Introduction to Bioengineering
BIOE/ENGR.80
Stanford University

Spring 2020 Class Slides

Day 10
27 April 2020

Week 3 reprise

CONCEPT
SKILL

Who are you and how are you motivated?

- Learn by understanding or learn by doing or other…

Analysis and design of biomolecules

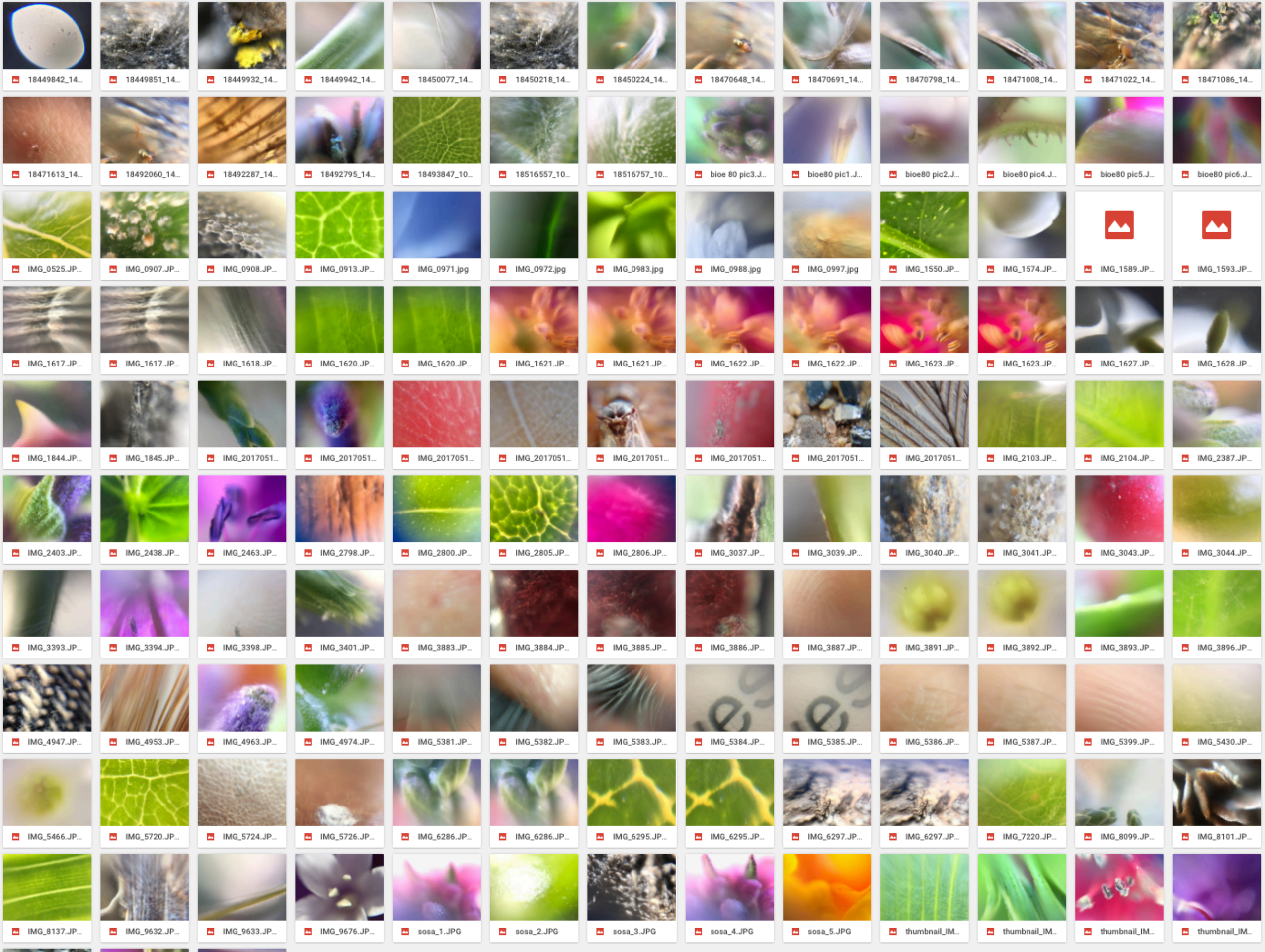
- DNA encodes useful molecules that can be redesigned

Analysis and design of genetic systems

- Biosystems can be designed bottom-up; profound noise?

Build & use your own microscope

- Foldscope
- Bioengineers make and improve tools
- The value of a technology is in large part defined by who can use the technology where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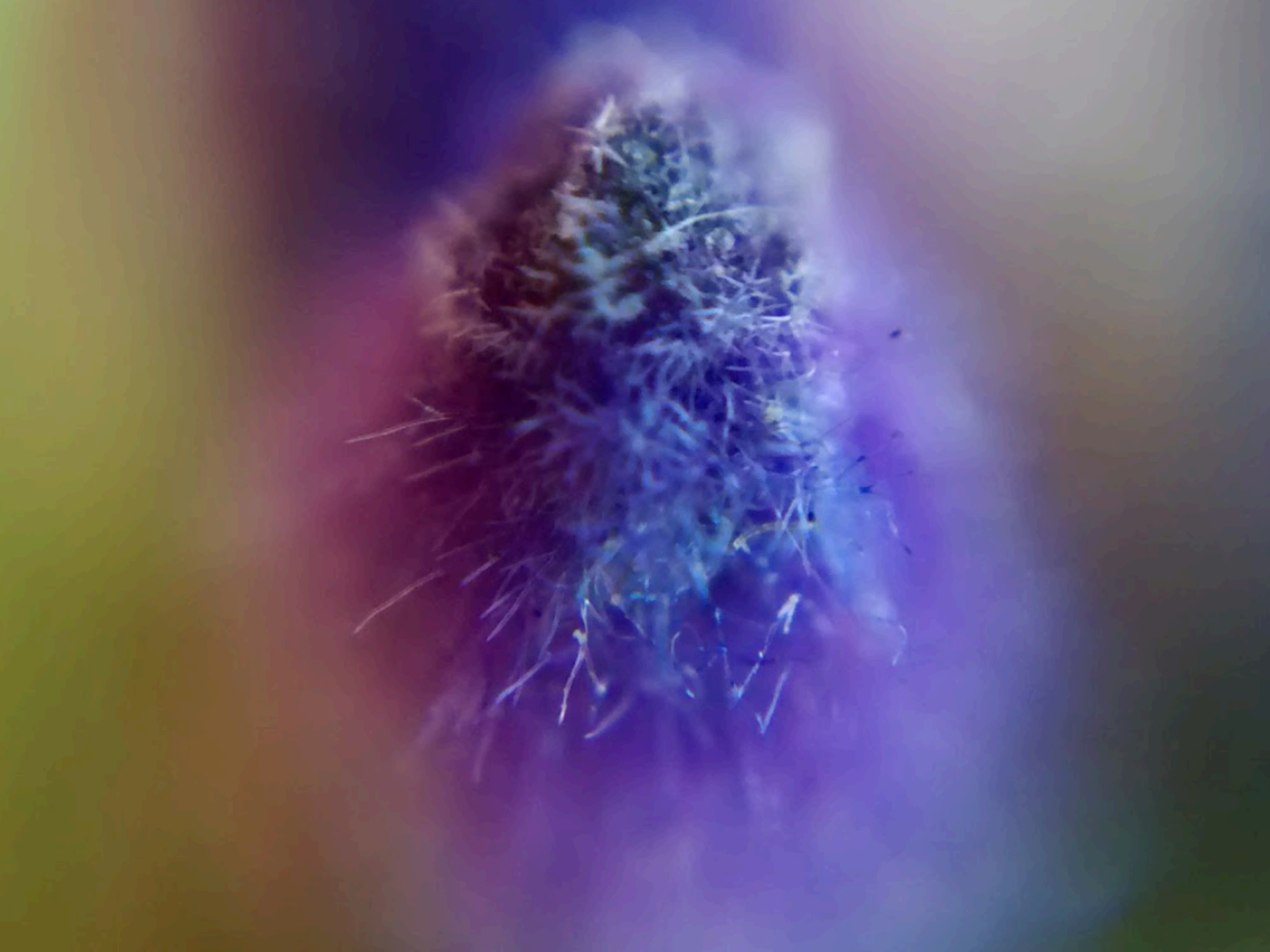


STATED DIFFERENTLY RE: FOLDSCOPE —
GO FOR IT; B.E. AWESOME; DISCOVER; INVENT; TEACH

Week 4 look ahead

CONCEPT
SKILL

Abstraction as a tool for **managing** biocomplexity

General system architecture for genetic engineering

I like, I wish, what if?

Team(s) rule(s)

SCIENCE | ESSAY

Taking Faster and Smarter to New Physical Frontiers

By DREW ENDY DEC. 5, 2011

The value of computers is often measured with terms like gigahertz, petaflop and exabyte — the speed, scale and efficiency with which they perform computations.

