

The background of the slide is a fluorescence microscopy image of chromosomes in interphase. The chromosomes are stained red, appearing as numerous long, thin, and somewhat irregular loops scattered across the field. Several small, bright green spots are visible, representing specific foci or markers on the chromosomes. The overall appearance is that of a dense, disorganized network of chromatin loops.

Emergent chromosome organization in interphase from loop extrusion

Krishna Suraj

Overview

Part 1: Background

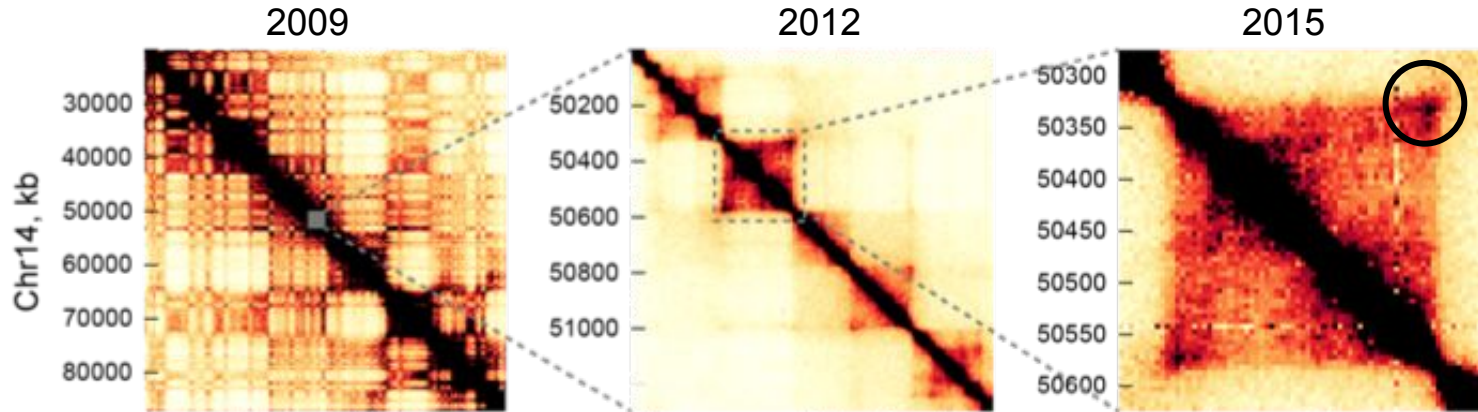
Part 2: Components of a polymer model

2.1: One-dimensional LEF dynamics

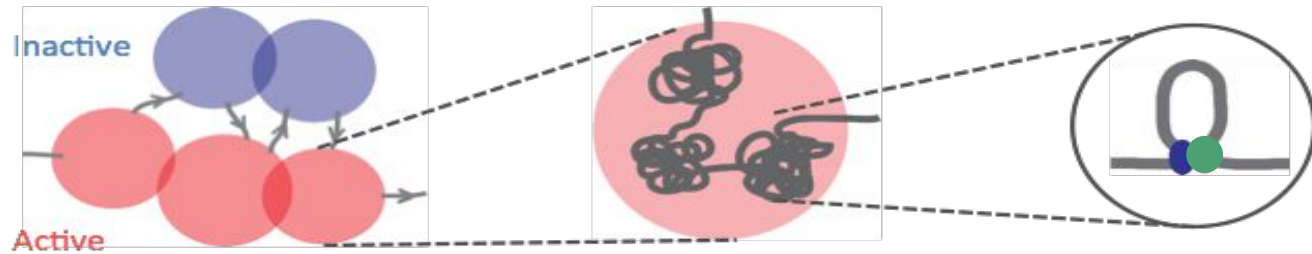
2.2: Three-dimensional molecular dynamics

Part 3: Future directions

How are loops and domains formed?



