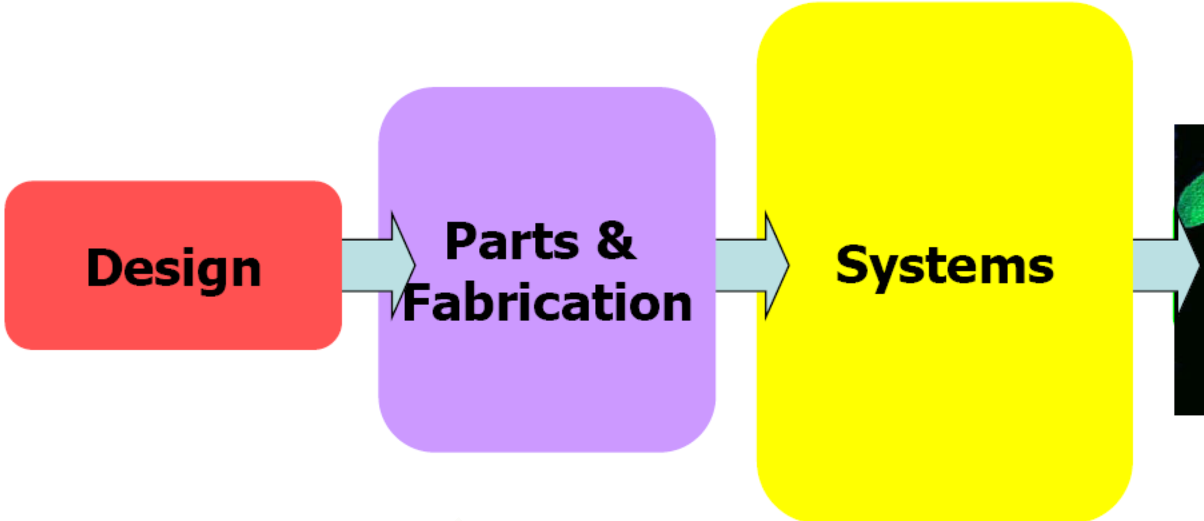
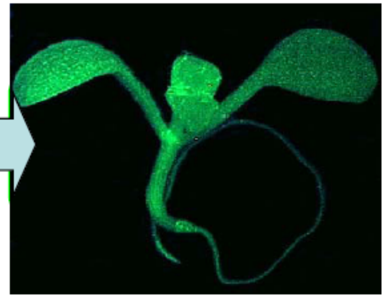
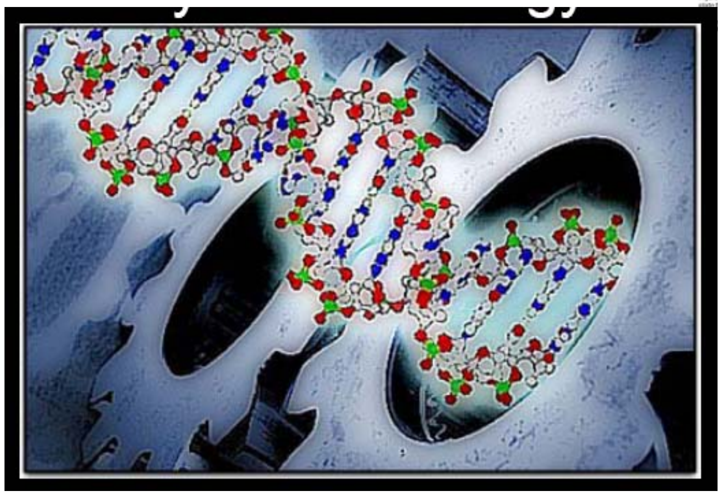
“Synthetic Biology: ENGINEERING LIFE”





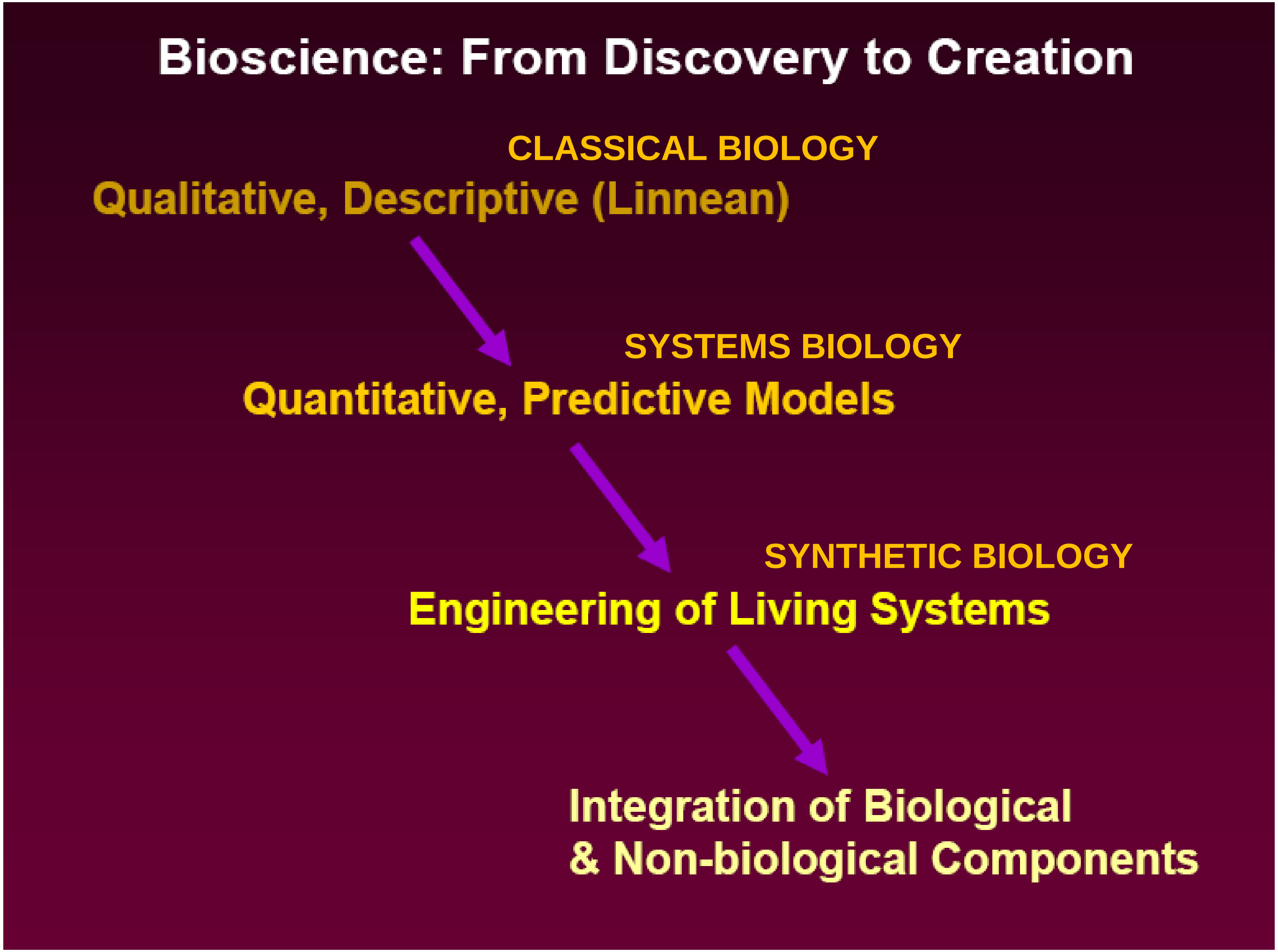


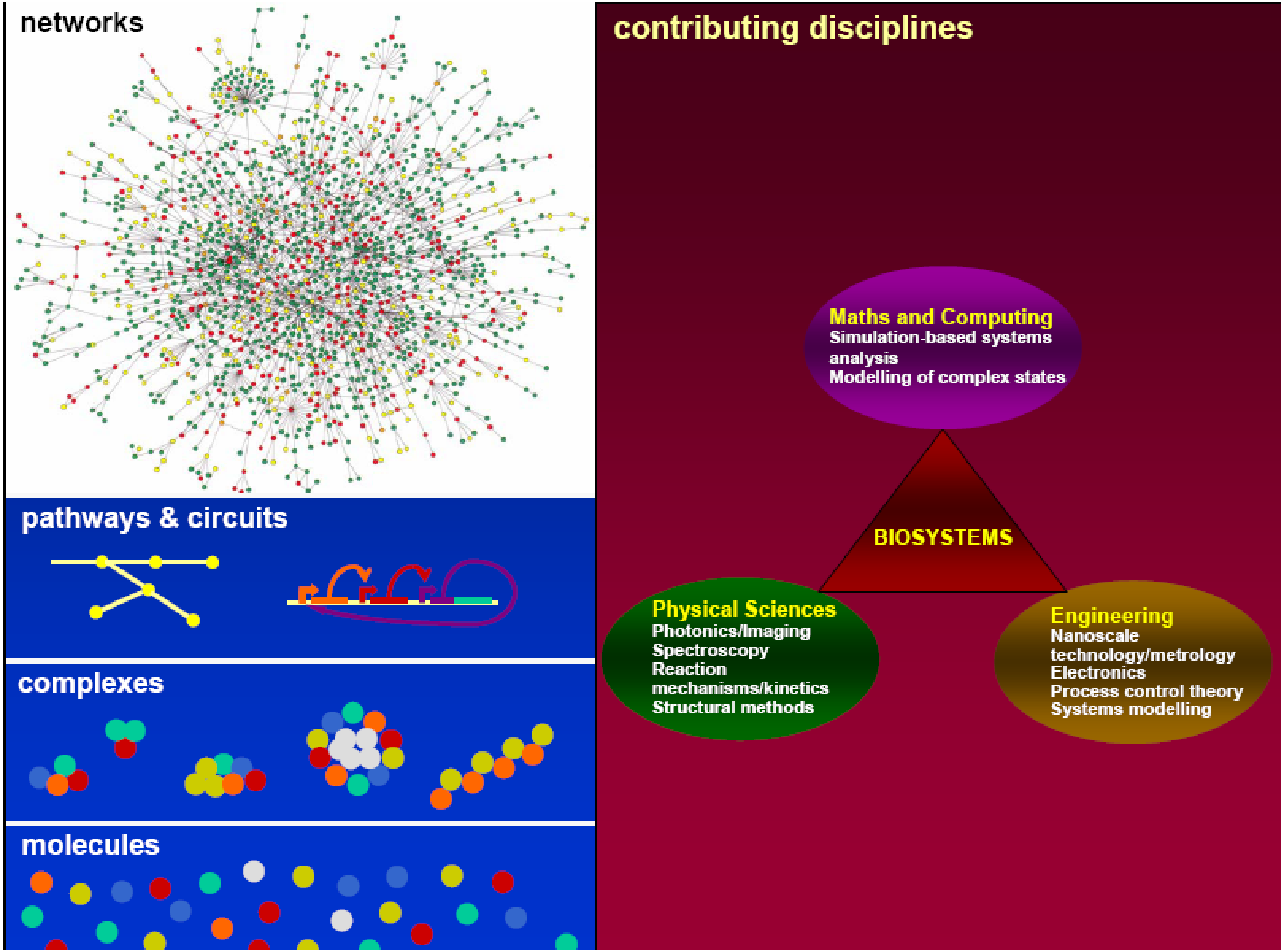
- There are many definitions of synthetic biology and each have varying ethical, legal, social and economic implications
- One general definition of synthetic biology is; the design and construction of new biological parts, devices, and systems and the re-design of existing, natural biological systems for useful purposes

- Synthetic biology contains elements of nanotechnology and biotechnology
- Synthetic biology can be a technology based on the traditional genetic code
- Or it can be based on artificial genetic code, artificial amino acids and proteins.
- It can also be the creation of biological system with non-biological material or making of non-biological system with biological material.

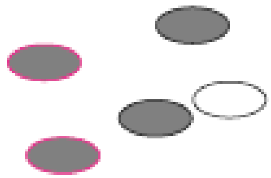
“Synthetic Biology: ENGINEERING LIFE”

Mainly developed at the USA , with some minor disperse efforts In Europe


Bioscience: From Discovery to Creation
CLASSICAL BIOLOGY
Qualitative, Descriptive (Linnean)
SYSTEMS BIOLOGY
Quantitative, Predictive Models
SYNTHETIC BIOLOGY
Engineering of Living Systems
Integration of Biological
& Non-biological Components


networks
pathways & circuits
complexes
molecules
contributing disciplines
Maths and Computing
Simulation-based systems analysis
Modelling of complex states
BIOSYSTEMS
Physical Sciences
Photonics/Imaging
Spectroscopy
Reaction mechanisms/kinetics
Structural methods
Engineering
Nanoscale technology/metrology
Electronics
Process control theory
Systems modelling

Biology poses unique challenges for engineering

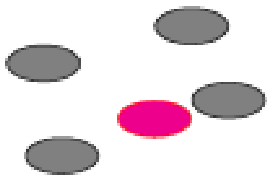


Cell growth/death

Crosstalk (no insulation)

CAT → ACT

Mutation



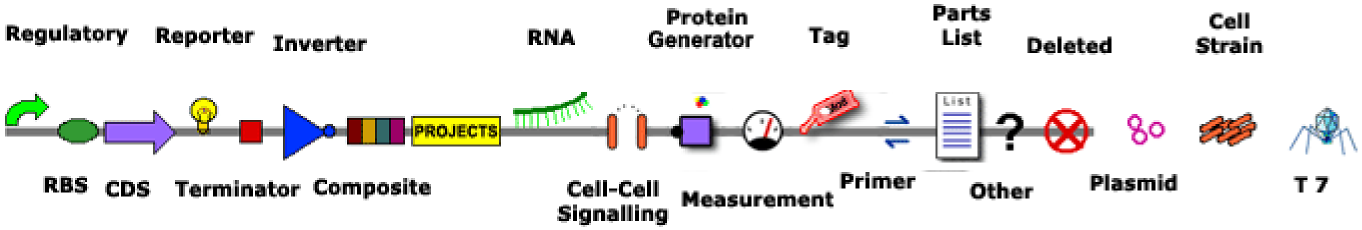
Evolution

Chemical diffusion

We need new engineering rules to control or utilize these properties.

SYNTHETIC BIOLOGY: ENGINEERING STANDARIZATION

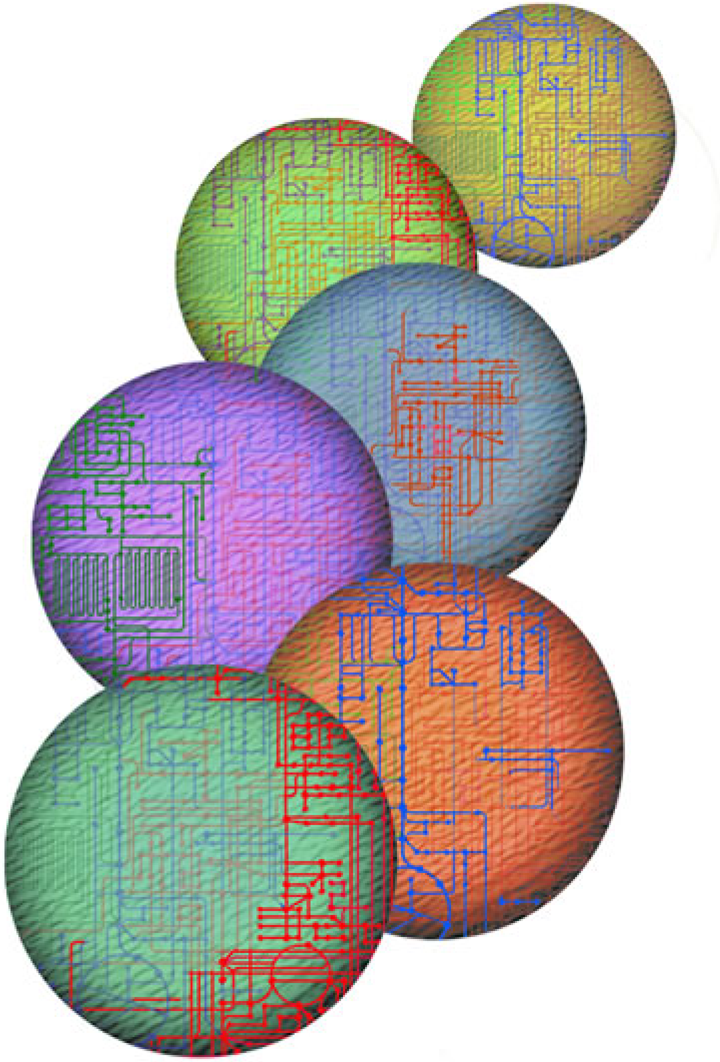
Massachusetts
Institute of
Technology



Why now Synthetic Biology?

Why now?

- Advances in computing power
- Genomic sequencing
- Crystal structures of proteins
- High through-put technologies
- Biological databases
- Diverse biological sampling/collection



How do advances in DNA synthesis affect synthetic biology?

Our capacity to assemble long stretches of DNA that approach the length of genomes has increased.

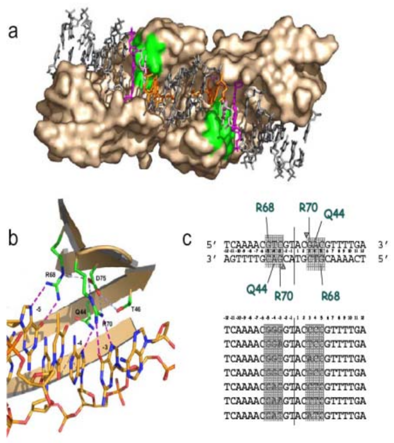
DNA synthesis is an enabling tool for construction of a genome of known sequence, in the absence of a **physical** template.

The genomes of known viruses have been synthesized.

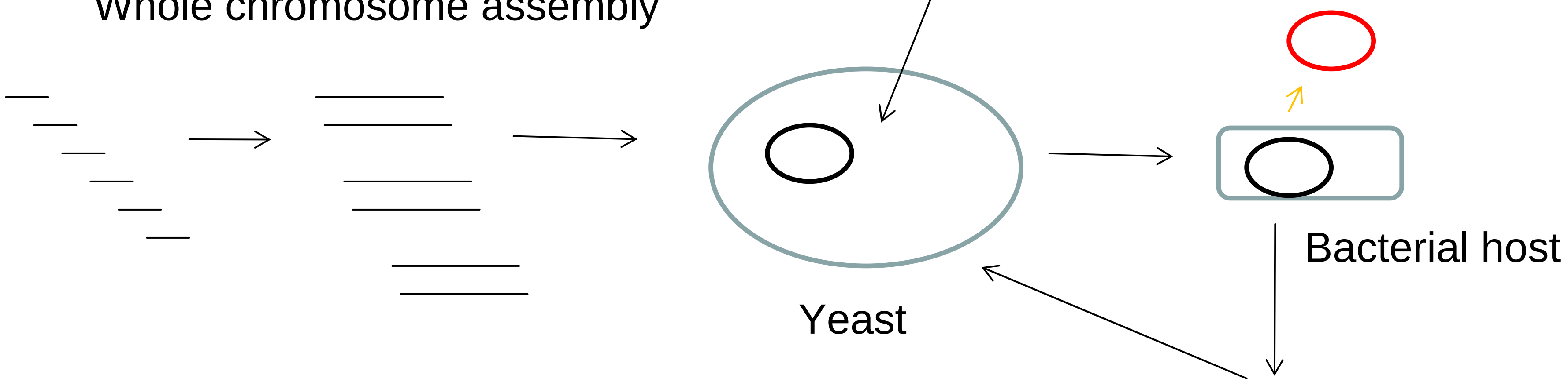
Improved DNA synthesis does not address the essential Issue of how to synthesize an organism with predefined, useful altered properties.

