# Synthetic Biology

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# Synthetic Biology
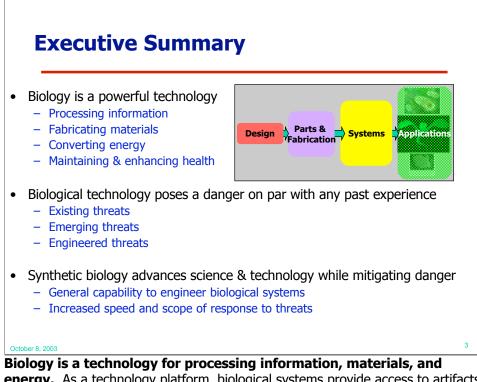
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October 8, 2003

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# Executive Summary

- Biology is a powerful technology
  - Processing information
  - Fabricating materials
  - Converting energy
  - Maintaining & enhancing health

- Biological technology poses a danger on par with any past experience
  - Existing threats
  - Emerging threats
  - Engineered threats

- Synthetic biology advances science & technology while mitigating danger
  - General capability to engineer biological systems
  - Increased speed and scope of response to threats

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**Biology is a technology for processing information, materials, and energy.** As a technology platform, biological systems provide access to artifacts and processes across a range of scales (e.g., the ribosome is a programmable nanoassembler, a bamboo shoot can grow 12" per day). Biology also forms the basis for human welfare (e.g., modest amounts of memory and logic, implemented as genetically encoded systems,would directly impact biological research and medicine). **However, our ability to deploy biology as a technology and to interact intentionally with the living world is now limited**; the charge to our study was to begin to specify enabling technologies that, if developed, would provide a general foundation for the engineering of biology and make routine the creation of synthetic biological systems that behave as predicted.

We focused on improvements to the process of engineering biological systems. **Three specific process improvements that should be pursued now are: (i) component standardization, (ii) substrate and component abstraction, and (iii) design and fabrication decoupling.**

The development of technologies that enable the systematic engineering of biology must take place within the context of current and future risks due to natural and engineered biological agents. While the development of technologies for engineering biology appears inevitable, and their distribution uncontrollable, the net impact such technologies will have on the creation of biological risk is not known. However, any technology-based increase in risk creation seems likely to at least be offset by a concomitant increase in the speed and scope of response to risks. **Consequently, any meaningful strategy for minimizing future biological risk requires that the development of technologies for engineering biology proceeds alongside the development of non-technical approaches to risk management**; new training programs and professional societies will serve an important role in creating a cadre of engineers who can work in biology and who will serve as a strategic resource for responding to natural and engineered biological threats.

2003 *Synthetic Biology Study*

## Study Participants

- Drew Endy (chair)
- Patrick Lincoln (co-chair)
- Richard Murray (co-chair)
- Frances Arnold (Caltech)
- Ralph Baric (UNC)
- Roger Brent (TMSI)
- Rob Carlson (U.Washington)
- Jim Collins (BU)
- Lynn Conway (Michigan)
- Ron Davis (Stanford)
- Mita Desai (NSF)
- Eric Eisenstadt (DARPA)
- Stephanie Forrest (U.New Mexico)
- Seth Goldstein (CMU)
- Homme Hellinga (Duke)
- Tom Kalil (UC Berkeley)
- Jay Keasling (UC Berkeley)

- Doug Kirkpatrick (DARPA)
- Tom Knight (MIT)
- Bill Mark (SRI)
- John Mulligan (Blue Heron)
- Radhika Nagpal (MIT/Harvard)
- Carl Pabo (Sangamo)
- Randy Rettberg (MIT)
- Pam Silver (Harvard)
- Brad Smith (Johns Hopkins)
- Christina Smolke (Caltech)
- Gerry Sussman (MIT)
- Jack Thorpe (ISAT)
- Claire Tomlin (Stanford)
- Jeff Way (Lexigen)
- Chris Webb (Stanford)
- Ron Weiss (Princeton)
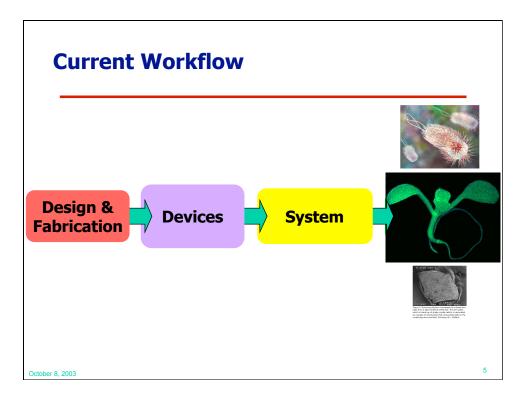- Erik Winfree (Caltech)

Study participants included representatives from universities, industry, and government. Participants provided expertise in basic biological research, biological systems modeling, DNA synthesis, device analysis & design, self-assembly, systems analysis & design, computer science, electrical engineering, engineering theory, and biological security. Rich Entlich and other staff provided expert organizational support throughout the study.

