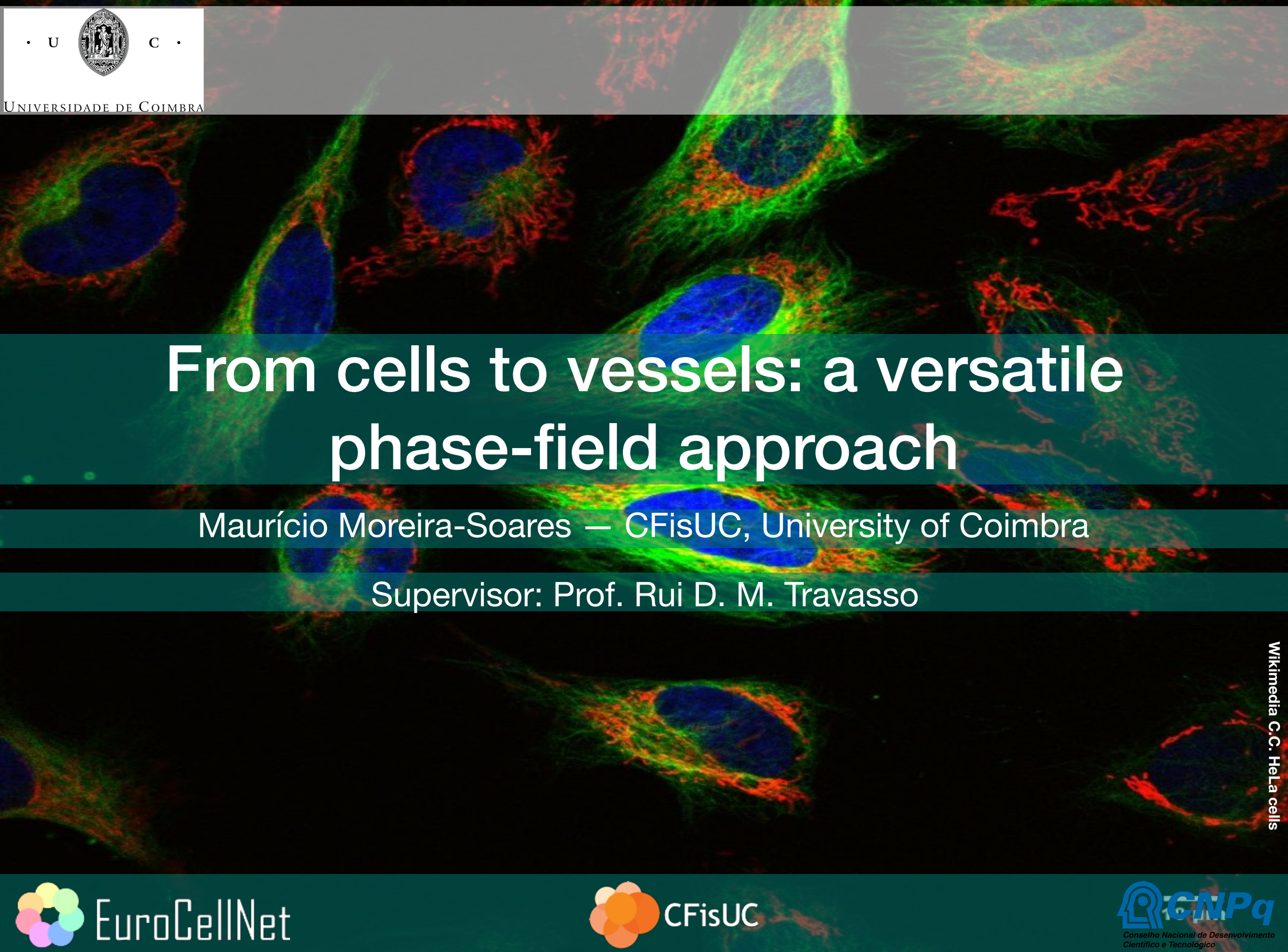


From cells to vessels: a versatile phase-field approach

Maurício Moreira-Soares — CFisUC, University of Coimbra

Supervisor: Prof. Rui D. M. Travasso

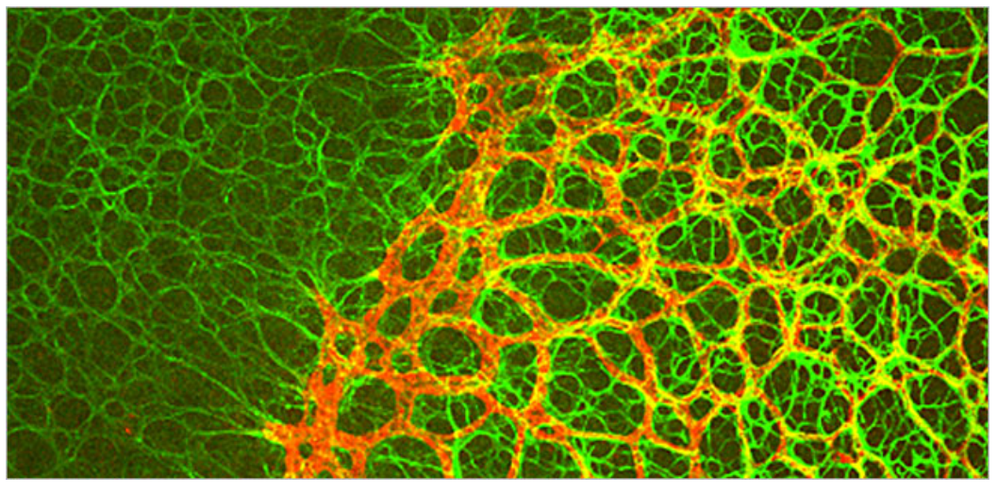
Wikimedia C.C. HeLa cells

EuroCellNet

CFisUC

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

:~$ Introduction > biological motivation

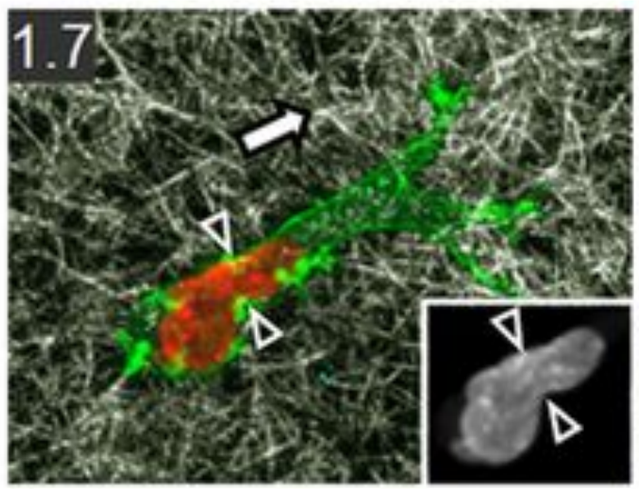


Scott et al, PLoS One 2010

~ Cell migration is key for life

~ The study of cell migration
allows to better understand diseases

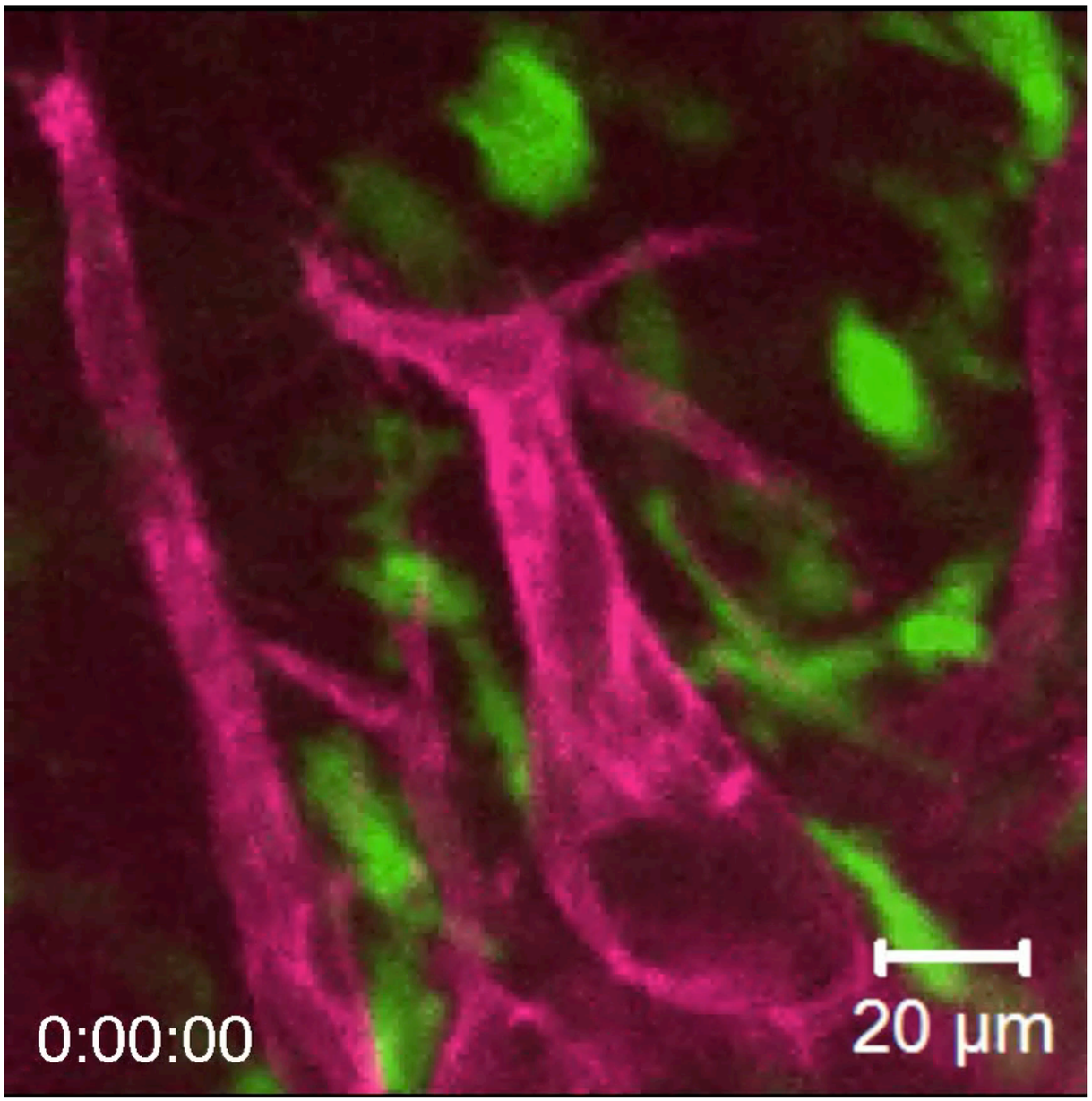
~ Metastasis is one of the most complex migration phenomena



