Introduction to Systems Biology
Lecture 14 Part B-1

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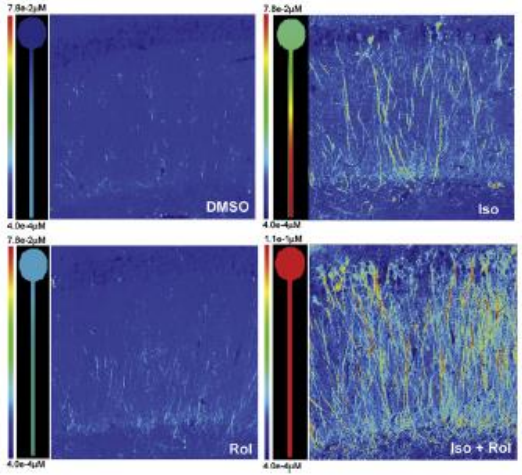
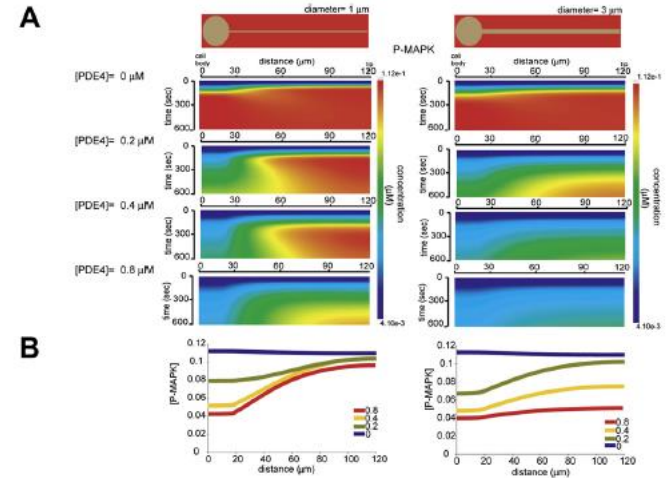
Origins of Microdomains : Both cellular geometry and enzymatic activity of negative regulators are needed

Simulations of MAPK activation in cell body and dendrites → → →

Experimental Verification :
Immunofluorescence of activated MAPK in brain slices ↓

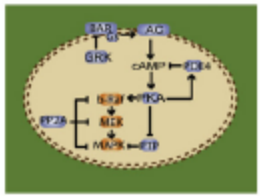




Neves et al (2008) Cell 133, 666–680

PDE4 – phosphodiesterase 4

Rolipram- a chemical inhibitor of phosphodiesterase 4



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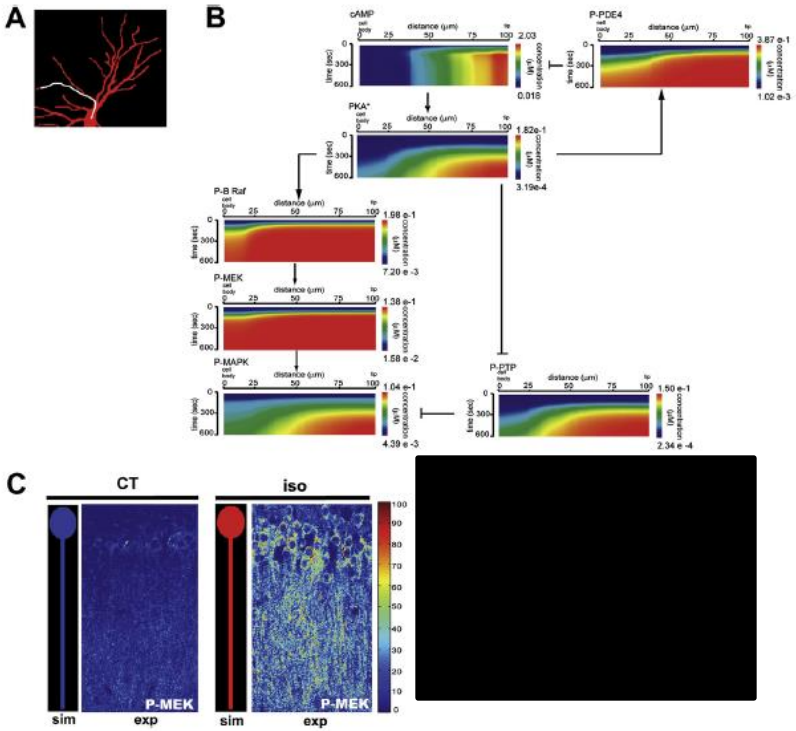
Following the flow of spatial information within a dendrite

Dendrite marked in white in (A) was used for simulations

Note how the shape of the PKA gradient , is recapitulated in the MAPK gradient.

