Modélisation mathématique de certains aspects de la dégénérescence maculaire liée à l'âge (DMLA)

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A modelling perspective on retinal (patho-)physiology

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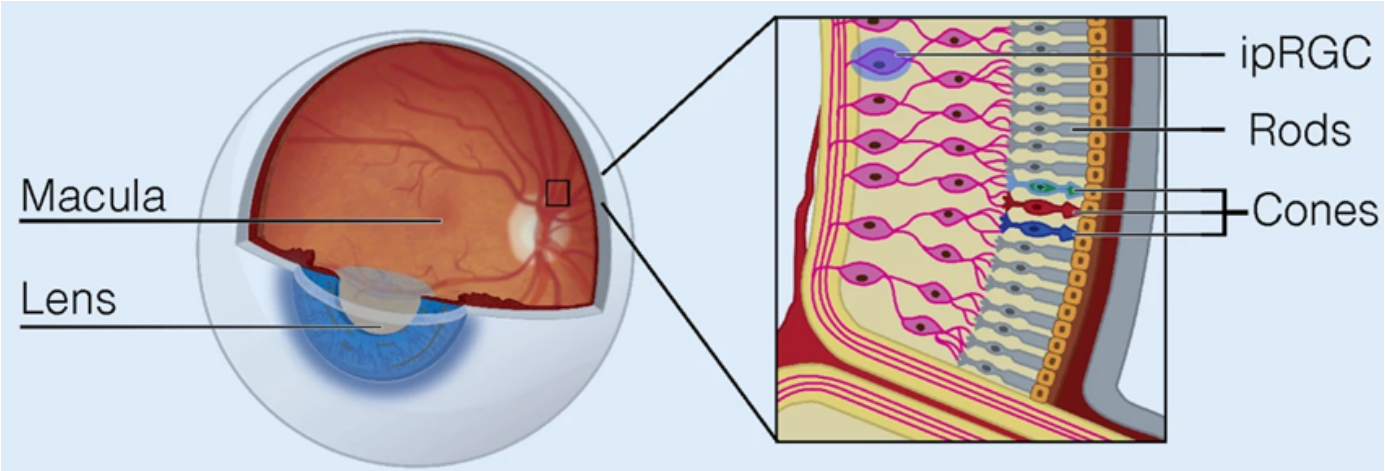
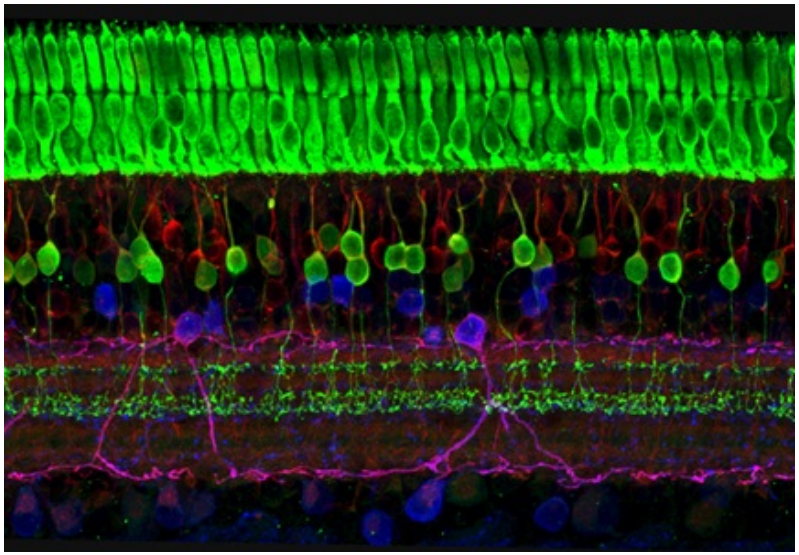
Séminaire du LJLL

Structure of the retina





[Top] Blume et al., 2019 https://doi.org/10.1007/s11818-019-00215-x.