K Wolf et al, JCB 2013

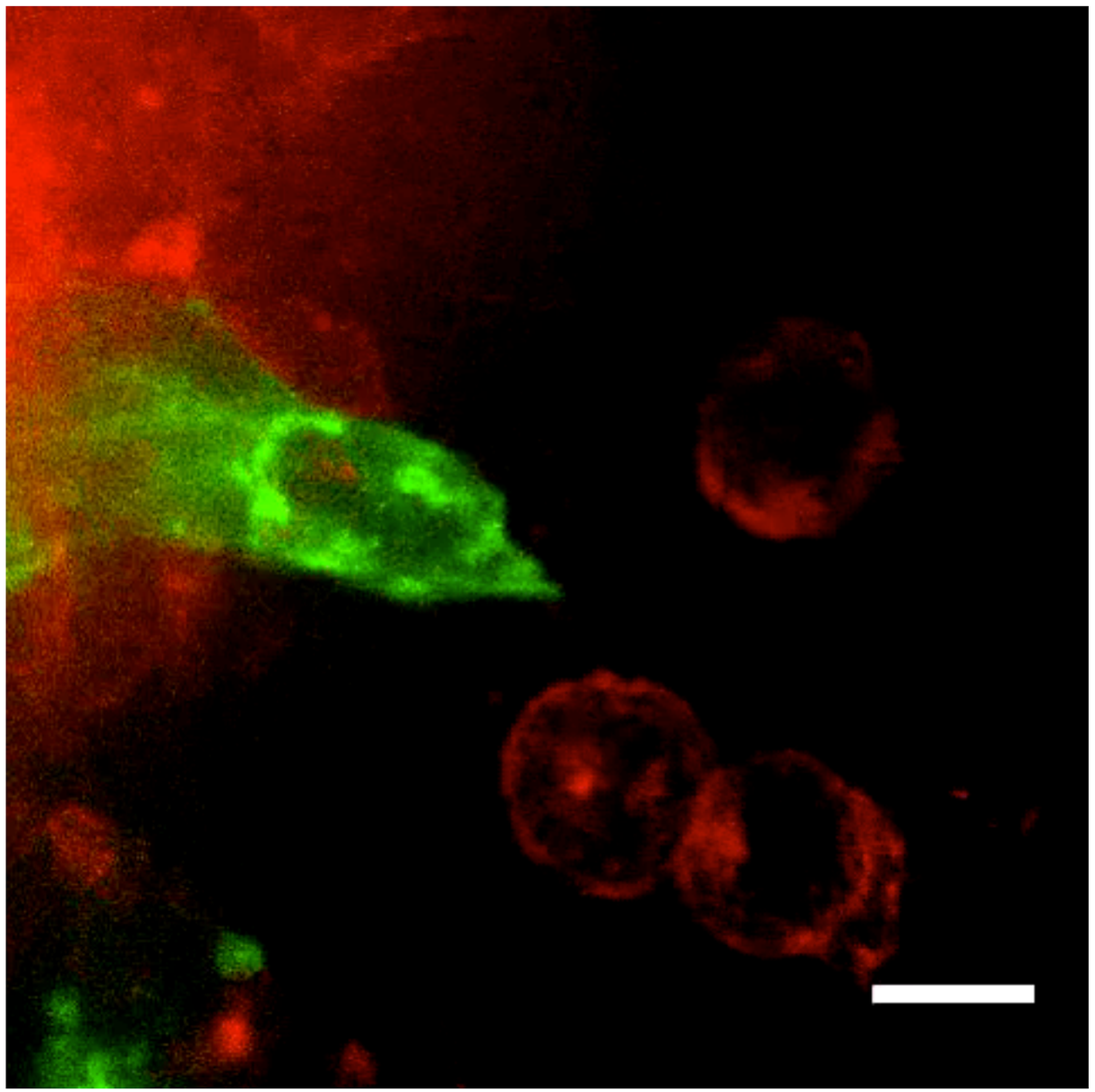
:~$ What does physics have to do with cell biology?

Macrophages



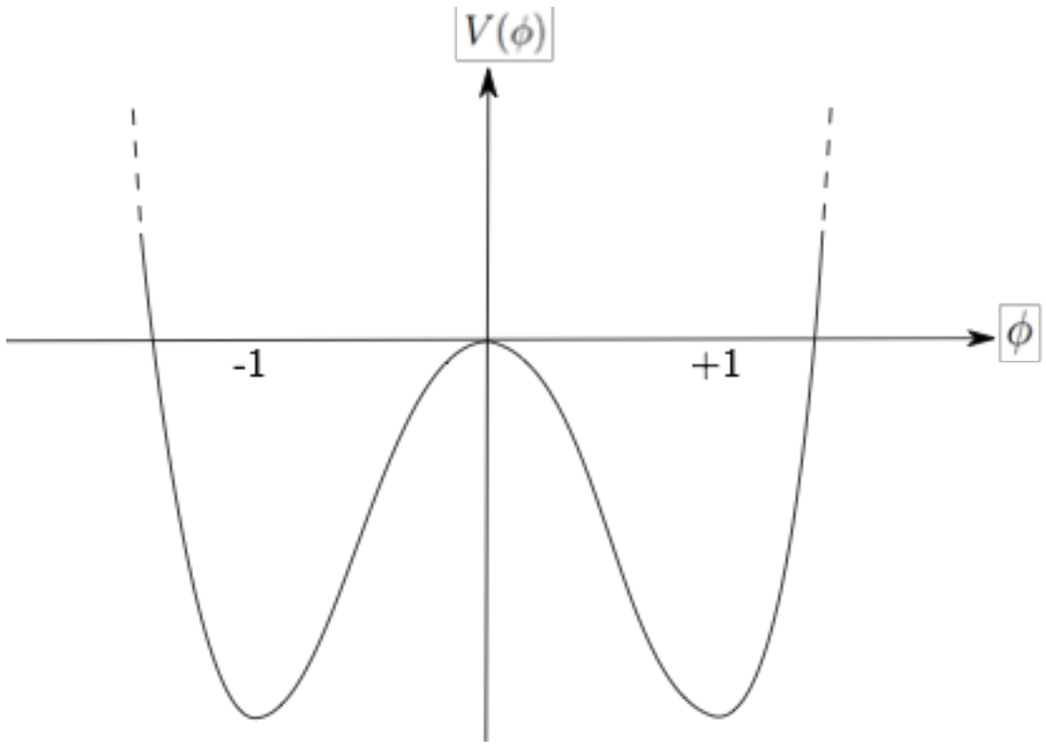
Sirka O. K. et al, JCB 2018

Myoepithelial cells



Chih-Wei Hsu et al, PLoS One 2015

:~$ Introduction > phase-field models



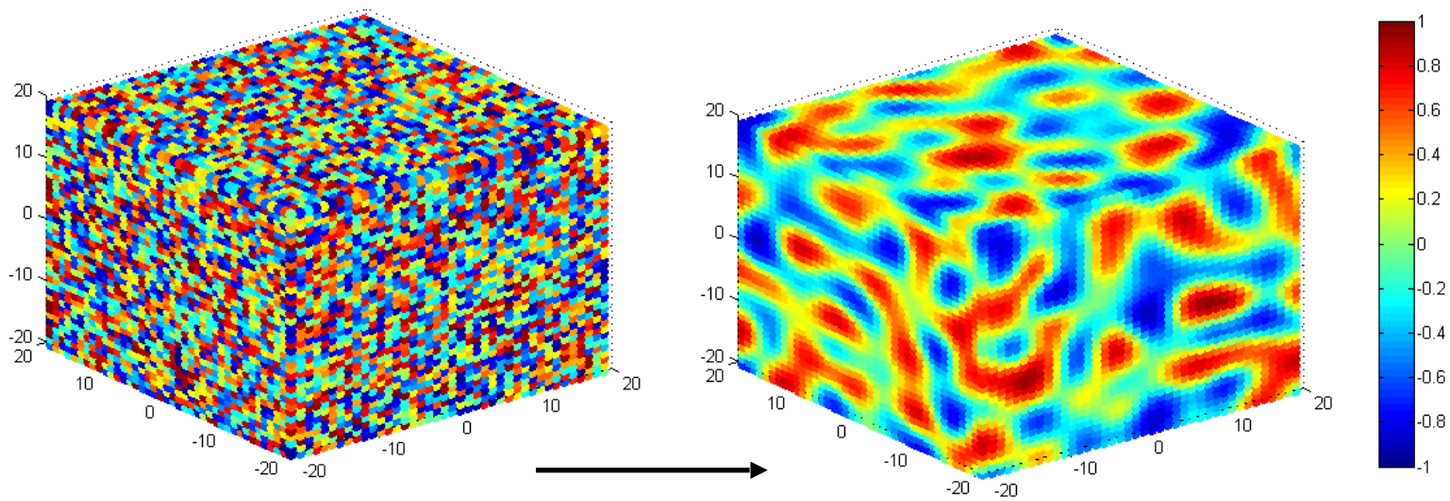
Free energy functional

$$F[\phi] = \int_{\Omega} \mathrm{d}\mathbf{r} \left[V(\phi) + \frac{\varepsilon^2}{2} |\nabla \phi|^2 \right]$$

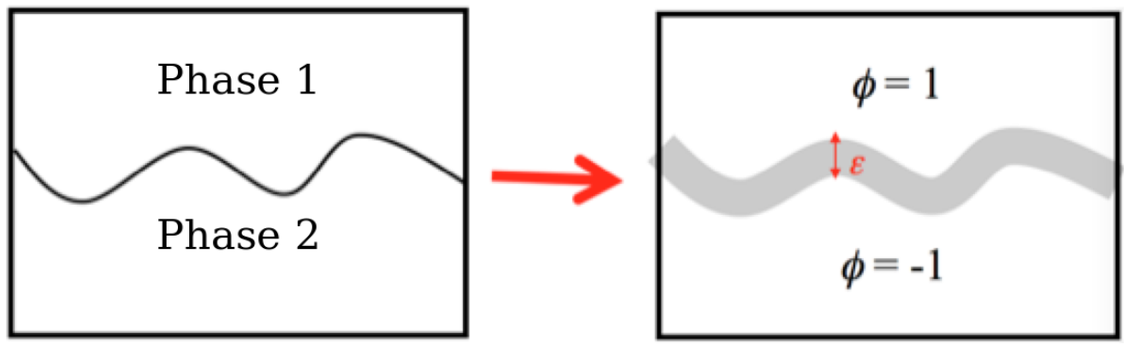
Dynamics equation

$$\partial_t \phi = \nabla^2 \left(\frac{\delta F[\phi]}{\delta \phi} \right) = \nabla^2 \left(\phi^3 - \phi - \varepsilon \nabla^2 \phi \right)$$

Cahn-Hilliard dynamics



:~$ Introduction > phase-field models



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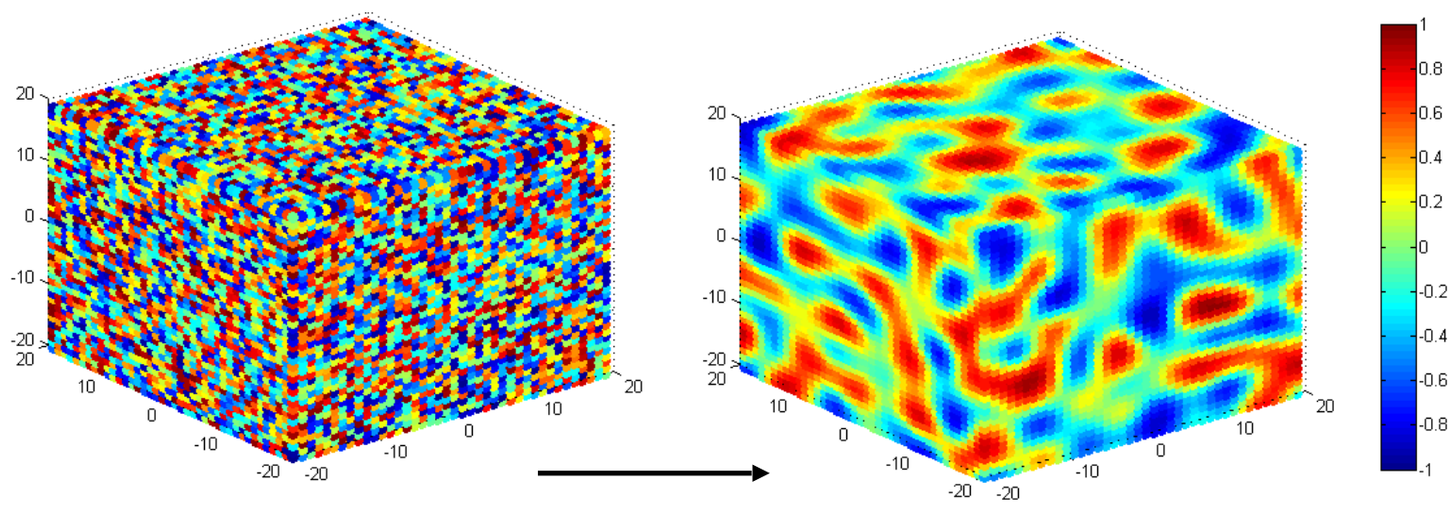
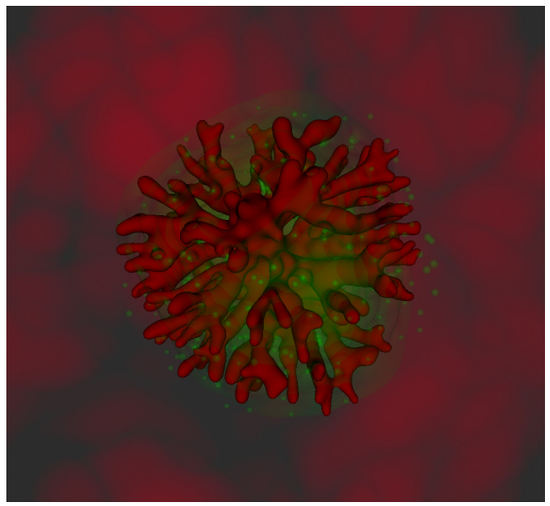
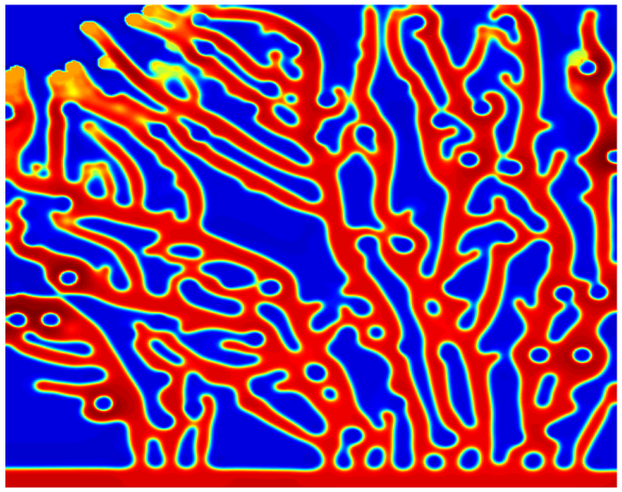


