

# Modeling chromosome organization in SARS-CoV-2 infected genomes with Polymer Physics

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New Frontiers in Theoretical Physics

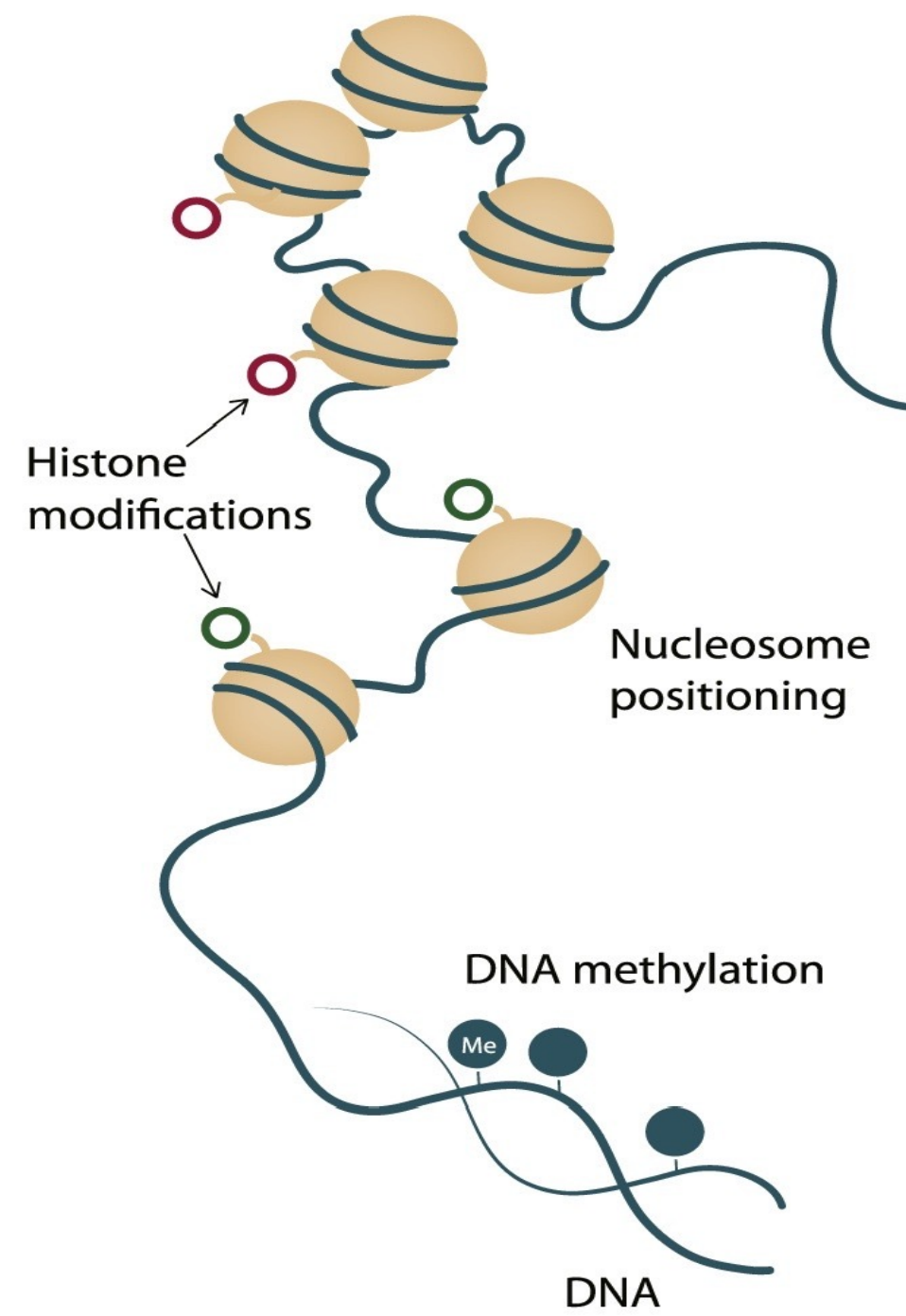
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Cortona, 27-29<sup>th</sup> September 2023



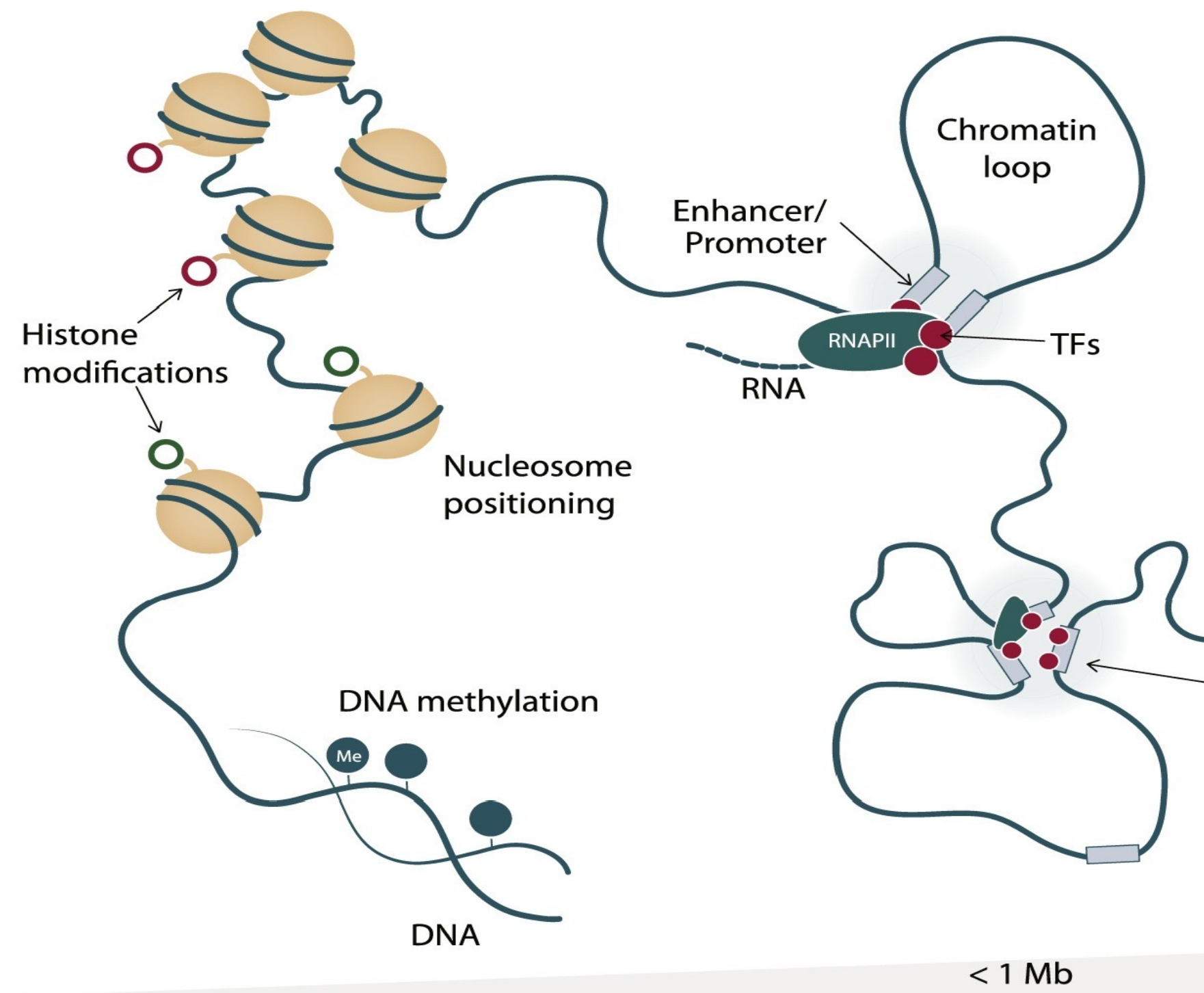


# Genomes exhibit a multiscale spatial organization



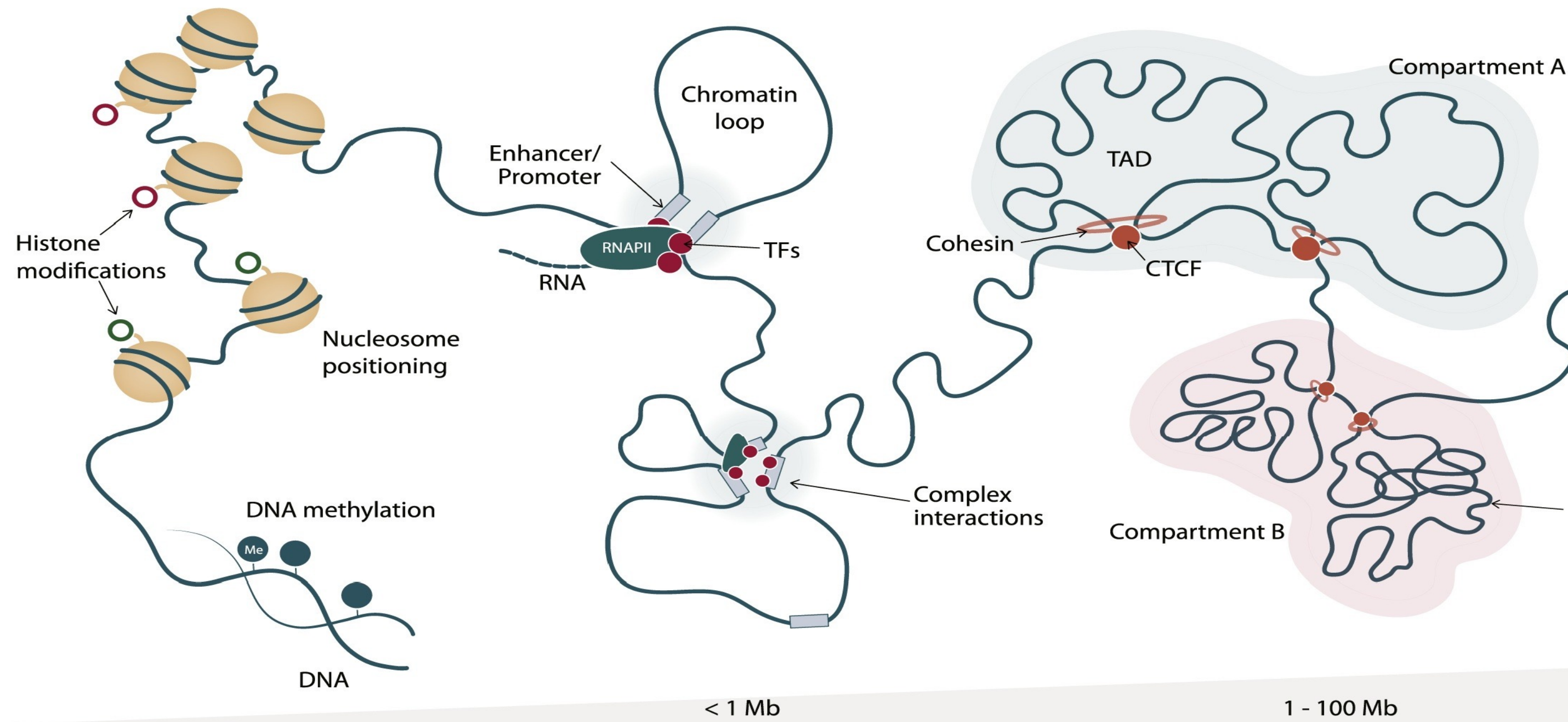


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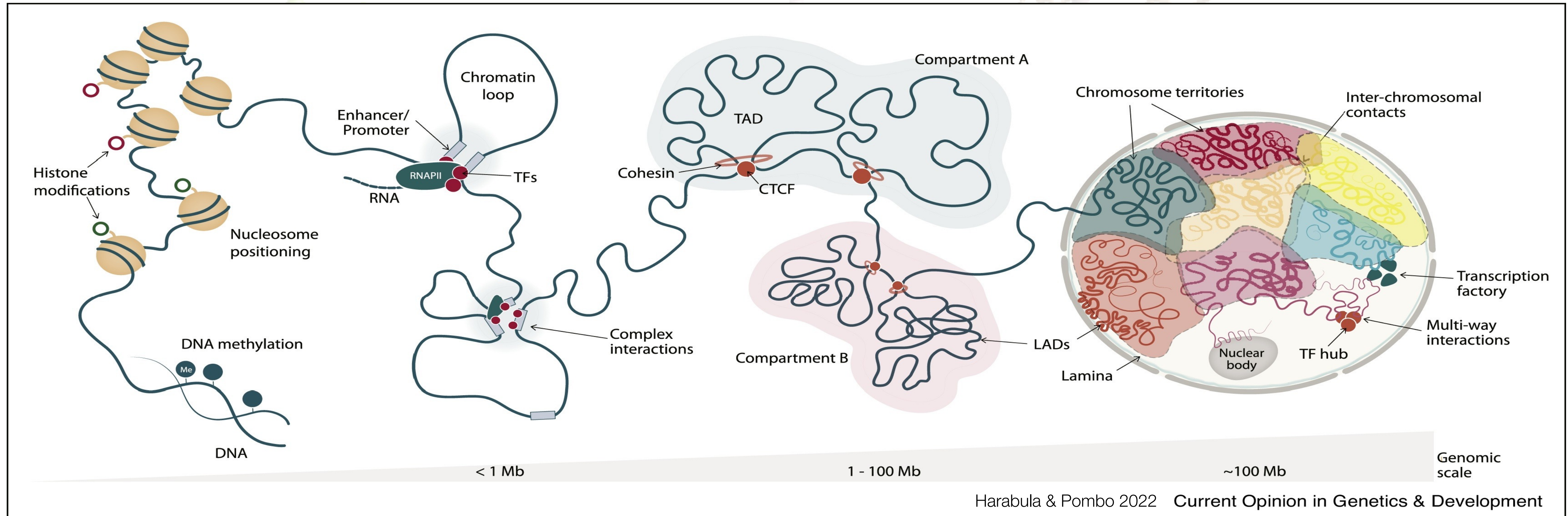


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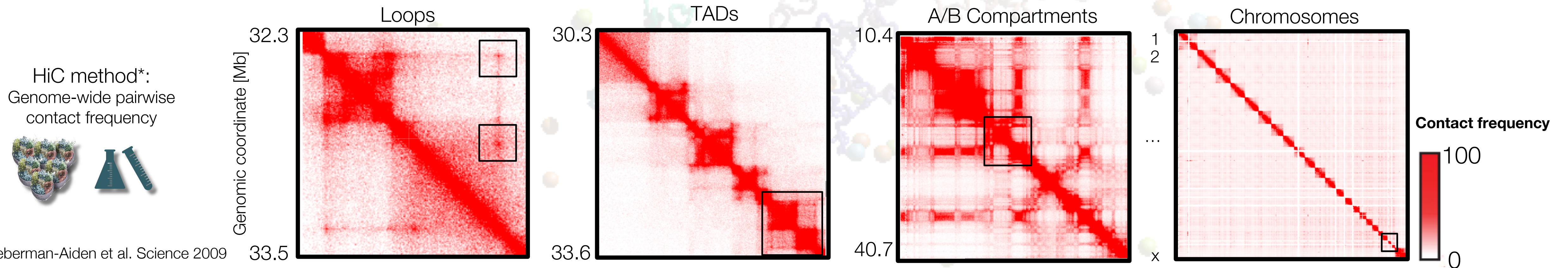
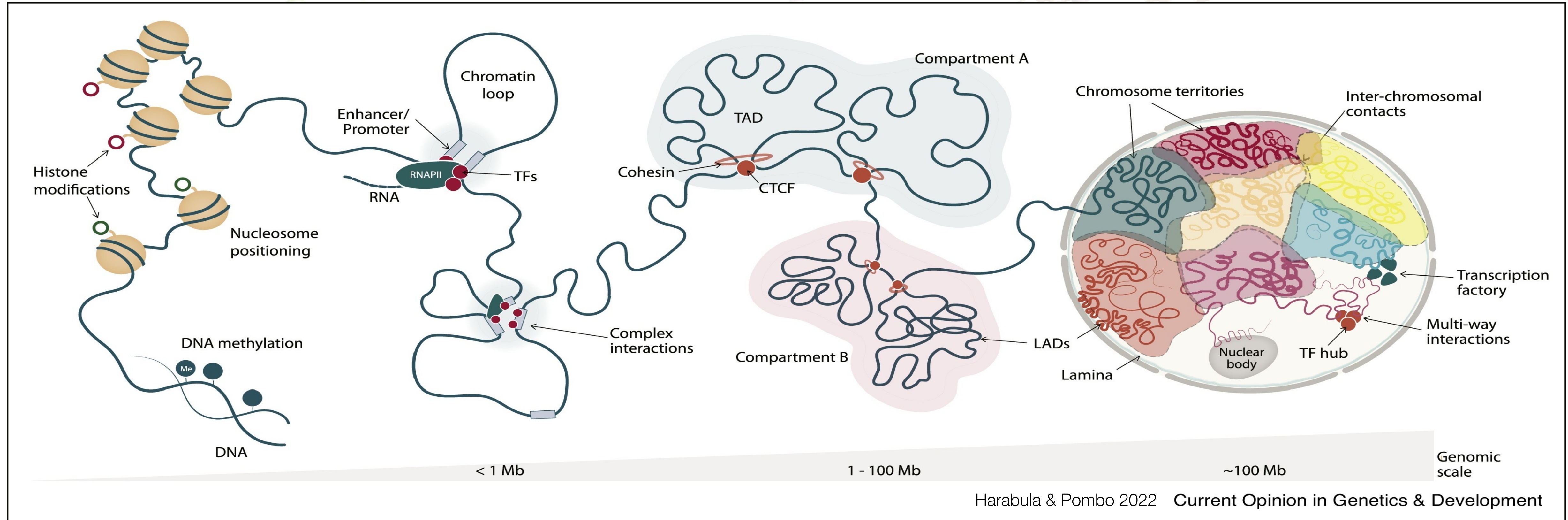


