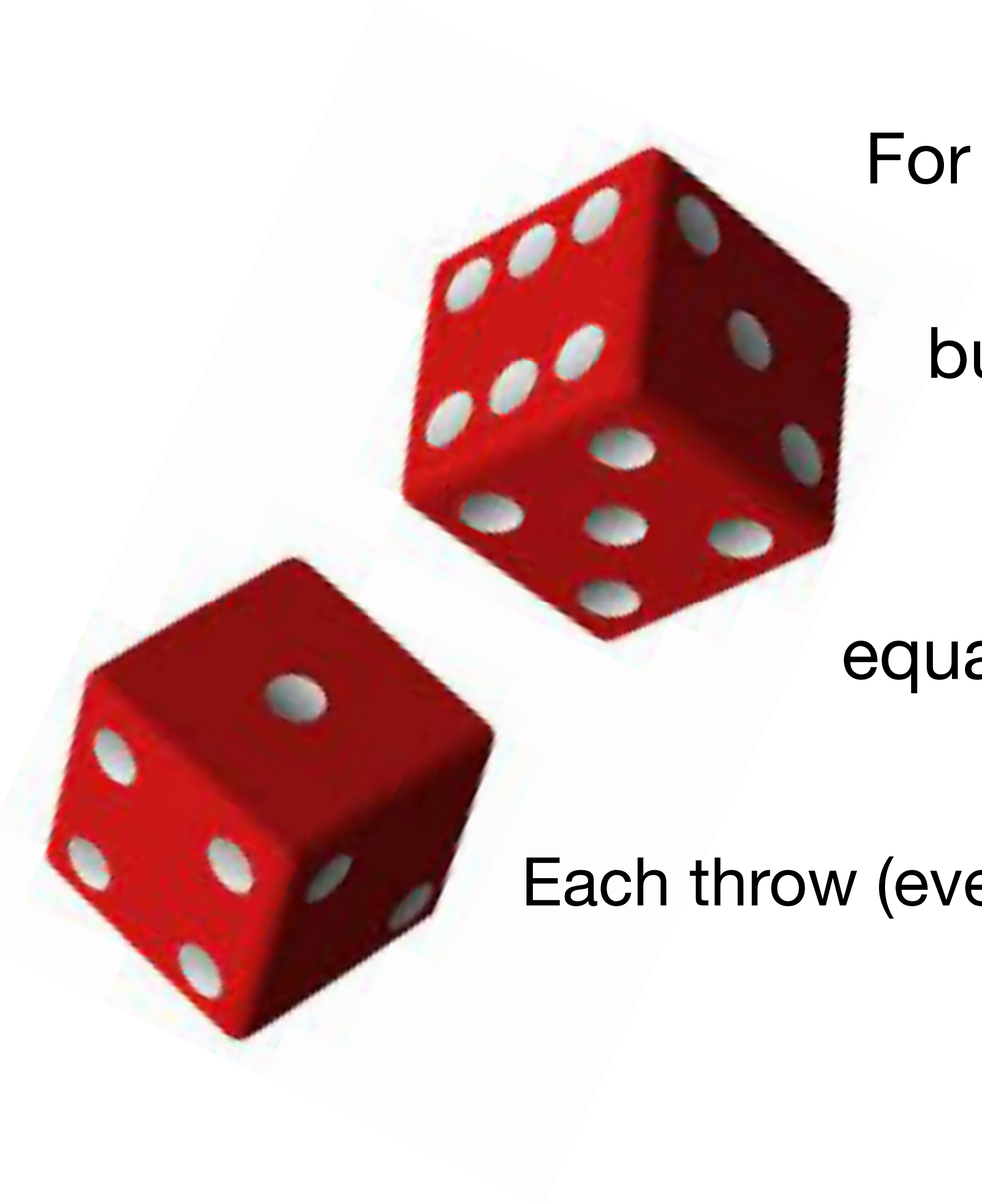

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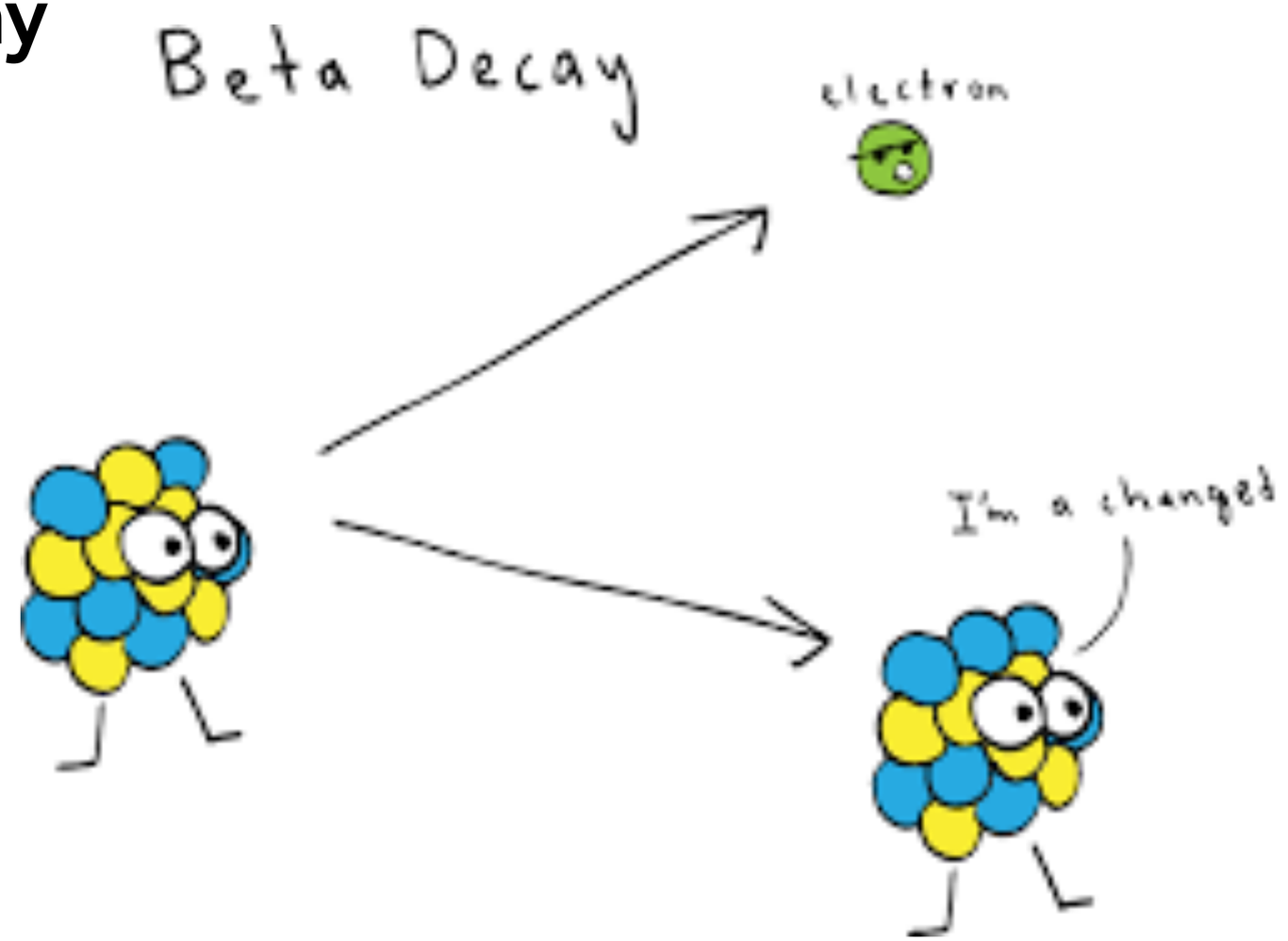
Each throw (event) is independent – gambler's fallacy

Same with radioisotope decay



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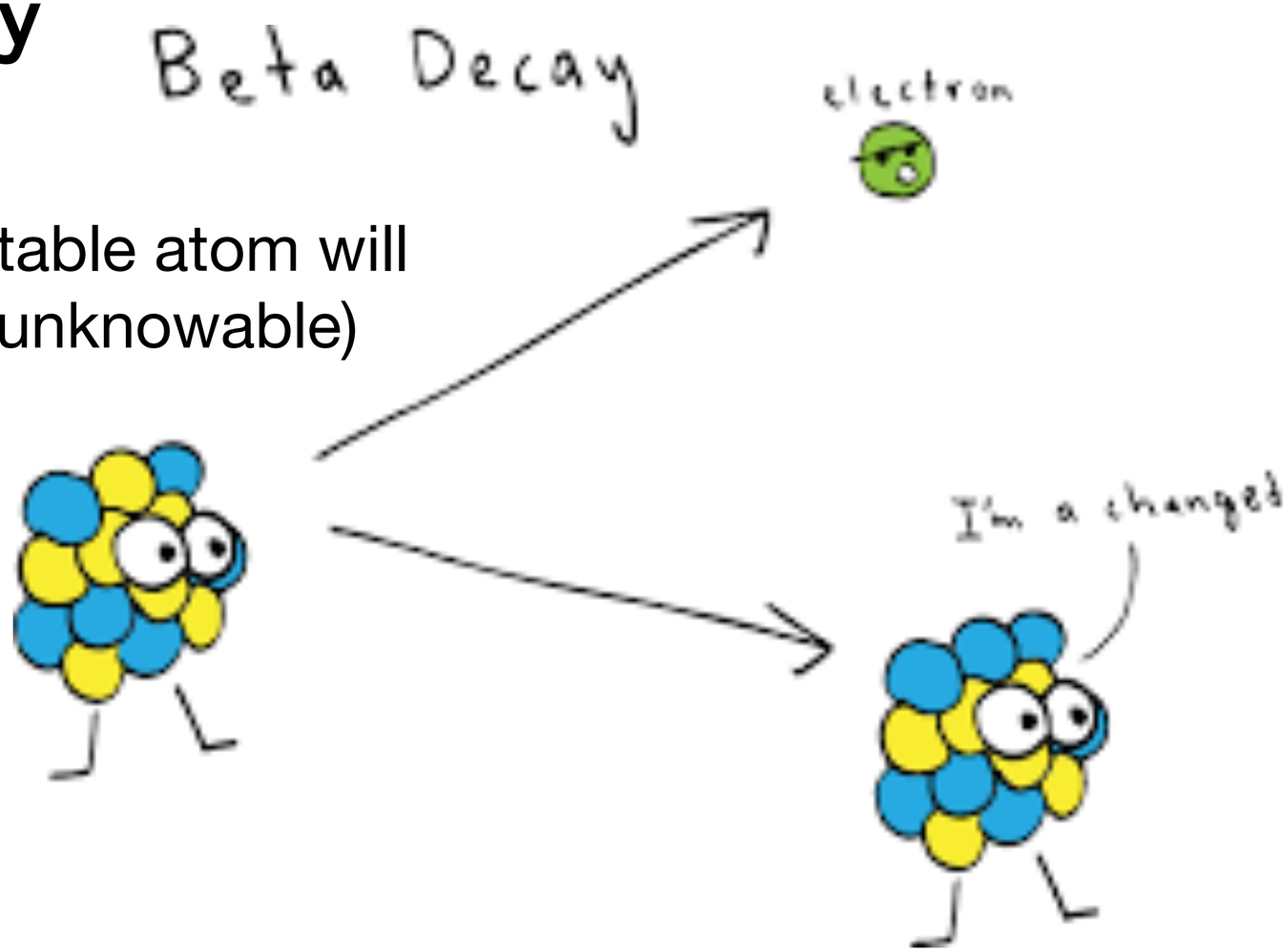

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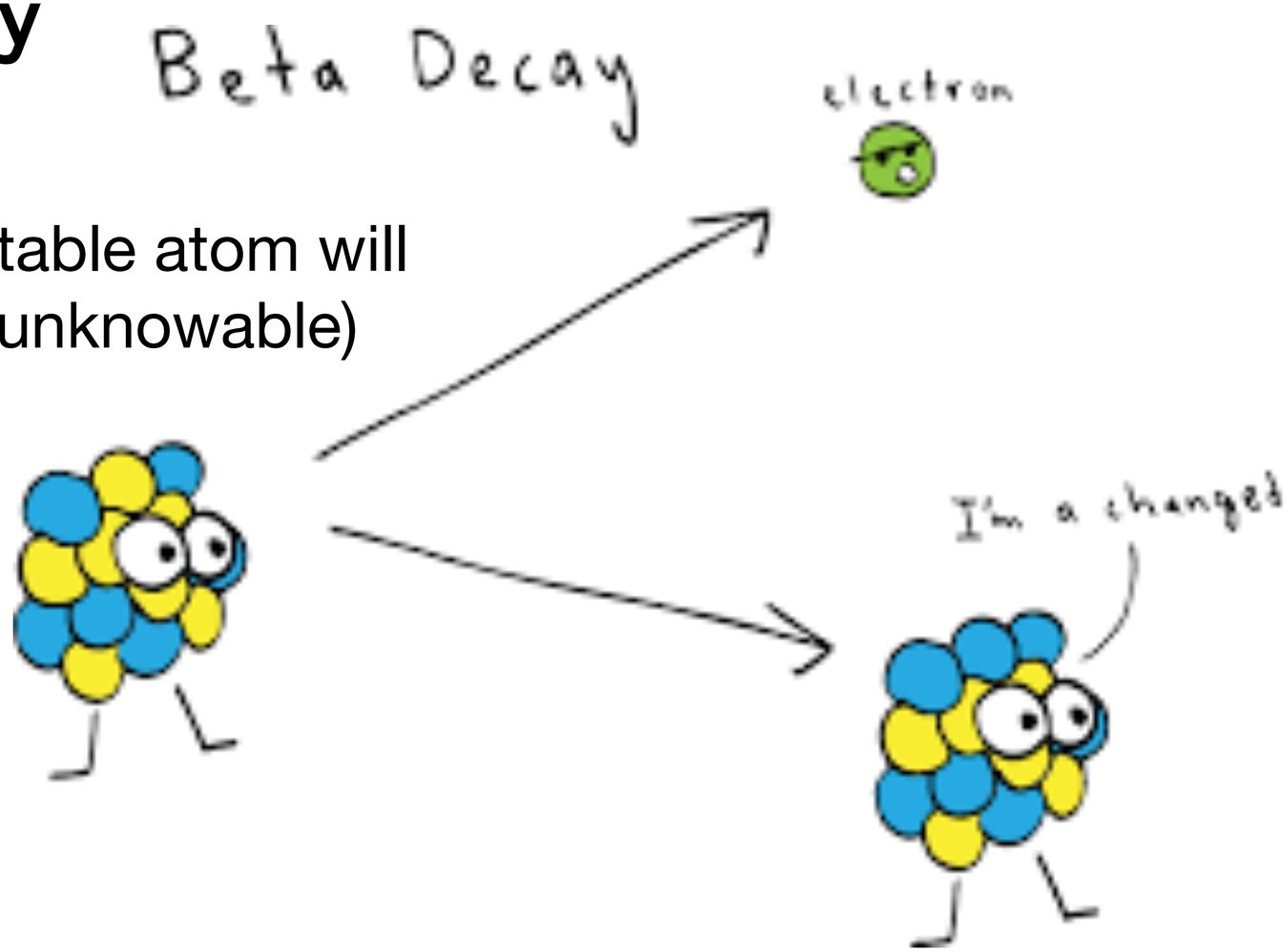

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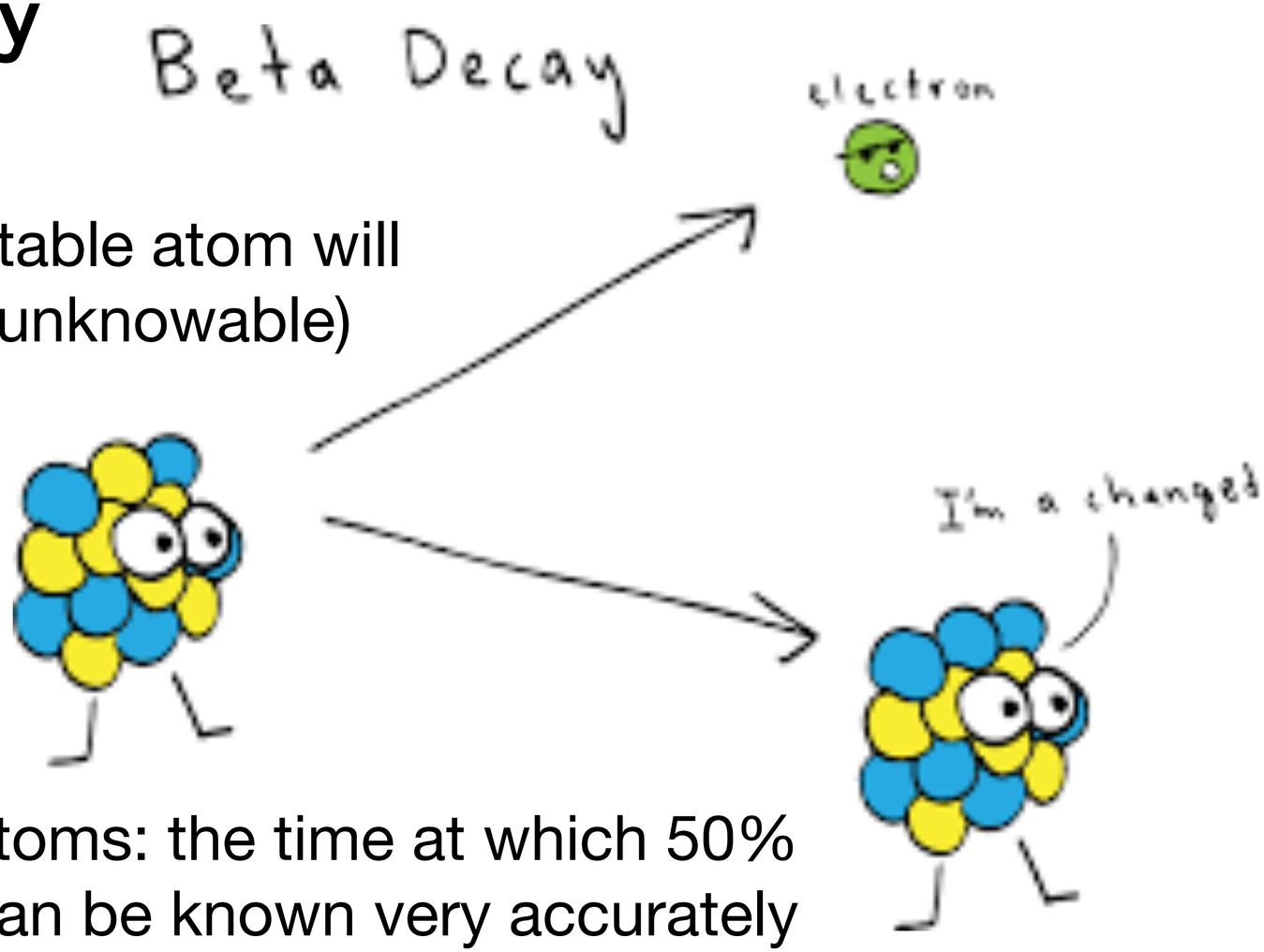

But consider bazillions of atoms: the time at which 50% have decayed can be known very accurately

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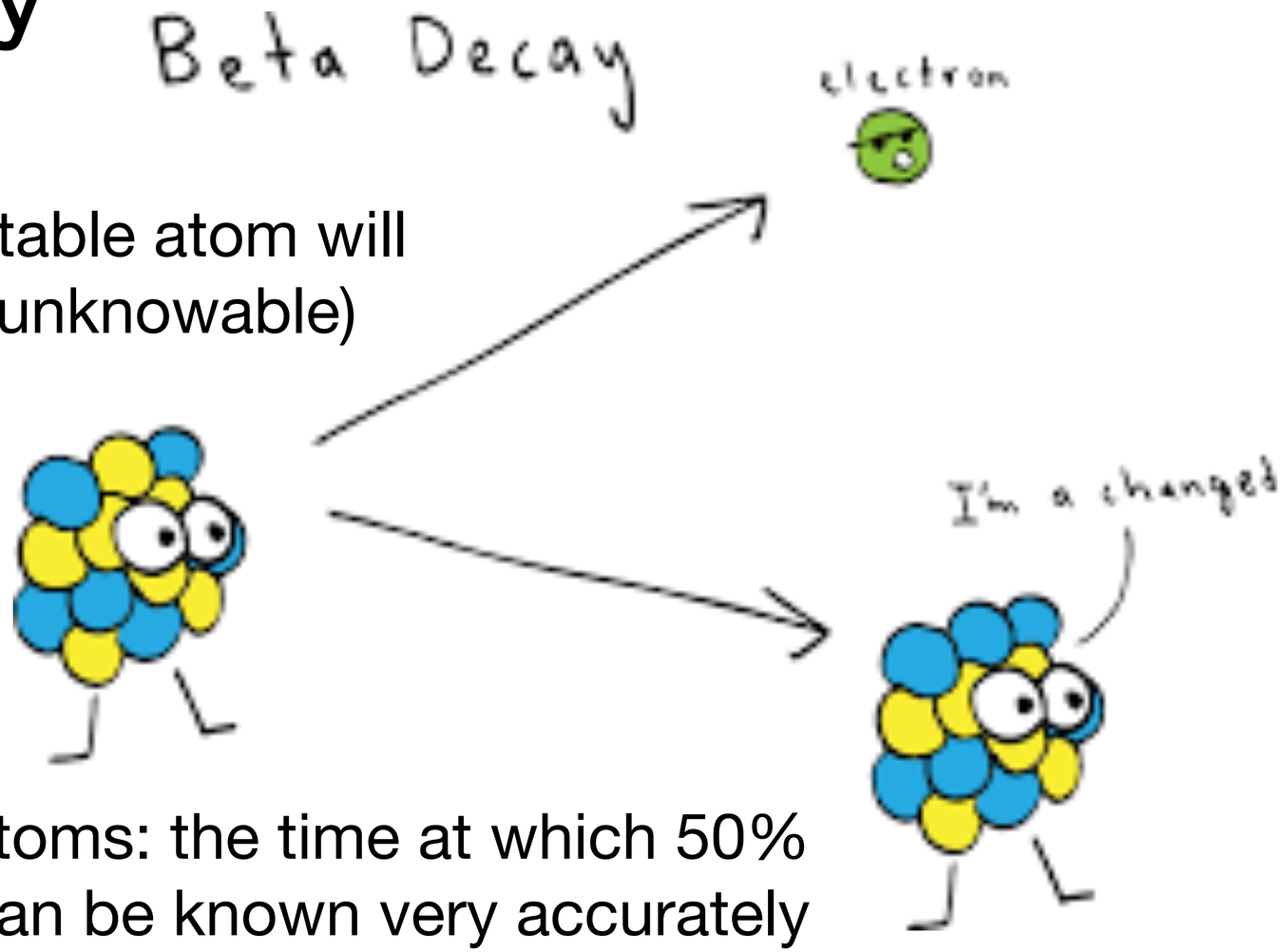

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generally (in chemistry and physics) individual events do not “matter “

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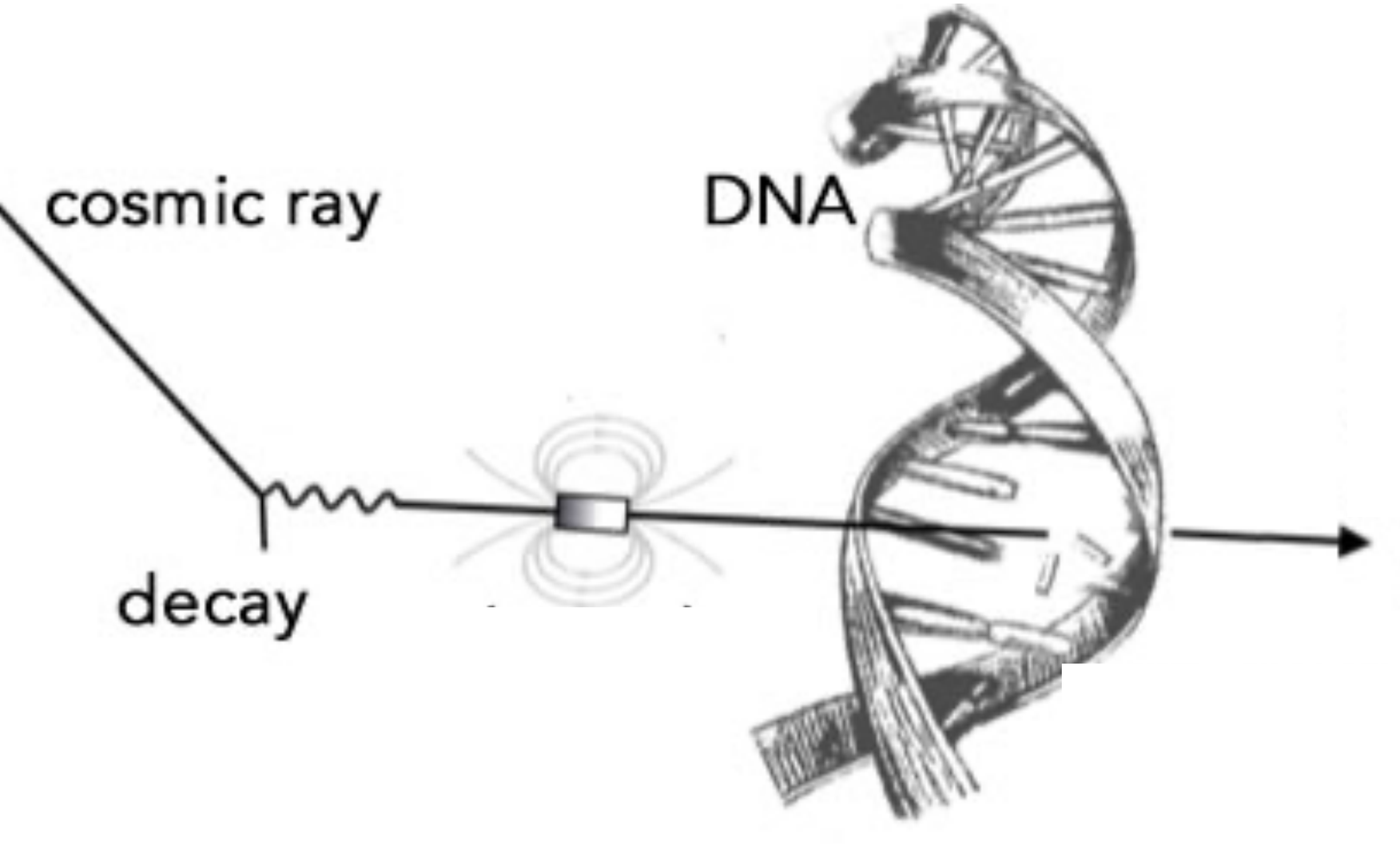

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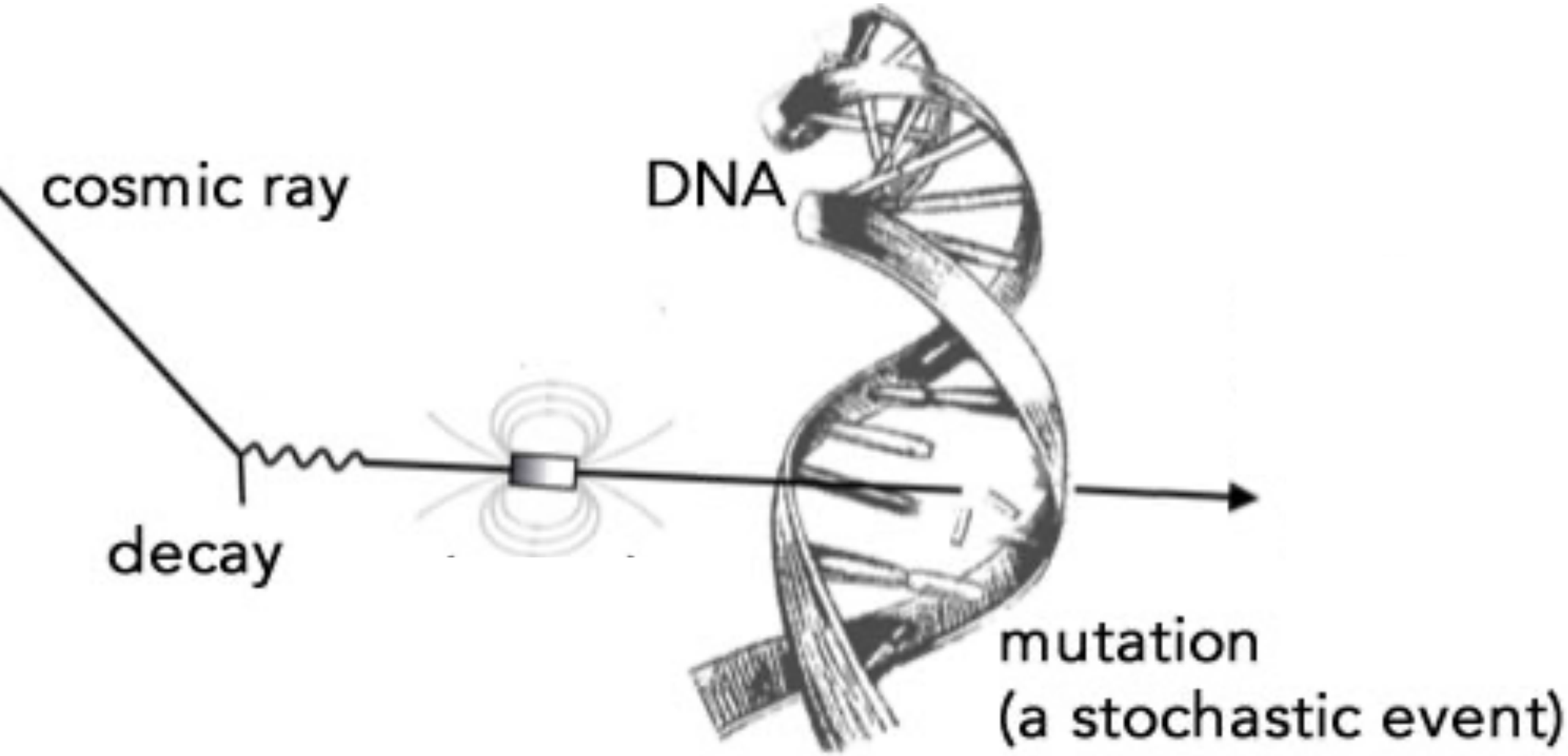

