Overview,
Synthetic Biology

Drew Endy
Stanford Bioengineering
The BioBricks Foundation

9 July 2009

The U.S. National Academies
The Organization for Economic Cooperation and Development
The Royal Society

Overview,
Synthetic Biology

What & why is synthetic biology?

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What and why is synthetic biology?

The recent and ongoing interest in 'synthetic biology' is being driven by at least four different groups: biologists, chemists, 're-writers' and engineers. Briefly, for biologists, the ability to design and construct synthetic biological systems provides a direct and compelling method for testing our current understanding of natural biological systems[4,15]; disagreements between expected and observed system behaviour can serve to highlight the science that is worth doing. For chemists, biology is chemistry, and thus synthetic biology is an extension of synthetic chemistry; the ability to create novel molecules and molecular systems allows the development of useful diagnostic assays and drugs, expansion of genetically encoded functions, study of the origins of life, and so on[16]. For 're-writers', the designs of natural biological systems may not be optimized for human intentions (for example, scientific understanding, health and medicine); synthetic biology provides an opportunity to test the hypothesis that the genomes encoding natural biological systems can be 're-written', producing engineered surrogates that might usefully supplant some natural biological systems[11]. Finally, for engineers, biology is a technology; building upon past work in genetic engineering, synthetic biology seeks to combine a broad expansion of biotechnology applications with—as the focus of this article—an emphasis on the development of foundational technologies that make the design and construction of engineered biological systems easier.

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- *Natural Science*
- *Synthetic Science*
- *Re-Writers*
- *Engineers*

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- *Natural Science*
- *Synthetic Science*
- *Re-Writers*
- *Engineers*
- *Humanity!*

The nature of synthetic biology

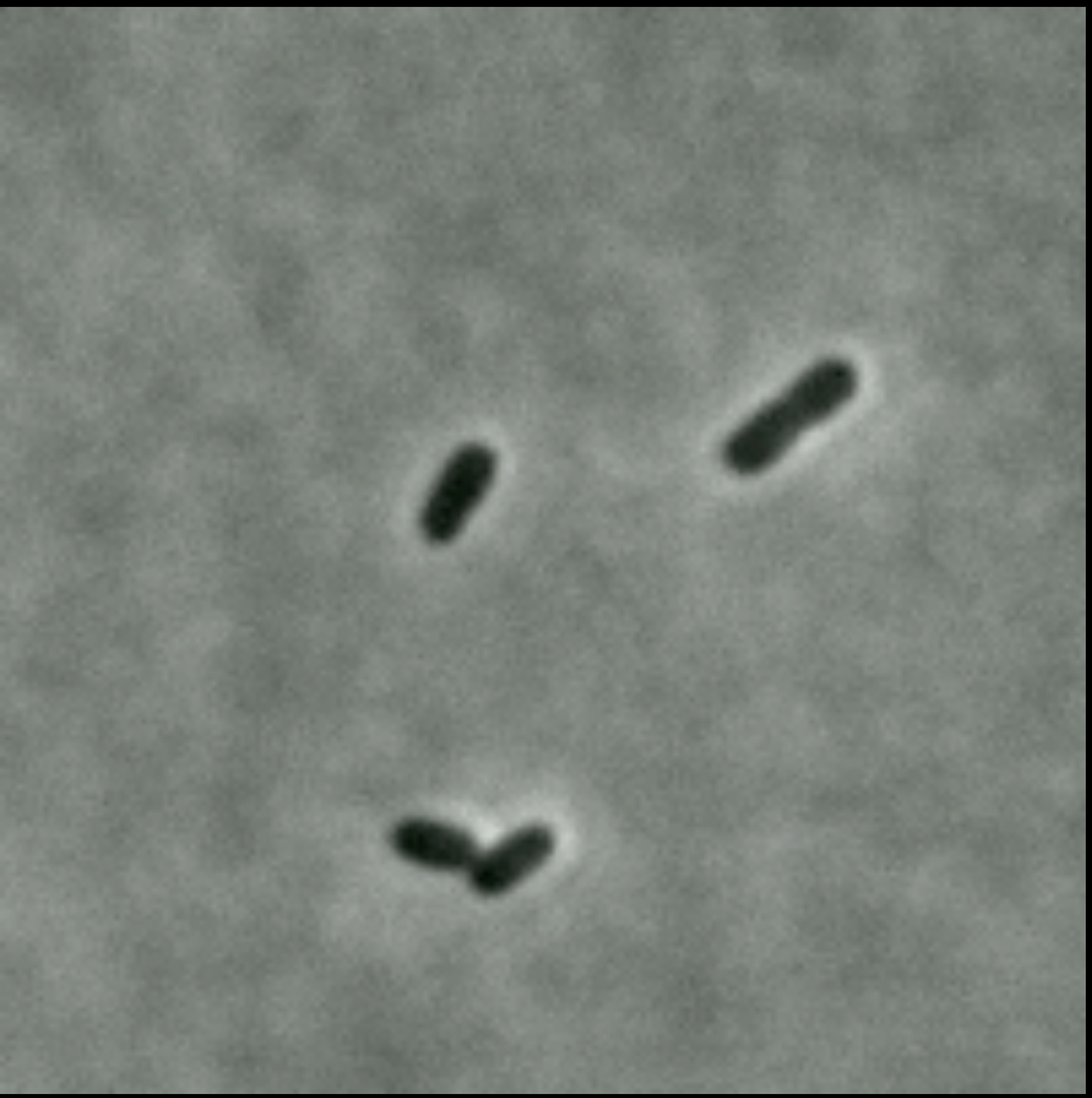
The nature of synthetic biology

http://www.cliquee.net/wp-content/uploads/2008/01/disassembly.jpg

The nature of synthetic biology

St-Pierre & Endy, PNAS USA (2008)

The nature of synthetic biology



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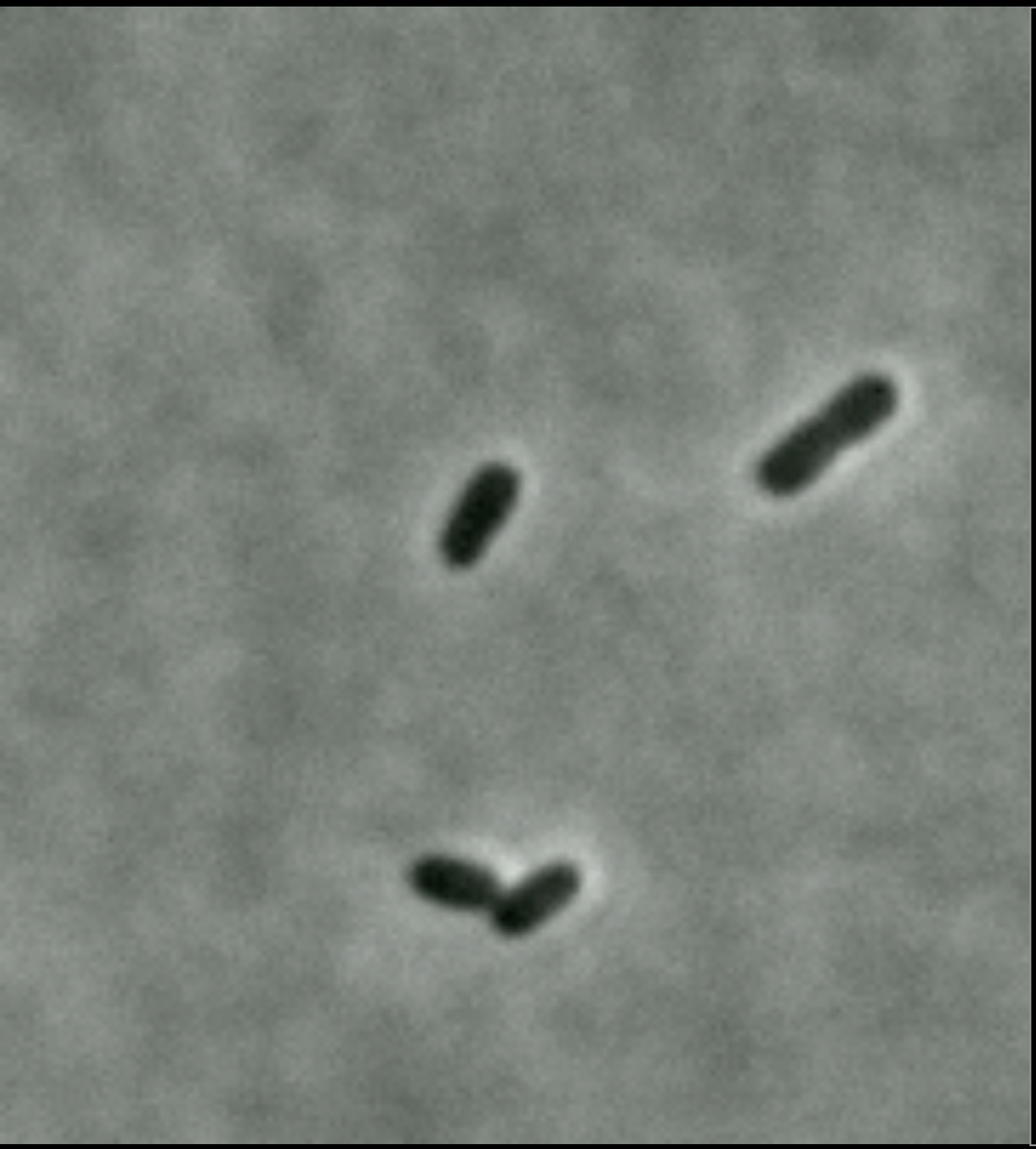

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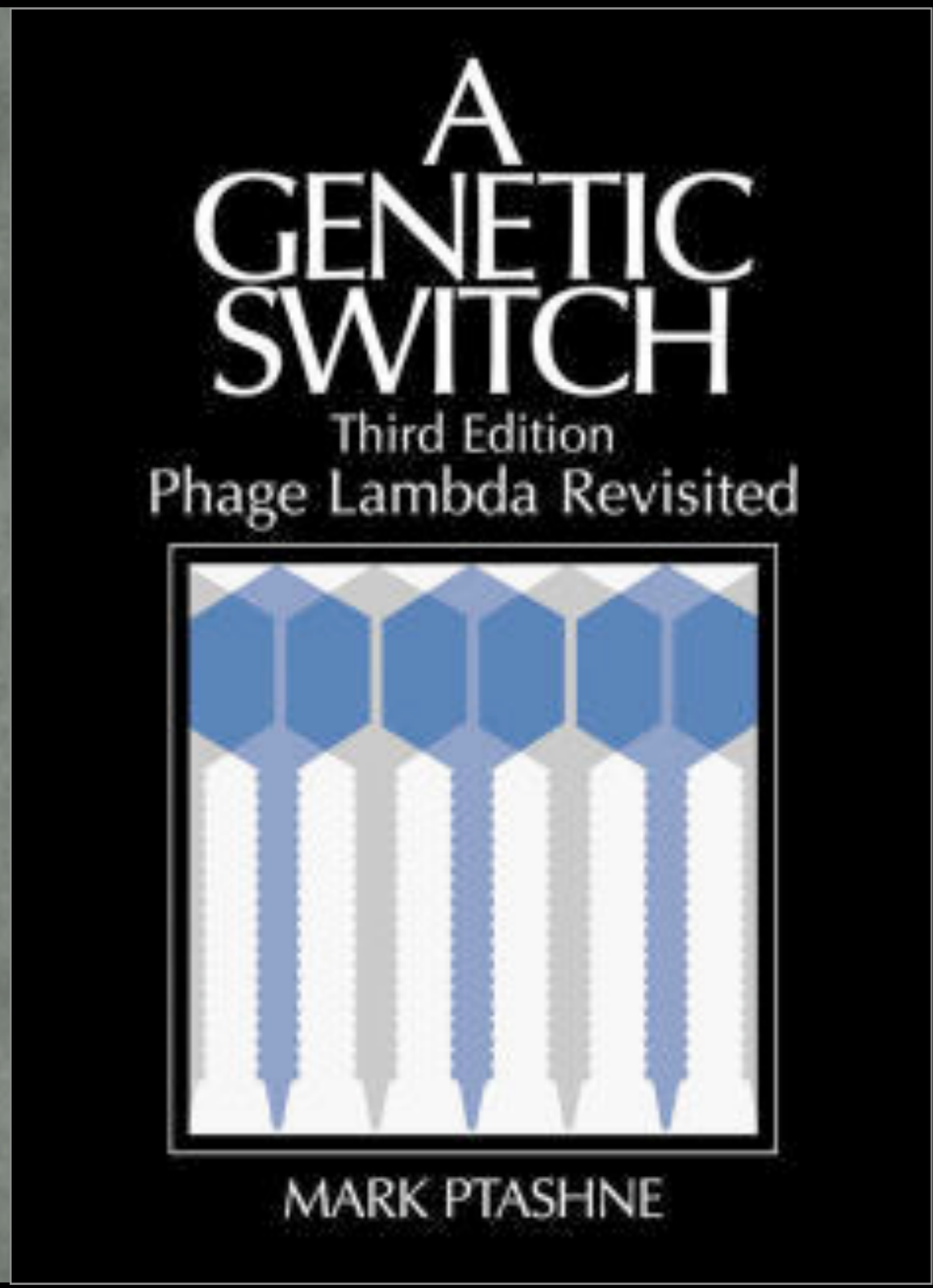

THE DECISION

Having described the two developmental pathways available to an infecting λ phage, we now must ask: what determines which pathway is taken? What factors drive the system toward lysis or lysogeny?

We do not have a complete understanding of these matters but we can construct a plausible scenario. Briefly put, the "decision" is effected by a single protein–CII.

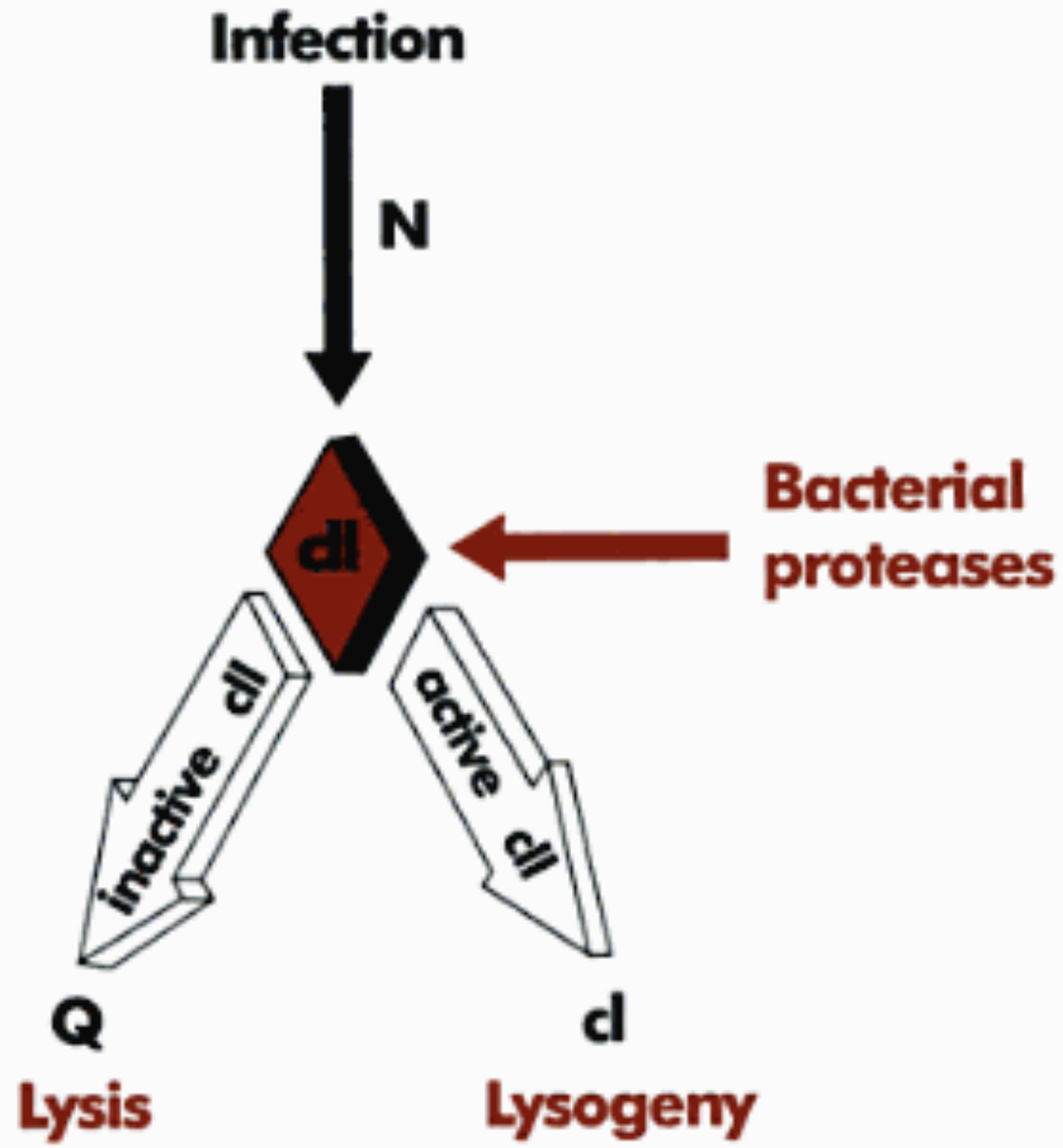

Figure 3.10. The lysis-lysogeny decision. Host proteases regulate the level of activity of CII protein. Although CIII protein is not shown here, the host factors may exert their effects by working on CIII, which protects CII. It is likely that other host proteins regulate translation of the CII mRNA as well.

