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*Judith N. Currano, Editor*
*University of Pennsylvania*
*currano@pobox.upenn.edu*

## Inside this issue:



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# Letter from the Editor

Greetings from Festive Philadelphia!

It is hard to believe that the end of the year is upon us. It is even harder for me to believe that the last editorial I wrote was about what to do with all the spare time that the summer provides. At the close of the year, I find myself fighting a war on two fronts; students' term projects, final exams, and an inevitable backlog of homework grading claim my attention by day, while winter holiday preparations and celebrations, along with the birthdays of all of my children, consume the remainder of my waking hours. Thus, the balance between work and life is maintained, even in December.

The close of the year is a good time to reflect on past accomplishments and activities, and I am pleased to be able to present you with this issue of the *Chemical Information Bulletin*, which will help you do just that. Those in the northern hemisphere can cozy up with it under an afghan and with a hot beverage in hand, while it will make perfect beach reading for colleagues in the southern hemisphere! Once again, I am eternally grateful to all of the contributors who took time out of their busy autumns to provide us with thought-provoking reading material.

Since fall in CINF is Herman Skolnik Award season, the bulk of the issue is devoted to that topic. I am happy to congratulate Professor Kimito Funatsu, who will receive the 2019 Herman Skolnik Award in August, on the many achievements that resulted in this prestigious recognition. Likewise, I send one last set of congratulations to Gisbert Schneider, recipient of the 2018 Herman Skolnik Award. For those who were not able to attend the award symposium held in Boston, Wendy Warr's detailed symposium report is the next best thing! Finally, Rajarshi Guha, CINF Awards Chair, sends some thoughts on gender and geographic trends amongst Herman Skolnik awardees. While CINF is not alone in seeing gender disparity in its most prestigious award, the statistics that he quotes are certainly eye-opening. As the current advisor to Penn's Women in Chemistry group and a woman myself, I know that seeing one's field honor exceptional women makes a profound impression on the younger generation. There is a huge difference between being told that you can succeed and actually seeing someone "like you" acclaimed as an example of success. I join Rajarshi in urging all CINF members to consider nominating worthy female colleagues for this and other divisional and national awards.

Those of you whose areas of interest lie outside of de novo molecular design may also enjoy reading the reports and musings about the fall meeting's symposia on the ethics of data sharing, reaction analytics, chemistry librarians of the future, and publishing chemical data. I would be remiss if I did not also highlight Bob Buntrock's latest book review, which this time focuses on a collection of books on the topic of scientific communication.

Seeing the collection of symposium reports and feature articles in each post-meeting issue of the CIB, combined with the job titles in the bylines of the authors who chose to report about them, reminds me of the vast diversity of our division, the aspect of CINF that I value most highly. Chemical information truly touches every branch of chemistry, something that is apparent from the number of cosponsored symposia that we hold at each national meeting. There is no other place where I could learn about anything from the use of artificial intelligence in drug design to indicators of what the future may hold for chemistry librarians in the United Kingdom! Thank you all so very much.

Wishing you the best of everything this winter, and a happy and healthy year to come!

Judith N. Currano, Editor
University of Pennsylvania
currano@pobox.upenn.edu

*(Photo credit: Peter Cutts Photography)*

# Awards and Scholarships

## 2019 Herman Skolnik Award: Kimito Funatsu

The American Chemical Society's Division of Chemical Information is pleased to announce that Professor Kimito Funatsu (http://funatsu.t.u-tokyo.ac.jp/en/home/) has been selected to receive the 2019 Herman Skolnik Award for his contributions to structure elucidation, de novo structure generation, and applications of cheminformatics methods to materials design and chemical process control.

The award recognizes outstanding contributions to and achievements in the theory and practice of chemical information science and related disciplines. The prize consists of a $3,000 honorarium and a plaque. Prof. Funatsu will also be invited to organize an award symposium at the Fall 2019 ACS National Meeting, to be held in San Diego, CA. The awarding of the 2019 Herman Skolnik Award to Prof. Funatsu recognizes his significant contributions to cheminformatics methods and his efforts to propagate these methods to multiple domains, including process control and materials design. The award also recognizes his key role in the development of the cheminformatics discipline in Japan and his mentoring of students in Asia. Many of his former students now fill important positions in industry and academia.

For more than 35 years, Prof. Funatsu has made pioneering scientific contributions to the evolving field of chemical informatics. Prof. Funatsu's seminal contributions include the conceptualization and implementation of algorithms and expert systems for structure elucidation and chemical synthesis design. To name just one, the AIPHOS system (1988; https://doi.org/10.1016/0898-5529(88)90006-1) represents one of the early applications of artificial intelligence in chemistry. The structure elucidation and synthesis design systems that Prof. Funatsu developed have been extensively applied in the pharmaceutical industry, demonstrating his dedication to first-class, problem-solving science. Beginning in 2000, Prof. Funatsu's highly active research program (http://funatsu.t.u-tokyo.ac.jp/en/research/) has been further expanded to materials design. In recent years, he has increasingly focused on inverse QSAR analysis, including *de novo* structure generation and the development of the soft sensor methodology for chemical process control (2011; https://doi.org/10.1002/9783527806539.ch13). The latter approach represents another par excellence example of ground-breaking research with immediate practical and industrial application potential. Given his unique research profile, Prof. Funatsu has been able to secure large amounts of funding from the chemical and pharmaceutical industries and drive large-scale collaborative projects at the interface between academia and industry, most recently in the context of the CREST Program on Big Data Applications, funded by the Japan Science and Technology Agency. Taken together, these efforts have left their mark on the scientific and industrial landscape of Japan. With more than 200 peer-reviewed and well-recognized publications, and a plethora of presentations and conference contributions, Prof. Funatsu is among the core of leaders of the broadly-defined chemical information and informatics field worldwide and is highly regarded as such.

Prof. Kimito Funatsu obtained his Doctoral degree (Dr. Sci.) in physical organic chemistry from Kyushu University (1983) and then joined Prof. Shinichi Sasaki's group at Toyohashi University of Technology in 1984. During his time with that group, he worked on a variety of cheminformatics applications including the structure elucidation system CHEMICS, the organic synthesis design systems AIPHOS and KOSP, other systems in the areas of *de novo* design, and chemogenomics. In 2004, he moved to the University of Tokyo to continue research in these areas as a full professor, and there, he expanded into material design and soft sensors for monitoring and controlling chemical plants. In addition to his professorship, he is also the research director of the Data Science Center (http://www-dsc.naist.jp/dsc_en/) at the Nara Institute of Science and Technology (NAIST).

Prof. Funatsu initiated the tradition of organizing biannual international Cheminformatics Schools in Japan, which have become a magnet for professionals and students alike. He recognized early in his career that the development of infrastructures for vital scientific exchanges and interdisciplinary activities would be essential to showcase, nurture, and further evolve this discipline in Japan. Prof. Funatsu initiated the Computer Aided Chemistry Forum for scientific communication and practical training in cheminformatics, and he established the Japanese Society of Cheminformatics as a forum to bring academia and the chemical and pharmaceutical industries together. Prof. Funatsu's relentless community service efforts also include his tenure as the President of the Division of Chemical Information and Computer Sciences of the Chemical Society of Japan (2004–2014). Over the years, he has received several awards in recognition of his many contributions, including awards from the Japan Information Center of Science and Technology in 1988, from the Society of Computer Chemistry Japan in 2003, and from the Society of Chemical Engineering in 2017.

Rajarshi Guha
Chair, CINF Awards Committee
rajashi.guha@gmail.com

## Scholarship for Scientific Excellence

CINF Scholarship for Scientific Excellence (S4SE) winners Jeremy Ash, Barbara Zdrazil, and Ariela Kaspi-Kaneti pictured with S4SE Co-ordinator Stuart Chalk and ACS Pubs (Sponsor) Michael Qiu *(Photo credit: Wendy Warr)*

# Applications Invited for CSA Trust Grants for 2019

The Chemical Structure Association (CSA) Trust is an internationally recognized organization established to promote the critical importance of chemical information to advances in chemical research. In support of its charter, the Trust has created a unique grant program and is now inviting the submission of grant applications for 2019.

## Purpose of the Grants:

The grant program has been created to provide funding for the career development of young researchers who have demonstrated excellence in their education, research, or development activities that are related to the systems and methods used to store, process, and retrieve information about chemical structures, reactions, and compounds. One or more grants will be awarded annually up to a total combined maximum of ten thousand U.S. dollars ($10,000). Grantees have the option of payments being made in U.S. dollars or in British pounds equivalent to the U.S. dollar amount. Grants are awarded for specific purposes, and within one year each grantee is required to submit a brief written report detailing how the grant funds were allocated. Grantees are also requested to recognize the support of the Trust in any paper or presentation that is given as a result of that support.

## Who is Eligible?

Applicant(s), age 35 or younger, who have demonstrated excellence in their chemical information-related research and who are developing careers that have the potential to have a positive impact on the utility of chemical information relevant to chemical structures, reactions, and compounds are invited to submit applications. Proposals from those who have not received a grant in the past will be given preference. While the primary focus of the grant program is the career development of young researchers, additional bursaries may be made available at the discretion of the Trust. All requests must follow the application procedures noted below and will be weighed against the same criteria.

## Which Activities are Eligible?

Grants may be awarded to acquire the experience and education necessary to support research activities; e.g. for travel to collaborate with research groups, to attend a conference relevant to one's area of research (including the presentation of an already-accepted research paper), to gain access to special computational facilities, or to acquire unique research techniques in support of one's research. Grants will not be given for activities completed prior to the grant award date.

## Application Requirements

Applications must include the following documentation:

1. A letter that details the work upon which the grant application is to be evaluated as well as details on research recently completed by the applicant;
2. The amount of grant funds being requested and the details regarding the purpose for which the grant will be used (e.g. cost of equipment, travel expenses if the request is for financial support of meeting attendance, etc.). The relevance of the above-stated purpose to the Trust's objectives and the clarity of this statement are essential in the evaluation of the application);
3. A brief biographical sketch, including a statement of academic qualifications and a recent photograph.

Two reference letters in support of the application. Additional materials may be supplied at the discretion of the applicant only if relevant to the application and if such materials provide information not already included in items 1-4. A copy of the completed application document must be supplied for distribution to the Grants Committee and can be submitted via regular mail or e-mail to the committee chair (see contact information below).

## Deadline for Applications

Application deadline for the 2019 grant is March 29, 2019. Successful applicants will be notified no later than May 8, 2019.

## Address for Submission of Applications:

The application documentation can be mailed via post or emailed to: Bonnie Lawlor, CSA Trust Grant Committee Chair, 276 Upper Gulph Road, Radnor, PA 19087, USA. If you wish to enter your application by e-mail, please contact Bonnie Lawlor at chescot@aol.com prior to submission so that she can contact you if the e-mail does not arrive.

## Chemical Structure Association Trust: Recent Grant Awardees

### 2018

***Stephen Capuzzi,*** *Division of Chemical Biology and Medicinal Chemistry at the University of North Carolina Eshelman School of Pharmacy, Chapel Hill (U.S.A.),* was awarded a grant to attend the 31th ICAR in Porto, Portugal from 06/11/2018 to 06/15/2018, where he presented his research entitled "ComputerAided Discovery and Characterization of Novel Ebola Virus Inhibitors."

***Christopher Cooper,*** *Cavendish Laboratory, University of Cambridge, U.K.,* was awarded a grant to present his current research on systematic, high-throughput screening of organic dyes for co-sensitized dye-sensitized solar cells. He presented his work at the Solar Energy Conversion Gordon Research Conference and Seminar held June 16-22, 2018 in Hong Kong.

***Mark Driver,*** *Chemistry Department, University of Cambridge, U.K.,* was awarded a grant to offset costs to attend the 7th EUCheMS conference, where he will present a poster on his research that focuses on the development and applications of a theoretical approach to model hydrogen bonding.

***Genqing Wang,*** *La Trobe Institute for Molecular Sciences, La Trobe University, Australia,* was awarded a grant to present his work at the Fragment-Based Lead Discovery Conference (FBLD2018) in San Diego, U.S.A. in October 2018. The current focus of his work is the development of novel anti-virulence drugs, which potentially overcome the problems of antibiotic resistance of Gram-negative bacteria.

***Roshan Singh,*** *University of Oxford, U.K.,* was awarded a grant to conduct research within Dr. Marcus Lundberg's Group at Uppsala University, Sweden, as part of a collaboration that he has set up between them and Professor Edward Solomon's group at Stanford University, California. He conducts research within Professor John McGrady's group at the University of Oxford. The collaboration will look to consolidate the experiments studies on heme Fe (IV)=O complexes currently being studied by Solomon's group with future multi-reference calculations to be conducted within Lundberg's group.

### 2017

***Jesus Calvo-Castro,*** *University of Hertfordshire, U.K.,* was awarded a grant to fund travel to present his work at the Fifth International Conference on Novel Psychoactive Substances, held in Vienna, Austria, from August 23-23, 2017. He works on the development of novel methodologies for the in-the-field detection of novel psychoactive substances (NPS), where chemical structure and information play a crucial role.

***Jessica Holien,*** *St. Vincent's Institute of Medical Research, Fitzroy, Victoria, Australia,* was awarded a grant to cover travel to present her work at the 2017 Computer-Aided Drug Design (CADD) Gordon Research Conference, scheduled to take place July 16-21, 2017 in Mount Snow, VT, U.S.A. She is a postdoctoral researcher at St. Vincent's and is responsible for a range of computational molecular modelling including; compound database development, virtual screening, docking, homology modelling, dynamic simulations, and drug design.

### 2016

***Thomas Coudrat,*** *Monash University, Australia,* was awarded a grant to cover travel to present his work at three meetings in the United States: the Open Eye Scientific CUP XVI, The American Chemical Society Spring Meeting, and the Molsoft ICM User Group Meeting. His work is in ligand directed modeling.

***Clarisse Pean,*** *Chimie Paris Tech, France,* was awarded a grant to cover travel to give an invited presentation at the 2016 Pacific Rim Meeting on Electrochemical and Solid State Science.

***Qian Peng,*** *University of Oxford, U.K.,* was awarded a grant to attend the 23rd IUPAC Conference on Physical Organic Chemistry. His research is in the development of new ligands for asymmetric catalysis.

***Petteri Vainikka,*** *University of Turku, Finland,* was awarded a grant to spend the summer developing and testing new methods for modelling organic solvents in organic solutions with Dr. David Palmer and his group at the University of Strathclyde, Glasgow, Scotland.

***Qi Zhang,*** *Fudan University, China,* was awarded a grant to attend a Gordon Conference on enzymes, coenzymes and metabolic pathways. His research is in enzymatic reactions.

**2015**

***Dr. Marta Encisco,*** *Molecular Modeling Group, Department of Chemistry, La Trobe Institute for Molecular Science, La Trobe University, Australia,* was awarded a grant to cover travel costs to visit collaborators at universities in Spain and Germany and to present her work at the European Biophysical Societies Association Conference in Dresden, Germany, in July 2015.

***Jack Evans,*** *School of Physical Science, University of Adelaide, Australia,* was awarded a grant to spend two weeks collaborating with the research group of Dr. Francois-Xavaier Coudert (CNRS, Chimie Paris Tech).

***Dr. Oxelandr Isayer,*** *Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, U.S.A.,* was awarded a grant to attend summer classes at the Deep Learning Summer School 2015 (University of Montreal) to expand his knowledge of machine learning to include Deep Learning (DL). His goal is to apply DL to chemical systems to improve predictive models of chemical bioactivity.

***Aleix Gimeno Vives,*** *Cheminformatics and Nutrition Research Group, Biochemistry and Biotechnology Dept., Universitat Rovira I Virgili, Spain,* was awarded a grant to attend the Cresset European User Group Meeting in June 2015 in order to improve his knowledge of the software that he is using to determine what makes an inhibitor selective for PTP1B.

**2014**

***Dr. Adam Madarasz,*** *Institute of Organic Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Hungary,* was awarded a grant for travel to study at the University of Oxford with Dr. Robert S. Paton, a 2013 CSA Trust grant winner, in order to increase his experience in the development of computational methodology that is able to accurately model realistic and flexible transition states in chemical and biochemical reactions.

***Maria José Ojeda Montes,*** *Department of Biochemistry and Biotechnology, University Rovira i Virgili, Spain,* was awarded a grant for travel expenses to study for four months at the Freie University of Berlin to enhance her experience and knowledge regarding virtual screening workflows for predicting therapeutic uses of natural molecules in the field of functional food design.

***Dr. David Palmer,*** *Department of Chemistry, University of Strathclyde, Scotland, U.K.,* was awarded a grant to present a paper at the fall 2014 meeting of the American Chemical Society on a new approach to representing molecular structures in computers based upon on ideas from the Integral Equation Theory of Molecular Liquids.

***Sona B. Warrier,*** *Departments of Pharmaceutical Chemistry, Pharmaceutical Biotechnology, and Pharmaceutical Analysis, NMIMS University, Mumbai, India,* was awarded a grant to attend the International Conference on Pure and Applied Chemistry to present a poster on her research on inverse virtual screening in drug repositioning.

**2013**

***Dr. Johannes Hachmann,*** *Department of Chemistry and Chemical Biology at Harvard University, Cambridge, MA, U.S.A., was* awarded a grant for travel to speak on “Structure-property relationships of molecular precursors to organic electronics at a workshop sponsored by the Centre Européen de Calcul Atomique et Moléculaire (CECAM) from October 22 – 25, 2013, in Lausanne, Switzerland. .

***Dr. Robert S. Paton,*** *University of Oxford, U.K.,* was awarded a grant to speak at the Sixth Asian Pacific Conference of Theoretical and Computational Chemistry in Korea on July 11, 2013. Receiving the invitation for this meeting has provided Dr. Paton with an opportunity to further his career as a principal investigator.

***Dr. Aaron Thornton,*** *Material Science and Engineering at CSIRO in Victoria, Australia,* was awarded a grant to attend the 2014 International Conference on Molecular and Materials Informatics at Iowa State University, with the objective of expanding his knowledge of web semantics, chemical mark-up language, resource description frameworks, and other on-line sharing tools. He will also visit Dr. Maciej Haranczyk, a prior CSA Trust grant recipient, who is one of the world leaders in virtual screening.

**2012**

***Tu C. Le,*** *CSIRO Division of Materials Science & Engineering, Clayton, VIV, Australia,* was awarded a grant for travel to attend a Cheminformatics course at Sheffield University and to visit the Membrane Biophysics group of the Department of Chemistry at Imperial College, London.

**2011**

***J. B. Brown,*** *Kyoto University, Kyoto, Japan,* was awarded a grant for travel to work with Professor Ernst Walter-Knappat the Freie University of Berlin and Professor Jean-Phillipe Vert of the Paris MinesTech to continue his work on the development of atomic partial charge kernels

**2010**

***Noel O'Boyle,*** *University College Cork, Ireland,* was awarded a grant both to network and to present his work on open source software for pharmacophore discovery and searching at the 2010 German Conference on Cheminformatics.

**2009**

***Laura Guasch Pamies,*** *University Rovira & Virgili, Catalonia, Spain,* was awarded a grant to do three months of research at the University of Innsbruck, Austria.

**2008**

***Maciej Haranczyk,*** *University of Gdansk, Poland,* was awarded a grant to travel to Sheffield University, Sheffield, U.K., for a 6-week visit for research purposes.

**2007**

***Rajarshi Guha,*** *Indiana University, Bloomington, IN, U.S.A.,* was awarded a grant to attend the Gordon Research Conference on Computer Aided Design in August 2007.

**2006**

***Krisztina Boda,*** *University of Erlangen, Erlangen, Germany,* was awarded a grant to attend the 2006 spring National Meeting of the American Chemical Society in Atlanta, GA, USA.

**2005**

***Dr. Val Gillet and Professor Peter Willett,*** *University of Sheffield, Sheffield, U.K.,* were awarded a grant for student travel costs to the 2005 Chemical Structures Conference held in Noordwijkerhout, the Netherlands.

**2004**

***Dr. Sandra Saunders,*** *University of Western Australia, Perth, Australia,* was awarded a grant to purchase equipment needed for her research.

**2003**

***Prashant S. Kharkar,*** *Institute of Chemical Technology, University of Mumbai, Matunga, Mumbai, India,* was awarded a grant to attend the conference, Bioactive Discovery in the New Millennium, in Lorne, Victoria, Australia, (February 2003) to present a paper, "The Docking Analysis of 5-Deazapteridine Inhibitors of Mycobacterium avium complex (MAC) Dihydrofolate reductase (DHFR)".

**2001**

***Georgios Gkoutos,*** *Imperial College of Science, Technology and Medicine, Dep. of Chemistry. London, U.K.,* was awarded a grant to attend the conference, Computational Methods in Toxicology and Pharmacology Integrating Internet Resources, (CMTPI-2001) in Bordeaux, France, to present part of his work on internet-based molecular resource discovery tools.

# Technical Program

## The Ethics of Data Sharing

CINF and the ACS Committee on Ethics (ETHX) cosponsored a session entitled "The Ethics of Data Sharing" on Monday morning, August 20. The session was crowded for a half-day symposium, with eight presentations by speakers with a wide variety of backgrounds. The first two presentations came from the chemical discipline's two largest funding agencies, the National Science Foundation and the National Institute of Health, and the remainder of the talks were presented by a broad swath of individuals interested in data integrity and management.

James Kroll, from the Office of the Inspector General (OIG) of the National Science Foundation (NSF), opened the session. The OIG is an independent office, reporting to Congress and NSF. NSF holds that researchers should make their data publicly available within a reasonable period of time. Those who do not share their data leave themselves vulnerable to concerns about research integrity and possibly even allegations of misconduct. Kroll presented the idea of a "fraud triangle," in which the three sides of the triangle represent opportunity, rationalization, and pressure. In order for fraud to occur, individuals must be motivated by some sort of pressure, must perceive that they have an opportunity to escape unscathed, and must be able to rationalize perpetrating the fraud. The number of fraud cases investigated by the OIG has risen significantly over the past 15 years, and the staff investigated eight cases of data fabrication in 2017 alone. While the trend can be combatted through training, checks, and balances, a large number of scientists confess to inadequate record-keeping, and most of these are students with limited mentorship who are under pressure from their PIs to achieve certain results. The students often have been found to store research data on their own personal computers rather than on institutional storage space, making these data difficult to find after publication, which is when issues are often identified.

Kroll shared a few recent cases that would have been amusing, had they not been true. In one, a post-doctoral fellow did not like the aesthetic look of his data, so, he chose random bands of the same intensity that looked similar. A Ph.D. student documented no raw data and no experiments; when challenged, the student claimed that the computer containing the data had been destroyed. A master's degree student fabricated data for three published articles published under two mentors, and later, while under the influence of alcohol, he admitted that he had falsified the data. Kroll suggests that a difference in attitude among students and younger scientists may be to blame for such disturbing trends. In the past, students would never have thought to risk their reputations or that of their mentors, but, over the past 20 years, narcissism has increased, and attitudes may have changed.

The types of misconduct perpetrated vary depending on the educational level of the fraudster. Faculty members mainly plagiarize, while students are more likely to fabricate data. Data issues tend to occur most frequently in the disciplines of chemistry and biology, and many of the individuals responsible appear to have received their educational training outside of the United States. Kroll suspects that the ultra-competitive environment of research may be a factor in the rise of fraud and that, although responsible conduct of research (RCR) training is required by Federal funding agencies, many institutions simply require funded individuals to "tick a box" that they have completed the required training, rather than worrying about whether or not the faculty and students have learned anything from it. Kroll closed with recommendations of best-practices, which included a hybrid training model for RCR training that includes the PIs, as well as using internal validation to check results prior to publication.

Scott Moore, Deputy Director of the Office of Research Integrity (ORI), gave the next presentation. ORI is part of the Office of the Assistant Secretary for Health and Human Services (HHS). He began with an outline of their organization and summarized the Federal policy on research misconduct. This policy is outlined in HHS Regulation 42 CFR Part 93, and it defines research misconduct as fabrication, falsification, and plagiarism (FFP) and indicates that, to qualify as misconduct, an act must be knowingly and willingly performed. When a misconduct case is brought to the attention of ORI, they give the affected institution the opportunity to resolve it before they begin their own investigation. ORI finds falsification and fabrication to be the most prevalent types of misconduct; between 2006 and 2015, the office investigated 55 cases of falsification alone, with image manipulation lying at the heart of many of them. Moore cited the example of the Murthy case, in which researchers fabricated 11 protein structures from nine publications and 12 Protein Data Bank (PDB) entities. The researchers in question

received a ten-year ban from *all* Federal programs except entitlement programs.

The National Institutes of Health (NIH) has identified a set of nine competencies that should be present in RCR training. These are:

- Conflict of interest;
- Human subjects, animal subjects, and safe laboratories;
- Mentor/mentee relationships;
- Collaborative research;
- Peer review;
- Data acquisition and management;
- Authorship;
- Research misconduct and the handling of misconduct; and
- Scientists as members of society.

NIH also focuses heavily on data and data management, indicating that data must be trustworthy for public use. Institutions are challenged to ensure the quality of their data, and one institution has chosen to have a unit within their library. Data dissemination and ownership are other issues with which researchers and institutions need to grapple; NIH grants name the institution with which the principal investigator (PI) is associated, so, those institutions are responsible for maintaining custody of and access to the data for a minimum of three or four years from the end of the project, disseminating it so that others can use it. In actuality, institutions should strive to retain those data necessary for reproducibility and replication and to serve as evidence that authenticates the experiments for as long as makes sense from a research perspective.

Kenneth Merz, Michigan State University, is the Editor-in-chief of the *Journal of Computational Chemistry*. He spoke about the long-term viability of computational chemistry and biology research data, focusing on the importance of archiving the things that are needed for computational chemists to do their work. He began his presentation by displaying an image of a daisy, the center of which was labelled “computational chemistry” and was surrounded by petals representing databases like the Protein Data Bank (PDB) and the Cambridge Structural Database (CSD); quantum mechanics; molecular mechanics; Quantitative Structure-Activity Relationship (QSAR) and Quantitative Structure-Property Relationship (QSPR); docking; and computers, operating systems, and compilers. In order to achieve optimal long-term storage of the data, a scientist needs to archive all of the data, the software and compiler versions used to acquire and analyze the data, the operating systems that will run that software, and the hardware needed to run the operating system. Merz gave an example, in which running the same software on two different machines yielded divergent results, indicating that sampling problems in statistical mechanics are one of the biggest problems that affect the results of these experiments. QSAR and QSPR requires the storage of really large data sets; in chemistry, the data sets are small, and systems have significant noise. He offered a few suggestions for improving the situation, including establishing a workflow and changing the mindset of the community. He closed with some discussion of some of the available data repositories. Currently, many individuals save material in GitHub and Dropbox, but Merz raised questions of the long-term viability of these solutions. He suggested saving all input and output files as article supporting information and then saving everything on GitHub.

Leah McEwen and Ralph Stuart took the conversation in a different direction, talking about laboratory safety and data sharing. In general, a substance’s safety data sheet (SDS) is the core information source for hazard recognition, but inconsistencies exist between vendors and sources. *Prudent Practices in the Laboratory*, published by the National Research Council, offers a template used to construct the Laboratory Chemical Safety Summaries (LCSSs) present for certain substances in the PubChem database. One highlight of McEwen’s presentation was a discussion of how students can approach risk assessment; one example is to teach students to build a risk assessment the way one bakes a cake.

1. Source ingredients: Check a public safety data warehouse for information.
2. Acquire recipe ingredients: Download the LCSSs for the substances being used.

3. Measure portions: Extract the necessary data from the LCSS.
4. Mix ingredients: Build a Recognize, Assess, Minimize, and Prepare (RAMP) template.
5. Bake: Perform a risk analysis.
6. Eat: Do the experiment.
7. Clean up: Dispose of wastes appropriately.
8. Annotate recipe: Tell others what they need to know to do the experiment safely.

McEwen also reiterated that complying with FAIR data principles represents the most responsible use of data. FAIR states that data should be:

- **F**indable: Data need to reside in an accessible location.
- **A**ccessible: Safety data need to be free and open.
- **I**nteroperable: Data provenance must accompany the data so that individuals can gauge trustworthiness.
- **R**eusable: Data must be interpretable by humans and machines.

Next, Olga Tarasova, from the Institute for Biomedical Chemistry in Moscow, presented a study that her team had performed, examining the reproducibility of biological activity data. Tarasova and colleagues devised and tested an algorithm to identify relevant scientific publications that included bioactivity studies. Their algorithm was designed to search the text of the bioassay protocols and analyze the medical subject headings (MeSH) and keywords associated with the articles. Her team focused on studies of HIV-1 reverse transcriptase, which is an important target for anti-HIV medications. The algorithm first classified the publications by their relevance and then examined their bioassay protocols, evaluated the reference data, and finally compared it with the publications. A publication was determined to be relevant if the substance was found to be active. Comparison of the full text and the abstracts led to similar "relevance" hits and resulted in over 150 papers. The team then collected MeSH and keywords for those papers.They discovered that these terms could not be used to screen the papers because the MeSH terms and keywords did not include names or assay details; as a result, they had to analyze the full text. The results reported indicated great variability of bioassay descriptions, as well as endpoint values.

