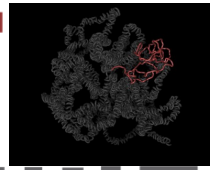
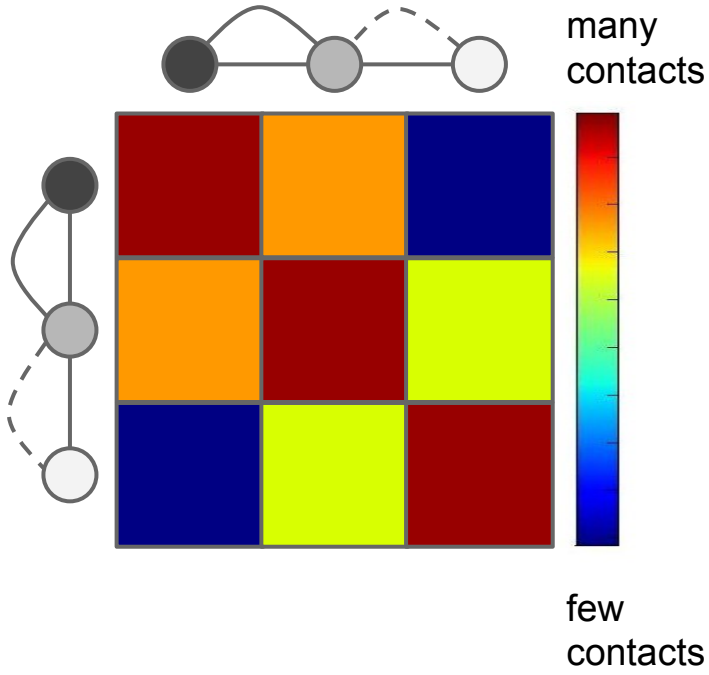


Loop Extruding Enzymes in Interphase: Dynamic Folding of Chromatin Domains

Carolyn Lu
Professor Leonid Mirny
Maxim Imakaev, Geoffrey Fudenberg

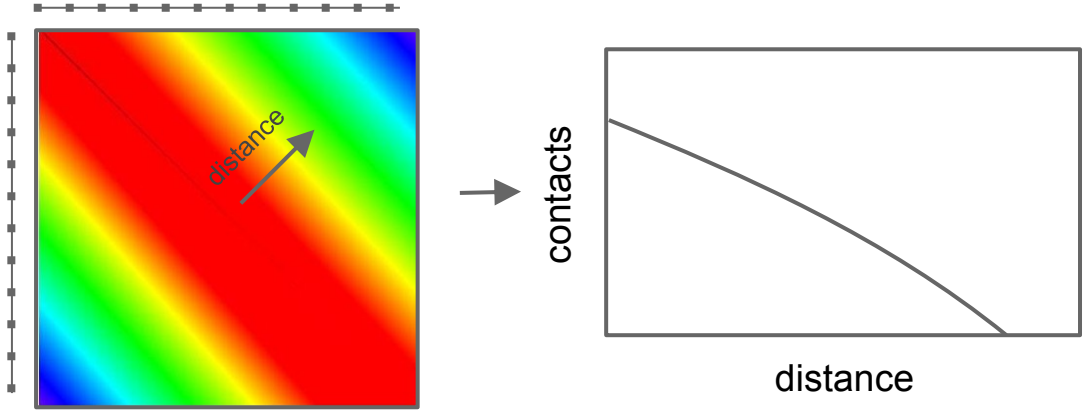
Characterizing Chromosomal Contacts: Contact maps and scalings

Contact maps

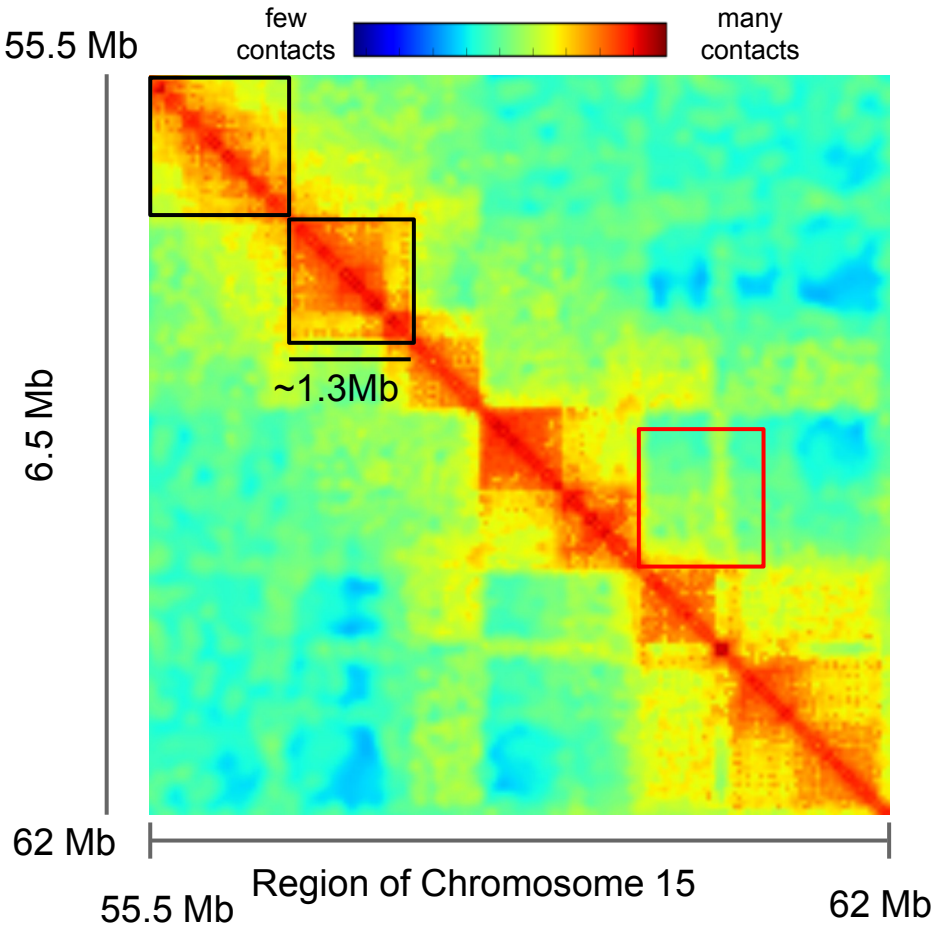


Contact probability scalings:

(contact probability vs. separation distance)

