Hands-on tutorial: Simulating DNA replication and dynamics with btree_chromo and LAMMPS

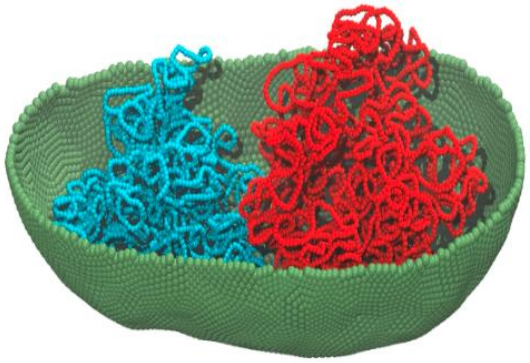
Science and Technology Center for Quantitative Cell Biology

Advanced Computational Workshop

Day 1: Monday, May 6 2024

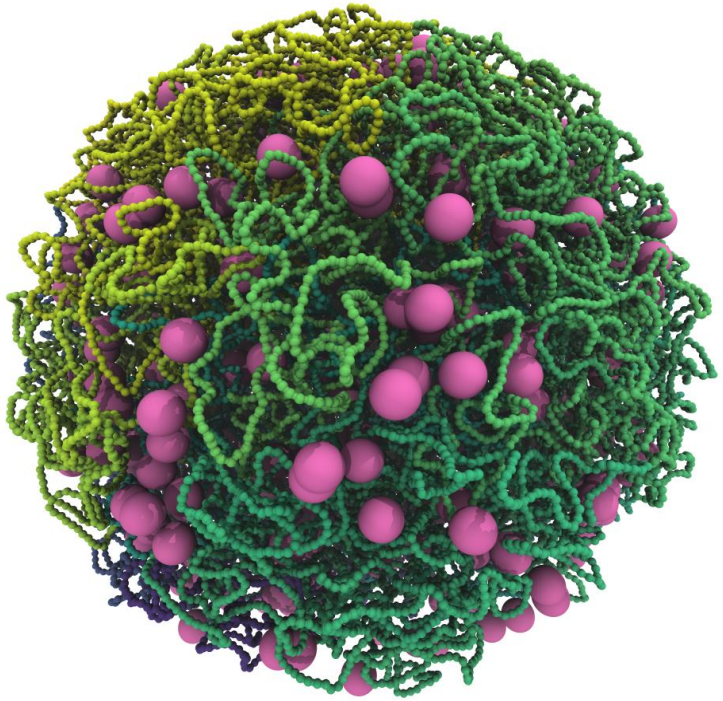
Presenters: Benjamin Gilbert, Andrew Maytin

Follow the tutorial at github.com/Luthey-Schulten-Lab/Workshop_2024/tree/main/DNA_model



Introduction: DNA in the minimal bacterial cell

- 543 kbp genome comprised of 493 genes
- Circular
- Organized as a fractal globule
- Syn3A retains structural maintenance of chromosomes (SMC) protein complexes for loop extrusion and topoisomerases.



- Here, we simulate DNA replication and dynamics using the program btree_chromo, available online at github.com/brg4/btree_chromo

Outline of tutorial:

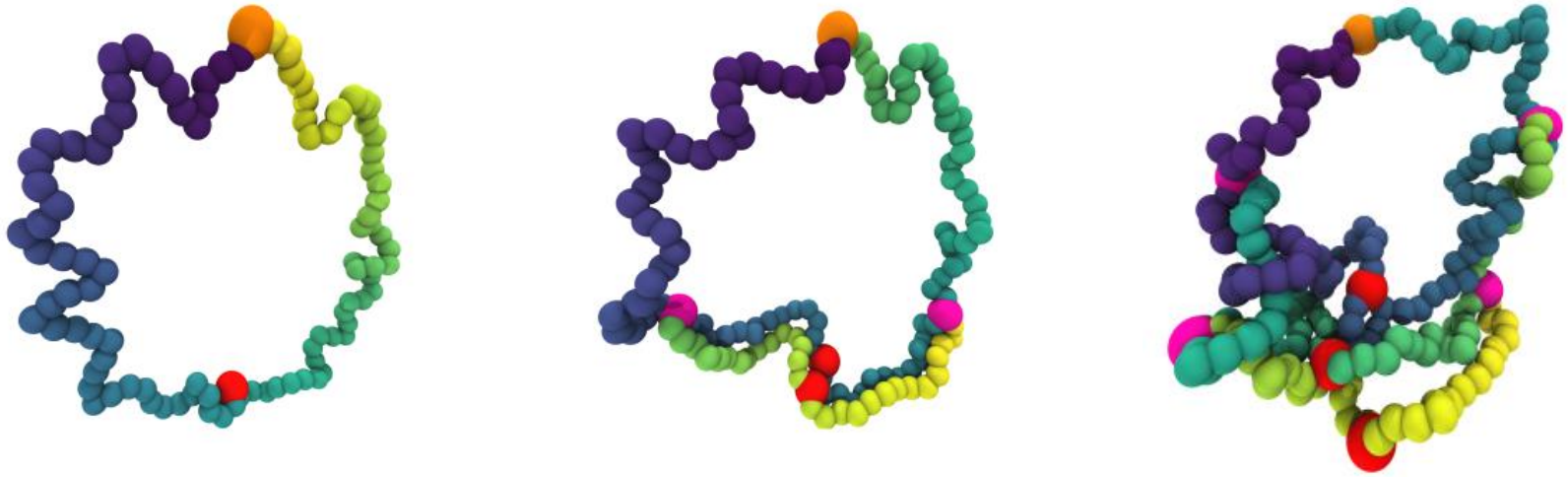
Part 1: Modeling Replication States

Part 2: Preparing the Physical Structure

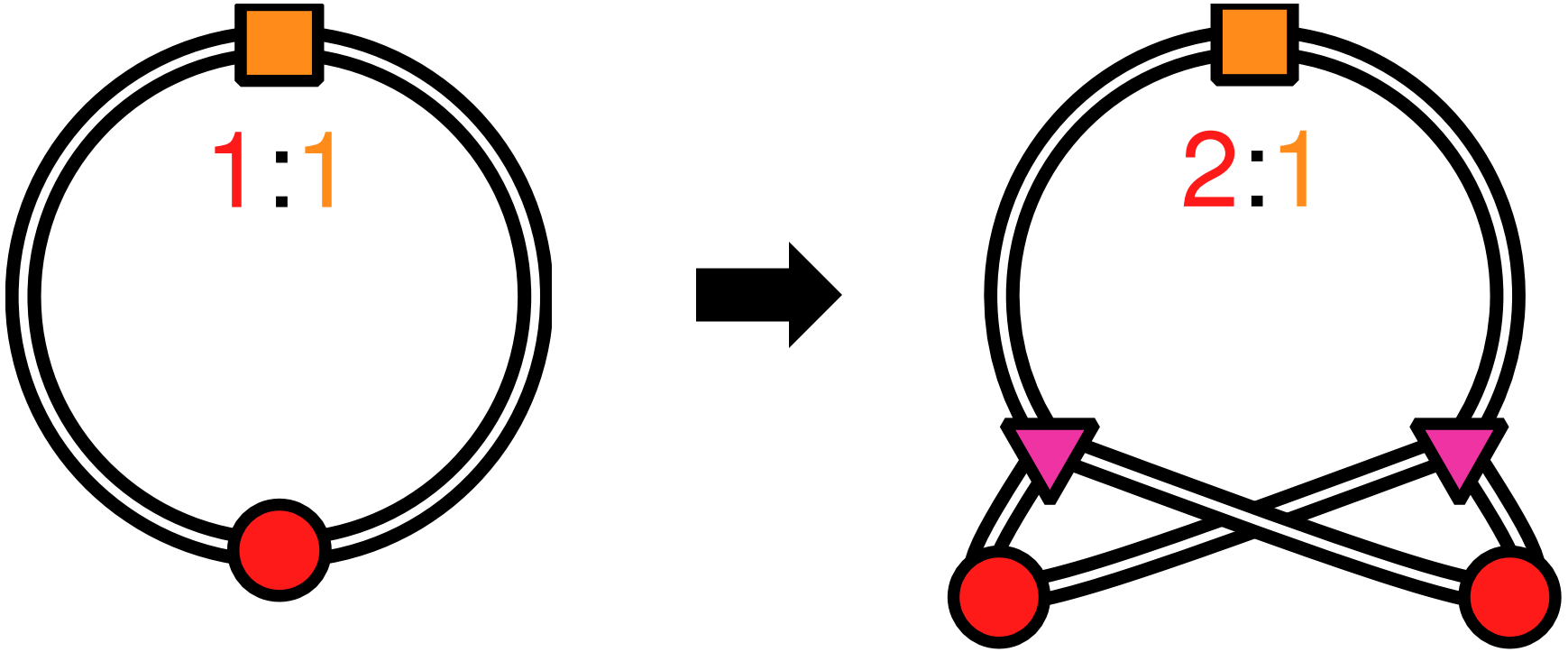
Part 3: Simulating Chromosome Dynamics

Part 4: Analysis, Conversion to LM and MARTINI

Part 1: Modeling Replication States



Replicating circular DNA: Theta structures

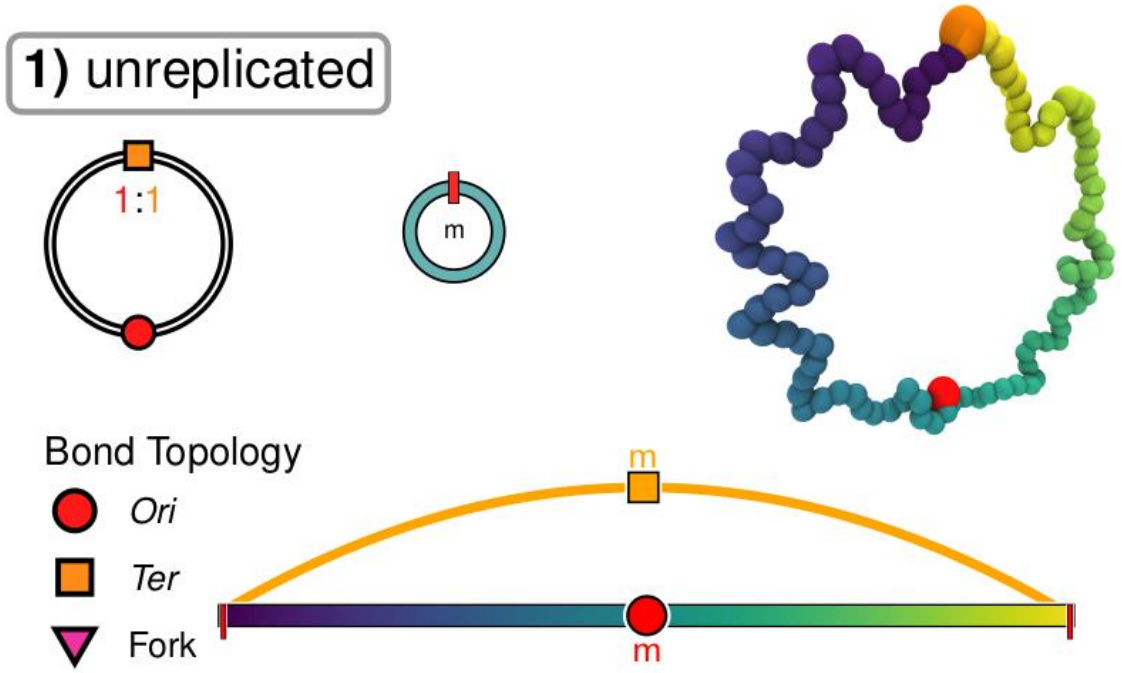


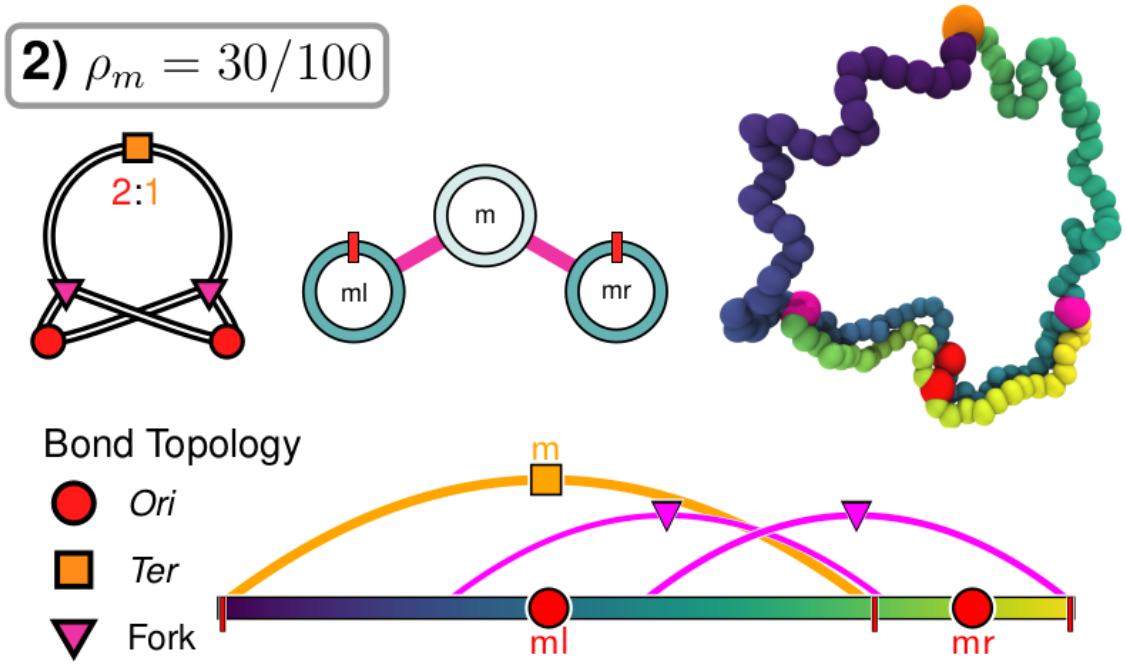
Ori (origin of replication)

Ter (terminus of replication)

Replication fork

Binary tree representation and bond topology

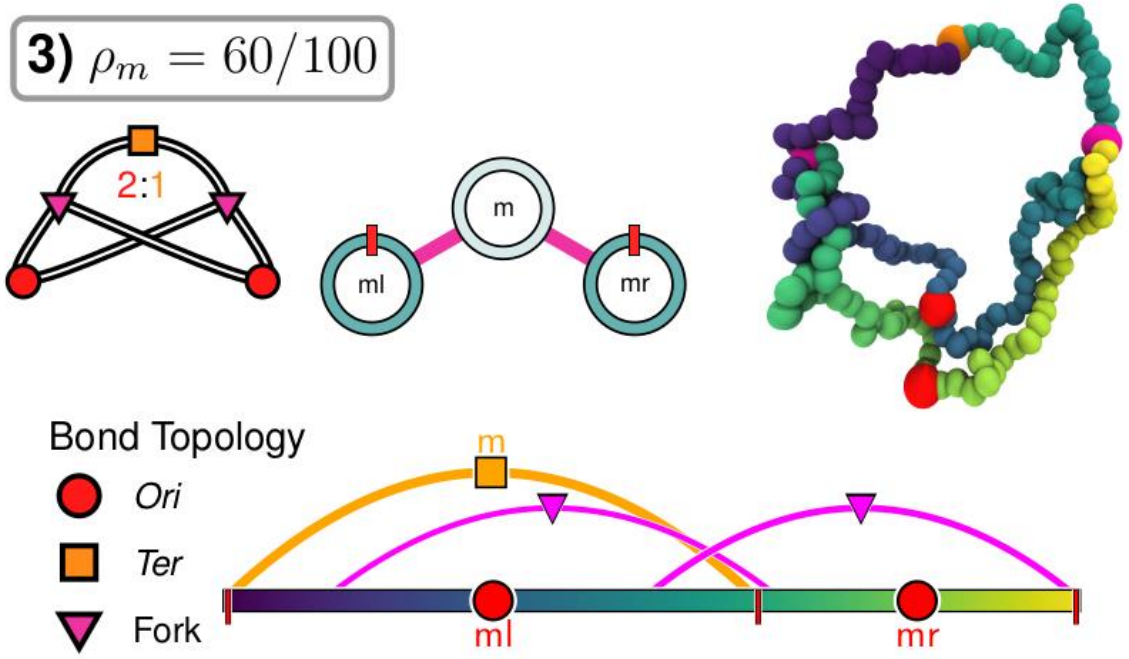




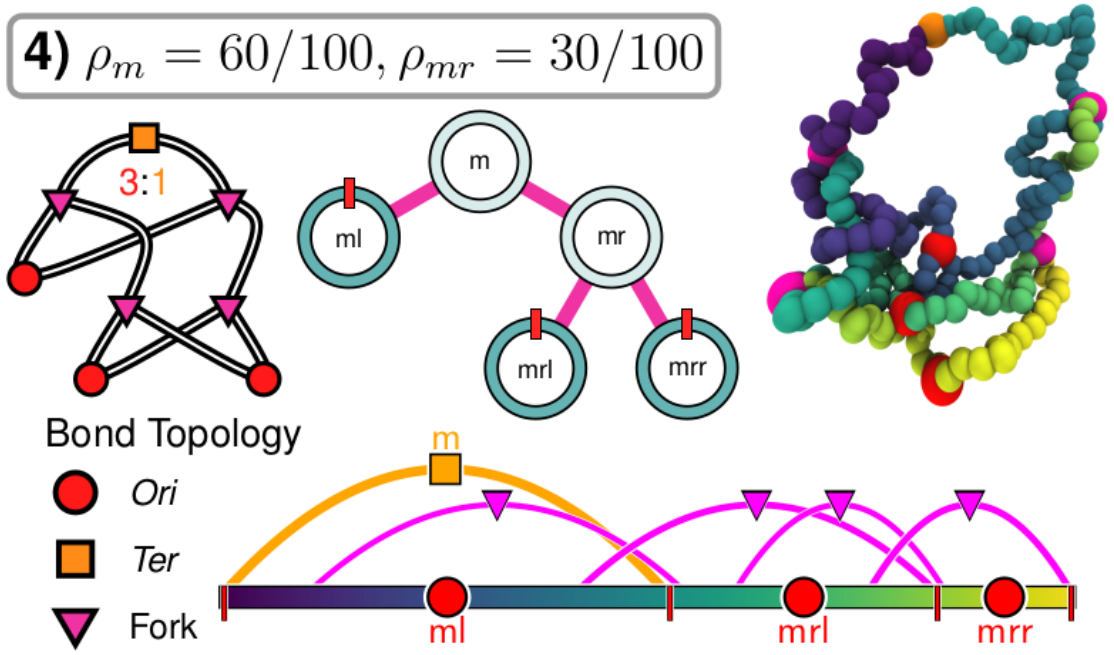
m_cw15_ccw15

A way to represent replication state #2: "replicate the mother chromosome by 15 monomers in the clockwise direction, and 15 monomers in the counterclockwise direction."

