Looping and Clustering model for the organization of protein-DNA complexes on the bacterial genome

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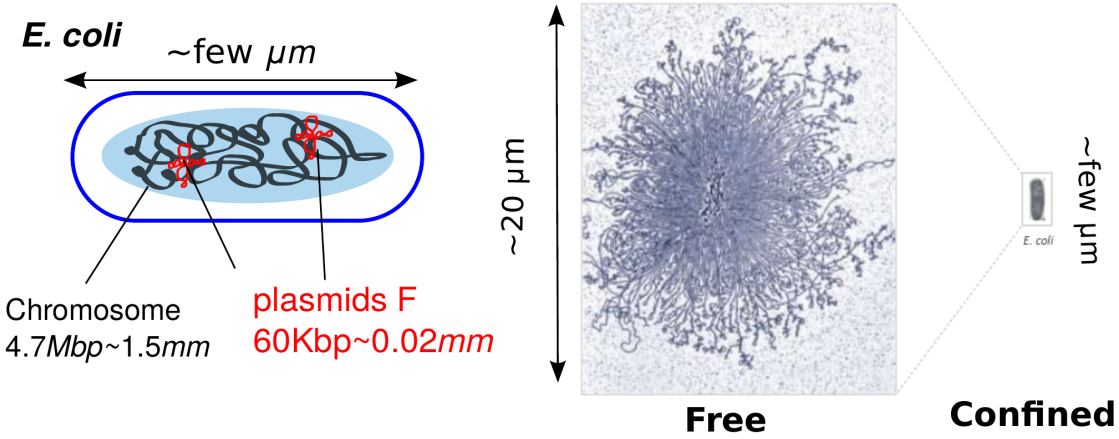
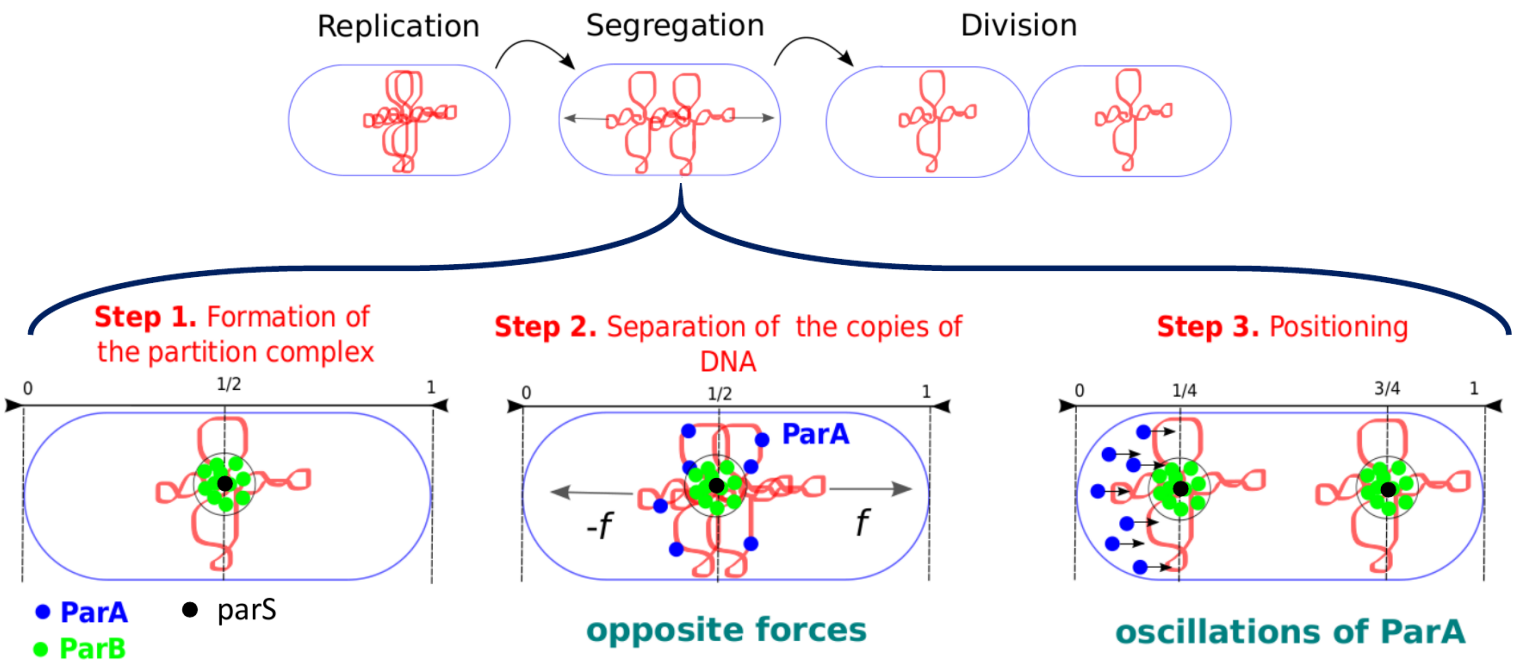
Outline