Kelly Elkins, a forensic chemist from Towson University, next spoke about the importance of sharing data, particularly raw data, in forensic science. Methods of data sharing include electronic laboratory notebooks (ELNs) and cloud services like Dropbox. "Clean" data are placed in public databases and repositories to ensure access by members of the public. It can be quite challenging to combine the data with experiments, which must be reported exactly as they were performed. Elkins presented some acceptable data manipulation practices based on norms developed for photography; these include always saving the originals, enhancing the brightness and contrast, cropping (while still avoiding acquisition bias), and acquiring multiple images under identical conditions. She also shared some data sharing "horrors": not releasing the raw data, releasing the best data instead of the best representation of the data, and not recording the experiment. She then described her best practices for data sharing: publishing negative results and caveats; publishing representative data using error bars; publishing the whole story, sharing reproducible results and all relevant details in a widely-accepted journal; and subjecting data to critical peer review. She closed her presentation by pointing out the field-dependent nature of data sharing, indicating that computer scientists are least likely to share their data, and that only about 13% of biomedical journals required data sharing for publication.

Amy Sarjeant, of the Cambridge Crystallographic Data Centre, easily had the best title ever written for a presentation about data ethics: "Crystallographic crime: Detection and prevention of fake data". She began by describing the history of data sharing amongst the crystallographic community starting in the early days of crystallography, when researchers drew structures by hand and tabulated data in the text or the supporting information of an article. In the early 1990s, with the advent of the CIF file, the crystallographic community developed standards that included recording specific information about the sample, experiment, and structure, and, to ensure integrity, they devised a system of crystallographic review; trained crystallographers could, of course, review the publications, but they also developed a program called CheckCIF to objectively evaluate data files. In 2009,

fraud “rocked” the protein community, when it was discovered that 11 crystal structures from nine documents cited more than 450 times had been faked. Then, in 2010, 140 more structures from *Acta Crystallographic Section E* were discovered to be fraudulent, a number that ultimately grew to 189. It is easy to fake a crystal structure by taking a known structure, making some substitutions, and then refining it against the original data, but these fraudulent structures came to light because CheckCIF produced some very strange results. Since the scientific record needed to be corrected immediately, the relevant publications were retracted, but they are still available online. The current CIF file format includes all of the information required to understand how the data have been processed. As of 2018, 65% of the crystallographic community has adopted the CIF file format.

Tony Williams, of the Environmental Protection Agency, was the final speaker in the session. He discussed the challenges presented by modern data sharing and the challenges presented by using public datasets. He highlighted many of the issues that other speakers had already discussed and focused on the CompTox Dashboard, which obtains its data from a variety of sources. Individual substance records give an indication of the quality of the data contained, and there are 8000 high-quality files and five different levels of quality. EPA is trying to map public data and identify suspect data and data sources. Unfortunately, the CAS Registry Numbers rarely map to the actual substances because of indexing processes and because deleted CAS Registry Numbers may be incorrectly associated with substances. In one memorable case, a substance had over 300 deleted Registry Numbers. Data curation is the truly challenging part. Public data should be curated, but, in some cases, four identifiers for the same substance actually go to four different substances, and some substances have multiple identifiers.The CompTox Dashboard allows crowdsourced comments, and users can highlight a cell in the database and make a comment. Williams noted that ensuring accurate structure representation was also important; it is insufficient simply to add a SMILES string as a table in a publication, and the author should provide the raw structural data in its original format. This will enable curators to be more accurate, and the responsibility falls on the authors since the publication process is not likely to change quickly.

*The author acknowledges the assistance of Pam Mabrouk, one of the session organizers, whose notes were invaluable in preparing this report.*

Judith N. Currano
Head, Chemistry Library, University of Pennsylvania
currano@pobox.upenn.edu

## Reaction Analytics Symposium: General Summary

On August 22 and 23, 2018, at the 256th ACS National Meeting, Dr. Frederik van den Broek organized a symposium on the application of big data and predictive analytics methods to chemical reactions as part of the CINF Division's program. Distinguished thought leaders in the field were invited to share their state-of-the-art research and thoughts.

Dr. Frederik van den Broek (Consultant R&D Solutions with Elsevier's Professional Services) opened the symposium with introductory remarks on the history of artificial intelligence (AI) in chemistry. Starting from the seminal work of Nobel Prize winner E.J. Corey and the development of the LHASA program[1] as a retrosynthetic chemistry planning tool in the 1970s, Dr. van den Broek discussed the motives behind introducing artificial intelligence approaches to synthetic chemistry, quoting J.B. Hendrickson's statement: "the intent is not to replace art in organic synthesis, but to show where the real art lies". The 1980s and 90s were described by Dr. van den Broek as the winter of AI in chemistry, primarily due to lack of capturing expert empirical knowledge as well as skepticism associated with fear of change to the normal working ways of synthetic organic chemists.

Another important realization at that time was the need for high quality, curated datasets with which to train machine learning tools. The lack of negative outcomes in published data sets, the absence of a uniform method to represent chemical reactions, and the limited sharing of data for fear of competition are all hurdles facing data curation for AI tools. Luckily, the development of InChI[2] chemical identifiers for reactions and the Unified Data Model[3] project, which attempts to create open, unified data formats for the storage of experimental information, are developments that provide optimal supervised learning conditions upon which smarter, more robust machine learning tools can be built. Finally, groundbreaking developments in total synthesis, including the pioneering use of free radical chemistry in the Baran Lab[4], offers alternative, pragmatic approaches to organic synthesis in the smallest number of reaction steps and using the most available, cost-effective starting materials possible.

Sara Szymkuć, a student of Prof. Dr. Bartosz Grzybowski at the Polish National Academy of Sciences, and Lindsey Rickershauser from Millipore Sigma gave talks about Synthia[5] (formerly Chematica), which claimed to be the most advanced organic retrosynthesis software[6] product on the market. Expert chemists coded more than 60,000 reaction rules as elaborate decision trees, which are then used to query the entire chemical synthetic space using a series of specialized algorithms that allow for the prediction of the most feasible synthetic route.

Lindsey Rickenhauser spoke about the successful lab bench validation[7] of Synthia as an organic retrosynthesis tool in the lab. It autonomously designed *de novo* organic synthetic routes for eight highly challenging compounds that were successfully executed in the lab; one was a natural product, and the rest were of medicinal chemical importance. These computer-planned routes provided significant cost-saving effects, avoided patented routes, and discovered routes for compounds previously considered impossible to synthesize chemically. Sara Szymkuć described the ability of Synthia automatically to discover new tactical combinations in organic synthesis, a series of counter-intuitive reaction planning steps early in the synthetic pathway of a molecule that lead to a significantly favourable progression of the synthesis route. These routes have been notoriously difficult to discover in the past and have great potential to take the optimization of organic chemical synthesis to unprecedented levels of efficiency.

Tackling the same challenge of retrosynthesis from a machine learning perspective, Prof. Mark Waller from the Waller Lab[8] gave a talk about his recently published AI tool[9] designed to plan chemical syntheses. A Monte Carlo tree search is augmented with three different neural networks; the first transfers knowledge onto novel molecules, the second predicts the feasibility of reactions needed to synthesize them, and the third adds more context to the next iteration of the algorithm. Inspired by the success of the AlphaGo[10] search algorithm, Prof. Waller and his lab created a robust retrosynthesis AI tool that is 30 times faster than traditional computer-aided search methods. Moreover, in a double-blind A/B test, chemists found the routes suggested by this AI tool equivalent to those manually designed by expert chemists and reported in literature.

A third alternative to honing the predictive capabilities of computer-assisted synthesis planning (CASP) programs[11] was presented by Dr. Hanyu Gao of the Jensen Research Group[12] at the Massachusetts Institute of Technology (MIT). He spoke of applying three unique constraints to machine learning approaches in reaction prediction. For the retrosynthetic reaction planning step, two constraints lead to the generation of high-quality

retrosynthetic disconnections: a learned synthetic complexity metric (SCS score[13]) to mitigate the search space's exponential growth, especially in multi-step reactions, and a nearest-neighbor model applied during recursive expansion. Dr. Gao also spoke of the neural network approaches in a forward-thinking, predictive element constraint that is trained on large experimental data sets and acts as a reaction validation step to the retrosynthetic CASP-generated route. Through diversification of the constraints applied to machine learning tools in retrosynthesis, Dr. Gao and his lab hope to create the most optimized, realistic synthetic routes possible for molecules.

Whilst all the previously mentioned approaches were built using chemical structures in reactions to eventually predict reactivity, Dr. Matthew Clark[14], Director of Scientific Services for Elsevier's R&D Solutions, discussed the use of electron density fields[15] instead, utilizing a conditional generative adversarial network (cGAN) in both forward and retrosynthetic analysis of reactions. Because the unsupervised machine learning model recognizes local electron density patterns, it is insensitive to functional group exact locations, making it also insensitive to rotations and thus useful in deconvoluting structural confirmations and able to address complex chemistry of tungsten, for example.

Applications of predictive organic synthesis in various chemistry fields were also discussed. In the world of drug discovery, Victorien Delannée from the National Institutes of Health discussed the prediction of reaction conditions for compounds in the Synthetically Accessible Virtual Inventory (SAVI) database[16], an international collaborative initiative to generate a database of one billion high-quality molecules that are commercially available through Sigma-Aldrich and easily synthesizable, with the most relevant properties for drug design listed for each one. Stephanie Ashenden from the Andreas Bender group[17] at the University of Cambridge gave an interesting talk about the analysis of matched molecular pair transformations in drug discovery projects carried out over the past decade at AstraZeneca. In flow chemistry, Pieter Plehiers, from the Laboratory of Chemical Technology at Ghent University, proposed the incorporation of two AI neural networks in a typical flow chemistry process for pharmaceutical synthesis to detect and to propose optimized reaction conditions, respectively.[18] In the field of combustion chemistry, Nathan Harms of the Department of Chemical Engineering[19] at Northeastern University discussed the application of AI to automatically detect and correct flaws in detailed kinetic models of combustion[20]. Roger Sayle of NextMove Software gave a commentary[21] about AI tools in the reaction analytics space and NextMove's approach towards tackling regioselectivity challenges. Finally, Martin Walker[22] and John Paliakkara from SUNY Potsdam presented an elegant, simple approach to representing reactions through InChI differences, which could contribute towards enriching the Unified Data Model[3] project.

The two-session symposium was well attended and triggered lively, informative discussions from the attendees. As the fields of machine learning and chemistry continue to intertwine, the benefits of collaborations across these disciplines hold great potential in transforming bench chemistry as we know it.

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Sally Makady
Chemistry Solutions Manager, R&D Solutions, Elsevier
s.makady@elsevier.com

## From the Bench to the Stacks: Attending My First CINF Symposia

I recently had the opportunity to attend the American Chemical Society's national meeting in Boston, MA. This particular meeting was my first after beginning a career in librarianship at Florida State University Libraries earlier this year. Prior to arriving at FSU, I obtained my Ph.D. in chemistry at Washington University in St. Louis, MO, and had been a member of the ACS Division of Inorganic Chemistry. Thus, while I have attended ACS meetings in the past, this was my first as a member of the Division of Chemical Information. I would like to briefly share some of my observations and experiences at the August 2018 meeting and explain why I am so excited about the future of CINF.

On August 21, I attended and spoke at the "Chemistry Librarians of the Future" symposium. This particular symposium brought together chemistry librarians from a wide swath of institutions to discuss the future of chemistry librarianship and the skills that may be important moving forward. While all of the presentations were informative and insightful, I wanted to briefly highlight two of particular note to me. First, we heard from Linda Humphries, Science Faculty Librarian at the University of Bath, about the state of science and chemistry librarianship in the United Kingdom. In her impromptu overview, Humphries discussed the increasing rarity of dedicated chemistry libraries in the U.K. and the trend seen in libraries of replacing the subject librarian model with a functional support model. Humphries also mentioned the importance of encouraging more students with science degrees to pursue degrees and careers in librarianship. Both of these points touch on topics of great importance to librarians in the U.S. and are under discussion here, as well. Later, Judith Currano, Head of the Chemistry Library at the University of Pennsylvania, talked about teaching opportunities for chemistry librarians of the future. Currano discussed identifying unmet needs at one's institution and using that information to determine what training and instruction the library can provide. She presented four case studies that put this idea into action, including trainings developed to teach graduate students proper research ethics, ways of determining journal impact and impact metrics, and personal data management.

I also had the opportunity to attend the "Publishing Chemical Data" symposium on August 20. This set of talks was very relevant to my current role, as one of my areas of focus is to increase and broaden the data services offerings that the library provides to STEM researchers at FSU. Much discussion throughout the symposium centered on PubChem, a public data repository for sharing chemical data. Speakers displayed PubChem's new interface, currently in beta and to be released soon, and described the types of data that can be uploaded to the repository. Efforts to import more datasets into PubChem by partnering with publishers such as SpringerNature were mentioned, and the data submission process for PubChem was also highlighted. ChEMBL, a platform for depositing drug discovery data, was also discussed. ChEMBL has already received data deposits from many projects, including the GSK Published Kinase Inhibitor Set, the University of Dundee Gates screening library, and the ADME and physchem datasets from AstraZeneca.

Overall, my first American Chemical Society meeting as a member of CINF was both exciting and inspiring. I had the opportunity to meet and chat with many CINF colleagues and hear their ideas and visions for the future of librarianship. As someone who is at the beginning stages of a librarianship career, these discussions were very informative and thought-provoking. As the ways in which we access information continues to evolve, I believe that the role that librarians play will become increasingly vital. I look forward to watching how libraries adapt and hope to increase my participation in those conversations.

Nicholas Ruhs
STEM Research and Learning Librarian, Florida State University Libraries
nruhs@fsu.edu

## Division of Chemical Information Special Events at the Boston Meeting

The ACS Division of Chemical Information hosted the following events at the Fall 2018 ACS National Meeting in Boston, MA.

**Sunday Welcome Reception & Division of Chemical Information's 75th Anniversary Celebration**
6:30-8:30 pm, Sunday, August 19th – Galleria, Westin Boston Waterfront

The reception, which also honored Herman Skolnik Awardee Prof. Dr. Gisbert Schneider of ETH Zurich, Switzerland, was co-sponsored by:

***Journal of Cheminformatics (Springer Nature)***,
**Bio-Rad Laboratories**,
**Collaborative Drug Discovery**,
**InfoChem**,
**PerkinElmer**
***Journal of Chemical Information & Modeling*** **(ACS Publications)**.

Attendees of the reception mingled and perused the Scholarship for Scientific Excellence posters, which were on display for the duration of the reception. The winners were announced during the reception and are pictured on PAGE X.

The Scholarships for Scientific Excellence were sponsored exclusively by **ACS Publications**.

**Tuesday Luncheon**
12:00-1:30 pm Tuesday, August 21st – Grand Ballroom A, Westin Boston Waterfront

***Speaker:*** *Dr. Alex M. Clark,* Scientist at Collaborative Drug Discovery and Founder of Molecular Materials Informatics

***Title:*** *Leveling up chemical information for the era of big data.*

*Slides of Dr. Clark's presentation are available at:* ***https://www.slideshare.net/aclarkxyz/acs-cinf-luncheon-talk-boston-2018***

The CINF Luncheon was sponsored exclusively by the **Royal Society of Chemistry**.

**Herman Skolnik Award Symposium:** ***De Novo Design***

# Feature: 2018 Herman Skolnik Award Symposium, Honoring Gisbert Schneider

## A report by Wendy Warr for the ACS CINF *Chemical Information Bulletin*

### Introduction

Gisbert Schneider, a full professor at ETH Zürich, holding the Chair for Computer-Assisted Drug Design, received the 2018 Herman Skolnik Award for his seminal contributions to de novo design of bioactive compounds, and the application of these innovative design concepts in both academia and industry. He is recognized as being a pioneer in the integration of machine-learning methods into practical medicinal chemistry, and for his coining the phrases “scaffold-hopping” and “frequent hitter”. A summary of his achievements has been published in the *Chemical Information Bulletin* (http://bulletin.acscinf.org/node/984). Gisbert was invited to present an award symposium at the Fall 2018 ACS National Meeting in Boston, MA. There were 10 speakers in addition to Gisbert himself.

Speakers at the 2018 Herman Skolnik Award Sympisum. From L to R: Ross King, Karl-Heinz Baringhaus, Gisbert Schneider, David Winkler, Jürgen Bajorath, Michael Schmuker, William Jorgensen, Yoshihiro Yamanishi, Kimito Funatsu, Alexandre Varnek, François Diederich (*Photo Credit: Wendy Warr*)

## Molecular recognition studies to advance structure-based drug design

François Diederich of ETH Zürich was the first speaker. His team pursues a multidimensional approach toward deciphering and quantifying weak intermolecular interactions in chemical and biological systems. Experimental study in this research involves the investigation of protein-ligand interactions, synthetic host-guest complexation, and dynamic processes in designed unimolecular model systems, such as molecular torsion balances. It is complemented by computational analysis and exhaustive database mining in the Cambridge Structural Database and the Protein Data Bank (PDB). The findings from this comprehensive investigation greatly aid structure-based drug design.

The first part of François' talk concerned halogen-bonded and chalcogen-bonded supramolecular capsules. Rigorous geometrical requirements for halogen bonding (XB) have been established by both theory[1,2] and experiment.[3-8] The size of the σ-hole on iodine increases with decreasing hybridization state of the carbon atom of the XB donor. In parallel, the electronegative area decreases from C($sp^3$) to C($sp^2$), and changes to an electroneutral surface potential for C(sp). XB strength also increases if X is on electron-deficient heterocycles or fluoroarenes.[9] Halogen bonding between (iodoethynyl)benzene donors and quinuclidine in benzene affords Gibbs binding free energies (ΔG, 298 K) between -1.1 and -2.4 kcal/mol. The enthalpic driving force ΔH is compensated by an unfavorable entropic term TΔS (due to the geometric constraints for XB).

Multidentate halogen bonding involving hydrogen bonding,[10] metal coordination,[11] and ion pair interactions[12] has been reported. More recently, Dumele et al. have highlighted the formation of supramolecular capsules based solely on halogen bonding interactions[13] and have published details of their host-guest binding properties in solution. François showed some single XB hemispheres highly preorganized by four alcohol molecules bridging benzimidazole walls by hydrogen bonding (Figure 1).

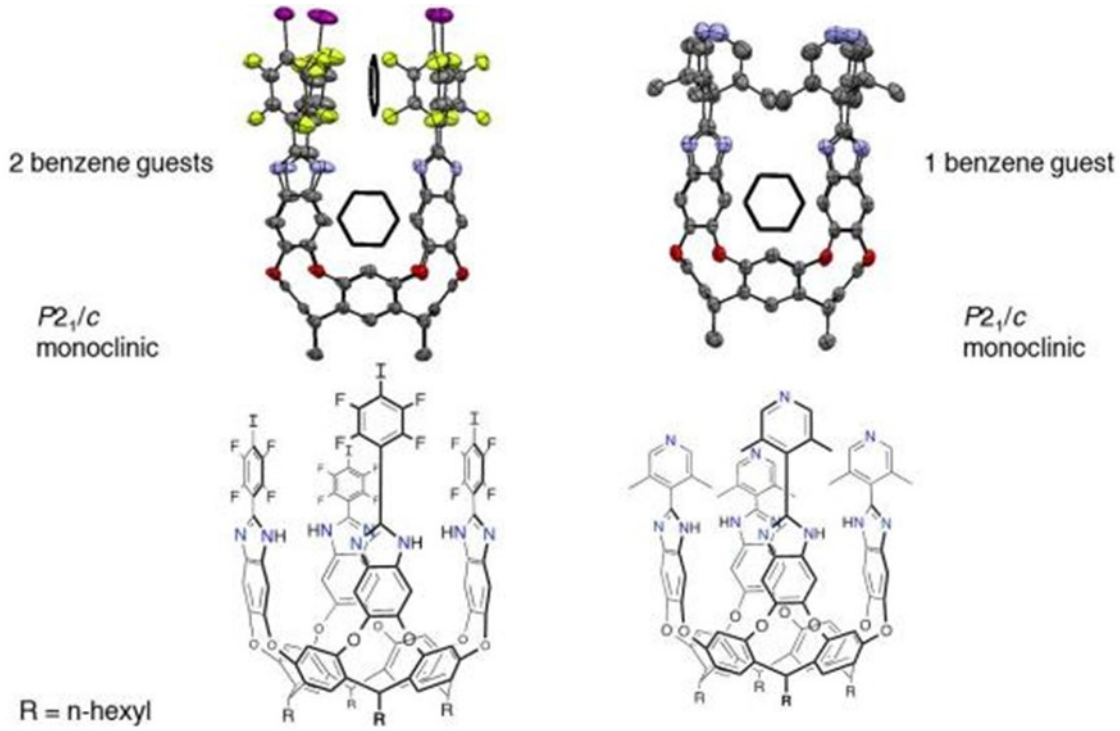



Figure 1

NMR binding data for the F, Cl, Br, and I cavitands as the XB donor showed association constants ($K_a$) of up to 5370 $M^{-1}$(ΔG283 K=-4.85 kcal $mol^{-1}$, for I), even in XB-competitive solvent, such as deuterated benzene, acetone, and methanol (70:30:1) at 283 K, where comparable monodentate model systems show no association. The thermodynamic profile showed that capsule formation was enthalpically driven.[13] The geometry of the highly organized capsules is shown by an X-ray crystal structure[14] which features the assembly of two XB hemispheres, geometrically rigidified by H-bonding to eight methanol molecules, and encapsulation of two benzene guests (Figure 2).

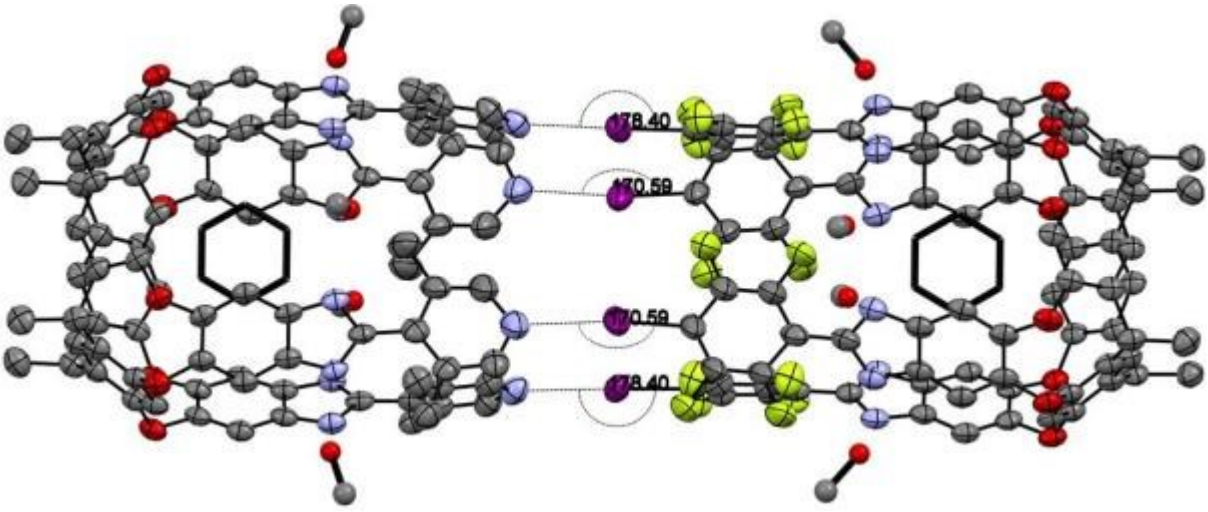


Figure 2

To enhance capsular association strength, tuning the XB donor is more efficient than tuning the XB acceptor, due to desolvation penalties in protic solvents, as shown for a tetraquinuclidine XB acceptor hemisphere (Figure 3).

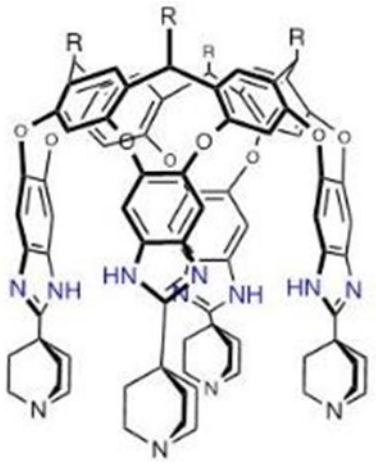


Figure 3

Desolvation of strong XB acceptors leads to “slow exchange” on the NMR timescale. The X-ray crystal structure in this case reveals a 10-component assembly (Figure 4).

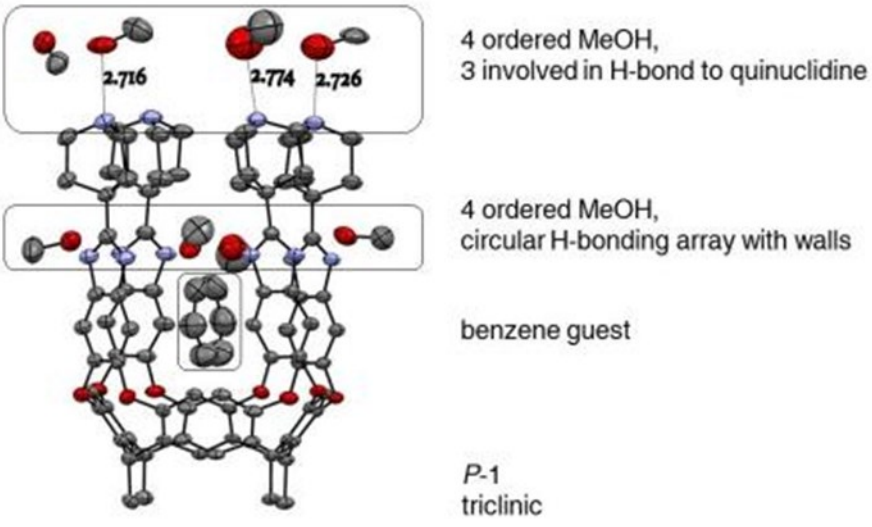



Figure 4

The second part of François' talk concerned cycloalkane and cycloalkanol binding in an enantiopure cage compound. 1,3-Diethynylallenes (DEAs) are chiral building blocks with exceptional chiroptical properties.[15,16] In work by Gropp et al.,[17] four enantiopure DEAs with OH termini were attached to the rim of a resorcin[4]arene cavitand. Alleno-acetylenic cage (AAC) receptors are soluble in polar and apolar solvents, thermally and optically stable, and easy to synthesize. The lean, all-carbon backbones of the four alleno-acetylene walls shape a sizeable cavity (Figure 5).

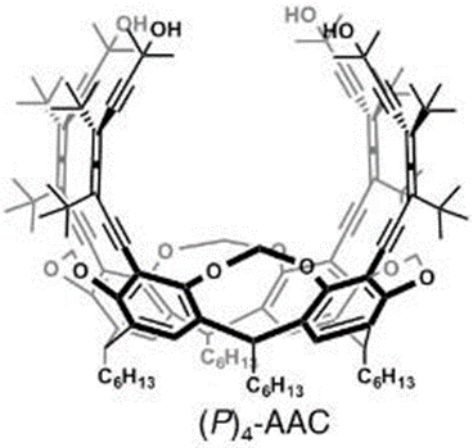



Figure 5

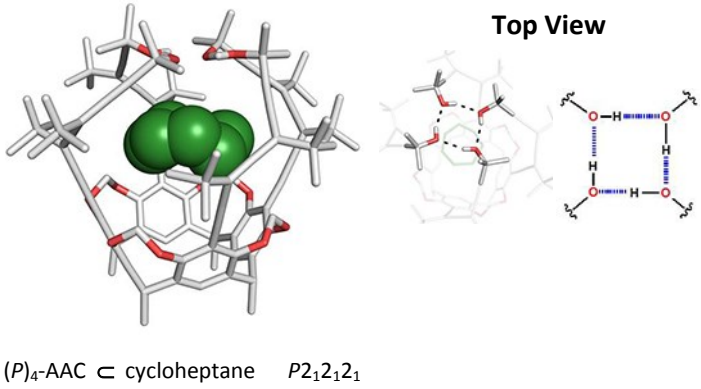



Figure 6

The system undergoes conformational switching between a cage form, closed by a circular H-bonding array (Figure 6), and an open form, with the tertiary alcohol groups reaching outwards. The cage form is predominant in apolar solvents, and the open conformation in small, polar solvents. Complete chiral resolution of (±)-*trans*-1,2-dimethylcyclohexane was found in the X-ray structures, with (P)4-AAC exclusively bound to the (*R*,*R*)-guest and (M)4-AAC to the (*S*,*S*)-guest (Figure 7).

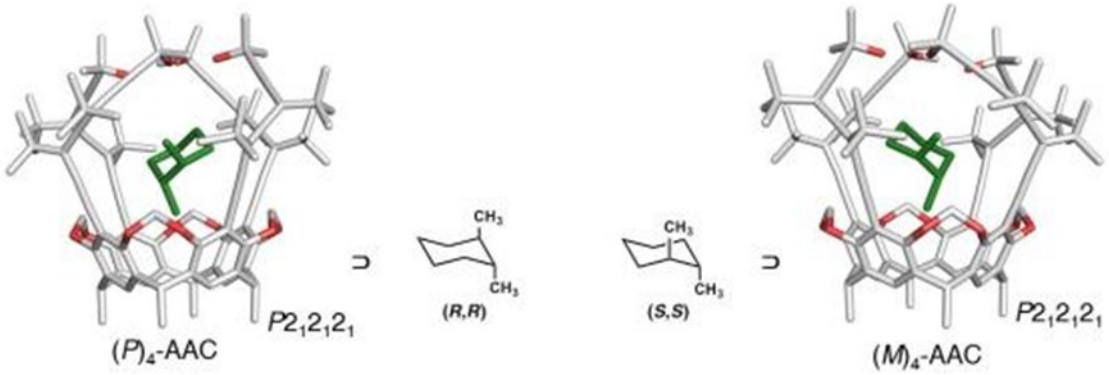



Figure 7

The directionality of the circular H-bonding array is imposed by the absolute configuration of the alleno-acetylenic arms.