However MEK activation is uniform and does not show a gradient

Experimental verification of MEK activation



Neves et al (2008) Cell 133, 666–680

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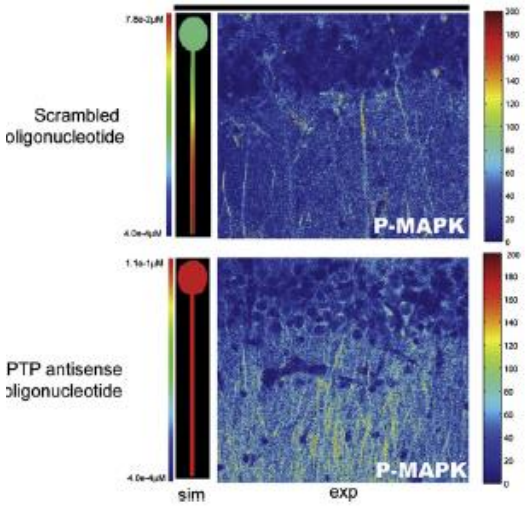
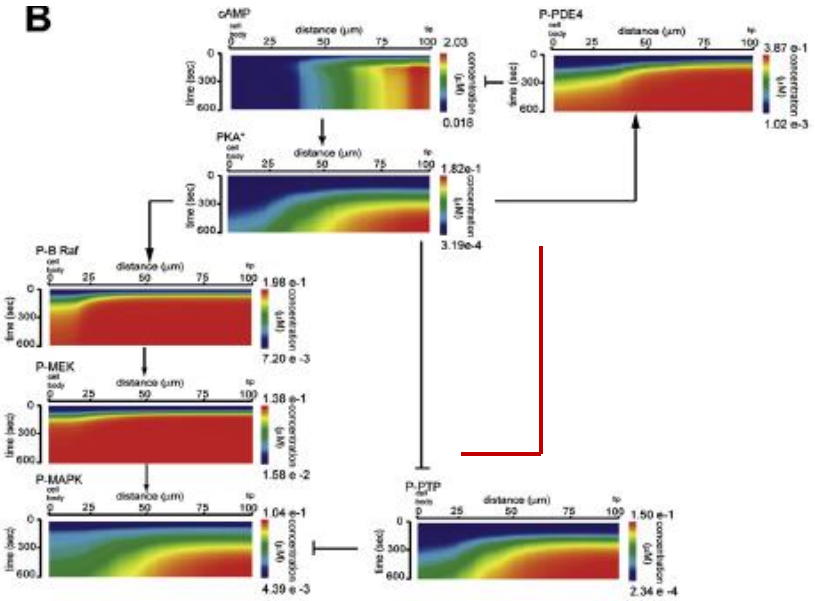
The activity of phosphotyrosine phosphatase (PTP), negative regulator of MAPK is required for PKA gradient to be recapitulated at the level of MAPK

