

Mechanical modeling of crawling cells

Pierre Recho

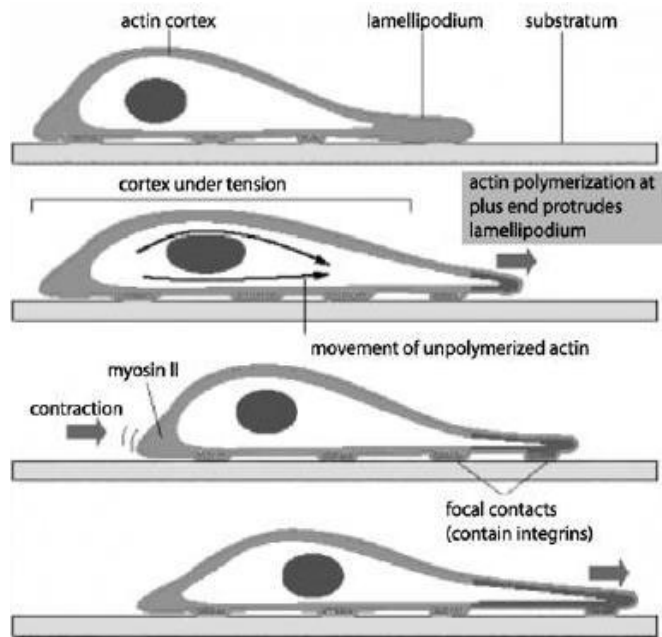
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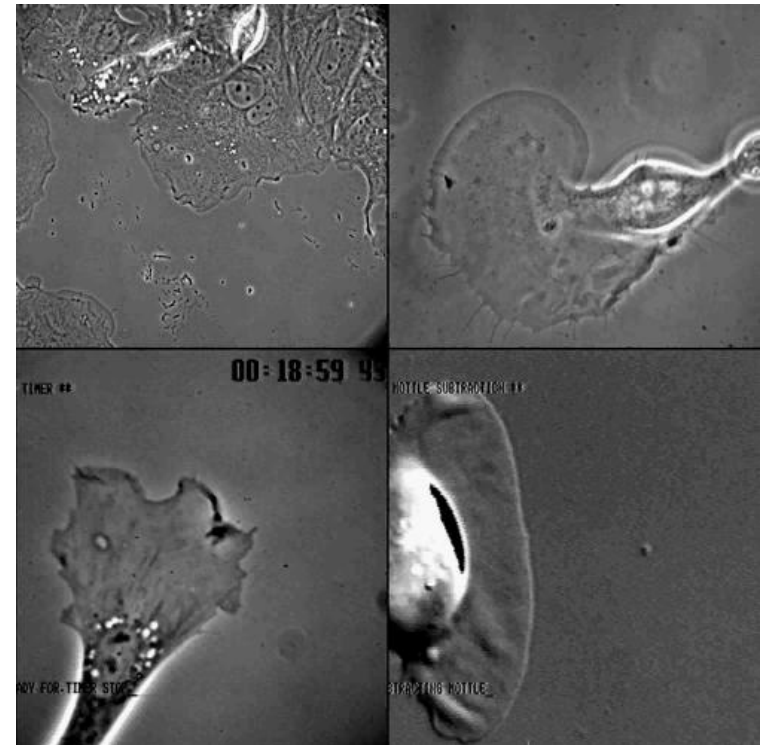
Crawling cells

Three main components of cell motility:

1. Protrusion
2. Adhesion
3. Contraction

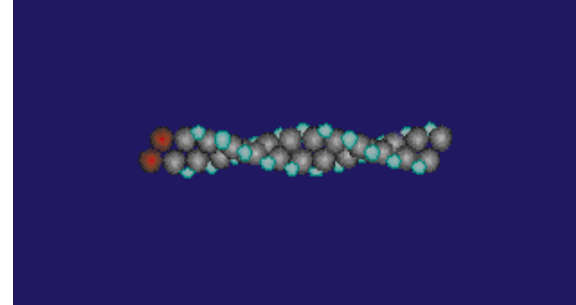
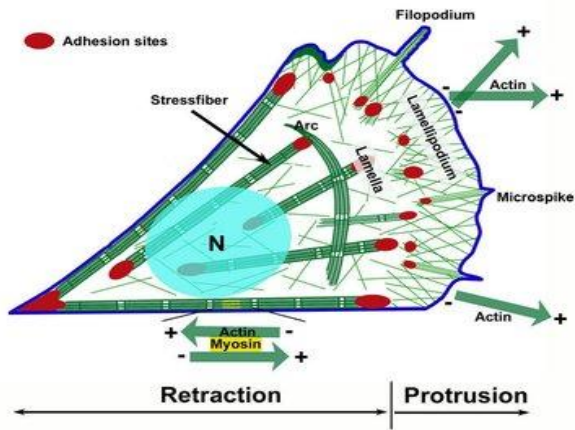


speed \simeq one body length/min

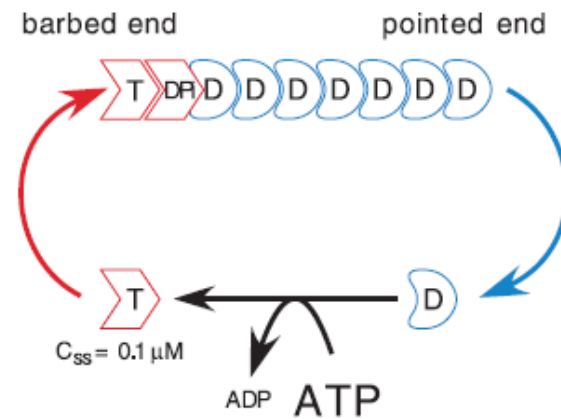
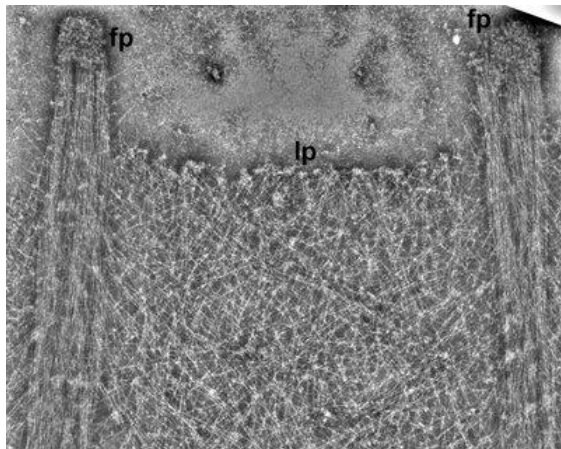


<http://cellix.imba.oeaw.ac.at>

1. Protrusion

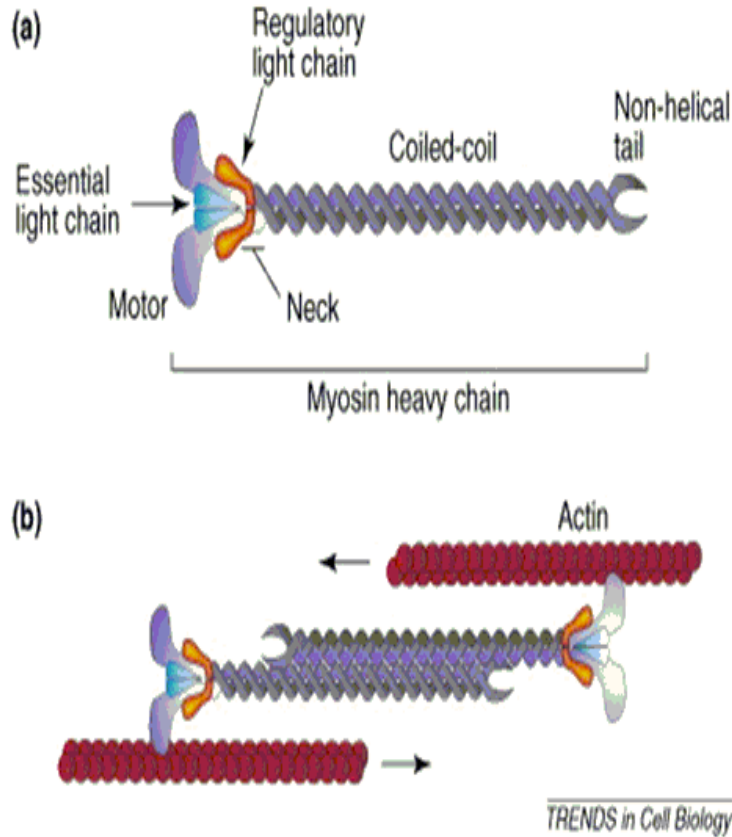


D. Pantaloni, et al. *Science*, 292(5521), 2001.



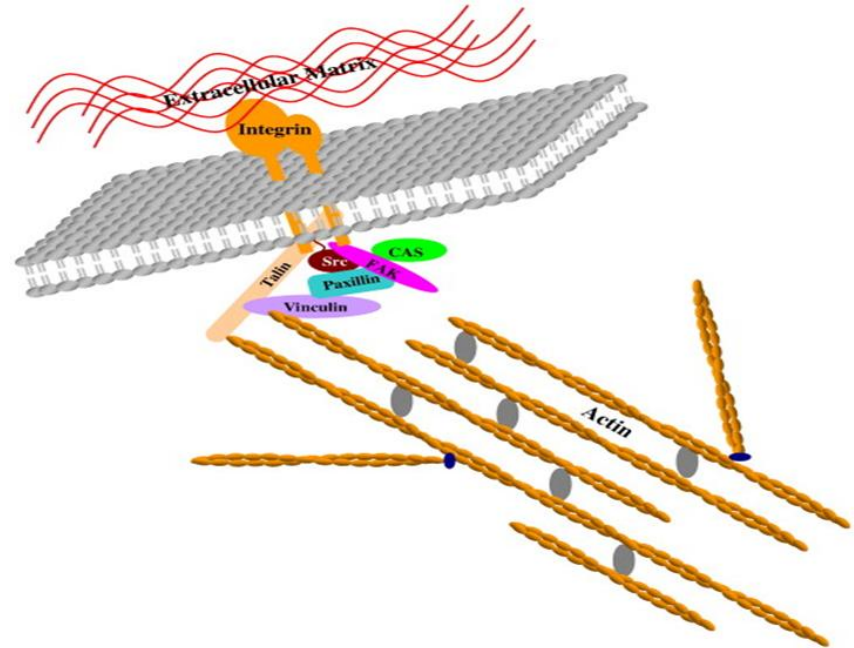
S.A. Koestler, et al. *Nat. Cell Biol.*, 10(3), 2008.

2. Contraction



K. Clark, et al. *Trends Cell Biol.*, 17(4), 2007.

3. Adhesion



N. Zebda, et al. *Microvasc. Res.*, 83(1), 2012.

Models for cell motility

- **Polymerization-driven, macroscopic**

- A Mogilner and L Edelstein-Keshet , *Biophys. J.*, 2002

- J. Prost, J.-F Joanny, P. Lenz and C. Sykes , *In Cell Motility, Biological and Medical Physics, Biomedical Engineering*, 2008

- F. Jülicher, K. Kruse, J. Prost and J.-F. Joanny , *Phys. Rep.*, 2007

- **Discrete models**

- P.A. DiMilla, K. Barbee and D.A. Lauenburger , *Biophys. J.*, 1991

- D. Bottino, A. Mogilner, T. Roberts, M. Stewart and G. Oster, *J. Cell Science*, 2002

- **Turing mechanism**

- B. Vanderlei, J.J. Feng and L. Edelstein-Keshet , *Multiscale Model. Simul.* , 2010

- **Two-phase flows**

- M. Herant and M. Dembo , *Biophys. J.*, 2010

- **Microscopic theory of active filaments**

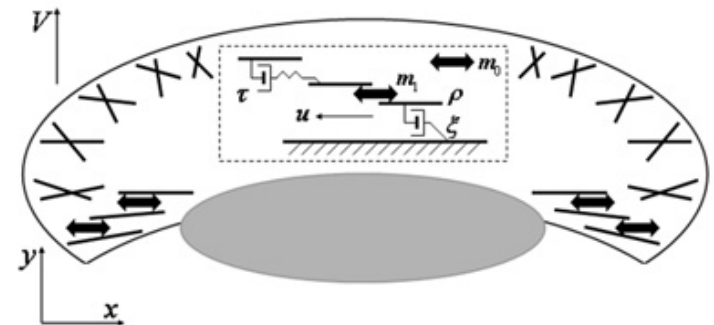
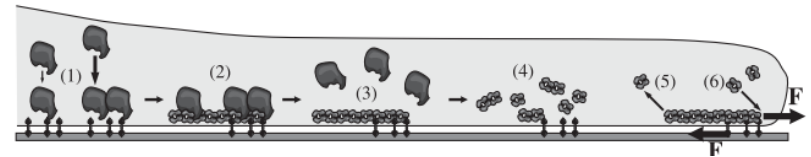
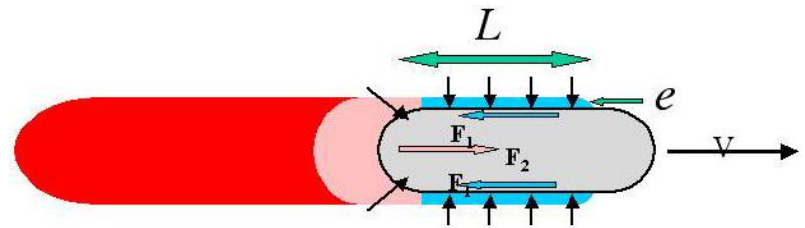
- K. Dubrovinski and K. Kruse, *Phys. Rev. Lett.*, 2011

- **Comprehensive models**

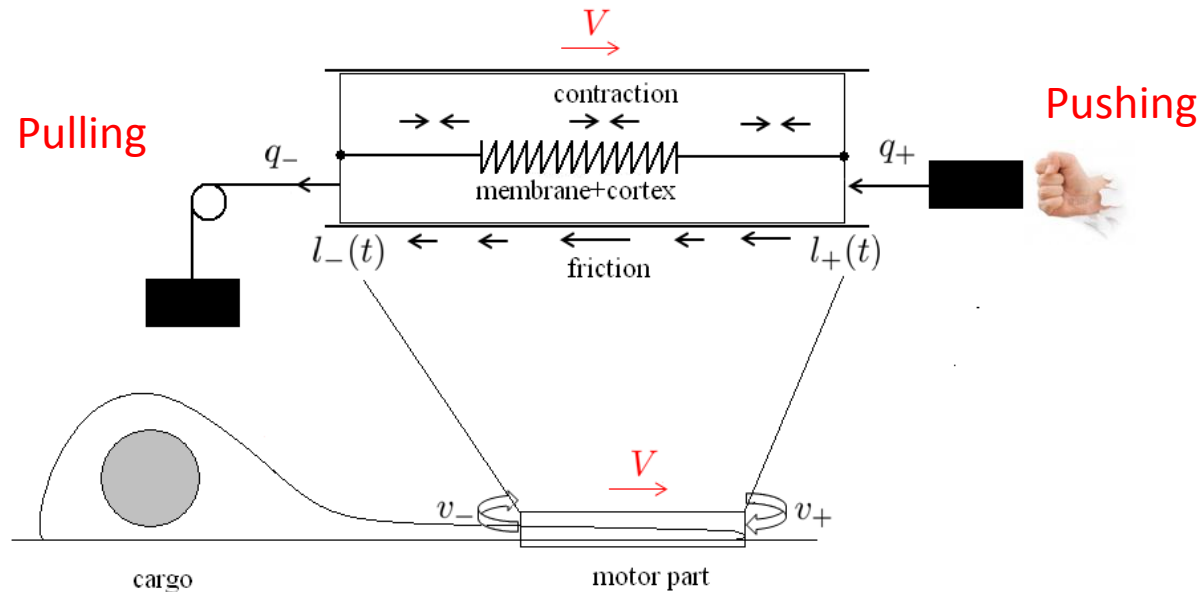
- D. Shao, W.-J. Rappel and H. Levine, *Phys. Rev. Lett.*, 2010

- B. Rubinstein, M.F. Fournier, K. Jacobson, A. B. Verkhovskiy, and A. Mogilner , *Biophys J.*, 2009

- Q. Wang, X. Yang, D. Adalsteinsson, T.C. Eleston, K. Jacobson, M. Kapustina and M.G. Forest, *Comput. Model. Biol. Syst.*, 2012



General setting



Cell is modeled as a visco-elastic **active gel** with moving boundaries: $l_-(t)$ and $l_+(t)$

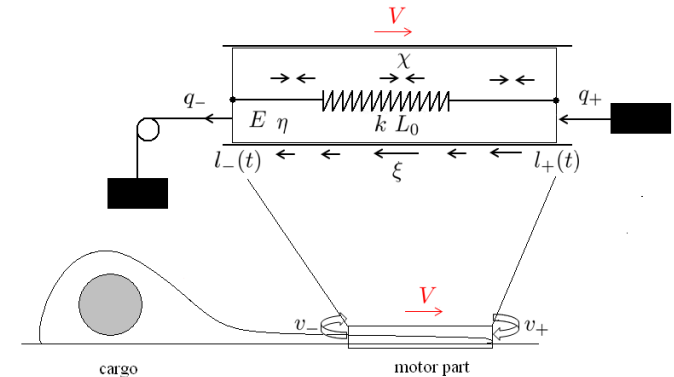
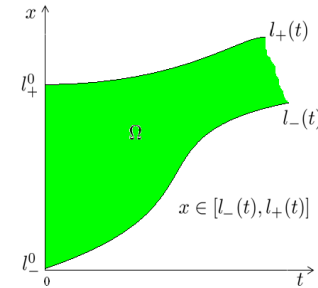
- Rates of de-polymerization and polymerization are fixed.
- Adhesion is modeled by viscous friction.
- Contraction is modeled as a distributed pre-stress.
- Cell membrane/cortex is assumed to be linear elastic.
- Cargo: loads at both rear (pulling) and front (pushing).