:~$ Phase-field models > biological systems

Angiogenesis

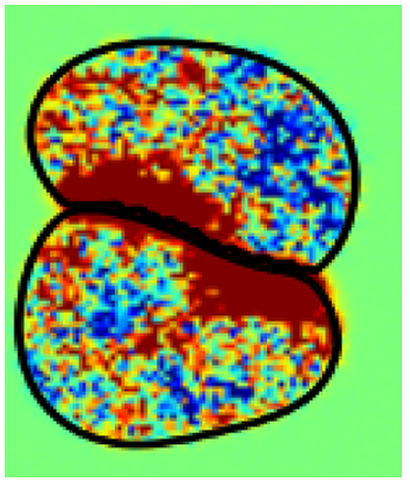


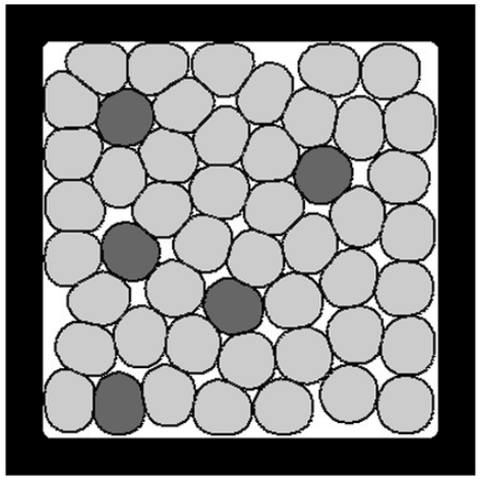


M Moreira-Soares et al, Sci Rep 2018

Cell Modelling

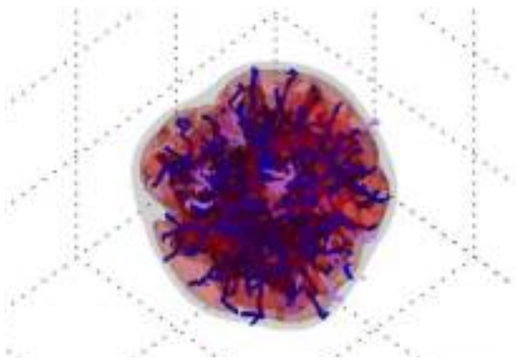
M Nonomura, PLoS One 2012





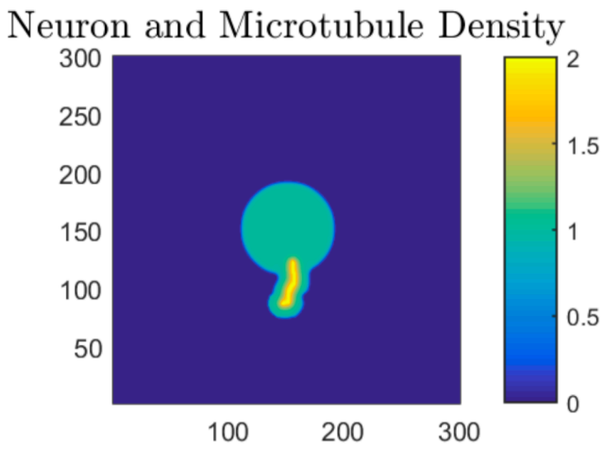
D Kulawiak et al, PLoS Comp Biol 2016

Tumour Growth

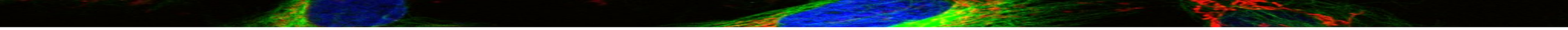


H Frieboes et al, J Teor Biol 2010

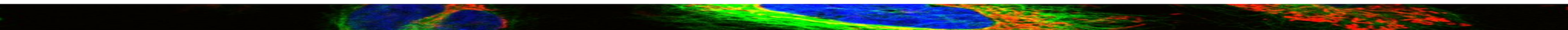
Axonal Growth



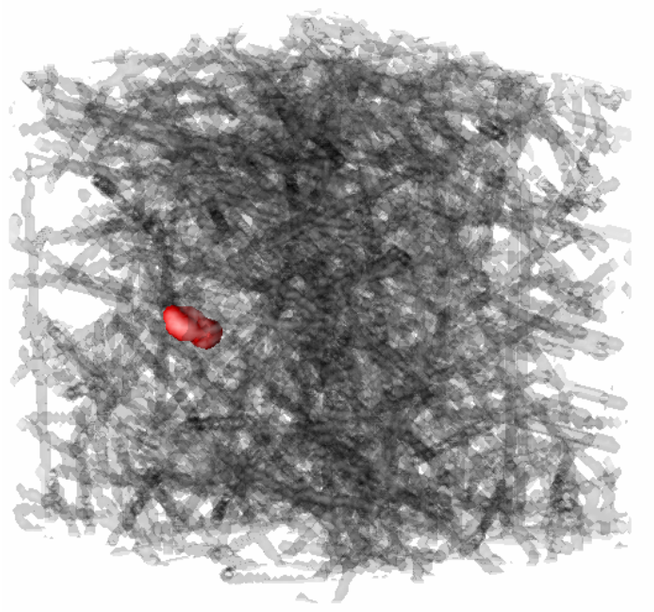
B Costa-Gomes, Master's Thesis, 2016



Part I - Cell Migration



:~$ Part I > cell migration



~ The cell is described by the parameter ϕ

~ and the fibres by ψ

~ they interact by <u>adhesion</u> and <u>repulsion</u>

Surface tension

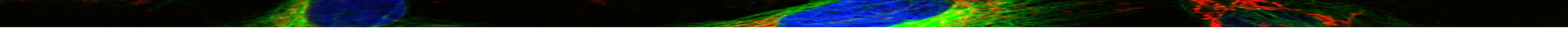
Lagrange multiplier

$$\partial_t \phi + \nu \cdot \nabla \phi = \varepsilon^2 \nabla^2 \phi + \phi(1-\phi)\left(\phi - \frac{1}{2} + \alpha_v\left(V_t - v(t)\right) + \eta \nabla^2 h(\psi) - \gamma h(\psi)\right)$$

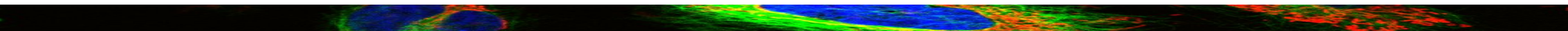
Advection

Adhesion

Repulsion



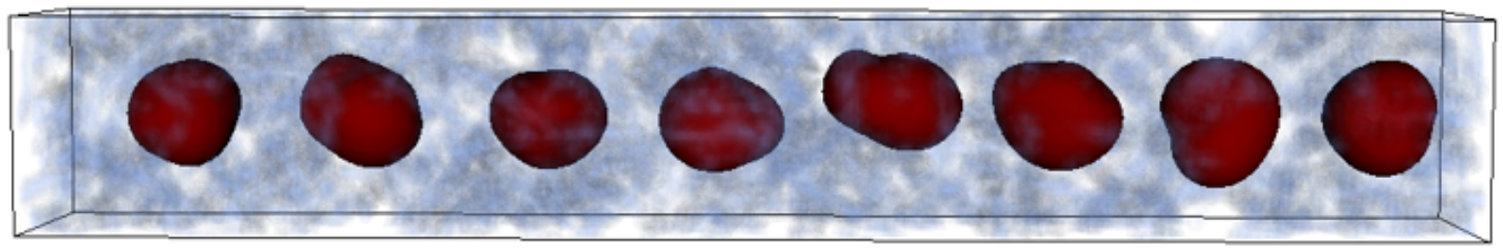
How is migration affected by mechanical constraints?



