IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Biomathematics in the development of personalised medicine in oncology – clinical perspectives

Alastair M Thompson

MD Anderson Cancer Center

athompson1 @ mdanderson.org

IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Disclosure slide

No disclosures relating to this presentation

Disclosure slide

No disclosures relating to this presentation

Clinical perspectives

- How you already use mathematical formulae and modelling
- Prognostic and predictive biomarkers
- Cell, intercellular and tissue level modelling
- Modelling DCIS
- Where to next?

Clinical perspectives

- **How you already use mathematical formulae and modelling**
- Prognostic and predictive biomarkers
- Cell, intercellular and tissue level modelling
- Modelling DCIS
- Where to next?

Clinical perspectives

- Medical oncology: BMI; GFR; response to chemotherapy
- Bench scientists: primers/conditions for PCR
- Radiotherapy planning: modelling dosimetry
- Pathology: grade 1-3; Nottingham Prognostic Index; RCB score
- Surgery: operative incision planning
- Statistics: simple and complex tests

Clinical perspectives

Bioinformatics for gene expression data

- Mammaprint
- Oncotype Dx (invasive ?and DCIS)

Bioinformatics for predictive scoring (ER+):

- SET index
- PEPI
- Endopredict

Clinical perspectives

Composite mathematical modelling of everyday use:

- Adjuvant! Online
- Predict score (includes HER2; symptomatic v screen detected)

Combines clinical and pathology data to guide therapeutic decision making

Clinical context

- Prognostic and predictive biomarkers
- Cell, intercellular and tissue level modelling
- Modelling DCIS

Clinical context

- Prognostic and predictive biomarkers
- Cell, intercellular and tissue level modelling
- Modelling DCIS

- Lack of boring formulae

Clinical context

- Prognostic and predictive biomarkers
- Cell, intercellular and tissue level modelling
- Modelling DCIS

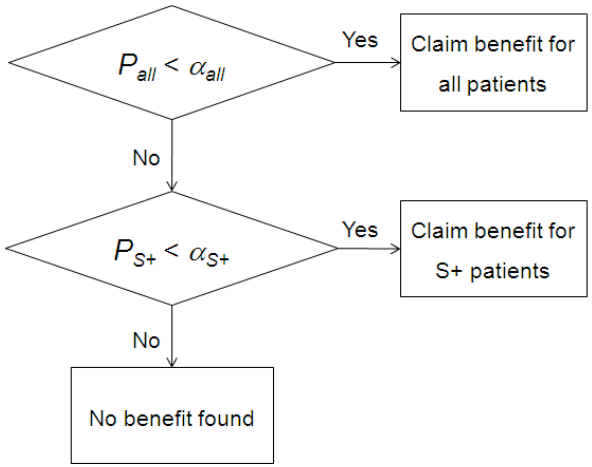
- Lack of boring formulae

Biomarkers as treatment modifiers

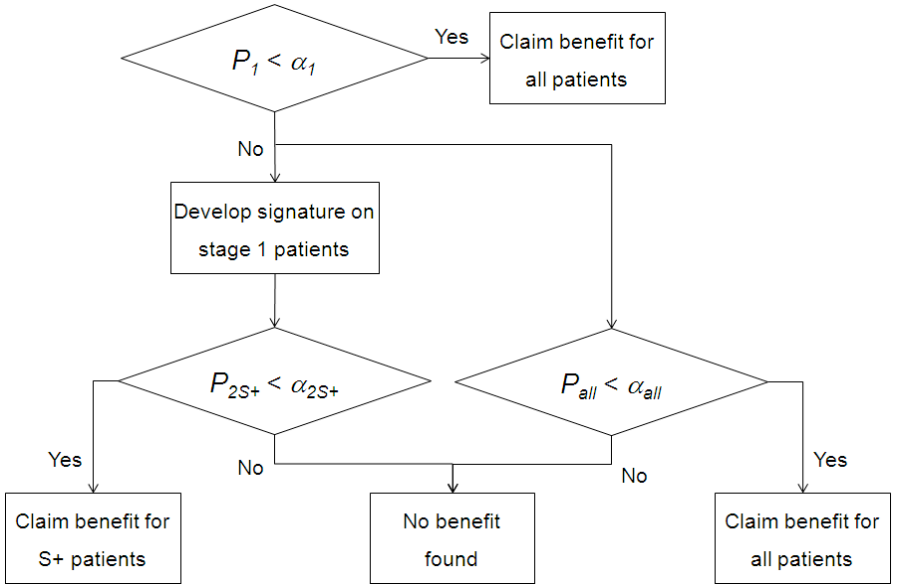
- Issues around prognostic and predictive biomarkers: interactions, cross validation (and examples)
- Need for some different thinking: predictive, prognostic markers……to gene signatures developed on RCT data as treatment modifier
- Challenges in controlling confounding

