PHARMASEL-PROSPERITY NEWSLETTER

PharmaSEL Prosperity

A bimonthly newsletter

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PharmaSEL-Prosperity wins the Pharma award at the 2023 IChemE Global Awards!

We are thrilled to announce that our Prosperity Partnership has been honoured with the prestigious IChemE Global Award 2023 in the Pharma category. The Pharma Award specifically acknowledges 'the best project, process, or product demonstrating chemical engineering excellence in the pharmaceutical sector' and is proudly sponsored by Bouygues Energies & Services.

Your dedicated co-editors-in-chief attended the IChemE Global Awards dinner in Birmingham, where the name of our partnership was announced as the winner—an incredibly emotional moment for us all. It was a touching reminder of the commitment and dedication that each researcher invested in this collaborative project involving multiple groups. Stepping onto the stage, we felt immense pride representing this outstanding team and, by extension, all of you.

Returning to London, we could not be happier to share this sensational news in this newsletter. Congratulations to each and every one of us for our collective efforts, which have rightfully led to this well-deserved success.

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Research Highlight: In-silico HPLC method development (WP3.2)

Work Package 3 (WP3) within the PharmaSEL-Prosperity Partnership aims to deliver novel methodologies in the field of downstream purification of small molecules and peptides by chromatography. Although chromatography has been used for over a century, model-based development of the process has occupied scientists for only a few decades. The process understanding is still rather limited, hence we aim to contribute to a deeper process understanding by studying physics-informed models that adhere to real world conditions, as well as transcribing hands-on expertise of the process into step-by-step model-based methodologies for developing optimal designs. This deeper process insight will assist the industry in delivering products of high quality in a more efficient and sustainable fashion, and to do this faster to reduce time-to-market.

My research focuses on developing tools for *in-silico* High Performance Liquid Chromatography (HPLC) development. More specifically, I dedicated my efforts to clarifying the expression and the range of applicability of the Equilibrium Dispersion Model, a commonly employed model in applications of small molecule and peptide purification. Chromatographic mass balance models are usually coupled with an isotherm model which describes the adsorption-desorption equilibrium that takes place during a chromatographic separation. The isotherm models includes parameters that generally need to be estimated from experiments as the first step of method development. The isotherm model selection and parameter estimation are procedures that traditionally have involved extensive experimentation. My aim is not only to reduce the experimental effort required for parameter estimation but also to make the estimation process more rigorous and clear by proposing a step-by-step methodology. The methodology employs statistical tests, experimental designs, as well as Model-Based Design of Experiments (MBDoE) techniques assisting the user into making step-by-step informed decisions in the design process.

Case study

Comprehensive model identification methodologies have been developed previously; however, the main domain of applications has been within the field of kinetic reaction models. We have developed a comprehensive model identification methodology for chromatography by a methodology previous used for kinetic model identification. We have tested the methodology using a case study based on *in-silico* experiments for the separation of a small peptide, that of tri-Leucine.

The methodology works as follows. First, we obtain initial guesses for the Henry coefficient (one of the fundamental isotherm parameters) by performing a few experiments at diluted conditions. The Henry coefficient in part of a variety of isotherm models with the form of the retention factor, hence this step would be applicable to any isotherm model of this kind (e.g. Langmuir based isotherm models). After obtaining initial guesses for H, screening experiments are performed using either a full or fractional factorial design, depending on the number of control variables. The chromatograms of the experiments performed with the factorial design indicate the nature of the binding (e.g, Langmuirian); consequently, isotherm models are proposed based on process knowledge. The proposed candidate models will then undergo parameter estimation. If they pass the *goodness of fit test*, a statistical model to determine if the simulations fit the experimental chromatograms, the models are potentially adequate as a model representation and should be considered further.

The next step is then that of *practical identifiability*. The practical identifiability test assesses whether independent parameters can be estimated for each model. Factorial designs in conjunction with MBDoE techniques are used to design experiments required for another parameter estimation. Statistics (i.e. *t*-test) are evaluated after the parameter estimation. If more than one models pass the practical identifiability test, then model discrimination must be considered. Model discrimination employed MBDoE to design experiments with high discriminating power. An experiment can be characterized as highly discriminative if, for the same given experimental conditions, simulations performed by different models yield relatively different results, and therefore most likely only one of the proposed models will pass the statistical tests. Finally, the prevailing model undergoes parameter refinement by MBDoE using D-, E-, or A- optimality criteria for designing a few final experiments. Parameter refinement continues until the

