Hydrodynamic models of tissue growth and skin cancer

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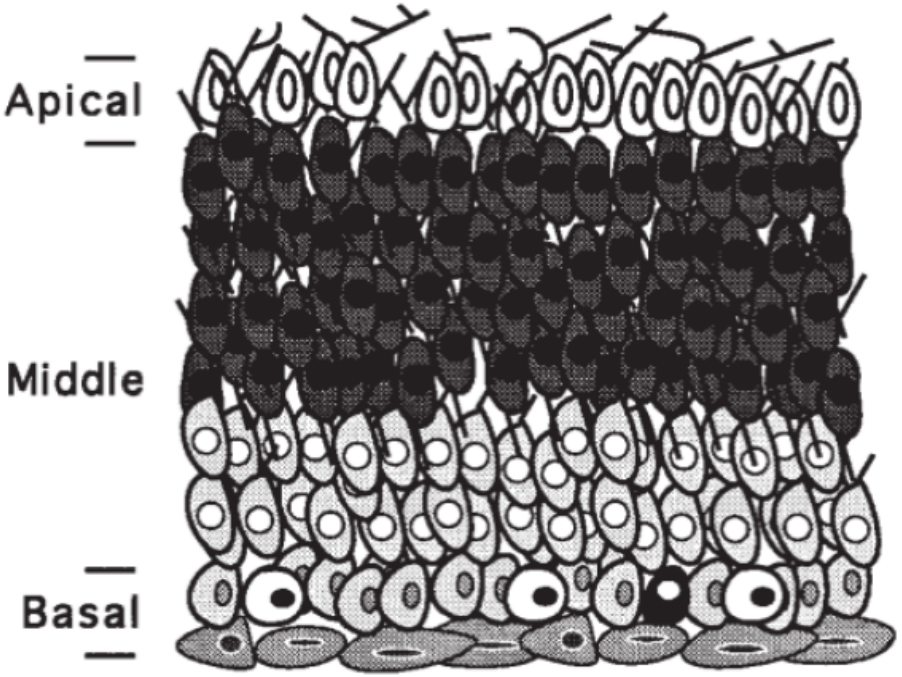
Stratified epithelium

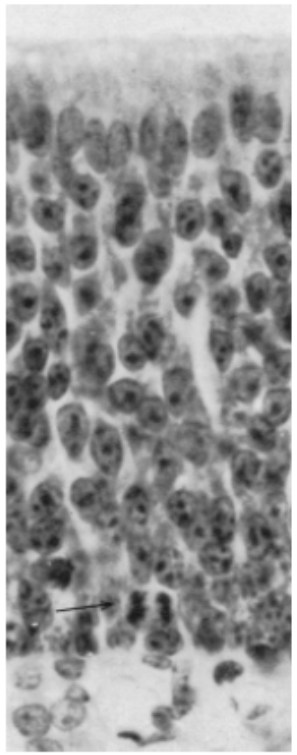
Olfactory epithelium (OE)



A. L. Calof, et alJ. Neurobiol., 36(2):190, 1998

The anatomy of OE of a 56 days-old mouse

cell "flow"



I. H. Smart. J. Anat., 109:243, 1971

Questions

1. Homeostasis state: dynamic, cell proliferation balanced by cell apoptosis.

2. General theory of homeostasis state stem cell distribution and velocity field? (WT Yeh and HYC, New J Phys, 3. 20, 053051 (2018))

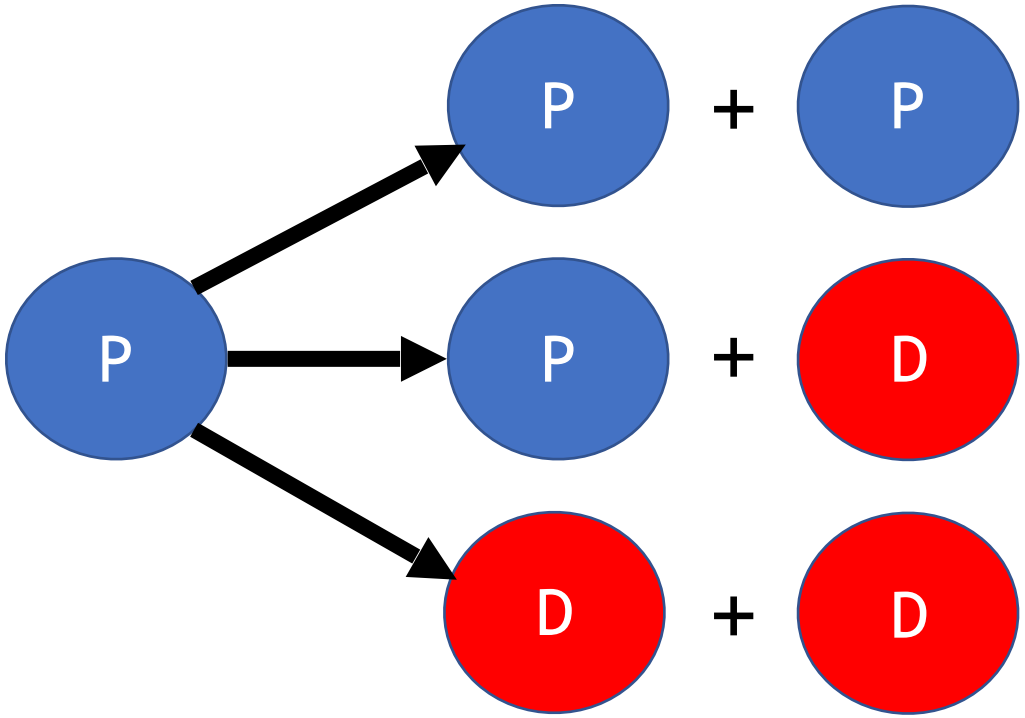
3. Tissue dynamics close to homeostasis state? Is homeostasis state stable? (YT Yeh and HYC, Phys. Rev. E, 93, 052421 (2016))

4. Far from homeostasis state (growth, wound healing, tumor, etc)?

(T Hoshino, MW Liu, KA Wu, H.Y Chen, T Tsuruyama and S Komura, PRE, 99, 032416 (2019)).

2 models for the simplest cell lineage

Stochastic differentiation



r_p: rate of cell proliferation

r_D: rate of cell apoptosis

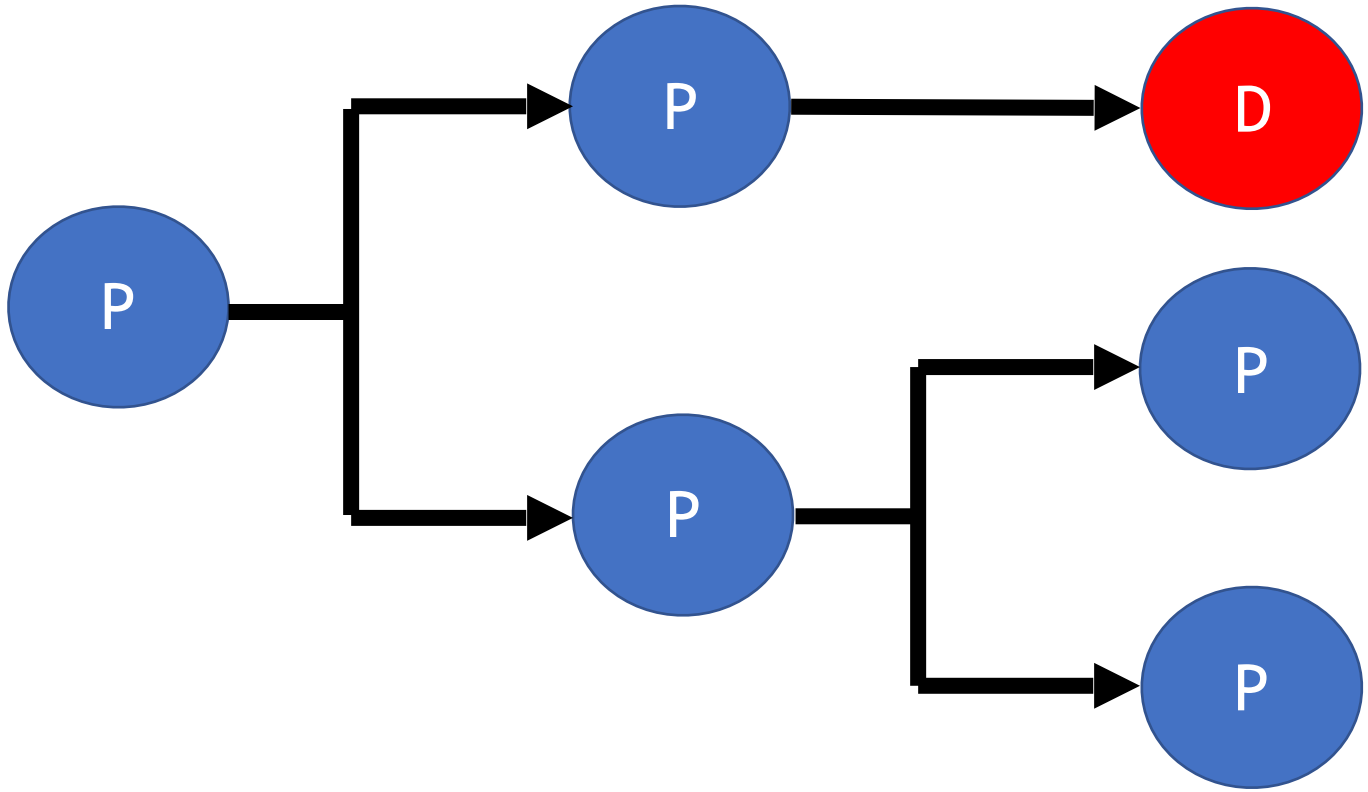
P_s: prob(a given daughter cell is proliferative)

v: velocity field in the tissue

$$\partial_t \rho_P + \partial_l(\rho_P v_l) = r_P(2P_S - 1)\rho_P$$
$$\partial_t \rho_D + \partial_l(\rho_D v_l) = 2r_P(1 - P_S)\rho_P - r_D\rho_D$$

Chou, Lo, Gokoffski, Zhang, Wan, Lander, Clof, Nie, 2010, Biophy. J. 99, 3145

Symmetric division



r_p: rate of cell proliferation

r_D: rate of cell apoptosis

r_d: rate of cell differentiation

v: velocity field in the tissue

$$\partial_t \rho_P + \partial_l(\rho_P v_l) = r_P \rho_P - r_d \rho_P$$
$$\partial_t \rho_D + \partial_l(\rho_D v_l) = r_d \rho_P - r_D \rho_D$$

Hannezo, Prost, Joanny, J. R. Soc. Interface, 11, 20130895 (2014)

