

**1/ What is evolution from an  
engineering perspective?**

**2/ How to use & change evolution?**

**Week - 5**

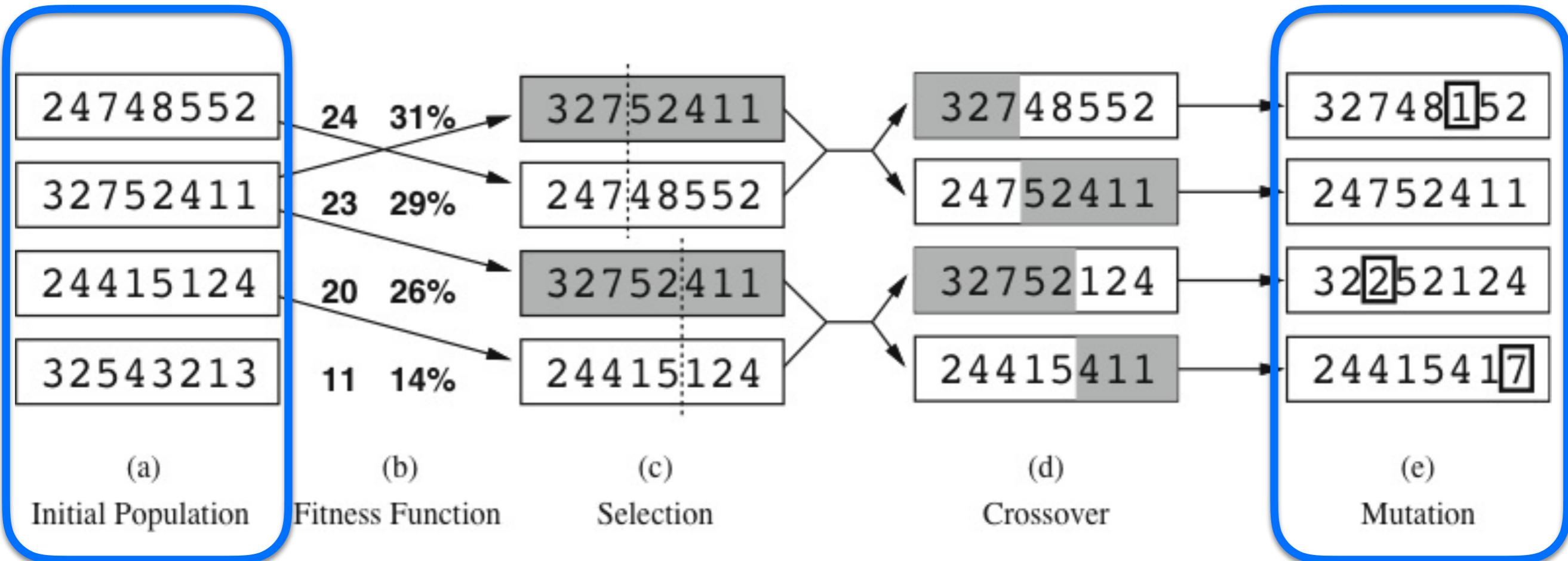
# Implication/Perspective

**Biology is a massively parallel chemical computer**

**and life (living matter) is the ongoing result of those calculations**

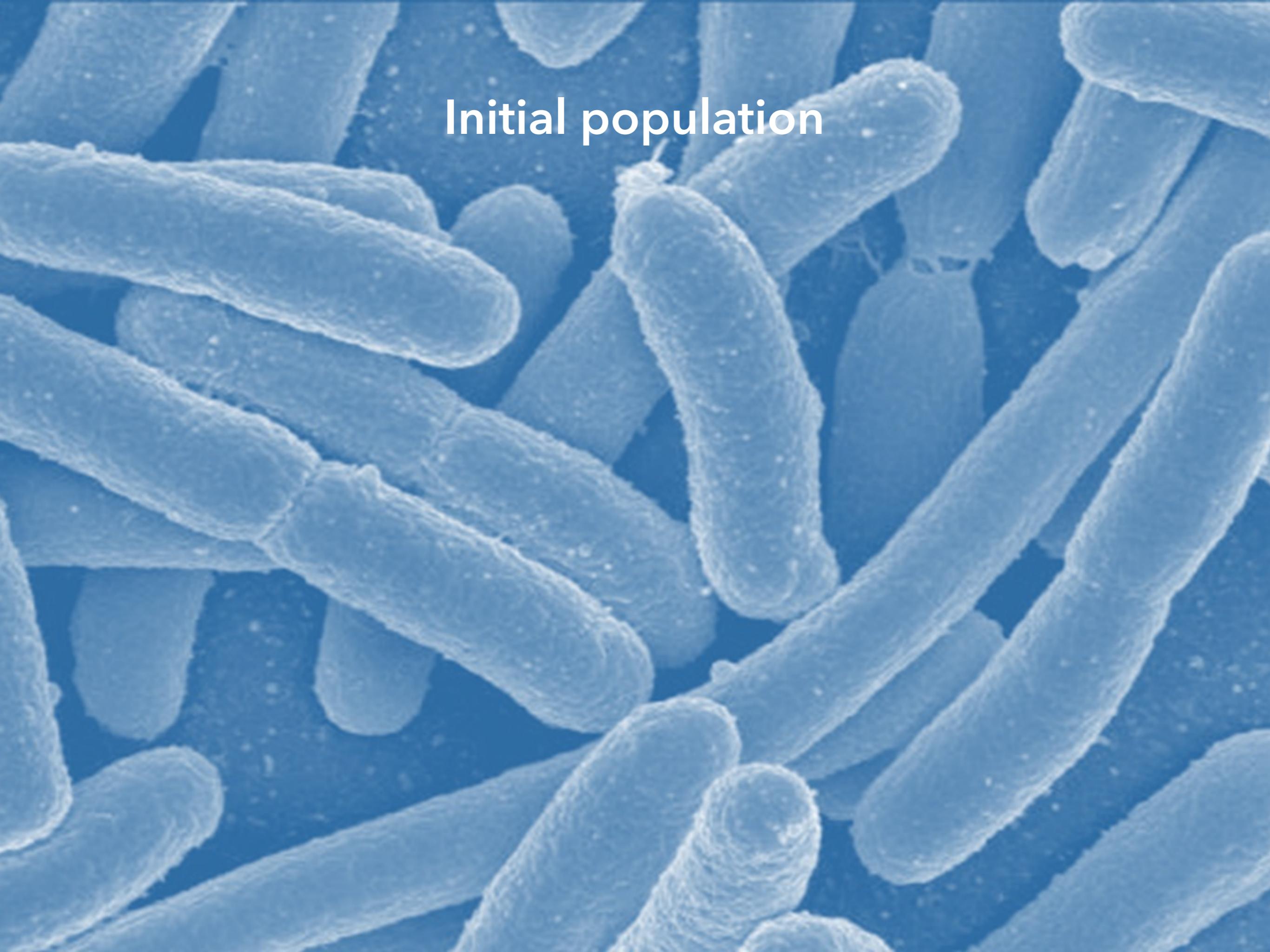
***Now - how does it actually work, and how can you use it?***

