Spiez CONVERGENCE

Report on the fifth conference
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Spiez CONVERGENCE 2022 was the fifth edition of this Swiss conference series that has recently been listed as a relevant initiative under the new Swiss strategy for arms control and disarmament. Spiez Laboratory hosted the event as an in-person conference again, after the fourth edition had to be conducted virtually. Ten days before the conference, participants had the opportunity to partake in a virtual “ice-breaker” event with two keynote presentations explaining the objectives of the conference series.

Switzerland was particularly delighted, that Ambassador Fernando Arias, Director-General from the Organisation for the Prohibition of Chemical Weapons (OPCW) opened this year’s conference.

As in the past, the conference discussed new developments in science and technology and how they may affect the regimes governing the prohibition of chemical and biological weapons. The 2022 conference looked at developments in Manufacturing Chemicals, in Expanding and Exploring the Chemical Space, in Building and Engineering Biological Systems – Toward a Bioeconomy, in Material Science and in Medical Devices, which are all summarised below.

Three presentations discussed advances that apply to the manufacturing of chemicals – Peptide Synthesis, developing orally available Peptides and using Coordination Cages.

Peptides fit size-wise between small and large molecules. Because of their remarkable properties and their ability to bind with high specificity to challenging targets, peptides are investigated for medical treatments. About 200 peptide therapeutics are currently in advanced stages of clinical development. Traditional manufacturing techniques include liquid phase peptide synthesis (LPPS), solid phase peptide synthesis (SPPS), and recombinant technologies. Although the toolbox is constantly increasing, the production processes show low overall performance. New methods for peptide manufacturing focus on improving synthesis as well as the purification steps and on reducing the environmental impact. From an arms control perspective, peptides that reach the blood stream and act systemically may have potential as novel chemical agents.
Orally Available Peptides are convenient for patients and for dosing and have various applications, but they must be sufficiently stable and be able to be resorbed in the gastrointestinal track. Bicyclic peptides have been found to be stable enough and they show high binding affinity. One method to discover high-affinity bicyclic peptides is phage display. If bicyclic peptides should be systemically available outside the gastrointestinal track, they must be able to cross the gastrointestinal epithelium, which they not readily do. In order to identify suitable cyclic peptides, large numbers of possible candidates are screened at nanoscale using combinatorial synthesis (3,840 cyclic peptides in a single experiment).

Coordination Cages are three-dimensional chemical structures that self-assemble in solution from metal ions and organic ligands and behave like “molecular flasks”, which selectively host “guest” molecules. Cages can be designed to optimise chemical reactions. They can be applied to increase the stability of intermediates and final products as well as the yield of a reaction or facilitate the purification of a desired product. Their unique properties enable chemical reactions that are difficult to implement otherwise. Coordination Cages may also offer opportunities for medical treatment or the protection against toxic chemicals.

In order to Expand and Explore the Chemical Space, Machine Learning (ML) and Artificial Intelligence (AI) have become important tools for the discovery of new chemicals with desired properties. In contrast to classical computer programming approaches, ML and AI deduct information from example data to make predictions. Molecules that are expected to meet a set of performance criteria are identified by virtual screening of libraries or by utilising de novo design algorithms. Algorithms can assemble de novo molecules based on large libraries with bioactive molecules and then compare the new structures to existing molecules.

Algorithms can also be used for Synthesis Planning in order to compute a synthetic pathway and propose precursors and reactions. An ML model is in development that should eventually contain information on 11 million established chemical reactions and their underlying rules. In a blinded test, the quality of two alternative synthetic routes, one developed by chemists and one proposed by a computer, could not be distinguished by the chemist assessing them. Certain limitations remain, e.g., the models need to be improved and their reliability is currently hard to assess, but in the coming years ML will become a routine tool for synthesis planning. From an arms control perspective, this may lead to synthesis methods for chemical weapons agents with new reactions or different precursors. While the chemistry community seems aware of these risks, the AI community seems not.

Under the overarching theme Building and Engineering Biological Systems – Toward a Bioeconomy the conference discussed topics related to Bacteriophages, Design of Artificial Organelles and Cells, Accurate Prediction of Protein Structure, de novo Design of Proteins and Era of Biological Technology.
**Bacteriophages** are viruses that target bacteria. They are not directly harmful to humans and abundant in the environment, and they are investigated in response to drug-resistant pathogens. Phages attach to specific receptors on the bacterial cell wall or the outer membrane and can therefore be used to target particular bacterial species. However, to combat multiple pathogenic bacterial species, “cocktails” of phages are required. In order to enhance the killing efficiency against bacteria, CRISPR-Cas3 targeted to cut specific DNA sequences, can be introduced. Issues to be further investigated include the pharmacokinetics for different administration routes of phages, the immune response and the benefits of using personalised phage cocktails versus a fixed cocktail composition. New developments will increase the efficacy of phage therapy as an alternative or complement to antibiotics. From an arms control perspective, phages could also be designed to cause harmful effects in humans.

**Artificial organelles** are made from polymers that self-assemble and that can take various forms to mimic cellular functions. Their compartments can be loaded with DNA strands, antibodies, encapsulate enzymes, etc. Thus, they can be designed to mimic or improve a biological process that additionally can be activated and deactivated by a trigger. Self-organised clusters of artificial organelles were constructed for the design of nanotheranostics, which integrate a diagnostic and a therapeutic function into one system. Artificial cells can be engineered to respond to stimuli, perform enzymatic reactions or trigger ion channel activity. Many challenges remain but the field is progressing towards applications such as cellular implants and molecular factories.

Once the 3D structure of a protein is known, its biological processes can be better understood. Today, the structures of only about 0.5% of known proteins are solved experimentally. Information about protein structure is contained in evolution history, in correlated mutations from multiple sequence alignments (MSA) of protein sequences. The residues that mutate together, are likely to make contact in 3D space. Algorithms are used to *Predict Protein Structures* based on large numbers of MSAs and combine this technology with AI tools that are similar to image processing and image prediction from text. AlphaFold and RoseTTAFold are two models available today that predict 3D protein structures with remarkable accuracy.

**De novo designed proteins** that exhibit desired functionality may have a range of practical applications as enzymes and small molecule binders, as assemblies and protein mini-binders or as new materials and even molecular machines. An AI method called “deep network hallucination” works well for image recognition, but it can also be applied to *de novo* protein design. Deep network hallucination can reliably predict structures of proteins of which the sequence is unrelated to any found in protein structure databases. Some of these structures have been experimentally confirmed. A SARS-CoV-2 receptor trap has also been designed utilising this method.
Synthetic biology is becoming a platform technology with applications that will affect various fields of everyday life. It is seen as strategically relevant by some countries and investment in a bioeconomy has become a matter of global competition in a new Era of Biological Technology. The combination of synthetic biology with AI and ML leads from understanding biology to designing biology. Combining it with process automation makes new biomedical applications and new bioengineered materials possible. Integrated cloud labs and biofoundries automate and accelerate the design cycle for synthetic biology construction. Biofoundries will also train the next generation of biodesign engineers. Such biofoundries have a dual use potential and international initiatives, such as The Global Biofoundries Alliance, aim to develop a governance system. From an arms control perspective, the construction of synthetic organisms enabled by the increasing global availability of low-cost synthetic DNA raises biosecurity concerns. Some private sector suppliers are self-regulating, but they cannot screen for unknowns. Because synthetic DNA is not traceable, edited, designed or naturally evolved genomes cannot be distinguished. This also applies to an accidental or a deliberate release of genetic material. If industry partners join efforts, commercial aspects of proprietary DNA designs could be addressed by encryption. There is still little discussion of dual use issues in early-stage synthetic biology start-ups, which creates challenges for developing effective (self)controls.

The synthetic biology community develops methods within Material Science to grow new materials that have properties which were programmed in DNA. An example is the use of bacteria to convert sugar into bacterial cellulose (BC), which can be functionalised with proteins. With a genetic toolkit, bacteria were engineered to grow BC in 2D sheets as well as into 3D shapes. A number of tools exist today to grow materials and fabrics with designed properties or desired shapes. Combining bacteria with yeast in symbiotic cell cultures allows to grow material with enzymatic properties. The research community for “Engineered living material” is growing fast. From an arms control perspective, materials are important for enhancing protection against chemical or biological agents.

Advances in Medical Devices and technology for the delivery or application of substances have an arms control perspective and this conference looked at Microarray Patches and at Electro Genetics.

Microarray patches (MAPs) have been selected as top priority for the delivery of vaccines as part of The Vaccine Innovation Prioritisation Strategy (VIPS) by the WHO, the Bill & Melinda Gates Foundation (BMGF) and UNICEF. MAPs eliminate the requirement for needles and syringes and they can be used for self-application of vaccines as a press on, a band aid or with an application device. MAPs contain microscopic needle-like projections that are solid, dissolving or hollow, which perforate the stratum corneum to deliver a payload into the skin. Because a vaccine can be applied to MAPs in a dried formulation, the requirements for a cold-chain are reduced, which significantly lowers costs, improves logistics and supports mass-scale distribution in a pandemic.
The field of Electro Genetics looks at the integration of the human body into the internet-of-things and develops respective interfaces. In one project for the development of opto-genetics, green light activates engineered cells implanted into a test animal to produce a protein, which diffuses through a membrane into the bloodstream. Another project focused on diabetes therapy using engineered human Electro-β cells that could secrete insulin in response to high blood glucose or an electrical current. The cells were able to release insulin after sensing a higher glucose concentration in a mouse model. A piezo push button combined with a membrane that holds engineered cells was then developed to make the system independent from an external power source. When pushed, the piezo element produces a voltage peak, which opens the Ca channel in the cells prompting the release of insulin. Insulin release could also be triggered through popular music, applying low-bass frequencies of about 50 Hz as external stimuli. To remove the requirement for an external stimuli altogether, a blood-glucose metabolic fuel cell was developed to supply opto- or electro-genetically stimulated cell implants with power.