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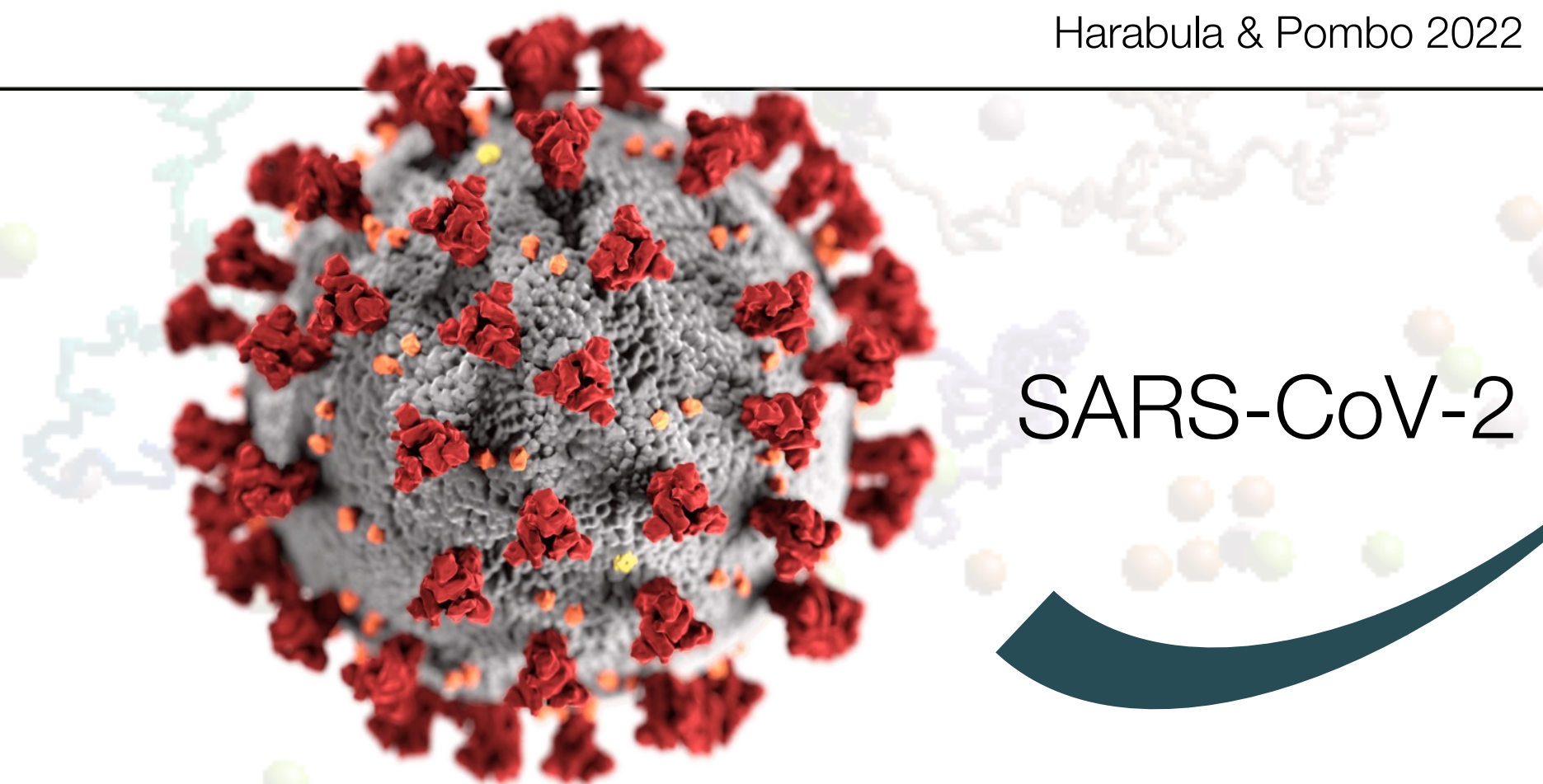
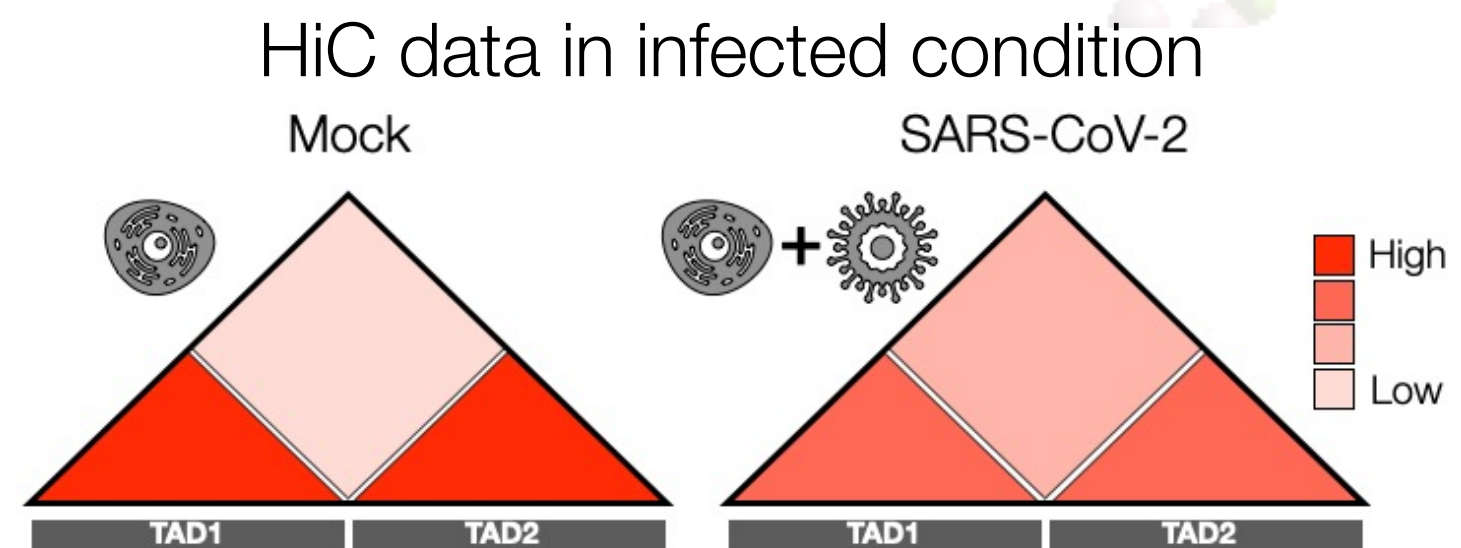
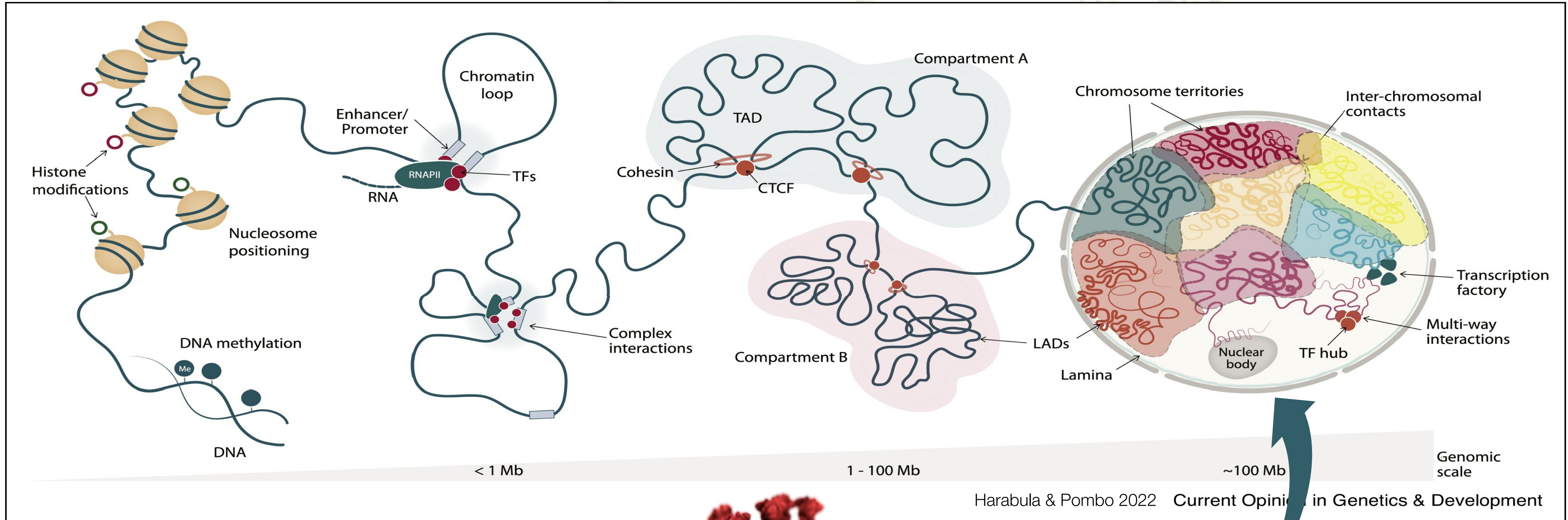


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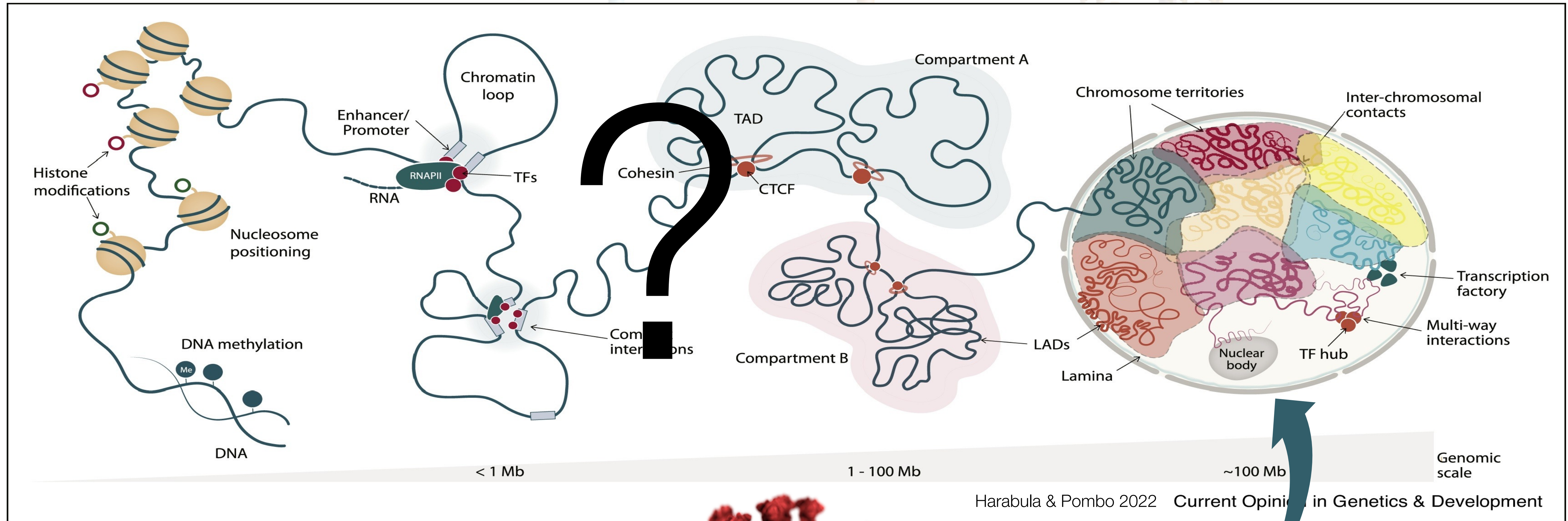


# SARS-CoV-2 alters genome organization of the host cell





# What mechanisms alter genome organization of the SARS-CoV-2 infected cell?



New Results

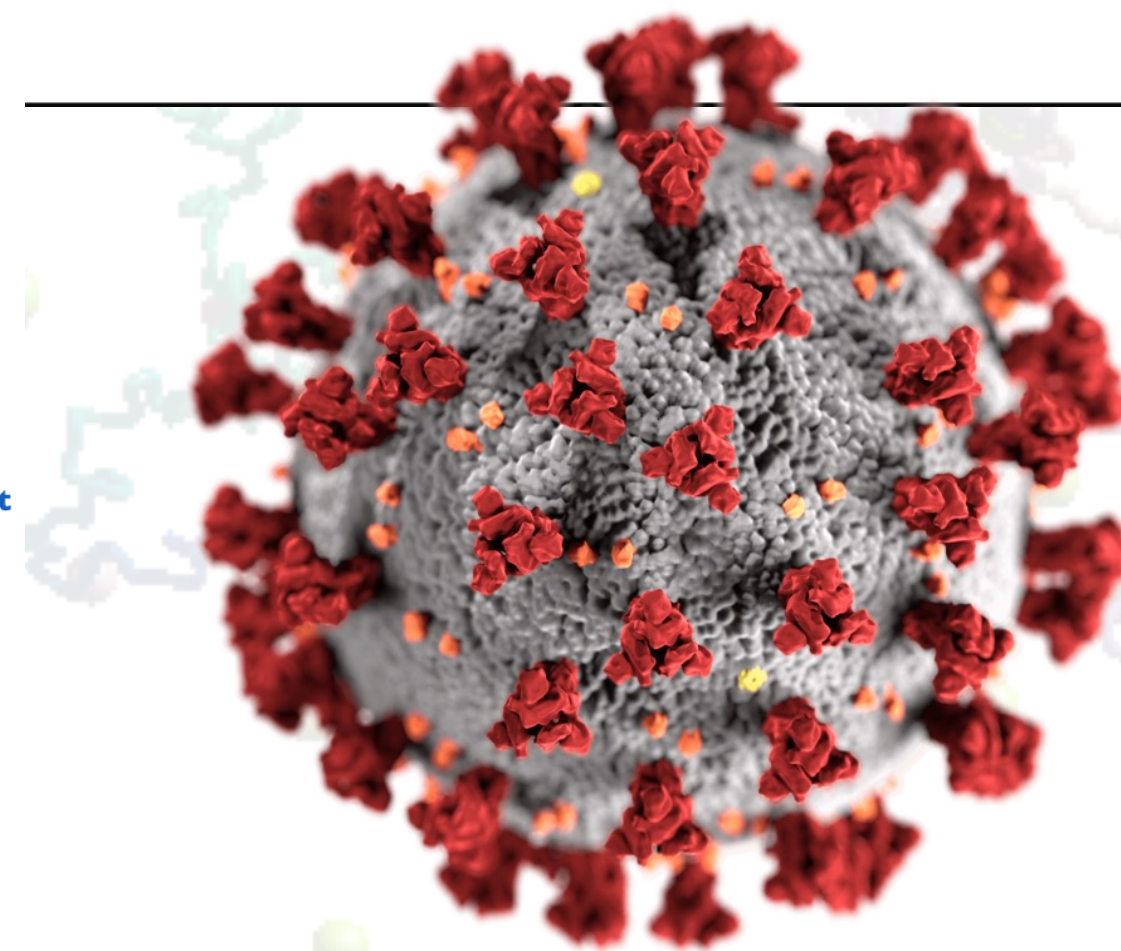
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## Multiscale modelling of chromatin 4D organization in SARS-CoV-2 infected cells

Andrea M. Chiariello, Alex Abraham, Simona Bianco, Andrea Esposito, Francesca Vercellone, Mattia Conte, Andrea Fontana, Mario Nicodemi

doi: <https://doi.org/10.1101/2023.07.27.550709>

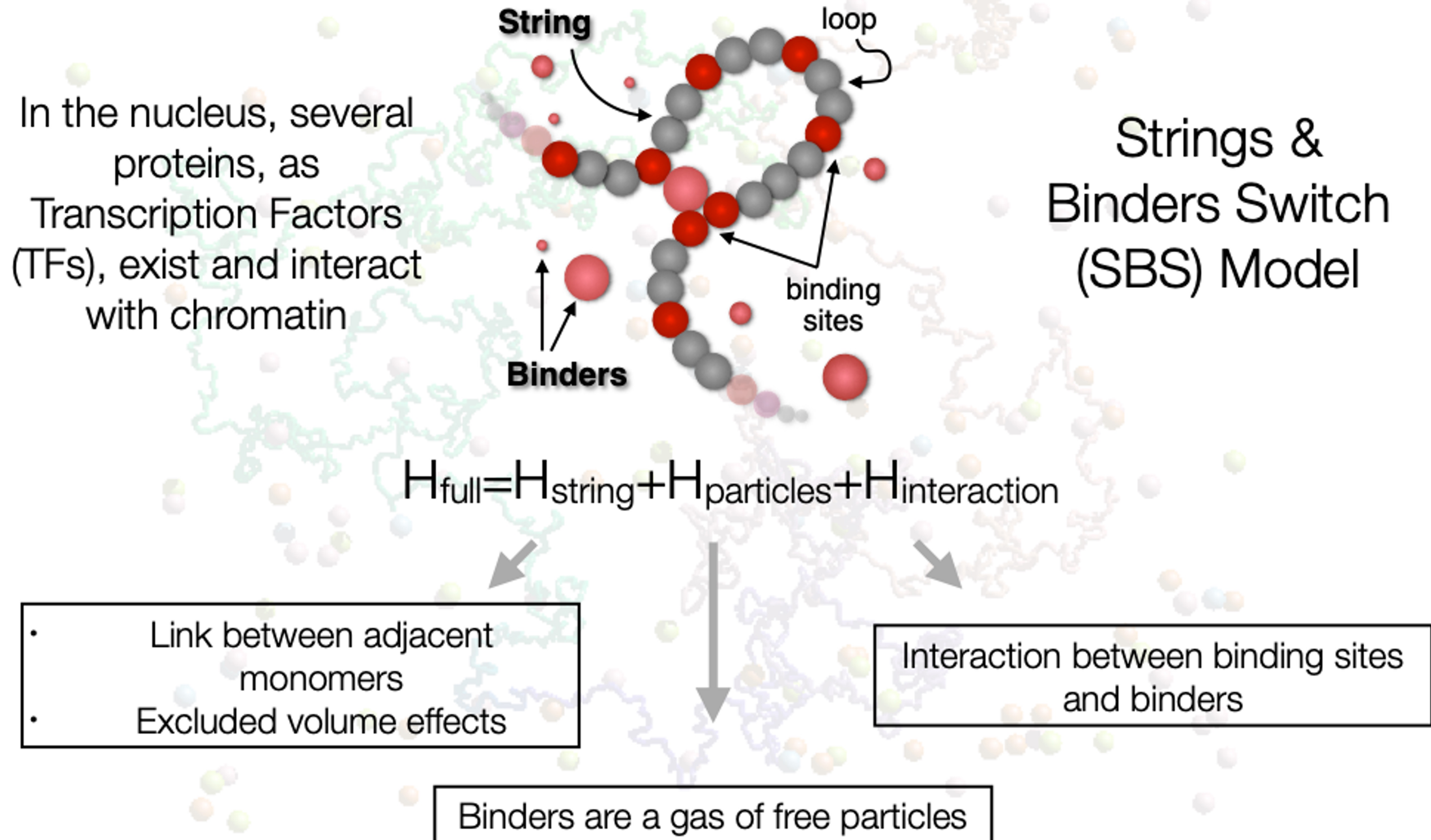
This article is a preprint and has not been certified by peer review [what does this mean?].



SARS-CoV-2

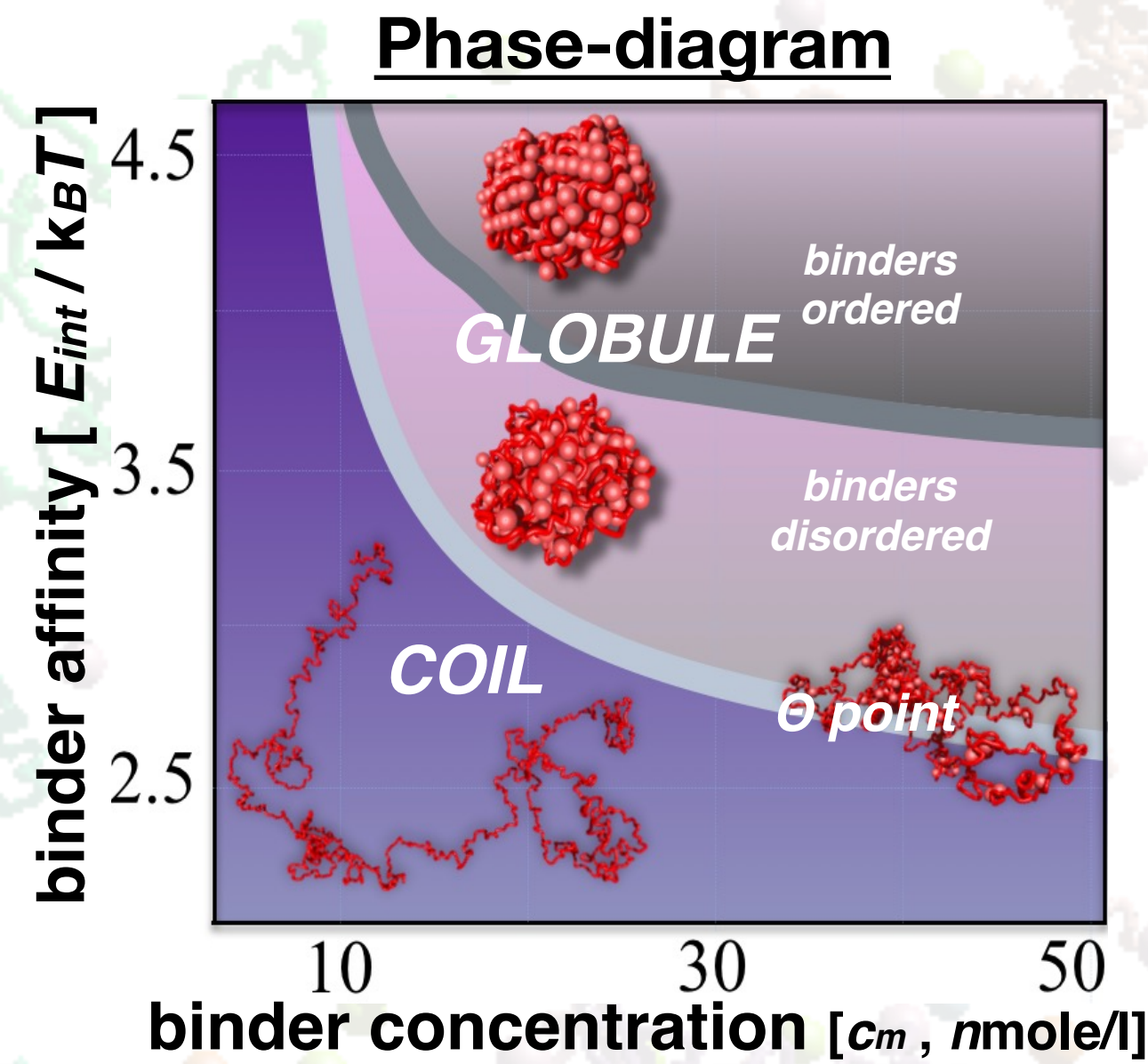
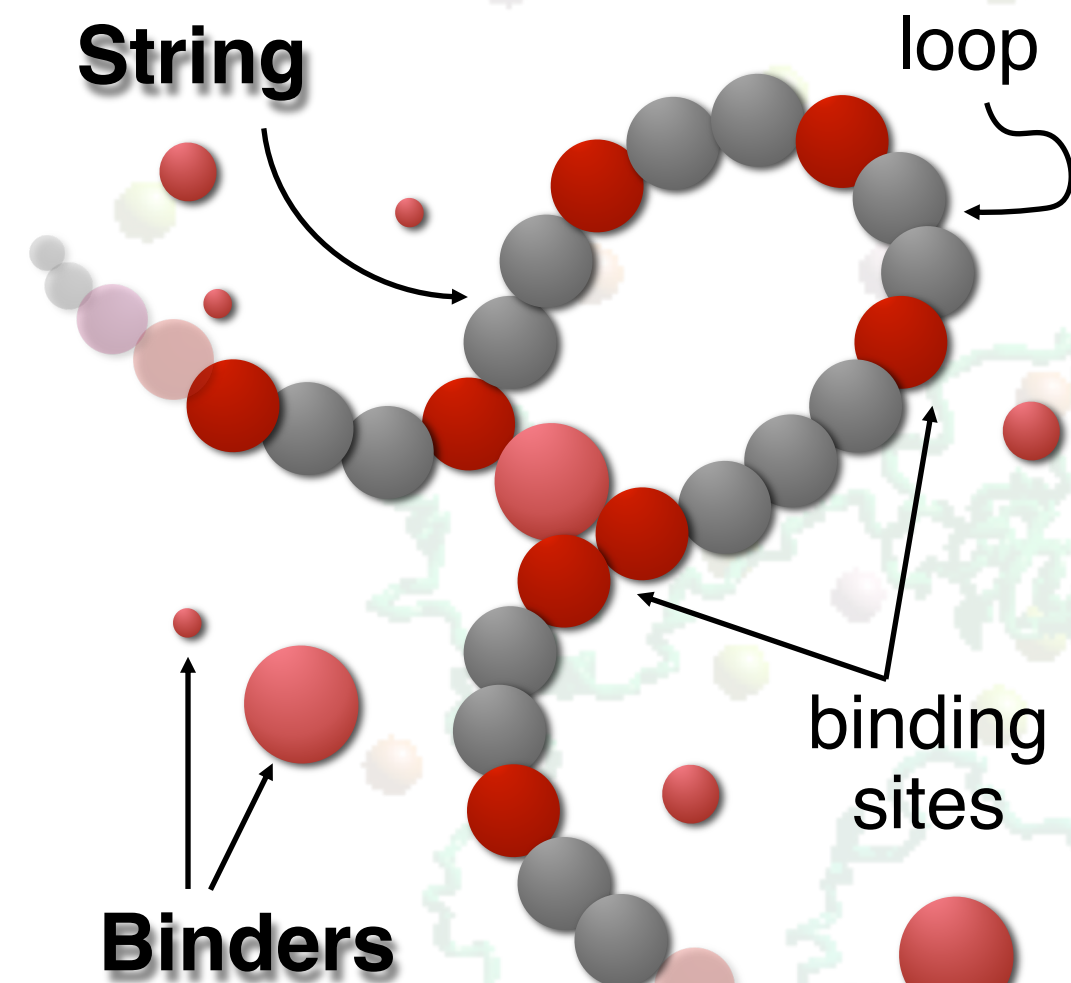


