Mathematics Institute

THE UNIVERSITY OF WARWICK

Centre for Scientific Computing

Application of Elastic Flows to Cell Motility

Björn Stinner

(joint work with C Venkataraman and C Elliott)

FBP - Theory and Applications 2012

Cell Migration

Important in: Embryonic development, wound healing, metastasis, immune responses.

movie

[Rodgers 1952], http://www.biochemweb.org/neutrophil.shtml

Ideas and Aims

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- Mechanics: Geometric evolution equations for the cell boundary,
  use methods from [Dziuk 2008], [Barrett, Garcke, Nürnberg 2008].
- Chemistry: Surface PDEs (reaction diffusion equations) on the cell boundary,
  use the method from [Dziuk, Elliott 2007].

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- Global force due to a constraint on enclosed volume (Lagrange multiplier).
- External forces, eg other cells, obstacles.

Geometric Evolution Equation:

$$\omega V = -k_s H + k_b\left(\Delta_\Gamma H + H|\nabla_\Gamma \boldsymbol{\nu}|^2 - \tfrac{1}{2}H^2\right) + k_p(\mathbf{a}) + \lambda \quad (+F_{ext}).$$

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- Phase field: [Du, Liu, Ryham, Wang 2005, 2009], [Wang, Du 2007, 2008], [Campelo, Hernández-Machdo 2006], [Lowengrub, Rätz, Voigt 2009], [Shao, Rappel, Levine 2010]

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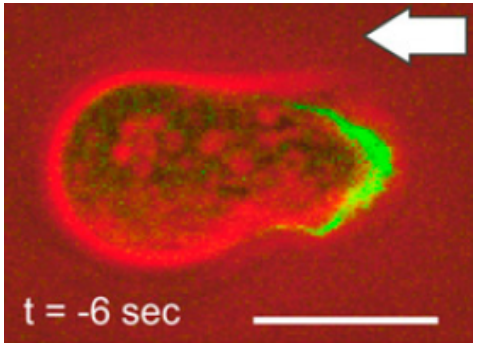
Fitting problems require highly efficient solvers $\rightsquigarrow$ parametric approach.

Issue: Robustness with respect to mesh distortions.
Remeshing method: [Clarenz, Dziuk].

Motivation: Surface PDEs

Reactions leading to polarisation take place (possibly not only) within the cortex close to the plasma membrane.



[Dalous et al 2008]

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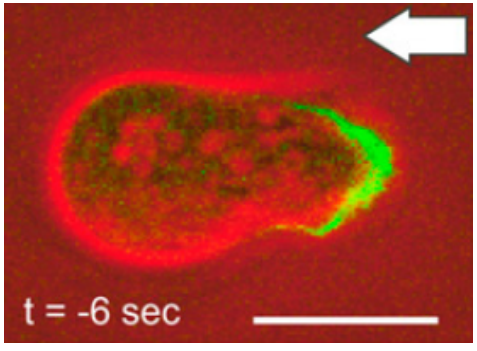

[Dalous et al 2008]

Postulate advected reaction-diffusion system on the plasma membrane.

Interpretation:

- Model for chemistry taking place on the plasma membrane itself,
- or quantities effectively account for mechanical impact due to chemical reactions within the cell.

Surface reaction-advection-diffusion equations:

$$\partial_t^\bullet \mathbf{a} + \left(\mathbf{a}\nabla_\Gamma \cdot \mathbf{v}\right) = D_\mathbf{a}\Delta_\Gamma \mathbf{a} + \mathbf{r}(\mathbf{a})$$

for the quantities $\mathbf{a} = (a_1, \ldots, a_N) : \Gamma \to \mathbb{R}^N$.

