Emerging Life Science Technologies: Synthetic Biology and Dual-Use Research of Concern

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1. Strengthening the Culture of Biosafety, Biosecurity, and Responsible Conduct in Life Science. - Dana Perkins (US)

2. Dual-Use Research: Addressing Biosecurity Concerns Related to Synthetic Biology - Ashok Vaseashta (US)

3. TBC - Selwyn R. Jamison (US)

4. Challenges for Biosafety in the Changing Field of Biotechnology - Gijsbert van Willigen (NL)
Dual-Use Research - Addressing Biosecurity Concerns Related to Synthetic Biology

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UNCLASSIFIED
Terrorism: Methods of Choice – CBRNE (CW)

- Complicated
- Non-linear
- Kinetic
- Asymmetric
- Game of illusion
- Unpredictable
- No rules of engagement
- Contradict Ethical values
- ...

Dual-Use Technologies/Nano-materials
BIOTERRORISM

The intentional or threatened use of *microorganisms* or *biologic toxins* to kill or incapacitate people, animals or crops.

- Create terror, panic, uncertainty/uneasiness
- Advance political/religious/apocalyptic beliefs
- Asymmetrical response a.k.a. “even the playing field”
- Doable and affordable
- Effective

**Reality**

Biotechnology represents a “dual-use dilemma” in which the same technology (ies) can be used legitimately for human improvement and also misused for bioterrorism”

www.bt.cdc.gov
Dual-Use Paradigm

The term "dual-use" traditionally has been used to describe technologies that could have both civilian and military usage, but this term has at least three different dimensions that pose a dilemma for modern biology and its possible misuse for hostile purposes:

(1) ostensibly civilian facilities that are in fact intended for military-terrorist may use for bioweapons development and production;

(2) equipment and agents that could be misappropriated and misused for biological weapons development and production; and

(3) the generation and dissemination of scientific knowledge that could be misapplied for biological weapons development and production.
Research Using the same biotechnologies

Dual-Use

- Public Health
- Biodefense
- Offensive Military

Biodefense
- Defends against military use of bioweapons
- Develops capabilities for military use of bioweapons

- Diagnostics
- Drugs
- Vaccines
- Antivirals

- Military
- Government
- Private companies
- Academics

Bioweapons
- States (Iraq vs Iran)
- Terrorists

A suspected mobile biological weapons facility in Iraq.

AP/Wide World Photo/
Department of Defense
Proliferation Risks of Dual-Use Research – Categories of Risks

- Technologies that deliver beneficial drugs to the body could be used for *weaponizing biological agents*
- Research could have *unintended consequences*
- Dangerous agents could be released accidentally from the lab through *infected personnel*
- Research *results can be published* in easily accessible journals and on the Internet
- Knowledge or techniques could help to create “*novel*” pathogens with unique properties or create entirely new classes of threat agents
- Dangerous agents could be *stolen or diverted* for non-peaceful purposes
Examples of Risk
Potential Weaponization of New Technologies

• 1997: Dr. David Edwards, then at Pennsylvania State University, developed a way to deliver aerosolized medicine using large porous carrier particles.

• The method dramatically increased the amount of drug that made it deep into the lungs, providing a revolutionary treatment for conditions like asthma.

• After the anthrax attacks of 2001, its dual-use implications became clear: This technology could be used to intentionally deliver inhalation anthrax in a superior way.

• His research appeared in Science, bringing into question whether someone could use the information for weaponizing anthrax and other aerosolized agents.
Examples of Risk
Unintended Consequences of Genetic Engineering

- Australian grain industry suffered millions of dollars in damage to crops by infestations of mice
- Australian researchers genetically altered mousepox, an infectious virus that affects mice, to induce sterility in the mice
- The researchers inadvertently produced a recombinant virus with greatly increased lethality
- The virus killed laboratory mice, both those with genetic resistance to the virus and those mice immunized against it
- Their paper was published in the *Journal of Virology* in 2001, leading to concern that the same technologies could be used to weaponize smallpox and other pox viruses that affect humans
- These weaponized viruses would be more lethal and resistant to vaccines

