Looping and Clustering: a statistical physics approach to protein-DNA complexes in bacteria

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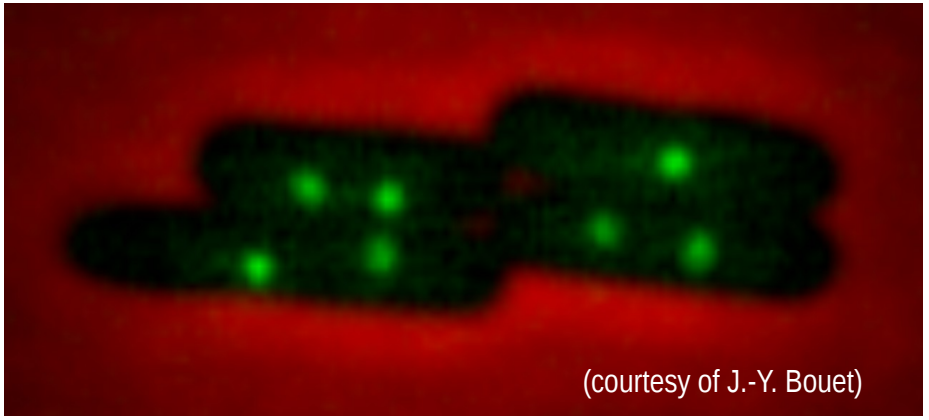
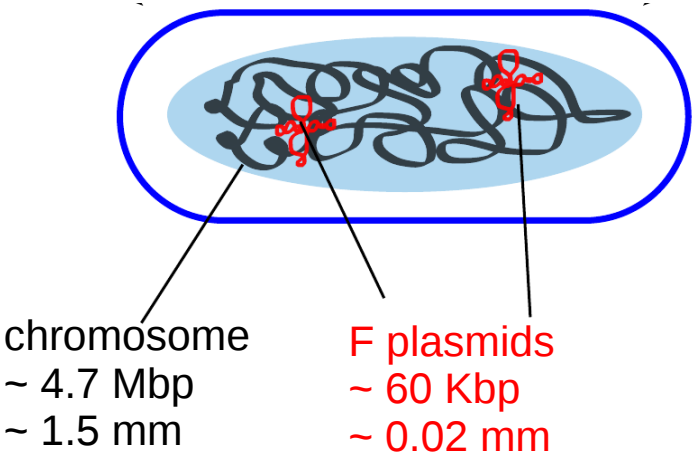
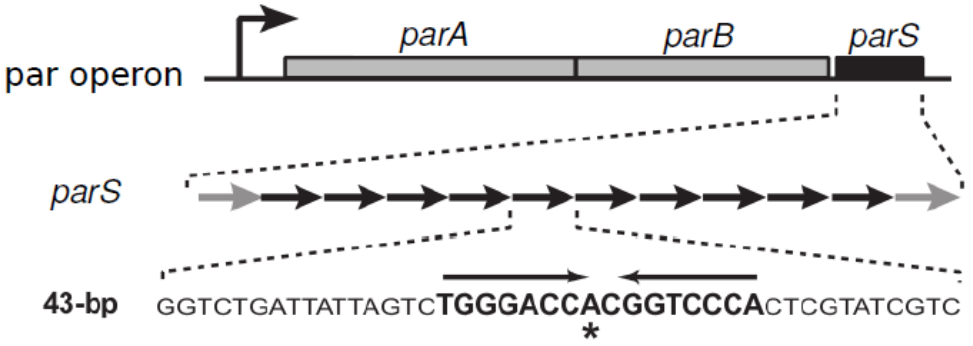


