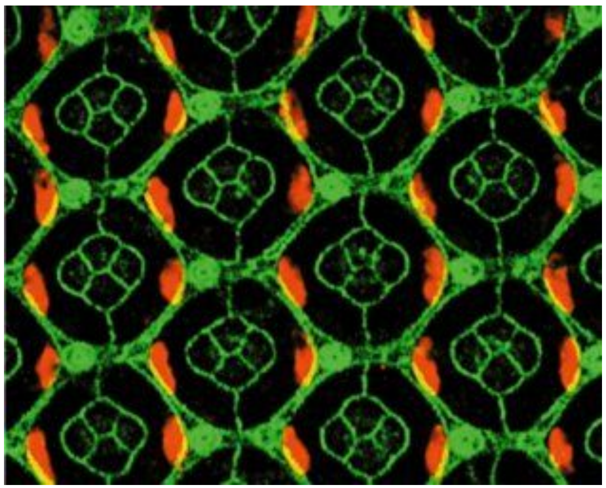
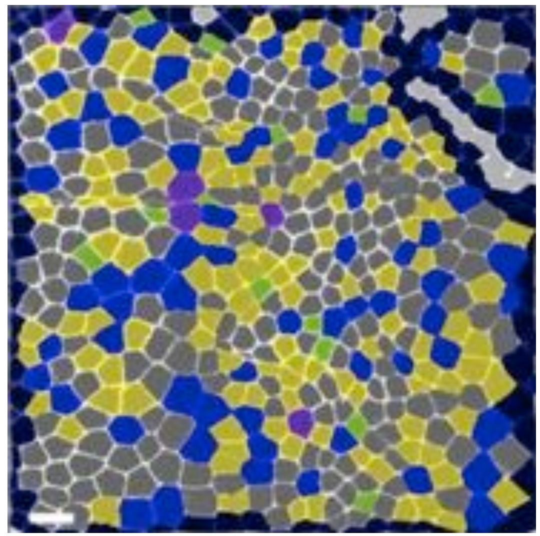
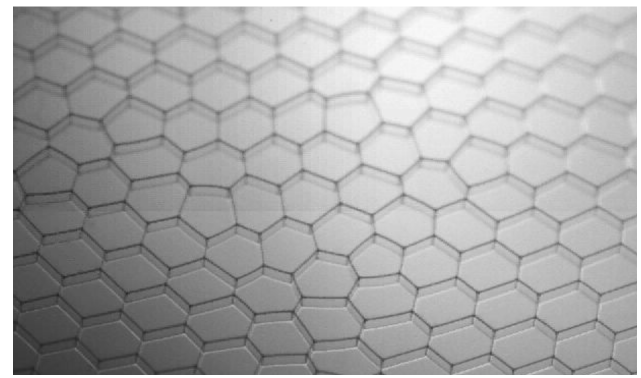
Recent advances in the understanding of biological tissues: what lessons for foam modelling?







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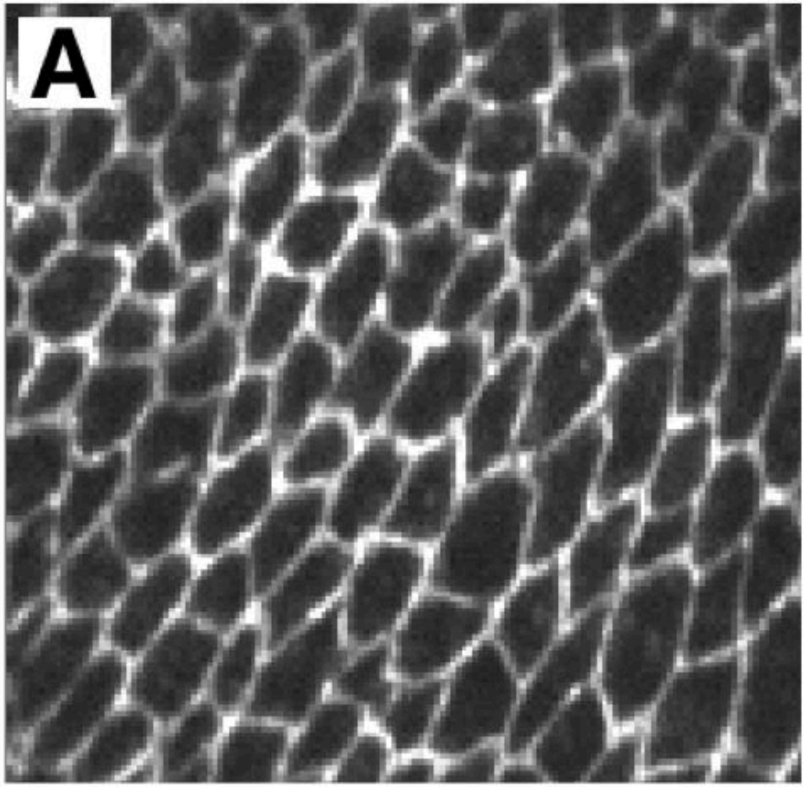
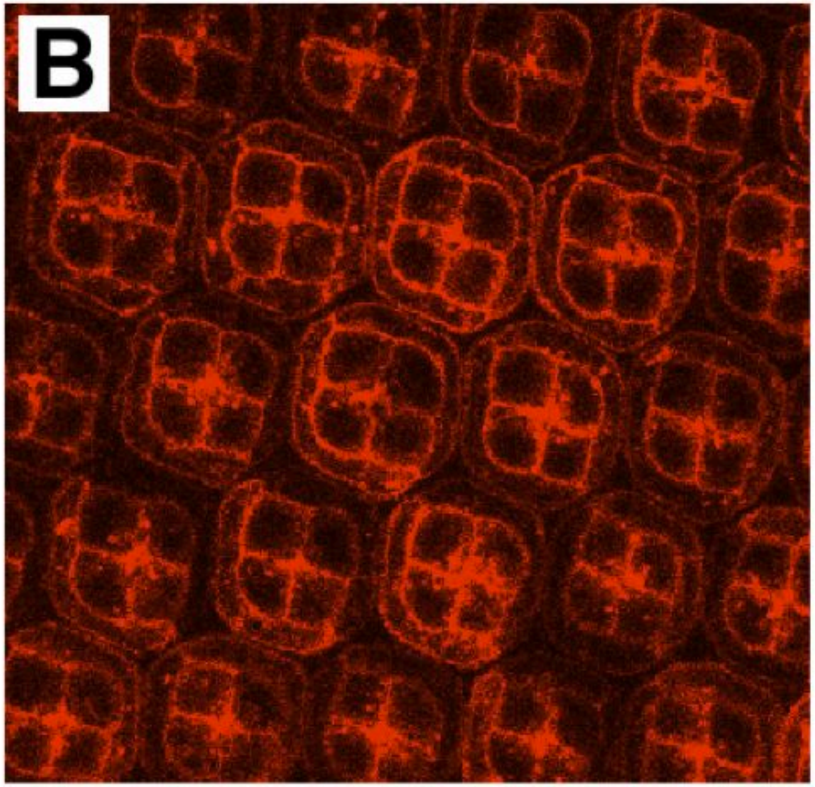
Outline – Describing and Understanding Tissue Structures

I. Disordered vs. Ordered Tissues
II. Role of Mathematics / statistics
III. Role of Physics / interactions /energy

Ordered vs. Disordered Tissues



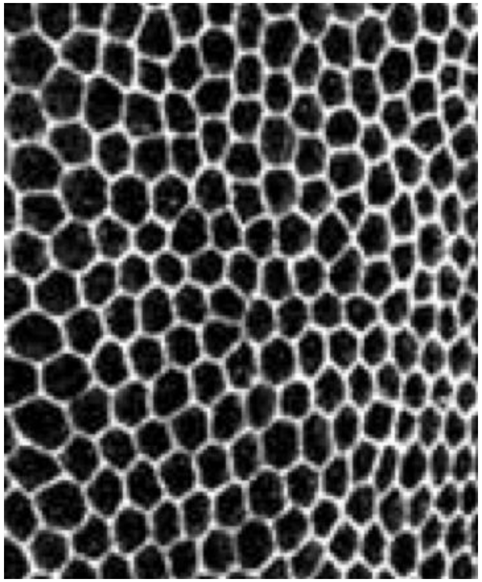
Drosophila wing



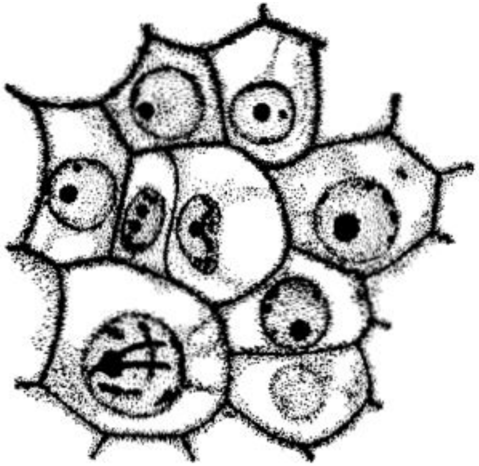
Drosophila eye

- Statistical vs. Deterministic model?
- Role of dynamics? Morphogenesis, growth, development, wound healing,…

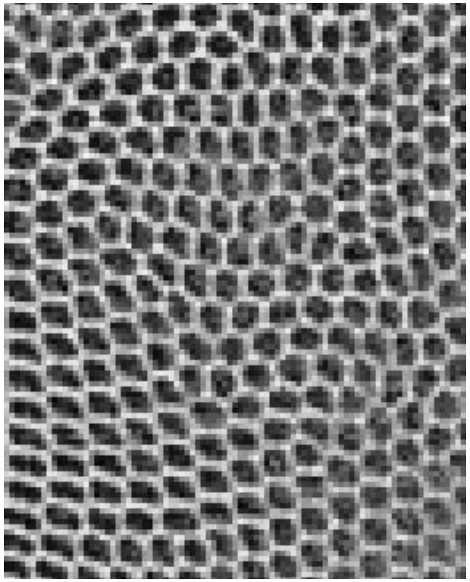
If it looks like a foam…



[Classen et al. 2005]



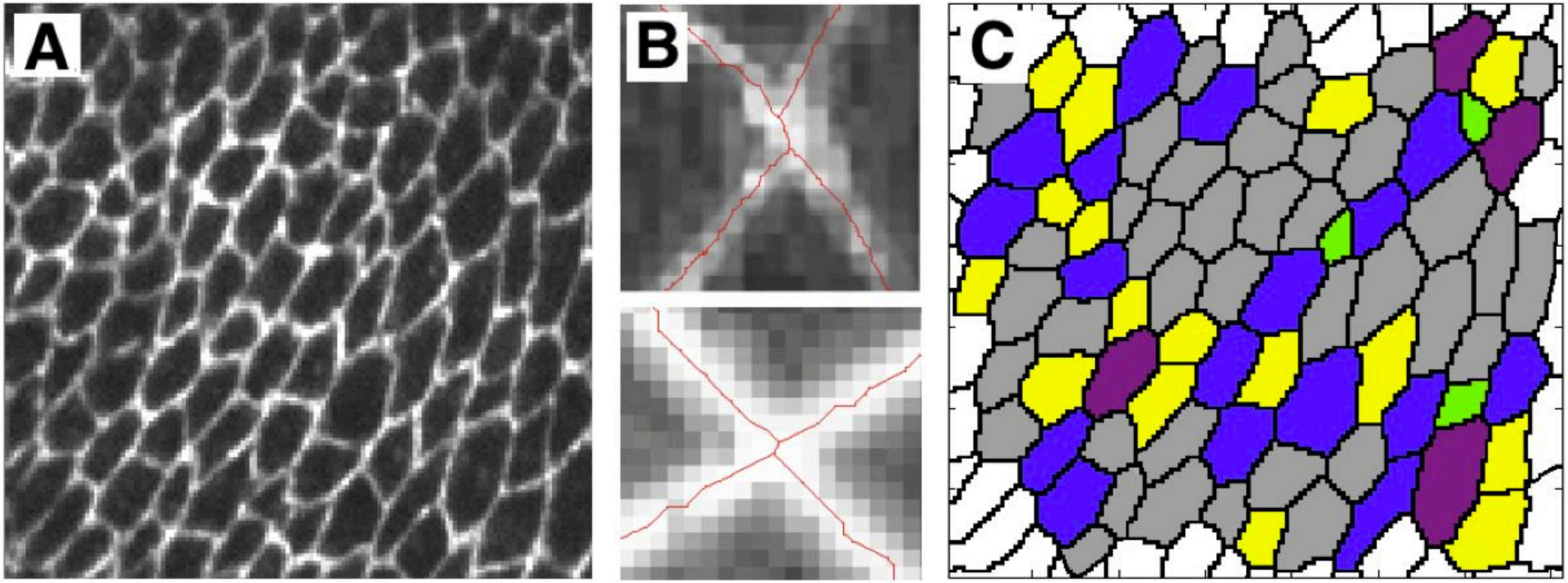
[Lewis 1928]



[Arif, Tsai, SH 2011]

- Universal properties? Explain through Mathematics/ geometry only?
- Physical Processes? Interactions?
- Specific Biological Effects?