Simulations →

Experiments ↓





Neves et al (2008) Cell 133, 666–680

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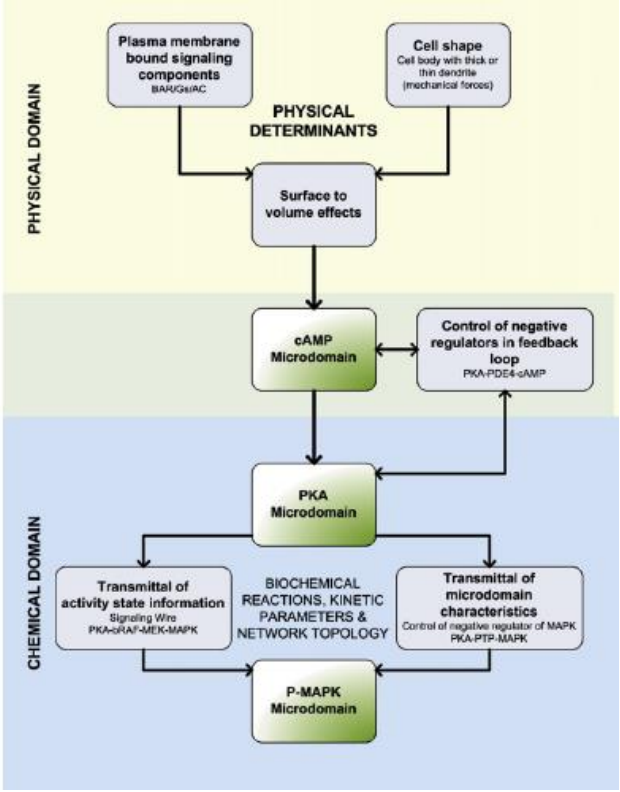
Conclusions

1. Multiple factors including subcellular geometry and enzymatic activities are responsible for microdomains

2. Spatial information is a distinct entity that can be separately transmitted fro information regarding activity states

3. Partial Differential Equation Models can provide deep insight into dynamics of subcellular processes.



Neves et al (2008) Cell 133, 666–680

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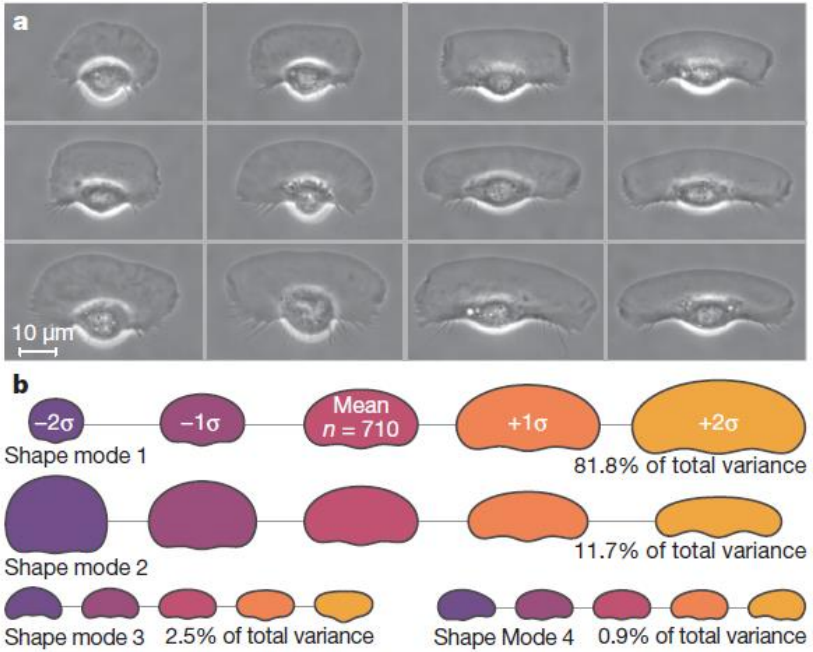
Case study: How do moving cells determine their shape?

Fish skin epithelial cells –keratocytes

Fast moving cells in culture
During movement they maintain shape and speed

Four characteristics (modes) provide a nearly complete (97%) description of The shape of a large population of keratocytes

Mode 1 D shaped
Mode 2 canoe shaped
Mode 3 cell body position
Mode 4 right-left symmetry