Mapping from one model to another

Stochastic differentiation

$$\partial_t \rho_P + \partial_l\left(\rho_P v_l\right) = r_P\left(2P_S - 1\right)\rho_P$$
$$\partial_t \rho_D + \partial_l\left(\rho_D v_l\right) = 2r_P\left(1 - P_S\right)\rho_P - r_D\rho_D$$

Symmetric division

$$\partial_t \rho_P + \partial_l\left(\rho_P v_l\right) = r_P\rho_P - r_d\rho_P$$
$$\partial_t \rho_D + \partial_l\left(\rho_D v_l\right) = r_d\rho_P - r_D\rho_D$$

- 3 “parameters” in each model:

$r_P,\ r_D\ (same)$

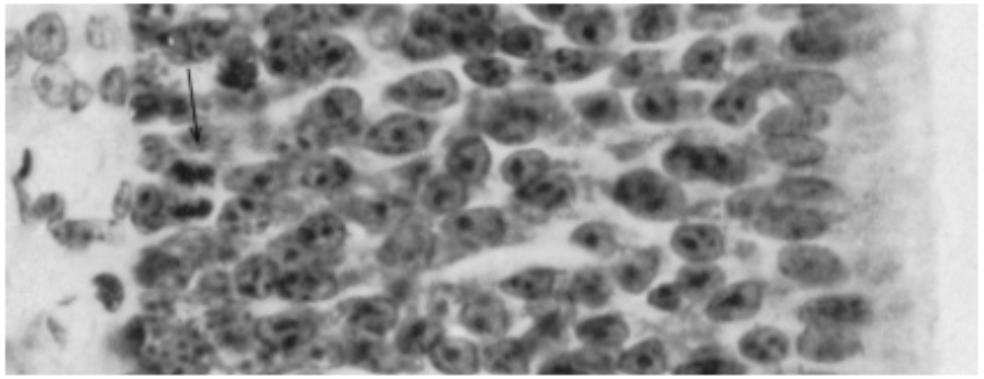
$r_d\ or\ P_S\ (different)$

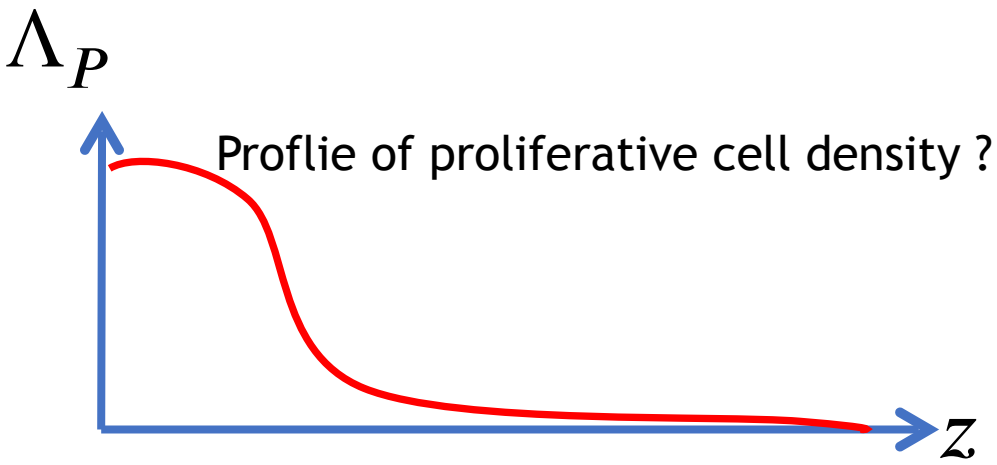
- Mapping: $r_d \leftrightarrow 2r_P\left(1 - P_S\right)$
- Constraint: $P_s \leq 1$
- r_d can take any values

→ stochastic differentiation model only maps to a region of the parameter space of symmetric differentiation model.

Short- and long-range interactions between cells

- Proportion of proliferative cells $\Lambda_P = \dfrac{\rho_P}{\rho_P + \rho_D}$





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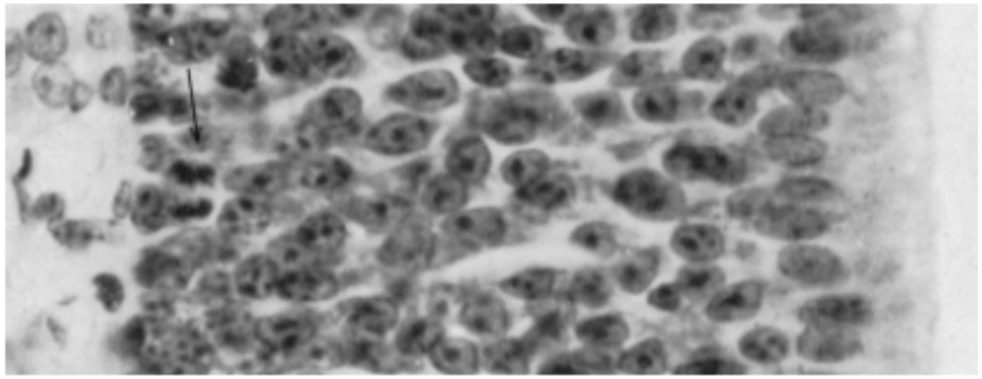
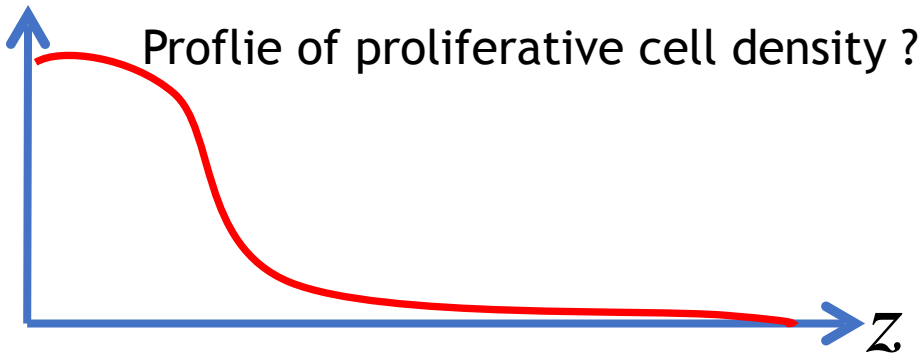


Λ_P



Evolution of proliferative cell density profi (assuming constant total cell density)

$$\partial_t \Lambda_P + v_l \partial_l \Lambda_P = \left[r_P + r_D - r_d - \left(r_P + r_D \right) \Lambda_P \right] \Lambda_P$$

$$\partial_l v_l = \left(r_P + r_D \right) \Lambda_P - r_D$$

- r_P, r_D, and r_d are regulated by neighboring cells (Λ_p) and density of “morphogen” (M)

Homeostasis state (steady state)

Homeostasis state is simpler

- Homeostasis state: time-independent. Λ_P, v_z, M only vary with z, $v_x = v_y = 0$.

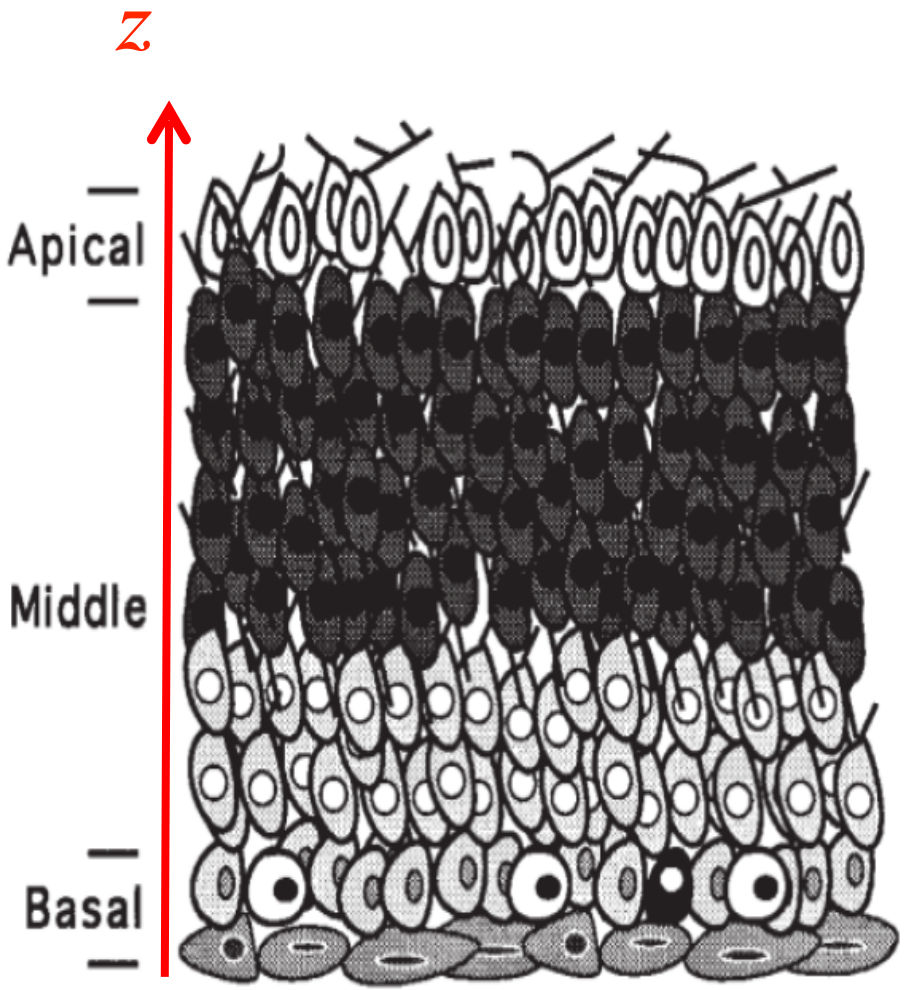
$$v_z \partial_z \Lambda_P = \left[r_P + r_D - r_d - (r_P + r_D)\Lambda_P \right] \Lambda_P$$

$$\partial_z v_z = (r_P + r_D)\Lambda_P - r_D$$

- Homeostasis state: $M = M^*(z) \rightarrow r_i = r_i(M, \Lambda_P^*) \rightarrow r_i(z, \Lambda_P^*)$, $i = d, P, D$.

- We only need to specify the z-dependence of r_i, no need to solve morphogen dynamics.

At basal and apical surfaces



- No flow on either surface:

$$v_z(0) = 0, \quad v_z\left(H^*\right) = 0$$

- Profile of $\Lambda_P(z)$ has to be smooth at $z = 0$, where there no flow, but……

$$\partial_z \Lambda_P = \frac{\left[r_P + r_D - r_d - \left(r_P + r_D\right)\Lambda_P\right]\Lambda_P}{v_z}$$

$\rightarrow \Lambda_P(z = 0) = 0$ (nonsense)

or

$$\Lambda_P(z = 0) = \frac{r_P(0,\Lambda_P(0)) + r_D\,(0,\Lambda_P(0)) - r_d\,(0,\Lambda_P(0))}{r_P\,(0,\Lambda_P(0)) + r_D\,(0,\Lambda_P(0))}$$

.

