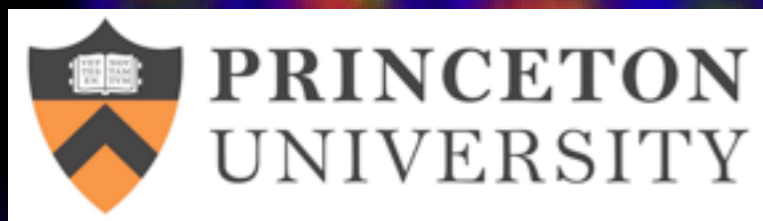


# Organizing the bacterial chromosome for division

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Chase Broedersz



Lewis-Sigler Institute for  
Integrative Genomics

Ned Wingreen    Princeton University

Xindan Wang, Joseph Loparo, and David Rudner    Harvard Medical School

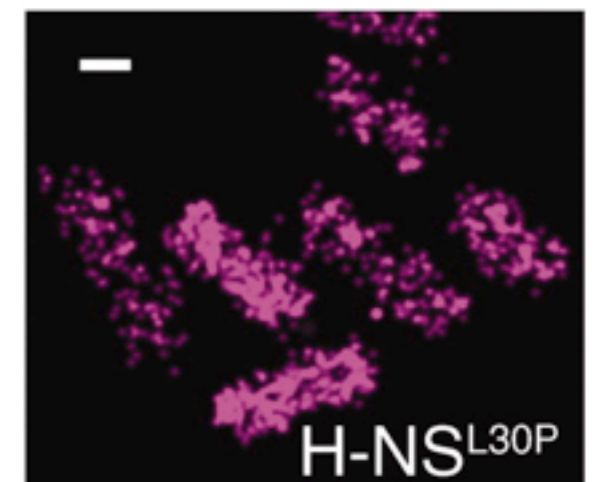
Yigal Meir    Ben Gurion University

# Organization of the Bacterial Chromosome

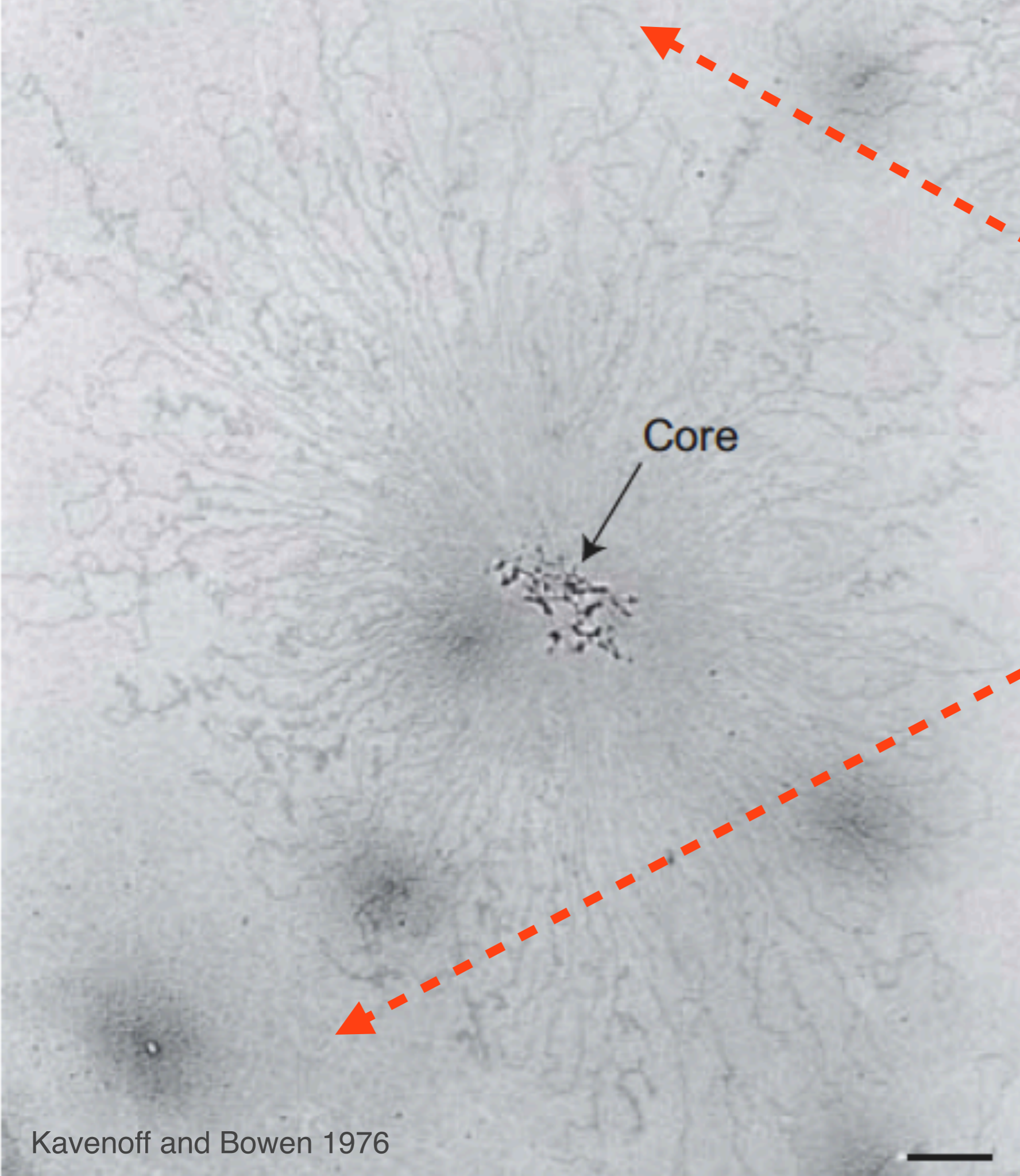
*E. coli*



**Nucleoid Associated Proteins**

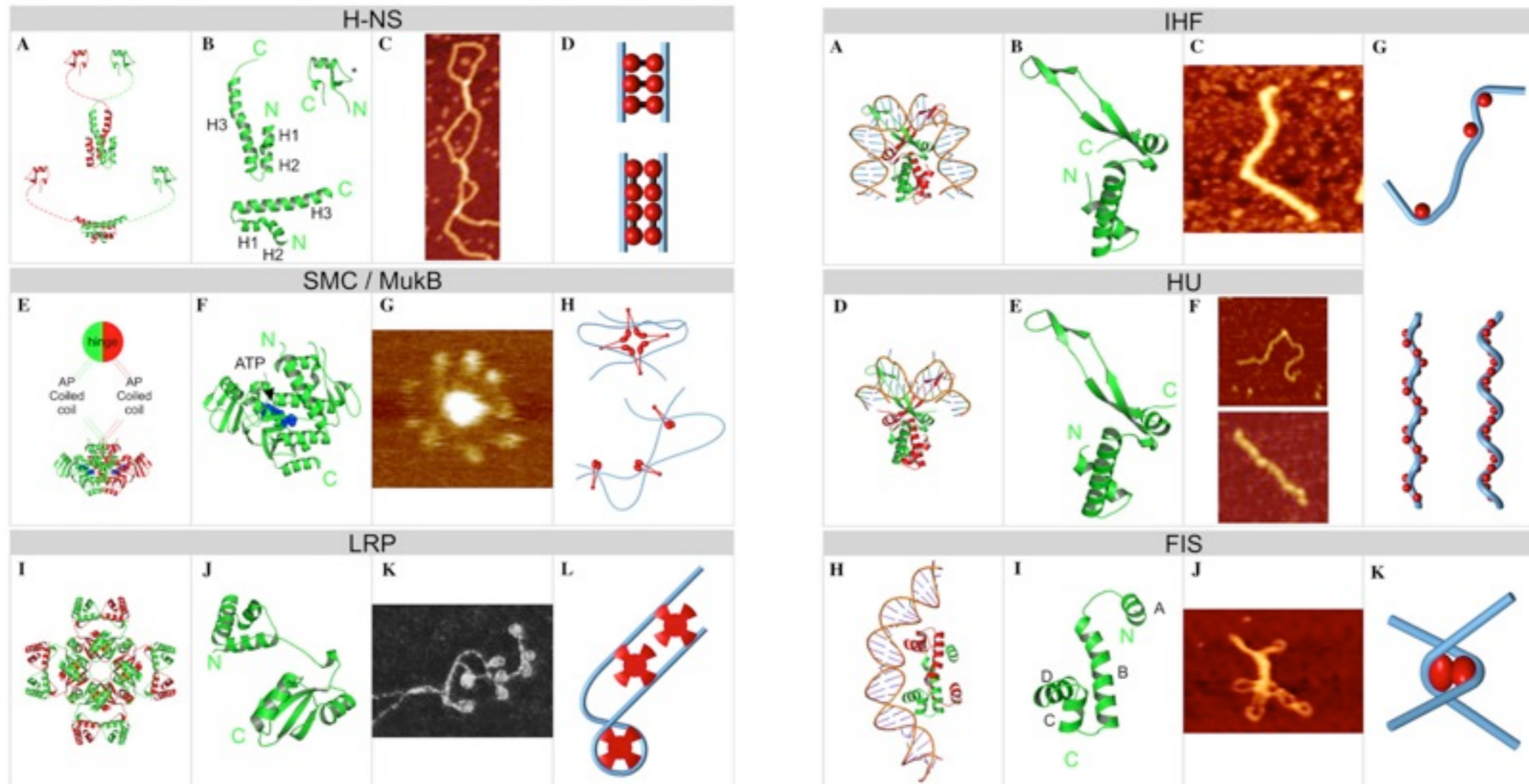


Wang et al. Science (2011)



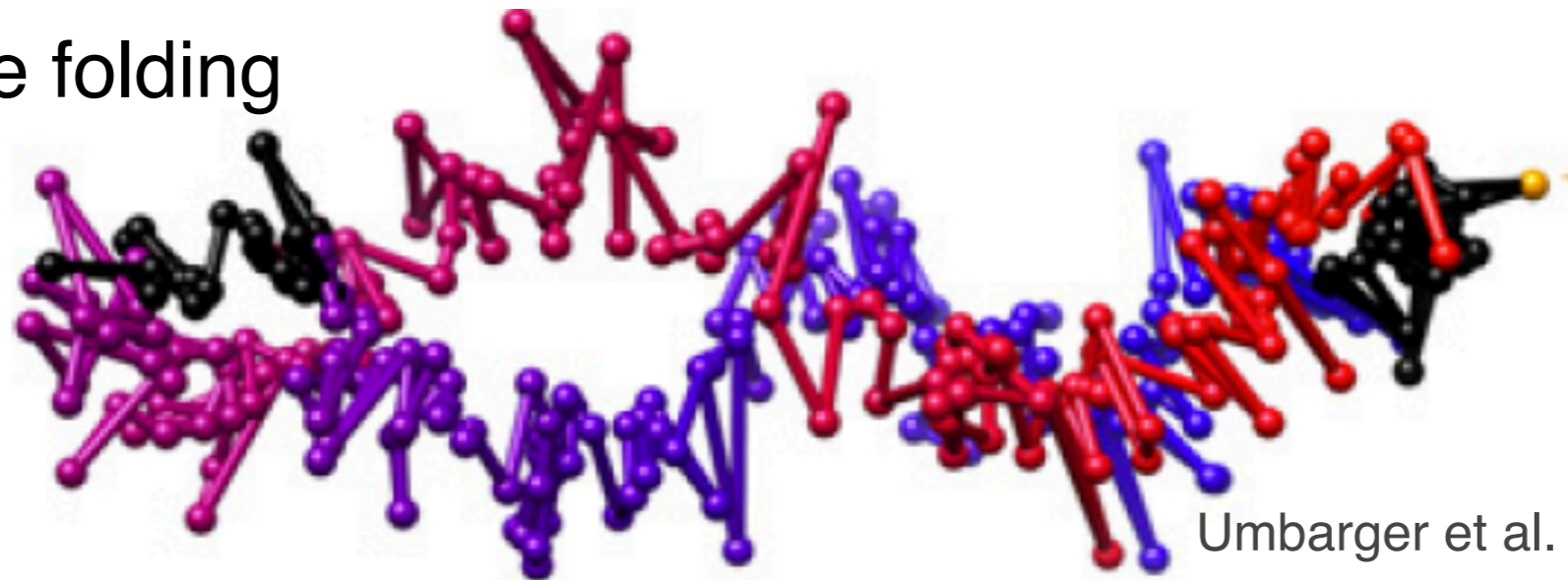
Kavenoff and Bowen 1976

# Chromosomal organization: Nucleoid-associated proteins



Luijsterburg et al.  
Journal of Structural Biology (2006)

