The Pace and Diffusion of Synthetic Biology

Tsinghua University, Beijing, January 2013

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The Past and Future Present of Biological Technologies

Photosynthetic Sea Slug
(Elysia chlorotica)
Evolved ~100 Myr BCE
The Past and Future Present of Biological Technologies

Photosynthetic Sea Slug (Elysia chlorotica) Evolved ~100 Myr BCE

Photosynthetic Fish (Danio rerio) Engineered 2010 +5 (?) yrs
Pam Silver, Harvard Univ.
## Parsing the Spread of Biological Technologies

### Drivers

<table>
<thead>
<tr>
<th>Economic Growth</th>
<th>Material and Energy Efficiencies</th>
<th>Carbon Load Reduction</th>
<th>Curiosity (It’s cool, dude.)</th>
<th>FOOD,WATER, ENERGY!</th>
</tr>
</thead>
</table>

### Characteristics

1. International
2. Distributed (Beer Vs. Oil)
3. Increasing Capabilities
4. Decreasing Costs
5. “Open Source”?  

### Consequences

1. Widespread access to tools, skills, and materials.
2. Lower environmental impact (emissions).
3. Lower energy usage.
4. Reduction in foreign energy and materials dependency.
5. More diverse bio-economy that can withstand shocks.

### Major Uncertainties

A Hierarchy of Engineering and Economic Complexities

**Multiple Cells**: Control of growth and differentiation; products are cells and structures that cells make (Tissues, Organs, Animals, Houses).

**Synthetic Single Cells**: Looks initially like Metabolic Engineering; products are chemicals and biologicals made by cells.

**Multiple Genes in a Single Cell Type**: Metabolic Engineering: Fuels, Plastics, Terpenoids for Drugs, Flavors, and Fragrances. RFS.

**Single Gene in a Single Cell**: Recombinant Proteins: Laundry Enzymes, HGH, EPO.

Claudia Cadillo
Transplant Recipient

J.C. Venter

Artemisinin pathway

Expression in *E. coli*
How Big is the Bioeconomy?
“Genetically Modified Stuff” in the US Bioeconomy (2010 est.): ≥$300B or Equivalent of ≥2% of GDP

U.S. Biotech Revenues (billions)

- GM Crops ~$110B
- Biologics ~$75B
- Industrial ~$115B

“Genetically Modified Stuff” in the US Bioeconomy (2010 est.): >$300B or Equivalent of >2% of GDP

GM Crops ~$110B

Biologics ~$75B

Industrial ~$115B

GM revenue growth: Crops 10%, Biologics 10%, Industrial 20%.
(Sources: Nat Biotech, Forbes)

McKinsey and E&Y estimates for industrial apps range from $70B to $140B.

Scale and Regulation

U.S. Biotech Revenues in $ Billions

GM Crops ~110B

Biologics ~75B

Industrial ~115B +

Highly regulated
Long lead times to market
~$1 billion

Medium regulation
Long lead times to market
~$100s millions

Market includes engineering tools
Operate closer to consumer
Could be much smaller, lower capital reqs.
As low as ~$10K-100K?

non-drug + non-food = not-so-regulated
US Market Value of GM Crops

US Farm Scale Revenues from Major GM Crops

January 2013

USD Billions

Year

GM Corn Revenues
GM Cotton Revenues
GM Soy Revenues
US GM Crop Revenues

Sources: USDA, Biodesic

Average US Corn Yields: No End in Sight

Average US Corn Yield, 1866-2009

bu/acre

Open Pollinated

Double Cross

Single Cross

Biotech/GM

U.S. Planted Area: Eight Major Crops

Year

Sources: USDA-NASS; Troyer, Crop Science 46.2 (2006): 528; Pioneer (Rupert and Butzen, Crop Sci, 19(2))

Average US Corn Yields: No End in Sight

Average US Corn Yield, 1866-2009

Current Test Yield: ~300 bu/acre


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## Economically Driven Global Adoption: Biotech Revenues as % of GDP

<table>
<thead>
<tr>
<th>Country</th>
<th>2010 Biotech Revenues</th>
<th>2020 Target Biotech Revenues</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>&gt; 2%</td>
<td>NA</td>
</tr>
<tr>
<td>China</td>
<td>2.5% (?)</td>
<td>8%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2.5%</td>
<td>10%</td>
</tr>
<tr>
<td>India</td>
<td>0.24%</td>
<td>NA</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Europe</td>
<td>~1%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Source: Biodesic

Main source of uncertainty is definition of “biotechnology”; i.e., all biology or only products of genetic modification.

