The Intelligent and Connected Bio-Labs of the Future:

Promise and Peril in the Fourth Industrial Revolution

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SUMMARY

A vast array of technologies are rapidly developing and converging to fundamentally change how research is performed, and who is able to perform it. Gene editing, DNA synthesis, artificial intelligence, automation, cloud-computing, and others are all contributing to the growing intelligence and connectivity of laboratories. It is currently possible to perform a growing number of research tasks automatically and remotely with a few clicks of the mouse. And with the barriers of entry to synthetic biology tools like CRISPR decreasing, they will no doubt be subject to automation as well, and may even be coupled with artificial intelligence to optimize the power of genetic engineering. While this may be a boon for the development of novel vaccines and therapeutics by parties that have traditionally not had access to the necessary tools, it also opens the risk of nefarious use to engineer or edit biological agents or toxins. While there have been attempts at governance to limit the avenues by which a bad actor may gain access to the pathogens or tools to create biological weapons, the ever-increasing pace of innovation has left gaps that may be exploited. Fortunately, investment in technologies such as artificial intelligence and sequencing may also function as the best defense against the growing threat of misuse of biological agents.

THE LANDSCAPE OF EMERGING AND CONVERGING TECHNOLOGIES

We are currently living in the Fourth Industrial Revolution, an age that builds upon the digital revolution with a global surge in big data capacities and uses. This new industrial era seeks to merge the physical and the digital, and laboratories are no exception. Technological advances in genomics, synthetic biology, artificial intelligence, automation and cloud-computing- all hallmarks of the Fourth Industrial Revolution- are increasingly converging and enabling each other. As a result, the biological lab of the future will be one that is more intelligent and connected than ever before, its machines requiring less tacit knowledge for use and analysis. In effect, we will continue to see techniques such as genetic engineering become more easily available to those with less or no formal biology training. In this context, it is crucial to assess how these emerging and converging technologies will drastically impact the tools of biological laboratories, and their dual-use potential to lead both to societal benefits and new vulnerabilities.

Genome-Editing Technologies: The technology known as CRISPR/Cas has generated headlines from top peer-reviewed journals and popular magazines alike for its ability to powerfully edit DNA. While the ability to do this isn't a new one, it has never been faster or easier. The technology functions through the use of an enzyme called Cas9, which uses a guide RNA sequence to know its DNA target, and then edits the DNA by changing, adding, or deleting sequences. This ease has led the technology to already escape the lab, as companies currently sell kits targeted towards use in homes, and middle schools are using the technology in their science classes.[1] These kits, for only $150, let you edit a bacterial gene using instructions made for those without expertise in little more than a weekend.[2] Functionally, CRISPR has been studied for uses ranging from more efficiently engineering crops to editing diseases out of the genome.[3] Further developments in gene drives, which use CRISPR to spread a genetic change through a sexually-reproducing population, will provide yet another avenue to affect change on genomes, but will no doubt increase the already expansive legal and ethical debates.

DNA Assembly, Synthesis and Printing: To affect change, we cannot simply read genomes: we must also be able to synthetize, or write, them. Advances in synthetic biology have done just that, allowing us to create genes and organisms from their DNA building blocks more easily than ever before. Companies like Gingko Bioworks have established entire businesses on engineering organisms and their parts for a myriad of functions. While many applications in their current portfolio focus on industrial use (better smelling perfumes, new sweeteners, etc.), they have shown the desire and capacity to expand into health. A $15 million partnership with DARPA has the vision of providing probiotics to soldiers as protection against a variety of stomach bugs and illnesses.[4] Other emerging companies such as Twist Bioscience can create and deliver a synthetic gene from a sequence uploaded by a researcher in a matter of days.