The ParABS segregation mechanism

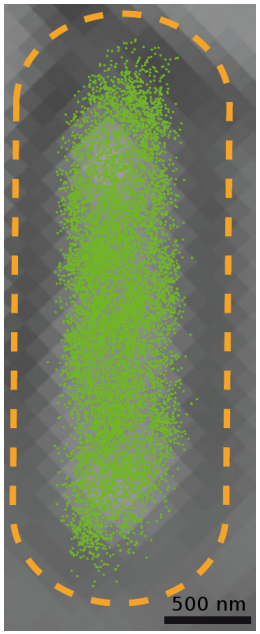


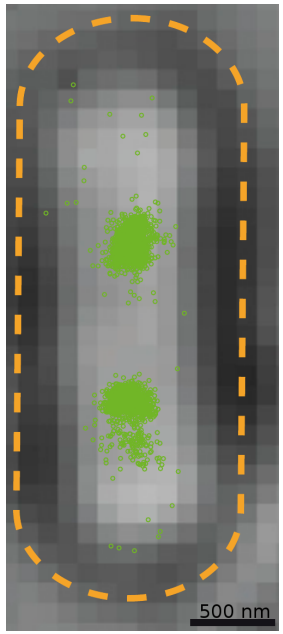


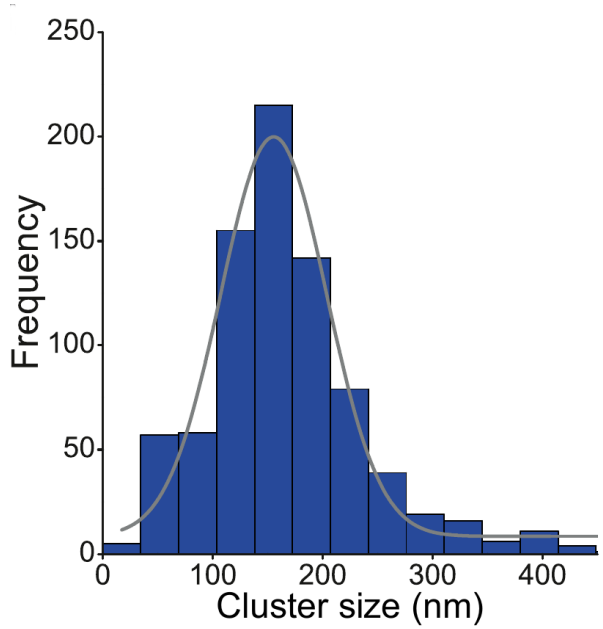
(Courtesy of Jean-Charles Walter)

The ParB-DNA complex

PALM detection of ParB proteins in *E. coli* in absence/presence of *parS* binding