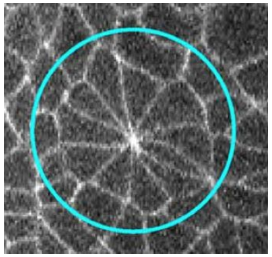
2D Cellular Matter Domain Geometry and Coordination



[Classen et al. 2005]

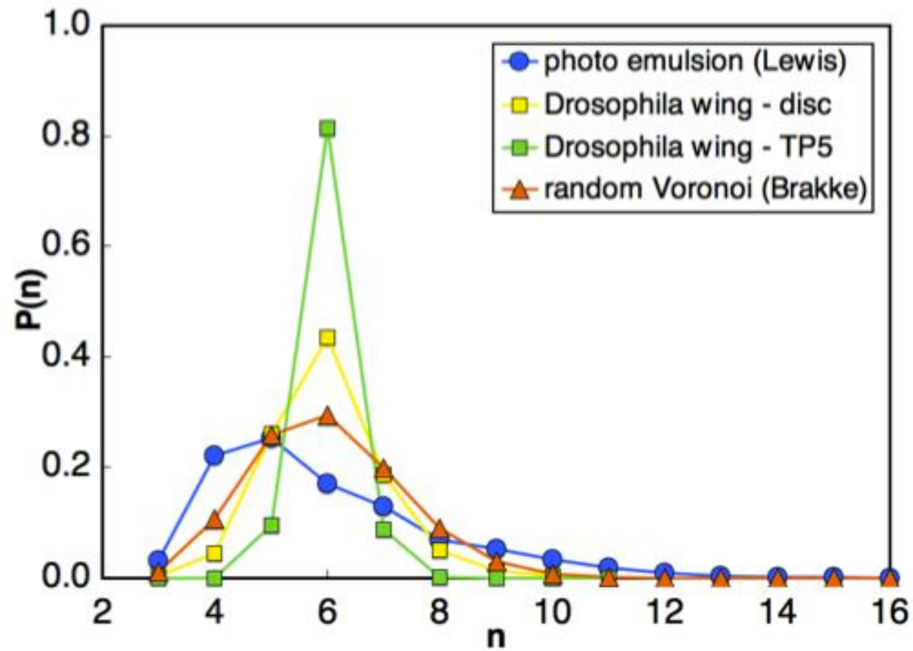
[Miklius 2011]

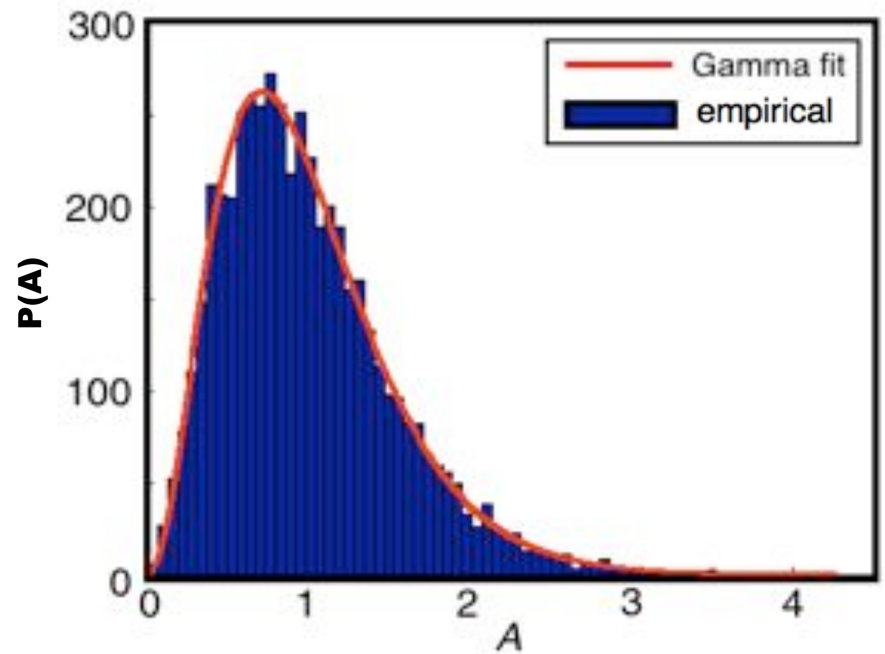
Topology: number of neighbors n
(note: 3-way vs. 4-way junctions)
Size: cross-sectional areas A_i, perimeters L_i
Shape: texture tensor M, …



[Blankenship et al. 2006]

2D Cellular Matter Domain Statistics





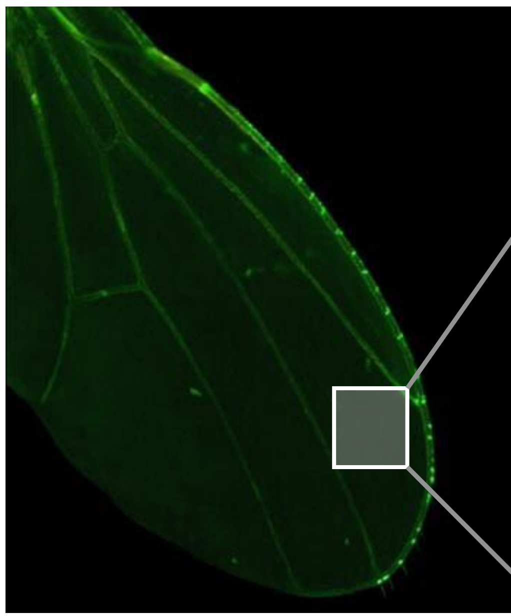
[cf. Gibson et al. 2006, Rivier 1980s/90s, Peshkin,…]

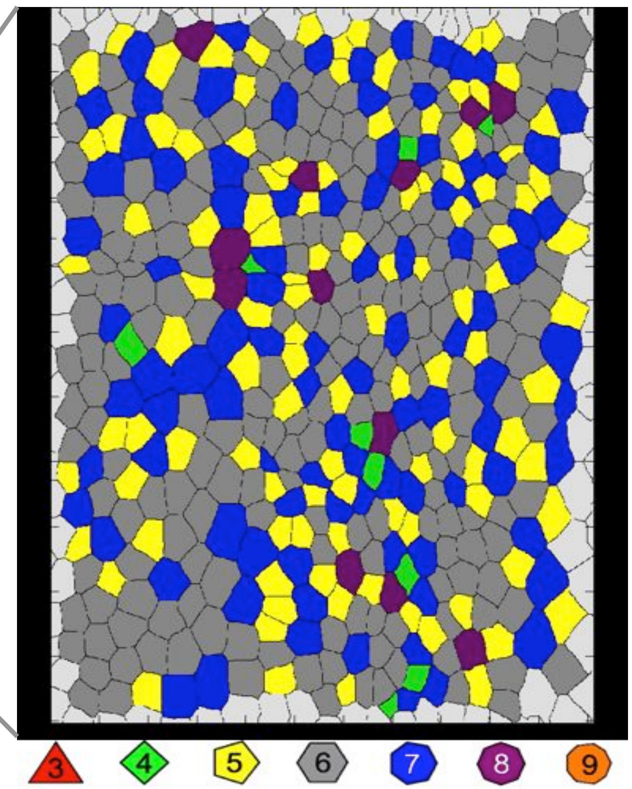
Topology: number of neighbors n (note: 3-way vs. 4-way junctions); Euler's theorem: $\bar{n} = 6$

Size: cross-sectional areas A_i, perimeters L_i

Shape: texture tensor M, …

Probabilistic biological tissues



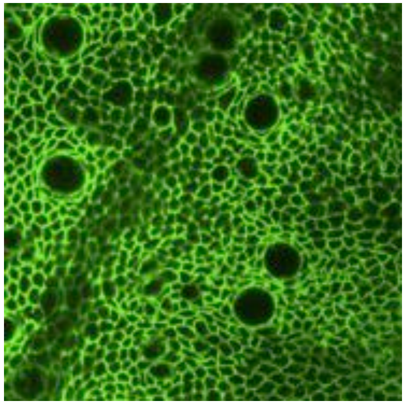


Drosophila wing epithelium:

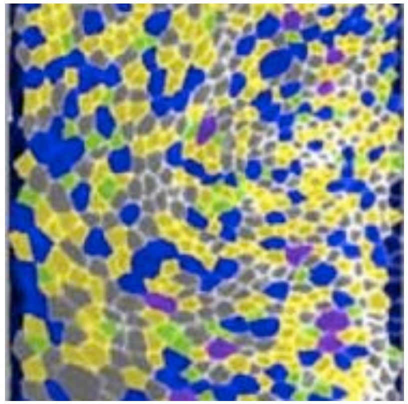
- Disordered structure
- Described by distribution functions: statistics of cell areas and neighbor numbers (“topology”) [M. Miklius & SH, EPJB 2011]

Drosophila wing development

Disc [Gibson]

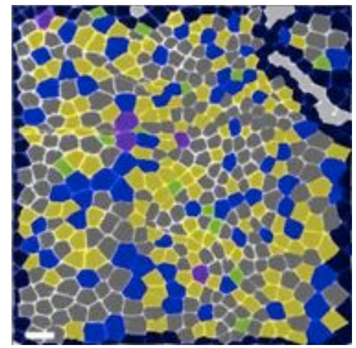


Disc [Classen]

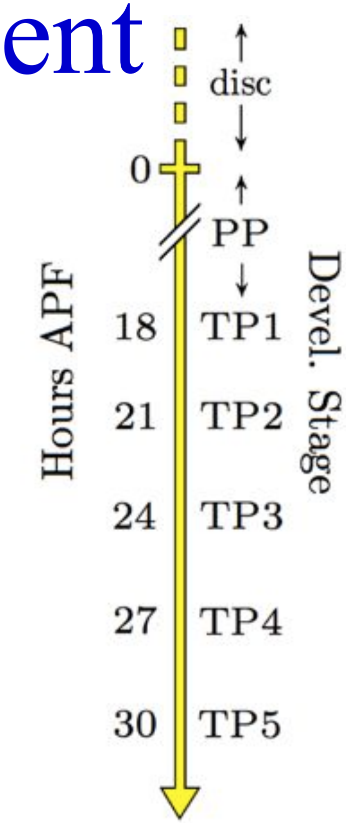


proliferating

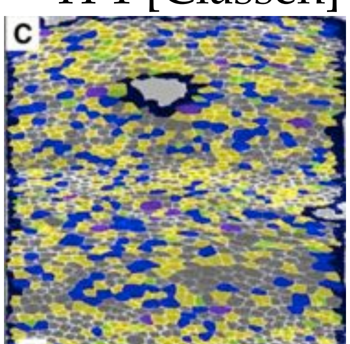
Prepupal [Classen]



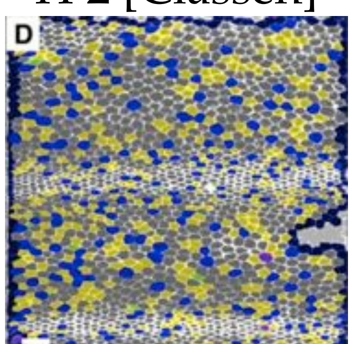
proliferation stops



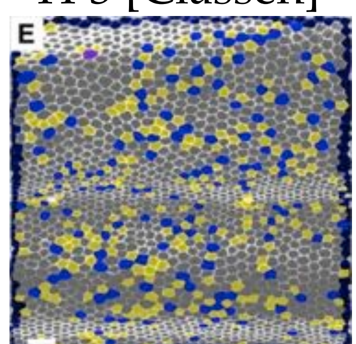
TP1 [Classen]



