Mathematical Modelling of Cancer from Cell to Tissue Level

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Talk Overview

- Intracellular modelling
  - gene regulatory networks
- Cell-scale modelling
  - *in vitro* cell migration and retinal angiogenesis
- Tissue-scale modelling
  - cancer invasion
- Future perspectives

Mathematical Modelling

"The Zeonians came with the answers to many secrets of the universe. Vern, regrettably, came with thick glasses and his deer rifle."

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Mathematical Modelling

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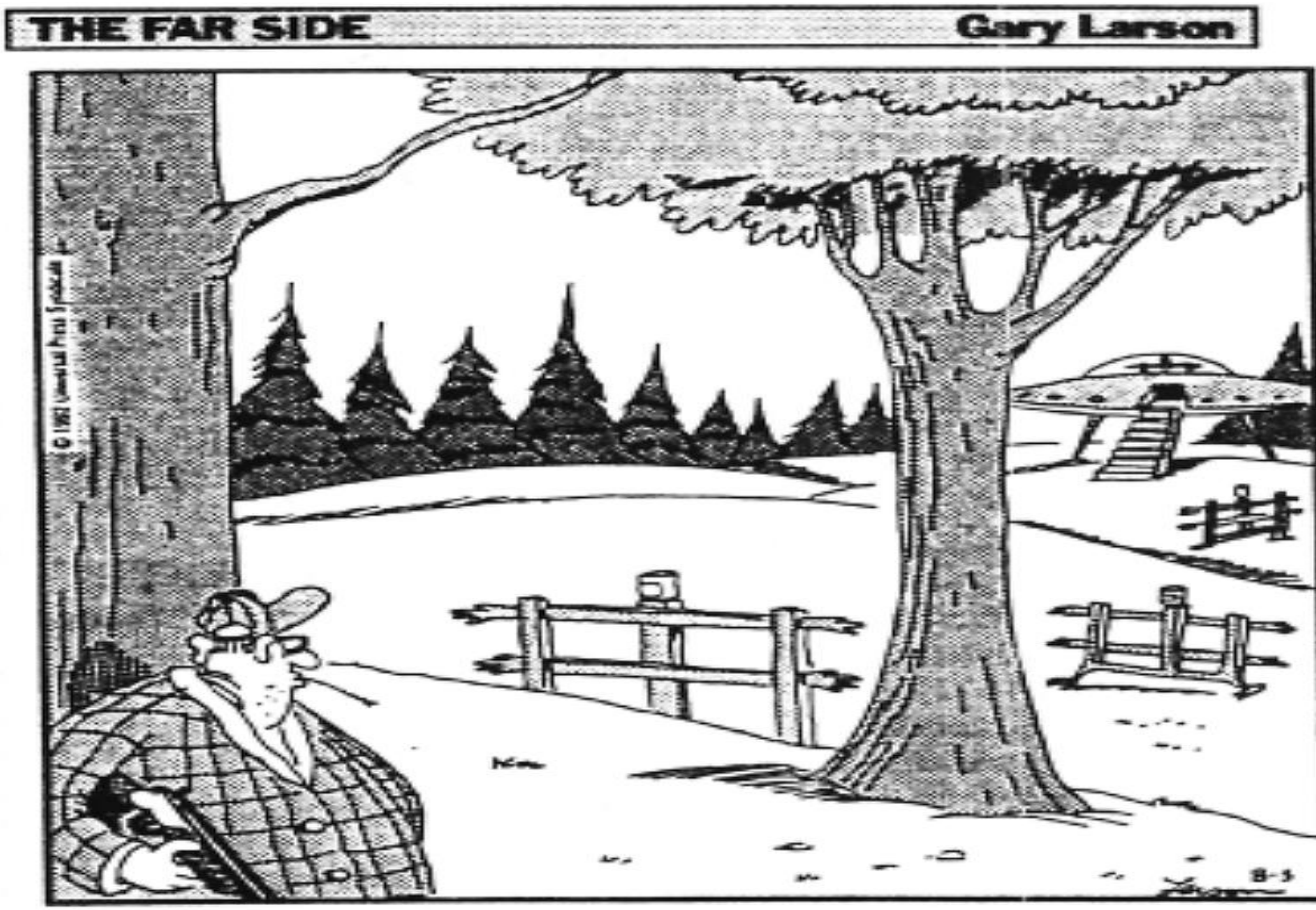
Mathematical Modelling at IMPAKT 2014

"The participants came with the answers to many secrets of Breast Cancer. M. Chaplain, regrettably, came with some mathematics and his equations."



The Zeonions came with the answers to many secrets of the universe. Vern, regrettably, came with thick glasses and his deer rifle.

The Art of Mathematical Modelling

Definition: Mathematical Model

A mathematical model is a description of a system using mathematical terminology

The process of developing or creating a mathematical model is known as mathematical modelling

Applications of Mathematical Modelling: Weather Forecasting

The Hallmarks of Cancer

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†
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evolve progressively from normalcy via a series of pre-malignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
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[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
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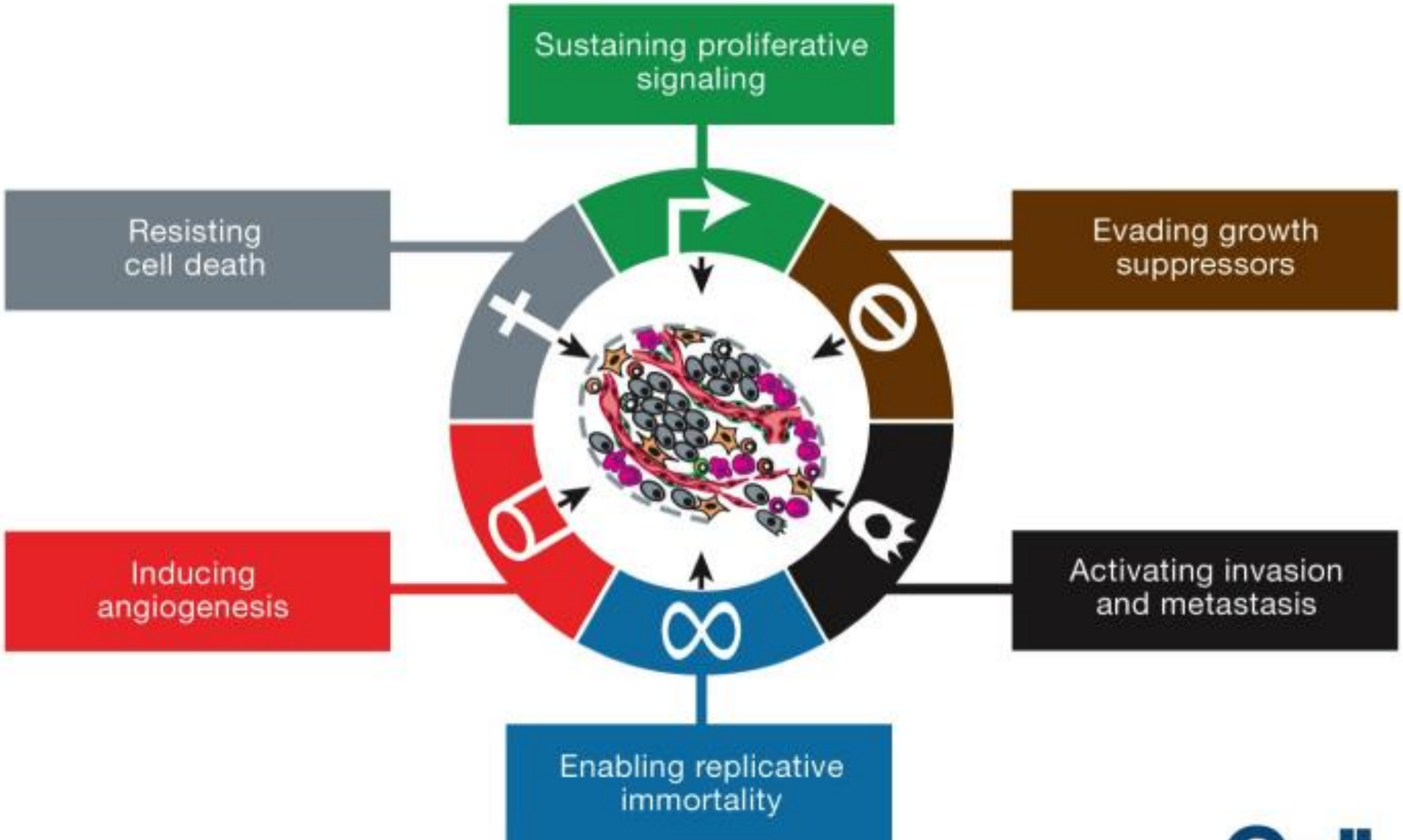
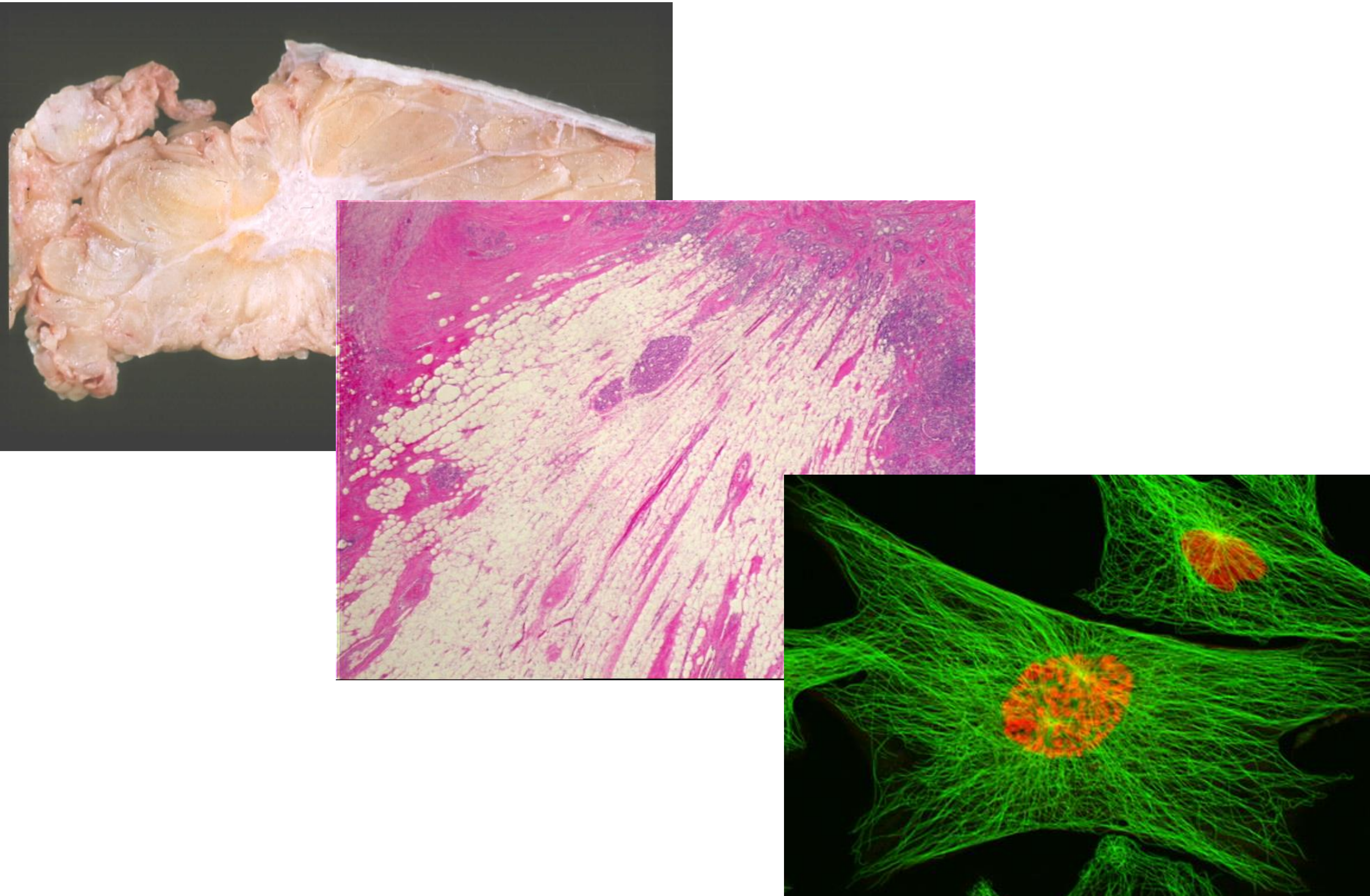
DOI 10.1016/j.cell.2011.02.013