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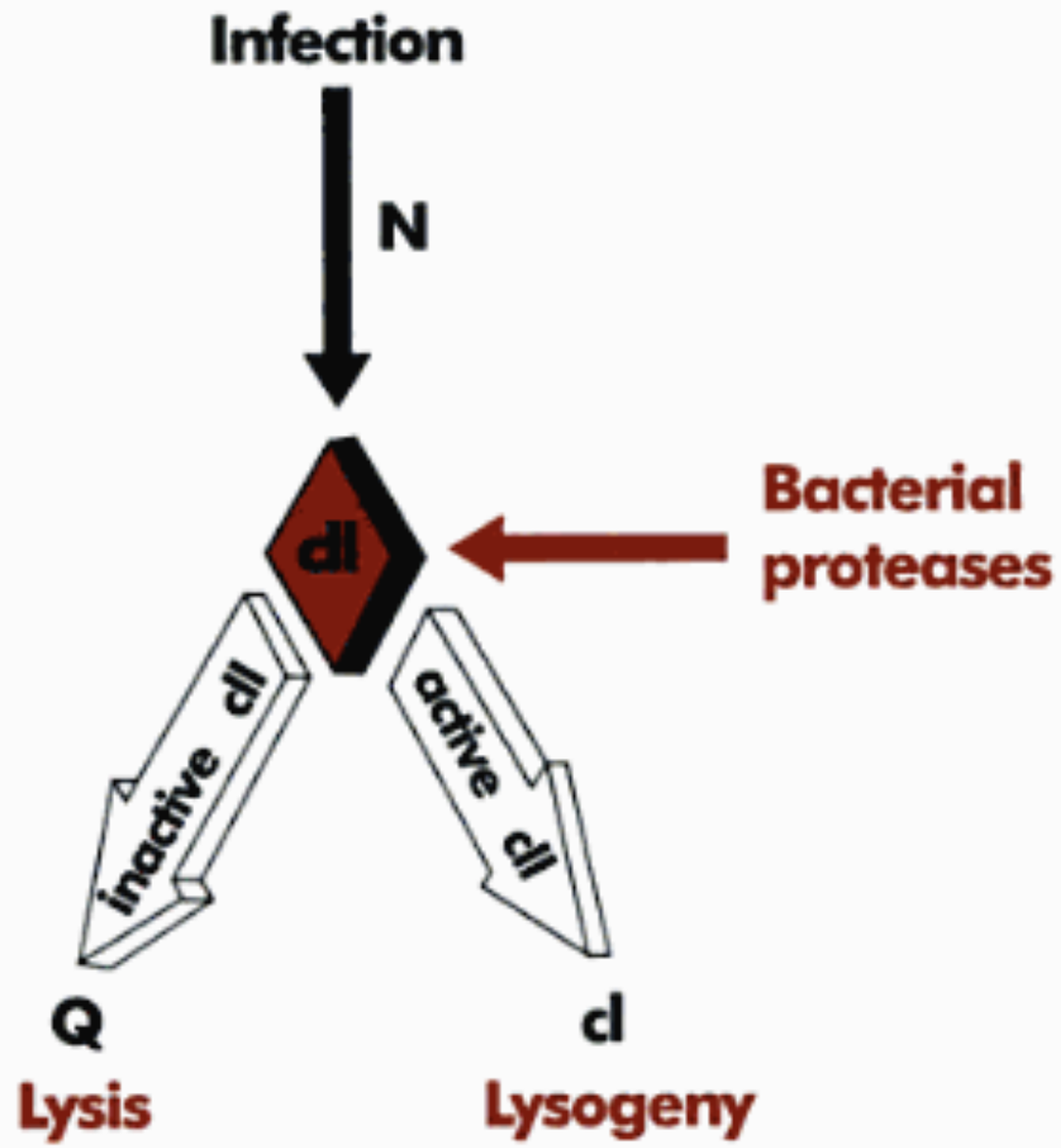

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Ptashne, The Genetic Switch, p58

http://en.wikipedia.org/wiki/File:Justso_rhino.jpg

Understanding nature via synthesis

Elowitz, M. B. & Leibler, S. A synthetic oscillatory network of transcriptional regulators. Nature 403, 335–-338 (2000)

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The synthesis of synthetic biology

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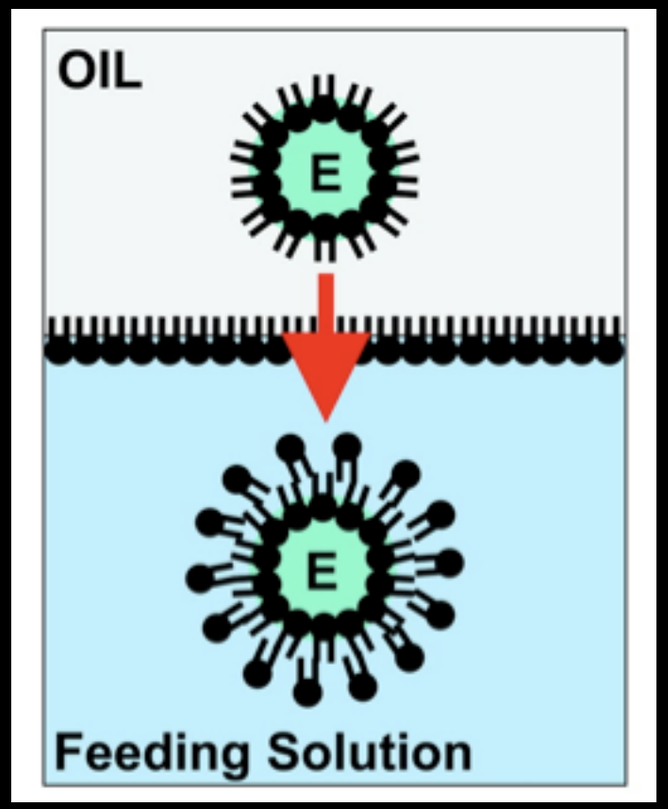
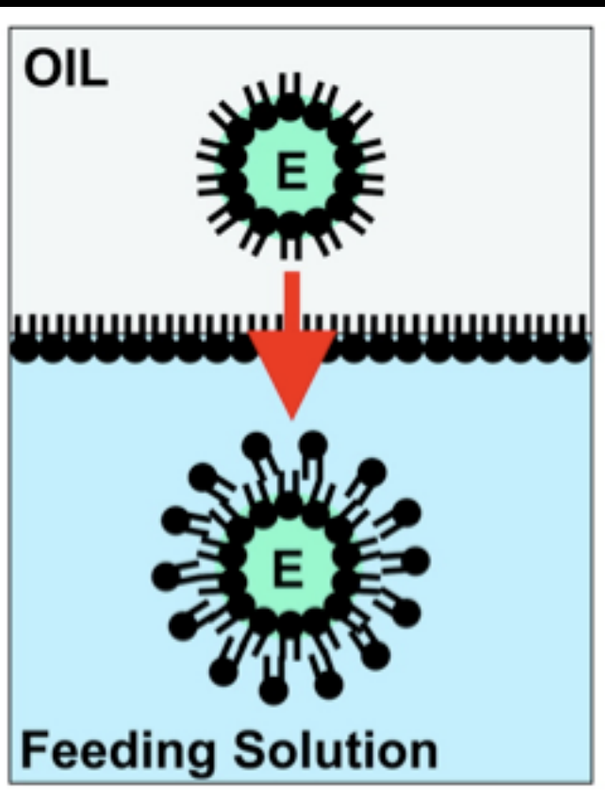
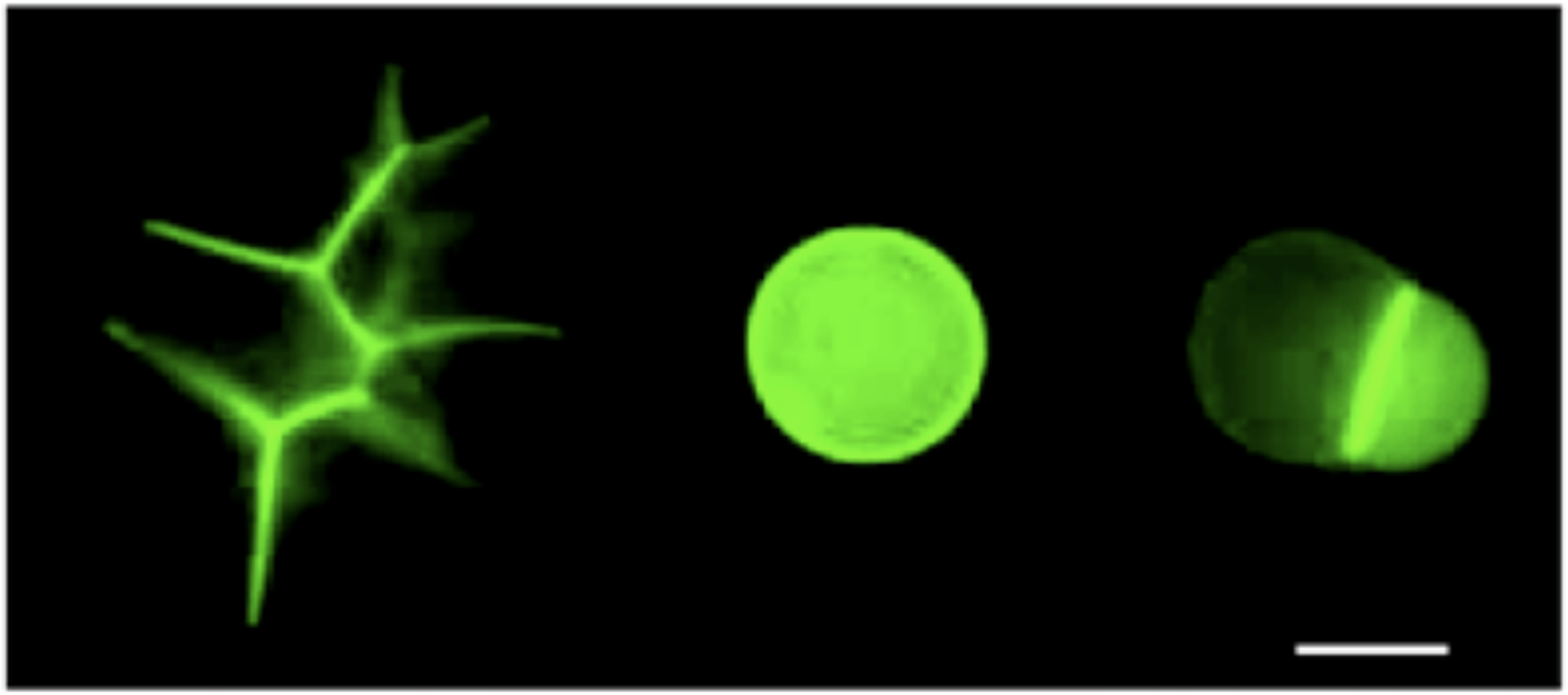


Noireaux & Libchaber, Proc Natl Acad Sci U S A. 2004 Dec 21;101(51):17669-74.

The synthesis of synthetic biology





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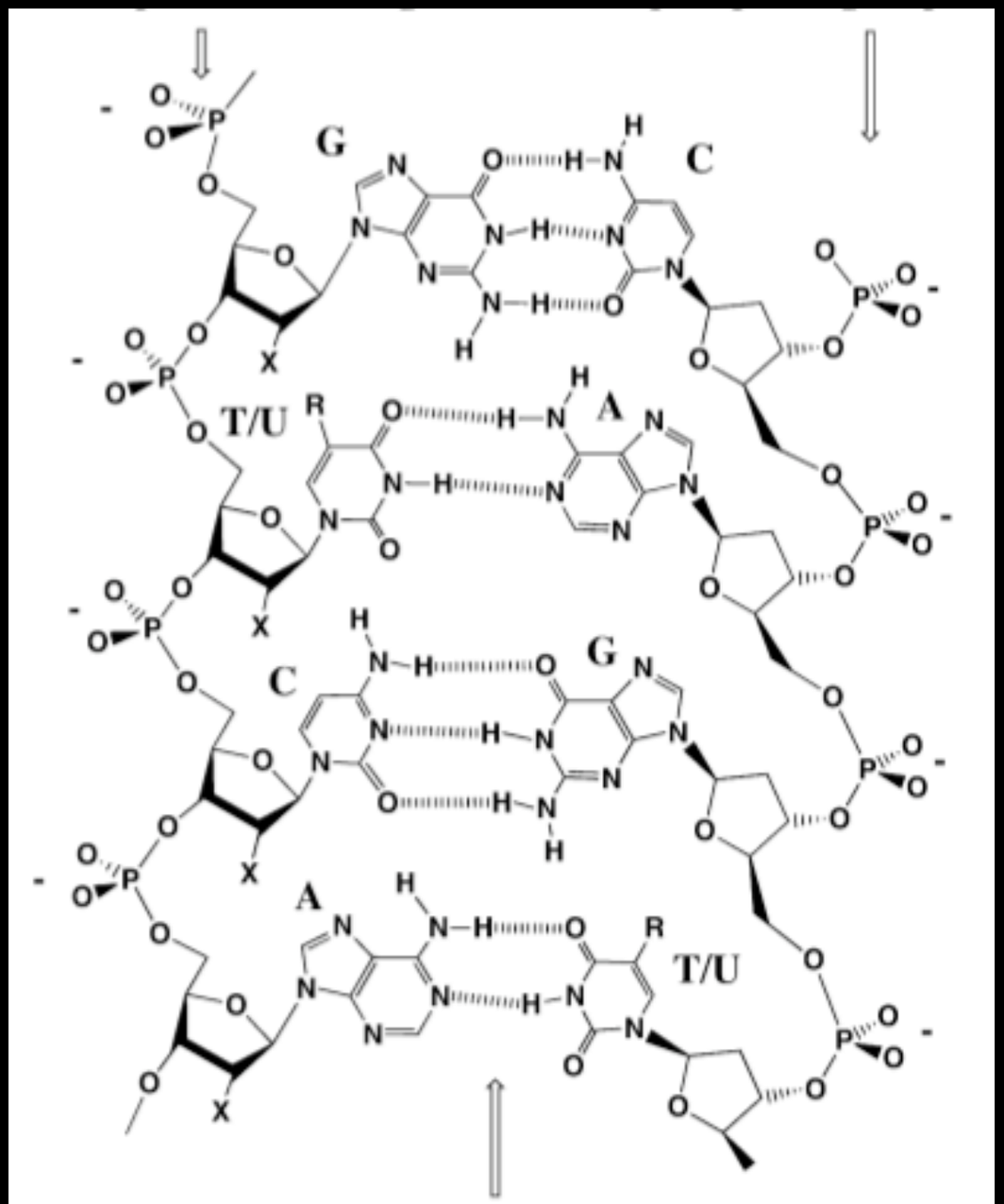
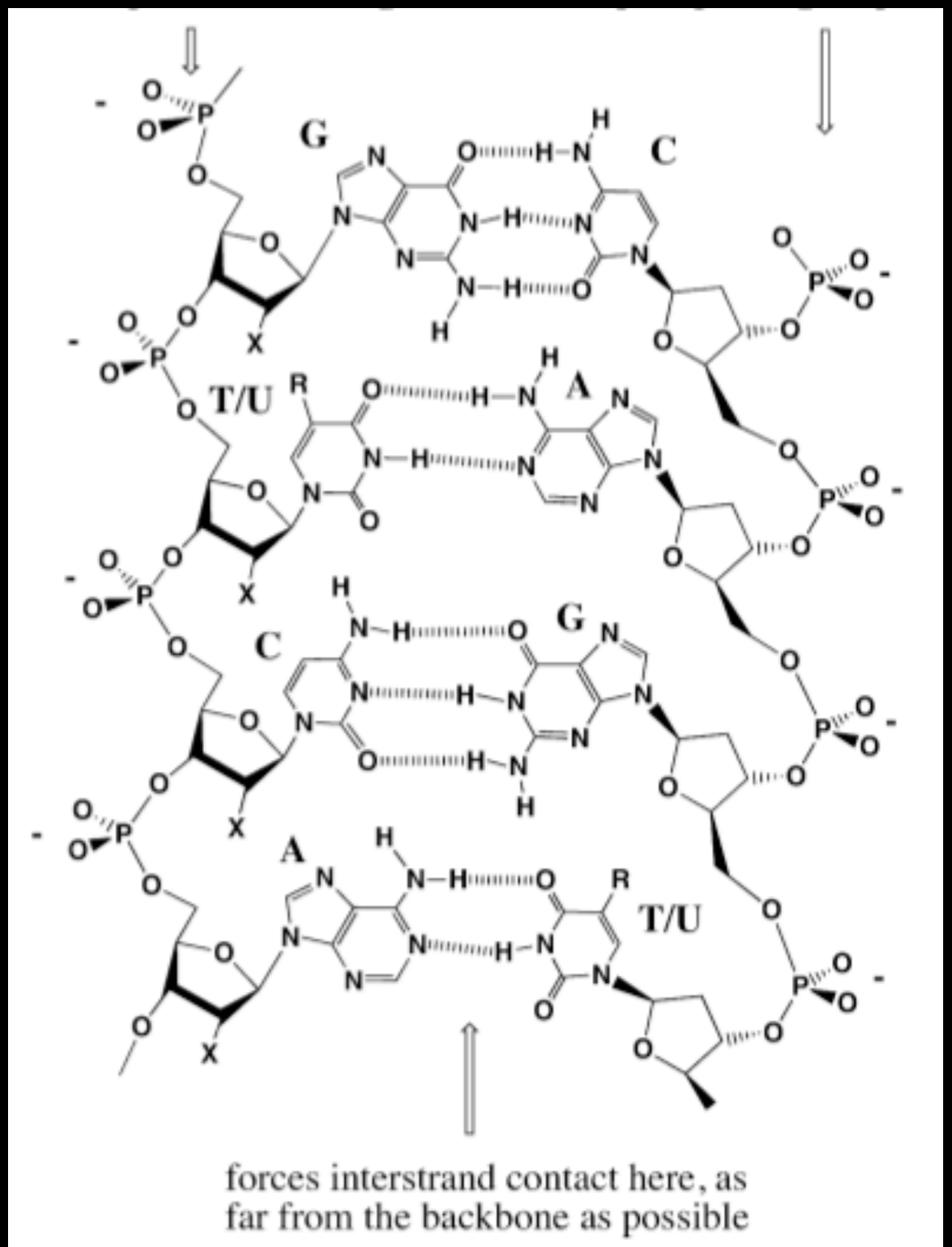


FIGURE 14. Backbone charges force interstrand contacts in a DNA duplex to the Watson–Crick edge of the heterocycles, hinder folding, and dominate physical behavior, allowing DNA/RNA to mutate and evolve.

Understanding Nucleic Acids Using Synthetic Chemistry, Steven Benner, Acc. Chem. Res. 2004, 37, 784-797

The synthesis of synthetic biology



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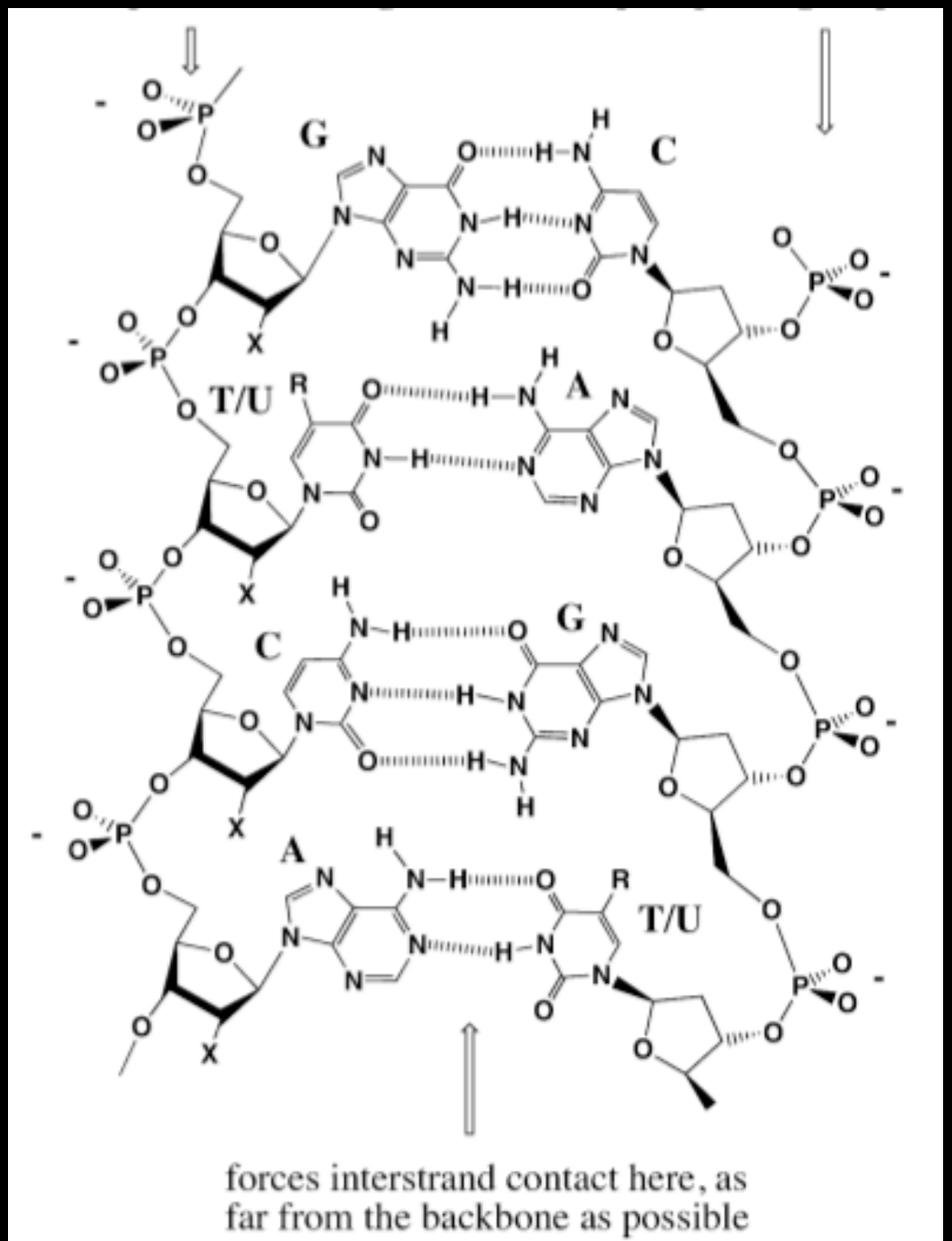

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- Why repeated negative charges?