No long-range interaction → no stratified homeostasis state

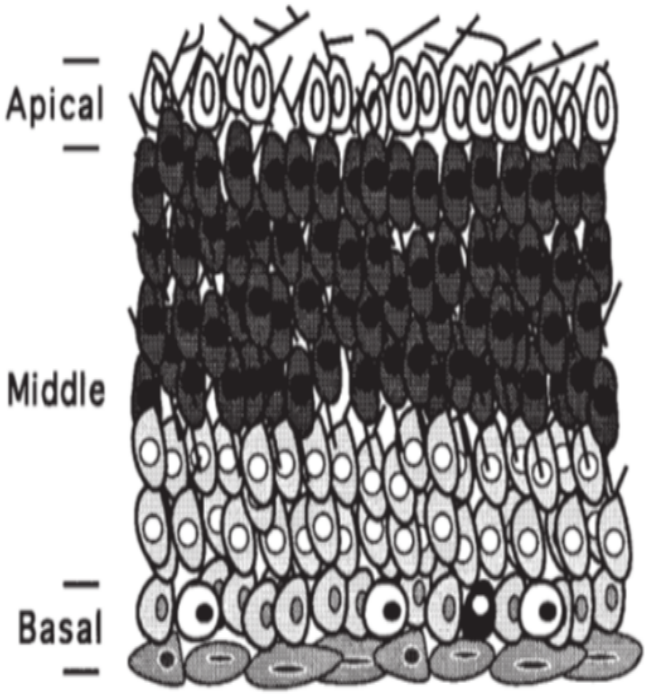
$$\partial_z \Lambda_P = \frac{\left[r_P + r_D - r_d - \left(r_P + r_D\right)\Lambda_P\right]\Lambda_P}{v_z}$$

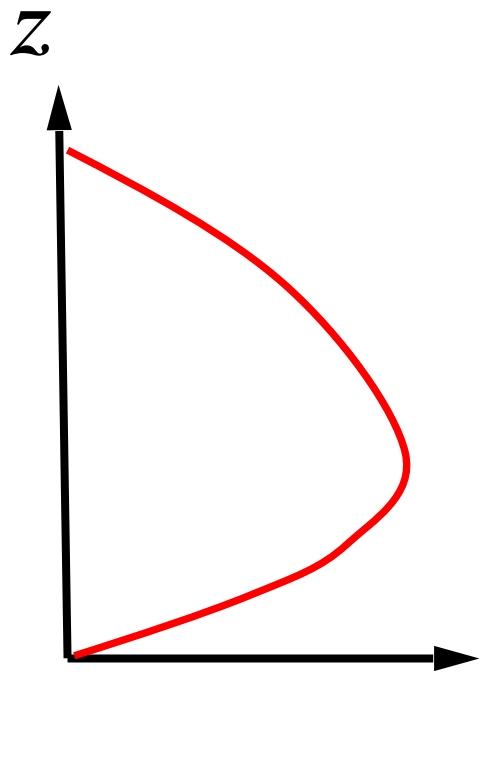
- Suppose there is no information from morphogen, then $r_P,\ r_D,\ r_d$ dep only on $\Lambda_p \rightarrow$ the solution $\Lambda_p(z) = \Lambda_p(0)$ is a fixed point.

- A necessary condition for a tissue to have a stratified homeostasis state is that cell differentiation, apoptosis, and proliferation have to be regulated by some long-range interaction so that the cells "know" its distance to the basal surface!

- This conclusion holds for more complicated models, but may not hold when fluctuations are taken into account.

Homeostasis tissue flow field





Flow field: from mass conservation

Tissue thickness: from boundary condition

$$v_z^* = \int_0^z k_p(z')dz',$$

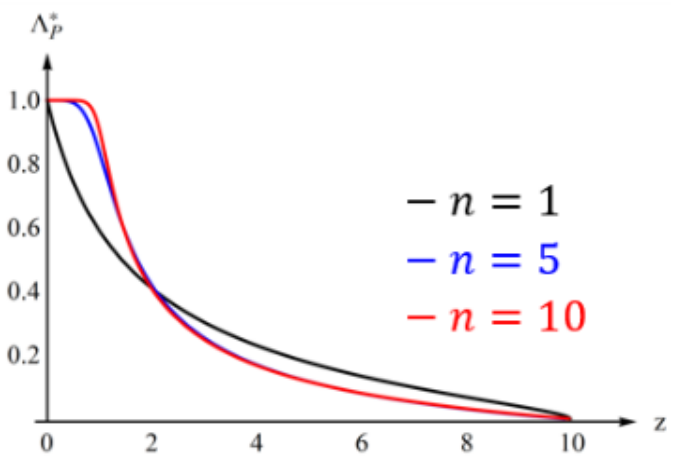
$$0 = \int_0^{H^*} k_p(z)dz$$

- Close to basal surface: cells divide, pushed upward, flow increases with distance from basal surface.
- Close to apical surface: cells die, removing the “upward push” from the lower part, flow decreases as apical surface is approached.

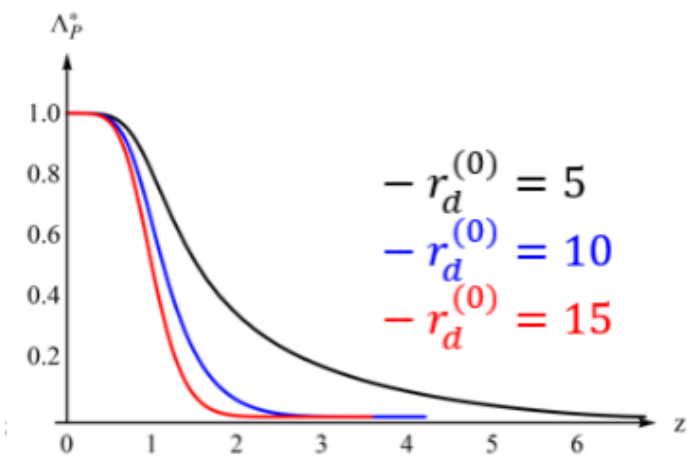
Making the most stratified tissue

The (simplest) model with only long-range interaction

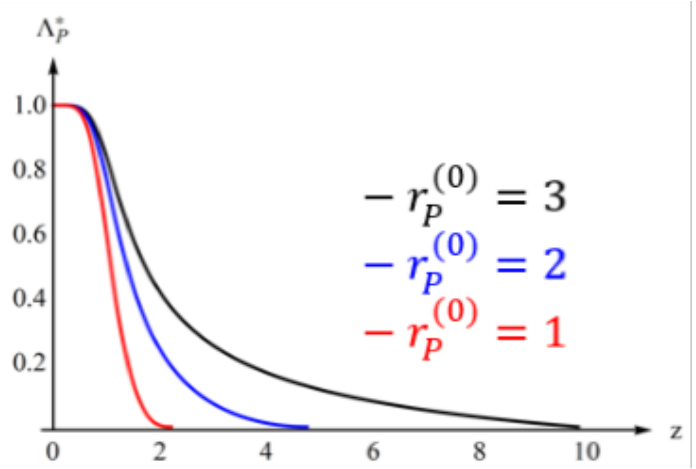
$$r_P = r_P^{(0)} \quad \text{and} \quad r_d = \frac{z^n}{1+z^n} r_d^{(0)}$$



Proportion of proliferative cell is insensitive to n as long as $n \geq 5$



Tissue is more stratified as $r_d^{(0)}$ increases

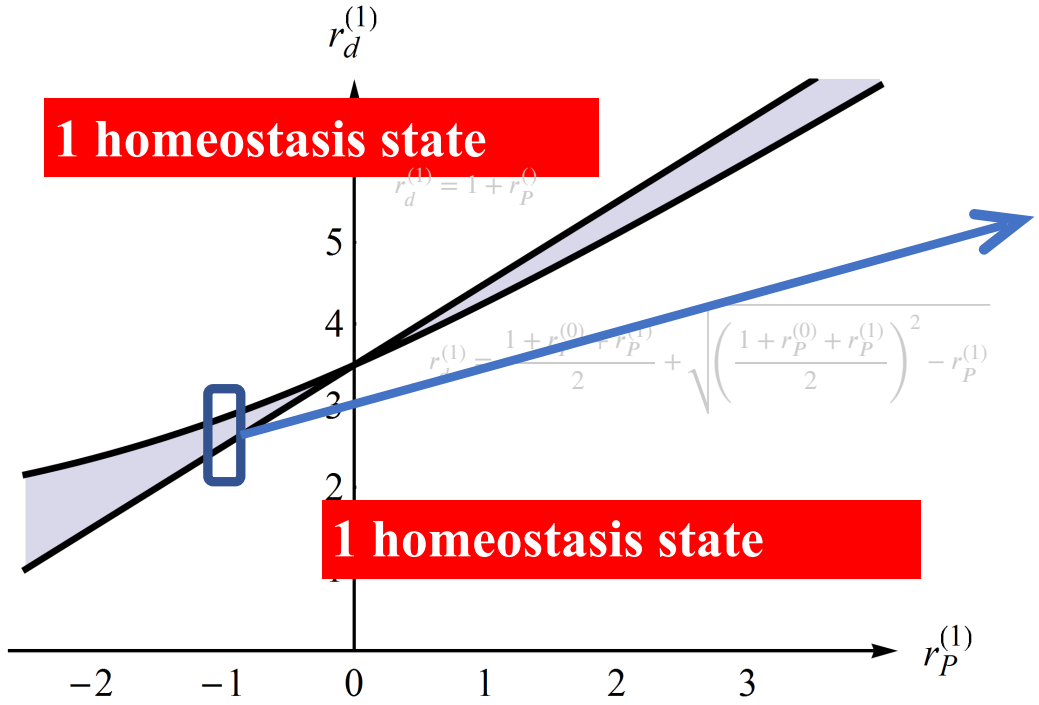


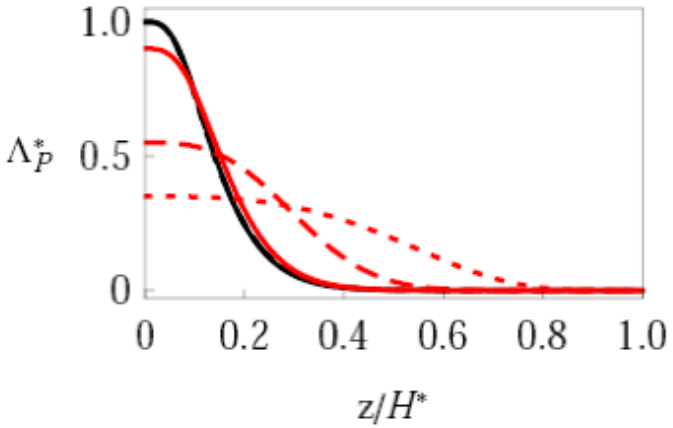
Tissue is more stratified as $r_P^{(0)}$ decreases.

