Physical modeling of active bacterial DNA segregation

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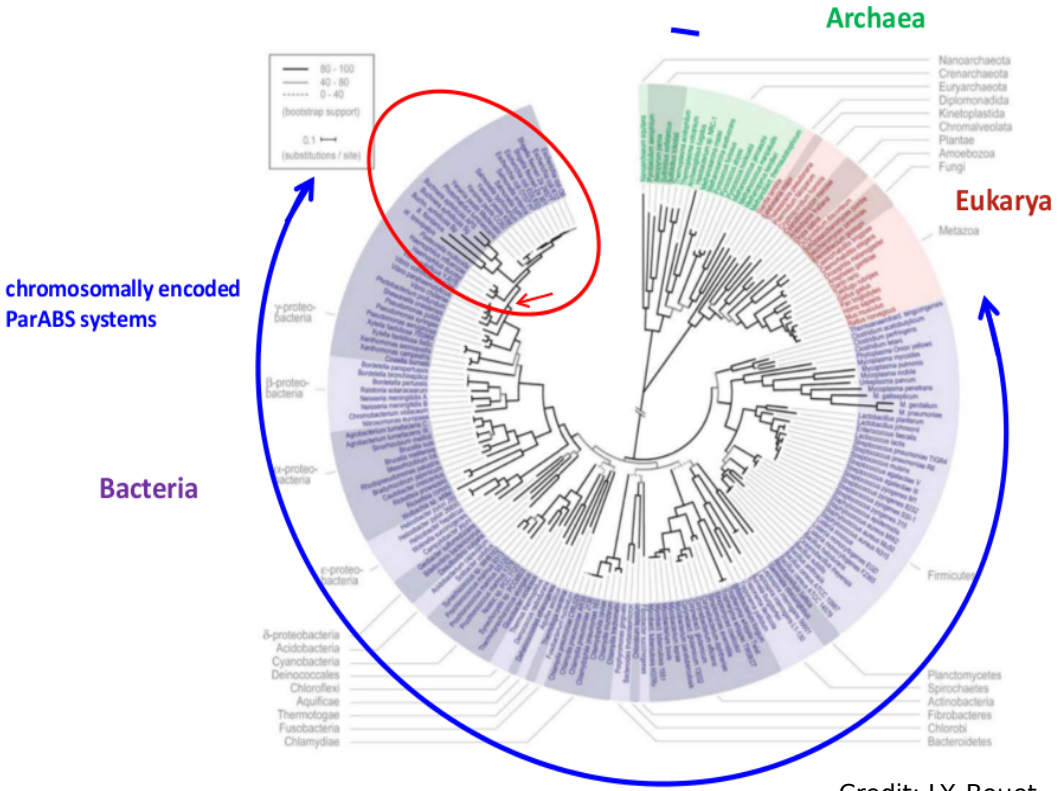
Outline

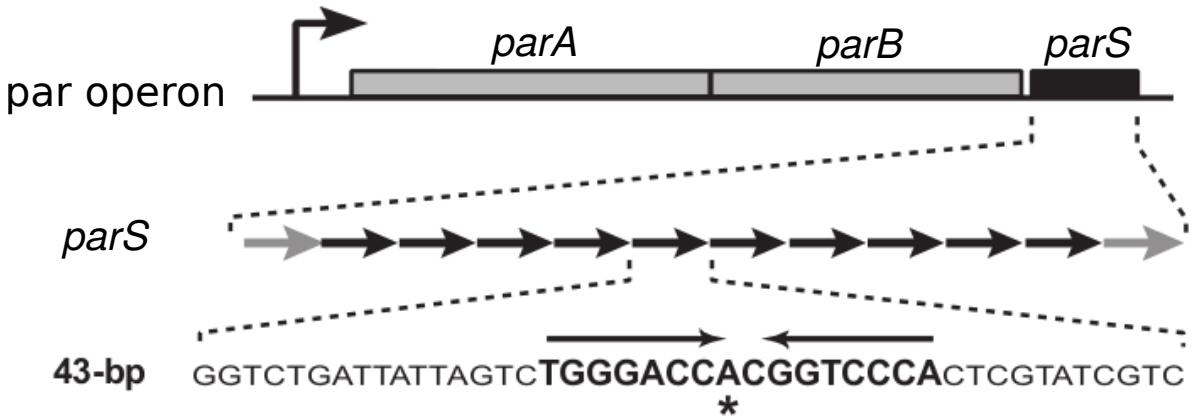
Active segregation of bacterial DNA



Credit: J-Y. Bouet

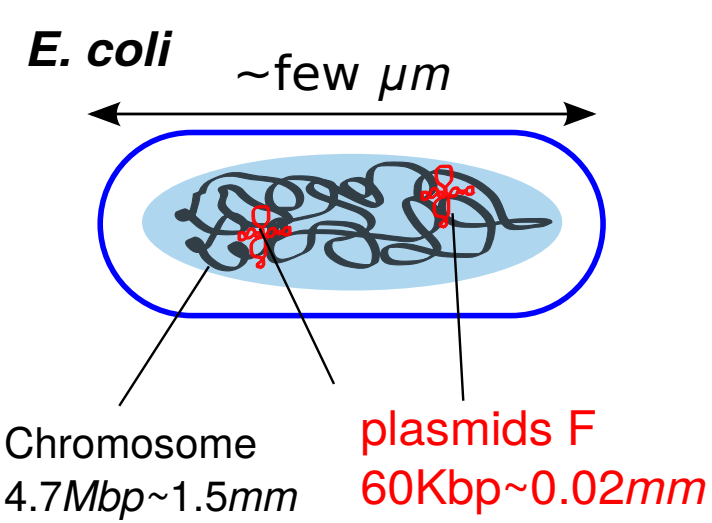
Partition system ParABS is strongly conserved