- Replace anionic phosphodiester linkers with uncharged dimethylene sulfones

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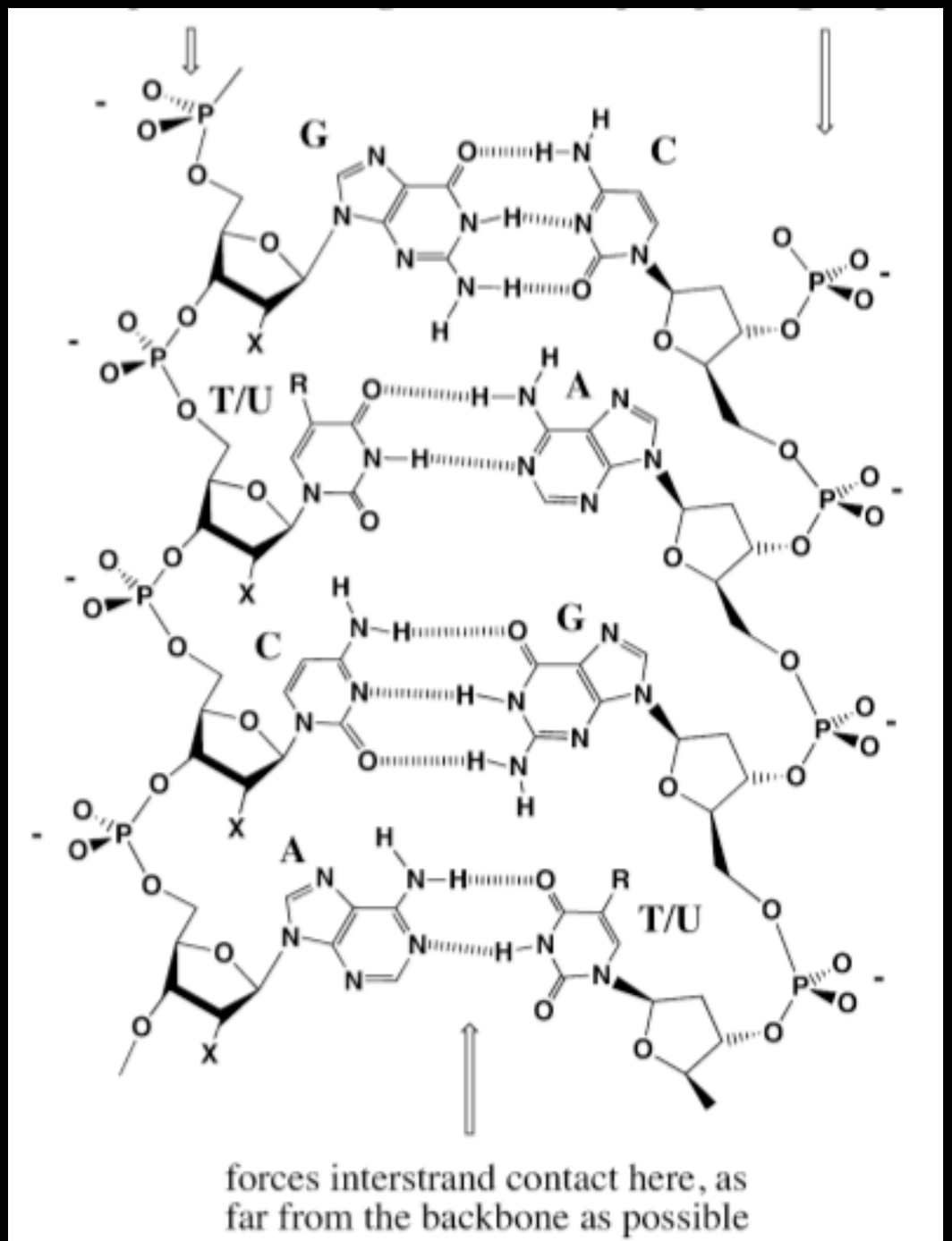

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- Why repeated negative charges?

- Replace anionic phosphodiester linkers with uncharged dimethylene sulfones

- Discover phosphate backbone hinders folding, enables base pairing, and allows for mutations

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The liberation of synthetic biology

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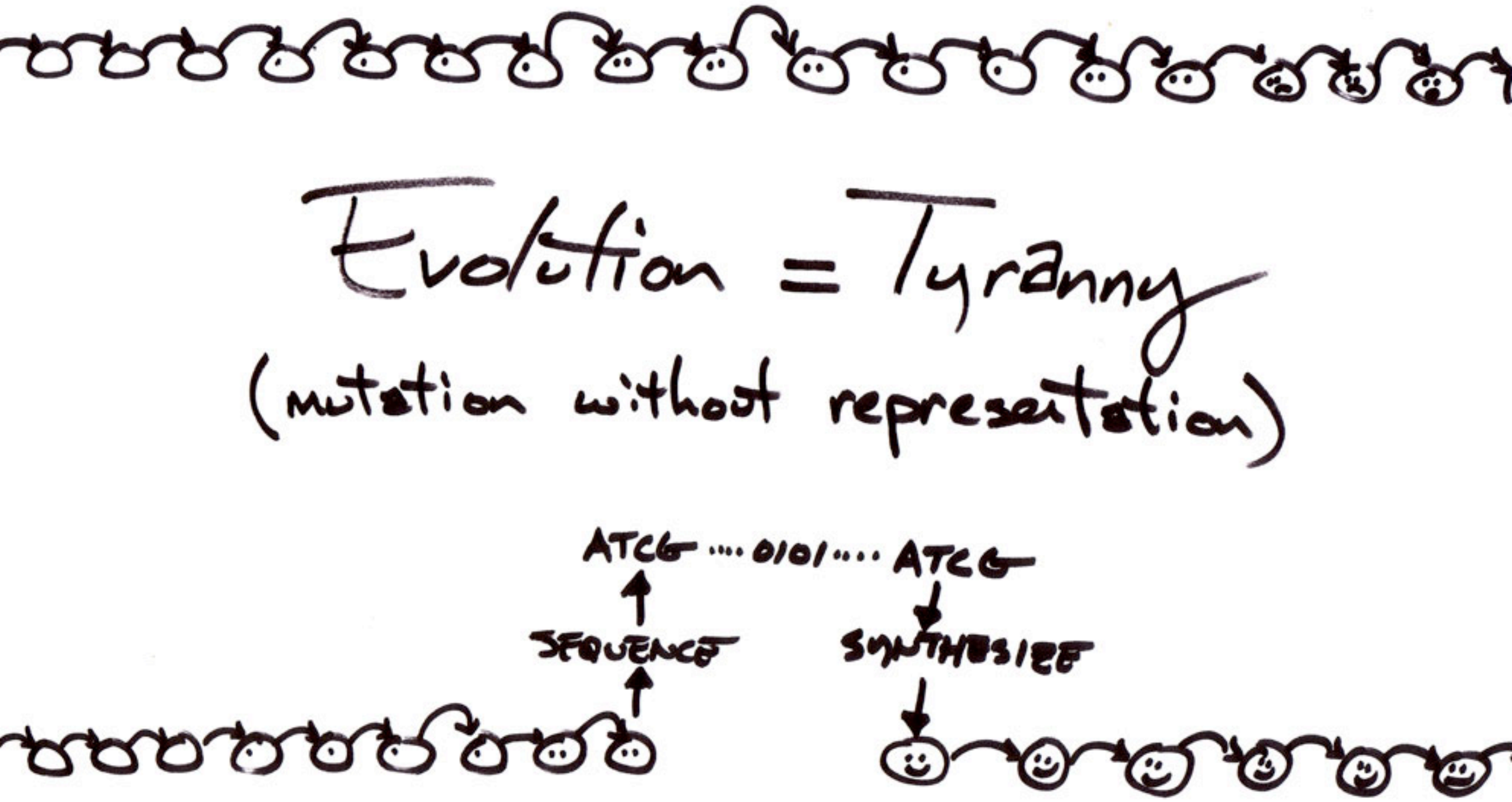
Evolution = Tyranny
(mutation without representation)

The liberation of synthetic biology



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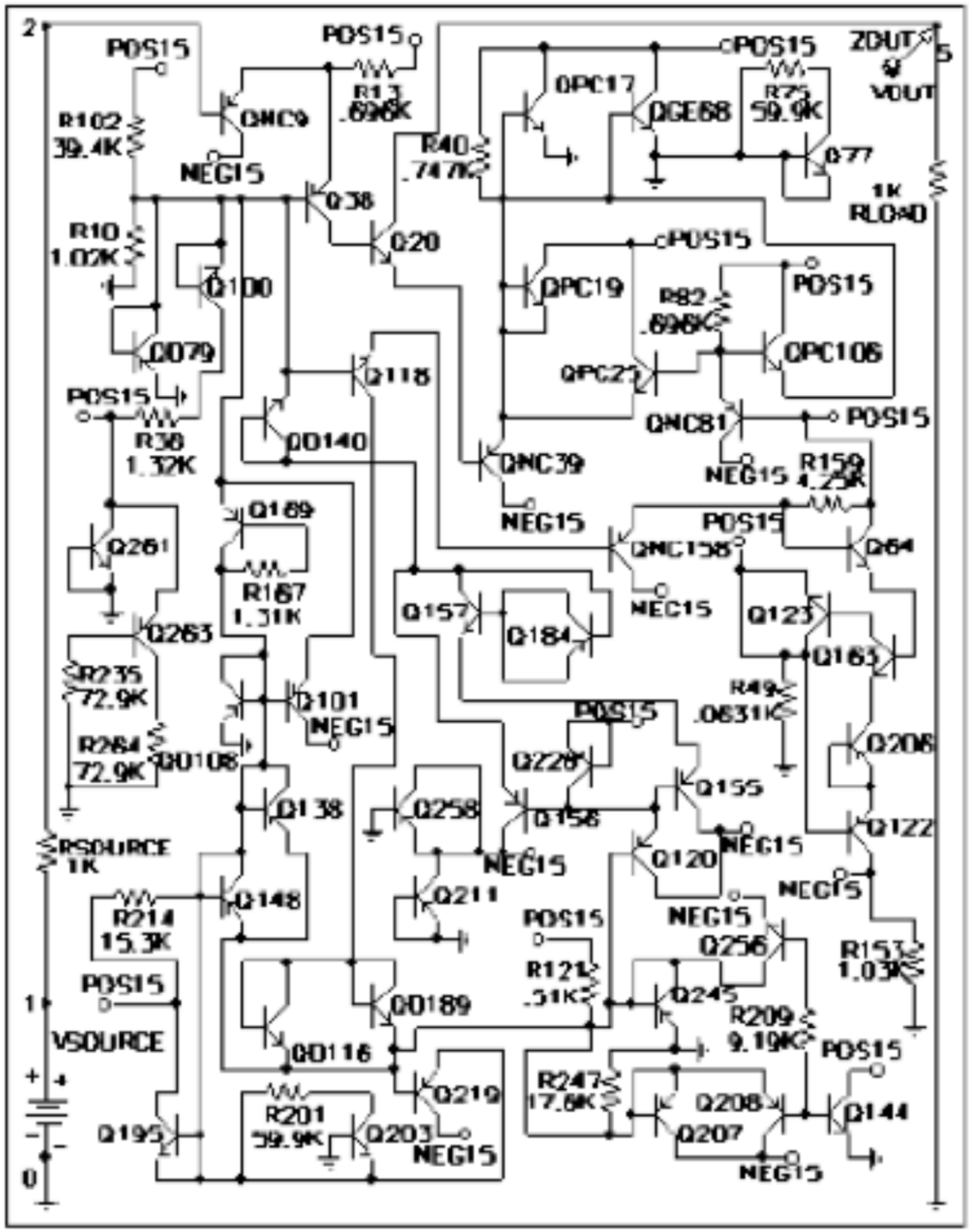

J.R. Koza et al.
Automated Synthesis of Computational Circuits using GeneticProgramming, 1997 IEEE International Conference on Evolutionary Computation

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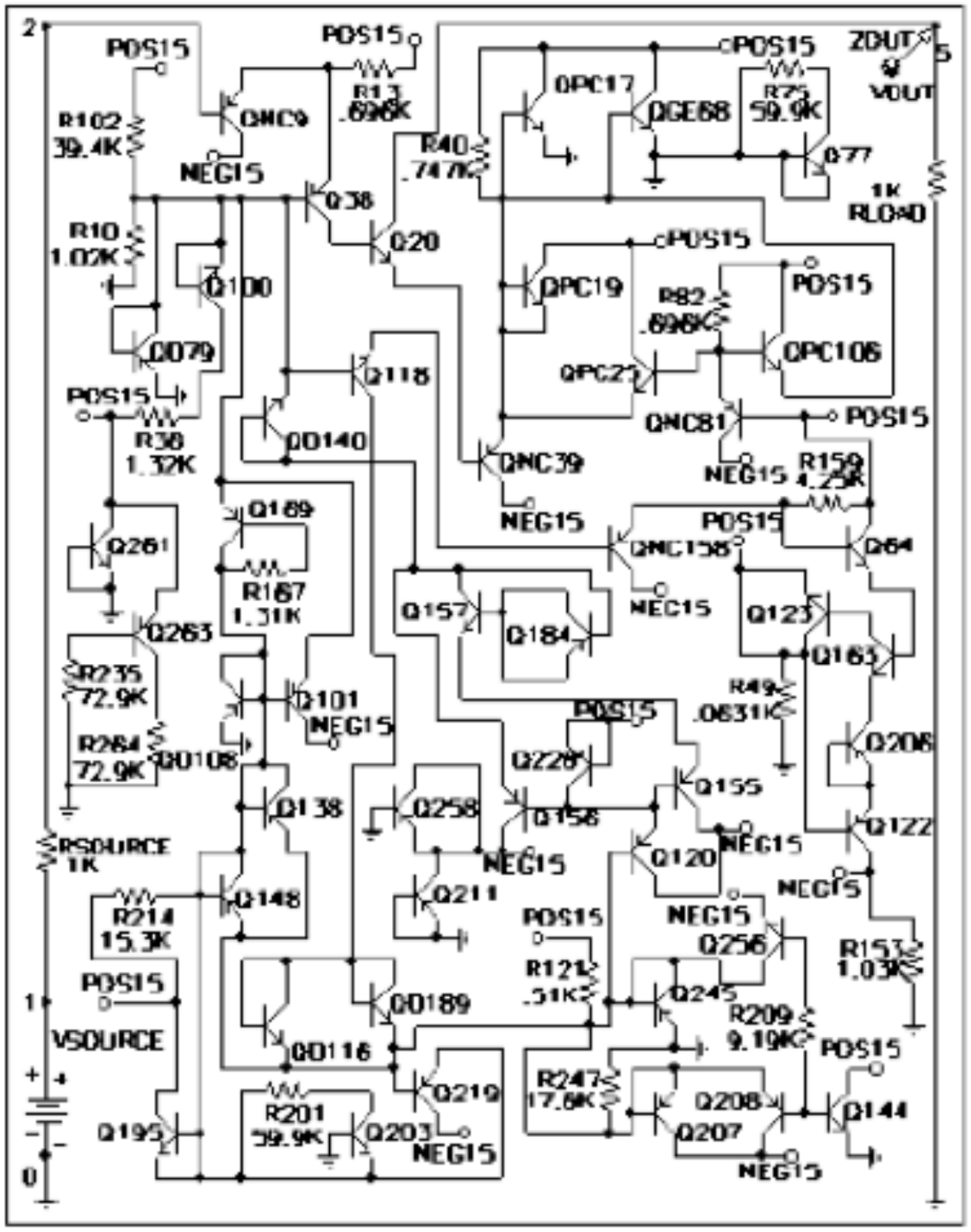

1. What does it do?
2. How does it work?
3. Why this design?

J.R. Koza et al.
Automated Synthesis of Computational Circuits using GeneticProgramming,
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The liberation of synthetic biology

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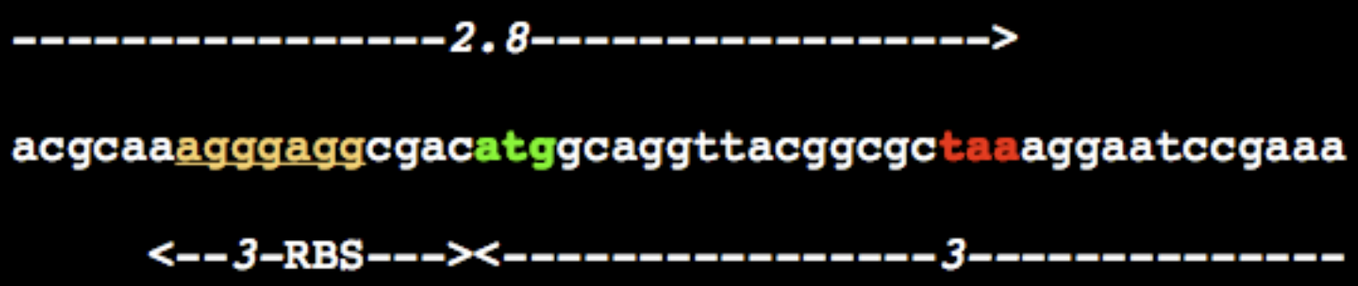

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----------------2.8----------------->

acgcaaaggggaggcgacatggcaggttacggcgctaaaggaatccgaaa

      <--3-RBS---><----------------3--------------

acgcaaGggggagAcgacaCggcaggttacggcgctaaggatccggccgcaaagggaggcgacatggcaggttacggcgctaaa

----------------2.8-----------------><D28R|D29L><--3RBS------><--------------3----
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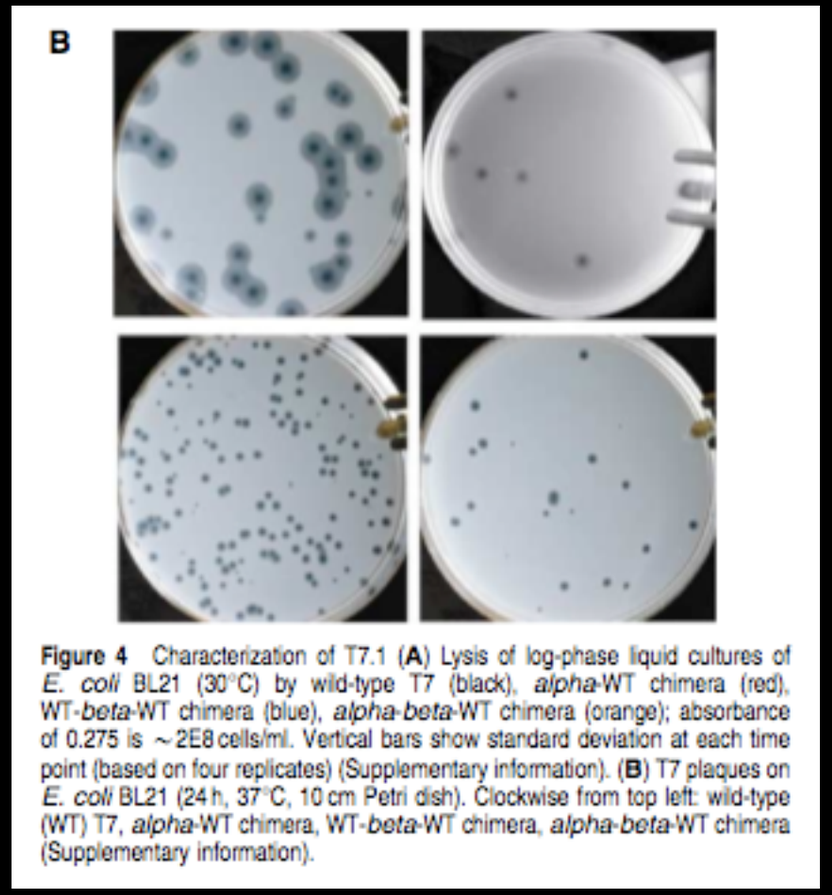

Figure 4 Characterization of T7.1 (**A**) Lysis of log-phase liquid cultures of *E. coli* BL21 (30°C) by wild-type T7 (black), *alpha*-WT chimera (red), WT-*beta*-WT chimera (blue), *alpha*-*beta*-WT chimera (orange); absorbance of 0.275 is ~2E8 cells/ml. Vertical bars show standard deviation at each time point (based on four replicates) (Supplementary information). (**B**) T7 plaques on *E. coli* BL21 (24 h, 37°C, 10 cm Petri dish). Clockwise from top left: wild-type (WT) T7, *alpha*-WT chimera, WT-*beta*-WT chimera, *alpha*-*beta*-WT chimera (Supplementary information).