Implications and Conclusions were discussed during guided group sessions and the final policy discussion. During the conference it was emphasised that the current geopolitical situation negatively affects access and exchange between scientists.

One year ago, during Spiez CONVERGENCE 2021, a presentation demonstrated the power of AI for discovering new toxic chemicals. The resulting publication Dual use of artificial-intelligence-powered drug discovery had a strong media impact worldwide. Subsequently, a second publication A teachable moment for dual-use discussed more broadly the implication for the AI community as well as for the scientific community.

The technologies for Machine Learning and Artificial Intelligence are close to becoming Game Changers; they may profoundly affect the regimes prohibiting chemical and biological weapons. The combination of AI with synthetic biology, automation and robotics, Big Data, high-throughput synthesis and screening, leads to a context shift in how experiments are performed.

Many of the reviewed advances in science and technology may provide new countermeasures and protection against chemical and biological weapons as well as new methods of verification of compliance.

Spiez CONVERGENCE 2022 showed that Governments have identified bio-engineering as a strategic capability that may help to solve many of today’s pressing problems. Countries are investing vast amounts of money, looking for technological and economic control and political influence. For industry, biotechnology has become an important growth market that will provide solutions to societal demands. For scientists, the drivers remain curiosity and a desire to push the frontiers of science.
Raising awareness about the dual use problem still requires sustained engagement with the science community, as well as with funders and investors. This holds true despite the efforts of the synthetic biology community, to teach ethics and dual use concepts, and the release of guidance documents from international organisations and others on ethical conduct.

It is important to recognise that the (common) perception about a limited military utility of CB weapons may no longer be shared by all. Concerns of the arms control community about utilising scientific advances for chemical or biological weapons may have to focus on states and less on terrorists or lone actors. This recognition is important with regards to the large strategic investment into a bioeconomy. The results will inherently contain also some misuse potential. That all states will resist the temptation is in today’s geopolitical climate not obvious and a challenge for the future.

Many discussions in the arms control communities are stuck in the past and no longer reflect the emerging misuse potential. The same applies to the verification system of the CWC and the compliance assurance mechanism of the BWC, which were designed for past weapons programmes. It is therefore important to also strengthen non-treaty mechanisms by embedding dual use ethics with scientists, they are the first line of defence. This can be done without hindering research or slowing down innovation.

As in previous conferences, Spiez CONVERGENCE 2022 has again demonstrated how important cross-community conversations between policy experts and practitioners from the worlds of science, technology and industry are. The next opportunity at Spiez will be during the sixth Spiez CONVERGENCE, in September 2024.
Spiez CONVERGENCE 2022 was the fifth in a conference series on convergence in chemistry and biology hosted by Spiez Laboratory. This series started in 2014 when Switzerland, following up on a recommendation of the OPCW Scientific Advisory Board (SAB), decided to provide a platform for discussing new developments in science and technology and how they may affect the regimes governing the prohibition of chemical and biological weapons. It facilitates well-informed conversations between different stakeholders from academia, industry and arms control. Spiez CONVERGENCE also plays an important role in pursuing the new Swiss Arms Control and Disarmament Strategy 2022–25.

Spiez CONVERGENCE is testimony to the long and productive partnership between Spiez Laboratory – inter alia one of the OPCW’s Designated Laboratories – and the OPCW. Director-General Arias attended the opening session of the conference and stressed that whilst the norm against chemical weapons remained strong, it was important to strengthen the trust in the OPCW. Monitoring and evaluating advances in science and technology was an essential task (to keep abreast of its developments relevant to the CWC). The SAB had already provided advice on the inclusion of new Schedule 1 chemicals of the Convention, and was working on issues such as artificial intelligence and aerosolised CNS acting chemicals. Scientific advice is essential for the effective functioning of the Convention, and the Fifth Review Conference in May 2023 is an opportunity to ensure that the OPCW can take advantage of as well as manage the impact of advances in science and technology.

As in the past, the conference focused on identifying trends and better understanding of the implications of emerging science and technology capabilities for the Chemical Weapons Convention (CWC) and the Biological Weapons Convention (BWC). It did not, however, attempt to formulate policy recommendations, draw up warning lists of risky technologies, or bless new technologies.

Not all participants and speakers from academia and industry are familiar with the CWC and the BWC. Ten days before the opening of the conference at Spiez, participants were given the opportunity to partake in a virtual “ice-breaker” event. Jonathan Forman from the Pacific Northwest National Laboratory and Filippa Lentzos from the King’s College London explained the two treaties and the objectives of the conference series in two keynote presentations.
Previous conferences have covered a wide array of themes. Amongst many other subjects, participants discussed how the growing chemical space is being explored to discover new molecules with interesting properties, the development and improvement of tools such as combinatorial synthesis and screening, CRISPR Cas, DNA origami, machine learning and artificial intelligence, evolving methods such as 3D printing and manufacturing in cloud laboratories, and new chemical and biological materials as well as applications of existing materials such as information storage using DNA.

Furthermore, participants talked about scientific advances, exchanged views to understand the state of maturity of new technologies, and identified drivers and constraints that steer current and future directions of research and development. They looked at opportunities as well as roadblocks and how they affect practical applications and global distributions. And they debated how all that might affect chemical and biological arms control.

This can take different forms: the discovery of new substances with advanced properties may increase the potential for new types of chemical or biological agents, but it also may lead to new treatments and protections against the effects of such weapons; new methods of manufacturing may change the implementation environment of the two Conventions, challenging existing practices of national implementation or verification, but at the same time offer new tools for treaty implementation. Changes may be incremental, requiring regular monitoring, evaluation and perhaps adapting certain implementation practices, or they may be non-linear, involving paradigm shifts and calling for rethinking of some of the fundamentals of how the norms have been framed and are being applied.

This report attempts to bring together the trends and findings presented and discussed at Spiez CONVERGENCE 2022.
Chemical manufacturing is a mature industry. Its current main drivers include sustainability and aim at reducing environmental footprints, increasing efficacy of manufacturing processes and product performance and decreasing manufacturing costs. As a result, manufacturing processes change, new chemicals are being synthesised, and well-known chemicals find new applications.

Peptide Synthesis

Peptides occupy the space between small molecules e.g. amino acids and large biologicals such as proteins and DNA. They display remarkable properties that can be adjusted by altering their sequence and which are exploited in medical treatments. Peptides can show high affinity and can potentially bind to challenging targets. They are highly target specific, and can bind to targets that small molecules may not be able to bind to. Some 200 therapeutics are currently in advanced stages of clinical development. Of particular interest are peptides with longer amino acids sequences, with aggregation tendencies, cyclic peptides, peptides with non-natural amino acids, and different conjugates. Peptides that act fast and in low dosage, and that meet regulatory requirements and expectations with regard to a smaller environmental impact, are in particular demand.

Traditional manufacturing techniques – liquid phase peptide synthesis (LPPS), solid phase peptide synthesis (SPPS), and recombinant technologies – have long lead times and high costs. Although the chemical toolbox for LPPS and SPPS is constantly increasing, there is as yet no catalytical synthesis process. Both technologies continue to suffer from low overall performance, mediocre throughput, modest productivity, poor environmental footprint, high purification demands to comply with regulatory requirements, and limitations with regard to upscaling.

The ACS Green Chemistry Industry Pharmaceutical Roundtable has called for innovation towards convergent hybrid synthesis, greener solvent choices, improvements in resins and recycling, more robust and effective coupling agents, unprotected peptide ligation to generate short peptide fragments, synthesis in flow processes, greener separation techniques and overall, a reduction in the amount of material used per unit of product. There are also calls to move away entirely from certain legacy chemicals such as resins, coupling agents, or the use of Fmoc as protecting groups (the peptide chain is assembled stepwise, one amino acid at a time, while attached to an insoluble resin, which allows to remove the reaction by-products at each step).
New and better manufacturing processes involve tag-assisted LPPS which uses soluble tags that can reduce the need for excess reagent amounts. Tag-assisted LPPS can also significantly reduce solvent use. Another emerging technology – flow synthesis – uses heated activation loops and flow reactors. It provides rapid access to small as well as large peptides. Greener separation technologies use organic nanofiltration and membrane-based reactor systems. Standard methods of peptide isolation and purification such as high-pressure liquid chromatography (HPLC) are often a bottleneck in the manufacturing process and result in poor environmental performance. Modern extraction strategies can increase overall mass efficiency by a factor of ten compared to classical processes. Late-stage functionalisation provides access to highly complex peptides. In a recent case study, computational models were used to accurately design de novo certain membrane-traversing structures – experiments confirmed their ability to permeate membranes in vitro and their bioavailability in vivo.

