Expanding the boundaries of DNA crystal simulations

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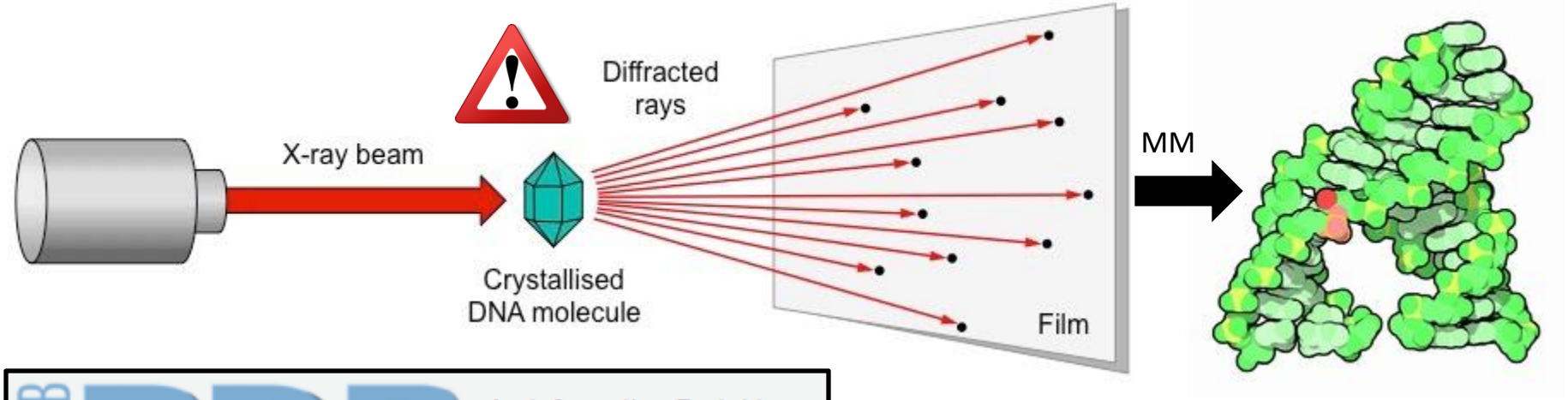
X-ray cristallography

The golden standard for 3D structure determination



RCSB PDB PROTEIN DATA BANK

An Information Portal to 133920 Biological Macromolecular Structures

- X-ray (119876)
- Solution NMR (11894)
- Electron Microscopy (1726)
- Hybrid (109)
- Solid-State NMR (93)
- Electron Crystallography (70)
- Neutron Diffraction (58)
- Fiber Diffraction (38)
- Solution Scattering (32)

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Communication

Radiation Damage and Racemic Protein Crystallography Reveal the Unique Structure of the GASA/Snakin Protein Superfamily

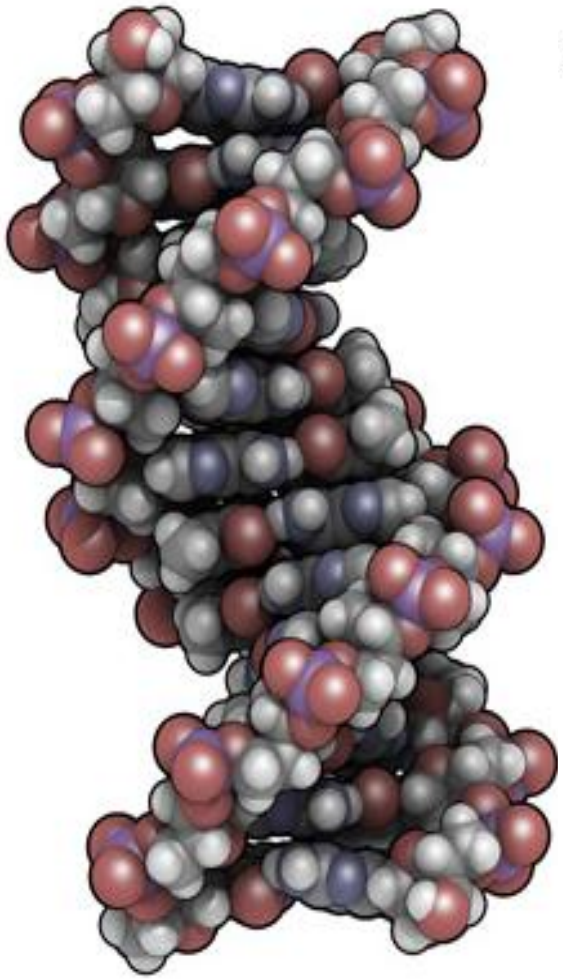
Ho Yeung, Dr. Christopher J. Squire, Yuliana Yosaatmadja, Dr. Santosh Panjikar, Gemma López, Prof. Dr. Antonio Molina, Prof. Dr. Edward N. Baker, Dr. Paul W. R. Harris, Prof. Dr. Margaret A. Brimble