# Evolutionary / Genetic algorithms

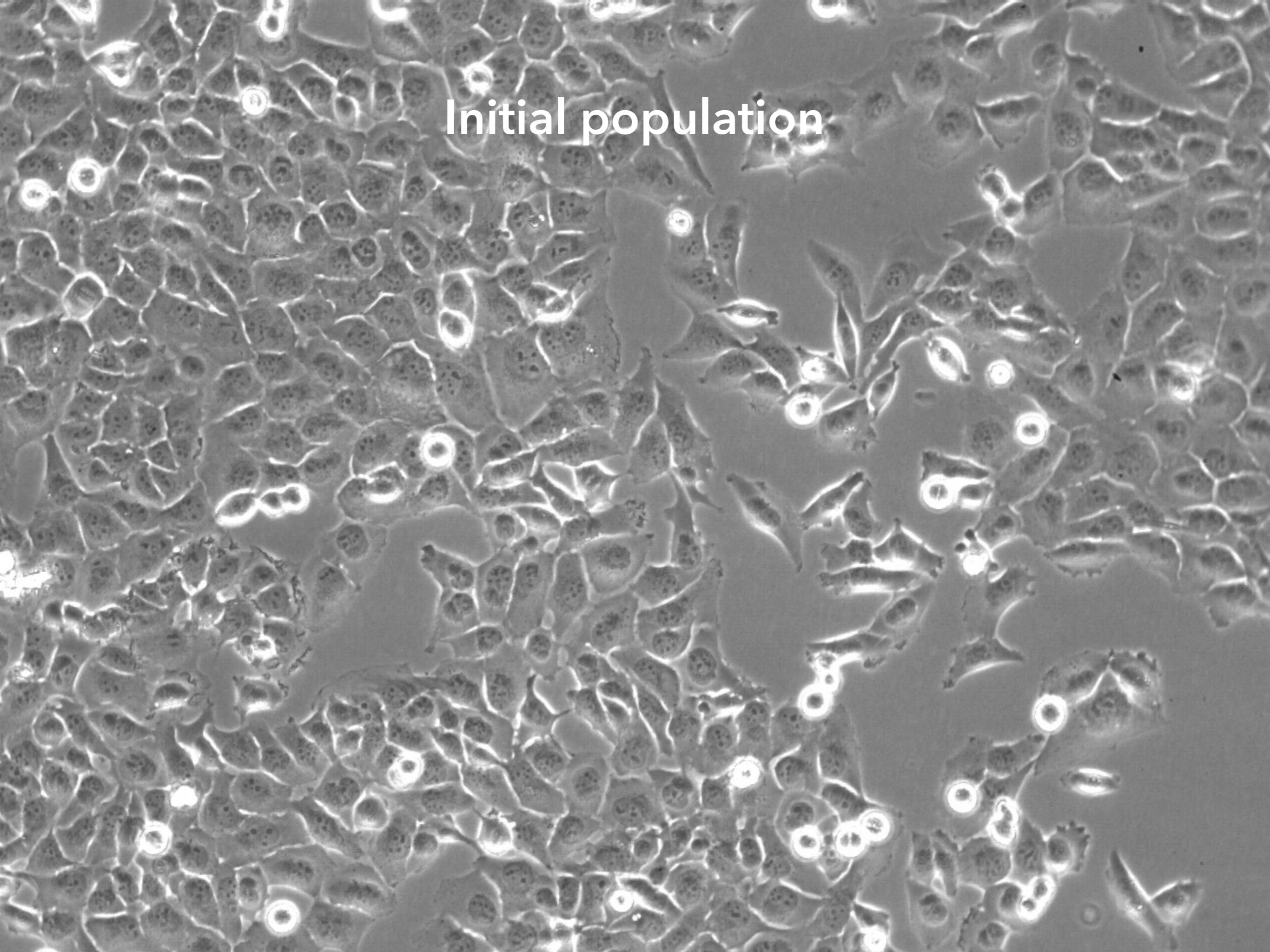


**There is nothing (inherently) biological about  
Evolutionary / Genetic algorithms.**

They are an exceptionally powerful set of tools for NASA,  
electrical engineers, nature, ...

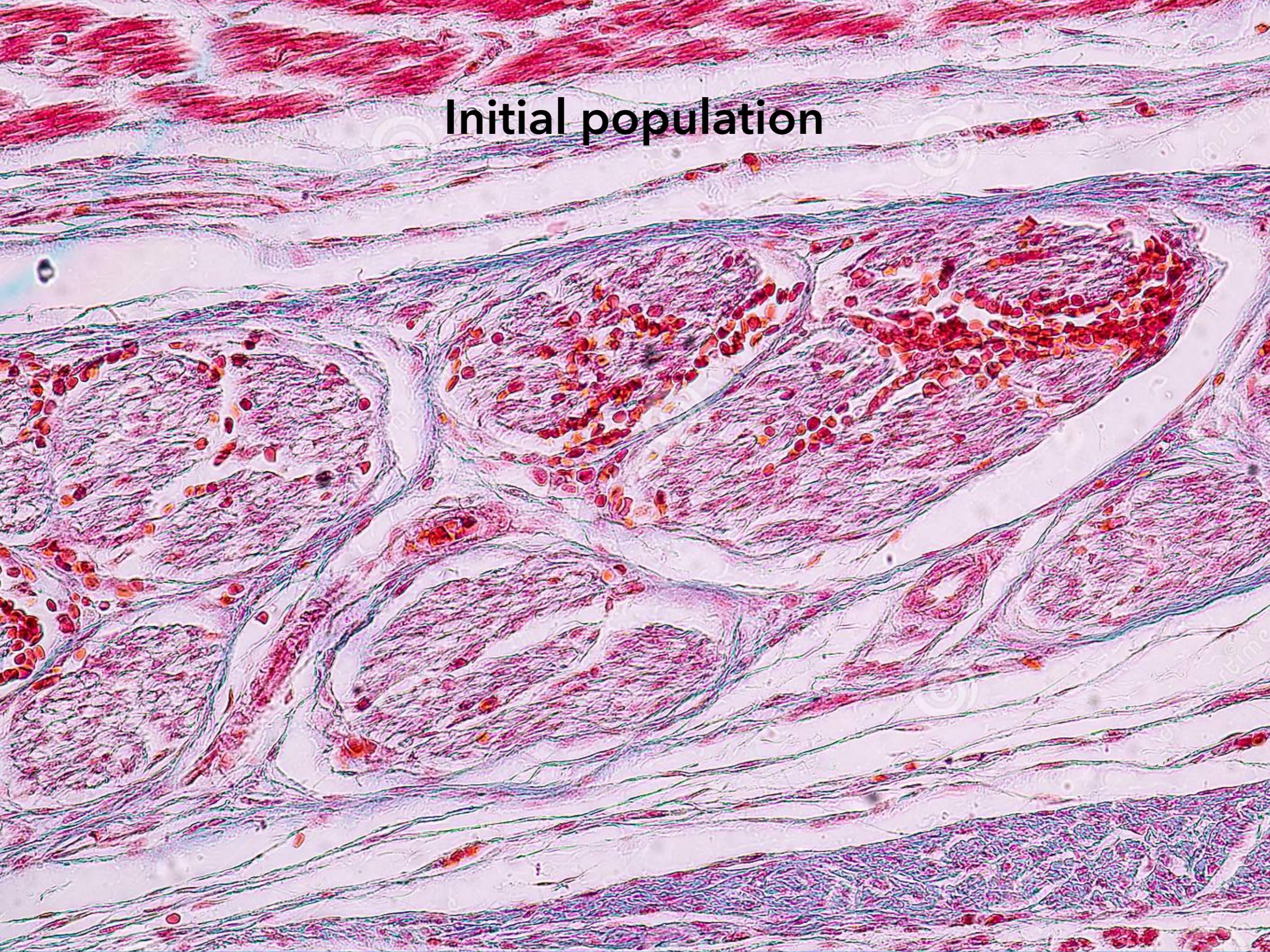
A scanning electron micrograph (SEM) showing a dense population of rod-shaped bacteria. The cells are elongated and slightly curved, with a textured surface. They are densely packed, filling the frame.

Initial population

A grayscale micrograph showing a dense, confluent population of cells. The cells are rounded and have distinct, irregular boundaries. Some cells contain small, dark, circular nuclei. The overall texture is somewhat mottled and lacks a clear, organized pattern.

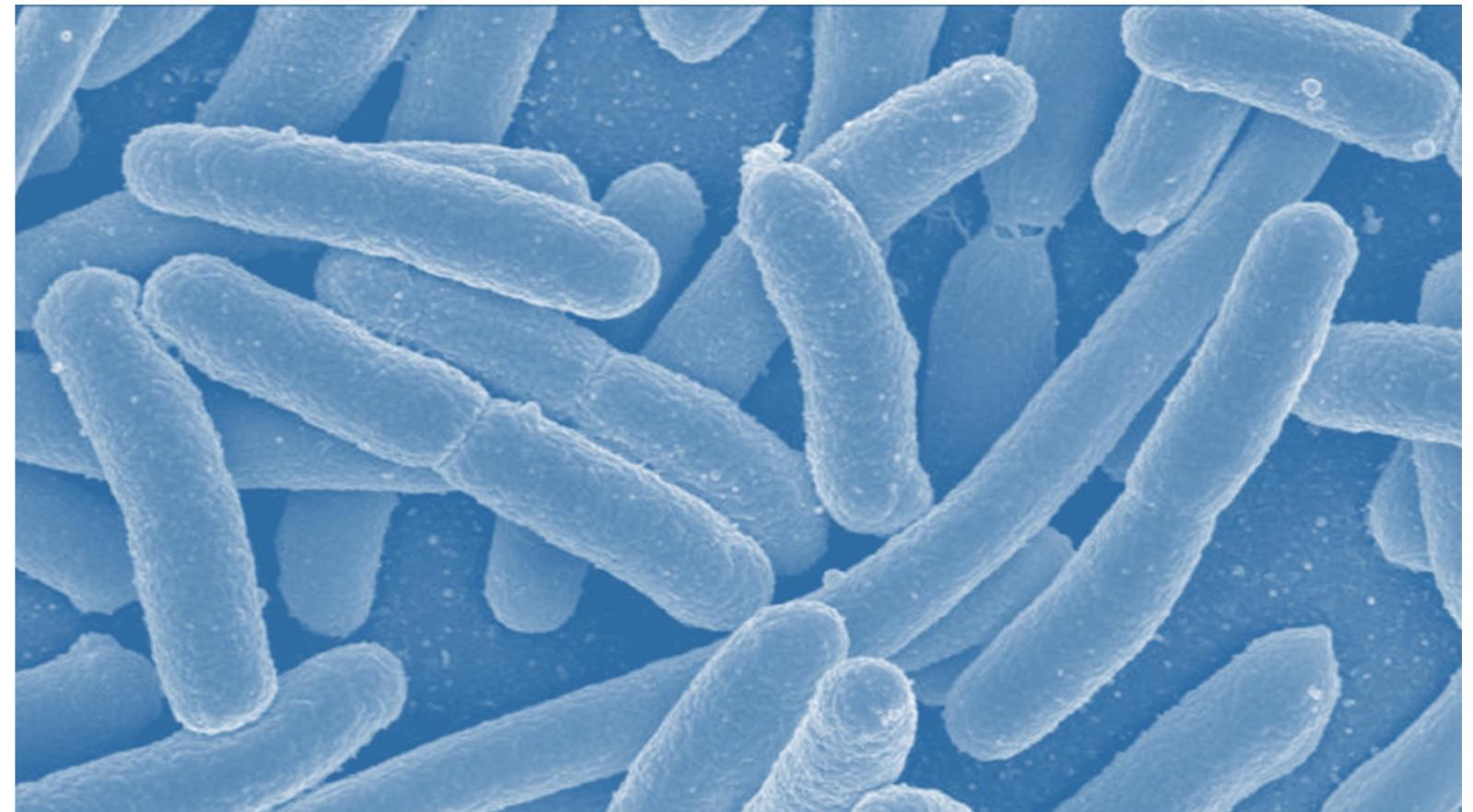
Initial population

Initial population



## Initial population

Each living cell has a genome, and those genomes are all unique\*



*\*Wait - all the cells in my body came from one cell, correct? How is that possible?*

