How does surface tension emerge from structure in biological tissues?

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PRINCETON CENTER FOR THEORETICAL SCIENCE

KITP

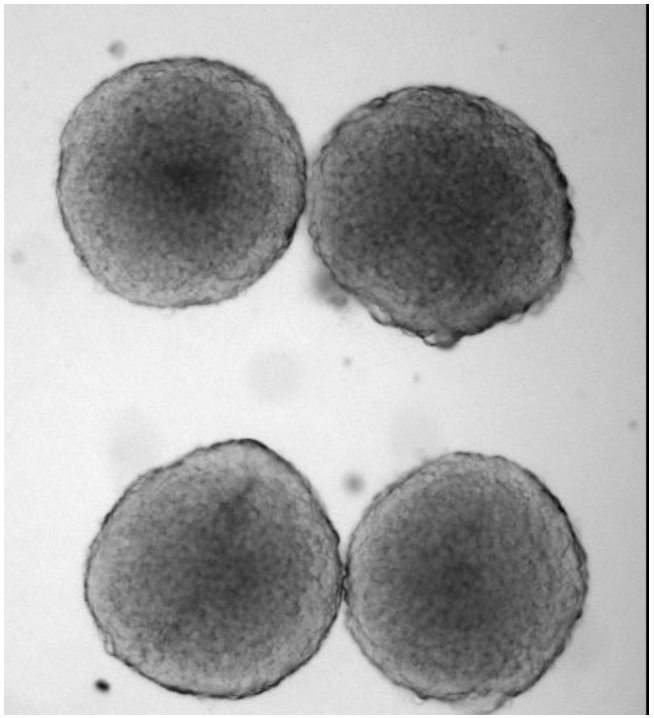
The physics of glasses

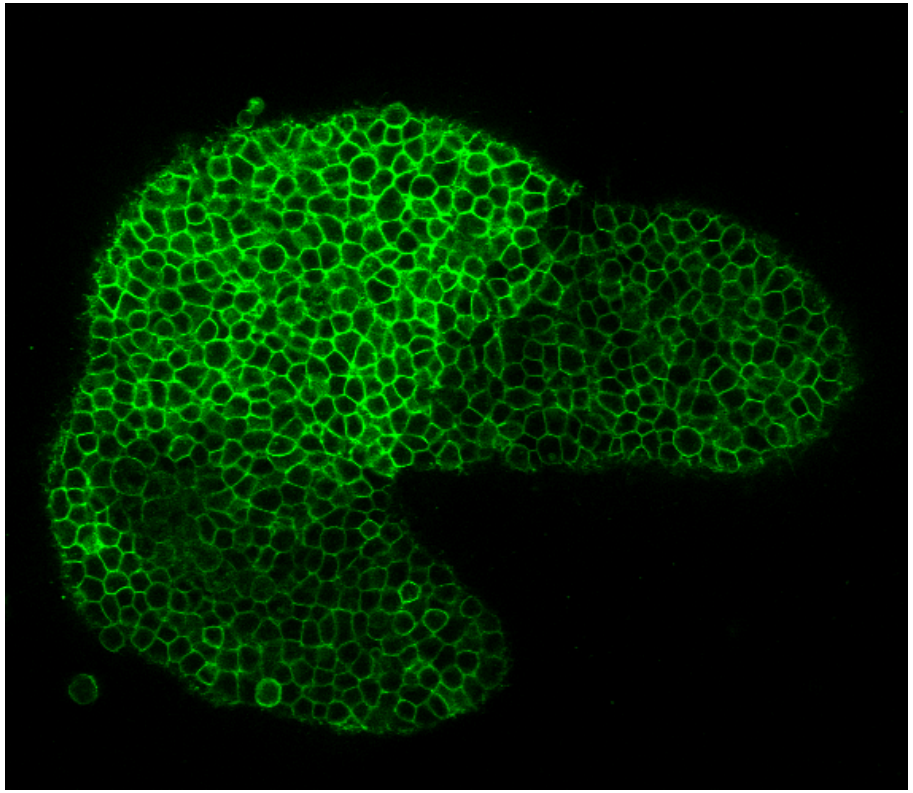
July 7, 2010

Email:lm2@princeton.edu

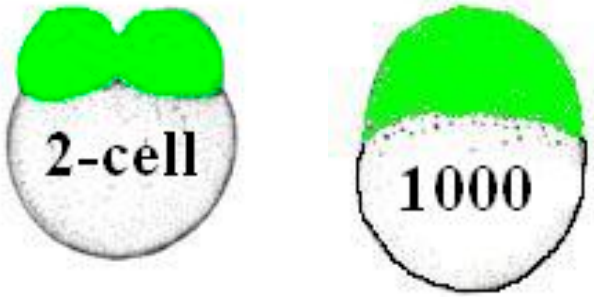
background image:
Schoetz lab

Many animal tissues behave like liquids on long timescales



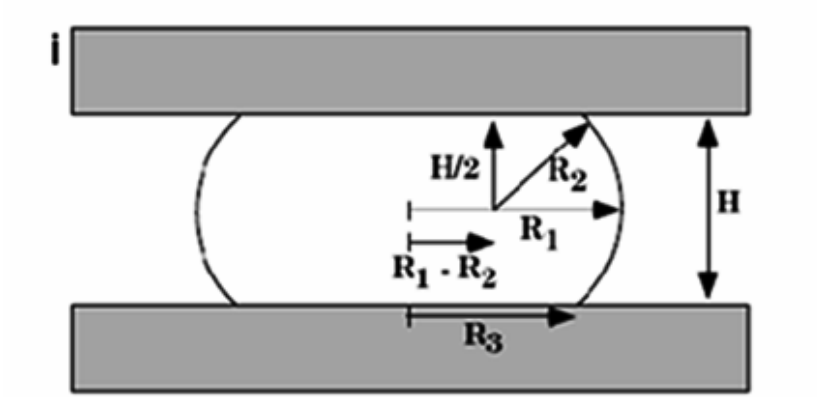


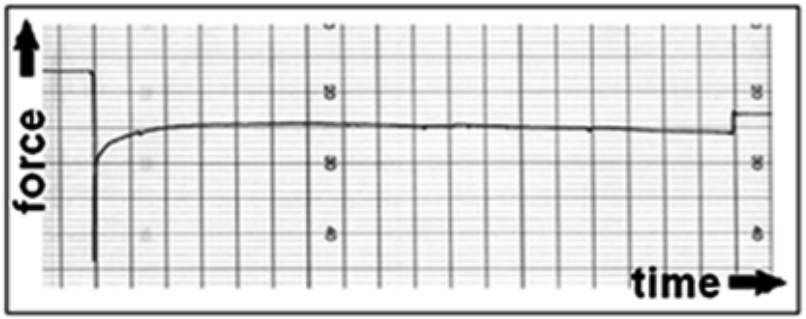
model system: zebrafish aggregates



1. early embryonic development
2. very few cell divisions
3. transparent

Measuring surface tension

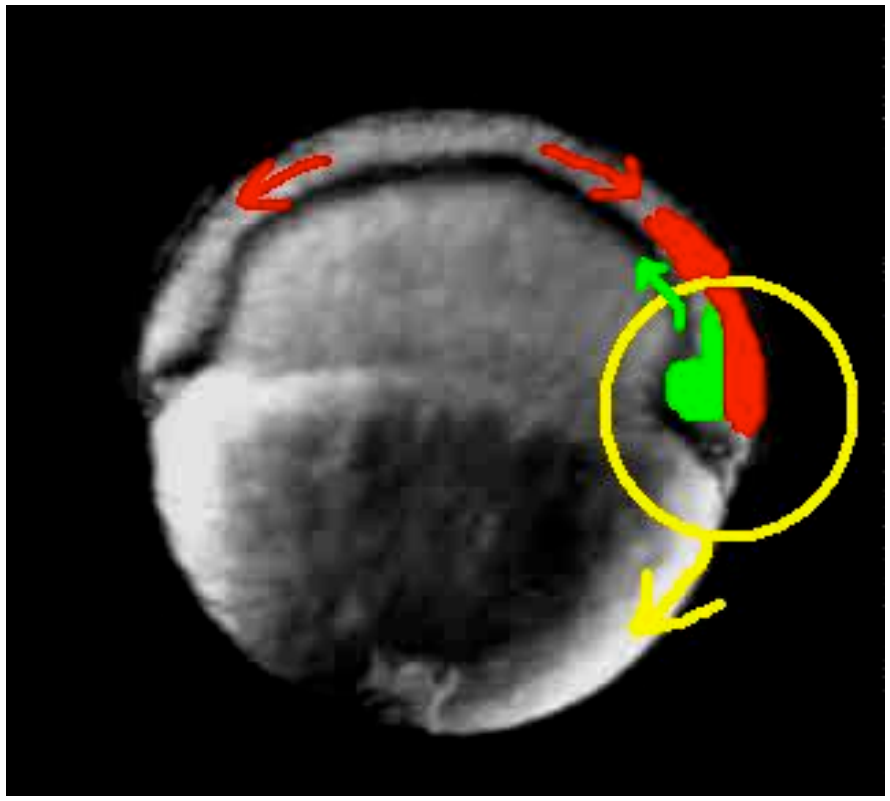




$$\frac{F_{eq}}{\pi R_3^2} = \sigma\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