How Fast Is The World Changing?
Looking ahead, ongoing improvements in the performance of key enabling technologies, including DNA sequencing and synthesis, are likely to deliver significant further increases in productivity and reductions in cost over the next decade. Intensifying global competition among companies and countries providing sequencing and synthesis services, coupled with abundant technological innovation, is driving the rapid diffusion of new technology. In turn, the overall market for these services is growing rapidly and is likely to continue to expand at rates as high as 10—20% annually. These trends will have significant direct economic impacts within the biotechnology industry itself and across the economy at large.

The implications of these trends for the U.S. economy are explored in Section 3. The combinational engineering approaches that have transformed the fields of electrical engineering and software design are now being leveraged to accelerate biological engineering. Already, these techniques are being utilized to produce high value products for a variety of commercial purposes, and the range of potential applications is huge. However, the continuing “buildout” of these technologies will be shaped in large measure by an array of outstanding legal, ethical, economic, social, regulatory and political questions and issues that have yet to be resolved.

The ways in which these perplexing questions are addressed by governments and societies around the world will have a significant affect on the future impact of biological engineering on the economy and the earth’s living systems.

**Genome Synthesis and Design Futures: Implications for the U.S. Economy**

Oligo Synthesis and Gene Assembly

double stranded DNA

A T G C T C T A A A G

single stranded DNA

Oligos

Double-Stranded DNA

Plasmids and Chromosomes
Enabling Technologies Are Improving Rapidly

Productivity in DNA Synthesis and Sequencing

Updated Spring 2008

- Number of transistors per chip
- Commercially Available Sequencers
- Commercially Available Synthesizers

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Moore’s Law is about vision, it's about what you're allowed to believe. Because people are really limited by their beliefs, they limit themselves by what they allow themselves to believe what is possible. So here's an example where Gordon [Moore], when he made this observation early on, he really gave us permission to believe that it would keep going. - Carver Mead

Also about finance and planning in a multi-billion dollar industry.

Finally, Moore’s Law is about exponential markets that, for some time period, grow faster than transistor costs fall.

Potentially very different than biology.
The Future?

Oxford Nanopore
**Constructing Genes and Genomes**

**Longest Published sDNA**


Contiguous Bases: 1.0E+02, 1.0E+03, 1.0E+04, 1.0E+05, 1.0E+06, 1.0E+07

- Khorana (1979)
- Mandecki (1990)
- Stemmer (1995)
- Cello (2002)
- Gibson (2008)
- Gibson (2010)

**Sources:** see [http://www.synthesis.cc/2010/05/booting-up-a-synthetic-genome-1.html](http://www.synthesis.cc/2010/05/booting-up-a-synthetic-genome-1.html)
“What we are doing with the synthetic chromosome is going to be the design process of the future.”

J. Craig Venter

Synthetic Biology: Geographic Distribution
iGEM 2011 Competitors
- 2005: Produced numerous papers.
- 2006: First-, second-year university students built systems with ~20 parts.
- 2007: ~400 students from ~60 schools. Bio-energy makes first appearance; all parts in public domain.
- 2008: ~1200 students (825@MIT), 77 presentations. Synthetic vaccines, hacked pro-biotics.
- 2009: ~1200 students @MIT, 110 presentations. More fuels, manufacturing, bio-pixels.
- 2010: ~1500 students, 128 presentations. Manufacturing, bio-nano, Slovenia wins again.
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- 2011 Grand Prize Winning team from University of Washington used FoldIt to design gluten dehydrogenase that works ~800X better than an enzyme currently in clinical trials.
- Also demonstrated first even and odd chain alkane synthesis in E. coli; direct diesel synthesis.
Where Should We Look For Innovation?
**Examples of Small Organization Inventions:**