The Hallmarks of Cancer

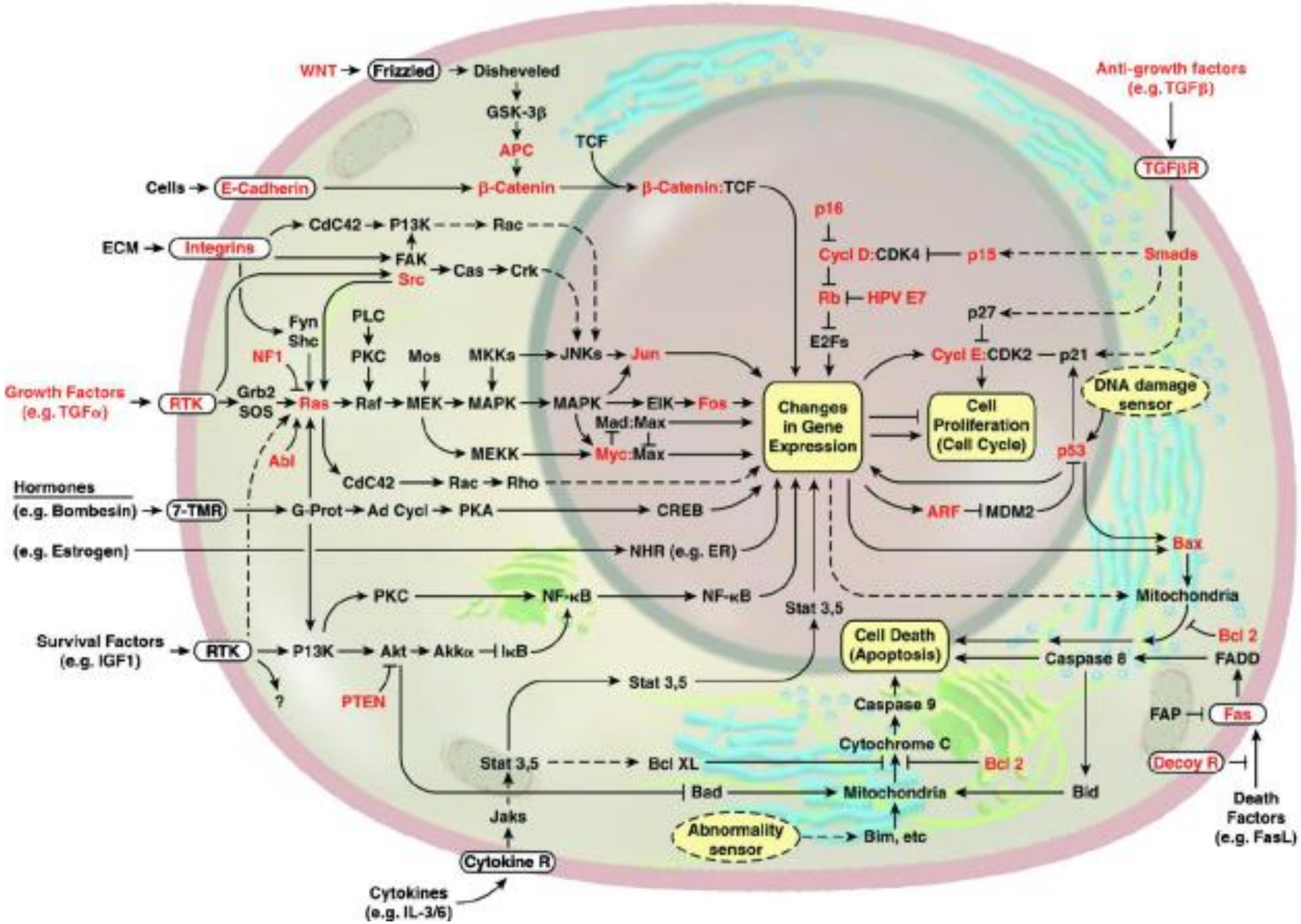


Hanahan and Weinberg, 2011

Cancer: A Multiscale System



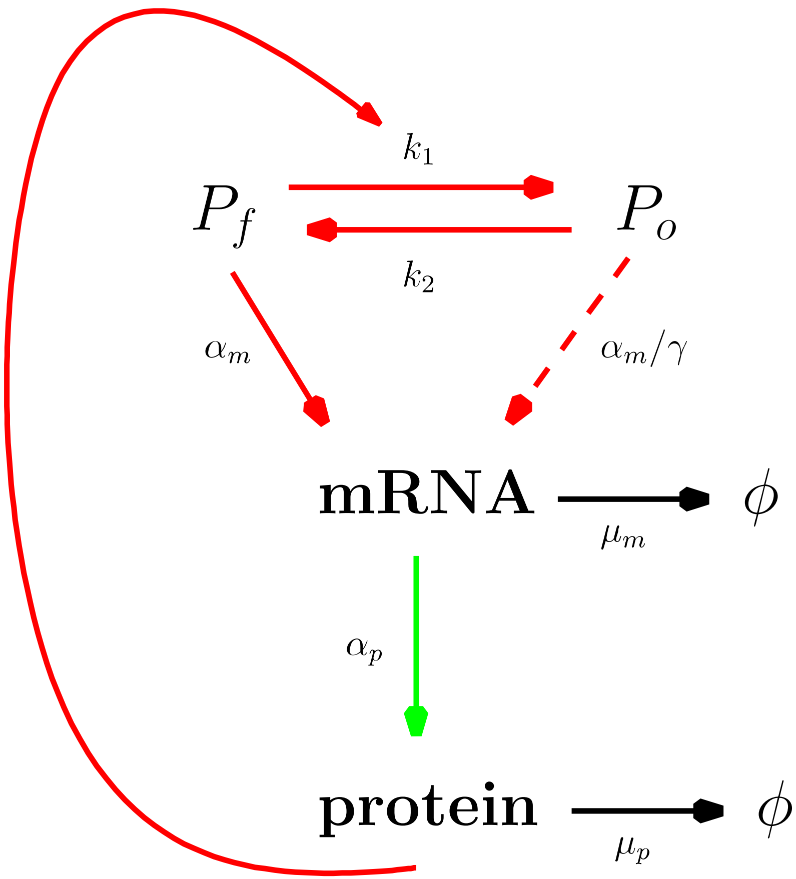
Intracellular modelling: Gene regulatory networks

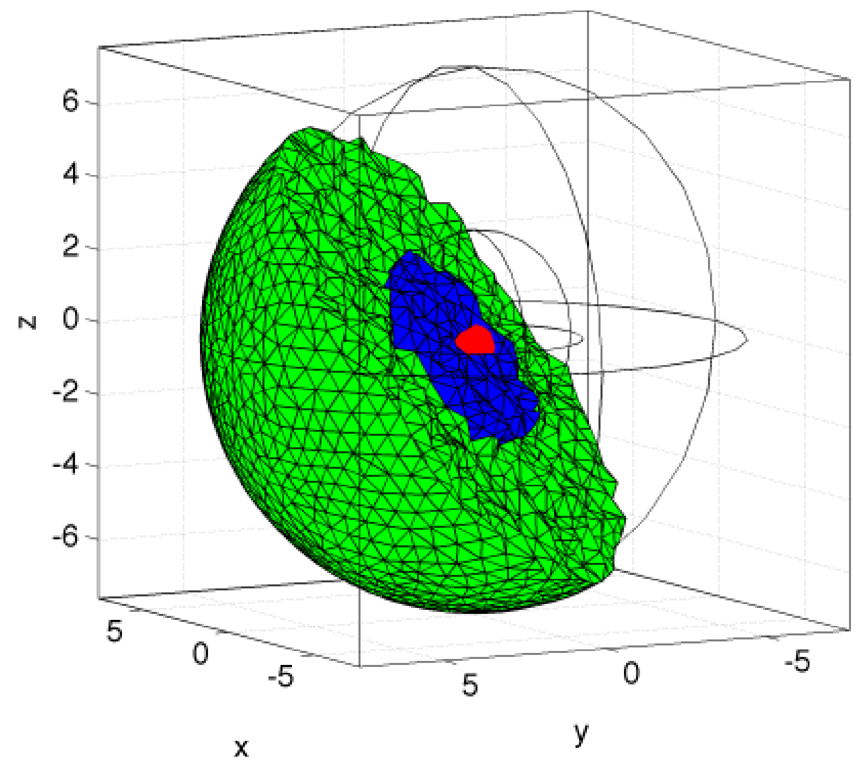


Gene regulatory networks: Negative feedback loops

A generic negative feedback loop: species x produces y which then inhibits x, in turn reducing levels of y...