A/B Compartments



Lieberman Aiden, et al. Science 2009

Nora et al. Nature 2012

Rao et al. Cell 2014

De Novo Polymer Modelling

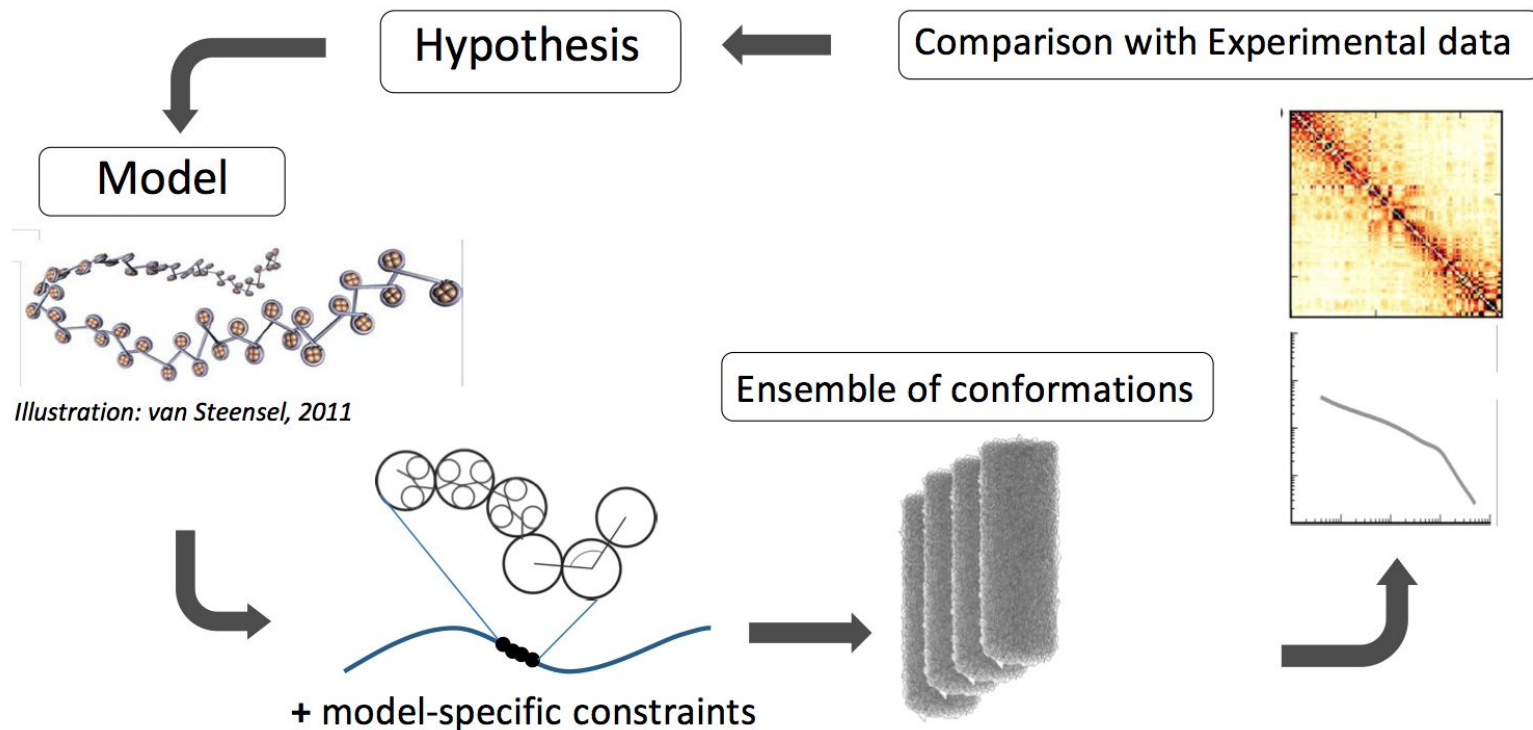


Image credits: Fudenberg, 2016

De Novo Polymer Modelling

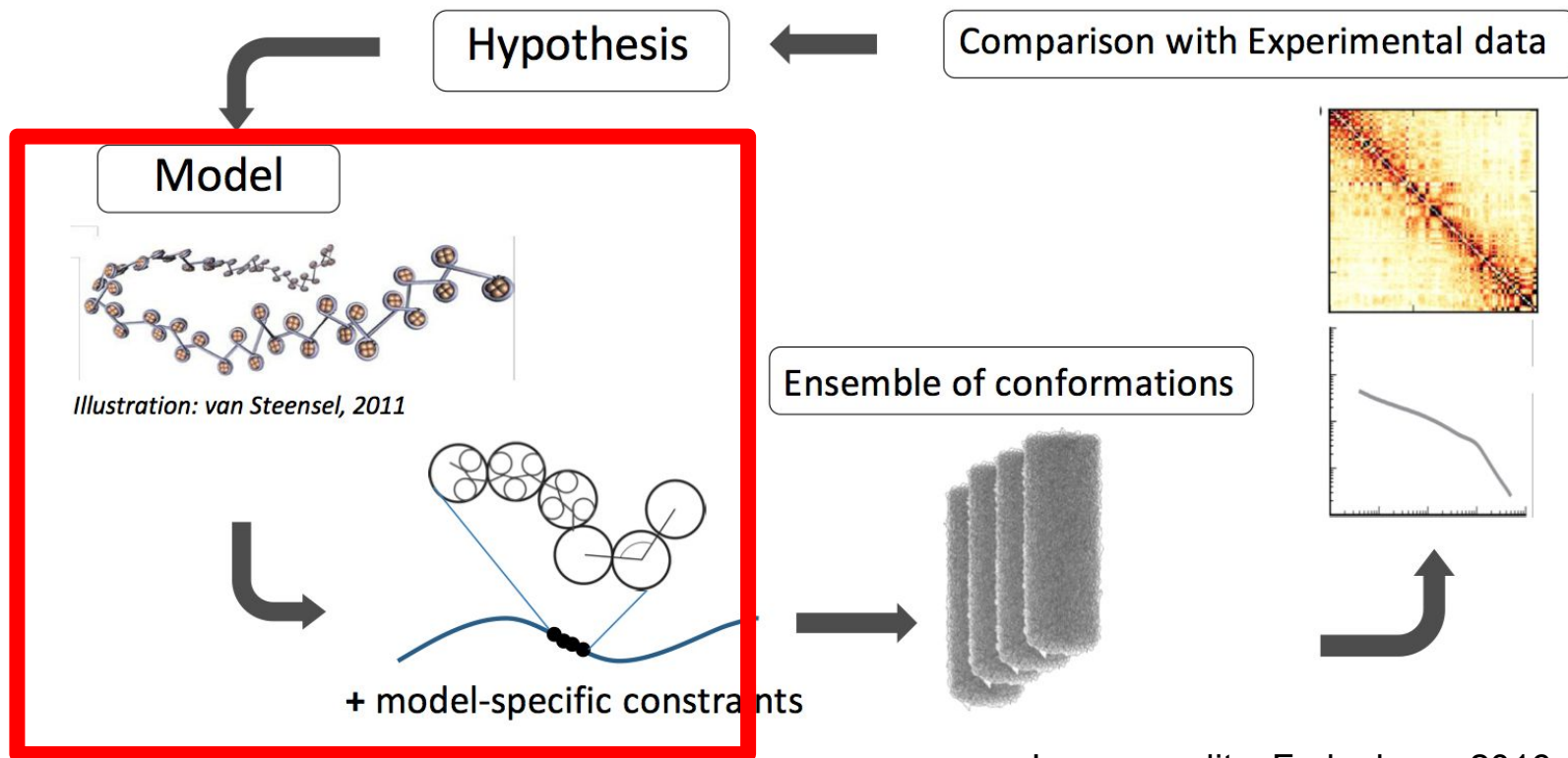


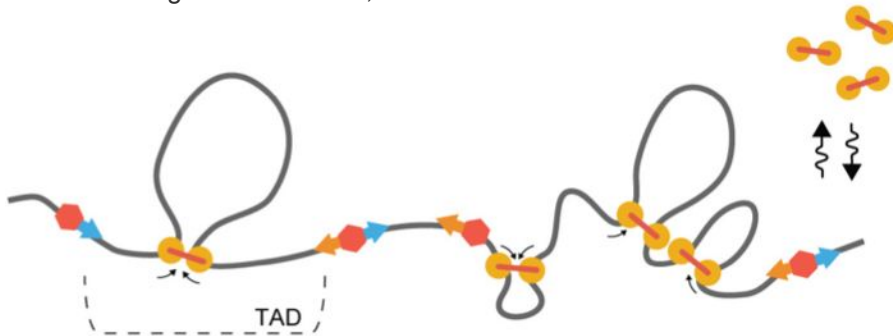
Image credits: Fudenberg, 2016

Interphase extrusion polymer model

1-D LEF Dynamics

