Mechanical modeling of actin growth

Giuseppe Tomassetti

DICII Department
University of Rome Tor Vergata

Collaboration with Rohan Abeyaratne and Tal Cohen

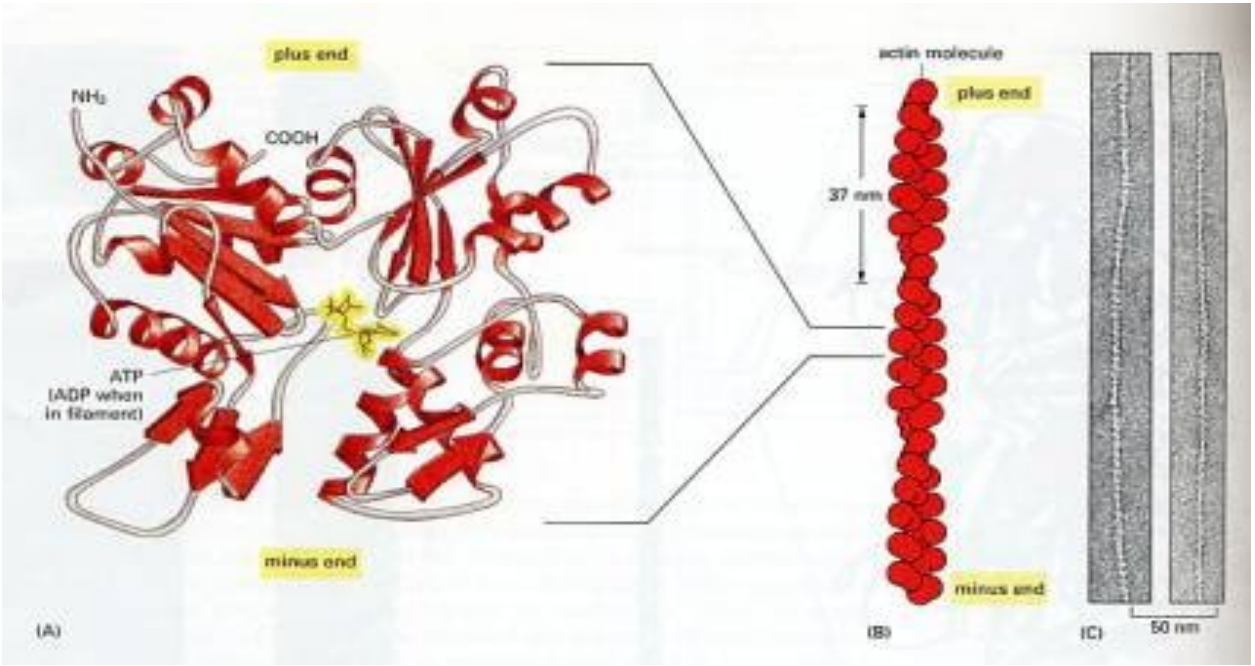
Outline:

- Motivation: actin-based motility
- Actin microfilaments: polymerization and treadmilling
- Modeling of gel growth

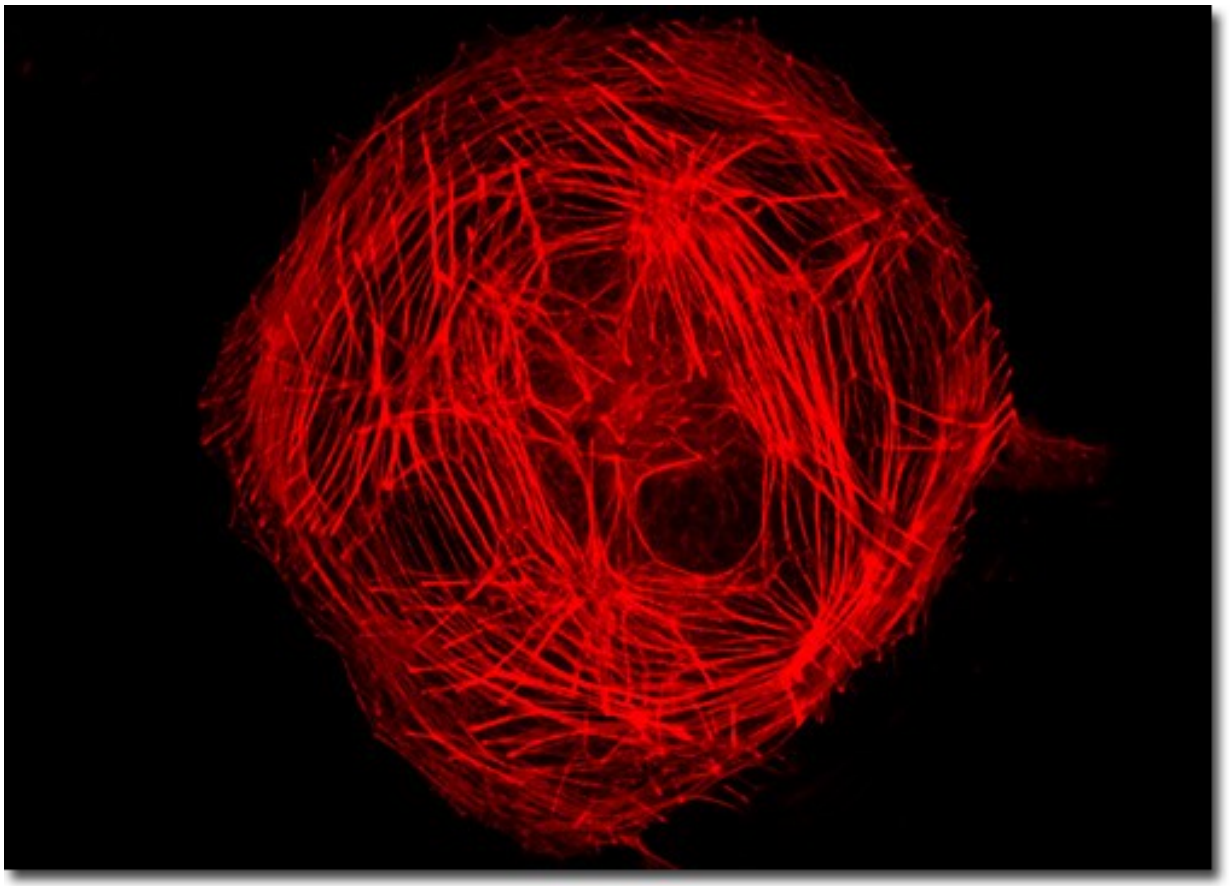
G-actin and F-actin

Actin

- Multifunctional protein found in almost all eukaryotic cells.
- It can be present as either a free monomer called **G-actin** or as part of a linear polymer microfilament called **F-actin**.



Actin filaments assemble to form complex networks in the cell

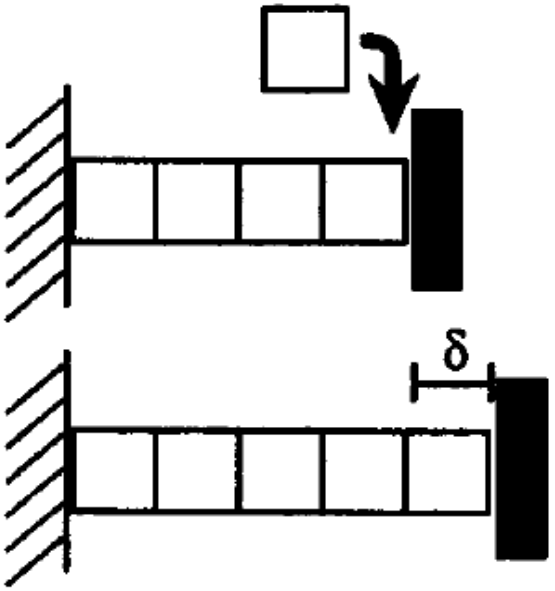


Fluorescence emission intensity of the intracellular cytoskeletal **F-actin network** in a bovine pulmonary artery endothelial cell.

Image from: https://www.microscopyu.com

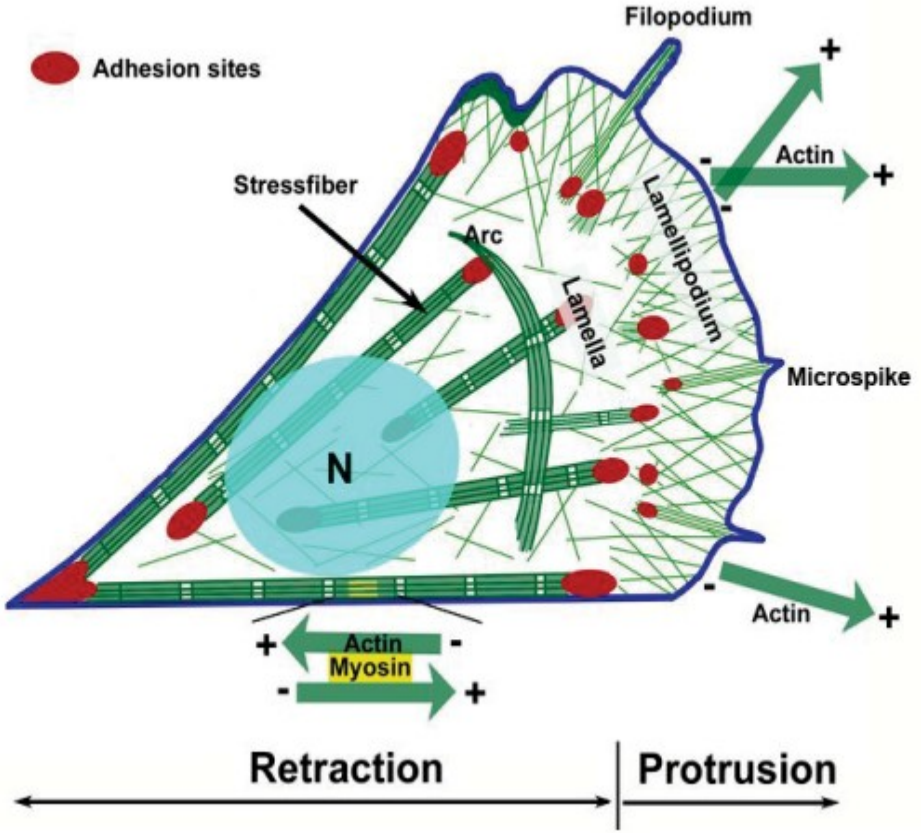
(Nikon microscopy)

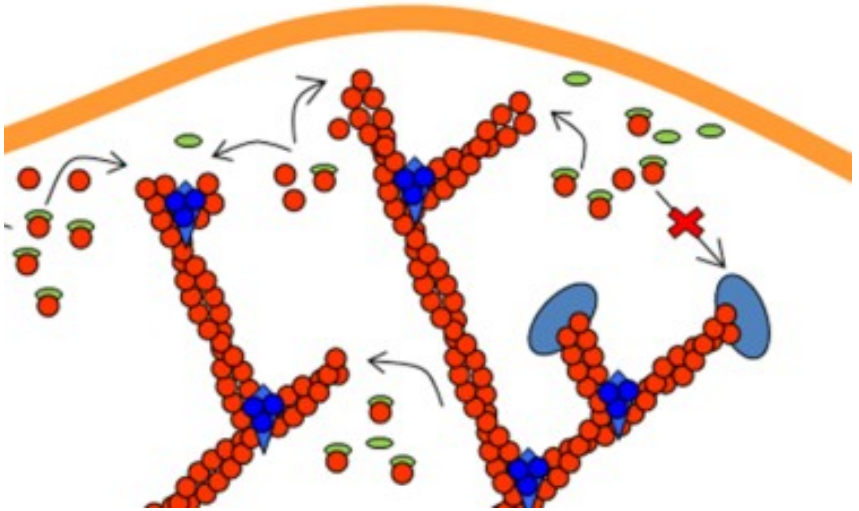
- Through polymerization, actin can function as a **motor**



$\delta \simeq 3$ nm

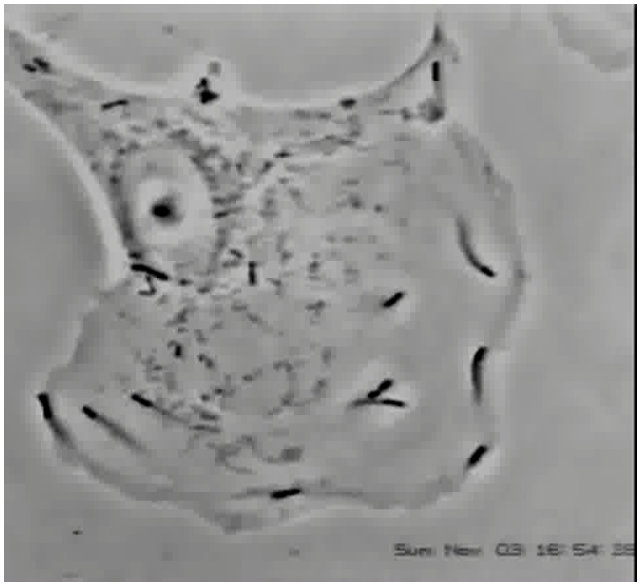
actuation force $\simeq$ pN

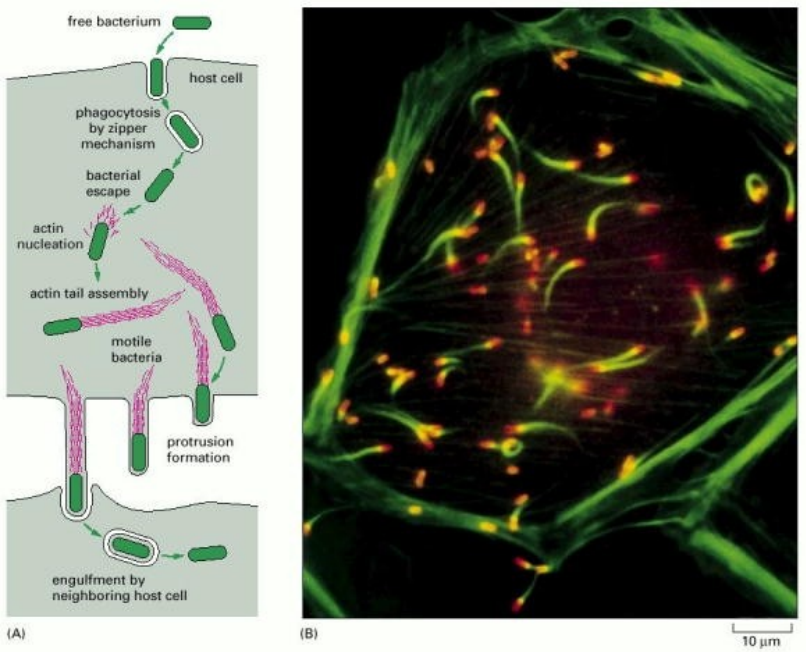

Filopodium
Adhesion sites
Actin
Stressfiber
Arc
Lamellipodium
Lamella
Microspike
N
Actin
Myosin
Actin
Retraction
Protrusion



Actin-based motility

- Intracellular bacterium **Listeria monocytogenes** rely on host cell actin for motility





- The *actin assembly inducing protein* (ActA) on the surface of the bacterium induces actin polimerization which results in a *comet tail* made of a network of cross-linked F-actin filaments.