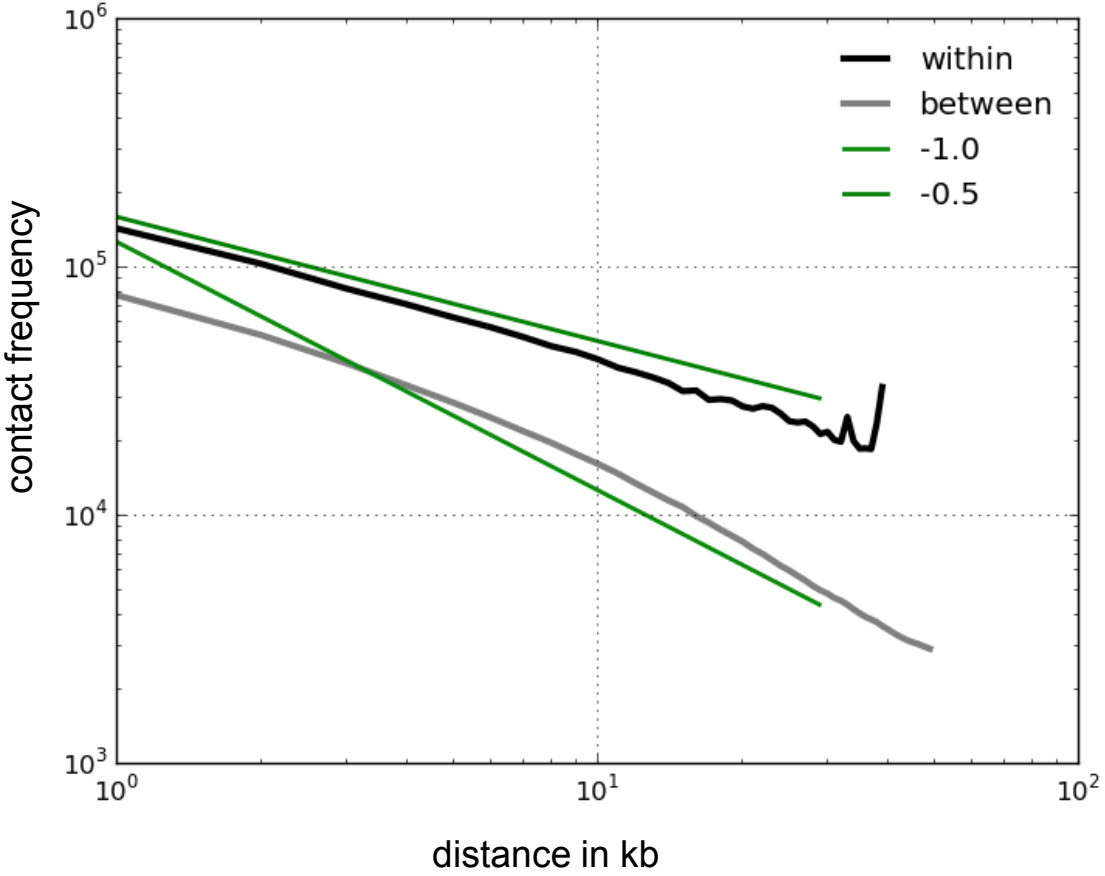


TADs: Topologically Associated Domains



- Regions of increased interaction
- Decreased interaction across boundaries

TAD Scalings

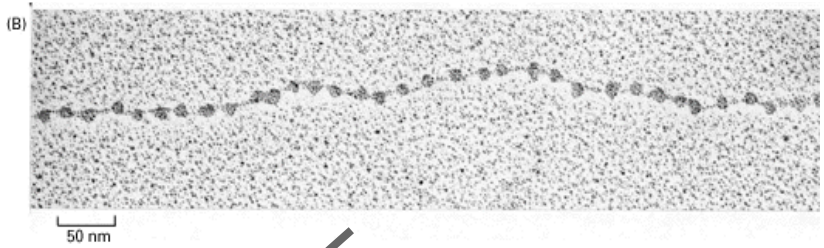


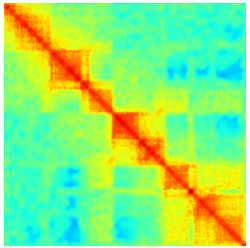
- Within TAD slope in log-log of contact probability over distance in kb is -0.5
- Between TADs slope goes from around -0.5 at closer distances to -1.0 at further

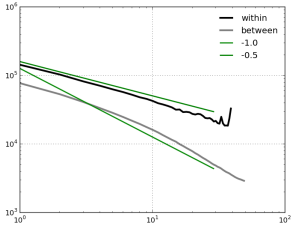
What mechanisms can define TADs and TAD boundaries consistent with experimental data?

Methods: Polymer simulations

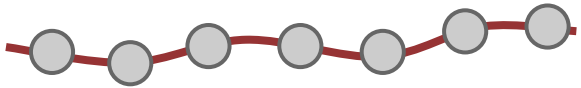
Experimental

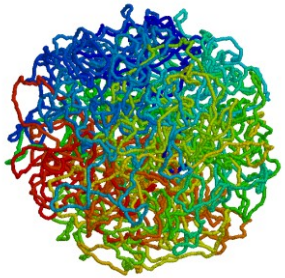






Simulation

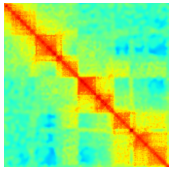




?
contact map

scaling?
??

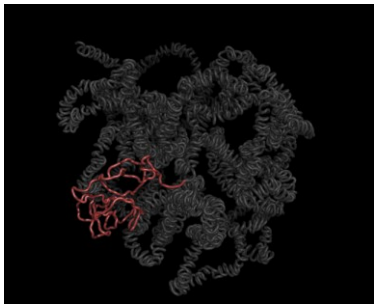
Previously explored models:

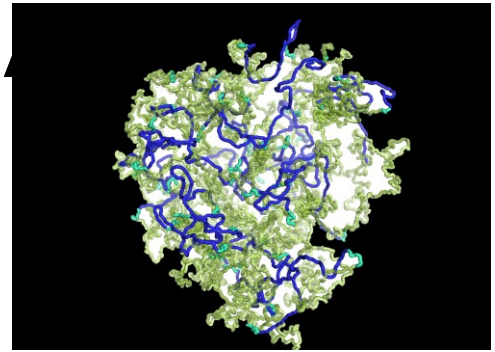


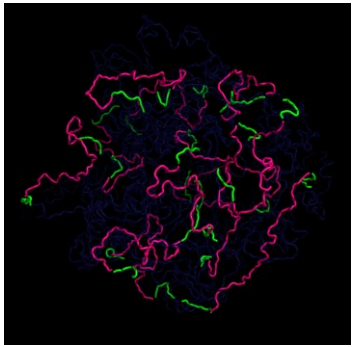
thick-thin

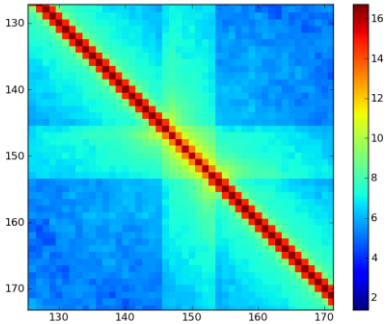
stiff-flexible

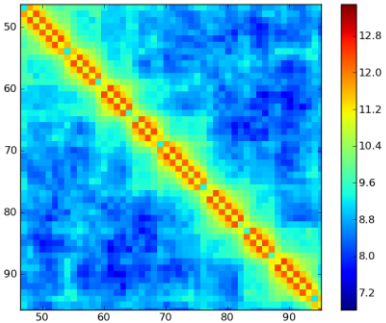
RNA

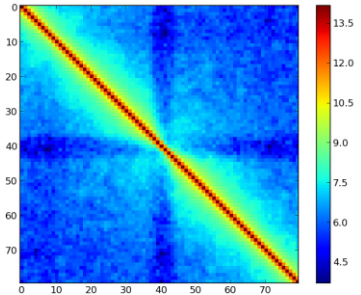




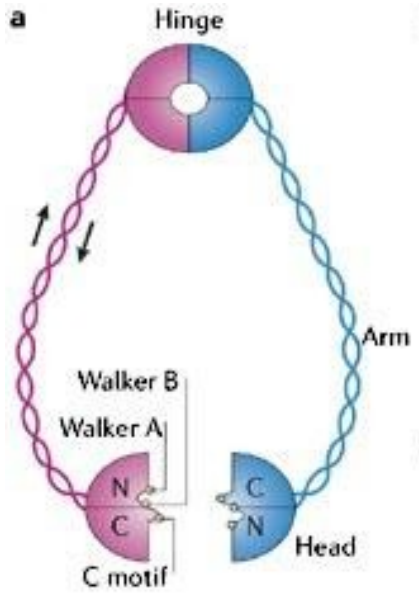




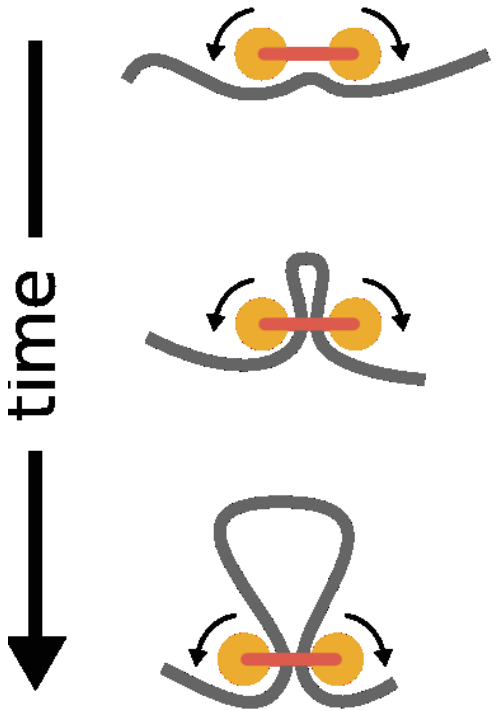




SMCs as loop-extruding proteins

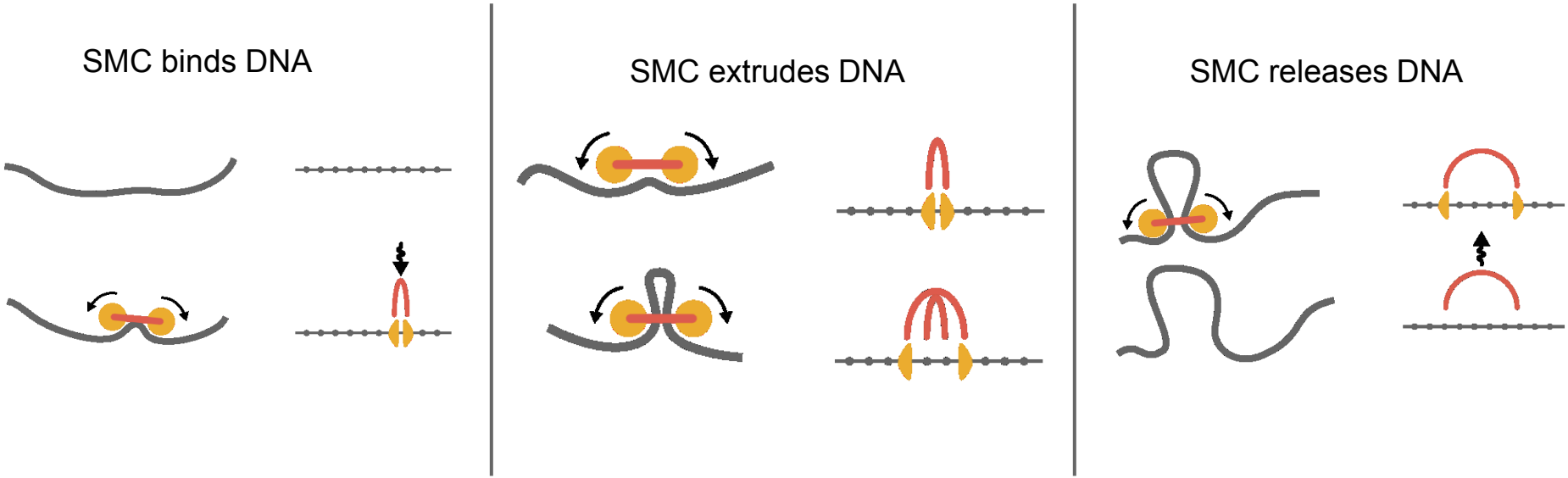


Alipour, Elnaz, and John F. Marko. "Self-organization of domain structures by DNA-loop-extruding enzymes." *Nucleic acids research* 40.22 (2012): 11202-11212.