Governing equations

- Force Balance:
$$\begin{cases} \partial_x \sigma = \xi a(x, t) v & \leftarrow \text{Adhesion} \\ \sigma(l_-(t), t) = q_- - k \frac{L(t) - L_0}{L_0} \\ \sigma(l_+(t), t) = q_+ - k \frac{L(t) - L_0}{L_0} \end{cases}$$

Cargo Elasticity
- Constitutive relation:
$$\sigma = \eta \partial_x v + \underbrace{\frac{F(\rho)}{E(1-\rho/\rho_0)}}_{\geq 0} + \underbrace{\chi c(x, t)}_{\geq 0} \leftarrow \text{Contraction}$$
- Protrusion:
$$\begin{cases} \dot{l}_- = v_- + v(l_-(t), t) \\ \dot{l}_+ = v_+ + v(l_+(t), t) \\ l_-(0) = l_-^0 < l_+(0) = l_+^0 \end{cases} \leftarrow \text{Treadmilling}$$
- Actin:
$$\begin{cases} \partial_t \rho + \partial_x(\rho v) = 0 \\ \rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+ \\ \rho(x, 0) = \rho^0(x) \end{cases} \leftarrow \text{(Auto)taxis}$$
- Myosin:
$$\begin{cases} \partial_t c + \partial_x(cv) - D \partial_{xx} c = 0 \\ c(l_-(t), t) v_- + D \partial_x c(l_-(t), t) = 0 \\ c(l_+(t), t) v_+ + D \partial_x c(l_+(t), t) = 0 \\ c(x, 0) = c^0(x) \end{cases}$$

$$L(t) = l_+(t) - l_-(t)$$



Unknowns: $l_-(t), l_+(t), \underbrace{\sigma(x, t)}_{\text{axial stress}}, \underbrace{v(x, t)}_{\text{velocity}}, \underbrace{\rho(x, t)}_{\text{actin density}}, \underbrace{c(x, t)}_{\text{myosin concentration}}$ and $\underbrace{a(x, t)}_{\text{integrin concentration}}$

Numerics

- Force Balance:
$$\begin{cases} \partial_x \sigma = \xi v \\ \sigma(l_-(t), t) = q_- - k \frac{L(t) - L_0}{L_0} \\ \sigma(l_+(t), t) = q_+ - k \frac{L(t) - L_0}{L_0} \end{cases}$$

- Constitutive relation:
$$\sigma = \eta \partial_x v + E(1 - \rho/\rho_0) + \chi c(x, t)$$

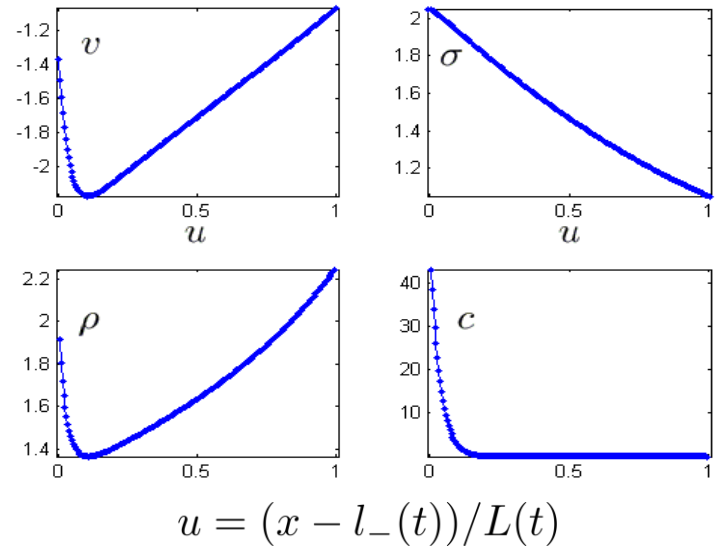
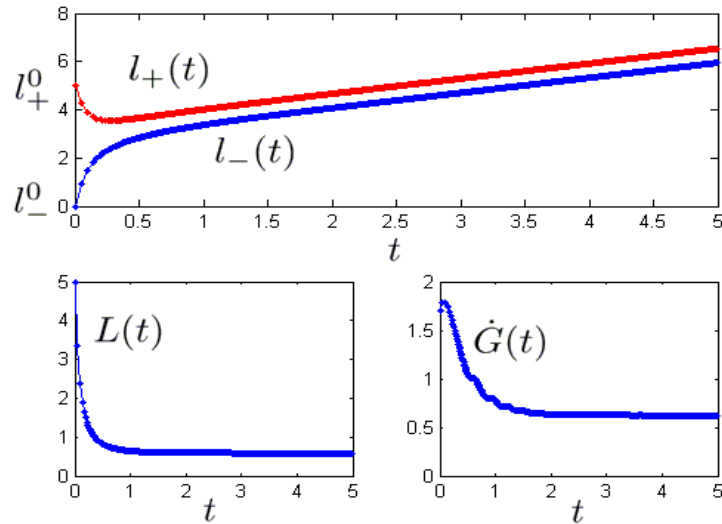
- Protrusion:
$$\begin{cases} \dot{l}_- = v_- + v(l_-(t), t) \\ \dot{l}_+ = v_+ + v(l_+(t), t) \\ l_-(0) = l_-^0 < l_+(0) = l_+^0 \end{cases}$$

- Actin:
$$\begin{cases} \partial_t \rho + \partial_x(\rho v) = 0 \\ \rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+ \\ \rho(x, 0) = \rho^0(x) \end{cases}$$

- Myosin :
$$\begin{cases} \partial_t c + \partial_x(cv) - D\partial_{xx}c = 0 \\ c(l_-(t), t) v_- + D\partial_x c(l_-(t), t) = 0 \\ c(l_+(t), t) v_+ + D\partial_x c(l_+(t), t) = 0 \\ c(x, 0) = c^0(x) \end{cases}$$

Unknowns: $l_-(t), l_+(t), \underbrace{\sigma(x, t)}_{\text{axial stress}}, \underbrace{v(x, t)}_{\text{velocity}}, \underbrace{\rho(x, t)}_{\text{actin density}}, \underbrace{c(x, t)}_{\text{myosin concentration}}$ and ~~$a(x, t)$~~
~~integrin concentration~~

Direct numerical simulation



$$\begin{cases} G(t) = \frac{l_-(t) + l_+(t)}{2} \\ L(t) = l_+(t) - l_-(t) \end{cases}$$

- Traveling wave ansatz
- Retrograde flow
- Realistic actin density distribution
- Myosin concentrated at the trailing edge

Efficiency (with no bulk elasticity)

$$\text{Traveling wave assumption: } \begin{cases} \dot{l}_-(t) = \dot{l}_+(t) = V \\ L(t) = L \\ y = x - Vt \end{cases}$$

$$\text{Balance of power} \quad [\sigma v]_{l_-(t)}^{l_+(t)} = \xi \int_{-L/2}^{L/2} av^2 + \eta \int_{-L/2}^{L/2} (\partial_y v)^2 + \chi \int_{-L/2}^{L/2} c \partial_y v$$

$$\underbrace{-\chi \int c \partial_y v}_{P_c > 0} - \underbrace{\left[\left(q - k \frac{L - L_0}{L_0} \right) v \right]_-^+}_{P_t > 0} = \underbrace{(q_- - q_+) V}_{P_m > 0} + \underbrace{\xi \int av^2 + \eta \int (\partial_y v)^2}_{P_d > 0}$$

$$\text{Efficiency } \Lambda = \frac{P}{H}$$

$$\begin{cases} P = \underbrace{P_m}_{\text{work against loads}} + \underbrace{\xi LV^2}_{\text{Stokes term}} \\ H = \underbrace{P_c + P_t}_{\text{active mechanisms}} + \underbrace{\mu}_{\text{"maintenance heat"}} \end{cases}$$

Outline:

1. Optimization of crawling: reverse engineering
2. Contraction driven motility: autotaxis
3. Protrusion and contraction driven motility: cell carrying cargoes

Optimal crawling: assumptions

- Force Balance:
$$\begin{cases} \partial_x \sigma = \xi a(x, t) v \\ \sigma(l_-(t), t) = q_- - k \frac{L(t) - L_0}{L_0} \\ \sigma(l_+(t), t) = q_+ - k \frac{L(t) - L_0}{L_0} \end{cases}$$

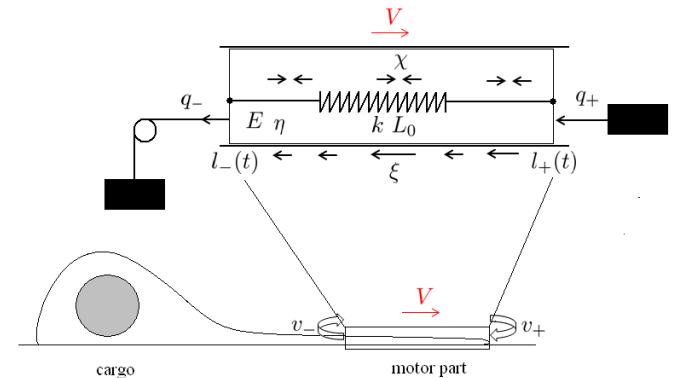
Traveling wave assumption:
$$\begin{cases} \dot{l}_-(t) = \dot{l}_+(t) = V \\ L(t) = L \\ y = x - Vt \end{cases}$$

- Constitutive relation:
$$\sigma = \eta \partial_x v + \rho + \chi c(x, t)$$

- Protrusion:
$$\begin{cases} \dot{l}_- = v_- + v(l_-(t), t) \\ \dot{l}_+ = v_+ + v(l_+(t), t) \\ l_-(0) = l_-^0 < l_+(0) = l_+^0 \end{cases}$$

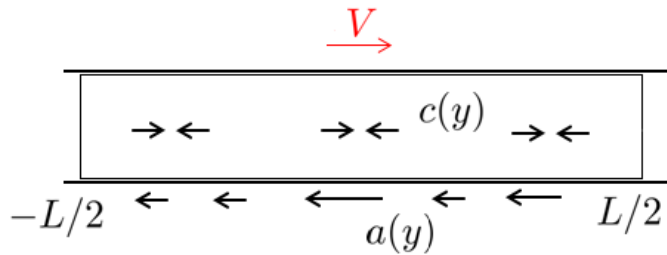
- Actin:
$$\begin{cases} \partial_t \rho + \partial_x(\rho v) = 0 \\ \rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+ \\ \rho(x, 0) = \rho^0(x) \end{cases}$$

- Myosin:
$$\begin{cases} \partial_t c + \partial_x(cv) - D \partial_{xx} c = 0 \\ c(l_-(t), t) v_- + D \partial_x c(l_-(t), t) = 0 \\ c(l_+(t), t) v_+ + D \partial_x c(l_+(t), t) = 0 \\ c(x, 0) = c^0(x) \end{cases}$$



Unknowns: $l_-(t), l_+(t), \underbrace{\sigma(x, t)}_{\text{axial stress}}, \underbrace{v(x, t)}_{\text{velocity}}, \underbrace{\rho(x, t)}_{\text{actin density}}, \underbrace{c(x, t)}_{\text{myosin concentration}}$ and $\underbrace{a(x, t)}_{\text{integrin concentration}}$

Optimization of velocity



$c(y), a(y)$ are the control functions

$$V = \frac{1}{2} \left(\frac{\partial_y \sigma}{a}(-L/2) + \frac{\partial_y \sigma}{a}(L/2) \right)$$

$$\begin{cases} -\partial_y \left(\frac{1}{a} \partial_y \sigma \right) + \sigma = c \\ \sigma(-L/2) = -k \frac{L-L_0}{L_0} = \sigma(L/2) \\ \frac{\partial_y \sigma}{a}(-L/2) = \frac{\partial_y \sigma}{a}(L/2). \end{cases}$$



Optimization problem:

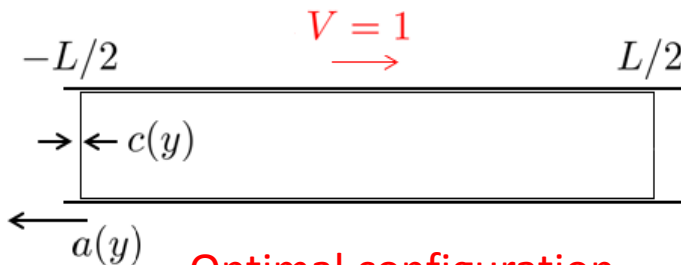
$$\begin{cases} \max_{c, a \in L^1_+([-L/2, L/2])} V(c, a) \\ \int_{-L/2}^{L/2} c(y) dy = \frac{1}{L} \int_{-L/2}^{L/2} a(y) dy = 1 \end{cases}$$



(σ, L)

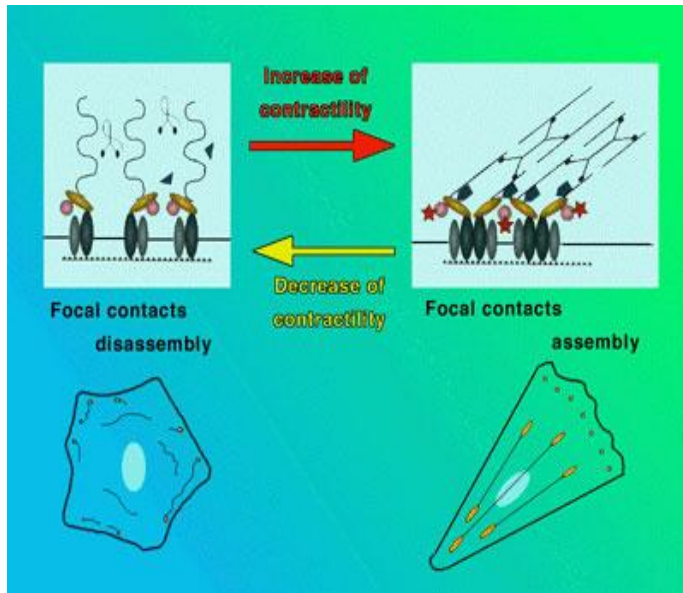
Solution:

$$\begin{cases} c(y) = \delta(y + L/2) \\ a(y) = \delta(y + L/2) \\ V = 1 \end{cases}$$

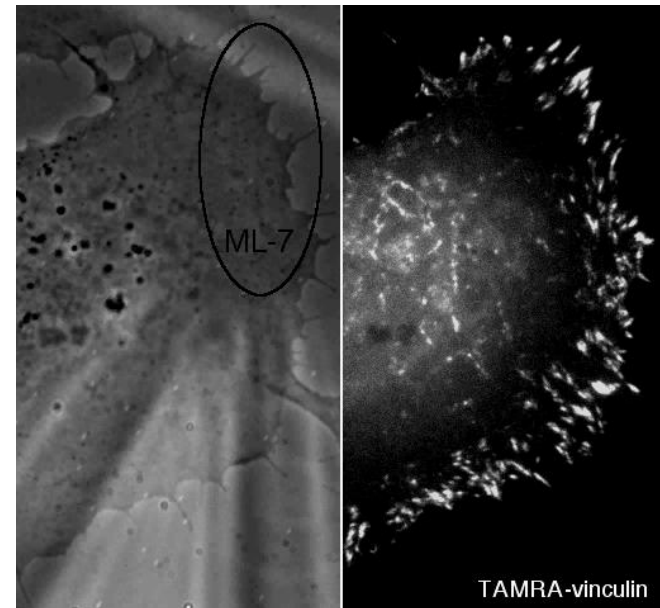


Optimal configuration

Contractility is correlated with adhesion

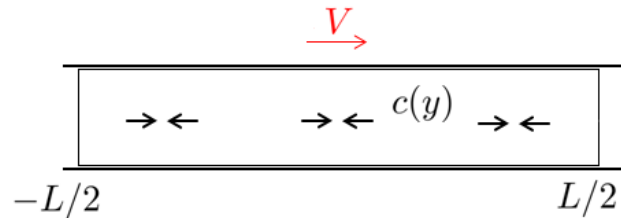


<http://www.mit.edu/~kardar/Videotour/>



I. Kaverina, et al. *Current Biology*, 10(12), 2000.

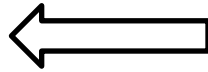
Optimization of efficiency



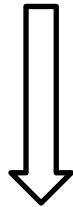
$a \equiv 1$, $c(y)$ is a control function

$$\begin{cases} -\partial_y(\partial_y\sigma) + \sigma = c \\ \sigma(-L/2) = -k\frac{L-L_0}{L_0} = \sigma(L/2) \\ \partial_y\sigma(-L/2) = \partial_y\sigma(L/2). \end{cases}$$

$$\Lambda = \frac{LV^2}{-\int_{-L/2}^{L/2} c\partial_{yy}\sigma + \mu}$$



$$V = \frac{1}{2} (\partial_y\sigma(-L/2) + \partial_y\sigma(L/2))$$



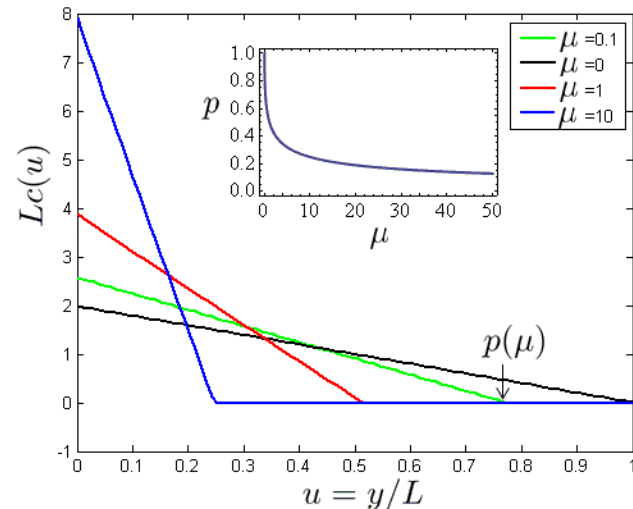
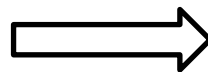
Numerator maximized by fully localized $c(y) = \delta(y + L/2)$.