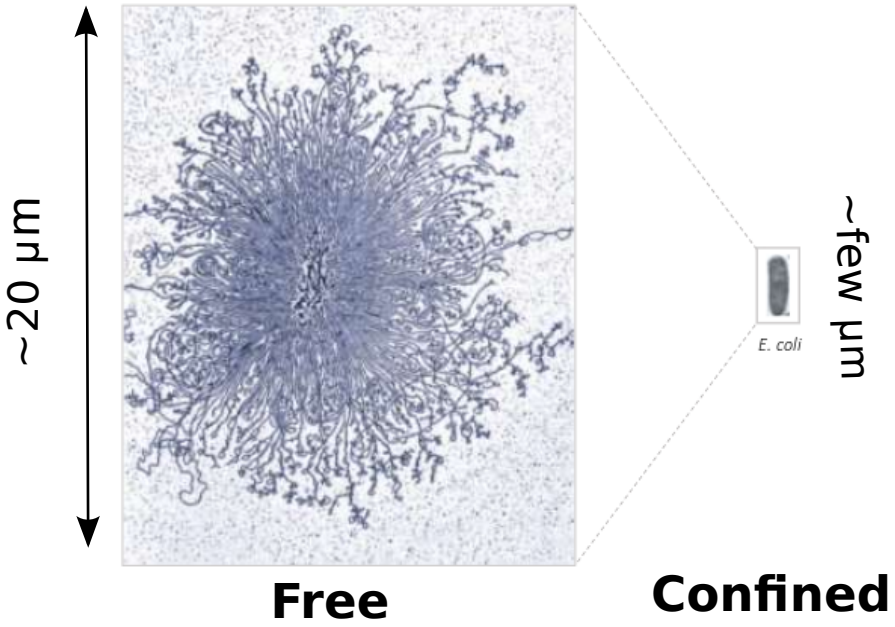
The ParAB*S* operon



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

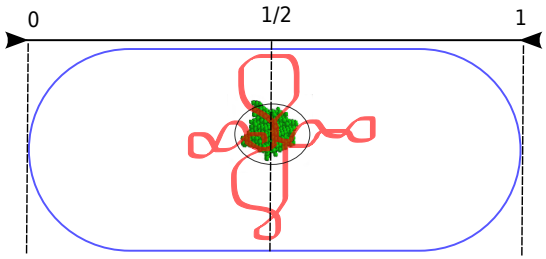
Physical dimensions of bacteria



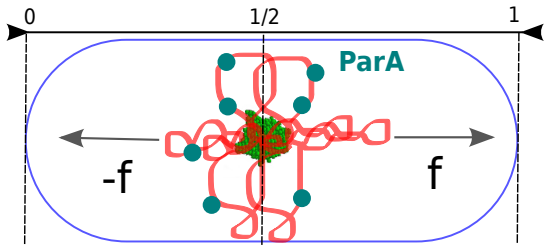


How does ParAB*S* work ?

Step 1. Formation of the partition complex

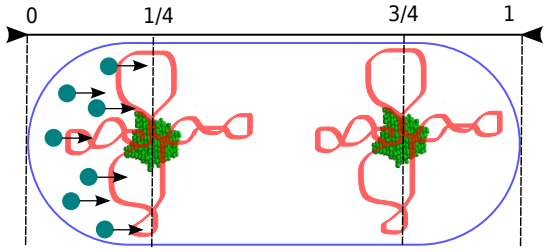


Step 2. Separation of the copies of DNA



opposite forces

Step 3. Positioning



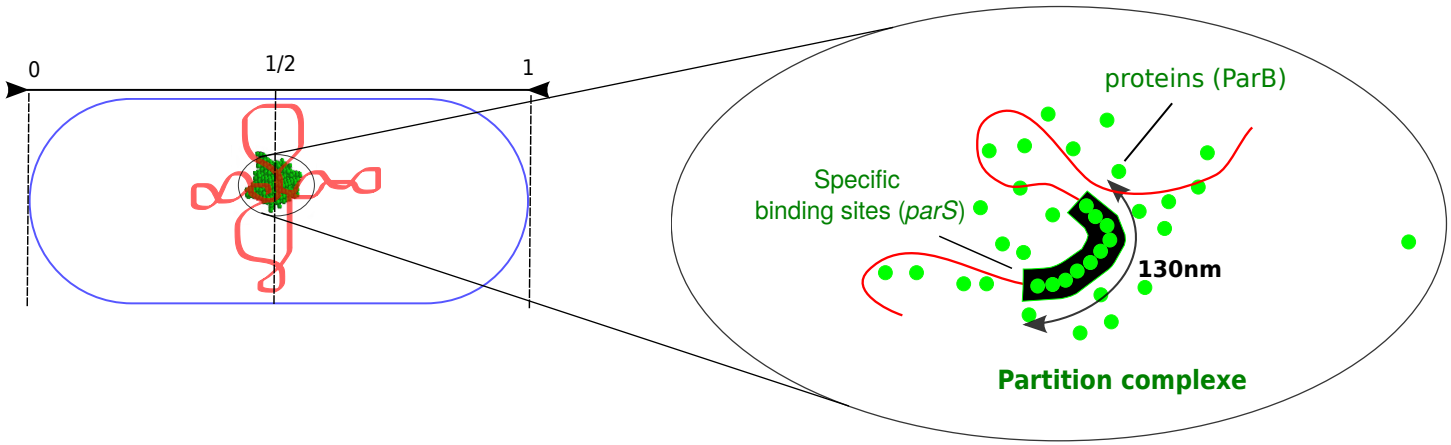
oscillations of ParA

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

"Reaction-Diffusion" or "Filament pulling" mechanisms

How does ParAB*S* work ?

Step 1. Formation of the partition complex



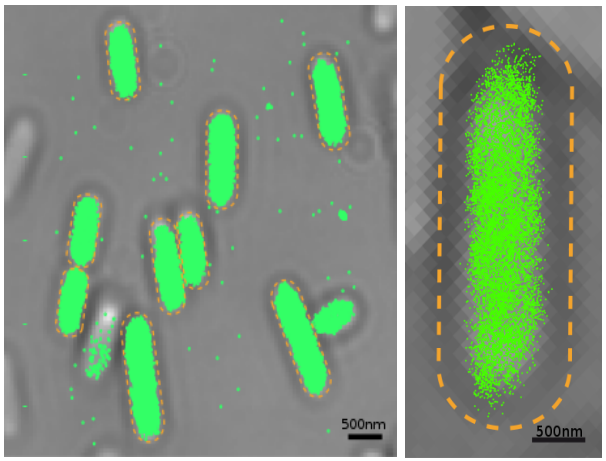
What is the architecture of the partition complex ?