[Bottom] Wei Li, National Eye Institute, https://www.flickr.com/photos/nihgov/

Retinal degeneration

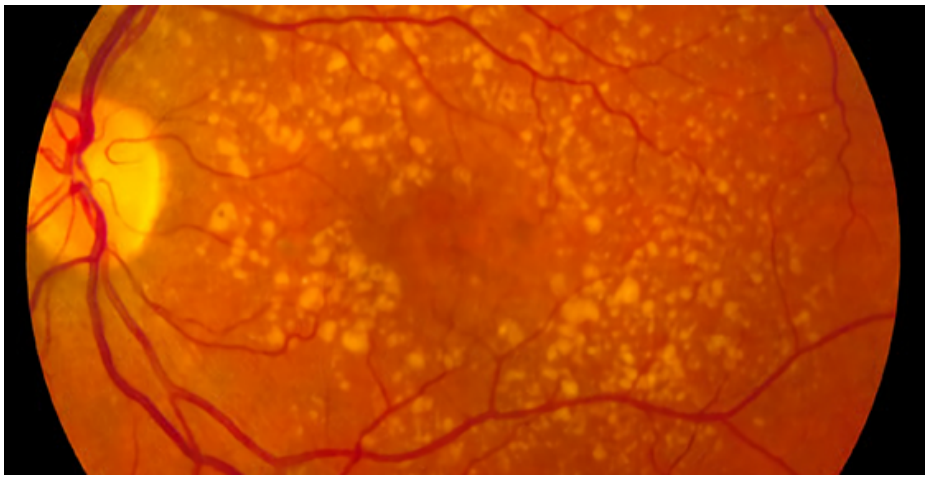
Dysfunctions of rods, cones and RPE are related to retinal degenerations.

Why is this urgent? - Age-related Macular Degeneration (AMD)

Public health issue: increasing projections of AMD patients worldwide,

- 196 million in 2020,
- 288 million in 2040. (Wong et al., The Lancet Global Health 2014)

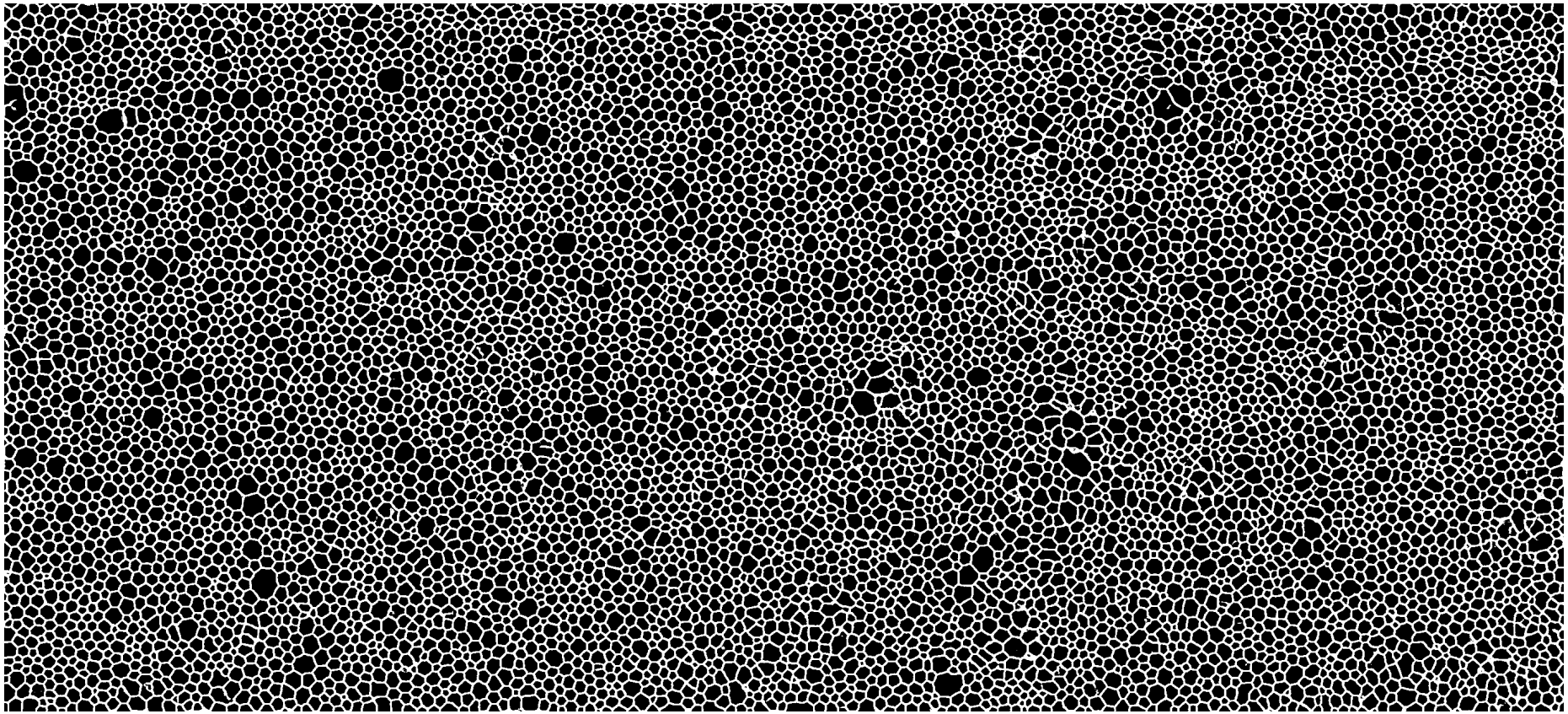
No treatment is currently available (for non-neovascular AMD).