Biomarkers as treatment modifiers

Prospective subset testing



Two-stage adaptive signature design



Buyse, Michiels, Curr Op Onc 2013; Freidlin et al CCR 2010

Clinical context

- Prognostic and predictive biomarkers
- **Cell, intercellular and tissue level modelling**
- Modelling DCIS

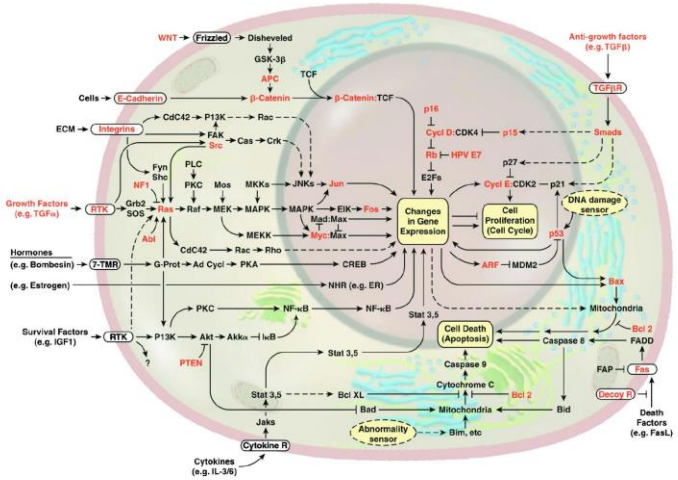
IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

From cellular to tissue level

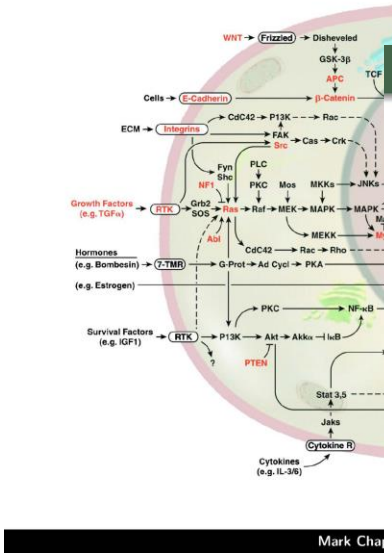
Intracellular modelling: Gene regulatory networks