Anton Goloborodko & Leonid Mirny (Unpublished)

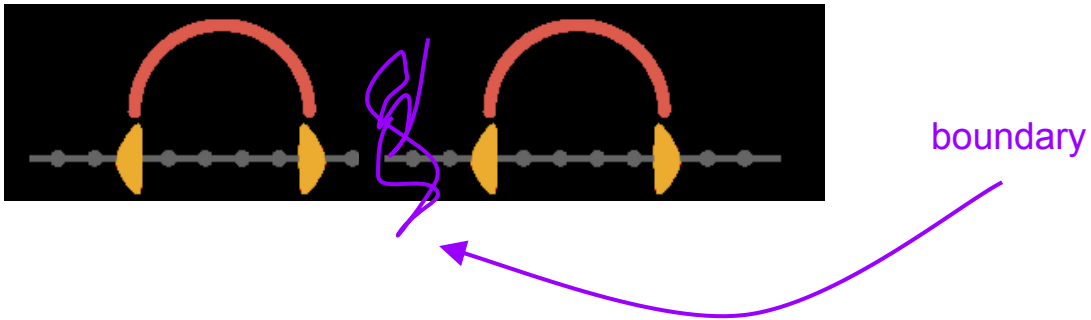
Basic kinetic model of SMC Loop Extrusion



SMC loop extrusion + boundary → TAD boundaries?

TAD boundaries have been shown to be highly bound by a number of key epigenetic regulators.

Hypothesis: Boundaries which halt SMC loop extrusion or release SMC loops can in turn create TAD boundaries

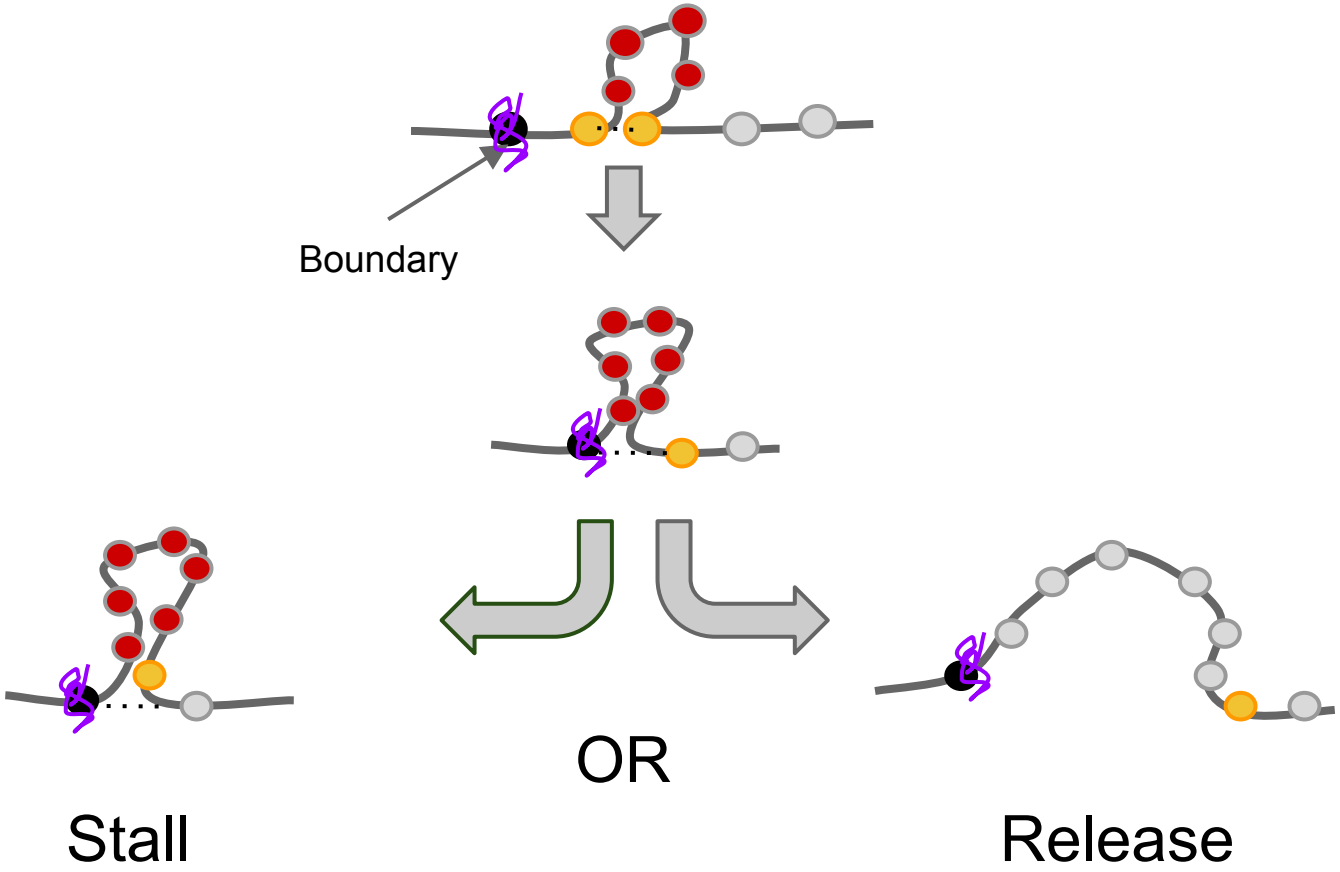


Complications of the kinetic model

1. What happens when a loop meets a boundary?

2. What happens when a loop meets another loop?

Kinetic SMC model: Loop-boundary behavior



Kinetic SMC model: loop-loop behavior

Stall

OR

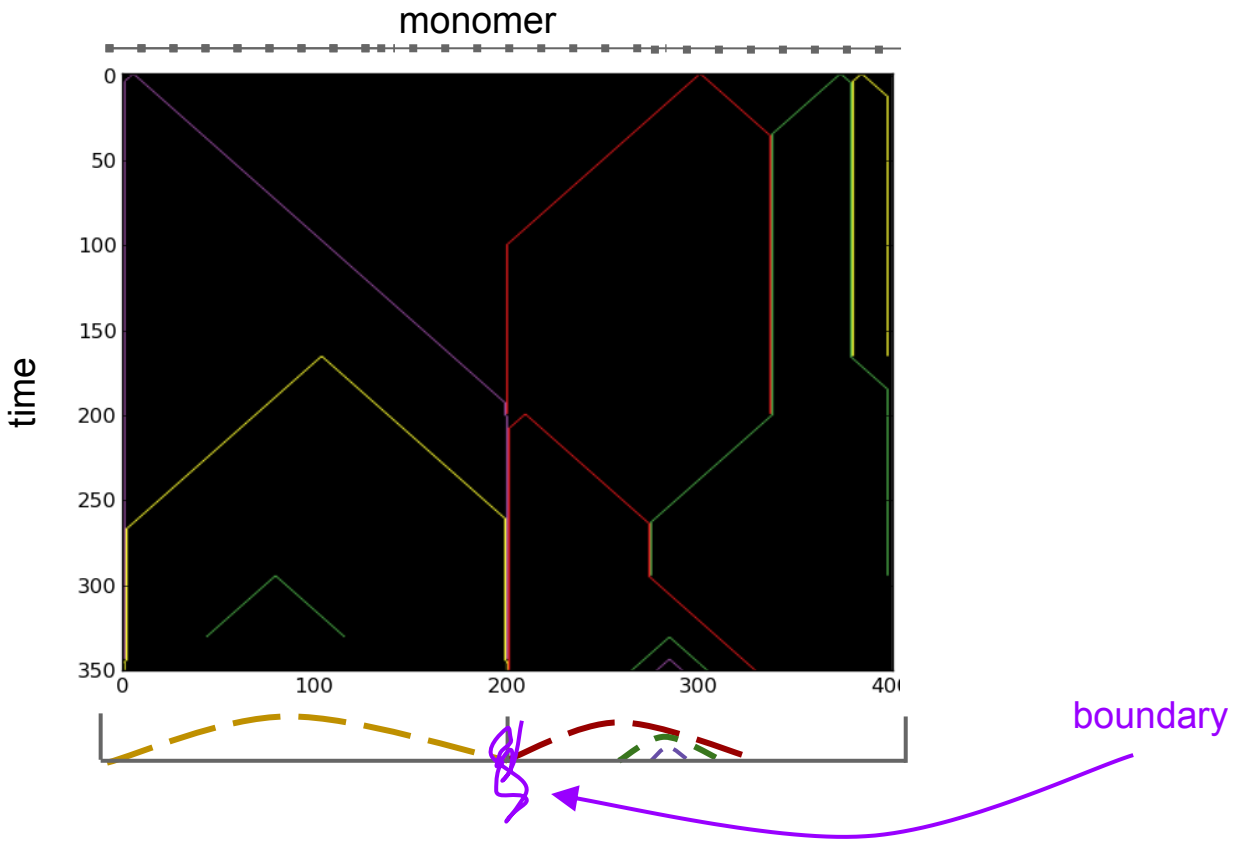
Cross

Four variations on the basic kinetic model of SMC loop extrusion

Since details of SMC loop extrusion are unknown, we tested a number of possible variations:

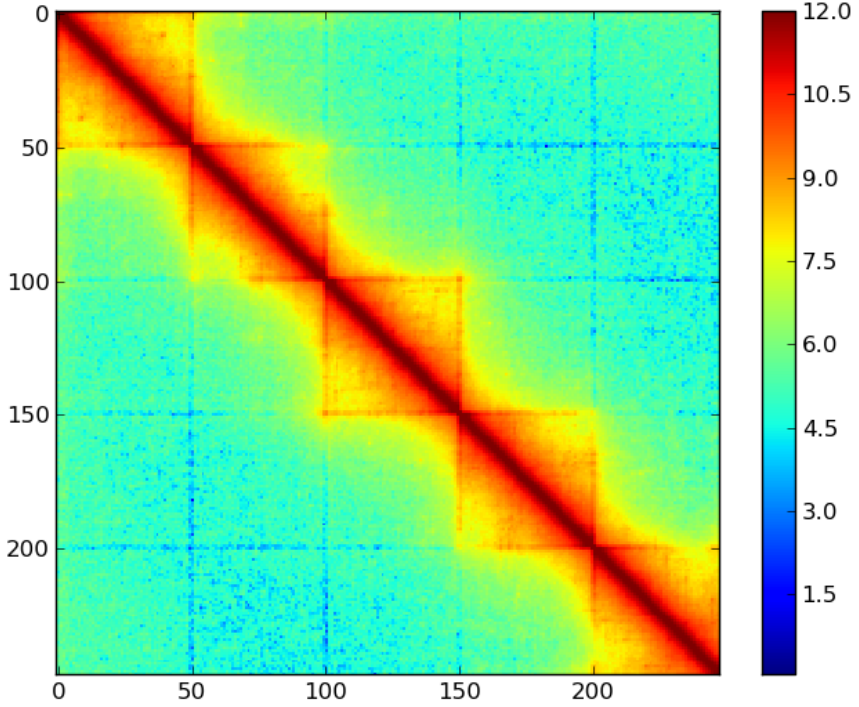
- Boundary stalling and loop-loop stalling (stalling/stalling)
- Long boundary stalling and loop-loop stalling (long-stalling/stalling)
- Boundary release and loop-loop crossing (release/crossing)
- Boundary release and loop-loop stalling (release/stalling)

SMC extrusion kinetic Model 1: Boundary stalling and loop-loop stalling

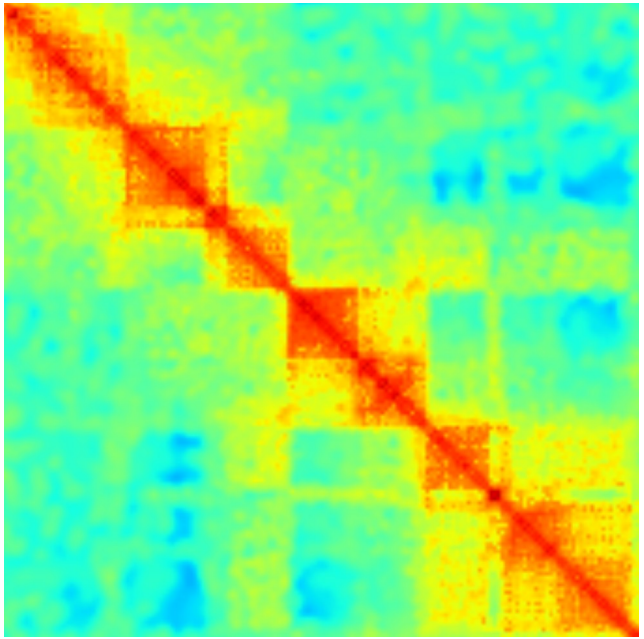


SMC extrusion kinetic model 1: Contact Map (stall/stall)

