

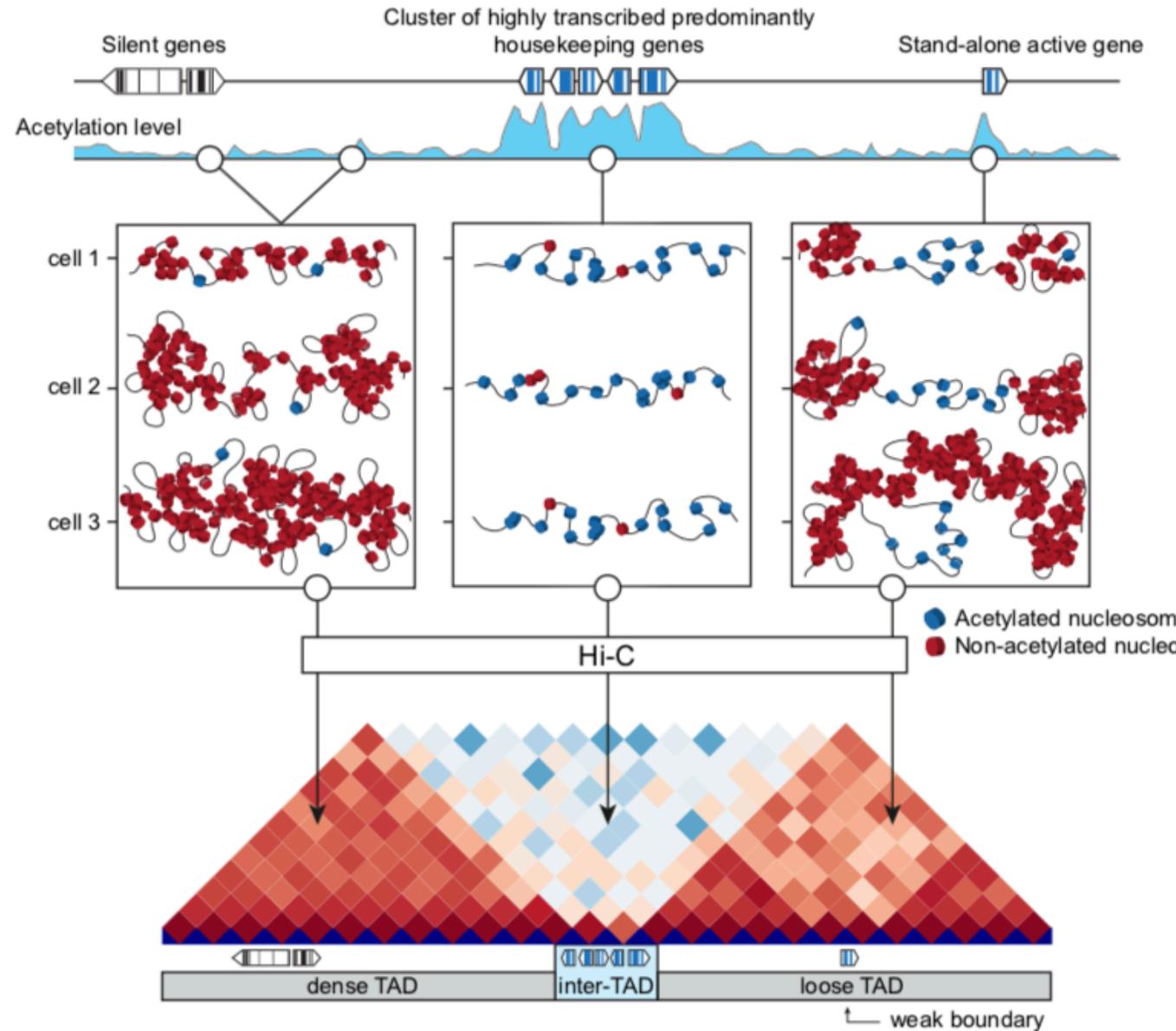
3D molecular modelling of chromatin structure in *D. melanogaster*

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March, 2021

Background

In the 2016 article by Ulianov et al. the following hypothesis was suggested: acetylation of histone tails affects chromatin structure and accessibility. Specifically, acetylated gene-rich segments of chromatin form less compact structures, non-acetylated chromatin regions form compact regions - TADs.