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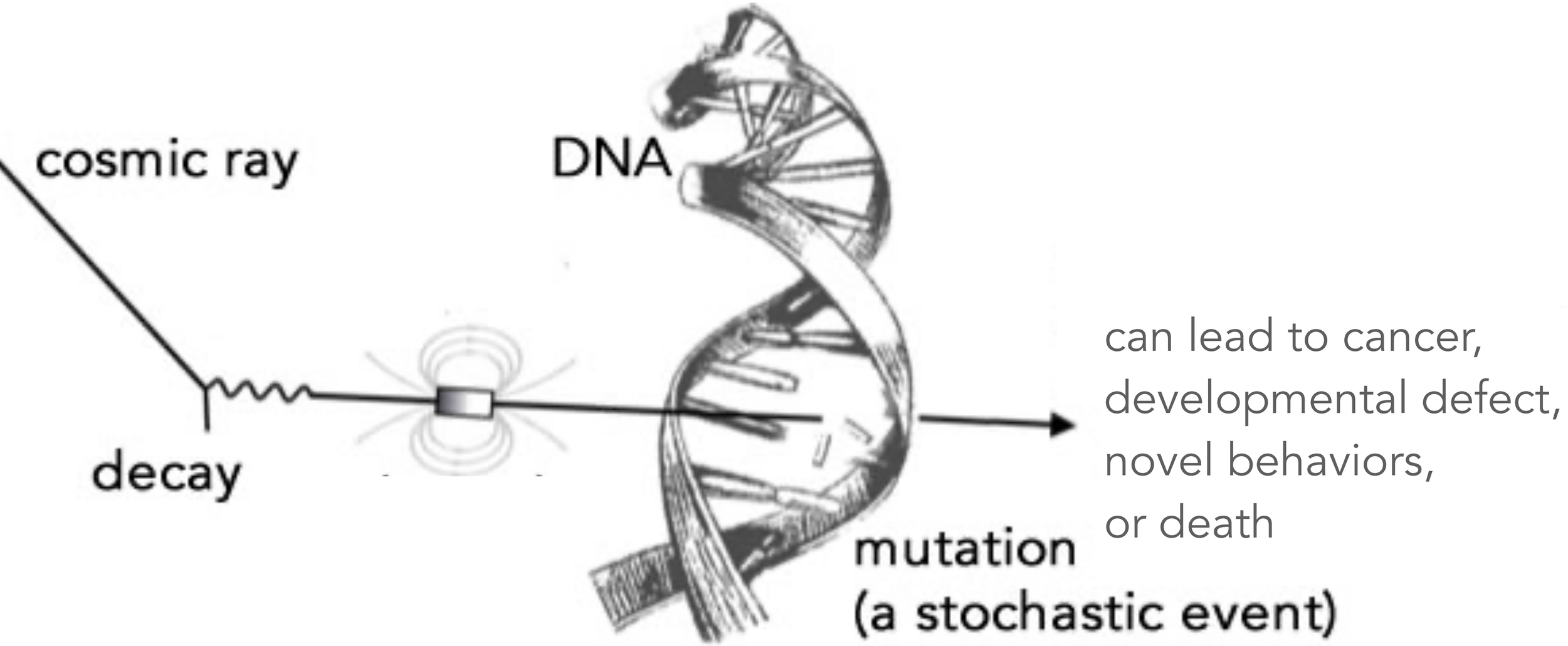
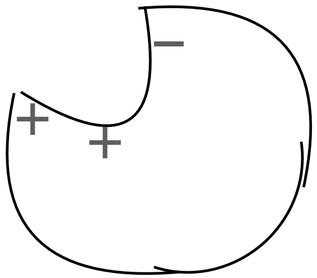


can lead to cancer,
developmental defect,
novel behaviors,
or death

beyond mutation: molecular interactions are stochastic

interactions based on surface +/– charges and molecular shape

regulator



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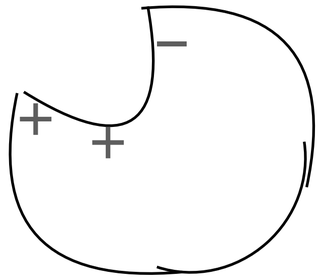

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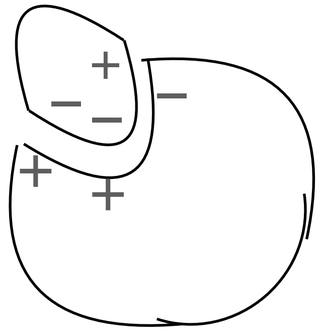

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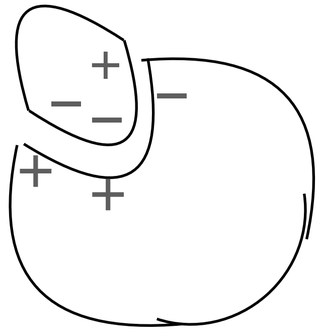

on binding, changes in shape and activity

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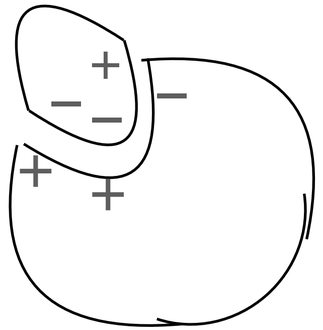

on binding, changes in shape and activity

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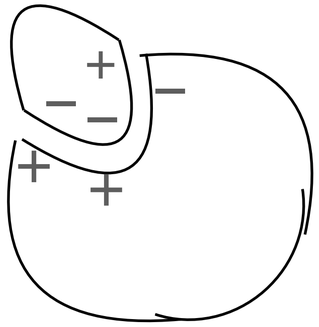
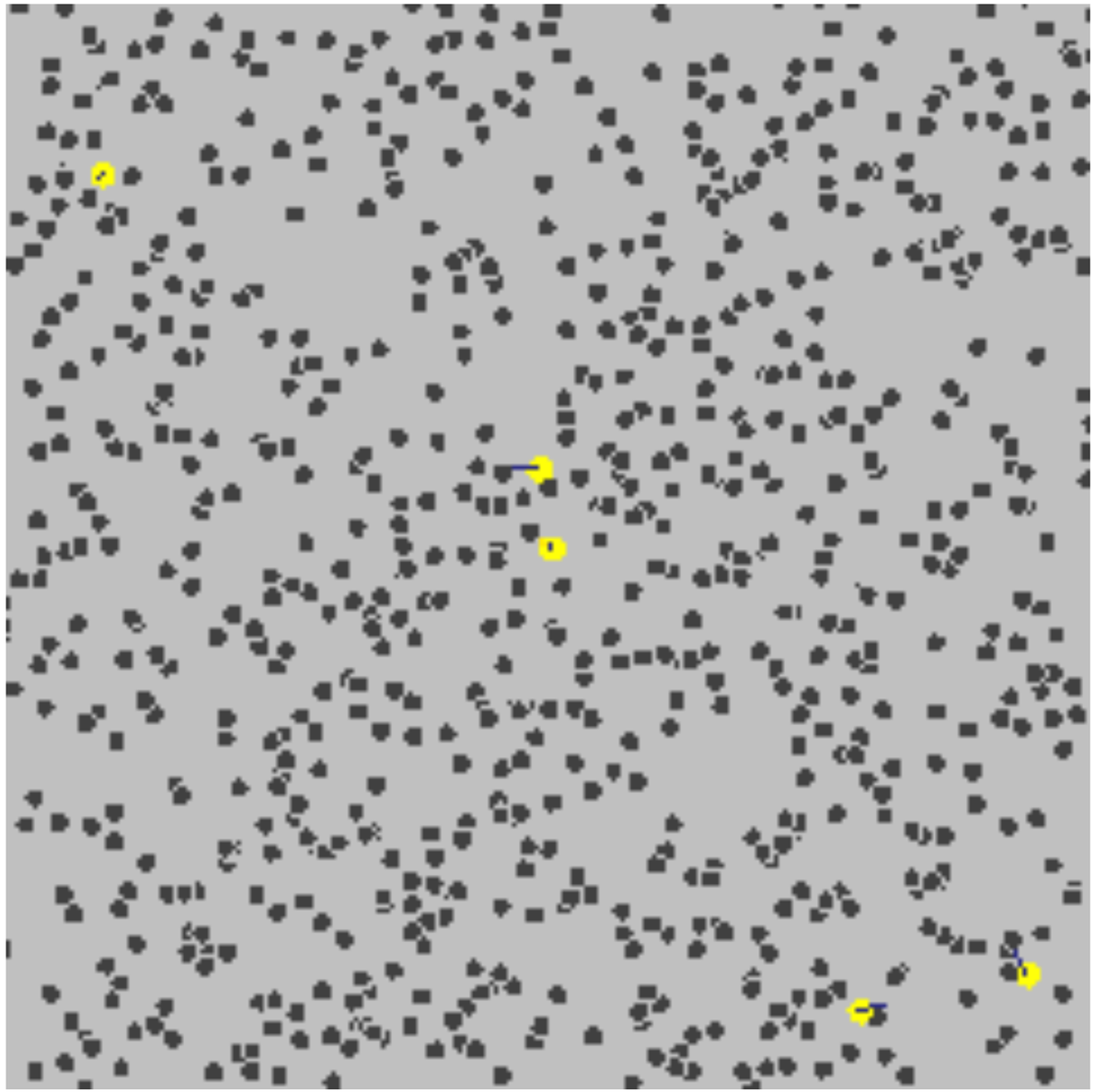
altered gene expression, etc.

the (kinetic) energy that breaks bonds is delivered through collisions with other molecules (brownian motion)





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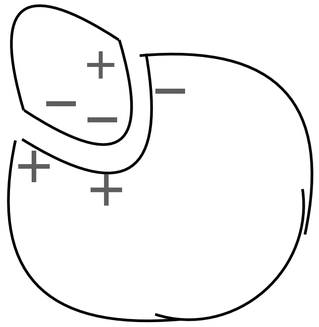

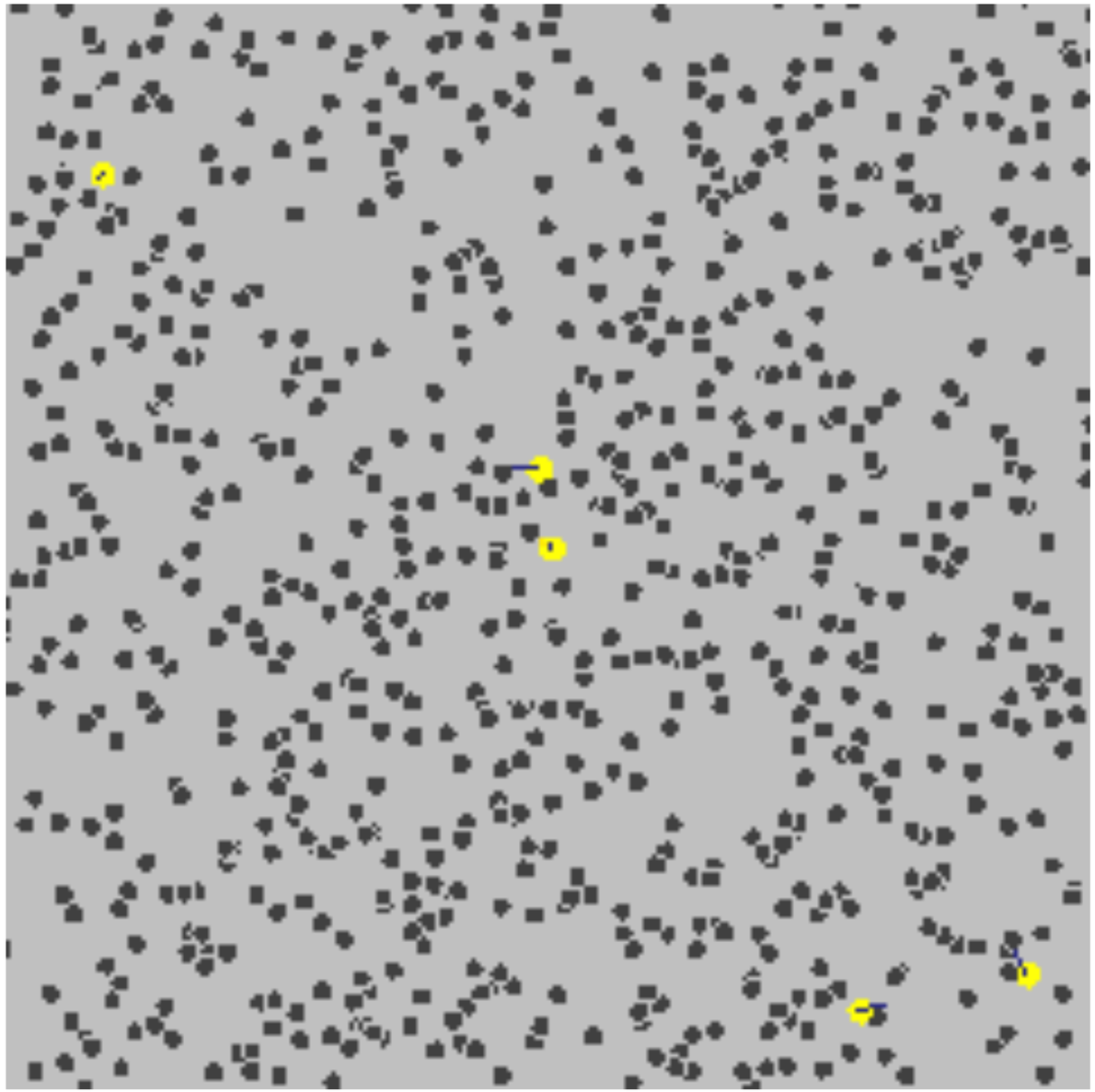

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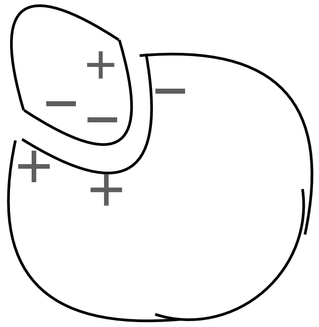

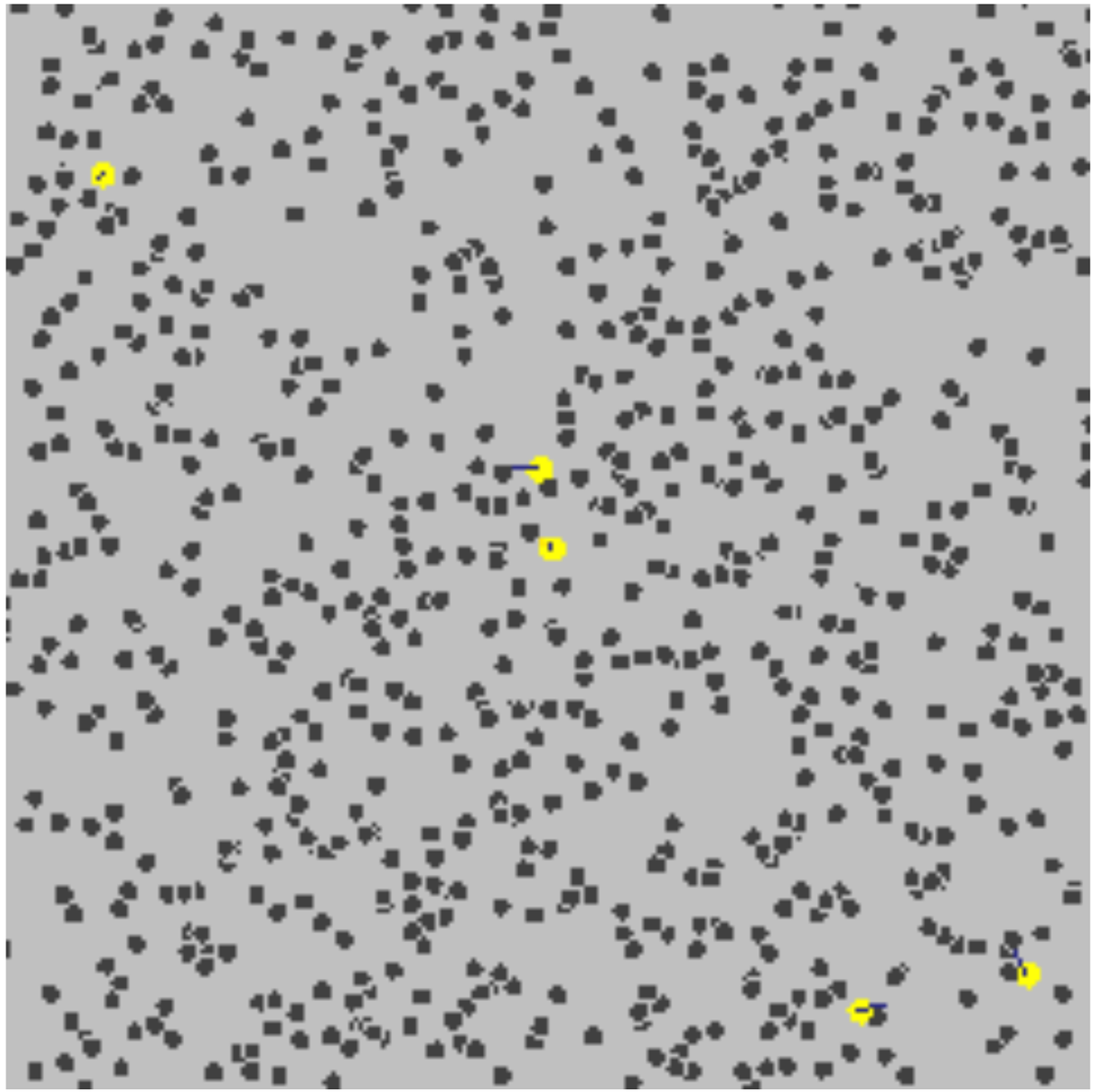

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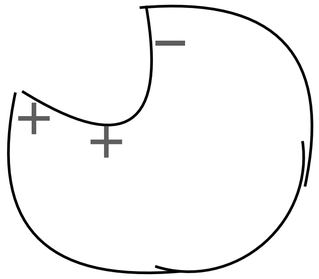

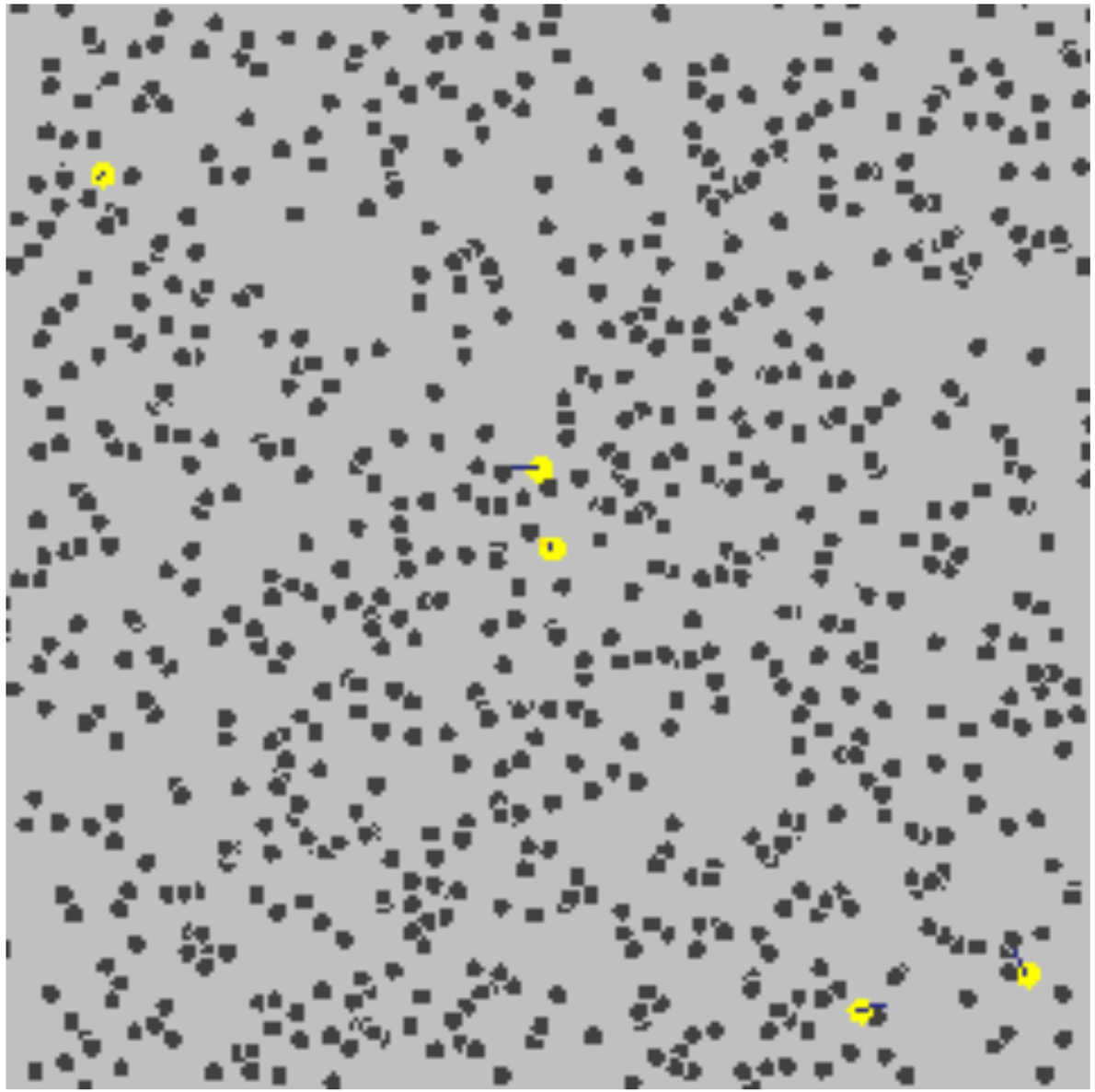

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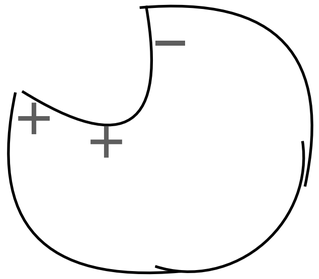
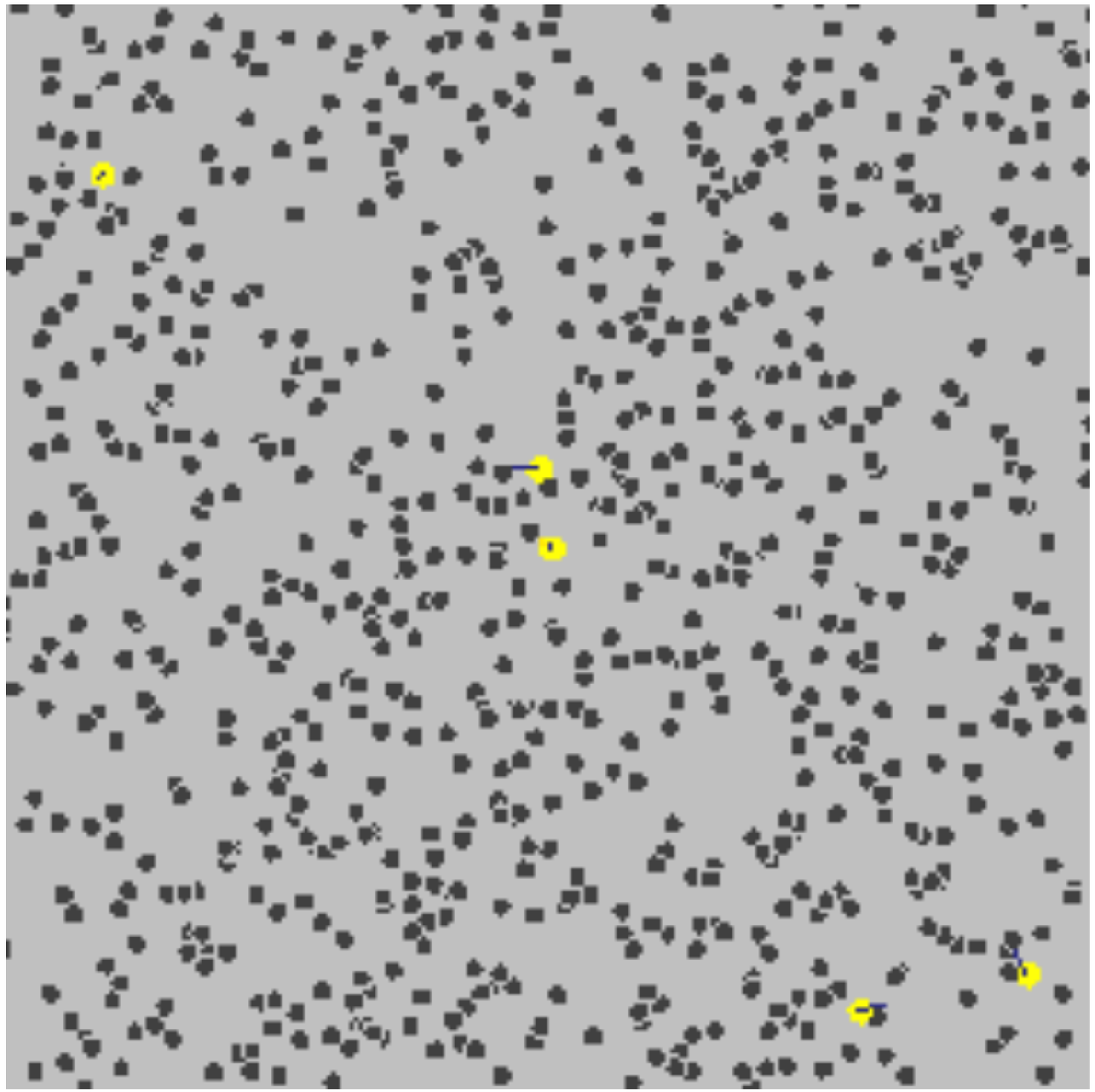


complex “half-life” (a population measurement) is based on strength of binding interaction



Stochasticity can be a difficult concept,often not taught explicity or effectively

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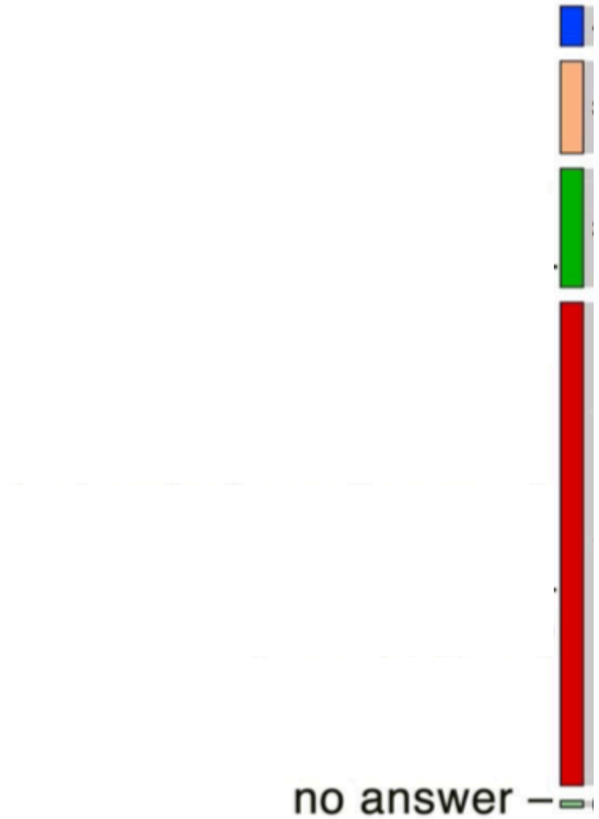

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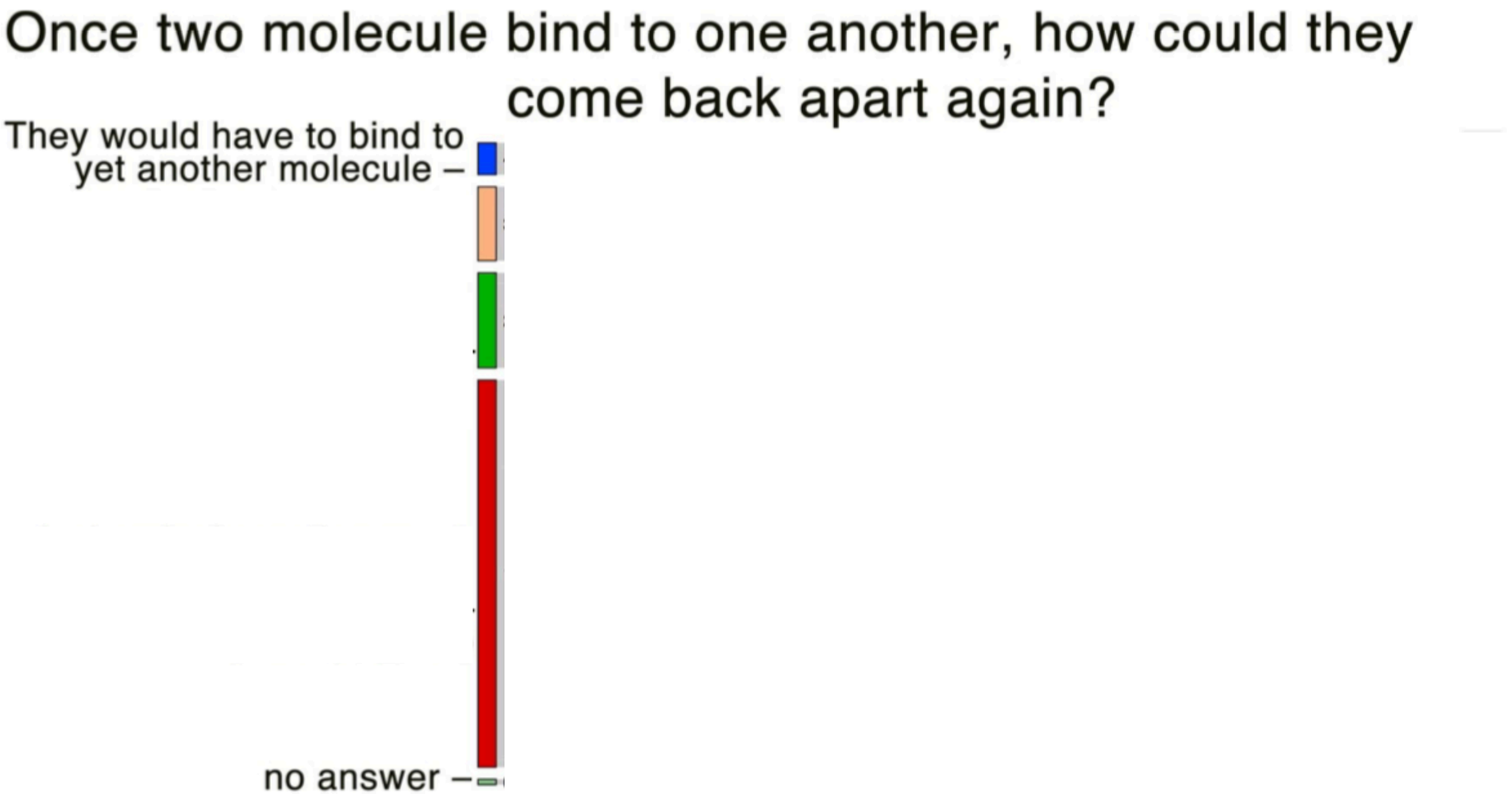