Hes1 Spatial Stochastic Model

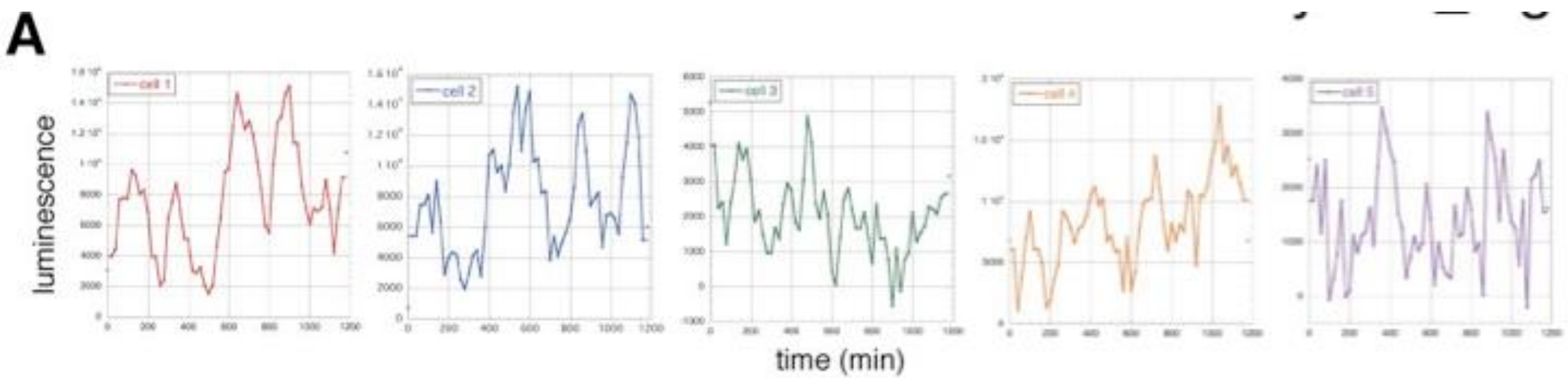




Hes1 Spatial Stochastic Model

$$
\begin{array}{rcl}
P_f + protein & \underset{k_2}{\overset{k_1}{\rightleftharpoons}} & P_o, \quad (\text{promoter}, x_m, \text{nucleus}) \\
P_f & \xrightarrow{\alpha_m} & mRNA, \quad (\text{promoter}, x_m, \text{nucleus}) \\
P_o & \xrightarrow{\alpha_m/\gamma} & mRNA, \quad (\text{promoter}, x_m, \text{nucleus}) \\
mRNA & \xrightarrow{\alpha_p} & mRNA + protein, \quad (\text{cytoplasm}, \Omega_c) \\
mRNA & \xrightarrow{\mu_m} & \phi, \quad (\text{entire cell}, \Omega) \\
protein & \xrightarrow{\mu_p} & \phi, \quad (\text{entire cell}, \Omega) \\
protein_i & \xrightarrow{D/h^2} & protein_{i+1}, \quad (\text{entire cell}, \Omega) \\
mRNA_i & \xrightarrow{D/h^2} & mRNA_{i+1}, \quad (\text{entire cell}, \Omega) \\
protein_i & \xrightarrow{D/h^2} & protein_{i-1}, \quad (\text{entire cell}, \Omega) \\
mRNA_i & \xrightarrow{D/h^2} & mRNA_{i-1}, \quad (\text{entire cell}, \Omega)
\end{array}
$$

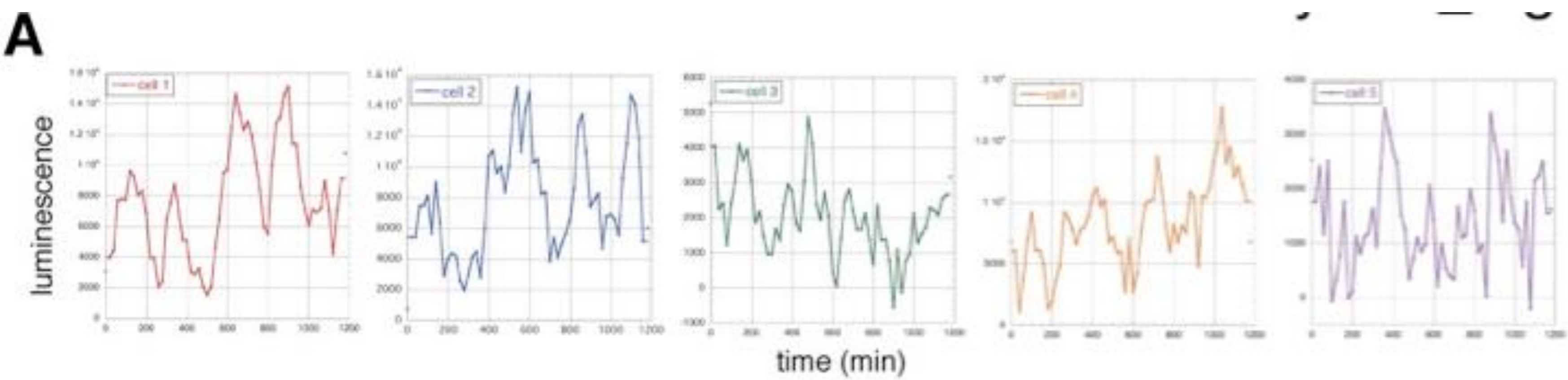
Hes1: Experimental Data/Simulation Results

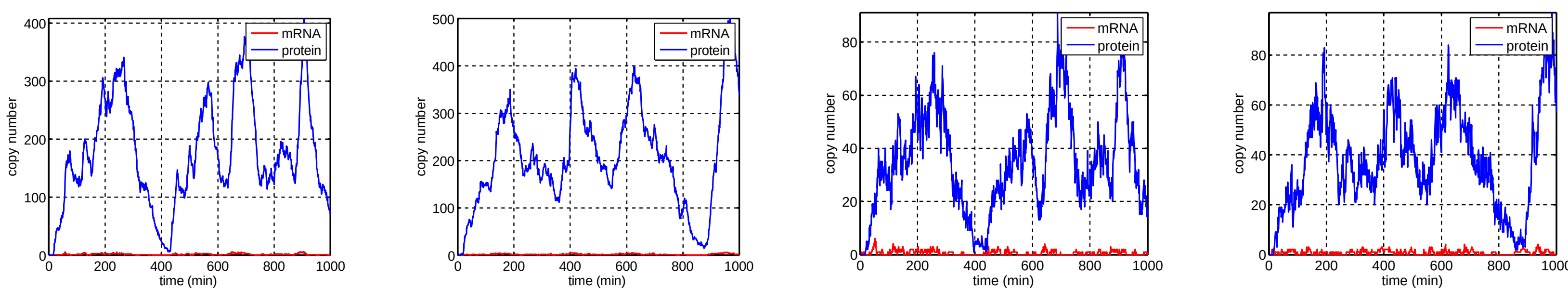


Experimental data from Kobayashi et al.[1] showing Hes1 protein levels in murine embryonic stem cells.

[1]Kobayashi et al. (2009) The cyclic gene Hes1 contributes to diverse differentiation responses of embryonic stem cells *Genes Dev.* 23, 1870 - 1875

Hes1: Experimental Data/Simulation Results





Corresponding simulation results from the spatial stochastic model[1].

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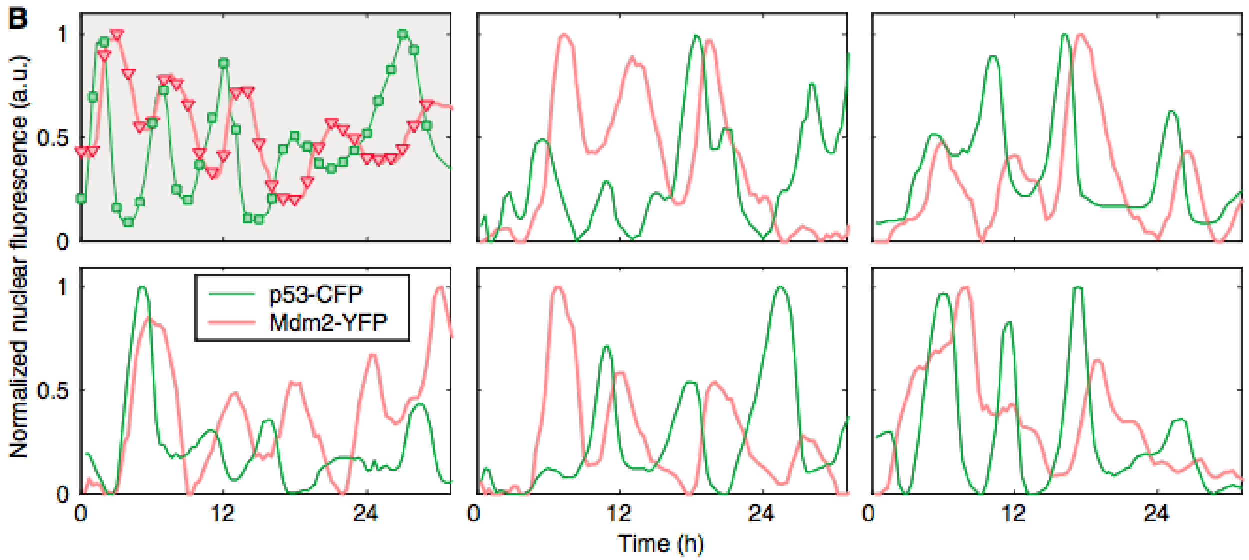
[1] Sturrock, Hellander, Matzavinos, Chaplain (2013) Spatial stochastic modelling of the Hes1 gene regulatory network: intrinsic noise can explain heterogeneity in embryonic stem cell differentiation. *J. R. Soc. Interface* 10, 20120988