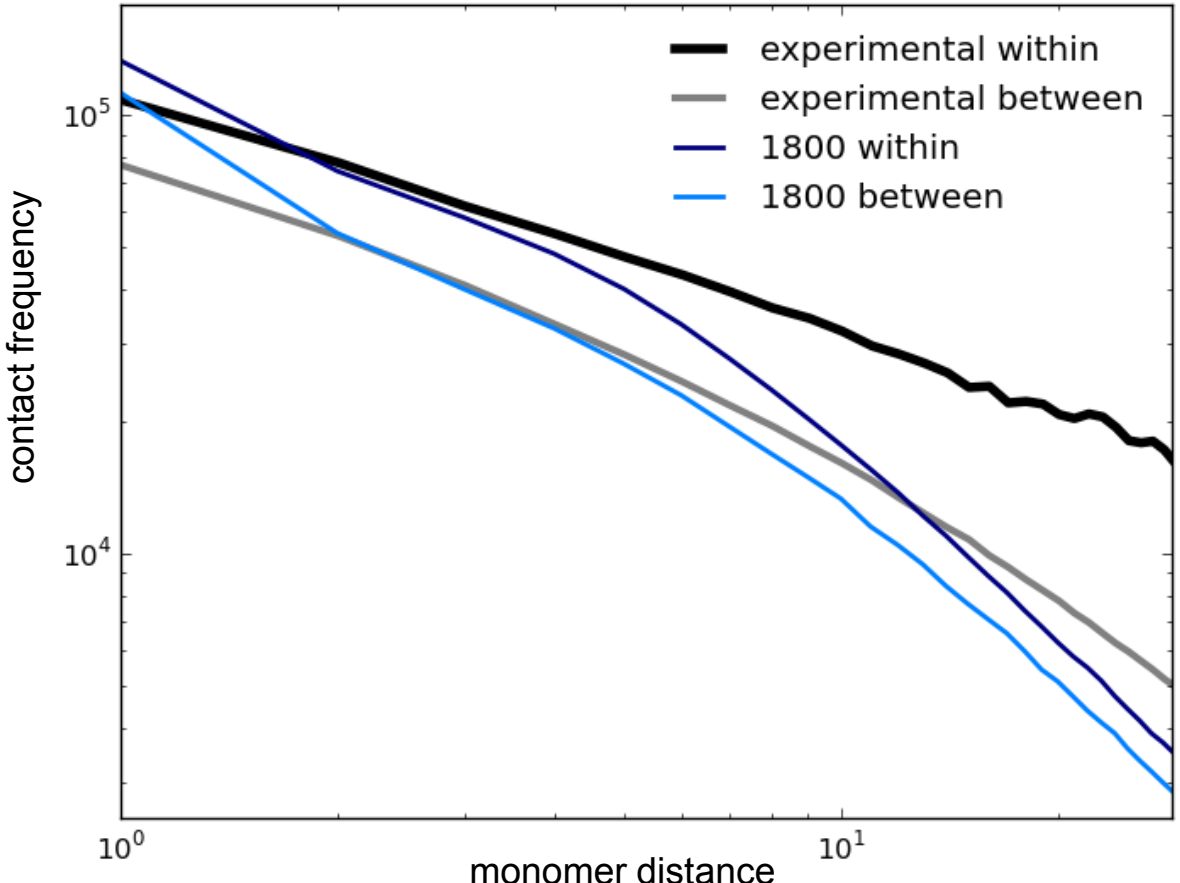
Simulated TADs

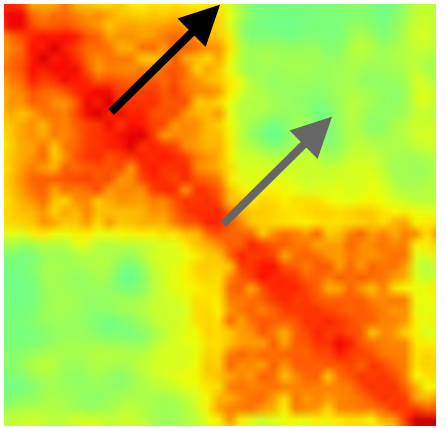


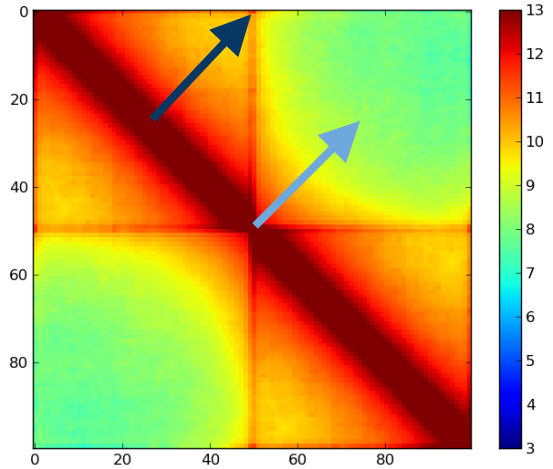
Experimental TADs



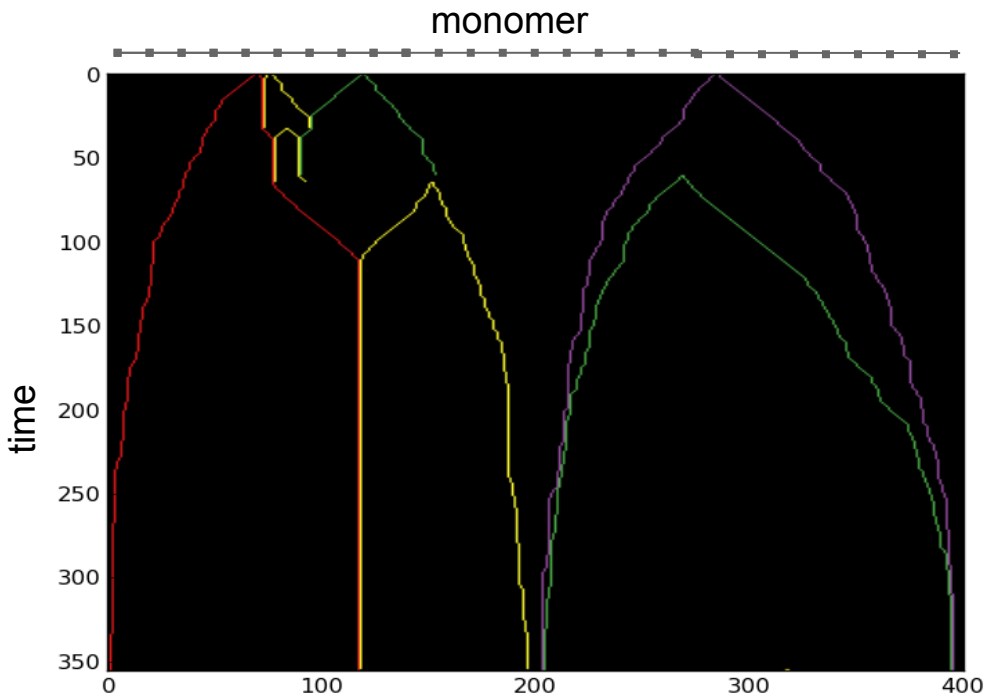
Stall-stall: Scalings



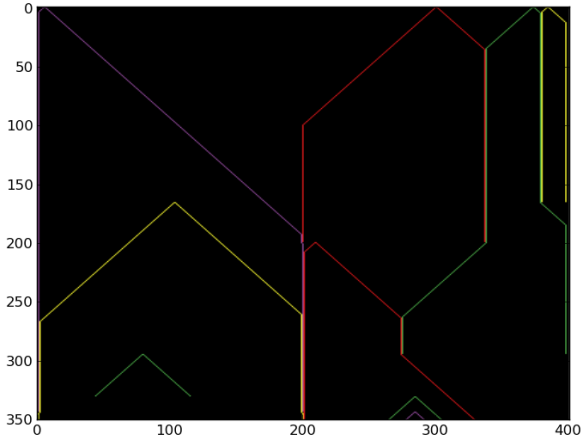




SMC extrusion kinetic Model 2: Long boundaries and loop-loop stalling

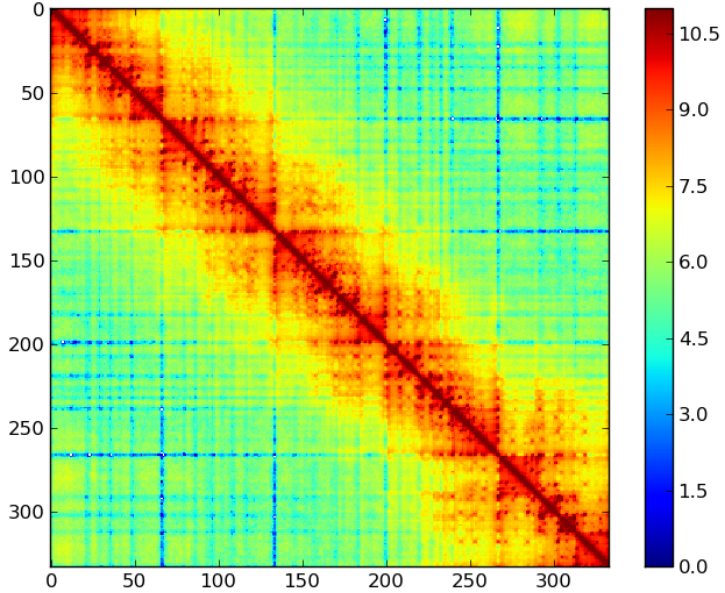


Point boundary stall/stall

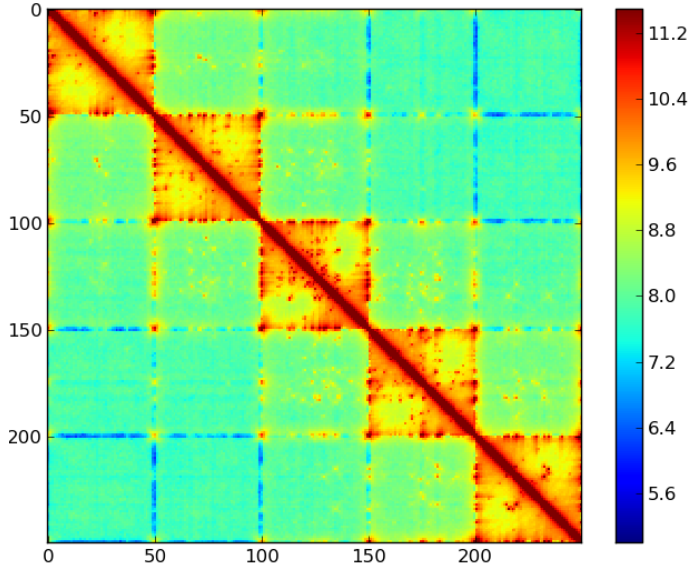


Long boundary: Contact maps

