# From HiC matrices to 3D structures

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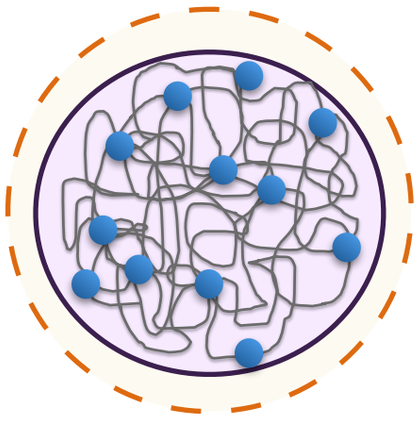
Genome Biology Group (CNAG)
Structural Genomics Group (CRG)

cnag
centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

CRG
Centre for Genomic Regulation

http://marciuslab.org
http://3DGenomes.org
http://cnag.crg.eu

# HiC experiment



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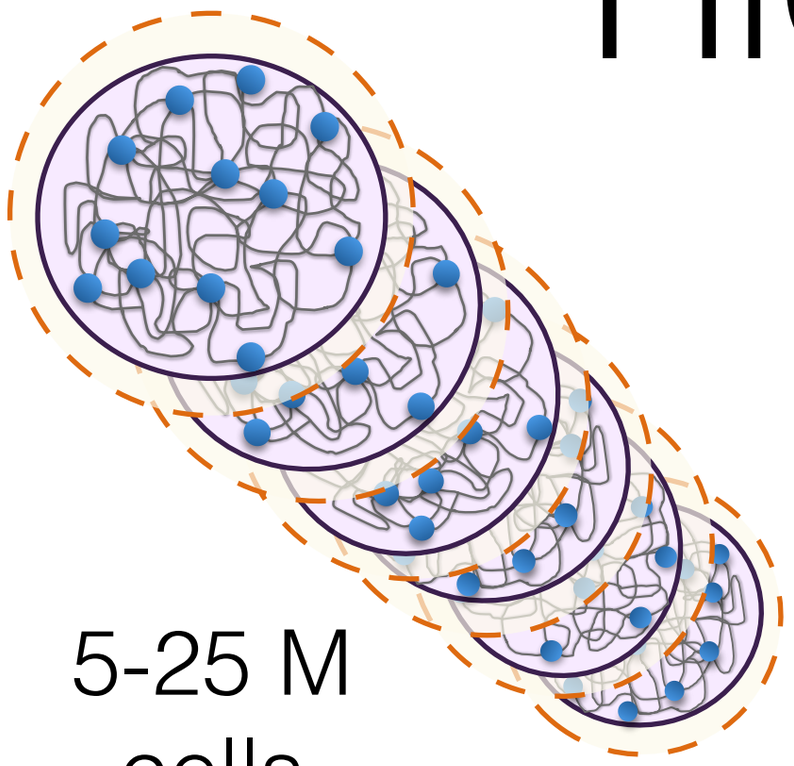

5-25 M cells

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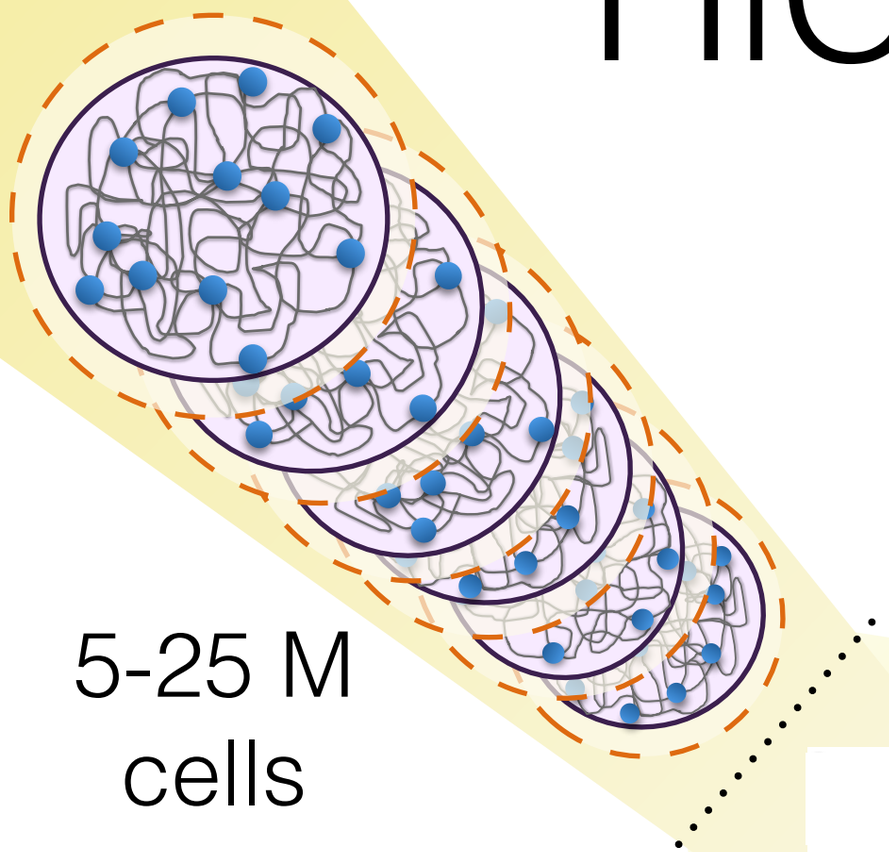
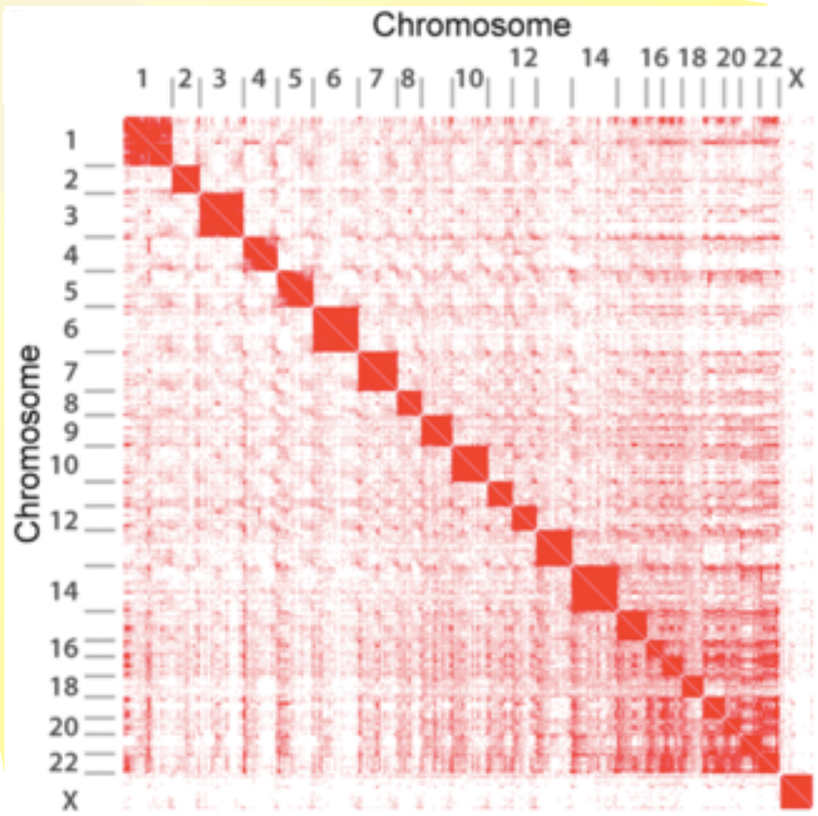


5-25 M cells

50-1000 M interactions




Kalhor R, Tjong H, Jayathilaka N, Alber F, Chen L. 2012.
Genome architectures revealed by tethered chromosome conformation capture and population-based modeling.
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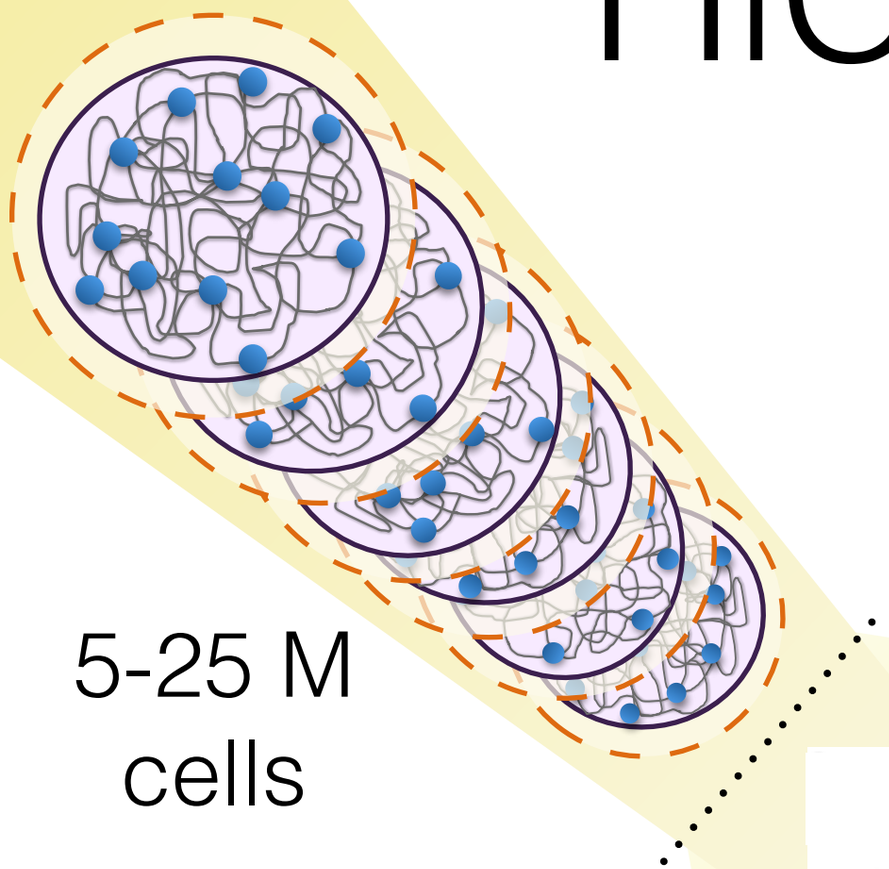

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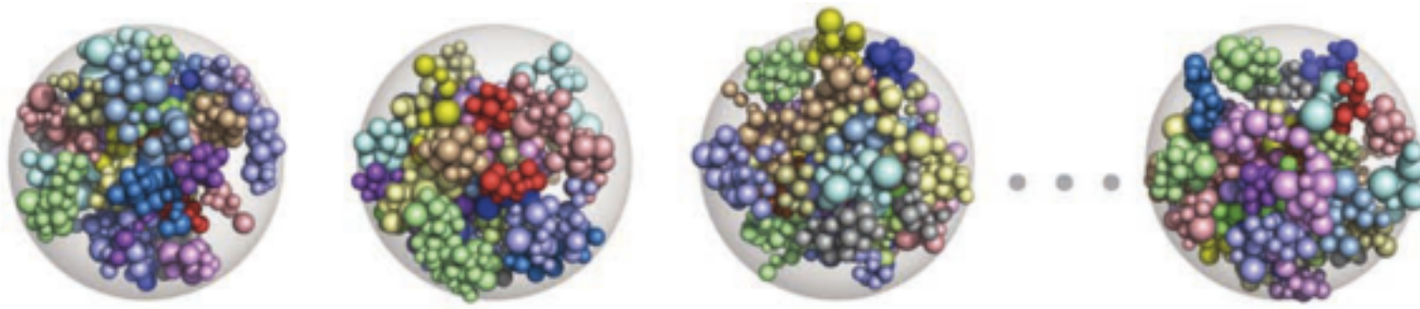
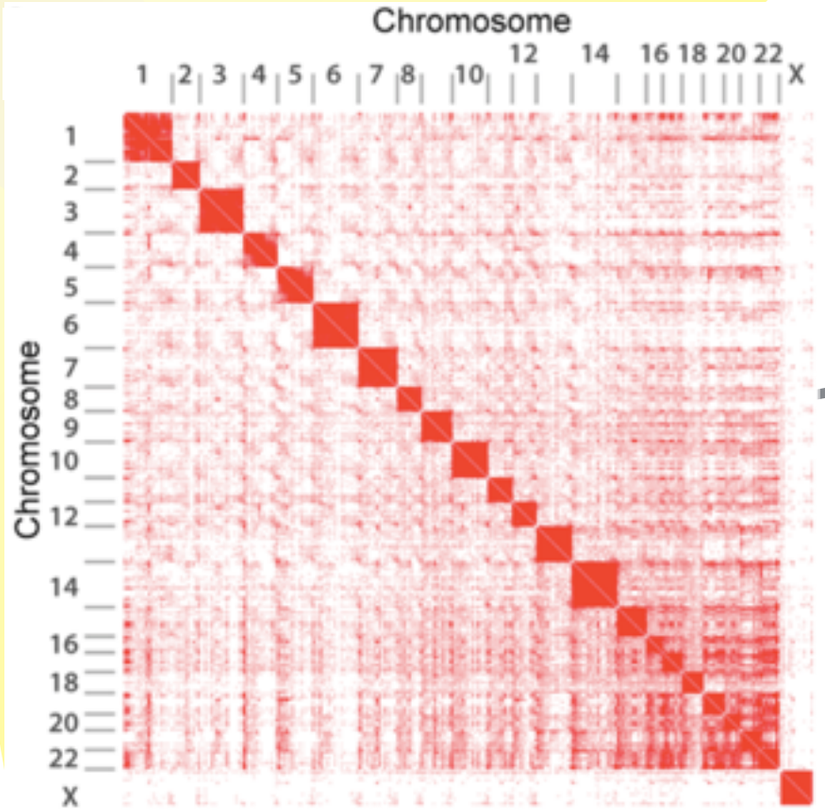


1-10,000 models

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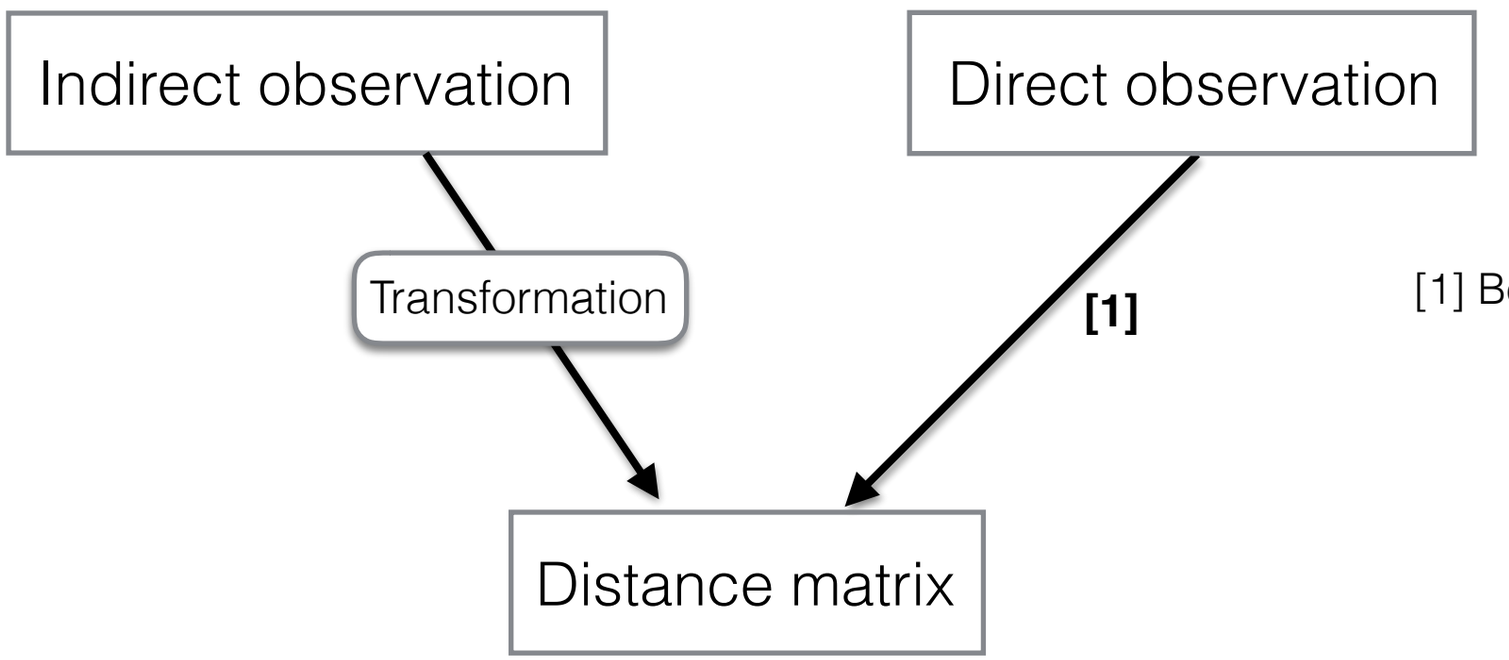
# Modeling strategies




[1] Bolzer A et al. 2005. PLoS Biol 3: 0826–0842.