Mark Chaplain | The excitement of cancer modelling

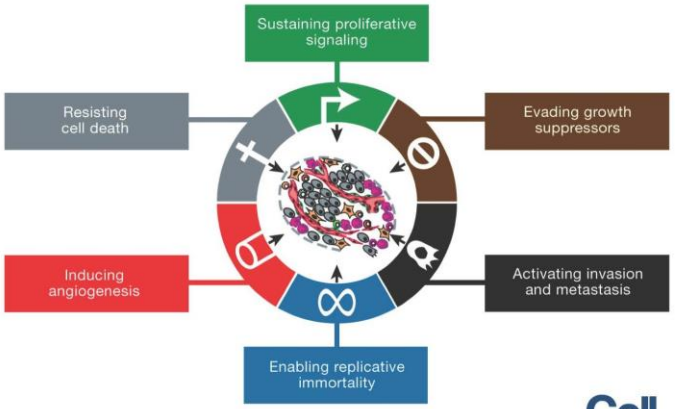
From cellular to tissue level

Intracellular modelling: Gene regulatory networks



Mark Cha

The Hallmarks of Cancer



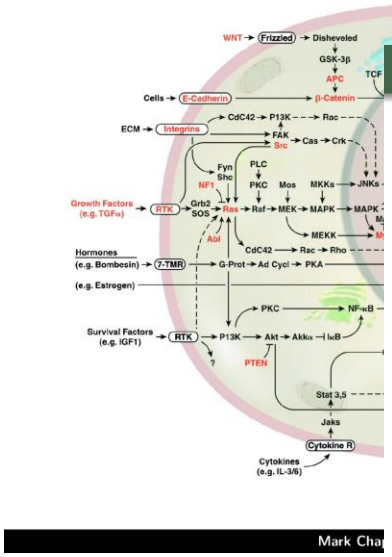
Hanahan and Weinberg, 2011

Cell PRESS

Mark Chaplain | The excitement of cancer modelling

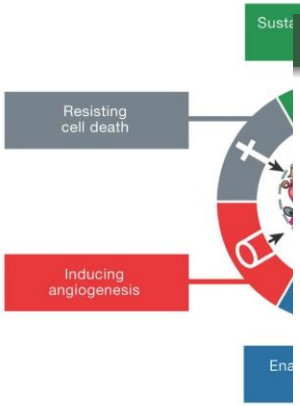
From cellular to tissue level

Intracellular modelling: Gene regulatory networks



Mark Cha

The Hallmarks of Cancer



Hanahan a

Mark Chap

Tissue scale modelling: Cancer invasion

Model extension - multiple cancer cell populations via mutations:

$$\frac{\partial c_1}{\partial t} = \nabla \cdot [D_{11}\nabla c_1 - \mathcal{A}_1(c_1, c_2, v)c_1] + \mu_{11}c_1(1 - c_1 - c_2 - v) - \delta c_1 F(t, v) \quad (7)$$

$$\frac{\partial c_2}{\partial t} = \nabla \cdot [D_{12}\nabla c_2 - \mathcal{A}_2(c_1, c_2, v)c_2] + \mu_{12}c_2(1 - c_1 - c_2 - v) + \delta c_1 F(t, v) \quad (8)$$

$$\frac{\partial v}{\partial t} = -\gamma m v + \mu_2(1 - c_1 - c_2 - v)^+ \quad (9)$$

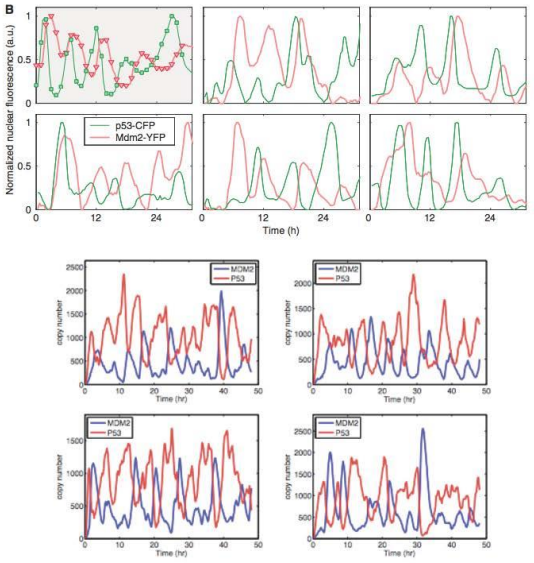
$$\frac{\partial m}{\partial t} = \nabla \cdot [D_3\nabla m] + \alpha_1 c_1 + \alpha_2 c_2 - \lambda m \quad (10)$$