:~$ Part I > Results > migration dynamics

$\rho = 0.2$

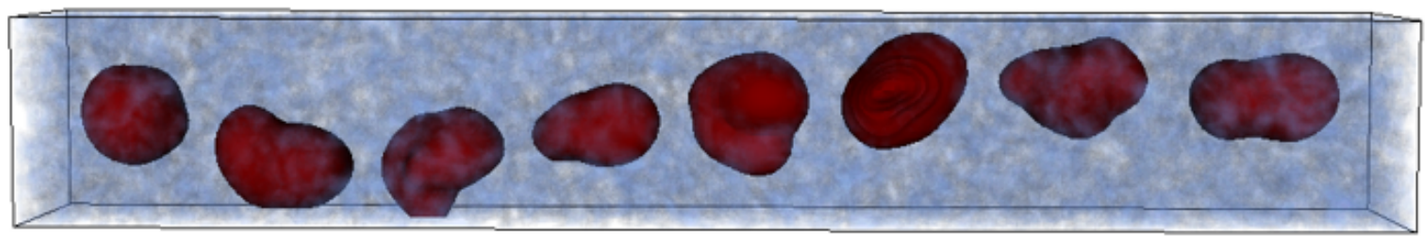
1D



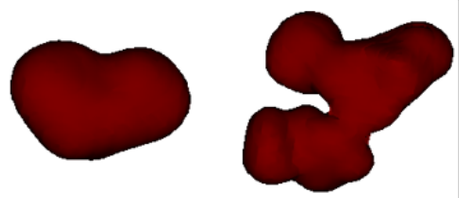
Transition

$\rho = 0.54$

3D

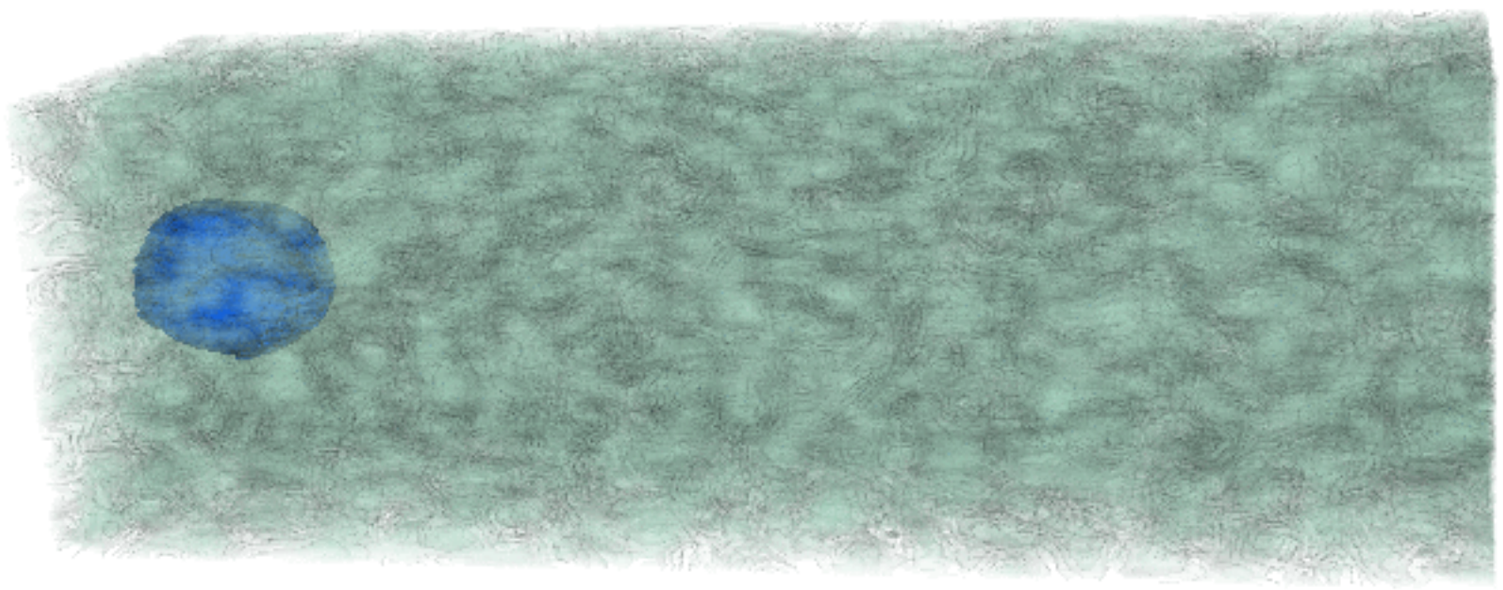


A.R = 2.30 - 5.23

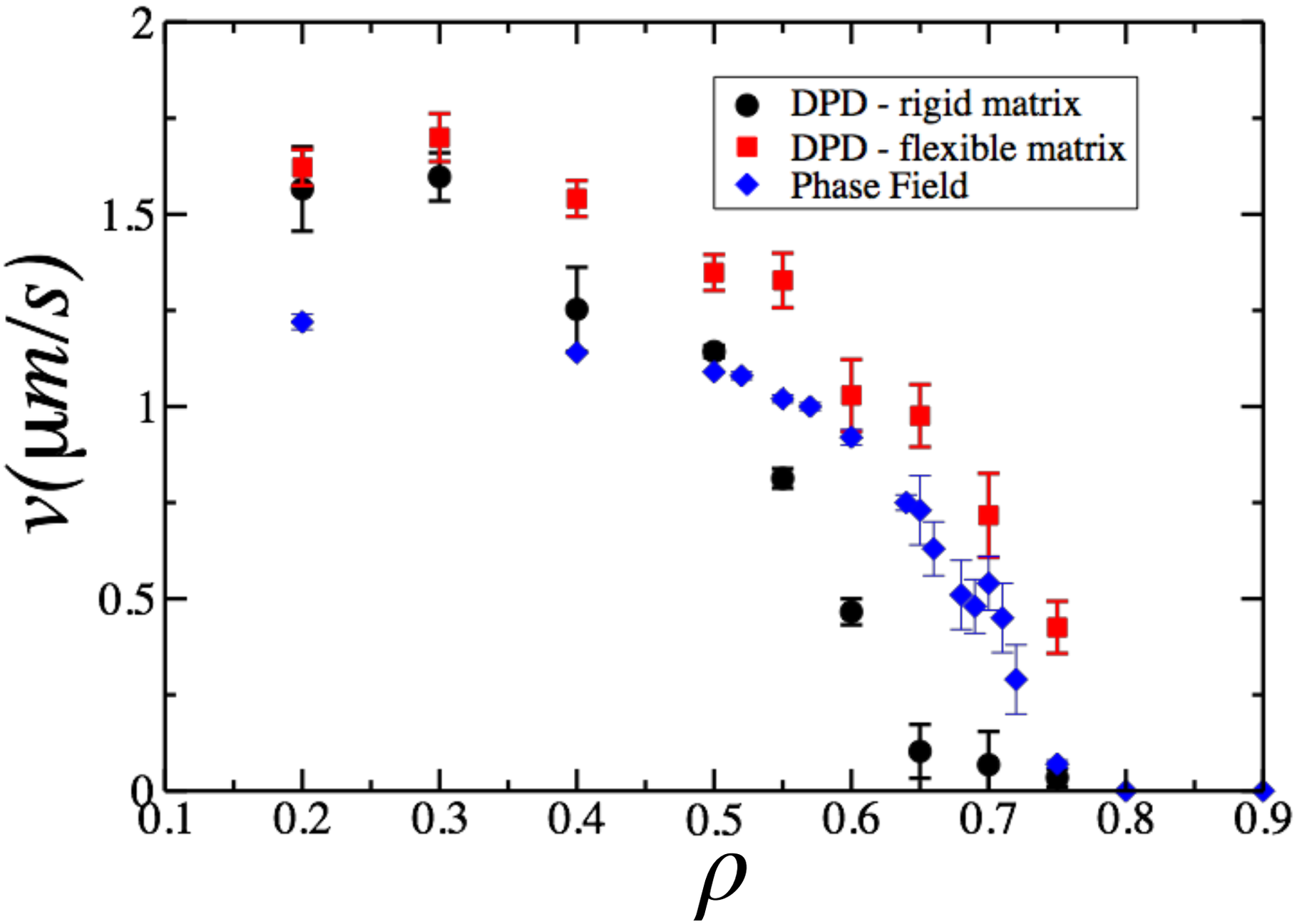


Adhesion

:~$ Did you bring the 3D glasses?



:~$ Part I > Results > mean velocity vs density

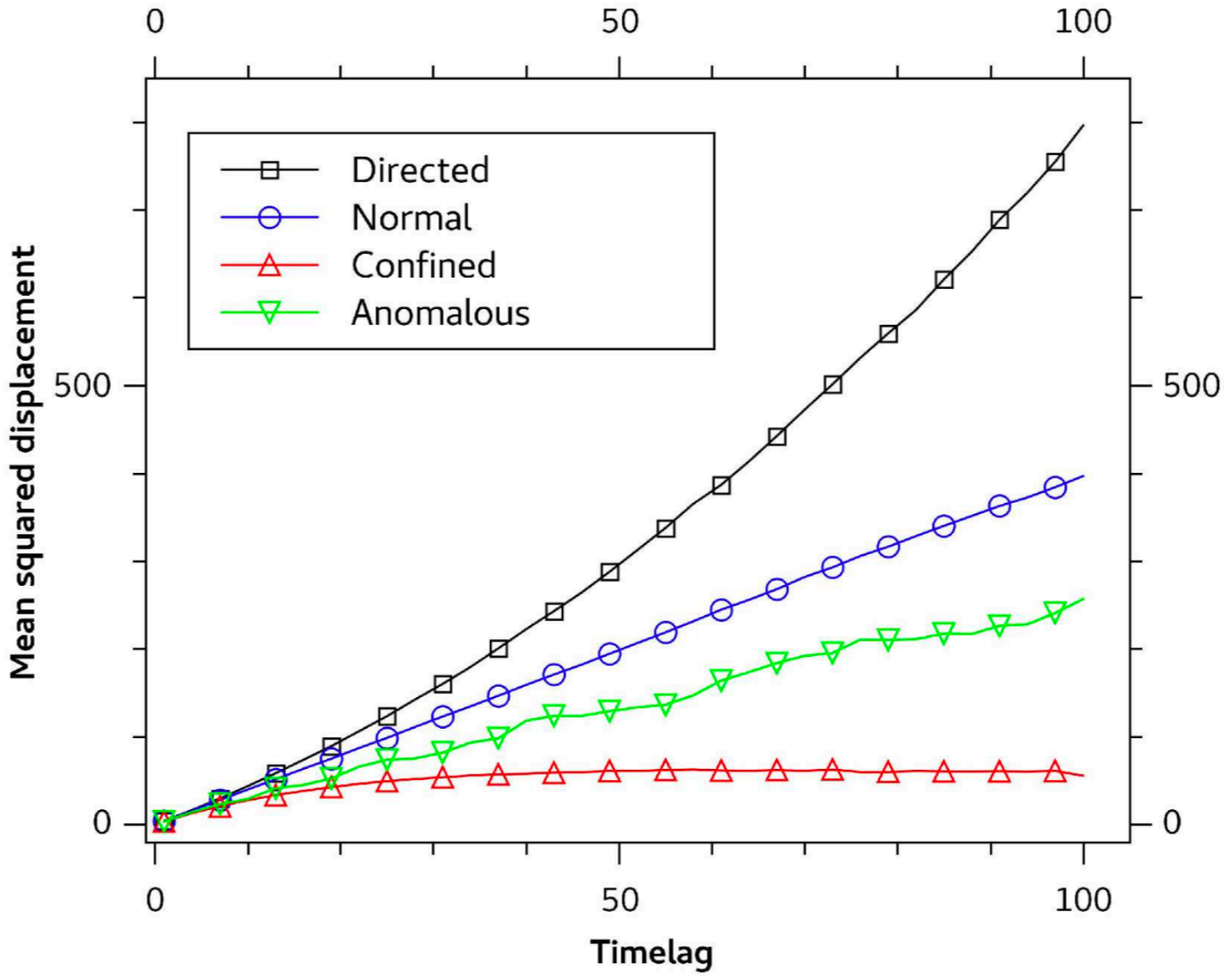


~ Mean velocity as a function of the density of fibres

:~$ Part I > Results > migration dynamics

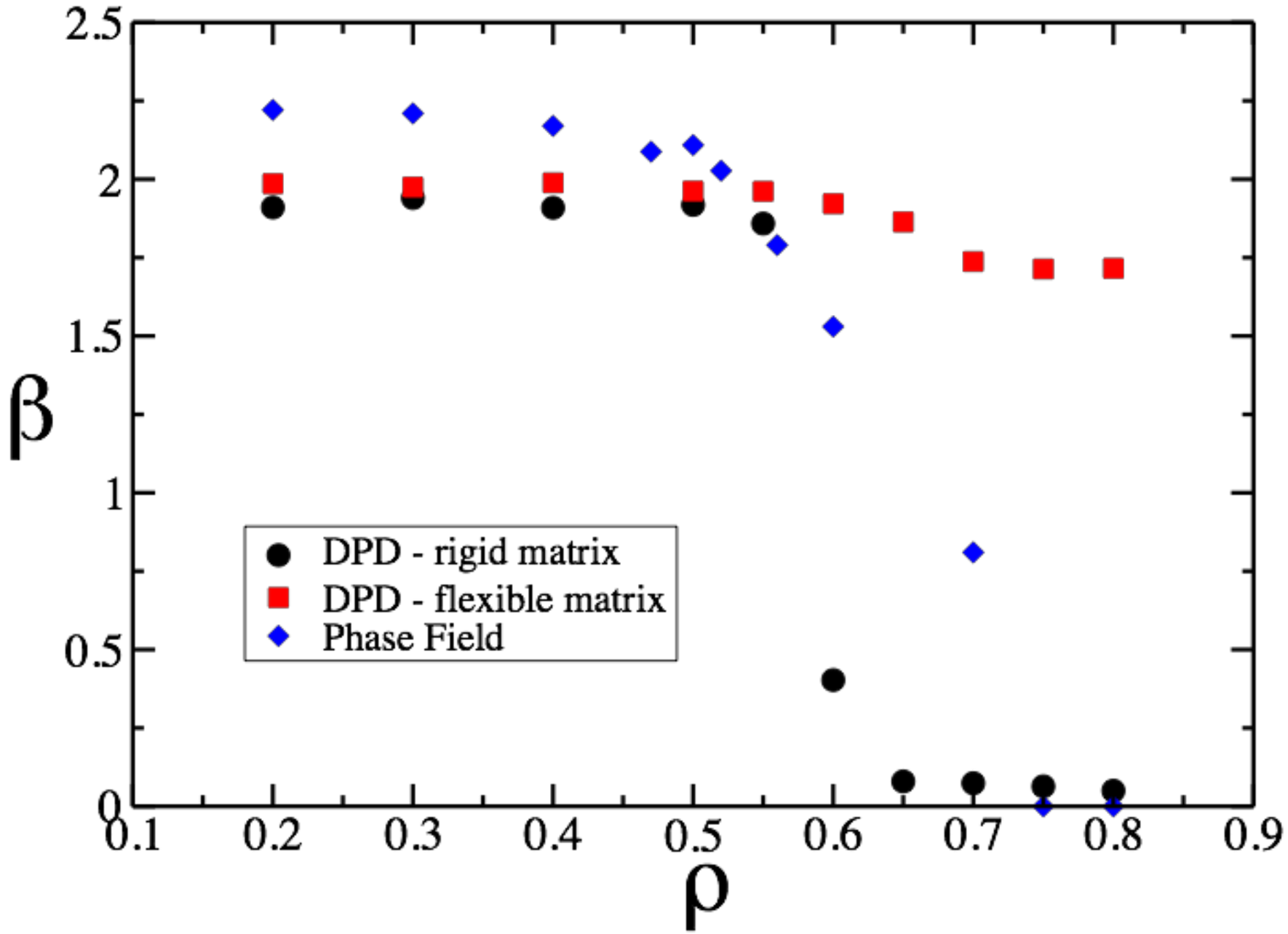
~ The diffusion exponent calculated helps us to characterise migration

