

Scientific Life

Hands-On
Introduction to
Synthetic Biology for
Security
Professionals

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The rapid pace of life sciences innovations and a growing list of nontraditional actors engaging in biological research make it challenging to develop appropriate policies to protect sensitive infrastructures. To address this challenge, we developed a five-day awareness program for security professionals, including laboratory work, site visits, and lectures.

Justification: Synthetic Biology Training Is Imperative for Security Officials

In 2006 the Federal Bureau of Investigation (FBI) created the Weapons of Mass Destruction (WMD) Directorate (WMDD) in response to the 2001 anthrax mailings and to the increasing number of incidents involving chemical, biological, radiological, and nuclear (CBRN) material. Each of the 56 FBI Field Offices has a WMD coordinator who is tasked with all CBRN matters in their geographic area (www.fbi.gov/contact-us/field-offices). Among their many responsibilities, WMD coordinators implement programs that build and maintain partnerships with the life sciences community, ranging from the private sector (e.g., agricultural and pharmaceutical industries), to academic institutions, and even to the amateur biology community [1]. These coordinators are trained in the basics of CBRN materials and how

they might be misused. However, very few of them have in-depth science backgrounds.

Synthetic biology [2,3] is an emerging field of research that combines elements of different sciences that rely on chemically synthesized DNA to create new biochemical systems or organisms with novel or enhanced characteristics. The capabilities of these technologies have increased by orders of magnitude over the past few years, and the costs associated with them have decreased by similar orders of magnitude. Although synthetic biology and related technologies offer substantial promise, they also remain inherently dual-use, with both nefarious and reputable applications [4,5].

The FBI WMDD established the Advanced and Emerging Biotechnology Program to proactively mitigate current and over-the-horizon risks posed by the exploitation of R&D advances in scientific fields such as synthetic biology. As part of this program, we developed a hands-on training course for security, intelligence, and law enforcement professionals who need to anticipate the security implications of life science innovations such as synthetic biology.

This course was created with the support and cooperation of the FBI and Colorado State University (CSU). The goals and objectives of the program were to enhance the understanding among law enforcement professionals of the steps necessary to carry out a research project, including experimental design, practical use of techniques, and possible applications.

The course curriculum was designed to engage a large range of students, ranging from those with little or no prior knowledge or experience in biology to

holders of advanced degrees. Eleven FBI personnel participated in the program in 2017. The students were junior to mid-career law enforcement professionals and intelligence analysts. None had post-secondary school training in biology and only one had a graduate degree in a scientific field. The mixture of backgrounds in the class allowed the more experienced participants to act as peer mentors, a method that has proved to be an effective teaching tool in science education [6].

Training Approach: A Unique Multifaceted Curriculum

Daily lectures provided students with the background information necessary to understand techniques of gene and protein synthesis. Lectures additionally discussed sensitive issues related to the security implications of synthetic biology, genome editing, cyber-physical security in biology, and biosecurity (Box 1). These lectures included in-depth discussions of hypothetical and actual examples. This interactive format helped to broaden the perspective of government employees by allowing them to compare the perspective of security professionals against the perspective of scientists and domain experts.

The laboratory component of the program provided the students an opportunity to practice basic molecular techniques essential for manufacturing genes and proteins. Using the Open Insulin Project (www.openinsulin.org) [7] as a test case, students learned how to assemble a DNA molecule including the gene and regulatory sequences that code for insulin. In only 5 days, students practiced polymerase chain assembly (PCA), Gibson assembly, PCR, capillary electrophoresis (Agilent Bioanalyzer), agarose gels, and spectrophotometry. They also went through basic cloning workflows including



Box 1. Lectures

The training included seven 60–90 minute lectures split among the five days. Because of the sensitive nature of their content, the lectures are not shared publicly. In addition to guest lectures, which introduced specific technologies such as CRISPR-mediated gene editing and synthetic biology in plants, the topics covered provided an overview of the following four main areas.

Introduction to DNA Synthesis

An introduction to the techniques the students would practice in the laboratory, with an overview of the DNA synthesis industry including manufacturing processes, intellectual property landscape, quality control, and other relevant considerations such as decisions to move manufacturing offshore.

Cyber-Physical Security in Biology

Discussion of the potential for cybersecurity breaches to impact on physical biomanufacturing machinery or biological samples [9,10]. Students were provided with an overview of DNA sequencing technologies, the methodologies used to verify sequences, and mistakes that can occur [11].

Biosecurity in the Age of Synthetic Biology

An overview of the legislative, regulatory, and policy frameworks aimed at preventing the misuse/dual-use of life sciences knowledge, materials, and research, and the limitations therein [12]. Examples were also provided of a broad range of biosecurity issues including restricting the gene flow of genetically modified organisms [13], preventing contamination of biomanufacturing facilities, and limiting access to controlled substances such as morphine [14].

