Emerging Trends and Drivers in the Global Biotechnology Industry

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Next-generation Manufacturing May be the Real Biotechnology “Killer App”

DARPA – Living Foundries: US$150M investment in next-generation bio-based manufacturing

“The biological world is displacing the machine as a general world of design.”

Neri Oxman, MIT Media Lab
Bio-based Markets Already Significant

“Genetically Modified Stuff” in the US Bioeconomy (2010 est.): >$250B or Equivalent of ~2% of GDP

U.S. Biotech Revenues in $ Billions

- GM Crops ~80B+
- Biologicals ~70B
- Industrial ~100B+

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

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

US DOC value added to GDP (2007): mining 2%, construction 4.1%, information and broadcasting 4.7%, all of manufacturing 11.7%, transportation and warehousing 2.9%, finance 20.7%, and all of government 12.6%.
But the Biggest Biotech Market Opportunities Remain, Plus Creation of New Ones (Berry 2011)
Next-generation Biotechnology as a Disruptive Game Changer: New Production Platforms and Value Chains Displace Former Methods of Production (Carlson 2010)

Challenges I: An Increasing Diversity of Energy Sources

- Chemical/Thermal decomposition to Synthesis Gas
- Combined industrial/biological decomposition (i.e., steam + enzymes) of cellulose into sugars (e.g., “biorefinery”)
- Centralized microbial or enzymatic processing of cellulose into sugar
- Distributed biological or industrial refining into sugar or starch

- Direct catalytic synthesis of fuel
- Direct fermentation of synthesis gas

Distillation/separation
- Alcohols
  - Fermentation
  - Biosynthesis
- Hydrocarbons
  - Biosynthesis
- Gas
- Hydrogen

To market

Fuel Cell: “The car is the refinery”?
Multi-use Core Platforms and Infrastructure as Evolving Business Model in Biotechnology
2. Disruptive Innovation Drives Biotechnology

*Shift to Solutions-driven, Problem-oriented S&T, even in Fundamental Research*

*Societal Grand Challenges and Value Creation – Research, Innovation, and Market Demand*
Increased Focus on Disruptive Innovation to Change the Cost Curves, Technology Frontiers and Scaling Options

PACE AND SCALE OF INNOVATIONS NEEDED IN ENERGY TECHNOLOGIES

Game Changers from 20th Century

- Artificial Fertilizers
- Green Revolution
- Polio Vaccination
- Antibiotics
- Airplanes
- Electrification
- Nuclear Energy
- Transistor
- Integrated Circuits
- Fiber Optic Communication
- Wireless Communication
- Internet

20 years

Imagine all of this happening in the next 20 years...

- Solar electricity generation at cost lower than that produced from fossil fuels ($1/W fully installed)
- Real-time optimization, security and storage for grid with two-way dispatchable electric power
- Carbon capture and utilization at net cost lower than its market price
- Car batteries with 3X energy density and 4X lower cost
- Transportation fuels from sunlight, CO₂ and/or agricultural waste at cost lower than petroleum
- 50-80% reduction in energy consumption in homes and buildings with energy use awareness and behavioral impact
- Low-cost desalination of water
- Low-cost and safe nuclear energy

arpa-e
Accelerating Transition to Low Carbon Economy Creates Huge New Innovation Opportunities for Biotechnology (IEA Roadmap 2011)
Biotechnology Builds on Open Innovation, Multi-directional S&T, University-Industry Partnering, and New Public-Private Collaborative Mechanisms to Enable Cutting-edge Developments
To offset the trends of rising development costs and shorter product life cycles (left bar), companies must experiment with creative ways to open their business models by using outside ideas and technologies in internal product development and by allowing inside intellectual property to be commercialized externally (right bar).
3. **Biotechnology increasingly is an Information Business**: “**Big Data**, Computation, Algorithms, and Cyber-enabled R&D

- More data will be created in next two years than in all past 40,000 years.
- Total data will quadruple in next two years.
- Business and government decision-makers **must** have a strategy for dealing with all that data.
Bioinformatics and Computational Biology have led to a proliferation of new bio- and genomic data.