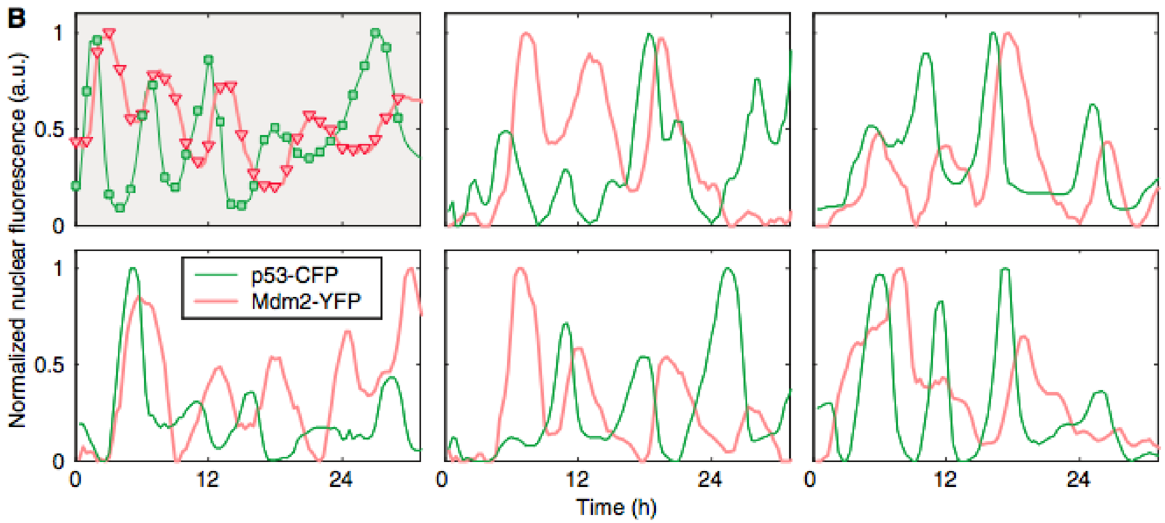
Intracellular modelling: p53-Mdm2 System

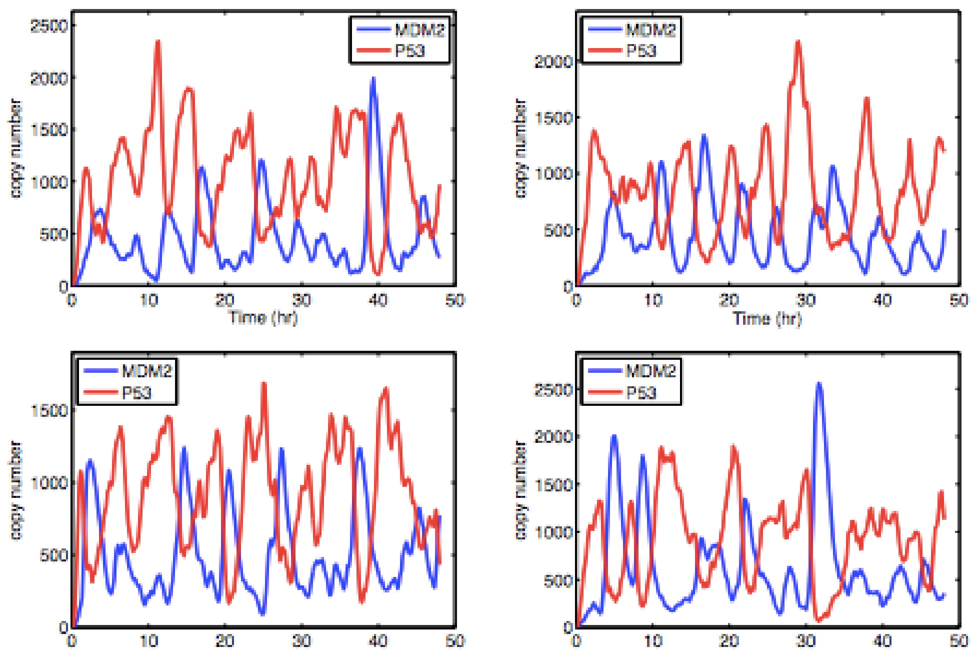


Experimental data from Lahav et al.[2] showing p53 and Mdm2 protein levels in individual cells.

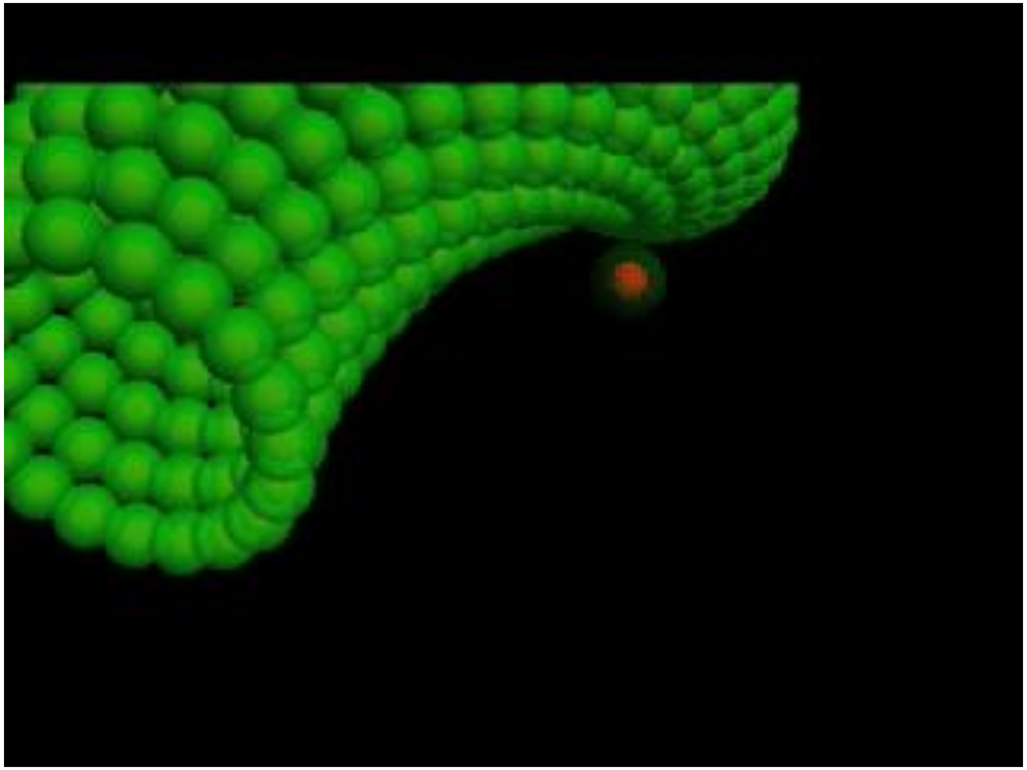
[2] Lahav et al. (2004) Dynamics of the p53-Mdm2 feedback loop in individual cells. *Nature Genetics* 36, 147 - 150

