Emergent chromosome organization in interphase from loop extrusion

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Overview

Part 1: Background

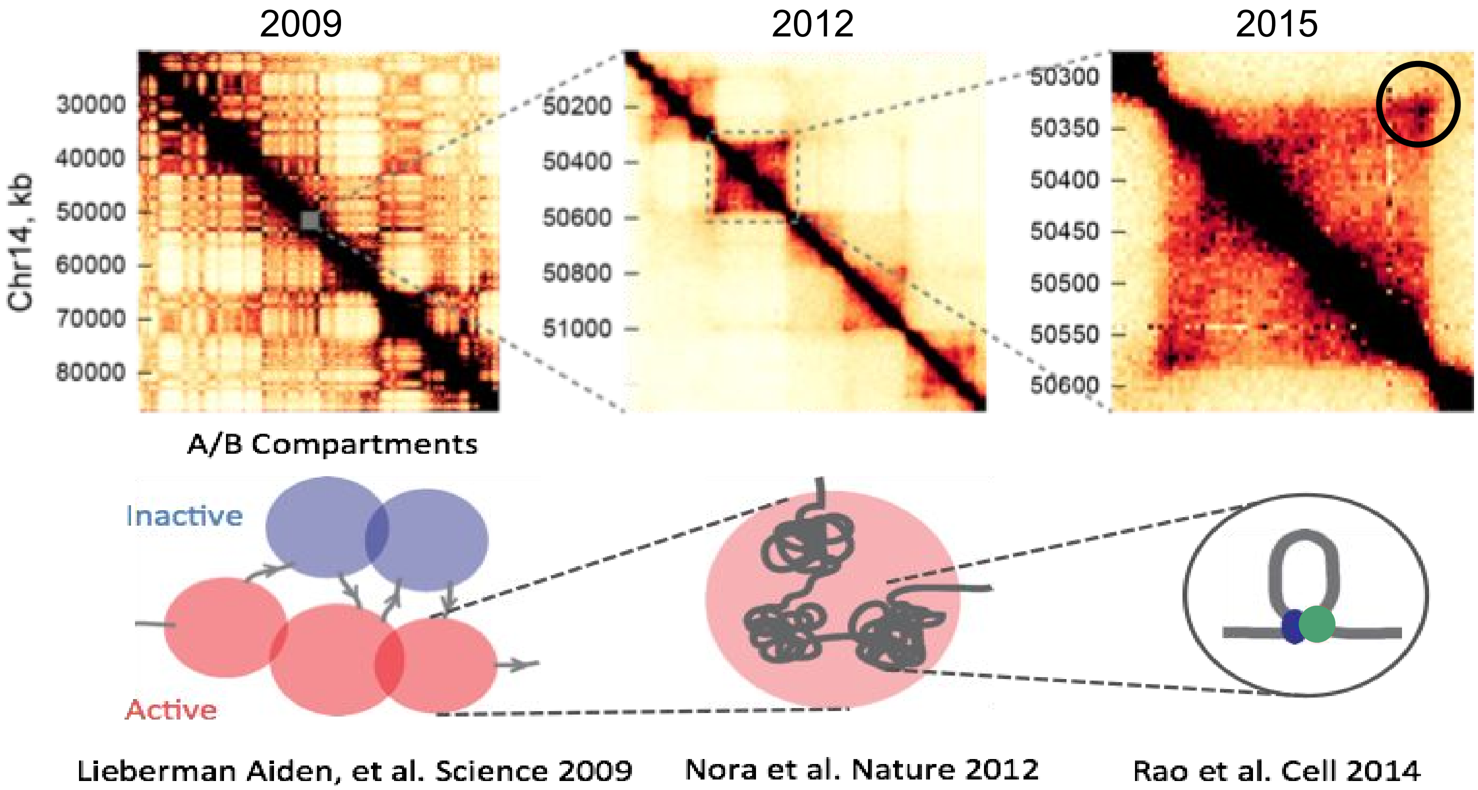
Part 2: Components of a polymer model

  2.1: One-dimensional LEF dynamics

  2.2: Three-dimensional molecular dynamics

Part 3: Future directions

How are loops and domains formed?