The crystals were grown in a protocol akin to that of Inokuma et al.[18] that does not require the crystallization of the sample: crystals of porous complexes are soaked in a solution of the target, such that the complexes can absorb the target molecules, and crystallographic analysis detects the absorbed guest structure along with the host framework. Occupancy was usually 100%. (*R,R*)- and (*S,S*)-*trans*-1,2-dimethylcyclohexane bind in the diaxial conformation with a remarkably small torsion angle. The diaxial conformation is the higher energy conformation.[19]

The dihedral angles $\vartheta_{a,a}$ (X-C(1)-C(2)-X/H) of the axial and diaxial conformers deviate substantially from 180°, down to 144°, accompanied by strong flattening of the ring dihedral angles. Theoretical calculations optimizing

the structure of the isolated guest molecules[20] demonstrate that the noncovalent interactions with the host hardly affect the dihedral angles, validating that the host is an ideal means to study the elusive axial/diaxial conformers. Moving from *trans*-1,2-dimethylcyclohexane to *trans*-1,2-dihalocyclohexane results in enhanced diaxial binding since 1,3-interactions are less important. This work[20] also showed that (±)-*trans*-1,2-dihalocyclohexanes (X = Cl, Br) engage in significant halogen bonding interactions C-X···||| (acetylene) with the hosts. X-ray co-crystal structures of AACs further allowed for a detailed investigation, both experimental and theoretical, on the interplay between space occupancy, guest conformation, and chiral recognition based purely on dispersion forces, and weak C-X···π (X = Cl, Br, I) and C-X···||| (acetylene) contacts (X = Cl, Br). A review[21] has been published recently.

The final part of François' talk concerned water solvation of new carbohydrate-conjugated ligands at the active site of tRNA-guanine transglycosylase (TGT), which was investigated in collaboration with Prof. Gerhard Klebe at the University of Marburg. The intestinal disease shigellosis caused by *Shigella* bacteria affects over 120 million people annually. There is an urgent demand for new drugs as resistance against common antibiotics emerges. Bacterial TGT is a druggable target and controls the pathogenicity of *Shigella flexneri*. TGT recognizes tRNA only as a homodimer[22,23] and performs full nucleobase exchange at the wobble position $G_{34}$. A posttranslational tRNA modification from guanine to queuine (Q) is introduced in the wobble position in the anticodon of tRNA of all organisms (except yeast and archaebacteria), coding for the amino acids Asn, Asp, His, and Tyr. Eukaryotes need Q as nutrient but procaryote TGT introduces 7-aminomethyl-7-deazaguanine (PreQ1) instead of Q. If TGT is blocked, bacteria become apathogenic since the translation of the key virulence factor virF is blocked.[24-26]

Prokaryotic TGT catalyzes replacement of guanine by PreQ1 at the wobble position of four specific tRNAs. The crystal structure of an intermediate has unexpectedly revealed that RNA is tethered to TGT through the side chain of Asp280. Thus Asp280, instead of the previously proposed Asp102, acts as the nucleophile for the reaction.[23] The crystal structure of the active site in *Zymomonas mobilis* TGT bound to tRNA after base exchange (PDB code 1Q2S) has been published.[23]

*lin*-Benzoguanines are strong binders at the base exchange site.[27] An example appears in Figure 8.


Figure 8

A well conserved five-water cluster is located in the ribose 34 pocket and solvates Asn70 and Asp280. Free energy calculations[28] show that only two of these water molecules can be replaced without penalty. François showed an X-ray structure, PDB code 2Z7K (Figure 9).

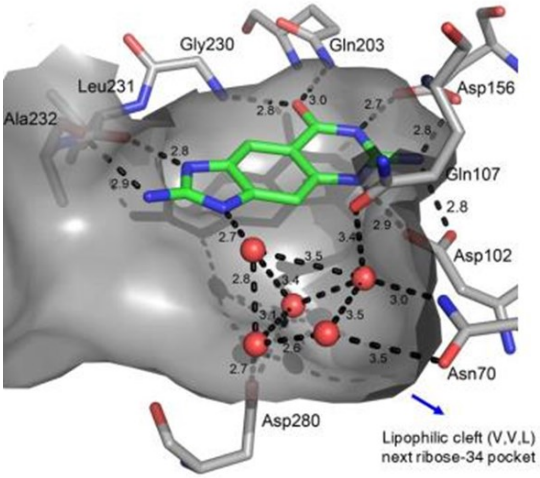
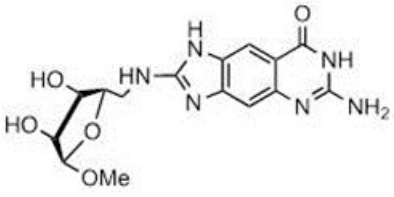
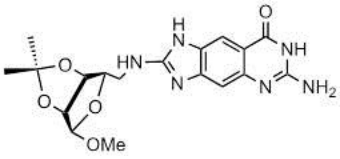



Figure 9

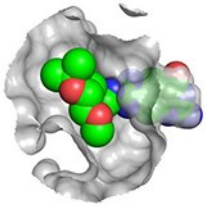
Movsisyan et al.[29] have reported the synthesis of sugar-functionalized *lin*-benzoguanines addressing the ribose-33 pocket of TGT from *Zymomonas mobilis*. Ligand binding was analyzed by isothermal titration calorimetry (ITC) and X-ray crystallography. Pocket occupancy was optimized by variation of size and protective groups of the sugars. In the following compound (Figure 10), the ribose moiety is too small to fill the ribose-33 pocket properly and adopts multiple conformations. This is in agreement with ITC: a lower gain in $\Delta H^o$ is compensated by reduced entropic loss $T\Delta S^o$. In another case (Figure 11), a [5 + 5 + 4] tricyclic water cluster is clearly solved. Together with six other conserved waters W10 to W15, the protein in the complex is efficiently solvated. There are no direct H-bonding contacts from the water cluster to the ligand.




$K_i$ = 1120 ± 110 nM




$K_i$ = 14 ± 7 nM



*C*2, PDB: 5JSV, 1.17 Å resolution

Figure 10

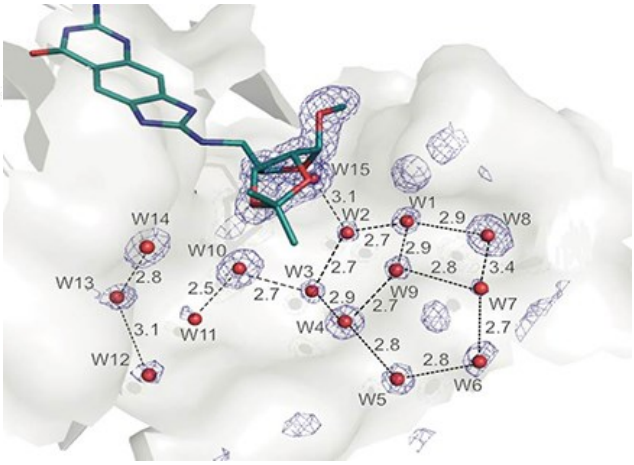
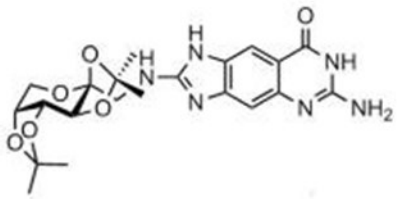
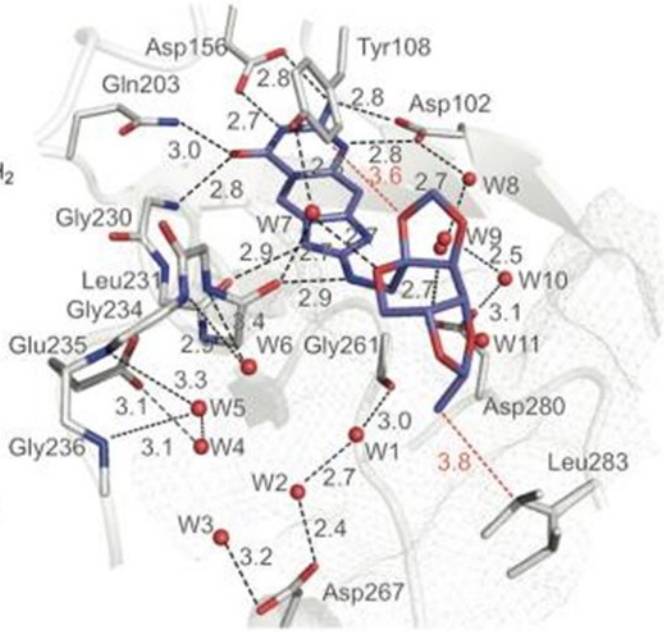



Figure 11

In the case of a larger fructose bisacetonide (Figure 12), the tricyclic water cluster is completely absent. Its formation is prevented by the terminal fructose acetonide. Leu283 moves toward the ligand and establishes a dispersive contact (d(C···C) = 3.8 Å). The ligand is too large and Tyr108 also moves.




$K_i$ = 321 ± 193 nM




*C*2, 1.38 Å resolution

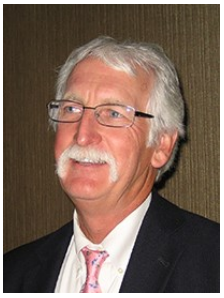
Figure 12

The ordered [5+5+4] water cluster in other complexes is formed between the sugar and protein hydrophobic surfaces to complete the optimal space filling of the 33-pocket. The situation is dramatically different for the complex above, where the solvent accessible surfaces of ligand and protein merge at the place where the tricyclic cluster is found in the other complexes.

Acetonide-protected ribo and psicofuranosyl derivatives are highly potent, benefiting from structural rigidity, good solubility, and metabolic stability. The authors concluded that sugar acetonides have a significant, but not yet broadly recognized, value in drug development. François' team continues to work[30] on the sugar-type inhibitors of the TGT homodimer.

Gisbert had asked all the speakers to conclude with a statement about the challenges they faced. François said that his own desire was to learn about the energetics of the ordered water clusters solvating protein-ligand complexes. How much do such stable clusters contribute to the overall Gibbs free energy? What effect has the replacement of individual water molecules in such clusters by a polar ligand substituent? What are the thermodynamic quantities ($\Delta H$ and $T\Delta S$) for these water cluster formations? Is desolvation of low log$D$ substrates (slow $k_{on}$) a general principle to achieve higher residency half-lives on target (slow $k_{off}$) of drugs?

## Computer-aided discovery of enzyme inhibitors



William ("Bill") Jorgensen of Yale University started by describing the basics of binding. Stronger binding of a ligand to an enzyme leads to greater potency of the ligand as a potential drug. The Gibbs free energy of binding, $\Delta G_b = -RT \ln K_a = RT \ln K_d$.

A $K_d$ of $10^{-9}$ M arises from $\Delta G_b = -12.4$ kcal/mol, and the molecule is referred to as a "1-nM binder or inhibitor". A $K_d$ of $10^{-6}$ M arises from $\Delta G_b = -8.3$ kcal/mol, and the molecule is referred to as a 1 μM binder or inhibitor". Screening hits are very rarely better than low-μM.[31] Lead optimization is needed to evolve them to low nM, to impart druglike properties, and to avoid toxicity and other liabilities. Lead identification and optimization can be automated (Figure 13).

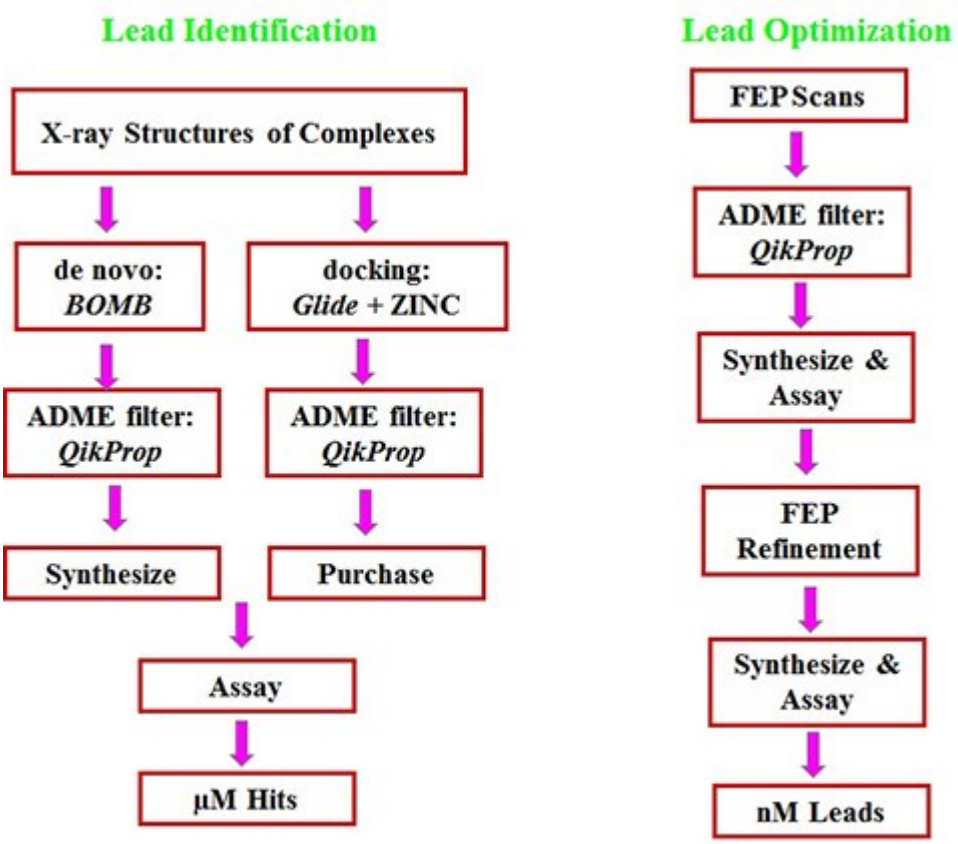



Figure 13

Bill has both computation and synthesis groups at Yale, and he has collaborators at Yale who can carry out assays. X-ray crystallography is also done in-house. Underlying all the modeling is the representation of the inter and intramolecular energetics, with Optimized Potentials for Liquid Simulations-All-Atom (OPLS-AA) force fields, and the software used is Biochemical and Organic Simulation System (BOSS), Biochemical and Organic Model Builder (BOMB), and MCPRO. Derived from BOSS, MCPRO[32] performs Monte Carlo statistical mechanics simulations of peptides, proteins, and nucleic acids in solution. For de novo lead generation, the BOMB program builds combinatorial libraries in a protein binding site using a selected core and substituents. The OPLS-AA force field[33] is a well-proven model which has been continually tested and improved.[34-38] Bill's group offers a web-based service, LigParGen (http://zarbi.chem.yale.edu/ligpargen/), that provides force field parameters for organic molecules or ligands.

Bill presented some applications of his group's software, centered on the design of inhibitors targeting macrophage migration inhibitory factor (MIF), and human immunodeficiency virus HIV-1 reverse transcriptase (HIV-1 RT). MIF is a cytokine released by T-cells and macrophages. It is also a keto-enol tautomerase. The MIF signaling cascade is initiated by binding to its receptor, CD74. MIF is a target for development of anti-inflammatory[39] and anti-cancer agents.[40] Strategies including in silico modeling, virtual screening, high-throughput screening, and screening of anti-inflammatory natural products have led to a large and diverse catalog of MIF inhibitors, as well as some understanding of structure-activity relationships.[40] MIF is also now of interest in neurological disorders.[41]

Bill's group prefers to measure $K_i$, the enzyme-inhibitor binding constant, rather than $IC_{50}$, which varies with substrate concentration and $K_m$. $K_i$ is determined by a *p*-hydroxyphenylpyruvate (HPP) tautomerase assay. In de novo design BOMB grows analogues from a core. It adds 1-4 substituents in five possible topologies; generates all conformations in the binding site; optimizes each with the host partly flexible; and scores and outputs the best as a PDB structure or Z-matrix. Bill's team has reported on design, synthesis, and protein crystallography of biaryltriazoles[42] as inhibitors of MIF. Compounds with $K_i$ from 37 to 0.65 μM were synthesized, and a crystal structure 4WRB was obtained showing a binding site with a possible cation-π interaction with Lys32. Additional BOMB modeling encouraged pursuit of 5- and 8-phenoxyquinolinyl analogues (C8 example shown below). Activity was further enhanced by addition of a fluorine atom. The compound below had $K_i$ = 0.014 μM (optimized from a C5 derivative with $K_i$ = 3.0 μM). This compound is much more potent than others in the literature. Bill showed the related PDB structure 5HVS (Figure 14).

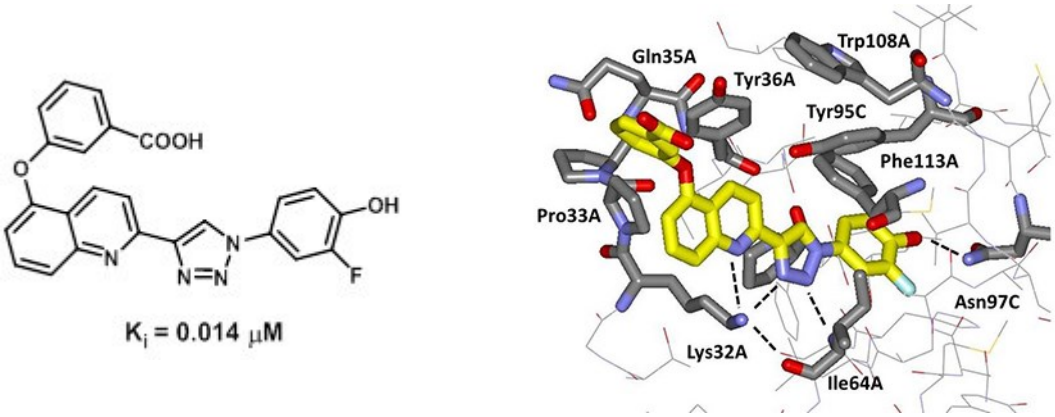
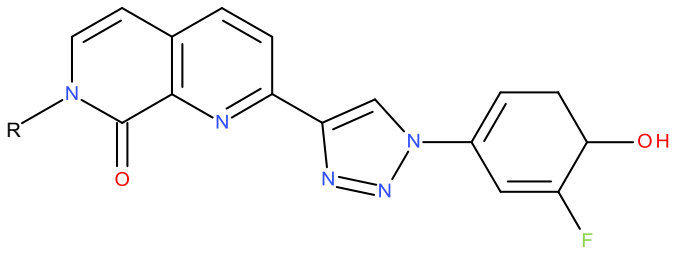



Figure 14

Development and use of fluorescence polarization assays using a fluorescein-labeled tracer provided direct binding data[43] and yielded $K_d$s in agreement with $K_i$. (This assay has also been used in Janus kinase 2 (JAK2 kinase)[44] studies.) Striking combinations of protein-ligand hydrogen bonding, aryl-aryl, and cation-π interactions are responsible for the high affinities. A new chemical series was then designed using this knowledge to yield two more strong MIF inhibitors. Coordination of the ammonium group of Lys32 in the active site using a 1,7-naphthyridin-8-one instead of a quinoline was investigated.[45] DFT calculations indicated potential benefits for an added hydrogen bond with the lactam carbonyl group, while free energy perturbation (FEP) results were neutral. Consistent with the FEP results, the naphthyridinones were found to have similar potency to the related quinolines in spite of the additional protein-ligand hydrogen bond (Figure 15).

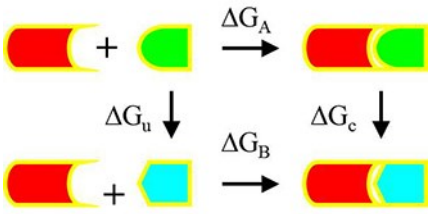



R = $CH_3$; $K_i$ = 0.075 μM  R = $CH_2COOH$; $K_i$ = 0.090 μM

Figure 15

Phenols often show low bioavailability owing to glucuronidation and sulfation, although 7% of all approved oral drugs contain a phenol. Most of the potent MIF tautomerase inhibitors incorporated a phenol, which hydrogen-bonds to Asn97 in the active site. Results of structure-based and computer-aided design, starting from a 113 μM docking hit, have provided substituted pyrazoles as phenol alternatives[46] with potencies of 60-70 nM. Crystal structures (6CBG, 6CBH) of complexes of MIF with the pyrazoles highlight the contributions of hydrogen bonding with Lys32 and Asn97, and aryl-aryl interactions with Tyr36, Tyr95, and Phe113 to the binding. A systematic study of aqueous solubility[47] has been carried out. Currently, 14 of the Yale compounds are being tested by Charles River Laboratories for their ability to inhibit MIF-induced proliferation of glioma cells.[48]

Bill next turned to the topic of free energy perturbation (FEP)[49], on which he has worked since 1980. Since 2005, he has applied it to lead optimization. The thermodynamic cycle for relative free energies of binding is as follows (Figure 16).




$$\Delta\Delta G_{binding} = \Delta G_B - \Delta G_A = \Delta G_c - \Delta G_u$$

Figure 16

FEP calculations are performed for the protein-ligand complex in water. Extensive Monte Carlo sampling is carried out for the protein, ligand, and water at 25 °C. The results identify modifications that should increase binding affinity. The software used is MCPRO.[32] During the 1980s, advances in the ability to perform computer simulations, and to calculate free energy changes, led to the expectation that such methodologies would soon show great utility for guiding molecular design. The 1980s also saw the rise of high-throughput screening and combinatorial chemistry, along with complementary computational methods for de novo design and virtual screening including docking. All these technologies appeared poised to deliver leads for any target, but realization of the expectations required significant additional effort and time. It was important to test if FEP could deliver in a prospective manner. Striking success has now been achieved for computer-aided drug lead generation and optimization.[50] FEP for drug lead optimization[51] is now accepted, with room for improvements: exciting challenges remain.

One application is optimizing the substituents on the phenol ring[42,43] of the MIF inhibitors described above, where the crystal structures confirm the position of F contacting Met101. Also a “heterocycle scan” was performed using FEP with Desmond[51] OPLS2.1. Experimentally, nothing has been found better than 1,2,3-triazole. A tetrazole and a thiadiazole are 1-5 μM inhibitors.

Most of the Yale FEP work has been on HIV-1 RT. Bill has reviewed[52] 10 years of efforts in his laboratory to discover anti-HIV agents. The work has focused on computer-aided design and synthesis of non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs), with collaborative efforts on biological assaying and protein crystallography. MT-2 assays were carried out in Karen Anderson's laboratory. X-ray crystallography was carried out in Eddy Arnold's laboratory.[53] Monte Carlo and FEP simulations have often been executed to identify the most promising choices for heterocycles, linking groups, and substituents on rings.[54,55] Numerous design issues were successfully addressed including the need for potency against a wide range of viral variants, good aqueous solubility, and avoidance of electrophilic substructures. Computational methods including docking, de novo design, and FEP calculations made essential contributions. The result is novel NNRTIs with picomolar and low-nanomolar activities against wild-type HIV-1, and key variants that also show much improved solubility and lower cytotoxicity than recently approved drugs in the class.

Members of the catechol diether class are highly potent NNRTIs. Many NNRTIs, such as rilpivirine, bear a cyanovinylphenyl (CVP) group, an uncommon substructure in drugs that gives reactivity concerns. Bill's team used computer simulations to design bicyclic replacements[56] for the CVP group. FEP results for 18 alternatives were obtained and 30 new compounds were synthesized, including three with $EC_{50}$ activity values of 10nM, 7nM and 0.38 nM. The team has also reported potent inhibitors active against HIV-1 RT with K101P, a mutation conferring rilpivirine resistance.[57] The results for K101P are explained by crystal structures: the Yale compounds do not make an H-bond with a K101 carbonyl (Figure 17).

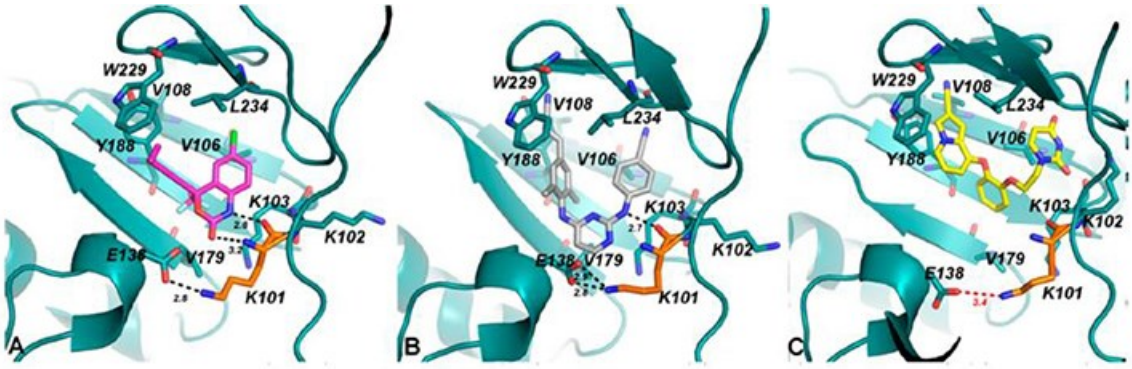



Figure 17

The clinical benefits of NNRTIs are hindered by their unsatisfactory pharmacokinetic (PK) properties, and the rapid development of drug-resistant variants. Bill's team used computational and structure-guided design to develop two next-generation NNRTI catechol diether drug candidates, and published PK and humanized mouse studies.[58,59] One candidate is JLJ636 (Figure 18).

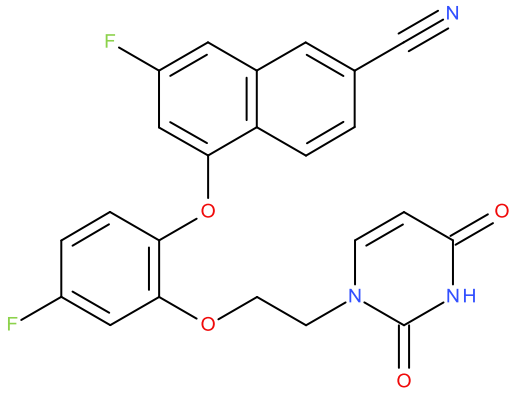



Figure 18

Resistance associated with the Tyr181Cys mutation in HIV-1 RT has been a key roadblock in the discovery of NNRTIs. The team at Yale has reported covalent inhibitors of Tyr181Cys RT that can completely knock out activity of the resistant mutant and of the particularly challenging Lys103Asn/Tyr181Cys variant.[59] Conclusive evidence for the covalent modification of Cys181 was provided from enzyme inhibition kinetics, mass spectrometry, protein crystallography, and antiviral activity in infected human T-cell assays.

## Massive computational docking experiments to identify noble gases target for new "atomic drugs"

Dave Winkler of the Monash Institute of Pharmaceutical Sciences and La Trobe University, Australia presented research carried out in collaboration with colleagues at the Commonwealth Scientific and Industrial Research Organization (CSIRO), Australia, and Air Liquide Santé in France. All chemists know that the noble gases are chemically inert, except to the most extreme reaction conditions. Paradoxically, several of these gases exhibit a wide range of fascinating biological effects, some of which have been demonstrated in vivo and in the clinic. Their most important physical properties are lipophilicity, size, polarizability, and arguably, their rarity. As they are such simple entities, modeling their properties and biological interactions is considerably more tractable than for small drugs where conformation, hydrogen bonding, charge, π interactions etc. are often the dominant interactions.

Dave and his colleagues have conducted an exhaustive review[60] of the literature on medical and pharmacological properties of noble gases. About 400 papers were studied, most of them published since 1980. The review was necessary for the authors to understand current experimentally verified interactions with proteins at atomic level, and to infer likely pharmacological effects of noble gases binding to human proteins from computational screening.

There is a strong correlation of anesthesia and other biological effects with solubility. Many potentially clinically useful properties are known or may emerge. It is impractical to carry out experiments to assess the effect of noble gases on every possible protein target; simulation predicts xenon binding sites and is the only feasible way to explore noble gas binding. Novel delivery systems are required to reduce cost and allow lighter noble gases to be used clinically.

Noble gases have many biochemical effects at the atomic level. Xenon affects a range of receptors involved in cell signaling; the N-methyl-D-aspartate receptor (NMDA receptor) is the receptor best studied experimentally. Two of the other molecular targets for xenon that have been identified[61] include the two-pore-domain potassium channel TREK-1, and the adenosine triphosphate-sensitive potassium channel (K(ATP)), but which of these targets are relevant to acute xenon neuroprotection is not clear.

Pharmacological effects of noble gases on cells, organs, and organisms include anti-apoptotic effects, cytoprotection, neuroprotection, analgesia, anticonvulsant effects, anesthesia, and effects on memory and addiction. Xenon is an ideal anesthetic. It is 1.5 times more potent than nitrous oxide, offers rapid induction and emergence, has low toxicity, and is devoid of teratogenicity. It protects neural cells from ischemic injury and has many other clinical advantages. Its unique combination of analgesia, hypnosis, and lack of hemodynamic depression makes it a very attractive choice for patients.