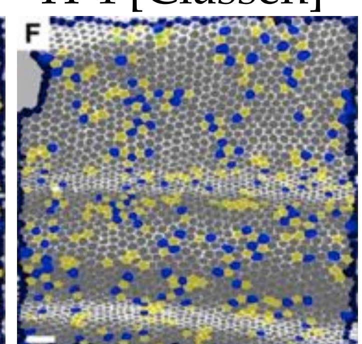
TP2 [Classen]



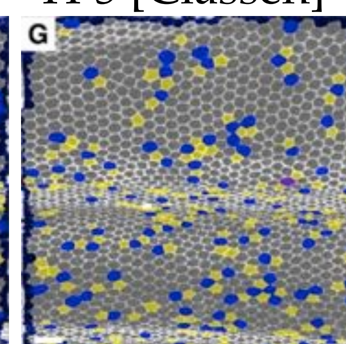
TP3 [Classen]



TP4 [Classen]

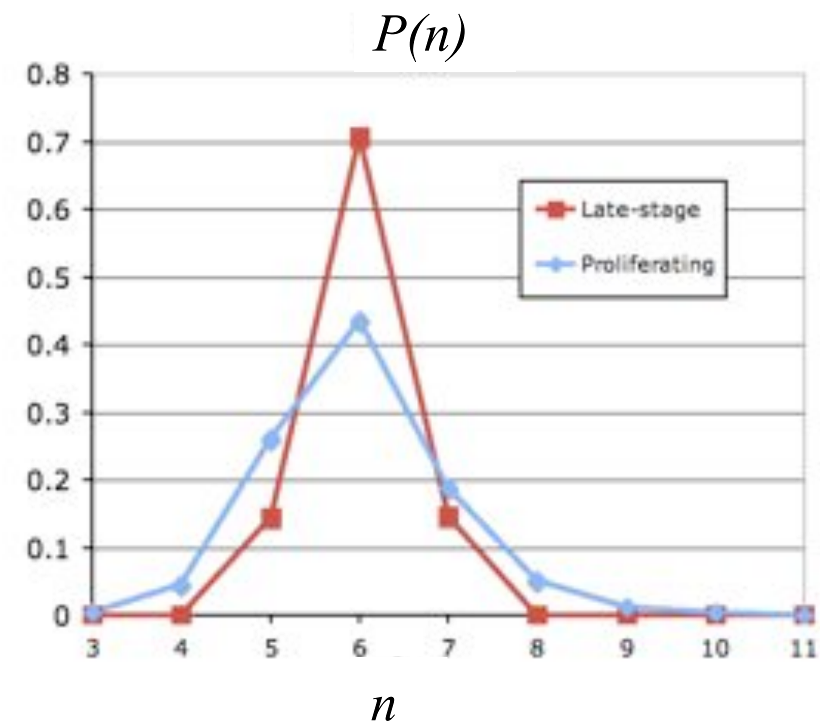


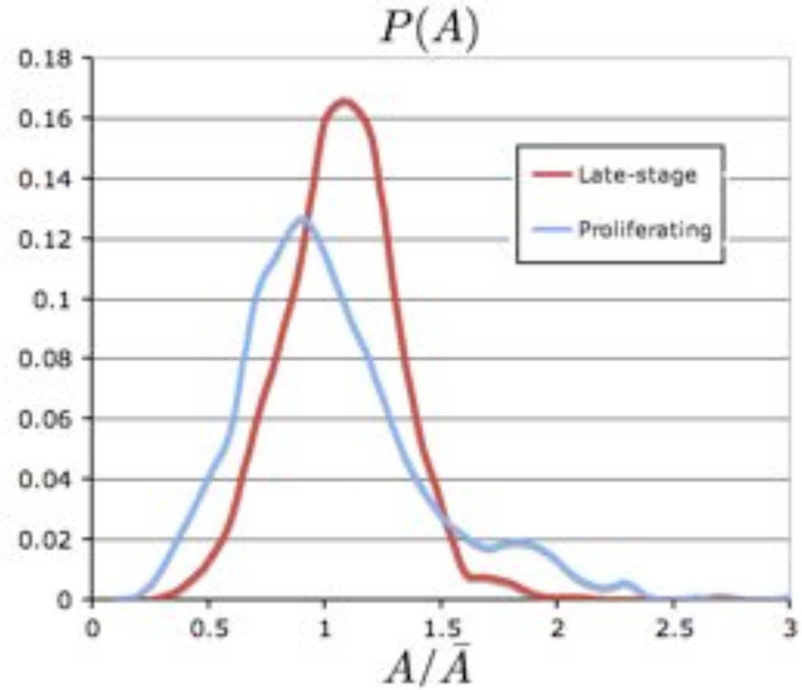
TP5 [Classen]



remodeling (T1)

Drosophila wing development



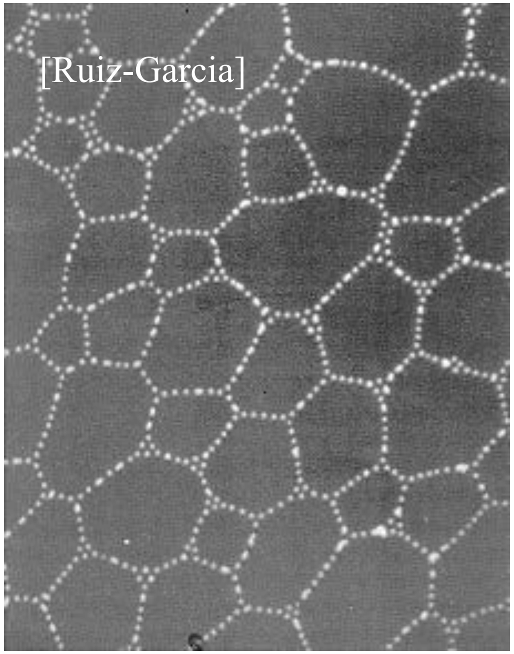


Both neighbor and area distributions narrow simultaneously over time

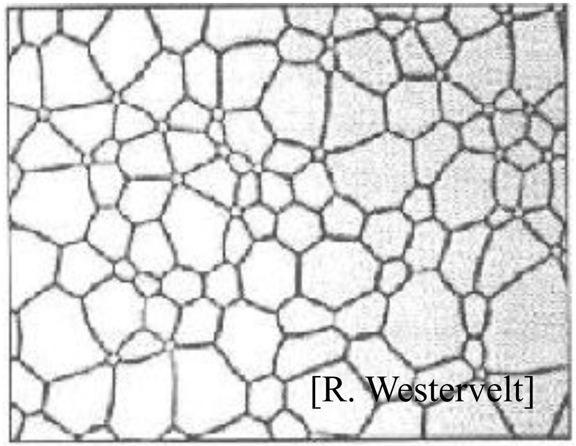
quantify width by coefficients of variation c_n, c_A

($= \Delta n/<n>, \Delta A/<A>$)

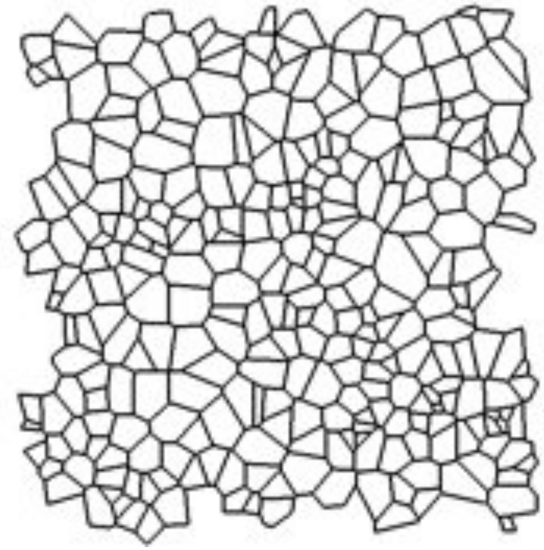
Many other polydisperse disordered systems…



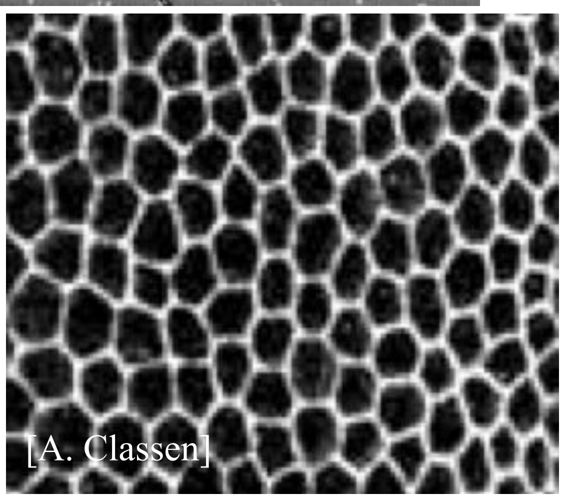
[Ruiz-Garcia]



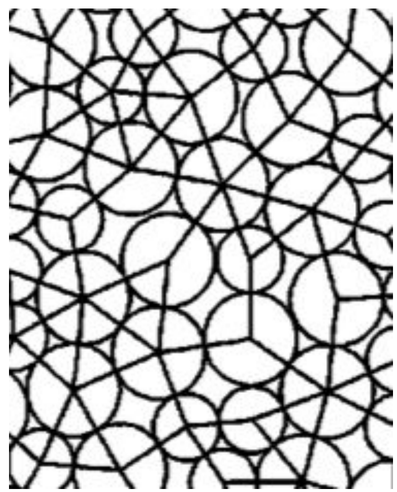
[R. Westervelt]



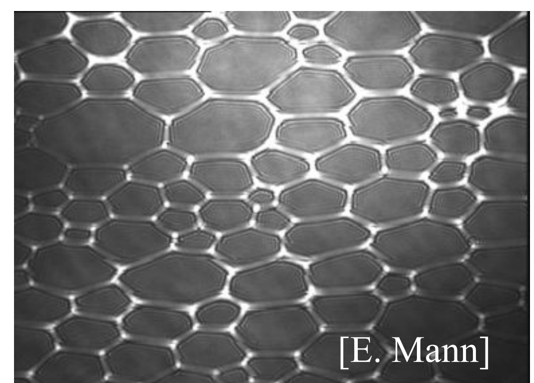
Voronoi tiling



[A. Classen]