De Novo Polymer Modelling

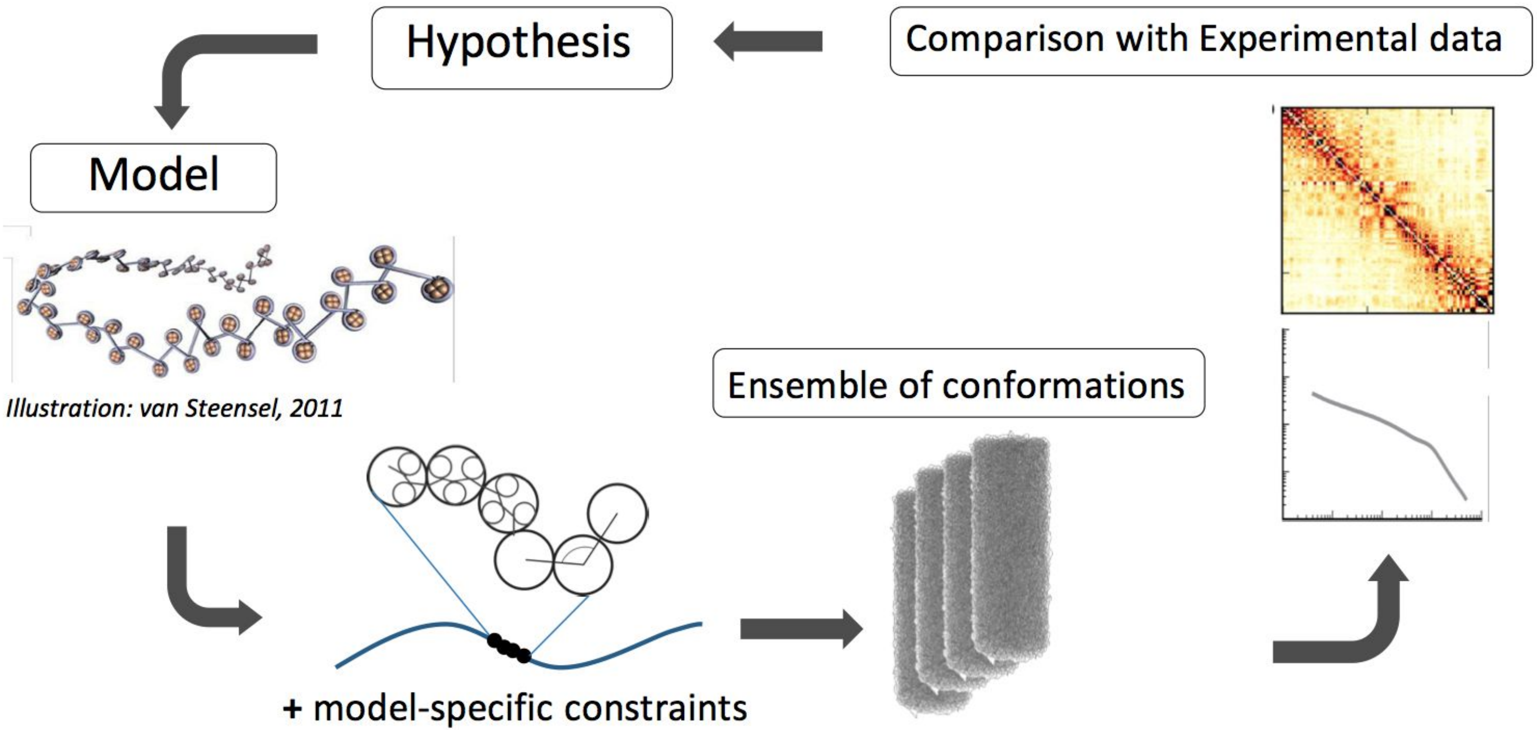


Image credits: Fudenberg, 2016

De Novo Polymer Modelling

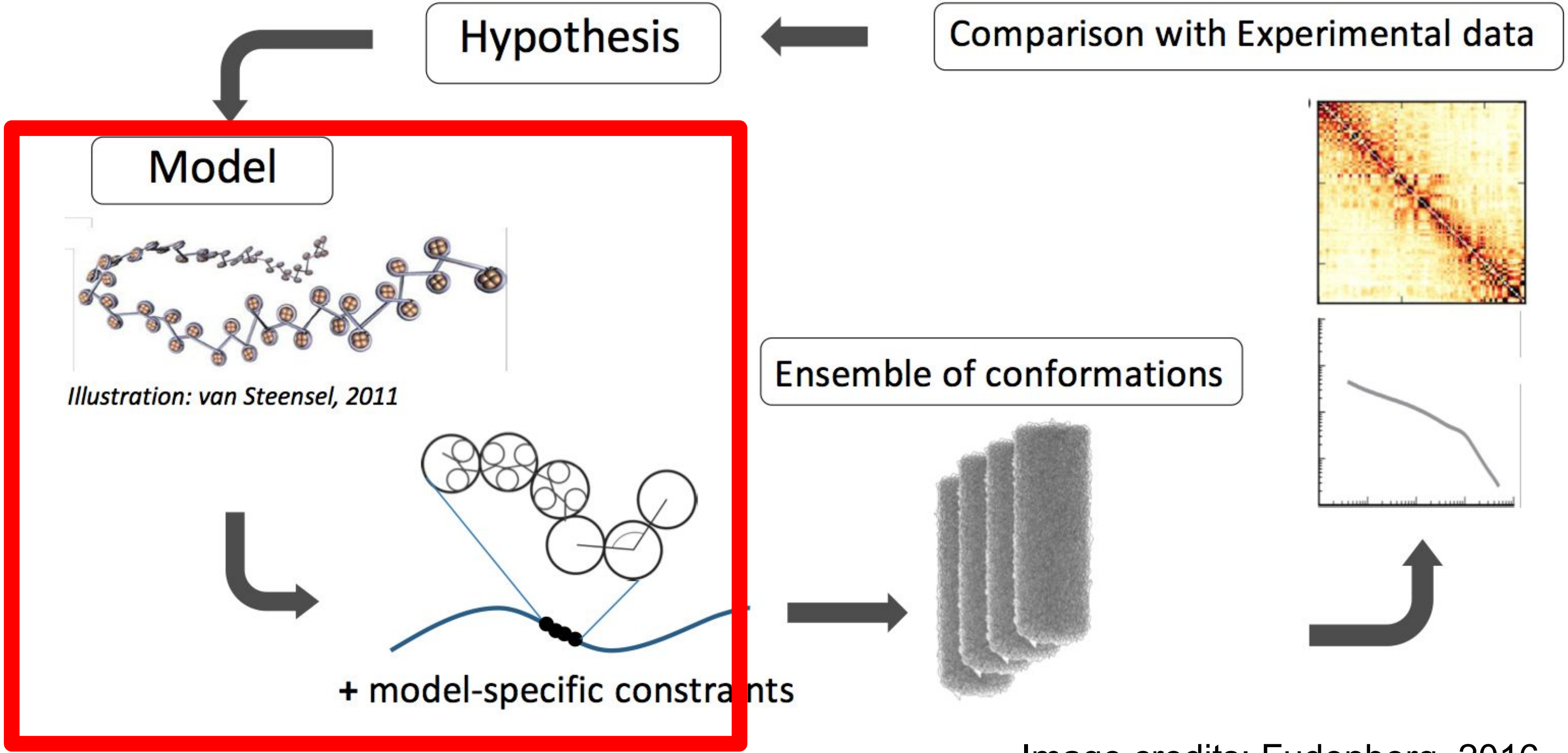


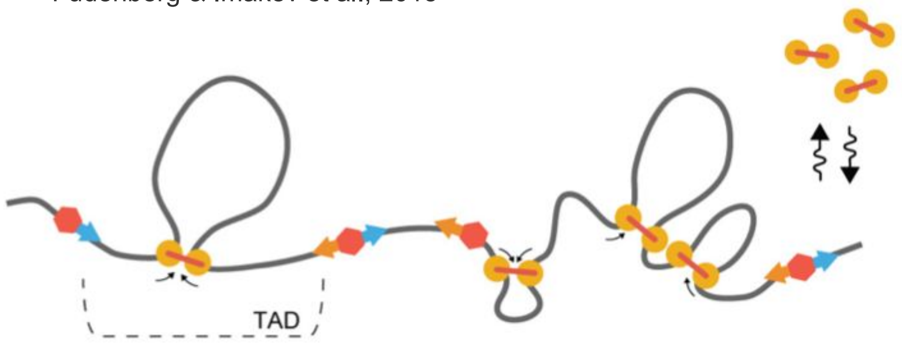
Image credits: Fudenberg, 2016

Interphase extrusion polymer model

1-D LEF Dynamics

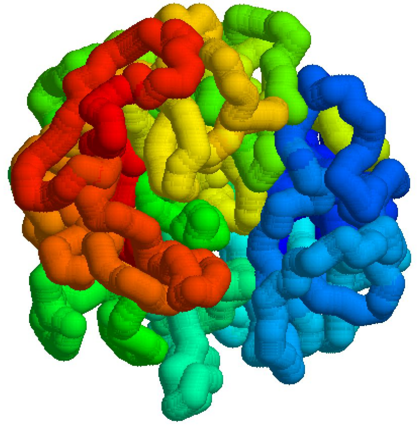