Keren et al (2008) Nature 453: 475

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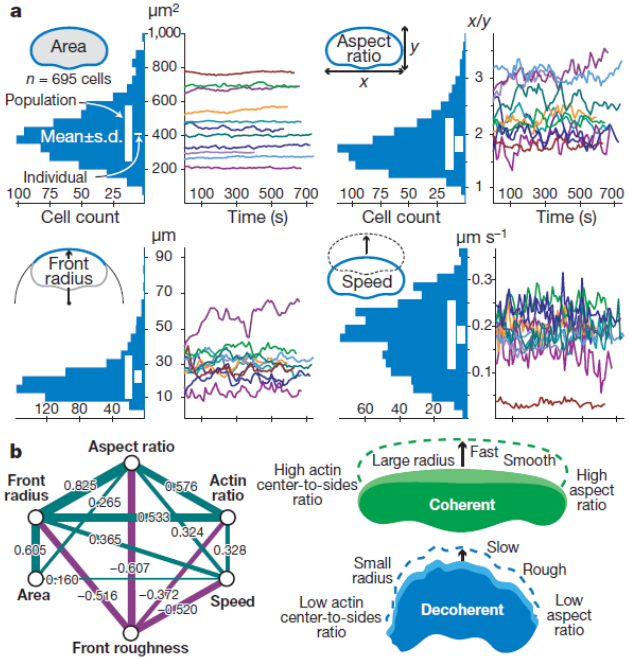
For moving cells shape and speed can be correlated

*"**A**. The distributions of measures across a population of live keratocytes (left panels) are contrasted with values through time for 11 individual cells (right). Within each histogram, the population mean ± one standard deviation is shown by the left vertical bar,.*

B, Significant pair-wise correlations(P,0.05; bootstrap confidence intervals) within a population of keratocytes are diagrammed (left panel). Two additional measures are included: front roughness, which measures the local irregularity of the leading edge, and actin ratio, which represents the peakedness of the actin distribution along the leading edge. The correlations indicate that, apart from size differences, cells lie along a single phenotypic continuum (right panel), from 'decoherent' to 'coherent'. Decoherent cells move slowly and assume rounded shapes with low aspect ratios and high lamellipodial Curvatures..Coherent cells move faster and have lower lamellipodial curvature.



Keren et al (2008) Nature 453: 475

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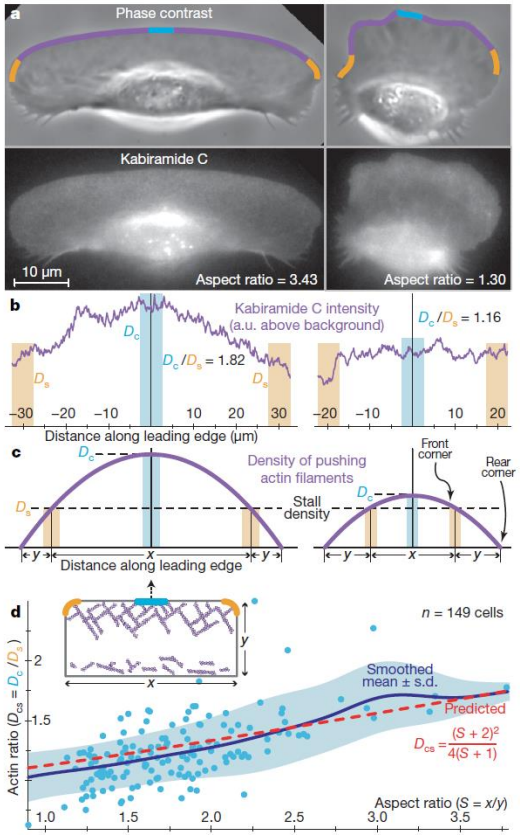
A mathematical model provides a direct link between the distribution of actin filaments and overall cell morphology

A: Cell shape and actin filament density as measured fluorescent kabiramide staining

B & C – Quantification of shape and actin filament density

D Comparison between model (red Line) and experimentally determined relationship between cell shape (aspect ratio) and actin filament density (Actin Ratio)

Match looks very good!



Keren et al (2008) Nature 453: 475

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Supplementary Table 1: Model Assumptions

