Life after the JAI: A cross disciplinary approach to cancer research

Lucy Martin

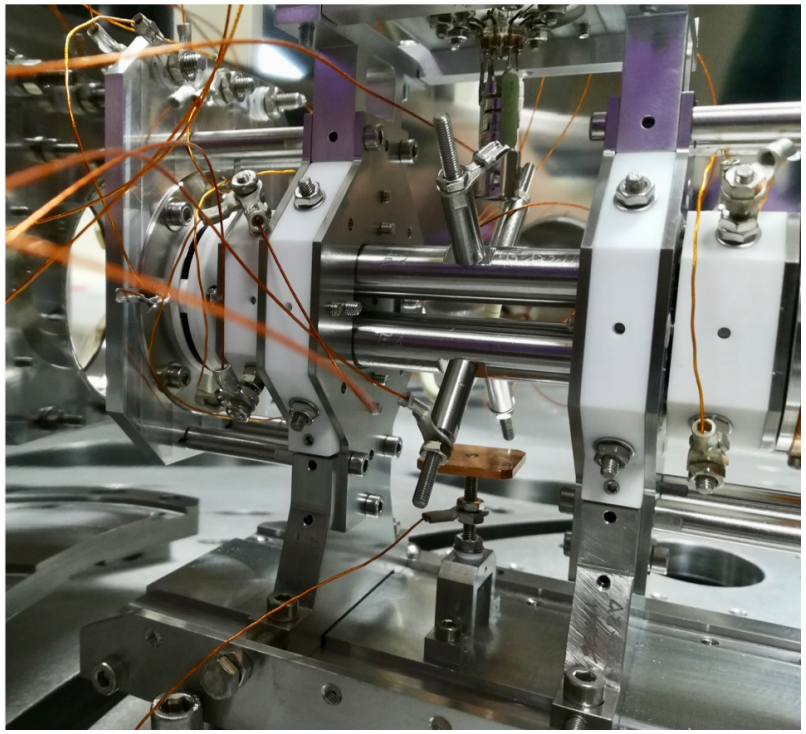
University of Edinburgh (JAI 2016-2020)

“Is this just going to be some holiday snaps from your time in Scotland?” – Chetan Gohil (2021)

- Cross disciplinary research fellow, University of Edinburgh
- Here for 4 years, already nearly 2 years in (!)
- Funded by Cancer Research UK as part of Edinburgh's brain tumour centre for excellence

What did I do as part of the JAI?

- IBEX linear Paul trap
- “Experimental investigation of Accelerator beam dynamics with a Linear Paul Trap” (2020)
- A bit of simulation, a bit of experiment, a tiny bit of maths



What do I do now?

Cross disciplinary research Fellow (XDF)

- Postdocs from maths, physics, chemistry, computer science etc. backgrounds applying their knowledge to quantitative bio-medicine.
- 3 “Cohorts”

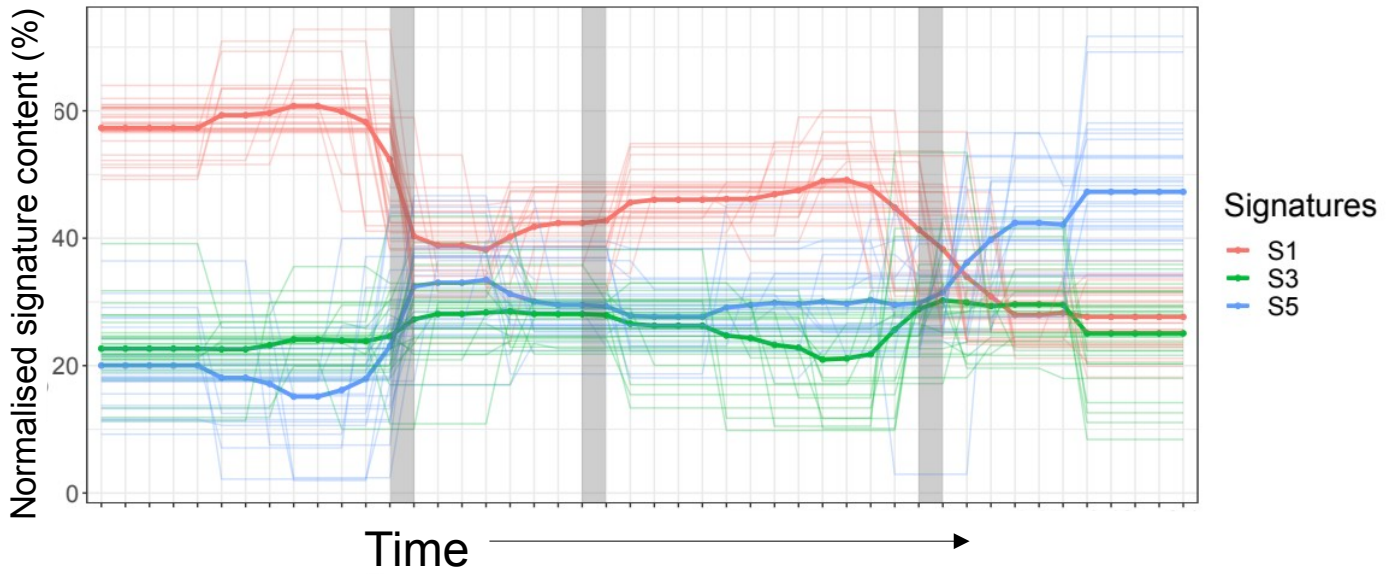
- Not just about learning the science:
  - How to find an area of research that suits your strengths
  - How to translate between biologists and computer scientists…