- Behavior of LEFs on the chromatin fiber provides model-specific forces for 3-D simulations

Fudenberg & Imakev et al., 2015

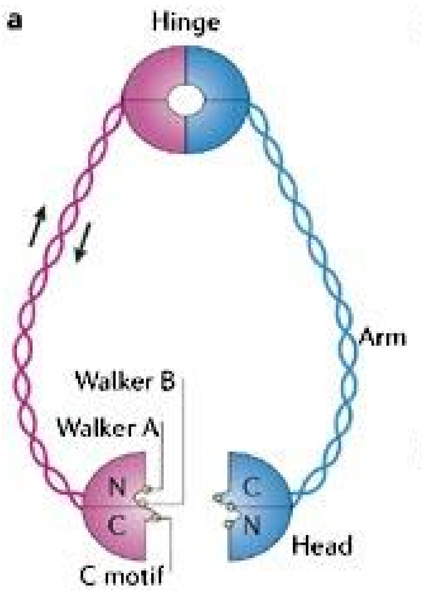


3-D Molecular Dynamics

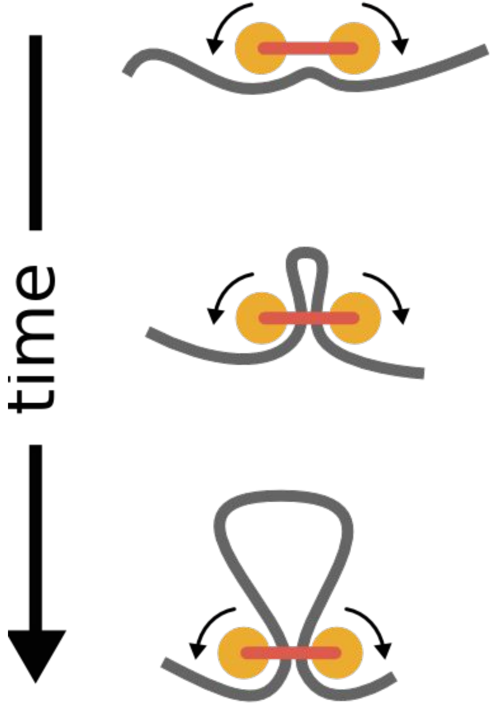
- Physical forces between DNA monomers (repulsion, springs) dictate structure plus model-specific constraints



