

Conference Call

Artificial Intelligence-Assisted Chemistry

by Ahmed Saeed, Peter Hotchkiss, Jeremy Frey, Hemda Garelick, Vladimir Gubala, Bipul Saha, Russell Boyd, and Jonathan E Forman

An International Workshop on “Artificial Intelligence Assisted Chemistry” was held at the headquarters of the Organisation for the Prohibition of Chemical Weapons (OPCW) in The Hague, The Netherlands on 16 and 17 June 2022. The program was jointly organized by the OPCW’s Scientific Advisory Board (SAB) and IUPAC, with representatives from the Committee on Chemistry and Industry (Bipul Saha), the Interdivisional Committee on Green Chemistry for Sustainable Development (Jonathan Forman), the Physical and Biophysical Chemistry Division (Jeremy Frey), Chemistry and the Environment Division (Hemda Garelick), and the Chemistry and Human Health Division (Vladimir Gubala). The objectives of the workshop were to (a) provide insight into current and future applications of Artificial Intelligence in Chemistry and (b) generate provocative discussions on the future of this emerging field and its potential impacts, both positive and negative, on the chemical sciences and society.

The SAB is tasked with monitoring the developments in science and technology of relevance to the Chemical Weapons Convention (CWC). The SAB’s guidance enables the OPCW Director-General to render science and technology advice relevant to the CWC, to the Conference of the States Parties, the Executive Council and States Parties. Every five years the OPCW holds a Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention, otherwise known as a Review Conference. These Review Conferences serve as fora for the assessment and evaluation of the CWC’s implementation and setting long-term views by providing strategic guidance to the OPCW. Particular focus is given to the verification regime, especially given the CWC’s guidance that the OPCW consider measures to make use of advances in science and technology in undertaking its verification activities (Article VIII, paragraph 6), the changing context within which the regime is implemented and scientific and technological advances in chemistry, engineering, and biotechnology. The Fifth Review Conference was scheduled for 15-19 May 2023.

To ensure that the OPCW Technical Secretariat and States Parties are apprised, the SAB prepares a report before each Review Conference which analyses



“Chemistry of the Future” by DALL.E2 for IUPAC and OPCW
(3 March 2023)

relevant developments in science and technology over the past five years and presents recommendations and observations that the SAB considers to be important for the review of the operation of the Convention and its future implementation.

IUPAC and OPCW have collaborated on various activities and workshops over the years [1-3]. The relationship was further strengthened in 2016 by the joint signing of a Memorandum of Understanding (MOU) officially establishing the relationship [4]. The MOU outlines the framework for cooperation between the two organisations with a view towards achieving common objectives and to providing benefits to their respective programmes and areas of work. These areas include, *inter alia*, science, education and outreach, ethics, and peaceful uses of chemistry. This workshop on AI-assisted chemistry is the latest example of this long-standing collaboration.

Summary of the Workshop

The workshop provided insight into current and future applications of AI in chemistry, with a focus on areas of chemistry of relevance to the OPCW. Topics such as synthetic design and retrosynthetic analysis, reaction conditions and optimisation, drug discovery, adoption and impact of AI in and on the chemical industry, and AI in agricultural chemistry were all considered via both presentations by world experts as well as during moderated discussions throughout the 1.5-day workshop. A brief overview of the presentations and discussions follows.

The workshop kicked off with an overview of the agenda and the impetus for convening on the AI theme. This was provided on behalf of the SAB by Board member Ahmed Saeed and Peter Hotchkiss of the OPCW. This opening presentation briefly touched on the various areas in which AI is impacting society before focusing on the many ways it is enabling the chemical sciences.