First published: 4 May 2016 Full publication history

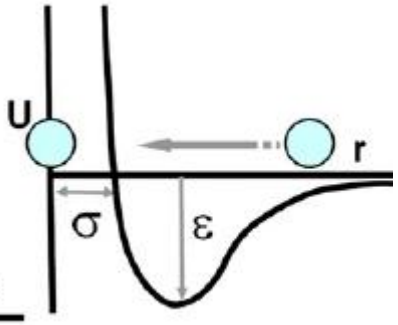
DOI: 10.1002/anie.201602719 View/save citation

480 different crystallization conditions

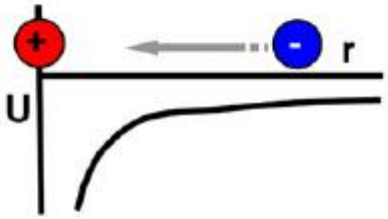
Representing molecules with a ball-and-spring approximation



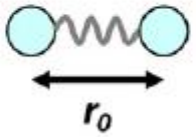
$$U = \sum_{i<j} \sum 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$



$$+ \sum_{i<j} \sum \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

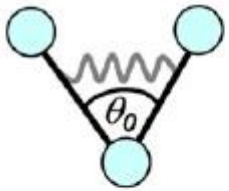


$$+ \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2$$

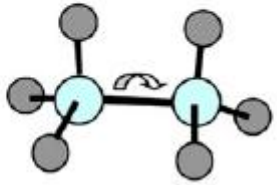


Classical Force field

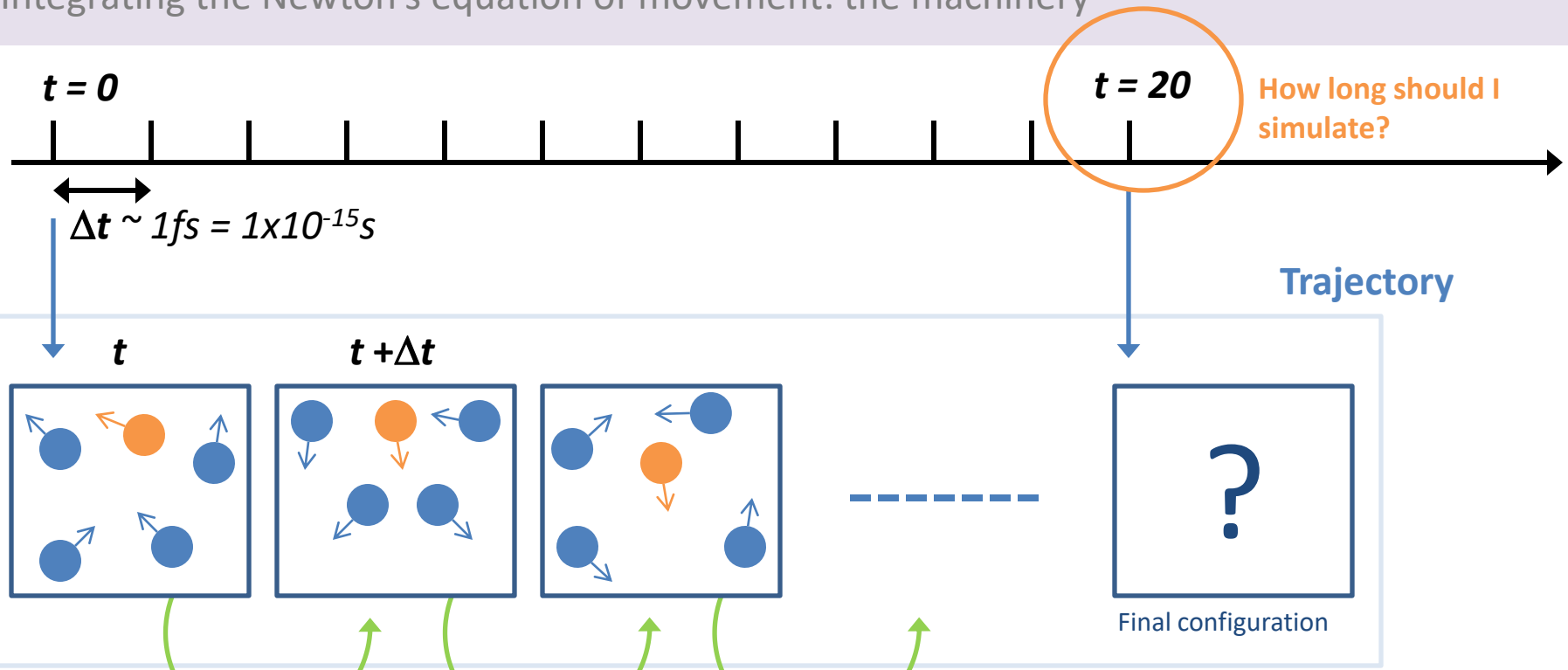
$$+ \sum_{angles} \frac{1}{2} k_a (\theta - \theta_0)^2$$