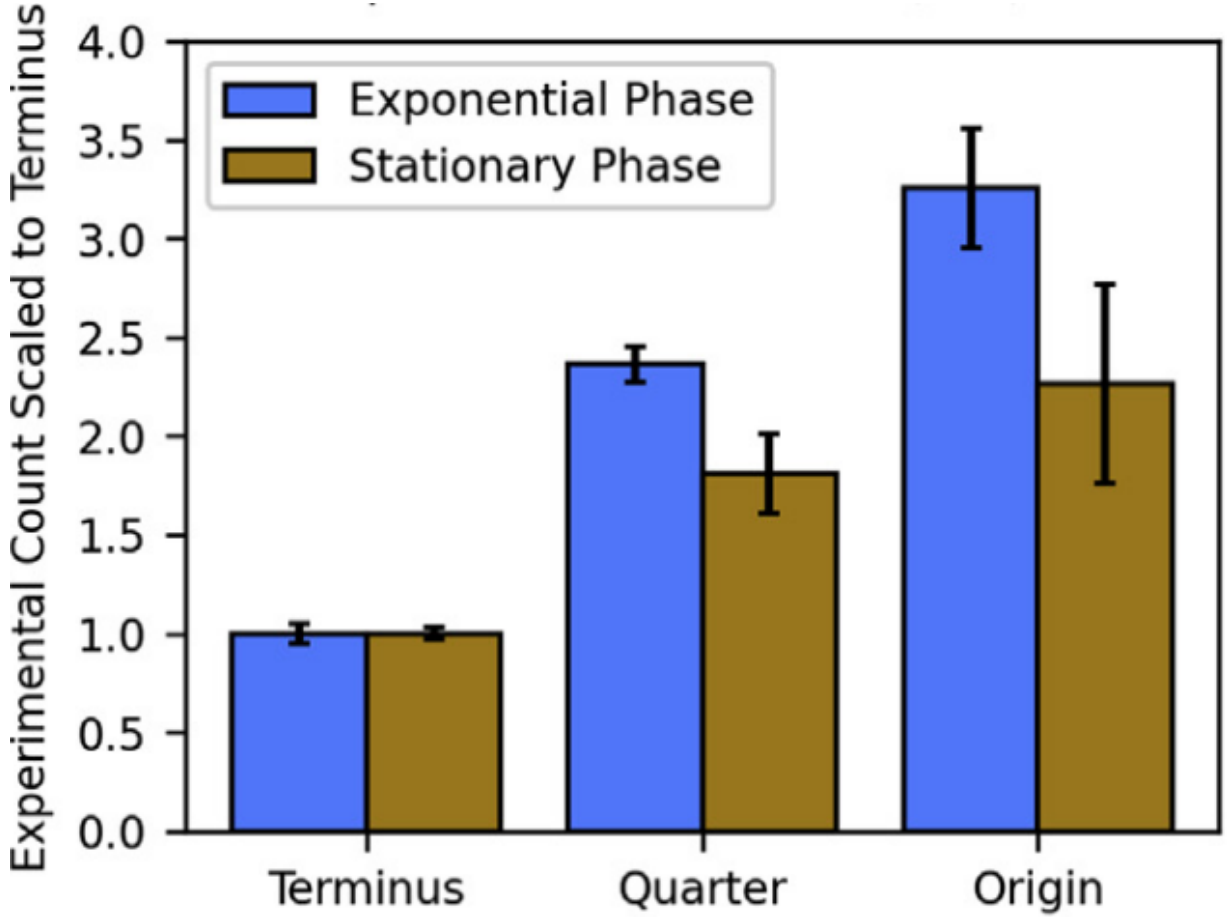
Nested theta structures



m_cw30_ccw30

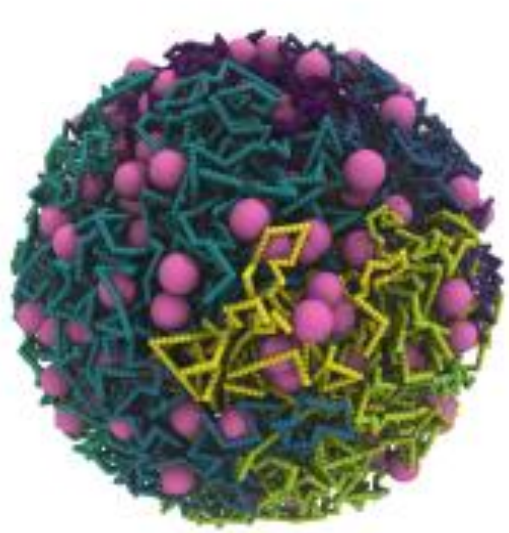


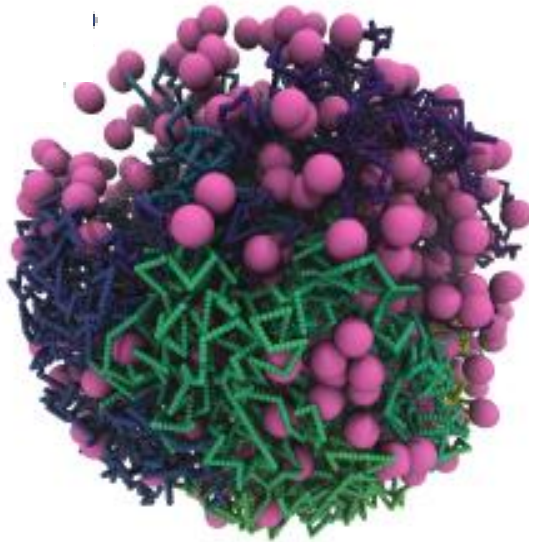
m_cw30_ccw30
mr_cw15_ccw15



Average Ori:Ter ratio from experimental qPCR measurements is 3.4 (Thornburg et al 2022)

Part 2: Preparing the Physical Structure





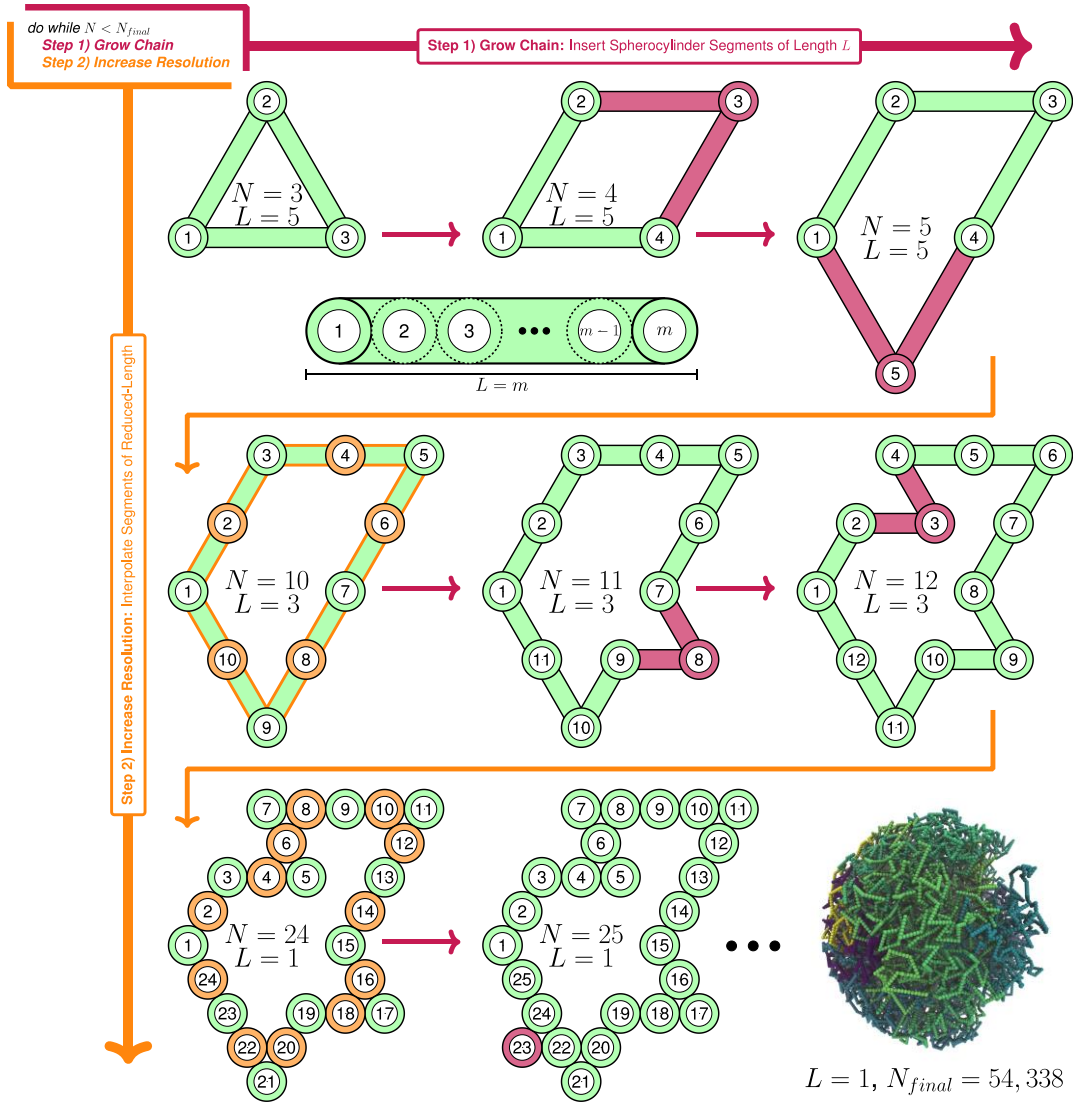
Preparing the physical structure

- We generate chromosome initial configuration using a midpoint-displacement algorithm
- Spherocylinder segments are added iteratively