Surface tension could be important for biological function

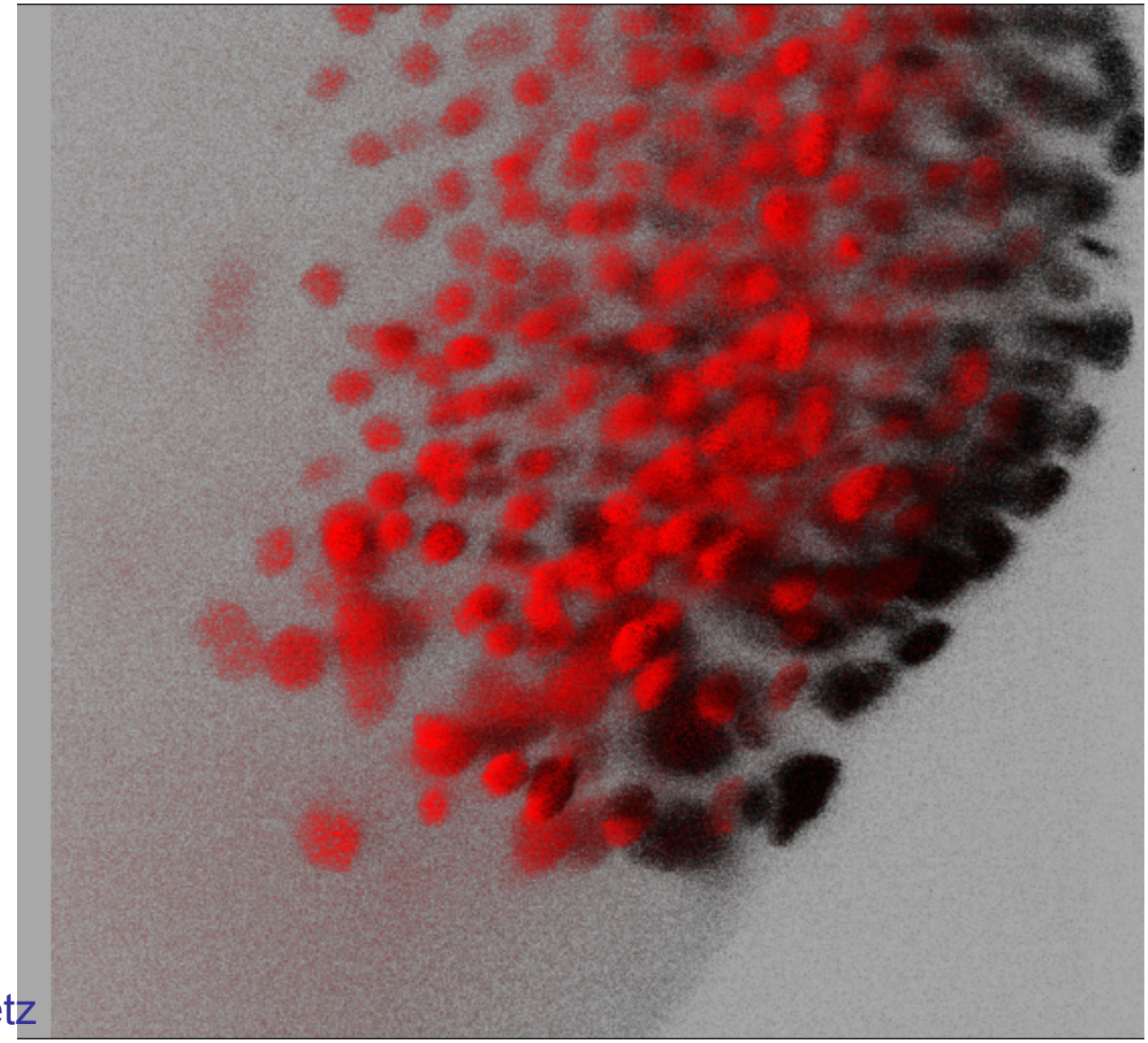
animal



vegetal

"shield stage": mesendoderm cells move upward, ectoderm cells move downward

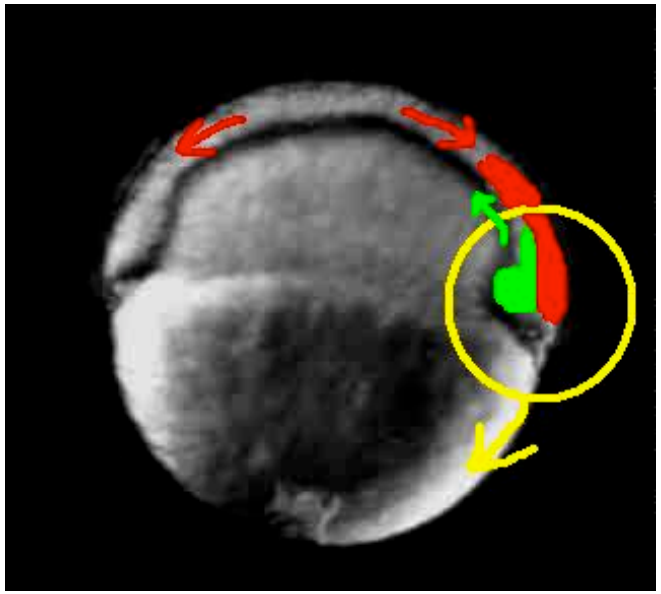
Zebrafish shield stage



EM Schoetz

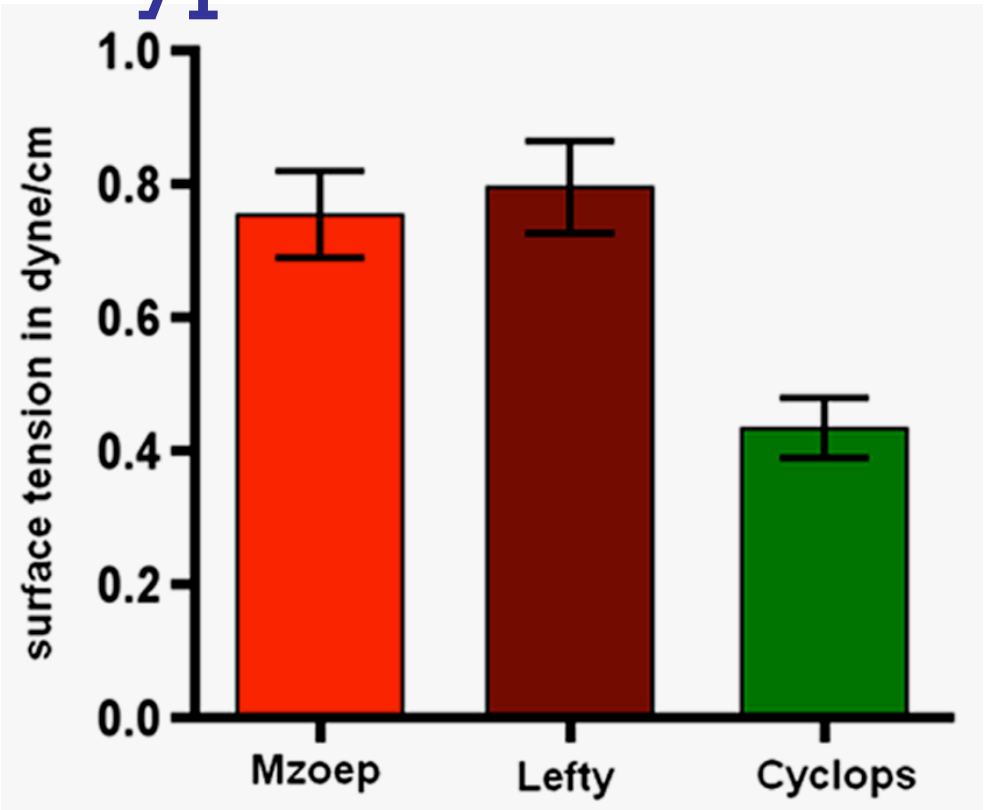
Surface tension varies between cell types

animal



vegetal

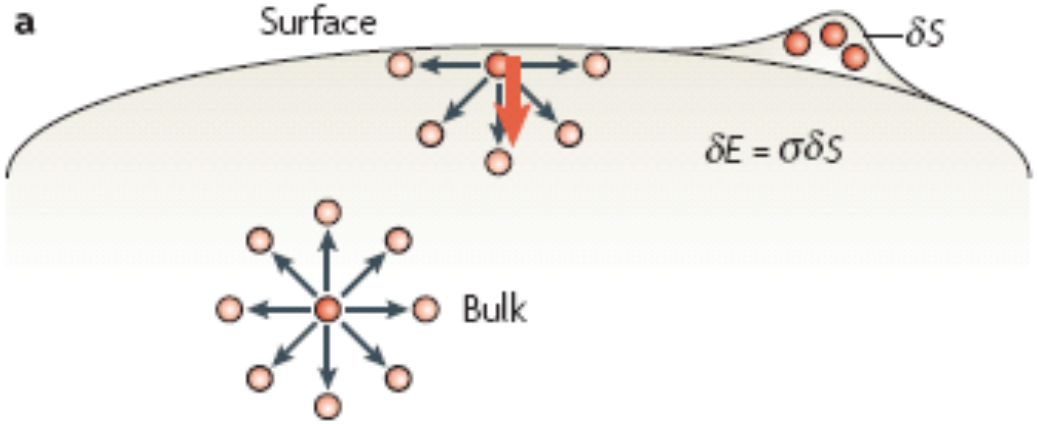
EM Schoetz thesis

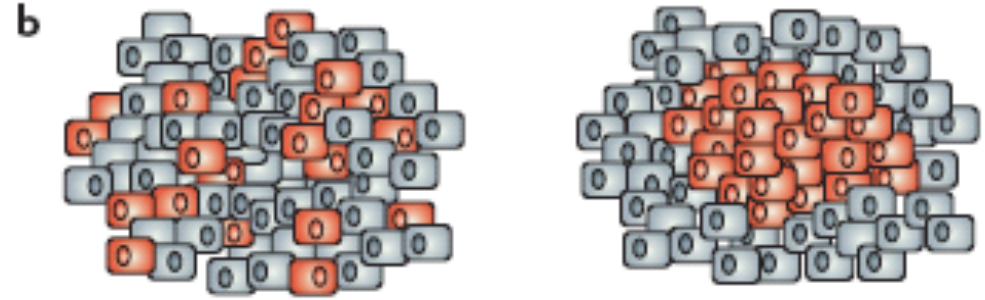


tissue	N (total)	σ (dyne/cm)
Mesendoderm	35	0.43 ± 0.04
MZoep (Ecto)	35	0.75 ± 0.06
Lefty (Ecto)	38	0.80 ± 0.07

Differential Adhesion Hypothesis (DAH) Steinberg

flow "arise[s] from tissue surface tensions that in turn arise from differences in intercellular adhesiveness"





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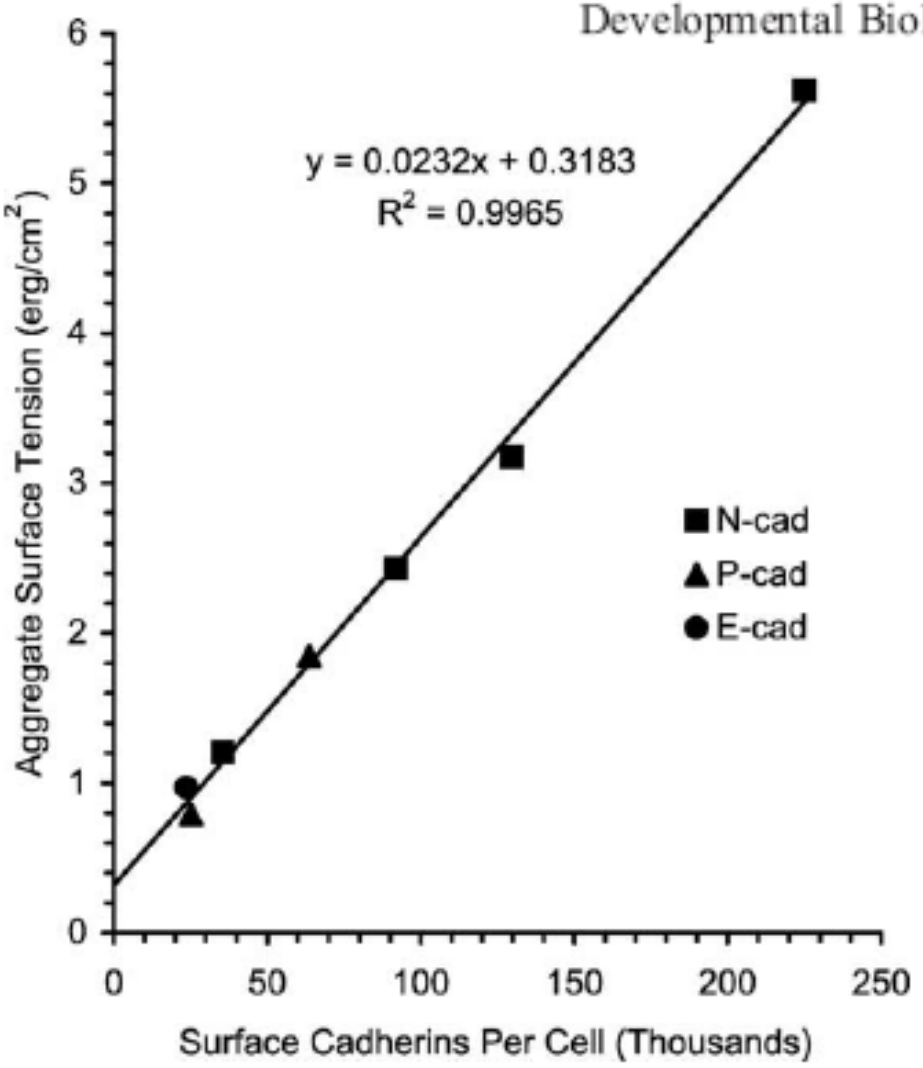
Lecuit and Lenne

The differential adhesion hypothesis: a direct evaluation

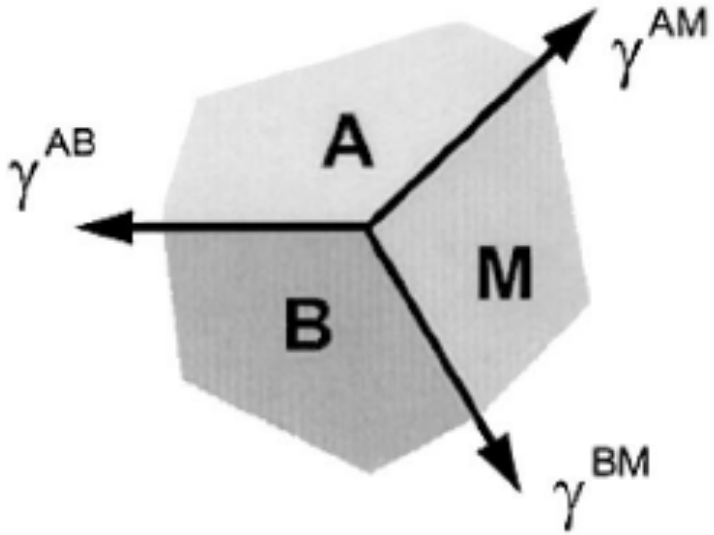
Ramsey A. Foty[a], Malcolm S. Steinberg[b,*]

Developmental Biology 278 (2005) 255–263



Differential interfacial tension or surface contraction hypothesis (DSC) Harris, Brodland

"interfacial tensions cause local displacements of the triple junctions and ultimately lead to specific patterns of cell rearrangement"



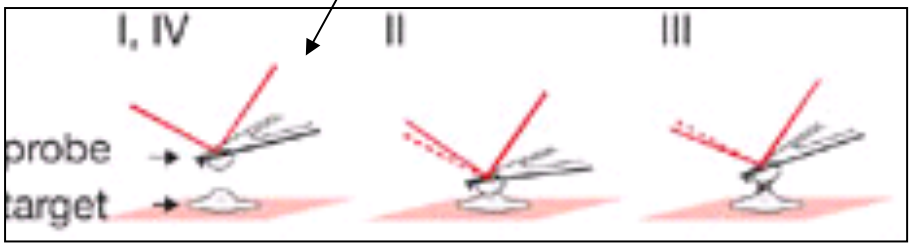
Brodland

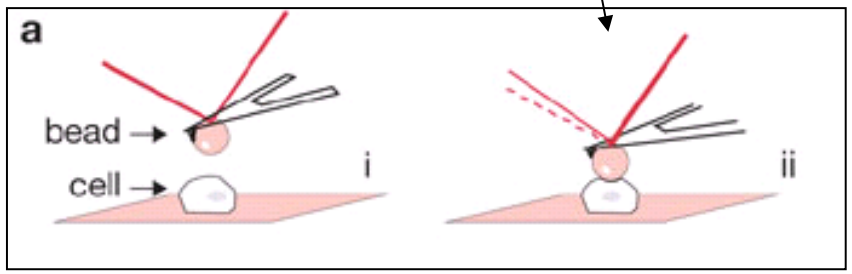
Appl Mech Rev vol 57, no 1, January 2004

Experiment: different tissues

Ordering, highest to lowest

surface tension	"adhesion"	"cortical tension"
1.Ecto	1. Meso	1.Ecto
2.Meso	2. Endo	2.Meso
3.Endo	3. Ecto	3.Endo





Krieg et al, Nature Cell Biology 10, 429 - 436 (2008)

Big Questions

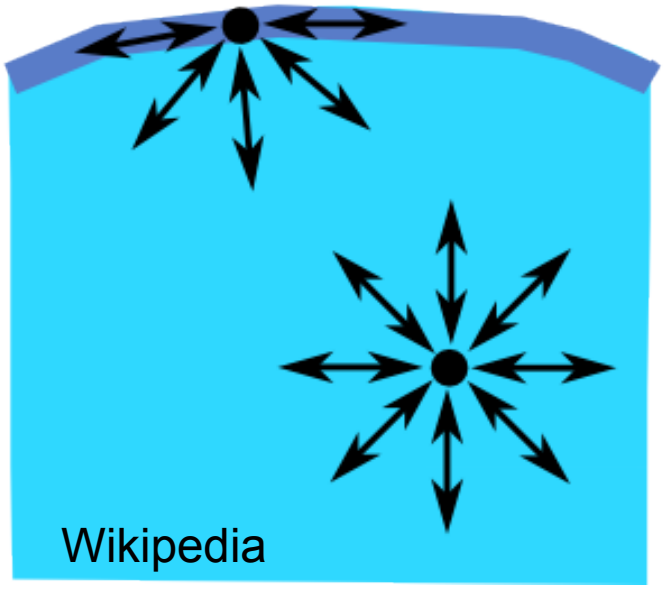
What specifies surface tension?