- The comet tail propels the bacterium through the host cell.

Growth of actin gels on spherical beads

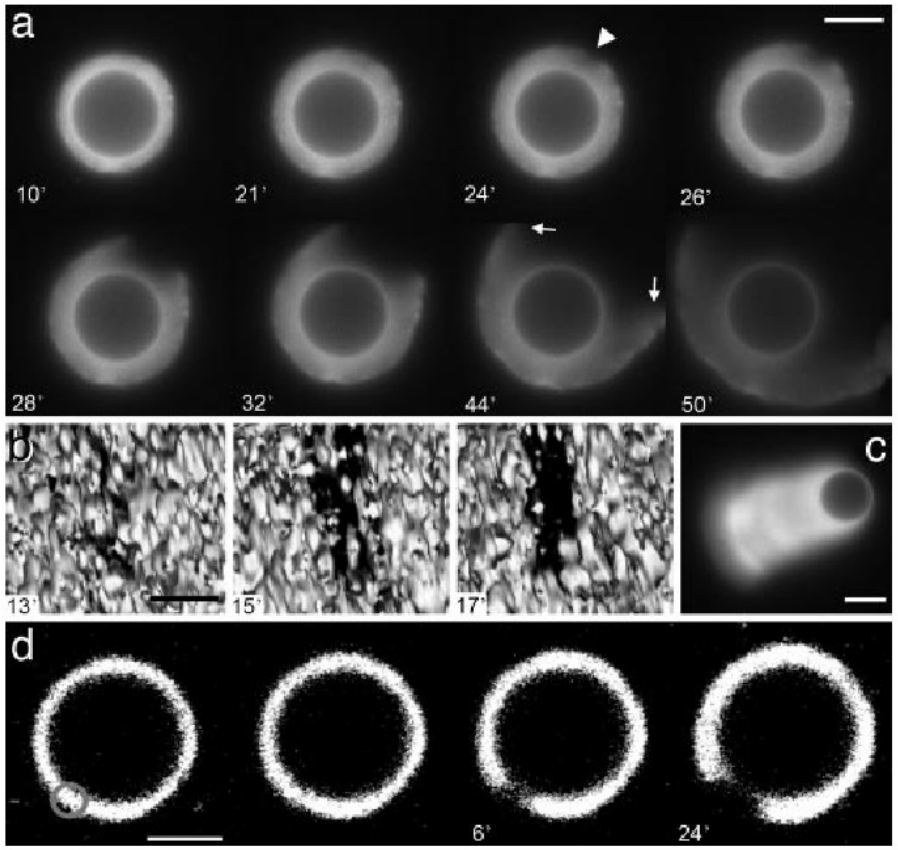


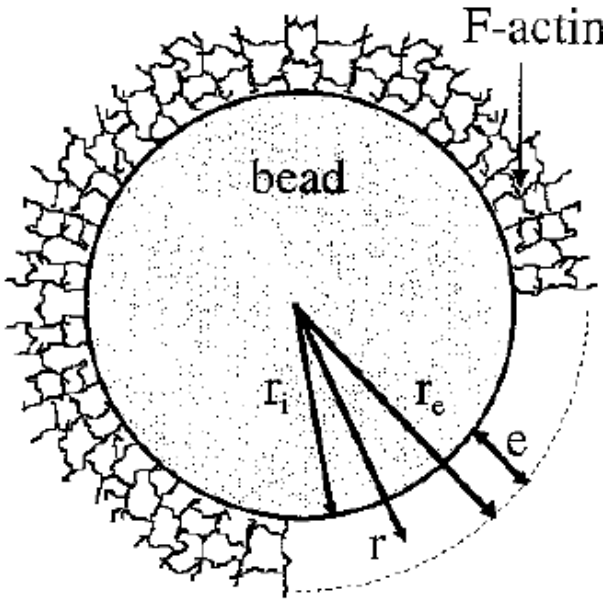
Fig. 1. Spontaneous and induced symmetry breaking around beads. VCA-

Stress release drives symmetry breaking for actin-based movement

Jasper van der Gucht†, Ewa Paluch, Julie Plastino, and Cécile Sykes

Laboratoire Physico-Chimie Curie, Unité Mixte de Recherche 168, Institut Curie, 11 Rue Pierre et Marie Curie, 75231 Paris, Cedex 5, France

Communicated by Pierre-Gilles de Gennes, Collège de France, Paris, France, April 7, 2005 (received for review February 24, 2005)



Biophysical Journal Volume 78 March 2000 1643–1654

Growing an Actin Gel on Spherical Surfaces

V. Noireaux,* R. M. Golsteyn,† E. Friederich,† J. Prost,* C. Antony,† D. Louvard,† and C. Sykes*

*Laboratoire Physico-Chimie "Curie," Unité Mixte de Recherche CNRS/Institut Curie (UMR 168), 75231 Paris Cedex 05, and †Laboratoire Compartimentation et Dynamique Cellulaire, Unité Mixte de Recherche CNRS/Institut Curie (UMR 144), 75248 Paris Cedex 05, France

ABSTRACT Inspired by the motility of the bacteria *Listeria monocytogenes*, we have experimentally studied the growth of an actin gel around spherical beads grafted with ActA, a protein known to be the promoter of bacteria movement. On ActA-grafted beads F-actin is formed in a spherical manner, whereas on the bacteria a "comet-like" tail of F-actin is produced. We show experimentally that the stationary thickness of the gel depends on the radius of the beads. Moreover, the actin gel is not formed if the ActA surface density is too low. To interpret our results, we propose a theoretical model to explain how the mechanical stress (due to spherical geometry) limits the growth of the actin gel. Our model also takes into account treadmilling of actin. We deduce from our work that the force exerted by the actin gel on the bacteria is of the order of 10 pN. Finally, we estimate from our theoretical model possible conditions for developing actin comet tails.

Experimental results

TABLE 1 Thickness of the actin gel as a function of the radius of the beads

r_i (μm)	Estimate of the ActA Density	e (nm)	Quotient e/r_i
0.48 ± 0.02	saturated (5.6 ± 0.6 10^{16} prot./m^2)	94 ± 10	2×10^{-1}
0.95 ± 0.04	saturated (5.6 ± 0.6 10^{16} prot./m^2)	146 ± 10	1.5×10^{-1}
4.72 ± 0.48	saturated (5.6 ± 0.6 10^{16} prot./m^2)	503 ± 20	1×10^{-1}
10.1 ± 0.5	saturated (5.6 ± 0.6 10^{16} prot./m^2)	790 ± 20	0.8×10^{-1}

A stationary state is attained (the gel stops growing)

The thickness of the gel appears to be proportional to the radius of the bead

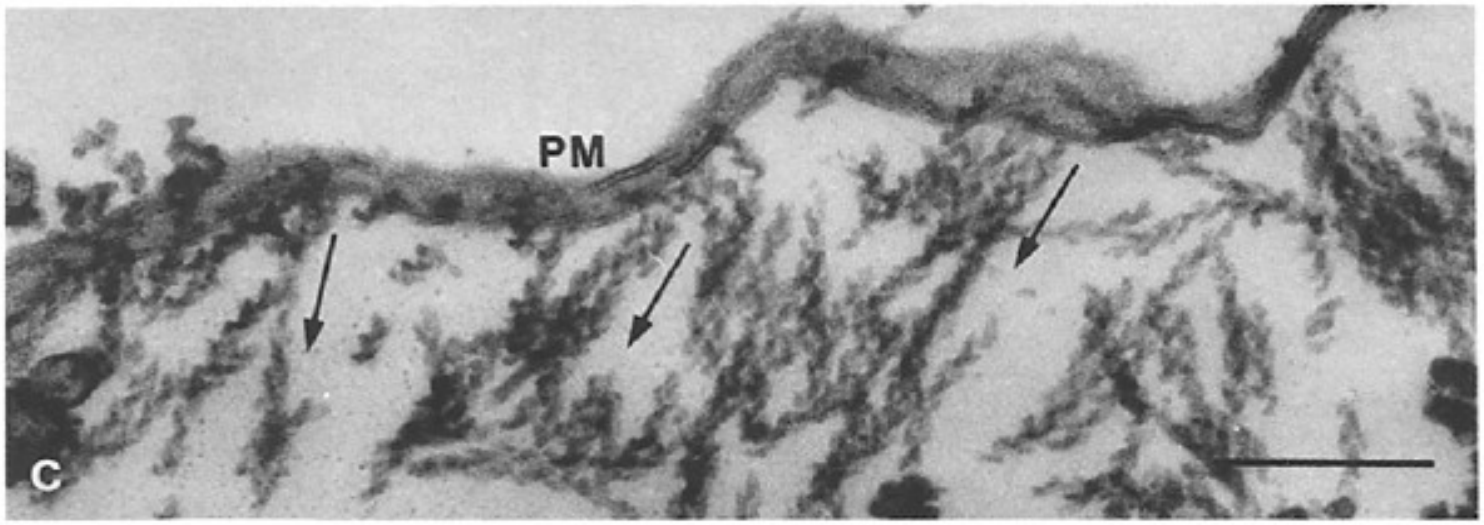
e=thickness

r_i radius of the bead

Outline:

- Motivation: actin-based motility
- Actin microfilaments: polymerization and treadmilling
- Modeling of gel growth

Myosin decoration: the barbed end and the pointed end.

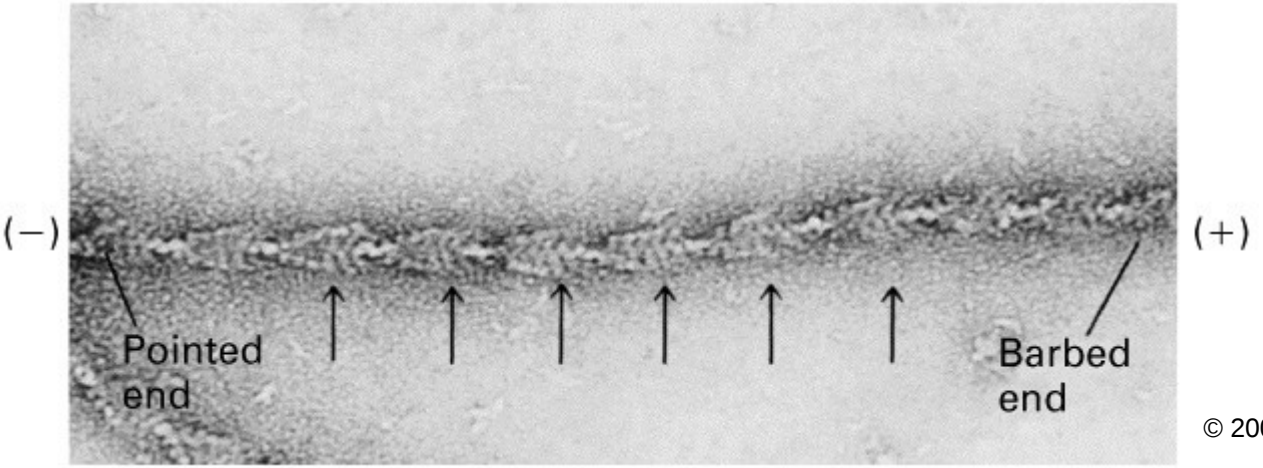


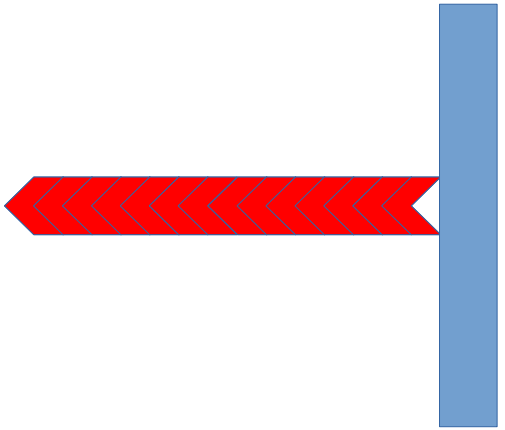
THE VISUALIZATION OF ACTIN FILAMENT POLARITY IN THIN SECTIONS

Evidence for the Uniform Polarity of Membrane-Associated Filaments

DAVID A. BEGG, RICHARD RODEWALD, and LIONEL I. REBHUN. From the Department of Biology, University of Virginia, Charlottesville, Virginia 22901