- Year 1:
  - ~2 months learning basic biology
  - 3× 3 month rotation projects
  - ~1 month to decide on a 3 year project
  - Write a “grant proposal” and defend project idea

Quantitative bio-medicine: rotation projects

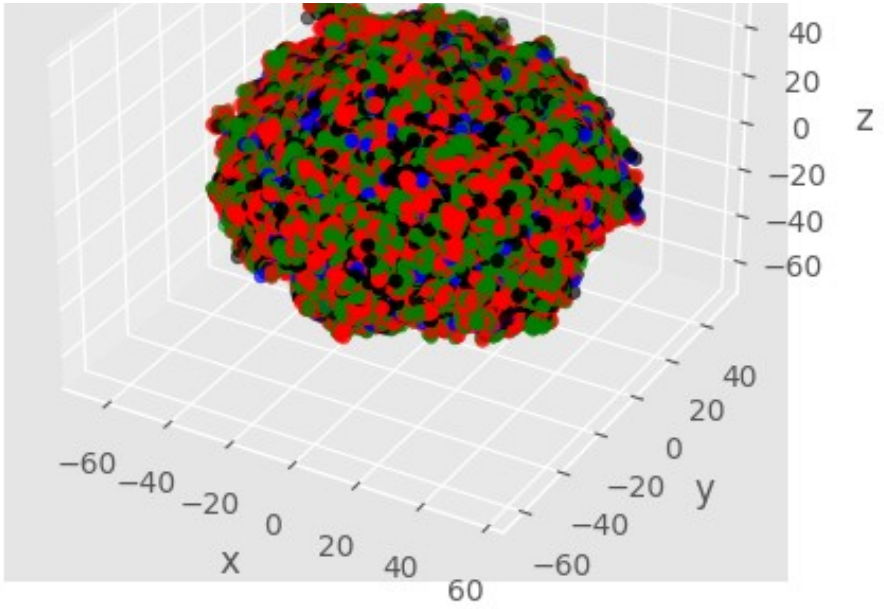
1) Timing mutational signatures in ovarian cancer

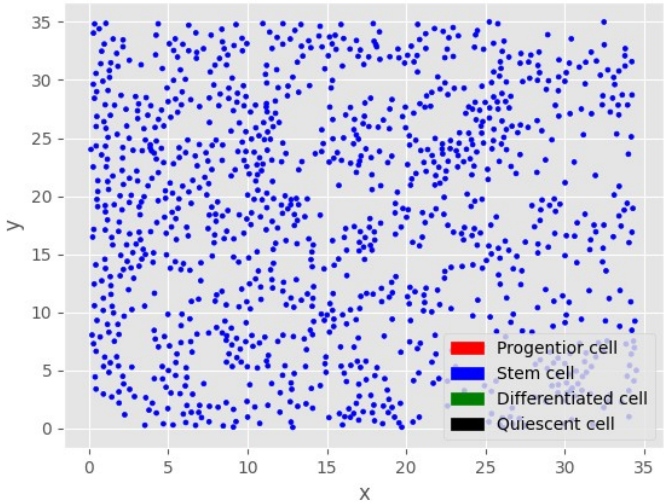
- Mutations in DNA lead to cancer
- Patterns of mutations come from different causes, e.g., smoking
- “Big(ger) data” – whole genome sequencing from tumours
- Reducing high dimensional data down to extract meaning