1) ONLY the adhesive interactions between individual cells?
2) or does cortical tension matter?

What is the role of geometry (cell shapes)?

Definition: surface tension

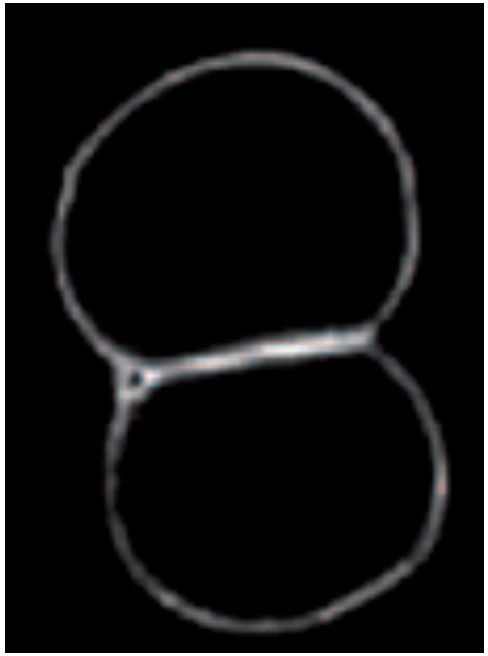
difference in mechanical energy (Δ W) between a surface cell and an interior cell, times the number of cells per unit surface area



$$\sigma = \left(\frac{\Delta W}{\text{per cell}}\right)\left(\frac{1 \text{ cell}}{\text{projected area}}\right)$$

Mechanical forces: coarse-grained on a single cell level

1. Cortical elasticity (passive) : actin networks
2. Active cortical tension: myosin motors (Joanny, Prost et al)
3. Surface adhesion: cadherins + associated actin network
4. Bulk effects: fluid resists dialation/ compression, cytoskeleton resists shear

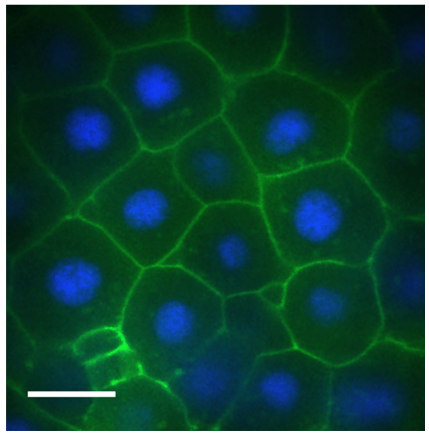


Devries et al, Development **131**, 4435–4445 (2004)

Coarse-grained energy: single cell

- Incompressible, so pressure is Lagrange multiplier

$$V = V_0, \quad (3D)$$
$$A = A_0, \quad (2D)$$



- Mechanical energy
  - sharp corners = elasticity negligible

$$W_{tot} = -\frac{\gamma P_c}{2} + \beta P_T \quad | \quad V = V_0$$

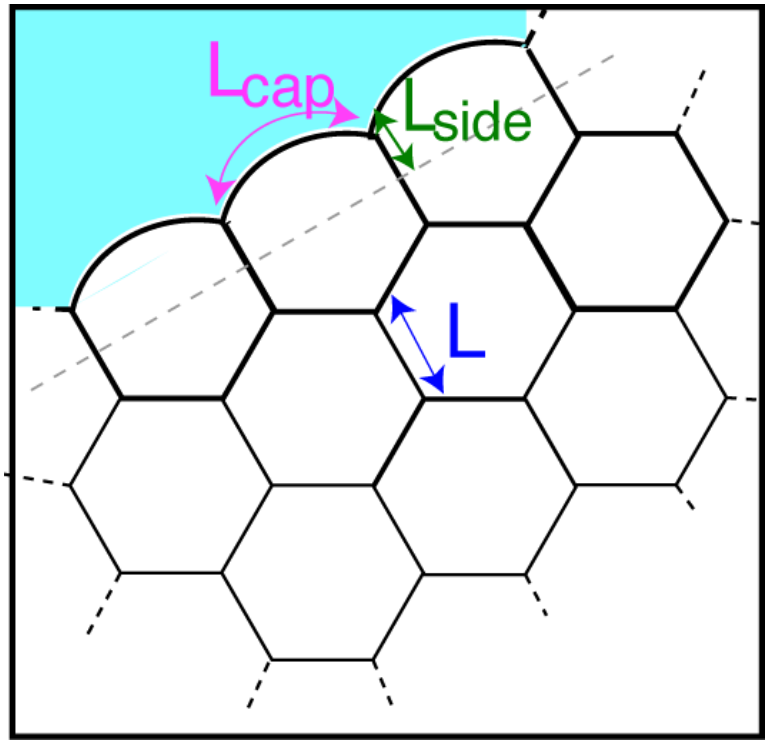
adhesion

cortical tension

incompressibility

Goal:

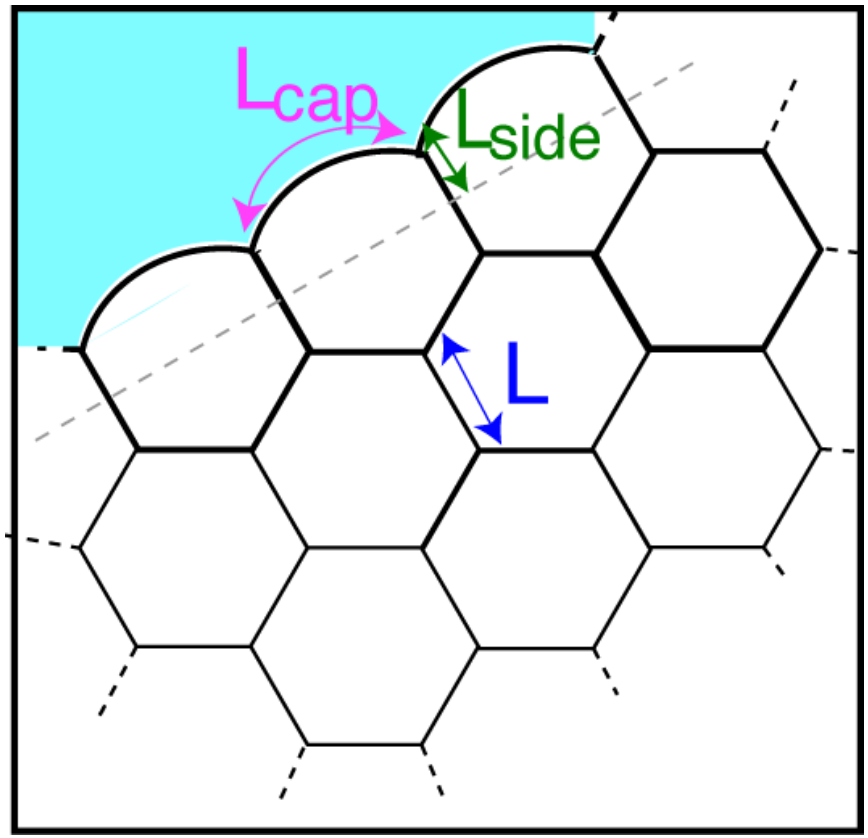
Find the global minimum energy shape for a collection of cells subject to constraints



- difficult in general
- begin with 2D ordered packing

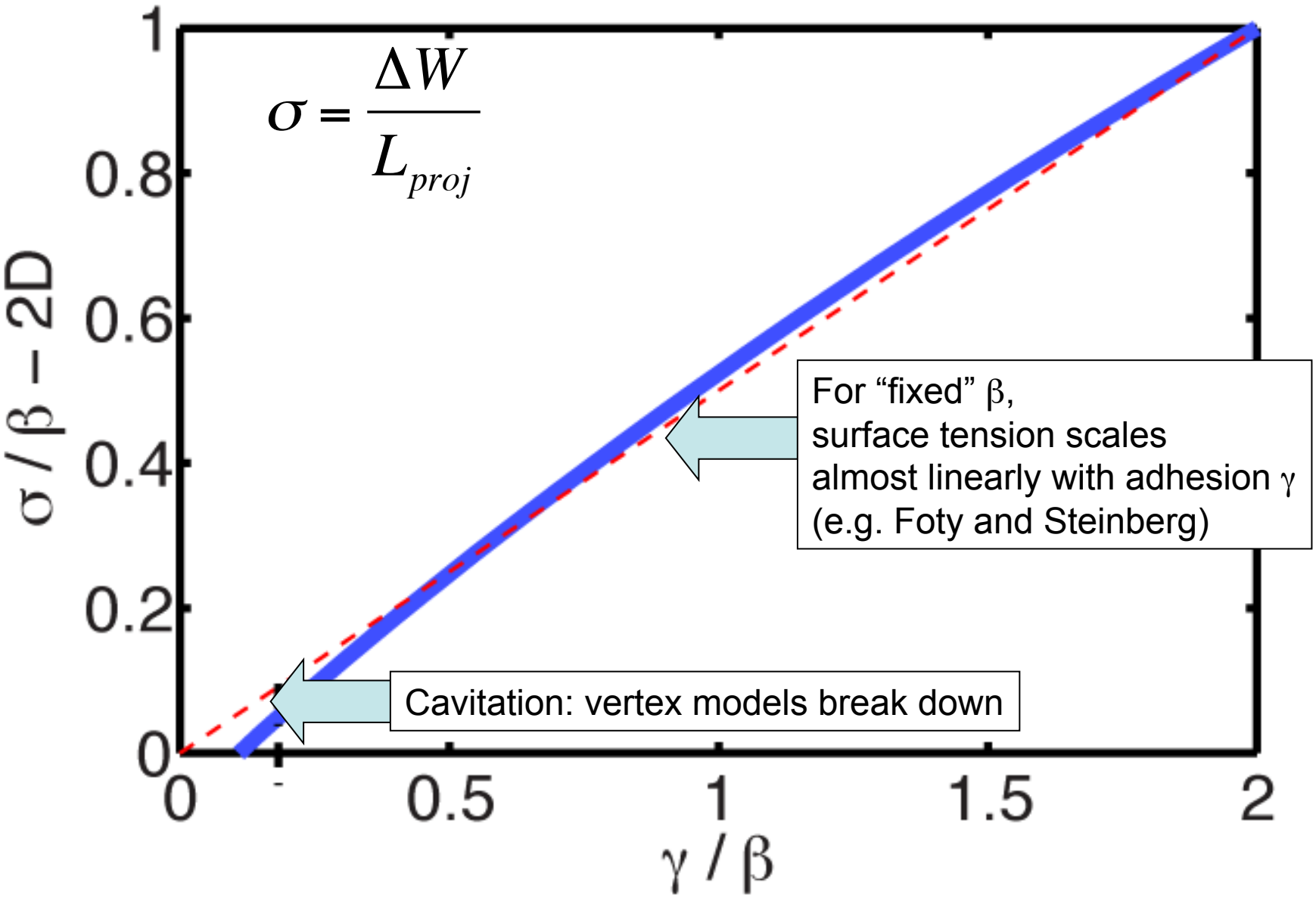
Exact solution:

- require force balance
- constant area constraint
- structure is completely parameterized by L_{side}



