From cells to tissues

Physical modelling of the collective behaviour of embryonic cells

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spectro

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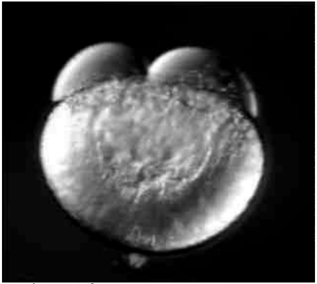

Karlstrom & Kane, Dev. 123:461, 1996

wikipedia

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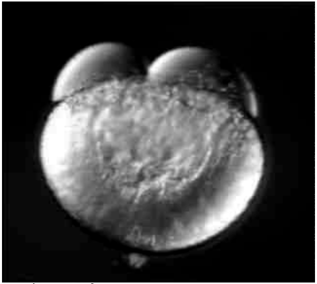
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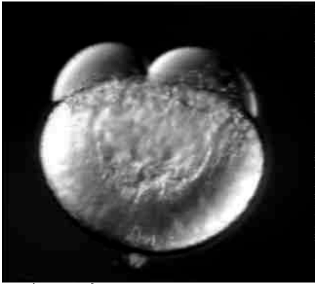
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1. Growth (from 0.5 mm to 6 cm)
2. Pattern formation
3. Morphogenesis: study its physical aspects

Simple physical analogies

Simple physical analogies

Understand how individual cell properties act on the collective level

Physical analogies suggested in the literature:

1. Cells and soap bubbles
2. Cell sorting and liquid demixion
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Soap bubbles and complex fluids: studied by the physicists in the lab

- Test the analogies by simulations
- Improve if necessary

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Physical analogies suggested in the literature:

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2. Cell sorting and liquid demixion: part 2
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Soap bubbles and complex fluids: studied by the physicists in the lab

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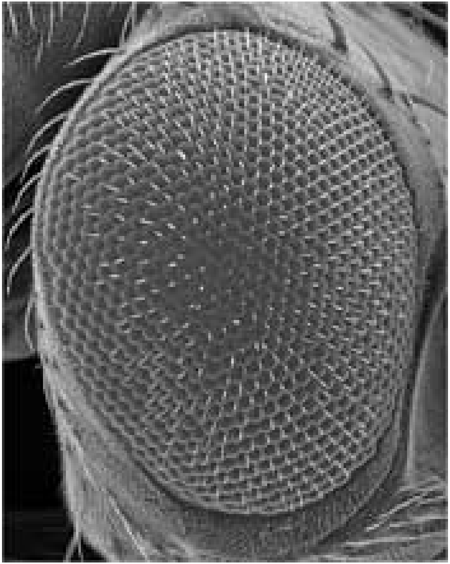
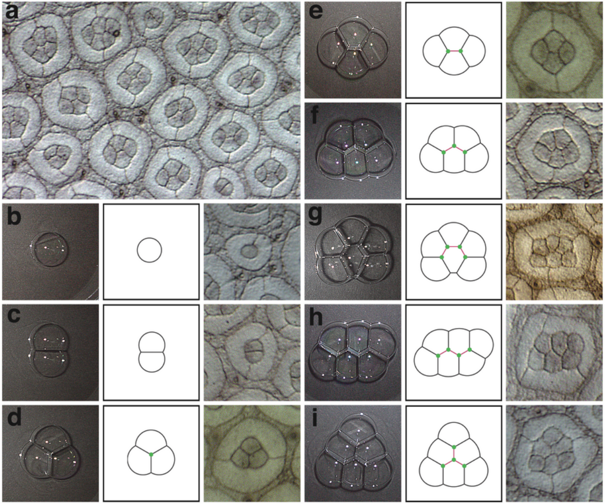
Drosophila eye


J. Kumar

With Takashi Hayashi
and Richard Carthew,
Northwestern University, USA

Starting point



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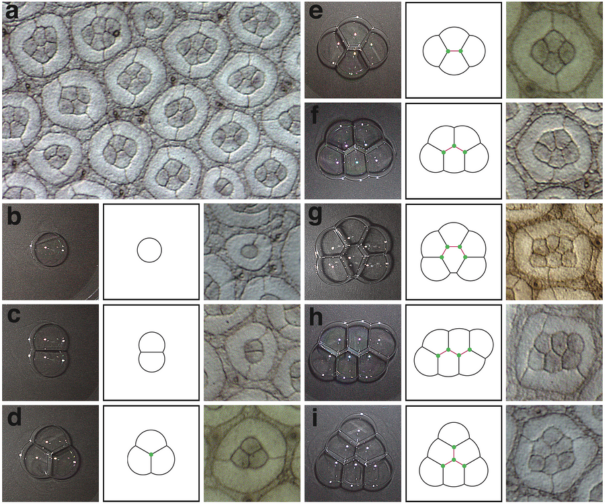

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Why does cell packing resemble bubble packing?

Same mechanics - surface minimisation?