Denominator minimized by homogeneous $c(y) = -k\frac{L-L_0}{L_0}$.

Optimization problem:

$$\begin{cases} \max_{c \in L^2_+([-L/2, L/2])} \Lambda(c) \\ \int_{-L/2}^{L/2} c(y)dy = 1 \end{cases}$$

Solution:



Contraction-driven motility: minimal model

- Force Balance:
$$\begin{cases} \partial_x \sigma = \xi v \\ \sigma(l_-(t), t) = q_- - k \frac{L(t) - L_0}{L_0} \\ \sigma(l_+(t), t) = q_+ - k \frac{L(t) - L_0}{L_0} \end{cases}$$

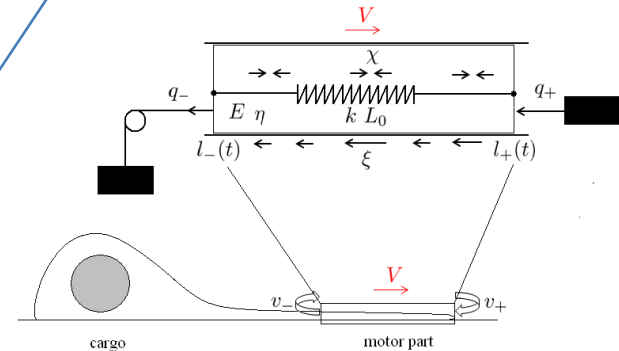
- Constitutive relation:
$$\sigma = \eta \partial_x v + F(\rho) + \chi c(x, t)$$

- Protrusion:
$$\begin{cases} \dot{l}_- = v_- + v(l_-(t), t) \\ \dot{l}_+ = v_+ + v(l_+(t), t) \\ l_-(0) = l_-^0 < l_+(0) = l_+^0 \end{cases}$$

- Actin:
$$\begin{cases} \partial_t \rho + \partial_x(\rho v) = 0 \\ \rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+ \\ \rho(x, 0) = \rho^0(x) \end{cases}$$

- Myosin:
$$\begin{cases} \partial_t c + \partial_x(cv) - D \partial_{xx} c = 0 \\ c(l_-(t), t) v_- + D \partial_x c(l_-(t), t) = 0 \\ c(l_+(t), t) v_+ + D \partial_x c(l_+(t), t) = 0 \\ c(x, 0) = c^0(x) \end{cases}$$

Autotaxis equations



Unknowns: $l_-(t), l_+(t), \underbrace{\sigma(x, t)}_{\text{axial stress}}, \underbrace{v(x, t)}_{\text{velocity}}, \underbrace{\rho(x, t)}_{\text{actin density}}, \underbrace{c(x, t)}_{\text{myosin concentration}}$ and $\underbrace{a(x, t)}_{\text{integrin concentration}}$

Autotaxis equations

Keller-Segel type system on a moving domain:

$$\left\{ \begin{array}{l} -\mathcal{Z}\partial_{xx}\sigma + \sigma = \mathcal{P}c/c_0, \\ \partial_t c + \mathcal{K}\partial_x(c\partial_x\sigma) - \partial_{xx}c = 0 \end{array} \right. \quad \left\{ \begin{array}{l} \sigma(l_-(t), t) = \sigma(l_+(t), t) = -(L(t) - 1) \\ \partial_x c(l_-(t), t) = \partial_x c(l_+(t), t) = 0 \\ \dot{l}_-(t) = \mathcal{K}\partial_x\sigma(l_-(t), t) \\ \dot{l}_+(t) = \mathcal{K}\partial_x\sigma(l_+(t), t) \end{array} \right.$$

equations

boundary conditions

Dimensionless constants :

- $\mathcal{Z} = \eta/(\xi L_0^2)$ frictional length over elastic length
- $\mathcal{K} = k/(\xi D)$ Peclet number relating diffusion and drift
- $\mathcal{P} = c_0\chi/k$ measure of motor activity

Travelling waves

$$\text{Traveling wave assumption: } \begin{cases} \dot{l}_-(t) = \dot{l}_+(t) = V \\ L(t) = L \\ y = x - Vt \end{cases}$$

$$\text{Introduce : } s(y) = \mathcal{K} [\sigma(y) + (L - 1)]$$

Then,

$$\mathcal{K}^{-1}(-\mathcal{Z}s'' + s) - (L - 1) = \mathcal{P} \frac{\exp(s - Vy)}{\int_0^L \exp(s - Vy) dy}$$

with:

$$\begin{cases} s(0) = 0 = s(L) \\ s'(0) = V = s'(L) \end{cases}$$

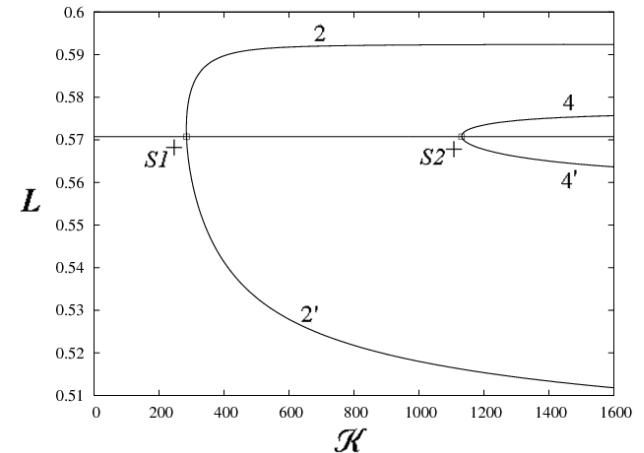
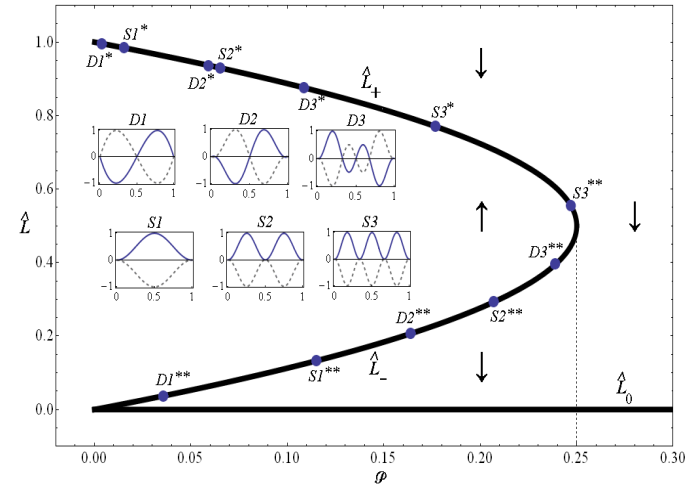
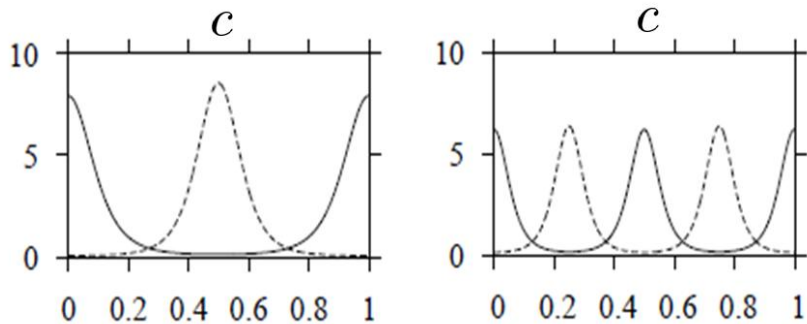
Myosin concentration:

$$c(y) = c_0 \frac{\exp(s - Vy)}{\int_0^L \exp(s - Vy) dy}$$

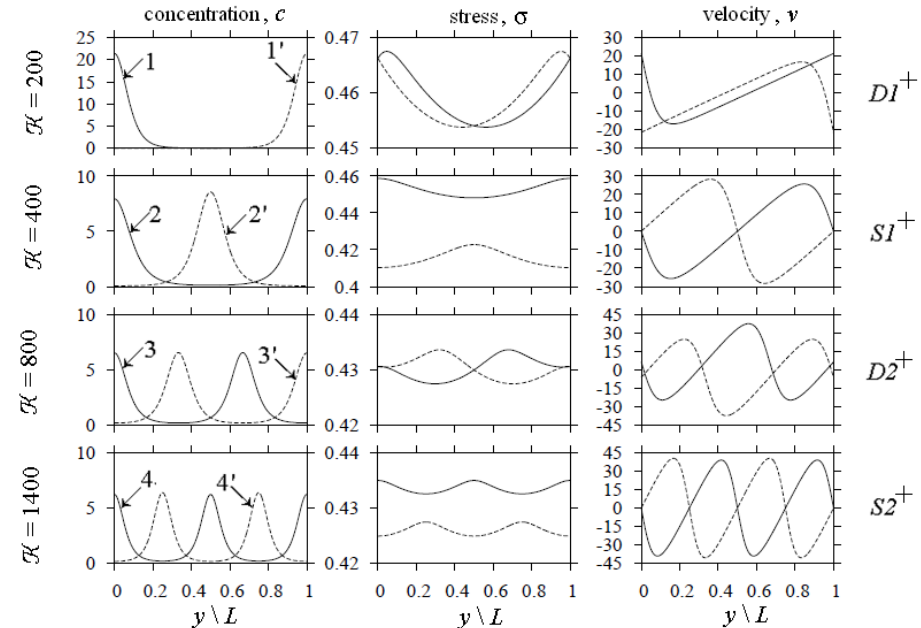
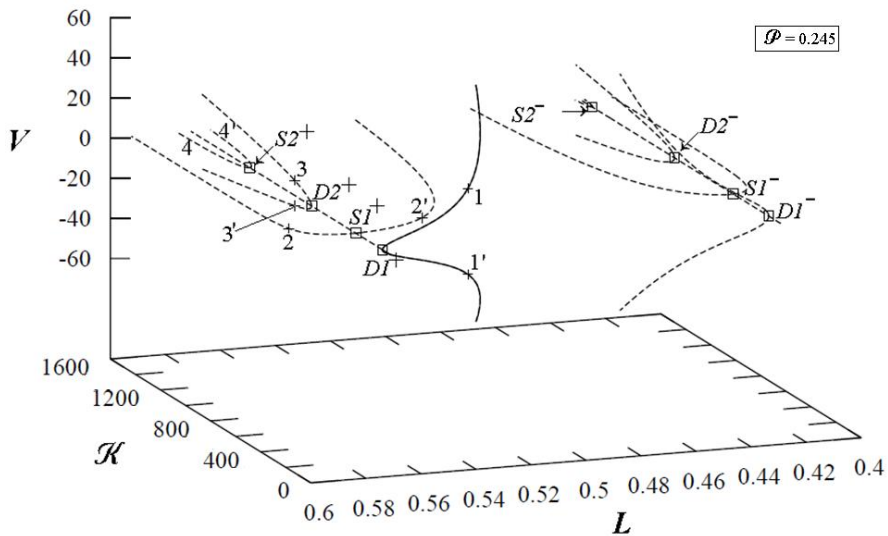
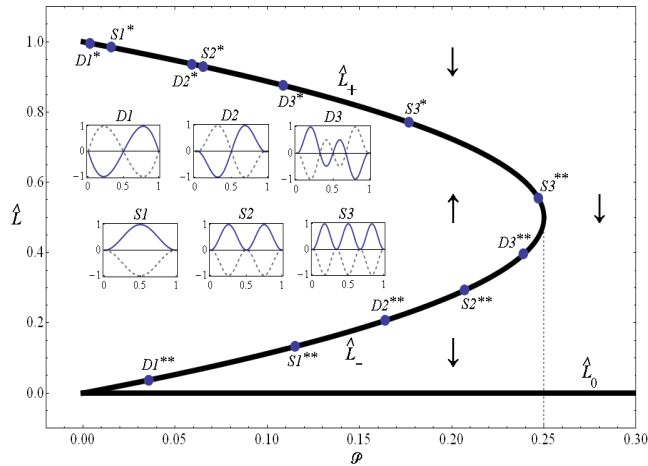
Static solutions

$$\begin{cases} \mathcal{K}^{-1}(-\mathcal{Z}s'' + s) - (L - 1) = \mathcal{P} \frac{\exp(s)}{\int_0^L \exp(s)} \\ s(0) = s(L) = s'(0) = 0 \end{cases}$$

- Homogeneous solutions
 $s = 0, L = \hat{L}_{\pm} = (1 \pm \sqrt{1 - 4\mathcal{P}})/2$
- Singular solutions
 $s = \lim_{r \rightarrow 0} r \frac{\mathcal{K}\mathcal{P}}{2} (y/r)(1 - y/r), L = 0$
- Inhomogeneous solutions

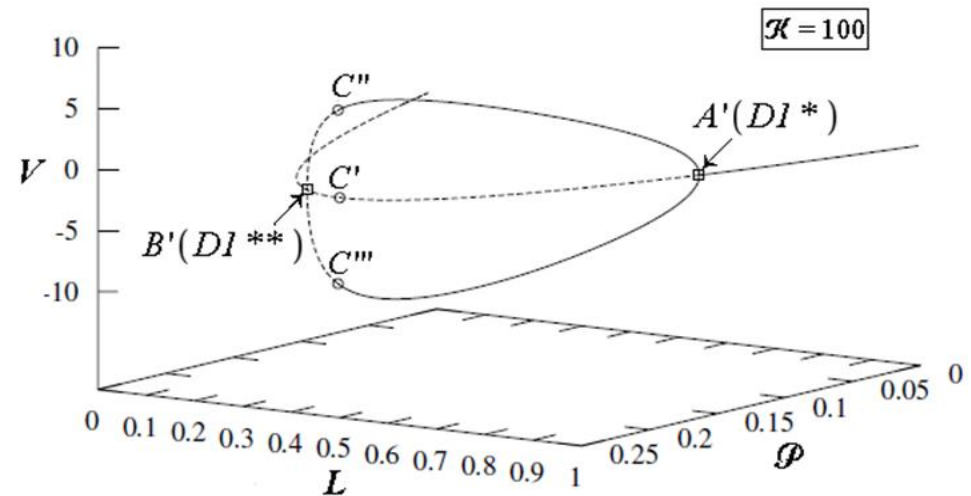
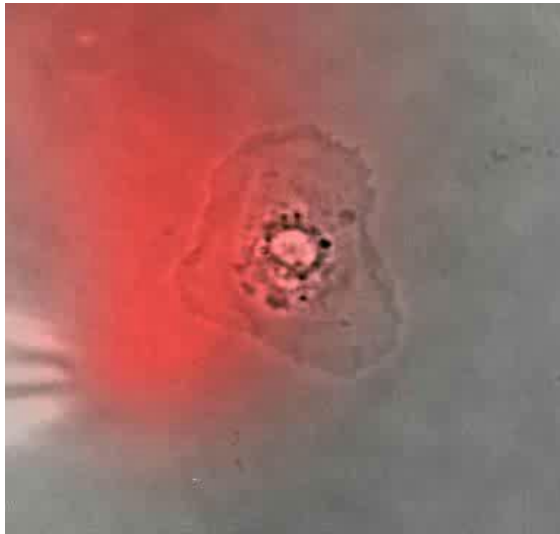


Bifurcational diagram: motile solutions

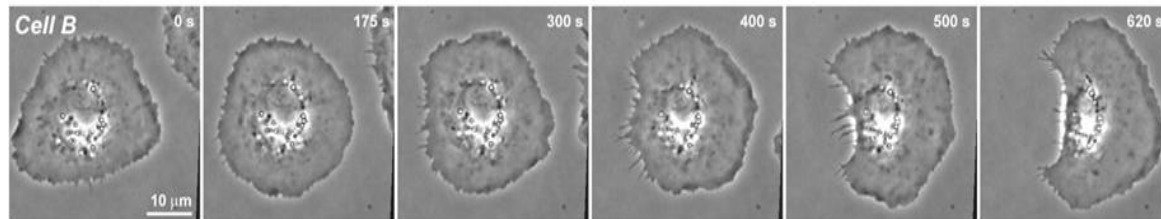


“ Local stimulation of myosin activity in stationary cells by the local application of calyculin A induced directed motility initiation away from the site of stimulation”

Verkhovsky et al. , Current Biology, 1999 , Yam et al, JCB, 2007



Symmetric configuration becomes unstable and steady state motion is generated



Protrusion and contraction: carrying cargo

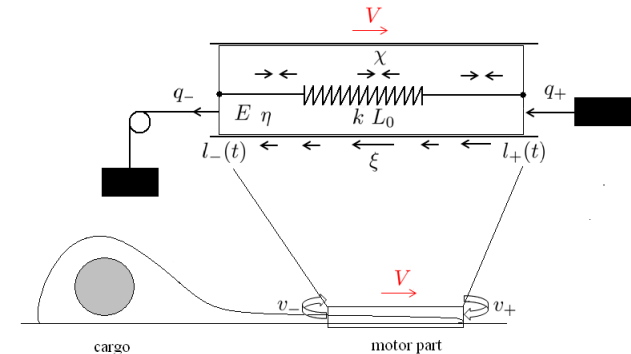
- Force Balance:
$$\begin{cases} \partial_x \sigma = \xi v \\ \sigma(l_-(t), t) = q_- - k \frac{l_-(t) - L_0}{L_0} \\ \sigma(l_+(t), t) = q_+ - k \frac{l_+(t) - L_0}{L_0} \end{cases}$$

- Constitutive relation:
$$\sigma = \eta \partial_x v + F(\rho) + \chi$$

- Protrusion:
$$\begin{cases} \dot{l}_- = v_- + v(l_-(t), t) \\ \dot{l}_+ = v_+ + v(l_+(t), t) \\ l_-(0) = l_-^0 < l_+(0) = l_+^0 \end{cases}$$

- Actin:
$$\begin{cases} \partial_t \rho + \partial_x(\rho v) = 0 \\ \rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+ \\ \rho(x, 0) = \rho^0(x) \end{cases}$$