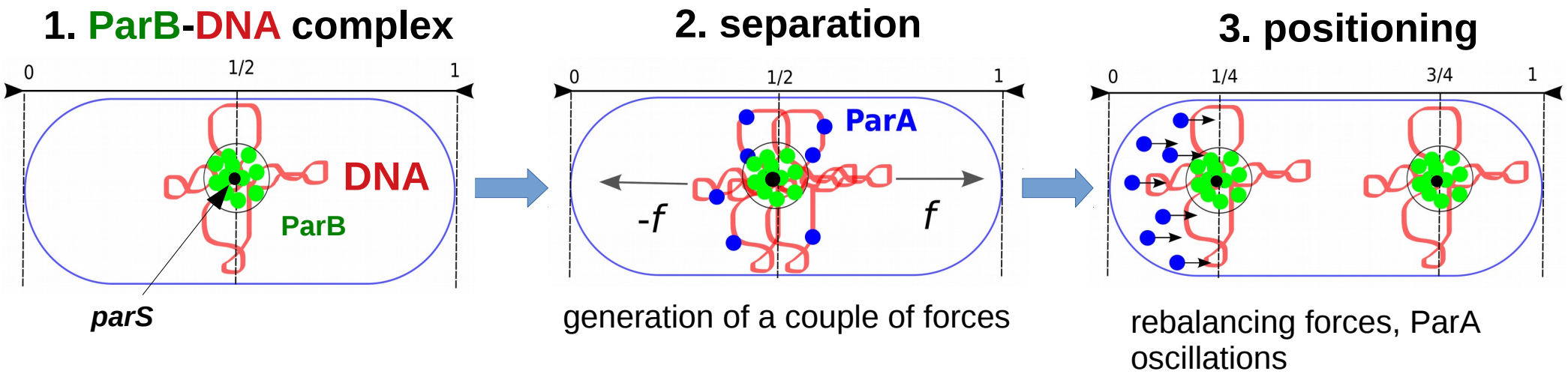
Walter J.-C., NOW, David G., Dorignac J., Geniet F., Palmeri J., Parmeggiani A., Wingreen N. & Broedersz C. (2018). *Looping and Clustering model for the organization of partitioning proteins on the bacterial genome*. New J . Phys., 20(3), 035002.

ParABS machinery actively segregates plasmid F in *E. coli*





- **ParA** : « motor protein » (ATPase Walker-type: non-equilibrium component)
- **ParB** : binding protein (specific or non-specific binding)
- ***parS*** : centromere-like DNA sequence (specific binding site for ParB)