SMCs as loop-extruding proteins

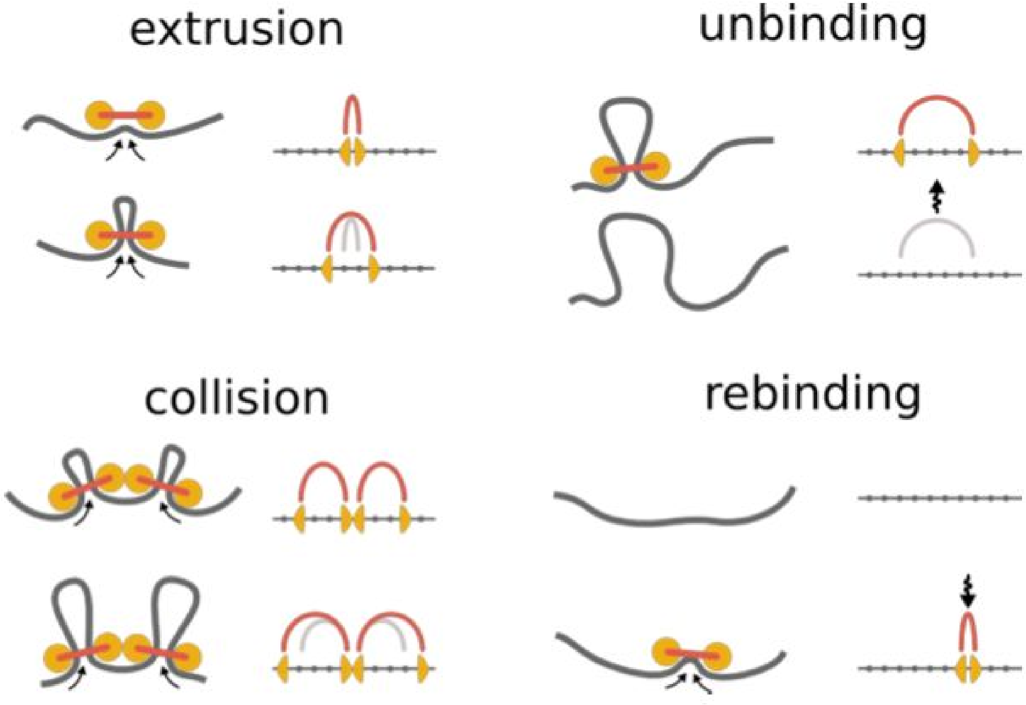


Alipour, Elnaz, and John F. Marko. "Self-organization of domain structures by DNA-loop-extruding enzymes." *Nucleic acids research* 40.22 (2012): 11202-11212.



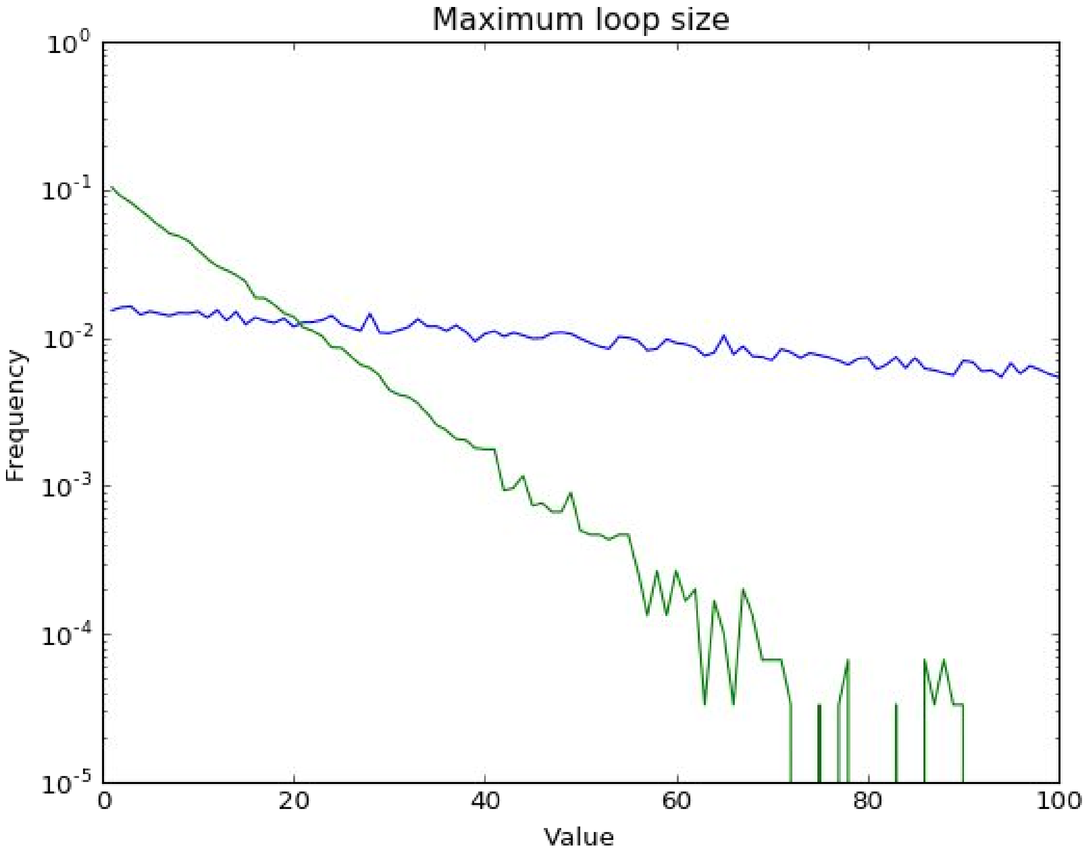
Goloborodko et al, 2016

Dynamics of LEFs



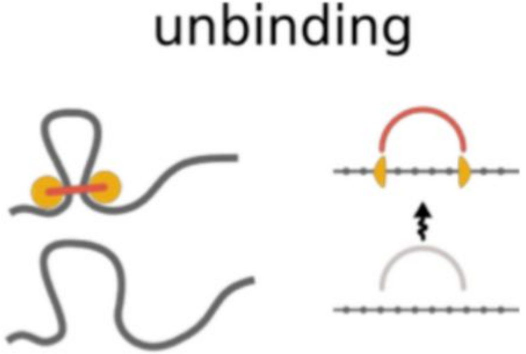
Goloborodko 2015 & Fudenberg & Imakev, 2015