Peptides that reach the blood stream and act systemically are potentially problematic from an arms control perspective – some may have potential as novel chemical agents.

Take-home points

- Peptides fit in size between small molecules and large ones such as proteins.
- Because of their remarkable properties and ability to bind with high specificity to challenging targets they are investigated for medical treatments. About 200 therapeutics are currently in advanced stages of clinical development.
- Traditional manufacturing techniques include liquid phase peptide synthesis (LPPS), solid phase peptide synthesis (SPPS), and recombinant technologies. Although the chemical toolbox is constantly increasing, the technologies continue to suffer from low overall performance.
- New methods for peptide manufacturing focus on improving the synthesis as well as the purification steps and on reducing the environmental footprint of the entire process.
- Peptides that reach the blood stream and act systemically are potentially problematic from an arms control perspective – some may have potential as novel chemical agents.
Orally available Peptides

Two techniques for the discovery and development of orally available peptides for therapeutic purposes are bicyclic peptides developed by phage display, and combinatorial synthesis and screening of cyclic peptides at nanoscale.

Making peptides orally available allows for needle-free application and is convenient for patients. It also enables better dosing, in particular during repetitive application. But orally applied drugs need to overcome several hurdles: proteases and low pH in the stomach, proteases in the small intestine, the crossing of the gastrointestinal epithelium, and metabolism in the liver. Bicyclic peptides have properties that make them resist these challenges. They show high binding affinity and stability.

One method of identifying them is phage display, which involves the selection of peptides with disulphide bonds in key positions from a peptide library using phages, ring closure using 1,3,5-tribromobenzene to create a library of bicyclic structures, binding to immobilised antigen and washing-away of the non-binders, and identification of the binding peptides. The first phage-selected bicyclic peptide reported in 2009 was PK15. It blocks human plasma kallikrein (hPK), a plasma hydrolase that plays a role in different diseases including hereditary angioedema (HAE). Experiments confirm that such bicyclic structures show a much stronger inhibition than the corresponding monocyclic or linear peptides, explained by the structural fit with the target and a large binding interface. Bicyclic peptides cover a wide range of possible targets, three are undergoing clinical trials at the moment.

Phage display technology can also be used to discover protease-resistant peptides. A linker-constrained peptide library is exposed to gastrointestinal proteases such as Pancreatin and then the peptides undergo affinity selection. The methodology has been used to target coagulation factor Xa which plays a role in thrombosis. A number of peptides were synthesised and their half-life was measured in simulated intestinal fluid. Structure elucidation shows that the peptide binds to the catalytic domain of the coagulation factor.

Animal experiments confirm that these peptides remain intact in the gastrointestinal tract, and that oral availability is good. Potential future applications could include the treatment of inflammatory diseases, the control of bacteria or exotoxins, and perhaps colon cancer treatments.

Bicyclic peptides, however, do not easily cross membranes. Key factors that influence membrane permeability are molecular weight, polar surface area and the number of hydrogen bonds.
Combinatorial synthesis and screening at nanoscale offer a way to identify cyclic peptides that can be made available systemically, or to screen the inhibition of protein-protein interactions. Using microwell plates, large libraries of appropriate cyclic peptides can be synthesised and screened in a single experiment without purification. A pilot-scale library of 1,176 cyclic peptides was so created, followed by larger libraries (8,988 peptides each) for screening of tissue kallikrein 5 and thrombin inhibition. Even larger numbers were achieved with 1536-well microwell plates using acoustic droplet ejection. Synthesis and assay are conducted on the same plate by turning the microplate up-side down after the successive ejection of the two reactants, and after reaction completion, target and substrate are added through an array of micropipettes. This allows for the synthesis and screening of 3,840 cyclic peptides in a single experiment.

With combinatorial methods, the time for synthesis of linear peptides, combinatorial synthesis of cyclic peptides and screening can be drastically shortened (1–2 days each); however, hit validation requires still weeks of experimental work.

Take-home points

- Orally available peptides are convenient for patients and enable better dosing, but must be able to pass through the gastrointestinal system to reach their target.
- Potential future applications could include the treatment of inflammatory diseases, the control of bacteria or exotoxins, and perhaps colon cancer treatments.
- Bicyclic peptides have been found to have the required properties and show high binding affinity and stability.
- Bicyclic peptides can be produced by phage display: selection of peptides from a library using phages, followed by ring closure of the peptides, binding to an antigen, and washing away the non-binders.
- Bicyclic peptides do not readily cross membranes.
- Combinatorial synthesis and screening at nanoscale are used to identify cyclic peptides that can cross membranes to become available systemically, and to study the inhibition of protein-protein interactions (3,840 cyclic peptides in a single experiment).
Coordination Cages

Coordination Cages are three-dimensional structures that self-assemble in solution from metal ions and organic ligands. They could be described as "molecular flasks". Because of their geometry, they can "host" other chemicals depending on their molecular size, charge and structure, and modulate their chemical reactivity. They can also be used as carriers for molecules in phase transfer reactions and in porous liquids.

Cages can be used for catalysis. For example, an enantiopure water-soluble [Fe₄L₆] cage has been shown to catalyse the hydrolysis of Dichlorvos, an organophosphate insecticide that is used as a chemical warfare agent simulant. Cages can also be used to perform chemical reactions that are selective with regard to size or shape of the product, or to increase the stability of intermediates and final products by shielding them from the external environment. Furthermore, chemical reaction pathways can be modulated by stabilising intermediates that would not be stable in solution, or by trapping reactive intermediates that would otherwise form unwanted side products. This can significantly increase the yield of chemical reactions and increase product purity.

Coordination cages may also be deployed to purify high-value compounds using the constraints they impose on guest molecules. They can act as molecular carriers across phase boundaries, enabling phase transfer reactions. Other examples include extractions or purification processes using crystalline cages or films. Recent developments include the construction of what has been called porous liquids – systems that combine the properties of liquids with the ability of cages to internalise other chemicals.

The unique properties of coordination cages can be used to enable chemical reactions that are difficult to perform otherwise. They can also be deployed to carry chemicals across barriers or to detoxify toxic chemicals. This creates opportunities for medical treatments, protection against toxic chemicals or decontamination.

Take-home points

- Coordination Cages are three-dimensional structures that self-assemble in solution from metal ions and organic ligands and behave like "molecular flasks".
- Cages can be designed to selectively optimise chemical reactions, to increase the stability of intermediates and final products and to significantly increase yield and increase product purity.
- The unique properties of coordination cages enable chemical reactions that are difficult to perform otherwise.
- They offer opportunities for medical treatment and protection against toxic chemicals.
Machine learning (ML) and artificial intelligence (AI) have become popular themes in current discussions. Previous Spiez CONVERGENCE meetings have highlighted the potential they have for the discovery of new molecules with predetermined properties, and of synthetic strategies to make them. The OPCW’s SAB reviewed the growing potential of AI and its relevance for the operation of the CWC, in preparation of the next Review Conference in May 2023.

Classical programming approaches are linear concepts limited by the knowledge of instructions, problem complexity, lack of data and other factors. ML/AI instead use example data and algorithms to induce instructions to make predictions. It uses pattern recognition rather than attempts to deploy ab initio theory to come to results.

Evolution of the chemical space

Property predictions, molecular design, ML force fields together with ML4Simulations, and synthesis planning have all benefited from open-source codes, cloud computing and access to big data. Along with these technical advances, mindsets and organisational processes shifted to include ML in Research and Development. Process automation and high-throughput testing have led to a new approach to chemicals discovery – a design cycle that links design, synthesis and testing into a loop. This aims at creating multi-property profiles, expanding the chemical space and making it easier to navigate and exploit.

Design profiles can map properties in relation to desired performance criteria to identify target chemicals. Virtual screening or de novo design algorithms identify molecules that are expected to meet a set of performance criteria.
Until recently, it was difficult to navigate this chemical space. However, generative models can now learn to generate reasonable molecules. One concept involves parametrisation with a recurrent neural network, the Simplified Molecular Input Line Entry System (SMILES), to represent molecular structures, and training on large molecular databases. The algorithm learns to generate molecules based on established training data (e.g., the ChEMBL database of one million bioactive molecules). It then generates new structures that will be compared to existing structures in the training set. De novo molecular designs are benchmarked using GuacaMol – or General & Unbiased Assessment of Construction Algorithms for Molecules.

Generative models can assemble de novo molecules atom by atom, or as a synthetic tree that picks reactants and predicts chemical reactions. Modern algorithms can perform multi-parameter optimisation better and faster (for example, not only focusing on toxicity but also including properties that affect synthesisability, stability, or susceptibility to medical countermeasures). Scoring of novel designs remains a challenge and the set-up of such algorithms is still an art.

Take-home points

• Machine Learning (ML) and Artificial Intelligence (AI) can support the discovery of new chemicals with predefined properties as well as the chemical methods to synthesise them, as pointed out in previous Spiez CONVERGENCE conferences.

• Different to classical programming approaches that are based on linear concepts, ML/AI induce instructions to make predictions using example data and algorithms.

• A new approach for the discovery of chemicals links design, synthesis and testing into a loop to create multi-property profiles.

• Molecules, with a set of performance criteria, are picked in computer-aided workflows using high-throughput screening, virtual screening of libraries, or unrestricted de novo design algorithms.

