Phase separation of DNA-bound proteins
GDR ADN - 29/03/2019

Phase separation of polymer-bound particles, David et al., arXiv:1811.09234

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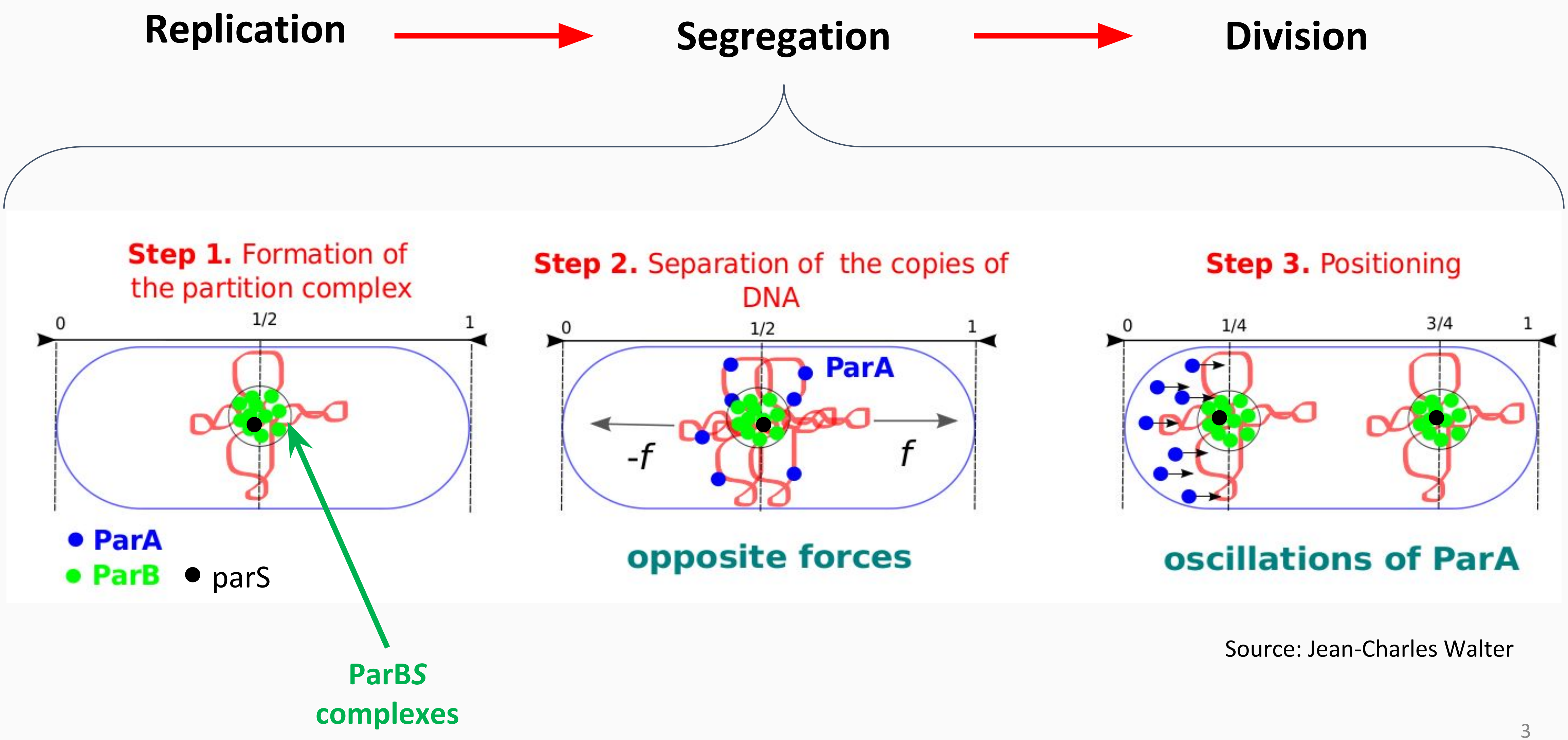
ParABS partition system

ParABS partition system and bacterial DNA segregation



Source: Jean-Charles Walter

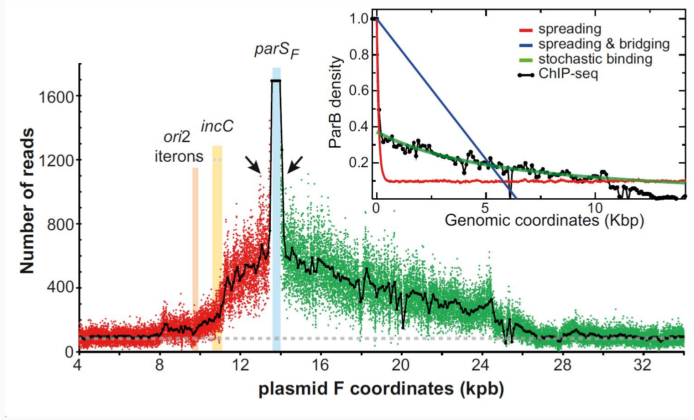
Overview

Overview of ParAB*S* modeling (non-exhaustive)

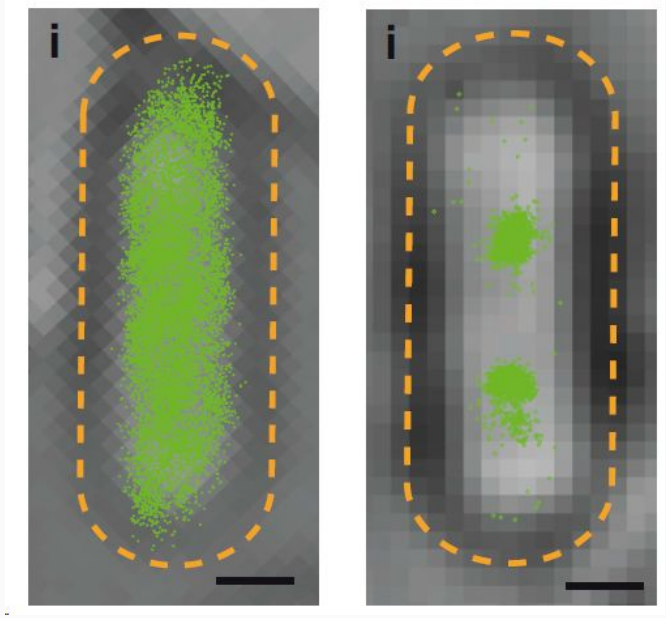
ParB*S* complexes formation | Positioning mechanism

Experimental data / Phenomena

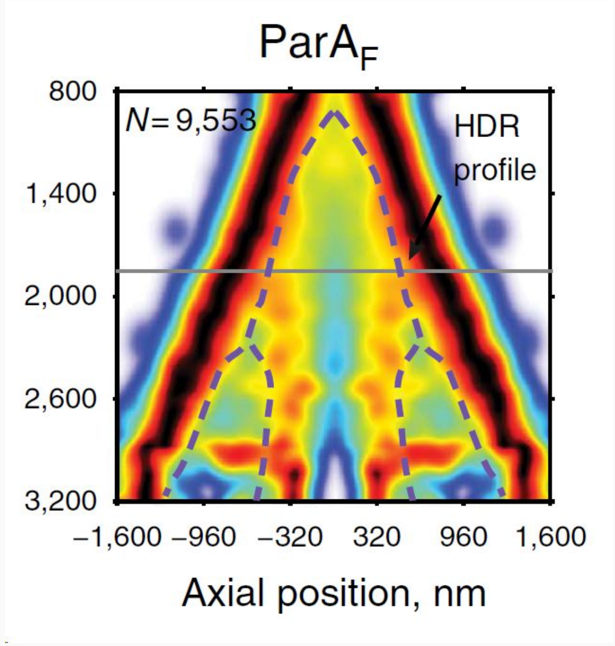
Sanchez et al., Cell Syst 2015, Debaugny et al., Mol Syst Biol 2018