Spontaneous LEF dissociation

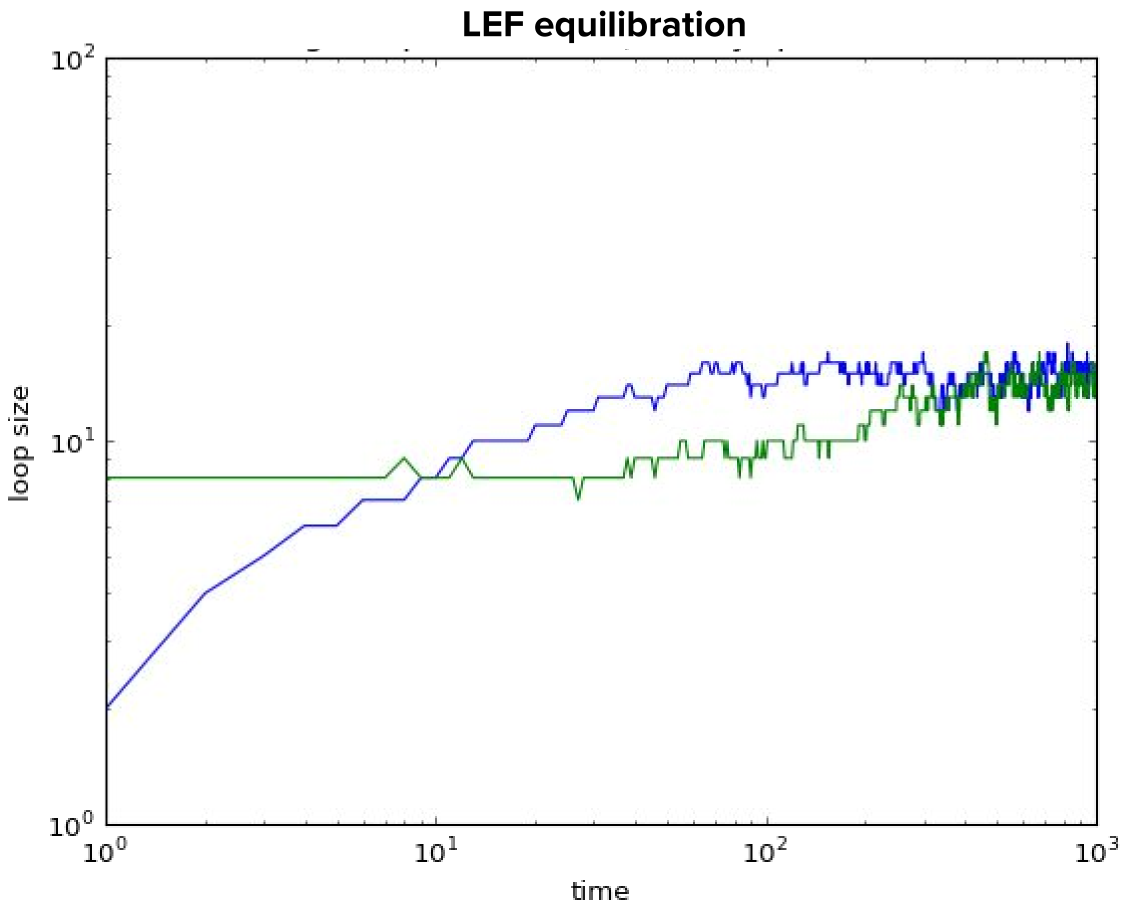


Dissociation probability

- 0.1 (green)
- 0.01 (blue)

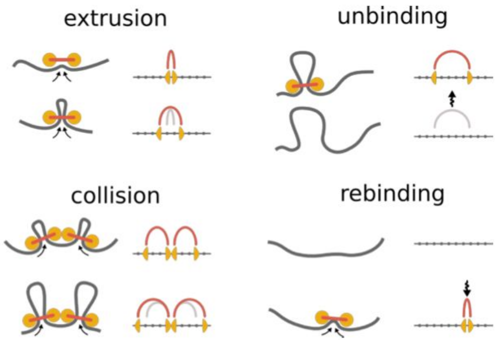


More LEF dynamics



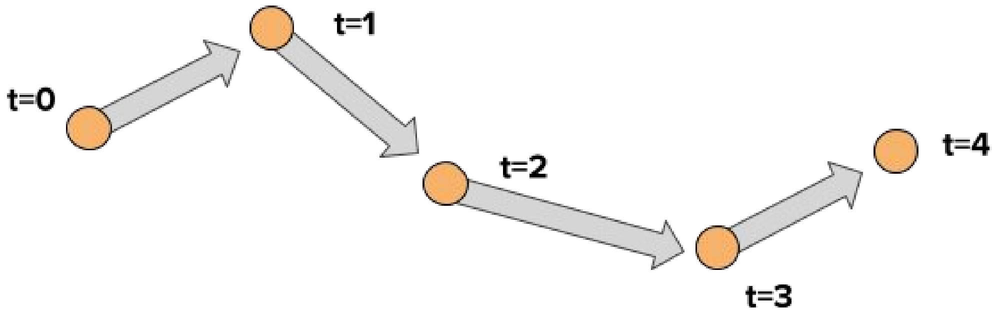
100 evenly spaced LEFS

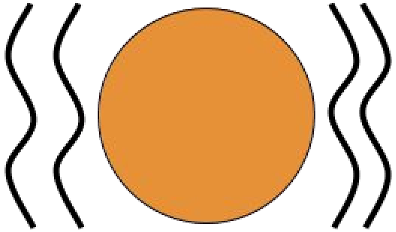
100 randomly placed LEFS



3-D molecular dynamics basics

- Numerical integration: calculating velocity and position of particles from one (very small) timestep to another
- Keep track of directional forces
- Stochastic forces - small, random forces in any direction (implicit solvent)