When neighbors affect your decision….

- Including short-range interaction to lowest order

$$r_P = r_P^{(0)} + r_P^{(1)}\left(1 - \Lambda_P^*\right) \quad \text{and} \quad r_d = \frac{z^n}{1+z^n} r_d^{(0)} + r_d^{(1)}\left(1 - \Lambda_P^*\right)$$

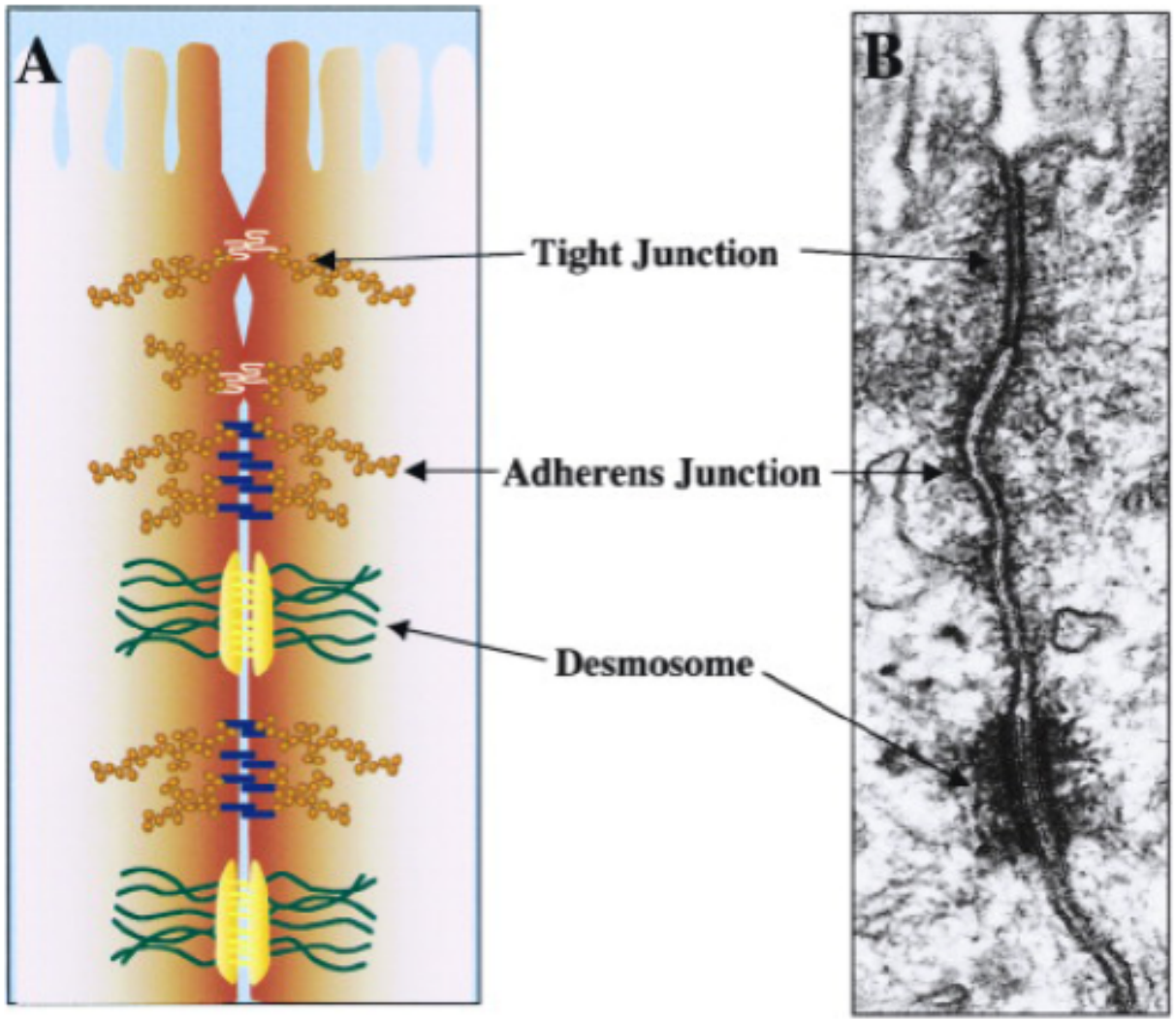




Two homeostasis states:
One is normal, one does not look healthy
Normal: affected by morhphogen,
Nonhealthy: affected by short-range interaction

A stratified epithelium flows

Tight junctions: a stratified epithelium is elastic at short time scale



M. Perez-Moreno, C. Jamora, and E. Fuchs, Cell, 4:535, 2003

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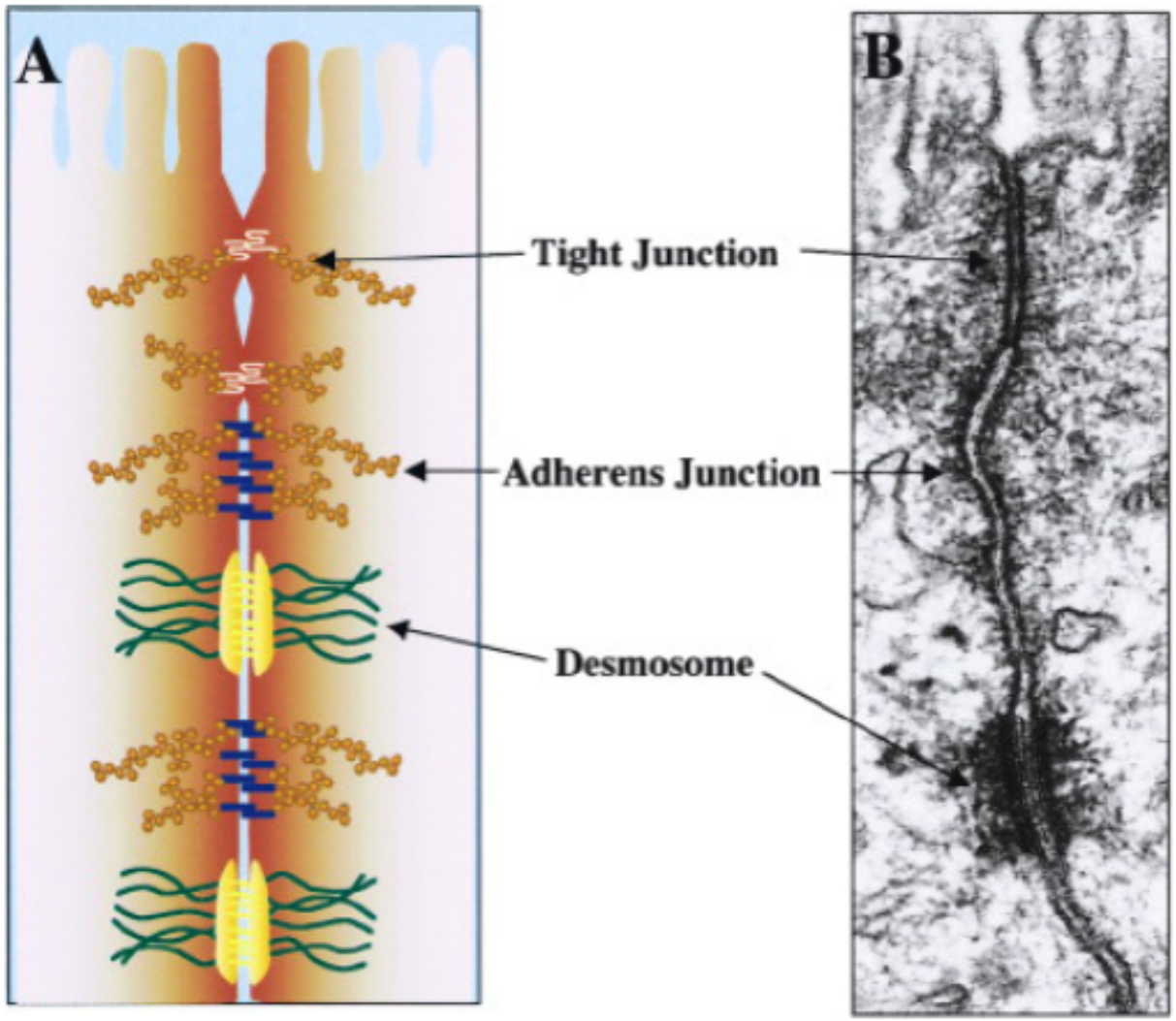


M. Perez-Moreno, C. Jamora, and E. Fuchs, Cell, 4:535, 2003

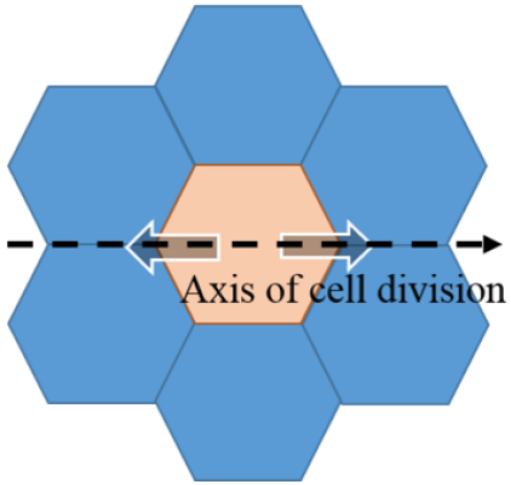
$$\sigma_{ij}^{E} = \left(K - \frac{2\mu}{3} \right) u_{ii}\delta_{ij} + 2\mu u_{ij}$$

Cell division/apoptosis push and pull the tissue from within

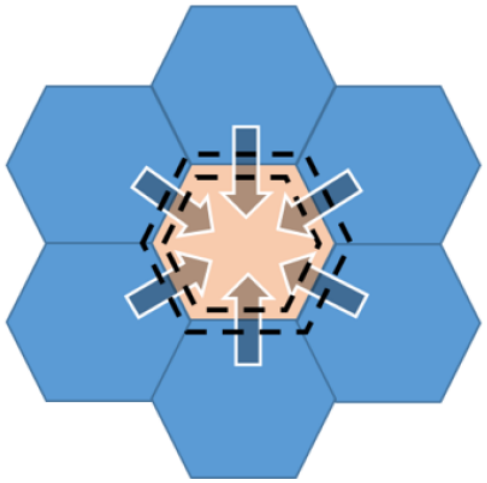
Ranft, Basan, Elgeti, Joanny, Prost, Julicher, 2010, PNAS, 107, 20863

Stress changes in time due to division and apoptosis “forces”

(a)



(b)



$$\left\langle d_{ij}^{div} \right\rangle = d_p(\delta_{ij} + \tilde{q}_{ij}^0 + \frac{\tilde{\sigma}_{ij}}{\sigma_0})$$

$$\left\langle d_{ij}^{apo} \right\rangle = d_D\delta_{ij} + \tilde{d}_D(\tilde{q}_{ij}^0 + \frac{\tilde{\sigma}_{ij}}{\sigma_0})$$

A mature stratified epithelium tissue is viscoelastic

$$D_t\sigma_{ij} = D_t\sigma_{ij}^{E} + D_t\sigma_{ij}^{A},$$

$$\Longrightarrow \left(1+\tau D_t\right)\tilde{\sigma}_{ij} = 2\eta\tilde{v}_{ij} + \tilde{\sigma}_{ij}^{I}$$

$$\sigma_{ik} = -p\delta_{ik} + 2\eta\tilde{v}_{ik} + \tilde{\sigma}_{ik}^{I}.$$

Due to elastic response and forces from cell division/apoptosis, tissue behaves as a gel.