A fundus photo showing intermediate age-related macular degeneration.

Credit: National Eye Institute, National Institutes of Health, Ref#: EDA2

Human RPE mosaic



Courtesy of Y. Borella, M. Darche, M. Paques, Paris Eye Imaging group, Hôpital Quinze-Vingts.

Mosaic changes due to ageing

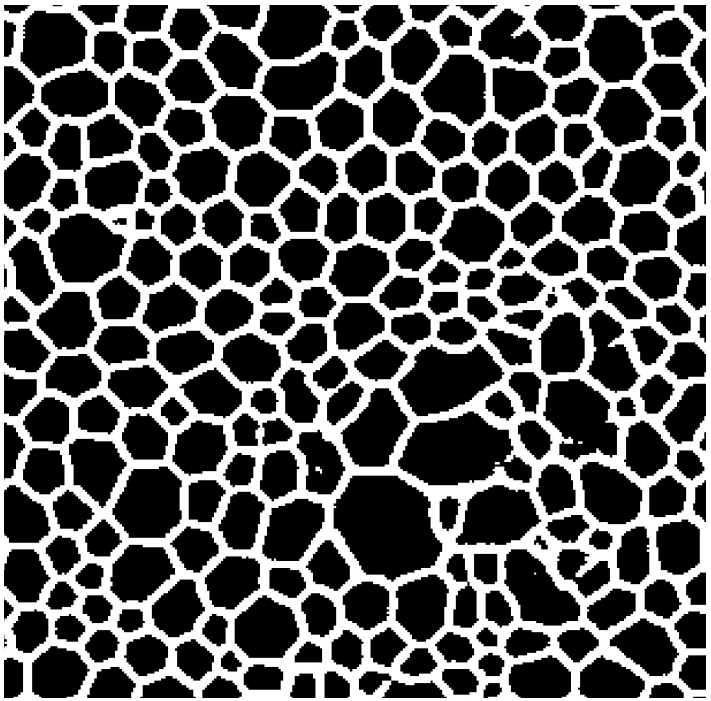
What is the expected behaviour of **ageing RPE** cells?

- no cell division, almost no migration;
- small gap closure, actin cable mechanism;
- senescence, size "relaxation".