Sanchez et al., Cell Syst 2015



Le Gall et al., Nat Com 2016



Models

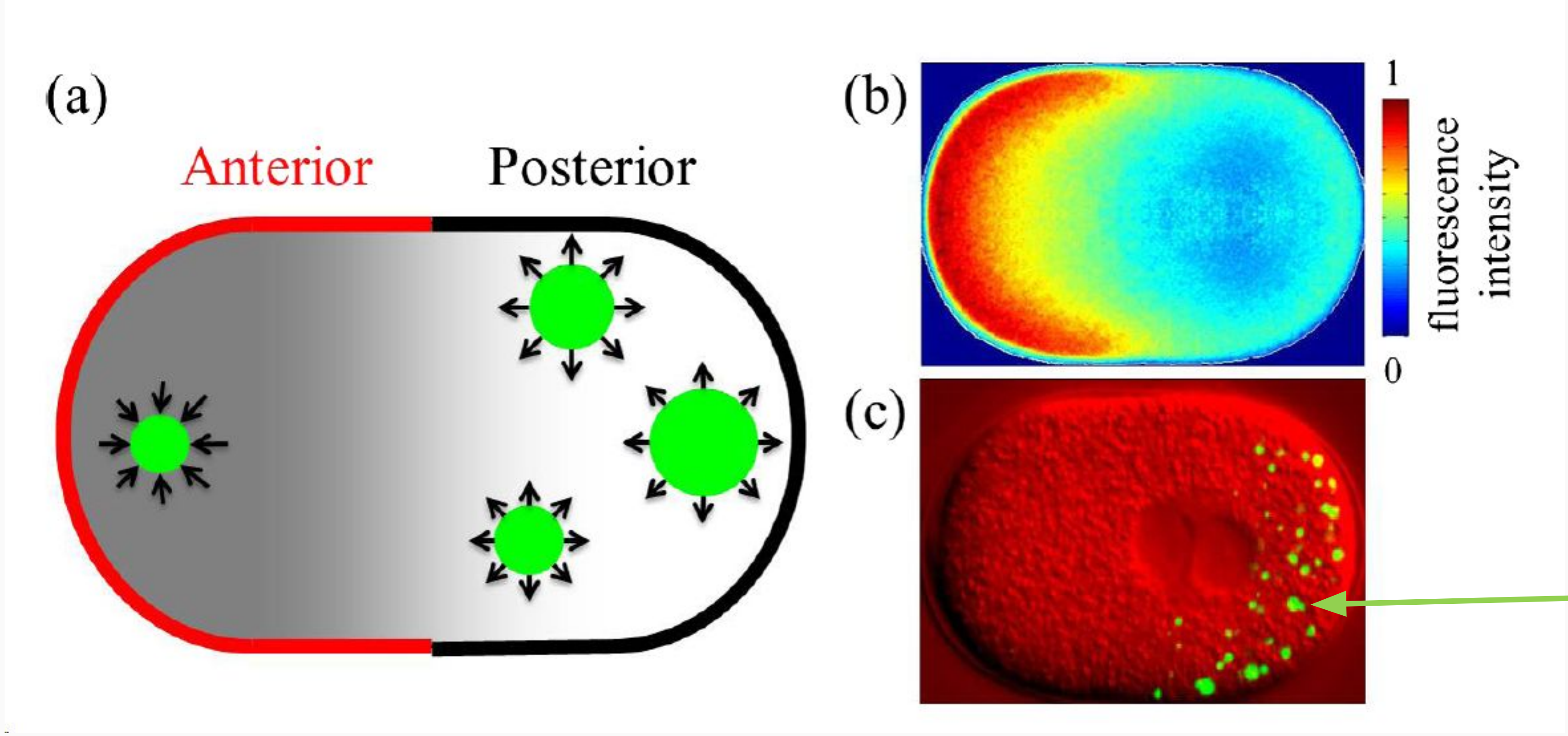
- **Spreading and/or Bridging (Broedersz et al., PNAS 2014)**
- **Stochastic Binding (Sanchez et al. Cell Syst 2015)**
- **Looping and Clustering (Walter et al., NJP 2018)**

- **Spreading and/or Bridging (Broedersz et al., PNAS 2014)**
- **Long Range Lattice Gas (David et al., re-submitted PRL)**

- **Proteophoresis force model (Walter et al., PRL 2017)**

Phase separation in biological systems

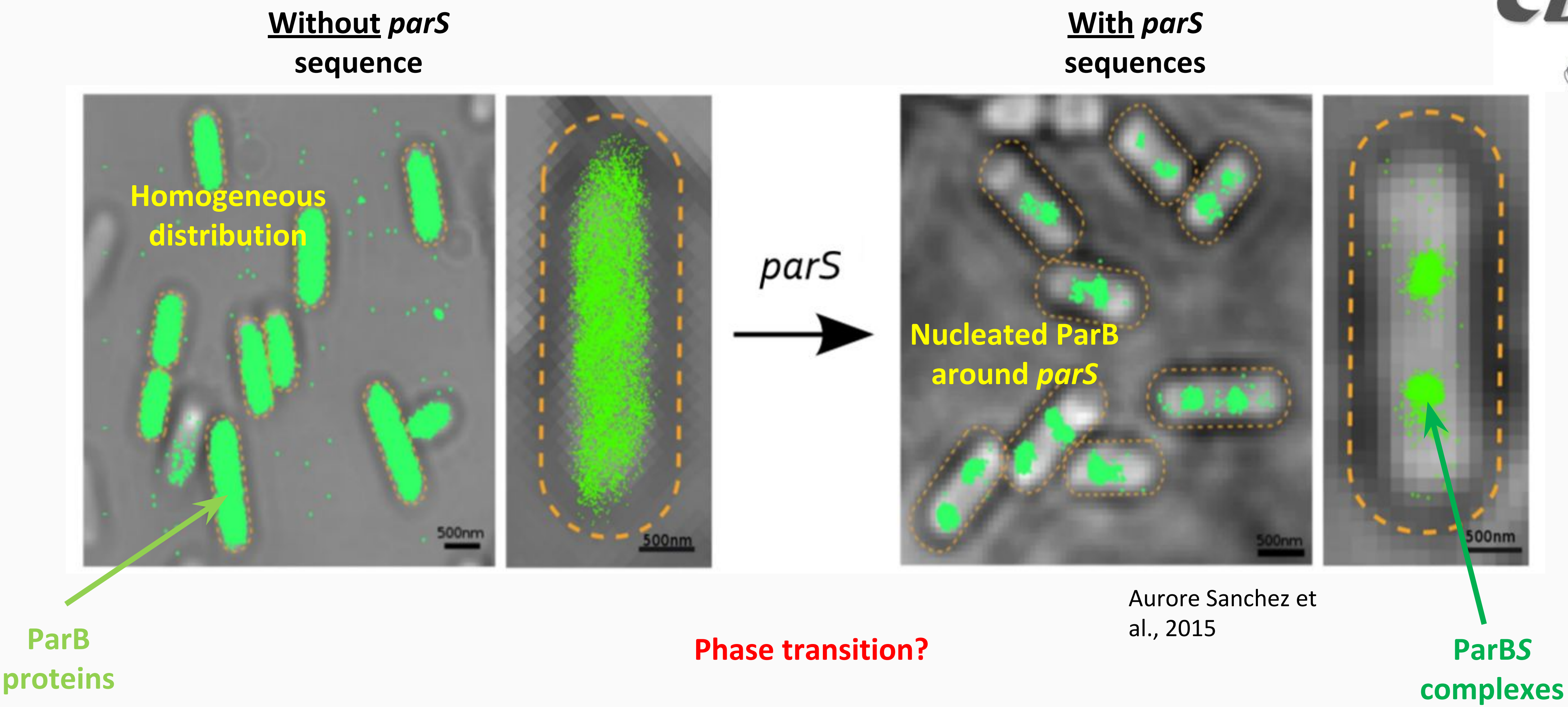
Phase Separation → **Non-membrane compartments** → **Confine and organize chemical reactions in intracellular space**