$$\beta = \frac{\partial \ln\langle \mathrm{MSD} \rangle}{\partial \ln t}$$



Wagner T et al, PLoS One 2017

:~$ Part I > Results > diffusion exponent vs density

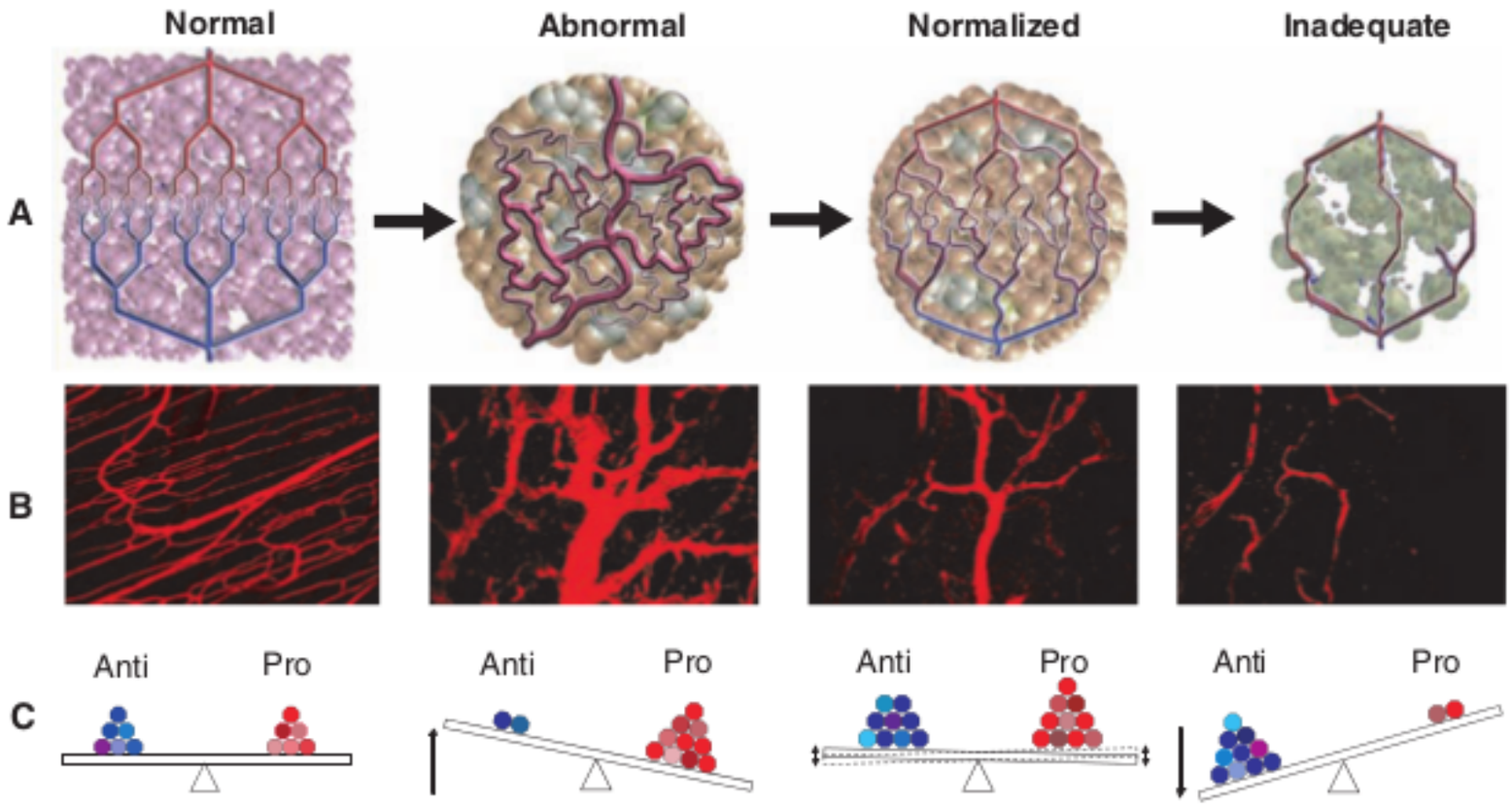


~ Diffusion exponent as a function of density of fibres

Part II - Angiogenesis

:~$ Part II > Angiogenesis

~ Growth of new blood vessels from a preexisting vasculature



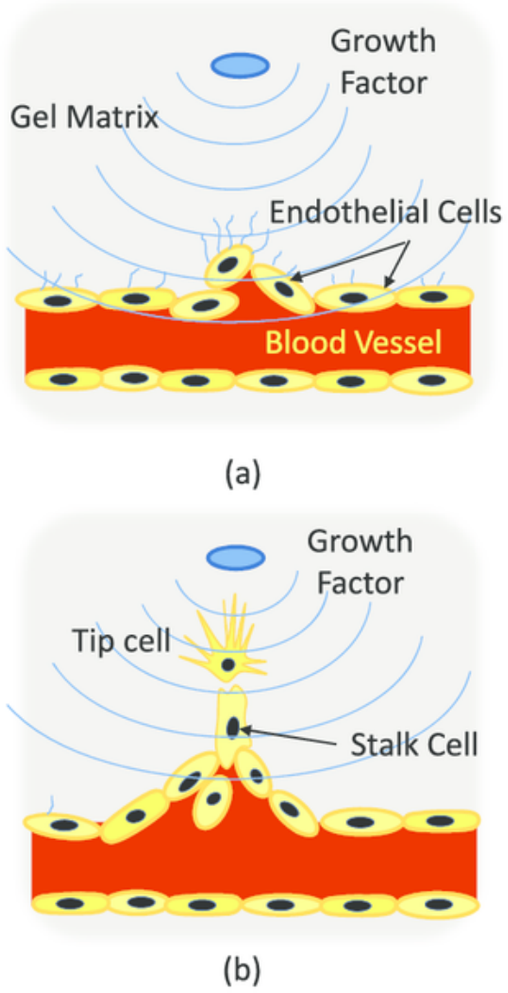
R K Jain, Nat Med, 2007

:~$ Part II > Angiogenesis

~ Endothelial Cells (ECs)
  ~ Tip Cells (ETCs)
  ~ Stalk Cells (ESCs)

~ Hypoxic Cells
  ~ Produce **V**ascular
  Endothelial
  Growth
  Factors

~ Blood flow
  ~ irrigates the tissue



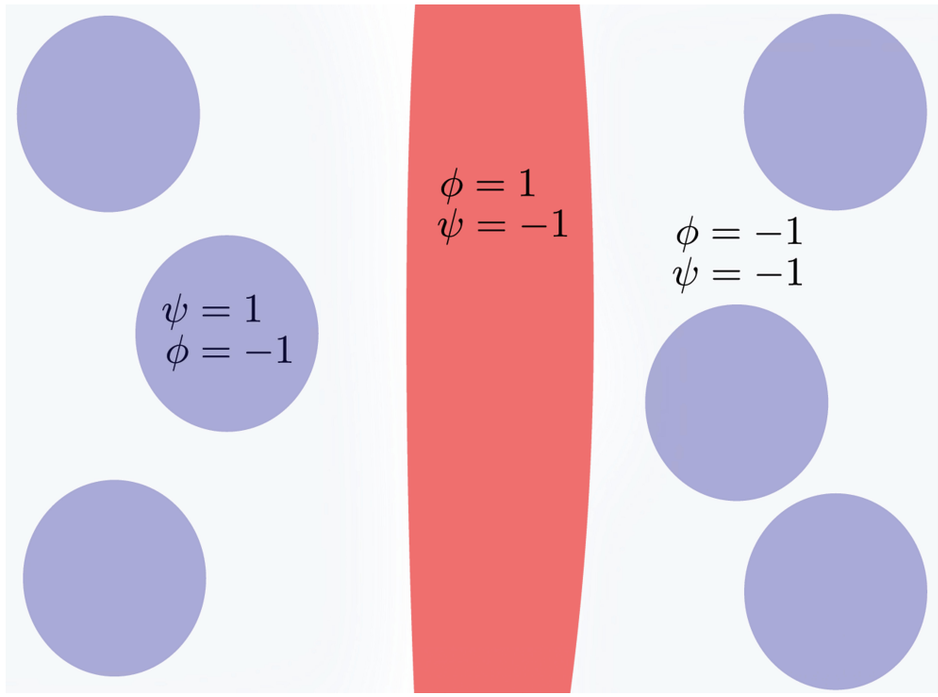
L B Wood, IJRR, 2011

:~$ Phase-field model for Angiogenesis

$$\partial_t \phi = \underbrace{M\nabla^2\left[\phi^3 - \phi - \varepsilon^2\nabla^2\phi + \gamma(\phi^2-1)(\psi-2)(\psi+1)^2\right]}_{\text{Interface Dynamics}} + \underbrace{\alpha_p(T)\ \phi\ \Theta(\phi)}_{\text{EC Proliferation}}$$

$$\partial_t T = D\nabla^2 T - \alpha_T \phi T \Theta(\phi)$$

$$\mathbf{v} = \chi_T(T)\nabla T\left[1 + \left(\frac{G_M}{G} - 1\right)\Theta(G - G_M)\right]$$