$$+ \sum_{torsions} k_\phi [1 + \cos(n\phi - \delta)]$$



Integrating the Newton's equation of movement: the machinery



$$f_{x,j}(R(t)) = -\frac{\partial U(R(t))}{\partial x_j}$$

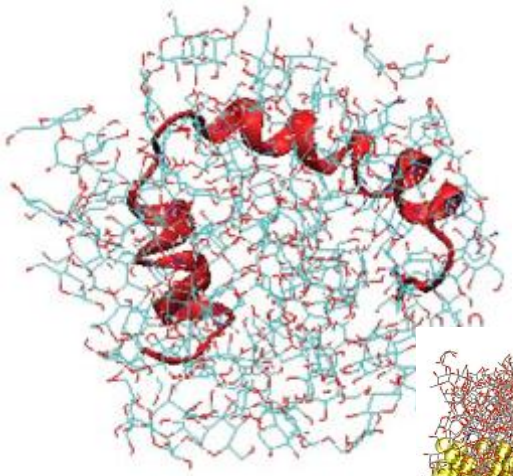
$$x_j(t+\Delta t) \approx 2x(t) - x(t-\Delta t) + \frac{f_{x,j}(t)}{m}\Delta t^2$$

$$U = \sum_{bonds} k_b \left(r_{ij} - r_{eq}\right)^2 + \sum_{angles} k_\theta \left(\theta - \theta_{eq}\right)^2 +$$

$$\sum_{dihedrals} \frac{V_k}{2}\left[1 + \cos\left(n_k\varphi - \gamma_k^{eq}\right)\right] +$$

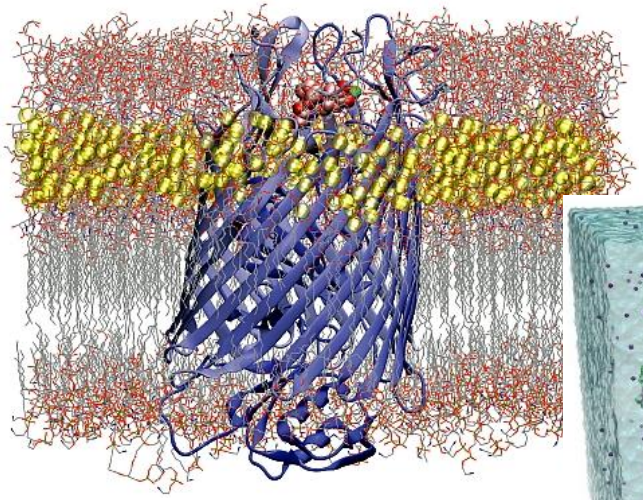
$$\sum_{l}^{N}\sum_{l>m}^{N}\left\{4\varepsilon\left[\left(\frac{\sigma}{r_{lm}}\right)^{12} - \left(\frac{\sigma}{r_{lm}}\right)^{6}\right] + \frac{q_l q_m}{\in r_{lm}}\right\}$$

