ChemE-Med 2024

Chemical Engineering as Applied to Medicine

Book of abstracts

20th May 2024, Salerno, Italy

EFCE event #806

ChemE Med

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Table of contents

Poster session 57

Welcome message

Dear Participants of ChemE-Med 2024,

Welcome to the second event of the *European Federation of Chemical Engineering's* Section on Chemical Engineering as Applied to Medicine (ChemE-Med).

Our first meeting was in Paris in 2022. We also arranged some sessions in the ECCE conference in Berlin in 2023. We are proud to have organized this second meeting and are very pleased to see the community growing. Thank you all for your participation.

The Section aims to bring together Chemical Engineers working in fields related to Physiology and Clinical Medicine. Chemical Engineers have an important role to play in this field, one so important for human well-being, to contribute their skills and expertise to research and in due course practice in Physiology and Medicine. Chemical Engineers are already bringing a significant skillset to physiology and medicine: modelling and systems engineering techniques to tackle the complexity of physiology, transport and reaction engineering to model medical instruments such as dialysis, designing artificial organs processing chemical entities, developing devices controlling drug and nutrient feeds, and considering the effects of particulates on human health to name a few.

The Section aims to run workshops (such as this), contribute to larger conferences (such as ECCE and in due course with clinical focus), promote publications, develop position papers, encourage developments to the Chemical Engineering curriculum, and promote research and exchange.

This second workshop has sessions on:

1. Functional materials and systems in biomedical applications,
2. Modelling in physiology and drug delivery,
3. Micro- and nanosystems, and
4. Diagnostics and pharmaceuticals.

We welcome to you the workshop and hope you have an interesting and fruitful time and make lots of new colleagues and friends.

The Organising Committee

Organising institutions

ChemE-Med section of EFCE

ChemE-Med (Chemical Engineering as Applied to Medicine) is one of the Scientific Sections of the *European Federation of Chemical Engineering.*

The inaugural meeting of the ChemE-Med Section was organized in December 2022 in Paris as the event of the *4th European Forum on New Technologies.* Seventeen participants from eight countries (UK, IT, GE, CZ, FR, ESP, NED, POL, POR) joined the Section and elected the Section Chair: Prof. Tomasz Sosnowski (Warsaw University of Technology, Poland) and the Section Secretary: Prof. Davide Manca (Politecnico di Milano, Italy).

In May 2023 the Section organized the webinar "Chemical engineering as applied to medicine: current challenges and opportunities" as a part of *the EFCE Spotlight Talks 2023* (*the webinar is available on-line*).

During the joint *ECCE & ECAB 2023 congress* in September 2023 in Berlin, the Section organized the dedicated oral sessions, which helped attract new scientists interested in participating in the section activities.

The current and planned activities of the Section are:

1. *ChemE-Med 2024* one-day conference in Salerno on May 20th, 2024.
2. Preparation of the book *"Chemical Engineering as Applied to Medicine: Engineering Principles in Modeling Physiology, Disease and Drug Delivery"* (D. Bogle and T. Sosnowski, Eds.) to be published by De Gruyter in 2025–26 (contributions to the book by personal invitation).
3. Participation in the next edition of the EFCE webinars "Spotlight Talks" (Autumn 2024 or Spring 2025).

Tomasz Sosnowski, Section Chair
Faculty of Chemical and Process Engineering,
Warsaw University of Technology, Poland

Warsaw (PL) – Salerno (IT), May 2024

Faculty of Chemical and Process Engineering, Warsaw University of Technology

Faculty of Chemical and Process Engineering, Warsaw University of Technology (FCPE WUT) is the leading academic entity in chemical engineering in Poland, known for high quality in scientific research and student education (B.Sc.Eng., M.Sc., and Ph.D.). In 2022, following the nationwide academic evaluation process (PKA), the Faculty obtained the distinction "The Excellence in Academic Education".

The academic staff of FCPE WUT is formed by 50 persons, with 8 full professors and 8 university professors. Five professors are members of the European Federation of Chemical Engineering (EFCE), and eleven professors are members of the Committee of Chemical and Process Engineering of the Polish Academy of Sciences. The Dean of the Faculty in 2020–2024 is Professor Marek Henczka.

The Faculty includes one chair (Chair of Dispersed Systems Engineering) and four departments: (i) Chemical Reactors Engineering and Dynamics, (ii) Intensification of Industrial Processes, (iii) Process Kinetics and Thermodynamics, and (iv) Biotechnology and Bioprocess Engineering.

Several specialized laboratories are operating within the Faculty of Chemical and Process Engineering:

- Aerosol Filtration Laboratory: AEROFIL (led by dr. Anna Jackiewicz-Zagórska)
- Laboratory of Medical Aerosols and Inhalers: RESPI-LAB (prof. Tomasz Sosnowski)
- Biomedical Engineering Laboratory: BIOMED-LAB (prof. Tomasz Ciach)
- Laboratory of Multifunctional Emulsion Systems (prof. Ewa Dłuska)
- Product Engineering Laboratory, including the Graphene Lab (prof. Łukasz Makowski)

- High Pressure Processing Laboratory (prof. Marek Henczka)
- Membrane Technology Laboratory (prof. Maciej Szwast)

Main scientific activities of the Faculty are related to:

- process intensification (supercritical technology, microwave-assisted processes, high-performance dispersion and mixing, etc.),
- nanotechnology and functional materials,
- processes for the environment and sustainability,
- experiments and computer simulations of fluid flows, heat and mass transfer, chemical reactors and bioreactors,
- applications of chemical engineering methods to physiology and medicine.

Organising committee

Prof. David Bogle

Prof. David Bogle is Professor of Chemical Engineering and has been Pro-Vice-Provost of the Doctoral School (Graduate Dean) at University College London (UCL) since 2005. He undertakes research and teaching in process design and process control and in Systems Biology, working with a number of Medical Science Departments at UCL including the UCL Institute for Liver and Digestive Health and the UCL Cancer Institute. He was a member of two key BBSRC (the UK Biological research council) committees: the Integrative and Systems Biology Strategy Committee and the Bioscience Skills and Careers Strategy Committee. He has also been a member of the EPSRC (Engineering and Physical Sciences Research Council) College of Engineering since 1996.

Prof. David Bogle studied Chemical Engineering at Imperial College at both undergraduate and graduate levels, receiving his PhD in 1983. Following this, he worked on modelling and control projects for British Gas before taking a position as lecturer at the University of Adelaide, a position he held from 1986 until 1990. Prof. Bogle joined UCL as a lecturer in 1990 and became full professor in 2000. He is Deputy Director of the Centre for Process Systems Engineering, a joint Centre between Imperial College and UCL. He is a Chartered Engineer and Fellow of the Institution of Chemical Engineers and was made a Fellow the Royal Academy of Engineering in 2005. He was Scientific Vice President of the European Federation of Chemical Engineering from 2018 to 2021 and President of the Institution of Chemical Engineers for 2022–23. He was awarded the Jacques Villermaux Medal of the EFCE in 2023 for contributions to European Chemical Engineering which included driving the foundation of the EFCE's Section on Chemical Engineering as Applied to Medicine.

Prof. Paolo Ciambelli

Paolo Ciambelli received a master degree in Chemical Engineering in 1970 at the University of Napoli "Federico II", where he served from 1972 to 1990. Since 1990 he served as full professor in Industrial and Technological Chemistry at the University of Salerno. Retired since November 1st, 2015, nominated Emeritus professor since November 2016.

Founder and CEO of NARRANDO, (NAno caRbon RAdiatioN DOsimeter), innovative start-up company (1st National Award for Innovation in 2012) since June 2013.

Elected Member of the Academic Senate, Head of the Department of Chemical and Food Engineering, Member elected of Board of Directors of the European Association of Professors Emeriti (EAPE), Director of, Interdepartmental Research Center for Nanomaterials and Nanotechnology (NANO_MATES), Coordinator of the PhD School in Chemical Engineering, Member of the Italian Chemical Society, American Chemical Society, and American Institute of Chemical Engineering (AICHE), Head of the South Section of the Italian Association of Chemical Engineering (AIDIC).

