Dynamics of Protrusive Oscillations in the Membranes of Fish Keratocyte Cells

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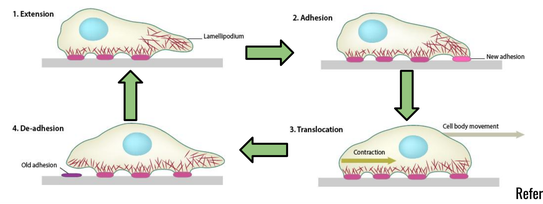
Introduction

Physiological Relevance of Adhesion-Driven Cellular Motility:

1. Wound Healing[2]
2. Neuronal/Embryonic Development[3]
3. Extravasation of tumor cells[4] (Metastasis)

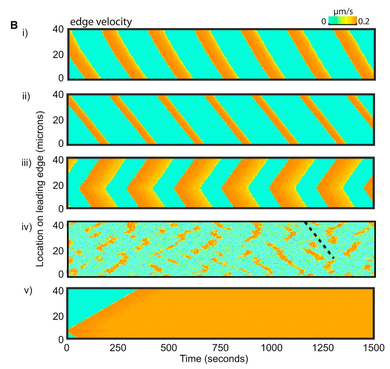


Reference 1

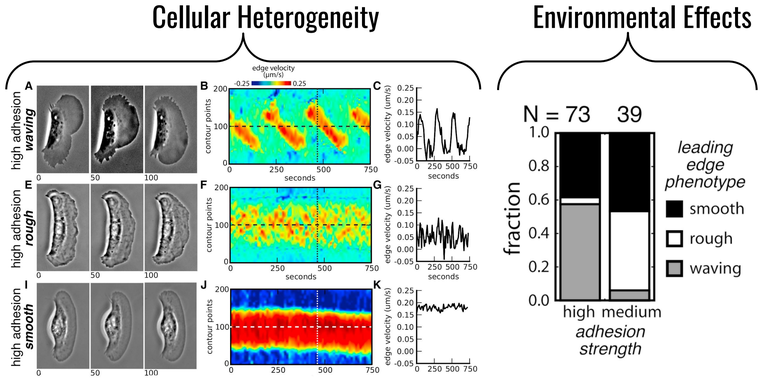
Adhesion-Dependent Wave Generation in Crawling Cells

Erin L. Barnhart, Jun Allard, Sunny S. Lou, Julie A. Theriot, Alex Mogilner.
Current Biology, Volume 27, Issue 1, 9 January 2017, Pages 27-38.

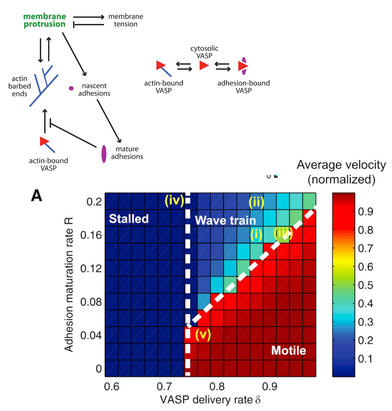
Numerical Simulations:



Experimental Work:



Mathematical Model:



Objective

To characterize the dynamics underlying the mathematical model, and use these characterizations to explain the rough motility phenotype.

Methods

Spatio-Temporal PDE Model

$$\text{Barbed Actin}: \quad \epsilon \frac{\partial}{\partial t} B(x,t) = (1+\eta_B V) - \frac{B}{\Gamma} + \epsilon^2 \overbrace{\partial_x \left(\frac{1}{\Gamma} \partial_x B \right)}^{\text{Lateral Transport}} + \Xi_t$$

$$\text{VASP}: \quad \frac{\partial}{\partial t} A(x,t) = d - A \frac{1+\eta_A V + \eta_M MV}{1+M+KB}$$

$$\text{Mature Adhesions}: \quad \frac{\partial}{\partial t} M(x,t) = RB - \Theta M - \eta_M MV$$

$$\text{Protrusion Velocity}: \quad V(B) = \begin{cases} 1-(B_c/B)^8 & B > B_c \\ 0 & \text{otherwise} \end{cases}$$

$$\text{Protrusion Threshold}: \quad B_c = \begin{cases} B_c^0 & \int V = 0 \\ B_c^0 (1+0.1) & \text{otherwise} \end{cases}$$