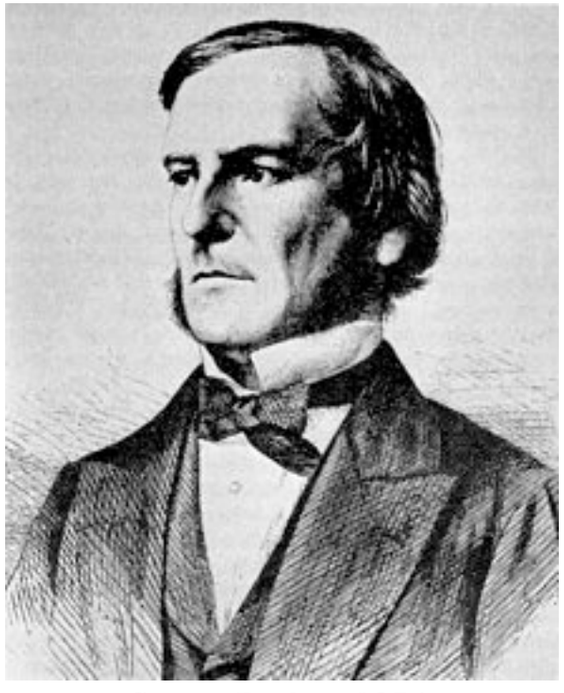
But so what? The intrinsic worth of computation ought to be a matter of the types of information being computed upon, and of when and where these computations occur. When you are lost, for example, a phone that will compute your route home is worth far more to you than an inaccessible desktop PC, no matter how fancy and powerful.

So a better way to think about the future of computing might be to ask when and where we could improve our ability to compute upon information that we greatly care about.

Consider a simple "computer" that counts to just 256, using eight bits of data storage. Could such a computer have any significant value?

Well, what if such computers could be installed inside every cell of your body? What if these computers were used to keep track of how many times each of your cells divided, forming the basis of systems that could track and control aging, development and cancer? If too many divisions are detected,

From George (logic) to Claude (electrical relays) to …



George Boole, c.1854

AN INVESTIGATION

OF

THE LAWS OF THOUGHT,

ON WHICH ARE FOUNDED

THE MATHEMATICAL THEORIES OF LOGIC AND PROBABILITIES.

BY

GEORGE BOOLE, LL. D.
PROFESSOR OF MATHEMATICS IN QUEEN'S COLLEGE, CORK.

11. *Signs of those mental operations whereby we collect parts into a whole, or separate a whole into its parts.*

We are not only capable of entertaining the conceptions of objects, as characterized by names, qualities, or circumstances, applicable to each individual of the group under consideration, but also of forming the aggregate conception of a group of objects consisting of partial groups, each of which is separately named or described. For this purpose we use the conjunctions "and," "or," &c. "Trees and minerals," "barren mountains, or fertile vales," are examples of this kind. In strictness, the words "and," "or," interposed between the terms descriptive of two or more classes of objects, imply that those classes are quite distinct, so that no member of one is found in another. In this and in all other respects the words "and" "or" are analogous with the sign + in algebra, and their laws are identical. Thus the expression "men and women" is, conventional meanings set aside, equivalent with the expression "women and men." Let x represent "men," y, "women;" and let + stand for "*and*" and "*or*," then we have

$$x + y = y + x, \tag{3}$$

Claude Shannon, c.1937

Analogue with the Calculus of Propositions. We are now in a position to demonstrate the equivalence of this calculus with certain elementary parts of the calculus of propositions. The algebra of logic (1), (2), (3) originated by George Boole, is a symbolic method of investigating logical relationships. The symbols of Boolean algebra admit of two logical interpretations. If interpreted in terms of classes, the variables are not limited to the two possible values 0 and 1. This interpretation is known as the algebra of classes. If, however, the terms are taken to represent propositions, we have the calculus of propositions in which variables are limited to the values 0 and 1*,

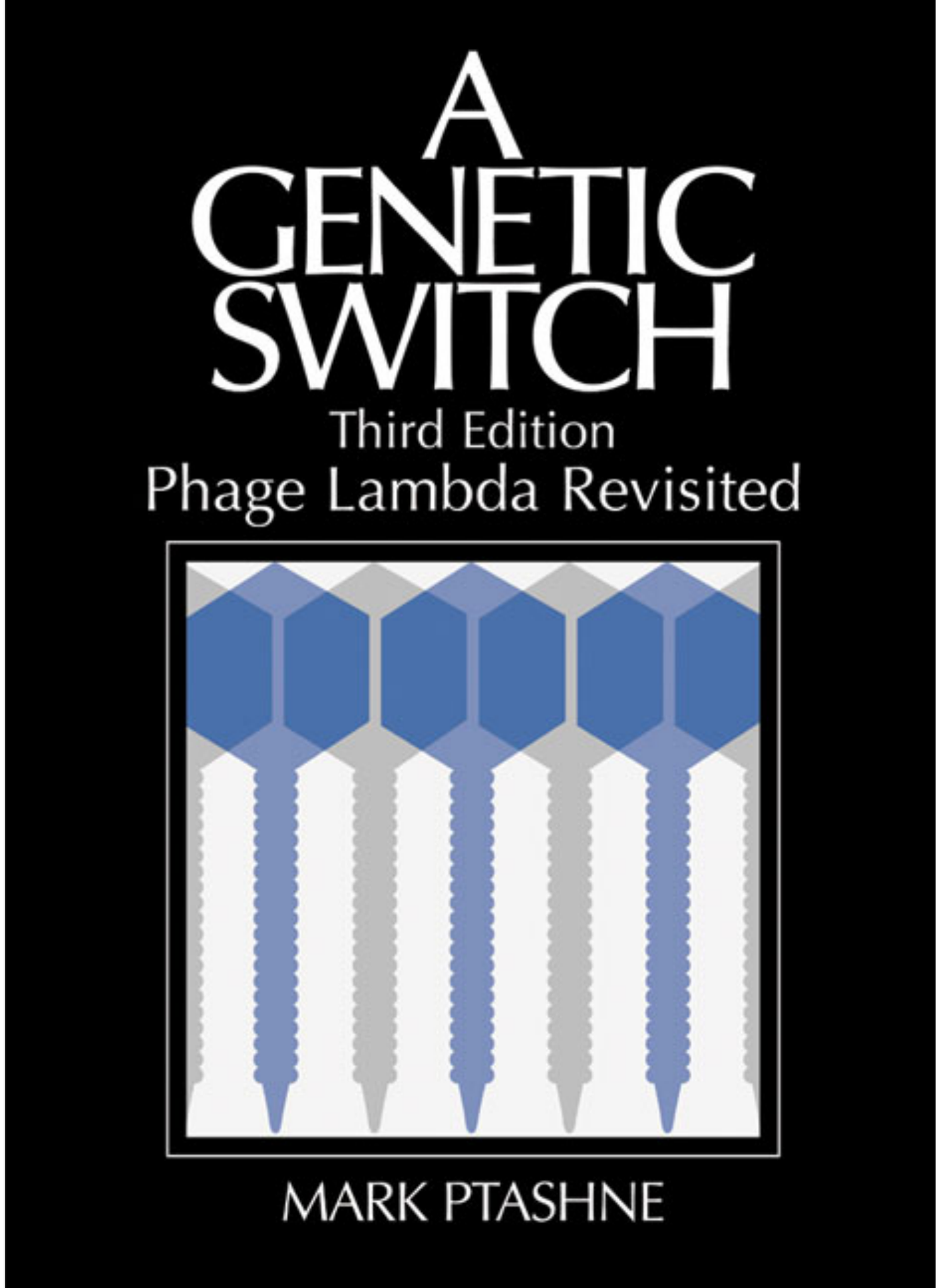
*This refers only to the classical theory of the Calculus of Propositions. Recently some work has been done with logical systems in which propositions may have more than two "truth values."

TABLE I

Analogue Between the Calculus of Propositions and the Symbolic Relay Analysis

Symbol	Interpretation in relay circuits	Interpretation in the Calculus of Propositions
X	The circuit X.	The proposition X.
0	The circuit is closed.	The proposition is false.
1	The circuit is open.	The proposition is true.
X + Y	The series connection of circuits X and Y	The proposition which is true if either X or Y is true.
XY	The parallel connection of circuits X and Y	The proposition which is true if both X and Y are true.
X'	The circuit which is open when X is closed, and closed when X is open.	The contradictory of proposition X.
=	The circuits open and close simultaneously.	Each proposition implies the other.