2) Modelling the growth and response to treatment of brain cancer

- Cancerous cells exist in a range of states which interact with each other
- We can detect these different cell states in tumour samples
- Stochastic modelling
- Image analysis
- Quantifying patterning in spatial data





Simulated distribution of a cell type

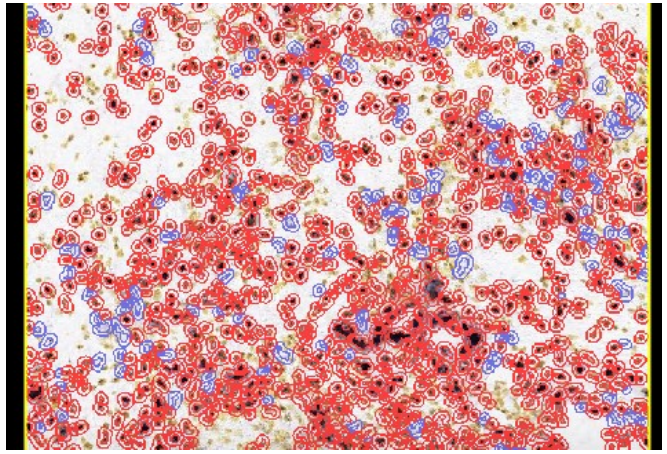


Image of patient tumour, stained to show only one cell type

A drastic change of field…

The bad bits / challenges

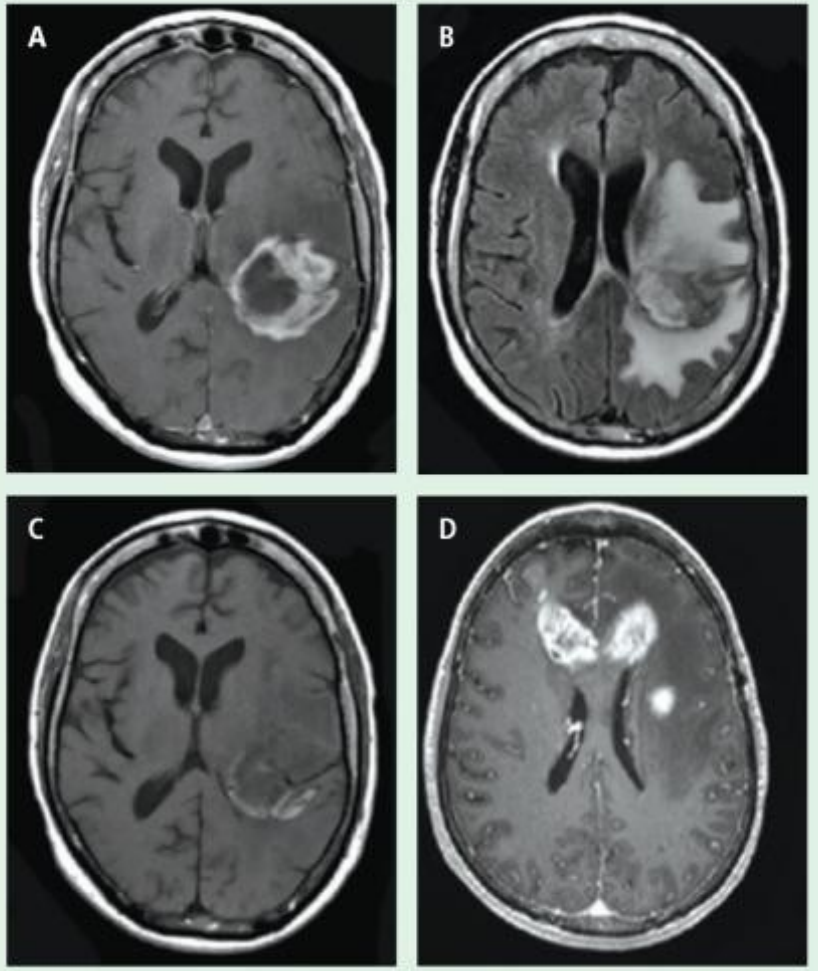
- Learning a new language
- Feeling entirely out of my depth
- Making every possible experimental mistake while learning
- Time management
- Huge quantities of literature to read

The good bits

- Huge quantities of literature to read
- Collaborative/ interdisciplinary environment
- Learning from experts
  - Dedicated facilities
- Learning grant writing, etc.
- Creative problem solving
- Research freedom