P-granules + RNA

Lee, …, Brangwynne, et al., PRL 2013, *C. elegans*

ParB*S* complexes formation: phase separation?



Aurore Sanchez et al., 2015

Phase transition?

1. Are phase transitions even possible?
2. Where are we in the phase diagram?

DNA + interacting DNA-bound particles = Spreading and Bridging

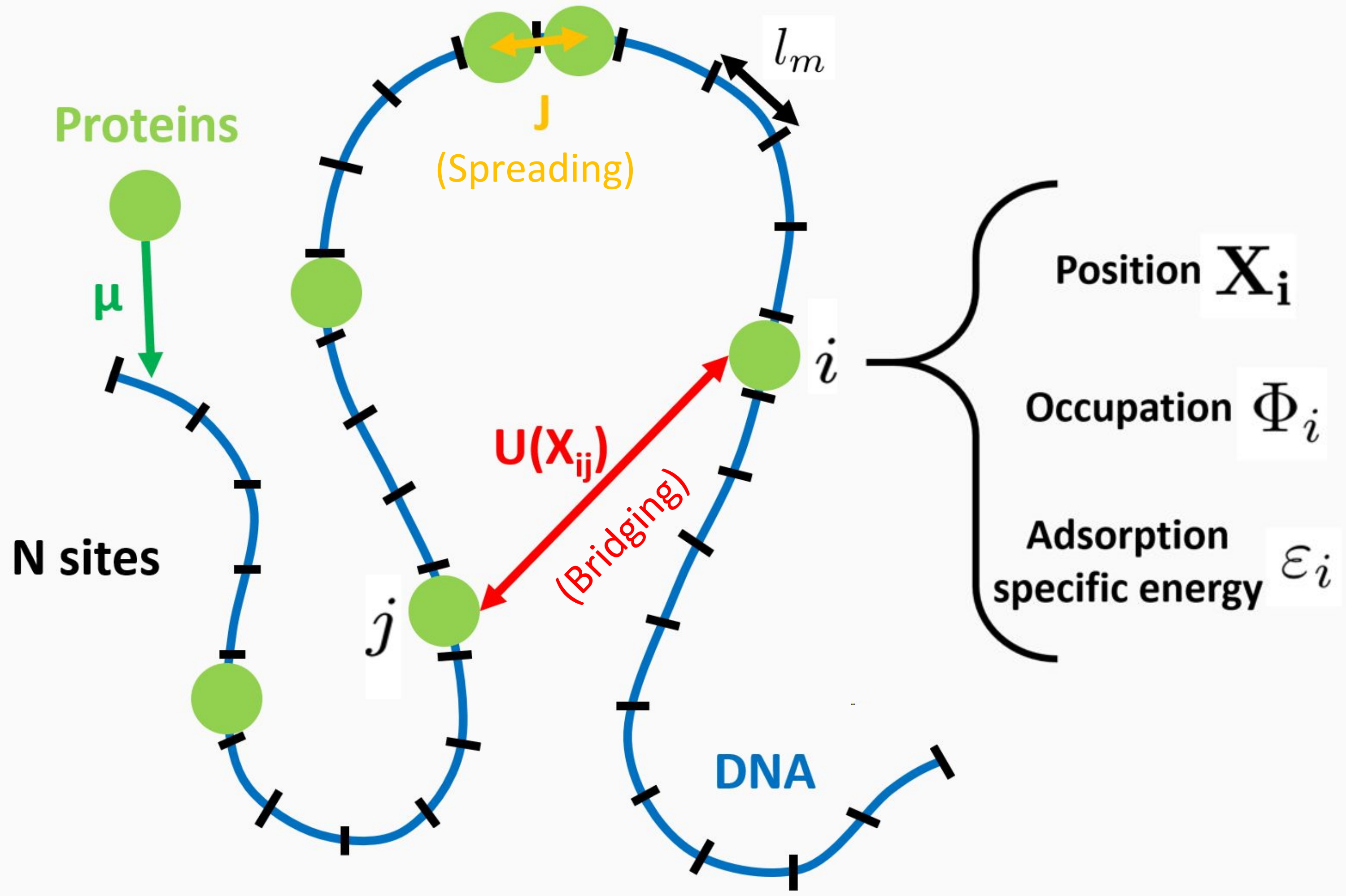
3D DNA-polymer spatial distribution

↕

1D protein occupation distribution

Broedersz et al., PNAS 2014

Spreading & Bridging Model



DNA-bound proteins interacting on DNA model

The S'n'B is an Hamiltonian approach

Short Range Lattice Gas (Spreading)

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

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

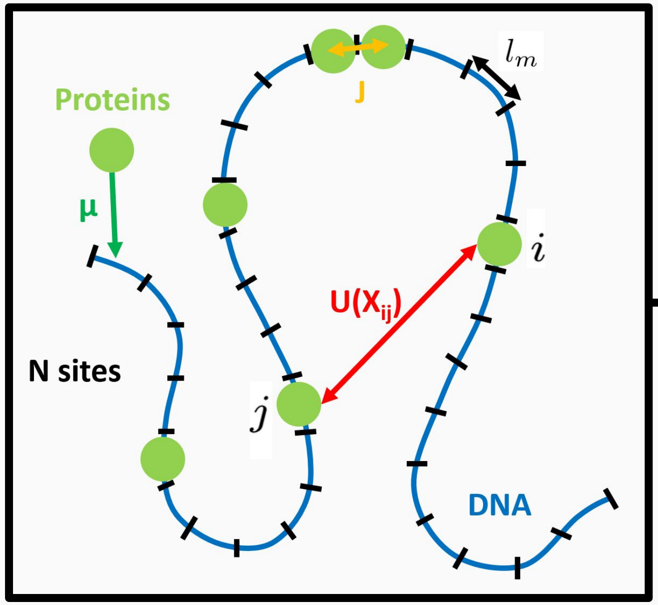
3D Polymer

Coupling between polymer and lattice gas (Bridging)