# Polymer models of chromatin structure & Phase-separation



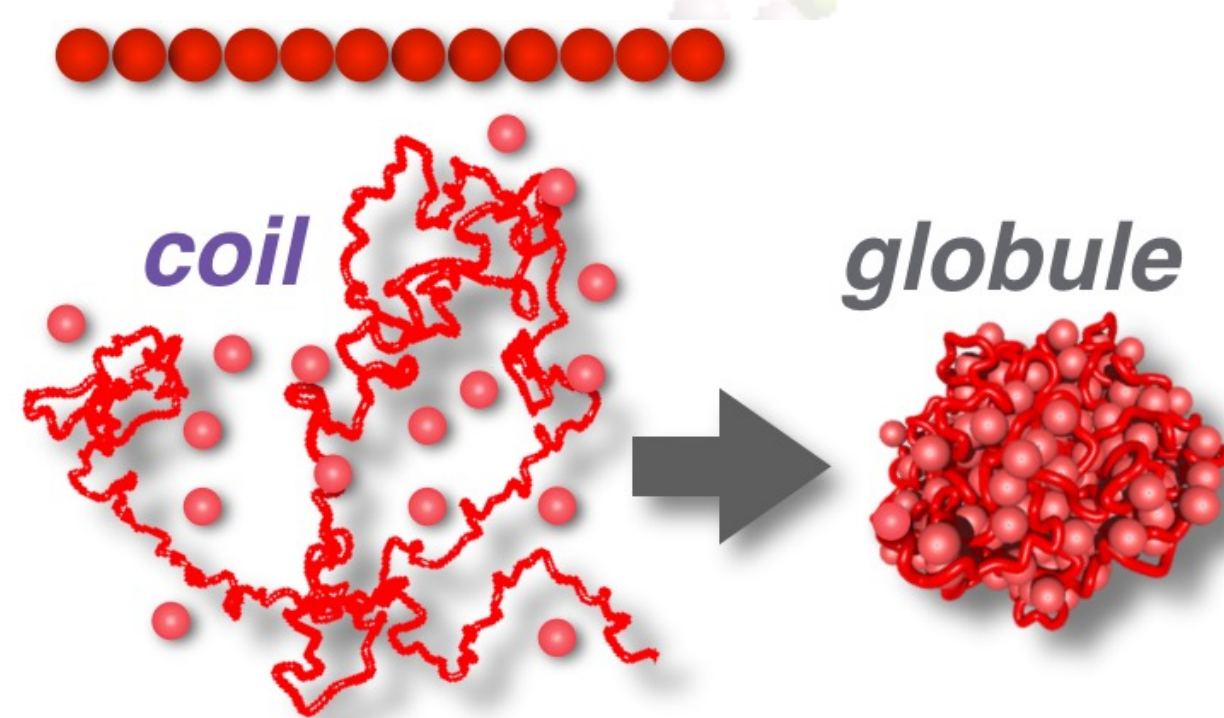


# Polymer models of chromatin structure & Phase-separation

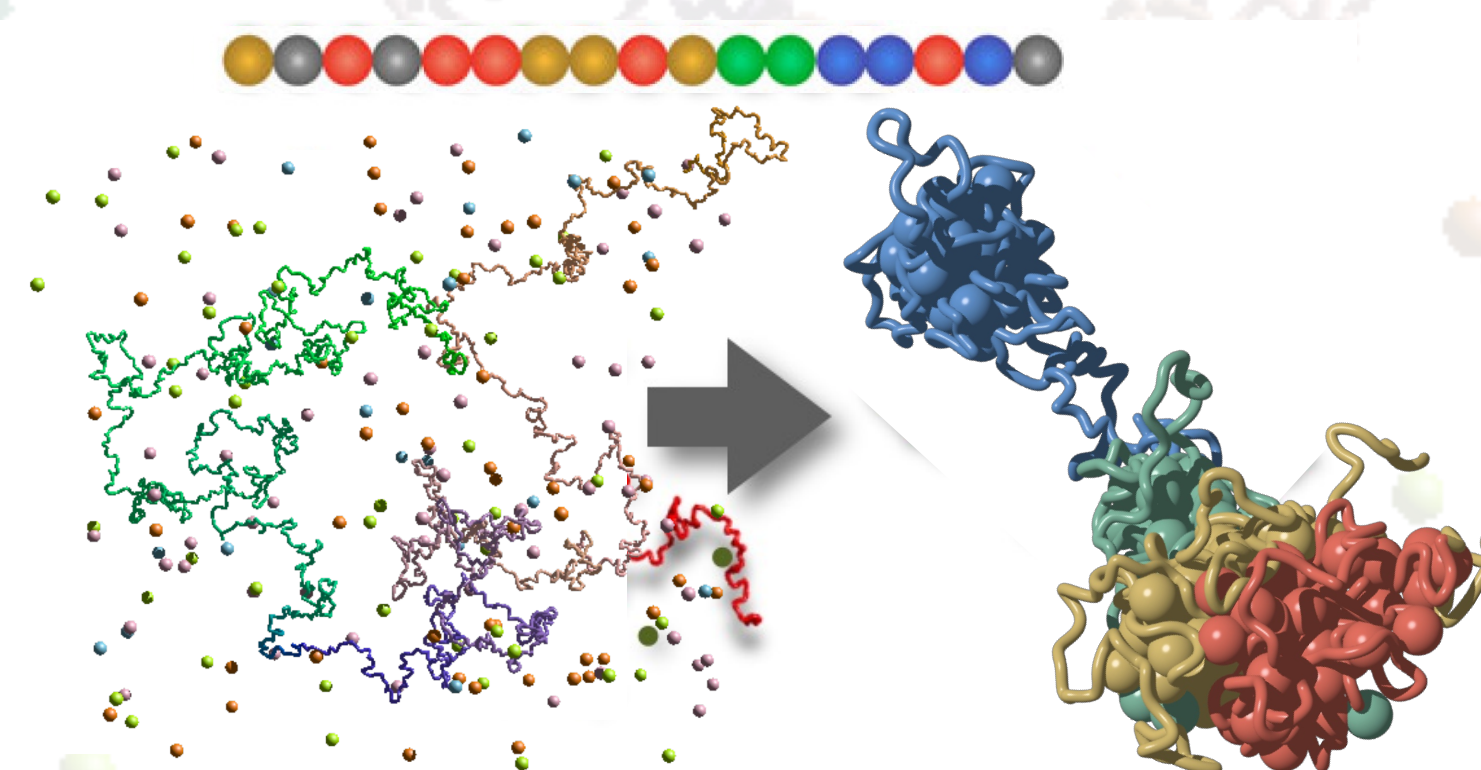


**Strings & Binders Switch (SBS) Model:**  
 nonrandom DNA conformations are established through attachment of diffusible factors (binders) to binding sites.

1 color (Red) polymer model



Multi-color polymer model (e.g. block co-polymers, heteropolymers)