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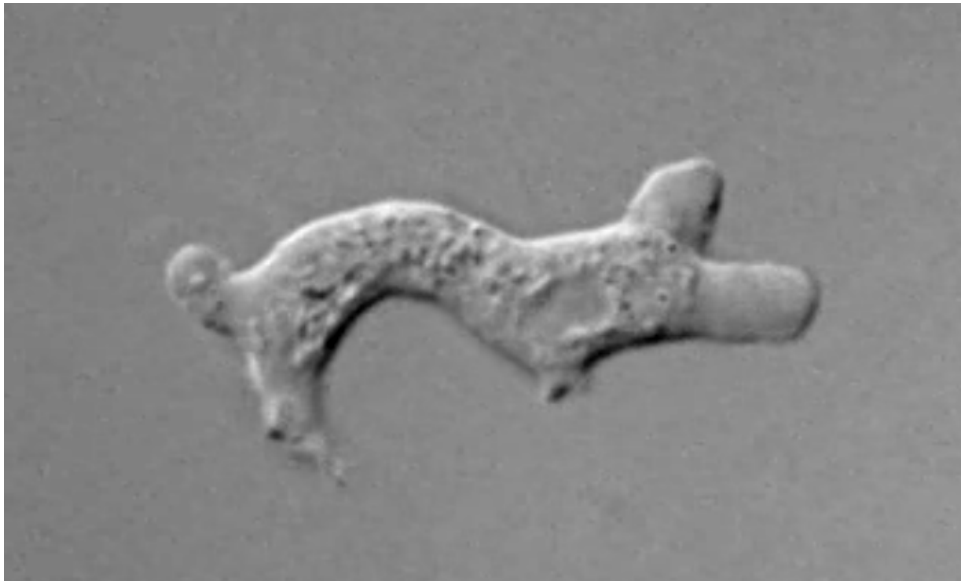
Other potential benefit: Computationally cheaper than bulk system.

Computational method: Extension of [Dziuk, Elliott 2007].

Ex 1: Moving Dictyostelium Cells Involving Pseudopod Formation



[King, Insall 2009]

Ex 1: Meinhardt-NMWI Model

Model for polarisation and cell boundary movement proposed by [Neilson, Mackenzie, Webb, Insall 2011] based on work by [Meinhardt 1999] for chemotaxis:

Cell boundary Γ is a curve moving with velocity $\mathbf{v} = V\boldsymbol{\nu}$,

$$\partial_t^\bullet a + a\nabla_\Gamma \cdot \mathbf{v} = D_a \Delta_\Gamma a + r_a\Big(s\frac{a^2/b + b_a}{(s_c + c)(1 + s_a a^2)} - a\Big),$$

$$\partial_t^\bullet b + b\nabla_\Gamma \cdot \mathbf{v} = D_b \Delta_\Gamma b + r_b\Big(\fint_\Gamma a - b\Big),$$

$$\partial_t^\bullet c + c\nabla_\Gamma \cdot \mathbf{v} = D_c \Delta_\Gamma c + b_c a - r_c c,$$

$$s = \eta_m^t + R_m^t \qquad \text{(signal, discretised)},$$

$$dR_m^t = \theta_m(L_m)\big(\mu_m(L_m) - R_m^t\big)dt + \sigma_m(L_m)dW_m^t \qquad (\eta_m^t \text{ similarly}),$$

$$V = K_{prot}\, a - \lambda\kappa \qquad \text{(enclosed area preserved)}.$$

Ex 1: Amended Model

MASDOC Research Study Group,
Problem formulations: [Brett, Eyers, McCormick, Scott],
Project implementation: [Amarasinghe, Aylwin, Madhavan, Pettitt].

Mathematics and Statistics Centre for Doctoral Training

Ideas:

- reduce system, remove equation for global inhibitor,
- account for membrane mechanics,
- hard constraint on enclosed area with Lagrange multiplier.

$$\partial_t^\bullet a + a\nabla_\Gamma \cdot \mathbf{v} = D_a \Delta_\Gamma a + r_a\left(s\frac{a^2/b + b_a}{(s_c + c)(1 + s_a a^2)} - a\right),$$

