(ENG012) Simulation-Guided Manufacturing of Synthetic Bone

School of Engineering – Materials and Bioengineering

**Overview**

Bone disorders, fractures, injuries, and musculoskeletal problems affect millions of people worldwide (20% of adults in Europe, amounting to 25% of the total cost of illness excluding trauma) [1]. These are usually treated by drug therapies or surgeries, which often involve partial or total replacement of the diseased tissue. Today's solutions to improve bone and joint health typically involve scaffolds, which provide a template for and stimulate the formation of new bone tissues (Fig. 1a). The morphology of these scaffolds at the micrometre level is the key to the success of the bone regeneration process, controlling in particular:

1. The yield of the process (regeneration rate and the final amount of new bone tissue);
2. The porous structure and mechanical properties of the new bone tissue.

Collagen is the one of the most used material to produce scaffolds, due to its abundance in the human body, biocompatibility, absorbability in the body, etc. [1]. However, using collagen alone limits the range of scaffolds mechanical properties that can be obtained, and thus the possibility to tailor the structure and properties of the final bone tissue. This recently led to new ideas for composite collagen-polymer scaffolds. The basic principle behind these new scaffolds is that collagen and polymer molecules are conjugated in a solution, following a biorthogonal chemistry under the drive of interaction forces that depend on a previous functionalization of the molecules themselves [2]. The assembly of these molecules leads to a 3D network microstructure: a biosynthetic substrate as scaffold [3].

![Figure 1](https://example.com/figure1.png)

Figure 1: (a) Collagen fibre scaffold with precipitation of white bone mineral [1]. (b) A model morphology from simulations of nanoparticle self-assembly [6].

Collagen-polymer scaffolds can be produced with a wide variety of morphologies, thanks to the multiple design variables involved: the type, size, and concentration of collagen and polymer molecules, and the type and extent of functionalization. However, having many design variables brings the problem of effectively exploring a vast multi-
dimensional design space. The current approach for scaffold optimisation is experimental, but producing a scaffold and testing it in vitro for the formation of bone tissue is a costly process taking approximately one month per scaffold type.

The aim of this project is to develop an alternative approach for scaffold design, to cut the time and cost of the experiments by orders of magnitude. The key idea is that the experiments can be guided by novel high performance simulations of the self-assembly of collagen-polymer scaffolds and of bone tissue precipitation. These simulations would take the above-mentioned design variables as inputs, and predict the evolution of scaffold morphology and bone formation with few hours of computation. This would help shortlisting the most promising combinations of design variables, to be then tested experimentally.

There is existing science which provides a sound basis for the simulation. In the field of cement-science, molecular dynamics and nanoparticle simulations are currently used to reproduce the precipitation of mineral phases from solution, and the self-assembly of mineral nanoparticles, interacting via electrostatic forces, to form complex morphologies (Fig 1b) [4,5,6]. Mapping the simulations from cement to bone-scaffolds means that instead of mineral nanoparticles one has collagen and polymer molecules, instead of electrostatic forces one has forces induced by functionalization, and instead of cement mineral precipitation from solution (calcium-silicate) one has bone tissue precipitation (calcium-phosphate) on the scaffold.

This project will bridge between two traditionally distant fields: high-performance simulations of cement formation, and experimental synthesis of scaffolds for bone regeneration. The new resulting simulation-guided approach may revolutionise the way in which scaffolds for bone regeneration are designed and manufactured, first in silico (i.e. on a computer) and then in vitro. At the end of this project, the main outcome will be to develop by simulation and produce experimentally (in vitro) a set of new collagen-polymer scaffolds with enhanced structural and mechanical properties.

Methodology

This project combines High Performance Computing (HPC) and laboratory experiments to produce collagen-polymer scaffolds for bone regeneration. On the simulations side, the student will use a program that has been recently developed Newcastle University [6]. The student will map the current parameters that are specific to the formation of cement, onto appropriate parameters to describe the process of collagen-polymer scaffold self-assembly, and the subsequent precipitation of bone mineral, as described in the Overview section. A range of design variables will be explored with the simulations: collagen and polymer molecule size, shape and concentration, and interaction forces obtainable by functionalization. Formation of bone minerals on the resulting scaffolds will be simulated referring to hydroxyapatite (calcium-phosphate) minerals. The mechanical properties of the resulting model scaffolds and precipitated bone will be simulated too. The simulations will identify formulations and production protocols leading to optimum scaffolds.