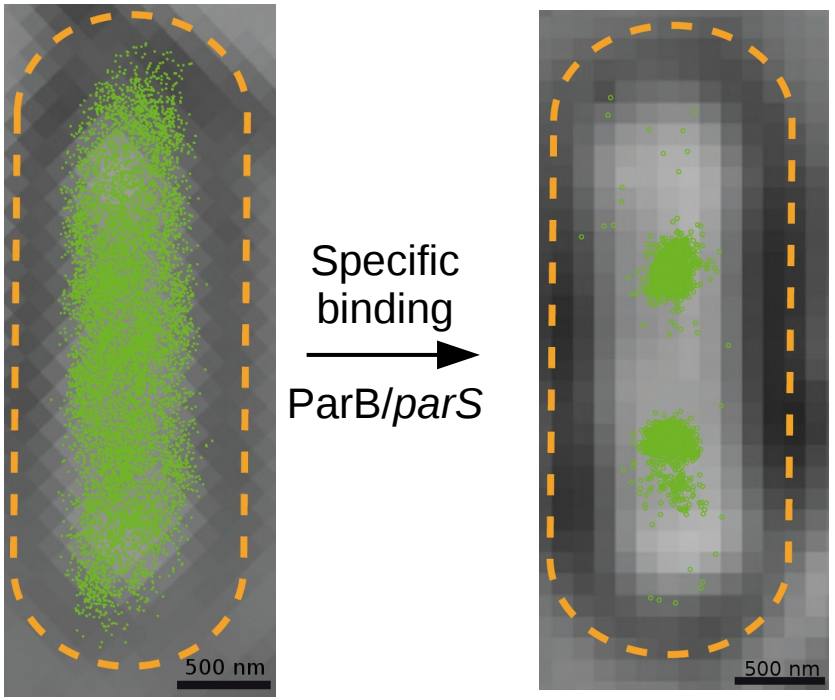


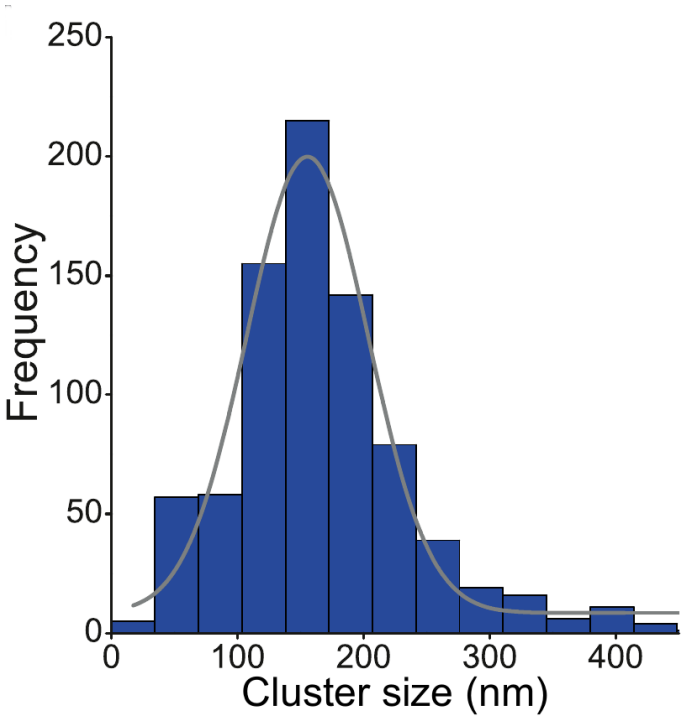
parS induces highly confined ParB clusters at defined locations

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

- D. Cattoni, A. Le Gall, M. Nollmann (Centre de Biochimie Structurale, Montpellier)

[Sanchez *et al.* 2015]



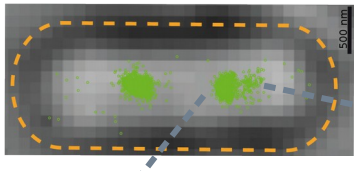


- Focus diameter 150 ± 20 nm
- Number of ParB dimers in a focus $\approx$ 300
- Most of the ParB in the cell (> 90 %) is located in the foci

