Computing structural and dynamic properties of biological systems at multiscale

4. Cell patterning

Jie Liang 梁杰

Dept. of Bioengineering

University of Illinois at Chicago

Cell pattern development and tissue growth:

How does local behavior of individual cell in division, orientation, and cell-cell interaction lead to formation of global tissue pattern?

Outline

1. Cell models

2. Regulation of cell topology

3. Regulation of tissue elongation

4. Wound healing

Background

- **Epithelia:**

  — Tightly adherent cells found on both internal and external surfaces of tissue

- **Proliferating epithelia:**

  — Continually dividing epithelia

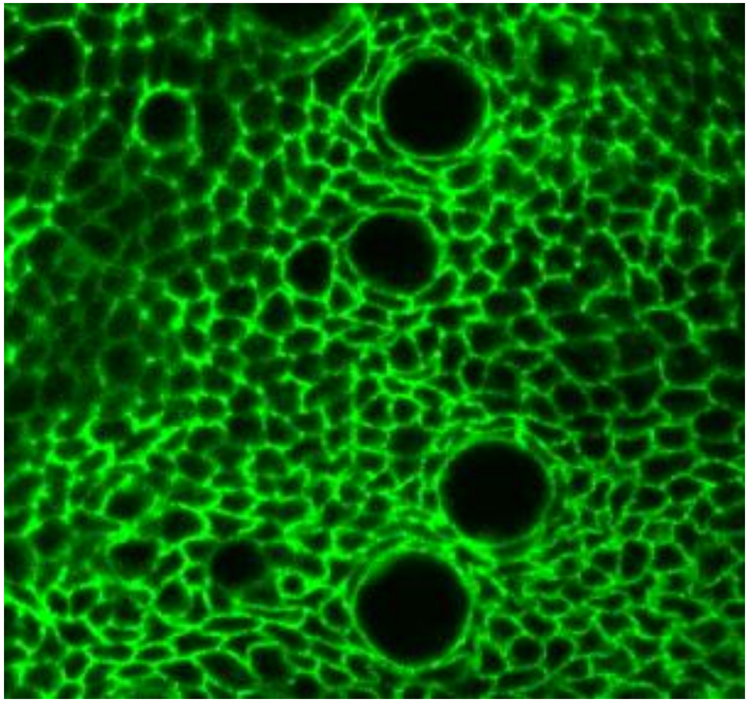
- **Epithelial morphogenesis:**

  — A fundamental component of development, organogenesis, and

  disease progression

- **Morphological properties:**

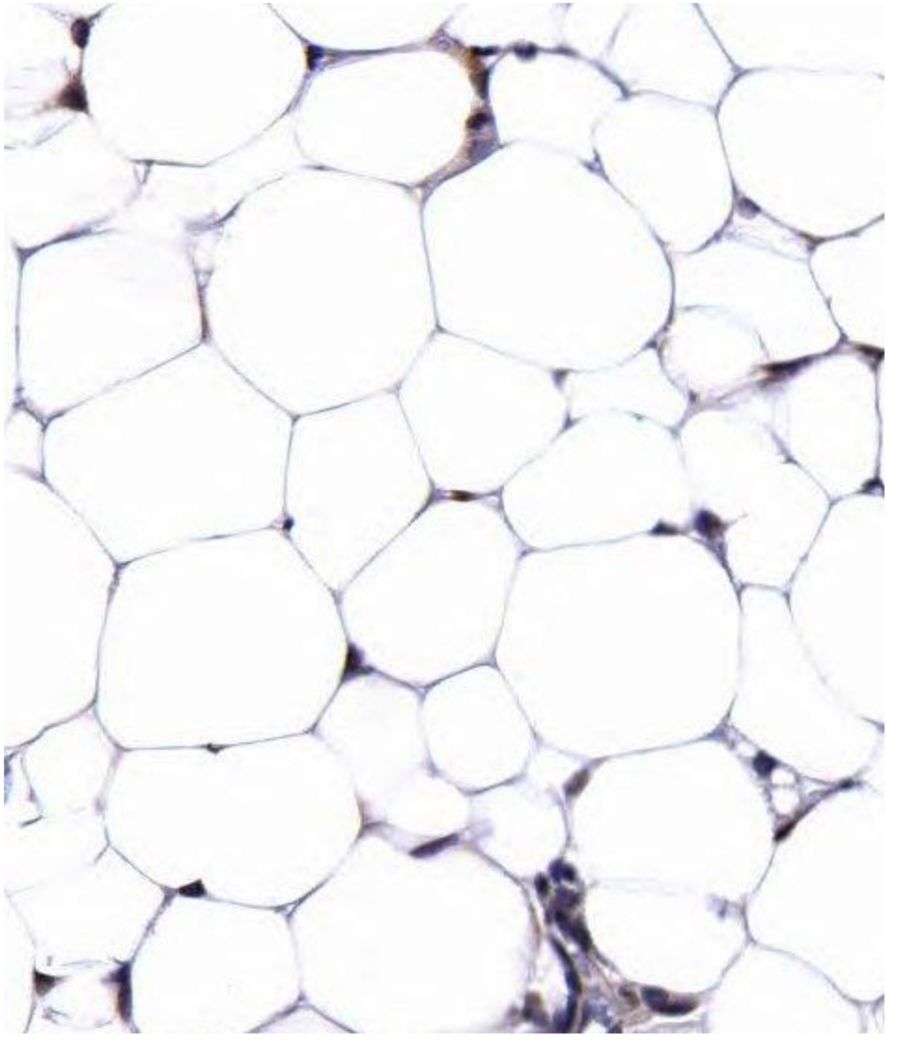
  — Dominance but varied amount of hexagonal cells in both animals and plants



Gibson,M.C. et al., Nature, 2006

Cell Model

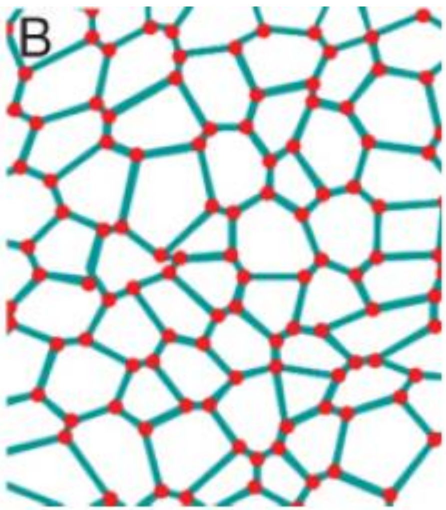
- Cellular automata and lattice model:
  - Ignore cell shape and size
- Finite element model:
  - No dynamics: cells cannot grow
  - Inflexible boundary conditions
- Our goal: more realist model of cell dynamics

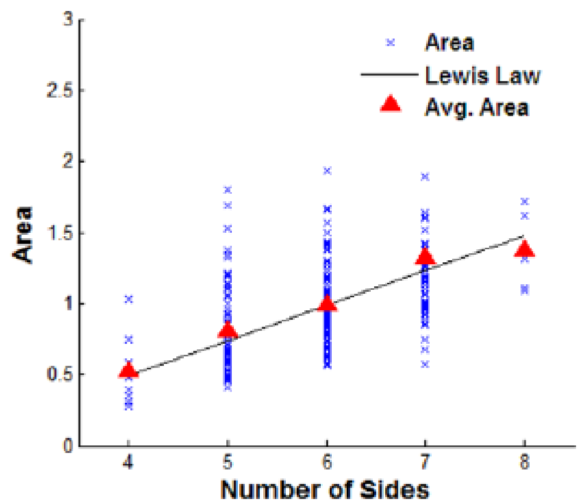


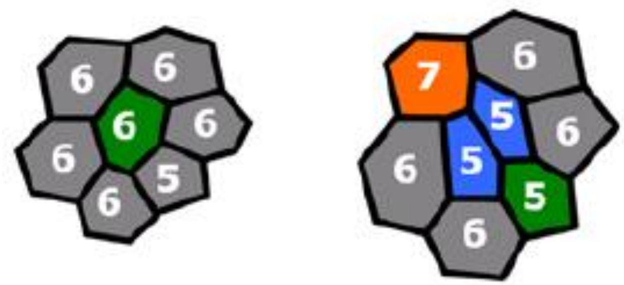
Lypocytes, courtesy of Prof. Kun Huang, OSU

Cell Geometry and Topology

- Cell geometry: cell shape, area, edge length, angle degree,
- Cell topology: connectedness between cells, *n*-sidedness,







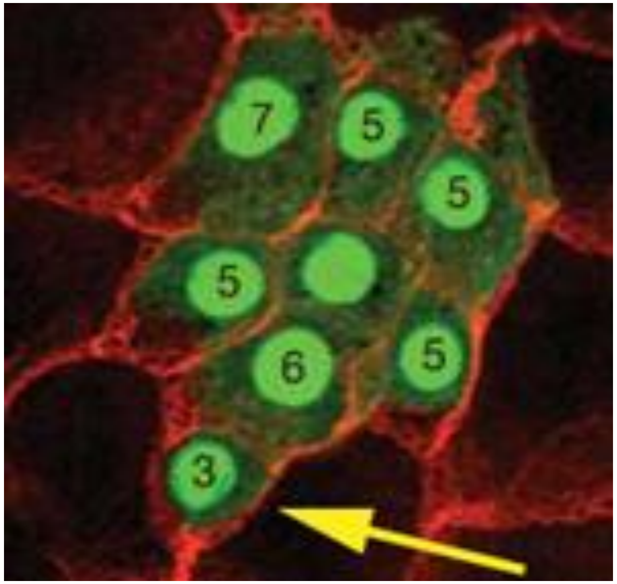
Nagpal & Gibson, Bioessays, 2008

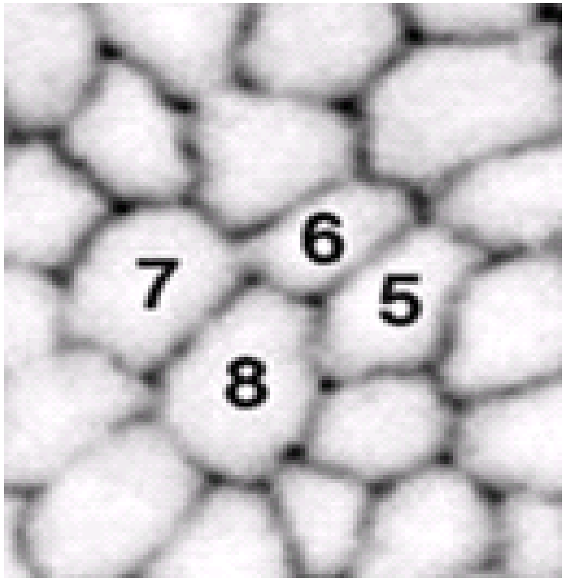
Patel et al., PLoS Comput. Bio, 2009

Mechanism of Regulating Cell Topology in Proliferating Epithelia

- Divisiton Plane
- Mechanical Forces
- Cell Memories

Problem





- **Experimental Observation:**

— Clones of proliferating cells bounded by quiescent cells had fewer sides than natural epithelial cells.

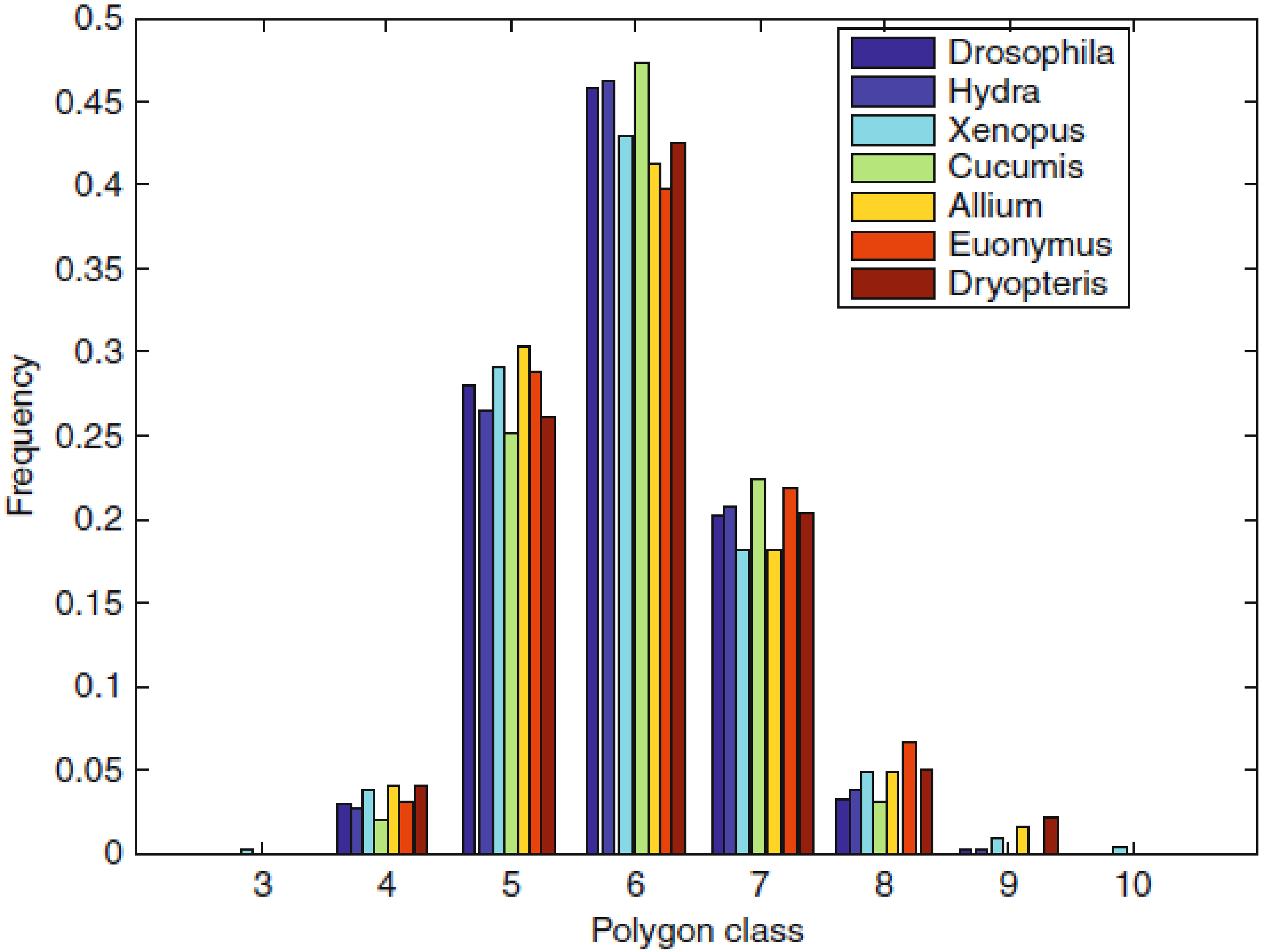
— Clones of proliferating cells (left, green).
— Quiescent cells (left, red).
— Natural proliferating cells (right).

