PHARMASEL-PROSPERITY NEWSLETTER

A bimonthly newsletter

ISSUE 9 MARCH 2023

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- *WP2 under the Microscope:* Demonstrative images from WP2 on their work on the crystallisation of peptides.
- *Research Feature:* Kennedy Kusumo, WP5, highlights his research on model-based design of experiments.
- *Researcher Highlight:* Ahmed Alyazidi, WP2, shares his background and perspective on the partnership.
- A *featured workshop* (including a call for posters) on model-based design of experiments.
- A glance at a *recent publication* on the applicability of population balance modelling to protein crystallisation.
- A highlight of our most recent *awards*, *conference presentations/posters*, and *publications*.

The Prosperity Partnership in Pictures: WP2 Under the Microscope

In lieu of a perspective article on the Partnership, this issue of the PharmaSEL-Prosperity newsletter features images from the experimental side of Work Package 2, who are working on developing methods for the successful crystallisation of peptides.

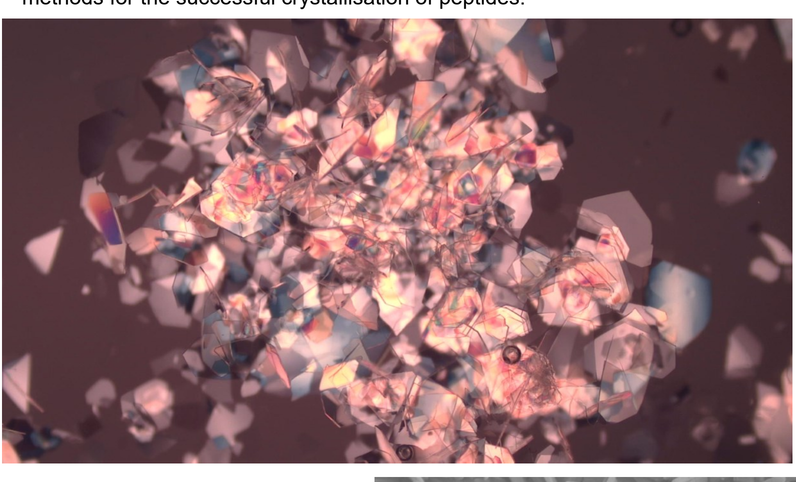


Figure 1. Peptide crystals viewed under polarised light, exhibiting birefringence.

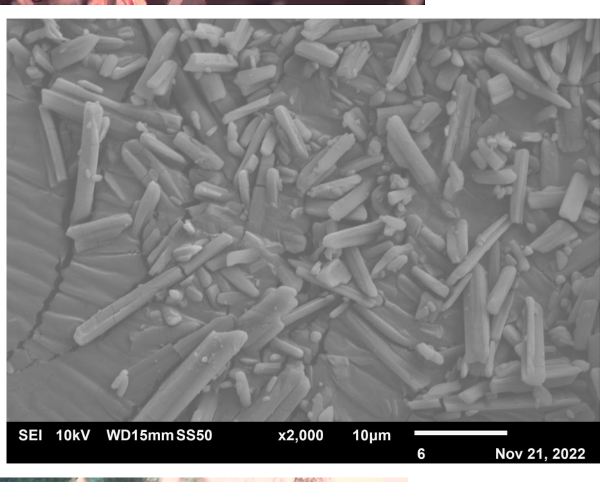


Figure 2. Scanning electron microscope images of triglycine dihydrate crystals obtained during cooling crystallisation.