And beyond generating whole organisms or genes for you, a multitude of other companies sell oligonucleotides (oligos), short strands of DNA that can be used to assemble genes, for very cheap. While these oligos are generally utilized on their own, they can be designed and ordered to fit together like puzzle pieces, allowing for much more complex genes (and even organisms) to be built. And instead of needing to go through a company to order oligos or genes, benchtop tools are available that create them in a matter of hours. Oligonucleotide synthesizers have been around for decades through companies such as Beckman-Coulter and Applied Biosystems, and continue to be subject to increasing automation and decreasing price. But because oligonucleotides take additional steps to assemble into larger genes, a newly developed tool will allow you to simply enter a DNA sequence and "print" a gene on demand. Synthetic Genomes Inc has created a Digital-to-Biological Converter (DBC), which functions as the world's first "DNA printer" that can create a physical gene which functions just like one from your body.[5] Since its recent introduction, the DBC has already assembled a striking portfolio of printed molecules and organisms: DNA, RNA, viruses, vaccines, and even a bacteria with over 400 genes.[6] More and more companies are expected to enter this space in the coming years.

Portable Genomics Sequencers: In 2003, a technological and human revolution in how we understand our health was born. The announcement of the completed human genome brought with it many promises for the understanding and treatment of disease. Unfortunately, the initial cost of sequencing the genome was nearly $3 billion, and even years later the price was out of reach for most labs.[7] Even with eventual price drops, the machines were hardly portable. Even the smallest sequencer made by industry giant Illumina requires space close to that of a microwave. But with the innovation of Oxford Nanopore, a U.K. based company, were constraints of cost and size reduced. Based on nanopore technology, a new method of sequencing that involves measuring current changes caused by DNA, their sequencers have signaled the start of a new revolution.[8] Their latest product, the MinION, is small enough to fit in a pocket and functions simply by plugging into the USB port of a computer.[9] The MinION has already been deployed to find new frog species deep in the jungle, detect pathogens on food before an outbreak occurs, and even to study DNA on the International Space Station. It has proved its worth in detecting Ebola and Zika outbreaks in real-time, a far cry from the lengthy time-to-action during the initial Ebola outbreak of 2014. With further decreases in price and level of preparation required, stated goals of Oxford Nanopore, this technology will soon reach community bio-labs (and even our homes) as another indispensable tool.[10]

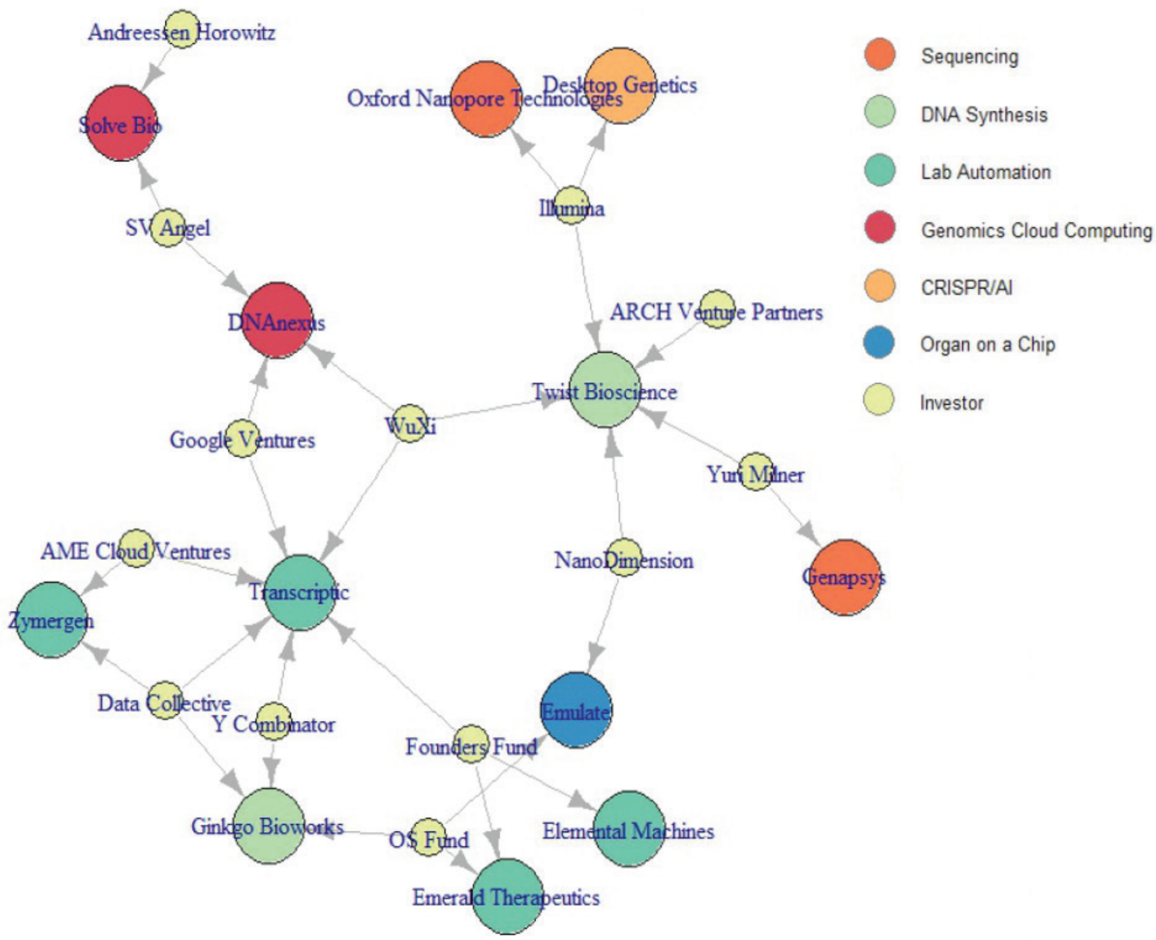
Artificial Intelligence to Manage Biological Complexity: What if humans were no longer required to perform the analysis, writing, and editing of DNA? Advances in artificial intelligence (AI) mean that these tasks are within reach of automated computers and machines. AI will help manage the complexity of engineering bio-organisms by synthetizing new knowledge in real-time and creating efficient organism engineering workflows, allowing us to push the limits of how we optimize human and non-human biologies. In analyzing DNA, large strides continue to be made through the abilities of machine learning to handle the enormous volume of data generated during sequencing. Machine learning involves utilizing machines that can teach themselves through pattern recognition, allowing for powerful analysis and response that humans do not need to program in beforehand. It could soon act as a potentially powerful approach to automated triaging of unknown biological samples. A small number of labs are already working on automated analysis pipelines to detect signatures of engineering but such work is in its infancy and poorly funded. Other work has combined DNA and machine learning to predict genes most important to particular functions, a task with implications on how a particular disease occurs or how a newly-discovered virus has high transmissibility.[11] Artificial intelligence will continue to be applied to answer a growing number of biological questions and will help us make sense of, and engineer, the biological world.

