The Biological Technologies Office develops new tools to support warfighter health, fitness, and training so that the force can perform at peak capacity no matter the mission. Technologies like embedded hydrogel sensors continuously measure body chemistry and give individuals and commanders real-time visibility into squad readiness.

U.S. AIR FORCE PHOTO BY TECH. SGT. GREGORY BROOK

SECURITY AND SURPRISE AT BIOLOGICAL SCALES

The evolution of defense technology

By Justin Sanchez and Jacob Jordan

The power and challenge of biology as the basis of technology reside in its adaptability and resilience, and from those attributes spring the seeds of surprise. DARPA's mission is to master surprise, and so the agency has embraced biotechnology and focused its investments on mitigating threats to human health and global stability, improving military training and readiness, and rethinking current approaches to traditional defense missions. In this seventh decade of DARPA-based innovation, the 4-year-old Biological Technologies Office (BTO) is set to transform biology from a niche specialization within the Department of Defense (DOD) into a fundamental source of high-impact capabilities, among them force protection, sensing, command, control, and communications.

DARPA is not alone in this game. Across the board, the growing affordability and accessibility of tools to modify biological systems means that other nations, and even individuals, have the resources to engineer systems and organisms to have altered or new functions. Consider the dramatic decrease in the cost of sequencing a genome, paired with widely available tools for editing genes. Now, virtually any person anywhere might experiment with genetic modifications. Much of that research has positive ends, but all biotechnologies have the potential to be dual-use. And there is always the risk of unintended consequences.

The application of biotechnologies by an adversary is an area where the United States could be most surprised as a nation, but it is also a source of great potential, where the United States could develop a host of new surprises of its own.

Incorporating biotechnologies into DOD operations requires a deliberate effort, beginning with familiarizing potential end users with emerging technologies, demonstrating capabilities in contexts relevant to DOD missions, and creating opportunities to integrate those capabilities into DOD organizations. Part of DARPA's challenge is breaking through subtle institutional preconceptions about what is and is not possible. A generation of military leaders raised on a diet of science fiction may be inclined to perpetually relegate certain biotechnologies to a vague future. But, in fact, BTO's talented roster of program managers and research performers not only operates at the frontiers of science, but thinks beyond them, and the seeds of those tools and capabilities that might sound fantastical already exist today.

The emerging importance of biological technologies for national security is an important decision-making driver for Dr. Steven Walker, Director of DARPA. "Biology percolates throughout every aspect of the Department of Defense. The people who serve, the missions they carry out, and the technologies that facilitate their performance all exist within an organic world, and we're building the tools to engage with that world in new ways," Walker said. "As the DOD accelerates its modernization push, the technologies coming out of BTO could transform how the services carry out their missions, and DARPA is committed to facilitating the integration of biological capabilities into the total force."

Since its establishment in 2014, BTO has optimized its approach, operations, and research portfolio to create opportunities to transition defense-relevant capabilities to military end users and, in some cases, to society at large. That strategy involves considering broad classes of challenges rather than individual threats, expanding the scope of biotechnology to missions that have not traditionally had an overt biological component, and reducing the various risks involved with embracing new technologies.

Reinventing Approaches to Bio Threats

The United States confronts a potential national security threat each time a new outbreak of infectious disease occurs anywhere in the world. The nationwide spread of H1N1 flu in 2009, the spread of Middle East Respiratory Syndrome in Indiana in 2013, and the presence of Ebola in Texas in 2014 are recent reminders of this reality. A single viral particle has the power to replicate billions of times over, introducing communicable disease to large cities, overwhelming hospital systems, inciting mass terror, and dramatically reducing the readiness of our military, governmental functions, and infrastructure elements, all of which require healthy personnel to run them. And in this connected world, a virus can circle the planet on jetliners in less than 36 hours.

U.S. AIR FORCE PHOTO BY AIRMAN 1ST CLASS DONALD HUDSON

The threat to force health and readiness posed by infectious disease is persistent and evolving. BTO is developing a range of countermeasures to natural and engineered threats, such as technologies to predict viral evolution and spread, contain diseases within animal reservoirs, disrupt disease vectors' ability to transmit viruses, and control or remediate the effects of gene editors.