- **Stochastic self-assembly of ParB proteins at centromeres builds bacterial DNA segregation apparatus**, A. Sanchez, D. Cattoni, J-C. Walter, J. Rech, A. Parmeggiani, M. Nollmann & J-Y. Bouet, *Cell Systems* (2015).

Experimental results: Super resolution microscopy and ChIP-sequencing

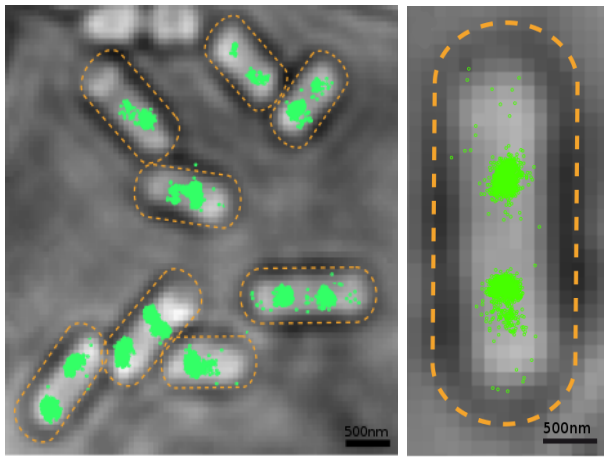
Foci are nucleated by *parS*

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



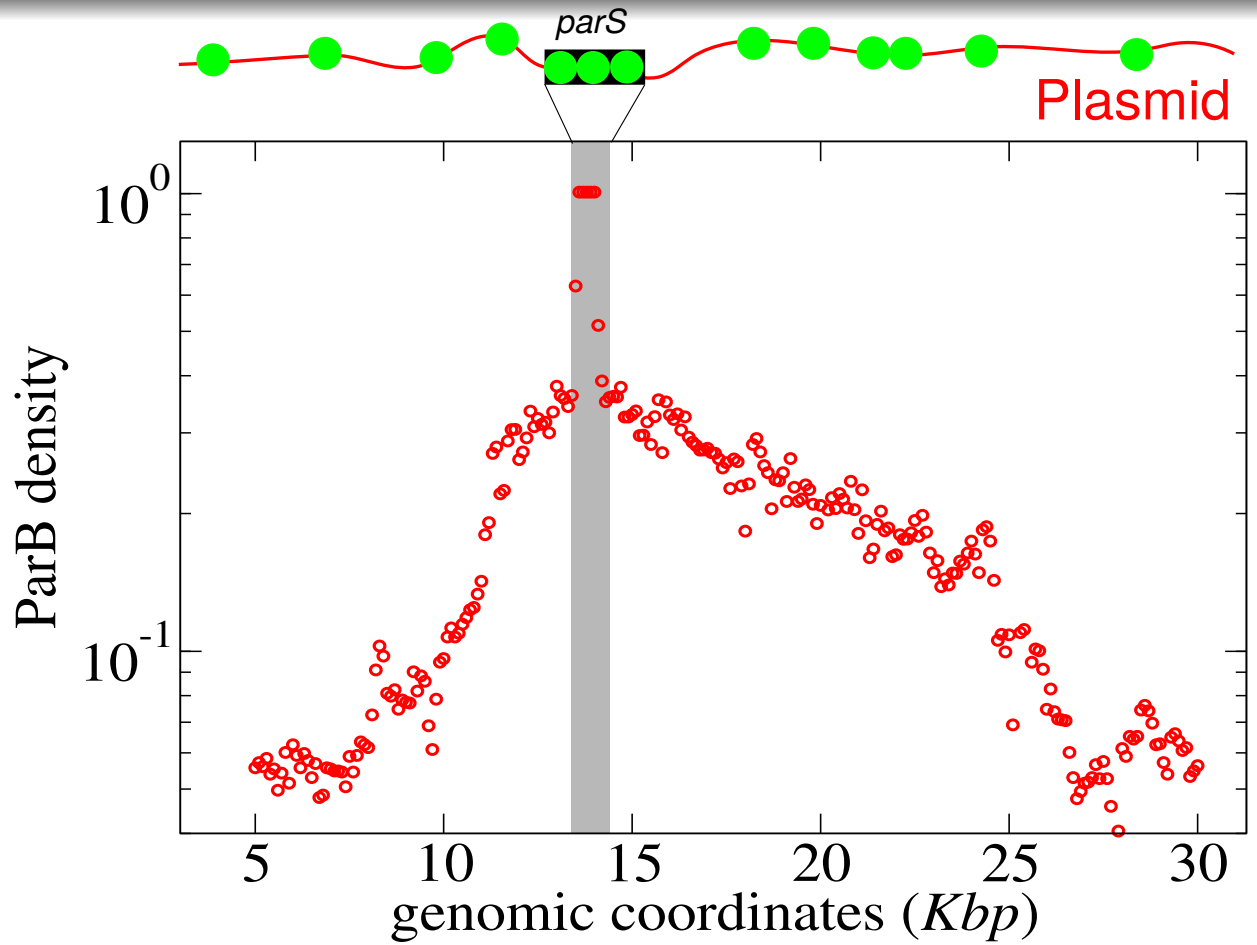
specific binding

ParB/*parS*



- Focus diameter (upper bound) $150 \pm 20nm$
- Fixed number of ParB in a focus [≈300 ParB dimers/focus]
- Most of the ParB (≈ 90%) are located in the foci