NEW TOOLS FOR GENOME ENGINEERING

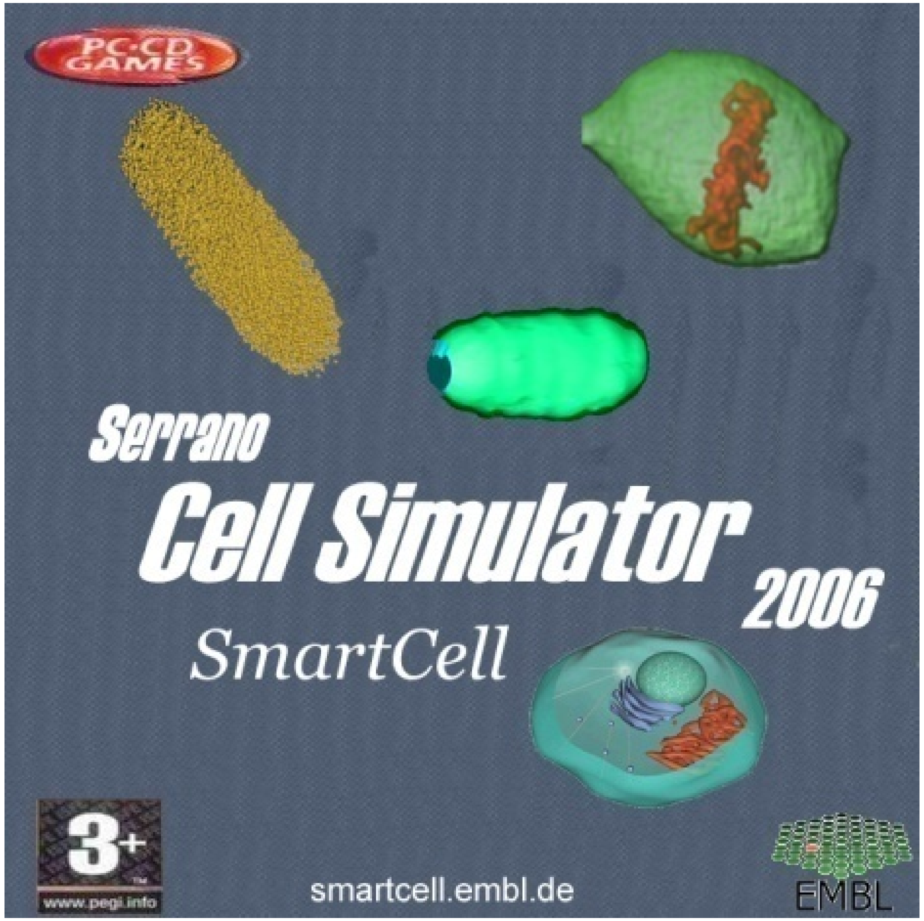
Precision scalpels
for genome engineering



Whole chromosome assembly



www.smartcell.crg.es



COMPUTER TOOLS TO SIMULATE BIOLOGICAL SYSTEMS

$$P + A \xrightleftharpoons[k_{off\_A}]{k_{on\_A}} PA \qquad (1)$$

$$PA \xrightarrow{k_{in}} PB + A \qquad (2)$$

$$PB \xrightarrow{k_{transcr}} M + P + B \qquad (3)$$

$$M \xrightarrow{k_{transl}} T \qquad (4)$$

$$M \xrightarrow{k_{deg\_M}} \varnothing \qquad (5)$$

$$P + Z \xrightleftharpoons[k_{off\_Z}]{k_{on\_Z}} PZ \qquad (6)$$

$$PY \xrightarrow{k_{in}} PY + Z \qquad (7)$$

$$PY \xrightarrow{k_{transcr}} P + Y \qquad (8)$$

$$T + A \xrightleftharpoons[k_{off\_T1}]{k_{on\_T1}} TA \qquad (9)$$

$$TaTc + A \xrightleftharpoons[k_{off\_T2}]{k_{on\_T2}} TaTcA \qquad (10)$$

$$T(aTc)_2 + A \xrightleftharpoons[k_{off\_T3}]{k_{on\_T3}} T(aTc)_2A \qquad (11)$$

$$TA + aTc \xrightleftharpoons[k_{off\_T4}]{k_{on\_T4}} TaTcA \qquad (12)$$

$$TaTcA + aTc \xrightleftharpoons[k_{off\_T5}]{k_{on\_T5}} T(aTc)_2A \qquad (13)$$

$$T \xrightarrow{k_{deg\_T}} \varnothing \qquad (14)$$

$$TaTc \xrightarrow{k_{deg\_T}} aTc \qquad (15)$$

$$T(aTc)_2 \xrightarrow{k_{deg\_T}} 2\ aTc \qquad (16)$$

$$P + C \xrightleftharpoons[k_{off\_C}]{k_{on\_C}} PC \qquad (17)$$

$$PC \xrightarrow{k_{in}} PD + C \qquad (18)$$

$$PD \xrightarrow{k_{transcr}} N + P + D \qquad (19)$$

$$N \xrightarrow{k_{transl}} G \qquad (20)$$

$$N \xrightarrow{k_{deg\_N}} \varnothing \qquad (21)$$

$$T + aTc \xrightleftharpoons[k_{off\_Ta1}]{k_{on\_Ta1}} TaTc \qquad (22)$$

$$TaTc + aTc \xrightleftharpoons[k_{off\_Ta2}]{k_{on\_Ta2}} T(aTc)_2 \qquad (23)$$

$$T + C \xrightleftharpoons[k_{off\_T6}]{k_{on\_T6}} TC \qquad (24)$$

$$TaTc + C \xrightleftharpoons[k_{off\_T7}]{k_{on\_T7}} TaTcC \qquad (25)$$

$$T(aTc)_2 + C \xrightleftharpoons[k_{off\_T8}]{k_{on\_T8}} T(aTc)_2C \qquad (26)$$

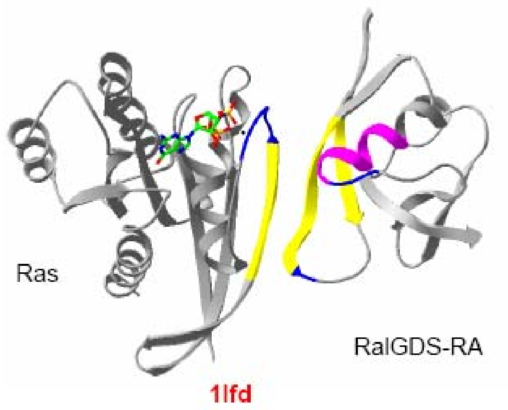
$$TC + aTc \xrightleftharpoons[k_{off\_T9}]{k_{on\_T9}} TaTcC \qquad (27)$$

$$TaTcC + aTc \xrightleftharpoons[k_{off\_T10}]{k_{on\_T10}} T(aTc)_2C \qquad (28)$$

$$G \xrightarrow{k_{deg\_G}} \varnothing \qquad (29)$$

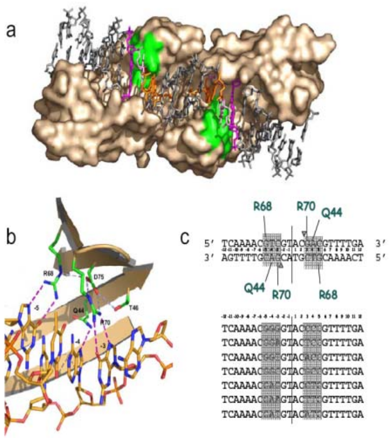
Successful examples for structure-based predictions and protein design

Ras - RA



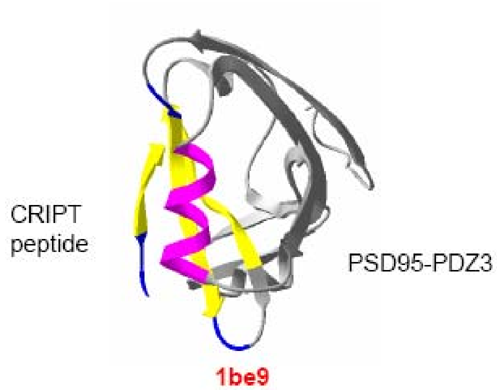
Kiel et al., J Mol Biol, **2005**
Kiel et al., J Mol Biol, revised, **2007**

Meganuclease-DNA



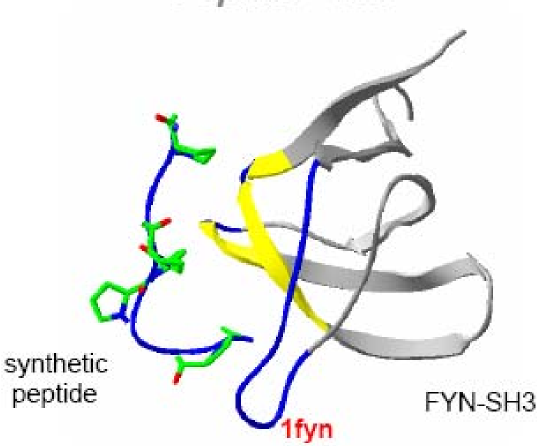
Arnould et al., J. Mol. Biol, **2006**

Peptide - PDZ

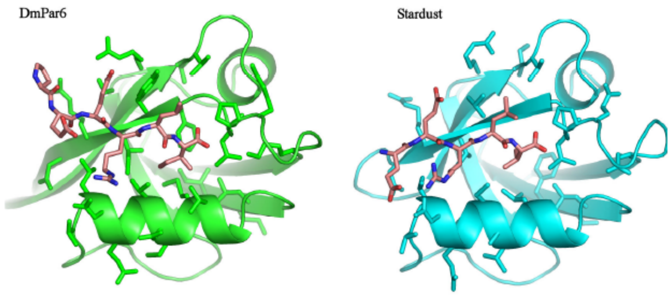


Kolsch et al., Science, **2007**

Peptide - SH3

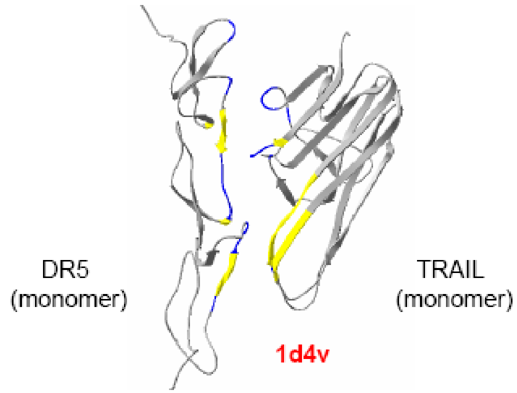


Musi et al., Protein Sci, **2006**



Kempkens, O., E. Medina, et al. (2006)

TNFR - TNF



Van der Sloot, et al, PNAS, **2006**

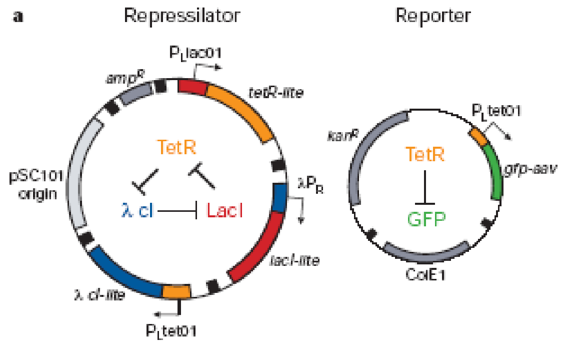
Defining the Rule Sets for Biological Design, Assembly and Function

- common genetic (digital) code in all life forms
- genomes encode a limited series of structural building blocks (protein motifs and programmed assembly)
- combinatorial assembly of protein building blocks generates extravagant structural and functional diversity

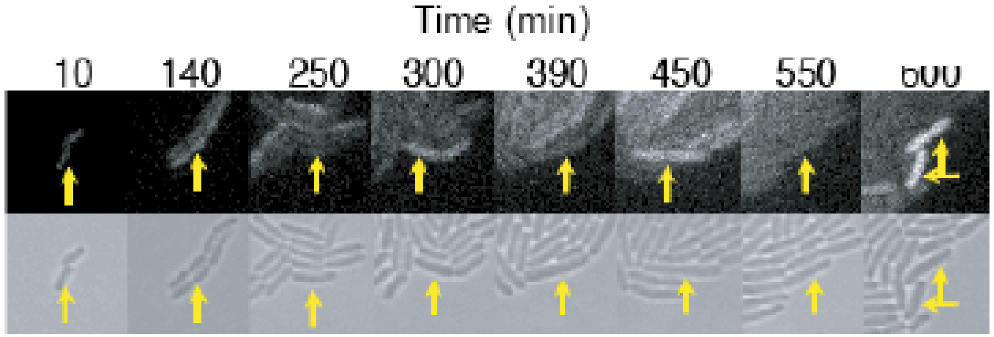
Playing with Synthetic Biology

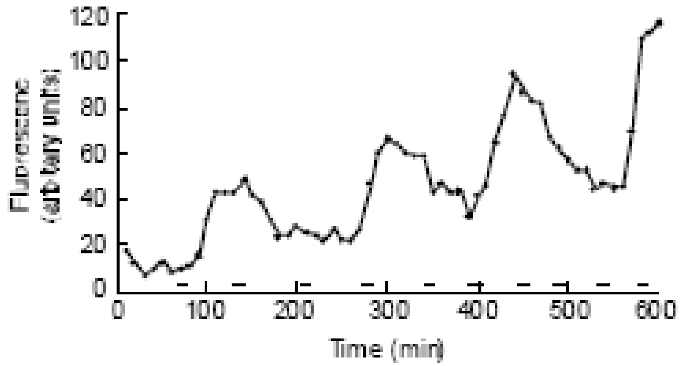
Engineering of Circuits

What sorts of modules have been made by synthetic biologists?

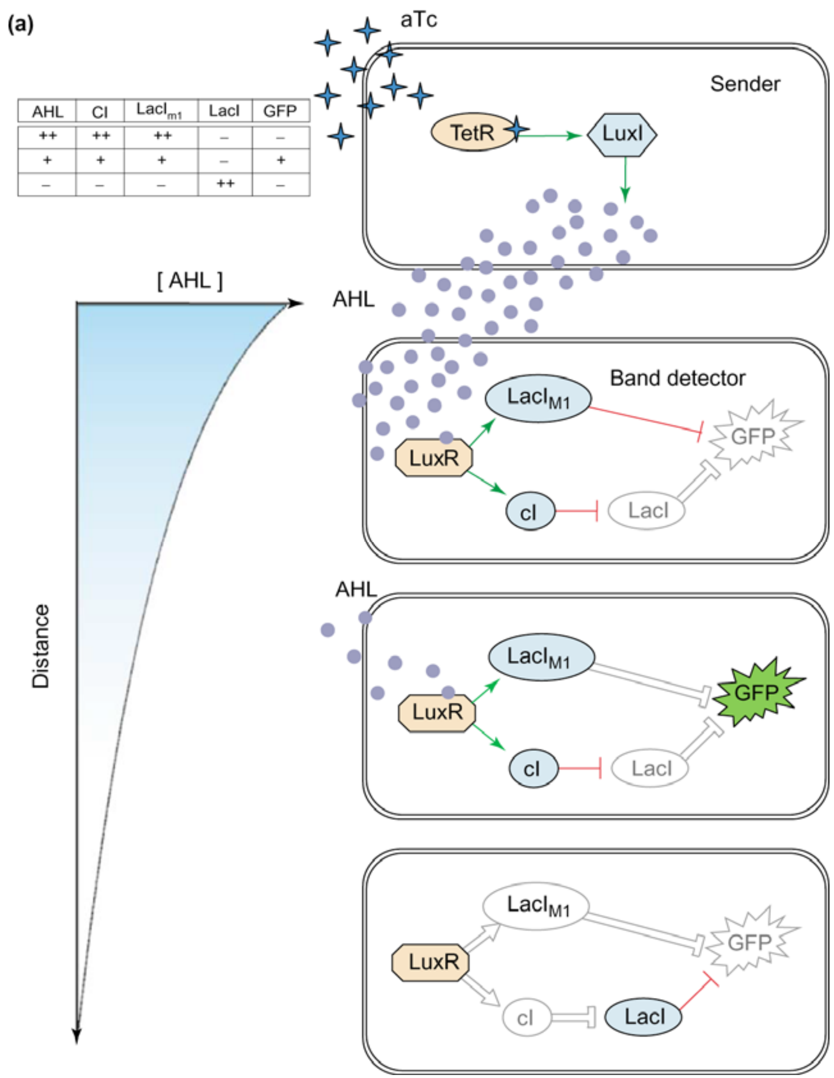


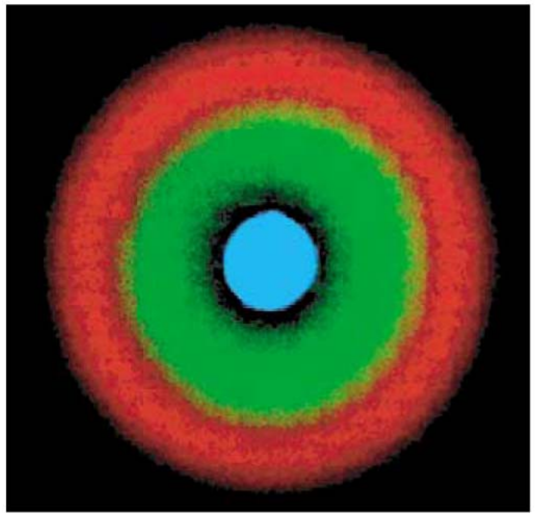
Oscillators





Engineering of Circuits
Building a sender & receiver

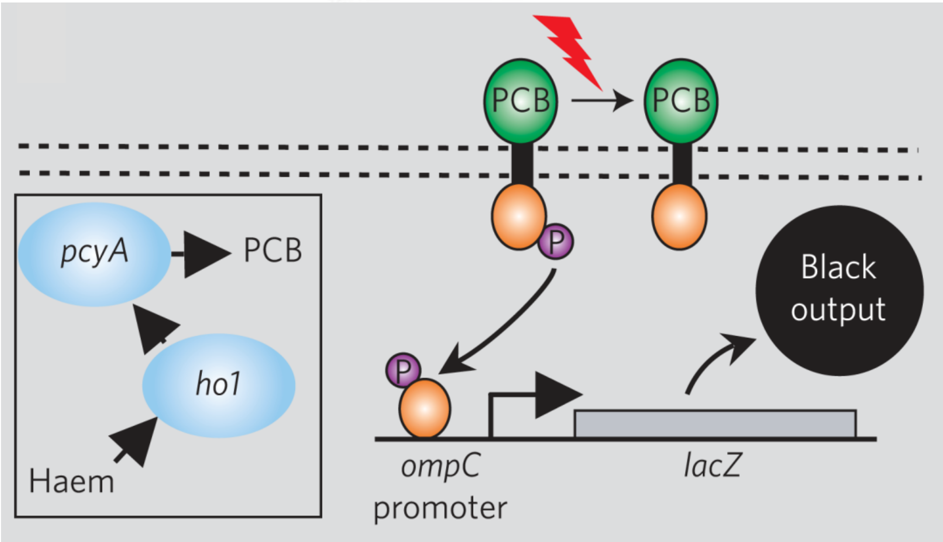




Basu *et al* (2005) *Nature*, 434, 1130

Engineering of Circuits

Bacterial photography



Synechosystis: Photoreceptor, Phytochrome synthesis genes (*ho1, pcyA*)
E. coli: osmotic shock response circuit (*omp*C), β-galactosidase

Levskaya *et al* (2005) *Nature*,

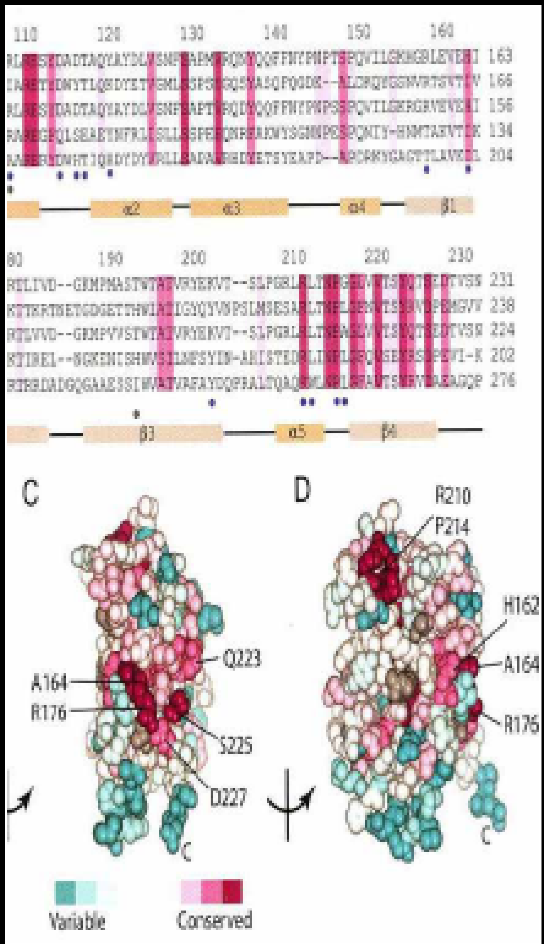
We need more Parts

Biological Design: "Endless Forms Most Beautiful": Limitless Diversity From Combinatorial Assemblies of Limited Building Blocks