with the conversion function

$$F(t, v) = H(t - t_{12}) \cdot H(v - v_{min}).$$

From cellular to tissue level

Intracellular modelling: p53-Mdm2 System

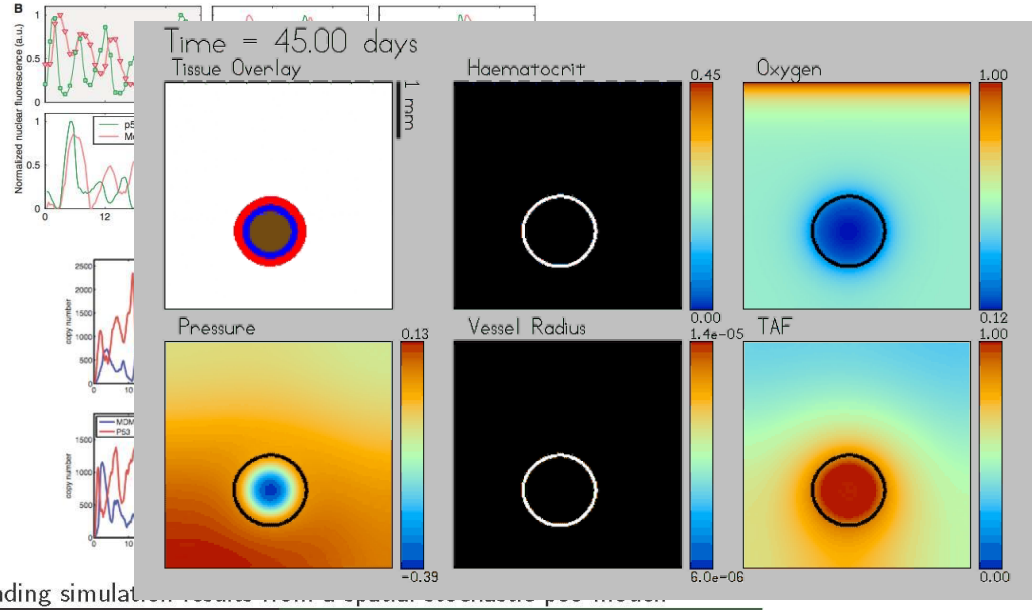


Corresponding simulation results from a spatial stochastic p53 model.

Mark Chaplain | The excitement of cancer modelling

From cellular to tissue level

Intracellular modelling: p53-Mdm2 System



Corresponding simulation results from a spatial stochastic PDE model

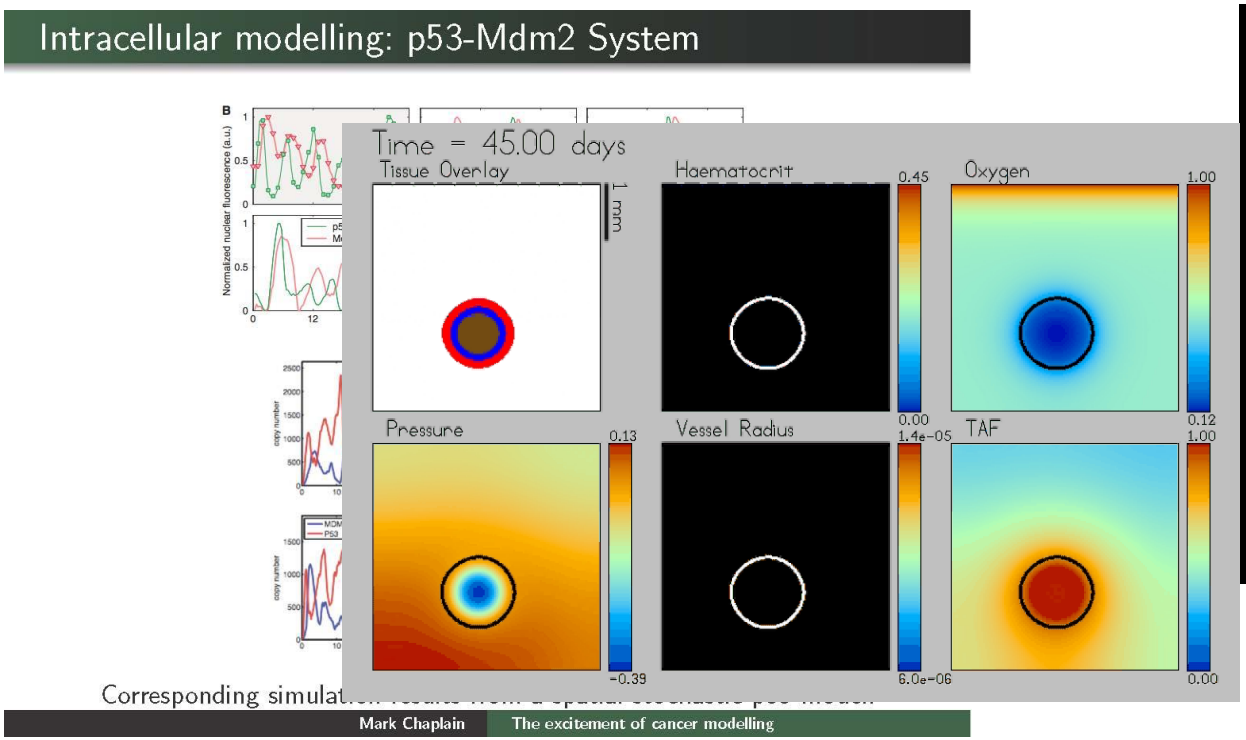
Mark Chaplain | The excitement of cancer modelling