Background

T1

{10n+5}

$$\Delta Lk \approx -1$$

weak supercoiling

highly transcribed genes

greater plasticity

PTM

T2

{10n}

$$\Delta Lk \approx -1.5$$

regions with a low level of transcription

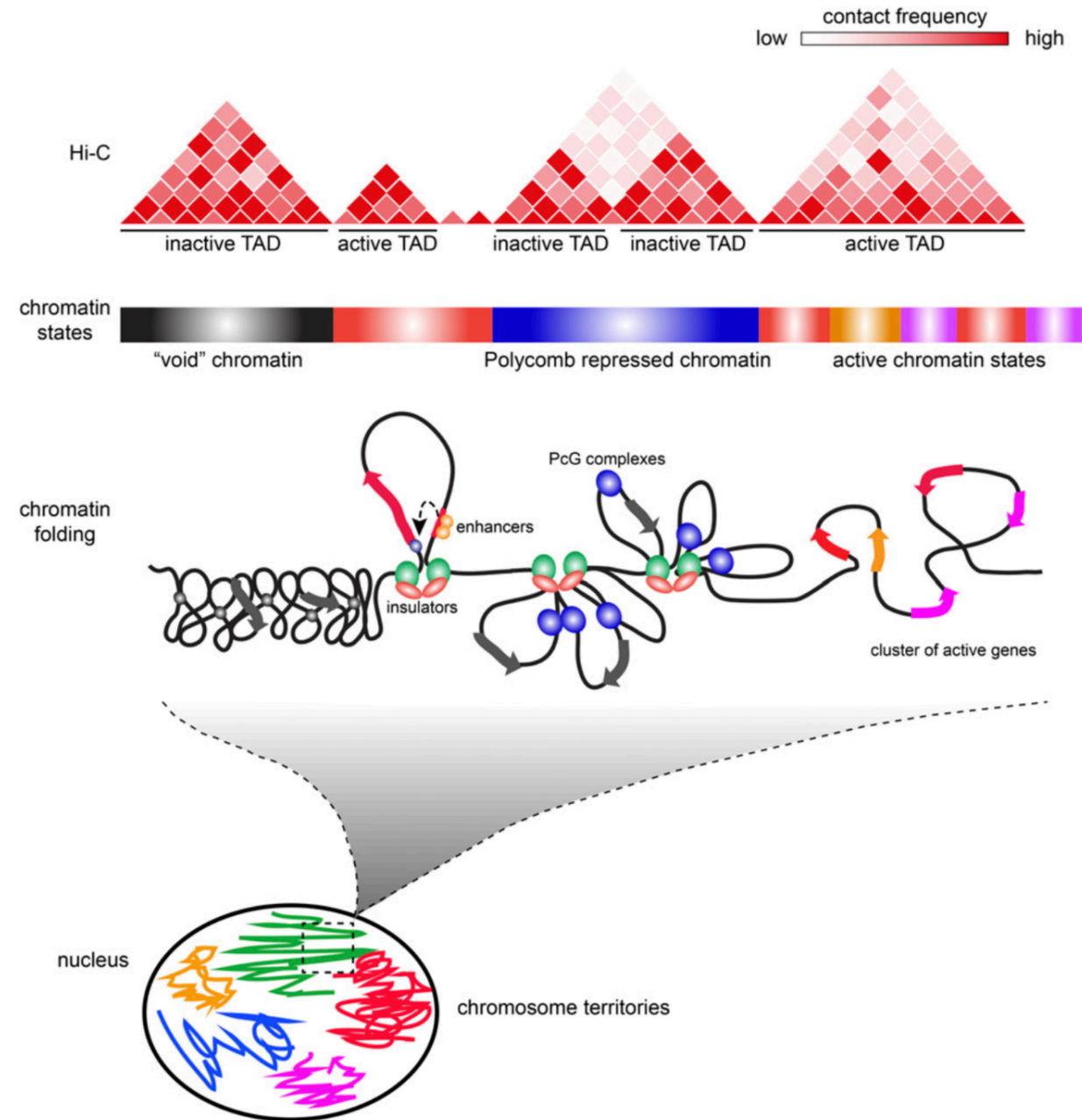
higher stability of the chromatin fiber

Background

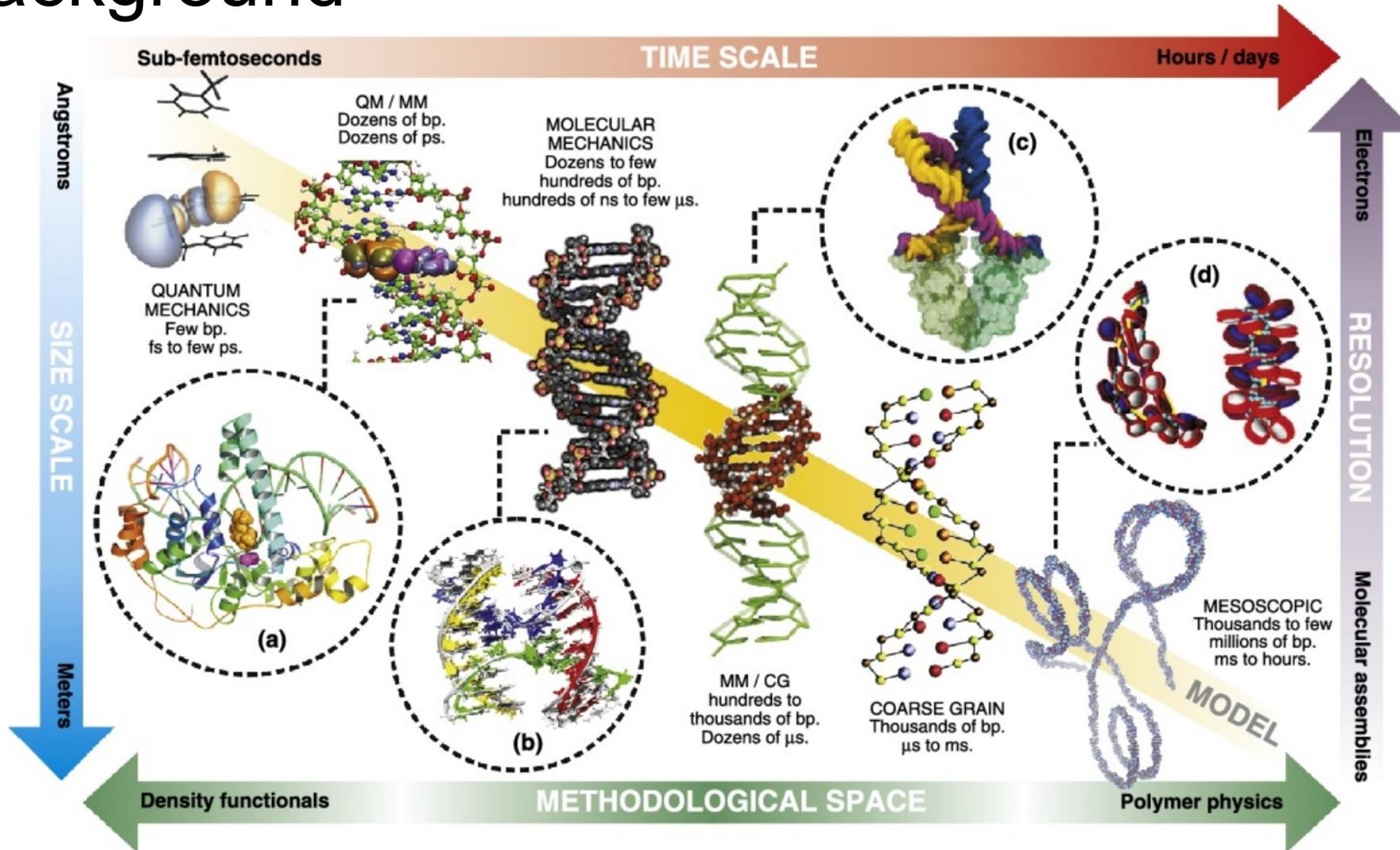
It is natural to proceed with hypothesis validation at a higher resolution in two ways.

C-TALE experiments will provide better resolution for experimental data.

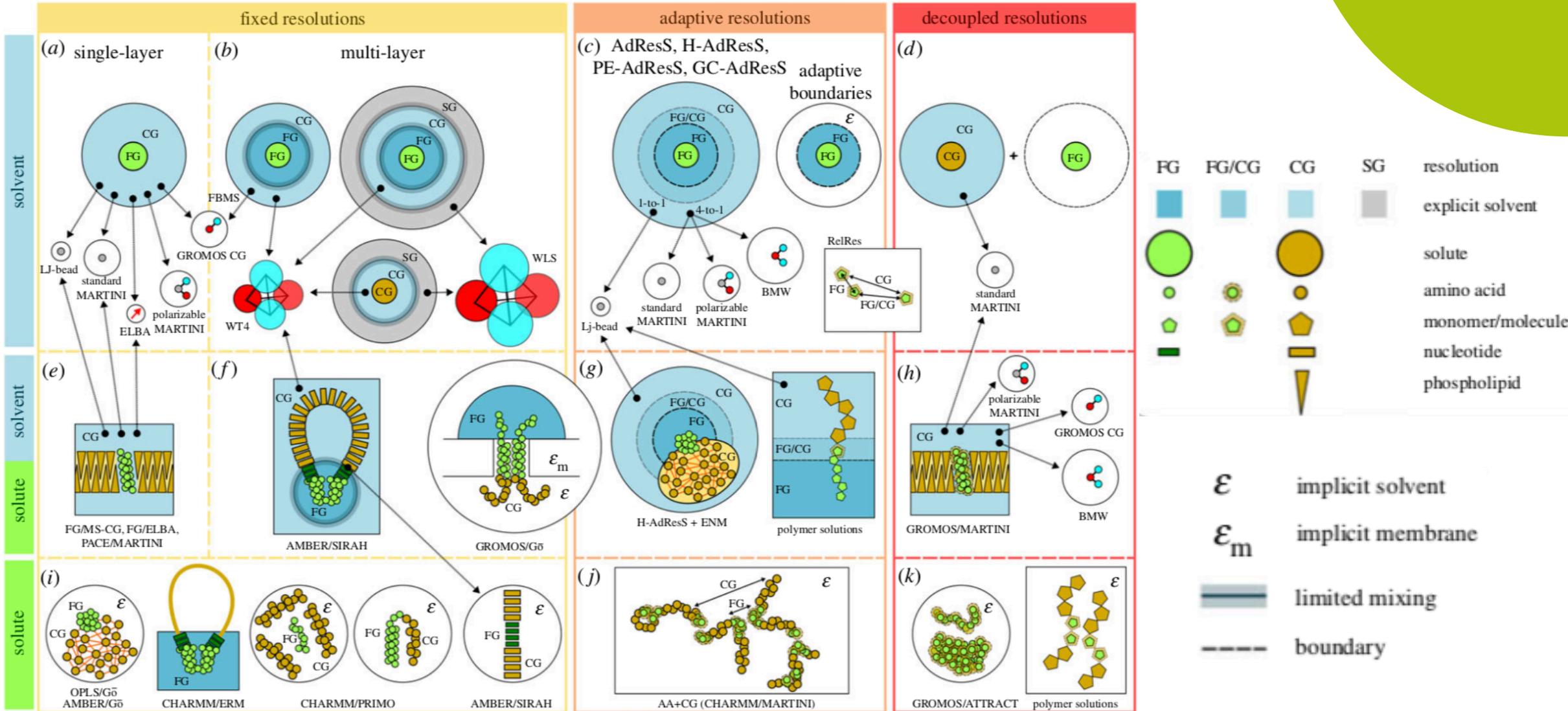
Coarse-grained molecular dynamics modelling will allow us to observe the effect of acetylation on nucleosomal density at resolution of single nucleosomes