The study held three workshops and four executive meetings:

1. October 23-24th (2002) at the Beckman Center in Irvine, CA
2. March 3-4th (2003) at SRI, Inc. in San Mateo, CA (workshop)
3. March 24-25th at Norton's Woods in Cambridge, MA (workshop)
4. April 10-11th at IDA in Alexandria, VA
5. May 29-30th at Caltech in Pasadena, CA (workshop)
6. August 18-22nd at Johnson House in Woods Hole, MA
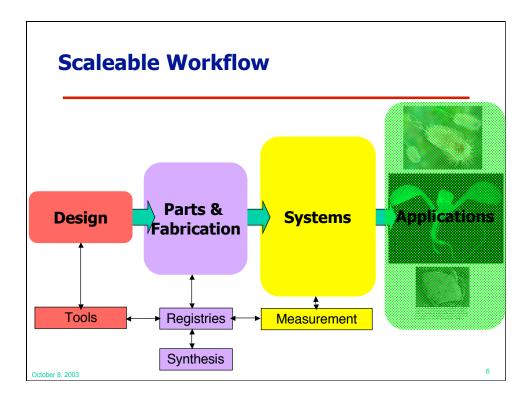7. October 8th in Alexandria, VA

The following related events occurred while the study was underway:

1. IBEA contracted by DOE to synthesize a bacterial genome (11/02)
   [see http://www.bioenergyalts.org/news.html]
2. MIT conducts Synthetic Biology Lab (1/03)
   [see http://web.mit.edu/newsoffice/nr/2003/blinkers.html]
3. Caltech announces Center for Biological Circuit Design (3/03)
   [see http://www.eas.caltech.edu/engenious/win03/cbcd.pdf]
4. EU NEST proposes Synthetic Biology research program (8/03)
   [see ftp://ftp.cordis.lu/pub/nest/docs/synthetic_biology.pdf]
5. Lawrence Berkeley Lab creates Dept. of Synthetic Biology (8/03)
   [see http://www.lbl.gov/LBL-Programs/pbd/news/newsletter/]

**Current Workflow**

Design & Fabrication → Devices → System

**At present, the design and fabrication of any specific engineered biological system is an ad hoc process.** The process often involves fundamental scientific research, making impossible accurate prediction of final system behavior and time-to-delivery. Furthermore, building any one system does not directly enable the construction of other engineered biological systems. For a given application, work begins with the coupled design and fabrication of unique, application-specific components that, given further work, can sometimes be assembled into a functioning system. By contrast, "mature" engineering disciplines (e.g., mechanical, electrical, civil, and software) can routinely integrate large numbers of well-characterized components to produce many functioning systems.

**Scaleable Workflow**

Design → Parts & Fabrication → Systems → Applications

Tools ↔ Registries ↔ Measurement

Synthesis

Biology presents a new medium for engineering; we expect to encounter many medium-specific challenges (e.g., evolution).  Still, a scaleable development path for biological systems engineering can make use of past successful experience in other engineering disciplines.  The approach that emerged over the course of the study is informed by three past lessons:

 **(1) Standardization of components** (mechanical engineering, 1800s). Libraries of standard parts that allow a combination of systems to be designed and assembled.

**(2) Component abstraction** (from physics to electrical engineering, 1900s). Standard parts can be defined prior to absolute scientific knowledge; many knowable facts are unnecessary.  Simpler representations of many-component devices help to manage complexity and increase attainable system scale.

**(3) Decoupling of design & fabrication** (VLSI electronics, 1970s). Engineered systems can be designed by experts to exploit every detail of a particular fabrication process. However, too much attention to such details limits both the rate of design and the complexity of designable systems.

In addition to the above, improvements in four technical areas would help to enable the engineering of biological systems:

**(1) Registries of standard biological parts** that coordinate parts synthesis and system assembly, and help to develop and promulgate standards of practice (e.g., design, fabrication, and characterization).