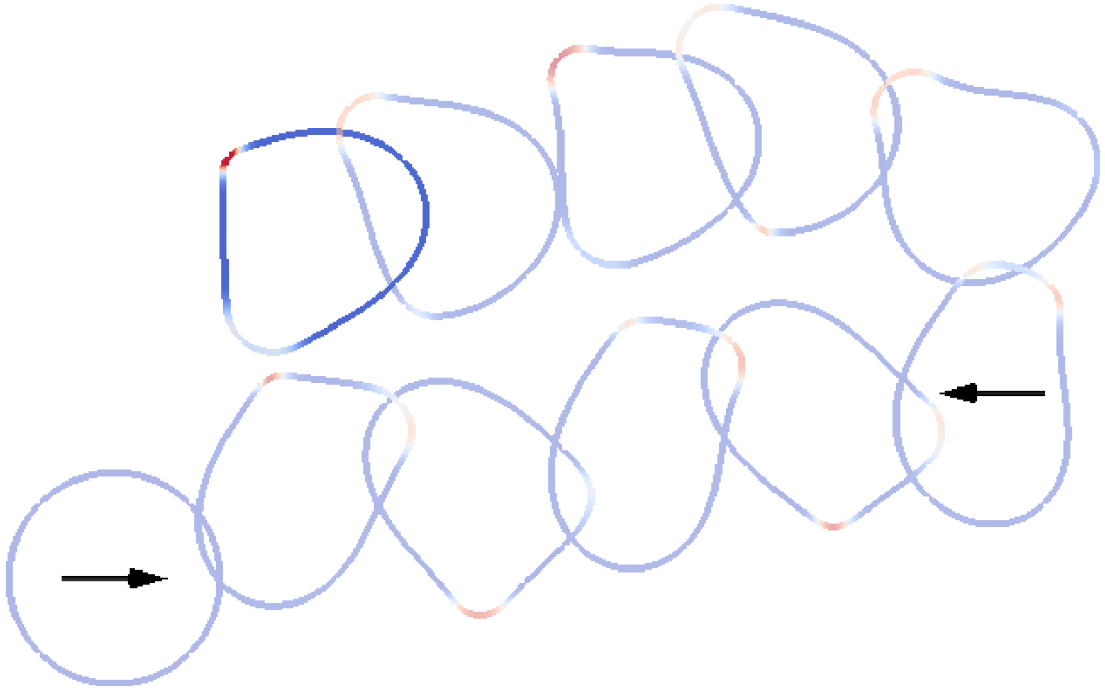
$$b = \fint_\Gamma a,$$

$$\partial_t^\bullet c + c\nabla_\Gamma \cdot \mathbf{v} = D_c \Delta_\Gamma c + b_c a - r_c c,$$

$$V = k_b \Delta_\Gamma H + k_b |\nabla_\Gamma \boldsymbol{\nu}|^2 (H - H_s) - \tfrac{1}{2} k_b (H - H_s)^2 H - k_s H + K_{prot}\, a - \lambda.$$

Ex 1: Effectivity

Simulated cell, response to the change of the direction to the chemotactic signal.



Parameters: Mostly from [Neilson, Mackenzie, Insall, Webb 2011] but rescaled.

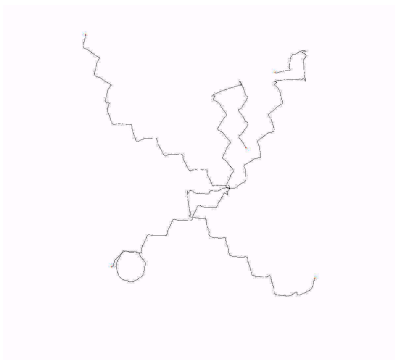
$D_1 = D_a$	$D_3 = D_c$	k_s	k_b
1.0	7.0	25.0	3.0
$2.22 \times 10^{-3}\,\mu m/s$	$1.55 \times 10^{-2}\,\mu m/s$	$1.0\,pN$	$1.92\,pN\,\mu m^2$

Ex 1: Signal Strength

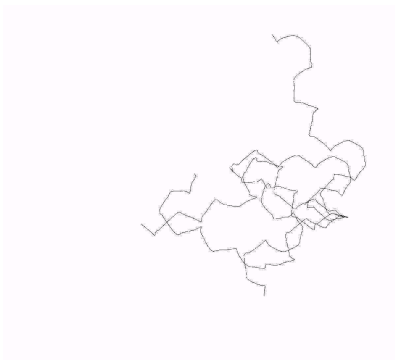
Choice of the 'signal':

