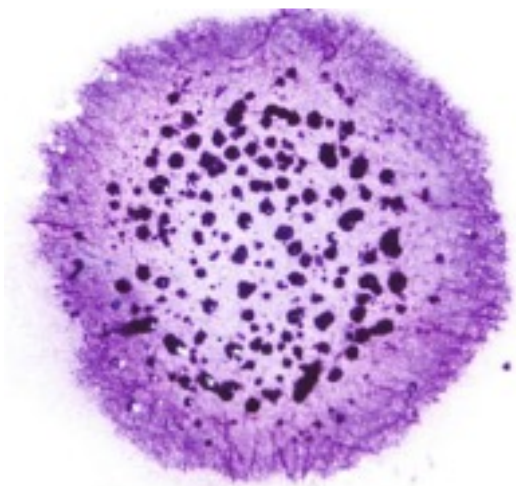
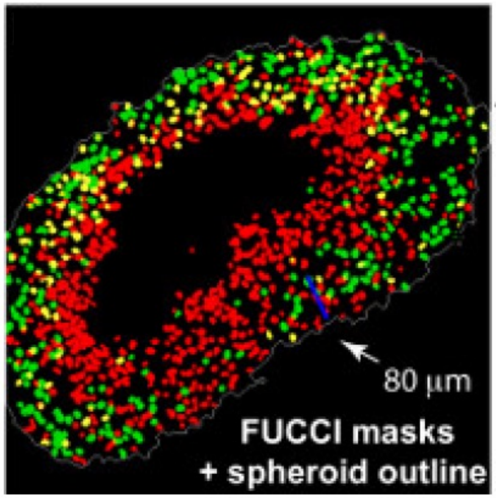
Mathematical models of cell migration with real-time cell cycle dynamics

Mat Simpson

@ProfMJSimpson



Haridas et al. 2018

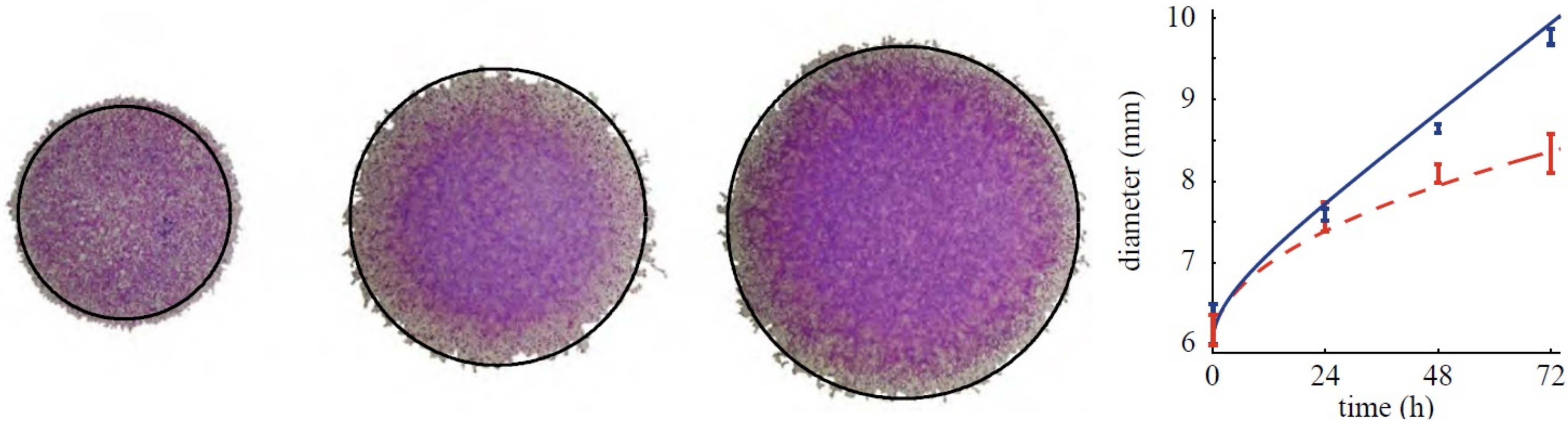


Beaumont et al. 2015

School of Mathematical Sciences
Queensland University of Technology

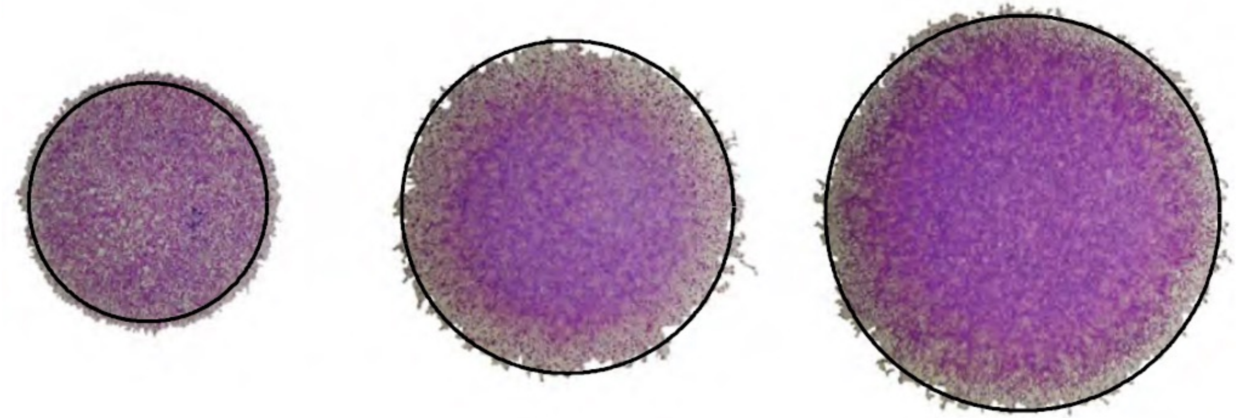
Brisbane

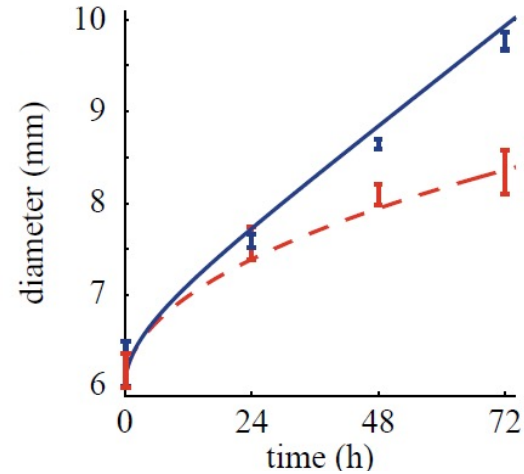
Cell invasion and the cell cycle



Simpson et al. 2013

Cell invasion and the cell cycle





Simpson et al. 2013

$$\frac{\partial u}{\partial t} = D\nabla^2 u + ru\left(1-u\right) \qquad c_{\min} = 2\sqrt{rD}$$

Sherratt and Murray 1990; Swanson et al. 2003; Maini et al. 2004; Sengers et al. 2007 and many others

Fluorescent ubiquitination-based cell cycle indicator technology (FUCCI)

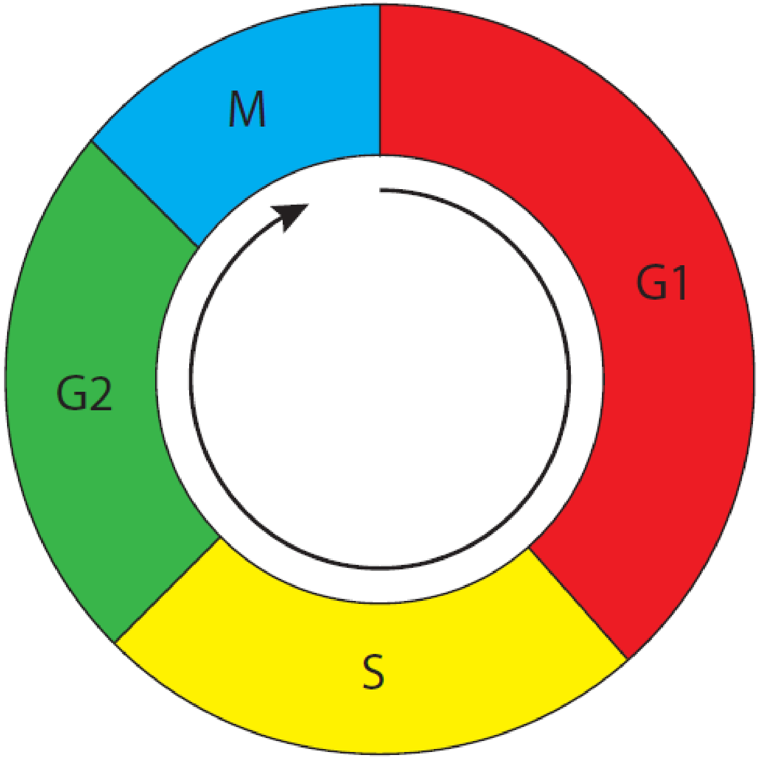
The cell cycle:

i. Gap 1 (G1)