Background



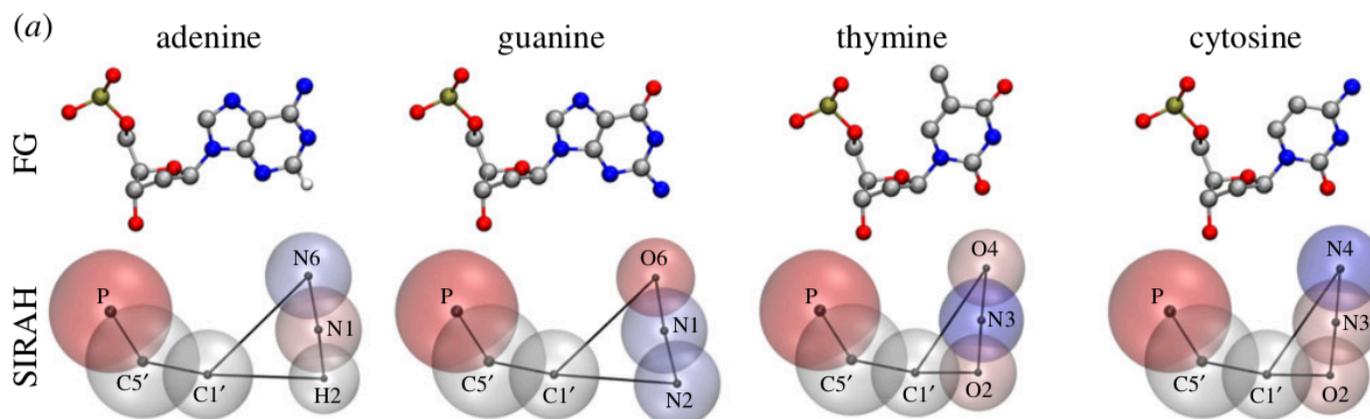
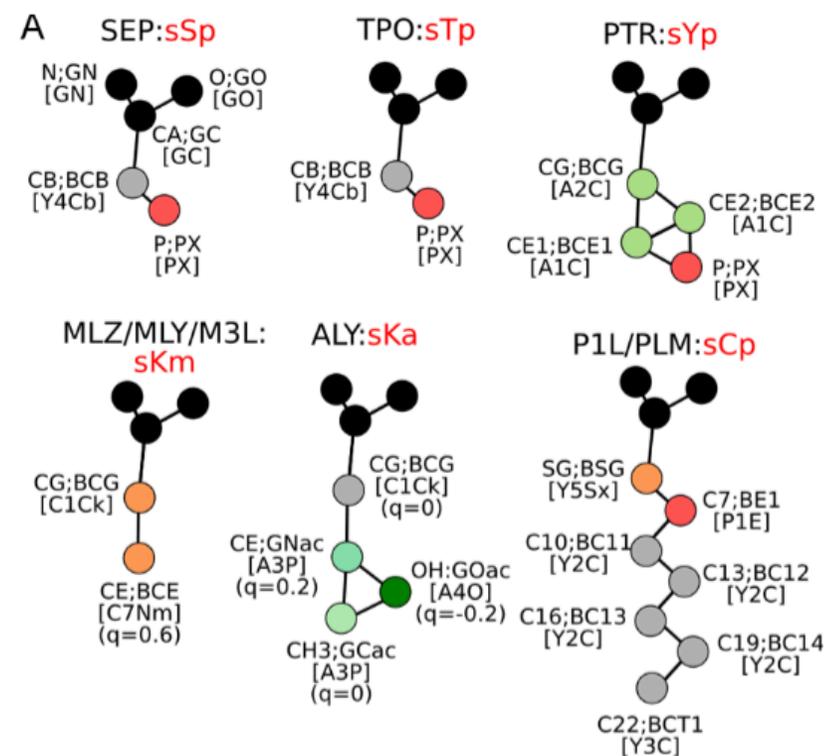
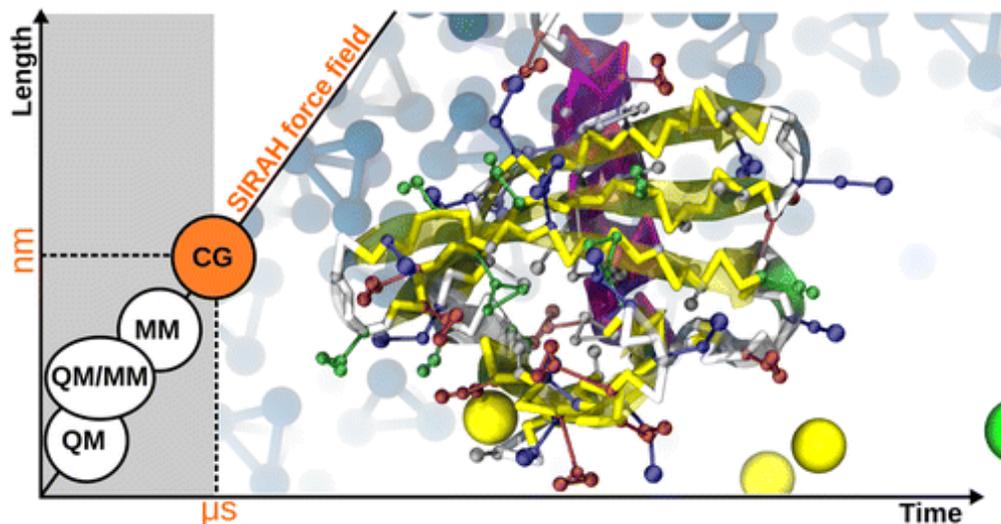
Background



Background

SIRAH forcefield

- Top-down approach
- Highly sensitive
- WT4 water model
- Built-in acetylation mapping



Aim and objectives

Aim

Compare and analyse Hi-C and C-TALE experimental data versus coarse-grained molecular modelling to estimate the effect of histone acetylation on chromatin density at multiscale resolution

Objectives

- Coarse-grained modelling
- Analysis of the modelling results
- Comparison of modelling results vs Hi-C and C-TALE