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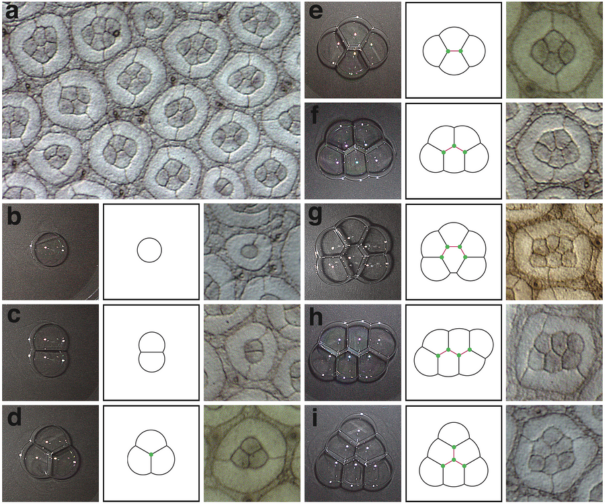

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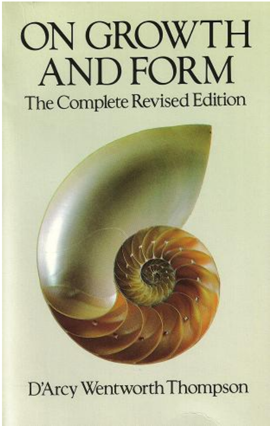

Idea first (?) published in 1917

Why does cell packing resemble bubble packing?
Same mechanics - surface minimisation?

Methods

Cellular Potts Model

Collaboration with S. Marée and V. Grieneisen, Utrecht University, The Netherlands

Methods — Cellular Potts Model

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4	4	4	4	4	3	3	3	3	3	3
4	4	4	4	4	3	3	3	3	3	3
4	4	4	4	2	2	3	3	3	3	3
5	4	4	2	2	2	2	2	3	3	0
5	5	2	2	2	2	2	2	0	0	0
5	5	2	2	2	2	2	0	0	0	0
5	5	2	2	2	2	0	0	0	0	0
5	5	5	2	2	2	1	0	0	0	0
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Lattice

- a cell = a set of pixels
  same size as in experiments
- a movement = a pixel changes
  to another cell

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- Energy cost at cell boundaries
- Size conservation

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Lattice

- a cell = a set of pixels
  same size as in experiments
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Energy

- Energy cost at cell boundaries
- Size conservation

Energy minimisation

- Surface minimisation
- Differential adhesion
- Membrane fluctuations
- ... and much more

Cellular ingredients "Key components"

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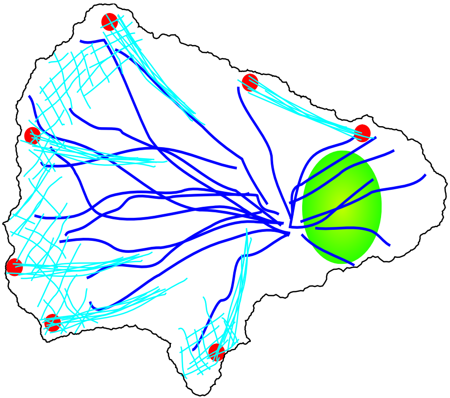


Migrating cell, top view

Cytoskeleton

microtubules

actin

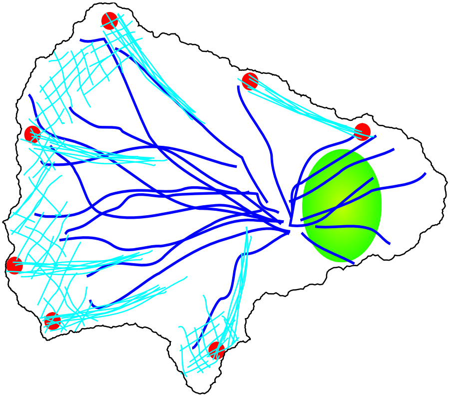
Rigidity

Activity: formation of protrusions

Adhesion

linked to the cytoskeleton

Cellular ingredients "Key components"



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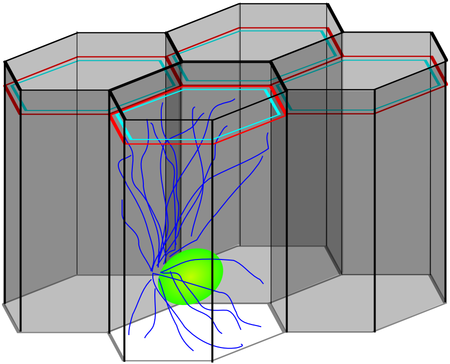
E.g.: Cellular Potts Model

Marée et al., Bull. Math. Biol. (2006) 68: 1169–1211

Simulations of keratocytes by A. Marée

Cellular ingredients "Key components"



Epithelial cells, side view

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actin + myosin

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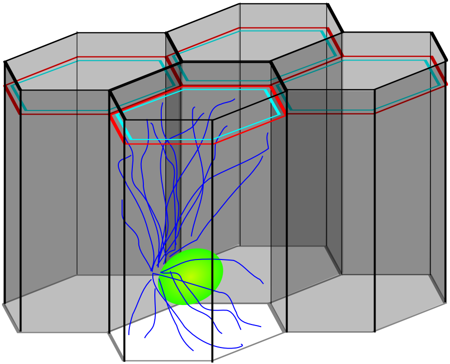

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Cellular Potts Model — Drosophila retina