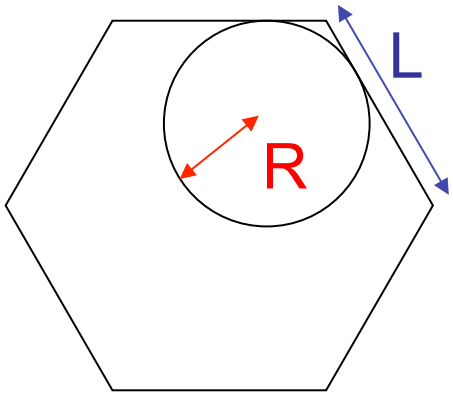
- no need for functional derivative; find minimum W(L) explicitly

Surface tension as a function of γ/ β

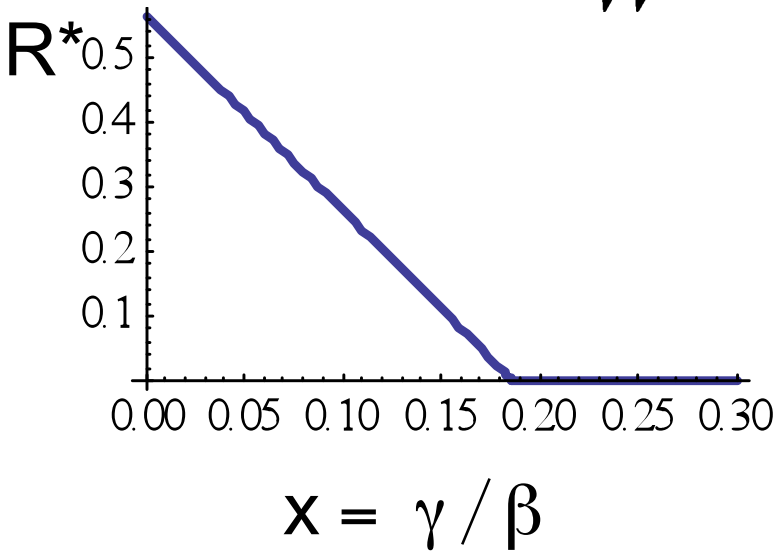


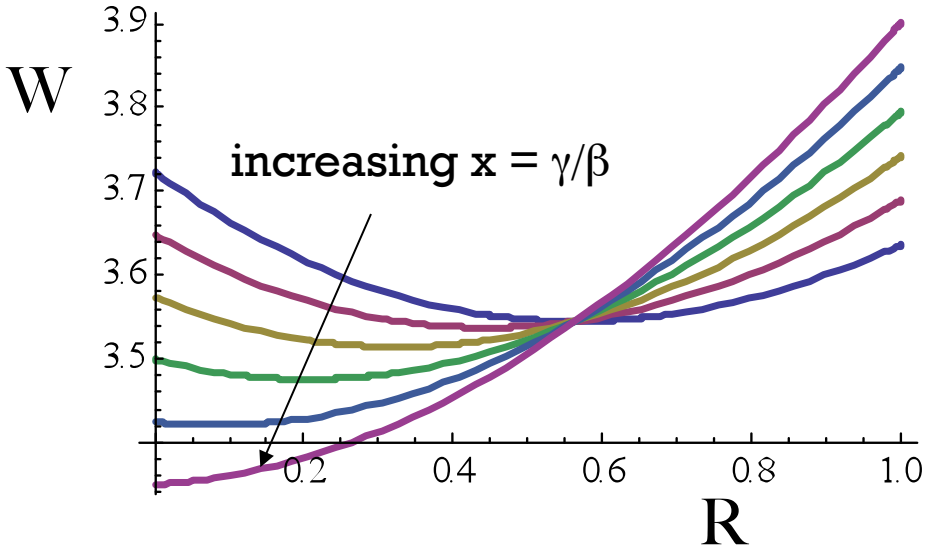
Cavitation transition

- Are minimum energy bulk cells truly hexagonal?
- Yes, for $\gamma / \beta < 0.186$

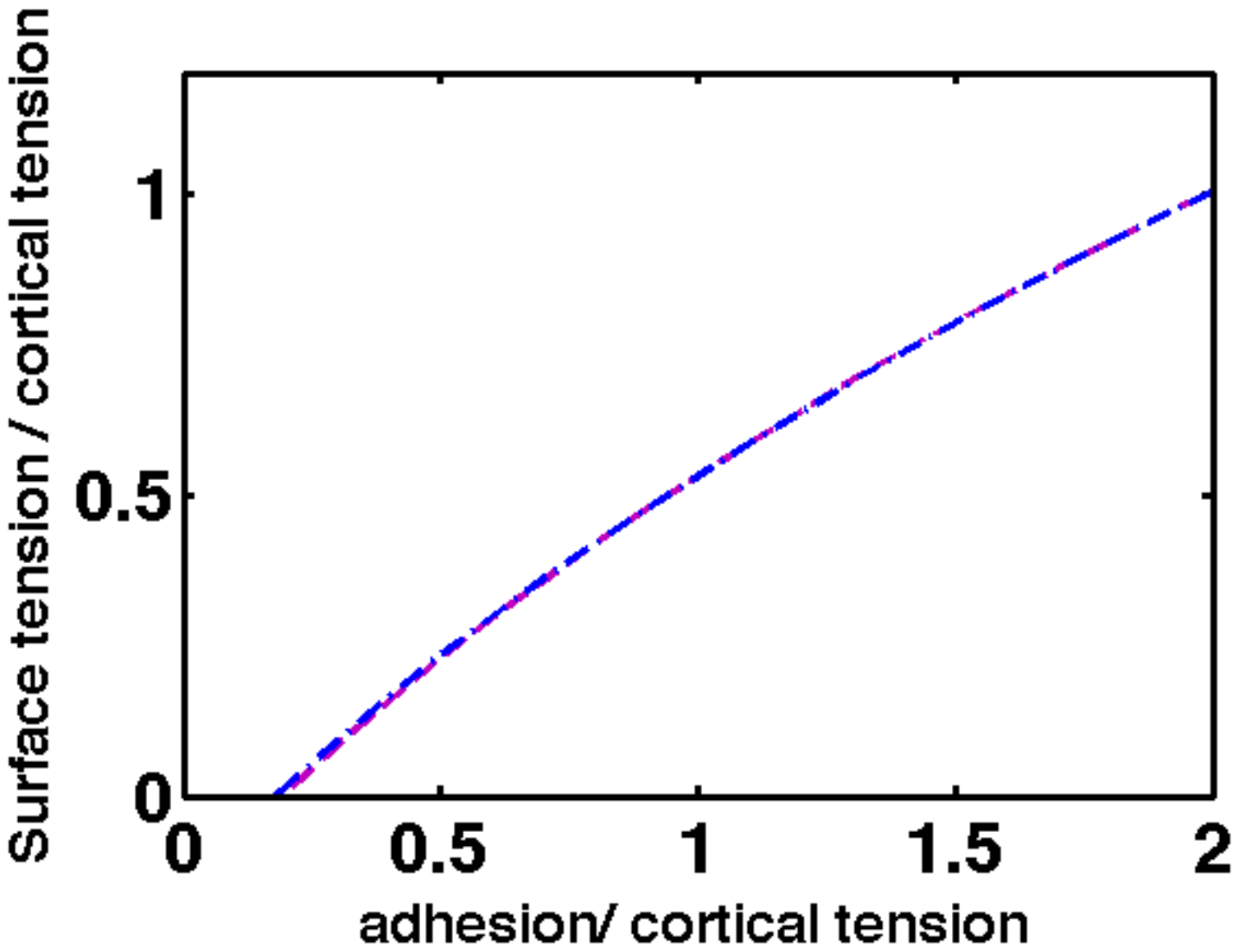


$$W = \alpha_1(x)R + \alpha_2(x)R^2 + \mathcal{O}(R^4)$$

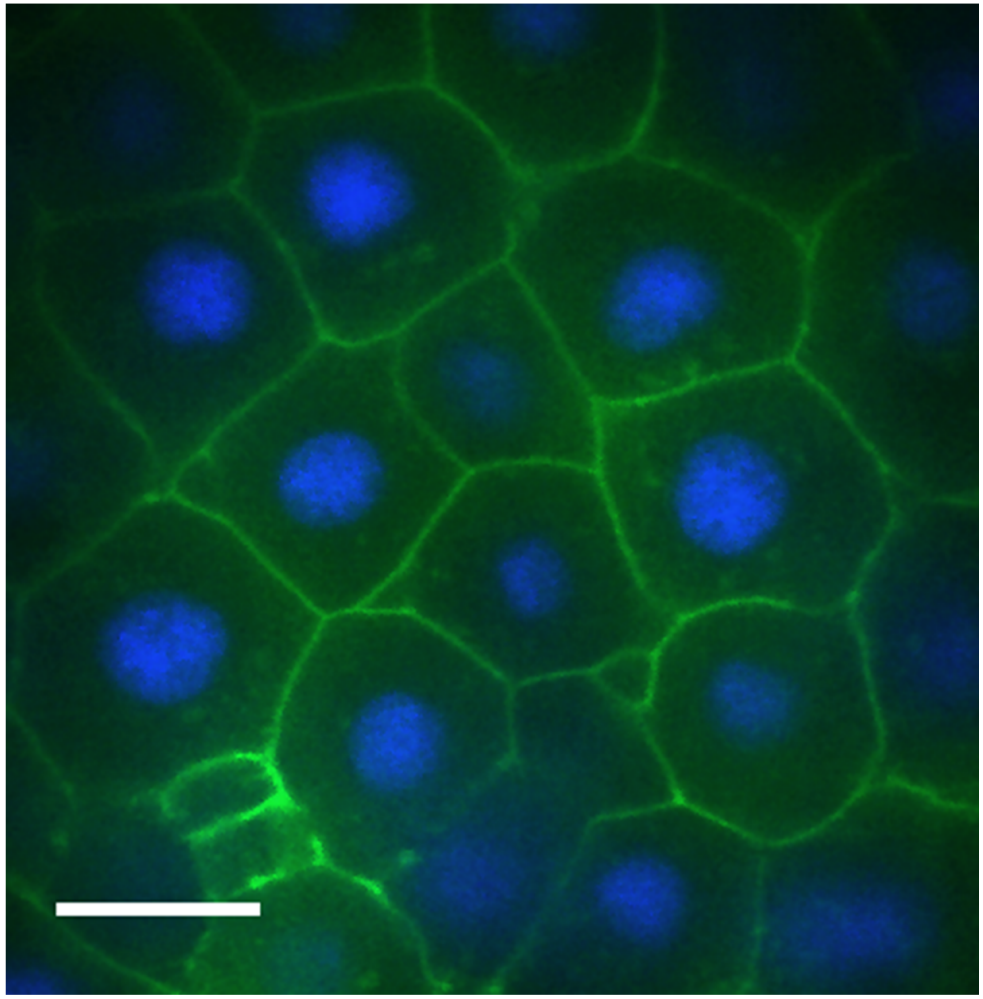




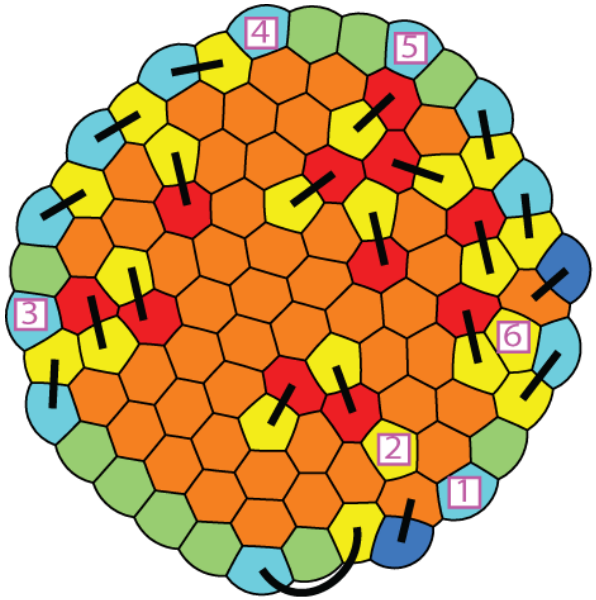
3D- ordered solution

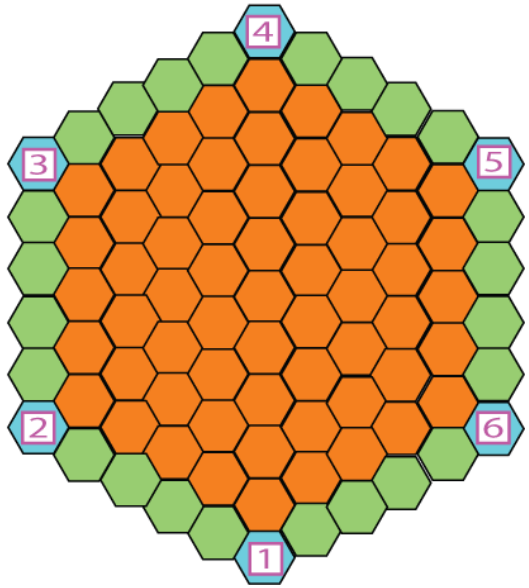


Real structures aren't ordered



disordered aggregates



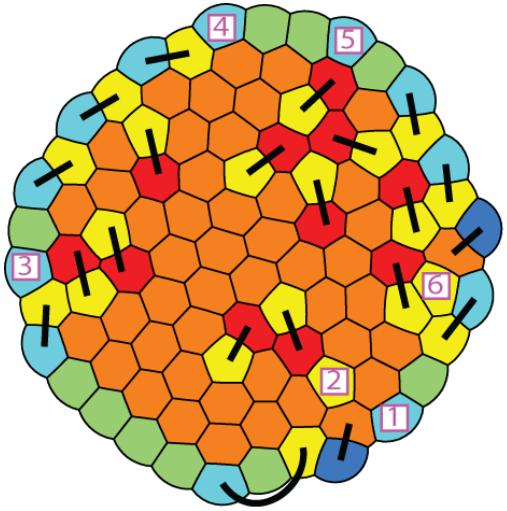


$$\sigma = \frac{\Delta W}{L_{proj}}$$

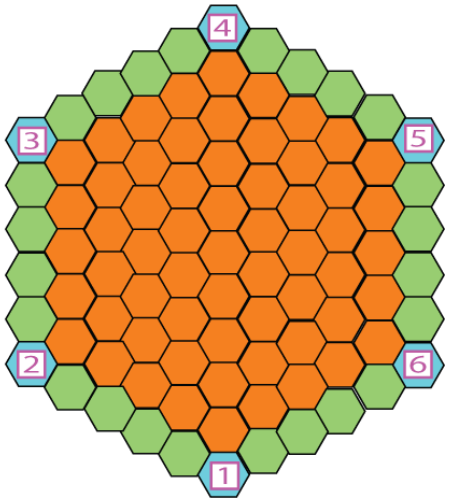
- In 2D, topology is constrained
  - 6 disclinations
  - many defect pairs
- Do defect pairs alter geometry (L_{proj}), energy (Δ W), or both?