Figure 3.5 Technology is Accelerating Data Generation

Development of new systems in bioinformatics has led to exponential growth in the amount of biodata.

This graph is exponential rather than semilog in proportion; with each increment showing a tenfold increase over the previous measure. To be reasonably proportional, with the quantity ten represented as one inch, the chart would have to be 1,578 miles tall.

- Single molecule?
- Short-read sequencers
- Massively parallel sequencing
- Capillary sequencing
- Automated slab gel
- Manual slab gel
- Second-generation capillary sequencer
- First-generation capillary sequencer
- Microwell pyrosequencing

Genomic Data is Increasing Faster than Computing Power

Arkin Lab (UC – Berkeley)

Some numbers to contemplate

- $10^6$ microorganisms per gram of soil ($10^{33}$ on earth)
- $10^9$ in a ml of rich media
- Divide every 20 minutes
- Flip-operations-per-molecule-per-second-per cell $\sim 0.01$
- 100-200 plasmids per cell.
- 5-6 “machines” per plasmid
- 100-1000 “machines” per genome
- Plasmids passed per cell per generation $\sim 0.01$

What is the computational capacity?

Promise of BIG DATA

- Provide a computing infrastructure that can capture, validate, and analyze high volumes of data
- Evaluate mixed data from multiple sources
- Tackle unpredictable content with no apparent structures
- Enable real-time analysis and answers
Algorithms: Data-Compression Algorithm for Genomes (Berger/MIT 2012)

• An algorithm that drastically reduces the time it takes to find a particular gene sequence in a database of genomes. Moreover, the more genomes it’s searching, the greater the speedup it affords, so its advantages will only compound as more data is generated.
The Fourth Paradigm, the Internet of Things, and Big Data in Biology Intersect to Fundamentally Transform Biotechnology (Gray 2009)

**Science Paradigms**

- Thousand years ago: science was **empirical**
  describing natural phenomena
- Last few hundred years:
  a **theoretical** branch
  using models, generalizations
- Last few decades:
  a **computational** branch
  simulating complex phenomena
- Today: **data exploration** (eScience)
  unify theory, experiment, and simulation
  - Data captured by instruments or generated by simulator
  - Processed by software
  - Information/knowledge stored in computer
  - Scientist analyzes database/files using data management and statistics

\[
\left( \frac{d}{dt} \right)^2 \frac{a}{M} = \frac{4 \pi G p}{3} - \frac{K \alpha^2}{a^2}
\]
Redrawing the Boundaries of Biotechnology in the “New Biology” (NAS 2009)

• *Who is Us?*

> “the merging of distinct technologies, processing disciplines, or devices into a unified whole that creates a host of new pathways and opportunities. It involves the coming together of different fields of study – particularly engineering, physical sciences, and life sciences – through collaboration among research groups and the integration of approaches that were originally viewed as distinct and potentially contradictory.”

MIT (2011)
5. Engineering Biology as the Transformative “New Normal” in Biotechnology: Standardization, Abstraction and Modularity create hierarchies of complexity and connectivity
“transits from an ANALOGY of the rational combination of genes [in modern biology] to a Engineering METHODOLOGY to construct complex systems and novel properties based on biological components” (US-EU Task Force, June 2010)
Predictive Platforms for Engineering Biology and Predictable Integration of new Genetic Designs

Need to Move from Engineering Biology Today

• Many iterations and small systems
• Lack of parts characterization and predictability
• Unknown design rules
• No reliable, interoperable design tools
• Time/money intensive processes

to:

• Complex Genetic Circuits that work in dynamic biological systems
• Later, Genome Rewrites (increased complexity)
Decoupling is Key: especially Decoupling Design from Fabrication/Manufacturing – Think Semiconductors

- Thomas Lee (DARPA – 2011): think of “Circuits on Demand with Biological Transistors”

