PHARMASEL-PROSPERITY NEWSLETTER

PharmaSEL Prosperity

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Academic Perspective on the Partnership

The Lilly Prosperity project is an exciting collaboration between EPSRC, Lilly, Imperial College London, University College London (UCL) and Queen Mary University of London, working across both experimental and modelling domains. There can be no doubt that the development of new methods for the synthesis, formulation and oral delivery of peptide therapeutics is of great health and economic importance for society.

I am fortunate to be involved in two work packages in this project. Work package 3 is a collaboration between the modelling efforts of Professor Eva Sorensen (work package leader) and her associates at UCL, and the experimental team of Dr Othman Almusaimi and Mr Oscar M. Mercado Valenzo working in my group. In this work package we are investigating the fundamental chromatographic process by which peptides are purified commercially. Our collaboration between the experimental and modelling experts in this project will allow us to obtain new insights into this important industrial separation process for peptides. We are also being greatly assisted by the team at Lilly. I am optimistic that the strong team we have working on work package 3 will develop not only improved elution methods for peptide separation, but key improvements to our fundamental understanding of the hydrophobic partitioning phenomena which control peptide purification in reverse phase liquid chromatography.

Work package 4 which I lead is a core project in peptide formulation for oral therapeutic delivery. A significant limitation in the commercial deployment of peptides for oral delivery, which is preferred by patients over injections, is their poor physical solution stability in the stomach as well as the difficulty in formulating for absorption in the gut. Dr Lucia Lombardi and Mr Maxim Bird are working on novel chromatographic methods which will allow us to not only improve our understanding of these key processes but will result in accelerated chromatographic methods for peptide formulation for both optimised solution stability and absorption in the gut. Our Lilly collaborators are key members of our effort who are able to share with us their valuable experience of this challenging problem. We are expecting that the high-fidelity experimental data on peptide performance generated in work packages 3 and 4 will link with the modelling and computational efforts of work package 5.

In conclusion, this exciting programme will allow us to work with Lilly to accelerate the deployment of new peptide therapeutics into society which will enable us to build a healthier world.

Professor Daryl R. Williams
Professor of Particle Science
Department of Chemical Engineering, Imperial College London

Research Feature: Peptide Solubility Predictions & Experimental Work

Approximately 40% of new chemical entities developed within the pharmaceutical industry have poor solubility. This inherent insolubility, in addition to the huge amount of effort, time, and resources that is devoted to developing new active pharmaceutical ingredients (APIs), poses a challenge that needs to be tackled in this field of research. These challenges apply to all types of pharmaceutical compounds, including peptides which have been gaining increasing attention in research and industry due to their specificity, potency, and low toxicity. In collaboration with their Lilly champions, the Molecular Systems Engineering (MSE) Group at Imperial College London (Prof. Amparo Galindo, Prof. George Jackson, Dr Andrew Haslam, Dr Felipe Antonio Perdomo Hurtado, Ahmed Al-Yazidi and Malak Wehbe) are working on developing a predictive tool for the solubility of peptide molecules in a wide range of thermodynamic conditions (i.e. temperatures, pH levels and solvents), using the SAFT-γ Mie group-contribution (GC) approach. The modelling of peptides is facilitated by the fact that they are made up of repeating units of amino acid residues. Therefore, having a good understanding of these building units and the different ways they interact with each other in various media allows for better modelling of the peptide molecules.

In the SAFT-γ Mie GC method [1-3], thermodynamic properties of a system of choice are derived from the expression of the Helmholtz energy of that system. In this model, a molecule is treated as a heteronuclear chain made up of tangentially-bonded segments which can contain associating site (in the case of complex interactions such as hydrogen bonding). The Helmholtz energy expression encapsulates the various like and unlike interactions between the different segments making up the system. This property of the model makes it ideal for modelling a class of molecules, such as peptides, since a lot of the interactions are transferable across different systems. In short, the SAFT-γ Mie GC method is utilized to calculate the activity coefficient of the solute (γ_s) which is used to calculate solubility as

$$\ln(x_s) = \frac{\Delta h_{\text{fus}}}{R}\left(\frac{1}{T_{\text{m}}} - \frac{1}{T}\right) - \ln\gamma_s + \frac{1}{RT}\int_T^{T_{\text{m}}} \Delta c_p\, dT - \frac{1}{R}\int_T^{T_{\text{m}}} \frac{\Delta c_p}{T}\, dT$$

where x_s , Δh_{fus} , T_{m}, and Δc_p are, respectively, the solubility, enthalpy of fusion, melting temperature, and isobaric heat capacity difference between the solid and liquid phases for the solute. In most cases, the heat capacity terms are neglected as they tend to cancel out at ranges of temperature close to the melting point. In this work, the enthalpy of fusion and melting temperature of the solute are obtained from experimental works. Unfortunately however, experimental melting properties are not available for many peptides, making this is one of the big challenges in the project.