Methods

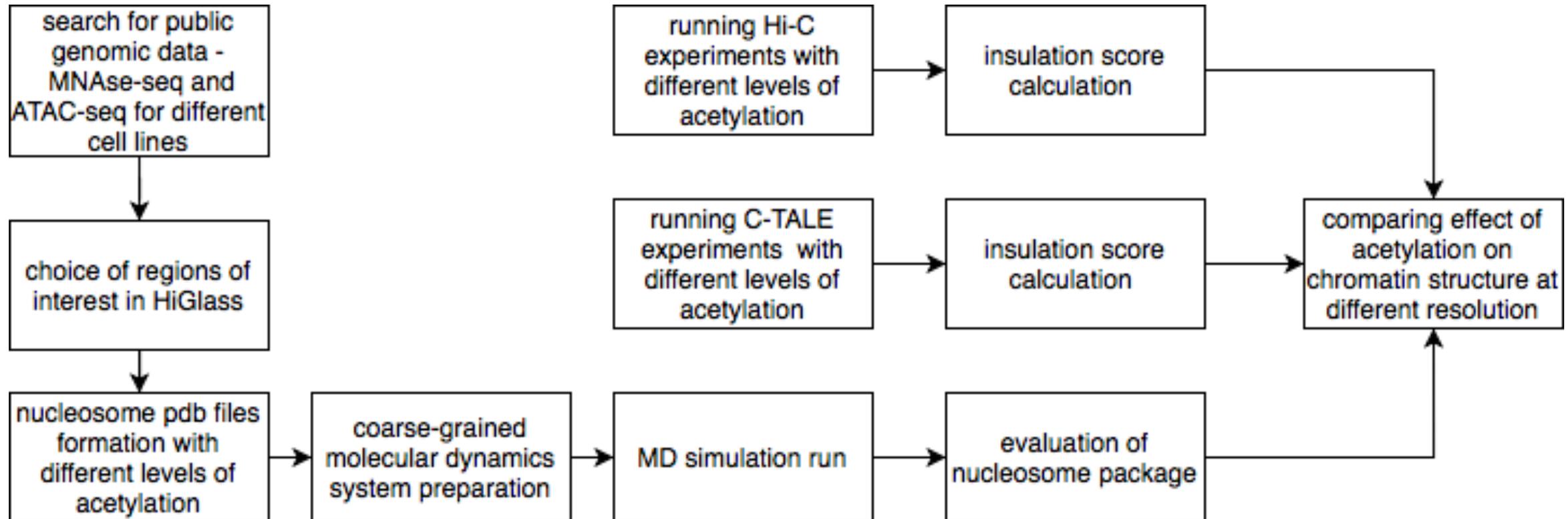
Genomic data processing

- HiGlass

MD simulations

- GROMACS
- SIRAH force field
- Newton cluster
- Arcuda cluster

Skoltech



Results

Literature and database analysis of MNase-seq and ATAC-seq data of different cell lines

- Selected dm3 genome assembly regions
- Selected histone acetylation sites

GAL4 induces transcriptionally active puff in the absence of dSAGA- and ATAC-specific chromatin acetylation in the *Drosophila melanogaster* polytene chromosome

Anita Ciurciu ¹, István Tombácz, Cristina Popescu, Imre Boros

Affiliations + expand

PMID: 19412618 DOI: [10.1007/s00412-009-0215-7](https://doi.org/10.1007/s00412-009-0215-7)

Published online 2016 Sep 27. doi: [10.1186/s13059-016-1057-2](https://doi.org/10.1186/s13059-016-1057-2)

PMID: [27678375](https://pubmed.ncbi.nlm.nih.gov/27678375/)

Genome-wide identification of *Drosophila* dorso-ventral enhancers by differential histone acetylation analysis

[Nina Koenecke](#),^{#1} [Jeff Johnston](#),^{#1} [Bjoern Gaertner](#),^{1,2} [Malini Natarajan](#),¹ and [Julia Zeitlinger](#)^{1,3}

Spatially uniform establishment of chromatin accessibility in the early *Drosophila* embryo