The research activity of Prof. Ciambelli mostly concerned the study of (i) catalytic and photocatalytic processes, production of petrochemicals and hydrogen, (ii) materials (zeolites, carbon nanotubes and graphene, nanoparticles), and their innovative applications such as nanocomposites, nanolubricants, nanodosimeters, supercapacitors, drug nano carriers, and (iii) sustainable development and circular economy.

Prof. Ciambelli is a co-author of 382 publications on books and international journals and 15 patents, h-index 51 (Scopus 2024). He was within the top 2% of world scientists (PloS Biol, 2020).

Prof. Davide Manca

Davide Manca is a professor of Process Systems Engineering and head of the PSELab at POLIMI since 2002.

He is a (co)author of more than 280 peer-reviewed publications on international journals and conferences with a few book chapters.

In almost thirty years of academic employment, he conjugated research activity and industrial advice to make these worlds better interact and get benefit from their mutual collaboration. Davide's research is grounded on the modeling activity that has the quantification of what is analyzed as the final target. Design, simulation, control, optimization, and assessment are the main features that use computer algorithms and methods to produce the quantification of phenomena, processes, and plants.

His favourite research topics span interdisciplinary activities: design, simulation, dynamics, control, data reconciliation, optimization, planning, scheduling, supply chain, economic assessment, market uncertainty, key performance indicators, process analytical technologies, pharmacokinetics, pharmacodynamics, accident simulation, consequence analysis, performance assessment, industrial safety, safety reports, landuse planning, and pandemic models.

Davide has worked on several industrial plants and processes, among them microencapsulation of active principles, *pharma* equipment, granulators, driers, perforated pans, optimal drug administration, individualized pharmacokinetics, automated control of intravenous anesthesia.

PSE-Lab website at *pselab.chem.polimi.it*.

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Prof. Tomasz Sosnowski

Professor Tomasz Sosnowski is the head of the Chair of Dispersed Systems Engineering and the Dean Deputy for Scientific Affairs at the Faculty of Chemical and Process Engineering, Warsaw University of Technology (WUT), Poland. He is also a chairman of the Scientific Council of the discipline Chemical Engineering at WUT.

He graduated from WUT (1993), where he also obtained a PhD (1997) and DSc (habilitation, 2006), all in the field of chemical and process engineering. In 1999–2000 he was a post-doc fellow in the aerosol group at the Lovelace Respiratory Research Institute (LRRI) in Albuquerque, NM (USA). In 2016 he was granted a title of professor in technical sciences from the President of the Republic of Poland.

Scientific activities of prof. Sosnowski have been focused on the applications of chemical engineering (mainly: the engineering of multiphase systems) to physiology and drug delivery systems, including:

- aerosol flow and deposition in the respiratory system in health and disease;
- dynamic properties of airborne particles and their impact on health (both: toxicity and drug delivery by inhalation);
- innovative inhalation devices;
- the role of the pulmonary surfactant and bronchial mucus in the mass transfer in the lungs.

In 2006–2011 he was the scientific expert of European Medicines Agency (EMA) in the field of inhalation products. He is a member of International Society for Aerosols in Medicine (ISAM, since 1993).

Prof. Sosnowski is an elected member of the Committee of Chemical and Process Engineering of Polish Academy of Sciences (since 2016) and serves as an elected member of the national Council for Scientific Excellence (since 2023).

In 2021 he was elected to the Executive Board of European Federation of Chemical Engineering (terms 2022–23, 2024–25). During his activity in EFCE, he proposed (together with prof. David Bogle) to launch

EFCE's Scientific Section on Chemical Engineering as Applied to Medicine (ChemE-Med). Prof. Tomasz Sosnowski was elected the Chairman of the ChemE-Med during the kick-off meeting in Paris in December 2022.

Abstracts

Advanced membrane systems and devices for biomedical applications

Sabrina Morelli, Antonella Piscioneri, Simona Salerno, Loredana De Bartolo

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Membranes are widely used in bioseparation due to their selective properties and modular nature that allows upscaling and downscaling separation processes. These systems find important applications in the biomedical field and clinical treatment for the replacement of organ functions and for the separation and concentration of subcellular components such as extracellular vesicles [1–3]. Functionalized membranes designed and operated according to well-defined engineering criteria were able to provide appropriate biochemical and biophysical stimuli for the biofabrication of organs and tissues analogous because of the highly selective properties, which allow to create a fully controlled microenvironment at molecular level mimicking the specific features of in vivo environment. Human liver microtissues were developed in a hollow fiber membrane bioreactor whose design and structural features ensured a uniform microenvironment and adequate oxygenation as demonstrated by the oxygen uptake rate and the mathematical modelling of the mass transfer.

A designed approach has been utilized for the development of a neuronal membrane bioreactor consisting of poly-L-lactic acid highly aligned microtube array membranes to modulate and enhance neuronal outgrowth. The bioreactor provides a 3D low-shear stress environment fully controlled at molecular level with enhanced diffusion of nutrients and waste removal that successfully develops neuronal-like tissue. This platform was used to reproduce an in vitro model of neuroinflammation and Amyloid beta (Abeta)-induced toxicity associated

to Alzheimer's disease to test the neuroprotective effect of molecules such as crocin and glycitein.

Biomimetic membrane systems have been developed to replicate the cell's hierarchy architecture and the interplay within the different cells as it occurs in the natural milieu of the tumor site. The membrane system consists of gas permeable fluorocarbon membranes, biofunctionalized with PolyL-lysine to mimic the extracellular matrix and to provide specific cues for modulating tissues growth. The selectivity, together with structural, physico-chemical and mechanical properties of PLL-FC membranes, allow the realization of a suitable biomimetic interface for the growth of cancer cells. These models increase the predictive value for the in vitro screening of new therapeutic strategies to counteract the growth and survival of tumor cells. The latest developments and innovations regarding the multifunctional role of membrane systems and devices for tissue engineering applications and as in vitro investigational platforms will be discussed.

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Membranes of cellulose acetate-silica/metal organic framework for the removal of uremic toxins

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Chronic kidney disease (CKD) is the gradual progression of kidney dysfunction and leads to the accumulation of uremic toxins (UTs) in the bloodstream. Haemodialysis (HD) constitutes a lifesupporting, membrane-based blood-purifying treatment for most patients with CKD. The accumulation of UTs, particularly protein-bound uremic toxins (PBUTs) which exhibit a high affinity for plasma proteins, represents one of the main concerns associated with kidney dysfunction. The build-up of PBUTs in the blood is associated with a reduction in the effectiveness of conventional membrane-based HD therapies because the PBUTs bound fraction is difficult to remove solely by filtration mechanisms [1]. In this work [2], a metal-organic framework (MOF) adsorbent, UiO-66(Zr), which has high affinity for p-cresyl sulfate and urea is introduced in cellulose acetate (CA)/silica (SiO_2) membrane synthesis, thereby producing asymmetric CA/SiO_2/UiO-66 membranes, to enhance p-cresyl sulfate and urea clearance through filtration and selective adsorption mechanisms. Asymmetric CA22, CA22/UiO-66, CA22/SiO_2, CA22/SiO_2/UiO-66 and CA34, CA34/UiO-66, CA34/SiO_2, CA34/SiO_2/UiO-66 membranes were synthesised from casting solutions with 22 wt.% and 34 wt.% formamide content, respectively, as described by Guerreiro et al. [2]. The membranes were characterised in terms

of pure water hydraulic permeability (L_p), molecular weight cut-off (*MWCO*) and apparent rejection coefficient (R) to urea and p-cresyl sulfate present in dialysis fluid solutions [2]. Figure 1 shows the hydraulic permeability, MWCO and Figure 2 shows the apparent rejection coefficients to urea and p-cresyl sulfate of all the membranes synthesised.