- Myosin:
$$\begin{cases} \partial_t c + \partial_x(cv) - D \partial_{xx} c = 0 \\ c(l_-(t), t) v_- + D \partial_x c(l_-(t), t) = 0 \\ c(l_+(t), t) v_+ + D \partial_x c(l_+(t), t) = 0 \\ c(x, 0) = c^0(x) \end{cases}$$



Unknowns: $l_-(t), l_+(t), \underbrace{\sigma(x,t)}_{\text{axial stress}}, \underbrace{v(x,t)}_{\text{velocity}}, \underbrace{\rho(x,t)}_{\text{actin density}}, \underbrace{c(x,t)}_{\text{myosin concentration}}$ and $\underbrace{a(x,t)}_{\text{integrin concentration}}$

Pushing vs pulling

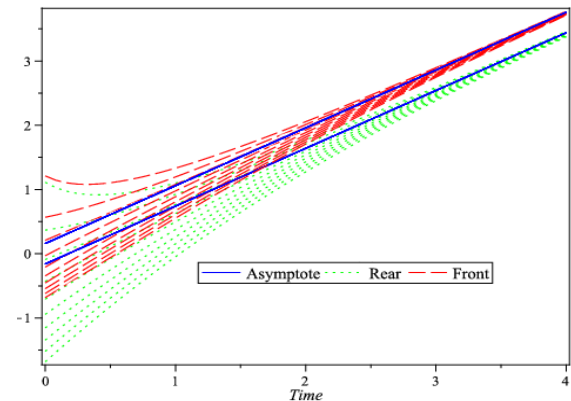
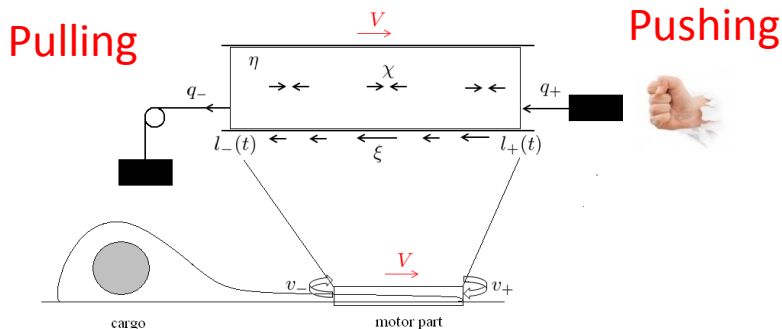
$$\left\{ \begin{array}{l} -\partial_{xx}\sigma + \sigma = 1 \\ \sigma(l_-(t), t) = q_- \text{ and } \sigma(l_+(t), t) = q_+ \\ \dot{l}_- = v_- + \partial_x\sigma(l_-, t) \text{ and } \dot{l}_+ = v_+ + \partial_x\sigma(l_+, t). \end{array} \right.$$

Dynamics is here

F. Jülicher, et al. *Phys. Rep.*, 449(1), 2007

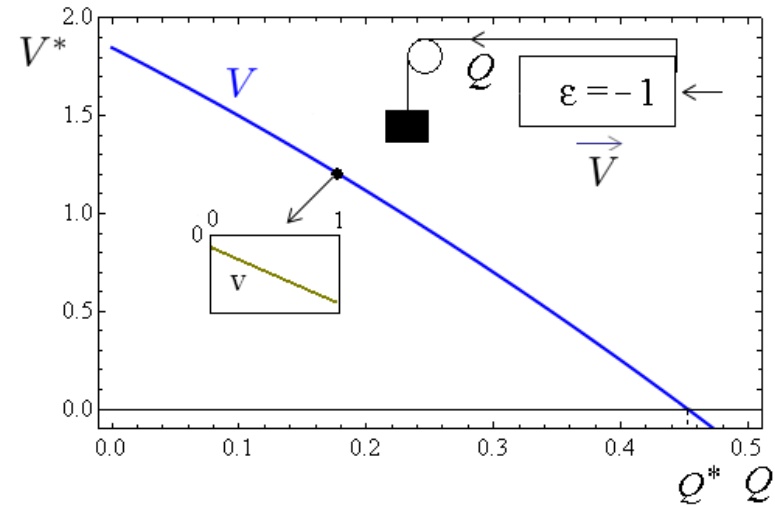
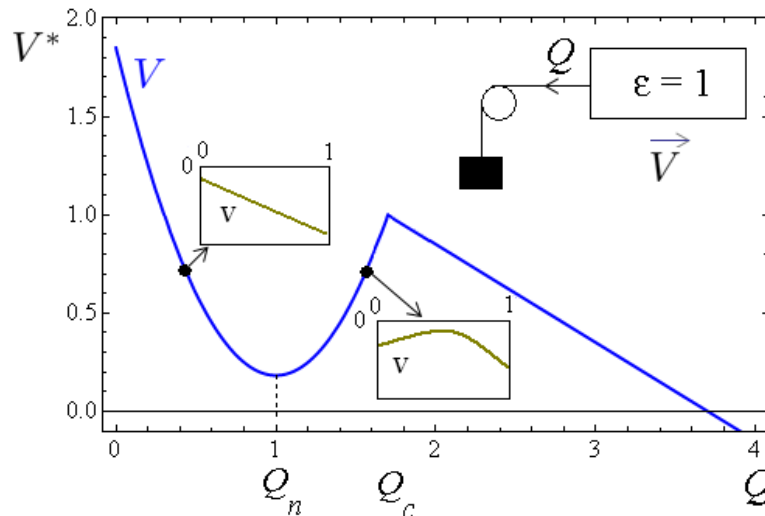
$$\left\{ \begin{array}{l} Q = q_- - q_+ > 0 \text{ (total force)} \\ \epsilon = (q_- + q_+)/Q \text{ (asymmetry factor)} \end{array} \right. \quad \text{and} \quad \left\{ \begin{array}{l} V_m = (v_- + v_+)/2 > 0 \\ \Delta V = v_+ - v_- \end{array} \right.$$

$$\left\{ \begin{array}{l} \dot{L} = \Delta V + (\epsilon Q - 2) \tanh(L/2), \\ \dot{G} = V_m - Q(2 \tanh(L/2))^{-1}. \end{array} \right.$$



Force-velocity relations

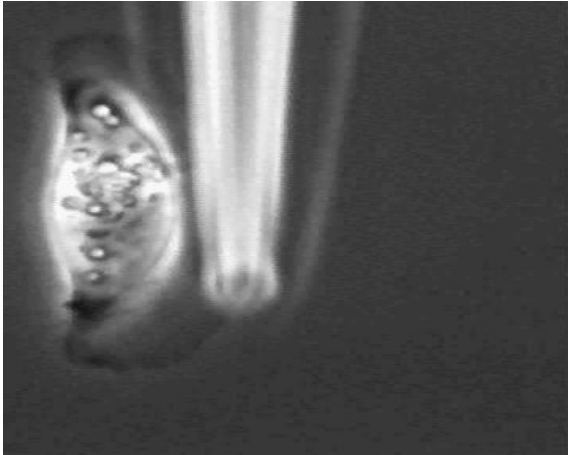
$$L = 2 \tanh^{-1}(\Delta V / (2 - \epsilon Q)) \quad \text{and} \quad V = V_m - Q / \Delta V + \epsilon Q^2 / (2\Delta V)$$



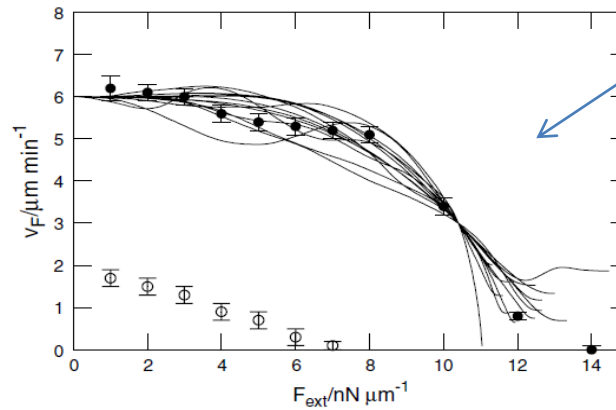
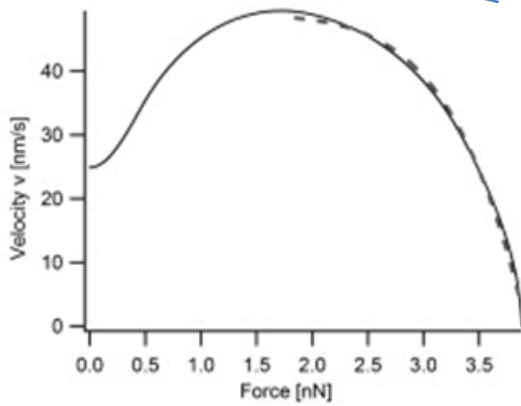
- Convexity/Concavity
 - Negative motility
- $$\left\{ \begin{array}{l} Q^* = (1 - \sqrt{1 - 2\epsilon\Delta V V_m}) / \epsilon \\ V^* = V_m \\ Q_c = (2 - \Delta V) / \epsilon \\ Q_n = 1 / \epsilon \end{array} \right.$$

J.-F. Joanny, et al. *Phys. Rev. Lett.*, 90(16), 2003.

Force-velocity relations: measurements

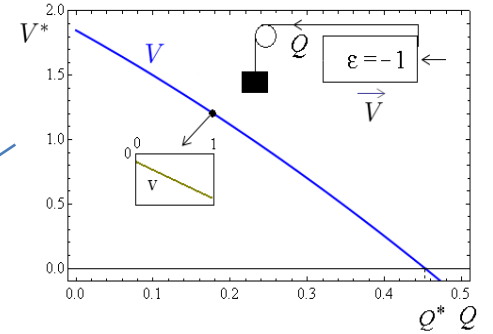
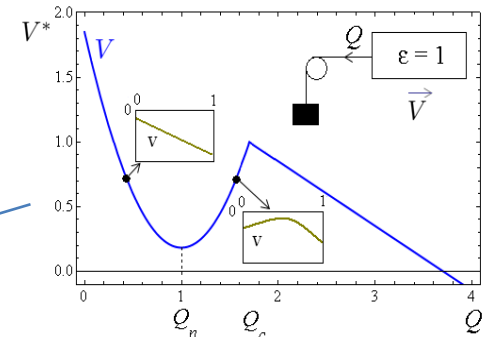


F. Heinemann et al. *Biophys. J.*, 100(6), 2011.



KI Anderson, et al. *J. Cell Biol.*, 134(5), 1996.

C.H. Schreiber, et al. *PNAS*, 107(20), 2010.



Pushers and pullers

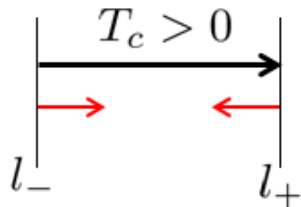
Global force balance, $\underbrace{\int_{-L/2}^{L/2} v}_{\text{friction}} = \underbrace{-Q}_{\text{applied forces}} < 0$: no active contributions

Balance of moments, $\underbrace{\frac{1}{L} \int_{-L/2}^{L/2} yv(y)dy}_{\text{friction}} + \underbrace{\epsilon Q/2}_{\text{applied forces}} = \underbrace{\frac{1}{L} \int_{-L/2}^{L/2} \sigma(y)dy}_{\text{Internal moments}}$
 External moments

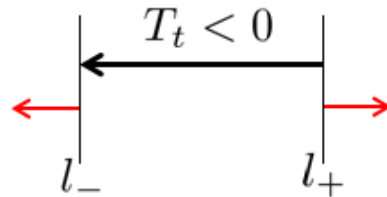
Decomposition of internal moments,

$$\frac{1}{L} \int_{-L/2}^{L/2} \sigma(y)dy = \frac{1}{L} \int_{-L/2}^{L/2} (1 + \partial_y v(y))dy = \underbrace{1}_{T_c > 0, \text{ contraction}} \underbrace{-\frac{\Delta V}{L}}_{T_t < 0, \text{ treadmilling}}$$

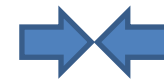
pullers



pushers



— Actions on exterior



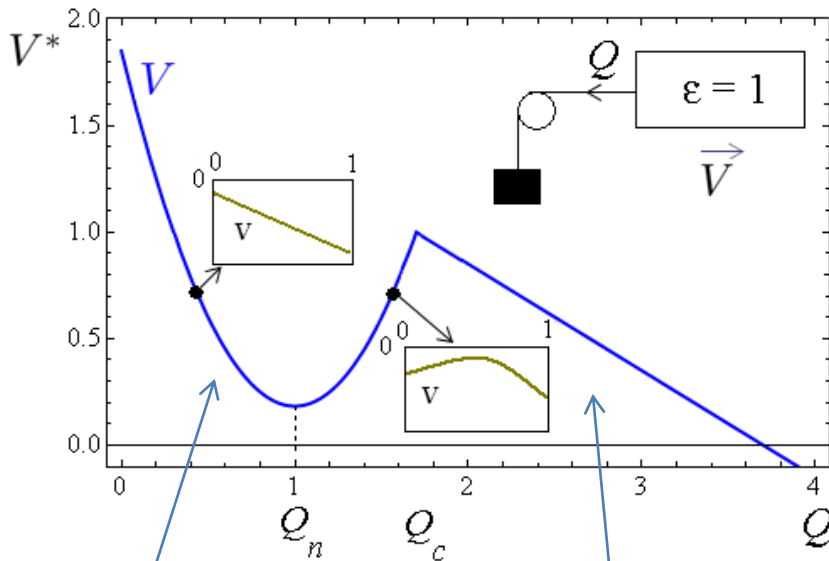
pullers



pushers

pushers: retrograde flow at l_+ /prograde flow at l_-
 pullers: prograde flow at l_+ /retrograde flow at l_-

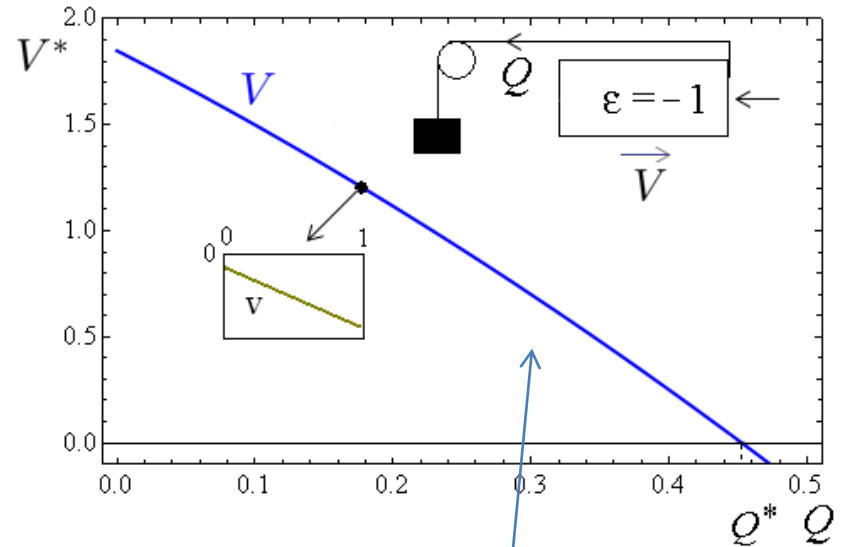
Force-velocity relation: pushers vs pullers



**Pushers
dominate**



**Pullers
dominate**

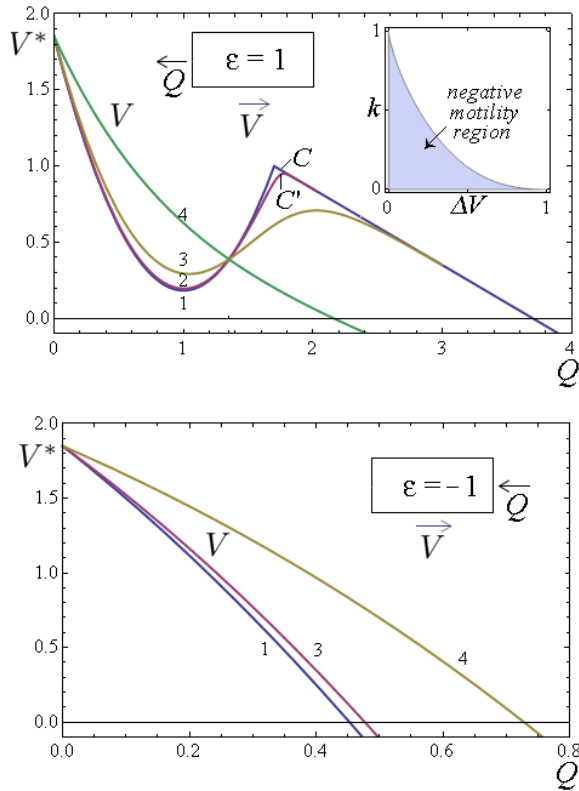


**Pushers
dominate**



Further regularization

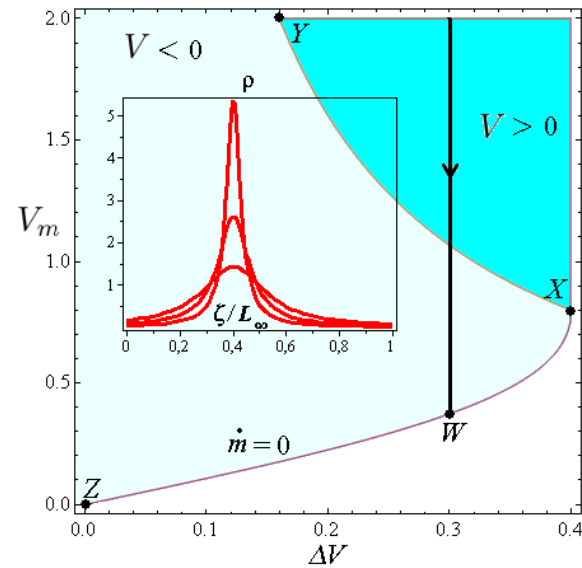
Role of membrane/cortex elasticity



$k_{1,2,3,4} = 0, 0.01, 0.1, 1, L_0 = 1$

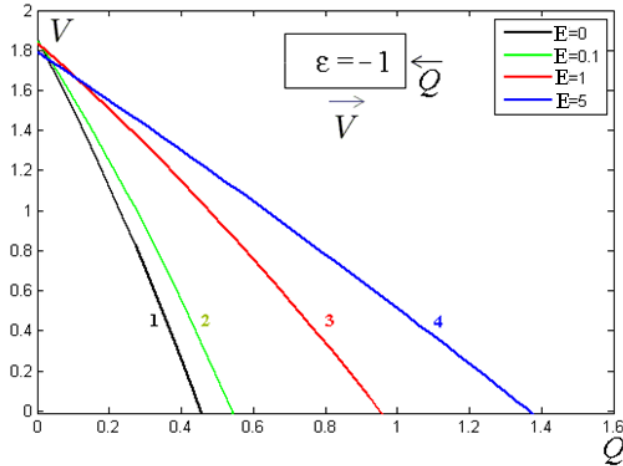
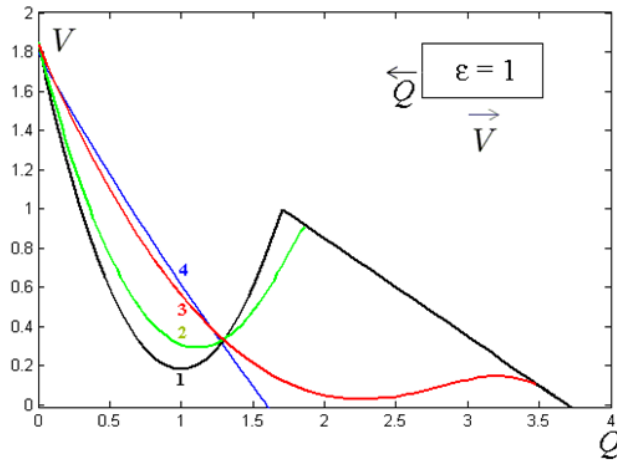
Dynamics of actin

$$\begin{cases} \partial_t \rho + \partial_x(\rho v) = 0 \\ \rho(l_-(t), t)v_- = \rho(l_+(t), t)v_+ \\ \rho(x, 0) = \rho^0(x) \end{cases}$$