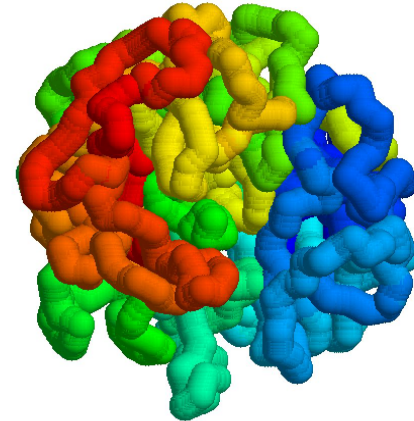
- Behavior of LEFs on the chromatin fiber provides model-specific forces for 3-D simulations

Fudenberg & Imakev et al., 2015

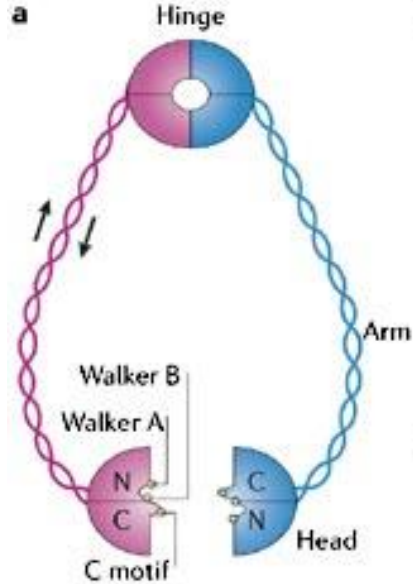


3-D Molecular Dynamics

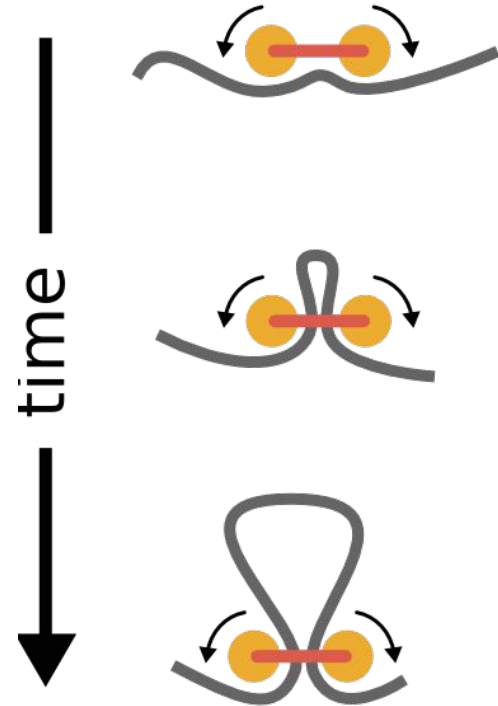
- Physical forces between DNA monomers (repulsion, springs) dictate structure plus model-specific constraints