Gibson,M.C. et al., Nature, 2006

- **Questions:**

— Does the reduced mean value of sides result from differential proliferation?

Topological Distribution of Epithelia



Gibson et al., Curr Top in Dev Biol, 2009

Previous models

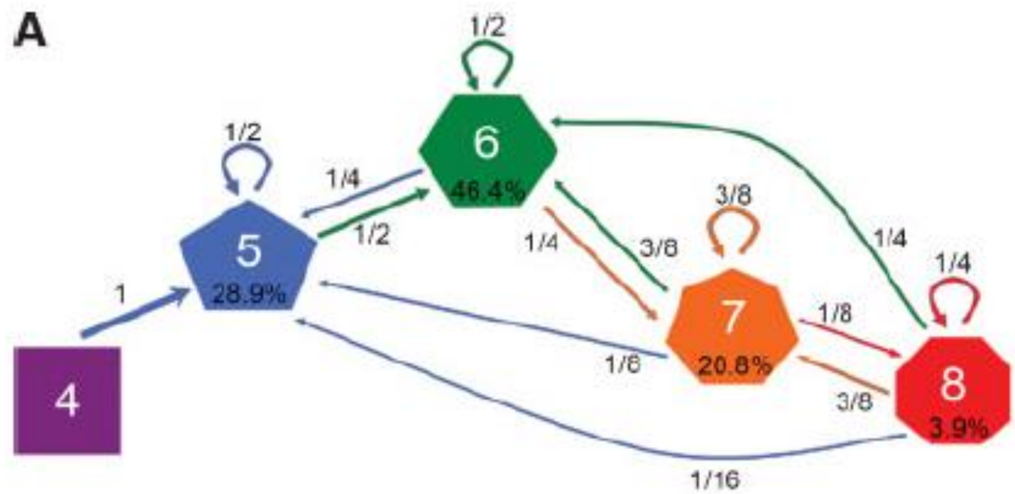
- **Theoretical hypothesis by topological model:**
  — **Differential proliferation should predict distorted local topology.**

(Gibson et al., 2006)

- **Limitations:**

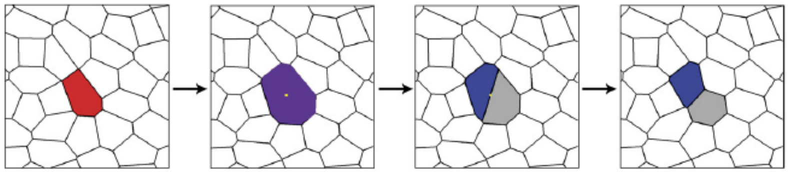
  — **No quantitative analysis on the effect of differential proliferation.**

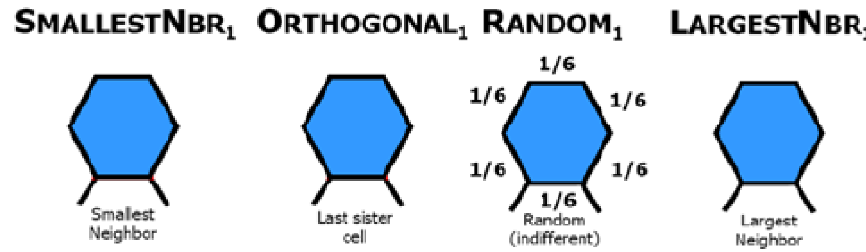
  — **No consideration of biological and physical properties.**
  — **Tension**
  — **Pressure**

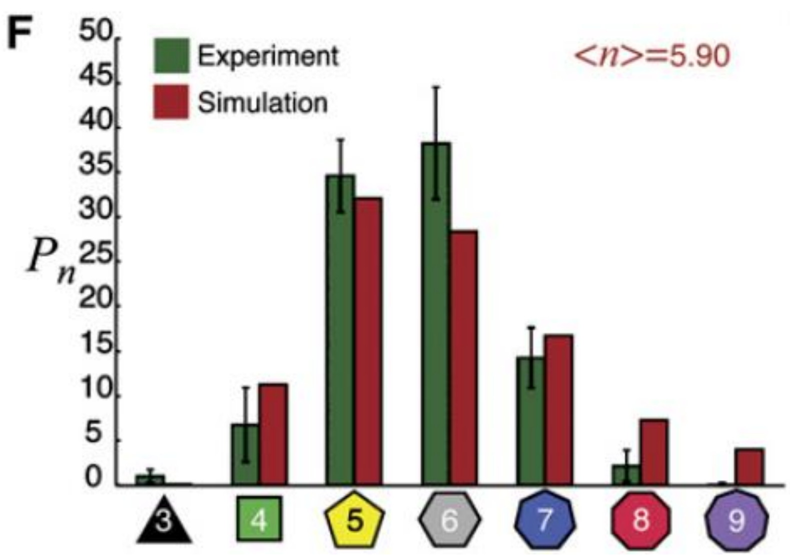


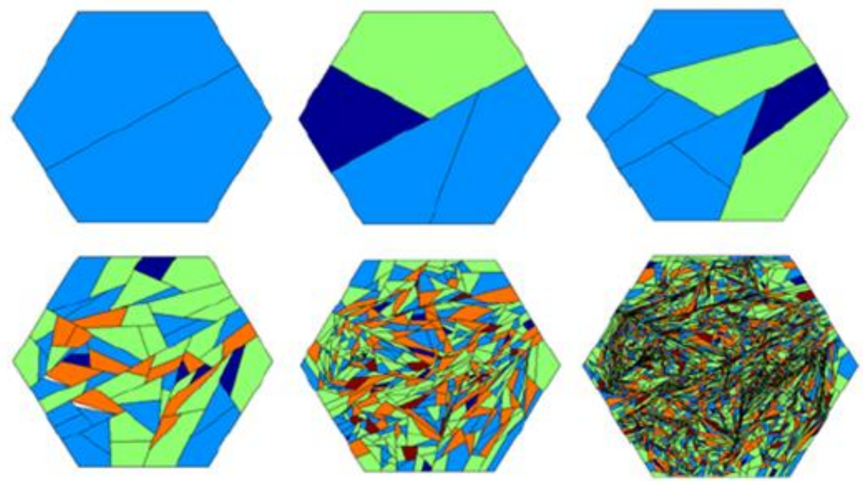
Nagpal,R. et al.,BioEssays, 2008

Previous Work









Farhadifar et al., Curr. Biol., 2007

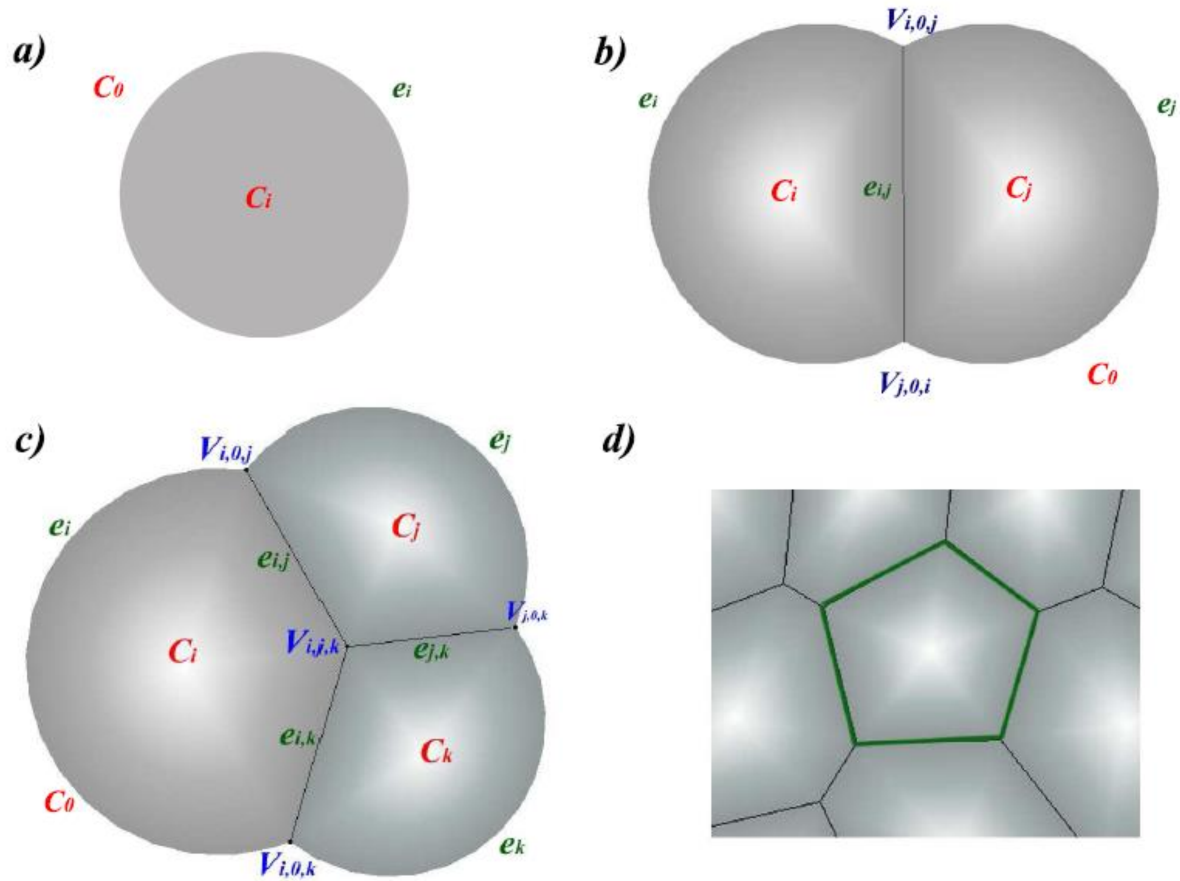
Patel et al., PLoS Comput. Bio, 2009

Cell Model:

- Minimize free energy
  - Soap bubble

- Cell in isolation
- 2-Interacting cells
- 3-Interactiong cells

- Fully buried cells
  - Polygon

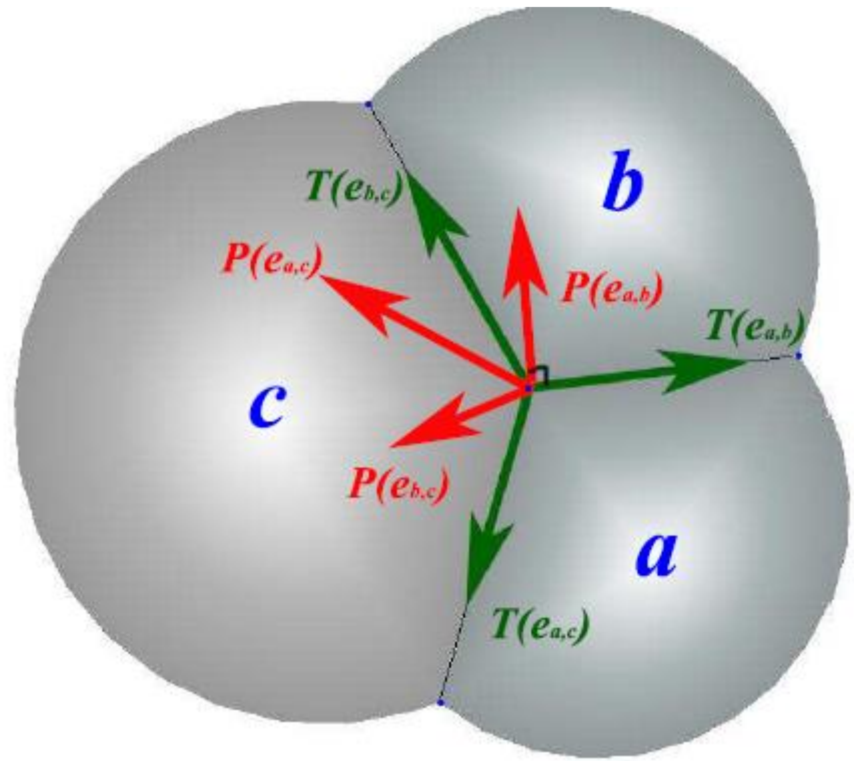


Forces

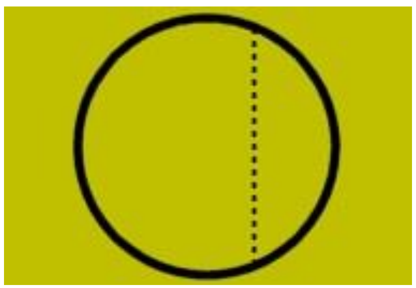
- Compression forces:
  - Cytoskeletal microfilaments; Intermediate filaments; Cell membrane; …
  - Modeled as **Tension**