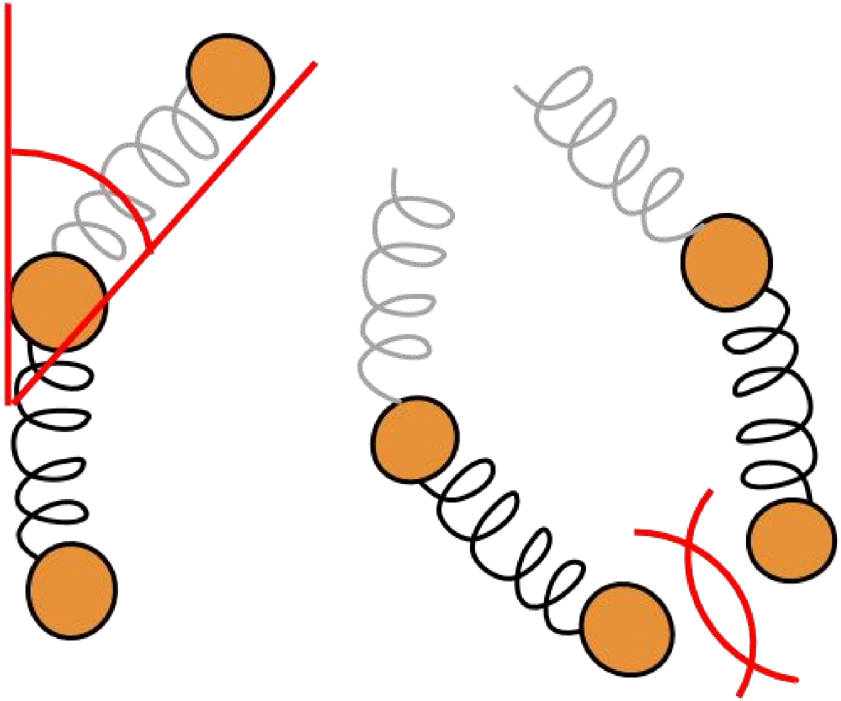


Forces that affect polymers

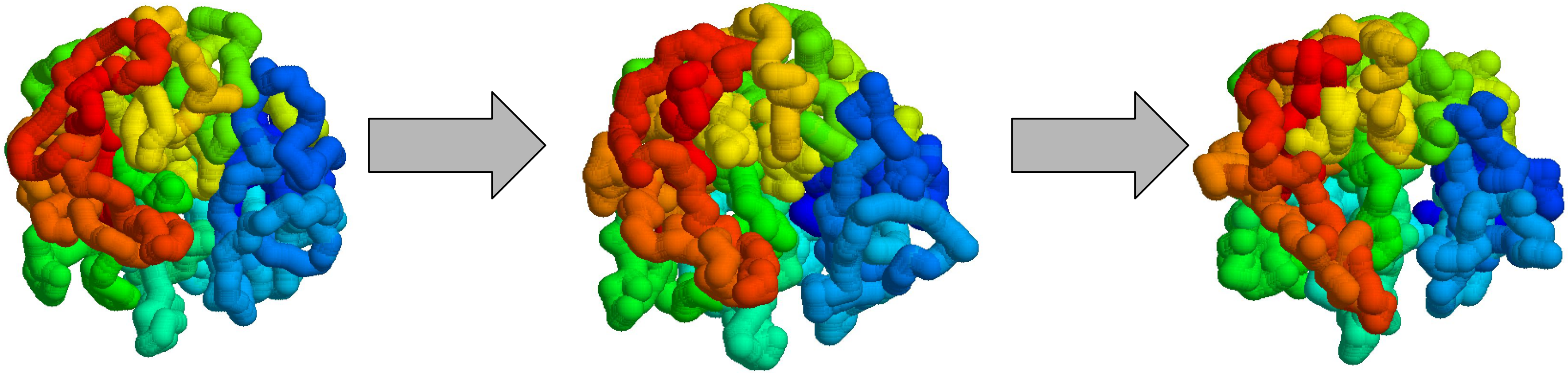
1. Harmonic bonds

2. Steric repulsion

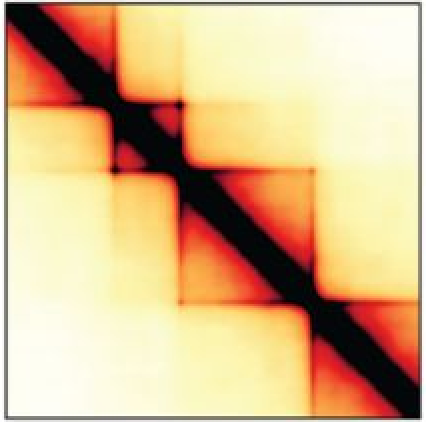
3. Bending energy

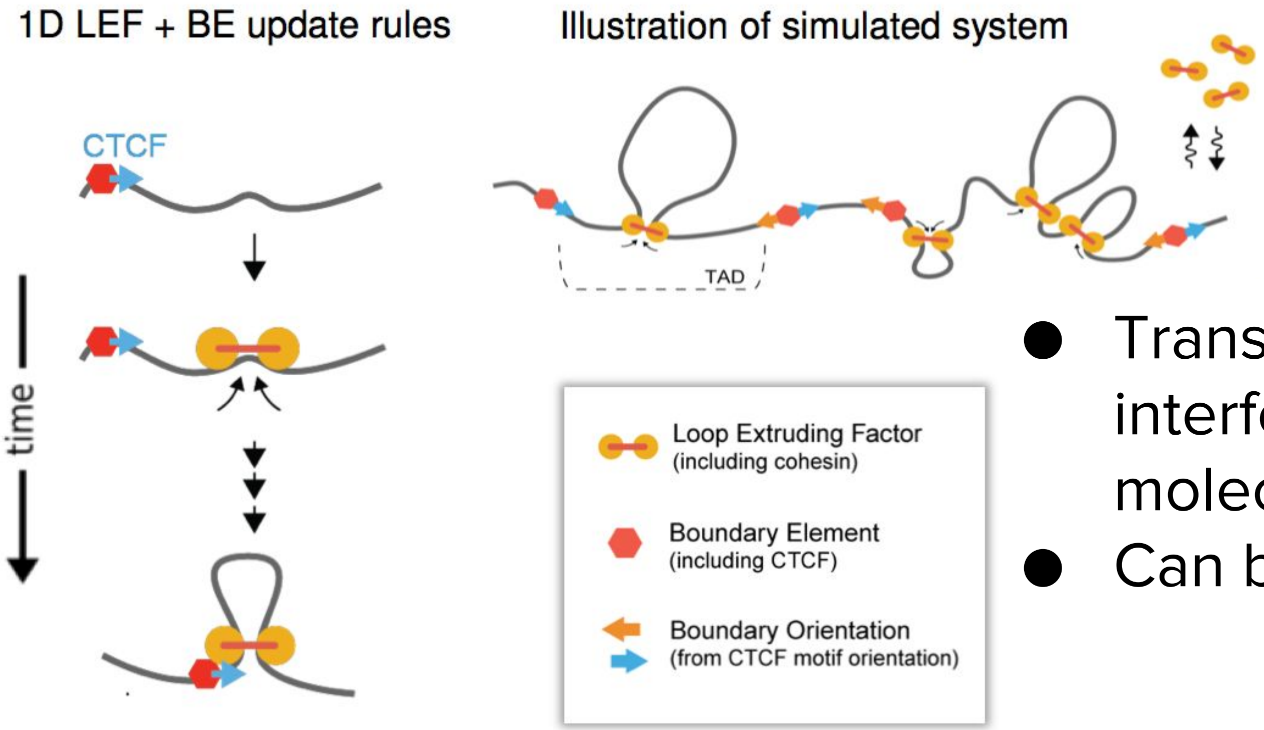


Molecular dynamics simulations



Boundary Elements





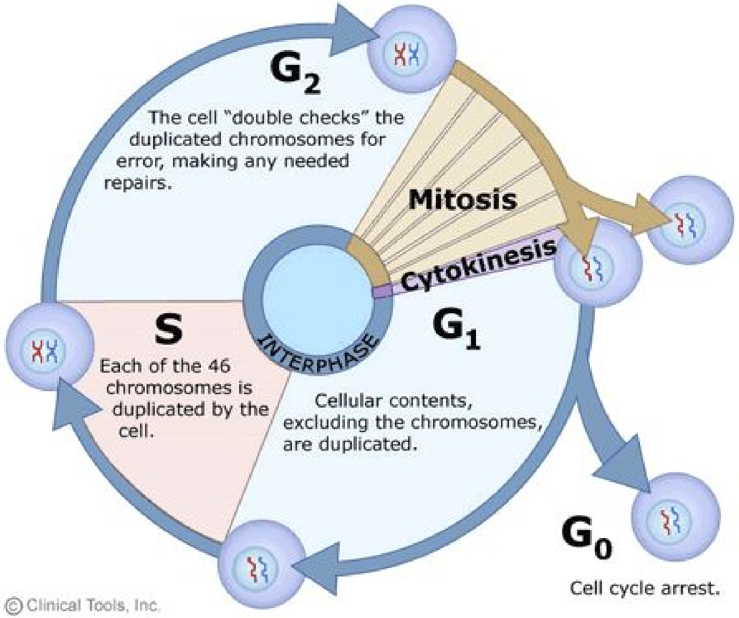
