PROACTIVE AND ADAPTIVE GOVERNANCE OF EMERGING RISKS
THE CASE OF DNA SYNTHESIS AND SYNTHETIC BIOLOGY

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J CRAIG VENTER INSTITUTE VARIANT: ARTIFICIAL LIFE
• Prospect for and inventory natural sequences
• Simplify natural organisms; develop minimal organisms
• Fabricate customized whole artificial organisms

SynBERC VARIANT: ENGINEERING BIOLOGY
“Develop well characterized biological components easily assembled into larger functioning devices ....”
• Develop and characterize standard parts
• Deposit standard parts in registries to allow reuse
• Deskill parts fabrication and assembly to cut costs
• Modularize designs to allow repurposing

TWO DEFINITIONS OF SYNTHETIC BIOLOGY
• Discover properties of natural biological systems by simplifying, decomposing, assembling synthetic systems
• Learn from failures as well as successes
COST OF CREATING KNOWLEDGE AND MATERIAL
Exponential change through DNA sequencing and synthesis 1985-2007

Cost of short oligo synthesis
Cost per base sequenced
Cost of gene synthesis

Carlson 2008
DE-SKILLING MAY LEAD TO DIFFUSION OF CAPABILITIES

Synthetic Biology seeks to transform tacit to explicit knowledge
• Parts performance and couplings standardized
• Biobricks assembly standards and knowledge pooling
• Well characterized standardized chassis
• Automated assembly

This flattens the gradient between elite and mass practitioners
• Can do more in less time
• Cuts investment needed to do work
• Broadens pool of people capable of constructing a weapon
• Allows easier replication of cutting edge work

LOWER COSTS MAY ENABLE MASS USE WITH EFFECTS ON ECONOMIC, ENVIRONMENTAL AND SECURITY IMPACT OF SYNTHETIC BIOLOGY. . .
# Proactive Environmental Risk Management Workshops

**Organizers**  
Smithsonian Woodrow Wilson Center  
MIT Program on Emerging Technologies

**Sponsors**  
Sloan Foundation, NSF SynBERC, EPA

**Goals**  
Assess risks, redesign applications, develop tests  
Evaluate proactive risk management processes

**Objects**  
Specific synbio applications near rollout -- *not* blue sky  
Incidental release expected or deliberate release planned

**Participants**  
Synthetic Biologists, Environmental Microbiologists,  
Risk Analysts, Regulators, Insurers, Civil Society, Firms

**Workshops**  
<table>
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<tr>
<th>Date</th>
<th>Topic</th>
<th>Location</th>
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<tr>
<td>Jan 2011</td>
<td>E. coli arsenic biosensor, rE. coli chassis</td>
<td>Edinburgh/Lumin, Harvard/MIT</td>
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<td>Jul 2011</td>
<td>Sucrose producing cyanobacteria</td>
<td>Harvard</td>
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<tr>
<td>Jun 2012</td>
<td>Testing cyanobacteria and rE. coli</td>
<td>Harvard/MIT</td>
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<tr>
<td>Future</td>
<td>Eukaryotic algae</td>
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DEVELOPERS PRESENT SPECIFIC SYNTHETIC BIOLOGY APPLICATIONS

Gautam Mukunda
Lumin, MIT, HBS

Daniel Ducat
Patrick Boyle
Silver Lab
Harvard Medical

Peter Carr
Lincoln Lab
George Church
Harvard Medical

Sucrose-producing Cyanobacteria

Because of large surface area required, cyanobacteria are often grown in outdoor environments for economical reasons. Genetic modification is also required for high yields. These needs present a unique issue for ecological containment.

rE. coli Chassis

Removal of TAG stop codon limits horizontal gene transfer

Engineered Genes Isolated in rE. coli

Foreign Genes Not Functional in rE. coli

DNA:
Gene

RNA:
Gene

Protein
Correct in Church Chassis
Incorrect in Other Organisms

DNA:
Gene

RNA:
Gene

Protein
Incorrect in Church Chassis
Correct in Other Organisms
Technologies that enable SynBio are changing understandings of effects

**Sequencing:** Observations on Fitness, Transfer, Stability of Genetic Elements

**Computational Methods:** Models of Networks and Communities
ECONOMICS DICTATE LIGHT CONTAINMENT TO PRODUCE LOW VALUE MATERIALS

• CONSEQUENCES OF INEVITABLE RELEASE?
• EFFECT OF METHODS OF INSERTION ON GENE FLOW?
• EFFECT OF INSTABILITY ON FUNCTIONALITY OF KILL SWITCHES?

Raceways and Sluices  Plastic Bags  Surface Ponds
EFFECTS OF ORTHOGANALITY ON GENE FLOW?
GENE TRANSFER ACROSS UNLIKE ORGANISMS?
MODULAR CHASSIS CERTIFICATION INDEPENDENT OF PATHWAYS INSERTED?