# Genome to genome variation

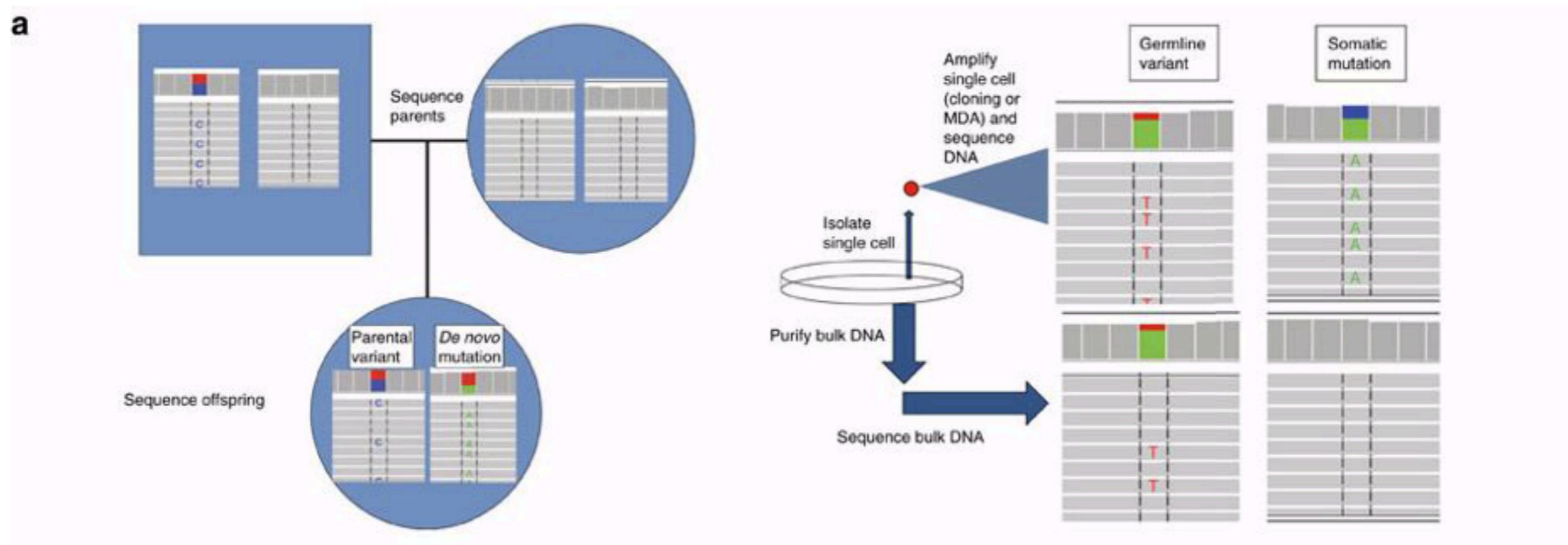
*It is (generally) impossible to copy physical objects with perfect fidelity - somehow, somewhere, mistakes will be made...*

The human [germline](#) mutation rate is approximately  $10^{-9}$  per [basepair](#) per year.

Let's clarify that...

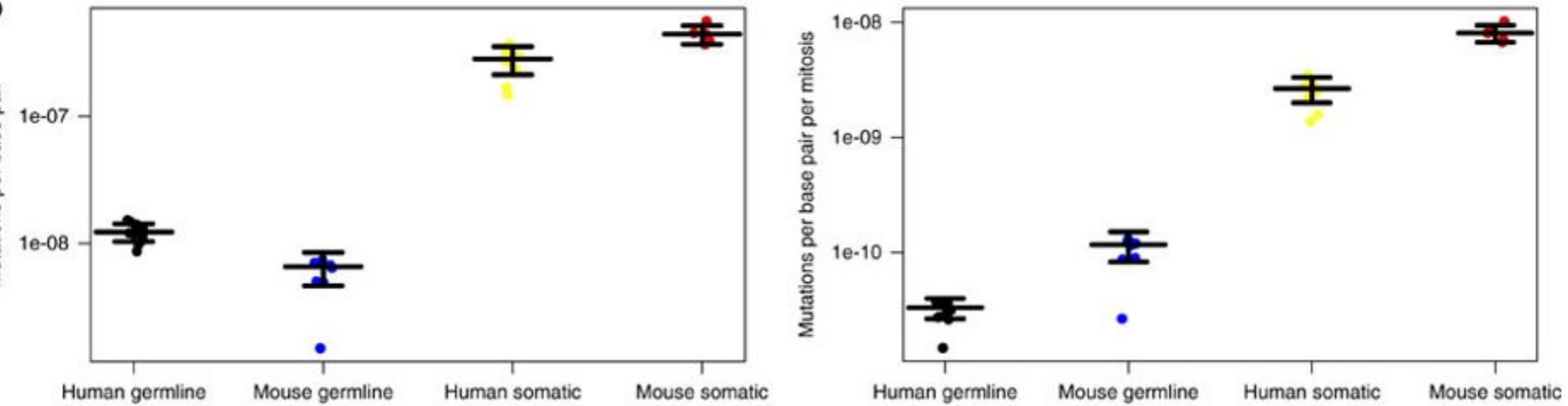
# Figure 1 : Direct comparison of somatic and germline mutation rates by high-throughput sequencing: experimental design and results.

From: [Differences between germline and somatic mutation rates in humans and mice](#)



# Every cell is (slightly) unique

b



Every time a human germ cell divides ('mitosis'), there are 0.1 mistakes. So for every ten divisions, one base changes. *This is remarkable molecular fidelity!*

*Every time a human somatic cell divides, there are 10 mistakes. You are a dynamic campsite of 10 trillion cells ( $10^{12}$  or  $2^{37!}$ ). So for a typical somatic cell, it's 37 divisions away from the fertilized egg = we expect 370 random errors compared to the egg.*

Or, in simple terms, each of the cells in your body is genetically (slightly) unique

# Every cell is (slightly) unique

Or, in simple terms, each of the cells in your body is genetically (slightly) unique.

And every cell, in every plant, and in every microbe, is every so slightly different.

Mind blowing calculation - typical genome size is millions to billions of bases - and  $10^6\text{-}10^9$  factorial is a COLOSSAL NUMBER! (That means that collisions in genome space will be rare)

Fun thought: With single cell sequencing, it should theoretically\* be possible to figure out the precise molecular history of every single living cell on this planet, and how they are all related - but that does not work in practice - why not?

# Every cell is (slightly) unique

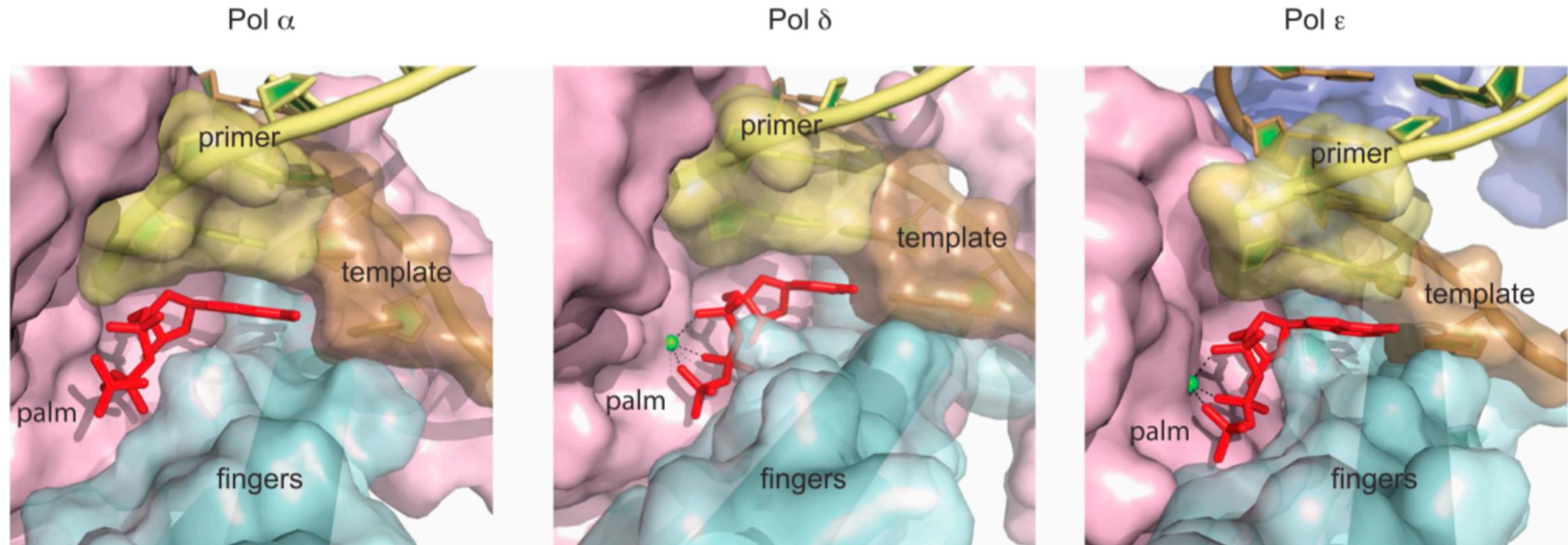
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What is the chemical origin of those differences?

# Chemical/thermodynamic origin of errors

Before we dig into where the errors are coming from, note that the presence of errors is not really that remarkable- the remarkable thing is that there are so few!