Zonal adhesion: possible to model in 2D

Experimental observations and surface minimisation

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Experiments

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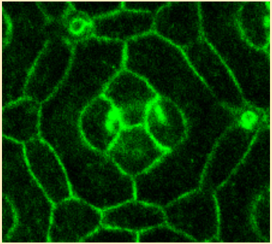
Experiments



Adhesion:
E-cadherin

Experimental observations and surface minimisation

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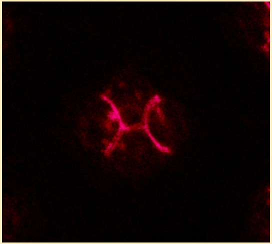

Adhesion:
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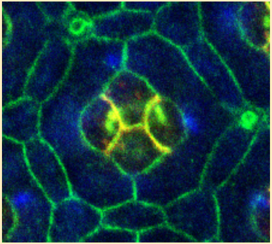

Adhesion:

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More adhesion between cone cells

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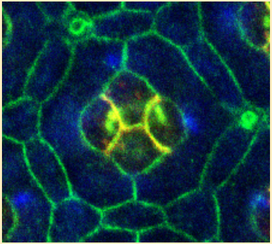

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Each interface has a constant tension

More adhesion = weaker tension = less minimisation

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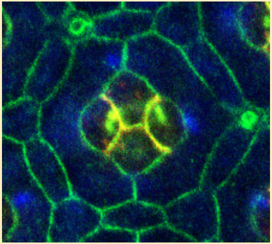

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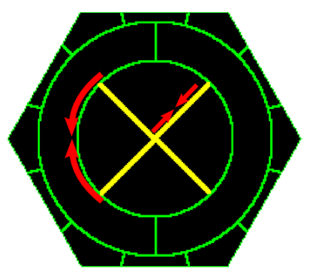
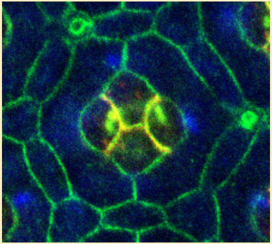


Strong adhesion between cone cells
With **all** cells

Experimental observations and surface minimisation

Experiments



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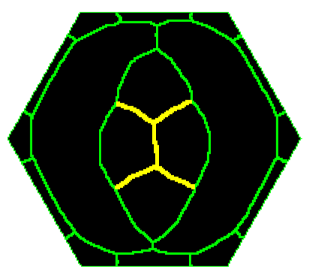

Wrong topology!

Strong adhesion between cone cells
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Experimental observations and surface minimisation

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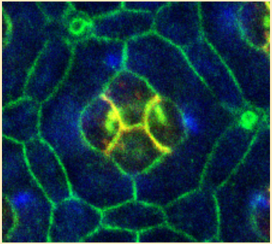

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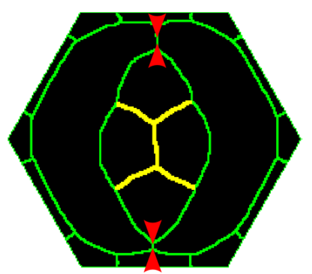

Wrong topology!
Neighbours matter.

Strong adhesion between cone cells

With **all** cells

Adhesion and the cortical cytoskeleton

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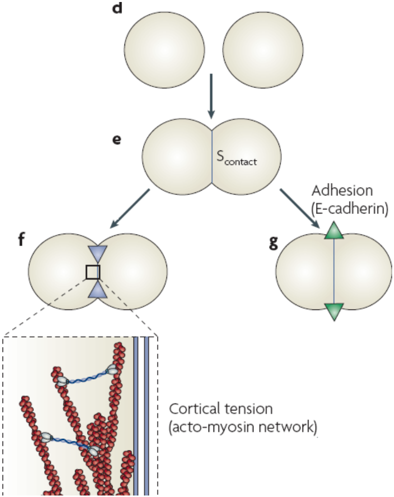
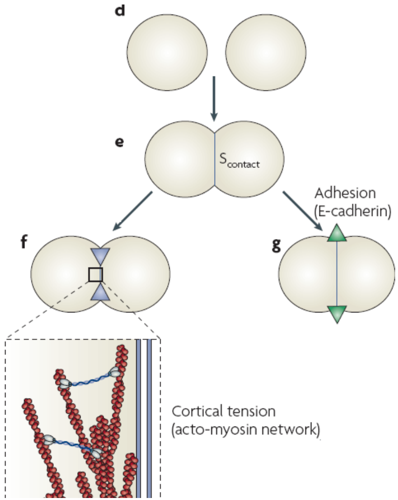


Lecuit & Lenne, Nat. Rev. Mol. Cell Bio. 2007

Model 2: **variable** tension

- cell tension = contraction − adhesion
- adhesion → spreading
- cortical contraction resists spreading
- contraction depends on contact area
- **feedback:** tension ⟷ cell shape

Adhesion and the cortical cytoskeleton



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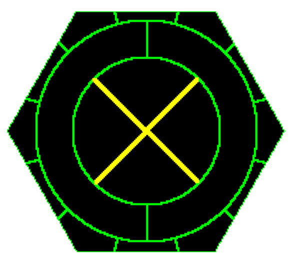

