Surfing on protein waves: modeling the bacterial genome partitioning

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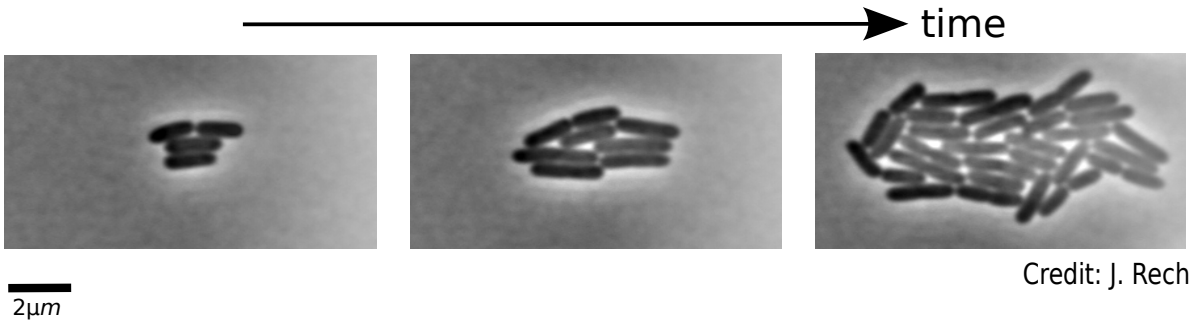
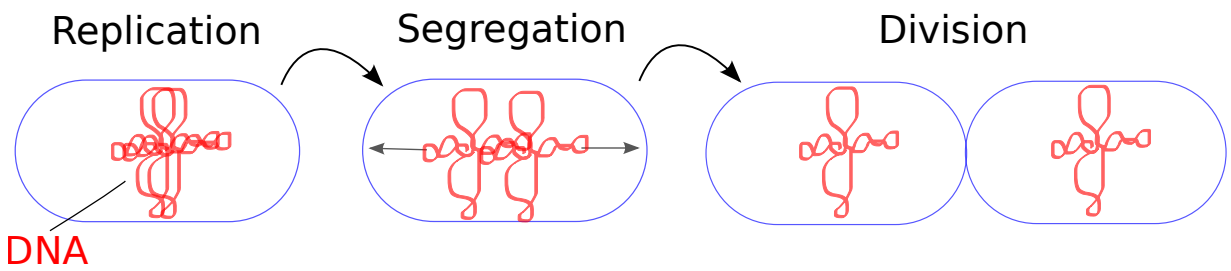
Modeling phase separation in health and disease: from nano- to meso-scale
Toulouse, France
Sept. 30 - Oct. 2 2019

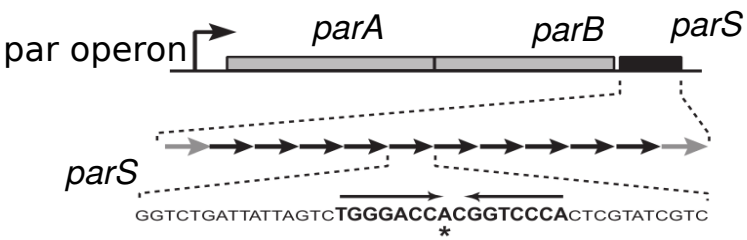
Segregation of bacterial DNA

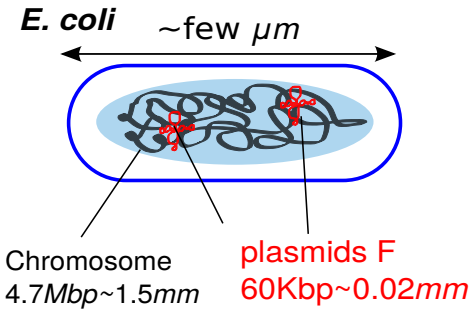




How is the bacterial genome segregated ?

The ParAB*S* operon

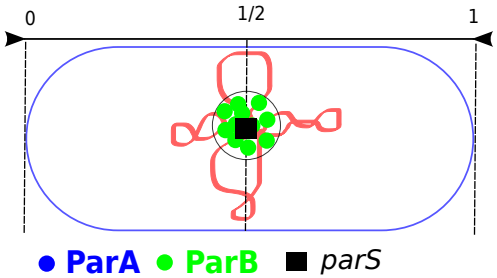




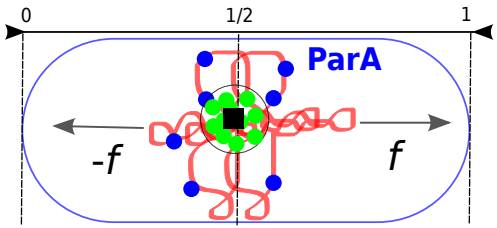
- ParA: "motor" protein (ATPase, Walker-type)
- ParB: binding protein (specific or non-specific binding)
- *parS*: centromere-like DNA sequence

The ParAB*S* segregation system: molecular actors

Step 1. Formation of the partition complex

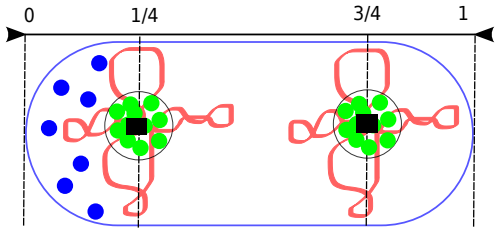


Step 2. Separation of the copies of DNA



opposite forces

Step 3. Positioning



stationary position

ParBS: Liquid-Liquid phase separation

David, JCW, ..., Palmeri (2019) submitted

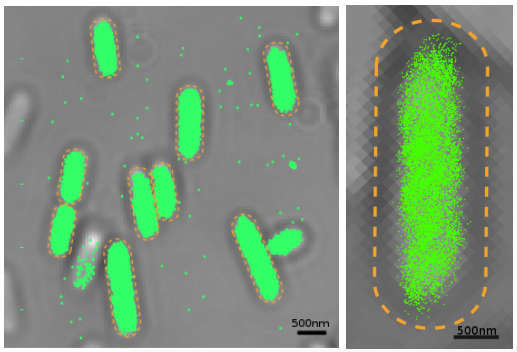
Guilhas, JCW, ..., Nollmann (2019) submitted

3 components: 2 proteins (ParA & ParB) + specific binding sites (*parS*)

How to describe formation, segregation and positioning of macromolecular assembly in a fluid phase ?

