Patterns of relatedness in spatially structured multicellular assemblies

Dr. Tibor Antal (School of Mathematics) and Dr. Rosalind Allen (School of Physics and Astronomy)

Multicellular organisms consist of many billions of individual cells, whose spatial location and reproduction are closely coordinated to produce a functional whole. Understanding how cells coordinate their proliferation to assemble into organised multicellular structures, and how the spatial organization of these structures influences their function, is a fundamental challenge in developmental biology and evolution, as well as having potentially important clinical implications. For example, understanding better the spatial organisation of reproducing cells in tumours might lead to better control of the spread of cancer through metastasis, while better understanding of how stem cells reproduce to form new tissue might improve our ability to produce designed structures for regenerative or therapeutic purposes. This is an area where mathematical and physical approaches have an important contribution to make: mathematics is needed to describe the evolution of a cell population including proliferation, cell death, interactions, mutations; while physical approaches can provide detailed understanding of the nature of cell-cell interactions and their consequences for the structural characteristics of the resulting cell assemblies.

We propose a new collaboration which will combine experiments and theory to study the patterns of relatedness between cells in a growing, spatially structured multicellular assembly. How do cell proliferation and death depend on spatial position? Do cells replicate everywhere at the same rate, or mainly at the edges of a colony? How does the ancestral tree of cells correlate with the cells' spatial position? Since mutations occur where cells divide the most, these questions might have broad implications. The spatial structure of mutations within growing tumors is a very new research direction in clinical studies. Spatial structure also tend to cluster related cells together, simply because the daughter cells are adjacent at cell division. Hence a given growth pattern results in some "relatedness" pattern. Related cells, on the other hand, tend to interact or cooperate better by sacrificing some individual advantages for the benefit of the community. For example, cells in a normal tissue behave cooperatively by suppressing their own reproduction, while cancer cells reproduce in an uncontrolled manner, eventually destroying the entire organism. Tracking the patterns of relatedness during the development of multicellular assemblies thus has the potential to lead to important insights; but this is a very difficult task for 3D spatial assemblies of, for example, mammalian cells.

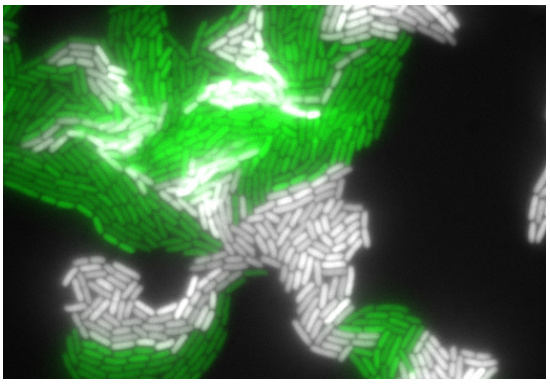

FIG. 1: Microscope image of several microcolonies of *Escherichia coli* bacteria, with differently coloured fluorescent labels, taken by PhD student Diarmuid Lloyd in Dr. Allen's lab. In this experiment several microcolonies have merged to produce complex interfaces; in the proposed project we will instead study spatial patterns of relatedness within isolated microcolonies.

In this project, we will take a simpler approach, using experiments with two-dimensional assemblies of *Escherichia coli* bacteria. In these experiments, we can track in the microscope the development of "microcolonies" of several hundred cells, from single cells, over a period of about 5 hours. Advanced image analysis software allows us to extract from the resulting movies the lineages of each cell in the microcolony, so that we can analyse the degree of relatedness between each cell and its neighbours. These experiments will be done in Dr. Allen's lab, where the technology and expertise required are already in place. To interpret these experiments, Dr. Antal plans to find the right analytical models of the cells' behavior. The exsisting tools include branching processes, coalescent theory, and branching random walks, each suited in their simplest forms to non-intercting cells. The challenge is to modify these models to account for interactions as well.

The results which we will obtain in this short project should provide an excellent basis for an application for more sustained funding from, for example, the Leverhulme Trust or EPSRC. Future avenues which we might include in such a proposal include using bacterial strains with mutations that make them behave more or less cooperatively, and studing the development of biofilms: 3D bacterial communities with important economic implications due to their ubiquitous growth on industrial devices, ship hulls and surgical implants.