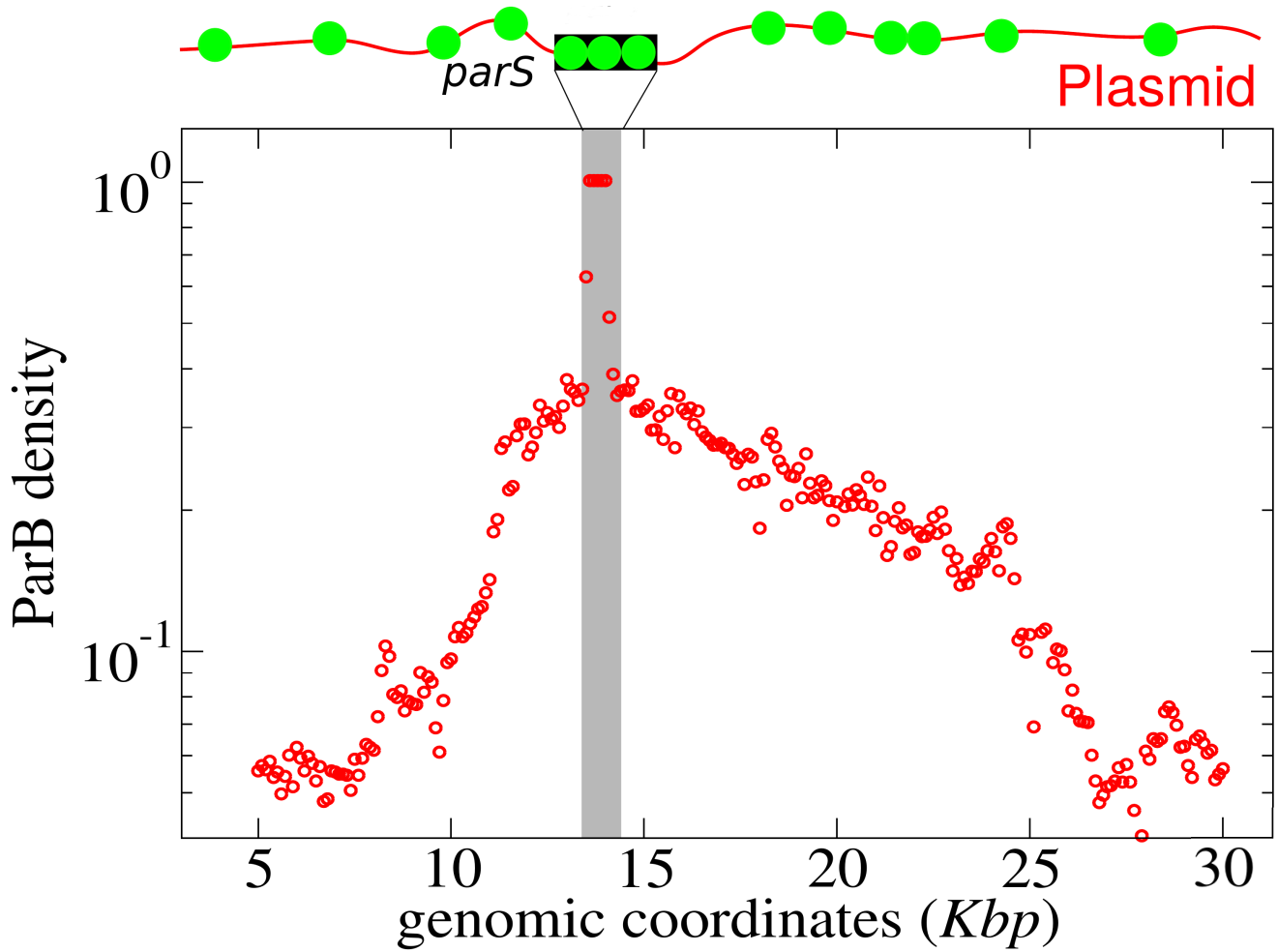


- Focus diameter 150 ± 20 nm
- Number of ParB in a focus ≈ 300
- Clusters contain $\sim 90\%$ of total ParB of the cell

Source: Sanchez *et al.* Stochastic self-assembly of ParB proteins builds the bacterial DNA segregation apparatus. Cell systems, 1(2), 163-173.