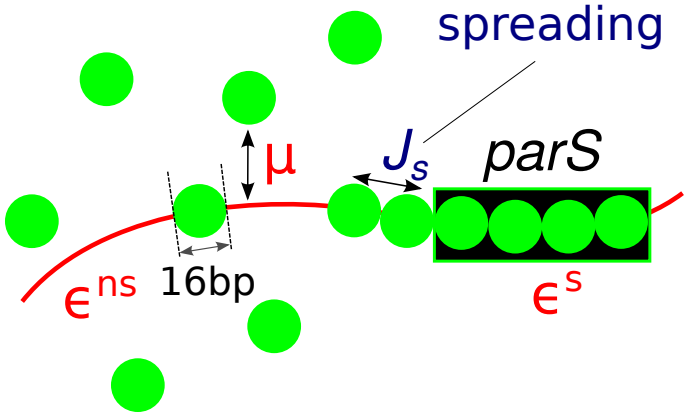
ParB density along the plasmid

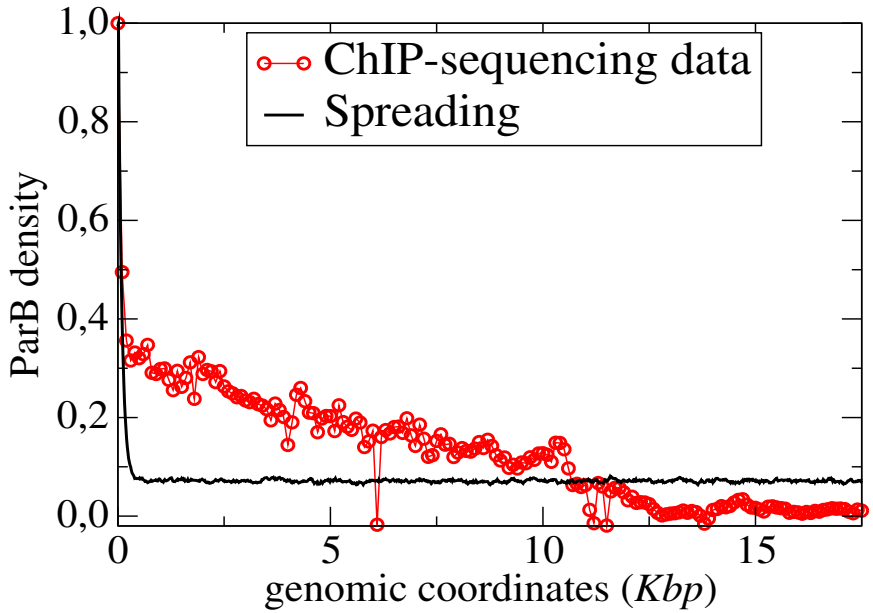


ChIP-sequencing: R. Diaz, A. Sanchez & J-Y. Bouet (LMGM, Toulouse, France)

Modeling of the partition complex

Spreading model

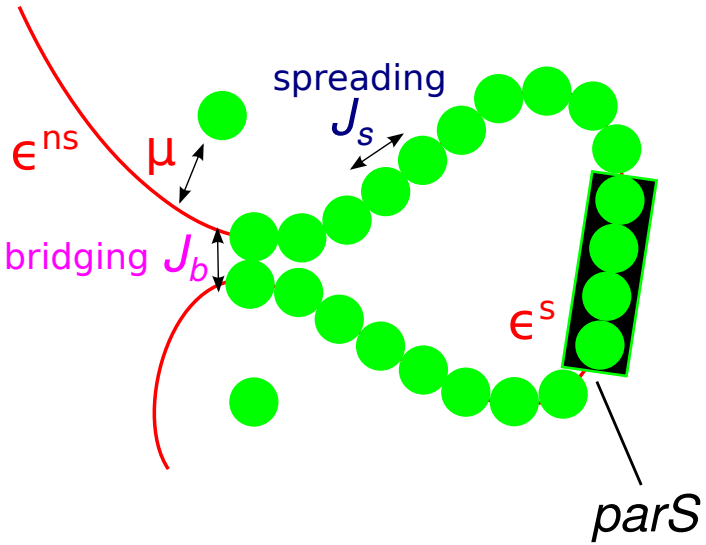


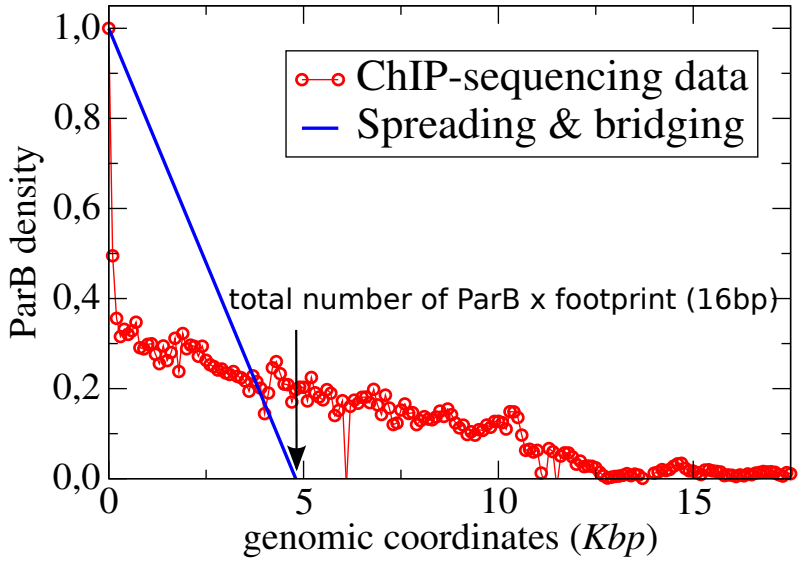


$$\mathcal{E} = -J_s \sum_i \phi_i \phi_{i+1} - \sum_i (\mu + \epsilon_i)\phi_i$$

- $\epsilon_i = \epsilon^s$ and $\epsilon_i = \epsilon^{ns}$ for specific and non-specific sites, respectively.
- Monte Carlo simulations: $J_s = 6kT$, $\epsilon^{ns} = 6kT$, $\epsilon^s = 15kT$ and $\mu = -12.17kT$ (300 particles).