My next 3 years of research: Glioblastoma

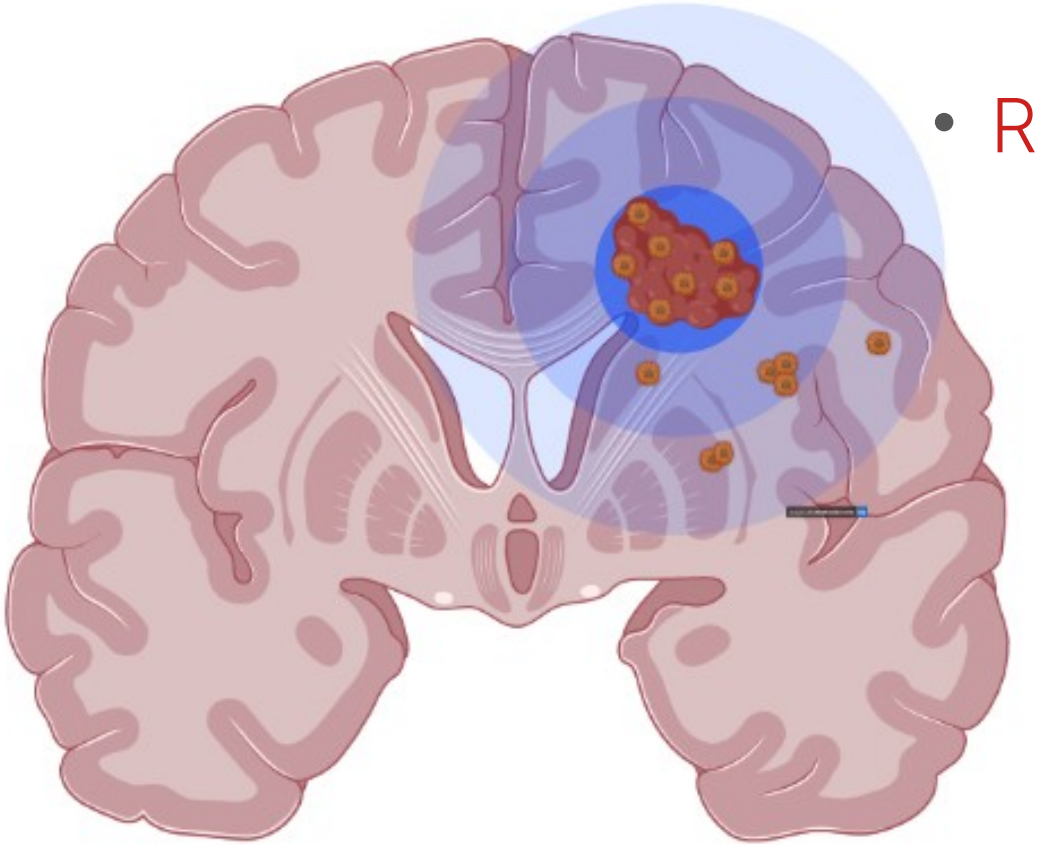
- Glioblastoma (GBM): Most common brain cancer, aggressive and fatal.
  - Median survival ~15 months
- Tumour has very diffuse edges
  - Hard to remove with surgery
- Tumours are very heterogeneous
  - Difficult to treat with drugs



A—T1 post-gadolinium contrast with dense rim enhancement; B—axial flair showing extensive vasogenic edema causing mass effect on the left lateral ventricle; C—T1 pre-gadolinium showing hemorrhage (white areas) along posterior lateral margin of tumor; D—multifocal bihemispheric disease

Davis, M. E. et al. Clin J Oncol Nurs. (2016)