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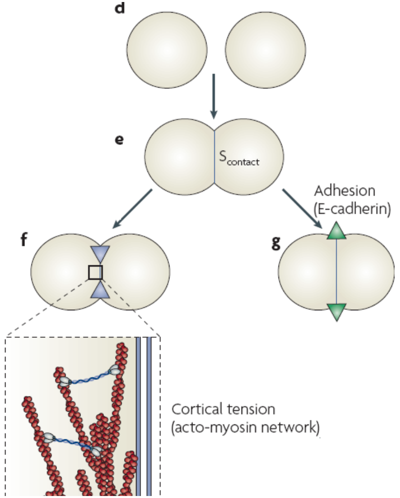

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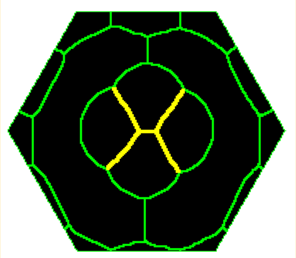

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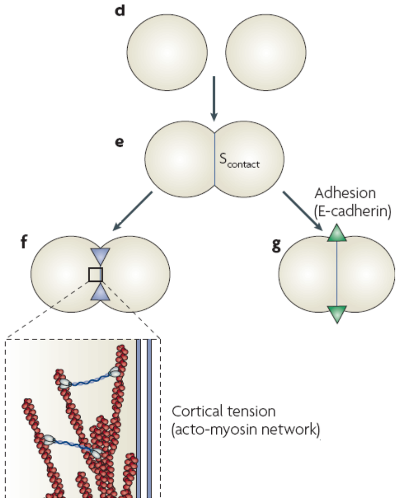

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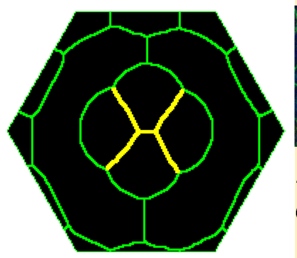

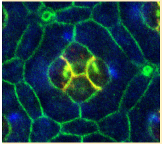

Agrees with observations!

Tests: mutants

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Mutation ➜ change only the corresponding parameter?

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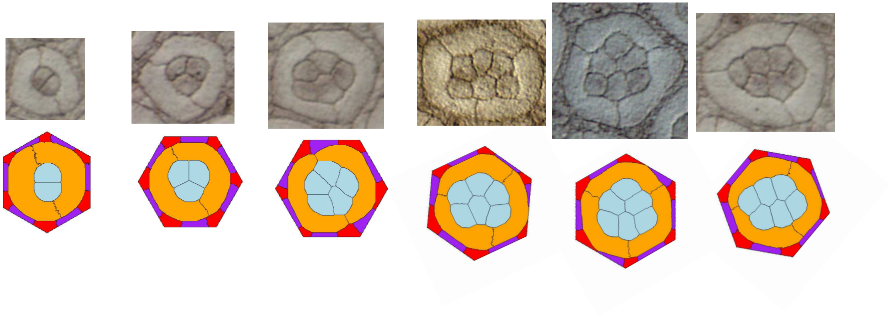
Mutation ➜ change only the corresponding parameter?

Rough eye mutants:

Tests: mutants

Mutation ➜ change only the corresponding parameter?

Rough eye mutants: **Topological** agreement



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Mutation ➜ change only the corresponding parameter?

Rough eye mutants: **Topological** agreement

Cadherin mutants

Wildtype: **N-cadherin** in cone cells, **E-cadherin** in all cells

Mosaic mutants: **decrease** (-) or **increase** (+) in adhesion

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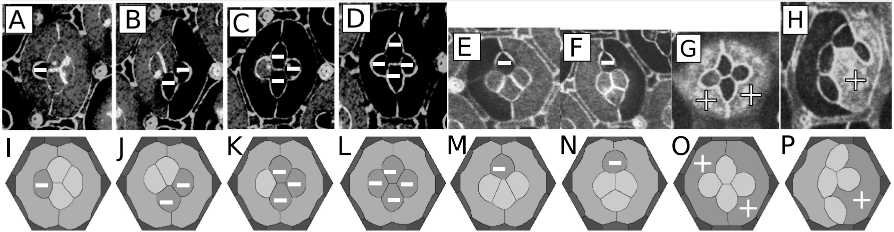

More examples: PNAS, 104:47, p 18549 (2007)

Topological & **geometrical** agreement

Tests: mutants

Mutation ➜ change only the corresponding parameter?

