University of BRISTOL
Bristol BioDesign Institute

The **physics and mathematics** of wound healing

Tanniemola B Liverpool

School of Mathematics

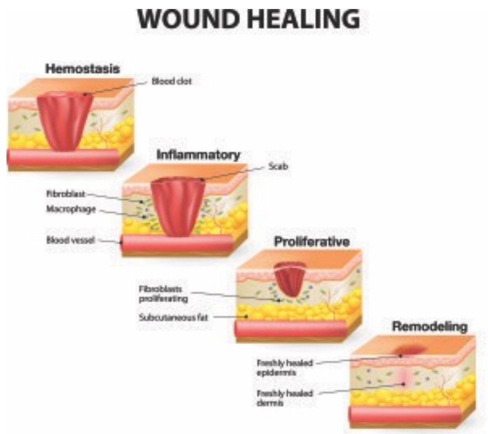
University of Bristol

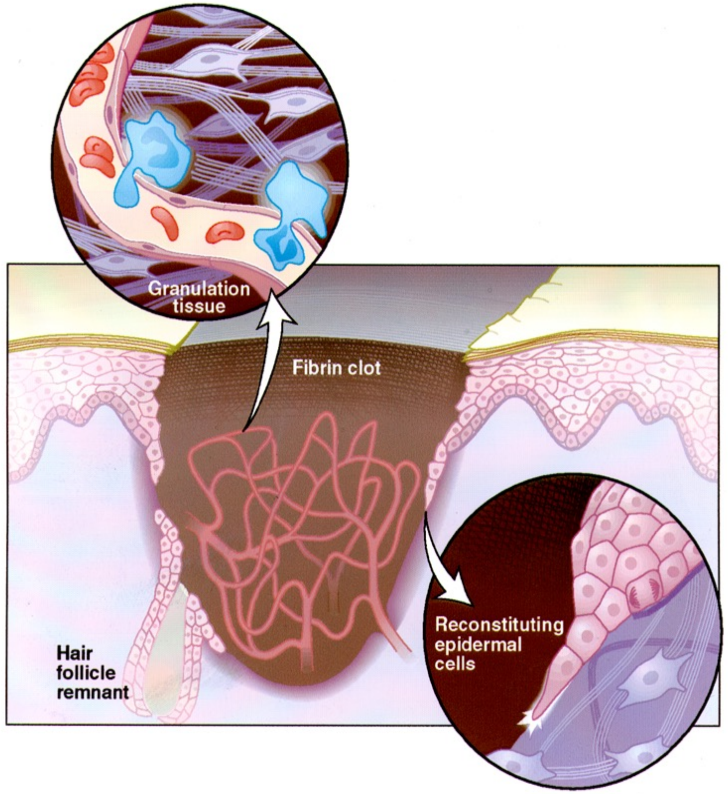
Erlangen
6 Nov 2024

University of BRISTOL
Bristol BioDesign Institute

Wound healing

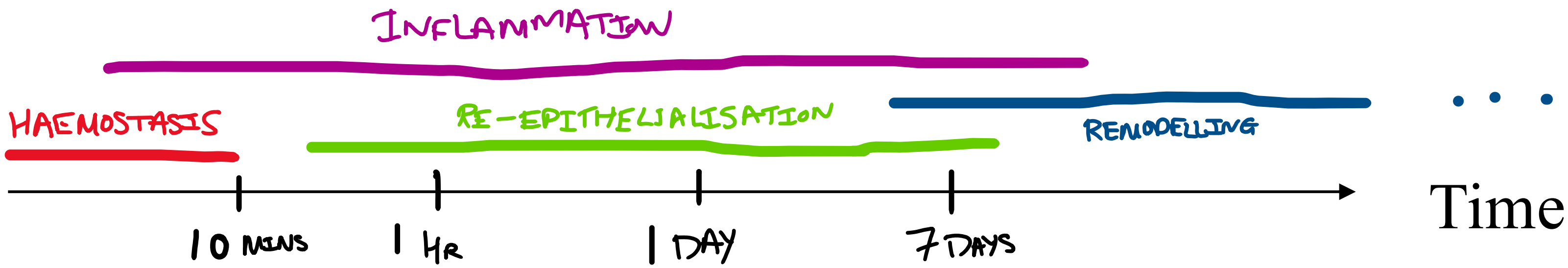
A complex process





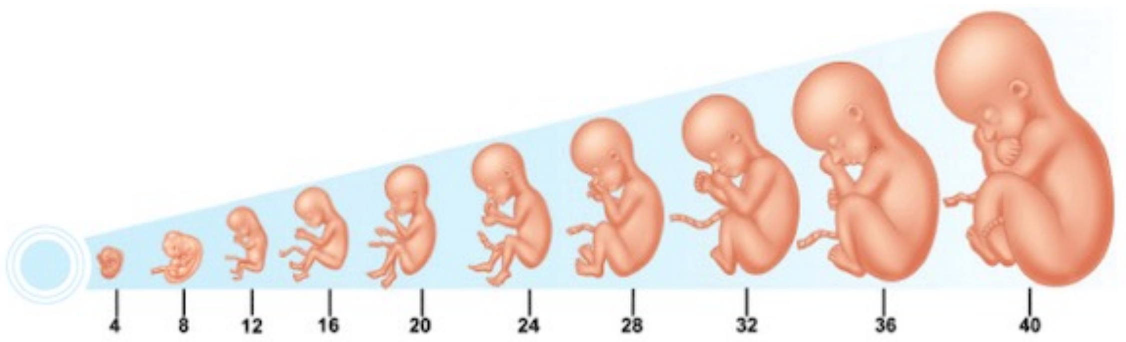
Martin (1997) *Science*

- Blood clotting
- Inflammation
- Tissue growth
- Tissue remodelling



Wound healing

Wound healing gives us a window into fundamental processes of **development**



Better understanding of **chronic wounds** which are wounds that do not heal – sometimes for years

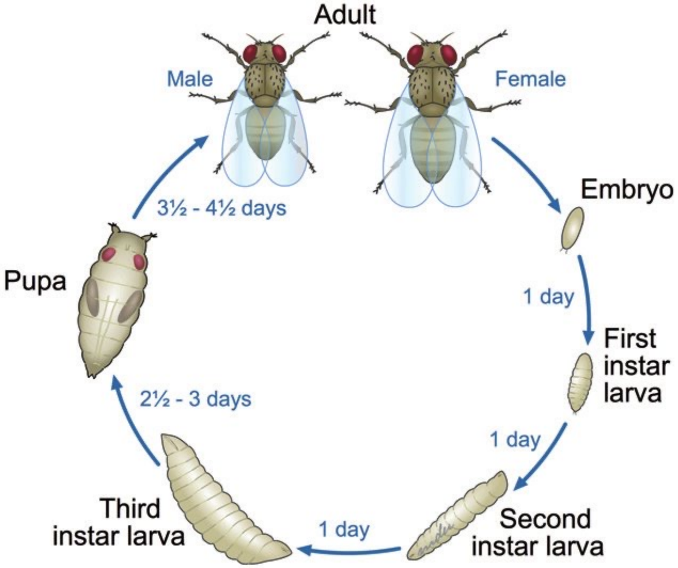
Chronic wounds are a huge burden on the health system

Falanga et al, *Nat Rev Dis Primers* **8**, 50 (2022)

University of BRISTOL
Bristol BioDesign Institute

Wound healing in model organisms

LIVING !

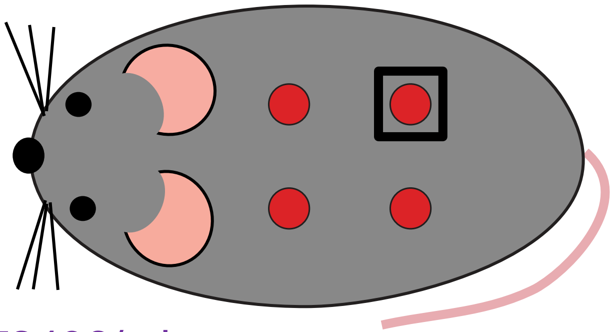


Drosophila melangoster

Wood, Jacinto et al (2002) *Nat. Cell Biol.*

Ong et al (2014) *Nanotoxicology*

Zebrafish



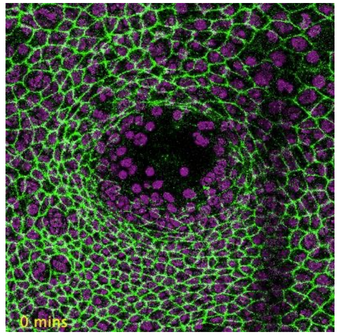
Mouse

https://www.mpg.de/10973406/mice

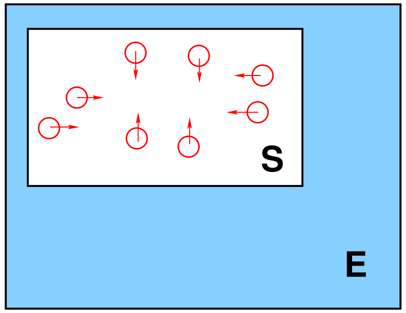
University of BRISTOL
Bristol BioDesign Institute

Overview

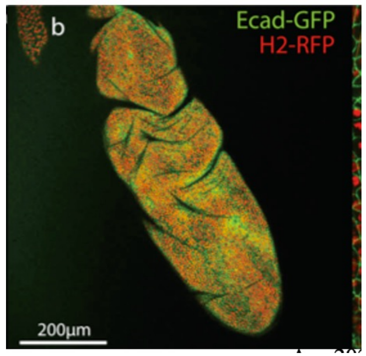
1. Quantifying wound healing at cellular scales



2. From statistical mechanics to active processes



3. Analysis of fluctuating tissue growth and repair



University of BRISTOL
Bristol BioDesign Institute

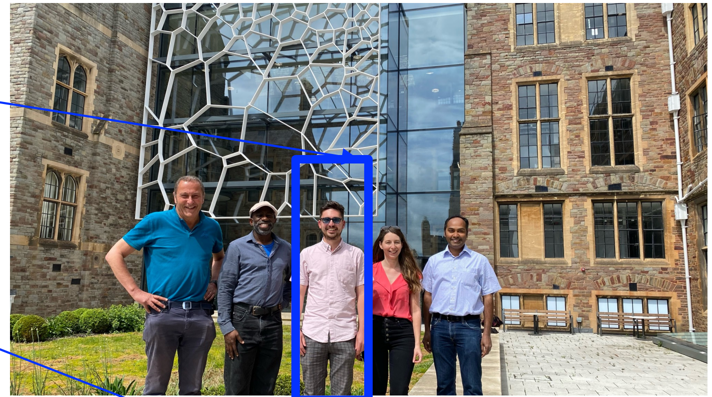
Acknowledgements

Jake Turley (Mathematics, Bristol)
Mark Olenik
Henry Andralojc
Isaac Chenchiah

Deems Ioratim-Uba
Silke Henkes

Helen Weavers (Biochemistry, Bristol)
Paul Martin
Stephen Cross

Keith Harding (Medicine, Cardiff)



BBSRC bioscience for the future

EPSRC Engineering and Physical Sciences Research Council

UKRI Medical Research Council

The Leverhulme Trust

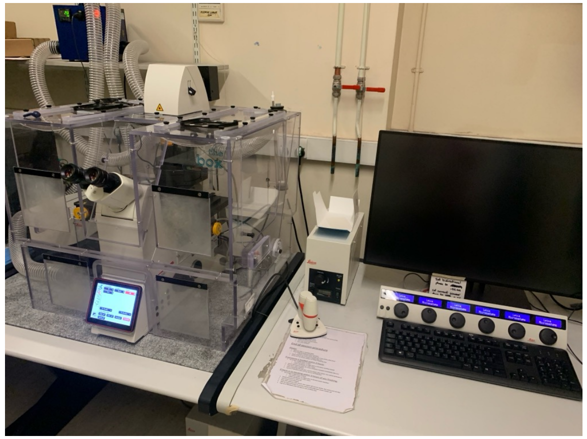
wellcome

Nov 2024

University of BRISTOL
Bristol BioDesign Institute

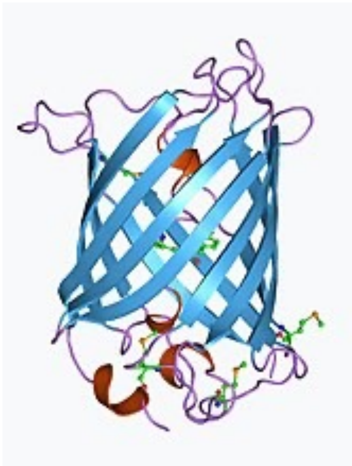
Confocal microscopy

Leica sp8 confocal



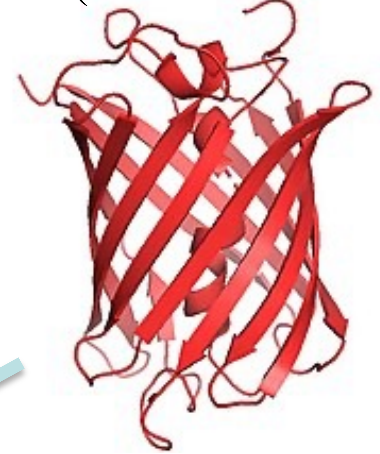
Fluorescent protein

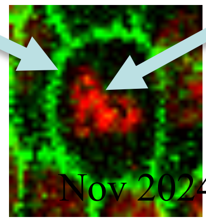
GFP (green fluorescent protein)



- First isolated from the jellyfish
- Flies can be genetically modified to have fluorescent protein fused on to other proteins we would like to image

RFP (red fluorescent protein)



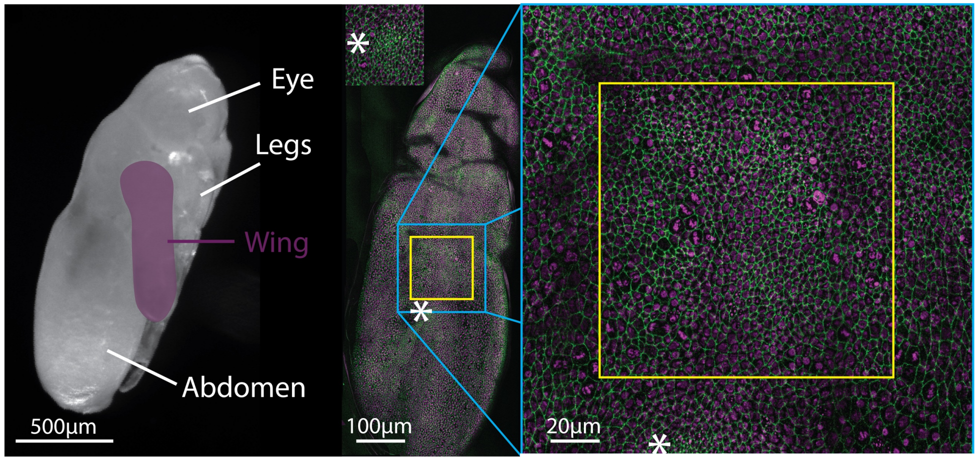


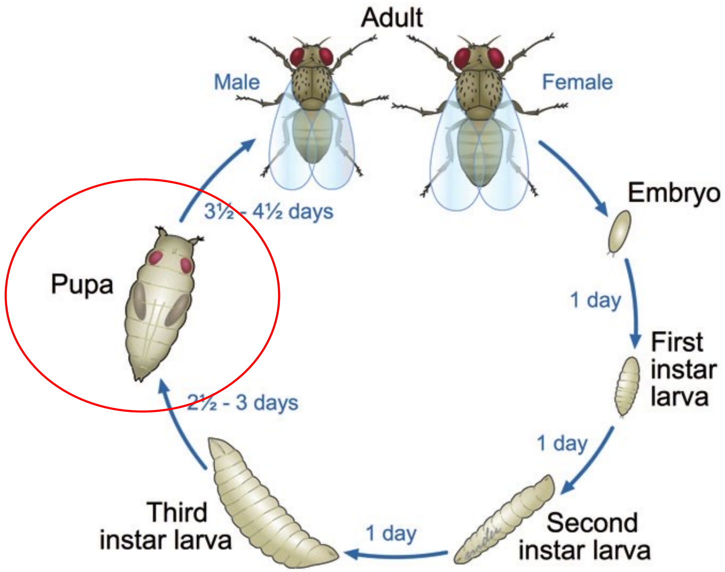
Imaging drosophila pupa

Long-term *In Vivo* Tracking of Inflammatory Cell Dynamics Within *Drosophila* Pupae