*This is Where the Economy Starts*

Source: Small Business Administration

<table>
<thead>
<tr>
<th>Small Organization Inventions</th>
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<tr>
<td>Air Conditioning</td>
<td>Geodesic Dome</td>
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<td>Air Passenger Service</td>
<td>Gyrocompass</td>
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<tr>
<td>Airplane</td>
<td>Heart Valve</td>
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<td>Articulated Tractor</td>
<td>Heat Sensor</td>
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<tr>
<td>Chassis</td>
<td>Helicopter</td>
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<tr>
<td>Assembly Line</td>
<td>High Resolution CAT Scanner</td>
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<tr>
<td>Audio Tape Recorder</td>
<td>High Resolution Digital X-Ray</td>
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<tr>
<td>Bakelite</td>
<td>Human Growth Hormone</td>
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<tr>
<td>Biomagnetic Imaging</td>
<td>Hydraulic Brake</td>
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<td>Biosynthetic Insulin</td>
<td>Integrated Circuit</td>
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<tr>
<td>Catalytic Petroleum Cracking</td>
<td>Kidney Stone Laser</td>
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<tr>
<td>Cellophane</td>
<td>Large Computer</td>
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<td>Artificial Skin</td>
<td>Link Trainer</td>
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<td>Computerized Blood Pressure Controller</td>
<td>Microprocessor</td>
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<td>Continuous Casting</td>
<td>Microscope</td>
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<tr>
<td>Cotton Picker</td>
<td>NMR Scanner</td>
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<td>Defibrillator</td>
<td>Optical Scanner</td>
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<tr>
<td>DNA Fingerprinting</td>
<td>Oral Contraceptives</td>
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<tr>
<td>Double-Knit Fabric</td>
<td>Outboard Engine</td>
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<td>Electronic Spreadsheet</td>
<td>Overnight National Delivery</td>
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<tr>
<td>Freewing Aircraft</td>
<td>Pacemaker</td>
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<tr>
<td>FM Radio</td>
<td>Personal Computer</td>
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<tr>
<td>Front-End Loader</td>
<td>Photo Typesetting</td>
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<td></td>
<td>Polaroid Camera</td>
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<td>Portable Computer</td>
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<td>Prestressed Concrete</td>
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<td>Prefabricated Housing</td>
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<td>Pressure Sensitive Tape</td>
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<td>Programmable Computer</td>
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<td>Quick-Frozen Food</td>
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<td>Reading Machine</td>
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<td>Rotary Oil Drilling Bit</td>
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<td>Safety Razor</td>
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<td>Six-Axis Robot Arm</td>
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<td>Soft Contact Lens</td>
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<td>Solid Fuel Rocket Engine</td>
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<td>Stereoscopic Map Scanner</td>
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<td>Strain Gauge</td>
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<td>Strobe Lights</td>
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<td></td>
<td>Supercomputer</td>
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<td>Two-Armed Mobile Robot</td>
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<td>Vacuum Tube</td>
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<td>Variable Output Transformer</td>
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<td>Vascular Lesion Laser</td>
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<td>Xerography</td>
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<td>X-Ray</td>
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<td></td>
<td>X-Ray Telescope</td>
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<td></td>
<td>Zipper</td>
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Micro-Brewing the Bioeconomy

US Brewery Count

Sources: Tremblay, et al, Rev Indust Org 2005; Brewers Assn

- Craft
- Large
- Total

Prohibition (1920-1933)

Deregulation (1979)

Number

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Conclusions:

1. Low or no barrier to entry: Small-scale, distributed biological production can emerge and compete against an installed large-scale infrastructure base.

2. Small producers can command a premium in a commodity marketplace -- i.e., can receive a disproportionate share of revenues.

Hypothesis:

Distributed biological manufacturing will be even more viable in markets that are higher value (not commodities).
Start-Ups Are Responsible for 100% of Net U.S. Job Creation

Figure 4: Job Creation and Loss by Firm Age
(Average per year, by year-group, 1992–2006)

Source: Business Dynamics Statistics, Tim Kane

Kauffman Foundation
Splice It Yourself
Who needs a geneticist? Build your own DNA lab
By Rob Carlson

The era of garage biology is upon us. Want to participate? Take a moment to buy yourself a molecular biology lab on eBay...

We can think of this as a threat, an opportunity, or even as a necessity.
My Garage Lab (c.2005)  
(Fashion is Important)

Credit: S.L. Keller
Carlson is not alone. Would-be 'biohackers' around the world are setting up laboratories in their garages, closets, and kitchens. The era of garage biology is upon us, he wrote in a 2005 article on Wired magazine.

Carlson penned essays and articles that fanned the embers of the DIYbio movement. The idea of transforming the field of biotechnology from a elite and expensive endeavor into a democratized, do-it-yourself activity would eventually bring in new talent to build "decentralized research institutions," he reasoned, and improve scientific instrumentation, and maybe help to uncover the public interest in making science more accessible.

Carlson's journey to garage biology began with a chance encounter on the train in 1996. Carlson, a physics PhD student, was travelling to New York to find a journal article that wasn't available at his home institution, Princeton University in New Jersey. He found himself sitting next to an inquisitive elderly gentleman. Carlson told him about his then-current efforts to turn a computer into a microscope and an espresso maker into an incubator. The name of the man who gave him the advice meant little to Carlson, who says he thought: "Yeah, Dr Sydney Brenner."

Brenner. The name meant little to Carlson, who says he thought: "Yeah, Dr Sydney Brenner."

The encounter on the train in 1996 was the beginning of a journey for Carlson. It wasn't until Carlson got back to Princeton and asked a friend if they knew Dr Sydney Brenner that the name meant something. The institute was a hotbed of creativity, and reminded Carl of the son of the scruffy hacker ethos that had spurred the personal-computing revolution just 25 years earlier. He began to wonder if the same thing could happen for biotechnology. What if a new industry, even a new revolution, could be created by giving everyone access to the high-tech machines, which amplify segments of DNA — cheaper and easier to use outside the confines of a laboratory, ultimately promising to make DIYbio more accessible.