Rough eye mutants: **Topological** agreement

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wildtype + 22 mutant configurations, 6 parameters

Lessons - Part 1

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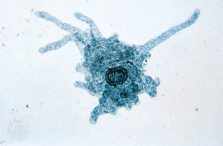
Cells and bubbles



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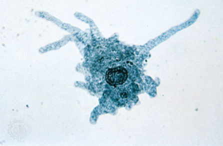
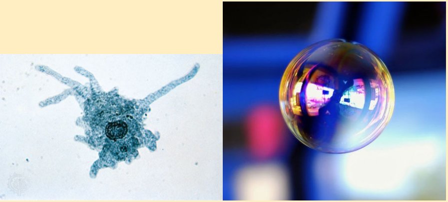


Different physical properties

Lessons - Part 1

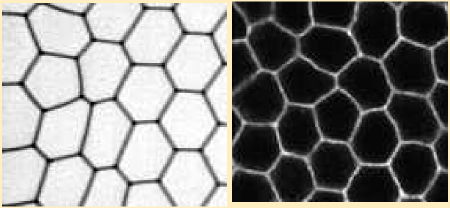
Cells and bubbles



Different physical properties

Tissues and foams

Image: M. Asipauskas, SPECTRO



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Lessons - Part 1

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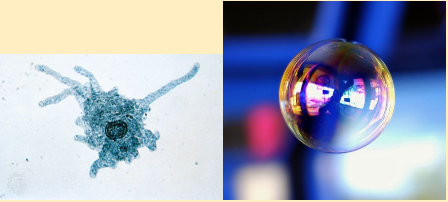

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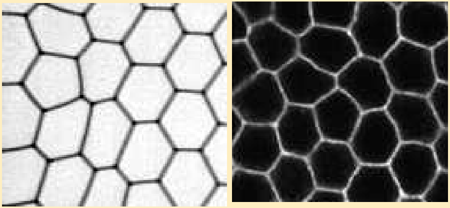

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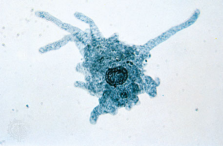
Analogy on collective level

Lessons - Part 1

Cells and bubbles



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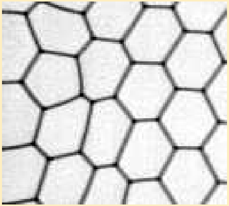

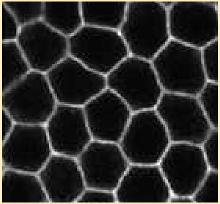

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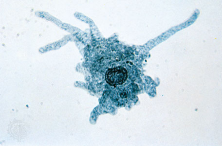
Analogy on collective level

Space tiling pattern:

no gap nor overlap

Lessons - Part 1

Cells and bubbles



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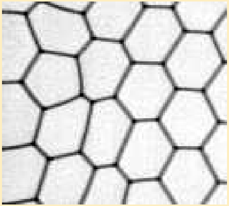

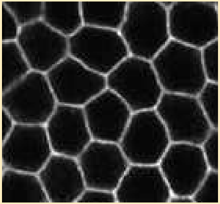

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Analogy on collective level

Space tiling pattern:

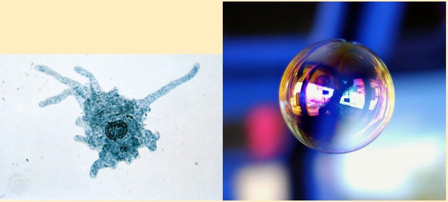
no gap nor overlap

Analogy

Feedback between a cell's shape and its neighbour's shapes

Lessons - Part 1

Cells and bubbles



Different physical properties

Specific for cells

Adhesion and cortical tension

Feedback between shape and tension

Tissues and foams

Image: M. Asipauskas, SPECTRO

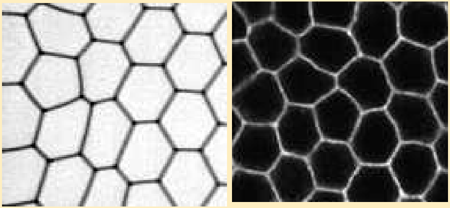


Image: Blankenship et al, Dev. Cell 2006

Analogy on collective level

Space tiling pattern:

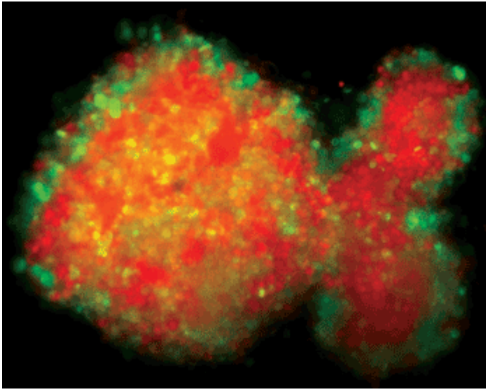
no gap nor overlap

Analogy

Feedback between a cell's shape and its neighbour's shapes

Cell sorting of zebrafish germlayer cells

With M. Krieg & D.J. Müller
Biotec, Technische Universität Dresden,
Y. Arboleda & C.-P. Heisenberg
MPI-CBG, Dresden

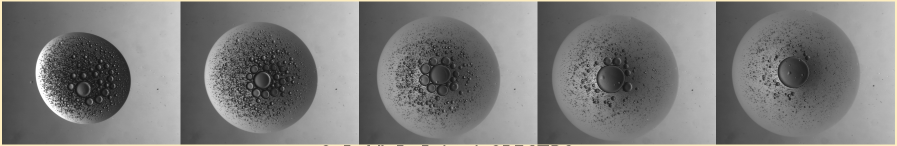


Krieg et al., Nat. Cell Biol. 2008, cover

Cell sorting and liquid phase separation

Cell sorting and liquid phase separation

Demixing of liquids: water and oil



S. Rafaï, D. Rabaud, SPECTRO

Water molecules have strongest affinity, and end up in the centre

Cell sorting and liquid phase separation

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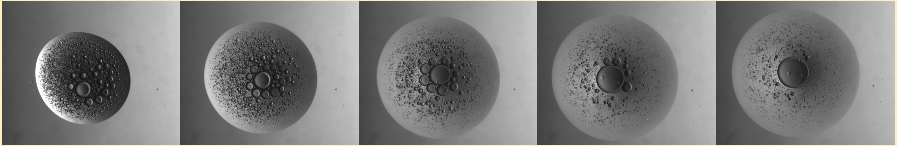