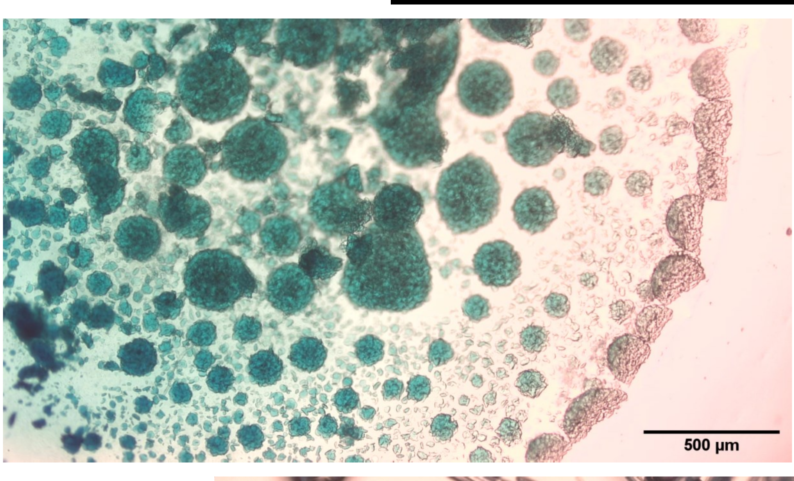


Figure 3. Peptide crystals stained with methylene blue dye to verify their structure and rule out the presence of salt crystals.

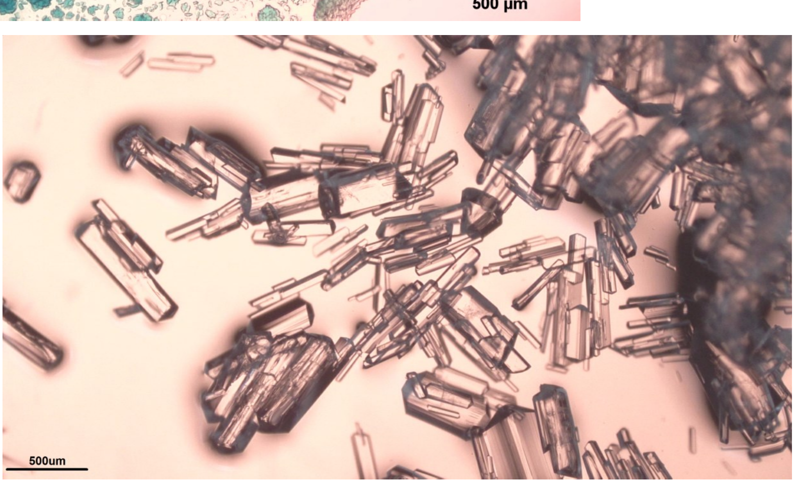


Figure 4. Glycine crystals obtained during cooling crystallisation experiments.

If you would like to feature any images (scientific or not) of the PharmaSEL-Prosperity Partnership in action, then please do get in touch with us via email or Teams!

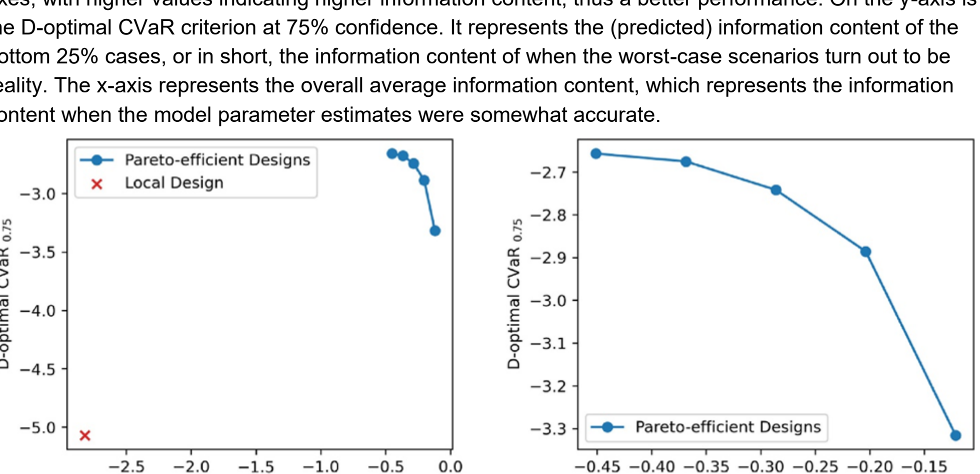
Research Highlight: Mitigating the risk of suboptimal experiments in model-based experiment design (WP5)

With model-based experimental design, we can leverage the information contained within a model to guide experimentation. The earlier we can implement the technique, the more valuable the technique is. At early stages of model development, a key challenge in maximizing the effectiveness of model-based design of experiments is the uncertainty one has on the model parameter values. Uncertainty hinders the model's ability to predict the information content that experiments will have.