Autonomous Systems/Robots in Cloud Labs: Our increased computational power isn't simply changing how we analyze genomes, it is altering how we actually perform experiments. In laboratories across almost all universities, tasks are completed through physical work of a researcher. For instance, a student may need to transfer miniscule volumes of DNA or separate proteins on a gel to see results. But soon, much of this work will be given to machines. Companies such as Transcriptic and Emerald Therapeutics are showing that lab work can be increasingly automated, improving efficiency and reproducibility at the same time.[12, 13] After sending samples to one of these companies, a simple click of your mouse sends tasks through the cloud. On the other end, the company's robots receive and automatically begin any of the over 40 tasks that they are capable of performing.[14] With the ability to run 24/7 and without worker intervention, these cloud labs may both raise the productivity of research programs and open the tools up to an increasing number of citizens. But as with other technologies, decreasing size and price have brought this automation physically into many labs. Soon, it may no longer be necessary to even ship samples across the country, but instead load them into a machine in your local community lab and start an entire workflow.

Lab-on-a-chip Technologies and Microfluidics: Technologies referred to as "Lab-on-a-Chip" (LOC) devices are designed to perform any number of different tasks, saving a researcher from manual manipulation. Advances in microfabrication and microfluidics have resulted in devices that can manipulate DNA molecules and liquids alike, bringing many processes into the automated world. While the field is still newly emerging, the breadth of functions of these technologies are already staggering. Companies apply LOC towards disease and pathogen detection, blood typing, and even sequencing preparation.[15] For example, the VolTRAX system from Oxford Nanopore, automatically prepares DNA to be sequenced, and may soon require only a drop of blood for a complete sequencing workflow.[16] And the near future promises a greater variety of automated tasks. Work to democratize the development and use of LOC technologies has been announced by a group at MIT Media Lab and has the potential to illuminate novel ideas across the globe.[17]