• Algorithms can assemble de novo molecules based on large libraries with bioactive molecules and then compare the new structures to existing molecules.
Synthesis Planning

Similar to satellite navigation systems, one can imagine algorithms that compute a synthetic pathway towards a target or intermediate molecule and propose possible precursors and reactions. Such an algorithm would use a module performing retrosynthetic analysis, an efficient search algorithm, stop criteria (building blocks for the pathway), and ranking criteria.

Synthetic chemistry by machines cannot, however, be achieved by simply cataloguing basic principles of synthesis; it requires a touch of artistry (Corey: *The logic of chemical synthesis*, 1968). This began to change when rule-based expert systems were proposed. These are deeply rooted in the language of chemists, albeit at a price: rules have to be written by hand and reactivity conflicts and selectivity have to be encoded explicitly. Furthermore, the mechanism and scope of many reactions are not well understood; purification, solubility and stability are ignored; and there is no inherent ranking mechanism.

As the amount of chemical reaction data continues to grow exponentially, a Learn Simulator of Organic Chemistry from Data has been proposed. It would initially learn off-line using a batch of experimental data and then expand this to all available data. Such a system would need to learn the rules, predict likely disconnects, filter for feasible reactions and enable efficient searches. Building it would require the incorporation of the data of the entire discipline of chemical synthesis: 11 million known reactions, each containing implicit knowledge. The underlying rules could be extracted automatically from the reactions to create classification labels. Retrosynthetic disconnection predictions would generate multi-class labels, and deep neural networks could extract the most probable reaction rules for a given intermediate or product.

There are challenges to all the above, but efficient search for results optimisation is probably the most demanding. A recent study compared a heuristic Breadth-first search (BFS) with two neural network searches including a Monte Carlo tree search (MCTS). All search modules were trained with data that had been acquired before 2015, and applied to 500 random molecules first reported thereafter. Neural networks by far outperformed the heuristic search, both with regard to time required and percentage of problems solved.

The search results quality was assessed in a double-blinded test involving 45 PhD students and postdocs. They compared two alternative synthetic routes, one developed by chemists and one proposed by computer. Statistical analysis showed that the quality of the two approaches could not be distinguished.
ML is today a core part of computer aided synthesis planning and offers alternative approaches for reactions and retrosynthesis. There remain certain limitations: reaction models are far from perfect, reaction conditions and experimental success are hard to predict, and production scale-up remains a challenge. Some of these issues may be resolved with more data, and by combining ML synthesis planning with automated high-throughput experimentation and robo-chemistry. AI can search through millions of synthetic routes and precursors, create ideas that competent chemists can build on, and generate analogues.

In the coming years, synthesis planning, reaction optimisation and the generation of new molecules by ML will become routine. New targets with new binding sites will be identified, atomistic simulations will become more accurate and algorithms will get better at extrapolations (proposing new pathways and molecules outside the scope of training data). Progress, however, remains evolutionary and human experience will still be needed.

These advances may lead to hitherto unchecked synthetic pathways to CW agents using uncontrolled precursors. At the same time, however, they create opportunities for regulators to apply different checks. The chemistry community is aware of the risks, to a degree – the AI community, it was suggested, is not. Risks may also emerge from the spread of self-drive laboratories and robo-chemistry.

Take-home points

- Similar to satellite navigation systems for vehicles, algorithms could be used for synthesis planning to compute a conceivable synthetic pathway and propose precursors and reactions.
- A Learn Simulator of Organic Chemistry from Data has been proposed. It should contain the information of 11 million known reactions and their underlying rules.
- There are still many challenges to overcome but an efficient search tool that allows the optimisation of results seems to be the most demanding.
- In a double-blinded test involving 45 PhD students and postdocs, the quality of two alternative synthetic routes, one developed by chemists and one proposed by computer, could not be distinguished.
- Certain limitations remain, but in the coming years, ML will become a routine tool for synthesis planning.
- This may lead to novel synthesis methods for CW agents. It seems, the chemistry community is aware of the risks, the AI community is not.
Engineering and recoding biological organisms to perform desired functions, constructing artificial systems that mimic the function of living cells, engineering biological units that perform non-biological roles such as acting as logic gates – all these avenues have been pursued for some time.

There have been concerns that along this path new types of harmful biological agents might be engineered. On the other hand, such technologies can help develop new treatments, enhance human performance, or manufacture novel materials in ways that are effective, environmentally sustainable, and cheap.

Bacteriophage Cocktails

The development of bacteriophage cocktails through screening and genetic engineering combined with high-throughput automation was discussed.

Bacteriophages are viruses that selectively kill bacteria. They are ubiquitous in the environment and not directly harmful to humans. The widespread appearance of multi-drug resistant pathogens and associated mortality highlight the need for alternatives to antibiotics. Phages are one possible alternative.

Phages recognise specific receptors on the bacterial cell wall or outer membrane and attach to them. They harness the bacterial replication machinery to replicate themselves. Due to their high specificity, phages can be used to precisely remove bacterial infections without affecting the rest of a complex microbial community. To broaden the useful spectrum of a therapy, phage cocktails can be designed, that target more strains of the same species.

Phage therapy has been used since the 1920s. After the discovery and subsequent mass production of Penicillin, however, investment in phage therapy dropped significantly. As interest is again increasing, safety and efficacy of phage therapy are being considered more thoroughly. To this end, high-throughput phage discovery platforms are being deployed to identify bacteriophages and rapidly develop them into pure, well-characterised phages. Phages are being collected globally to ensure broad wildlife diversity. They are isolated with high-throughput liquid handlers, amplified, and characterised with respect to their efficiency against clinically relevant bacterial isolates. The process is organised in “waves” to rapidly identify desirable characteristics and optimise the phage cocktails.
Phage cocktails can be further enhanced by combining them with CRISPR-Cas3. This combines two species-specific killing mechanisms (DNA cleavage and lysis by phages). Such enhanced cocktails have been shown to increase efficacy by 100 to 1000 times over wild-type phages \textit{in vitro} and in small animal models, and over standard-of-care antibiotics in small animal models.

Further developments aim at better controlled, randomised clinical trials, a better understanding of phage delivery (pharmacokinetics for different administration routes, immune response), regulatory clarity (use of personalised phage cocktails versus fixed cocktail composition) and better companion diagnostics to optimise the cocktail mix to the pathogen(s) to be treated. Standardisation and quality control, too, need to be addressed. A deeper understanding of phage biology will enable predictive modelling through phage genome annotations, a better understanding of determinants of host ranges and corresponding improvements of host range predictions based on genetics, a better understanding of interactions between phages, and between them and antibiotics.

All these developments will increase the efficacy of phage therapy as an alternative or complement to antibiotics. At the same time, they could also lead to the development of phages that express a toxic or otherwise harmful gene, or that confer antibiotic resistance to harmful bacteria, or to target bacteria that are used in industrial processes or agriculture.

**Take-home points**

- Bacteriophages are viruses that selectively kill bacteria, they are harmless to humans and abundant in the environment and they are investigated as response to drug-resistant pathogens.

- Phages attach to specific receptors on the bacterial cell wall or outer membrane and can be used to treat bacterial infections. In order to target multiple pathogenic bacterial species, phage cocktails have to be used.

- To ensure a broad diversity of phages, they are collected globally, isolated, amplified and characterised for efficacy against clinically relevant bacterial isolates.

- In order to enhance species-specific killing mechanisms of phage cocktails, they are combined with CRISPR-Cas3, a DNA cleavage mechanism.

- A range of issues need to be further investigated, including the pharmacokinetics for different administration routes of phages, the immune response or the benefits of using personalised phage cocktails versus fixed cocktail composition.

- New developments will increase the efficacy of phage therapy as an alternative or complement to antibiotics.

- Phages that express a toxic or otherwise harmful genes or that target the native microbiota, or bacteria used in industrial processes or agriculture, may also become possible.
Design of artificial Organelles and Cells

A number of motivations drive the development of artificial organelles or cells, including the production of diagnostics, the search for new biologically active compounds/systems with improved activity (lower effective dose), and the need to find global solutions for a growing population as well as the desire to optimise treatment conditions for each individual.

Artificial organelles or clusters mimic or improve cell functions. Building blocks for such constructs can be made from polymers that self-assemble. They can be modified to perform specific biological functions. Bio-hybrid compartments can be interfaced and loaded with catalysts, and other functionalities such as DNA or antibodies can be attached to these vesicles. For example: amphiphilic copolymers with a central hydrophobic part and two external hydrophilic parts can form polymersomes (structures similar to liposomes), freestanding films, micelles or nanotubes. Their membrane permeability and mechanical properties can be tuned; they can be functionalised (biotin, fluorescent dyes, antibodies). Such bio-hybrid compartments have several advantages: they show full activity of the encapsulated enzymes, protect them and the substrates from the external environment, can be activated and deactivated by triggers such as a change in pH, functionalised to allow targeting, and immobilised on solid supports for diagnostic assays or treatments.

An example of their possible application is the mitigation of oxidative stress. Biological antioxidants all suffer from low bioavailability. To overcome this limitation, polymersomes with antioxidant functions have been synthesised. These artificial peroxisomes contain enzymes that detoxify both superoxide radicals and hydrogen peroxide (H₂O₂). Several formulations have been successfully tested in a Zebrafish embryo model to demonstrate that artificial organelles are non-toxic, biocompatible and functional in vivo.