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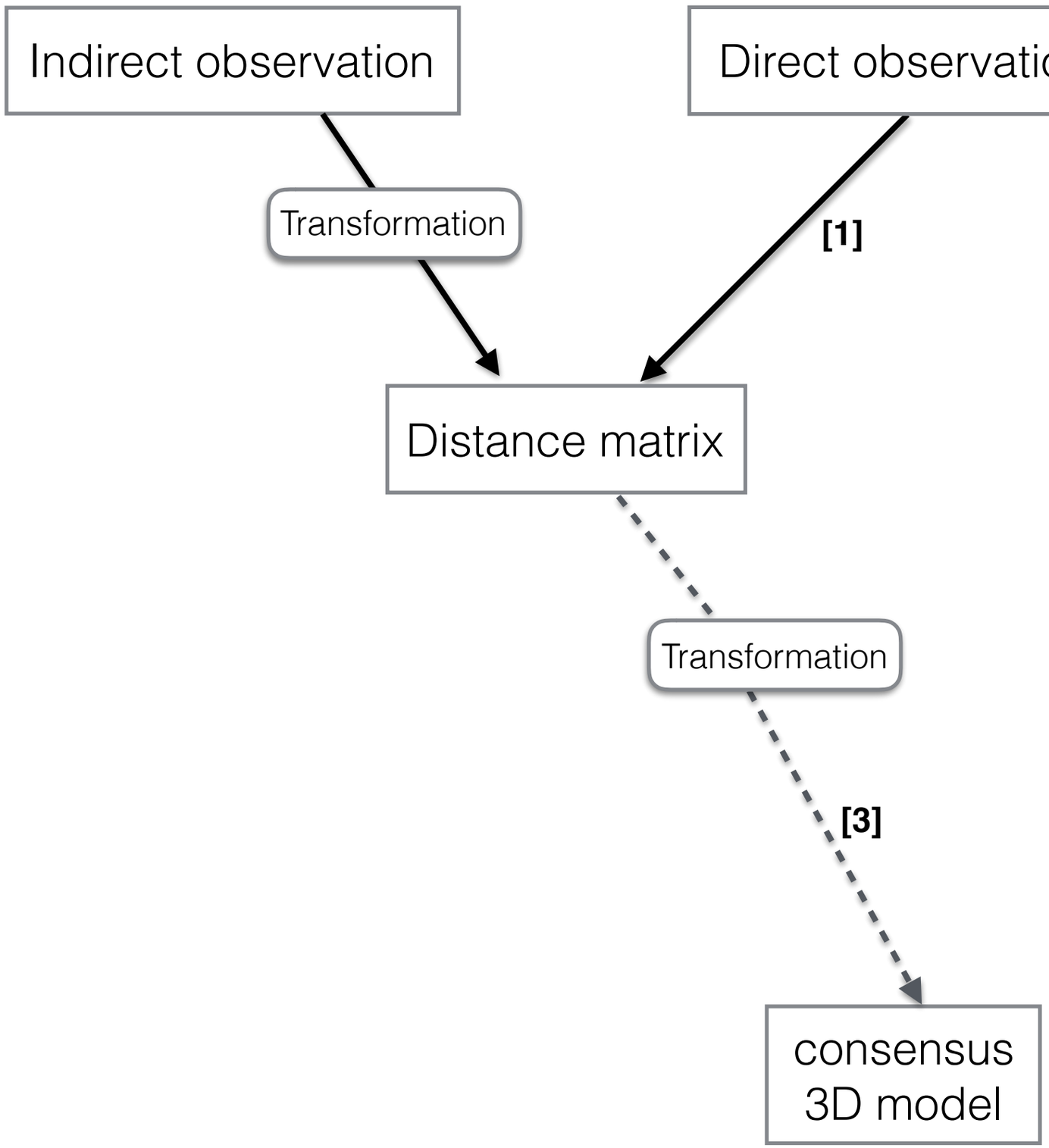


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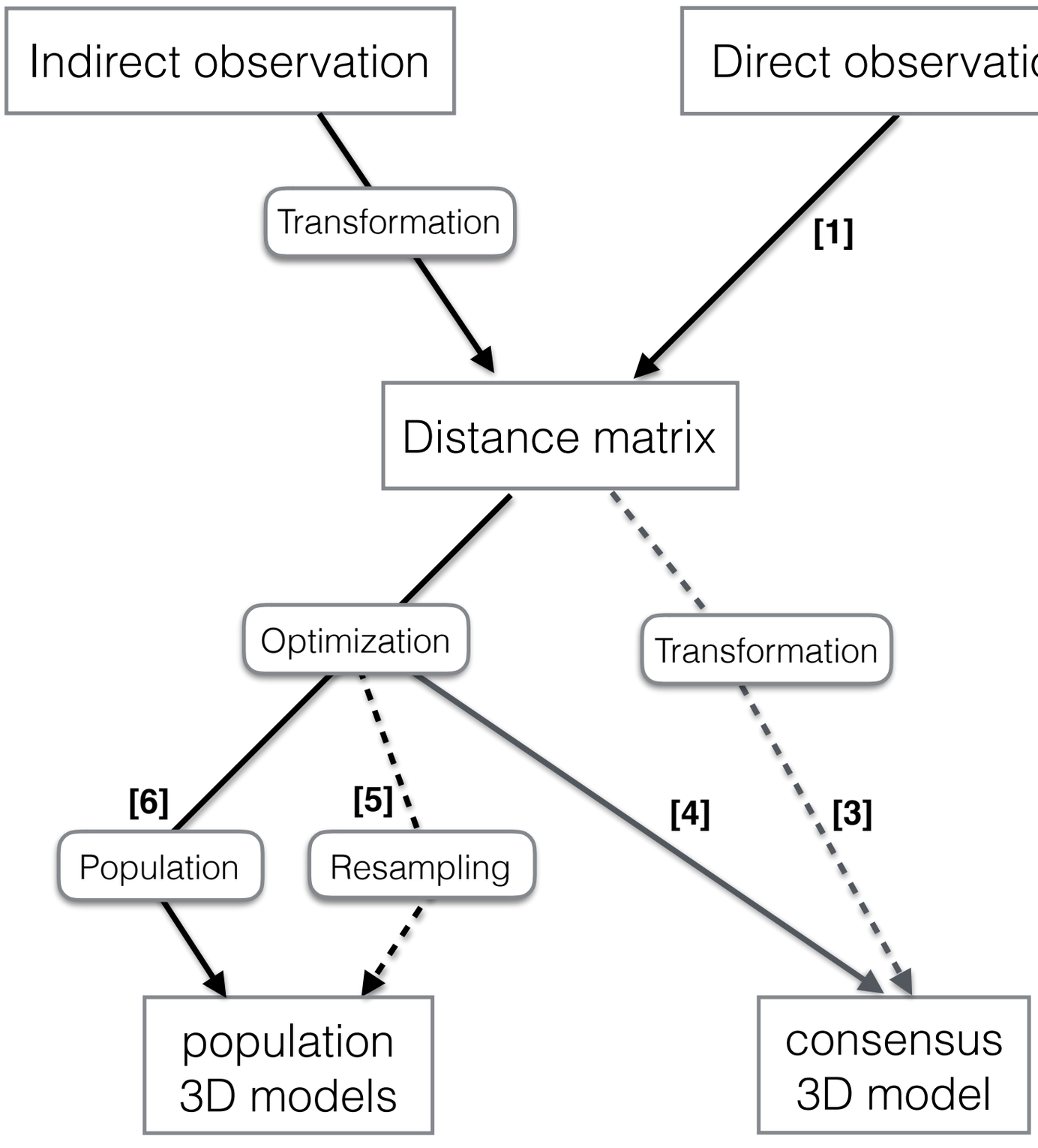



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[5] Meluzzi D, Arya G. 2013. Nucleic Acids Res 41: 63–75.
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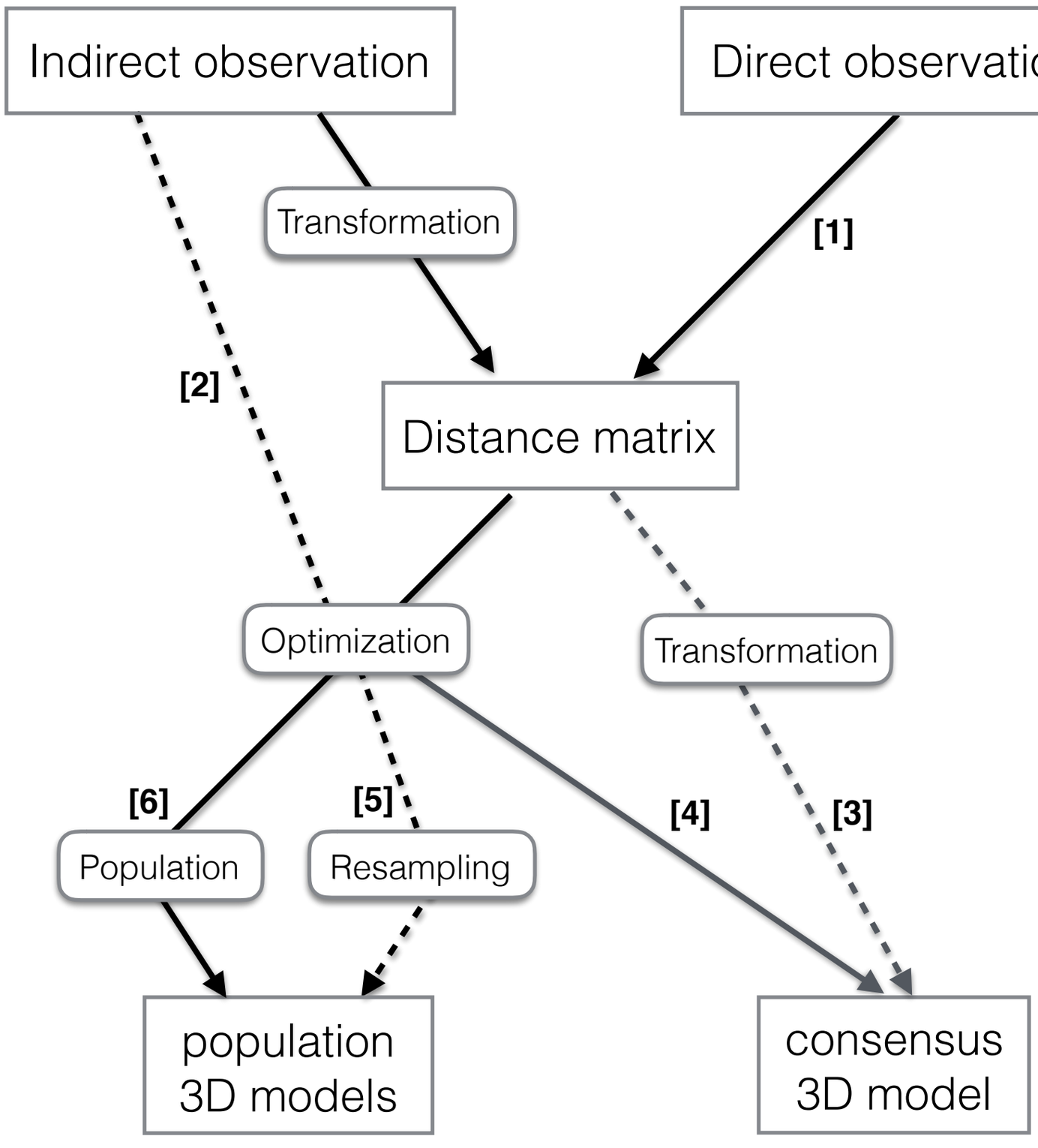



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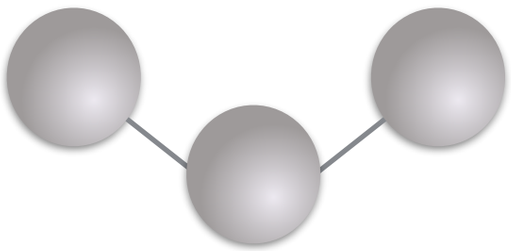

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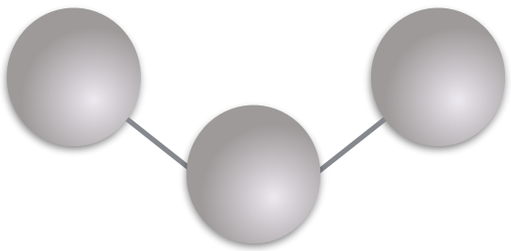

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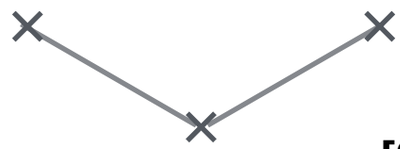

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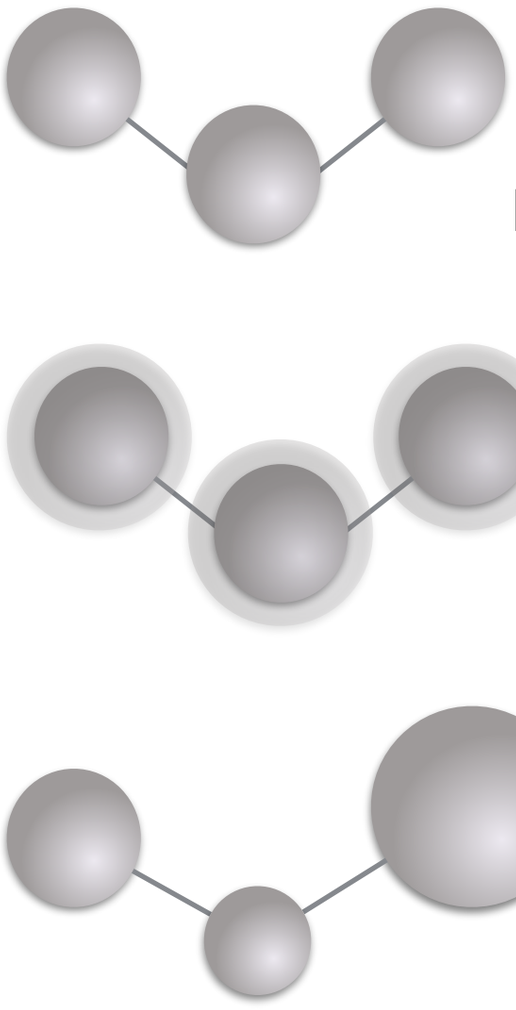

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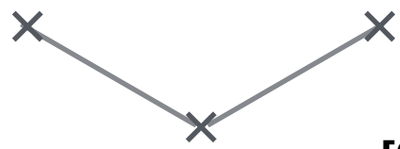

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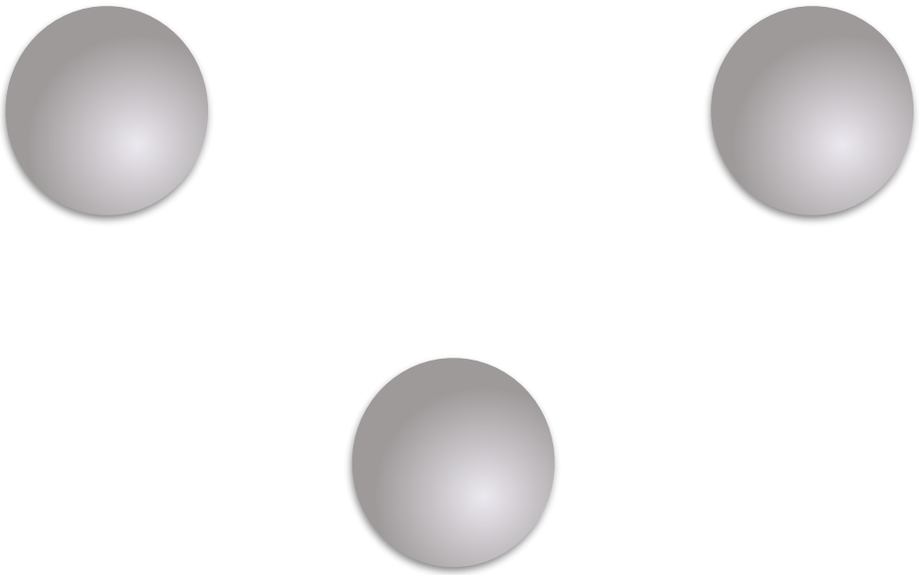

$$S = U_{3C} + U_{Biol} + U_{Phys}$$

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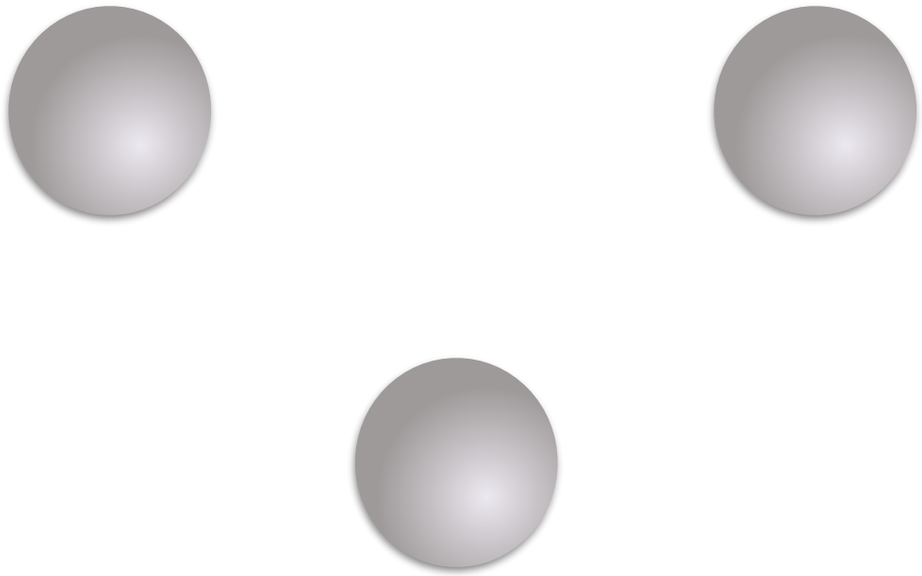

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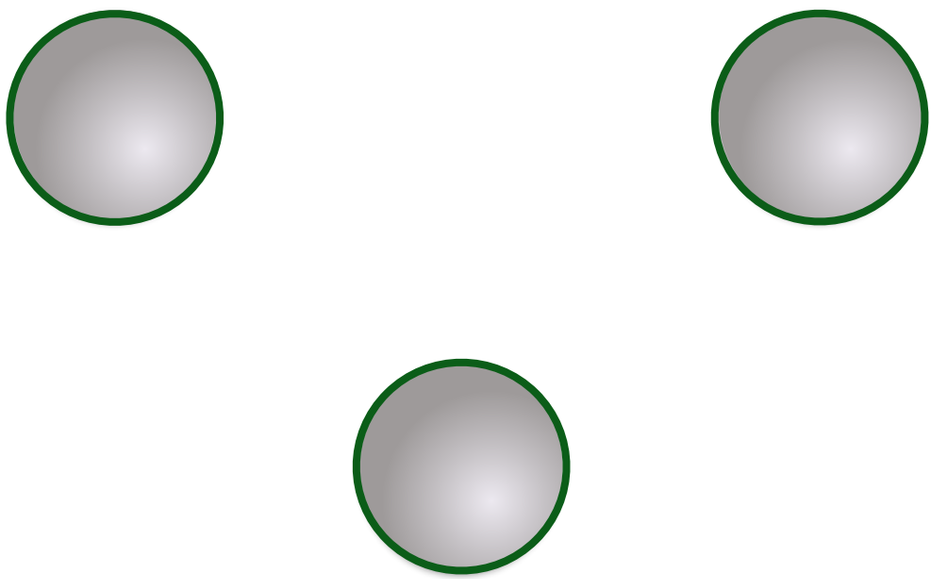
Tethering
Nucleus size

# The representation



$U_{Excl}$

$S = U_{3C} + U_{Biol} + U_{Phys}$

Tethering
Nucleus size

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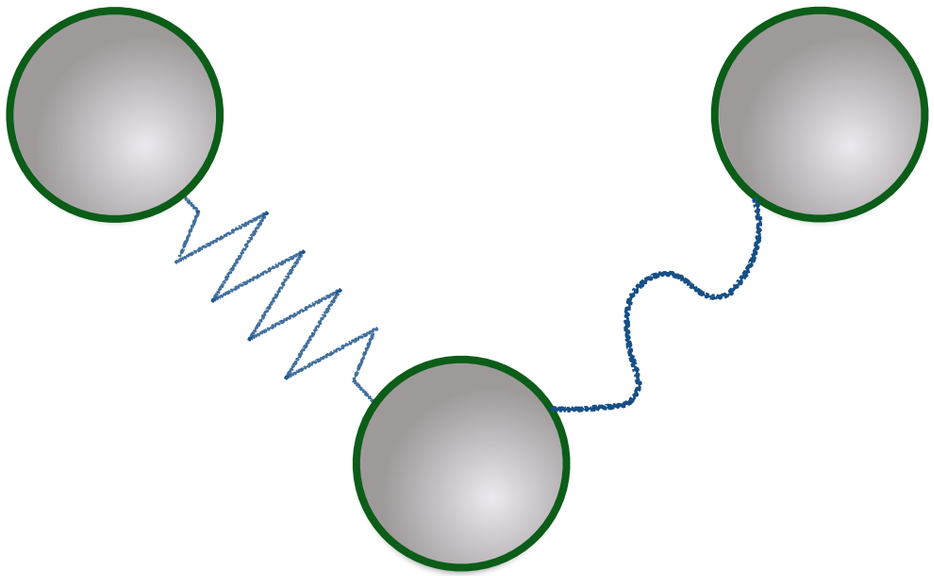
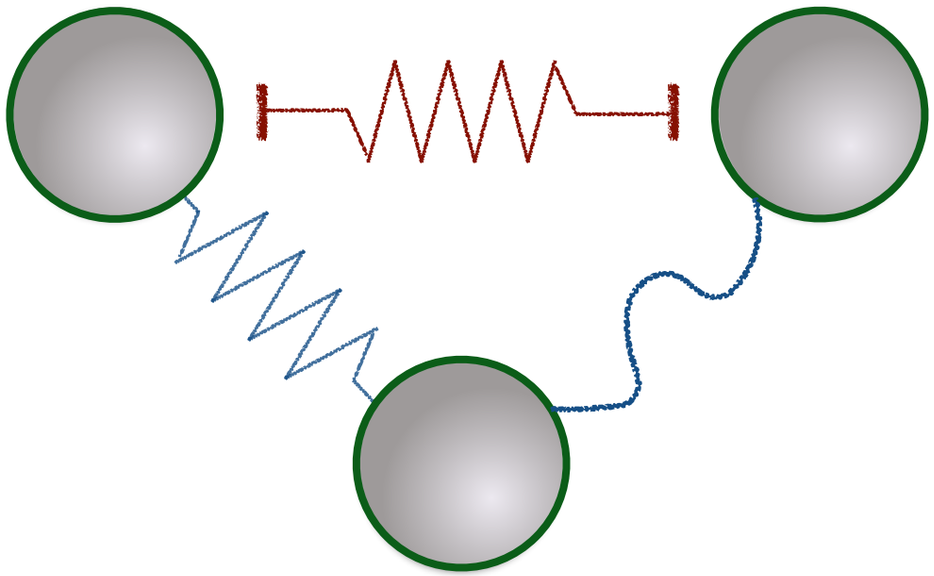


$U_{Excl} + U_{Bond}$

$$S = U_{3C} + U_{Biol} + U_{Phys}$$

Tethering
Nucleus size

# The representation



$$U_{Excl} + U_{Bond} + U_{Bend}$$

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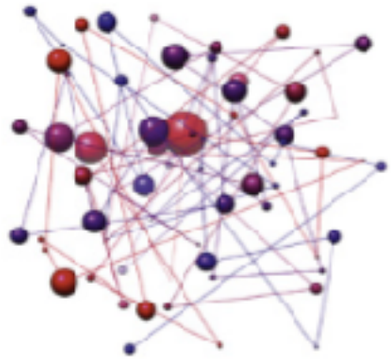
Nucleus size

# Model optimization



Baù D, Marti-Renom MA. 2012.
Genome structure determination via 3C-based data integration by the Integrative Modeling Platform.
Methods 58: 300–6.