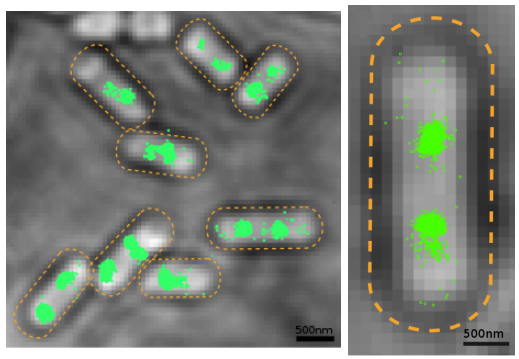
Liquid-Liquid Phase Separation

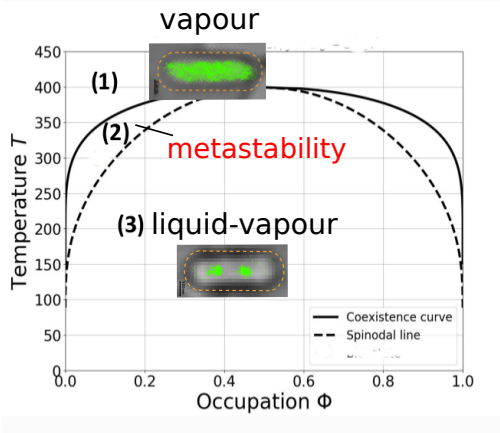
Super-Resolution microscopy (PALM)
D. Cattoni, B. Guilhas, A. Le Gall, M. Nollmann (CBS, Montpellier)

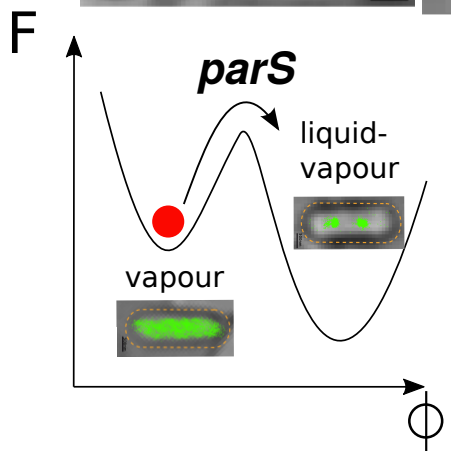


specific binding

ParB/*parS*





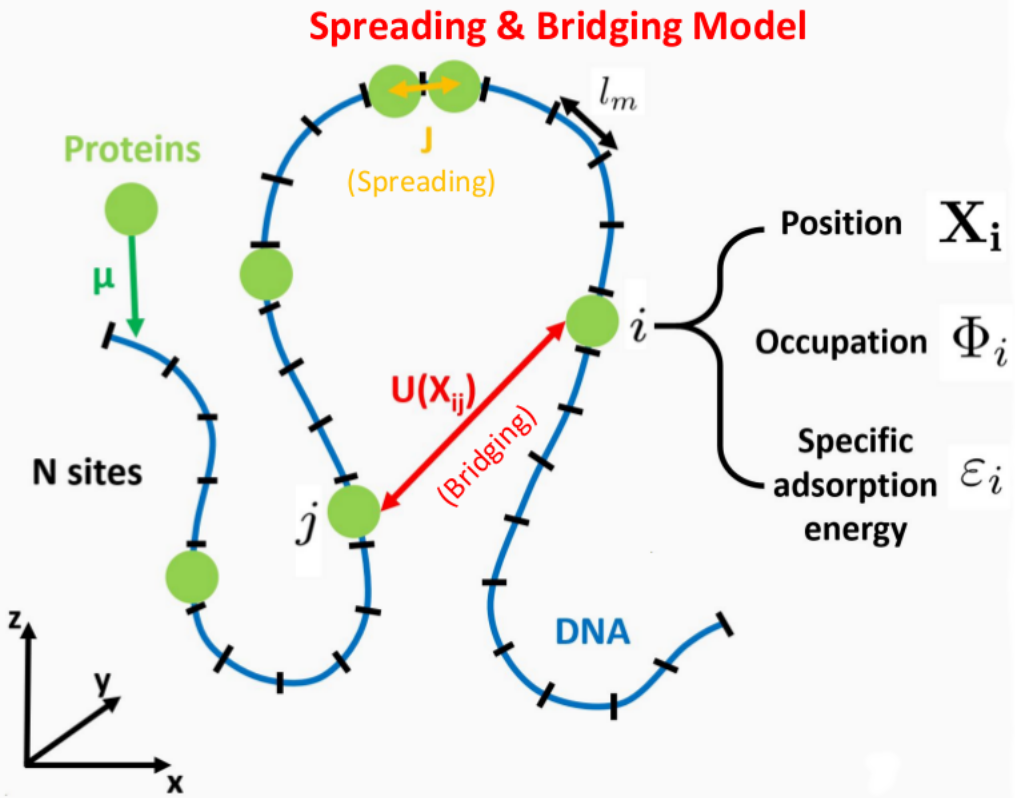


The Spreading and Bridging Model (S&B)

Broedersz et al., PNAS 2014

3D DNA-polymer spatial distribution

1D protein occupation distribution



The Spreading and Bridging Model (S&B)