**(2) Long polymer nucleic acid synthesis** enabling rapid delivery of new components and systems.

**(3) Design, simulation, and analysis tools** that make use of standard parts and methods of assembly.

**(4) Methods and standards for measurement** that enable rapid system characterization and refinement.

**Synthetic Systems**

*Michael Elowitz c.1999*

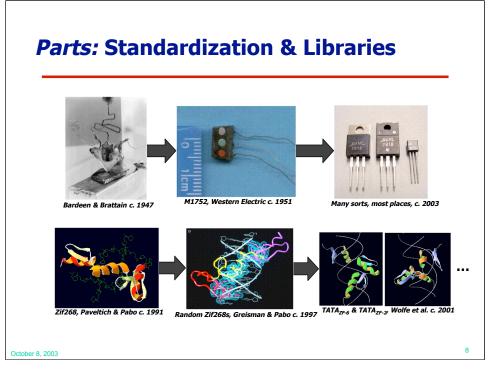**Synthetic biological systems are currently created from natural biological "parts" via an expert-driven design and fabrication process.**

For example, a genetic "inverter" based on well-known natural biological parts regulating gene expression in bacteria is shown (top left). The inverter is built from a "repressor" protein (LacI) that acts on an operator (O_Lac) to inhibit transcription of the DNA-encoded elements to the right of O_Lac. Absent inhibition at O_Lac, RNA molecules encoding both a ribosome binding site (RBS) and the gene cI-857 are produced. The resulting RNA are translated to create a new protein (cI).

The inverter's transfer function (bottom left) depicts the relationship between inverter input (concentration of LacI protein) and output (concentration of cI protein). A ring oscillator can be created by linking three such inverters in a cyclic system (A inverts B inverts C inverts A).
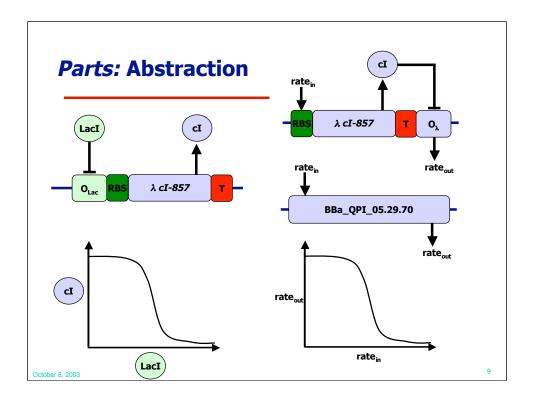
The actual behavior of bacterial cells containing a genetically-encoded ring oscillator is shown (right); cells blink over time as a function of oscillator state - see Elowitz et al. in Nature v403 p335, "A synthetic oscillatory network of transcriptional regulators."

**Parts: Standardization & Libraries**

*Bardeen & Brattain c. 1947*   *M1752, Western Electric c. 1951*   *Many sorts, most places, c. 2003*

*Zif268, Paveltich & Pabo c. 1991*   *Random Zif268s, Greisman & Pabo c. 1997*   *TATA$_{ZF-6}$ & TATA$_{ZF-2}$, Wolfe et al. c. 2001*   ...

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The ring oscillator on the preceding page took an expert over a year to design and build; the system makes use of three of the best-characterized natural proteins that regulate gene expression in bacteria. Today, an electrical engineer could build a ring oscillator in ~5 minutes by, for example, taking a N7404A hex-inverter "off the shelf" and connecting three of the inverters in a cycle using standard gauge wire.
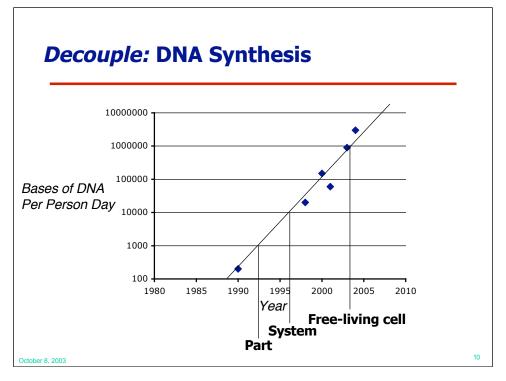
**To enable the routine production of many-component integrated biological systems we should develop libraries of standard biological parts.** Initially, most parts will be "harvested" from natural systems. Development of domain specific parts would enable the engineering of systems responsive to different applications of biological technology. Parts specific to the following application areas would find immediate use: biological information processing and control, material fabrication, metabolism and energy production, and human health.