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

From the S’n’B to the Long Range Lattice Gas model

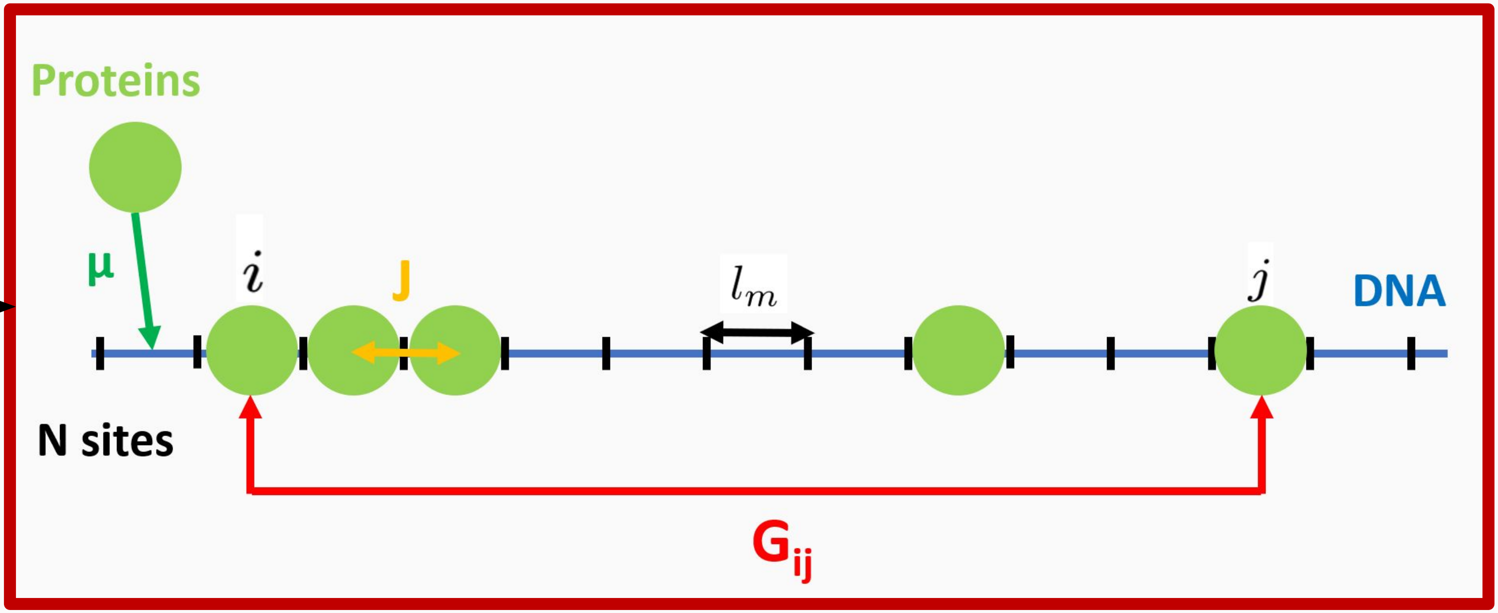
Spreading & Bridging



Cluster expansion, two-body interactions only (low density)

3D → 1D

Long Range Lattice Gas



$$\mathcal{F}_{\mathrm{LRLG}}[\Phi_i] = H_{\mathrm{SRLG}}[\Phi_i] - \frac{1}{2}\sum_{i,j}^{N}{}' \Phi_i G_{ij} \Phi_j$$

Definition of the kernel G_{ij}

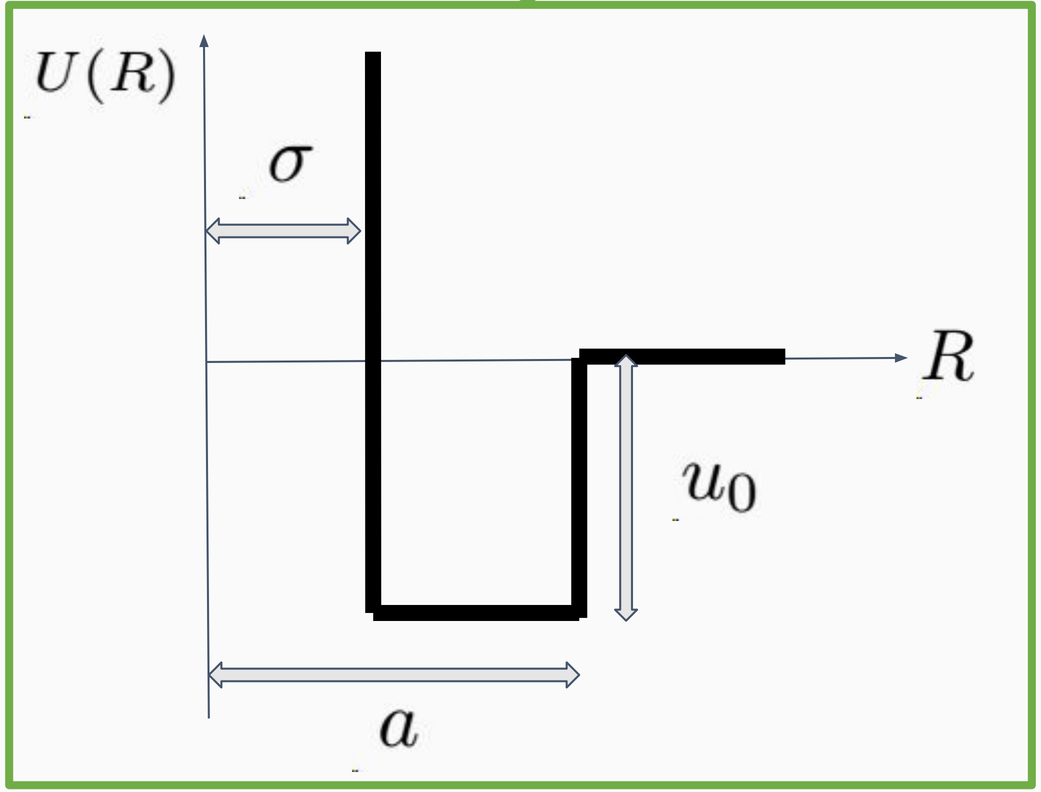
2nd order virial expansion coefficient

Spatial potential

$$G_{ij} = 4\pi\beta^{-1} \int_0^{+\infty} dR \; R^2 \left[e^{-\beta U(R)} - 1 \right] P_{ij}(R)$$

Polymer distribution function ⇔ Chain connectivity !