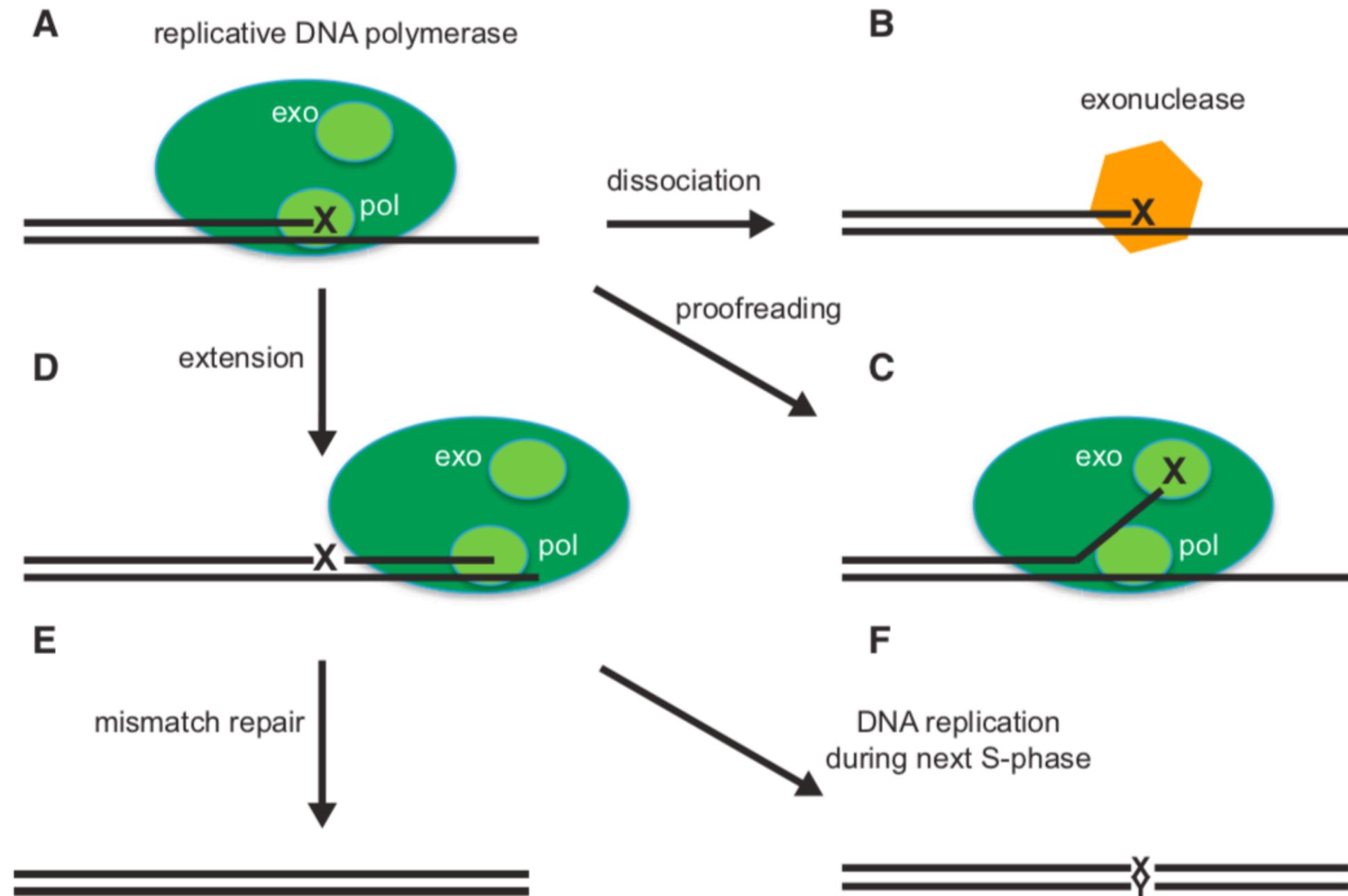
**Figure 1. Selection of a Correct Nucleotide**

The incoming nucleotide is stabilized by interactions in a tight pocket that is formed by the palm domain, fingers domain, template base, and primer base. The three structures are surface representations of Pol  $\alpha$  (PDB: 4FYD), Pol  $\delta$  (PDB: 3IAY), and Pol  $\epsilon$  (PDB: 4M8O) together with DNA and the incoming nucleotide.

The business end of DNA polymerases - they match shapes

# Chemical/thermodynamic origin of errors

And if a mistake happens, the cell actively tries to spellcheck and autocorrect\*



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**Autocorrection in biology: how?**

**Dozens of processes - mismatch repair, base excision, etc.**

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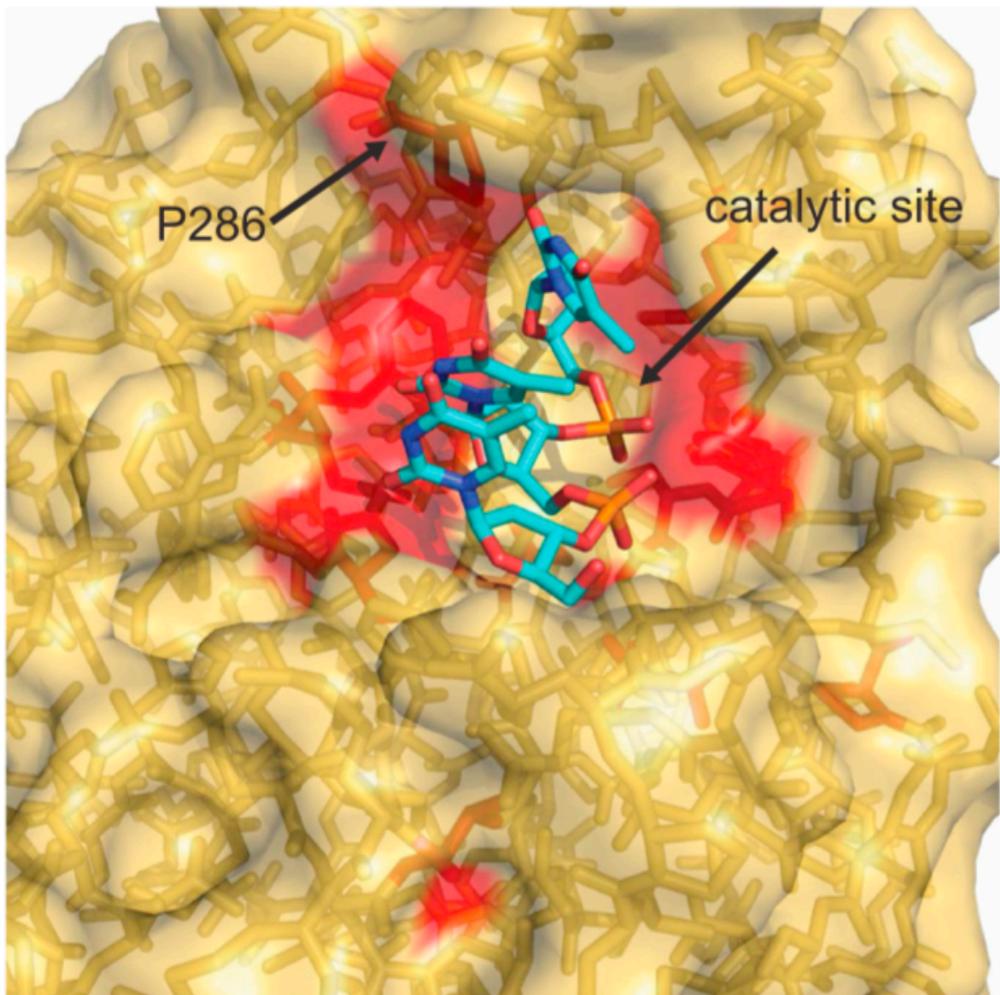
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IMAGINE - you are cell, and you grow more quickly than others, take over, and withstand drugs... what do you think will be molecular characteristics of those cells?

# Chemical/thermodynamic origin of errors

IMAGINE - you are cell, and you grow more quickly than others, take over, and withstand drugs... what do you think will be molecular characteristics of those cells?



How to be a good cancer cell - hack fidelity of DNA polymerase, and hack mismatch repair, and now you can play safecracker, evolve faster, and resist!