Interestingly, NMDA receptors have recently been shown to play a major role in alcohol craving and relapse, and other addictions. A study of the effect of xenon on alcohol-seeking and relapse-like drinking behavior in rats[62] showed that even a brief exposure to xenon can induce an anti-reward effect lasting several days. Xenon may also usefully interfere with craving in human alcoholics, and potentially in other addictive settings.

Dave's team aimed to discover new, useful therapeutic applications for noble gases. Given the simplicity of the ligands, and the steady improvement of computational docking algorithms, it is feasible to conduct computational studies on a large number of proteins for their likely affinity for the noble gases. Dave hypothesized[60] that the results of simulations can identify which proteins bind the gases most tightly, and where the gases bind relative to ligand or cofactor binding sites, thus allowing proteins to be prioritized in terms of potential medical interest. Interpreting and visualizing data allows inferences of pharmacological pathways affected by noble gases. Confirmatory experiments will be run on the top candidates. Efficient delivery of noble gases by nanoparticles, to overcome issues with cost (for xenon), and the need for hyperbaric administration (for noble gases other than xenon and perhaps krypton), would greatly increase the added value.

The aims of the in silico screen were:

- to identify whether the xenon binding is in or very near the endogenous ligand binding pocket and could block ligand binding

- to quantify how tightly xenon binds, and how many xenon atoms the site will accommodate
- to identify sites with very good xenon binding where the binding may also be favorable for the smaller noble gases
- to identify the structural rules for noble gas binding sites
- to carry out a detailed analysis of interesting results using molecular dynamics (MD)
- to validate the predictions in laboratory experiments
- to lead into experiments on efficient drug delivery.

An essential requirement for such a massive computational study is to validate the methods. If the methods can reliably locate the known experimental binding positions of noble gases in diverse proteins, a much larger computational study is more likely to yield useful new knowledge. To this end, a diverse subset of about 60 proteins in the PDB containing at least one xenon atom and having <50% sequence identity was analyzed to study how xenon binds to the protein, and how close xenon approaches site residues. In most of the cases, the closest approach is 3.5 – 4.5 Å. Activity originates from one of two mechanisms: xenon directly binds to the binding site, or xenon binds elsewhere causing an expansion in the cavity volume, which then presumably modifies the active site conformations or flexibility.

For docking, Dave used the AutoDock 4 package from the Scripps Institute. Liu et al. had previously found good agreement[63] between the xenon binding sites and energies for the NMDA receptor predicted by AutoDock and MD calculations. Force fields and energy cut-offs were fine-tuned by identifying all known xenon crystallographic binding sites; Andrew Warden of CSIRO carried out the DFT calculations.

There were 116 protein structures with xenon ligands in the validation set, 12 with krypton, and four with argon. Automated protein preparation was essential if the results were to be valid and useful: this was one of the most time-consuming parts of the project. The docking method was validated by quantifying how well simulations could predict binding positions in 132 diverse protein X-ray structures containing 399 xenon and krypton atoms. Dave and his co-workers found excellent agreement[64] between calculated and experimental binding positions of noble gases: 94% of all crystallographic xenon atoms were within 1 xenon van der Waals (vdW) diameter of a predicted binding site, and 97% lay within 2 vdW diameters; 100 % of crystallographic krypton atoms were within 1 krypton vdW diameter of a predicted binding site. Dave gave some examples (Figure 19), for example, porcine elastase (1C1M) with a single xenon atom in the structure (left) and T4 lysozyme mutant (1C6A) with two krypton atoms in the structure (Figure 19, right).

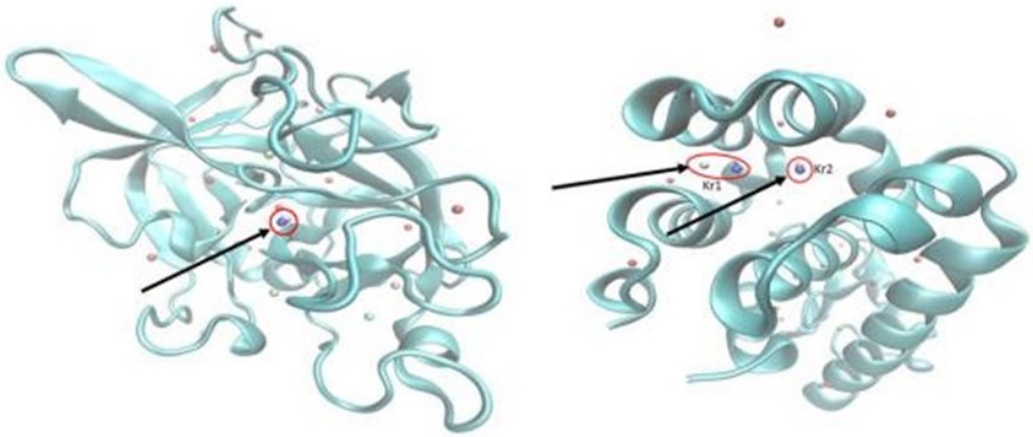



Figure 19

The PDB contains about 70,000 mammalian protein structures and about 130,000 structures in total. There is considerable redundancy in the PDB. Imposing sequence similarity allows redundancy to be removed, leaving representative structures for each protein. After these redundancy filters are applied the PDB contains 20,000 human protein structures at 100% similarity. Systematically mapping the energy of the noble gases at all grid locations (in 0.375 Å steps) in all 130,000 PDB structures is a formidable computational task. This task has now been completed and the resulting dataset (http://group18.csiro.au/#/about) is freely available on the CSIRO website. Dave encourages interested scientists to explore the dataset, perhaps by looking at how various noble gases bind to their favorite protein targets.

The team is now using automated and manual methods to analyze the massive dataset to find proteins with the most promising interactions with noble gases, primarily xenon and krypton. For these, they will explore the pharmacological effects of hits using the published literature; report on protein structure, and function, and known synthetic modulators of the protein's action, and infer pharmacological effects; and design experiments to validate the in silico predictions.

Proteins of special interest will be given detailed analysis using higher level modeling techniques: docking and molecular dynamics. Advanced docking can study in more detail the interactions of noble gases with specific sites in proteins, allow the binding partners to be characterized, and allow competition with natural ligands to be modeled. Molecular dynamics[63] can reveal the time course of interactions between noble gases with proteins, the trajectories of gases through proteins, the effect of the binding on protein structure, and so on. Delivery systems for noble gases are also important. Britton et al.[65] have demonstrated that in vivo xenon delivery via echogenic liposomes is neuroprotective. Microbubbles are another potential method for therapeutic noble gas delivery.

Dave concluded, as requested by Gisbert, with a list of grand challenges for molecular design. We need better mapping of structures into mathematical objects (deep learning), generative models that can predict real molecules with improved properties from models, use of evolutionary algorithms to explore more of the vast chemical space, and generation of autonomous systems.

## Progression saturation analysis of analogue series using virtual candidate compounds

Jürgen Bajorath of the University of Bonn presented new work on lead optimization. In optimization, it is difficult to estimate when an analogue series might be saturated and synthesis of additional compounds would be unlikely to yield further progress. Only a few approaches are currently available to monitor series progression, and aid in decision making. Jürgen presented a new computational method to assess progression saturation of analogue series by comparing existing compounds to virtual candidates. In this method, virtual analogues are generated for an existing analogue series, and virtually extended series are projected into a chemical reference space. Chemical neighborhoods (NBHs) of existing analogues are defined and a dual scoring scheme is applied to quantify the saturation of analogue series focusing on neighborhoods. Different saturation categories are established on the basis of characteristic scores.

The NBH of each experimental analogue is defined on the basis of compound distance relationships in chemical space. NBH radii are adjusted for score calculations. The raw global saturation score quantifies chemical space coverage by existing and virtual analogues. The NBH radius of experimental analogues is set to the median of distances between each virtual analogue and its top 1% nearest virtual neighbors. The raw local saturation score quantifies the distribution of virtual candidates across the NBHs of active analogues. The NBH radius of active analogues is set to the median of pairwise distances between active analogues.

The raw global saturation score, *S*, is given by

$$(S) = \frac{\left|v_{\exp tl}\right|}{\left|V\right|}$$

where $V$ = set of virtual analogues, and $v_{exptl}$ = set of virtual analogues in NBHs of experimental analogues. In the following example (Figure 20), the raw global saturation score is 8/15.

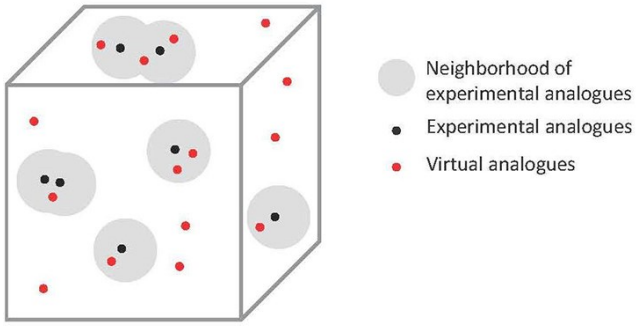



Figure 20

The raw local saturation score, *A*, is given by

$$(A) = \frac{|A|}{|v_{active}| + 1}$$

where *A* = set of active analogues, and $v_{active}$ = set of virtual analogues in NBHs of active analogues. In the following example (Figure 21), the raw local saturation score is 4/7.

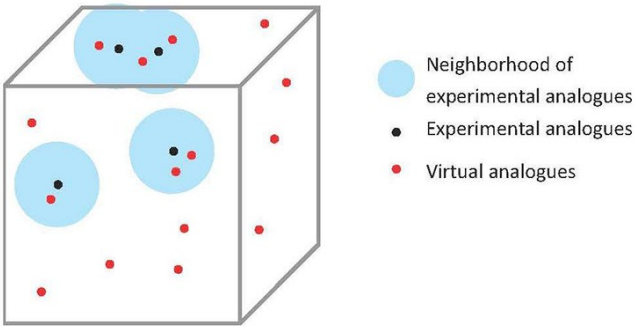



Figure 21

The global saturation score increases with increasing numbers of virtual candidates falling into NBHs of experimental analogues, indicating extensive global chemical space coverage. The local saturation score increases with decreasing numbers of virtual candidates in NBHs of active analogues ("active NBHs"). For ensembles of series, raw global and local scores are converted into z-scores.

A dual scoring scheme is obtained by combining global and local saturation scores (global/local). Combined scores define different saturation categories (Figure 22).

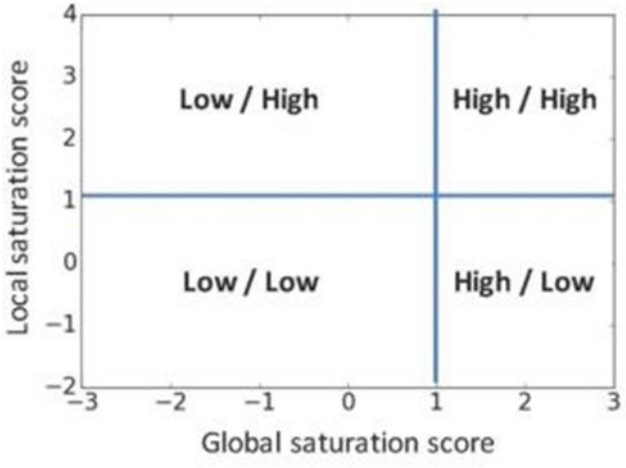



Figure 22

Early-stage series are categorized low/high: there is low chemical space coverage with only a few virtual candidates in active NBHs. Mid-stage series are categorized low/low: there is low chemical space coverage with many virtual candidates in active NBHs. Late-stage series are categorized high/low: there is extensive chemical space coverage with many virtual candidates in active NBHs. Saturated series are categorized high/high: there is extensive chemical space coverage with only a few virtual candidates in active NBHs.

Jürgen carried out a proof of the concept. Using an in-house algorithm, 80 analogue series were extracted from PubChem Bioassays. A total of 1618 compounds (for 23 targets) had single substitution sites, and active and inactive analogues were included. Also, 64 analogue series were extracted from ChEMBL. In this case a total of 1422 compounds (for 62 targets) had multiple substitution sites, and only active analogues were included.

The first descriptor set included seven simple and chemically intuitive numerical descriptors: molecular weight, number of H-bond acceptors, number of H-bond donors, number of rotatable bonds, log*P*, aqueous solubility, and molecular surface area. The second descriptor set included seven "abstract" numerical descriptors (topological and shape indices, complex surface and charge descriptors, and synthetic feasibility index) with little correlation. Set one gave a seven-dimensional reference space; set one plus set two gave a fourteen-dimensional reference space.

Analogue series-based (ASB) scaffolds extracted from ChEMBL were enumerated with 13,203 unique R-groups to generate "diverse" virtual analogues (ASB_VAs) (Figure 23).

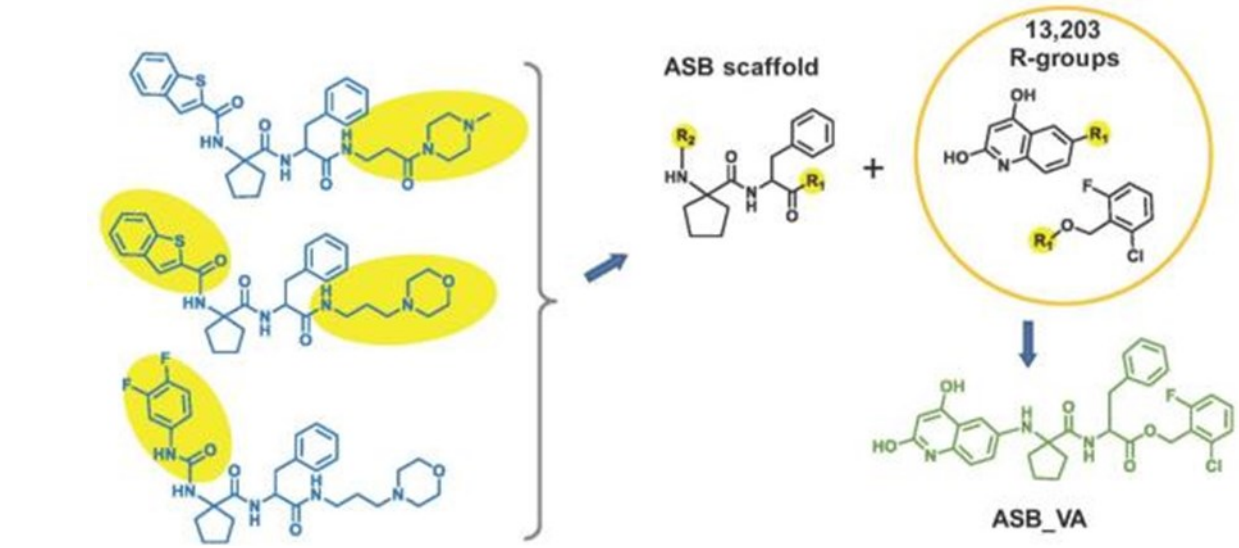



Figure 23

Series-specific design gave variable numbers of virtual analogues from SAR matrices (SARMs)[66], that is, "close-in" virtual analogues (SARM_VAs) (Figure 24).

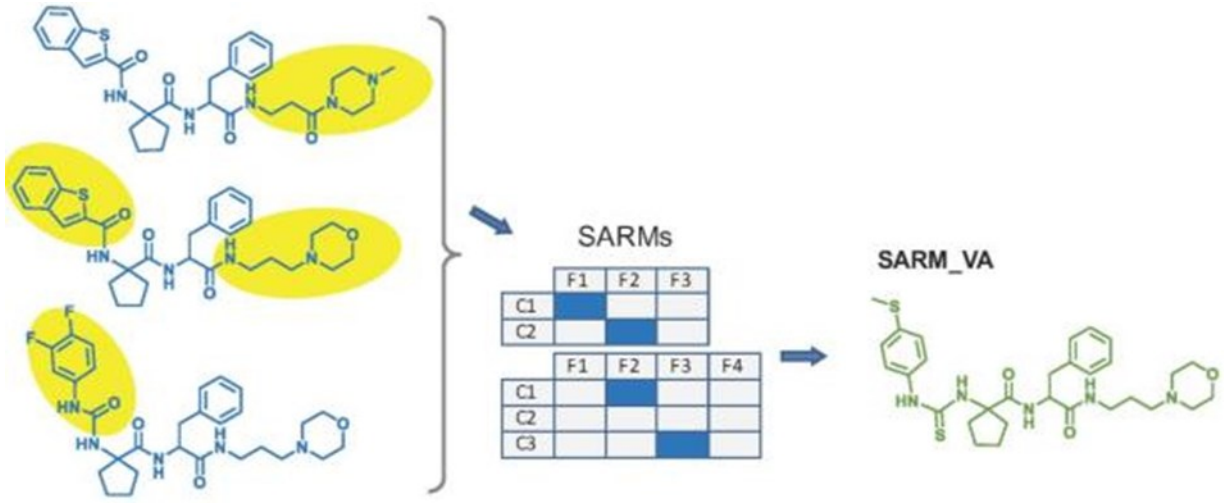



Figure 24

Jürgen briefly described the SARM methodology[66] for structural organization of compound sets. Systematic fragmentation of compounds yields matched molecular pairs (MMPs). In a dual fragmentation scheme, step 1 (standard fragmentation) gives cores and R-groups, and step 2 (core fragmentation) gives core MMPs. A matrix contains a subset of compounds with analogous core structures (that only differ at a single site). By design, SARMs are obtained only from series with multiple substitution sites (Figure 25)

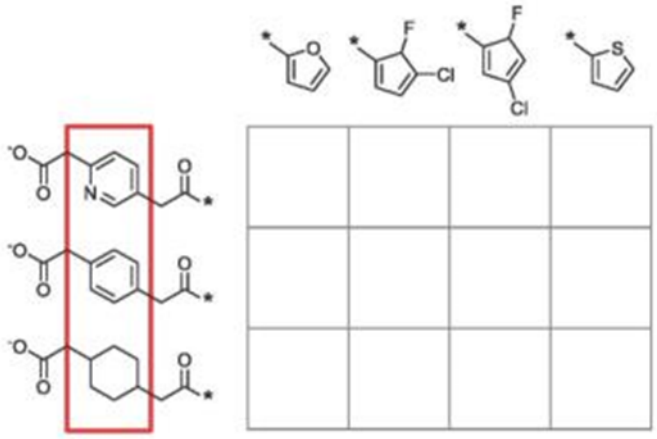


Figure 25

A matrix is filled with available core structures and R-groups (see below). Large series typically yield multiple SARMs. Cells are colored by increasing potency (from red to green below). "Empty" cells represent virtual analogues: unexplored (core plus R-group) combinations. These close-in virtual analogues form a "chemical space envelope" around compound series (Figure 26).

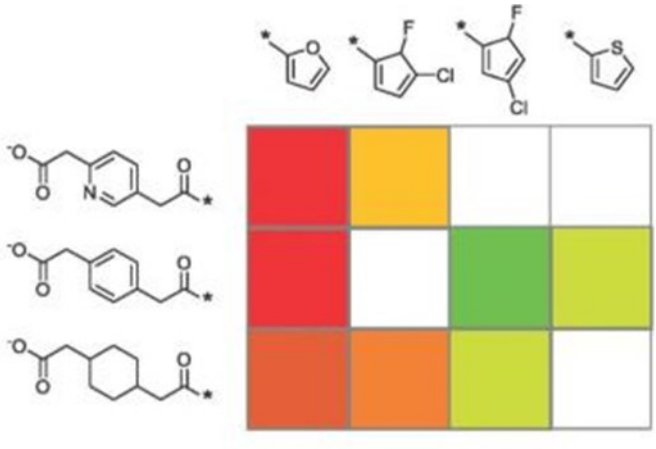


Figure 26

Jürgen presented his results. There was no detectable correlation between global and local saturation scores for the 80 PubChem series (Figure 27).

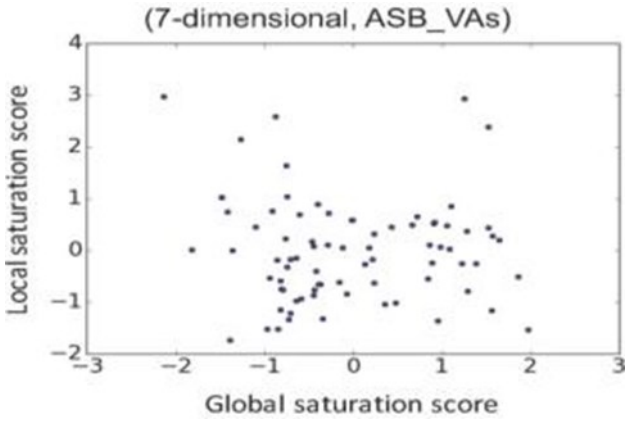



Figure 27

As regards reference space sensitivity, a comparison of 80 PubChem series in 7- and 14-dimensional chemical reference space (ASB_VAs) showed that 63 of 80 series retain their category assignment (Figure 28).

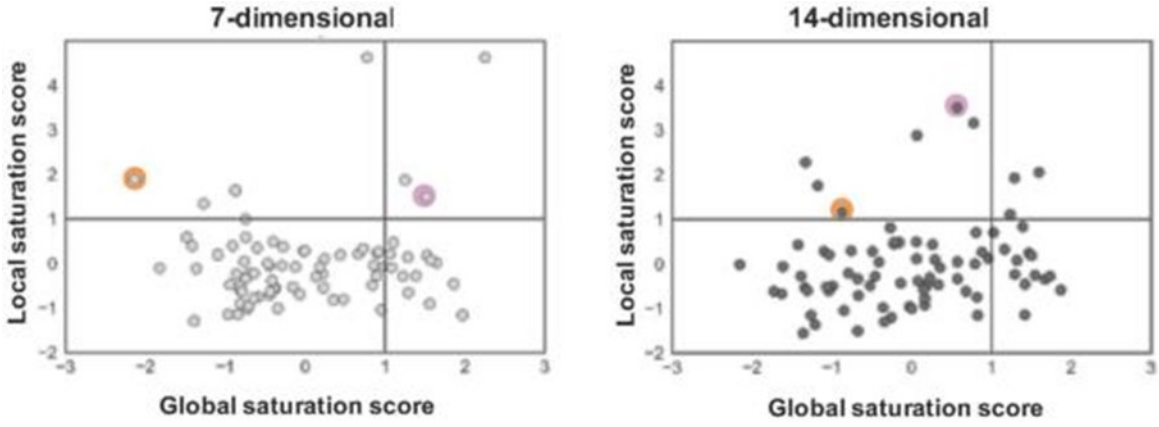



Figure 28

The category distributions of PubChem and ChEMBL series were similar as shown by the 14-dimensional ASB_VAs plot below. Both sets are dominated by series with mid-stage character (Figure 29).

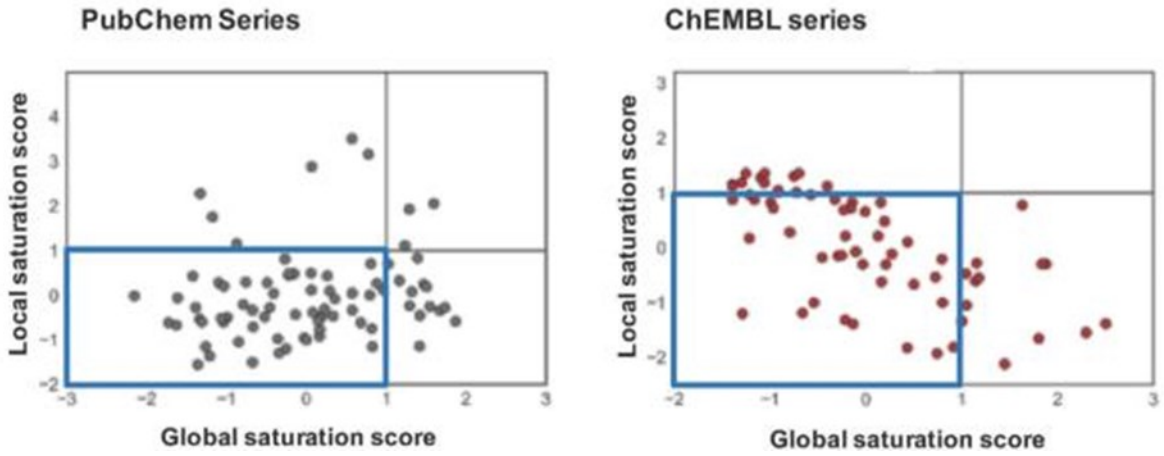



Figure 29

Categorization of series is also only moderately influenced by varying analogue design strategy, although a small shift from late-stage towards mid-stage series is observed for SARM_VAs compared to ASB_VAs, for the ChEMBL series (Figure 30).

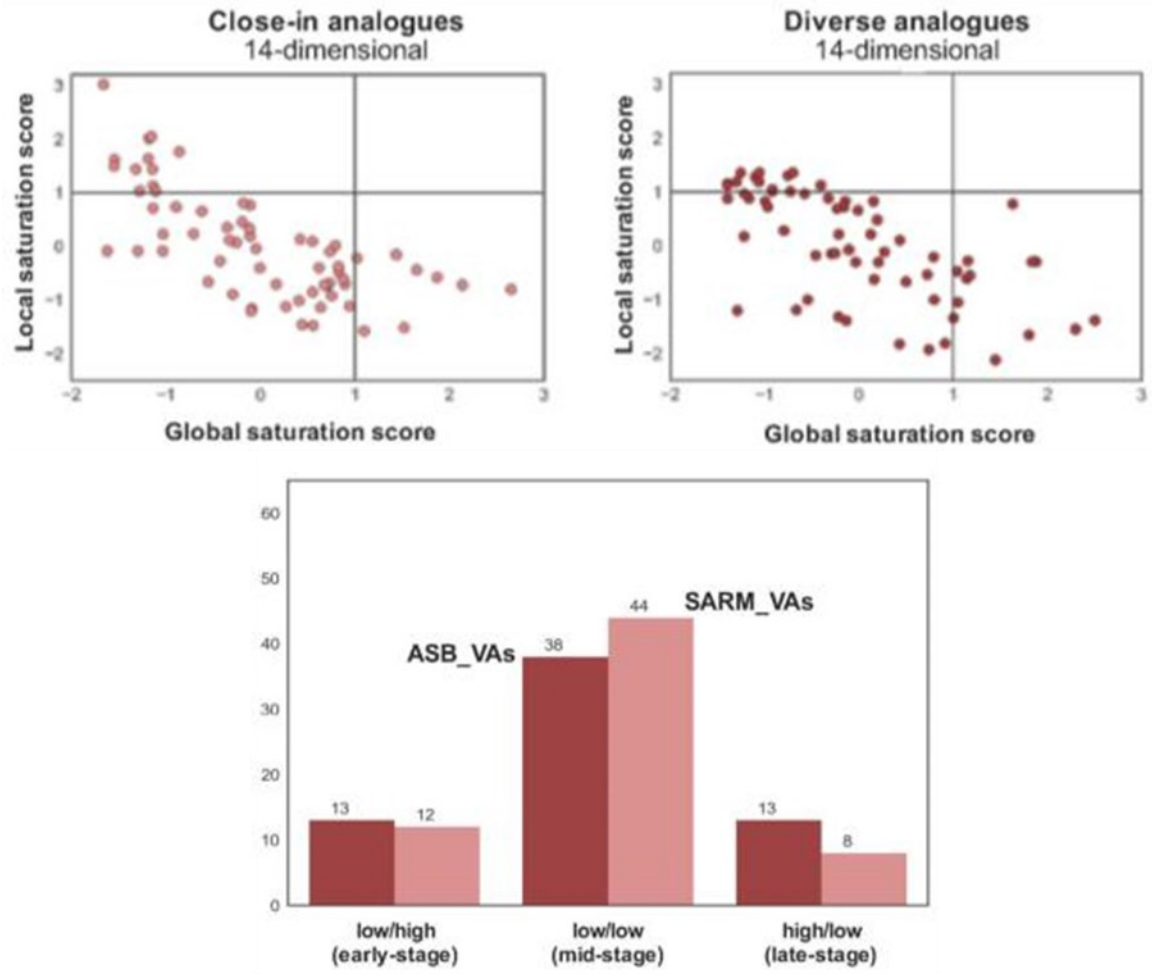



Figure 30

Jürgen presented three models for evolving series with more than 100 analogues (evaluated in cumulative increments). There was a consistent increase in saturation scores for subsets of increasing size, and the saturation level increases from the left to the right (Figure 31).