- Changing metaphors -- Biology as a Design Space

- ACCELERATE the BIOLOGICAL DESIGN-BUILD-TEST cycle with increased COMPLEXITY of designs
Standardized Information and Biology – Abstraction of Component Properties in Systems, Precise Description of Objects, Reference Standards, and Composition of Blueprints/Designs

Standardized Rules for Physical Assembly of Biological (Expression) Devices – Make Functional Composition Easier

Universal Reference Points

E.g., Adoption of RNA polymerase per second (PoPs) units as a universal reference to express promoter strength
Engineering Biology: Multiple Approaches Proliferate to Drive Innovation

Top-down perspective

Interactions

Orthogonality

Analysis in context

Biological design

Construction and implementation

Bottom-up perspective

Configurations

Modules
Engineering Biology Approaches Create New Business Models focused on Value-Added Functions

• Combining Genes in new and useful ways (but not necessarily as evolution decreed) – “Mix and match” functions from natural/synthetic worlds
• Doing things in nature more efficiently

• Getting microbes to perform tasks nature never intended (Microbial Bio-factories)
• Rapid and reliable construction, evolution, and manipulation of Biological Circuits
• Rewriting new genetic programs and design
• Routine system characterization and debugging that informs the design-build-test cycle

• Design molecular components and tools that span from high level description to fabrication in cells
  – Biosensing
  – Bioremediation
  – Bioproduction
6. Robust Biotechnology Toolkit as a Driver of Economic Inflection Points: (Bio Economic Research Associate 2007; B Erickson 2011)

Recombinant DNA technology:
- Horizontal transfer of genetic material
- Homologous recombination
- Gene shuffling; directed evolution

Synthetic biology techniques:
- Standard biological parts
- Low-cost sequencing and synthesis
- Simplified chassis, operating system
- System modeling and simulation
- Metabolic pathway design

B Erickson et al. Science 2011;333:1254-1256

Published by AAAS
Biotechnology Toolkit Markets are Growing Rapidly

**Synthetic Biology: Globally Distributed Capacity, c.2007**

Gene Synthesis Foundries

Gene Synthesis Companies Play an Increasing Role

Consolidation since 2007, but no technical or economic barriers to participation.
Sequencing Costs Continue to Fall Faster than Moore’s Law (NHGRI 2012)
Key Technical Drivers - Enabling Technologies, Read-Write DNA, and Synthesis Capabilities (R. Carlson 2010)

Exponential Progress in Reading DNA and Writing DNA

Sources: Biodesic, www.synthesis.cc
Interconvertibility Increasingly Drives Biotech - Reading and Writing Genomes

• FROM PHYSICAL LIVING MATERIAL/DNA to INFORMATION, and back, BECOMES KEY DRIVER
  – “Bits and Pieces come together” (Collins 2012)
  – “IT from Bits” (Poste 2010)
  – Programming: increasing ability to both Read and Write DNA

• DNA Construction (analog to Read/Write; 1’s and 0’s manipulation in ICTs)
  – Genetic Expression Operating Systems; Scale DNA construction engineering

• Decoupling biological processes from descent and replication -- Biological tools of synthesizing and sequencing (Reading and Writing DNA)
Tools to Edit Genomes: MAGE + CAGE

(Church/Isaacs 2011, 2012)
Rapid Growth in CAD-like software and Computer Operating Systems for Biotechnology

AUdACiOus (Towards a Biological Cell Operating System) – U. Nottingham

UC –Berkeley: JBEI and SBI
BIOFABs – Mapping the Central Dogma Pipeline

STANFOD BioFAB  Model Organisms
7. New Biotechnology Approaches Transform the Therapeutic and Diagnostic Spectrum in Human Health – and Provides New Insights about Basic Biology (NAS 2011)
Building a Biomedical Knowledge Network for Basic Discovery and Medicine (Toward Precision Medicine: NAS 2011)
Biotechnology Helps Drive Precision Medicine

