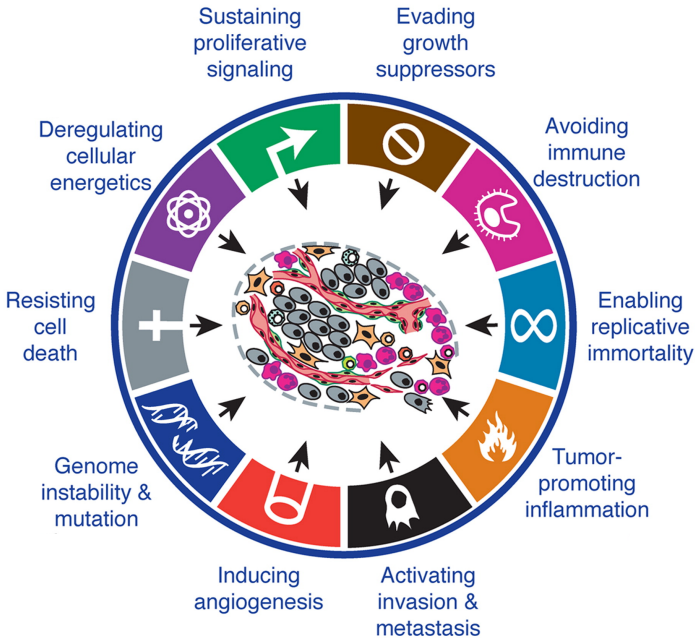
Modelling spatial heterogeneity in 3D tumour growth driven by phenotypic changes due to local oxygen concentration

Tumour masses contain spatially heterogenous populations of cells, typically structured by their local environment along with their response to that environment. Cell phenotypes (broadly categorised as behaviours specific to the cell) govern this structuring. One driver of phenotype is cell response to local oxygen concentration i.e. cell behaviour changing based on a cell's access to this vital nutrient. Hypoxia is the term given to describe tissue/cells with a low supply of oxygen. Hypoxic cells may respond aggressively, switching from healthy behaviours to more malignant ones. Indeed hypoxia is frequently indicated in the epithelial-to-mesenchymal (EMT) transition in which cells change from being proliferative, locally adhesive and with little motility to favouring motility, breaking adhesive bonds and invasion. EMT is a hallmark of cancer [1-2].

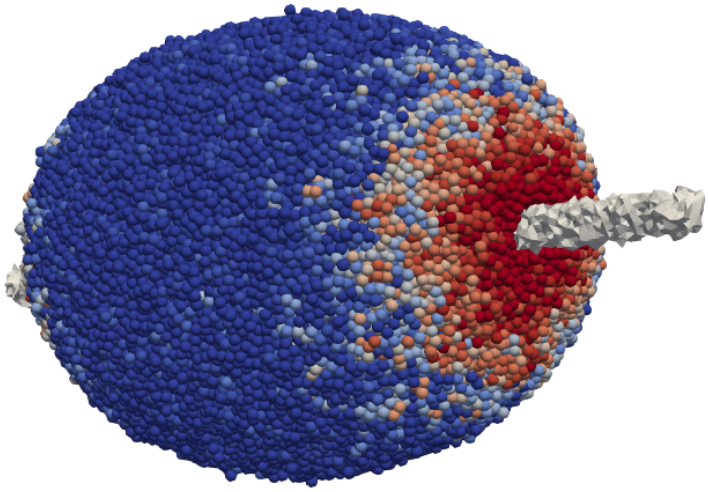


Adapted from Hallmarks of Cancer, Copyright Hanahan & Weinberg, Cell , 2011

[1] Hanahan & Weinberg, *Cell*, **2000**, doi: 10.1016/S0092-8674(00)81683-9
[2] Hanahan & Weinberg, *Cell*, **2011**, doi: 10.1016/j.cell.2011.02.013

Project Overview

In this project we will use a previously developed c++ 3D off-lattice agent-based multi-scale model [2] which simulates the behaviour of, and spatio-temporal interactions between various tumour agents (namely cells and blood vessels) to investigate how tumour growth patterns and inherent spatial heterogeneity are driven by oxygen phenotypes of cells. Within the existing model mechanical interactions between agents occur through repulsion and adhesive forces and these are coupled to a finite element solver which solves a reaction-diffusion equation for chemical substances (e.g. oxygen) which diffuse throughout the 3D tissue domain from sources (e.g. blood vessels) and are consumed by agents (e.g. cells). Agent behaviour is governed both by the mechanical interactions and changes to their phenotype. In this project we will allow cells to sample across a discrete range of phenotypes representing a continuum between normoxic and hypoxic behaviour in order to investigate how cell phenotype is structured by the local environment and how in turn cell phenotype affects patterns of tumour growth. Thus allowing us to better understand the specific mechanisms that occur in the tumour microenvironment and underpin tumour development. This project seeks to apply an agent-based approach to compare to an earlier continuous PDE formalism of phenotypic heterogeneity in vascularised tumours [3].