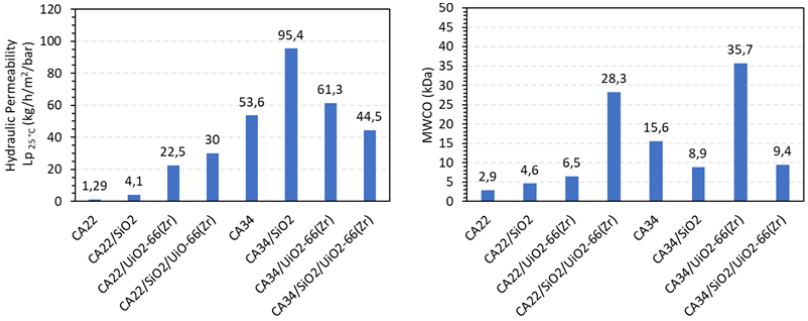

Figure 1 Hydraulic permeability, L_p, and *MWCO,* for all the membranes synthesised.

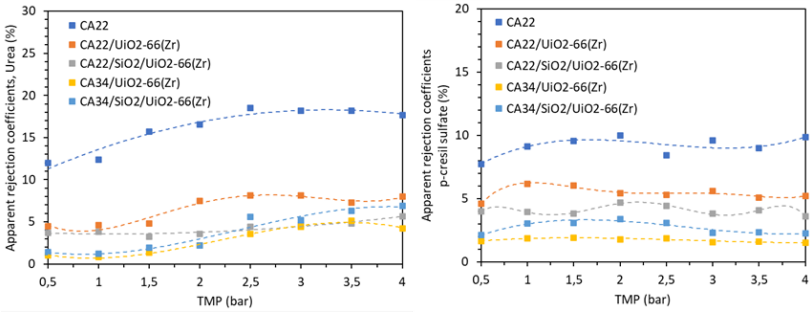

Figure 2 Apparent rejection coefficients to urea and p-cresyl sulfate of all the membranes synthesised.

MWCO of the CA22 membrane series ranges from 2.9 to 28.3 kDa and for the CA34 membrane series ranges from 8.9 to 35.7 kDa. The incorporation of UiO-66 yielded higher hydraulic permeabilities for the CA22/UiO66 and CA22/SiO_2/UiO-66 membranes and lower values for the CA34/UiO-66 and CA34/SiO_2/UiO-66 membranes. All membranes exhibited low rejection coefficients to urea and p-cresyl sulfate, averagely below 5% over the 0.5–4.0 bar transmembrane pressures.

Acknowledgement Acknowledgement to FCT for financial support through CeFEMA & LaPMET (UIDB/04540/2020), CERENA (UIDB/04028/2020), and PhD grants to M. Bordonhos (SFRH/BD/147239/2019) and M.P. da Silva (2023.03206.BD).

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Advanced organotypic membrane systems and mesenchymal stem cells in skin and liver tissue engineering

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Advanced organotypic tissues made of polymeric membranes and human cells, in both homotypic and heterotypic co-culture systems with mesenchymal stem cells (MSCs), were developed as an ambitious attempt for the bio-fabrication of self-renewing human tissue models. Polymeric membranes mimic the in-vivo 3D microenvironment, recapitulating the natural niches for hosting cells and promoting cell-cell and cell-matrix interactions. Through the modulation of the preparation process parameters, membranes with specific functionalities and structural features can be designed, representing a challenging strategy for the control of the cellular fate. Specific membranes properties provide the biochemical stimuli and mechanical support able to boost cellular adhesion, proliferation and differentiation, and thus the overall morpho-functional behaviour [1–3]. Porous semipermeable membranes enable the compartmentalization and the physical separation of cells allowing in the meantime their crosstalk by the selective mass transfer of the secreted paracrine factors, and therefore mimicking the in-vivo physiological cell niches [4–5]. Moreover, the membrane loading with a bioactive molecule constantly released in the time, represents a further strategy to trigger or modulate biological processes needed for tissue regeneration and repair. Innovative culture strategies, by using engineered membrane biohybrid systems for cell compartmentalization and colonization will be presented in this work. Engineered microenvironments made by the combination of biodegradable membranes with human skin cells were created as skin models. Organotypic membrane bioreactors utilizing primary human hepatocytes in direct and connected co-culture systems with human

endothelial and MSCs offered interesting opportunities for the design of bioartificial livers as in-vitro models with high morpho-functional performance.

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PLGA membrane tool for brain tissue engineering

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The treatment of brain diseases by means of a tissue-engineered approach, requires the development of neuro-tissue analogues able to mimic the in vivo tissue structure and functions. Membrane technology approaches have led to the successful realization of in vitro advanced neuronal biohybrid devices that provide specific features of the in vivo neuronal environment, and are widely used as in vitro brain tissue model for pharmacological screening, and studying neurodegenerative disorders including oxidative stress, cerebral ischemia, Alzheimer's disease, neuroinflammation [1–3]. Nevertheless, the availability of reliable, easily accessible and low cost in vitro models of brain diseases remains a big challenge in the treatment of neuro-pathologies. Our strategy was to develop a realistic and biomimetic membrane-based platform for a breakthrough analysis of the pathogenic mechanisms at the basis of the fatty acids/diet neuroinflammation, and for the screening of biomolecules to evaluate their pharmacological potential.

A biohybrid membrane system, consisting of poly(D,L-lactide-co-glycolide) (PLGA) membranes for the culture of human hypothalamic gonadotropin-releasing hormone (GnRH) neurons, was set up to drive the *in vitro* development of a GnRH hypothalamic tissue analogue. PLGA membranes, thanks to their morphological, mechanical and physico-chemical properties, enable adhesion, growth and functional differentiation of the neurons, by providing a well-controlled microenvironment. The PLGA membrane tool served as model system to test for the first time the ability of the phytoestrogen daidzein to stop and reverse the imbalanced neuroinflammatory responses caused by high fat diet. The pathological features of the obesity-related neuroinflammation were recapitulated within the membrane system to investigate daidzein potential in controlling high-fat diet-induced hypothalamic inflammation. Our findings highlighted the neuroprotective role of daidzein in neutralizing palmitate-induced neurotoxicity by reversing

the neuroinflammatory cascade, which is associated with severe consequences, including obesity, type 2 diabetes, cardiovascular and neurodegenerative diseases.

Acknowledgement This work was supported by EU funding within the NextGeneration EU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no. PE00000007, INF-ACT), and by MUR, National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006, DN. 1553 11.10.2022).

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Smart hydrogels in biomedical applications: pH role on their behaviour

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Hydrogels are polymeric materials characterized by the presence, on their polymeric chain, of hydrophilic groups. These groups lead the hydrogels to absorb large quantities of water and swell. Hydrogels are widely used in different scientific fields i.e., pharmaceutical, biomedical as well as in the field of tissue engineering. In the huge family of hydrogels, particularly interesting are the so-called *Smart Hydrogels* whose behaviour is influenced by the external conditions such as temperature, electrical field, ionic strength and, among them, polyelectrolytes (PEs) whose behaviour is connected to variation of the external pH. PEs are formed by ionizable groups which can dissociate or associate in solution at different pH; association or dissociation of the groups linked to the different pH, influence the behaviour of the swelling. This study, keeping on the work done by the research group [1–3], aims to tune and validate the written model for PEs considering the swelling behaviour of a general anionic hydrogel in solution in a range of pH 1 to 14. Experiments were carried out considering a commercial hydrogel: Orbeez™ made of sodium polyacrylate, a super absorbent polymer. A gravimetric analysis at the steady state conditions and compression mechanical tests were performed on the swollen hydrogels. These experimental data were used to tune the parameters of the developed model. The model is based on the monophasic approach, starting from the Dissipation Inequality, and particularizing the Helmholtz Free Energy for the PEs, the constitutive equations were derived. The model is described by seven parameters, among them the association and dissociation constants were taken from literature for carboxylic acid [4], while the concentration of salt and the elastic modulus were extracted from the experimental part. The Flory Huggins parameter and the

percentage of ionizable groups were calculated using an optimization tool. Particularly interesting is the analysis of the Flory Huggins parameter, which has been described as a function of the external pH. As main conclusion, the general behavior of an anionic hydrogel is well described by the model in the range of pH 1–14 with only two optimization parameters and a good comparison with experimental data was observed. Further studies are ongoing to understand the effect of the concentration of salt on the swelling. Furthermore, this model could be a good starting point to extend the study to the dynamic behavior of swelling polyelectrolytes.