GF & Imakev et al., *biorxiv*

- Translocation-interfering molecules/proteins
- Can be directional

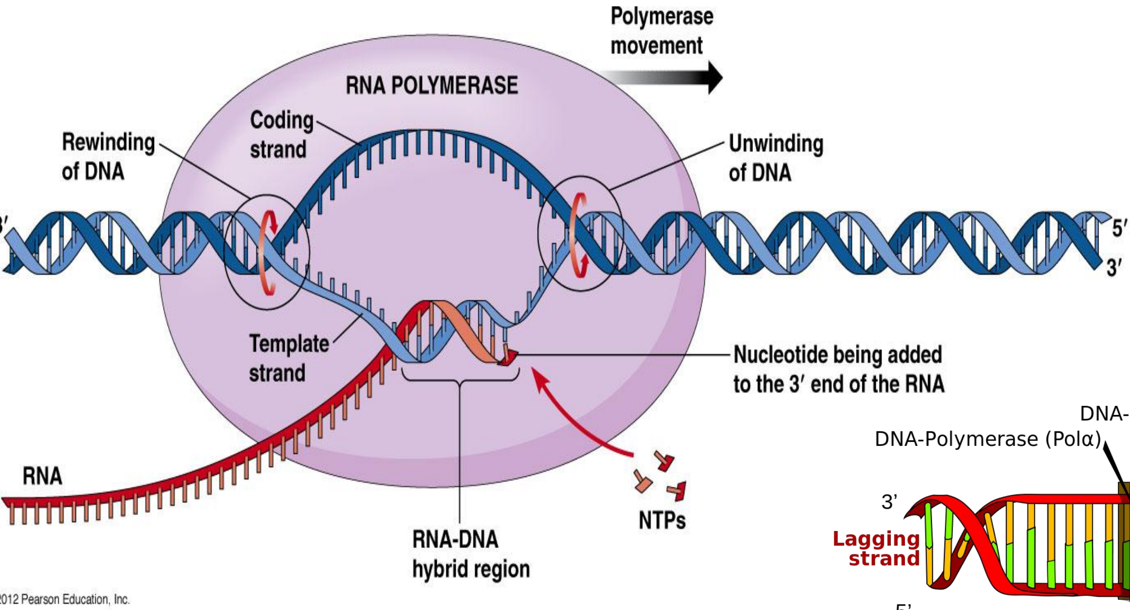
Future directions

-Complications to the **interphase model:**

-Would **RNA transcription** or **DNA replication** interfere with SMCs on the chromatin fiber?

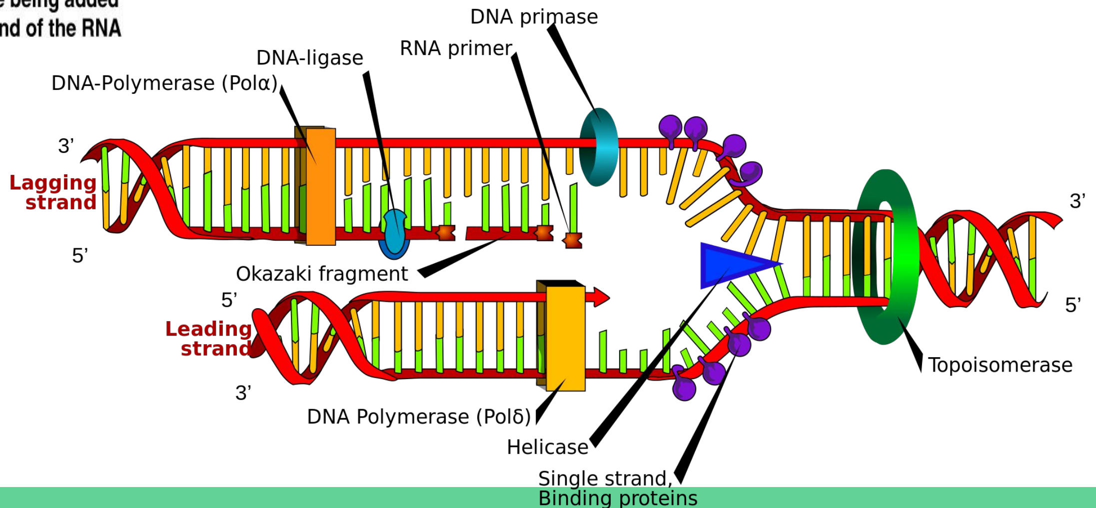