Intracellular modelling: p53-Mdm2 System

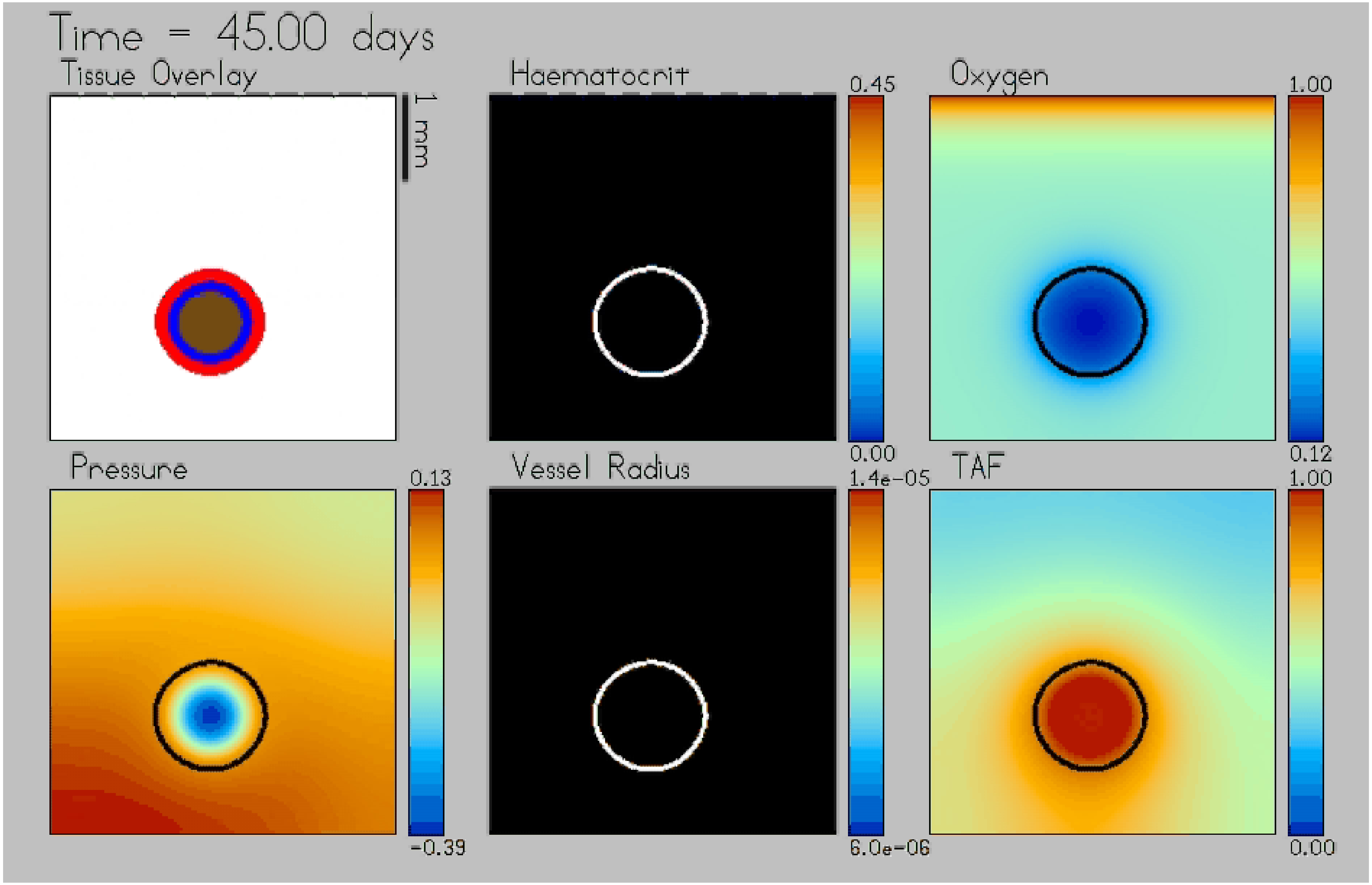




Single Cell Migration: Intravasation and Metastatic Spread



Individual Cell Migration: Tumour-induced Angiogenesis



Tissue scale modelling: Cancer invasion

$$
\begin{array}{ccccccc}
\text{cancer cells} & \rightarrow & \text{MDE}^{2} & \rightarrow & \text{ECM}^{3} & \leftrightarrow & \text{cancer cells} \\
 & & \uparrow & & \leftarrow & & \hookleftarrow
\end{array}
$$

Cancer cells, $c(\mathbf{x}, t)$: secrete MDE, invade ECM, proliferate

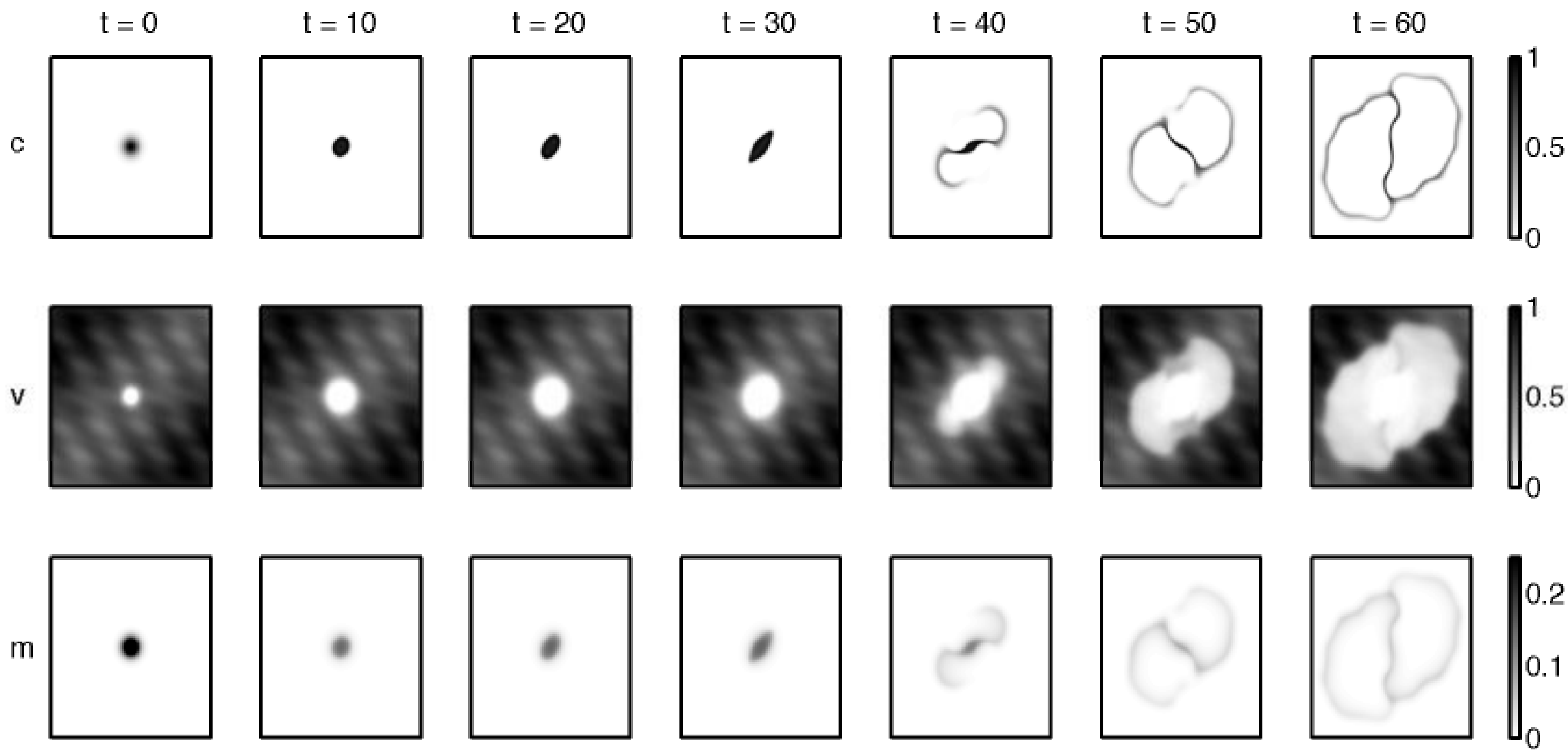
ECM, $v(\mathbf{x}, t)$: degraded by MDE, re-modelling

MDE, $m(\mathbf{x}, t)$: secreted by cancer cells, diffuse, degrade ECM, decay

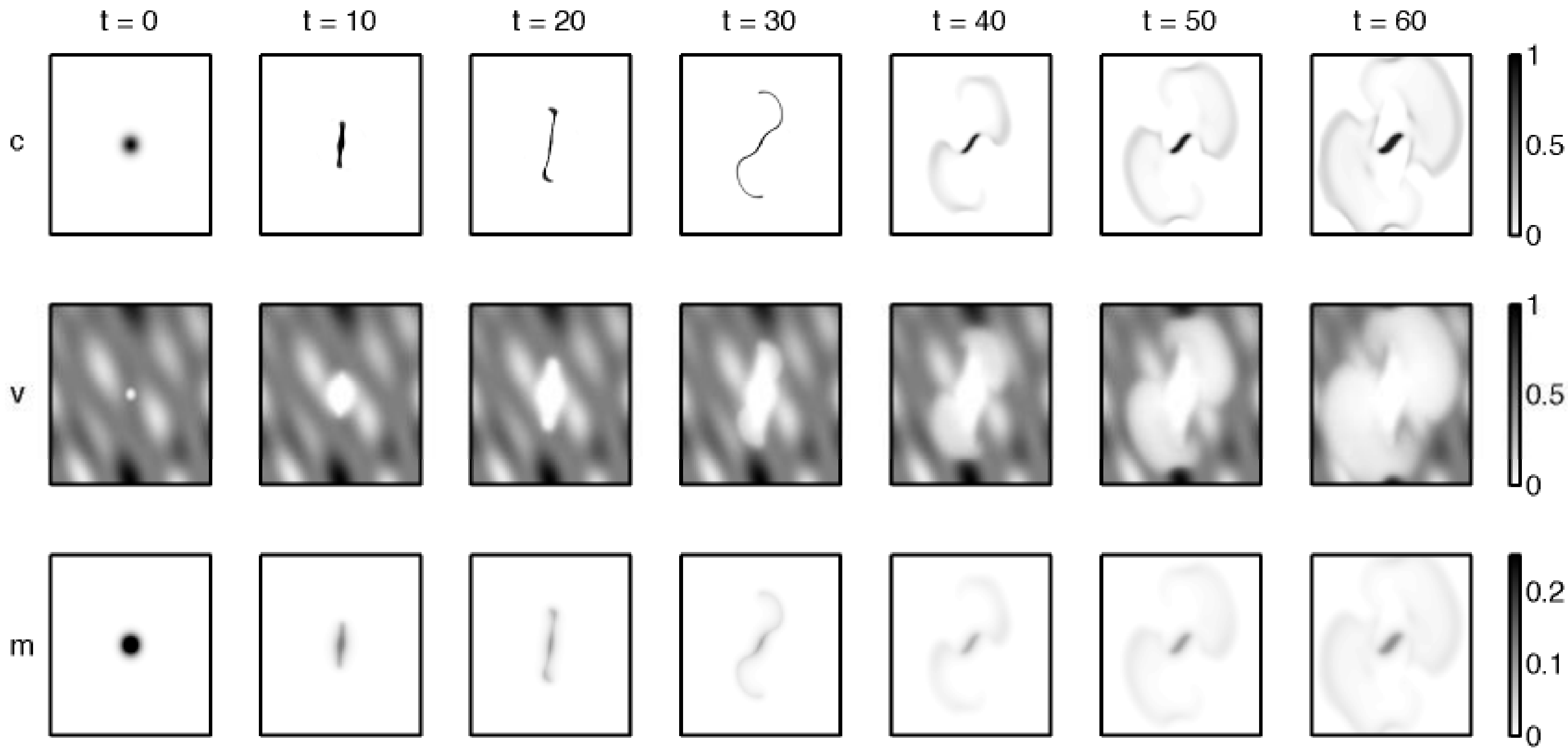
[2] matrix degrading enzymes
[3] extracellular matrix