Short Range Lattice Gas (Spreading)

$$H_{\mathrm{SRLG}}[\Phi_i] = -J \sum_{i=1}^{N-1} \Phi_{i+1}\Phi_i - \sum_{i=1}^{N} (\mu - \varepsilon_i)\,\Phi_i$$

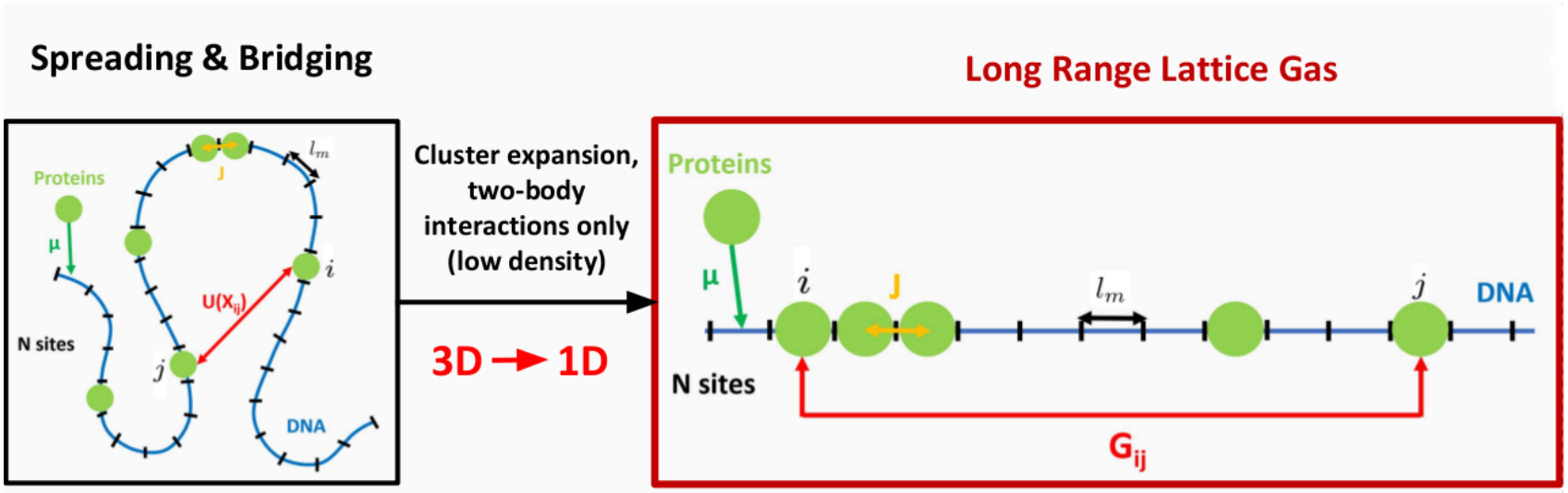
$$H[\Phi_i, \mathbf{X}_i] = H_{\mathrm{P}}[\mathbf{X}_i] + H_{\mathrm{SRLG}}[\Phi_i] + H_{\mathrm{B}}[\Phi_i, \mathbf{X}_i]$$

3D Polymer

Coupling between polymer and lattice gas (Bridging)

$$H_{\mathrm{B}}[\Phi_i, \mathbf{X}_i] = \frac{1}{2} \sum_{i,j}{}' \Phi_i U(X_{ij}) \Phi_j$$

Mapping the S&B onto a Long Range Lattice Gas



$$G_{ij} = 4\pi\beta^{-1}\int_0^{+\infty} dRR^2\left[e^{-\beta U(R)} - 1\right]P_{ij}(R) \quad \rightarrow \quad H_{LRLG} = H_{SRLG} - \frac{1}{2}\sum_{i,j}^{N}\phi_i G_{ij}\phi_j$$

Existence of a phase transition

Asymptotic behavior

$$G_{ij} \underset{|i-j|\to+\infty}{\longrightarrow} K_{\mathrm{SW}}|i-j|^{-\alpha}$$

$$\alpha = (3+g)\nu$$

Enhancement exponent of the polymer partition function

$$\mathcal{Z}_P \sim \bar{\mu}^N N^{\nu g}$$

Polymer size exponent

$$R_{ij} \sim |i-j|^{\nu}$$

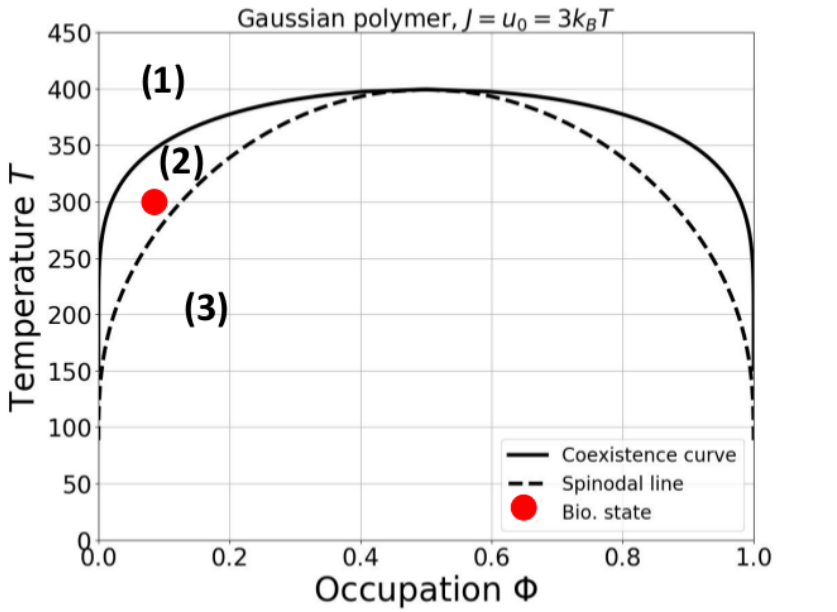
Phase transition only if $1 < \alpha < 2$