Risks posed by naturally occurring outbreaks are only one concern. Recent advances in synthetic biology and gene editing have reduced long-standing barriers to entry for nefarious actors wishing to develop engineered biothreats. Doing so no longer requires a detailed understanding of molecular biology, wet lab skills, or access to live pathogens. The widespread availability and reduced cost of DNA sequencing, and more importantly DNA synthesis, have made it possible to reconstitute eradicated pathogens – U.S. and Canadian researchers reported in 2017 that they had synthesized horsepox virus – and to create new ones *de novo*. Advances in gene editing also open the way for direct modifications to the human genome and the construction of "gene drives" that override traditional inheritance in offspring in ways that can propagate specific traits and biological functions throughout an entire population.

There is currently a mismatch between the rapidity at which bio threats can emerge and proliferate and the response time for developing and deploying effective countermeasures. Traditional biodefense technologies are designed primarily to counter known pathogens, and even still, they require long lead times to develop responses. If a successful countermeasure can be created, it must then be mass-produced and stockpiled in preparation for a large-scale emergency. This cycle is time-consuming enough for known and predictable threats. It can be tragically slow when it comes to unfamiliar pathogens, which can spread at pandemic scales before researchers can devise countermeasures.

The Advanced Plant Technologies program envisions plants as discreet, self-sustaining sensors capable of detecting signals of interest and reporting them via remotely monitored, programmed responses to environmental stimuli.

Cognizant of this time-sensitive dynamic, DARPA structures its medical countermeasures R&D to pursue generalizable, threat-agnostic technology platforms that can be tailored on demand, rather than building one-off solutions to address individual threats as they emerge. The flu vaccine must be reformulated every year because the flu virus mutates, so the medical community is always playing catch-up. Imagine if, in preparation for the next flu season – or worse, the next outbreak of Ebola or Zika – an existing therapeutic tool could be quickly and easily customized to fight the specific pathogen, stopping the outbreak in its tracks. This type of technological firebreak could eliminate the national security risks posed by infectious disease.

BTO's Pandemic Prevention Platform (P3) program encapsulates one such approach, with the ambitious goal of halting a pandemic in 60 days or less. It builds on pioneering DARPA research into gene-encoded therapeutics and is designed to achieve higher therapeutic potency and efficiency compared to traditional countermeasures by using the human body as a bioreactor.

When individuals are exposed to pathogens, their bodies respond by producing protective antibodies and other immunological responses. Some of these are strong and highly protective, while others are weak and nearly ineffective. P3 aims to deliver the genetic code for the most potent antibodies directly into a person in need of protection so they can produce their own defense agents *in situ*. This approach circumvents slower, traditional, vaccine-based approaches or biotherapeutic production protocols involving chicken eggs, animals, or plants. Used in combination with other high-throughput screening methods for identifying anti-virus therapeutics, all that is needed to combat a known, emerging, or engineered virus is the genetic code (its sequence of A, T, G, and C nucleotides) of an effective antibody. By translating the genetic code of that antibody into a therapeutic manufactured directly by cells within the body, researchers can dramatically reduce the time from virus identification to creation of an effective and approved countermeasure, and ultimately open the way for the timely distribution of the countermeasures within the time window before an outbreak can rage into a pandemic.

The P3 program manager, Col. Matt Hepburn, M.D., is now working to translate an initial proof of concept into a deployed capability by overcoming the remaining bottlenecks in the process. "We're working to demonstrate an ability to quickly grow the quantities of virus needed to test and evaluate therapies, identify antibodies, and increase their potency within the first weeks of an outbreak, and scale methods for delivering treatments into humans," Hepburn said.

Moving from Discovery to Real-world Capabilities

Key to BTO's vision is that biotechnology capabilities have a role in the DOD well beyond human health and biowarfare defense. Central to this vision is the increasing interactions among the fields of gene editing, materials science, artificial intelligence, and other specializations.