846 J. CELL BIOLOGY © The Rockefeller University Press · 0021-9525/78/1201-0846$1.00
Volume 79 December 1978 846–852





ADENOSINETRIPHOSPHATE
THE FUNCTIONAL GROUP OF ACTIN*

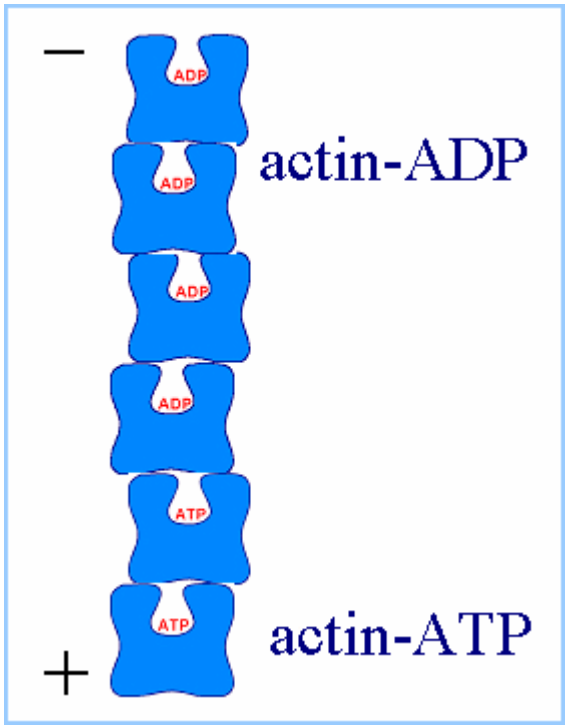
by

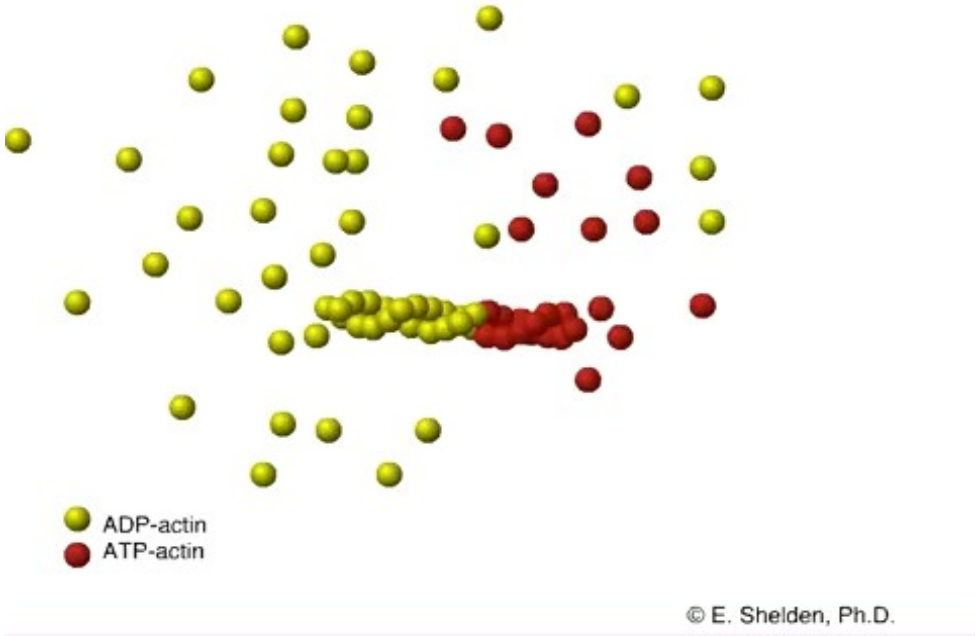
F. B. STRAUB AND G. FEUER

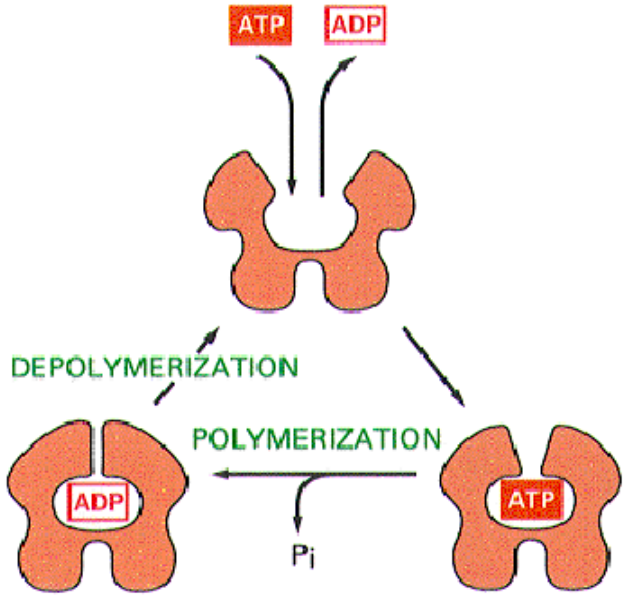
Institute of Medical Chemistry, University of Szeged (Hungary)

INTRODUCTION

In a previous communication we have reported the presence of a heat-stable, dialysable substance in actin, the removal of which leads to the inactivation of actin[1]. Recently we were able to show[2] the regular presence of a considerable amount of adenosine-triphosphate (ATP) in actin solutions. It will be shown in the present paper that ATP is actually the functional group of actin, firmly bound to the protein. The most characteristic property of actin, its polymerization in presence of salts, is connected with the disappearance of ATP.





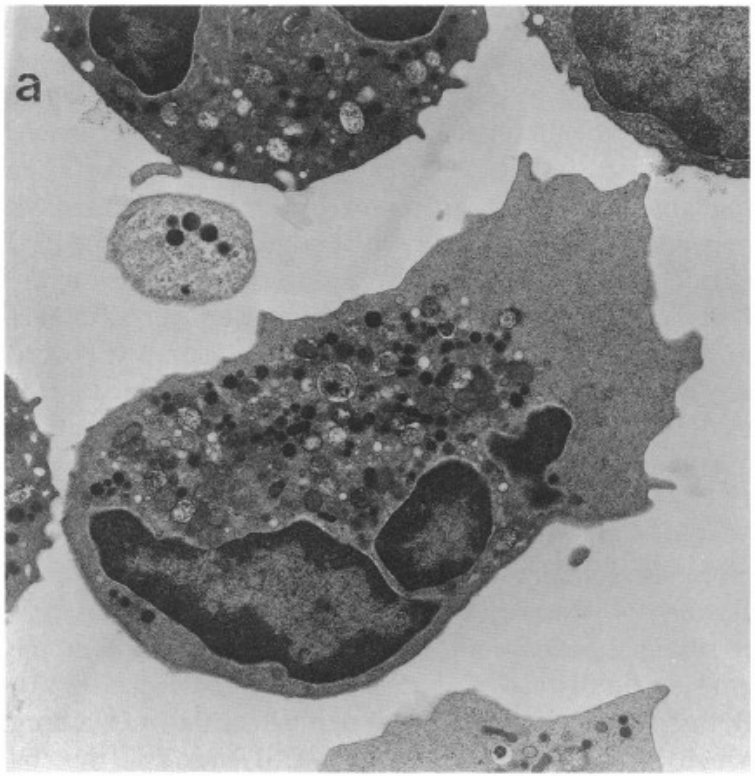


Mechanical modeling

A CONTINUUM MODEL OF PROTRUSION OF PSEUDOPOD IN LEUKOCYTES

BIOPHYS J. © Biophysical Society
Volume 54 December 1988 1115–1137

CHENG ZHU AND RICHARD SKALAK
Bioengineering Institute, Department of Civil Engineering and Engineering Mechanics, Columbia University, New York, New York 10027



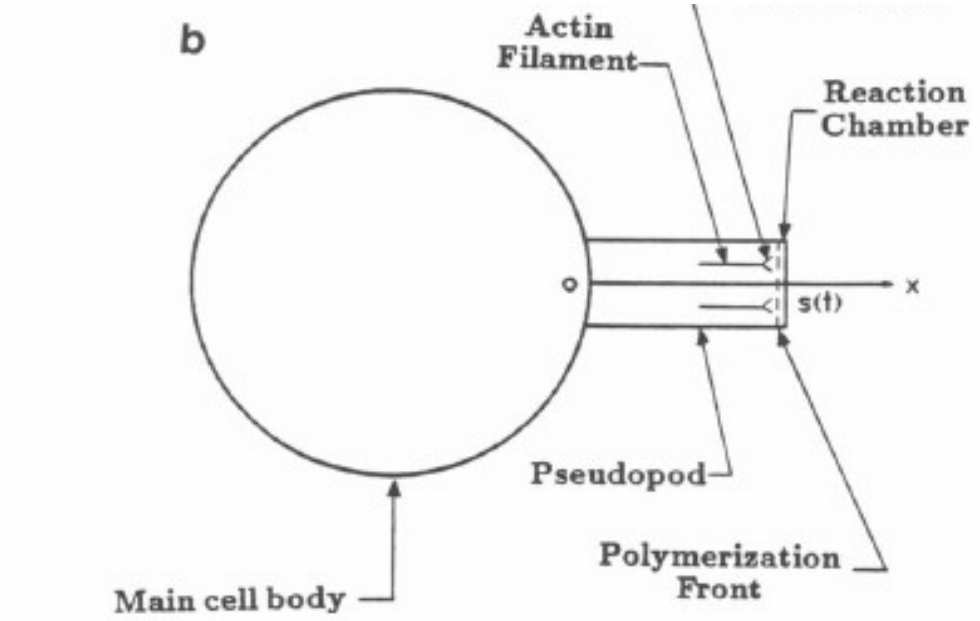


FIGURE 1 (*a*) Transmission electron micrograph of a human neutrophil with a pseudopod (provided by G. W. Schmid-Schönbein). The main cell body can be seen to contain nucleus and granules. The pseudopod consists of a uniform structure. (*b*) Schematic illustration of *a*. The main cell body is represented by viscoelastic sphere. The pseudopod is represented by a cylinder or sheet with constant cross-sectional area. The origin of the coordinate system is at the base of the pseudopod, and $x - s$ is the position of the growing tip. Illustrated also in the figure are actin filaments with their barbed ends attached to the growing tip, polymerization front, and the reaction chamber at the tip (see text).

(*a*) The pseudopod is assumed to be a porous medium of actin gel. The network of actin filaments forms a stiff framework which provides the rigidity of the pseudopod.

(*b*) Monomeric actin is considered as slowly diffusing solute dispersed within the fluid phase, transported by convection and diffusion, and is converted to actin filaments at the sites of polymerization.

(*c*) Elongation of actin filament, powered by chemical free energy liberated form polymerization reaction, does mechanical work by pushing the cell membrane outwards against an opposing pressure. The membrane motion cre-

(*d*) The pseudopod extends as a result of actin polymerization at the tip of the pseudopod. The building blocks are transported from the main cell body through the gel to the growing tip.

(*e*) The actin polymerization is governed by a simple reaction kinetics equation. The rate of growth is modulated by regulatory proteins.

chemical free energy

velocity of the pseudopod

$$\Delta\mu \frac{n}{l}\frac{ds}{dt} + \alpha\left(\frac{ds}{dt}\right)^2 + q = (p_e - p)\frac{ds}{dt} + \frac{dU}{dt}$$

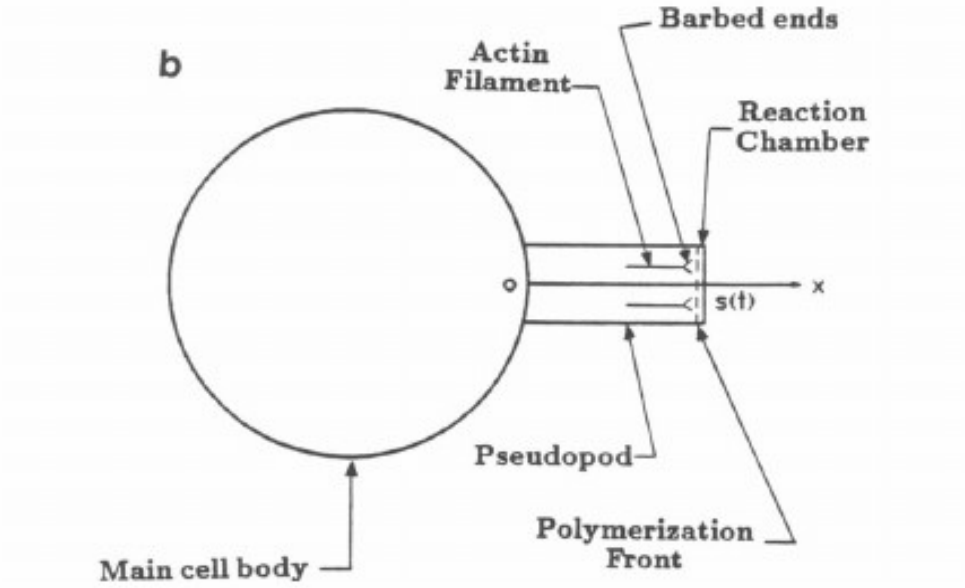
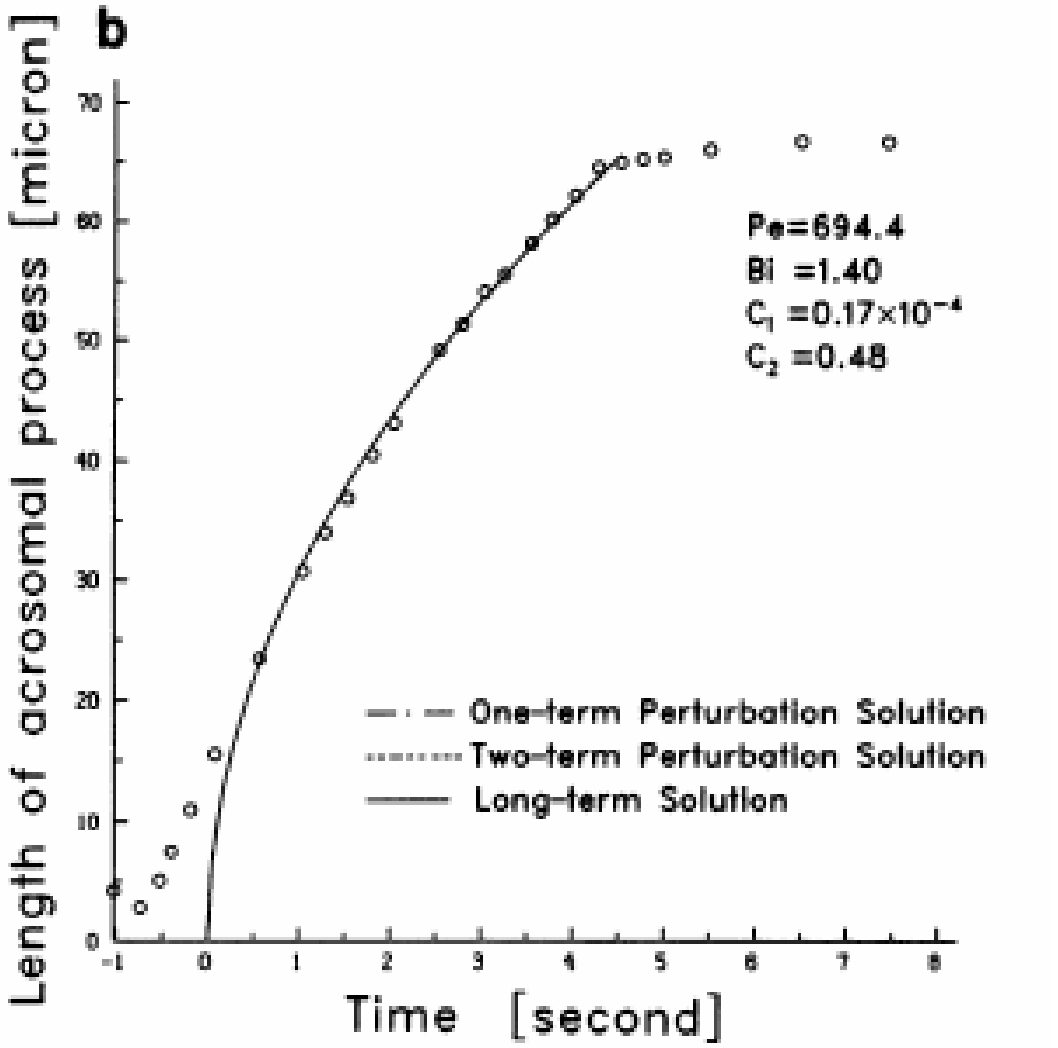