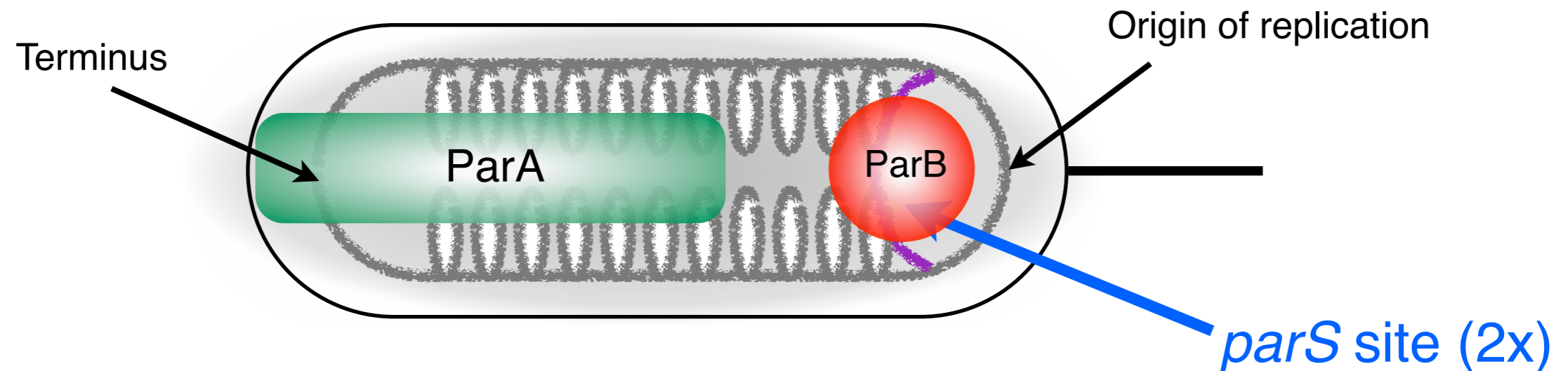
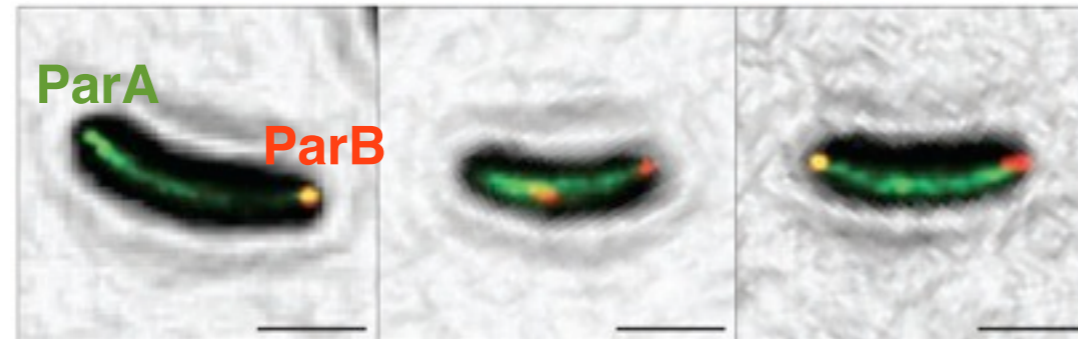
## Whole-genome folding



Umbarger et al. Molecular Cell (2011)  
Le et al. Science (2013)

# Segregation machinery in *Caulobacter crescentus*: ParABS system

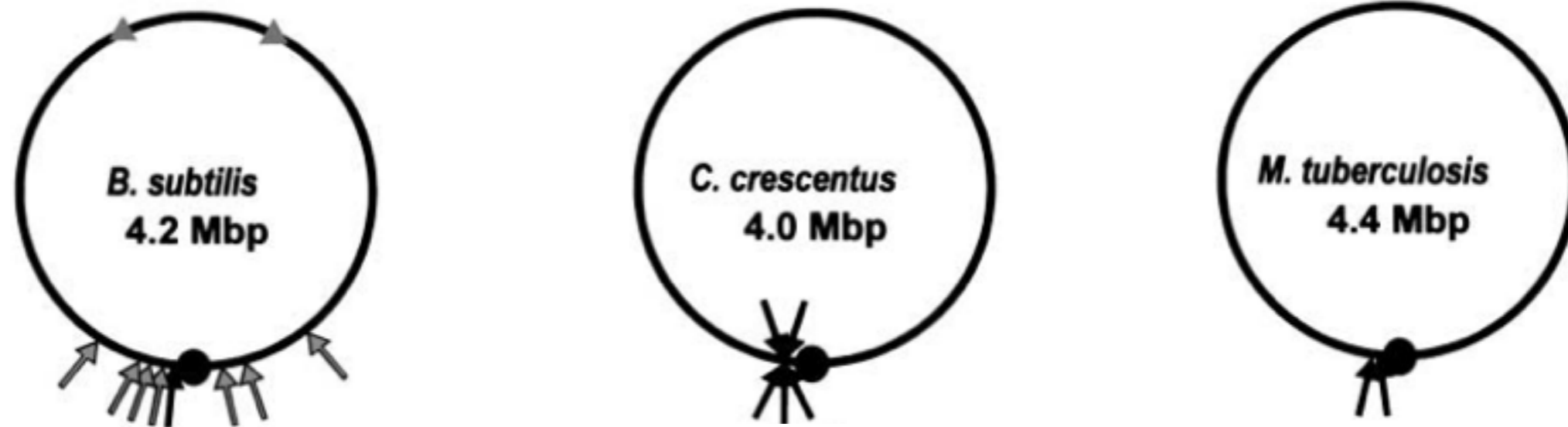
The ParB-DNA complex is translocated by binding & retraction of ParA spindle-like structure



Ptacin et al. Nature Cell Biology (2010)  
Banigan et al. PLOS COMPUT BIOL (2011)  
Shebelut et al. PNAS (2010)

- How are ~1000 parB proteins **localized** on the DNA?
- What's the **structure** of the partitioning complex?
- What's the nature of ParB-ParB **interactions**?
- What controls the **formation** of the ParB partitioning complex?

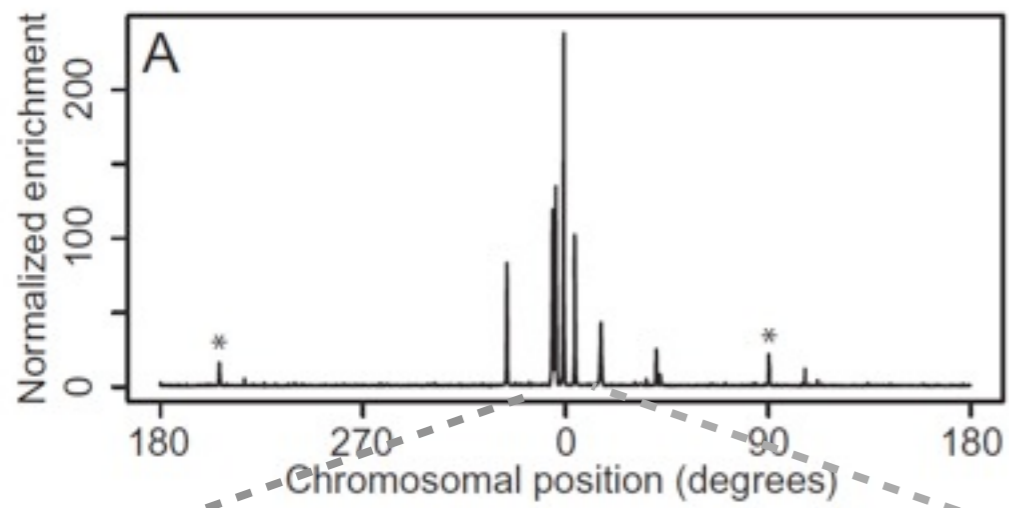
Number of *parS* motifs ranges from 1 in *B. burgdorferi* to 24 in *S. coelicolor*



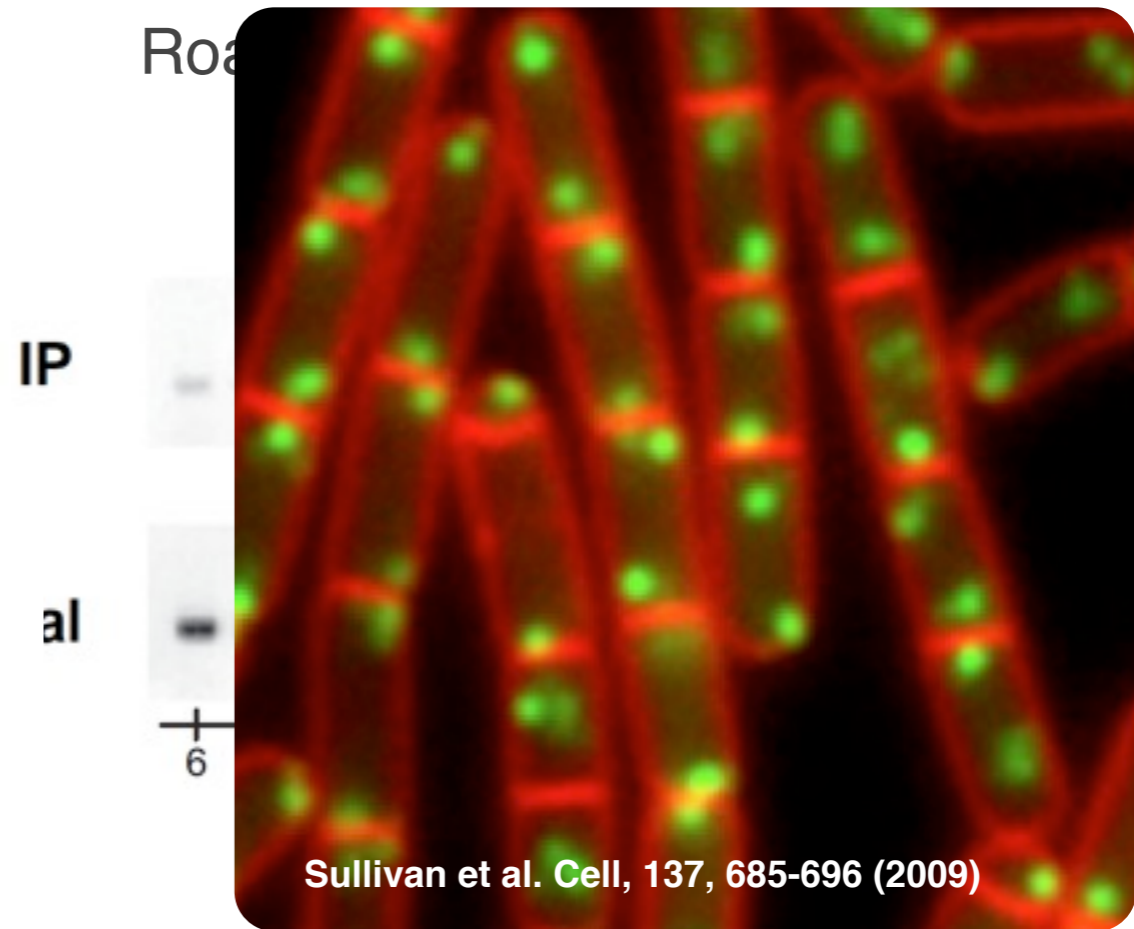
ParB<sub>2</sub> (Spo0J<sub>2</sub>) can bind DNA both specifically and nonspecifically

Lin and Grossman, Cell (1998)  
Jakimowicz et al., Molecular Microbiology (2002)  
Breier and Grossman, Molecular Microbiology (2007)

# ParB clusters around *parS* centromere-like sites in *B. subtilis*



Breier and Grossman, Molecular Microbiology (2007)



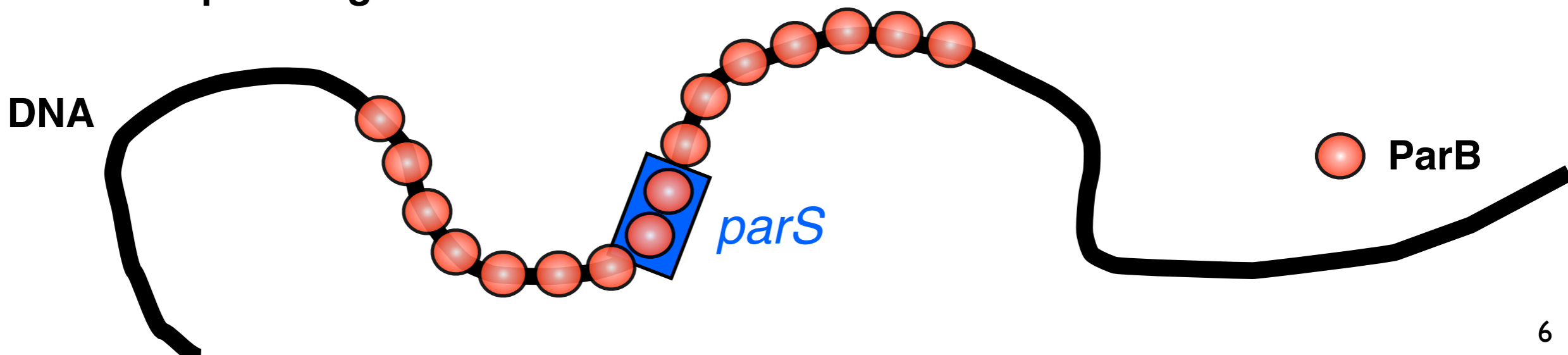
Murray et al., Molecular Microbiology (2006)

Rodionov et al. Science (1999)

Leonard et al. Mol. Microbiol. (2004)