Artificial Intelligence in Drug Discovery

The first invited speaker was Sean Ekins of Collaborations Pharmaceuticals Inc, USA. Collaborations Pharmaceuticals uses AI to develop clinical candidates for rare, neglected, and unmet therapeutic needs. However, in a meeting with science, industry, and arms control communities, they started to consider how the technology they use may be misused in the development of chemical and biological weapons. His team and some colleagues from the Swiss Federal Institute for NBC-Protection (Spiez Laboratory) and Kings College London recently published the results of a thought experiment in which his team used a pre-existing machine learning model for bioactivity and rat acute LD₅₀ (in order to identify toxic molecules) along with a generative algorithm trained on the ChEMBL database to develop molecules with the aim of assessing if the algorithm could generate molecules similar to nerve agent VX. In just 6 hours the generative algorithm produced 40,000 molecules including VX, related known analogues as well as thousands of other molecules that looked similar.

The work, published in March 2022 in *Nature Machine Intelligence*, garnered a lot of global and media attention allowing Ekins to both present the team's work to various audiences, but also the story of the work and how they learned a lot about the potential for misuse that this technology allows [5]. Ekins mentioned that the number of companies using AI for drug discovery is growing and AI is used across many sectors such as consumer products (e.g., to identify for non-animal testing options for cosmetics) and animal health (e.g., to discover cost effective new treatments). He emphasized the importance of security and ethics to control misuse of AI.

Artificial, Augmented and Automated chemistry

Jeremy Frey of the University of Southampton, UK spoke about machine learning in chemistry and how it is useful for a host of applications to include drug design, materials design, complex mixture and formulation design, and device design. However, large amounts of quality data are required for machine learning to

be successful. Obtaining these data is a major driving force for the development of new synthetic and characterisation techniques. In posing the question of whether scientific discovery can be automated, Frey indicated that he thought so, but that automation is just one piece to the puzzle. Frey also highlighted that despite the opportunities and efficiencies that artificial, augmented, and automated chemistry may offer, that students should not forsake traditional chemistry. These computer-aided techniques and approaches are only tools, and the human mind will still be needed in these processes (i.e., keeping the human in the loop).

Use of neural networks and symbolic AI in chemical synthesis planning

Marwin Segler of Microsoft Corp explained how the AI/machine learning landscape has evolved in last few years through different stages, from automated synthesis planning and molecular design, to property prediction of new molecules, to readily available open-source code and cloud computing. He suggested that AI should be used for designing property profiles, not compounds *per se*. In reviewing the history of computer-aided synthesis planning, Segler noted that AI can serve as an idea generator for competent chemists and software is openly available [6]. Some limitations of current approaches were also highlighted, such as: the difficulties in predicting reaction conditions, experimental success and scale-up, and the subsequent limitations of reaction models. However, these will continue to improve with more data and combining this with automated approaches, such as robot-assisted synthesis/experimentation.

Segler believes that, in the next 5-10 years, we should expect to see:

- Synthesis planning, reaction optimization and new molecule generation using AI [7]
- An increased ability to identify new targets and binding sites
- More accurate atomistic simulations
- Algorithms better at extrapolation

He concluded by saying that chemistry expertise will still be needed in the future, but tools like AI will make some of these complex undertakings more accessible.

Application of Artificial Intelligence in Agricultural Chemistry and Agriculture

Bipul Saha of the Sagar Group of Institutions in India spoke about the application of AI in the discovery and synthesis of safe and highly effective crop protection chemicals, listing a number of recent use-cases such as



Participants in the International Workshop on "Artificial Intelligence Assisted Chemistry" held at OPCW in The Hague, The Netherlands on 16-17 June 2022. Facilitations for remote presentations and attendance were also provided.

the discovery of a new selective herbicide for sorghum (Benquitrione). AI can also be used in the prediction of risk of resistance and toxicity of new molecules, saving time and money when developing a new agricultural chemical. When it comes to formulation development, machine learning can be used for prediction of physical stability, dispersion rate and stability of emulsion, *etc.*

Saha noted that the population of the world is expected to grow to 9.7 billion by the year 2050. To feed this population, agricultural output must increase by at least 50%. At the same time, availability of agricultural land is decreasing due to urbanization and other factors. There is also the increased potential for substantial loss of crops due to pests, crop diseases and weeds.