**Figure 5. Cancer-Associated Amino Acid Substitutions in Pol ε**

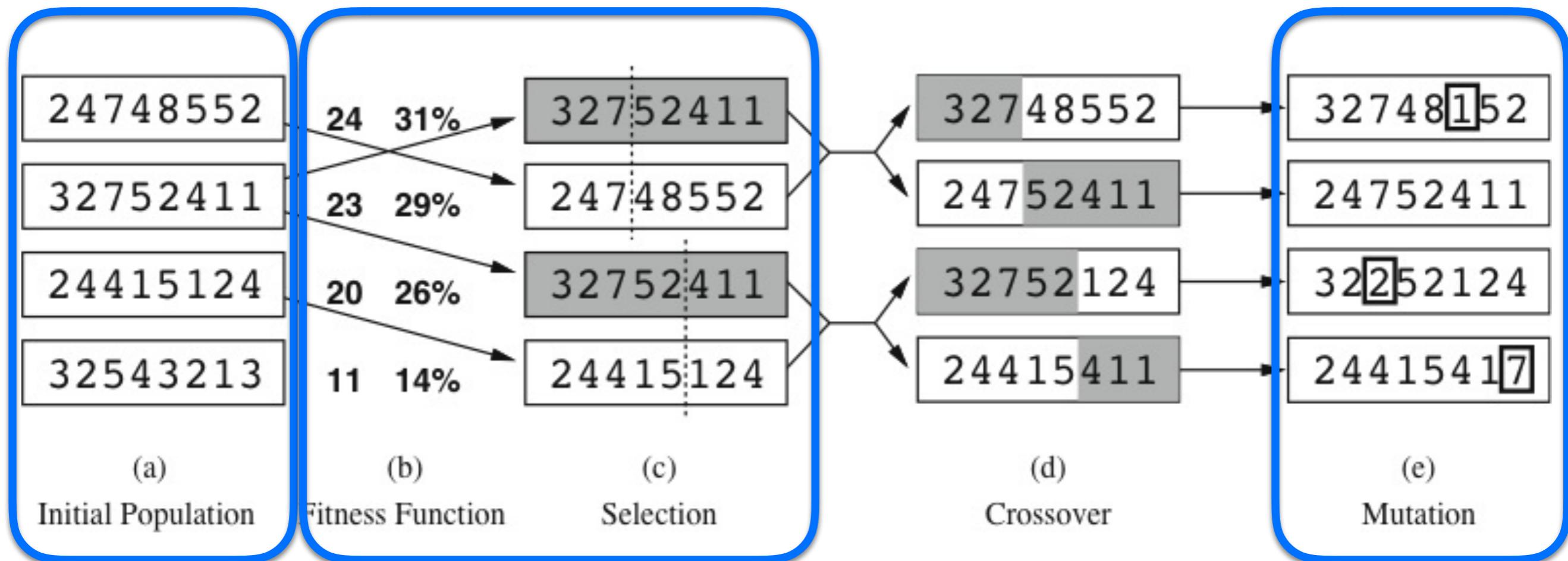
The majority of the cancer-associated amino acid substitutions in the exonuclease domain of Pol ε are found in central hydrophobic regions, the cavity where single-stranded DNA binds, and within the catalytic site. Cancer-associated amino acids are highlighted in red, with the given position of the most frequently reported P286 residue based on an alignment with yeast Pol ε. The single-stranded DNA from the structure of the exonuclease domain of T4 bacteriophage (PDB: 1NOY) (Wang et al., 1996) is modeled into the exonuclease domain in yeast Pol ε (PDB: 4M8O).

# Regrowth of cancer weeks or months later

*"Tumor cells employ numerous tactics—most of which remain unknown—to escape being killed by chemotherapeutic drugs, cytotoxic agents that indiscriminately kill both cancerous and noncancerous cells in the process of dividing.*

*Even these so-called molecular-targeted therapies are plagued by resistance problems, with rapid tumor shrinkage often followed by regrowth of the cancer weeks or months later."*

# Evolutionary / Genetic algorithms



Short note on selection

# Selection - anything the environment does to favor some cells over others

Examples - differences in...

predation risk (red mice in green fields vs. hawks),  
metabolites/growth rates, immune clearance rates,  
temperature, size, shape...

In the lab, good parameters to think about are temperature, growth media, or automated cell picking

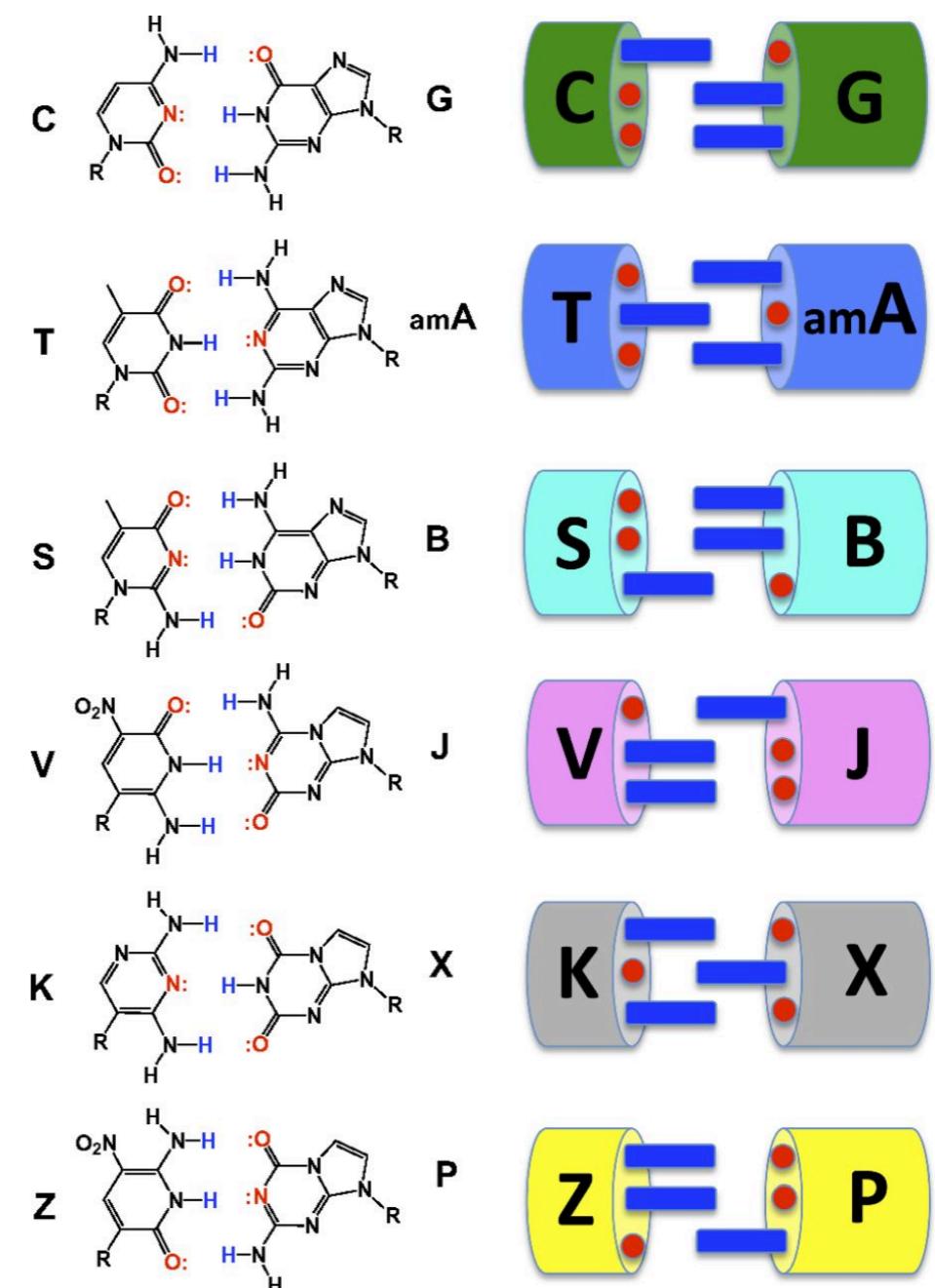
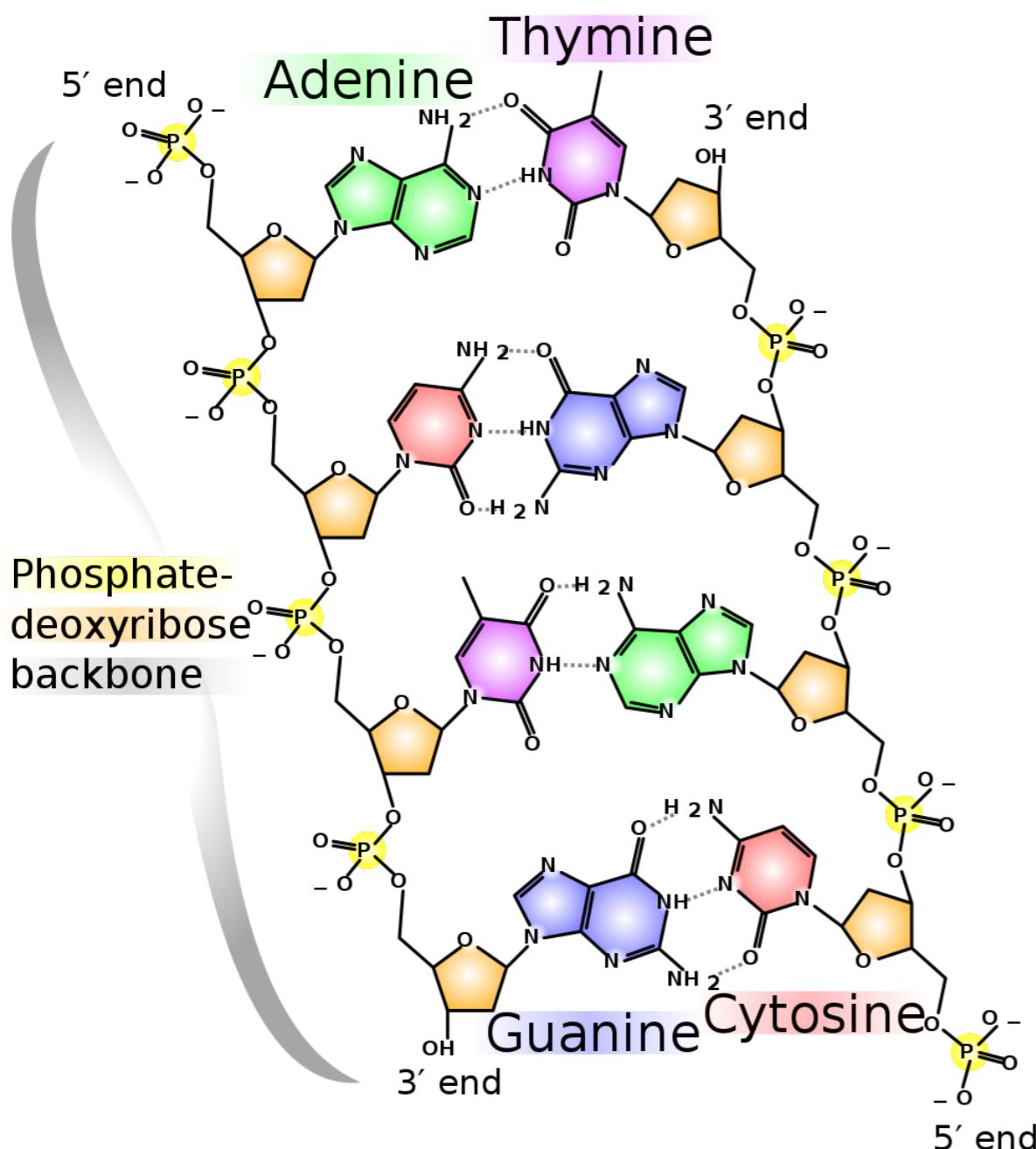