Metagenomics: Sampling the Extravagant Functional Diversity of Microorganisms

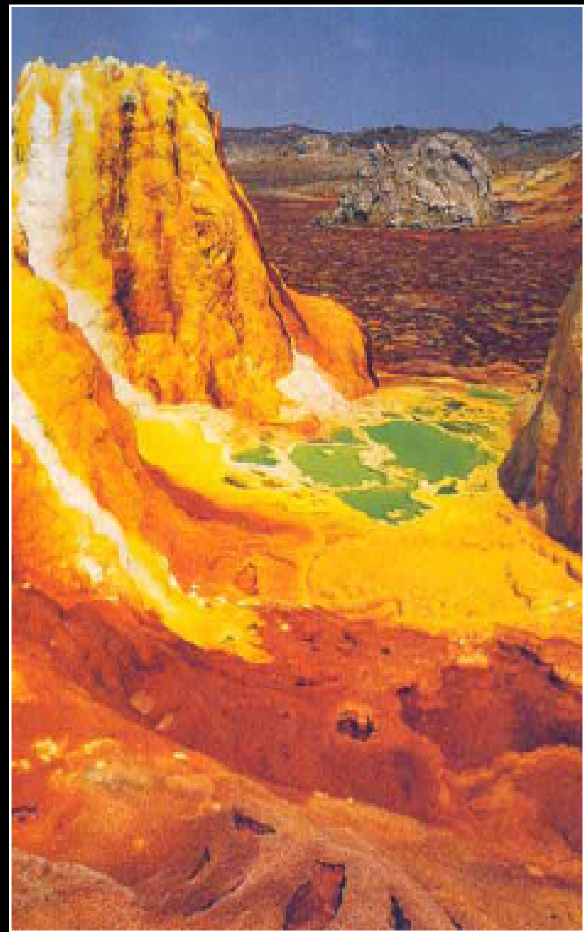
- estimated 100 billion microbial species
- only 6000 species cultivated and characterized
- massive repertoire of uncharacterized genes/proteins/metabolomes
- metagenomic sampling
  - mass screening of complete genomes of unknown/unculturable organisms
  - high throughput profiling to identify transfer of gene(s) with desired function into ‘universal acceptor’ organisms

Ecogenomics:
Mapping the Extraordinary Genomic Diversity and Biosynthetic Capabilities of Microbial Life



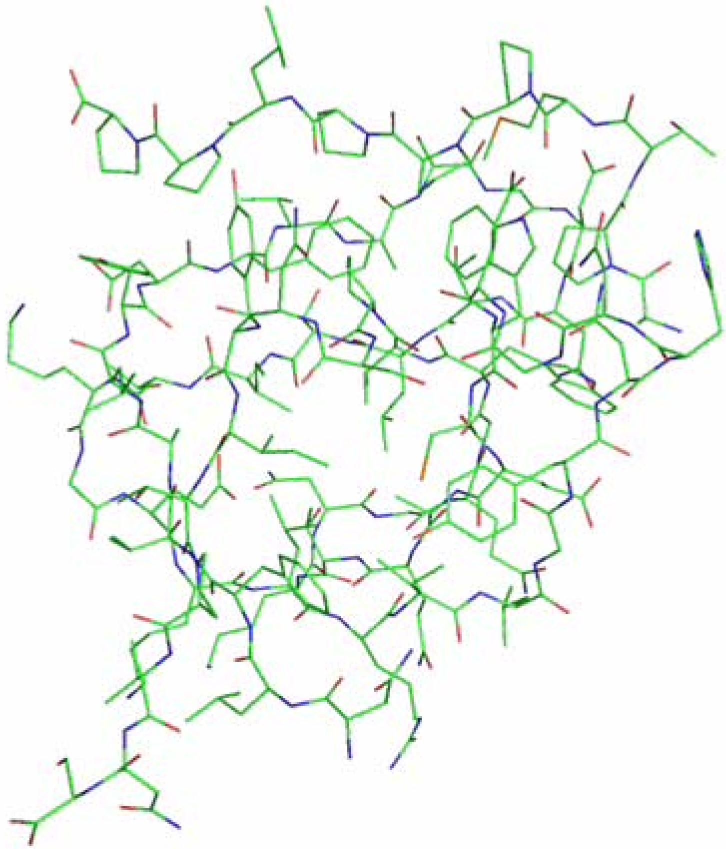
genomics

eco-niches

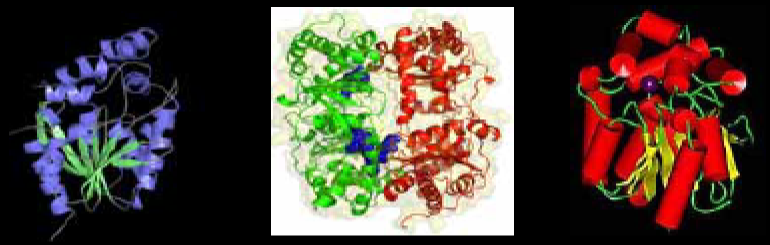


extremophiles

PROTEIN DESIGN

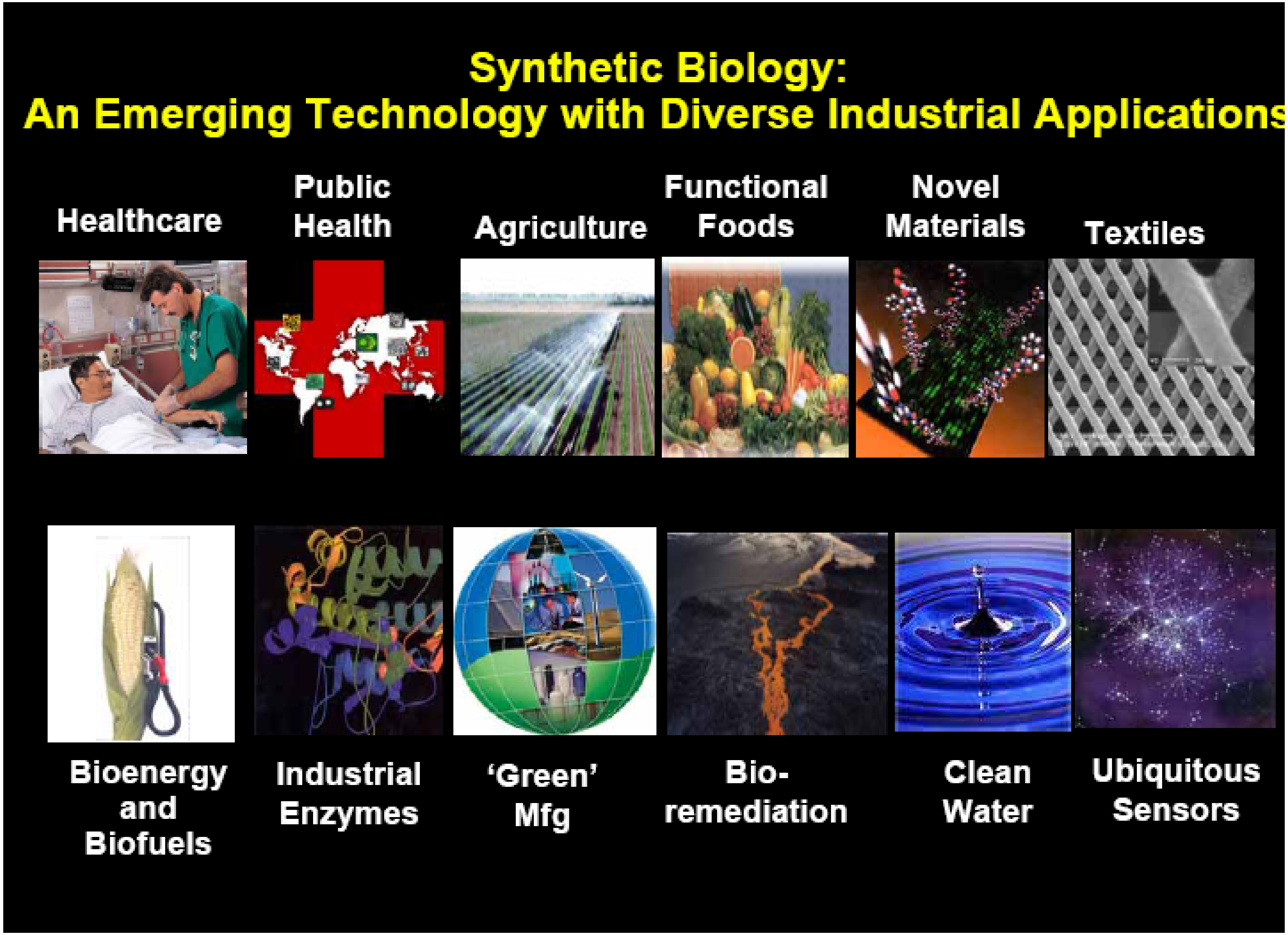


Exploring Biospace:
Iterative Selection of Novel Variants for Substantial Functional Performance Improvements Versus Naturally Occurring “Parent System”



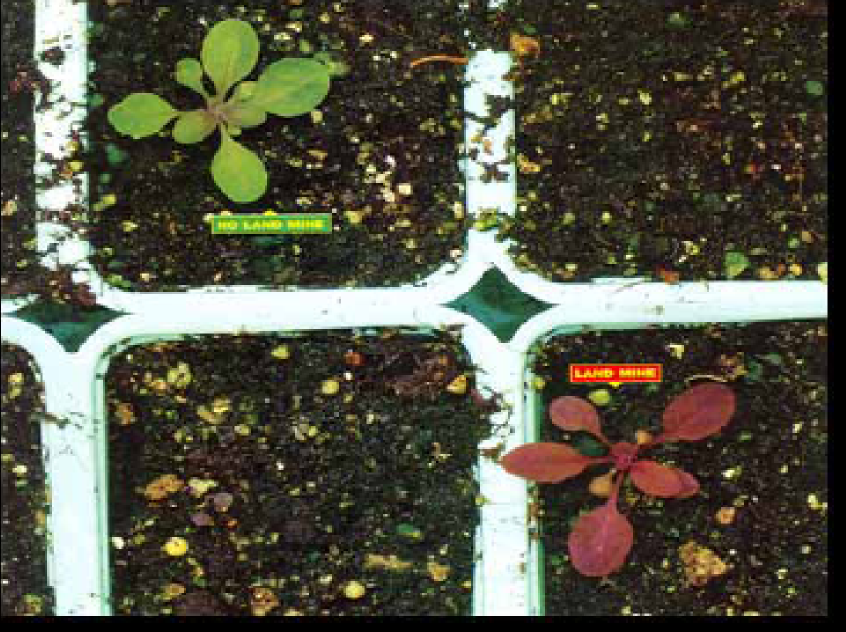
Activity Versus Starting Material

Possible applications of Synthetic Biology


Synthetic Biology:
An Emerging Technology with Diverse Industrial Applications
Healthcare
Public Health
Agriculture
Functional Foods
Novel Materials
Textiles
Bioenergy and Biofuels
Industrial Enzymes
'Green' Mfg
Bio-remediation
Clean Water
Ubiquitous Sensors

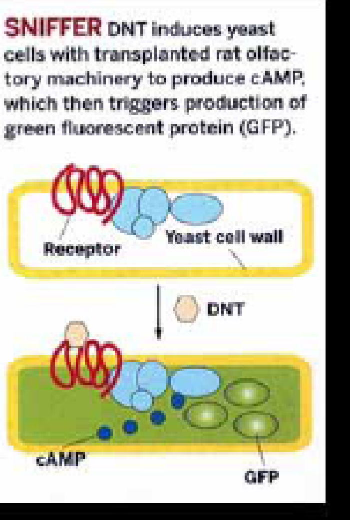
Biological Sensor Systems for Environmental Monitoring and Ecosystem Status

Genetically-Engineered *Arabidopsis thaliana* Change-Color when Exposed to Landmine Degradation Products



Aresa Biotection, Demark

Engineering Sentinel Organisms as Environmental Sensors



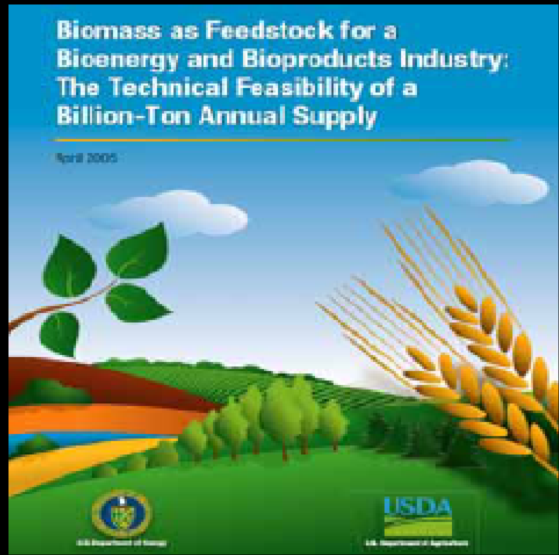
D. N. Dhanasekaran et al (2007) Nature Chem. Biol.

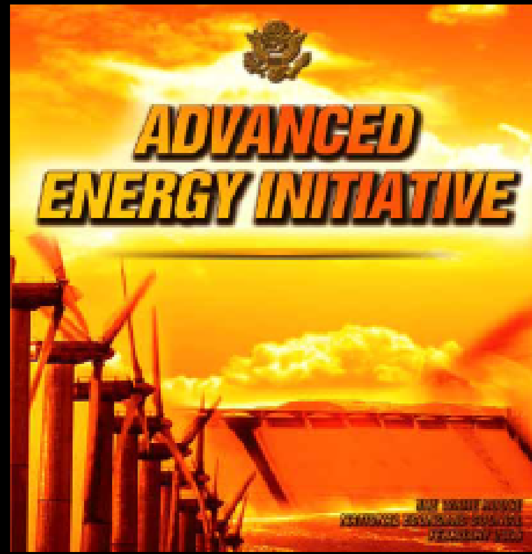
DOI: 10.1038/nchembio882

Directed Evolution and Design of Novel Enzymes for Catalysis of Lignocellulosic Biomass

- cellulosic energy crops
- agricultural, forestry and mill residues
- food processing residues
- municipal solid waste
- non-recycled paper
- construction and demolition wood

Bio-Inspired Systems for Energy Production





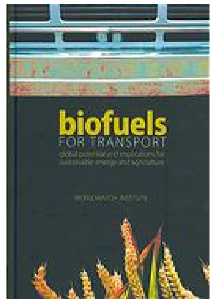
Production of Biodiesel from Biomass: A Widely Differing Yield Spectrum*

Source	Yield US gal/acre	Yield L/Km^2
• Soybean	40-50	35-45,000
• Rapeseed	110-145	100-130,000
• Mustard	140	130,000
• *Jatropha*	175	160,000
• Palm oil	650	580,000
• Photosynthetic Microbes	10-20,000	9-18,000,000

* http://en.wikipedia.org/wiki/Biodiesel

Biofuels

- First generation
  - Food feedstock: sugar, starch, vegetable oil or animal fats using conventional technology (food for fuel debate)
  - Fuel types: vegetable oil, biodiesel, butanol, ethanol, syngas
- Second generation (Needs Synthetic Biology)
  - Non food crop feedstock: cellulose, waste biomass: wheat, corn, wood
  - Fuel types: biohydrogen, biomethanol, DMF, bio-DME, Fischer-Tropsch diesel, biohydrogen diesel, mixed alcohols and wood diesel
- Third generation (Needs Synthetic Biology)
  - Algae feedstock
- Fourth generation (Needs Synthetic Biology)
  - CO_2 feedstock: CO_2 converted to methane by bacteria