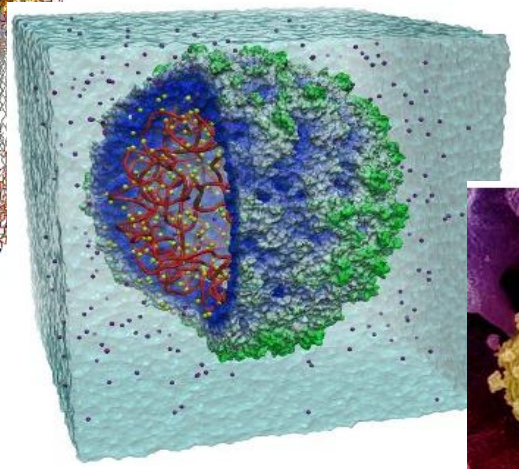
Biomolecular Simulations: A matter of size… (1/2)



Small peptides
~ 1.000 atoms

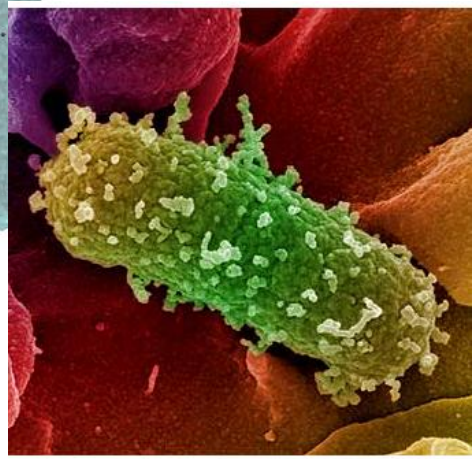
Macromolecular complexes
~ 50.000 to ~ 1.000.000 atoms



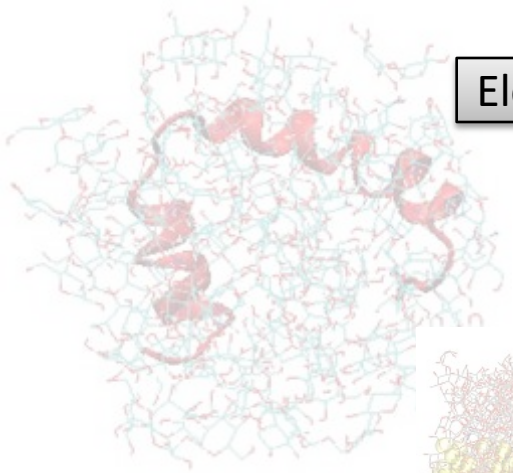


Virus
several millions of atoms

Bacteria/cells?
7e+9 carbon atoms



Biomolecular Simulations: And a matter of time! (2/2)