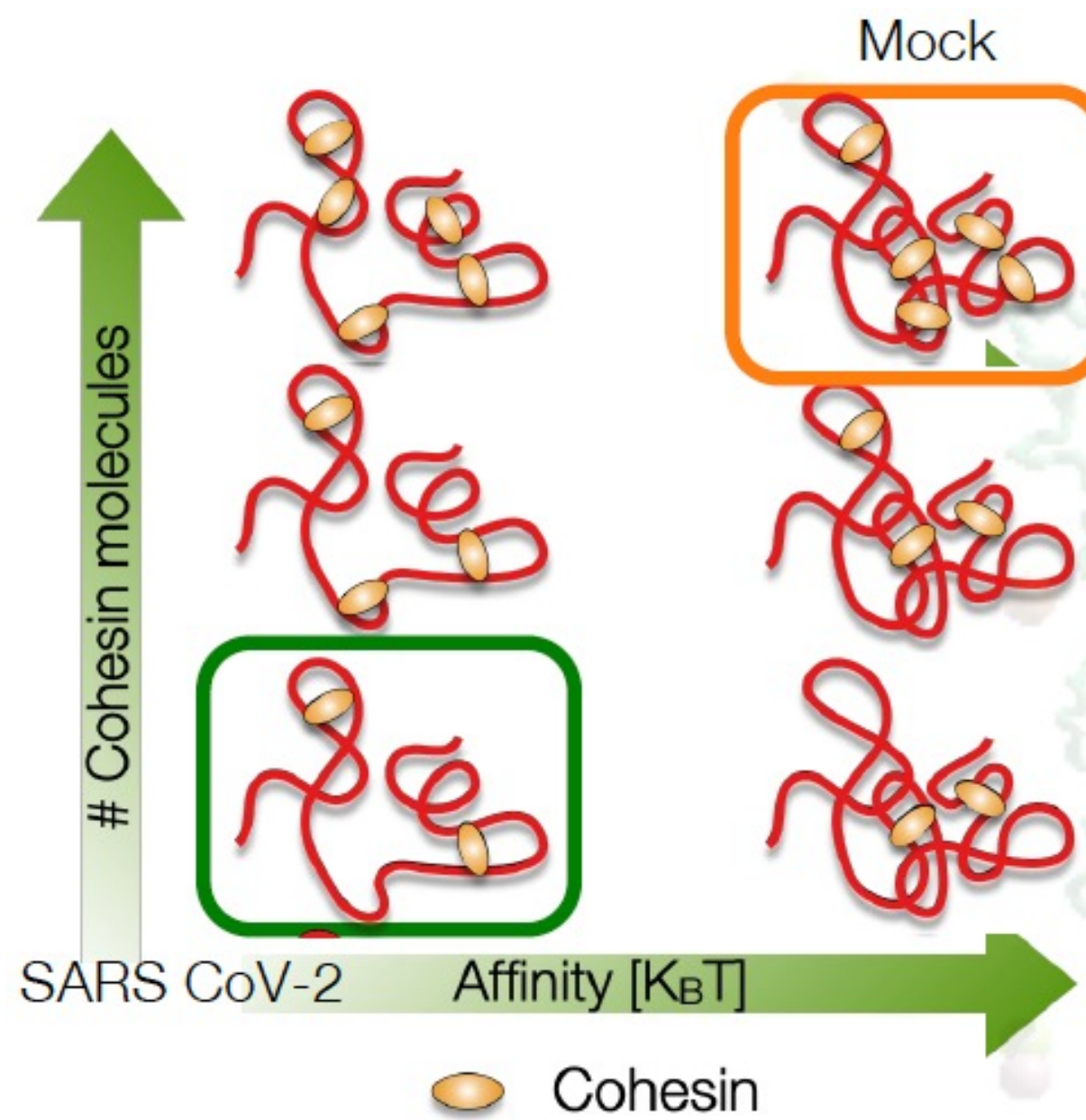


Interaction bead-binder:  
**Micro phase-separation (microPS)**

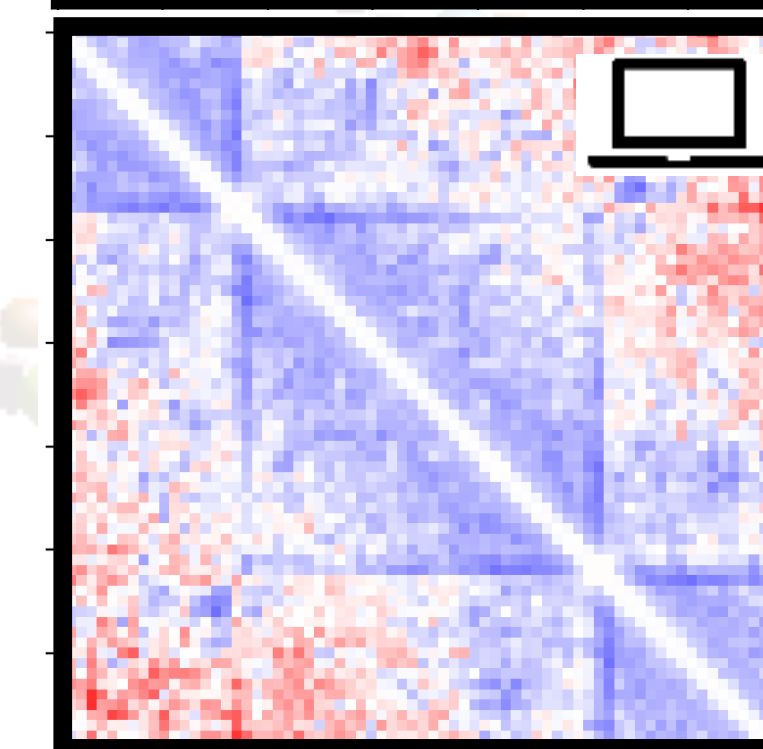
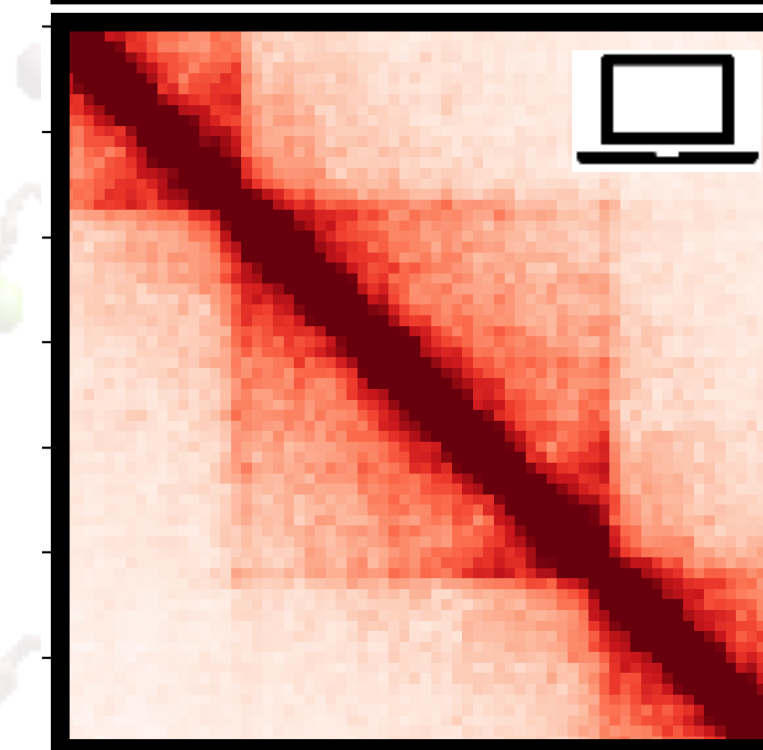
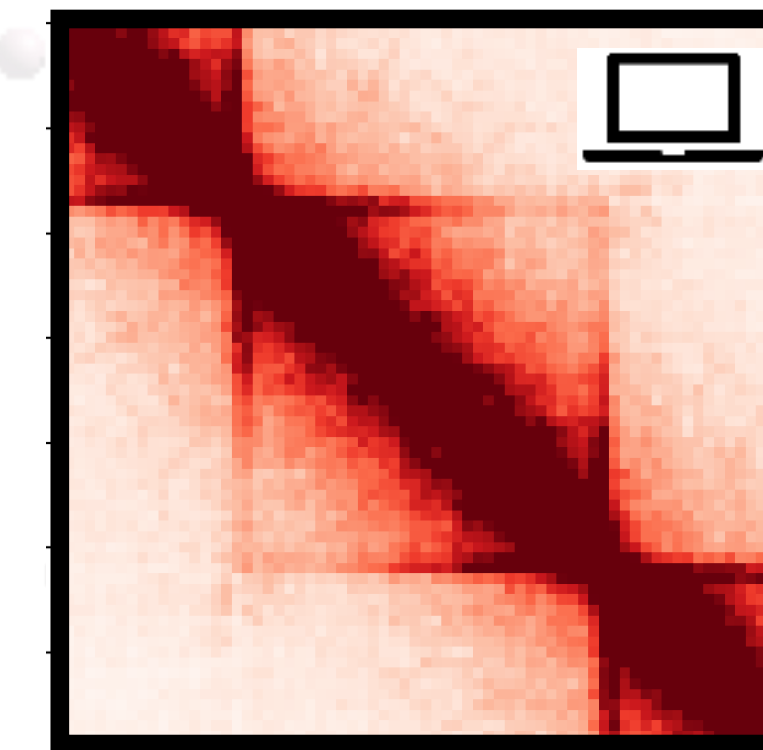
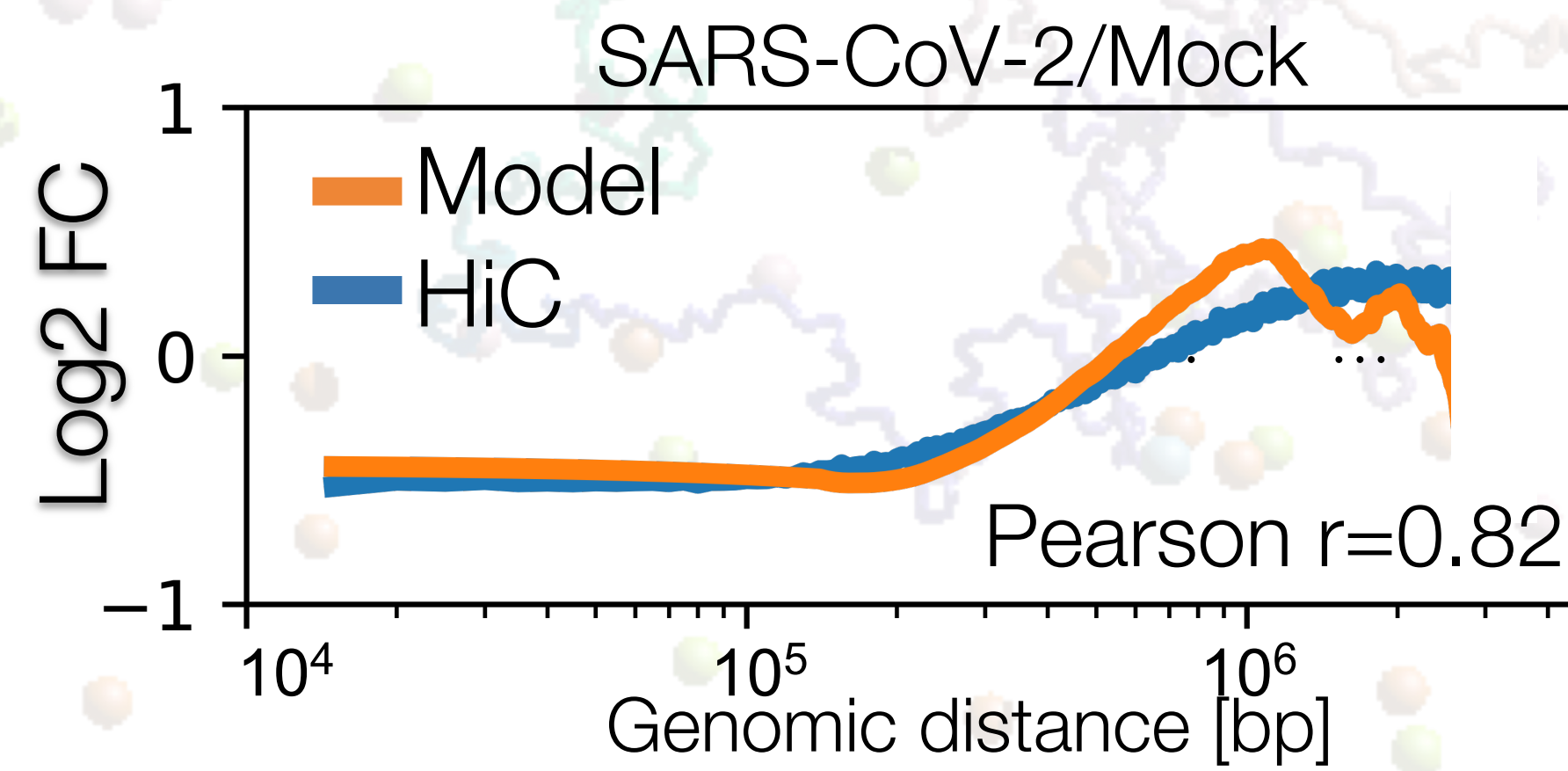
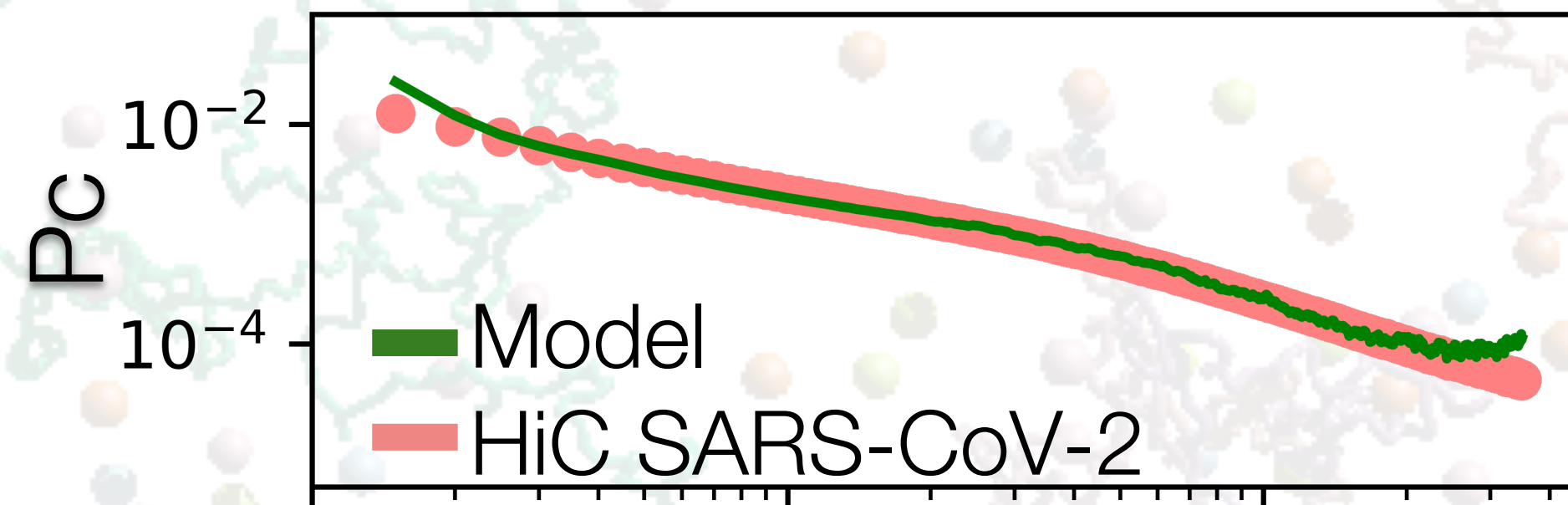
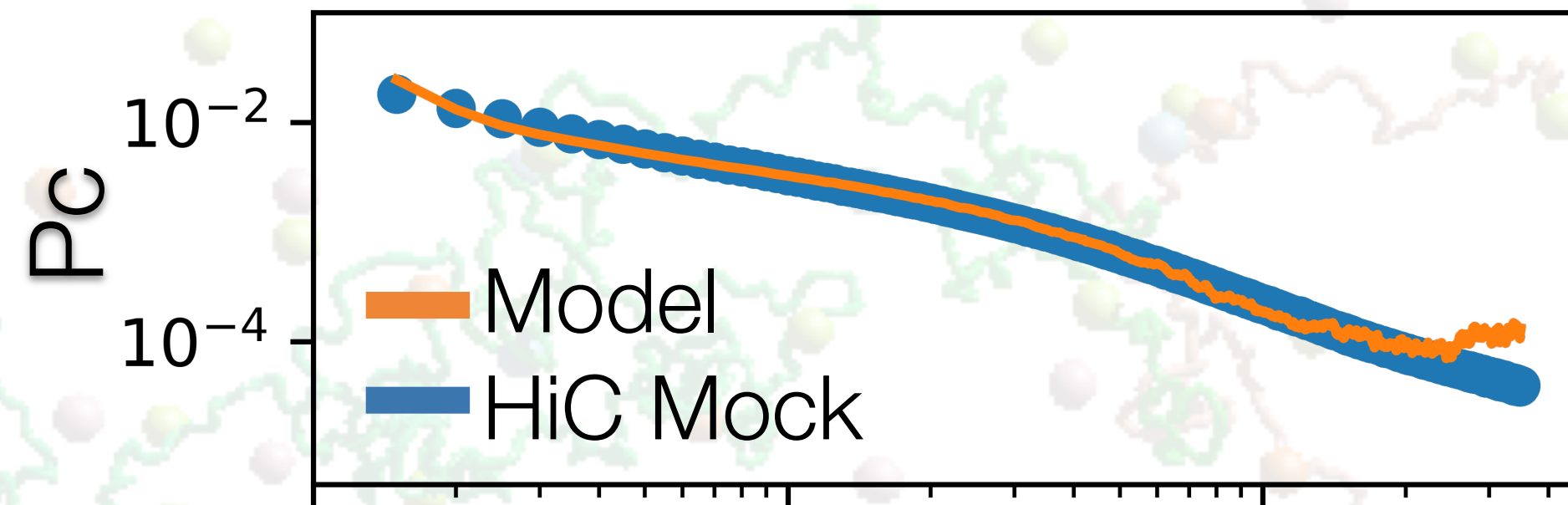
Binder types can include e.g.:  
 Cohesin, PolII, p300, ...



# Does the polymer model explain SARS-CoV-2 contact probability decay? **YES!**



The model suggests that SARS-CoV-2 alters interaction term  $H_{\text{interaction}}$  (approx 20% smaller)



Aggregate TAD

0.025 Contact Frequency  
0

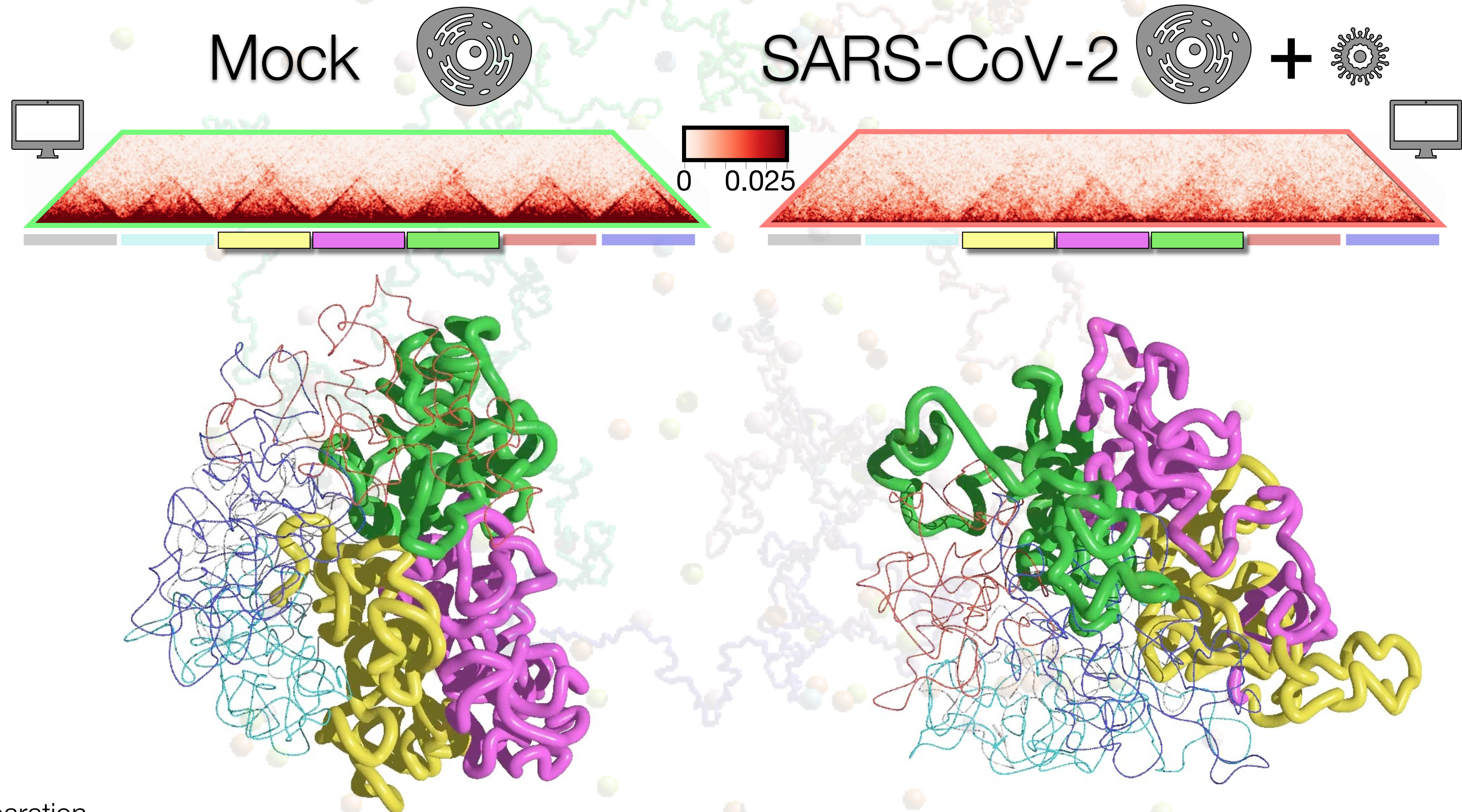
Aggregate TAD

+2 Log2 FC  
-2

Aggregate TAD

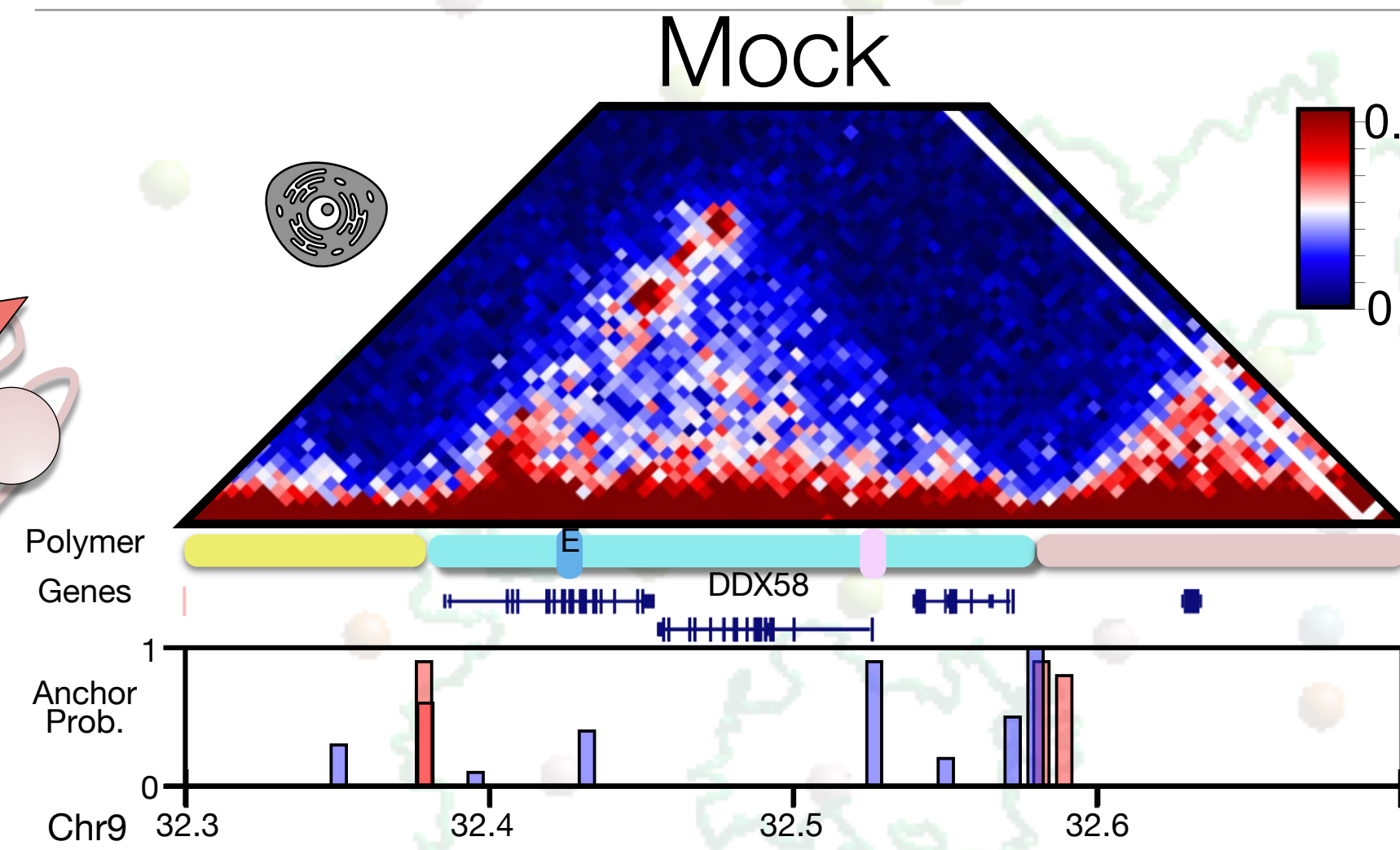
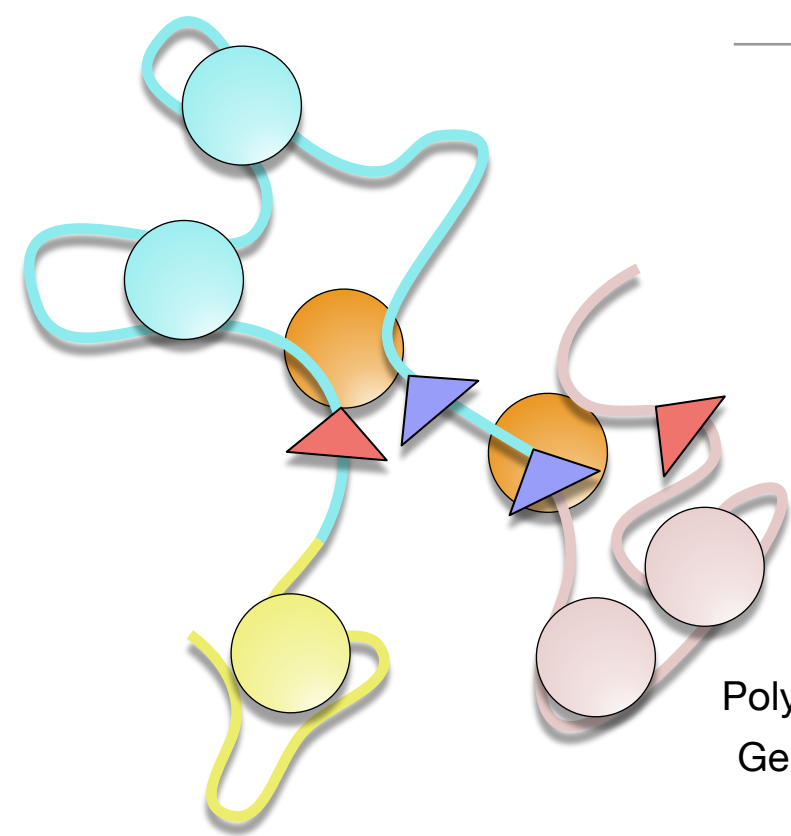