FIGURE 1 (*a*) Transmission electron micrograph of a human neutrophil with a pseudopod (provided by G. W. Schmid-Schönbein). The main cell body can be seen to contain nucleus and granules. The pseudopod consists of a uniform structure. (*b*) Schematic illustration of *a*. The main cell body is represented by viscoelastic sphere. The pseudopod is represented by a cylinder or sheet with constant cross-sectional area. The origin of the coordinate system is at the base of the pseudopod, and $x - s$ is the position of the growing tip. Illustrated also in the figure are actin filaments with their barbed ends attached to the growing tip, polymerization front, and the reaction chamber at the tip (see text).

Main result:

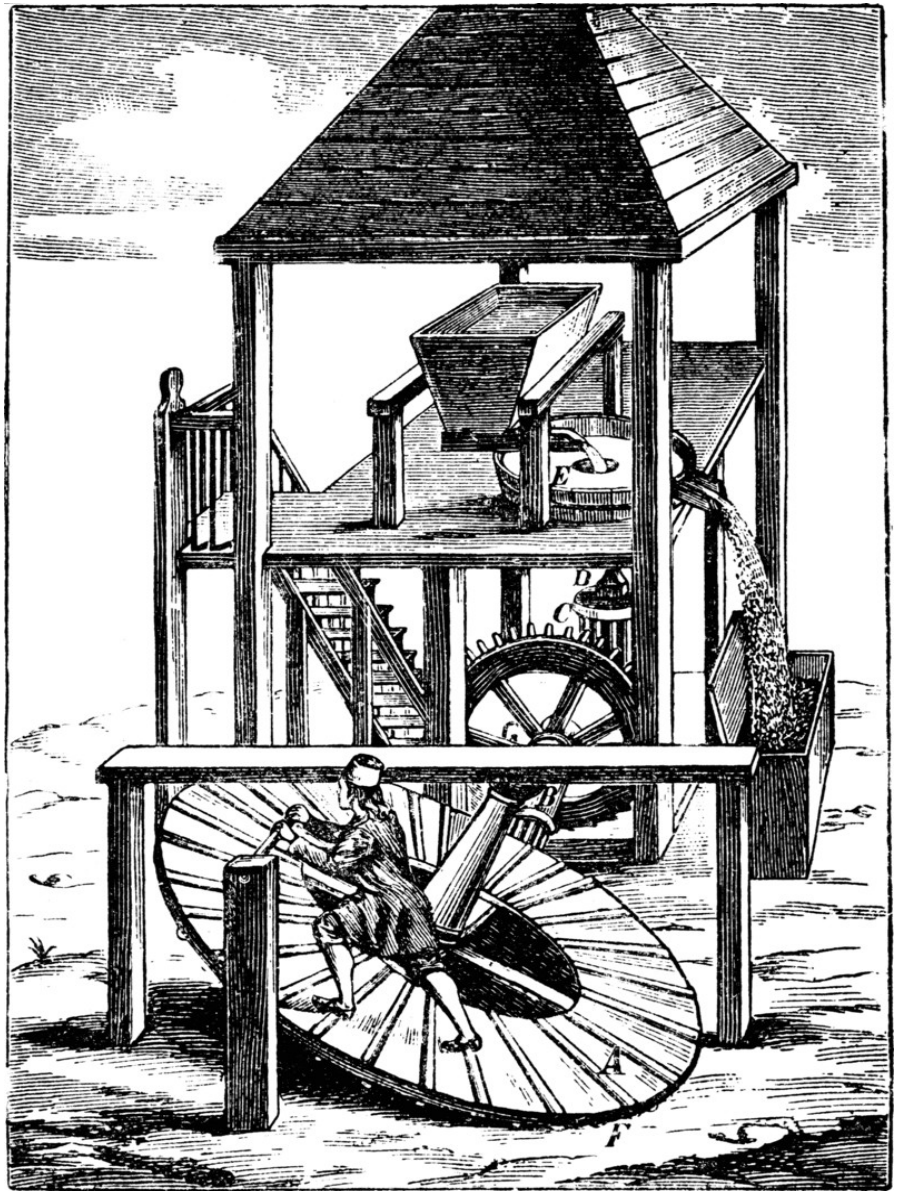
$$s(t) \propto \sqrt{t}$$

(c.f. Stefan problem)


b
Length of acrosomal process [micron]
Time [second]
Pe=694.4
Bi =1.40
C_1 =0.17×10^{-4}
C_2 =0.48
One-term Perturbation Solution
Two-term Perturbation Solution
Long-term Solution

Treadmilling

Treadmills



Source: Wikipedia

Ancient times: a type of **mill** that was operated by a person or animal treading steps of a **tread-wheel** to grind grain.

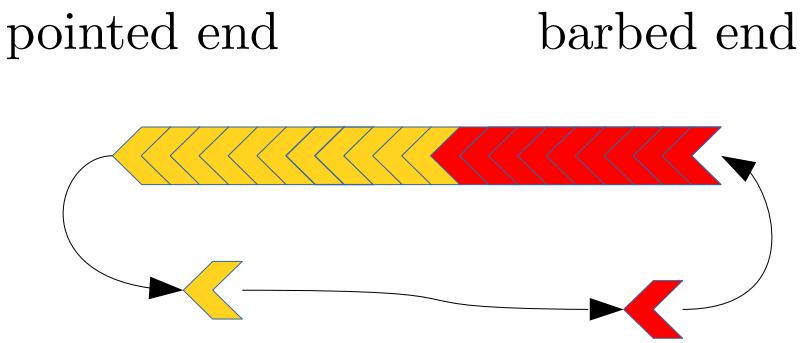
Treadmills

Treadmill used to punish prisoners at Breakwater Prison, Cape Town

The “tread-wheel” was also used as punishment device for people sentenced to prisons.

Today: a device for walking or running while staying in the same place.

- **Treadmilling regime**: the actin added per unit time at one end is *equal* to that removed at the opposite end.

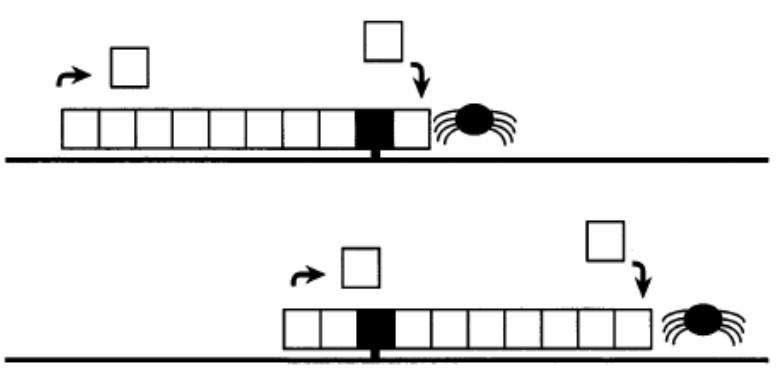


type-A treadmilling

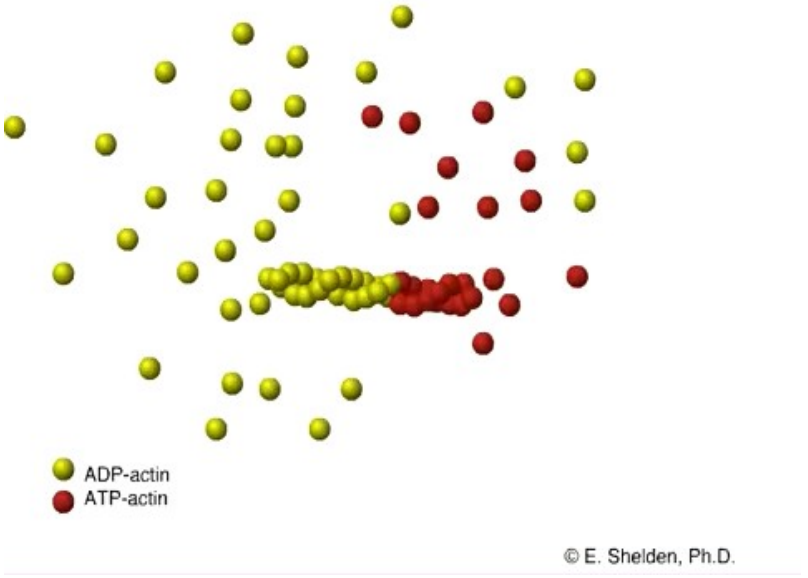
type-A treadmilling

In type-A treadmilling the spatial velocity of the polymerized actin units in zero

We can identify a polymerized actin unit with its position



from Theriot, *Traffic*, 2000



type-A treadmilling

J. Math. Biol. (2000) 40: 64–96

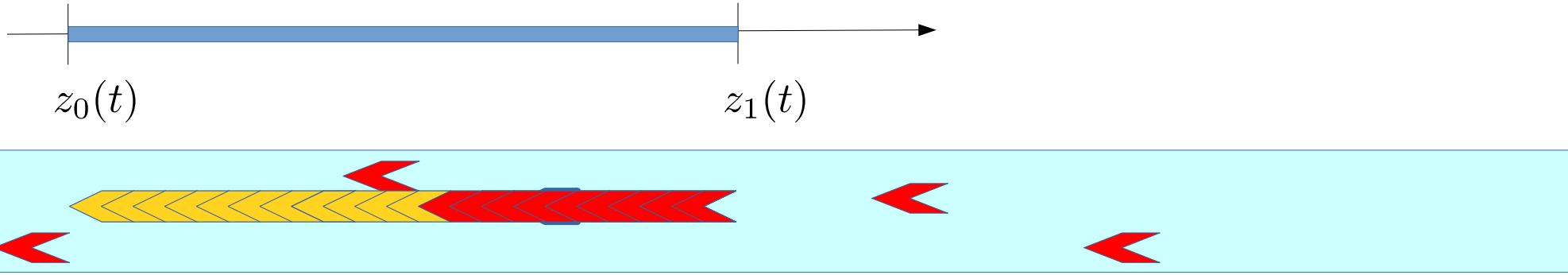
Journal of Mathematical Biology

Models for spatial polymerization dynamics of rod-like polymers

Leah Edelstein-Keshet[1,*], **G. Bard Ermentrout**[2]

[1] Department of Mathematics, University of British Columbia, Vancouver, BC, Canada, V6T 1Z2. e-mail: keshet@math.ubc.ca
[2] Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260, USA. e-mail: bard@math.pitt.edu

A single filament in a long 1D reservoir of diffusing "actin fuel"



A continuum model, both in space and time: the filament is an interval and the addition/removal of units is characterized by polymerization rates

ADP actin is instantaneously converted into ATP actin when released from the pointed end

Treadmilling: $\frac{\mathrm{d}z_0}{\mathrm{d}t} = \frac{\mathrm{d}z_1}{\mathrm{d}t}$

Main results:

- If concentration is spatially constant and equals the *treadmilling concentration* C_{tr}, then treadmilling of filaments of every length is possible.
- For each prescribed length ℓ there exists a (spatially-nonuniform) concentration profile such that only filaments with length ℓ can treadmill.
- For a filament of length ℓ moving in a 1D infinite domain filled with diffusing actin with concentration C_∞ prescribed at infinity, there exists a treadmilling solution for C_∞ in a finite interval.