On the experimental side, the student will prepare collagen-polymer scaffold samples, first to validate the simulations and then following the guidance of the validated simulations in order to produce the optimum scaffolds. For this, new collagen-based biosynthetic co-polymers will be prepared by using non-toxic chemistries. Two different chemistries will be explored to conjugate collagen protein to polyesters: (i) carbodiimide chemistry, and (ii) bioorthogonal click chemistry, which offers a much more scalable method of creating the co-polymer. Then, the bioactivity and biomineralisation will be assessed using the Kokubo’s method, as described in previous works [7,8].

Timeline

Year 1: Literature review on bone regeneration, scaffold production, bone and cement mineral precipitation, and particle simulations; Familiarising with the simulation platform and experimental synthesis as they are available now; Learning synthesis and programming skills.

Year 2: Mapping of cement simulations onto scaffold formation and bone precipitation simulations; Running experiments of scaffold production, bone generation, and mechanical testing, with trial-and-error choice of design variables; Validation of the simulations against the experimental results; First journal paper.

Year 3: Simulations to explore the space of design variables, searching for scaffolds with good mechanical properties and desirable porosities of the regenerated bone; Experiments guided by the simulations, implementing in vitro the optimum design solutions indicated by the simulation; Second journal paper.

Year 3 to 3.5: Preparation of the PhD dissertation.

Training & Skills
The student will learn about synthesis of scaffolds for bone regeneration, bone tissue formation mechanisms, and mineral precipitation kinetics. For the simulations, the student will learn several methods of statistical mechanics: Transition State Theory, Kinetic Monte Carlo, and molecular dynamics. They will also learn programming in C++ at intermediate level, in order to modify an existing code which interfaces with the open-source HPC simulator LAMMPS. The student will learn how to obtain mechanical properties from model structures. The experimental training will involve the functionalization of polymers and collagen molecules, the synthesis of composite collagen-polymer scaffolds with a range of formulations and morphologies, and the in vitro precipitation of bone tissue on the scaffolds. The rate of bone regeneration and the morphology of the scaffolds and final tissue will be tested using a range of techniques: thermal calorimetry, thermogravimetry, electron microscopy and Energy-dispersive X-ray spectroscopy, calcium colorimetric staining, X-ray photoelectron spectroscopy and Fourier-transform infrared spectroscopy. The mechanical performance of scaffolds and tissues will be analysed in terms of indentation strength, tension/compression tests, stress-relaxation, and rheological analysis. During the course of this programme, the student will also be trained in presenting results via scientific writing and conference presentations (posters and oral).

References & Further Reading


Further Information

This project would align with the EPSRC Centre for Innovative Manufacturing in Medical Devices (MeDe Innovation) and the Arthritis Research UK Tissue Engineering Centre, two national collaborative programmes that Newcastle is a partner in. This will offer the project, the student, and the two ECR supervisors exposure to a wide range of potential collaborators, including industrial collaborators. The University already collaborates with Collagen Solutions Ltd on the development of new collagen based biosynthetic materials.

The student will have the opportunity to collaborate with another PhD student in the school of Mathematics, Statistics, and Physics, on developing numerical methods based on the Renormalisation Group theory (Dr Gerasimos Rigopoulos), to predict also the long-term degradation and durability of the scaffolds and bone tissues.

The supervisory team: Dr. Ana Ferreira-Duarte is expert in bone regeneration and in the experimental synthesis of collagen-polymer scaffold. Dr. Enrico Masoero is expert in microscale modelling and simulation of mineral precipitation. Prof. Kenneth Dalgarno is expert in manufacturing, Deputy Director of the Arthritis Research UK Tissue Engineering Centre, and Deputy Director of the EPSRC Centre for Innovative Manufacture in Medical Devices.

Perspective candidates are encouraged to contact the supervisors Dr. Ana Ferreira-Duarte and Dr. Enrico Masoero to discuss the terms of the studentship before submitting an application: Ana.Ferreira-Duarte@newcastle.ac.uk enrico.masoero@newcastle.ac.uk.
How to apply

You must apply through the University’s online postgraduate application system. To do this please ‘Create a new account’.

All relevant fields should be completed, but fields marked with a red asterisk must to be completed.

The following information will help us to process your application. You will need to:

- insert the programme code 8090F in the programme of study section
- select PhD in Mechanical Engineering (FT) - Mechanical and Systems Engineering as the programme of study
- insert the studentship code ENG012 in the studentship/partnership reference field