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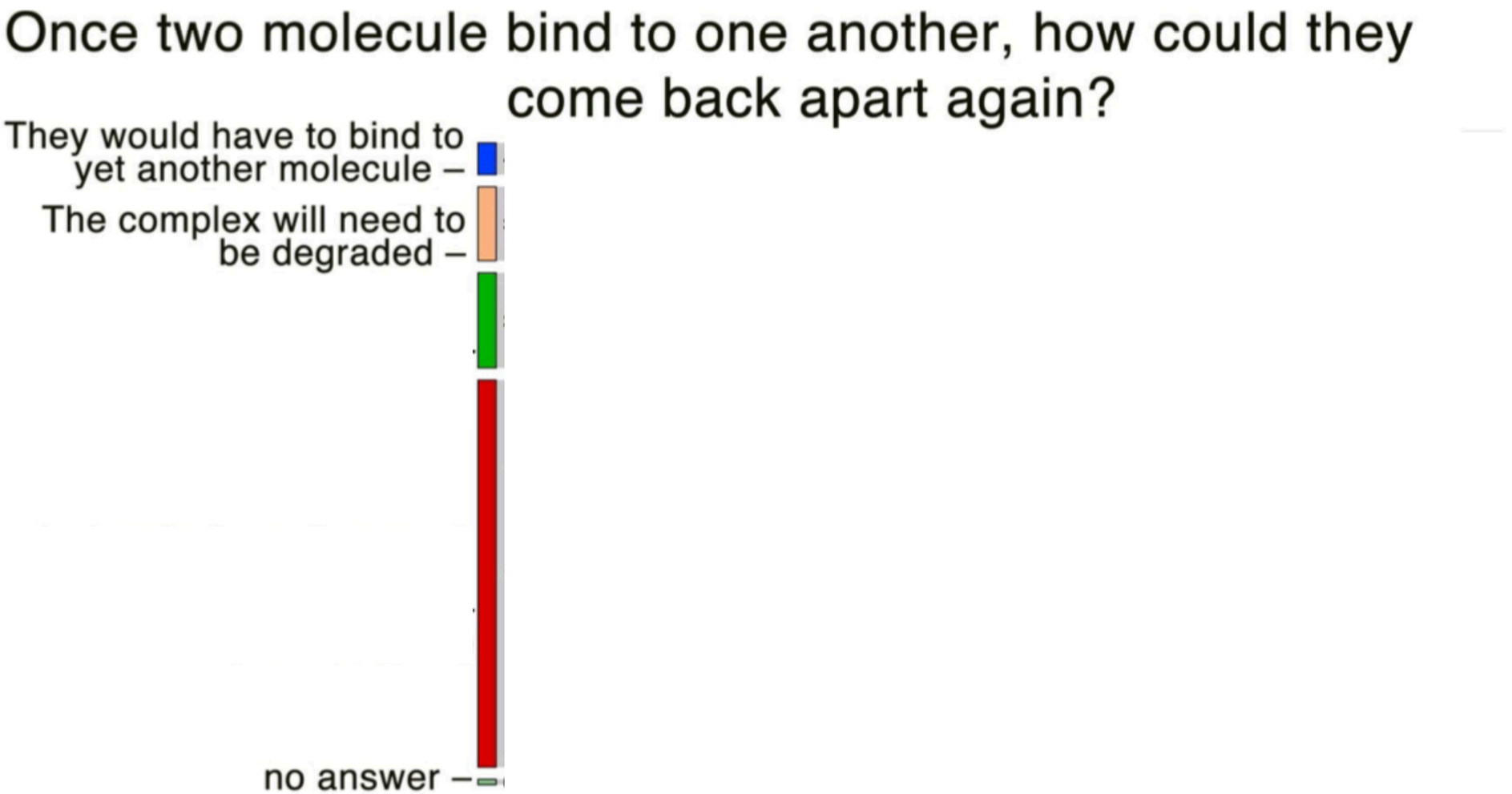

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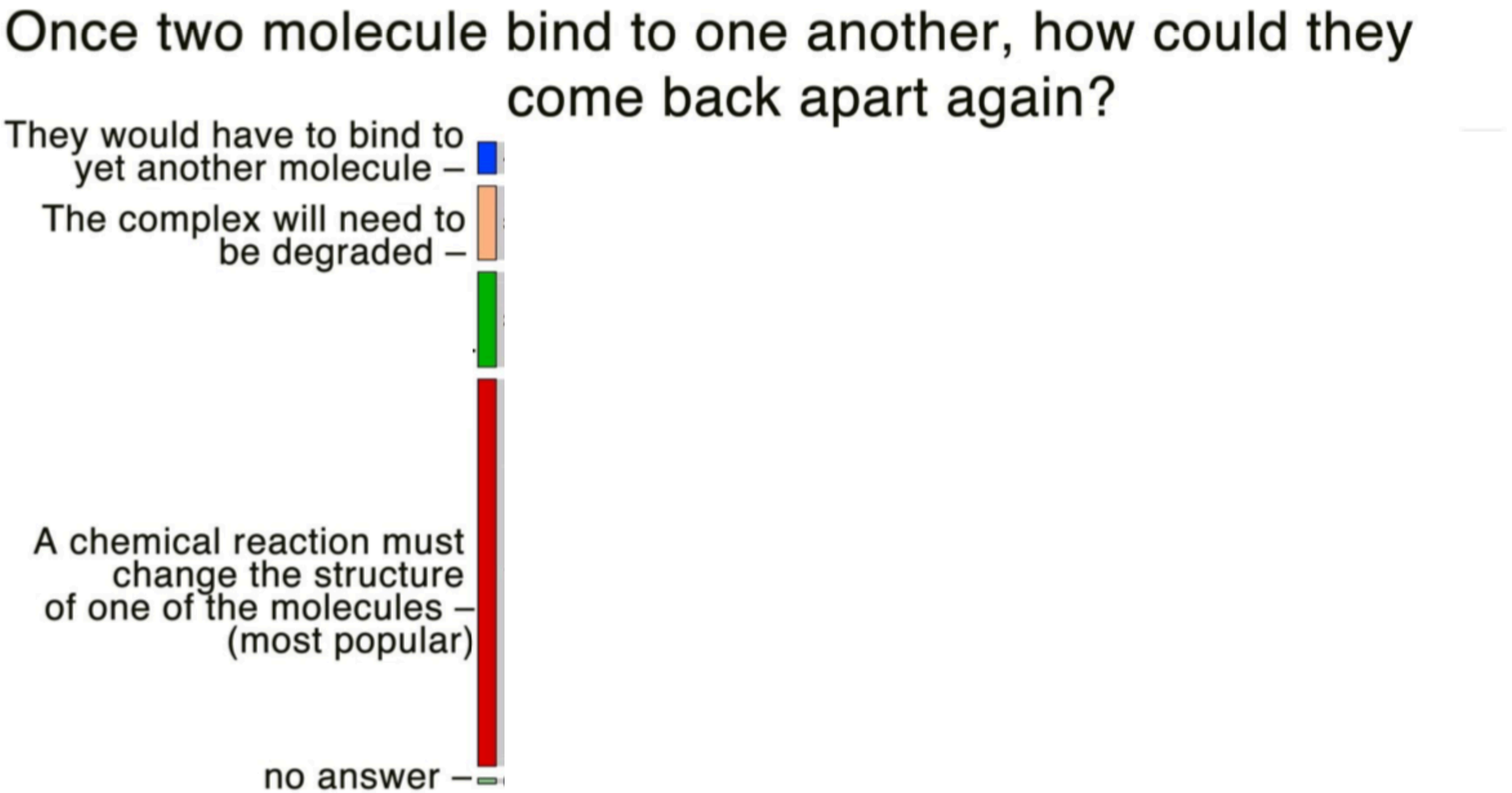

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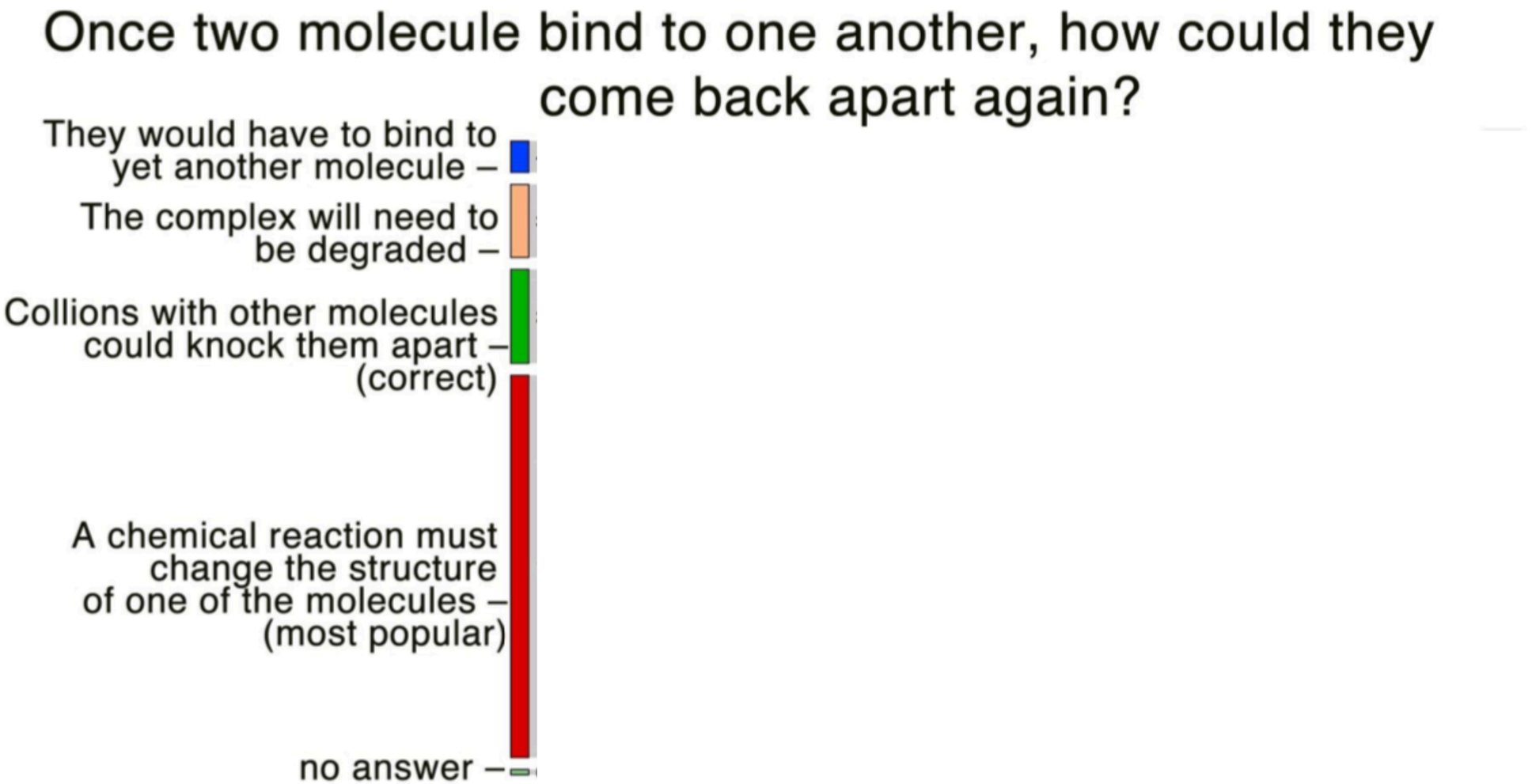

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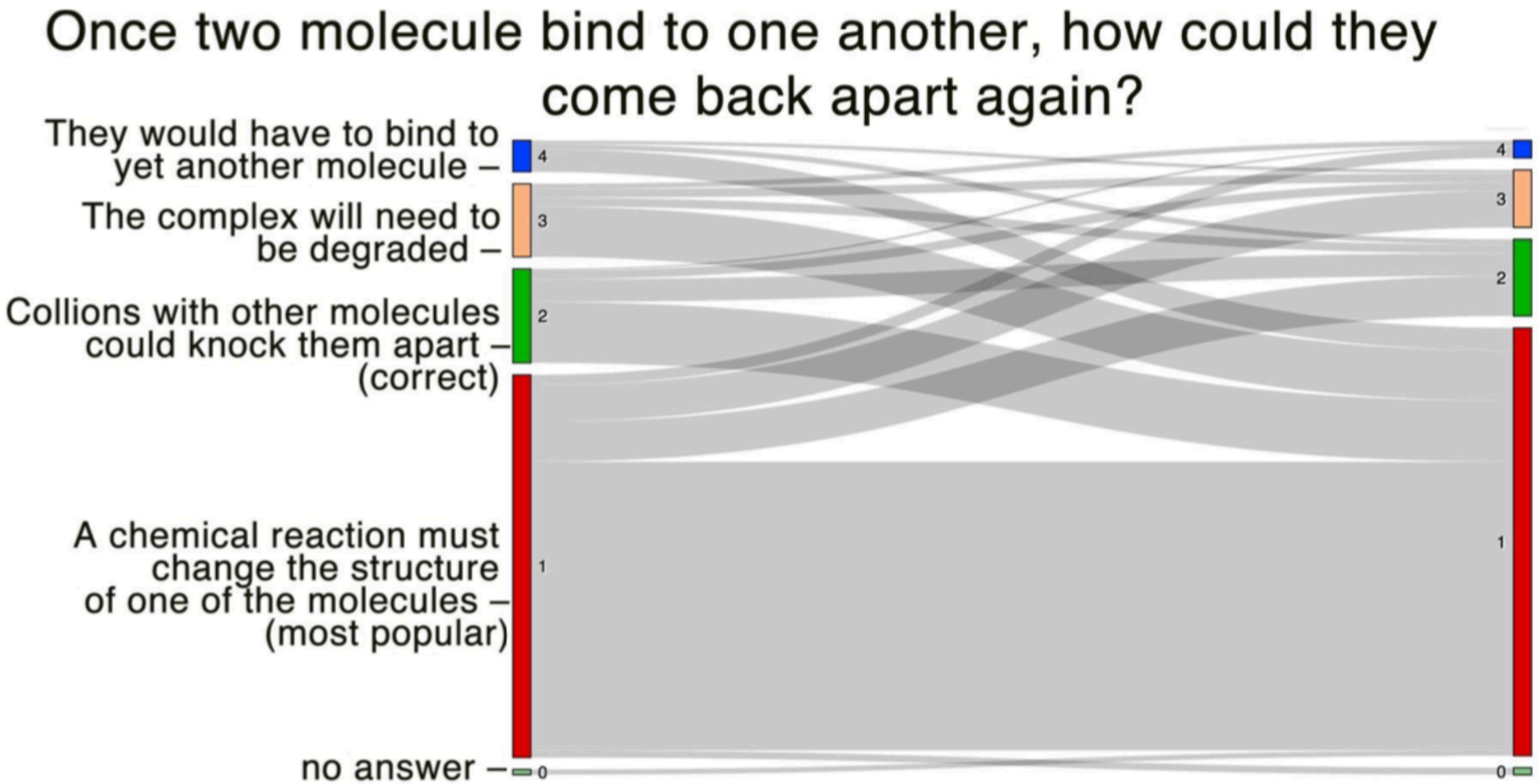

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stochastic gene expression in bacteria: lac operon

(a flash from the past for Larry)

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(a flash from the past for Larry)

- lactose (mammalian milk sugar) is energetically expensive for bacteria to use
  - requires synthesis of lactose-specific enzymes
- a bacterium may never encounter lactose in their environment
- what to do?

How does one sense the presence of lactose?

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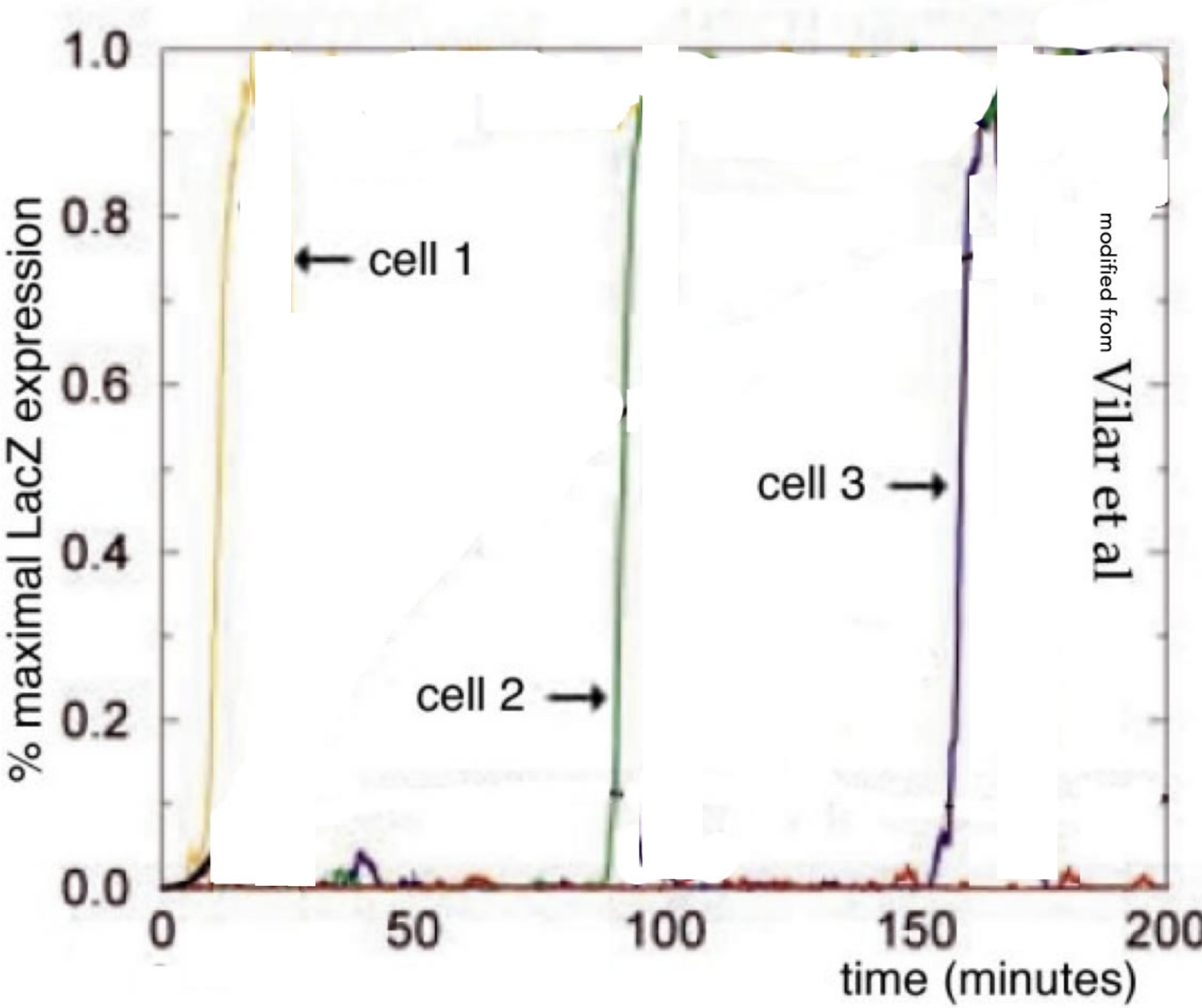

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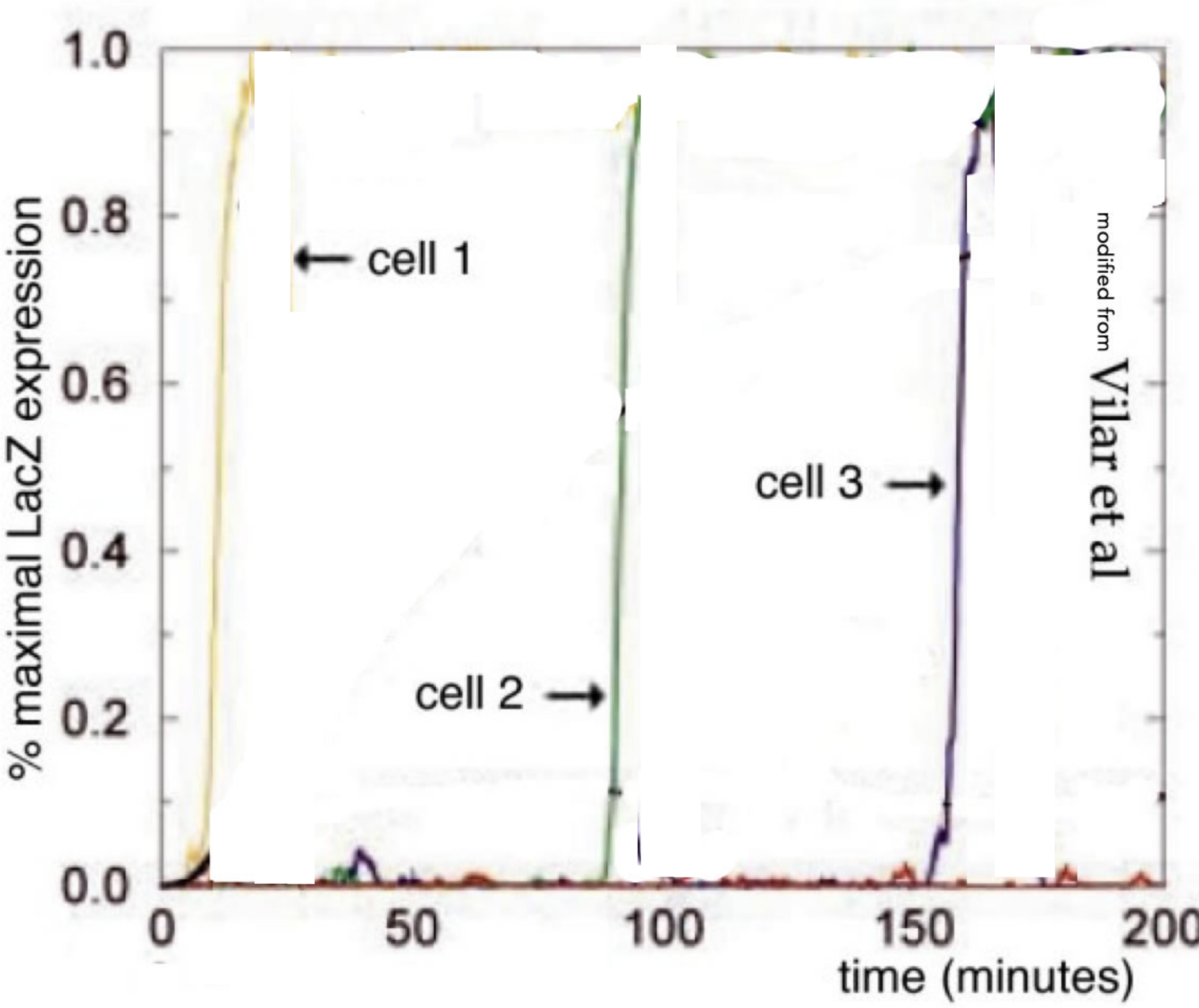

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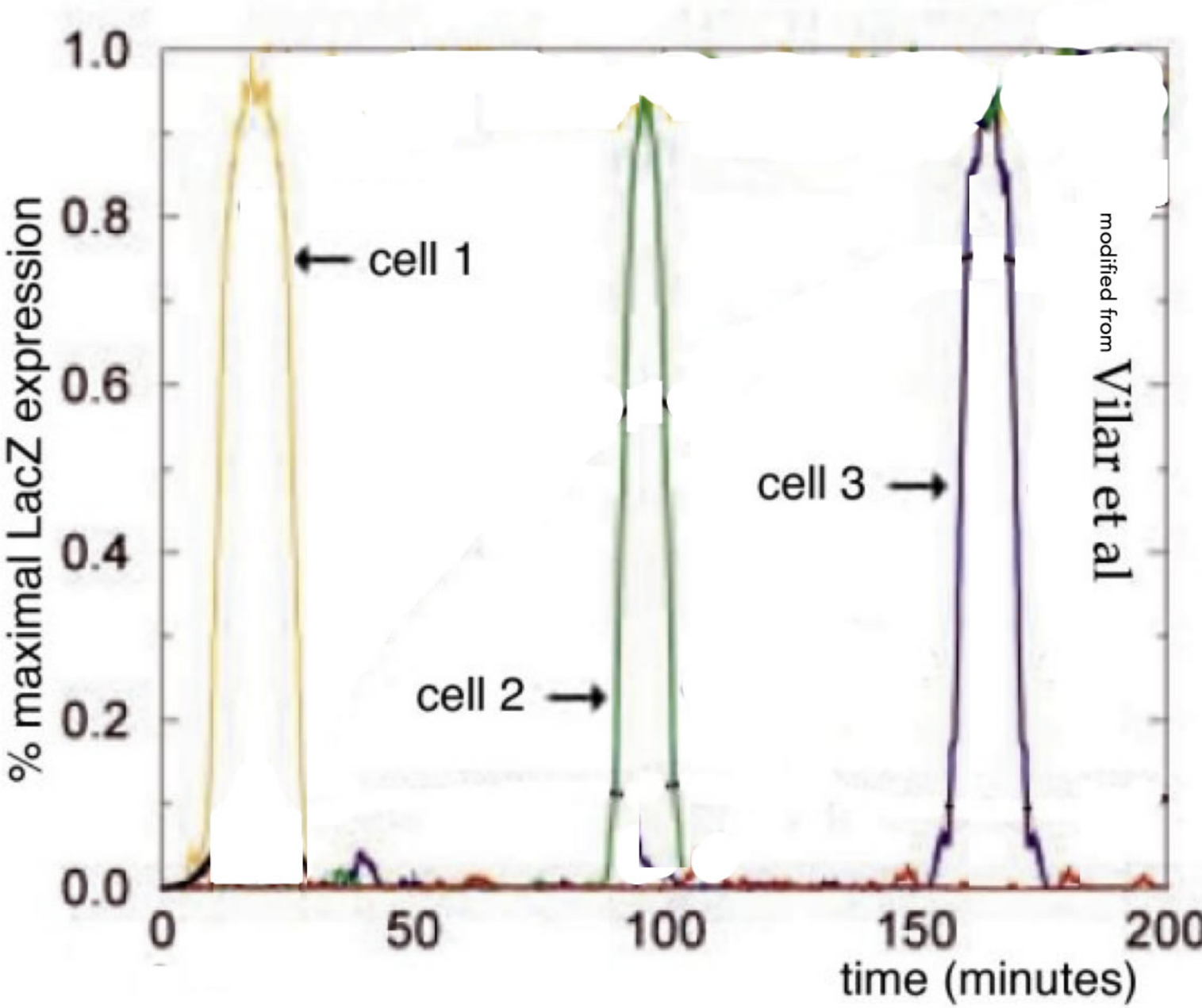

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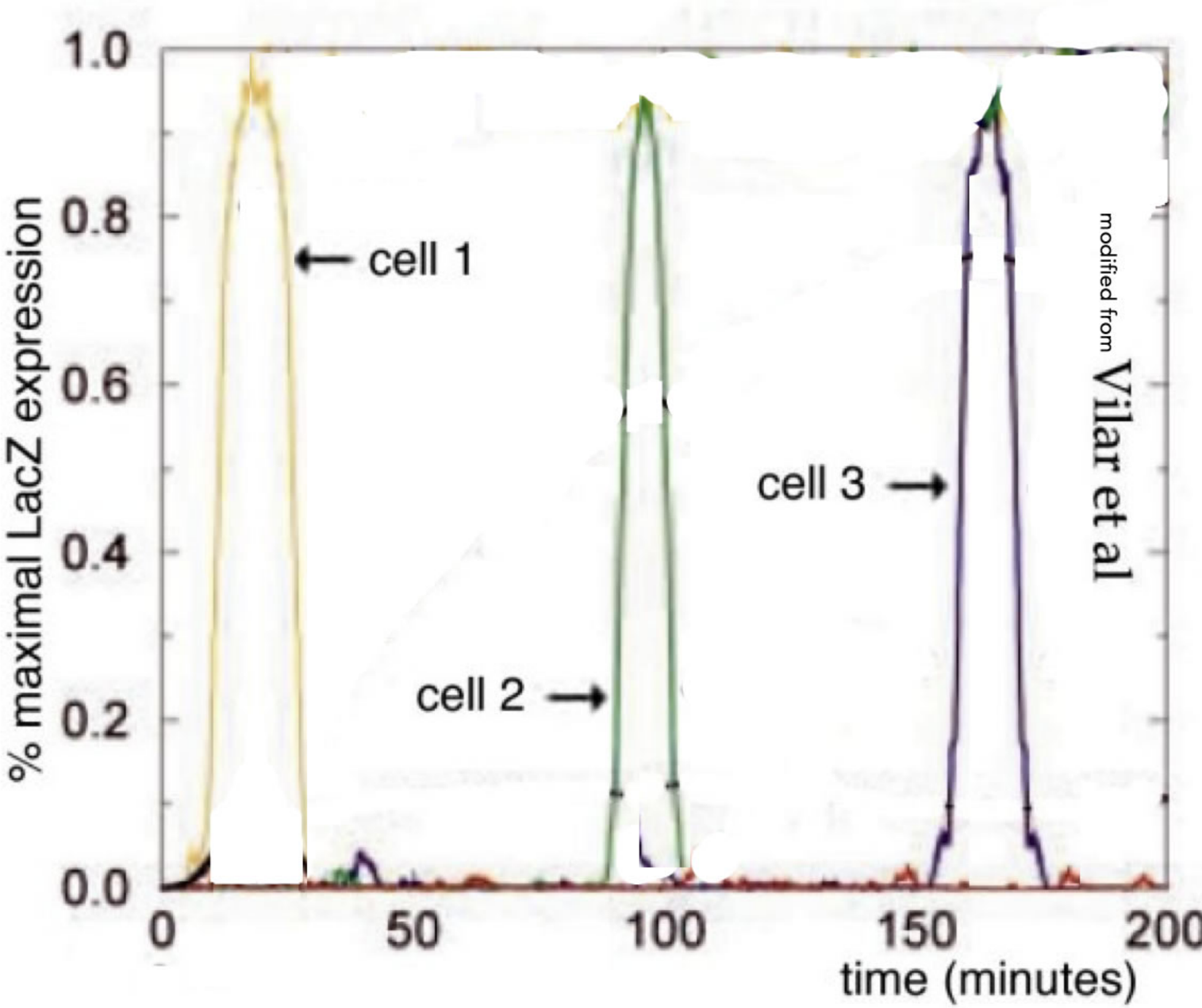
no need to express lac sensing system all the time (expensive)