Small molecules
~ 1.000 atoms

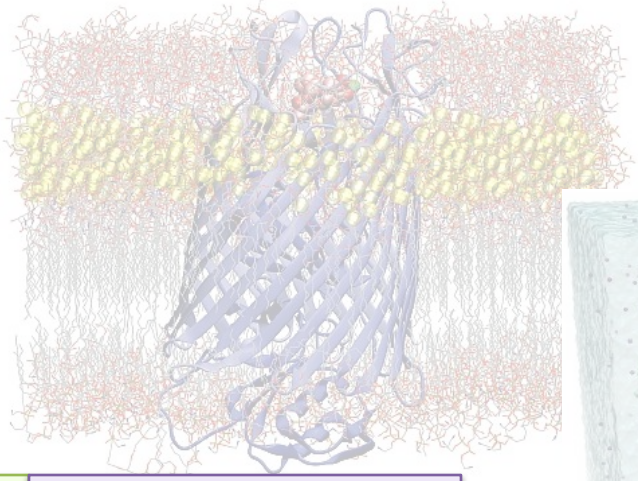
fs — Electronic exitations

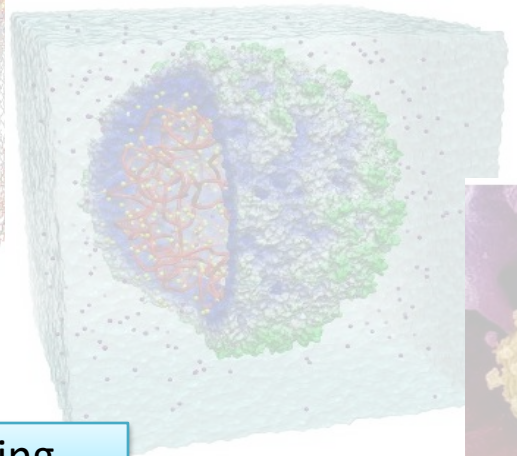
100 fs - ps — Vibrations

μs — Rotations

ms — Conformational Transitions

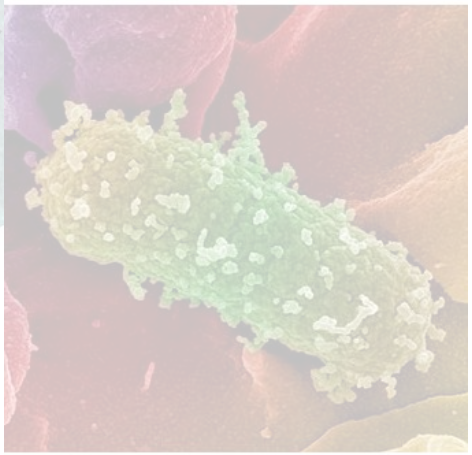
Macromolecular complexes
~ 50.000 to ~ 1.000.000 atoms





Virus
several millions of atoms

Bacteria/cells?
7e+9 carbon atoms



ps — e-tranfer reactions

ps — Enzymatic reactions

ns — Peptide folding

μs - s — Protein folding

μs — DNA melting

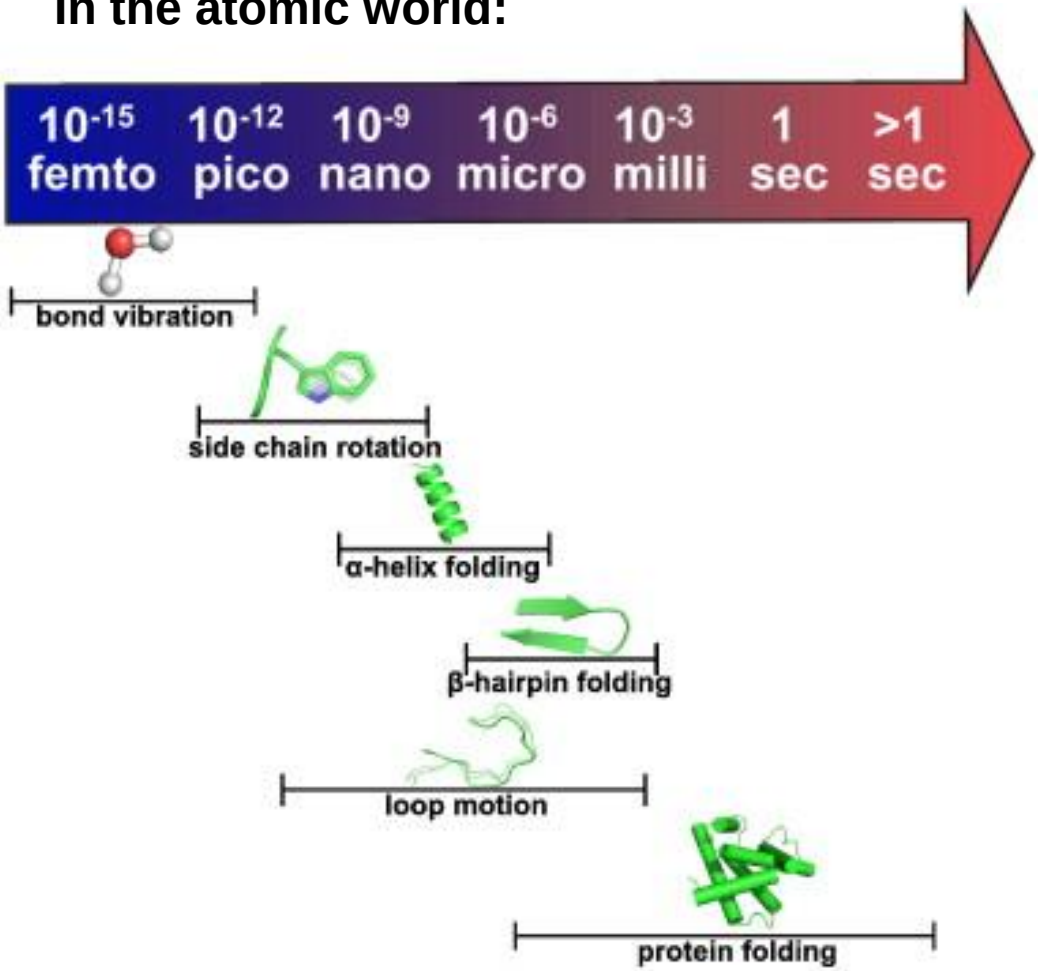
Molecular Dynamics: limitations

How long should I simulate? = What do I want to see?