## What's the structure of the ParB-DNA complex?

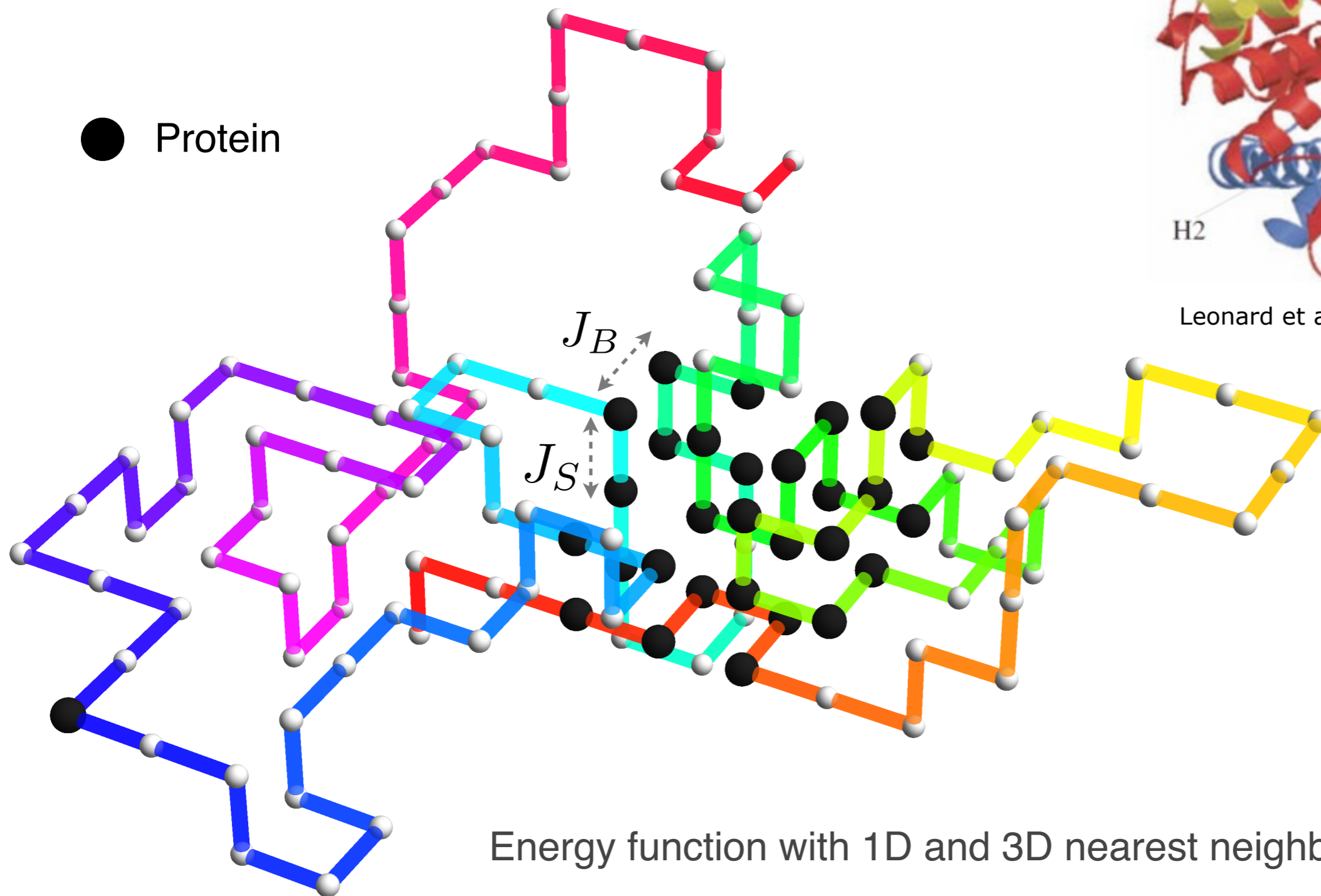
### Nucleofilament: spreading model



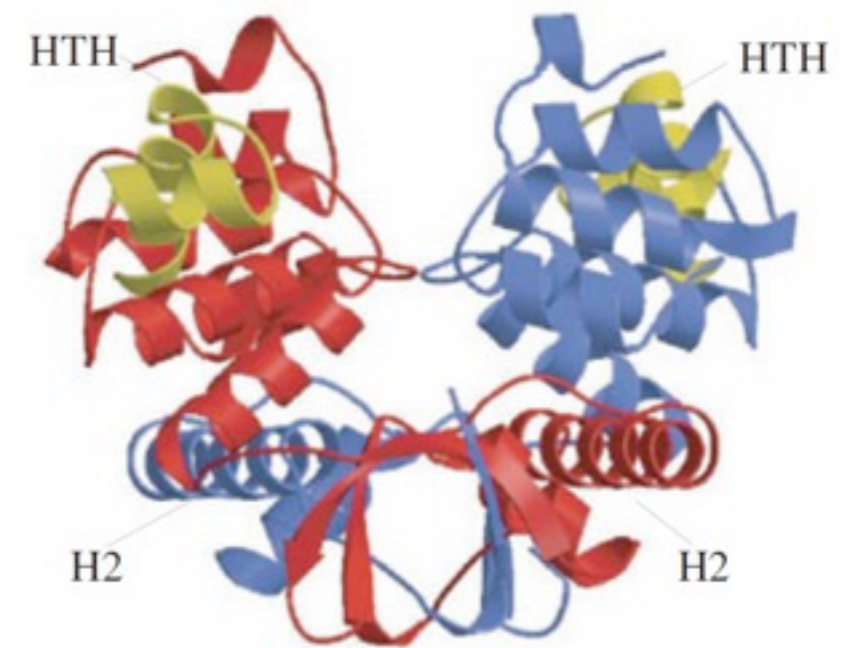
# Minimal model for DNA-bound proteins

1D and 3D protein-protein interactions on a self-avoiding polymer

● Protein



## ParB structure



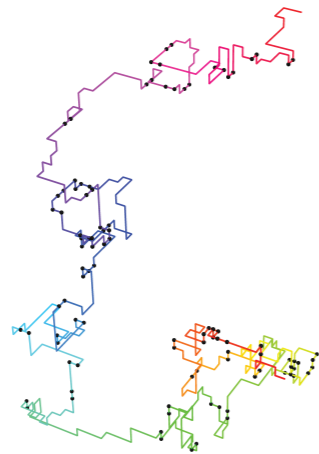
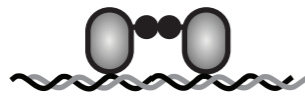
Leonard et al. Mol. Microbiol. (2004)

Energy function with 1D and 3D nearest neighbor interactions

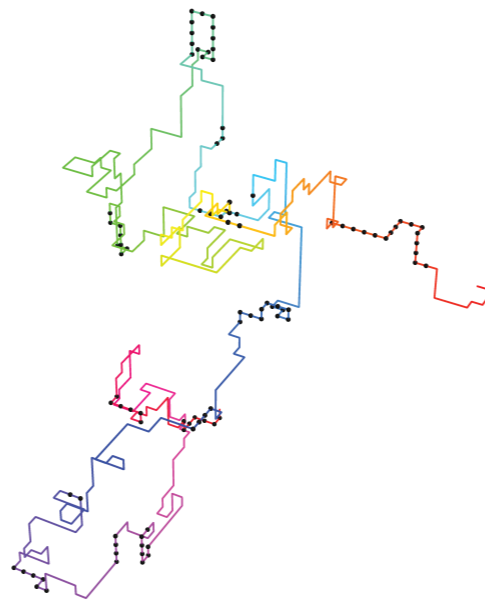
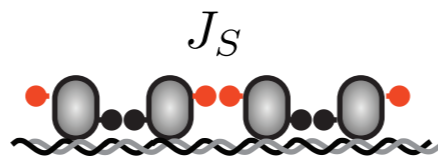
$$H_{\text{int}} = J_S \sum_{i=1}^{N-1} \phi_i \phi_{i+1} + \frac{J_B}{2} \sum_{|i-j|>1} \phi_i \phi_j \delta_{|\mathbf{r}_i - \mathbf{r}_j|, 1} + \sum_{i=1}^N \epsilon_i \phi_i.$$

# Searching for a minimal model

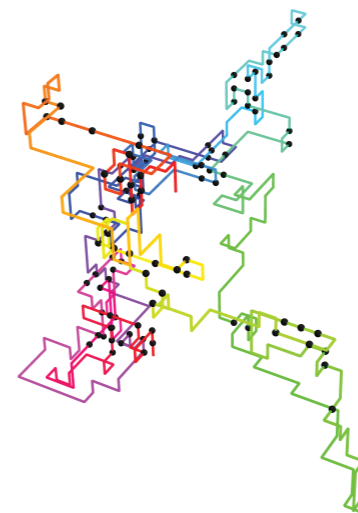
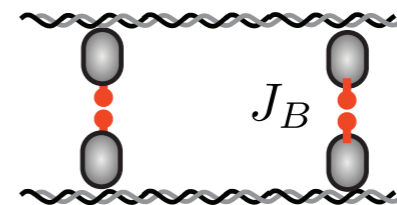
**Dimer model**



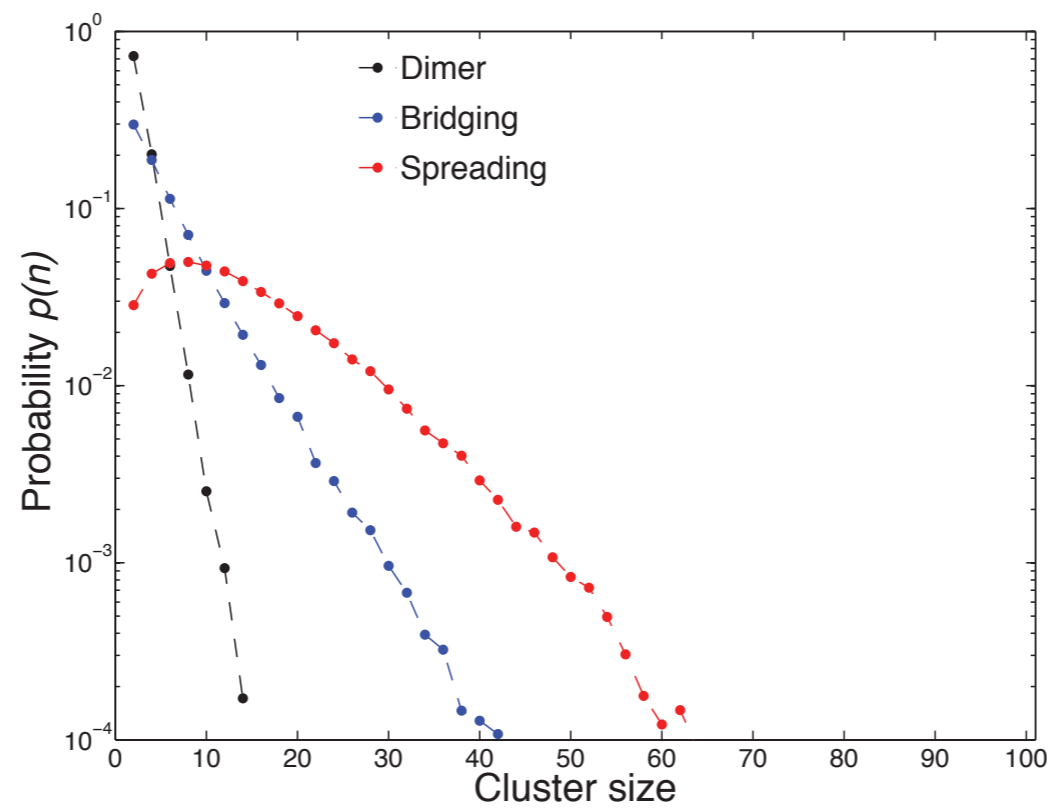
**Spreading model**



**Bridging model**



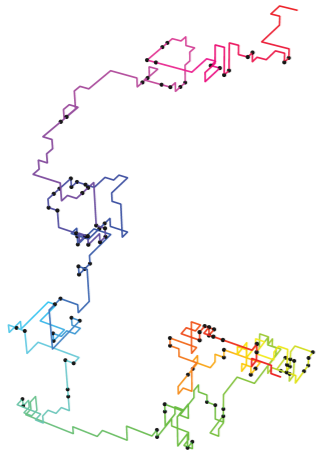
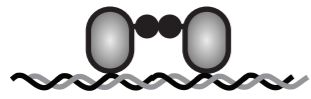
**Cluster size distribution**



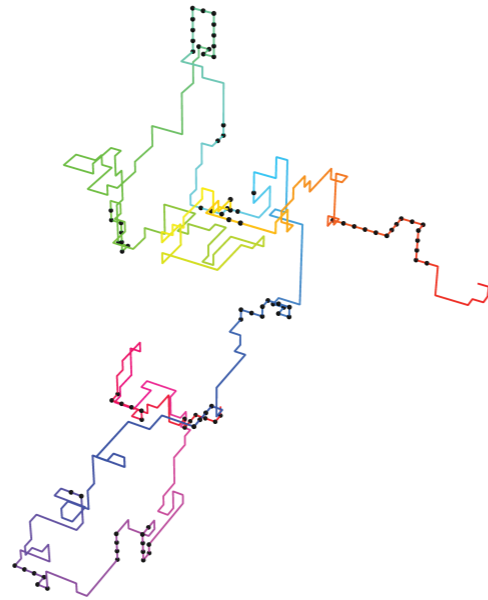


# Searching for a minimal model

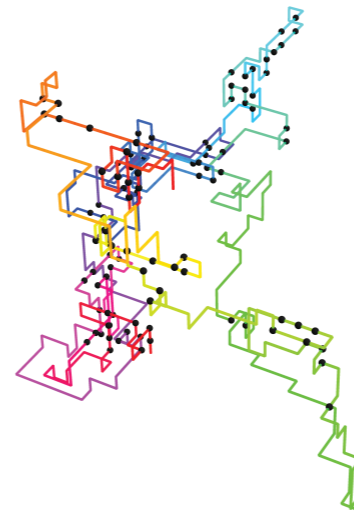
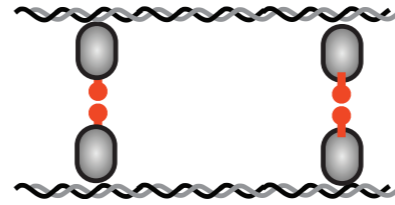
## Dimer model