We developed a novel methodology to exploit prior probability distributions (obtained from parameter estimation) of model parameter estimates in a bi-objective optimization formulation, where a conditional-value-at-risk criterion is considered alongside an average information criterion. We achieved a tractable formulation after coming up with a convex optimization formulation for any type of model.

Case Study

We demonstrated the method to a fed-batch reactor, and was able to demonstrate the benefits of the methodology when designing experiments under uncertainty. Because of uncertainty, information content of an experiment is uncertain. The figure below presents the main result of the case study. Each point on the figure represents a complete experimental design, consisting of multiple descriptions of how to run experiments and how many times to repeat them. The figure presents information content values on both axes, with higher values indicating higher information content, thus a better performance. On the y-axis is the D-optimal CVaR criterion at 75% confidence. It represents the (predicted) information content of the bottom 25% cases, or in short, the information content of when the worst-case scenarios turn out to be reality. The x-axis represents the overall average information content, which represents the information content when the model parameter estimates were somewhat accurate.



The blue points represent the designs that our methodology came up with. Compare this against the red point, which represents a "standard" model-based experiment design. As the left subplot shows, the blue points are drastically better in performance in both the worst-case scenarios and the average information. The right subplot shows a further benefit of the method over existing methods to mitigate risks. Experiment 1 (Exp-1) and 5 on the right subplot represent the performance of designs that comes from existing risk mitigation methods, whilst Exp-2, 3, and 4 are unique to our method. What our method can do is uncover the best trade-off for an experimenter. For instance, a risk-averse experimenter would appreciate the benefit of opting for Exp-4 over Exp-5, because it offers a relatively large improvement in the CVaR criterion at the cost of a small loss in the mean criterion.

Relevance to Lilly

With such a method, modelers can apply the model-based experimental design technique earlier into the development process with less risk of designing suboptimal experiments when significant uncertainty still exists due to lack of informative experimental data. This is hoped to further increase the adoption and effectiveness of model-based experimental designs in accelerating the drug development process at Lilly. In fact, we have implemented this technique into our open-source Python package Pydex which is available for use.

Further references

For those interested, we discuss the methodology in detail and showcase it in further case studies in our publication which you can find here.

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Researcher Spotlight: Ahmed Alyazidi, WP2

Ahmed earned his Bachelor's and Master's degrees in Chemical Engineering from Texas A&M University at Qatar. During his Master's program, he focused on developing a framework to model the thermodynamic properties of confined fluids in porous media. To achieve this, he combined the SAFT-VR Mie equation of state with the multi-component potential theory of adsorption (MPTA) to model the density profiles and adsorption isotherms of single-component gases, as well as binary and ternary gas mixtures in activated carbon and molecular sieves.

Throughout his undergraduate and graduate studies, Ahmed worked part-time on various tasks related to international student living and housing, as well as graduate teaching roles during his Master's degree.

Pursuing a PhD has always been a goal of his, as it presents an opportunity to address scientific questions that are relevant to society. He is thrilled to be doing so at Imperial College, where he can work alongside intelligent and enthusiastic peers and supervisors.

Ahmed began his PhD in 2020, focusing on solubility prediction of amino acids and peptides. Peptide therapeutics have become increasingly popular in recent years, but their low solubility poses a significant challenge in drug manufacturing and purification processes. To overcome this, he is developing a computational model using the SAFT-γ Mie group-contribution method which can predict the solubility of peptide molecules under various conditions of temperature, solvent composition, and pH.