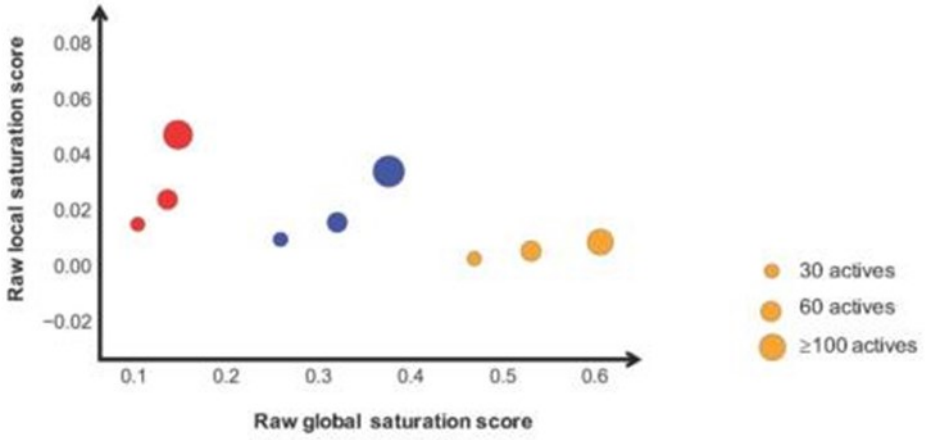
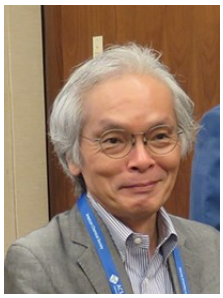



Figure 31

In summary, Jürgen's computational progression analysis of analogue series relies on a neighborhood concept and a virtual analogue-based scoring scheme. Progression states are categorized on the basis of combined global and local saturation scores. For proof-of-concept, large sets of analogue series were profiled. Categorization of series is only moderately influenced by varying space representations and analogue design strategies. Different saturation characteristics are detected for analogue series including the largest publicly available series. In response to Gisbert's question about grand challenges, Jürgen suggested rationalizing compound optimization, and demystifying AI approaches in chemistry beyond the hype.

## Novel method proposing chemical structures with a desirable profile of activities based on chemical and protein spaces



Kimito Funatsu of the University of Tokyo, Japan spoke about a new method for predicting relationships between compounds and proteins. Computational methods to generate models that zoom out from a single protein with a focused ligand set to a larger and more comprehensive description of compound-protein interactions, and that are valid in prospective experiments, are of importance in drug discovery.[67] Nevertheless, constructing a simple prediction model against one protein does not completely help drug design, because detecting chemical structures that act similarly against multiple proteins is necessary for preventing side effects of the potential drug. To tackle this problem, Kimito's team proposes a new method that visualizes the chemical and protein spaces.

By visualizing chemical descriptor space in 2D (using a self-organizing map or generative topographic map), it is possible to determine an activity profile and to decide on target areas. By visualization of protein descriptor space, the activity profile of proteins (including an orphan protein) can be determined. Kimito's objectives were simultaneous visualization of chemical space and protein space, considering compound-protein interaction, and development of a structure search method. His strategy was to expand counterpropagation neural networks (CPNN)[68] into a multi-input and single-output system.

CPNN is a supervised learning method combined with a Kohonen neural network. Two maps can be created: a chemical map (a profile of chemical descriptors) and an activity map (a profile of activity values). In multi-input CPNN (MICPNN) the strategy is to create two maps of chemical space and protein space, and to associate activity values to the combination of two coordinates (Figure 32).

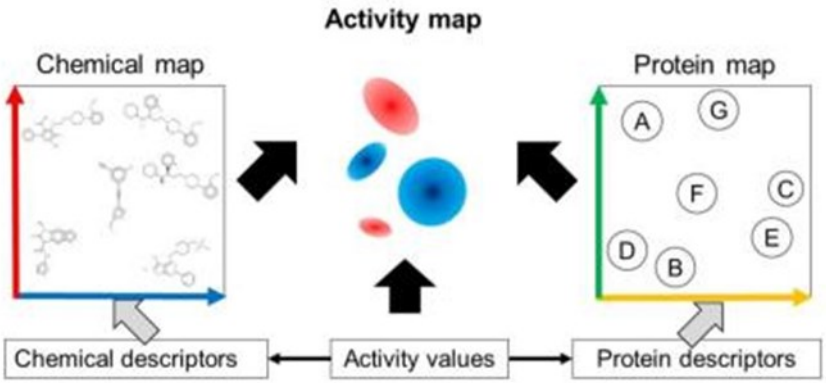



Figure 32

The activity profiles of chemical structures for several proteins can then be obtained (Figure 33).

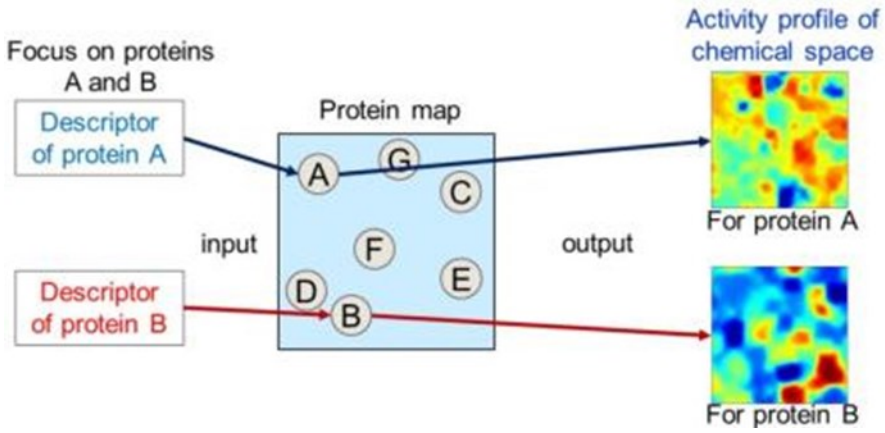



Figure 33

The procedure for drug discovery using MICPNN is to input descriptors of a protein and get the activity profile of compounds; to determine grids from the condition of activity value; and to obtain molecular descriptors corresponding to the grids. These descriptors can then be used in virtual screening, or in de novo design, to get new chemical structures.

G protein–coupled receptors (GPCRs), also known as seven-(pass)-transmembrane domain receptors, or 7TM receptors, are drug targets related to many diseases. A ligand binding site is known. In a case study Kimito used the GPCRSARfari dataset in ChEMBL.[69] This has 40,000 activity data points ($pK_i$ > 4.0) for 21,272 compounds and 124 proteins in GPCR class A. Kimito used 20,000 as activity pairs for the MICPNN learning set, 10,000 as validation pairs for convergence determination, and 10,000 as test pairs to examine MICPNN.

The chemical descriptors were 137 descriptors from Dragon 7.0. The 288 protein descriptors were z-scores[70] of 7TM domain regions obtained from GPCRdb.[71,72] The z-score is the score vector obtained by applying principal component analysis to the physical property value of the amino acid; *z*3 (up to the third principal component) was used in this case study. Kimito presented these results (Figure 34).

Mapping accuracy:

| | Chemical map | | Protein map | |
|---|---|---|---|---|
| | $R^2$ | RMSE | $R^2$ | RMSE |
| Training pairs | 0.976 | 0.132 | 0.951 | 0.234 |
| Validation pairs | 0.915 | 0.246 | 0.952 | 0.232 |
| Test pairs | 0.917 | 0.244 | 0.951 | 0.234 |

Prediction accuracy:

| | Activity map | |
|---|---|---|
| | $R^2$ | RMSE |
| Training pairs | 0.799 | 0.559 |
| Validation pairs | 0.489 | 0.891 |
| Test pairs | 0.484 | 0.885 |

Figure 34

Having proposed MICPNN to visualize chemical space and protein space, and developed a chemical structure search process, Kimito showed that combination with a structure generation method[73] led to more effective chemical structure search. The target protein Kimito chose to illustrate structure search was histamine receptor H1 (HRH1), a class A GPCR related to diseases such as abnormality of airway function and atopic dermatitis.[74] HRH1 antagonists are bronchodilators, and anti-allergy and anti-nausea drugs. The structure of the human histamine H1 receptor complex with doxepin[75] has been published. First generation HRH1 antagonists have affinity for muscarinic acetylcholine receptors (CHRM),[76] and cause anticholinergic effects. So Kimito wanted to find compounds with high activity for HRH1 ($pK_i$ > 8) and low activity for CHRM1 ($pK_i$ < 5). Using these settings, he obtained limited areas on the Kohonen maps of HRH1 and CHRM1 when these two maps were overlapped (Figure 35).

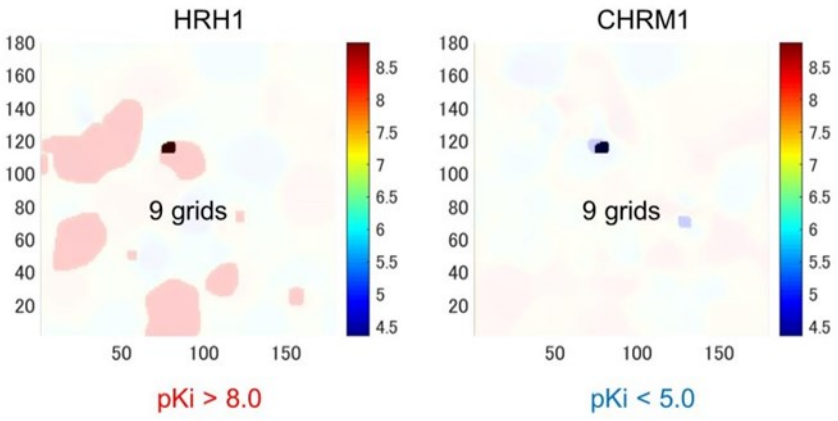



Figure 35

The nine pairs of descriptor values (and number of substructures) are shown in Table 1.

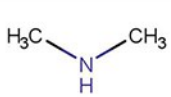
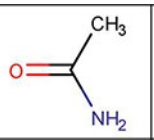
| Coordinate |  |  | ... |
|---|---|---|---|
| (76, 114) | 1 | 0 | ... |
| (77, 114) | 1 | 0 | ... |
| (77, 115) | 1 | 0 | ... |
| (78, 114) | 1 | 0 | ... |
| (78, 115) | 1 | 1 | ... |
| (79, 114) | 1 | 0 | ... |
| (79, 115) | 1 | 1 | ... |
| (79, 116) | 1 | 1 | ... |
| (80, 115) | 0 | 0 | ... |

Table 1

For testing the ability of the model Funatu used a GPCRSARfari dataset not used in modeling. One selected compound[77] (below) had predicted HRH1 activity of $pK_i$ 8, and predicted CHRM1 activity of $pK_i$ 4.88 (Figure 36).

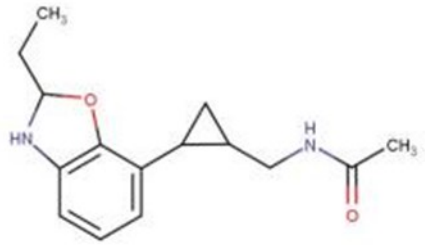


Figure 36

A docking simulation was run for the best 100 compounds, using AutoDock4.2.6,[78] and AutoDockTools-1.5.6,[78,79], and protein structures from the PDB. A plot of the binding energies indicated selectivity for HRH1 (Figure 37).

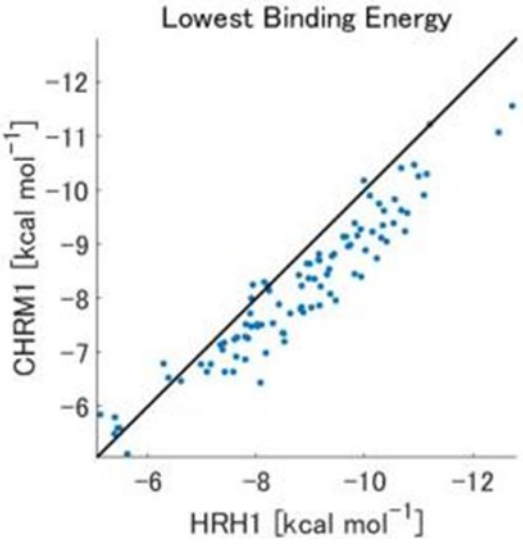


Figure 37

Kimito showed docking simulations for ChEMBL343024, where the binding energy for HRH1 was -8.08 kcal mol$^{-1}$, and for CHRM1 was -6.44 kcal mol$^{-1}$.

It is a problem that interpretation of a quantitative structure-activity relationship (QSAR) model is dependent on descriptors. Kimito has used a graph convolution neural network in descriptor-independent QSAR analysis. It is possible to extract and visualize positive and negative features on substructure on each structure, and to summarize important substructure profiles for a specific target. This idea has been applied to the compound-protein interaction model: it is possible to extract, visualize and summarize important pairs of substructure profiles between compound and target.

## Chemography: toward "universal" maps of druglike space

Alexandre (Sasha) Varnek of the University of Strasbourg, France had the goal of making a map encompassing all known compounds and activities in druglike chemical space. Oprea and Gottfries[80] were the first to use the term "chemography" in cheminformatics; Varnek's team continues to follow the theme.

To go from multidimensional descriptor space to 2D latent space requires dimensionality reduction. Sasha uses In Silico Design and Data Analysis (ISIDA) descriptors[81-83] of which there are several hundred. A great many dimensionality reduction methods have been reported but Sasha chose to use Generative Topographic Mapping (GTM),[84-86] a probabilistic extension of self–organizing maps (SOM).

GTM relates the latent space with a 2D "rubber sheet" (or manifold*)* injected into the high-dimensional data space. The visualization plot is obtained by projecting the data points onto the manifold and then letting the rubber sheet relax to its original form. GTM generates a data probability distribution in both initial and latent data spaces. GTM can thus be used not only to visualize the data, but also for structure-property modeling tasks.[86]

Sasha showed a probability density distribution in the latent space. Projection of an object on a GTM is described by the probability distribution ("responsibilities") over the lattice nodes. Using GTM, one can, for each molecule, evaluate the probability of finding it in a point on the grid. This probability distribution can be used to prepare an "activity landscape" or "class landscape" on a 2D map which, in turn, allows the user to make predictions of activities, or the probability that new compounds will be active or inactive.[87]

A “universal” map is expected to accommodate a variety of known chemotypes; to be able to distinguish different activity classes; and to separate actives and inactives within a given activity class. It needs to exhibit neighborhood behavior (NB). A given molecule may display several different activities, so several different descriptor spaces might be needed to construct the NB-compliant maps. This is equivalent to separating objects into different maps according to the color or the shape of the descriptors.

The choice of descriptors is a vital issue for chemical space construction. Optimal descriptors are supposed to be provided by the best GTM-based regression or classification models built on some “scoring” dataset(s). The more the activities that are used, the more universal is a map.[88] Descriptors leading to the largest scores are selected. Sasha showed the modeling workflow for producing universal maps (Figure 38).

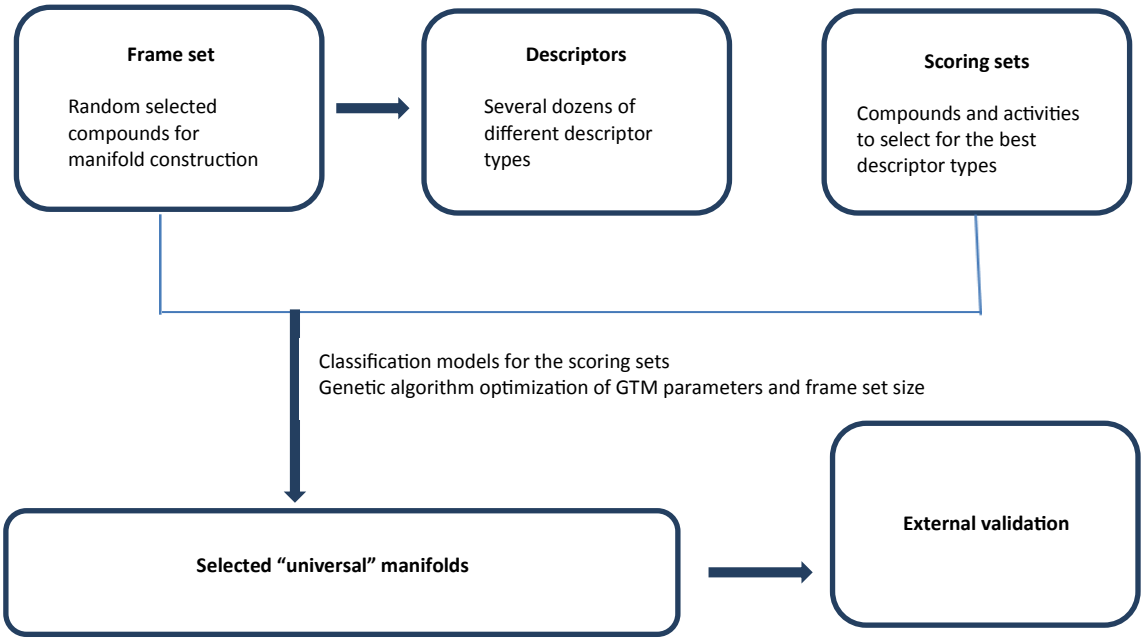
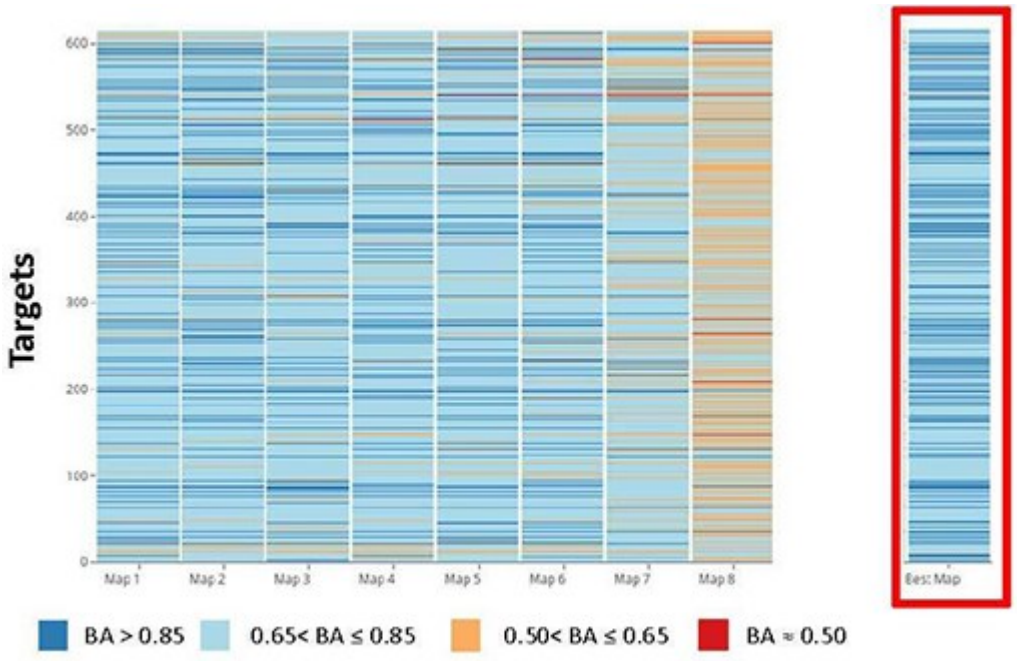



Figure 38

Frame sets from the ChEMBL database were used: five sets containing from 8,500 to 30,000 compounds. There were 100 ISIDA descriptor types. The scoring sets were 236 targets, including GPCRs, kinases, and nuclear receptors; and more than 30,000 compounds. From the scoring sets, universal manifolds were determined, and cycled through 382 validation datasets of over 100,000 compounds, and the scoring sets, in order to find the best universal manifolds. All of the ChEMBL compounds were then projected on the manifolds. Eight universal maps described more than 1.5 million compounds and 618 targets from the ChEMBL database (Figure 39).




**BA** varies from 0.5 (random selection) to 1 (ideal model)
**BA** = balanced accuracy (defined as the mean of specificity and sensitivity)

Figure 39

Seven maps correctly predict the classes (active/inactive) for ligands against more than 600 targets (Figure 40).

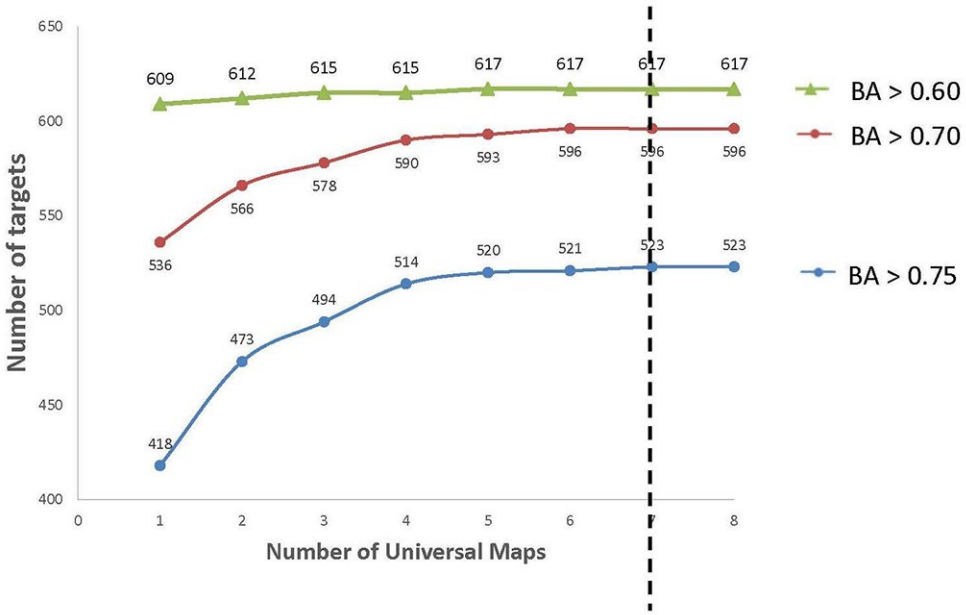
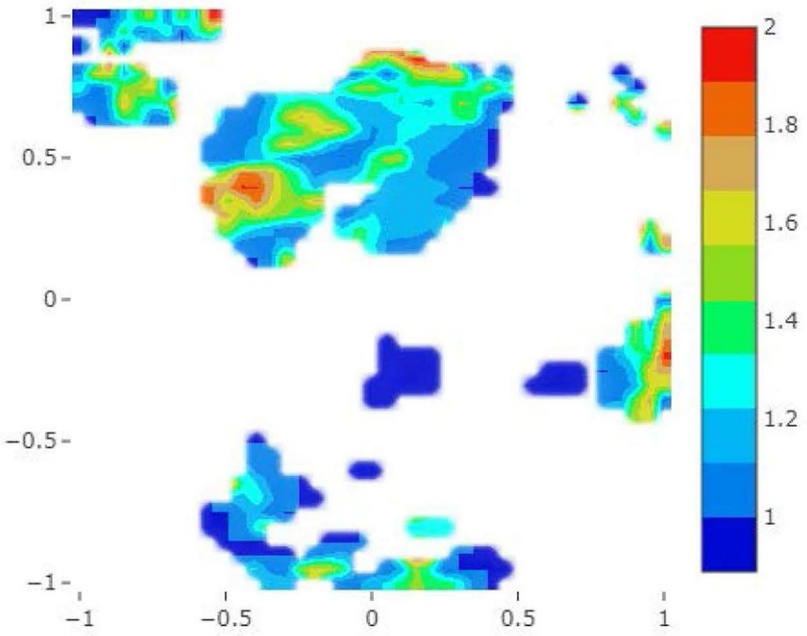



Figure 40

Universal maps can be applied to virtual screening. In a case study, Sasha's team virtually screened the Directory of Useful Decoys (DUD; http://dude.docking.org/) using the activity landscape for adenosine receptor A2a. Molecules dropping into empty areas are not considered (Figure 41).




Red = active, blue = inactive. There were 1,303 actives in ChEMBL and 3,618 inactives.

Figure 41

Sasha presented the results below (79 actives and 28,002 inactives found in DUD). The molecules in empty zones (schematically shown by red ellipses) were discarded in virtual screening (Figure 42).

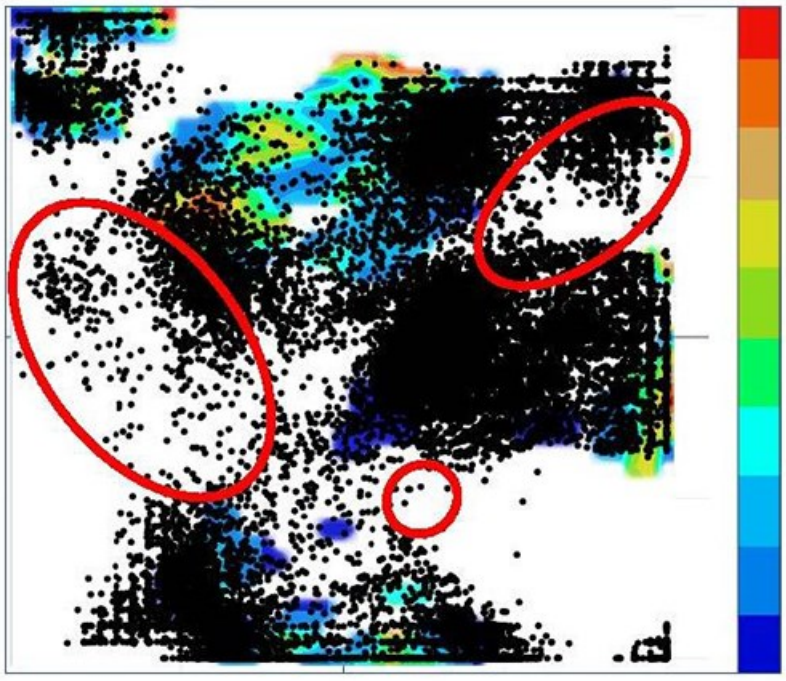


Figure 42

A consensus model performed better than its seven, constituent individual models. The number of molecules discarded by the GTM applicability domain ranged from 348 to 1643 for the seven maps, but was zero for a consensus model, showing that a consensus model provides better data coverage than the individual models.

Universal maps can also be used to detect privileged structures. Privileged substructures recur in compounds active against a given target, and are associated with biological activity. They are important in the design of novel bioactive compounds. The classical approach to detection of privileged substructures is scaffold-centric. In the GTM-based approach, structurally related structures are extracted from the responsibility distribution. Compounds with similar responsibility vectors are expected to be related. In recent work,[89] zones of a map preferentially populated by target-specific compounds were delineated. This helps to capture common substructures. On the basis of the common substructures, compounds were grouped together by GTM. Such privileged structural motifs were identified across three major target superfamilies including proteases, kinases, and G protein coupled receptors. Three universal maps are needed in order to extract the privileged structural motifs for the main classes of antivirals in ChEMBL.[87]

In summary, universal maps are able to support predictive models for a broad spectrum of biological activities and, thus, they could be used as a pharmacological profiling tool. Several (at least seven) maps are needed in order to achieve good performance in separating actives from inactives. Privileged substructures (not necessarily scaffolds) can be extracted from universal maps. Other cheminformatics applications with universal maps are virtual screening, target prediction, and drug repurposing.

Finally, Sasha touched briefly on de novo design using a deep learning and GTM combination. This is work reported in the master's thesis of Sasha's student Boris Sattarov. An autoencoder produces an efficient, dense representation of an input object by performing specific compression of learned data. A long short-term memory (LSTM) sequence-to-sequence autoencoder can perform SMILES reconstruction. An LSTM encoder takes a SMILES string, and produces real numbers (as latent variables) from which the LSTM decoder reconstructs the SMILES. A database of SMILES strings can then be used as input to the trained encoder, and a GTM built on the latent variables of the autoencoder. Novel structures from specific areas of the map are generated by the trained decoder, which produces SMILES strings of the novel compounds from latent variables.

A case study was generation of analogues of A2a inhibitors. De novo structures were generated by sampling of GTM zones populated by existing ChEMBL structures. Validation was carried out by docking the ligands on the 2YDO PDB X-ray structure using the Sampler For Multiple Protein-Ligand Entities (S4MPLE)[90] tool. The distribution of the docking scores of the generated structures closely followed that of real actives.

## Artificial intelligence in drug design

Much of the afternoon session centered on artificial intelligence (AI). Representing five co-authors at Sanofi-Aventis in Germany, Karl-Heinz Baringhaus addressed the subject of AI in drug design. A recent review has analyzed the relative contributions of each of the steps in the drug discovery and development process to overall R&D productivity.[91] Karl-Heinz said that there are opportunities for AI in *all* areas of the drug discovery and development value chain. It has been estimated that the AI market in healthcare will be worth $6.6 billion in 2021 (https://www.accenture.com/us-en/insight-artificial-intelligence-healthcare). AI is a system for problem solving, making automated decisions, perceiving the environment, and taking actions. A "strong" AI system has the same capabilities as human thinking and reasoning; a "weak" AI system transfers a single human capability to a system (e.g., recognition of texts, voice, or images).

Drug design plays a pivotal role in lead identification and optimization, and AI has a role in this through deep learning, in particular for compound classification, de novo design and in silico profiling. For example, the majority of adverse drug reactions (ADRs) are dose-dependent, and ADRs can often be predicted on the basis of the pharmacology profiles of the candidate compound.[92]

The application of AI in particular in the field of ADMET and antitarget modeling was the main focus of Karl Heinz's talk. He started with an overview of some predictive data mining methods (Figure 43).