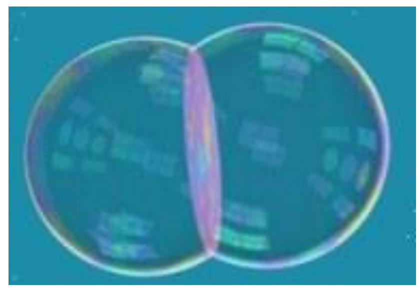
- Forces resisting compression:
  - Microtubules; Extracellular matrix; …
  - Modeled as **Pressure**

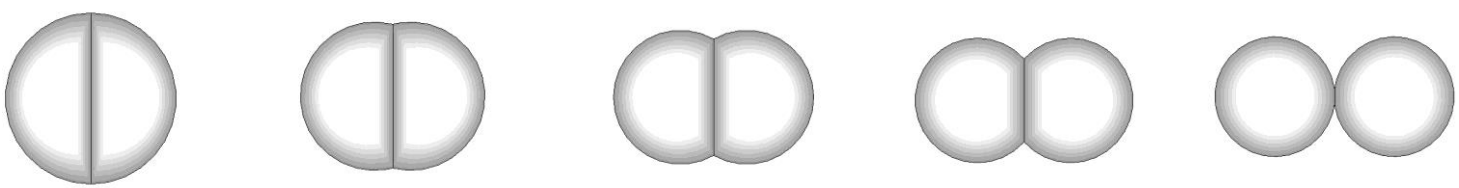
- Cell adhesion or repulsion
  - Modeled as an additional term in **Tension** coefficient



- Tension coefficient: Soap bubble model
  - Minimize free energy







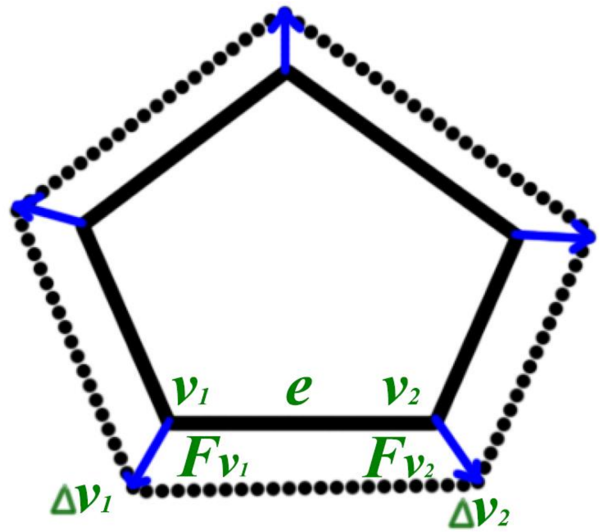
η=0.0 η=0.5 η=1.0 η=1.5 η=2.0

Low η: Strong adhesion, low tension

High η: Weak adhesion, strong tension

Cell Volume Change

- Specify volume change at time *t*
  - incrementally add 5-10% at a time
- Result in expansion/shrinkage of cell
  - movement of cell vertices
- Assuming stationary state before and after increment
  - Zero net forces



$$\Delta V_i \approx \sum_{\boldsymbol{e}} \Delta V_{\boldsymbol{e}},$$

$$\Delta V_{\boldsymbol{e}} = \frac{1}{2} \sum_{v(\boldsymbol{e})} |\Delta \boldsymbol{v}(\boldsymbol{e}) \times \boldsymbol{e}|$$

$$\Delta V_i \approx \sum_{\boldsymbol{e}} \sum_{v(\boldsymbol{e})} \frac{1}{2} |\Delta \boldsymbol{v}(\boldsymbol{e}) \times \boldsymbol{e}|$$

$$= \sum_{\boldsymbol{e}} \sum_{v(\boldsymbol{e})} \frac{1}{2} |[\frac{1}{2} \boldsymbol{a}_{v(\boldsymbol{e})} (\Delta t)^2] \times \boldsymbol{e}|,$$

$$\Delta V_i \approx \sum_{\boldsymbol{e}} \sum_{v(\boldsymbol{e})} \frac{1}{2} \cdot \frac{1}{2} |\frac{\boldsymbol{F}_{v(\boldsymbol{e})}}{m} (\Delta t)^2 \times \boldsymbol{e}|$$

$$= \frac{(\Delta t)^2}{2m} \frac{1}{2} \sum_{\boldsymbol{e}} \sum_{v(\boldsymbol{e})} |\boldsymbol{F}_{v(\boldsymbol{e})} \times \boldsymbol{e}|$$

$$= \frac{1}{2} \sigma_1 \sum_{\boldsymbol{e}} \sum_{v(\boldsymbol{e})} |\boldsymbol{F}_{v(\boldsymbol{e})} \times \boldsymbol{e}|.$$

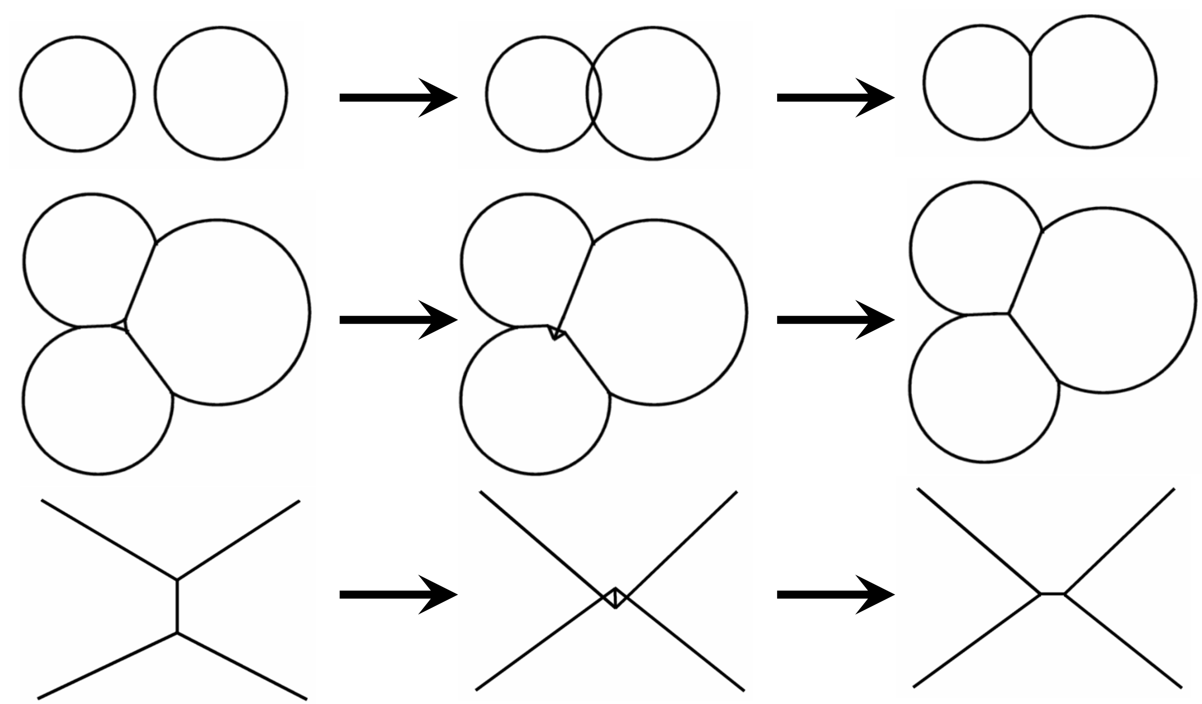
$$\sigma = (\Delta t)^2 / 2m$$

Geometry and topology changes

Topological Changes: Due to cell growth

Avoid same space occupied by two cells

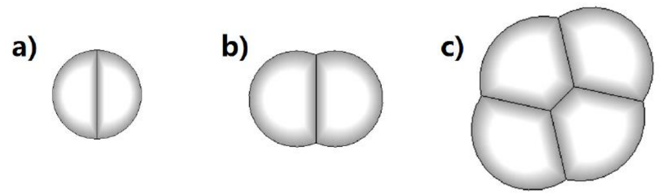
Edge Swap: when 2 disconnected cells contact
Void Removal: 3 cells grow together



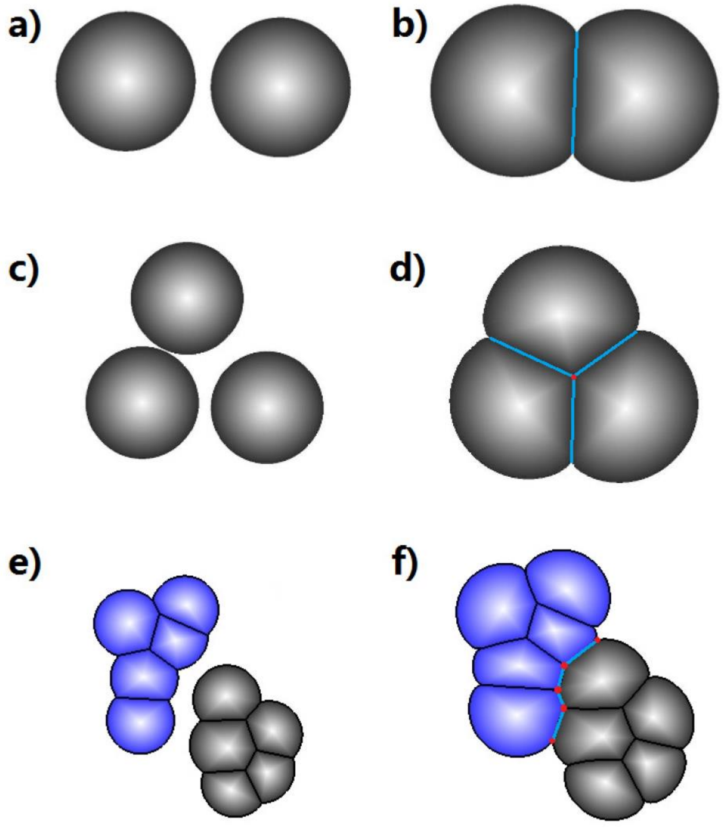
geometry topology

Model and Algorithm for Developmental Biology

- Can model tissue development starting from a single cell



- Can model cell and tissue fusion



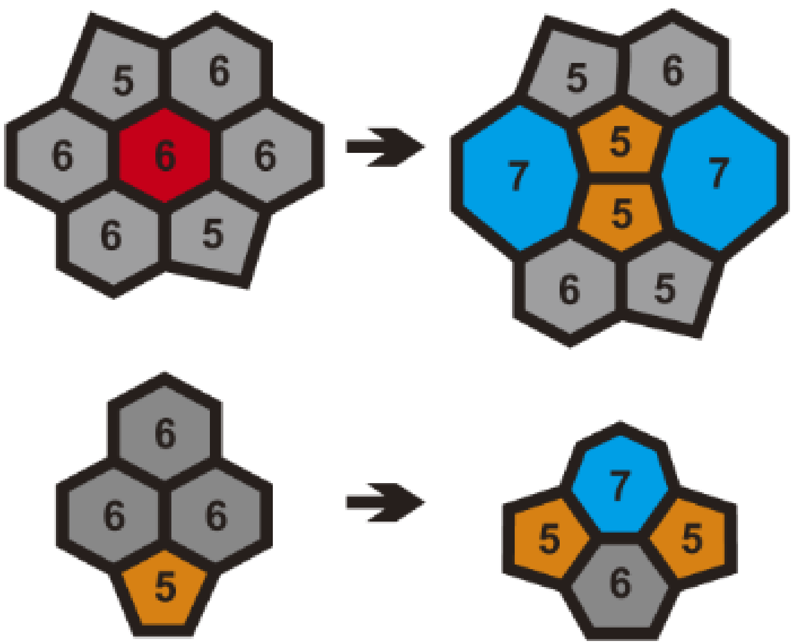
Algorithm 1 UpdateCellPattern ($\boldsymbol{V}(t)$, $\Delta\mathcal{V}(t)$, $\Delta\eta(t)$, σ, k)

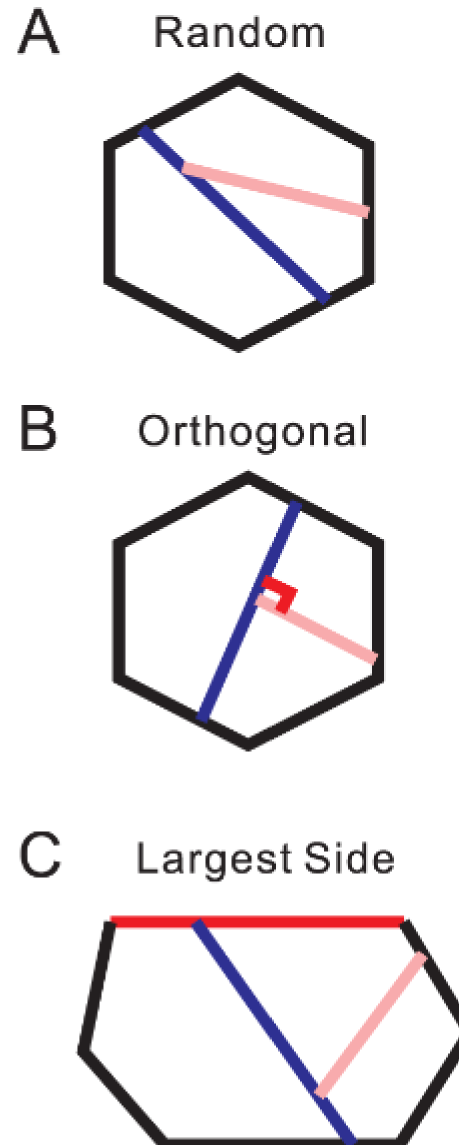
$//\epsilon$: Threshold
$//k$: Determines step size in incremental volume change.
while $\boldsymbol{F}_v > \epsilon$ for any vertices or $\Delta\mathcal{V}(t)$ not reached yet **do**
  Solve Eqn 2 to obtain updated forces $\boldsymbol{F}_v$ for all vertices.
  if desired amount of changes in $\Delta\mathcal{V}(t)$ not reached yet **then**
    Introduce incremental changes $\Delta\mathcal{V}(t)/k$,
  end if
  Obtain new positions for all vertices using $\boldsymbol{v}_i' = \boldsymbol{v}_i + \sigma\boldsymbol{F}_{v_i}$
  Update topological changes if required
end while
Assign $\boldsymbol{v}_i(t+1) = \boldsymbol{v}_i'$ for all vertices
return $\boldsymbol{V}(t+1) = (\boldsymbol{v}_1(t+1), \cdots, \boldsymbol{v}_m(t+1))$