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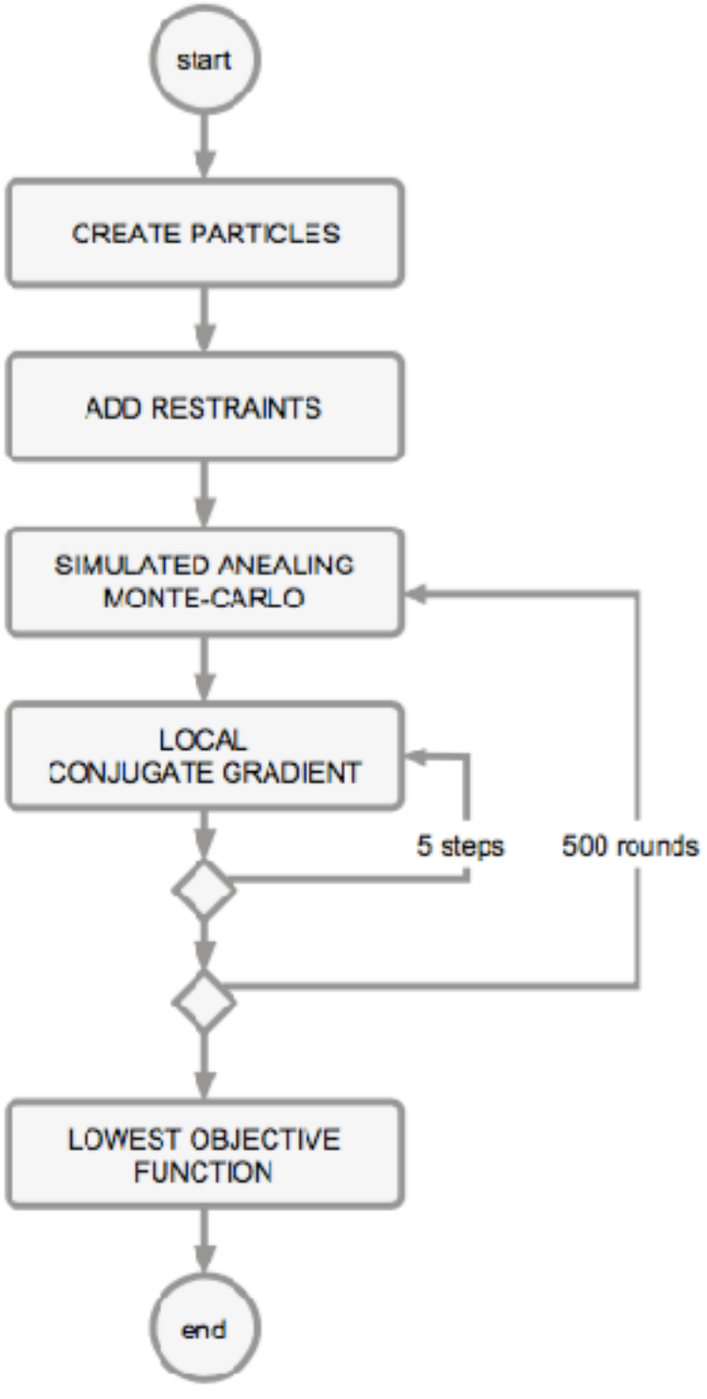


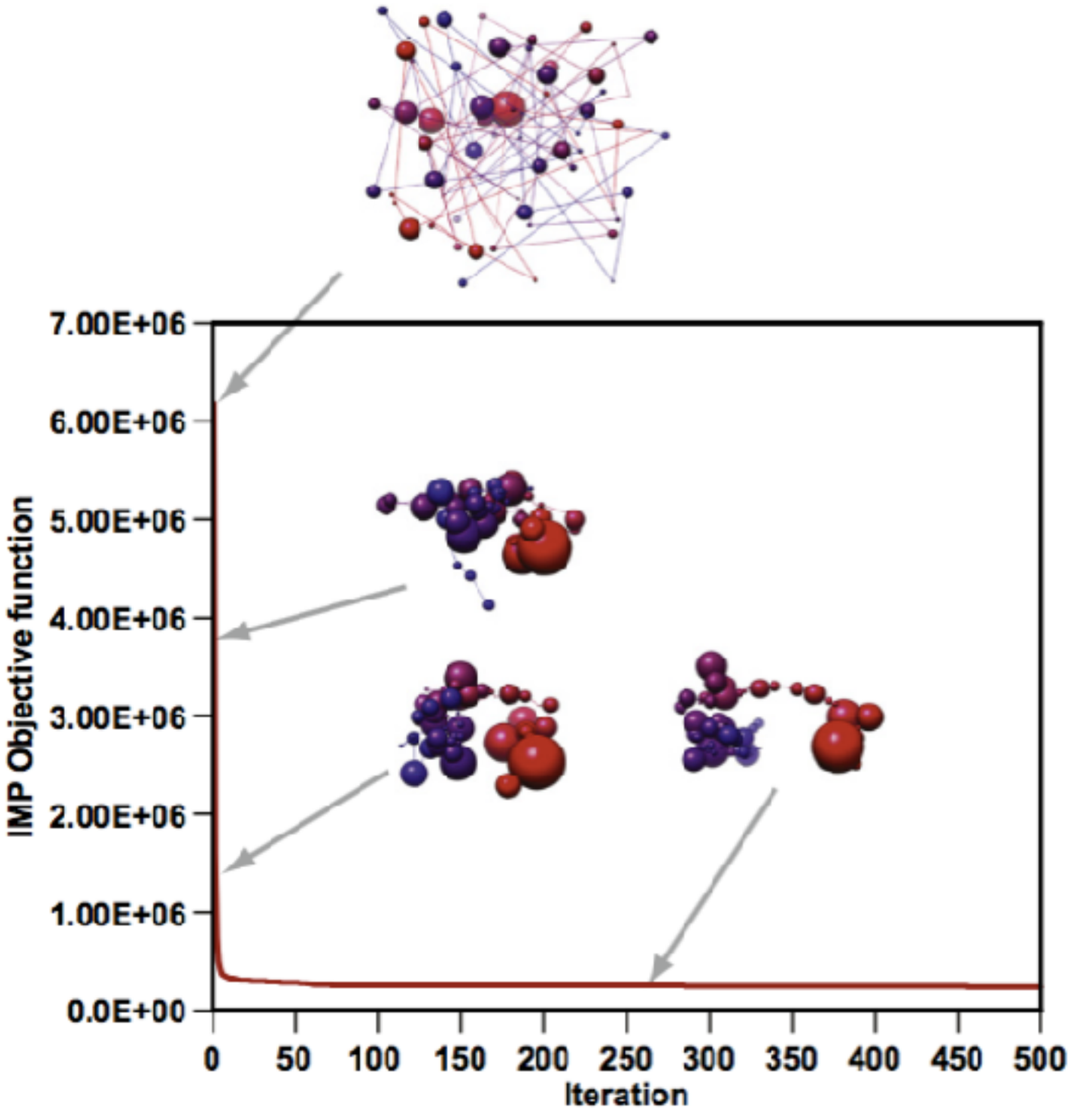


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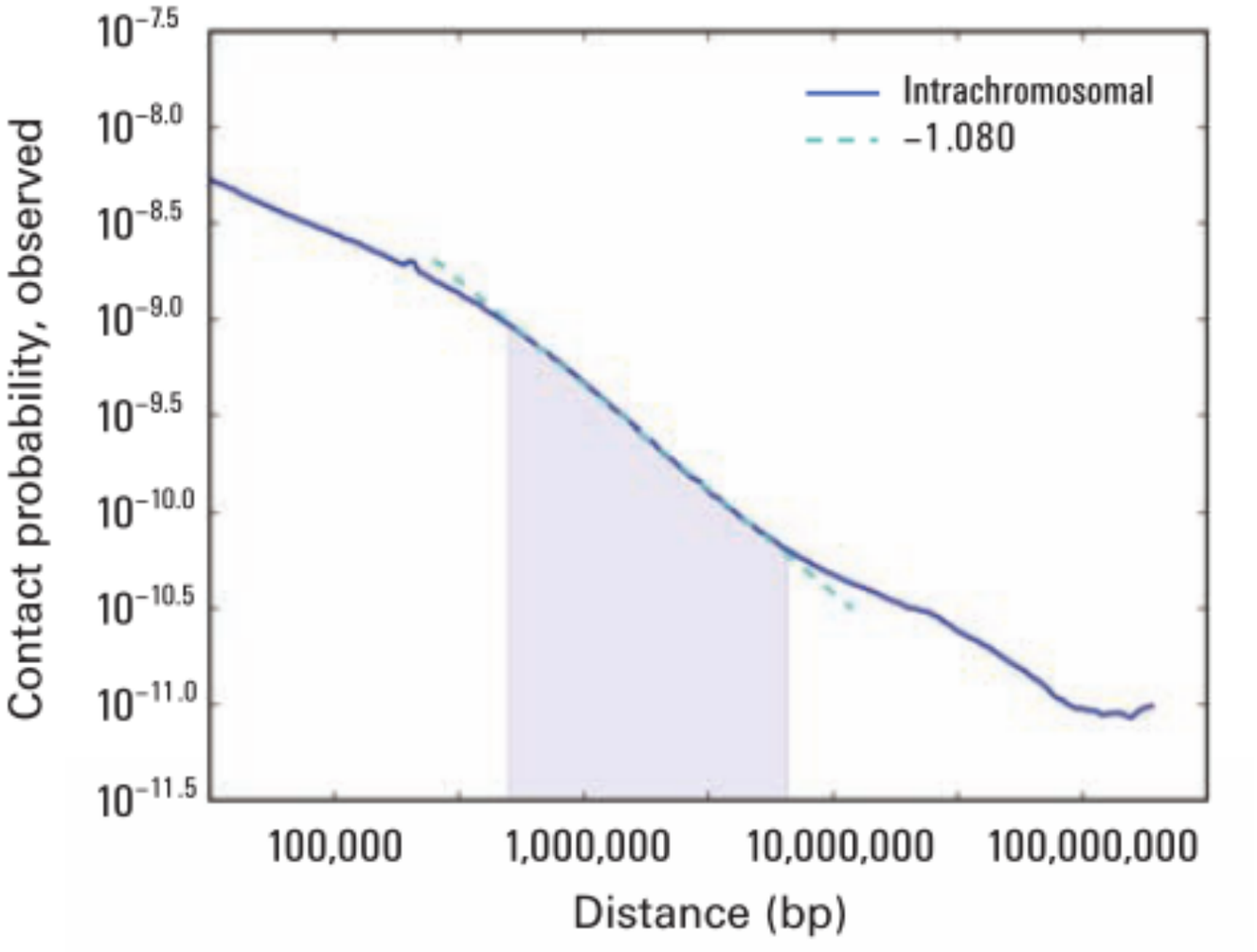
# From interactions to distance

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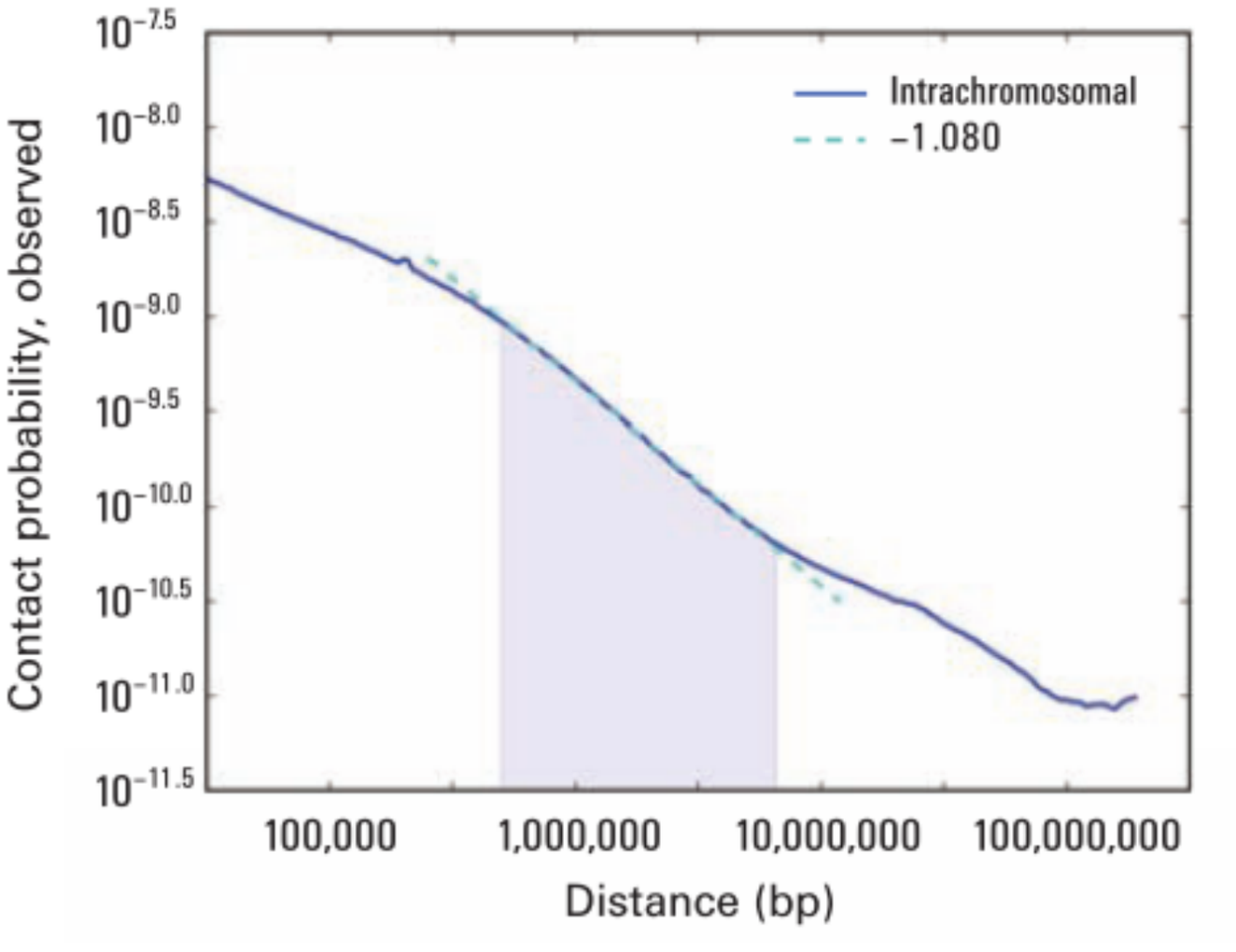


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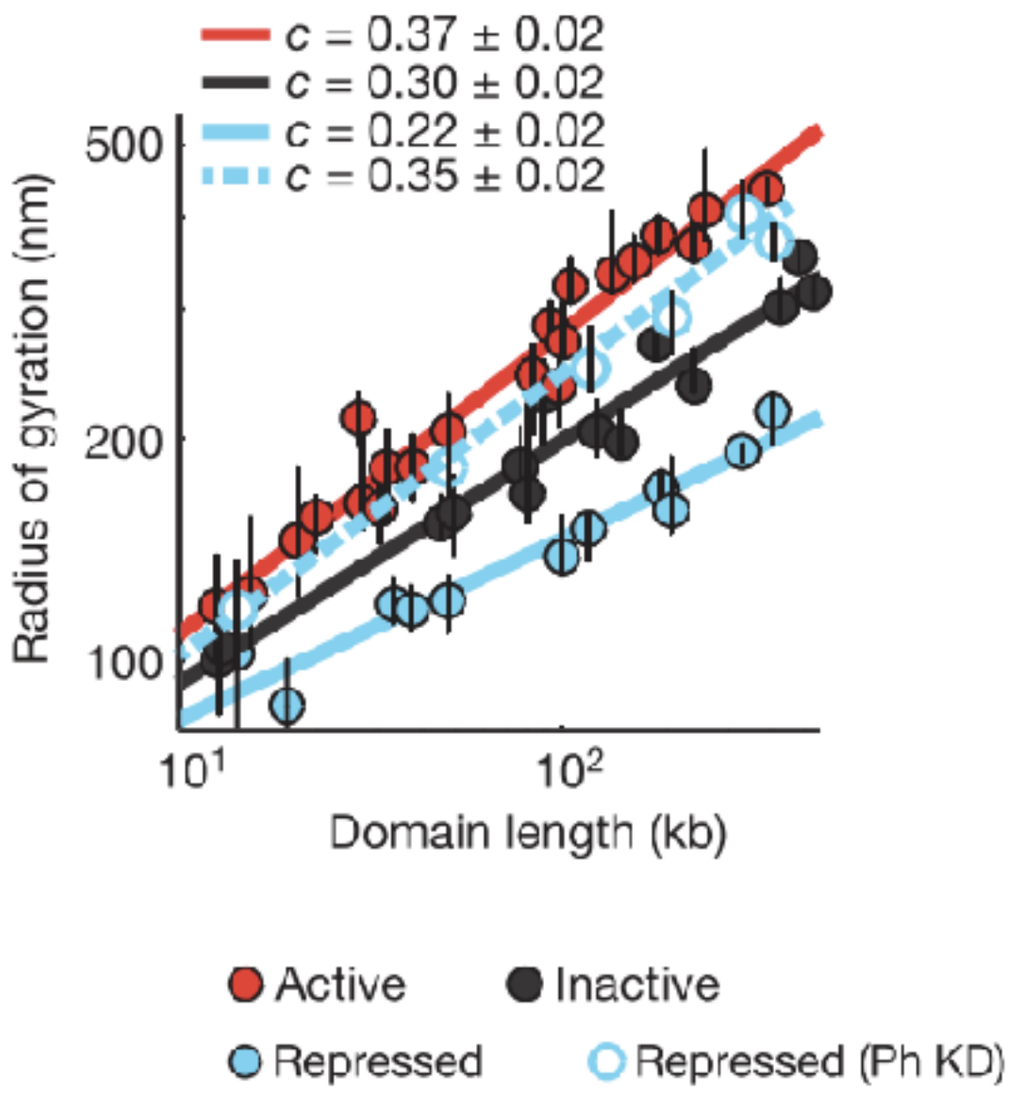


Boettiger AN, Bintu B, Moffitt JR, Wang S, Beliveau BJ, Fudenberg G, Imakaev M, Mirny LA, Wu C, Zhuang X. 2016.
Chromatin Folding for Different Epigenetic States.
Nature 1–15.