“one step away from the ultimate bioweapon”

Rachel Nowak, New Scientist Online News
Examples of Risk
Accidental Exposure of Laboratory Personnel

• 2005: Three Boston University researchers became ill after being exposed to tularemia, a highly lethal pathogen
• Two researchers became ill in May and a third in September, but their illnesses were not linked to tularemia until October. The cases were not reported until November.
• Tularemia is not transmitted from human to human, but the lab was seeking approval to study anthrax, plague, and other highly infectious deadly pathogens.
• The scientists believed they were working with a research strain that would not cause illness, but a highly infectious strain was accidentally mixed with the harmless variety.
• The researchers also violated biosafety procedures that required them to work with tularemia inside an enclosed box, called a hood, that sends air through sophisticated filters.
• "The assurances that BU has given that it can maintain perfect control of these facilities are called into question," said Philip Warburg, leader of Conservation Law Foundation.

Stephen Smith, Boston Globe, January 19, 2005
Examples of Risk
Novel Microorganisms and Synthetic Biology

• The Synthetic Biology Working Group at M.I.T. is attempting to engineer a set of genetic building blocks called “BioBricks,” short pieces of DNA with functional genetic elements
  – A BioBrick sends and receives biochemical signals to be cut and pasted into a linear sequence of other BioBricks, like pieces in a Lego set

• Goal: to convert bioengineered cells into tiny programmable computers
• Bioengineered microorganisms (and possibly other life forms) could potentially produce pharmaceuticals, detect toxic chemicals, break down pollutants, repair defective genes, and destroy cancer cells
• These functions could also potentially be used for intentional, malevolent purposes
• Synthetic microorganisms with new, poorly understood, “emergent properties” could be accidentally released from the laboratory, possibly spreading into new ecological niches and causing the evolution of novel and potentially harmful characteristics

“The Promise and Perils of Synthetic Biology”
Jonathan B. Tucker and Raymond A. Zilinskas
Practical Definition of Synthetic Biology

- Making biology easier to engineer
- Applying engineering principles to biological systems

**Key enabling technology**: DNA synthesis

Technological innovations are not limited to beneficial uses ONLY!
Regenerative Medicine & Gene Editing

Proteins can be fused to DNA modifying enzymes to manipulate genes and gene functions.
The concept of **minimal genome** assumes that genomes can be reduced to a bare minimum, given that they contain many non-essential genes of limited or situational importance to the organism.

To create a new organism, the **minimal set of genes required for metabolism and replication** can be achieved by experimental and computational analysis of the biochemical pathways.

Genome reduction occurs most commonly in endosymbiotic, parasitic or pathogenic bacteria that live in their hosts. Examples include species of *Buchnera, Chlamydia, Treponema, Mycoplasma*, and many others.

<table>
<thead>
<tr>
<th>Species name</th>
<th>Number of genes</th>
<th>Size (Mbp)</th>
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<tbody>
<tr>
<td>Candidatus Hodgkinia cicadicola Dsem</td>
<td>169</td>
<td>0.14</td>
</tr>
<tr>
<td>Candidatus Carsonella ruddii PV</td>
<td>182</td>
<td>0.16</td>
</tr>
<tr>
<td>Candidatus Sulcia muelleri GWSS</td>
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<tr>
<td>Candidatus Sulcia muelleri SMDSEM</td>
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<tr>
<td>Buchnera aphidicola str. Cinara cedri</td>
<td>357</td>
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<tr>
<td><strong>Mycoplasma genitalium G37</strong></td>
<td>475</td>
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<tr>
<td>Candidatus Phytoplasma Mali</td>
<td>479</td>
<td>0.60</td>
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<tr>
<td>Buchnera aphidicola str. Baizongia pistaciae</td>
<td>504</td>
<td>0.6224</td>
</tr>
<tr>
<td>Nanoarchaeum equitans Kin4-M</td>
<td>540</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Genotoxicity vs. Carcinogenic - Necrosis to apoptosis