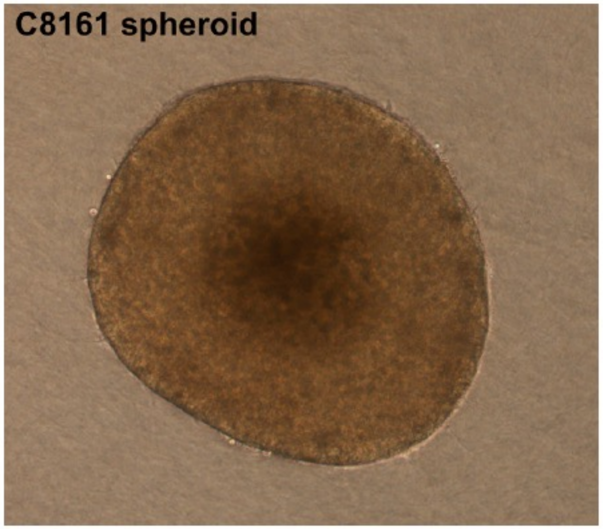
ii. Synthesis (S)

iii. Gap 2 (G2)

iv. Mitotic phase (M)



FUCCI technology



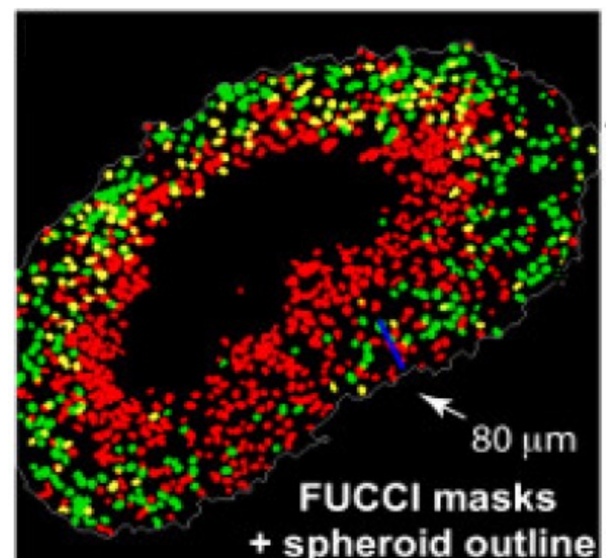
Beaumont et al. 2015

Before FUCCI

- Melanoma spheroid 500-600 μm
- Limited information about cell cycle
- Morphological changes

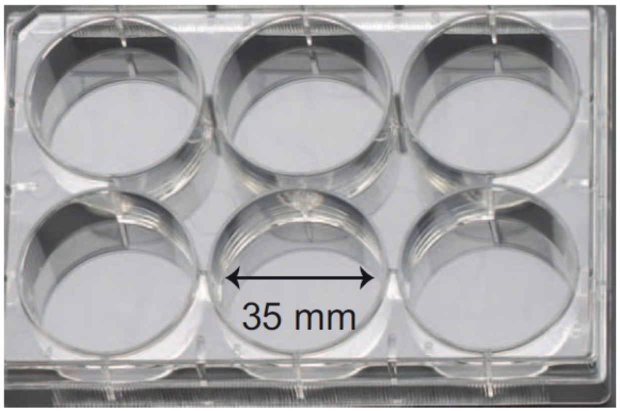
With FUCCI

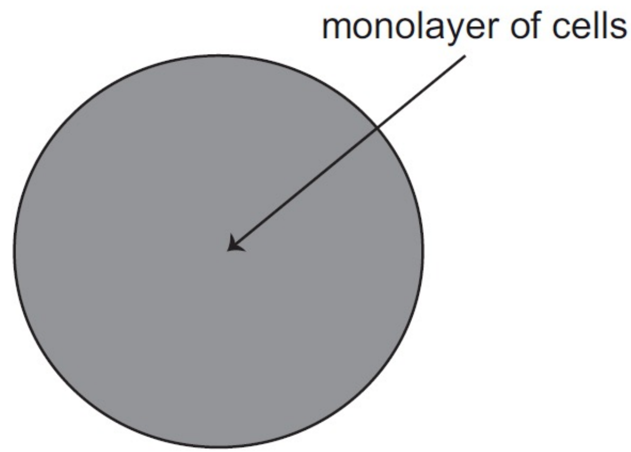
- Slice through melanoma spheroid
- Cell cycle related to position
- Cell cycle strongly related to microenvironment