Mosaic changes in AMD, initial anomalies

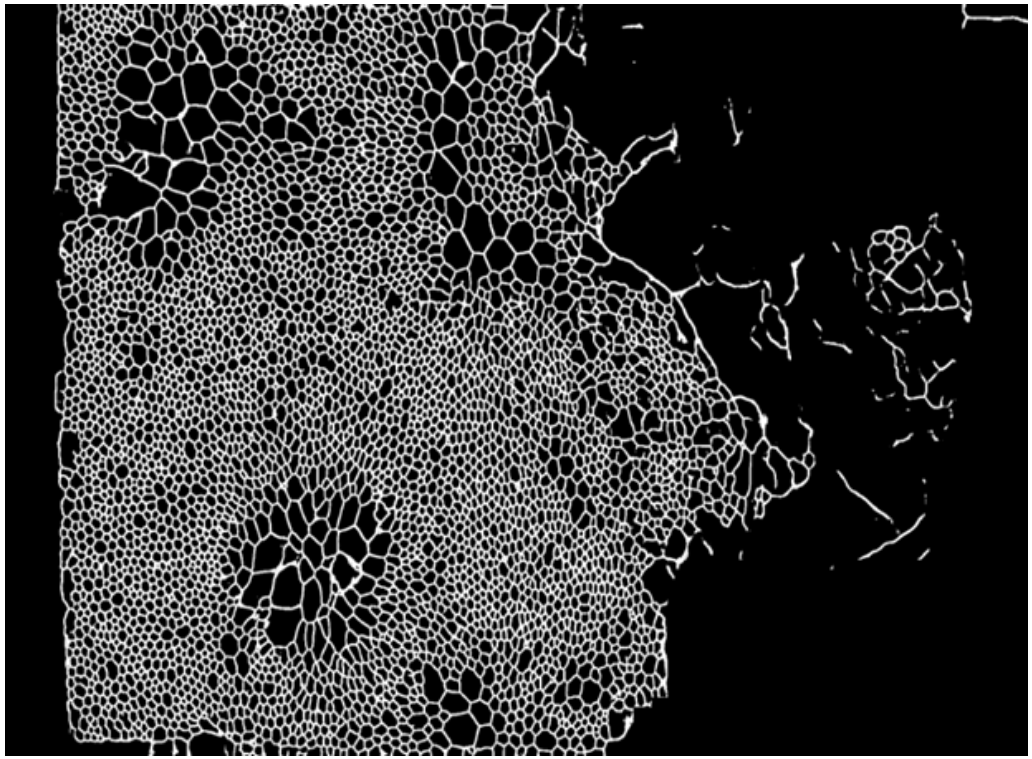
What happens as age-related macular degeneration progresses?

- drusen formation;
- hyper- and hypo- contracted cells;
- (eventually) tissue discontinuity.



Courtesy of Y. Borella, M. Darche, M. Paques, Paris Eye Imaging group, Hôpital Quinze-Vingts.