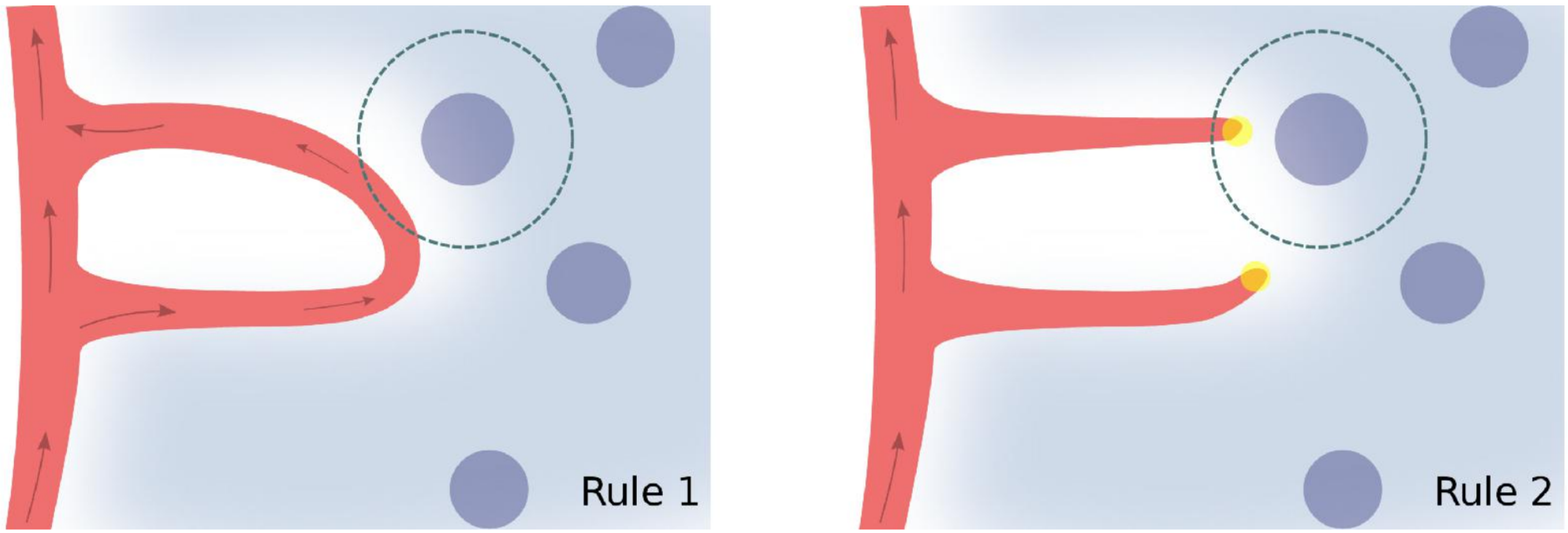


~ We model the vessels ϕ and the hypoxic cells ψ

~ The tissues cannot superpose

~ Endothelial Tip Cells are guided by chemotaxis

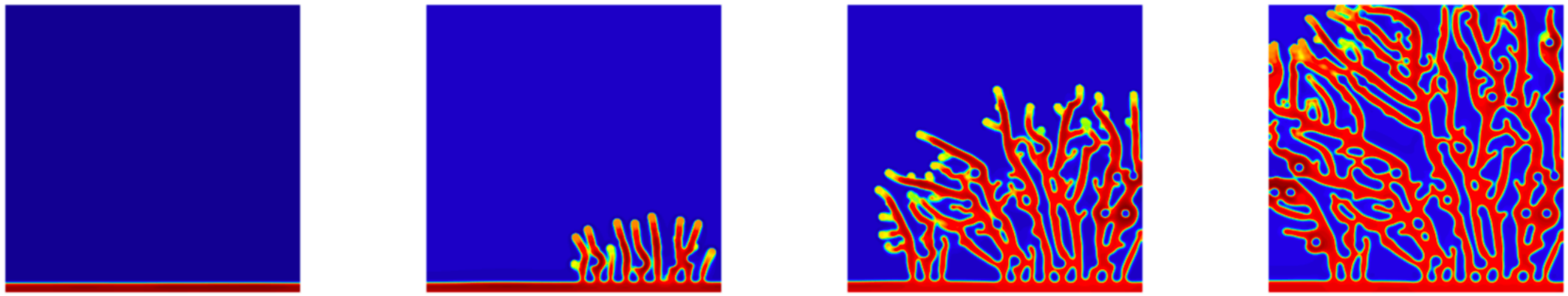
:~$ Phase-field model for Angiogenesis



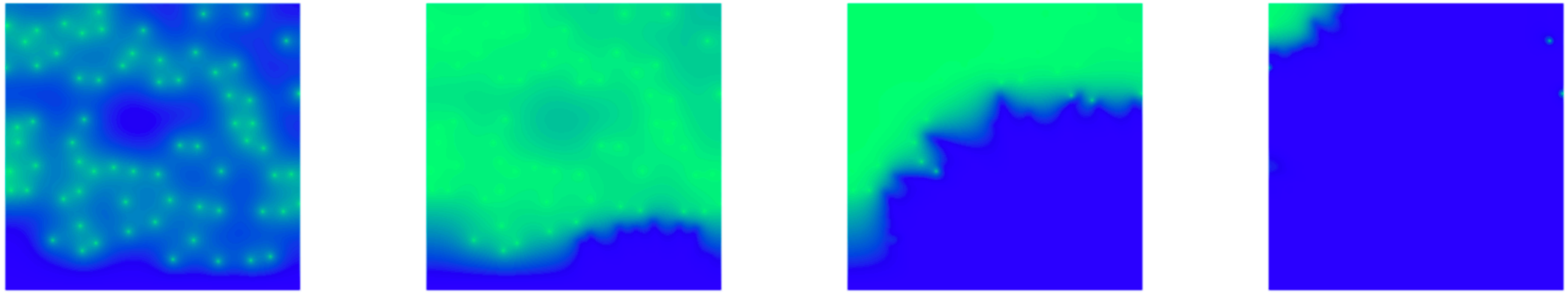
~ Two rules for deactivating VEGF production were tested

:~$ Phase-field model for Angiogenesis

Vessels



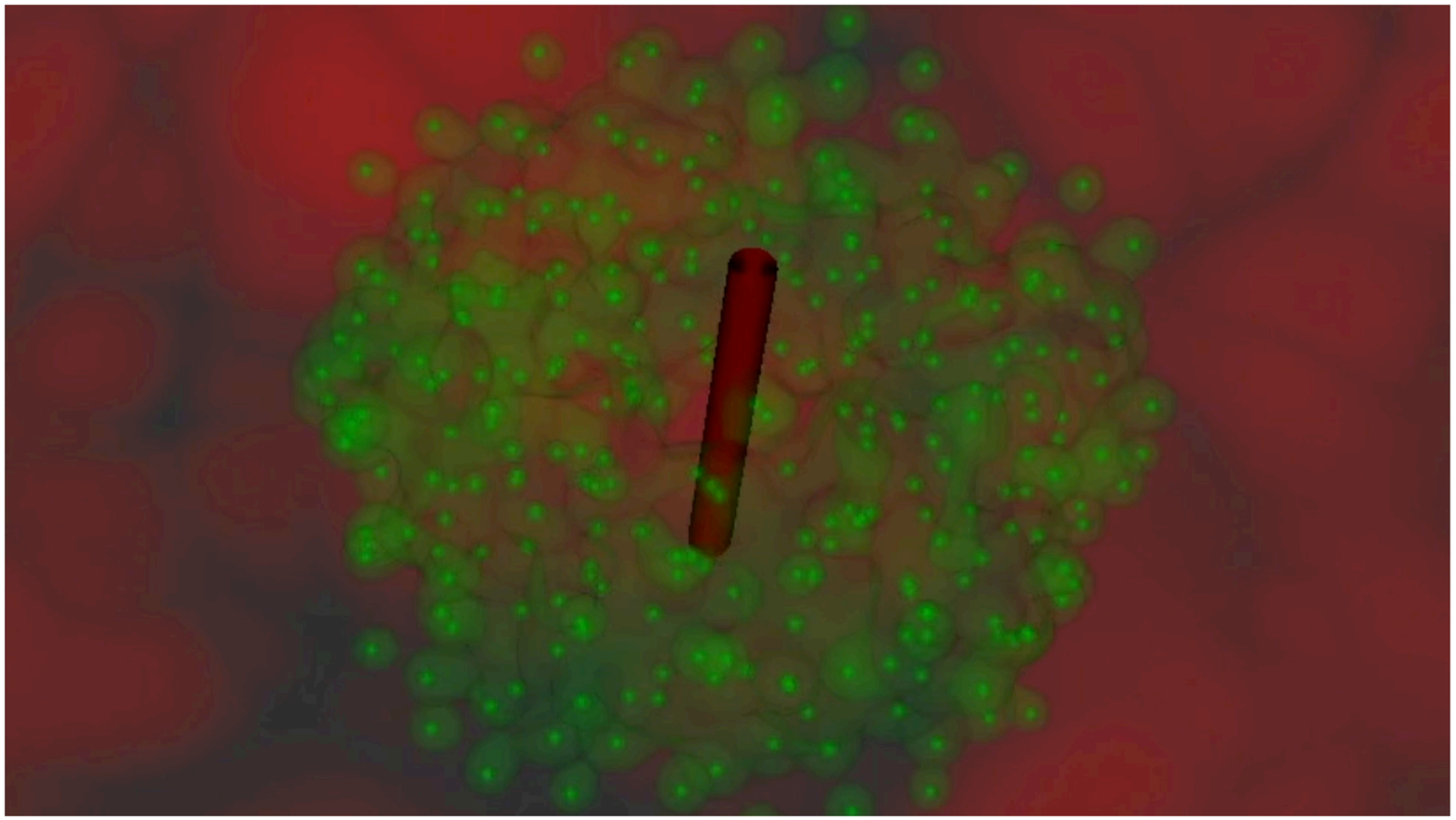
VEGF

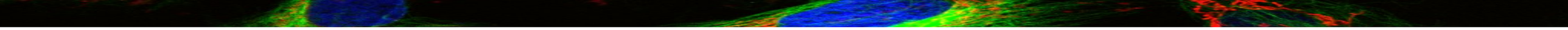


$t = 2$ h $t = 8$ h $t = 16$ h $t = 25$h

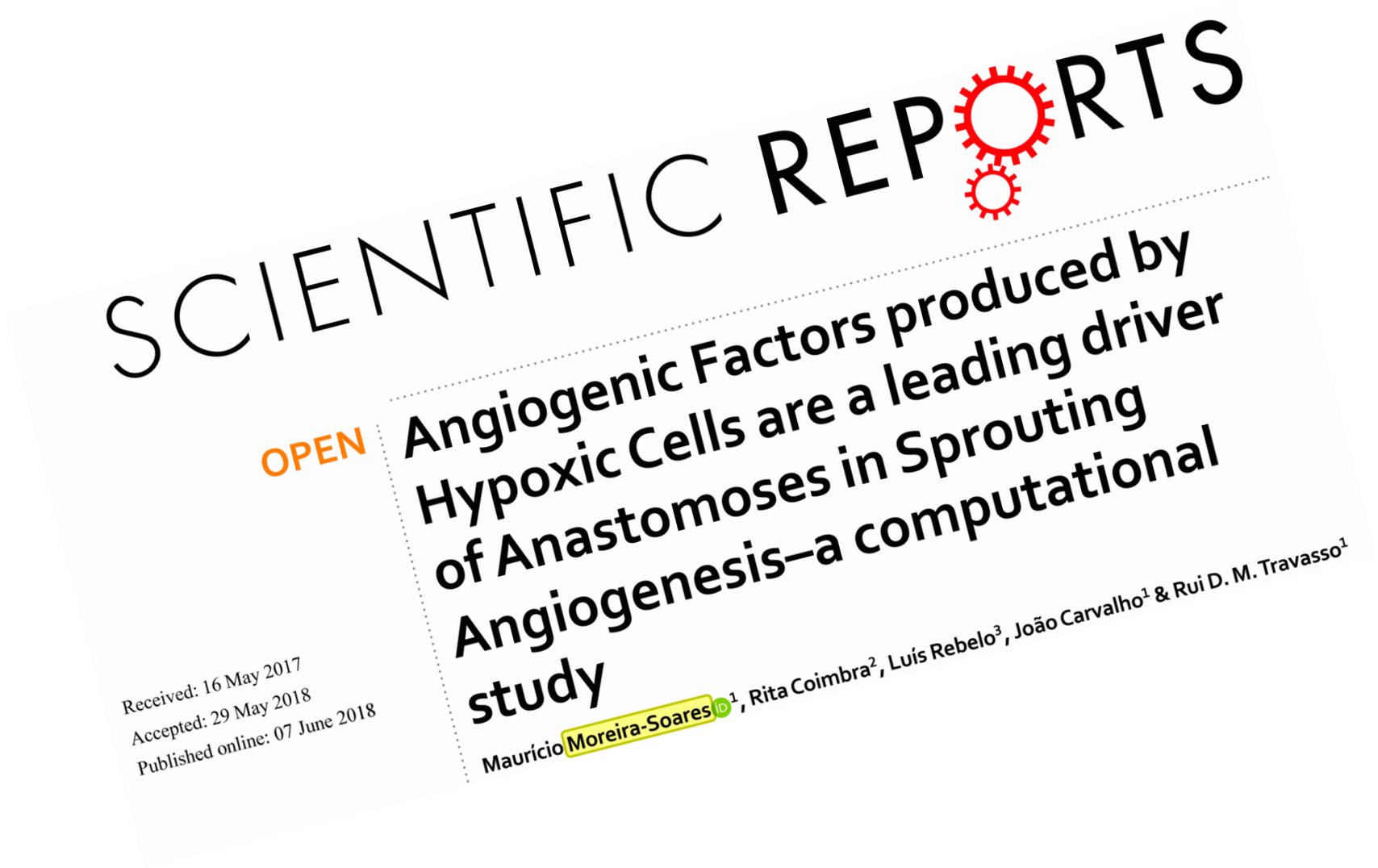
~ while the vessel network grows, the growth factor is consumed

:~$ Ready for more movies?





What is the role of VEGF gradients in driving anastomoses?