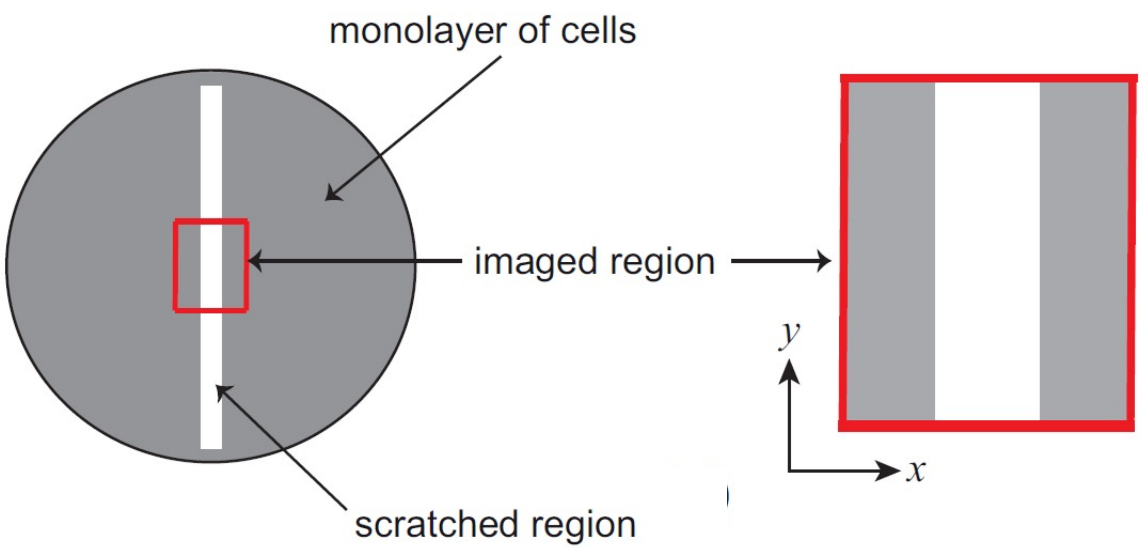


Beaumont et al. 2015

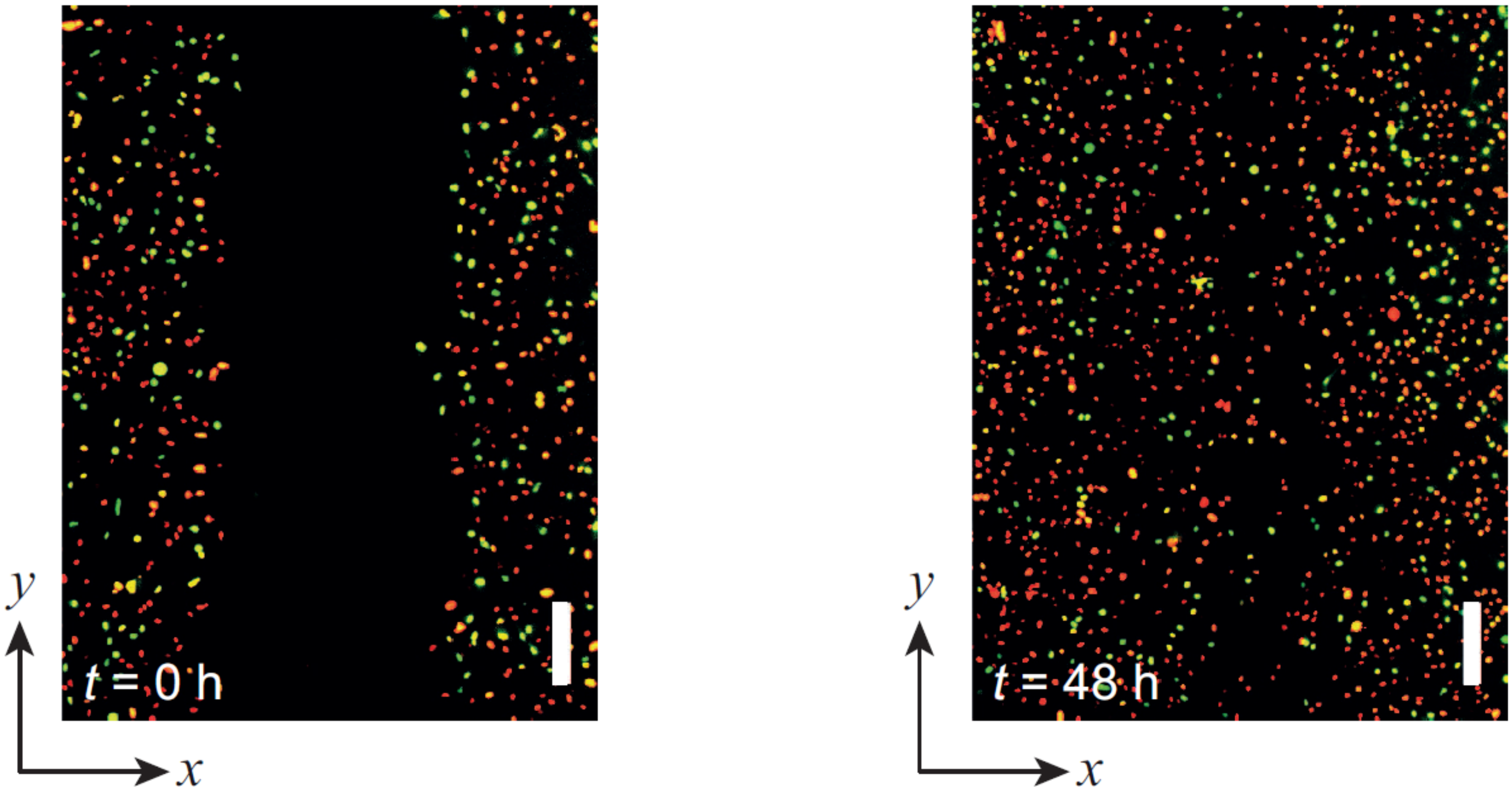
Scratch assay





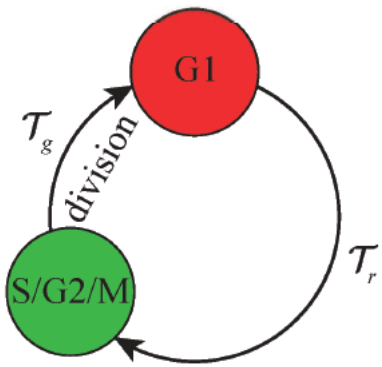


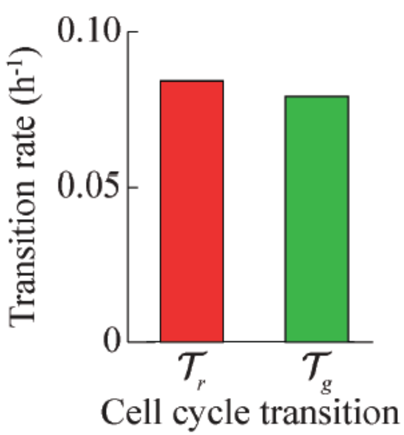
Connecting mathematical models with experimental images



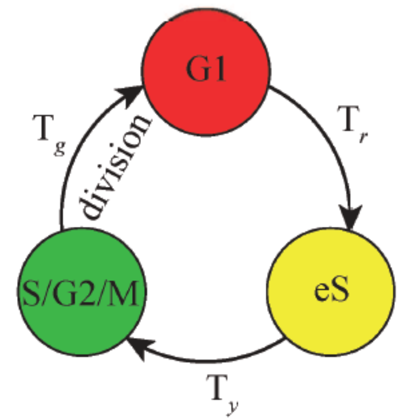
Connecting mathematical models with experimental images

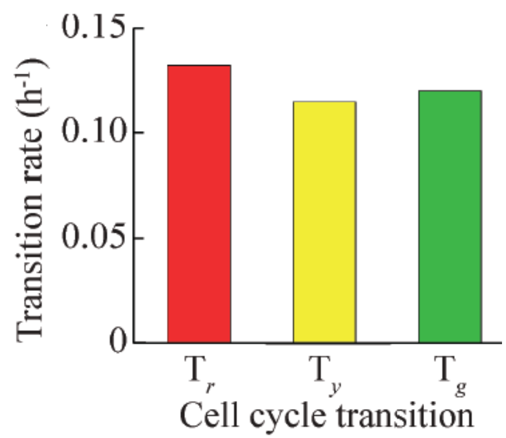
Fundamental model



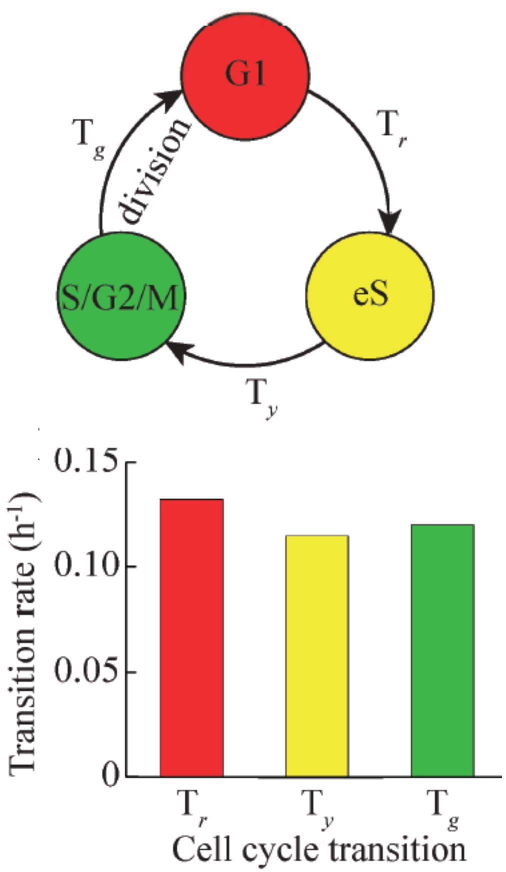


Extended model





Extended mathematical model



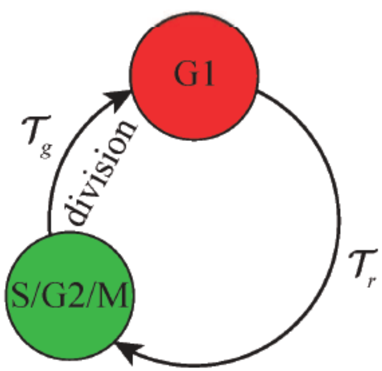
$$\frac{\partial u_r}{\partial t} = D_r \frac{\partial^2 u_r}{\partial x^2} - k_r u_r + 2k_g u_g (1 - s),$$

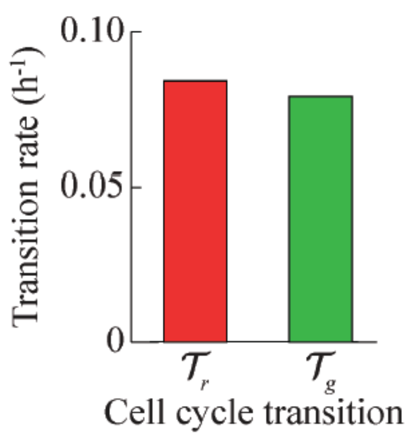
$$\frac{\partial u_y}{\partial t} = D_y \frac{\partial^2 u_y}{\partial x^2} - k_y u_y + k_r u_r,$$

$$\frac{\partial u_g}{\partial t} = D_g \frac{\partial^2 u_g}{\partial x^2} - k_g u_g (1 - s) + k_y u_y$$

$$s = u_r + u_y + u_g$$

Fundamental mathematical model



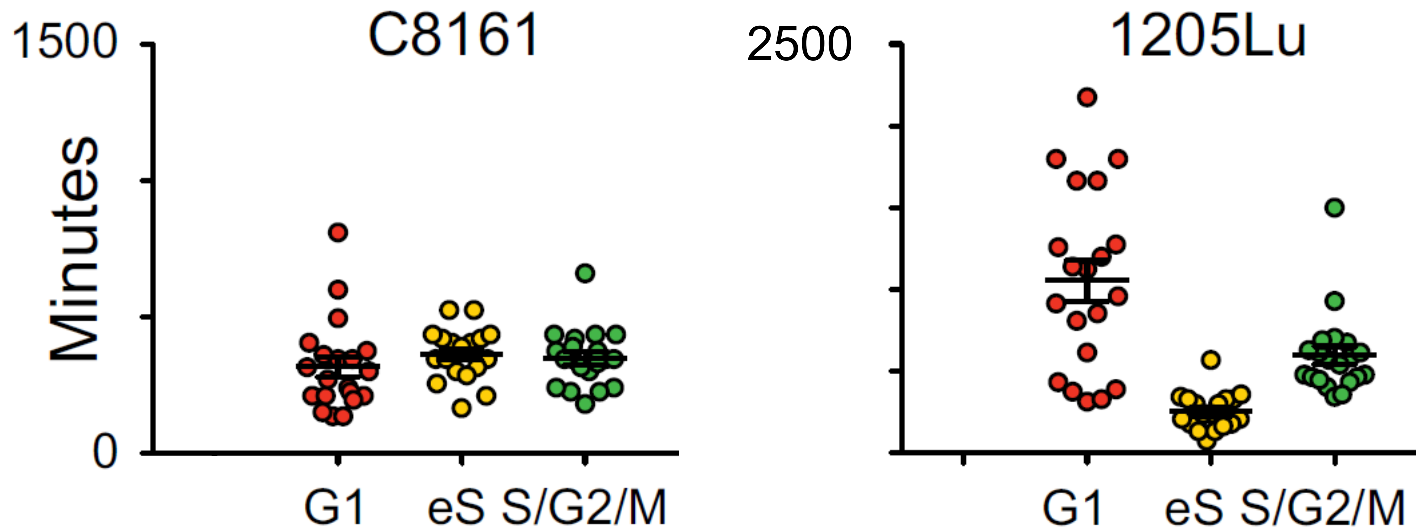


$$\frac{\partial v_r}{\partial t} = \mathcal{D}_r \frac{\partial^2 v_r}{\partial x^2} - \kappa_r v_r + 2\kappa_g v_g (1 - s),$$