# Structural implications of contact probability weakening

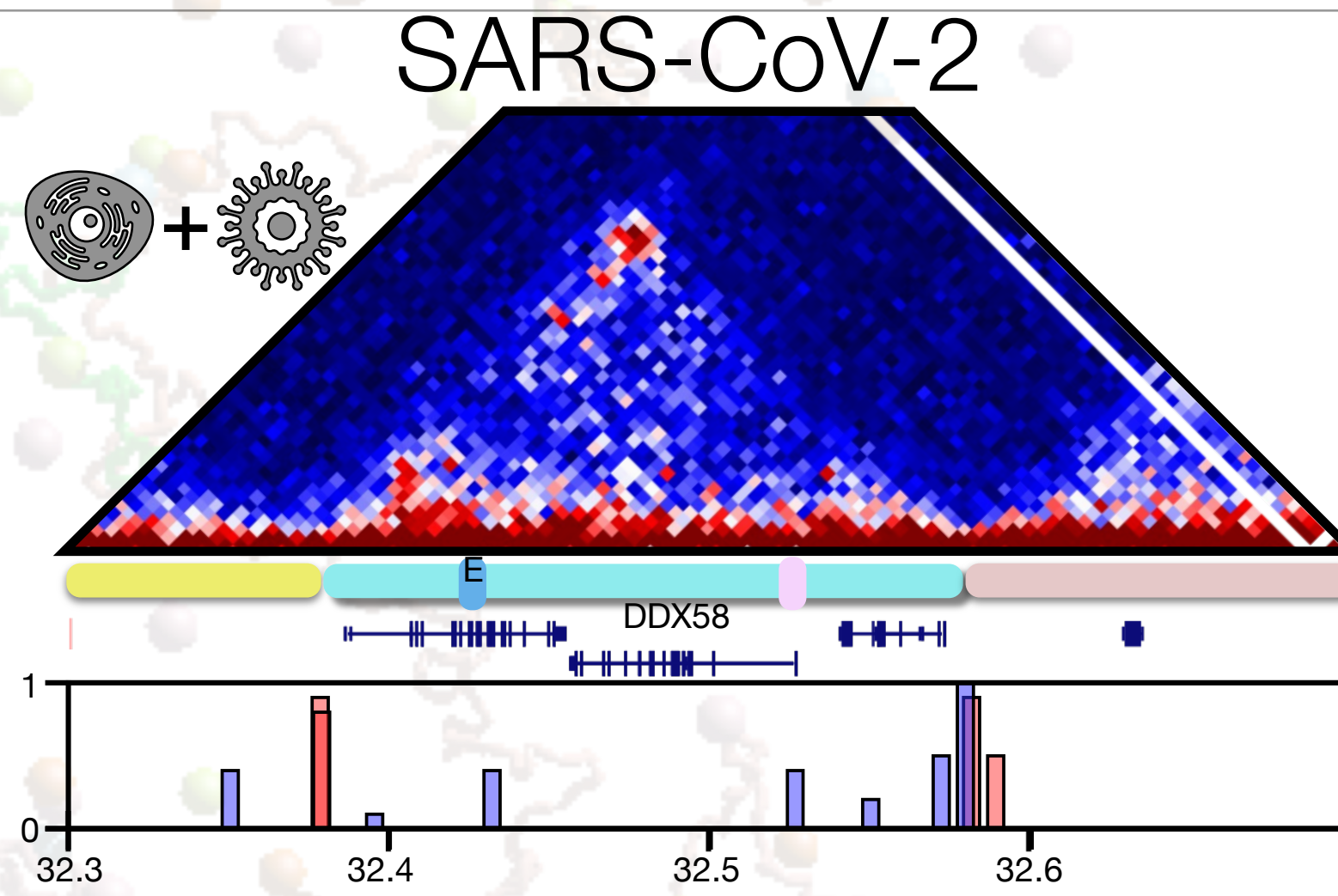




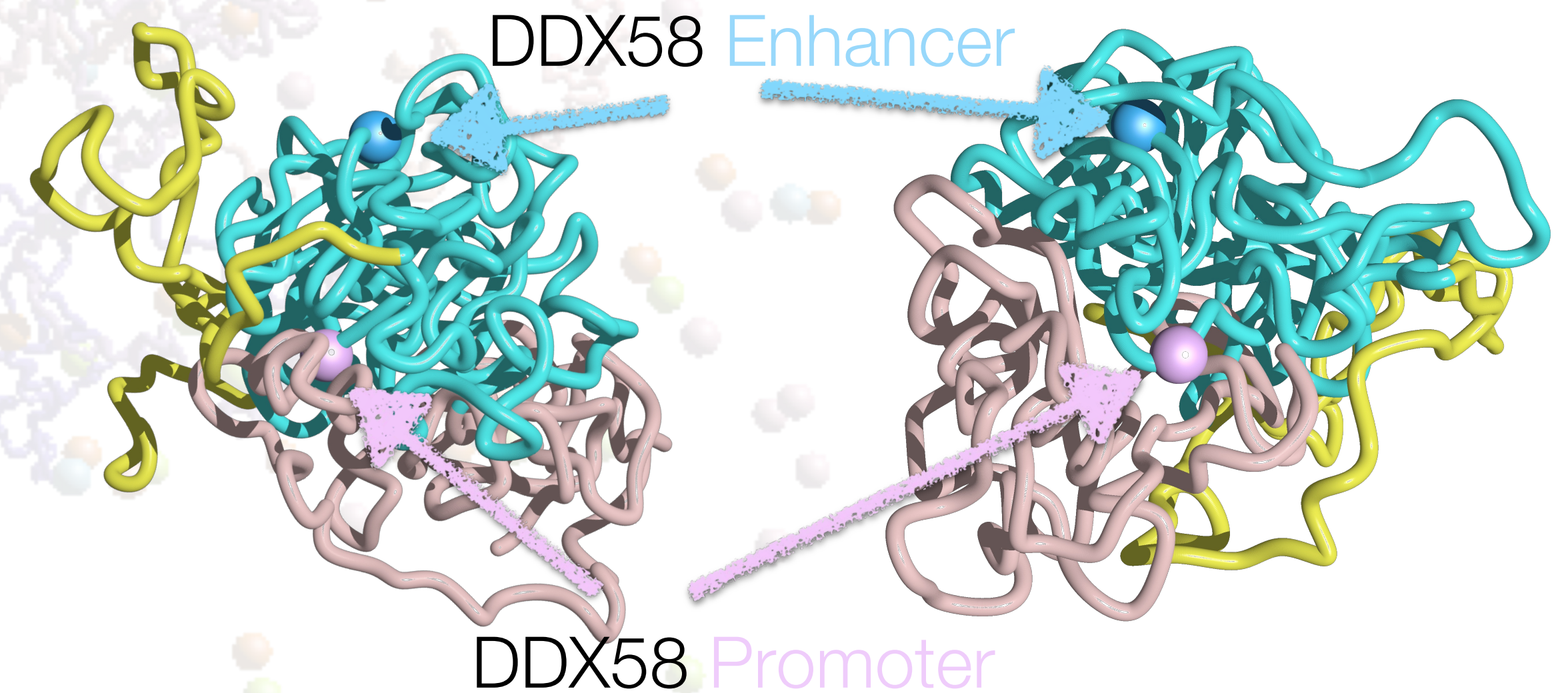
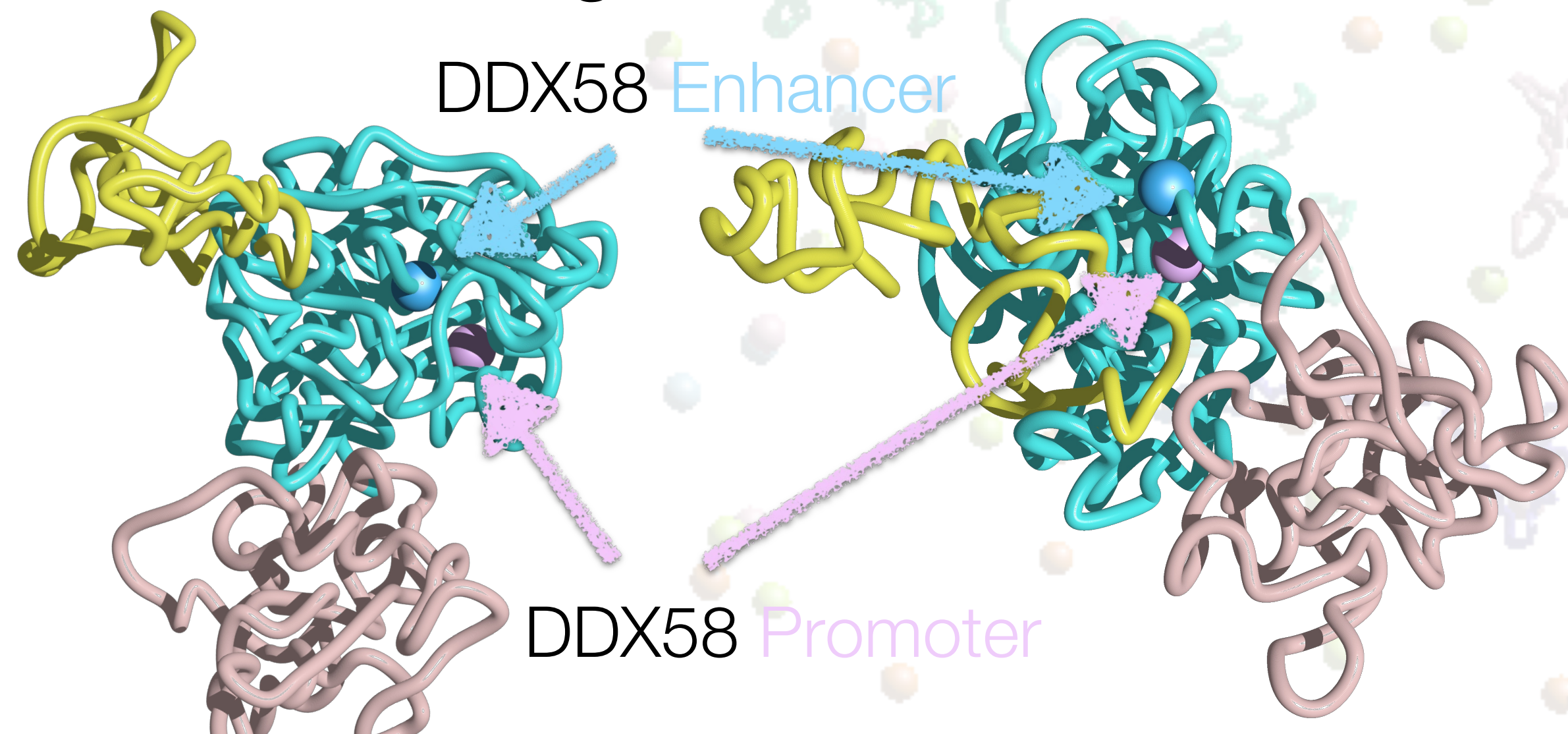
# Single molecule analysis reveal structural differences



Mock **single molecule** 3D structure

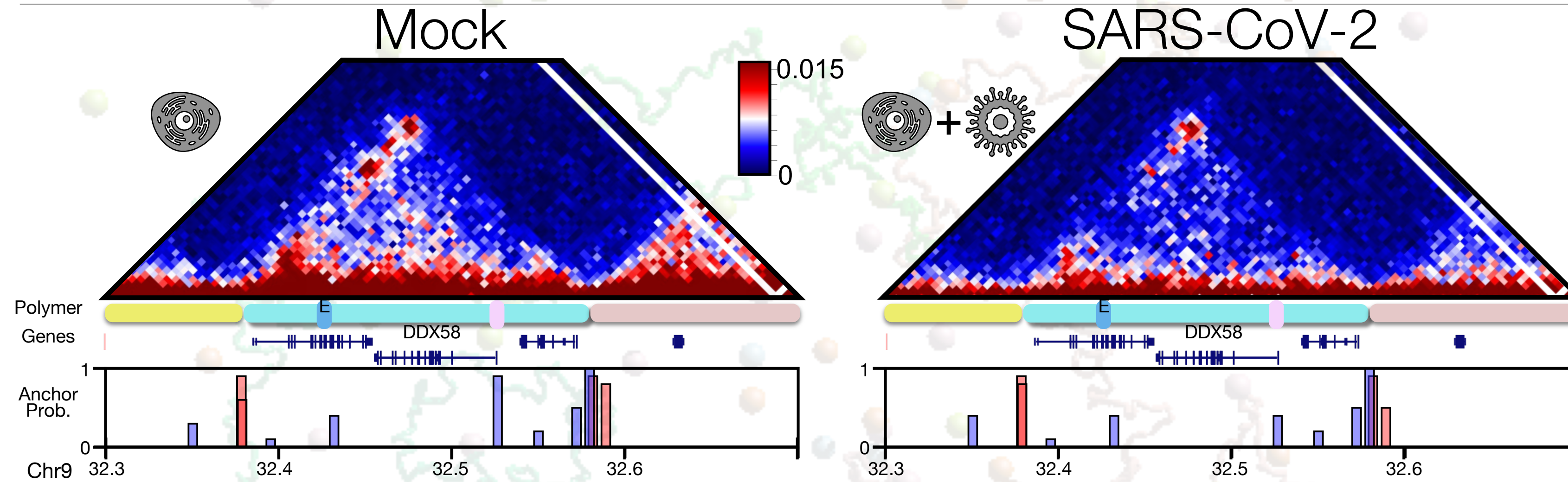


SARS-CoV-2 **single molecule** 3D structure

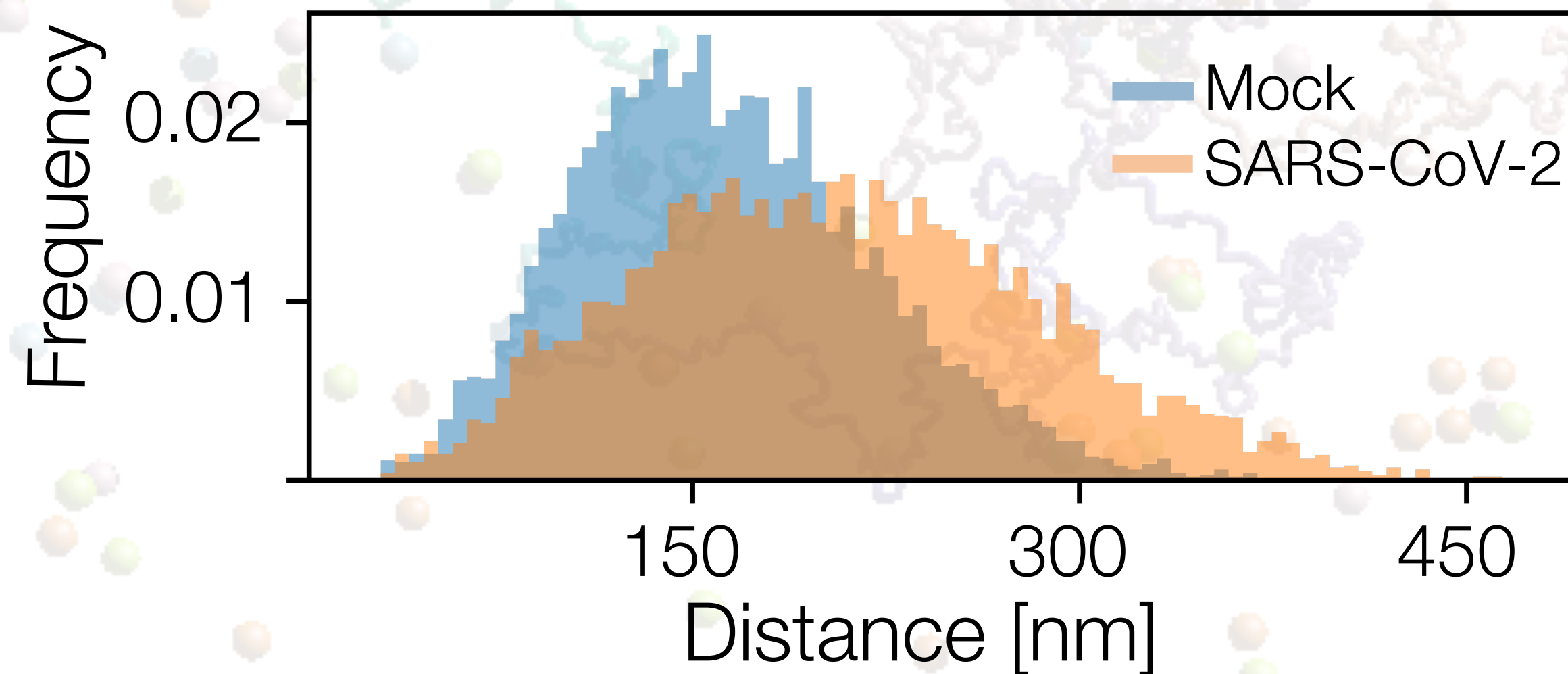




# DDX58-Enhancer distance distribution

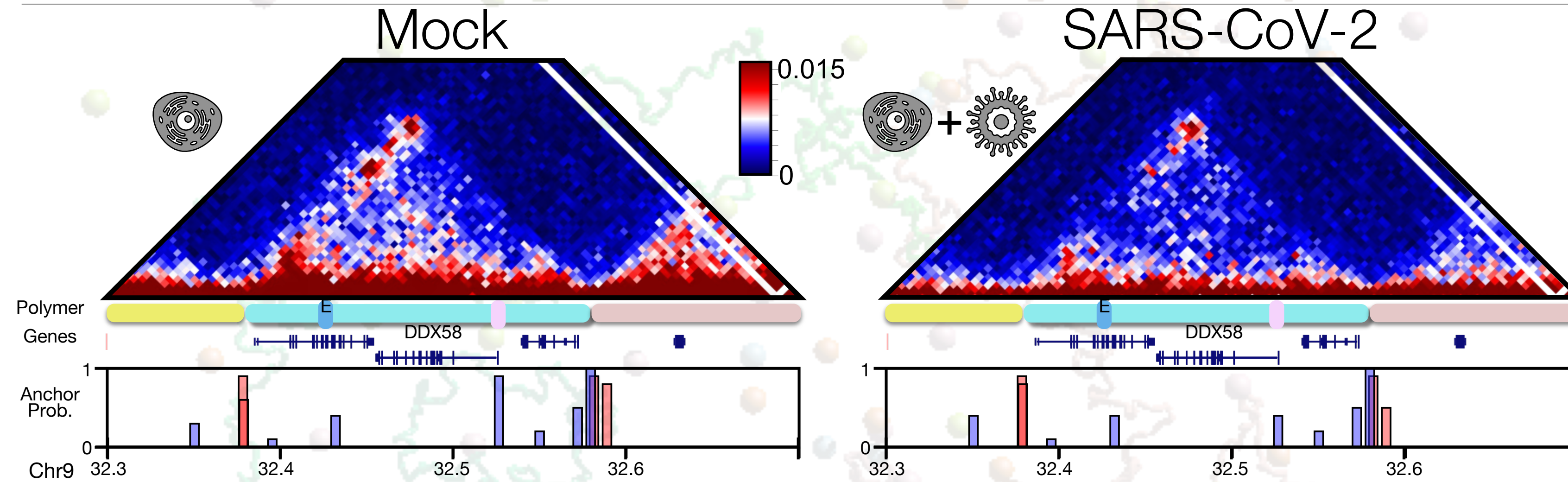


## DDX58 Promoter-Enhancer 3D spatial distance





# Shape descriptors in SARS-CoV-2 3D structures



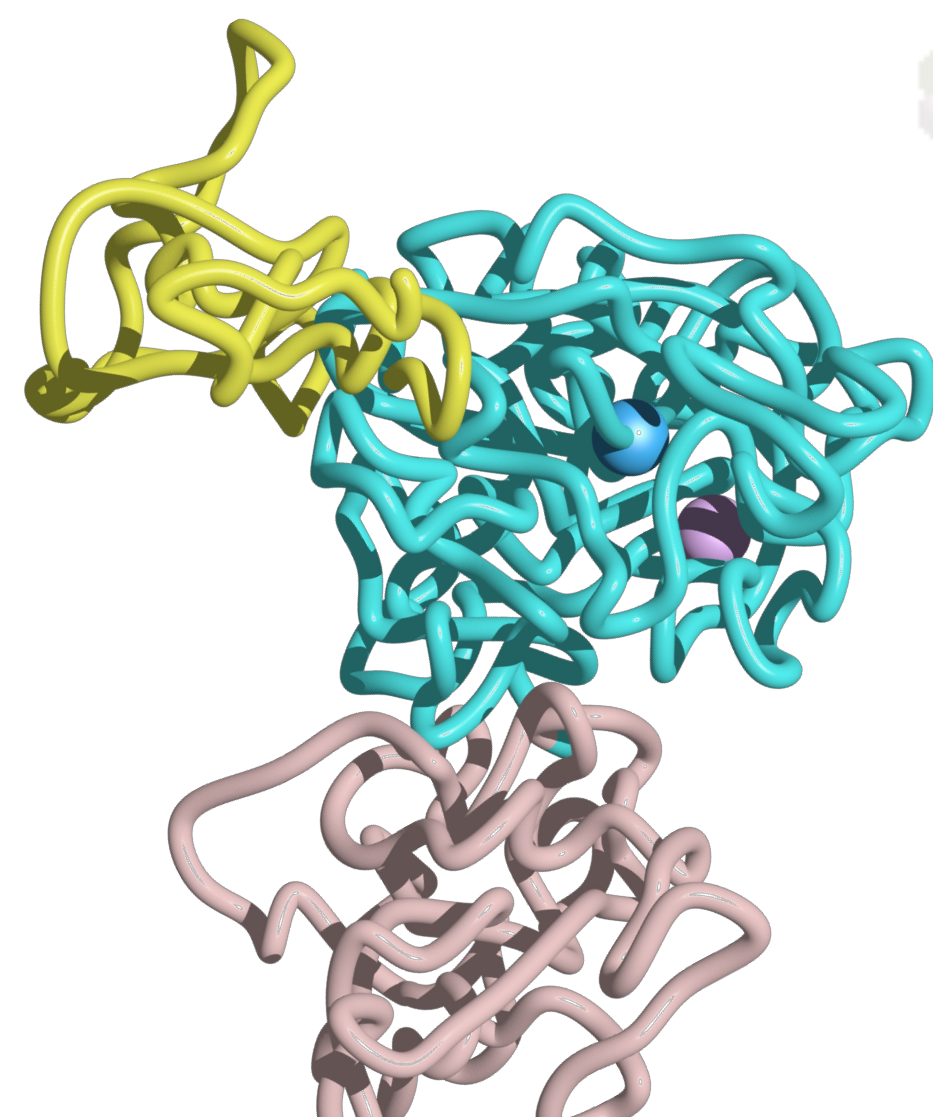
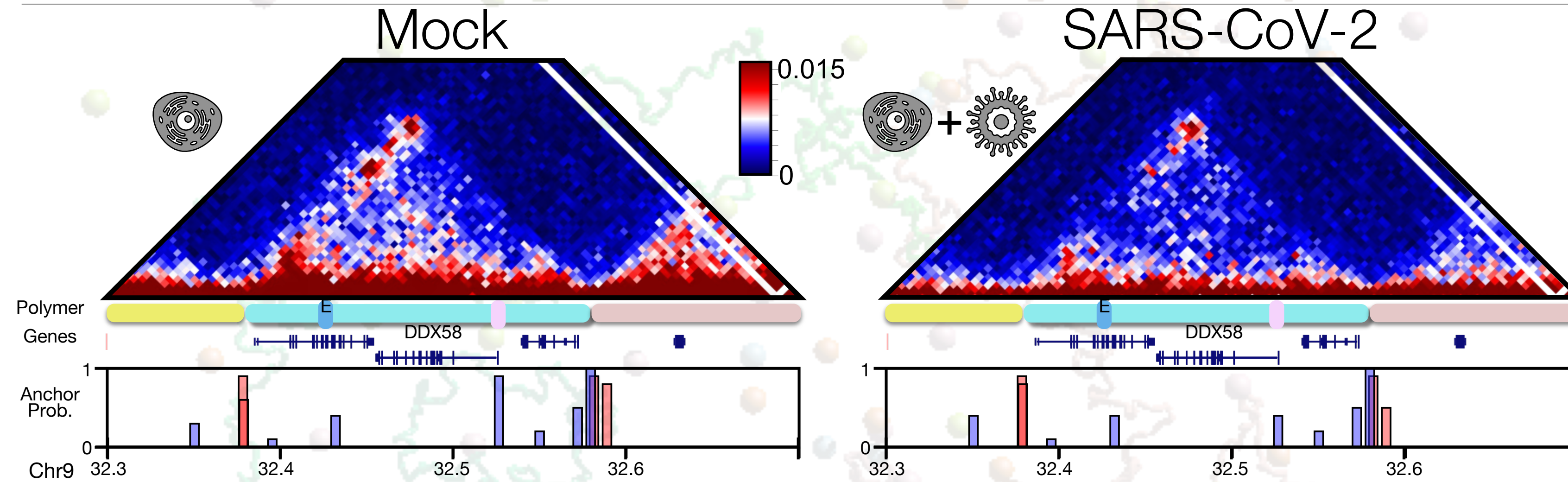
Gyration tensor



$$S = \frac{1}{N} \begin{pmatrix} \sum_i (x_i - x_{cm})^2 & \sum_i (x_i - x_{cm})(y_i - y_{cm}) & \sum_i (x_i - x_{cm})(z_i - z_{cm}) \\ \sum_i (x_i - x_{cm})(y_i - y_{cm}) & \sum_i (y_i - y_{cm})^2 & \sum_i (y_i - y_{cm})(z_i - z_{cm}) \\ \sum_i (x_i - x_{cm})(z_i - z_{cm}) & \sum_i (y_i - y_{cm})(z_i - z_{cm}) & \sum_i (z_i - z_{cm})^2 \end{pmatrix}$$