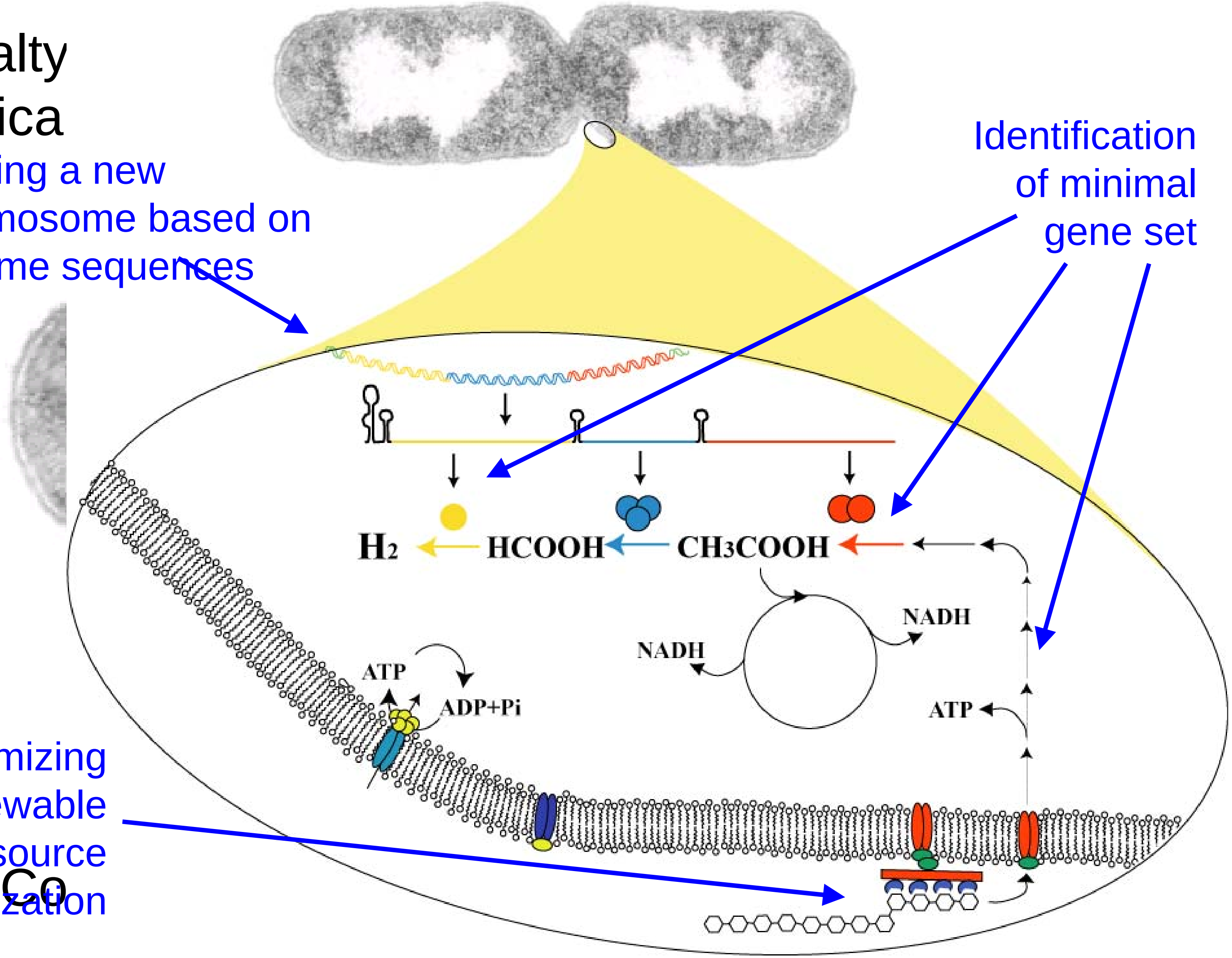


Building a Super H_2 Producer

Specialty
Chemica

Building a new chromosome based on genome sequences

Identification of minimal gene set



Maximizing renewable resource utilization

Co

THE biodesign INSTITUTE
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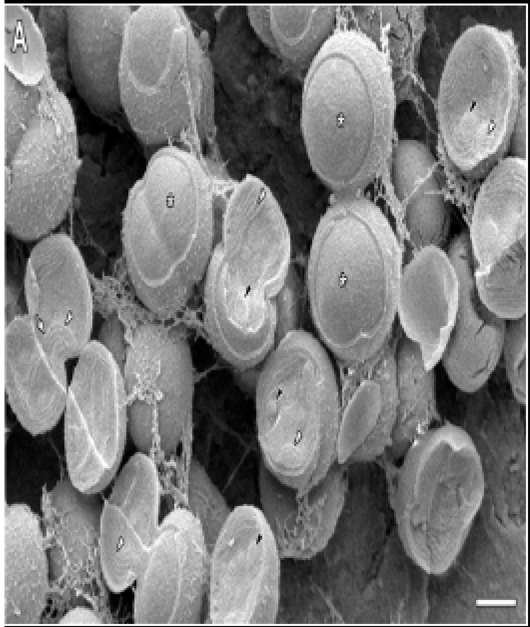
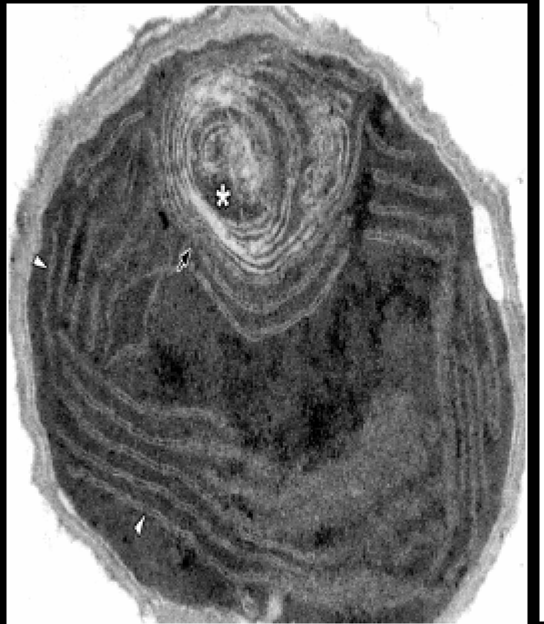
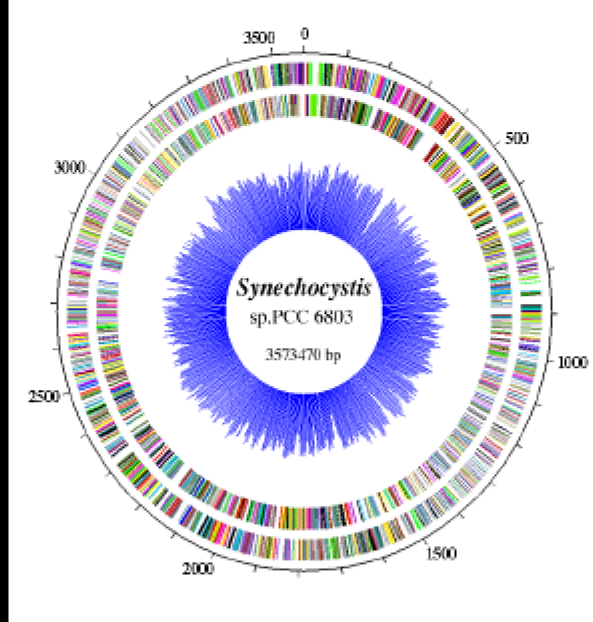
Biomass to Energy: The Merits of Cyanobacteria as a Feedstock







- well characterized, tractable genome for trait enhancement
- no celluose
- compositional homogeneity
- rapid assay of genetic modifications
- siting flexibility
- no or limited transport costs
- CO_2 fixation

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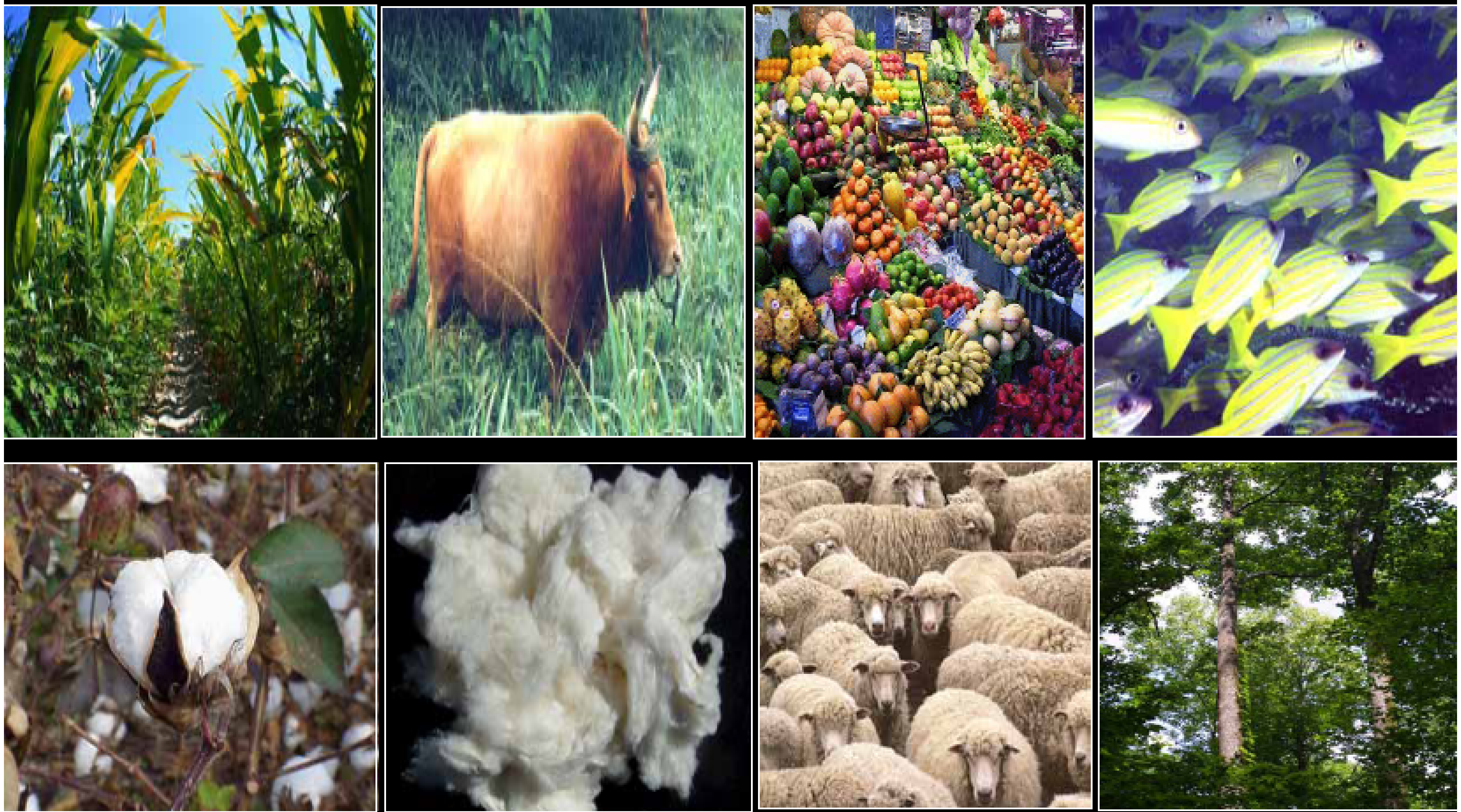
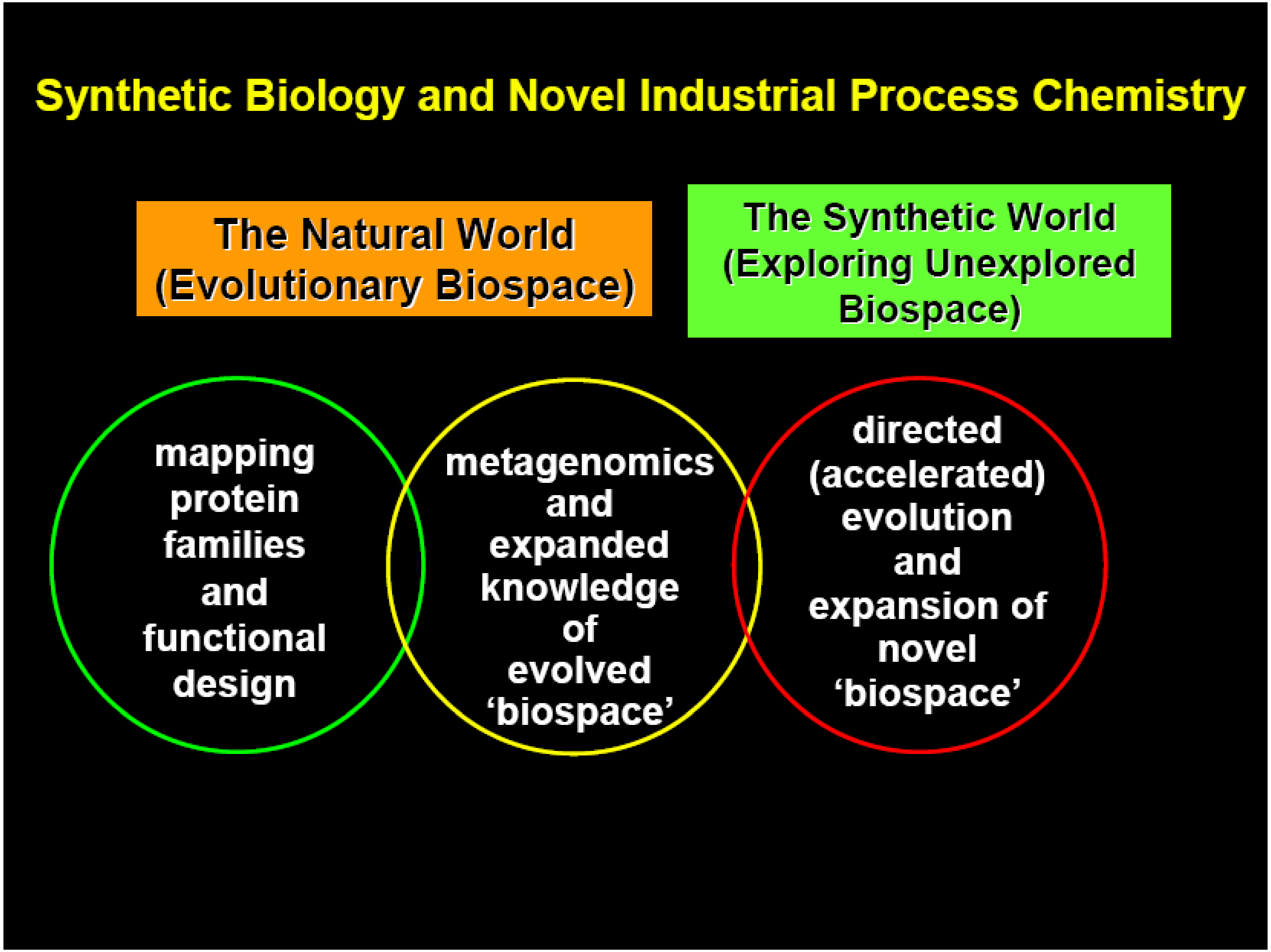
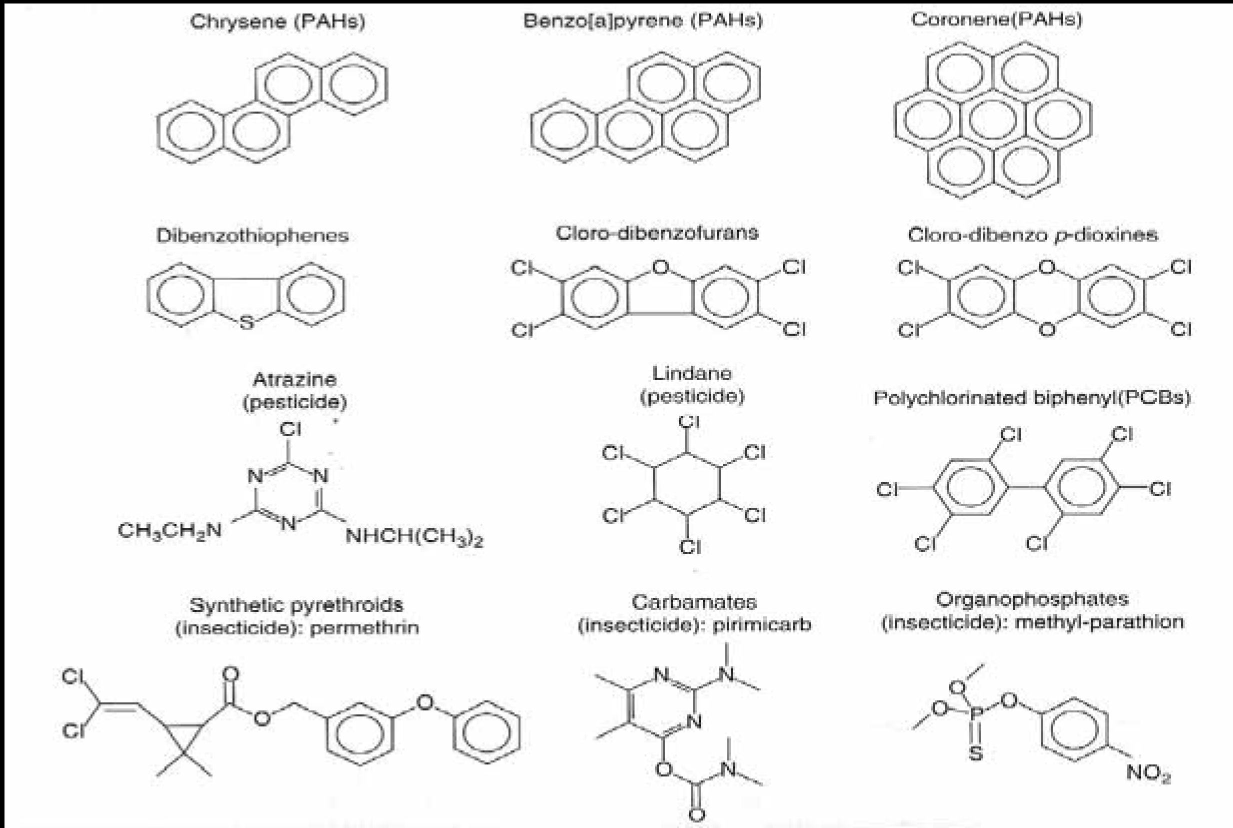
Synthetic Biology and Engineering Enhanced Traits in Food, Feed and Fiber Products




Synthetic Biology and Novel Industrial Process Chemistry
The Natural World (Evolutionary Biospace)
The Synthetic World (Exploring Unexplored Biospace)
mapping protein families and functional design
metagenomics and expanded knowledge of evolved 'biospace'
directed (accelerated) evolution and expansion of novel 'biospace'

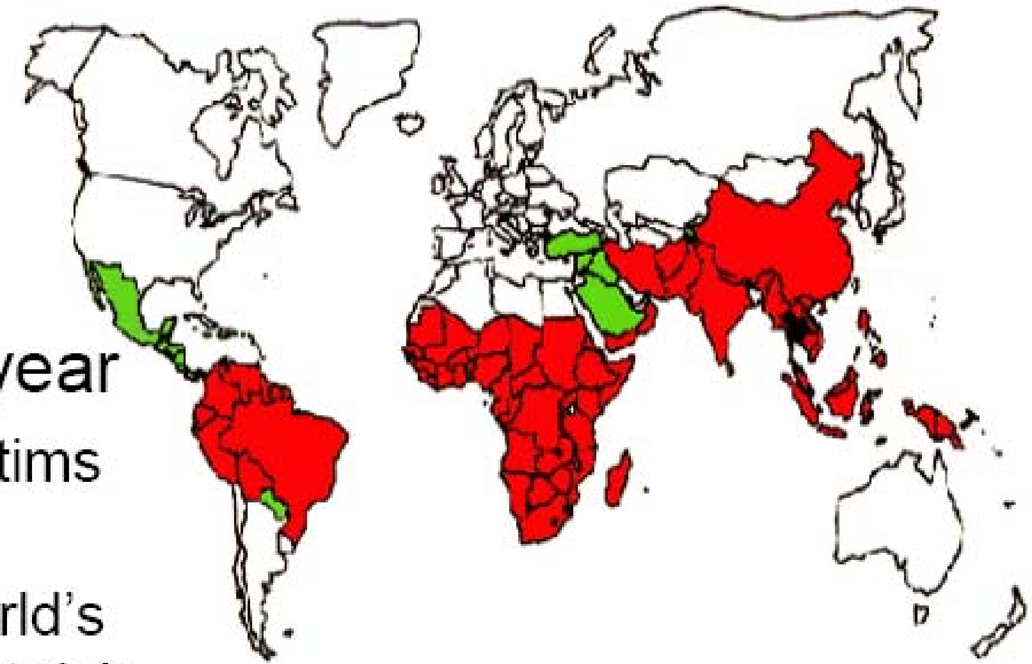
Microbial Genomics and Synthetic Biology: New Technology Platforms for Bioremediation and Improved Efficiency of Wastestream Management



Bio-Inspired Engineering: Removal of Perchlorate Contamination by Chemical Reduction by Biofilms of Hydrogen Producing Bacteria

- ✓ pilot scale project at La Puente, CA (400 L/min)
- ✓ influent: 25 mg/L of NO_3^- and 60 μg/L ClO_4^-
- ✓ ≈ 95% removal of ClO_4^-, from 60 μg/L to below the CA action level of 4 μg/L
- ✓ ≈ 98% NO_3^- removal of 25 mgN/L to ≈ 0.5mgNO_3^-/L
- ✓ essentially 100% H_2 usage

Malaria

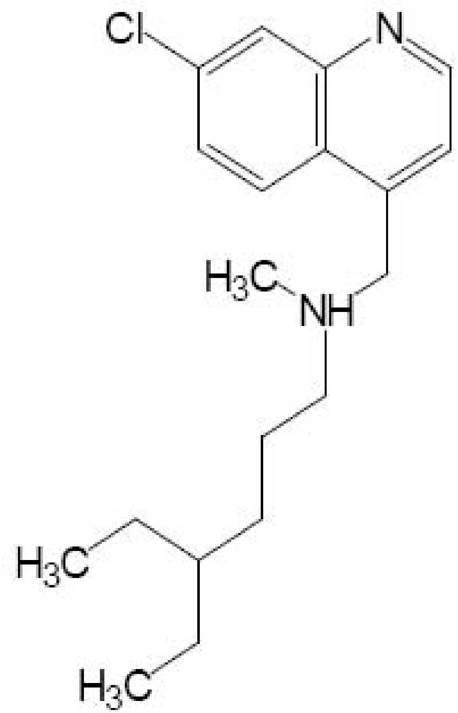


- 1.5-2.7 million people die of malaria every year
  - 90% of the victims are children
  - 40% of the world's population is at risk
- Economists have proposed that malaria decreases the GDP of affected countries by as much as 50%.