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*ENZYME INDUCTION AS AN ALL-OR-NONE PHENOMENON**

By Aaron Novick and Milton Weiner 1957

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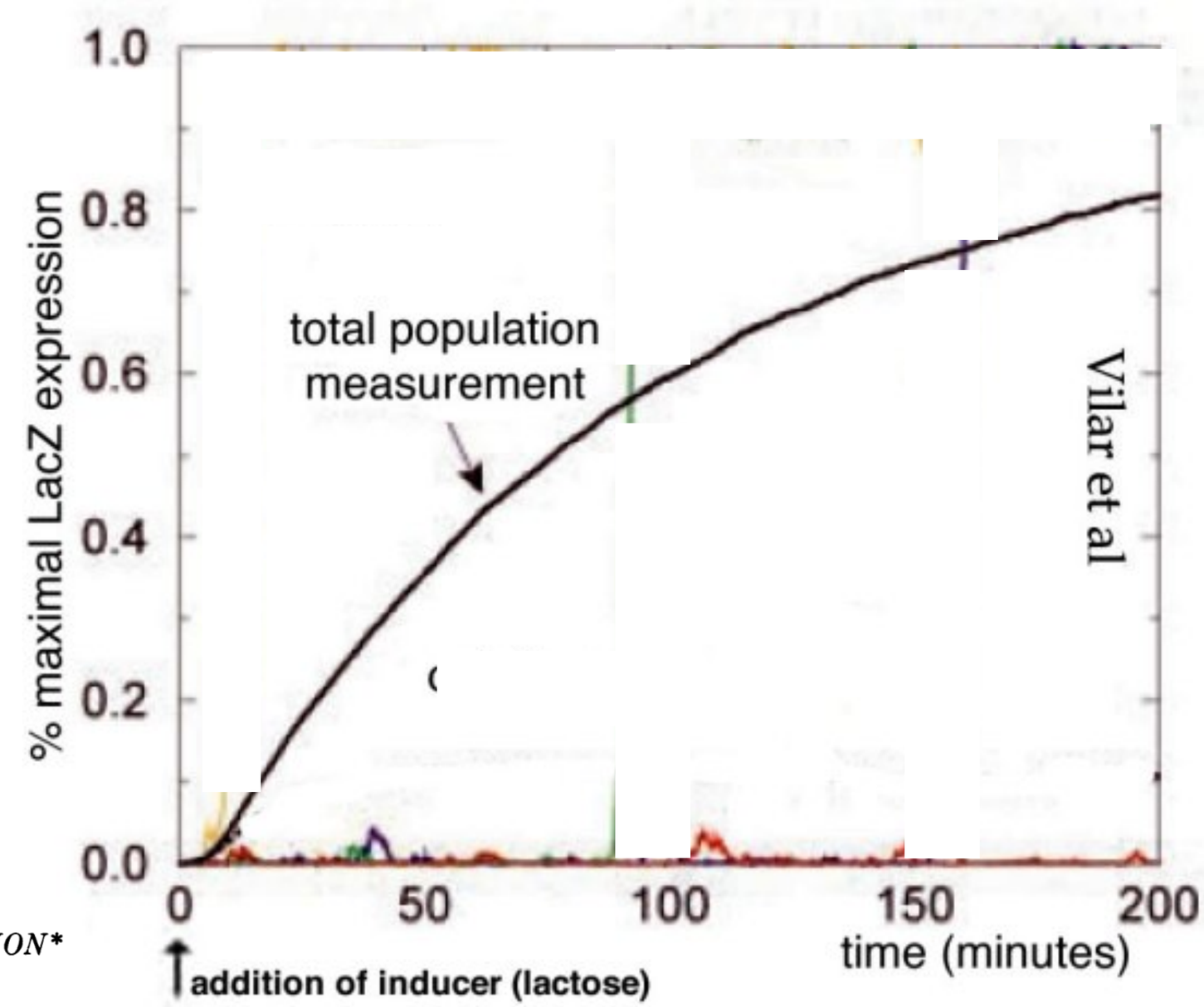

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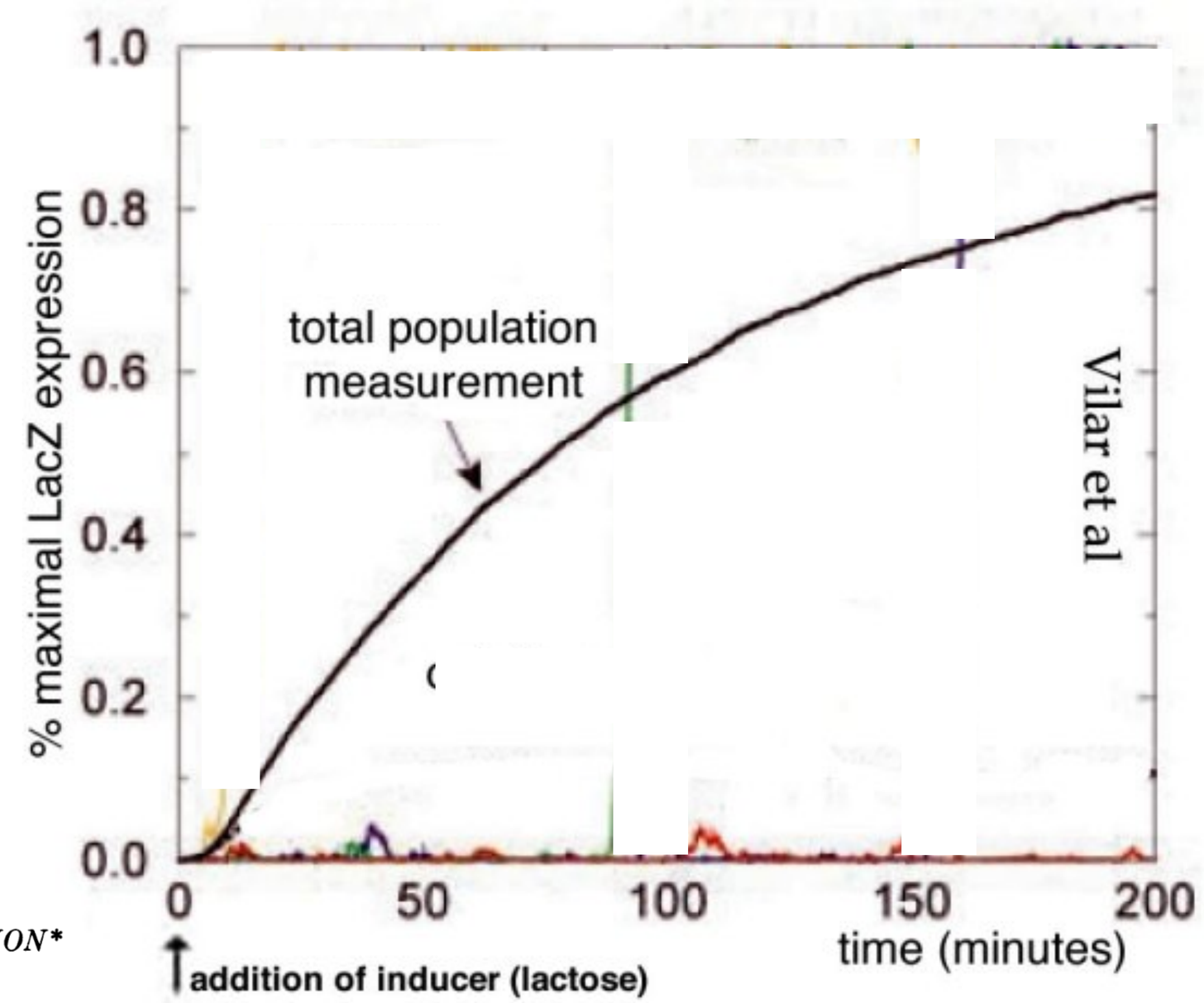

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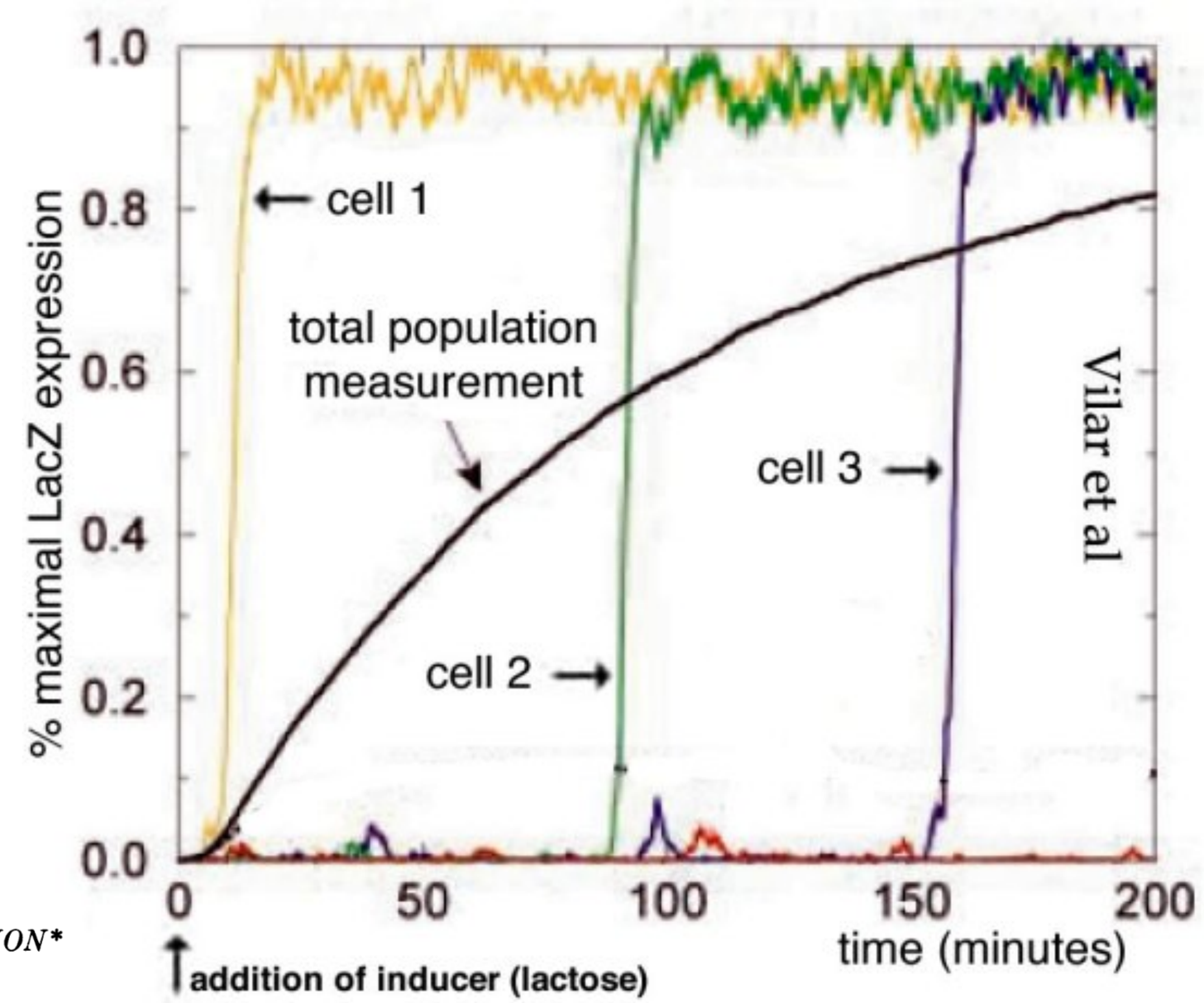

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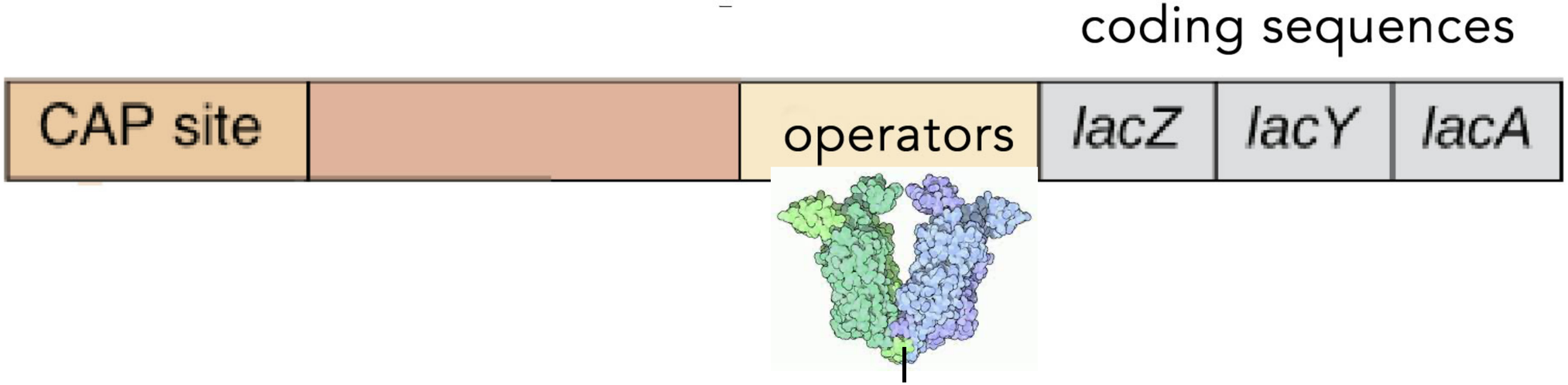


lac Repressor (aways present)

~10 copies / cell

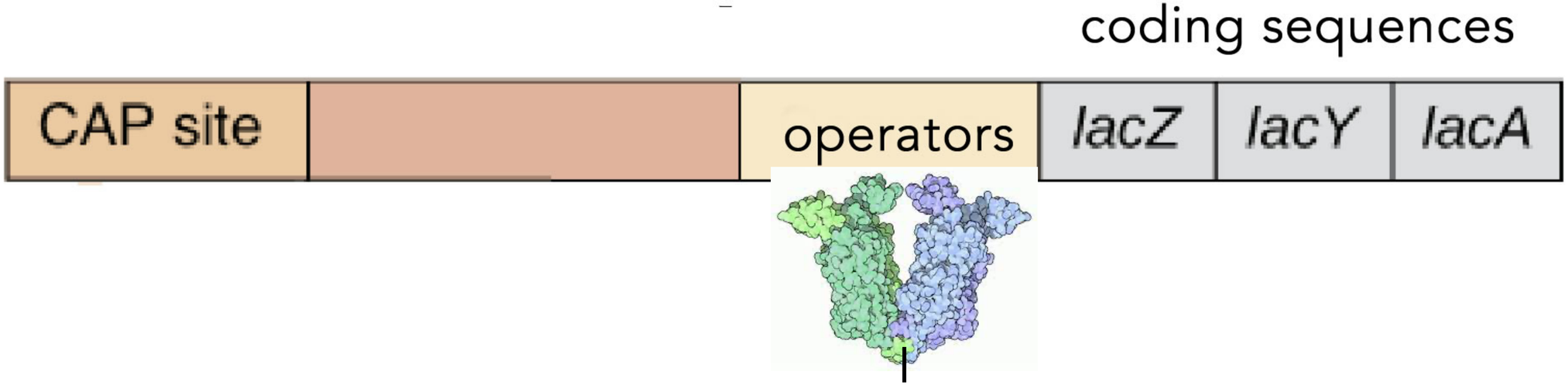
(bopping on an off)

* original image from Khan academy, worth watching: Sal Khan's 2023 talk on AI powered learning

How does the cell do it?

when other (more easily digestible) energy sources present

genes are off



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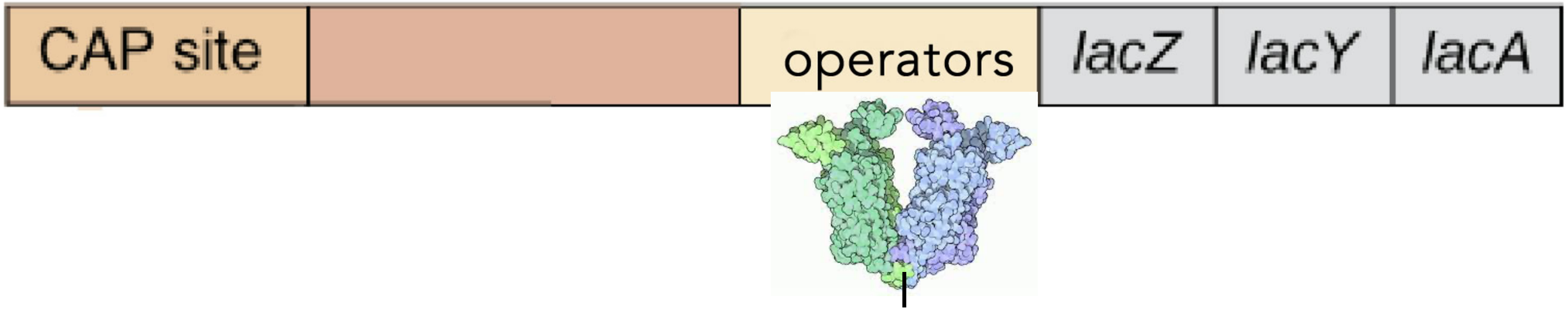

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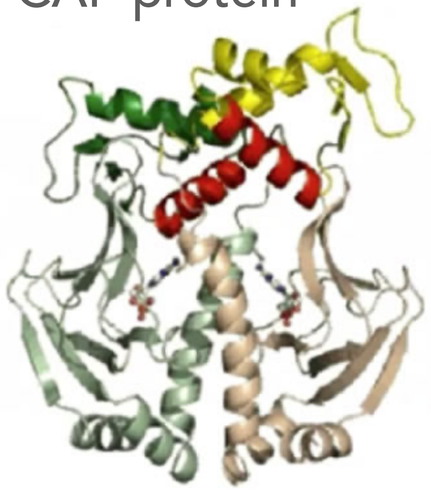
CAP protein



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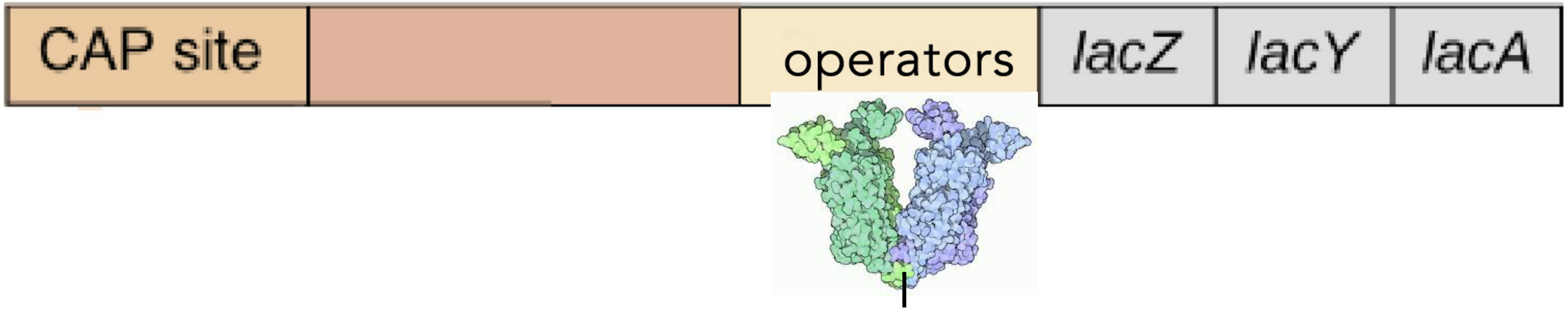

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(activator not active)

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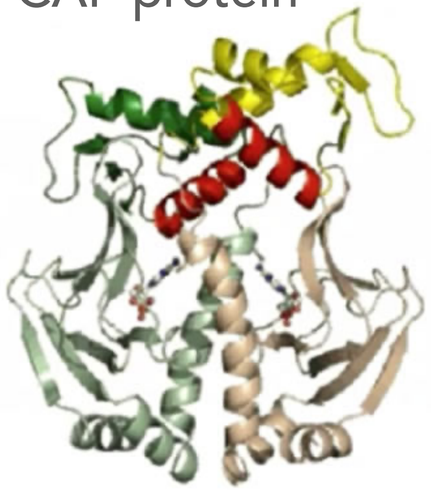

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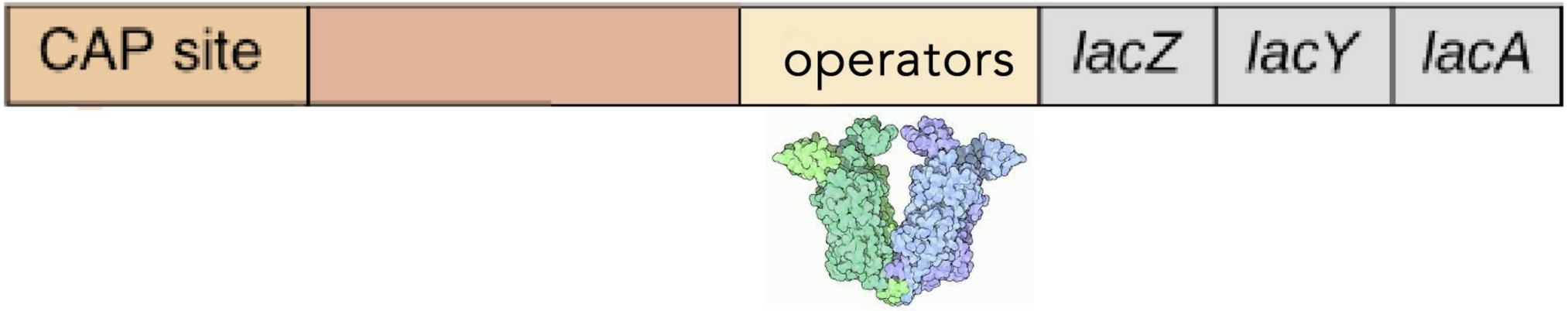
In a starving cell



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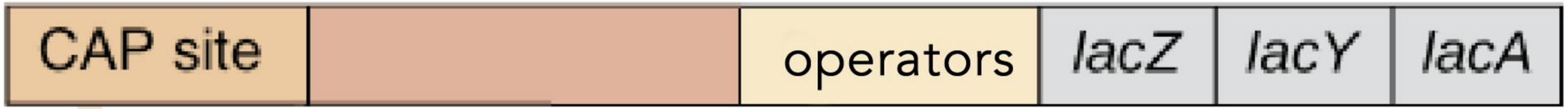

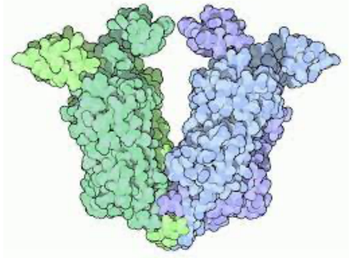

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(bopping on an off)

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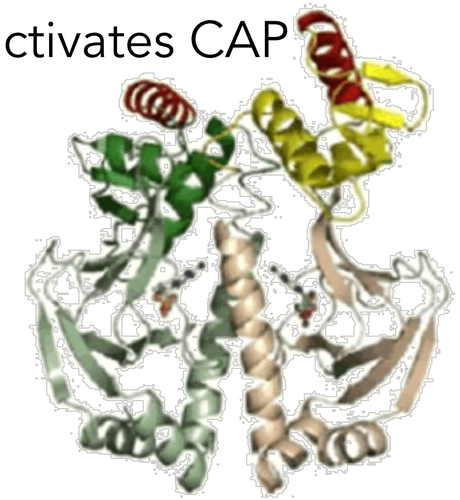

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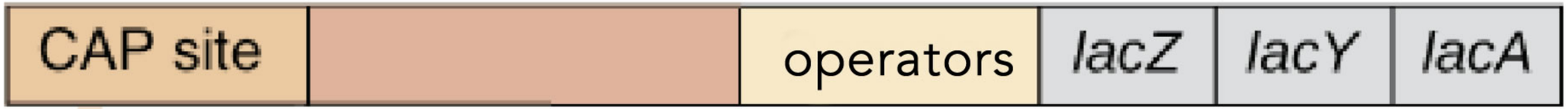

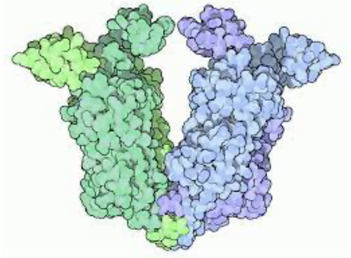

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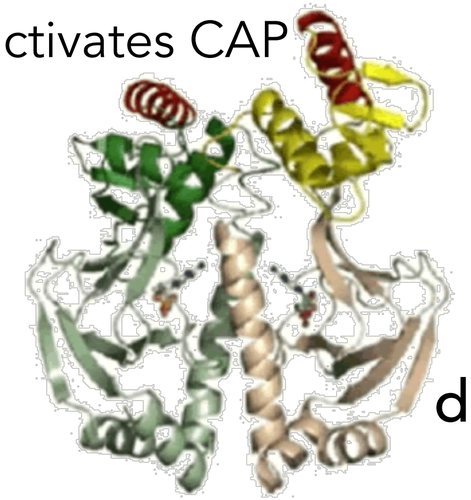

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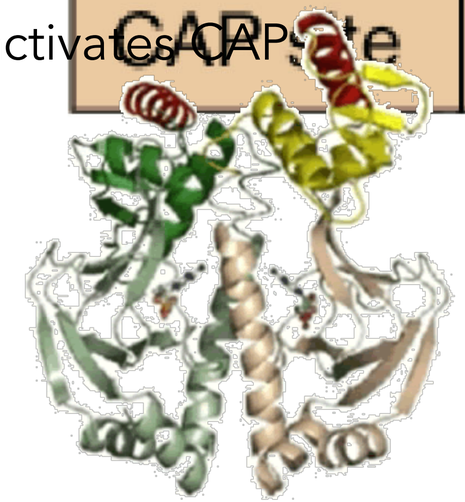

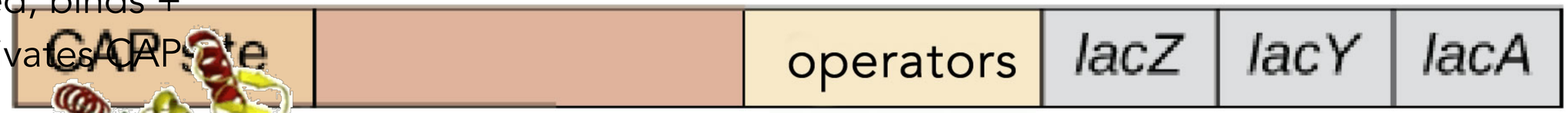

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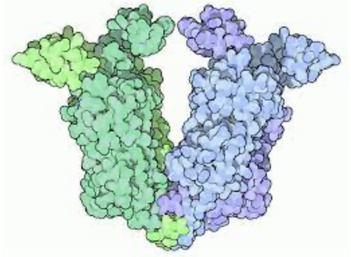

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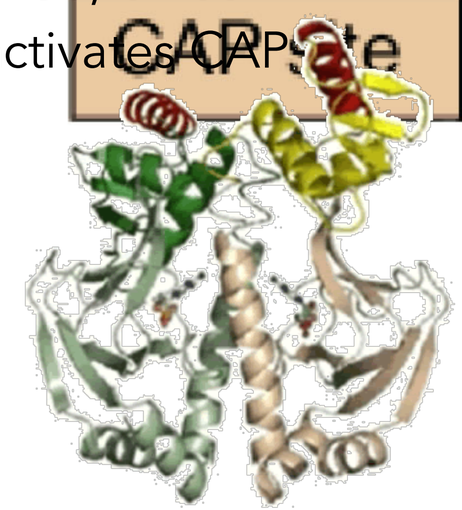

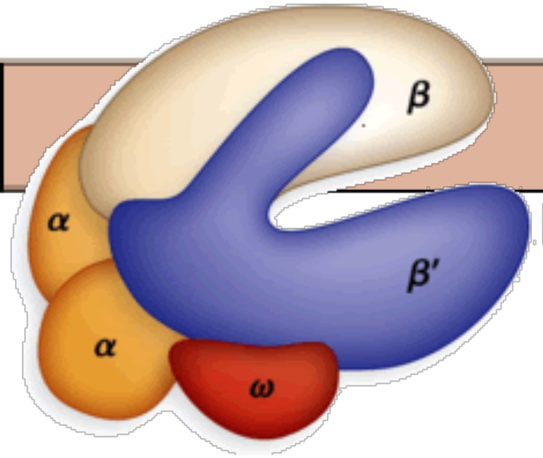

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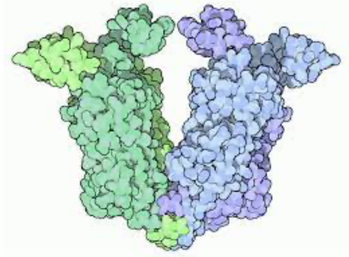

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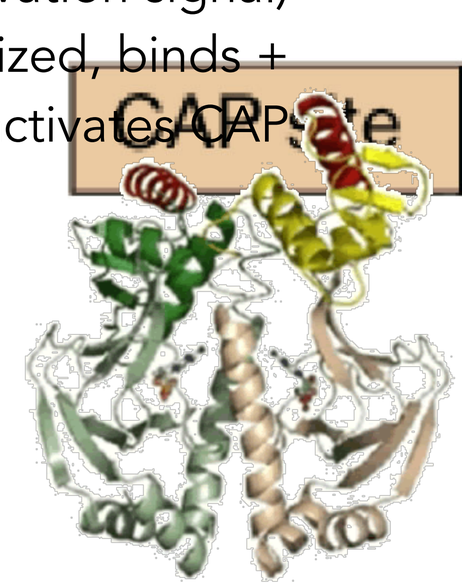