$$dR_m^t = \theta_m(\mu_m - R_m^t)\,dt + \sigma_m dW_m^t.$$

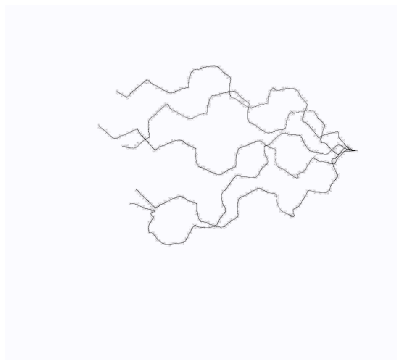
1. Given a direction $\mathbf{d}_r \in \mathbb{R}^n$ towards the source of the chemoattractant, $\mu = 0.5 + \rho$ closest to the source, $\mu = 0.5$ furthest away, linear interpolation.
2. Given the origin $\mathbf{x}_c$ of the chemoattractant, $\mu = exp(-c|\mathbf{x} - \mathbf{x}_c|)$, $\mathbf{x} \in \Gamma$, with a given parameter $c > 0$.



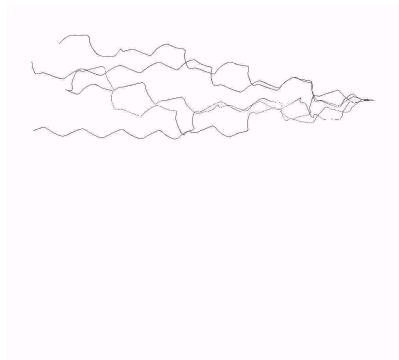
$\rho = 0.0$



$\rho = 0.2$



$\rho = 0.4$



$\rho = 1.0$

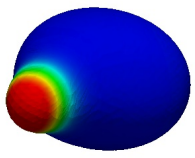
Ex 1: Statistics

ρ	CI	PL(x)	PL(y)	Speed ($\mu m/s$)
0	N/A	0.4336 (0.2346)	0.4601 (0.2442)	0.0445
0.02	0.7196 (0.2877)	0.4938 (0.2188)	0.3418 (0.1999)	0.0440
0.04	0.9423 (0.0742)	0.6968 (0.1177)	0.2005 (0.1163)	0.0446
0.06	0.9888 (0.0133)	0.8510 (0.0511)	0.1088 (0.0685)	0.0470
0.08	0.9860 (0.0120)	0.8490 (0.0350)	0.1288 (0.0676)	0.0478
0.1	0.9898 (0.0141)	0.8489 (0.0272)	0.0987 (0.0734)	0.0476

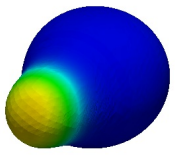
Mean value (standard deviation) of chemotaxis measures at $t = 0.5$ for 100 migrating cells,
CI (chemotactic index): Cosine of angle between the direction of the chemotactic gradient and the direction of cell movement, [Hecht, Skoge, Charest et al. 2011],
PL (persistence length): Displacement in x or y direction divided by trajectory length, [Cheng, Heilman, Wasserman et al. 2007].

Results are quantitatively comparable to those in [Ramsey 1972] for migrating leukocytes and in [Hecht, Skoge, Charest et al. 2011] on Dictyostelium cells.

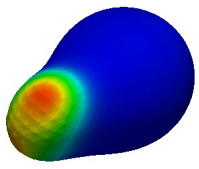
Ex 1: Extension to 3D



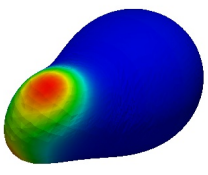
$t = 0.055$



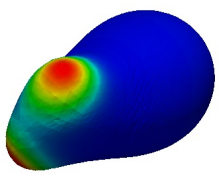
$t = 0.075$



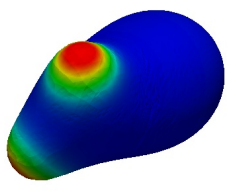
$t = 0.085$



$t = 0.09$



$t = 0.095$



$t = 0.1$

Ex 2: Persistent Motion of Keratocytes

Steady state motility, nearly constant shape.