Investing in the Fourth Industrial Revolution

Perhaps unsurprisingly, many of the technologies encompassing the Fourth Industrial Revolution have seen investment surges in recent years. The synthetic biology industry received over $1 billion in investments across hundreds of companies in 2016.[18] Artificial intelligence has likewise seen a boom, with AI-centric companies reportedly receiving in excess of $5 billion in investments in 2016.[19] An examination of some emergent companies with technologies contributing to the growing intelligence and connectedness of biological labs shows investment from Silicon Valley leads the charge, though other hubs such as Boston and Shanghai are not shying away. Interestingly, some investment firms appear to place bets on one technology in particular, such as Founder's Fund's heavy backing of robotic cloud labs, while others are diversifying their investments, such as Illumina and OS Fund.



Investment in the Fourth Industrial Revolution. *Money is heavily flowing to companies providing technologies that are either directly or indirectly contributing to the growing intelligence and interconnectedness of biological laboratories, and the subsequent lowering of barriers to entry in performing biological engineering. Investment and innovation both are strongest in Silicon Valley, but the Fourth Industrial Revolution truly is a global effort on both ends.*

GOVERNING THE LAB OF THE FUTURE

The emerging technologies that are making biology and genomics more powerful and intelligent have the potential to revolutionize disease monitoring, prevention, and treatment for infectious and chronic diseases alike. At the same time, the possibilities for misuse in such an inexpensive and effective way have never been greater. Automation and artificial intelligence coupled with lowered barriers of entry to biotechnology experimentation mean that biological toxins and even entire genomes of pathogens are within reach of being made over the internet. Unfortunately, many of the historical policies aimed at preventing the use of biological technologies for nefarious use are quickly growing obsolete with advances in new technologies that now accomplish previously difficult tasks with relative ease. Yet, as the second genomics revolution is quickly dawning, few new governance and regulatory initiatives have been implemented to confront the security issues posed by the increasingly intelligent and connected emerging technologies. Of those that have been enacted, the rapid pace of technological development means that gaps have already formed and may be used to get around attempts to limit misuse.

Biological Weapons Convention: Going into effect on March 26, 1975, the Biological Weapons Convention (BWC) aimed to ban the development, production, and stockpiling of weapons derived from biological agents. The 178 current parties to the treaty affirm their commitment to diverting any biological weapons research to peaceful research, and must not "encourage or induce anyone else to acquire or retain biological weapons".[20] Since initial ratification, review conferences have sought to discuss the implications of emerging technologies such as bio-engineering and automation on access to and use of biological weapons. Unfortunately, this has not resulted in new guidance on behalf of the signatory states. Additionally, a lack of compliance has been confirmed or suspected in multiple cases, bringing into question the global adherence to the treaty.[21] And further, the emerging technologies highlighted above mean that access to the tools needed to create potential bioweapons are no longer maintained only with well-funded government or academic programs- a non-state group or rogue actor may be just as dangerous.