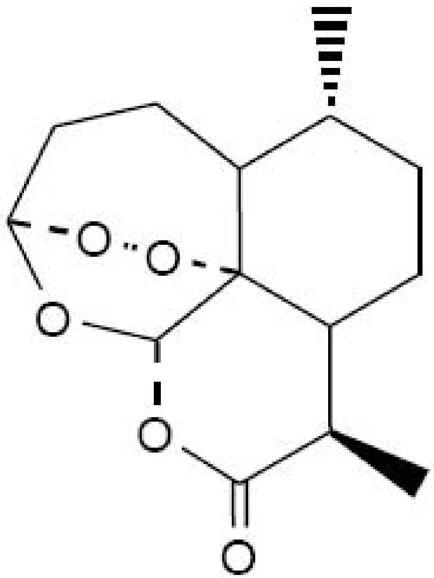
BERKELEY CENTER FOR SYNTHETIC BIOLOGY

Chloroquine-based drugs

- Most widely-used drugs to treat malaria
- *Plasmodium* in South America and Southeast Asia is largely resistant to chloroquine



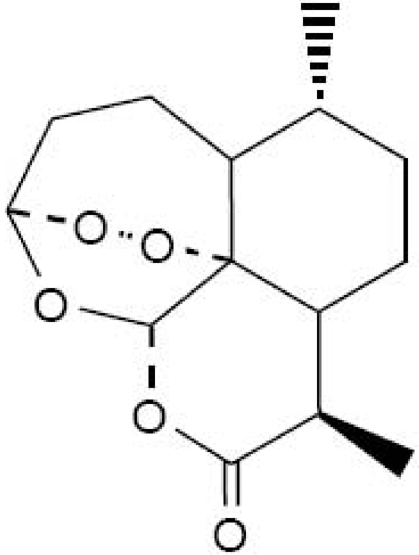
BERKELEY CENTER FOR SYNTHETIC BIOLOGY



Artemisinin-based drugs

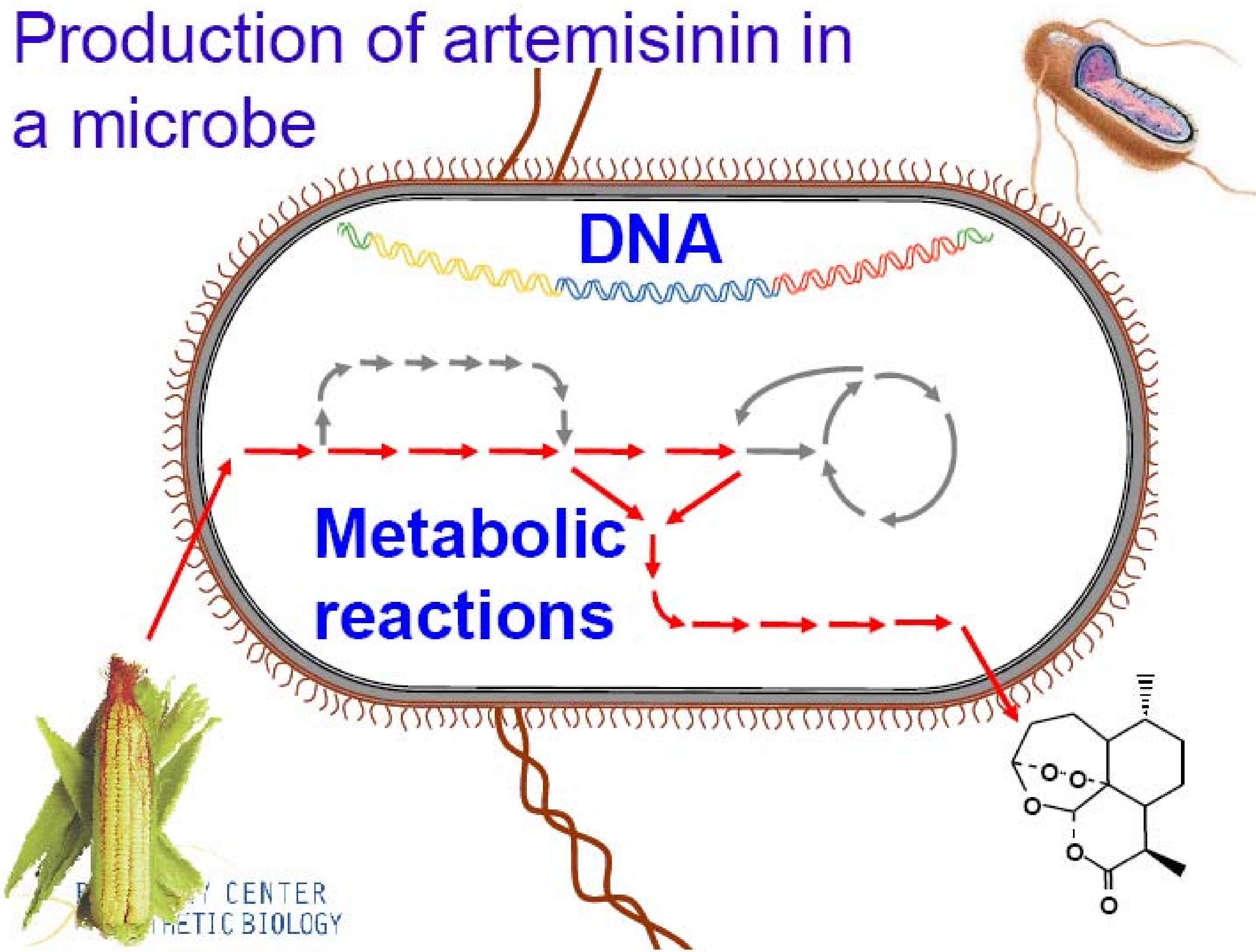
- The current cost is approximately $2.40.
  - Artemisinin adds $1.00-1.50 to the cost for drugs
  - Most developing countries spend less than $4/person/year on health care
- As many as 10-12 treatments are needed for each person annually
- World Health Organization estimates that 700 tons will be needed annually

Potential sources for artemisinin

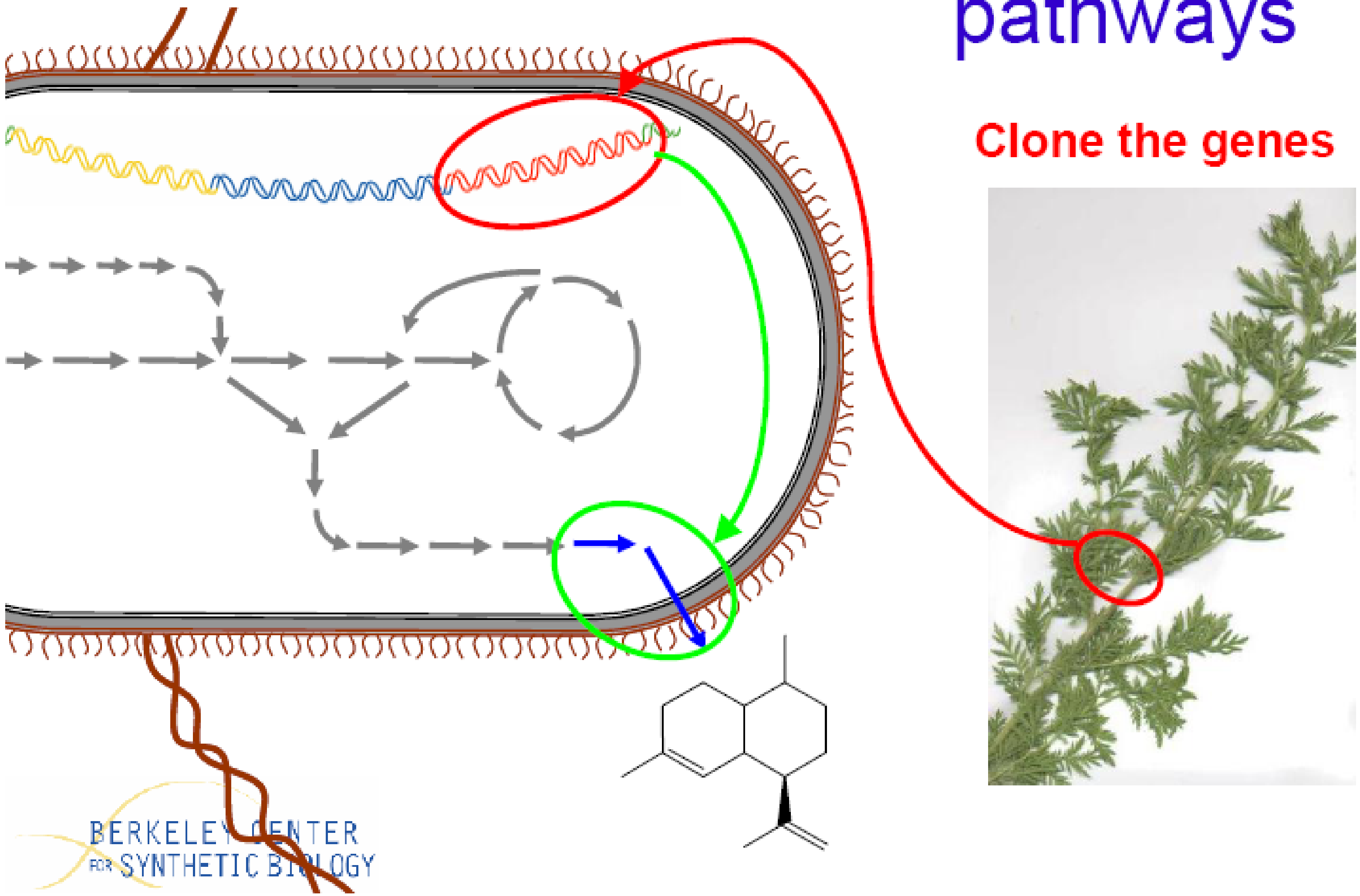


- Agriculture
  - Efforts are under way to plant *Artemisia annua* around the world
- Chemical synthesis
  - A synthesis route is known but it is too complicated for economical production
- Microbial
  - Need all of the genes from the plant

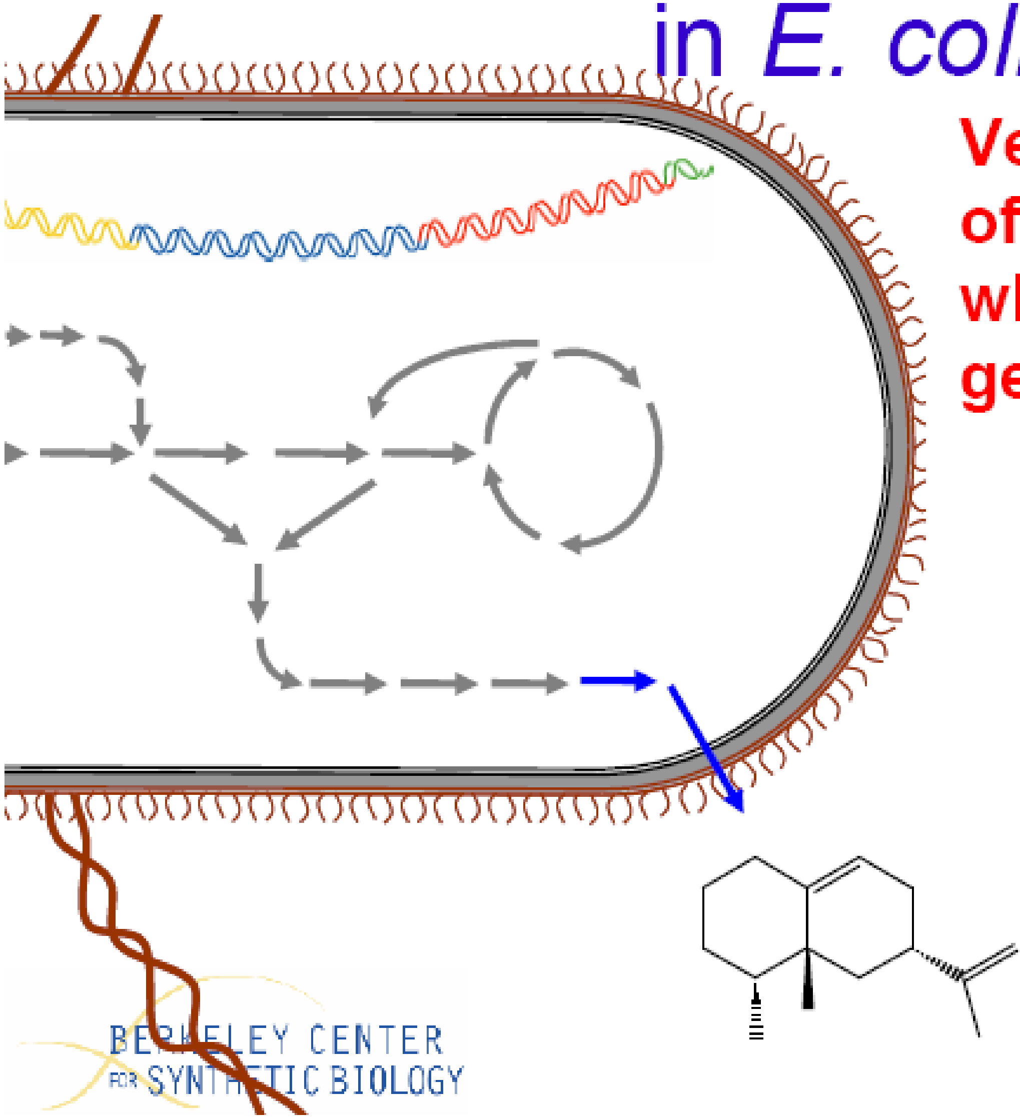
Production of artemisinin in a microbe



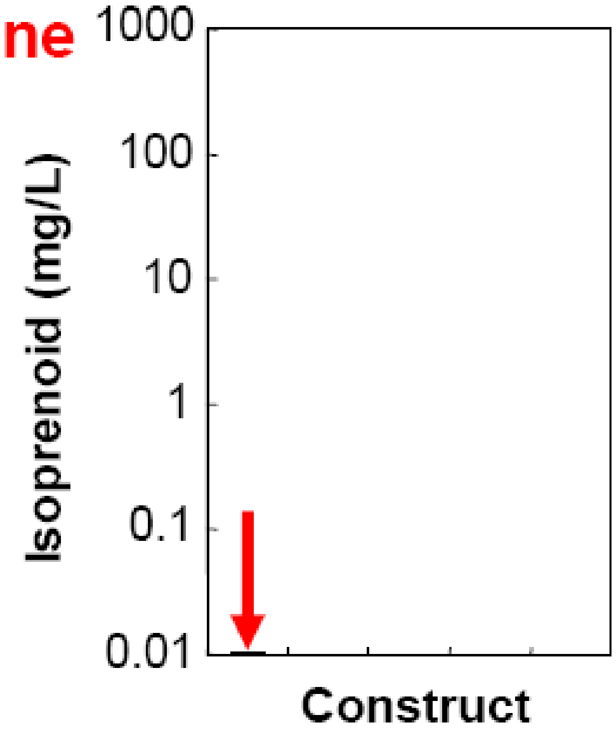
Transplanting artemisinin pathways



Production of a model isoprenoid in *E. coli*



Very low production of isoprenoid resulted when using the native gene



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ggcagctttc atgcttctga tgctgaatct tggtctctat ttcgtcatca ccatcatcgc
ttcttgggct gttaatcacg gcatcgagag aactcgcgag tctggtaact aacaaagata
acaactgatt aagtaacaat taatccaacg ttagaaaatg tcatcatcaa tcttcttttt
gtggtatttt gcagcgtcga cactgtcact tccggcgaag atattcccga tatacttccc
ggtggggaac atggcgaccg gtttttcgt aatattcacg ttaatcgccg gcgtcgtcgg
```

Making a plant gene look like a microbial gene

```
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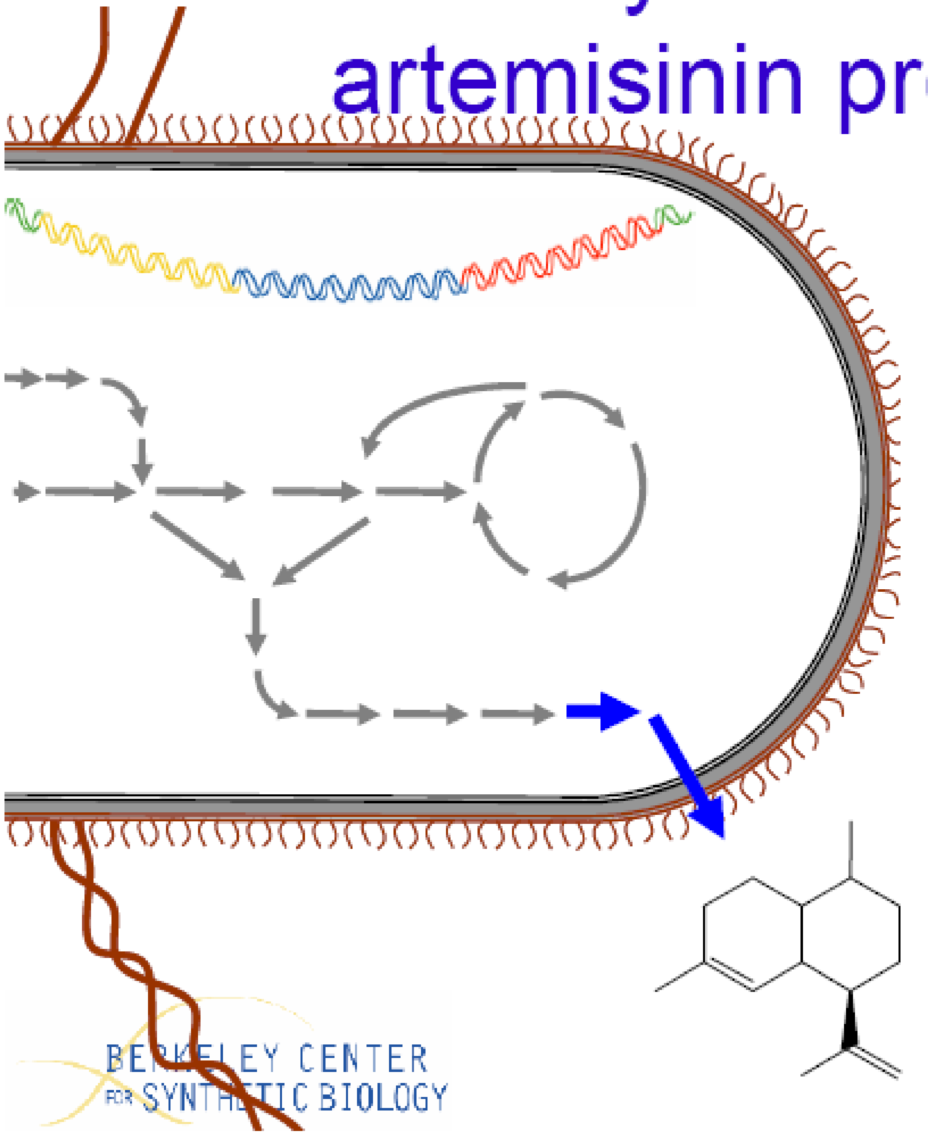
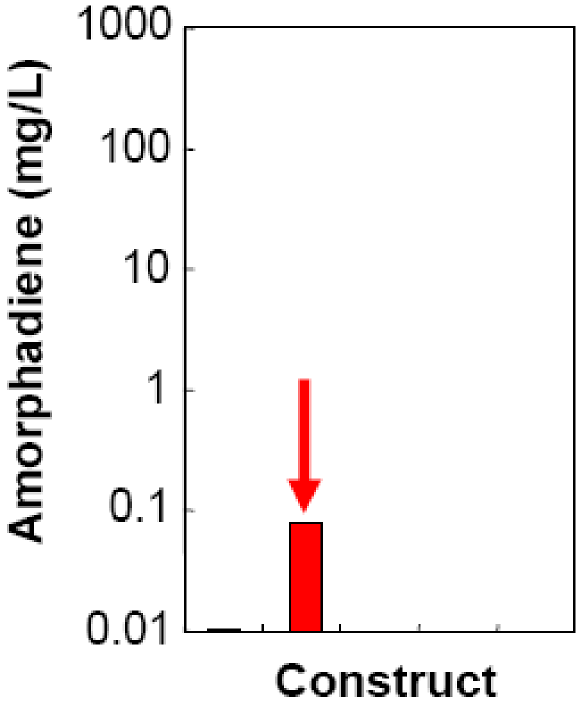
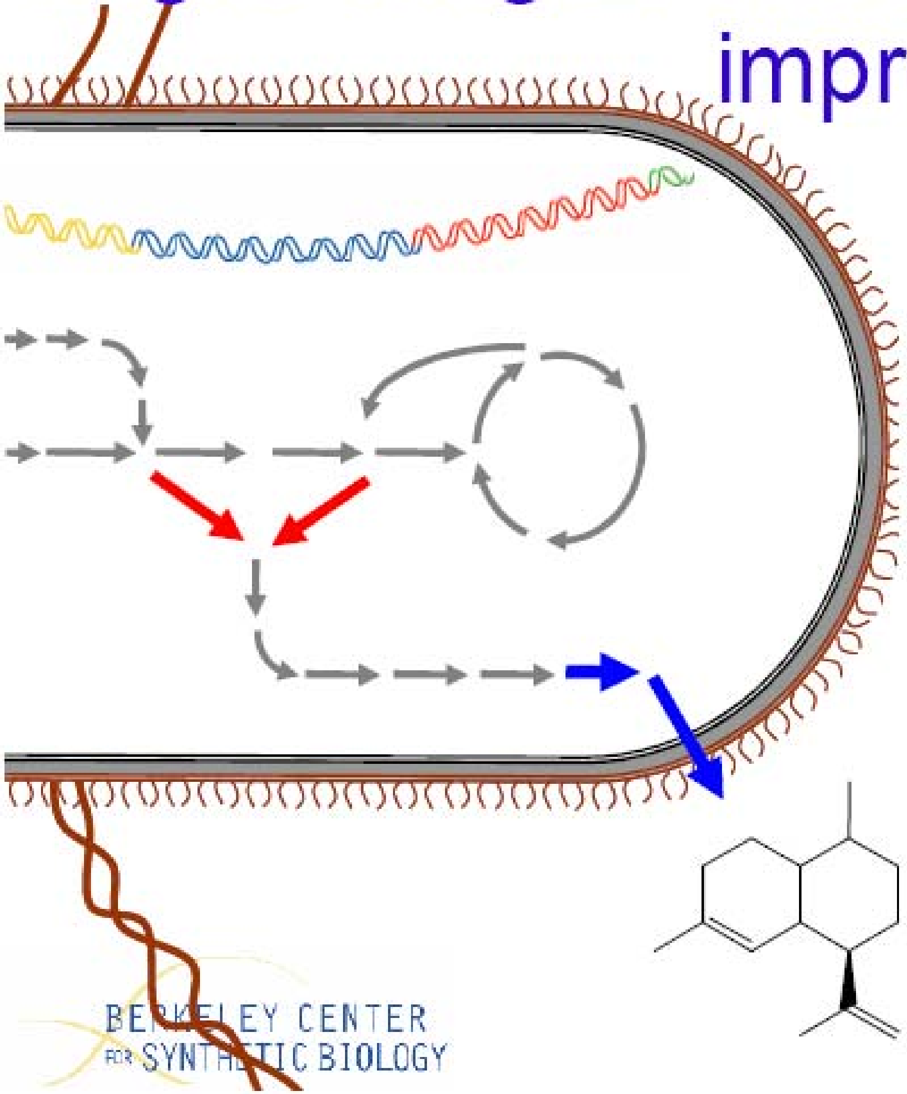
Gene resynthesis improves artemisinin production