 Jenna E. Haines,  Michael B. Eisen

doi: <https://doi.org/10.1101/195073>

Results

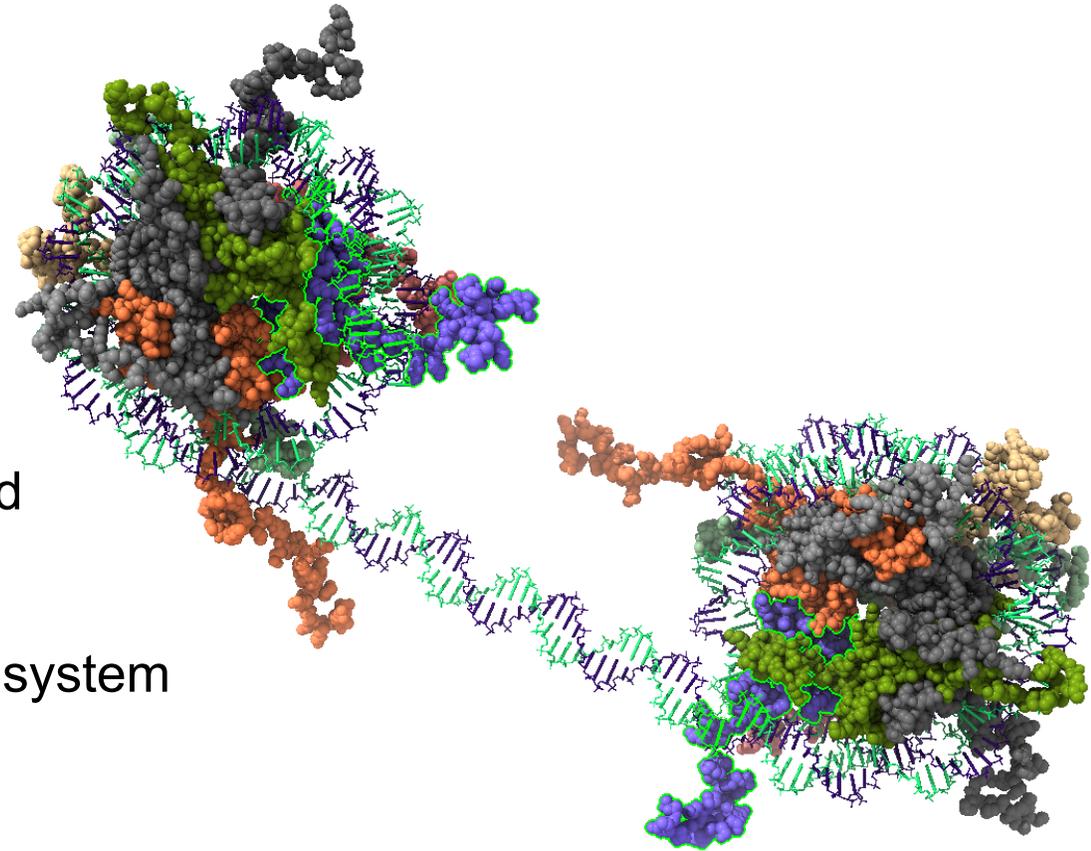
MD system preparation

Atomic representation

- Nucleotide sequence
- Histone octamer

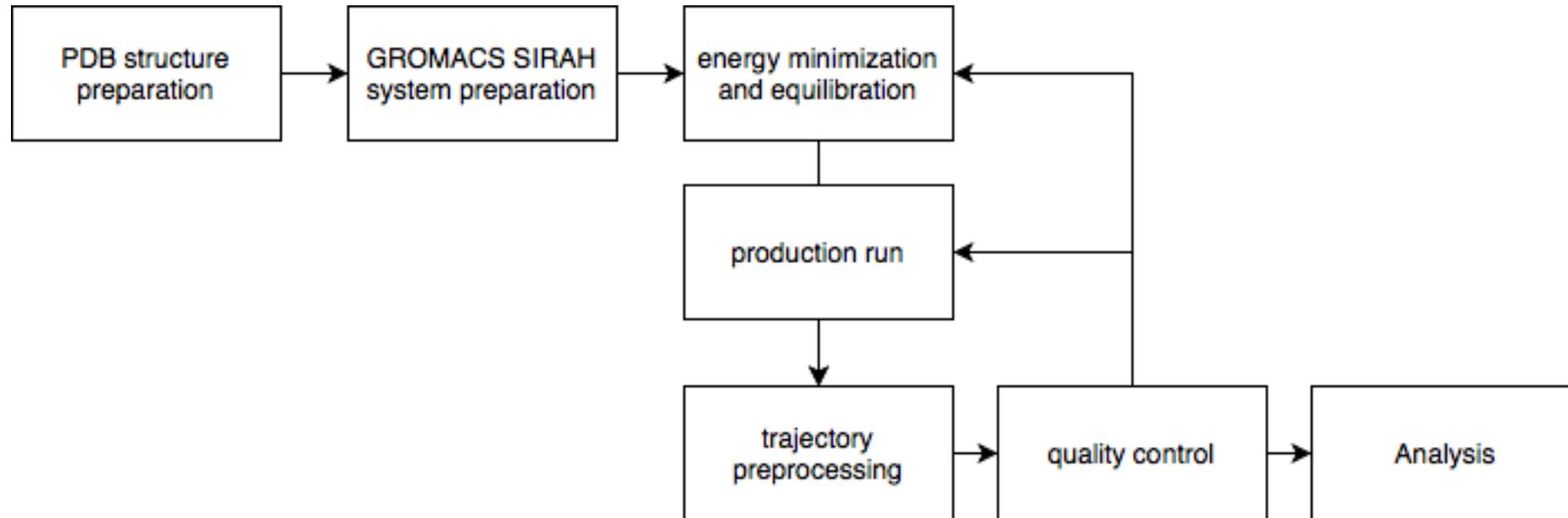
PDB files assembled and preprocessed

Successful main run on dinucleosome system



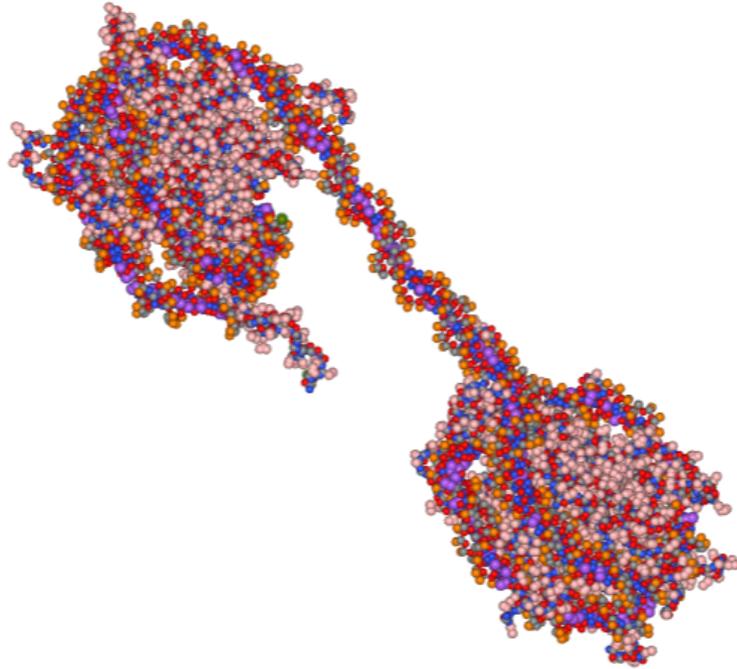
Results

Coarse-grained molecular modelling script pipeline validated



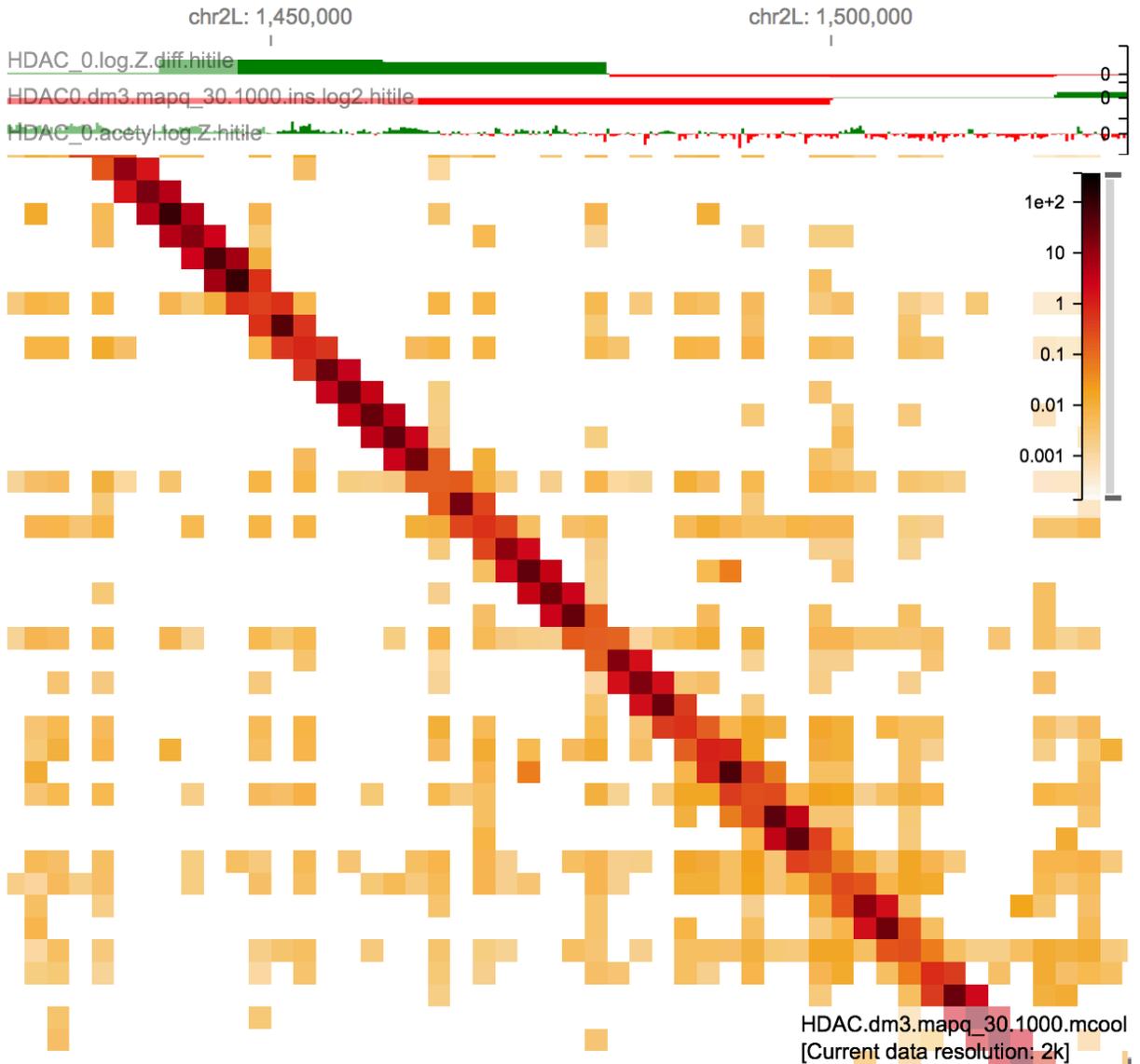
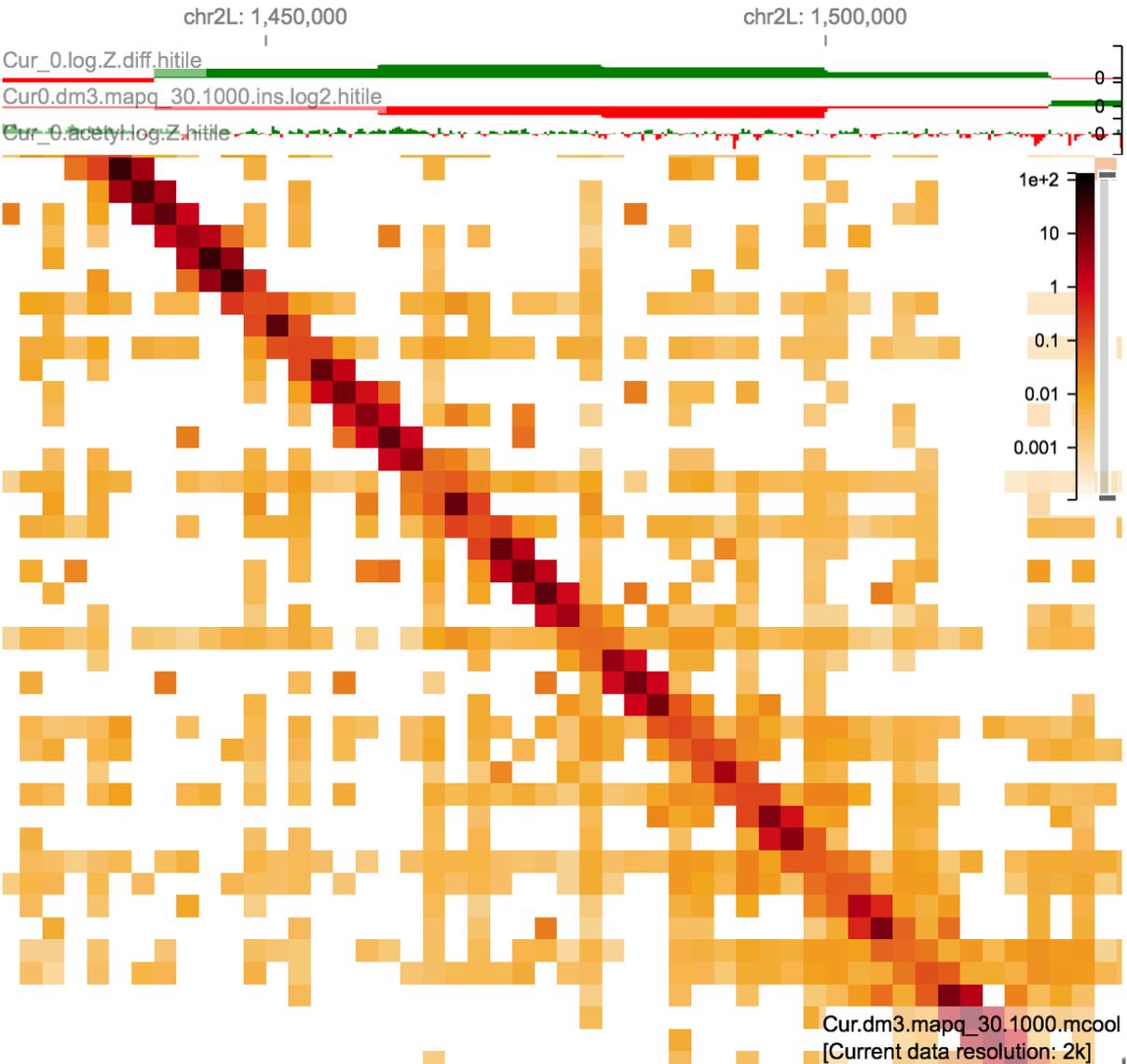
Results