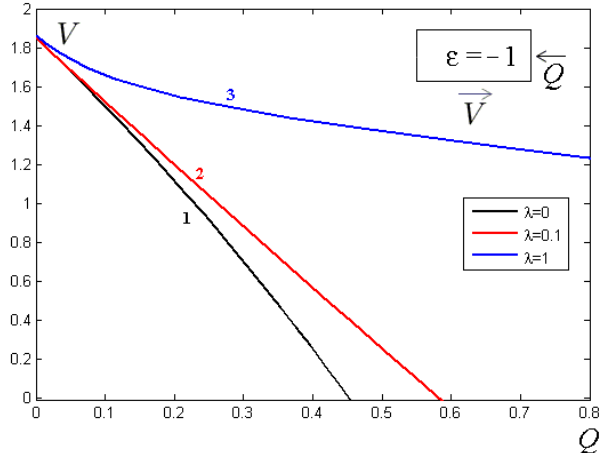
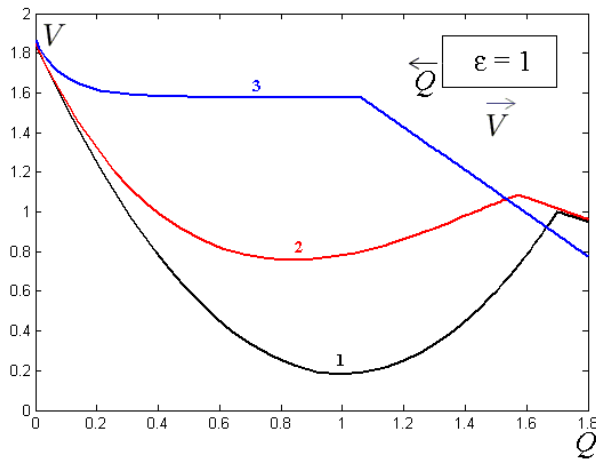


- $F(\rho) = E(1 - \rho/\rho_0)$, bulk elasticity
- Impose energy and mass influx instead of kinematic driving

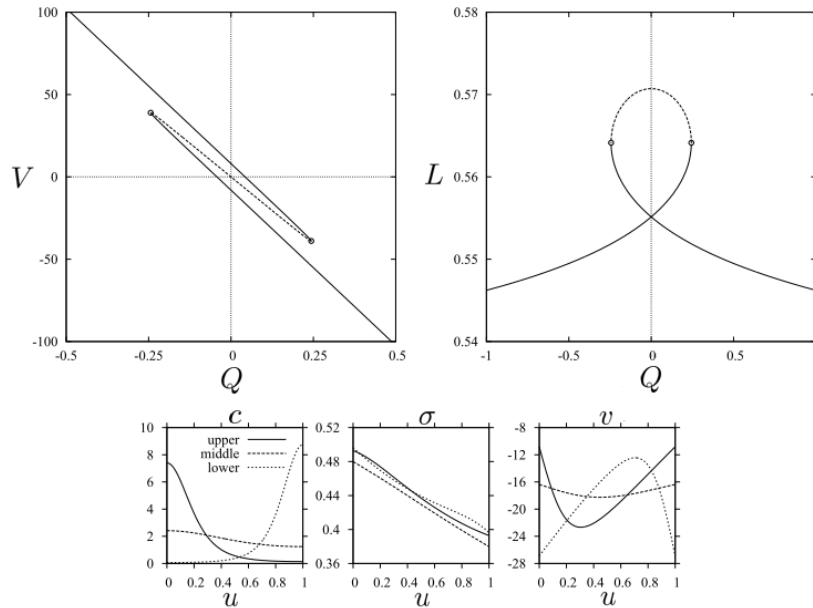
$$\text{Kelvin-Voigt: } \sigma = \eta \partial_x v + E(1 - \rho/\rho_0) + \chi$$



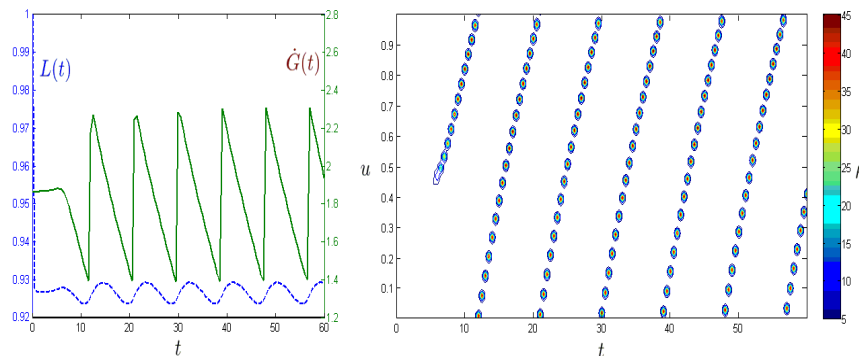
$$\text{Maxwell: } \lambda(\partial_t \sigma + v \partial_x \sigma) + \sigma = \eta \partial_x v + \chi$$



Other effects



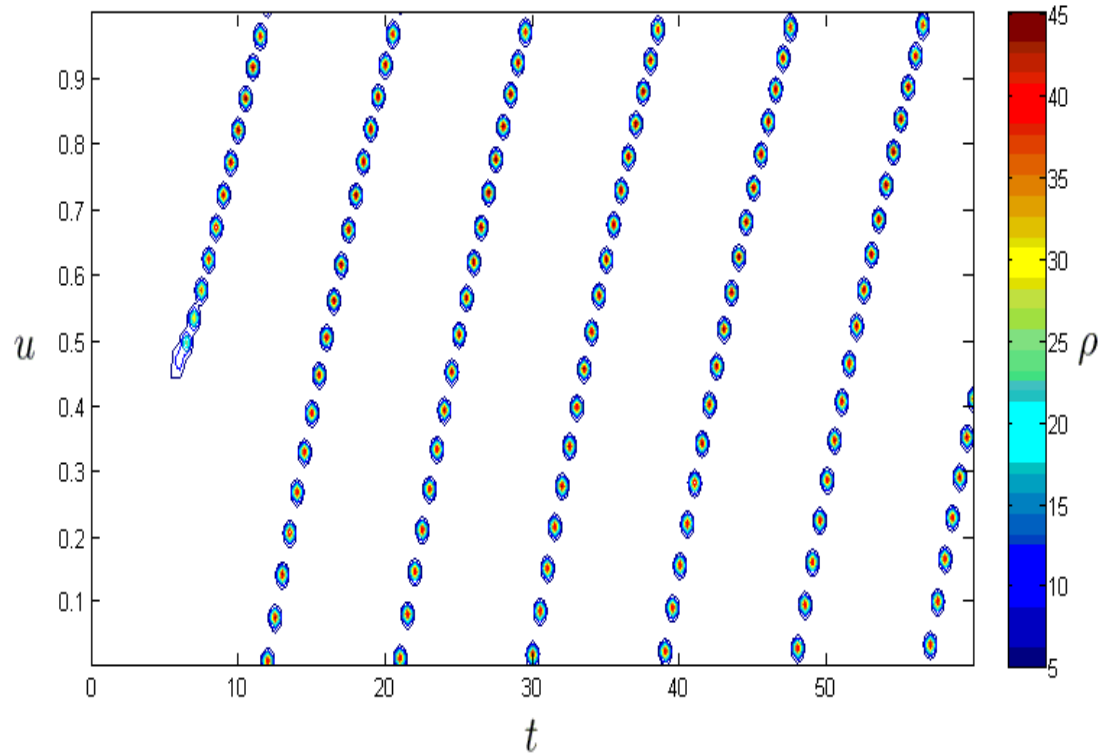
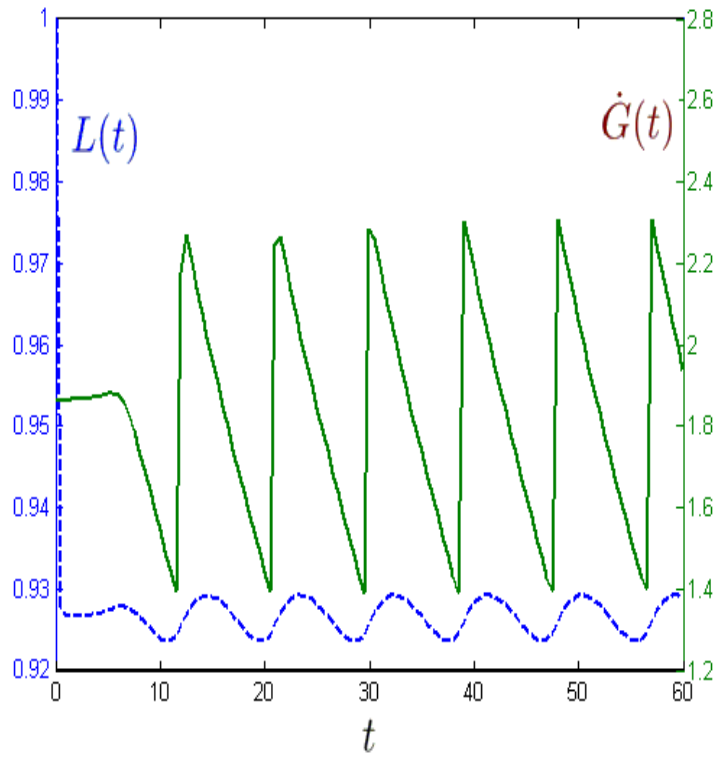
Autotaxic model in the presence of cargoes generates multivalued force velocity relations implying dynamic hysteresis

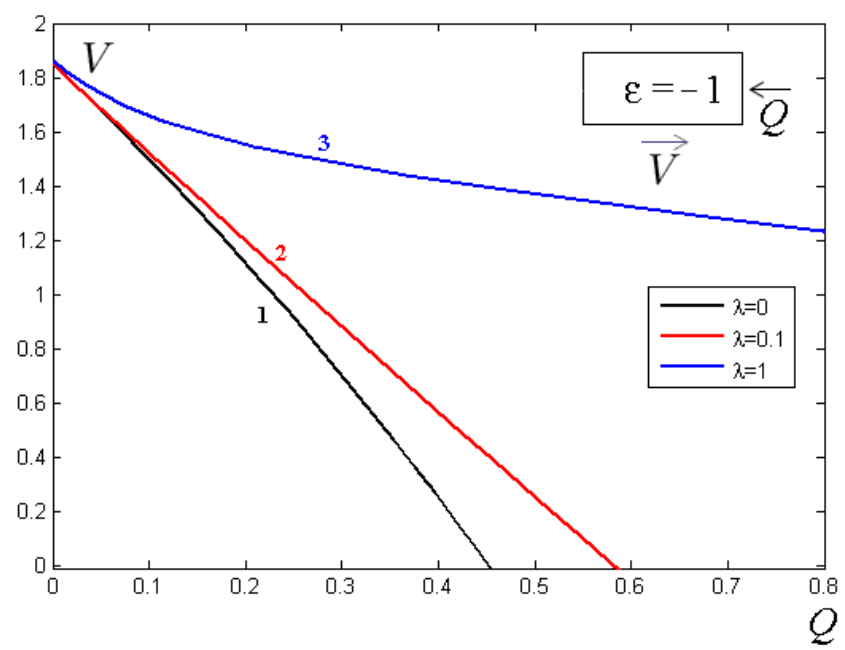
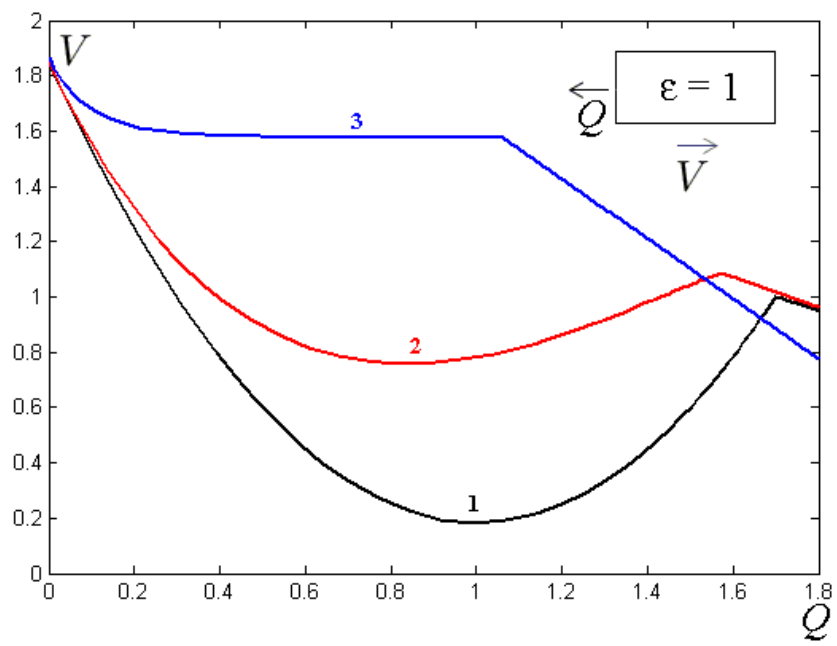
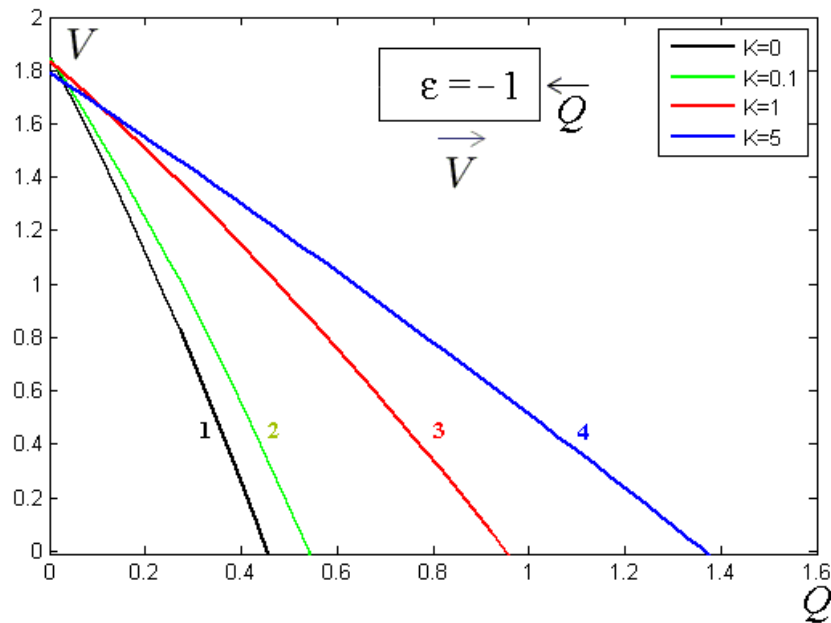
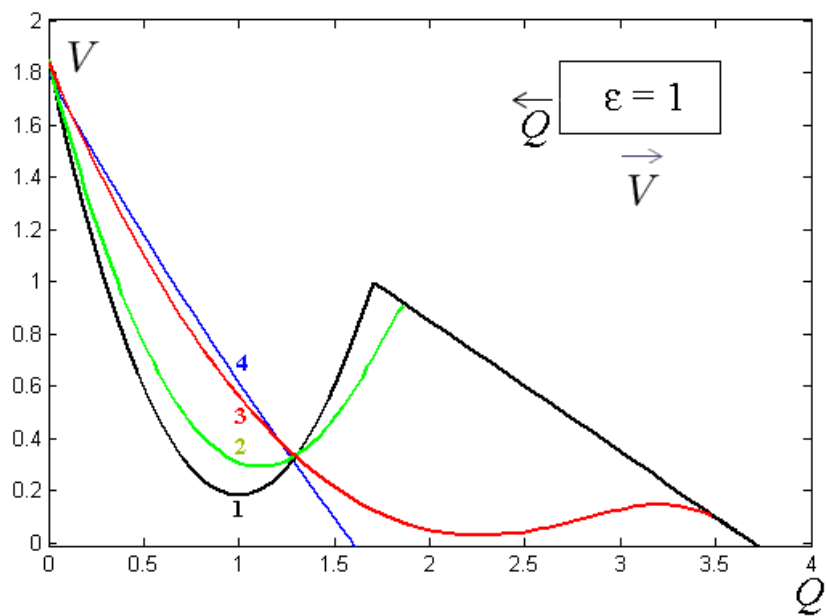