Short range hard core + square well



Criterion for phase transitions/separation

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

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

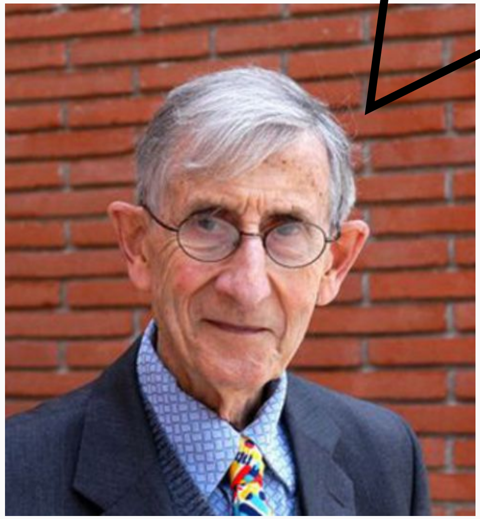
Polymer size exponent

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

PDF asymptotic behavior $P_{ij}(R) \sim \dfrac{R^g}{R_{ij}^{3+g}}$

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

Freeman J. Dyson, 1969



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

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

1. Are phase transitions even possible?
2. Where are we in the phase diagram?

Thermodynamics

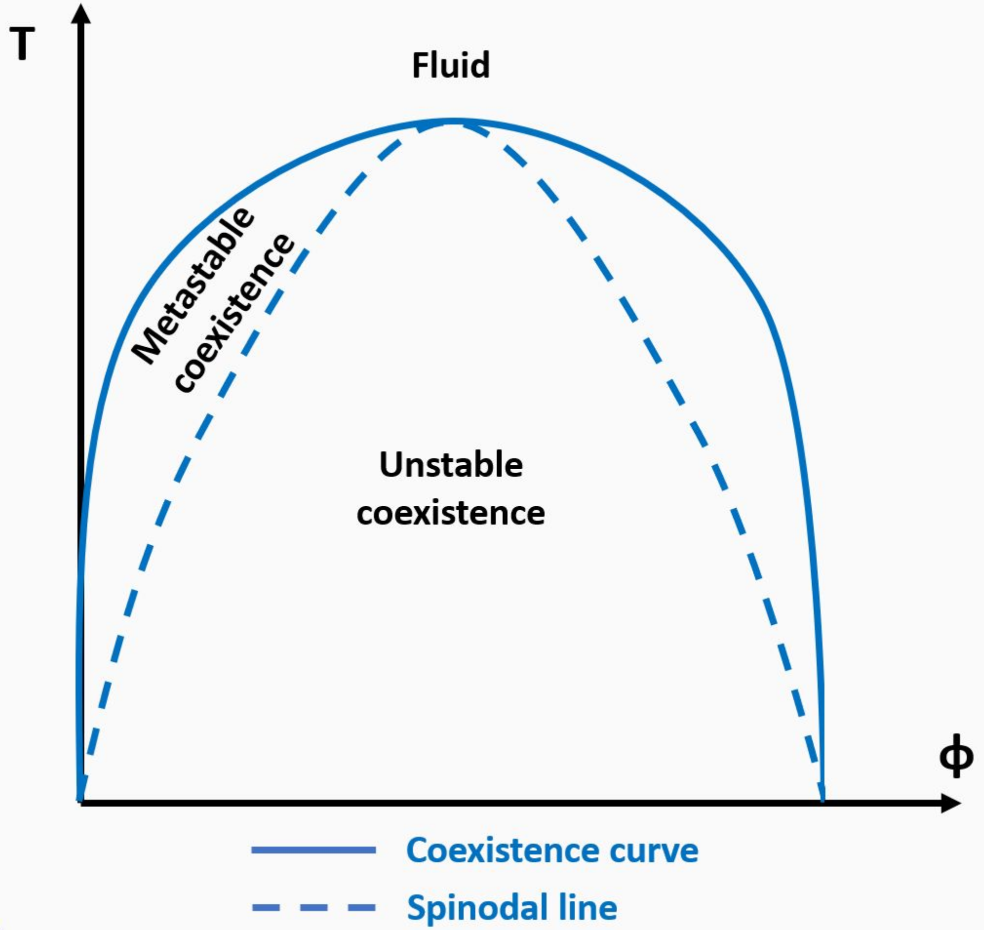
Phase separation ⟺ **Coexistence of high ϕ_h and low occupation ϕ_l states**

- **Coexistence curve:**

$$\begin{cases} P(T,\Phi_l) = P(T,\Phi_h) \\ \mu(T,\Phi_l) = \mu(T,\Phi_h) \end{cases}$$

- **Spinodal line:**

$$\left(\frac{\partial P}{\partial \Phi}\right)_T = 0$$



Variational method

$$\mathcal{F}_{\mathrm{LRLG}}[\Phi_i] = H_0 + \Delta H \longrightarrow \Omega_{\mathrm{LRLG}} \leq \Omega_{\mathrm{V}} = \Omega_0 + \langle \Delta H \rangle_0$$

Hamiltonian of reference = 1D SRLG

$$H_0 = -J \sum_{i=1}^{N-1} \Phi_{i+1}\Phi_i - \mu_0 \sum_{i=1}^{N} \Phi_i$$

$$\Delta H = -\frac{1}{2} \sum_{i,j}^{N}{}' \Phi_i G_{ij} \Phi_j - (\mu - \mu_0) \sum_{i=1}^{N} \Phi_i$$

Minimization

$$\left(\frac{\partial \Omega_{\mathrm{V}}}{\partial \mu_0}\right)_{\mu_0 = \mu_0^\star}$$

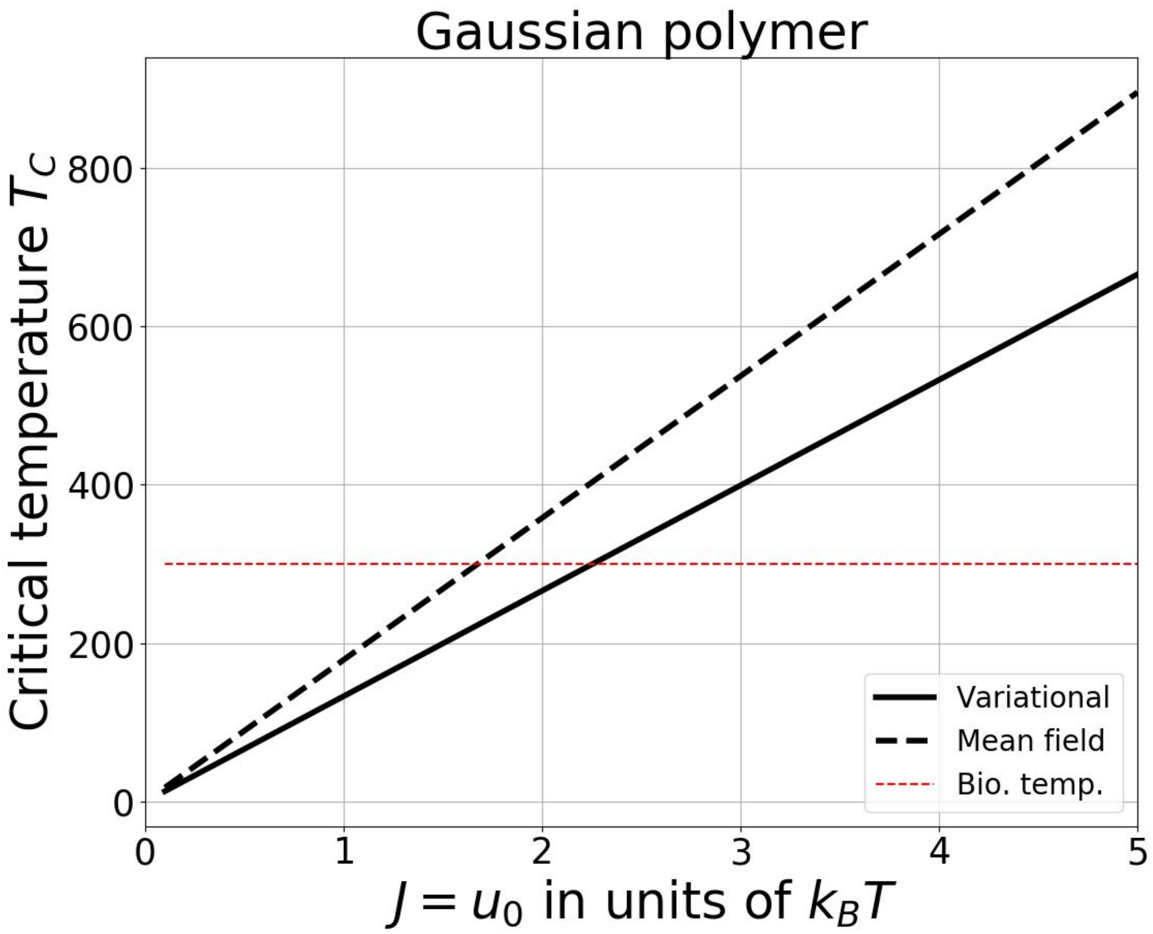
$$\Omega_{\mathrm{LRLG}} \approx \Omega_{\mathrm{V}}^\star$$