MD system parameters:

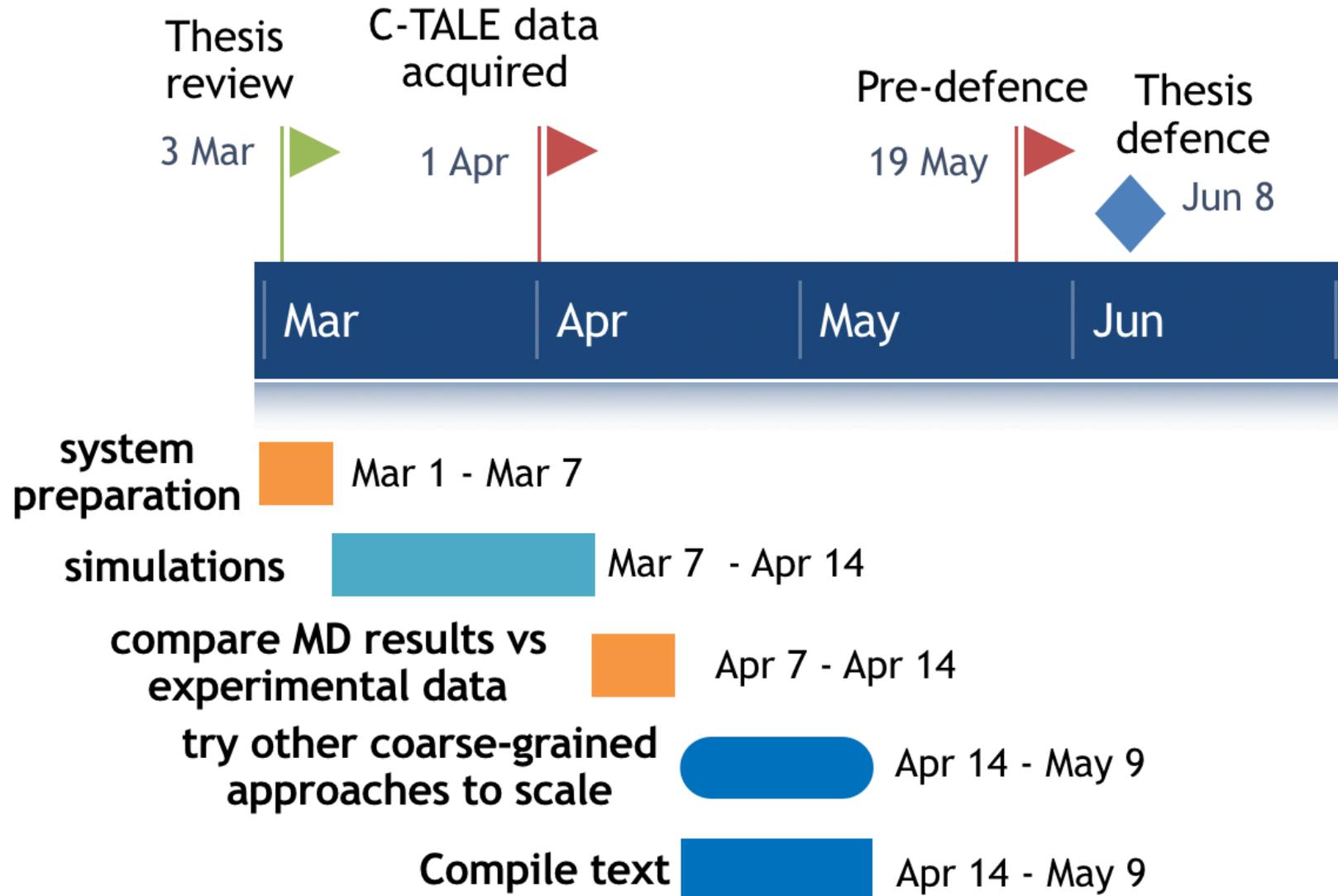


- Linker length 35 to 95 bp
- Energy minimization: steepest descent gradient method 10000 steps with POSRED constraints
- Equilibration 100 ps with positional restraints of 500 kJ/mol/A² and 0.5 fs time step
- Equilibration 200 ps with positional restraints of 50 kJ/mol/A²
- Equilibration 200 ps with positional restraints of 5 kJ/mol/A²
- Equilibration 200 ps with positional restraints of 0.5 kJ/mol/A²
- Main run duration 50 000 000 steps = 1 microsecond

Results



Plans



Computational time evaluation

	baseline system	Zhang, 2017	Kameda, 2019
simulation	70 ns	100 ns	100 ns
actual time	~ 4 days		

~ 17 ns/day

less than ~20 days in total

Analysis metrics

Method	Resolution	Metric to measure acetylation effect
Hi-C	5 - 20 kbp	chromatin density - insulation score for 3 cases
C-TALE	expected higher than Hi-C	chromatin density - insulation score for 3 cases
Coarse-grained modelling	near-atomic	C-alpha RMSD H4 tail - acidic patch binding

MD analysis metrics

- Center mass of nucleosomes distance
- Linker length geometry dependance
- Angles, rotation
- Histone tails - acidic patch binding
- Electrostatic charge distribution

Conclusions

Multiscale validation of acetylation effect on chromatin structure

- Coarse-grained modelling
- Analysis of the modelling results
- Comparison of modelling results vs Hi-C and C-TALE

Estimation of specific acetylation sites contribution into chromatin spatial organisation

