Acadamh Ríoga na hÉireann
Royal Irish Academy

Charlemont grant report

Recipient name:	Dr Kevin Moroney
Discipline and subject area:	Sciences
Amount and year awarded:	€2,024 in 2022
Title of project:	Micro-continuum modelling approach to simulate drug release from eroding porous delivery devices.

Summary of findings:

The main objective of the project was to learn about the micro-continuum modelling approach developed by Dr Cyprien Soulaine and others with a view to applying it to modelling drug release from pharmaceutical devices (e.g., tablets and granules). Dr Soulain and his group have developed this approach chiefly to simulate single and multi-phase fluid, flow and dissolution of minerals in the subsurface. Similar physical mechanisms apply to solvent flow and dissolution and transport of drug in porous devices, so there is an opportunity to adapt and leverage the models to this application. In particular, Dr Soulaine and his collaborators have developed a package in the open source OpenFOAM® software called porous Media4Foam, which is a dedicated package for solving flow transport and chemical processes in heterogenous porous media. Thus, the specific aims included completing intensive training in OpenFOAM®, and specialist training in porous Media4Foam to facilitate the implementation of advanced drug release modelling on the platform. The Charlemont grant supported this by funding a research visit to work with Dr Cyprien Soulaine who is a CNRS (French National Centre for Scientific Research) associate scientist and head of the Porous Media Research Group at the Institute of Earth Sciences of Orléans (ISTO).

The main outcomes were as follows:

- Advanced training in OpenFOAM® and porous Media4Foam: I completed intensive training in OpenFOAM® and porous Media4Foam under direct tuition of Dr Soulaine over the course of the first week of my visit. This greatly reduced the time needed to learn as a newcomer to using OpenFOAM®. In particular, this enabled me to adapt parts of the porous Media4Foam package to allow simulation of dissolution of cylindrical drug particles both for solid and porous drug particles. I continued this work in the second week of my visit and while there is still further work to do, the micro-continuum method offers an efficient way to simulate dissolution of drug particles, drug-excipient granules and tablets. Importantly, the methodology allows for evolution of particle size, shape and porosity without having to explicitly resolve the location of the solidliquid boundaries.

- Developing networks with researchers involved in experimental and modelling research in porous media: The visit afforded me the opportunities to meet a large group of people who are working on both experimental investigation and mathematical modelling of processes in porous media. In the first week of my visit, I gave a seminar on my research titled 'From coffee brewing to drug delivery:

transport processes in porous media.' This allowed me to effectively introduce myself and my research to the wider group and facilitated discussions with a number of researchers at ISTO. Their areas of application are different to my own, covering decontamination of polluted soils, carbon capture and storage microfluids, reactive dissolution and transport of minerals and permeability of rock samples using micro-computed tomography coupled with flow simulation (to name a few). However, it was interesting to see the same mechanisms and modelling challenges arising as I have seen in my own work on drug release and modelling of coffee brewing. Dr Soulaine introduced me to a number of these researchers. I met and had discussions with Dr Sophie Roman, who specialises in microfluidics experiments and we discussed the possibility of doing microfluidics experiments of drug dissolution. I also met Dr Florain Osselin who works on experimental and modelling techniques for modelling the shape of dissolving grains in microfluidic experiments. He also works on carbon capture and natural generation and extraction of hydrogen in the subsurface. He gave me a tour of some of the extensive experimental capability available in ISTO. I discussed modelling of multiphase flow and dissolution with PhD student Nathan Bernard. Nathan also does simulations of permeability on rock sample images gathered using micro-computed tomography in ISTO labs. We discussed the feasibility of imaging a pharmaceutical tablet to allow direct simulation of its permeability and effective diffusivity. Other researchers I met included PhD student Laurez Maya (reactive transport of fine particles in porous systems), Dr Saideep Pavuluri (co-developer of porous Media4Foam) and Dr Flore Rembert (temporal monitoring of dissolution-precipitation processes). From all these discussions I learned of new experimental and modelling approaches being used to study porous media in the field of geophysics, which may be equally applied to porous media such as drug delivery devices or coffee beds. This will be a valuable network for me to leverage when working on future projects of mutual interest in the area of modelling highly coupled Multiphysics problems in porous media.

- Identification of key challenges of modelling porous media with evolving structure: Dr Soulaine and I identified a number of key challenges we have in common concerning capturing microscale processes in macroscale models which arise in the micro-continuum methodology as well as other scale-up techniques. These include proper estimation of choice of model for the evolving specific surface area for dissolution (e.g. accounting for the local flow) as well as other properties like permeability and diffusivity. Furthermore, while the micro-continuum model is very efficient at modelling dissolving solid surfaces using immersed boundary conditions, it is of interest how best to ensure specific surface area model employed correctly represents reality, using for example a diffuse interface function. These topics may form the basis of future investigation.