A mature stratified epithelium tissue is viscoelastic

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Long time behavior: viscous

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$$\tau = \frac{\sigma_0}{\left(r_p d_p - r_D\tilde{d}_D\right)\rho_p + r_D\tilde{d}_D\rho},$$

$$\eta = \frac{\sigma_0\mu}{\left(r_p d_p - r_D\tilde{d}_D\right)\rho_p + r_D\tilde{d}_D\rho},$$

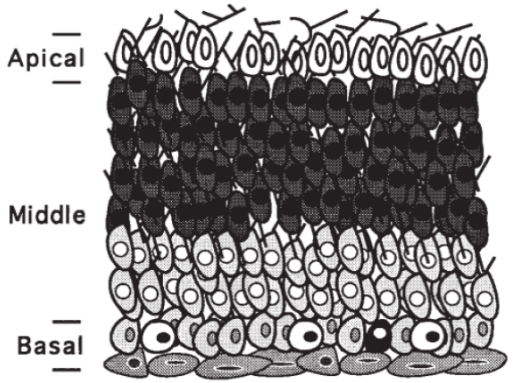
$\tilde{\sigma}_{ij}^{I} = \sigma_0 q_{ij}^{0}$

Due to elastic response and forces from cell division/apoptosis, tissue behaves as a gel. Long time behavior: viscous

The "viscosity" of a tissue depends on cell division/apoptosis, tissue anisotropy, local tissue composition.

Stratified epithelium → "stratified" viscosity

$$\partial_i \sigma_{ik} = 0,$$
$$\sigma_{ik} = -p\delta_{ik} + 2\eta v_{ik},$$
$$\eta = \frac{\sigma_0 \mu/\rho}{\left(r_p d_p - r_D \tilde{d}_D\right)\Lambda_P + r_D \tilde{d}_D}$$
$$\partial_t H = v_z(z = H)$$



- Force balance in a tissue determines flow field.
- Viscus stress is related to viscosity that depending on proportion of proliferative cells.

Stratified epithelium → "stratified" viscosity

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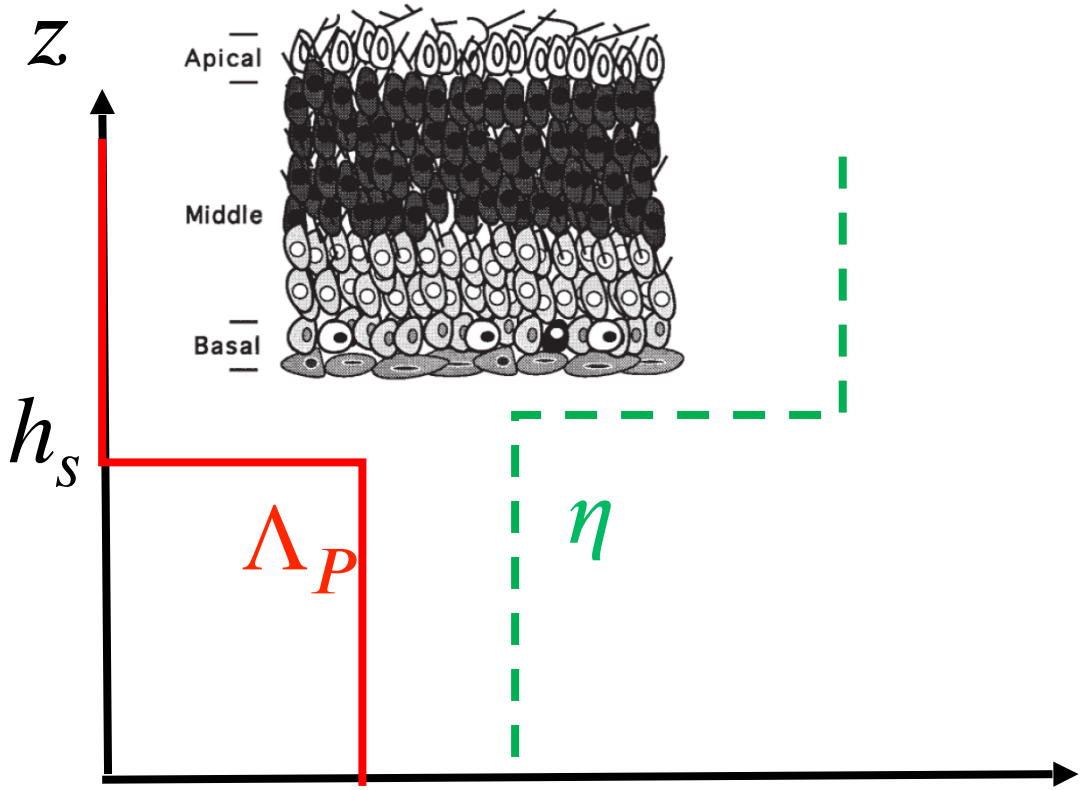


- Force balance in a tissue determines flow field.
- Viscus stress is related to viscosity that depending on proportion of proliferative cells.

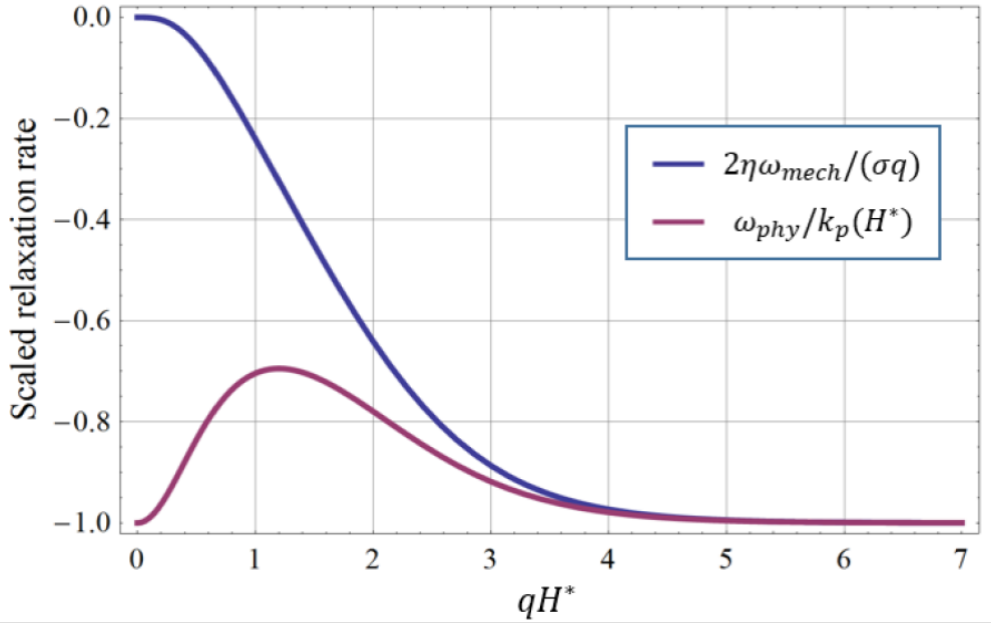
Flow close to homeostasis state affects tissue dynamics

Perturbing a tissue around its homeostasis state

$$\delta H \sim \delta H_0 \cos qx \; e^{\omega t},$$

$$\omega = \omega_{mech} + \omega_{phy},$$

A fixed-wavelength perturbation decays exponentially in time.

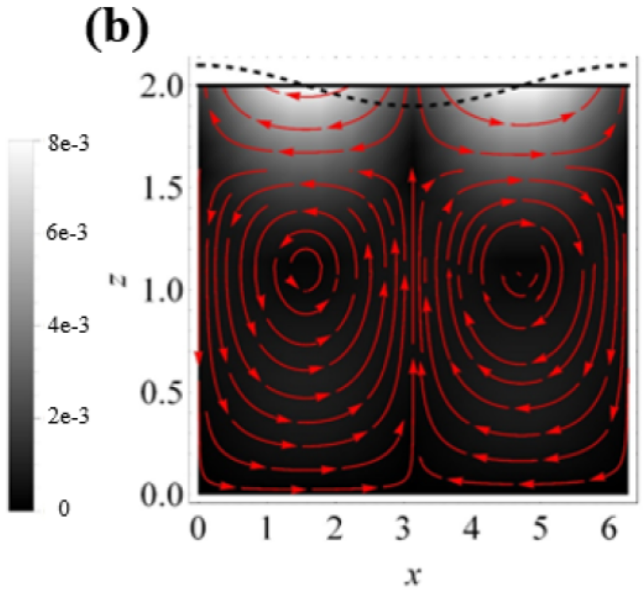


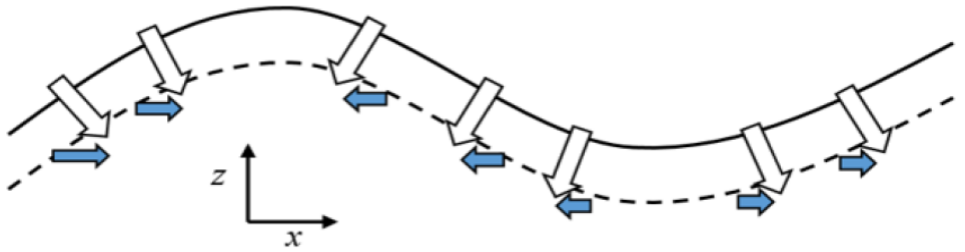
- Tissue flows, but it is not a “physical viscous fluid”.
- The “relaxation rate” of a tissue combines “flow effect” and “pure cell division/apoptosis”.
- Flow does not help relaxation that much when perturbation wavelength is comparable to tissue thickness.