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Multi physics modelling for predicting drug release from hydrogels in breast tumour treatment

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Numerous studies have proposed the utilization of hydrogels for targeted delivery of chemotherapeutic drugs following tumour resection surgery. This approach aims to achieve two objectives: filling the surgical cavity and preventing the recurrence of cancer [1]. Multiphysics simulation emerges as a valuable strategy to minimize experimental actions, offering insights into the drug release dynamics within the tissue and enabling the optimization of design.

This study introduces a mathematical model that takes into account the movement of liposomes within a hydrogel, traversing breast tissue modelled as a porous system. The model also incorporates the internalization of liposomes by breast cells, their impact on cell viability, and their interaction with lymphatic drainage.

Initially, studies on cell viability were conducted to examine the response of BT474 cells to MZ1, aiming to adapt the experimental data to a lag exponential cell death model. Subsequently, D_0 and D_R values were determined for different MZ1 concentrations and fitted to exponential or sigmoidal curves, respectively. From those data, it is estimated an equation capable of predicting these values based on both MZ1 concentration and time. These equations, derived from experimental data, were integrated into the model, along with equations for mass and momentum conservation and Darcy's law. Additionally, the effect of gravity was also incorporated as a vector dependent on the relative position of the human body and the duration spent in each position per day.

The model's performance was assessed by predicting cell survival in diverse locations under various case studies. Different concentrations of liposomes, as well as varying hydrogel sizes, shapes, and locations based on real geometries obtained from MRI scans of six patients, were evaluated. The findings indicated that even low concentrations of liposomes (0.1% wt.) could significantly reduce cell viability in the vicinity of the hydrogel location (by less than 10%) when cells were exposed to them for extended periods. This observation could be critical for minimizing the dose within the hydrogel.

Lastly, the study explored the significance of lymphatic drainage in liposome availability. The results revealed that its contribution could be deemed negligible during the initial three months after filling the cavity with the hydrogel, as global transport is predominantly governed by diffusion, and cells uptake liposomes as long as they are accessible.

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Molecular dynamics and quantum chemistry modelling of dehydration and exposure effect on skin lipid bilayer structure and barrier property

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For the large industry of skincare and dermatology, a significant challenge is that the development of new products requires expensive and time-consuming in vitro permeation tests and clinical studies to gain regulatory approval of product safety and quality. Understanding is very limited on how different product formulations and forms affect percutaneous absorption and associated biophysical pathways for the repair and maintenance of skin barrier function. We report progress in applying molecular dynamics (MD) and quantum chemistry (QC) modelling capable of simulating how dehydration and exposure to skin care and dermatological ingredients affects the molecular assembly and barrier property of stratum corneum (SC) lipids. MD simulations have been carried out to build lipid bilayer assemblies at typical SC lipid compositions [1]. With the simulated lipid bilayer assemblies equilibrated through energy minimization, further MD simulations have been performed to expose the equilibrated bilayer to glycerol, urea and ethanol at different hydration levels and temperatures. The results revealed that dehydration does not induce significant structural change of SC lipid bilayer, nor affects water diffusivity within the bilayer, but reduces water mobility at the interfacial region. Exposure to glycerol and urea solution does not induce significant change of bilayer structure. Exposure to ethanol significant disrupts bilayer structure and barrier integrity. Quantum chemistry modelling using COSMOmic has been also conducted to predict the thermodynamic property of SC lipid partition for a number of chemicals and the predicted results are in good agreement with published experimental data [2]. This suggests that the combined molecular dynamics and quantum chemistry modelling method can be exploited for fast in-silico screening of how

ingredients of skin care and dermatological drug products interact with hydration management to affect skin lipid bilayer structure integrity and barrier function.

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Computational modelling of fructose-induced lipid deposition and liver disease

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is the latest nomenclature and definition for steatotic liver disorders previously identified as non-alcoholic fatty liver disease (NAFLD). The condition is characterized by excessive lipid build-up in the liver without substantial alcohol consumption. Due to the ongoing obesity epidemic it is now the commonest chronic liver condition and the leading cause of liver-related morbidity and mortality. One significant contributor to MASLD is the over-consumption of fructose, a common component of modern processed foods. However, the underlying mechanism remains unclear and no pharmacotherapy has been approved for MASLD. Therefore, this study adopts a systems engineering approach to elucidate the metabolic mechanisms through which fructose induces lipid deposition in hepatocytes, contributing to the development and progression of MASLD.

The project was conducted in an "experiment-model-experiment" cycle, reflecting the iterative nature of systems biology methodology. Our computational kinetic model integrated key elements of hepatic metabolic pathways involved in fructose metabolism and lipid homeostasis. By simulating the dynamic interplay of these pathways, we aimed to identify critical nodes that drive the excessive lipid accumulation observed in MASLD and elucidate potential therapeutic points for further experimental exploration.

Through this computational model, we sought to provide insights into the metabolic events triggered by fructose intake, offering a predictive framework for understanding individual susceptibility to MASLD. The outcomes of this study may inform targeted interventions and therapeutic strategies to mitigate fructose-induced lipid deposition

and, consequently, the development of MASLD. Our research contributes to the intersection of computational modelling, fructose metabolism, and liver disease, fostering a deeper understanding of the complex dynamics underlying MASLD pathophysiology.

Keywords MASLD, fructose metabolism, computational modelling, systems biology.

Hemolysis risk assessment in cardiovascular defects using Computational Fluid Dynamics simulations

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Hemolysis, the destruction of erythrocytes, poses a critical health risk, especially in patients with circulatory disorders. Pathologies that may be accompanied by hemolysis are often associated with constriction of blood vessels and leaks between cardiac cavities. It appears that many factors correspond to pathogenesis of hemolysis, whereas shear stresses seem to be one of the more important ones (suspected factors include also turbulent pattern of blood flow, interactions of erythrocytes with prosthetic material and others) [1,2]. Medical practice lacks a rapid diagnostic tool to quantitatively analyze the risk of hemolysis, whereas shear stresses and also other important flow parameters in blood vessels can currently be relatively accurately predicted using specialized computer software and principles of computational fluid dynamics (CFD) [3].

This work presents different options for hemodynamics modeling of cardiac contraction affected by the mitral paravalvular leak and blood flow through arteries with atherosclerotic stenosis. Several alternative approaches to the problem were studied, using, among others, different representation of the motion of the left ventricle and two non-Newtonian blood rheology models: the population balance based model (PBBR) [4] and the Carreau-Yasuda model [5].

The general patterns of changes in hemolysis parameters based on the hemolysis criterion (150 Pa) during left ventricular contraction and

flow through atherosclerotic lesions show the same trends for the compared variants. On the other hand, there is clear advantage of the PBBR model, as it makes possible to determine the exact value of the hemolysis index, and thus determine the number of red blood cells undergoing destruction. Moreover, the PBBR model much better represents the viscosity of blood, as the change in viscosity due to shear rate does not occur instantaneously. This shows that the analysis of hemolysis in cardiovascular defects can be conducted using common methods from the field of chemical engineering and within the near future has a chance to take its place in daily medical diagnostics.

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Optimizing levothyroxine dosage for hypothyroidism treatment: a model-based approach

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In recent years, there has been a surge in interest in developing novel approaches for predicting the optimal dosage of levothyroxine (LT4), a synthetic drug used in the treatment of hypothyroidism to supplement the deficient T4 hormone produced by a healthy thyroid. This paper introduces a quantitative methodology for the precise administration of LT4, employing a model-based strategy that leverages individualized patient parameters to enhance dosing accuracy and alleviate the reliance on imprecise estimations by endocrinologists [1].