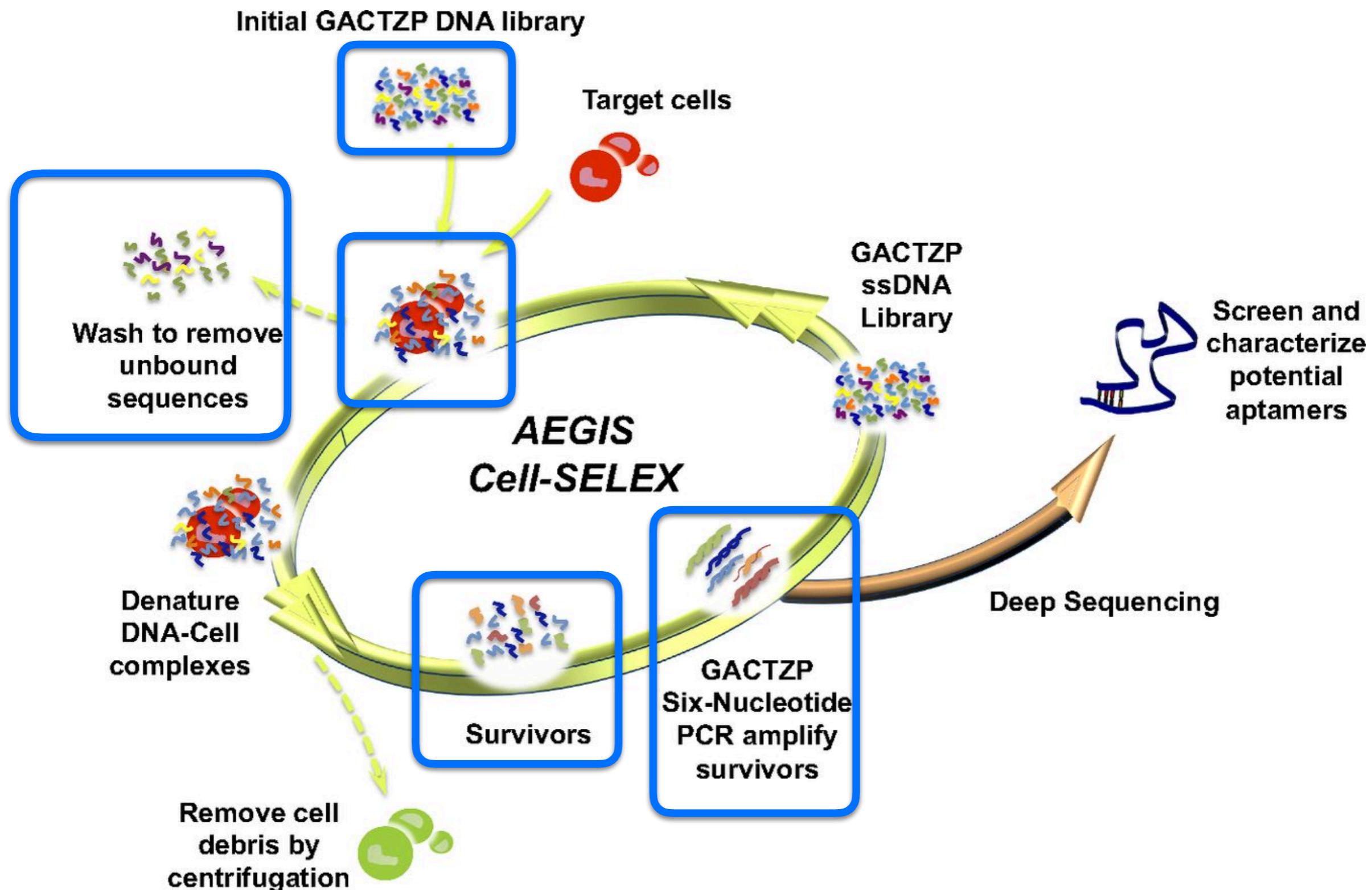
# In vitro selection with artificial expanded genetic information systems

Kwame Sefah, Zunyi Yang, Kevin M. Bradley, Shuichi Hoshika, Elizabeth Jiménez, Liqin Zhang, Guizhi Zhu, Savita Shanker, Fahong Yu, Diane Turek, Weihong Tan, and Steven A. Benner

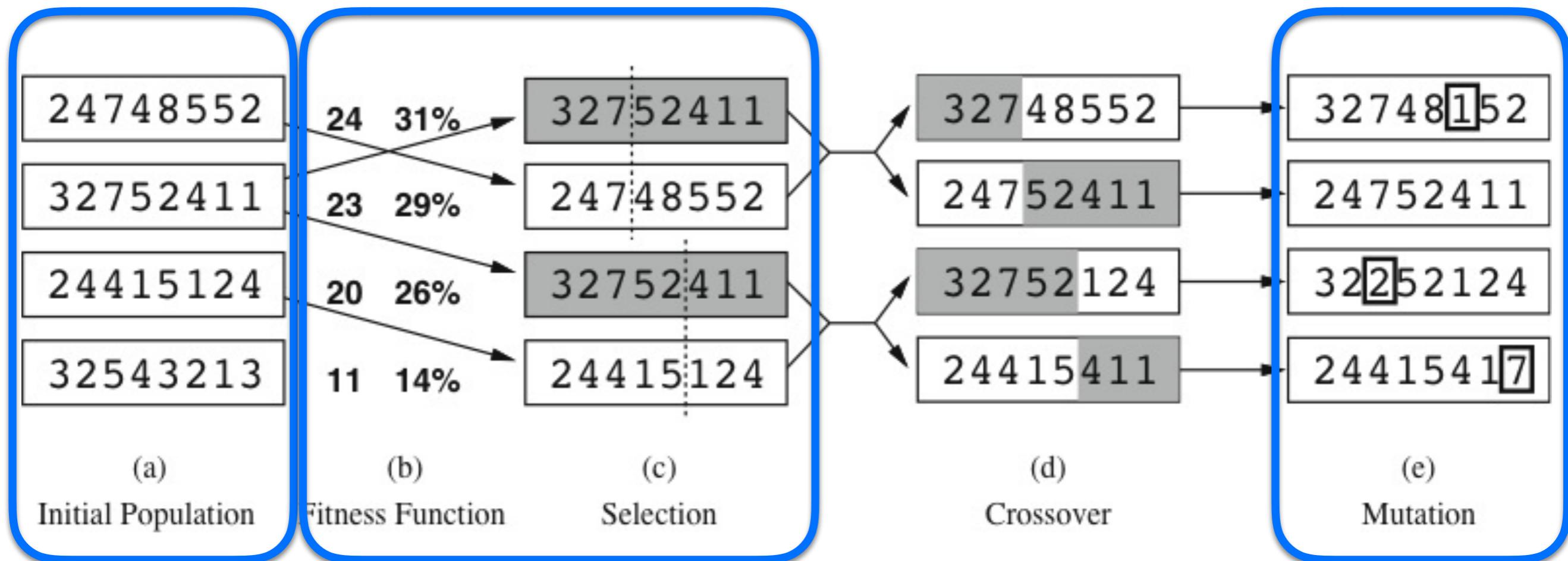
PNAS January 28, 2014 111 (4) 1449-1454; <https://doi.org/10.1073/pnas.1311778111>

Edited by Jack W. Szostak, Howard Hughes Medical Institute and Massachusetts General Hospital, Boston, MA, and approved November 19, 2013 (received for review July 2, 2013)