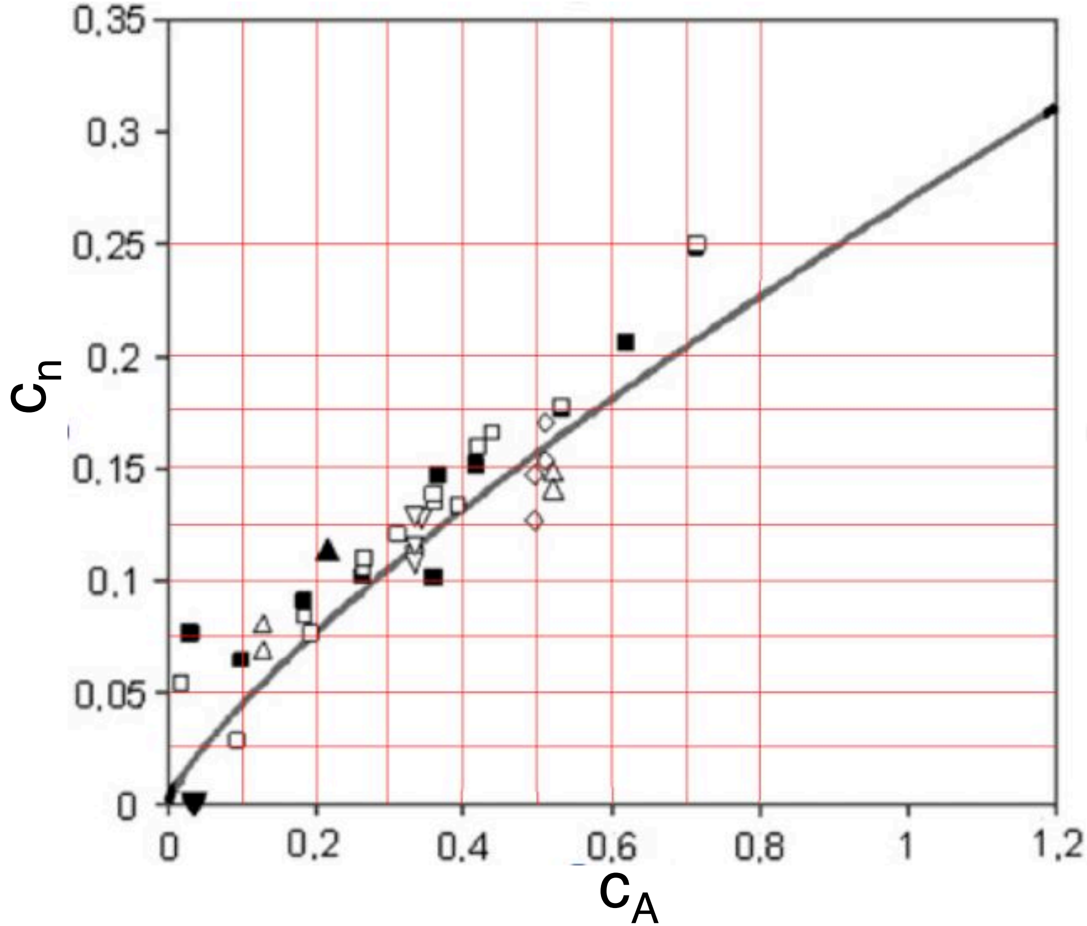


[Torquato & Stillinger]



[E. Mann]

Size-topology Correlations



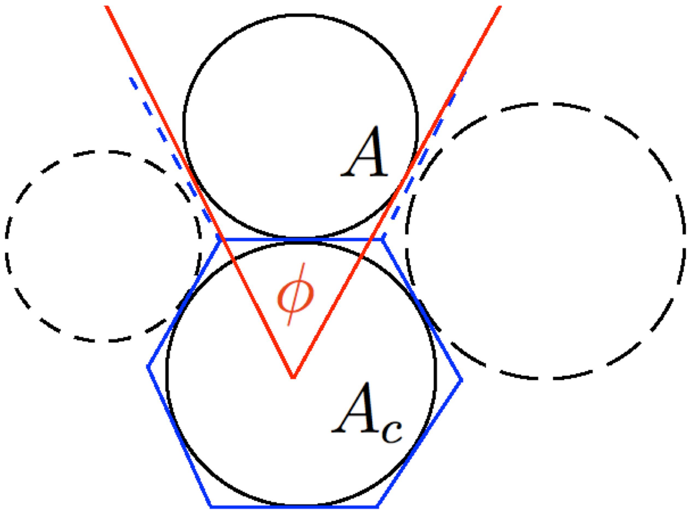
from Quilliet et al., Phil. Mag. Lett. 2008

How to describe the statistics?

- Packing / space-filling constraints only?
- Interactions?
- Interfacial energies?
- More specific (biological) processes?

Local (mean field) model? Are spatial neighbor correlations important?

The Granocentric Model in 2D



$$\phi = 2\,\mathrm{arcsin}\left(1/(1+\sqrt{A_c/A})\right)$$

given $P(A) \Rightarrow f_c(\phi)$

For fixed A_c, draw neighbors until $\phi > \phi_{max}$

disk areas $\Leftrightarrow$ regular polygonal areas

$\boxed{\text{Euler's theorem: mean number of neighbors } \bar{n} = 6}$

Computing probabilities

Conditional probability:

$$P(n|A_c) = \int_0^{\phi_{max}} R_{c,n}(\phi) F(\phi_{max} - \phi) d\phi$$

$R_{c,n}(\phi)$: PDF of sum of *n* angles $F(\psi) \equiv \int_\psi^\infty f_c(\phi) d\phi$

Unconditional probability:

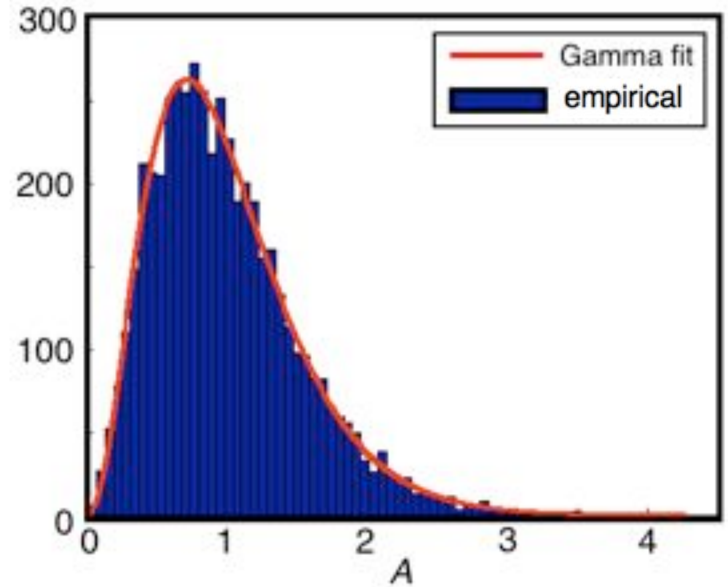
$$P_n = \int P(n|A_c) P(A_c) dA_c \quad \Rightarrow c_n, \mu_{2,n}$$

explicit results ("GM simulations") using *P(A)* as input

[M. Miklius and SH, *PRL* 2012]

Analytical Approximations

Realistic area distributions: gamma, Weibull, log-normal,…



But correlations use (at most) c_A

$\Rightarrow$ use Gaussian fits: integrals become analytically solvable!

Analytical Approximations

$$P(n|A_c) = \Phi_{n+1}(c_A, A_c) - \Phi_n(c_A, A_c)$$ with

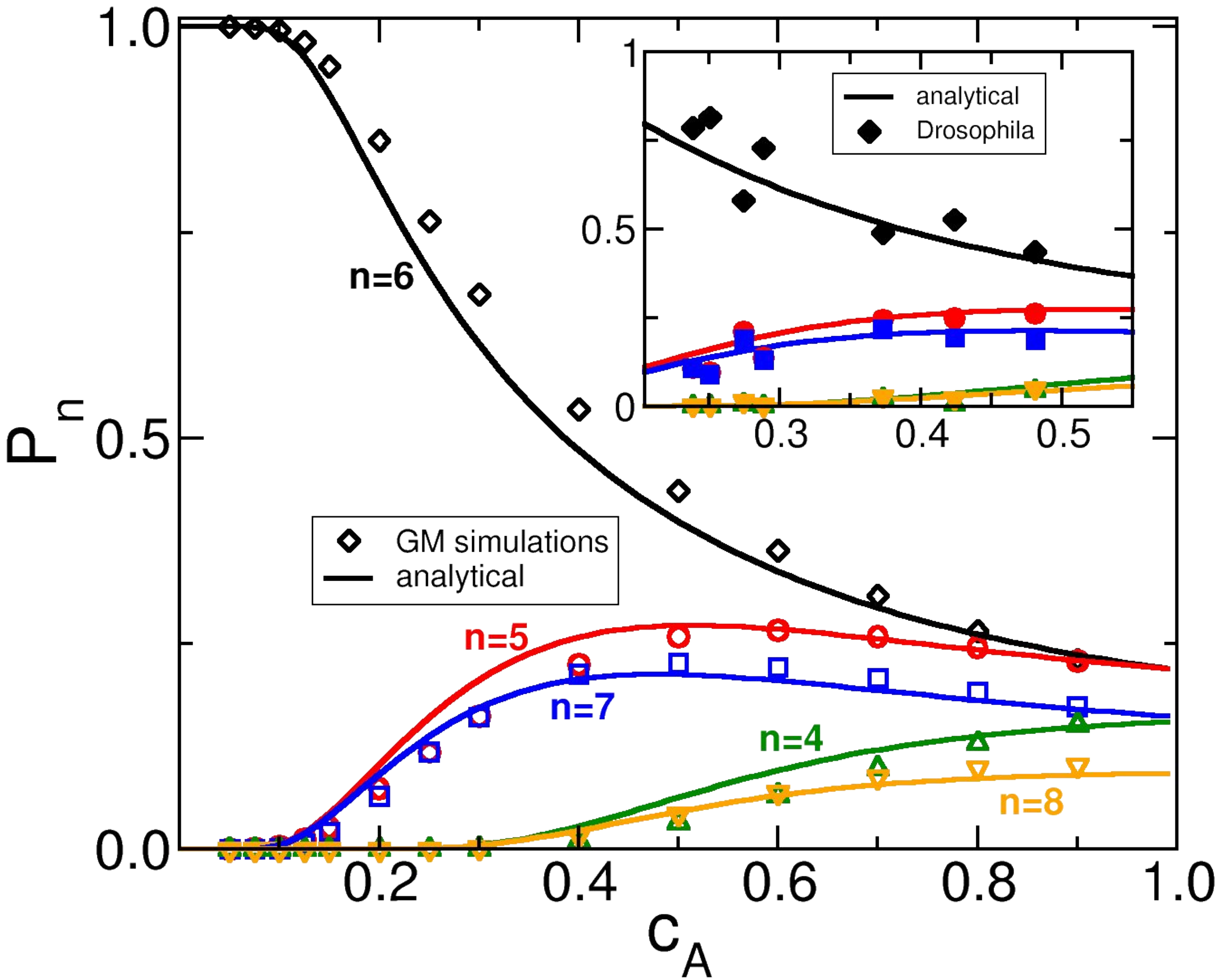
$$\Phi_n(c_A, A_c) = \frac{1}{2}\mathrm{erf}\left(\frac{n\bar{\phi}(A_c) - \phi_{max}}{\sqrt{2n}\sigma_\phi(c_A, A_c)}\right)$$