Effects of disorder (2D)?

- disorder: voronoi tessellation of point pattern with g(r)~ nuclei locations
- Surface Evolver (Brakke): local minimum energy structures
- RESULT: for defect pairs, projected length changes much more than energy



Disordered – perimeter has circular symmetry

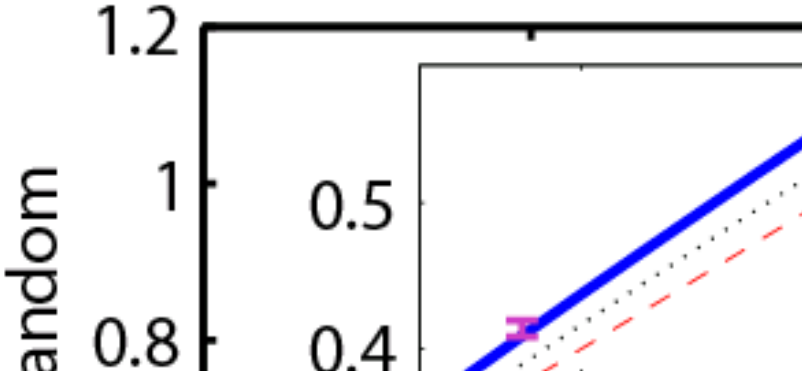


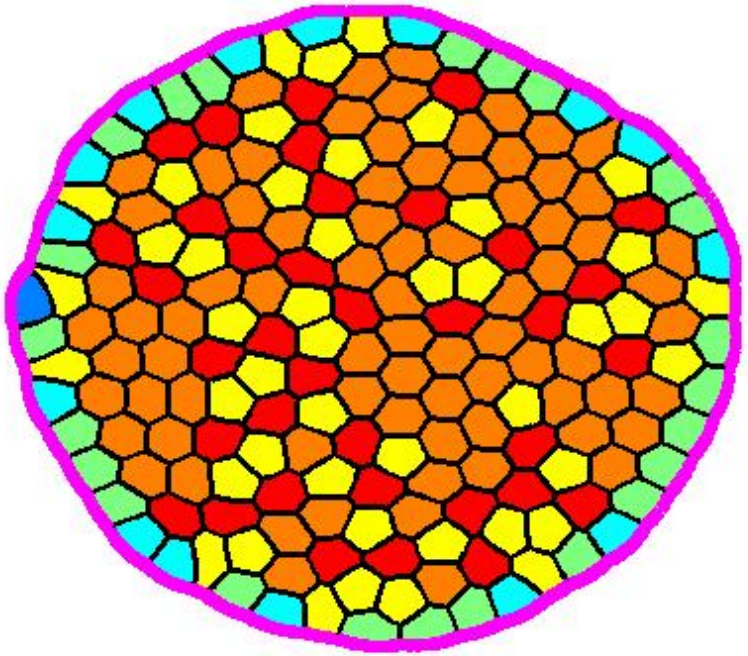
Ordered – perimeter is hexagonal

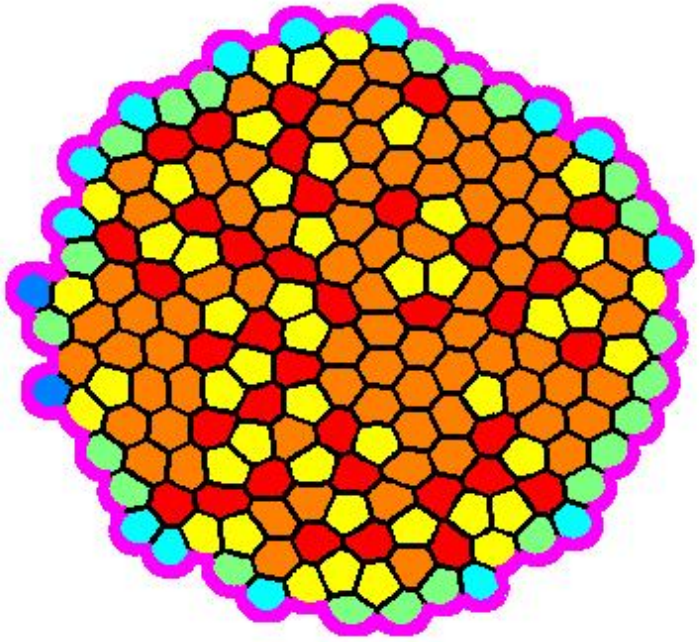
$$\sigma_{disordered} = \frac{L_{hex}}{L_{circ}} \cdot \sigma_{ordered}$$

$$\sigma_{disordered} \approx 1.05 \cdot \sigma_{ordered}$$

disordere







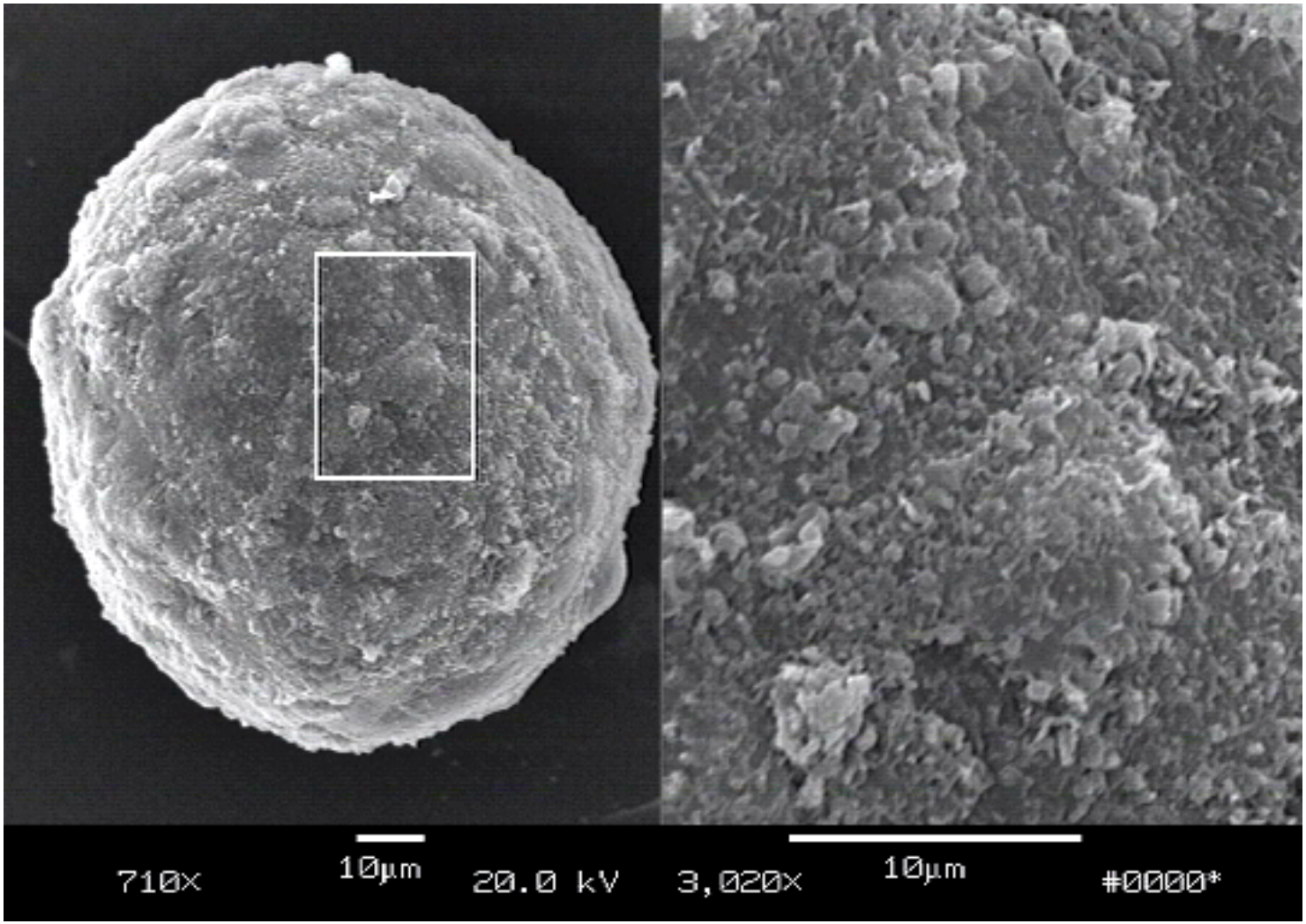
Dry foam: $\gamma/\beta \sim 1$

$$\sigma_{rand} = 1.05\,\sigma_{order}$$

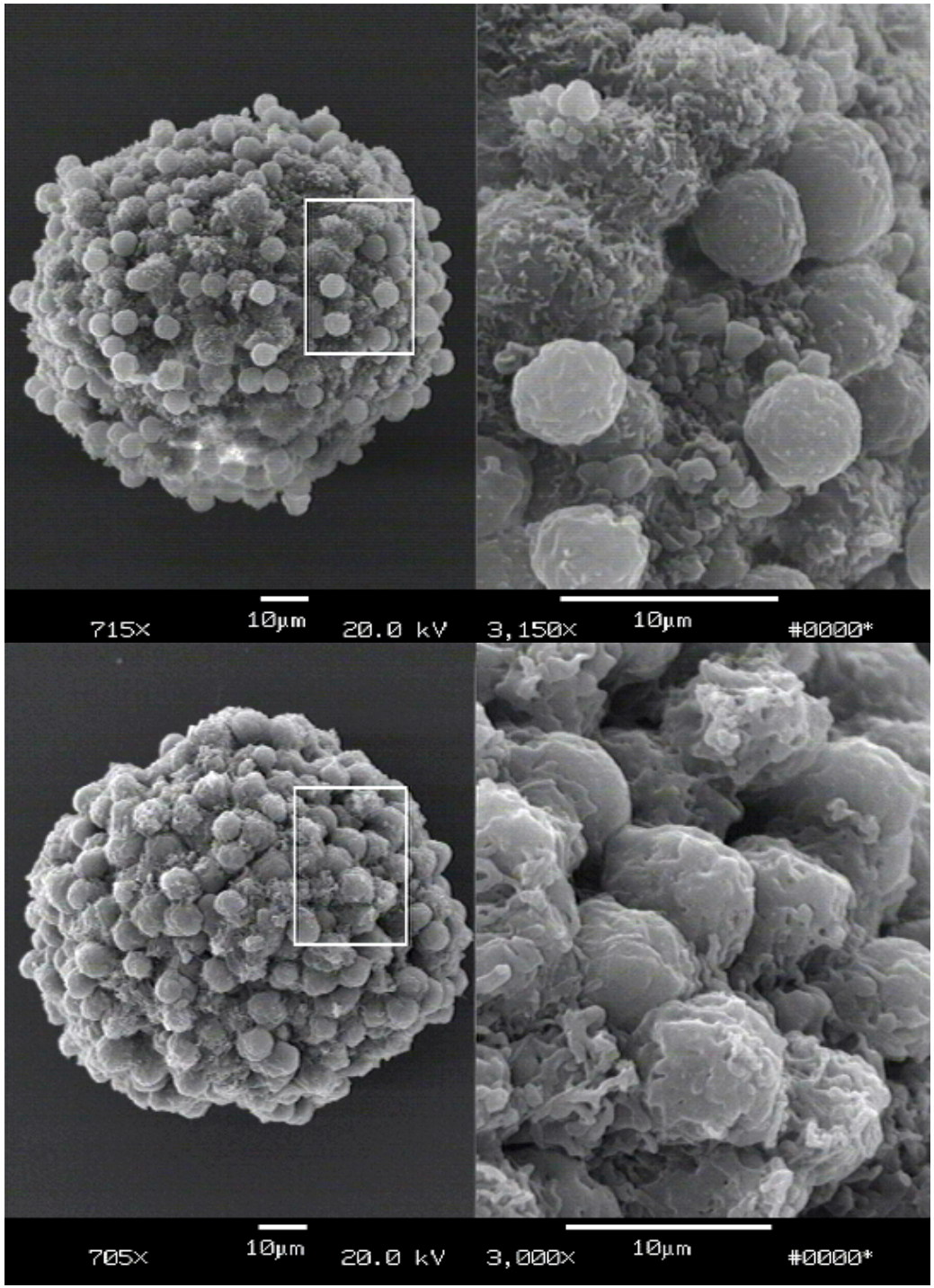
1.5 2

β

LP1 cells, SEM, high surface tension



Control:
$\sigma = 3.61$
erg/cm^2



Latrunculin A

(prevents g-actin from polymerizing)