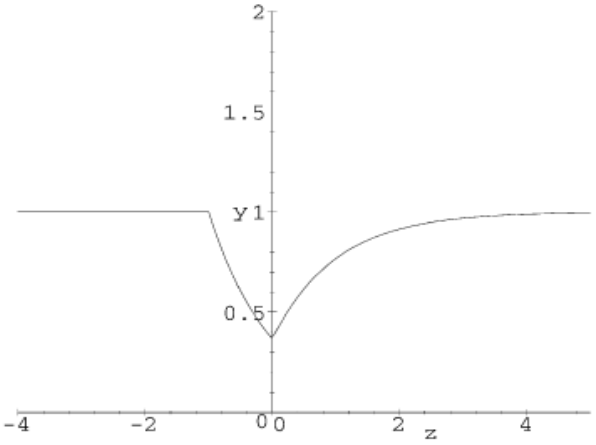
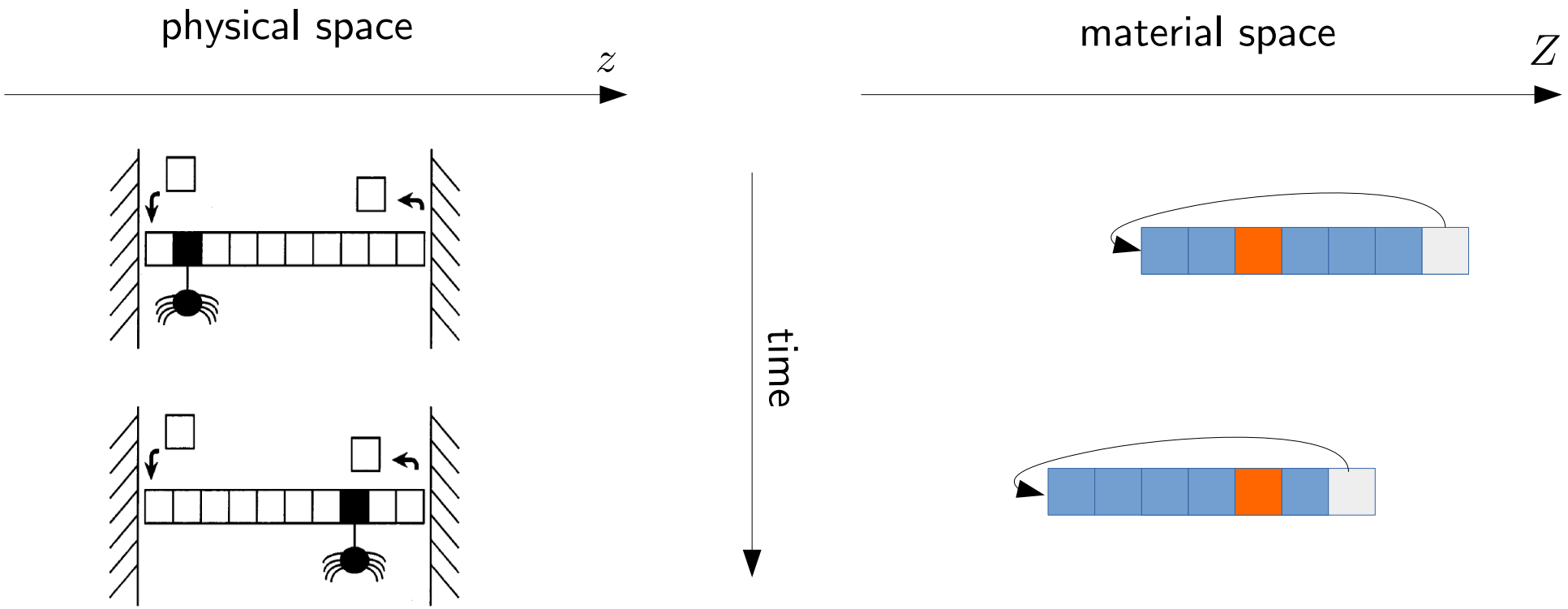


Fig. 3. A typical monomer profile in the case of a treadmilling filament consuming the monomer as it moves in one dimension. The explicit solution given by equations (11) is

Edelstein-Keshet & Ermentrout, J. Math. Biol. 2000

type-B treadmilling

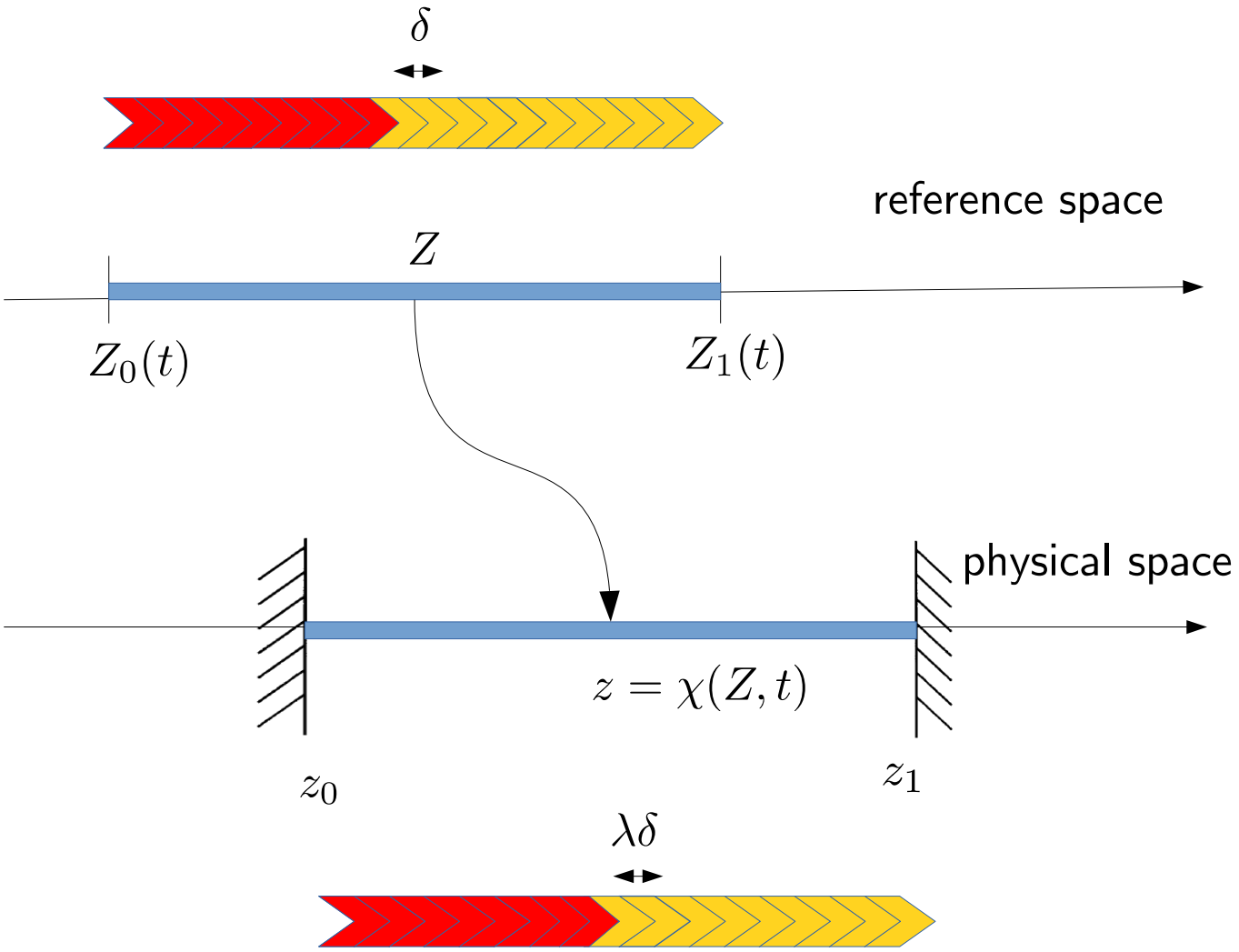
type-B treadmilling



In type-B treadmilling, both free units and polymerized units can move

In order to distinguish motion from accretion we introduce a reference configuration whose elements uniquely identify a polymerized unit.

Mechanics



Compatibility equation

$\lambda(Z,t) = \dfrac{\partial \chi}{\partial Z}(Z,t)$ stretch

Constitutive equation

$N(Z,t) = W'(\lambda)$

Force-balance equation

$\dfrac{\partial N}{\partial Z} = 0$

Constraints

$\chi(Z_0,t) = z_0$
$\chi(Z_0,t) = z_1$

On choosing the strain energy $W(\lambda) = \frac{1}{2}EA(\lambda-1)^2$ we have $N = EA(\lambda-1)$

Steady-state diffusion

Relevant fields:

- $\mu(z)$ chemical potential
- $h(z)$ flux

Fick's law

$$h = -M\frac{\mathrm{d}\mu}{\mathrm{d}z}$$

Balance of free actin units:

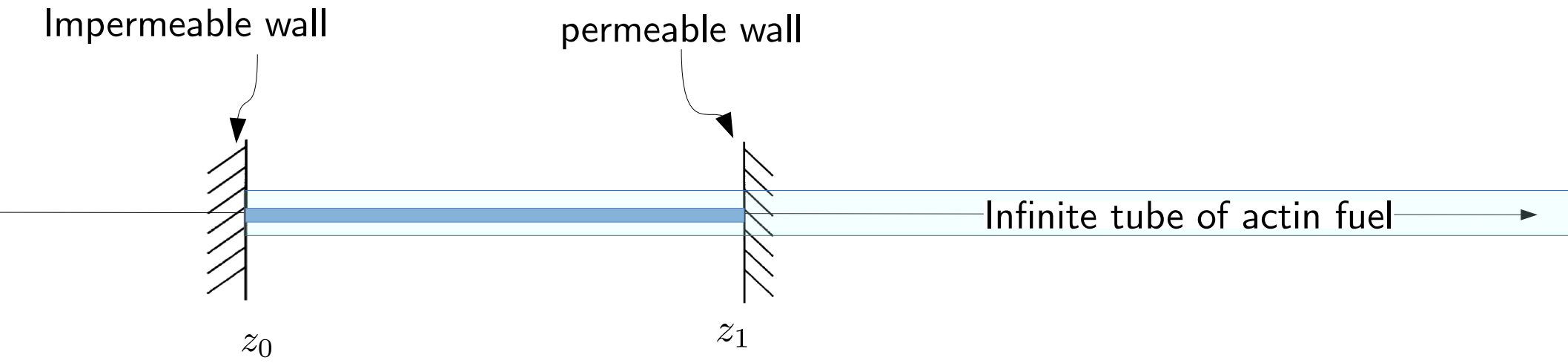
$$\frac{\mathrm{d}h}{\mathrm{d}z} = 0 \text{ in } (z_0, z_1) \cup (z_1, +\infty)$$

$$h(z_0) = \frac{\dot{Z}_0}{\delta}$$

$$h(z_1+) - h(z_1-) = -\frac{\dot{Z}_1}{\delta}$$

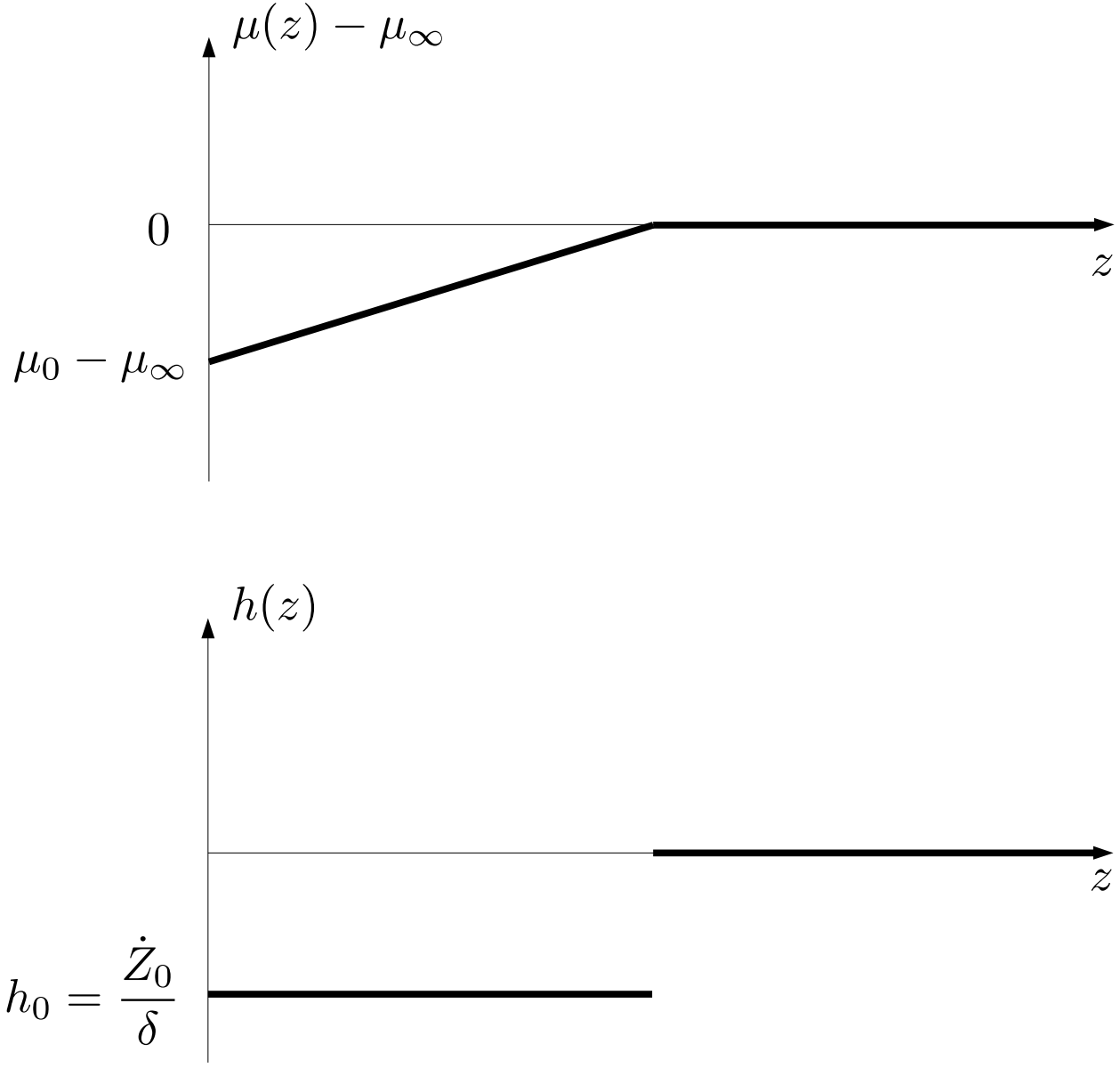
Boundary condition:

$$\lim_{z\to+\infty} \mu(z) = \mu_\infty$$



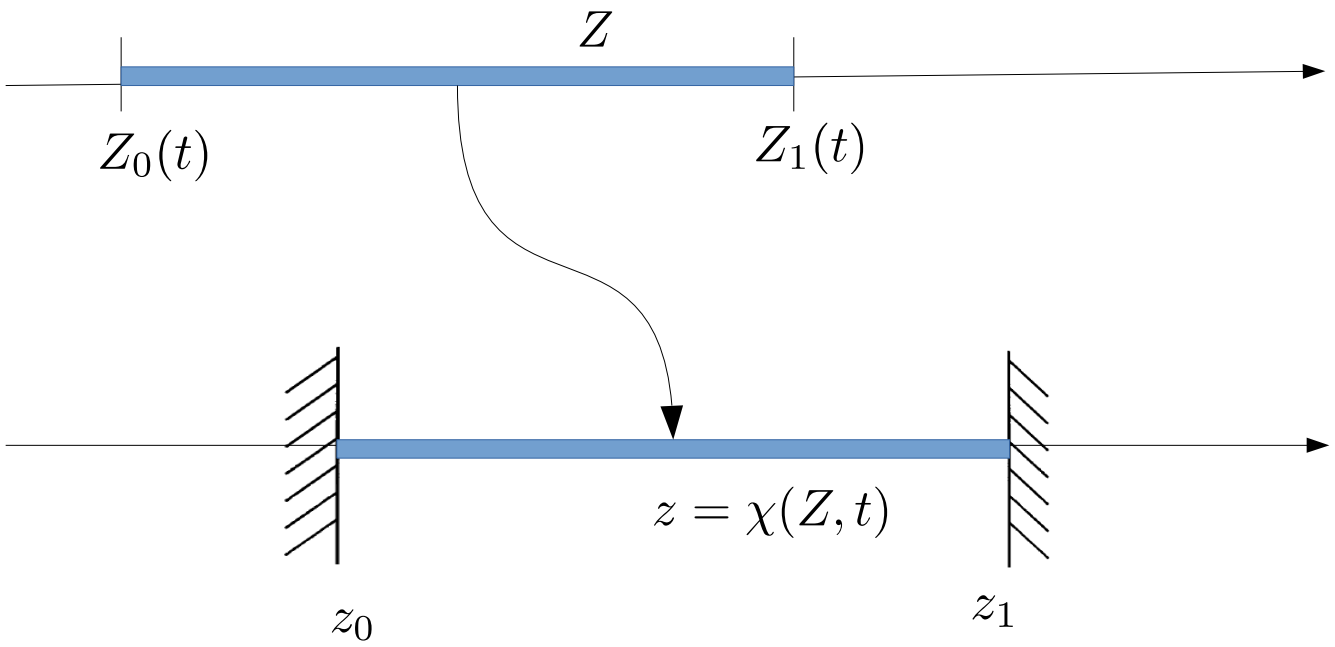
Steady state $\Rightarrow$ treadmilling

Treadmilling regime with $\dot{Z}_0 = \dot{Z}_1 < 0$



The kinetic law

$$\dot{Z}_0 =? \ \dot{Z}_1 =?$$



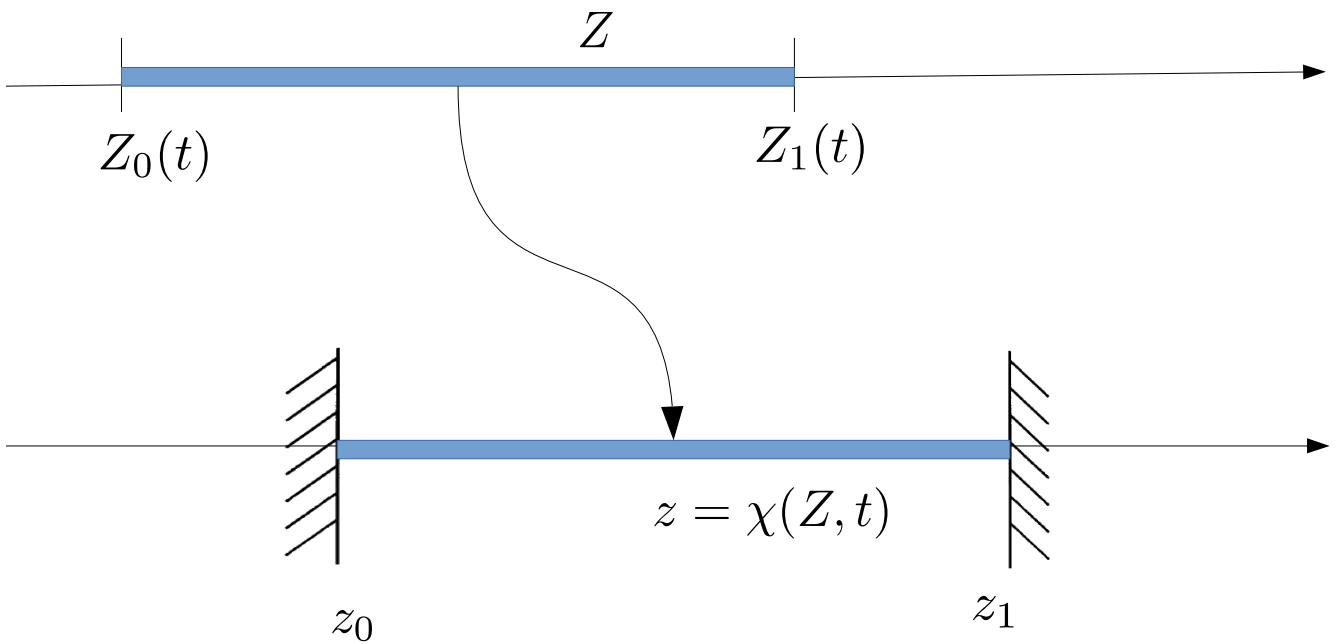
Kinetic law governing accretion at Z_0:

$$b_0 V_0 = \frac{\mu_0 - \mu_{R,0}}{\delta} + W^*(N_0)$$

where

$$V_0 := -\frac{\mathrm{dZ_0}}{\mathrm{d}t},\ \mu_0 := \mu(z_0),\ N_0 := N(Z_0)$$

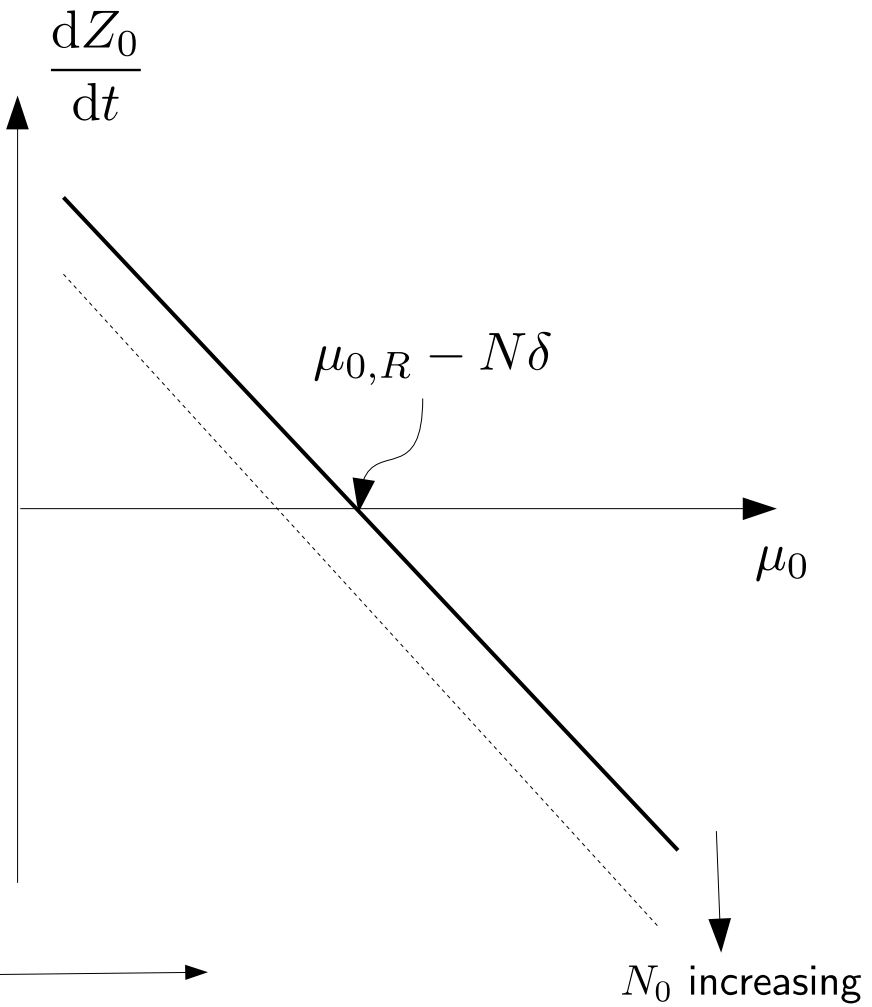
$W^*(N) :=$ Legendre transform of the strain energy $W(\lambda)$