$$\frac{\partial v_g}{\partial t} = \mathcal{D}_g \frac{\partial^2 v_g}{\partial x^2} - \kappa_g v_g (1 - s) + \kappa_r v_r,$$

$$s = v_r + v_g$$

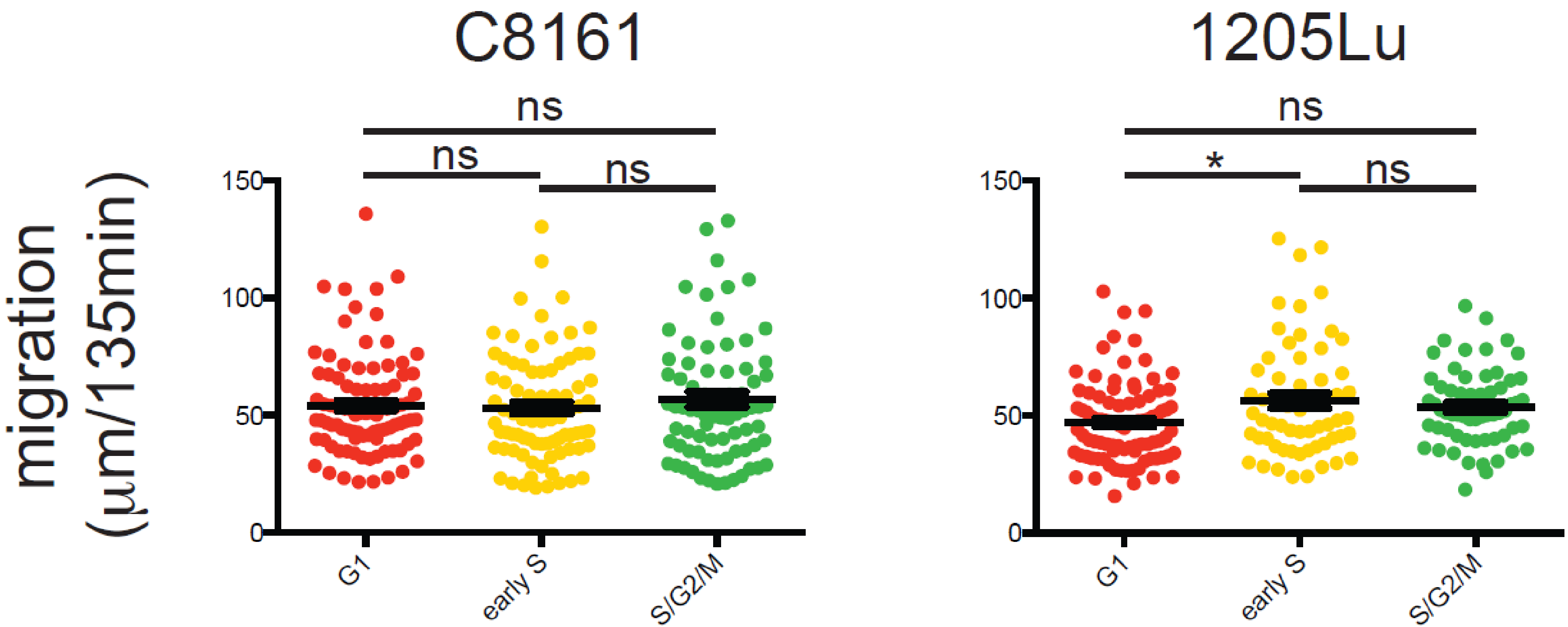
Parameter estimates: transition rates



κ_r κ_g

Haass et al. 2014

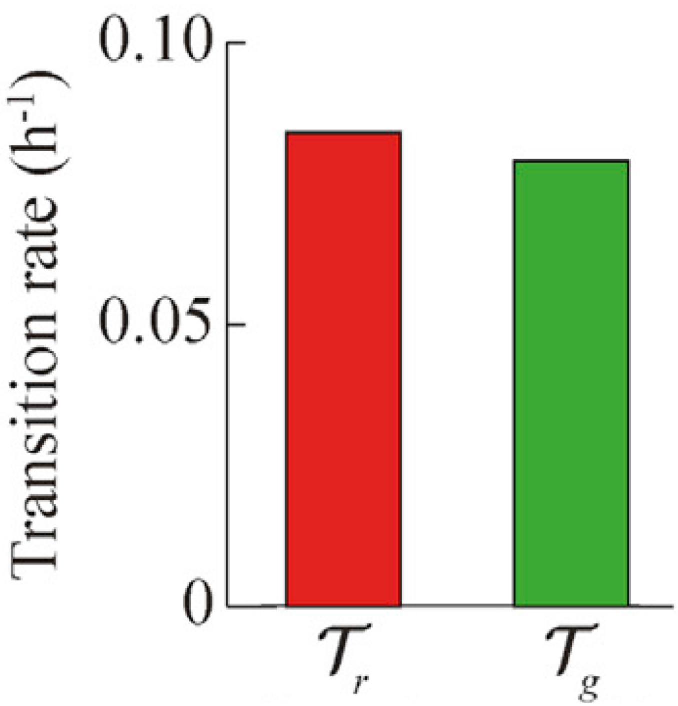
Parameter estimates: diffusivities

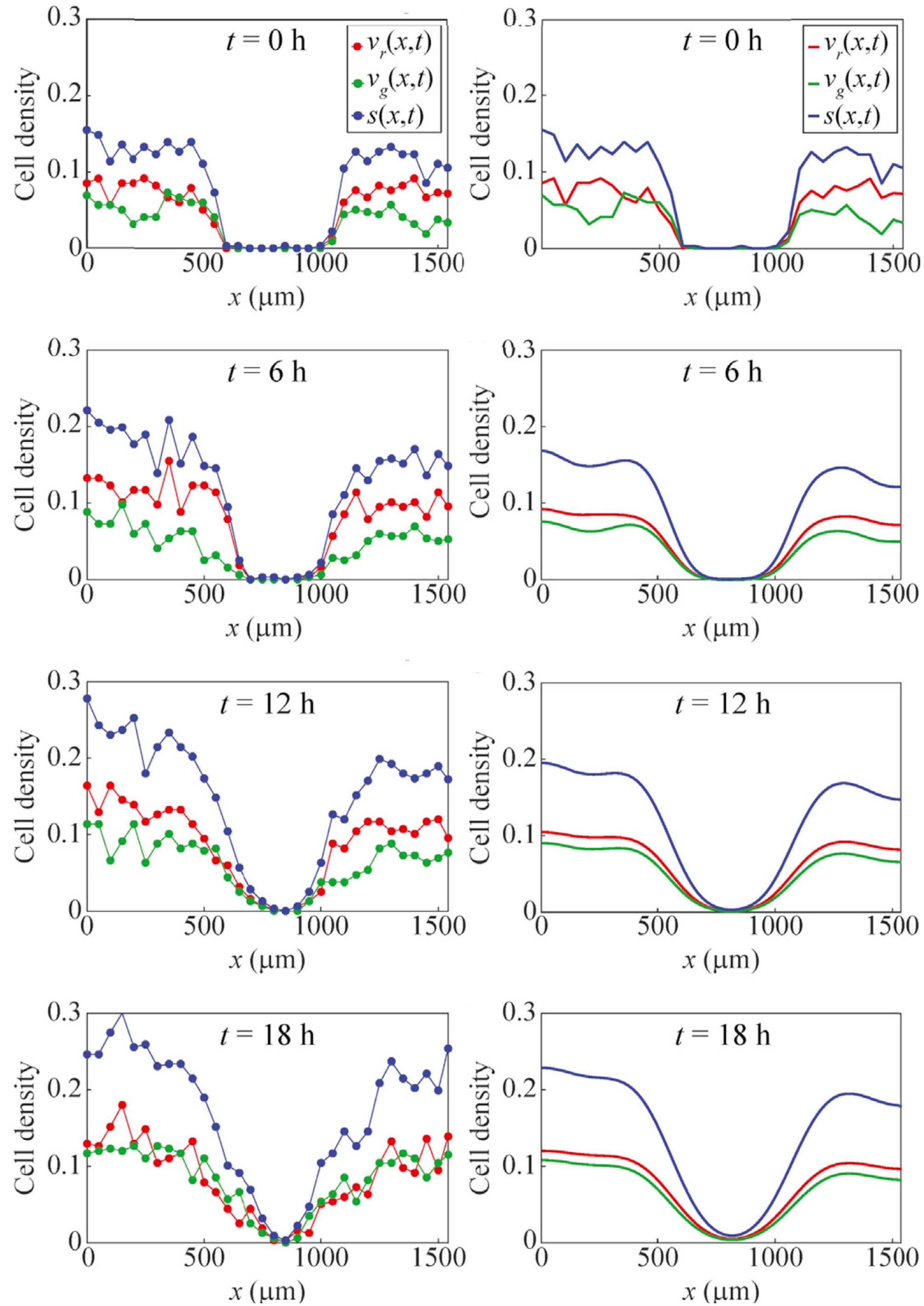


$$\mathcal{D}_r = \mathcal{D}_g$$

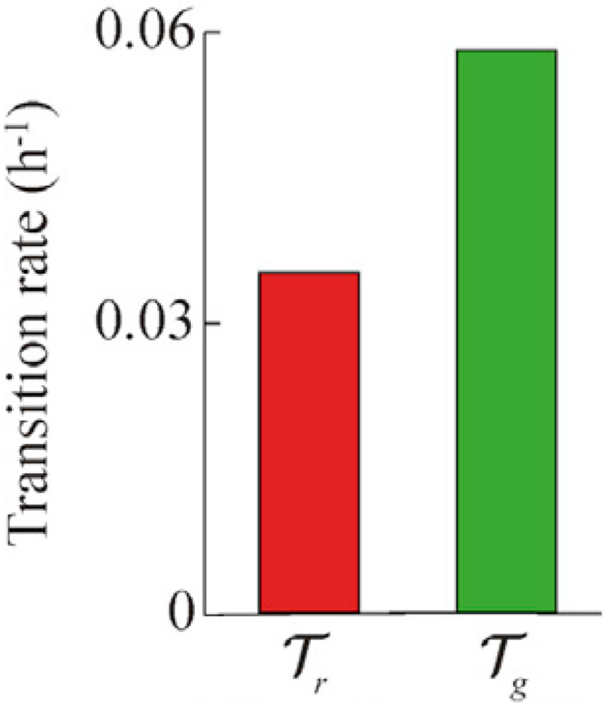
Haass et al. 2014

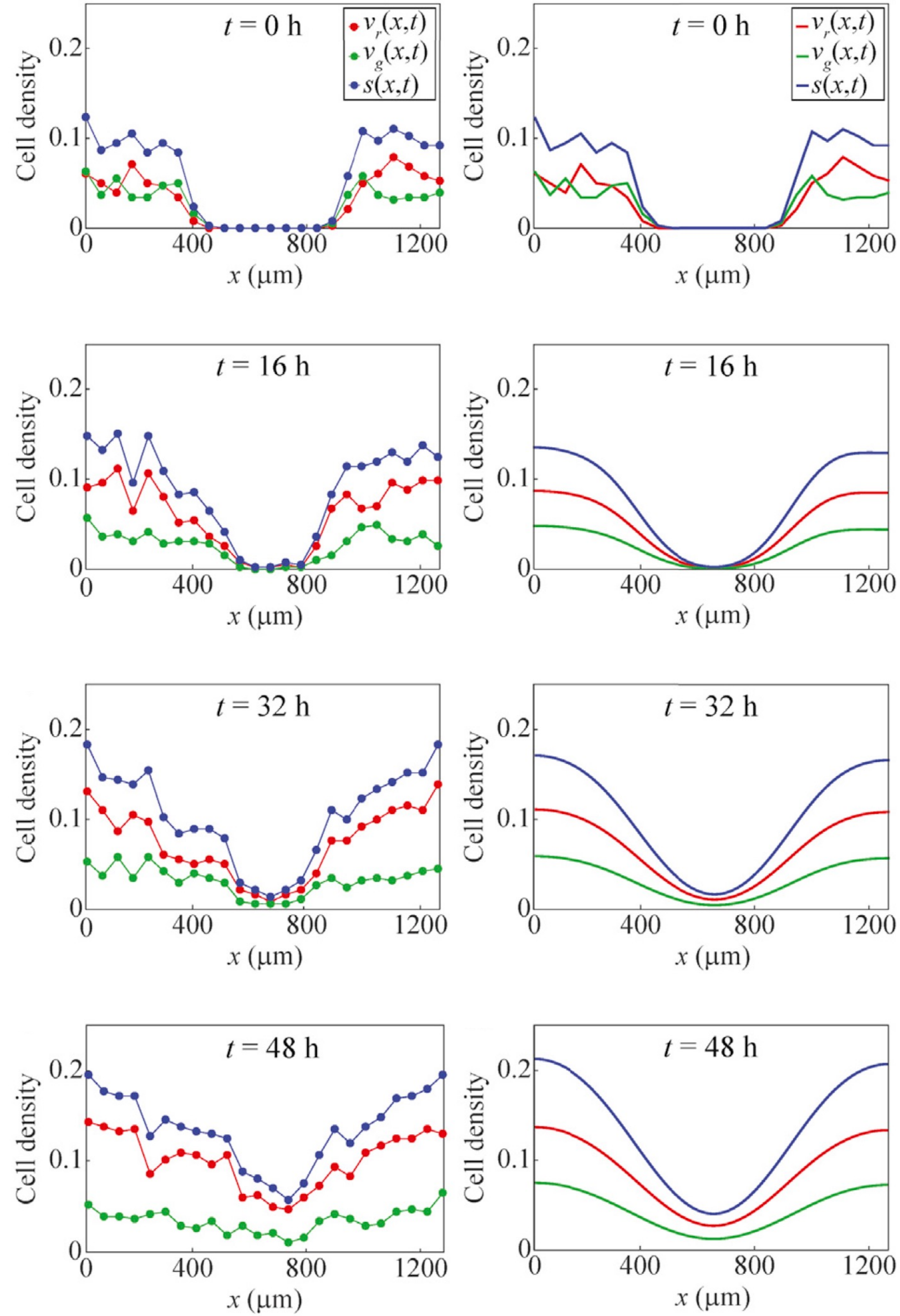
C1861 cell line



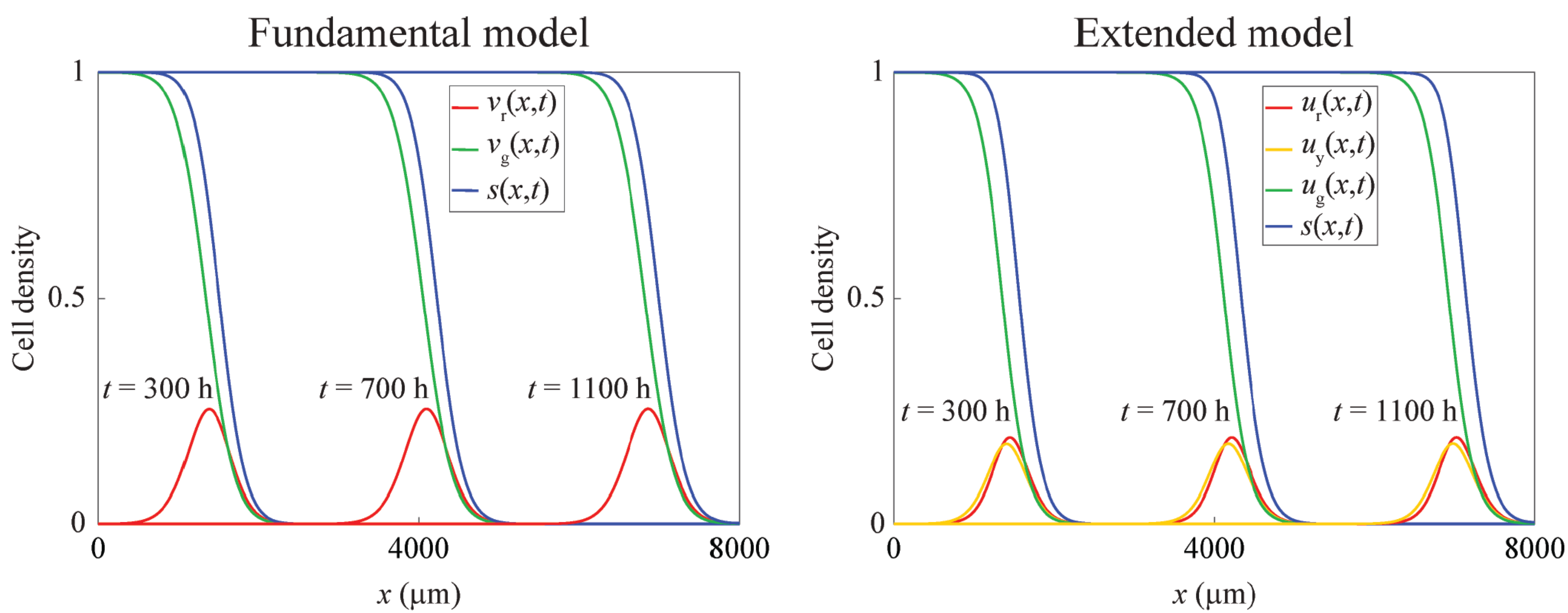


1205Lu cell line





Analysis: travelling waves



Fisher-Kolmogorov

$$\frac{\partial u}{\partial t} = u(1-u) + \frac{\partial^2 u}{\partial x^2}$$

$$u(x,t) = U(z), \quad z = x - ct$$

Murray, 2002

Fisher-Kolmogorov

$$\frac{\partial u}{\partial t} = u(1-u) + \frac{\partial^2 u}{\partial x^2} \qquad u(x,t) = U(z), \quad z = x - ct$$

$$U'' + cU' + U(1-U) = 0$$

$$\lim_{z\to\infty} U(z) = 0, \quad \lim_{z\to-\infty} U(z) = 1$$

Murray, 2002

Fisher-Kolmogorov

$$\frac{\partial u}{\partial t} = u(1-u) + \frac{\partial^2 u}{\partial x^2} \qquad u(x,t) = U(z), \quad z = x - ct$$