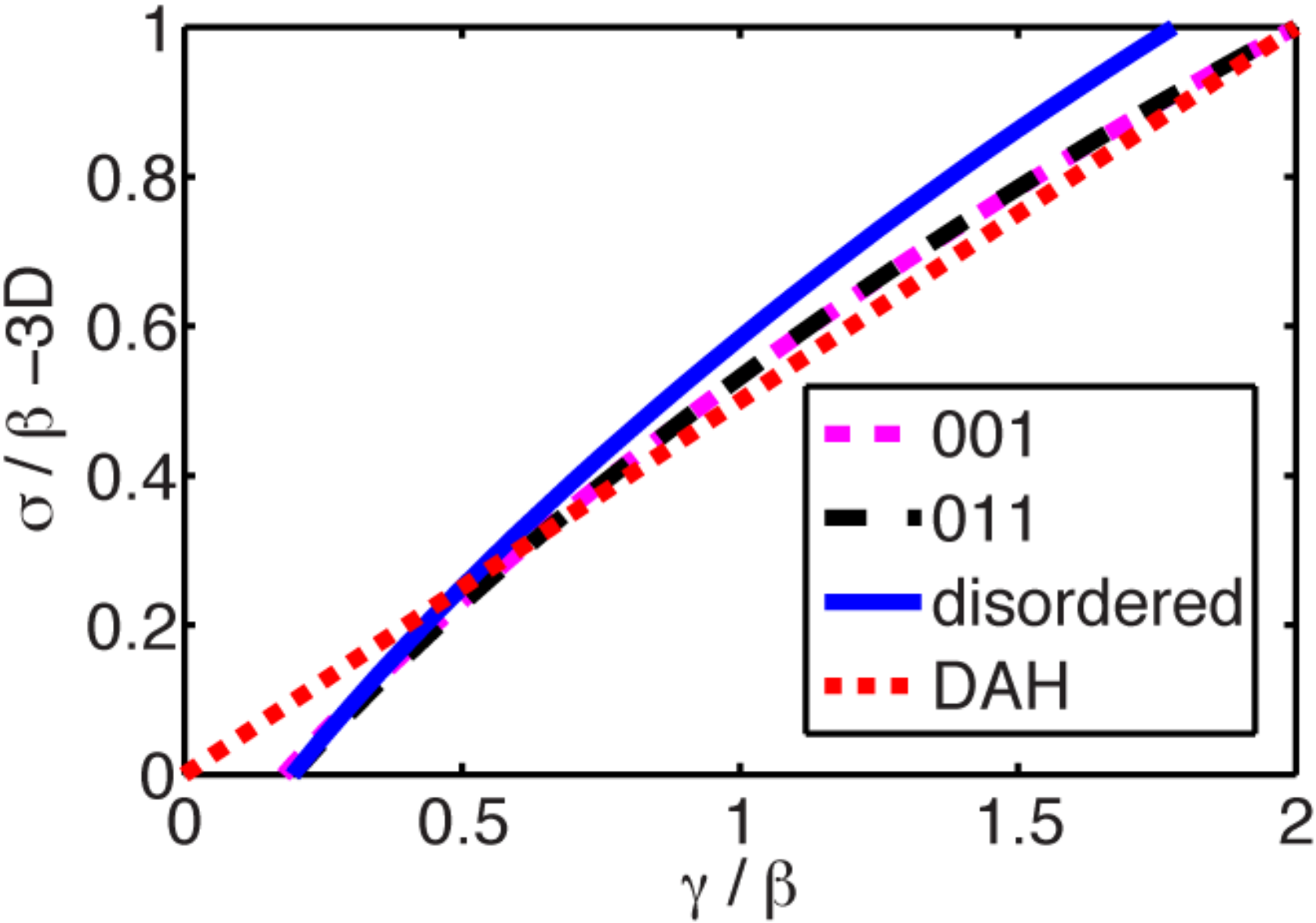
$\sigma = 0.15$ erg/cm^2

Cytochalisin D

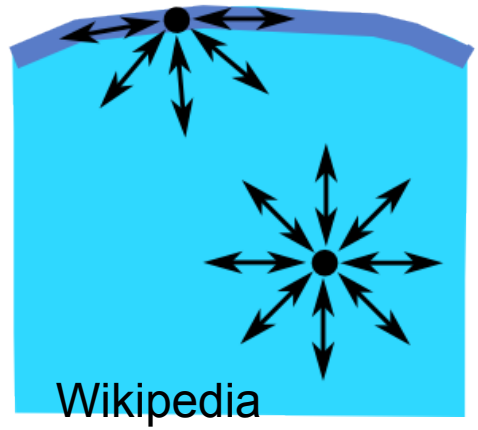
(caps growing end of actin filaments)

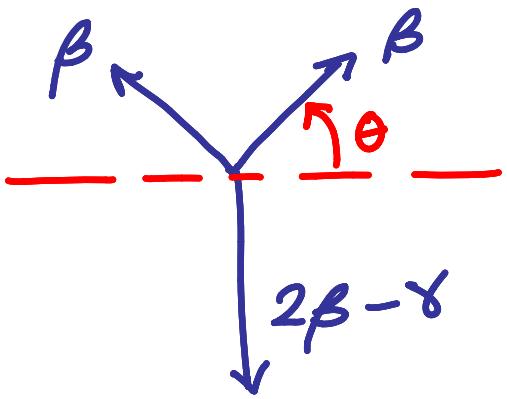
$\sigma = 0.31$ erg/cm^2

3D surface tension



- Like DAH:
  - cells get energy bonus for having adjacent neighbors
- Like DITH:
  - cells are not point objects and energy depends on shape
  - interfacial tensions differ
- Different from both:
  - account for cell shape changes due to both adhesion and cortical tension
  - bottom line: DAH mostly right



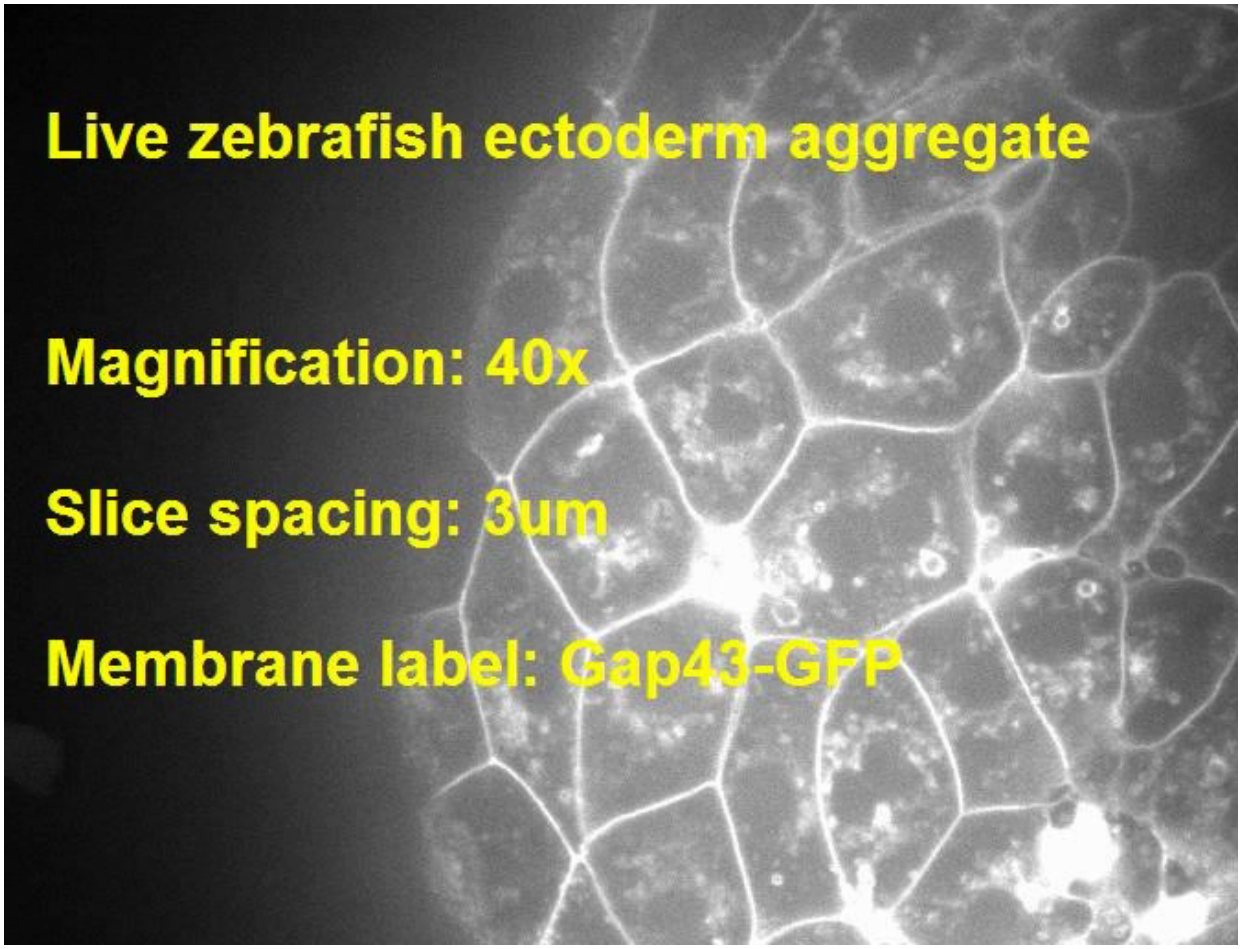


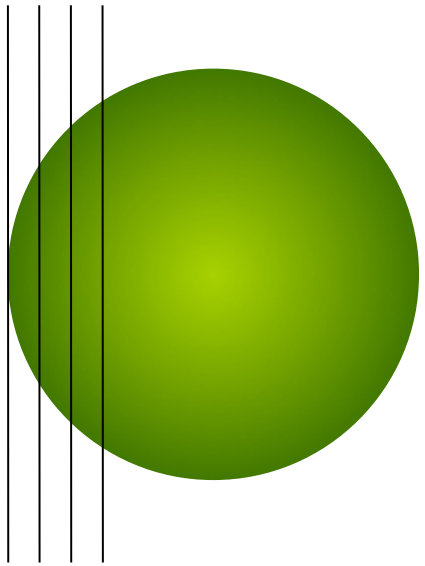
Manning, Foty, Steinberg and Schoetz.
PNAS 1003743107 (2010)

not the end of the story. . .