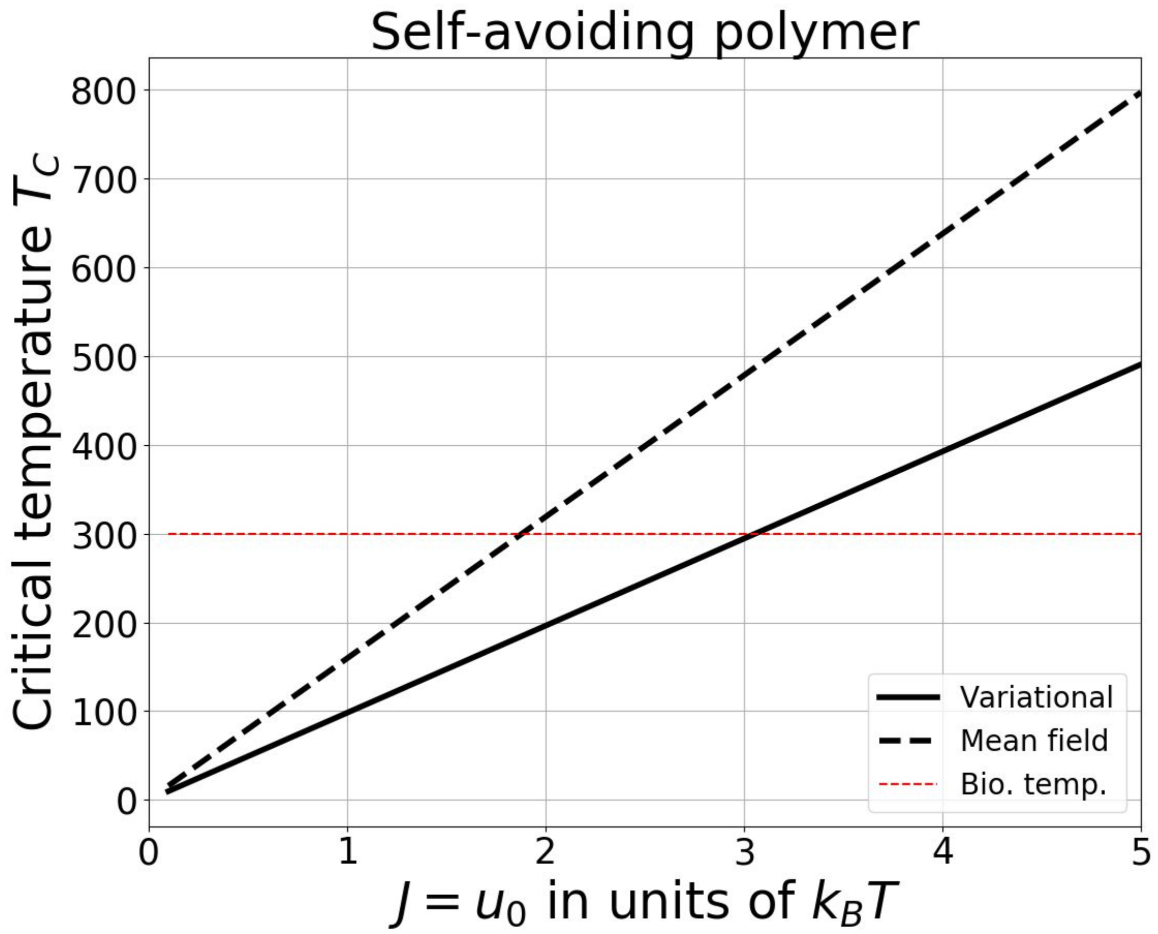
Analytical results !