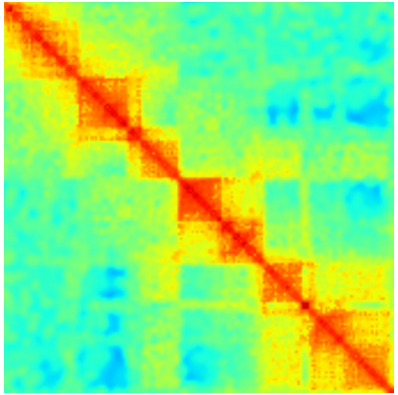
Loop density 20



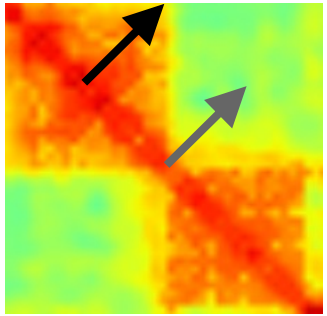
Loop density 5

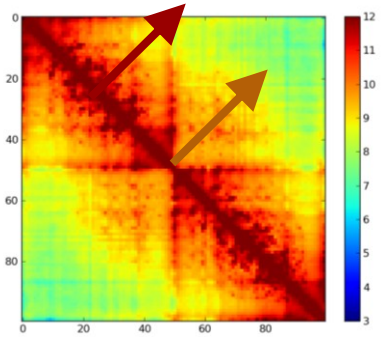


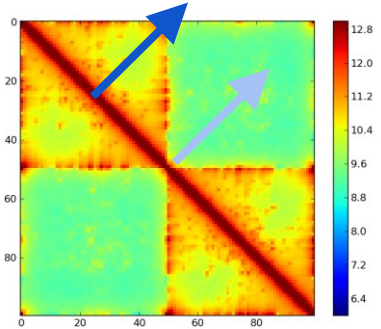
Experimental TADs



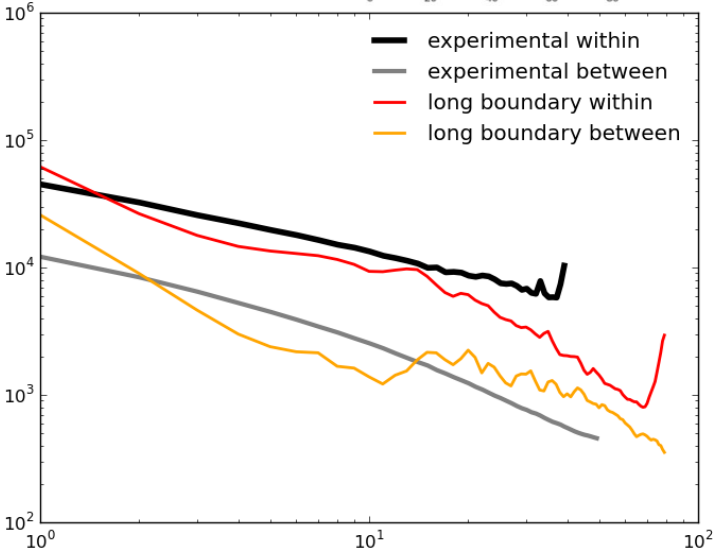
Long boundary: Scalings



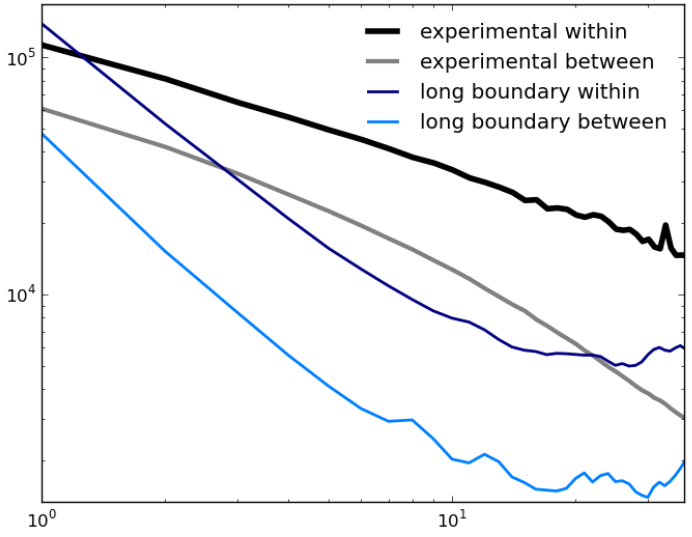




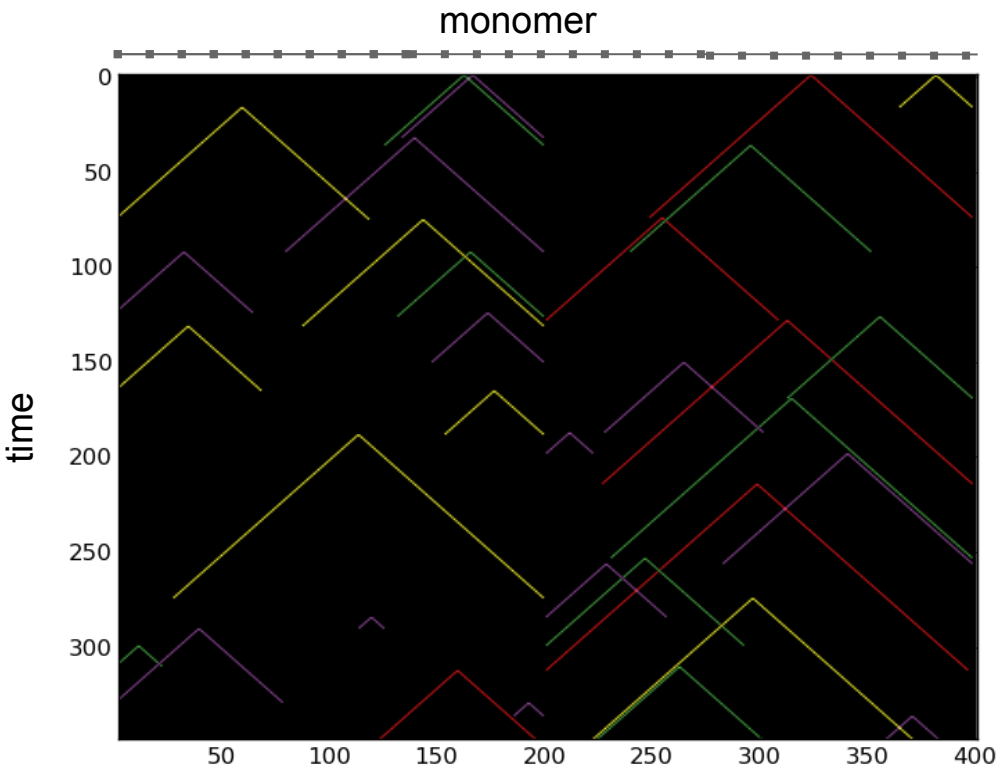
Loop density 20



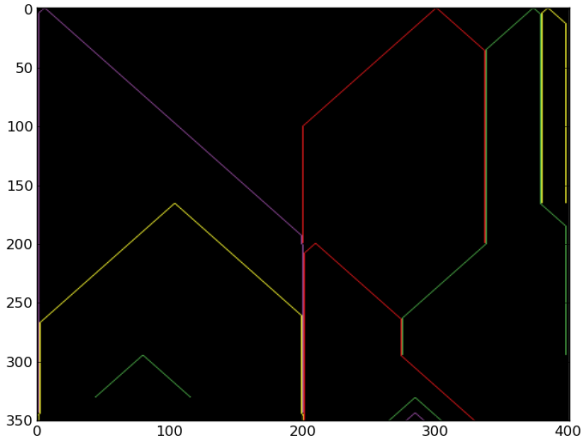
Loop density 5



SMC extrusion Model 3: Boundary release and loop crossing