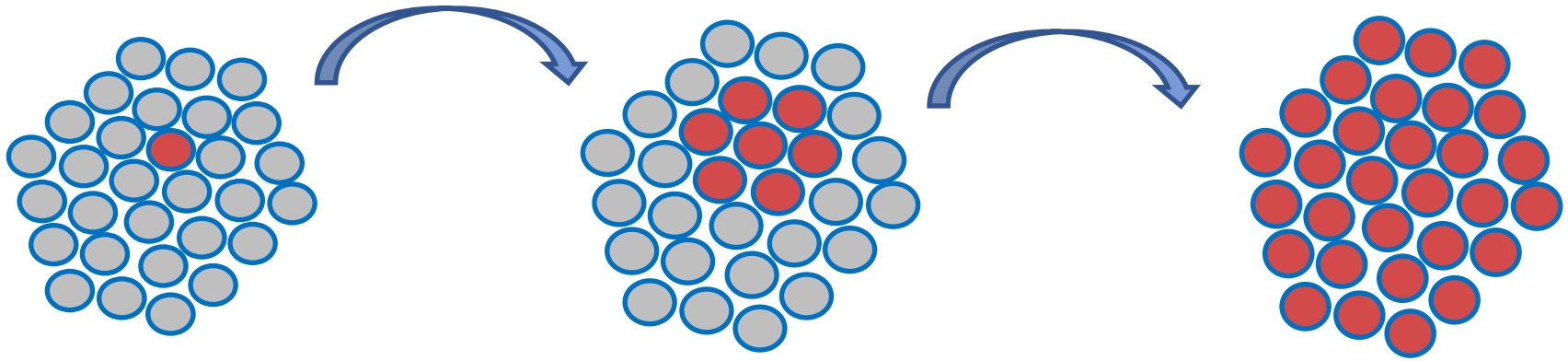
Radiation treatment



- Radiation → DNA damage → Apoptosis, Senescence, Proliferation

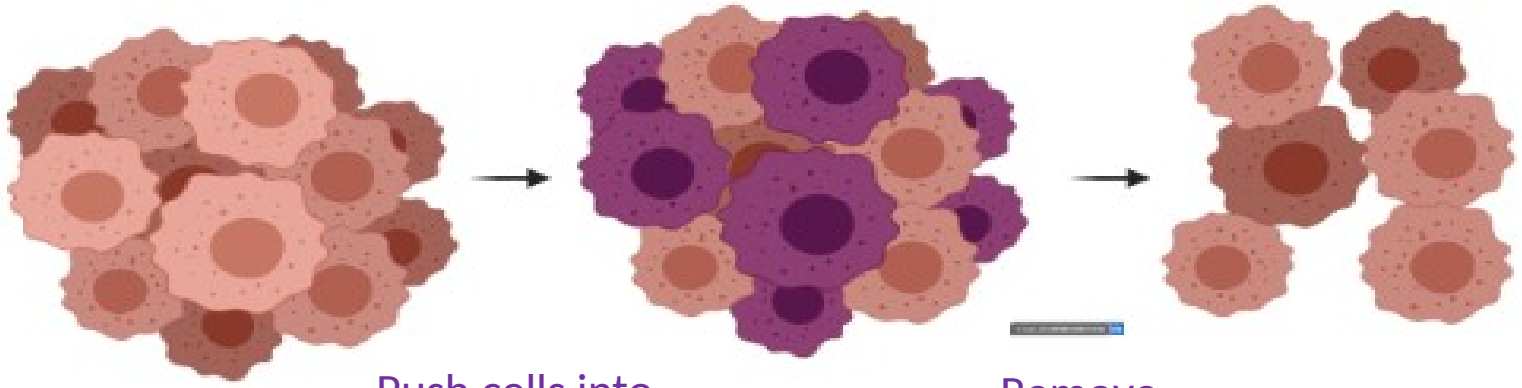
Senescence

- Damaged cells stop growing and dividing but still produce proteins
- Helpful in the short term in wound healing and cancer prevention
- Senescent cells produce proteins which can lead to chronic inflammation
  - Age related diseases
  - Tumour recurrence
- Senescence can spread
- Very little understanding of the spread of senescence



Can senescent cells be removed?

We can do something about senescent cells with senolytics



Push cells into senescent state

Remove senescent cells

= A “two punch” strategy

- Push cells into a senescent state
- Maximise senescence
- Remove senescent cells
- Effective treatment

Project Proposal

"Induced senescence in glioblastoma radiation therapy – Inferring dynamics of senescence spread with simulation, in vitro and in vivo experiments."

- Stochastic simulation
- Pattern recognition/ clustering
- Single cell "big data"
- Bayesian inference
- Tissue culture
- Probabilistic description
- Fluorescence microscopy