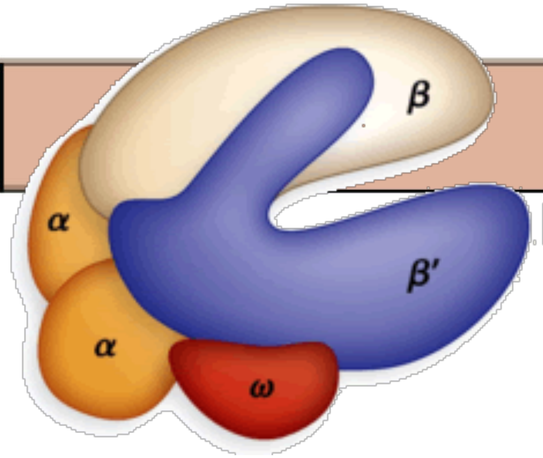

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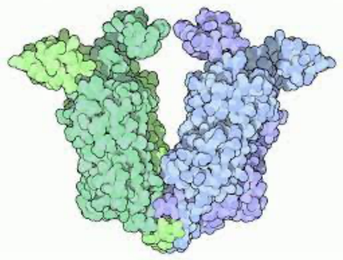

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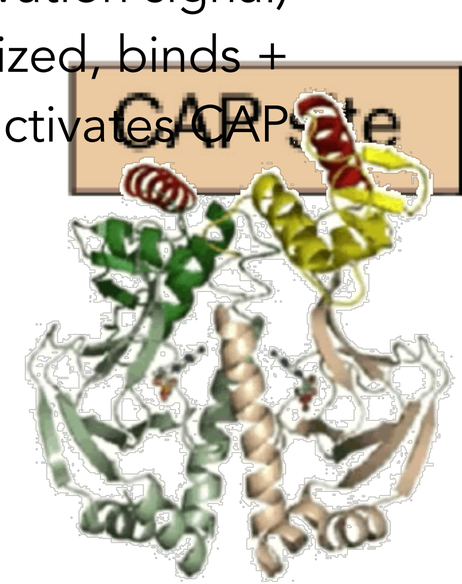

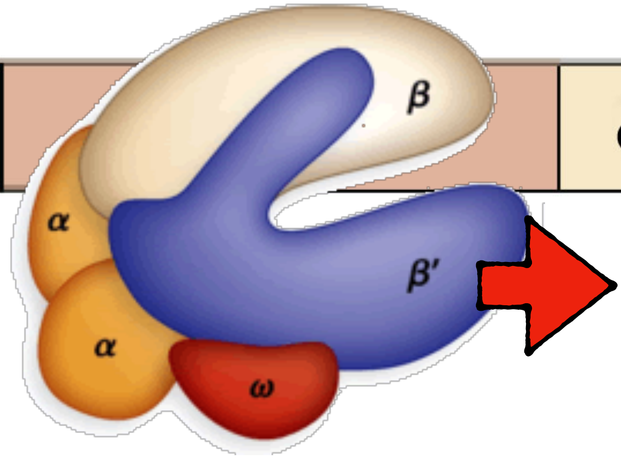

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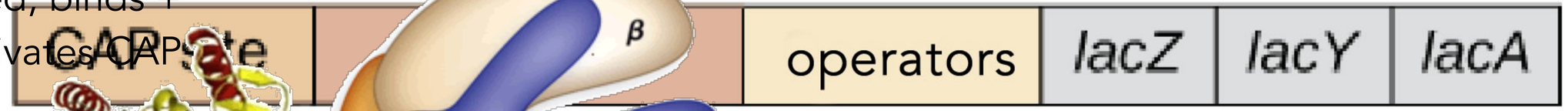

polymerase moves, gene “expressed”

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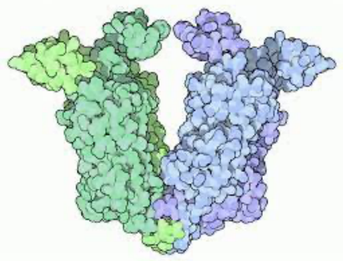

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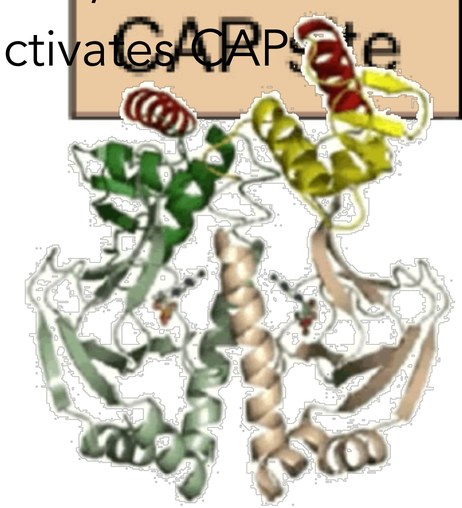

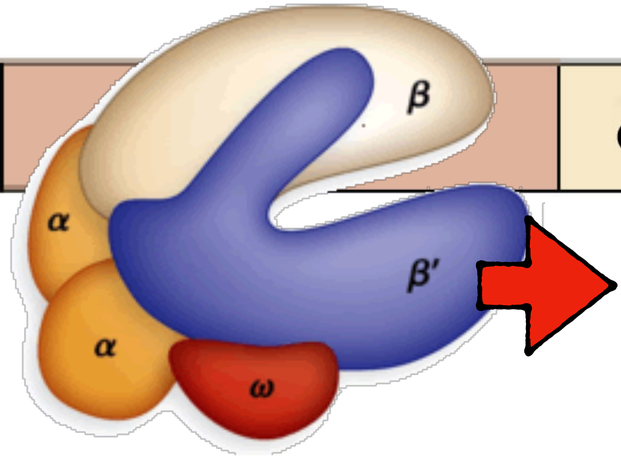

coding sequences

CAP site		operators	lacZ	lacY	lacA

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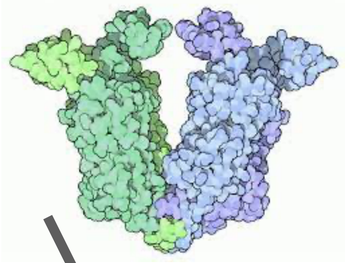

lactose enters, metabolized to allolactone → binds to and inactivates Lac repressor

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Visualizing stochastic gene expression

classic study on gene expression Elowitz et al 2002.

Stochastic Gene Expression in a Single Cell

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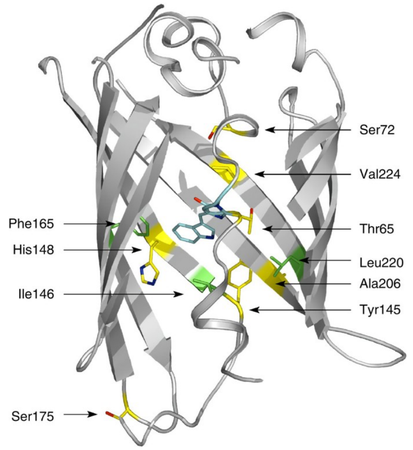

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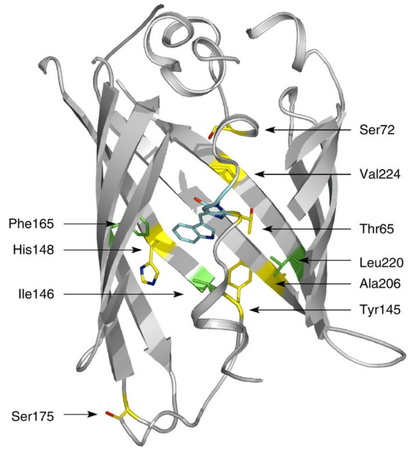

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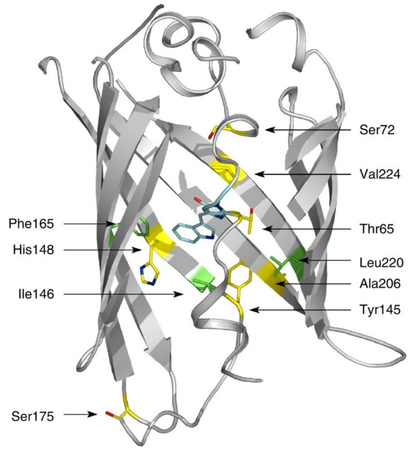

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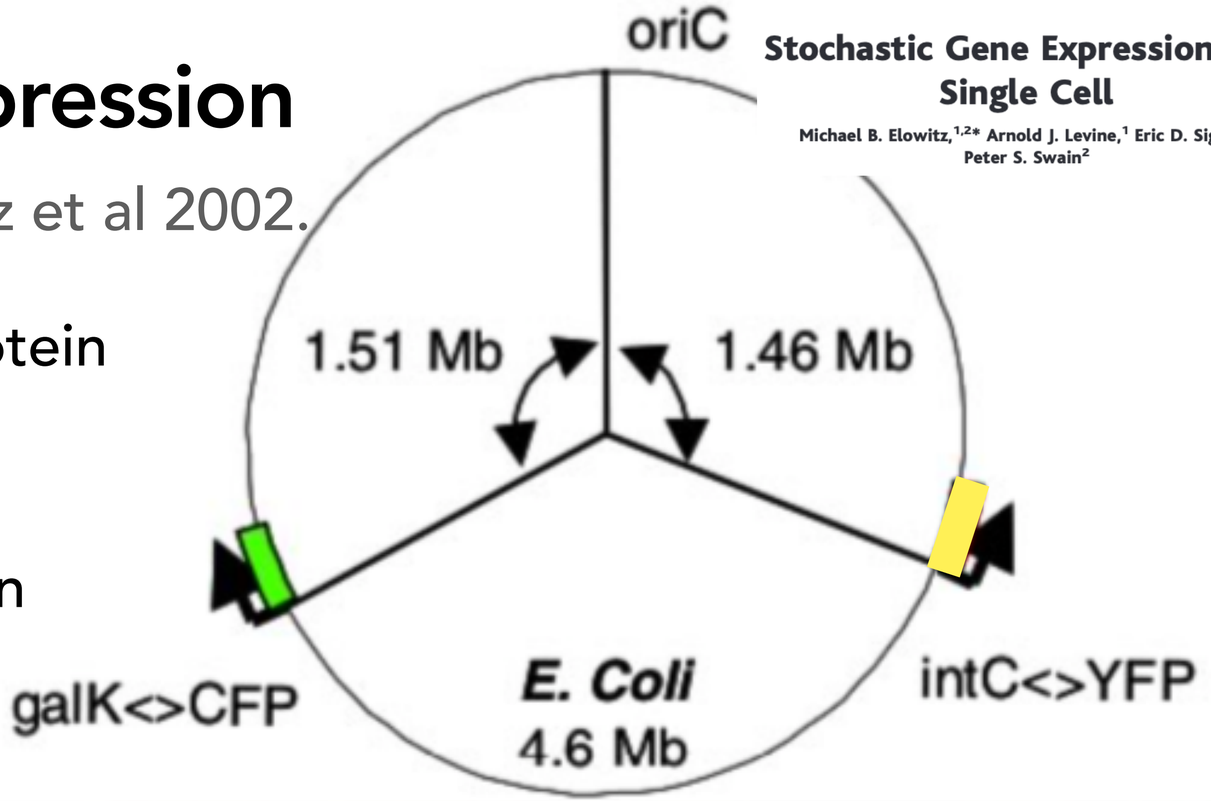

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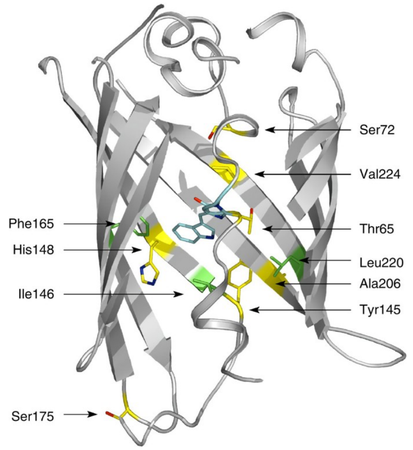

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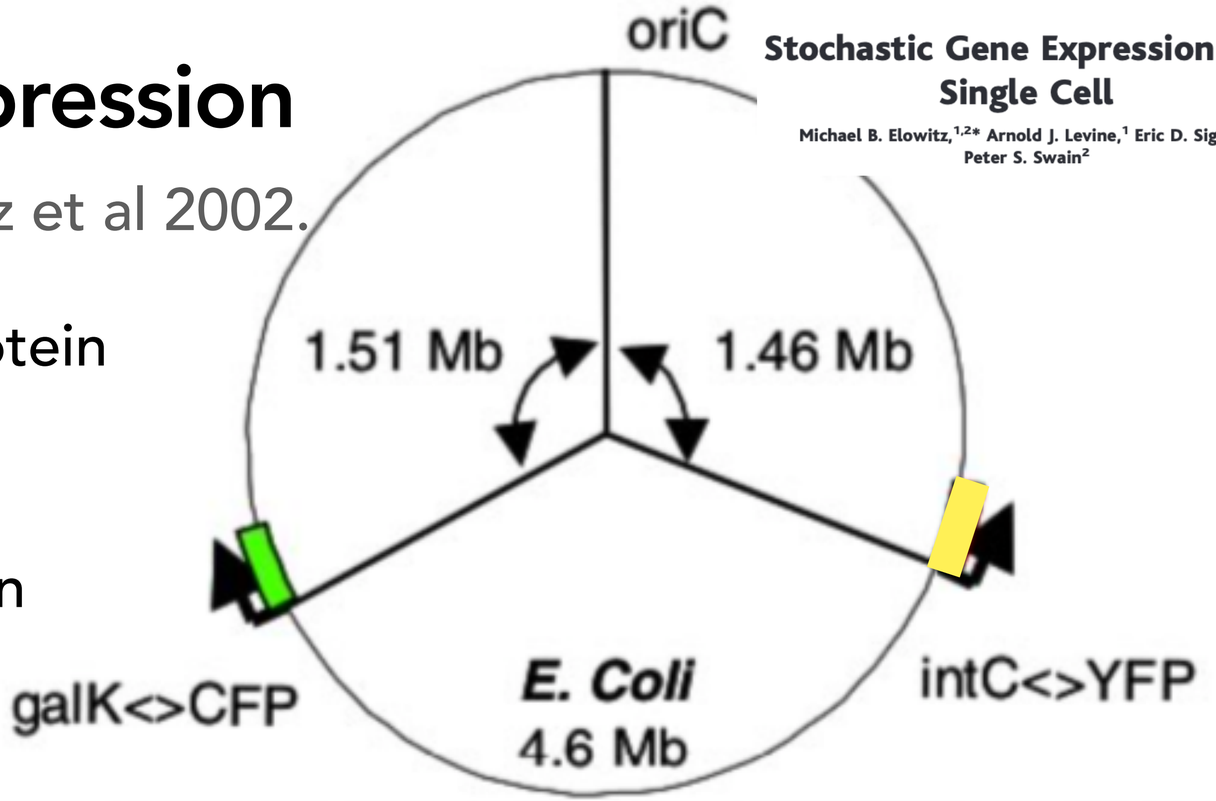

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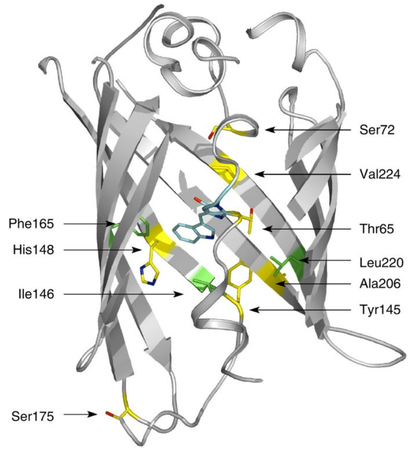

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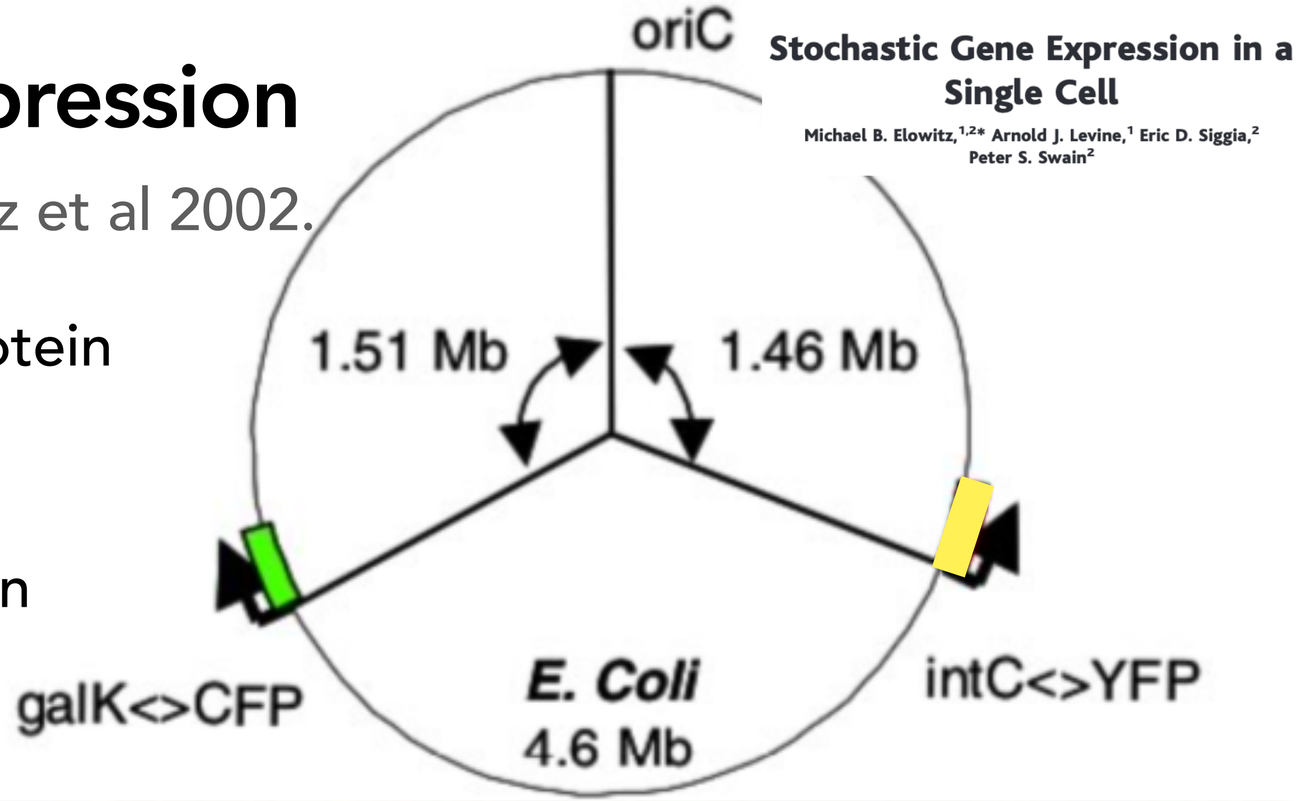

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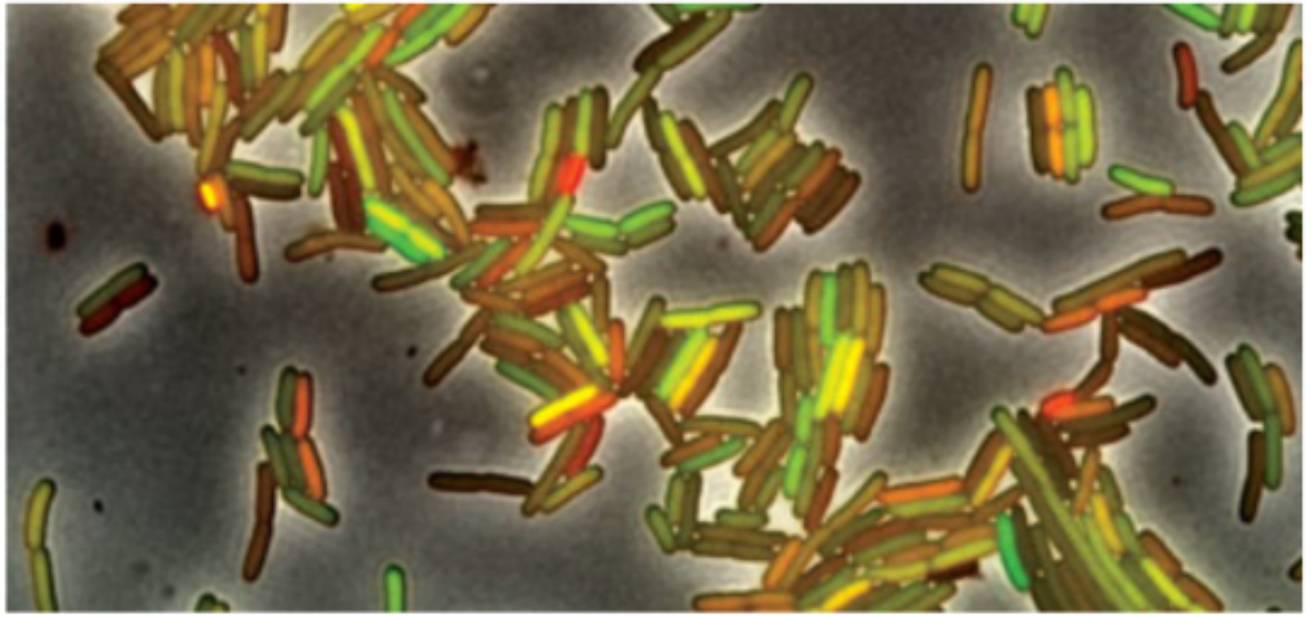

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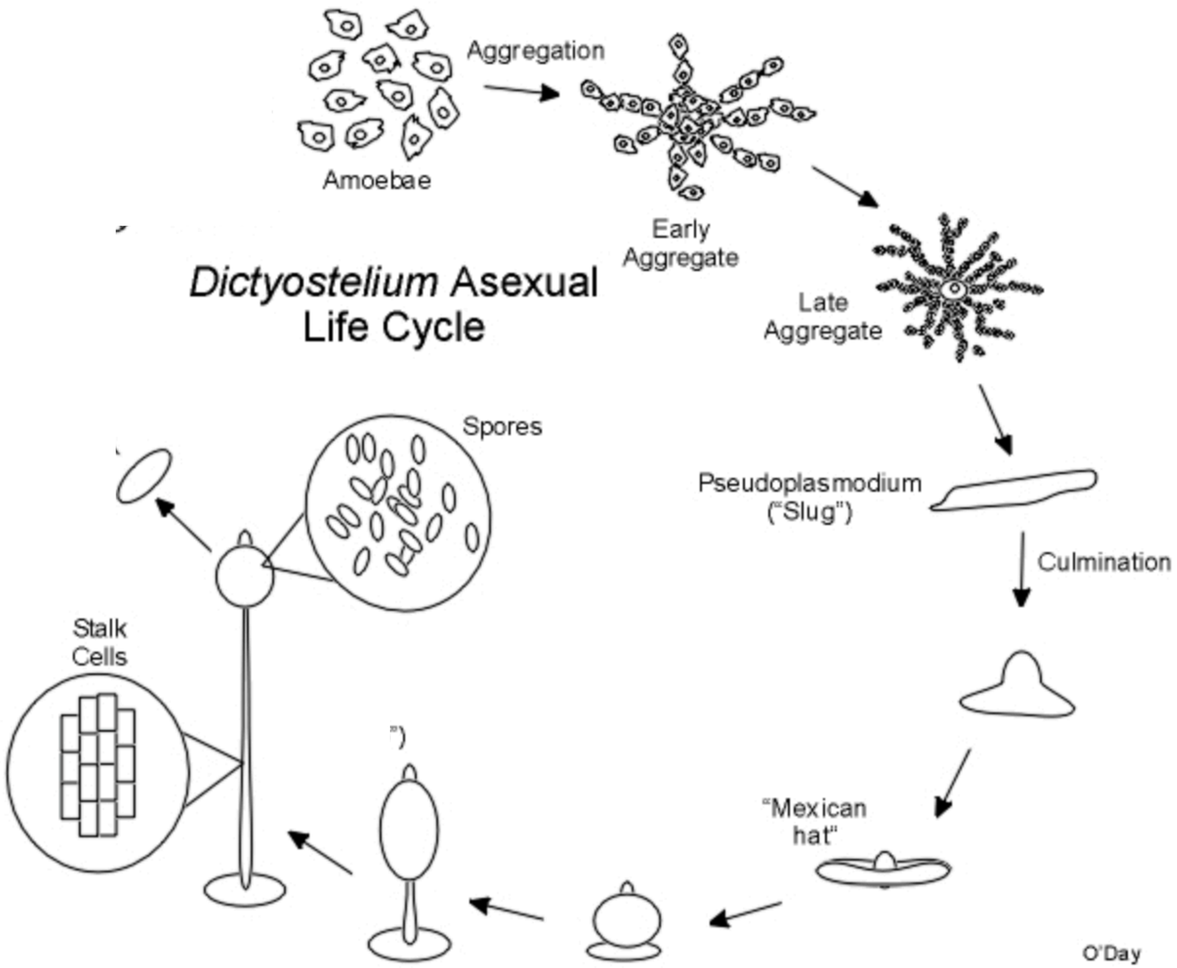

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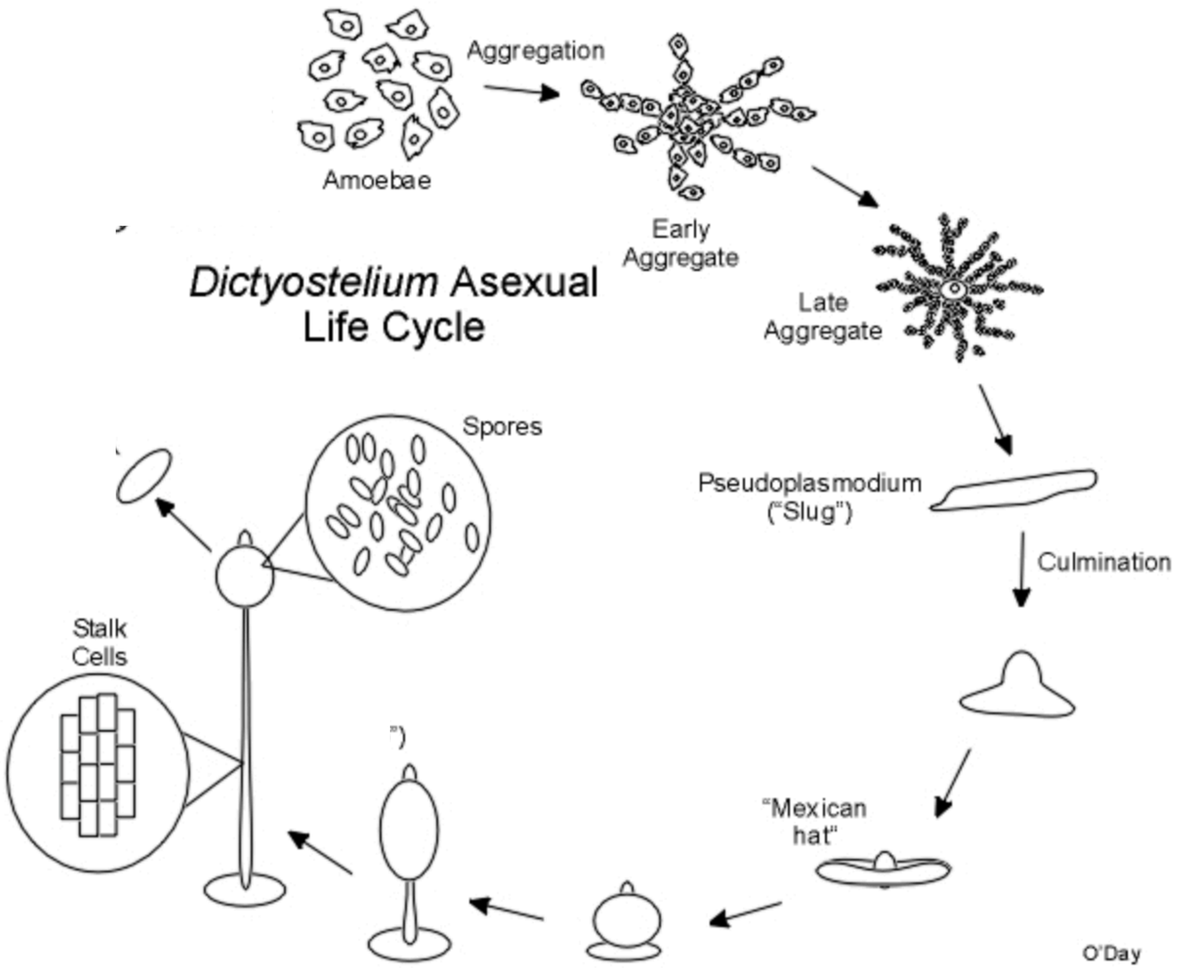