Spreading & bridging model

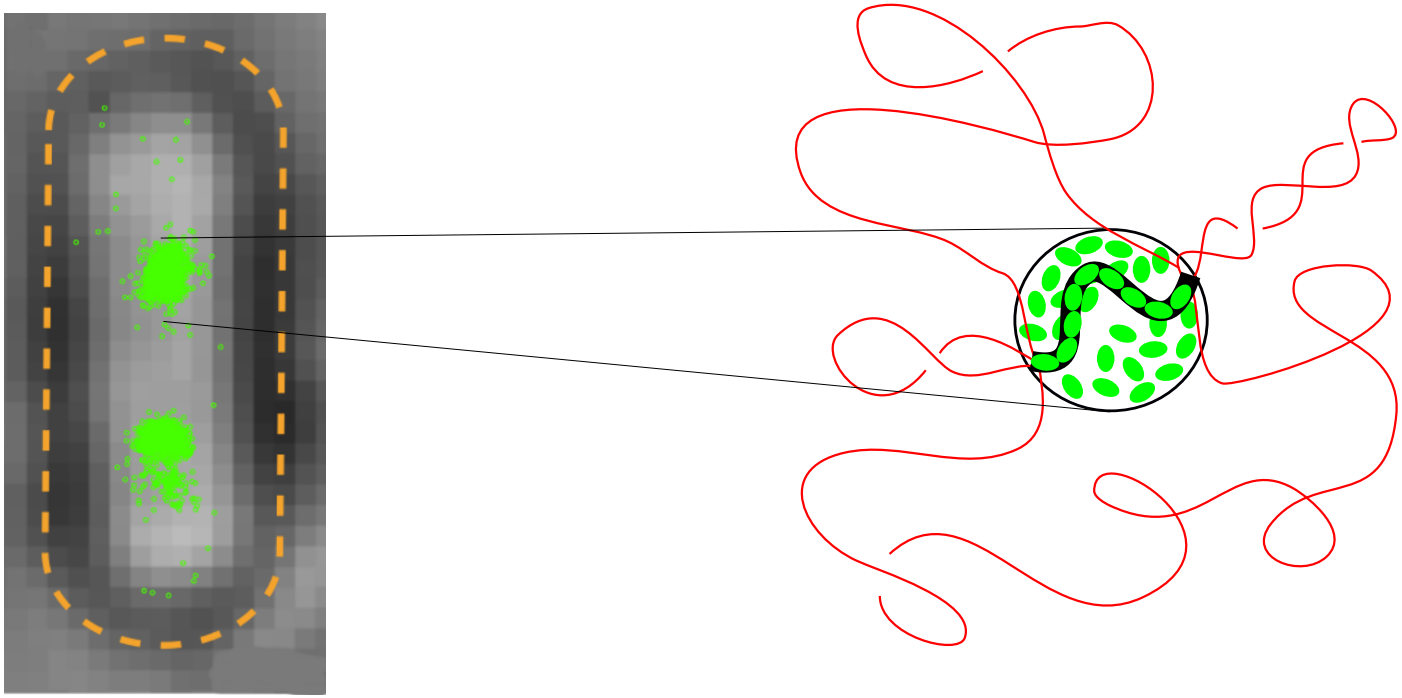




C.P. Broedersz, X. Wang, Y.M. Meir, J.J. Loparo, D.Z. Rudner & N.S. Wingreen, PNAS (2014).

$$\mathcal{E} = \mathcal{E}_{DWLC} - J_s \sum_i \phi_i \phi_{i+1} - J_b \sum_{\langle i,j \rangle_{3D}} g_{ij} \phi_i \phi_j - \sum_i (\mu + \epsilon_i) \phi_i$$

The stochastic binding model



The stochastic binding model: polymer conformation

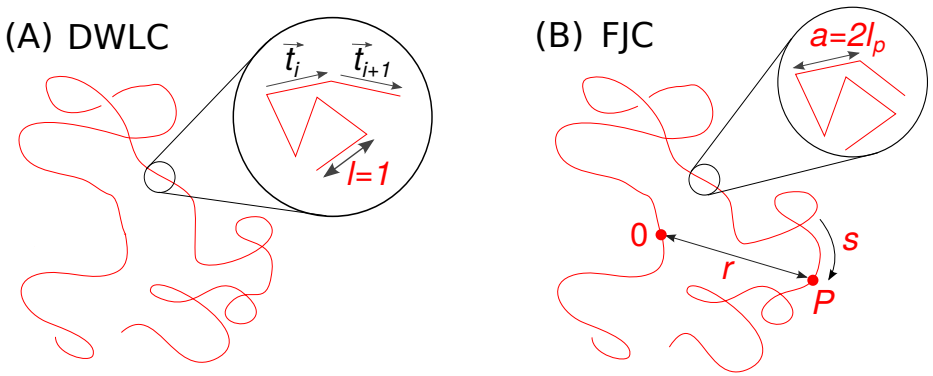
(A) Discrete Wormlike Chain (DWLC):

$$\mathcal{E}_{DWLC} = -\kappa \sum_i \vec{t}_i \cdot \vec{t}_{i+1}$$

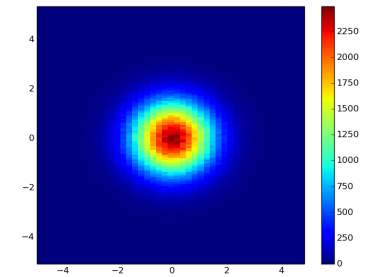
$$\langle \vec{t}_i \cdot \vec{t}_j \rangle = e^{-\frac{l|i-j|}{l_p}} \qquad \text{and} \qquad l_p \approx l\beta\kappa \qquad (\beta\kappa \gg 1)$$

(B) Freely-Jointed Chain (FJC):

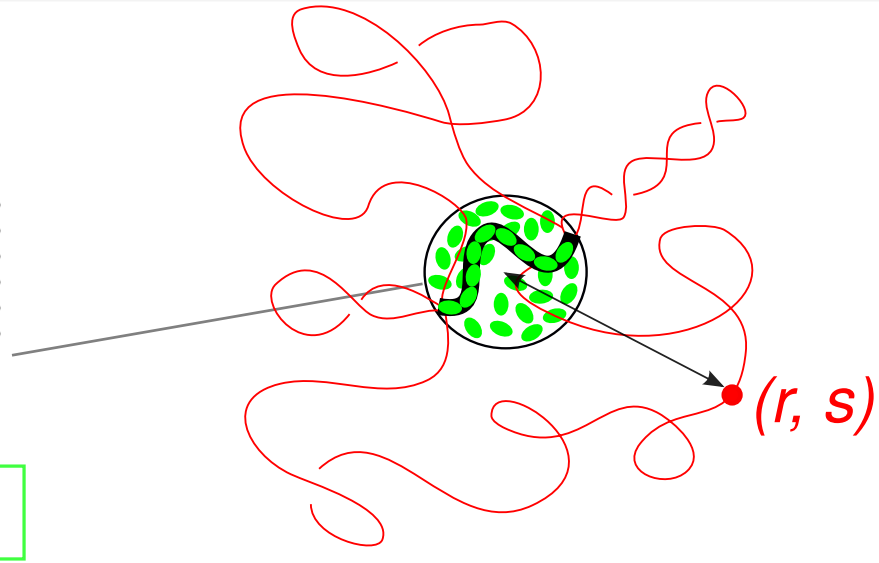
$$P(r,s) \sim \frac{1}{s^{3/2}} e^{-\frac{3r^2}{2R(s)^2}} \qquad \text{where} \quad R(s) = a\sqrt{s}$$