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The engineering of synthetic biology

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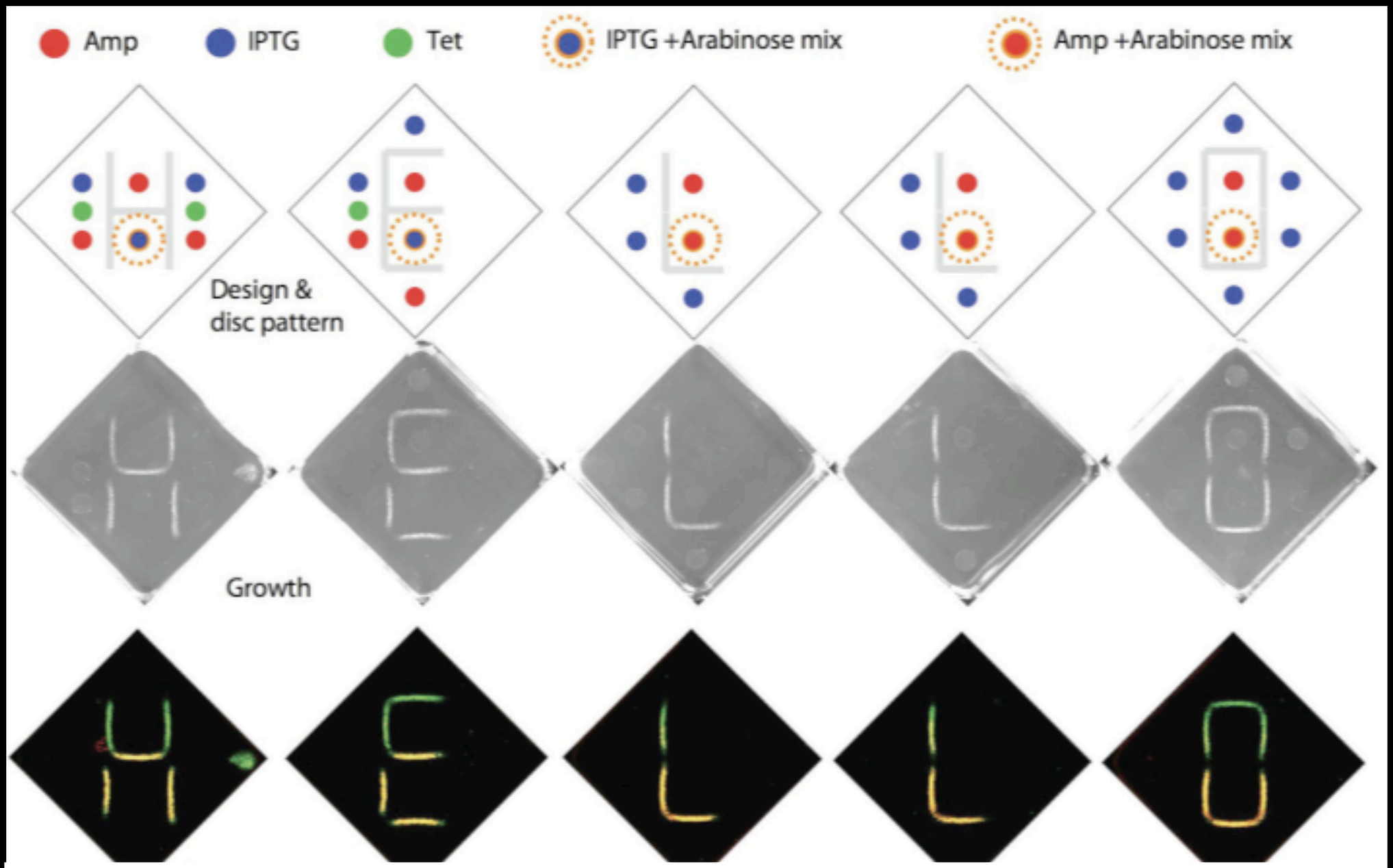


Morphogen-defined patterning of Escherichia coli enabled by an externally tunable band-pass filter

Journal of Biological Engineering 2009, **3**:10 doi:10.1186/1754-1611-3-10

Takayuki Sohka (takayuki2003jp2003@gmail.com)
Richard A Heins (rheins2@jhu.edu)
Marc Ostermeier (oster@jhu.edu)

The engineering of synthetic biology

The engineering of synthetic biology

Teach me how to...

The engineering of synthetic biology

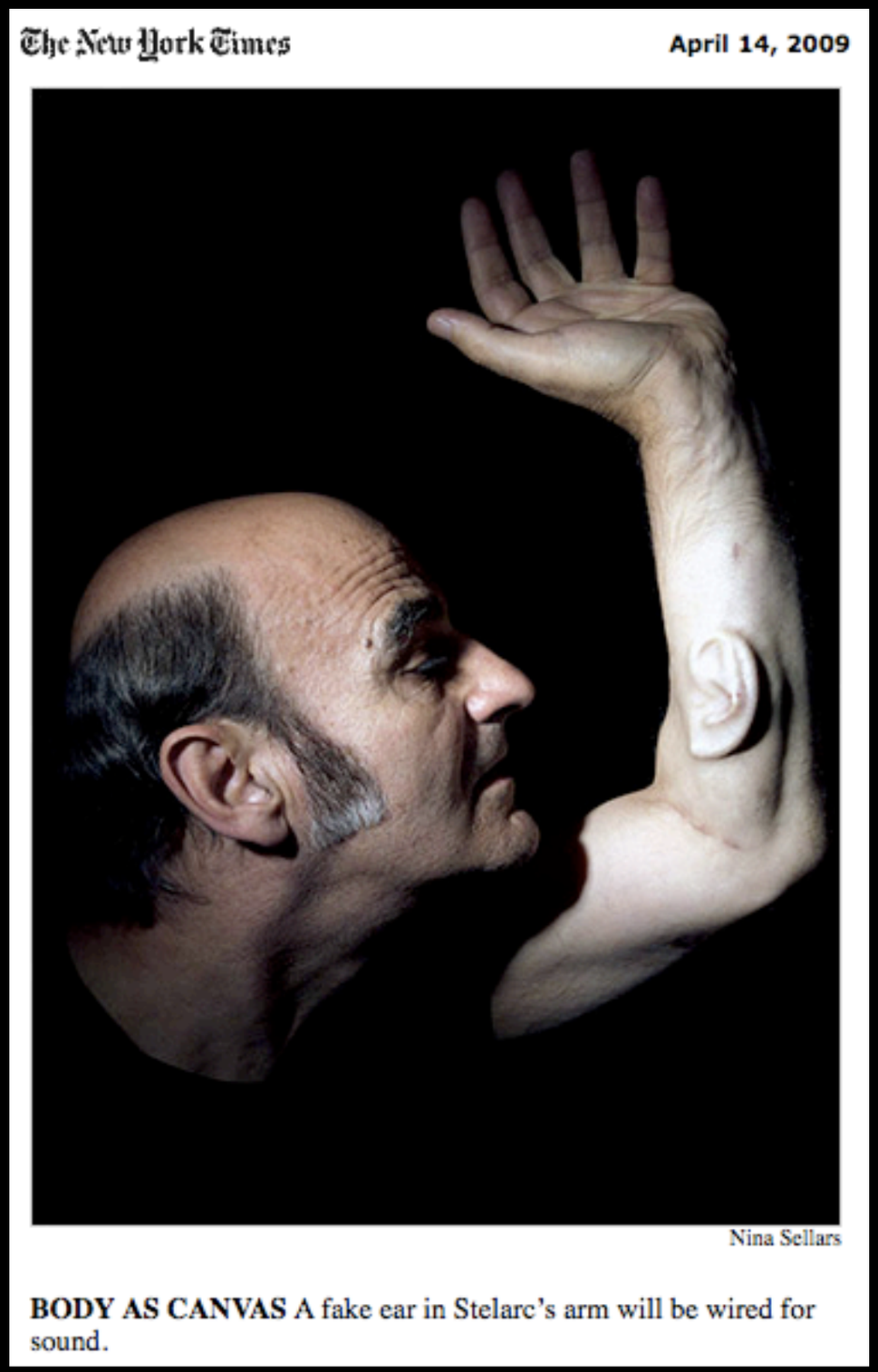
Teach me how to...

Design and build living organisms that behave as expected.

Debug existing or write new genetic programs to do my bidding.

The humanity of synthetic biology

The humanity of synthetic biology



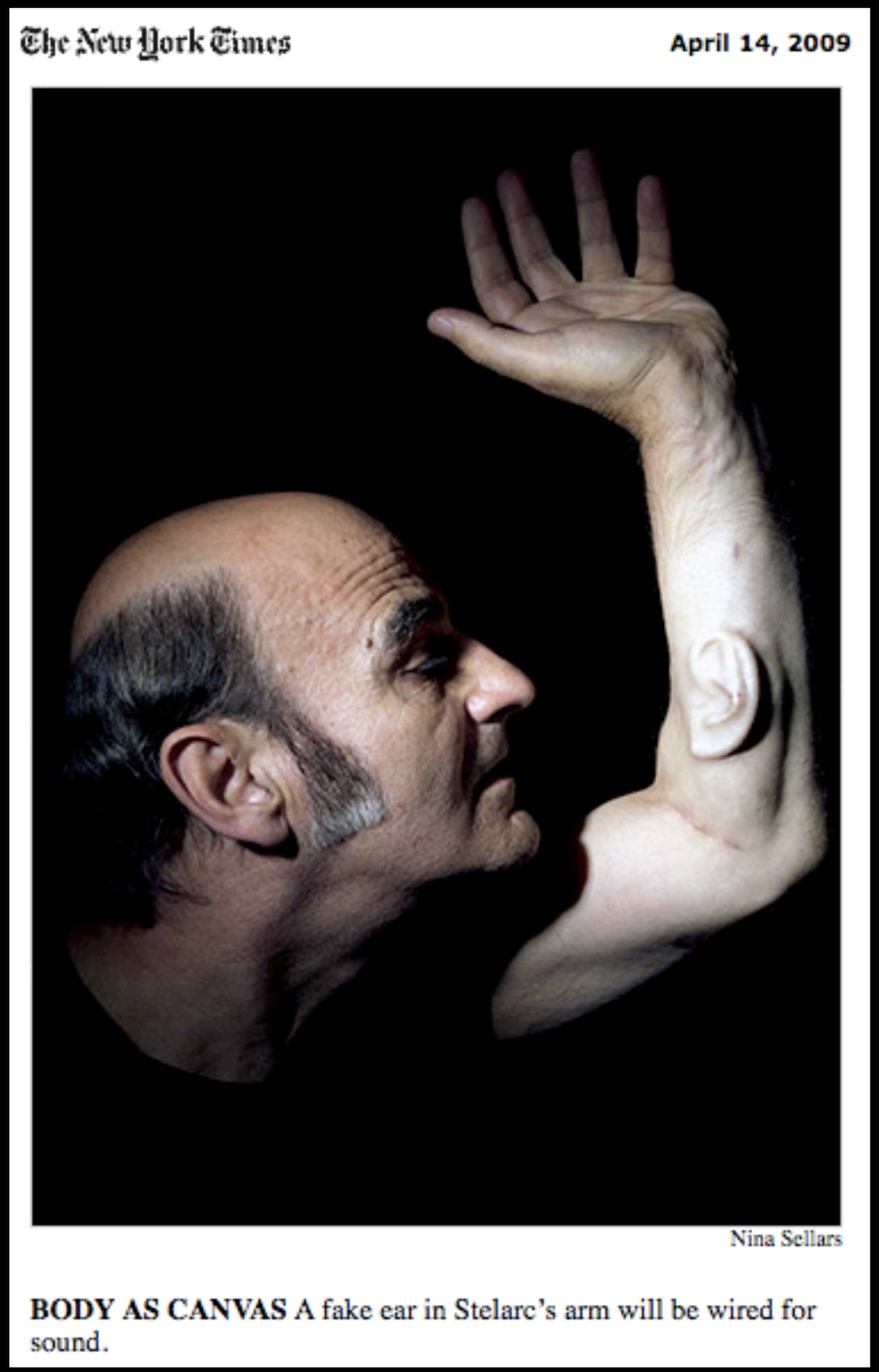
The New York Times April 14, 2009

Nina Sellars

BODY AS CANVAS A fake ear in Stelarc's arm will be wired for sound.

http://www.nytimes.com/2009/04/14/science/14corp.html

The humanity of synthetic biology



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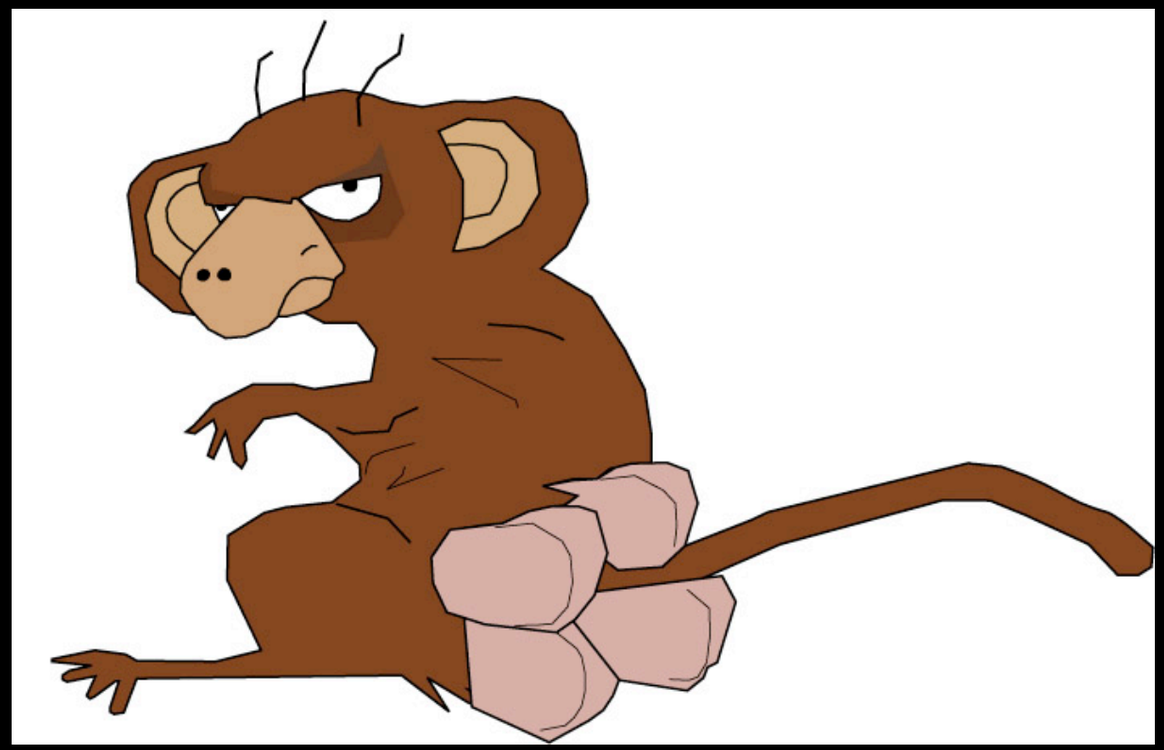

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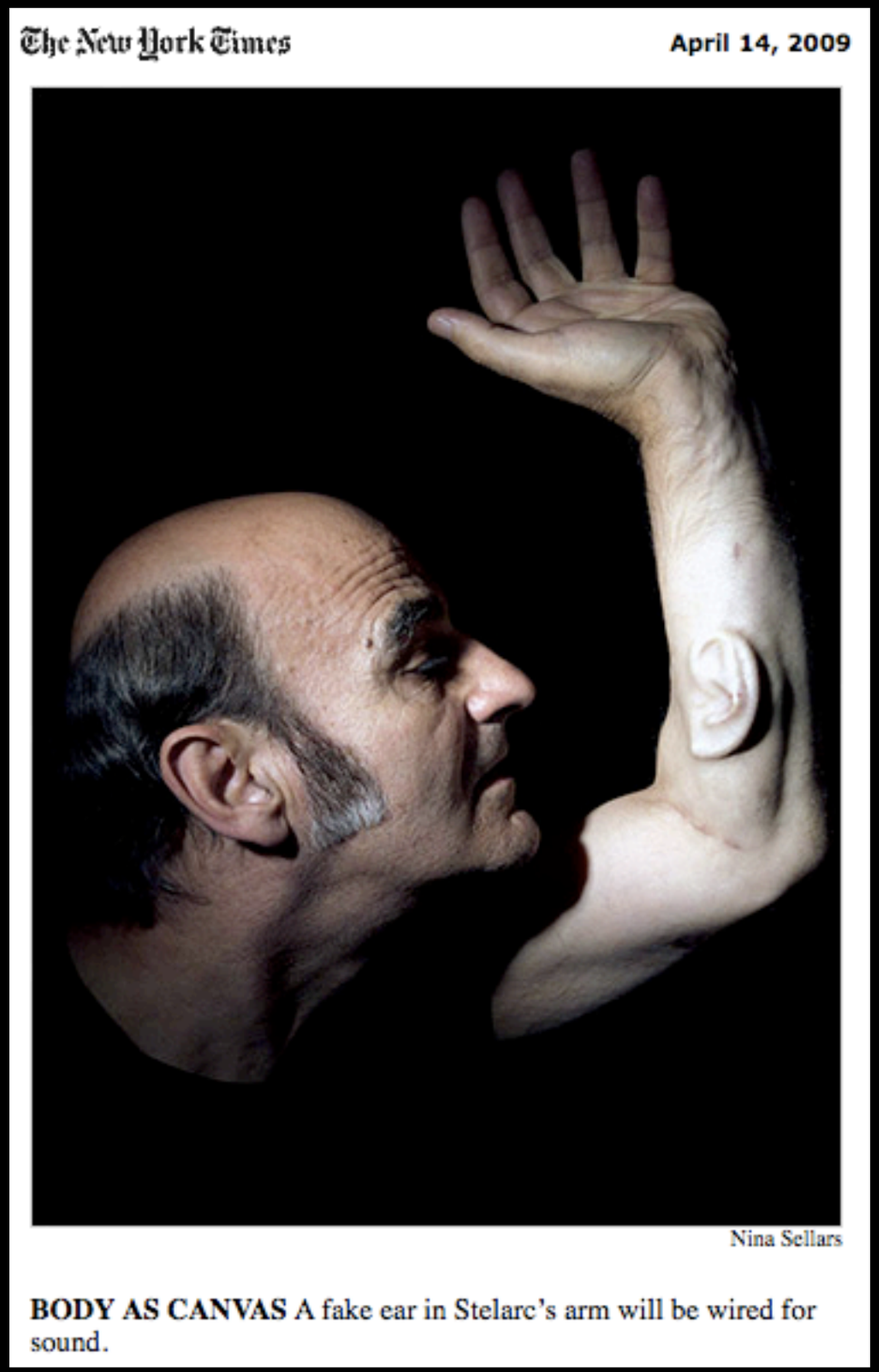