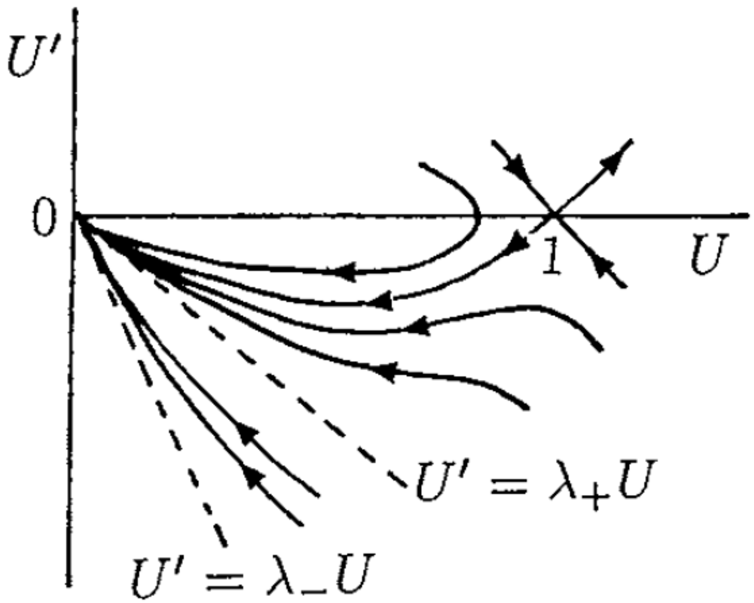
$$U'' + cU' + U(1-U) = 0$$

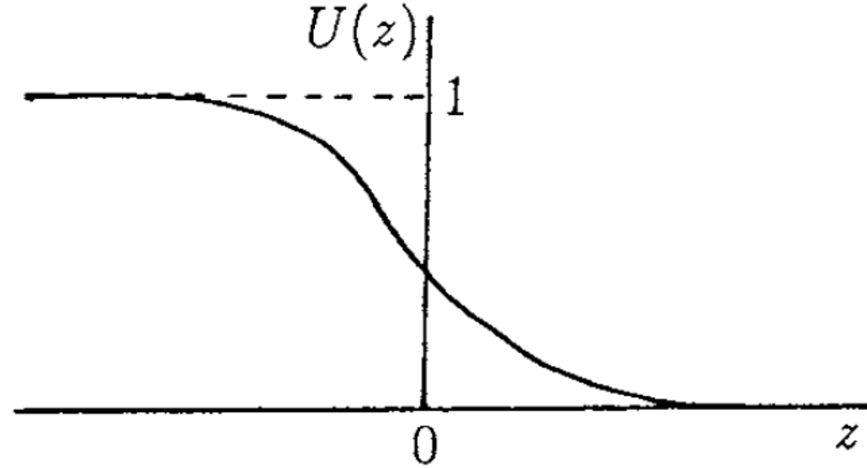
$$\lim_{z\to\infty} U(z) = 0, \quad \lim_{z\to-\infty} U(z) = 1$$

$$U' = V, \quad V' = -cV - U(1-U)$$

Murray, 2002

Fisher-Kolmogorov





Murray, 2002

Analysis: travelling waves

$$\frac{\partial v_r}{\partial t} = \mathcal{D}_r \frac{\partial^2 v_r}{\partial x^2} - \kappa_r v_r + 2\kappa_g v_g (1 - s),$$

$$\frac{\partial v_g}{\partial t} = \mathcal{D}_g \frac{\partial^2 v_g}{\partial x^2} - \kappa_g v_g (1 - s) + \kappa_r v_r,$$

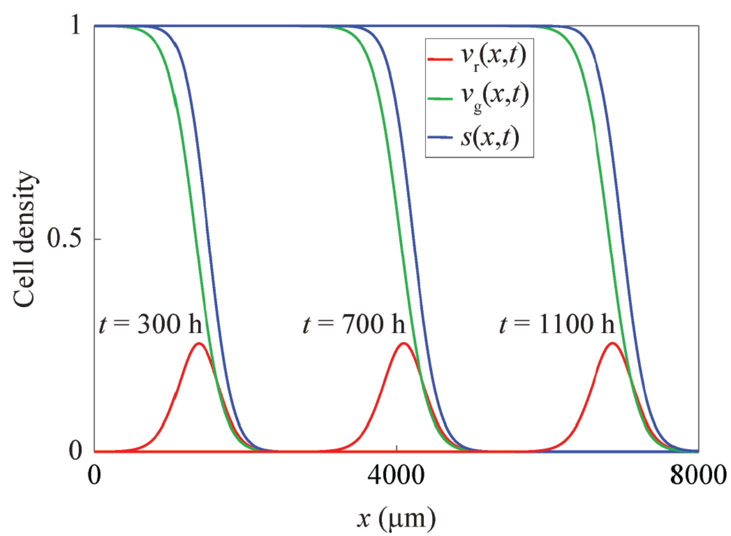
$$t^* = \kappa_g t \qquad x^* = x\sqrt{\frac{\kappa_g}{\mathcal{D}_r}}$$

$$\mathcal{D} = \frac{\mathcal{D}_g}{\mathcal{D}_r} \qquad \kappa = \frac{\kappa_r}{\kappa_g}$$

Analysis: travelling waves

$$\frac{\partial v_r}{\partial t} = \frac{\partial^2 v_r}{\partial x^2} - \kappa v_r + 2v_g(1-s),$$
$$\frac{\partial v_g}{\partial t} = \mathcal{D}\frac{\partial^2 v_g}{\partial x^2} - v_g(1-s) + \kappa v_r.$$

$$z = x - ct \qquad v_g(x,t) = V(z) \qquad v_r(x,t) = U(z)$$



Analysis: travelling waves

$$U'' + cU' - \kappa U + 2V(1 - U - V) = 0,$$

$$V'' + \frac{c}{\mathcal{D}}V' + \frac{\kappa}{\mathcal{D}}U - \frac{1}{\mathcal{D}}V(1 - U - V) = 0.$$

$$U > 0, \quad \lim_{z \to -\infty} U(z) = 0 \quad \text{and} \quad \lim_{z \to \infty} U(z) = 0,$$

$$V > 0, \quad \lim_{z \to -\infty} V(z) = 1 \quad \text{and} \quad \lim_{z \to \infty} V(z) = 0.$$

Analysis: travelling waves

$$U' = W,$$

$$V' = X,$$

$$W' = -cW + \kappa U - 2V(1 - U - V),$$

$$X' = -\frac{c}{\mathcal{D}}X - \frac{\kappa}{\mathcal{D}}U + \frac{1}{\mathcal{D}}V(1 - U - V).$$

$$(0, 1, 0, 0)$$

$$(0, 0, 0, 0)$$

$$\mathcal{D}\lambda^4 + c(\mathcal{D} + 1)\lambda^3 + (c^2 - 1 - \mathcal{D}\kappa)\lambda^2 - c(1 + \kappa)\lambda - \kappa = 0.$$

Analysis: travelling waves

$$\mathcal{D} = 1$$

$$\lambda_1^{\pm} = -\frac{1}{2}c \pm \frac{1}{2}\sqrt{\alpha^-(\kappa, c)} \qquad \lambda_2^{\pm} = -\frac{1}{2}c \pm \frac{1}{2}\sqrt{\alpha^+(\kappa, c)}$$