- **Probable non-genotoxic (non-mutagenic) carcinogens, tumor promoters or negative for genotoxicity in vivo**
- **Questionable carcinogens**
- **Probable genotoxic carcinogens**
- **Mode of carcinogenic action unknown, in vivo genotoxicity unknown or unclear**
- **Necrosis to apoptosis (?)**
Dimensions Comparable with many Fundamental Physical Quantities

- Effective free-path length of the electrons, phonons, etc.
- De Broglie electron wavelength
- Penetration depth of the magnetic field
- Abrikosov vortex lattice, Josephson fluxons, Magnetic flux quantum (Qubits)
- Radius of electron correlation length (coherent length)
- Wavelength of the electromagnetic field
- Cyclotron Radius in Magnetic field
- Relaxation length of the quasi particles.

Materials by design – specs based on materials vs. materials based on specs

- Nanostructured
- Nanoparticles \(\{\text{< 100 nm}\}
- Nanosized
- Micro - \(d < 2 \text{ nm}\)
- Meso - \(2 < d < 50 \text{ nm}\)
- Macro - \(d > 50 \text{ nm}\)

IUPAC recommendation
Some known examples

- Weaponized Nanomaterials
  - Anthrax attack in 2001
  - $^{210}\text{PO}$ Poisoning of Alexander Valterovich Litvinenko in 2006
  - Yasser Arafat and the Mysteries of $^{210}\text{PO}$

- Nanoenergetics - World trade center
  Mixture of $\text{Fe}_2\text{O}_3$ and $\text{Al}_2\text{O}_3$

Other Threats

- User-controlled threat (sensors?)
- Organometallics
- Biomimicking
- ......
Methods attempted so far – Subways, tunnels, ...

Under Consideration: water, aerial dispersion
Enhanced data fusion (collection/analysis)
Risk Assessment and Management
Consequence Management
Convergence of technologies
Enhanced situational awareness
Stand-off detection
Dial-a-beacon (remote and auto detection of “new” contaminants)
Sample in-answer out
In-situ sampled (point contact) detection
Triaging pathogens and forensics
Eradicate contaminants at POO (point of origin)
Assessment (LC, LCA, LCO, …)
Mitigation strategies – environmental management
Use of decision support tools
Evolutionary and Disruptive Approach vs. Revolutionary Approach

Revolutionary 5-15 Years
- Future Combat systems
- Adaptive, self-reflective and Self-Morphology
- Symbolic Regression
- Nanorobotics in vasculopathies
- Plasmonic computation
- 3D data Storage
- Molecular Surveillance & Detection of Biothreat Agents
- Ubiquitous testing, validation & Simulation - Superbrain

Disruptive 2-5 years
- Nanocatalysis
- Bio Engineered materials
- Meta materials – NRI
- E-textile
- AI and Self-assembly
- Robotics
- Genomics

Current approach
- CISTecK Approach

Evolutionary present
- Suit, gloves, boots & various masks
- Point & “standoff” detection
- Handheld decon unit including tank trucks
- Shelters and filters

Impregnated suit & masks
- Placing pigeon in cage at trench entrance
- Handheld decon unit & decon tank truck
- Trench fan and entrance way

Accelerated Evolutionary 0-2 Years
- Enhanced vision/interactive screen
- Personal communication
- Network connectivity
- Security
- Embedded smart systems
- Gait analysis probe points
- Personal entertainment
- Personal fitness

Superbrain
Data Analytics, Big Data and Decision Support Tools

5.2 Transition-Based Parsing

5.2.1 Models

The common model for transition-based parsers is one inspired by shift-reduce parsing, where a parser state contains a stack of partially processed tokens and a queue of remaining input tokens, and where transitions add dependency arcs and perform stack and queue operations. This type of model is used by the majority of transition-based parsers (Attardi et al., 2002; Duan et al., 2007; Hall et al., 2007b; Johannson and Nivre, 2007b; Mannen, 2007; Titov and Henderson, 2007; Wu et al., 2007b). Sometimes it is combined with an explicit probability model for transition sequences, which can be conditional (Duan et al., 2007) or generative (Titov and Henderson, 2007). An alternative model is the MatchMatic (Hall et al., 2007) system, which iterates through a set of states, each of which is an ordered list of tokens in the sentence. This model is used by the Charniak system (Hall et al., 2007) and the CoNLL-2007 shared task (Sagae and Tsuru, 2007). Watson and Brickowe, 2007).