SMCs as loop-extruding proteins

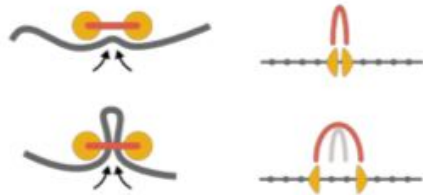


Alipour, Elnaz, and John F. Marko. "Self-organization of domain structures by DNA-loop-extruding enzymes." *Nucleic acids research* 40.22 (2012): 11202-11212.

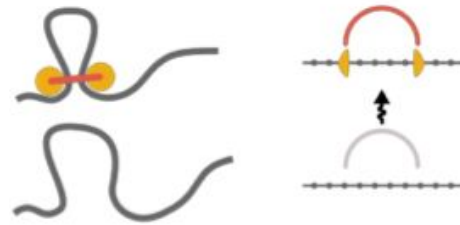


Dynamics of LEFs

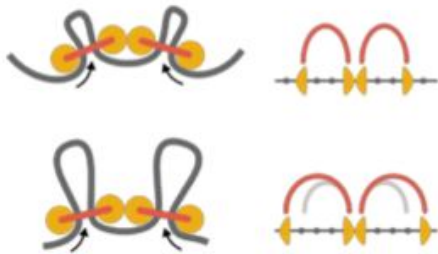
extrusion



unbinding



collision

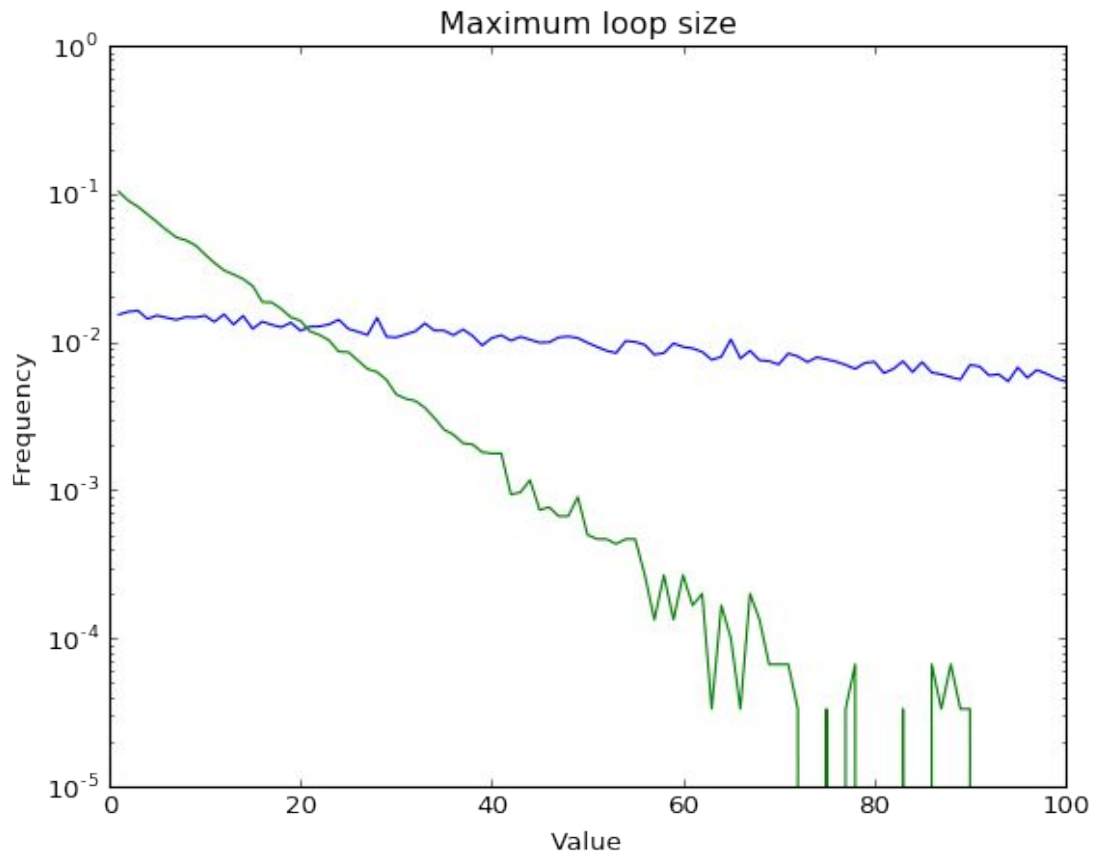