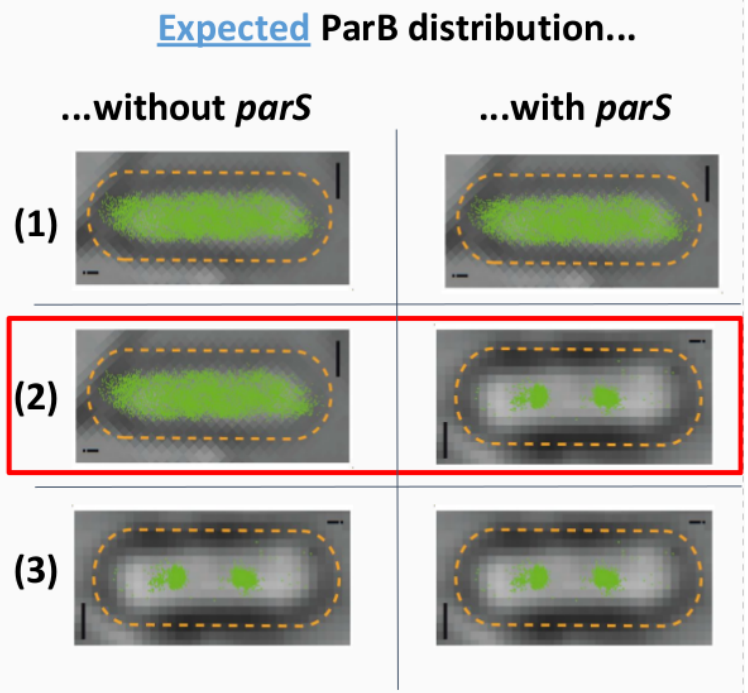
Freeman J. Dyson, 1969

Gaussian Polymer:
$\alpha_{GP} = 1.5$

Self-Avoiding Polymer:
$\alpha_{SAP} \approx 1.92$

ParBS complexes are in the metastable region





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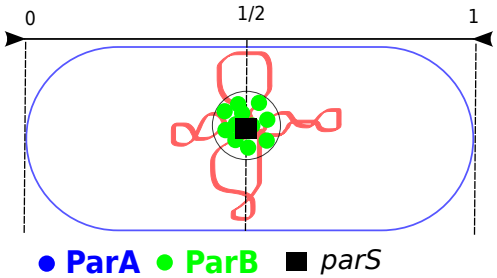

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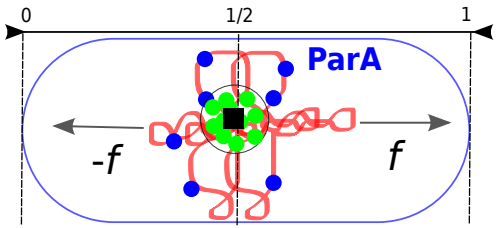

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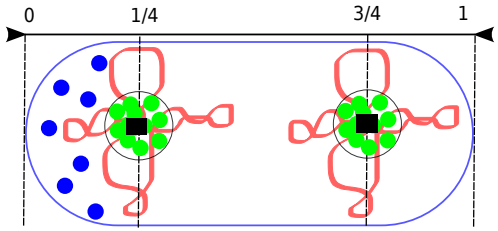

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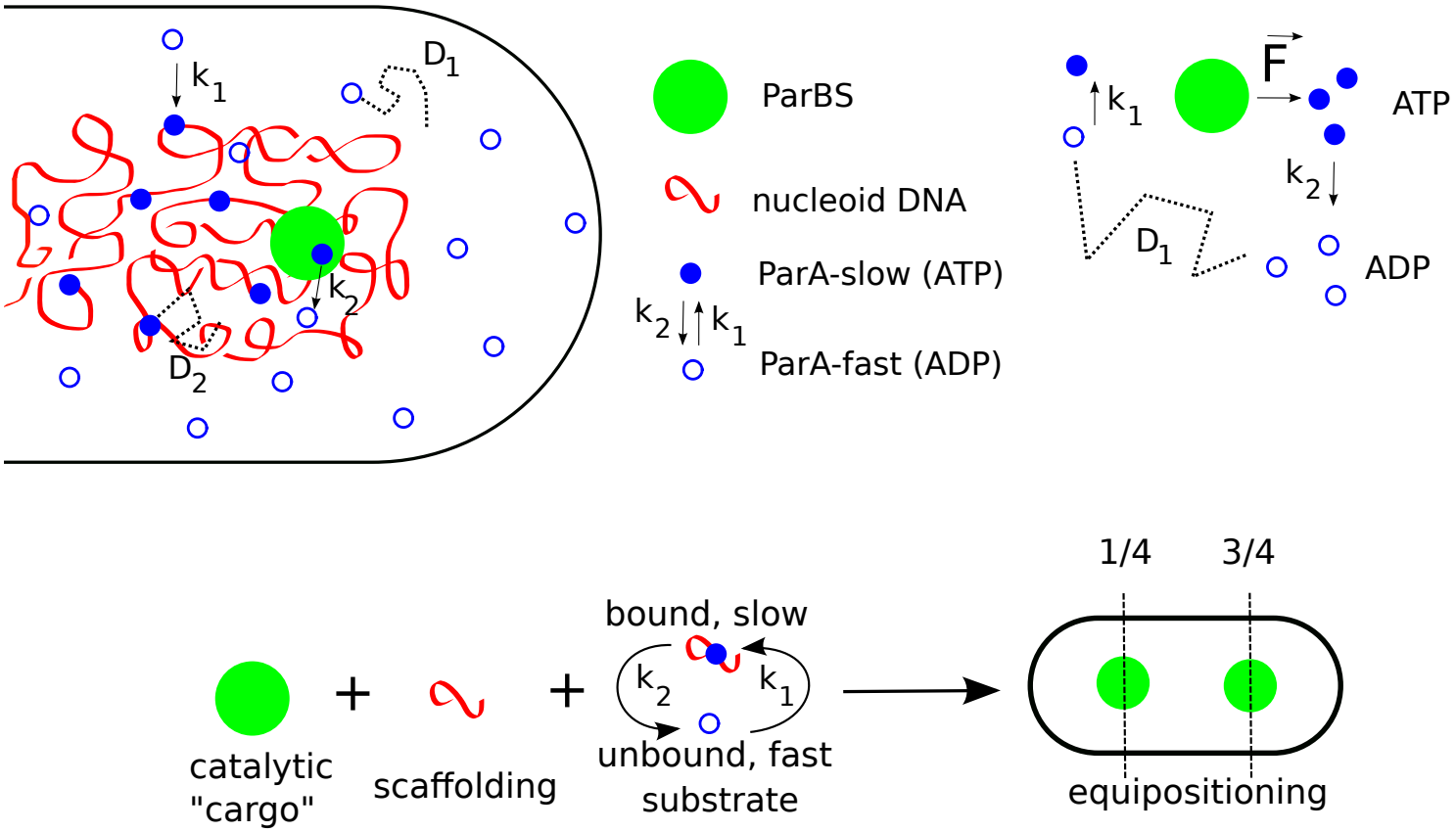
How to describe both segregation and positioning of macromolecular assembly in a fluid phase ?