The proposed algorithm utilizes patient-specific data, including key thyroid status indicators such as the serum concentration of Thyroid-Stimulating Hormone (TSH), to compute the Residual Thyroid Function (RTF), a metric that reflects thyroid efficiency, and subsequently determines the optimal LT4 dosage. In addition to existing quantitative models in the literature [2,3], this approach integrates patient age to tailor dosing recommendations, ensuring optimal prescriptions for hypothyroidism across different age groups, from young to elderly individuals.

The primary objective of the paper is to establish a streamlined procedure that reduces treatment duration and minimizes the frequency of blood tests required for accurately determining the appropriate levothyroxine LT4 dosage.

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Constructing 3D Voronoi structures: a toolkit with biomedical case studies

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3D Voronoi scaffolds are widely applied in the field of additive manufacturing as they are known for their light-weight structural resilience and share many topological similarities to various natural (bone [1], tumours [2], lymph node [3,4]) and synthetic environments (foam [5], functionally gradient porous materials [6]). Unfortunately, the structural design features that promote these topological similarities (such as the number of vertices) are often unpredictable and require the trial and error of varying design features to achieve the desired 3D Voronoi structure. This research provides a toolkit, consisting of equations, based on over 12,000 3D Voronoi structures. These equations allow design features, such as the number of generating points (G), to be efficiently and accurately predicted based on the desired structural parameters (within ±3 G). These equations have been validated for a wide range of parameter values and Voronoi network sizes. A design code has been completed allowing any of over 12,000 structures to be selected, easily adjusted based on user requirements, and 3D printed. Biomedical case studies relevant to T-cell culturing, bone scaffolds and kidney tumours have been conducted demonstrating the accuracy and efficiency of the design code.

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An aerosol generator for the direct pulmonary delivery of micro and nanoparticles

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Direct lung administration of aerosolized drugs to treat respiratory diseases enables local delivery of the drug, allowing for the decrease of the total administered dose, lowering systemic exposure and minimizing side effects, compared to other drug administration routes. As a consequence, it is attracting more attention than ever, especially in the wake of the COVID pandemic. In addition to pulmonary infections direct lung administration could be used for a variety of respiratory ailments, such as lung cancer, asthma and EPOC.

Pulmonary delivery of aerosolized drugs is therefore smart route that increases efficiency thanks to the high local drug bioavailability. However, particle dynamics are key in the drug aerosol performance. Particle size is the main parameter, as it determines the possibility of reaching distal areas of the lung, such as alveoli. When the drug is suspended in liquid aerosols with sizes in the tens of micron range, the drug is delivered to the upper airways only. Reaching alveoli efficiently requires dry powder administration, with a size in the micron or, better, submicron range.

However, creating highly dispersed micro and nanoparticle aerosols is extremely challenging due to the tendency of the particles to form agglomerates. Existing commercial dry powder inhalers present a wide particle size distribution (PSD), and substantial particle agglomeration, making it difficult to reach target areas or even to control the

dose received by the patient. To avoid these drawbacks, we have developed a novel aerosol generator [1,2] that allows the production of monodisperse NPs aerosols with a PSD close to that of the pristine nanoparticles. This device can be used to disperse micro and nanoparticles [2,3] of inorganic and polymeric nature with a size suitable for direct alveolar delivery, thus opening a new route for the direct pulmonary delivery of drugs.

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A comparative study on liposomes and niosomes produced by a supercritical CO_2 assisted process

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Liposomes and niosomes are widely proposed as drug delivery systems [1,2]. The conventional techniques used for their production consist of batch and time-consuming methods that require homogenization post-processing steps, do not assure a good control on particle size and size distribution, and low drug encapsulation efficiencies are generally obtained. These disadvantages can be overcame using an innovative and green process assisted by supercritical CO_2 [3,4]. In this work, liposomes and niosomes were produced at 100 bar and 40 °C, with the aim of comparing mean diameter, size distribution, ζ-potential, and stability over time of these vesicles. The results showed that no relevant differences in mean diameter (140 ± 60 nm and 160 ± 53 nm for liposomes and niosomes, respectively) and stability at least up to 1 month were detected between liposomes and niosomes. When a model active compound (i.e., ascorbic acid) was loaded in the vesicles, it emerged that niosomes were able to encapsulate a larger amount of it (99%) than liposomes (92%); whereas the ascorbic acid DPPH-scavenging activity was preserved in both the nanocarrier systems.

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Blood-on-a-chip for real-time investigation of blood clotting dynamics

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Thrombosis is a pressing global health concern, significantly contributing to morbidity and mortality rates. Traditionally, platelets have been considered the primary drivers of coagulation, with red blood cells (RBCs) viewed as passive bystanders [1]. However, emerging clinical and laboratory evidence challenges this perception, suggesting that RBC flow properties play an active role in hemorheology, platelet activation, thrombin generation, clot structure and stability [2–4]. Although multiple mechanisms have been proposed for the different effects, they remain largely theoretical. This research endeavour aims to investigate the intricate interplay between haemodynamic parameters and the physicochemical behaviour of blood components in thrombotic events, particularly concerning the active involvement of RBCs in blood coagulation. To address this knowledge gap, this study leverages microfluidic techniques coupled with confocal microscopy. Microfluidics empowers the development of blood-on-a-chip devices, providing a physiologically relevant model of microcirculation [5–8]. This approach ensures precise control on flow parameters and minimizes the requirement for blood samples. Additionally, the microfluidic channels are functionalized with coagulation-activating substances, such as collagen, allowing for the emulation of pathological conditions. Microfluidic platforms, coupled with advanced imaging techniques, such as confocal microscopy, allow real-time visualization and analysis of the interactions between RBCs, platelets, and the surrounding fluid flow [9]. Accurate quantitative measurements, achieved by advanced image and data analysis algorithms, are paramount for acquiring a comprehensive understanding of the intricate interactions underlying thrombosis. The proposed methodology underscores the pivotal role of integrating microfluidics and confocal microscopy in shedding light on the complexities of thrombotic events, and lays the groundwork for

the development of innovative early diagnostic techniques for thrombosis. This advancement holds significant promise for enhancing patient outcomes through timely and targeted interventions.

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Nanoliposomal formulations in medicine: the coaxial-injection method as reliable and high throughput process

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Liposomes are spherical vesicles comprising phospholipid bilayers. Offering superior attributes over conventional delivery methods, liposomes boast targeted delivery, exceptional biocompatibility, biodegradability, minimal toxicity, enhanced sustained drug release, and improved therapeutic efficacy. Various new technologies have been developed to produce nanoparticles including methods based on supercritical fluid technology; microfluidic technique and microfluidic-like (similmicrofluidic) technique [1]. Interestingly, Lim et al. [2] and Saad and Prud'homme [3] have shown that turbulent regimes, such as a "turbulent jet", can also be used to generate nanoparticle in controlled manner. Since the "simil-microfluidic" and the "turbulent jet" methods employ a common architecture, namely the coaxial-injection setup, this study aims to explore the influence of various fluid dynamic conditions within a single coaxial injection mixer on nanoparticle production and properties. A coaxial injection mixer was constructed to replicate laminar and turbulent flows, utilizing a 23G needle within a 3 mm ID PVC tube. Push-pull syringe pumps ensured smooth flow. A tracer aided in identifying fluid dynamics, revealing laminar, turbulent, and intermediate behaviours. By adjusting flow rates, the system was characterized using dimensionless parameters: Reynolds number and flow momentum ratio (FMR). Such a well characterized system was used to produce liposomes loaded with a model liposoluble drug. Phosphatidylcholine was extracted from soy lecithin using ethanol at three different concentrations. Cholesterol was then added to these solutions at a ratio of 20% w/w relative to the phosphatidylcholine, while the model drug was added at a ratio of 10% w/w relative to both

the phosphatidylcholine and cholesterol. These solutions served as the inner fluid (solvent) in the coaxial injection mixer, while water acted as the antisolvent in the outer tube. Production occurred under both laminar and turbulent conditions, maintaining a consistent volumetric flow ratio between the solvent and antisolvent to ensure in all cases the same final product concentration. The product characterization revealed that the loading and encapsulation efficiency closely matched theoretical values in all instances, with a consistent 10% loading and encapsulation efficiency exceeding 99%. However, a lower and narrower particle size distribution was obtained in turbulent conditions, which reflected also on a lower turbidity of the solutions. Furthermore, productivity increased by 8 times under turbulent conditions, enabling the production of nearly 400 mL/min of liposomal suspension. In conclusion, this study demonstrates the significant impact of fluid dynamic regimes on the production and characteristics of nanoliposomal formulations using the coaxial-injection method. The results underscore the potential of turbulent regimes to optimize nanoliposomal formulation processes, paving the way for improved drug delivery systems.