Also, it is worth noting that the continued improvement and successful application of computation-based design of ligand-domain reactions will help to enable the engineering of synthetic parts libraries - e.g., see Looger et al. in Nature v423 p185, "Computational design of receptor and sensor proteins with novel function." **We should foster the transition from the collection and characterization of natural parts, to the design and fabrication of libraries of synthetic parts.** One early example of the transition from natural to synthetic parts is likely to be the development of a library of synthetic DNA binding proteins for use in the regulation of gene expression; "back of the envelope" estimates suggest that a standard library of ~1,000 zinc-finger protein:DNA binding site pairs can be created with < 1% intra-library component "crosstalk." Crosstalk refers to the fact that biological systems are often composed of self-mixing molecules. Specificity of interaction is determined by non-covalent interactions between molecule surfaces (in contrast to wires that determine component interactions in electrical circuits); non-specific or unintended molecule-molecule interactions can create undesirable side-effects in biological systems.

**Parts: Abstraction**

LacI

cI

O_Lac | RBS | λ cI-857 | T

cI

rate_in

RBS | λ cI-857 | T | O_λ

rate_out

rate_in

BBa_QPI_05.29.70

rate_out

cI

LacI

rate_out

rate_in

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**We also need to promote the characterization and representation of standard biological parts in ways that insulate relevant physical characteristics from overwhelming physical detail.** For example, the four DNA elements defining a typical genetic inverter (above left) are organized such that the concentration of the LacI and cI protein are the inverter input and output, respectively; the result is a unique device with characteristics specific to LacI and cI (transfer function, bottom left). If LacI protein were used to regulate a different output (e.g., TetR protein) then a new device, requiring additional characterization, would be created. Instead, by reorganizing the genetic components, we can create an inverter that is independent of specific input and output chemicals (top right); device characteristics are now defined as a function of input and output rates (bottom right). The resulting inverter can be used in combination with any other so-structured device. Also, for the purpose of integrated system design, the four component inverter (top right) can be replaced with a simpler representation of a new part, a "quad-part inverter" (middle right).
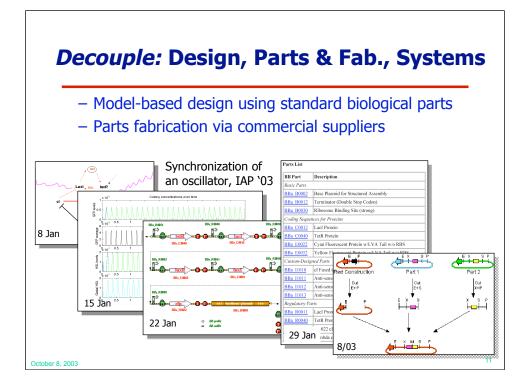
**Again, representations of biological systems should (1) provide simple descriptions of complex, oftentimes poorly understood, biological components and processes and (2) allow the creation of parts that can be used in combination with other parts (e.g., parts whose inputs and outputs are not specific to other parts).**

**Decouple: DNA Synthesis**

Bases of DNA Per Person Day

Year

Free-living cell

System

Part

The above plot gives the bulk number of nucleotides that can be assembled into short chain oligomers by an individual during an 8-hour work day - see Carlson, Biosecurity & Biotechnology v1(3), "Pace & Proliferation of Biological Technologies." The increase in DNA synthesis capacity has been driven largely by process parallelization; **anecdotal reports suggest that equivalent technology is available worldwide.** For scale, the length of a typical part is ~1,000 bases, the length of a small integrated system is ~10,000 bases, and the length of a genome encoding a "simple" free-living cell is ~1,000,000 bases.

**One critical factor not represented on the above plot is the time to delivery of a fully-assembled long chain oligomer.** Commercial delivery times for an assembled 10,000 base DNA oligomer are now ~10 weeks. Other limiting factors are specific to various fabrication processes. For example, methods based on short chain oligomer-assembly followed by cloning and ligation allow for exact synthesis but require extra time for the processing of assembly intermediates (e.g., cloning and sequencing); such methods are also limited by the potential genetic instability of assembly intermediates. Synthesis methods based on in-vitro assembly (e.g., PCR) can be faster but often accrue errors during synthesis and assembly that carry forward into the final product.