# Shape descriptors in SARS-CoV-2 3D structures

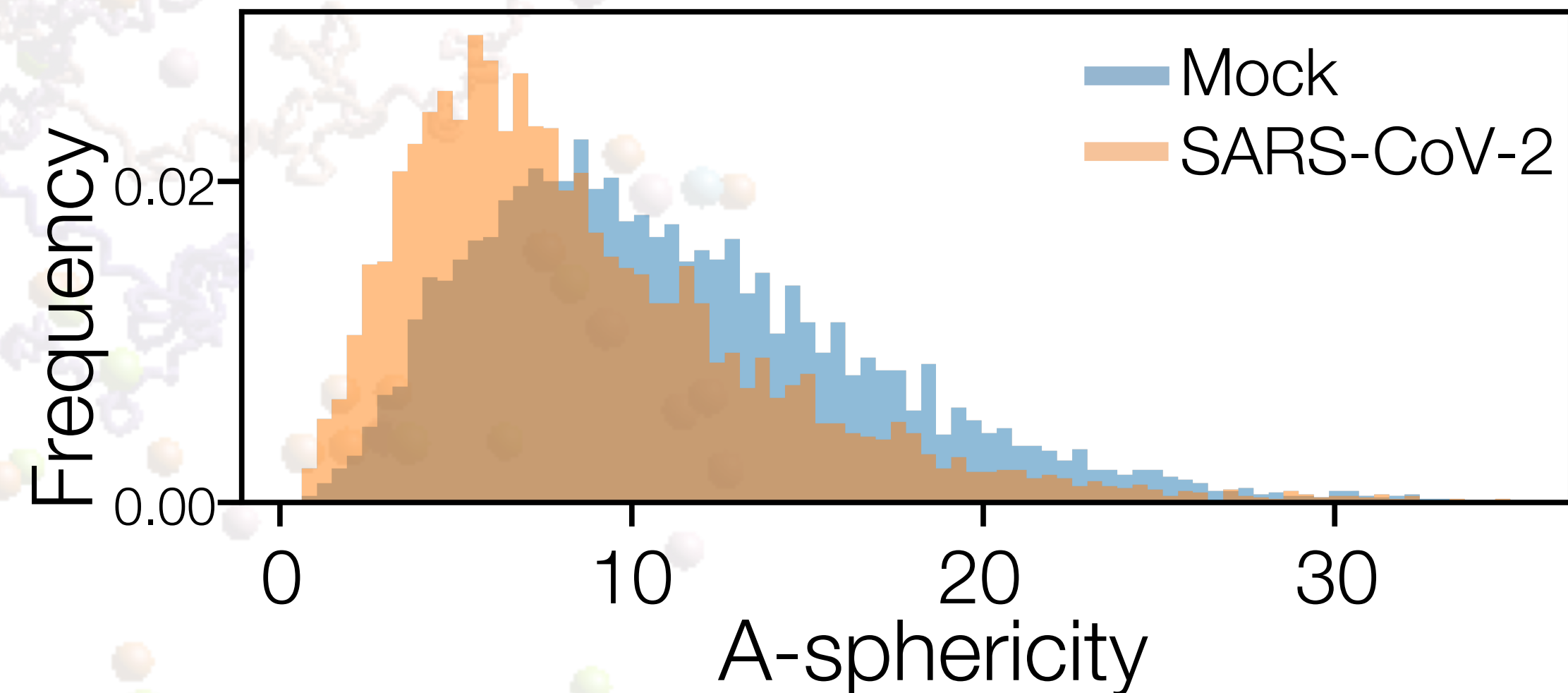


Eigenvalues:  $\lambda_1 > \lambda_2 > \lambda_3$

Shape descriptors:  
a-sphericity b

$$b = \lambda_1 - \frac{1}{2}(\lambda_2 + \lambda_3)$$

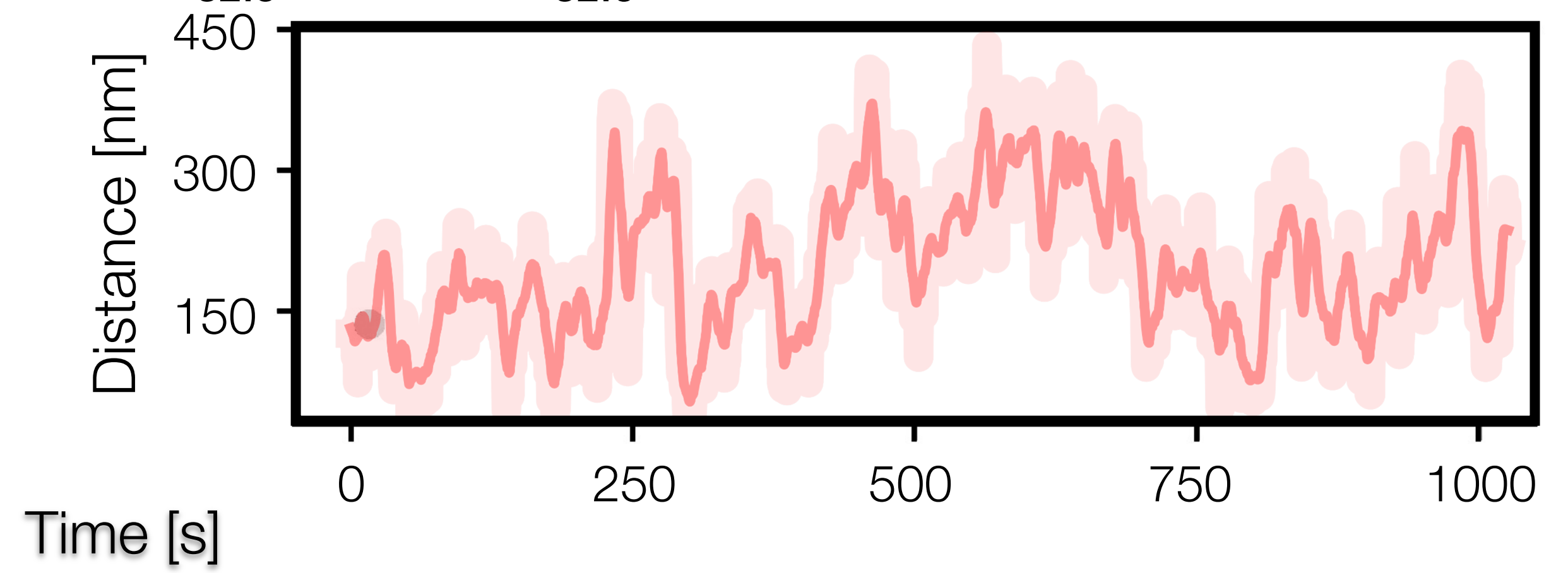
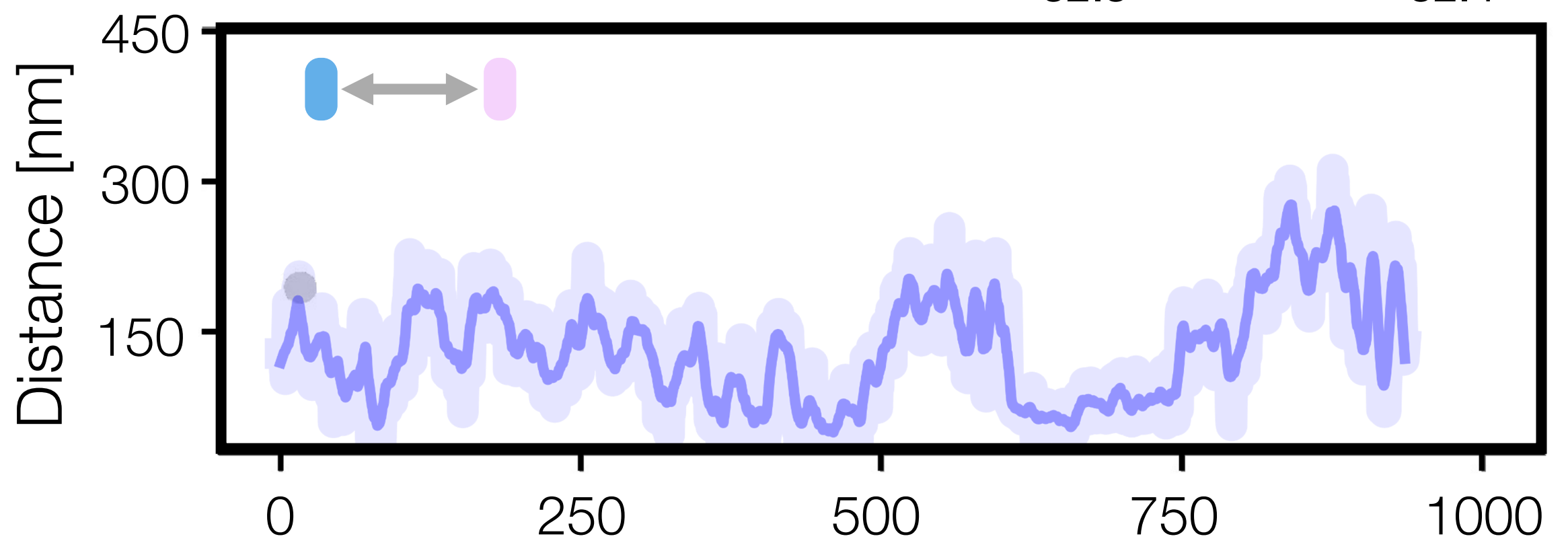
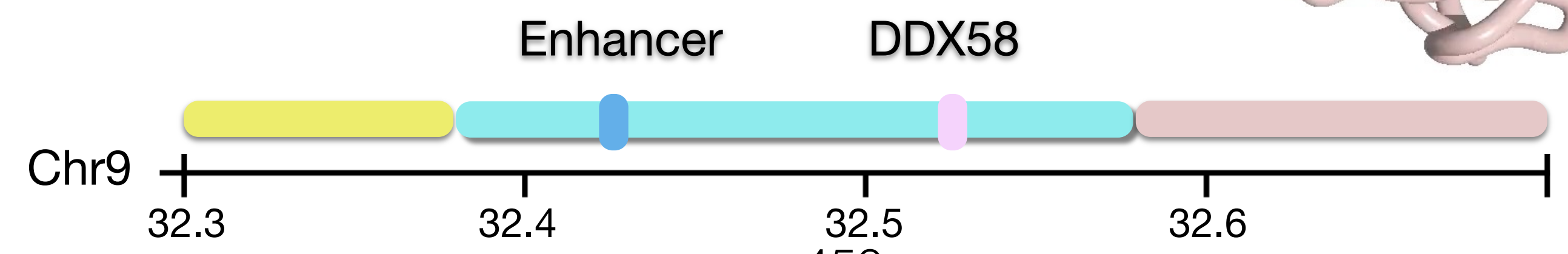
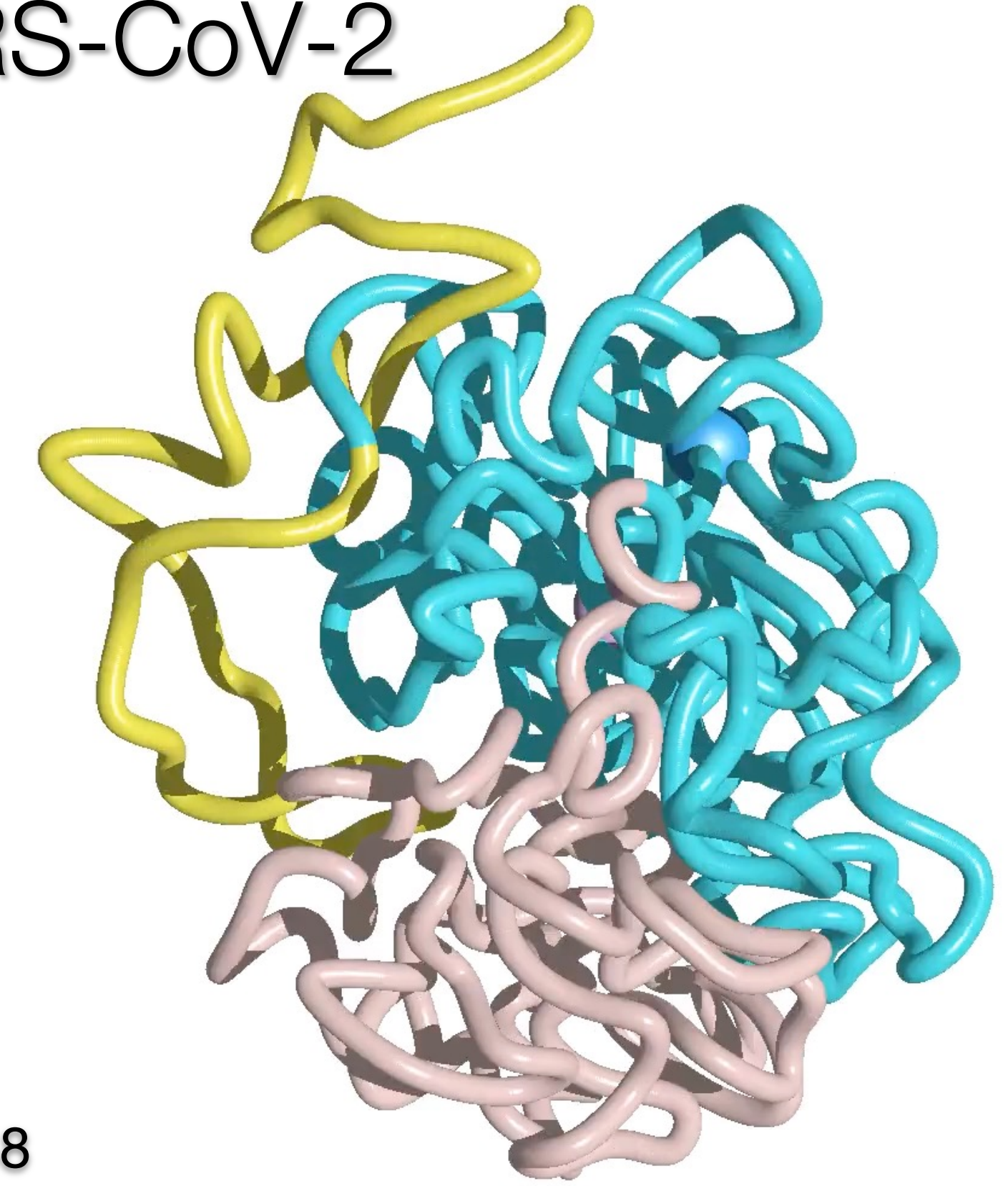
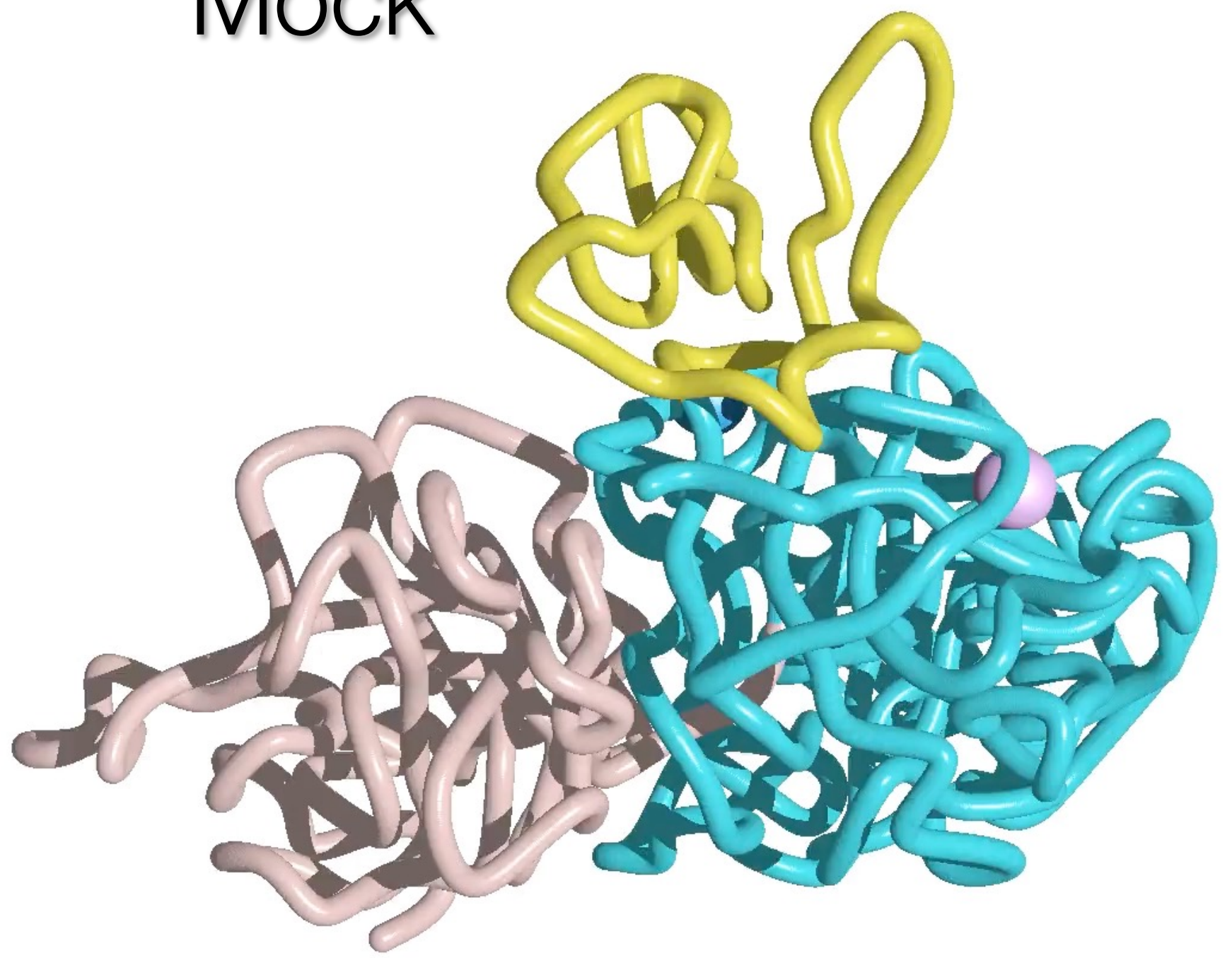
A-sphericity distribution