SCIENTIFIC REPORTS

OPEN

Angiogenic Factors produced by Hypoxic Cells are a leading driver of Anastomoses in Sprouting Angiogenesis–a computational study

Maurício Moreira-Soares[1], Rita Coimbra[2], Luís Rebelo[3], João Carvalho[1] & Rui D. M. Travasso[1]

Received: 16 May 2017
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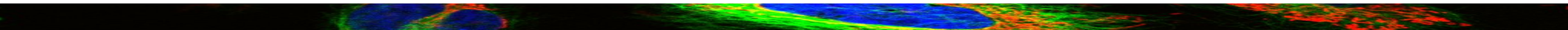
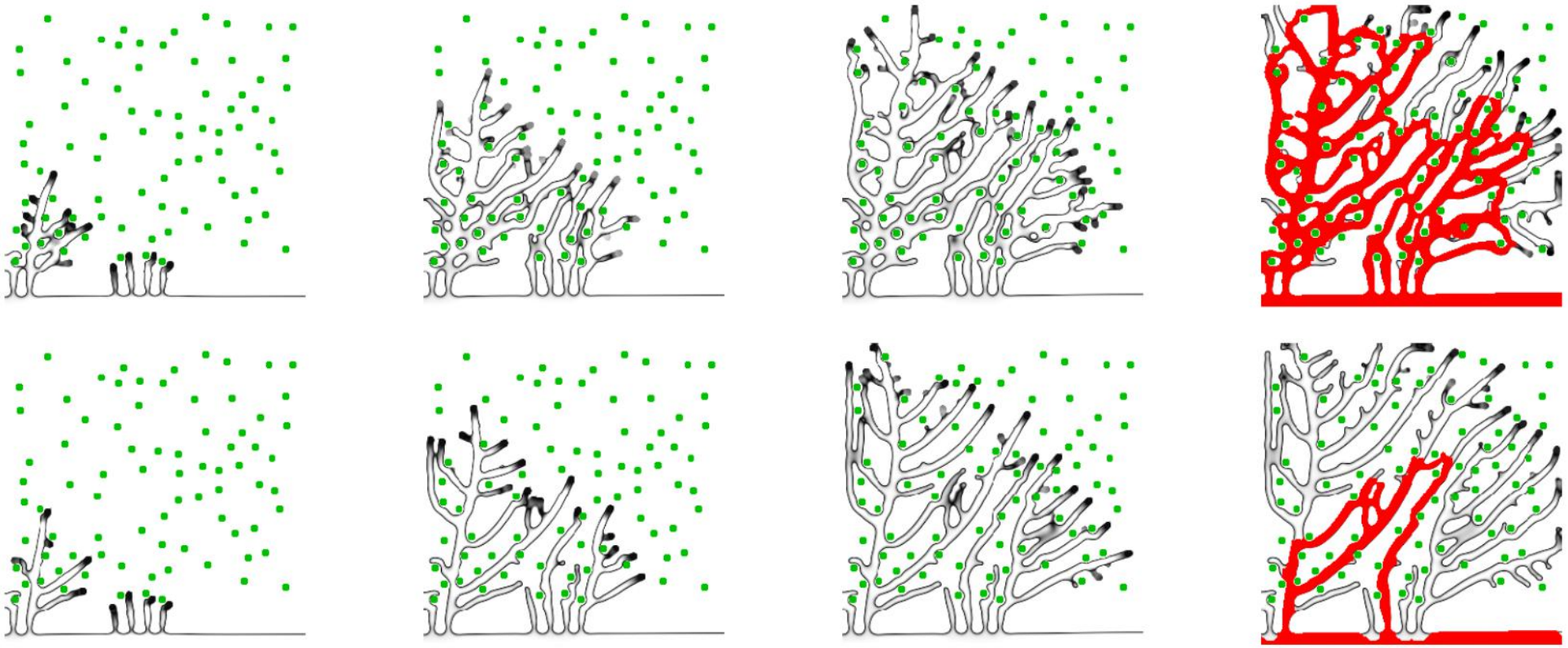
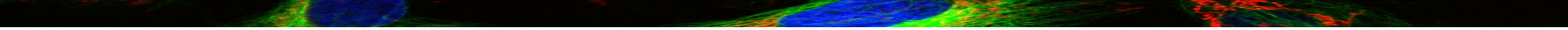


:~$ Part II > Results > angiogenesis in 2D



~ There are major differences when blood flow is considered



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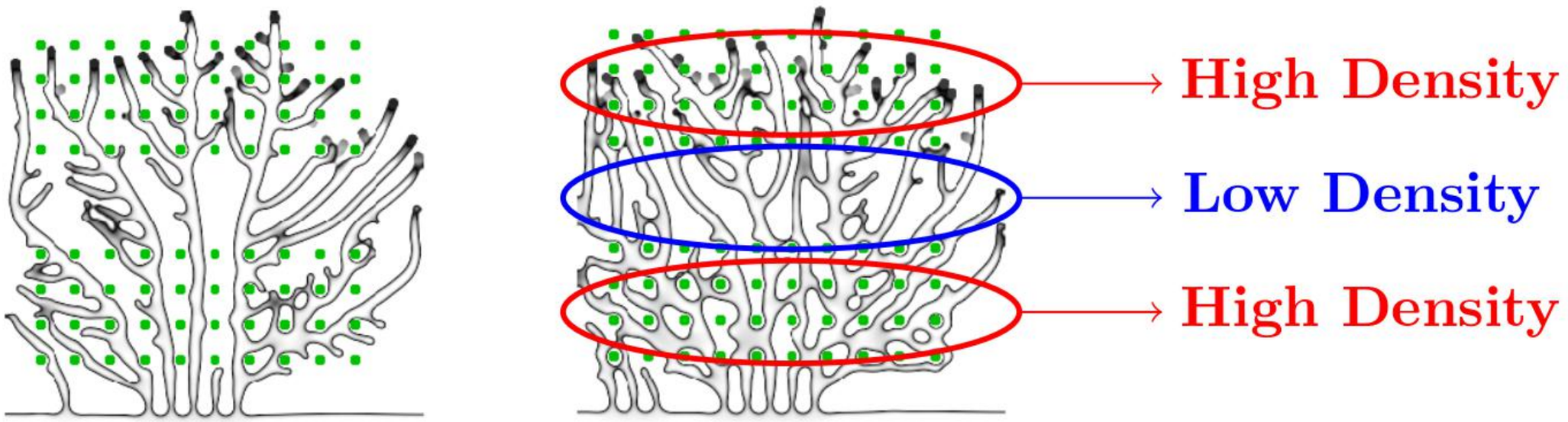
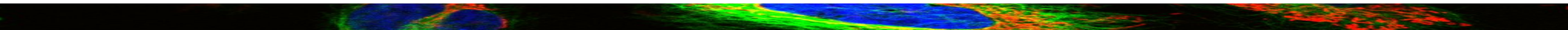


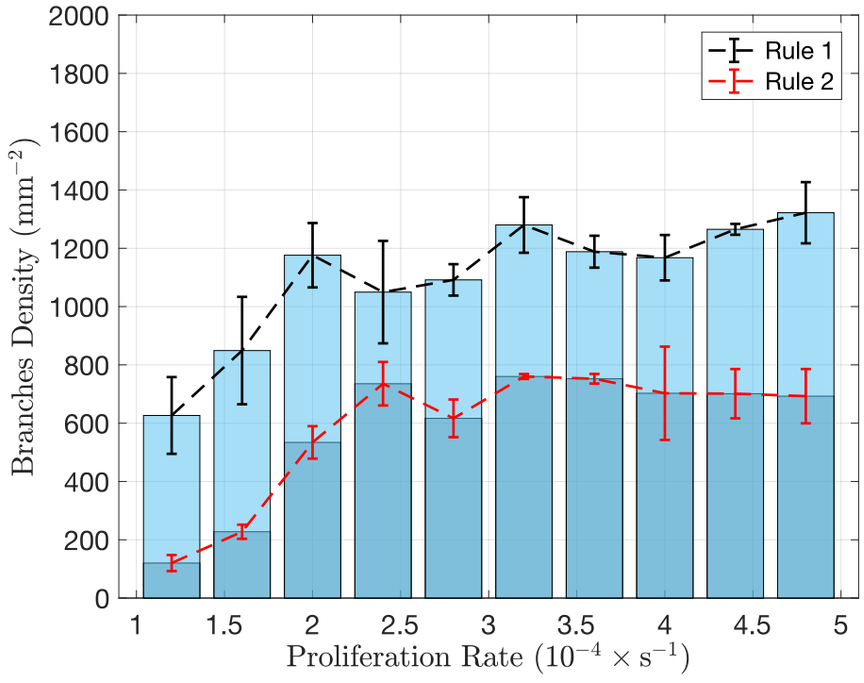
Rule 2 Rule 1

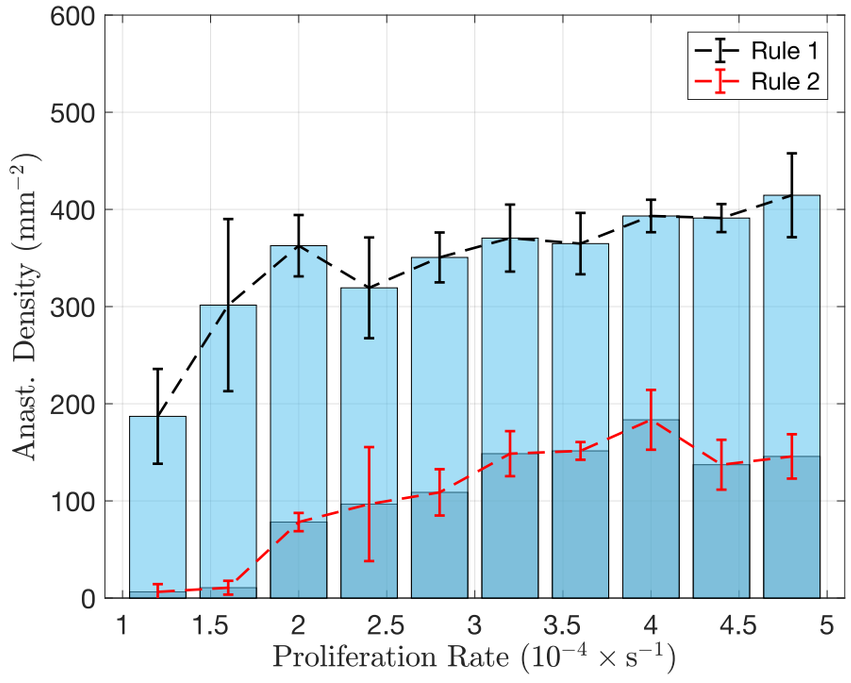
~ Hypoxia driven VEGF production is able to tailor the vessel network to fulfil the needs of the tissue

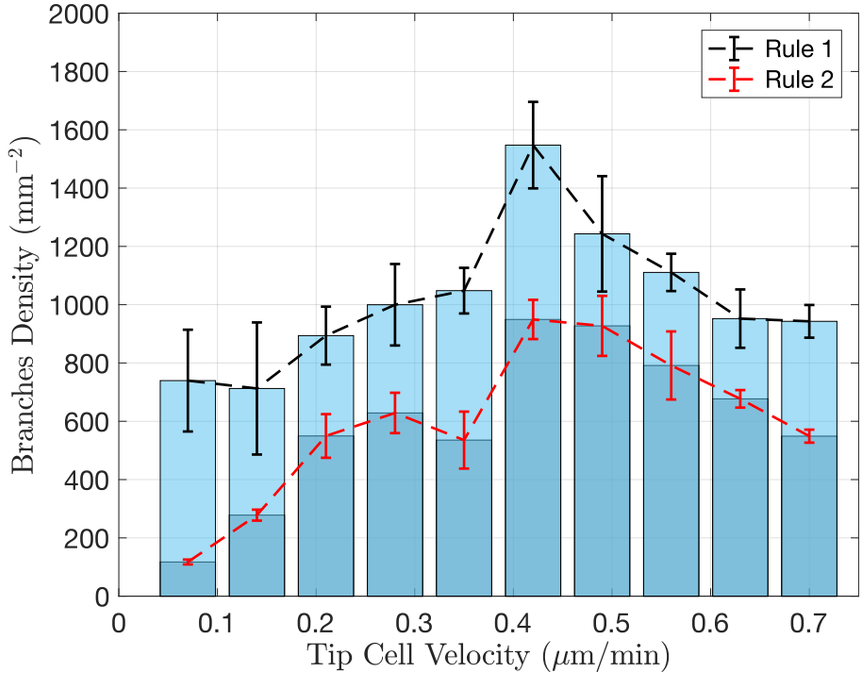
~ the tissue is a major regulator of the blood vessel network morphology