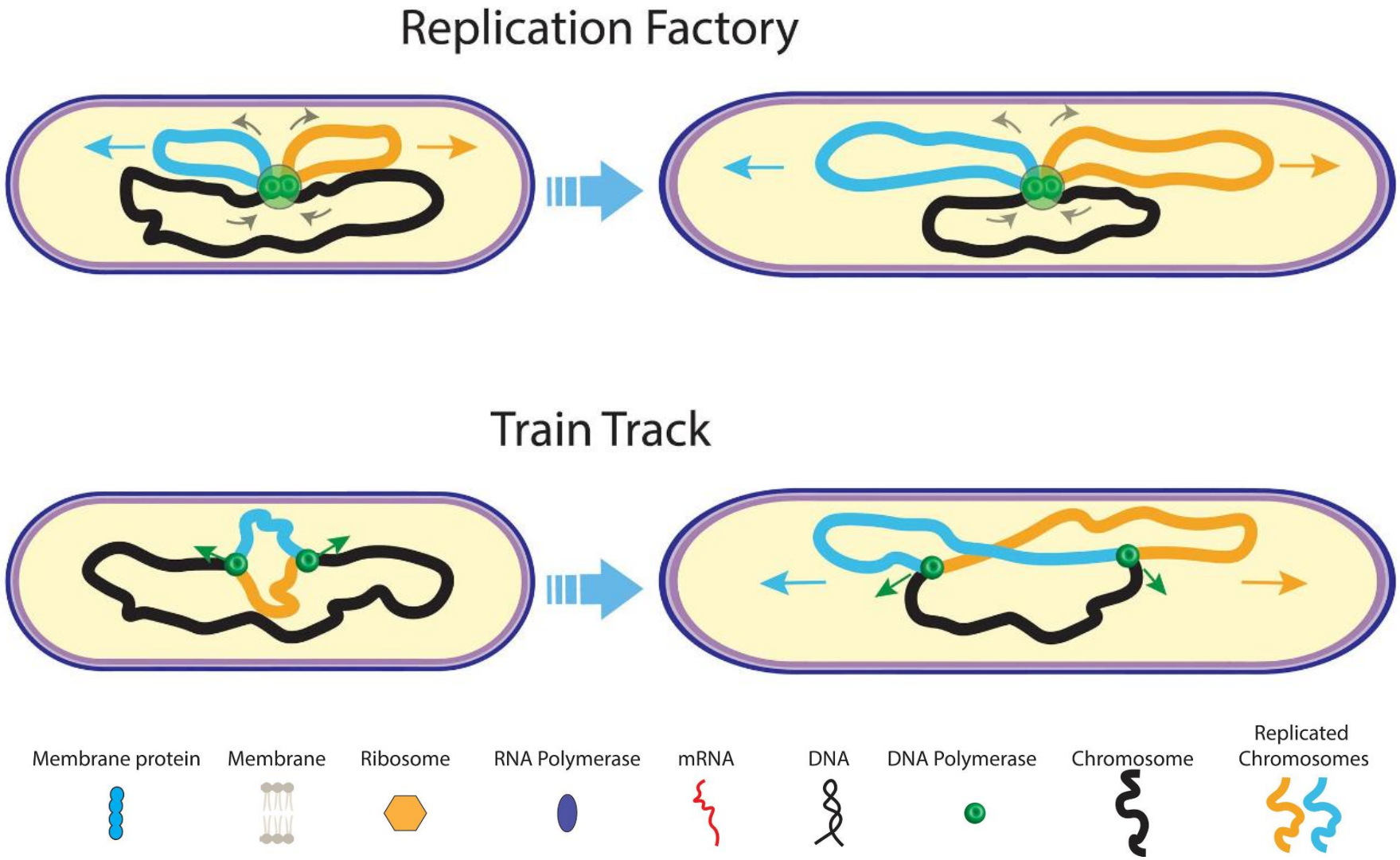
We won't use it here, but the code is available at:

github.com/brg4/sc_chain_generation

- Ribosome distributions reconstructed from cryo-ET

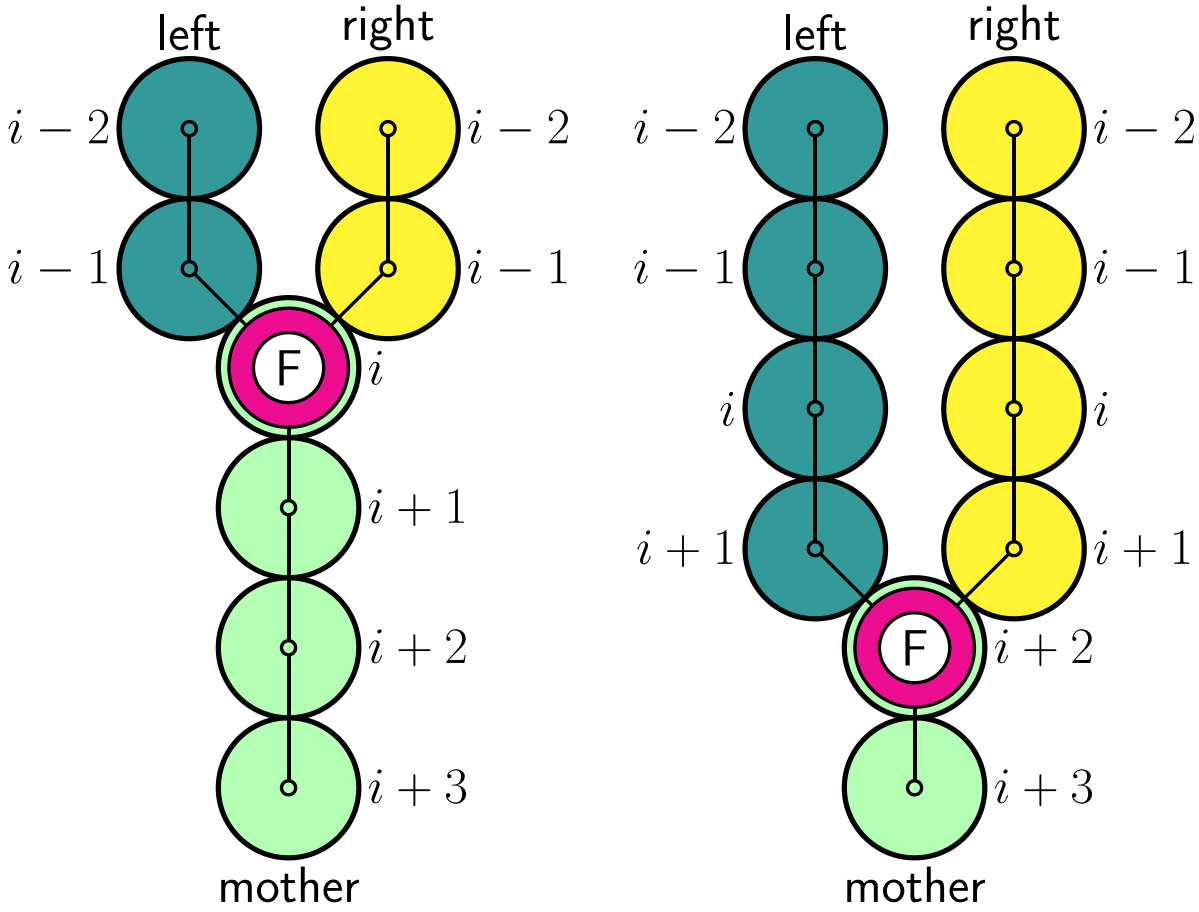


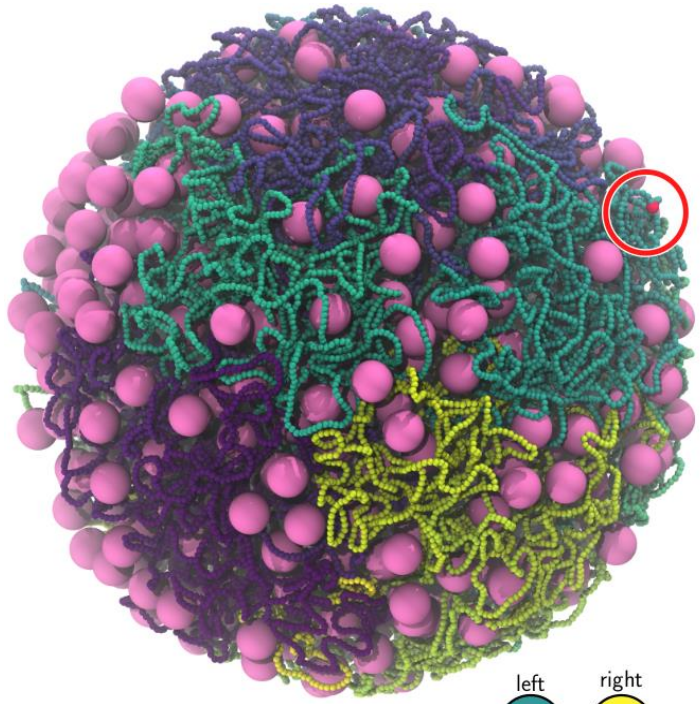
Preparing the physical structure: Replication