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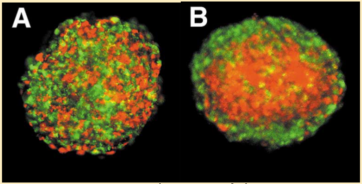
Differential Adhesion Hypothesis (DAH): Steinberg, 1963



Duguay et al, Dev. Biol. 2003

- Different cell types adhere with different strengths
- Cell sorting is like liquid demixing: weakly adhering cells surround strongly adhering cells

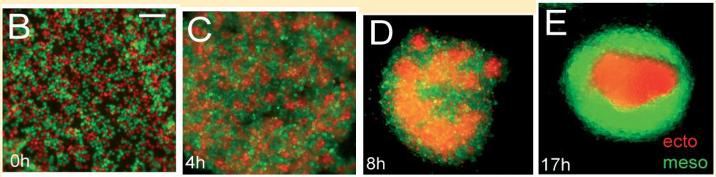
Zebrafish experiments

M. Krieg, Y. Arboleda & C.-P. Heisenberg

Zebrafish experiments

M. Krieg, Y. Arboleda & C.-P. Heisenberg

Cell sorting



DAH predicts: ectoderm cells adhere most

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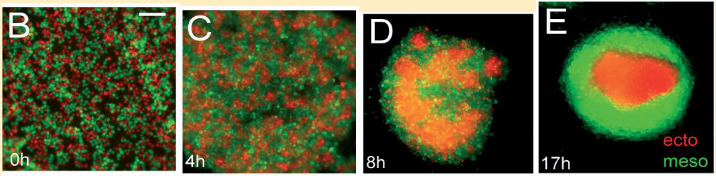

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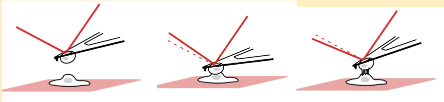
Atomic Force Microscopy - measure cell-cell adhesion pairwise



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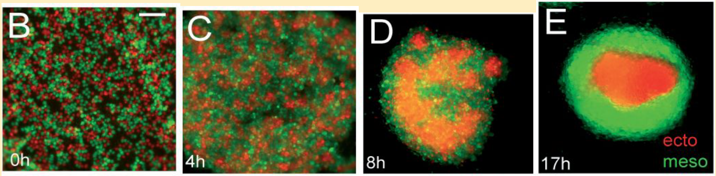

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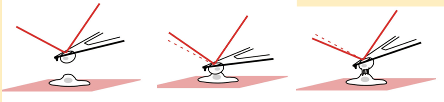


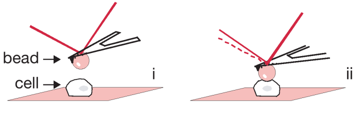
mesoderm cells adhere most!

Contradicts DAH!

Cortex tension

Cortex tension

Alternative explanation? AFM



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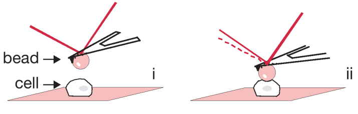

ectoderm cells have higher cortex tension

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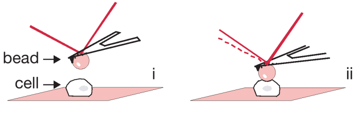

ectoderm cells have higher cortex tension

Simulations

Ectoderm

weak adhesion, high cortex tension

Meso-/Endoderm

strong adhesion, weak tension

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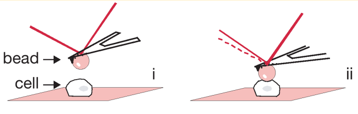

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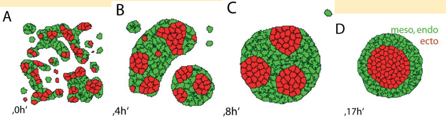

Prediction: only works IF cortex-tension is interface-specific

Cortex tension

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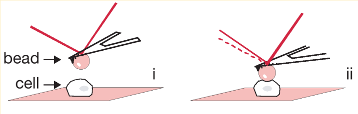

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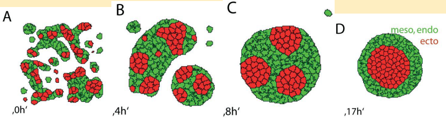

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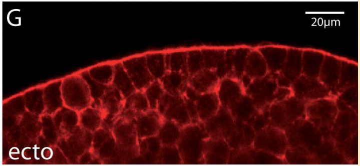
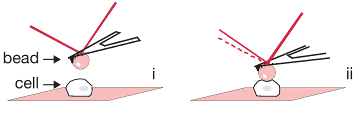


Y. Arboleda, MPI-CBG

Interface-specific density of actin!