$$P_n = \Psi_{n+1}(c_A) - \Psi_n(c_A)$$ with

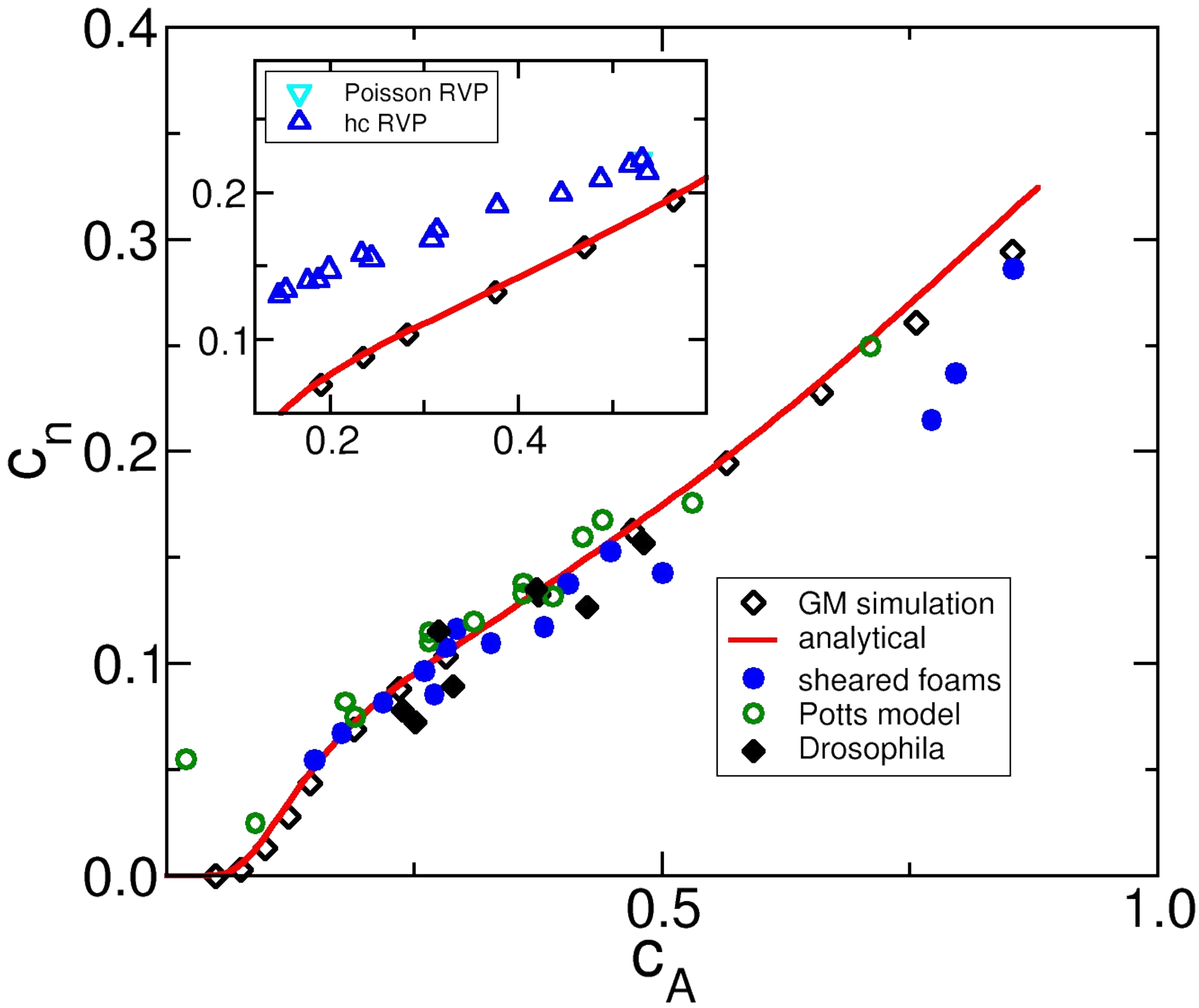
$$\Psi_n(c_A) = \frac{1}{2}\mathrm{erf}\left(\frac{\sqrt{2n}(1-(2-c_A^2/8)\Sigma)}{c_A\left((1-\Sigma)^2 + n(1-c_A^2/8)\Sigma^2\right)^{\frac{1}{2}}}\right), \; \Sigma \equiv \sin(\phi_{max}/2n)$$

[M. Miklius and SH, *PRL*, 2012]

Result: Neighbor probabilities

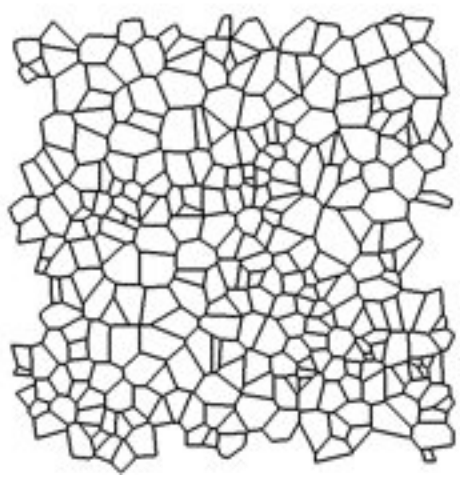


Result: Size-topology correlation



Non-conforming tilings

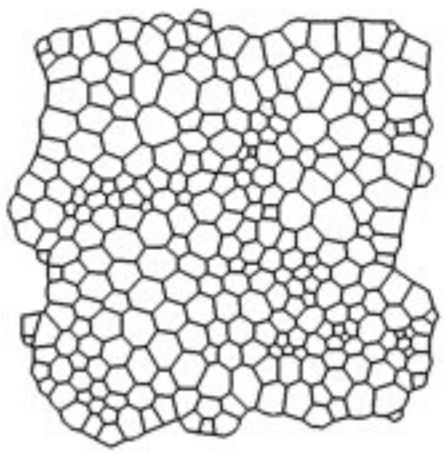
Voronoi



Surface Evolver

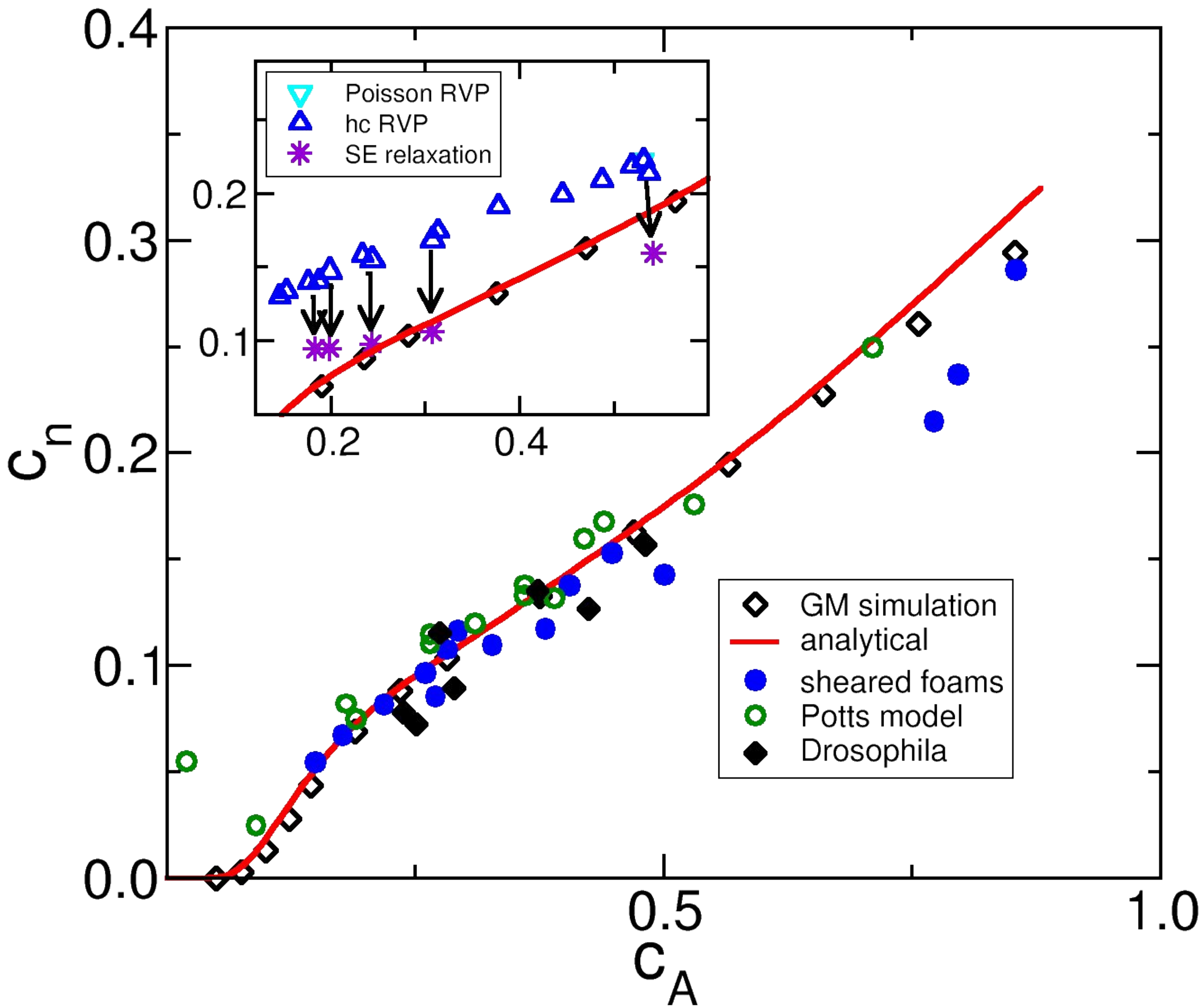
T1 transitions

relaxed



Introducing an interfacial energy establishes compactness of domains and reduces c_n!

Result: Size-topology correlation

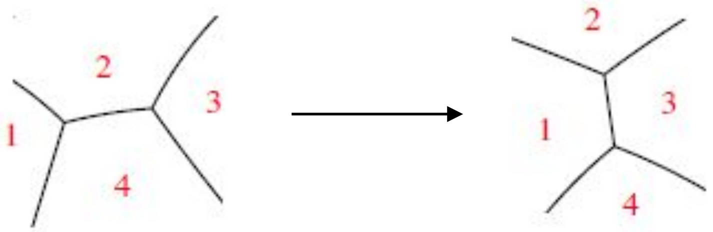


Alternative theory for Foams: Statistical Physics approach

M.Durand EPL (2010)
M. Durand, J. Käfer, C. Quilliet, S. Cox, S. Ataei Talebi, F. Graner *PRL* (2011).

Foam = tiling of space (no overlaps and no gaps)

Must satisfy Euler, Plateau, Laplace laws (low shear rate)



"shuffling": T1s
(compactness of domains!)

Each bubble exchanges sides *n* and curvature with rest of foam, such that :

$$n + n_{\text{rest of foam}} = \text{constant} \quad = 6N$$ (large foam)

$$\kappa + \kappa_{\text{rest of foam}} = \text{constant} \quad = 0$$

$$\boxed{p_A(n) = \chi(A)^{-1} \exp(-0.28\beta \frac{n(n-6)}{\sqrt{A}} + \mu n)}$$

where effective « temperature » and « chemical potential » are related to the shape of area distribution.

For moderate dispersities :

$$\boxed{\beta^{-1} \simeq 5.06 \frac{\langle A^{1/2} \rangle \langle A^{-1/2} \rangle - 1}{\langle A^{1/2} \rangle}}$$

$$\boxed{\mu' \simeq \frac{1.69}{\langle A^{1/2} \rangle}}$$

correlates geometrical disorder ($p(A)$) and topological disorder ($p(n)$):

$$p(n) = \int_0^\infty p(A) p_A(n) dA$$

For **moderate** dispersities, *i.e.*

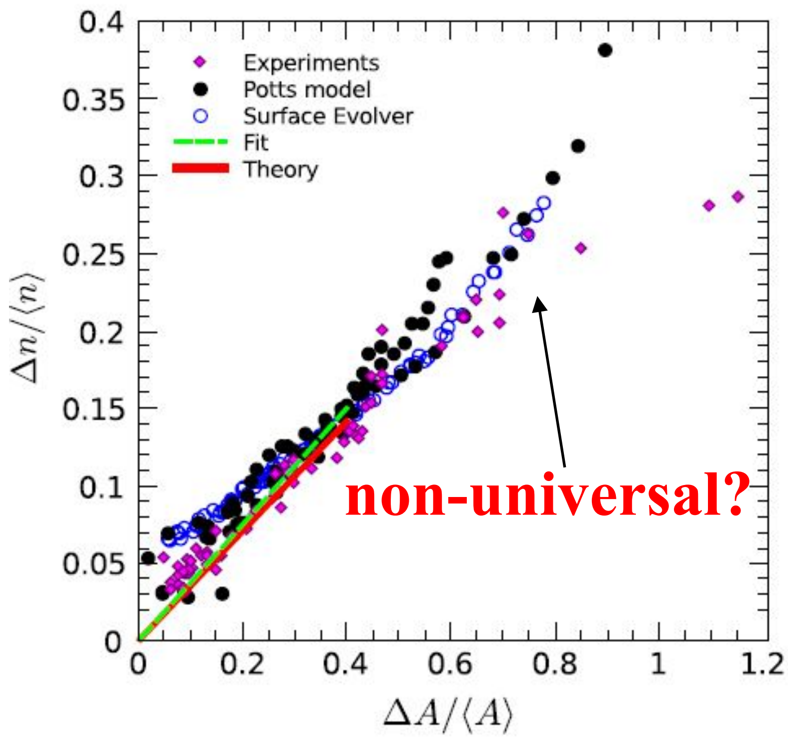
$(\Delta A/\langle A\rangle)^2 \ll 4$

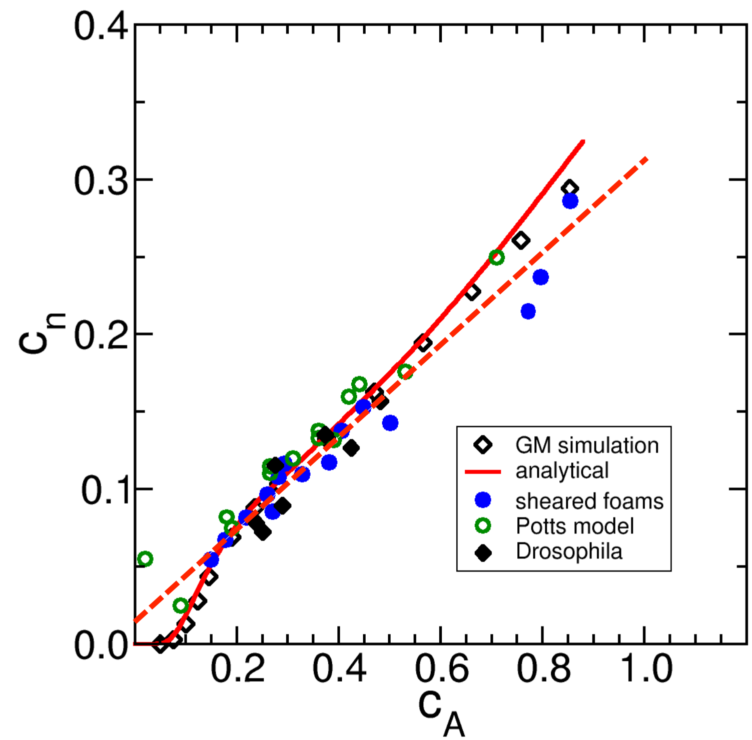
$$\frac{\Delta n}{\langle n\rangle} \approx \frac{1}{2^{3/2}}\frac{\Delta A}{\langle A\rangle} \approx 0.35\frac{\Delta A}{\langle A\rangle}$$