Assumption	Rationale for assumption	Level of confidence in assumption	How critical is the assumption
There is a constant number of branching events per second per cell.	It produces prediction of the scaling property of the graded actin filament density that many models fail to produce[1].	Moderate	Moderately critical; other models could predict graded density.
The density of pushing filaments at the rear corners of the lamellipodium is zero.	It is likely that this density is small; assuming it zero simplifies the model and produces excellent parameter-less fit.	Moderate	Moderately critical; assuming a small, non-zero density produces reasonable fits as well.
Membrane tension is spatially constant.	Known for in vitro membrane physics; see estimates in this paper.	High	Highly critical.
Cell shape can be approximated by a slightly bent rectangle.	Shape analysis.	High	Not very critical; it makes the model algebra much easier.
Membrane resistance is distributed equally locally among the growing filaments.	Theoretical arguments previously published[2,3].	High	Highly critical.
Protrusion is force-limited; the force–velocity relation is concave down.	Indirectly indicated by our data; previously published measurements[4,5].	High	Highly critical.
Filaments grow on average in a direction locally normal to the boundary.	Previously published work[6].	Moderate	Moderately critical; other mechanisms would complicate the model.
Growing filaments are stalled or buckled at the cell sides.	Speculation	Moderate	Highly critical; this is the central assumption of our force-balance model.
Myosin-powered contraction produces a significant centripetal actin network flow only at the very rear of the cell.	Measurements of actin network flow[7].	High	Not very critical; otherwise, relatively small corrections to the model required.

Even simple models have underlying assumptions in writing out the equations for the model

This table clearly lays out the assumptions

A very straightforward and useful way to show How you are building a model

Note the speculative assumption !
Since the model calculations agree with the the experimentally observed relationship it is reasonable to assume that this speculative assumption is correct

However no direct experimental proof such as visualization of stalled or buckled filaments is provided

Keren et al (2008) Nature 453: 475

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" To describe cell shape with more accuracy and to relate cell speed to morphology, we must consider the relationship between the growth rate of actin filaments and the magnitude of force resisting their Growth ".

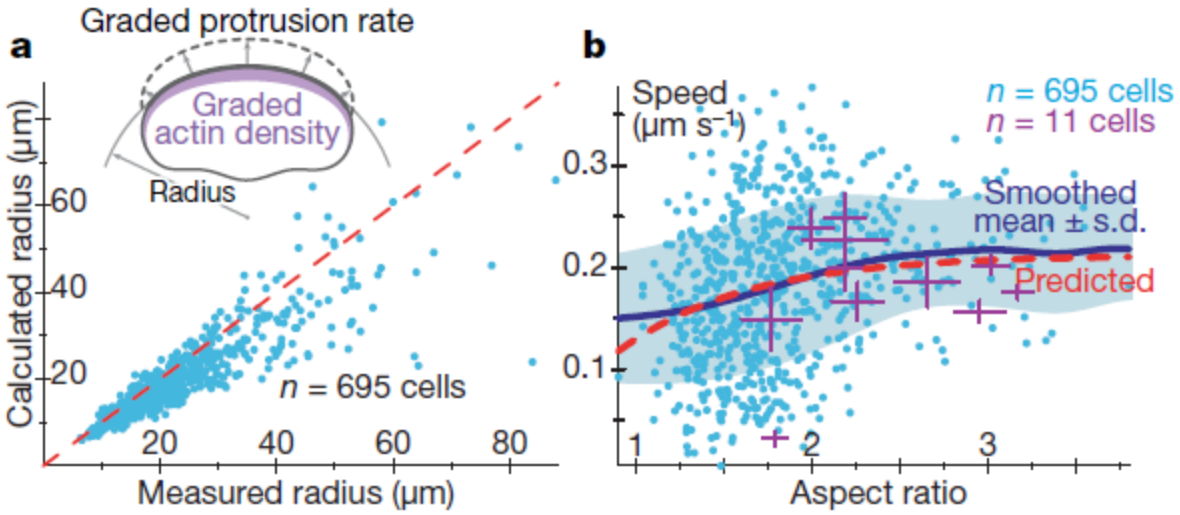
A Comparing experimental vs model derived radius of the leading edge - good co-relation

From this shape of cells the speed of movement can be predicted using the mathematical formula that relates speed to aspect ratio of the cell. .

B relationship between speed and cell shape (aspect ratio)

Good agreement between model and experiments

High level relationship between cell shape and cell speed



Keren et al (2008) Nature 453: 475

Conclusions – Cell Spreading Model

Relatively simple mathematical models can accurately describe complex cellular behaviors

All models have underlying assumptions and these should be clearly stated

The relationship between speed of movement of whole cells and shape of cells can be accurately predicted by using the dynamics of actin cytoskeleton and its interaction with the plasma membrane

Feasibility of building complex models: Knowing what details to include in a model is critical