rebinding



Goloborodko 2015 &
Fudenberg & Imkev,
2015

Spontaneous LEF dissociation

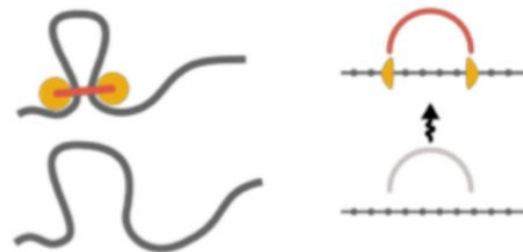


Dissociation probability

 **0.1**

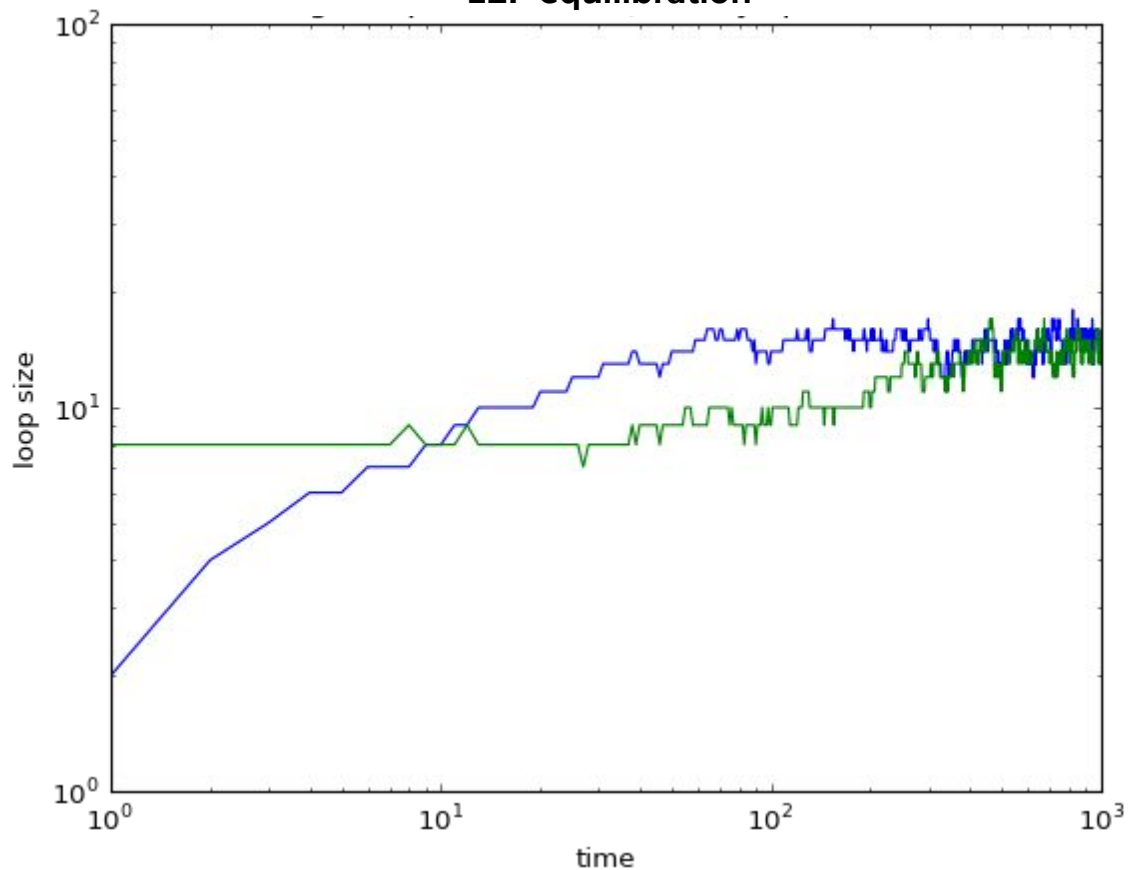
 **0.01**

unbinding



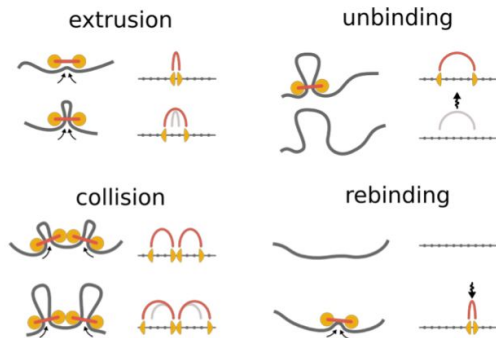
More LEF dynamics

LEF equilibration



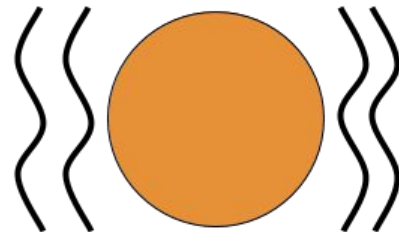
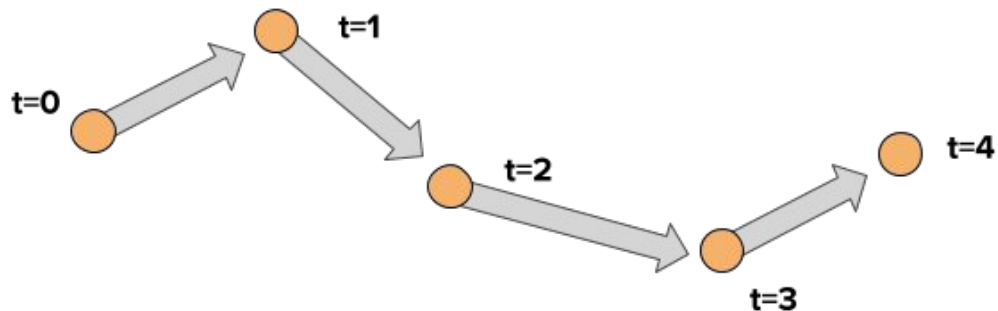
100 evenly spaced LEFS