We Are Moving to an Age of Genomic Medicine

<table>
<thead>
<tr>
<th>Past</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Definition by Symptoms</td>
<td>Mechanism</td>
</tr>
<tr>
<td>Uniformity of Disease</td>
<td>Heterogeneity</td>
</tr>
<tr>
<td>Uniformity of Patients</td>
<td>Variability</td>
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<tr>
<td>Universal Treatment</td>
<td>Individualized Therapy</td>
</tr>
<tr>
<td>Sickness</td>
<td>Predictive/Preventative Care</td>
</tr>
</tbody>
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Source: Burrill & Company
Biotechnology Increasingly Addresses Unmet Grand Challenges in Health

AGING, Biomarkers, and Alzheimer’s Disease

VACCINES for Neglected Diseases

Figure 2.4 As global population grows, an increasing proportion is over 65
REGENERATIVE MEDICINE: SPARE PARTS

Biotech companies and medical universities are developing technology for regenerating and replacing damaged and worn body parts. Here are some of the projects and their developers:

Heart Valves, Arteries, and Veins
Genetically engineered proteins have already been successfully used to re-grow blood vessels. And researchers have successfully implanted manipulated fibroblast cells into mice that transformed into functional, beating muscles within weeks.
Companies:
- Athyrna
- Tangion
- Organogenesis

Skin
Shire bought Advanced BioHealing for $750 million in 2011, an indication of more interest in regenerative medicine. Companies like Advanced BioHealing and Organogenesis are pursuing bioengineered skin grafts for chronic conditions like venous leg ulcers and diabetic foot ulcers.
Companies:
- CytomX
- Advanced BioHealing
- LifeCell
- Integra LifeSciences
- Advanced Tissue
- Organogenesis
- Stratatech
- ACell
- Theragen
- McGowan Institute for Regenerative Medicine at the University of Pittsburgh

Bone
Bone-growth factors or stem cells are inserted into a porous material cut to aspecific shape, creating saw limbs. Masobi is developing a new technology that can generate both new bone and new blood vessels, enabling better bone regeneration in leg fractures.
Companies:
- BioMimetic Therapeutics
- Cytogenix
- Oasis Therapeutics
- MedisBlast

Bladder
After successfully growing bladders from stomach cells and implanting them in sheep, Children’s Hospital in Boston is planning on trying the same process in babies born without a bladder.
Companies:
- Tangion
- McGowan Institute for Regenerative Medicine at the University of Pittsburgh
- ACell
- Children’s Hospital in Boston
- Regeneron
- StemCells Inc.
- ReNaun
- AsoGen
- Axon Medical

Trachea
Surgeons in Sweden removed a malignant tumor from a man’s trachea and replaced it with a tissue-engineered trachea created from the man’s own stem cells.
Companies:
- McGowan Institute for Regenerative Medicine at the University of Pittsburgh
- Advanced Center for Translational Regenerative Medicine

Spinal Cord/Nerve Regeneration:
Rather than treating spinal cord injuries with amnion, stem-cell based approaches, Axon Medical is exploring ways to use a novel technology to grow axons outside the body and then implant them in injured limbs.
Companies:
- Regeneron
- StemCells Inc.
- ReNaun
- AsoGen
- Axon Medical

Cartilage
Ganzyme’s Cartical is the first and only FDA-approved cell therapy product used to repair cartilage damage in knees using a patient’s own cells.
Companies:
- Ganzyme
- Histogenics
- Ortho Therapeutics
- TGenix
- CellSeed
- Medistem
- BioMimetic
- StemCells Inc.
- ReNaun
- AsoGen
- Axon Medical

SOURCE: Burrill & Company, Business Week, Company Websites
8. Beyond Health – The New Focus for High Growth Biotechnology Business

• “White” biotechnology – especially industrial biotechnology, biofuels, and biorefineries

• “Green” biotechnology and “Green Growth”