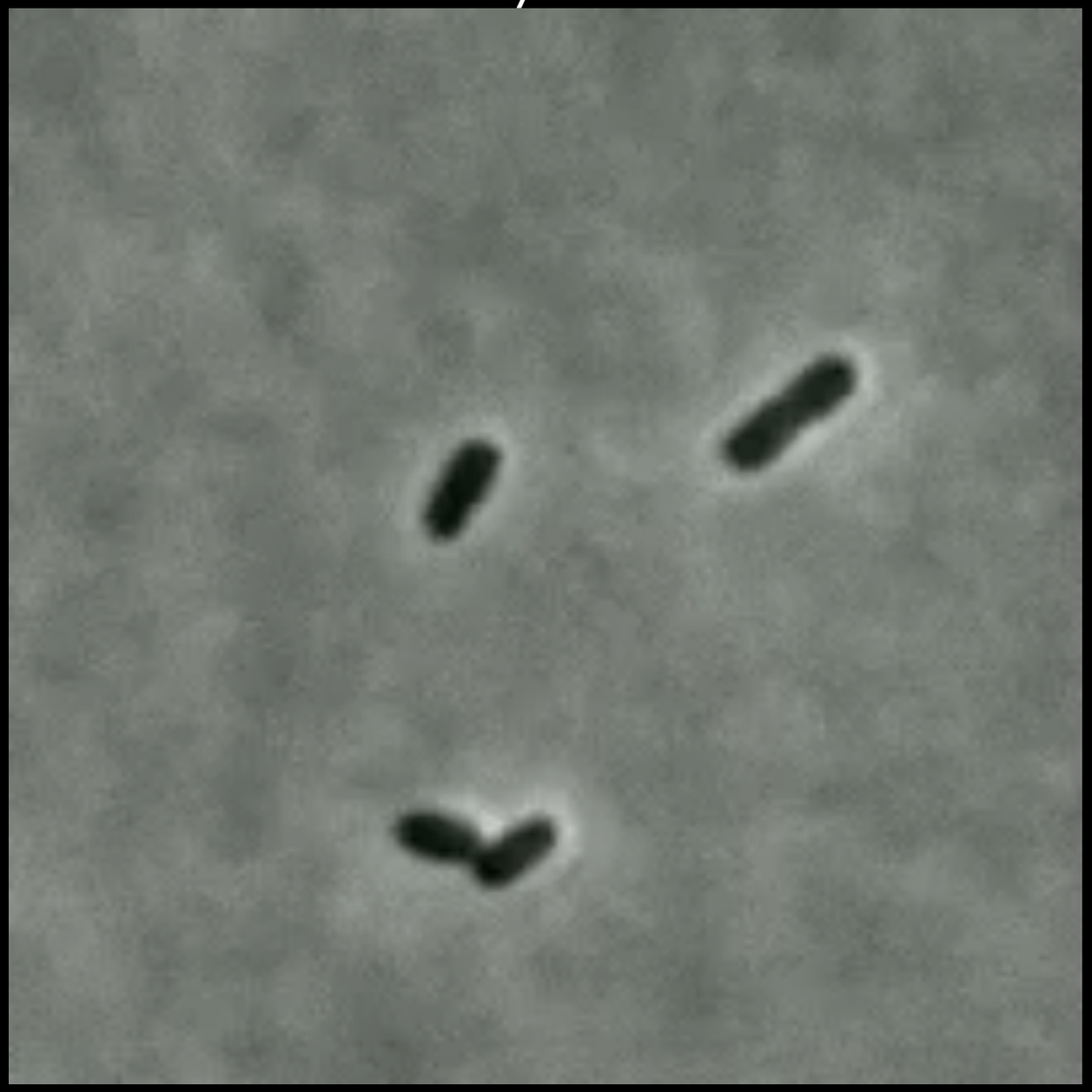
Let’s bioengineer living computers!!!



Hmm. As an engineer I was expecting a switch I could use, but instead I got a super complicated never-ending story.

https://www.cshlpress.com/link/genswitp.htm

St-Pierre & Endy PNAS USA 2008



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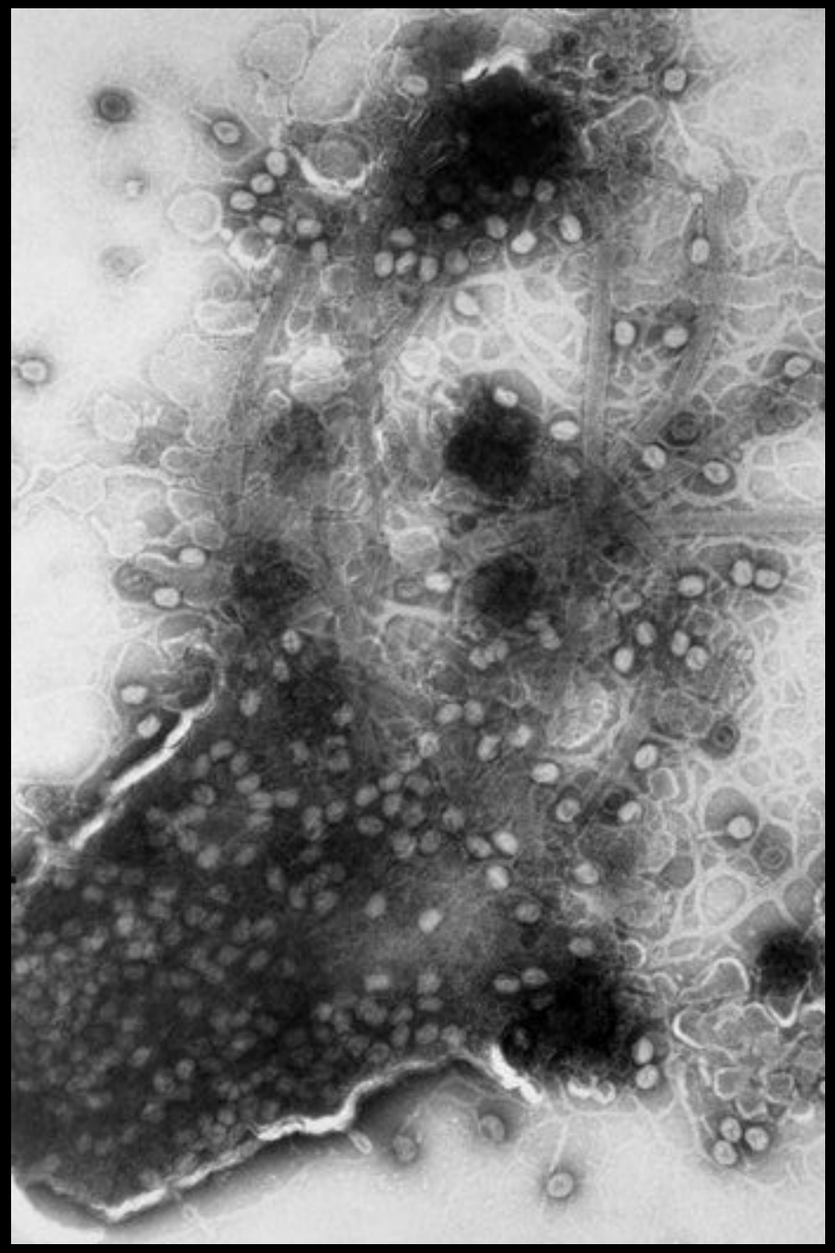


c/o Dinsdale Lab, SDSU

JOURNAL OF BACTERIOLOGY, June 2004, p. 3677–3686 Vol. 186, No. 12
0021-9193/04/$08.00+0 DOI: 10.1128/JB.186.12.3677–3686.2004

MINIREVIEW

Phage-Host Interaction: an Ecological Perspective

Sandra Chibani-Chennoufi, Anne Bruttin, Marie-Lise Dillmann, and Harald Brüssow*

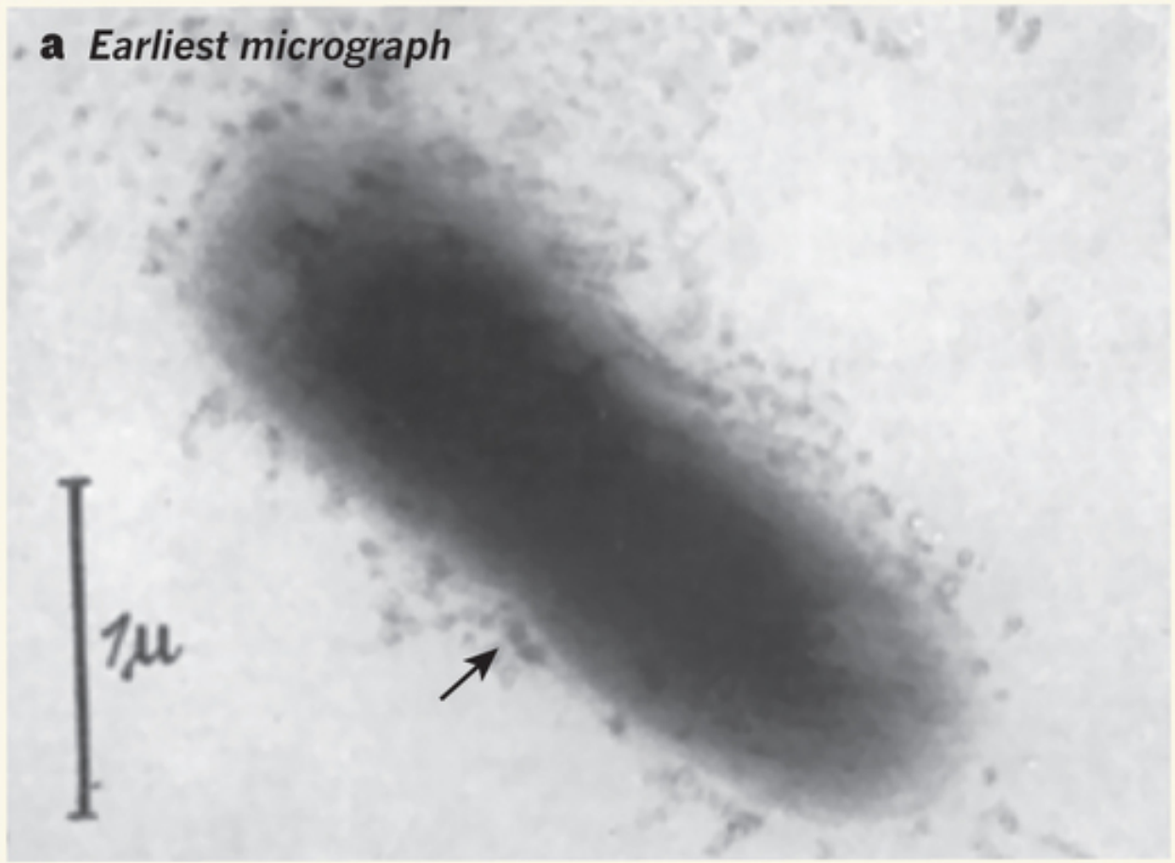
Nestlé Research Centre, CH-1000 Lausanne 26, Switzerland