The stochastic binding model

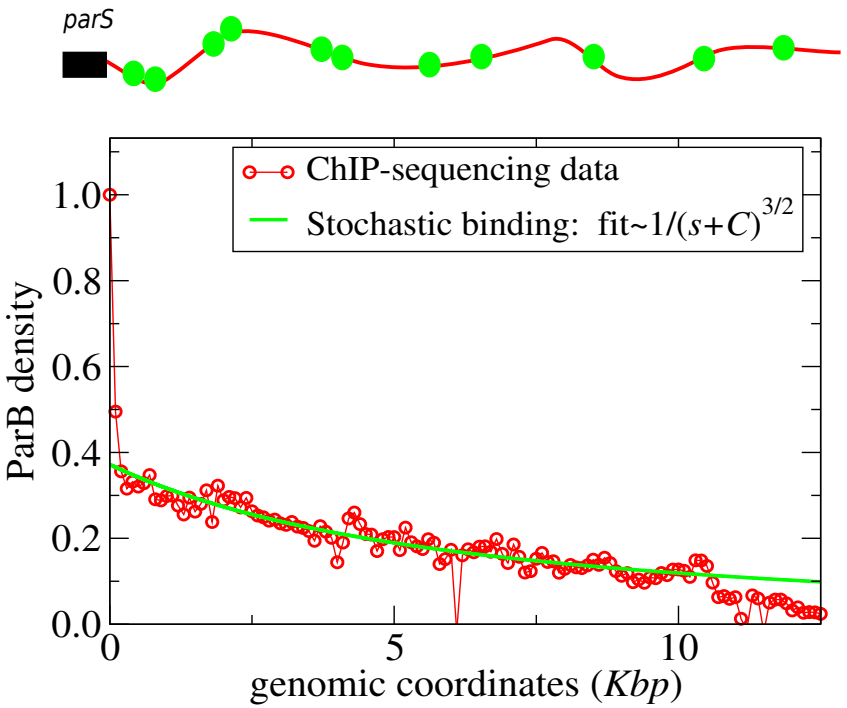


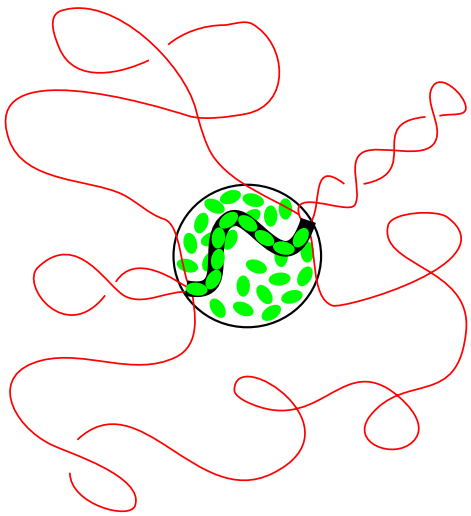
$C(r) \sim e^{-r^2/(2\sigma^2)}$



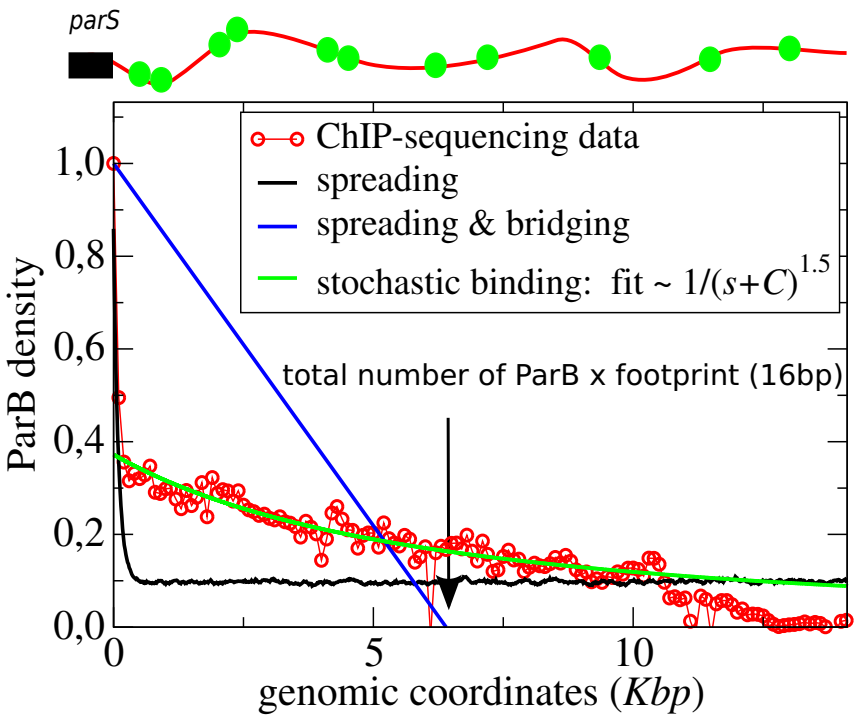
$$
\begin{aligned}
P_{binding}(s) &= \int_V d^3\vec{r}\; P(r,s)\, C(r)\,, \\
&\propto \int_V d^3\vec{r}\; \frac{1}{s^{3/2}} e^{-\frac{3r^2}{2R(s)^2}} e^{-\frac{r^2}{2\sigma^2}}\,, \\
&\propto \frac{1}{(s+C)^{3/2}} \quad \text{where } C = 3\frac{\sigma^2}{a}
\end{aligned}
$$