• “Blue” biotechnology – the oceans, biomass, sustainable food and energy
Rapid Growth in Industrializing Biotechnology
(Berry, Flagship Ventures 2011)

- A large and growing set of market opportunities
- Technologies improving exponentially
- Commercialization times progressively decreasing
- Innovations occurring in scaling and industrialization
- Need for regulations and government to keep up with technology
- Potential for profound positive impact to society across a number of fronts
Industrial Biotechnology: Cooperation all over the Value-Chain
Compelling Economics for Biofuels and Biorefineries

Biotech algae = 30x more energy per acre than land crops (DOE 2008)

Key Trends
- 27% of transport fuels by 2040, up from 2% today (IEA)
- Investing in more flexible end-product technologies
- Derive fuels from multiple feedstocks using SB methods
- Major Corporate Investors and Deals
- Growing investment late stage: scale-up
- Genetically diverse end-products
“Green” Biotech and Green Growth –
(Belcher Lab – MIT)

Bio-fab Batteries and Solar Cells: Benign viruses were genetically engineered to incorporate battery materials and, then, they self-assemble into +/-charged sides of lithium-ion battery. Co-opted a biological process to create a super battery that is environmentally benign, non-toxic and cheap through bio-nanotechnology

Using biotechnology-directed evolution of living organisms at the nanoscale to work with the elements in the rest of the periodic table. New hybrid organic-inorganic electronic and magnetic materials using useful properties and insights from biology

- self-repair mechanisms
- sustainable and non-toxic
- precise self-assembly through directed evolution
- natural ability for these materials to adapt and evolve to become better over time
Broad Range of New Environmental Markets

NSF – Use biotechnology for production of biodispersants based on soy feedstock – more than 300K lines of code to design and engineer
Biotechnology and Food Security – especially in Developing Countries
“Blue” Biotechnology – Oceans, Biomass, and Sustainable Growth

Seaweed is the Ideal Biomass and is Already Cultivated at Commercial Scale With a Proven Supply Chain

**ABUNDANT**
- Well studied biomass
- Perennial biomass
- *One of fastest growing plants on earth*
- Worldwide availability

**SCALABLE**
- Significant coastline cultivation potential
- *Existing commercial scale farms in Asia*
- Proven supply chain

**ENVIRONMENTAL**
- No competition with food for land use
- No fresh water
- *Beneficial to the oceans*
- Low carbon footprint

**LOW COST**
- High sugar content
- *No lignin to degrade*
- Cost competitive with Brazilian sugar cane
- Co-product opportunities
9. The Challenges of Scaling Up to Commercially Competitive Levels to Bend Cost Curves and Create Demand
Current Scaling and Infrastructure Challenges in Biotechnology – The Case of Biofuels

Great technologies and Proof of Concept, but can they be done cheaply, competitively, and commercially at scale?

Can you produce enough at low enough cost? – the costs of organism’s feedstock and infrastructure are critical
Scaling and Prototyping Large-scale Biotechnology to Commercially Competitive Levels

Scaling Up New Technologies To Commercial Scale Requires Vast Amounts Of Capital

Seed  Series A  Series B, C, D  IPO, Debt, Project Finance

$50,000 – $500,000  $1M – $10M  $10M – 50M per Series

- Founders
- Friends, family
- Angel investors
- Venture capital
- Venture capital
- Strategic investors

Capital expenditure for a commercial plant could cost $100-300m

Investments from venture capital sources are insufficient!!