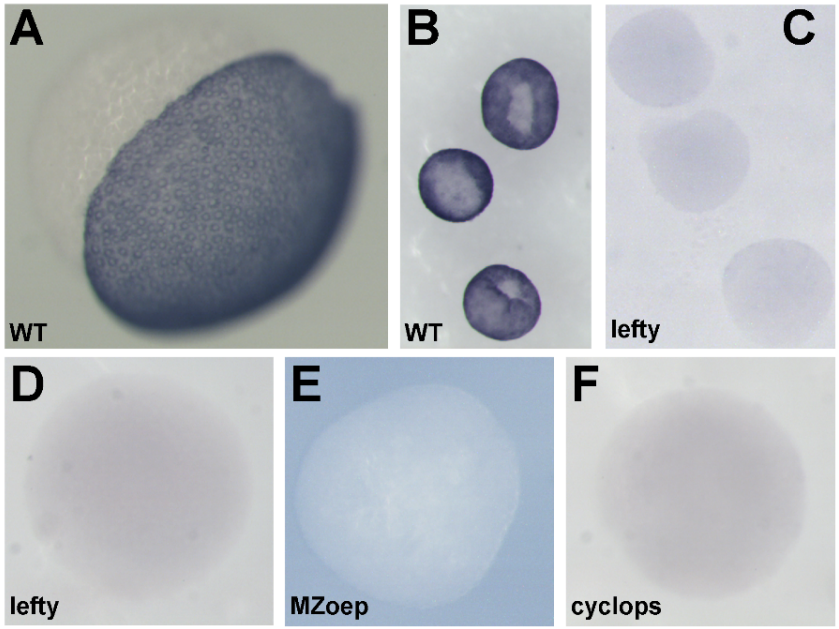
interesting surface cell morphology

For high tension aggregates, surface cells are surprising

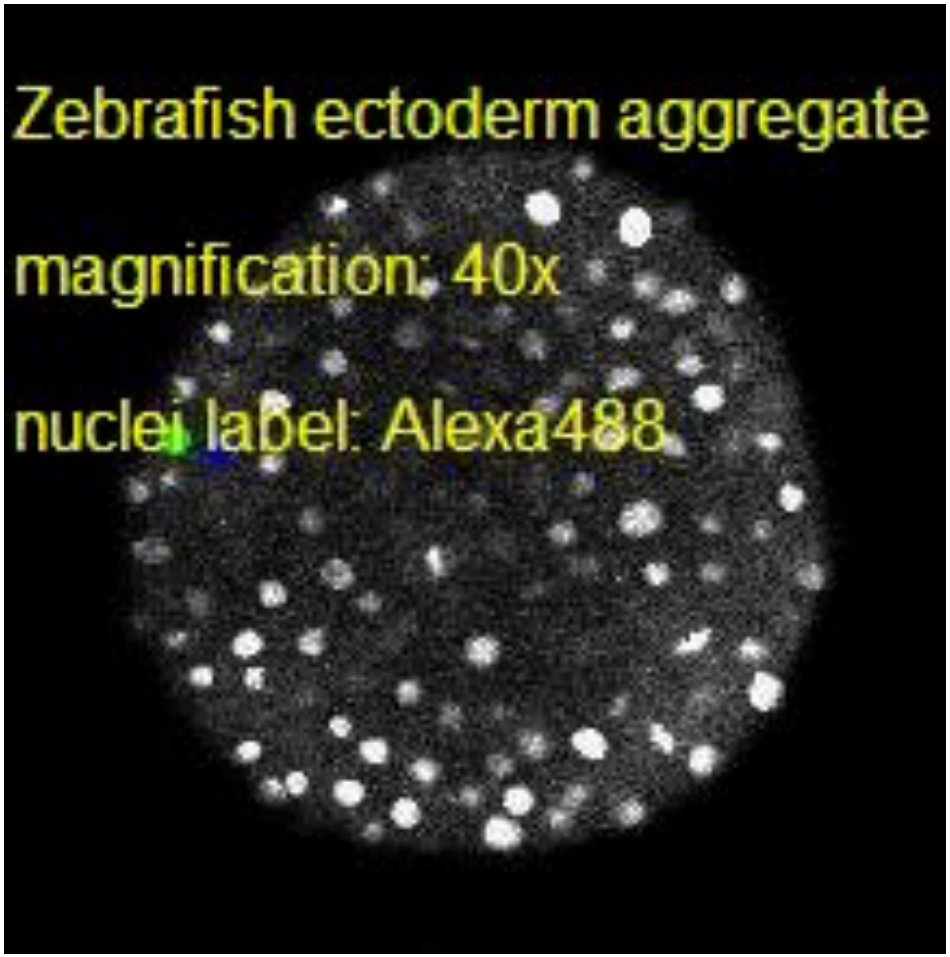




surface cells not differentiated

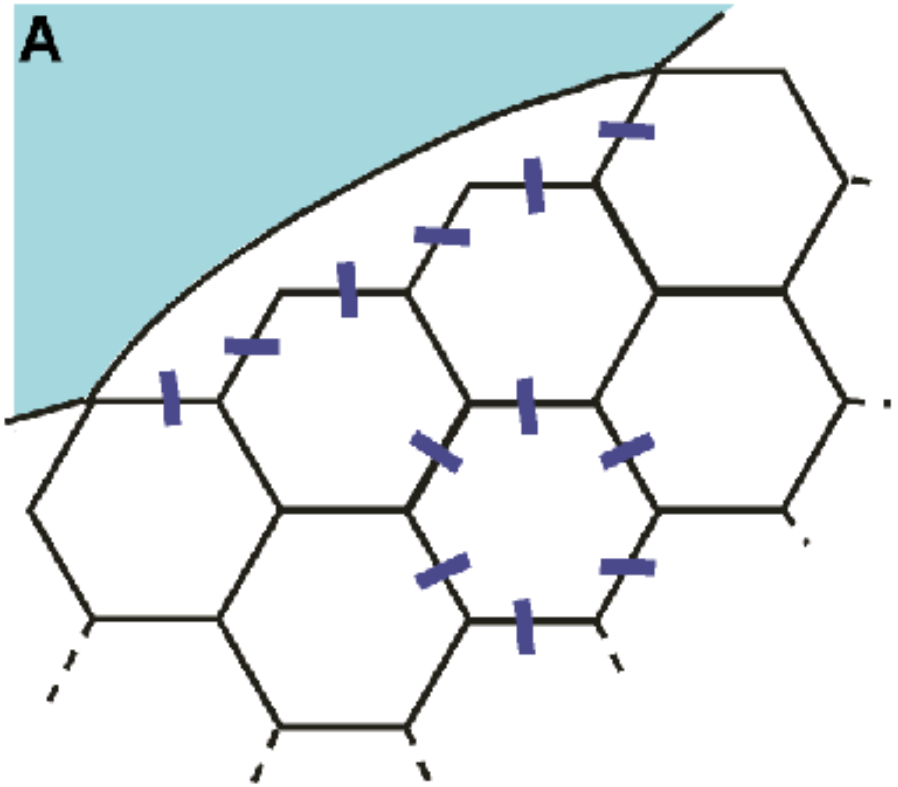


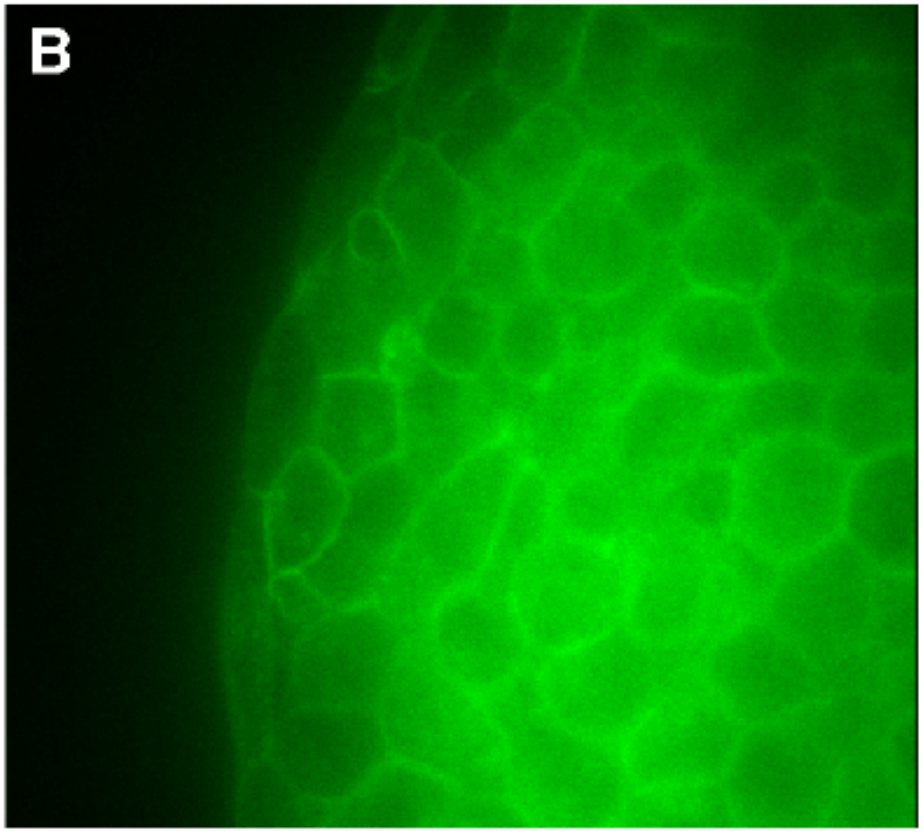
No epithelial markers in aggregates



Surface and bulk cells exchange places

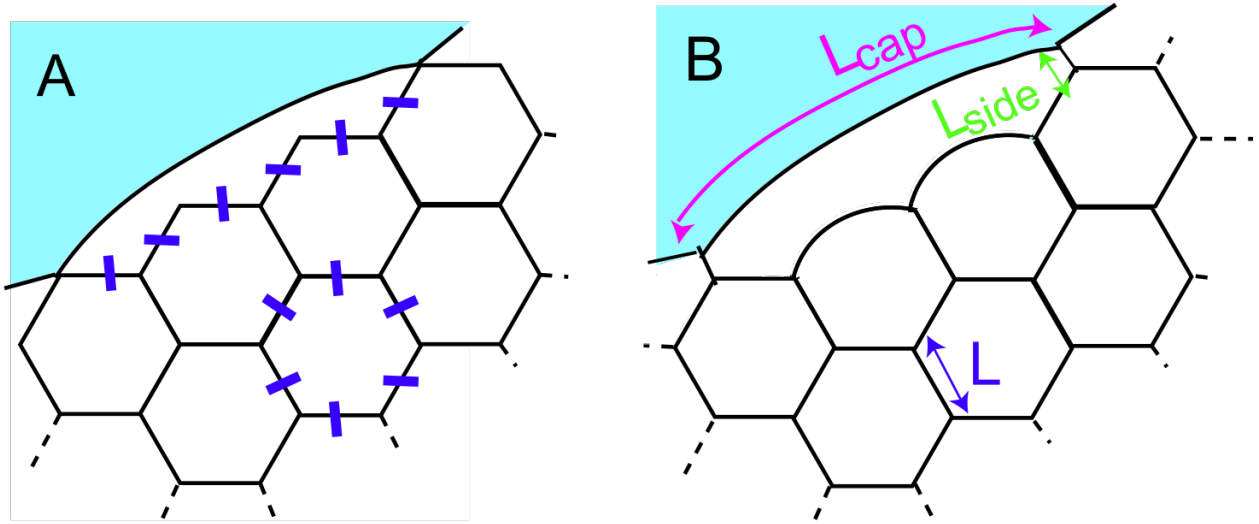
Intuitive idea:





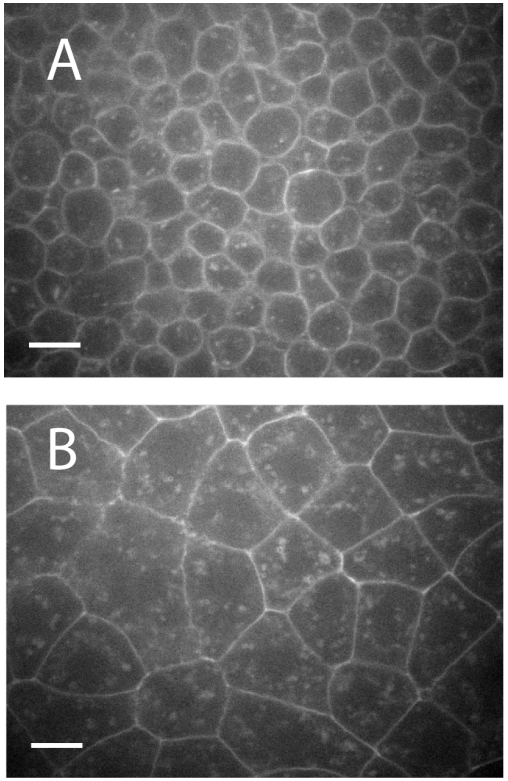
If adhesive energy is much larger than other energies, surface cells spread out to make surface area the same as in the bulk

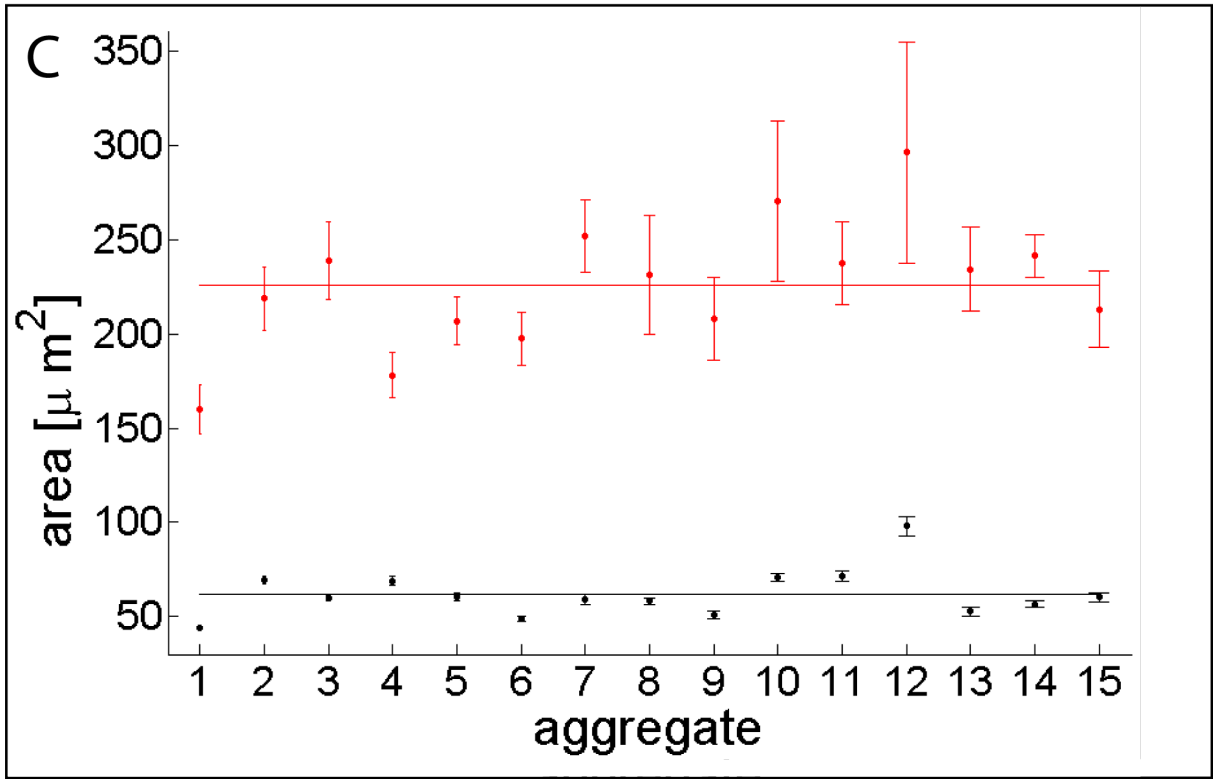
How far do cells stretch?