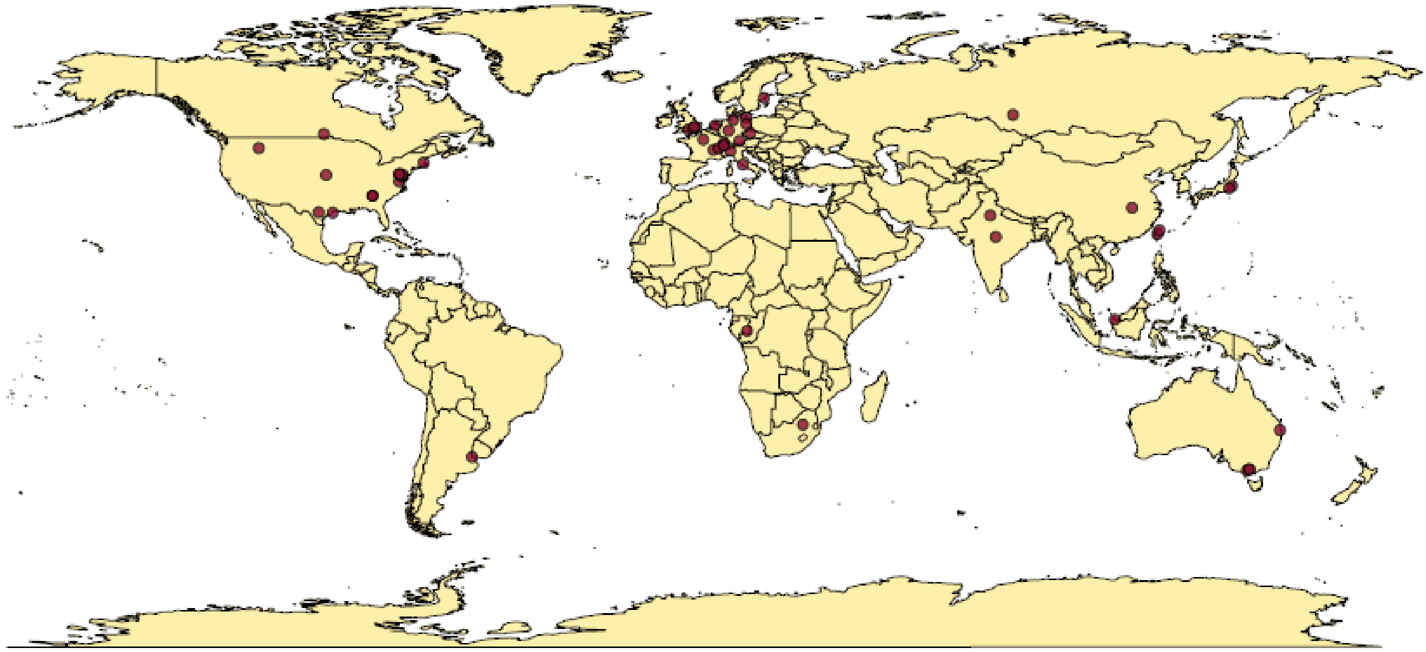
Australia Working Group: Designed to provide export controls for chemical and biological weapons, the Australia Working Group (AG) is an informal group composed of a subset of signers of the BWC. The AG conducts yearly meetings to provide guidance over toxins, pathogens, and laboratory equipment in which the member countries should take extra precaution when exporting in order to decrease the risk of proliferation from a rogue state or actor. Of note in the Common Control List Handbook is an extensive list of known pathogens and toxins, but focus is also directed to DNA synthesizers, calling for controls on machines that can generate DNA strands over 1.5 kilobases with an error rate of less than 5%.[22] With many DNA sequences publicly available, though, the genetic recipes of pathogens previously required to be kept under lock-and-key in BSL4 labs are just a few clicks away. Further, advances in one-step methods to "glue" together multiple strands of DNA now mean one can easily stitch together a gene from many pieces. And the advent of communities like LabX, which sell and auction used lab equipment suggests that someone may even be able to order a machine with little oversight and monitoring of who the recipient is in the first place.

International Gene Synthesis Consortium: Following guidance issued from the US Department of Health and Human Services in 2010 entitled "Screening Framework Guidance for Providers of Synthetic Double-stranded DNA", the International Gene Synthesis Consortium (IGSC) was formed. The IGSC is composed of many of the world's leading DNA synthesis companies. Combined, these companies represent a global spread and account for over 80% of the world's DNA synthesis. Functionally, the Consortium provides biosecurity screening through a two-pronged approach. The first involves screening of the DNA sequence to be synthesized through consultation of both federal and international known-pathogen and toxin lists. Customers are also screened against government lists curated from the Office of Foreign Assets Control, the Department of State, the Bureau of Industry and Security, and others. If the sequence has high similarity to a known pathogen, or if the customer is flagged by one of the lists, the member companies must take actions ranging from obtaining more information to cancelling the order and alerting authorities, depending on the severity.[23] But recently, the ability of a researcher to re-create the horsepox virus using standard synthetic biology tools stirred concern in the community. At the time, it cost $100,000 and took 6 months, all using DNA fragments designed from genomic data that is publicly and freely available and purchased through GeneArt, a German synthesis company now part of Thermo-Fisher.[24] Further, with an absence of oligonucleotide order screening amongst the industry, there still exist penetrable gaps through the ability to connect them together to form larger genes or even entire genomes.