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)

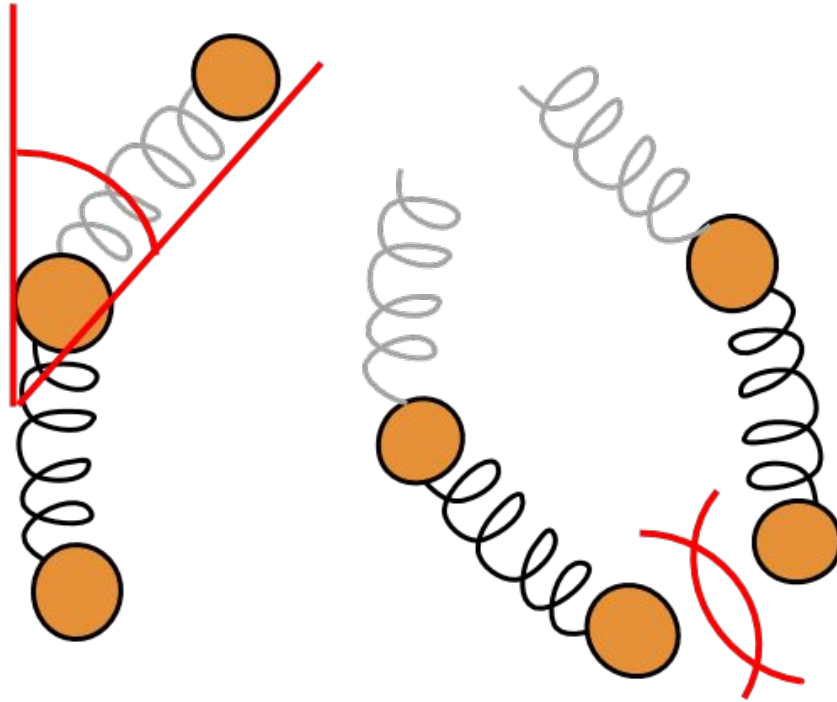


Forces that affect polymers

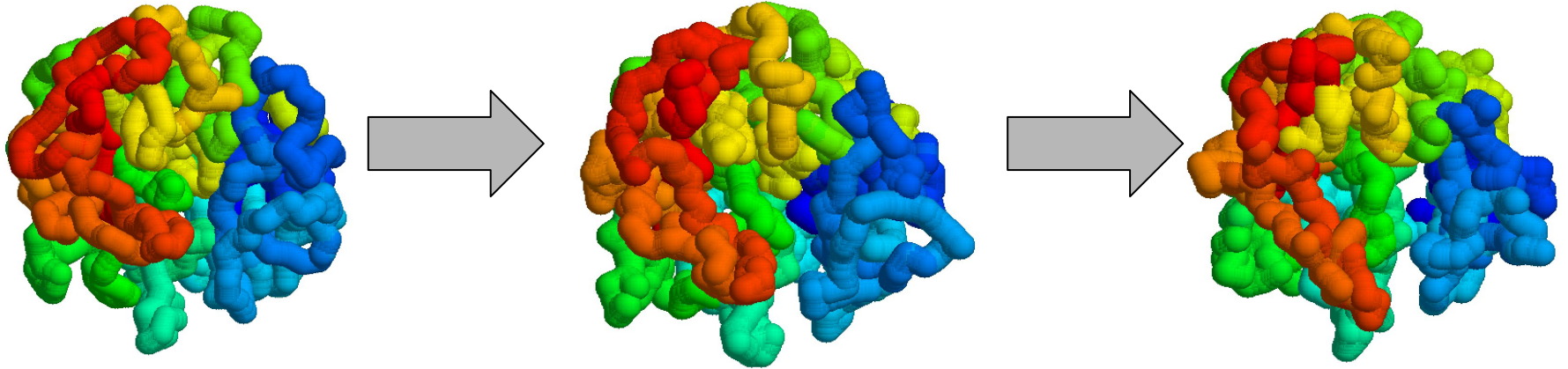
1. Harmonic bonds

2. Steric repulsion

3. Bending energy



Molecular dynamics simulations



Boundary Elements

1D LEF + BE update rules

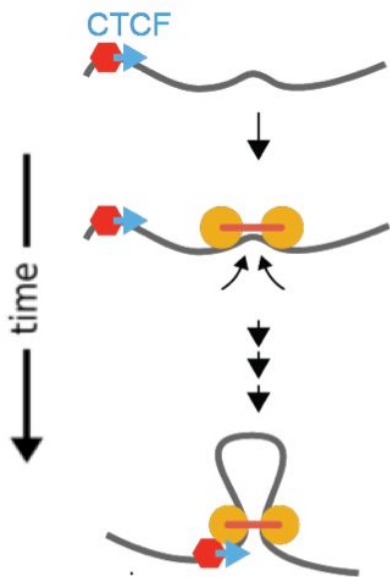
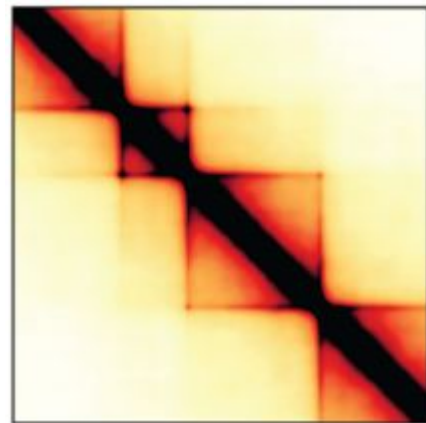
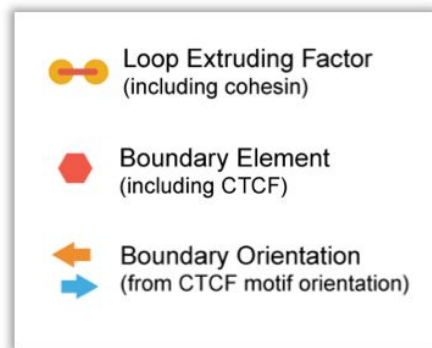
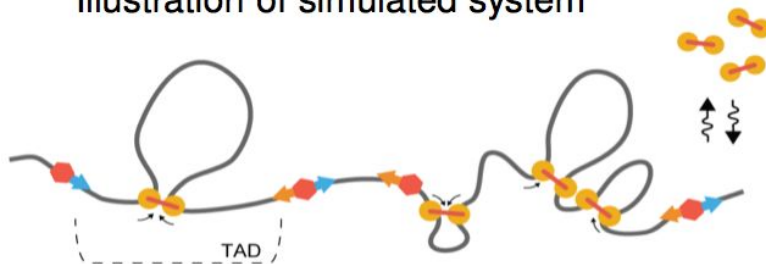