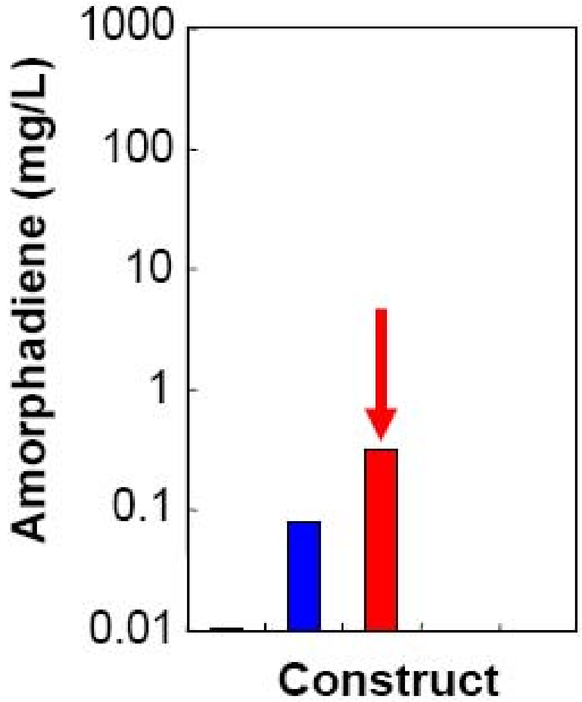
142-fold improved production!



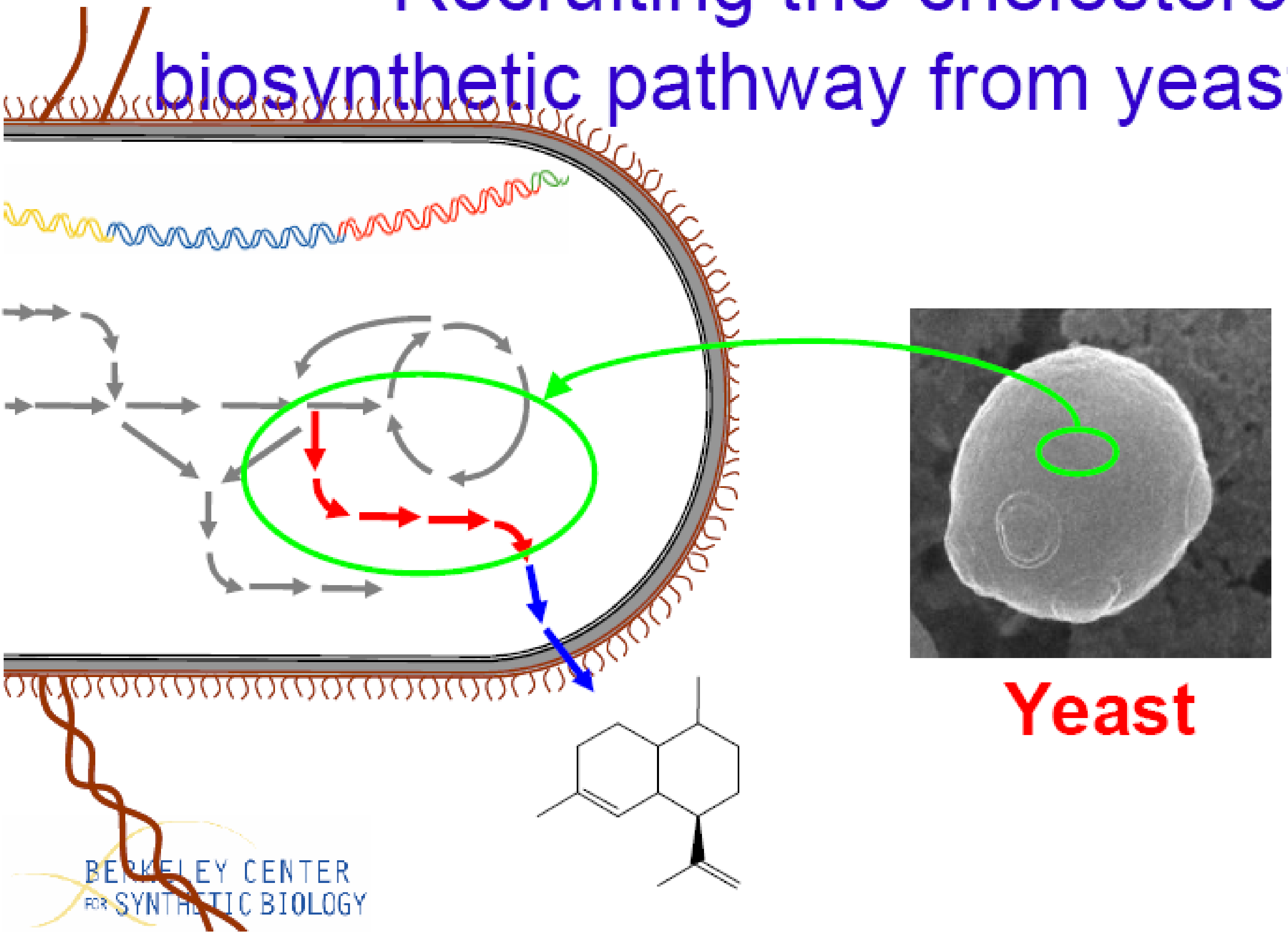
Engineering *E. coli's* native pathway improves production



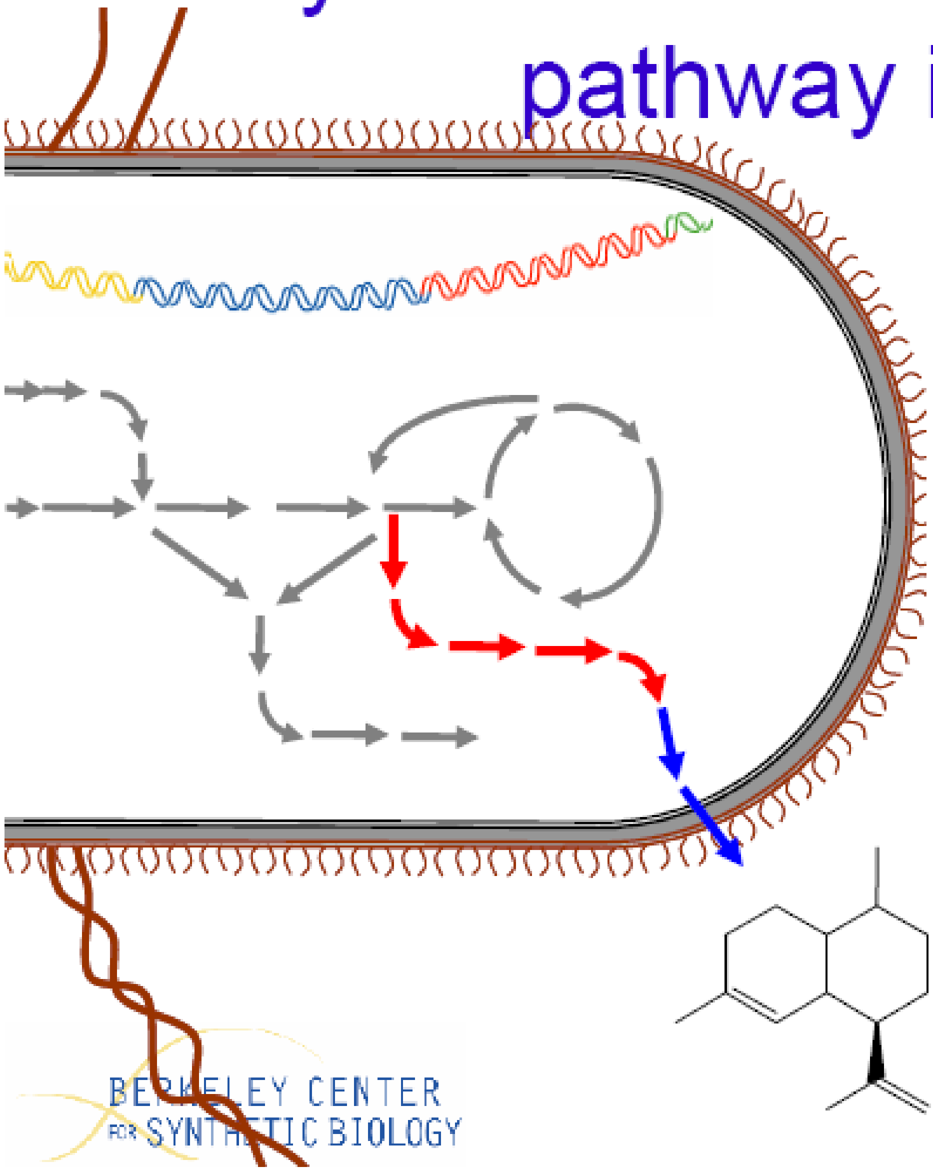
Three-fold improvement in production



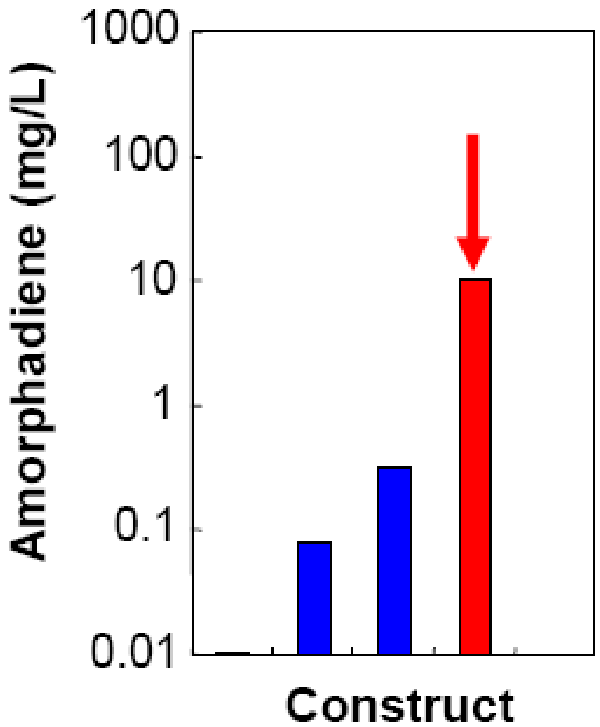
Recruiting the cholesterol biosynthetic pathway from yeast

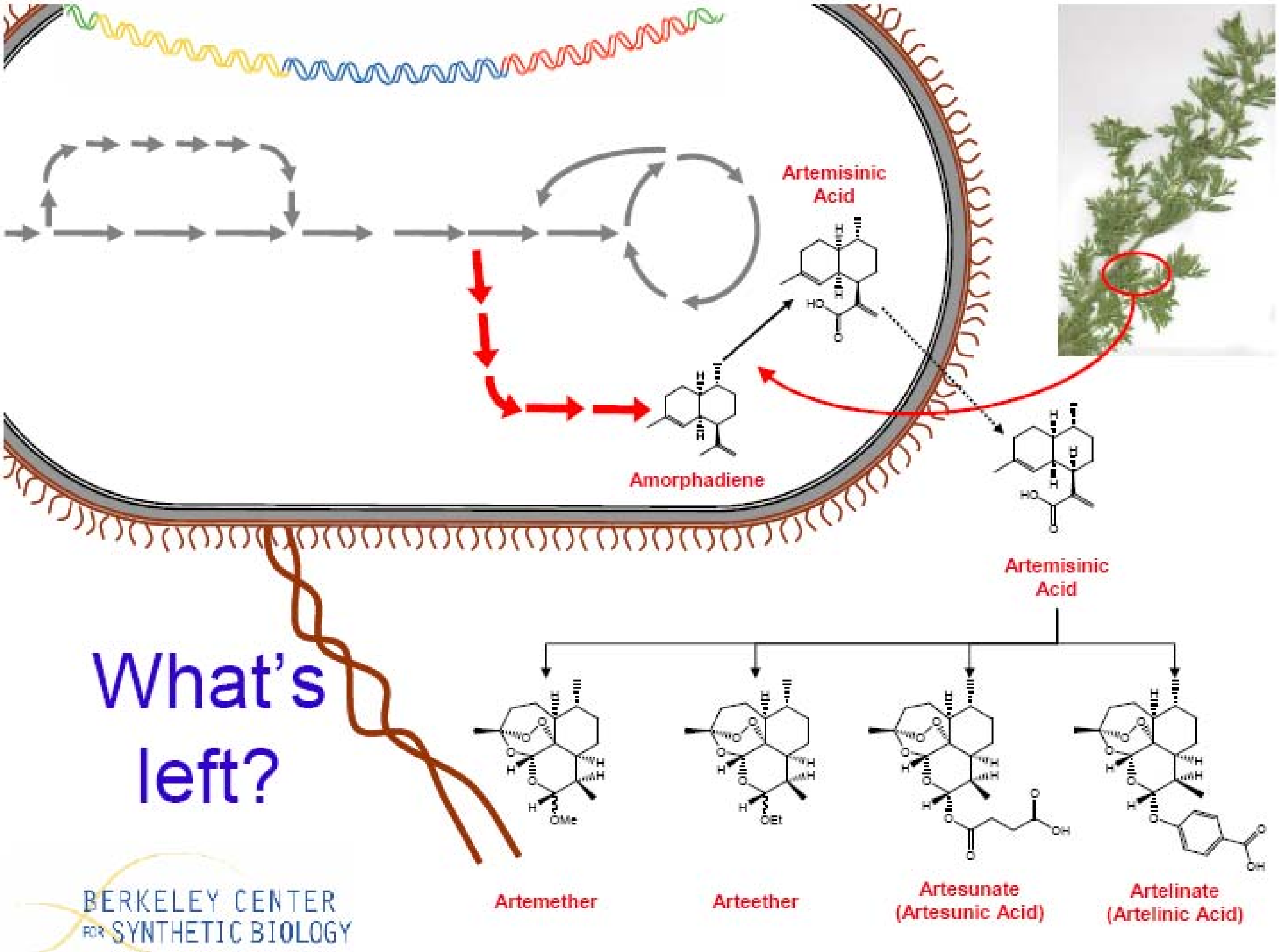


The yeast cholesterol biosynthetic pathway improves yields



~90-fold improvement in production





Artemisinic Acid
Amorphadiene
Artemisinic Acid
What's left?
Artemether
Arteether
Artesunate (Artesunic Acid)
Artelinate (Artelinic Acid)
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Artemisinin costs

	Artesunate combination treatment
Current cost of drug	**$2.25-2.50**
Cost with new process	**$.21/.12**

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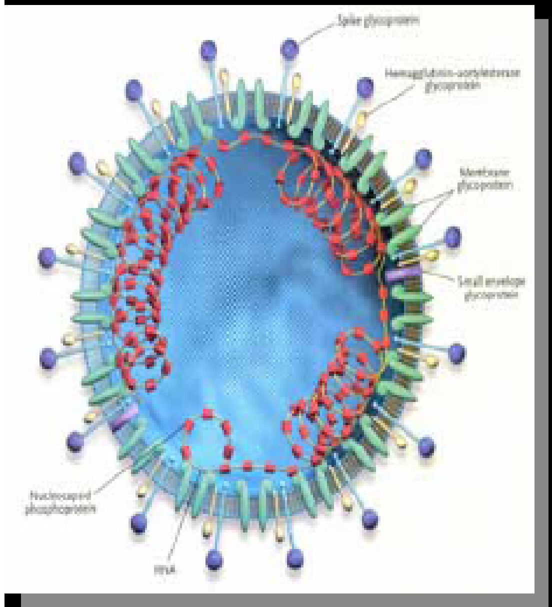
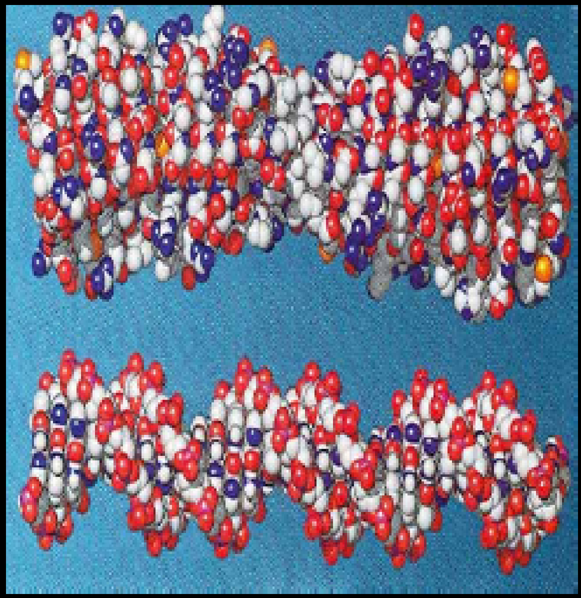
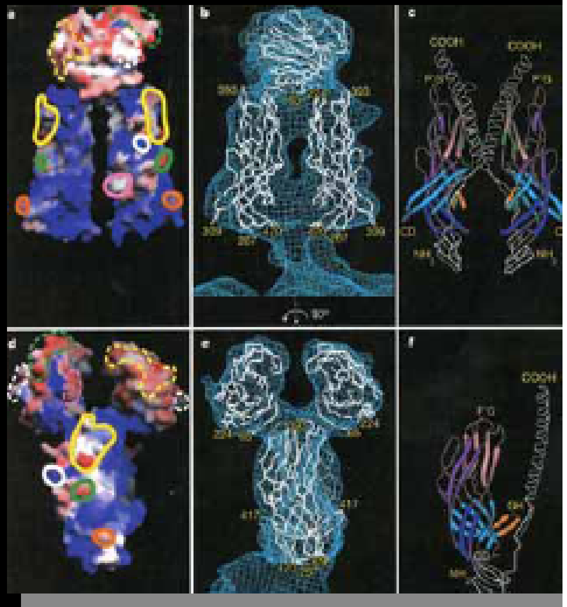
Engineered Microorganisms and Cells