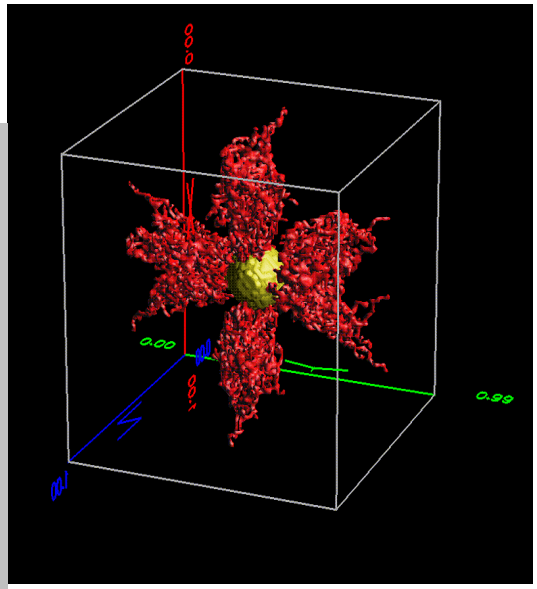
IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

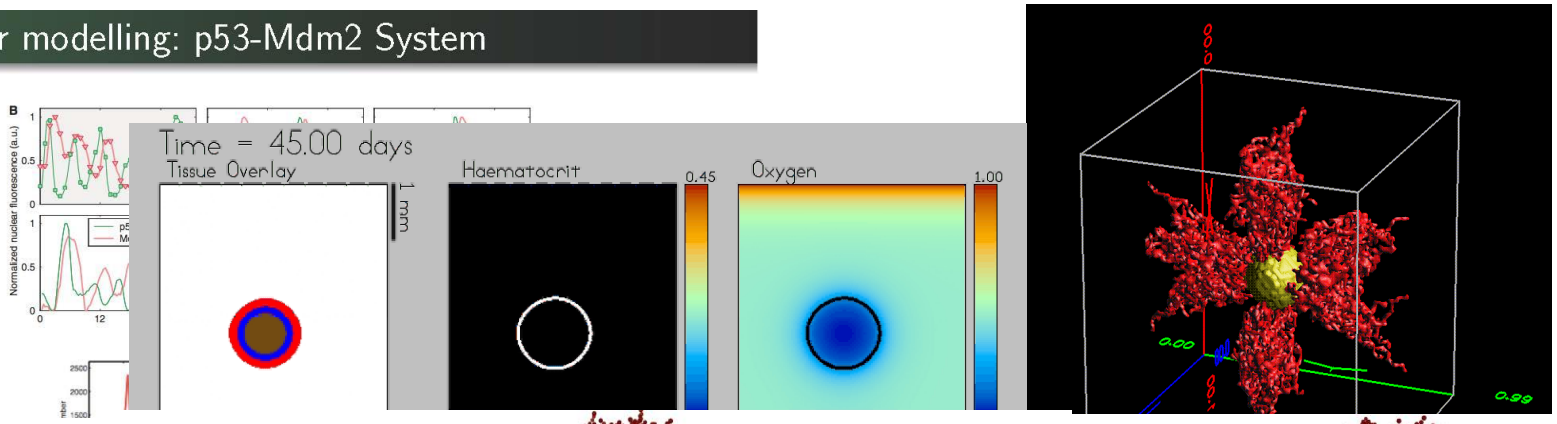
From cellular to tissue level

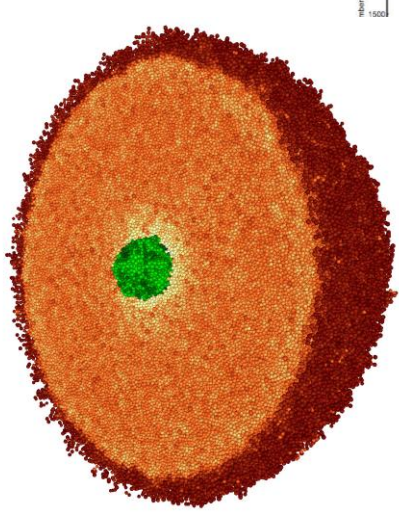


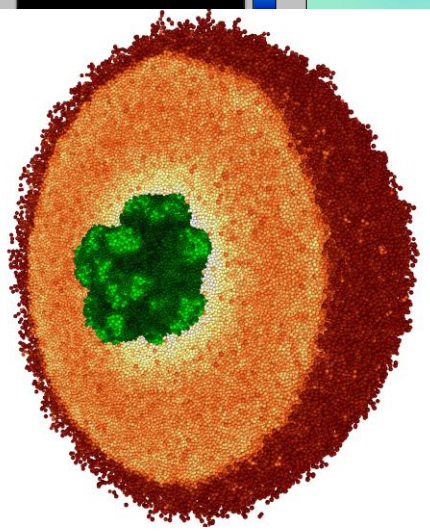


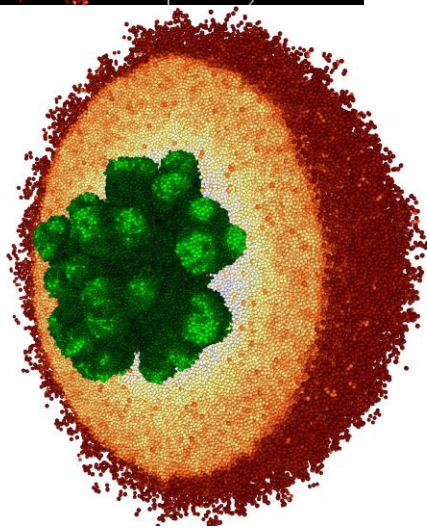