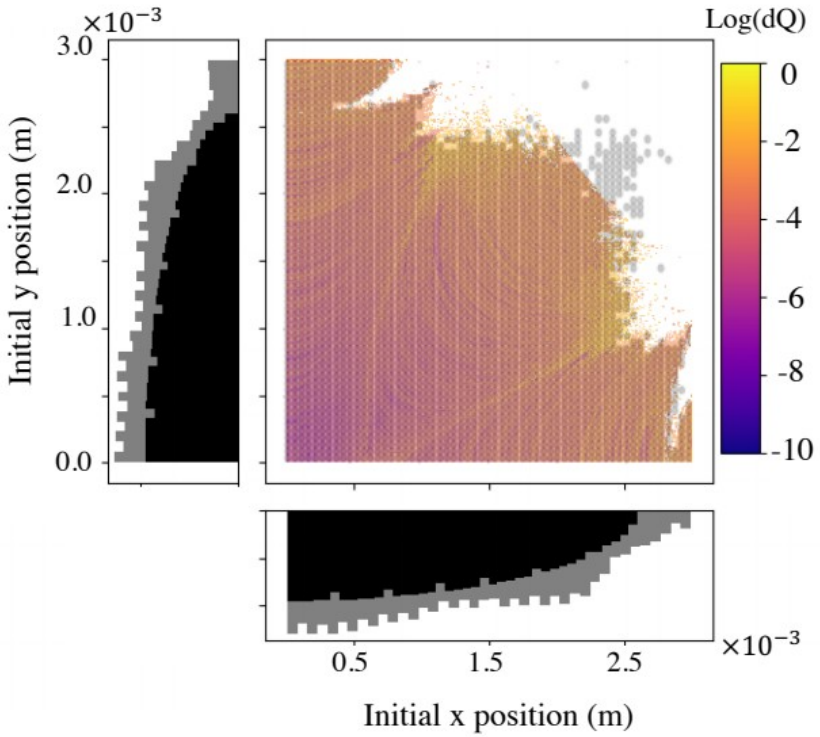
… but is this really that different from accelerator physics?

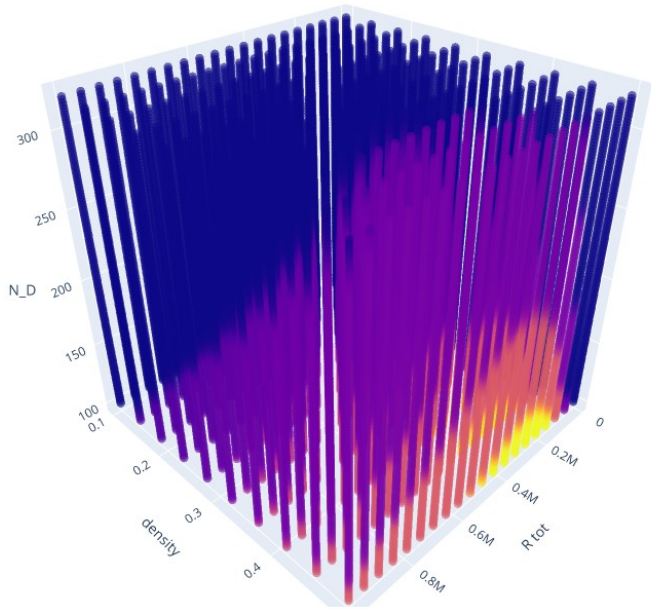
An approximate analytical description of a system...

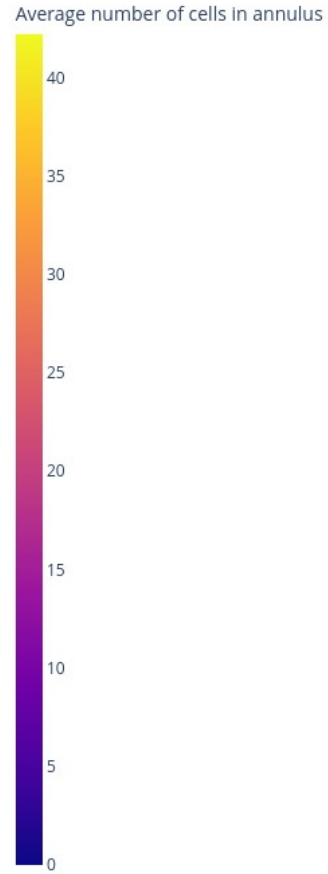
$$\frac{d^2a}{ds^2} + K_a(s)a - \frac{\epsilon_x^2}{a^3} - \frac{K_{\mathrm{sc}}}{2(a+b)} = 0,$$
$$\frac{d^2b}{ds^2} + K_b(s)b - \frac{\epsilon_y^2}{b^3} - \frac{K_{\mathrm{sc}}}{2(a+b)} = 0.$$