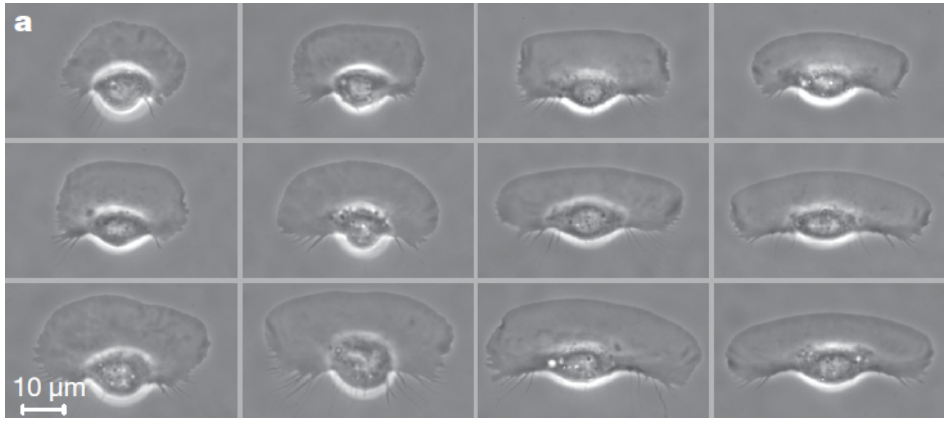


Figure 1a from [Keren, Pincus, Allen et al. 2008]

Ex 2: SRL Model

Proposed by [Shao, Rappel, Levine 2010]:

Phase field model for cell domain (force balance on plasma membrane):

$$\tau\partial_t\phi = -k_b\big(\Delta - \tfrac{1}{\varepsilon^2}G''(\phi)\big)\big(\Delta\phi - \tfrac{1}{\varepsilon^2}G'(\phi)\big) + k_s\big(\Delta\phi - \tfrac{1}{\varepsilon^2}G'(\phi)\big) - M_A\Big(\int\phi - A_0\Big)|\nabla\phi| + \big(\alpha V - \beta W\big)|\nabla\phi|.$$

Turing type system within cell,

$$\partial_t(\phi V) = D_V\nabla\cdot(\phi\nabla V) + \phi(a - bVW^2 - cV),$$
$$\partial_t(\phi W) = D_W\nabla\cdot(\phi\nabla W) + \phi(bVW^2 - eW).$$

V: actin filaments (protrusion), W: actin bundles with myosin (retraction).

Ex 2: Surface Model

Observation: Coupling term to the concentrations only lives on cell membrane.

Idea: Activator-depleted substrate model [Lefever, Prigogine 1968]:

$$\partial_t^\bullet a_1 + a_1 \nabla_\Gamma \cdot \mathbf{v} = D_1 \Delta a_1 + \gamma(k_1 - a_1 + a_1^2 a_2),$$
$$\partial_t^\bullet a_2 + a_2 \nabla_\Gamma \cdot \mathbf{v} = D_2 \Delta a_2 + \gamma(k_2 - a_1^2 a_2).$$

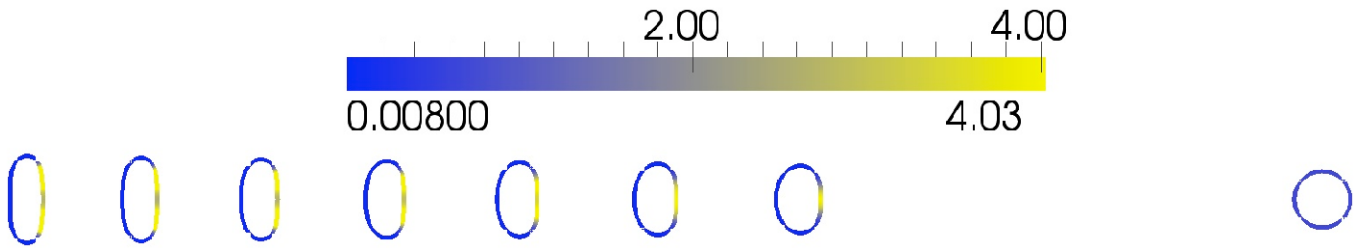
Coupling term:

$$F_p = k_1 a_1 + k_2 a_2$$

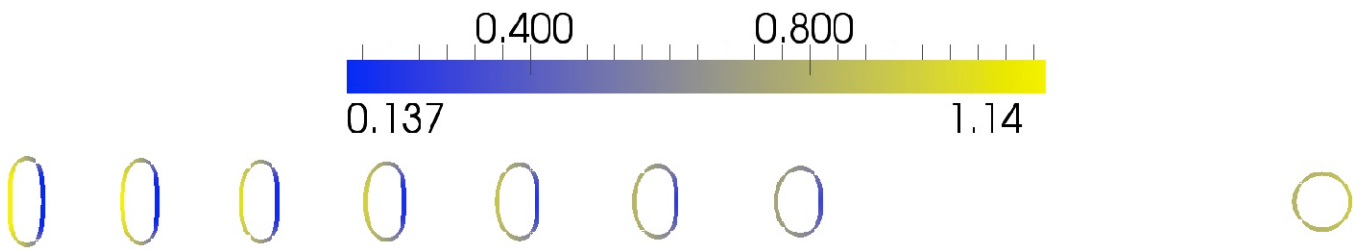
with $k_1 < 0$ (retraction) and $k_2 > 0$ (protrusion).

Ex 2: Effectivity

Initial position (right) and position at $t = 5$ for $k_2 = 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8$



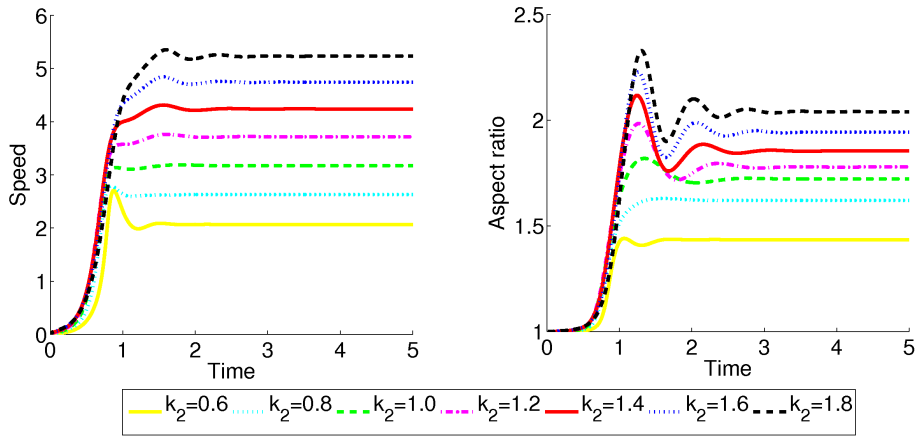
a_1 concentrations

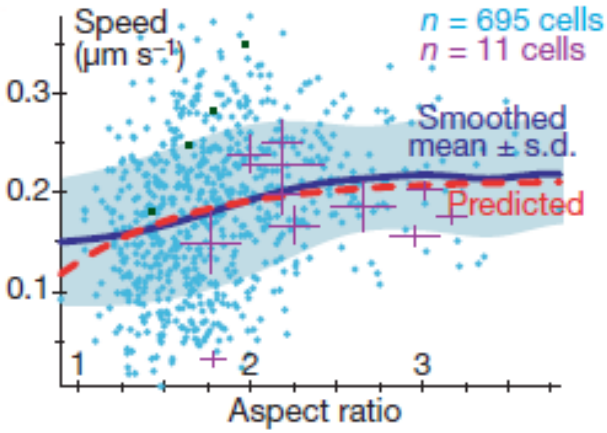


a_2 concentrations

D_1	D_2	k_s	k_b	k_2
0.5	50.0	2.0	2.0	0.6-1.8
$4.44 \times 10^{-2}\ \mu m/s$	$4.44\ \mu m/s$	$1.0\ pN$	$16.0\ pN\ \mu m^2$	$1.33–4.0 \times 10^{-2}\ s^{-1}$

Ex 2: Statistics





Data: [Keren, Pincus, Allen et al. 2008]

Conclusion

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This is motivated by

- availability of numerical methods to deal with such equations,
- efficiency thanks to the reduced dimension.

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We presented a general model for cell motility based on a geometric evolution equation for and a reaction-diffusion system on the moving cell boundary.

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Evidence for the effectivity of this approach has been provided by reproducing some results on

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- persistently crawling keratocytes, [Keren, Pincus, Allen et al. 2008], [Shao, Rappel, Levine 2010].

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Reference: [Elliott, S., Venkataraman, Royal Society Interface 2012]

Thanks for your attention!