Cortex tension

Alternative explanation? AFM



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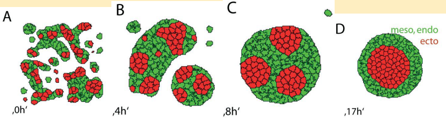

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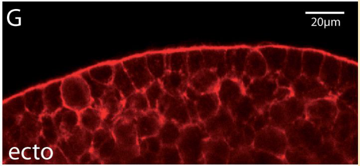

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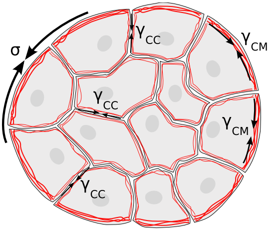
Interface-specific density of actin!

New hypothesis, beyond DAH

Both adhesion AND cortex tension

Lessons - Part 2

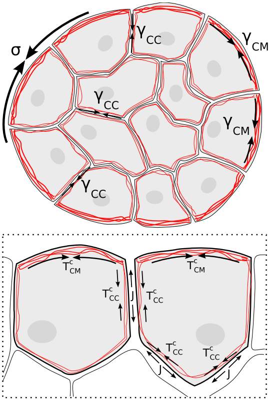
Lessons - Part 2



Like liquids

Aggregate surface tension σ determines cell sorting
Difference of interfacial energy γ determines σ

Lessons - Part 2



Like liquids

Aggregate surface tension σ determines cell sorting
Difference of interfacial energy γ determines σ

Specific for cells

Interfacial energy γ = contraction T - adhesion J
Differential contraction influences σ and cell sorting

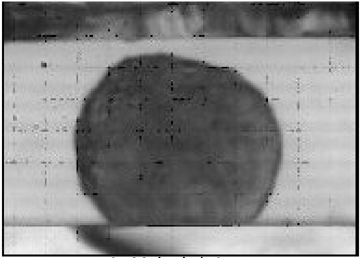
Compression of cell aggregates

With A. Mgharbel, H. Delanoë-Ayari, J.-P. Rieu: experiments

LPMCN, Lyon

P. Marmottant: physical model

SPECTRO, Grenoble



A. Mgharbel, Lyon

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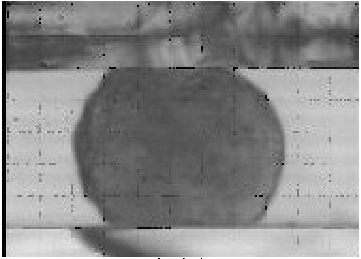

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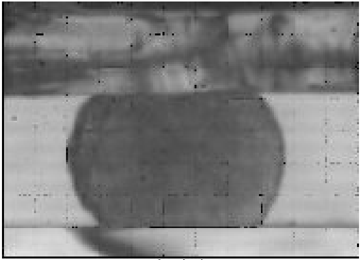

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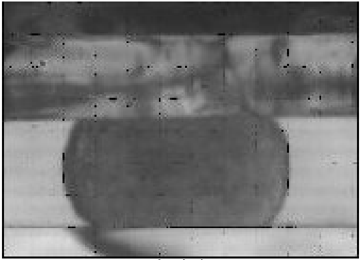

A. Mgharbel, Lyon

Aggregate compression

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Motivation

Measuring aggregate surface tension

In vitro study of effect of cell properties on collective level

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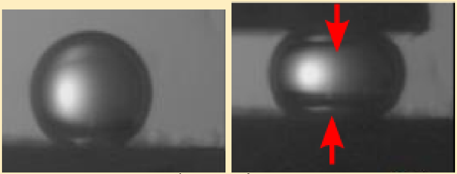
In vitro study of effect of cell properties on collective level

Analogy with liquid drops



Norotte et al., Europhys. Lett. 2008

Compression requires force

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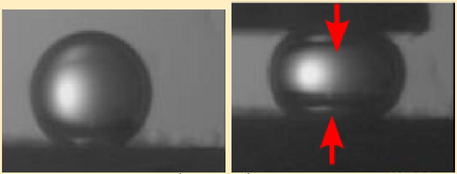

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surface tension =

pressure difference / curvature

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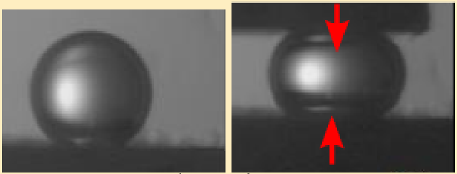

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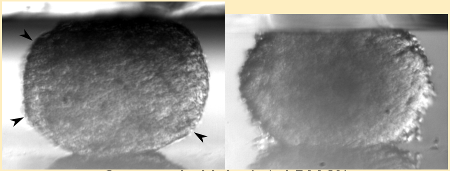

Courtesy A. Mgharbel, LPMCN

Asymmetry Irregular interface

➜ Not completely liquid?