5.2.2 Inference

The most common inference technique in transition-based dependency parsing is greedy deterministic search, guided by a classifier for predicting the next transition given the current parser state and history, processing the tokens of the sentence in sequential left-to-right order (Hall et al., 2007b; Mannen, 2007; Marinov, 2007; Wu et al., 2007). Optionally, multiple passes over the input are conducted until no tokens are left unattached (Attardi et al., 2007). As an alternative to deterministic parsing, several parsers use probabilistic models and maintain a beam of partial transition sequences. To choose the most probable sequence of transitions, the parser can use a scoring function that combines the probabilities of the transitions with the probabilities of the dependency relations (Wu et al., 2007). In the case of grammatical rules, the grammar is specified in terms of a first-order Markov model (Brickowe, 2007).

5.2.3 Learning

To train these classifiers and probabilistic models, several approaches are used. SVMs (Duan et al., 2007; Hall et al., 2007b; Sagae and Tsuru, 2007), modified finite Newton SVMs (Wu et al., 2007), maximum entropy models (Sagae and Tsuru, 2007), and maximum likelihood estimation (Watson and Brickowe, 2007). In order to calculate a global score or probability for a transition sequence, two systems use a Markov chain approach (Duan et al., 2007; Sagae and Tsuru, 2007). These probabilities from the output of classification are then multiplied across the sequence of actions. This is followed by a locally normalized model. Two other models use MRFs (Mannen, 2007) on the premise that the probabilities of actions are not independent. To train a globally normalized model, Titov and Henderson (2007) used an incremental sigmoid Bayesian network to model the probability of a transition sequence and estimated model parameters using neural network learning.
<table>
<thead>
<tr>
<th>Very Feasible</th>
<th>Emerging</th>
<th>Significant</th>
<th>Very Significant</th>
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</thead>
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<td>Sensor network grid</td>
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<td>Water monitoring</td>
<td>Nanocomposites</td>
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<td>release drug/vaccine</td>
<td>nano-bio sensors</td>
<td>for suits &amp; worn</td>
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<td>delivery</td>
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<td>wearable electronics</td>
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<td>Very unlikely</td>
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Technology Gaps

**Biointerfaces** – effective and robust integration of biological and engineered systems.

**Biodetection** – sensitivity and broad-spectrum sampling capabilities of autonomous detection systems.
  - *Molecular signature* development and bioinformatics analyses for broad-spectrum threat characterization and countermeasures.
  - *Biotic-abiotic interface* development for diagnostics, sensor design and cognitive augmentation.
  - *Systemic host bioresponse* - rapid recognition/differentiation of chem.-bio threat exposure.
  - Miniaturization of multiple analytical systems on a single platform - sensor network.

**Bioforensics** – physico-chemical characterization of engineered and emerging biothreats

**Biotoxicity** of Nanomaterials

**Self Sustaining, self-healing, and adaptive nanomaterials**

**Sample in/Answer out** – sensor devices and systems

**Portability** – light weight, autonomous, bi-directional capability

**Multiplexing, parallel processing and Networking solutions**

**Stand-alone (bio) Energy harvesting**
Risk

Probability

Risk assessment

Risk management

Risk Assessment
- Hazard identification: What is the hazard?
- Probability of risk: How likely is the event?
- Consequences of risk: What is the likely damage?

Risk Management
- Comparative risk analysis: How does it compare with other risks?
- Risk reduction: How much should it be reduced?
- Risk reduction strategy: How will the risk be reduced?
- Financial commitment: How much money should be spent?