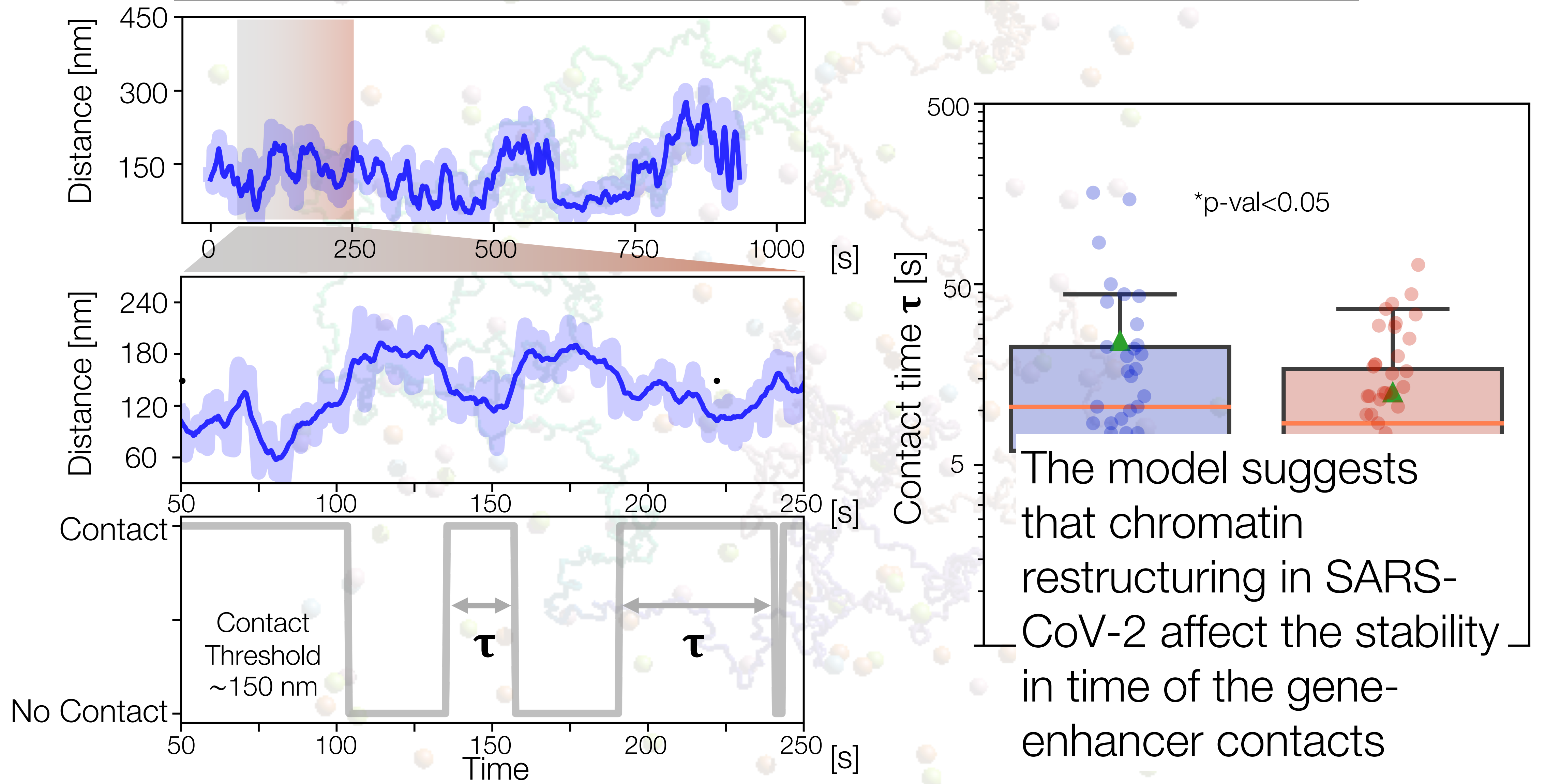
Mock

SARS-CoV-2





# Dynamics in SARS-CoV-2 affected genome makes less stable contacts





# Conclusions

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- Genomes are very complex systems whose three-dimensional structure is non-random and linked to its functions;
- SARS-CoV-2 re-structures the host genome at multiple levels;
- Theoretical (Polymer) Physics suggests that SARS-CoV-2 restructures the host genome by altering physical phase-separation mechanisms;
- Consequently, SARS-CoV-2 alters the regulation of IFN genes, such as DDX58.



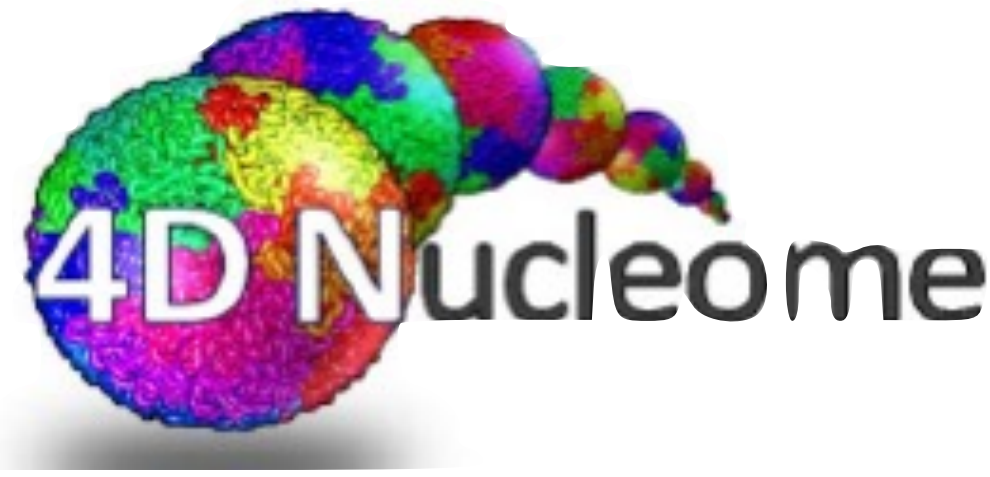
# Acknowledgements

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Andrea Esposito  
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Fabrizio Tafuri

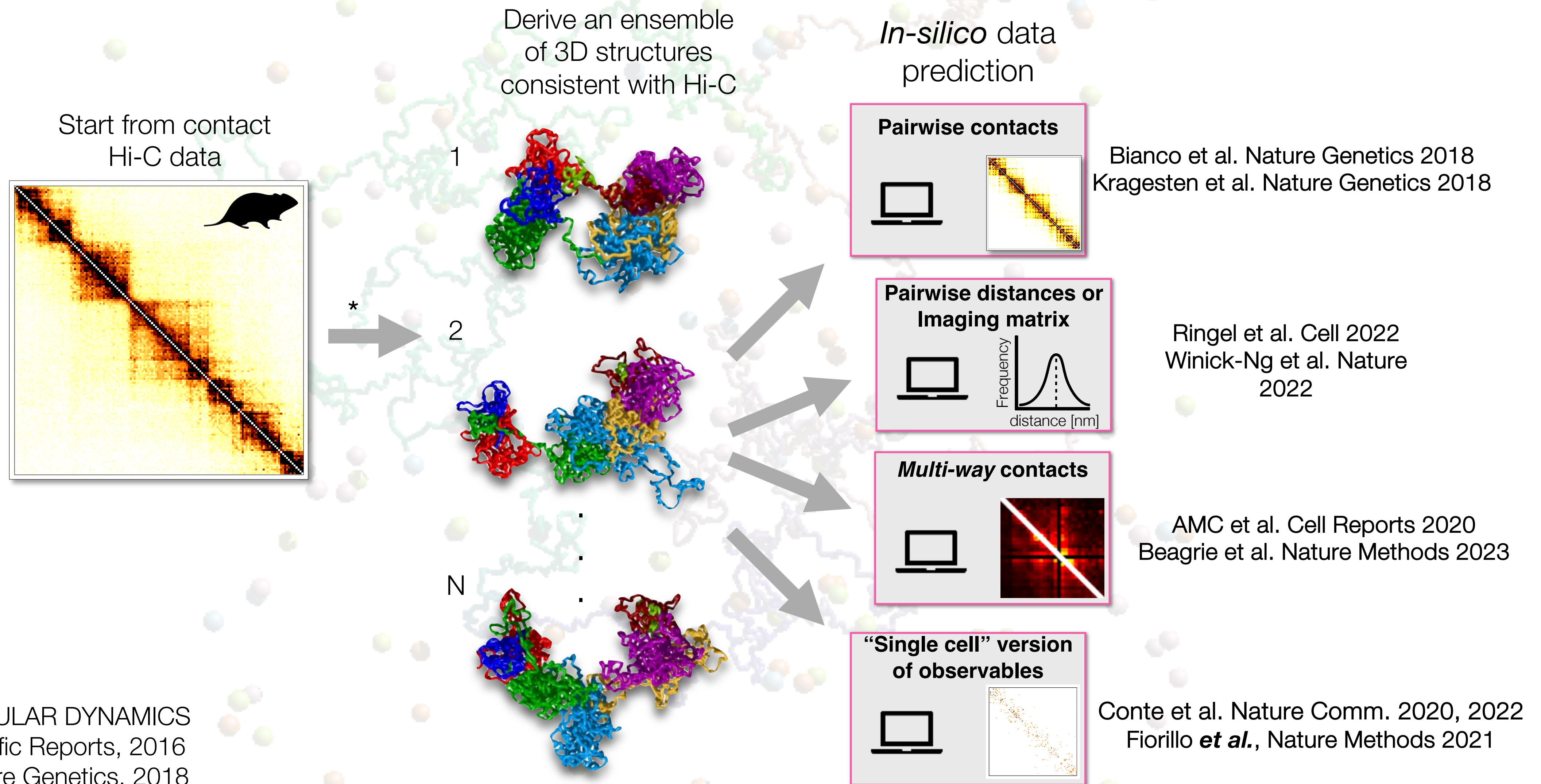


## Collaborators:

- Prof. Ana Pombo, Max Delbrück Center for Molecular Medicine, Berlin
- Dr. Wenbo Li, Texas University, Houston
- Dr. Sarah Kinkley, Max Planck Institute for Molecular Genetics, Berlin
- Prof. Stavros Lomvardas, Columbia University, New York
- Prof. Bing Ren, UC San Diego
- Prof. Pier Giuseppe Pelicci group, IEO,



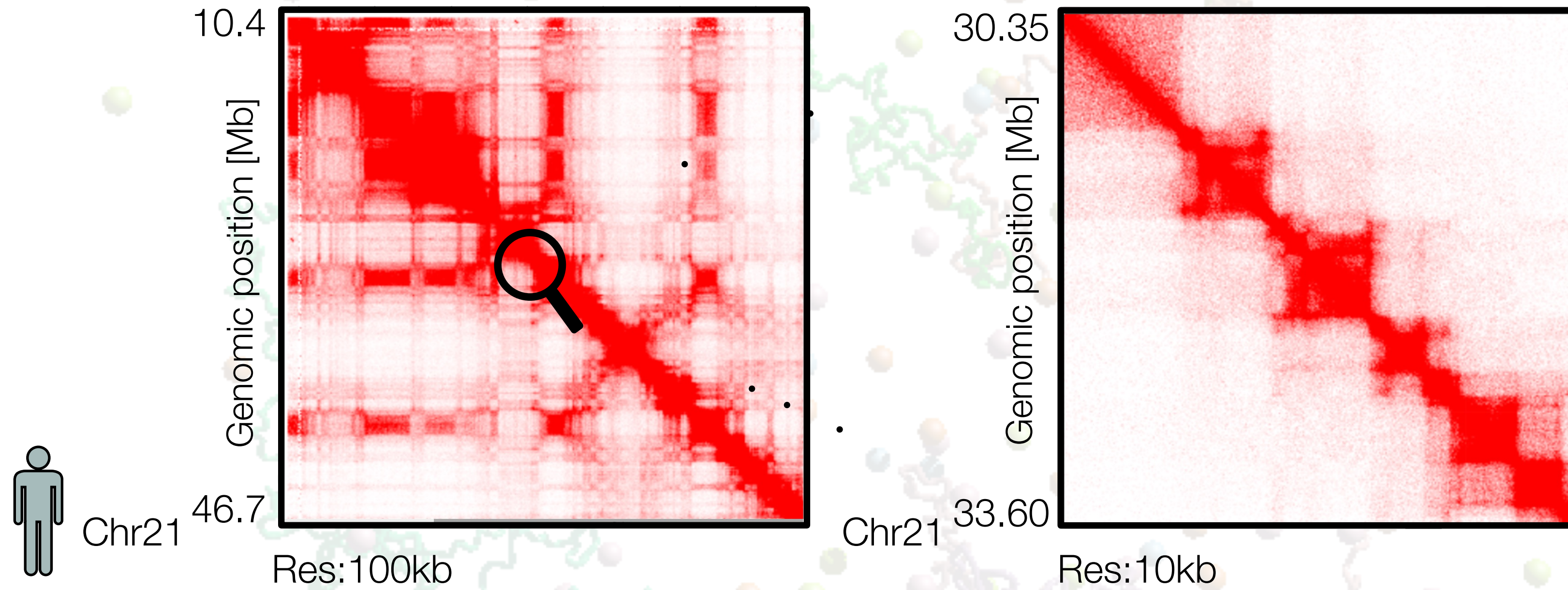
# Computational strategy to simulate real loci



\*PRISMR+MOLECULAR DYNAMICS  
AMC et al., Scientific Reports, 2016  
Bianco et al., Nature Genetics, 2018

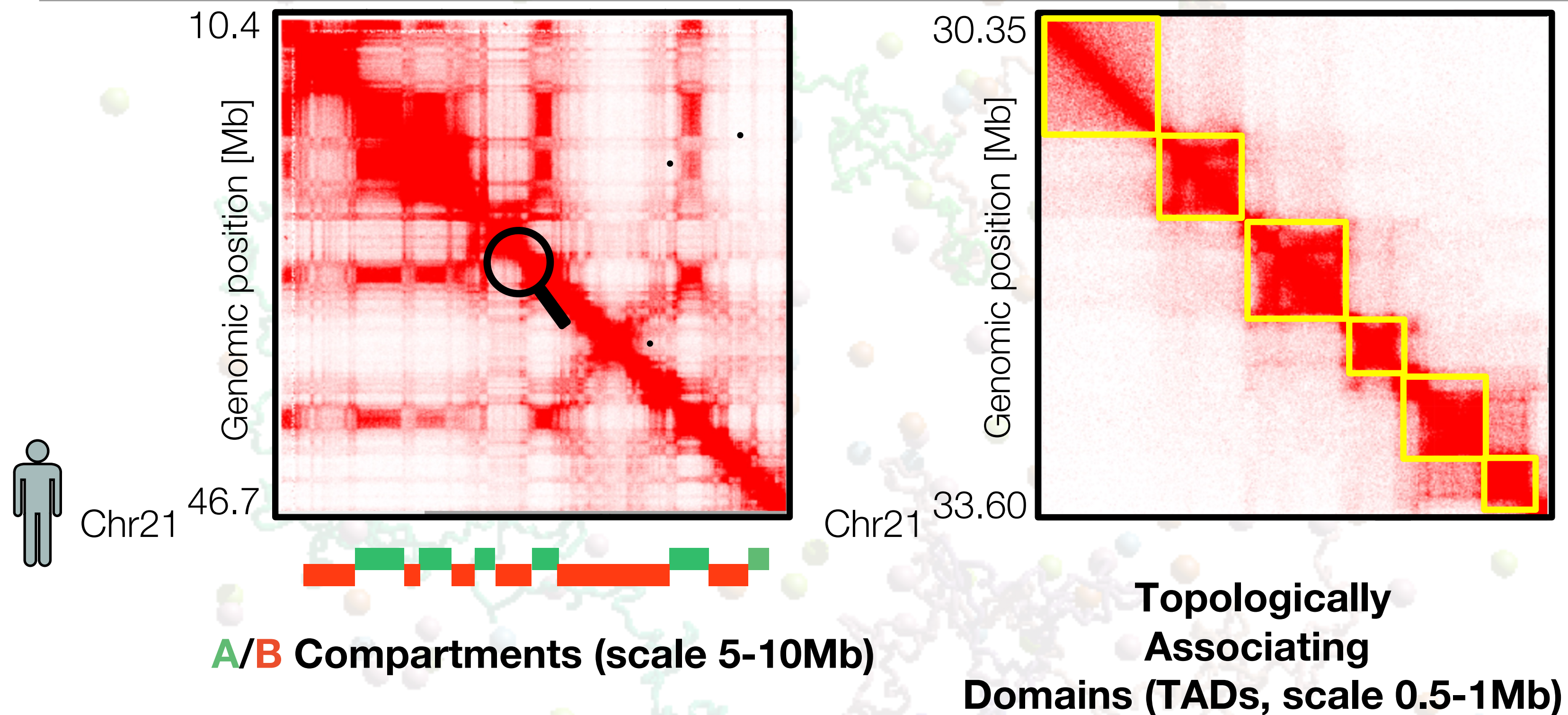


# A/B Compartment, TADs, loops: a hierarchical organization





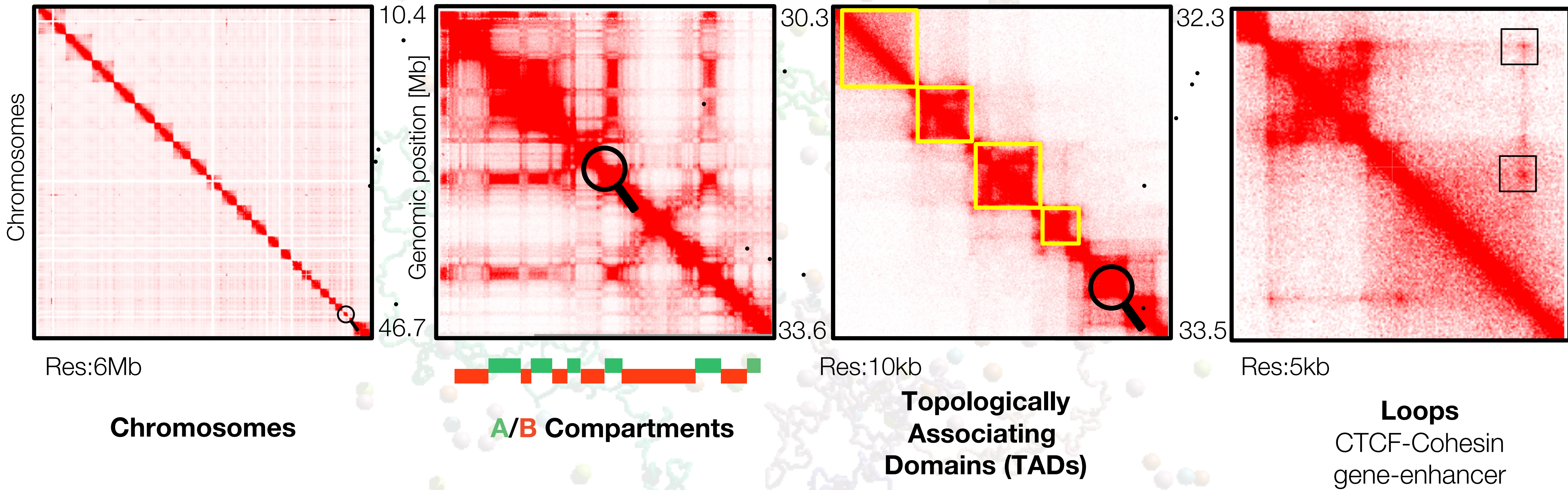
# A/B Compartment, TADs, loops: a hierarchical organization



- A/B correlate with eu- and hetero-chromatin respectively;
- TADs are highly self-interacting chromatin and are typically conserved across tissues and species;
- Represents regulatory as they limit of gene-enhancer interaction;
- Boundaries correlates with several features (epigenetic enrichment).