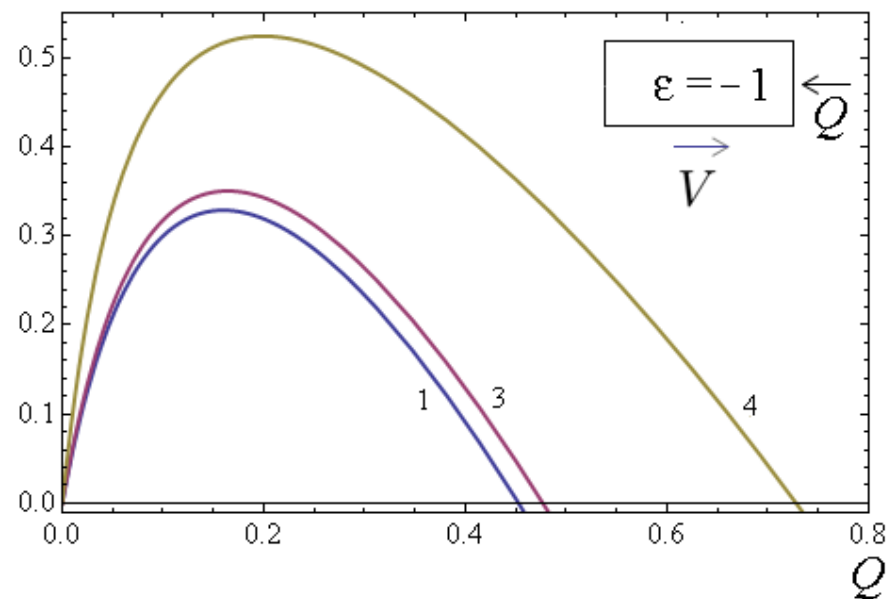
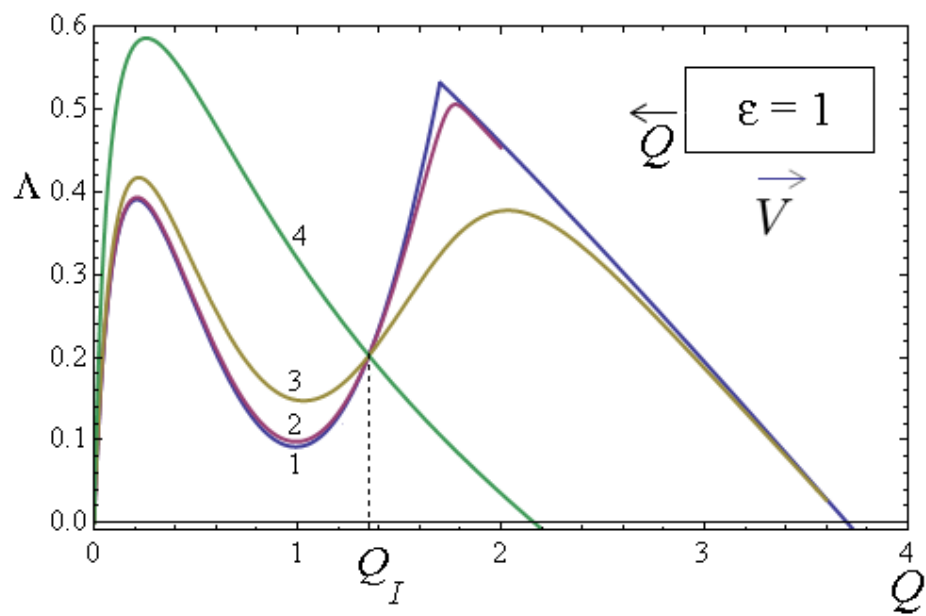
In addition to traveling wave regimes the system with actin dependent contractility shows oscillatory dynamics

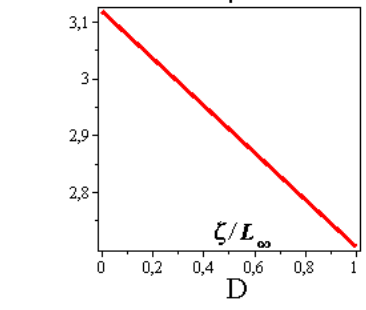
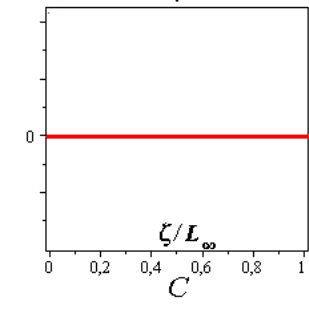
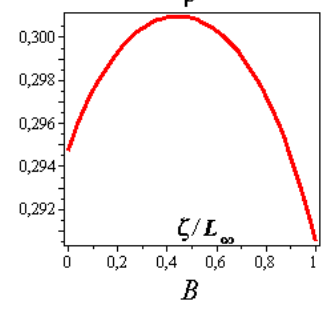
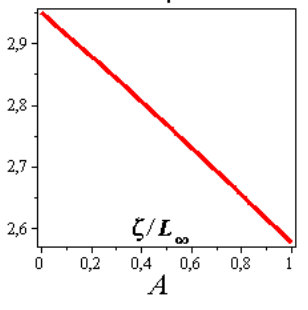
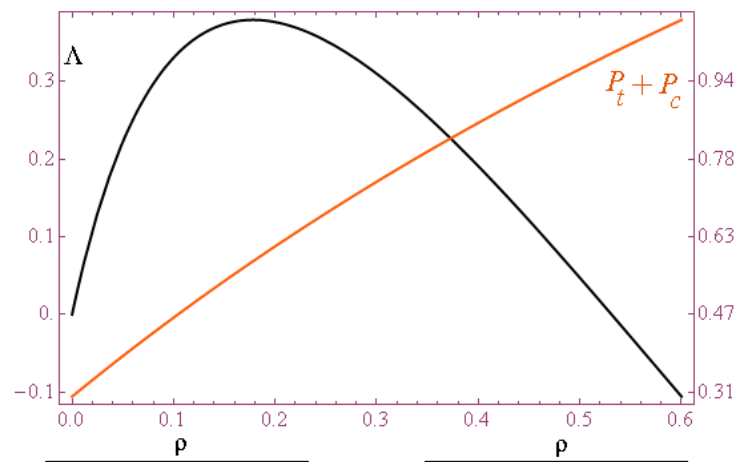
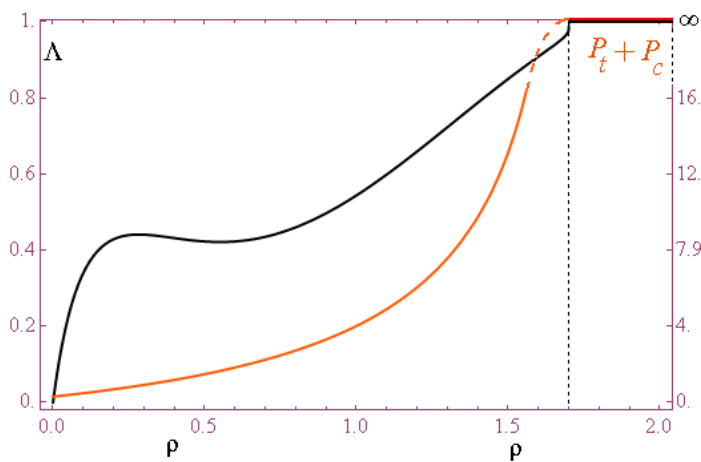
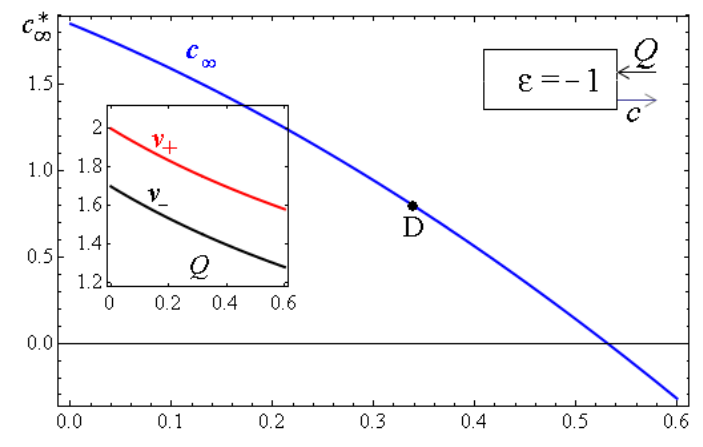
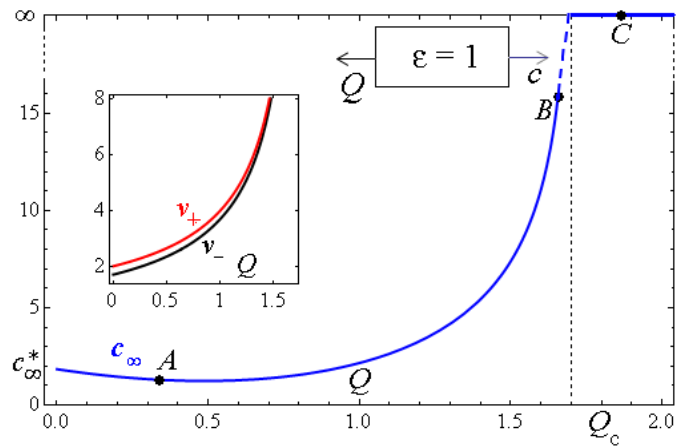
«Take home» messages:

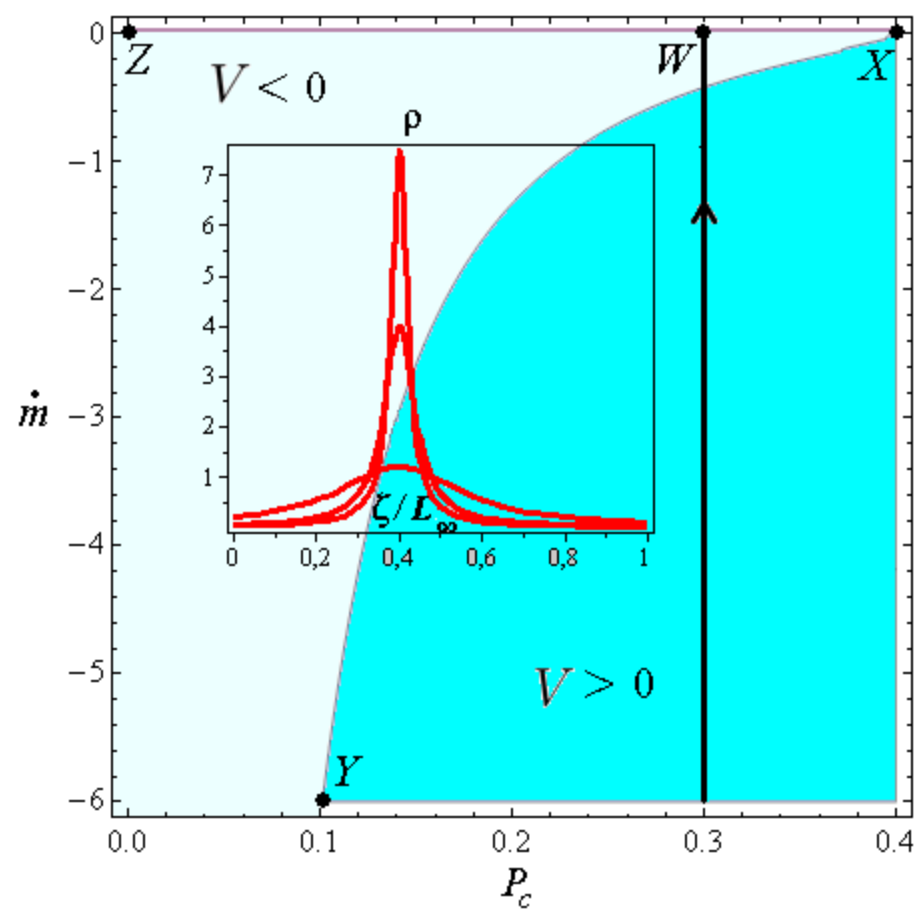
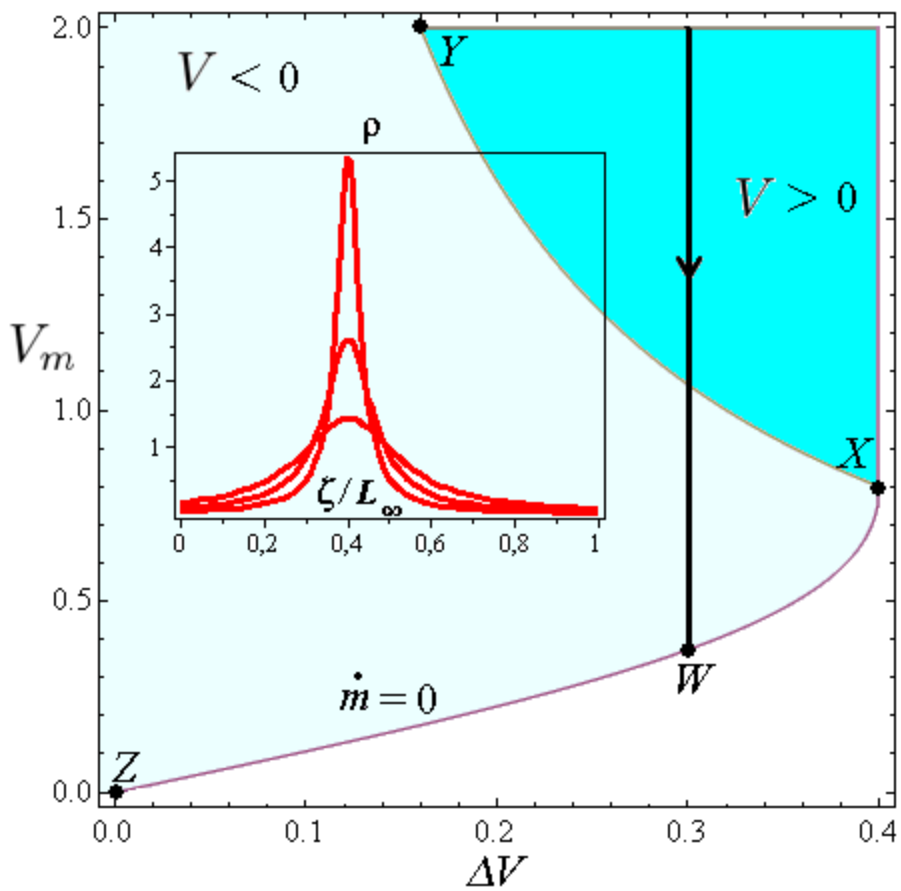
- To show that contraction and adhesion must **conspire** in optimizing mechanical performance of a cell we took a **reverse engineering** approach and posed a problem of finding the optimal spatial organization ensuring either maximum velocity or maximum efficiency. Our analysis shows that the obtained optimal distributions and the real, observed distributions are in good agreement.
- We have shown that active contractility can generate both spontaneous polarization and steady translocation of a cell. The morphological instability is due to internal motion of the cytoskeleton which is generated by **active cross-linkers** and simultaneously transports them. In this way myosin motors use passive actin network as a medium through which they interact and **self-organize**.
- The model predicts a shift from **protrusion dominated** motility to **contraction dominated** motility when the pulling force is sufficiently strong. The possibility of such active adjustment plays an important role in the response of active media implying that if necessary **'pullers'** can replace **'pushers'**. While the detailed shape of the force velocity relation depends on the driving mode, its loading-sensitive **convexity-concavity structure** appears to be a robust feature of the model.