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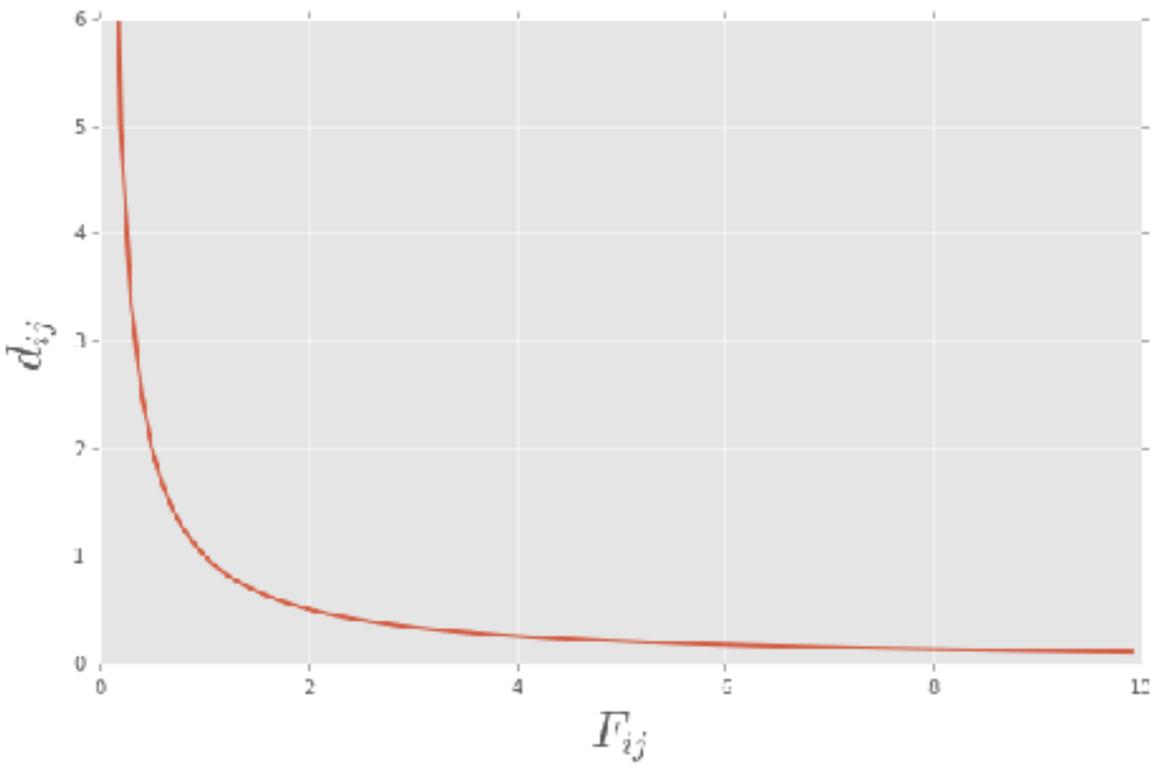
$$d_{ij} \propto \left(\frac{1}{F_{ij}}\right)^{\alpha}$$



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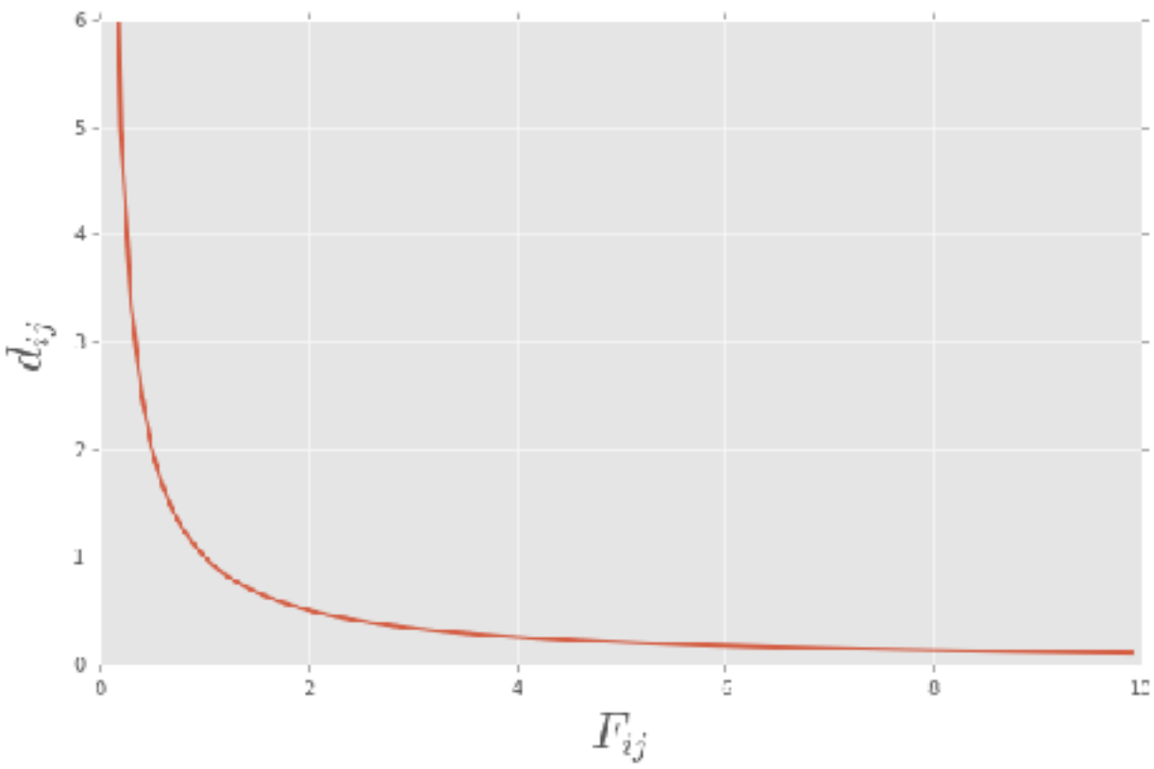
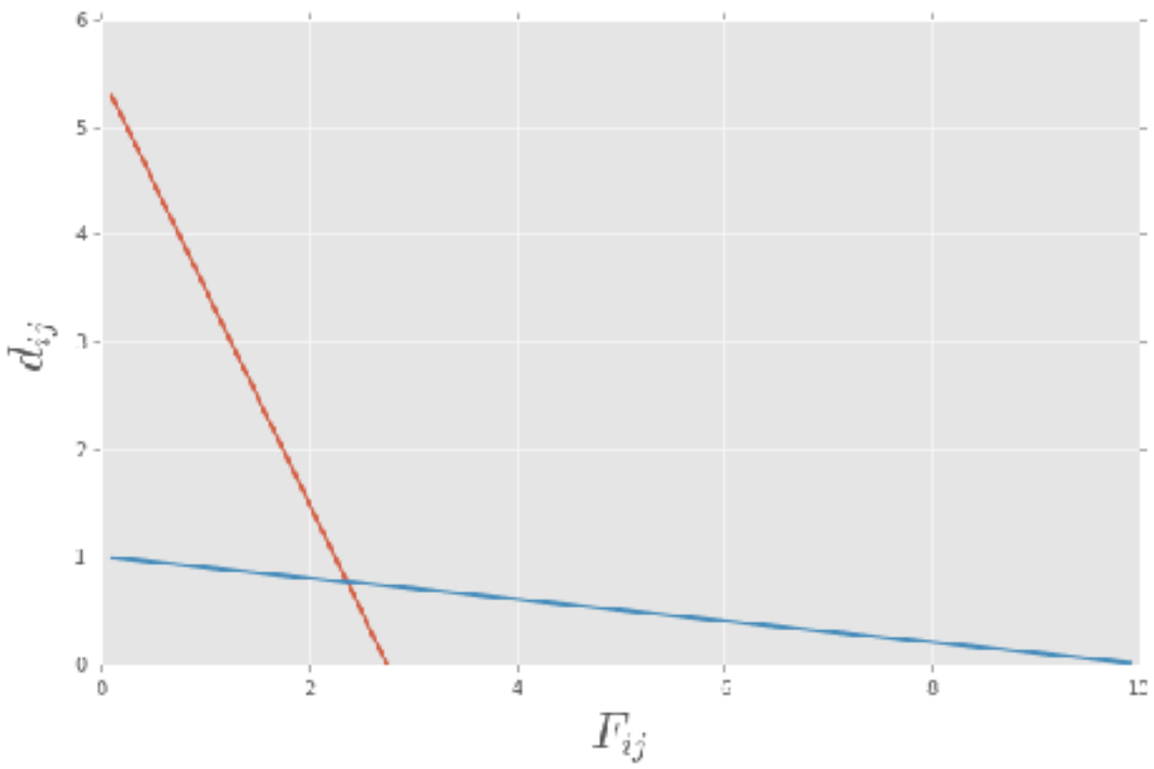



$$d_{ij} \propto \alpha F_{ij} + \beta$$



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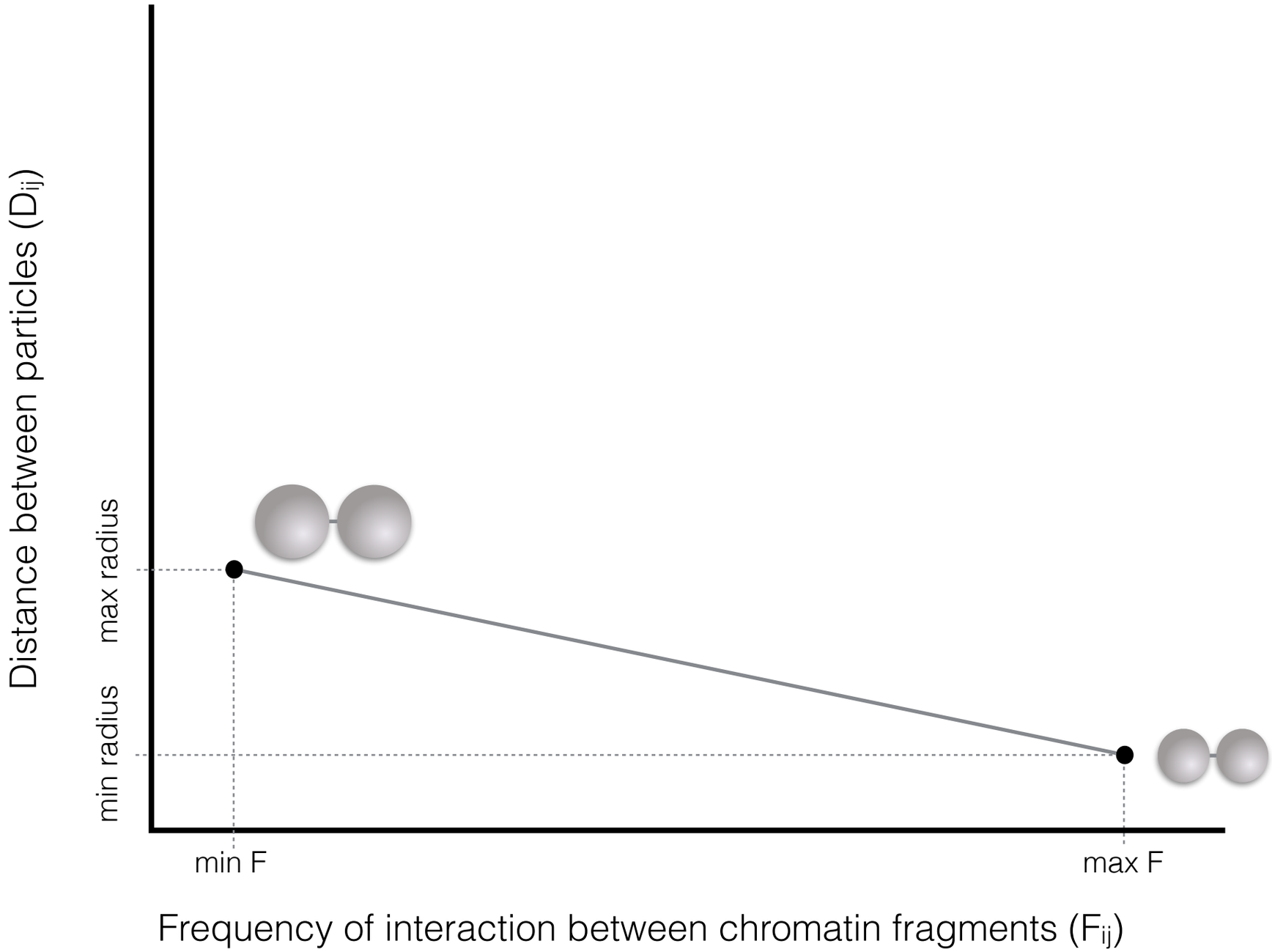


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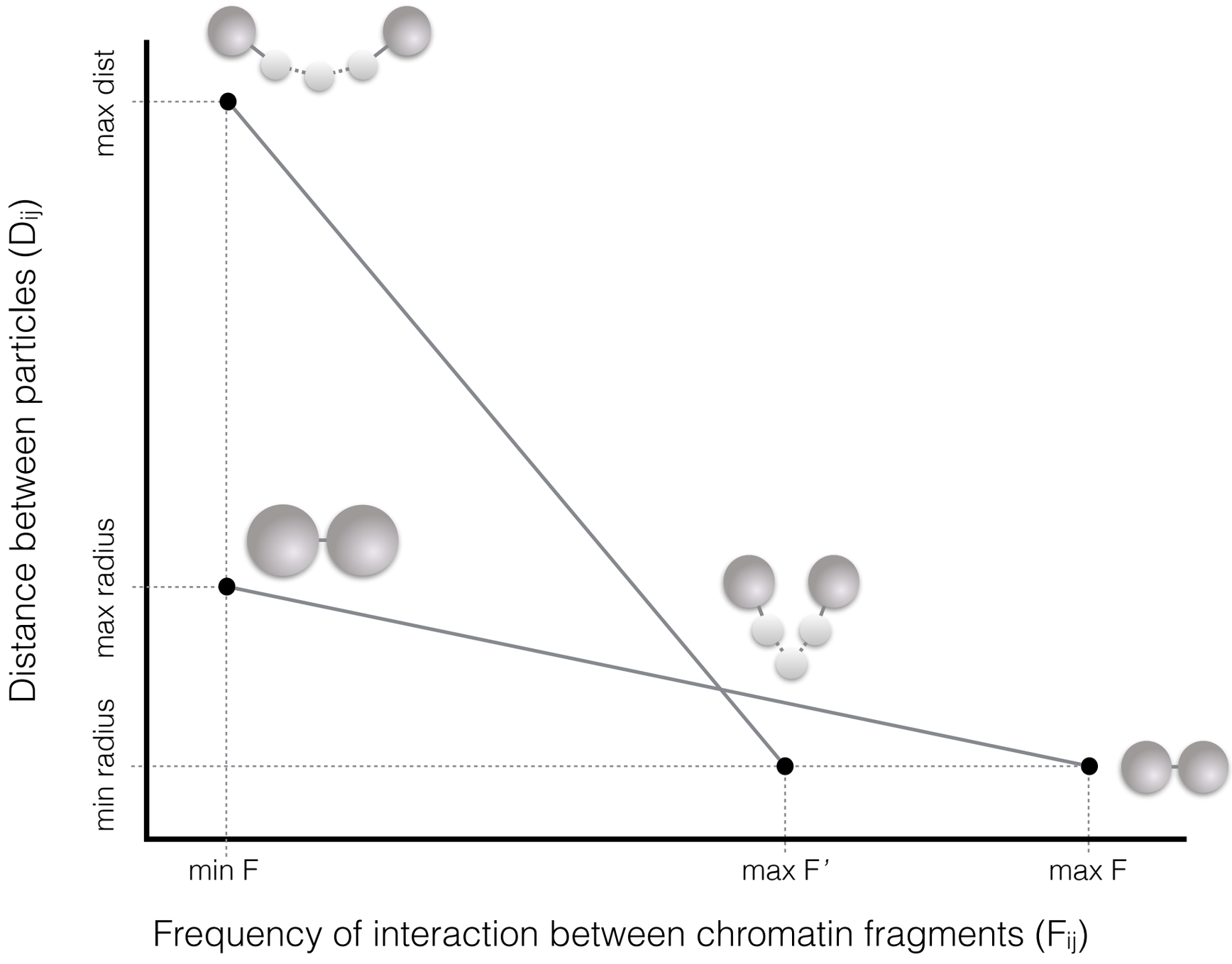


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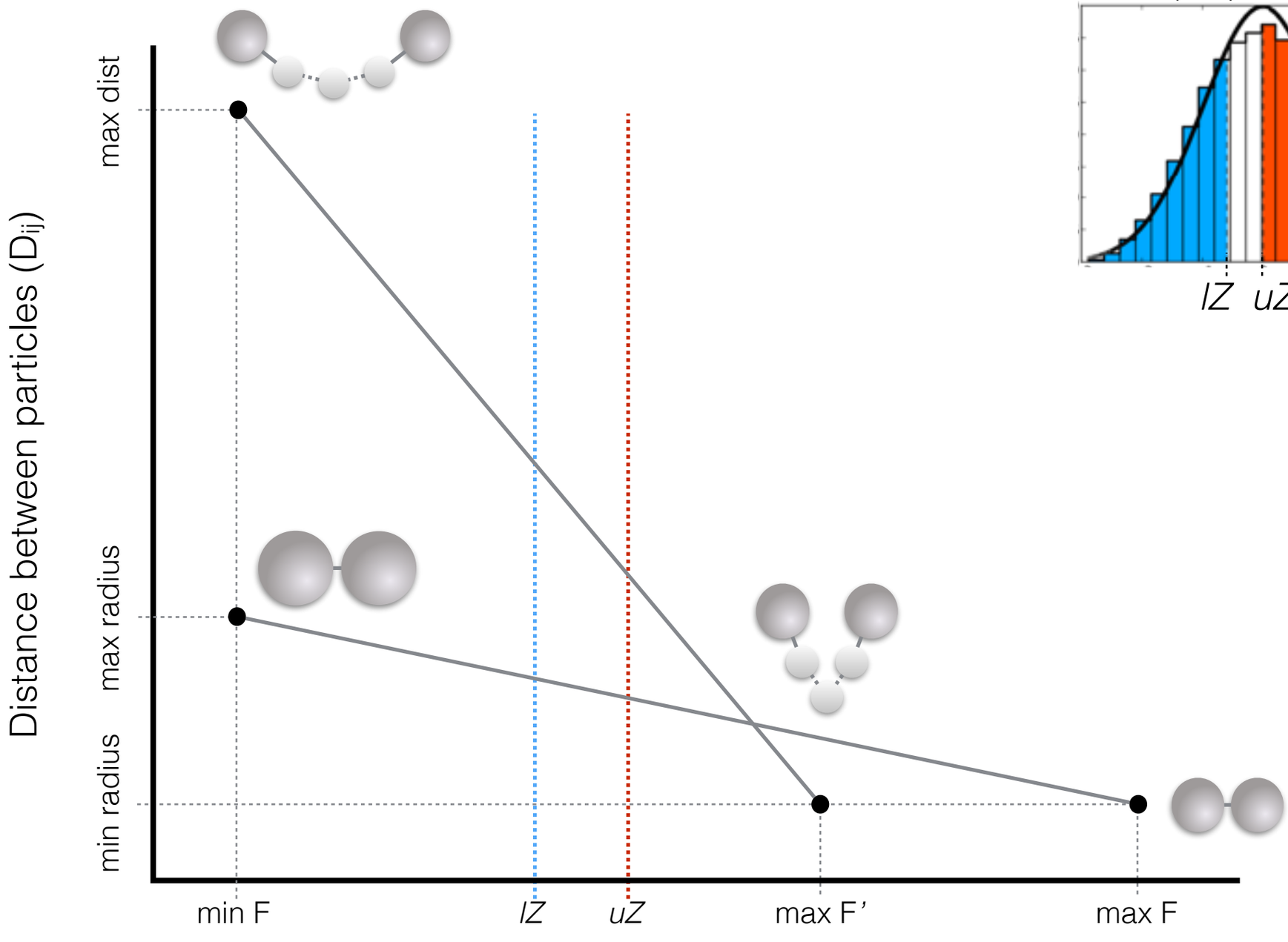