Spatially-Homogenized ODE Model

$$\epsilon \frac{d}{dt} B = (1+\eta_B V) - \frac{B}{\Gamma}$$

$$\frac{d}{dt} A = d - A \frac{(1+\eta_A V + \eta_M MV)}{1+M+KB}$$

$$\frac{d}{dt} M = RB - (\theta + \eta_M V) M$$

$$V(B) = \begin{cases} \exp\left(\frac{0.0001}{B-B_c}\right)\left[1-(B_c/B)^8\right] & B > B_c \\ 0 & \text{otherwise} \end{cases}$$

$$B_c(B) = B_c^0 \left(1 + 0.1 \left(1 - \exp\left(\frac{B-B_0}{0.0001}\right)\right)\right)$$

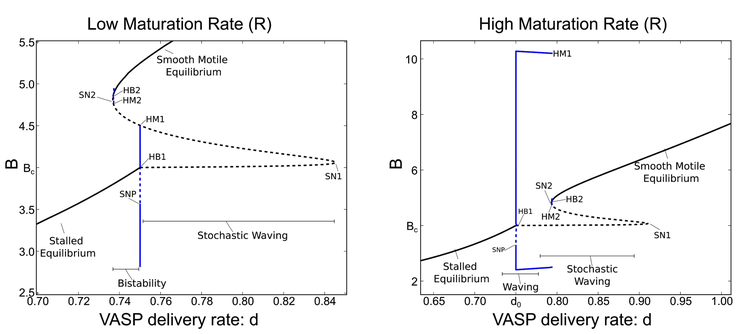
Analysis Methodologies:

- Bifurcation Analysis / Numerical Continuation
- Slow-Fast Analysis
- PDE Simulations

Results

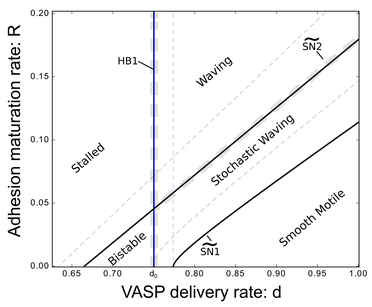
1. Bifurcation Analysis

One Parameter Bifurcations



- Stalled, Waving, and Smooth Motile phenotypes all have a corresponding parameter regime in the ODE model.
- We have identified two novel regimes: Bistable and Stochastic Waving.

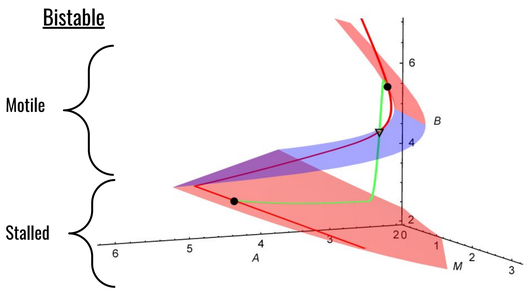
Two Parameter Bifurcation



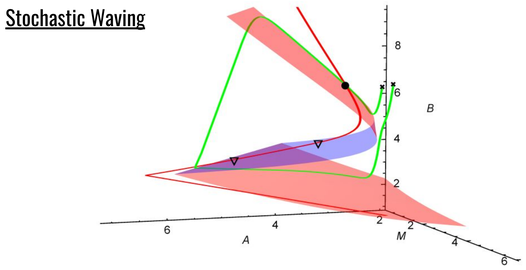
- Two Parameter bifurcation shows that the ODE model is highly predictive of the PDE model's behaviour:
  - Compare thick grey dashed line with the map of PDE regimes in Introduction.