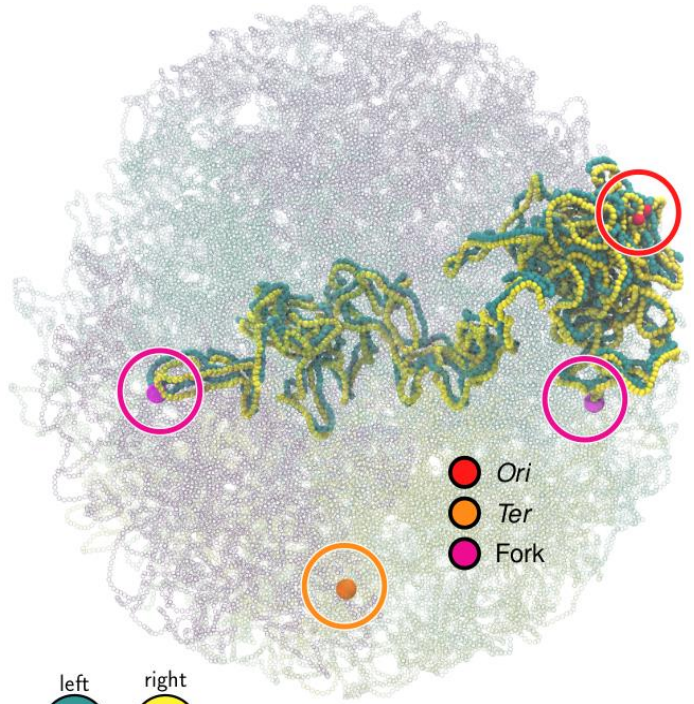


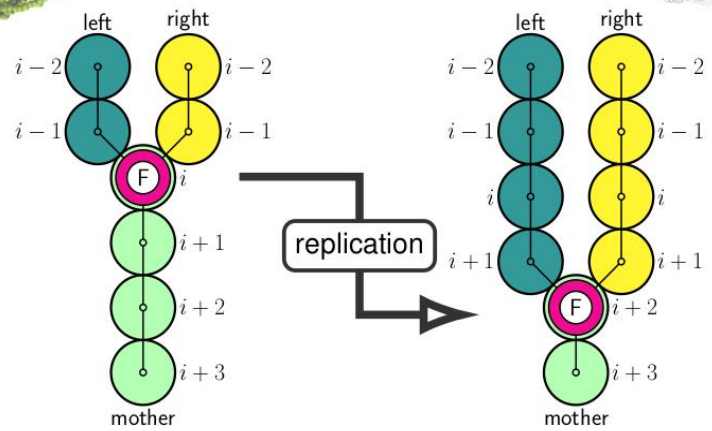
Preparing the physical structure: Replication

- We implement the "train-track" model of bacterial DNA replication
- Monomers are added to left and right daughter chromosomes
- Coordinates for new monomers are determined using position and orientation of corresponding mother monomer

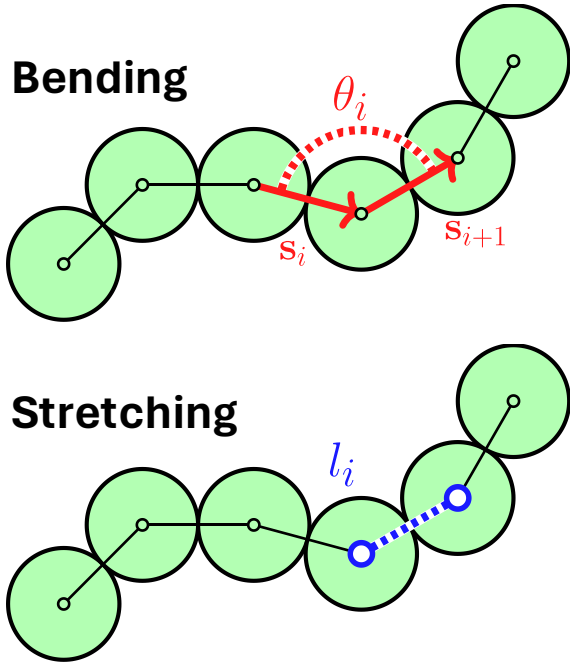


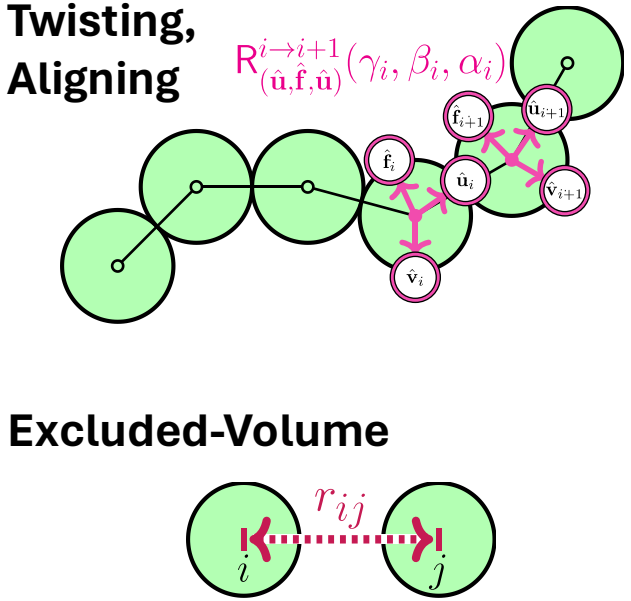


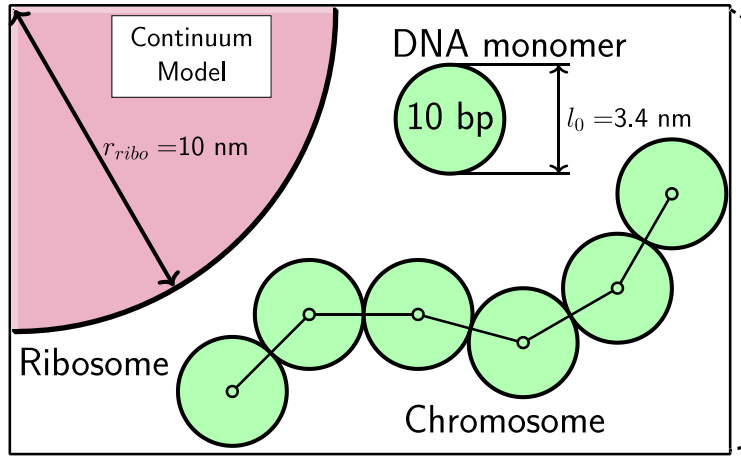

Ori
Ter
Fork

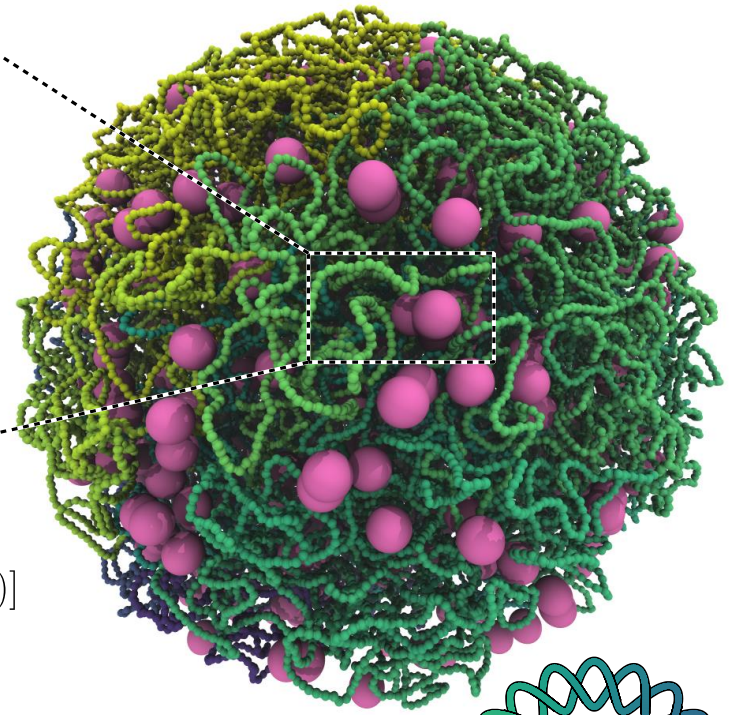

left
right
$i-2$
$i-1$
F
i
$i+1$
$i+2$
$i+3$
mother
replication

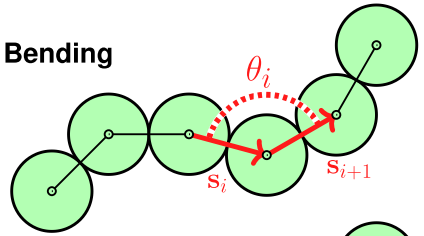
Part 3: Simulating Chromosome Dynamics



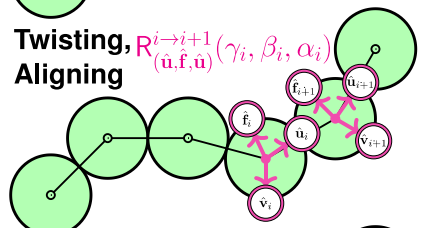








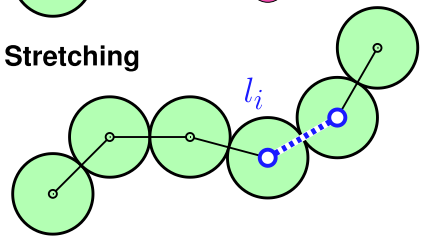
$$U_i^b = \kappa_b[1-\cos(\pi-\theta_i)]$$