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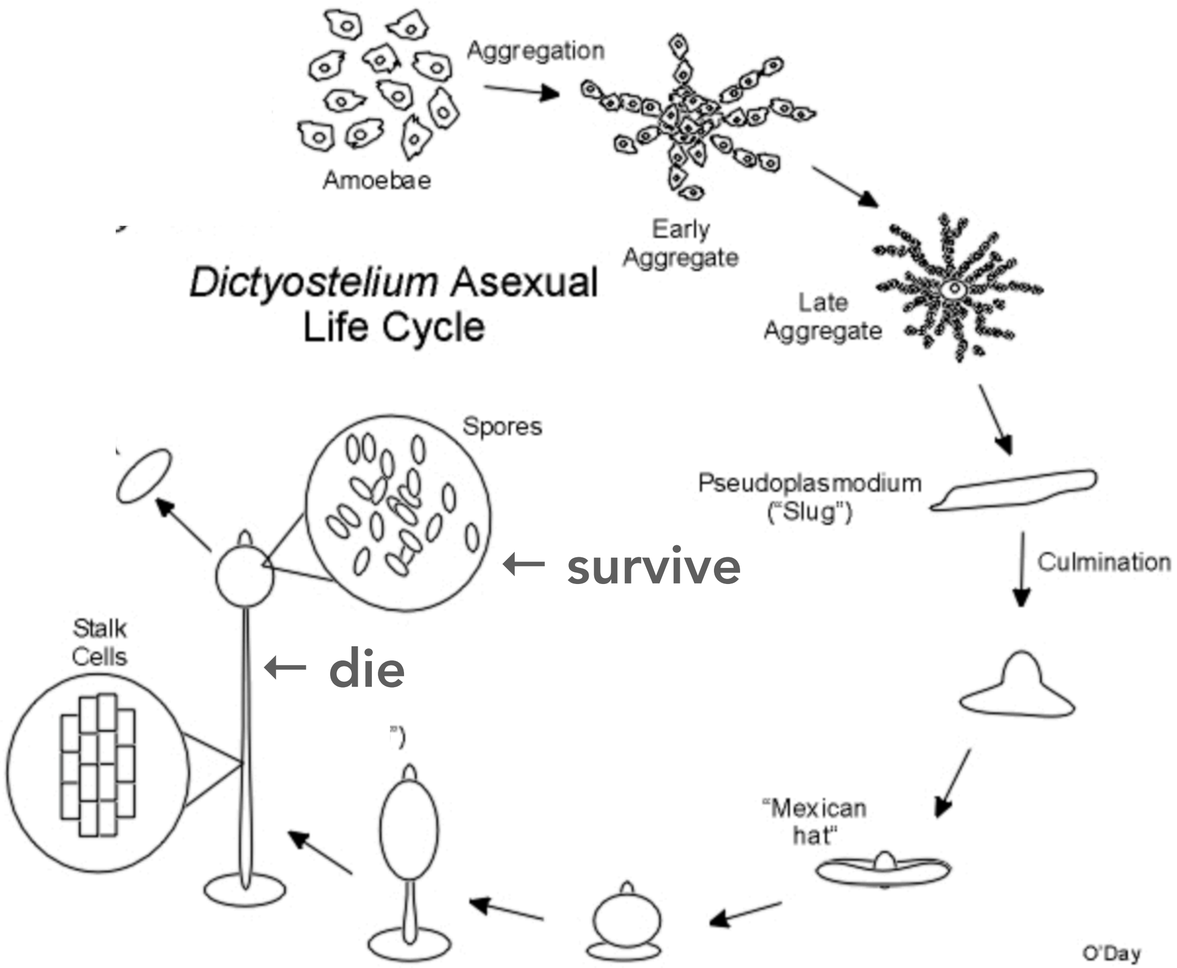

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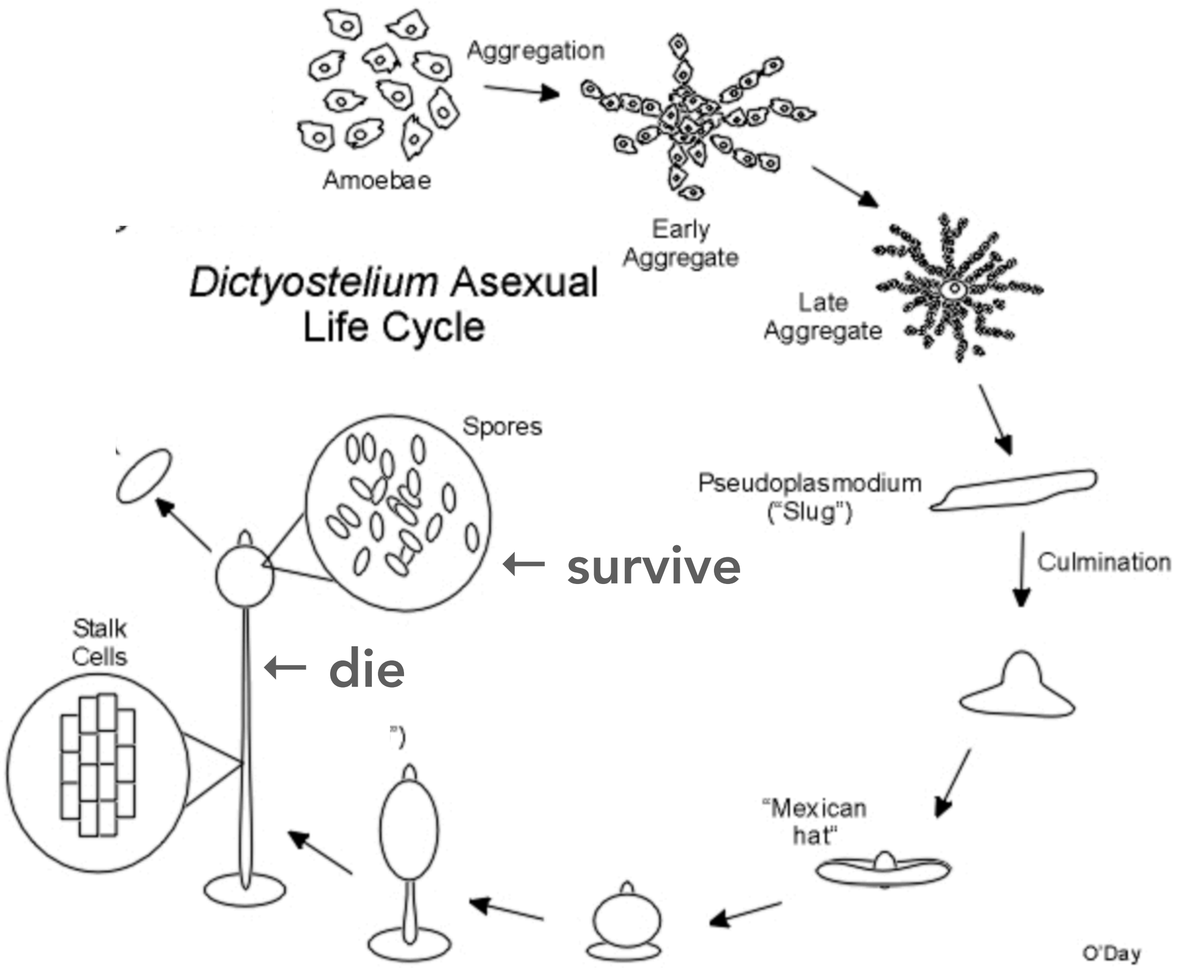

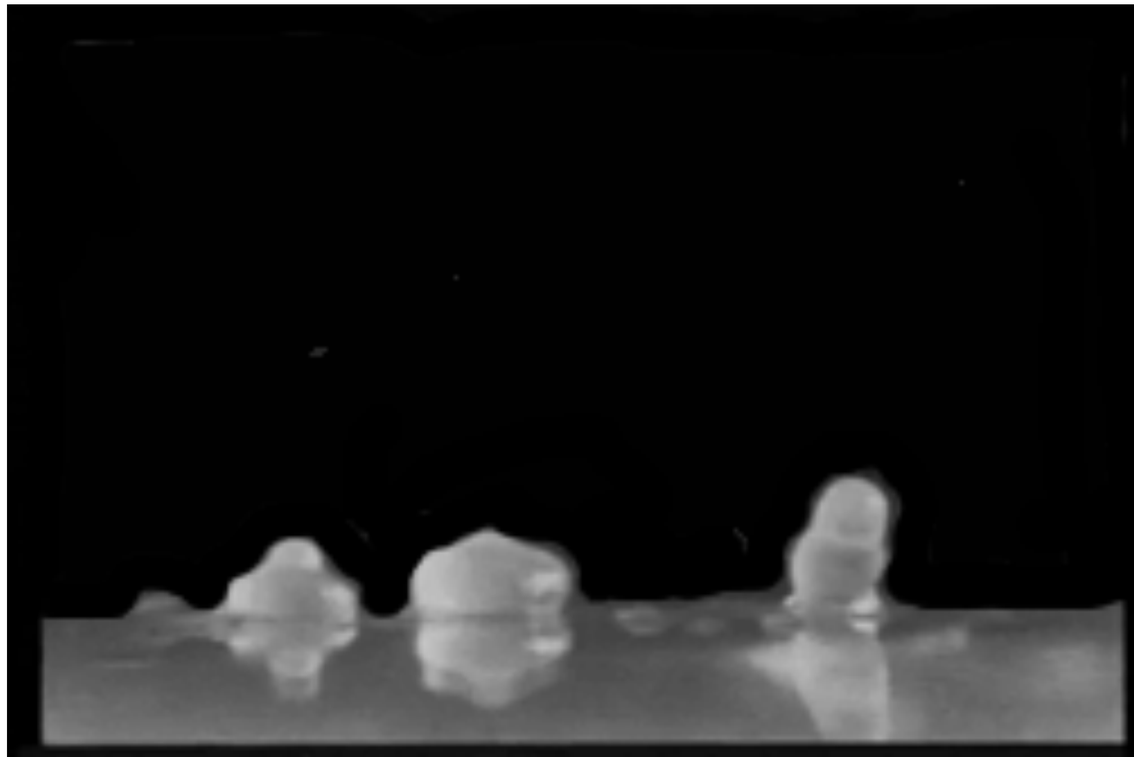

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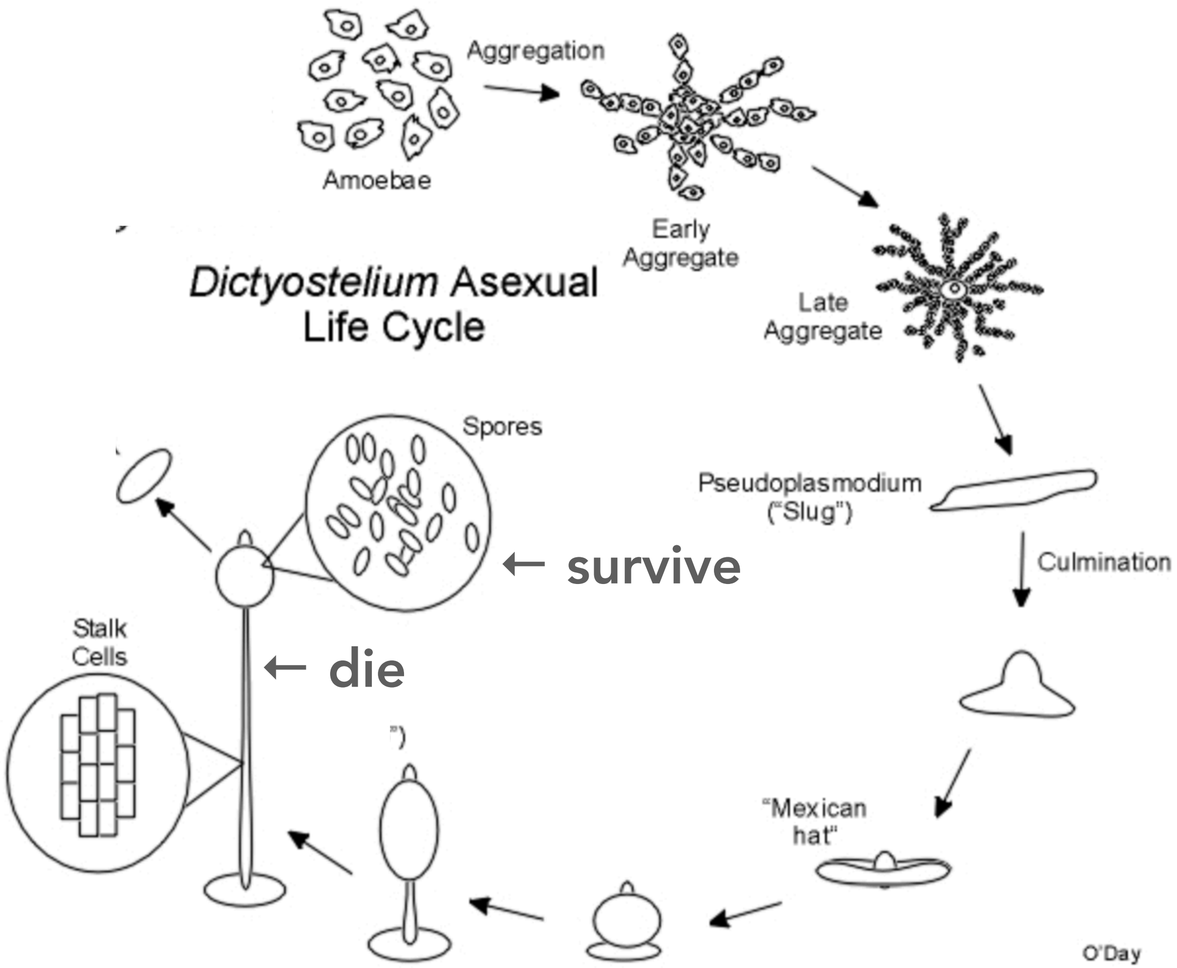
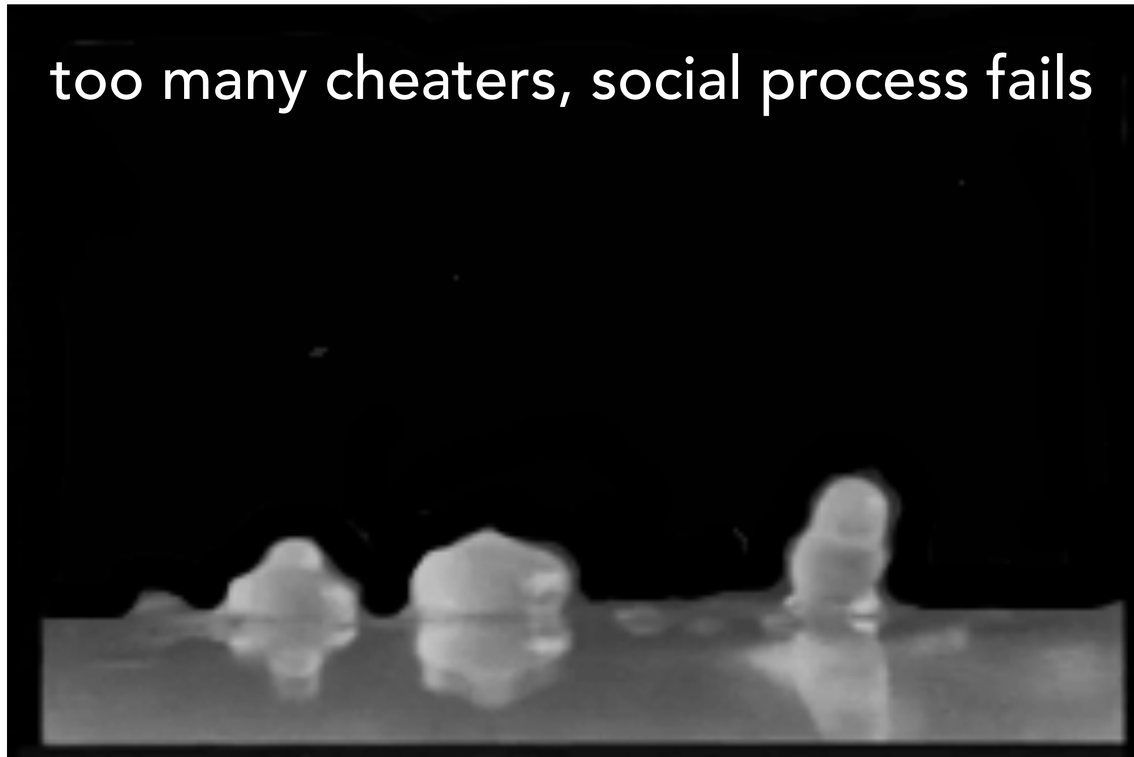


sacrifice best achieved through stochastic choices (suppress social cheaters)



Cooperative behavior + stochastic choices

Order by chance: origins and benefits of stochasticity in immune cell fate control

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Neural precursors of decisions that matter—an ERP study of deliberate and arbitrary choice

Uri Maoz[1,2,3,4,5,6]*, Gideon Yaffe[7], Christof Koch[8], Liad Mudrik[9,10]

RESEARCH ARTICLE | NEUROSCIENCE

Mice exhibit stochastic and efficient action switching during probabilistic decision making

Celia C. Beron, Shay Q. Neufeld, Scott W. Linderman, and Bernardo L. Sabatini Authors Info & Affiliations

Contributed by Bernardo L. Sabatini; received July 28, 2021; accepted March 3, 2022; reviewed by Anne Collins and Jonathan Pillow

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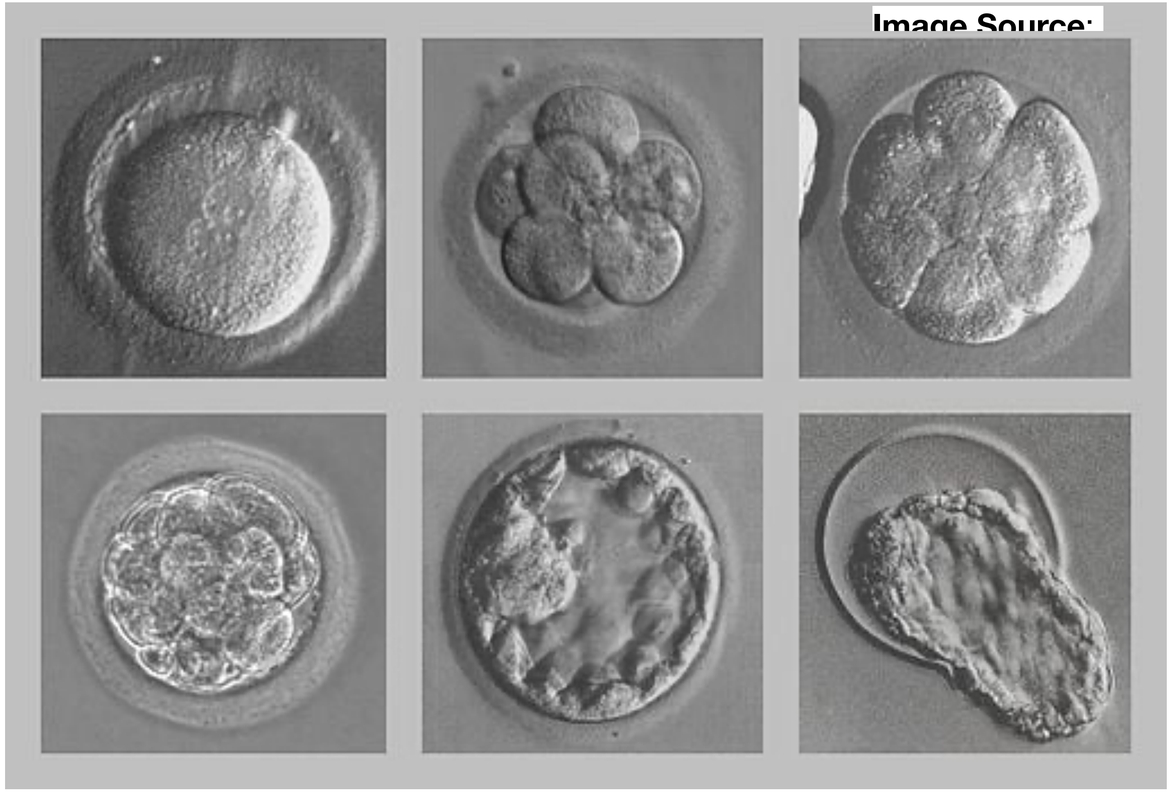
In early mouse (human) embryo, which cells become the organism and which the placenta is stochastic



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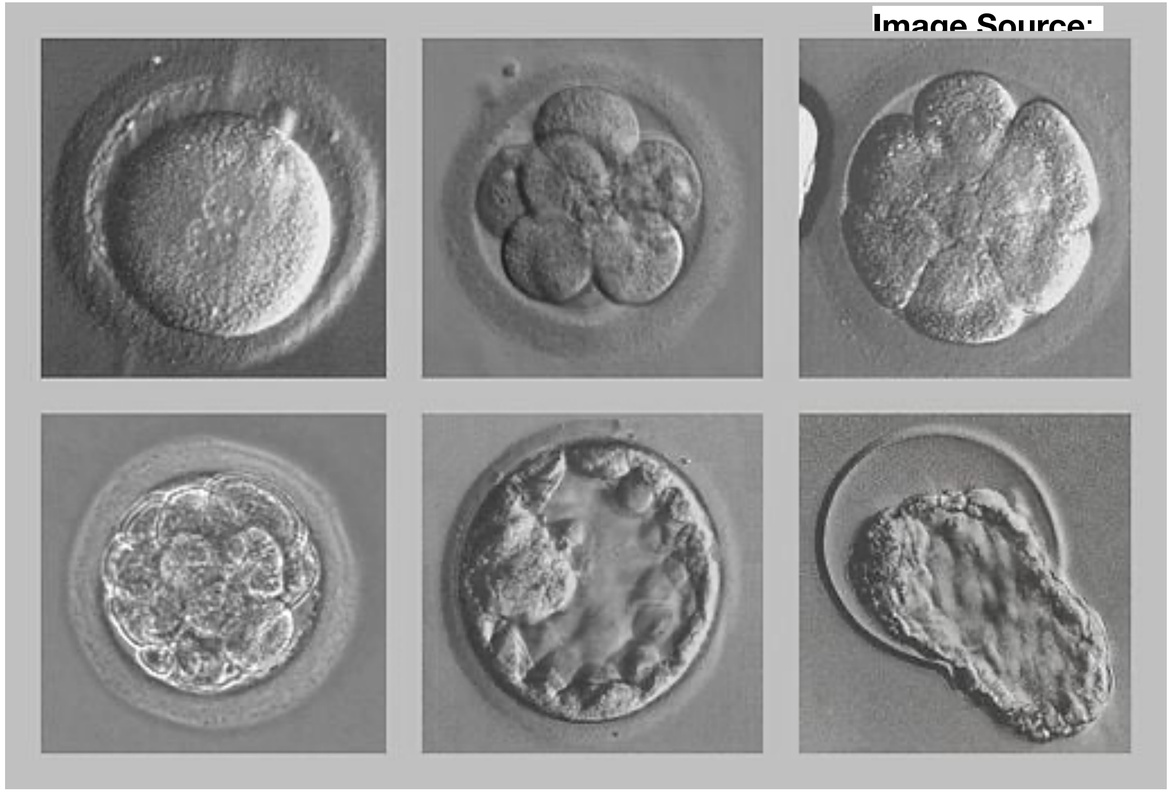

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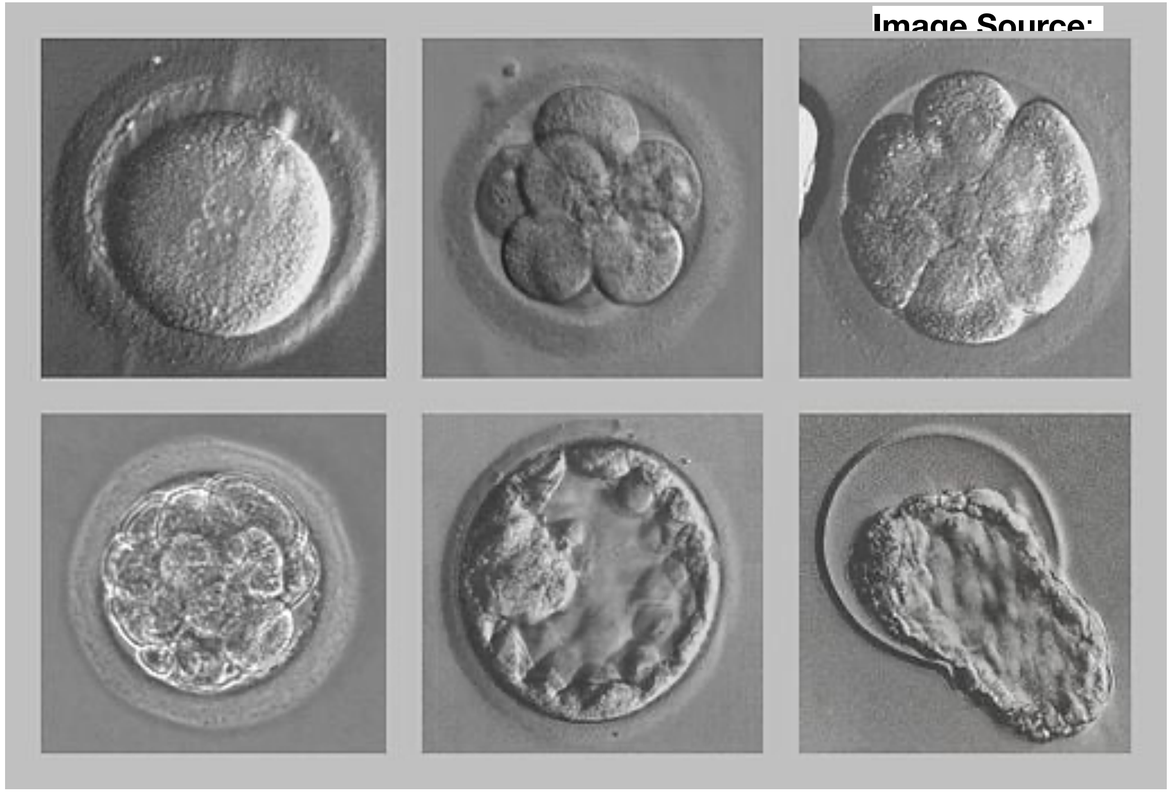
stochastic effects influence development of behavior of immune and nervous systems



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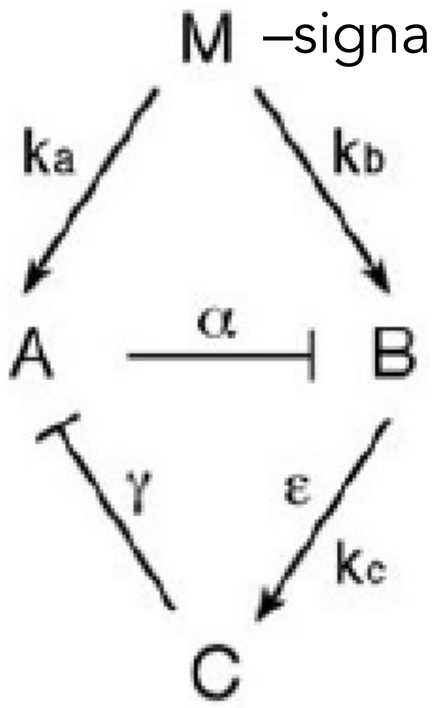
Stochastic event can have down stream effects



–signal molecule

regulates expression
of gene regulators

Research article

A mechanism for the sharp transition of morphogen interpretation in *Xenopus*

Yasushi Saka*[1,2] and James C Smith[1]

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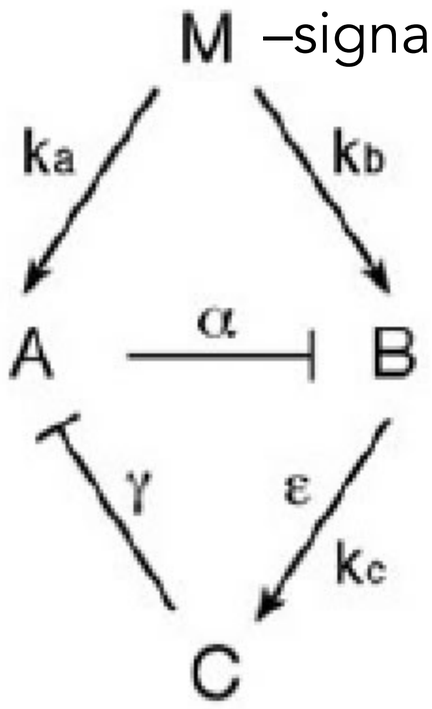
Stochastic event can have down stream effects



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regulates expression
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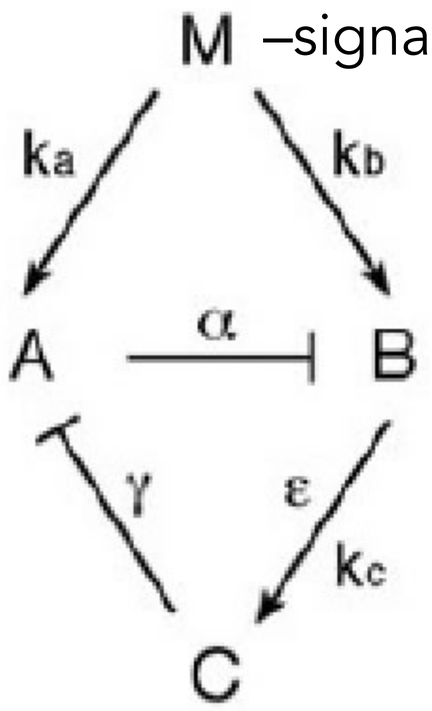

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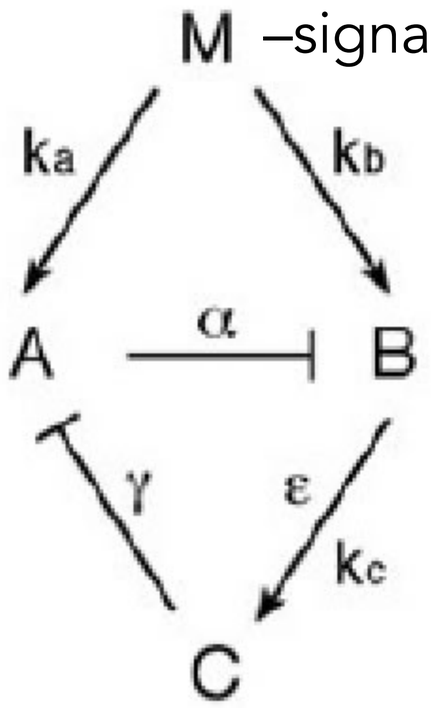

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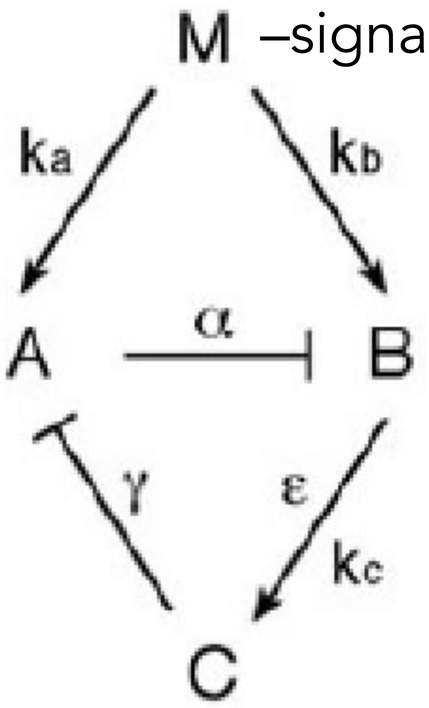