Flow affects tissue evolution

Steady state flow does help the tissue to evolve toward homeostasis state.

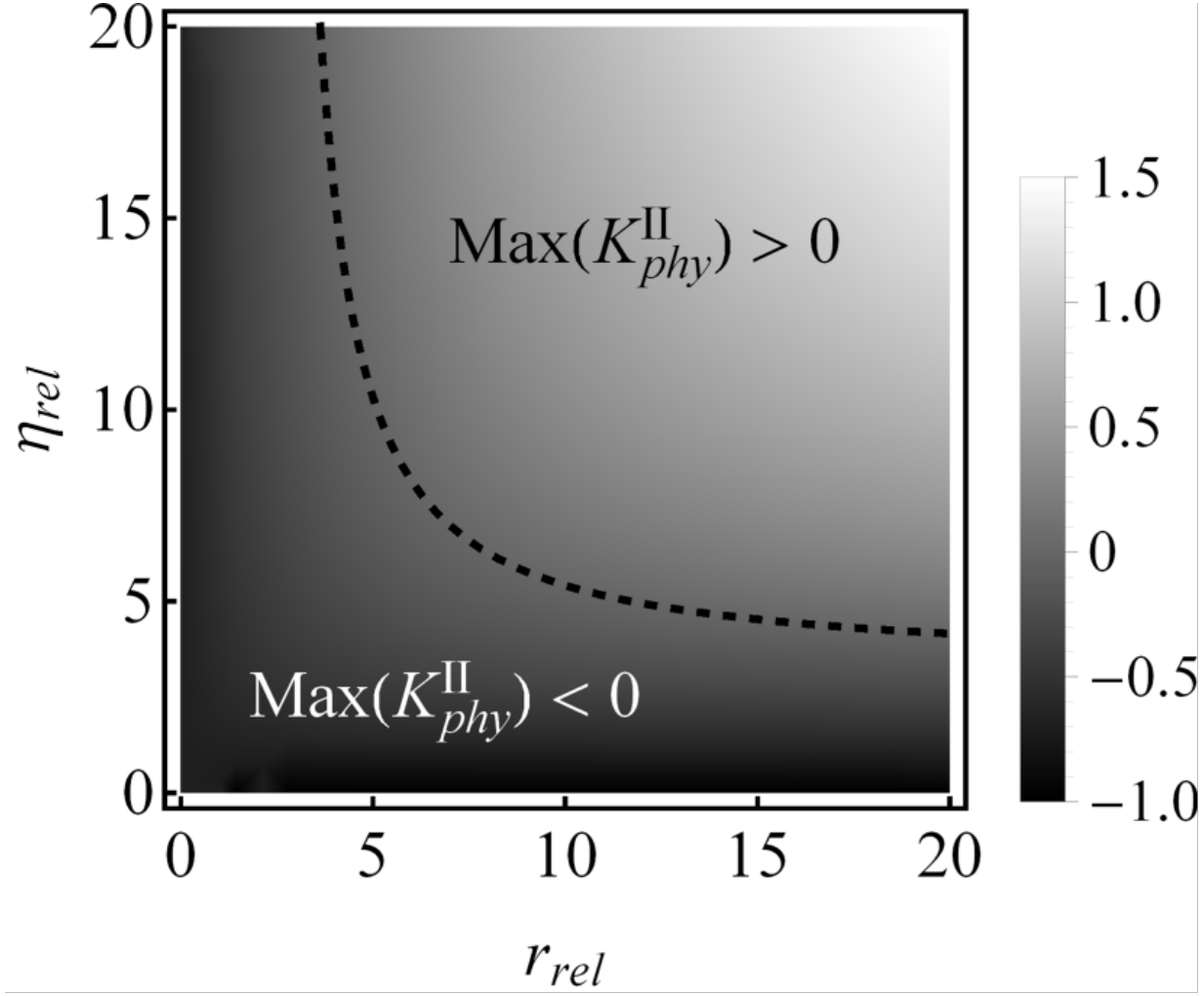
However, deviation of flow field from steady state profile actually brings cells from “thin regions” to “thick regions”.





This effect is most significant when perturbation wavelength is comparable to tissue thickness.

Tissue with thick proliferative layer can behave "surprisingly"

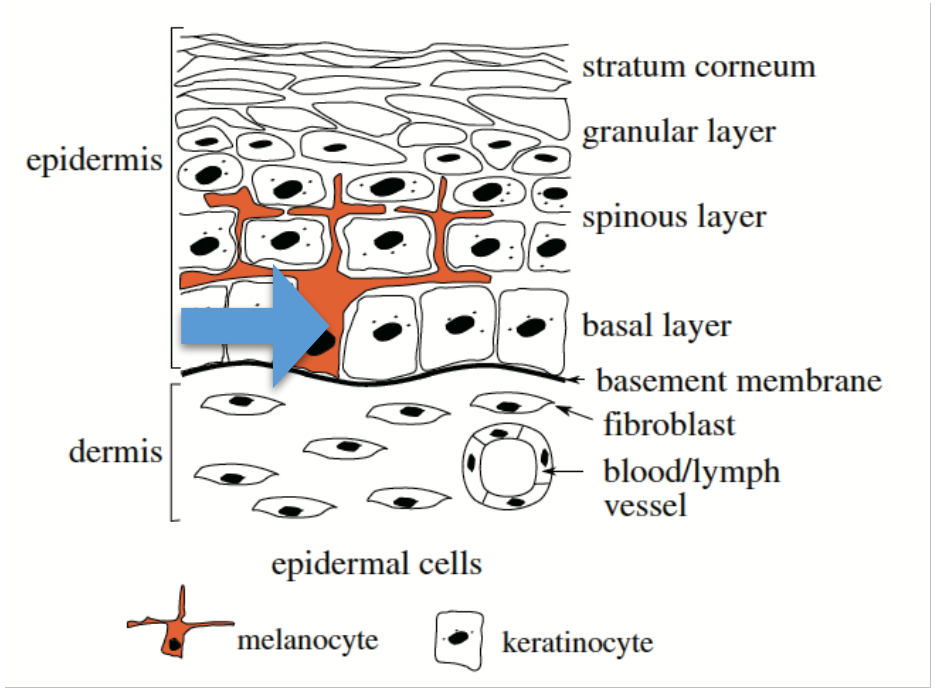


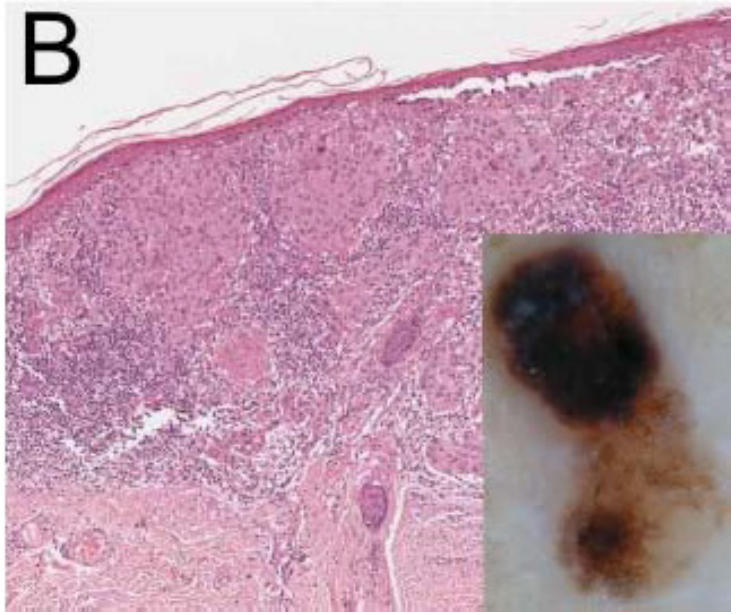
- Thick proliferative layer, strong viscosity difference between lower and upper part of the tissue. → Flow slows down tissue evolution toward homeostasis state.
- Depending on the physical properties of the apical surface, this effect can destabilize homeostasis state!

Skin cancer pattern formation

Melanoma

- Less than 5% of skin cancers but more than 75% of skin cancer-related deaths
- A phase of horizontal growth: invasion of the epidermis (early stage of a melanoma)
- A phase of vertical growth: invasion of the dermis