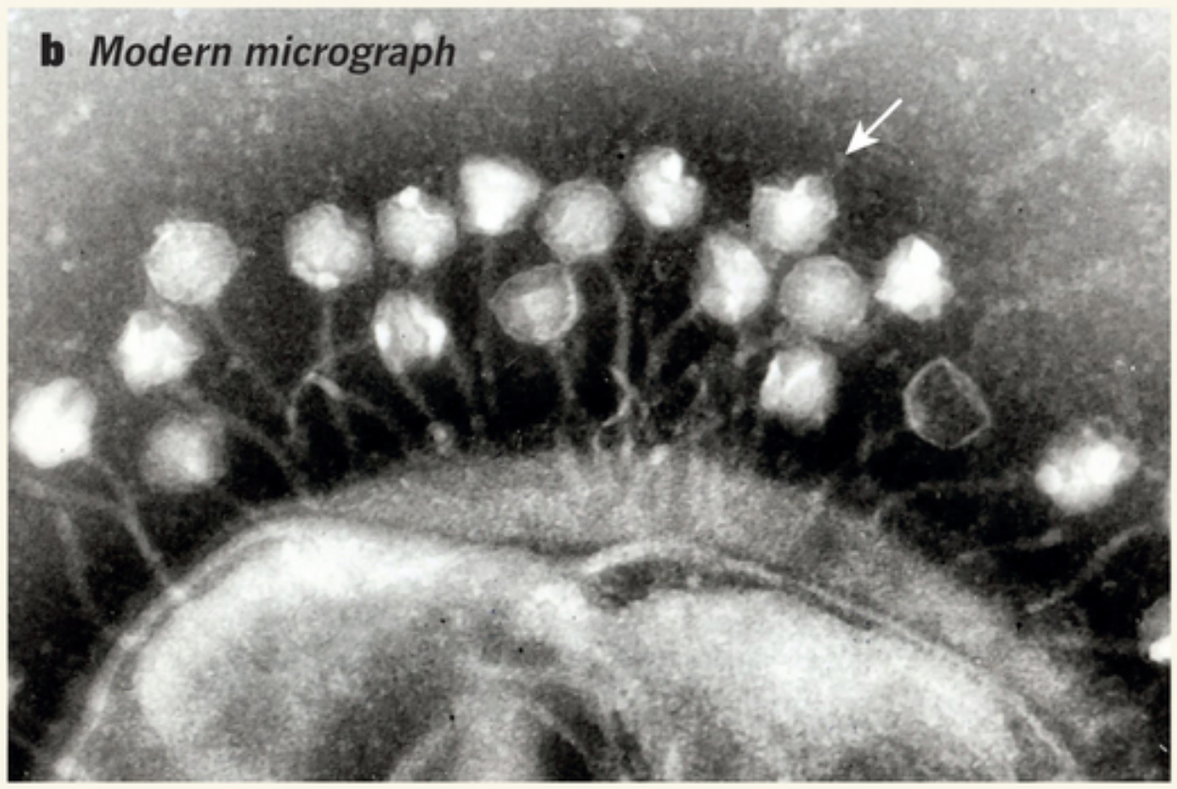
Nearly 100 years ago, Felix d'Herelle, the codiscoverer of bacteriophages, used bacteria to control insect pests and used phages against bacterial disease. His approaches reflected ecological insights before this branch of biology became an established scientific discipline. In fact, one might have predicted that phage research would become the springboard for biotechnology and ecology. However, d'Herelle was ahead of his time, and the zeitgeist in the 1930s pushed physicists into the question "What is life?" Phages as the simplest biological systems were the logical choice for this question, and phage research became the cradle of molecular biology.

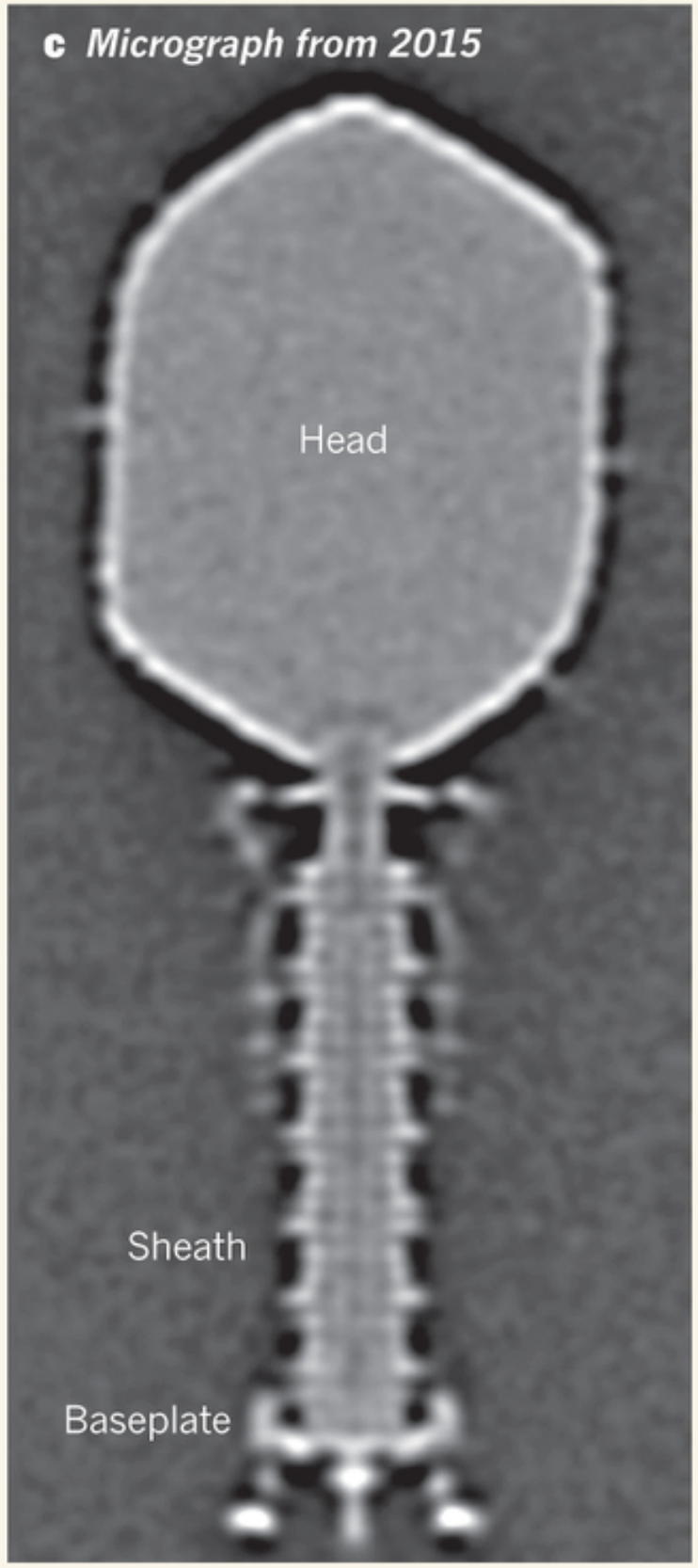
NUMBERS: PHAGE TITERS IN THE BIOSPHERE

Just 14 years ago, a Norwegian group surprised the scientific community with a report on the high concentration of phage-like particles in coastal water and the ocean and even higher concentrations in lakes (5). In eutrophic estuarine water, bacteria are found at a density of 10^6 cells/ml and viruses with a concentration of 10^7 particles/ml. These concentrations are estimates that vary with the seasons and the geographical location. In addition, these figures refer to physical and not viable entities. A popular model postulates about 10 to 50 different bacterial species and 100 to 300 different phage