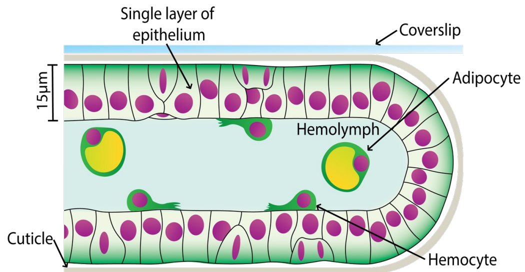
Helen Weavers[1,2], Anna Franz[1], Will Wood[3], Paul Martin[1,4]

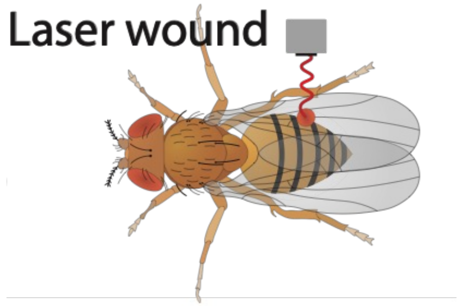
[1]School of Biochemistry, Biomedical Sciences, **University of Bristol**, [2]School of Cellular and Molecular Medicine, Biomedical Sciences, **University of Bristol**, [3]MRC Centre for Inflammation Research, **University of Edinburgh, Queens Medical Research Institute**, [4]School of Physiology, Pharmacology, and Neuroscience, Biomedical Sciences, **University of Bristol**





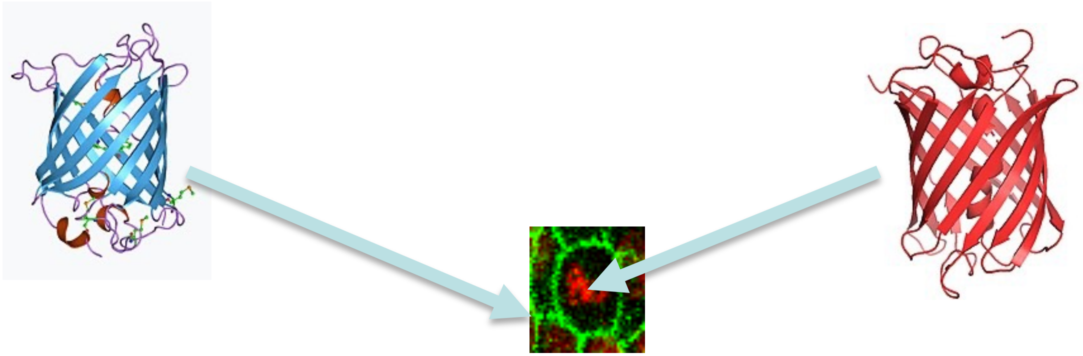
Cross Section of the Wing

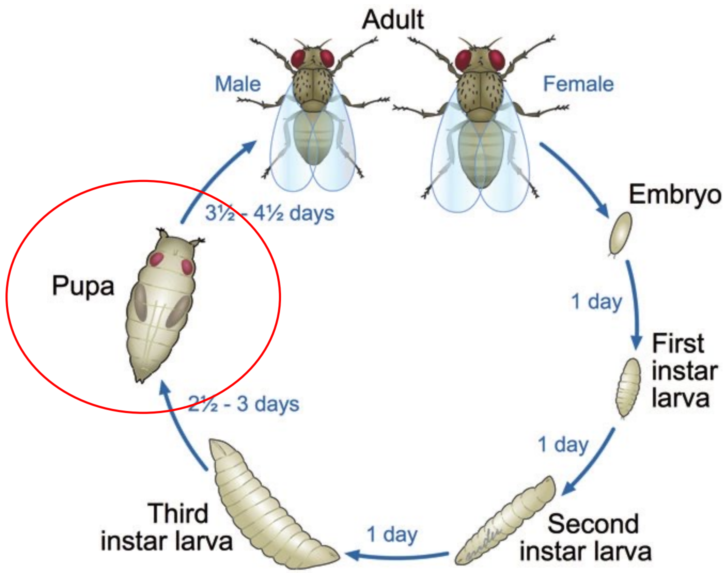




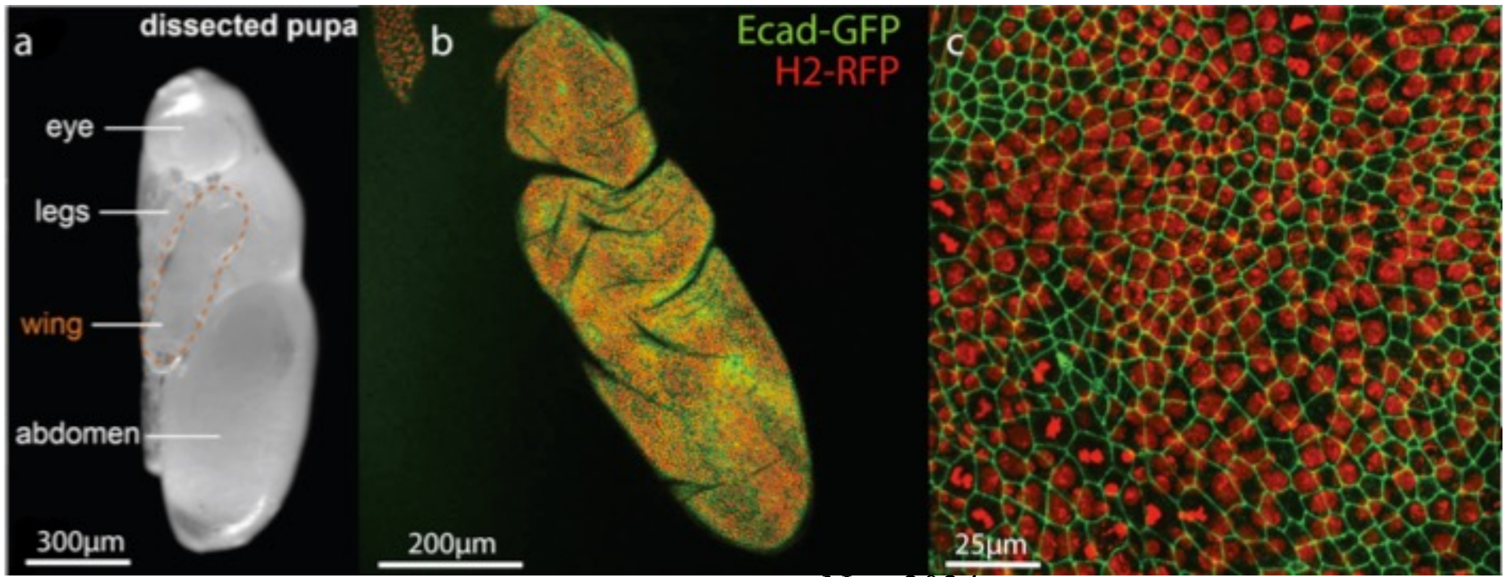
University of BRISTOL
Bristol BioDesign Institute

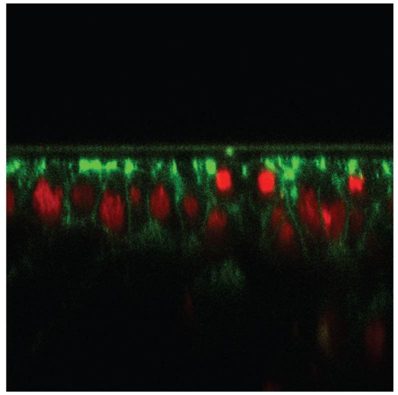
Imaging drosophila pupa





- Collect confocal videos

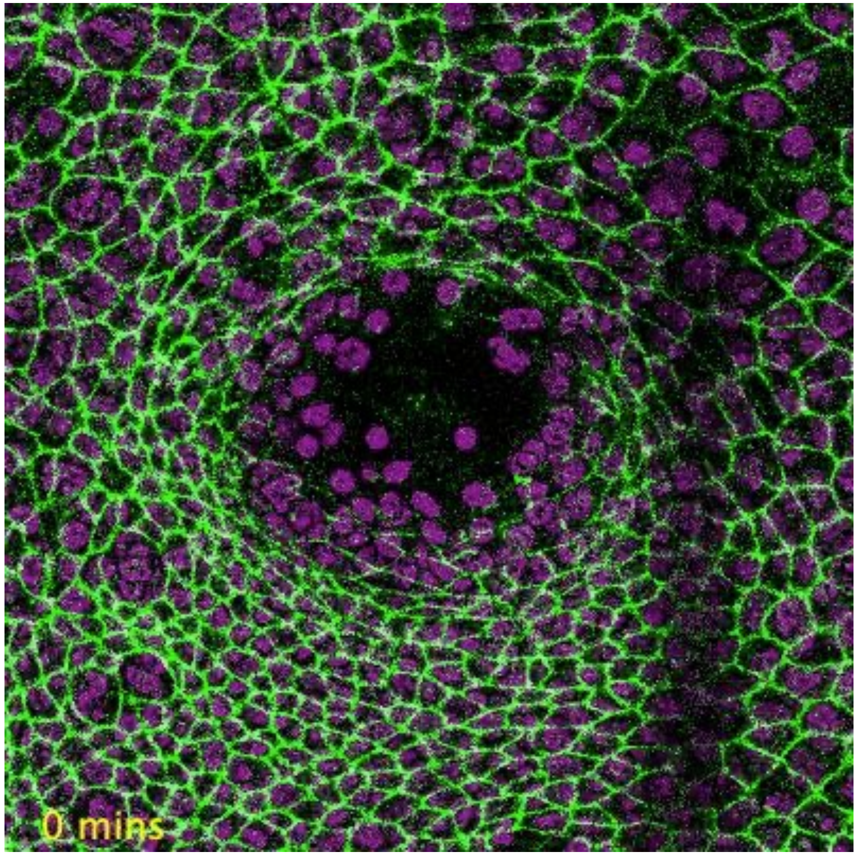




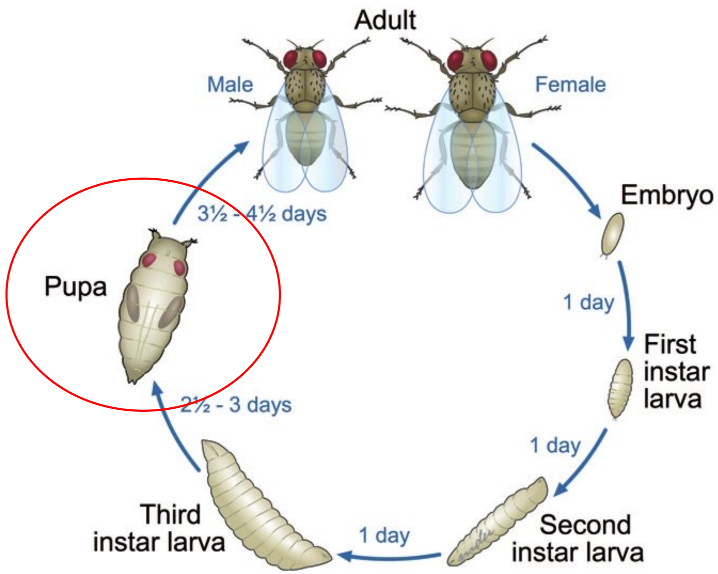
University of BRISTOL
Bristol BioDesign Institute

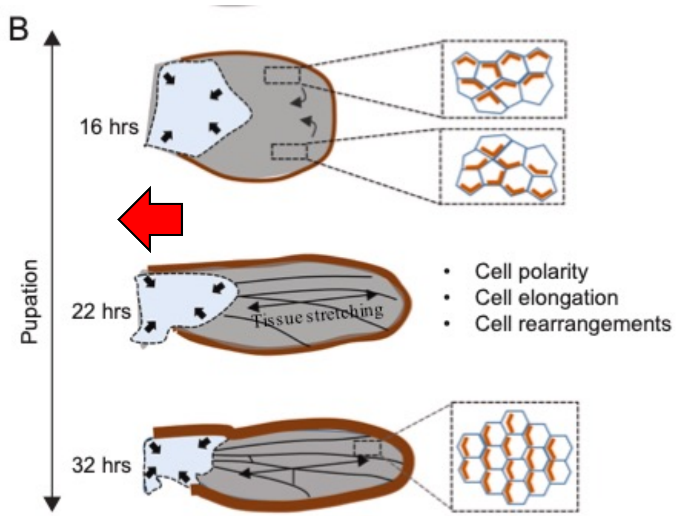
Imaging drosophila pupa

Laser ablation wound



18 hours after puparium formation



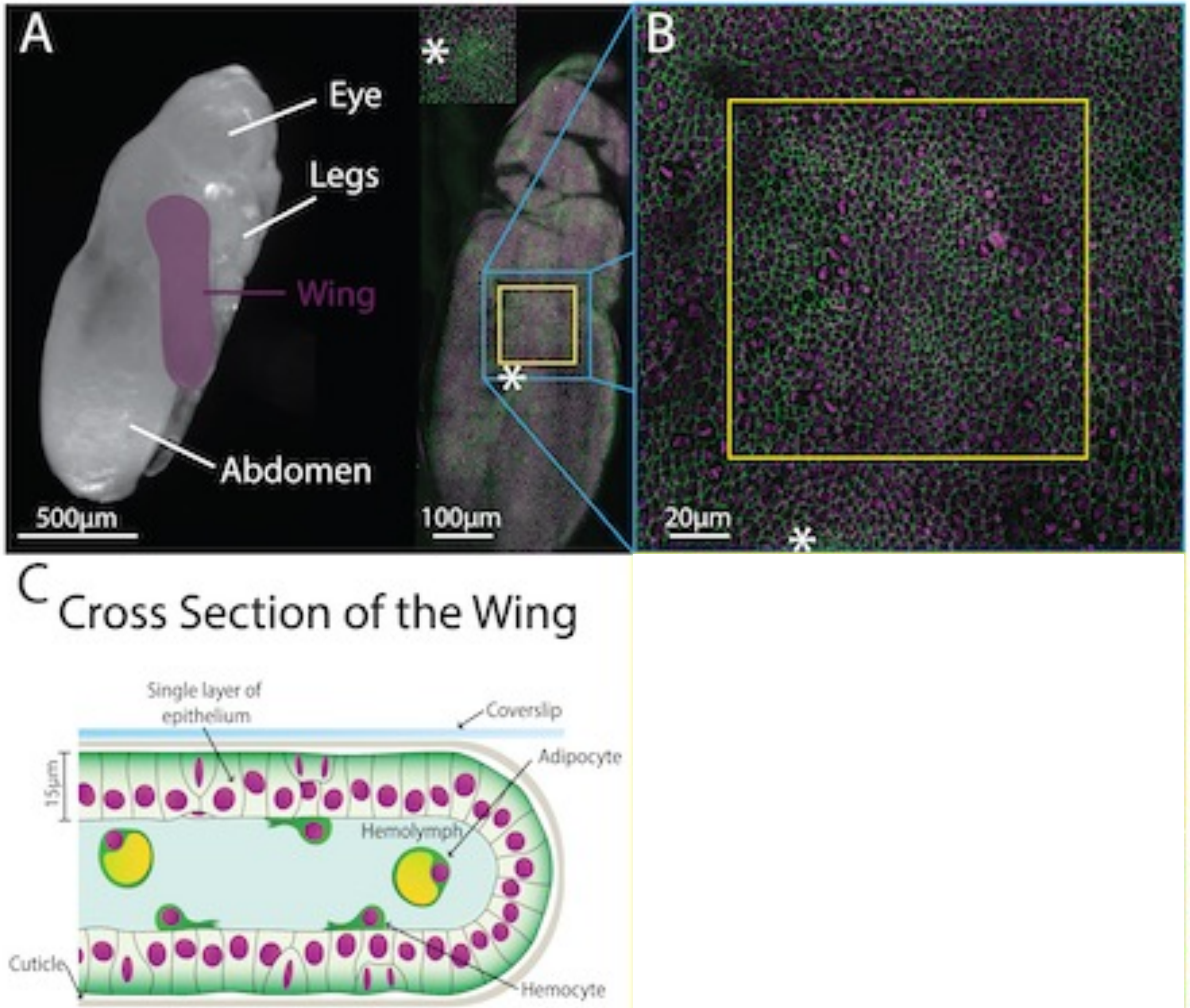


Athilingam et al, *Sem. Cell. Dev. Bio*, (2021)

Imaging drosophila pupa

How **does** the

epithelium heal ?