Tissue discontinuity - large lesions



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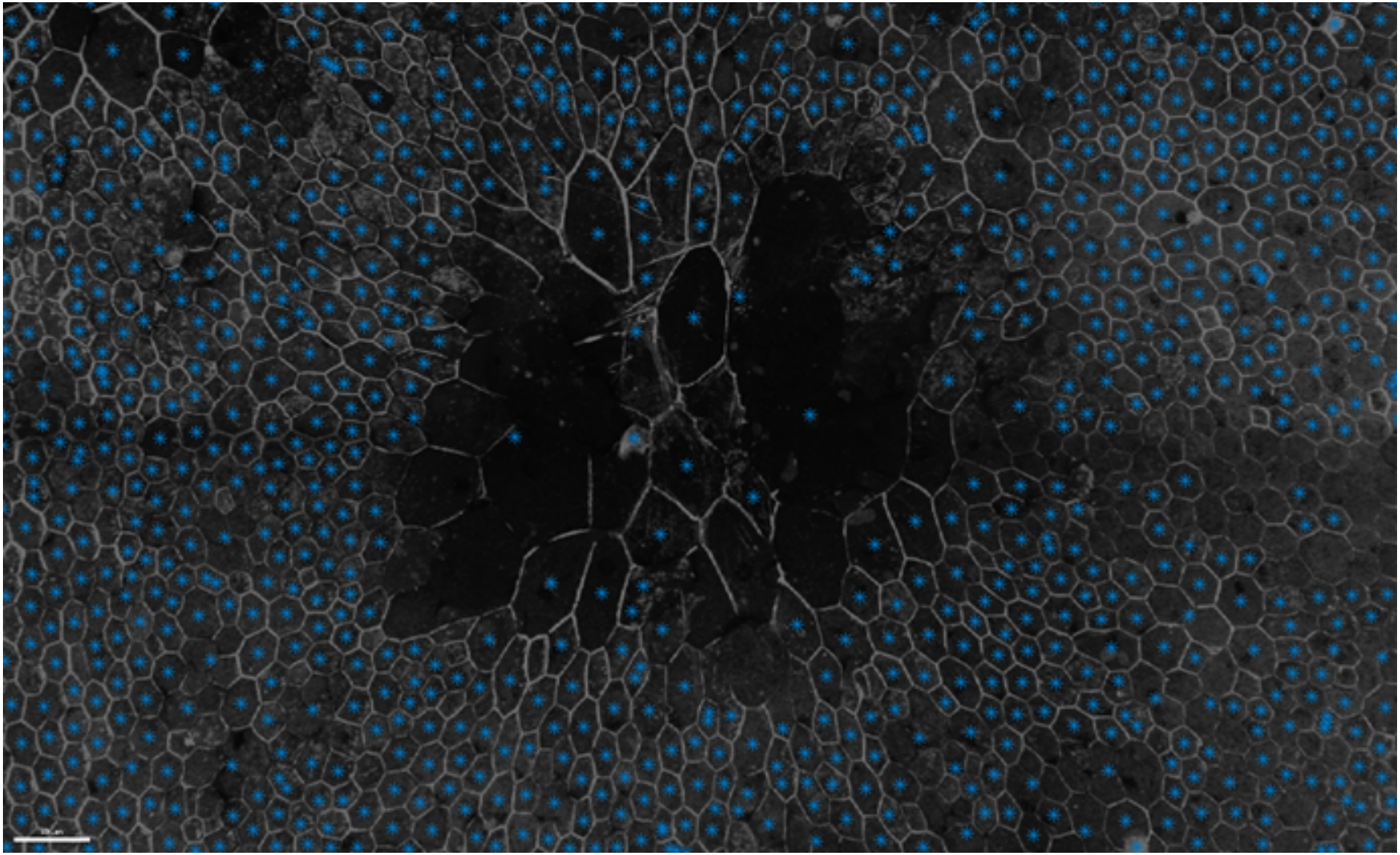
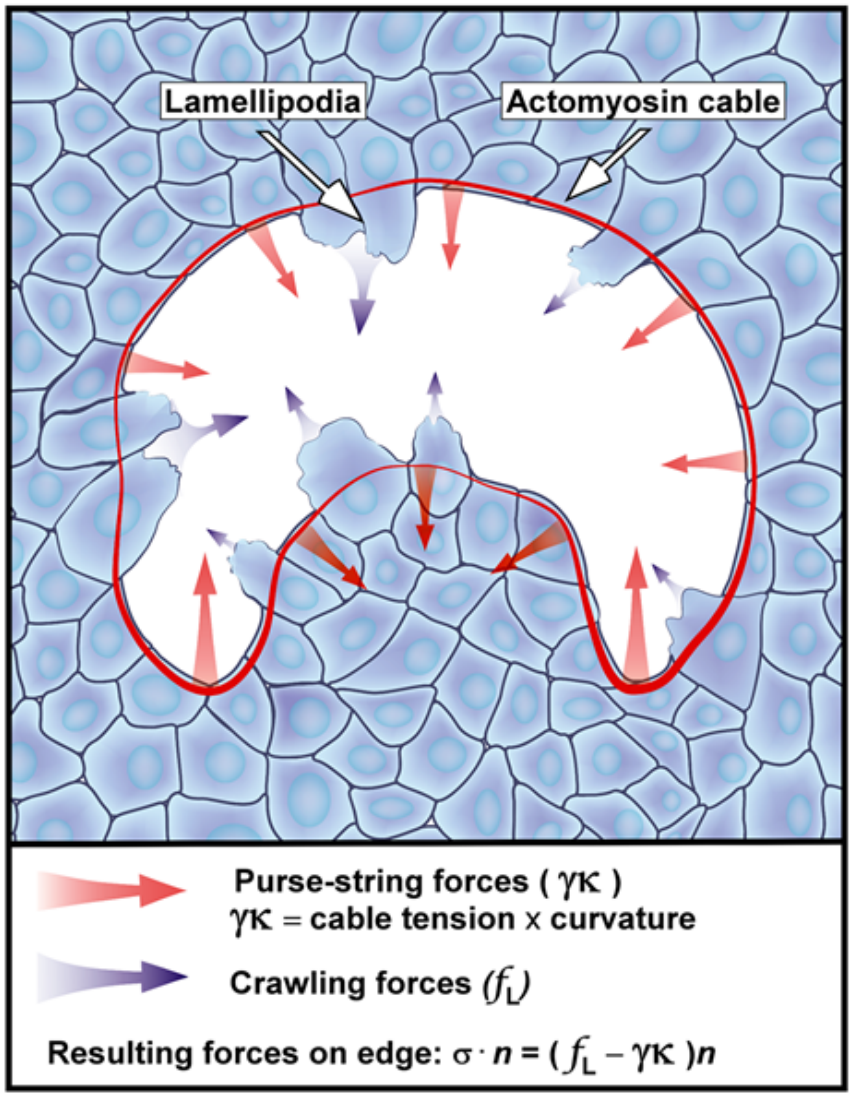


Courtesy of Y. Borella, M. Darche, M. Paques, Paris Eye Imaging group, Hôpital Quinze-Vingts.