EXAMINING OUR VULNERABILITIES

A Growing Accessibility

Unlike when the BWC and other initial governance aimed at biological attack was formulated, the greatest threat may no longer be a biological agent escaping a BSL-4 laboratory. Instead the potential for peril is increasingly accessible and global. While the remaining strains of smallpox are only believed to be stored at 2 highly-secured BSL-4 labs (one in the United States and one in Russia), the complete genetic sequence is available to anyone with internet access. While the process to bring the virus 'to life' may currently take technical know-how, it will not always remain this way. The reconstitution of horsepox proves that this feat is currently possible given when performed by experimentally capable actors, but the global number of capable actors is increasing at a staggering rate due to technological advances.



Global BSL4 Capability. *Red dots indicate a laboratory with BSL-4 (or the local equivalent) capability. Increasingly, the threat is not a biological agent leaving one of these laboratories, but instead an agent being engineered using publicly available sequences, synthetic biology tools, and automated and intelligent processes. This is greatly increasingly who has access to dangerous toxins and agents for malicious use.*

Taking Note of the Threat

The potential of new biotechnologies to become weaponized has not escaped the notice of the US Intelligence Community. Their 2016 Worldwide Threat Assessment noted:

> *"Research in genome editing conducted by countries with different regulatory or ethical standards than those of Western countries probably increases the risk of the creation of potentially harmful biological agents or products. Given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications."*[27]

Further, the President's Council of Advisors on Science and Technology (PCAST) noted in a 2016 report of the potential for intentional misuse of technology developments such as CRISPR. PCAST notes that "a pathogen might be deliberately modified to affect its spread or be resistant to current preparedness and response capabilities".[28] Yet, while these reports work to show the acknowledged threat posed by genome editing and synthetic biology, they fail to acknowledge the increased risks and decreased timeframe posed by the convergence of biology with other emerging technologies. The bioterrorism events we have seen in the past largely relied on the weaponization of known pathogens such as anthrax or glanders that were taken from laboratories or hospitals.[29] As many of these agents have been studied in the context of response to an attack, we have readied responses for them. The United States, for instance, keeps a Strategic National Stockpile housing vast quantities of an anthrax vaccine.[30] With the convergence of synthetic biology with artificial intelligence, though, we may be unable to mount such a rapid response. Soon, a pathogen may be engineered to evade current vaccines and therapies, causing an event intended to reach WMD potential.