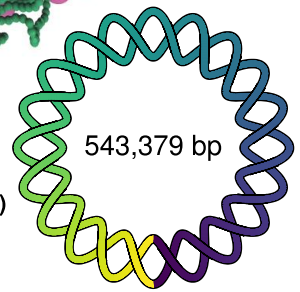
$$U_i^t = \kappa_t[1-\cos(\alpha_i+\gamma_i)]$$

$$U_i^a = \kappa_a[1-\cos\psi_i],$$

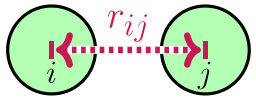
$$\cos\psi_i = \frac{(\mathbf{s}_i\times\hat{\mathbf{v}}_i)\cdot(\mathbf{s}_i\times\hat{\mathbf{v}}_{i+1})}{|\mathbf{s}_i\times\hat{\mathbf{v}}_i||\mathbf{s}_i\times\hat{\mathbf{v}}_{i+1}|}$$



$$U_i^s = -\frac{\kappa_s L_0^2}{2}\log\left[1-(l_i/L_0)^2\right] + 4\epsilon_s[(\frac{\sigma_s}{l_i})^{12}-(\frac{\sigma_s}{l_i})^6]\times \Theta(2^{\frac{1}{6}}\sigma_s - l_i)$$

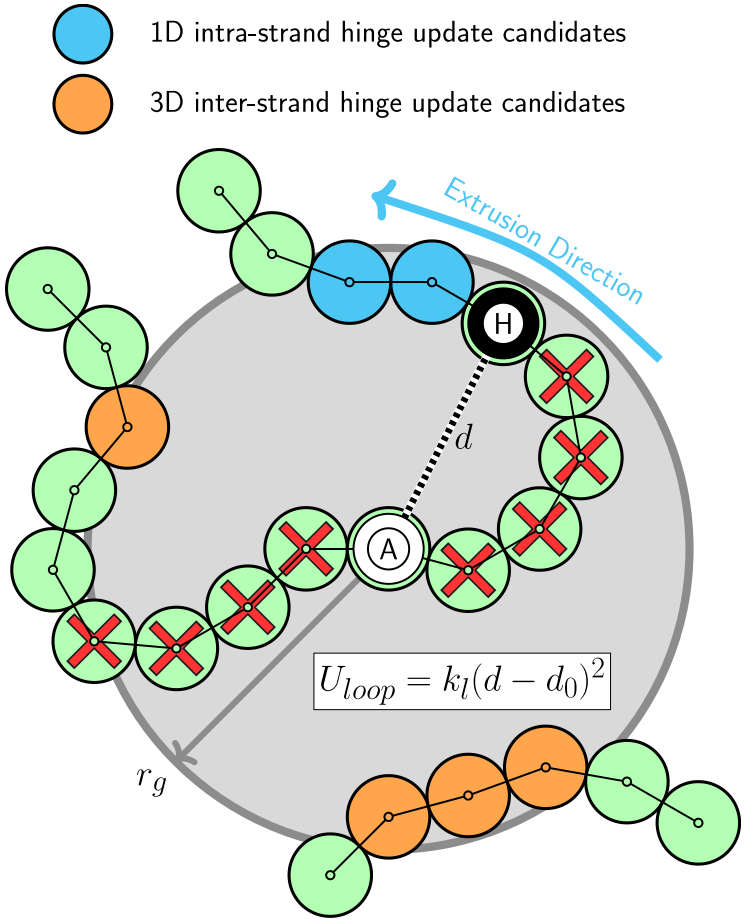


Excluded-Volume
(DNA-DNA,DNA-ribo,ribo-ribo)



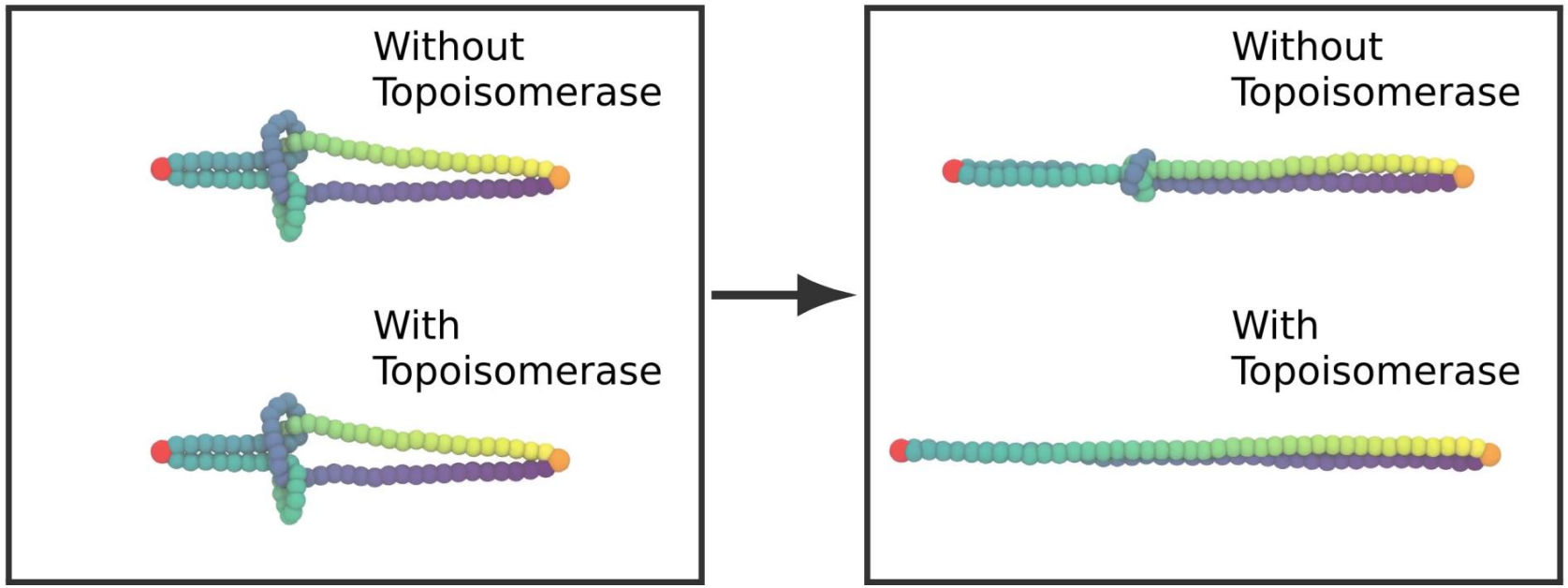
$$U_{ij}^{e.v.} = 4\epsilon_{e.v.}[(\frac{\sigma_{e.v.}}{r_{ij}})^{12}-(\frac{\sigma_{e.v.}}{r_{ij}})^6]\times \Theta(2^{\frac{1}{6}}\sigma_{e.v.} - r_{ij})$$

SMC looping

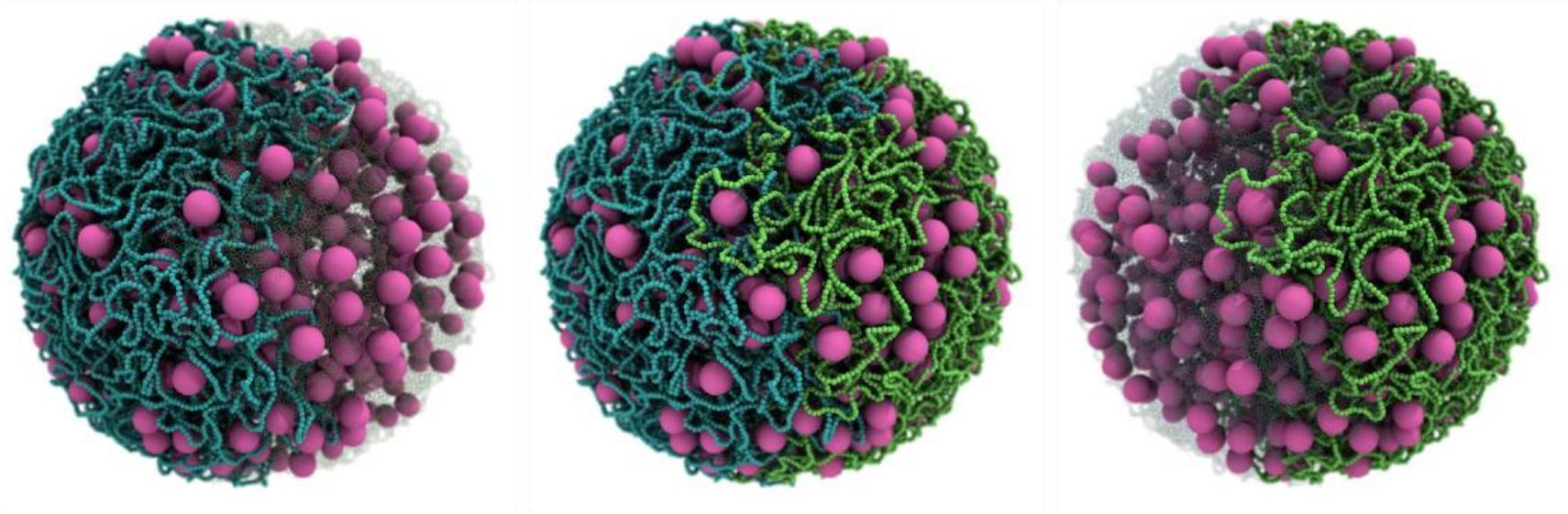

1D intra-strand hinge update candidates
3D inter-strand hinge update candidates
Extrusion Direction
H
A
d
$U_{loop} = k_l(d - d_0)^2$
r_g