DNA sequencing technology underwent a similar increase in capacity beginning ~1980; the science of biology changed in response (e.g., the genome projects, bioinformatics, and systems biology). Today, researchers in an average biology lab might spend half their time manipulating DNA molecules. **Continued improvements in DNA synthesis technology should, in addition to promoting biological engineering, help change biology from a "discovery" science to a "synthetic" science (a lá the development of synthetic chemistry) and help to enable a more rapid response to future biological risks.**

# *Decouple:* Design, Parts & Fab., Systems

– Model-based design using standard biological parts
– Parts fabrication via commercial suppliers

Synchronization of an oscillator, IAP '03

8 Jan

15 Jan

22 Jan

29 Jan

8/03

Colony concentrations over time

| Parts List | |
|---|---|
| **BB Part** | **Description** |
| *Basic Parts* | |
| BBa_B0002 | Base Plasmid for Structured Assembly |
| BBa_B0012 | Terminator (Double Stop Codon) |
| BBa_B0030 | Ribosome Binding Site (strong) |
| *Coding Sequences for Proteins* | |
| BBa_C0012 | LacI Protein |
| BBa_C0040 | TetR Protein |
| BBa_E0022 | Cyan Fluorescent Protein w/LVA Tail w/o RBS |
| BBa_E0032 | Yellow Fluorescent Protein w/LVA Tail w/o RBS |
| *Custom-Designed Parts* | |
| BBa_I1010 | cI Fused t |
| BBa_I1011 | Anti-sens |
| BBa_I1012 | Anti-sens |
| BBa_I1013 | Anti-sens |
| *Regulatory Parts* | |
| BBa_R0011 | LacI Prom |
| BBa_R0040 | TetR Prom |
| | 022 cI |
| | nbda c |

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Just as being able to read DNA via genome-scale sequencing efforts has not immediately translated into a perfect understanding of nature's designs, **our increasing ability to write DNA via de novo synthesis will not, by itself, result in useful engineered biological systems.**

During January 2003, MIT conducted a four-week long experimental course in which 16 students were asked to design genetically-encoded oscillators using an early version of what future biological engineers might call "protein-DNA logic" (or PDL). Students were given a 20,000 base pair DNA synthesis budget. In addition, students were asked to design their systems using standard biological parts such that the resulting parts could be used in more than one system (i.e., parts were shared across the class). The course workflow was: (i) model-based system design, (ii) model-driven simulation, (iii) layout, documentation, and plan of characterization, (iv) parts ordering via commercial suppliers, and (v) parts return and system assembly. Design, simulation, layout and documentation took one month. Editing the student-specified parts and placing the parts synthesis order took two months. Parts synthesis required another one to five months. System assembly from standard parts is taking an additional four months, for a total elapsed time of one year. Current estimates are that the 2004 course will run to completion in five months and that, given current technology, three months start-finish will be realized. **The students who participated in the course did not perform laboratory experiments, instead they worked as standard biological parts, device, and system engineers.**
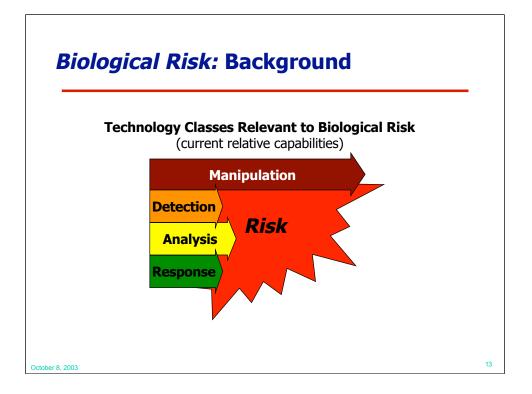
By decoupling design and fabrication it will become possible to build more complex systems. **The decoupling of system design and fabrication will simultaneously enable a new cadre of engineers to participate in the analysis and design of biological systems.**

# *Decouple:* Registries of Standard Parts

- Maintain & promulgate standards of practice
  - Design
  - Characterization
  - Protocols & Exchange
  - Applications
- Coordinate parts synthesis
- Coordinate system assembly

**Parts List**

| BB Part | Description |
|---------|-------------|
| *Basic Parts* | |
| BBa_B0002 | Base Plasmid for Structured Assembly |
| BBa_B0012 | Terminator (Double Stop Codon) |
| BBa_B0030 | Ribosome Binding Site (strong) |
| *Coding Sequences for Proteins* | |
| BBa_C0012 | LacI Protein |
| BBa_C0040 | TetR Protein |
| BBa_E0022 | Cyan Fluorescent Protein w/LVA Tail w/o RBS |
| BBa_E0032 | Yellow Fluorescent Protein w/LVA Tail w/o RBS |
| *Custom-Designed Parts* | |
| BBa_I1010 | cI Fused to TetR Promoter |
| BBa_I1011 | Anti-sense RNA (KISS) |
| BBa_I1012 | Anti-sense RNA (micRNA) |
| BBa_I1013 | Anti-sense RNA (IS10) |
| *Regulatory Parts* | |
| BBa_R0011 | LacI Promoter |
| BBa_R0040 | TetR Promoter |
| BBa_R0050 | HK022 cI Promoter |
| BBa_R0051 | Lambda cI Promoter |