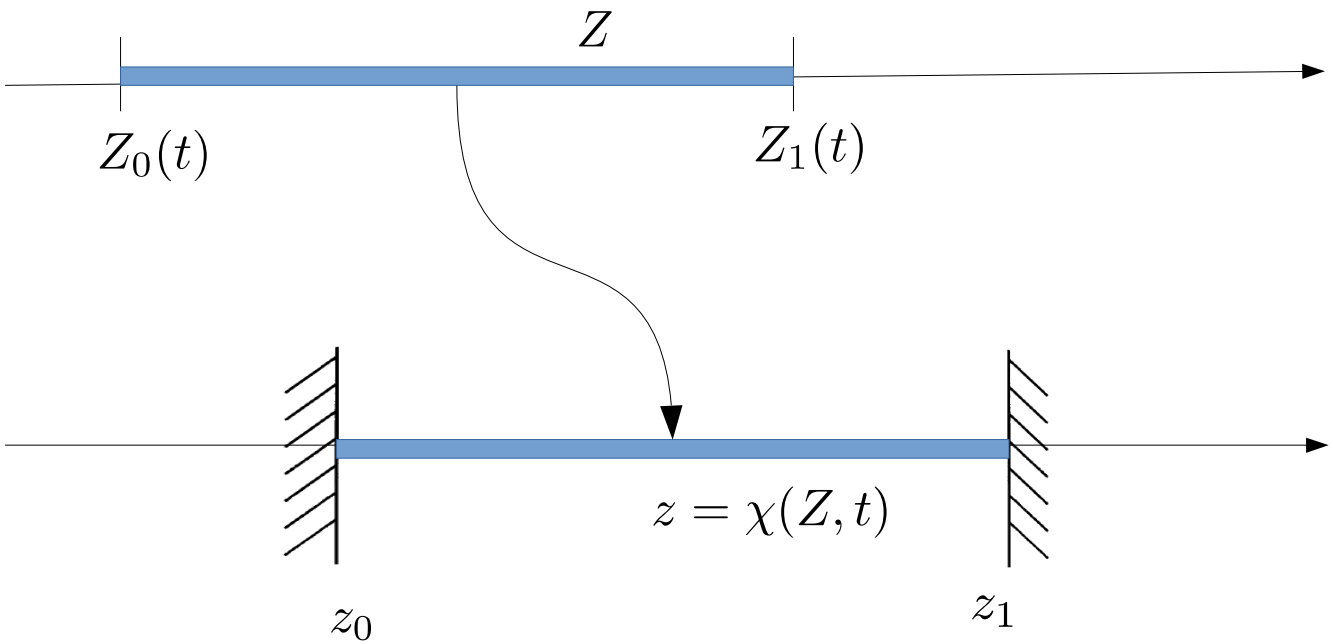


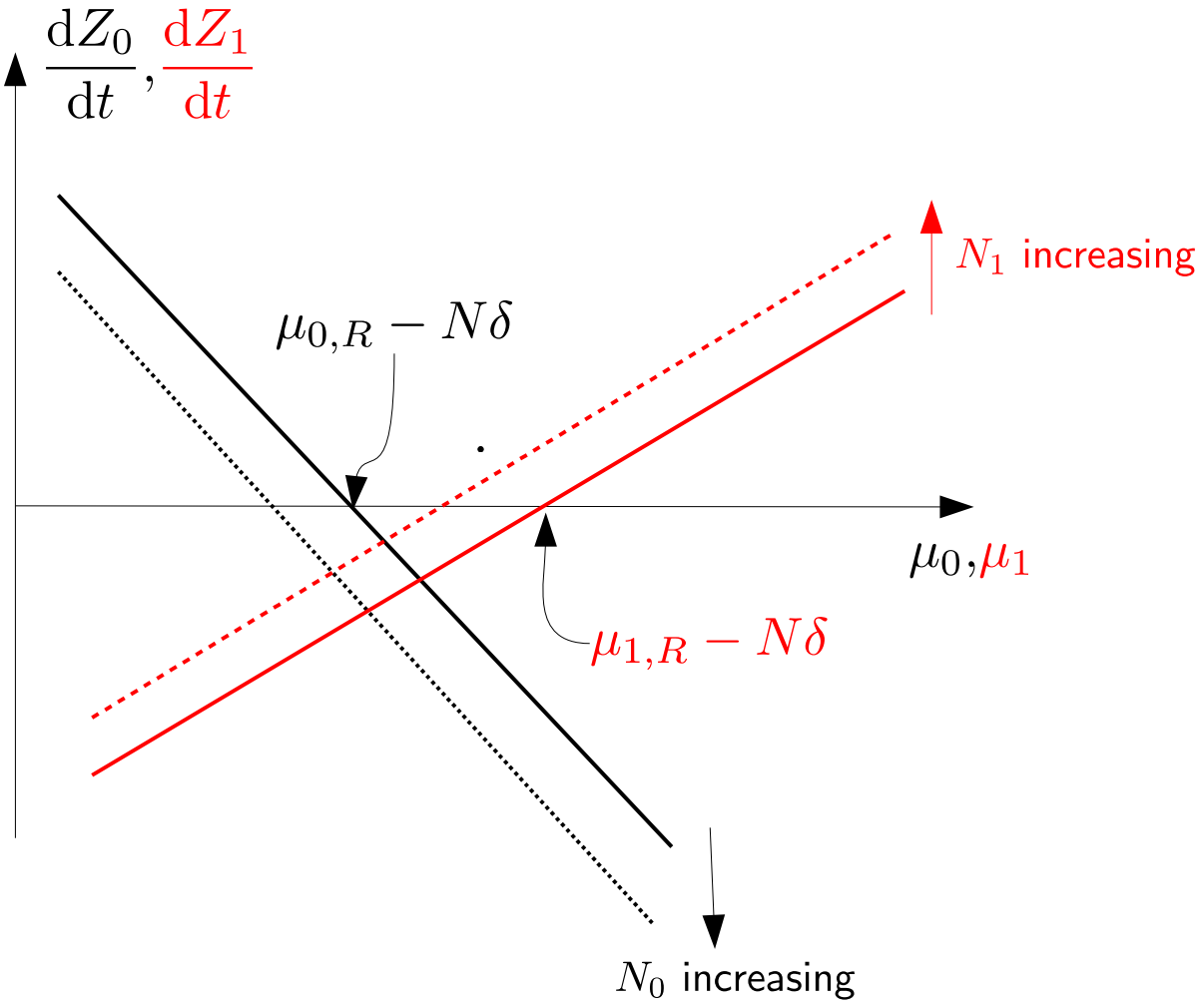
Kinetic law governing accretion at Z_0:

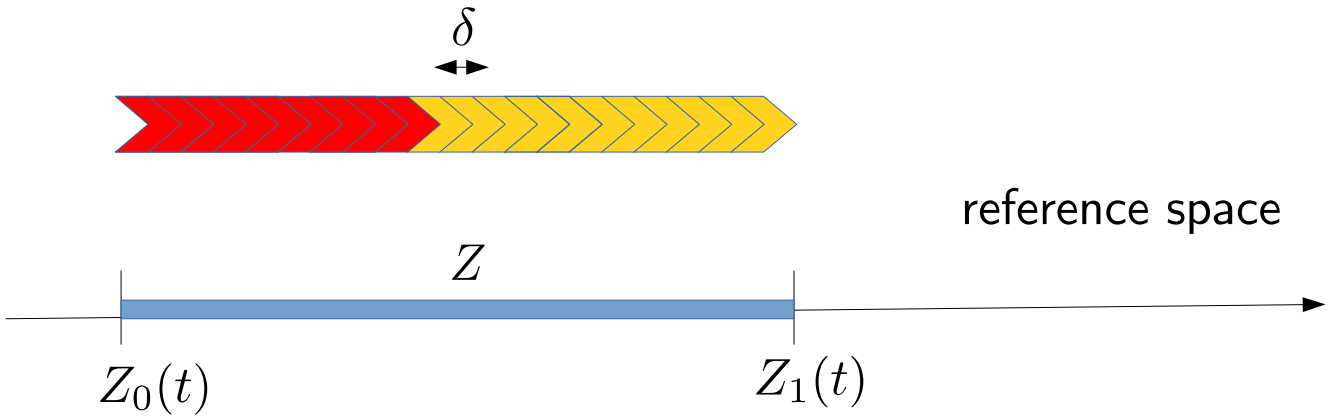
$$b_0 V_0 = \frac{\mu_0 - \mu_{R,0}}{\delta} + W^*(N_0)$$

$$W^*(N) \simeq N \text{ for } \frac{|N|}{EA} << 1$$






$\frac{\mathrm{d}Z_0}{\mathrm{d}t}, \frac{\mathrm{d}Z_1}{\mathrm{d}t}$
N_1 increasing
$\mu_{0,R} - N\delta$
μ_0, μ_1
$\mu_{1,R} - N\delta$
N_0 increasing


δ
reference space
Z
$Z_0(t)$
$Z_1(t)$

Computing the treadmilling velocity

$$(1+\eta)\,(b_0+b_1)V_0 = \frac{\mu_{R,1}-\mu_{R,0}}{\delta}$$

$$\eta = \frac{\ell}{\ell_*} \qquad \ell = z_1 - z_0 \qquad \ell_* = (b_0+b_1)M\delta^2$$

$$N = \widehat{N}(\mu_\infty, \eta)$$

$$\eta \to \infty \longrightarrow -N \to \frac{\mu_1 - \mu_{R,0}}{\delta}$$

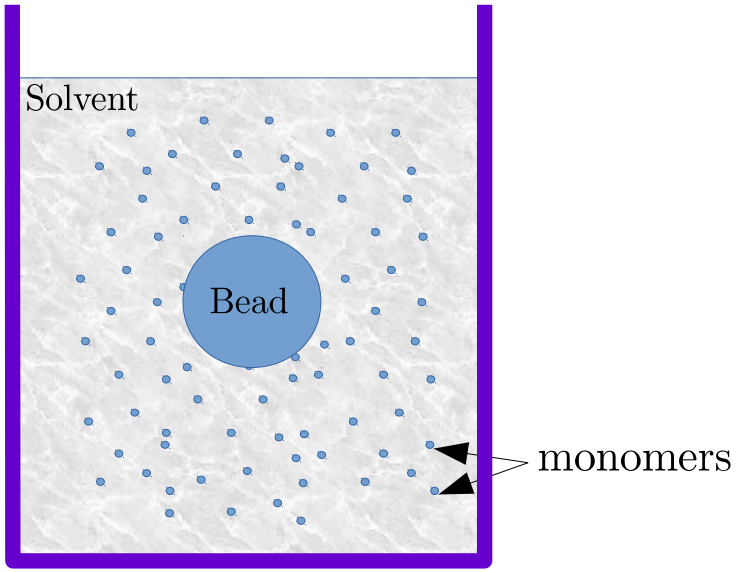
$$V_0 \to 0$$

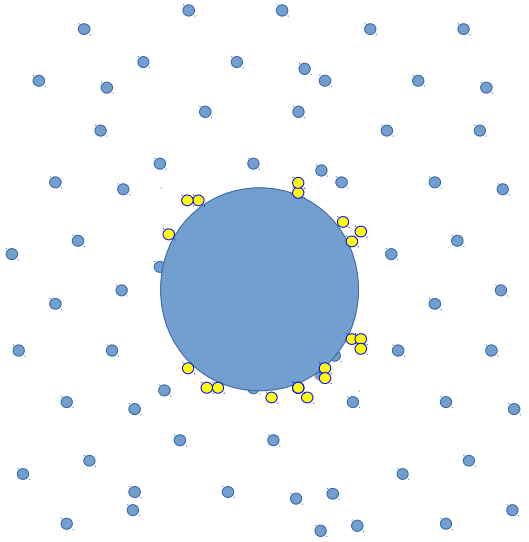
Even though the system is statically undeterminate, N does not depend on the stiffness at treadmilling

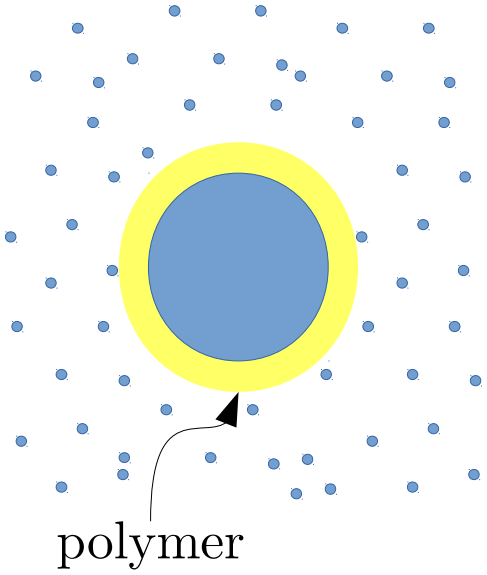
Outline:

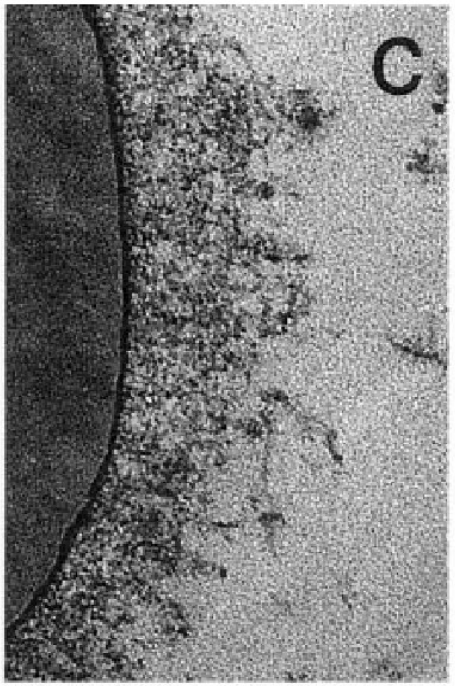
- Motivation: actin-based motility
- Actin microfilaments: polymerization and treadmilling
- → Modeling of gel growth

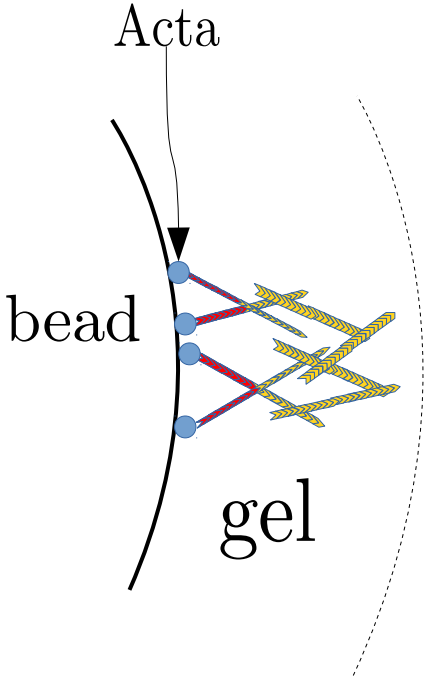
Accretion of a polymer gel on a spherical support