Culture of Security in Life Sciences

An overview of the culture of security in the life sciences; security implications of the academic culture of openness; inconsistent verification of samples received from reputable sources [15].

media preparation, culture inoculation, transformation, colony PCR, and mini-preps. Students expressed their insulin cassettes in bacterial cells *in vivo* and *in vitro* using the myTXTL® cell-free expression system. Protein samples generated *in vivo* and *in vitro* were analyzed by SDS-PAGE/immunoblots and the Bioanalyzer, respectively.

The program also included site visits to life science facilities ranging from a do-it-yourself community laboratory [1] to a high-containment facility (Box 2). These visits exposed students to the diversity of environments involved in life science research and biotechnology. In addition, the visits offered the opportunity for students to interact with staff and researchers in these diverse settings.

Outcomes: Confidence and Competence in Laboratory Settings

This pilot is believed to be the first in which law enforcement professionals with little to no science background gained practical experience in basic synthetic biology techniques. Responses from an informal survey of the students indicated that the laboratory portion was of most use because it allowed more insight into the capabilities of the science, especially the contrast of what is possible under a variety of conditions (e.g., trained versus untrained personnel, well-equipped laboratory vs a DIY set-up).

Despite their lack of technical experience, the students were very engaged in the laboratory exercises. For each

step of the protocols, back-up samples were pre-prepared to ensure that mistakes made by the students did not result in an inability to advance through the workflow. In practice, few of these fallbacks were necessary. The performance of the FBI personnel appeared to be in line with that of undergraduate students with no laboratory experience. Unfortunately, none of the students obtained positive results with the myTXTL® *in vitro* expression kit. However, the students did not react negatively to experimental setbacks. They seemed to enjoy the challenge and remained engaged throughout the entire week.

Discussions and interactions were encouraged throughout the five-day program. The level of engagement during site visits and lectures gradually increased throughout the course, peaking at the end. During the final site visit, the students were suggesting possible security risks that site representatives had not previously considered. It is conceivable that the training experience not only educated the students on relevant questions to ask but also emboldened them by increasing their comfort levels in a laboratory setting.

Future Prospects: Expanding and Improving the Training

This course was developed to align with requirements specific to the FBI WMD Coordinator Certification Program. However, the broader community of security professionals may also benefit from similar training programs. The Department of Defense, the Department of Homeland Security, Health, and Human Services, regulatory agencies such as the FDA and the US Department of Agriculture, and members of the intelligence community all need to consider the security implications of recent and continuing developments in life sciences.

Box 2. Site Visits

The program also included site visits representing different scales of operations, different demographics, and different regulatory environments. The goal was to build knowledge and familiarities with the unique security strengths and vulnerabilities of each that could translate into improved relationships and interactions that are an essential part of the official duties of the students.

Colorado State University (CSU) Protein Production Facility

This core facility is located in the Department of Biochemistry and Molecular Biology. It provides CSU with instrumentation, equipment, and technical expertise for the expression and purification of proteins from bacteria and yeast (www.bmb.colostate.edu/protein-expressionpurification-facility).

CSU Infectious Disease Research Center (IDRC)

The IDRC is a biosafety level 3 research facility where university researchers, government scientists, and industry representatives collaborate on projects involving infectious agents such as West Nile virus and tuberculosis (<https://vpr.colostate.edu/idrc/>).

CSU Bio-Pharmaceutical Manufacturing and Academic Resource Center (BioMARC)

BioMARC is a not-for-profit, high-containment, manufacturing facility for biologic drugs and diagnostics such as vaccines (<http://biomarc.colostate.edu/>).

Biosafety Level 3 Training Facility at CSU

This visit familiarized students with biosafety measures instituted at academic institutions such as the IDRC and BioMARC.

Denver Biolabs

This is a community laboratory (<http://denverbiolabs.com/>) hosted on the campus of the University of Colorado–Denver Inworks facility. The Executive Director of Denver Biolabs gave a tour of the facility and led a discussion about the DIY biology (DIYBio) movement derived from her experience in creating Denver Biolabs and former involvement with Counter Culture Labs (www.counterculturelabs.org) and Biocurious (www.biocurious.org) in California.

It is useful to surmise how this program might be scaled up to meet the training needs of potentially hundreds of government employees. The use of a modern learning management system (LMS) would make it possible for a limited number of instructors to supervise the progress of a large number of trainees enrolled in a self-paced asynchronous training program.

The program could be broken down into training modules forming a training sequence corresponding to increasing levels of domain expertise. Module I would correspond to the lectures (Box 1). Module II would correspond to laboratory work. A self-contained laboratory-in-a-box and student reagent kits

would be shipped to local training facilities (government laboratories or teaching laboratories at a local university) to deliver this part of the training locally to small groups of students. Module III would correspond to site visits. Visits to sites across the country could be scheduled throughout the year to represent a broader range of facilities. Students would need to participate in four site visits to complete this module. Module IV would be a 'train-the-trainer' and certification program ensuring the availability of certified trainers who are capable of mentoring students enrolled in the program.