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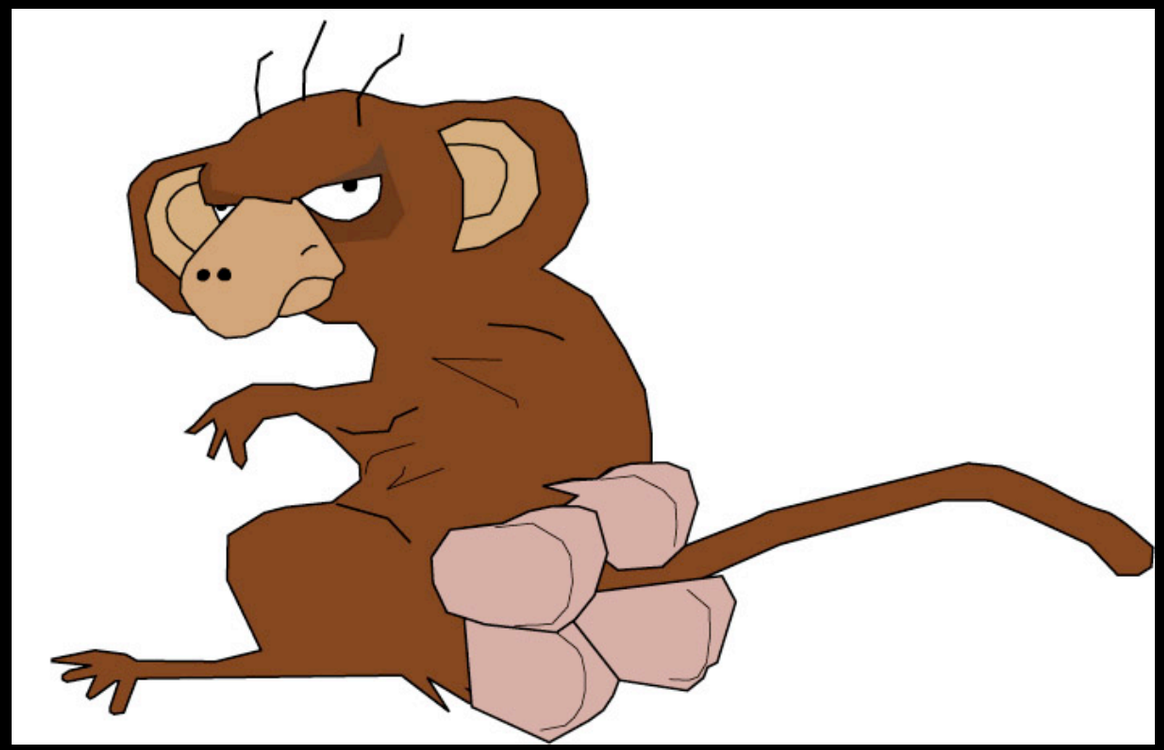

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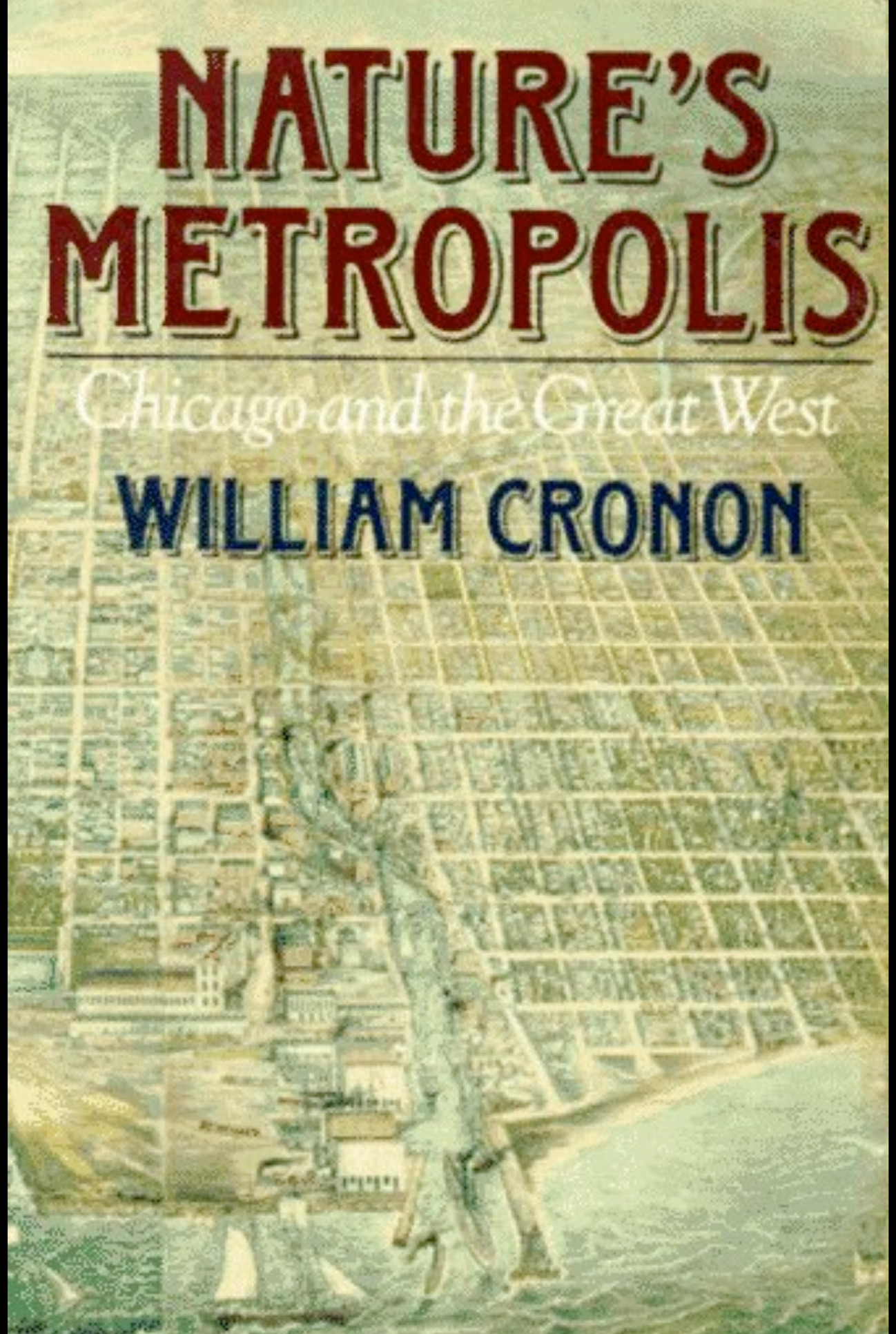
http://s3.amazonaws.com/listverse/scifiseries/rama.jpg

NATURE'S METROPOLIS

Chicago and the Great West

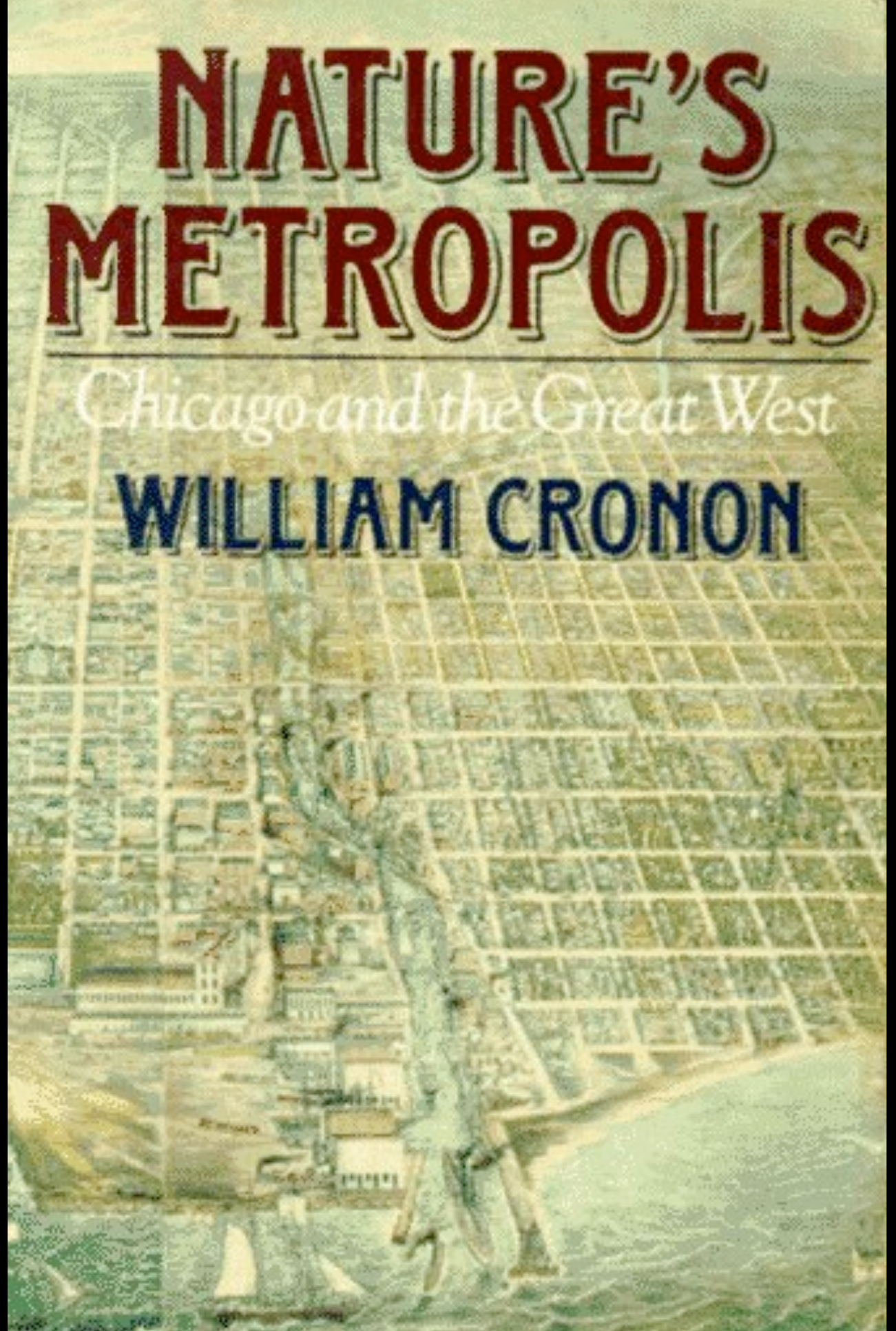
WILLIAM CRONON

- How will (should?) we change ourselves and our environments?



- How will (should?) we change ourselves and our environments?

- New schools of science and engineering? E.g., integration without isolation?



- How will (should?) we change ourselves and our environments?

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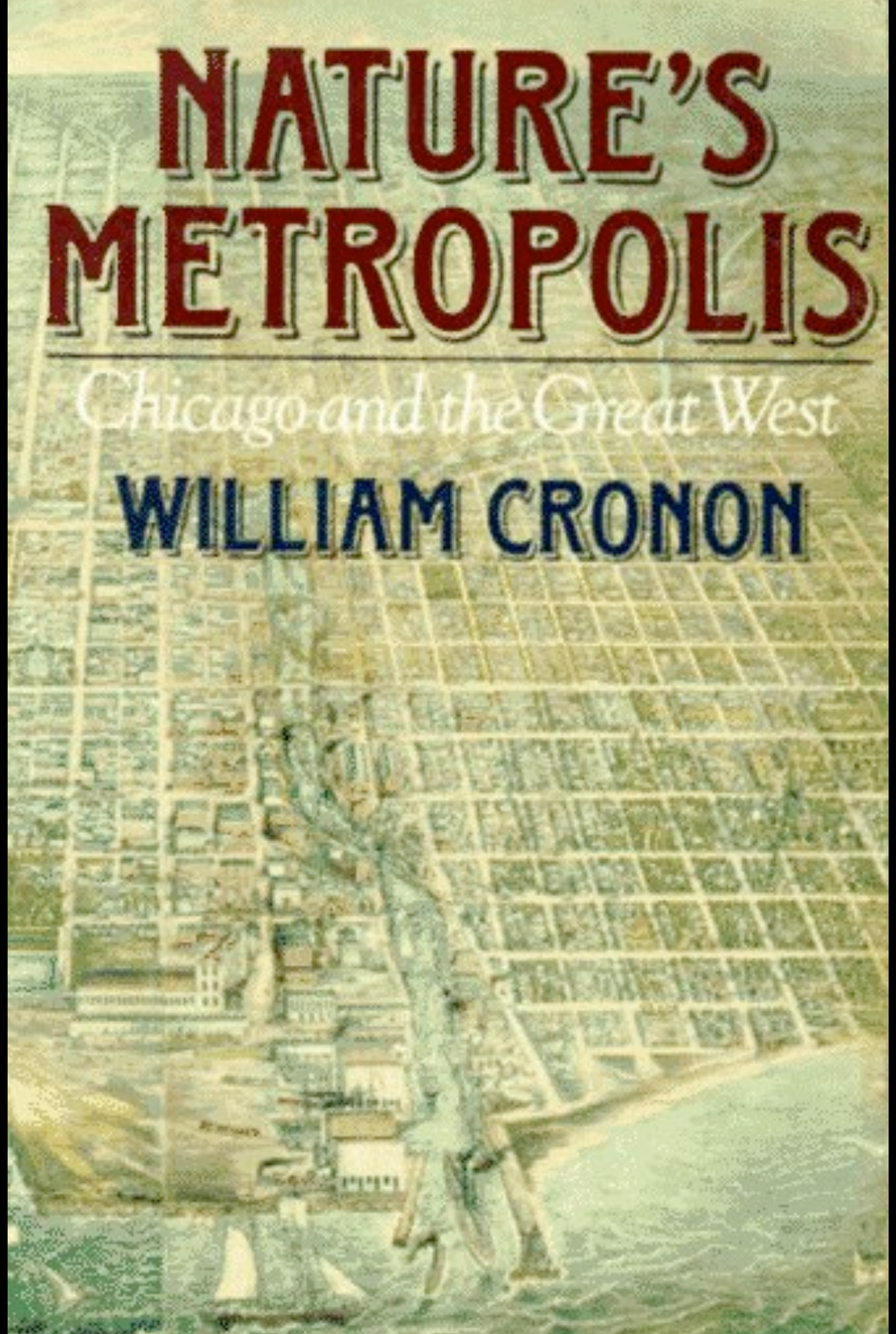
- New modes of humanity? E.g., responsibility with representation?



Learn (& play) by making

Help (& enable) by building

http://i.pbase.com/u47/hodero/large/30691408.jungle.jpg

http://i.pbase.com/u47/hodero/large/30691408.jungle.jpg

Challenges

Make biology easy to engineer.

Enable humanity.

http://i.pbase.com/u47/hodero/large/30691408.jungle.jpg

Challenges

Make biology easy to engineer.

Enable humanity.

Opportunities

Enable all constructive biotechnologies.

Better understand nature.

Food

Energy

Environment

Agriculture

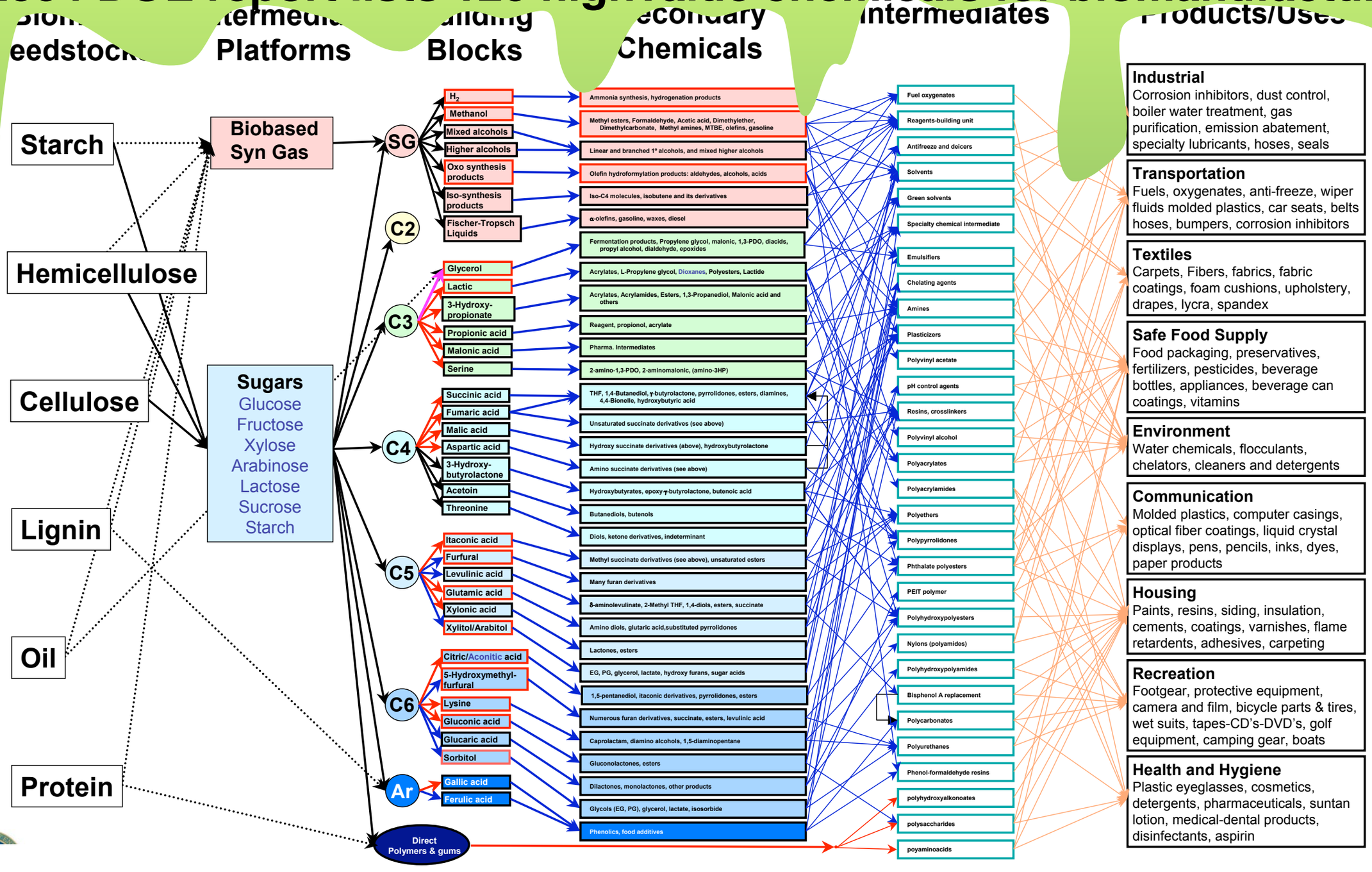
Health

Chemicals

Security

Food | Energy | Environment | Agriculture | Health | Chemicals | Security

2004 DOE report lists 120 highvalue chemicals for biomanufacturing



Food

Energy

Environment

Agriculture

Health

Chemicals

Security

Food | Energy | Environment | Agriculture | Health | Chemicals | Security

Doebley Lab
Department of Genetics
University of Wisconsin-Madison

Food | Energy | Environment | Agriculture | Health | Chemicals | Security

3 crop species (rice, wheat and maize) provide 60% of all calories and 54% of all protein in human food