ParB density along the F Plasmid of *E. coli*

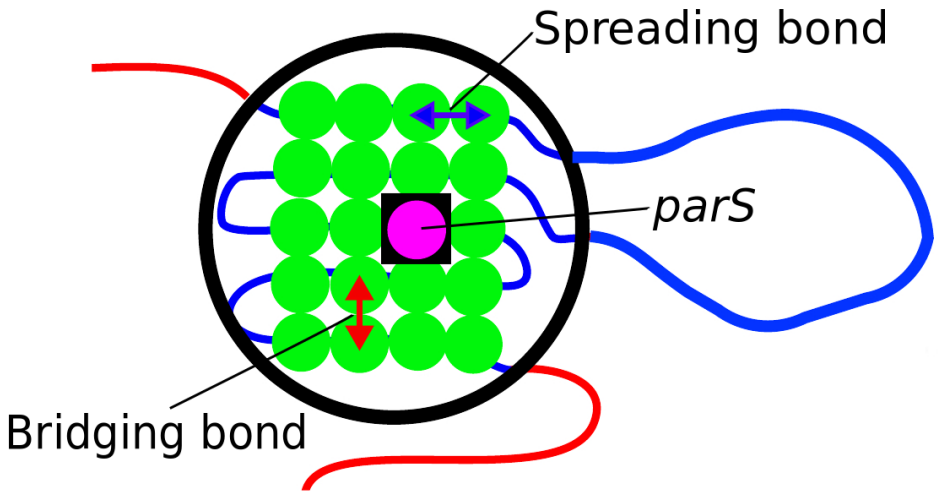
High-resolution ChIP-sequencing of ParB binding pattern in *E. coli*



ChIP-Seq of ParB on F-plasmid of *Escherichia coli* : Sanchez *et al.* Stochastic self-assembly of ParB proteins builds the bacterial DNA segregation apparatus. Cell systems, 1(2), 163-173.

Spreading & bridging interactions

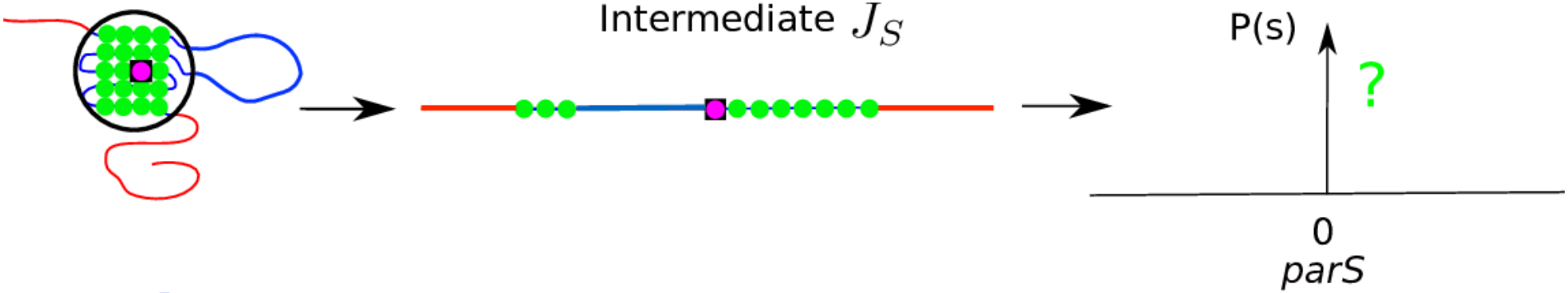
A *minimal* model for condensation of ParB proteins on DNA requires two types of interactions between bound proteins [Broedersz *et al.* 2014]



- **Spreading interactions** $\sim J_S$ **:** between proteins at nearest neighbor-sites (nns) along the polymer
- **Bridging interactions** $\sim J_B$ **:** between proteins at nns in 3D space (but at *non* nns along the polymer)

- DNA is described as a linear self-avoiding chain on a cubic lattice in 3D
- Proteins interact via spreading or bridging interactions

Modeling the ParB-DNA complex: Looping and Clustering



- All bridging bonds are satisfied ($J_B = \infty$) $\Longrightarrow$ cluster
- Loops can extrude from cluster by breaking spreading bonds
- Canonical ensemble: the complex has a fixed number of proteins m
- Adjustable parameters: m and J_S

Competition between

- the costs of **generating loops**: break spreading bonds + loop closure entropy
- the **positional entropy** associated with placing loops on the cluster