Topoisomerase

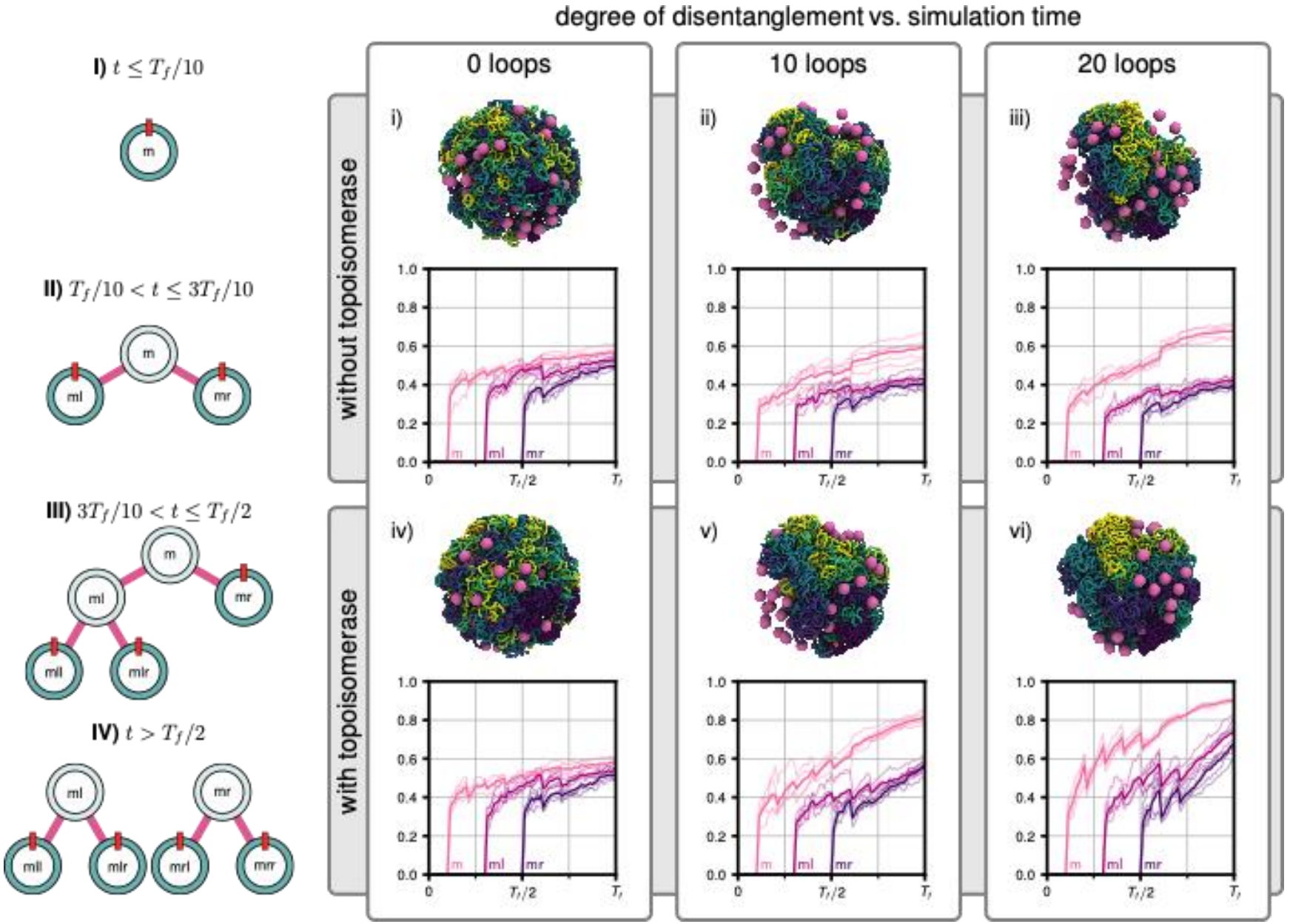
DNA-DNA pair interactions are periodically replaced with $U_{ij}^{topo} = \epsilon_{topo}[1 + \cos(\frac{\pi r_{ij}}{\sigma_{ij}})]$, where $r_{ij} < \sigma_{ij}$.