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Production of sodium alginate droplets in an X-microdevice

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Sodium alginate, a polysaccharide derived from brown algae, has attracted considerable interest in medical and biological applications due to its biocompatibility, biodegradability, and gel-forming ability. These unique properties make alginate suitable for various uses such as drug delivery, tissue engineering, and wound dressing.

In drug delivery applications, the encapsulation of Active Pharmaceutical Ingredients (APIs) within alginate matrices enables the modulation of drug release [1]. This modulation allows for sustained or targeted delivery, thereby enhancing treatment efficacy while minimizing side effects. Precise control over the droplet size and quality is crucial for these kinds of applications; thus, microfluidics methods have emerged as a promising approach to control the characteristics of the droplets [2].

In this work, experiments and numerical simulations are carried out jointly to investigate the production of alginate droplets via the segmentation of the dispersed phase method in an Xmicrodevice operating in hydrodynamic flow focusing configuration. The two opposite inlets are fed with sunflower oil and 0.5 wt% of Span80 (continuous phase). The other inlet is fed with water and 2 wt% of sodium alginate (dispersed phase). The droplet formation follows three stages. Firstly, the dispersed phase fills the confluence region and stretches in the outlet channel (Fig. 1a). Then, the oil causes the necking of the liquid thread of the alginate solution, followed by the pinch-off of the thread. This mechanism leads to the formation of droplets as can be seen in Fig. 1b. The higher viscosity of the water-phase compared to the continuous phase leads to the formation of undesirable satellite droplets. To capture this process, the numerical method was optimized with Adaptive Mesh Refinement. A sensitivity analysis of the model parameters was also performed.

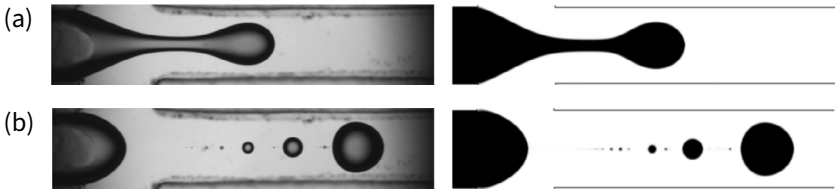

Figure 1 Comparison between experiments (left) and numerical simulations (right) at two different instants. The continuous-to-dispersed flow rate ratio is equal to 80.

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Unveiling the mechanical properties of cancer cell spheroids by rheo-microscopy

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Cancer remains a significant global threat, with metastasis responsible for approximately 90% of cancer-related deaths. This complex process, involving the migration and colonization of tumour cells in secondary sites, plays a pivotal role in fatalities, often overshadowing the impact of primary tumours. Understanding the mechanisms behind cancer spread, particularly influenced by the microenvironment and mechanical factors, is imperative for developing effective treatments.

While current research methods like atomic force microscopy, indentation, and confocal microscopy provide valuable insights, they often require specialized equipment and expertise not readily available in cell biology labs. Moreover, most studies rely on 2D or animal models, which do not fully replicate the 3D complexity of human tumours. In this regard, 3D cell spheroids offer a more representative model, bridging the gap between 2D cultures and animal systems.

Our innovative approach utilizes a rheo-optical compression assay, a cost-effective and accessible method for biomechanical characterization of cell spheroids, aimed at distinguishing between tumoral and non-tumoral cells. This is vital due to the significant contrast in biomechanical properties between healthy and cancerous tissues. The technique involves applying loads using standard microscopy glass coverslips and employing straightforward image acquisition methods, such as optical microscopes or smartphones with suitable lenses, to monitor and analyze spheroid deformation under varying stress levels. By correlating the applied load with deformation, we derive the mechanical properties of the spheroids. We conducted the compression

test on two cell lines: the cancerous PANC-1 and the non-tumorous NIH/3T3 as a control. This study represents a significant advancement in mechanobiology, providing a novel tool for cell biology and cancer research. It holds the potential to enhance cancer treatments and improve patient outcomes.

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Investigating the response of organic electrochemical transistors for biosensing applications

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Due to their intrinsic ability to amplify ionic-electronic transduction, organic electrochemical transistors (OECTs) are currently the subject of intense scientific investigation for potential applications in the field of biosensing [1,2]. These devices feature a relatively straightforward architecture, comprising three electrodes (source, drain, and gate) and an active layer of conductive polymer (specifically, PEDOT:PSS in this study). The polymer channel establishes the connection between the source and drain contacts and is immersed within an electrolyte, where the gate electrode is also immersed. Application of a voltage, V_{GS}, to the gate induces the diffusion of ions from the electrolyte solution into the polymeric channel, thereby reversibly altering the electronic current (I_{DS}) flowing between the drain and source. Notably, these devices can operate at voltages below 1 V, enabling interaction with biological fluids without significant hydrolysis or molecule denaturation effects. Through systematic experimentation and analysis, this study focuses on investigating the response of OECTs when employed for biosensing purposes; in particular the performance of OECTs in detecting biomolecules and analytes present in biological samples is studied. The experimental design encompasses the characterization of OECT response under different operating conditions, including variations in electrolyte composition, applied voltage, and device configuration. Additionally, the influence of surface modifications and

biofunctionalization strategies on sensor performance is examined. The results obtained shed light on the feasibility and potential limitations of utilizing OECTs for biosensing applications, providing valuable insights for further optimization and development in the field of bioelectronics.

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Development of antibacterial materials based on in-situ synthesis of volatile allicin

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Plants and animals have unique ways of preventing bacterial colonization and biofilm formation. The most common form of a passive protective barrier is a topologically structured surface with high hydrophobicity and self-cleaning properties, such as the lotus leaf or gecko skin. Some surfaces, like the wings of cicadas, have been reported to actively disintegrate adhered bacterial cells. Potent phytochemicals are another group of natural self-defence solutions recognised and utilised in herbal medicine since the dawn of mankind.

Allicin, found in extracts of some *Allium* species (garlic, onion), belongs to the most biologically active substances found in nature. Short-lived allicin is enzymatically formed from stable allicin only when the tissue structure is mechanically compromised. In contrast to common antibiotics, allicin is highly active even as a vapour. This property can be beneficial in applications where access to the target site is limited or obscured or where direct contact with concentrated allicin solution may be harmful, e.g. tissue irritation.

To fully utilise the potential of allicin, it is essential to produce it in a controlled fashion near the desired location from its precursors. This requires spatial separation and stabilisation of allicin's precursors while introducing a mechanism to control its synthesis rate. We suggest developing structured particles, films and 3D-printed materials that can be used for the synthesis and controlled release of antibacterial allicin. We believe that such materials will address challenges hindering the practical application of allicin as a natural antibiotic in modern medicine.