Compare wounded to healthy tissue

Nov 2024

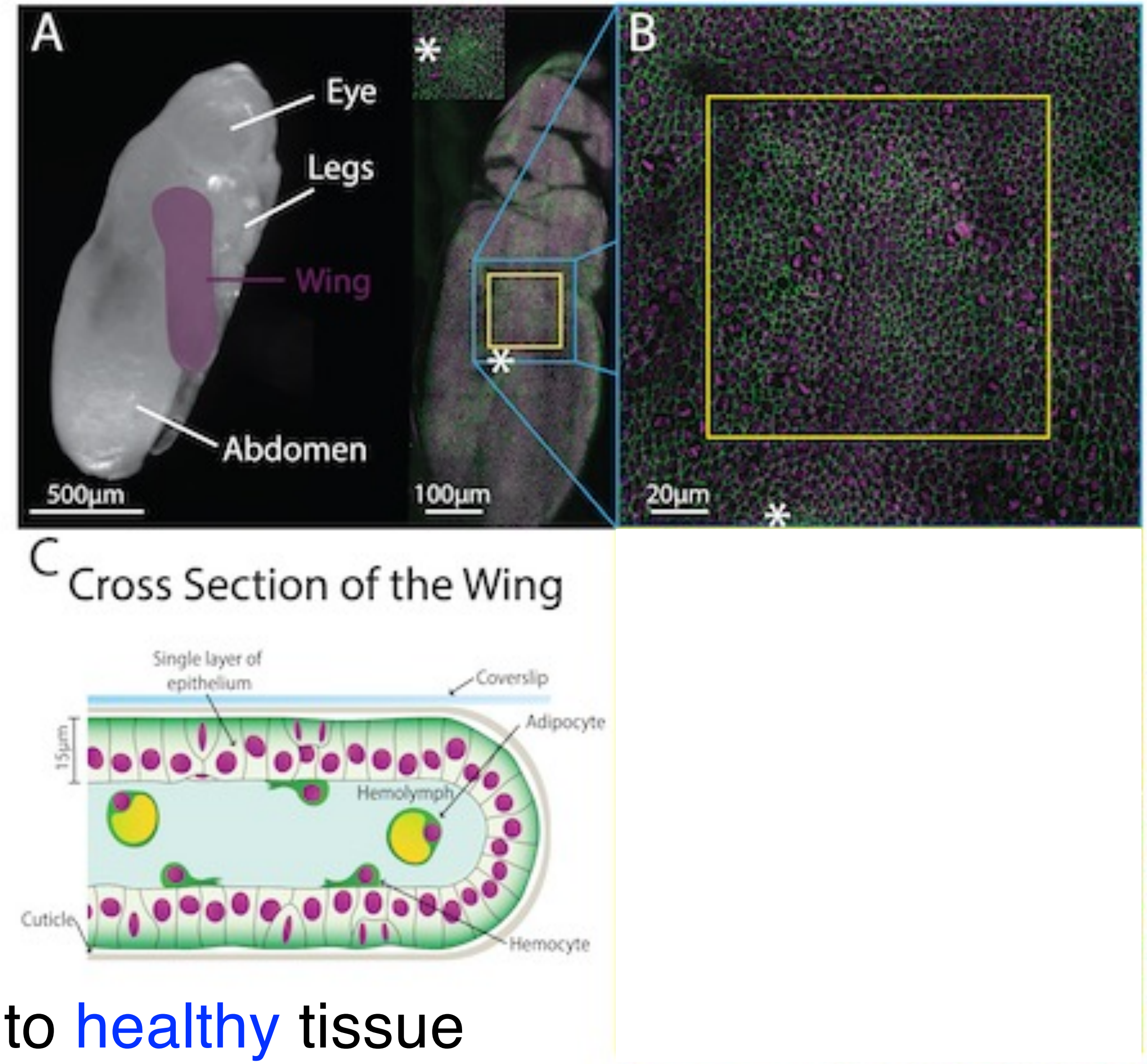
University of BRISTOL
Bristol BioDesign Institute

Imaging drosophila pupa

How do

cell shape
cell motion
cell division

evolve during reformation of epithelia?

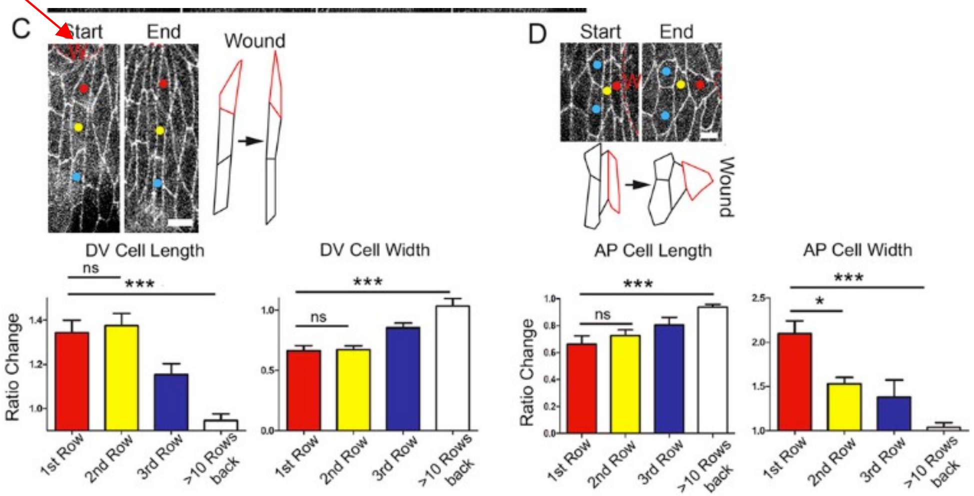


Compare wounded to healthy tissue

Why **mathematics** is needed

- BIG data is difficult to collect and fuzzy (noisy)

wound



Razzell et al, *Development (2014)*

cell shape

cell motion

cell division

Each video is data of dimension $\mathbb{R}^{2\times 93\times 42\times 512\times 512}$

- How do you extract the "signal" from the "noise" ?

Q: What (else) should one measure ?

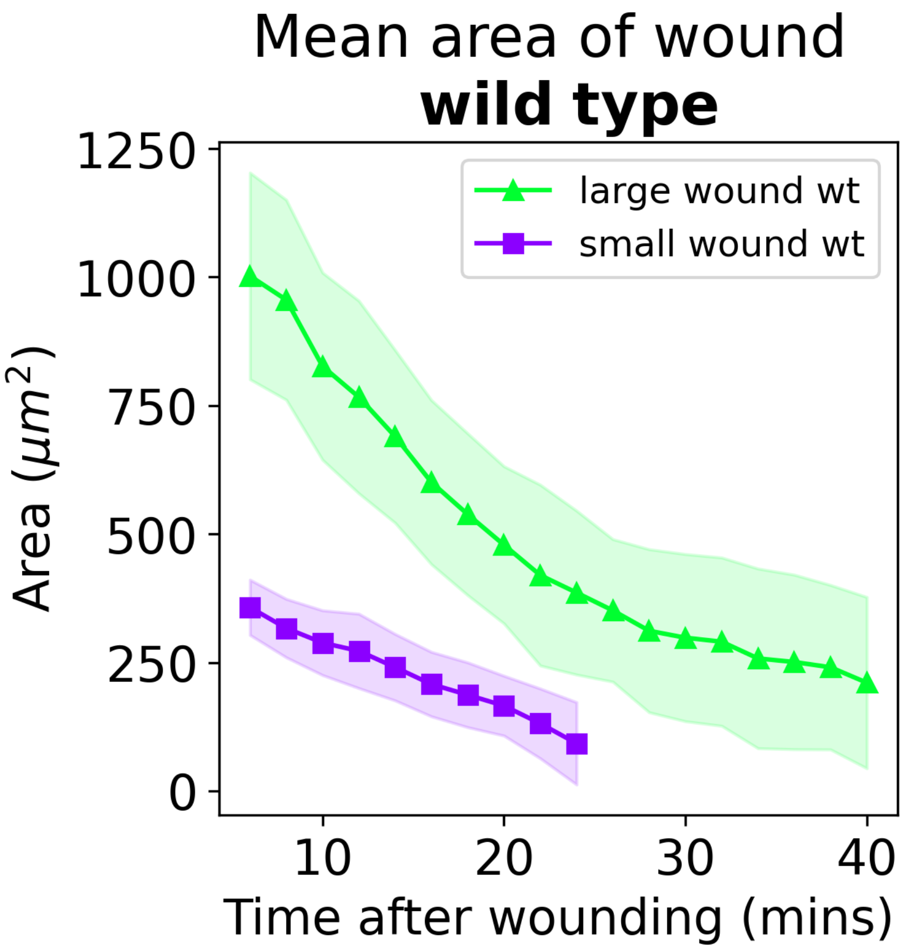
University of BRISTOL
Bristol BioDesign Institute