A solar saltern, whose occupants benefit from archaea-to-bacteria transfer of salinity adaptations

Pea aphids, whose distinctive coloration is believed to result from fungus-to-animal gene transfer

In this bacteria-to-animal transfer, a nematode parasitizes plants using genes from parasitic bacteria.
GROUP TAKEAWAYS

Environmental microbiologists critical of risks and benefits of synbio
• Reproductive disadvantage / diminished fitness not enough
• Focus on interaction between engineered and wild type populations
• Focus on mutation and potential changing traits of organisms
• Context sensitivity, complexity, epigenetics, not modularity, simplicity

Civil society expressed concern and sought more information:
• Flagged uncertainty, potential irreversible changes, bio-economy
• Noted complexity barrier to engagement with civil society, regulators
• Requested boot camp to enable understanding and participation

Regulators and NSABB/RAC members
• Favored analysis of concrete examples, not blue sky discussion
• Flagged issue of evaluating and certifying modular safe chassis
• Favored algae fuel production and bioremediation for later workshops (immediate needs)
• Noted regulatory variation complicates product development
• Favored inclusion of AIC, NIC and LDC regulators and insurers
CONSENSUS TAKEAWAYS

AGREEMENT ON ADVANTAGES OF EARLY PROACTIVE ENGAGEMENT
Good at Flagging Broader Array of Risks
Good at Identifying Proactive Measures
Mutual exchange bolstered legitimacy and credibility
Good at identifying policy relevant sources of uncertainty

AGREEMENT ON NEED TO STRENGTHEN SENSING AND ADAPTING
Now: Form small technical working groups to address testing issues
Soon: EPA may use workshop as model to frame assessments
Later: NSF/OSTP/DARPA/EPA may fund research to reduce uncertainty
  • Design and certification of microcosms for safe trials
  • Assess effects of methods of insertion on stability and gene transfer
  • Assess effect of genetic instability on functionality of kill switches
  • Establish observational baselines for detection of environmental effects
  • Assess effect of phylogetic difference on probability of gene transfer
  • Continue work on gene flow, genetic stability, fitness with sequencing
  • Evaluate effects on biomes using advanced computational methods
DNA SYNTHESIS SCREENING REGIME

HYBRID REGIME
INTERGOVERNMENTAL - AUSTRALIA GROUP
NATIONAL – HHS SCREENING FRAMEWORK GUIDANCE
TRANSNATIONAL – TWO SCREENING CONSORTIA WITH TWO LEAD FIRMS

WHY DO VOLUNTARY ARRANGEMENTS WORK IN THIS CASE?
CONCENTRATED INDUSTRIAL STRUCTURE – FOR NOW
FIRMS COSTS OF COMPLIANCE LOW – SCREENING COSTS, LOST CUSTOMERS
FIRMS ACT AS IF HHS GUIDELINES ARE REGULATIONS TO LIMIT COMPLAINTS
FIRMS FEAR OF LIABILITY IF IGNORE GUIDANCE
FIRMS SEEK TO REDUCE DEMANDS FOR MANDATORY REGULATIONS
WILL HYBRID REGIME/VOLUNTARY ARRANGEMENTS CONTINUE TO WORK?

TRENDS IN INDUSTRIAL STRUCTURE . . .
HORIZONTAL DECONCENTRATION
VERTICAL DECONCENTRATION

FIRMS IN CHINA AND INDIA ENTER HIGH END IN HOUSE OPTIONS
BIOFABS NTERMEDIATE CUSTOMERS

IRONY OF CONTROLS – INCENTIVES FOR INDEPENDENCE
IRAN, PAKISTAN BUILDING DNA SYNTHESIS CAPACITY
DIYBio SEEK SMALL DESKTOP UNITS

TRENDS IN TECHNOLOGY
ORGANISM BASED CONTROLS OBSOLETE
NEED FUNCTIONAL SEQUENCE BASED CLASSIFICATIONS
IGEM International Genetically Engineered Machine Competition

2012 – 250 Teams

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<thead>
<tr>
<th>Year</th>
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<tr>
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<td>5</td>
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<td>130</td>
<td>1300</td>
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<tr>
<td>2011</td>
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<td>1650</td>
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2010 130 teams 1300 participants from Asia, Europe, Americas, Africa
Home

The "SWITCH" Project

The Problem

Producing complex therapeutic proteins requires biosynthesis in mammalian cells. Such proteins can sometimes have a certain level of toxicity for the cells and limit their productivity if they are produced constantly and are accumulating. To avoid this, the pharmaceutical industry use 'rewired' cells that synthesize toxic proteins only when a special molecule is added to the bioreactor. This solution has two disadvantages. First, cell rewiring affects several pathways and decreases cell productivity. Second, the 'special' molecule will mix with the final product and a purification will be needed to get rid of it.
The Case of iGEM Safety Committee (SC) Project Screening