Although the training was developed primarily for students without any life

science background, we have also received requests for this training from security professionals with graduate degrees in the life sciences. After a few years away from the bench, they expressed difficulties in keeping up with the rapid evolution of the technology. For these more advanced participants, the LMS would offer students the possibility of 'testing out' of a module (i.e., earn credits for material they already have a strong foundation in), thus allowing them to concentrate on select modules.

The core curriculum could be complemented by an assessment of the effectiveness of the program in preparing students for their responsibilities. This assessment could be as simple as administering quizzes and surveys assessing knowledge levels before and after the training [8], or could be more experiential. For example, we could use scenario-based training in which students are given a test scenario at the beginning and the end of the course to see if their interpretation of the situation changes. This type of assessment could be customized to reflect scenarios that trainees from different agencies or with different responsibilities may encounter.

In conclusion, the integration of lectures, hands-on laboratory experience, and site visits to technology facilities enabled students to better understand existing vulnerabilities in synthetic biology workflows, the potential and limitations of current technologies, and the anticipated evolution of some of these technologies. This training could be adapted and expanded for a variety of purposes in government, academic, and commercial settings.

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References

- Landrain, T. et al. (2013) Do-it-yourself biology: challenges and promises for an open science and technology movement. *Syst. Synth. Biol.* 7, 115–126
- Cameron, D.E. et al. (2014) A brief history of synthetic biology. *Nat. Rev. Microbiol.* 12, 381–390
- Peccoud, J. (2016) Synthetic biology: fostering the cyber-biological revolution. *Synth. Biol.* 1, ysw001
- Marris, C. et al. (2014) Negotiating the dynamics of uncomfortable knowledge: the case of dual use and synthetic biology. *Biosocieties* 9, 393–420
- Wimmer, E. (2018) Synthetic biology, dual use research, and possibilities for control. In *Defence against Bioterrorism, NATO Science for Peace and Security Series A: Chemistry and Biology* (Radosavljevic, V. et al. eds), pp. 7–11, Springer
- Secomb, J. (2008) A systematic review of peer teaching and learning in clinical education. *J. Clin. Nurs.* 17, 703–716
- Gallegos, J.E. et al. (2018) The open insulin project, a case study for 'biohacked' medicines. *Trends Biotechnol.* 36, 1211–1218
- Mangul, S. et al. (2017) Addressing the digital divide in contemporary biology: lessons from teaching UNIX. *Trends Biotechnol.* 35, 901–903
- Peccoud, J. et al. (2018) Cyberbiosecurity: from naive trust to risk awareness. *Trends Biotechnol.* 36, 4–7
- Murch, R.S. et al. (2018) Cyberbiosecurity: an emerging new discipline to help safeguard the bioeconomy. *Front. Bioeng. Biotechnol.* 6, 39
- Wilson, M.L. et al. (2013) Sequence verification of synthetic DNA by assembly of sequencing reads. *Nucleic Acids Res.* 41, e25
- National Academies of Sciences, Engineering, and Medicine. (2018) *Biodefense in the Age of Synthetic Biology*, The National Academies Press
- Oye, K.A. et al. (2014) Regulating gene drives. *Science* 345, 626–628
- Galanie, S. et al. (2015) Complete biosynthesis of opioids in yeast. *Science* 349, 1095–1100
- Peccoud, J. et al. (2011) Essential information for synthetic DNA sequences. *Nat. Biotechnol.* 29, 22

Science & Society

Synthetic Biology and the United Nations

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Synthetic biology is a rapidly emerging interdisciplinary field of science and engineering that aims to redesign living systems through reprogramming genetic information. The field has catalysed global debate among policymakers and publics. Here we describe how synthetic biology relates to these international deliberations, particularly the Convention on Biological Diversity (CBD).

Synthetic biology or engineering biology is a fast-moving field that em-

braces and drives state-of-the-art technologies for designing and reconstructing living systems at different scales, primarily by reprogramming cellular genetic information. As such, the field has catalysed global debate among the wider circles of legislative policymakers, including multiple international conventions, treaties, and protocols. Various international treaties and organisations are currently examining the impacts of synthetic biology and engineered gene drive systems on their respective agreements (Table 1). One main United Nations (UN) convention of importance to synthetic biology is the UN Convention on Biological Diversity (CBD). In simple terms, the CBD has three main objectives: (i) conservation of biological diversity, (ii) sustainable use of its components, and (iii) fair and equitable sharing of benefits arising from the use of genetic resources. Since 2010, the CBD has discussed whether synthetic biology should be classified as a new and emerging issue and its objectives and activities are of considerable importance to the synthetic biology research community. For example, one objective of the CBD is to grant sovereign rights of countries over their genetic resources. Furthermore, the CBD is also deliberating whether or not new/adapted regulations are needed for synthetic biology, how access and benefits sharing agreements (ABS) should be managed with digital sequence information (DSI) and also whether or not moratoriums on synthetic biology research and/or applications to the environment should be implemented (Table 1). The CBD is also debating whether the products of synthetic biology should be considered under the convention, in addition to the process or technology used to produce them. The synthetic biology community should follow these deliberations closely and take the opportunity to engage directly within these processes.