Long-standing problems of national security are growing in complexity and beginning to push up against the limits of traditional engineering in a variety of operational contexts. Whether on land or at sea, the DOD deploys people and equipment to maintain military overmatch across vast and diverse spaces. And the people carrying out these missions must now

U.S. AIR NATIONAL GUARD PHOTO BY TECH. SGT. MARK OLSEN

U.S. NAVY PHOTO BY MC2 TYLER PRESTON

The Persistent Aquatic Living Sensors program promises to bring new resources to the challenge of detecting and characterizing underwater vehicles in strategic waters.

interact more frequently with autonomous or semi-autonomous systems that work at speeds faster than humans can process without assistance.

Biotechnology approaches are beginning to present an intriguing alternative to solutions that were previously based solely in engineering, because unlike electrical and mechanical systems, biological systems are persistent, adaptable, autonomous, power-efficient, and discreet when deployed in their native environments. BTO's team of program managers and leadership – a cadre of life scientists and engineers – has set out to evolve national security capabilities by embracing those unique properties.

Dr. Blake Bextine, an entomologist by training who joined DARPA in 2016, understood that plants could complement traditional military sensors in complex environments to detect signals of interest. "Plants are highly attuned to their surroundings and naturally manifest physiological responses to stimuli such as light and temperature, so DARPA asked if it's possible to reprogram those detection and reporting capabilities for stimuli like pathogens and threat agents," said Bextine.

He wants to apply the latest advances in genome-editing technologies to develop persistent plant sensors that not only detect and report on signals of interest – that is, chemical, biological, radiological, nuclear, and explosive (CBRNE) threats – but that are also robust enough to survive in place and reproduce. By also engineering into these systems response mechanisms that can be remotely monitored using existing ground-, air-, or space-based hardware, this new plant-based technology ultimately could reduce the risk to troops now tasked with maintaining traditional hardware-based sensors in contested areas.

Many of the researchers working with BTO are not used to thinking about their work in the context of national security. "DARPA has awakened the agriculture and horticulture communities to opportunities that didn't used to exist," Bextine said. "Now that we've made these connections to the defense and intelligence worlds, I'm excited to see what else biologists can contribute."

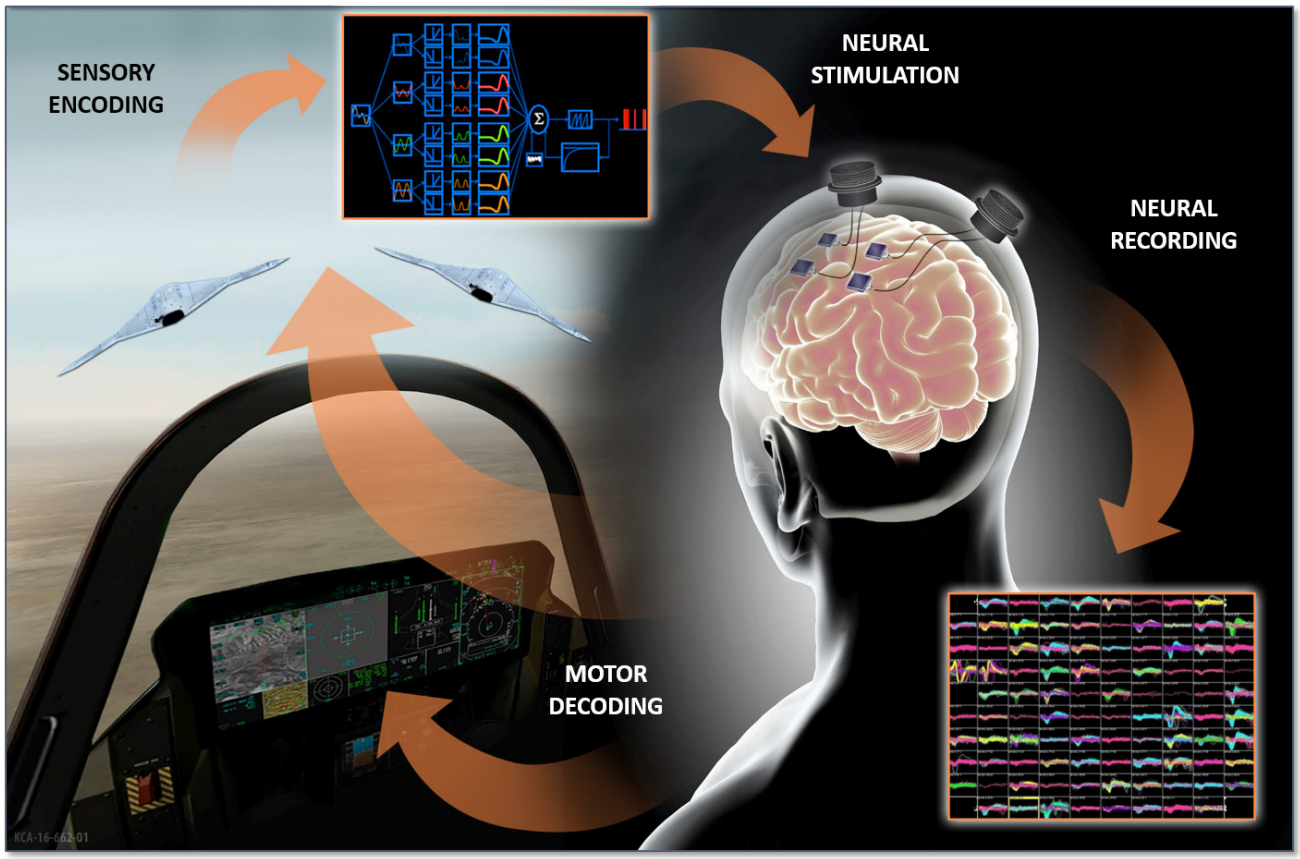
BTO is putting similar concepts to work in the maritime domain.