Molecular interactions and diffusion



Reaction-Diffusion equations (ParA) coupled to Brownian motion (ParB*S*)

ParA-slow (ATP): $$\frac{\partial v}{\partial t} = D_2\,\Delta v + k_1\,u(\mathbf{r},t) - k_2\,v(\mathbf{r},t)\sum_i S(\mathbf{r}-\mathbf{r}_i(t))$$

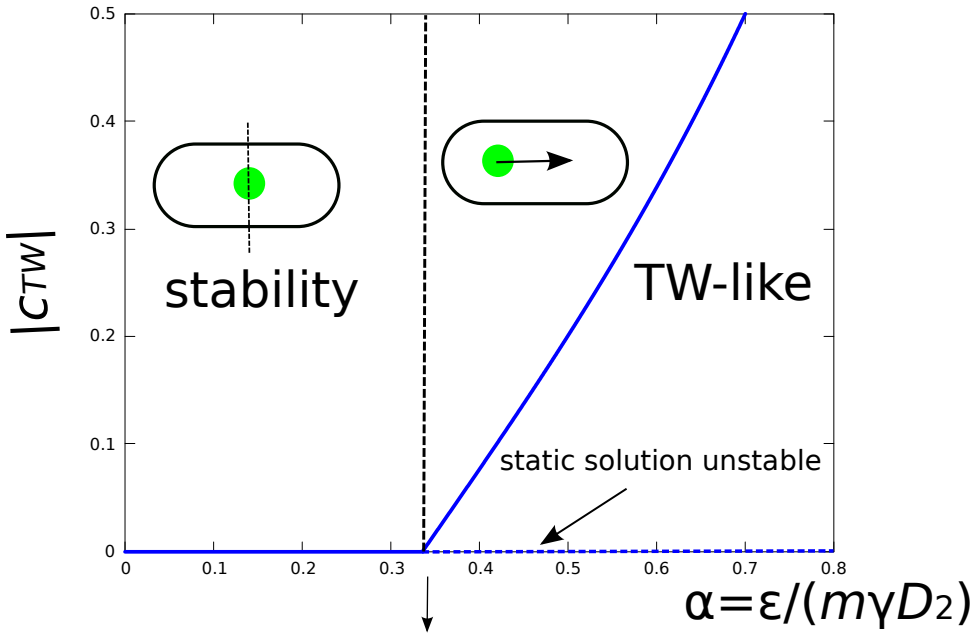
ParA-fast (ADP): $$\frac{\partial u}{\partial t} = D_1\,\Delta u - k_1\,u(\mathbf{r},t) + k_2\,v(\mathbf{r},t)\sum_i S(\mathbf{r}-\mathbf{r}_i(t))$$

ParB*S*: $$m\gamma\frac{d\mathbf{r}_i}{dt}(t) = \varepsilon\int_V \nabla v(\mathbf{r}',t)\,S(\mathbf{r}'-\mathbf{r}_i(t))\,d^3\mathbf{r}'$$

- Feedback between the partition complexes and ParA densities
  $\rightarrow$ Non-linear system with dynamical instability

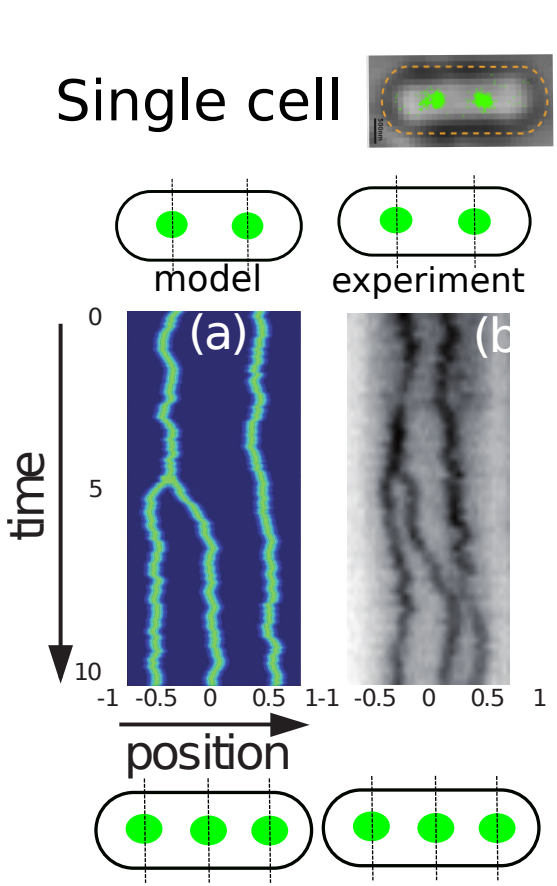
Dynamical instability: supercritical pitchfork bifurcation