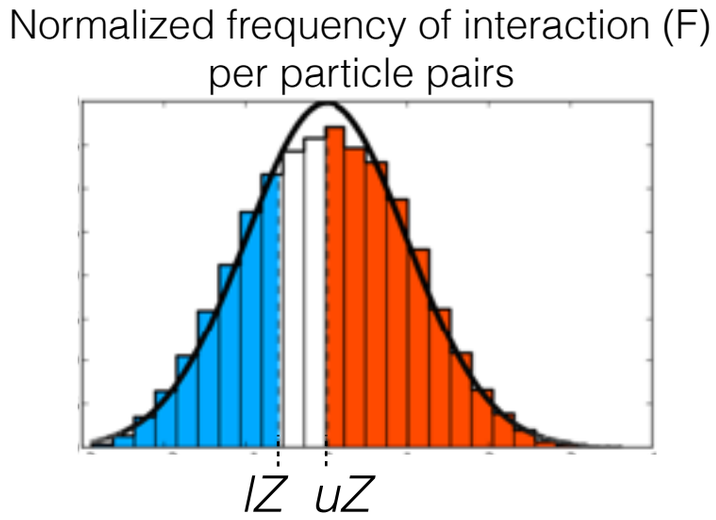


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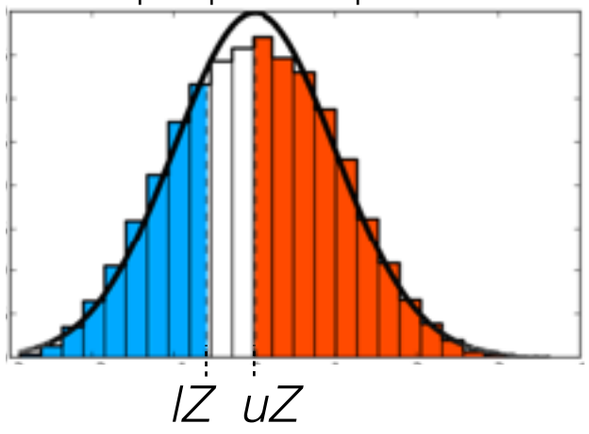
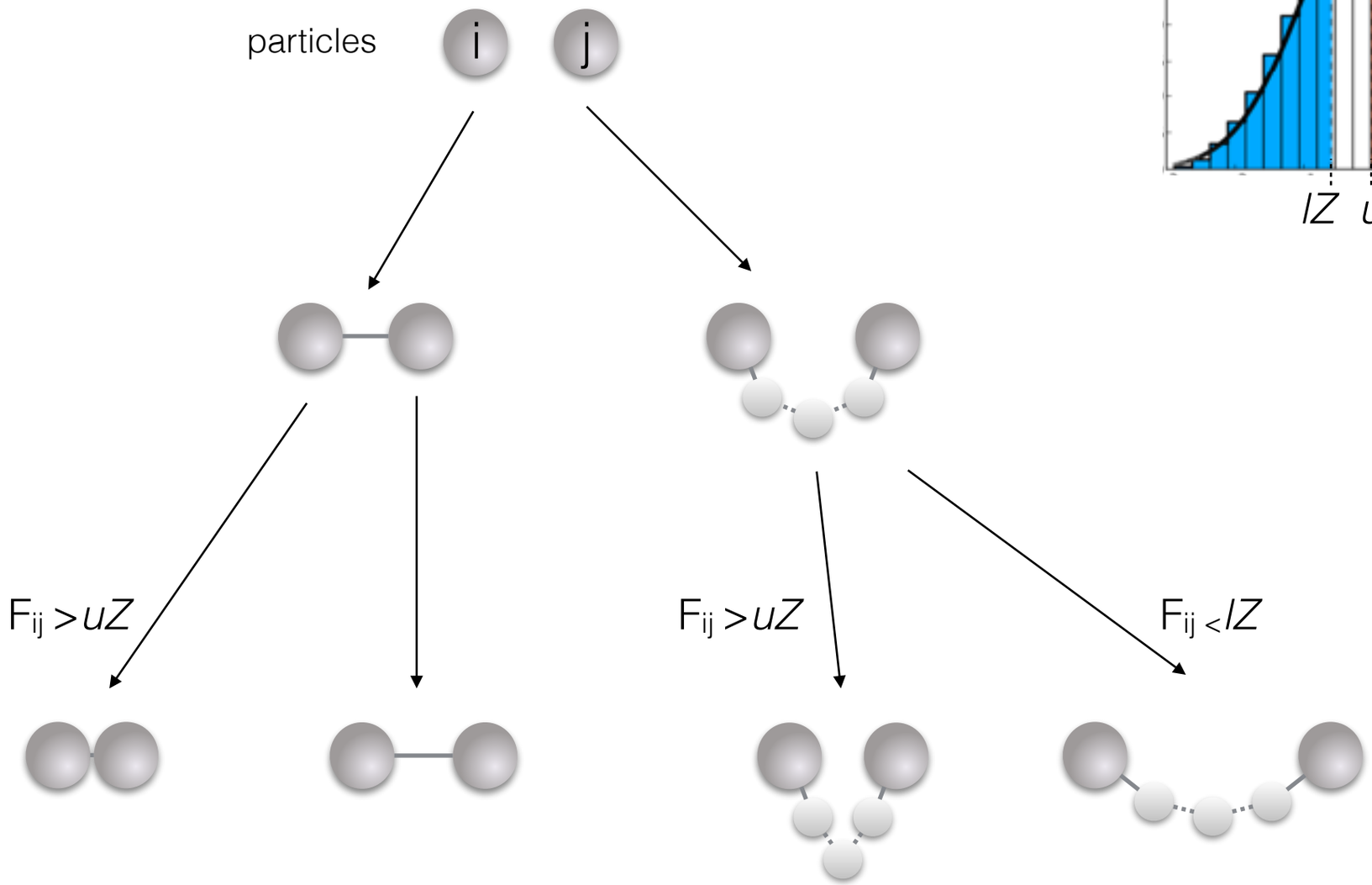
# Restraints

Normalized frequency of interaction (F)
per particle pairs



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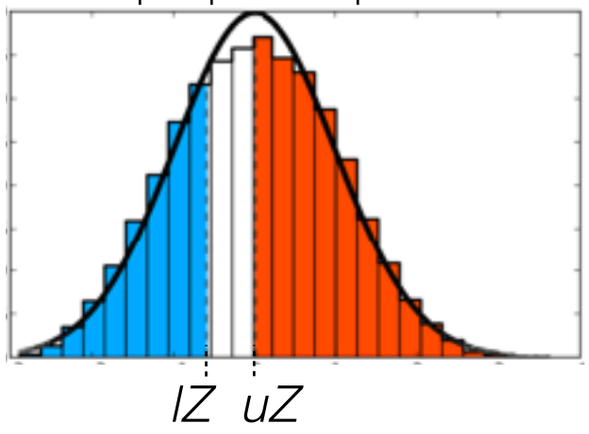
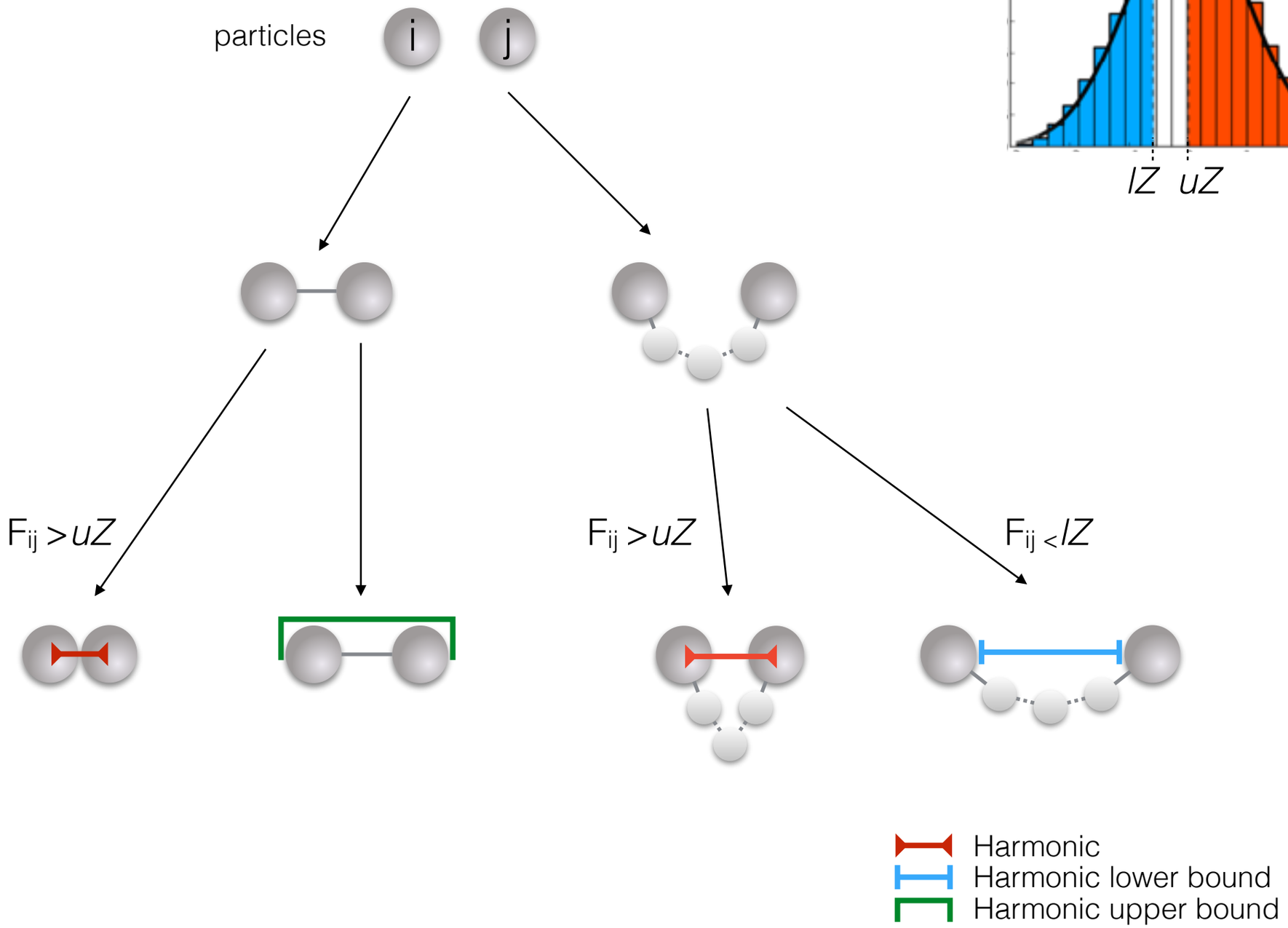
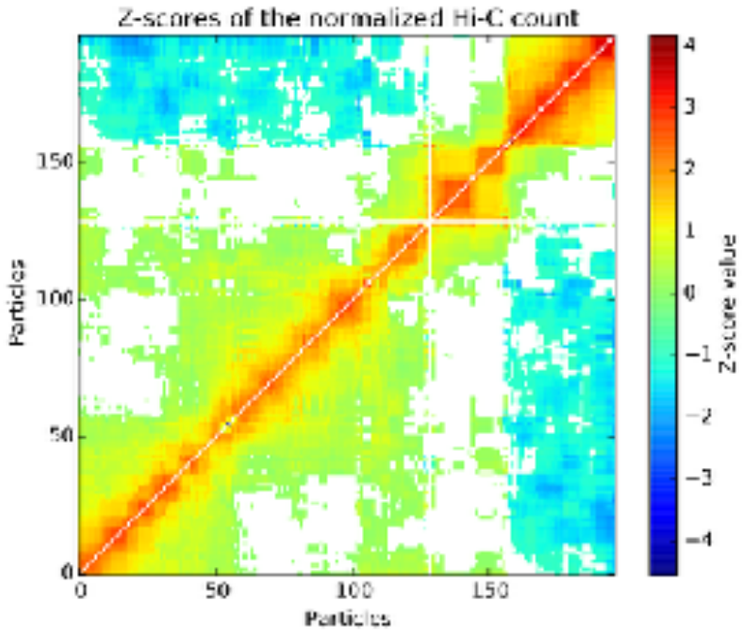
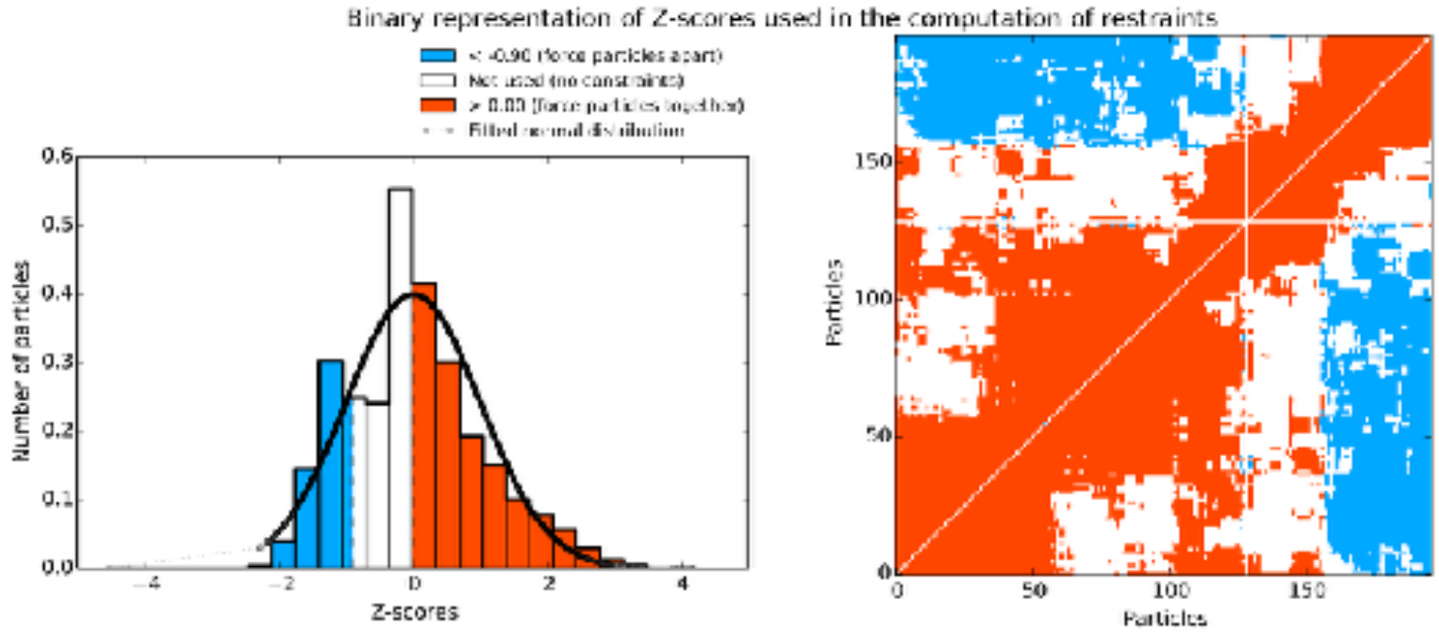