From cellular to tissue level

Intracellular modelling: p53-Mdm2 System









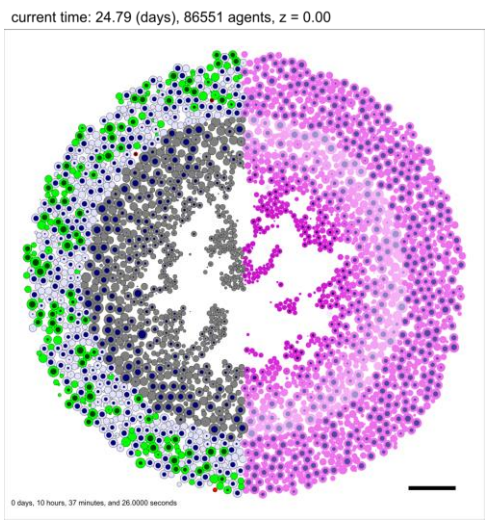
Clinical context

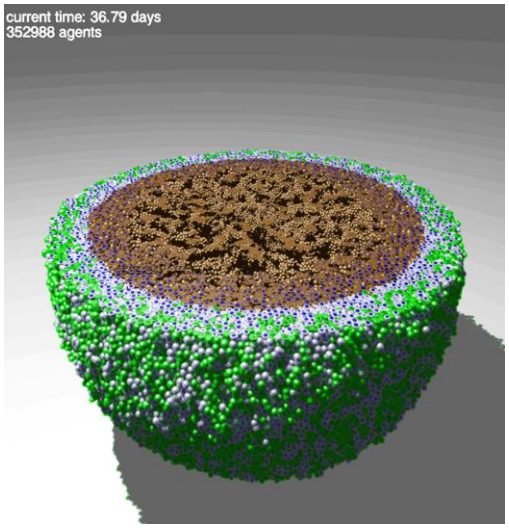
- Prognostic and predictive biomarkers
- Cell, intercellular and tissue level modelling
- **Modelling DCIS**

IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

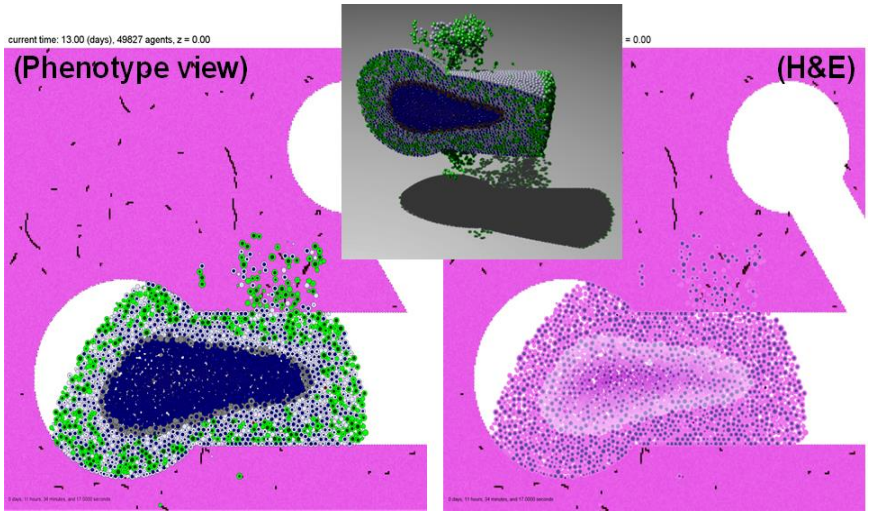
DCIS





Via 2D & 3D

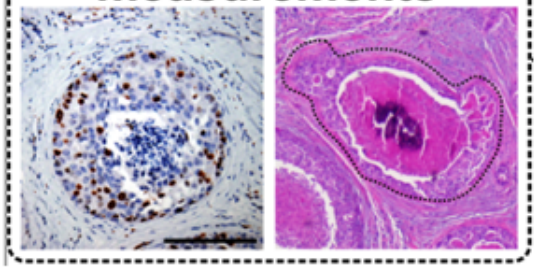
By way of: cell line, spheroids, mice & pathology



Invasion

Calibrating simulations + pathology

Patient pathology measurements



Math Analysis

$$0 = \begin{cases} D\sigma'' - \lambda\sigma & 0 < x < \langle T \rangle \\ D\sigma'' - \Lambda_0\lambda\sigma & \langle T \rangle < x < \langle R_{burr} \rangle \end{cases}$$

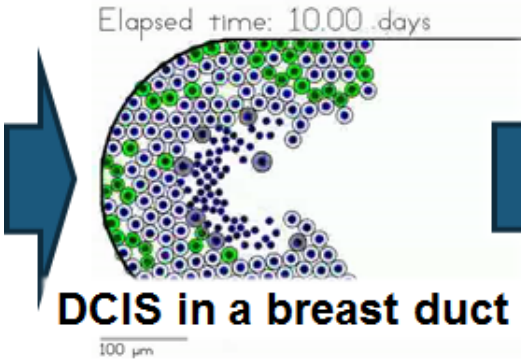
Microenvironment estimate

$$\begin{aligned} \frac{dPI_1}{dt} &= \langle \alpha_P \rangle (1 - PI_1 - PI_2 - AI) - \frac{1}{\tau_1}\left(PI_1 + PI_1^2\right) \\ \frac{dPI_2}{dt} &= \frac{2}{\tau_1} PI_1 - \frac{1}{\tau_2} PI_2 - \frac{1}{\tau_1} PI_1 PI_2 + \frac{1}{\tau_A} AI \cdot PI_1 \\ \frac{dAI}{dt} &= \alpha_A (1 - AI - PI) - \frac{1}{\tau_A}\left(AI - AI^2\right) - \frac{1}{\tau_P} AI \cdot PI \end{aligned}$$

Phenotype: cell cycle timescales

XML Representation:

This was an early digital cell line!

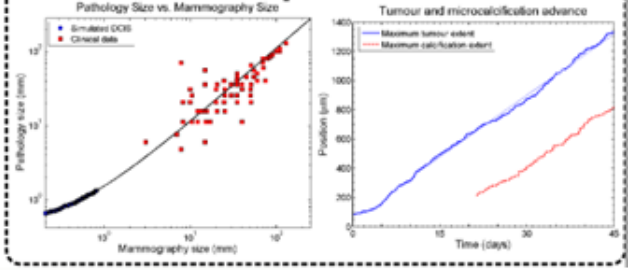


DCIS in a breast duct

XML Representation:

Digital snapshots!

clinical predictions



Clinical perspectives

- ✓ How you already use mathematical formulae and modelling
- ✓ Modelling DCIS
- ✓ Cell, intercellular and tissue level modelling
- ✓ Prognostic and predictive biomarkers
- **Where to next?**

IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

If you are interested……..