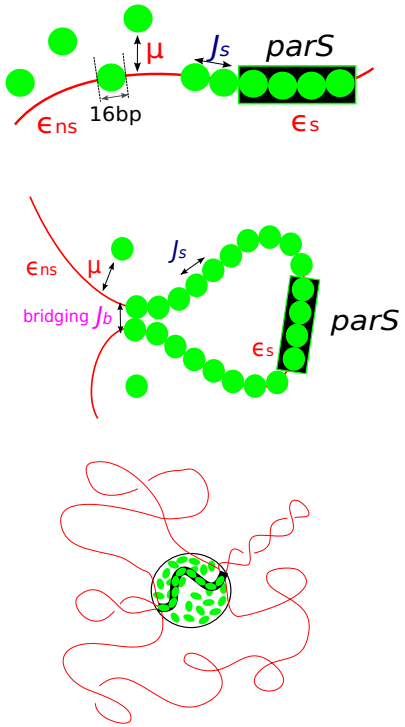
The stochastic binding model



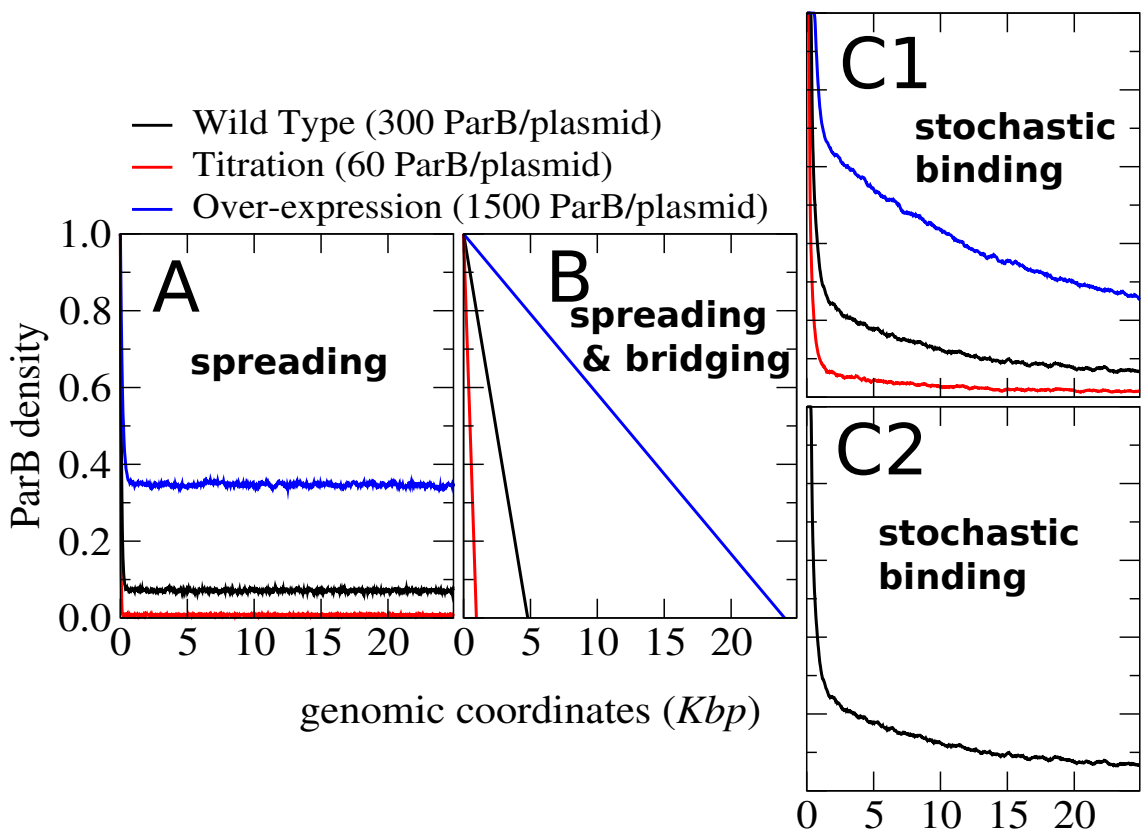


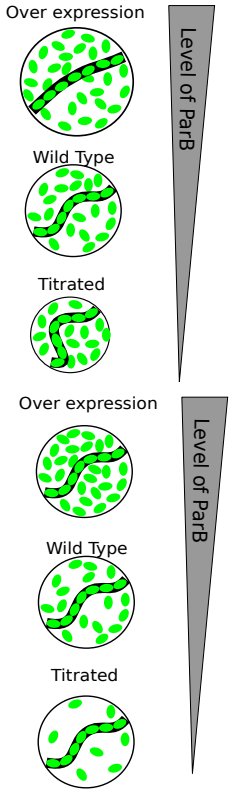
The stochastic binding model



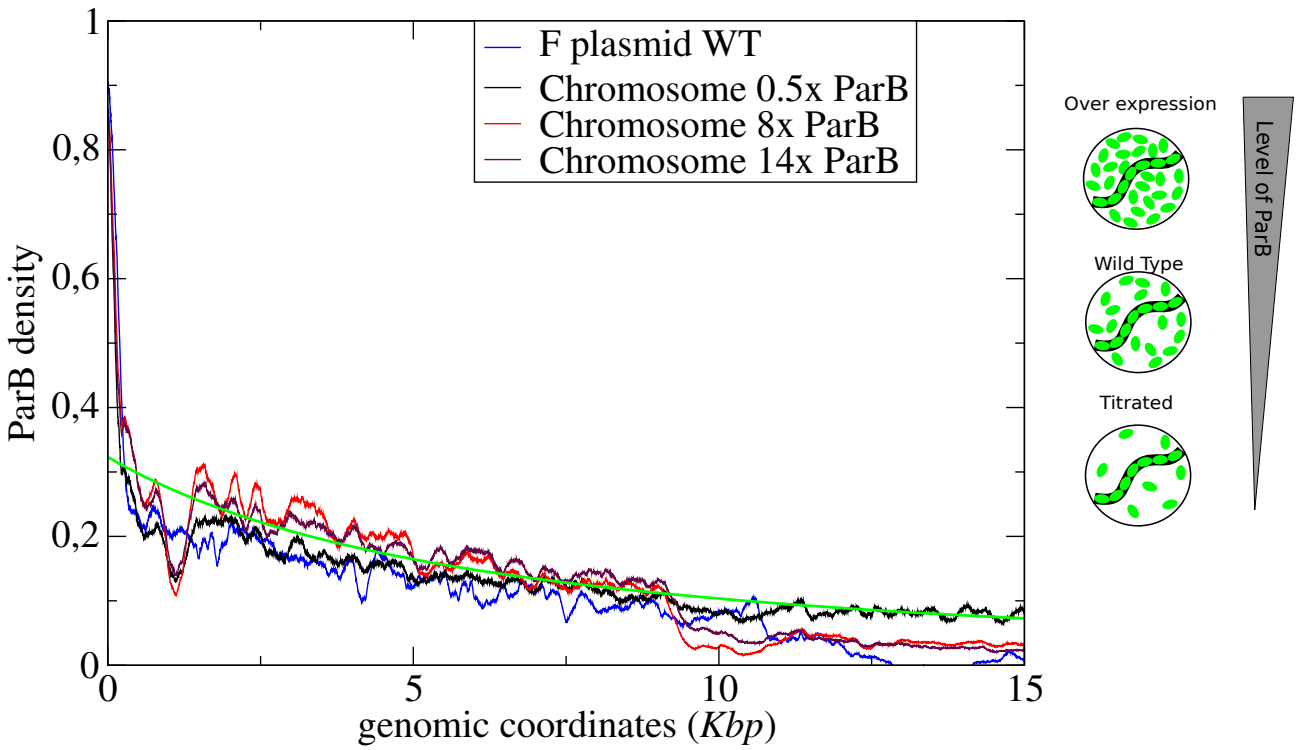


Variation of the ParB expression level

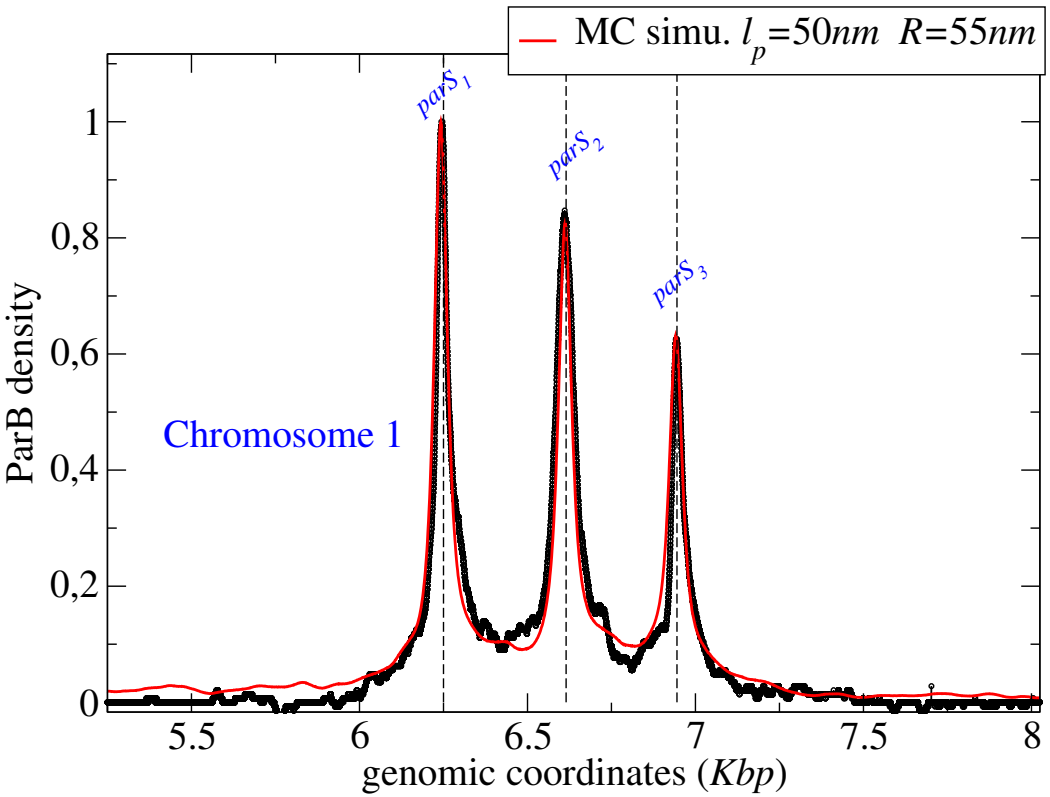


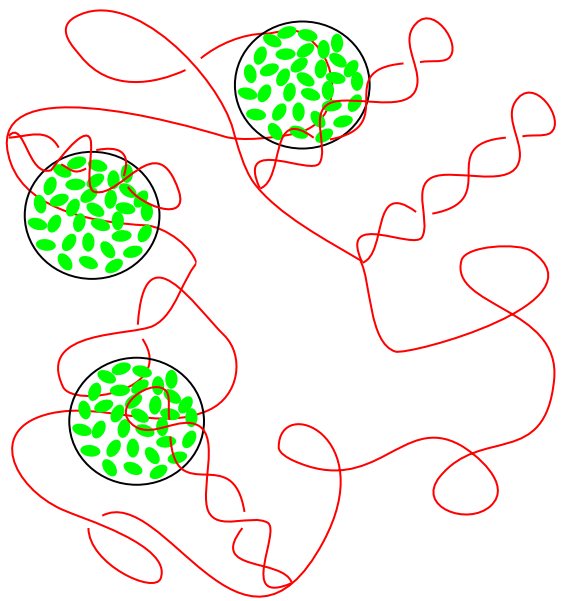


Variation of the ParB expression level



Different architecture: Chromosome I of *V. cholerae*





Summary

- Combination of approaches: Super-resolution microscopy, ChIP-sequencing & physical models: decipher the architecture of the partition complex.
  - ParB organized spatially in foci,
  - Linear density: freely fluctuating plasmid in a focus of ParB.
- Functional implication for the interactions with ParA in the dynamical steps
- Perspectives: modeling of the dynamical phase with ParA.

ChIP-sequencing

R. Diaz
A. Sanchez
J. Rech
J-Y. Bouet

Super-resolution microscopy PALM

D. Cattoni
A. Le Gall
M. Nollmann

Physical modeling

J. Dorignac
F. Geniet
V. Lorman
J. Palmeri
A. Parmeggiani