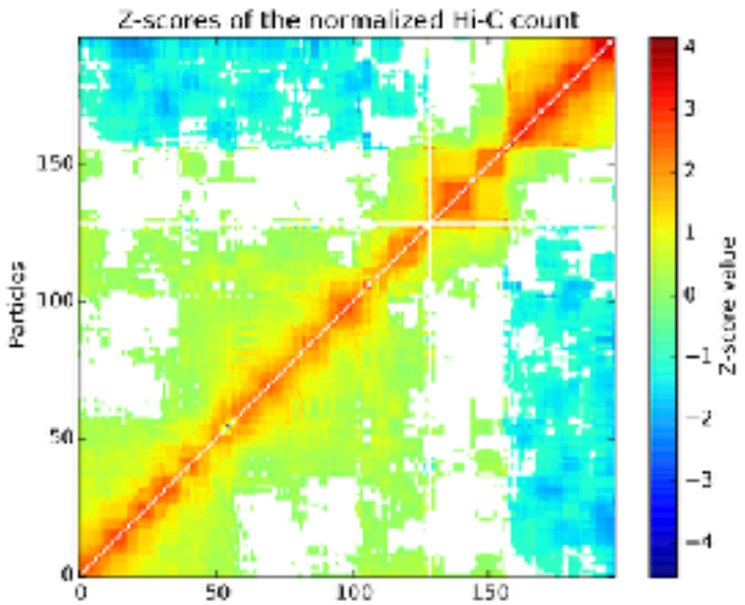



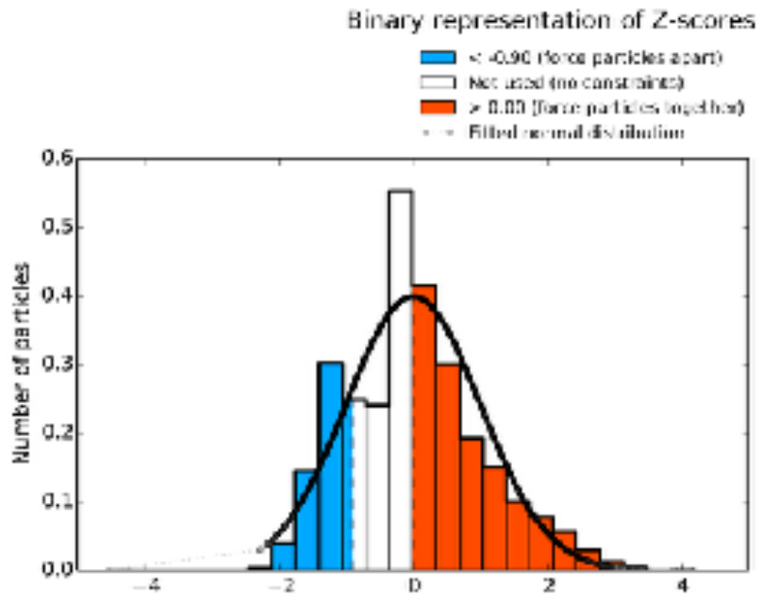
# Parameter optimisation

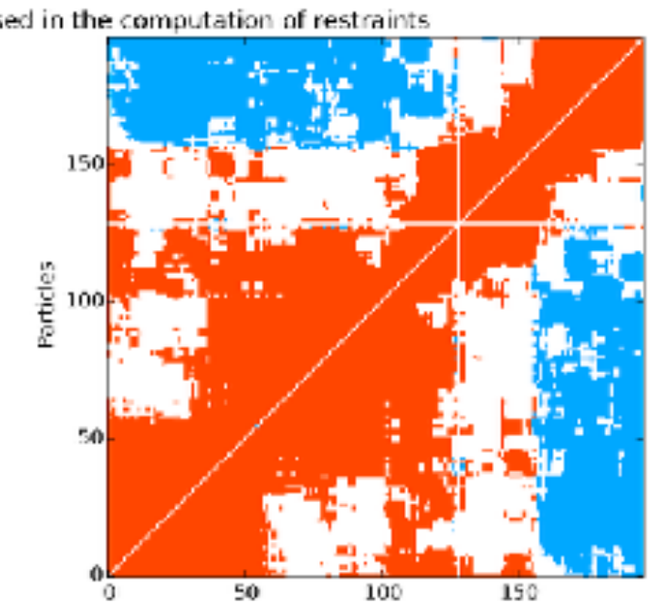


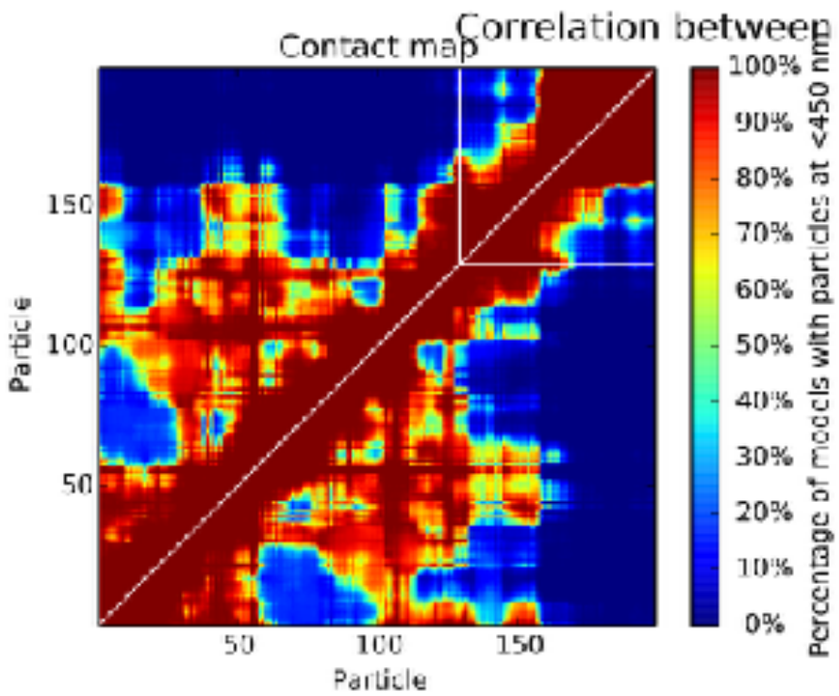



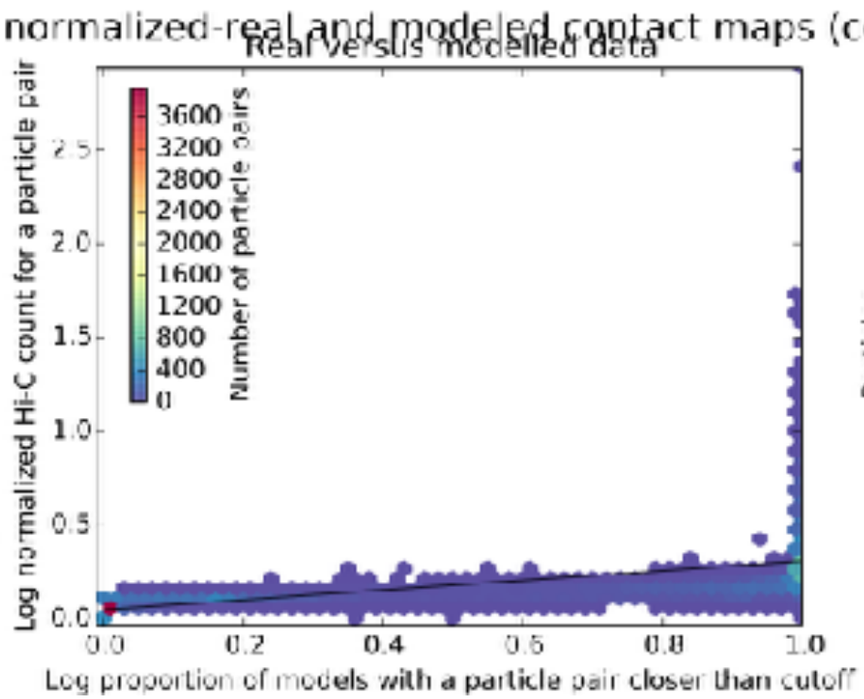
# Parameter optimisation

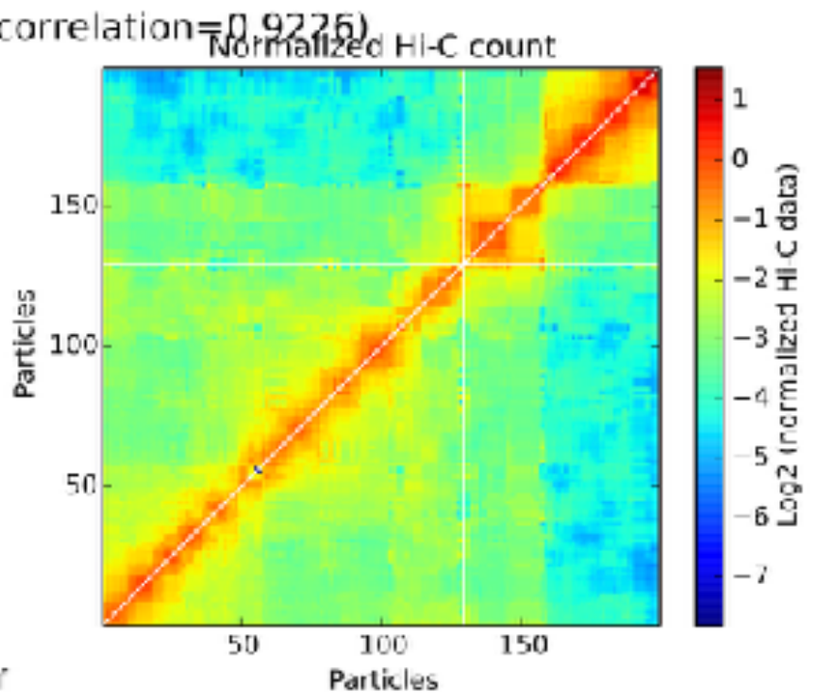


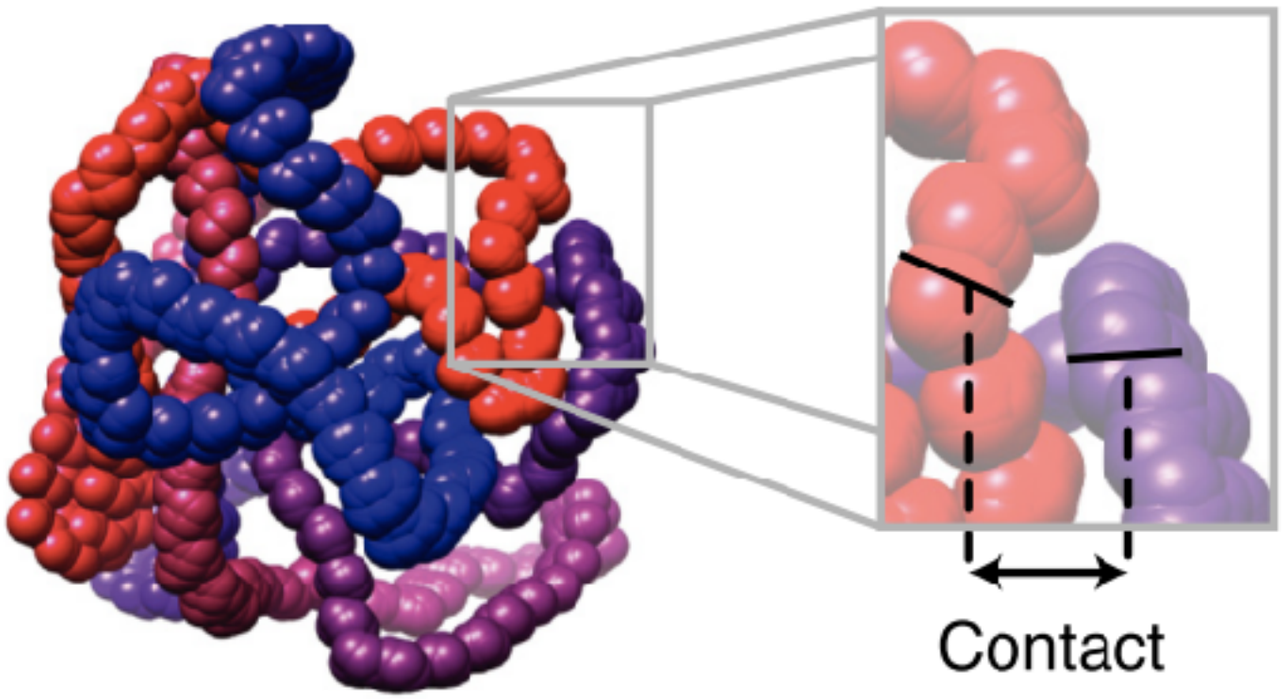



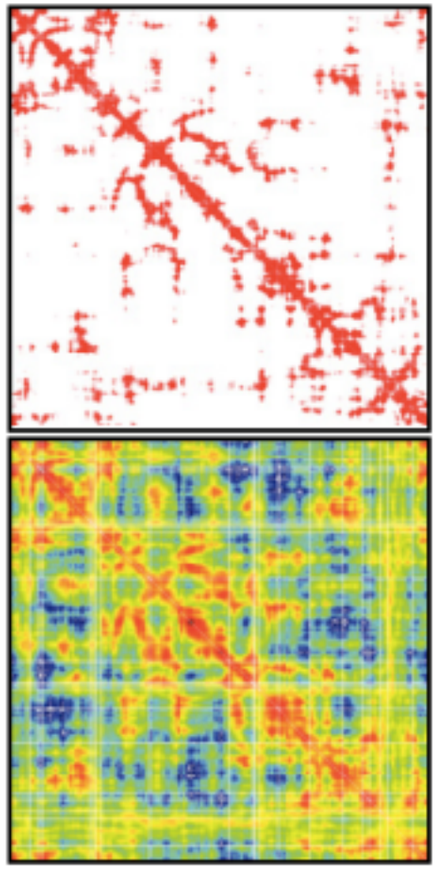




Correlation between normalized-real and modeled contact maps (correlation=0.9226)

# Parameter optimization



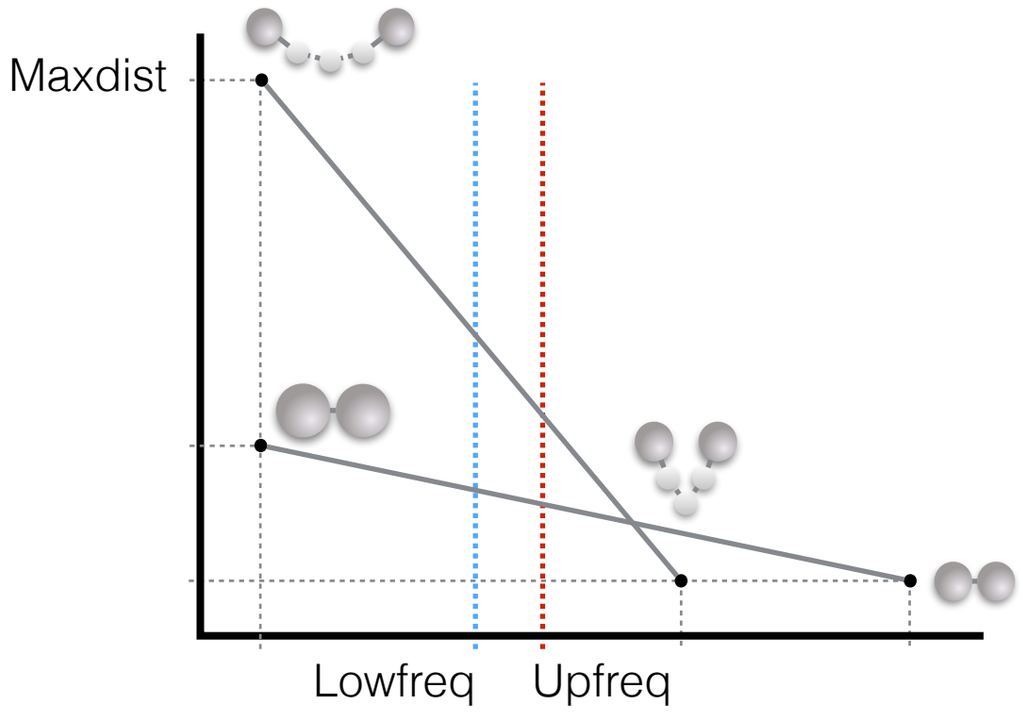
Contact matrix

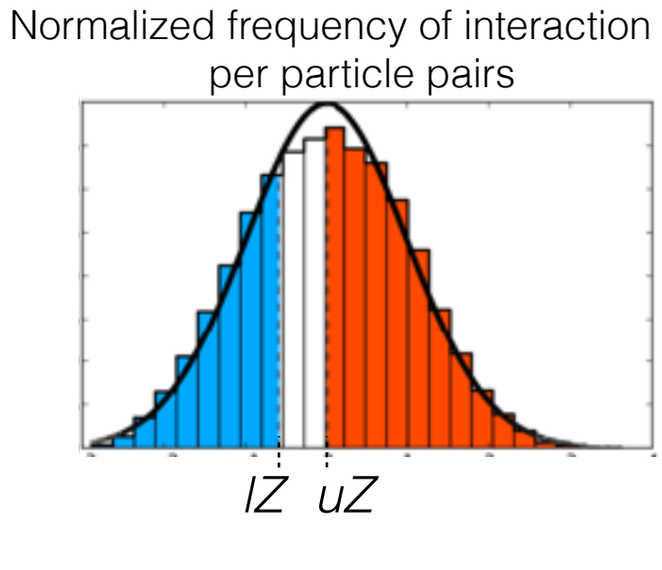
Hi-C data

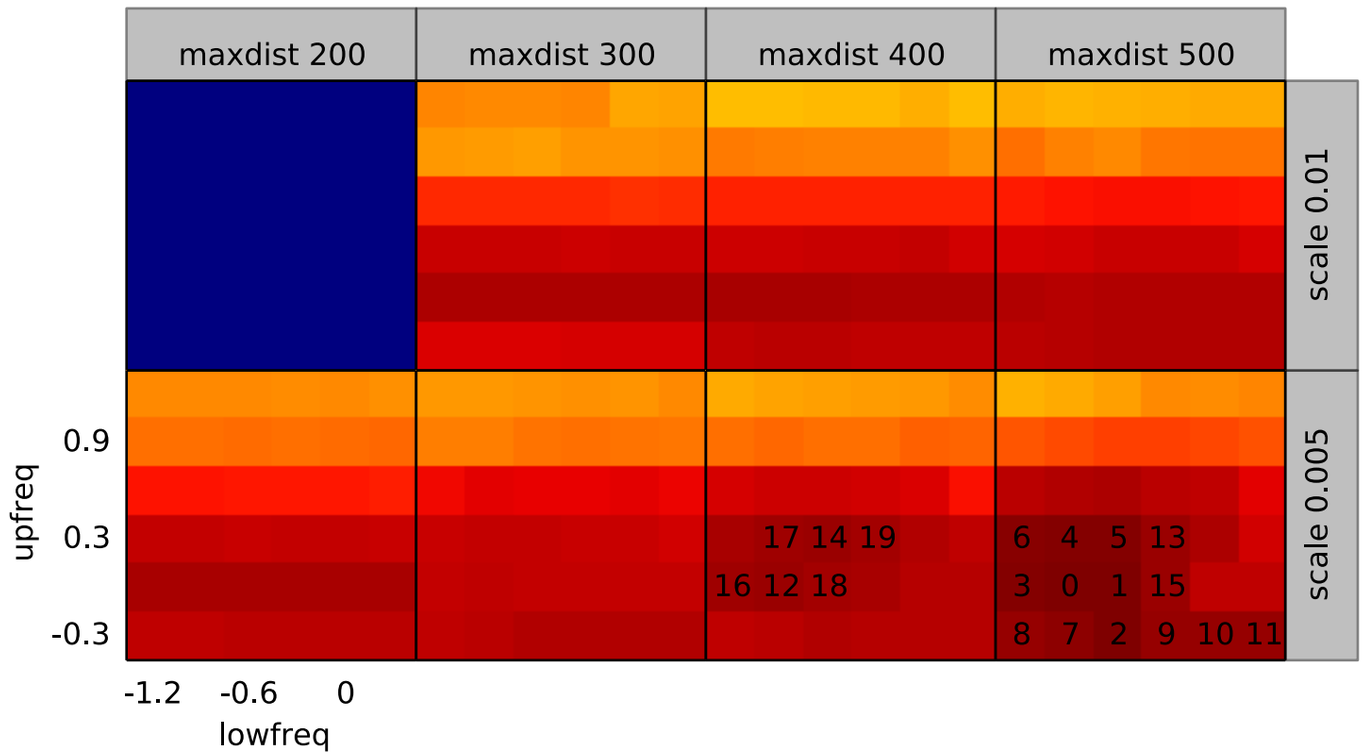
**Adapted from**

Trussart M, Serra F, Baù D, Junier I, Serrano L, Marti-Renom MA. 2015.
Assessing the limits of restraint-based 3D modeling of genomes and genomic domains.
Nucleic Acids Res 43: 3465–77