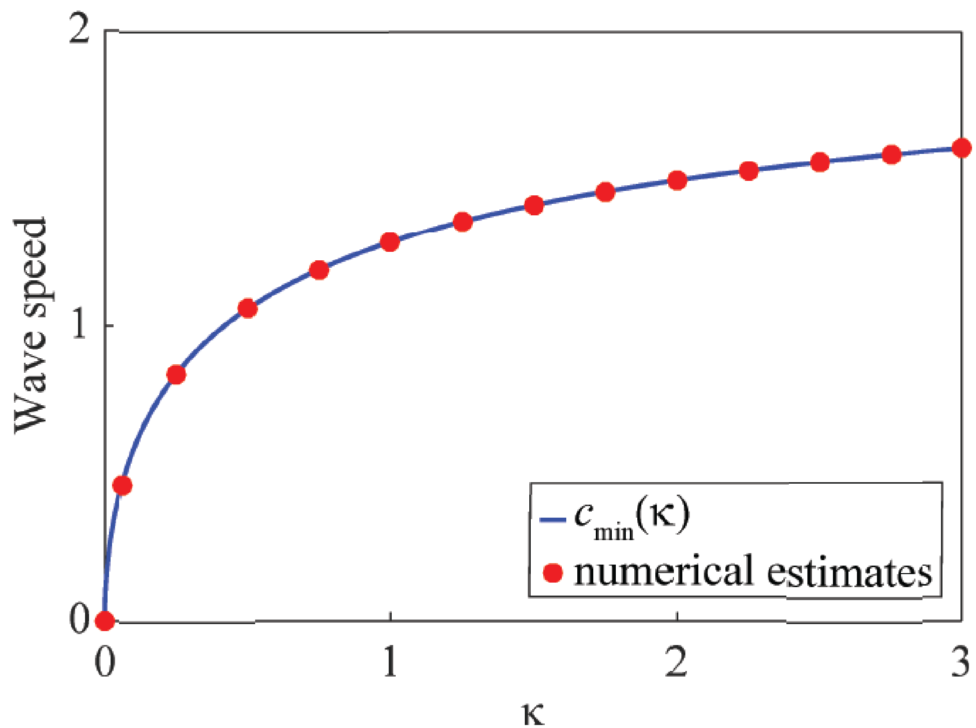
$$\alpha^{\pm}(\kappa, c) = 2\kappa + c^2 + 2 \pm 2\sqrt{\kappa^2 + 6\kappa + 1},$$

$$c_{\min}(\kappa) = \sqrt{-2\kappa - 2 + 2\sqrt{\kappa^2 + 6\kappa + 1}}$$

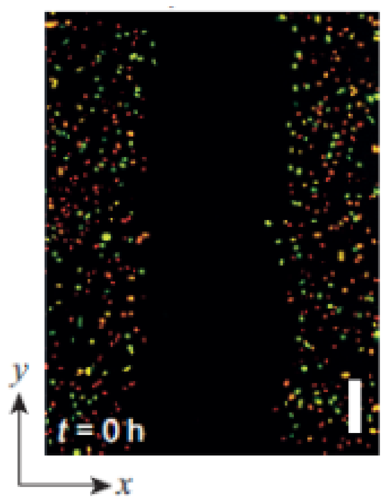
Analysis: travelling waves

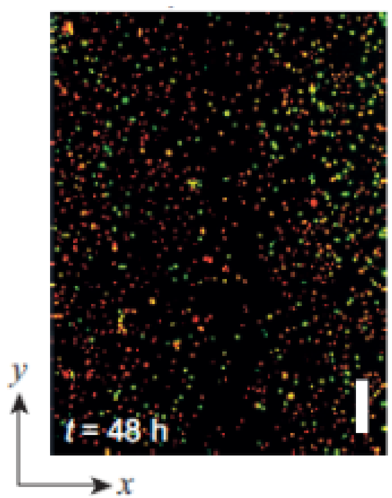
$\mathcal{D} = 1$

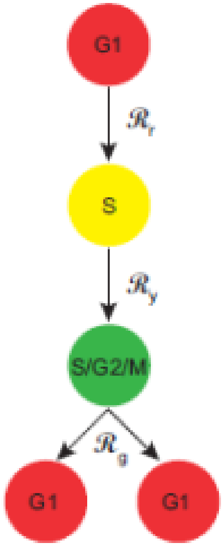
$$c_{\min}(\kappa) = \sqrt{-2\kappa - 2 + 2\sqrt{\kappa^2 + 6\kappa + 1}}$$

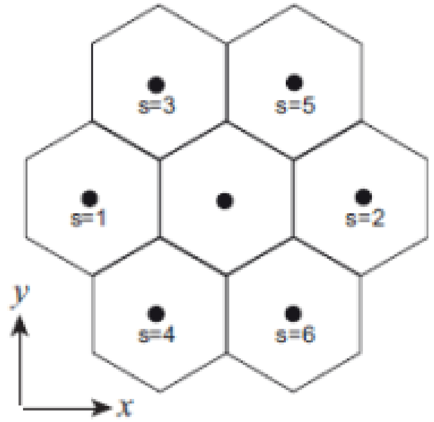


What about individual cells?

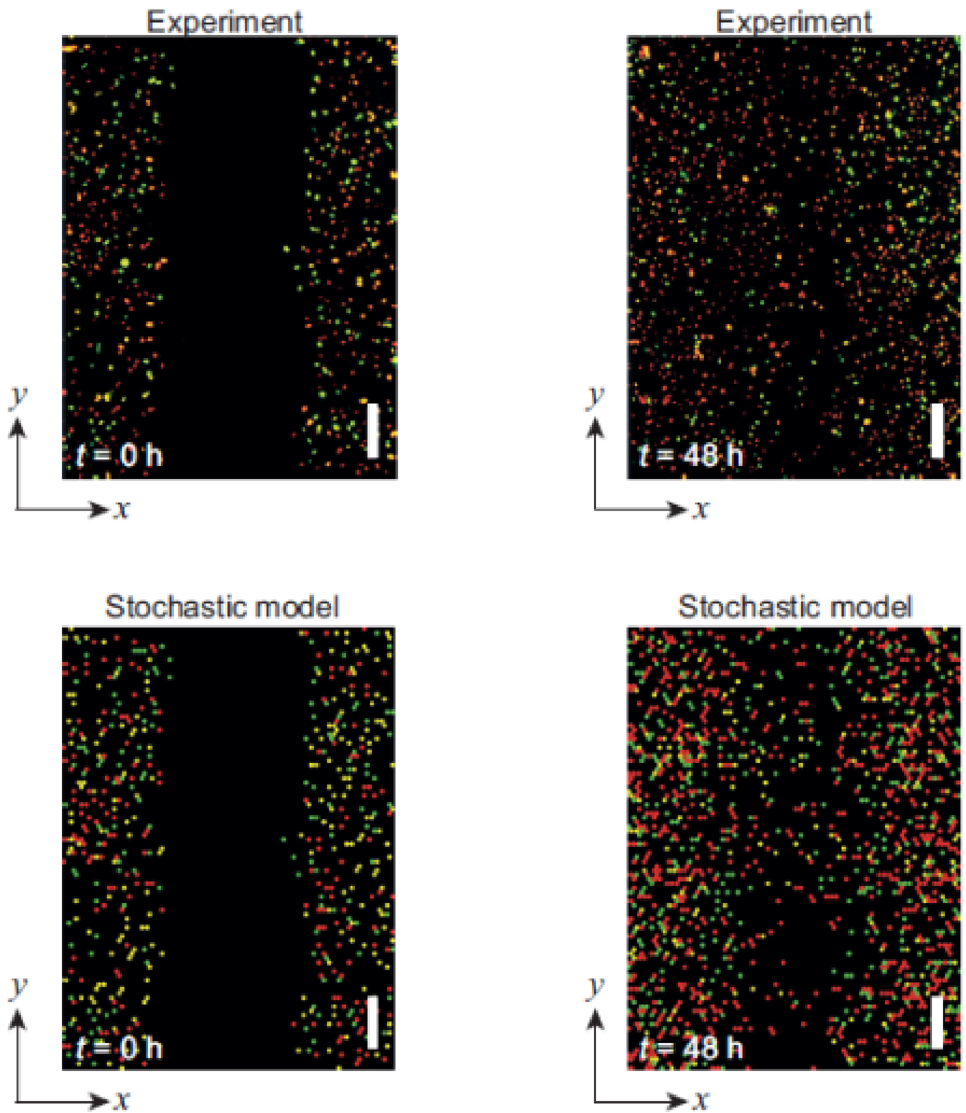








What about individual cells?