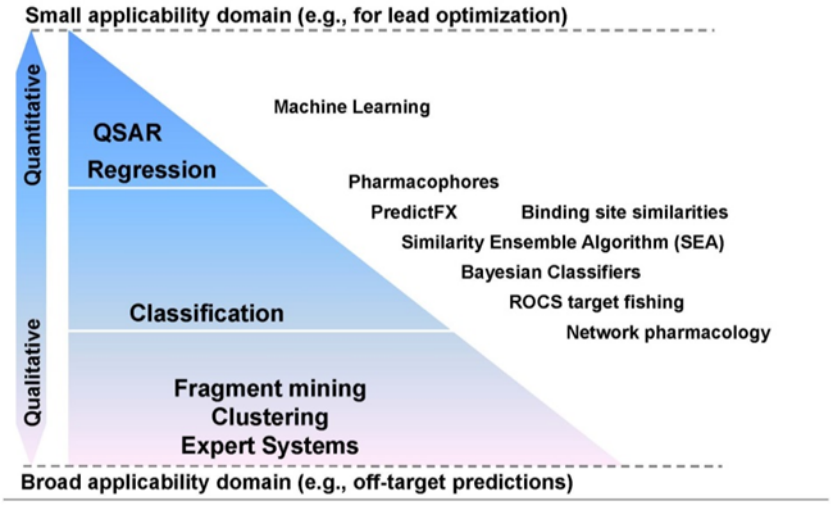
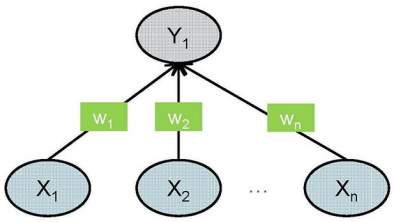



Figure 43

Many 2D descriptors describing molecular topology have been used, as well as pharmacophore fingerprints, and 1D descriptors such as log*P*. Machine learning algorithms generate knowledge from experience: they learn iteratively from data without being explicitly programmed. The models generated can be used for prediction of novel instances. Classification methods and quantitative models have been developed. Different algorithms include linear regression, decision trees, random forest, support vector machine, etc. An example is building (Q)SAR with Cubist (http://www.rulequest.com/cubist-info.html), in which both a decision tree and regression are combined.

Different QSAR models have different validity domains (e.g., hERG or CYP450). For a domain to be valid, predicted compounds must be similar to training molecules, and the descriptor range of predicted compounds must relate to the training set molecules. Karl-Heinz and his colleagues have reported some CYP450 2D-QSAR models, among others.[93]

Deep learning is a subsection of machine learning. It has been particularly effective due to the use of neural networks. It is based on analysis of large volumes of data (big data) (Figure 44).




$$Y_1 = f(Z)$$

$$Z = \sum_{k=1}^{n} X_k w_k + b$$

- Each **neuron** (*Y*) receives input from all other **input** units (*X*)
- Effect of each input is controlled by a **weight** (*w*) and **bias** (*b*)
- **Learning**: adapting the weights and biases to perform useful computations
- Neurons are activated via **activation function** (*f*)
- **Features** are extracted automatically

Figure 44

A single-task, deep neural net (DNN), aims to generate a model for just one activity. Molecules are described by a set of descriptors which are used as input for the network. Most often, fully connected and sequential deep neural nets with several hidden layers are applied for model building. Multitask deep networks have yet to be widely deployed in the pharmaceutical industry but recent work[94] has demonstrated that multitask deep networks are surprisingly robust, and can offer strong improvement over random forests. In a multitask network, a set of descriptors is used for model building of multiple activities in parallel, yielding multiple outputs (one for each input activity). Within model building all weights are shared.

Karl-Heinz compared Cubist and DNN results from a benchmark of internal prediction models of human liver microsome (hLM) stability and hERG inhibition. Application of multitask DNNs gave results superior to those for single-task DNNs. Multitask models capitalize on hidden trends (Figure 45).

| data set | Cubist | DNN (single task) |
|---|---|---|
| hLM | 0.593 | 0.646 |
| hERG | 0.518 | 0.533 |

| ML | Single-task test $R^2$ | Multi-task test $R^2$ |
|---|---|---|
| Human | 0.65 | 0.69 (+ 6.2%) |
| Rat | 0.68 | 0.76 (+ 11.8%) |
| Mouse | 0.69 | 0.77 (+ 11.6%) |

Figure 45

TensorFlow (https://www.tensorflow.org/) is an open source software library for high performance numerical computation originally developed by Google. It comes with strong support for machine learning and deep learning. Keras (https://keras.io/) is a high-level neural networks API, written in Python and capable of running on top of TensorFlow.

Karl-Heinz gave a lead optimization example[93] concerning diacylglycerol O-acyltransferase 1 (DGAT1) inhibitors.

A lead structure had $IC_{50}$ = 0.25 μM with metabolic lability = 53% (Figure 46).

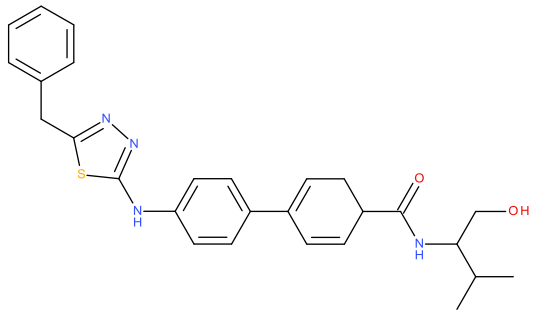


Figure 46

A global model for metabolic lability, which is predictive for the chemical series of DGAT1 inhibitors in question, was successfully used to guide the lability optimization of the lead structure. A follow-up structure (Figure 47) had $IC_{50}$ = 0.03 μM, and metabolic lability = 1%, but it had poor permeability. After rescaffolding, a permeable structure was found with $IC_{50}$ = 0.04 μM and low metabolic lability (Figure 48).

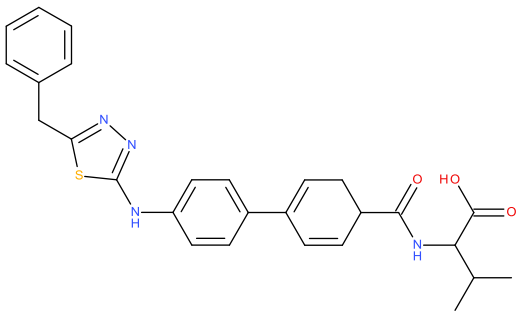


Figure 47

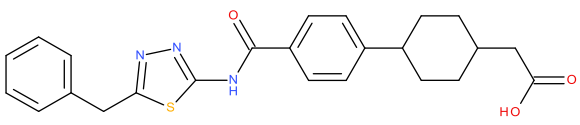


Figure 48

Karl-Heinz's final topic was in silico profiling of compounds and polypharmacology. Sanofi has numerous off-target profiling panels for receptors and enzymes, kinases and ion channels, covering important and promiscuous antitargets. In total, Sanofi has biological data available for about 3 million compounds against about 2,000 biological targets. These data were used for QSAR model generation in order to generate profiling models. Data for multiple targets (receptors, protein kinases, and ion channels) are retrieved, normalized, and filtered. Genetic algorithms are used for variable selection, in combination with Cubist regression trees as machine learning tool. Each in vitro profiling assay has an in silico counterpart, but only core panels have a large applicability domain. Forward prediction for external, experimental data after model generation has been successful ($R^2$ and $Q^2 > 0.6$) and a web application (CT+) for in silico profiling was rolled out.

Challenges in in silic*o* profiling are the high number of experimental data for model building, and the building of reliable and predictive models, including validity domain estimation (VDE). Sanofi builds predictive models for about 400 targets of interest. All models are thoroughly validated, including VDE. The combination of the predictProfile models with CTlink, developed by Jordi Mestres' team,[95] is very powerful in selecting the most attractive hit series out of a high throughput screening run, and in the identification of potential side effects of lead series prior to subsequent optimization. Compound repurposing as well as polypharmacology of compounds can be addressed by both CTlink and the Sanofi models.

AI "leapfrogs" early off-target predictions and annotations, identification of series-related potential issues, prioritization of hit and lead series, and design of preclinical candidates. As Johann-Wolfgang von Goethe said "Es ist nicht genug, zu wissen, man muß auch anwenden; es ist nicht genug, zu wollen, man muß auch tun". ("It is not enough to know, you also have to apply; it is not enough to want, you also have to do".)

## Robot Scientists automating drug design

Ross D. King, of the University of Manchester, United Kingdom, gave a talk on the automation of drug design. (The following talk, "Accelerating drug discovery through a fully automated design-make-test-analyze workflow", by Michael Kossenjans of AstraZeneca, was unfortunately withdrawn.) Ross said that the technology drivers behind his own work were improved computer hardware, improved data availability, and improved software (new machine learning methods, deep mining, etc.).

There have been multiple AI hype cycles, but this time it seems different. The speed of advance of AI, and especially machine learning, has surprised Ross. Machine learning is the core technology of Google, Facebook, Amazon, Tencent, Alibaba, Baidu, and many other systems. AI systems have superhuman scientific reasoning powers. They flawlessly remember vast numbers of facts; execute flawless logical reasoning, and optimal probabilistic reasoning; learn more rationally than humans, from vast amounts of data; extract information from millions of scientific papers, and so on. Yet AI systems have to be balanced with human abilities.

Science is a good application area for AI. Scientific problems are abstract, and restricted in scope, which suits AI, but also involves the real world. Nature is also honest and not trying to fool us, which also helps AI reasoning. Nature is also a worthy object of our study, unlike addictive advertising, and the generation of open scientific knowledge is a public good.

The first application of AI to science was the DENDRAL project in the 1960s and 1970s, the primary aim of which was to study hypothesis formation and discovery in science. Using knowledge of chemistry, it helped organic chemists to identify unknown organic molecules by analyzing their mass spectra. Meta-DENDRAL[96] was the project's machine learning system.

King's laboratory and collaborators[97] have developed "Robot Scientists": physically implemented robotic systems that apply techniques from artificial intelligence to execute cycles of automated scientific experimentation. A Robot Scientist can automatically execute cycles of: hypothesis formation, selection of efficient experiments to discriminate between hypotheses, execution of experiments using laboratory automation equipment,

and analysis of results. The motivation for developing Robot Scientists is to understand science better, and to make scientific research more efficient.

Robot Scientists have the potential to increase the productivity of science. They can work more cheaply, faster, more accurately, and for a longer time than humans. They can also be easily multiplied. Thus, they enable the high-throughput testing of hypotheses. They also have the potential to improve the quality of science by enabling the description of experiments in greater detail and semantic clarity.

The Robot Scientist "Eve" was designed to automate and integrate drug screening, hit confirmation, and QSAR development. Its combination of novel automation with synthetic biology assays enables faster and cheaper drug design.[98] Eve's focus was originally on malaria, and neglected tropical diseases such as shistosomiasis, leishmaniasis, and Chagas disease. Hundreds of thousands of people die of these diseases, and hundreds of millions of people suffer infection. It is clear how to cure such diseases (unlike many diseases): kill the parasites. There is also little competition from the pharmaceutical industry. Enzymes targeted are dihydrofolate reductase (DHFR), N-myristoyl transferase (NMT), and phosphoglycerate kinase (PGK).

Eve uses graphs and standard cheminformatics methods to represent background knowledge. Eve uses induction (QSAR learning) to infer new hypotheses, active learning to decide efficient experiments, and an econometric model[98] to decide which compounds to test. Eve currently uses processes.[98] This has the advantages of being generative, and of outputting probabilities. Eve uses active learning to select compounds to test its hypotheses. This machine learning method can select its own examples, in this case from a set.

Standard chemical library screening is brute force, but Eve uses intelligent screening. In the standard "pipeline", the processes are not integrated, but in Eve they are automated and integrated (Figure 49).

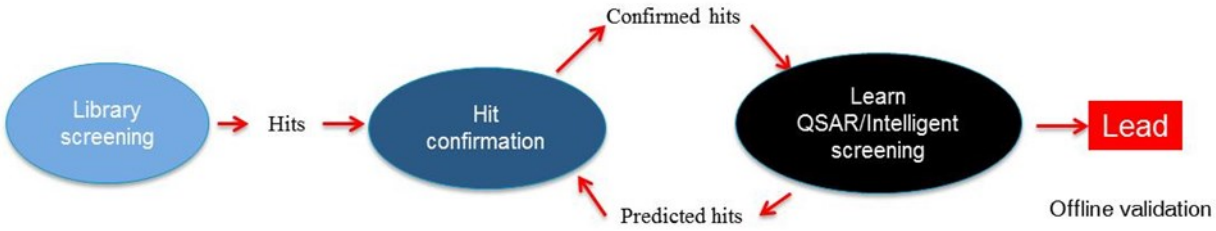



Figure 49

Eve's hardware has acoustic liquid handling, high throughput 384-well plates, two industrial robot arms, an automated 60x microscope, liquid handlers, fluorescence readers, barcode scanners, a dry store, an incubator, a tube decapper, and other items.

Ross and his co-workers wanted to compare their AI-based screening against the standard brute-force approach. While simple to automate, standard screening is slow and wasteful of resources, since every compound in the library is tested. It is also unintelligent, as it makes no use of what is learnt during screening. To do the comparison, an econometric model was used.[98] Factors involved in the calculation of the utility of Eve were the number of compounds not assayed by Eve; the cost of the time to screen a compound using the mass screening assay; the cost of the loss of a compound in the mass screening assay; the number of hits missed by Eve; the cost of the time to screen a compound using a cherry-picking assay (a confirmation or intelligent assay); the cost of the loss of a compound in a cherry-picking assay; the utility of a hit; and the number of compounds assayed by Eve. The researchers demonstrated that the use of AI to select compounds economically outperforms standard drug screening.

Eve has discovered hits and leads against targets in multiple parasites, most notably that triclosan inhibits *Plasmodium* DHFR.[98] Triclosan is a simple compound, generally regarded to be safe: it is used in toothpaste. It targets both DHFR and fatty acid synthase II (FAS-II), well established targets. Activity has been demonstrated using multiple wet experimental techniques. Triclosan works against wild-type and drug-resistant *Plasmodium falciparum*, and *Plasmodium vivax*.

The goal of science is to increase our knowledge of the natural world through the performance of experiments. This knowledge should be expressed in formal logical languages which promote semantic clarity, which in turn supports the free exchange of scientific knowledge, and simplifies scientific reasoning. Robot Scientists provide excellent test beds for the development of methodologies for formalizing science. Using them it is possible to capture completely, and curate digitally, all aspects of the scientific process. The LABoratory Ontology for Robot Scientists (LABORS)[99,100] is designed to give the scientific community open access to the Robot Scientist experimental data and metadata.

The effect of AI on intellectual property is an interesting question. U.S. patent law is clear that only humans can invent patents. U.K. and European Union patent laws allow non-human inventors. Many patents in the United States are possibly invalid as the named inventor is incorrectly named as a human. AI-generated copyright works would seem to be in the public domain, except in a few countries such as the United Kingdom. Making AI systems legal entities is favored by companies to shield themselves from legal liabilities.

In chess there is a continuum of ability from novices up to grandmasters. Ross argues that this is also true in science, from the simple research of Eve, through what most human scientists can achieve, up to the ability of a Newton or Einstein. If you accept this, then just as in chess, it is likely that advances in computer hardware and software will drive the development of ever smarter Robot Scientists. In favor of this argument is the ongoing development of AI and laboratory robotics.

In response to Gisbert's request for a grand challenge, Ross said that, in his opinion, the deepest challenge in applying AI to science is finding radically new representations. Einstein, for example, noticed, in his concept of space-time, that the same physical phenomenon was described in two different ways, depending on what was moving.

Ross believes that the collaboration between humans and Robot Scientists will produce better science than either humans or robots can alone. Even though a computer first beat the world chess champion over 20 years ago, teams of humans and computers still play better chess than either a human or a computer alone. Scientific knowledge will be primarily expressed in logic with associated probabilities, and published using the Semantic Web. Improved productivity of science leads to societal benefits: better food security, better medicines, etc.

## Data-driven drug discovery and repositioning by machine learning methods

Yoshihiro Yamanishi of Kyushu Institute of Technology, Japan, spoke about drug repositioning. The identification of new indications of drugs, or in-house compounds, is an efficient strategy for drug development, and it has received much attention recently. A great deal of information (e.g., safety, pharmacokinetics, and manufacturing process) is available on existing drugs. The drug repositioning approach can increase the success rate of drug development, and reduce the cost in terms of time, risk, and expenditure. Well-known examples are sildenafil (Viagra) developed for angina, but now used in the treatment of erectile dysfunction, and pulmonary hypertension; and minoxidil (Riup, Rogaine) developed for hypertension but now used to treat alopecia.

In the past, the approach to drug repositioning has been dependent on serendipity. The aim of the current work was computational drug repositioning based on biomedical big data (compounds, genes, proteins, and diseases). The researchers have developed novel machine learning methods to predict new associations between drugs and diseases, based on the molecular understanding of a variety of diseases: disease-causing genes, disordered pathways, environmental factors, and abnormal gene expression. Characteristic molecular features are often shared among different diseases, and networks of disease-disease relationships can be produced based on those molecular features. Yoshihiro and his co-workers set out to predict drug-protein-disease networks by machine learning. There are many approved drugs (about 60%) whose targets remain unknown. Using the networks, unknown interactions can be predicted. The genomic space (of proteins) is inter-related with chemical space in chemogenomics, with phenotypic space in phenomics, and with transcript space (drug-induced gene expression) in transcriptomics.

In the chemogenomics approach, it is postulated that chemically similar drugs are predicted to interact with similar target proteins.[101-106] Compound similarity (chemical space) is measured based on descriptors for chemical structures, and protein similarity is calculated based on motifs, domains, and amino acid sequences. In the chemogenomics approach, Yoshihiro and his co-workers have used the generalized Jaccard coefficient for compound similarity, and the normalized Smith-Waterman score for protein similarity.[107] They investigated the relationship between drug chemical structure, target protein sequence, and drug-target network topology. They then developed a new supervised method to infer unknown drug-target interactions by integrating chemical space and genomic space into a unified space that they call “pharmacological space” (Figure 50).

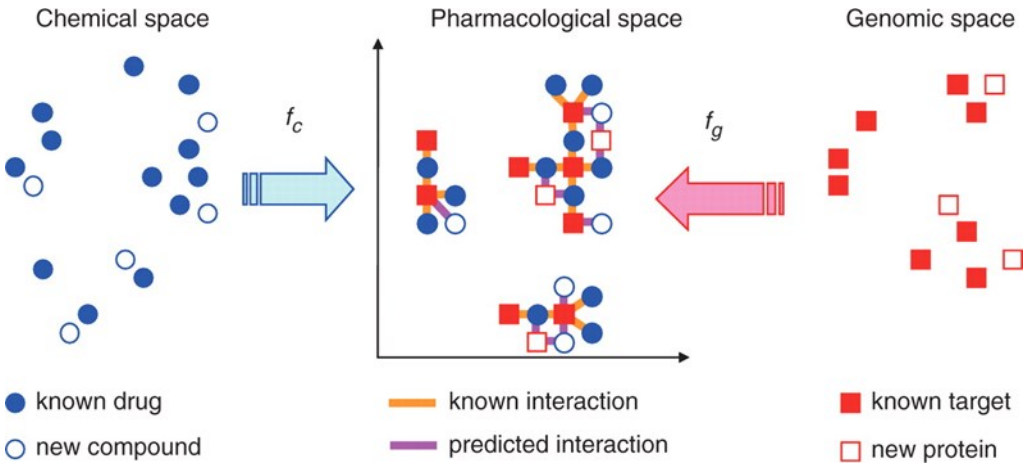



Figure 50

The supervised method is a two-step process. First, a model is learned to explain the “gold standard”’. Second, this model is applied to compounds and proteins absent from the “gold standard” in order to infer their interactions.[104,108,109] The novel method used is the bipartite graph learning method.[104,110] Details of the kernel-based distance learning algorithm[108,110] have been published.

The performance of the system was evaluated using a benchmark set of 6,769 interactions involving 1,874 drugs and 436 proteins from the Kyoto Encyclopedia of Genes and Genomes (KEGG; https://www.genome.jp/kegg/), DrugBank (https://www.drugbank.ca/), and Matador (http://matador.embl.de/). Performance was superior to that of nearest neighbor and pairwise support vector machine (P-SVM) methods (Figure 51).

| Method | AUC (S.D) |
|---|---|
| Random | 0.500 |
| Nearest neighbor | 0.808 (0.010) |
| Pairwise SVM | 0.855 (0.013) |
| Proposed method | 0.869 (0.006) |

AUC = Area under ROC curve
S. D. = standard deviation

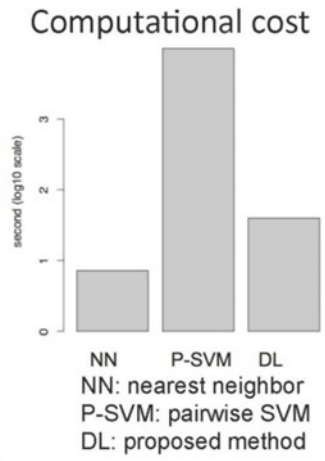



Figure 51

In the transcriptomics approach, it is postulated that drugs with similar gene expression patterns are likely to share common target proteins.[107,111-113] Each drug is represented by a gene expression profile in which each element is the ratio of drug treatment against control condition (ratio of gene expression value after drug treatment to gene expression value before drug treatment). The Library of Integrated Cellular Signatures (LINCS; http://software.broadinstitute.org/software/cprg/?q=node/40) is an NIH program which funds the generation of perturbational profiles across multiple cell and perturbation types, as well as read-outs, at a massive scale. The Connectivity Map (CMap; http://software.broadinstitute.org/software/cprg/?q=node/12) is a catalog of gene-expression data collected from human cells treated with chemical compounds. The Open Toxicogenomics Project-Genomics Assisted Toxicity Evaluation System (TG_GATEs; https://toxico.nibiohn.go.jp/english/) is a toxicogenomics database that stores gene expression profiles with chemical treatments. Gene expression profiles for 20,220 compounds, 22,277 genes, and 77 cells were analyzed (Figure 52).

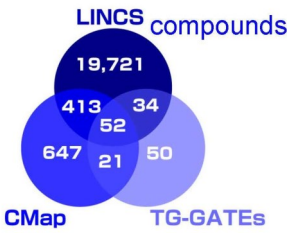



Figure 52

Performance evaluation on several benchmark datasets of different chemical diversities proved that the transcriptomics approach enables the prediction of target proteins without dependence on prior knowledge of chemical structures,[107] whereas the prediction accuracy of the chemogenomics approach is highly dependent on chemical structure similarities.

Yoshihiro and his team were able to perform large-scale prediction of new drug indications: from 8,270 drugs and 1,401 diseases, they predicted 196,048 new drug-disease associations, involving 6,301 drugs and 762 diseases. Yoshihiro showed a drug-protein-disease network (Figure 53).

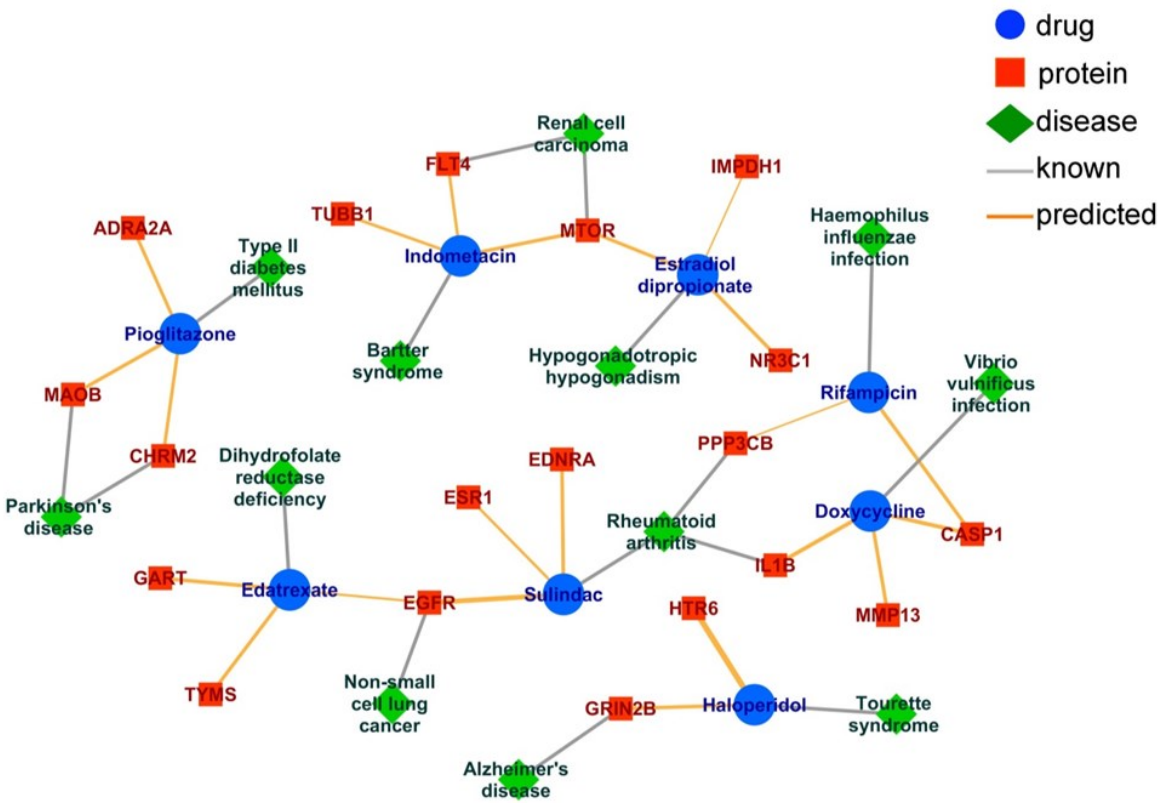



Figure 53

An example of a transcriptomics-based prediction was the predicted indication of prostate cancer for phenothiazine, an antipsychotic drug.[113] The estimated protein was the androgen receptor (AR). A similar compound in the learning set was enzalutamide. The predicted inhibitory effect on AR was experimentally confirmed (Figure 54).

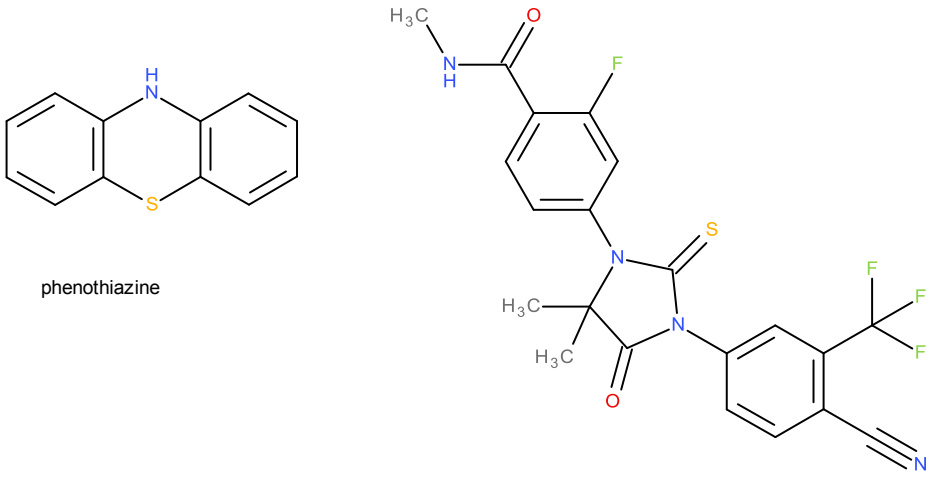



Figure 54

Yoshihiro and his co-workers have elucidated pathway activities from differentially regulated genes: they performed pathway enrichment analyses of regulated genes to reveal active pathways among 163 biological pathways.[113] They studied the relationship between identified pathways (activated and inactivated) and drug efficacy classes.

They have also worked on repositioning of natural medicines such as herbal medicines, crude drugs, and Kampo drugs. Target proteins and target pathways for Kampo drugs have been predicted from biomedical data by machine learning.[114] Daikentyuto (a Kampo drug for stomach ache) was predicted to work for colitis-associated colon cancer, and this was experimentally validated by mice models (Figure 55).

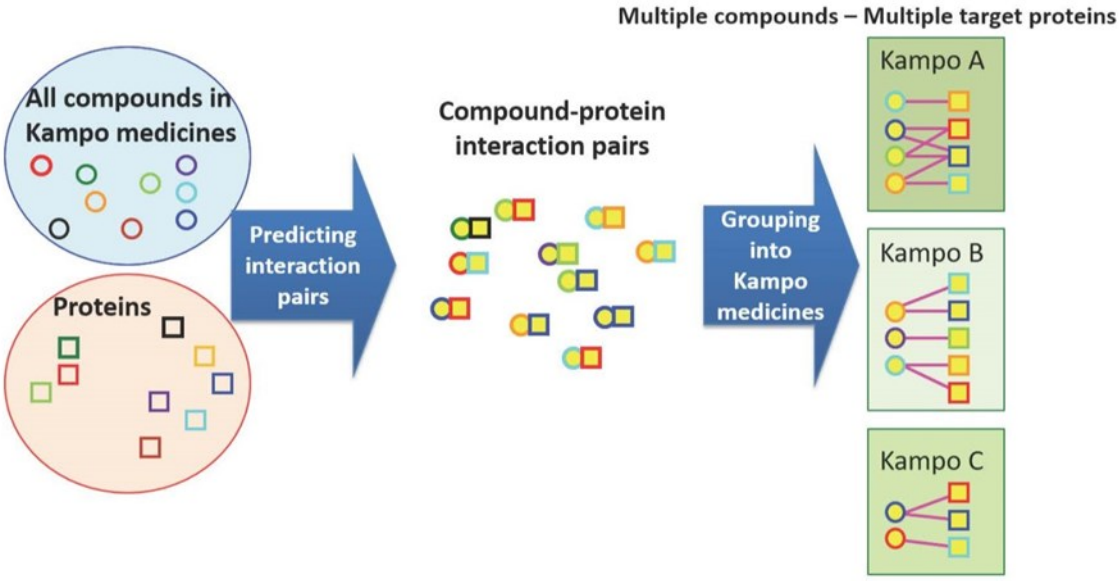



Figure 55

The methods proposed by Yoshihiro can predict potential target proteins, pathway activities, and new therapeutic effects of drug candidates, moving from organ-based disease classification to mechanism-based disease classification. Yoshihiro listed two challenging issues in the integration of cheminformatics and bioinformatics. They are computational methods (a) to take into account the biological systems (various molecular interaction networks) for target identification and drug screening, and (b) to use multilayered omics data for drug discovery in diseasome analysis, patient stratification, biomarker detection, target identification, and drug screening.