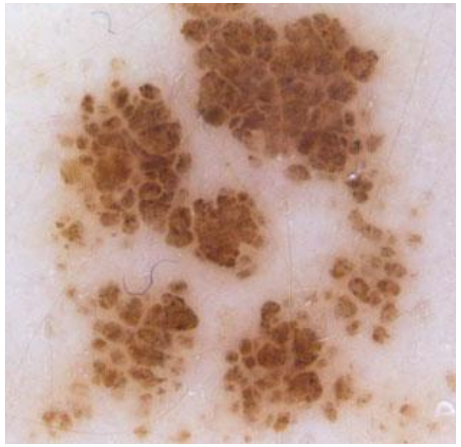


Patterns seen in melanoma

Stripe

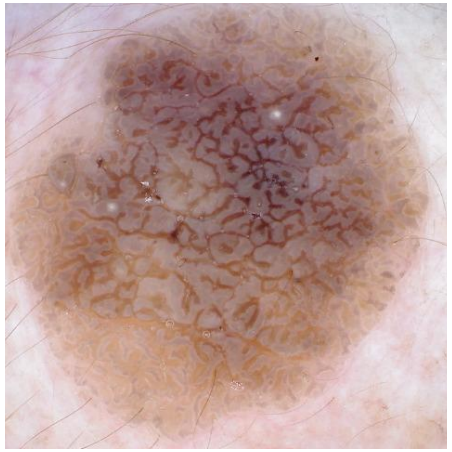
DermNetNZ.org

Globules



DermNetNZ.org

Thick curved lines



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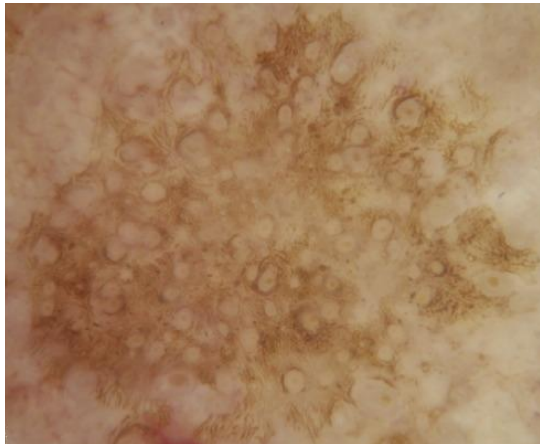
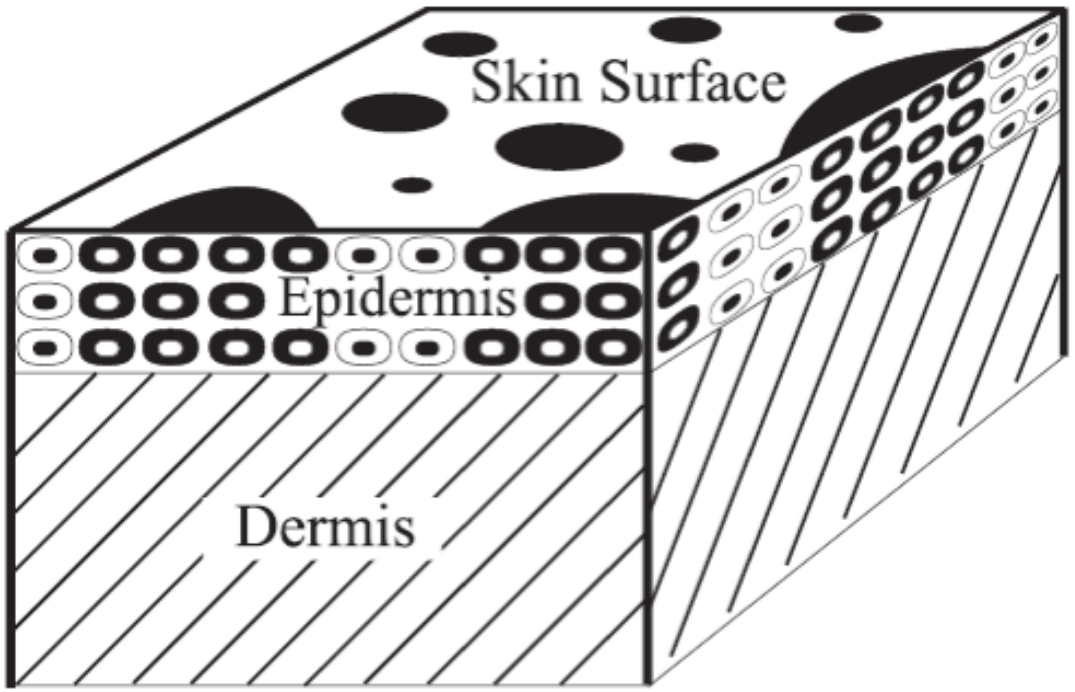
Globules



DermNetNZ.org

Mechanism of patterns: useful diagnosis tools

Skin cancer pattern formation



2d model

$$\frac{\partial \phi}{\partial t} = -\nabla \cdot (\phi \mathbf{v}) + L\nabla^2 \mu + \Gamma(\phi),$$

$$\rho \frac{\partial \mathbf{v}}{\partial t} = \eta \nabla^2 \mathbf{v} - \nabla p + \nabla \cdot \boldsymbol{\Sigma} - \zeta \mathbf{v},$$

$$\Gamma(\phi) = \gamma \phi \left(1 - \frac{\phi}{\phi_\infty}\right) \qquad \phi_\infty \approx 0.6\text{-}0.8$$

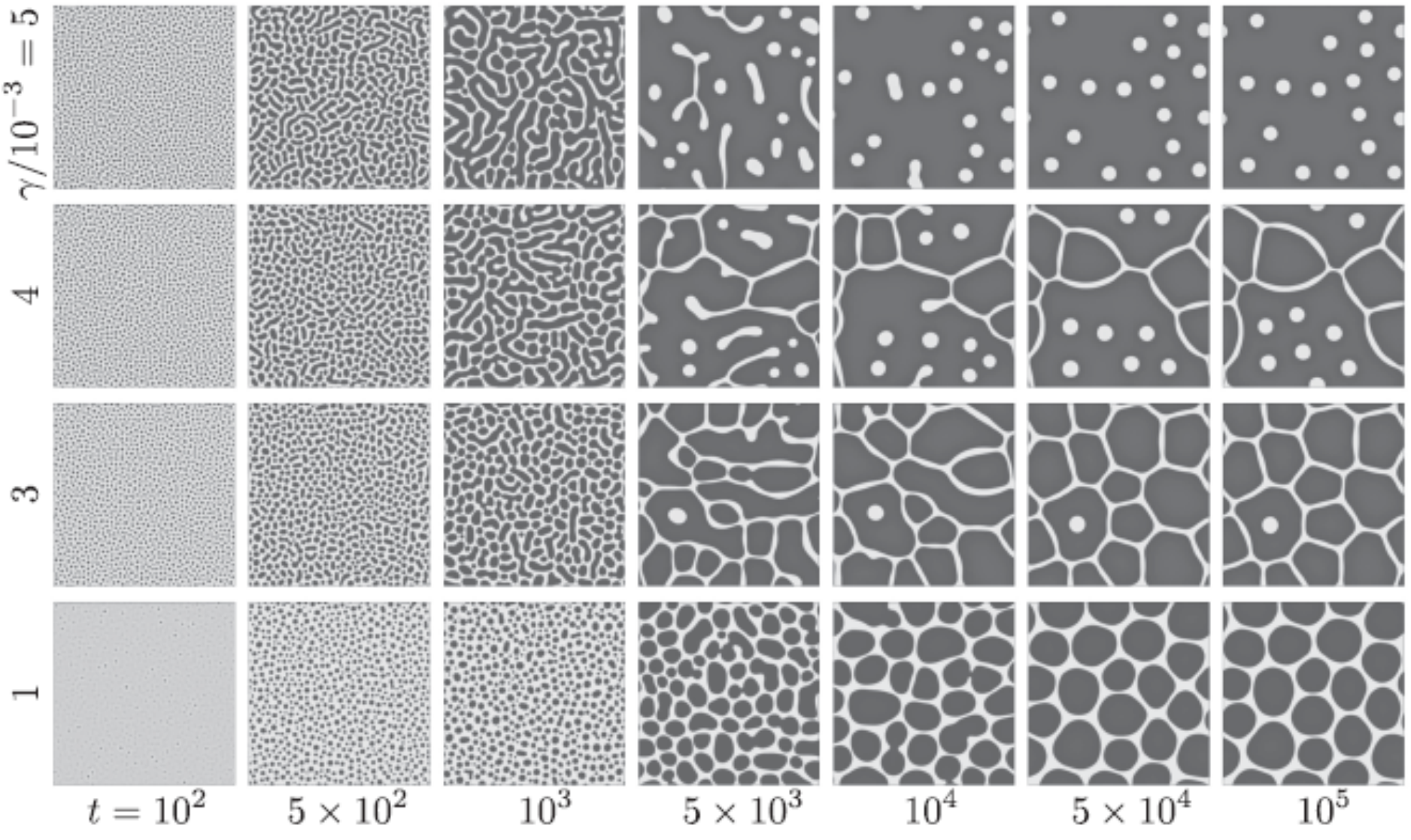
$$\mu = \frac{\delta F}{\delta \phi} = \frac{1}{a^2 \beta}\left[\ln \frac{\phi}{1-\phi} + \chi(1-2\phi)\right] - \kappa \nabla^2 \phi$$

$$\Sigma_{ij} = -\kappa \frac{\partial \phi}{\partial r_i} \frac{\partial \phi}{\partial r_j}$$