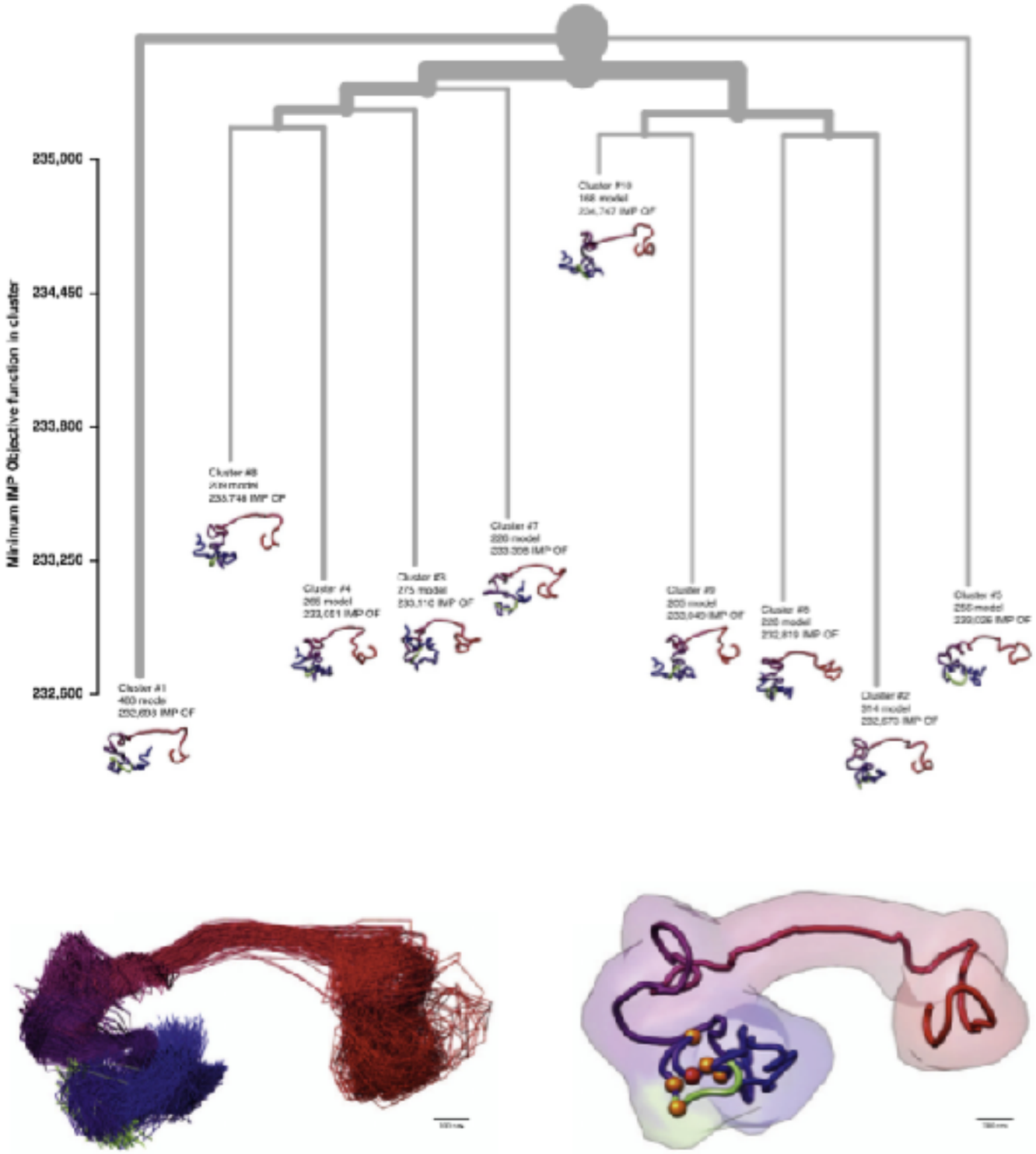
# Parameter optimization



# Model clustering



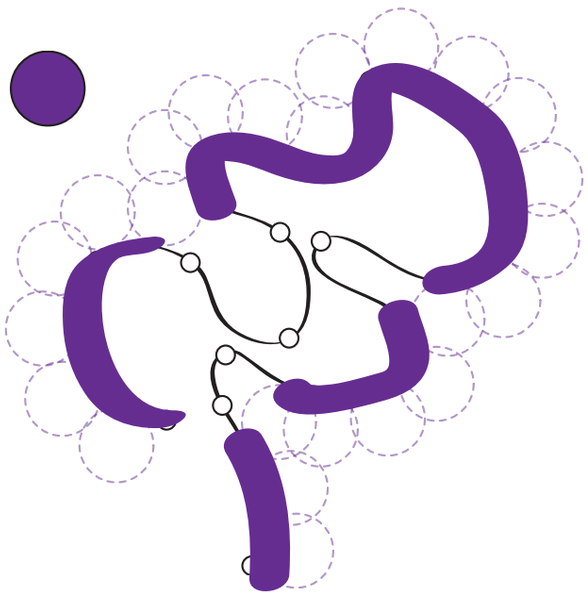

Baù D, Marti-Renom MA. 2012.
Genome structure determination via 3C-based data integration by the Integrative Modeling Platform.
Methods 58: 300–6.

# Population of models

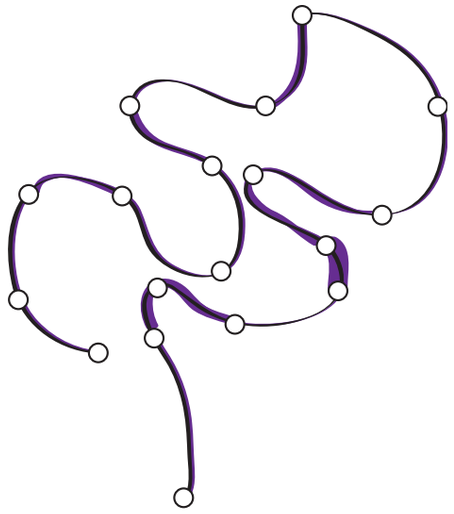
- Consensus model
  - single model
  - assumption of structural homogeneity (very fast)
- Resampling
  - independent model optimization
  - parameter optimization population based
  - assumption that structural heterogeneity is directly reflected in local minimums of the model optimization
- Population
  - models optimized in parallel
  - risk of overfitting, computationally expensive

# Model analysis

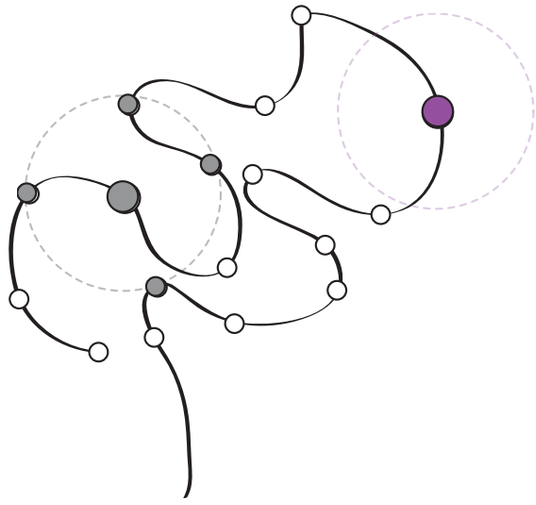
Accessibility (%)



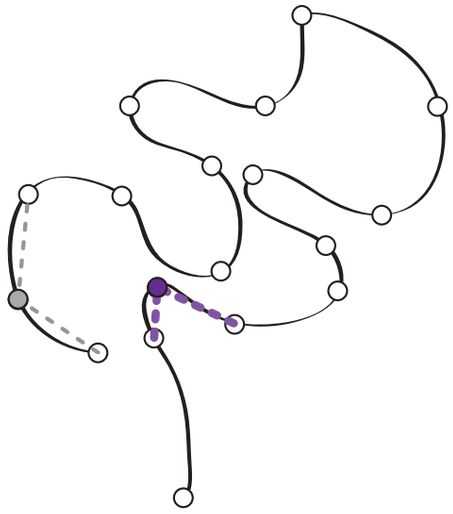
Density (bp/nm)



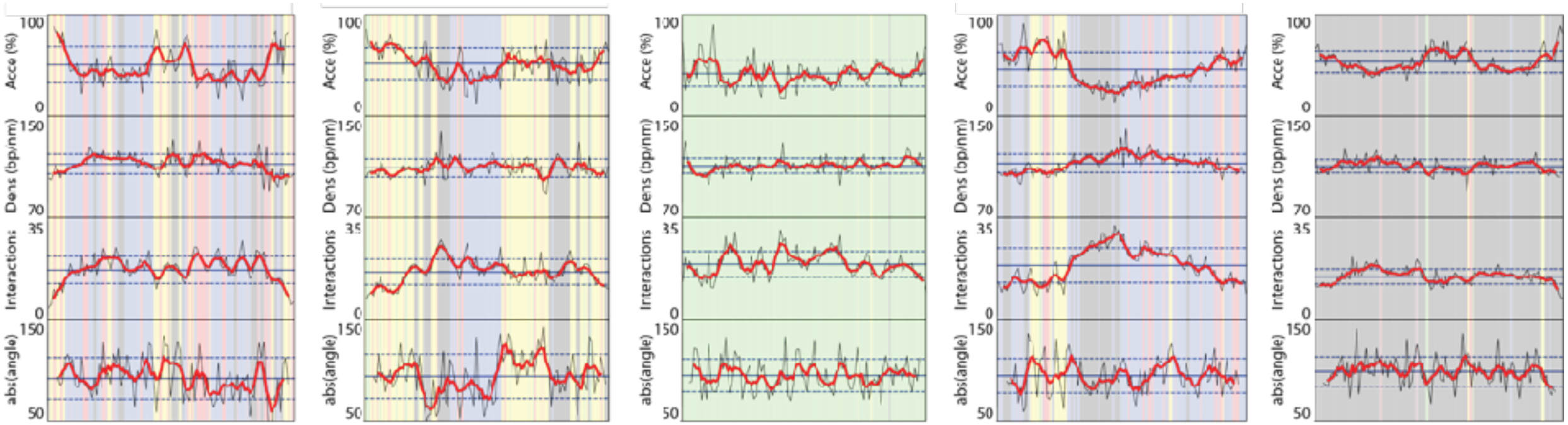
Interactions

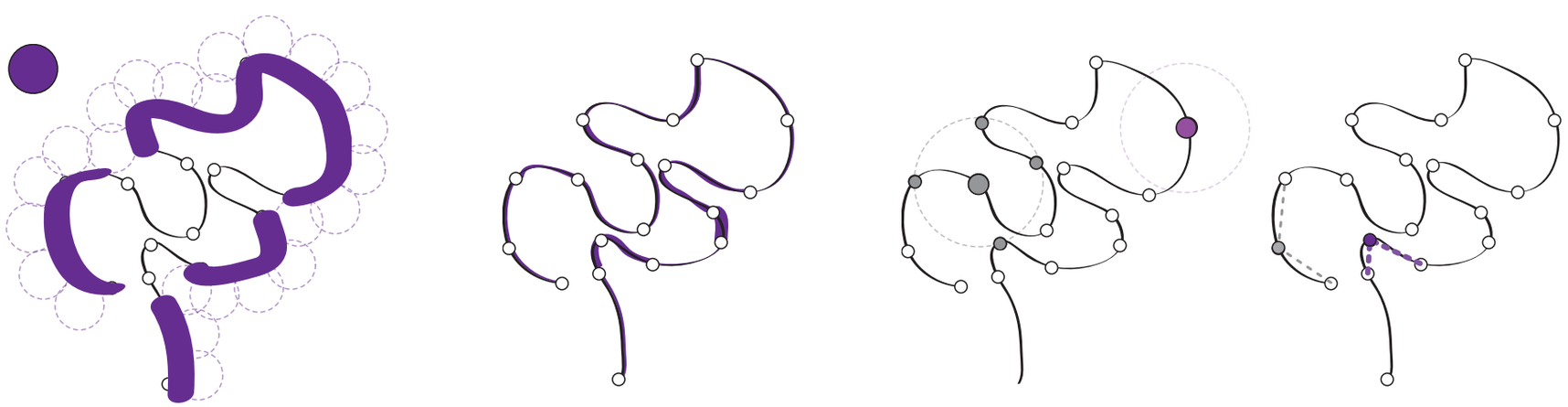


Angle

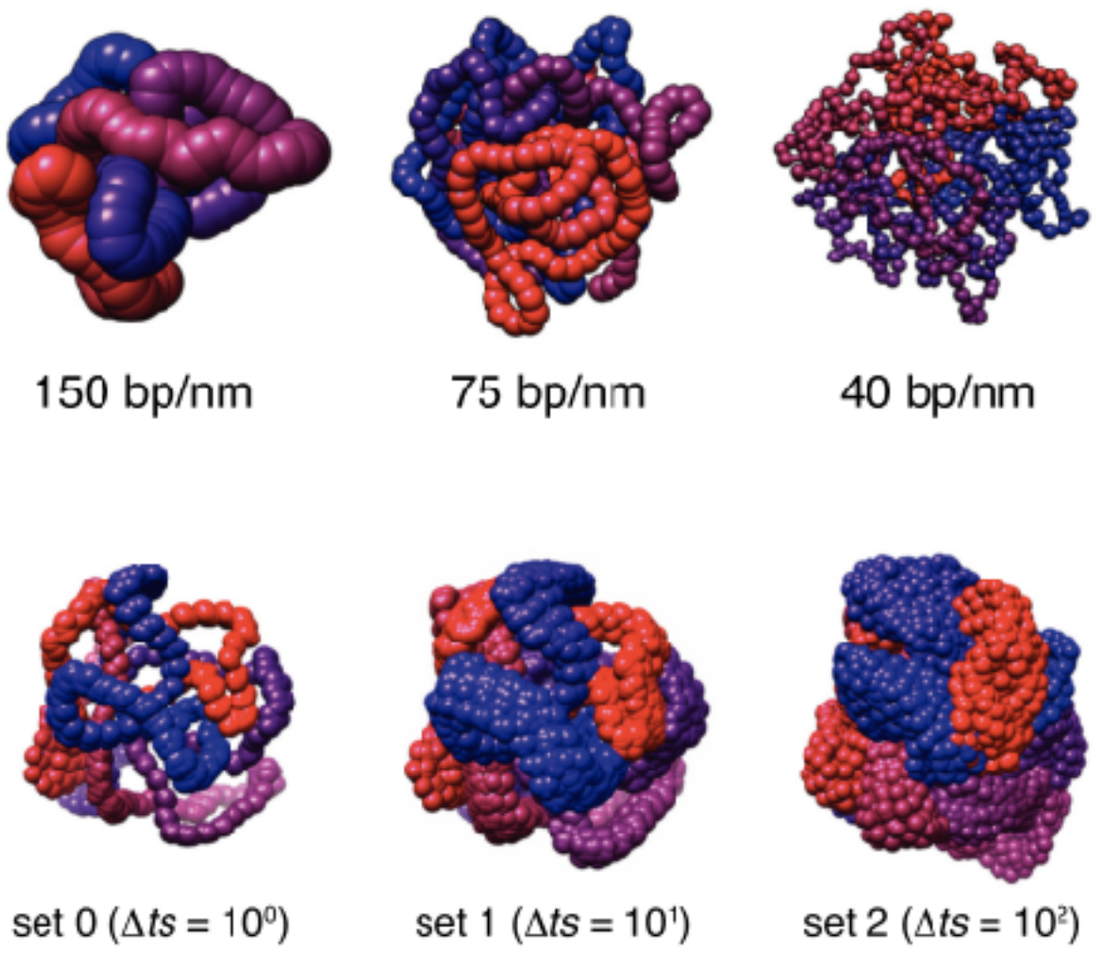


# Model analysis: structural features



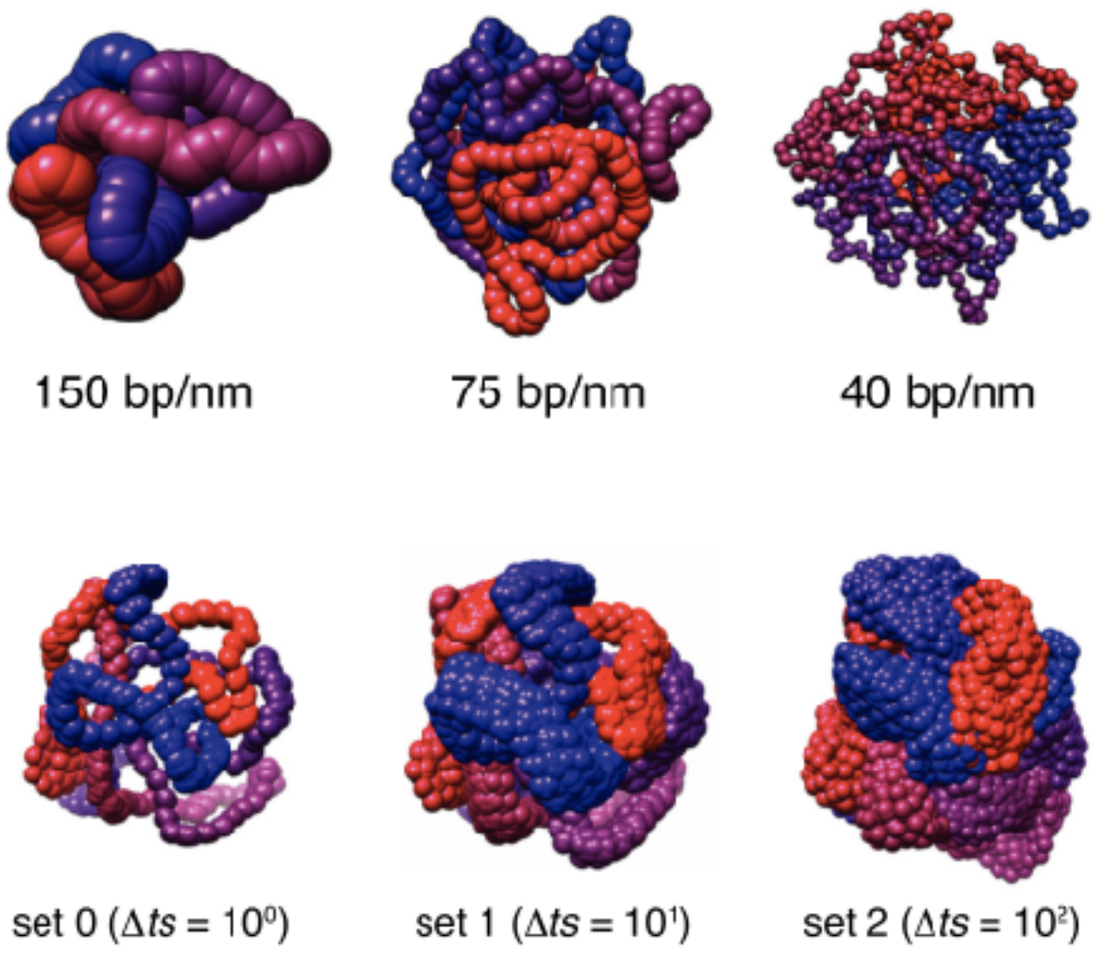



# Modeling potential




Trussart M, Serra F, Baù D, Junier I, Serrano L, Marti-Renom MA. 2015.
Assessing the limits of restraint-based 3D modeling of genomes and genomic domains.
Nucleic Acids Res 43: 3465–77

# Modeling potential




Study the effect of:

- **structural variability**
- **noise**
- number of particles
- presence of TADs