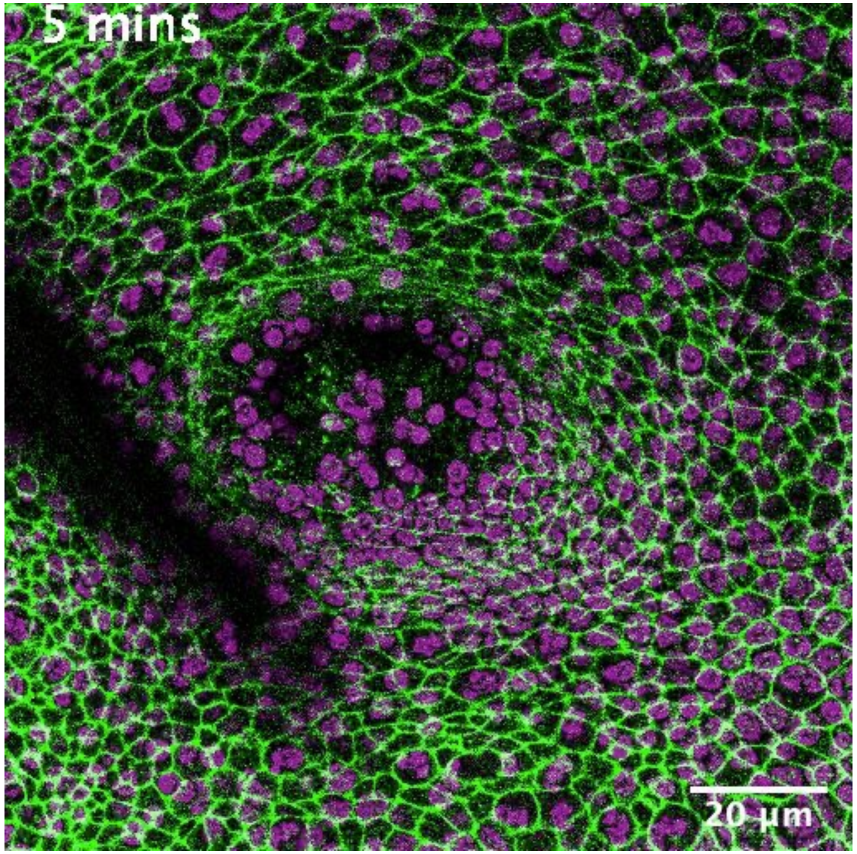
Physical models are needed for …

- Observation
- Explanation
- Analysis

Bristol BioDesign Institute

Dynamics of wound healing



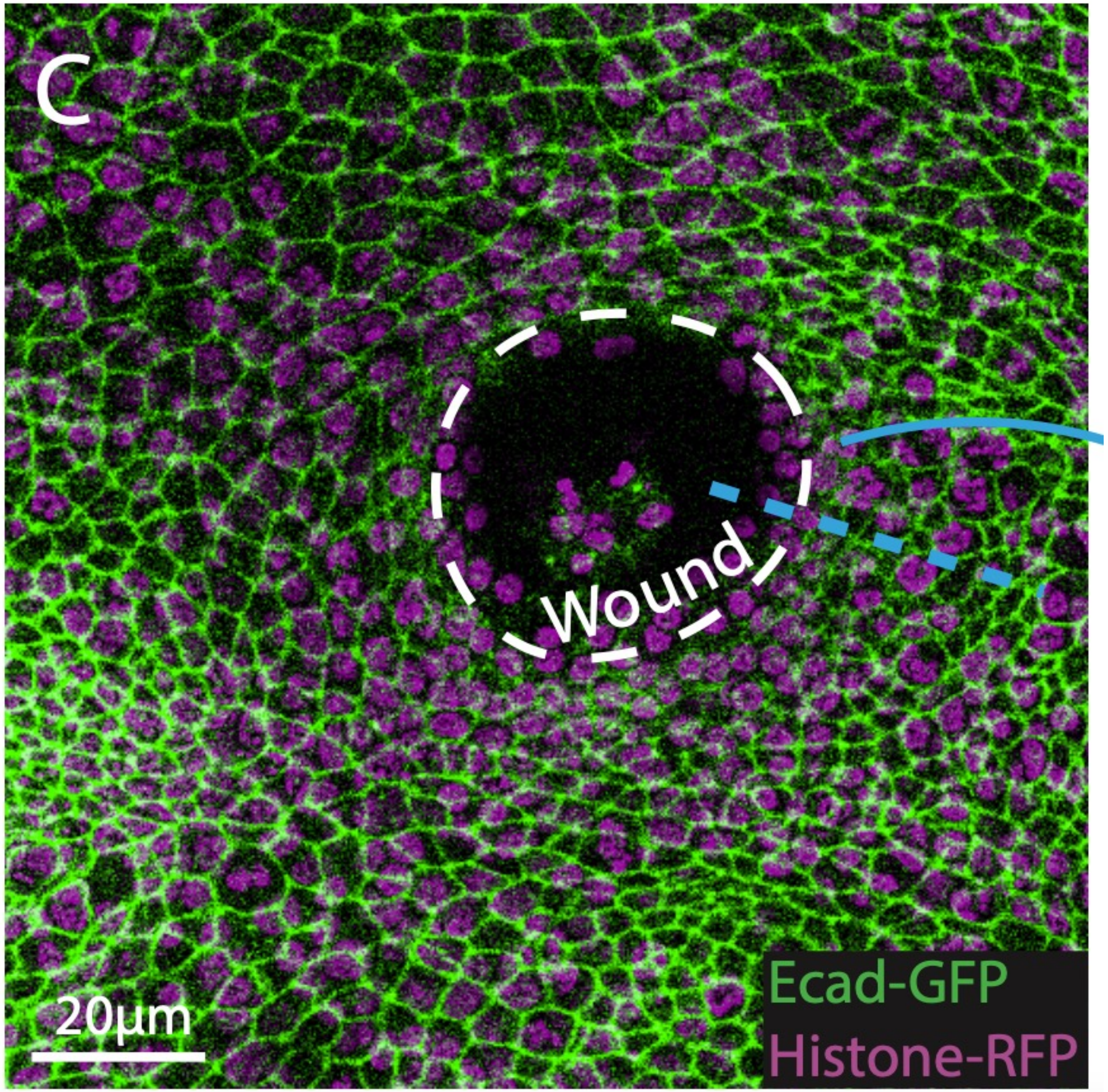


University of BRISTOL
Bristol BioDesign Institute

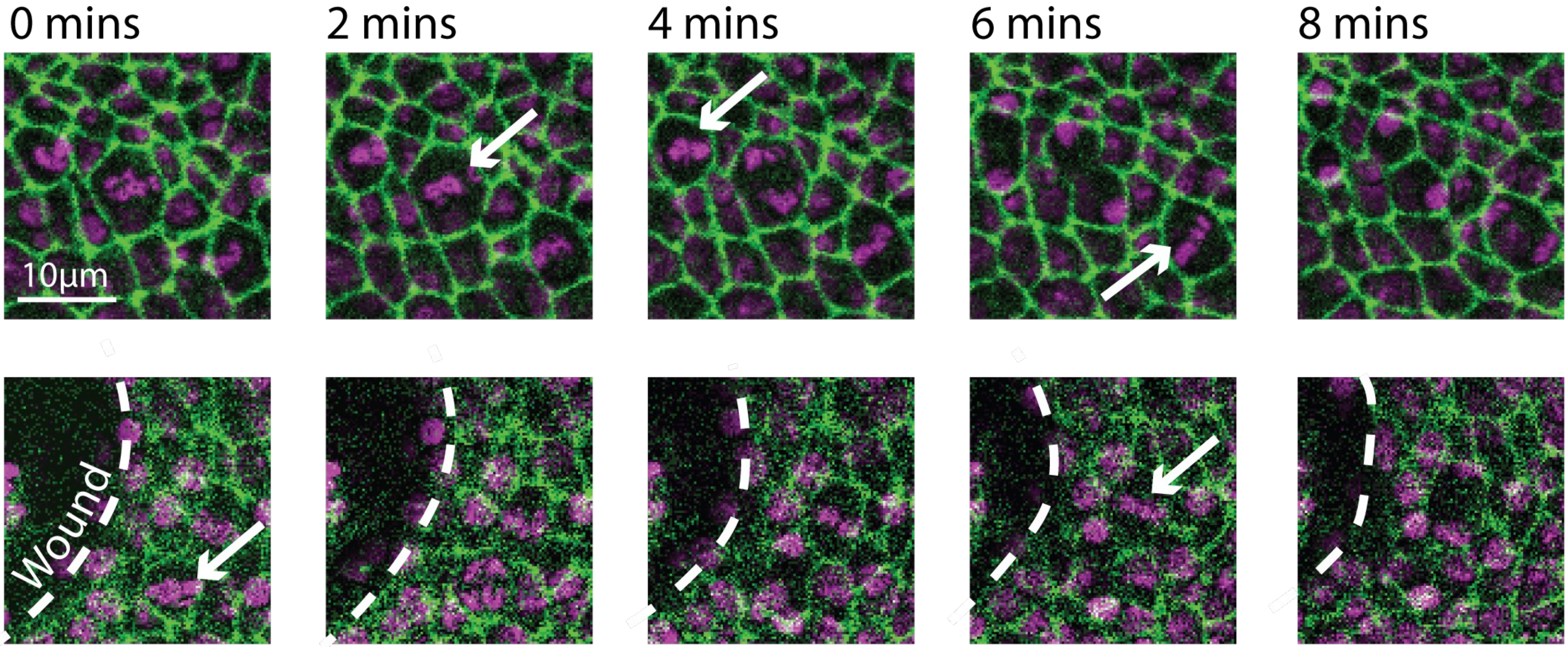
shape

motion

divisions



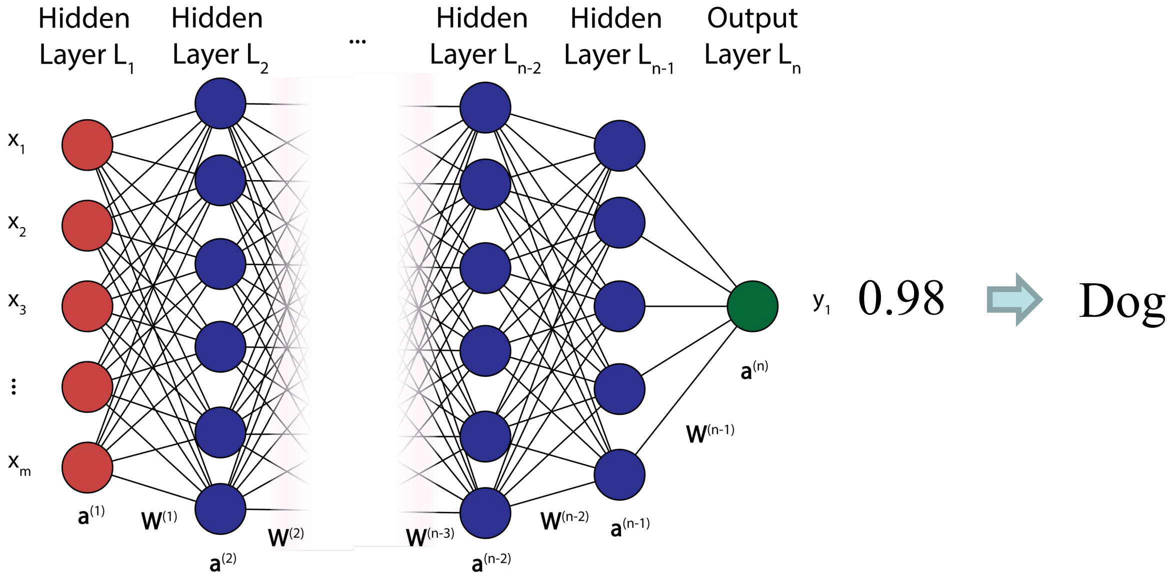
Cell divisions in unwounded and wounded tissue



University of BRISTOL
Bristol BioDesign Institute

Deep learning

Deep Learning



Example Layer:

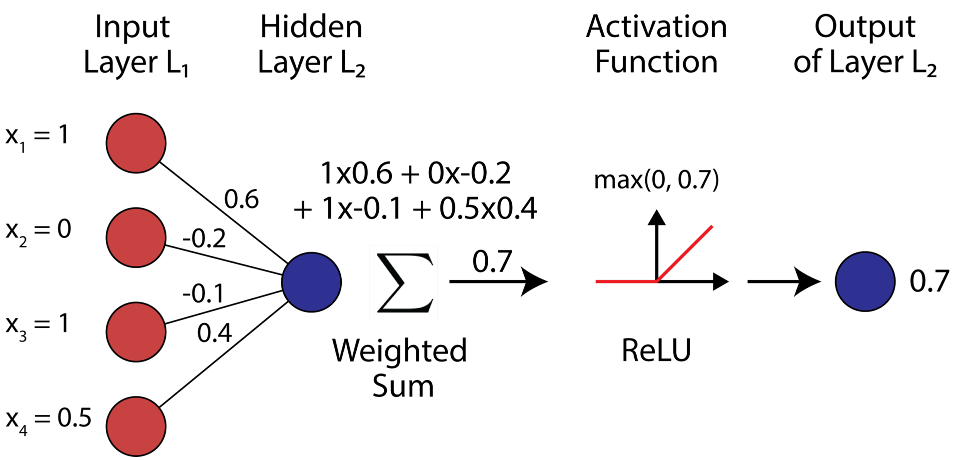
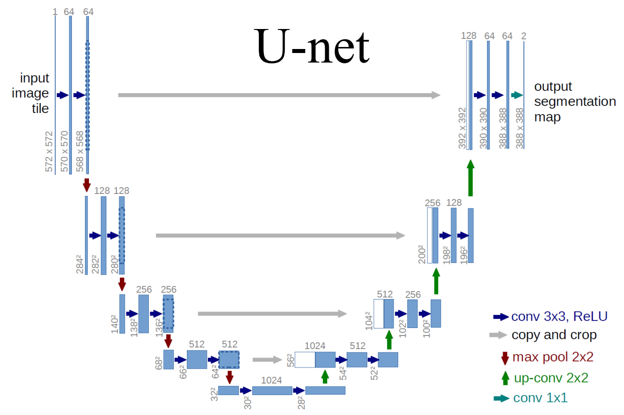


Image segmentation models



Use U-net architecture to segment images into categories

Falk, T. et al. U-Net: deep learning for cell counting, detection, and morphometry. *Nat. Methods* **16**, 67–70 (2019).

Input

U-net model

Output

Training models – finding best weights

$$Y = M(\boldsymbol{W}, X)$$

Where M is the model, $\boldsymbol{W}$ is a vector of the weights and X, Y the in and outputs.

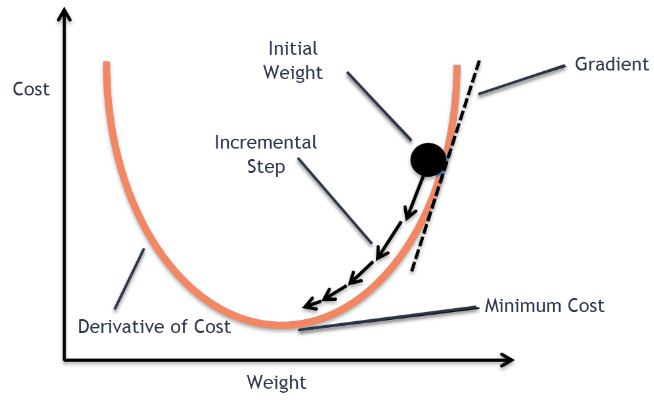
Loss function

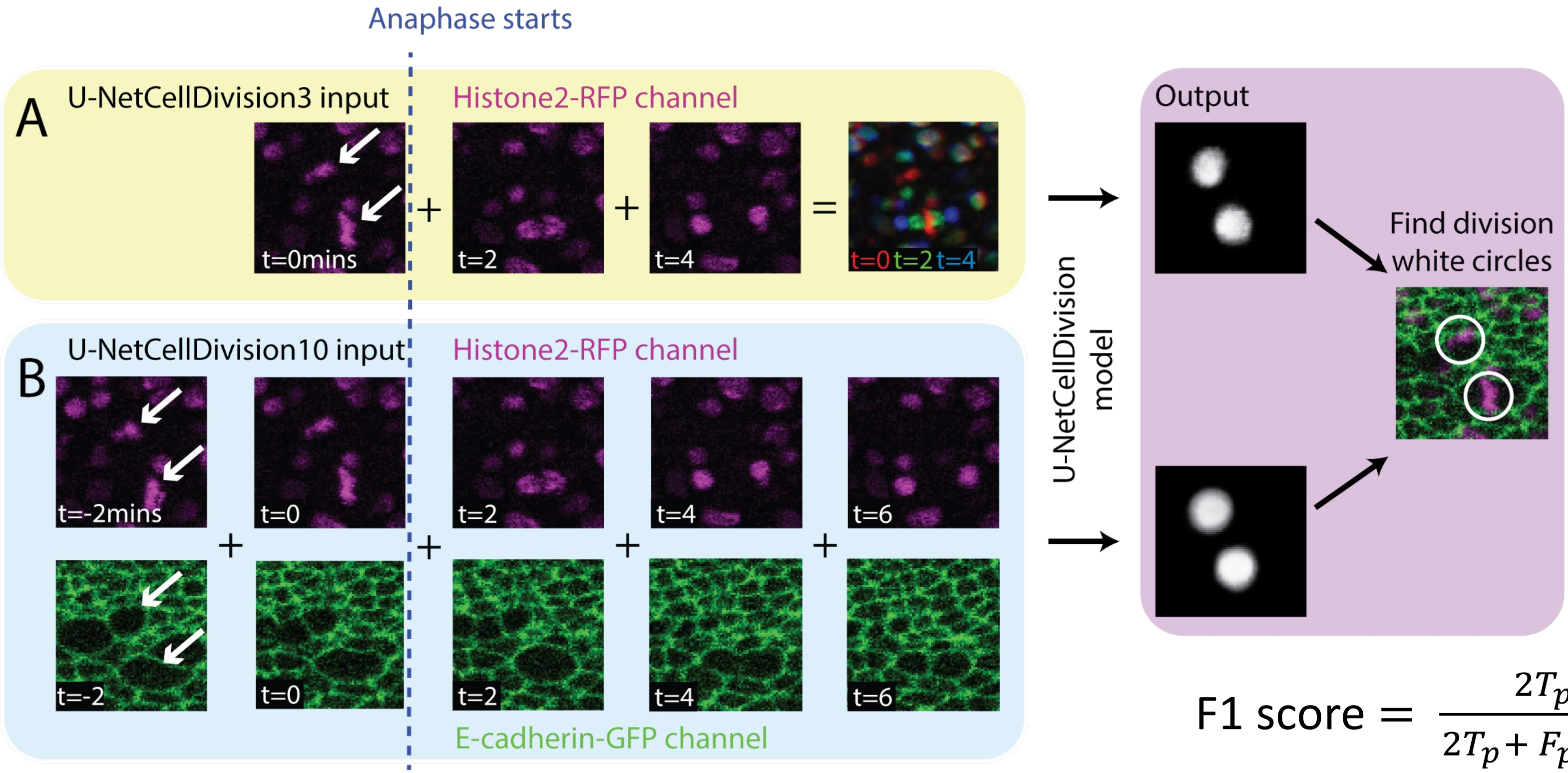
$$L(\boldsymbol{W}, X) = (\hat{Y} - M(\boldsymbol{W}, X))^2$$

$\hat{Y}$ is the ground truth. To optimize the loss function we use stochastic gradient descent.

$$\boldsymbol{W} = \boldsymbol{W} - l_r \, \boldsymbol{\nabla} L(\boldsymbol{W}, X_i)$$

Where l_r is the learning rate.