All these figures have important consequence for our biological view of the world. If phages outnumber bacteria in the ocean, phages are likely to be numerically the most prominent biological systems on earth, with an estimated population size of $\geq 10^{30}$ phage particles. With these numbers, even rare





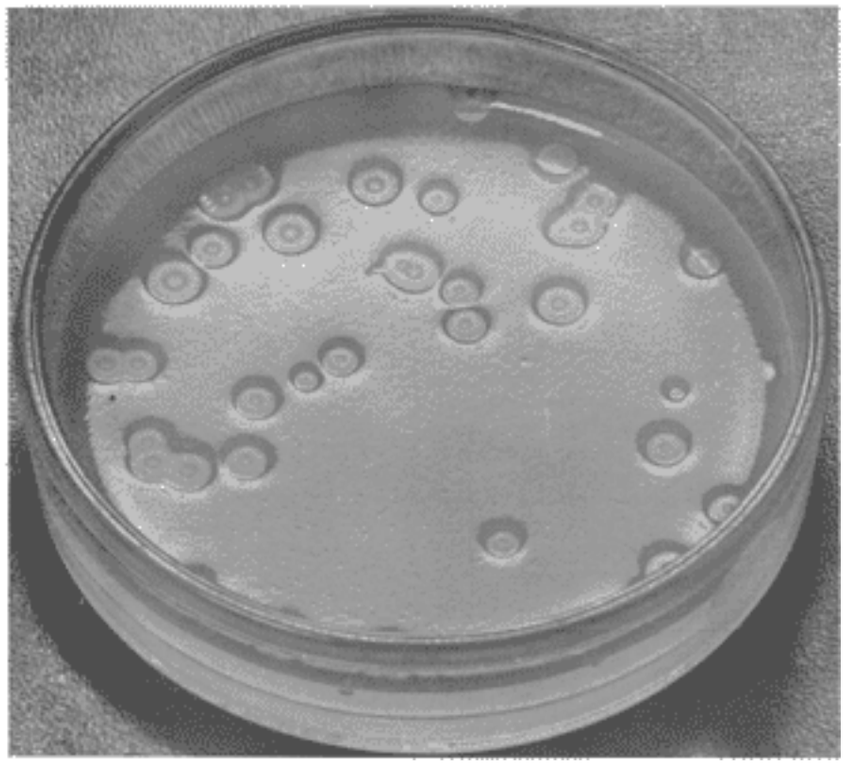


https://en.wikipedia.org/wiki/Bacteriophage

“In 1910, I was in Mexico, in the state of Yucatan, when an invasion of locusts occurred; the Indians reported to me that in a certain place the ground was strewn with the corpses of these insects. I went there and collected sick locusts, easily picked out since their principal symptom was an abundant blackish diarrhoea. This malady had not as yet been described, so I studied it. It was caused by bacteria, the locust coccobacillus, which were present almost in the pure state in the diarrhoeal liquid. I could start epidemics in columns of healthy insects by dusting cultures of the coccobacillus on plants in front of the advancing columns: the insects infected themselves as they devoured the soiled plants.”

https://en.wikipedia.org/wiki/F%C3%A9lix_d%27Herelle

http://bio.classes.ucsc.edu/bio105l/EXERCISES/PHAGE/dH.pdf



“During the years which followed, I went from the Argentine to North Africa to spread this illness. In the course of these researches, at various times I noticed an anomaly shown by some cultures of the coccobacillus which intrigued me greatly, although in fact the observation was ordinary enough, so banal indeed that many bacteriologists had certainly made it before on a variety of cultures.”

“The anomaly consisted of clear spots, quite circular, two or three millimeters in diameter, speckling the cultures grown on agar. I scratched the surface of the agar in these transparent patches, and made slides for the microscope; there was nothing to be seen. I concluded from this and other experiments that the something which caused the formation of the clear spots must be so small as to be filtrable, that is to say able to pass a porcelain filter of the Chamberland type, which will hold back all bacteria.”

http://bio.classes.ucsc.edu/bio105l/EXERCISES/PHAGE/dH.pdf

BACTERIOPHAGE

FELIX D'HERELLE

Sur un microbe invisible antagoniste des bacilles dysentériques

FÉLIX D'HÉRELLE

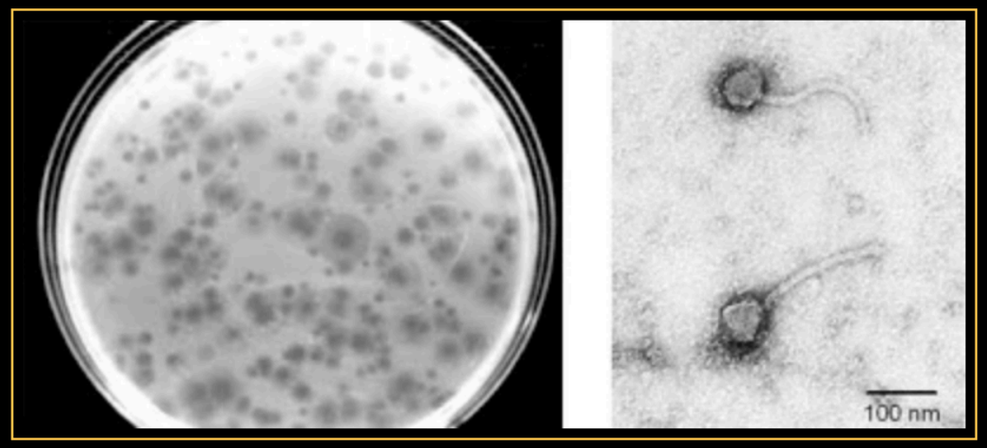
1917

THE EVILUTIONARY BIOLOGIST

ALL SCIENCE, ALL THE TIME

THURSDAY, SEPTEMBER 10, 2009

Phage Hunters



18 freshmen students have enrolled in my Genomics Research Experience course aka *Phage Hunters*. This course is supported by the Howard Hughes Medical Institute's Science Education Alliance. My students have begun the process of isolating novel Mycobacteriophages by collecting soil samples from the wild and plating them on lawns of *Mycobacterium smegmatis*, a *M. tuberculosis* relative. Unlike *M. tuberculosis*, *M. smegmatis* is non-pathogenic and is easier to grow and manipulate under experimental conditions. Nonetheless, by virtue of their close phylogenetic relationship, the two bacteria are quite similar in many respects. Thus, *M. smegmatis* may be an excellent model for deriving treatments against tuberculosis.

Collecting Mycophage is already paying handsome dividends. Albert Einstein College of Medicine Professor William Jacobs isolated a phage he named the Bronx Bomber from soil from his own backyard in the Bronx. With University of Pittsburgh Professor Graham Hatfull, Jacobs characterized this phage in the laboratory. They found that this phage is able to insert itself into the genome of *M. smegmatis* at a very specific location in the groEL1 gene, thus disabling the gene. One of groEL1's functions is to facilitate the production of biofilms.

ME

ABOUT ME

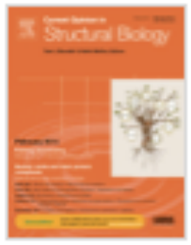
JOHN DENNEHY
QUEENS, NY, UNITED STATES

I'm an evolutionary biologist who studies bacteriophage life history stochasticity and the population dynamics of host/pathogen interactions I'm currently affiliated with Queens College and the CUNY Graduate Center. I can be reached at