Trussart M, Serra F, Baù D, Junier I, Serrano L, Marti-Renom MA. 2015.
Assessing the limits of restraint-based 3D modeling of genomes and genomic domains.
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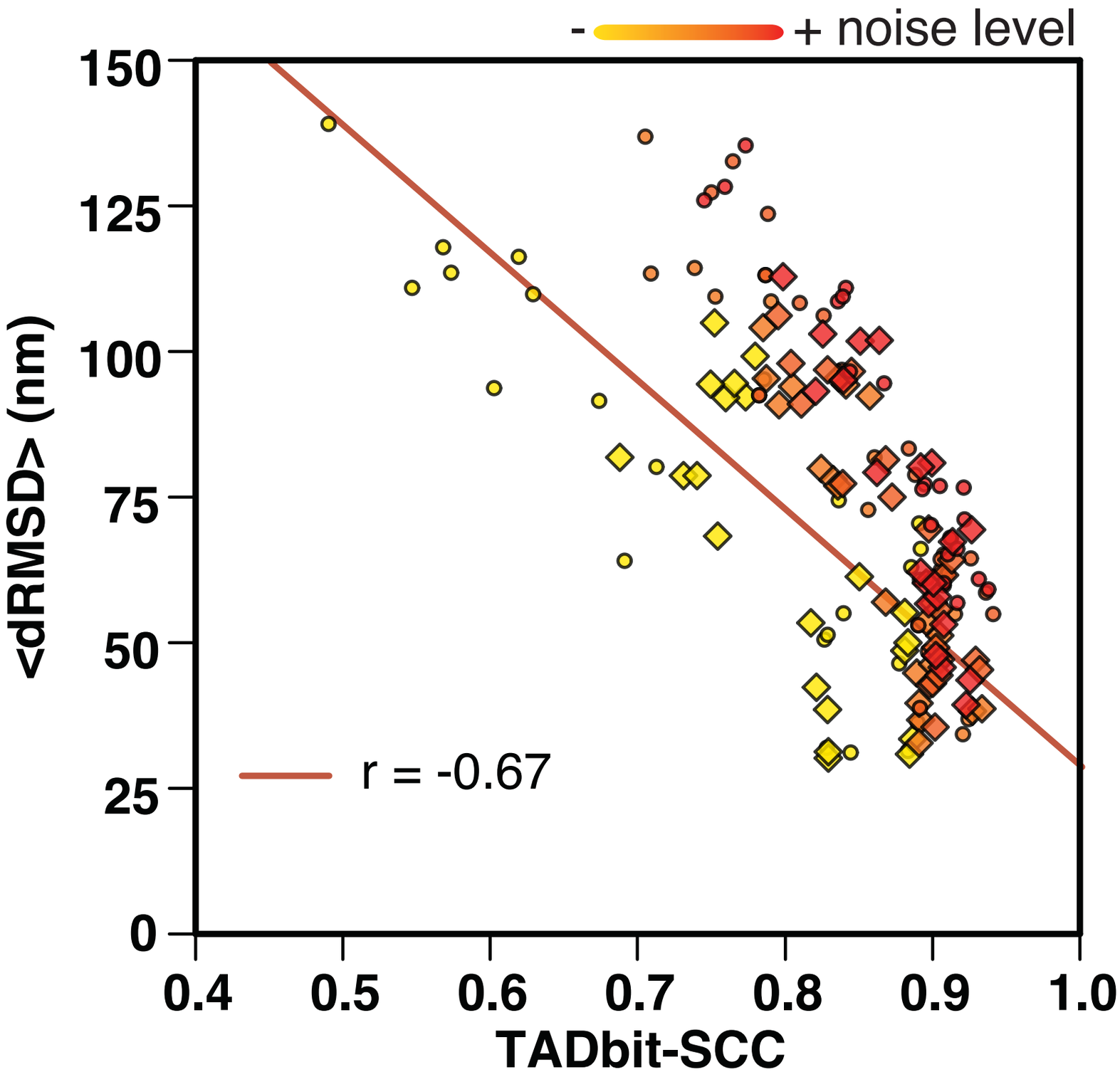
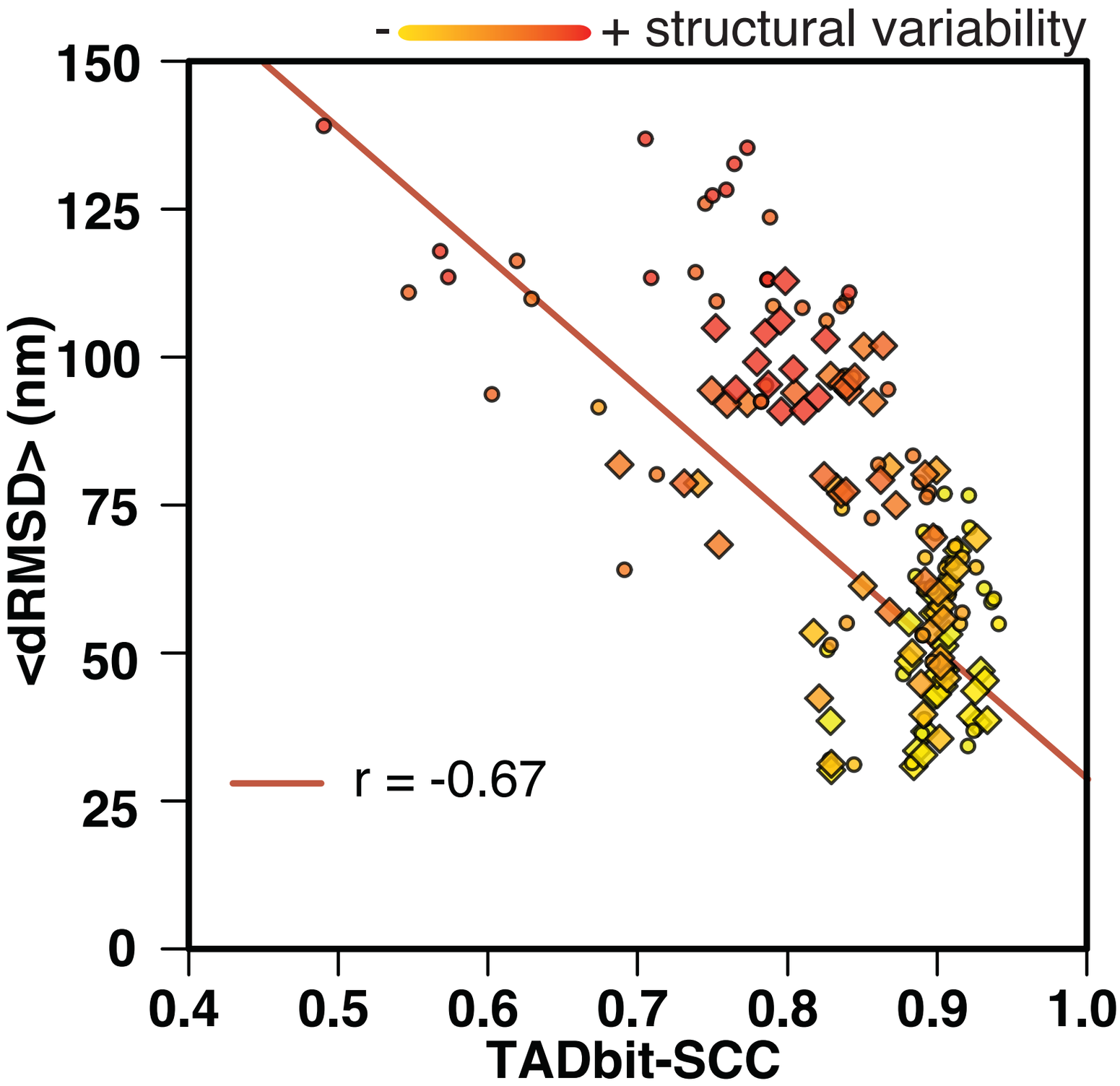
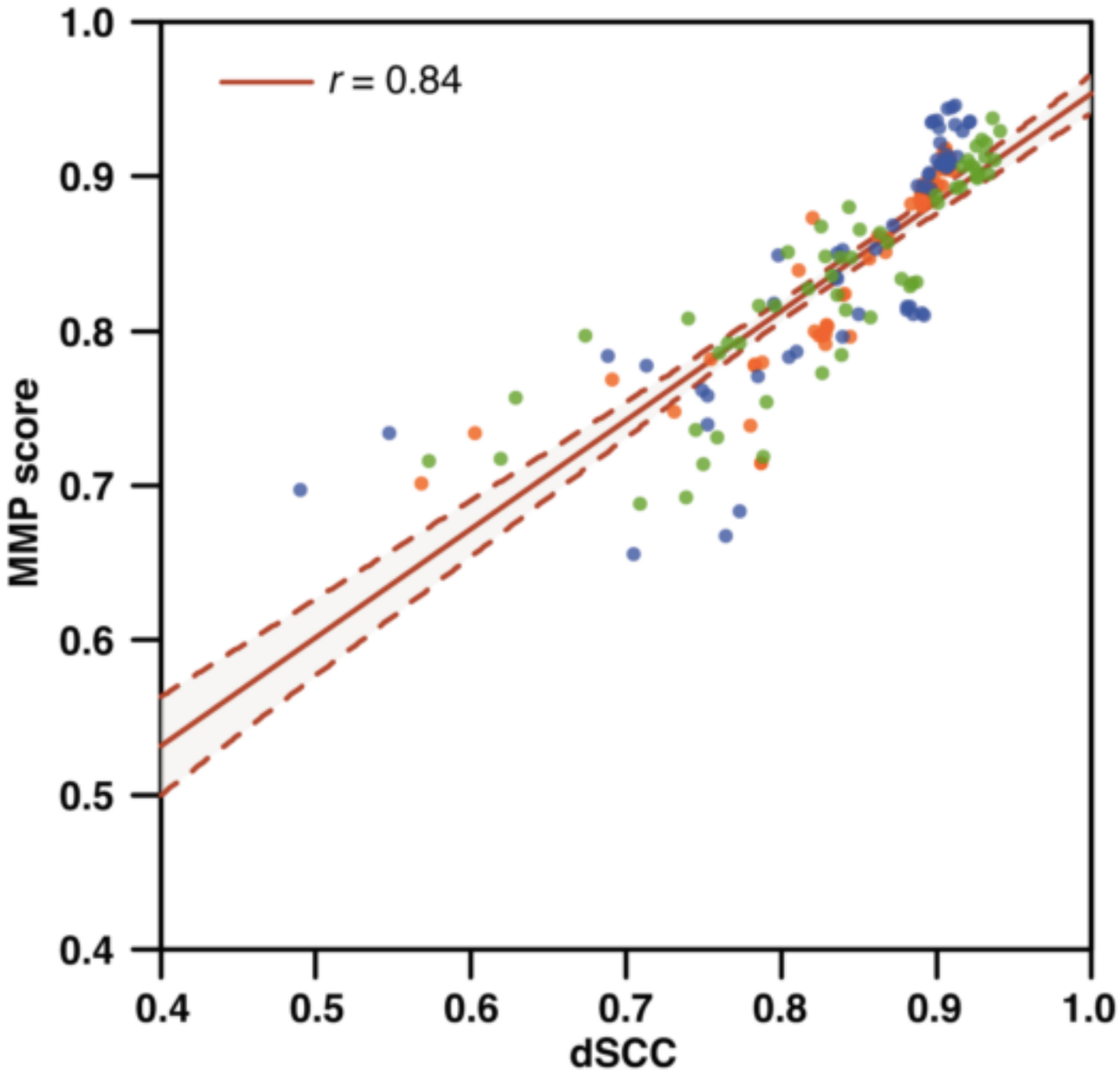
# Noise is "OK"


- + noise level
150
125
100
75
50
25
0
<dRMSD> (nm)
r = -0.67
0.4
0.5
0.6
0.7
0.8
0.9
1.0
TADbit-SCC

# Structural variability is "NOT OK"

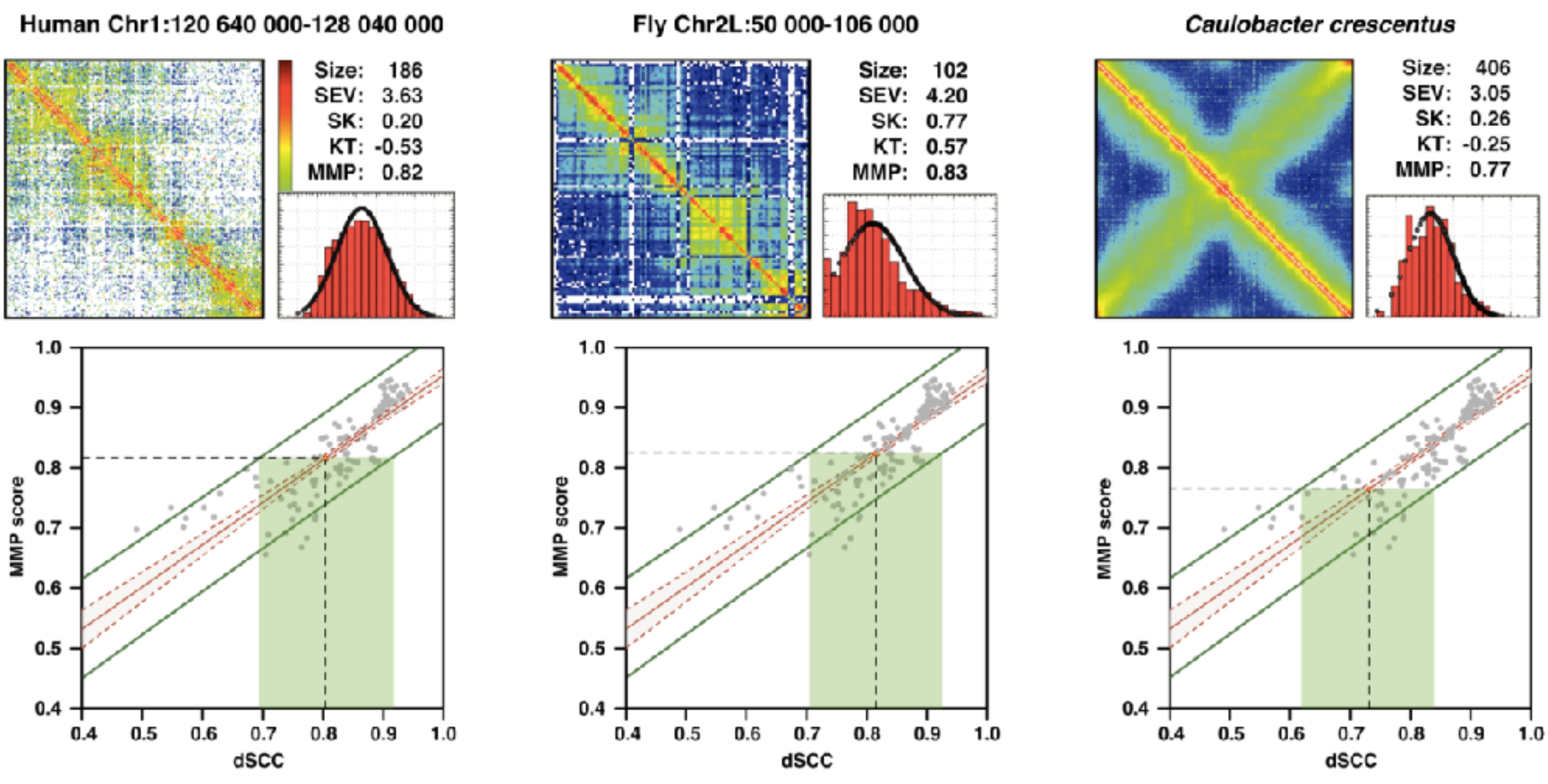


# Modeling potential




Trussart M, Serra F, Baù D, Junier I, Serrano L, Marti-Renom MA. 2015.
Assessing the limits of restraint-based 3D modeling of genomes and genomic domains.
Nucleic Acids Res 43: 3465–77

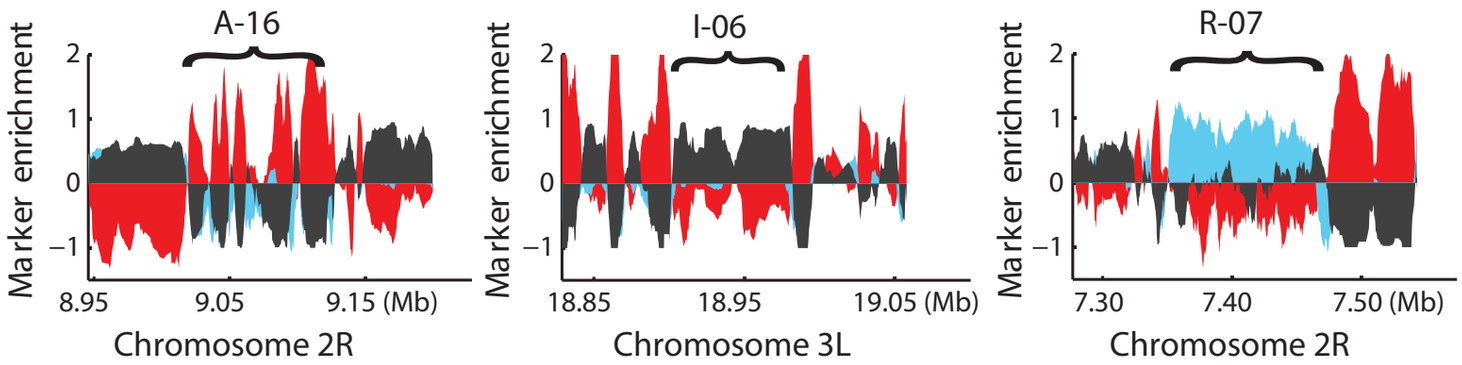
# Modeling potential

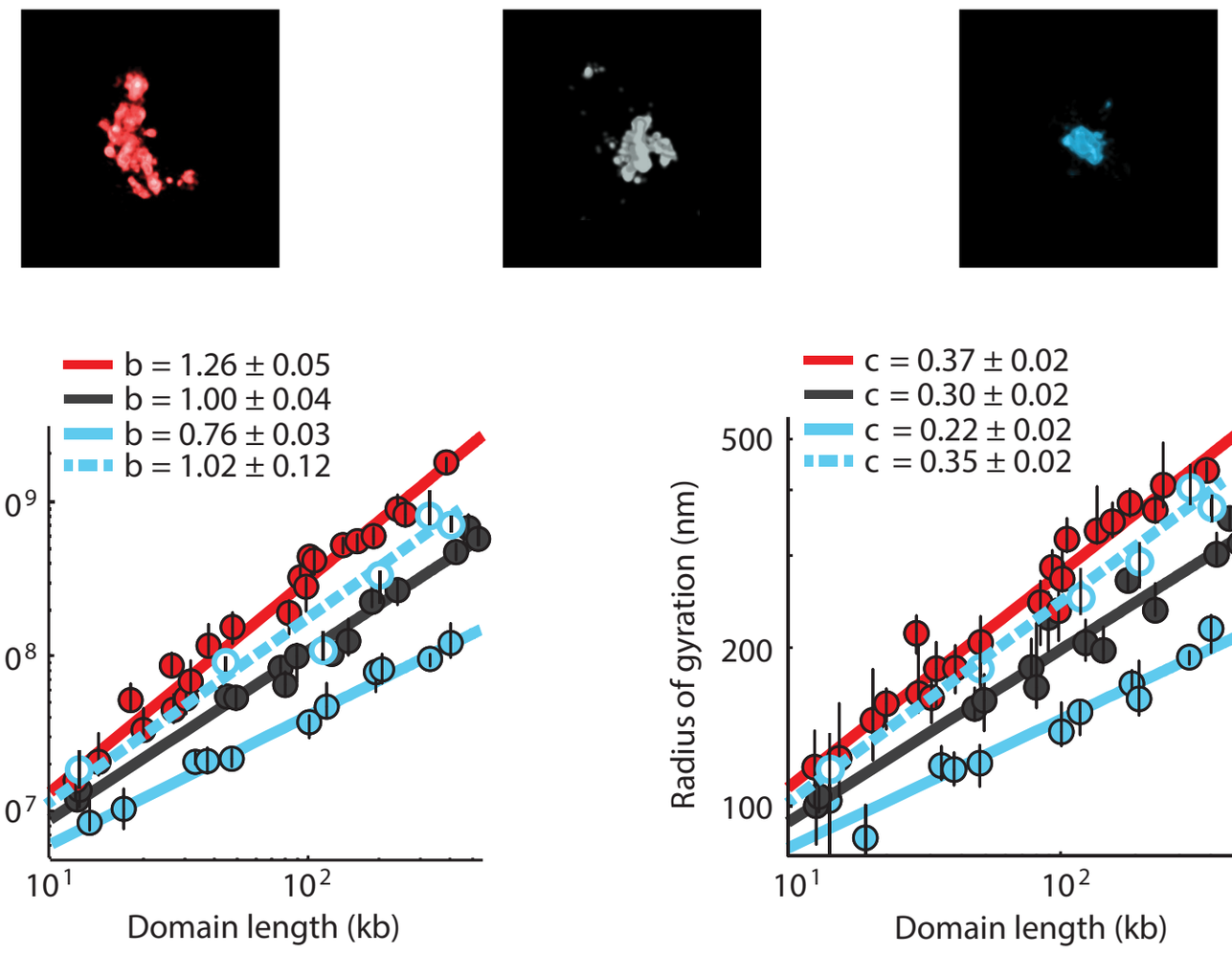



Trussart M, Serra F, Baù D, Junier I, Serrano L, Marti-Renom MA. 2015.
Assessing the limits of restraint-based 3D modeling of genomes and genomic domains.
Nucleic Acids Res 43: 3465–77

# Model accuracy

Boettiger, A. N., et al. (2016). Nature, 529, 418–422.



# Model accuracy (fly@2Kb)

Boettiger, A. N., et al. (2016). Nature, 529, 418–422.