The usefulness of standard biological parts depends on parts characterization via common standards of description and also parts availability via common protocols of exchange. In addition, system assembly requires coordination of de novo DNA synthesis and final system assembly with bulk-service providers; as with DNA sequencing, DNA synthesis will benefit from economies of scale. **Registries of standard biological parts should be created to best meet these requirements.**

A standard biological parts registry is similar in concept to the MOSIS service provided to the VLSI electronics community [see http://www.mosis.org/]. **By serving as a focal point for community organization registries will provide a mechanism for community-wide organization and the development and propagation of standards of practice.** Furthermore, such community-wide organization will help launch the future organizations (private and public) that will support the engineering of many-component integrated biological systems.

At present, DNA synthesis and system assembly is slow and expensive (i.e., fabrication is currently a limiting technology). As a result, early registries will need to provide both the physical DNA itself and the information specifying DNA sequence and encoded genetic function. In the future, if and when DNA sequence information becomes fungible with DNA molecules, knowledge of what to synthesize will be limiting. At such time, the role of registries should shift to serve as maintainers and providers of the information specifying and describing parts.

**Biological Risk:** Background

Technology Classes Relevant to Biological Risk
(current relative capabilities)
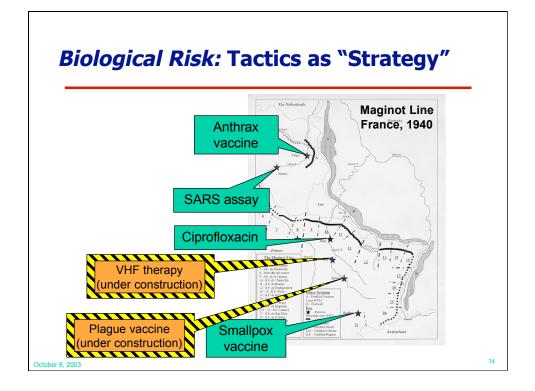
Manipulation
Detection
*Risk*
Analysis
Response

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Both nature's, and our own, ability to manipulate biological systems outpaces our ability to detect biological agents, analyze the resulting data, and respond appropriately.  As a result, we risk exposure to existing, emerging, and engineered biological threats (graphic above).

While the purpose of our study was to specify general technologies that, if developed, would directly enable the systematic engineering of biological systems, **these discussions necessarily took place in the context of current and perceived future biological risks.**

Two issues dominated our risk-related discussions.  First, the "dual-use" dilemma as it relates to biological technology - any useful technology might also be intentionally or accidentally misapplied to cause harm.  A recent National Academies report provides expert background, analysis, and discussion of the dual-use dilemma for past and current biotechnology - see Fink et al., National Research Council of the National Academies (2003), "Biotechnology Research in an Age of Terrorism: Confronting the "Dual Use" Dilemma."   Second, **the probable inability to control the distribution of technologies needed to manipulate biological systems and, lacking advances in other technology classes (i.e., detection, analysis, and response), a consequent increasing future vulnerability to engineered biological threats.**

**Can the current gap between manipulation and detection, analysis, and response be closed?**
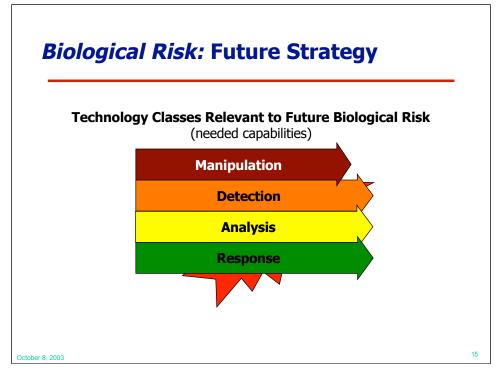
**Do technologies that enable biological engineering help or hinder closure of the risk gap?**

The "conventional wisdom" within the biological research community is that current threat dynamics are largely driven by nature, and take the form of emerging infectious diseases.  For example, the 2002 SARS outbreak killed more people than the 2001 anthrax attacks; both would pale in comparison to a repeat of the 1918 influenza pandemic. Many biologists ask if it is possible to intentionally "improve" existing pathogens, somehow bettering nature's designs. Importantly, the rate of natural threat emergence is slow enough such that the development and deployment of threat-specific responses are oftentimes considered to be "adequate."