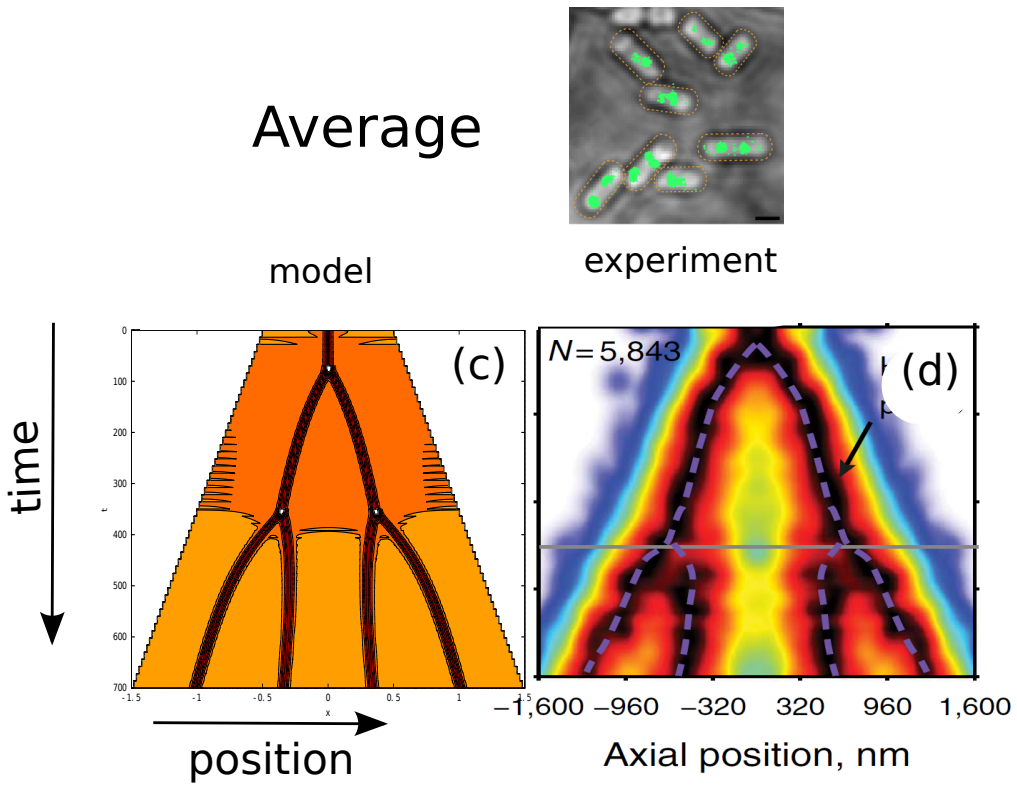
Threshold of dynamical stability obtained with Traveling Waves (TW) *ansatz*: $u(x,t) = u(\xi)$; $v(x,t) = v(\xi)$, where $\xi = x - c_{TW}\, t$



$$\alpha_c = N^{-1}_{ParA \in \mathcal{C}}$$

Comparison with experiments





Summary

- Complexes are formed by LLPS mechanisms in the metastable regime:
  $\rightarrow$ bound particles are interacting at long range due to polymer fluctuations

  David G., JCW, Broœdersz C., Dorignac J., Geniet F., Parmeggiani A., Walliser N. & Palmeri J. *Long range interactions generated by polymer fluctuations induce phase separation*, submitted, [arXiv/1811.09234]

  Guilhas B., JCW, Rech J., Mathieu-Demaziere C., Palmeri J., Parmeggiani A., Walliser N., Bouet J-Y., Le Gall A. & Nollmann M. *ATP-driven separation of liquid phase condensates in bacteria*, submitted.
- ATP-driven segregation of equilibrium complexes via ParA
  $\rightarrow$ Reaction-diffusion mechanism with a dynamical transition

  JCW, Dorignac J., Lorman V., Rech J., Bouet J.-Y., Nollmann M., Palmeri J., Parmeggiani A. & Geniet F., *Surfing on protein waves: proteophoresis as a mechanism for bacterial genome partitioning*, *Phys. Rev. Lett.* **119**, 028101. `arXiv:1702.07372 [q-bio.SC]`

Theory
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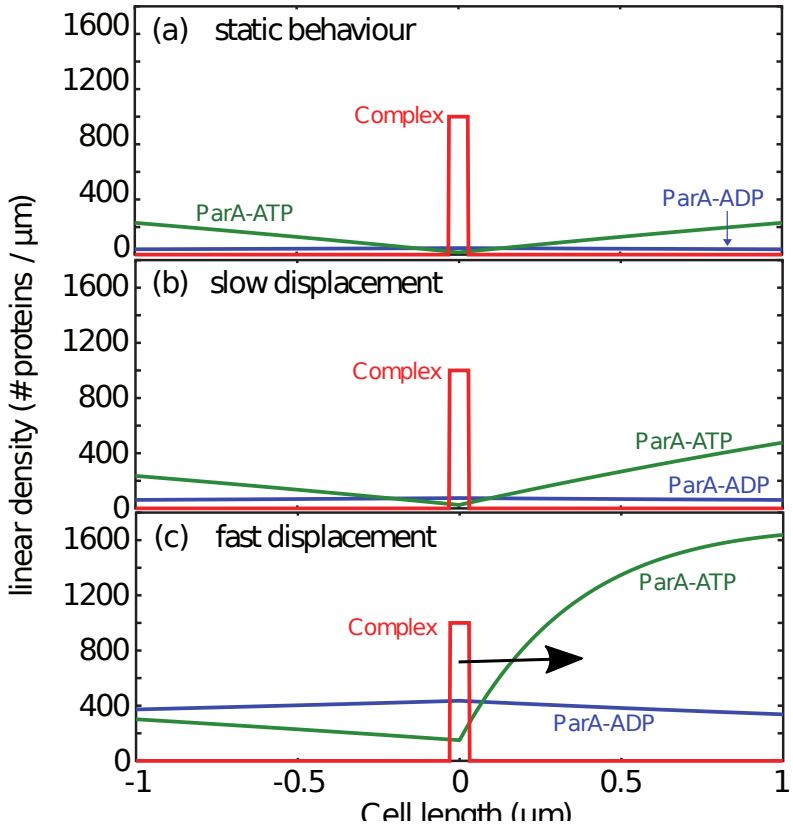
C. Chevalier
G. David
J. Dorignac
F. Geniet
V. Lorman
J. Palmeri
A. Parmeggiani
P. Soudon
N. Walliser
LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
C. Broedersz
Molecular biology
SR microscopy
R. Diaz
A. Sanchez
J. Rech
J-Y. Bouet
UNIVERSITÉ TOULOUSE III PAUL SABATIER
LMGM
CBS
D. Cattoni
B. Guilhas
A. Le Gall
M. Nollmann