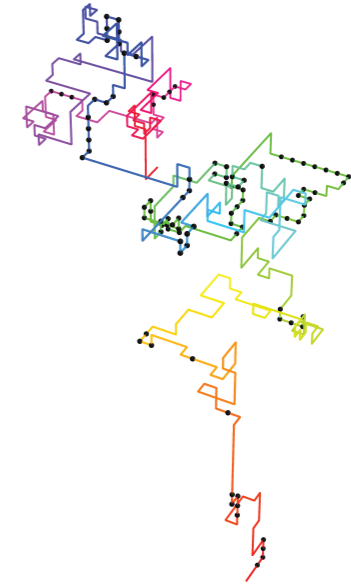
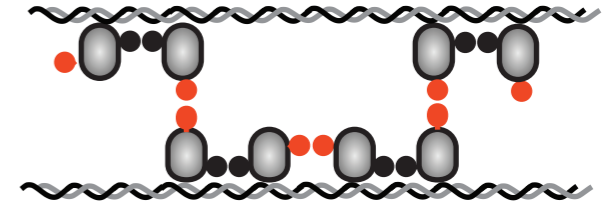
## Spreading model



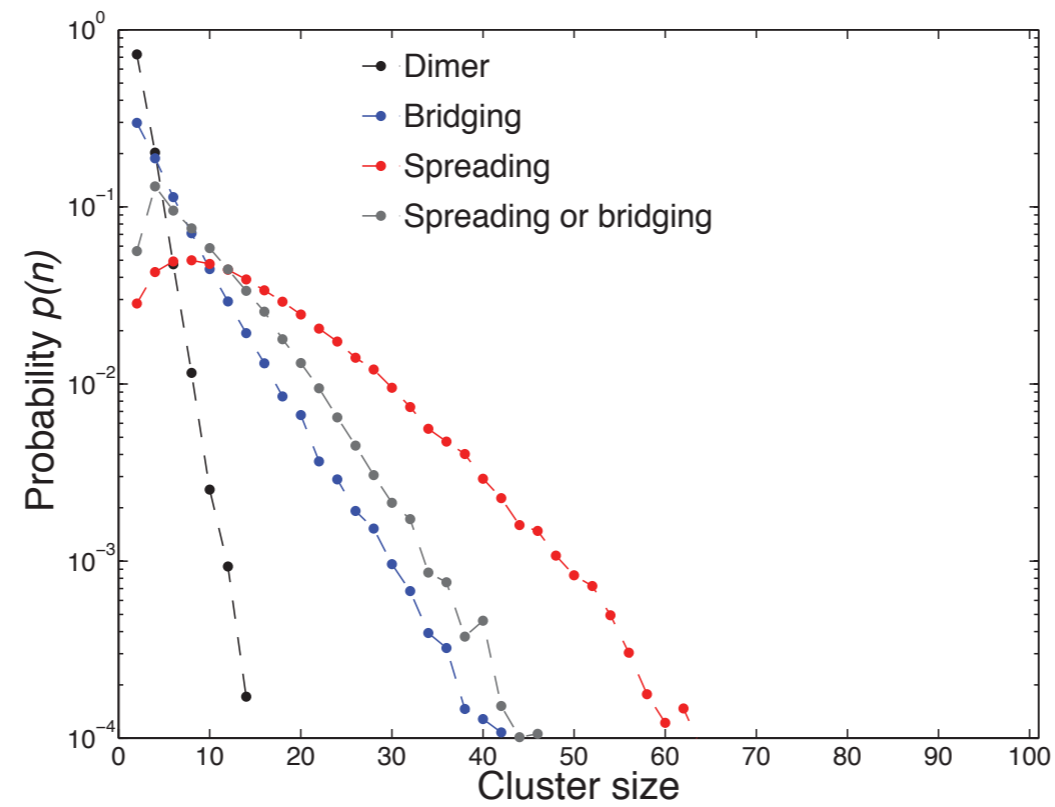
## Bridging model



## Spreading//Bridging model

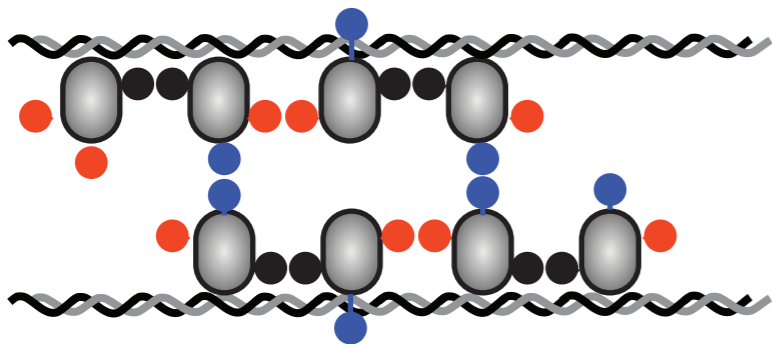


## Cluster size distribution

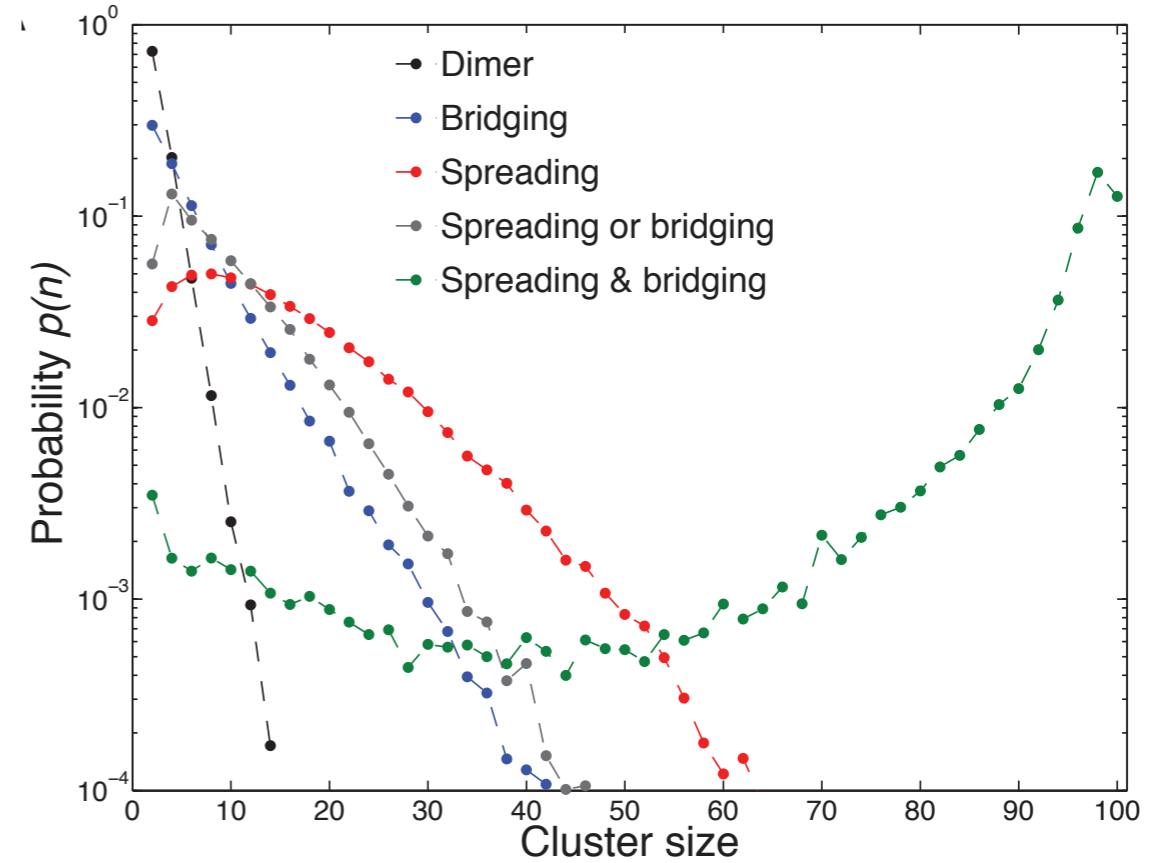


# Surface tension in **Spreading & Bridging model** condenses ParB-DNA complex

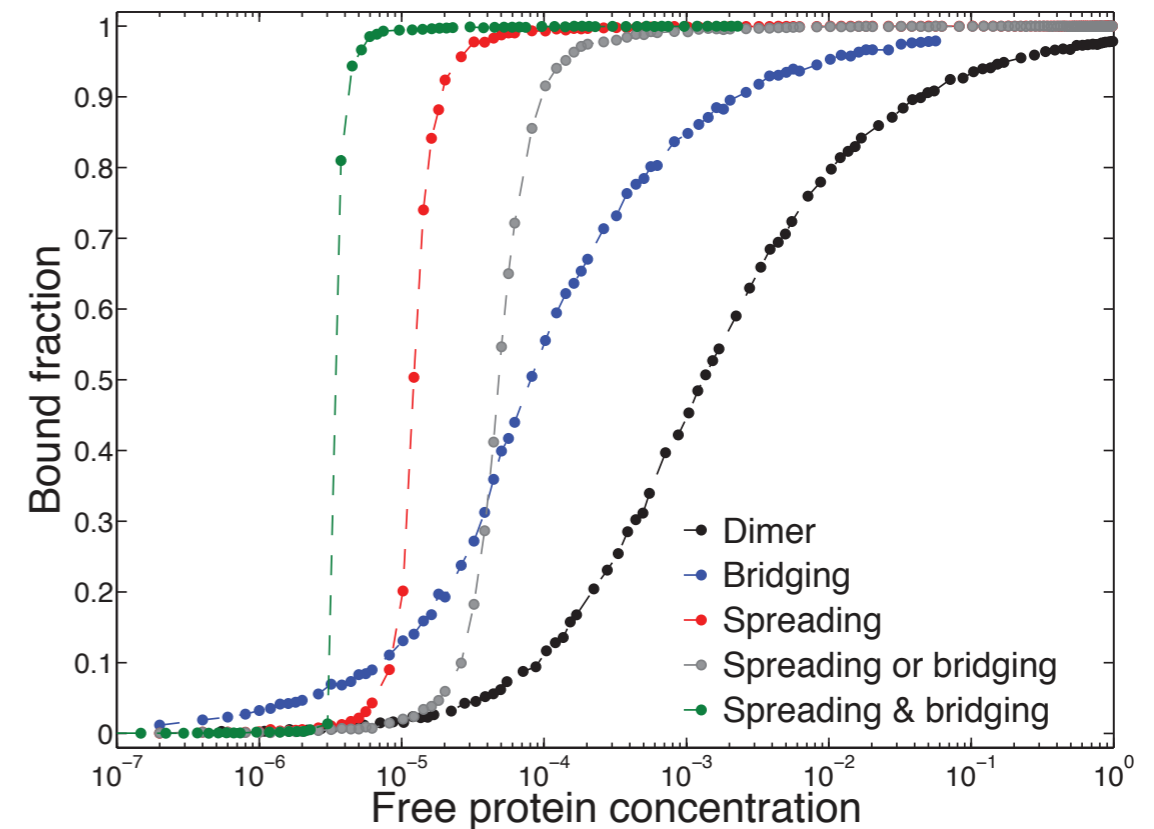
## Spreading & Bridging model



## Cluster size distribution



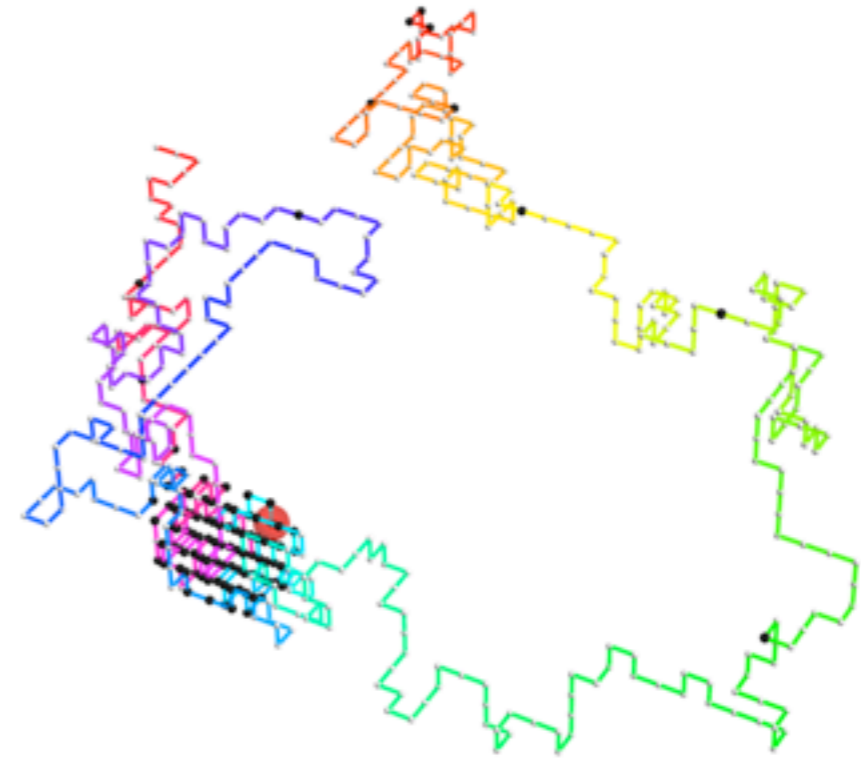
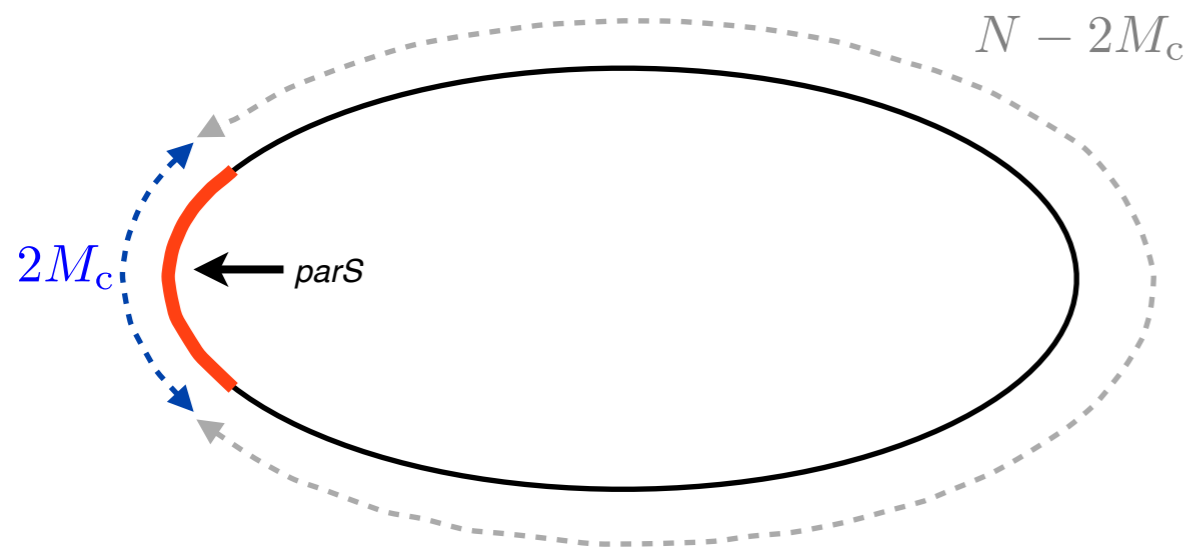
## Binding isotherms