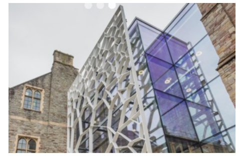




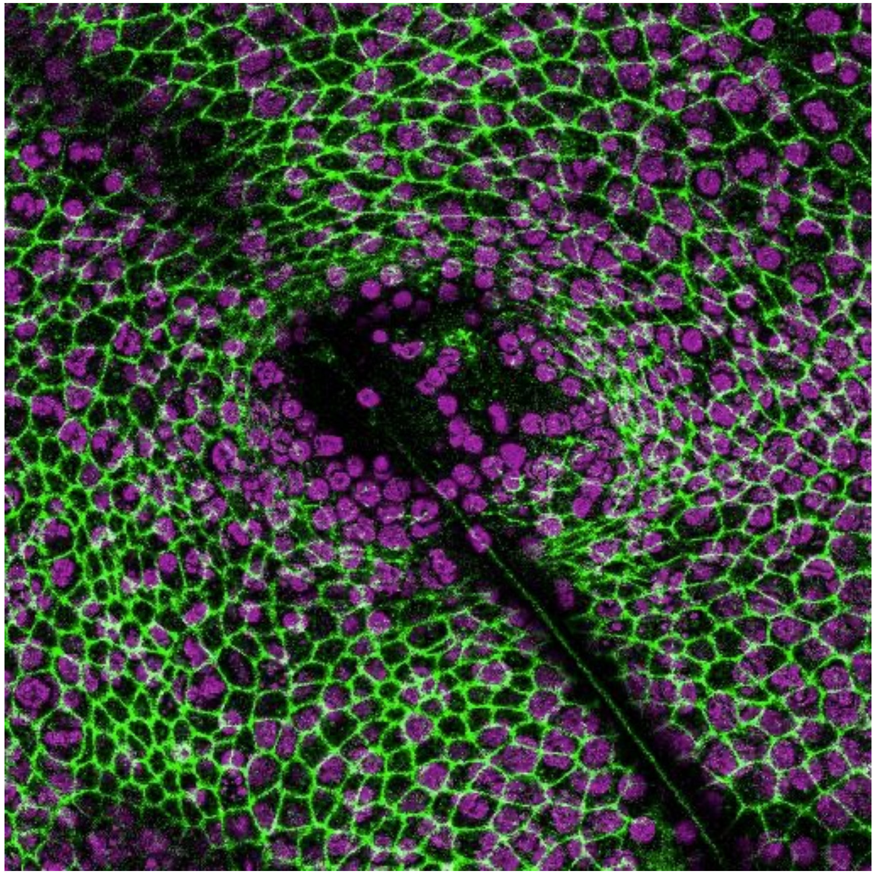
$$\text{F1 score} = \frac{2T_p}{2T_p + F_p + F_n}$$

Model	True Positives	False Positive	False Negative	F1 score
U-NetCellDivision3	797	216	310	0.752
U-NetCellDivision10	1057	28	50	0.964

University of BRISTOL
Bristol BioDesign Institute



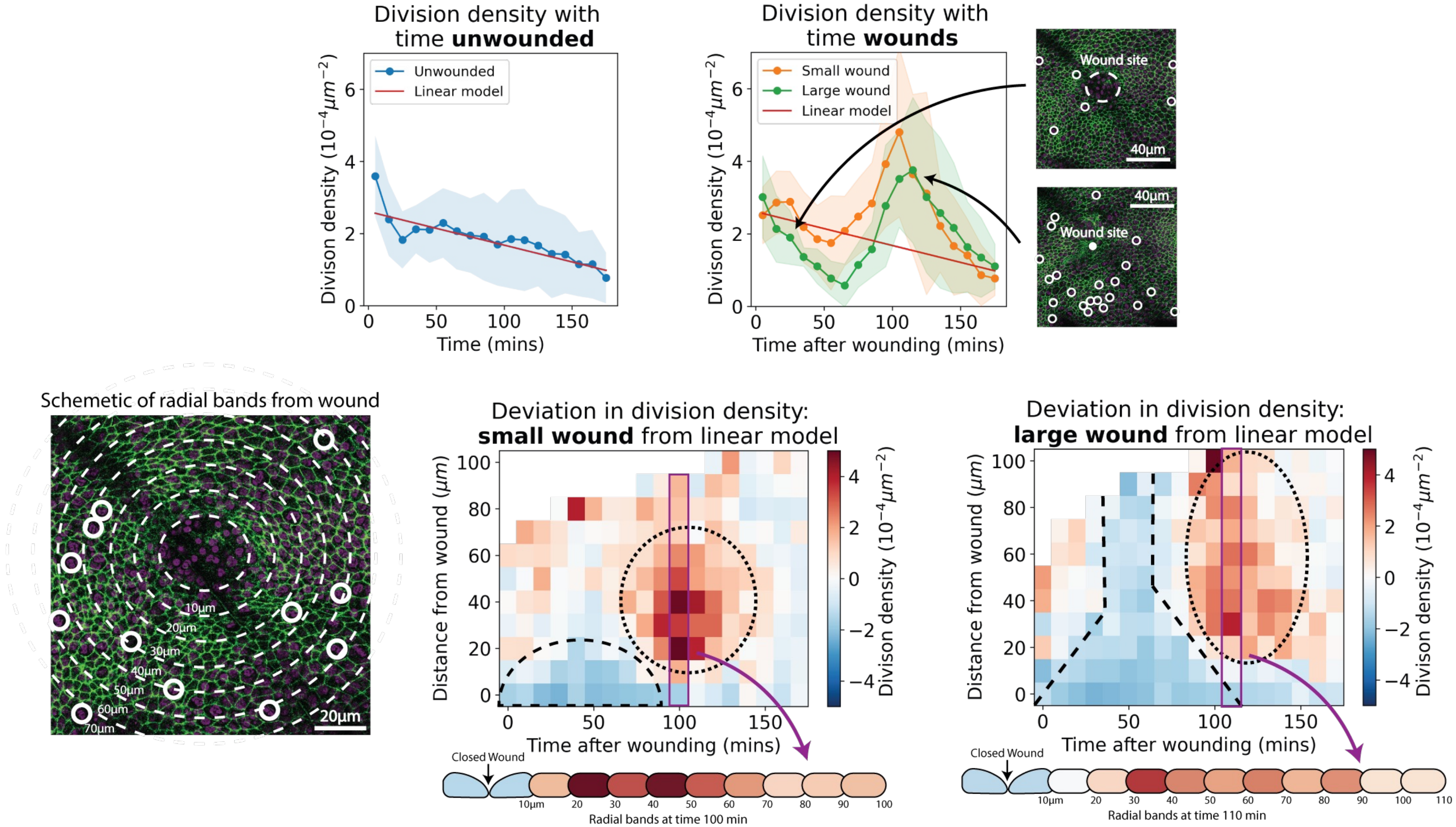
Detected cell divisions



Nov 2024

University of BRISTOL
Bristol BioDesign Institute

Division density in living epithelial tissue *in vivo*



J Turley et al, biorXiv: 10.1101/2023.03.20.533343

Nov 2024

University of BRISTOL
Bristol BioDesign Institute

Division density in living epithelial tissue *in vivo*

- Epithelial cell divisions are oriented according to lines of tissue tension

- Wounding triggers a delayed and synchronised (whose orientations are not affected by wound) wave of cell divisions back from the leading edge

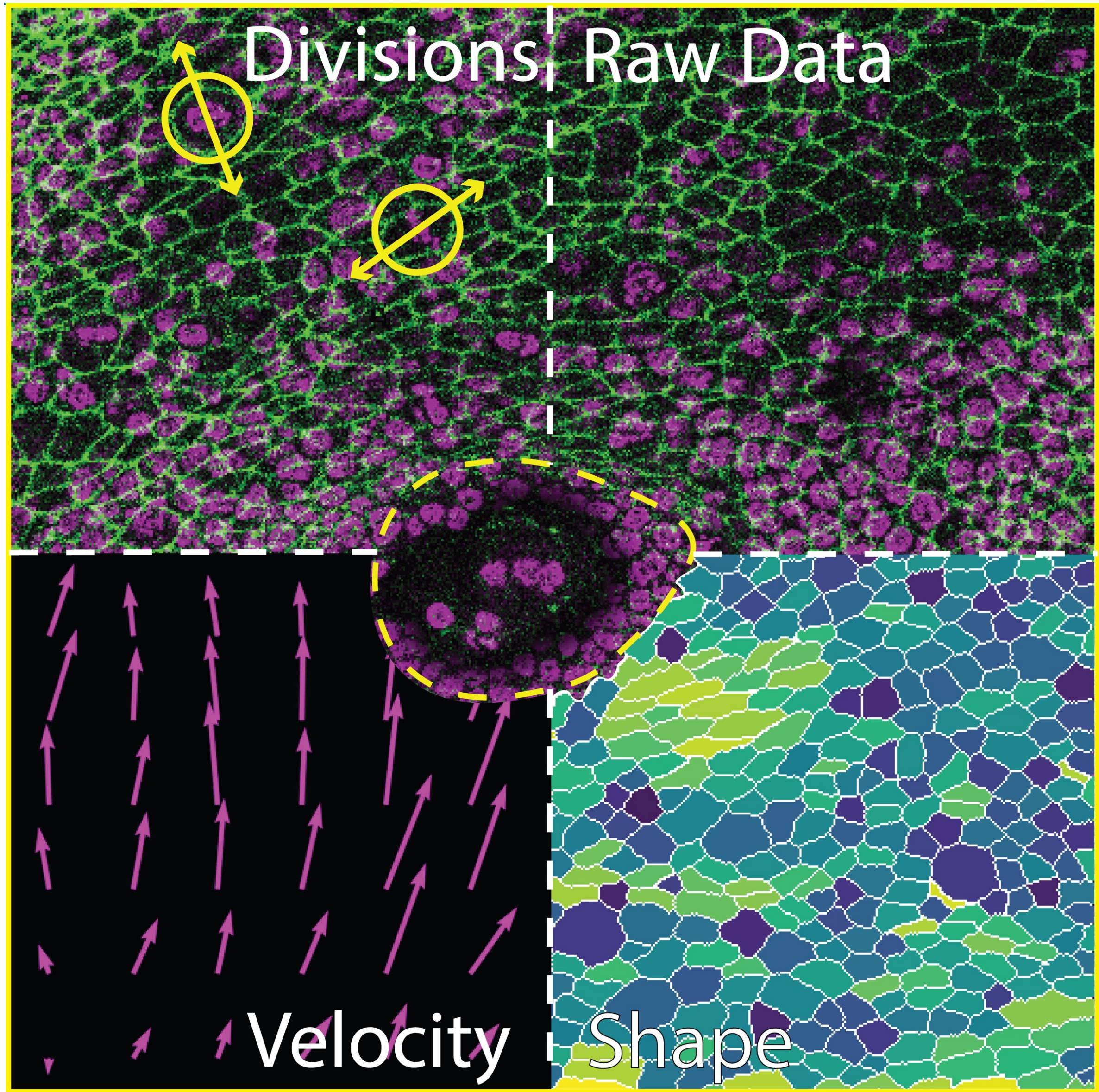
- Spatio-temporal cell division analyses following wounding reveal spatial synchronicity that scales with wound size

- Additional deep learning tools enable rapid analysis of cell division orientation

J Turley et al, eLife 12 : RP87949 (2023)

divisions

motion



shape

University of BRISTOL
Bristol BioDesign Institute

Overview

1. Quantifying wound healing at cellular scales	
2. Statistical mechanics of active processes	
3. Analysis of fluctuating tissue growth and repair	

University of BRISTOL
Bristol BioDesign Institute

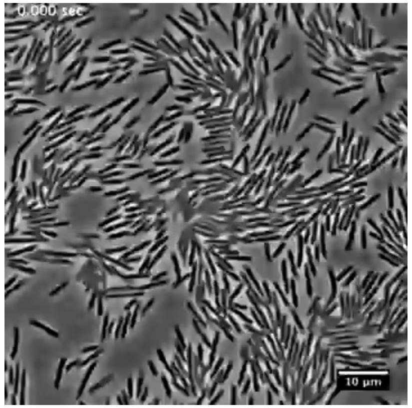
Tissue is “active matter”

	Traditional (Soft) Condensed Matter	Active Matter
Many “particles”	✓	✓
Interactions	✓	✓
$k_B T$	✓	✗
Local energy conservation	✓	✗

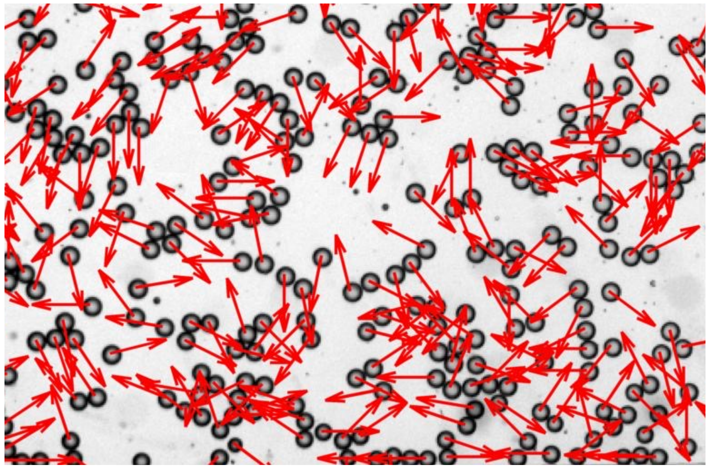
University of BRISTOL
Bristol BioDesign Institute

active matter

E-coli bacteria swarm



Starling murmurations

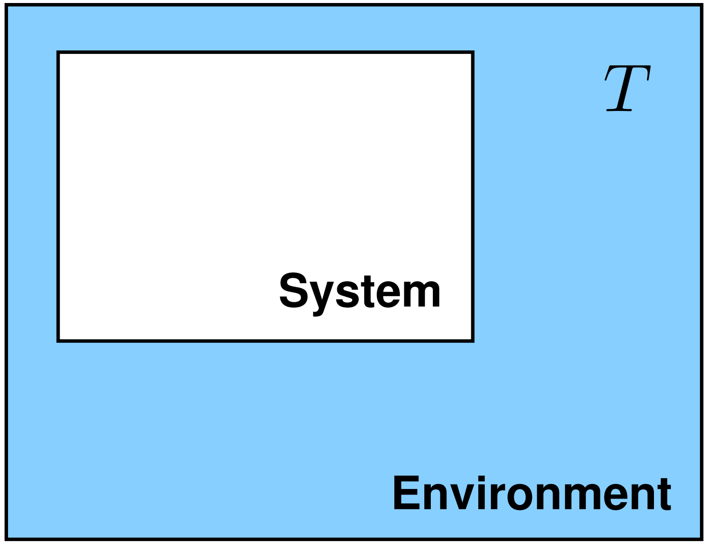


Self-propelled colloids

S. Thutupalli et al., NJP 13, 073021 (2011)

Thermodynamic equilibrium

"coarse-grained" system with "many" degrees of freedom



$$\{r_i\} \qquad i \in \{1, \ldots, N\} \qquad N \gg 1$$

$$\vec{r} = (r_1, \ldots, r_N)$$

"Hamiltonian" $\quad \mathcal{H}\left(\vec{r}\right)$

Canonical Ensemble

$$\mathrm{Tr}\left(\rho\right) = 1 \qquad \mathrm{Tr} \equiv \int_{\vec{r}}$$

Equilibrium = steady state with Gibbs-Boltzmann distribution

$$\rho(\vec{r}) = \frac{1}{Z} \exp\left[-\mathcal{H}/T\right]$$

which maximises entropy

$$S[\rho] = -\int_{\vec{r}} \rho(\vec{r}) \ln \rho(\vec{r})$$

$\rho(\vec{r}) \quad \Rightarrow \quad$ Macroscopic properties $\quad A = \langle A(\vec{r}) \rangle = \mathrm{Tr}\left(A\rho\right)$