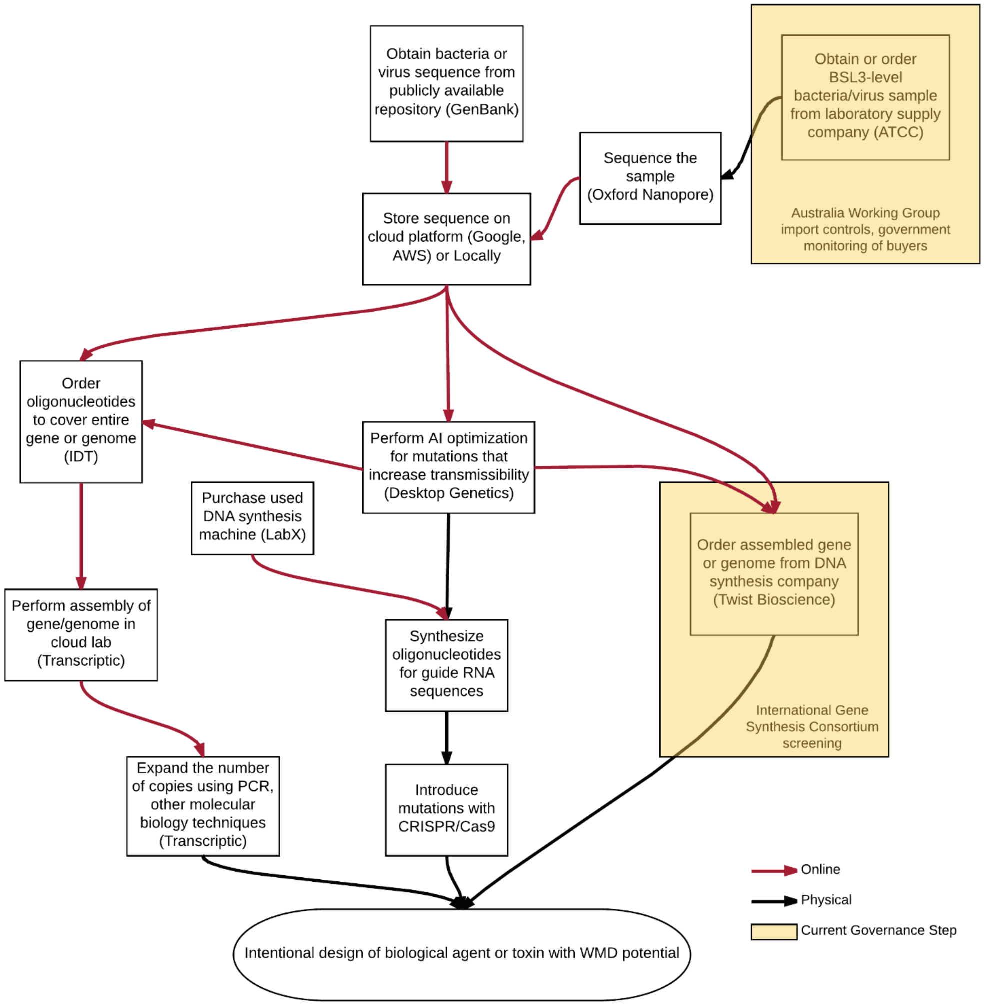
Exploiting the Gaps

While the technologies that are emerging and converging to form more intelligent and connected labs have great promise, they do indeed also have great risk. The combination of synthetic biology with AI and automation, all of which are becoming more pervasive, means that tools traditionally siloed in academic and government labs are slowly becoming accessible to a wider audience. Indeed, the technologies are already nearly in place for an actor to co-opt synthetic biology tools to re-create a biological agent or a toxin, and largely accomplish this in a hands-free manner.

- **Scenario 1:** DNA synthesis companies largely lack screening systems for oligonucleotide orders, and with relatively little work, multiple oligos can be combined to form larger genes and sequences. Further, a forged partnership between Integrated Data Technologies (IDT) and Transcriptic means that oligos ordered from IDT can be sent directly to Transcriptic, saving the user from needing to produce a physical address showing they are affiliated with a university or company. Once the synthesized oligos arrive at Transcriptic, the process to combine them is fully automated through Transcriptic's automation infrastructure and user-generated instructions sent through the Cloud. And further capabilities in Transcriptic's cloud lab allow for the automated reproduction of the combined sequence using polymerase chain reaction (PCR), which can exponentially increase the number of copies of the created gene. With increased experimental options coming soon that will allow for work with bacterial cells, it will soon be possible to clone the harmful genes into a harmless bacterial vector to produce the toxin of interest autonomously. Currently, the synthesized gene can be shipped to the actor, who may then choose to produce the toxin using commercially available bacteria and few other reagents and tools.

- **Scenario 2:** By purchasing a used DNA synthesis machine online for less than $10,000, an actor may wield the power to engineer biological agents without the need to order pre-assembled oligos or genes from a vendor. While this machine could be used to assemble much larger genes or even genomes, a much faster way to engineer a sufficiently dangerous agent would be to synthesize short guide RNA sequences. When coupled with the easily available Cas9 enzyme, an actor could edit a virus or bacteria to be more pathogenic using the CRISPR system. In possibly only a few edits, a pathogen could be made to be more virulent or transmissible. The bird flu virus H7N9, for instance, appears to require only 3 mutations to gain the functionality of easily spreading among human populations. In a virus that already causes a death rate exceeding 40%, it is easy to imagine that an engineered form of H7N9 would cause havoc across the healthcare system and the economy. And shortly, AI advances may allow anyone to sequence the genome of an obtained virus or bacteria, and determine edits that may optimize a number of dangerous traits.

Both of these examples function to show avenues that may be exploited to avoid current governance roadblocks and create a pathogen or toxin with WMD potential. More sobering, they are inspired by events and research that have occurred, such as the recent synthesis of horsepox and studies of H7N9. With both examples, the costs are exceedingly low and could easily be affordable by a small group or even a lone-wolf actor seeking to do harm. With increasingly advanced bioinformatics tools along with automated and cloud-connected lab capabilities, one may not even need much tacit knowledge of biological experimentation to obtain an agent capable of widespread incapacitation and even death, nor would they need to handle the agent extensively before deployment. While it would currently be much easier to procure a reconstituted organism or toxin through its available genetic sequence than edit it to make it more virulent, the barriers to edit genes and genomes are steadily decreasing. With other advances forthcoming, current governance surrounding the access to and sales of biological agents and technologies could be easily circumvented.



