PHARMASEL-PROSPERITY NEWSLETTER

PharmaSEL Prosperity

A bimonthly newsletter

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In this issue:

- Stephen Webb, portfolio manager at the Engineering and Physical Sciences Research Council (EPSRC), shares the EPSRC's view on Prosperity Partnerships.
- Research from the Molecular Systems Engineering (MSE) Group on selecting reaction solvents with minimal experimental effort.
- Lucia Lombardi, a Research Associate working on Work Package 4 (WP4) shares her background, research interests and her role towards WP4.
- A highlight of the researchers' participation in upcoming conferences.
- A glance at a prominent publication on the latest achievements in the SAFT-γ Mie Group-Contribution Equation of State.

EPSRC Perspective on Prosperity Partnerships

The PharmaSEL-Prosperity Partnership is a co-investment opportunity which is part of the Engineering and Physical Sciences Research Council (EPSRC) Prosperity Partnerships programme. This programme is EPSRC's flagship approach to co-investing with business in long-term, use-inspired, multidisciplinary, basic research with the potential to transform business R&D and productivity. The partnerships, which are business-led, co-created and co-delivered, are between leading UK-based businesses and their long-term strategic academic partners, with EPSRC matching the business contribution (at 80% fec). The Prosperity Partnership programme helps business unlock the transformative potential of investing in discovery science and engineering.

Launched in 2016, there are now 47 Prosperity Partnerships, with a total value of £335m. That figure includes: £167m investment from business; £39.2m from academic institutions; £128.8m from EPSRC (which includes £3.6m co-funding with BBSRC). The research undertaken covers all areas of the research landscape, from quantum software optimisation to decarbonising commodity chemicals; from acoustic platforms for haptic displays to machine learning for air traffic control; from AI for the creative economy to transforming synthetic drug discovery.

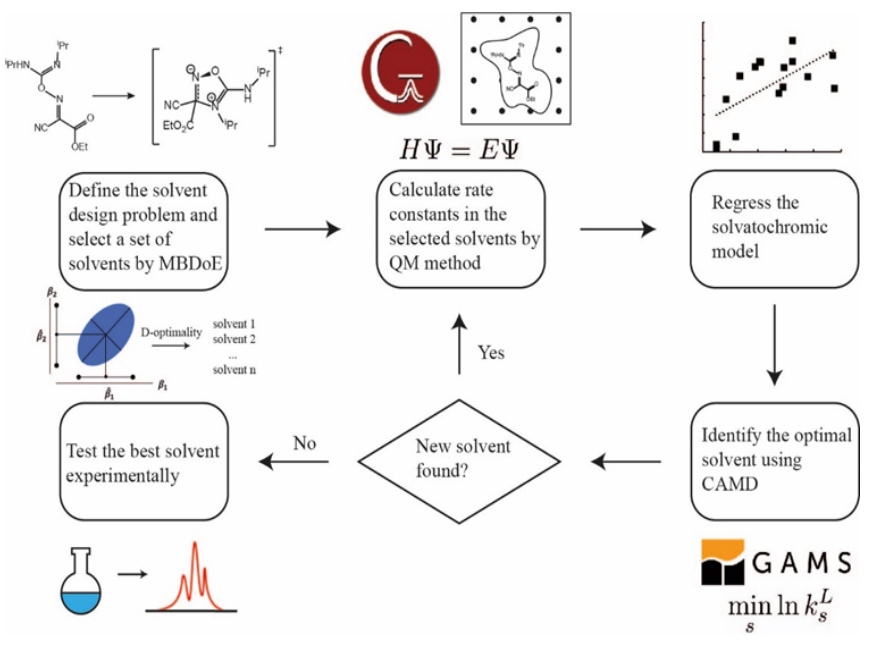
Stephen Webb
Portfolio Manager, EPSRC

Research Feature

Selecting reaction solvents with minimal experimental effort

Solvents play an important role in achieving the desired product yield and selectivity in pharmaceutical synthesis. However, finding the best solvent for a chemical reaction often involves experimental trail-and-error that is time- and resource-consuming. Under the supervision of Prof Claire Adjiman, Prof Amparo Galindo and Prof Alan Armstrong at Imperial College London, and Dr Stanley Kolis and Dr Fareed Bhasha Sayyed at Lilly, Mr Lingfeng Gui (Griffin) is developing a computational method capable of efficiently identifying promising solvents for optimal reaction kinetics of a chemical reaction in an aim to address the challenges in pharmaceutical manufacture.