Our model

- Cell process
  - cell growth
  - cell division
  - cell rearrangement

- Division plan:
  - random
  - orthogonal
  - largest side

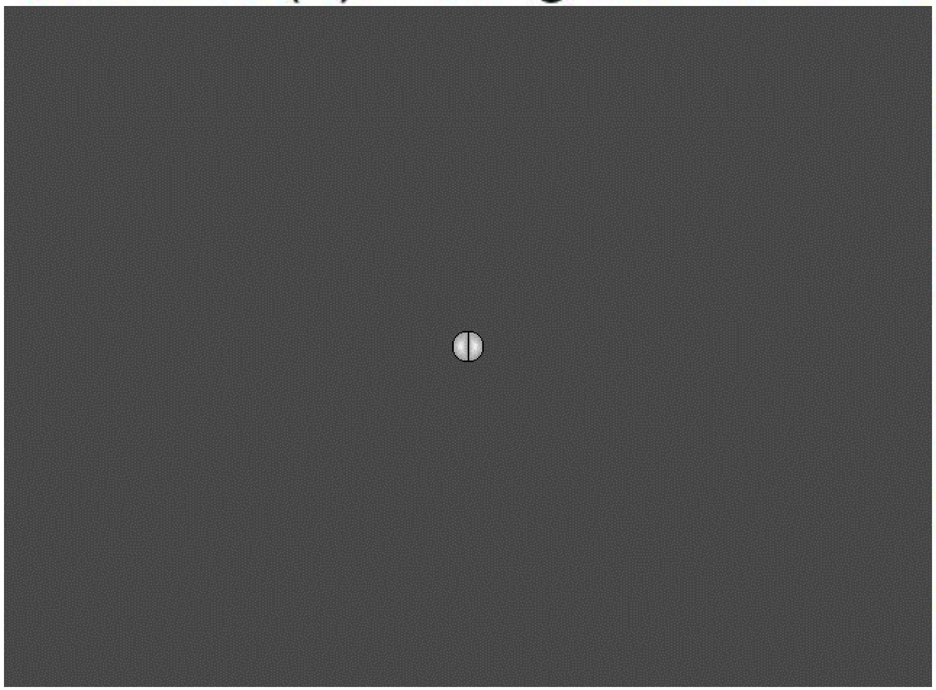




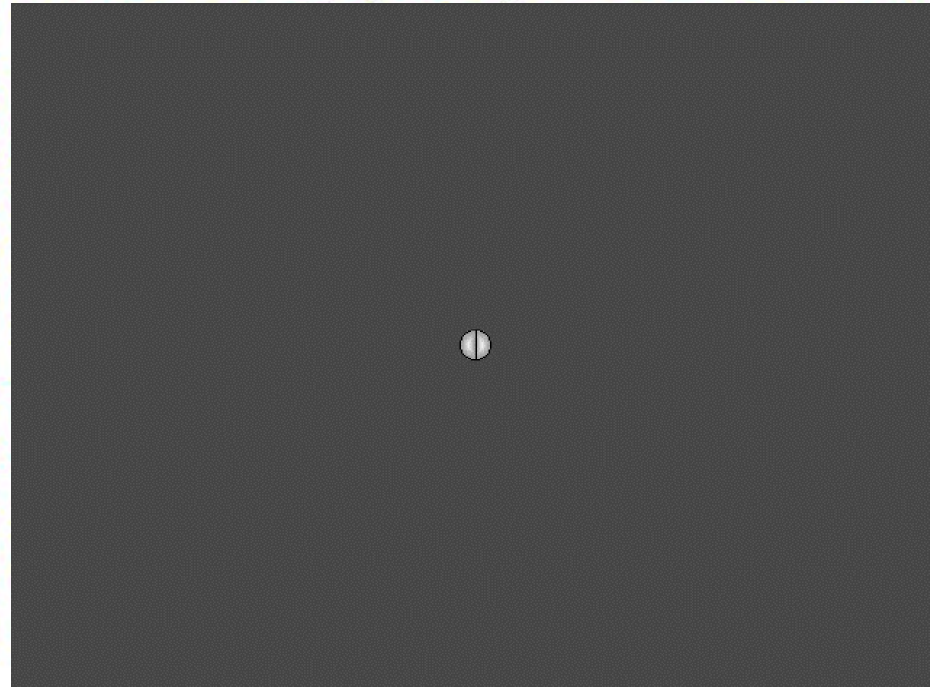
(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

Results

(a) Orthogonal



(b) Largest



- Equilibrium distribution achieved
  - Regularly shaped

- Pentagon
- Hexagon
- Heptagon
- Others

(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

Our Results

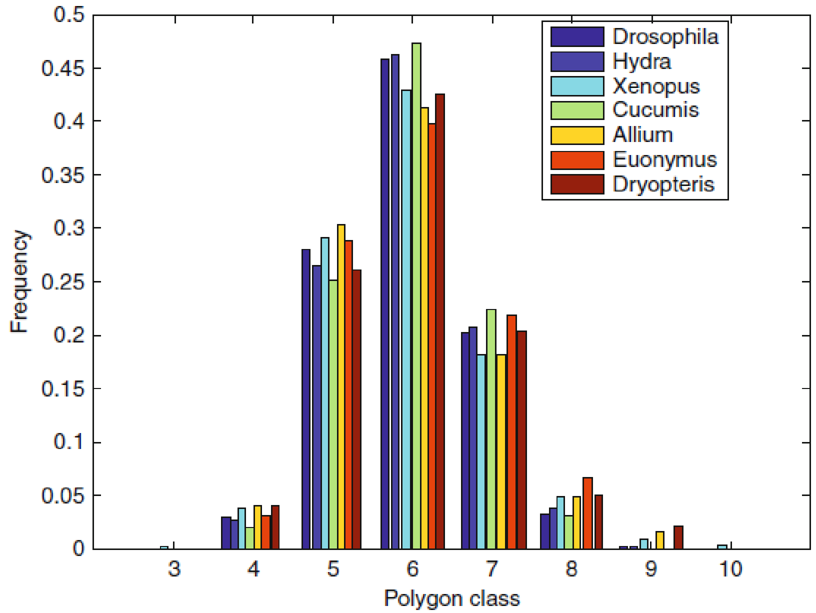
(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012)

Dynamic geometric model:

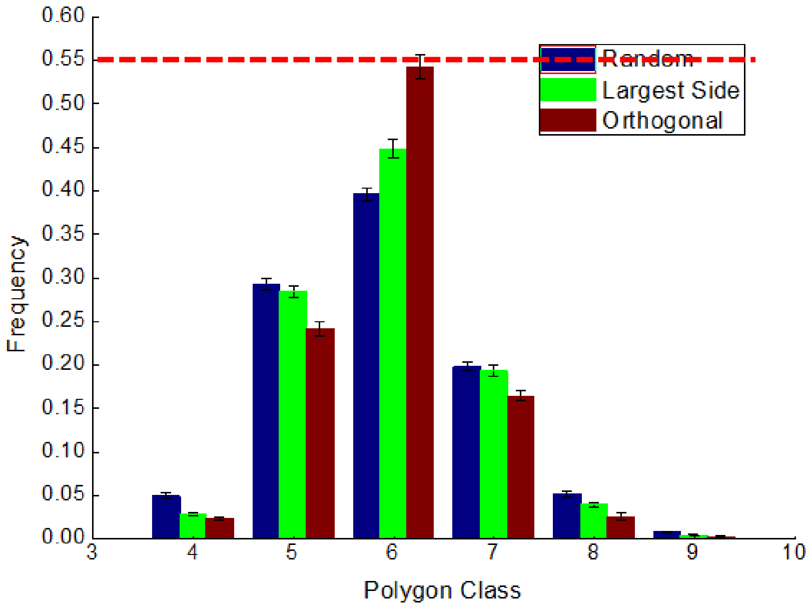
reproduce common topological distributions

Different division plan:

generate differential distribution of different hexagon content



Gibson et al., Curr Top in Dev Biol, 2009



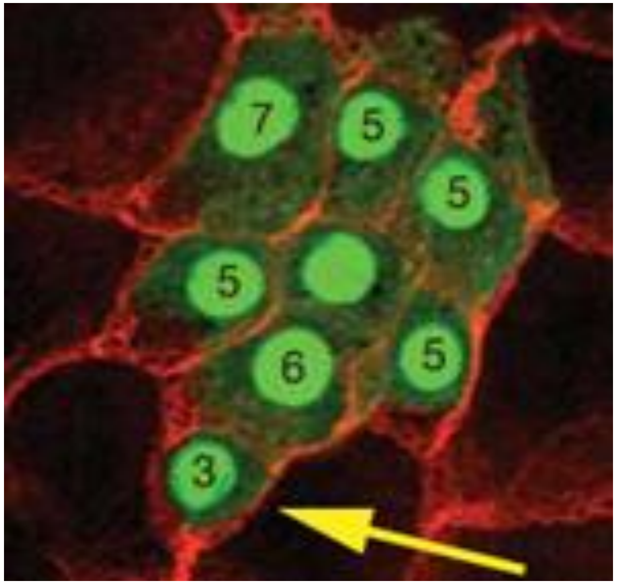
(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

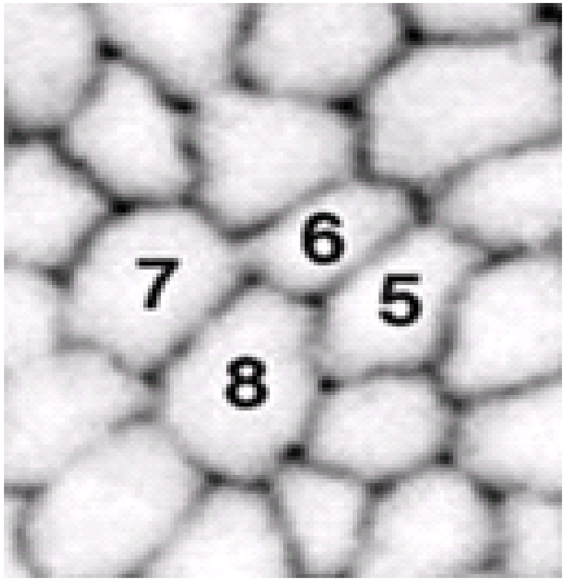
Conclusion

- Division plane
  - Different schemes can account for observed differences
    - Hexagon max: 55%
      - Orthogonal division plane
      - Requires deterministic cell memory

- Mechanical force
  - Reduce stress
    - Both orthogonal and longest plane dvisions have
      - Much less rearrangements (ca 150 vs 437)
      - More regular shape

Problem





- **Experimental Observation:**

— Clones of proliferating cells bounded by quiescent cells had fewer sides than natural epithelial cells.

— Clones of proliferating cells (left, green).
— Quiescent cells (left, red).
— Natural proliferating cells (right).

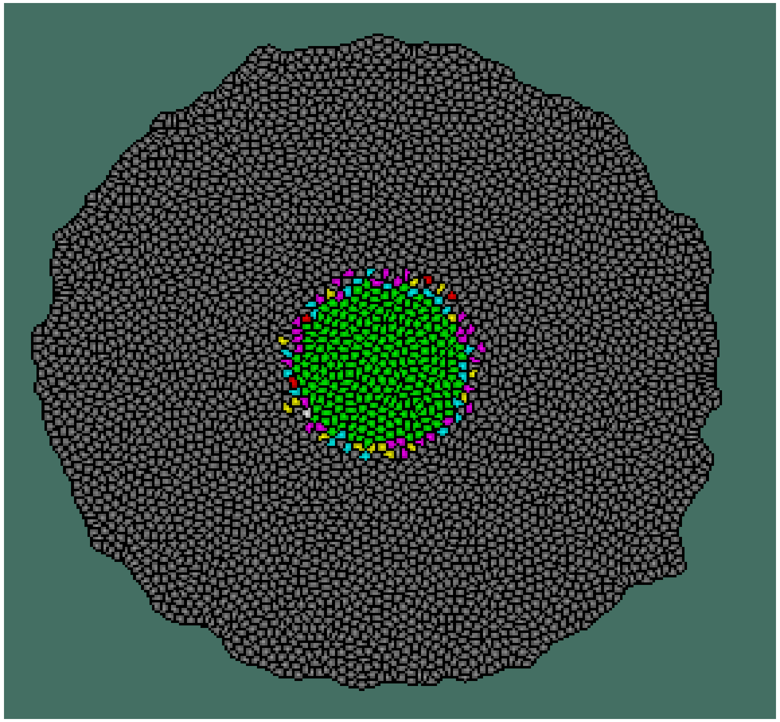
Gibson,M.C. et al., Nature, 2006

- **Questions:**

— Does the reduced mean value of sides result from differential proliferation?