- SC screened safety pages and project descriptions of all 180 iGEM teams, with focus on work with pathogens.
- SC approved project with safeguards and IRB approval. SC flagged project w/o safeguards w/o IRB for review.
- 3 external biosafety experts did fast review, found insufficient info to determine safety. iGEM inquiries to team/advisor failed.
- SC disqualifies team, recruits regional biosafety expert to work with team on potential safety issues.
- Team redefines project as “software only / no wet lab work” and requalifies for iGEM.
- SC screens parts submitted by team in previous year and finds team submitted parts from a pathogen.
- SC seeks guidance from US agencies on operational definition of “parts associated with infectivity” under Australia Group.
- George Church screens parts, finds no problem. (Not scalable.) Archetype used to screen parts, generates no red flags.

Implications for iGEM? US policies and practices? Policies and practices abroad? Australia Group?
DIFFUSION – GARAGE AND CLOSET BASED SYNBIO

Do-It-Yourself-Biology (DIYB)
Kay Aull’s closet lab – low cost, self diagnostics
Low Cost Desk Top DNA Synthesis Units
Potential for bio-hackers and malevolent action?
Amateurs Are New Fear in Creating Mutant Virus

Just how easy is it to make a deadly virus?

This disturbing question has been on the minds of many scientists recently, thanks to a pair of controversial experiments in which the H5N1 bird flu virus was transformed into mutant forms that spread among mammals.

WORRY An outbreak of the H5N1 bird flu virus was reported in Vietnam in February.

Related
Genetically Altered Bird Flu Virus Not as Dangerous as Believed, Its Maker Asserts (March 1, 2012)

Despite Safety Woes, Work on Deadly Flu to Be Released (February)

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 SID E EFFECTS
D.I.Y. Biology, on the Wings of the Mockingjay

By JAMES GORMAN
Published: May 10, 2012 | 34 Comments

Genetically modified organisms are not wildly popular these days, except one: a fictional bird that is central to the hugely popular movie and book trilogy “The Hunger Games.” That’s the mockingjay, a cross between a mockingbird and a genetically engineered spy bird called a jabberjay.

The action in “The Hunger Games” takes place in a fictional future in which teenagers are forced to hunt and kill one another in annual competitions designed to entertain and suppress a highly controlled population. The mockingjay first appears as a symbol, when Katniss Everdeen is given a pin that depicts the bird. Mockingjays, although not the birds, have spread to the real world.

“They’re funny birds and something of a slap in the face,” Katniss explains in the first book, a nature of that slap in face is a new twist on the

The Gazette
montrealgazette.com

'Doomsday' virus revealed, along with DIY instructions

BY MARGARET MUNRO, POSTMEDIA NEWS MAY 3, 2012
8-Points (1)

• Striving for integration
  – Synthetic biology risk governance cases should be seen as cautionary tales with respect to integration across different impacts and risks
8-Points (2)

- Prioritizing risks
  - In practice, synthetic biology risks have been prioritized by the immediacy and potential severity of emerging threats
  - Prioritization is taking place within security and environmental domains, but not across domains
8-Points (3)

• Ascertaining accountability
  – Most of those generating risks in synthetic biology have been accepting responsibility for evaluating and managing foreseeable risks that they may be creating.
8-Points (4)

• Ensuring flexibility and adaptability over time
  – Synthetic biology is a strong candidate for adaptive approaches to risk management
  – In the realm of biosecurity, DNA synthesis screening appears to be an exemplary case for adaptive risk management
  – In the realm of env. risks, with less immediate and clearly defined risks, the need for adaptive and proactive risk governance methods is even clearer
Creating transparency

– Synthetic biology cases include both exemplary and cautionary tales with respect to the transparency of risk assessment and management

– As the focus of synthetic biology moves from academic actors to commercial firms, the heart of the problem rests confidential business information

– IP claims and licensing provisions may be used to prevent some research by third parties on risks associated with synthetic biology
8-Points (6)

• Approaching inclusive governance
  – Bad News: increasing polarization and mutual isolation of civil society, biotechnology firms and academic synthetic biologists
  – Good News: workshops conducted at the Wilson Center have continued to engage constructively in identifying risks and setting priorities for next stage research on risks
8-Points (7)

• Providing convincing methods and procedures for evaluating threats and designing options to deal with threats
  – Cases described provide examples of reasonably convincing methods and procedures for dealing with threats
  – Succeeded in identifying areas of agreement on risks and benefits, in flagging uncertainty and tagging points where agreement would be difficult because of conflicting values
8-Points (8)

• Demonstrating the value of professional emerging risk identification, assessment and management
  – Professionals have played a key role in identifying, assessing and managing risks in the synthetic biology cases treated in this paper, with professional competencies including both risk governance processes and technical and scientific specializations needed to assess and manage risks