- Baseline - no acetylation
- H4K16
- H3K9, 14, 18, 23, 27, H4K5, 8, 12

Acknowledgements

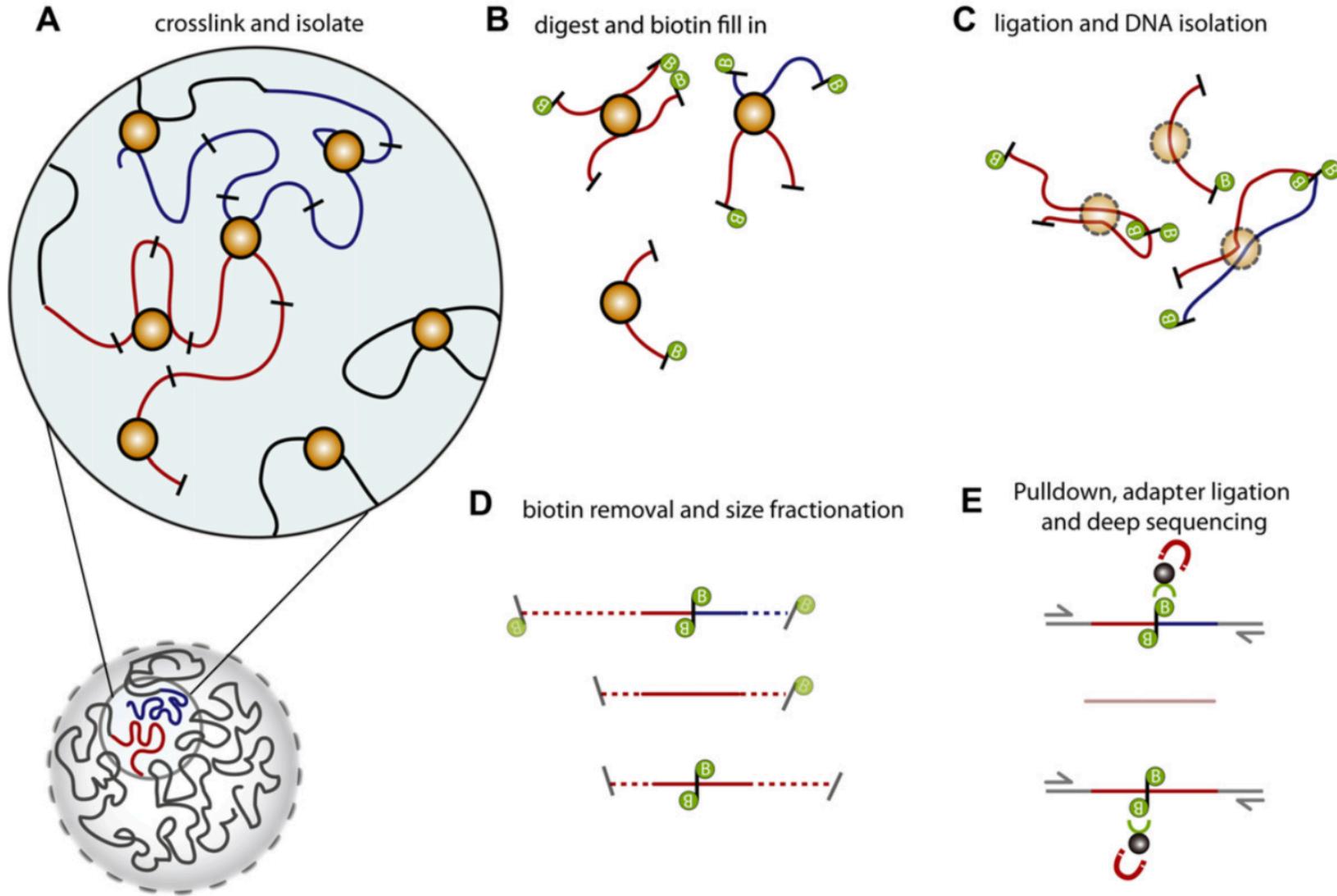
Alexey Shaytan, MSU, Leading Researcher

Grigoriy Armeev, MSU, PhD

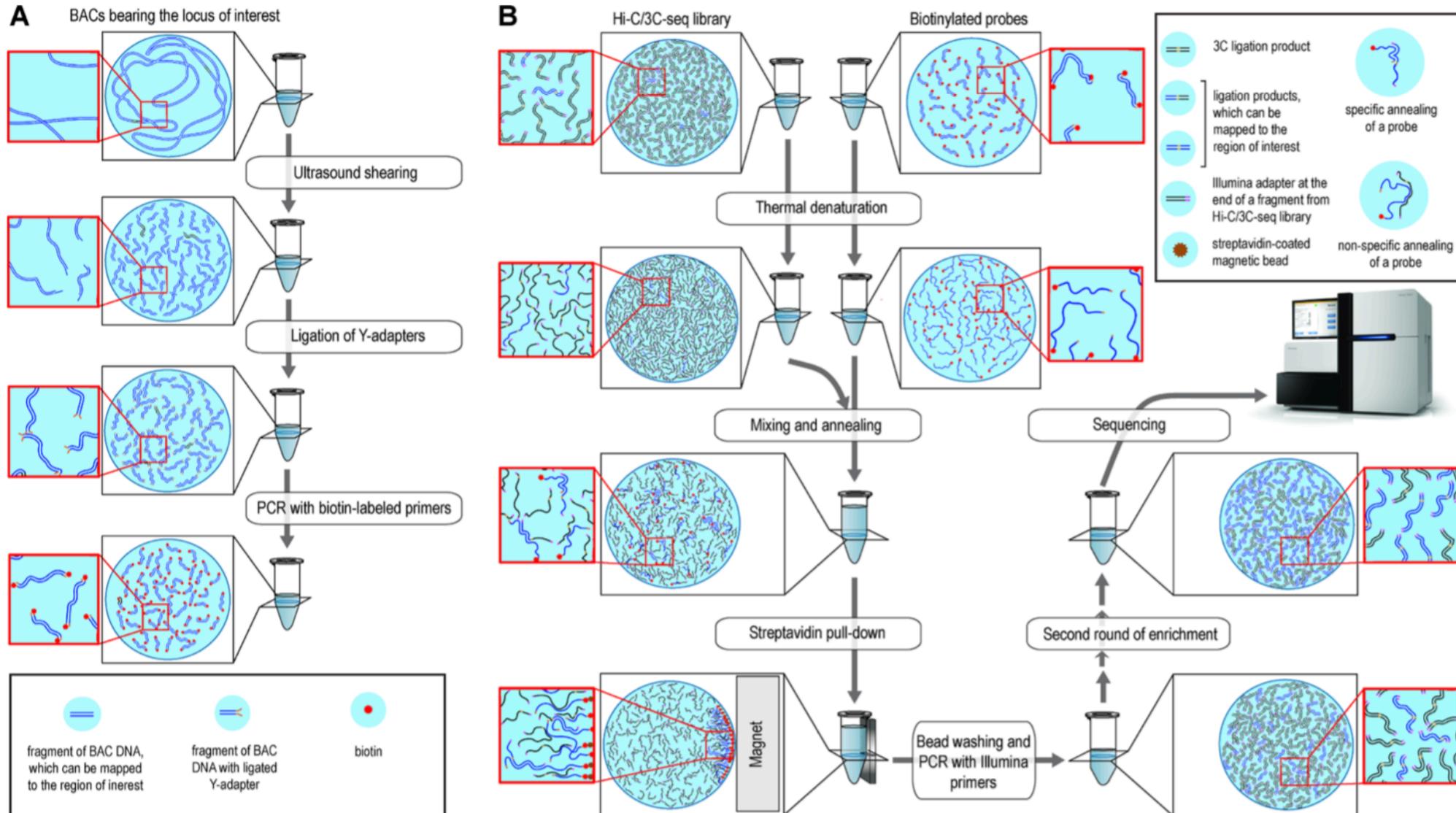