The statistical physics scheme

Goal: Weighted average over all possible loop numbers and sizes to obtain $P_{\mathrm{LC}}(s)$ for given m and J_{S}

Ingredients:

1) Partition function Z_{LC}
2) Binding profile of ParB proteins for a fixed configuration of loops $P_n\left(s, \{\ell_1, \ldots, \ell_n\}\right)$
   - exact 1-loop binding profile $P_1(s, \ell)$
   - approximate n-loop profile by means of the 1-loop profile
3) Perform (numerical) integration

Test: MC simulations of the model as a benchmark for the approximations used in the analytic approach

Other quantities:

- Average number of loops $\langle n \rangle$
- Average accumulated loop length $\langle \ell \rangle$
- Average loop density $\langle p_{\mathrm{loop}}(s) \rangle$

Averaged binding profile of ParB

The central result

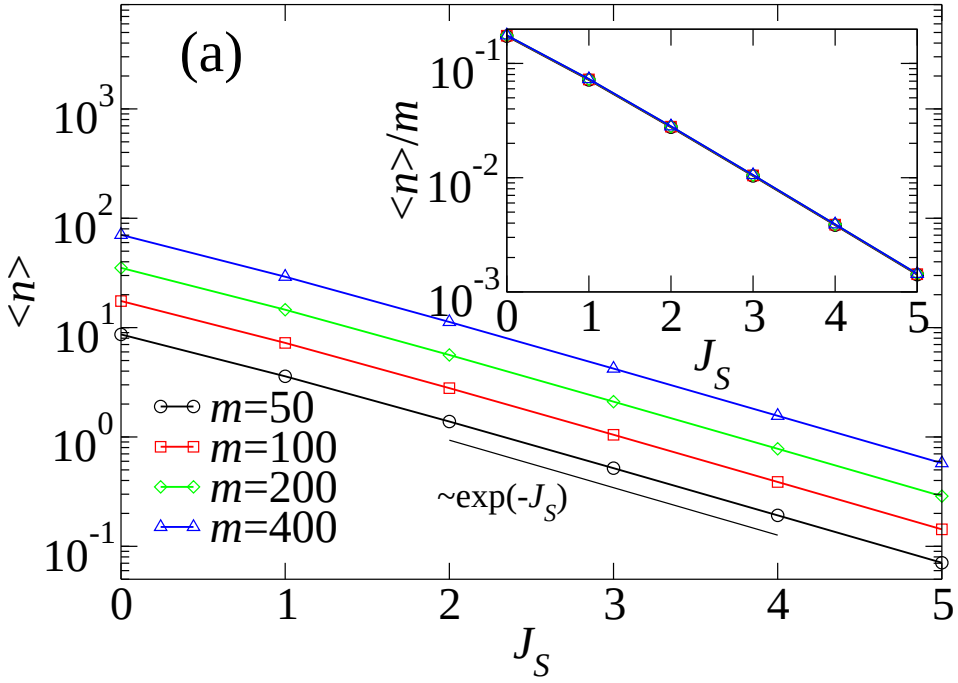
$$P_{\mathrm{LC}}(s) = \frac{1}{Z_{\mathrm{LC}}} \sum_{n=0}^{m-1} \binom{m-1}{n} e^{-n J_S} \times$$
$$\times \int_{\ell_0}^{\ell_{\max}} \dots \int_{\ell_0}^{\ell_{\max}} \ell_1^{-d\nu} \dots \ell_n^{-d\nu} P_n\left(s, \{\ell_1, \dots, \ell_n\}\right) d\ell_1 \dots d\ell_n$$