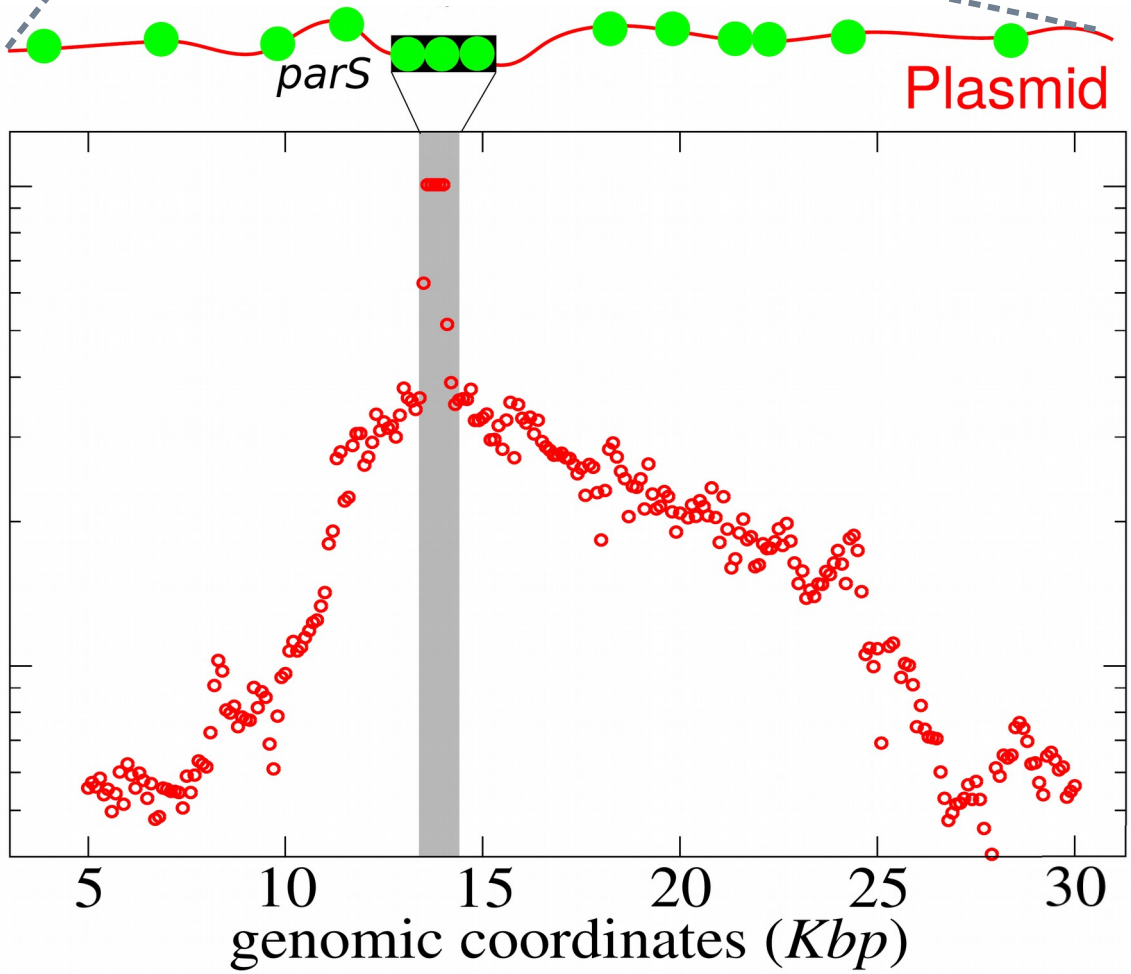
ParB binds over a large region of centromere-flanking DNA

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

- R. Diaz, A. Sanchez, J.-Y. Bouet (Laboratoire de Microbiologie et Génétique Moleculaire, Toulouse)



[Sanchez *et al.* 2015]

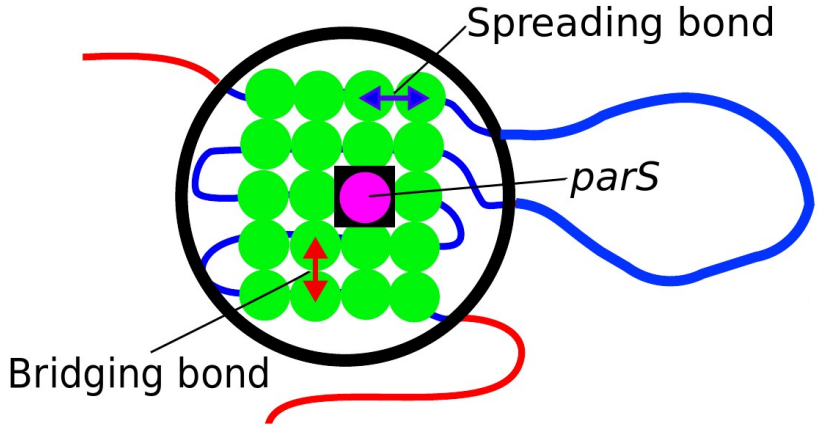


- Density profile of ParB proteins for one cluster in the vicinity of the specific binding site *parS*
- ParB always bind at *parS*
- The protein density decreases with the distance from *parS*
- The profile is about 30 kpb wide

Spreading and Bridging interactions are necessary to form condensed ParB-DNA complexes

Modelling of the DNA:

- **Linear self-avoiding chain** on a cubic lattice along which **proteins** can bind, unbind, **diffuse** and **interact** with each other.
- *Minimal model* for condensation of ParB-DNA complex requires two types of interactions between bound proteins [Broedersz *et al.* 2014]



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

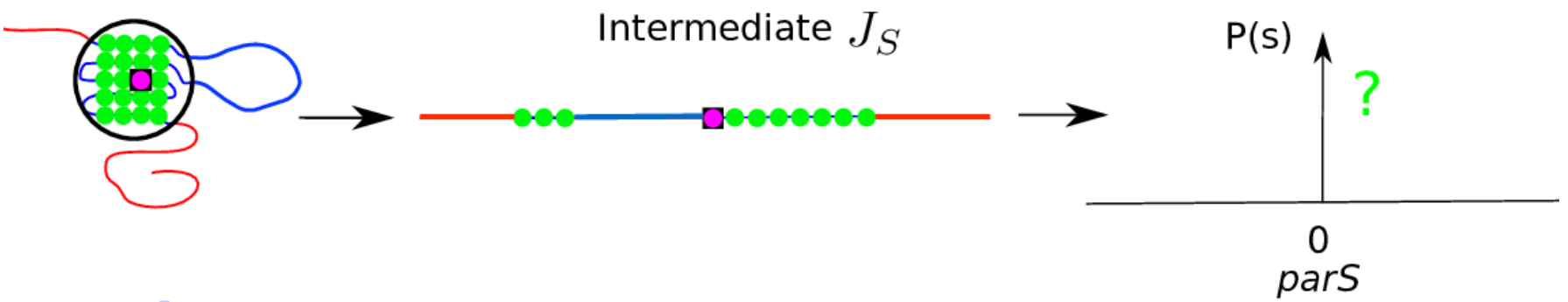
The *Looping and Clustering* model combines polymer and statistical physics to yield analytical results

Simplifying assumptions:

- All bridging bonds satisfied: $J_B >> J_S \rightarrow$ cluster
- Loops can extrude from cluster by breaking spreading bonds
- The complex has a fixed number of proteins *m*

The main idea:

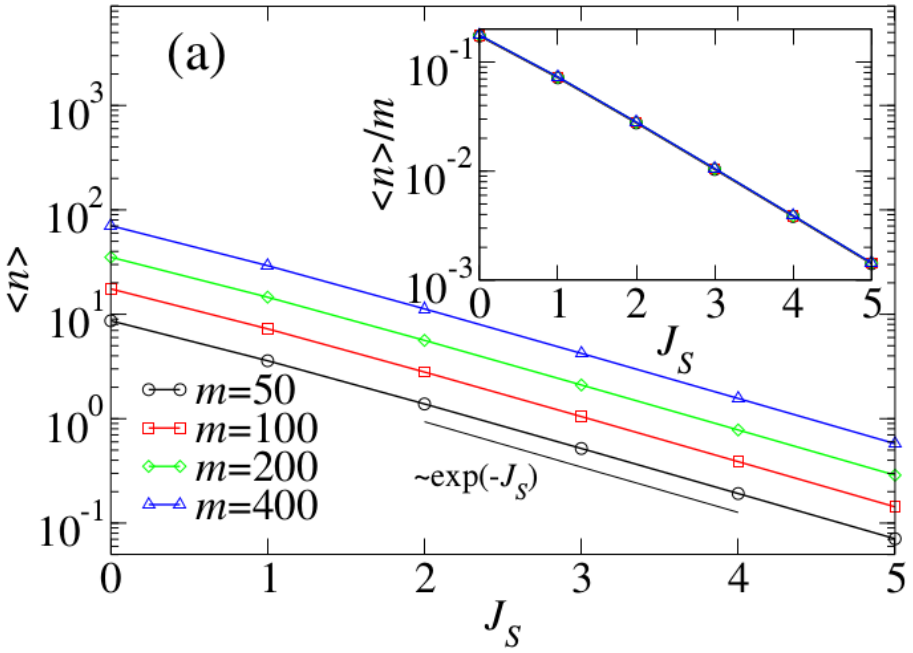
- Study the loop statistics in the regime of strong bridging interactions to infer the distribution *P(s)* of ParB proteins along the DNA.