Victoria Kobets, Skoltech, PhD

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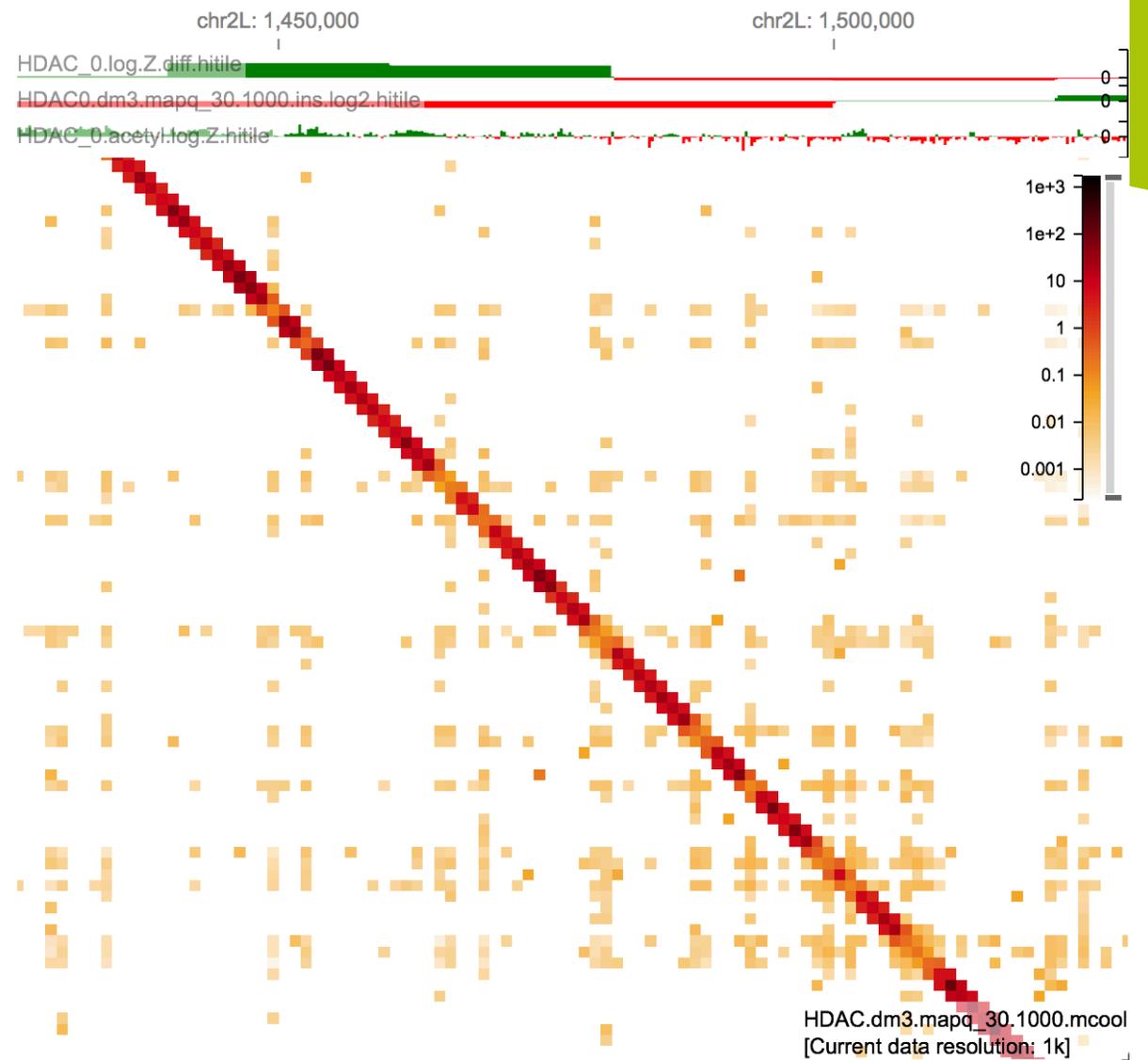
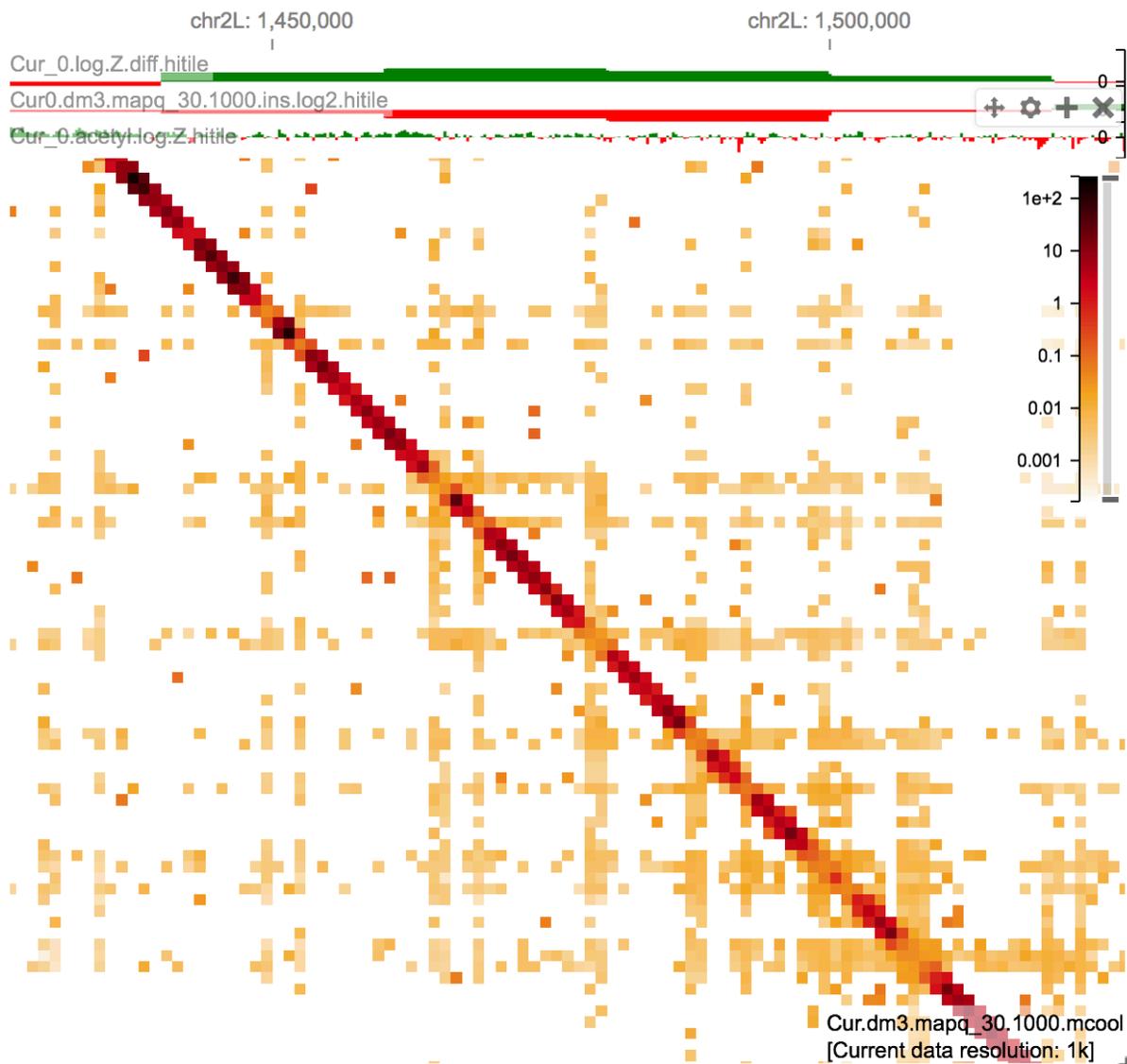
Hi-C protocol



C-TALE



Discussion of results 1k



Discussion of results 5k