A further step was the construction of self-organised clusters of artificial organelles. Practical applications could include the development of nanotheranostics for the treatment of arteriosclerosis by linking a therapeutic compartment with a fluorescent signalling compartment to spatially image the therapeutic effect. The clusters can be functionalised to produce dopamine that triggers the expression of the SEAP (a reporter gene), and enable imaging for precise location.

Next came the construction of artificial cells with a synthetic or natural cell membrane. Such constructs can be engineered to respond to stimuli, perform enzymatic reactions, and trigger ion channel recruitment. This allows imaging, controlled substrate release, and stimulation of, for example, the formation of F-actin, which is essential for the shape of eukaryotic cells.
Artificial cells can also be constructed from donor cells. Giant plasma membrane vesicles (GPMVs) can be supplemented with artificial organelles, resulting in a multicompartment architecture with artificial sub-compartments. These sub-compartments can be loaded with enzymes to catalyse reactions of interest. An example is the incorporation of artificial organelles that produce resorufin, which detoxifies H$_2$O$_2$ to mitigate oxidative stress.

In short, artificial organelles can be used to produce desired compounds or detoxify harmful radicals in vivo. Artificial cells can perform both signalling and controlling functions, and allow the analysis and production of desired compounds or nano-assemblies. Many challenges remain (encapsulation, biodegradability, efficiency in vivo, location targeting and scale up), but the field is progressing towards applications such as cellular implants and molecular factories.

**Take-home points**

- Artificial organelles are made from polymers that self-assemble and can take various forms to mimic or improve cell functions.
- Their compartments can be loaded with catalysts, DNA, antibodies, enzymes, etc., to obtain a certain functionality in order to mimic or improve a biological behaviour/function, which can be activated and deactivated by a trigger.
- Artificial organelles can be used to produce desired compounds or to detoxify harmful radicals in vivo.
- Enzyme-containing polymersomes that detoxify superoxide radicals and H$_2$O$_2$ have been synthesised for the treatment of oxidative stress.
- Self-organised clusters of artificial organelles were constructed for the design of nanotheranostics, integrating a diagnostic and therapeutic function into one system.
- Artificial cells were constructed with a synthetic or natural cell membrane that can be engineered to respond to stimuli, perform enzymatic reactions or trigger ion channel activity.
- Artificial cells can perform both signalling and controlling functions, and allow the analysis and production of desired compounds or nano-assemblies.
- Many challenges remain but the field is progressing towards applications such as cellular implants and molecular factories.
Accurate Prediction of Protein Structure

Proteins are essential components of life, involved in transport, signalling, metabolism, the immune system and more. Understanding protein structure helps to better understand biological processes as well as design drugs, vaccines and biosensors. Today, the structures of only about 0.5% of known proteins are solved experimentally. Computational predictions can help in closing this gap.

Structural information can be extracted from evolution history, by identifying correlating mutations. Coevolution modelling finds correlated mutations from multiple sequence alignments (MSA). Such alignments are likely to make contact in 3D space, which can be used to predict structure. This requires large numbers of sequence alignments.

AI can help solving the problem of contact prediction given its strength in pattern recognition. An initial approach – extracting structural information from MSA, 2D coevolution models to refine contacts and improve distance prediction, initial model building, and refinement of the initial structural model with classical methods – is similar to AI image recognition. This approach has its limits and does not reach the quality of experimental structure elucidation. Moving from MSA to interactions between residues, an iterative approach was developed to extract structural information from MSA and refine contact signal and distance prediction using 2D convolution networks. Then followed the use of attention-based networks, somewhat similar to image generation from text using inductive bias. Finally, structure representation changed from 2D distance/orientation maps to 3D atomic coordinates, using an AI structure generator.

AlphaFold and RoseTTAFold are two models available today to predict 3D protein structures with remarkable accuracy. AlphaFold and RoseTTAFold are two models available today to predict 3D protein structures with remarkable accuracy. AlphaFold is an attention-based end-to-end model. So is RoseTTAFold, with tighter connection of the 1D, 2D and 3D information. These AI models are specifically developed for protein structure prediction and come close to experimental quality. They allow the prediction of protein-protein interactions (PPI) and of the structure of protein-protein complexes. Such in silico predictions have been experimentally validated in yeast. Going beyond PPI screening, the models can be used for disease related PPI modelling leading to structure-based drug discovery. Another field is protein design via “inpainting” of structural information into partial protein structures. This uses neural networks to complete the amino acid sequence, and RoseTTAFold to generate the completed 3D structure. In this way, a PD1/PD-L1 binding inhibitor (PD1 is an important target in cancer immunotherapy) was designed by removing the non-interface aspects and inpainted to create an anti-cancer drug. RoseTTAFold is being improved further to increase efficiency and accuracy, and to extend its application to nucleic acid structure predictions.
AI deployment for predicting and changing protein structures has been called a game changer. But there remain important challenges: in single sequence-based protein prediction, can AI learn/understand physical principles and can it reliably design proteins *de novo*? Can AI help better understand causes of disease and enable protein engineering by accurate prediction of mutation effects? Can it be developed toward multi-state modelling? Can it be developed to model the interaction of proteins with other molecules (antigen-antibody, host-pathogen where there was no coevolution, post translational modifications, protein interactions with small molecules or nucleic acids)?

**Take-home points**

- Knowing the structure of a protein helps to understand its biological functions.
- Coevolution data contains structural information of proteins in correlated mutations from multiple sequence alignments (MSA).
- MSAs can be used by algorithms to predict protein structures and the technique has been further developed utilising AI tools that are similar to image processing and image prediction from text.
- AI deployment for predicting and changing protein structures has been called a game changer, and AlphaFold and RoseTTAFold are two programs available today that predict 3D protein structures with remarkable accuracy.
**De novo** Design of Proteins

One major question was if *de novo* protein structure prediction is accurate for proteins that are in no database and do not have any homologs. Such proteins may have a range of practical applications, from enzymes and small molecule binders to assemblies and protein mini-binders, to new materials and even molecular machines.

There is a large space of natural proteins, and *de novo* design can exponentially expand this space for all possible proteins. An AI method called *deep network hallucination* aids in the *de novo* structure prediction. Network hallucination inserts a step between the structure prediction network and the module creating a sharp distance map. In this way, a blurry distance map is created first and looped back into the neural network for sequence optimisation. This loop can be passed multiple times, to refine the output.

This approach works well for image recognition, but it can also be applied to protein design. Starting with a random amino acid sequence, the system output can be tweaked to direct the emerging protein structure toward proteins with desired features. Deep neural network hallucination has been shown to be very creative in generating diverse random protein structures, and some generated structures have been confirmed experimentally.

This approach offers a way to design functional proteins alternative to inpainting (see above *Accurate Prediction of Protein Structure*). Both techniques use predefined structure motifs as design targets. Using network hallucination, a SARS-CoV-2 receptor trap has been designed. Other designs included cobalt binding proteins as well as protein binding proteins. Accessibility is no longer a barrier for a wider application of protein design. The pipeline exists, understanding the underlying theoretical concepts, however, is still lacking.

One of these challenges is the application of AI for the *de novo* design of proteins. Such proteins may have a range of practical applications, from enzymes and small molecule binders to assemblies and protein mini-binders, to new materials and even molecular machines.

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**Take-home points**

- An AI method called *deep network hallucination* can be used to *de novo* predict protein structures.
- This AI method contains algorithms for sequence optimisation and can design proteins with specific features.
- Some structures generated by *deep network hallucination* have been experimentally confirmed, and a SARS-CoV-2 receptor trap has been designed utilising this method.
Era of biological technology

These scientific advances signal a step into a new technological era – the era of biological technology. Synthetic biology is further developing as an engineering discipline for designing living systems. Reproducibility, modularity and robustness are increasing and an abstraction hierarchy has been established from DNA to biological parts, devices and ultimately biological systems. Biology is finally moving from discovery to design.

Like with any new technology, one has to separate hype from reality. Engineering biology is hard: biology is noncompliant. Biological functionality is context dependent. It has evolved through evolution, adaptation and natural selection and involves non-predictive random behaviour. Processes can be non-linear and dynamic or steady-state. Interactions are multi-scale.

However, synthetic biology is developing new tools to manipulate biological systems at the genetic level. It is driven by promises of sustainable applications in many fields. As a platform technology, it will likely enable the development and production of diagnostics and therapeutics, improve crops production and enhance soil productivity, change the manufacturing of commodity and specialty chemicals, improve environmental remediation, bioenergy production, the manufacturing of new materials and much more.

Many countries are investing vast amounts of money into this field – synthetic biology is seen as a strategic domain. In terms of accumulative research output over the past 18 years, the United States leads with 34%, ahead of the UK (14%) and China (13% and fastest growing). Investments at that scale have already produced a steady stream of new inventions, from simple genetic oscillators in 2000 to the creation of a functional single-chromosome yeast (2018), the resynthesis of the entire E. coli genome (2019) and in 2022 the reconstitution of the complete biosynthesis of D-lysergic acid in yeast as an example of a synthetic route toward therapeutic alkaloids. Many of these steps led themselves to new platform technologies that in turn enabled other, new processes and applications.