$$P(T \leq t) = 1 - e^{\lambda_{spread}t}$$

Computationally intensive simulations…







Fiddly experimental setup…

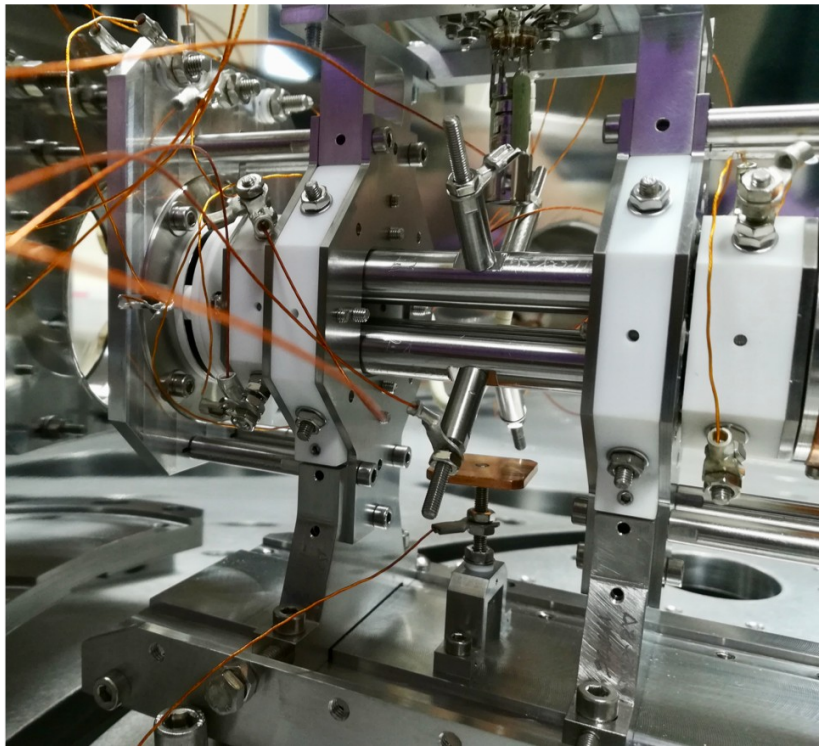
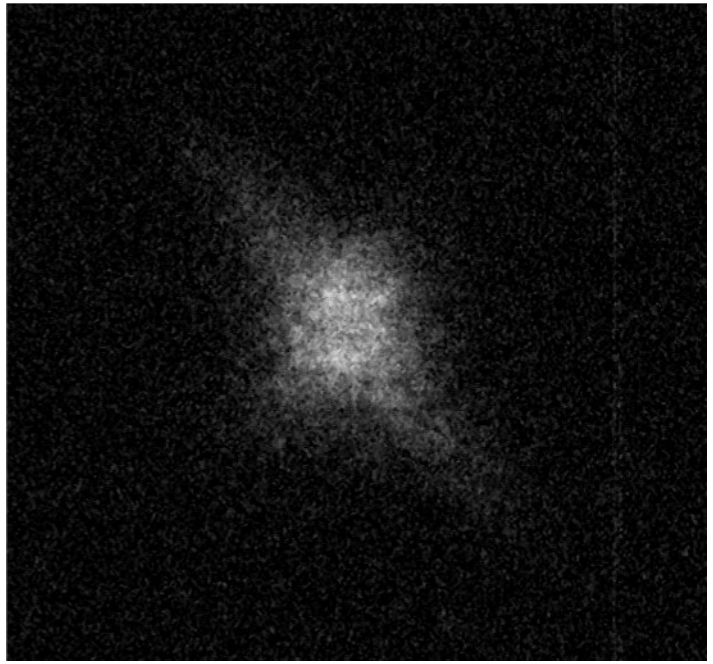
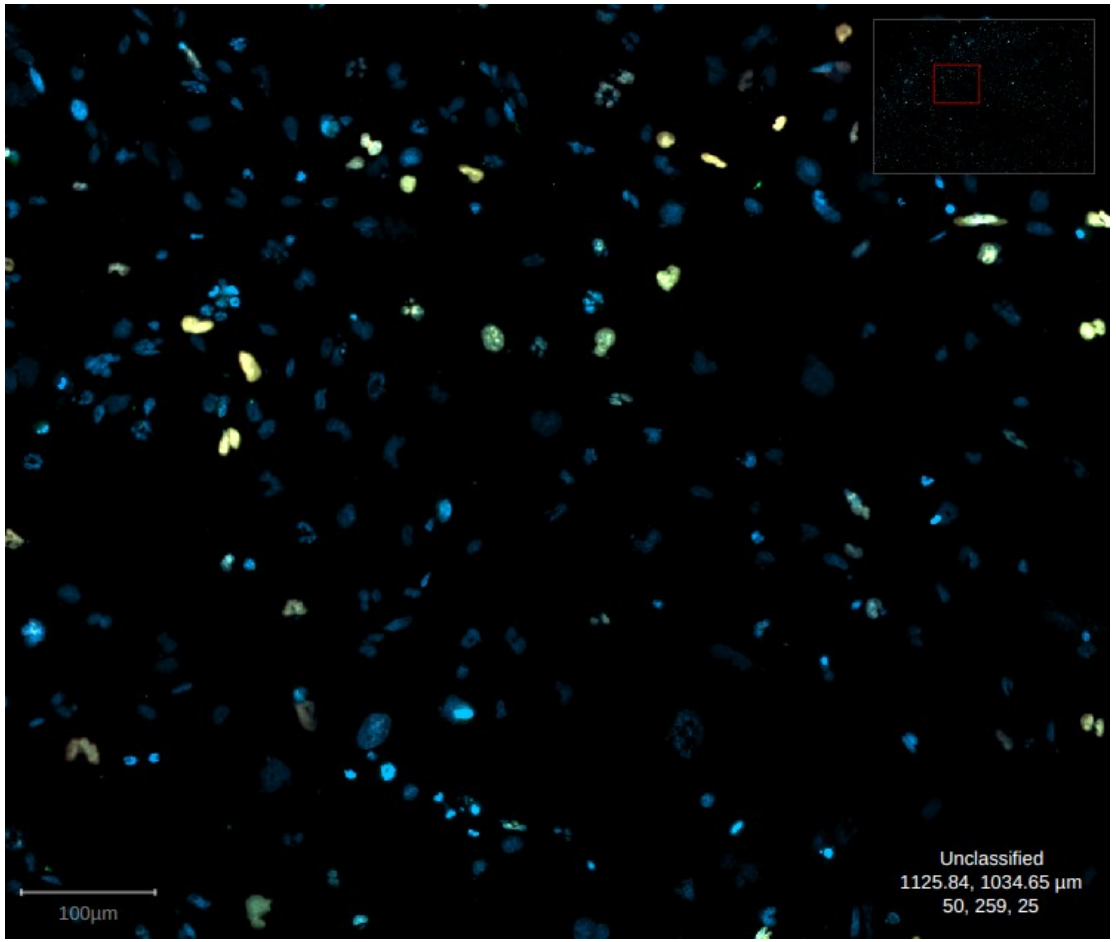