Parameters of the model

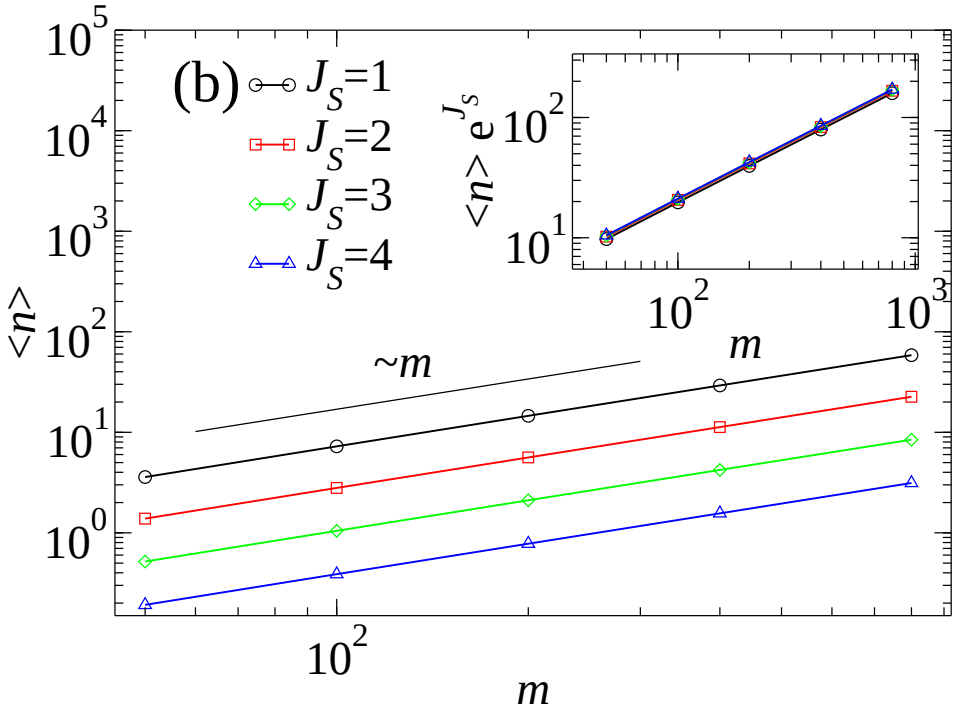
- Number of proteins in the cluster: $m = 100, 200, 400$
- Spreading energy: $J_S = 1, 2, 3, 4$

Numerical evaluation of multidimensional integrals

- lower cutoff: $\ell_0 = 10$
- upper cutoff: $\ell_{\max} = 10\,\ell_0$
- truncate the summation at $n = 15$



- Average number of loops as a function of J_S (loop-size cutoff $\ell_0 = 10$)
- Exponential decrease $\langle n \rangle \propto e^{-J_S}$
- Inset: same data with dependence of average loop number on m scaled out.