[Durand et al. PRL 2011]

$$\text{slope} \approx \frac{3}{2\pi}\sqrt{\frac{5}{13}} \approx 0.296$$

[SH & M.Miklius, PRL 2012]





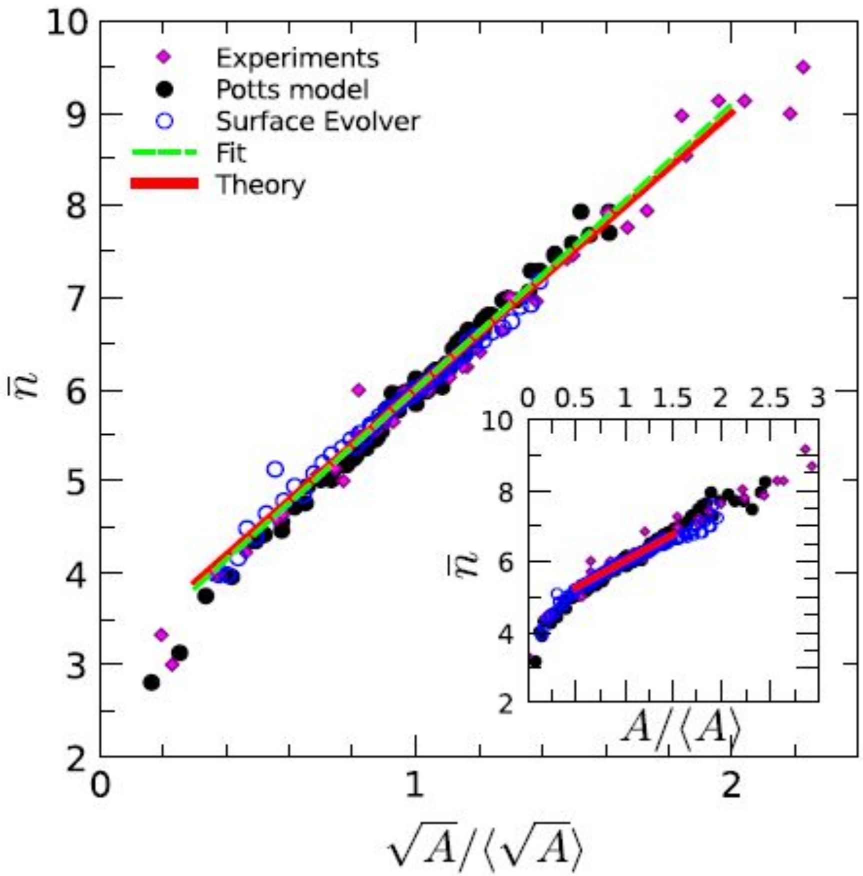
For **moderate** dispersities, *i.e.*

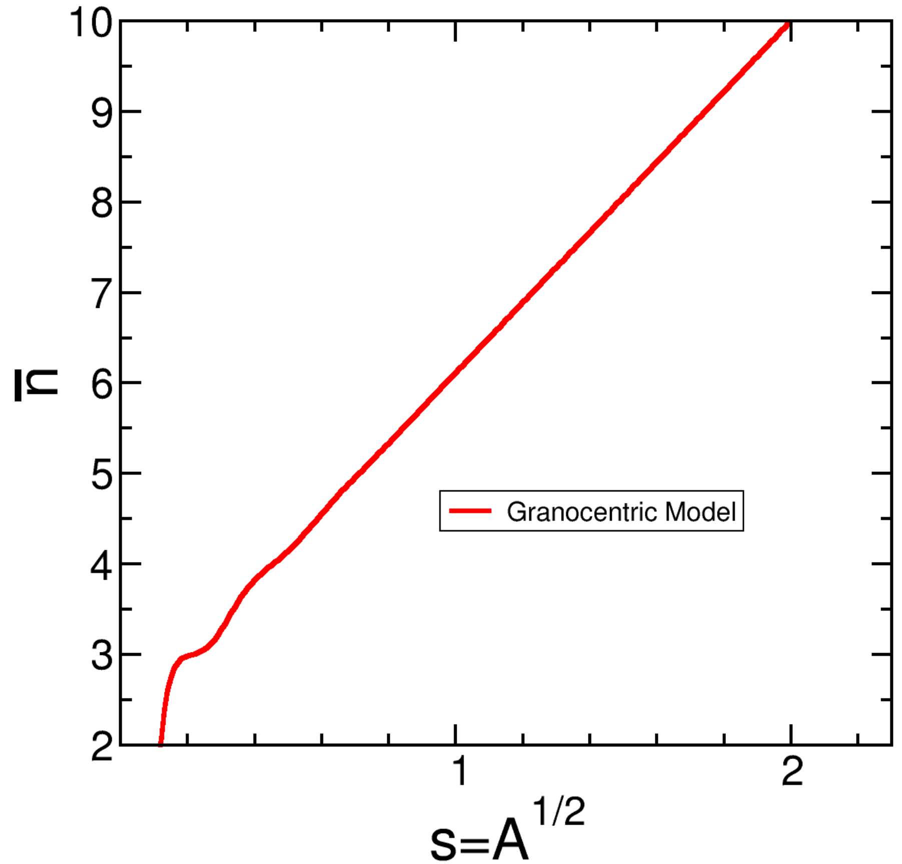
$(\Delta A/\langle A\rangle)^2 \ll 4$

$$\boxed{\bar{n}(A) \simeq 3\left(1 + \frac{\sqrt{A}}{\langle\sqrt{A}\rangle}\right)}$$

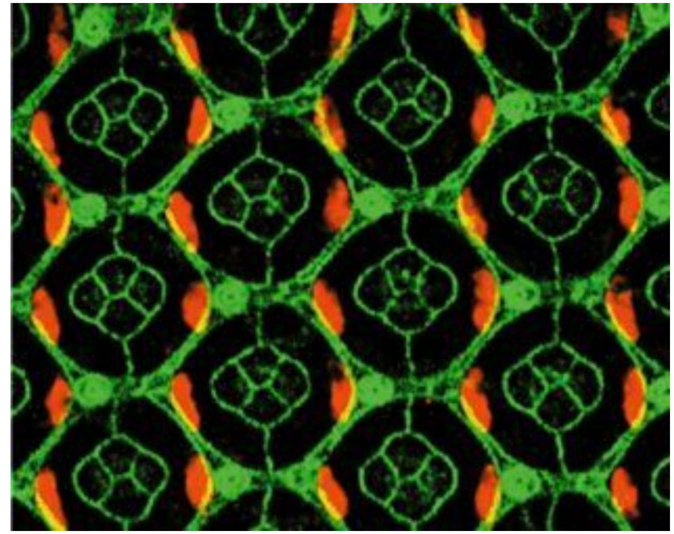
[Durand et al. PRL 2011]

[after SH and M.Miklius, PRL 2012]





Deterministic biological tissues

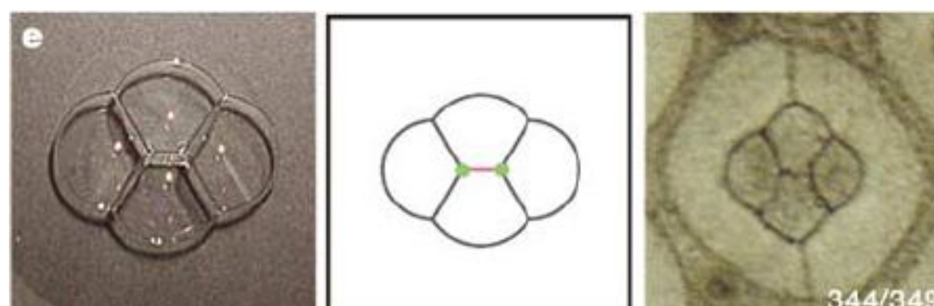


Drosophila eye (retinal epithelium):

- Strictly deterministic structure
- Described quantitatively by energy functional minimization

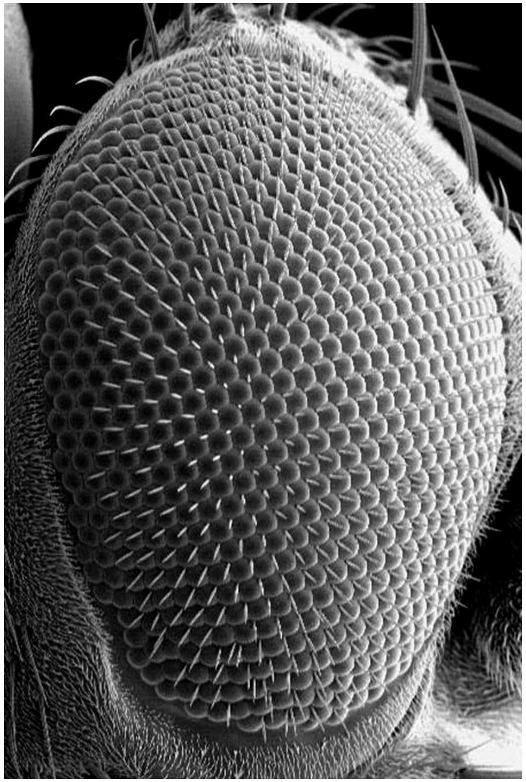
But not liquid foam energy!