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Food | Energy | Environment | Agriculture | Health | Chemicals | Security

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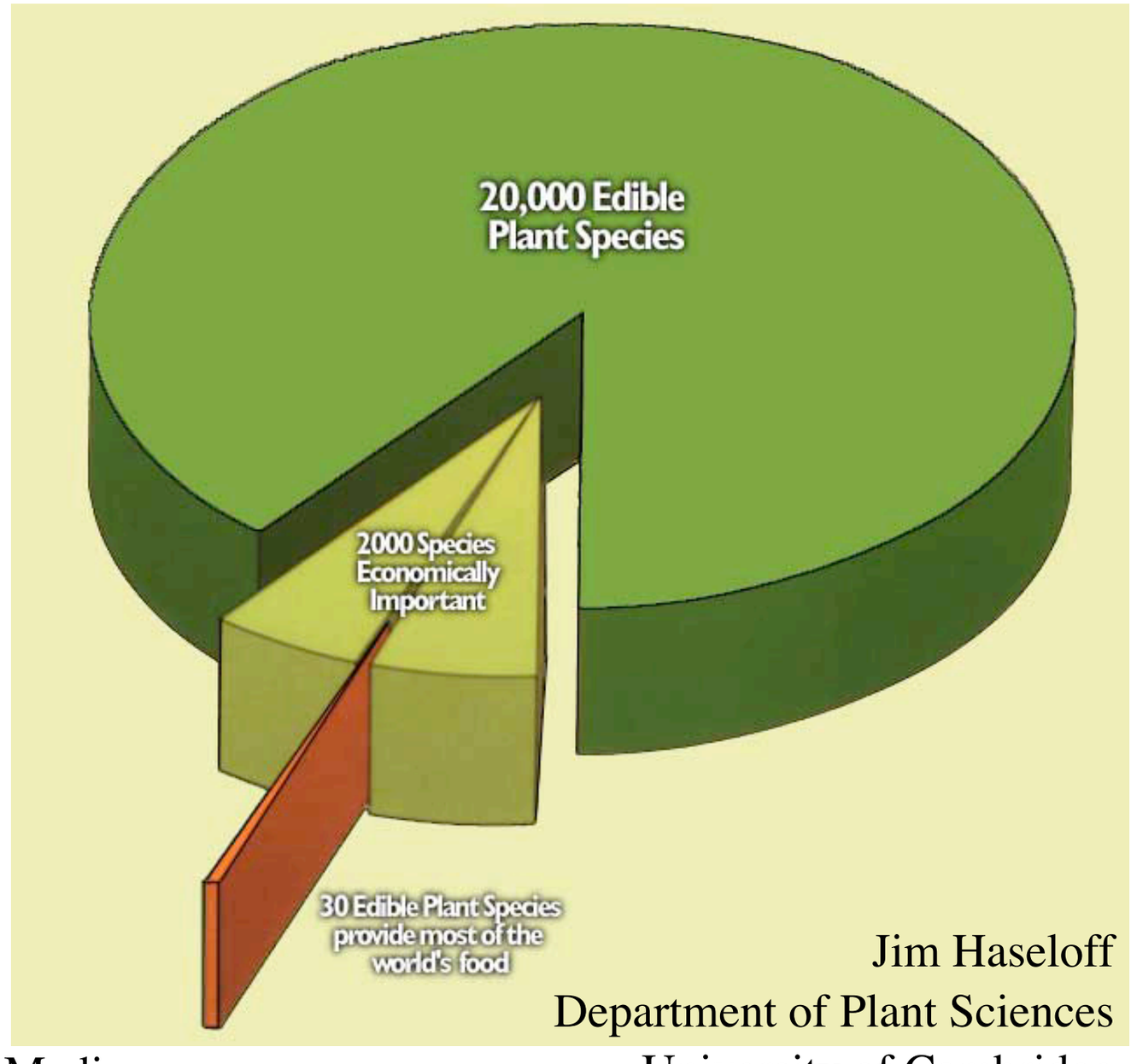
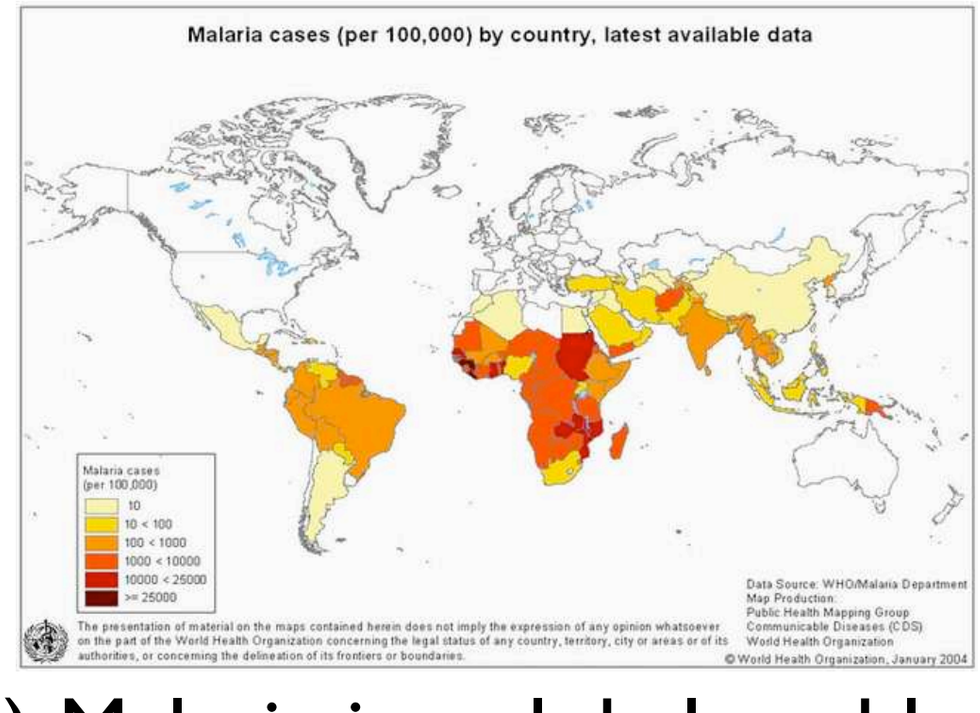


Doebley Lab
Department of Genetics
University of Wisconsin-Madison

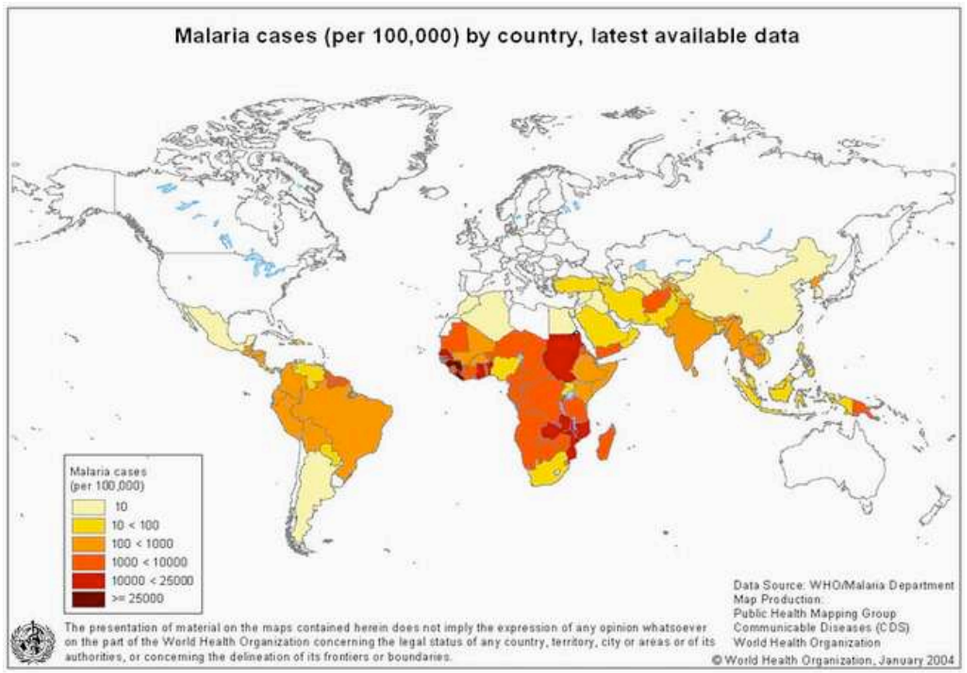
Jim Haseloff
Department of Plant Sciences
University of Cambridge

FAB.TREE.HAB
Joachim et al.
MIT Arch.

Where are we today?



1) Malaria is a global problem, artemisinin offers a cure.



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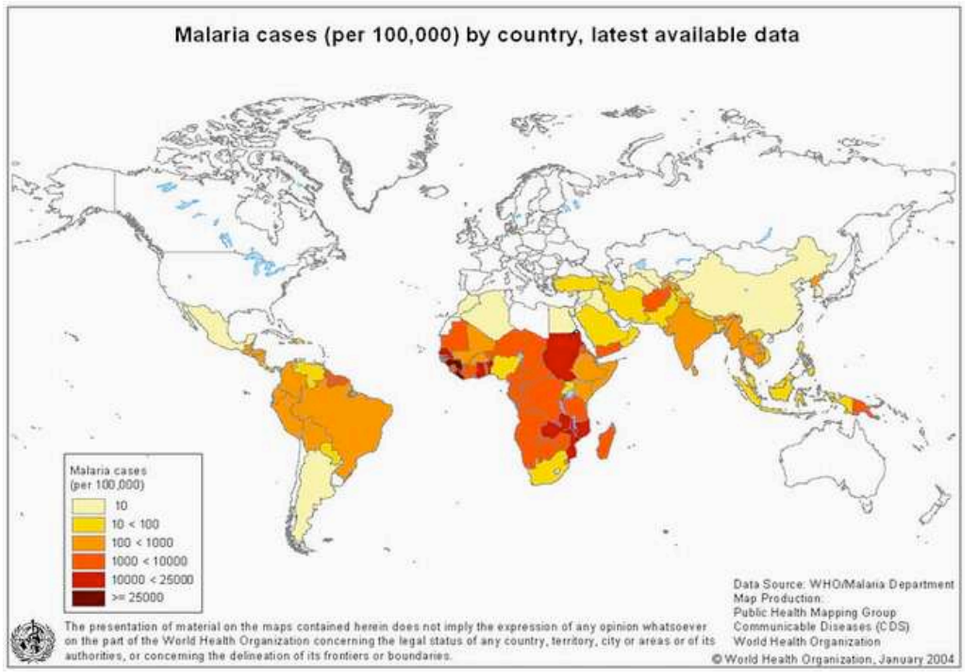
2) Jay Keasling's team spent $25M to make artemisinin via biotechnology.

Today, each project is Herculean



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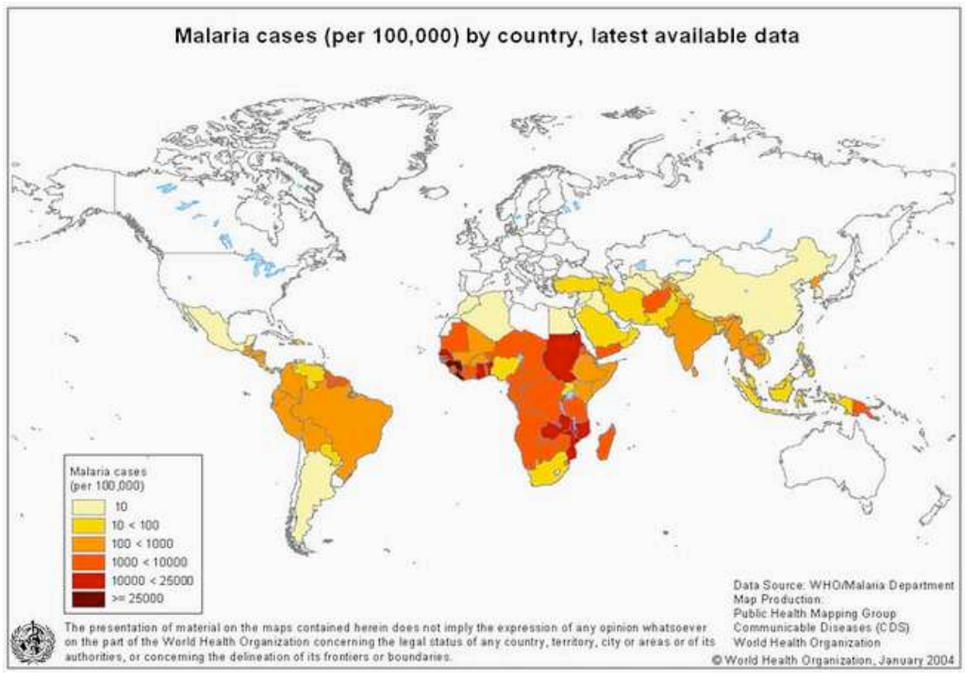
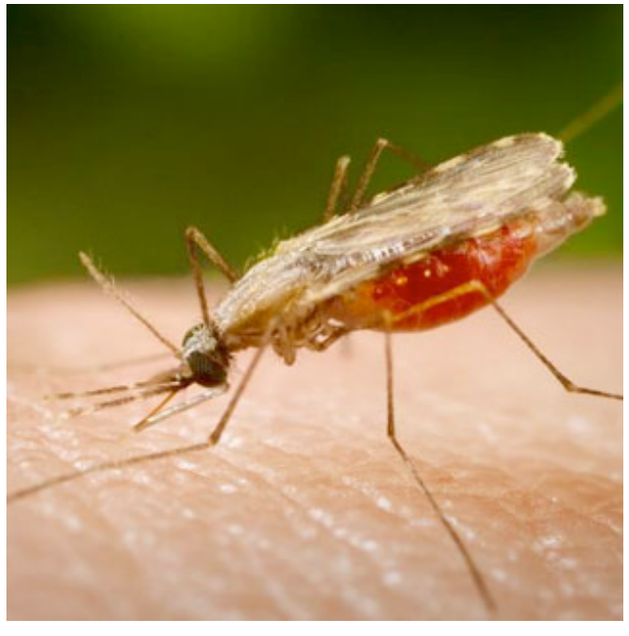


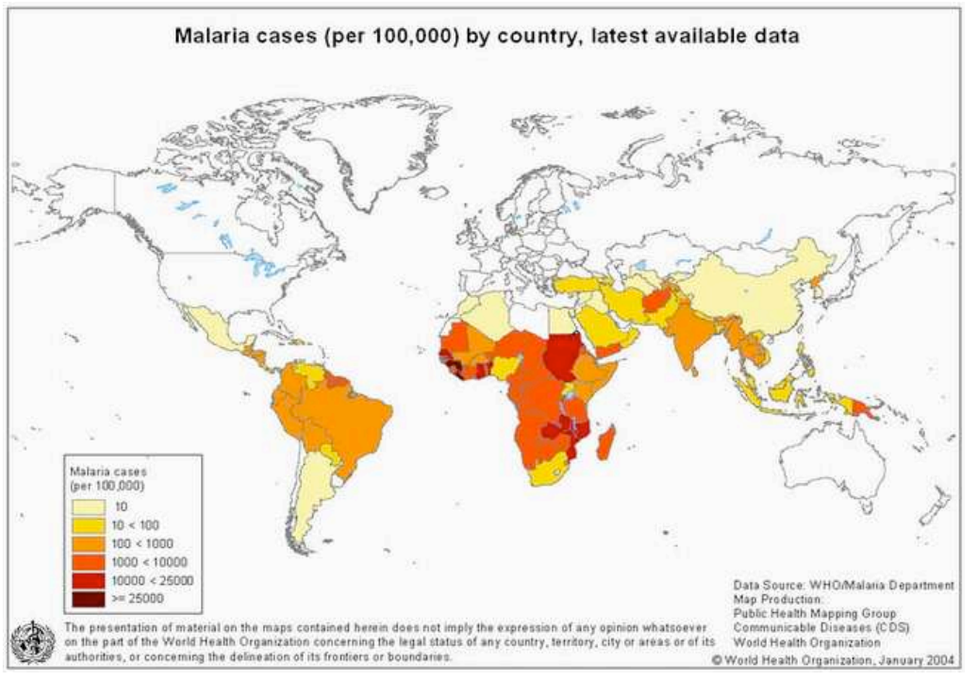
1) Malaria is a global problem, artemisinin offers a cure.

2) Jay Keasling's team spent $25M to make artemisinin via biotechnology.



3) But artemisinin resistance is already occurring.

Today, each project is Herculean



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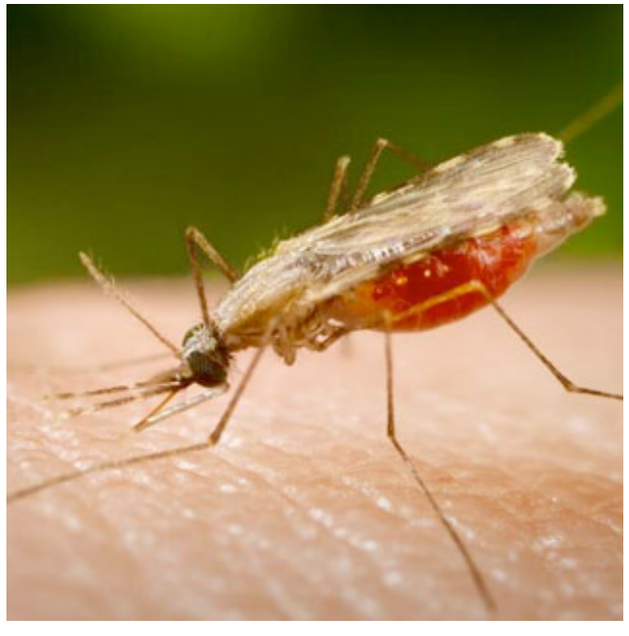

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Must we always spend many years and $25M for each pressing biotech project?