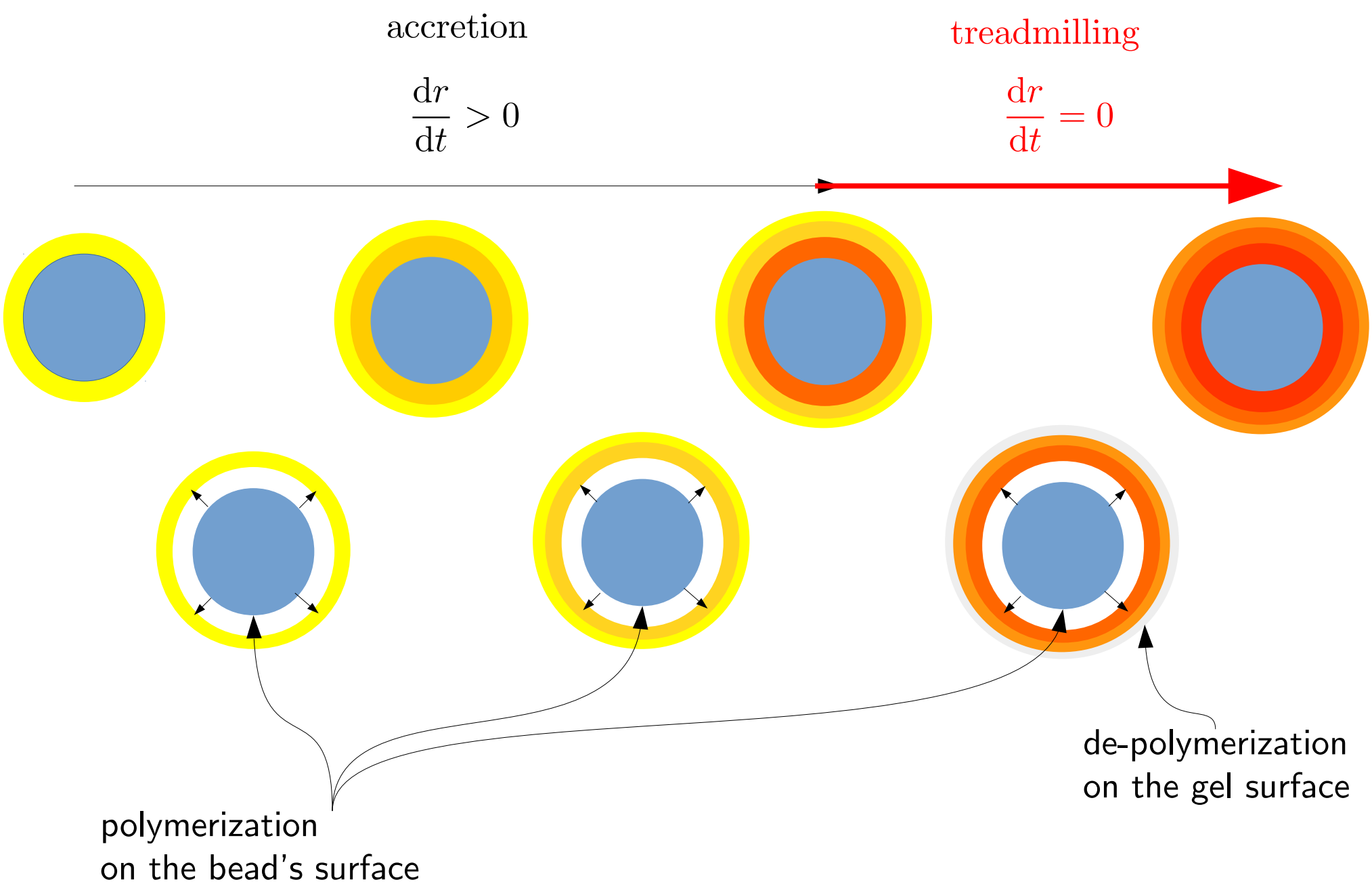






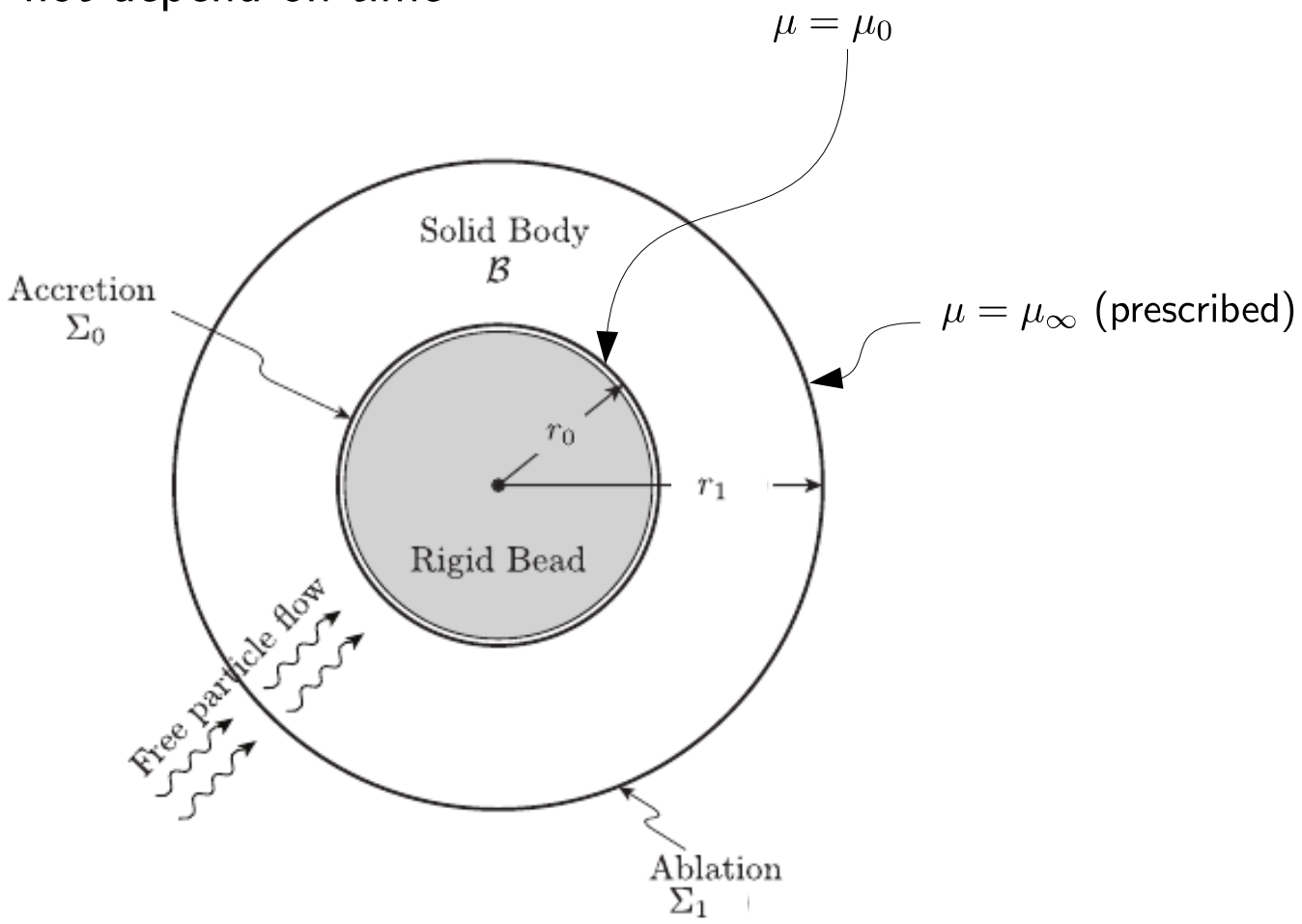





accretion
$\frac{\mathrm{d}r}{\mathrm{d}t} > 0$
treadmilling
$\frac{\mathrm{d}r}{\mathrm{d}t} = 0$
polymerization
on the bead's surface
de-polymerization
on the gel surface

Assumptions:

- polymerization and depolymerization can take place only at the inner and outer surface
- the material comprising the elastic body is isotropic and incompressible
- spatial fields do not depend on time



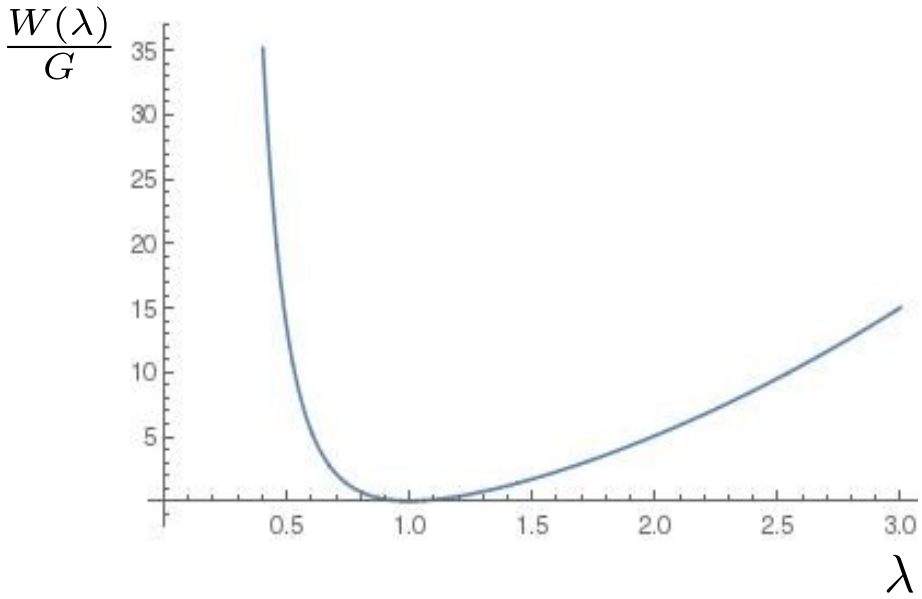
Radial and circumferential stresses

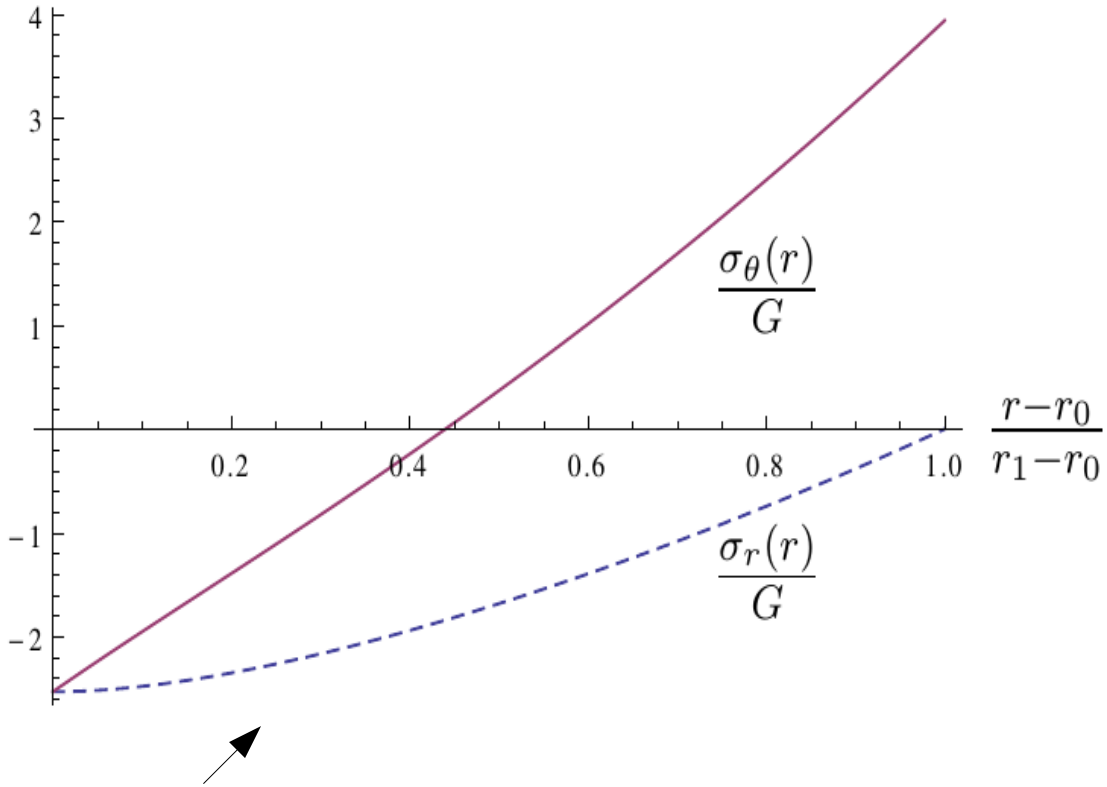
$\widehat{W}(\lambda_1, \lambda_2, \lambda_3)$ strain energy

$W(\lambda) = \widehat{W}\left(\frac{1}{\lambda^2}, \lambda, \lambda\right)$ effective energy

For a neo-Hookean material:

$$W(\lambda) = \frac{G}{2}\left(\frac{1}{\lambda^4} + 2\lambda^2 - 3\right)$$





here $\frac{r_1}{r_0} = 2$

on the inner surface:
$\sigma_r = \sigma_\theta = -W(r_1/r_0) < 0$

on the outer surface:
$\sigma_\theta = \frac{1}{2}W'(r_1/r_0) > 0$

Data:

r_0 radius of the bead

M mobility $(L^{-1}T^{-1})$

$W(\lambda)$ effective strain energy (FL^{-2})

b_0, b_1 kinetic moduli (FTL^{-4})

$\mu_{R,0}, \mu_{R,1}$ chemical potentials (FL)

$\varrho_R = \dfrac{1}{\delta^3}$ referential volume density of polymerized units

μ_∞ remote chemical potential

diffusion equation (3D) + kinetic equations (inner and outer surface)

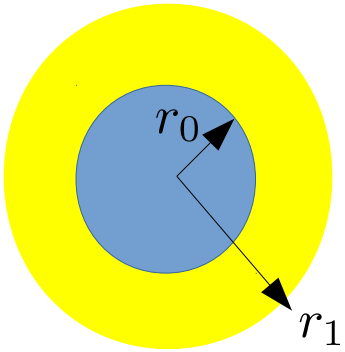
↓

Treadmilling system

↙

Unknowns:

- r_1 external radius (or σ_r at the inner surface)
- V accretion velocity at the inner surface
- μ_0 chemical potential at the interior surface



Data:

r_0 radius of the bead

$W(\lambda)$ effective strain energy (FL^{-2})

$\mu_{R,0}, \mu_{R,1}$ chemical potentials (FL)

μ_∞ remote chemical potential

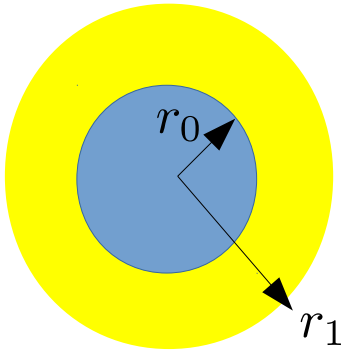
M mobility $(L^{-1}T^{-1})$

b_0, b_1 kinetic moduli (FTL^{-4})

$\varrho_R = \dfrac{1}{\delta^3}$ referential volume density of polymerized units

$\ell_* = (\delta^3)^2(b_0 + b_1)M$ characteristic length

$\eta = \dfrac{r_0}{\ell_*}$ renormalized bead size



Main results

Necessary and sufficient conditions for treadmilling:

$$\ell_* = (\delta^3)^2(b_0 + b_1)M$$

$$\mu_{R,0} < \mu_{R,1}$$

$$\eta = \frac{r_0}{\ell_*}$$

$$\mu_\infty > \mu_{R,*} = \frac{b_1\mu_{R,0} + b_0\mu_{R,1}}{b_0 + b_1}$$

Stress-governed regime

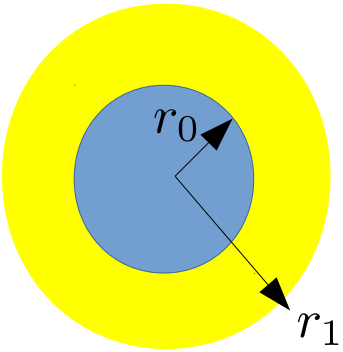
$\eta << 1$ small beads

$$\frac{r_1 - r_0}{r_0} \simeq \sqrt{\frac{2(\mu_\infty - \mu_{R,*})\varrho_R}{W''(1)}}$$

Diffusion-governed regime

$\eta >> 1$ large beads

$$r_1 - r_0 \simeq \ell_* \frac{\mu_\infty - \mu_{R,*}}{\mu_{R,1} - \mu_\infty}$$



Thanks for your attention

Paper: http://arxiv.org/abs/1603.03648