## Pattern recognition on neuromorphic hardware inspired by the chemical sense

Michael Schmuker of the University of Hertfordshire, United Kingdom, introduced us to “odor space”. The sense of smell plays an important role in everyday life, but while we readily understand how to describe visual stimuli with light wavelengths and contrast, or sounds with frequency and amplitude, we lack understanding of the fundamental features of odors. In other words, we do not understand odor space[115] the notion of which describes different aspects of the sense of smell. There is chemical space, in which odorants are arranged along their physicochemical properties. The encoding of odors into neuronal responses defines the sensory space. The perceptual organization and meaning of odors is the basis for perception space. Finally, odors are embedded in a physical space that governs how odorants move from their sources to our noses.

Michael presented a diagram of the olfactory system from a data processing point of view (Figure 56).

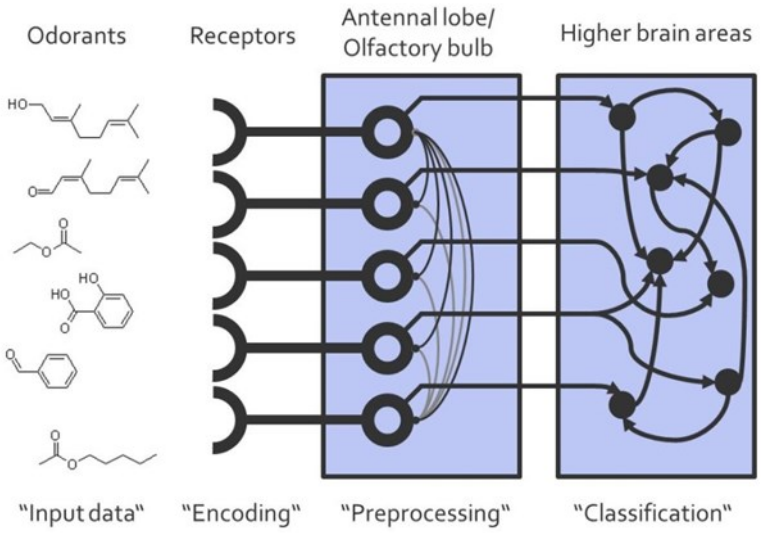



Figure 56

In the encoding stage, olfactory receptors are broadly tuned and their “receptive fields” overlap: a class of receptor neurons responds to a wide range of odorants, and an odorant typically triggers responses in several different receptor neuron classes. The input space is vast, and large overlapping receptive fields ensure coverage.

In neurobiology, lateral inhibition is the capacity of an excited neuron to reduce the activity of its neighbors. Lateral inhibition disables the spreading of action potentials from excited neurons to neighboring neurons in the lateral direction. This creates a contrast in stimulation that allows increased sensory perception. It occurs primarily in visual processes, but also in tactile, auditory, and olfactory processing. Preprocessing through lateral inhibition in the data processing system above acts as a filter to enhance the representation of the input data. In this particular setting it counteracts the negative aspects of overlapping receptive fields.[116-118]

After the sensory input is processed in the antennal lobe (AL) network, projection neurons (PNs) convey the sensory code from the AL to higher brain regions. Michael and Gisbert have used a computational network model[119] of the olfactory system which serves as blueprint for a pattern recognition pipeline. They applied this model to predicting the smell of molecules and validated it on bioactivity data for druglike compounds, demonstrating that the computational model can be used not only for olfaction, but for any data in general.

The brain remains the ultimate benchmark for energy-efficient pattern recognition. Much of its efficiency is attributed to its massively parallel architecture and sparse messaging via action potentials, called spikes. The brain's architecture has long inspired engineers in building computing machines. Recently, major chip designers like IBM and Intel, and also academic research teams, have produced neuromorphic hardware systems, that is, silicon chips containing a large number of neuron-like small computing units, which communicate *via* short messages with precise timing. The Spikey (https://www.kip.uni-heidelberg.de/vision/previous-projects/facets/neuromorphic-hardware/single-chip-system/spikey/) chip is a neuromorphic chip developed at the University of Heidelberg.[120] It is a mixed signal system with analog neurons and digital routing. It is 10,000 times faster than biology, and supports a wide range of network topologies with a few hundreds of neurons. The challenge is to solve real-world computing tasks with spiking networks on the hardware system.

Michael and his colleagues have constructed a spiking neural network for the classification of multivariate data. The data are converted into spike trains using "virtual receptors" (VRs). Their output is processed by lateral inhibition and drives a winner-take-all circuit that supports supervised learning. VRs are conveniently implemented in software, whereas the lateral inhibition and classification stages run on accelerated neuromorphic hardware. When the network had been trained and tested on real-world datasets, the classification performance was on a par with a naive Bayes classifier ($R_K$=0.87 with 5-fold cross-validation, and 50 repetitions, compared to $R_K$=0.89 for naive Bayes).

An example is handwritten digit recognition,[121,122] using the Modified National Institute of Standards and Technology (MNIST; http://yann.lecun.com/exdb/mnist/) database. The network used by Michael and his colleagues outperformed naive Bayes through the preprocessing by lateral inhibition. The neuromorphic advantage is that lateral inhibition scales in constant time on hardware, whereas with conventional computers, scaling is with input dimensionality.

Today's pattern recognition runs on GPUs, performing matrix operations (linear algebra), involving dense communication, and very high bandwidth. Energy consumption is high: 300 W per GPU. Modern AI systems run on hundreds of GPUs plus hundreds of thousands of CPU cores (see, for example, the OpenAI Five Dota agent, https://blog.openai.com/openai-five/). Compare these computers with the brain, which has amazing pattern recognition, reasoning, and control capabilities; massively parallel computation with lightweight compute units; and sparse communication via timed events (i.e., action potentials). Moreover the brain's entire energy consumption is only 20 watts.

GPU-based AI is incredibly powerful, but also incredibly power-hungry. Moore's law is to be abandoned, and alternative architectures are on the rise. Neuromorphic computing is event-based computing, and is power efficient. Big companies have launched neuromorphic chips: take, for example, IBM TrueNorth and Intel Loihi. Academic projects include SpiNNaker[122] at the University of Manchester (http://apt.cs.manchester.ac.uk/projects/SpiNNaker/), and BrainScaleS at the University of Heidelberg (https://brainscales.kip.uni-heidelberg.de/), both of them involved in the Human Brain Project (https://www.humanbrainproject.eu/en/).

SpiNNaker is a specialized, many-core system, with an ARM-based architecture. It consumes low power, is portable, and connects through a 100 Mbit Ethernet. Spikey is a mixed-signal system with analog neurons and digital routing (see above). It is low power, and portable, and has a USB 2 connection. GPU-enhanced Neuronal Network (GeNN) is a meta-compiler that generates optimized CUDA-kernels for spiking networks. GeNN compiles networks for accelerated execution on GPUs, which are high power, not portable, and connect by PCIExpress. On all neuromorphic platforms, the workstation controlling the hardware consumes the largest fraction of the power. For network simulation, a GPU is more efficient than a CPU for large networks; for small networks, the CPU simulation is the more efficient. SpiNNaker uses less power than a GPU. Moreover, power requirements are invariant to network size (up to the maximum size supported), which gives it an edge in power efficiency over both CPUs and GPUs.[122]

Michael's next topic was the physical component of odor space. In an open sampling system, where the chemosensory elements are directly exposed to the environment being monitored, the identification and monitoring of chemical substances presents a challenge due to the dispersion mechanisms of gaseous chemical analytes, namely diffusion, turbulence, and advection. Vergara et al.[123] examined electronic nose sensors in a turbulent wind tunnel. The sensors were at varying distance from the odor source. The authors made publicly available 18,000, 72-dimensional time-series recordings. The concentration of a gas decreases with distance from source, but in order to predict distance, the concentration at the source must be known. In a turbulent environment, gas intermittency also depends on source distance. Michael and his co-workers aimed to use spatiotemporal features of gas plumes for distance estimation, using Vergara's dataset.

They have demonstrated[124] that by appropriate signal processing, off-the-shelf metal-oxide sensors are capable of extracting rapidly fluctuating features of gas plumes that strongly correlate with source distance. They showed that with a straightforward analysis method it is possible to decode events of large, consistent changes in the measured signal, so-called "bouts". The frequency of these bouts predicts the distance of a gas source in wind-tunnel experiments with good accuracy. In addition, they found that the variance of bout counts indicates cross-wind offset to the centerline of the gas plume. The results offer an alternative approach to estimating gas source proximity that is largely independent of gas concentration. The analysis method employed demands very few computational resources, and is suitable for low-power microcontrollers.

While neuromorphic hardware generally delivers on the promise of energy efficiency, the challenge is to develop algorithms that harness the full potential of these chips. A natural choice for inspiration was the neural circuits that perform sensory computation in the brain. Of these, the olfactory system stands out for its capability to rapidly extract information from its extremely high-dimensional input that is chemical space. Based on previous work on olfactory sensory computation, Michael and his colleagues have used the computational architecture of the olfactory system as a template for a neuromorphic pattern recognition. They implemented this algorithm on several accelerated hardware platforms, and assessed recognition performance and power efficiency. Their work pioneers use cases for high-dimensional pattern recognition on neuromorphic architectures. The results highlight the energy-efficiency of neuromorphic hardware, and suggest a use in mobile and embedded platforms.

## Rethinking molecular design

Gisbert Schneider concluded the symposium with the award address to which he gave the full title "Rethinking molecular design (…with artificial intelligence)". Medicinal chemists need to know "what to make next", but drug designers have to face the challenges of nonlinearity, errors, and incompleteness. The problem is difficult because the scientist is dealing with an adaptive, dynamic organism, but we *can* go from serendipity, narratives, and "gut feeling" to causality−driven engineering.[125] Algorithms for generating, scoring, and optimizing molecular structure are known as de novo drug design.[126] "De novo", meaning "from the beginning" or "from scratch" is a misnomer since you cannot begin from scratch: you have to input *something*. But "novo" might also be correctly interpreted as "new", "novel", or "latest".

In the midst of the fourth industrial revolution, there is much excitement about the potential of artificial intelligence (AI) to further pharmaceutical research.[127] Essentially, an intelligent agent, human or machine, demonstrates an ability to solve problems, to learn from experience, and to deal with new situations. With regard to these three central criteria, certain machine learning modalities for de novo molecular design may be considered instances of AI.

Small-molecule drug discovery can be viewed as a challenging multidimensional problem in which various characteristics of compounds, including efficacy, pharmacokinetics and safety, need to be optimized in parallel to provide drug candidates. Recent advances in areas such as microfluidics-assisted chemical synthesis and biological testing, as well as AI systems that improve a design hypothesis through feedback analysis are now providing a basis for the introduction of greater automation into aspects of this process. This could potentially

accelerate time frames for compound discovery and optimization and enable more effective searches of chemical space.[128]

In this context, the umbrella term “constructive learning” describes an entire class of problem–solving techniques, including generative deep networks, for which the ultimate learning goal is not necessarily to find the optimal model for the training data but rather to identify new instances (molecules) from within the applicability domain of the model which are likely to exhibit the desired properties. Several such systems have been designed, and developed to rationalize and articulate next steps in compound selection, synthesis, and testing.

The first automated ligand-based de novo design program was the TOPology-Assigning System (TOPAS). An evolutionary algorithm was developed for fragment-based de novo design of molecules.[129] This stochastic method aims at generating a novel molecular structure mimicking a template structure. A set of about 25,000 fragment structures serves as the building block supply. The fragments were obtained by a straightforward fragmentation procedure, applied to 36,000 known drugs. A strategy very similar to the Retrosynthetic Combinatorial Analysis Procedure, RECAP, developed by Hann and co-workers[130] was applied. At the time, only 11 reaction schemes were implemented for both fragmentation and building block assembly. This combination of drug-derived building blocks and a restricted set of reaction schemes proved to be a key for the automatic development of novel, synthetically tractable structures. In a cyclic optimization process, molecule architectures were generated from a parent structure by virtual synthesis, and the best structure of a generation was selected as the parent for the subsequent TOPAS cycle. Similarity measures were used to define fitness, based on 2D-structural similarity or topological pharmacophore distance between the template molecule and the variants.

First experimental proof[131] of the TOPAS concept was demonstrated by the successful de novo design of a new structural class of potent potassium channel inhibitors. Gisbert and his co-workers selected a known potent potassium channel blocking agent as the template molecule. Two molecules were synthesized based on the original design recommended by TOPAS. Electrophysiological measurement proved potassium channel blocking activity for both (Figure 57).

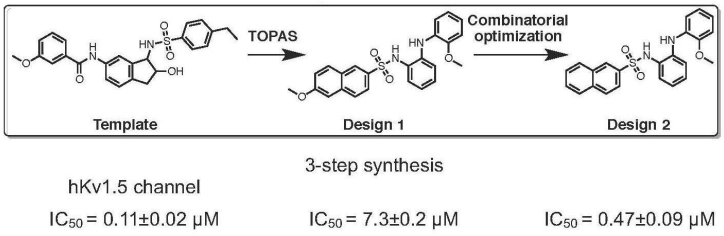



Figure 57

At that time, Gisbert coined the term “scaffold hopping” for the identification of isofunctional molecule structures with significantly different molecular backbones.[132]

Gisbert’s software called Design of Genuine Structures (DOGS)[133,134] features a further advanced ligand-based strategy for automated in silico assembly of potentially novel bioactive compounds. The quality of the designed compounds is assessed by a graph kernel method measuring their similarity to known bioactive reference ligands in terms of structural and pharmacophoric features. A deterministic compound construction procedure was implemented that explicitly considers compound synthesizability, based on a compilation of 25,144 readily available synthetic building blocks (from Sigma-Aldrich) and 58 established reaction principles, encoded as SMILES. This enables the software to suggest a synthesis route for each designed compound. DOGS performs ligand growing by reaction forecasting. Pseudo-reaction products are formed from a starting fragment, the most promising pseudo-reaction product is selected and full enumeration then takes place with the selected reaction scheme. This controls the combinatorial explosion that would result from full enumeration of all 58 reactions with over 25,000 building blocks.

The design of a fragment-like inhibitor of death-associated protein kinase 3 (DAPK3)[135] was one of many successful applications of DOGS. The starting point was the DAPK3 inhibitor Fasudil. After 521 designs and predicted targets, the fourth-ranked selected design (Figure 58) was chosen. (The top three looked less innovative.)

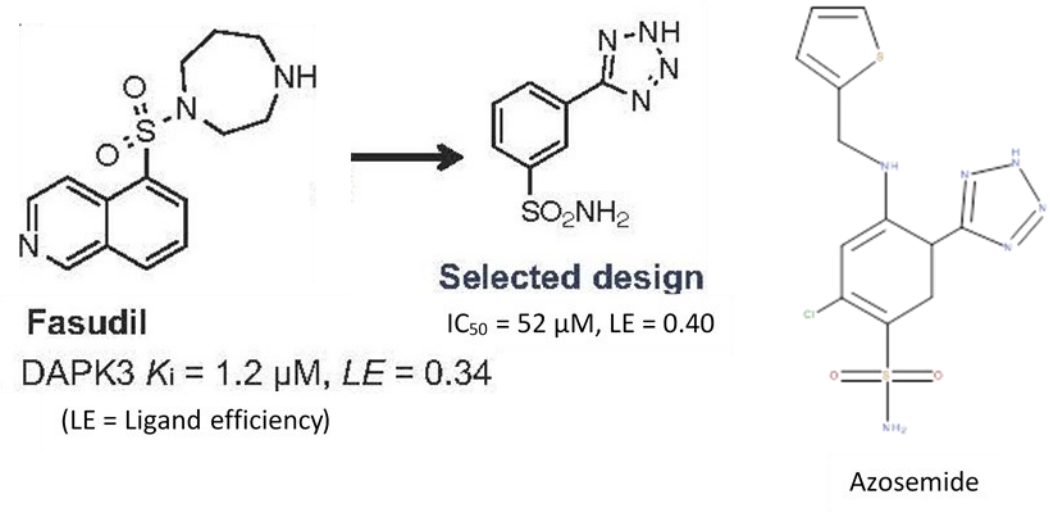



Figure 58

A new crystal structure (PDB 5A6N) of the inactive DAPK3 homodimer showed the fragment-like hit bound to the ATP pocket. Azosemide is an approved diuretic in Japan and it contains the designed structural framework. The researchers acquired a sample, tested it, and found an $IC_{50}$ of 2 µM. Target prediction software based on machine learning models correctly identified additional macromolecular targets of the computationally designed compound, and of azosemide.

In work done in collaboration with Novartis,[136] Gisbert's team has applied ant colony optimization to combinatorial building block selection. By relying on publicly available structure-activity data, the researchers developed a predictive quantitative polypharmacology model for 640 human drug targets. By taking reductive amination as an example of a privileged reaction, they obtained novel subtype-selective and multitarget-modulating serotonin receptor antagonists, as well as ligands selective for the sigma-1 receptor, with accurately predicted affinities. Automated flow synthesis with inline analytics was carried out with reaction chips on the bench. The nanomolar potencies of the hits obtained, their high ligand efficiencies, and an overall success rate of up to 90% demonstrate that this ligand-based computer-aided molecular design method may guide target-focused combinatorial chemistry. The results of this work with Novartis[136,137] suggest that seamless amalgamation of computational activity prediction and molecular design with microfluidics-assisted synthesis enables the swift generation of small molecules with the desired polypharmacology.

Gisbert and co-workers have also reported the computational de novo design of synthetically accessible chemical entities that mimic the complex sesquiterpene natural product (-)-Englerin A.[138] This natural product kills kidney cancer cells, but it is toxic. It also requires a 14-step synthesis,[139] and the target was unknown. Gisbert's team synthesized lead-like probes from commercially available building blocks and profiled them for activity against a computationally predicted panel of macromolecular targets. Both the design template (-)-Englerin A and its low-molecular weight mimetics presented nanomolar binding affinities, and antagonized the transient receptor potential calcium channel (TRPM8) in a cell-based assay, without showing target promiscuity or frequent-hitter properties. (Incidentally, Gisbert credits his wife and co-worker Petra with the actual invention[140] of the term "frequent hitter".) DOGS suggested a three-stage synthesis (Figure 59).

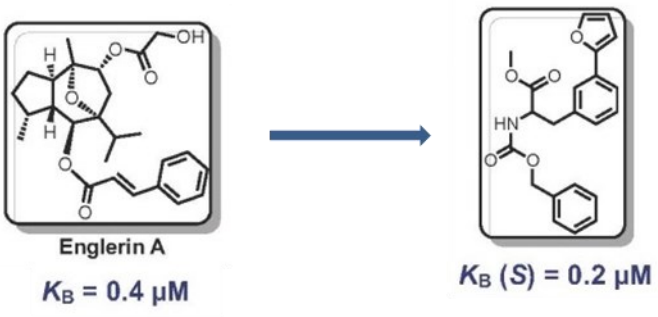



Figure 59

Very recently Gisbert's team has reported a method for de novo design that uses generative recurrent neural networks (RNN) containing long short-term memory (LSTM) cells.[141,142] This computational model captured the syntax of molecular representation in terms of SMILES strings with close to perfect accuracy. The SMILES strings were from compounds in ChEMBL with nanomolar activity. The learned pattern probabilities can be used for de novo SMILES generation by fragment growing. This molecular design concept eliminates the need for virtual compound library enumeration. By employing transfer learning, the researchers fine-tuned the predictions of the RNN for specific molecular targets. This approach enables virtual compound design without requiring secondary or external activity prediction, which could introduce error or unwanted bias. The results obtained advocate this generative RNN-LSTM system for high-impact use cases, such as low-data drug discovery, fragment-based molecular design, and hit-to-lead optimization for diverse drug targets.

By transfer learning, the general RNN model was fine-tuned on recognizing retinoid X and peroxisome proliferator-activated receptor (PPAR) agonists.[142] Five top-ranking compounds designed by the generative model were synthesized. Four of the compounds revealed nanomolar to low-micromolar receptor modulatory activity in cell-based assays. Apparently, the computational model intrinsically captured relevant chemical and biological knowledge without the need for explicit rules.

In another example (unpublished work) a first-in-class C-X-C chemokine receptor type 4 (CXCR4) agonist was designed by transfer learning from CXCR modulators in the literature. They were ranked by pharmacophore similarity according to chemically advanced template search (CATS) topological pharmacophores.[143] A one-stage synthesis was proposed and successfully implemented.

Scaffold hopping by automated computational de novo design works. De novo structure generation and optimization is almost a solved problem: new structures can be generated by explicit or implicit knowledge-based systems. Most of the designs are readily synthesizable. Nevertheless, many more applications are needed to assess the method. Scoring remains inherently difficult: a review on the "edge of chaos" discusses this.[125] Deep learning systems, and generative models, build on implicit medicinal-chemical knowledge. This mix of "mind and machine" will inspire and change drug design.[128]

## Conclusion

Erin Davis, chair of the ACS Division of Chemical Information, formally presented the Herman Skolnik Award to Gisbert Schneider at the end of the symposium.


Erin Davis and Gisbert Schneider (*Photo Credit: Wendy Warr*)

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Wendy Warr
Wendy Warr & Associates
wendy@warr.com

# Feature: Tackling Gender Disparity in the Skolnik Award

Gender disparities have been studied in various fields, examining disparities in pay, promotions, awards, and representation in general.[1] Recently, a number of studies have focused on computational sciences, in particular biology[2] and chemistry[3]. Conferences in science and computing have also been the subject of disparities in gender representation, sometimes so severe that some panels or symposia consist only of male speakers. For example, Sacquin-Mora recently reported that the French Network for Theoretical Chemistry (RFCT) noted that, of 280 invited speakers, only 24% were women,[4] whereas women make up 35% of the computational and theoretical chemistry community[3]. Interestingly, a gender analysis of presenters at the Fall 2018 ACS National Meeting identified 30% (n=142) and 21% (n=317) of speakers as female within the CINF and COMP programs, respectively.

Unsurprisingly, gender disparities also occur in the context of awards.[5-7] CINF organizes a number of awards every year, with the Herman Skolnik award being the flagship award of the division. This award is made to recognize outstanding contributions to and achievements in the theory and practice of chemical information science. Since 1976, 43 awards have been made, and only one woman (Y.C. Martin, 2009) has been the recipient. While this article focuses on gender, it is also worthwhile to note that all awardees have been located in North America and Europe, with the exception of David Winkler (2017, Australia) and Kimito Funatsu (2019, Japan).

Given that the award recognizes significant contributions to the field, it is natural that the awardees tend to be older, having worked in the field for 20 to 30 years. While gender disparities are actively recognized now, this was not the case during that time period, and, as a result, women were underrepresented in the scientific workforce. While one might argue that this translates to fewer women making significant contributions to the field, it is surely reasonable to expect that more than one woman has made such contributions and thus warrants consideration for the Skolnik award.

While the CINF Awards Committee will not consider gender as a deciding factor in making the Skolnik award, we do intend to encourage nominations of women scientists working in the field of chemical information science. It is important to note that the Awards Committee does not identify candidates and is dependent on receiving nominations of candidates for consideration. To this end, the Call for Nominations will be updated specifically to make note of gender and geography, and outreach efforts will encourage nominators to consider women for consideration.

While we recognize that there are *fewer* women than men who have worked in the chemical information sciences, we also believe that, within that subset, there are scientists who have made significant contributions to the field. We encourage the community to consider their achievements and nominate them for the Herman Skolnik Award in the coming years.

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Rajarshi Guha
Chair, CINF Awards Committee
rajashi.guha@gmail.com

# Book Reviews

The book review column in this issue marks a departure from the style of my previous book reviews; instead of a review of one book, I present a group of "mini-reviews", or "thumbnail" reviews of books on a common subject: technical writing. I was inspired by two articles in the *Journal of Chemical Education*, which discussed teaching chemistry students to communicate science to non-experts[1] and to write review articles[2].

Although I wrote essays for in my first-year English class in college, the topics of my papers were always humanities subjects, and I felt hindered by the lack of formal instruction in scientific and technical writing, which I had to learn on the fly later in my career. Scientists, as a whole, have historically received very little training in communicating science to the public, but this is becoming a topic of interest within scientific organizations, including the ACS. I remember CINF symposia from a few years ago that focused on the need for more communication outside our field, including the ability to give one-minute "elevator talks". In addition to this, technical writing is now being covered in many more college courses, including in Chem 393 at the University of Maine, a seminar for juniors preparing for senior research, which has at least one session devoted to writing reports.

I personally received training in writing reviews because Ted Taylor, my PhD advisor at Princeton in 1966, asked his graduate students to write reviews publishable in *Chemical Reviews* as the introductions to our theses. When I did this, he also encouraged me to search for citations to my bibliographic references in the *Science Citation Index*, then available only in print and housed in the nearby Biology Library. I did as he asked and found several new references. These exercises were the foundations of my later career in chemical information. My review article was published in *Chemical Reviews*[3], as was that of my lab-mate, Gavin Spence[4], but, as far as I know, ours were the only ones published.

Another champion of the value of writing and publishing reviews was Gene Garfield, who regularly promoted the genre in "Current Comments", his weekly editorials in the issues of "Current Contents". My efforts towards writing reviews, described above, were also documented in my tribute to Garfield, published in a previous issue of the *Chemical Information Bulletin*[5]. Garfield stressed the value and efficiency of locating reviews while searching for information because they present "pre-packaged" collections of references and analysis of the topic of interest. I had always planned to write more reviews, but other things like my major job responsibilities always got in the way. I did utilize reviews when conducting searches for researchers at Amoco. I routinely began my search by consulting printed resources and handbooks first, after which I searched for reviews. I let the scope of those results determine the rest of the search schedule.

I have reviewed several books on scientific writing in the past, some of which covered writing for nontechnical audiences, but I was not familiar with this book by Randy Olson, used in the classes described by Angelo in the *Journal of Chemical Education* article[1]:

> *Don't be Such a Scientist: Talking Substance in an Age of Style*, Olson, Randy; Island Press, Washington, 2009.

I borrowed a copy from Fogler Library at the University of Maine, but I was not that impressed with the book; the primary topic is the author's second career as a film maker. However, the chapter headings illustrate topics of substance, including "Don't be so cerebral", "Don't be so literal minded", "Don't be such a poor storyteller", Don't be so unlikable", and "Be the voice of science".

I have reviewed other books for other audiences that may be more appropriate both for course work and for individual instruction. These include:

> *Write Like a Chemist: A Guide and Review, Robinson, M. S., et al.; Oxford University Press, New York, 2008*
> (reviews: *CHOICE*, 46-5029, May 2009, vol. 46 no. 9, Review DOI: 10.5860/CHOICE.46-5029 (R.E. Buntrock) ; *J. Chem. Educ.*, **2009**, *86* (2), 170 (J. Kovac))
> A course resource, this book studies 250 examples of articles in ACS journals and NSF research proposals. Interaction with the *ACS Style Guide* is exemplary.

*The Chicago Guide to Your Career in Science: A Toolkit for Students and Postdocs.* Bloomfield, V. A., El_Fakany, E. E.; Univ. of Chicago Press, Chicago, 2008

*(Review: J. Chem. Educ., **2010**, 87 (4), 373–373, DOI: 10.1021/ed800142u)*

Although this is primarily a career guide, one section includes material on communicating including speaking, writing, meetings, and presentations.

*Introducing Science Communication: A Practical Guide.* Brake, M. L., Weitkamp, E.; Palgrave Macmillan, New York, 2010

*(Review: J. Chem. Educ., **2010**, 87 (11), 1138–1139, DOI: 10.1021/ed1008552)*

Scientists should be able to communicate with a variety of audiences, including policy makers and the general public. Applications include science journalism, broadcasting, other emerging media, and live demonstrations. The book covers communicating science in general, but the applications to chemistry are obvious. It is suitable for courses in both science and journalism and is accessible to all chemistry faculty, students, and researchers.

*Taking Science to the People: a Communication Primer for Scientists and Engineers*, Johnsen, C., ed.; Univ. of Nebraska Press, Lincoln, 2010.

*(Review: CHOICE, 48-5046, May 2011)*

This book, authored by multiple experts, gives advice for communication by STEM practitioners to a variety of nontechnical audiences including politicians, journalists, and the general public.

*Explaining research: How to Reach Key Audiences to Advance Your Work*, Meredith, D.; Oxford, University Press, Oxford, New York, 2010

A key quote from this work is, “You do not really understand something unless you can explain it to your grandmother.”