Illustration of simulated system

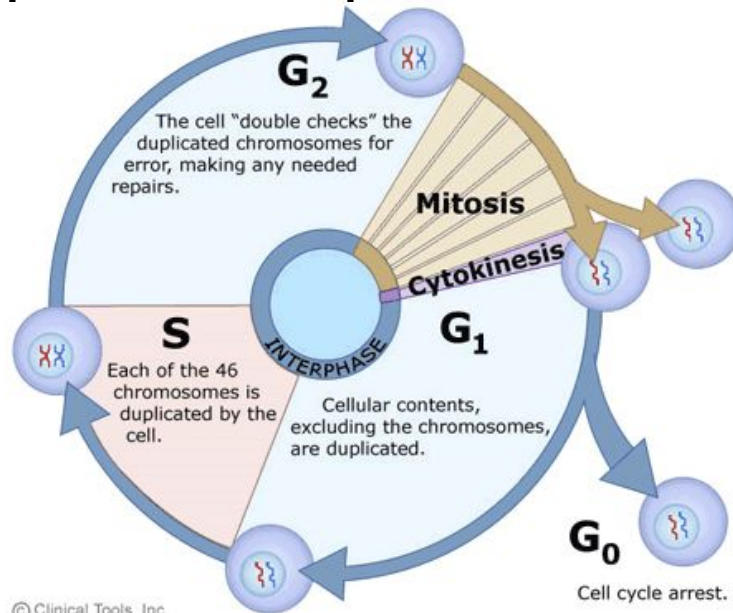


- Translocation-interfering molecules/proteins
- Can be directional

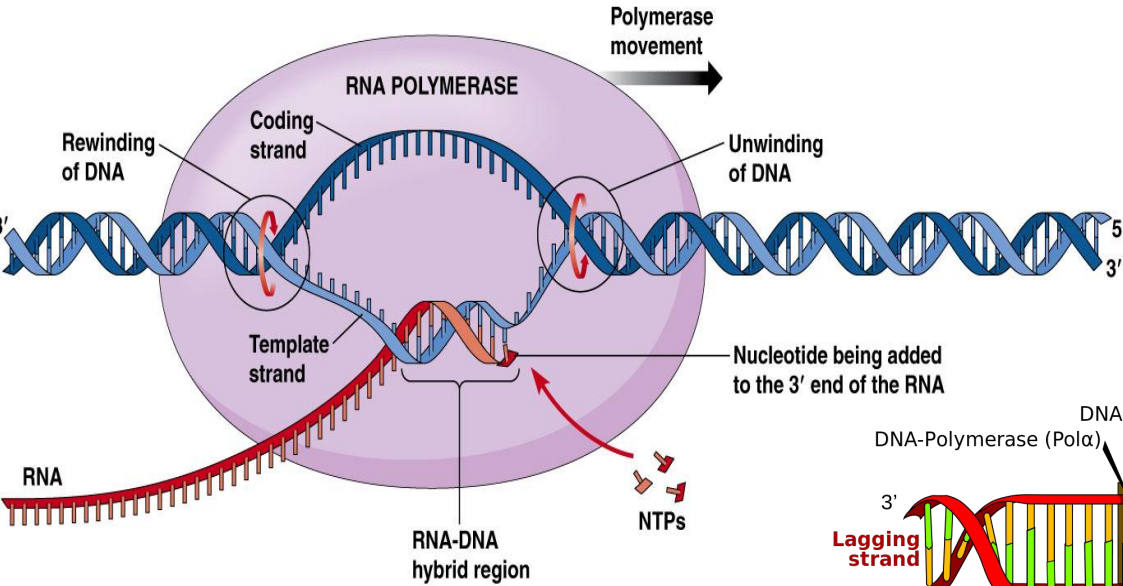
Future directions

-Complications to the **interphase model**:

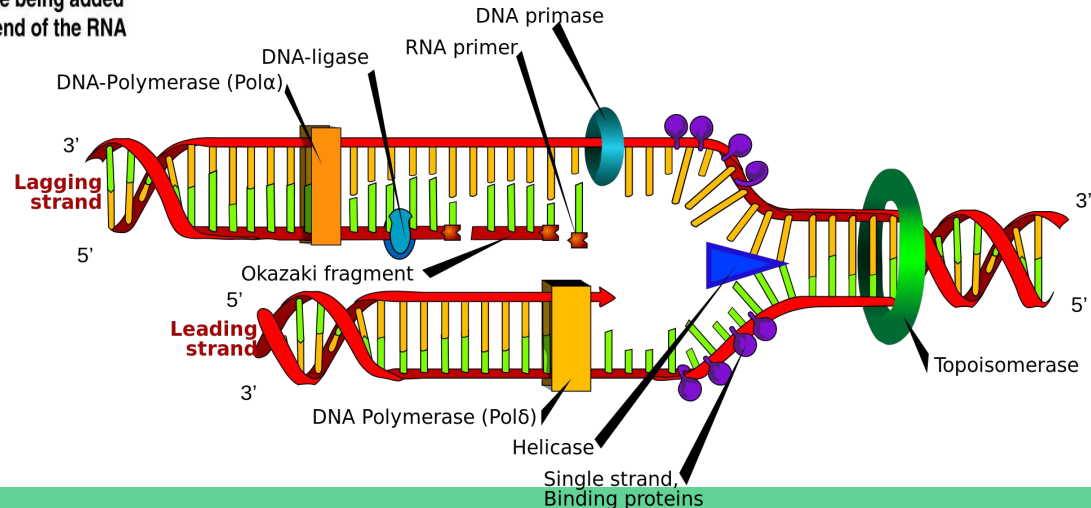
-Would **RNA transcription** or **DNA replication** interfere with SMCs on the chromatin fiber?