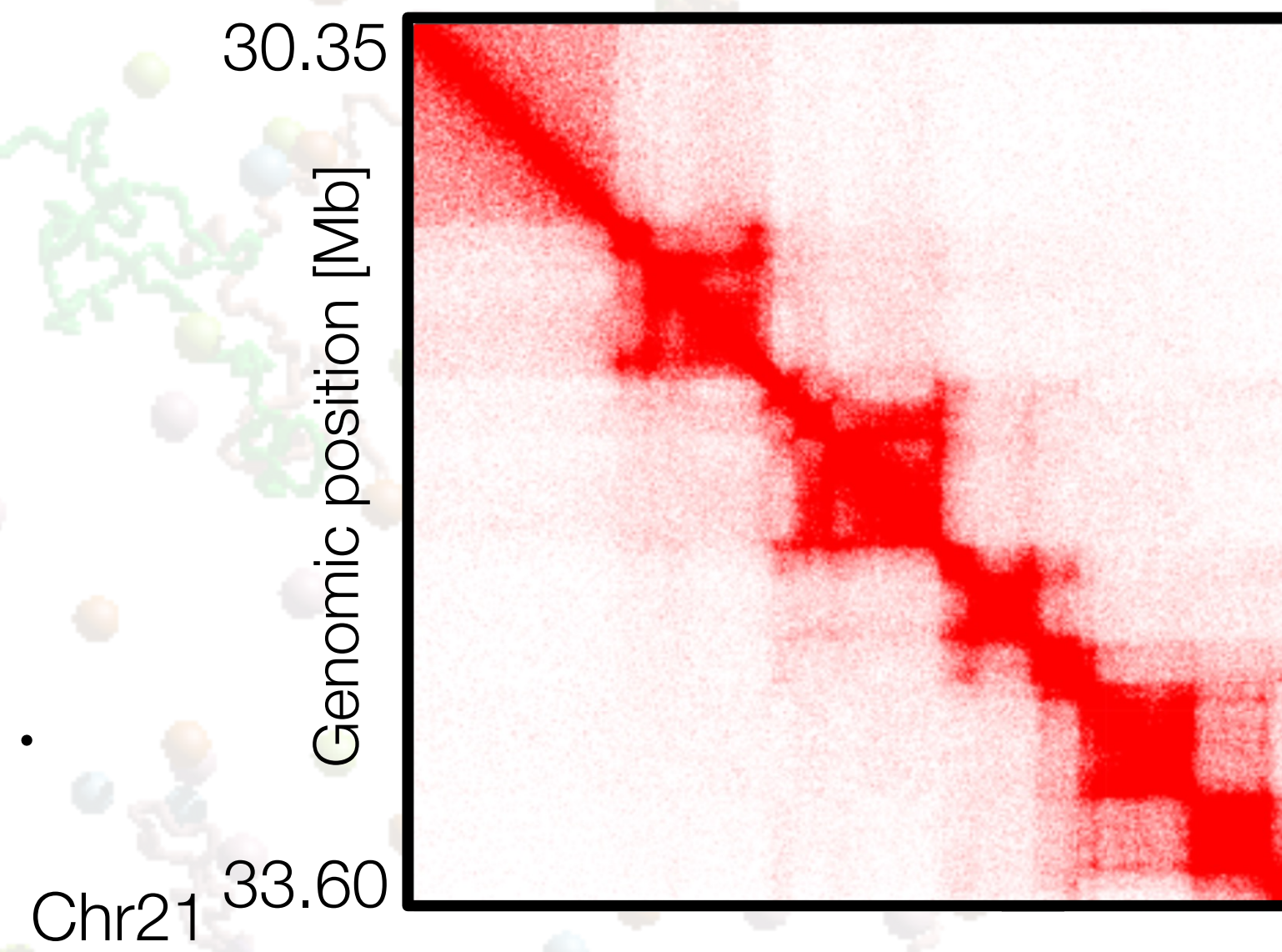
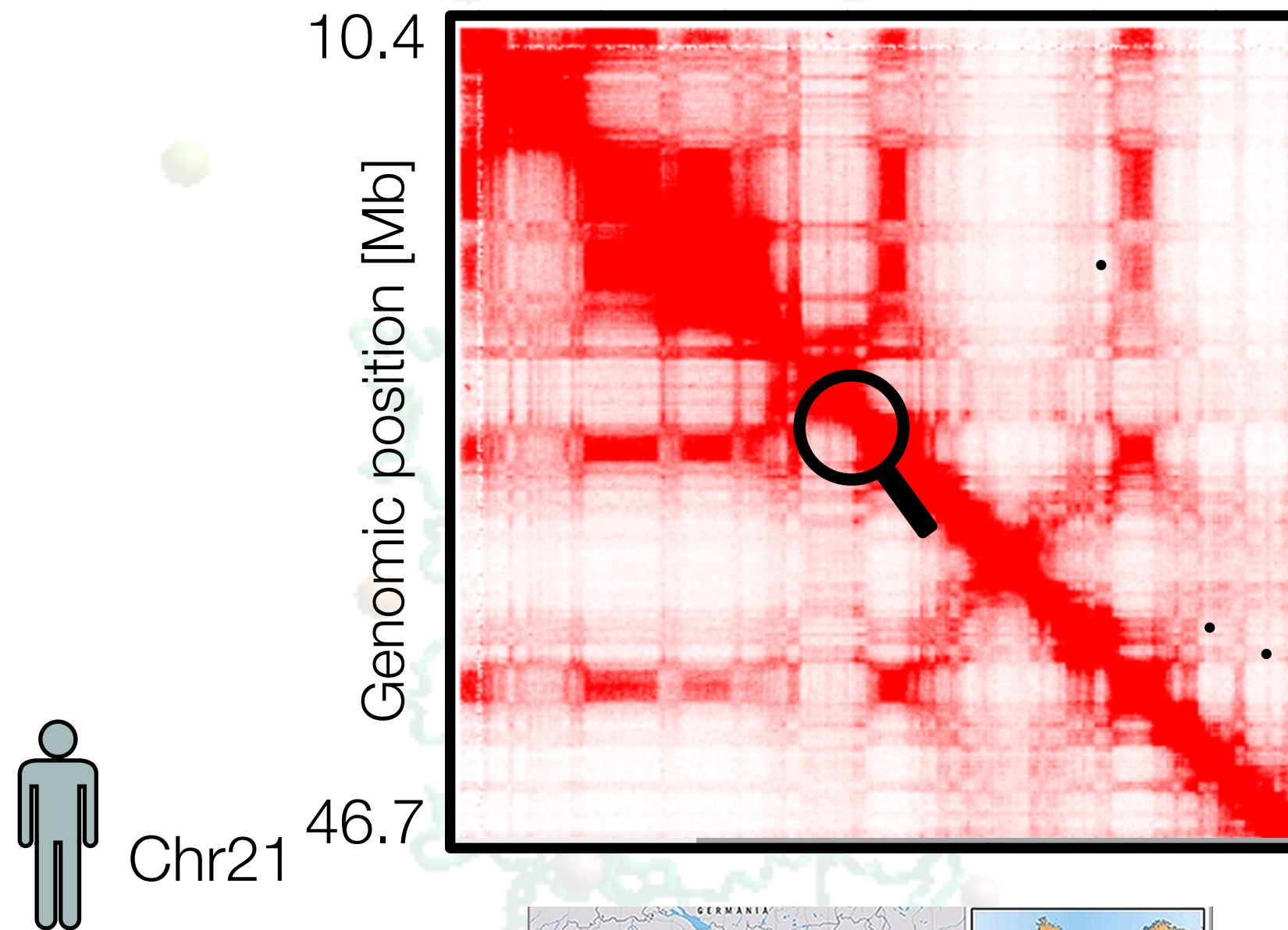


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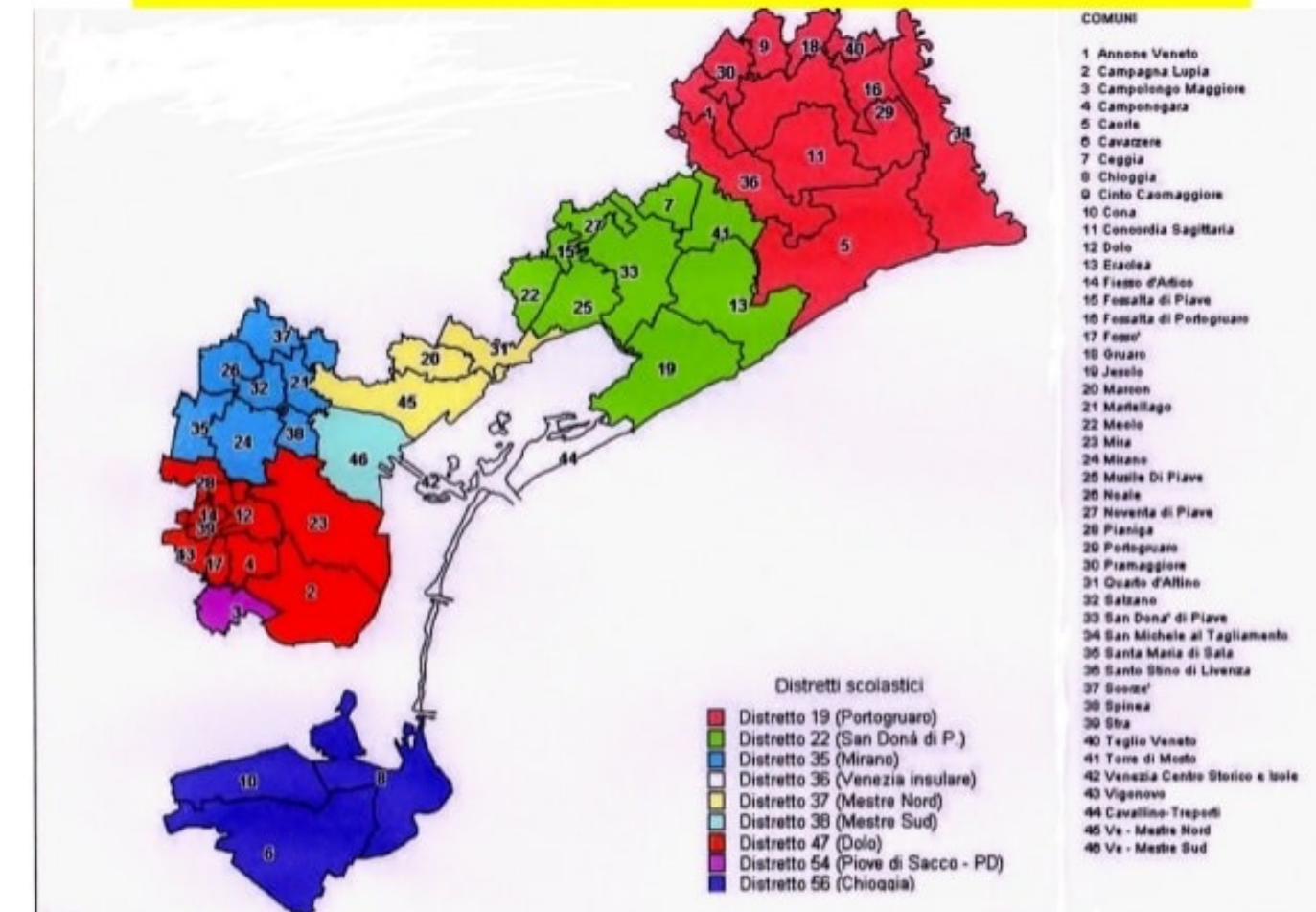
# Genome geography



Sense of  
the scale:

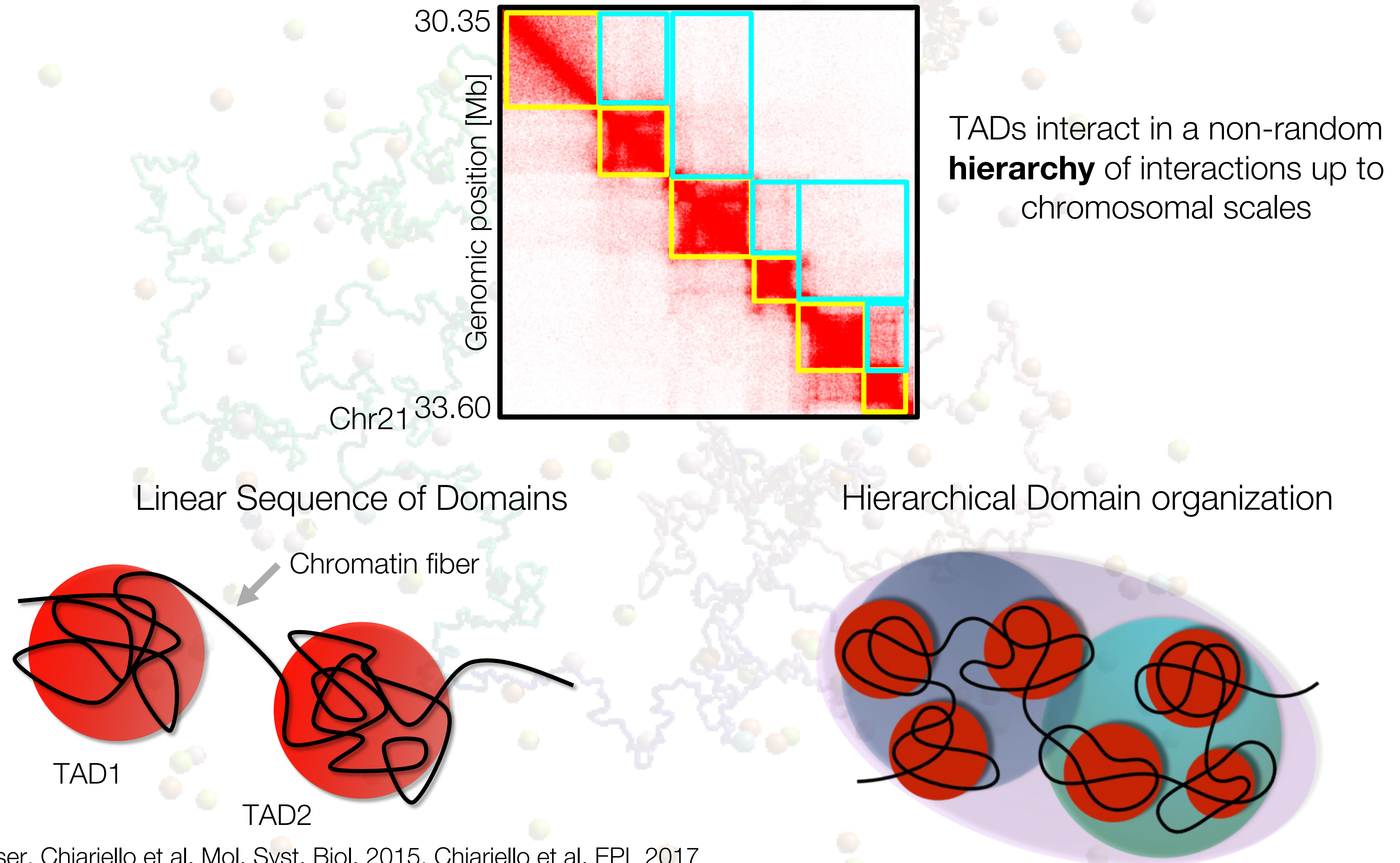


Metropolitan City of Venice





# A/B Compartment, TADs, loops: a hierarchical organization





# Molecular Dynamics details

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$$m \frac{d^2 \mathbf{x}_i}{dt^2} = -\nabla_i V - \gamma \frac{d\mathbf{x}_i}{dt} + \sqrt{2k_B T \gamma} \boldsymbol{\eta}(t)$$

Langevin Equation

$$\langle \boldsymbol{\eta}(t) \rangle = 0; \quad \langle \eta_\alpha(t) \eta_\beta(t') \rangle = \delta_{\alpha\beta} \delta(t - t'),$$

Uncorrelated  
stochastic force

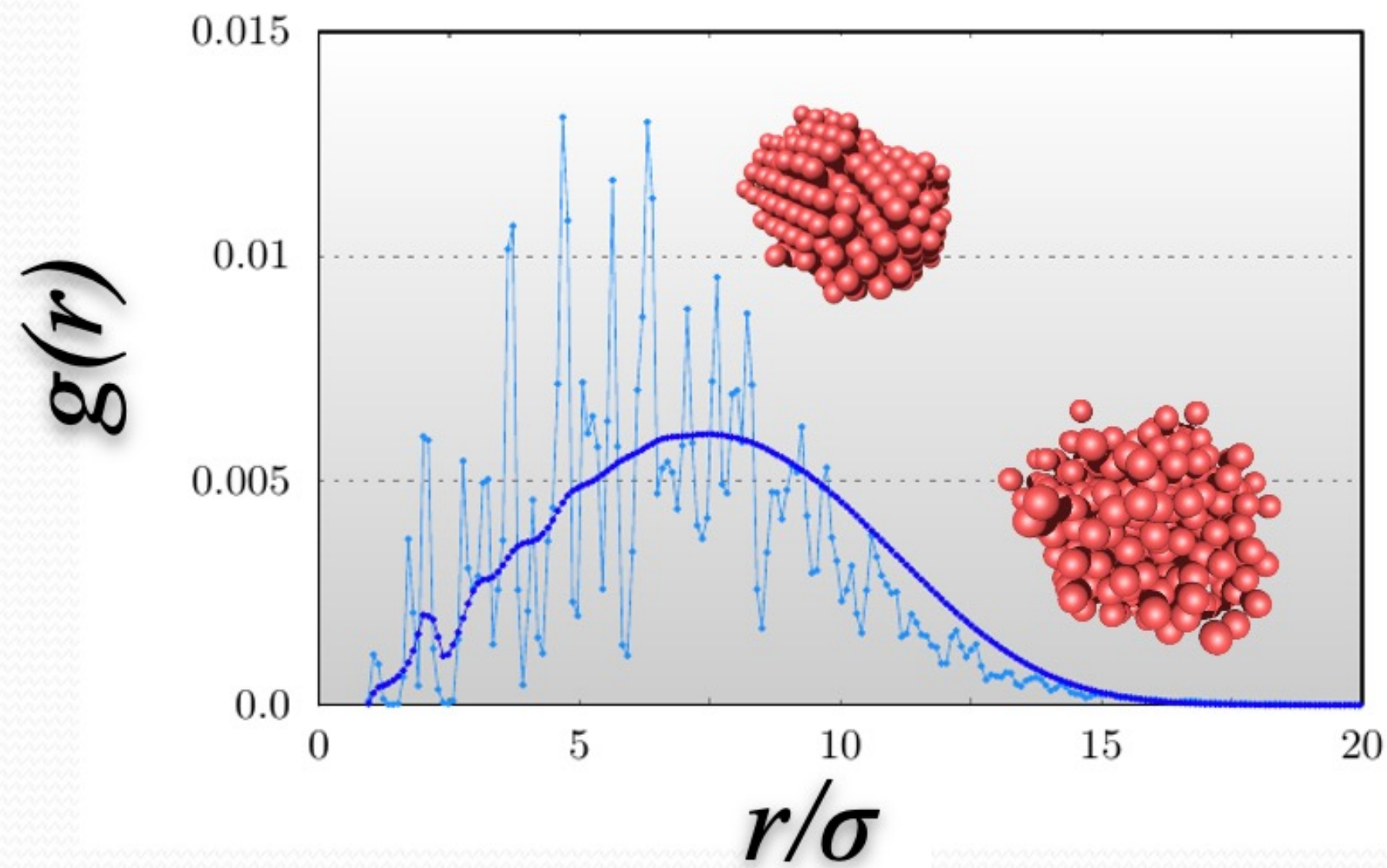
$$1) \quad V_{\text{LJ}}(r_{ij}) = \begin{cases} 4\epsilon \left[ \left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^6 \right] + \epsilon & \text{if } r_{ij} < 2^{1/6} \sigma \\ 0 & \text{otherwise,} \end{cases}$$

$$2) \quad V_{\text{FENE}}(r = |\mathbf{r}_{i+1} - \mathbf{r}_i|) = -\frac{K_{\text{FENE}} R_0^2}{2} \log \left[ 1 - \left(\frac{r}{R_0}\right)^2 \right]$$

$$3) \quad V_{\text{LJ}}^{\text{ab}}(r_{ij}) = \begin{cases} 4\epsilon_{ab} \left[ \left(\frac{\sigma_{ab}}{r}\right)^{12} - \left(\frac{\sigma_{ab}}{r}\right)^6 - \left(\frac{\sigma_{ab}}{r_{\text{thr}}}\right)^{12} + \left(\frac{\sigma_{ab}}{r_{\text{thr}}}\right)^6 \right] & \text{if } r < r_{\text{thr}} \\ 0 & \text{otherwise,} \end{cases}$$



# Order-Disorder transition



$$g(\mathbf{r}) = V/N^2 \langle \sum_i \sum_{j \neq i} \delta(\mathbf{r}_{ij} - \mathbf{r}) \rangle$$

$$S(k) = 1 + 4\pi(N/V) \int r^2 \sin(kr)/(kr) g(r) dr$$