AI can therefore play an important role in areas such as:

- Early diagnosis of disease and fungal growth in crops to reduce loss of yield
- Monitoring crop health to diagnose nutrient deficiency, moisture content, and pest damage
- Advising farmers on the right time to sow fields for maximum yield
- Helping farmers in selective removal of weeds to reduce cost and environmental impact
- Reducing labor needs by incorporating autonomous robots in crop harvesting
- Predicting crop yields and forecasting prices to help empower farmers

One recent example of the impact of AI is in the collaboration in India between the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) and Microsoft Corp to generate sowing advice for farmers resulting in a 30% increase in yield. There are other companies and organisations in India looking to harness the power of AI to strengthen the agricultural industry.

Self-Optimising Reactors for Industry 4.0 Process Development

Richard Bourne of the University of Leeds spoke on self-optimising reactors. He indicated that, compared to conventional methods, self-optimizing reactors:

- Provide a cheaper, faster and greener route to reaction optimization
- Enhance researcher capabilities by removing the need for labour intensive experimentation
- Align with growing use of flow chemistry in the chemicals and pharmaceuticals industry

Bourne highlighted an example from his laboratory in which 46 experiments were conducted in 37 hours using only 200 mg of sample per experiment, allowing for the most efficient reaction conditions to be determined [8]. This experiment highlights the efficiency a self-optimising reactor can realise.

Bourne also identified some potential risks and opportunities for OPCW in automated DMTA (design,

make, test and analysis) cycles. It is clear that automated DMTA can positively impact the pharmaceutical industry, but could it also be used maliciously in CW research? It may also prove beneficial in developing automated processes to chemical destruction and remediation and could allow for more remote processes which tend to be inherently safer to human life.

Bourne in summary explained that automation of flow chemistry for process development will enable enhanced productivity, reproducibility, data analysis, and exploration of chemical space.

Sustainability Implications of AI in the Chemical Industry

Prof Yuan Yao of Yale University began by explaining how AI is helping society achieve the United Nations Sustainable Development Goals. There are also sustainability implications of AI in the chemical industry. Yao and her team have reviewed relevant literature and categorized their findings by applications, including AI applications to R&D, unit operations, chemical plants and supply chains. Most studies assessed the energy, economic, and safety implications of AI applications, while relatively few have looked at the environmental impacts of AI [9]. Previous studies also did not consider the impacts of AI systems themselves (*e.g.*, AI infrastructure). As AI has received increasing interest in the chemical industry, it is important to evaluate the potential environmental, economic, and societal impacts of different AI applications.

Yao presented a conceptual framework to assess the sustainability impacts of AI, which includes approaches from industrial ecology, economics, and engineering. As an emerging tool, AI can also be used to support a better understanding of the sustainability of chemicals and materials. This was illustrated with a case study integrating machine learning and chemical process simulation for bio-based materials [10]. Similar applications were identified for bioenergy and other bio-based chemicals [11].

Use of AI in molecular design, reaction planning and reaction execution

Connor Coley of the Massachusetts Institute of Technology gave the final invited talk of the workshop. The Coley Research group focuses on developing new computational strategies to accelerate molecular discovery, with particular emphasis on small molecule therapeutic discovery. Among the major themes of the group are computer-aided molecular design and data-driven predictive chemistry. He noted that most molecular discovery workflows proceed iteratively

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Workshop participants (* indicates speaker, 1 indicates IUPAC representative, 2 indicates SAB member)

through design-make-test-analyze cycles, exemplified by lead optimization in the pharmaceutical industry.

Coley noted that the canonical approach to computer-aided molecular design is virtual screening. In virtual screening, large pre-enumerated libraries of molecules are evaluated and the ones with the most favorable values are advanced to experimental testing. A second approach to computer-aided molecular design is generation. Generative models perform a computational optimization by proposing new molecules, estimating their performance (typically with a QSPR model) and revising the rules by which they generate molecules to bias generation towards higher-performing candidates.