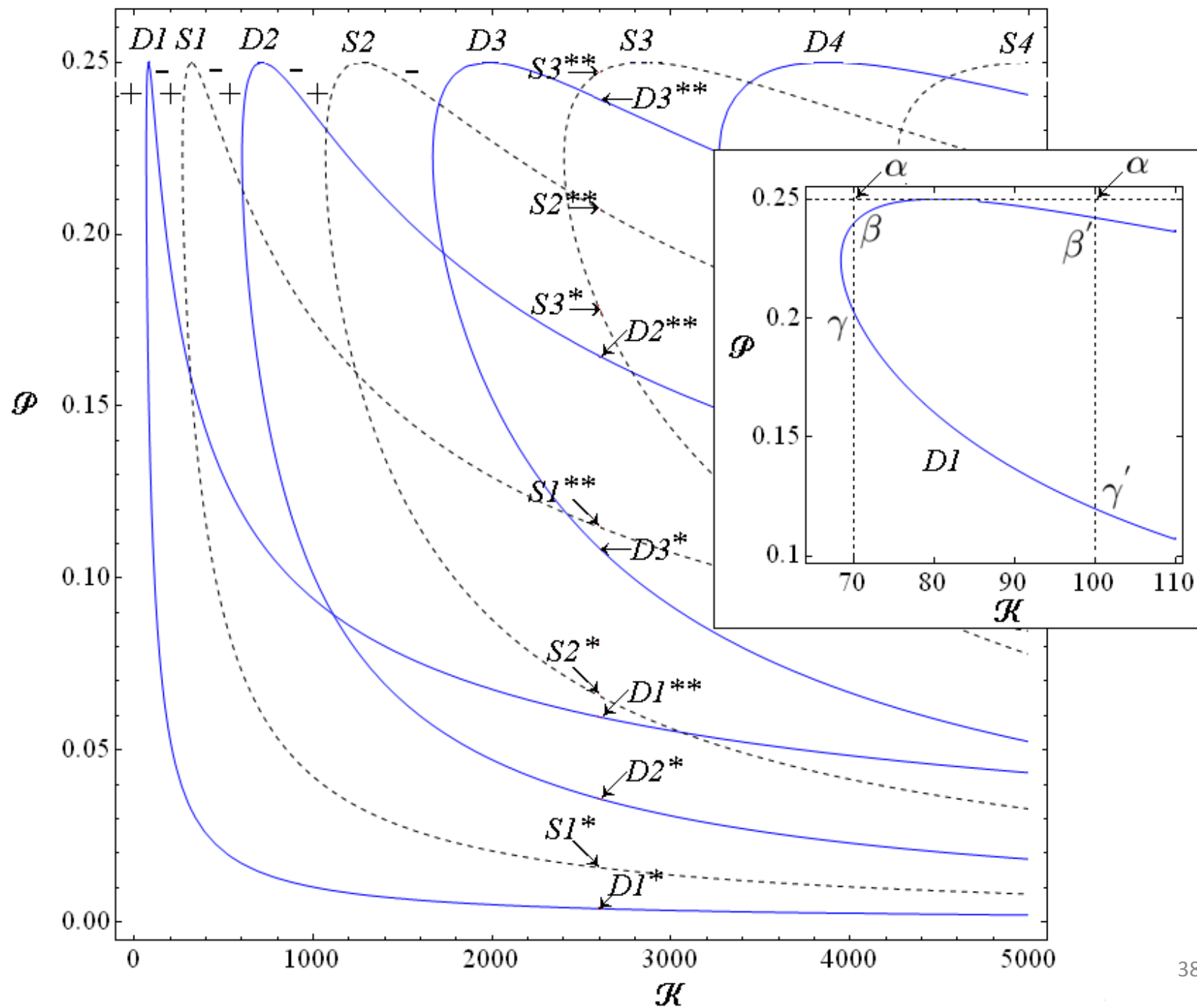


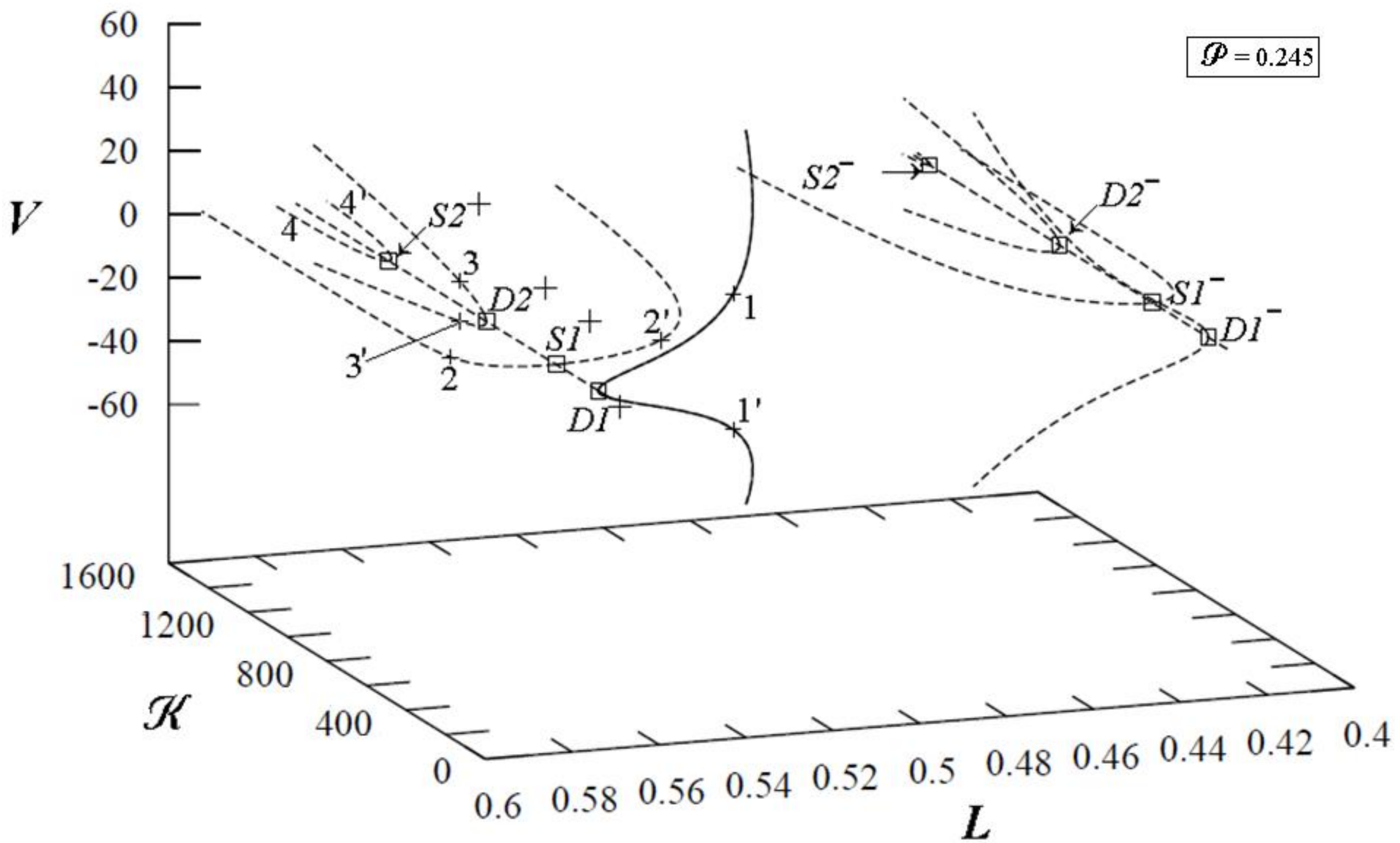


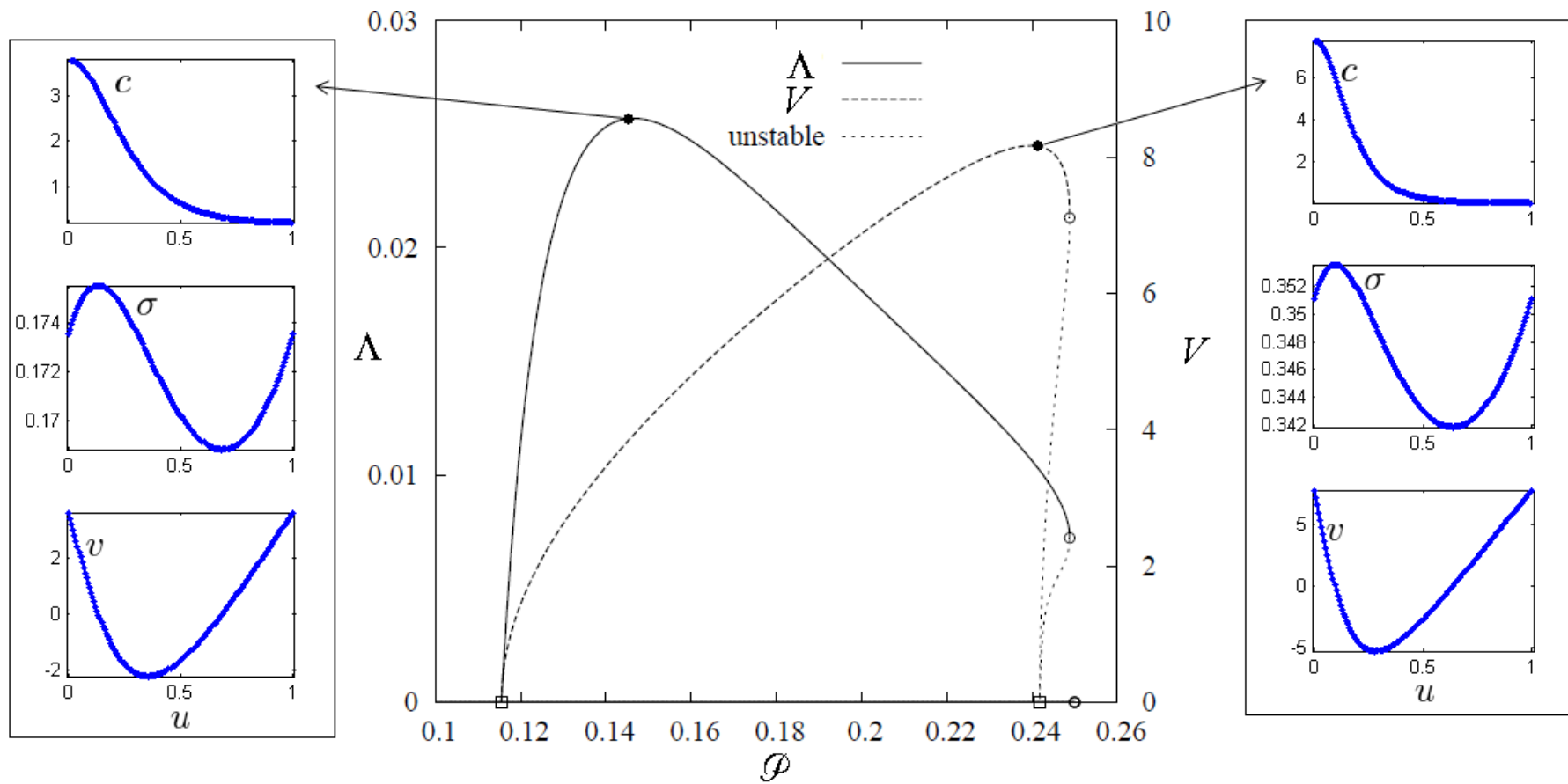


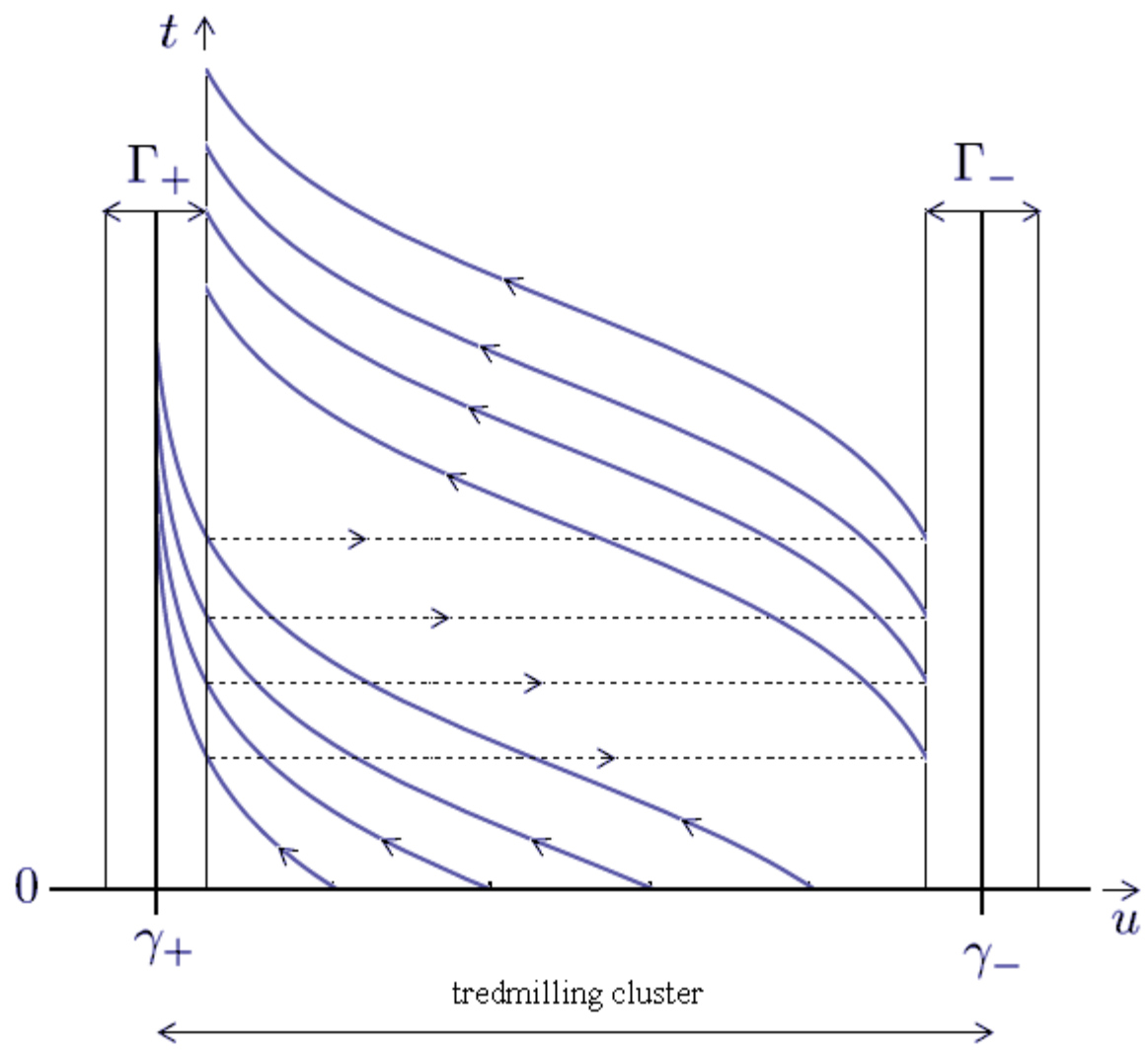


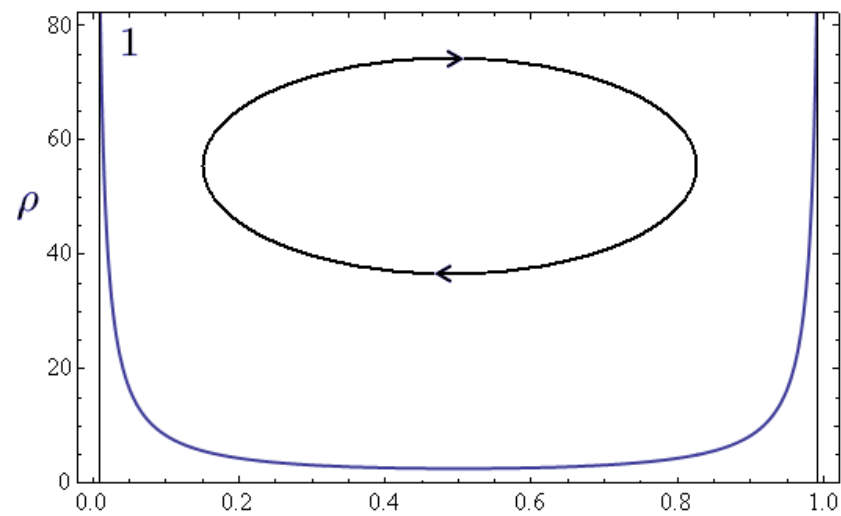
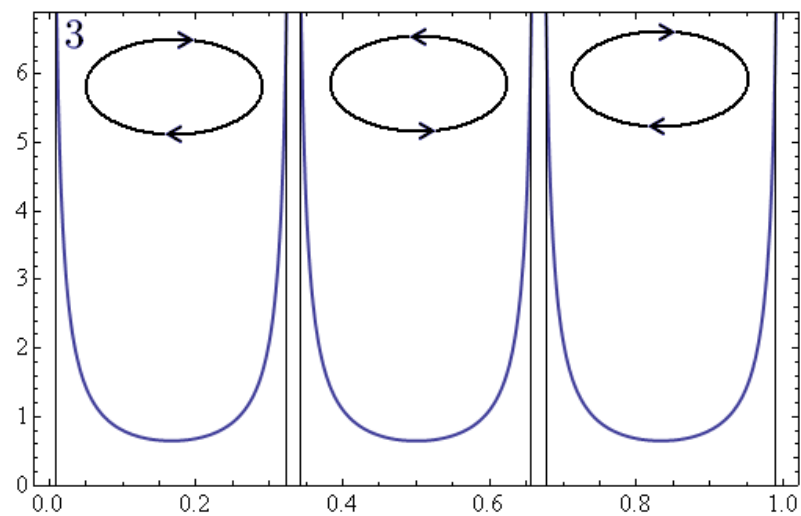
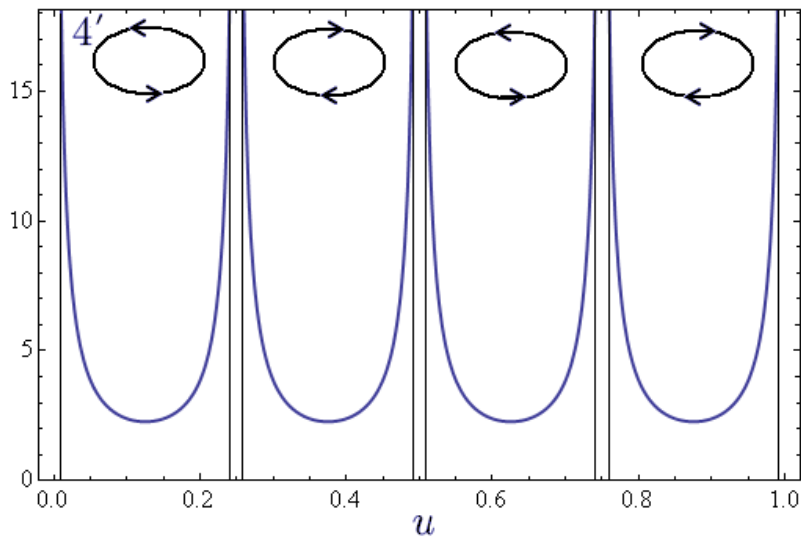
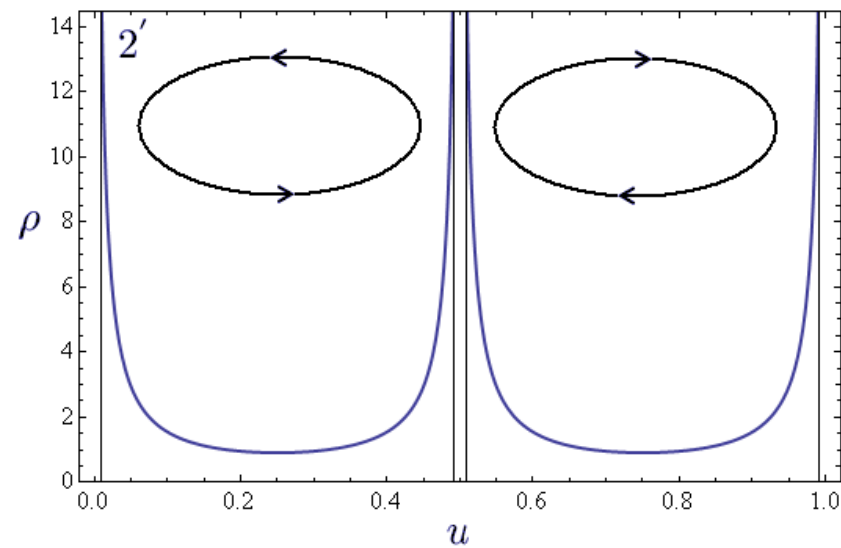