Our model—procedure

- **Start from the equilibrium state.**
  - **— 12 generations from two cells.**
  - **— About 4,000 cells.**
- **Mutate the inner part of the cells so that they are proliferating.**
  - **— Peripheral cells are quiescent.**
  - **— Different tension coefficients on the boundary (0.5, 1.0, 1.5, 2.0, with 1.0 being default).**
- **Examine topological properties.**
  - **— Result is average of 5 simulations.**



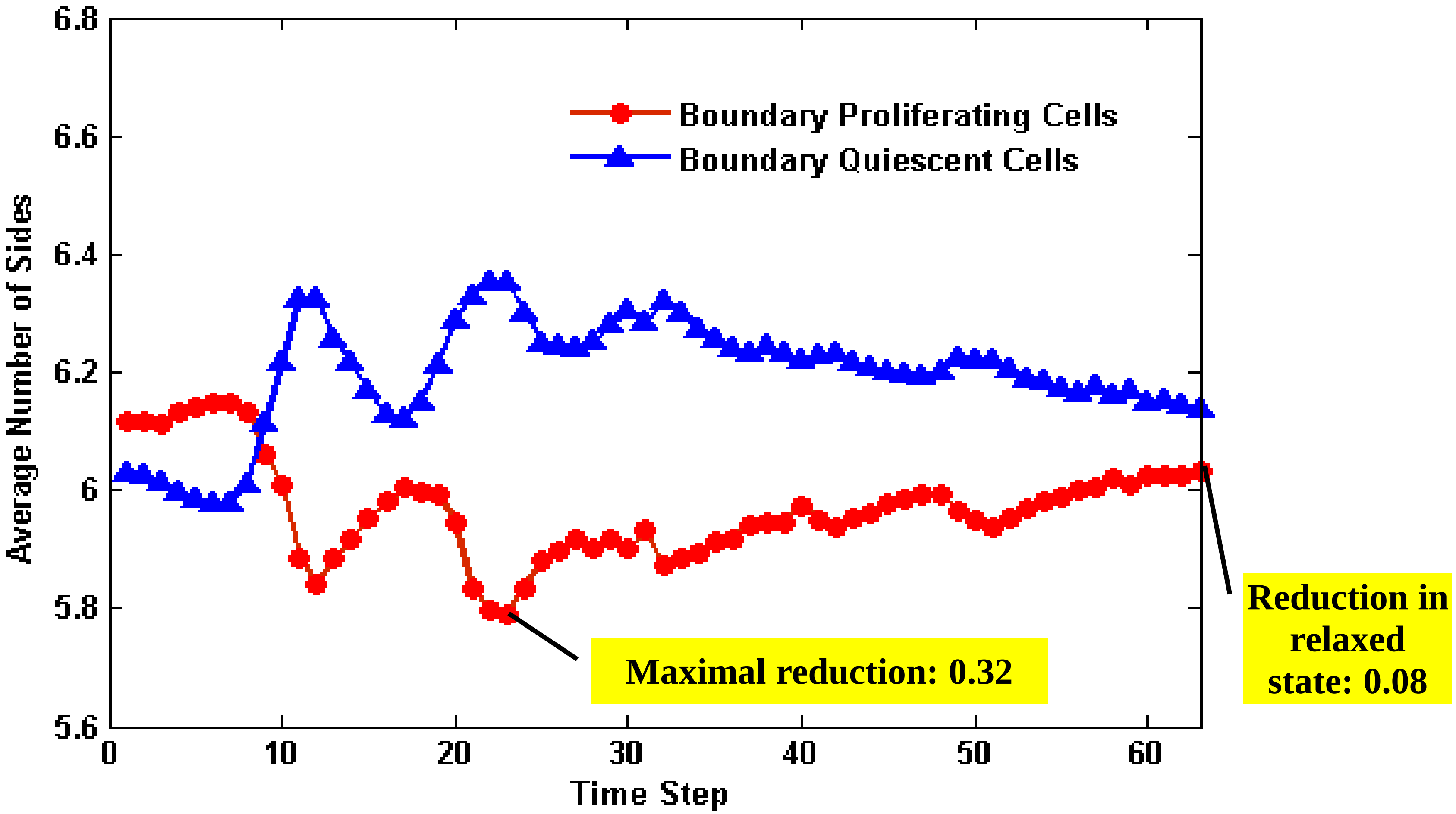
— Proliferating cells (colored) .
— Quiescent cells (gray).

(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

Results

- $\eta(p,q) = \eta(p,p) = \eta(q,q) = 1.0$

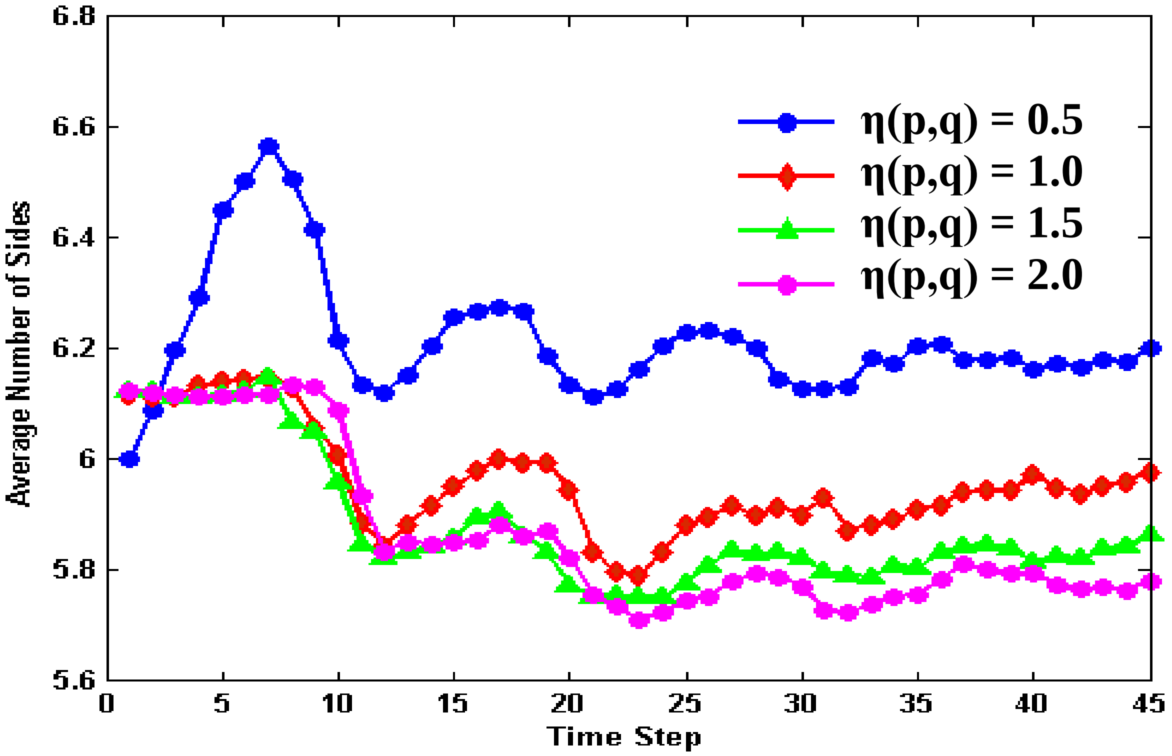
- Differential proliferation alone does not affect the topology of boundary proliferating cells significantly.



(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

Results

- Mutate the inner part (proliferating cells).
- Tension coefficients between cells are different:
  η(p,p) = η(q,q)= 1.0 ; η(p,q) = 0.5/ 1.0/ 1.5/ 2.0 .
- Increased tension coefficients can further decrease the average number of sides of boundary proliferating cells.



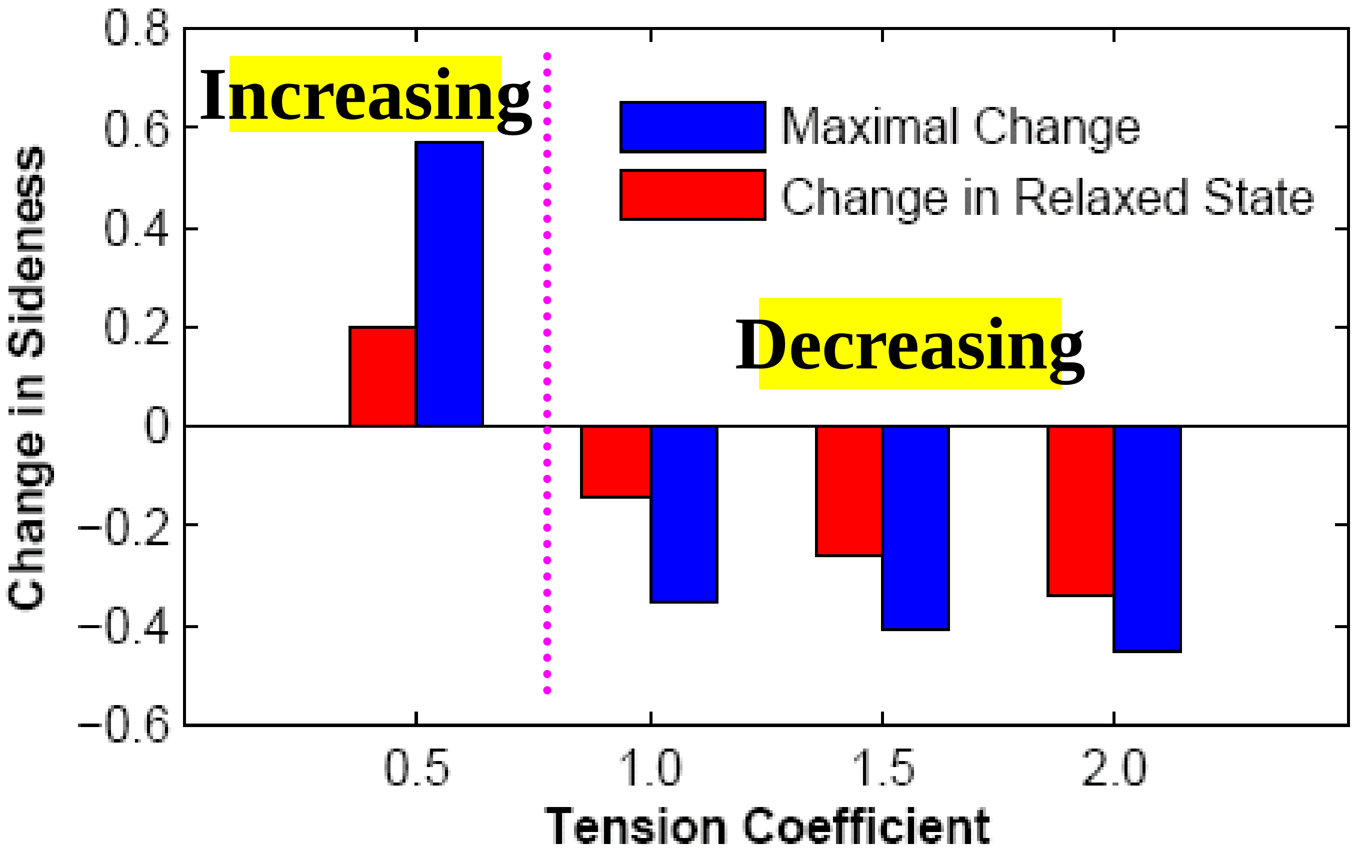
(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

Results

- $\eta(p,p) = \eta(q,q) = 1.0$; $\eta(p,q) = 0.5/ 1.0/ 1.5/ 2.0$.

- Decreased tension coefficient leads to increased average number of sides of boundary proliferating cells.

- The overall decrease in the average number of sides of boundary proliferating cells is significantly influenced by mechanical forces.



Comparison with experiments

- **Experimental data from Gibson *et al.* :**

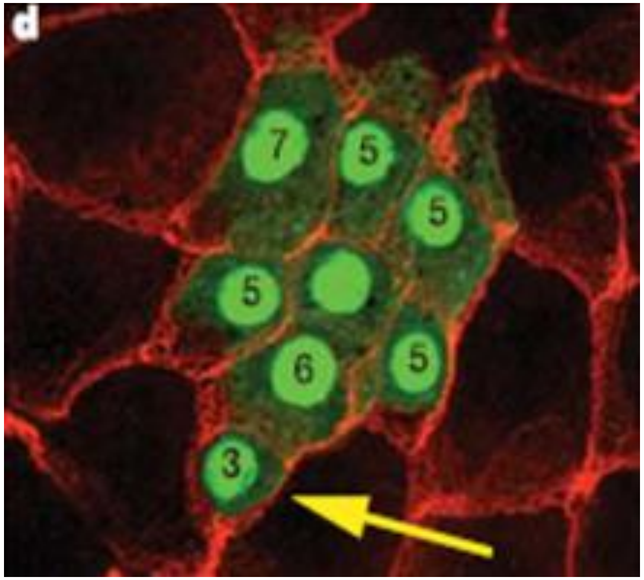
  — **Decrease in average number of sides (~ 0.52)**

  — **Small clones (295 cells in 24 clones)**

Difference probably results from statistic variations.

η(p,q)	N_{max}	$N_{relaxed}$
0.5	+0.56	+0.20
1.0	-0.32	-0.08
1.5	-0.37	-0.26
2.0	-0.42	-0.34

Almost consistent.



Gibson,M.C. et al., Nature, 2006

N_{max}: Maximal change in average number of sides of boundary proliferating cells.
$N_{relaxed}$: Change in average number of sides of boundary proliferating cells in relaxed state.