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Machine Learning-aided tools in personalised medicine supply chains

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As personalised cancer cell therapies have secured regulatory approval in the United States [1], Europe [2], Australia [3] and Japan [4], the demand for personalized cancer treatments is expected to exponentially grow over the next decade. Given the product's sensitive nature and patient-specificity, supply chain management is considered an emerging challenge for the commercialisation of such therapeutics. To ensure therapy availability and promote drug price affordability, pharmaceutical companies are challenged to invest in novel, agile and cost-efficient supply chain structures. Unlike batch produced pharmaceuticals, personalised cell therapies require bespoke manufacturing and distribution lines, resulting into 1:1 business model. Parallel lines in the manufacturing facilities and therapy delivery should be coordinated based on the clinical condition and location of each patient separately. The supply chain further involves the coordination and availability of different raw materials, as well as expert handling during the transportation of the samples and/or therapies [5]. Industry standard for all the processes involved should take place within a tight time period (minimum reported is 3 weeks) to maximise clinical impact. So far, the industry has been operating based on white-glove logistics, which as demand increases become a suboptimal or even inefficient way forward. In this context, Process Systems Engineering (PSE) approaches that can guide investment planning and scheduling offer a promising alternative. Nonetheless, modelling and optimising patient-specific supply chains is a challenging task. It often translates into complex, large-scale formulations that grow exponentially as the demand increases. In this work, we will showcase how Machine Learning-enhanced Mixed Integer Programming optimisation can aid the decision making in personalised cancer cell therapies. Different candidate supply chain configurations that allow the selection of decentralised manufacturing models versus the traditional centralised will be presented. Lastly, the

use of such models to assist investment planning during clinical trials will be discussed.

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Supercritical CO_2 used as sterilization agent for polymeric medical devices

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Nowadays, the main methods employed to sterilize implantable medical devices are gaseous treatment using ethylene oxide or γ irradiation. Concerning the first method, ethylene oxide might be soon prohibited because of healthy issues as it is genotoxic and carcinogenic. The second method is also problematic because γ rays might alter the mechanical properties of polymeric medical devices and create radicals.

The study proposed here is part of a French project called FasteCO_2 which involves 2 medical devices manufacturers (Lattice Medical and Cousin Surgery) and 2 academic laboratories from Aix-Marseille University and the University of Lille. The aim of the project is to implement an environmentally friendly, non-toxic, and economically viable sterilization method at large scale compatible with polymeric medical devices. Supercritical CO_2 ($scCO_2$) could be the alternative to classical methods since it has already proven effectiveness for the inactivation of resistant microorganisms [1] but under high pressure and quite high temperature. The challenge of the FasteCO_2 project is to propose a $scCO_2$ sterilization method under smooth pressure and temperature in order to preserve the polymeric material properties while respecting the Sterility Assurance Level (SAL) imposed by EN 556-1:2002 standards; it means at least a 6-log bacterial reduction. This work deals with the $scCO_2$ sterilization inactivation of *Bacillus subtilis,* a Gram-positive spore-forming bacterium. The choice fell on this microorganism because it is quite easy to cultivate and resistant to $scCO_2$. The experiments performed confirmed the efficiency of $scCO_2$ since more than 6-log reduction on *B. subtilis* spores could be reached after a 20 min treatment under 110 bar, 40 °C with the addition of 200 ppm of hydrogen peroxide [2]. The efficiency has been proven on *B. subtilis* spores

deposited on glass slides and inoculated on polymer pieces, as well. Finally, the $scCO_2$ process is repeatable. A standard is being drafted to apply $scCO_2$ sterilization method at industrial scale for implantable medical devices.

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Current engineering challenges in the targeting aerosolized medicines to the nasal cavity

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Aerosols are commonly utilized as carriers for targeted drug delivery to various parts of the respiratory system. Targeting specific regions can be achieved by manipulating the particle size distribution; inhaled fine particles (< 5 μm) can reach the lungs while coarse particles (> 10 μm) are primarily captured in the nasal cavity (NC) or throat. The efficacy of drug delivery to different regions depends on the mechanisms of particle deposition. Drug delivery to the nose is important in the treatment of allergic rhinitis, in vaccination, and nose-to-brain delivery of neurotherapeutics.

This contribution will discuss novel possibilities of applying the approach and concepts of chemical engineering to enhance drug delivery to the NC. Recently, it has been argued whether large aerosol droplets produced by nasal pumps are appropriate for homogenous drug delivery to the NC, which has a very complex geometrical structure. It has been shown that high outflow velocity (> 10 m/s) and conical shape of the aerosol plume emitted from the nozzle result in inertial deposition of droplets in the anterior part of the NC [1]. Impaction leads to the elimination of most drug droplets from the aerosol stream, preventing their penetration into deeper parts of the nose. The clinical efficacy of drugs delivered in this form requires its action in the various regions of the nasal cavity, and it may be explained by convective mass transfer of the deposited liquid film driven by mechanical interactions with the inhaled air [2,3]. Other methods for improving nasal delivery of aerosolized drugs which have attracted attention recently, rely on applying pressure pulsations on the fine (< 5 mm) aerosols flowing through the nose. During typical inhalation, fine mists penetrate beyond the NC, potentially reaching the lungs (such as during the inhalation of pulmonary drugs using a medical mask). However, if the aerosol flow inside the nose is destabilized, e.g., by acoustic pulsations, drug deposition

on the nasal surface is increased. This method of enhancing local drug delivery represents the adaptation of process intensification techniques to medicine [4]. Optimal outcomes can be achieved through the proper synchronization of aerosol delivery and pulsation timing. This approach can be integrated into "smart nebulizers" equipped with electronic monitoring of a patient's inhalation dynamics, facilitating adjustments in aerosol release and pulsations accordingly. It should allow to achieve high drug deposition in the NC while minimizing aerosol penetration into the lower airways, thereby reducing potential side effects. Control algorithms in such devices can be further optimized using artificial intelligence (AI) approach. Detailed discussions on the flow and mass transfer phenomena underlying these strategies for targeting drugs to the nose will be presented and discussed during the conference.

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Computational modelling of the impact of evaporation on in-vitro dermal absorption

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Purpose Understanding skin permeation is crucial for developing effective skincare and pharmaceutical products. In-vitro permeation tests have been widely used and recently there has been a shift towards performing finite dose, unoccluded experiments to account for evaporation. We aim to expand an in-silico model to better understand the impact of evaporation on dermal delivery and pharmacokinetics.

Method An in-silico model has been developed to simulate the evaporation rate of volatile permeants from the vapour pressure. The evaporation model is then integrated with a physiologically based pharmacokinetics (PBPK) model of skin permeation. The integrated evaporation PBPK dermal model is validated with published penetration data from the Cosmetics Europe ADME Task Force.

Results The evaporation model shows improved predictions, of the extent of evaporation of volatile permeants over our original dermal PBPK model. The results are in good agreement with published experimental data, where the importance of cutaneous distribution and receptor fluid kinetics have been considered. The simulation results indicate evaporation reduces the amount of chemical delivered into the receptor fluid and improves agreement with experimental data.

Conclusion This work has highlighted that evaporation of volatile permeants has significant impact on the pharmacokinetics of dermal absorption under finite in vitro permeation test conditions. The rate of evaporation can be reasonably predicted from the intrinsic volatility indicated by vapour pressure. We recommend that evaporation

is included in PBPK modelling for accurate experimental recreation – where evaporation modelling significantly improved the agreement with experimental results. We further discuss the model's effectiveness in assessing skin evaporation and highlighting its potential to aid in the reduction of IVPT experiments required for assessing the safety and effectiveness of formulations in industry.