There are multiple drivers for this move toward biology as a technology. At the policy level, environmental concerns as well as energy demands call for sustainable products and solutions and cause a transition to a global bioeconomy. Economic drivers, too, are important. The Synbio market is expected to reach USD 33.2 billion in revenue by 2026, and current private investment exceeds USD 40 billion. Investment in the bioeconomy has become a matter of global competition for economic domination.
Technology itself is creating drivers for this transition. The convergence of synthetic biology with AI/ML brings together advances in reading and writing DNA, moving DNA between species, and understanding the fundamentals of the genetic machinery. The cost of reading (and to a lesser extent writing) DNA is falling. ML helps transition from a descriptive biology based on data integration to a predictive capacity of biology. Biomedical applications as well as new bioengineered materials are emerging from the combined deployment of synthetic biology, machine learning and process automation. The design cycle for synthetic biology is being automated through cloud labs and biofoundries. Biofoundries in particular will accelerate this cycle given their high degree of automation and integration; they are both training grounds for the next generation of biodesign engineers and a pathway to upscaling. Their ability to rapidly accelerate responses to public health emergencies, for example by rapidly spinning off diagnostic tools and capacity, became apparent during the COVID-19 pandemic.

But biofoundries also have a dual use potential. Efforts are under way internationally to develop a governance system for the field. The Global Biofoundries Alliance, established in 2019, aims to promote the development of non-commercial biofoundries around the world, promote collaborations and communication in the field, develop responses to challenges, enhance visibility, impact and sustainability, and explore globally relevant and societal impactful grand challenge collaborative projects. It aims at mobilising infrastructure and expertise to tackle global emergencies.

One interesting technology is cell-free in vitro transcription/translation systems as a rapid prototyping platform. It speeds up and simplifies work with complex proteins and assemblies, can perform protein modification, and work with genetic networks. The technology is easily accessible and can be implemented with standard laboratory equipment. Cell-free systems can be used in vaccine and therapeutic production, distributed manufacturing, to manufacture low-cost biosensors, make new molecules, synthesise natural products, prototype gene expressions, and optimise protein synthesis.
An example is the combination of cell free lysates with synthetic organic chemistry to produce Violacein and certain analogues – a natural bacterial product that has a broad spectrum of interesting therapeutic activities. A GenoChemetic process was developed to derivatise Violacein and generate a large number of analogues, which were tested for biological activity (in this case inhibition of parasite growth). The work is at the proof-of-concept stage, but it underlines that cell-free systems will be useful for prototyping, bio-manufacturing of high-value low-volume products, and performing synthetic chemistry. They are amenable to local distributed biomanufacturing.

The next grand challenge is the construction of synthetic organisms. This raises biosecurity concerns. Low-cost synthetic DNA is increasingly available globally. Around 3 billion DNA base pairs are currently synthesised every year by private-sector companies. New low-cost desk-top multiplex DNA synthesis technologies and automation are available. Start-ups in synthetic biology are very active, and although private sector suppliers self-regulate, they lack methods to screen for unknowns.

Furthermore, synthetic DNA (the design, the designers, the organism) is hardly traceable: edited, designed or naturally evolved genomes cannot be distinguished. This means that proprietary DNA designs or organisms cannot be protected, but also that it is difficult to forensically distinguish between accidental and deliberate releases of genetic material. There is no clear line between synthetic and natural pathogens. This also poses questions for privacy of human genetic information.

Commercial aspects related to intellectual property protection might be addressed by encryption (of synthetic DNA and plasmids, industrially used organisms, and commercial synthetic DNA) if industrial partners and others join such efforts. That will require education and outreach to industry, biofoundries and other stakeholders. At this stage, there is very little discussion of dual use issues in early-stage synthetic biology start-ups. The technology, however, is advancing very fast. This creates challenges for developing effective (self)controls without inhibiting innovation, and to engagements between the security and arms control communities and actors such as synbio start-ups and international biofoundry partners.
There appears to be a need for a global forum on synthetic biology to engage policymakers with practitioners across borders at the highest level. In *nature communications*, under the title *A global forum on synthetic biology: the need for international engagement* (Article number, 3516, 2022), an initiative to this end has recently been launched as a confidence measure focused on policy futures for the age of engineering biology. To quote from this proposal: “… the international dimensions of the policy-practitioner interface will be essential in realising the many benefits of synthetic biology while minimising the downsides. Synthetic biology itself is agnostic and rapid change remains the only constant.”

**Take-home points**

- Synthetic biology is further developing as an engineering discipline and is becoming a platform technology with applications that will affect various fields of everyday life.

- Synthetic biology is seen as a strategic domain and investment in a bioeconomy has become a matter of global competition for economic domination.

- The convergence of synthetic biology with AI/ML brings together advances in reading and writing DNA and leads from a descriptive to a prescriptive biology linking (bio)chemical compounds and genes with functions.

- Integrated cloud labs and biofoundries automate and accelerate the design cycle for synthetic biology construction and train the next generation of biodesign engineers.

- Biofoundries have a dual use potential and there are international initiatives to develop a governance system such as The Global Biofoundries Alliance.

- Cell-free *in vitro* transcription/translation systems offer a rapid prototyping platform. The technology can be implemented with standard laboratory equipment. Work is under way to use such systems for high-yield protein synthesis and other biosynthesis for DNA templates, or novel natural product discovery.

- The construction of synthetic organisms raises biosecurity concerns and low-cost synthetic DNA is increasingly available worldwide. Private sector suppliers self-regulate, but they lack methods to screen for unknowns.

- Synthetic DNA is not traceable and edited, designed or naturally evolved genomes cannot be distinguished, which also applies to an accidental or deliberate release of genetic material.

- There is little discussion of potential dual use issues in early-stage synthetic biology start-ups.
From an arms control perspective, materials are important for enhancing protections against the effects of chemical and biological agents. They may improve physical barriers to prevent such agents from entering the body whilst increasing the comfort for the wearer; they may remove agents from breathing air or drinking water, or decontaminate surfaces, equipment and building structures; they may detect agents with faster response times, higher sensitivity and selectivity; or be used in medical treatments.

Synthetic Biology methods are being developed to grow materials that exhibit DNA-programmed properties. Baker’s yeast, for example, has been used to secrete antibiotics, make pigments, sense human hormones or produce antivirals. Proteins can be spun into silk fibroids, curli fibres, keratin fibres and more. Plants grow different materials to requirement (composites, structures with well-defined spatial arrangements), using the very same DNA of the plant genome. The challenge for synthetic biology is to achieve something similar: write DNA programmes to grow various materials to design requirements. This could lead to the development of new polymers, modified enzymes, patterned depositions of materials, functional modules and even living components.

An example is the use of bacteria to convert sugar into bacterial cellulose (BC). BC is of interest given its strength and high purity compared to plant cellulose, and because it can easily be functionalised with proteins. Building on a competition entry for iGEM 2014 (using Kombucha bacteria and certain biobrick standards to create customisable ultrafiltration membranes for water purification), a start-up was created that uses chemically modified cellulose as a high-performance filter material to clean up per- and polyfluoroalkyl substances (PFAS) pollution. The group developed the first genetic toolkit to engineer BC-producing bacteria and perfected methods to grow BC in 2D sheets as well as 3D forms. Other groups have further expanded the synthetic biology toolkit for BC-producing bacteria and others.
These are steps toward writing DNA programmes to genetically encode material properties. A number of tools exist today: self-organised microstructures, biopolymer composites, cells that implement living functions, and enzymatic modification. These tools have been used to create rigid and lightweight 3D structures, imprint optical patterns on materials, create materials with different colours using chromoprotein expression or enzymatic pigment production, weave customised bio-textiles and composites, grow fabrics of different colours into desired 3D shapes such as shoes to replace animal and petrochemical based products, and more.

Some bacteria of interest don’t secrete proteins, however. Combining them with yeast into a symbiotic cell culture gets around that hurdle. With this approach, material can be grown that shows enzymatic properties (e.g., self-decontaminating clothing), or that incorporates living cells (e.g., biosensors to detect pollutants, or drug delivery in response to certain activators). “Engineered living material” (ELM) for biosensing, wound healing, stem-cell-based tissue engineering and drug delivery are feasible today, and the research community developing such new materials is growing fast.

**Take-home points**

- Synthetic biology methods are being developed to grow materials that have DNA-programmed properties.
- An example is the use of bacteria to convert sugar into bacterial cellulose (BC), which can be functionalised with proteins.
- With a genetic toolkit, BC-producing bacteria were engineered to grow BC in 2D sheets as well as into 3D shapes.
- A number of tools exist today to grow materials and fabrics with designed properties or desired shapes.
- Combining bacteria with yeast in symbiotic cell cultures allows to grow material that shows enzymatic properties.
- The research community for “Engineered living material” is growing fast.
Devices for the application of medical treatments can offer easier and better controlled ways of administering antidotes, vaccines, and other treatments, reduce the effective dose of a therapeutic drug, allow targeted delivery and reduce side effects. They may be designed to release and deliver drugs in response to certain triggers.