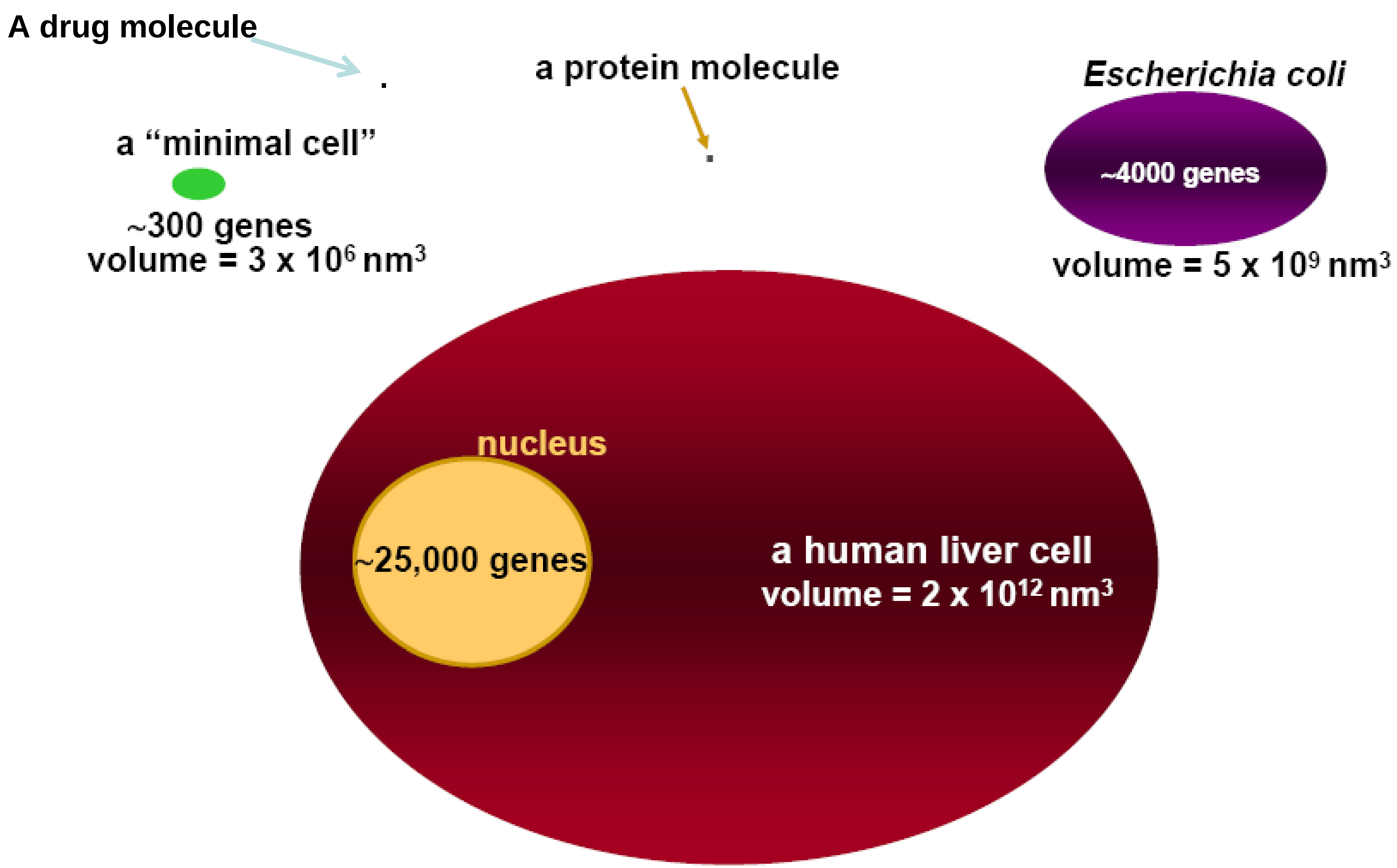
As living pills



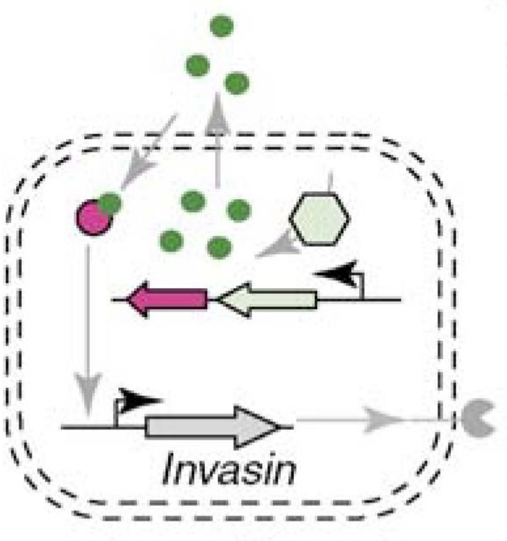


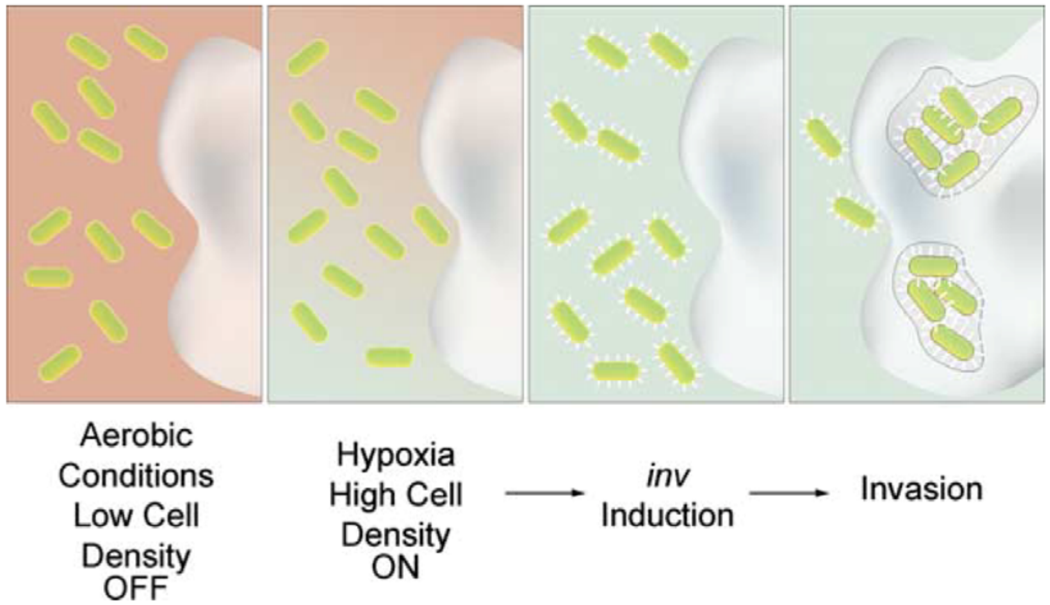


Coding Capacity vs Physical Limitations



Towards "biobots": cancer invading bacteria



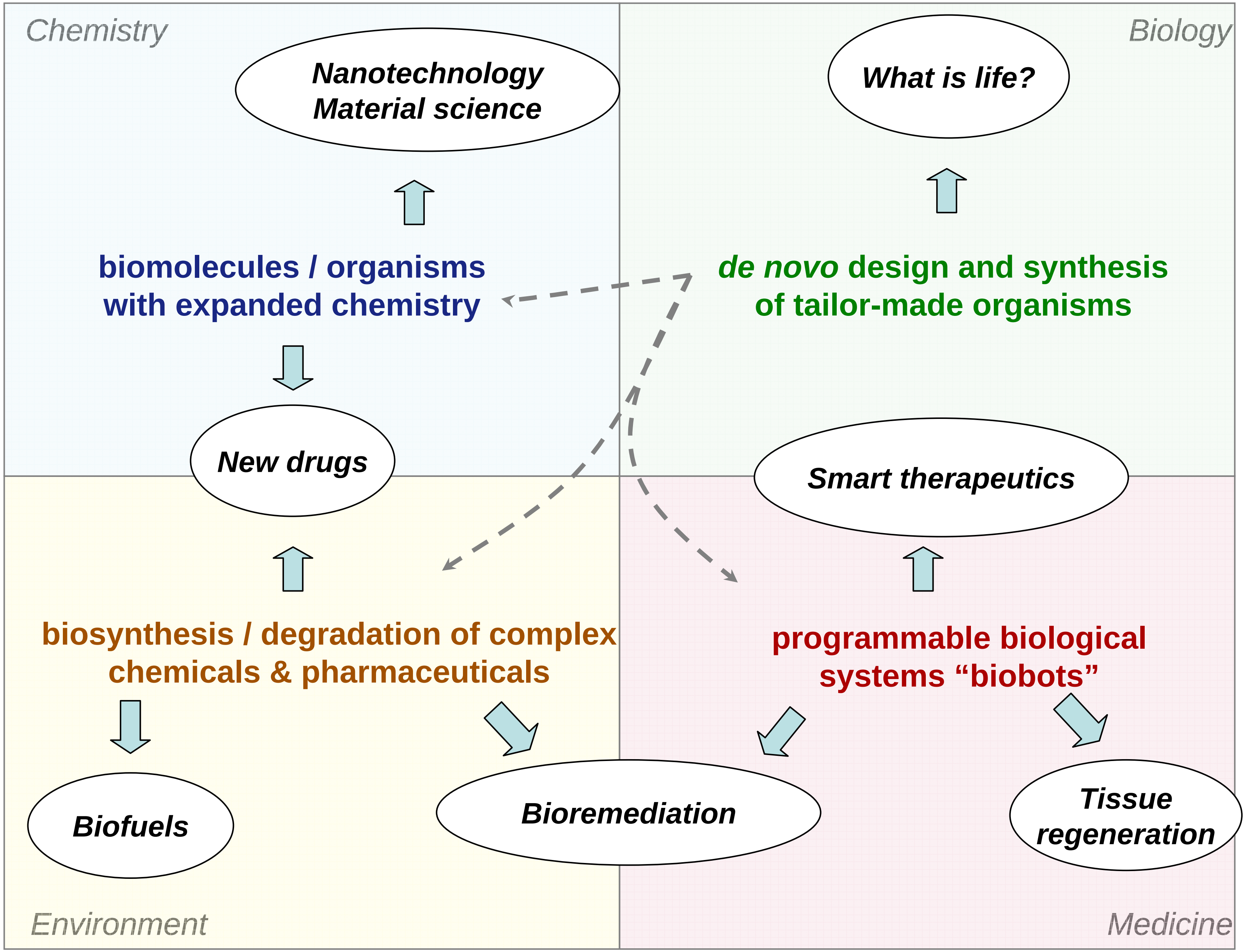


Vibrio fisheri: Quorum sensing (cell density sensing)
E.coli: hypoxia responsive promotor (*fdh*F)
Yersinia pseudotuberculosis: invasin (*inv*)

Anderson *et al* (2006) *J Mol Biol*. 355, 619

Perspectives and Ethics

What can synthetic biology deliver (in 5-10 years time)?

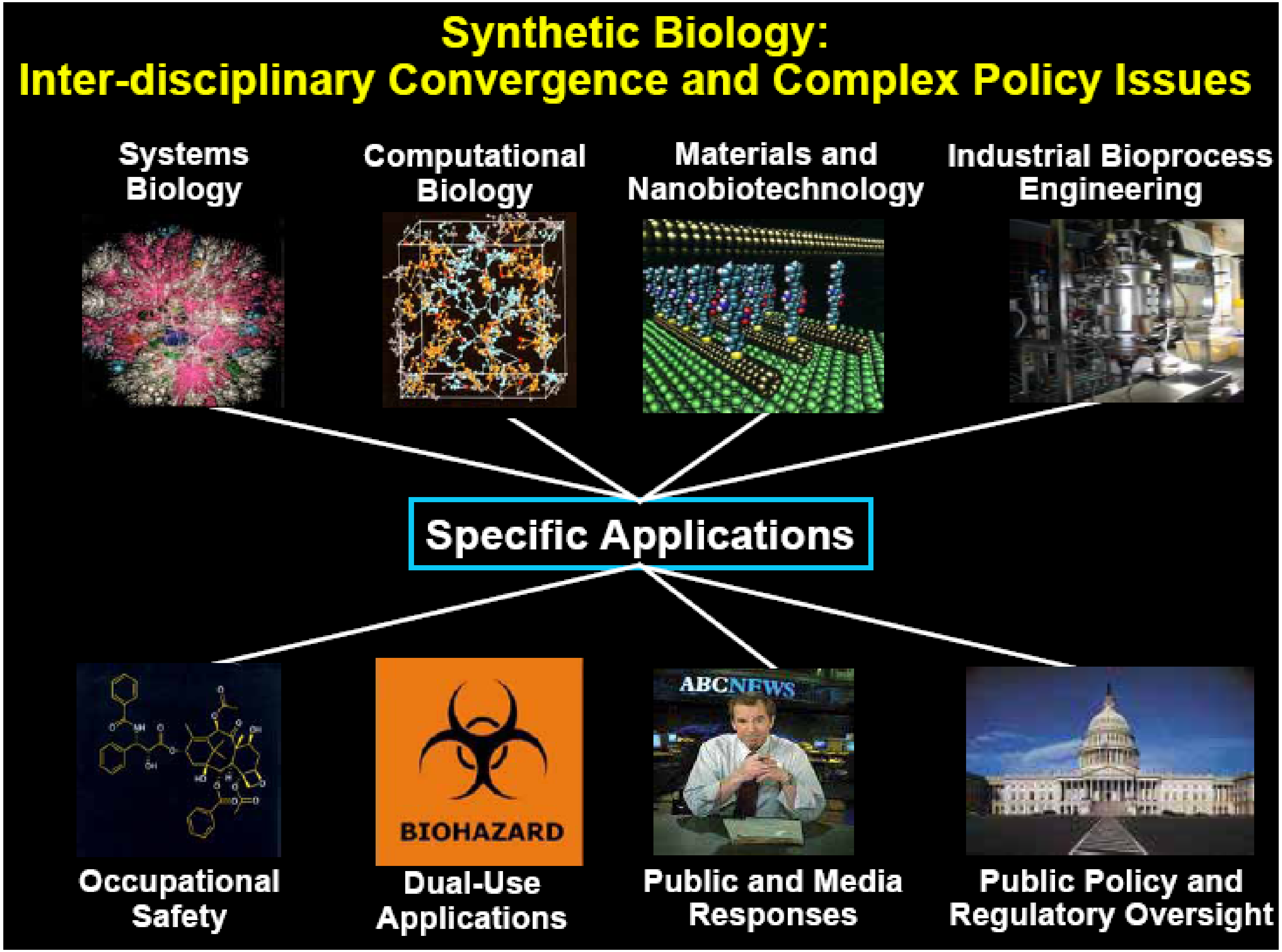


Synthetic Biology

- anticipated powerful driver of industrial innovation and market disruption
- new aspirants, new cross-sector relationships and new markets
- the next era in the evolution of human mastery of the environment
  - agronomic, industrial, informational, genetic, biomimetic, designed life forms
  - enhancement and eugenics?

The End of the Darwinian Interlude

- early 'biotic' world
  - massive lateral gene transfer and 'loose' definition of species
  - rapid evolution as a communal affair
- the Darwinian interlude
  - majority period in evolution (3 billion plus) years
  - slow pace of change and species 'isolationism'
- synthetic biology
  - revival of pre-Darwinian era of horizontal gene transfer


Synthetic Biology:
Inter-disciplinary Convergence and Complex Policy Issues
Systems Biology
Computational Biology
Materials and Nanobiotechnology
Industrial Bioprocess Engineering
Specific Applications
ABCNEWS
BIOHAZARD
Occupational Safety
Dual-Use Applications
Public and Media Responses
Public Policy and Regulatory Oversight

Synthetic Biology

- complex policy issues
- design of novel life forms and societal response
- dual-use applications
- public and media attitudes to perceived risks and benefits
- proactive, predictable, evidence-based regulatory frameworks

Key points raised in 2009

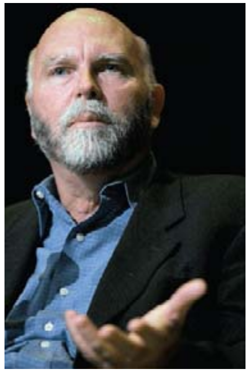
Samuel, Selgelid, Kerridge, EMBO reports

- Misuse for weapons/terrorism
  - Spelled out in greater detail
- Environmental impact
- Health impact
- Justice--patents, ownership
- Commerce and self-regulation

Science 15 June 2007:
Vol. 316. no. 5831, p. 1557
DOI: 10.1126/science.316.5831.1557
Prev | Table of Contents | Next

News of the **Week**

SYNTHETIC BIOLOGY:
Attempt to Patent Artificial Organism Draws a Protest



An activist group's concern about maverick genome sequencer J. Craig Venter's intention to patent an entirely synthetic free-living organism has thrown a spotlight on the emerging intellectual-property landscape in this hot new field. The protesters claim that Venter wants his company to become the Microsoft of synthetic biology, dominating the industry.

Venter hopes to use the artificial life form, which he says does not yet exist, as a carrier for genes that would enable the bug to crank out hydrogen or ethanol to produce cheap energy. Duke University law professor Arti Rai says the patent, if awarded, "could be problematic" only if Venter's product became the standard in the field. But Venter says this application is just the start: He plans to patent methods that would cover more than the single microbe described in the application. "We'd certainly like the freedom to operate on all synthetic organisms" that could serve as a chassis for swapping out genes, says Venter, whose research team is at the nonprofit J. Craig Venter Institute in Rockville, Maryland, but who recently started a company to commercialize the work.

Filed last October and published by the U.S. Patent and Trademark Office on 31 May, the application describes "a minimal set of protein-coding genes which provides the information required for replication of a free-living organism in a rich bacterial culture medium." The application cites work by Hamilton Smith and others on Venter's team on a simple bacterium called *Mycoplasma genitalium* that they are using to determine the minimum number of genes for life. They want to synthesize this "minimal genome" from scratch, get it working inside a cell, then add genes to produce cheap fuels (*Science*, 14 February 2003, p. 1006).

In a press release, the ETC Group, a technology watchdog in Ottawa, Canada, called Venter's "monopoly claims ... the start of a high-stakes commercial race to synthesize and privatize synthetic life forms." ETC calls for the U.S. and international patent offices to reject the patent so that societal implications can be considered. ETC also cited a recent *Newsweek* interview in which the scientist says he wants to create "the first billion- or trillion-dollar organism."

Venter says this is just one of several patent applications that would give his company, Synthetic Genomics Inc., exclusive rights to methods for making synthetic organisms. The artificial *Mycoplasma* "may or may not be" the one used to generate hydrogen or ethanol, he says; his team is working on several species. "We haven't given any thought to" the licensing conditions, but in any case, they would not impede work in academic labs, says Venter, adding, "This is a problem that we hope will have hundreds of solutions."