What we learned

- **Localized differential proliferation alone is not sufficient to produce distorted topological change.**

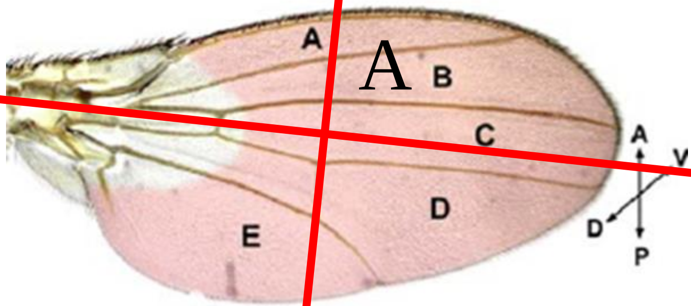
- **Increased surface tension on the boundary with differential proliferation can significantly decrease the average number of sides, which is consistent to the experiments.**

Regulation of mechanical forces

- Ensure regular tissue structure in proliferating epithelia
- Respond to local changes and control tissue morphogenesis

(Li, Naveed, Kachalo, Xu and Liang, PLoS ONE, 2012, 7(8): e43108.)

Tissue Elongation in Drosophila wing



P

A

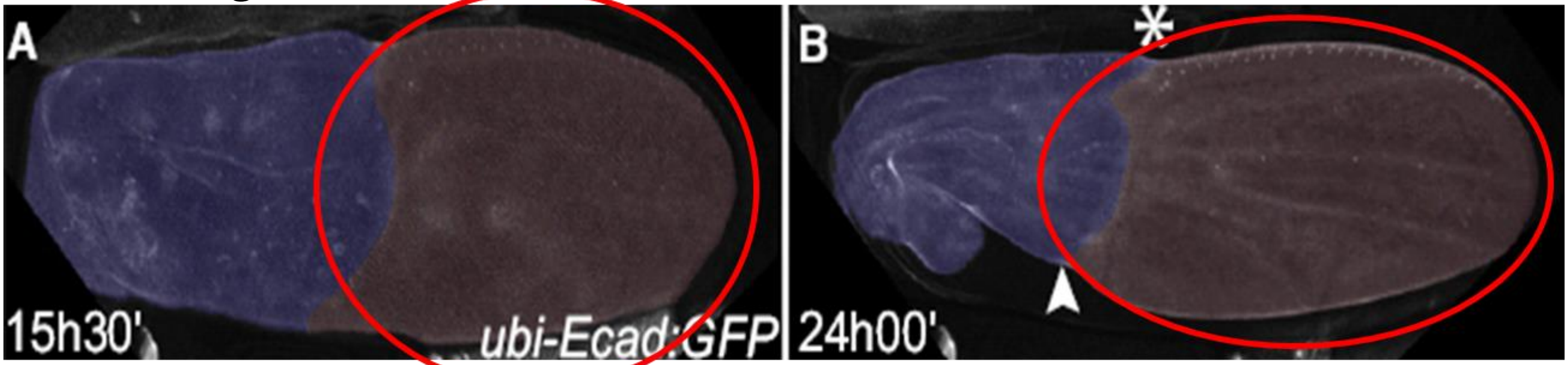
D

P

- Simple epithilia
- Classical developmental model
- Growing from 30 to 50,000 cells
- Tissue elongation（PD axis）

  - PD， proximal-distal
  - AP, anterior-posterior

Non-growth cell proliferation: 1-2 generations, same area, division w/o growth



Aigouy et al., Cell, 2010

Mechanism Controlling Tissue Elongation

- Cell growth
- Cell division

- Directional cues and their relative contributions?
  - Oriented cell division
    - Dach mutation can alter division plane by disrupting mitotic spindle
    - Ds mutant altering microtubule and disrupt mitotic spindle
  - Oriented mechanical forces
    - Contractile force from Dachs
    - More tension along PD-axis
    - Shear force
  - **Reduced cell size**
    - After 1-2 round of oriented division during pupal development

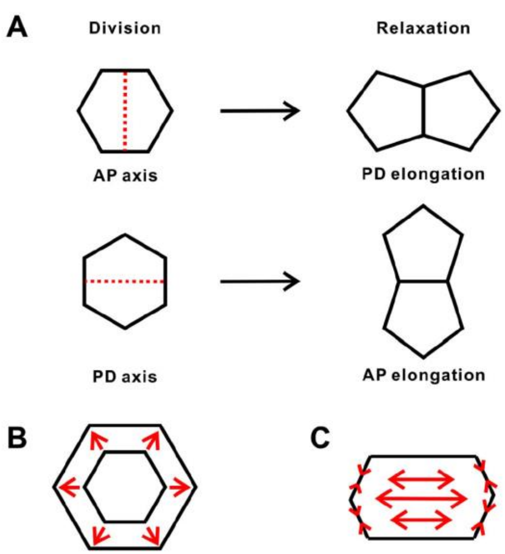
Li, Naveed, Kachalo, Xu and Liang, PLOS ONE, 2014, 9(2): e86725

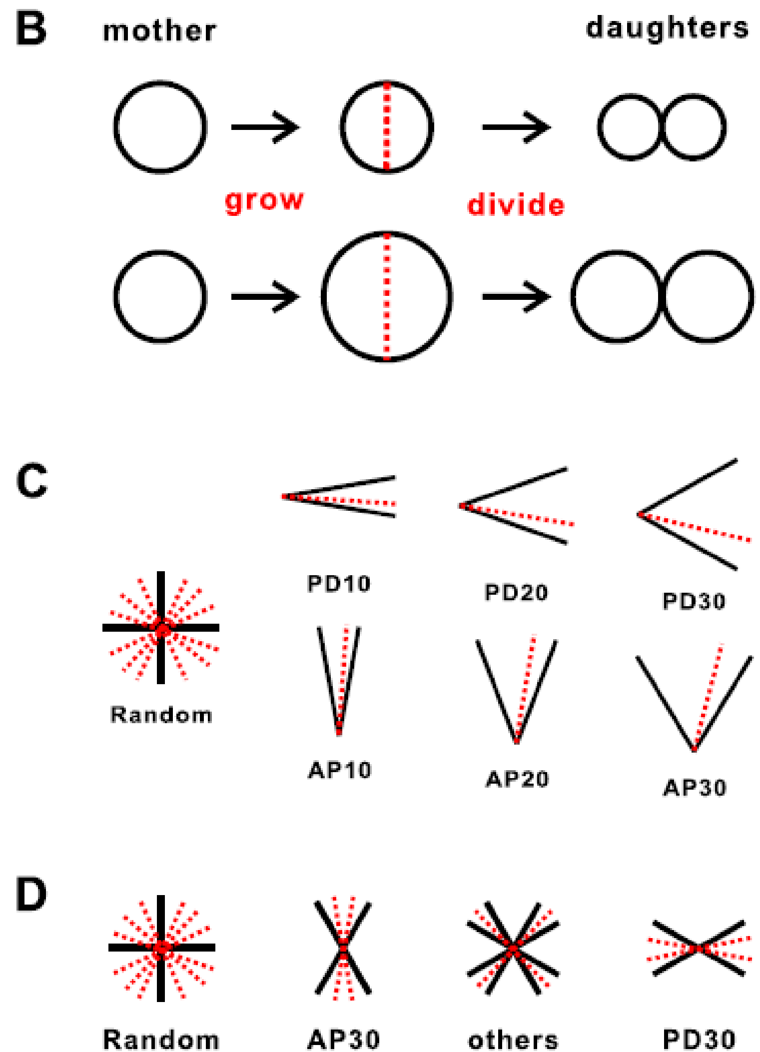
Our model

- Proliferation
  - Non-growth
  - With growth

- Oriented division

- Oriented mechanical force

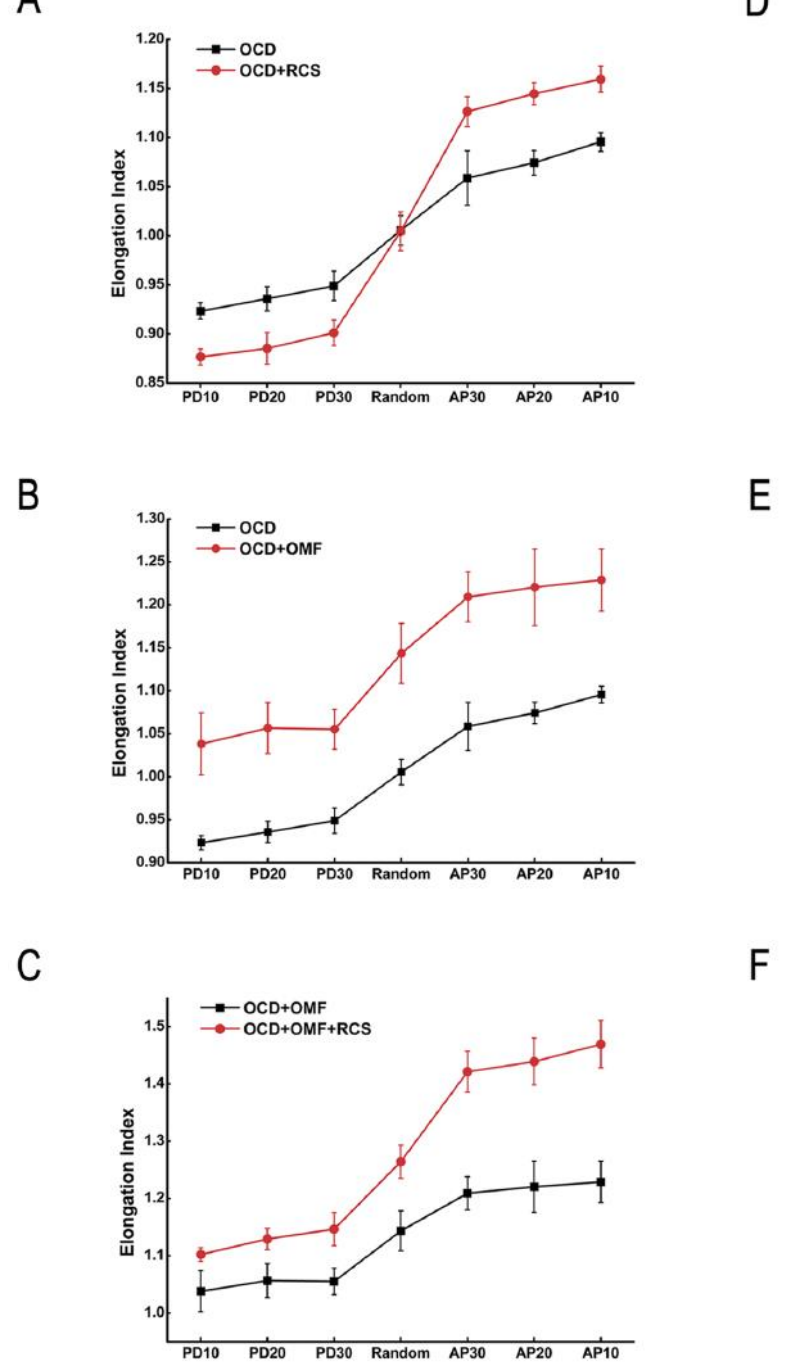




Li, Naveed, Kachalo, Xu and Liang, PLOS ONE, 2014, 9(2): e86725

Our Findings

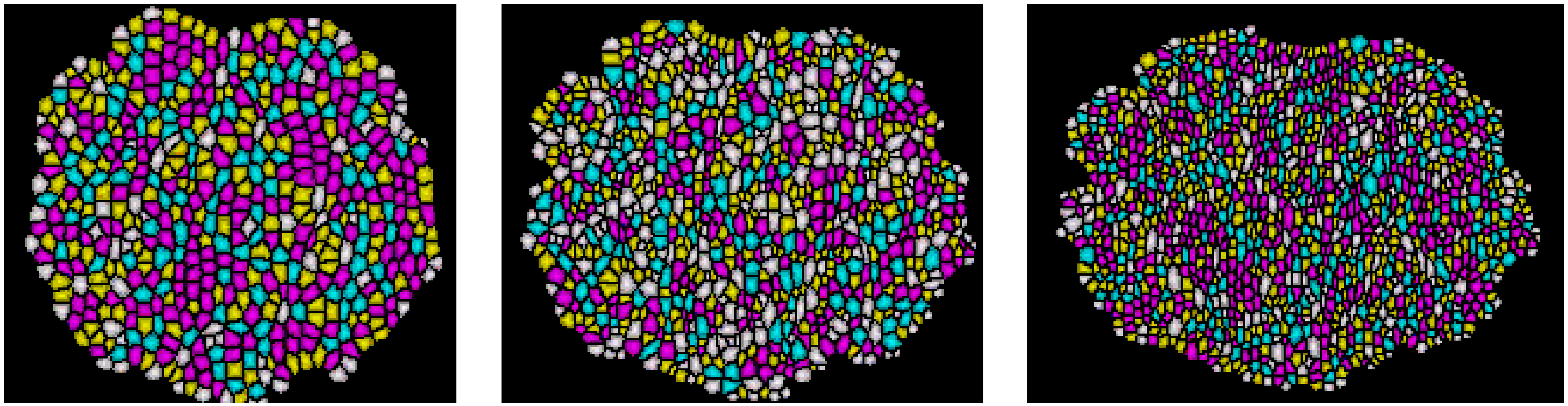
- Oriented cell division
  - Can drive elongation
  - But limited elongation
- Oriented mechanical force
  - Can generate elongation even with random division
  - Stronger influence than cell division
- Reduced cell size
  - No effect alone
  - Enhance elongation when directional cue is present
  - Multiplying factor if both present