# Evolutionary / Genetic algorithms



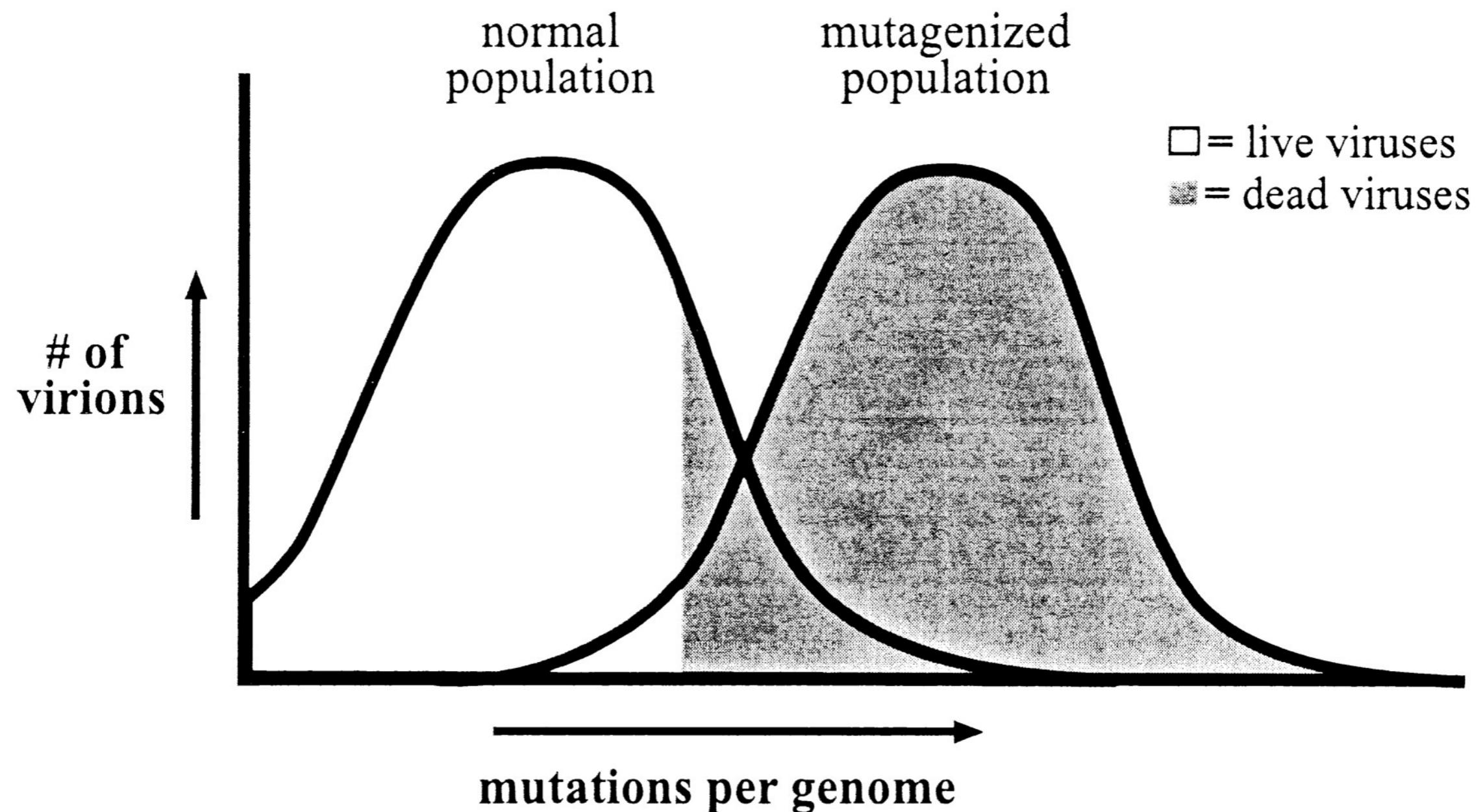
Too much of a good thing?

I've been implying that mutations are a good thing - can the basic algo runs faster but....

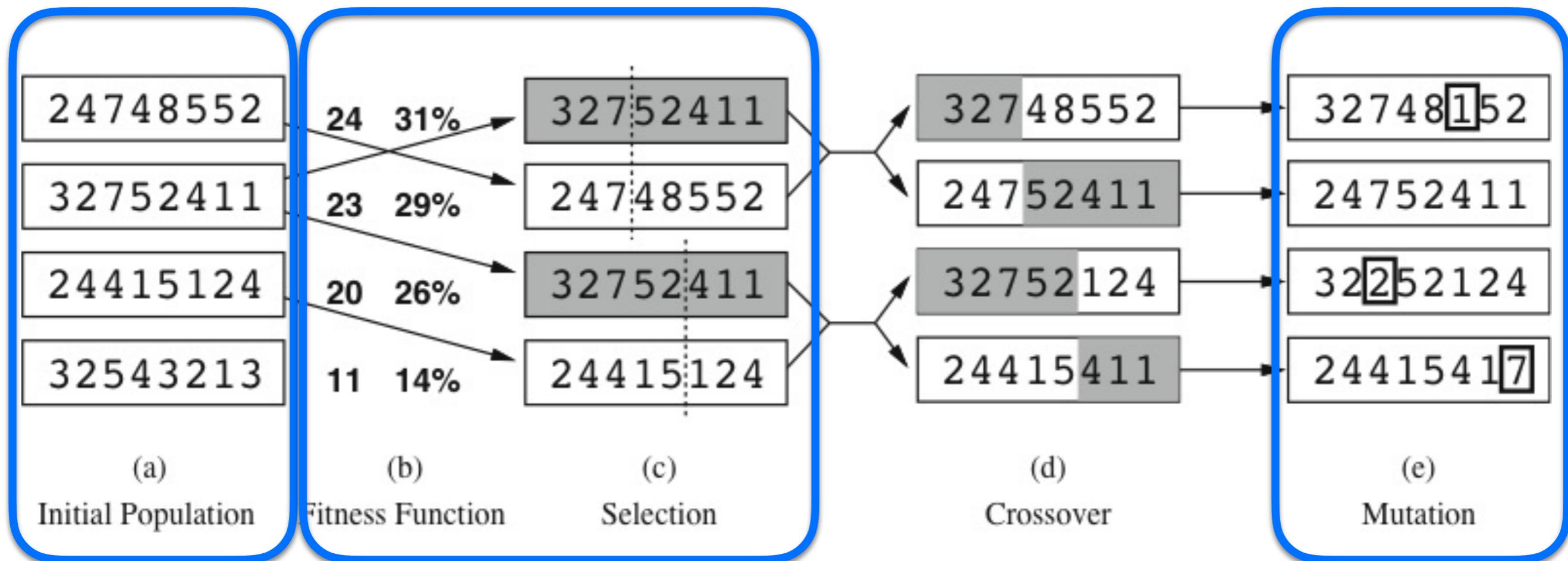
**What's the issue?**

I've been implying that mutations are a good thing - can the basic algo runs faster but....

**Error threshold** - a limiting value of error or mutation rate that must not be surpassed if the wild type is to be kept stable.



# Evolutionary / Genetic algorithms



A final thought...

# What does this actually look like in the real world?

RESEARCH ARTICLE

## Design and synthesis of a minimal bacterial genome

Clyde A. Hutchison III<sup>1,\*†</sup>, Ray-Yuan Chuang<sup>1,†‡</sup>, Vladimir N. Noskov<sup>1</sup>, Nacyra Assad-Garcia<sup>1</sup>, Thomas J. Deerinck<sup>2</sup>, Mark H. Ellisman<sup>2</sup>, John Gill<sup>3</sup>, Krishna Kannan<sup>3</sup>, Bogumil J. Karas<sup>1</sup>, Li Ma<sup>1</sup>, James F. Pelletier<sup>4,§</sup>, Zhi-Qing Qi<sup>3</sup>, R. Alexander Richter<sup>1</sup>, Elizabeth A. Strychalski<sup>4</sup>, Lijie Sun<sup>1,||</sup>, Yo Suzuki<sup>1</sup>, Billyana Tsvetanova<sup>3</sup>, Kim S. Wise<sup>1</sup>, Hamilton O. Smith<sup>1,3</sup>, John I. Glass<sup>1</sup>, Chuck Merryman<sup>1</sup>, Daniel G. Gibson<sup>1,3</sup>, J. Craig Venter<sup>1,3,\*</sup>

<sup>1</sup>J. Craig Venter Institute, La Jolla, CA 92037, USA.



(table S6). it became segments cell more helped to es.

## yields

G, we re-  
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duced ge-  
% reduc-  
e n-genes  
retained—

was then transplanted out of yeast to test for viability. Each of the eight reduced segments produced a viable transplant; however, segment 6 produced only a very small colony in the first 6 days. On further growth over the next 6 days, sectors of faster-growing cells developed (fig. S18). Several isolates of the faster-growing cells were sequenced and found to have destabilizing mutations in a transcription terminator that had been joined to an essential gene when the non-essential gene preceding it was deleted (figs. S19 and S21). Another mutation produced a consensus TATAAT box in front of the essential gene (fig. S20). This illustrates the potential for expression errors when genes are deleted, but it shows that these errors can sometimes be corrected by subsequent spontaneous mutation. Ultimately, we identified a promoter that had been overlooked and erringly deleted. When this region was resupplied in accordance with the design rules, cells containing designed segment 6 grew rapidly. This solution was incorporated in later designs.