Wound healing, actin cable, mean curvature

Source: Ravasio, Almeida et al., Gap geometry dictates epithelial closure efficiency, Nature Communications, 2015.



Wound healing, actin cable, mean curvature

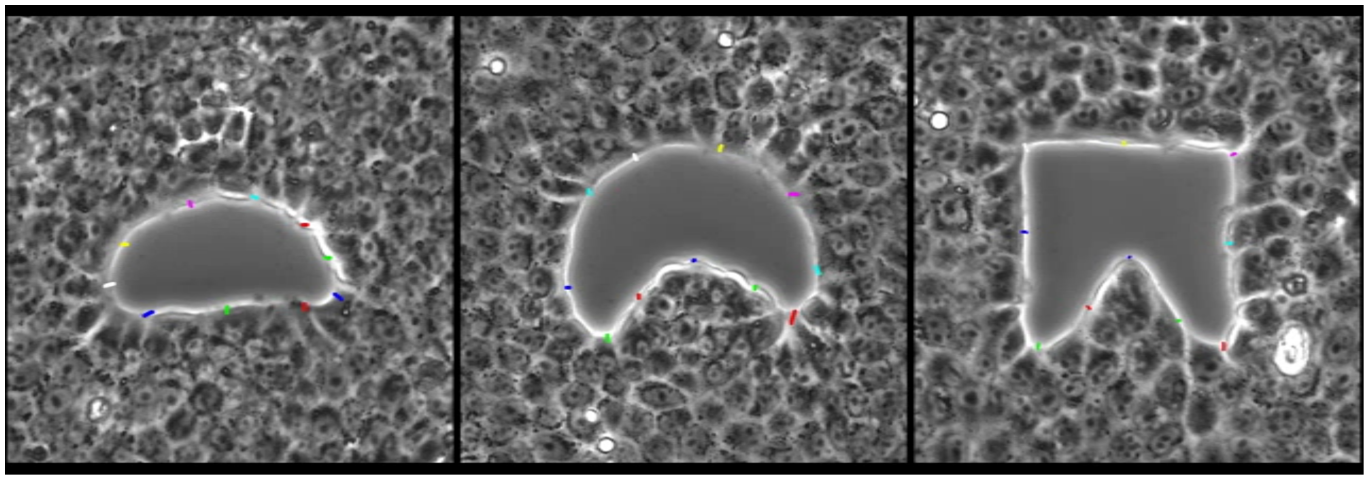


Figure: Closure of in-vitro gaps of different shapes. Life cell imaging of gap closure experiments shown in Fig. 1 B. Tracking over time of randomly chosen point and the edge of the gap are used to illustrate the different speed at different curvatures. Frame rate = 1 frame every 5 minutes.

Source: Ravasio, Almeida et al., Gap geometry dictates epithelial closure efficiency, Nature Communications, 2015.

What mathematical descriptions?

Can we model the tissue, small lesions, large lesions and their evolution?

Depending on the specific application, we find in the literature:

- Vertex models
- Potts models
- Particle-based models
- Continuum mechanics
- Cahn-Hilliard
- Thresholding scheme (MBO multiphase)
- ...
- Structured model with position and radius

Merriman-Bence-Osher scheme

Given an initial configuration $\mathbb{1}_{C^0} : \mathbb{R}^d \to \{0, 1\}$,

given a time step $h > 0$,

let G_h be the heat kernel at time $h/2$,

compute $\chi^n = \begin{cases} 1 & \text{where } G_h * \mathbb{1}_{C^{n-1}} > \frac{1}{2}, \\ 0 & \text{otherwise.} \end{cases}$

This is an approximation of the mean curvature flow for the support of χ^0.