- Are surface cells making same area of contact as bulk cells?
- Calculate "projected area" for this case:
  - 2D ordered packing: surface cells must cover 3 cells below.
  - 3D ordered packing (2 facets): 3.7

Data:





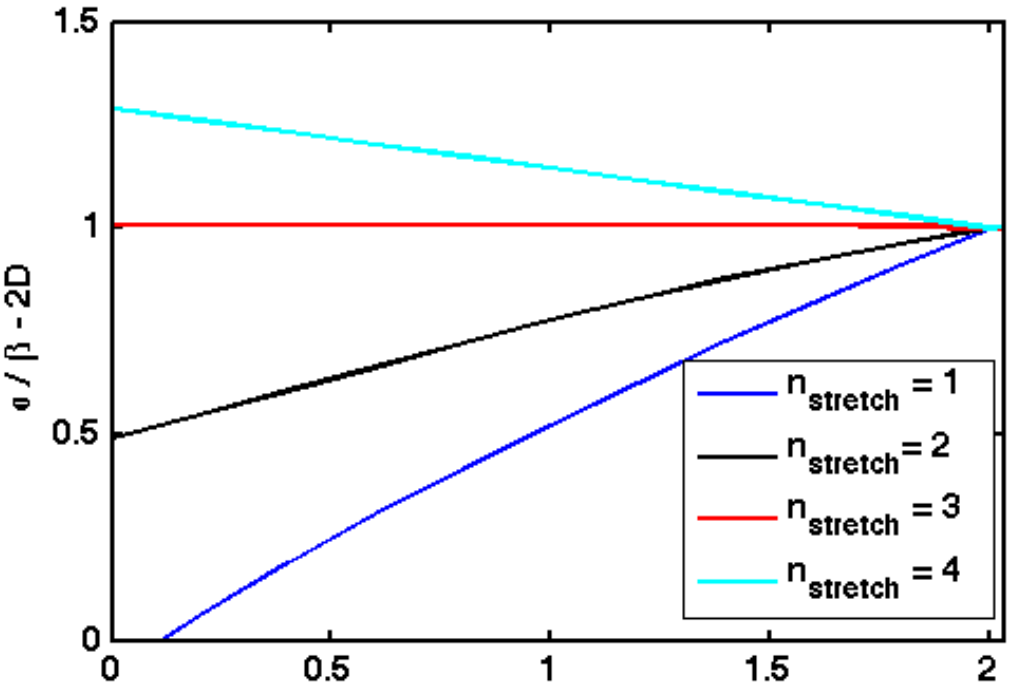
Surface cells have projected areas

3.7 ± 0.4 times greater than interior cells

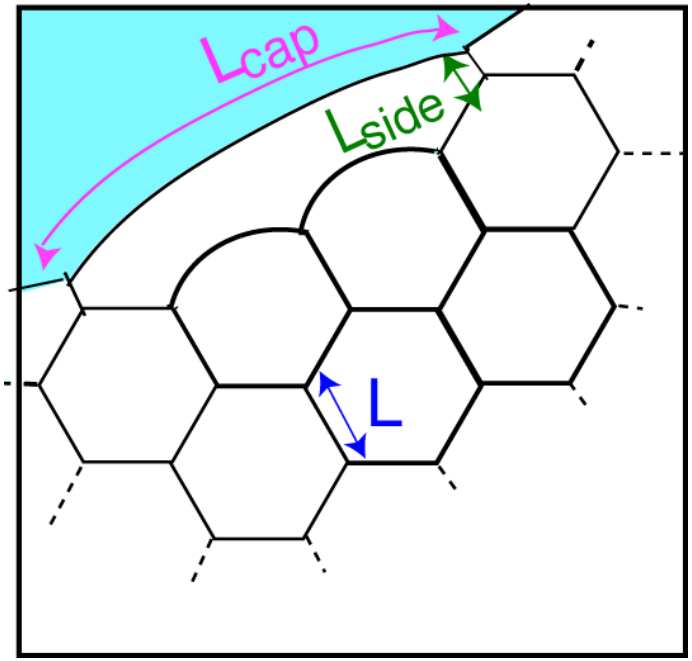
Model independent observation:

- DAH: just as in fluids, surface cells make fewer neighbor contacts
- If surface cells stretch to make the same contact surface area as bulk cells, then there is no difference in their number of adhesive contacts
- In this regime the DAH, as stated, can not be correct.

Can a minimal model explain these observations, predict surface tension?



adhesion/ cortical tension



nstretch = 3

Current model: stretched cells have higher surface energy, should not occur often!

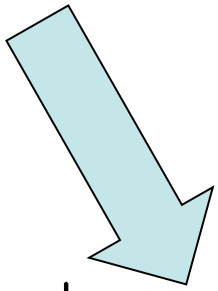
What happens when adhesion is large ($\gamma/2 > \beta$)?

$$W_{tot} = -\frac{\gamma P_c}{2} + \beta P_T \quad | \quad V = V_0$$

- instability in the bulk, dW/dP < 0
- of course, second order terms could provide restoring force

Restoring forces?

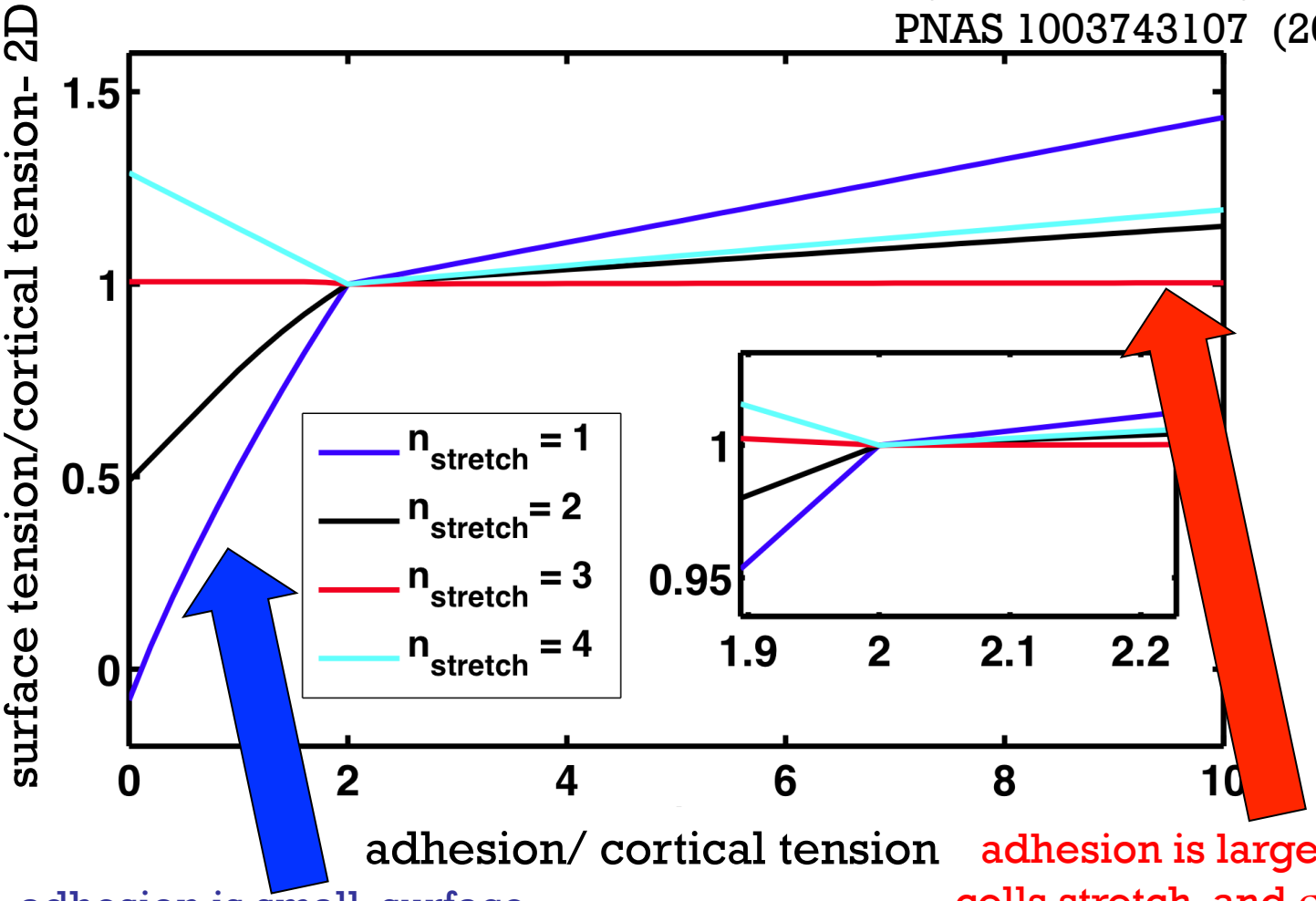
- Adhesion molecule regulation
  - adhesive energy per cell bounded
  - restricts contact area
- Cortical elasticity
  - cortical network more dense near contacts



$$W_{tot} = -\frac{\gamma P_c}{2} + \beta P_T + \alpha P_c^2 \quad | \quad V = V_0$$

surface tension

Manning, Foty, Steinberg and Schoetz.
PNAS 1003743107 (2010)



adhesion is small, surface cells compact and DAH holds (Foty + Steinberg?)

adhesion is large, surface cells stretch, and σ depends on cortical tension (Krieg et al?)

Conclusions

- Confocal images + AFM suggest that adhesion and cortical tension dominate cell-cell mechanics in aggregates
- Using this as a minimal model, we develop method to calculate exact solutions for ordered structures
  - surface tension increases with ratio b/w adhesion and cortical tension
  - DAH approximately satisfied

Conclusions

- Surprisingly, disordered structures are related to ordered structures in simple way
- For very high adhesion aggregates, surface cells are stretched
  - DAH can not hold in this regime
- If adhesion > cortical tension, a simple restoring force can explain stretched structures and crossover to strong dependence on cortical tension

Manning, Foty, Steinberg and Schoetz.
PNAS 1003743107 (2010)

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Funding:
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Future directions

- explanation for “large” surface tension compared to adhesion energies
- laser ablation to study line tensions
- study interfaces between two tissue types
- dynamics!

thanks for your attention!

Surface energy of foams?

- **Fortes and Rosa** J. Coll. and Interface Sci. **241**, 205-214 (2001)
  - parameterize crystal surface by angle θ
- **But, wrong answer for ordered foam!**

Fortes and Rosa

$$\sigma_{max} = \frac{2E}{\sqrt{3}a}$$

$$\sigma_{min} = \frac{4E}{3a}$$

$\neq$

Actual

$$\sigma_{max} = \frac{2E}{\sqrt{3}a}$$

$$\sigma_{min} = \frac{3E}{2a}$$

- **Random foam: average over θ (Is this right?)**

$$\sigma = \frac{E}{a}\int_0^{\pi/6} \frac{4\cos\theta}{3} d\theta \sim 0.55\beta$$

Numerical results:

γ/β	σ	$\%\Delta l_{proj}$	$\%\ \Delta W_{surf}$	$\%\ \Delta W_{int}$
0.33	0.147 ± 0.004	-9.2 ± 3.3	-0.2 ± 0.2	0.1 ± 0.2
0.75	0.414 ± 0.006	-8.4 ± 3.6	-0.4 ± 0.6	0.1 ± 0.2
1.0	0.553 ± 0.006	-7.9 ± 3.7	-0.7 ± 0.9	0.1 ± 0.2
1.5	0.795 ± 0.005	-7.6 ± 2.9	-2.4 ± 1.4	0.1 ± 0.2
1.66	0.868 ± 0.004	-7.7 ± 2.8	-3.6 ± 1.6	0.1 ± 0.2

- for small γ/β: different L_{proj}, same W
- break symmetry: macroscopic perimeter changes from hexagon to circle
- simple ansatz:

$$\sigma_{disordered} \sim (P_{hex}/P_{circ})\ \sigma_{ordered}$$
$$\sim 1.05\ \sigma_{ordered}$$