Deciphering population heterogeneity in vaccine-induced immunity: a mechanistic model for immune fingerprinting

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Vaccines are pivotal in combating infectious diseases, saving millions of lives worldwide and vastly improving public health. Despite their success, the effectiveness of vaccines varies across individuals, posing a significant challenge in achieving optimal community-wide immunity. Several host factors such as virus pre-exposure, age, sex, genetics, and co-morbidities can influence the strength of the vaccine-induced immune response [1,2]. This variability thus affects the population-scale efficacy of vaccines and underlines the necessity for an approach to optimize the use of vaccines to improve outcomes. To tackle this challenge, we developed a model based on a system of ODEs that meticulously delineates every phase of the immunogenic response. In a preliminary study we demonstrated that variations in immune response among populations can be attributed to differences in a key scaling parameter within our model, suggesting the potential for devising customized vaccination strategies for specific demographic groups [3]. To further unravel the reasons behind immunogenicity variation, we streamlined our model to focus on the essential phenomena driving immune response variability. Our initial step involved assembling an extensive dataset for SARS-CoV-2 vaccines from literature, which included a wide range of measurements for key immune response variables, enabling us to precisely estimate the unknown parameters that influence immune response dynamics following vaccination. After achieving a thorough understanding of the phenomena at the

population level, we identified the three pivotal parameters influencing antibody titer through global sensitivity analysis. Next, we repeated the estimation of these parameters for individual profiles within a diverse cohort of about 1,700 subjects, using population averages as a baseline. This in-depth analysis provided a parameter value profile for each participant, combining demographic details such as age and sex with parameters characterizing the dynamics of the immune response. We then searched for patterns within the antibody response data using clustering algorithms; this analysis identified three main clusters into which the cohort could be separated based on differences in the magnitude of their immune response. The corresponding parameter combinations for the groups result in well-defined distributions with which specific populations can be reconstructed, thus defining an *immune fingerprint* that allows us to simulate scenarios tailored toward those who respond worse. Based on this evidence, our next goal focuses on adapting vaccine protocols to achieve balanced immunogenicity in the population. By simulating the identified immune response clusters, we intend to uncover their unique attributes and develop targeted strategies that can increase vaccine efficacy for each segment. This holistic strategy marks a significant step toward the realm of personalized medicine, with the ultimate goal of refining vaccine approaches to fit the intricate immune profiles of various demographic sub-populations.

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Supercritical fluid extraction of active pharmaceutical ingredients from iris

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Iris spp. exhibit antioxidant, anticancer, anti-inflammatory, hepatoprotective, neuroprotective and antimicrobial properties. Aromatherapy recommends the use of Iris oil for the treatment of bronchitis and whooping cough. Iris root oil has a regulating effect on nervous disorders and can be used in the case of emotional shock, stress and depression [1,2]. In this work, supercritical fluid extraction (SFE) was used to extract the essential oil from an Iris concrete (i.e., a semi-solid material obtained after the evaporation of the organic solvent used to perform the traditional extraction of the vegetable matter). In particular, Iris concrete was mixed with 3 mm glass spheres (concrete to sphere mass ratio equal to 1.30%) and processed by SFE at 90 bar and 40 °C (CO_2 density = 0.480 g/cm^3) [3]. Operating in this way, a total extraction yield equal to 13% w/w was obtained. Gas chromatography-mass spectrometry results showed that α-irone (4.40% w/w) and dihydro-β-irone (3.60% w/w) were successfully extracted; these compounds, that indicate the authenticity of the Iris oil, are responsible for the characteristic violet-like smell of the plant and exhibit mucolytic action [4].

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High pressure homogenization as advanced process for the fabrication of antimicrobial hydrogel nanoparticles

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High-pressure homogenization (HPH) is an advanced process that provides the formation of nanoparticles with defined features of technological importance by the control of process parameters including pressure and number of homogenization cycles [1]. The construction of nano-engineered particles with functional coatings of various composition gives an opportunity of tailoring their physicochemical and biological properties to form multipurpose systems with many therapeutic applications. The surface functionalization of colloidal nanoparticles with antimicrobial polyelectrolyte (PE) layer provides the formation of multifunctional materials with long-term antibacterial efficacy for the treatment of various pathogenic infection [2].

The main goal of this work was to fabricate hydrogel nanoparticles decorated with antimicrobial PEs using HPH process and layer-by-layer (LbL) technique. Thus, poly(acrylic acid) (PAA) was functionalized with different percent degrees of substitution (n) of antimicrobial agents such as thymol, menthol, and carvacrol using the Steglich esterification. We formed nanogels composed of sodium alginate core and LbL coatings consisting of chitosan and the modified PAA as an outer layer with antimicrobial function. The structure of synthesized PEs was characterized by ^{1}H NMR analyses. The nanoparticles were characterized by dynamic light scattering (DLS), scanning electron microscopy (SEM) as well as transmission electron microscopy (TEM). The adsorption kinetics and viscoelastic properties of the functional coatings were studied using Quartz Crystal Microbalance with

Dissipation Monitoring (QCM-D). The antimicrobial properties of the nano-products were assessed against *Escherichia coli* and *Staphylococcus aureus* using broth microdilution method. The design and usage of new advanced functionalized polyelectrolytes as outer coatings of nanogels allowed for the formation of nanocapsules that could be applied in antimicrobial therapy.

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Toward anaesthesia management via physiologically based PKPD models

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During surgery, the attending anaesthesiologist consistently fine-tunes the administration of anaesthetic substances to ensure a steady and sufficient level of anaesthesia depth. This entails maintaining appropriate levels of *hypnosis* (absence of consciousness), *analgesia* (absence of pain perception and its consequent effects on the autonomic system such as increased heart rate and blood pressure), and *muscle relaxation* (absence of movement)[1]. The management of anaesthesia, today, is mainly performed based on informed operator decisions. Several parameters are monitored during the intervention, the most common of which, among many others, are the electrocardiogram (EKG), the bispectral index (BIS), and the minute ventilation (MV) [2]. Currently, there is no universally accepted indicator to assess the adequacy of anaesthesia among anaesthesiologists. It's evident that relying on a single indicator would be insufficient for accurately assessing the appropriate levels of the three main components of anaesthesia. Consequently, during surgery, anaesthesiologists operate as multivariable feedback controllers: they monitor various patient indicators while concurrently fine-tuning and regulating the dosage and administration of multiple anaesthetic agents. This ensures the patient's health and safety [2]. The *automated anesthesia*, i.e. the connection of apparatuses and models used to make these activities automatically driven, could be seen from a modelling point of view as the control of a system with the drug infusion rate as the input and the clinical effects of drugs as output. The input is related to the output through the pharmacokinetics (PK) and the pharmacodynamics (PD) of the patient [3]. Usually, the pharmacokinetics is described by compartmental models, while the pharmacodynamics is described in terms of a single effect compartment [4],

with or without information on population [5]. Much more effective could be the robustness and the usability of the full modelling if the PK model is physiologically based, and this is the case dealt with in [6], also predicting EEG and MV. The basics for an automated system to analyse the anaesthesia levels and to control the anaesthetic drugs delivery were thus given in terms of a physiologically based PKPD model, which will be extended in the very next future to other PD parameters and developing the control model.

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In-situ production of allicin vapour from composite films to treat skin infections

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Although allicin has potent antibiotic properties, its practical use as a therapeutic agent is currently limited due to its low stability. To harness the healing benefits of this phytochemical, we propose a controlled in-situ synthesis of allicin vapour near the site of infection. Considering the critical need for novel approaches to prevent pandemic scenarios caused by multidrug-resistant bacteria, this study aims to create a compartmentalised garlic system, where substrate alliin and enzyme alliinase are physically separated in multiple layouts, i.e., film-solution, film-particles, and double-film. The antibacterial activity of in-situ formed allicin vapour against selected bacterial strains (*E. coli, S. epidermidis* and *S. aureus*) will be demonstrated using a custom film holder. This approach addresses issues linked to its limited shelf-life (rapid conversion to various compounds, high reactivity, low thermal stability, and volatility) and skin irritation caused by unrestrained allicin release. The study will also discuss the transport and diffusion of alliin to the enzyme active site, a rate-limiting step in allicin formation. This allows for the enzymatic reaction to be controlled and the antibacterial effect to be prolonged by varying the thickness and composition of the film materials. The prepared composite film may find its applications in the long-term healing of open wounds or skin-related infections alone or in conjunction with traditional antibiotics.

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