Current Opinion in Structural Biology

Volume 24, February 2014, Pages 125–131

Folding and binding / Nucleic acids and their protein complexes



The ins and outs of serine integrase site-specific recombination

Karen Rutherford, Gregory D Van Duyne

Show more

http://dx.doi.org/10.1016/j.sbi.2014.01.003

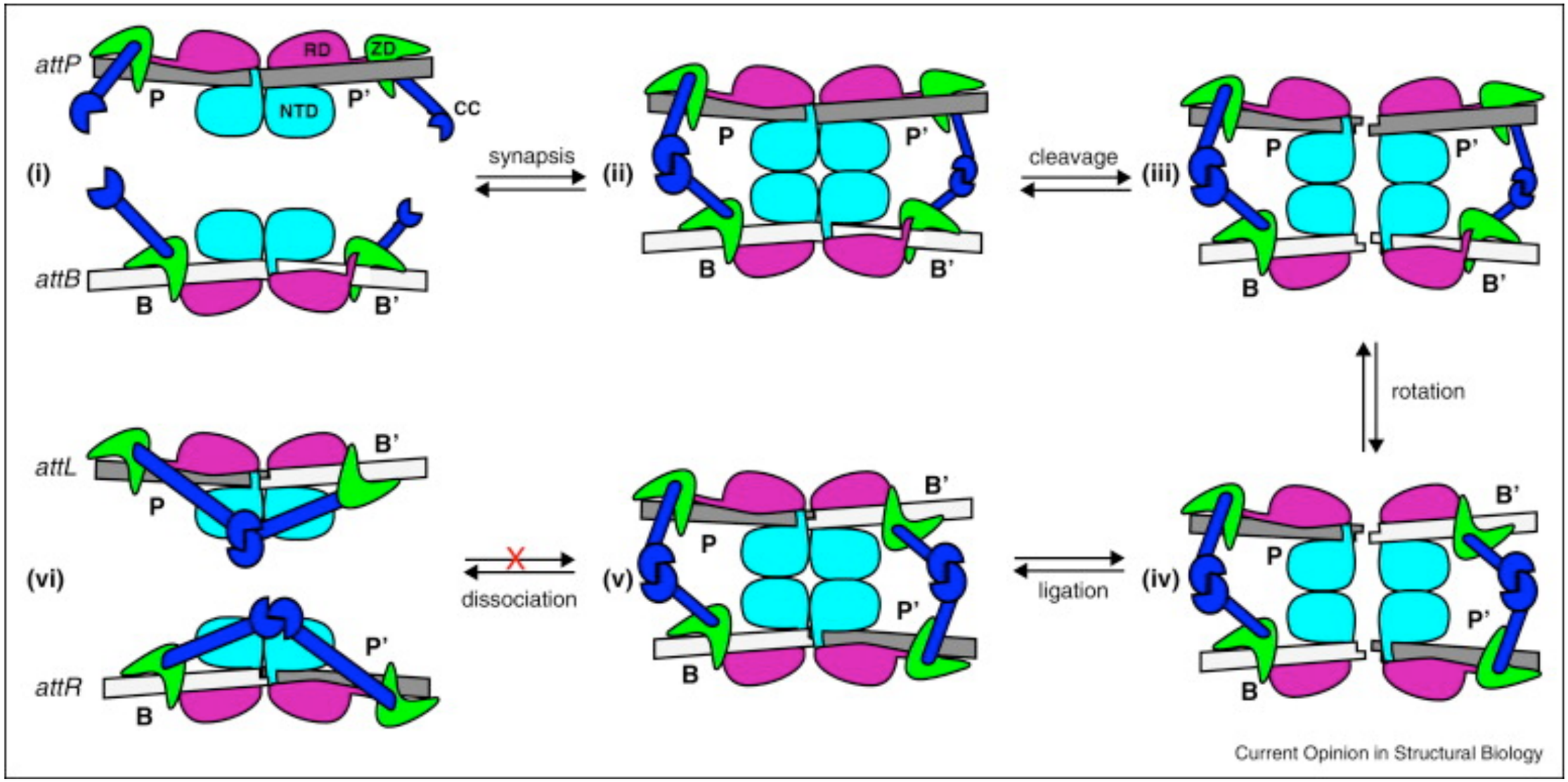
Highlights

- A serine integrase–DNA complex structure provides the basis for site selectivity.
- A coiled-coil motif influences synaptic efficiency and promotes *attP* × *attB* recombination.
- A recombination directionality factor stimulates excision and inhibits integration.
- The RDF may bind the coiled-coil motif, altering site-dependent synapsis efficiency.

Serine integrases catalyze the integration and excision of phage genomes into and out of bacterial chromosomes in a highly specific and directional manner, making these proteins powerful tools for genome engineering. In 2013, the first structure of a serine integrase–DNA complex was reported. This work revealed how the phage *attP* sequence is recognized by the integrase and provided important clues about how serine integrases bind to other attachment site sequences. The resulting structural models indicate that distinct spatial arrangements of integrase domains are present for each attachment site complex. Here we describe how serine integrases may exploit this site-dependent domain arrangement to regulate the direction of recombination. We also discuss how phage-encoded recombination directionality factors could change this directionality by altering the nature of inter-subunit interactions.

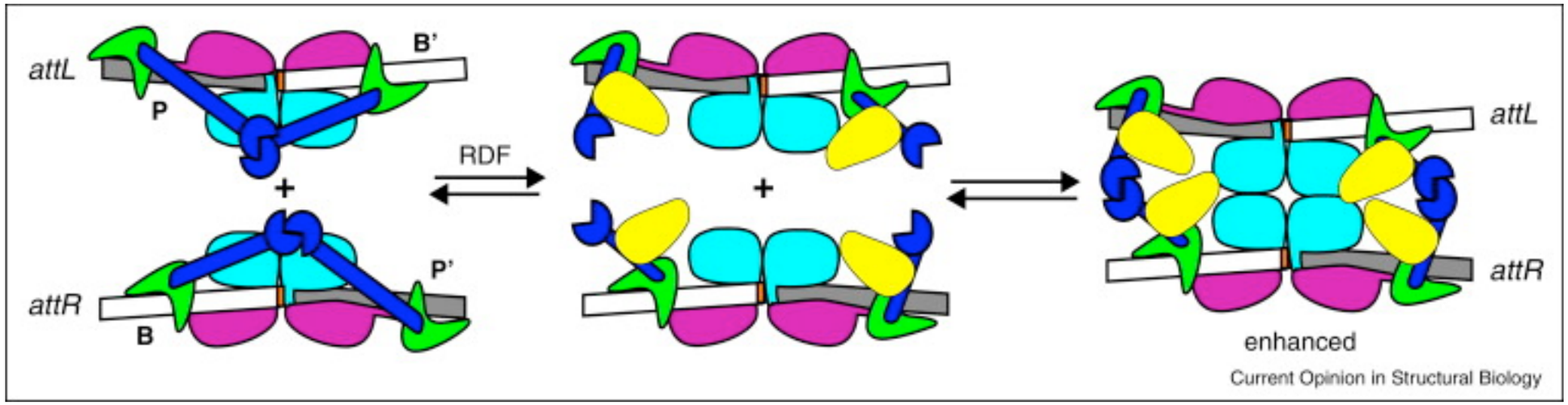
Current Opinion in Structural Biology 2014, **24**:125–131

“Recombinases” mediate “cut, exchange, & paste” among two DNA molecules



Karen Rutherford & Gregory D Van Duyne (2014)
The ins and outs of serine integrase site-specific recombination
http://dx.doi.org/10.1016/j.sbi.2014.01.003

Recombinase Directionality Factors (RDFs) can reverse the recombination reaction



A plausible model for recombination directionality factor (RDF)-stimulated excision. The RDFs (yellow) could bind to the Int CC motifs and disrupt the intra-molecular interactions responsible for inhibiting attL × attR recombination. The RDFs may also interact with additional integrase domains and in some systems may interact with one another. Integrase domains are colored as in Figure 1.

Karen Rutherford & Gregory D Van Duyne (2014)
The ins and outs of serine integrase site-specific recombination
http://dx.doi.org/10.1016/j.sbi.2014.01.003