Tissue scale modelling: Cancer invasion

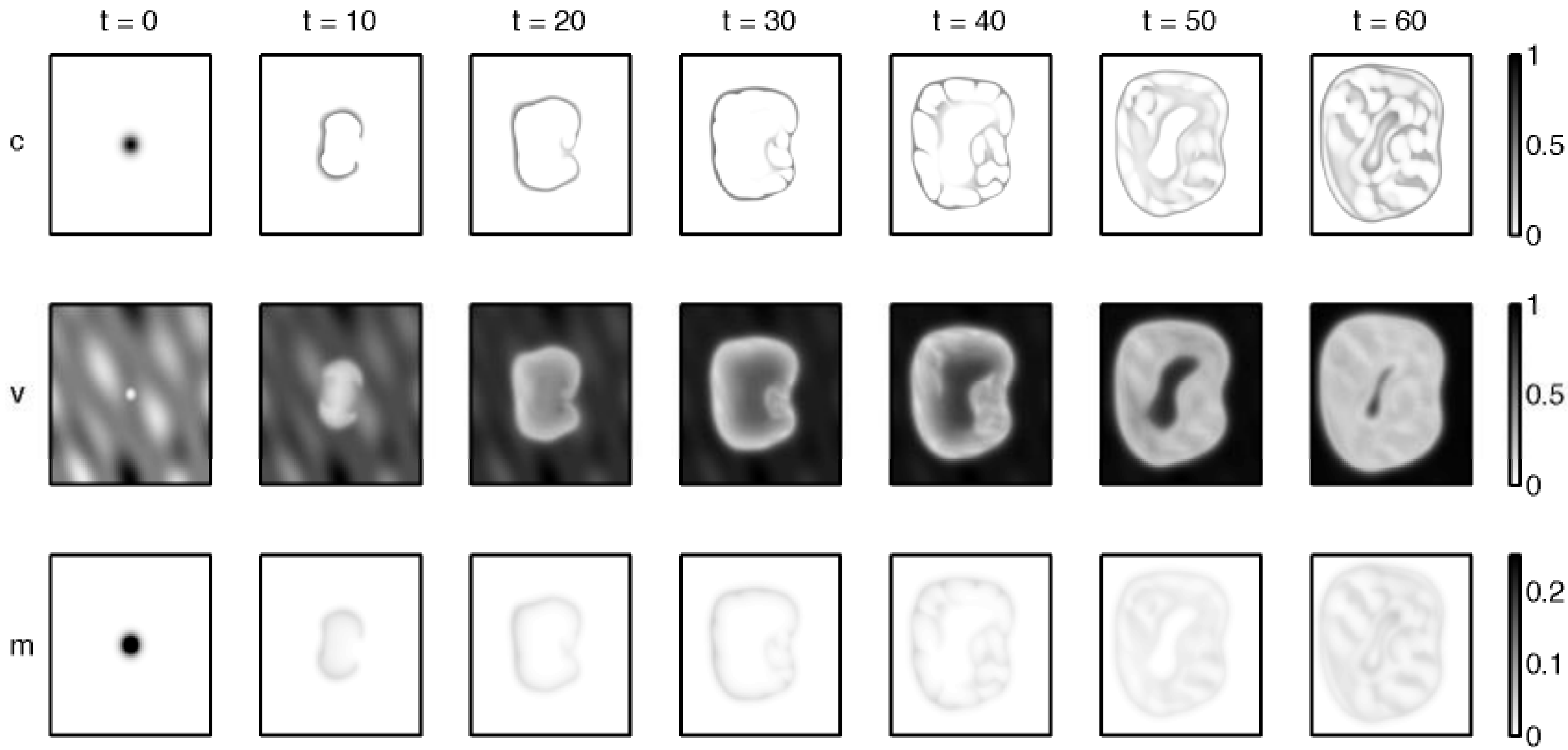
2D simulation results, time-dependent adhesion parameters:



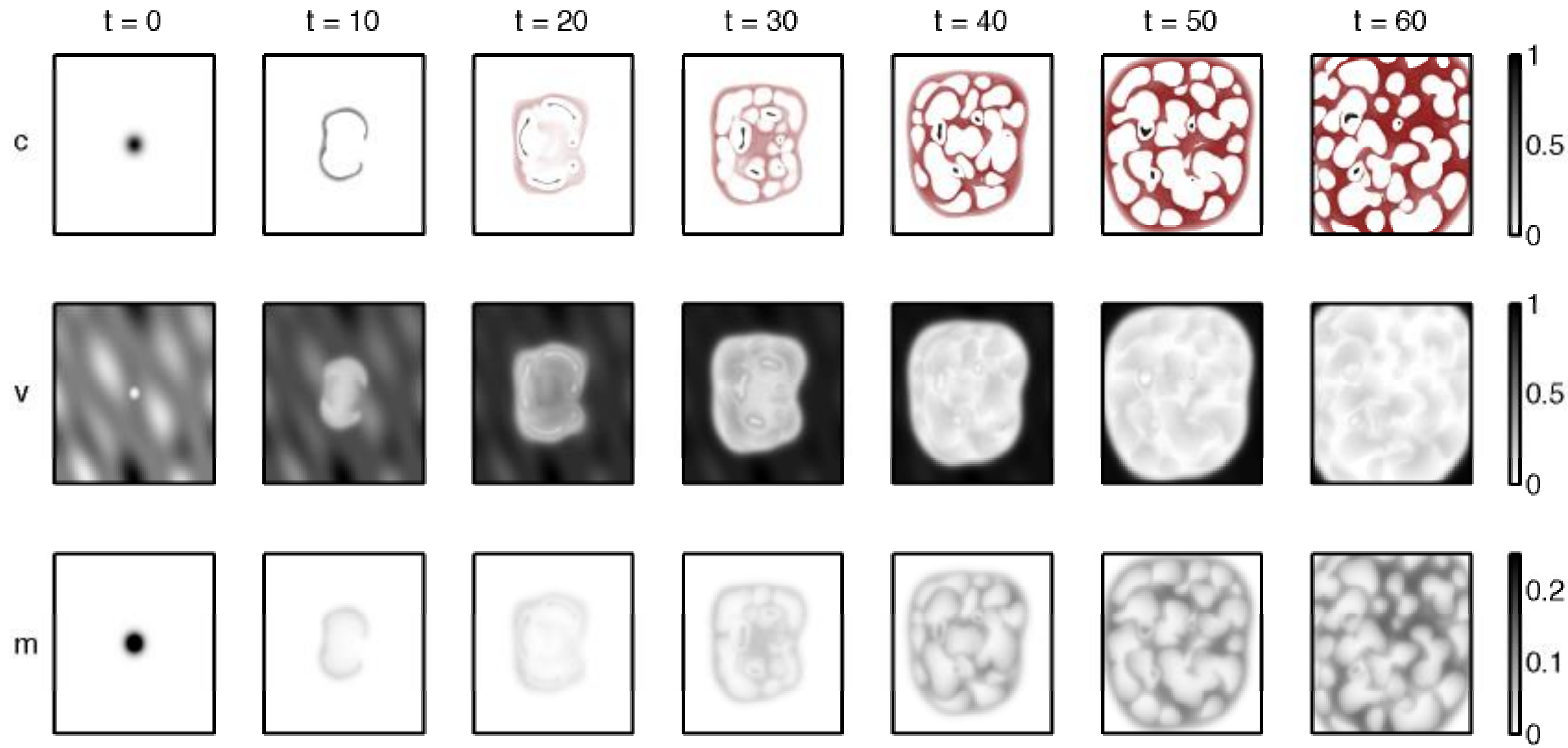
Tissue scale modelling: Cancer invasion



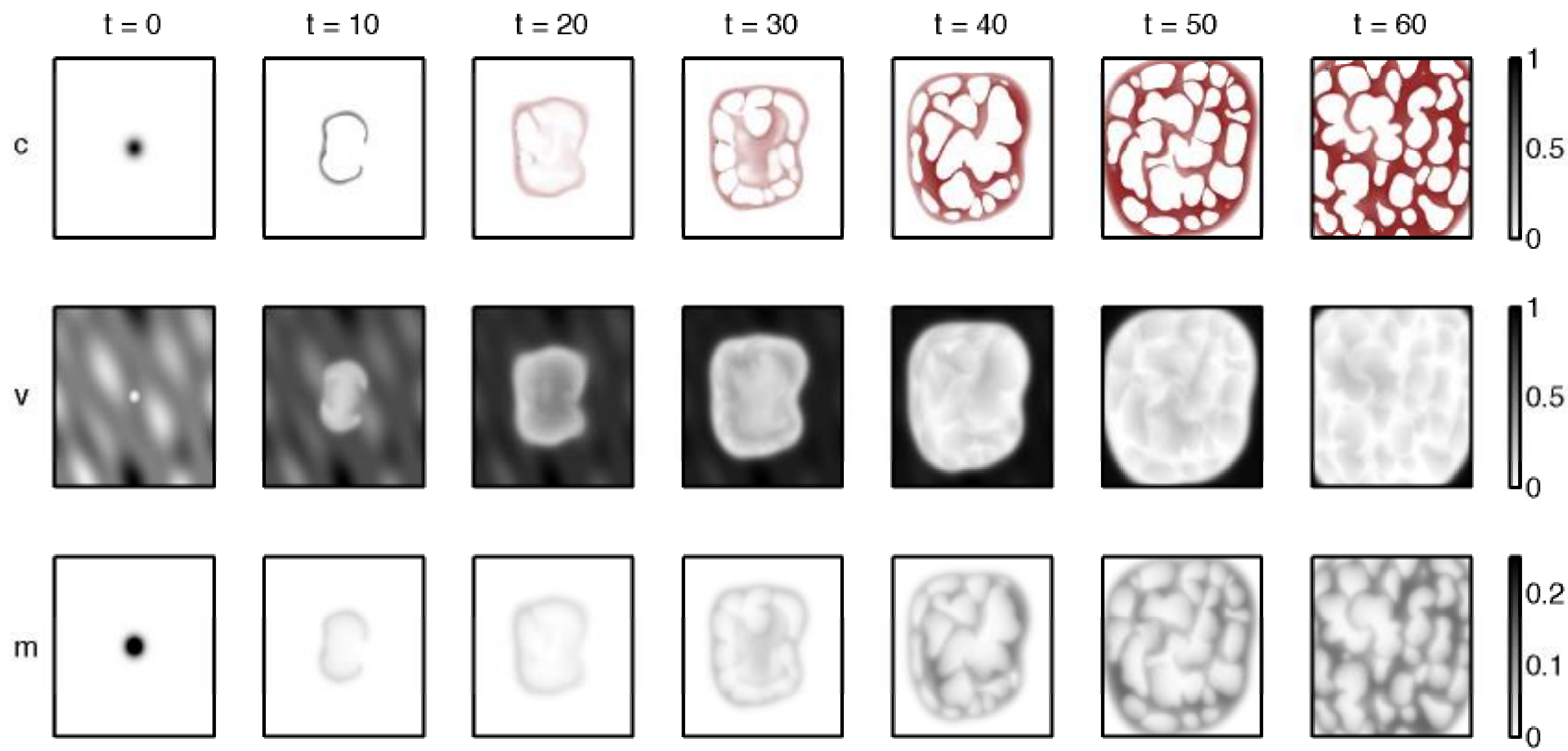
Tissue scale modelling: Cancer invasion



Tissue scale modelling: Cancer invasion



Tissue scale modelling: Cancer invasion



Tissue scale modelling: Experimental Data

Infiltrative growth pattern (INF) classification[4]:

J Gastroenterol (2012) 47:1279–1289 1281

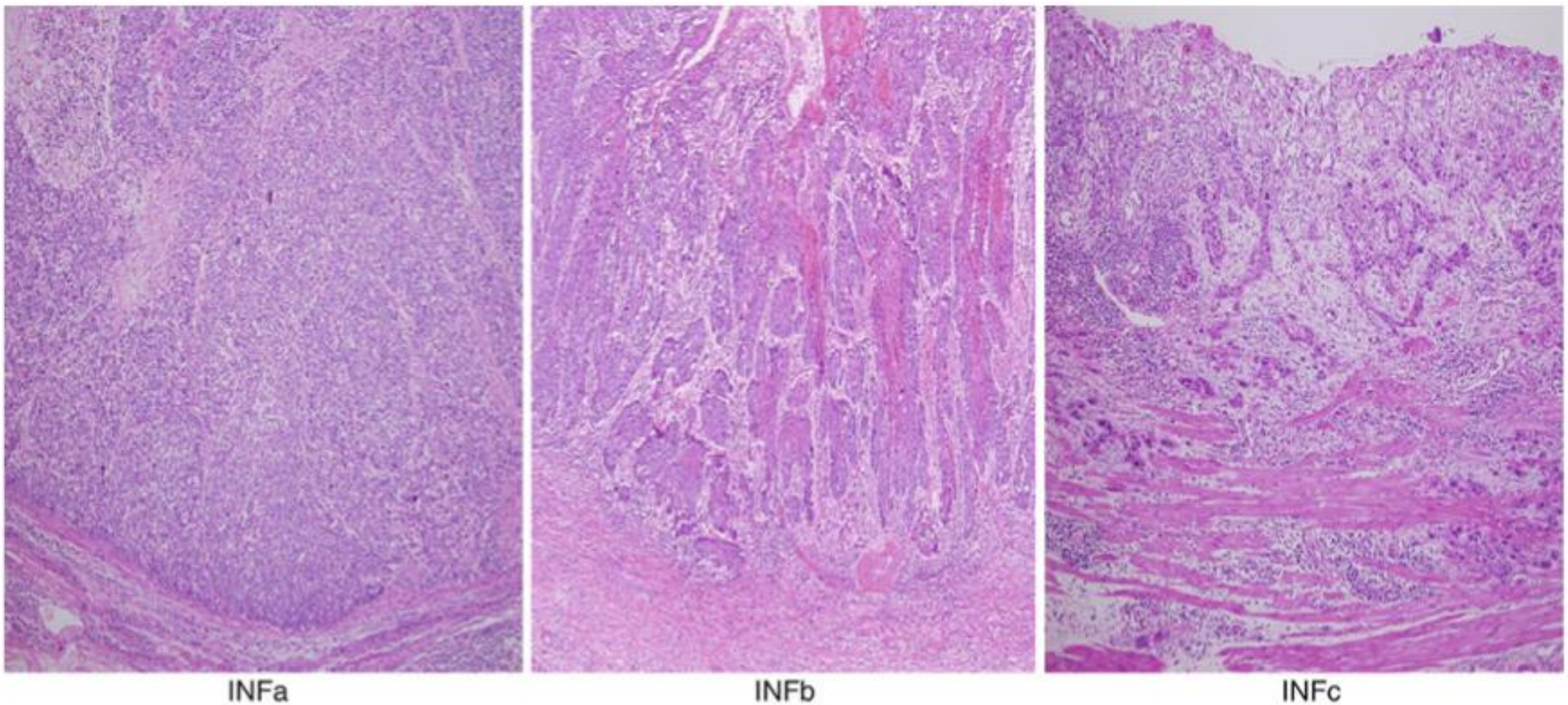
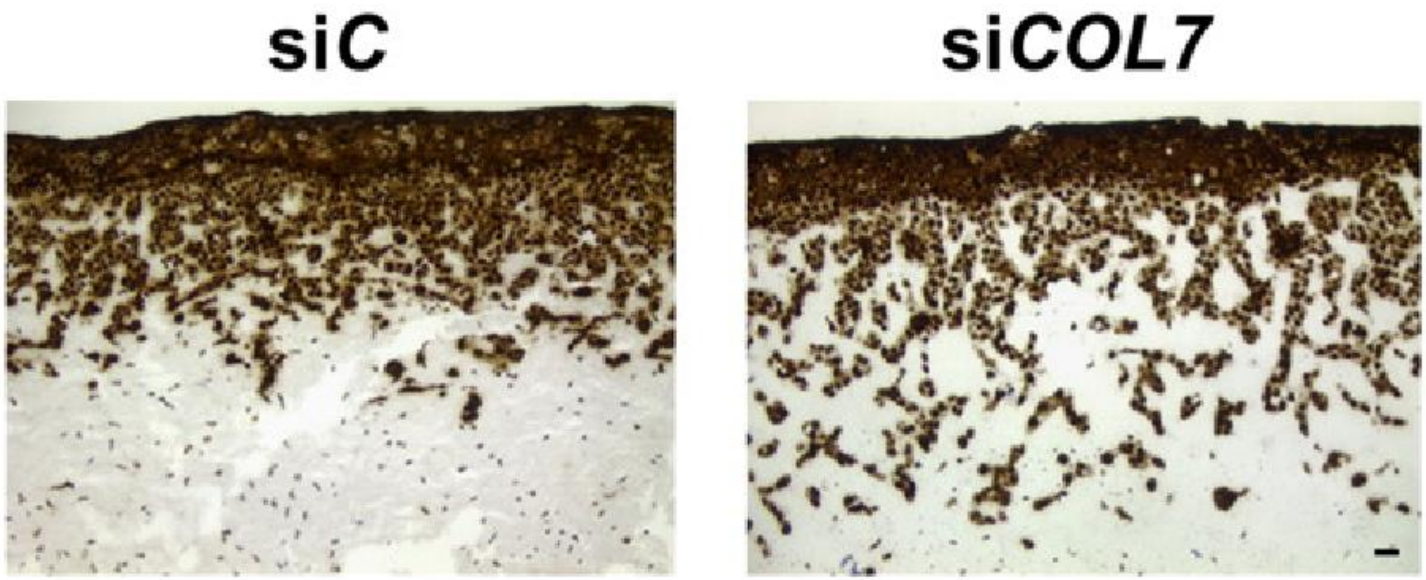


Fig. 1 Hematoxylin–eosin findings of esophageal cancer invasive patterns. *INFa* tumor extends downward continuously and expansively from the epithelium, *INFb* intermediate pattern between INFa and INFc, *INFc* tumor infiltrates with a pattern of single cells, small and large tumor nests, or a trabecular arrangement of tumor cells in the lamina propria mucosa or submucosa (×40)

[4] Ito et al. (2012) New invasive patterns as a prognostic factor for superficial esophageal cancer. *J. Gastroenterol.* 47, 1279 - 1289

Tissue scale modelling: Organotypic Invasion Assay

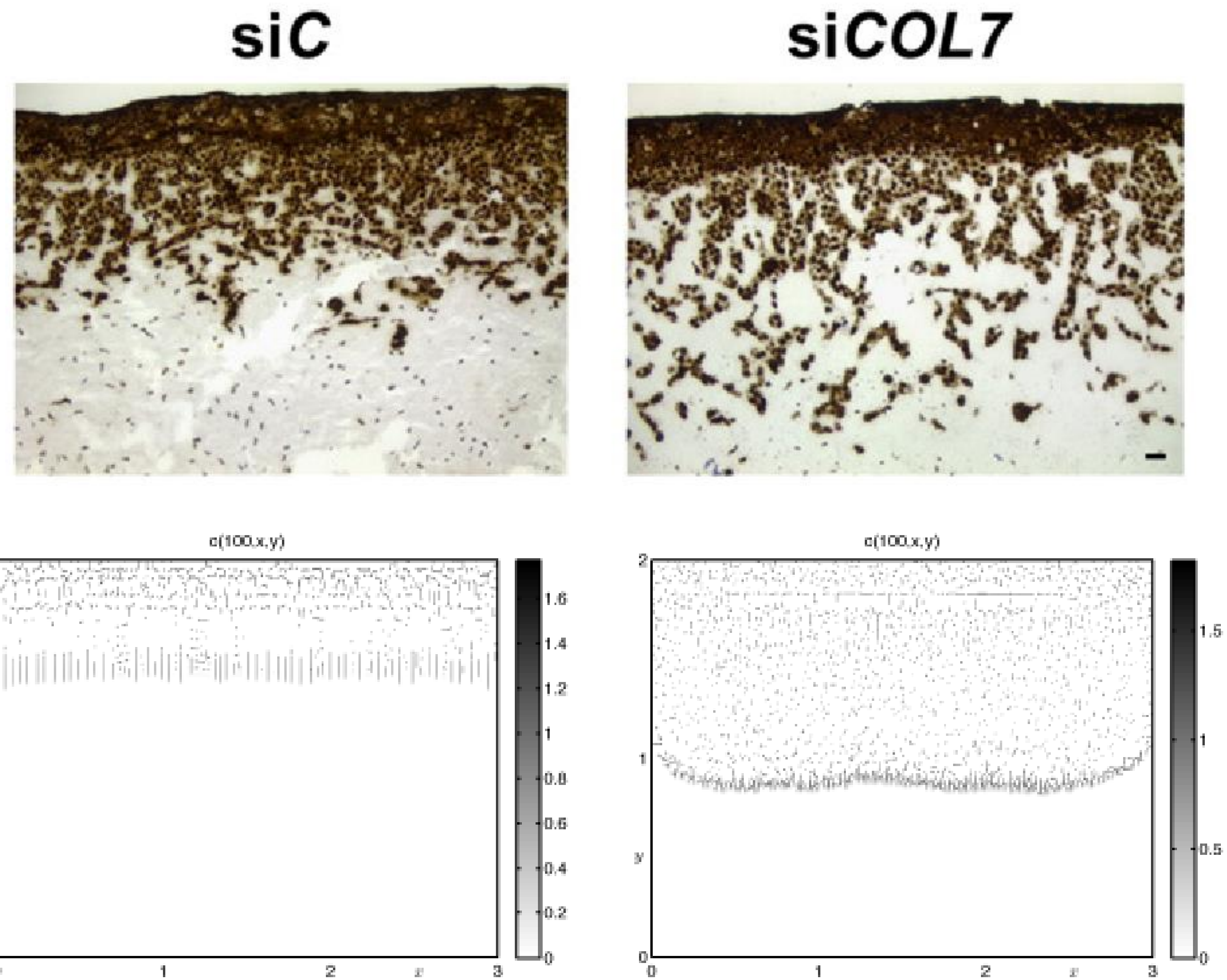
Organotypic assay results:



Cancer cell invasion in an organotypic invasion assay. Image on the left shows reduced invasion in a gel with collagen VII. Image on the right shows an increased invasion into a gel without collagen VII. Collagen VII is a key ECM component involved in anchoring cells[5].

[5] Martins et al. (2009) Increased invasive behaviour in cutaneous squamous cell carcinoma with loss of basement-membrane type VII collagen. *J. Cell Sci.* **122**, 1788-1799

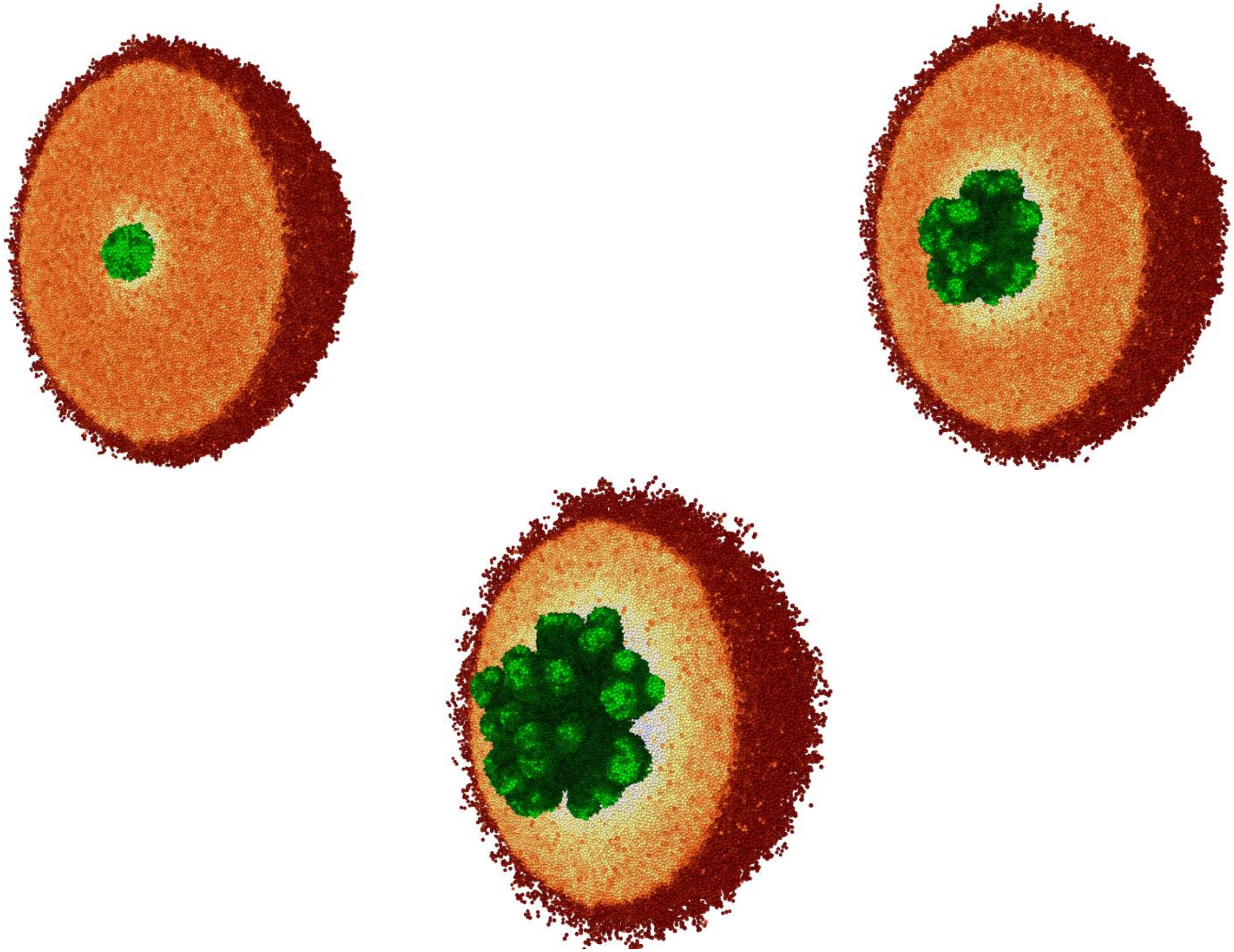
Tissue scale modelling: Organotypic Invasion Assay



Corresponding simulation results with baseline cell-cell adhesion on the left and reduced cell-cell adhesion on the right.

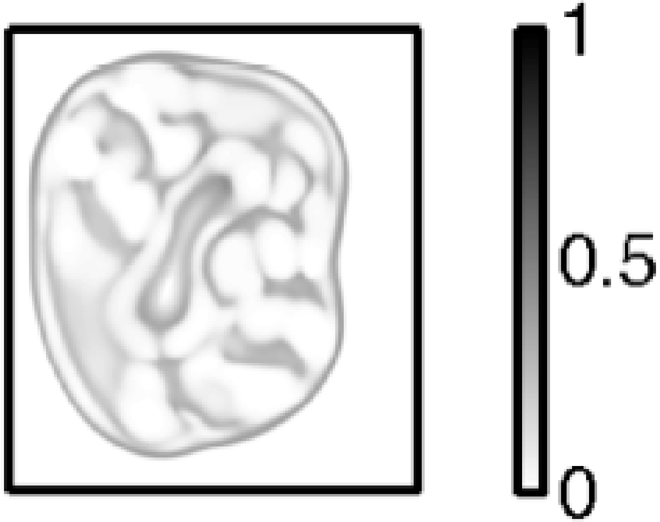
Future Perspectives

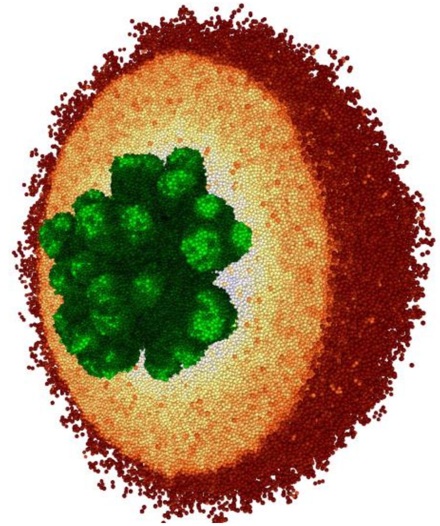
IBM Blue Gene/Q Supercomputer: Interdisciplinary Centre for Mathematical and Computational Modelling (ICM), Warsaw

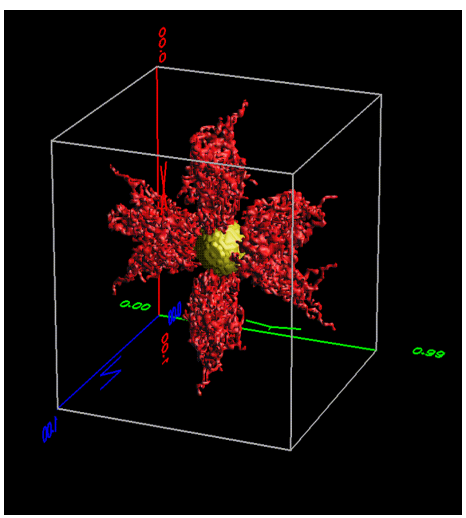


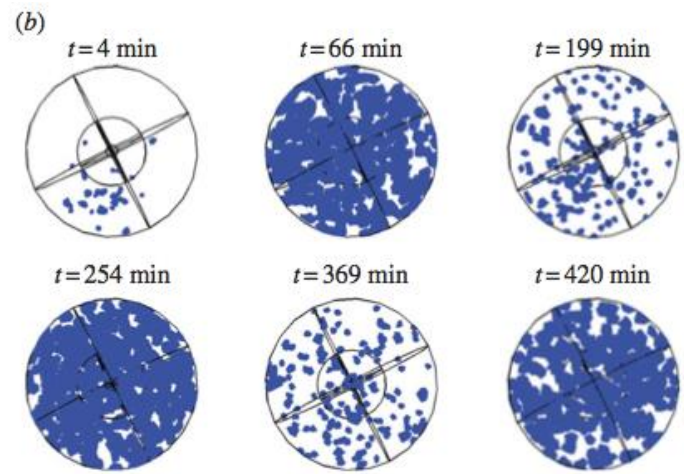
10^9 individual cells...

Future Perspectives: Creating a Virtual Solid Tumour









Thank You