Given the current uncertainty in the world, Ahmed plans to keep his options open in terms of future plans. Ideally, he would like to gain experience in the industrial R&D field before deciding whether to return to academia in the long run.

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Model-Based Design of Experiments (MBDoE) Workshop - 23rd June 2023

The Sargent Centre for Process Systems Engineering is proud to present their upcoming workshop on the model-based design of experiments on the 23rd of June. This one-day event will feature a number of talks from both academic and industrial speakers, including a keynote presentation from Professor Kim McAuley (Queen's University, Canada), as well as industrial participation from companies such as Syngenta, AstraZeneca, and Eli Lilly and Company. Attendees will gain valuable information on the methodologies used for efficient experimentation via model-based design of experiments.

The workshop will also feature a poster session, allowing for participants to present their work related to model-based design of experiments. This poster session will feature a prize for the best presentation, alongside runner-up prizes. For those who wish to submit a poster, a short abstract (<300 words) describing the poster should be submitted via email to sargent.centre@imperial.ac.uk, with the email subject name as "Poster: Author". The deadline for poster abstracts is the 9th of May, 2023.

Registration is **free** for PharmaSEL-Prosperity Partnership members! To register for this event or for any further information, please contact sargent.centre@imperial.ac.uk.

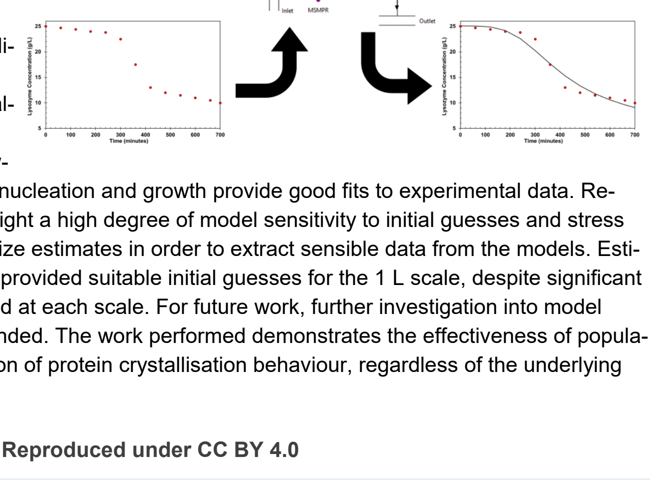
Featured Publication

Process modelling of protein crystallisation: A case study of lysozyme

Hamish Mitchell, Derrick Jovannus, Ian Rosbottom, Frederik J. Link, Niall Mitchell, and **Jerry Y. Y. Heng**

DOI: 10.1016/j.cherd.2023.02.016

Abstract



With the rise in interest of protein crystallisation as a purification step in downstream processing, there is significant interest in the process modelling of these crystallisation steps. Herein, we demonstrate and compare the applicability of "traditional" nucleation and growth models, commonly used to model small molecule crystallisation, for the successful population balance modelling of lysozyme crystallisation at the 100 mL and 1 L scales. Results show that both empirical power-law and first-principles models for nucleation and growth provide good fits to experimental data. Results from parameter estimation highlight a high degree of model sensitivity to initial guesses and stress the importance of providing particle size estimates in order to extract sensible data from the models. Estimates obtained for the 100 mL scale provided suitable initial guesses for the 1 L scale, despite significant differences in the final values obtained at each scale. For future work, further investigation into model validation upon scale-up is recommended. The work performed demonstrates the effectiveness of population balance modelling in the prediction of protein crystallisation behaviour, regardless of the underlying physical phenomena.

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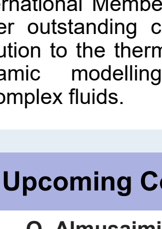
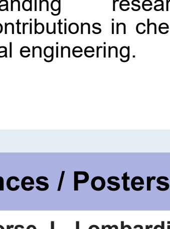
Awards



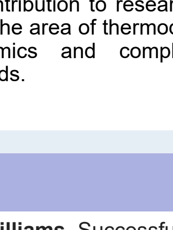
Claire Adjiman

Has been elected to the National Academy of Engineering as an International Member, for her outstanding contribution to the thermodynamic modelling of complex fluids.