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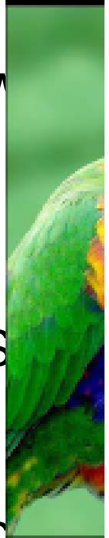
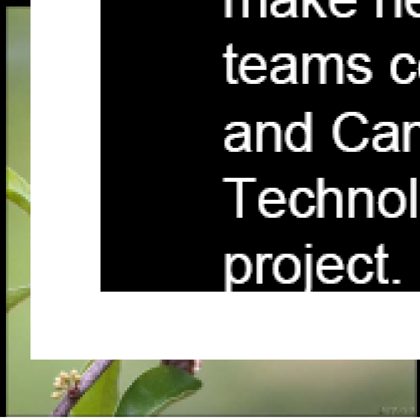


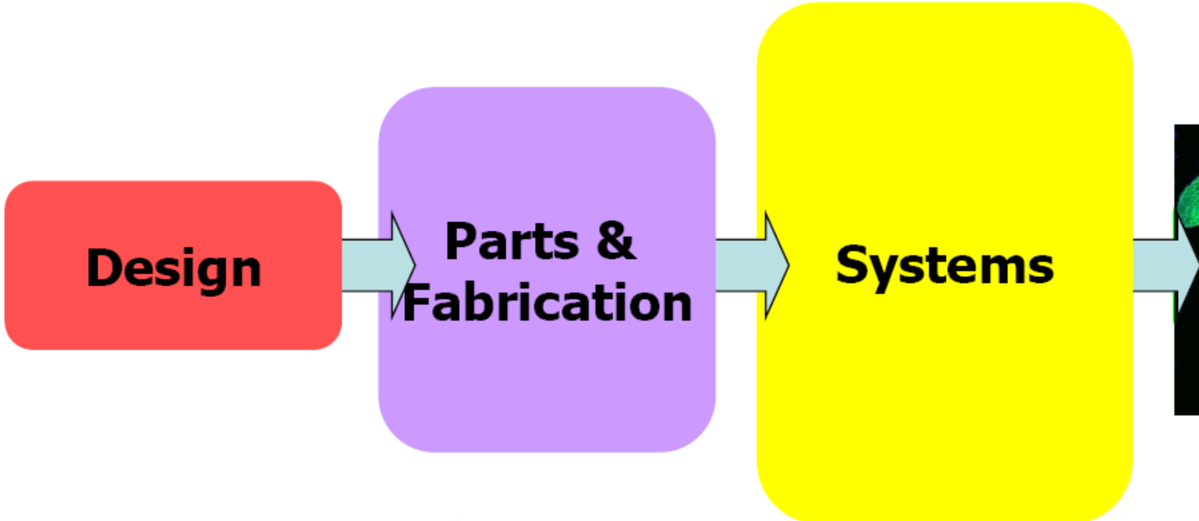


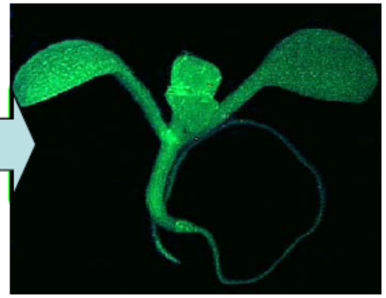
iGEM

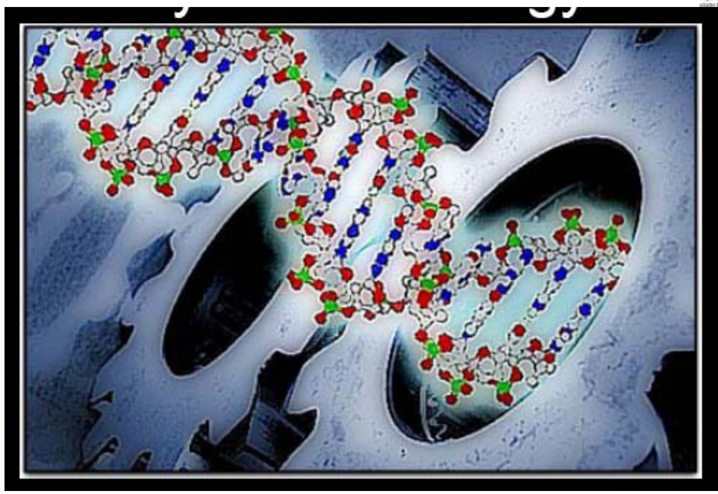
The International Genetically Engineered Machine (iGEM) competition is a worldwide competition between teams of undergraduate, graduate and PhD students from different universities who are interested in the field of synthetic biology. When creating their projects, the teams use the BioBricks (standardized biological parts) from the iGEM registry to make new, functional biological systems. The teams come from Asia , Europe, United States and Canada to the Massachusetts Institute of Technology (MIT) in Boston to present their project.

“Synthetic Biology: ENGINEERING LIFE”

IMAGINATION IS THE LIMIT







Questions
?

Acknowledgements

ZNIP

INTERACTION PROTEOME

MEGATOOLS FOR FUNCTIONAL GENOMICS

NetSensor

3D repertoire

PENELOPE

unicellsys

SEVENTH FRAMEWORK PROGRAMME

PROSPECTS PROTEOMICS IN TIME AND SPACE

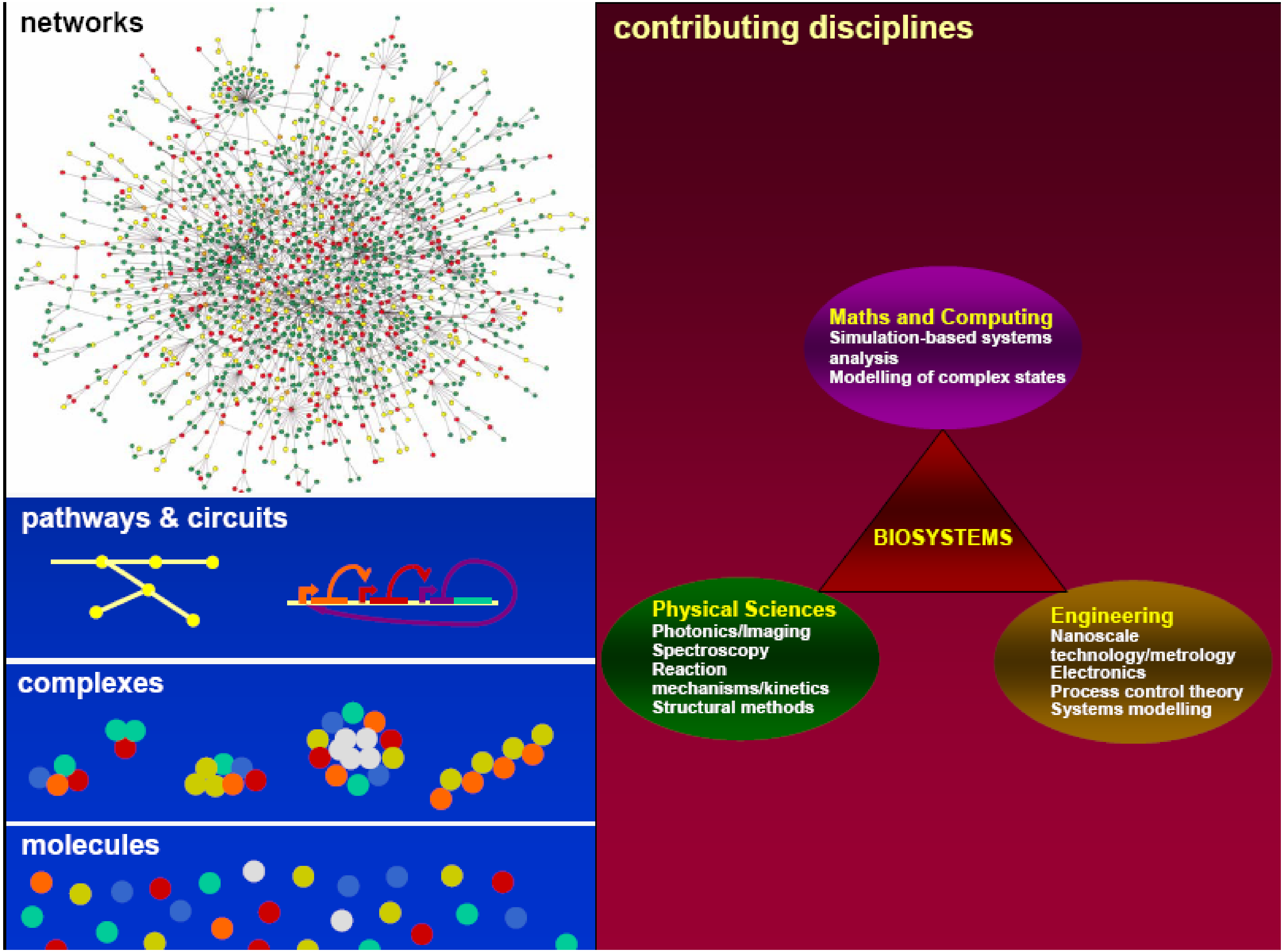
Fundación Marcelino Botín

PROGRAMA ingenio 2010

The Future of Synthetic Biology?

What are the key issues? Not these

- Misuse for weapons/terrorism
  - Any technology can be misapplied/put to pernicious use
  - Issue is into whose hands does the technology fall?
- Environmental impact
  - Can be handled through regulation
- Health impact
  - Can be handled through regulation and enforcement
- Justice--patents, ownership, commerce
  - No special issue relative to synthetic biology


networks
pathways & circuits
complexes
molecules
contributing disciplines
Maths and Computing
Simulation-based systems analysis
Modelling of complex states
BIOSYSTEMS
Physical Sciences
Photonics/Imaging
Spectroscopy
Reaction mechanisms/kinetics
Structural methods
Engineering
Nanoscale technology/metrology
Electronics
Process control theory
Systems modelling

Defining the Rule Sets for Biological Design, Assembly and Function

- common genetic (digital) code in all life forms
- genomes encode a limited series of structural building blocks (protein motifs and programmed assembly)
- combinatorial assembly of protein building blocks generates extravagant structural and functional diversity

Ethics of new technology: dual-use

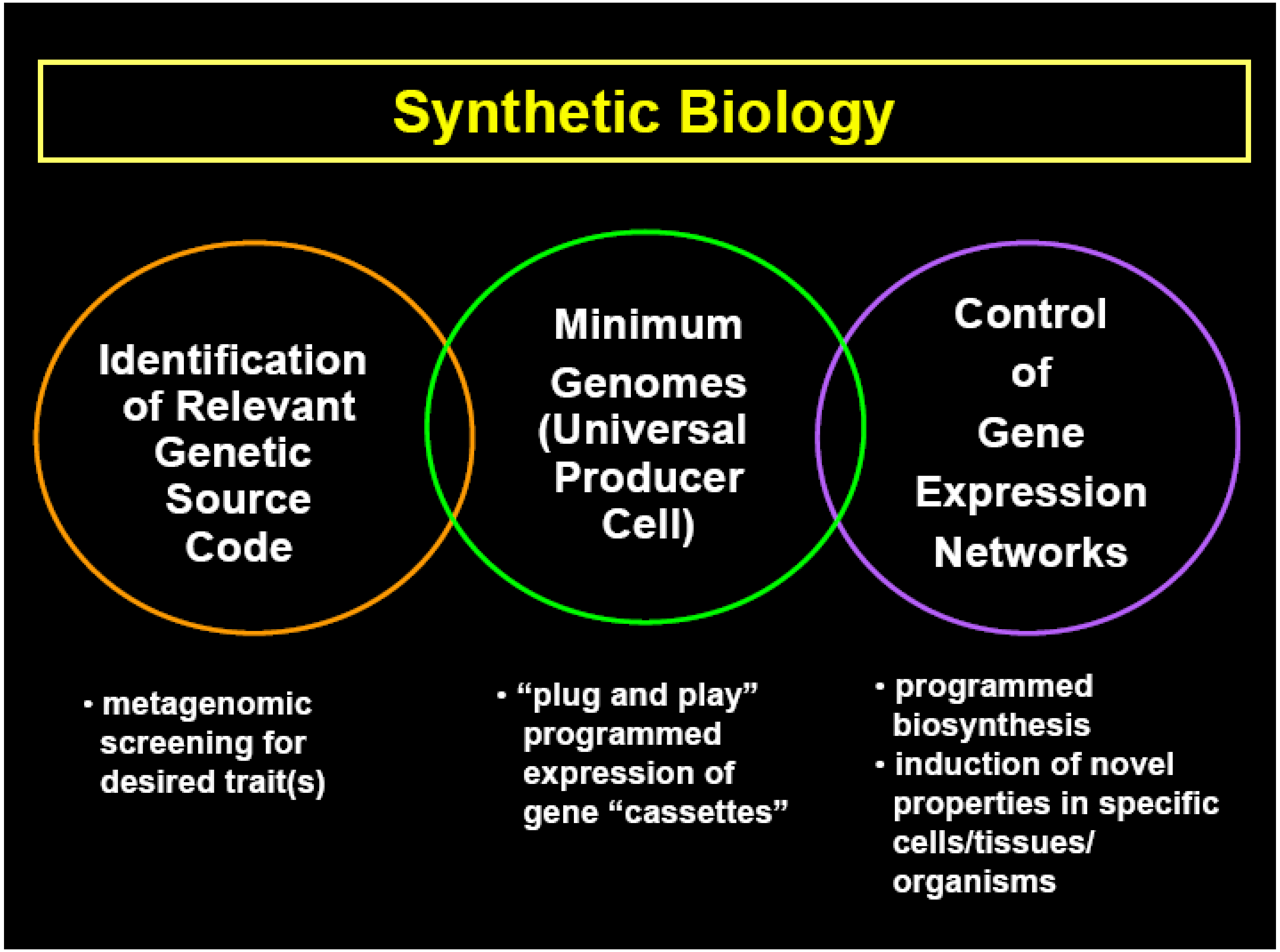
"evil" Technophobic (Bill Joy)	"good" Technophilic (Ray Kurzweil)
▪ Control and if necessary extinguish technology ▪ Top-down monitoring and control, hierarchical, few in power (surveillance) ▪ Philosophy of secrecy ▪ Licensing, monitoring, gated access, tracking, inspection ▪ Challenges are concentrated, government provides national security	▪ Technology is inevitable ▪ Bottom-up monitoring, democratic, participatory, many in power (sourveillance) ▪ Philosophy of openness ▪ Proliferation of open source projects (OpenWetWare, diybio, biopunk, biohack) ▪ Challenges are distributed, citizen defense, biosensors

Biological warfare and public health

- Can these technologies be weaponized?
- Risk assessment
  - Access to existing samples
  - Creating pathogens is difficult
  - Superbugs (Staph aureus), emerging infections
- Simultaneous development of defenses
  - Sensors

Exploring Biospace
The Design Power of Combinatorial Interactions and Assemblies

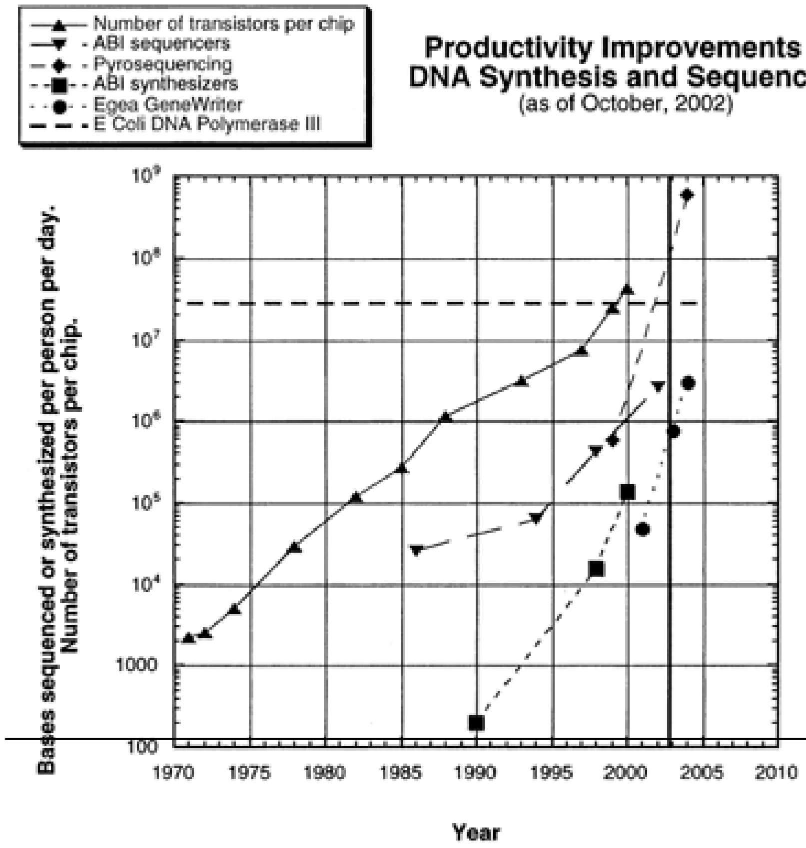
- 30,000 genes
- two genes cooperate to create a function
  =(30,000 x 29,999)/2 = 449,985,000 potential combinations
- 100 genes generate a complex function
  $=10^{289}$ potential combinations
- if any combination of genes can generate a function
  $= 2 \times 10^{72,403}$ potential combinations
- number of theoretical possibilities for synthetic assembly (biospace) far exceed narrow molecular space sampled in evolutionary time

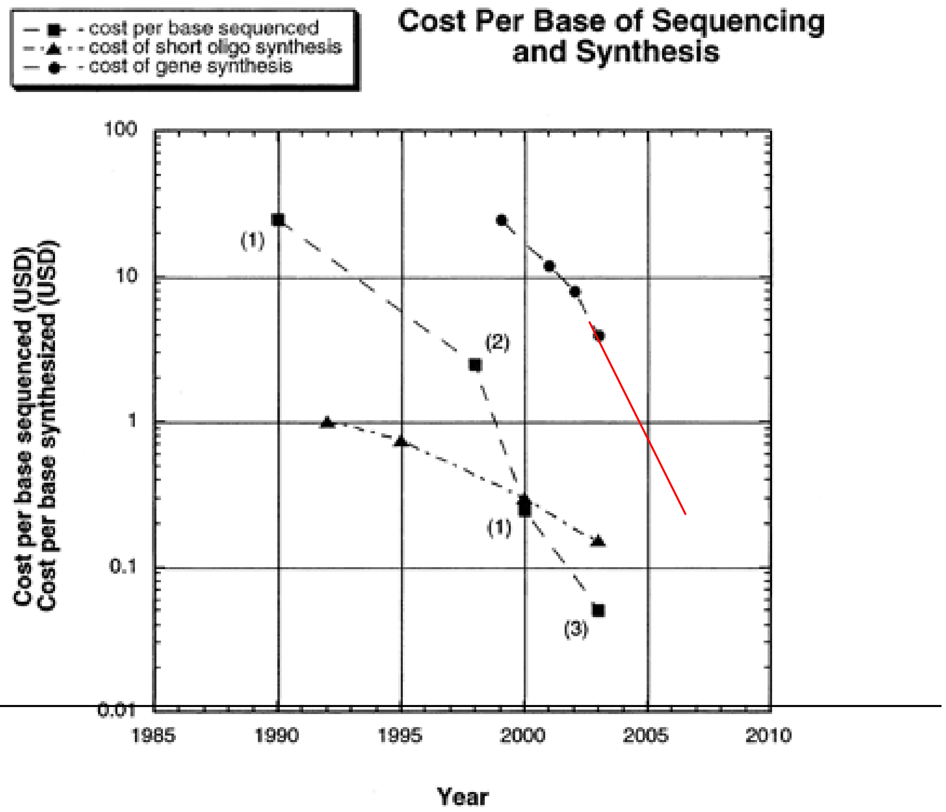


Synthetic Biology
Identification of Relevant Genetic Source Code
Minimum Genomes (Universal Producer Cell)
Control of Gene Expression Networks
• metagenomic screening for desired trait(s)
• "plug and play" programmed expression of gene "cassettes"
• programmed biosynthesis
• induction of novel properties in specific cells/tissues/ organisms

Biological Design: "Endless Forms Most Beautiful": Limitless Diversity From Combinatorial Assemblies of Limited Building Blocks

Sequencing & synthesis follow Moore's law





Human genome sequence (2001): 10 yrs, $ 3 billion / (2007) 2 months $ 2 million

Total synthesis of bacterial genome (2008)