Double “Valley of Death”

Investment Challenge

Transforming ideas into applications

Creating business models

Researchers and entrepreneurs create new ideas

No capital

Dead ideas

Dead firms

Firm creation and innovation success

Graphic concept from Dr. Charles Westner, National Academies

Washington economic development commission
Also – Scaling and Optimization at the Cellular Level: the Challenge of Interoperability and Exchange of Biological Components (Arkin Lab 2012)
10. Globalization – an emerging era in biotechnology with dispersed capacity, new value chains, new players, and new risks

THE WORLD IS NOT FLAT – IT’S SPIKED THE GLOBAL NETWORK OF REGIONS
Figure 7.8  Relative World R&D in 2011

Size of circle represents relative amount of country's annual R&D spending. Position on grid shows R&D spending as percent of GDP and number of scientists and engineers per million population

Source: Battelle, R&D Magazine: 2012 Global R&D Funding Forecast
Emerging Markets to Become Largest Consumer of Drugs

Pharmaceutical Sales 2010 to 2020 by Major Geographic Market

- **United States**: $856 billion (2010E), $1,081 billion (2015E), $1,318 billion (2020E)
- **Europe**: $188 billion (2010E), $238 billion (2015E), $300 billion (2020E)
- **Other**: $205 billion (2010E), $205 billion (2015E), $195 billion (2020E)

CAGR: 3% (2010E-2015E) | 4% (2015E-2020E)

Source: 2010, 2015 IMS Health; 2020 KPMG estimates
Trends in Global Biotechnology Health Markets Show Emerging Markets Dominance (Burrill 2012)
BRICS Emphasize Biotechnology in National Innovation and Economic Growth Strategies

China’s life science and biotechnology research system

(MOST as a coordinator on behalf of central government)

- CAS institutes
- CAMS institutes (National and local)
- Medical universities
- Others

Research

- NSFC
- 937 program (MOST)
- 863 and supporting program (MOST)
- State key laboratory system (MOST)
- CAS innovation programs (CAS)
- 985/211 programs (MOE)
- Infrastructures (NDRC)
- Major science & technology projects

Funding

* CCDC, military academies, research centers in enterprises, etc.
** Drug innovation and Infectious diseases prevention

Figure 7.32 India’s Biotech Industry

Growth by Industry Sector

Industry Segment Share

- Biopharma
- BioPharmaceuticals
- BioIndustrial
- BioAgriculture
- BioServices

Source: BioSpectrum, AIBL
Multiplicity of New Players Increases Global Capacity (and Potential Risks)

iGEM: 30+ countries, 160 university teams, and 2,000+ participants

DIY Biotechnology, Patient Advocacy Groups, Venture Philanthropists, Non-BioPharma Companies

Where market power was: The Big Three (1/3, 1/3, 1/3)

Where it's going:

BRICS: Brazil, Russia, India, China, South Africa

CIVETS: Colombia, Indonesia, Vietnam, Egypt, Turkey
10 Key Biotechnology Trends and Drivers

• **The Century of Grand Synthesis**: A New Bio-based Production Economy

• **Disruptive Innovation directed at Societal Grand Challenges and Value Creation** – Shift to Solutions-driven, Problem-oriented S&T Research, Innovation, and Market Demand

• **Biotechnology increasingly is an Information Business**: “Big Data”, Computation, Algorithms, and Cyber-enabled R&D

• **Who is Us? Redrawing the Boundaries of Biotechnology in the “New Biology”** -- Convergence, Integration, Cross-sectoral and Interdisciplinary Approaches Drive Biotechnology Science, Innovation and Markets

• **Engineering Biology Increasingly Transforms Biotechnology**
10 Key Biotechnology Trends and Drivers

• Robust 21st Century Biotechnology Toolkit as a Driver of Economic Inflection Points: Tools, Infrastructure, Design, Software, and Platforms

• New Biotechnology Transforms the Therapeutic and Diagnostic Spectrum in Health and our Understanding of Basic Biology – Aging, Precision Medicine, Regenerative Medicine, Complex Diagnostics, Unmet Global Health Needs

• Biotechnology Moves Beyond Health (“Red’) – “White”, “Green”, and “Blue” Biotechnology Take Center Stage

• Scaling Up to Commercially Competitive Levels that Bend Cost Curves, Create Demand, and Drive Sustainable Growth

• The Globalization of Biotechnology Capacity - shifting markets and global value chains, and a multiplicity of new players (and risks)
Thank you!

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