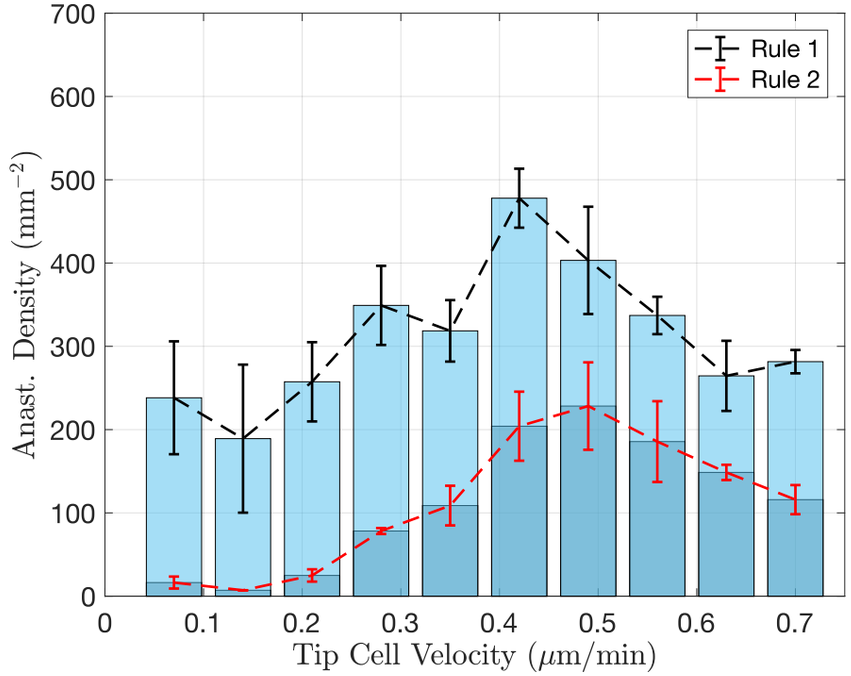


:~$ Part II > Results > angiogenesis in 2D



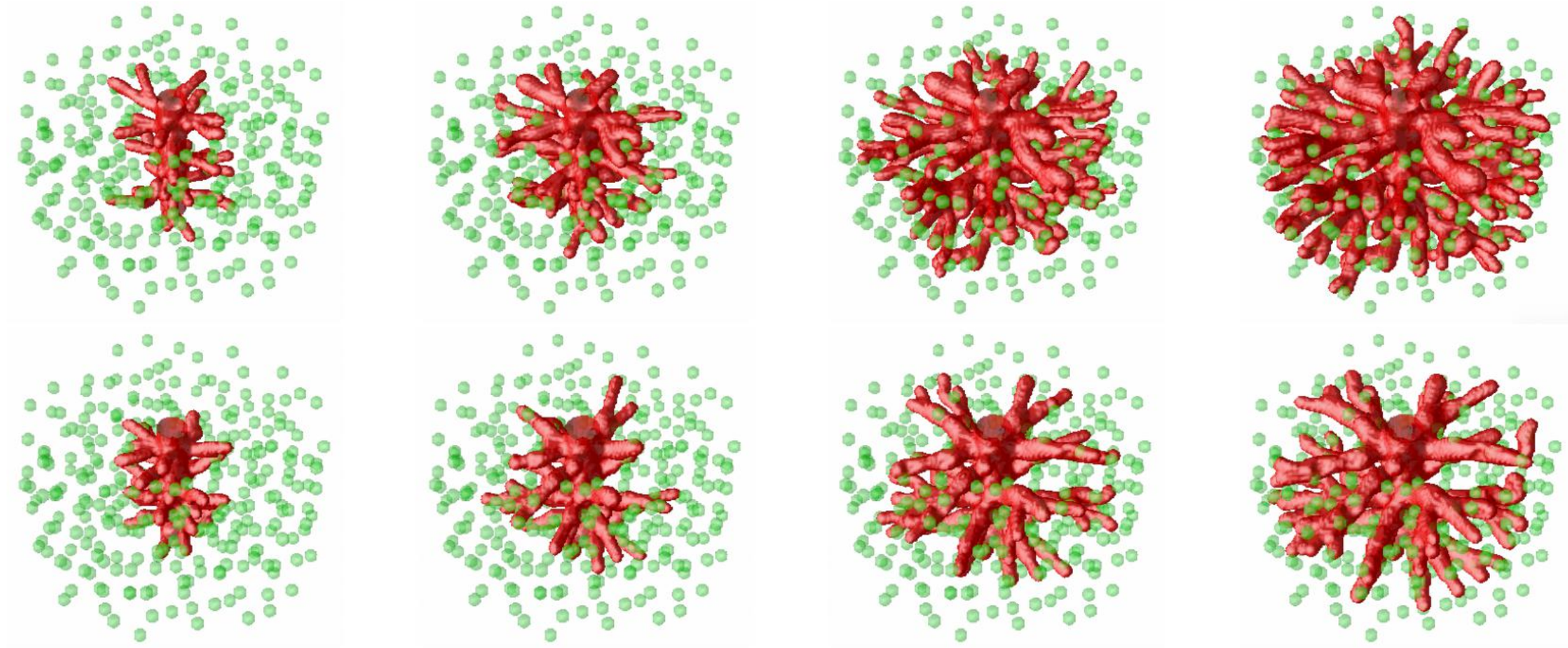






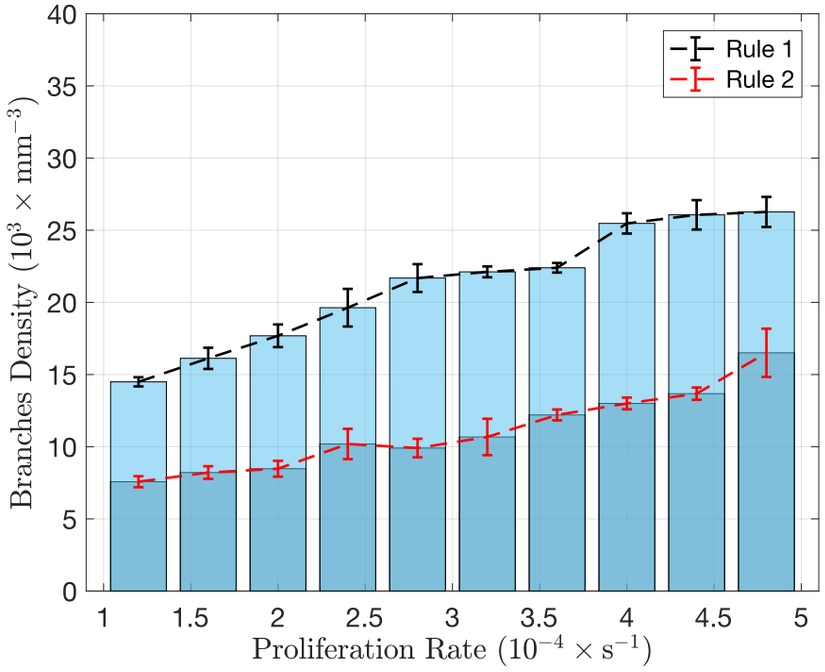
~ The networks are resilient to changes in the cell metabolism.

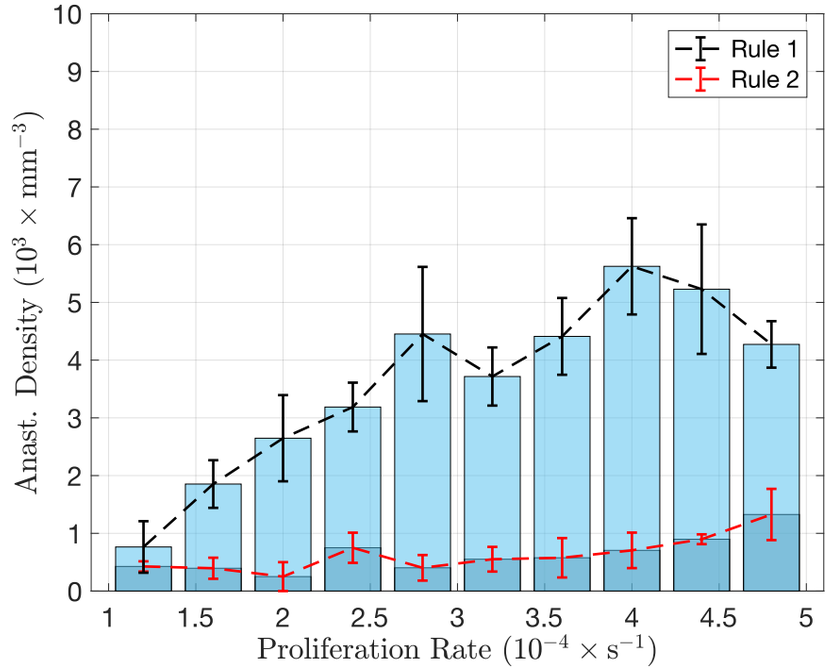
:~$ Part II > Results > angiogenesis in 3D

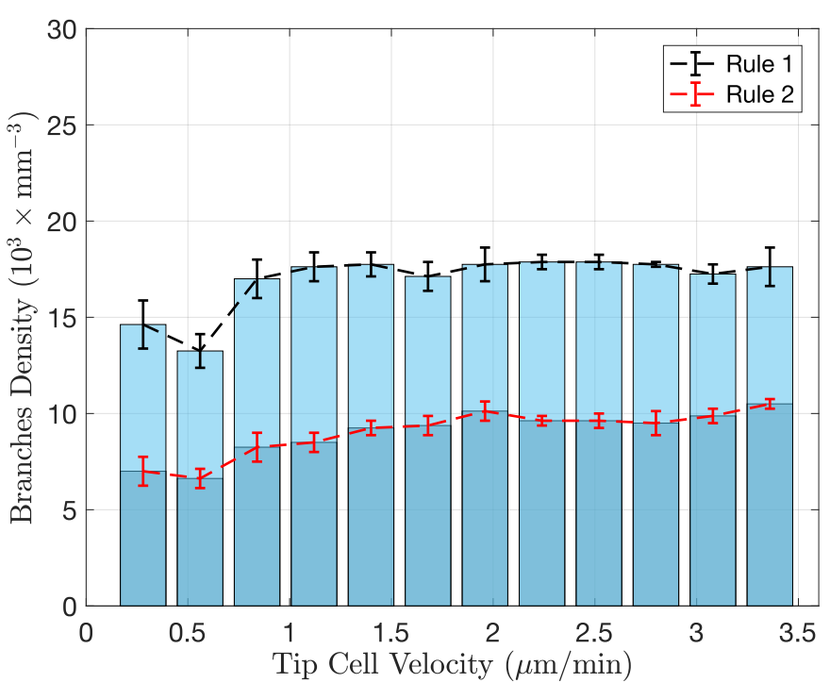


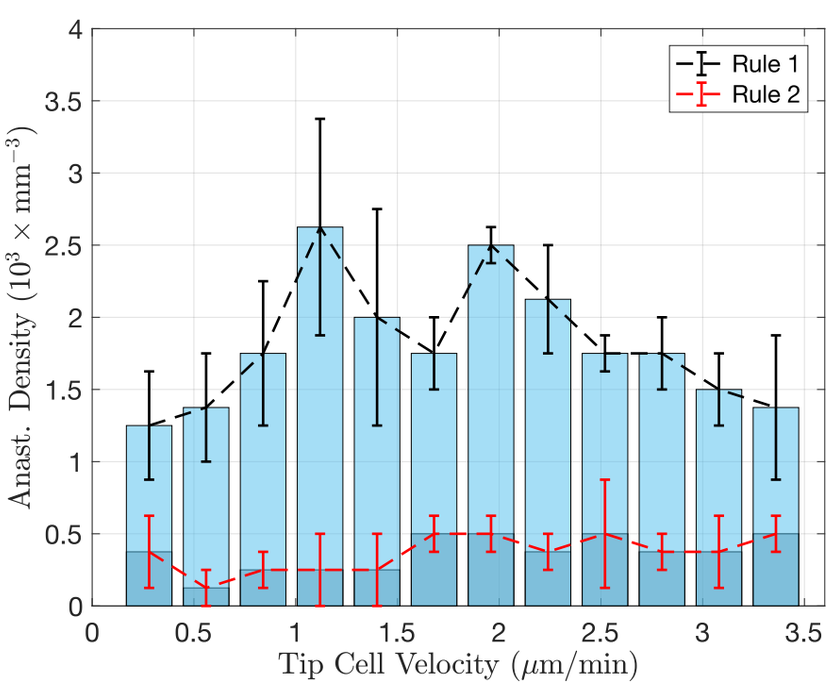
~ The differences between the networks are even more pronounced in 3D

:~$ Part II > Results > angiogenesis in 3D

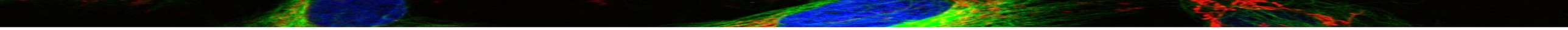








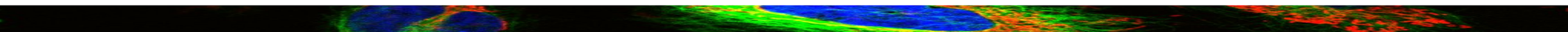
~ Blood flow regulation is an essential ingredient for anastomoses in 3D!



:~$ Part II > Conclusions

~ The morphology of the vessel networks is resilient to changes in cell metabolism, such as proliferation rate and chemotactic response;

~ The distribution of tissue cells and the concentration of the growth factors they produce are the major factors in determining the final morphology of the network.



:~$ Conclusions && future work

overview:

~ phase-field approach is easy to implement and versatile

~ it allows the development of minimalistic models to build hypothesis

~ the number of parameters is reduced when compared with other models

perspectives:

~ model angiogenesis with cells producing VEGF while migrating

~ study of angiogenesis in Non-Alcoholic Fat Liver Disease (NAFLD)

Try PF modelling with my Python implementation (for teaching purposes):
https://gitlab.com/phydev/PhyBio

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Thank you and come visit us in Coimbra!

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