Li, Naveed, Kachalo, Xu and Liang, PLOS ONE, 2014, 9(2): e86725

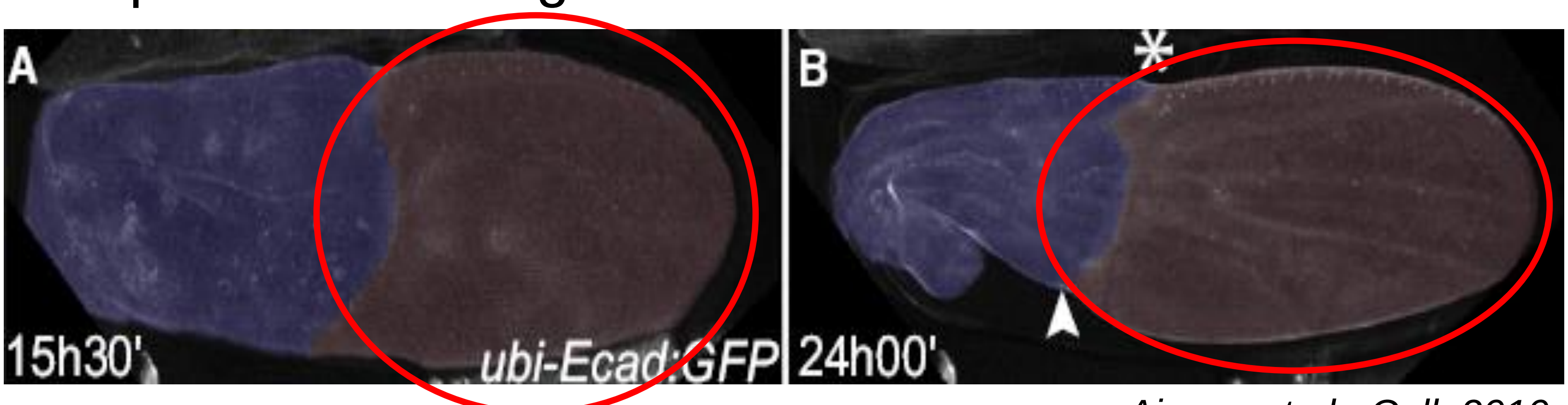
Our Results

- Simulation （elongation factor: ~ 1.42）



Li, Naveed, Kachalo, Xu and Liang, PLOS ONE, 2014, 9(2): e86725

- Experiment（elongation factor: ~ 1.39）

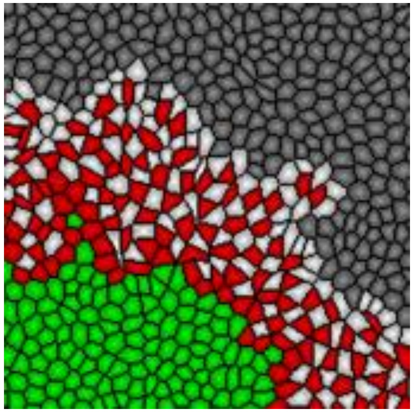


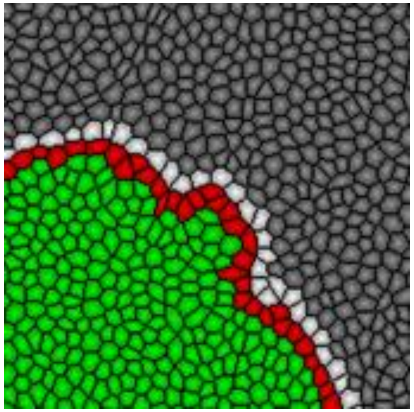
Aigouy et al., Cell, 2010

Cancer Invasion

Increased Adhesion

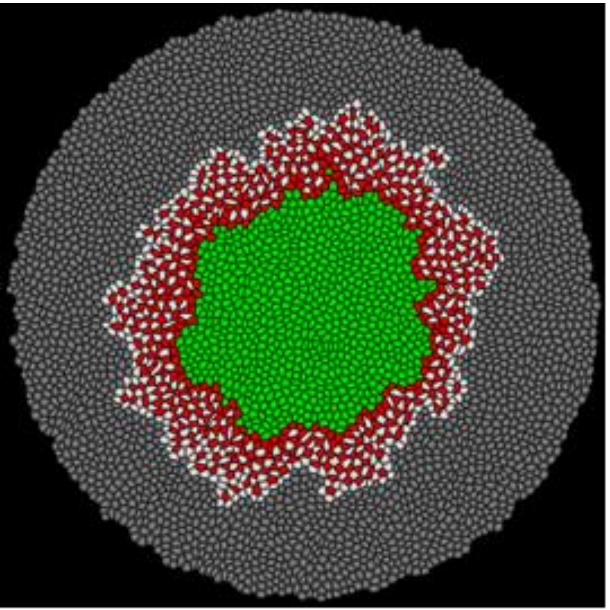
Reduced Adhesion

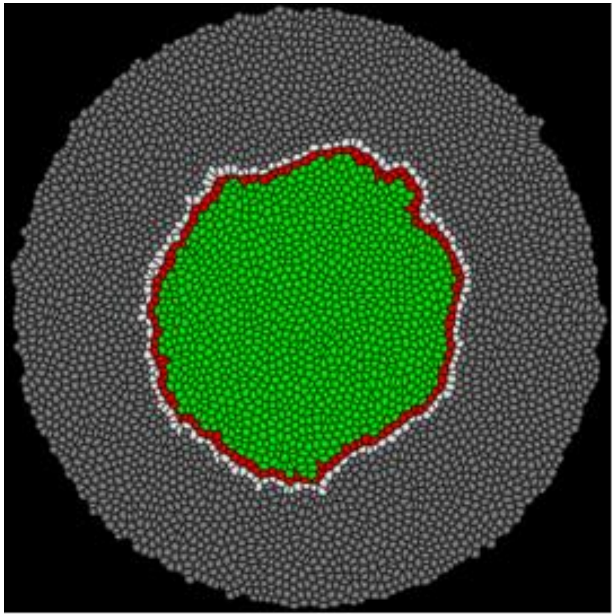




Green： interior tumor
Red： peripheral tumor cell

White： boundary ECM
Grey： exterior ECM





Yingzi Li, Hammad Naveed, Jie Liang, and Lisa X. Xu, *Conf Proc IEEE Eng Med Biol Soc.* , **2014.**

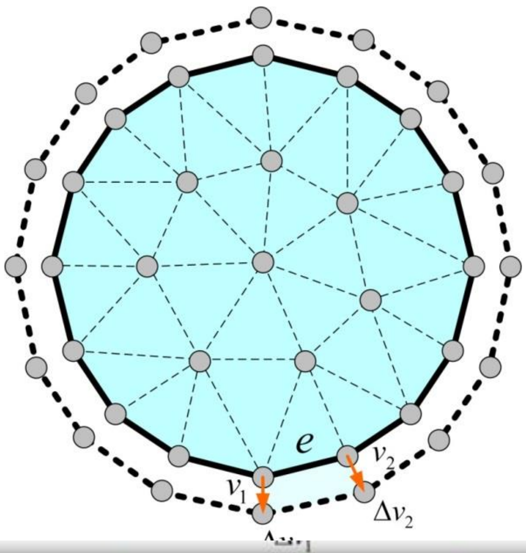
The dynamic Finite Element Model of Cell (dFEMC)

Cell Representation

- Boundary: 20-30 dynamic nodes
- Domain: dynamically partitioned into triangular meshes

Forces and Dynamics

- Spring system connecting internal and boundary nodes
- Tissue dynamics modeled by solving the stiffness matrix eq
- Internal mesh points dynamically



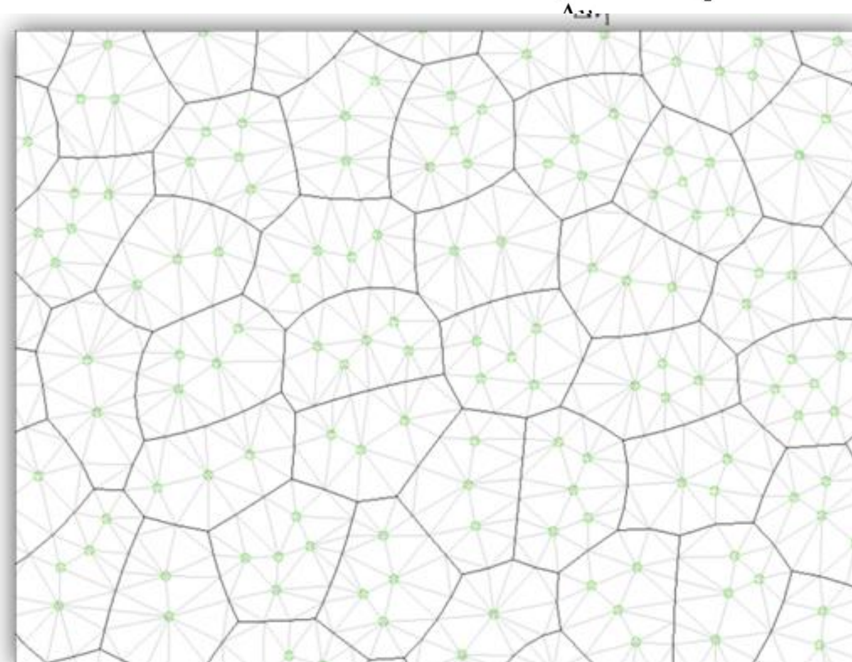
Cell physical properties

- Stiffness and elasticity

Mechanical forces

- Tension
- Pressure
- Cell-cell adhesion

Jieling Zhao



Cell behaviors

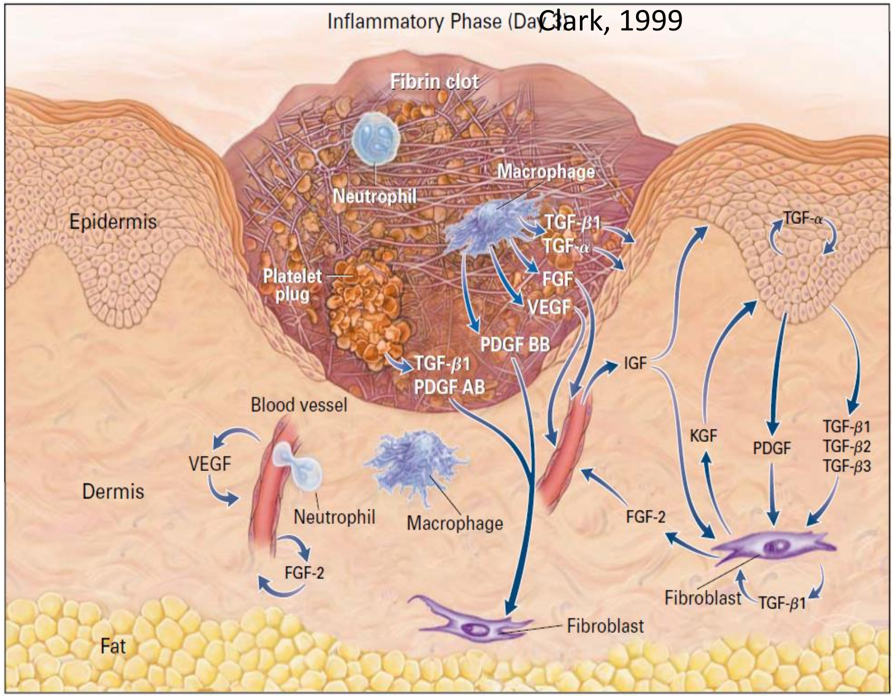
- Growth/Division
- Migration
- Apoptosis
- Shrinkage

(Zhao et al, *Conf Proc IEEE Eng Med Biol Soc.* , **2013.**2013:4517-20. PMC4148913)

Human Skin Wound Healing

- Rapid restoring of skin structure is critical
- Complex process involving multiple cell types and multiple paracrine and autocrine signaling
- Connections between wound healing and cancer