For either approach, synthesis is an essential consideration. Virtual libraries are often “make-on-demand” libraries enumerated using chemical transformation rules we believe to be robust and generative models produce new compounds for which we must plan synthetic routes. He said that rational molecular design is an iterative, multi-objective optimization, and computation can accelerate discovery by making it easier to generate and test hypotheses. He further mentioned that although AI can help us to design molecules and develop retro-synthetic pathways, it can’t do everything and anything [12]. He raised the following questions:

- What catalysts, solvents, reagents, temperature do we use?
- What concentrations and reaction time do we use?
- What kind of flask/vessel do we use?
- What order do we add species in, and how quickly or slowly do we add?
- For multi-step sequences, what isolation steps are required?

In conclusion, Coley remarked that AI-assisted chemistry is changing how researchers approach the design and discovery of new functional molecules. The dual use concern is obvious but should not be overblown. Computational predictions of molecular properties are just that—predictions—and one should always consider what a model’s domain of applicability and uncertainty is, or whether biases during training are influencing its predictions. Computer-aided retrosynthesis to medchem-like compounds works well for data-driven programs; the distribution shift when working with small, highly-functionalized compounds presents a challenge (e.g., fentanyl is easy, nerve agents are hard).

Moderated Discussions

In addition to the invited speakers, there were

several moderated discussion sessions to probe participants’ thoughts on where the use of AI in the sciences is headed and what opportunities and concerns these may present. Discussions were moderated by Hemda Garelick, Vladimir Gubala and Jonathan Forman. These discussions probed several areas of relevance to the work of the OPCW, including synthesis automation, AI in Chemical Safety and Security Management, AI and sustainable technologies and green chemistry, Life Cycle analysis, and AI ethics.

Conclusion and Next Steps

All participants appreciated the workshop program. AI already plays an important role in the field of chemistry, and its adoption and role in the chemical sciences will only expand. Noting this, we should focus on developing positive applications and aspects of AI.

While limitations remain, AI-based synthesis planning makes continued progress. The conversation should hasten with AI ethics institutes and other experts regarding guidance for ethical guidelines to prevent the misuse of AI in the sciences—the Hague Ethical Guidelines provides a framework from which to have these deliberations [13]. Increased training and awareness of scientists to recognize potential for dual-use concerns of AI-assisted chemistry will be critical. Increased security around the software methods and tools that enable AI-assisted chemistry may be appropriate.

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Malta X, Women in Science

by Rachel Mamluk-Naaman

The Malta X conference, *Frontiers of Science: Innovation, Research and Education in the Middle East—A Bridge to Peace*, took place in November 2022 in Malta. The president of the Malta Conferences Foundation is Professor Zafra Lerman, who initiated the conferences. One of the goals of these conferences is to ensure inclusive and quality education for all (Zajdela and Lerman, 2021). An important activity in these conferences is establishing a women forum in science. Thus, during Malta X, a three-hour workshop on Women in Science was conducted. The coordinators and co-chairs of the workshop were Rachel Mamluk-Naaman, Rana Raddawi, and Noha Taymour. In addition, two posters on the topic of women education were presented in the poster session at that afternoon. The women who participated in the workshop came from different countries in the Middle East. They were asked to refer to three questions:

1. What kind of challenges did you face during your career?
2. How did you cope with the different challenges?
3. What are your recommendations for coping with

challenges and problems that women face during their careers?

The women's stories were exciting and sometimes heart breaking. The discussions revealed that women still need to cope with discrimination, with an unconscious bias, as well as with family demands. Below you may find one of the most touching stories that one of the young chemistry researchers told:

I was born in the West Bank. My parents are not familiar with reading or writing. The main goal for daughters in our society is to raise and take care about the family.

I am the first born to my family, and despite the atmosphere in our community, my mother encouraged me to study. My curiosity and interest in science stimulated me to study chemistry in the university. There was no person happier than my mother was when she attended the ceremony in which I received my PhD in chemistry. She said that I accomplished her dream, becoming a scholar and an independent woman. She did not care about getting married or having children, but rather prayed that I will get my PhD, and become a scientist. My mother's attitude made me very happy! I started believing that there might be a change in the Palestinian society towards women's role in society.

Their experiences in both educational and employment settings are consistently less positive than those



Professor Zafra Lerman (right) and Dr. Rachel Mamluk-Naaman