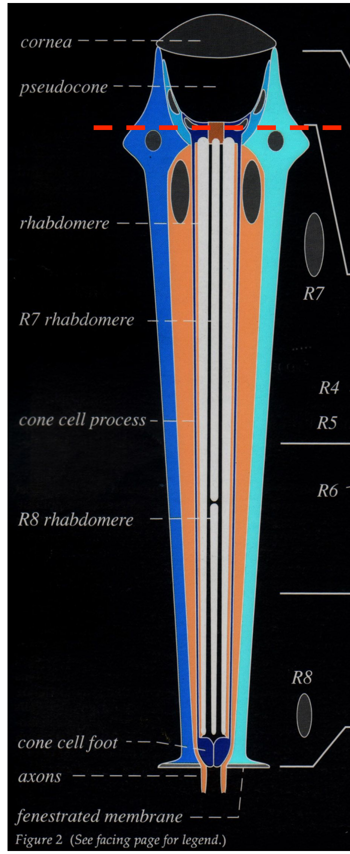
$$\boxed{\mathcal{E} \neq \gamma_0 \int dA}$$



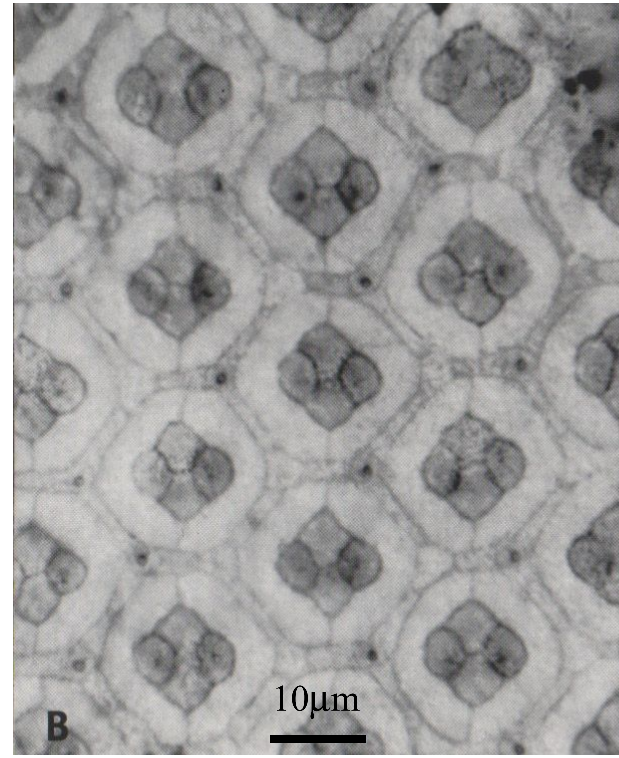
[Hayashi & Carthew, *Nature* 2004]

The *Drosophila* eye





One Ommatidium



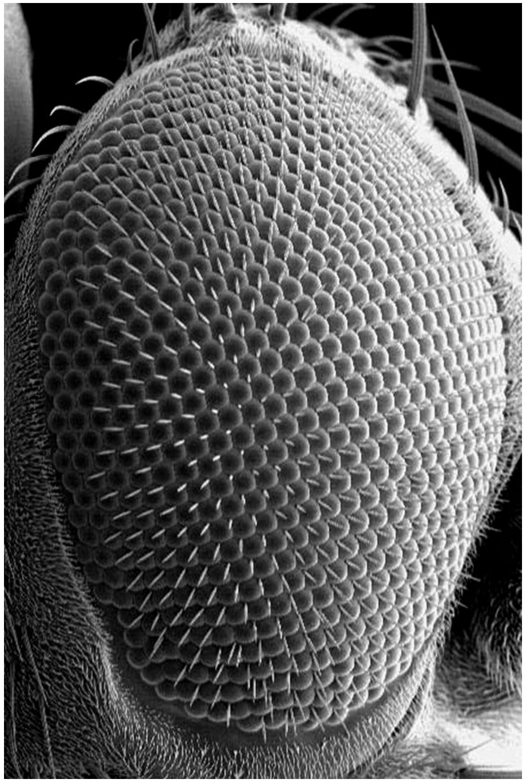
F-actin, adherens junction

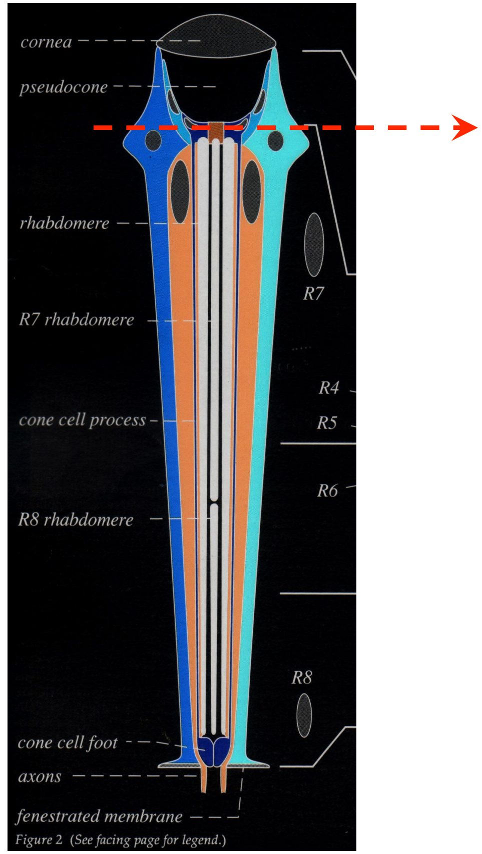
Highly conserved structure – complex genetic regulation

Interface Mechanics, without bulk terms, describes these shapes!

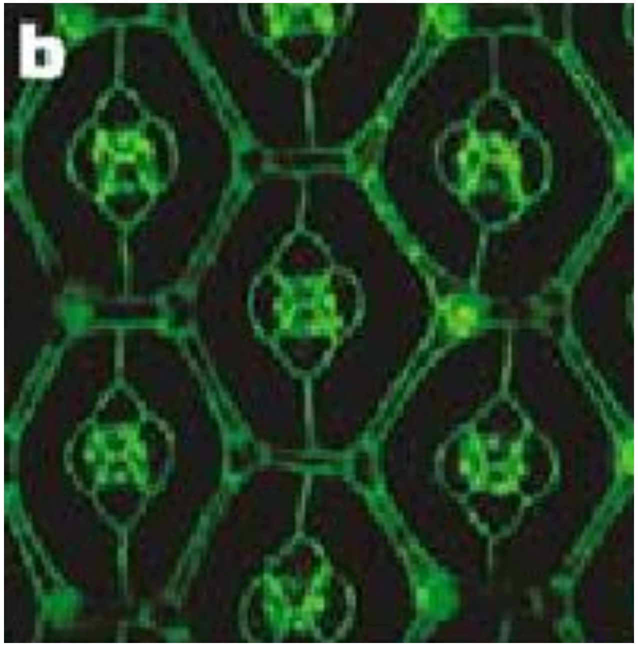
Adherens junction cross section: 2D mechanics

The *Drosophila* eye





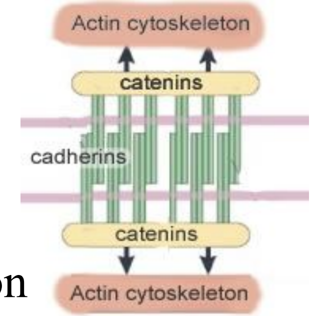
One Ommatidium



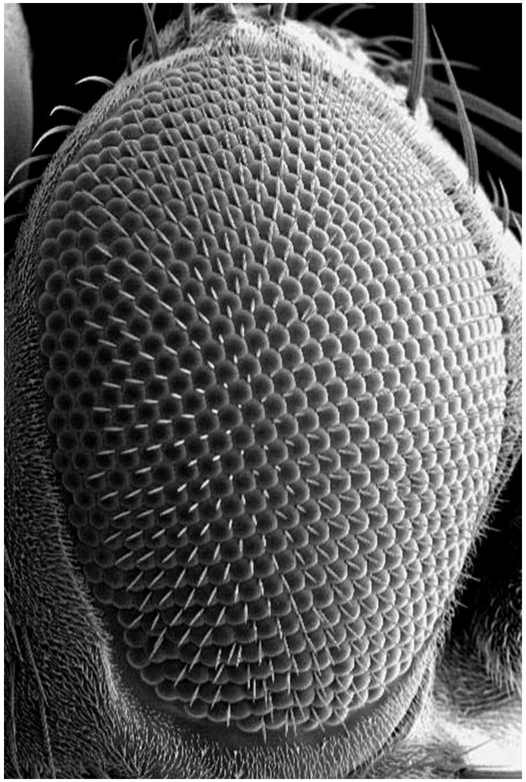
E-cadherin, adherens junction
Hayashi & Carthew, *Nature* 2004

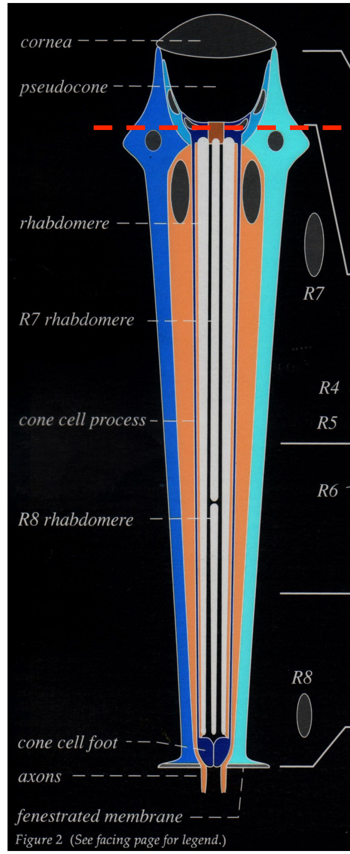
Cells adhere by two kinds of cadherins!

homophilic interaction

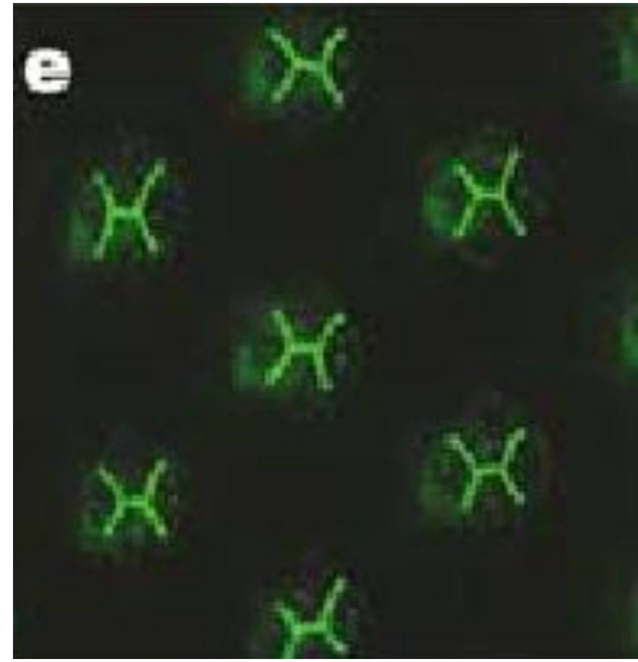


The *Drosophila* eye



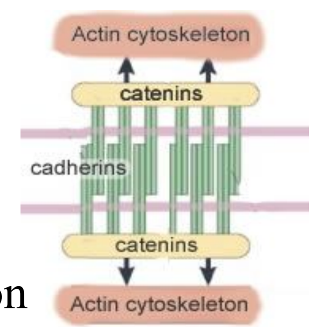


One Ommatidium



N-cadherin, adherens junction
Hayashi & Carthew, *Nature* 2004

Cells adhere by two kinds of cadherins!



homophilic interaction

Adhesive Membrane Model

Surface energy functional (cells *i*, edges *ij*):

$$\boxed{\mathcal{E} = \sum_i \frac{1}{2}\Delta_i^2 L_{0i} - \sum_{i,j} L_{ij}\gamma_E \delta_{i,E}\delta_{j,E} - \sum_{i,j} L_{ij}\gamma_N \delta_{i,N}\delta_{j,N}}$$

interfacial elasticity E-cadherin binding N-cadherin binding

Essential: contains competing energy terms nonlinear and linear in geometric parameters, respectively.

$\Delta_i \equiv \frac{L_i - L_{0i}}{L_{0i}}$ membrane strain; note: this is not a film!