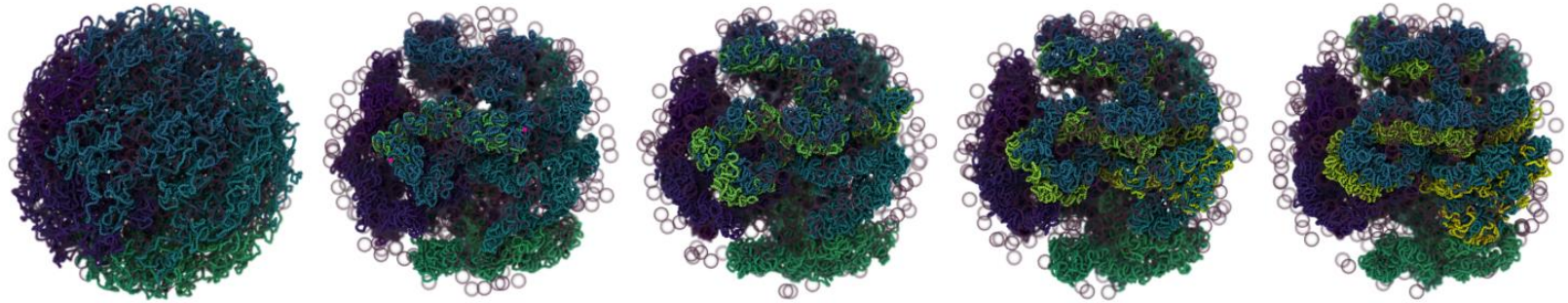
Part 4: Analysis + Fun Stuff

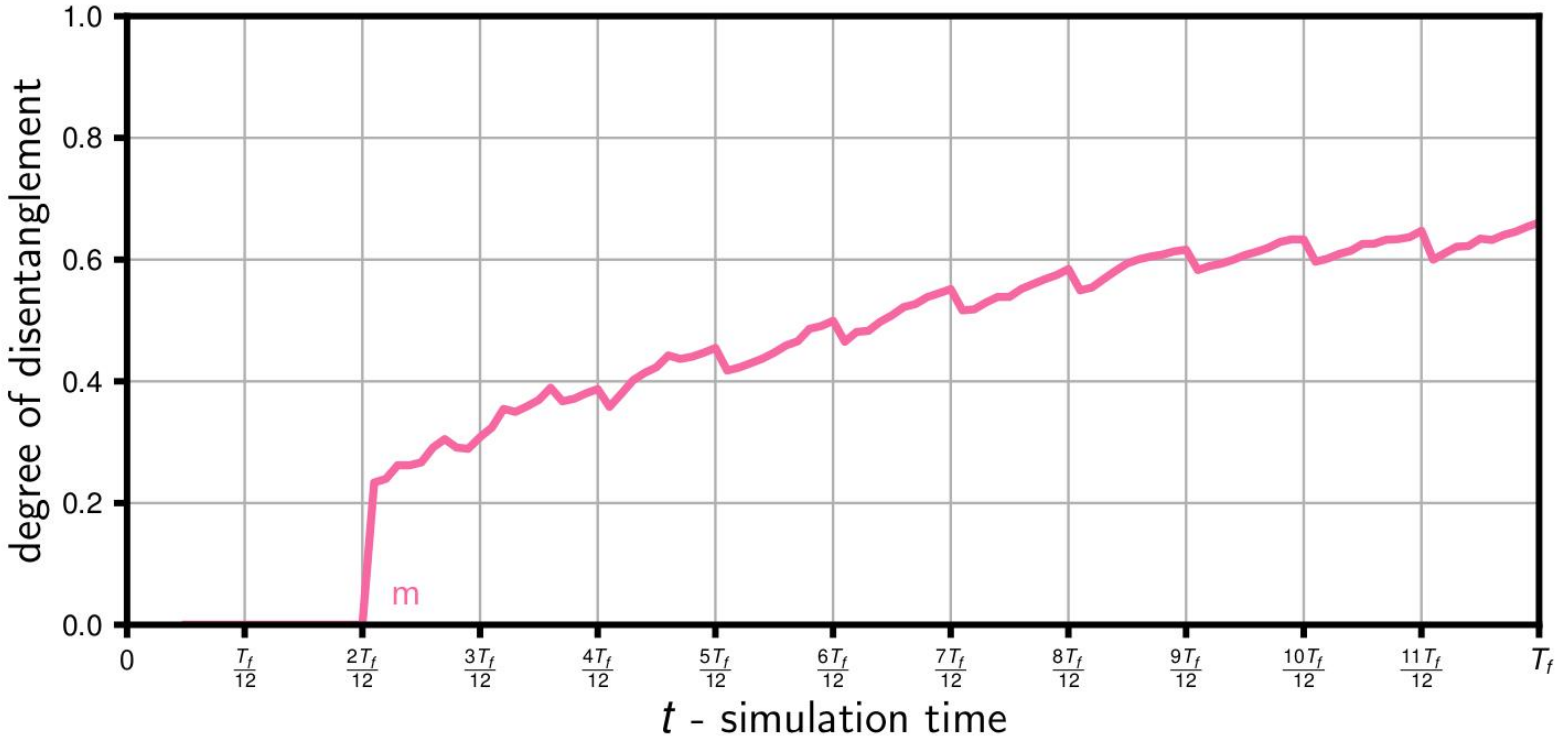


Degree of disentanglement

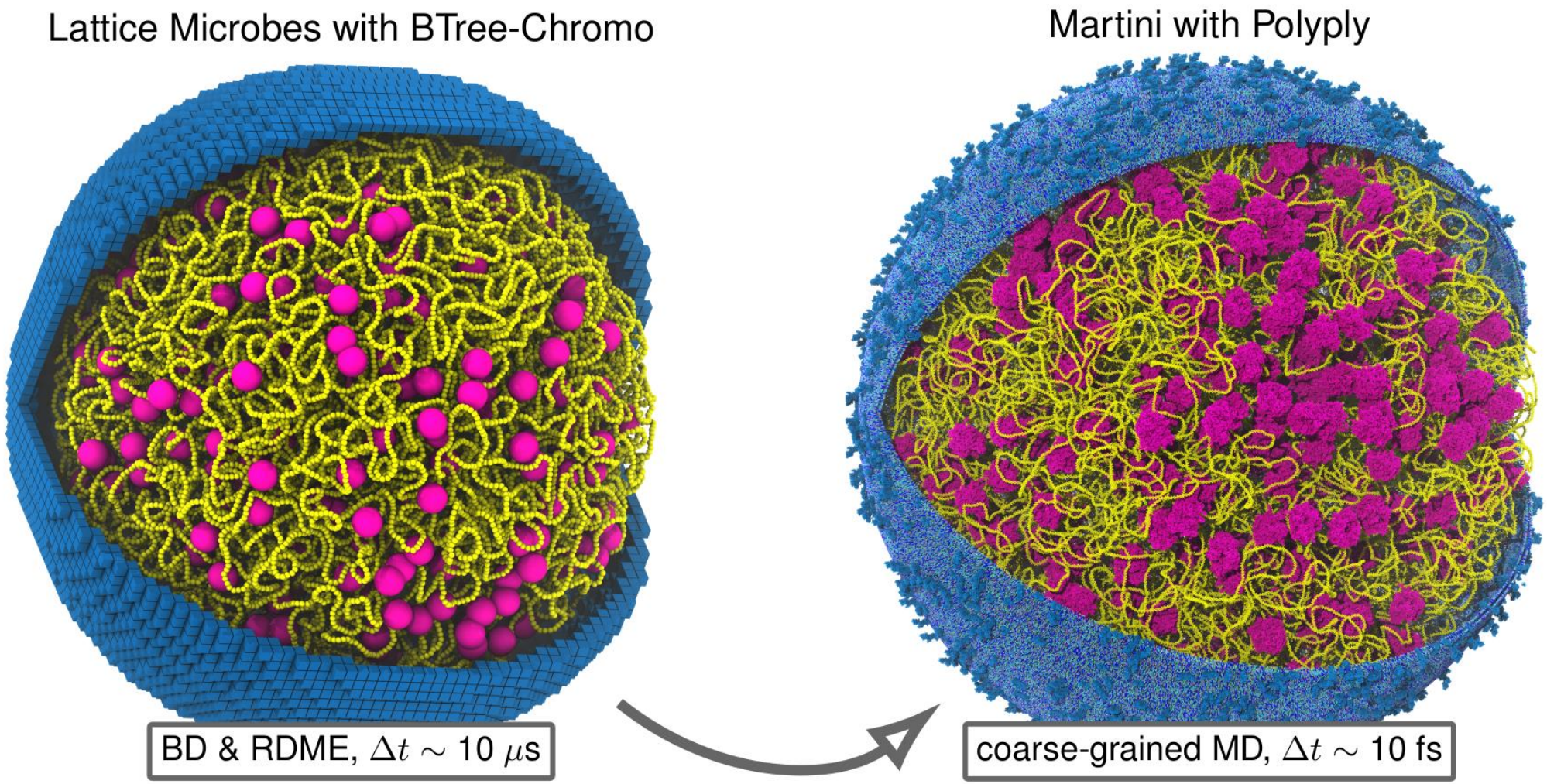


Degree of disentanglement

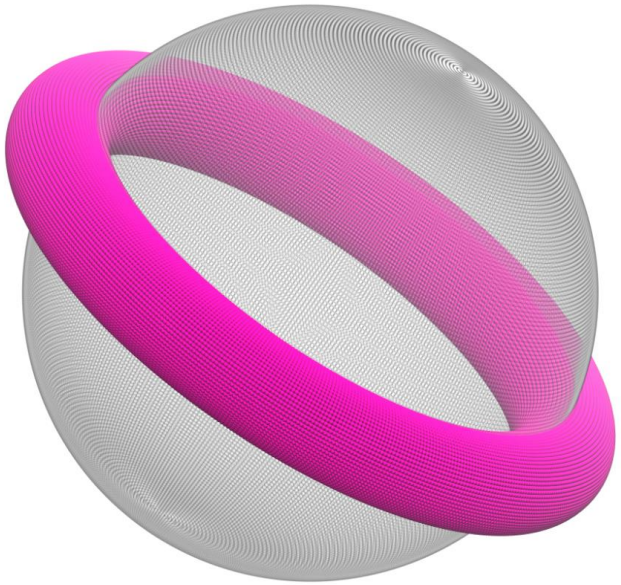


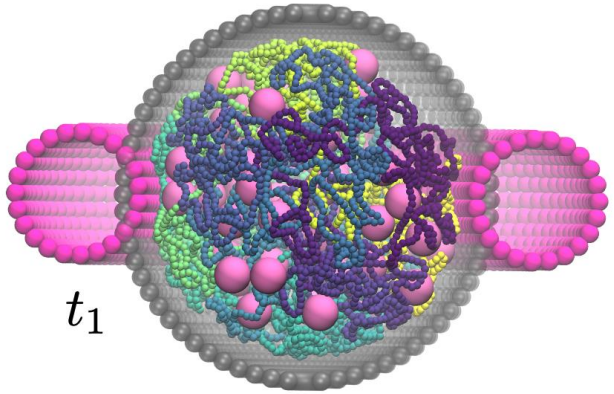


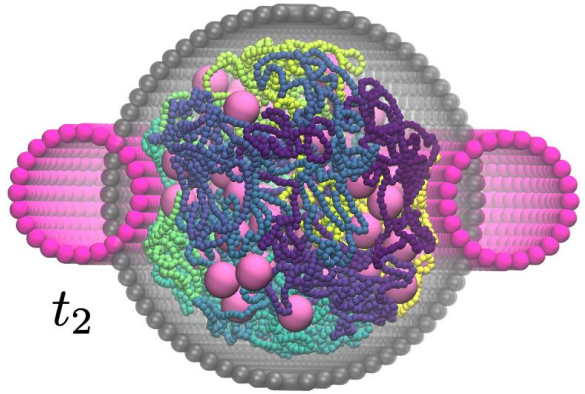
Conversion to LM and MARTINI

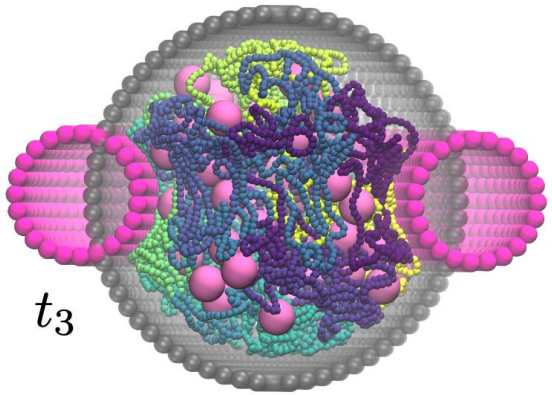


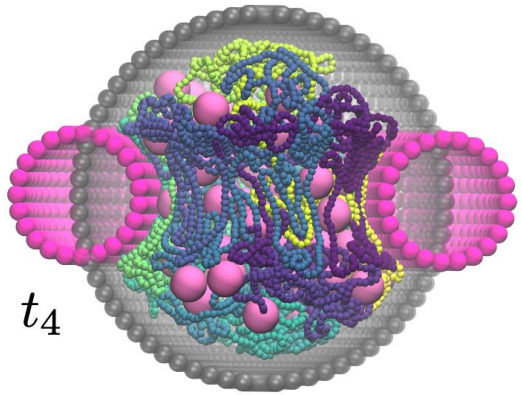
Emulating constriction during cell division











Wrap-Up

In this tutorial, we learned how to:

- Represent replication states, including nested theta structures, with a binary tree model.
- Prepare input coordinates for monomers (iterative algorithm) confined by boundary particles and avoiding ribosomes, and obtain daughter monomer positions using the train track model.
- Simulate Brownian dynamics of DNA calling LAMMPS as a library, including SMC complexes and topoisomerase.
- Analyze disentanglement of daughter chromosomes.

Link to Software bTreeChromo Github

Link to Pubilication Gilbert et al. *Frontiers in Cell & Dev. Bio.*, 2023