"Projecting power and maintaining awareness in the oceans has always been critical for national security, but the vast scale and harsh environment is an endless source of challenges," said Dr. Lori Adornato, a chemist and ocean scientist who joined DARPA in 2017. "Biology presents new opportunities for DOD to achieve better results with fewer resources."

Adornato launched the Persistent Aquatic Living Sensors program this year with the vision of tapping into the natural sensing capabilities of marine organisms to help detect, track, and monitor adversary submarines, unmanned underwater vehicles, and divers. In true DARPA form, her concept takes signals once considered background noise and transforms them into a new sensing modality.

"Sonar operators on submarines often hear shrimp and other organisms become active when vessels pass by, and they've worked for years to minimize those signals. DARPA asked, 'Well, can't we use those signals to our advantage?'," Adornato explained.

In other domains where DOD operates, it is human biology that could come into play. Service members already control complex military systems in stressful circumstances, and, in the future, the pace and complexity



As the pace and complexity of modern combat increases, warfighters require new tools to help them stay meaningfully engaged. BTO continues to demonstrate new capabilities for intuitively interfacing with complex systems. For example, emerging technologies such as noninvasive neural interfaces could, in the future, allow pilots to control groups of unmanned aircraft by delivering high-level commands and maintaining oversight while the systems adjust to rapidly changing conditions to complete the mission.

of missions will only increase as more semi-autonomous systems come online. BTO is developing technologies that can help personnel operate more collaboratively and intuitively with these systems and make informed decisions at tactically relevant speeds.

Building on a rich history of DARPA-funded breakthroughs, performers supporting BTO's brain research portfolio are delivering increasingly sophisticated tools and methods to allow a person's brain to communicate with external devices [see "Taking Neurotechnology into New Territory"]. DARPA has demonstrated direct neural control of a robotic limb, restoration of touch sensation to a paralyzed patient, improvement in short-term memory, and acceleration of training times.

These previews of the power of neurotechnology have mostly involved surgically implanted devices, and so far, they have been directed at restoring functionality to individuals who have suffered the effects of injury or illness. It will take additional breakthroughs to move neurotechnology into a form factor that makes it widely applicable to DOD operations, including for tactical mission execution and strategic planning.

Dr. Al Emondi, a neuroscientist and electrical engineer, joined BTO last year to take on this challenge. "Our No.1 goal is to develop communications links to the brain that do not require surgery," Emondi said. "A high-performance, noninvasive neural interface would open up possibilities such as immersive training, new forms of interaction with AI systems, improved situational awareness and intelligence analysis, and distributed task management with machines to speed tactical decision-making and free up cognitive function for strategic planning. It's a potentially foundational technology for the next generation of DOD systems."