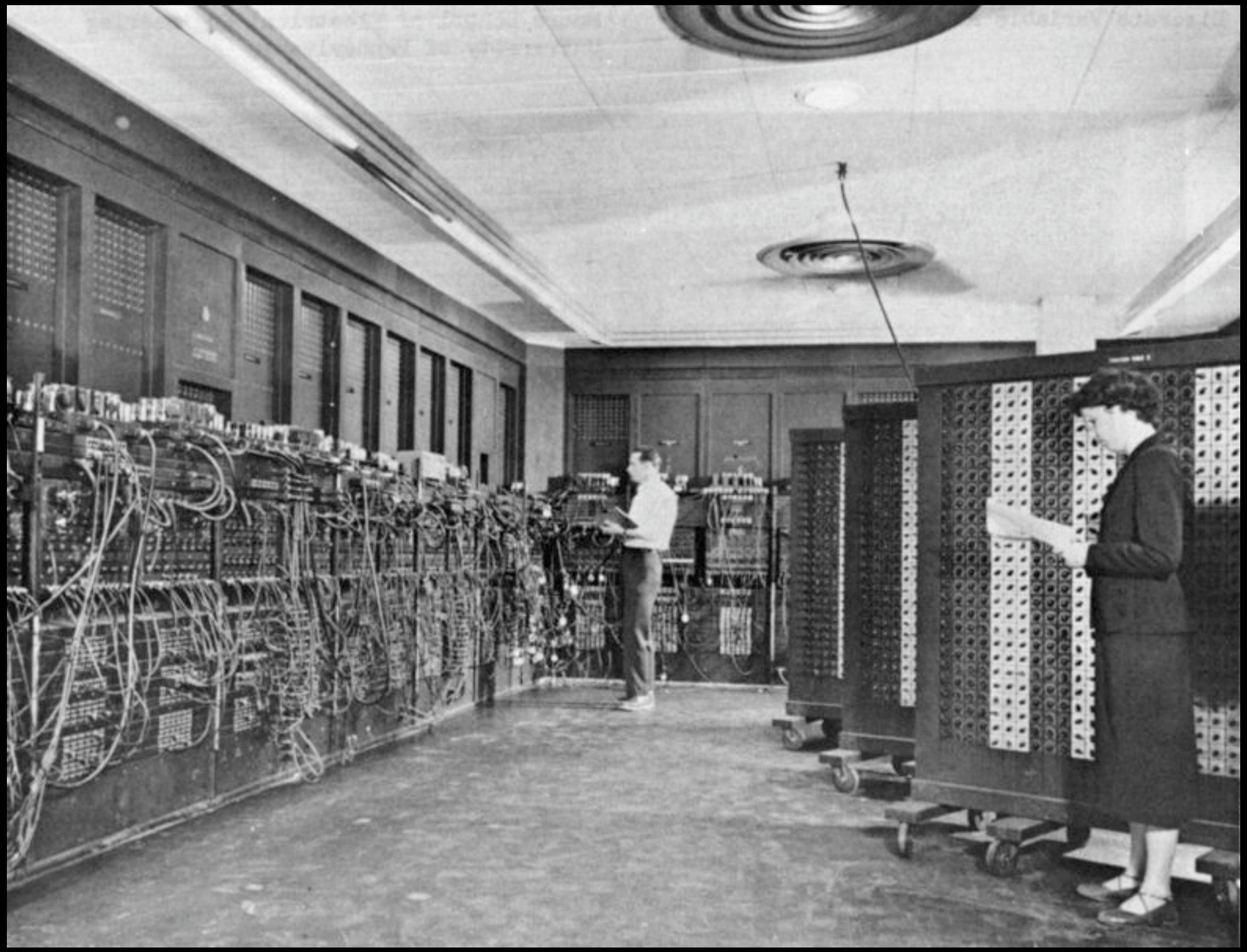
Unknown
Our Lord's Candle (Yucca whipplei), Lakeview Mountains, 22 Apr 2006
Smugmug.com

Unknown
http://www.rootsweb.com/~usgenweb/mn/stearns/postcards/quarry.jpg

Washington National Cathedral

http://www.cathedral.org/cathedral/discover/1930photos/5.shtml

http://www.nicmyers.com/media/hongkong_large_pano_nicmyers.jpg



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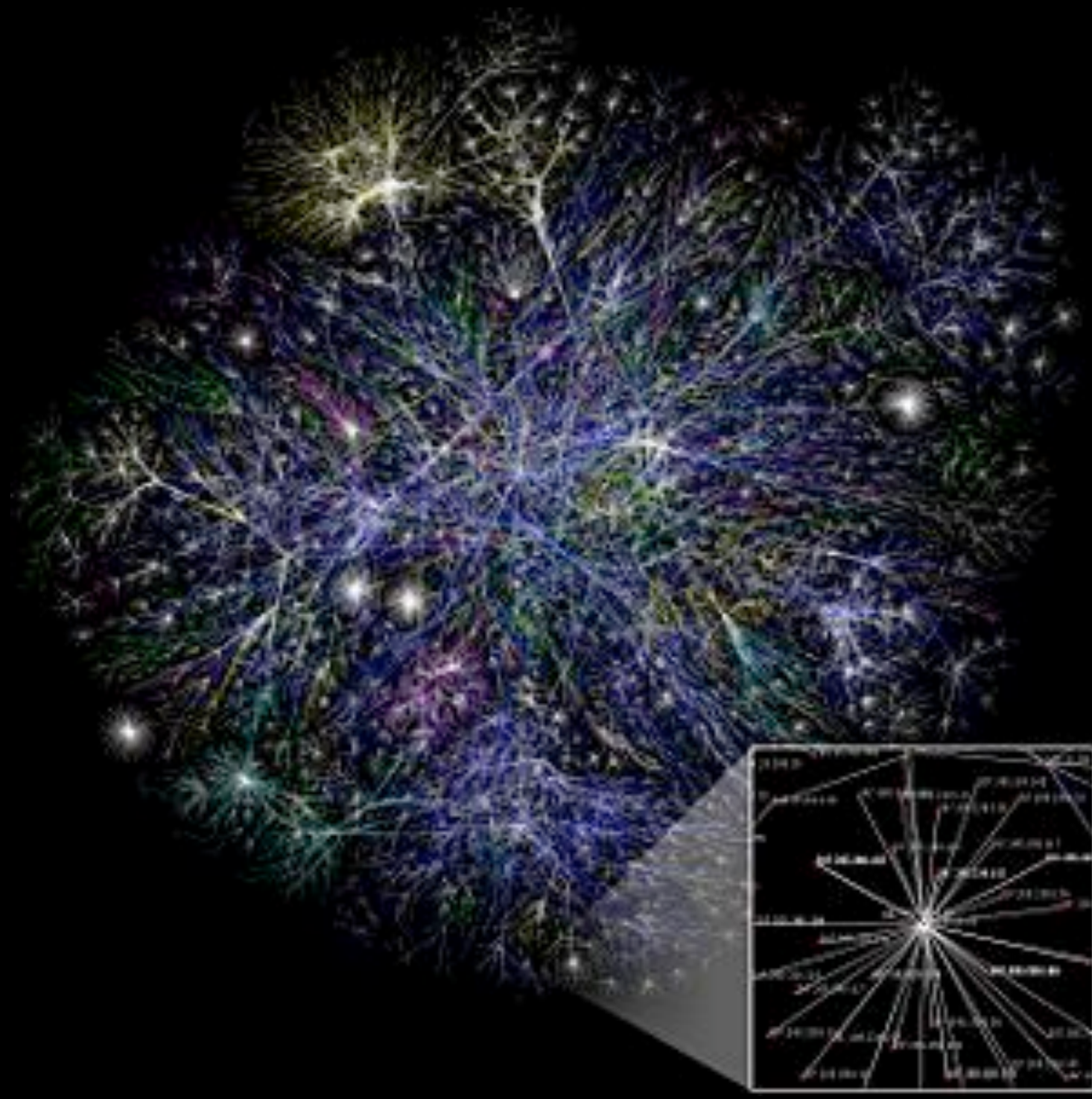

http://en.wikipedia.org/wiki/Internet

Apps

Tools

I. Info. theory & signal proc.

7. Control & dyn. systems
6. Reverse engineering
5. Fab, CAD & EDA
4. Standards & abstraction
3. Languages & grammars
2. Device design
1. Info. theory & signal proc.

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Construction of biologically functional bacterial plasmids in vitro

Cohen et al., PNAS, 1973

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Cloning and expression of the human erthropoietin gene

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Production of the antimalarial drug precursor artemisinic acid in engineered yeast

Ro et al., Nature, 2006

rt: 2005-11-12577

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Genetic engineering basics unchanged past 30+ years

We need new tools

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Genetic engineering basics unchanged past 30+ years

Synthetic Biology as Tools Revolution

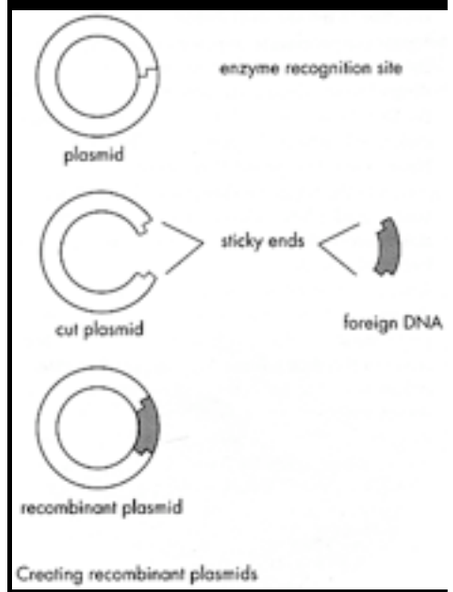
Synthetic Biology as Tools Revolution

First Gen. Biotech =

Synthetic Biology as Tools Revolution

First Gen. Biotech =

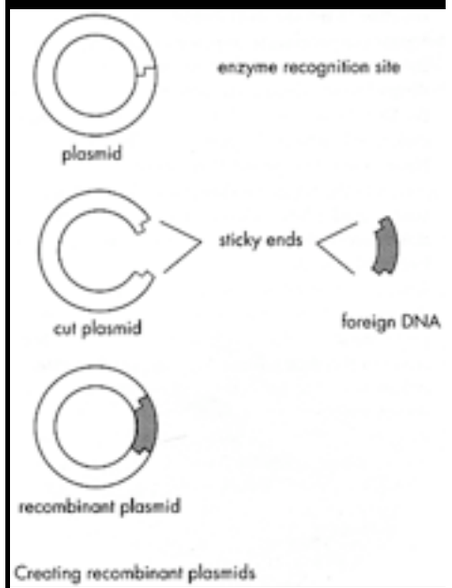
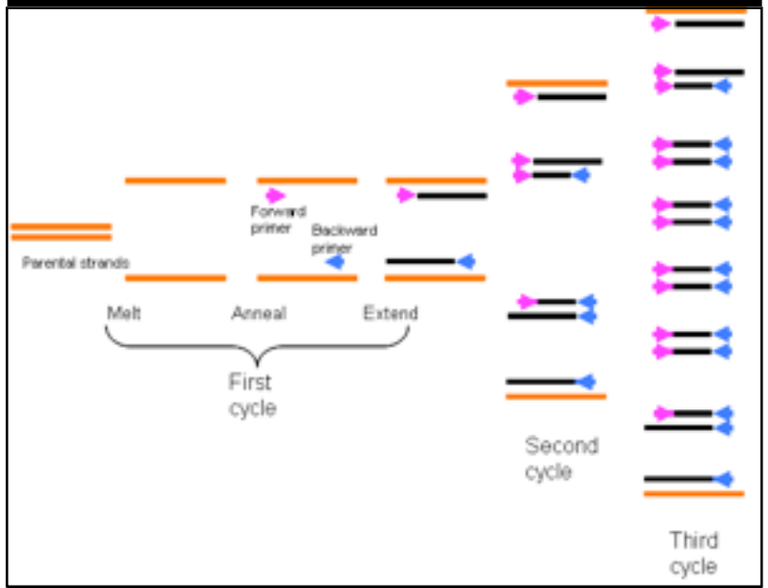
Recombinant DNA



Basic "Cut" & "Paste"

Synthetic Biology as Tools Revolution

First Gen. Biotech =

Recombinant DNA	Polymerase Chain Reaction
	
Basic "Cut" & "Paste"	Amplify & Make Simple Changes

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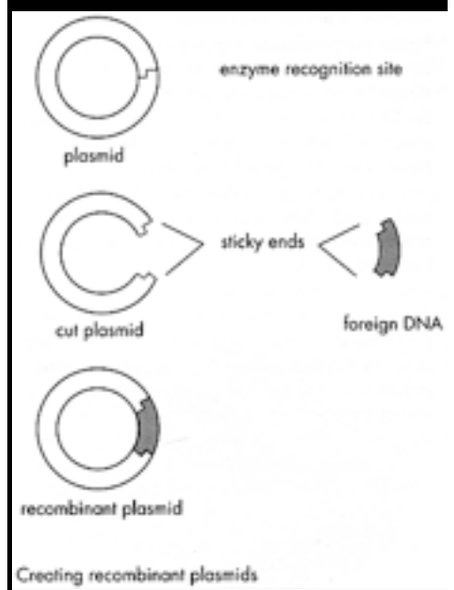
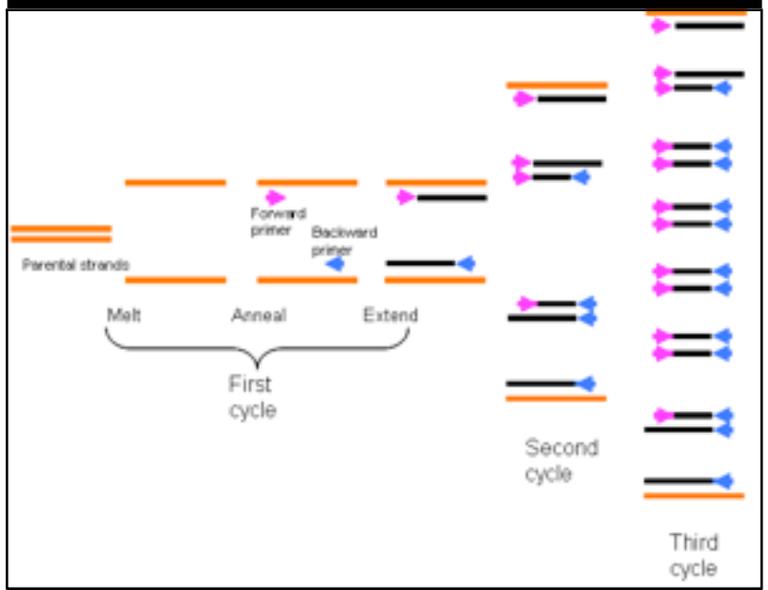


Basic "Cut" & "Paste"

Polymerase Chain Reaction



Amplify & Make Simple Changes

DNA Sequencing

Read Out the Genetic Code

Synthetic Biology as Tools Revolution

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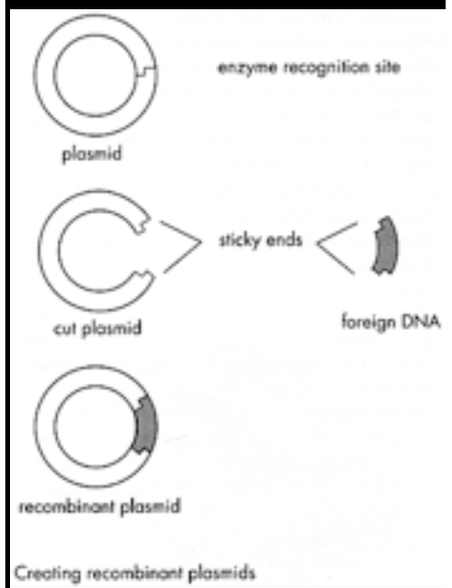

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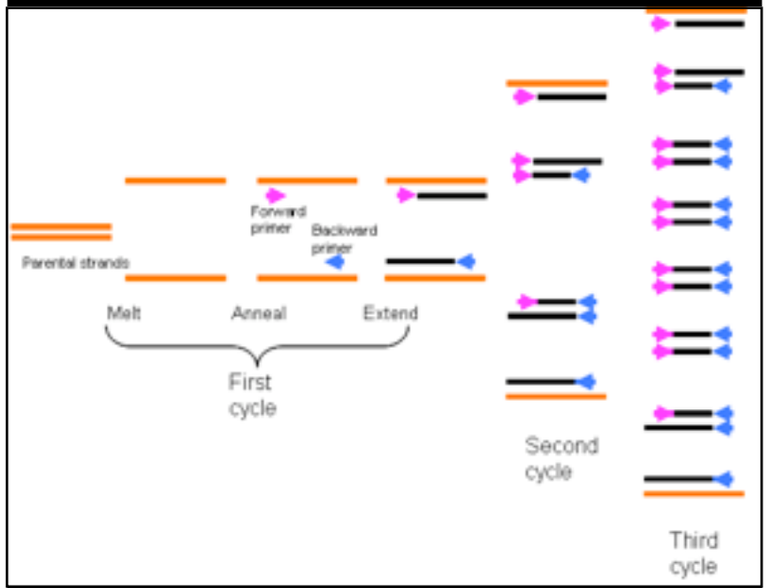

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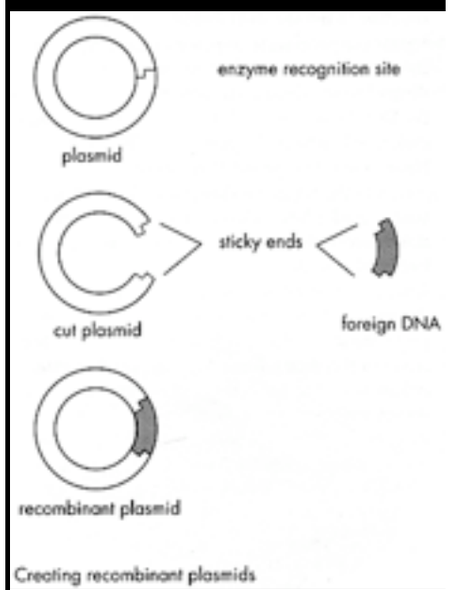
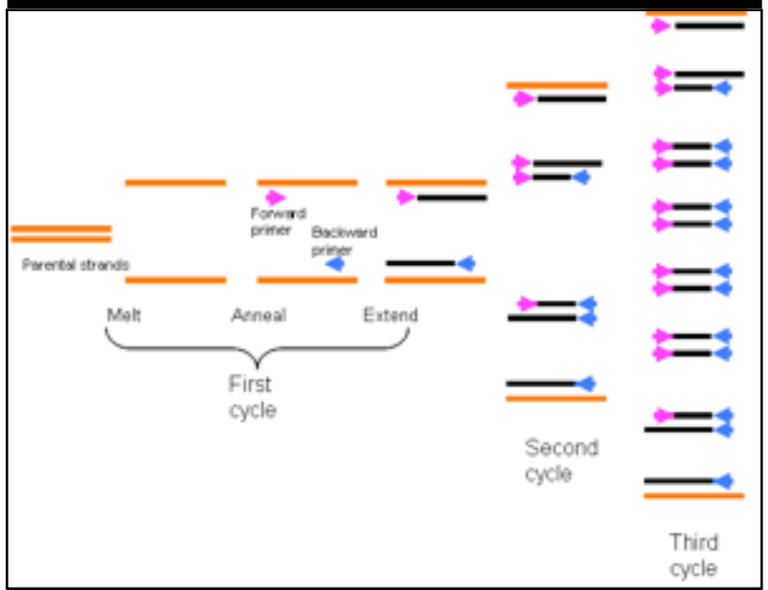
Recombinant DNA	Polymerase Chain Reaction	DNA Sequencing
		
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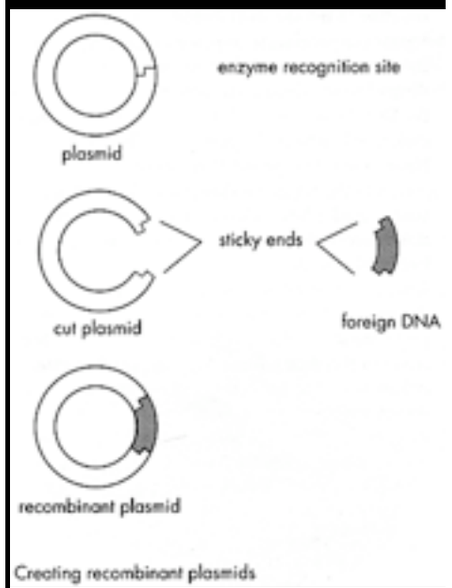

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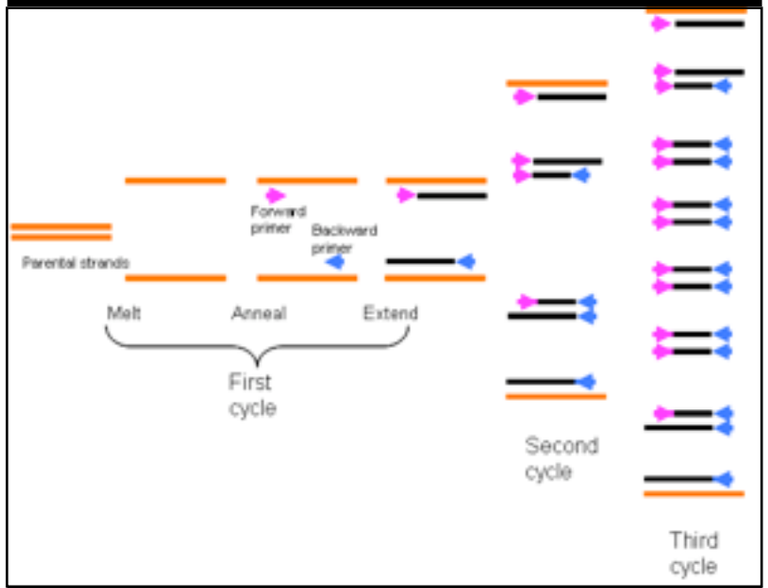

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Next Gen. Biotech Adds New Tools =

Synthesis

Decoupling of design & fabrication, leading to CAD and EDA.