Thermodynamic equilibrium

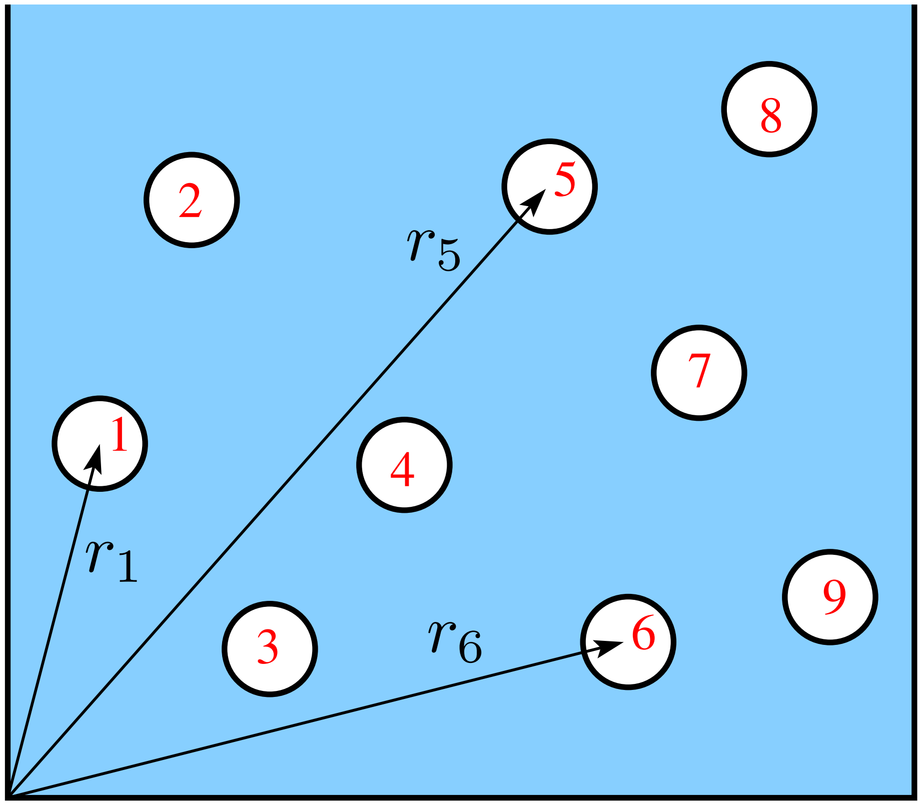
Example : stabilised colloidal suspension

Interaction potential

$$V_{ij} = U(|\mathbf{r}_i - \mathbf{r}_j|)$$

"Hamiltonian"

$$\mathcal{H}(\vec{r}) = \frac{1}{2} \sum_{i \neq j} V_{ij}$$



Phase diagram

(colloidal fluids, gels, glasses, crystals)

microscopic ⟶ MACROSCOPIC

University of BRISTOL
Bristol BioDesign Institute

Driven systems

"slow" d.o.f. $r_i(t)$ Langevin equation $i \in \{1, \ldots, N\}$ $N \gg 1$

addition of ➟ non-equilibrium driving

$$T = \zeta = 1$$

$$\dot{r}_i = -\nabla_i \mathcal{H} + v_i(\vec{r}) + f_i(t) \qquad v_i \neq \nabla_i \Phi(\vec{r})$$

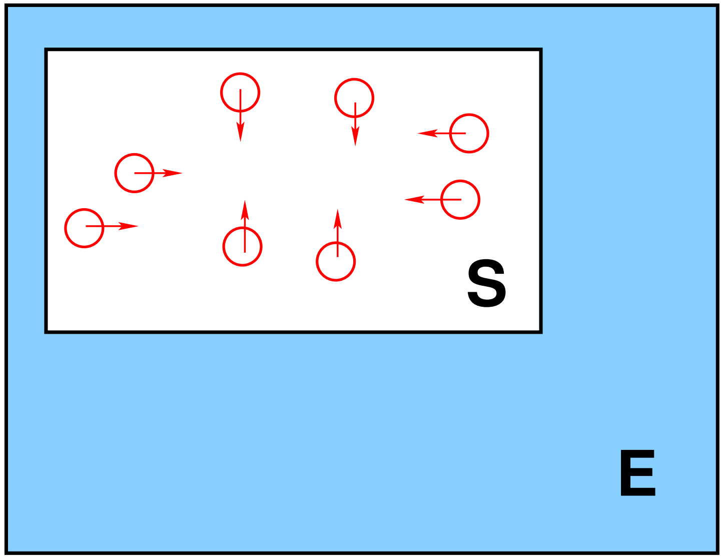
$$\langle f_i(t) \rangle = 0 \qquad \langle f_i(t) f_j(t') \rangle = 2\theta \delta_{ij} \delta(t - t')$$

Driving in bulk

e.g. active matter

$$\int_S |v_i| \propto S$$

Classical



University of BRISTOL
Bristol BioDesign Institute

Driven systems

Langevin equation ➟ Fokker-Planck

Many particle density $P\left(x_1, \ldots, x_N; t\right) = \left\langle \prod_{i=1}^{N} \delta\left(x_i - r_i(t)\right) \right\rangle$

$$\frac{\partial}{\partial t} P\left(\vec{x}; t\right) + \sum_{i=1}^{N} \nabla_i J_i = 0$$

$$J_i = -\theta \nabla_i P - \left(\nabla_i \mathcal{H} - v_i\right) P$$

Q: Is there an equivalent to equilibrium for these systems?

A: Yes, but we must generalize the idea of a steady state

Non-equilibrium steady states

Bakry, Emery, Guionnet, …

University of BRISTOL
Bristol BioDesign Institute

A theorem

Active matter has non-equilibrium steady states characterized by 2 quantities

1) A **stable** many particle distribution (like equilibrium)

2) A **deterministic** dynamical system (unlike equilibrium)

$$\rho_{ss}(\vec{x}) \equiv \frac{1}{Z} \exp\left[-h(\vec{x})\right]$$

Bakry, Emery, Guionnet, …

The system follows the **typical** trajectories

$$\vec{X}(t) = (X_1(t), \ldots, X_N(t))$$

$$\frac{d}{dt}\vec{X} = \vec{V}[h(\vec{X})]$$

$$V_i = v_i - \nabla_i \mathcal{H} + \theta \nabla_i h$$

The stationarity condition

$$\sum_i \nabla_i \left(\rho_{ss} V_i\right) = 0 \;\Rightarrow\; h(\vec{x}) \qquad (*)$$

Summary

equilibrium

$$\rho(\vec{r}) = \frac{1}{Z} \exp\left[-\mathcal{H}/T\right]$$

$$\vec{J}_{eq} = 0 \quad \Rightarrow \quad \frac{d\vec{X}}{dt} = 0$$

T.B. Liverpool, PRE 101, 042107 (2020)

ness

$$\rho_{ss}(\vec{x}) \equiv \frac{1}{Z} \exp\left[-h(\vec{x})\right]$$

$$\sum_i \nabla_i \left(\rho_{ss} V_i\right) = 0 \;\Rightarrow\; h(\vec{x})$$

$$\vec{J}_{ss} = \rho_{ss}\vec{V} \quad \Rightarrow \quad \frac{d\vec{X}}{dt} = \vec{V}$$

$$\vec{V} = \vec{v} - \vec{\nabla}\mathcal{H} + \theta\vec{\nabla}h$$

sufficient but not necessary

University of BRISTOL
Bristol BioDesign Institute

Quantifying the tissue dynamics on a cellular scale

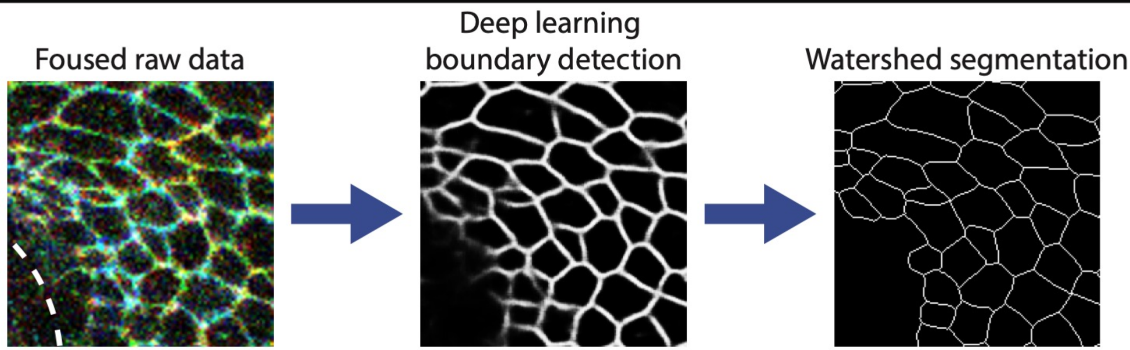
Nov 2024

University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

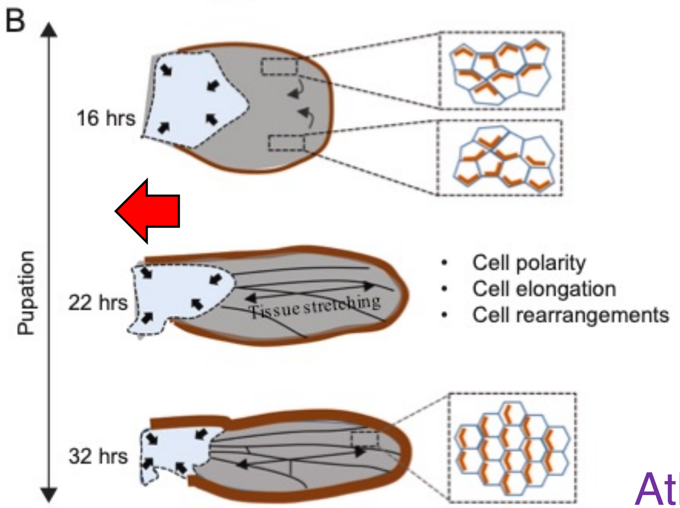
Let's look at cells of healthy unwounded tissue in detail

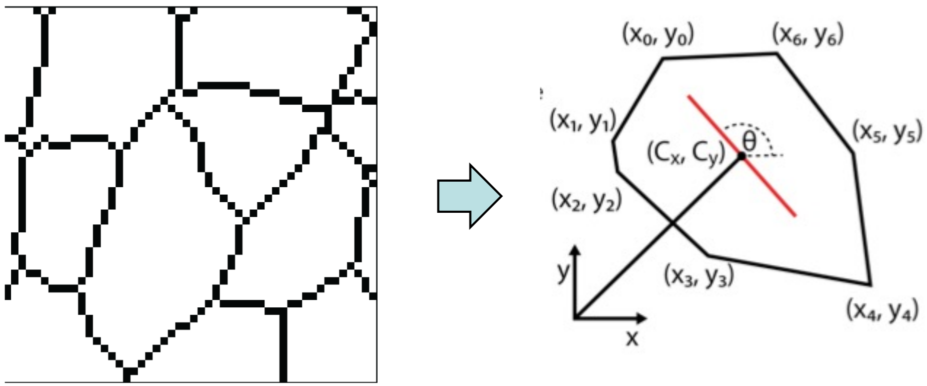
Binary Shape Detection



Polygon
5-16 sides

Stage of development



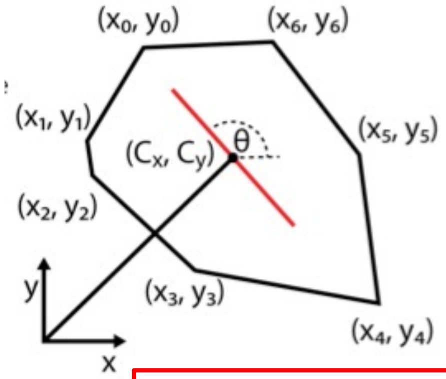


Athilingam et al, *Sem. Cell. Dev. Bio,* (2021)

University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

Cell shapes & protein distributions



$$\boldsymbol{s} = \begin{pmatrix} s_{xx} & s_{xy} \\ s_{xy} & s_{yy} \end{pmatrix}$$

Area $$A = \iint_A dx\, dy$$

Centre $$C_x = \frac{1}{A}\iint_A x\, dx\, dy$$
$$C_y = \frac{1}{A}\iint_A y\, dx\, dy$$

Shape tensor $f(x, y) = 1$

$$s_{xx} = -\frac{1}{A^2}\iint_A f(x', y')y'^2\, dx'\, dy'$$
$$s_{xy} = \frac{1}{A^2}\iint_A f(x', y')x'y'\, dx'\, dy'$$
$$s_{yy} = -\frac{1}{A^2}\iint_A f(x', y')x'^2\, dx'\, dy'$$

Protein distribution tensor

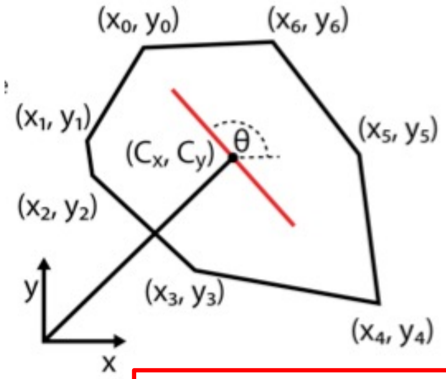
$$f(x, y) = \text{prot. conc.}$$

$$y' = y - C_y \quad , \quad x' = x - C_x$$

University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

Cell shapes & protein distributions



$$\boldsymbol{s} = \begin{pmatrix} s_{xx} & s_{xy} \\ s_{xy} & s_{yy} \end{pmatrix}$$

Area $$A = \iint_A dx\, dy$$

Centre $$C_x = \frac{1}{A}\iint_A x\, dx\, dy$$
$$C_y = \frac{1}{A}\iint_A y\, dx\, dy$$

Shape tensor $f(x,y) = 1$

$$s_{xx} = -\frac{1}{A^2}\iint_A f(x',y')y'^2\, dx'\, dy'$$
$$s_{xy} = \frac{1}{A^2}\iint_A f(x',y')x'y'\, dx'\, dy'$$
$$s_{yy} = -\frac{1}{A^2}\iint_A f(x',y')x'^2\, dx'\, dy'$$

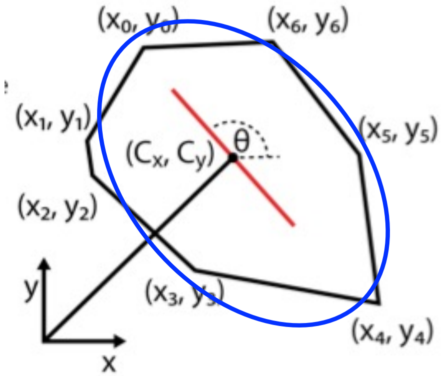
Protein distribution tensor

$$f(x,y) = \text{prot. conc.}$$

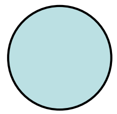
University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