Density profiles obtained with biological paramaters

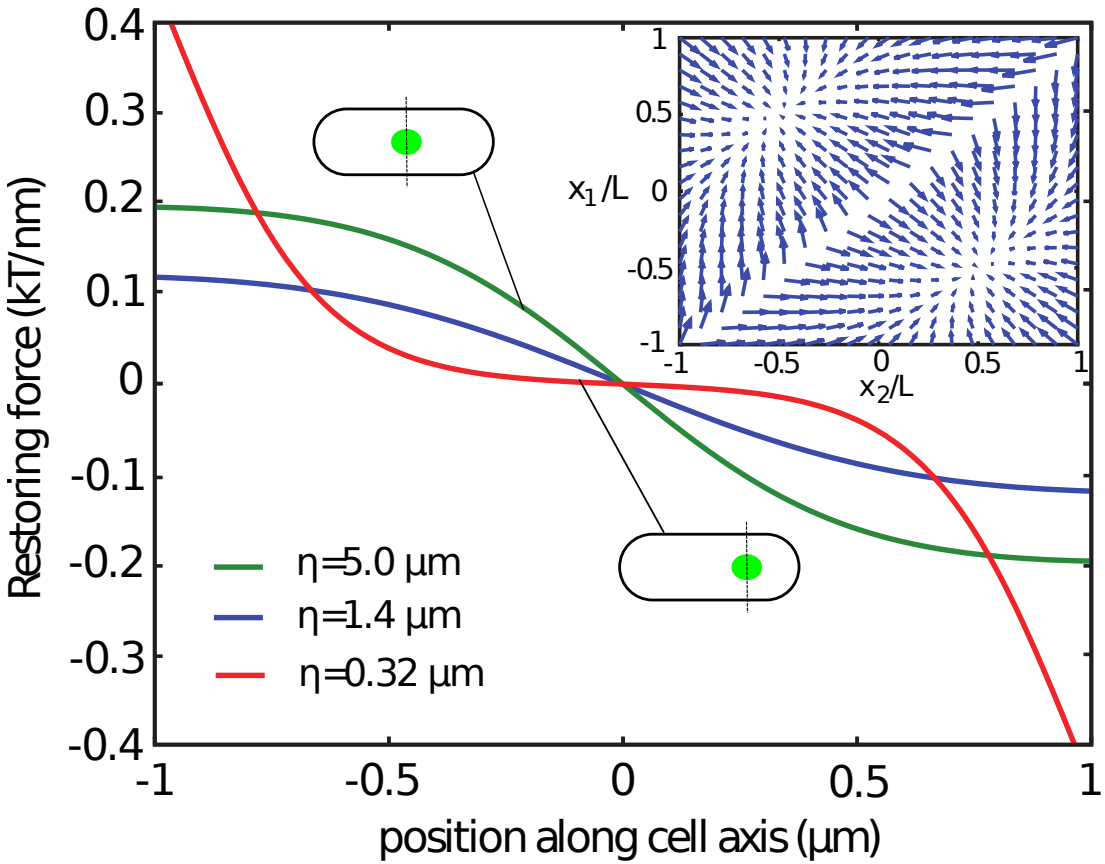


$\alpha < \alpha_c$

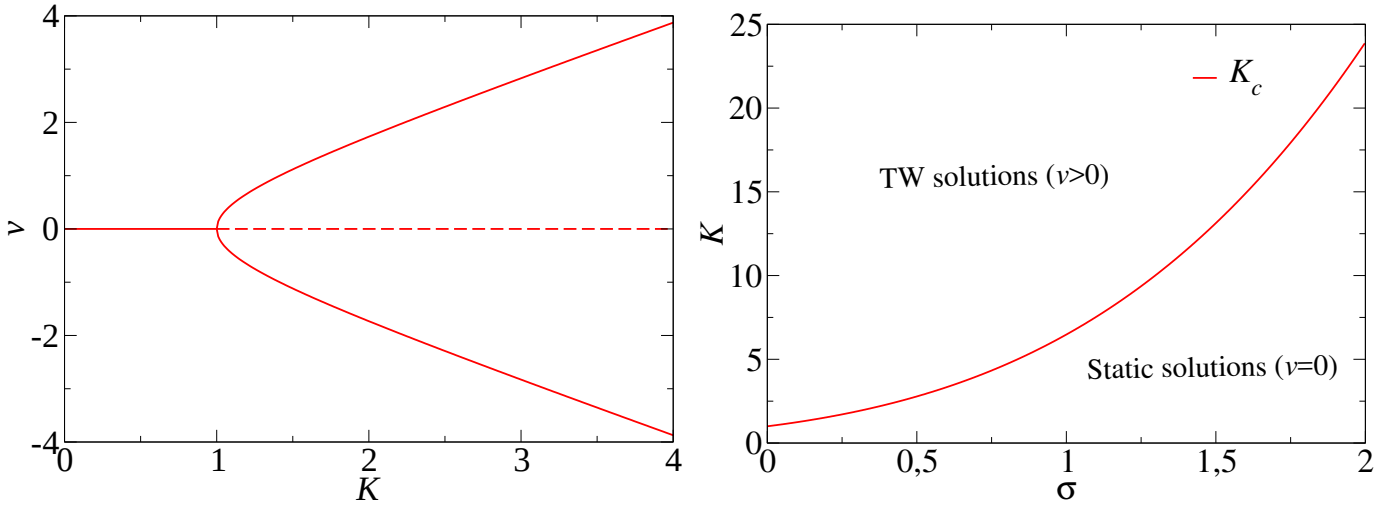
$\alpha = \alpha_c$

$\alpha > \alpha_c$

Screening length



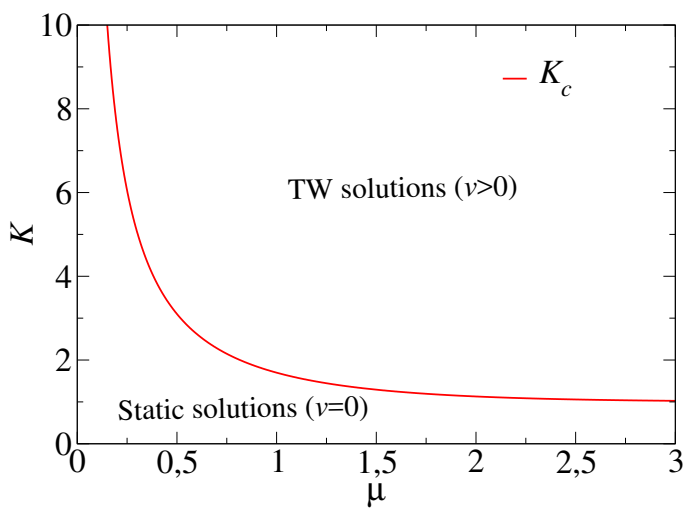
Supercritical pitchfork bifurcation

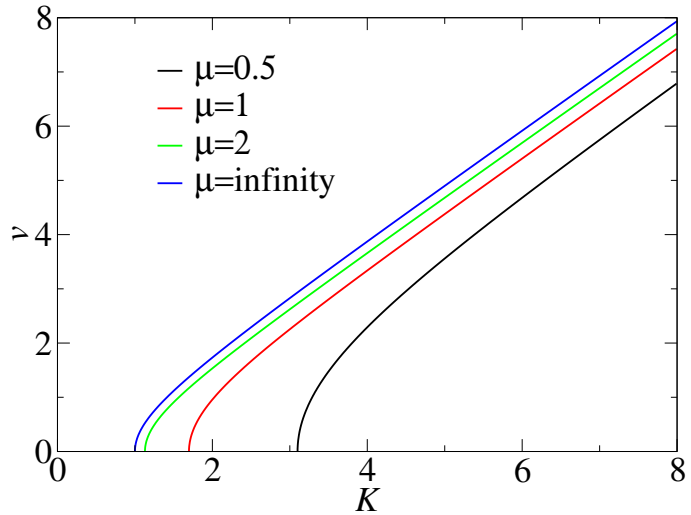


Infinite system (left) Supercritical pitchfork bifurcation diagram of reduced system in the (K, v) space.

(right) Dynamical phase diagram in the plane (K, σ) where $K = \alpha m_0/(4D\ell)$ and σ is the dimensionless width of a gaussian source. The red curve represents the boundary (critical value K_c vs. σ).

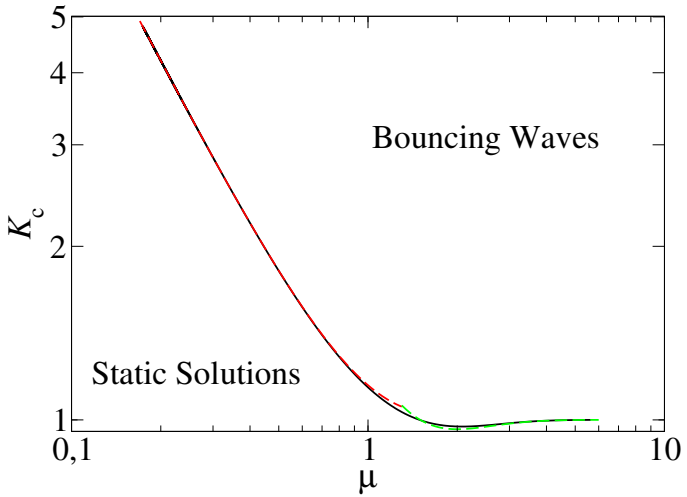
Supercritical pitchfork bifurcation





Periodic Boundary Conditions (left) Dynamical phase diagram in the plane (K, μ) where $K = \alpha m_0/(4D\ell)$ and $\mu = L/\ell$ is the dimensionless ratio between L (size domain $2L$) and the screening length $\ell = \sqrt{D/k}$. (right) TW dimensionless velocity v (positive) vs. parameter $K = \alpha m_0/(4D\ell)$ for different values of $\mu = L/\ell$ from 0.5 to 2 and for $\mu \to \infty$. The blue curve is the same as the upper part for infinite system, thus the right limit is recovered.

Supercritical pitchfork bifurcation



No-Flux Boundary Conditions (Log-log plot of the instability threshold $K_c(\mu)$ versus the system size to screening length ratio $\mu = L/\ell$ for a Dirac source.