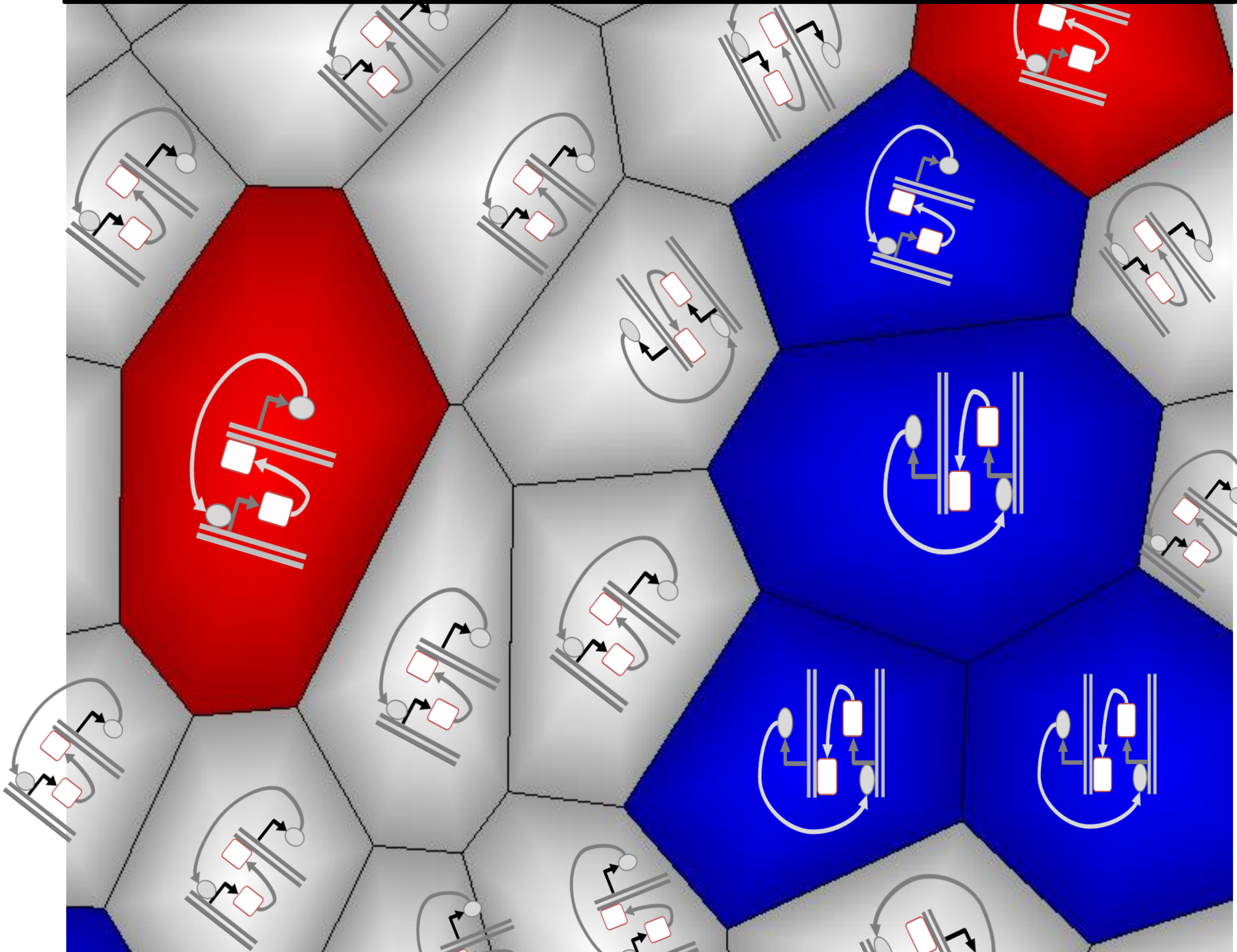
Singer and Clark, 1999



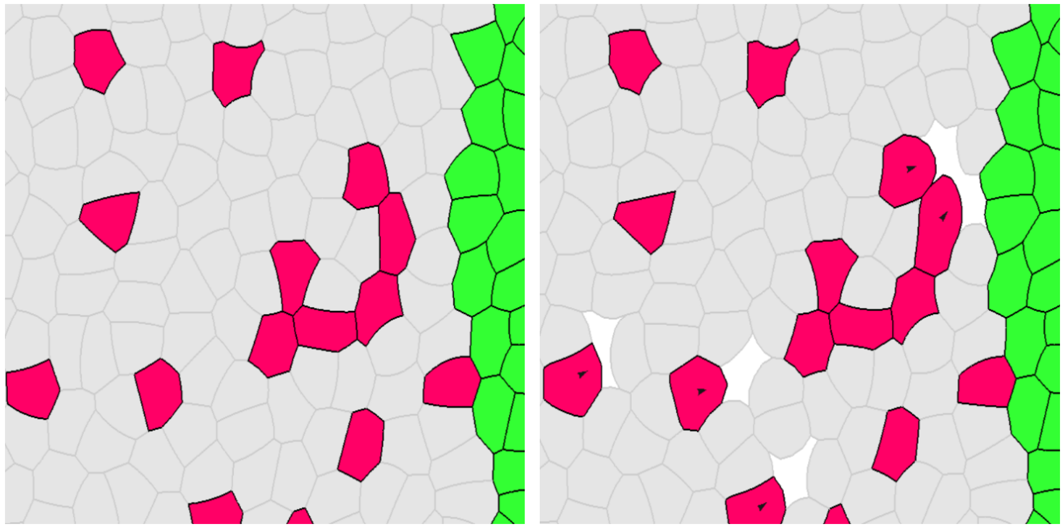
It is NOT clear how wound healing is precisely coordinated and regulated through cell-cell signaling and communications

Computational model can shed some light

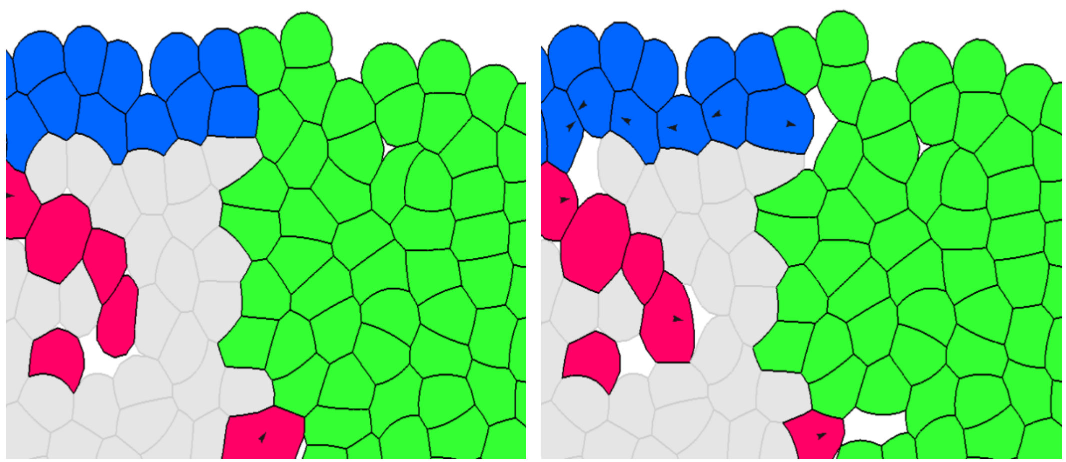
Hybrid of cell growth model and intracellular genetic circuits dictating cell-cell communications



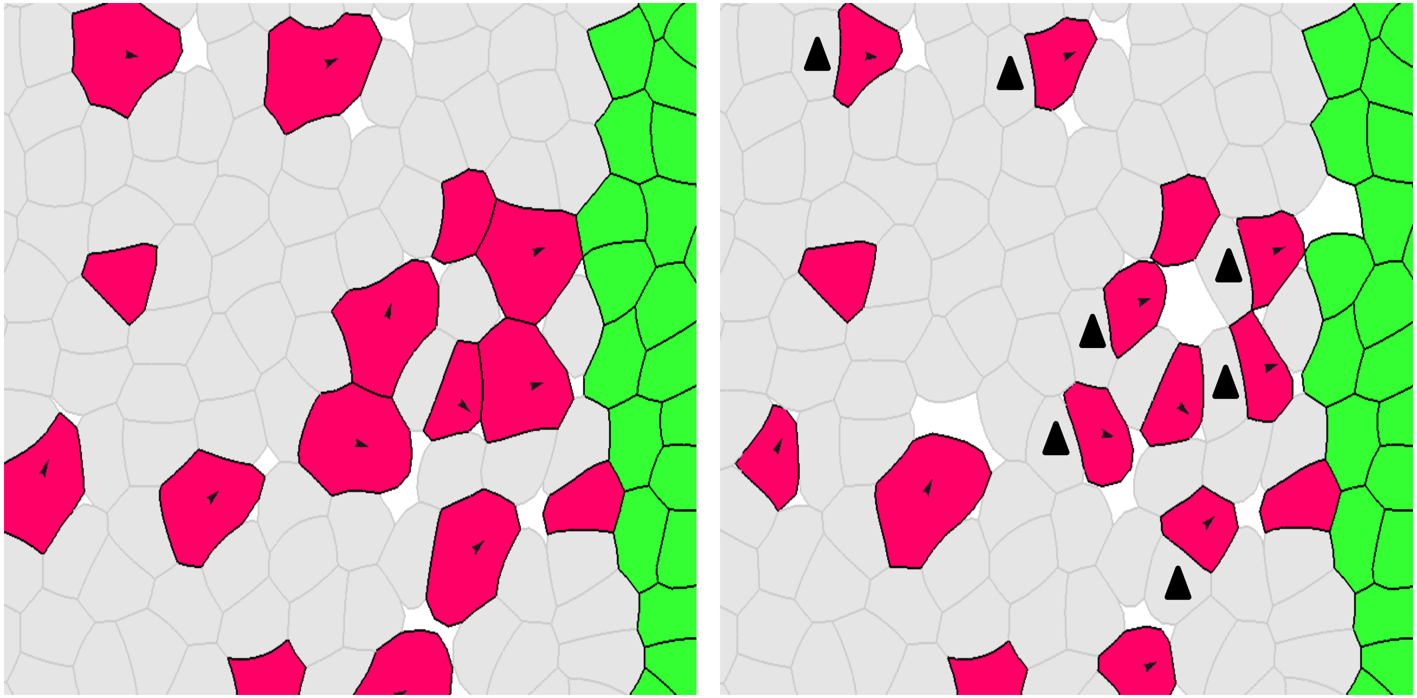
Fibroblast migration by cleaving and degrading collagen and clot (element) ahead.



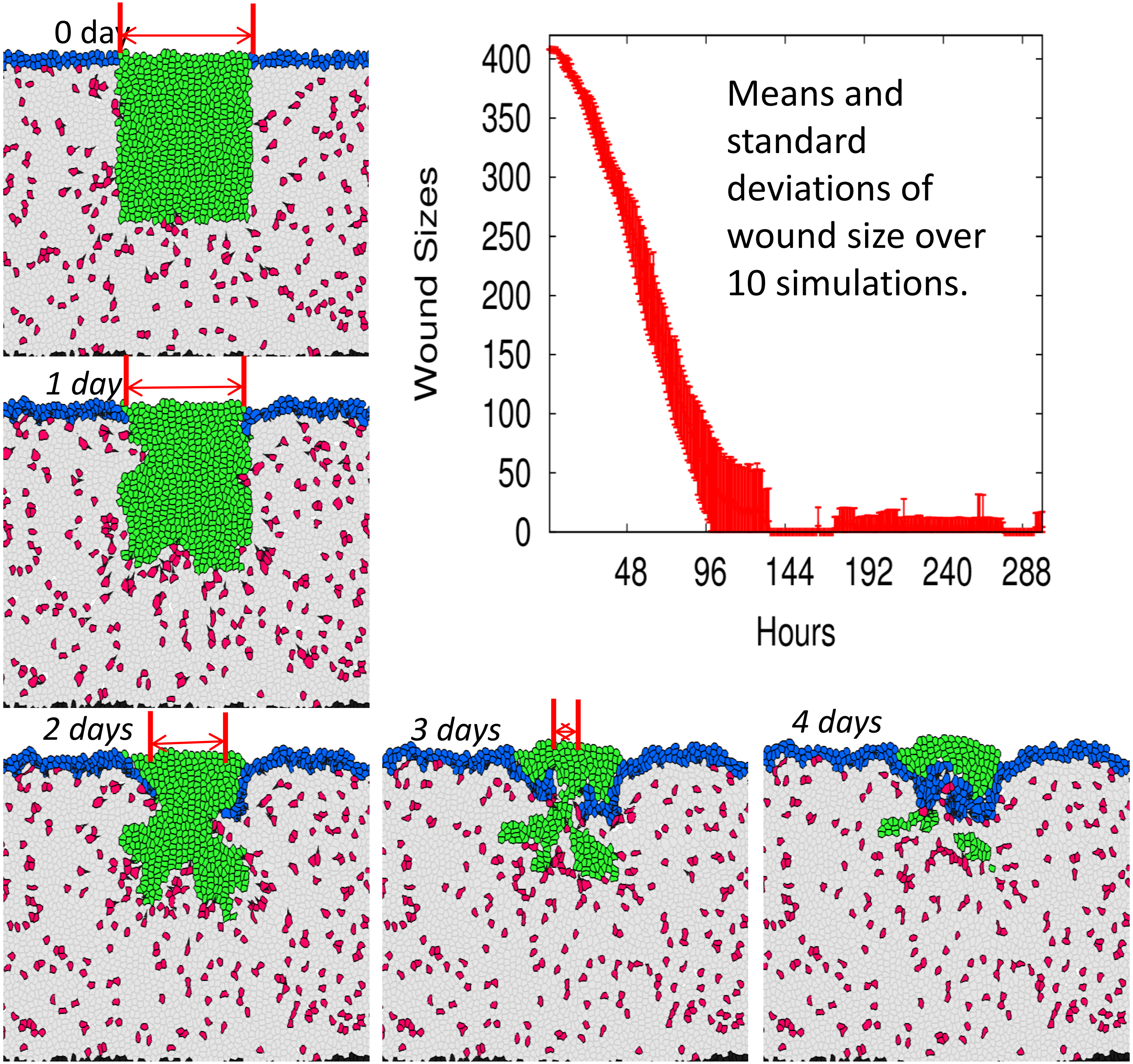
Keratinocyte migration by cleaving and degrading fibrin clots (element) ahead.



Fibroblast synthesize new collagen element behind the migration direction.



Wound Closure Rate from Simulations



Summary

- Cell and tissue pattern formation from dynamics of local cell behavior and cell-cell interactions
  - Effects of cellular networks and interactions on pattern formation
  - Wound healing

→ Acknowledgement!

Collaborators

- **Youfang Cao (**(UIC)
- **Dennis Gessmann (UIC)**
- **Gamze Gursoy** (UIC)
- Sema Kachalo (now Intel graphics unit)
- Ronald Jackups, Jr (Wash U, Assist Prof)
- Yingzi Li (SJTU)
- **Meishan Lin** (UIC)
- **Hammad Naveed** (UIC/now Toyota Institute)
- **Ke Tang** (UIC)
- **Anna Terebus** (UIC)
- Wei Tian (UIC)
- **Yun Xu** (UIC)
- **Jieling Zhao** (UIC)
- Jinfeng Zhang (FSU, Associate Prof)

- David Stone (UIC)
- **Luisa Di Pietro (UIC)**
- **Linda Kenney (UIC)**
- **Amy Kenter (UIC)**
- John Marko (NWU)
- Lisa Xu (SJTU)

Papers: http://gila.bioe.uic.edu/lab/ (left column)

Acknowledgement

- NSF DBI
- NIH NIGMS
- CBC Catalyst