Building Partnerships, Controlling Risk, and Maximizing Benefit

For advanced biotechnology systems like neural interfaces and gene editors, the path from demonstrating a capability to the end user is neither simple nor direct. BTO structures its programs to systematically reduce various forms of risk to ease that transition. From facilitating regulatory review to attracting additional investment to initiating dialogue on potential legal and ethical concerns, BTO program managers shepherd their technologies to a point where they can thrive after DARPA's involvement ends.

Ethically, DARPA's leadership and program managers understand that any technology can be used for good or ill. Whether it's nuclear energy or the internet, a capability developed for one purpose may easily be put to another in a way that ultimately affects society as a whole. DARPA expects that biological technologies especially will permeate many aspects of both the national security and commercial worlds. In anticipation of future use of the tools and capabilities it develops, BTO emphasizes transparency,

PHOTO BY TAD BROWNING, U.S. ARMY OPERATIONAL TEST COMMAND TEST AND DOCUMENTATION TEAM

Programs such as Biological Control, Biostasis, BRICS, ElectRx, HAPTIX, and Neural Engineering System Design lay the foundations for powerful new capabilities to preserve troop health, facilitate recovery, and restore function.

data-sharing, and publication of results, and initiates critical discussions concerning the ethical, legal, and social implications (ELSI) of active and proposed research.

At all stages of BTO programs, including initial development of program concepts, program managers consult with independent, unpaid ELSI advisors to assess potential concerns, provide feedback on proposed research plans and results as they become available, and participate in program meetings with researchers. In addition, these advisors help to share DARPA ideas with the larger research community so that others may join the dialogue on technologies that could find broad application.

Operating at the frontiers of science and technology means that BTO and its research partners are among the first to confront the implications of new capabilities, and often there is no clear guidance on how to address concerns. Because it's not an option to stay away from those spaces, as BTO explores this *terra incognita*, it tries to lead by example regarding how to incorporate ethical norms into the research.

Practically, BTO forms interagency partnerships early in the program life cycle to ensure that technology development follows a path that is relevant to regulators and potential end users. Organizations such as the Environmental Protection Agency, the Food and Drug Administration, and the Department of Agriculture lend expertise on drugs, medical devices, and technologies involving plants and animals. Those interactions provide valuable guidance on how to facilitate regulatory review, while the Defense Threat Reduction Agency and the Biomedical Advanced Research and Development Authority provide tangible pathways for moving BTO-developed technologies into operational test and evaluation.

Beyond these intragovernmental relationships, BTO needs the help of companies, universities, venture capitalists, and entrepreneurs to refine technologies and move innovations to service members, patients, and consumers. Because many biotechnologies are so new, despite promising early results, it may still be several years before a mature product is ready for direct integration into DOD operations. In the meantime, the timing could be ripe for a commercial venture to invest additional research and development funds into a consumer application. BTO aims to engage with potential commercial transition partners at the earliest possible opportunities in the technology development cycle to inform early research and increase the chances of creating a product that can move beyond the lab bench.

Looking Over the Horizon

Future BTO programs and focus areas will continue to more closely integrate biotechnology and national security. Through its exploratory investments and technology demonstrations, BTO seeks to establish new and more powerful technical foundations for a wide array of critical DOD missions and challenges. BTO cannot succeed alone, though. The collaborations that have been formed to date will only become more important as engineered biology reveals its full potential, and BTO looks forward to engaging the military services, integrating with the defense-industrial complex and commercial industry, and deepening its connections with non-DOD agencies to scale up the use of biological solutions.

DARPA has opened the door to a vast new range of opportunities for the Department of Defense. It needs to seize the moment, consider missions in the new context of what is becoming possible with biology, and work with collaborators to develop capabilities that used to exist only in science fiction.

After all, biology adapts to thrive, and any system that evolves can become a source of surprise. DARPA and the DOD finally have the tools to work with biology and to harness that potential.

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