Abstraction

Engineered simplicity enabling many component systems.

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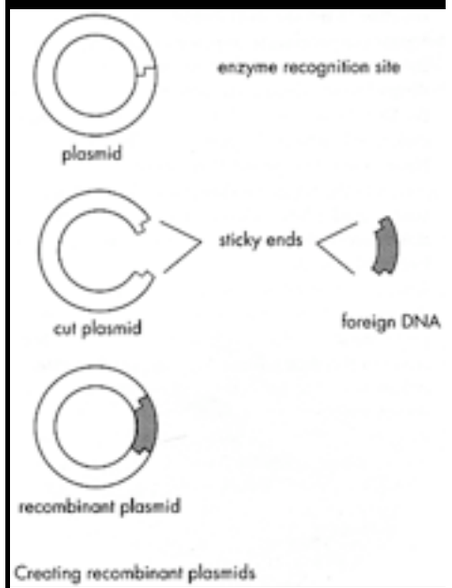

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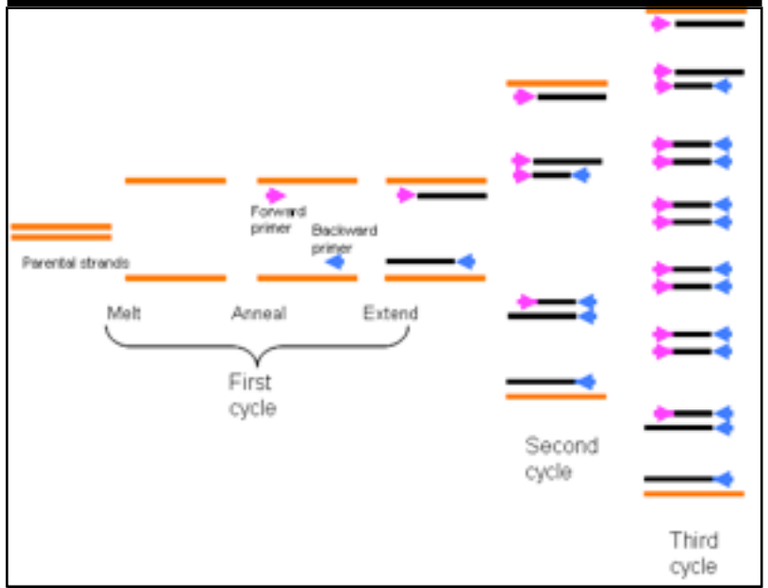

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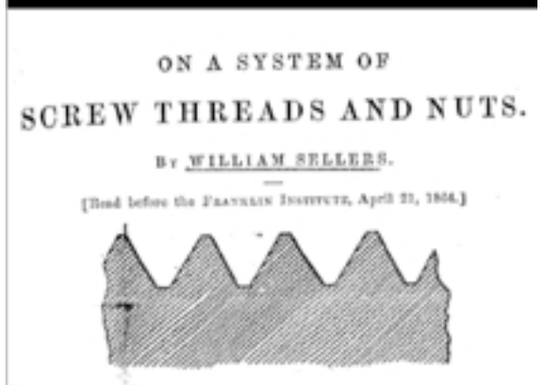
Standardization



Refined genetic components supporting "off the shelf" reuse.

Synthetic Biology as Tools Revolution

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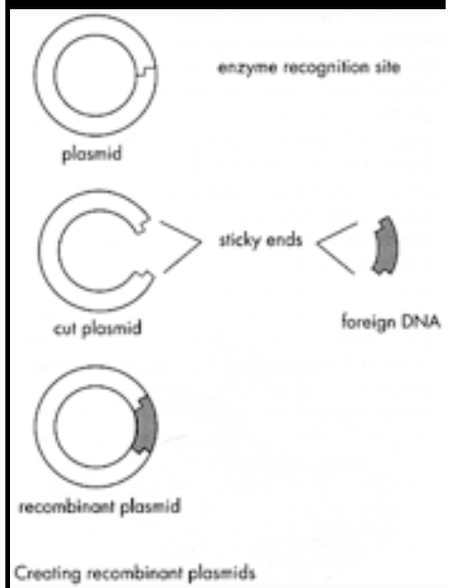

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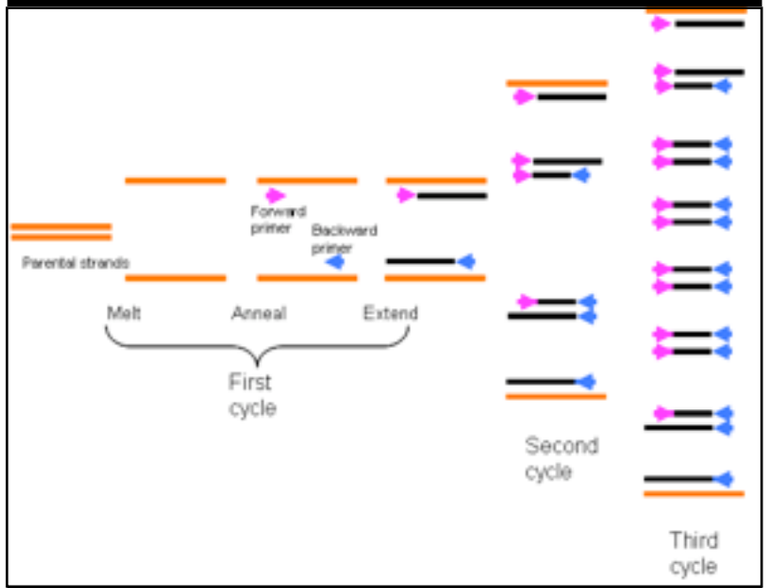

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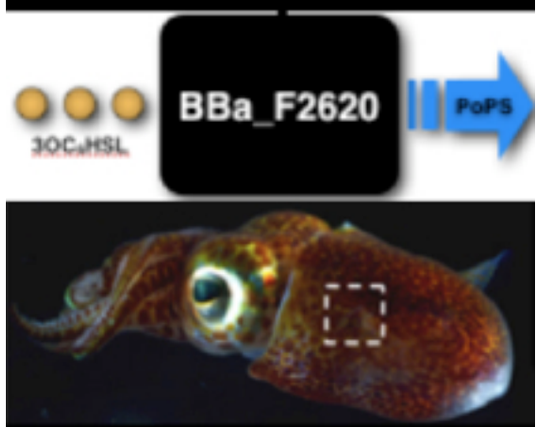
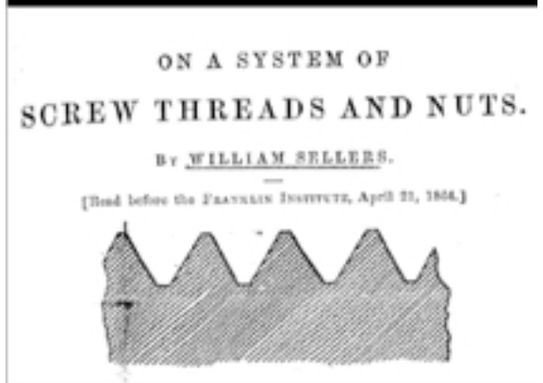


Engineered simplicity enabling many component systems.

Standardization


ON A SYSTEM OF
SCREW THREADS AND NUTS.
By WILLIAM SELLERS.

Refined genetic components supporting "off the shelf" reuse.

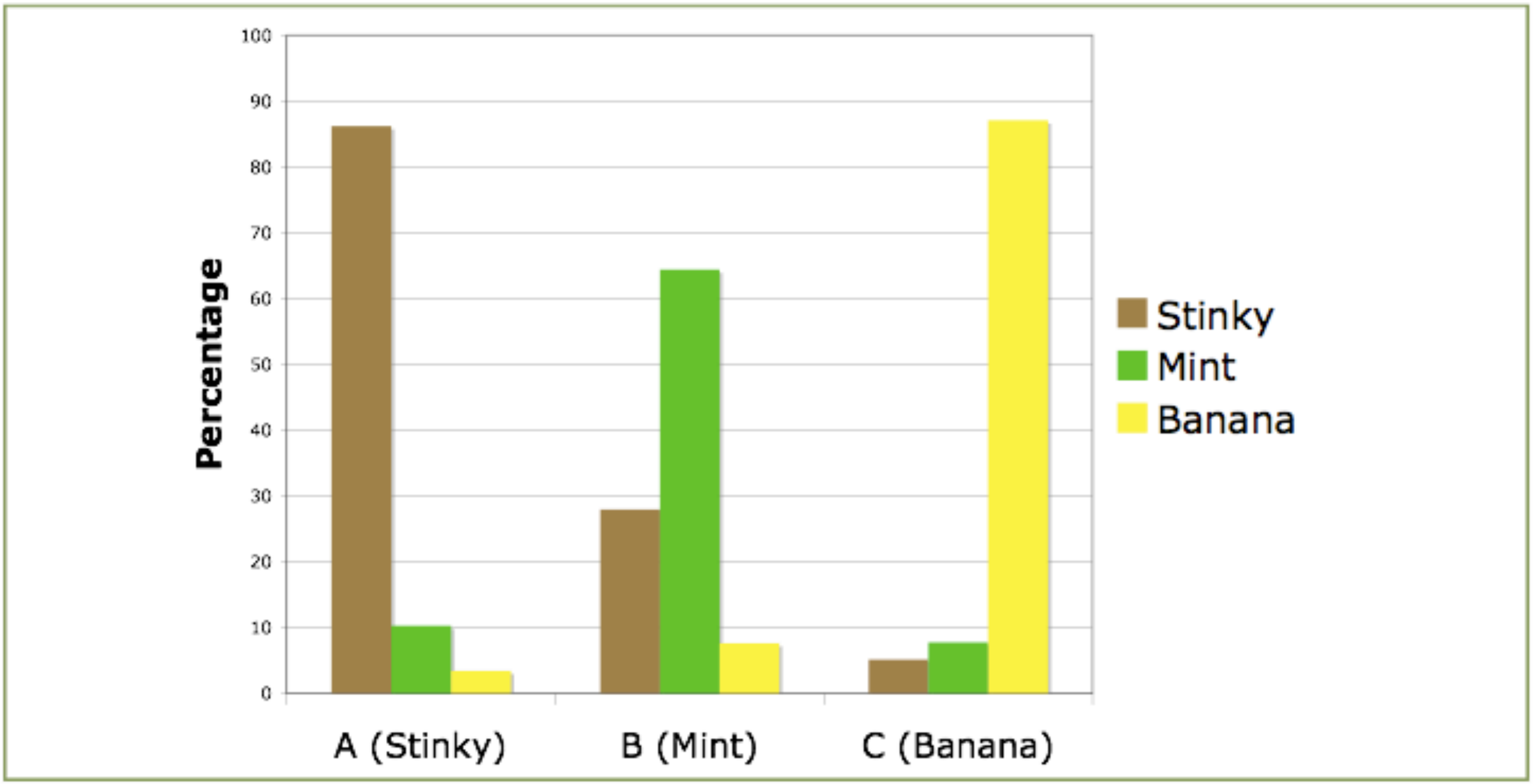
•••

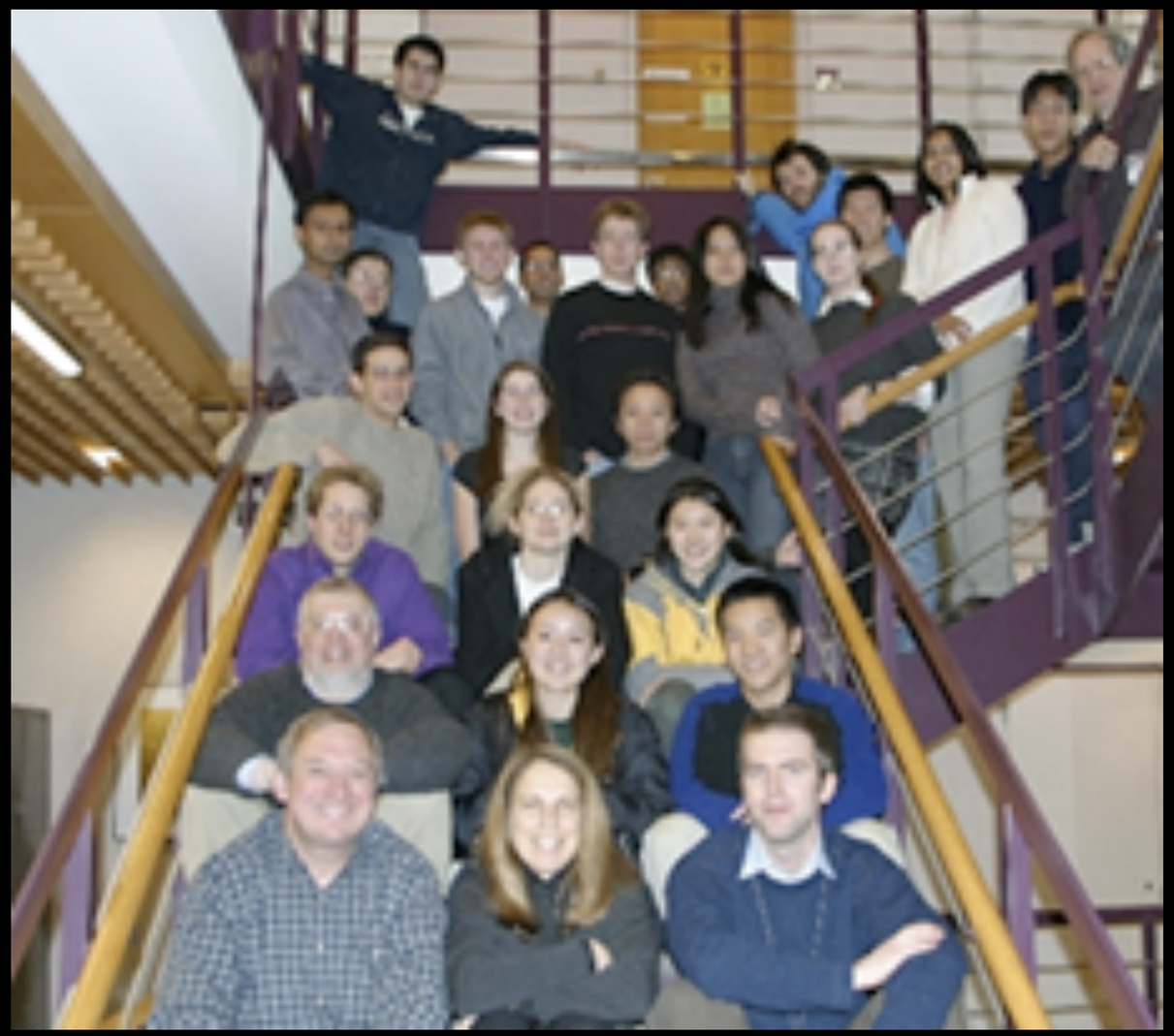

VWR Scientific


```
if {growing}
    call wintergreen()
else
    call bananas()
```

smell test: iGEM jamboree

smell test results





International Genetically Engineered Machine Competition

Global Distribution of Competing Teams


教学楼
Massachusetts Institute of Technology
CALTECH
iGEM

Should teenagers practice genetic engineering?

Yes

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Should military force include biotechnology?	No

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Will biohackers be good or bad?	Good

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Should the public support foundational research & the development of open technology platforms?	Yes!!!

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Should genetic engineers sign their work?	Yes

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Should genetic engineers sign their work?	Yes
How much can we produce with biology?	???

The Imperative of Synthetic Biology: A Proposed National Research Initiative

Drew Endy
Stanford University

Ed Lazowska
University of Washington

Version 6: December12, 2008[1]

The oxygen in the air we breathe, the plants or animals we eat, the environments we cherish and struggle to protect, the fuels that keep us warm and power our industries and vehicles, our medicines and clothes, ourselves and future generations as yet unborn – we are of biology and dependant upon her. In turn, our ability to develop and deploy biology as a technology – for sustainable energy production, green manufacturing, agile crop development, affordable healthcare and medicines – depends on the tools we have for engineering life itself.

35 years ago researchers learned to directly manipulate DNA using crude molecular tools to construct relatively simple genetic programs. These first tools gave birth to the biotechnology industry, resulting in new drugs and therapies (e.g., from recombinant insulin for treating diabetes to cheap artemisinin for fighting malaria), concerns (e.g., biological security), controversies (e.g., genetically engineered foods), and unmet promises (e.g., nitrogen fixing crops). Today, more powerful tools are being developed to help make biology easier to engineer via an emerging field of research known as "synthetic biology." Using early versions of these new tools, researchers have begun constructing genomes – the entire DNA program encoding an organism – from scratch[2]. Catalogs containing thousands of standardized DNA parts are being produced and freely distributed[3]. Undergraduates and high school students are developing genetic programs of their own designs such as bacteria that take living photographs, smell as bananas, detect and warn of arsenic contaminated well water, or provide probiotic supplements[4].

Endy & Lazowska (2008), doi:1721.1/43950

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1. Invest in DNA synthesis & construction tech.

2. Invest in open libraries of standard biological parts

3. Explore and test improved legal frameworks for biotech.

4. Develop & implement integrated strategy for biosecurity

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