- Treatment modifiers: in your RCT design? stefan.michiels@gustaveroussy.fr
- Multiscale modelling: your lab data or clinical trials? Laboratory data for protein expression, tissue oxygenation, cancer, stromal and vascular cells chaplain@maths.dundee.ac.uk
- Heterogeneity? Clonal evolution?
- Modelling tumour responses to chemotherapy

IMPAKT BREAST CANCER CONFERENCE

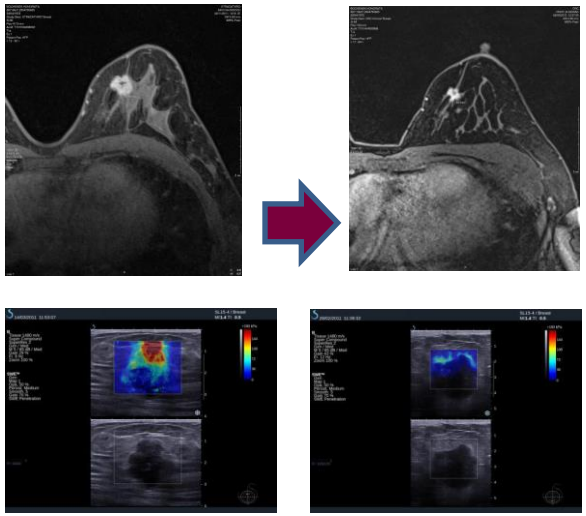
IMProving cAre and Knowledge through Translational research

BREAKTHROUGH BREAST CANCER

UNIVERSITY OF DUNDEE

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

- Using mathematical modelling to predict and measure response to neoadjuvant chemotherapy through novel imaging, tissue analyses and modelling of *peritumoral* tissues:



- ❖ Imaging responses
- ❖ Tumor and stromal immunohistochemistry
- ❖ Stromal fibroblast gene expression
- ❖ TNBC or HER2+ cancers

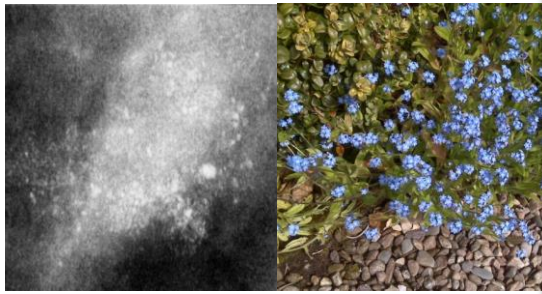
IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

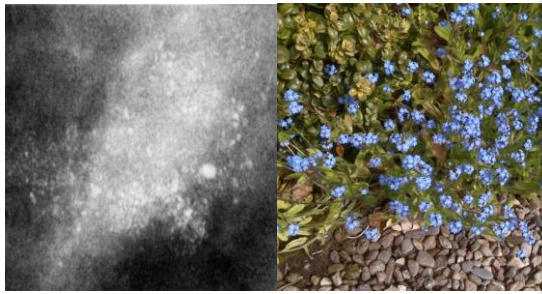
If you are interested……..

- DCIS non-treatment study: patients (20) mammographic DCIS "forget-me-not" study



If you are interested……..

- DCIS non-treatment study: patients (20) mammographic DCIS
- DCIS Modelling: LORIS trial
  - RCT of surgery v observation
  - for low risk DCIS



LORIS
The Low Risk DCIS Trial

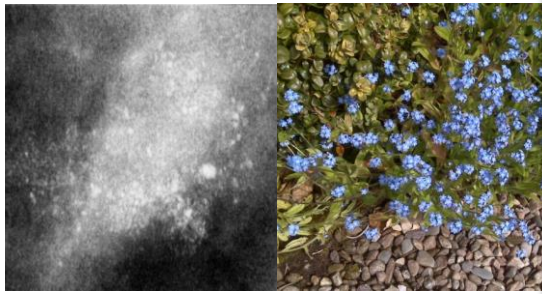
IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

If you are interested……..

- DCIS non-treatment study: patients (20) mammographic DCIS
- DCIS Modelling: LORIS trial
  - RCT of surgery v observation
  - for low risk DCIS
- Testing growth over time of DCIS using imaging & pathology biopsy data
- Progression from DCIS



LORIS

The Low Risk DCIS Trial

paul.macklin@usc.edu

Biomathematics and personalised medicine in oncology

- We are using biomathematics already!
- Could help us design “smarter” clinical trials
- Potential for modelling response to drug therapy, extent of surgical excision, likelihood of progression of DCIS
- Great opportunity for cross discipline working

How to make sense of this:

How to make sense of this:

"You're the first scientist to make sense of cancer"

IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

athompson1 @ mdanderson.org