The broad goals of the visit were achieved although work is continuing on further developments. The porous Media4Foam package was successfully used to model dissolution of a solid cylindrical drug particle, a porous cylindrical drug particle and a porous cylindrical granule consisting of a soluble drug and an insoluble carrier in 2D. However, it remains to adapt the idealised cases to assess the agreement between the modelling approaches. This work is ongoing.

Plans for continuing collaboration:

Subsequent to the visit, I attended the 'fluid flow and phase change of a solid' week-long workshop held at the Centre International des Sciences Mécaniques, in Udine, Italy on the recommendation of Dr Soulaine. This workshop was organised by Professor Piotr Szymcak (University of Warsaw, Poland) and Professors Michael Berhanu and Sylvain Courrech du Pont (Université de Paris, France) and involved presentation from leading researchers, including Dr Soulaine, in the field of porous media problems involving fluid, flow and structural evolution due to phase change. Following this I have a much broader knowledge of the state of the art research in the field. I am continuing on the work initiated in Orléans with Dr Soulaine on adapting his micro-continuum modelling approach to modelling drug release from complex porous devices. Once I have progressed sufficiently, I plan to apply to the MACSI International Visitor Programme fund to invite Dr Soulaine to the University of Limerick (UL) to present to our group and further work on this project of mutual interest.

The MACSI International Visitor Programme is an internal fund available in our group, the Mathematics Applications Consortium for Science and Industry (MACSI). Challenging extensions to consider include multiphase flow accounting for solid wettability and swelling of the solid matrix. Besides continuing our collaboration, this potential visit will allow Dr Soulaine to connect with other researchers in UL who work on topics of interest including volume-averaging and homogenisation methods for scale-up in porous media. Once we have reviewed the success of my initial work, we will assess the viability of further work to apply these methods in the pharmaceutical industry.

Published work and publication plans:

Work is ongoing to apply the micro-continuum modelling approach to drug release from (i) a solid spherical drug particle, (ii) a porous spherical drug particle, (iii) a binary drug-excipient granule with insoluble excipient and (iv) a binary drug-excipient granule with soluble excipient. These models will be compared with existing simplified models that I and others have published previously in the literature. Once complete I plan to publish this work in a journal such as the International Journal of Pharmaceutics, the Journal of Pharmaceutical Sciences, or a similar highly regarded journal in the field of pharmaceutical science. Further work on pore-scale modelling facilitated by micro-continuum modelling for a drug carrier system to determine effective transport relationships may also be pursued to include upscaling to a representative granule or tablet system. This may lead to future publications but it is too early to assess the potential for publication of this work.

Dissemination and plans for future dissemination:

It is planned to disseminate this work via contributed talks at the British Applied Mathematics Colloquium Bristol 2023 (BAMC 2023) and the European Consortium for Mathematics in Industry 2023 (ECMI 2023), while a future dissemination will also take place within the SSPC (Synthesis and Solid-State Pharmaceutical) Centre in which I am a funded investigator.

Collaborations and planned collaborations:

As detailed above, during the visit Dr Soulaine introduced me to a number of experimentalists at ISTO and the experimental capabilities there. While I haven't initiated any direct collaborations so far based on this, future opportunities may arise where projects I am involved in in SSPC (Synthesis and Solid State Pharmaceutical) Centre may require advanced microtomography imaging or microfluidics experiments. There are currently no collaborations with industry, but dissemination of our work through the SSPC network will ensure visibility of the work to the pharmaceutical industry.

Besides this, I have also discussed related work with Dr Soulaine on mathematical modelling of coffee brewing, which involves similar mechanisms of reaction and transport in porous media. I have collaborated previously in this area with Professor William Lee (University of Huddersfield, UK) and Dr Jamie Foster (University of Portsmouth, UK). I am currently working with Dr Foster on a related topic which may lead to the development of further avenues of research with Dr Soulaine's group.

Outreach and engagement activities:

I have not carried out any major public engagement activities since my trip, however, I have met prospective students at UL's open days and discussed my research. I have also engaged with the Science and Engineering faculty in UL to prepare a public lecture aimed at secondary students based around the mathematics of coffee brewing. This topic is closely related mathematically to that of reactive transport in drug delivery devices or the subsurface. It was planned to run this during Science week 2022, however, unfortunately, this was not possible for logistical reasons. I plan to develop this talk further for delivery in the future. In the meantime, I have continued to promote my research on social media and have published an article in the past in RTÉ Brainstorm which was re-promoted by RTÉ and UL for Maths Week 2022.