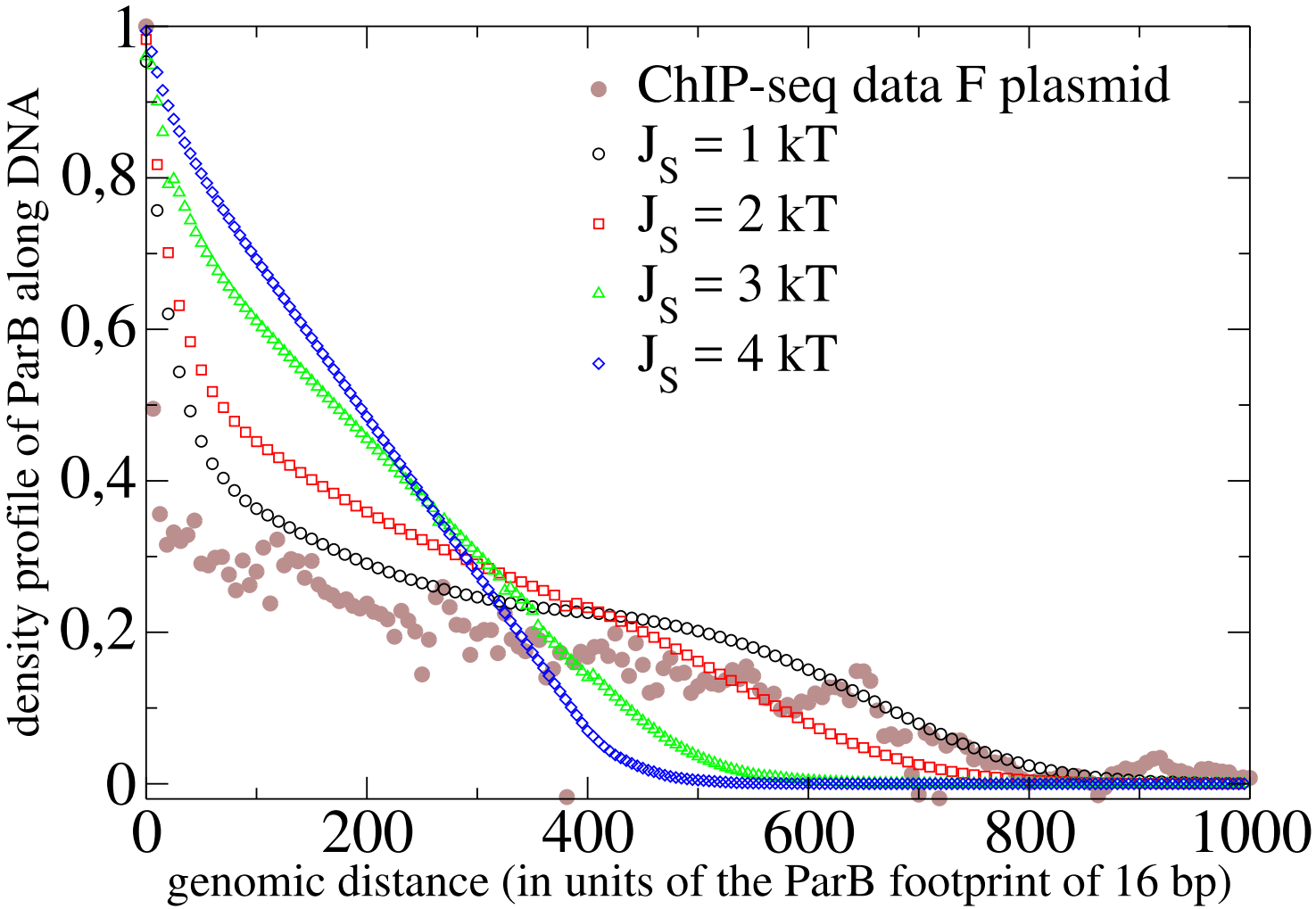


- Average number of loops as a function of m
- Linear dependence on m
- Inset: the vertical shift between the curves scales with e^{-J_S}