Exploiting the gaps. *Given advances in DNA synthesis techniques and the advent of robotic cloud laboratories, one may find ways to circumvent current governance barriers. Example companies to complete each step are listed in parenthesis.*

POLICY RECOMMENDATIONS

The rapid emergence and convergence of autonomous systems, artificial intelligence, and cloud computing has greatly intensified the dual-use problem long associated with biology. To avoid stifling innovation, yet protect against the possibility of harmful use, we propose a series of recommendations across the governance landscape:

- While oligonucleotide orders are difficult to monitor, some governance steps could be taken to limit their potential dual use. Perhaps most easily accomplished, the U.S. government should urge oligonucleotide companies to monitor their customers using similar databases as the IGSC. Providing legitimacy for their customers, both domestically and globally, may work to limit easy access to non-trusted actors. To realize this, the U.S. government or a multi-state entity such as the Australia Working Group, could take steps to enact a database that acts as a repository for ordered oligo sequences. In this, the danger posed by splitting oligo orders across multiple companies to avoid suspicion, will be mitigated. Artificial intelligence could possibly be employed in this database, in order to more quickly assess if ordered oligos fit together to form more malicious genes.

- Guidance should be put in place for companies that provide laboratory services through the cloud. The ability to complete biological experiments remotely without any physical handling may have great impacts on biomedical research, especially for productivity and reproducibility, but may also work to provide an avenue that could be exploited for ill-intent. Currently, it is unclear if any standards exist across cloud lab companies to ensure that access to their systems are controlled and monitored for malicious use. In this, we propose that these companies add steps to discern the intent of their customers, including examination of the affiliation and experimental purpose of the user.
- The U.S. Congress should request a study into the growing connectedness of genomics technologies, artificial intelligence, automation, and others. By engaging academia, government, military, and private companies whose work is contributing to the future of biological labs in these areas, we may raise conversation into a topic that is providing an ever-increasing threat of malicious use. Such interdisciplinary dialogue will function to elucidate our preparedness to handle an engineered biological attack, including our ability to prevent, detect, and respond to an engineered pathogenic threat.
- While the barriers to obtain biological agents are much lower than those to obtain weapons-grade nuclear materials, spending on biodefense still remains slightly lower than that dedicated to protection from nuclear weapons.[32] The entities of Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) should seek to boost funds for research into better identifying and characterizing genetically engineered biological weapons. Using current capabilities and available resources, it may be possible to detect genetically engineered organisms, but would likely take substantial time (weeks).[33] This long

	Biological	Nuclear
Cost to Obtain	+/++	++++
Technical Complexity	+	+++
Military/Civil Dual-Use Potential	+++	+++
Destructive Potential	+++	+++
Monitoring Difficulty	+++	++

Note: + = Low, ++ = Medium, +++ = High, ++++ = Very High length of time may even be increased when continued advances in genomics and biotechnologies are coupled with unprepared detection capabilities. In the event of an intentional biological attack, this is far too long of a period to detect and assess. Possible avenues include research grants for artificial intelligence projects examining better methods to characterize unknown biological agents, or the provision of a means of on-the-go DNA sequencing to be widely distributed across both the US global military presence and the homeland.

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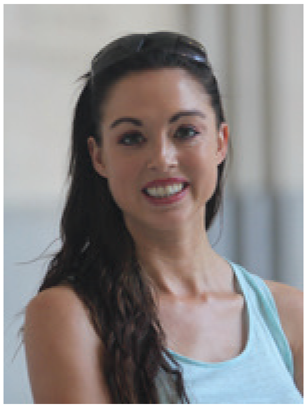

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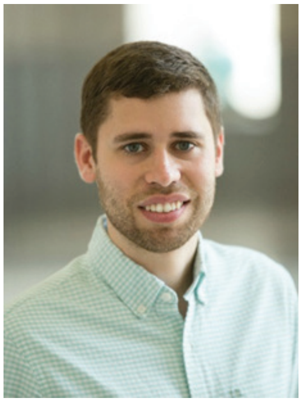

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