Parameters overview

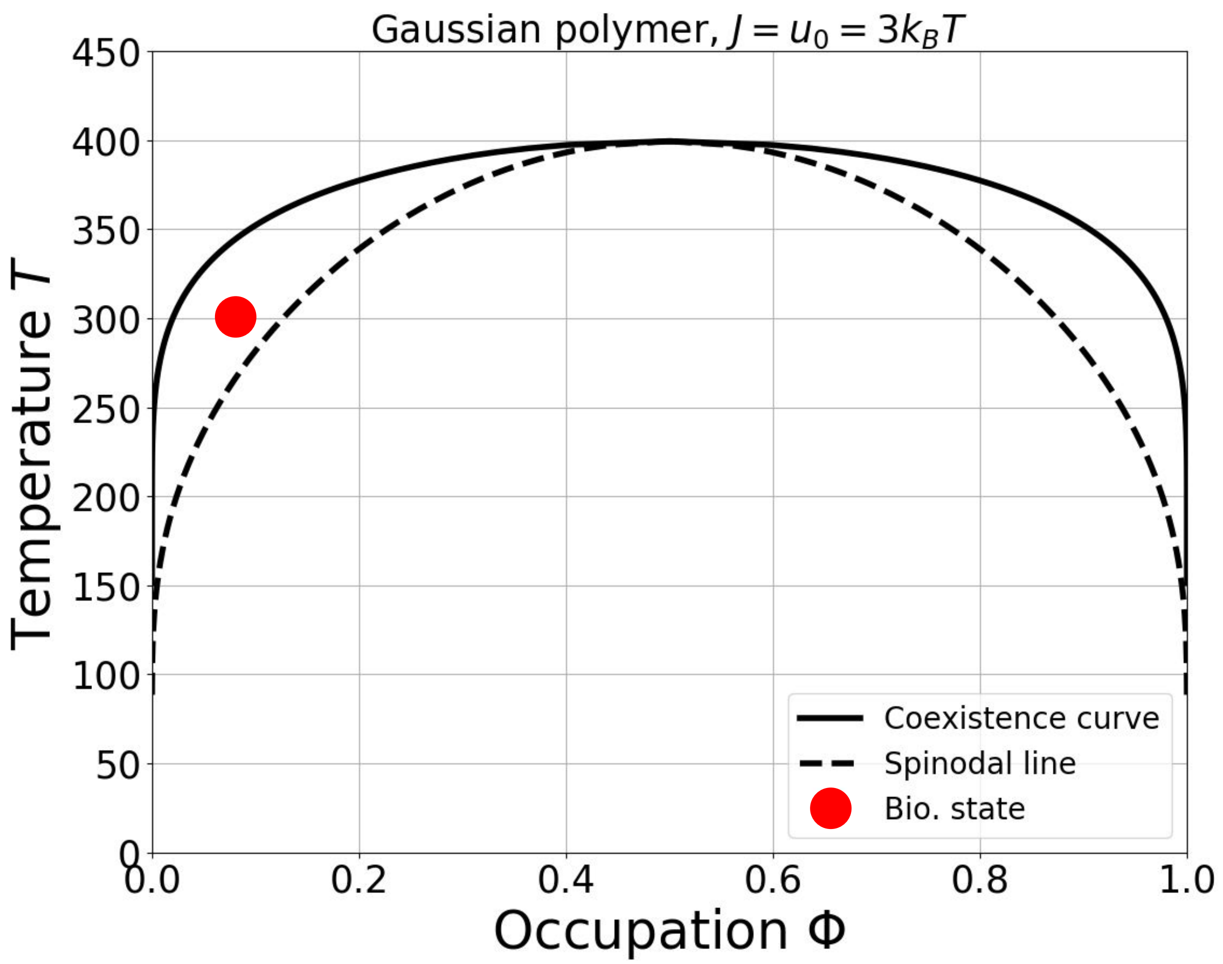
	Parameter	Symbol	Value
	Physiol. Temperature	T_{bio}	300 K
Polymer parameters	Monomer length	l_m	16 bp ($\sim$ 5.4 nm)
	DNA persistence length	l_p	150 bp ($\sim$ 50 nm)
	Kuhn length	b	23.6 nm
	PDF LR behavior exponent	g	SAP: 0.27, G: 0
	Flory exponent	ν	SAP: 0.588, G: 0.5
Spatial potential U(R)	Hard-core int. range	σ	l_m
	Spatial int. range	a	2σ ($\sim$ 10.8 nm)
Work parameters	Spatial int. intensity	u_0	$u_0 = J$
	Spreading intensity	J	0 to $5k_BT$
	Mean occupation	Φ	0 to 1

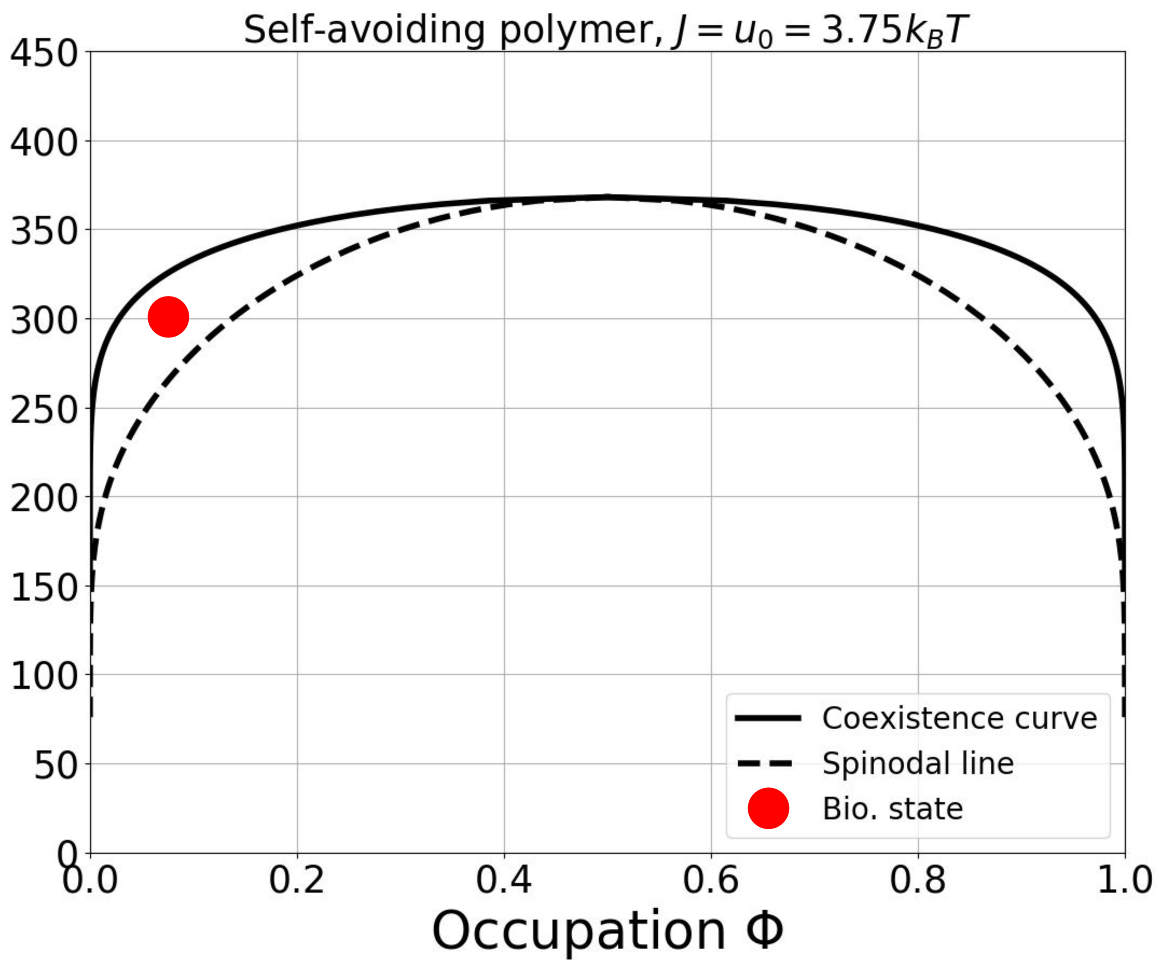
1D Long Range Lattice Gas: critical temperature