Microarray Patches

The development of microarray patches was discussed as next-generation vaccine delivery tools. Today, most vaccines are being administered using a 170-years old technology – the syringe. Despite its efficiency as a vaccine and drug delivery system, it comes with many issues. The Vaccine Innovation Prioritisation Strategy (VIPS) – a three-year collaboration between GAVI (formerly: Global Alliance for Vaccines and Immunisation), the World Health Organization (WHO), the Bill & Melinda Gates Foundation (BMGF), the United Nations Children’s Fund (UNICEF) and PATH (Program for Appropriate Technology in Health) – set forth three priorities for development, policy and access: microarray patches as novel delivery devices, vaccines management with heat stable and Controlled-Temperature-Chain qualified vaccines, and barcoding of primary packaging. For all three innovation areas, end-to-end strategies and action plans are being defined.

Microarray patches (MAPs) have been selected as top priority as they allow to address all three priorities. MAP devices contain microscopic needle-like projections that perforate the stratum corneum of the skin, creating punctures that allow the delivery of a payload into the skin. They can be designed as solid, dissolving, or hollow MAPs, and used by hand or as applicators.

Vaccine delivery into the skin targets antigen presenting cells (APCs) present in skin tissue. The MAPs design uses dried vaccine formulations which eliminates or reduces the requirement of a cold-chain. Application times are short, no needle/syringe is involved in the delivery, and self-administration is possible.

In solid MAPs “coat and poke”, the vaccine is coated on the surface of the micro-projections, which are made of metal or polymers. The advantage of these patches is that they enhance immune response, excipients are only required for vaccine stabilisation, and the wear times of the patch are short (10 seconds to 2 minutes). On the down side, the payload is limited and the vaccine formulation may blunt the projection tips.
Dissolving MAPs “poke and release” are patches where the vaccine is dissolved within the projections. Dried vaccine is mixed into a matrix of polymers and biodegradable materials to form the projections, which dissolve upon skin insertion. The needles completely dissolve, which can be used for timed release. Excipients can be formulated in higher concentrations than for solid MAPs. A challenge is to create formulations that impart vaccine stability as well as mechanical strength. Wear times are generally longer than for solid MAPs (10–20 minutes).

Hollow MAPs “poke and flow” inject liquid vaccine formulations into the epidermal and dermal skin layers through an array of microneedles. No complex vaccine formulation is required, and patient acceptance is still higher than for traditional needles/syringes. However, these patches are complex to manufacture and there is a risk of clogging.

MAPs can be designed as press on/band aids, or as applicators. Applicators have been tested for self-application and demonstrated to be easy to use. No vaccine reconstitution is required, the applicator self-deactivates after a single use, no needle stick injuries were observed and there is no hazard from sharp waste.

Tests with a MAP for delivery of an H1N1 vaccine formulation showed no change in vaccine potency at 40°C over a period of 1 to 12 months, demonstrating the potential to eliminate the cold chain. This could significantly reduce costs, improve logistics, and support mass-scale distribution in pandemic response including direct deliveries to homes/points of use.

The device is compact in design. It stores and protects the different components, allows for gamma- and gas sterilisation, and is optimised for skin conditioning/tensioning. A large-scale clinical validation study has demonstrated superior immune response and a 6-fold dose sparing. The immune response of MAP vaccination against SARS-CoV-2 showed faster kinetics, a broader immune response and higher mucosal immune response. Potent neutralising IgG-titers against SARS-CoV-2 and early variants of concern were present after a single dose. Enhanced protection could be demonstrated by the absence of disease outbreak in a mouse model, and by the absence of virus breakthrough in brain or lungs.
A White Paper on the estimated economic and public health impact of MAP administered vaccines in pandemics (published in March 2022) highlights the benefits of using MAPs in future pandemics achievable through dose sparing as well as storage and distribution streamlining. Estimates show that the use of MAPs during the SARS-CoV-2 pandemic could have reduced the global number of cases by 16.4 million, and of global deaths by 200,000. The pandemic duration could have been shortened by 150 days, and the two-year economic impact on the US economy reduced by more than USD 500 billion.

Future work focuses on positioning MAPs for use in future pandemics, developing platforms for mRNA, Modified Vaccinia Ankara and adenovirus vaccinations, developing systems for the delivery of small molecule drugs, developing diagnostic systems, and countermeasures.

Take-home points

- Microarray patches (MAPs) have been selected as top priority for the delivery of vaccines as part of The Vaccine Innovation Prioritisation Strategy (VIPS) by international organisations and other stakeholders.
- MAPs eliminate the use of needles/syringes and self-application as press on, band aids or with an applicator is possible.
- MAPs devices contain microscopic needle-like projections that are solid, dissolving or hollow, which perforate the stratum corneum of the skin to deliver a payload into the skin.
- Because the vaccine can be applied to MAPs in a dried formulation, the requirements for a cold-chain are reduced, which significantly lowers costs, improves logistics, and supports mass-scale distribution in a pandemic.
Electrogenetic Implants

Human performance enhancement as well as certain medical treatments could benefit from integration of the human body into the Internet of Things. The way towards such integration would be the development of electro-genetics. There is, however, an interface problem: electronic systems use fast electrons to transfer information whilst the human body uses slow ions. Research is under way to overcome this mismatch.

An interim approach is the development of optogenetics. To illustrate the concept, imagine a human wearing a headset that captures brainwave activity such as meditation or concentration; it electronically communicates with a microcontroller that triggers an implanted LED; the light activates engineered cells to produce a protein, which diffuses through a membrane into the bloodstream.

The building blocks to construct such a treatment system exist today: a light emitter (such as a smart watch) can be placed on the skin of test animals and linked to gene expression in subcutaneous cells to produce insulin. The insulin output can be controlled by light, leading to a programmable diabetes therapy that could be connected to the Internet for remote therapy management.

To further this concept to practical application and without the need for light, one needs to understand whether and how human cells can sense and respond to electricity. A model has been developed in which engineered Electro-β cells sense glucose using a voltage-gated Ca channel and release insulin in response to higher glucose concentration. This Ca channel can be stimulated using an electrical pulse generator. The system has been implanted in a mouse model, resulting in a functioning bioelectronic implant for electro-genetic Insulin control.

The next goal is to develop electro-genetics that are power-source independent and free of electronics. Power independence can be achieved by using a piezo element as part of a push button. Each push produces a current which is transmitted to a semipermeable platinum-coated polyvinylidene difluoride (PVDF) membrane that holds engineered cells (a conductive cell culture chamber). Electrical pulses stimulate membrane depolarisation in the cells, open the Ca channel and prompt the release of insulin. The system has been tested in a Type-1 diabetes animal model. It is robust, provides reliable dosing and is easy to use. It is, however, a rather complex device.

This posed the question whether music could be used to induce insulin release. Such a system of music inducible cellular control would trigger the Ca channel opening by specific frequencies whilst remaining unresponsive to other frequencies and ambient noise. Beats of low-bass frequencies of around 50 Hz were found to work best – typical for popular music as well as certain movie soundtracks, less so for other (classical, guitar, piano) music, natural sounds or speech. A patient could select appropriate sound tracks for stimulating insulin release in response to increased glucose levels. The feasibility of the concept was demonstrated in a mouse model.
An alternative solution to the power supply issues that does not depend on external stimuli is a fuel cell based on metabolic processes. Such a fuel cell would allow a closed-loop control over glucose levels using a biofuel cell driven by glucose levels that would power opto- or electro-genetically stimulated bioelectronic cell implants. The system would release insulin when the glucose concentration in the blood increases, and stop doing so when concentrations of glucose fall to desired levels. The anode of such an experimental fuel cell was made of Cu$_2$O-multiwalled carbon nanotubes (MWCNTs) converting glucose into gluconic acid / gluconates. The cathode was a Pt-nanoparticle Carbon block with Nafion (sulfonated tetrafluoroethylene-based fluoropolymer-copolymer), which converts H$^+$ and oxygen to water. This blood-glucose powered metabolic fuel cell was shown to produce more than adequate voltage to power both electro- and opto-stimulated insulin release in a mouse model.

The system would release insulin when the glucose concentration in the blood increases, and stop doing so when concentrations of glucose fall to desired levels. These examples illustrate the feasibility of medical devices that can be implanted in patients and remain in operation for long periods of time without the need for battery changes. Applications in the treatment of chronic diseases and conditions that require long-term medication are obvious. In the context of chemical and biological safety, it may also be possible to conceive devices that, for example, sense and respond to changes in certain enzyme activities and that could be used as prophylactic devices to protect individuals that are at risk of exposure to certain hazards.

**Take-home points**

- Electro Genetics looks at developing interfaces for the human body for performance enhancement and medical treatments.
- One application used opto-genetics to activate engineered cells, which were implanted into a test animal, to produce a protein that diffuses through a membrane into the bloodstream.
- In an application of electro-genetics, engineered human Electro-β cells could sense insulin concentration with a voltage-gated Ca channel. They would release insulin after sensing a higher glucose concentration. The system worked successfully for insulin control in a mouse model.
- This system was made independent from an external power-source and electronics by developing a Piezo-PET device that could be implanted and which produces a voltage peak when pushed, which opens the Ca channel in the cells triggering the release of insulin.
- Insulin release could also be triggered through popular music, with low-bass frequencies of about 50 Hz.
- To remove the requirement for an external stimuli, a fuel cell was developed that is driven by glucose levels. This fuel cell supplies opto- or electro-genetically stimulated cell implants with power.
Implications and Conclusions

One of the objectives of Spiez CONVERGENCE is to identify scientific advances that are, or may soon become, game changers. Of the many themes that have been discussed over the past eight years, machine learning / deep learning / artificial intelligence has emerged as a field that may radically change the science and technology landscape, and that could profoundly affect the regimes prohibiting chemical and biological weapons. There was hardly a presentation at Spiez CONVERGENCE 2022 that did not talk at least at its periphery about AI/ML. Scientists can accurately read and write DNA, and are getting better at understanding DNA language in cell free systems. This is not yet the case in living systems. Expectations, however are, that this will be possible within the coming ten years.