A mathematical model of a cylindrical tumour mass growing around a blood vessel. Phenotypic structuring shows more normoxic (well oxygenated) cells, red, closer to the vessel and hypoxic (poorly oxygenated) cells, blue, away from the vessel.

[2] Macnamara et al. doi: 10.1016/j.jocs.2019.101067
[3] Villa et al. doi: 10.1137/19M1293971

Weeks 1-2 (18th-29th July)

Goal 1. Read the 4 papers referenced above (I've attached pdfs of these to the introduction e-mail) and use as a starting point to survey the literature around this research topic.

Goal 2. Download the source code from GIT (https://github.com/CicelyKrystyna/SummerVacationProject2022) and ensure it runs. You will find instructions of how to do this in the README.md file.

Goal 3. Make sure you have Matlab (https://uk.mathworks.com/academia/tah-portal/the-university-of-glasgow-294300.html) and Paraview (https://www.paraview.org/download/) downloaded and installed. Follow the Paraview_guide.pdf to open and visualise the simulation results from Goal 2. Read through the Matlab files and execute to create plots of the results from Goal 2.

Stretch Goal: Change the model using the input.dat file. What happens when you change hypoxic_friction from 1.0 to 0.1? What happens when you change death from 0.0 to 2e-3? Investigate your own changes.

Weeks 3-4 (1st-12th August)

Goal 1. Create a new folder in examples for a new simulation. Copy the .dat .edp and .mesh files into this. Set up the new input.dat file with 64 initial cells arranged in an equally spaced grid in the z=400 plane and change the number of iterations to 3000.

Goal 2. Run simulations for the following cases: (1) *mutation_probability = 1e-1*; (2) *mutation_probability = 1e-3.* Visualise results in Paraview and Matlab and make observations.

Goal 3. Investigate the two cases above when you turn death on (*death = 2e-3*) and increase the mobility of hypoxic cells (*hypoxic_friction = 0.1*).

Goal 4. Write a short report including figures detailing your findings. A good report writing tool is LaTeX https://www.latex-project.org/ and you can create documents online really quickly using Overleaf https://www.overleaf.com/learn/latex/Learn_LaTeX_in_30_minutes

Stretch Goal: Run your own experimental simulations.

[Sign up for the math bio conference https://cbc.dcs.gla.ac.uk/]

Additional Information

Future weekly goals will be decided upon together as we go and will be largely dependent on the particular successes and your interests.

Conferences play a big part of our role as researchers. Glasgow's annual Computational Biology conference is to be held on Thursday 1st and Friday 2nd September in the brand-new ARC building on the main campus and will be free to attend. This is a great opportunity to learn more about the exciting research across computational biology at Glasgow. You can register to attend on the conference website: https://cbc.dcs.gla.ac.uk/

Soft Skills: Take the opportunity to use this project to develop your soft skills such as report writing and oral/visual presentation of your work. For example, it would be a good idea to keep a rolling report of the project.

CPD: As researchers we dedicate a proportion of our time to continual professional development. Throughout this 8 week project aim to spend up to 1.5hrs per week on CPD. This may take the form of journalling and reflecting on the week's progress. It may also be useful to use this time to develop a CV, LinkedIn profile, personal website. I would be happy to review these.

Most importantly enjoy these 8 weeks of research but also make plenty of time to rest and relax. A good researcher is a healthy and happy one!

Supervision Contract and Working Arrangements

Answer these questions. We will discuss them and agree on the boundaries for the project together at our first meeting.

	Agreement
What will your working hours be?	
Where will you work?	
How frequently will we meet?	
Where/when will we meet?	
How will we communicate?	
How much assistance do you expect?	
What is your main aim for this internship?	
Complete this sentence: *The internship will have been a success if…*	