Aggregate compression

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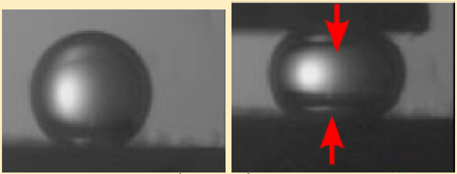

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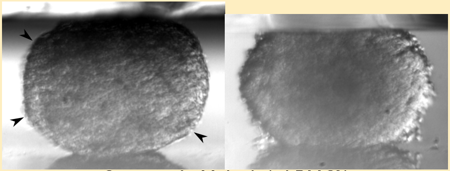

Courtesy A. Mgharbel, LPMCN

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➜ Not completely liquid?

Laplace's law only works for liquids: throw away these experiments?

Experiments, simulations, model

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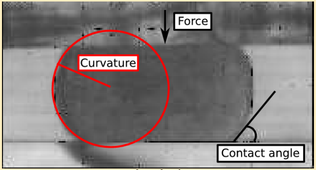
Experiments

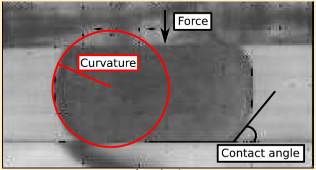


A. Mgharbel, Lyon

Measure force, curvature
Vary cell properties (cell types, mutants, drugs)

Experiments, simulations, model

Experiments



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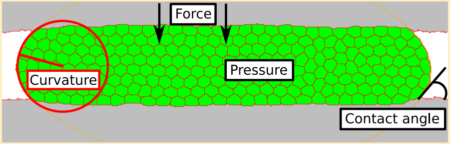


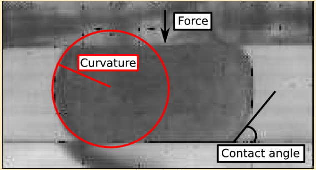
Measure force, pressure, curvature

Cell properties are known

Control the parameters one by one

Experiments, simulations, model

Experiments



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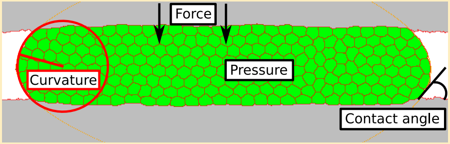

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P. Marmottant et al, PNAS 2009 106:17271-17275

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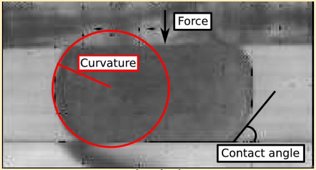

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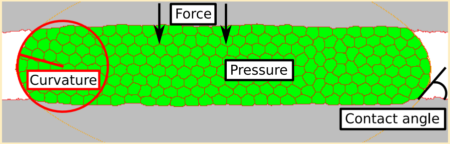

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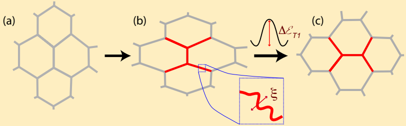

- Rearrangements
- energy barriers vs fluctuations
- link to cell parameters
- $\tau = 2\tau^* \tanh^{-1}\left[\tanh\left(\frac{\tau_0}{2\tau^*}\right)\exp\left(-\frac{t}{t_c}\right)\right]$

time over which stress disappears: $t_c \sim \exp\left(\frac{\Delta\mathcal{E}_{T1}}{\xi}\right)$

Lessons - Part 3

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Physics

Aggregate: from complex liquid to plastic solid - multiple time scales

Need an explicit model for cell rearrangements

➜ foam physics: space-tiling without gap nor overlap

Lessons - Part 3

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Adhesion, cortical tension, active fluctuations

Lessons - Part 3

Physics "The way cells *interact*"

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Bio-physical model

Allows to answer specific biological questions

Wishes

Wishes

Modeller

Experimentalist

Wishes

Modeller

- Finer - simulations or physical model of intracellular cytoskeleton
- Coarser - physical model (e.g. part 3)
- Time - dynamics of development, cell differentiation

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Measure individual cells quantitatively

- in vitro
- in vivo

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- Time - dynamics of development, cell differentiation

Experimentalist

Measure individual cells quantitatively

- in vitro
- in vivo
- forces, constraints (e.g. laser ablation)
- shape, packing (time-lapse microscopy, 2 & 3D)

Combine experiments & computation

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Experimental biology

- Starts with a **complex** organism
- When doesn't it function anymore (knockouts)?
- identify genes, reconstruct pathways, supply hypotheses

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- How to get the observed behaviour?
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and 'compute' it back together

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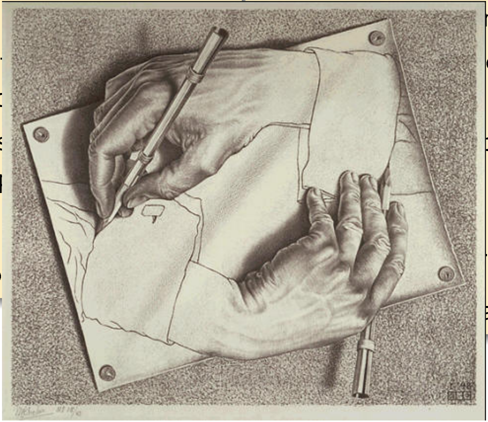

M.C. Escher, Drawing hands, 1948

Close collaboration between modellers and experimentalists
Experiments and models progress **together**