# Can a *parS* localize the ParB-DNA complex?

Condensation is essential for localization

## The cost of localization



$$\Delta\epsilon_{parS} < k_B T \log \left( \frac{2M_c}{N - 2M_c} \right)$$

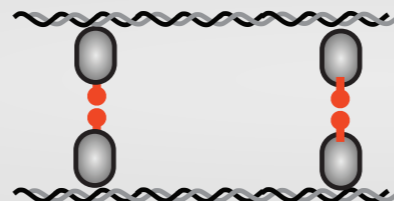
### Dimer



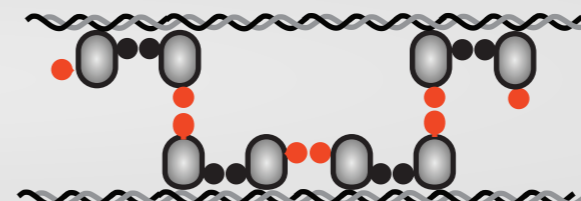
### Spreading



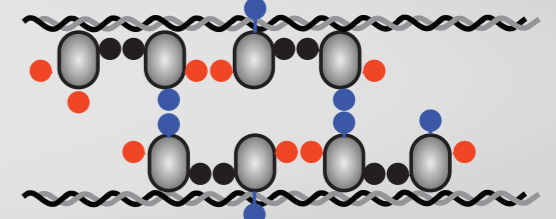
### Bridging



### Spreading//Bridging

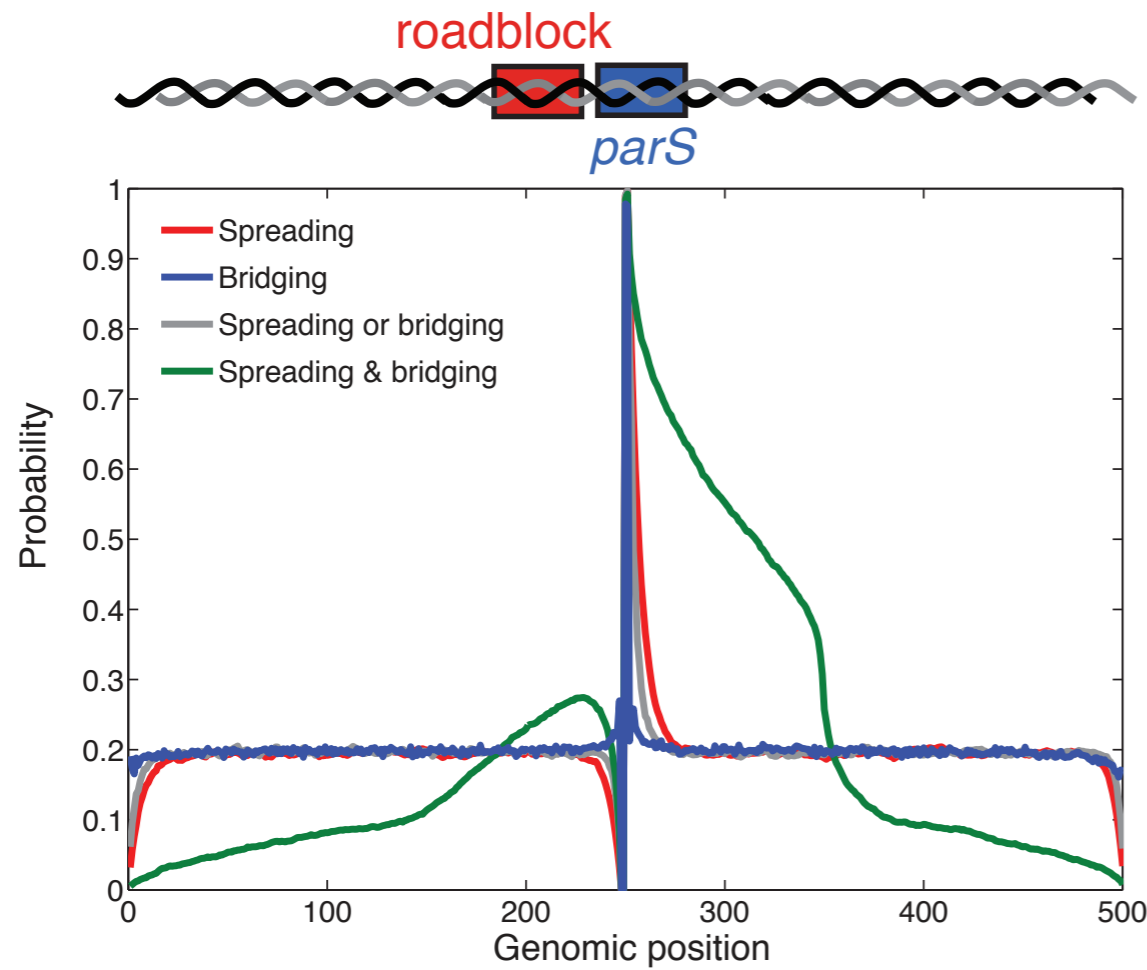


### Spreading & Bridging

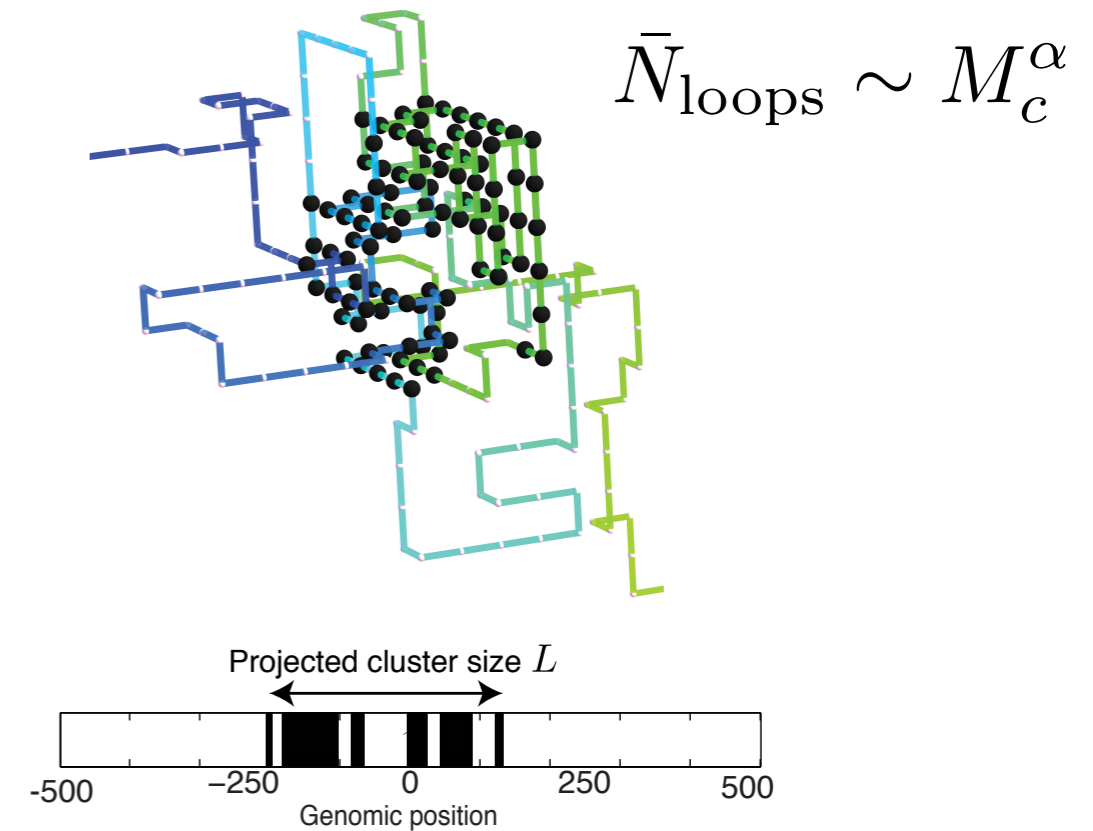


# Can the ParB-DNA complex bypass a “roadblock” by looping?

Murray et al., Molecular Microbiology (2006)