Multiphase thresholding scheme

Given an initial configuration of m cells indexed by i, i.e. a collection of indicator functions $\mathbb{1}_{C_i^0} : \mathbb{R}^d \to \{0, 1\}$,

given a time step $h > 0$,

let G_h be the heat kernel at time $h/2$,

compute $\psi_i^n = G_h * \mathbb{1}_{C_i^{n-1}}$,

compute $\mathbb{1}_{C_i^n} = \begin{cases} 1 & \text{where } \psi_i^n(x) \geq \max_{j \neq i} \psi_j^n(x), \\ 0 & \text{otherwise.} \end{cases}$

Tim Laux, Felix Otto, Calc. Var. (2016),
Convergence of the thresholding scheme for multi-phase mean-curvature flow

Tim Laux, Theresa M. Simon, CPAM (2018),
Convergence of the Allen-Cahn Equation to Multiphase Mean Curvature Flow

A modified thresholding scheme

$x \in \Omega \subset \mathbb{R}^2$ n itaration number i cell number

$$\psi_i(0, x) = \mathbb{1}_{C_i^n}$$ initial condition

$$\partial_t \psi_i = \Delta \psi_i + \nabla \cdot (\psi_i \nabla V_i)$$ drift-diffusion, no-flux b.c.

$$V_i = |x - \xi_i(t)|^2$$ confinement potential

$$\xi_i(0) = \frac{1}{|C_i^n|} \int_\Omega \mathbb{1}_{C_i^n} \, x \, \mathrm{d}x$$ center of mass

$$\frac{d}{dt}\xi_i = -\frac{1}{m} \sum_{j=1}^{m} \frac{\xi_i - \xi_j}{|\xi_i - \xi_j|} F(|\xi_i - \xi_j|)$$ interaction of centers

Work in progress - MBO scheme for epithelia?

Case study 1, closure of small lesions in the epithelium

Working hypotheses:

- small lesions filled via actin cable contraction,
- analogy with wound healing,
- motion by mean curvature at the boundary.

Partial results: agreement with observations, ongoing numerical study.

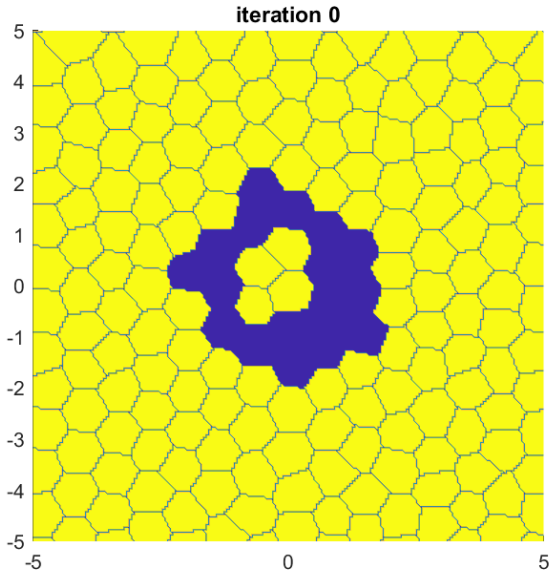
Case study 2, formation of large lesions in the epithelium

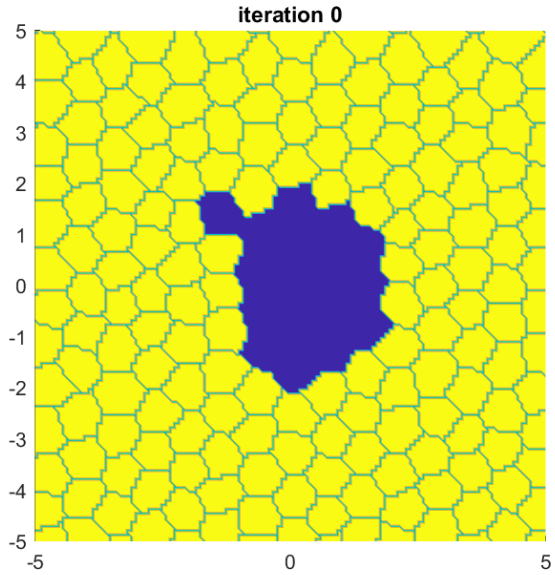
Working hypotheses:

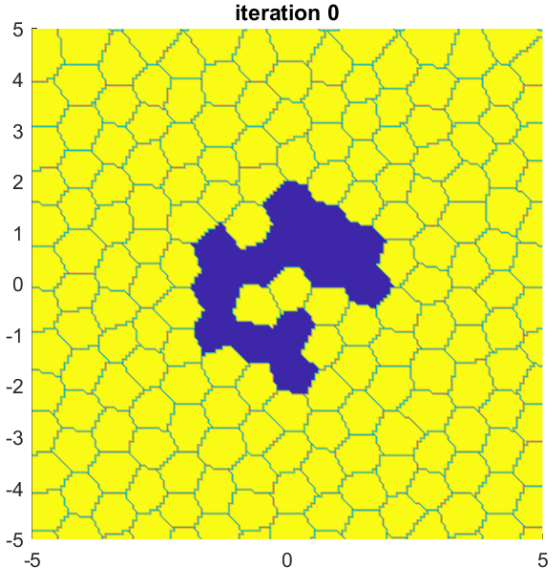
- cells adhere to their neighbours and have a preferred size,
- RPE is subject to a resulting tension;
- larger, senescent cells can't fill gaps effectively, drusen reduces adhesion to the basal membrane.

Partial results: ongoing refinement with adherence, size, tension...

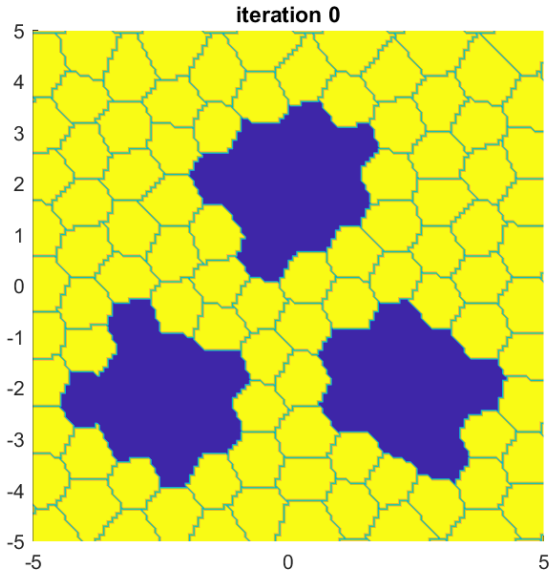
Preliminary simulations I

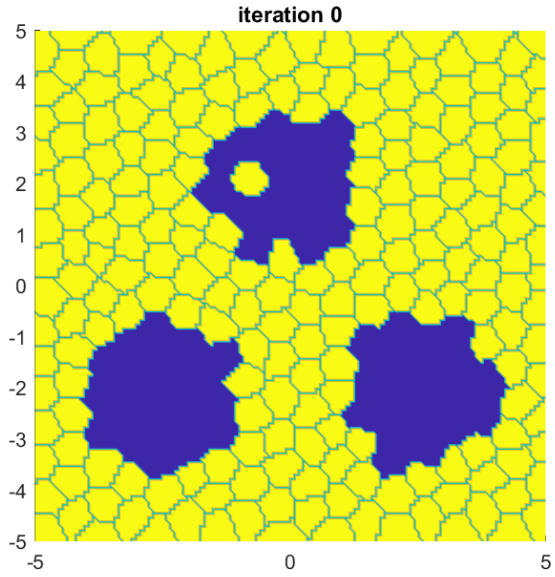


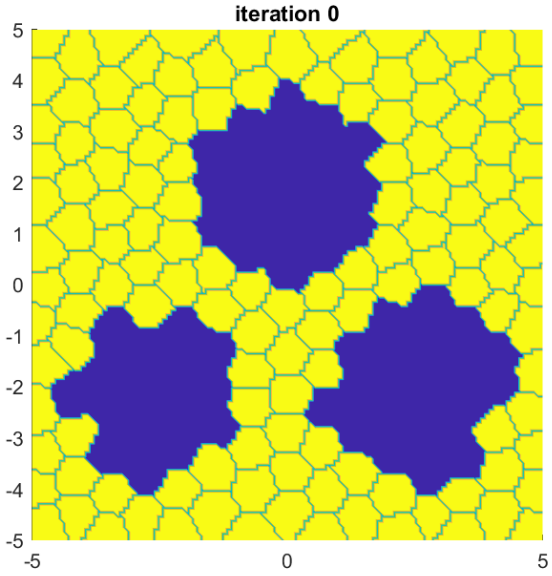




Preliminary simulations II







Thank you for your attention!