By integrating the original quantum mechanical computer-aided molecular design (QM-CAMD) method [1] with model-based design of experiments (MBDoE), an enhanced solvent design method, DoE-QM-CAMD, is proposed (see Scheme 1). In DoE-QM-CAMD, MBDoE is employed to identify an initial set of solvents in which the rate constants of the studied reaction are calculated by a QM model in conjunction with an implicit continuum solvation model. The generated QM rate constants serve as training data for the regression of a much simpler surrogate model that relates reaction kinetics and solvent properties. These solvent properties can be predicted based on the constituent atomic groups of the solvent molecules, i.e., group contribution (GC) methods. The GC methods along with the aforementioned surrogate kinetic model makes it possible to formulate a solvent design problem into an optimization problem, where the reaction kinetics (e.g., rate or selectivity) are the objective function to be maximized or minimized and all the other factors can be taken as constraints, generating a list of promising solvents.



Scheme 1. Schematic representation of DoE-QM-CAMD algorithm

Earlier, Dr Stanley Kolis and his colleagues at Lilly reported [2] that HCN is generated from the reaction of Oxyma (Ethyl Cyano(hydroxyimino)acetate) and DIC (Diisopropylcarbodiimide) during the process of amino acid activation in peptide synthesis, causing serious safety concerns. To address the issue, the collaborative team of Imperial College London and Lilly are applying DoE-QM-CAMD to suppress HCN generation via a judicious choice of the reaction solvent.

Via a validation set of common solvents used in a lab, the surrogate model generated by MBDoE was proven to give much closer predictions to the benchmark QM model than those generated by a surrogate model trained by a diverse set of solvents chosen by chemical intuition. The MBDoE surrogate model was then incorporated into a mixed-integer linear programming (MILP) optimisation problem to find the optimal solvent. 2,3,4-trimethyl-2-pentene was obtained as the optimal solvent that can suppress HCN generation.

In the future, the main reactions of amino acid activation and amidation will be taken into consideration so that solvents can be designed not only to suppress side reactions but also to maintain or accelerate the main reactions. The power of DoE-QM-CAMD will be further tested by experiments and other case studies. In the meantime, DoE-QM-CAMD has shown promise in selecting solvents for a wide range of organic reactions with minimum experimental effort.

[1] Struebing, H.; Ganase, Z.; Karamertzanis, P. G.; Siougkrou, E.; Haycock, P.; Piccione, P. M.; Armstrong, A.; Galindo, A.; Adjiman, C. S. *Nature Chemistry* **2013** *5* (11), 952–957.

[2] McFarland, A. D.; Buser, J. Y.; Embry, M. C.; Held, C. B.; Kolis, S. P. *Organic Process Research and Development* **2019** *23* (9), 2099–2105.

Early Career Researcher Profile

Dr Lucia Lombardi

Lucia obtained her BSc and MSc in Chemistry from the University of Naples (Italy) and a PhD from the University of Campania (Italy). During her PhD, she has worked in the field of supramolecular chemistry and nanotechnology. She has focused on lipids and their interactions with membranotropic peptides. In collaboration with Prof. Marcus Weck (NYU) and Dr. Helena Azevedo (Queen Mary University of London), Lucia has been designing and synthesising novel antiviral, antimicrobial and cell-penetrating peptides and studied their biophysical characterization. She had her postdoctoral training at Columbia University (USA), University of Naples (Italy), University of Tours (France) and University of Bristol (UK).