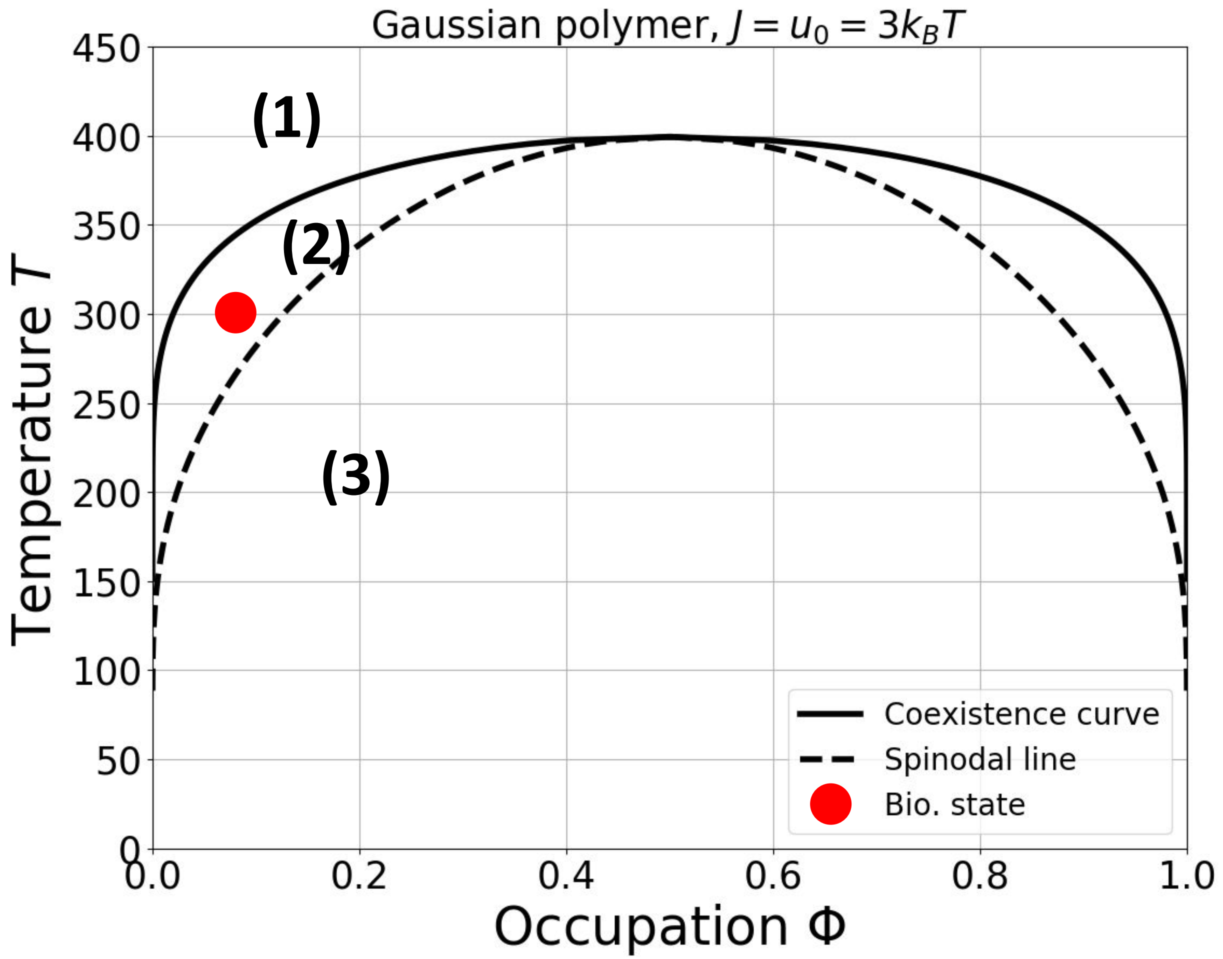
1D Long Range Lattice Gas: phase diagrams



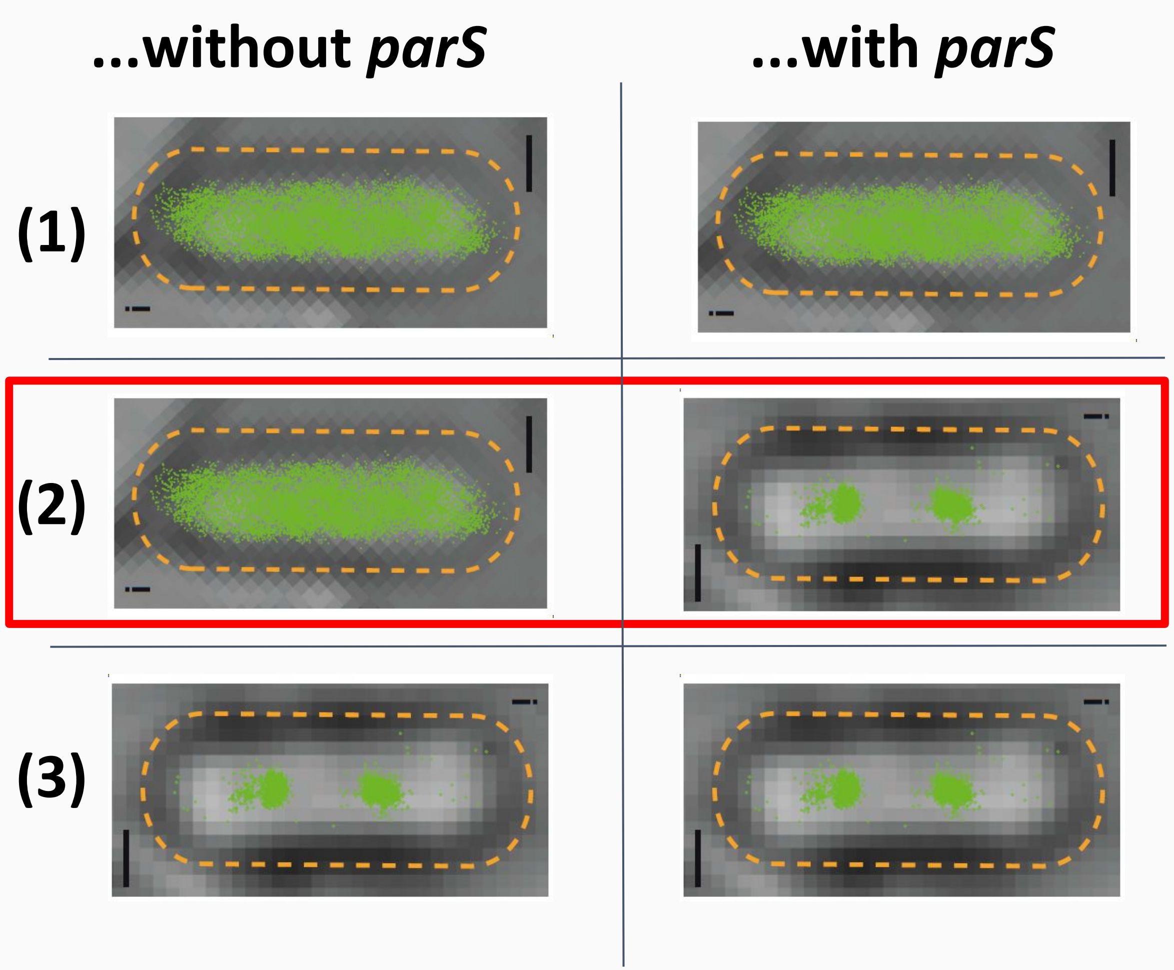


Biological regime for F-plasmid: ● **ϕ = 300 ParB / 3750 sites ≃ 0.08 (upper bound)**
T = 300 K

Low occupation metastable regime



<u>Expected</u> ParB distribution...



In short

Sum up and perspectives

1. **Polymer fluctuations ⇒ effective long-range interactions between bound-particles ⇒ phase separation of bound-proteins on the polymer.**

2. **Variational method ⇒ whole mean-occupation/temperature phase diagram.**

3. **The low occupation metastable coexistence region explains the experimental data for ParB distribution.**

- **What is the consequence for the polymer distribution?**
- **Occupation/density profile?**
- **Quantitative test? Accurate prediction of J or u_0?**

Team and collaborators in France

Physical modeling (Montpellier)

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