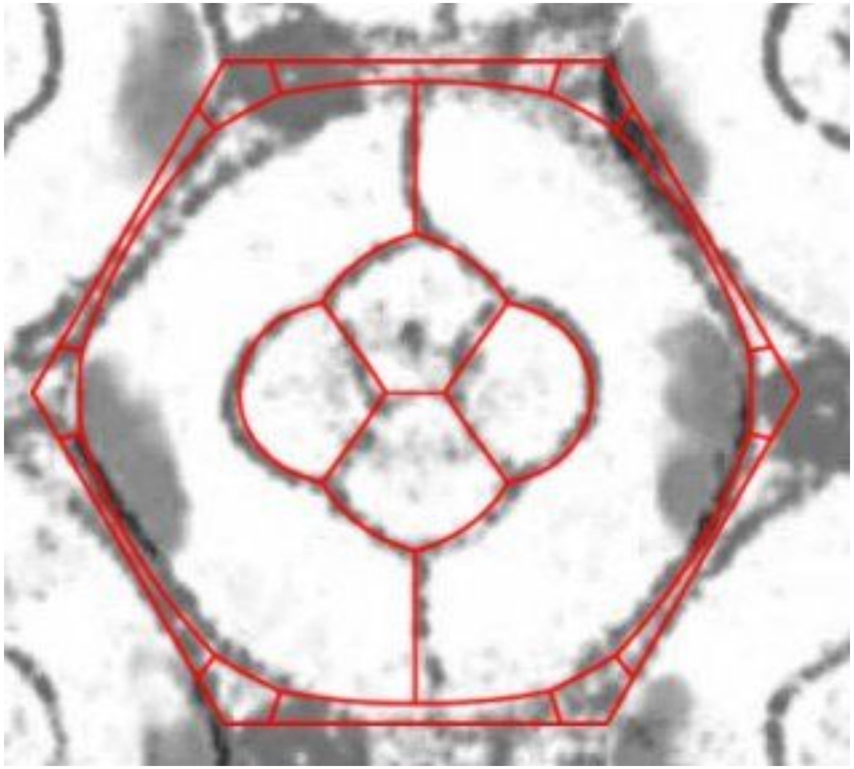
$\gamma_E, \gamma_N \sim 10^{-2}$ dimensionless adhesion strengths

Very similar functionals in work by Brodland; Jülicher, Eaton; Aegerter-Wilmsen et al.; Graner…

Modeling *Drosophila* eye morphology

Numerical modeling:
optimize all L_{ij}, θ_i,…

- Surface Evolver simulations
- find local minimum of energy functional
- optimization parameters: γ_E, γ_N



SH, S. Erisken, R. Carthew, PNAS 2008

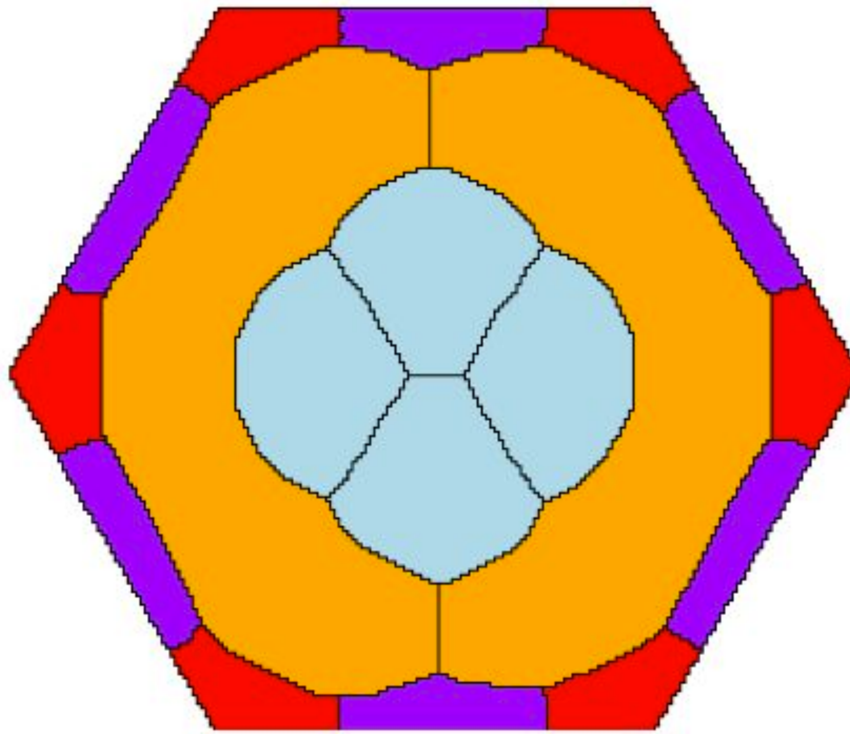
Modeling results

Geometry feature	Experimental value	Model simulation	Physical parameter	Modeled value
w_1/w_2	0.53±0.08	0.55	τ_f/K_A	0.8±0.2
θ_1	109°±6°	105°	$L_{0P}/2(\pi S_P)^{1/2}$	1.40±0.01
θ_2 θ_3 L_{cen}/D	118°±6° 130°±9° 0.0792±0.0055	122° 128° 0.0776	γ_E γ_N	0.025±0.005 0.032±0.005

Validated by comparison with mutants!

Alternative: Potts Model simulations

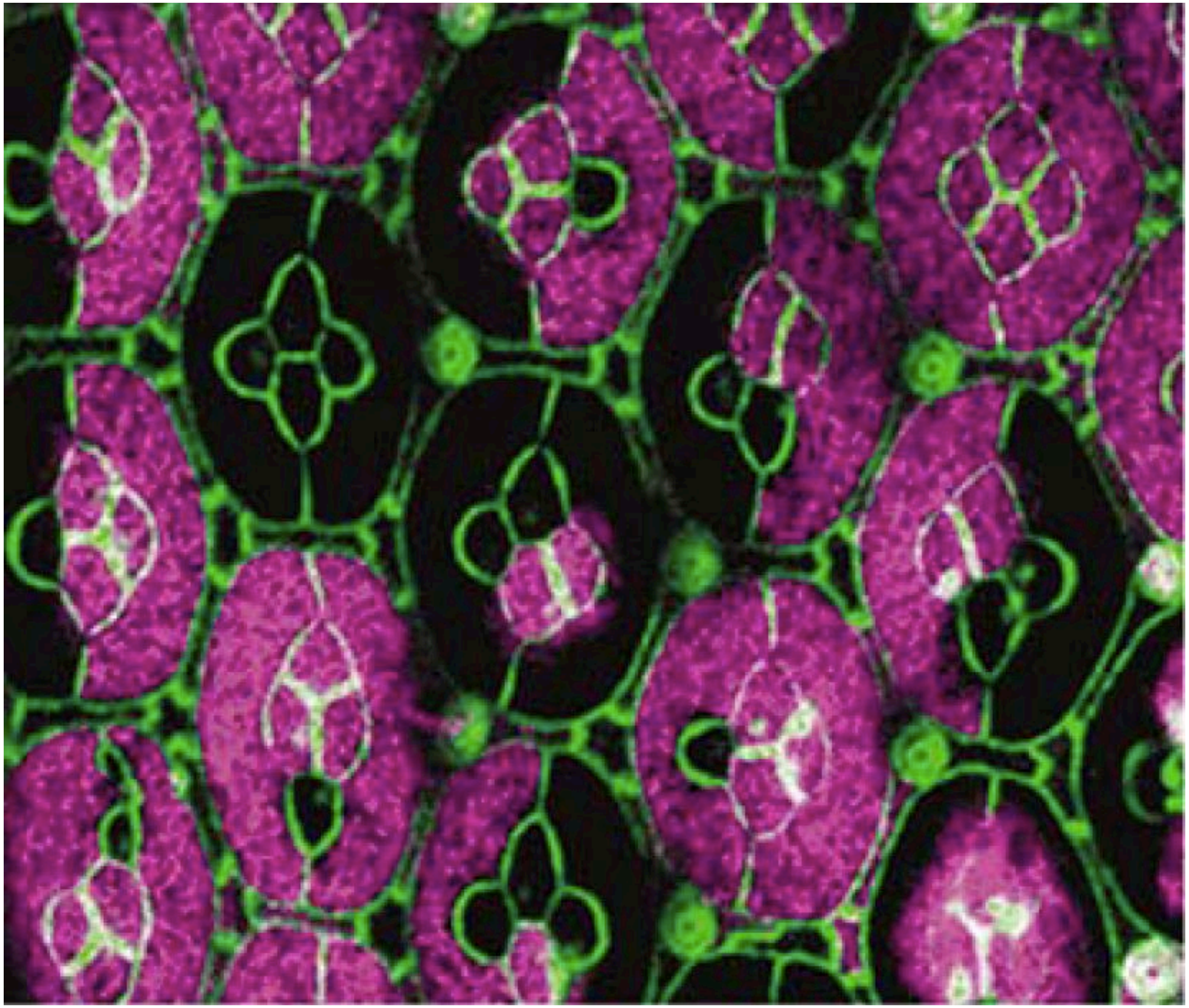
- Grid elements with neighbor "spin" energies
- interfacial energy penalty
- evolution to local equilibrium



Käfer et al. PNAS 2007

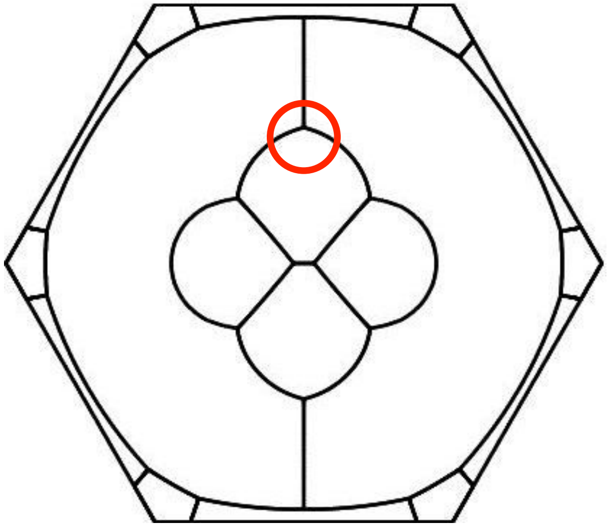
Two independent calculations confirm:
Shape can be obtained by energy minimization!

….but how about *mutants*?

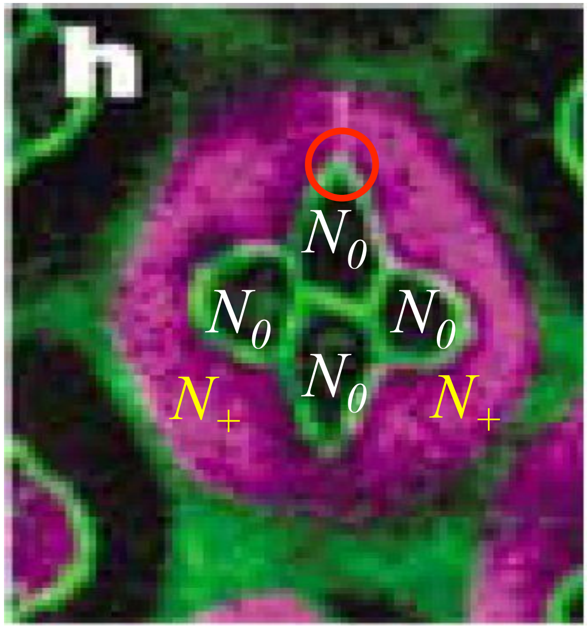


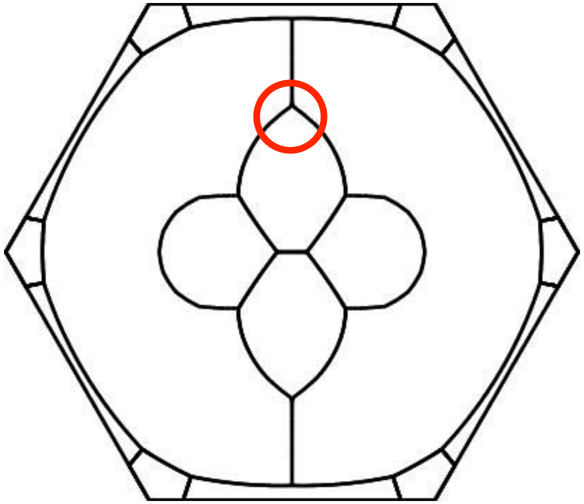
Mosaic mutants: N^+, N^-, E^+

N^+ (extra N-Cadherin) Mutants: temporal sequence of cell contact



simultaneous cell contact





P cells contact *after* N+ cadherin expression

a feature of morphogenesis!

[I. Gemp, R. Carthew, SH PLoS Comp. Biol. 2011]

Conclusions

- Strictly local neighbor statistics capture size-topology correlations in 2D (foams, biological tissues,…)

- Analytical, general expressions

- Domain compactness (interface energy penalty) is important, but does not specifically enter statistics

- Individual cell shapes governed by membrane elasticity and cell-cell adhesion

- Geometric constraints + Interfacial energy + Quasistatic dynamics are all important determinants of structure/morphology/morphogenesis