"I made the prediction, " he says, "so I figured maybe I should do the experiment."

To follow his own advice, setting up a garage lab in 2005. "I made the new industrial applications for biotechnology."

Within a year, Carlson was working with a motley crew of biologists, physicists and engineers at Brenner's Molecular Sciences Institute (MSI) in Berkeley, California, learning molecular biology techniques as he went along. The institute was a hotbed of creativity, and reminded Carl of the son of the scruffy hacker ethos that had spurred the personal-computing revolution. He took the job.

OK. Whatever, 'Dr Sydney Brenner. '"

For now, most members of the do-it-yourself, or DIY, biology community are hobbyists, rigging up cheap equipment and tackling projects they would consider too easy or too risky to warrant the efforts of professional scientists keeping a side project at home to individuals who have never set up labs in their garages, closets and kitchens — from professional bioengineers to amateur hobbyists are creating home-brew molecular-biology labs, and at the end of the journey, the stranger made him an offer. "You should come work for me, " said the man, "I'm Dr Sydney Brenner."

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Carlson related this story to an audience recently at the University of California, Los Angeles, who has followed the field. This, " says Christopher Kelty, an anthropologist at the University of California, Los Angeles, who has followed the field.

"But what should we do?" Kelty asked. "How should we think about this?" His audience laughed at the implication that there was anything to be done.

"I think there's been a lot of hype and enthusiasm writing about this," Kelty said. "And it's not clear yet what the implications of this are."

"Things are very much at the beginning stages. " Critics of DIY biology are also hyped and enthusiastic writing about the potential for a "biotechnology revolution." But authorities will take one look at the gear in their garages and label them as bioterrorists. Some call the 'doyenne of DIYbio' , made glow-in-the-dark yogurt by engineering the bacteria within to produce a fluorescent protein. Others prefer to keep their labs under wraps, concerned about weaponized biohacks.

"We're making anthrax. " "We're making smallpox. " "We're making E. coli in your armpit. (It's cheaper than shelling out $100 or more on a $180–$500 °C incubator.) Some share protocols and ideas in open forums. Others prefer to keep their labs under wraps, concerned that — although not exactly pushing the boundaries of molecular biology, some groups are focused on making standard instruments — such as PCR machines, which amplify segments of DNA — cheaper and easier to use outside the confines of a laboratory, ultimately promising to make DIYbio more accessible.

Some standard laboratory equipment such as fume hoods can get quite expensive, but one should not sacrifice safety for cost. For guidance on the necessary equipment, consult with local biohacker groups. Another option is to join the institutional biosafety committee at your local university or medical centre. These committees often have slots for nonscientists.
Garage Biology is Somewhere, Anywhere

Garage lab, undisclosed location, CA (c.2010).
Cell culture and anti-cancer compound screening.
Europe Joins the Garage Bio Party

You can grow 20mg of recombinant protein in a 50ml reaction with some effort, overnight. That's $1.1M worth of EcoRI. #what #synbio
Distributed Innovation:
“Innovation has gone public” - Bruce Perens

RepRap

http://ng.cba.mit.edu/dist/fab.pdf

Fab Lab

Fab@Home

Objet Alaris™30

Graphtec CE5000
What About Safety and Security?
President of the United States: “Garage biology is good.”

“The beneficial nature of life science research is reflected in the widespread manner in which it occurs. From cutting-edge academic institutes, to industrial research centers, to private laboratories in basements and garages, progress is increasingly driven by innovation and open access to the insights and materials needed to advance individual initiatives.”
Unexpected Impacts of Policy on Proliferation

Cocaine:


Meth:

“...Marked success in decreasing domestic methamphetamine production through law enforcement pressure and strong precursor chemical sales restrictions has enabled Mexican DTOs to rapidly expand their control over methamphetamine distribution.”

http://www.usdoj.gov/dea/concern/18862/meth.htm

Increased enforcement efforts have created a larger, blacker market that is “[M]ore difficult for local law enforcement agencies to identify, investigate, and dismantle because [it is] typically much more organized and experienced than local independent producers and distributors.”

“Methamphetamine Strategic Findings”:
http://www.usdoj.gov/dea/concern/18862/

Restricting access to commodities can create dedicated technology development efforts to meet supply:
- “Narco-sub”
  - Cost of Construction: $.5-2 million.
  - Cargo: ~$1 billion in cocaine.
  - Now moved on to fully submersible

Safety in the stalls of Akihabara: Maximize Knowledge, Skills, Awareness
Reading and Thanks

Biology is Technology:
The Promise, Peril, and New Business of Engineering Life
Robert Carlson

PROSE Award for Best Engineering and Technology Book of 2010

Best Books of 2010, The Economist

Best Books of 2010, Foreign Policy