# **Evolutionary / Genetic algorithms**

**Whatever you do - this will be happening in the background, anyway.**

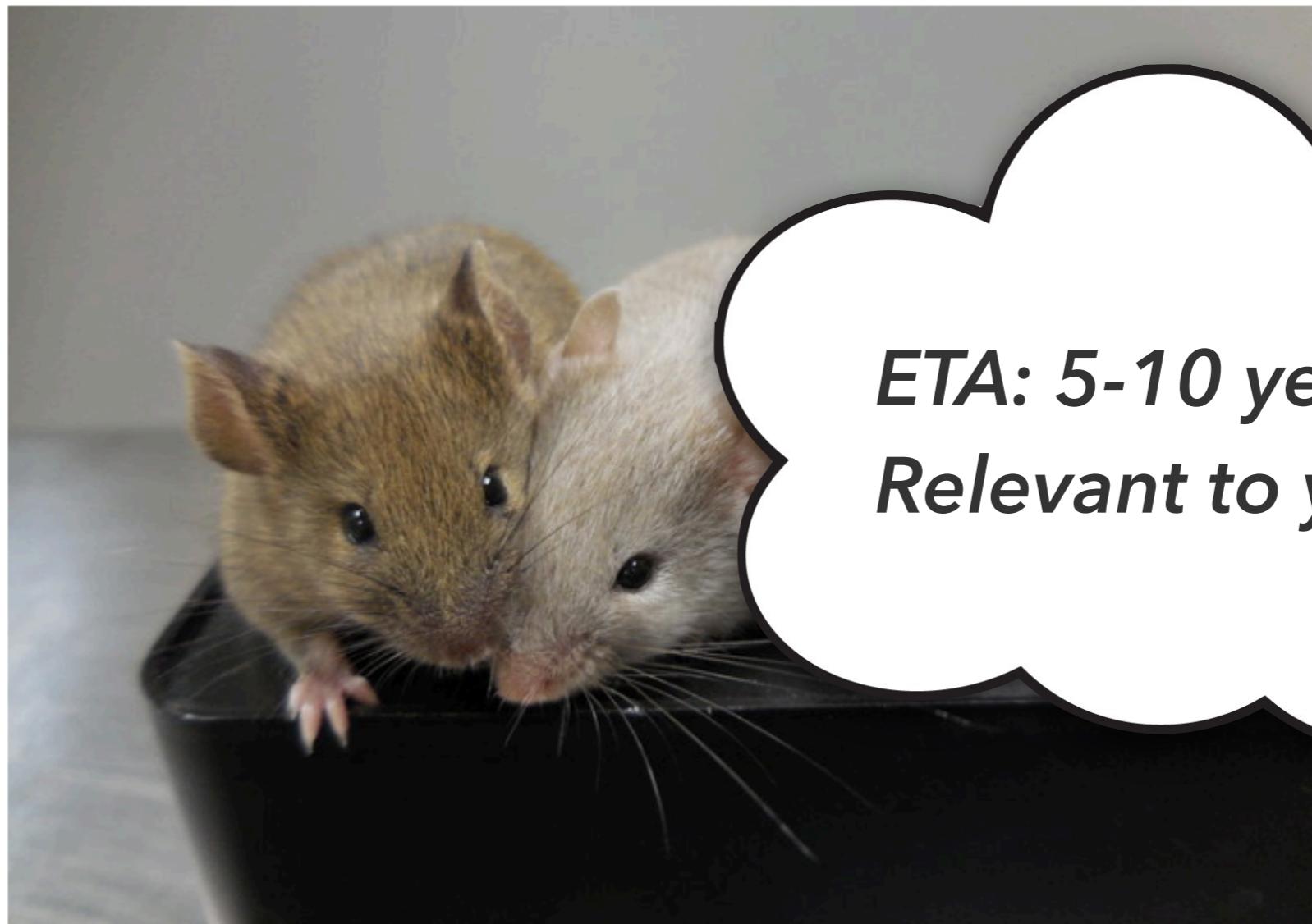


# News flash - Human Reproduction

HEALTH

## ***Babies From Skin Cells? Prospect Is Unsettling to Some Experts***

By TAMAR LEWIN MAY 16, 2017



***ETA: 5-10 years  
Relevant to you!***

Mice that were created from tail cells. Researchers in Japan made viable eggs from the skin cells of adult female mice, and produced embryos that were implanted into female mice, who then gave birth to healthy babies. Katsuhiko Hayashi

*"I.V.G. may raise the specter of 'embryo farming' on a scale currently unimagined, which might exacerbate concerns about the devaluation of human life,"*

*Dr. Eli Y. Adashi, a medical science professor at Brown; Glenn Cohen, a Harvard Law School professor; Dr. George Q. Daley, dean of Harvard Medical School, wrote in the journal [Science Translational Medicine](#).*

*The process strikes some people as inherently repugnant.*

*"There is a yuck factor here," said Arthur Caplan, a bioethicist at New York University. "It strikes many people as intuitively yucky to have three parents, or to make a baby without starting from an egg and sperm. But then again, it used to be that people thought blood transfusions were yucky, or putting pig valves in human hearts."*

*Whatever the social norms, there are questions about the wisdom of tinkering with basic biological processes. And there is general agreement that reproductive technology is progressing faster than consideration of the legal and ethical questions it raises.*

*"We have come to realize that scientific breakthroughs don't always mean we have the ability to think them through," Dr. Adashi said. "It's a challenge for us as a society to figure out how to have the conversation before we actually do it. It's good to be having the conversation before we actually do it."*

**Where is the US right now  
are these conversations  
taking place?**



# News flash - Polygenic Scores

## **Genetic Associations with Mathematics Tracking and Persistence in Secondary School**

K. Paige Harden, Ph.D.\*<sup>1</sup> and Benjamin W. Domingue, Ph.D.\*<sup>2</sup>

Daniel W. Belsky, Ph.D.<sup>3</sup>

Jason D. Boardman, Ph.D.<sup>4</sup>

Robert Crosnoe, Ph.D.<sup>5</sup>

Margherita Malanchini, Ph.D.<sup>1</sup>

Michel Nivard, Ph.D.<sup>6</sup>

Elliot M. Tucker-Drob, Ph.D.<sup>1</sup>

Kathleen Mullan Harris, Ph.D.<sup>7</sup>

\*The first two authors contributed equally.

<sup>1</sup>Department of Psychology and Population Research Center, University of Texas at Austin

<sup>2</sup>Graduate School of Education, Stanford University

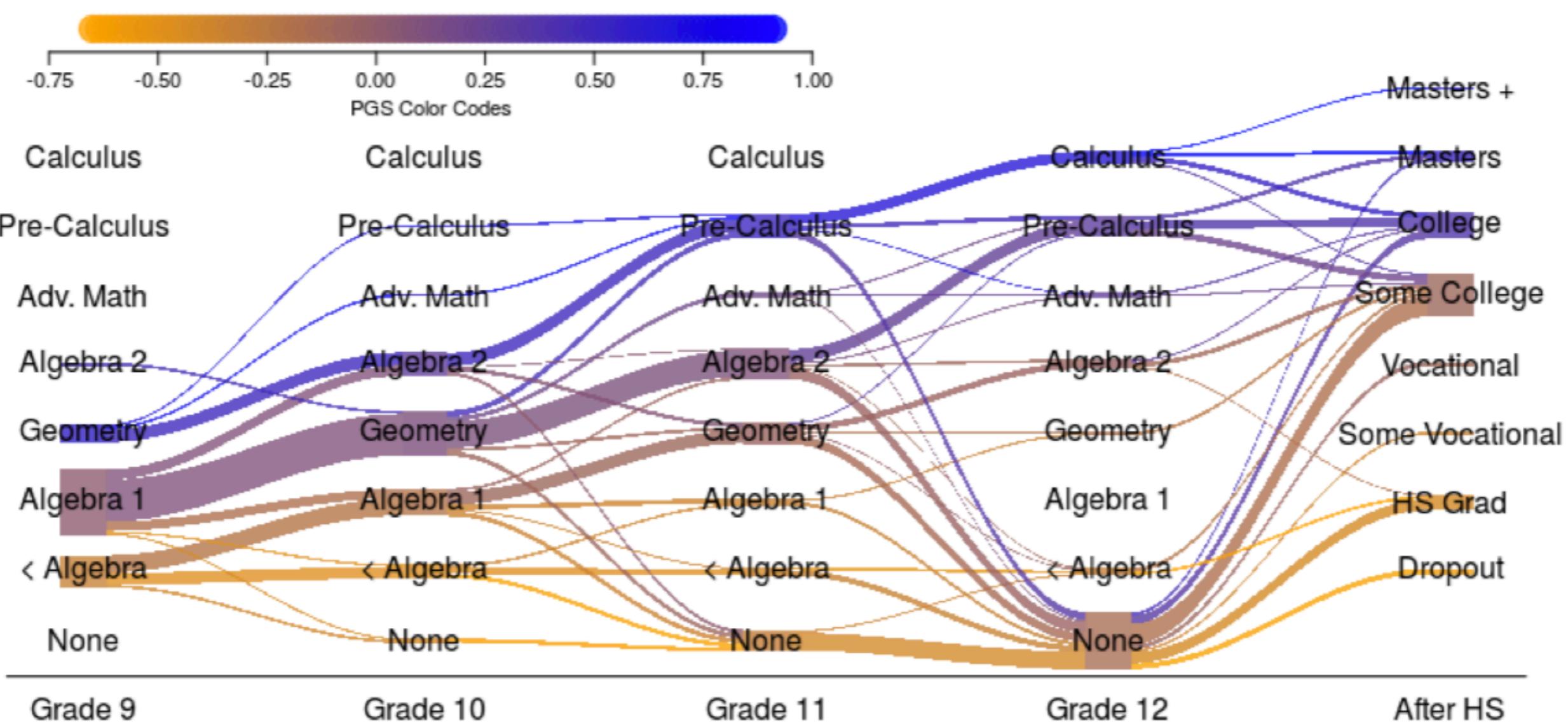


# News flash - Polygenic Scores

Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature Genetics* **50**, 1112–1121 (2018).

*Here we conducted a large-scale genetic association analysis of educational attainment in a sample of approximately 1.1 million individuals and identify 1,271 independent genome-wide-significant SNPs. For the SNPs taken together, we found evidence of heterogeneous effects across environments. The SNPs implicate genes involved in brain-development processes and neuron-to-neuron communication. In a separate analysis of the X chromosome, we identify 10 independent genome-wide-significant SNPs and estimate a SNP heritability of around 0.3% in both men and women, consistent with partial dosage compensation. A joint (multi-phenotype) analysis of educational attainment and three related cognitive phenotypes generates polygenic scores that explain 11–13% of the variance in educational attainment and 7–10% of the variance in cognitive performance. This prediction accuracy substantially increases the utility of polygenic scores as tools in research.*

**Figure 3. Student DNA can be used to visualize the flow of students through the high school math curriculum.** Columns represent year of secondary school; rows represent mathematics course sequence ranging from least to most advanced. Width of the rivers connecting columns proportional to number of students. Shading of rivers represents the average education polygenic score for students in a particular course in a particular year, ranging from low (orange) to high (blue).



# Why am I bringing this up?

This is precisely the sort of thing where we need more debate and thought

Many possible positive and negative implications

Insurance, education, opportunities, health, equality, discrimination

Everyone of us has at least one problem lurking in our genomes - and we all need to be concerned as a society, what we want that society to look like

PS - Just because something is published in the scientific literature does not guarantee it's true.