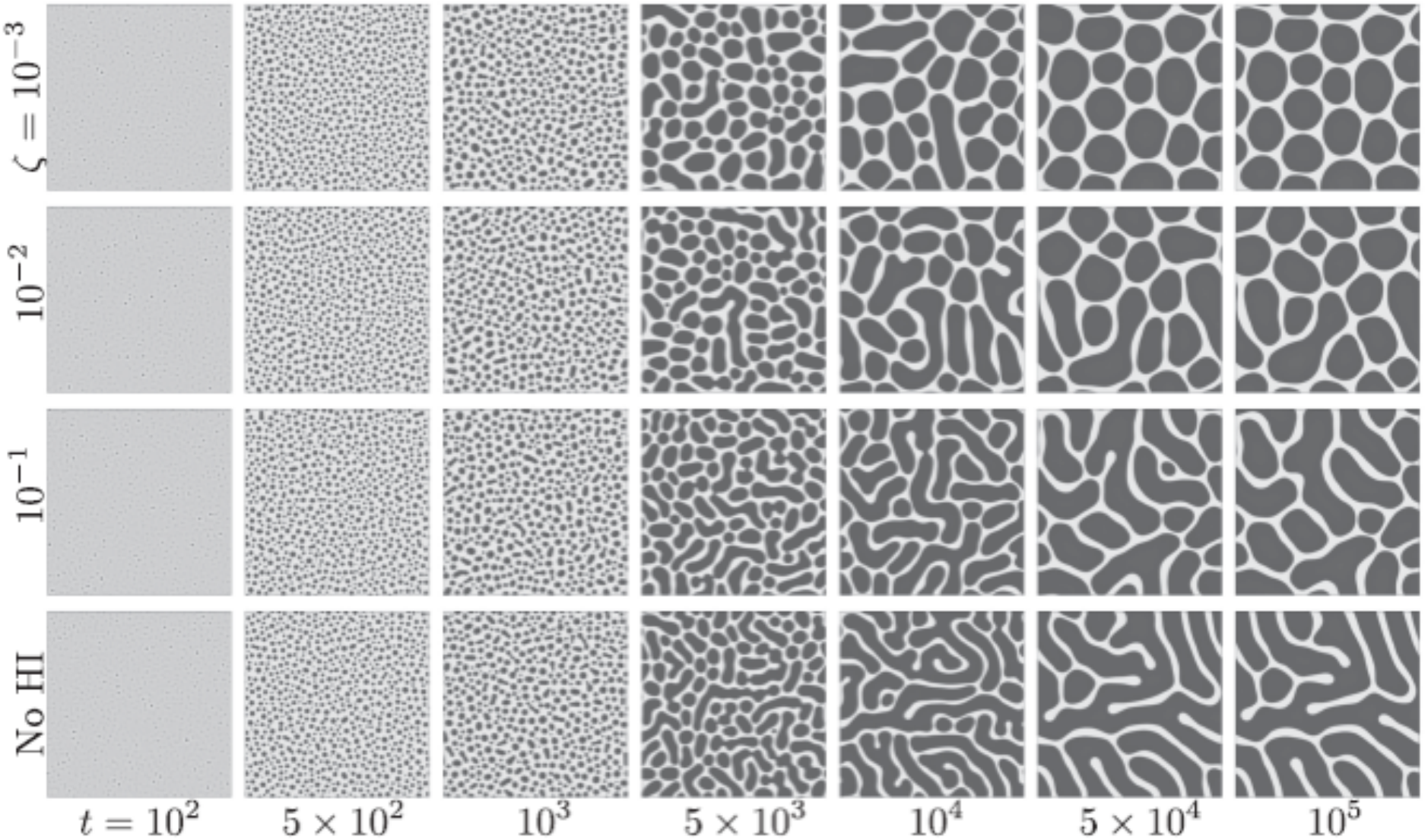
$\gamma = 0, \zeta \to 0$: model H

$\gamma = 0, \zeta \to \infty$: model B

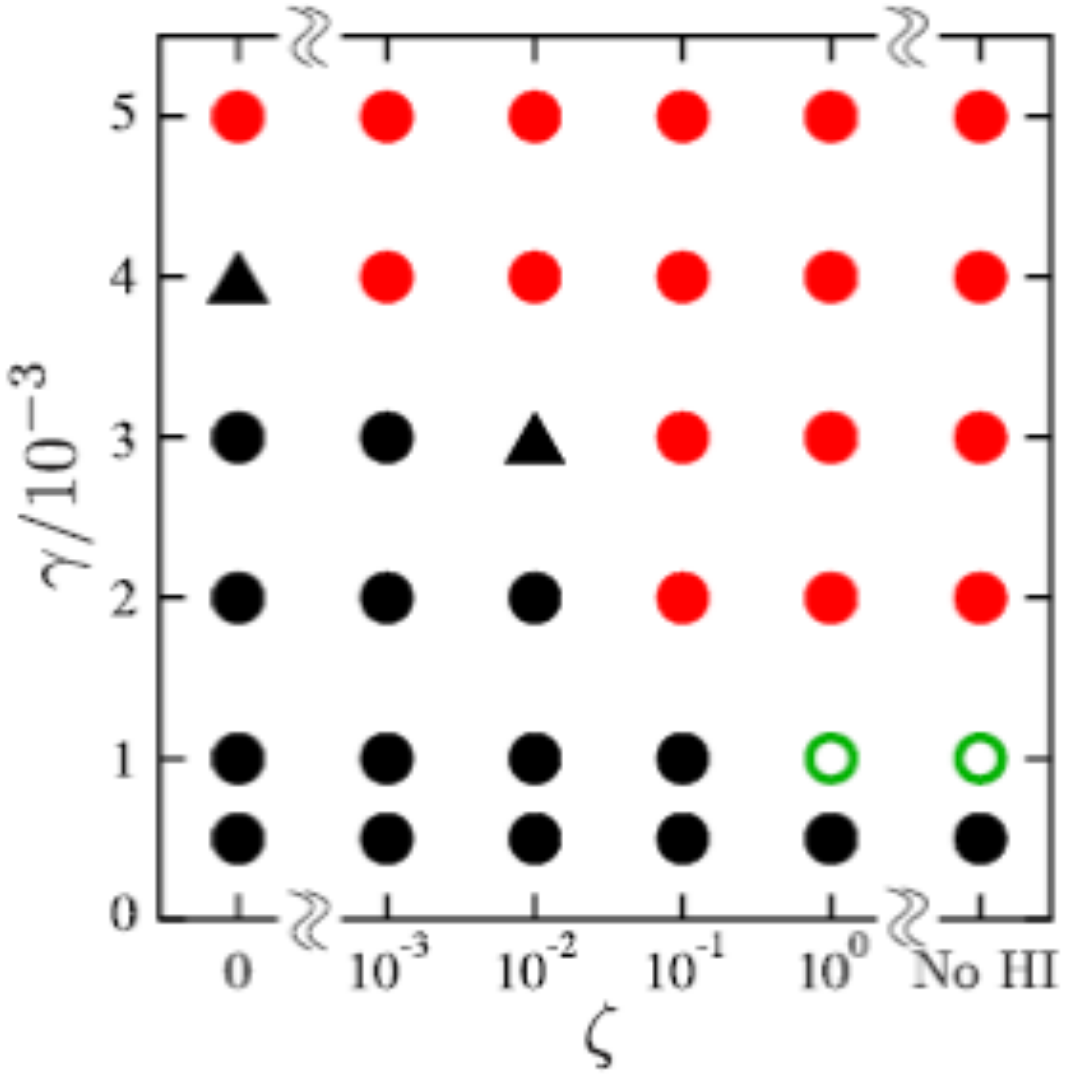
Cancer cell proliferation rate affects skin cancer patterns (no epidermis-dermis sliding drag)



Strength of hydrodynamic interaction affects cancer cell patterns



Phase diagram for cancer cell patterns



Black: Cancer-in-healthy patterns

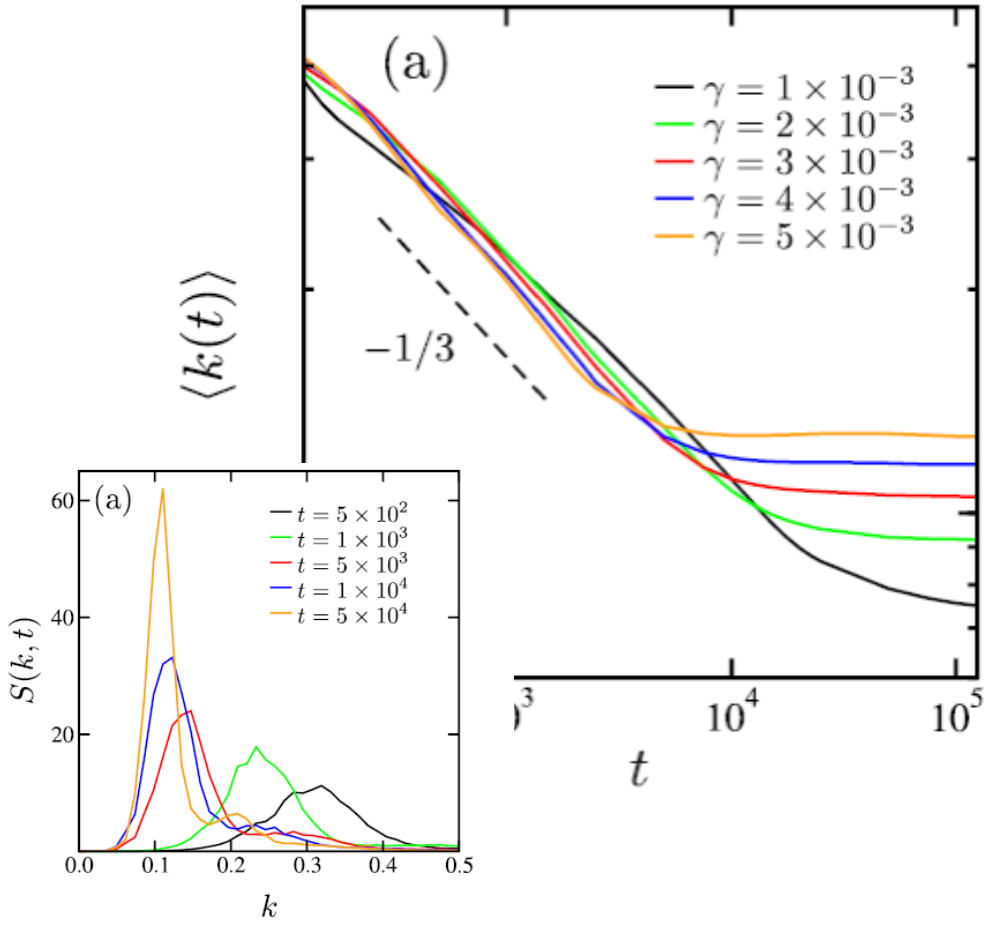
Red: Healthy-in-cancer patterns

Green: asymmetric-bicontinuous patterns

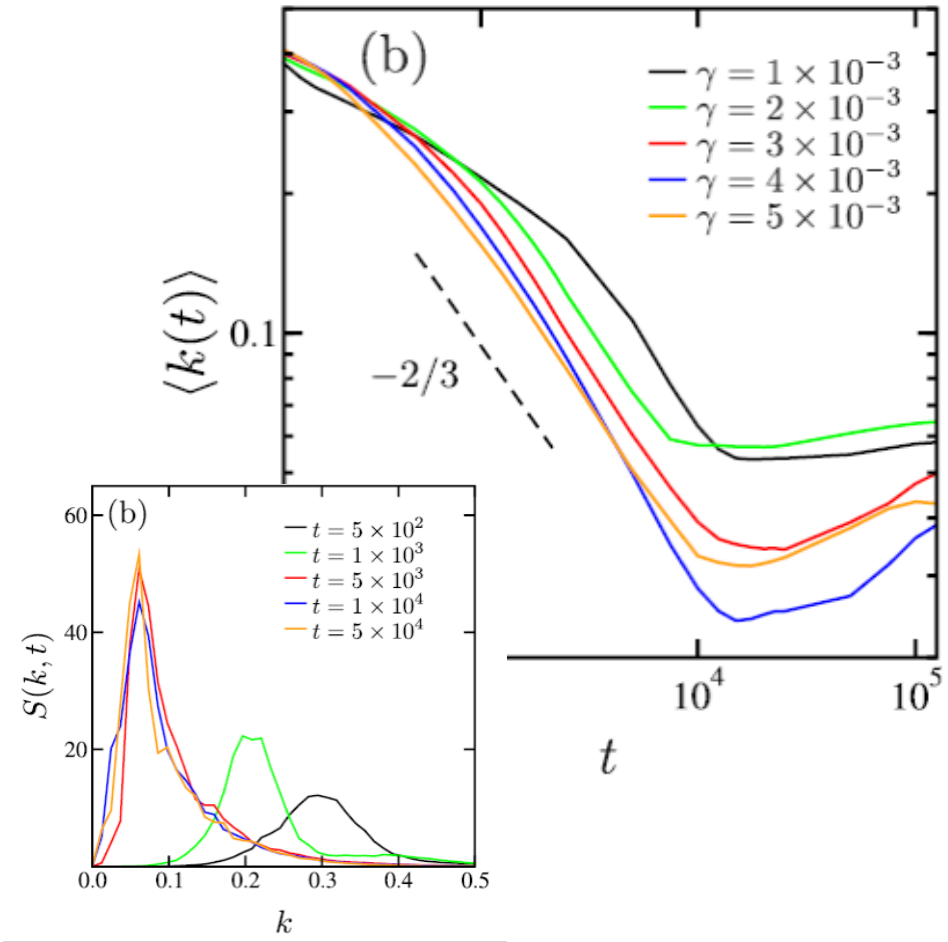
Black triangles: cancer-in-healthy and healthy-in-cancer coexistence.

Growth rates of percentage of cancer cells

No HI



No drag



Conclusion

- General hydrodynamic models of tissue homeostasis, linearized dynamics, and cancer pattern formation are developed.
- Analysis: purely mathematical and physical, general.
- Biological details: lumped in the phenomenological coefficients.
- Future works: growth dynamics of tissues, active traction and motility of cells, ……