How much should I wait if I expect to see:

- A rainy day in March? One week
- A hurricane? One year
- A glaciation? Hundreds of years

In the atomic world:



Werner et al. Adv Drug Deliv Rev. ***2012****, 64: 323.*

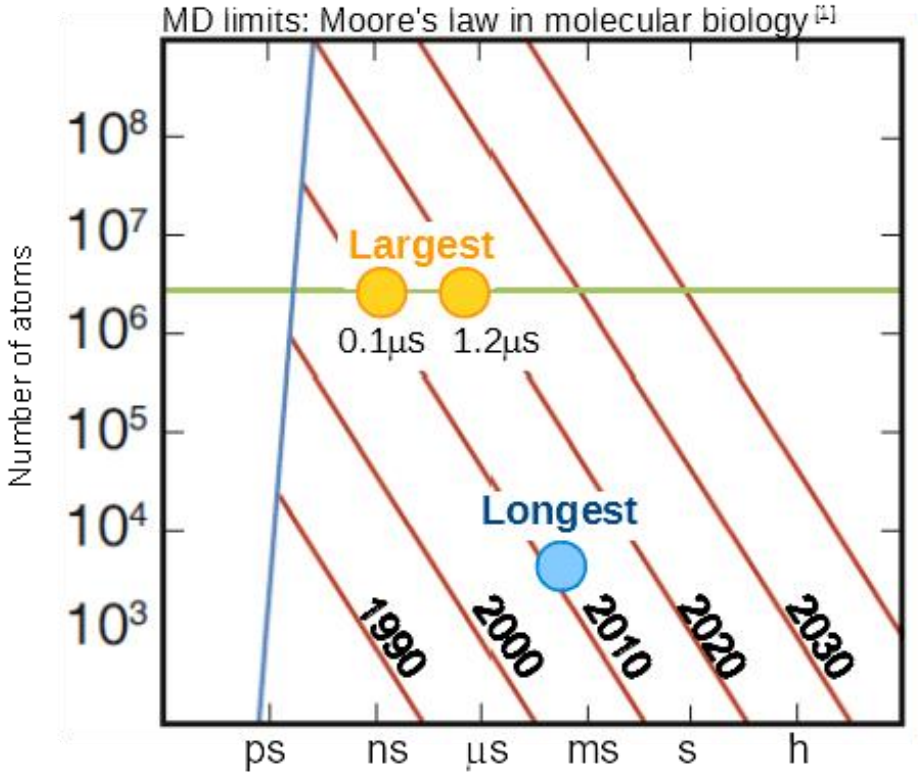
Molecular Dynamics: limitations

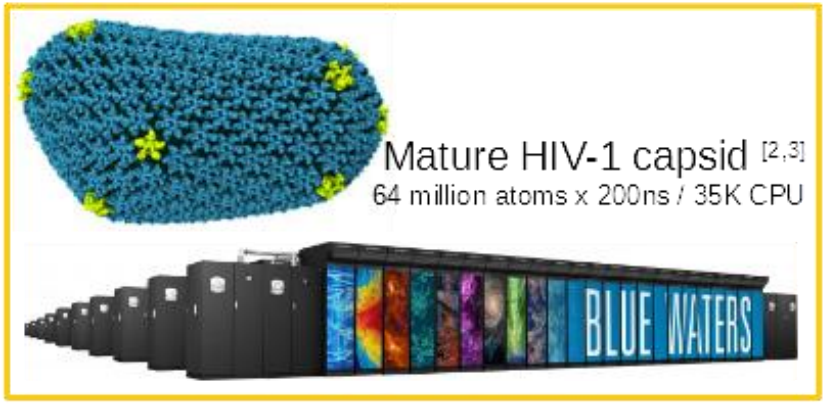
Dr. Evil
University of Bad Guys, Evil Island,
Somewhere in the Pacific