Wait…

Unending biological details…

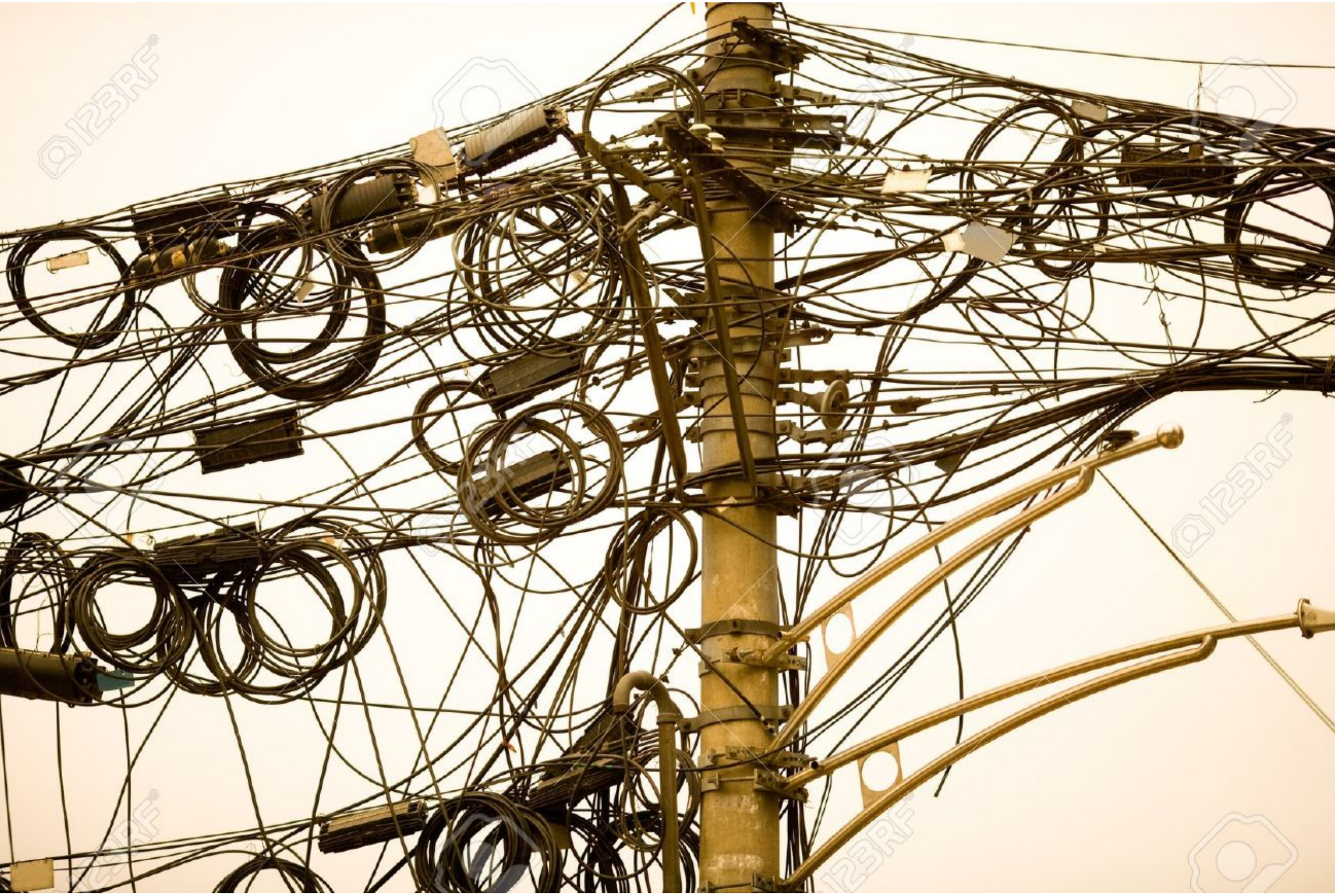
Overwhelming complexity…

Having to do science…

No end in sight…

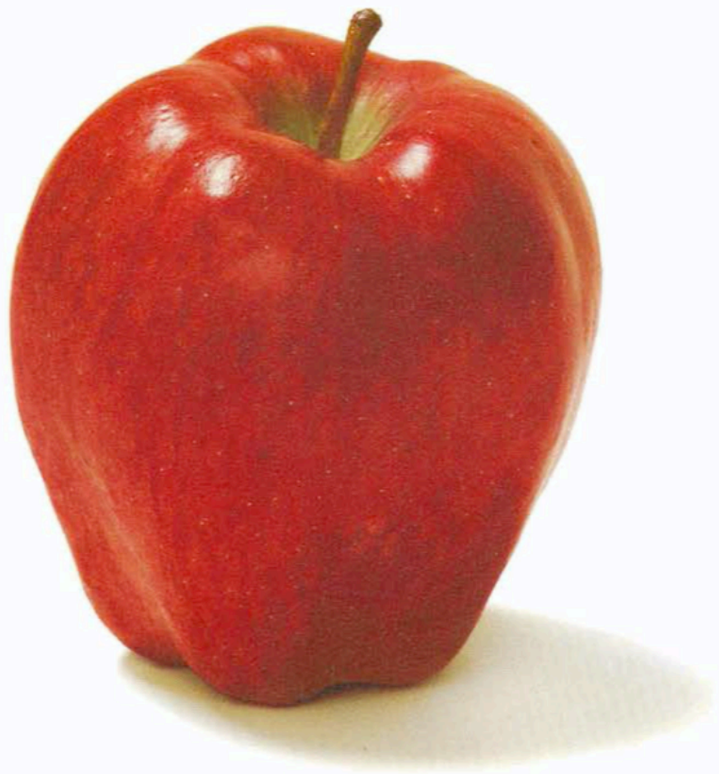
http://images2.layoutsparks.com/1/210989/beach-paradise-deault-trees.jpg

Q. What is the magnetic field? A. Who cares!

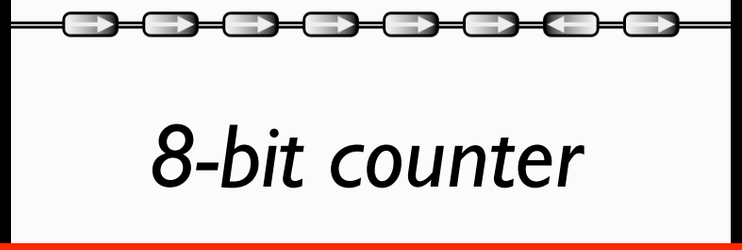


https://www.123rf.com/photo_7546464_a-tangle-of-cables-and-wires-in-shanghai-china.html

Simplicity is the ultimate sophistication.



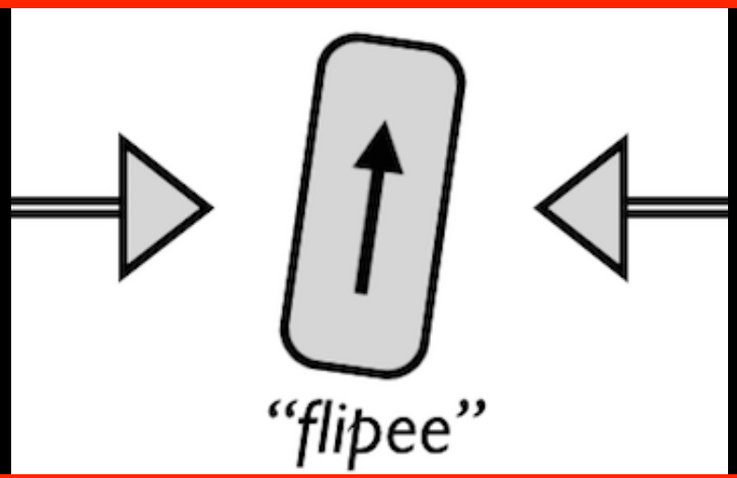
Introducing Apple II™, the personal computer.



8-bit counter

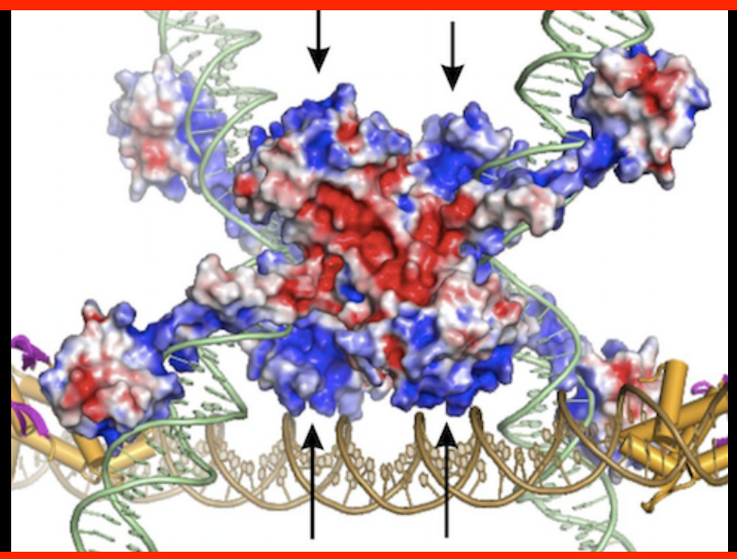
Systems = One or more devices encoding a human defined function(s).

Abstraction barrier! Do not cross!



Devices = One or more parts encoding a human defined function(s).

Abstraction barrier! Do not cross!



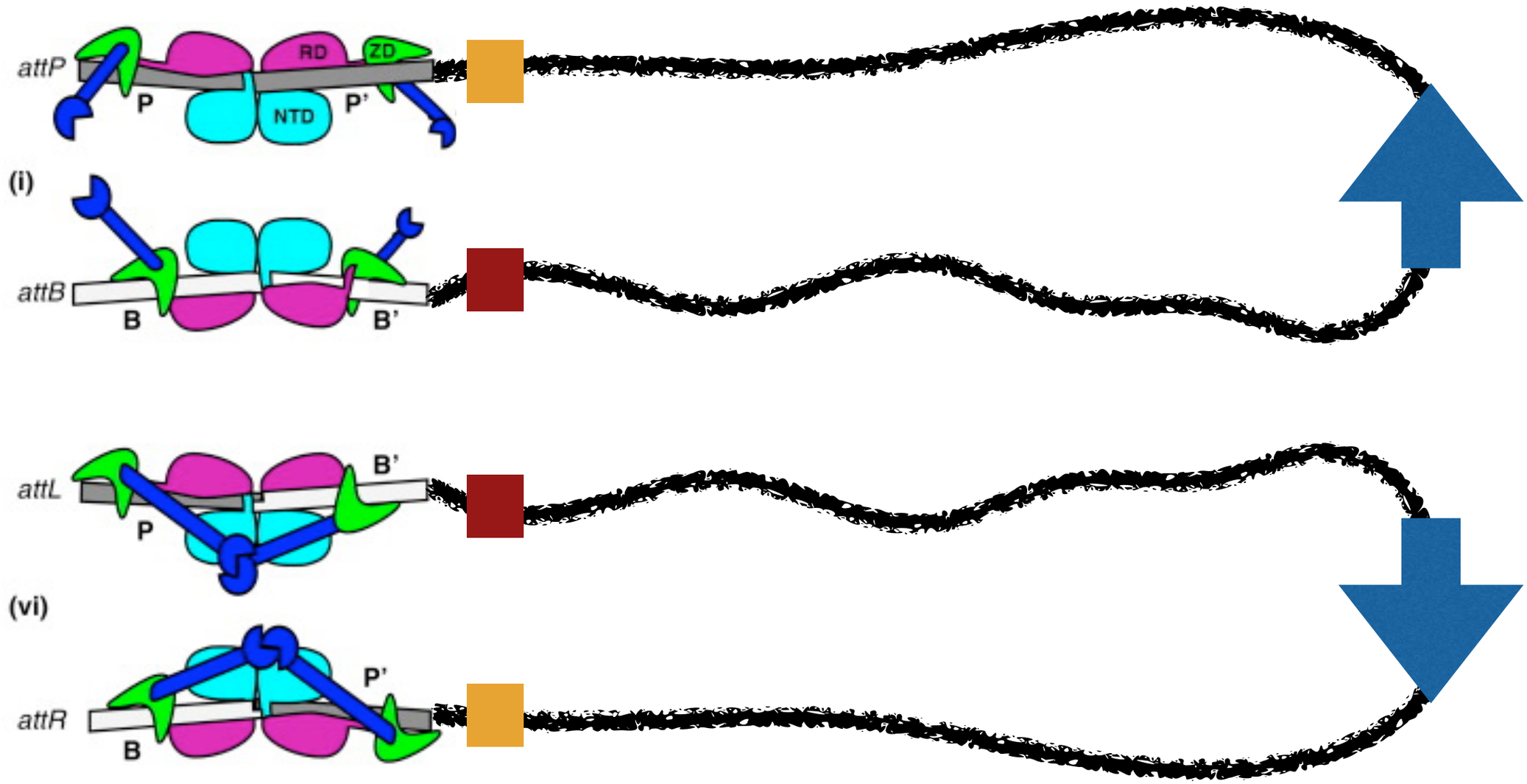
Parts = Basic biological functions encoded via molecules.