Game Changers

Is AI a game changer? And if so, what are the consequences for chemical and biological weapons arms control?

To illustrate where AI stands today, the conference returned to discussions about a generative machine learning model that was presented at the 2021 Spiez CONVERGENCE conference. This model had been tasked to generate toxic molecules targeting acetylcholinesterase. The training data came from publicly available databases. The model generated a large number of structures which included known CW agents and analogues as well as many new molecules, among them some de novo structures expected to have an even higher lethality than VX. As the report on Spiez CONVERGENCE 2021 observed: “Using ML, the steps from molecular design to synthesis are becoming easier and they can be automated, with the downside, that such ML methods could be deployed to actively avoid control measures.”

The dual use dimension of this experiment inspired a collaboration between scientists and arms control experts that resulted in high impact publications on Dual use of artificial-intelligence-powered drug discovery and A teachable moment for dual-use. This sparked global media interest in the issue of the dual use potential of AI, and led to invitations to present at the White House, at an OPCW – IUPAC workshop on AI application in chemistry, a host of other gatherings, and an invitation to take part in a documentary to be broadcasted by Netflix.
Ten recommendations on preventing AI from creating chemical threats have been developed in these conversations. They address professional ethics, self-regulation, training, and awareness raising. There is also a call for certain regulations and for limitations of access to certain tools, knowledge and expertise.

AI is an example for how scientific advances can lower the bar: tools are getting easier to use, are more widely distributed, and enabled by open access to data and software. The human contribution remains critical from design to validation, but our role is changing. AI is being deployed alongside other technologies (synthetic biology, automation and robotics, Big Data, high-throughput synthesis and screening). This combined approach will result in a context shift in how experiments are being performed, and capabilities are growing fast.

So, is AI a game changer? Maybe not yet. And perhaps more on the biological side than in chemistry. It was pointed out that as for now, progress remains evolutionary. But this is only a matter of time.

What it means for Arms Control

What is possible is not what is likely to happen – context, actors, intents and resources matter. It is important to understand the drivers that steer the advancement of the sciences and their application – for good or bad.

Governments have clearly understood the importance of the move into a bioengineered world. Countries are spending vast amounts of money in this field, seen as strategic investments. There are strong expectations that the outcomes will help in managing the challenges of climate change, energy demand, food security, supply chain vulnerability, and public health including preparedness for the next pandemic. But this is also about technological and economic dominance, and thus political influence.

But there are other drivers and actors. Industry is heavily investing in a green economy, aiming for ecological solutions, sustainability, and providing solution to societal demands such as managing and combating antibiotics resistance or offering personalised medicines. Biotechnology is seen as an important growth market.

Life scientists and those working in enabling fields are eager to push the frontiers of science further from discovery to design, and to understand and construct biological functionality. This will lead to new applications, but in essence, science is mainly driven by curiosity – to see how things work, or can be made to work.
Despite the pace of scientific advancement, dual use issues remain under-represented in discussions within the scientific community, and in conversations between scientists and other stakeholders. Within the synthetic biology community, this may actually indicate that past efforts to embed concepts of dual use into their professional ethics and conduct have been successful. Other research communities, including the AI/ML community, have barely addressed these issues. Funders, too, need to be aware of the dual use potential of the work they are funding.

The OPCW, the BWC Implementation Support Unit, the WHO and other national and international organisations continue to raise awareness for responsible conduct in the life sciences. Guidance documents such as The Hague Ethical Guidelines or the WHO’s recent guidance on responsible conduct in life science research make important contributions, but need to lead to sustained engagements.

At a broader level, concerns about chemical and biological threats have clearly shifted back from terrorists and lone actors to States. The terrorist threat cannot be neglected, but it remains unclear what exactly terrorists would gain from using scientific advances for their goals, compared to the tools and methods they already command. While life science is getting easy for experts, it remains hard for the non-expert.

Some States, on the other hand, have demonstrated to employ toxicity and biological activity as weapons, under certain circumstances. Recent events have shown that the perceptions about the limited military utility of CB weapons may not be shared by all States. Even chemical weapons dating back a century have been used.

At the same time, strategic investments into the bioeconomy will inevitably bring results that also have misuse potential. As geopolitical tensions mount, will States resist the temptation of turning them into new forms of imposing power, or is the world heading for a biological arms race? In today’s worsening geopolitical climate, the answer is not obvious.

Geopolitical changes and the war in Ukraine already affect scientific collaborations. Exchanges and access between scientists from certain countries is becoming difficult. Losing such relationships, however, is likely to hinder progress, hamper beneficial applications of scientific advances, and obstruct the resolution of global problems.
With regard to arms control specifically, many discussions are still stuck in the past. They are constrained by definitions that no longer reflect the emerging misuse potential. A return to chemical and biological warfare would likely be about disrupting society rather than killing large numbers of people. It might involve agents and methods that have societal impact (for example by affecting the mental state of the victims, or harming the economy of a country in ways difficult to attribute) rather than act as weapons of mass destruction.

At the same time, science and technology is providing new countermeasures and protection against such weapons. This clearly has a deterrent effect against a recurrence of chemical and biological warfare. Science and technology may also lead to new ways of verifying compliance with the norms, perhaps by employing AI and machine learning in investigations. Today’s verification methodology primarily mirrors past programmes in terms of footprint, capacity and characteristic signals. These signatures are less and less relevant in the emerging threat landscape, but AI is good at detecting patterns that humans may not see. If new types of agents were to be used, AI may help identifying them if established methods fail. In any case, the changes in the science, technology and industry environments may require reviewing the objectives, capabilities and limitations of the verification system of the CWC, and help establishing compliance assurance mechanisms for the BWC.

Perhaps as important is the strengthening of non-treaty mechanisms. Scientists are in the first line of defence against any abuse of their work. Embedding dual use ethics into the thinking and behaviour of scientists, starting from an early age, will be ever more important. Codes, too, are important – less as a set of fixed rules than as a process of engagement and discussion within and between communities about responsible conduct and risk management. This needs to be better reflected in education and training – avoiding the risk that bio- or chemical security may be monopolised by certain actors, whilst ensuring that research and innovation can progress unhindered yet without being misused to cause harm.

As previous Spiez CONVERGENCE conferences, Spiez CONVERGENCE 2022 has again demonstrated how beneficial cross-community conversations between policy experts and practitioners from the worlds of science, technology and industry are. Gaging how advances in the sciences may affect the norms and measures of chemical and biological weapons arms control is a complex undertaking. Spiez CONVERGENCE remains a place where such exchanges can take place in an open, well-informed and cordial manner.
Take-home points

• The technologies for Machine Learning and Artificial Intelligence are close to becoming Game Changers; they may profoundly affect the regimes prohibiting chemical and biological weapons.

• A presentation demonstrating the power of AI for discovering new toxic chemicals during Spiez CONVERGENCE 2021 resulted in a high impact publication on *Dual use of artificial-intelligence-powered drug discovery* and the publication that followed, *A teachable moment for dual-use*, had a strong media impact worldwide and resulted in a number of recommendations for the AI community.

• The combination of AI with synthetic biology, automation and robotics, Big Data, high-throughput synthesis and screening leads to a context shift from hardware (equipment/laboratories) to data and people.

• Governments have identified bioengineering as a strategic capability that may help solving many of today’s pressing problems and countries are investing vast amounts of money; also looking for technological and economic control and political influence.

• For industry, biotechnology has become an important growth market that will provide solutions to societal demands. For scientists, the main drivers remain curiosity and a desire to push the frontiers of science.

• Despite efforts in the synthetic biology community to teach ethics and dual use concepts and guidance documents about ethical conduct from international organisations and others, teaching awareness about the dual use problem still requires sustained engagement with the science community, as well as with funders and investors.

• The perception about a limited military utility of CB weapons may not be shared by all. Concerns of the arms control community about utilising scientific advances for chemical or biological weapons may have to focus on states and less on terrorists or lone actors.

• The large strategic investment into a bioeconomy will produce results that will also have a misuse potential. That all states will resist the temptation is in today’s geopolitical climate not obvious.

• The current geopolitical situation negatively affects access and exchange between scientists.

• Many discussions in the arms control communities are stuck in the past and no longer reflect the emerging misuse potential. The same applies to the verification system of the CWC and the compliance assurance mechanism of the BWC, which were designed for past weapons programmes.

• Advances in science and technology may provide new countermeasures and protection against chemical and biological weapons as well as new methods of verification of compliance.

• Important is also to strengthen non-treaty mechanisms by embedding dual use ethics among scientists, they are the first line of defence. This can be done without hindering research or slowing down innovation.