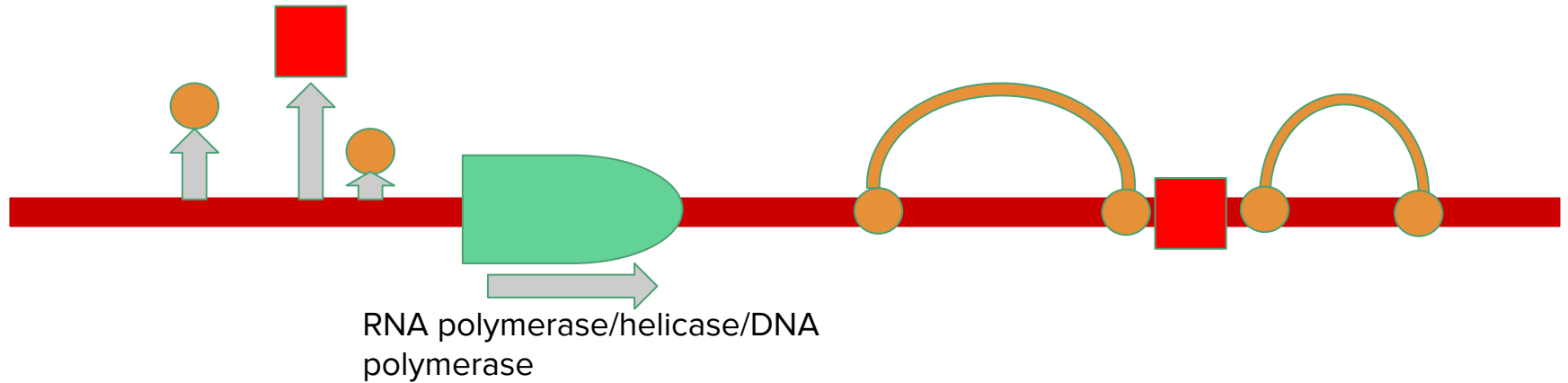
Thinking biologically about interphase events...



© 2012 Pearson Education, Inc.



Interference during transcription or replication



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

Acknowledgements

- Special thanks to my mentor, Dr. Geoffrey Fudenberg
- Professor Leonid Mirny and the rest of the Mirny Lab
- My parents and family
- MIT PRIMES program