2. Slow-Fast Analysis

Bistable

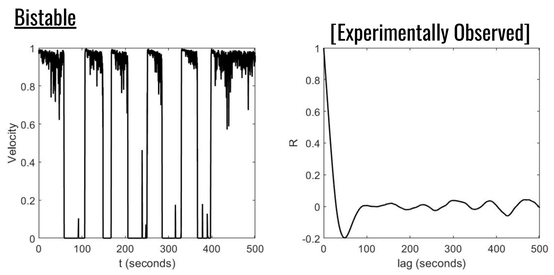


Stochastic Waving

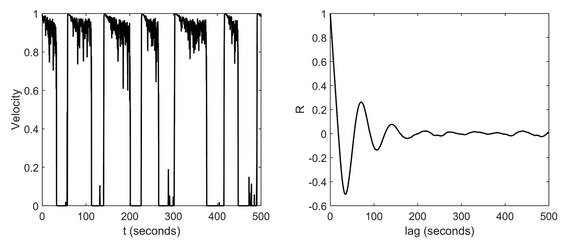


3. Noise-Driven Dynamics & Autocorrelation

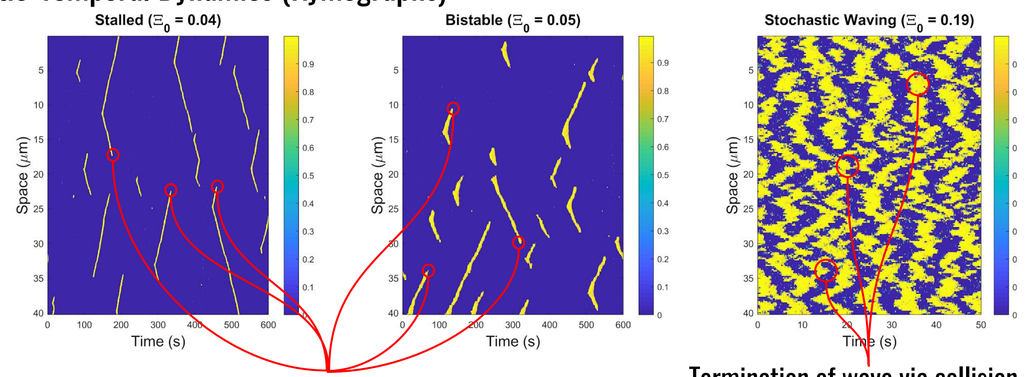
Bistable



Stochastic Waving (or Stalled)



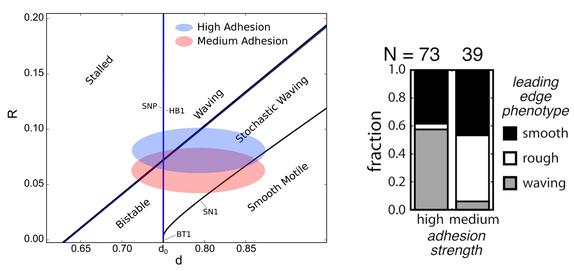
4. Spatio-Temporal Dynamics (Kymographs)



Termination of wave via collision with refractory zone. [Experimentally Observed]

Termination of wave via collision with protruding zones.

5. Population Statistics



- Changes in phenotype distribution are consistent the shape of the Bistable regime in the two-parameter bifurcation.

Conclusions

The, newly-identified, Bistable regime is the most compatible with the rough motility phenotype, based on its:

1. Autocorrelation Structure
2. Spatio-Temporal Dynamics
3. Population Statistics

References & Acknowledgements

[1] https://www.mechanobio.info/cytoskeleton-dynamics/what-are-lamellipodia-and-lamella/what-mechanisms-drive-extension-pause-and-stasis-of-the-lamellipodia/
[2] Chen MB, Lamar JM, Li R, Hynes RO, Kamm RD. Elucidation of the Roles of Tumor Integrin β1 in the Extravasation Stage of the Metastasis Cascade. *Cancer Res.* 2016;76(9):
[3] Jonkman JE, Cathcart JA, Xu F, et al. An introduction to the wound healing assay using live-cell microscopy. *Cell Adh Migr.* :8(5):440–451. doi:10.4161/cam.36224
[4] Rinon A, et al. p53 coordinates cranial neural crest cell growth and epithelial-mesenchymal transition/delamination processes. Development. 2011 May;138(9):1827-38.
[5] Barnhart, et. al.. Adhesion-Dependent Wave Generation in Crawling Cells. *Curr Biol.* 2017:27(1):27–38. doi:10.1016/j.cub.2016.11.011

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