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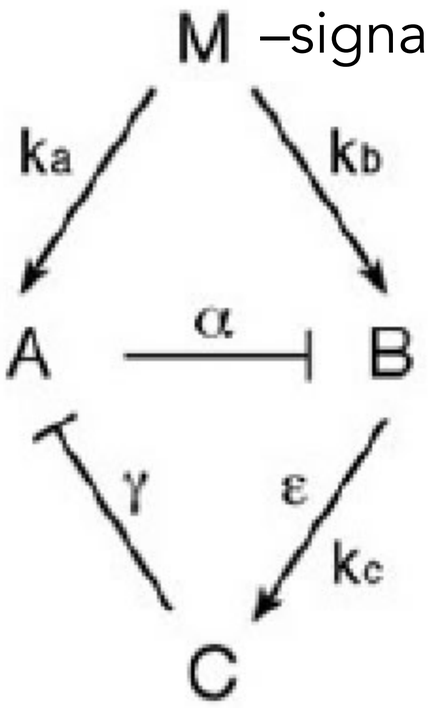

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↓
prepares system for next signal

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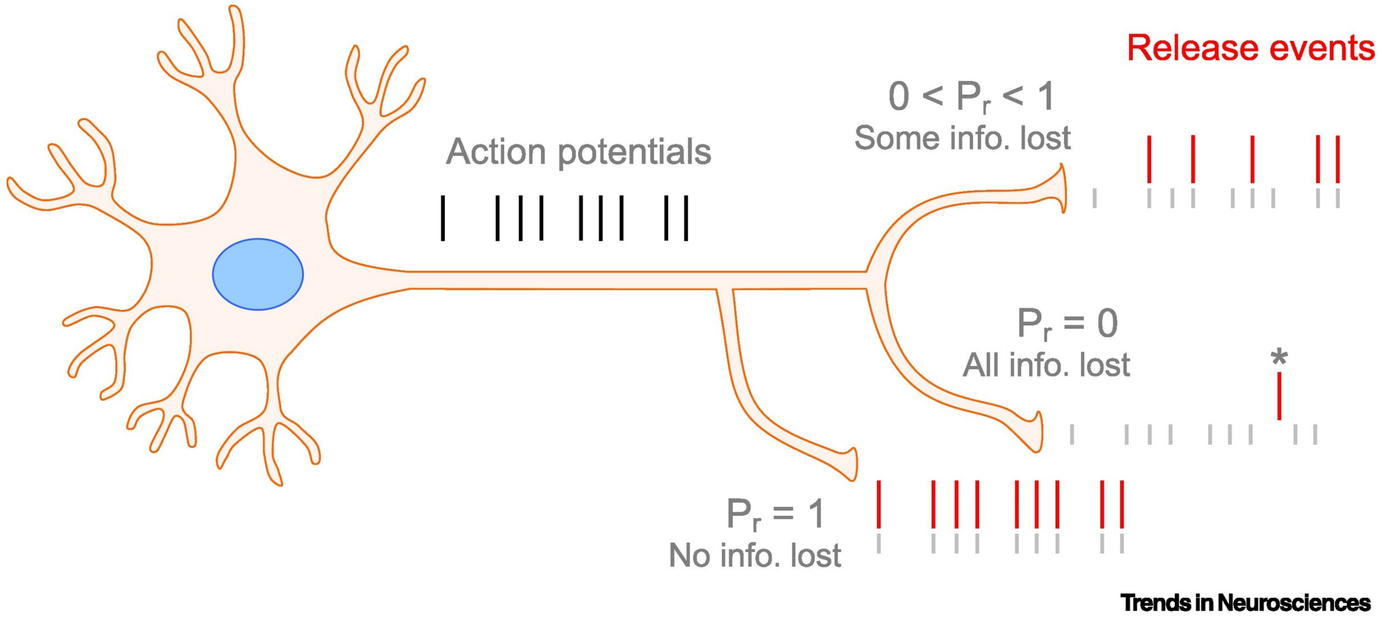

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RESEARCH ARTICLE | NEUROSCIENCE |

Mice exhibit stochastic and efficient action switching during probabilistic decision making

Celia C. Beron, Shay Q. Neufeld, Scott W. Linderman, and Bernardo L. Sabatini Authors Info & Affiliations

Contributed by Bernardo L. Sabatini; received July 28, 2021; accepted March 3, 2022; reviewed by Anne Collins and Jonathan Pillow

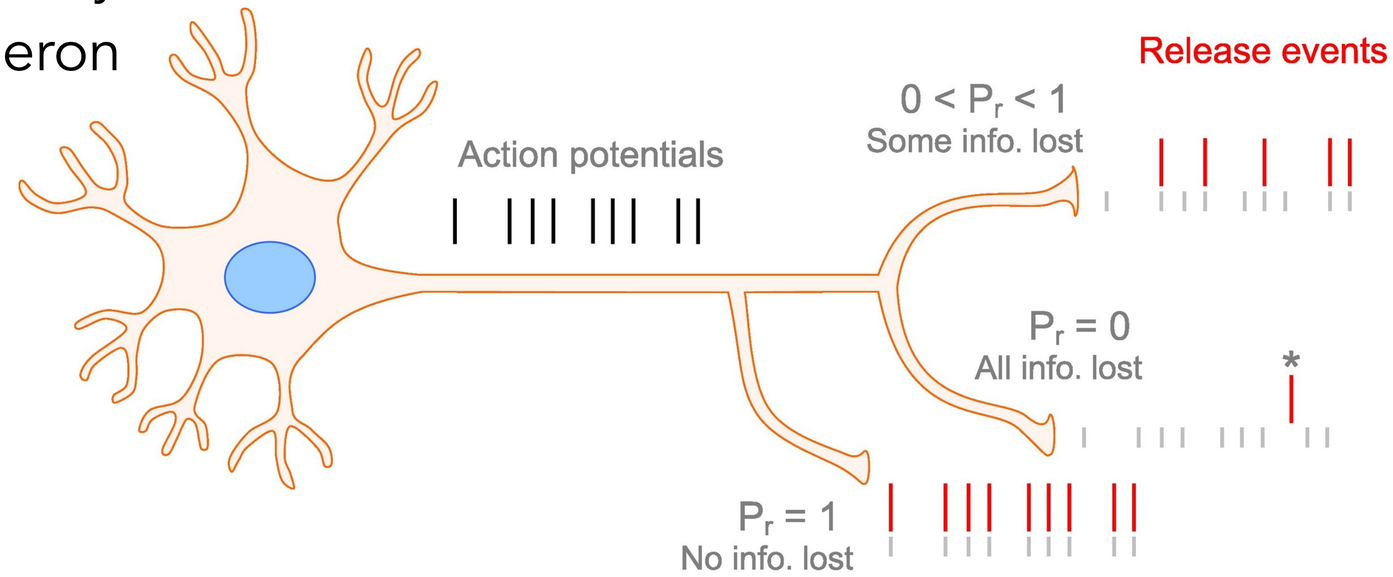
April 6, 2022 | 119 (15) e2113961119 | https://doi.org/10.1073/pnas.2113961119

Noisy Synaptic Conductance: Bug or a Feature?

Dmitri A. Rusakov, [1,*] Leonid P. Savtchenko, [1,*] and Peter E. Latham [2,*]

Noisy neural networks*

stochastic effects generate noisy responses - like the lac operon



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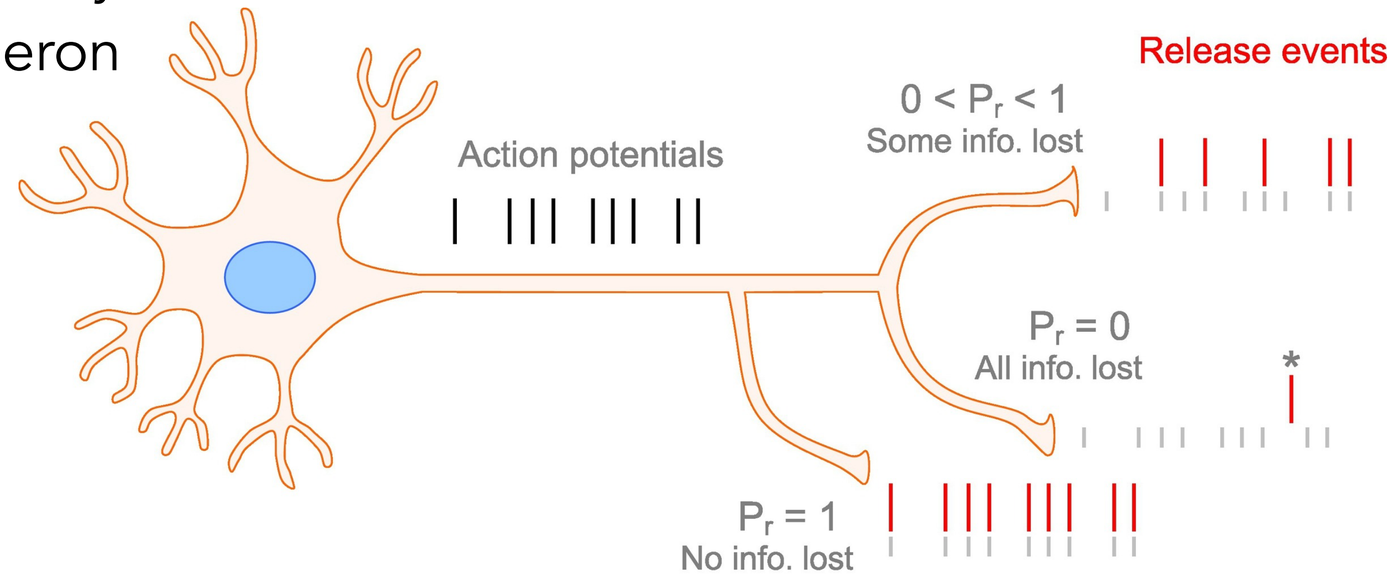

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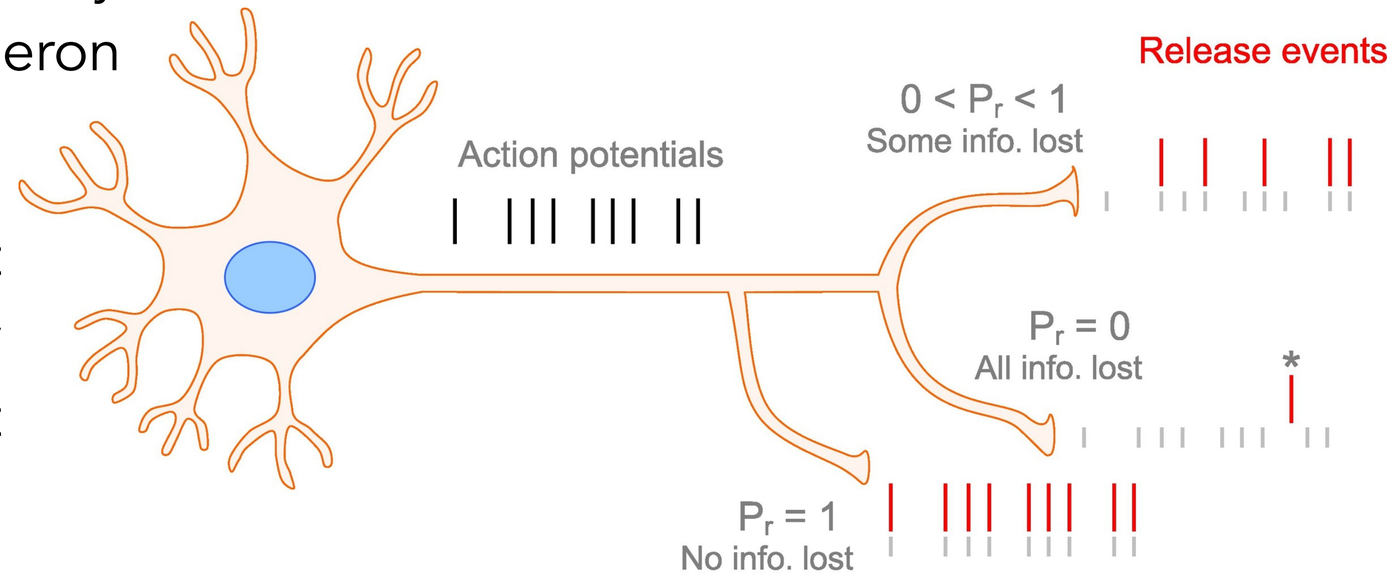

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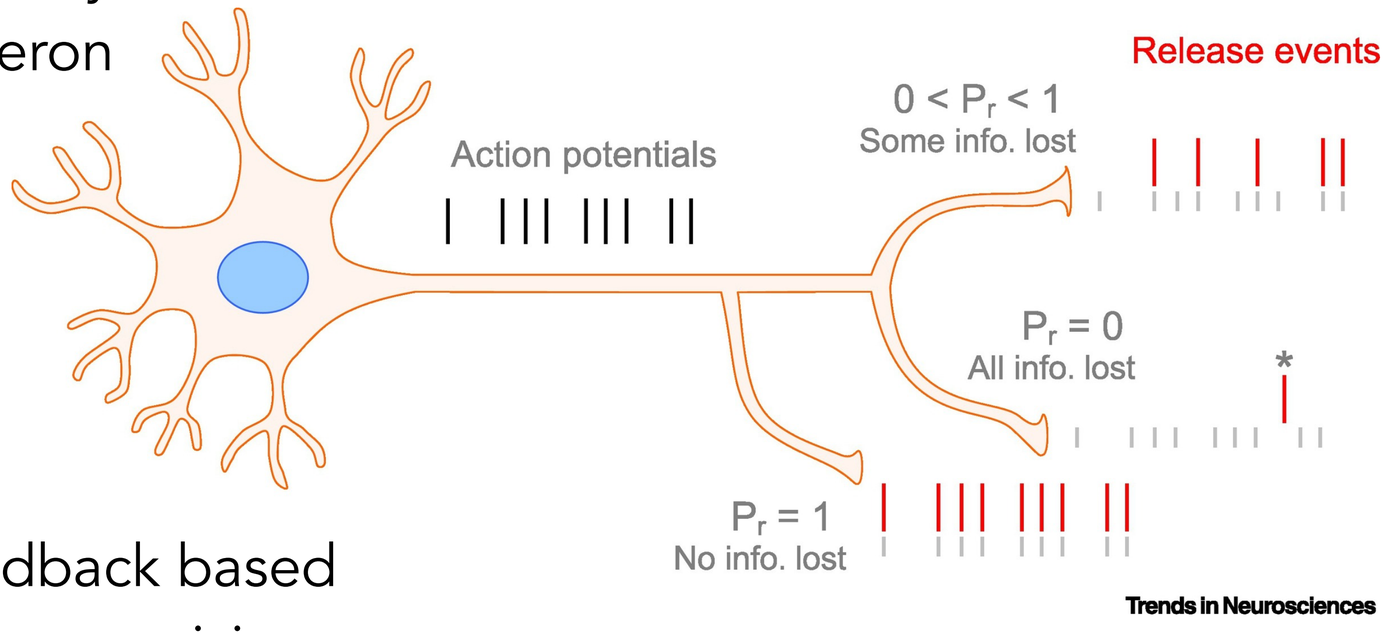

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At various levels (cellular and organismic),
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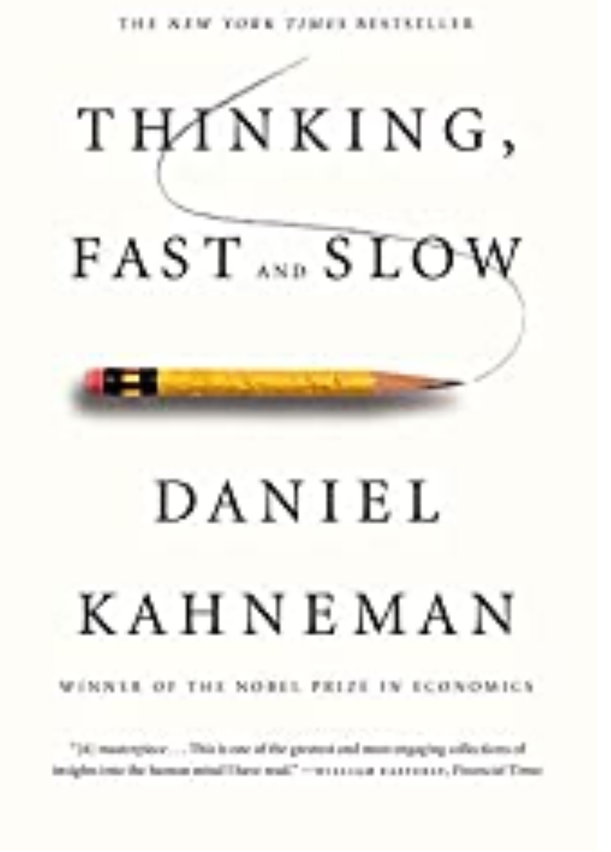
"We are prone to overestimate how much we understand about the world and to underestimate the role of chance in events." — Daniel Kahneman



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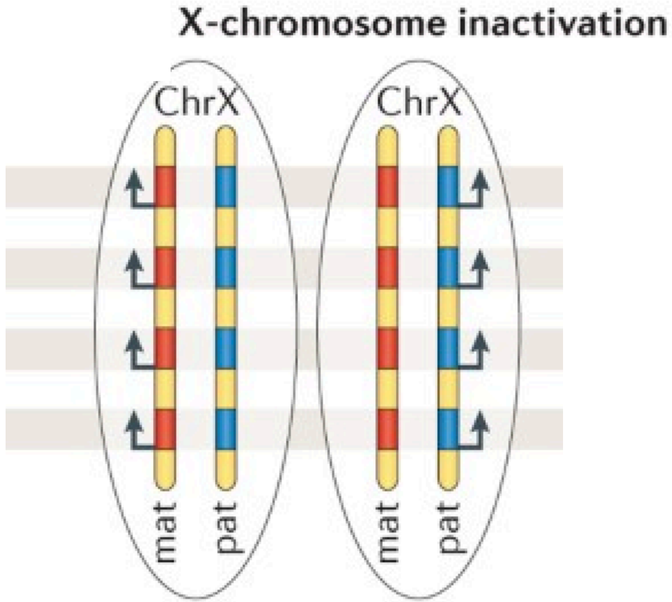

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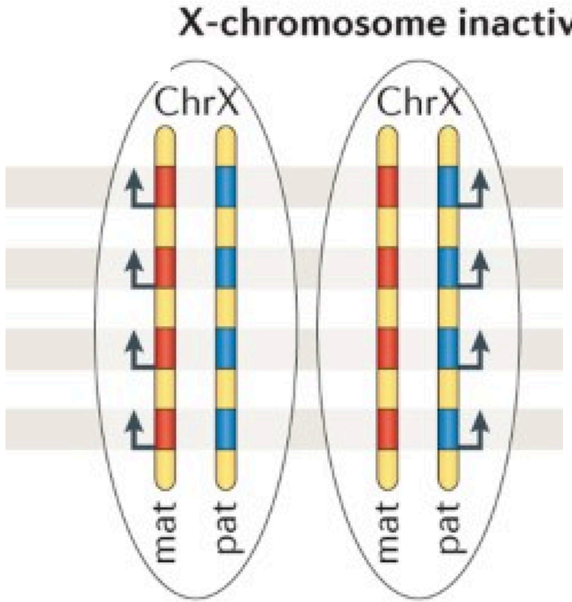

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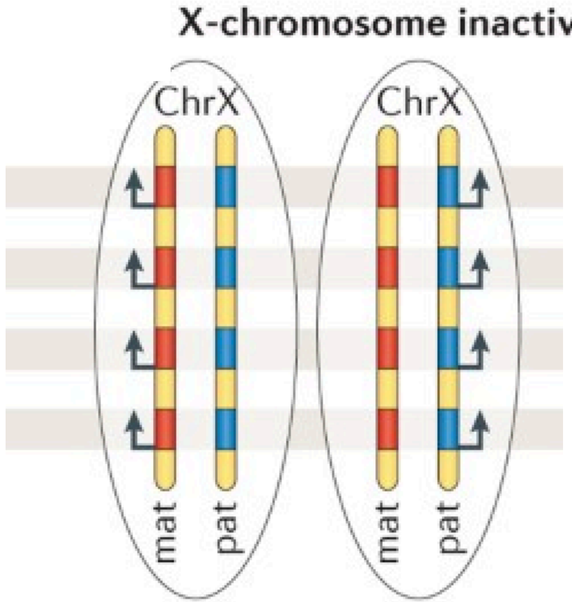

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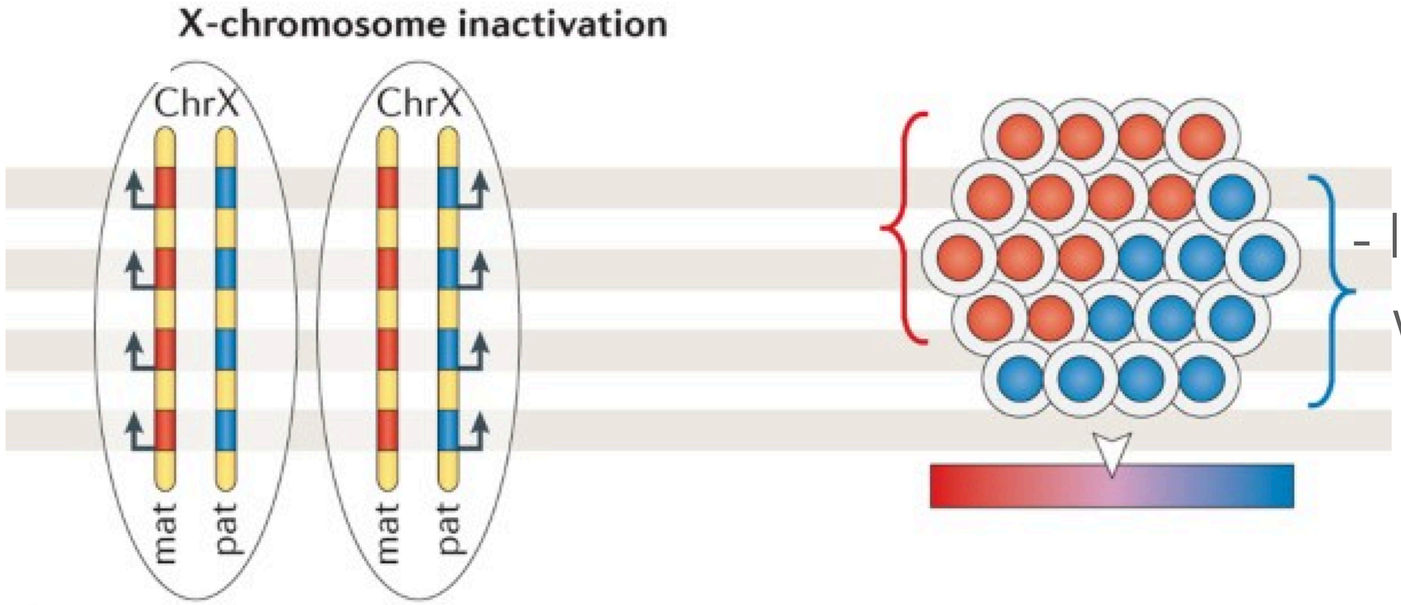

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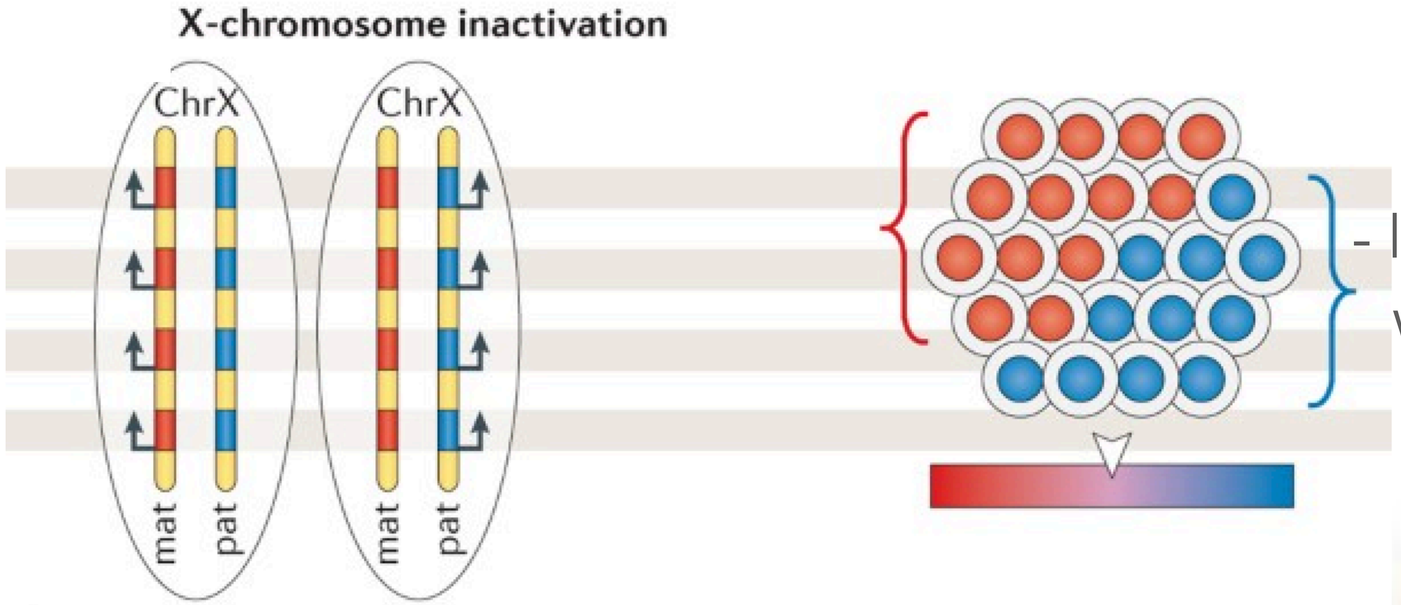

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unexpected stochastic processes - monoallelic gene expression

Resource

Random allelic expression in the adult human body

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[7]Lead contact
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Random monoallelic expression: regulating gene expression one allele at a time.

Eckersley-Maslin MA[1], Spector DL[1]

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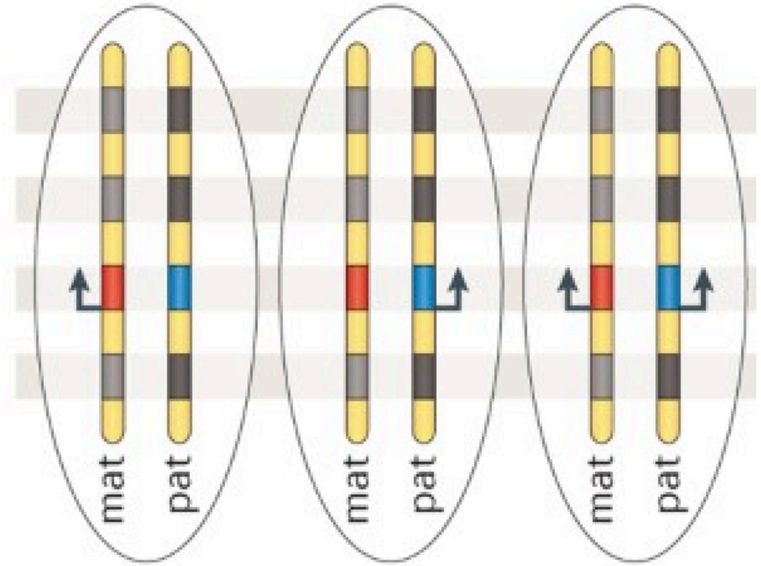

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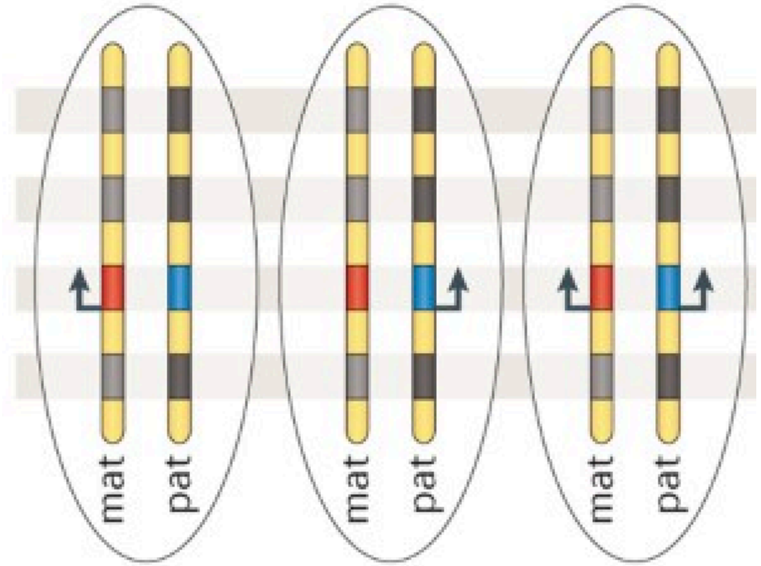

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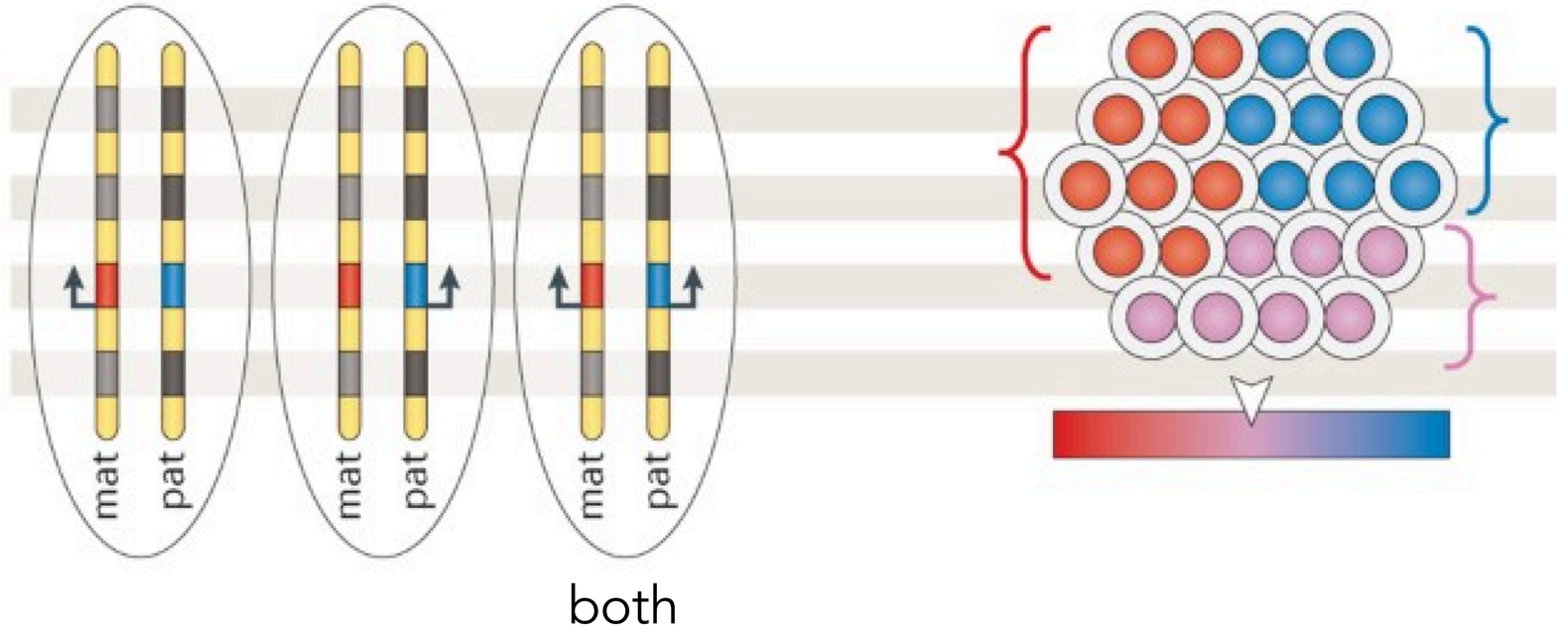