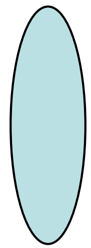
Cell shapes & protein distributions



Eigenvalues of shape tensor λ_1, λ_2

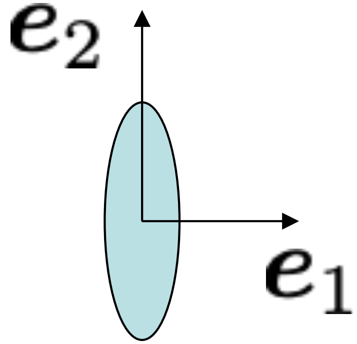


$\lambda_1 = \lambda_2$



$|\lambda_1 - \lambda_2| > 0$

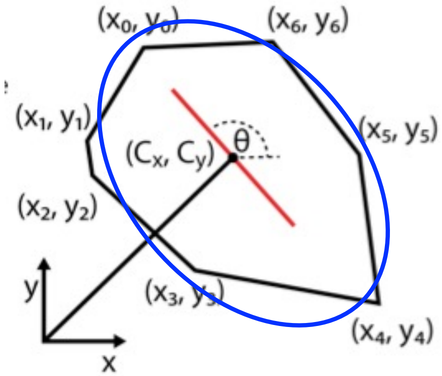
Eigenvectors ➡ orientation



University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

Cell shapes & protein distributions



Q-tensor $\boldsymbol{q} = \boldsymbol{s} - \mathrm{Tr}(\boldsymbol{s})\boldsymbol{I}$

$$\boldsymbol{q} = \begin{pmatrix} q_1 & q_2 \\ q_2 & -q_1 \end{pmatrix} \neq 0$$ ➡ elongated cell

$$\boldsymbol{q} = \begin{pmatrix} q_1 & q_2 \\ q_2 & -q_1 \end{pmatrix} = \frac{q_0}{\sqrt{2}} \begin{pmatrix} \cos 2\theta & \sin 2\theta \\ \sin 2\theta & -\cos 2\theta \end{pmatrix} = q_0 \hat{\boldsymbol{q}}$$

$$q_0^2 = ||\boldsymbol{q}||^2 = \frac{1}{2}\mathrm{Tr}(\boldsymbol{q}^2)$$

Average over N cells

$$\alpha \in [1, 2, \cdots, N]$$

Mean

$$Q\hat{\boldsymbol{Q}} = \frac{1}{N} \sum_{\alpha=1}^{N} \hat{\boldsymbol{q}}_\alpha$$

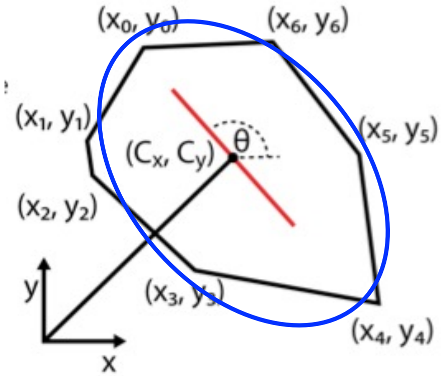
Variance

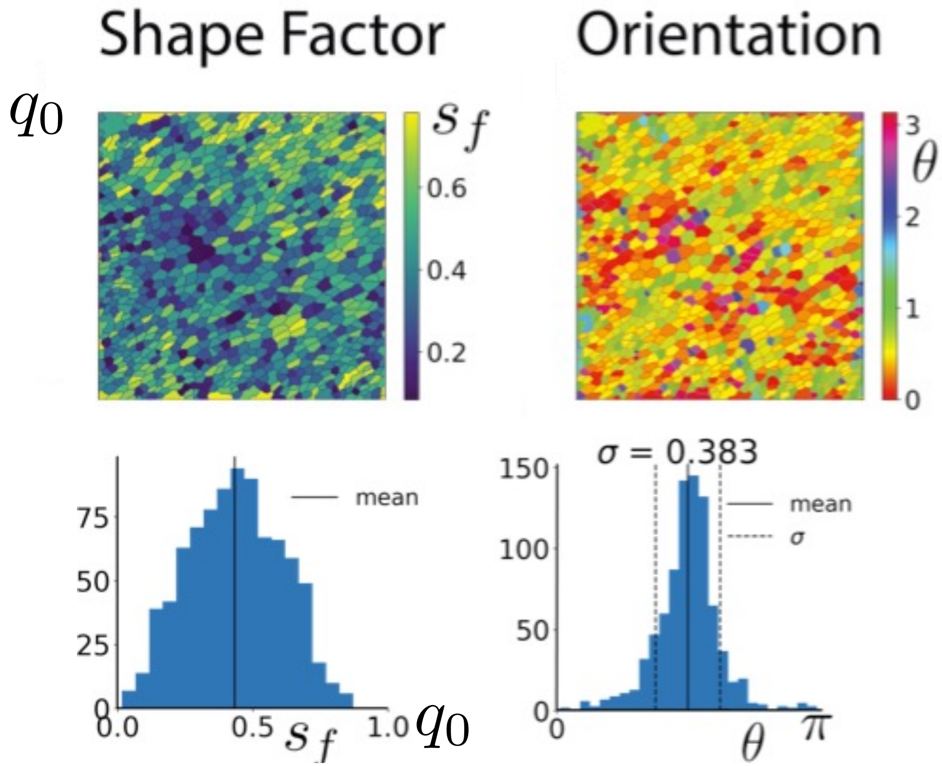
$$\sigma_q^2 = \frac{1}{N} \sum_{\alpha=1}^{N} \left\| \hat{\boldsymbol{q}}_\alpha - \hat{\boldsymbol{Q}} \right\|^2$$

University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

Cell shapes & protein distributions





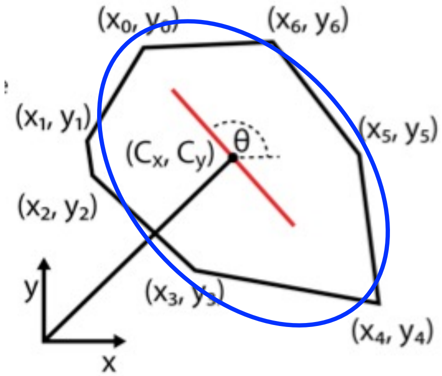
Average over cells

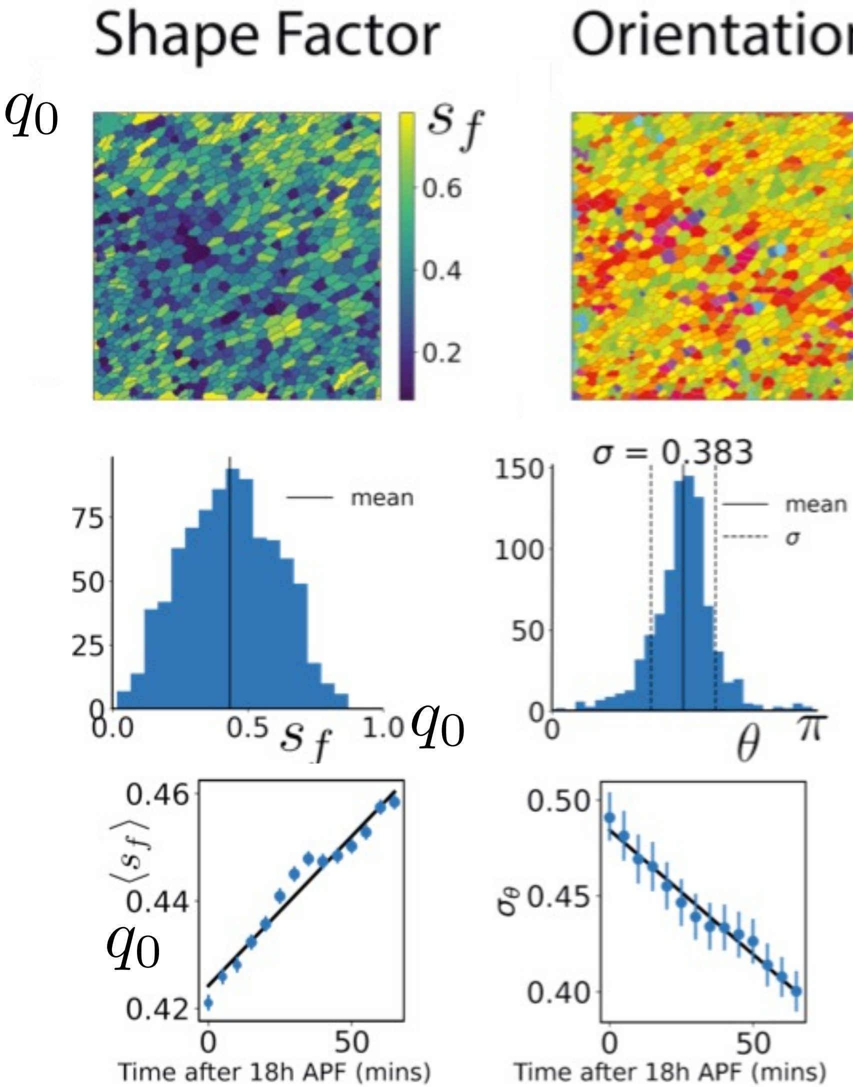
mean and variance

University of BRISTOL
Bristol BioDesign Institute

Analysis of shapes

Cell shapes & protein distributions





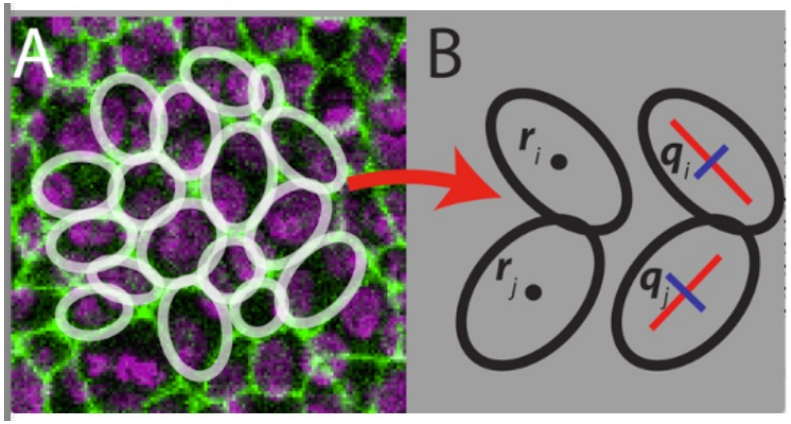
Average over cells

mean and variance

University of BRISTOL
Bristol BioDesign Institute

“Noisy” dynamics of tissue

Microscopic degrees of freedom, “atoms” $\vec{X} = (\boldsymbol{r}_1, \boldsymbol{q}_1, \ldots, \boldsymbol{r}_N, \boldsymbol{q}_N)$



Positions $\boldsymbol{r}_i(t)$

Shapes $\boldsymbol{q}_i(t)$

$$U = \sum_{i \neq j} \left[W_0(\boldsymbol{r}_i - \boldsymbol{r}_j) + W_2(\boldsymbol{r}_i - \boldsymbol{r}_j) \mathrm{Tr}\left(\boldsymbol{q}_i \boldsymbol{q}_j\right) \right]$$

$$\zeta_q \partial_t q_i^{\alpha\beta} = -b\left(q_i^{\alpha\beta} - \bar{q}^{\alpha\beta}\right) - \frac{\partial U}{\partial q_i^{\alpha\beta}} + \xi_i^{\alpha\beta}$$

$$\zeta \partial_t r_i^{\alpha} = \bar{V}^{\alpha}(t) - \frac{\partial U}{\partial r_i^{\alpha}} - b' \sum_j \left(q_i^{\alpha\beta} - q_j{}^{\alpha\beta}\right) \cdot \left(r_i^{\beta} - r_j^{\beta}\right) f(|\boldsymbol{r}_i - \boldsymbol{r}_j|) + \eta_i^{\alpha}$$

$$\left\langle \xi_i^{\alpha\beta}(t) \right\rangle = 0 \qquad \langle \eta_i^{\alpha}(t) \rangle = 0$$

$$\left\langle \xi_i^{\alpha\beta}(t) \xi_j^{\alpha'\beta'}(t') \right\rangle = C_q \delta_{\alpha\alpha'} \delta_{\beta\beta'} \delta_{ij} \delta(t - t') \qquad \left\langle \eta_i^{\alpha}(t) \eta_j^{\alpha'}(t') \right\rangle = C_v \delta_{\alpha\alpha'} \delta_{ij} \delta(t - t')$$

University of BRISTOL
Bristol BioDesign Institute

"Noisy" dynamics of tissue

Collective degrees of freedom

Density $\left(\frac{1}{\text{Area}}\right)$

$$\rho(\boldsymbol{r},t) = \sum_i \langle \delta(\boldsymbol{r} - \boldsymbol{r}_i(t)) \rangle$$

Shape

$$\rho(\boldsymbol{r},t) Q_{\alpha\beta}(\boldsymbol{r},t) = \sum_i \left\langle q_i^{\alpha\beta}(t) \delta(\boldsymbol{r} - \boldsymbol{r}_i(t)) \right\rangle$$

Velocity

$$\rho(\boldsymbol{r},t) V_\alpha(\boldsymbol{r},t) = \sum_i \langle \partial_t r_i^\alpha(t) \delta(\boldsymbol{r} - \boldsymbol{r}_i(t)) \rangle$$

Coarse grain ➡ Hydrodynamic equations

$$\partial_t \rho(\boldsymbol{r},t) + \nabla_\alpha J_\alpha[\rho, \boldsymbol{Q}, \boldsymbol{V}] = d - a$$

$$\partial_t Q_{\alpha\beta}(\boldsymbol{r},t) = \Theta^{\alpha\beta}[\rho, \boldsymbol{Q}, \boldsymbol{V}]$$

$$V_\alpha(\boldsymbol{r},t) = \nu^\alpha[\rho, \boldsymbol{Q}, \boldsymbol{V}]$$

+ other fields …

University of BRISTOL
Bristol BioDesign Institute

"Noisy" dynamics of tissue

Linearised fluctuating hydrodynamics

Density $$\rho(\boldsymbol{r},t) = \rho^*(t) + \bar{\rho}(\mathbf{r}) + \delta\rho(\boldsymbol{r},t)$$

Shape $$Q_{\alpha\beta}(\boldsymbol{r},t) = Q^*_{\alpha\beta}(t) + \bar{Q}_{\alpha\beta}(\mathbf{r}) + \delta Q_{\alpha\beta}(\boldsymbol{r},t)$$

Velocity $$V_\alpha(\boldsymbol{r},t) = V^*_\alpha(t) + \bar{V}_\alpha(\mathbf{r}) + \delta V_\alpha(\boldsymbol{r},t)$$

Deterministic + Fluctuations

$$\partial_t \delta\rho(\mathbf{r},t) = D\nabla^2\delta\rho + \nabla_\alpha \xi^\rho_\alpha(\mathbf{r},t)$$

$$\partial_t \delta Q_{\alpha\beta}(\mathbf{r},t) = \left[-b - 2B\rho^* + \rho^* L_{\gamma\epsilon}\nabla_\gamma\nabla_\epsilon\right]\delta Q_{\alpha\beta} + \xi^Q_{\alpha\beta}(\mathbf{r},t)$$

$$\delta V_\alpha(\mathbf{r},t) = -A\nabla_\alpha\delta\rho + \xi^Q_\alpha(\mathbf{r},t)$$