$$\langle n \rangle \sim m\, e^{-J_S}$$

Binding profiles of ParB vs genomic distance to *parS*

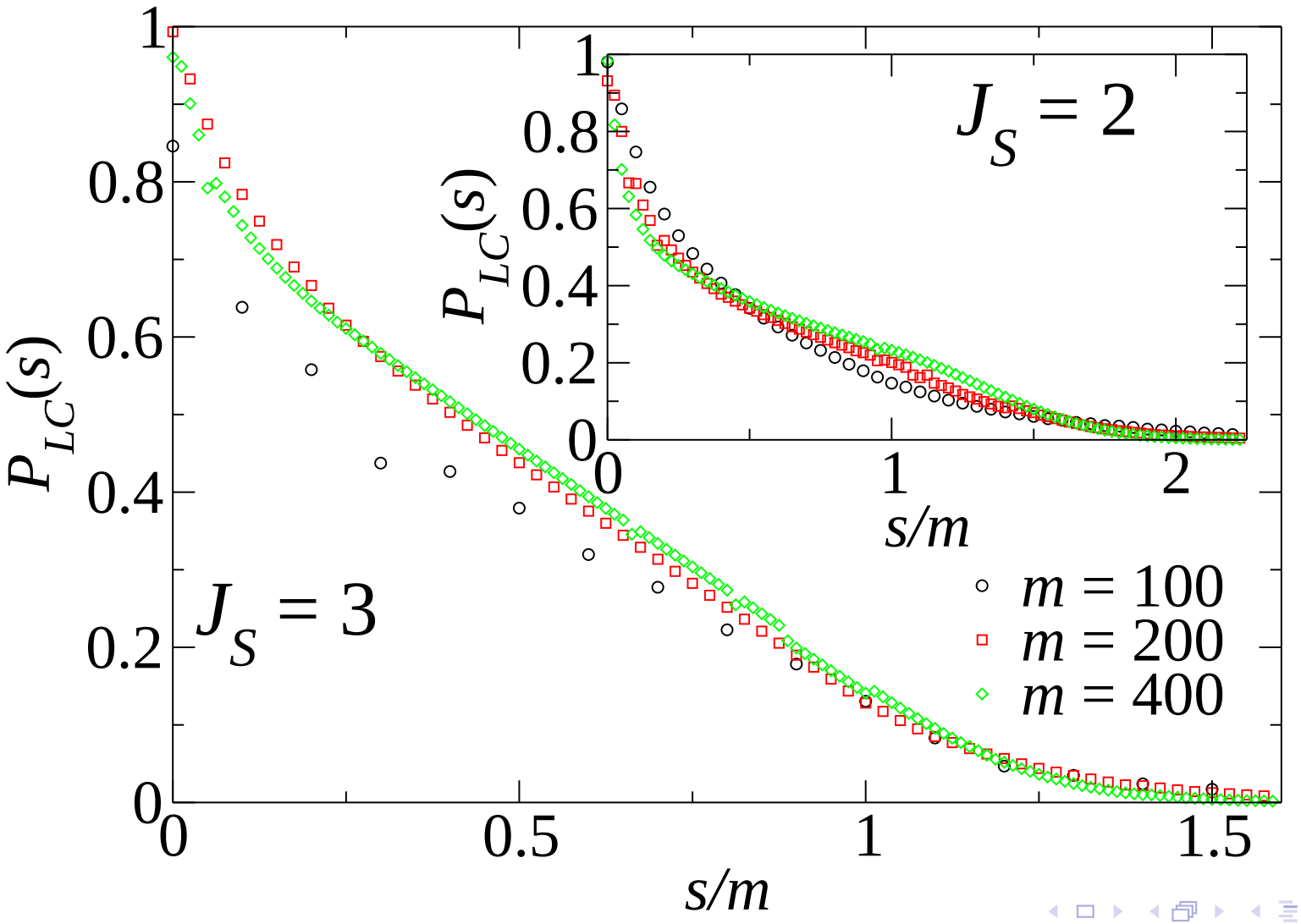
(For a cluster with 400 proteins)



ChIP-Seq of ParB on F-plasmid of *Escherichia coli* : Sanchez *et al.* Stochastic self-assembly of ParB proteins builds the bacterial DNA segregation apparatus. Cell systems, 1(2), 163-173.

Functional shape

- $m = 100, 200, 400$ and $J_S = 2, 3$



Summary and outlook

- Protein-DNA complexes important for DNA organization: e.g. the ParB-DNA in ParAB*S* segregation mechanism
- The LC model
  - Statistical physics approach $\rightarrow$ easy to interpret analytic results
  - Parameter range not accessible by previous models
  - Connects two limits ($J_S \rightarrow \infty$ and $J_S = 0$) investigated in preceding studies resolving the apparent contradiction between these previous models
  - Good agreement with experimental data
  - Predicts $J_S \approx 1\,kT$ and $m \approx 400$
- Open questions and future developments:
  - How do protein interactions affect the 3D structure and mobility of the ParB-DNA cluster?
  - Include exclusion volume effects: loop-loop & loop-DNA filament outside the cluster
  - Experiments: how does the conformation (compaction, size, form) of the protein-DNA cluster change by varying number of ParB proteins and/or number of *parS* sites?
  - Interpret and analyze ChIP-Seq and fluorescence data of other ParB-like protein-DNA complexes on chromosomes and plasmids

SCPN
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Super-resolution microscopy

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Walter, J. C., Dorignac, J., Lorman, V., Rech, J., Bouet, J. Y., Nollmann, M., Palmeri, J., Parmeggiani A. & Geniet, F. (2017). Surfing on protein waves: proteophoresis as a mechanism for bacterial genome partitioning. Physical Review Letters 119(2), 028101.


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Sanchez, A., Cattoni, D. I., Walter, J. C., Rech, J., Parmeggiani, A., Nollmann, M., & Bouet, J. Y. (2015). Stochastic self-assembly of ParB proteins builds the bacterial DNA segregation apparatus. Cell systems, 1(2), 163-173.


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