Competing effects:

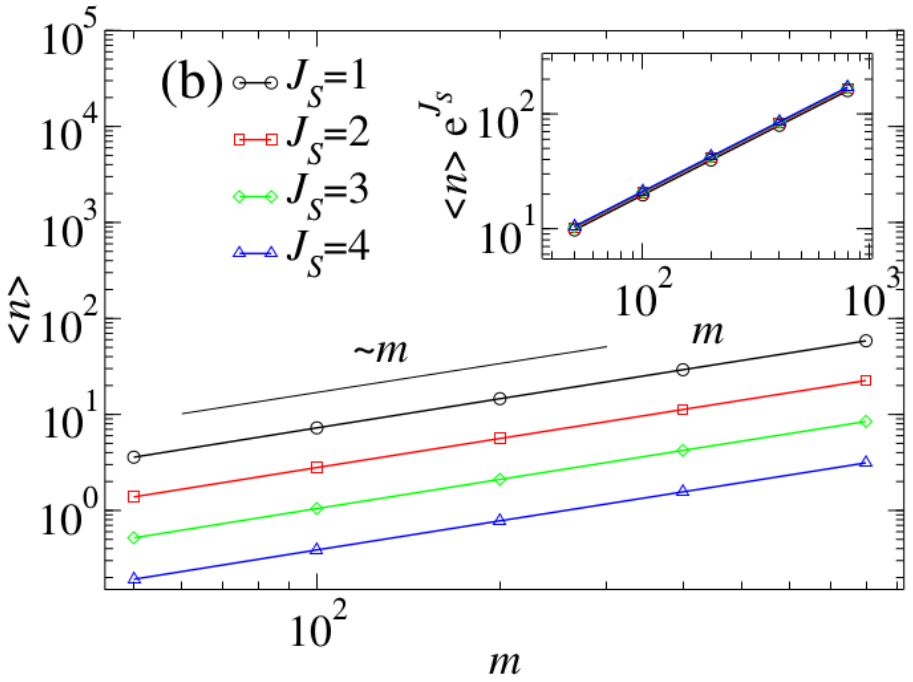
- the costs of ***generating loops***: break spreding bonds + loop closure entropy
- the ***positional entropy*** associated with placing loops on the cluster

Loops form and disappear continuously: J_s controls their formation



Average number of loops as a function of J_s

- Exponential decrease: $\langle n \rangle \propto \mathrm{e}^{-J_S}$
- Inset: same data with dependence of average loop number on *m* scaled out