Thinking biologically about interphase events...

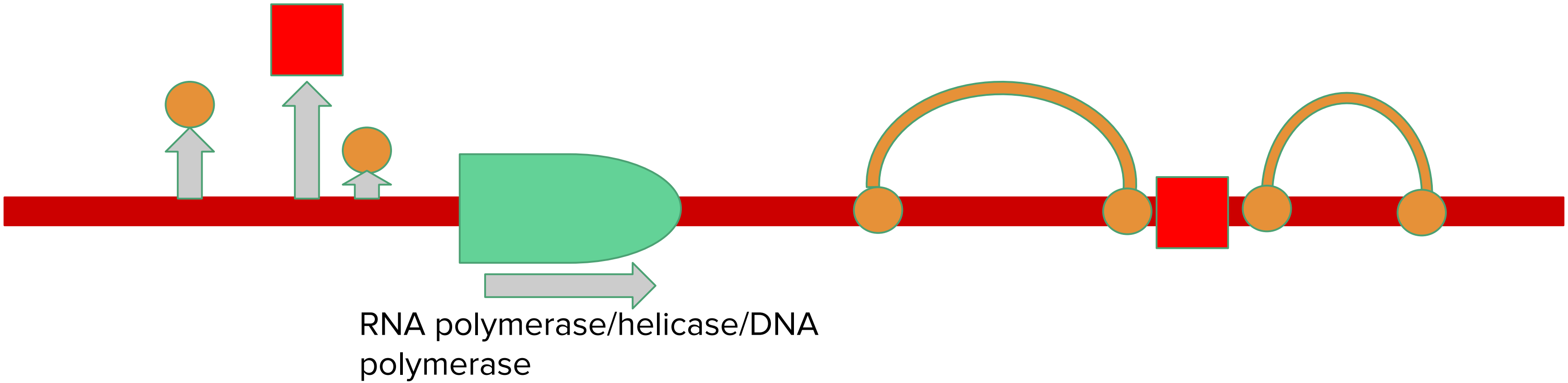


www.mun.ca

en.wikipedia.org



Interference during transcription or replication



Biological processes during interphase could interfere with SMCs - possibly causing them to dissociate

Acknowledgements

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