The model developed thus far provides good predictions of solubility for a number of di- and tri-peptides. The SAFT-γ Mie solubility predictions are validated by comparison to experimental data obtained by Jerry Heng's group at Imperial College London, using the UV-Vis spectroscopy method [4], as shown in Figure 1. Good agreement between experimental data and model predictions is evident, especially considering the small scale used for the axes. It is worth highlighting that, the SAFT-γ Mie solubility calculations shown for glycine are fully predictive as no group interaction parameters were fitted to solubility experimental data. The SAFT-γ Mie calculations for the solubility of diglycine and triglycine provided in the figure are preliminary results obtained by using combining rules for some unlike group interaction parameters within the SAFT-γ Mie framework. The solubility predictions for these peptides are expected to improve when the unlike interactions are parameterized by regression to experimental data in future work.

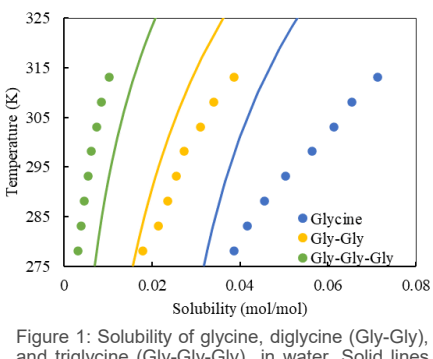

Figure 1: Solubility of glycine, diglycine (Gly-Gly), and triglycine (Gly-Gly-Gly) in water. Solid lines are predictions using the SAFT-γ Mie GC approach and points are experimental data obtained from Jerry Heng's group at Imperial College London [4].

The work done by the Heng group (Prof. Jerry Heng, Dr Mingxia Guo, Enshu Liang and Hamish Mitchell) in collaboration with their Lilly champions, seeks to provide an understanding of the effect of chain length on the solubility of glycine homopeptides and the effect of side chains on the solubility of other dipeptides, to establish a rational design of the conditions for peptide crystallization. The research includes three parts: firstly, establishing a thermodynamic foundation for the design of peptide crystallization processes and exploring the application of the SAFT-γ Mie GC approach to biomolecular thermodynamic properties. Secondly, applying the classical nucleation theory to short-chain glycine homopeptide crystallization, to explore the nucleation theory of macromolecules. Thirdly, exploring the relationship between conformation and the peptides' crystallization conditions.

Future work in this area of research will focus on determining the solubility of longer chain peptides in complex solvent systems and under variable pH using experimental and thermodynamic modelling tools by the Heng and MSE research groups in collaboration with the respective Lilly champions.

[1] Papaioannou, V. et al. *J. Chem. Phys.* 140, 054107 (2014).
[2] Dufal, S. et al. *J. Chem. Eng. Data* 59, 3272–3288 (2014).
[3] Haslam, A. J. et al. *J. Chem. Eng. Data* 65, 5862–5890 (2020).
[4] Guo, M. et al. *J. Mol. Liq*. 352, 118681 (2022).

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Early Career Researcher Profile

Dr Lauren Lee

Lauren is a Research Associate at Imperial College London and joined the Molecular Systems Engineering (MSE) research group in October 2017 as a PhD student. During her PhD, she has focused on the development of robust computer-aided molecular and process design frameworks aiming to provide a reliable method to accelerate the identification of optimal solvents for CO_2 capture. In order to treat trade-offs between conflicting performance criteria, she has also developed novel mixed-integer nonlinear programming (MINLP) class multi-objective optimisation (MOO) algorithms to address the numerical challenges associated with the solution of general nonconvex and discrete bi-objective optimization (BOO) problems.

Before joining the research group, Lauren worked as a Research Engineer in Daewoo Shipbuilding and Marine Engineering Co. Ltd (DSME). During her time working at DSME, Lauren led an R&D project for the development of a new concept of offshore oil & gas production process, in collaboration with the Norwegian University of Science and Technology (NTNU), Prosernat and Equinor. She also had the opportunity to experience the development of Liquefied Natural Gas (LNG) Partial-Re-liquefication System (PRS) from the research stage to full industrial scale within an interdisciplinary working environment. This multi-disciplinary experience allowed Lauren to learn how to merge research ideas into a theoretical framework and how to be a better team player.

As a postdoc, Lauren recently joined Work Package 1 of the PharmaSEL-Prosperity partnership, which focuses on the development of an optimisation-based approach to the design of solvents and reaction processes. The main objective of her research is to develop data-driven robust optimisation approaches for the design of reaction solvents under uncertainty, where uncertain parameters associated with a reaction kinetic model can be considered and integrated into the computer-aided molecular design framework.

"I look forward to collaborating on this project with academics and industrial partners. I believe this experience will be an ideal step for me to step forward as an expert in the area of process systems engineering."

Lauren Lee
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Awards & achievements

Dr Lucia Lombardi

Won a project under Imperial College London Seeds for Success funding scheme to develop a new tool for studying neurodegenerative diseases utilizing protocells.

Dr Felipe Antonio Perdomo Hurtado

Received a Gold Award from the Department of Chemical Engineering at Imperial College London in recognition of his many contributions as a researcher, in teaching and as a mentor.

Dr Lauren Lee

Attained her PhD from Imperial College London, Chemical Engineering

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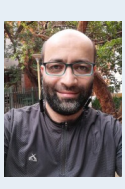

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