The experience of the biological research community with modern technology-based risk dates to the creation of recombinant DNA technology - in the 1970s it became possible to create chimeric DNA absent a perfect ability to predict the properties of the resulting molecule. Today, **three additional factors are beginning to impact the biological risk landscape:** (i) public databases of DNA sequence and computation-based design tools are enabling rapid and "lab-free" access to knowledge of what DNA to synthesize, (ii) public access to DNA synthesis is enabling anonymous fabrication (e.g., website, credit card, and FedEx), (iii) individuals might act to intentionally misapply biological engineering technologies.
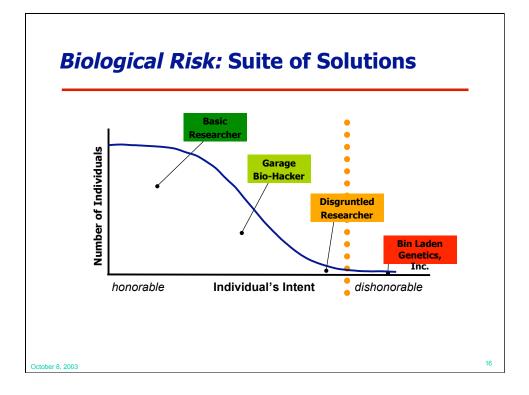
**In considering these new factors, study participants concluded that future biological threats will increasingly arise via the intentional or accidental (i.e., "michanikogenic") application of biological technology. Importantly, the rate of biological threat emergence is likely to become great enough to overwhelm current response technologies. We are (appropriately) developing and deploying "fixed assets" against existing, relatively-static biological threats (graphic above).  However, future biological risks are likely to be greater in number, more sophisticated in design and scope, and more rapidly developed and deployed.** *2003 Synthetic Biology Study*

A conservative discussion of strategy for minimizing biological risk would begin with three grounding assumptions. First, **that we already can not control the distribution of technology and information enabling the manipulation of biological systems** and that future technologies are also unlikely to be controllable. Second, **ineffective attempts to forbid access to some of the basic technologies for manipulating biology would likely incur prohibitive costs in the form of lost opportunities for improving human health and gaining scientific knowledge**. Third, that threats could arise from nature, nation states, loosely organized groups, and individuals, and could be targeted against any part of the living world relevant to human welfare (i.e., **biological threats are asymmetric in (i) source of agent, (ii) choice of target, and (iii) time to create versus respond, below**).
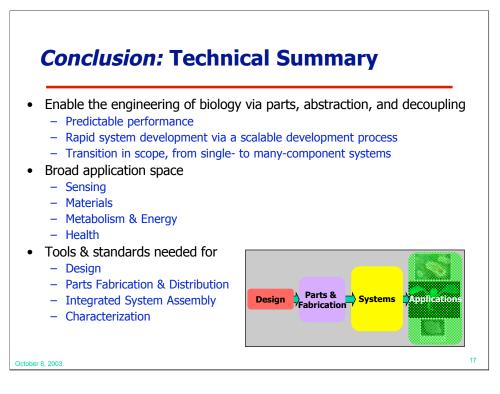
Given the above context, **the rate of detection, analysis, and response to new threats becomes critical**; a biological agent that took years to evolve and emerge, or be engineered and released, might require coordinated detection, analysis, and response within weeks. In addition, the breadth of possible targets requires that detection, analysis, and response capabilities be as general as practically possible and are, at least in part, accessible to a distributed network of end users. By analogy, computer network security relies heavily on the fact that all users have access to tools and resources for the detection, analysis, and response to network threats - but note that any net contribution via distributed security requires that most users have a vested interest in maintaining network function (next page).

**Technologies enabling the engineering of biology would directly contribute to a rapid and predictable response to biological threats** (e.g., pre-positioning components of standard vaccine vectors, 24h synthesis of DNA encoding multi-antigen-domain proteins, et cetera). In addition, **a cadre of engineers familiar with the design of biological systems would help to enable more rapid threat analysis.** 2003 *Synthetic Biology Study*

**Biological Risk: Suite of Solutions**

However, the same technologies that are needed to help enable rapid responses to new biological threats could also be used to help create the threats themselves. **Thus, it is necessary to consider how future biological technology can be combined with non-technical solutions in order to minimize both the number of sources of future biological risks, and the scope of the risks themselves. What steps can be taken now, at the beginning of the field, to minimize the number of individuals who could or would act to cause harm via future biological technology (graphic above)?** As one simple example, biological engineering training could include professional development programs and codes of ethics; a well conceived and responsibly implemented plan for educating future generations of biological engineers would help to expand strategic human resources for future biological defense. As a second example, registries managing standard biological parts could encourage responsible practice on the part of commercial DNA synthesis providers (e.g., "we'll only renew our synthesis contract if you can assure us that you are not synthesizing known threat agents").

