DIGITAL TWIN OF FREEZE-DRYING OF PROBIOTICS

Context:

Freeze drying, or lyophilization, is a highly effective preservation method that can dramatically reduce losses of fruits, berries, and vegetables by extending their shelf life far beyond that of fresh produce. By removing 98–99% of the water content, freeze drying inhibits the growth of spoilage microorganisms and enzymatic reactions that lead to decay, allowing products to remain stable and safe for consumption for more than 3 years under proper storage conditions. Similarly, Freeze-drying is extensively used in the pharmaceutical industry to improve the shelf life of products such as vaccines and probiotics.

Batch lyophilization is currently the prevalent method of freeze-drying of bio-pharmaceuticals where modelling is used to gain valuable process insights[1]. Although innovative continuous lyophilization equipment is becoming increasingly available on the market, it remains a niche technology. In this proposal we limit ourselves to the batch lyophilization process. Typically batch lyophilization is modelled both at the product scale (typically vial with pro-biotics or fruits) and at the chamber scale. Pseudo-steady-state heat and mass transfer balances are solved at the product scale[2]. The chamber and the condenser are modelled using computational fluid dynamics (CFD). Process Analytical Technologies (PAT) are often an integral part of freeze-dryers. These include hardware sensors such as temperature probes, capacitance- and conductivity-based pressure sensors (Pirani gauges), wireless temperature sensors, as well as soft sensors such as manometric temperature measurement (MTM) systems that use data analytics and modelling to monitor the process. Soft sensors fall under the ambit of digital shadows. Besides process optimization and design, process control is key to ensuring product quality and consistency. Process simulations and model-guided control systems yield robust process performance.

The concept of Digital twins is closely associated with process control and monitoring. The Digital twin represents a virtual replica of the freeze-drying process that enables real-time monitoring, simulation, and optimization[3]. By integrating process data with predictive models, digital twins allow for precise control over critical parameters such as temperature, pressure, and drying time. This enhances process efficiency, reduces variability, and improves product quality by anticipating and mitigating potential issues before they occur. The application of digital twins in freeze drying supports the development of more robust, scalable, and cost-effective manufacturing processes, making them invaluable tools in pharmaceutical, food, and nutraceutical industries.

Research problem statement:

Smart Lyo concept based on MTM measurement provides for first version of the digital twin for a freeze-dryer[4]. This has severe limitations due to the inherent assumptions involved in the models used for the creation of the digital twin. It is well documented in literature that spatial variability in the heat transfer rates exists inside the lyophilizer. The products which are placed at the edge receive higher radiation flux, thus a higher heat transfer rates and the vials at the centre of the shelf receive less radiation leading to lower heat transfer rates. This is popularly known as the "edge vial effect". However, MTM measurements only provide a single averaged product value deduced from the pressure rise tests. The other alternative to follow the temperature of the product is thermocouples, but they come with the added complications of inducing a nucleation site and are thus not representative of the neighbouring products. This spatial variation and the simplifications of just following the average product temperatures from the MTM measurements results in process scientists designing a conservative cycle. Moreover, the developed methods are only valid for Bio-Pharmaceutical applications where the geometry is with vials. For food applications such as freeze drying of strawberries is done with trays, MTM models with geometric factors are yet to be developed, although recently some studies with blueberries have been carried out[5]

The various freezing conditions experienced by the products due to these variations is also an important factor as freezing parameters are known to impact the drying kinetics. Digital twins with accurate models also are also quintessential to have higher product quality and lower costs. Precisely, due to these limitations the SMART freeze dryer technologies are mostly limited to the lab-scale, as the spatial variations are lower in smaller freeze dryers compared to industrial scale freeze dryers.

This internship offers the potential for progression into a PhD thesis on the same topic, with a start date of September 2026.

Objectives of the internship:

A) Perform experiments with the lyophilizer to quantify the heat transfer variability in trays.
B) Analyse Pressure rise test data to develop new MTM equations including the heat transfer variability.
C) Compare the performance with the SMART MTM temperature predictions at the centre and edge trays with probiotic solutions.

Profile: Preferably a person with a taste for both experimentation and modelling. Basic capabilities in scripting languages such as Python, R or MATLAB, image analysis, process engineering, and exposure to simulation softwares such as COMSOL. Willingness to get their hands dirty with the experimentation data collection and analysis. B2 or higher level in English, competency in French appreciated.

About the research lab

The internship will be based at UMR SayFood on the AgroParisTech/INRAE campus in Palaiseau, Ile-de-France. It will be supervised by Arnesh Palanisamy and Cristian Trelea, professors at AgroParisTech school of engineering, part of Paris-Saclay University.

General information:

Level: Master 2/ Engineering 5th year.
Duration: March to August 2026 (around 6 months, flexible).
Place: UMR SayFood(Campus Agro Paris-Saclay, Palaiseau).
Allowance: around 650€ per month, depending on the number of working days for each month.
Benefits: reimbursed public transport (75%), flexible working hours, multidisciplinary scientific group.
Secularism: the recruited person will be subject to the charter on secularism in public services (French law 2021-1109 of 24 August 2021, https://www.fonction-publique.gouv.fr/etre-agent-public/mes-droits-et-obligations/laicite-et-neutralite-de-la-fonction-publique). In particular, no religious symbols may be worn in the workplace.

Contact:

Arnesh PALANISAMY, arnesh.palanisamy@agroparistech.fr
Cristian TRELEA, cristian.trelea@agroparistech.fr

(Curriculum Vitae; Motivation letter with around 250 words)

References:

[1] Kasper, Julia Christina, and Wolfgang Friess. "The freezing step in lyophilization: Physico-chemical fundamentals, freezing methods and consequences on process performance and quality attributes of biopharmaceuticals." European journal of pharmaceutics and biopharmaceutics 78.2 (2011): 248-263.

[2] Pikal, Michael J., Michael L. Roy, and Saroj Shah. "Mass and heat transfer in vial freeze-drying of pharmaceuticals: Role of the vial." Journal of pharmaceutical sciences 73.9 (1984): 1224-1237.

[3] Zadravec, M., Metsi-Guckel, E., Kamenik, B., Remmelgas, J., Khinast, J., Roscioli, N., ... & Sarkar, A. A Digital Twin of Primary Drying in Lyophilization Using Coupled 3-D Equipment Cfd and 1-D Vial Scale Simulations. Available at SSRN 5015657.

[4] Automated process control using manometric temperature measurement, US Patent: US6971187B1, patent no: US 6,971,187 B1, Date of patent: Dec. 6, 2005

[5] Trelea, I. C., Passot, S., Marin, M., & Fonseca, F. (2009). Model for heat and mass transfer in freeze-drying of pellets.