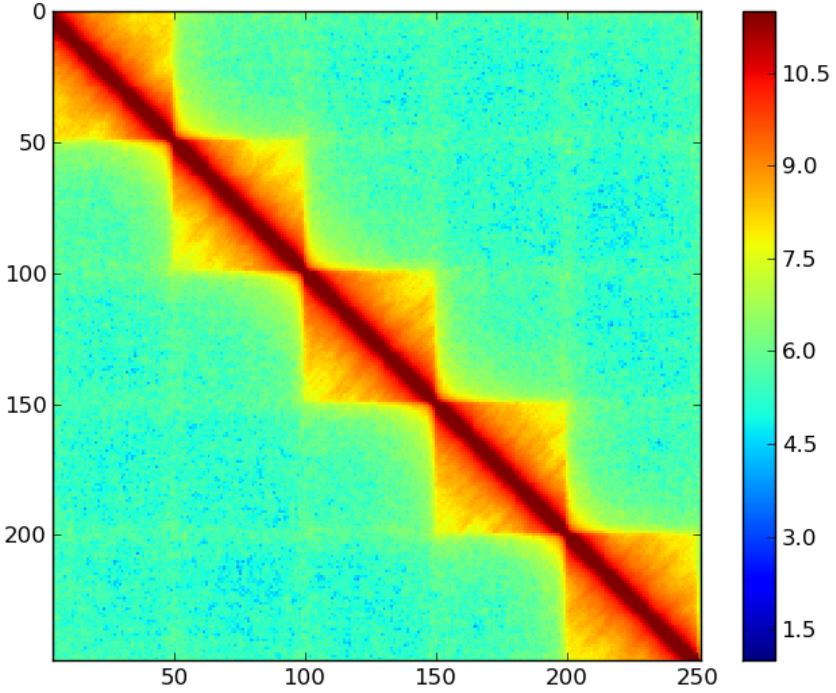


Point boundary stall/stall

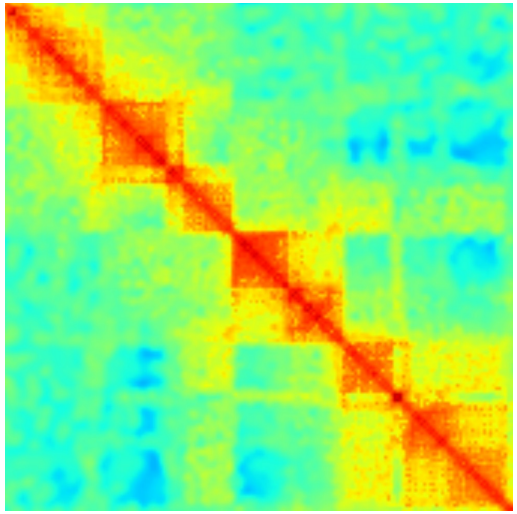


Release/cross: Contact map

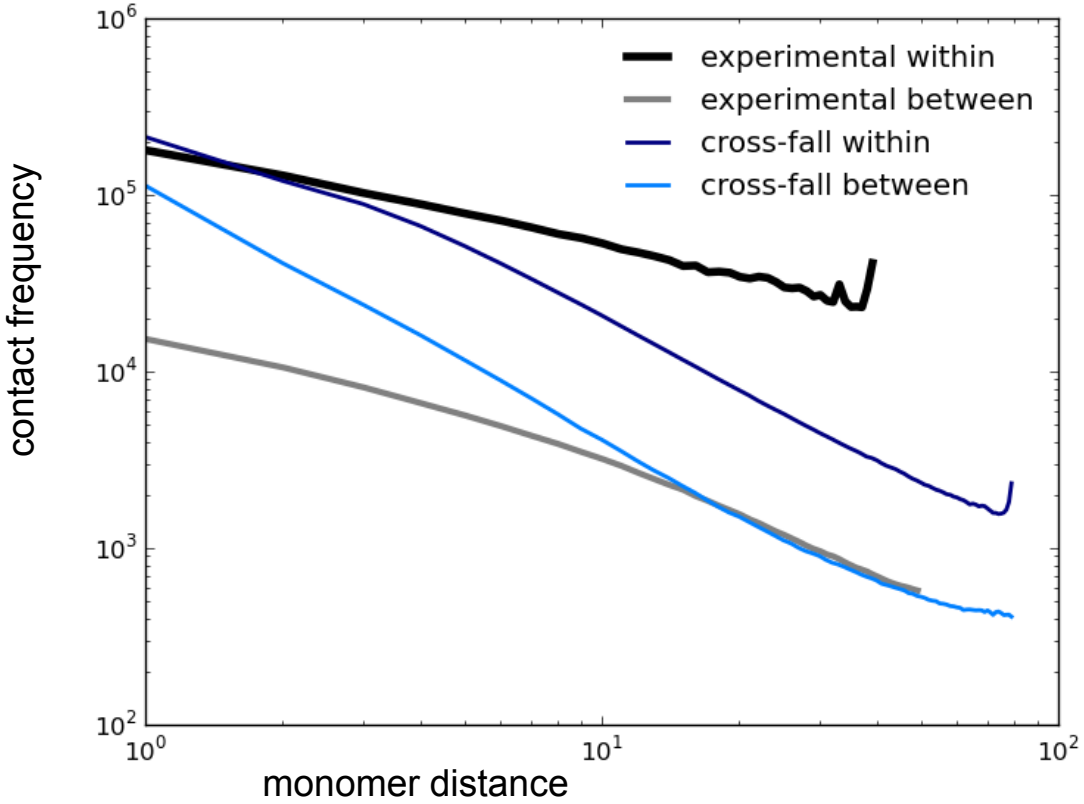
Simulated TADs

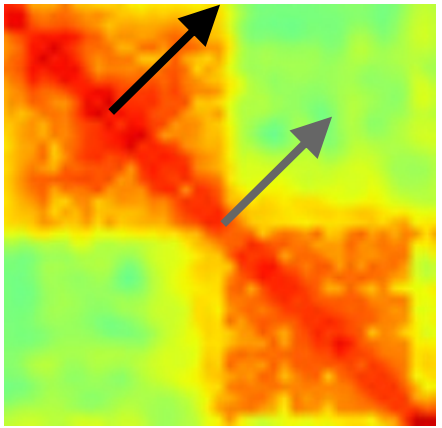


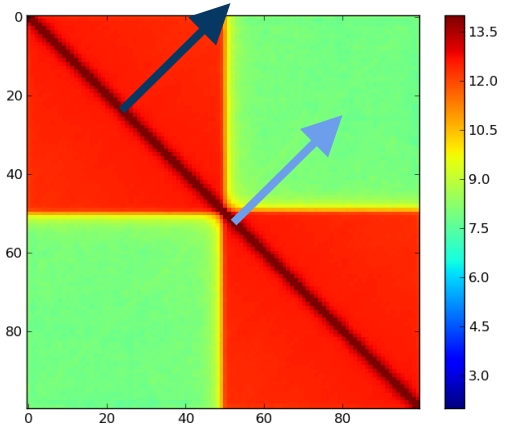
Experimental TADs



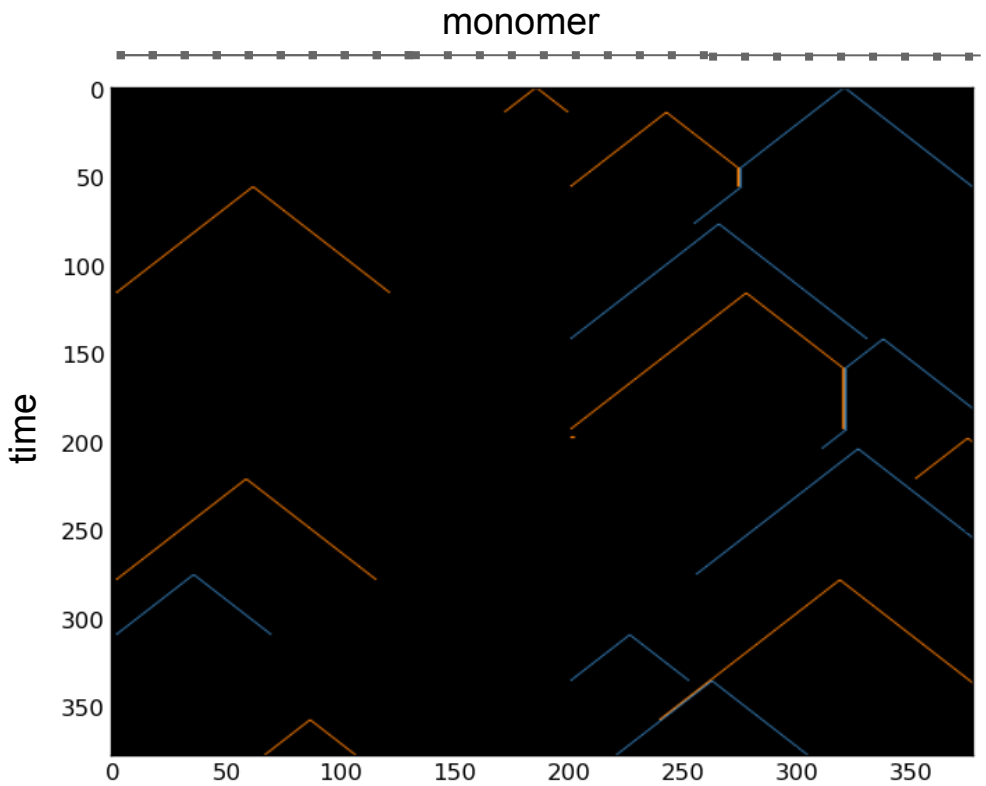
Release/cross: Scalings



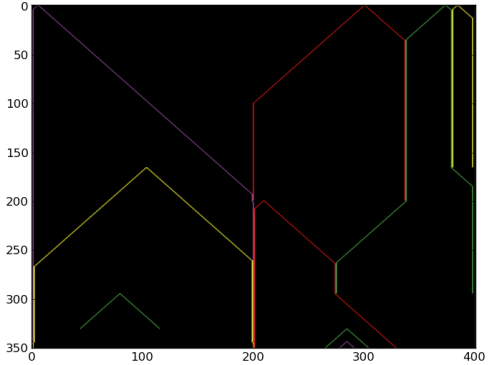




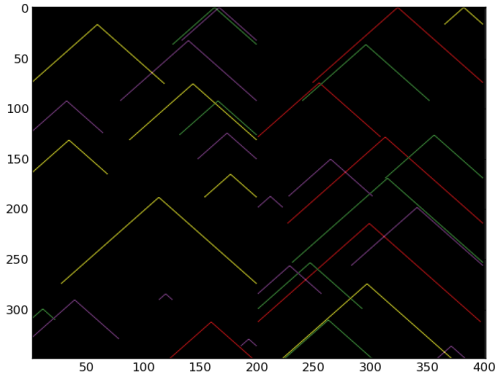
SMC extrusion Model 4: Boundary release and loop stalling