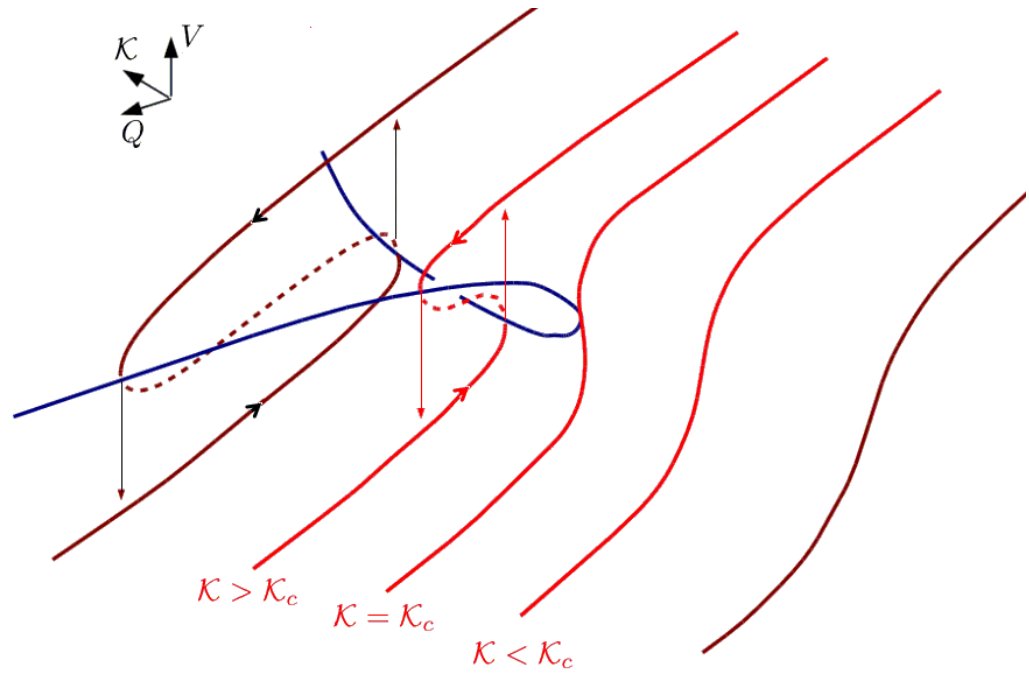
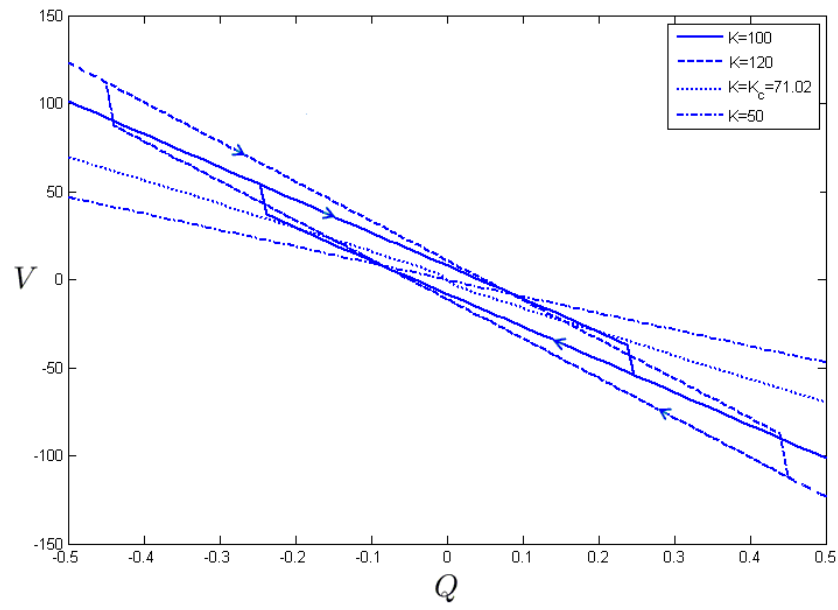








m=1**m=2****Motile****Non Motile**



Optimization of velocity

Homogeneous adhesion ($g_i \equiv 1$)

Existence of TW:

$$-2k \frac{L - L_0}{L_0} \sinh\left(\frac{L}{2}\right) = \int_{-1/2}^{1/2} \cosh(Lu) g(u) du$$

Suppose $L_0 \ll 1$, $4 < kL_0$

Optimization problem:

$$\begin{cases} \max_{g_2 \in L^1([-1/2, 1/2])} - \frac{1}{2 \sinh(L/2)} \int_{-1/2}^{1/2} \sinh(Lu) g(u) du \\ \int_{-1/2}^{1/2} g(u) du = 1 \\ -2k \frac{L-L_0}{L_0} \sinh(L/2) = \int_{-1/2}^{1/2} \cosh(Lu) g(u) du \end{cases}$$

Optimal configuration:

$$\boxed{\begin{cases} g(s) = \delta_{-1/2}(u) \\ V = \frac{1}{2} \end{cases}}$$

General case

Set,

$$\begin{cases} (\frac{1}{g_i} h')' = L^2 h \\ h(-1/2) = 1 \text{ and } h(1/2) = 1 \end{cases}, \begin{cases} (\frac{1}{g_i} f')' = L^2 f \\ f(-1/2) = -1 \text{ and } f(1/2) = 1 \end{cases}$$

Existence of TW:

$$\hat{g} = \frac{\int_{-1/2}^{1/2} g(u) h(u) du}{\int_{-1/2}^{1/2} h(u) du} = -kL \frac{L - L_0}{L_0}$$

Optimization problem:

$$\begin{cases} \max_{g, g_i \in L^1([-1/2, 1/2])} \frac{1}{2} \int_{-1/2}^{1/2} f(u) (g(u) - \hat{g}) du \\ \int_{-1/2}^{1/2} g(u) du = \int_{-1/2}^{1/2} g_i(u) du \\ \hat{g} = -kL \frac{L-L_0}{L_0} \end{cases}$$

Optimal configuration:

$$\boxed{\begin{cases} g(s) = \delta_{-1/2}(u) \\ g_i(s) = \delta_{-1/2}(u) \\ V = 1 \end{cases}}$$

Existing models for cell motility

- **Protrusion dominated**

- A Mogilner and L Edelstein-Keshet (2002) Regulation of actin dynamics in rapidly moving cells: A quantitative analysis. *Biophys. J.*
- J. Prost, J.-F Joanny, P. Lenz and C.Sykes (2008) The physics of listeria propulsion. *In Cell Motility, Biological and Medical Physics, Biomedical Engineering.*
- F. Jülicher, K.Kruse, J. Prost and J.-F. Joanny (2007) Active behavior of cytoskeleton. *Phys. Rep.*

- **Discrete models**

- P.A. DiMilla, K. Barbee and D.A. Lauenburger (1991) Mathematical-model for the effects of adhesion and mechanics on cell-migration speed. *Biophys. J.*
- D. Bottino, A. Mogilner, T. Roberts, M. Stewart and G. Oster (2002) How nematode sperm crawl. *J. Cell Science*

- **Turing**

- B.Vanderlei, J.J.Feng and L.Edelstein-Keshet (2010) A computational model of cell polarization and motility coupling mechanics and biochemistry. *Multiscale Model. Simul.*

- **Phase flow models**

- M.Herant and M.Dembo (2010) Form and function in cell motility: from fibroblasts to keratocytes. *Biophys.J.*

- **Active filaments**

- K.Dobrovinski and K.Kruse (2011) Cell motility resulting from spontaneous polymerisation waves. *Phys.Rev.Lett*
- Q.Wang, X.Yang, D.Adalsteinsson, T.C.Eleston, K.Jacobson, M.Kapustina and M.G.Forest (2012) Computational and modeling strategies for cell motility. *Comput.Model.Biol.Syst : From molecules to pathways*

- **Comprehensive models**

- D.Shao, W.-J. Rappel and H.Levine (2010) A computational model for cell morphodynamics. *Phys.Rev.Lett*
- B. Rubinstein, M.F. Fournier, K. Jacobson, A. B. Verkhovsky, and A. Mogilner (2009) Actin-Myosin Viscoelastic Flow in the Keratocyte Lamellipod. *Biophys J.*

Optimal crawling

Non-dimensionalize length by $\sqrt{\eta/\xi}$, time, by η/χ and stress by χ .

Combinig force balance and constitutive reallion

$$\left\{ \begin{array}{l} -\partial_x \left(\frac{1}{c_i} \partial_x \sigma \right) + \sigma = c \\ \sigma(l_-(t), t) = -k \frac{L(t) - L_0}{L_0} = \sigma(l_+(t), t) \\ \dot{l}_- = \frac{\partial_x \sigma}{c_i}(l_-(t), t) \text{ and } \dot{l}_+ = \frac{\partial_x \sigma}{c_i}(l_+(t), t). \end{array} \right.$$

Arbitrary c and c_i with constraints, $\int_{l_-(t)}^{l_+(t)} c(x, t) dx = 1$ and $\frac{\int_{l_-(t)}^{l_+(t)} c_i(x, t) dx}{L(t)} = 1$

E.M. Purcell. *Am. J. Phys*, 45(1), 1977.

F. Alouges, et al. *Eur. Phys. J. E*, 28(3), 2009.

Traveling wave assumption

Traveling Wave assumption: $\left\{ \begin{array}{l} \dot{l}_-(t) = \dot{l}_+(t) = V \\ L(t) = L \\ y = x - Vt \in [-L/2, L/2] \end{array} \right.$ with V, L unknowns

Shape definition, $g_i(u, \cancel{L}) = c_i(Lu)$ and $g(u, \cancel{L}) = Lc(Lu)$ with $u \in [-1/2, 1/2]$

$$\left\{ \begin{array}{l} -\partial_y \left(\frac{1}{c_i} \partial_y \sigma \right) + \sigma = c \\ \sigma(-L/2) = -k \frac{L-L_0}{L_0} = \sigma(L/2) \\ V = \frac{\partial_y \sigma}{c_i}(-L/2) = \frac{\partial_y \sigma}{c_i}(L/2). \end{array} \right. \Rightarrow \boxed{\left\{ \begin{array}{l} -\partial_u \left(\frac{1}{g_i} \partial_u \sigma \right) + L^2 \sigma = Lg \\ \sigma(-1/2) = -k \frac{L-L_0}{L_0} = \sigma(1/2) \\ LV = \frac{\partial_u \sigma}{g_i}(-1/2) = \frac{\partial_u \sigma}{g_i}(1/2) \\ \int_{-1/2}^{1/2} g = \int_{-1/2}^{1/2} g_i = 1 \end{array} \right.}$$

$$u = y/L$$

Optimization of velocity

Set,

$$\left\{ \begin{array}{l} (\frac{1}{g_i} h')' = L^2 h \\ h(-1/2) = 1 \text{ and } h(1/2) = 1 \end{array} \right. , \left\{ \begin{array}{l} (\frac{1}{g_i} f')' = L^2 f \\ f(-1/2) = -1 \text{ and } f(1/2) = 1 \end{array} \right.$$

Existence of TW:

$$\hat{g} = \frac{\int_{-1/2}^{1/2} g(u) h(u) du}{\int_{-1/2}^{1/2} h(u) du} = -kL \frac{L - L_0}{L_0} \implies \text{Suppose } L_0 \ll 1, 4 < kL_0$$

Optimization problem:

$$\left\{ \begin{array}{l} \max_{g, g_i \in L^1([-1/2, 1/2])} \frac{1}{2} \int_{-1/2}^{1/2} f(u) (g(u) - \hat{g}) du \\ \int_{-1/2}^{1/2} g(u) du = \int_{-1/2}^{1/2} g_i(u) du \\ \hat{g} = -kL \frac{L - L_0}{L_0} \end{array} \right.$$

Optimal configuration:

$$\boxed{\left\{ \begin{array}{l} g(s) = \delta_{-1/2}(u) \\ g_i(s) = \delta_{-1/2}(u) \\ V = 1 \end{array} \right.}$$

Optimization of efficiency ($g_i \equiv 1$)

$$\Lambda = \frac{LV^2}{-L^{-2} \int_0^1 g \partial_{uu} \sigma + \mu} \quad \text{with,} \quad \begin{cases} \sigma(u; g) = \frac{f_L \cosh(L(\frac{1}{2}-u))}{\cosh(\frac{L}{2})} + \int_0^1 \Psi(v, u) g(v) dv \\ V = \frac{1}{2 \sinh(L/2)} \int_0^1 \sinh(L(\frac{1}{2}-u)) g(u) du \\ 2f_L \sinh(\frac{L}{2}) = \int_0^1 \cosh(L(\frac{1}{2}-u)) g(u) du. \end{cases}$$

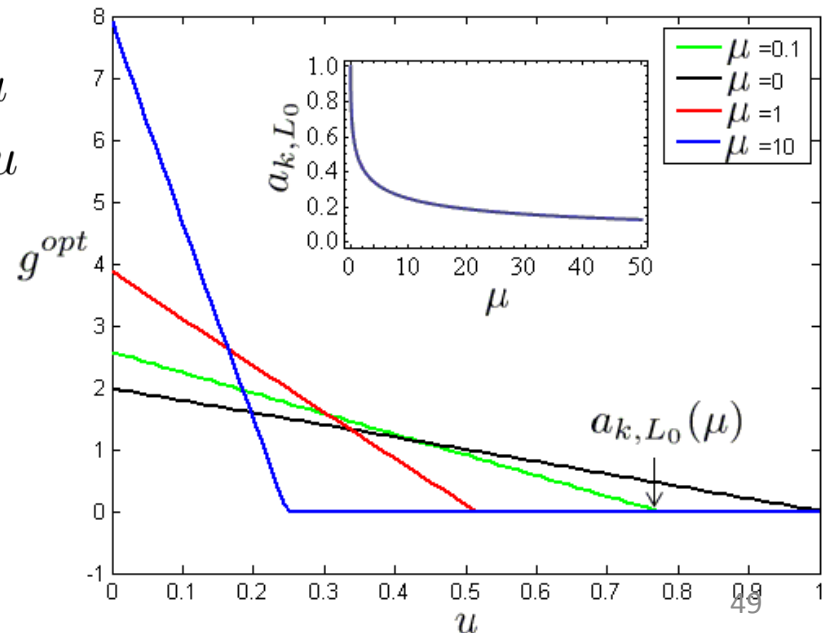
Numerator maximized by fully localized $g(u) = \delta_0(u)$.

Denominator minimized by homogeneous $g(u) = -kL \frac{L-L_0}{L_0}$.

$$\left\{ \begin{array}{l} \max_{g \in L^2([0,1]), L \in \mathbb{R}_+, V \in \mathbb{R}} \Lambda(g, L, V) \\ 2V \sinh(\frac{L}{2}) = \int_0^1 \sinh(L(\frac{1}{2}-u)) g(u) du \\ 2f_L \sinh(\frac{L}{2}) = \int_0^1 \cosh(L(\frac{1}{2}-u)) g(u) du \\ \int_0^1 g(u) du = 1 \\ g \geq 0. \end{array} \right.$$

Maintenance heat and diffusion of motors

$$a_{k, L_0}(\mu) \sim \sqrt{\frac{D\xi}{\chi}}$$



Efficiency (in a special framework)

- Force Balance:
$$\begin{cases} \partial_x \sigma = \xi a(x, t) v \\ \sigma(l_-(t), t) = q_- - k \frac{L(t) - L_0}{L_0} \\ \sigma(l_+(t), t) = q_+ - k \frac{L(t) - L_0}{L_0} \end{cases}$$

- Constitutive relation:
$$\sigma = \eta \partial_x v + \cancel{F(\rho)} + \chi c(x, t)$$

- Protrusion:
$$\begin{cases} \dot{l}_- = v_- + v(l_-(t), t) \\ \dot{l}_+ = v_+ + v(l_+(t), t) \\ l_-(0) = l_-^0 < l_+(0) = l_+^0 \end{cases}$$

- Actin:
$$\begin{cases} \partial_t \rho + \partial_x (\rho v) = 0 \\ \rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+ \text{ (treadmilling)} \\ \rho(x, 0) = \rho^0(x) \end{cases}$$

- Myosin:
$$\begin{cases} \partial_t c + \partial_x (c v) - D \partial_{xx} c = 0 \\ c(l_-(t), t) v_- + D \partial_x c(l_-(t), t) = 0 \\ c(l_+(t), t) v_+ + D \partial_x c(l_+(t), t) = 0 \\ c(x, 0) = c^0(x) \end{cases}$$

Unknowns: $l_-(t), l_+(t), \underbrace{\sigma(x, t)}_{\text{axial stress}}, \underbrace{v(x, t)}_{\text{velocity}}, \underbrace{\rho(x, t)}_{\text{actin density}}, \underbrace{c(x, t)}_{\text{myosin concentration}}$ and $\underbrace{a(x, t)}_{\text{integrin concentration}}$

Polarization and symmetrization