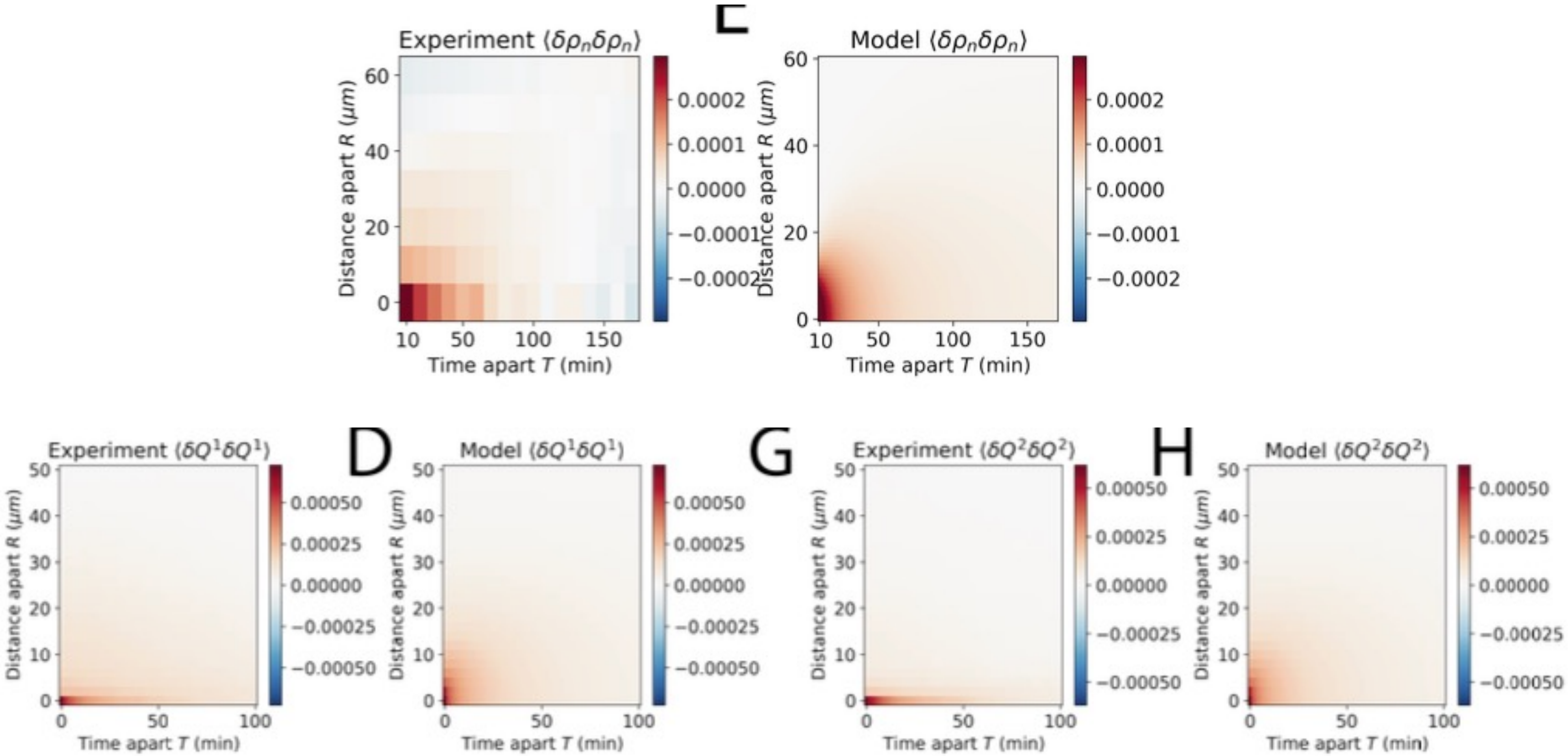
$$D, B, L, A \Leftrightarrow W_0, W_2, b, b'$$

University of BRISTOL
Bristol BioDesign Institute

“Noisy” dynamics of tissue

Correlation functions

$$\langle \delta\rho(\mathbf{r},t)\delta\rho(\mathbf{r}',t')\rangle \quad , \quad \langle \delta Q_{\alpha\beta}(\mathbf{r},t)\delta Q_{\alpha'\beta'}(\mathbf{r}',t')\rangle$$



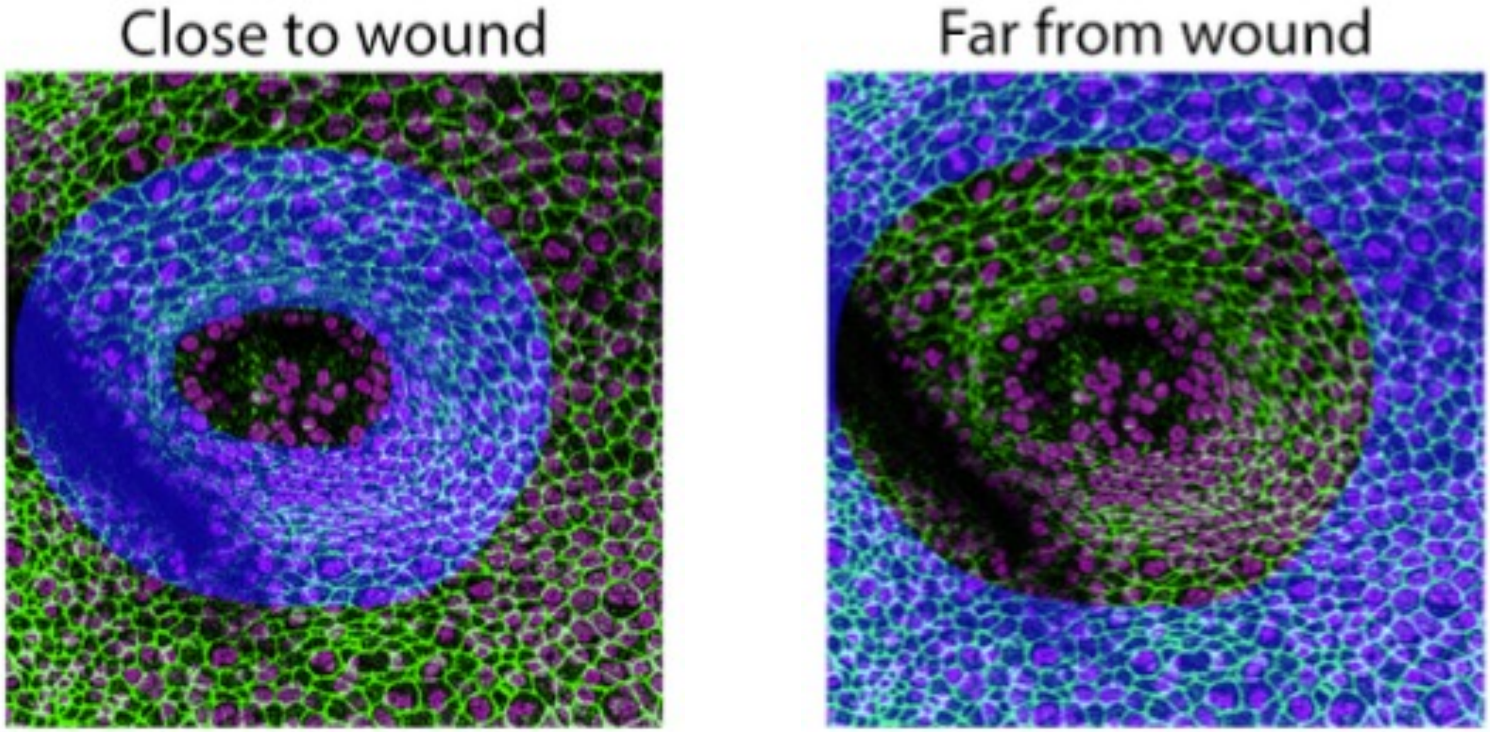
$$D, B, L, A \Leftrightarrow W_0, W_2, b, b'$$

University of BRISTOL
Bristol BioDesign Institute

“Noisy” dynamics of tissue

Example

$$\langle \delta\rho(\mathbf{r},t)\delta\rho(\mathbf{r}',t')\rangle \quad , \quad \langle \delta Q_{\alpha\beta}(\mathbf{r},t)\delta Q_{\alpha'\beta'}(\mathbf{r}',t')\rangle$$



Compare to unwounded - major change only in b close to wound !!

Calcium wave, JNK signalling and inflammation

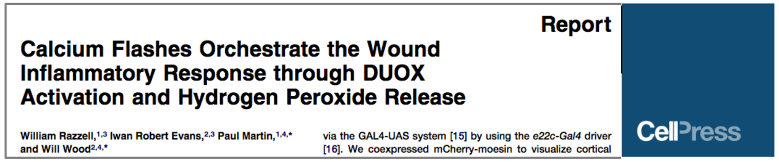
Wound-induced epithelial signals

Calcium wave – one of the first signals that occurs within seconds of wounding (using *act > trpm-RNAi*). Does it drive these cell behaviours?

JNK signalling – Associated in literature with shape changes in development (using *act > bsk*^{DN})

Inflammation

Test wound healing after genetic macrophage ablation (using *srp > reaper*)

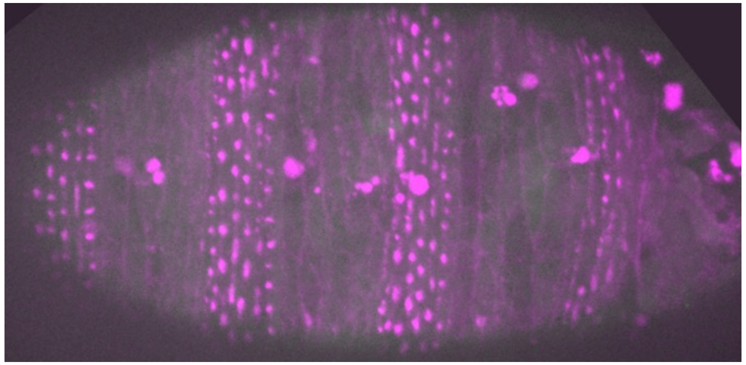

Report

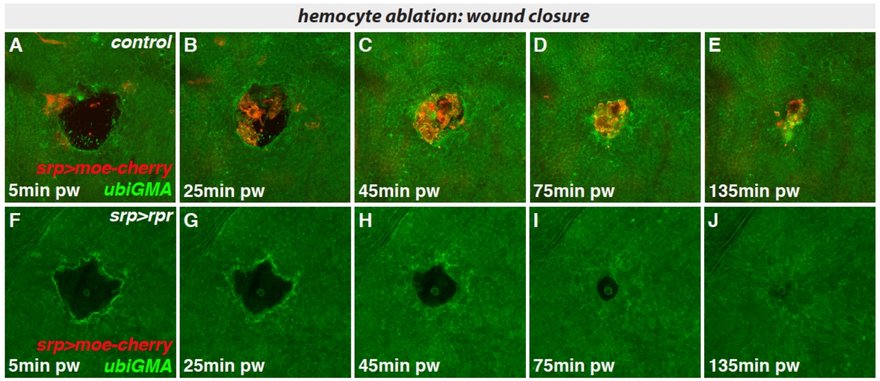
Calcium Flashes Orchestrate the Wound Inflammatory Response through DUOX Activation and Hydrogen Peroxide Release

William Razzell,[1,3] Iwan Robert Evans,[2,3] Paul Martin,[1,4,*] and Will Wood[2,4,*]

via the GAL4-UAS system [15] by using the *e22c-Gal4* driver [16]. We coexpressed mCherry-moesin to visualize cortical

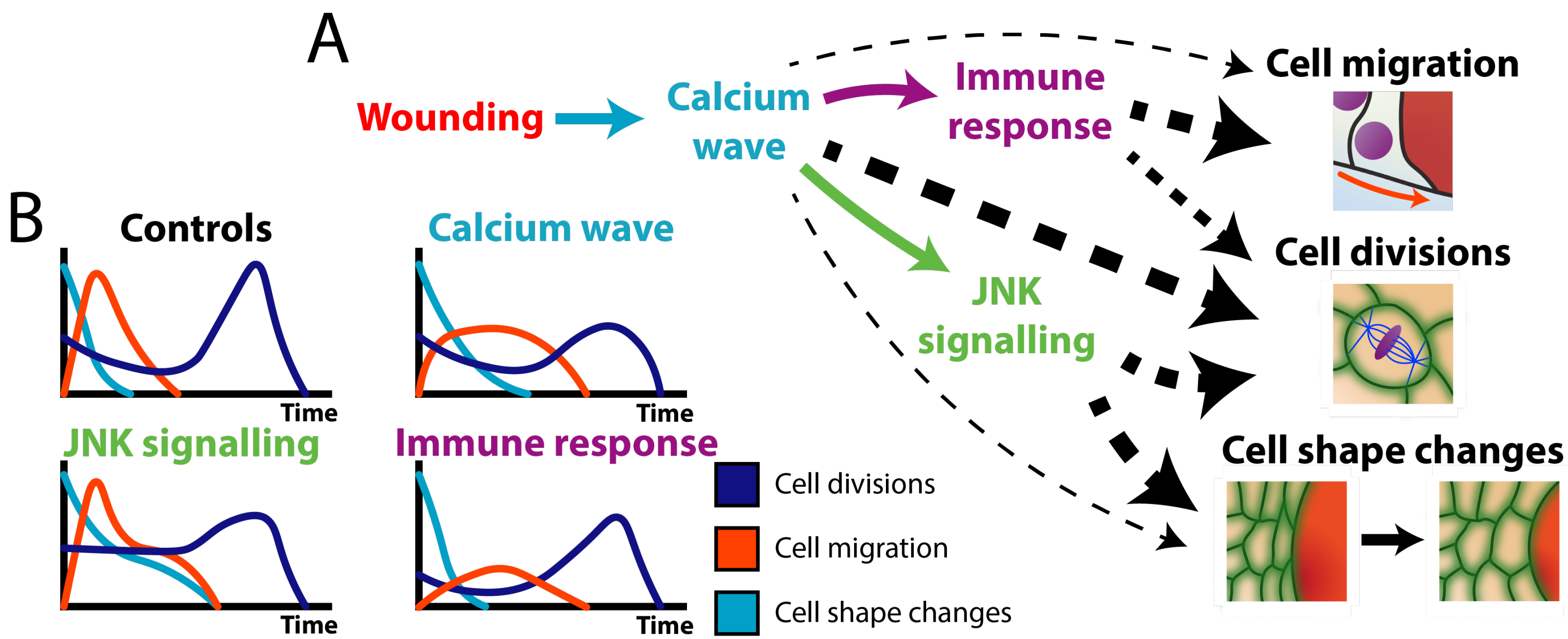
CellPress





Calcium wave, JNK signalling and inflammation

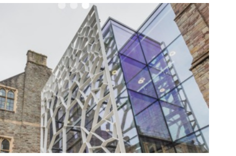
- Quantify how perturbations change parameters



J Turley et al, bioarxiv (2024)

University of BRISTOL
Bristol BioDesign Institute

conclusions and perspectives



machine learning tools have been developed and are being used to **observe** fruitfly pupa wounds in wing tissue

We can thus **analyse** the tissue behaviour at the cellular scale with unprecedented detail (in particular fluctuations!)

We are beginning to come up with mathematical models that give **explanations** of some of the emergent behaviour that we see ….

… but we are definitely closer to the beginning of the story than the end

M. Olenik et al, PRE, 107, 014403 (2023)

J Turley et al, eLife 12 : RP87949 (2023)

J Turley et al, Development 151 : dev202943 (2024)