Non-technical approaches contributing to future biological security might range from legal incentives and penalties, to social rewards and stigmatization, to methods of training and practice, et cetera. **Much more investigation and discussion of the role of non-technical components in a suite of solutions for biological risk mitigation is warranted.**

**Conclusion: Technical Summary**

- Enable the engineering of biology via parts, abstraction, and decoupling
  - Predictable performance
  - Rapid system development via a scalable development process
  - Transition in scope, from single- to many-component systems
- Broad application space
  - Sensing
  - Materials
  - Metabolism & Energy
  - Health
- Tools & standards needed for
  - Design
  - Parts Fabrication & Distribution
  - Integrated System Assembly
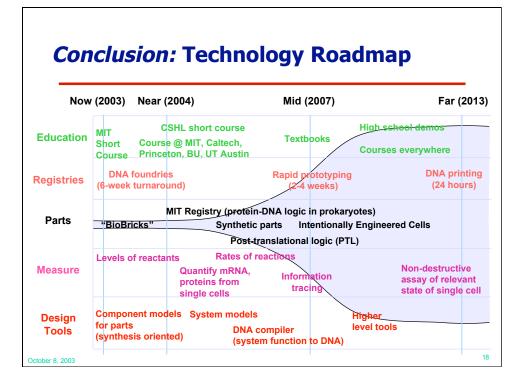  - Characterization

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Biology is a technology for processing information, materials, and energy. However, our ability to deploy biology as a technology and to interact intentionally with the living world is now limited.

A scaleable development path for engineering biology can be realized by combining (i) component **standardization**, (ii) substrate and component **abstraction**, and (iii) design and fabrication **decoupling**.

These three general advances should be combined with the development of "registries" that create and maintain libraries of standard biological parts, improvements in DNA synthesis technology, device and system design tools, and methods and standards for measurement and characterization.

Lastly, the development of technologies for engineering biology must be accompanied by ongoing discussions of non-technical approaches that help to minimize future biological risk.

## Conclusion: Technology Roadmap

| | Now (2003) | Near (2004) | Mid (2007) | Far (2013) |
|---|---|---|---|---|
| **Education** | MIT Short Course | CSHL short course<br>Course @ MIT, Caltech, Princeton, BU, UT Austin | Textbooks | High school demos<br>Courses everywhere |
| **Registries** | | DNA foundries<br>(6-week turnaround) | Rapid prototyping<br>(2-4 weeks) | DNA printing<br>(24 hours) |
| **Parts** | "BioBricks" | MIT Registry (protein-DNA logic in prokaryotes)<br>Synthetic parts<br>Post-translational logic (PTL) | Intentionally Engineered Cells | |
| **Measure** | Levels of reactants | Quantify mRNA, proteins from single cells | Rates of reactions<br>Information tracing | Non-destructive assay of relevant state of single cell |
| **Design Tools** | Component models for parts (synthesis oriented) | System models<br>DNA compiler (system function to DNA) | Higher level tools | |

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A general foundation for engineering biology will require newly developed training programs, standard parts libraries, tools for parts management & system assembly (i.e., registries), measurement technologies, and design tools. The development of these capabilities over the next decade will depend on the successful combination of past and ongoing results from basic biological research with advances in biological systems engineering. The chart above depicts a "best-case," funding-driven timeline for the development of such capabilities.

Specifically, education of biological engineers is transitioning from stand-alone courses like the one at MIT, to a cooperative five-school NSF-funded competition in 2004, to the broader education community. Registries of standard biological parts, like the one created at MIT, should be "mirrored" and expanded elsewhere. Parts creation and characterization is underway at the "protein-DNA logic" (PDL) level and is just beginning to be extended to what might be called "post-translational logic" (PTL); **the engineers and scientists who are now learning to engineer biology by building simple "toy" parts and systems should be encouraged to create more sophisticated artifacts that find immediate and widespread practical use.** Physical measurement technologies are now being developed by the entire biological research community; synthetic biology will help to (i) specify new types of measurements that better define composable parts and devices (e.g., transcription rate in place of protein concentration) and (ii) develop biological systems that can themselves be used to measure cellular state. Lastly, tools that compile designs into encoded DNA are now being developed for PDL systems; tool extension to other levels is necessary.