## Loop trapping



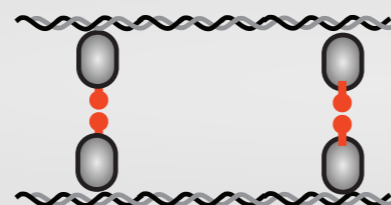
### Dimer



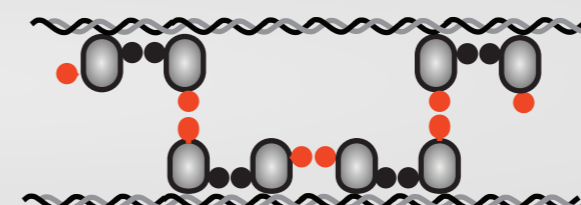
### Spreading



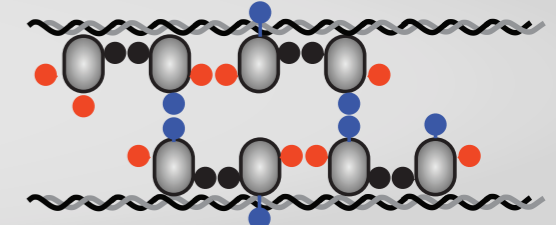
### Bridging



### Spreading//Bridging

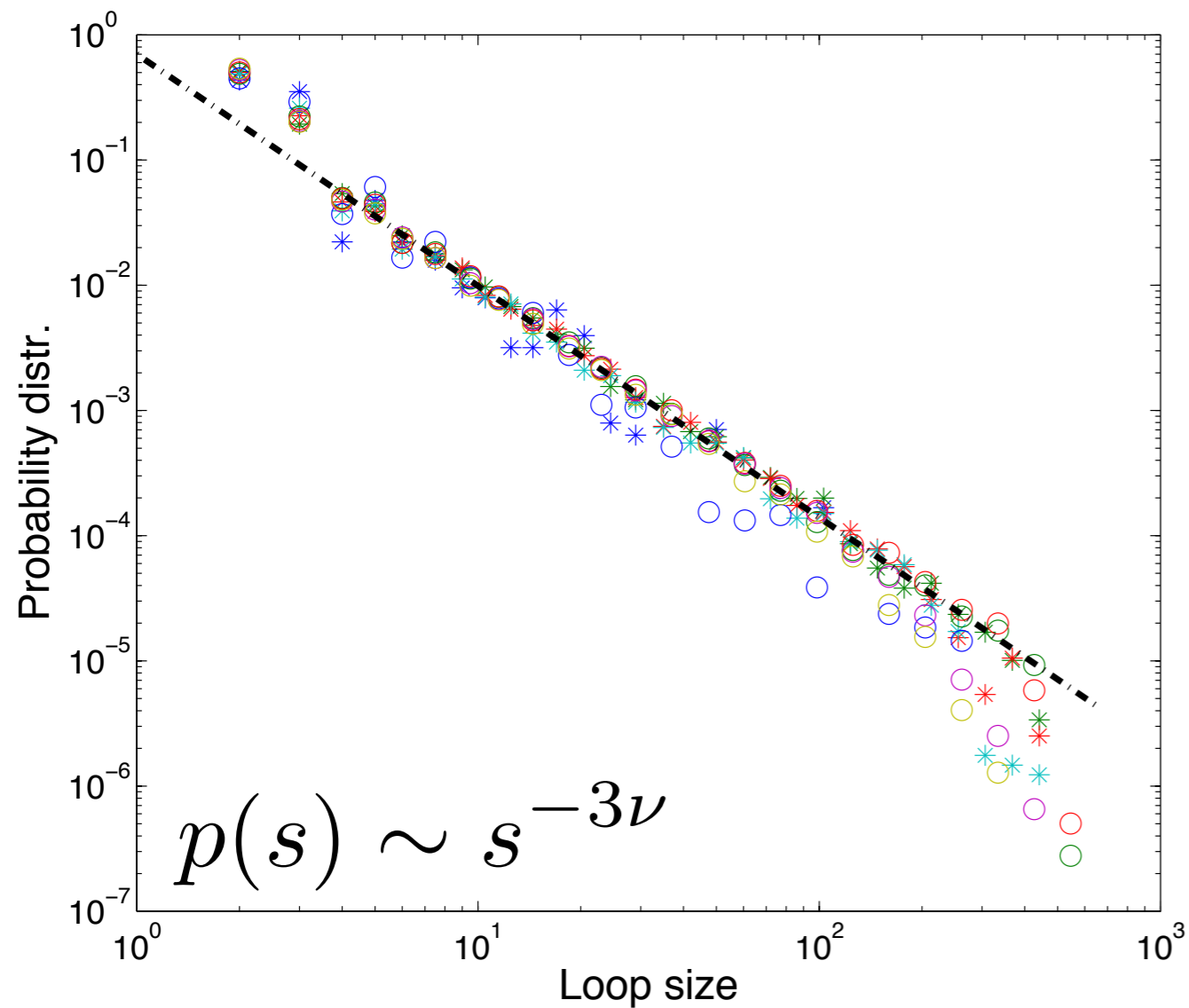


### Spreading & Bridging

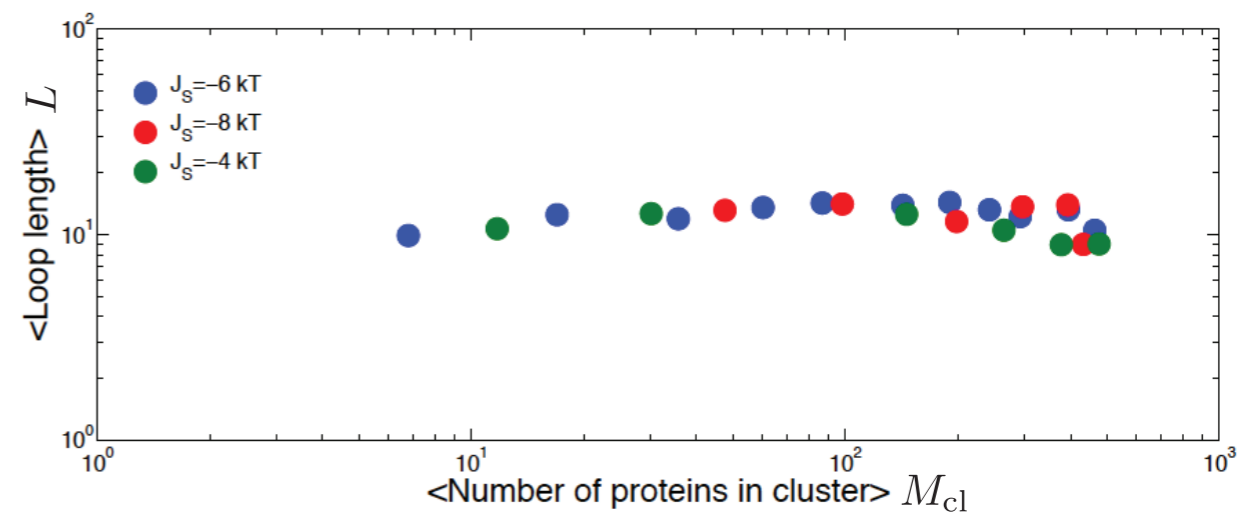


# The statistics of DNA looping

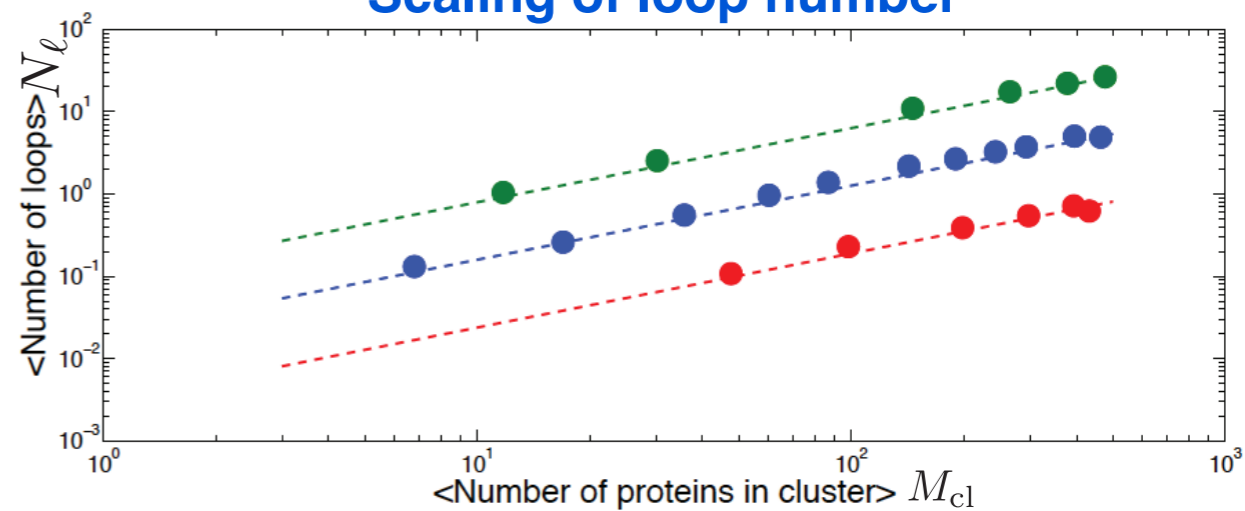
## Universal loop size distribution



## Constant average loop size

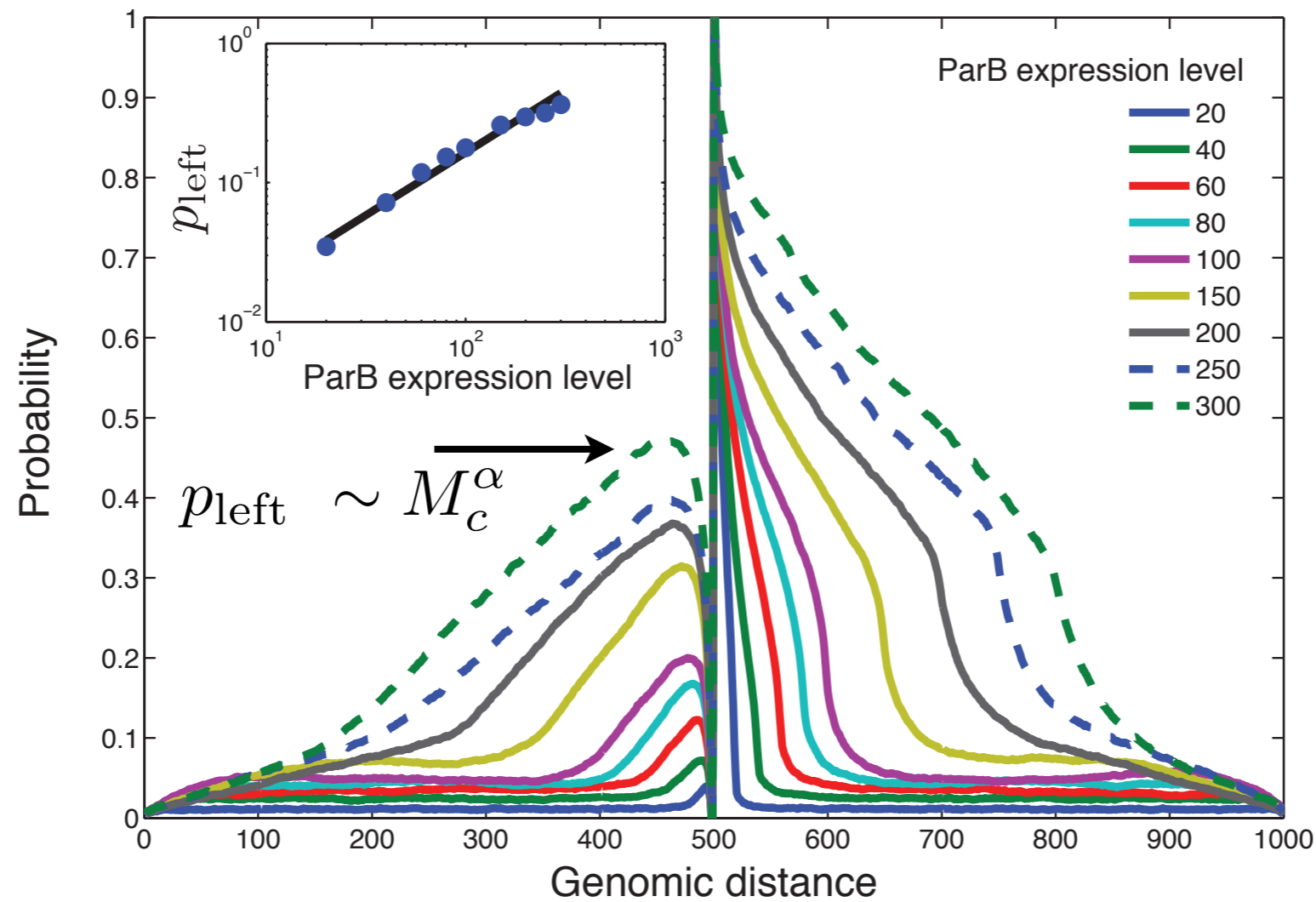
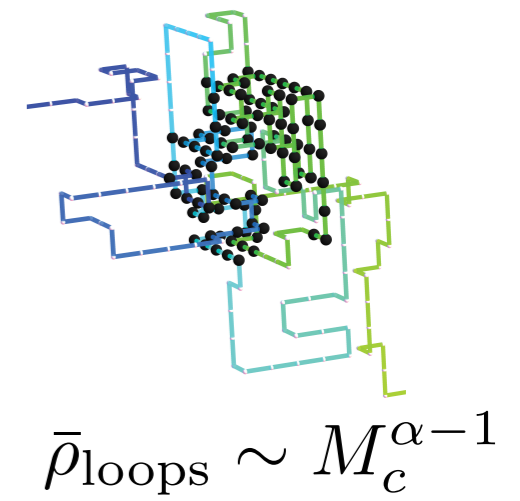
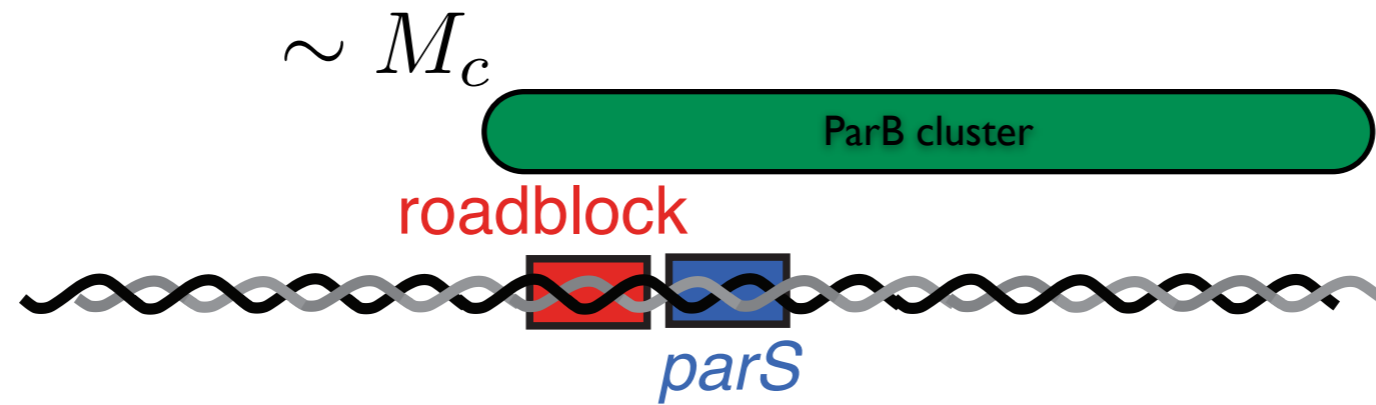