Risk Assessment Diagram:
- Risk characterization
  - Dose-response assessment
  - Hazard identification
  - Exposure assessment
- Risk characterization
  - Socioeconomic
  - Technical
  - Regulatory decisions
  - Political
  - Other factors
- Risk Management
  - Exposure
    - Air/Water Quality
    - Epidemiology
    - • Integrated Science Assessment
      - • Risk and Exposure Assessment
      - • Risk Management
Future Integrated Nano-Systems

- 3D Terabit Memory
- Ultra Sensitive Bio-sensor
- Nano Fluidic Circuits
- Ultra Compact light source & integrated photonics

Sensors/Detectors - SOC, NOC, NP-OIC, SoF

- Biosensors
- Sensitivity
- Specificity
- Reliability
- Accuracy

Fluidic circuit

- Guided wave optics
- Free space optics
- Aqueous bio/chem sensors
- Physical sensors
- Gas/chem sensors

Electronics (communication, powering)
Verification center
- Online monitoring
- Water treatment
- Decontamination/filtration
- Water Management

PC-based rapid risk assessment tool: TechFARM, ADAMS, NESTTS

Threat scenario simulations and screening level risk analyses - TTX/FTX

Threat Assessment
Disease surveillance
“Triaging Unknown Pathogen” Pipeline

-> genomics approach

Bacterial and viral forensics

• Conventional
  • Microbial characterization: Physical, Growth, Chromosome[s]
  • Biochemical characterization: Immunochemistry, Proteins
• “Leading-edge”
  • Genomics and Bioinformatics: genome sequencing, microarray
  • Proteomics

DNA @10μg

• PCR profiling
• Microarray profiling
• Genome sequencing: “Determining primary data”
• Physical mapping: “Complementing primary data”
  • Optical Map
  • PFGE Map

Genomics and Bioinformatics:

DNA sequencing at 20x

• Fragment QA/QC
• Assembly into contig[s]
  • Consensus genome
  • Contigs gapped genome: 100-800 contigs

• Physical Characterization
  • Optical Map
  • Genome closure
Convergence of Social Media, Federal Agencies, and Outcome (intended/unintended) – What’s Trending!
Joint Intelligence Preparation of the Operational Environment (JIOPE) is a continuous doctrinal process that provides:

- Predictive intelligence
- Comprehensive analysis of the operational environment
  - Strategic to tactical level view of the world
  - Input from multiple disciplines
- Visualization of the full spectrum of adversary capabilities/intent
- Potential threat courses of action (COAs)
- Indicators that describe enemy COAs
- Basis for intelligence direction and synchronization

- TRUST: Tools for Recognizing Unconscious Signals of Trustworthiness - Neural activation, behavioral pattern, physical signals, neurophysiological signals

**Worldwide monitoring of swamp**

**Socio-cultural modeling**

**Group / Decision theory**

**WMD pathways analysis**

**Boom**

**JIPOE Process**
Dual-Use – Ethical Dilemma

- Encourage discoveries – new dimensions in safety and security – yet keeping it from proliferation
- Dissemination – is part of academic freedom but comes at the cost of adversaries having access to the same literature.
- Regulation of Dual-use experiments and information comes at the expense of complete autonomy of the individual scientists, institutional control, Government control, slow progress, independent authority and Government control.
Biosafety and Biosecurity

• Related but not the same
• Biosecurity – is to prevent loss, theft, or misuse
• Biosafety – reduce or eliminate exposure of the individuals and the environment to potentially hazardous biological agents
• Practices may conflict with each other and hence it requires policies and guidelines involving both to accommodate both sets of objectives.
• Nuances will always be there – collateral damage!
• A joint Biosafety and Biosecurity task force.
Conclusions and Path Forward

- Paradigm shift using nexus of technological innovations
- Convergence of interdisciplinary fields to address challenges
- Diplomacy in Policy Implementation - RE: dual use nanomaterials, more accountability in labs, especially labs dealing with synthetic biology. Strict Compliance – consistent with federal labs
- Balance in publication and dissemination
- Promoting social values
- New challenges – creation of new opportunities