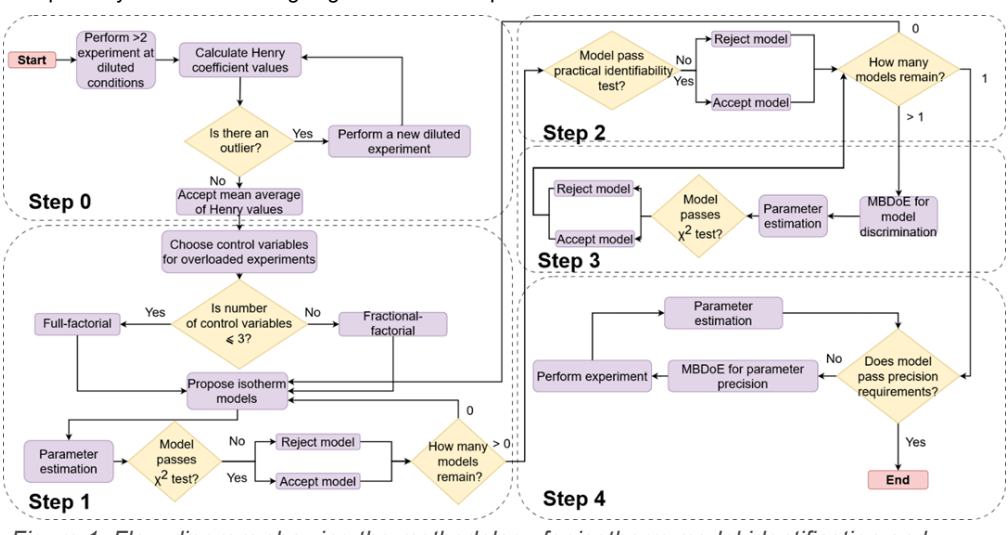

Figure 1: Flow diagram showing the methodology for isotherm model identification and parameter estimation.

parameters meet the precision requirements. In our work, we evaluate the precision requirements by performing stochastic simulations. When the outputs of the stochastic simulation (i.e. chromatograms) are identical to each other for number of scenarios, we terminated the step-by-step methodology. The isotherm model with parameters thus obtained can now be used reliably in model-based method development.

Relevance to Eli Lilly

Running a large-scale separation requires time and costly resources. Therefore, process development and process optimization are of crucial importance. However, a suitable model and its parameters must first be identified through rigorous considerations to ensure that the model is representative of the actual plant behaviour. Our work can benefit Lilly by enabling fast, rigorous, and precise estimation of model parameters and identification of the most suitable models to use. Moreover, this work can also be the precursor to automatic isotherm identification platforms.

Future Work

Our future plan involves delving further into improving the methodology by employing more elaborate algorithms, other than deterministic-based optimization, to speed up the solution time and ensure global optimality. We would also like to test our methodology in comparison or in synergy with the work of WP5 (pydex) for HPLC. We also need to test the methodology on real systems of interest to Lilly.

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Responsible Research & Innovation training course, 1st February

As a component of PharmaSEL-Prosperity's educational initiatives for researchers involved in the project, a one-day in-person course on Responsible Research and Innovation has been organised for researchers in the PharmaSEL-Prosperity Project on the **1st of February**. The course will be held at the **Sargent Centre at Imperial**.

This course is designed to enhance the collective understanding of responsible innovation within the context of our research efforts. The course aims to encourage researchers and innovators to adopt a broader perspective, considering the overarching impact of their work and its societal value in the long term.

We are partnering with an external provider, ORBIT, who will facilitate the course. Your participation in this course fosters a culture of responsible and impactful research within our PharmaSEL-Prosperity community. Thank you to those of you who signed up and see you there!

Featured Publication

Modeling the Thermodynamic Properties of Saturated Lactones in Nonideal Mixtures with the SAFT-γ Mie Approach

Thomas Bernet, **Malak Wehbe**, Sara A. Febra, **Andrew J. Haslam**, **Claire S. Adjiman**, **George Jackson**, and **Amparo Galindo**

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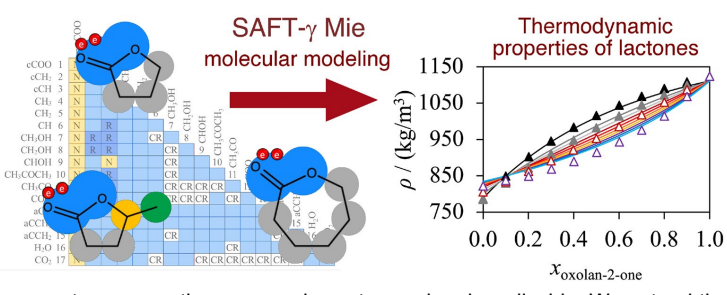
Abstract

The prediction of the thermodynamic properties of lactones is an important challenge in the flavor, fragrance, and pharmaceutical industries. Here, we develop a predictive model of the phase behavior of binary mixtures of lactones with hydrocarbons, alcohols, ketones, esters, aromatic compounds, water, and carbon dioxide. We extend the group-parameter matrix of the statistical associating fluid theory SAFT-γ Mie group-contribution method by defining a new cyclic ester group, denoted cCOO. The group is composed of two spherical Mie segments and two association electron-donating sites of type e1 that can interact with association electron-accepting sites of type H in other molecules. The model parameters of the new cCOO group interactions (1 like interaction and 17 unlike interactions) are characterized to represent target experimental data of physical properties of pure fluids (vapor pressure, single-phase density, and vaporization enthalpy) and mixtures (vapor–liquid equilibria, liquid–liquid equilibria, solid–liquid equilibria, density, and excess enthalpy). The robustness of the model is assessed by comparing theoretical predictions with experimental data, mainly for oxolan-2-one, 5-methyloxolan-2-one, and oxepan-2-one (also referred to as γ-butyrolactone, γ-valerolactone, and ε-caprolactone, respectively). The calculations are found to be in very good quantitative agreement with experiments. The proposed model allows for accurate predictions of the thermodynamic properties and highly nonideal phase behavior of the systems of interest, such as azeotrope compositions. It can be used to support the development of novel molecules and manufacturing processes.



Awards

Ruth Misener

Has been honoured with the 2023 British Computer Society (BCS) Roger Needham award for her exceptional contributions to computer science, particularly in the intersection of computational optimisation and machine learning for energy efficient engineering and biomedical systems.

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