## Scaling of loop number

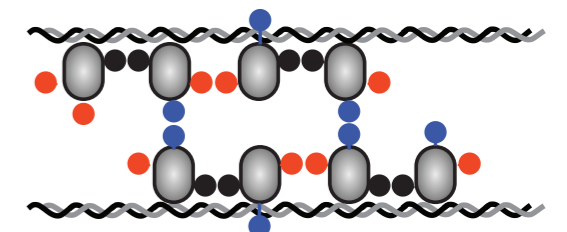


$$N_{\text{loops}} \sim \exp(-J_s/k_B T) M_c^\alpha$$

# Can the ParB-DNA complex bypass a “roadblock” by looping?

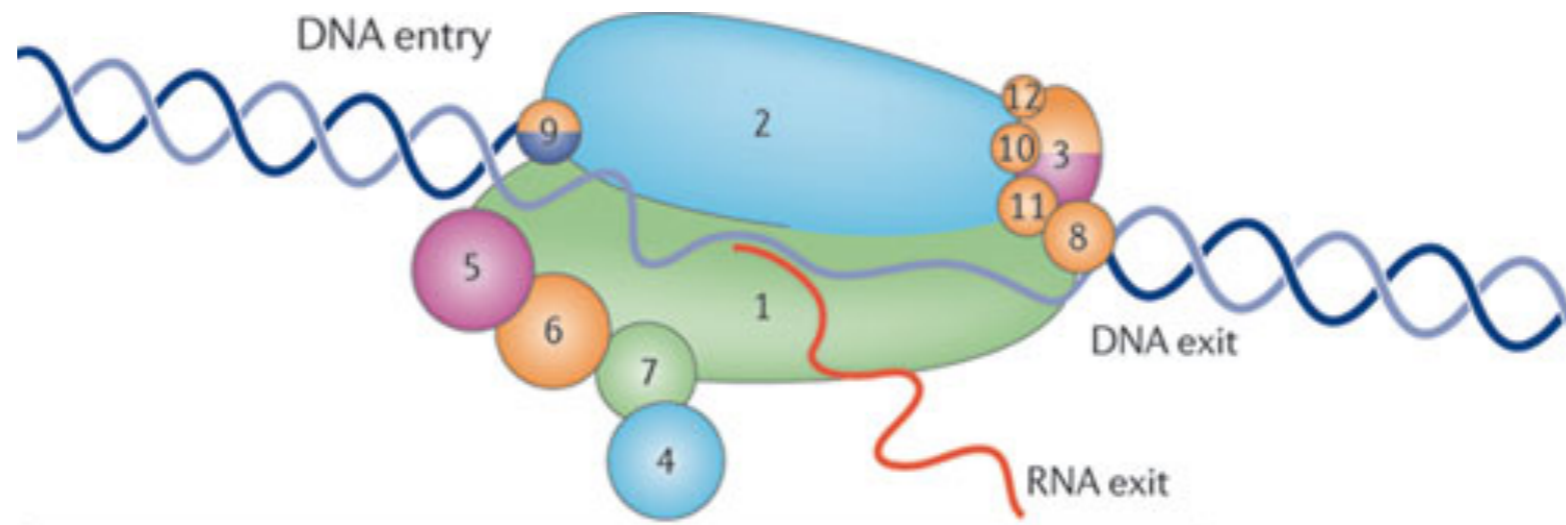


## Spreading & Bridging



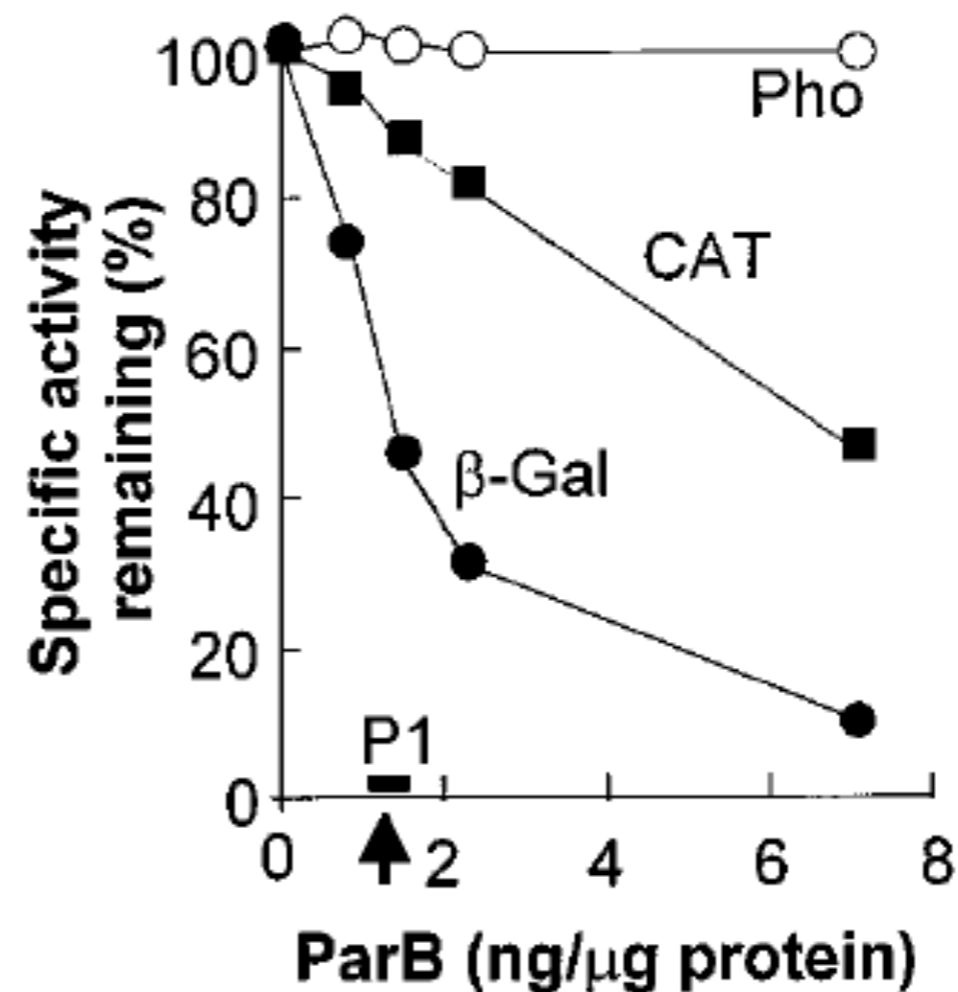
# The ParB DNA complex can silence genes

Haag and Pikaard, Nature Rev. Mol. Cell Biol. (August 2011)



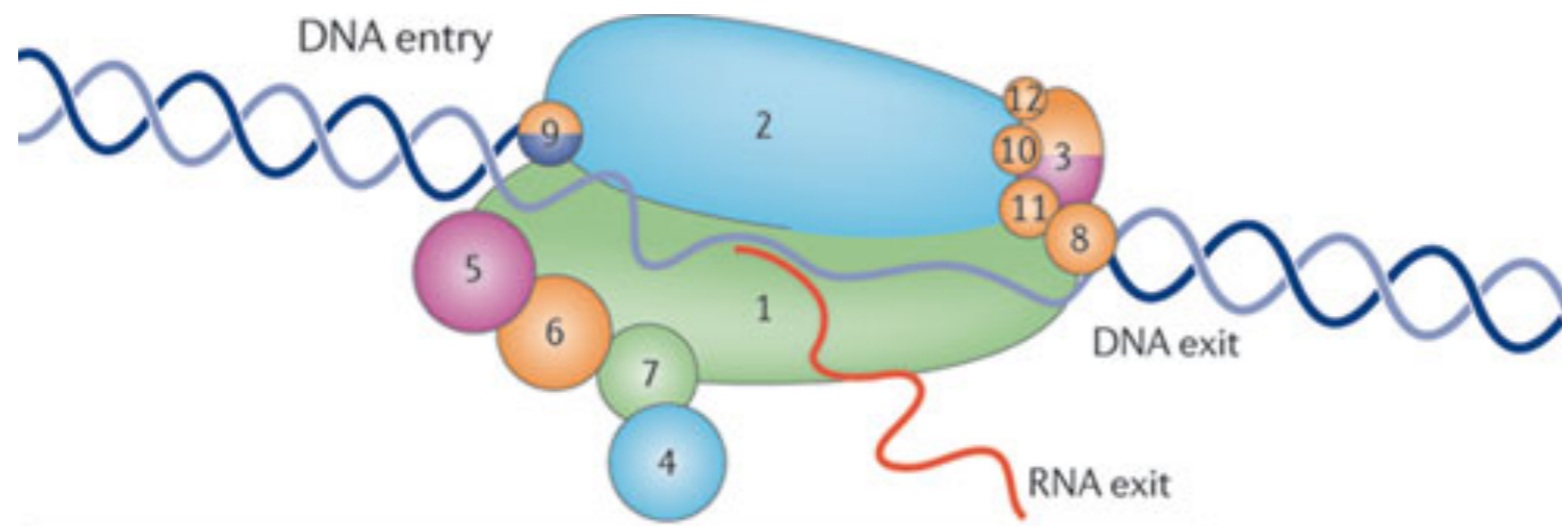
ParB silences genes flanking the *parS* site in P1 plasmids

Rodionov et al. Science (1999)



# Modeling gene silencing by ParB complex formation

Haag and Pikaard, Nature Rev. Mol. Cell Biol. (August 2011)