Books are also available for instruction in writing reviews. Notable examples are the following:

*A Short Guide to Writing about Chemistry, Davis, H. B., Tyson, J. F., Pechenik, J. A.; Longman, Boston, 2010.*

The context of this book is collegiate education, and the reviews are for writing about research in many formats, from essays in course work to research proposals and papers. Preparing and writing reviews is fundamental to the entire research process.

*Scientific Writing and Communication: Papers, Proposals, and Presentations*, Hofmann, A. K.; Oxford University Press, Oxford, New York, 2010.

This book is very thorough, with an entire chapter on writing reviews. (Obviously 2010 was a very good year for such books).

My advice for any *Chemical Information Bulletin* readers associated with an academic institution is to promote and support the incorporation of technical writing in science and journalism courses at all levels.

## References


(1) Encouraging the Art of Communicating Science to Nonexperts with *Don’t be Such a Scientist*, St. Angelo, S. K.; *J. Chem. Educ.*, **2018**, *95* (5), 804-809.

(2) Writing a Review Article: A Graduate Level Writing Class, Ogunsolu, O. O., Wang, J. C., Hanson, K.; *J. Chem. Educ.*, **2018**, *95* (5), 810-816.

(3) Buntrock, R. E., Taylor, E.C.; “Cyclization reactions of 2,2'-disubstituted biphenyls,” *Chem. Rev.*, **1968**, *68* (2), 209–227, **DOI:** 10.1021/cr60252a003, Publication Date: April 1968

(4) Spence, G. GF., Taylor, E. C., Buchardt, O.; "Photochemical reactions of azoxy compounds, nitrones, and aromatic amine N-Oxides," *Chem. Rev.*, **1970**, *70* (2), 231–265, **DOI:** 10.1021/cr60264a003, Publication Date: April 1970

(5) Eugene Garfield: A Tribute to a Great Man and Great Legacy, *Chemical Information Bulletin*, **2018**, *70* (1), 18-2, http://bulletin.acscinf.org/PDFs/CIB_70_1.pdf

Robert E. (Bob) Buntrock
Buntrock Associates, Orono, ME
buntrock16@roadrunner.com

*Did you miss key events at the recent national meeting? Do you miss your CINF compatriots? Do you just want to see what people were up to at the conference?*

Visit the CINF Flickr stream at https://www.flickr.com/photos/cinf/collections/72157671745659567/. Wendy Warr, CINF's resident photographer, has published the photos that she took at the Fall 2018 ACS National Meeting in Boston. They appear in six separate albums, entitled:

- Boston 2018 CINF Reception
- Boston 2018 COMP Reception
- Boston 2018 Herman Skolnik Award Symposium
- Boston 2018 J Cheminf Editorial Advisory Board
- Boston 2018 Miscellaneous
- Boston 2018 Schrödinger Reception

If you want to delve further into the past, you can also browse other collections by clicking on the "Collections" link at the top of the page or by visiting https://www.flickr.com/photos/cinf/collections/.

# Committee Reports

## Report from the Council Meeting Held on August 22, 2018

The Council of the American Chemical Society met in Boston, MA, on Wednesday, August 22, 2018, from 8:00 a.m. until approximately 12:30 p.m. in Ballroom A-C of the Hynes Convention Center. Below are the highlights of the meeting.

### Nominations and Elections

The Committee on Nominations and Elections presented the candidates for membership on the Council Policy Committee (CPC). These were Lawrence J. Berliner, Michelle V. Buchanan, Alan B. Cooper, Ella L. Davis, Lissa A. Dulany, Lydia E. M. Hines, Lisa Houston, Will E. Lynch, Martin D. Rudd, and Barbara P. Sitzman. Council must elect five individuals. The four candidates who received the highest numbers of votes, Ella Davis, Lissa Dulany, Lisa Houston, and Martin Rudd, were elected for the 2018 -2021 term, and the candidate receiving the fifth highest vote, Will Lynch, was elected for a one- year term for 2019.

The candidates for membership on the Committee on Nominations and Elections were also presented. Candidates were Allison Aldridge, Christopher J. Bannochie, Mary K. Engelman, Kenneth P. Fivizzani, Anne M. Gaffney, David S. Gottfried, James M. Landis, R. Daniel Libby, Silvia Ronco, and Frankie K. Wood-Black. The five candidates elected for the 2019-2021 term were Allison Aldridge, Christopher Bannochie, Mary Engelman, Silvia Ronco, and Frankie Wood-Black.

Finally, the candidates for membership on the Committee on Committees were presented. Candidates were: Rodney M. Bennett, Richard S. Danchik, Jacqueline A. Erickson, Rick Ewing, Russell W. Johnson, Donivan R. Porterfield, Carolyn Ribes, Frank Romano, and Peter Zarras. The five candidates elected for the 2019-2021 term were Rodney Bennett, Jaqueline Erickson, Judith Iriarte-Gross, Donivan Porterfield, and Carolyn Ribes.

Ballots for the 2018 fall national election (Directors and 2019 President-Elect) will be distributed October 1-3, with a voting deadline four weeks later, on October 31. ACS members eligible to vote and with an email address on file will receive an electronic ballot, with the option to request a paper ballot. Those members with no email address on file will be sent a paper ballot, with the option to vote electronically. The ACS election vendor, Survey & Ballot Systems, will send three email reminders during the voting period to those who have not voted as of the reminder date.

### Petitions for Vote

*Petition on Affiliation with Other Technical Organizations*

Council voted to approve the Petition on Affiliation with Other Technical Organizations. The petition adds the Divisional Activities Committee (DAC) and the Local Section Activities Committee (LSAC) to Bylaw XI, Sec. 3, because each is charged with approving the affiliation of divisions or local sections with other technical organizations under their respective duties in Bylaw III, Sec. 3, d, (1), (c), that DAC and LSAC act for Council, in collaboration with the Committee on Constitution and Bylaws (C&B)::

> DAC: (vii) acting for the Council, in collaboration with the Committee on Constitution and Bylaws, in approving the affiliation of Divisions with other technical organizations. (6/1/73)
>
> LSAC: (xi) acting for the Council, in collaboration with the Committee on Constitution and Bylaws, in approving the affiliation of Local Sections with other technical organizations. (11/7/07)

The Committee on Constitution and Bylaws reviewed the petition and found that it is legal, it is not inconsistent with the Bylaws of the society, and it will have no impact on the finances of the society.

*Petition to Remove Restrictions for International Chemical Sciences Chapters*

After a lengthy discussion Council voted to approve the Petition to Remove Restrictions for International Chemical Sciences Chapters. The actual vote was 81% in favor and 19% opposed.

The petition addresses concerns that were raised at the recent ACS Council Meeting in Washington, D.C., when a similar petition failed by fewer than eight votes; it did not receive the required two-thirds approval. Bylaw IX

was written more than 25 years ago when International Chemical Sciences Chapters were created. In addressing concerns raised on the council floor in D.C., this simplified petition creates a pathway for International Chemical Sciences Chapters to have a role in the society to help to carry out Article II, Section 3 of the ACS Constitution: "The SOCIETY shall cooperate with scientists internationally and shall be concerned with the worldwide application of chemistry to the needs of humanity". The International Chemical Sciences Chapters are governed and operated by ACS member volunteers in the same way as divisions and local sections. International chapter leaders are ACS members, including: U.S. citizens working and teaching abroad; chemists, chemical engineers and chemistry educators who have received their education in the U.S. or abroad; ACS award recipients, editors, authors, donors, and national/regional meeting presenters based outside the United States. These volunteers donate their time to hold meetings and conduct activities within their countries to benefit chemistry and the society. The leaders and members of these International Chemical Sciences Chapters provide ACS with valuable international networks within the worldwide chemistry enterprise, and the Society cannot afford to be insular, considering the value that members of International Chapters bring to the Society. The proposed, revised language removes the allotment restriction, which states that International Chemical Sciences Chapters shall not receive funds, but it does not authorize any allotment of funds from ACS; thus, while it does not take away any dues funds from divisions or local sections, it allows the Board of Directors to grant funds for a specific, requested purpose. The petition also removes the stipulation that International Chemical Sciences Chapters are not entitled to elected representation on the council; it does not permit them to have councilors at this time, but it paves the way for future Bylaws changes that could permit this.

The Committee on Constitution and Bylaws reviewed the petition and found that it is legal, it is not inconsistent with the Bylaws of the society, and it will have no impact on the finances of the society.

## Petition for Consideration

*Petition to Streamline the ACS Governing Documents*

As a result of a Joint Board - Council Policy Committee (CPC) Task Force on Governance Design, a project was undertaken to reorganize the fundamental governing documents of the society, the Constitution and Bylaws. The objective was to preserve the current governance structure and all current provisions, while creating a third document: Standing Rules. The manner in which the Standing Rules can be modified will have the additional benefit of engaging more committees and members in the design and execution of ACS governance. Organizationally, these three documents should work as a hierarchy. The Constitution should define, the Bylaws should authorize, and the Standing Rules should operationalize. In general, moving from Constitution to Bylaws to Standing Rules on any topic should provide progressively more detail and become progressively easier to amend. The task force avoided making substantive changes, choosing instead to move blocks of text among the documents. A summary of document changes to the Constitution and Bylaws can be accessed at: https://www.acs.org/content/dam/acsorg/about/governance/councilors/council-agenda-8-17.pdf - see pages 93-148. Since this petition is 58 pages long, an appeal was made to create a clearer, more digestible version before the 2019 spring meeting, at which the actual vote will take place.

## Petition for Action from the International Activities Committee (IAC)

Council voted to approve the petition for the formation of a new International Chemical Sciences Chapter, to be known as the Colombia International Chemical Sciences Chapter. The chapter will consist of the individual territory, and is not part of any other chapter or local section of the society. The petition was initiated and signed by ACS members in good standing and residing in the territory. The application meets all of the requirements of Bylaw IX of the society, and includes a statement that the applicants are familiar with and will abide by all governing documents of the society, specifically including Bylaw IX Section 2(c), which states that the chapter and its officers, as representatives of the chapter, shall not engage in political activity, shall avoid any activities that may adversely affect the interests or public and professional image of the society, and shall ensure that all activities of the chapter shall be open to all members of the society. The application includes proposed budgets for chapter operation. The petition was reviewed by the ACS Joint-Board Committee on International Activities (IAC), which recommended council approval. Having gained the approval of the council, this action now requires approval from the ACS Board of Directors, after which the chapter will begin operation.

## Highlights from Committee Reports

*Committee on Budget and Finance*

The Society's 2018 Probable 1 Projection for year-end calls for a net from operations of $31.8 million. This is

$1.3 million favorable to the approved budget. Total revenues are projected to be $565.1 million, which is $5.7 million or 1.0% favorable to the budget. Total expenses are projected at $553.3 million, which is $4.4 million or 0.8% unfavorable to the budget. The favorable revenue is entirely due to income from CAS, ACS Publications, and investments. Both CAS and ACS Publications are expected to have record years. Unrestricted net assets are estimated to reach $342.8M by year end; for comparison purposes, the total at the end of 2017 was $284M.The committee considered one 2019 program funding reauthorization request, and, on its recommendation, the board subsequently approved funding the *ACS Festival Series* for inclusion in the 2019 Proposed Budget and the 2020-2021 Forecast Budgets.

The society is expected to end the year in compliance with each of the five board-established financial guidelines. Additional information can be found at www.acs.org; at the bottom of the page, click “About ACS”, and then click “Financial”.

*Membership*

As of August 21, ACS had 149,584 members, which is a decline of only eight-tenths of one percent from the over 150,000 members in 2017. This year-to-date figure represents an increase of over 1,200 members, compared to the last two years. It was noted that five of the last seven months have been seen the largest increases in membership since at least 2014. The current membership count suggests that ACS will have a strong close to the year, and there is cautious optimism that total membership will rise for the first time since 2011. Usually, 15% - 20% of the attendees at the national meetings are not ACS members. At the Boston meeting, the figure dropped to 11%; this is likely due to the fact that, when registering for this conference, individuals were also offered the option of renewing membership or joining the society.

*Committee on Committees*

Council approved the recommendation made by the Committee on Committees to continue the Committee on Chemical Safety, subject to concurrence by the Board of Directors.

*Meetings and Expositions*

Attendance at the 2018 Boston meeting totaled 14,235, as of Tuesday, August 21, 2018. The breakdown was as follows:

| | |
|---|---|
| Regular attendees: | 8,294 |
| Students: | 3,671 |
| Guests: | 513 |
| Exhibit-only: | 576 |
| Exhibitors: | 1,181 |

Attendance at the fall national meetings since 2004 is as follows:

| | |
|---|---|
| 2004: Philadelphia, PA | 14,025 |
| 2005: Washington, DC | 13,148 |
| 2006: San Francisco, CA | 15,714 |
| **2007: Boston, MA** | **15,554** |
| 2008: Philadelphia, PA | 13,805 |
| 2009: Washington, DC | 14,129 |
| **2010: Boston, MA** | **14,151** |
| 2011: Denver, CO | 10,076 |
| 2012: Philadelphia, PA | 13,251 |
| 2013: Indianapolis, IN | 10,840 |
| 2014: San Francisco, CA | 15,761 |
| **2015: Boston, MA** | **13,888** |
| 2016: Philadelphia, PA | 12,800 |
| 2017: Washington, DC | 12,904 |
| **2018: Boston, MA** | **14,235** |

Attendance at this year’s Boston meeting was higher than the Boston attendance in 2015. Boston is not listed on the conference rotation for the foreseeable future (through 2025). It was also noted that printed program books will no longer be made available for purchase.

## Special Discussion

ACS President, Peter Dorhout, introduced and led a special discussion on what role ACS should play in preventing sexual harassment in the sciences. He highlighted several recent articles, workshops, and studies that have called attention to the issue, notably "Science of Sexual Harassment", a symposium organized during the ACS National Meeting in New Orleans (Spring 2018) by the Women Chemists Committee and *Chemical & Engineering News*; and a National Academies of Sciences, Engineering, and Medicine consensus study report: "Sexual Harassment of Women: Climate, Culture, and Consequences in Academic Sciences, Engineering, and Medicine" (2018). He directed the council's attention to existing ACS codes and initiatives to address sexual harassment, and offered items for discussion and possible action:

- More signs and information at national meetings regarding ACS policies and supporting information
- Trained volunteers at national meetings for reporting sexual harassment
- A Webinar on preventing sexual harassment for local sections or divisions

To inform further the discussion and councilor input, a brief survey was conducted using the audience electronic response system. The results of the survey are listed below. The ACS Volunteer/National Meeting Attendee Conduct Policy appeared in the Council Agenda and can be found online at http://www.acs.org/content/acs/en/about/governance/councilors.html. A summary of the discussion and additional information will be sent to councilors at a later time.

1. **Have you ever witnessed or experienced sexual harassment at an ACS meeting or ACS event?** (413 responses). Yes 23% (94) No 77% (319)
2. **Have you ever witnessed or experienced sexual harassment at an ACS meeting or ACS event, or in your professional workplace or learning environment?** (182 women / 223 men responded).
   Women (Yes 77% (141), No 23% (41); Men (Yes 57% (127), No 43% (96)
3. **How familiar are you with the ACS Codes and initiatives for professional conduct?** (417 responses).
   Very Familiar 38% (157), Vaguely Familiar 46% (192), Not Familiar 16% (68)
4. **Has your local section or division instituted a sexual harassment policy of its own?** (419 responses).
   Yes 3% (12), No 73% (309), Don't Know 23% (98)

## Resolutions

The council passed the following resolutions:

- In memory of deceased councilors;
- Congratulations to ACS Treasurer and Chief Financial Officer Brian A. Bernstein on the occasion of his retirement after nearly 40 years of service to the society (34 as ACS Treasurer);
- In gratitude, to the officers and members of the Northeastern Section, host section for the 256th National Meeting, the divisional program chairs and symposium organizers, and ACS staff, and;
- Acknowledging Peter K. Dorhout's service as ACS President and presiding officer of the council.

*Note: The Council Agenda Book can be accessed at:* https://www.acs.org/content/dam/acsorg/about/governance/councilors/council-agenda-8-17.pdf.

## Actions Taken by the ACS Board of Directors during the 2018 Fall National Meeting

### The Board's Executive Session

At this meeting, the ACS Board of Directors focused on a number of key strategic issues and took several related actions.

*The Board's Committees*

The Board of Directors received and discussed reports from its committees on Corporation Associates, Professional and Member Relations, Executive Compensation, the Governing Board for Publishing, and the Society Committee on Budget and Finance. On the basis of those reports and with regard to the board's strategic vision for the society:

- The board approved, on the recommendation of the Committee on Professional and Member Relations, the society's nominees for the 2019 Perkin Medal and the 2019 National Science Board Public Service Award.

- The board voted to approve the appointments or reappointments of several editors-in-chief for ACS journals, as recommended by the Joint Board-Council Committee on Publications and Editor Selection Committees. Information about those appointments will appear in *C&EN* once the individuals concerned have been notified.

- In light of the recent financial performance of the technical-meeting component of our national meetings, the board voted to approve an advance member registration fee of only $490 for national meetings held in 2019 (i.e., the current advance member registration fee escalated to account for inflation only); to reauthorize a program funding request for the Chemistry Festival program; and, in accordance with past practice, to allocate on a pro-rated basis to qualified ACS divisions any net revenues accrued to the society from the 2020 International Chemical Congresses of the Pacific Basin Societies (Pacifichem), as well as all future Pacifichem meetings.

- The board liaison to the Committee on Corporation Associates presented a proposed committee Future State Operating Model and considered options for committee member terms and appointment processes. The Board expressed support for the value of industry to ACS and acknowledged Corporation Associates as being positioned within the society to represent the voice of industry to the board and ACS.

- The Board's Society Programs global liaison offered an update on efforts to strengthen the global presence of society programs to serve our international members and the global chemistry enterprise better. Efforts are underway to clarify and articulate the current state of international activities, products, and services; to clarify the challenges associated with globalization of existing domestic activities; and to offer recommendations for moving forward. Next steps include interviewing key stakeholders, reviewing past efforts, and exploiting existing market research with a view toward developing a strategic plan, activities, and timelines for board consideration.

- The board liaison to the Leadership Advisory Board (LAB) provided an update on initial efforts geared towards the development of a next-generation ACS leadership program. A small task force has been charged with investigating the state of the art in leadership development, assessing the future needs of the society as well as those of individual members and their employers, and then proposing, by the end of 2019, a strategic vision for and the specifications of a next-generation ACS leadership program focused on 2030 and beyond.

*Executive Director and CEO Report*

The board also received an extensive report from the Executive Director and CEO on adopting "Passion for Chemistry" and "Diversity and Inclusion" as core values of the society, on membership, ACS financial performance, and upcoming events and activities. He reported initial success with several initiatives that address and reverse the decline in membership. His immediate subordinates provided updates to the board on the activities of Chemical Abstracts Service (CAS), the ACS Publications Division, and the Office of the Secretary and General Counsel. As part of his report, he also invited the Executive Vice President for Human Resources to brief the board on the activities, opportunities, and challenges of the Human Resources Division.

*Other Society Business*
The board approved the foundation documents of the newly created endowment for the Henry H. Storch Award in Energy Chemistry, which was originally established as a national award in 1964.

As is customary, the board heard reports from members of the presidential succession on their current and planned activities for 2018-2019. Several presidential symposia and events incorporating and supporting the Boston national meeting's theme, "Nanoscience, Nanotechnology & Beyond", were highlighted in those reports.

*The Board's Regular Session*
The board held a well-attended regular session on Sunday, August 19. It featured a presentation by Nobel Laureate Sir Fraser Stoddart who spoke on transformative research and reviewed his contributions in supramolecular chemistry and molecular recognition. Also, as a champion of the ACS Project SEED program, he advocated for the program on this, its fiftieth anniversary. Prior to the presentation, members of the presidential succession and the Executive Director and CEO offered brief reports on their activities. The officers provided more extensive reports on their activities and future plans as part of their written and oral reports to the council, which can be found within the council agenda.

Respectfully submitted,
August 24, 2018

Svetlana Korolev
CINF Councilor
skorolev@uwm.edu

Bonnie Lawlor
CINF Councilor
chescot@aol.com

Andrea Twiss-Brooks
CINF Councilor
atbrooks@uchicago.edu

## CINF Membership & Engagement Committee

Do you like people more than data?
Do you like data more than people?
Do you like people and data equally?

MemComm has a spot for you!

CINF MemComm performs a number of important duties for the division, and is looking to grow its engagement with members in the new year. We track membership changes and trends and report to division leadership and the CINF membership at large. We also keep the membership informed of any relevant changes coming from the division and from ACS national leadership. In the coming year, we plan to launch a brand new, members-only newsletter, grow engagement on social media and other virtual spaces, and increase our presence at national and regional meetings. So, whether you like analyzing demographic data or enjoy actually meeting the demographics behind the data, we would love to have you on our team!

Donna Wrublewski
CINF Membership Chair
dtwrub@caltech.edu

# Sponsor Announcements

## Division of Chemical Information Sponsors, Fall 2018

The American Chemical Society Division of Chemical Information is very fortunate to receive generous financial support from our sponsors to maintain the high quality of the division's programming; to promote communication between members at social functions at the Fall 2018 ACS National Meeting in Boston, MA; and to support other divisional activities during the year, including scholarships to graduate students in chemical information.

The Division gratefully acknowledges contribution from the following sponsors:

| | |
|---|---|
| **Silver** | **ACS Publications** |
| | **Bio-Rad Laboratories** |
| | **Royal Society of Chemistry** |
| **Bronze** | ***Journal of Cheminformatics (Springer)*** |
| | **Collaborative Drug Discovery** |
| | **InfoChem** |
| | **PerkinElmer** |
| **Contributor** | ***Journal of Chemical Information & Modeling*** **(ACS Publications)** |

Opportunities are available to sponsor Division of Chemical Information events, speakers, and material. Our sponsors are acknowledged on the CINF web site, in the *Chemical Information Bulletin*, on printed meeting materials, and at any events for which we use a sponsor's contribution. For more information, please review the Sponsorship Brochure at http://www.acscinf.org/PDF/CINF_Sponsorship_Brochure.pdf.

Please feel free to contact me if you would like more information about supporting CINF.

Graham Douglas
Chair Pro Tem, Fundraising Committee 2016
Email: Sponsorship@acscinf.org
Tel: 510-407-0769

The ACS CINF Division is a non-profit tax-exempt organization with taxpayer ID no. 52-6054220.

## Bio-Rad Offers Advanced Stereochemical Recognition in Its Software

Bio-Rad's KnowItAll 2018 software now offers advanced stereochemical recognition, which is able to interpret structures (drawn or imported) using traditional stereochemical drawing conventions that are not supported in other available solutions. KnowItAll's ability to understand and preserve the stereochemical intent of each structure is critical to building scientific databases containing structures and relating those records to one another.

"The ability to relate records to one another is critical in large chemical databases, and this is most often done through chemical structures," said Gregory M. Banik, Ph.D., Bio- Rad General Manager, Informatics. "Whenever software interprets the stereochemistry in the original structure incorrectly, records cannot be related to one another and the connection is lost. However, the way KnowItAll is able to interpret implicit information in chemical structures is a game-changer for those working with large datasets of chemicals, including those in chemical and pharmaceutical information".

The new advanced stereochemistry feature is included in all editions of the KnowItAll software including the ChemWindow, Vibrational Spectroscopy, and Analytical editions. Bio-Rad is also offering a KnowItAll Stereochemical Toolkit (TK) to developers who wish to incorporate KnowItAll's advanced stereochemistry technology into their platform.

- **Contact us for more information: www.knowitall.com/contactus**
- **Learn more at www.knowitall.com/stereochem**

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## KnowItAll Spectral Databases and Spectroscopy Software

Bio-Rad's award-winning KnowItAll software (**http://www.knowitall.com**) offers comprehensive solutions to identify, search, analyze, and manage spectral data in multiple instrument vendor file formats and techniques (IR, Raman, NIR, NMR, MS, UV-Vis, and chromatography). KnowItAll's integrated tool sets eliminate the need for multiple software packages and increase overall lab efficiency. Combined with the world's largest spectral reference database of over 2 million spectra, KnowItAll provides the most advanced technology available for fast, accurate spectral analysis! **For a trial, please visit: http://www.knowitall.com/trial2018.**

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## Bio-Rad's Chemistry Software for Schools

| | |
|---|---|
| **SpectraBase -** FREE access to spectra online | **http://spectrabase.com** |
| **KnowItAll U**<br>Campus-Wide Access to Over 2 Million Spectra | **Request a trial: http://www.knowitallu.com** |
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## ACS Publications


ACS Publications launches new ACS Publishing Center

ACS Publications announces the debut of the all-new ACS Publishing Center (https://pubs.acs.org/publish/), a centralized hub for researchers to prepare and track their manuscripts. This Web site features centralization of information for ease of discovery of resources on submission, open access licensing, peer review education, and more. Once researchers log in, the Web site is customized for them and allows them to track the impact of their current publications and reviews and to check the status of submitted manuscripts. Discover how the ACS Publishing Center helps researchers more easily navigate the publishing process at https://pubs.acs.org/publish/.

Michael Qiu, MLIS
Senior Global Library Relations Manager
American Chemical Society, Publications Division
M_Qiu@acs.org

## *Journal of Chemical Information and Modeling*

JOURNAL OF
CHEMICAL INFORMATION
AND MODELING

*Journal of Chemical Information and Modeling* is excited to be sponsoring the Division of Chemical Information, and our team looks forward to working with many CINF members in the coming months. In the past, I mentioned changes at the journal, which involved creating two new manuscript types: Reviews and Application Notes. We have published several Application Notes describing software appropriate to chemical information, and we are in the process of publishing several Reviews in other areas. If you have an idea for a Review please contact me at eic@jcim.acs.org, and we can discuss your idea further. We also are expanding our support in the area of molecular simulation and materials informatics, so please consider sending your manuscripts in these areas to the journal.

All the best in 2019!

Kennie Merz
Editor-in-Chief
*Journal of Chemical Information and Modeling*

# CINF Officers

## Chair

Erin Davis
Schrödinger, Inc.
erinsdavis@gmail.com

## Chair-Elect

Elsa Alvaro
Northwestern University
elsa.alvaro@northwestern.edu

## Past-Chair

see Chair

## Secretary

Tina Qin
Vanderbilt University
qinnamsu@gmail.com

## Treasurer

Stuart Chalk
University of North Florida
schalk@unf.edu

## CINF Councilors

Bonnie Lawlor
chescot@aol.com

Andrea Twiss-Brooks
University of Chicago
atbrooks@uchicago.edu

Svetlana N. Korolev
University of Wisconsin, Milwaukee
skorolev@uwm.edu

## CINF Alternate Councilors

Carmen Nitsche
Pistoria Alliance
carmen@cinformaconsulting.com

Charles Huber
University of California, Santa Barbara
huber@library.ucsb.edu

Jeremy Ross Garritano
University of Virginia
jg9jh@virginia.edu

## Archivist/Historian

Bonnie Lawlor
chescot@aol.com

## Audit Committee Chair

TBD

## Awards Committee Chair

Rajarshi Guha
Vertex Pharmaceuticals
rajarshi.guha@gmail.com

## Careers Committee Chair

Neelam Bharti
Carnegie Mellon University Libraries
nbharti@andrew.cmu.edu

## Communications and Publications Committee Chair

Graham Douglas
communications@acscinf.org

## Procedures Chair

Bonnie Lawlor
See Councilor

## Education Committee Chair

Grace Baysinger
Stanford University
graceb@stanford.edu

## Finance Committee Chair

Stuart Chalk
University of North Florida
schalk@unf.edu

## Fundraising Interim Committee Chair

Graham Douglas
communications@acscinf.org

# CINF Officers

## Membership Committee Chair

Donna Wrublewski
Caltech Library
dtwrub@caltech.edu

## Nominating Committee Chair

Erin Davis
Schrödinger, Inc.
erinsdavis@gmail.com

## 2018–2019 Program Committee Chair

Rachelle Bienstock
RJB Computational Modeling LLC
rachelleb1@gmail.com

## 2019–2020 Program Committee Chair

Sue Cardinal
University of Rochester
scardinal@library.rochester.edu

## Tellers Committee Chair

TBD

## Chemical Information Bulletin Editor Spring

Kortney Rupp
Lawrence Livermore National Laboratory
kortneyrupp@gmail.com

## Chemical Information Bulletin Editor Summer

David Shobe
Patent Information Agent
avidshobe@yahoo.com

## Chemical Information Bulletin Editor Fall

Teri Vogel
UC San Diego Library
tmvogel@ucsd.edu

## Chemical Information Bulletin Editor Winter

Judith Currano
University of Pennsylvania
currano@pobox.upenn.edu

## Webmaster

Rachelle Bienstock
RJB Computational Modeling LLC
rachelleb1@gmail.com

## Assistant Webmaster

Stuart Chalk
University of North Florida
schalk@unf.edu

### *Contributors to this Issue*

*Articles and Features*
Rajarshi Guha
Bonnie Lawlor
Wendy Warr

*Symposium Reports*
Judith N. Currano
Sally Makady
Nicholas Ruhs

*Committee Reports*
Svetlana Korolev
Bonnie Lawlor
Andrea Twiss-Brooks
Donna Wrublewski

*Book Reviewer*
Robert E. Buntrock

*Sponsor Information*
Graham Douglas

*Production*
Judith N. Currano
David Shobe
Teri Vogel
Wendy Warr