Point boundary stall/stall

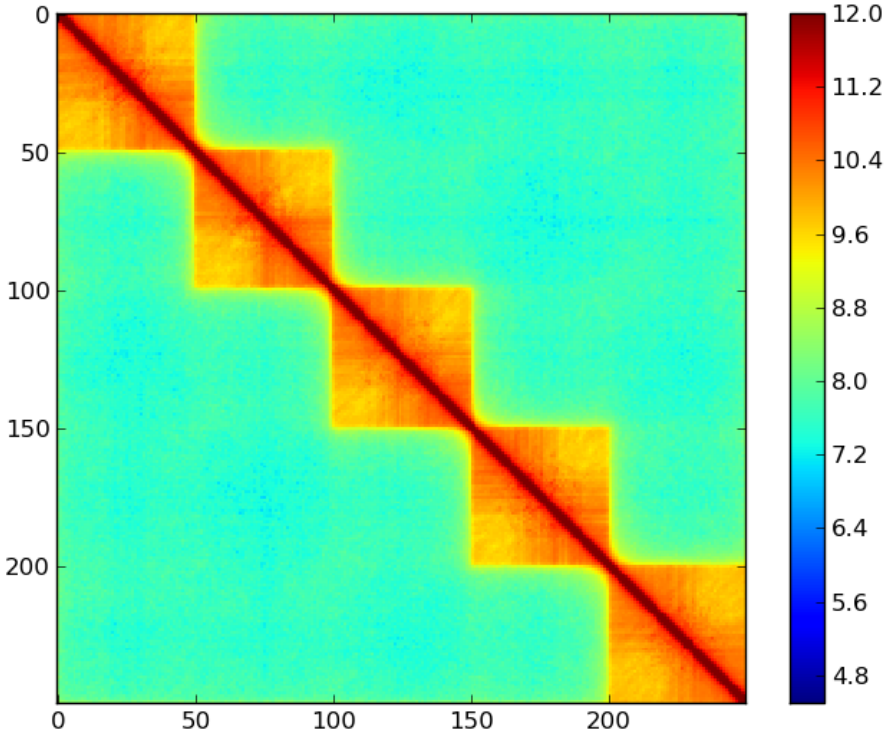


Model 3: release/cross

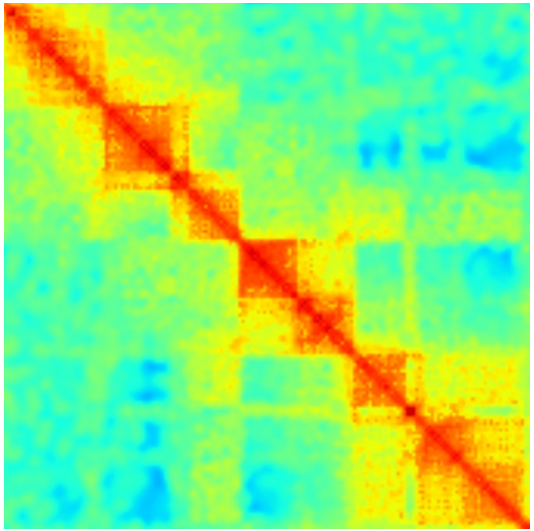


Release-stall: Contact map

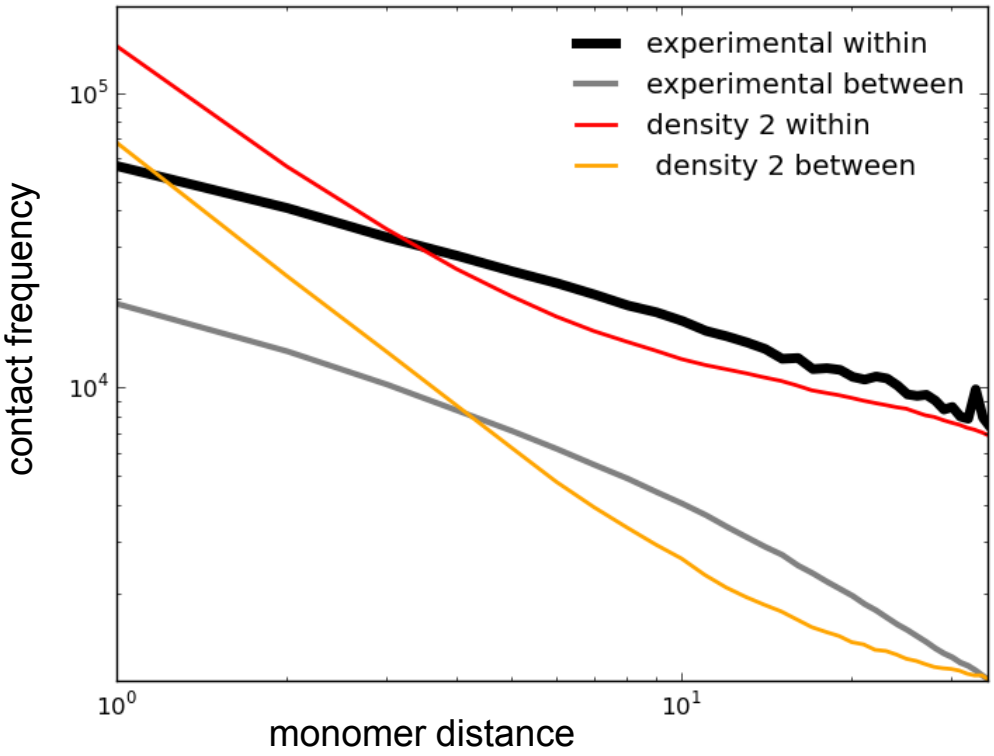
Simulated TADs

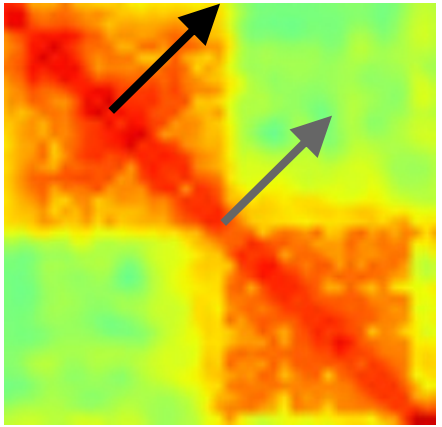


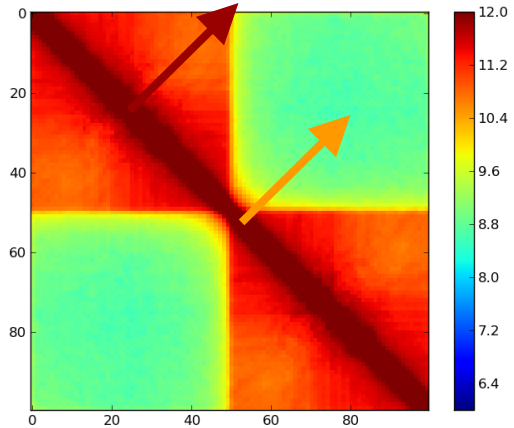
Experimental TADs



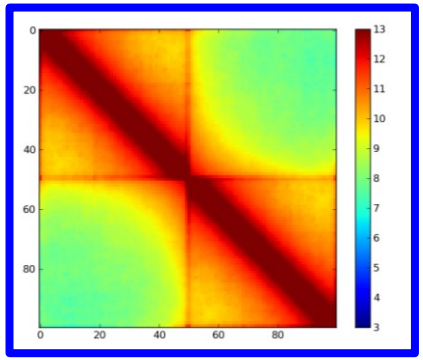
Release-stall: Scalings

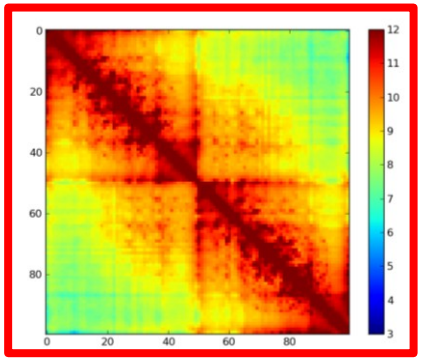


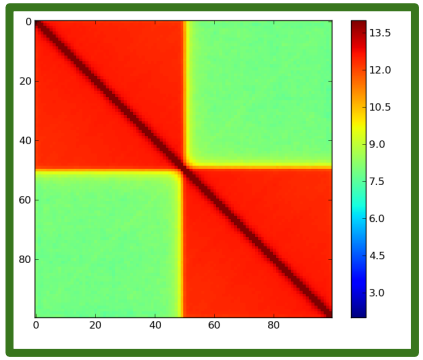


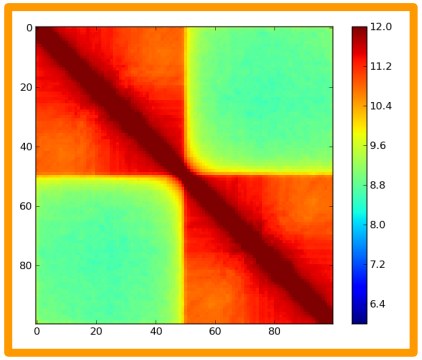


Comparison of models

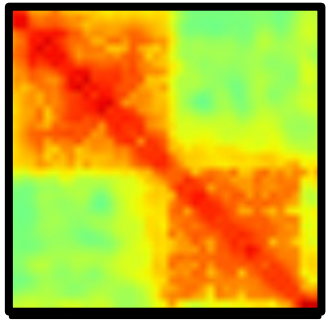


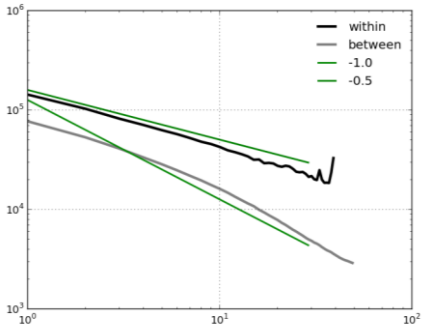




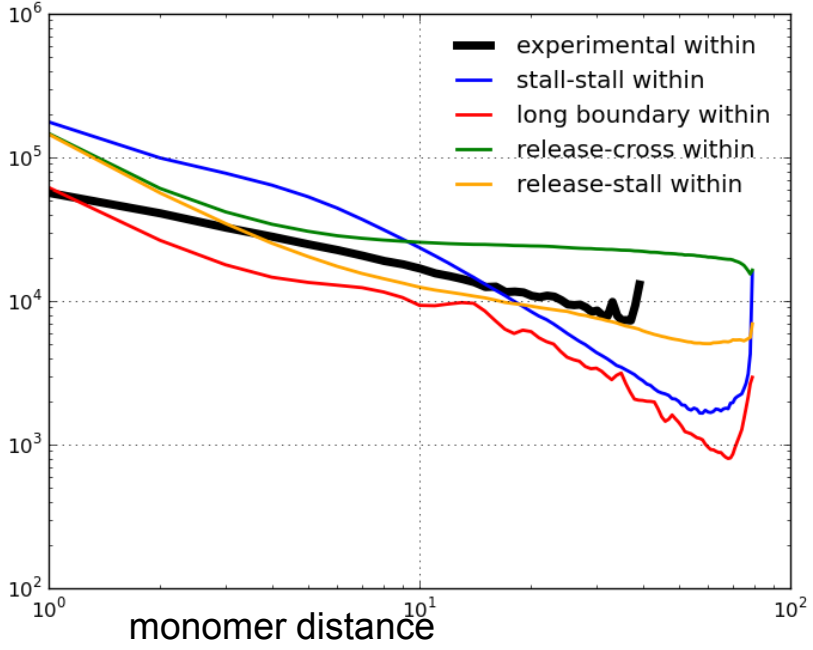


experimental





contact frequency



Conclusions and Discussion

- Our models of SMC loop extrusion can reproduce some features of TAD contact maps but do not completely reproduce TAD scalings

- Details of SMC behavior strongly affect simulated contact maps and scalings
    - Release at boundaries / stalling between loops best reproduced experimental data

- Further biological experiments are necessary to determine detailed mechanisms of SMC action & TAD formation

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