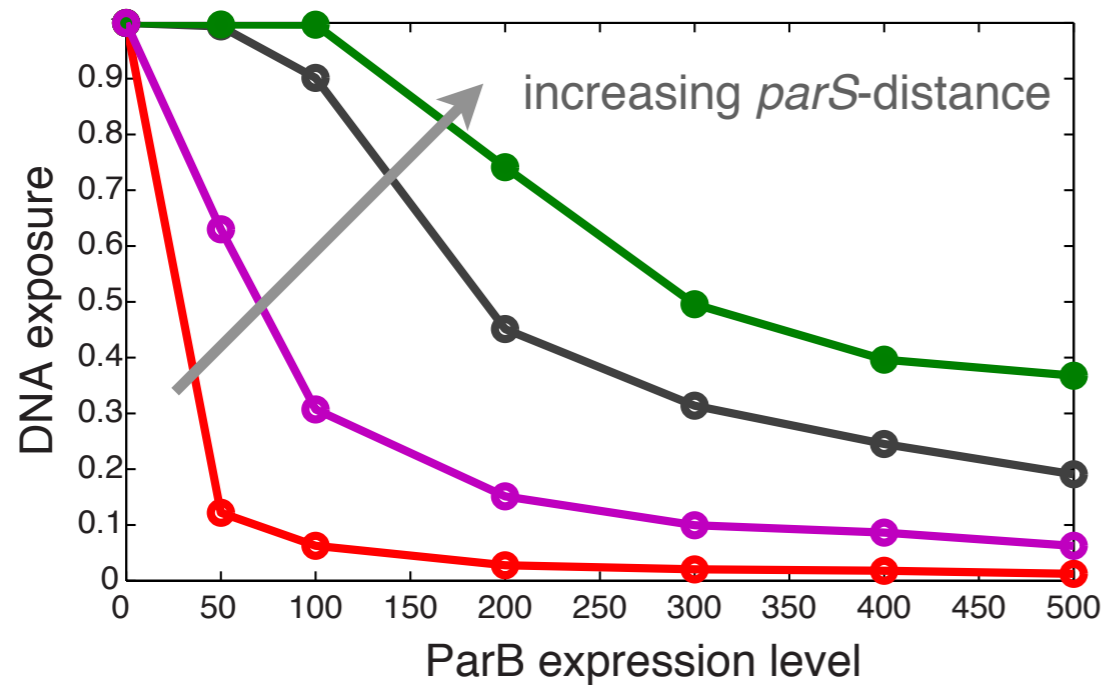


DNA exposure ~ Remaining activity of gene

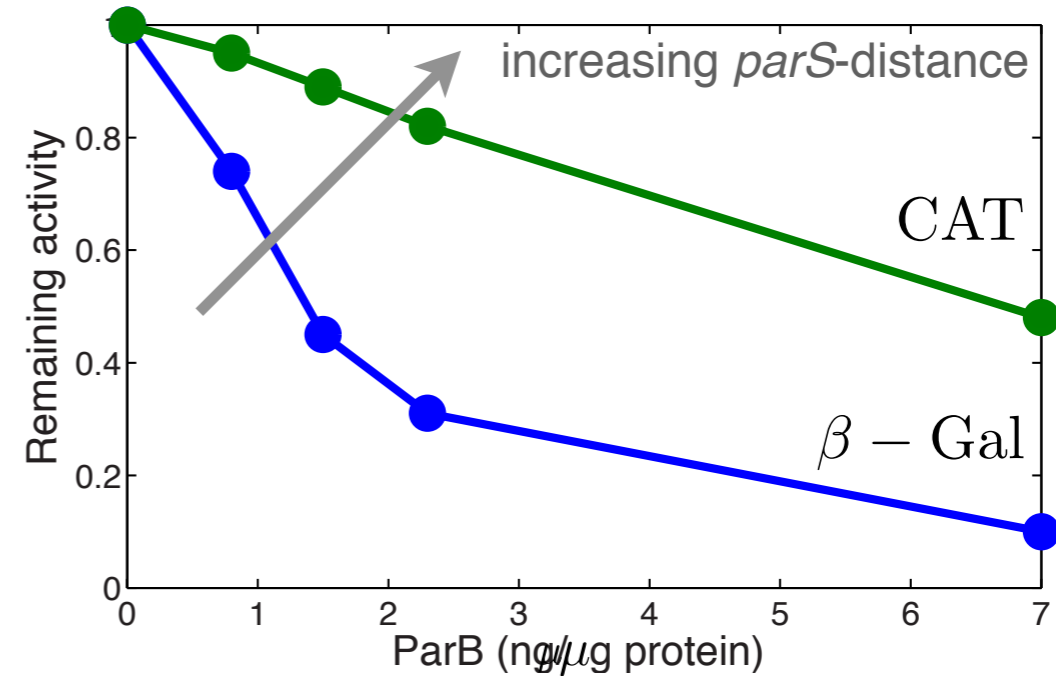


# Gene-silencing profiles captures by the spreading & bridging model

## DNA exposure at fixed *parS*-distance

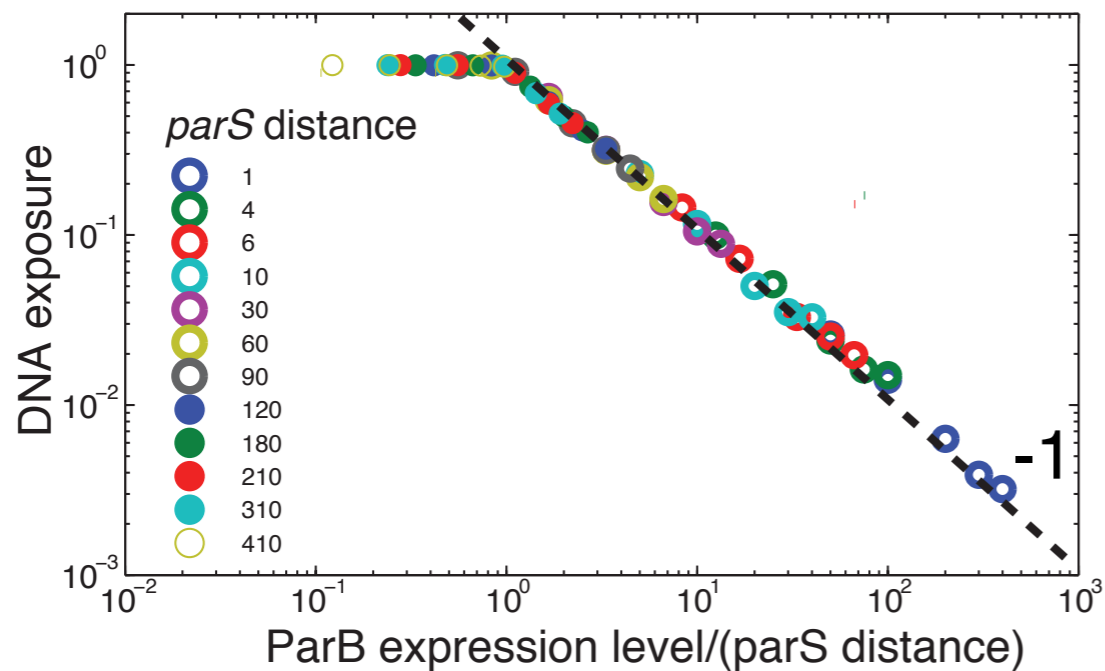


## Remaining gene activity at fixed *parS*-distance

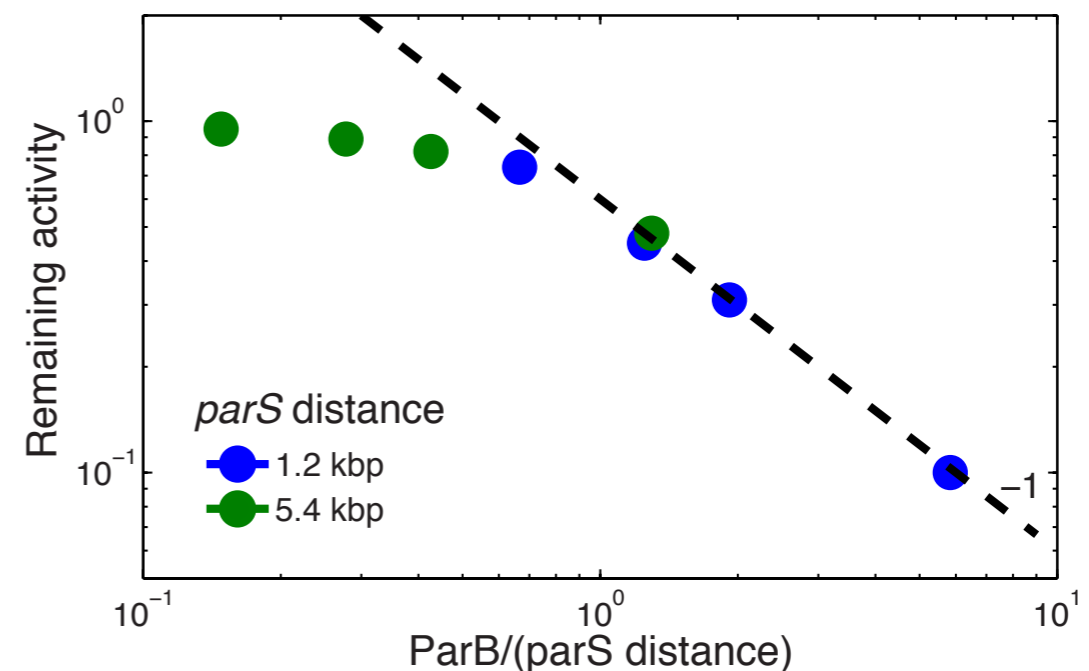


$$\text{Remaining activity} = f(\text{ParB footprint} / \textit{parS} \text{ distance})$$

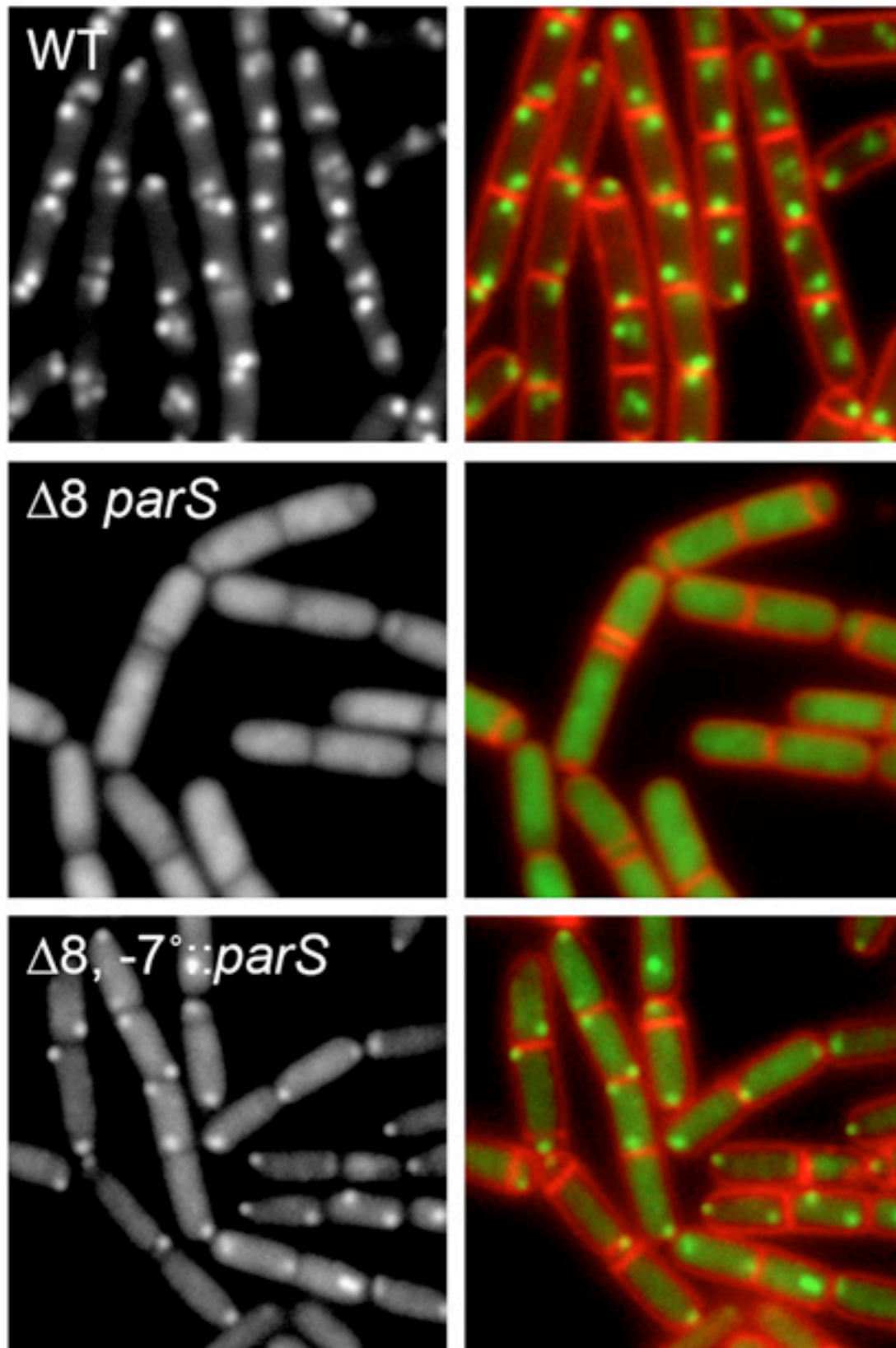
## Collapse numerical data



## Collapse experimental data



# One *parS* site is necessary and sufficient for foci formation



Requirement for nucleation @ *parS*:

$$\Delta F_{parS} < -k_B T \log(N) \approx -11.8 k_B T.$$

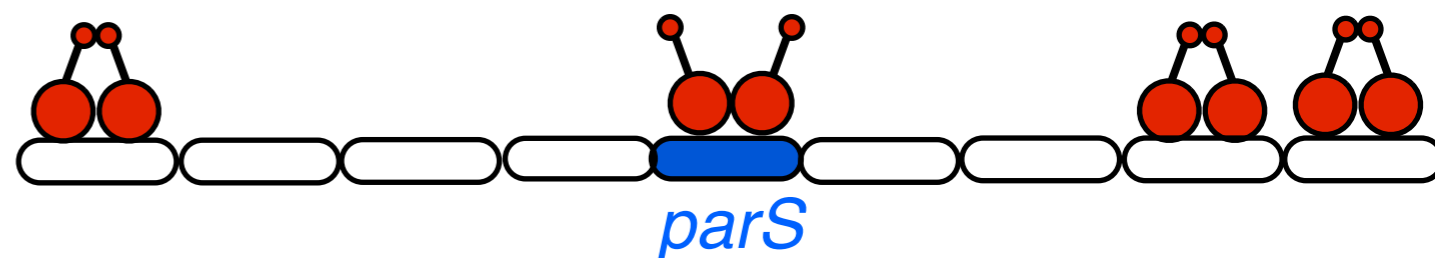
*In vitro* experiments show:

$$\Delta \epsilon_{parS} \approx -2.3 k_B T$$

Requirement for localization @ *parS*:

$$\Delta F_{parS} < k_B T \log \left( \frac{2M_c}{N - 2M_c} \right) \approx -4.2 k_B T$$

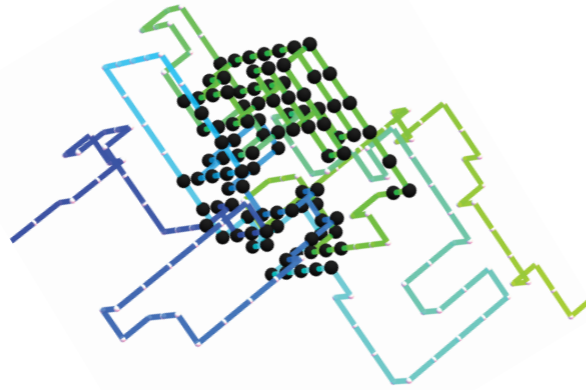
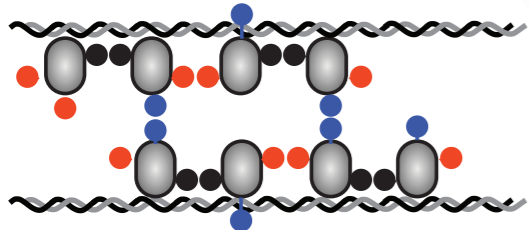
Two-state model can explain role of *parS* as a nucleation site.



Leonard et al. Mol. Microbiol. (2004)

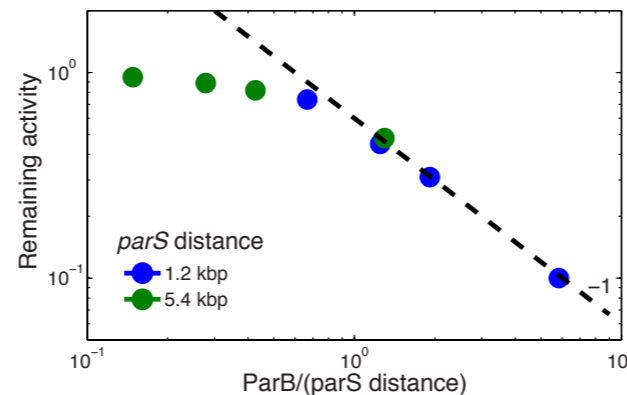
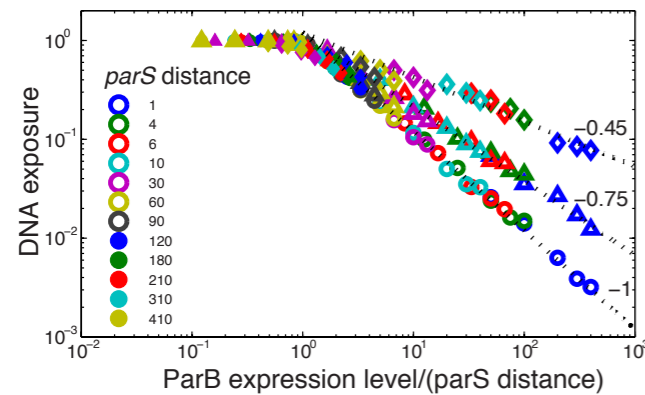
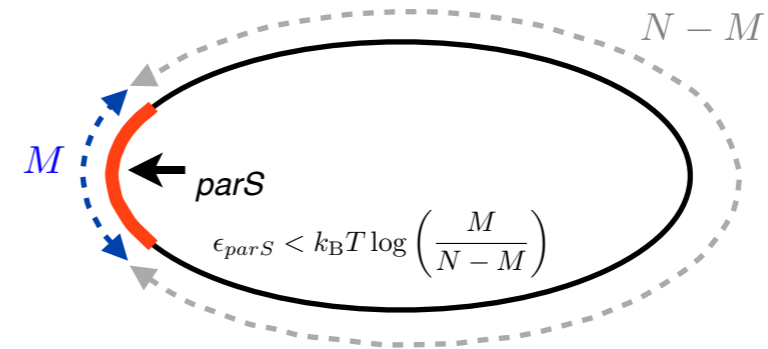
# Conclusions

## Spreading & Bridging



3D model for the condensation of interacting proteins on DNA  
Formation of clusters with extruding loops of DNA

Moderate binding energies at a *parS* can ensure the localization the ParB-DNA complex



Looping affect exposure of DNA flanking *parS*  
Simple scaling analysis accounts for data in P1 plasmids

## Acknowledgements

Ned Wingreen (Princeton University)

Joseph Loparo, Xindan Wang and David Rudner (Harvard)

Yigal Meir (Ben Gurion)

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