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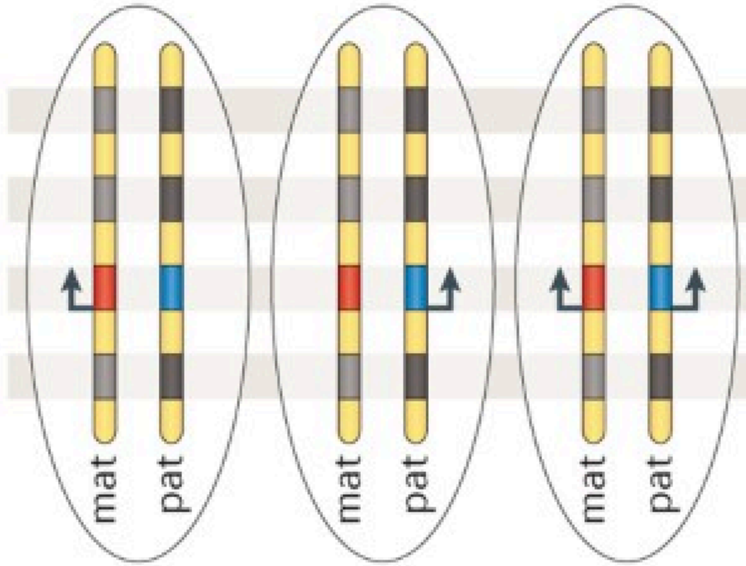

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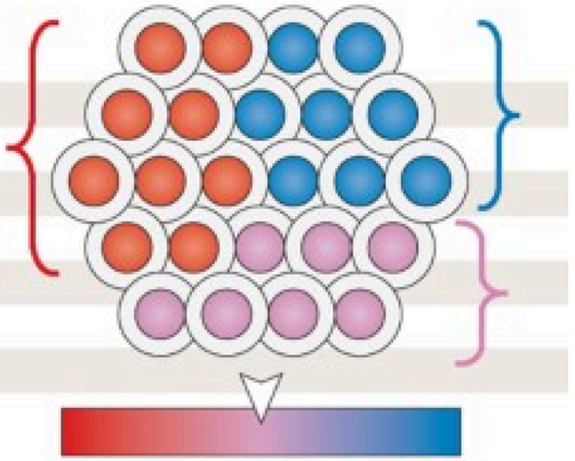

- produces clones that can compete with or interact with one another

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Abidemi A. Adegbola, Gerald F. Cox, Elizabeth M. Bradshaw, +2, and Andrew Chess Authors Info & Affiliations

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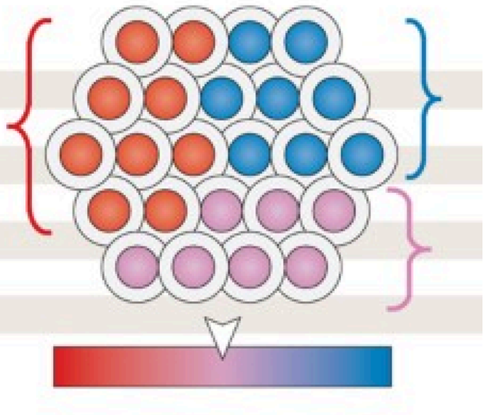

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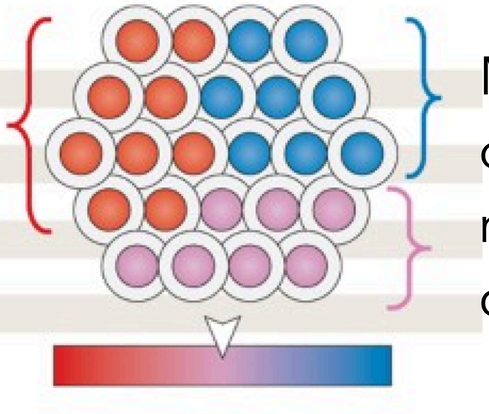

Monoallelic expression of FoxP2 can produce multiple, competing clones

RESEARCH ARTICLE | BIOLOGICAL SCIENCES |

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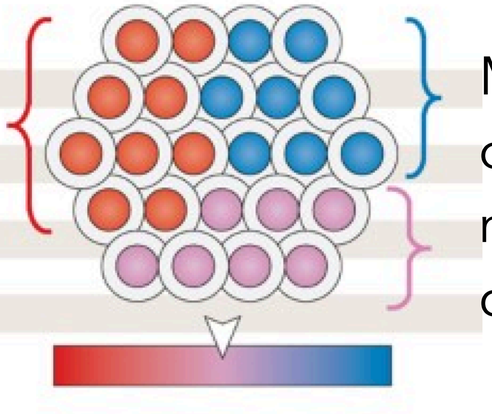

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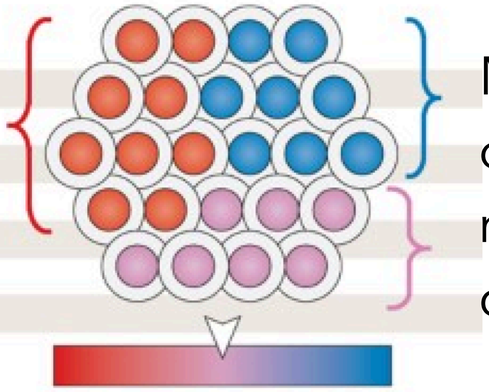

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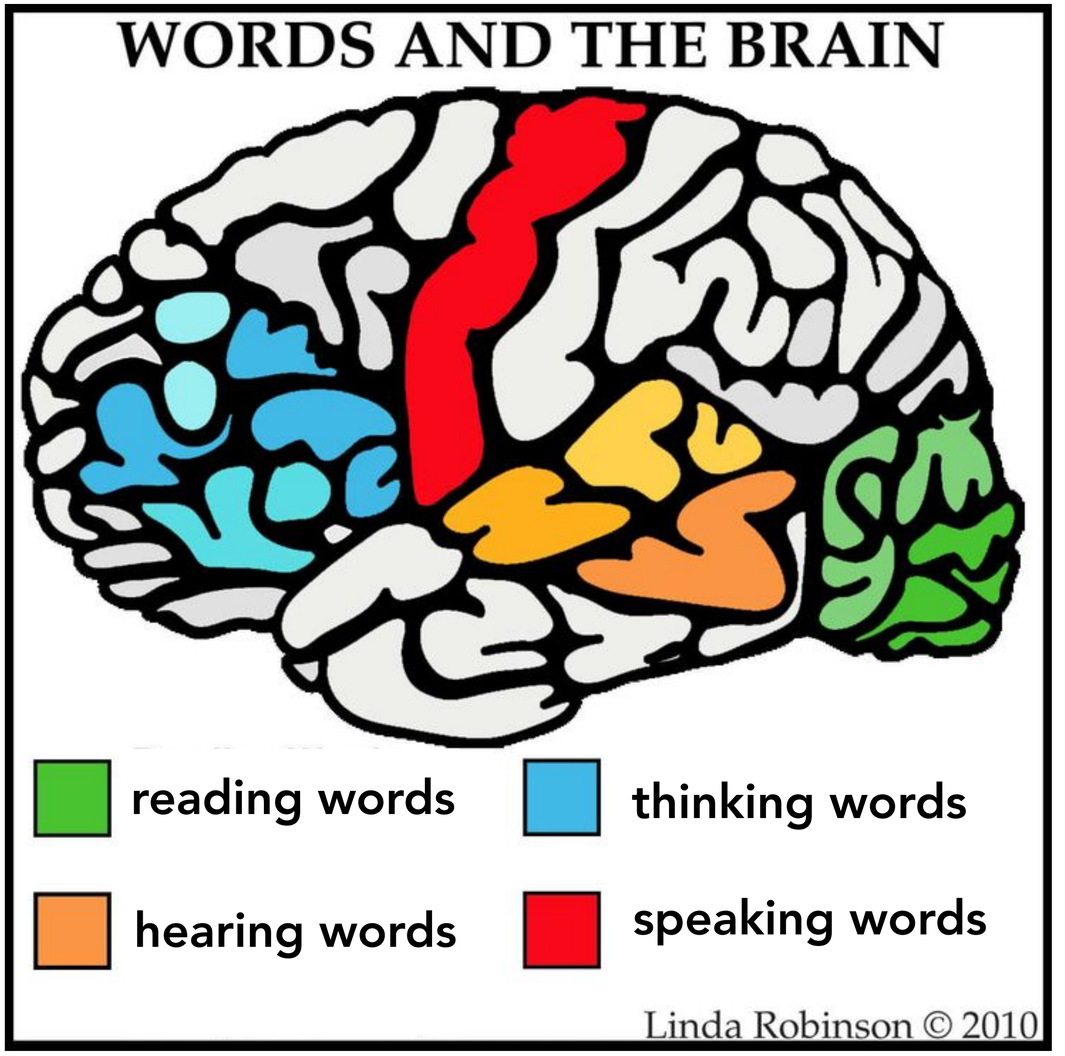

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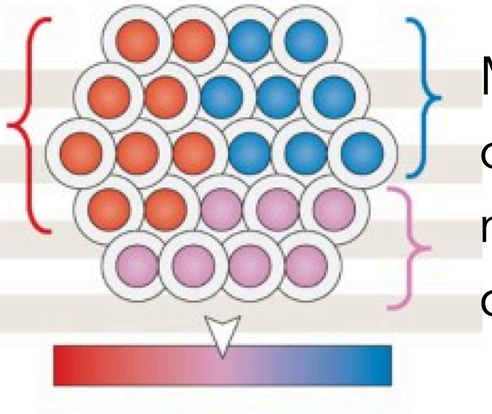

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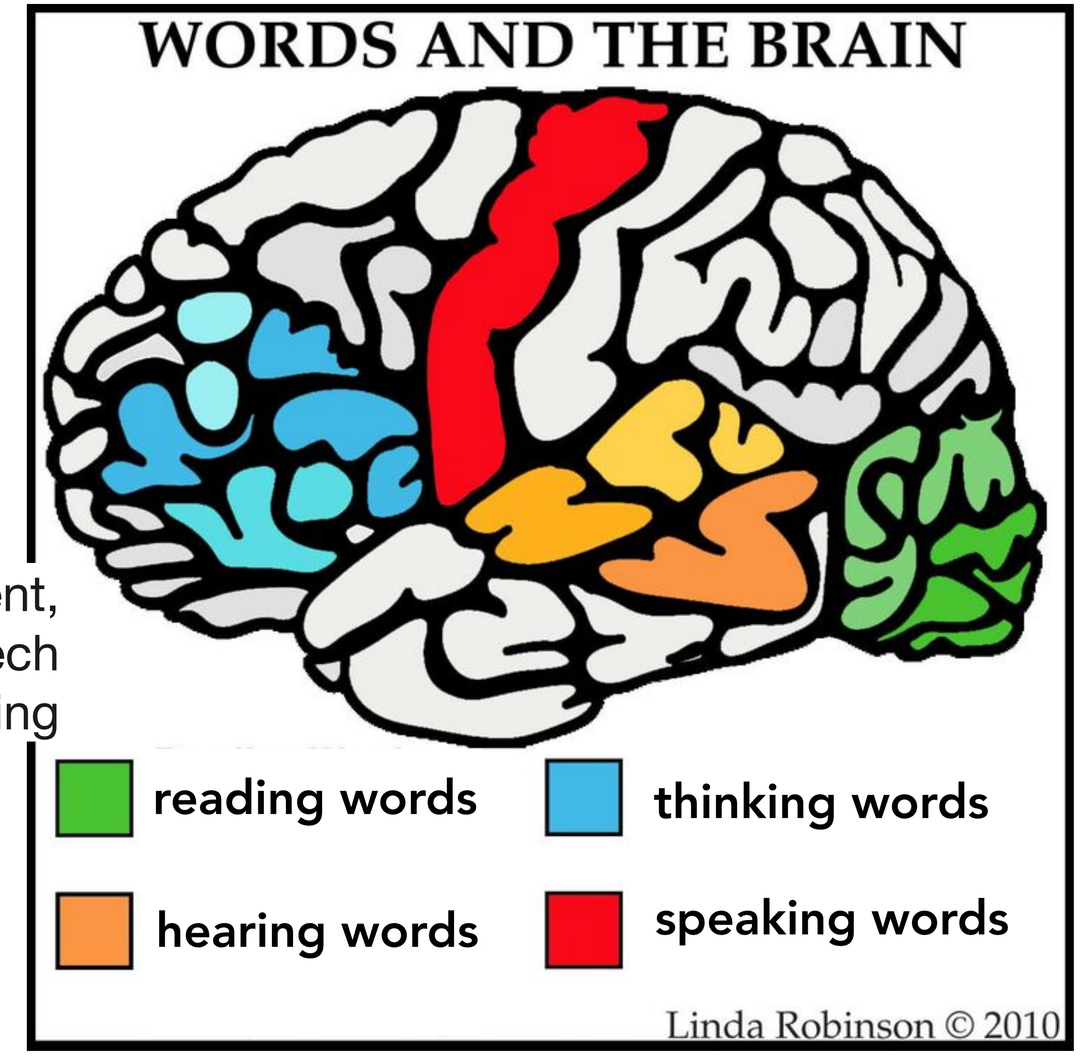

e.g **Wernicke's Aphasia**: Fluent, grammatically correct speech with little meaning

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single cell RNA sequencing (identifies gene expressed)

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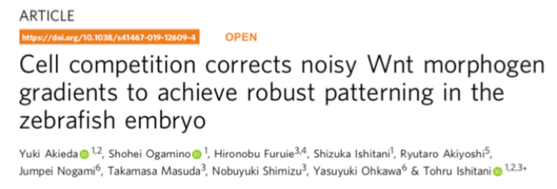

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https://doi.org/10.1038/s41467-019-12609-4 OPEN

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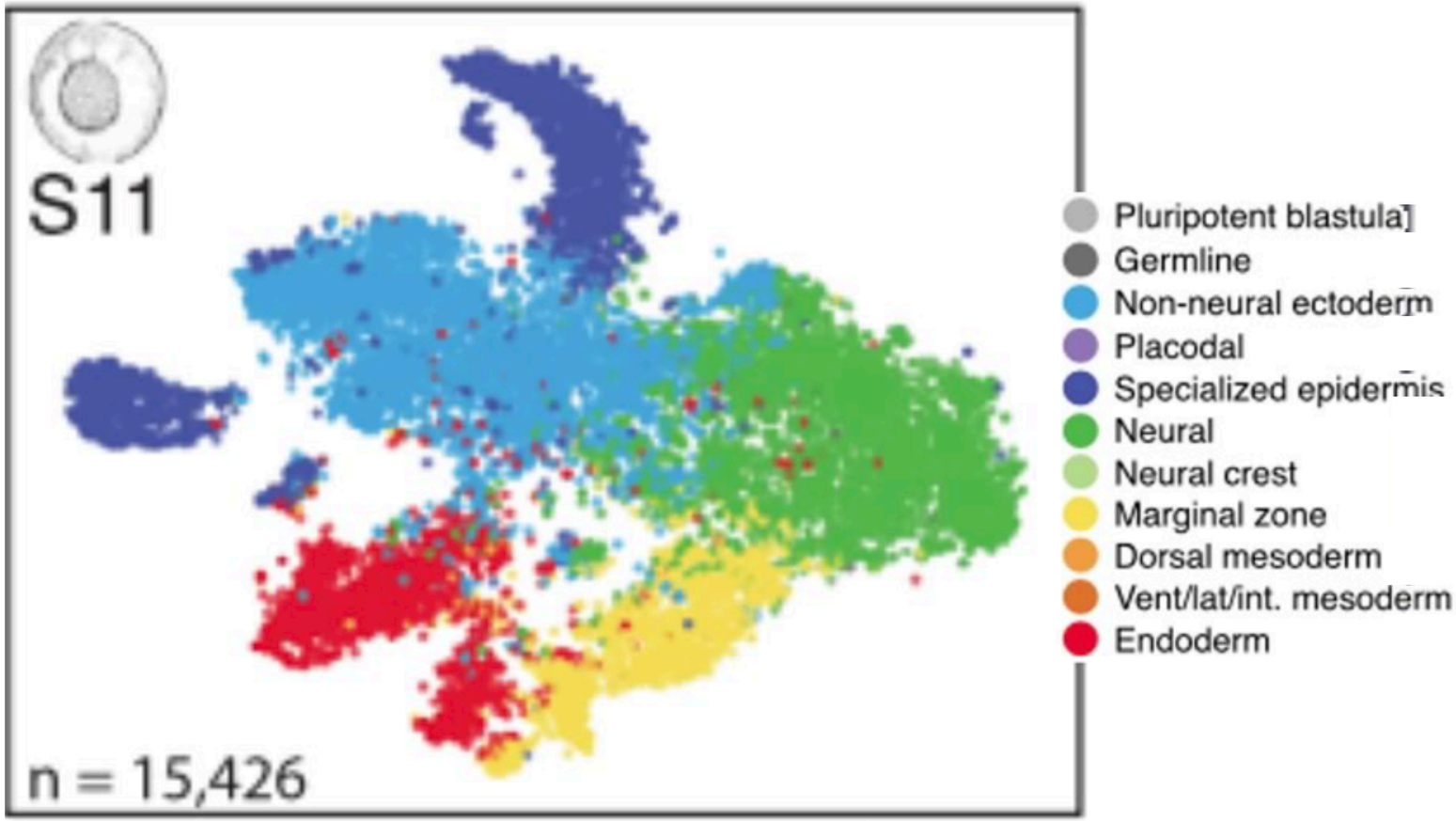

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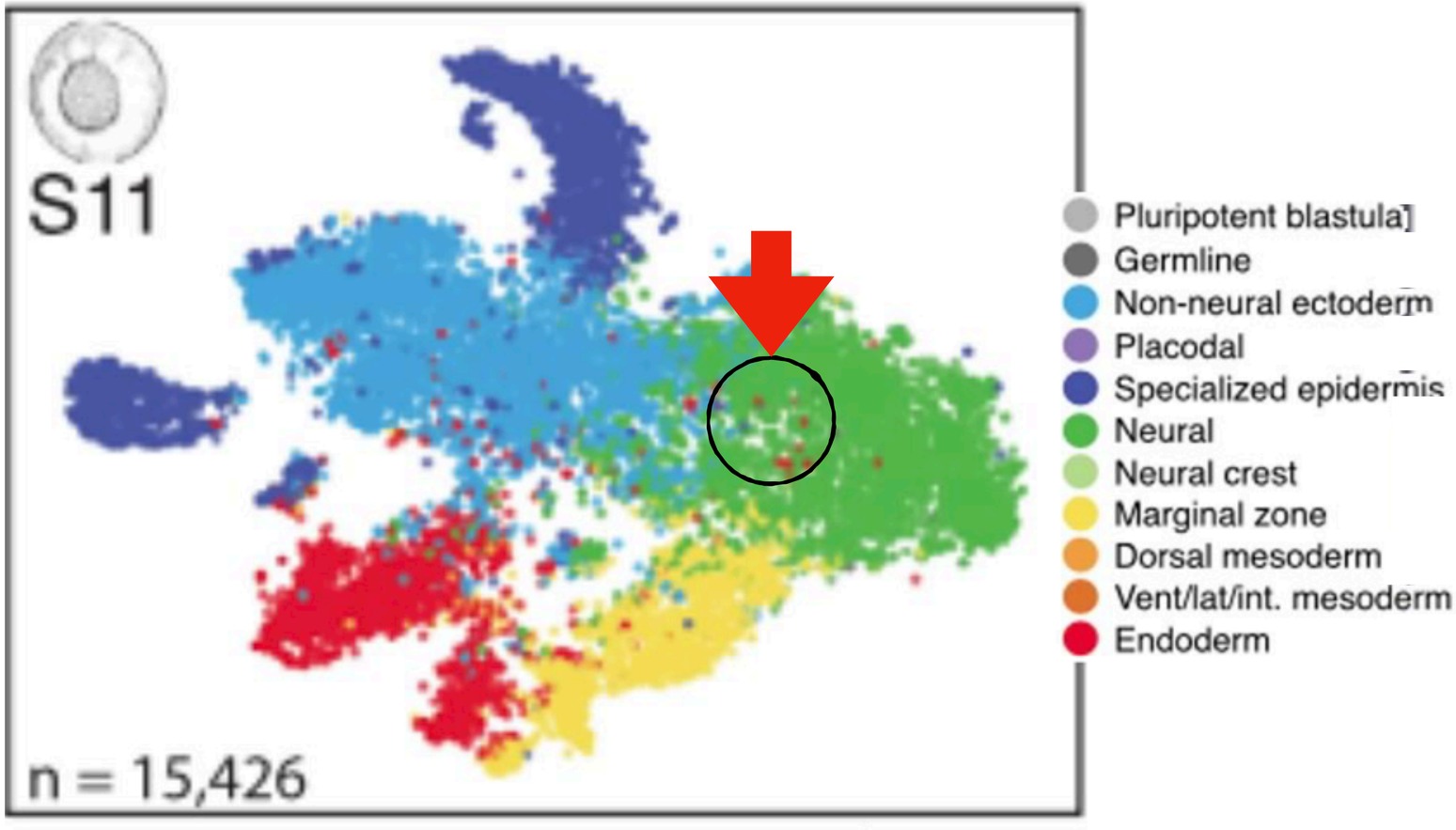

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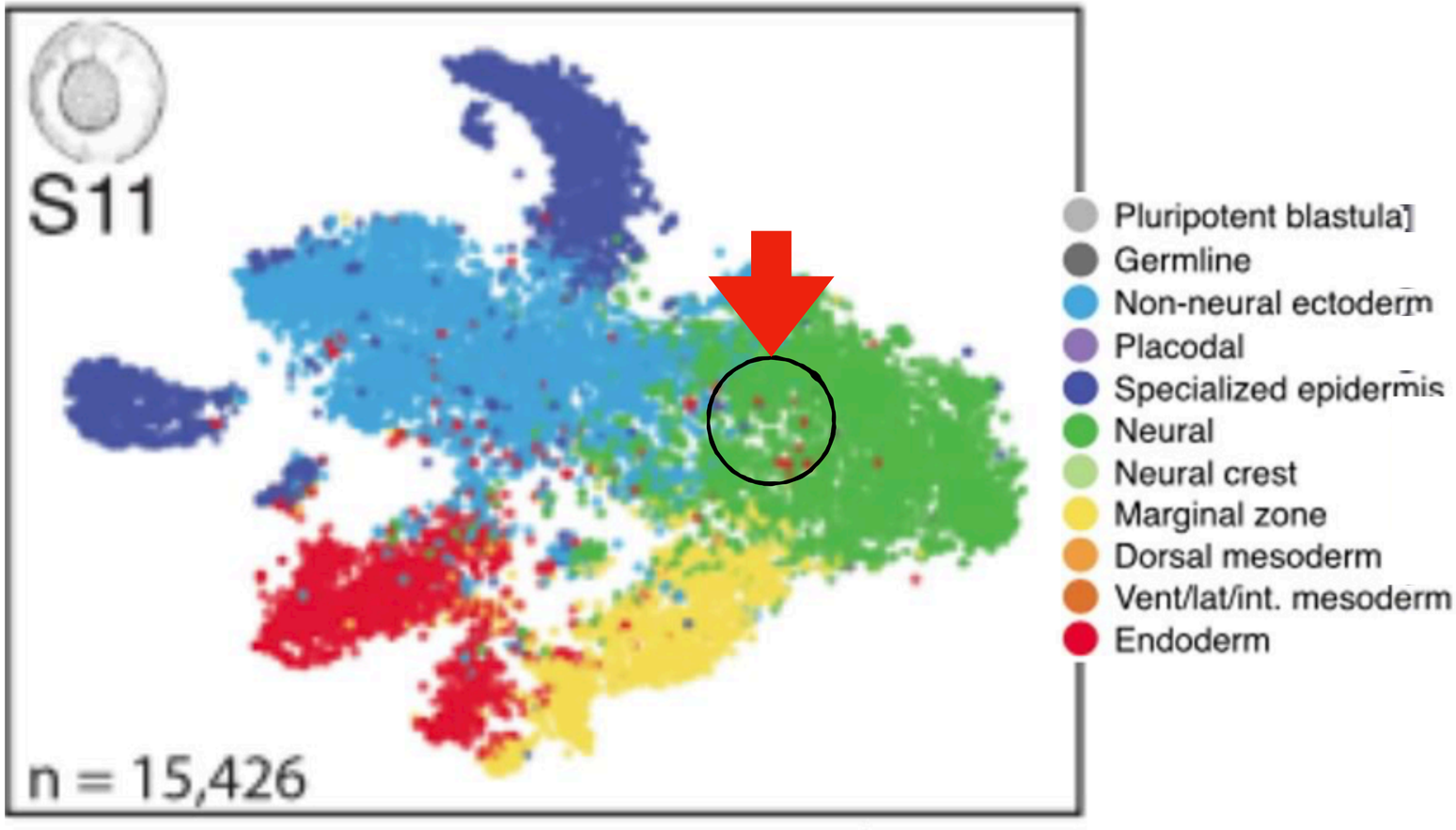

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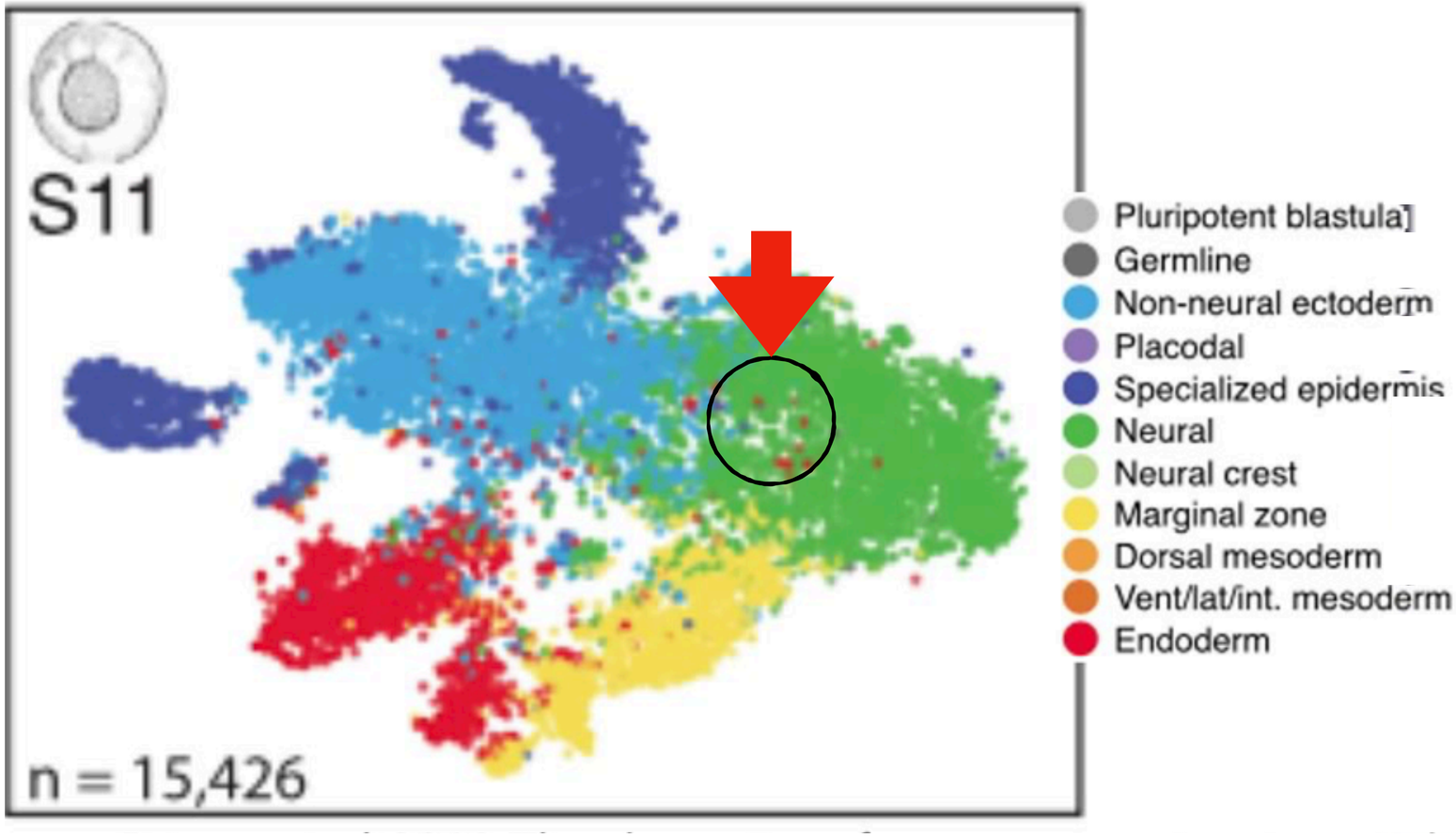

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Laboratory Animals (1990) **24**, 71–77

A third component causing random variability beside environment and genotype. A reason for the limited success of a 30 year long effort to standardize laboratory animals?

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Kyle Honegger and Benjamin de Bivort

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→ unpredictable variation can be useful, keeps others guessing

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My first act of free will is to believe in free will

- William James, 1842-1910 pragmatist

thanks!