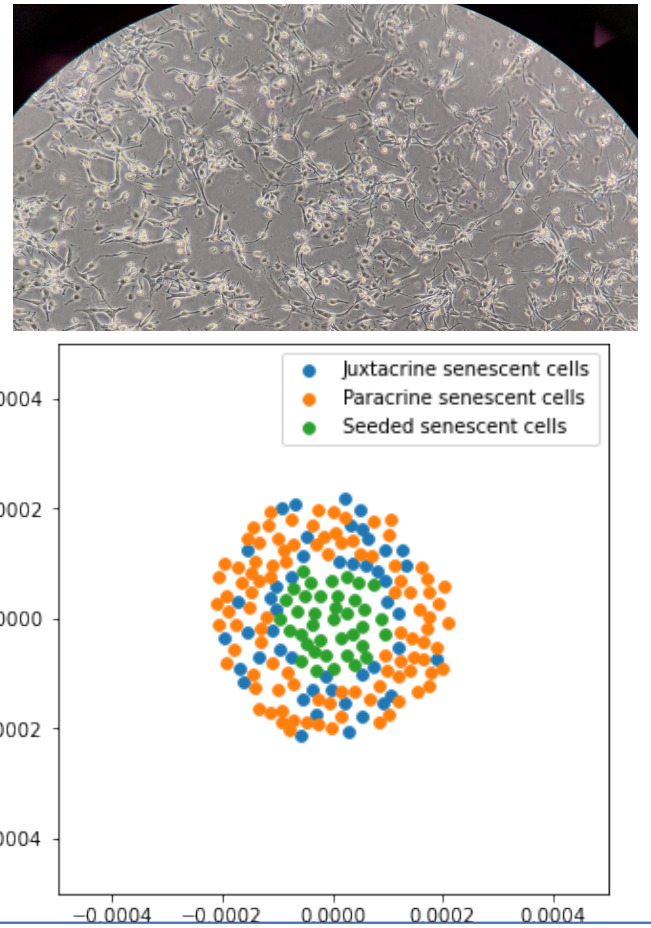


Image analysis…





Using a simplified model of a real system...



So maybe not!

Thanks!

The University of Edinburgh
Cancer Research UK
XDF Directors
Chandra lab, Schumacher lab, Pollard lab