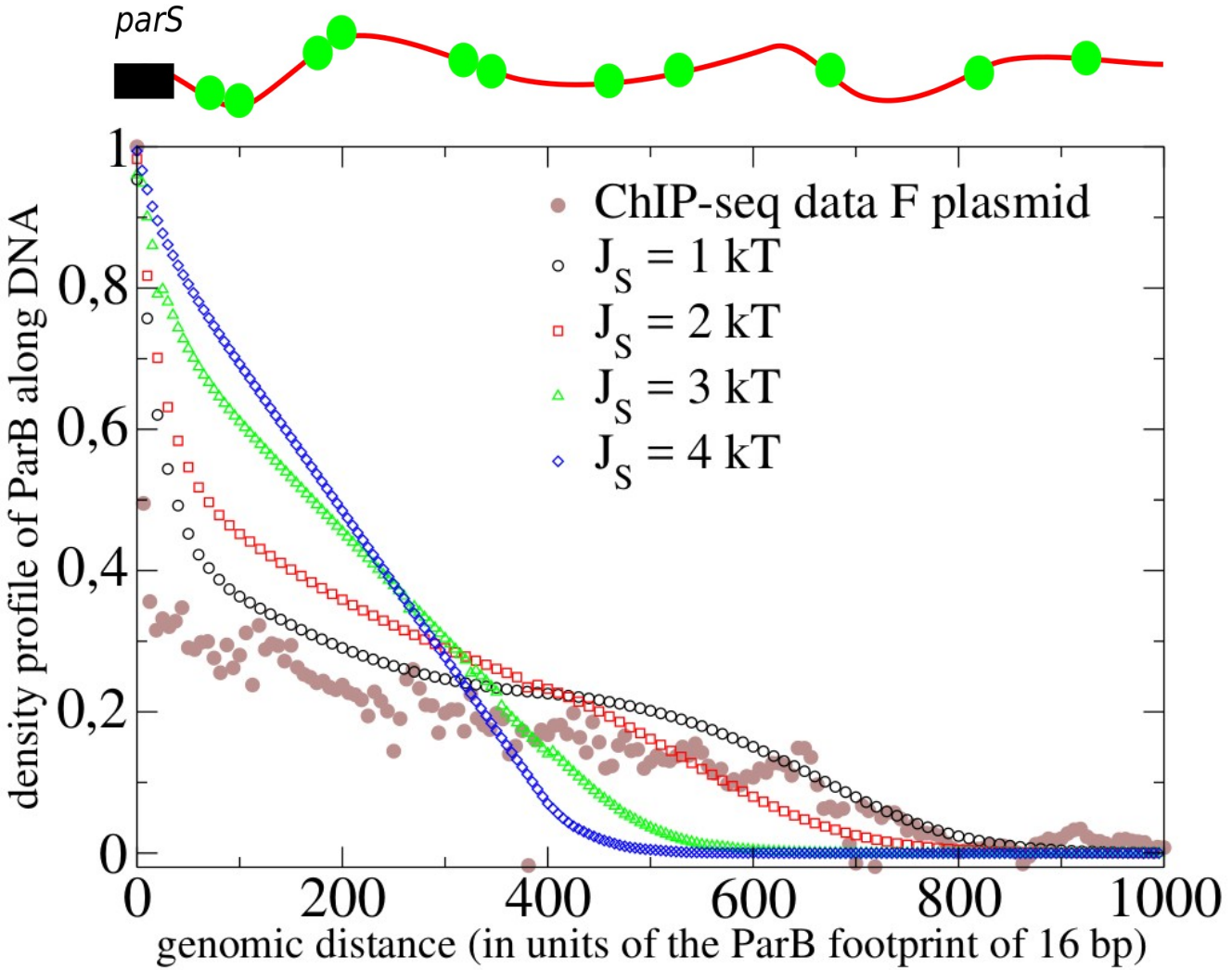
Average number of loops as a function of *m*

- Linear dependence on *m*
- Inset: the vertical shift between the curves scales with e^{-J_S}

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

LC model: predicted binding profile broadens as the interaction strength decreases

Binding profiles of ParB *vs* genomic distance to parS
(for a cluster with m = 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

Conclusions and perspectives

- Looping and Clustering combines statistical and polymer physics
  - Simplifying assumptions on *Spreading and Bridging interactions* → accessible semi-analytical model → 2 main parameters: J_s and m
  - Parameter range not accessible by previous models: $J_S \sim kT$
  - Connects two previously studied limits: $J_s >> kT$ and $J_s \to 0$
  - Good agreement with ChIP-seq data
  - Predicts $J_s \sim 1$ kT and $m \sim 400$

Perspectives:

- What does happen by changing the expression of ParB proteins?
- *parS* is an extended nucleation region (~140 nm linear length)
- Account for the biomolecular structure of ParB dimers → unstructured protein regions
- ParB-DNA complexes are dynamical
- What role do ParA play in the formation/stabilization of ParB-DNA clusters?

SCPN:

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Super-resolution microscopy

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Molecular biology

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