Alternative continuum description

$$R_k(t) = \frac{1}{N} \sum_{n=1}^{N} \mathbf{R}_k^{(n)}(t), \forall\, k = 1, 2, \ldots, K,$$

$$Y_k(t) = \frac{1}{N} \sum_{n=1}^{N} \mathbf{Y}_k^{(n)}(t), \forall\, k = 1, 2, \ldots, K,$$

$$G_k(t) = \frac{1}{N} \sum_{n=1}^{N} \mathbf{G}_k^{(n)}(t), \forall\, k = 1, 2, \ldots, K,$$

Alternative continuum description

$$R_k(t) = \frac{1}{N}\sum_{n=1}^{N}\mathbf{R}_k^{(n)}(t), \forall\, k = 1, 2, \ldots, K,$$

$$Y_k(t) = \frac{1}{N}\sum_{n=1}^{N}\mathbf{Y}_k^{(n)}(t), \forall\, k = 1, 2, \ldots, K,$$

$$G_k(t) = \frac{1}{N}\sum_{n=1}^{N}\mathbf{G}_k^{(n)}(t), \forall\, k = 1, 2, \ldots, K,$$

$$\frac{\mathrm{d}R_k}{\mathrm{d}t} = \begin{cases} +\text{ increase in occupancy of red agents at site } k \text{ due to migration of red agents into site } k \\ -\text{ decrease in occupancy of red agents at site } k \text{ due to migration of red agents out of site } k \\ -\text{ decrease in occupancy of red agents at site } k \text{ due to red agents transitioning to yellow} \\ +\text{ increase in occupancy of red agents at site } k \text{ due to green agents transitioning to red} \end{cases}$$

$$= \frac{M_r}{6}\left[(1-T_k)\sum_{s=1}^{6}R_s - R_k\sum_{s=1}^{6}(1-T_s)\right] - \mathcal{R}_r R_k + \frac{\mathcal{R}_g}{6}\left[G_k\sum_{s=1}^{6}(1-T_s) + (1-T_k)\sum_{s=1}^{6}G_s\right],$$

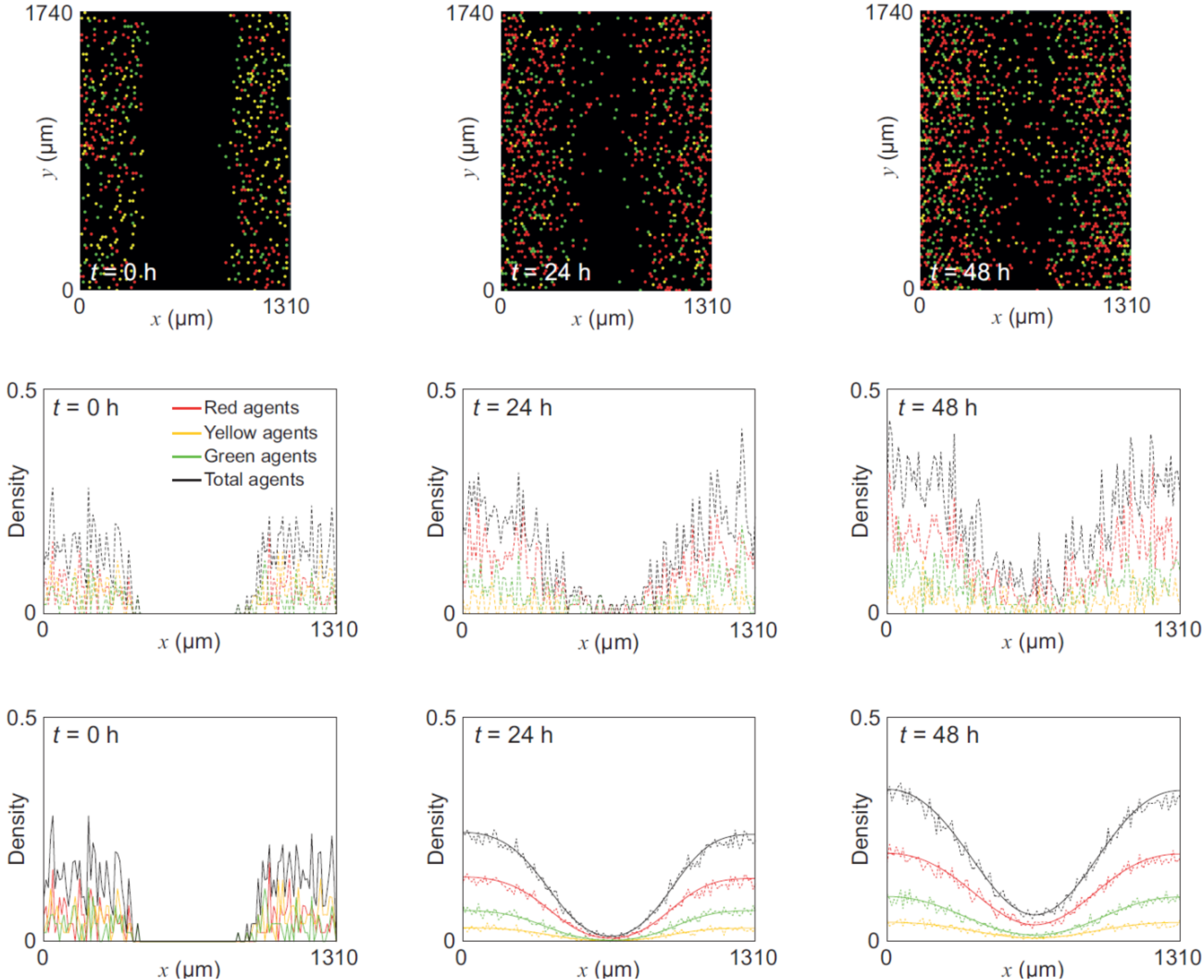
Alternative continuum description

$$\frac{\partial R}{\partial t} = D_r \nabla \cdot [(1 - T)\nabla R + R\nabla T] - \mathcal{R}_r R + 2\mathcal{R}_g G(1 - T),$$

$$\frac{\partial Y}{\partial t} = D_y \nabla \cdot [(1 - T)\nabla Y + Y\nabla T] - \mathcal{R}_y Y + \mathcal{R}_r R,$$

$$\frac{\partial G}{\partial t} = D_g \nabla \cdot [(1 - T)\nabla G + G\nabla T] - \mathcal{R}_g G(1 - T) + \mathcal{R}_y Y,$$

$D_r = \lim_{\Delta \to 0}(M_r \Delta^2)/4$, $D_y = \lim_{\Delta \to 0}(M_y \Delta^2)/4$ and $D_g = \lim_{\Delta \to 0}(M_g \Delta^2)/4$



1740
0
y (μm)
x (μm)
1310
t = 0 h
t = 24 h
t = 48 h
0.5
Density
Red agents
Yellow agents
Green agents
Total agents

Conclusions

- New (extended) continuum models for cell migration and proliferation explicitly tracking the cell cycle within a population of cells
- Connecting new models with experimental data
- Future work:
    - Formal analysis of travelling wave solutions
    - Experimental: modelling the action of anti-cancer drugs

Biophysical Journal
Article

Biophysical Society

Mathematical Models for Cell Migration with Real-Time Cell Cycle Dynamics

Sean T. Vittadello,[1] Scott W. McCue,[1] Gency Gunasingh,[2] Nikolas K. Haass,[2,3] and Matthew J. Simpson[1,*]
[1]School of Mathematical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia; [2]The University of Qu
The University of Queensland Diamantina Institute, Translational Research Institute, Woolloongabba, Brisbane, Queensland, Aus
[3]Discipline of Dermatology, Faculty of Medicine, Central Clinical School, University of Sydney, Sydney, New South Wales, Austra

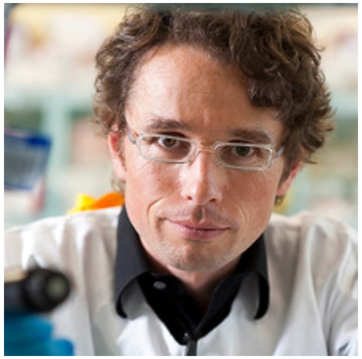
ELSEVIER
Contents lists available at ScienceDirect
Physica A
journal homepage: www.elsevier.com/locate/physa

Stochastic models of cell invasion with fluorescent cell cycle indicators

Check for updates

Matthew J. Simpson[a,*], Wang Jin[a], Sean T. Vittadello[a], Tamara A. Tambyah[a], Jacob M. Ryan[a], Gency Gunasingh[b], Nikolas K. Haass[b,c], Scott W. McCue[a]
[a] School of Mathematical Sciences, Queensland University of Technology, Brisbane, Australia
[b] The University of Queensland, The University of Queensland Diamantina Institute, Translational Research Institute, 37 Kent St, Woolloongabba, Brisbane, QLD 4102, Australia
[c] Discipline of Dermatology, Faculty of Medicine, Central Clinical School, University of Sydney, Sydney, NSW, Australia

Acknowledgements


Nikolas Hass, UQ


Sean Vittadello, QUT


Gency Gunasingh, UQ


Scott McCue, QUT

Australian Government

Australian Research Council


Mat Simpson, QUT


Brisbane


PhD scholarship:
OCTOBER 31
matthew.simpson@qut.edu.au
@ProfMJSimpson

Link back to Fisher-Kolmogorov

$$c_{\min} = \sqrt{2\mathcal{D}_r\Big(- \kappa_r - \kappa_g + \sqrt{\kappa_r^2 + 6\kappa_r\kappa_g + \kappa_g^2}\Big)}$$

$$\mathcal{D}_r = \mathcal{D}_g$$

$$c_{\min} \sim 2\sqrt{\kappa_r \mathcal{D}_r}(1 - \kappa_r/\kappa_g) \quad \text{as} \quad \kappa_r/\kappa_g \to 0$$

$$c_{\min} \sim 2\sqrt{\kappa_g \mathcal{D}_g}(1 - \kappa_g/\kappa_r) \quad \text{as} \quad \kappa_g/\kappa_r \to 0$$