Abstraction barrier! Do not cross!

CTATAGGGAGA

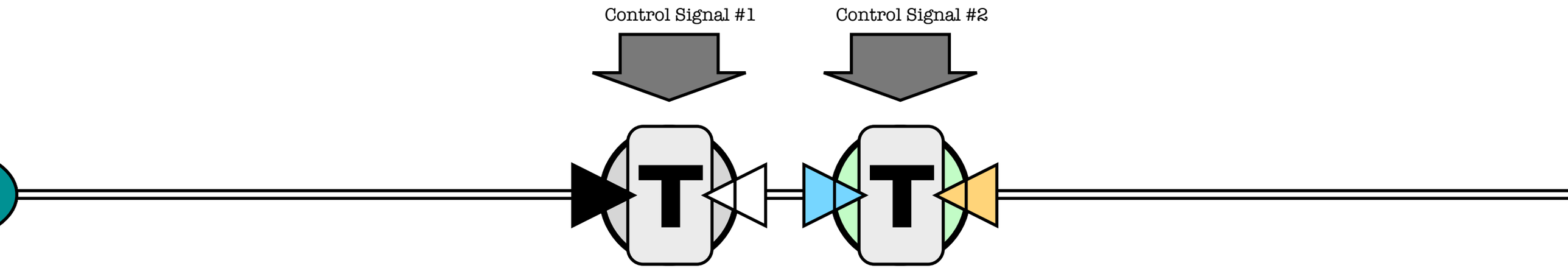
DNA = Material encoding molecules

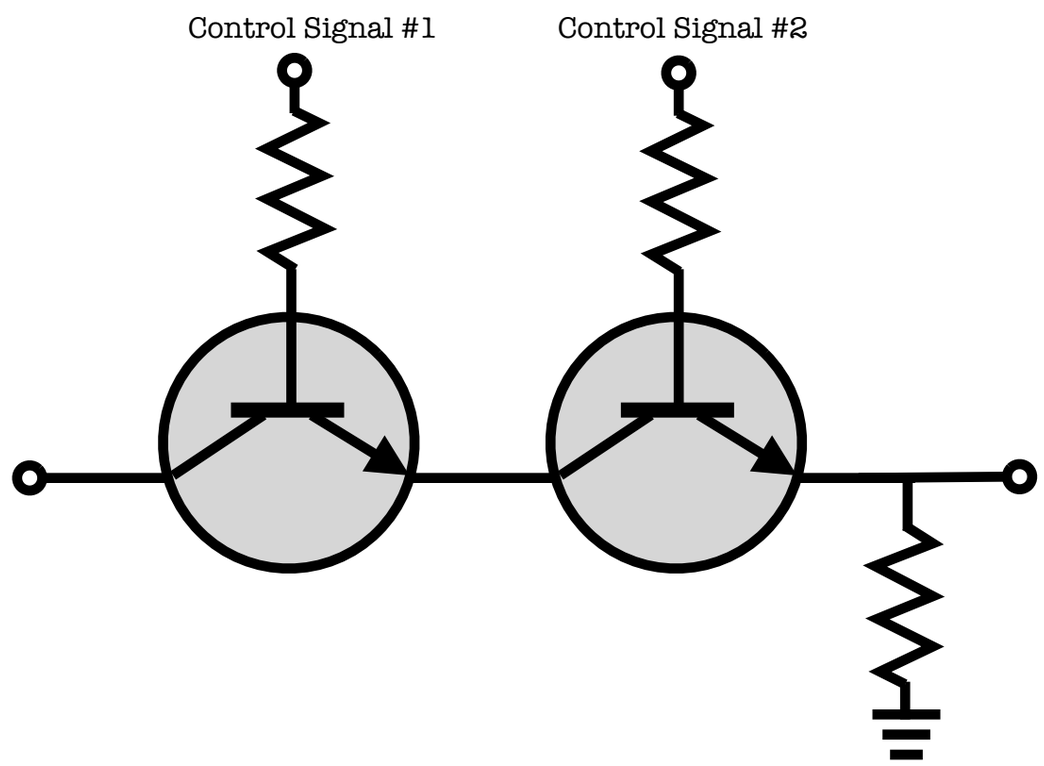
If we connect the two pieces of DNA then the connecting fragment would be flipped!



Karen Rutherford & Gregory D Van Duyne (2014)
The ins and outs of serine integrase site-specific recombination
http://dx.doi.org/10.1016/j.sbi.2014.01.003

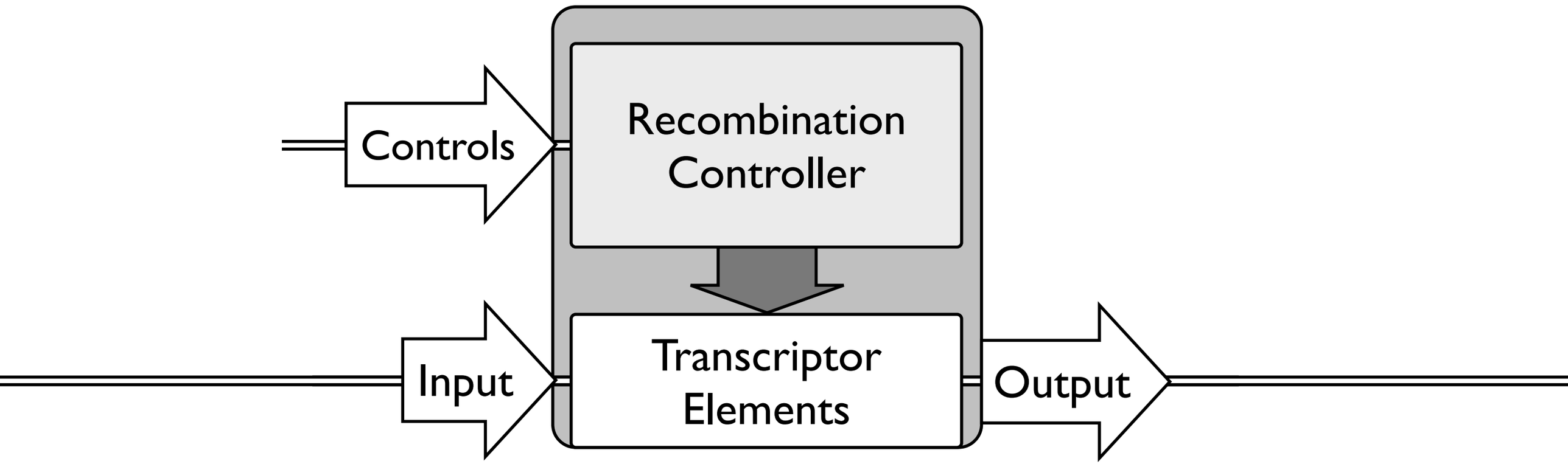
Mr. Boole's AND in DNA





Bonnet et al., Science, 2013

Generic device-level architecture for recombinase-based genetic logic gates



Bonnet et al., *Science*, 28 March 2013

Setting up goal of engineering genetic "black box" that allows us readily reuse higher-level, human-defined functions…

Inputs: generic (i.e., device agnostic) signals that control levels of gene expression

Output: generic signals that control levels of gene expression

Dr. Jennifer Brophy

BREAKOUT

Imagine Your Biocomputer

Where in biology (i.e., living matter) would you wish to bioengineer a computation?

How many bits need to be handled?

How fast does your biocomputer need to be?