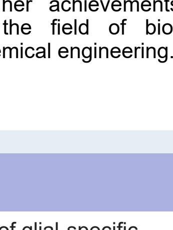
Nilay Shah

Has been awarded the Sharma Medal for his sustained outstanding research contributions in chemical engineering.



Amparo Galindo

Has been awarded the IChemE Guggenheim Medal, recognising her contribution to research in the area of thermodynamics and complex fluids.



Cleo Kontoravdi

Has been awarded the IChemE Donald Medal in recognition of her achievements in the field of biochemical engineering.

Upcoming Conferences / Posters

1. **O. Almusaimi, S. V. Morse, L. Lombardi, D. R. Williams**. Successful synthesis of glial-specific blood-brain barrier shuttle peptide following fragment condensation approach on solid-phase resin. APS 2023, At the Peptide Frontier, Sccotsdale, AZ, 24th to 29th June 2023.
2. **L. Lombardi, Y. Shi, A. Falanga, H. Azevedo, S. Galdiero**. Enhancing the potency of antimicrobial peptides through molecular engineering and self-assembly. APS 2023, At the Peptide Frontier, Sccotsdale, AZ, 24th to 29th June 2023.
3. **Claire S. Adjiman**. Molecular engineering for pharmaceutical product and process design. PPEPPD 2023, Properties and Phase Equilibria for Product and Process Design, Tarragona, Spain, 21st to 25th May 2023.
4. F. A. Perdomo, **G. Jackson**, **A. Galindo**, **C. S. Adjiman**. An approach for modelling simultaneous fluid-phase and chemical reaction equilibria in multicomponent systems via Lagrangian duality: the reactive HELD algorithm. ESCAPE 33, 33rd European Symposium on Computer-Aided Process Engineering, Athens, Greece, 18th-21st June 2023.

Publications

1. **Othman Al Musaimi**, Varshitha Gavva, and **D.R. Williams**. *Greener Cleavage of Protected Peptide Fragments from Sieber Amide Resin*. *ChemistryOpen.* **2022**. 10.1002/open.202200236.
2. **Hamish M. Mitchell**, Derrick Jovannus, Ian Rosbottom, Frederik J. Link, Niall A. Mitchell, and **Jerry Y. Y. Heng**. *Process modelling of protein crystallisation: A case study of lysozyme*. *Chemical Engineering Research and Design.* **2023**. 10.1016/j.cherd.2023.02.016
3. Vivek Verma, **Hamish M. Mitchell**, Ethan Errington, **Mingxia Guo**, and **Jerry Y. Y. Heng**. *Templated Crystallisation of Glycine Homopeptides: Experimental and Computational Developments*. *Chemical Engineering & Technology*. **2023**. 10.1002/ceat.202200575
4. **James Odgers**, **Chrysoula Kappatou**, **Ruth Misener**, **Salvador García Muñoz**, and Sarah Filippi. *Probabilistic predictions for partial least squares using bootstrap*. *AIChE J.* **2023**. 10.1002/aic.18071.
5. **Mingxia Guo**, Marie J. Jones, Racheal Goh, Vivek Verma, **Emily Guinn**, and **Jerry Y. Y. Heng**. *The Effect of Chain Length and Conformation on the Nucleation of Glycine Homopeptides during the Crystallization Process*. *Crystal Growth & Design.* **2023**. 10.1021/acs.cgd.2c01229.

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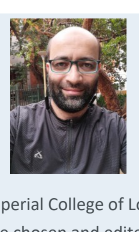

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Disclaimer: This research program is funded by Eli Lilly and Company, Imperial College of London, University College London and from EPSRC Grant Ref: EP/T518207/1. The contents of this newsletter are chosen and edited by researchers and students of Imperial College London. Their editorial work is independent of Eli Lilly and Company and EPSRC.

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