Lucia joined Imperial College London in May 2021 as a Research Associate in Professor Daryl Williams' research group in the Department of Chemical Engineering. She contributes to Work Package 4 of the PharmaSEL-Prosperity which focuses on oral peptide delivery. The aim of her research is to develop a high-performance liquid chromatography (HPLC)-based method that can replace, in the first phase, the use of cells. The main goal is the creation of an immobilised lipid bilayer that mimics the plasma membranes of intestinal cells. Thereafter, it will be employed to study the interaction among peptides, cell permeation enhancers and lipids. This approach will be advantageous because it will provide a better understanding into the insight of drug permeation processes through the membranes, and allows to extract essential chemical-physical characteristics that peptides must possess to improve their solubility, stability and permeation potential. It's envisaged to be a high-throughput method, allowing the automatic screening of peptides across a wide solution formulation space, leading to time savings and cost reduction. Indeed, the first lipid bilayers (liposomes) have been immobilised onto silica beads. However, further different reactions to covalently bind the liposomes will also be evaluated as well as the formation of cushioned bilayers. The experiments will be carried out in simulated GI tract fluids and the elution will be accomplished through the chromatographic column with various types of stationary phases.

Upcoming Conferences

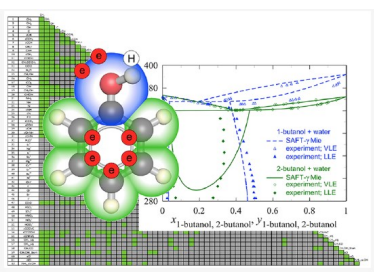
- **Almusaimi, O., Albericio, F. de la Torre. B. G.** Propylphosphonic anhydride (T3P) as green coupling reagent for solid-phase peptide synthesis. Bonding Through Chemistry, ACS spring 2022, San Diego, CA, 20th to 24th March 2022.
- **Muhieddine, M. H.**, **Jonuzaj, S., Viswanath, S. K., Garcia-Munoz, S., Armstrong, A., Galindo, A., Adjiman, C. S.** Model-based solvent selection for the integrated synthesis, crystallisation and isolation of pharmaceutical compounds, 32nd European Symposium on Computer Aided Process Engineering (ESCAPE-32), June 12th to 15th, 2022.
- **Gui, L., Armstrong, A., Galindo, A., Adjiman, C. S., Sayyed, F. B., Kolis, S. P**. Computer-aided solvent design for suppressing HCN generation in amino acid activation, 32nd European Symposium on Computer Aided Process Engineering (ESCAPE 32), June 12th to 15th, 2022
- **Muhieddine, M. H., Viswanath, S. K., Garcia-Munoz, S., Armstrong, A., Galindo, A., Adjiman, C. S.** Multi-objective optimisation for early-stage pharmaceutical process development, 14th International Symposium on Process Systems Engineering (PSE 2021+), June 19th to 23rd, 2022.

Featured Publication

Expanding the Applications of the SAFT-γ Mie Group-Contribution Equation of State: Prediction of Thermodynamic Properties and Phase Behavior of Mixtures

Andrew J. Haslam, Alfonso González-Pérez, Silvia Di Lecce, Siti H. Khalit, **Felipe A. Perdomo**, Spiros Kournopoulos, Maximilian Kohns, **Tom Lindeboom**, **Malak Wehbe**, Sara Febra, **George Jackson, Claire S. Adjiman, and Amparo Galindo**

Journal of Chemical & Engineering Data **2020** *65* (12), 5862-5890
DOI: 10.1021/acs.jced.0c00746



Abstract

We present the latest developments in thermodynamic modeling using the SAFT-γ Mie group-contribution equation of state. The group database is updated, featuring now 58 groups; this expanded database incorporates new parameters for interactions between both like and unlike groups. This provides the capability to treat mixtures including alcohols, ethers, ketones, carboxylic acids, and acetates, amines, aromatic and cyclic compounds, electrolytes, inorganic acids, and some common solvents, such as water and acetone. A discussion is provided relating to the assignment of the groups, including some secondary groups that are introduced for multifunctional molecules to capture the influence of molecular polarization effects on the thermodynamic properties. Performance of the SAFT-γ Mie approach is illustrated for a wide variety of systems, highlighting its use in describing solid–liquid as well as vapor–liquid and liquid–liquid equilibria.

Feature in the next newsletter

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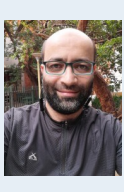

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