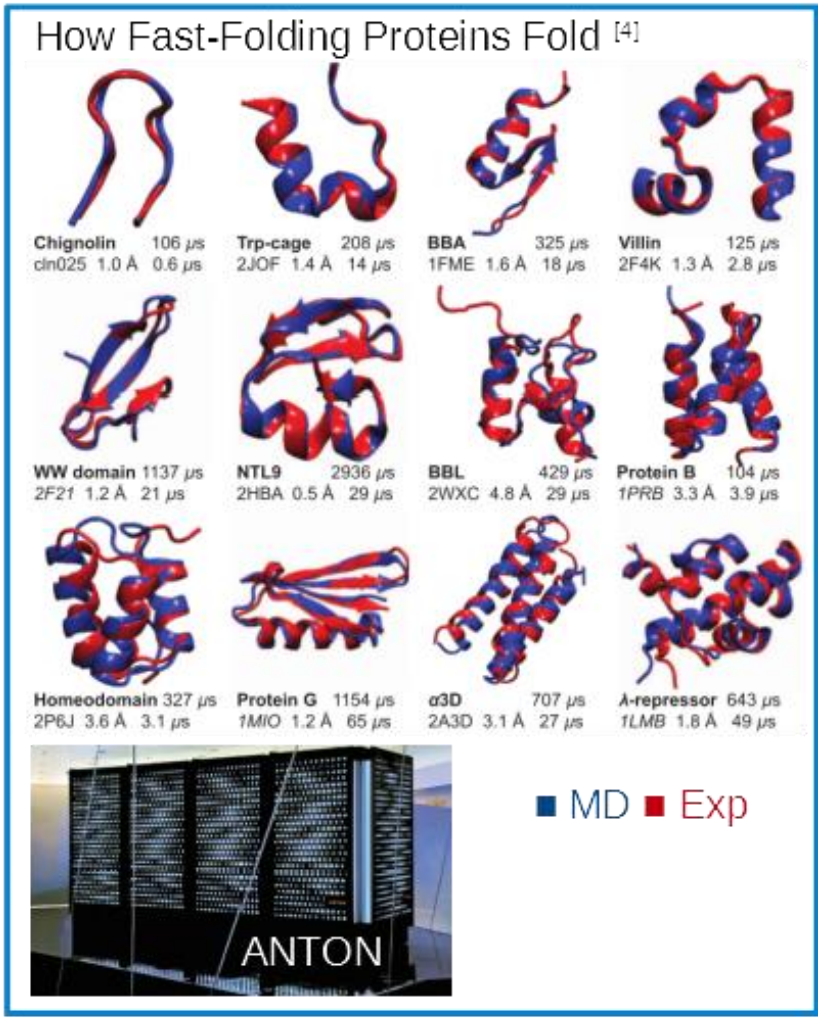
Catching up with experiments is a matter of "time"...

Computational power and time vs cost

Catching up with experiments is a matter of “time”…







[1] Vendruscolo M. *Curr Biol.* **2011**,21:R68-70.
[2] Zhao G,..., Schulten K,... *Nature.* **2013**,497:643-646.
[3] Perilla JR, Schulten K. *Nat. Comm.* **2017**
[4] Lindorff-Larsen K,...,Shaw DE. *Science.* **2011**,334:517-520.

µABC: a systematic microsecond molecular dynamics study of tetranucleotide sequence effects in B-DNA

Marco Pasi, John H. Maddocks ✉, David Beveridge, Thomas C. Bishop, David A. Case, Thomas Cheatham, III, Pablo D. Dans, B. Jayaram, Filip Lankas, Charles Laughton ... Show more

Nucleic Acids Research, Volume 42, Issue 19, 29 October 2014, Pages 12272–12283, https://doi.org/10.1093/nar/gku855
Published: 26 September 2014 **Article history** ▾

2014

39 sequences of 18 bp
Multi-microsecond timescale
~50 µs / ~50K atoms

2016

1 sequence of 12 bp in 15 different conditions
Multi-microsecond timescale
~100 µs / ~30K atoms

Long-timescale dynamics of the Drew–Dickerson dodecamer

Pablo D. Dans, Linda Danilāne, Ivan Ivani, Tomáš Dršata, Filip Lankaš, Adam Hospital, Jürgen Walther, Ricard Illa Pujagut, Federica Battistini, Josep Lluis Gelpí ... Show more

Nucleic Acids Research, Volume 44, Issue 9, 19 May 2016, Pages 4052–4066, https://doi.org/10.1093/nar/gkw264
Published: 15 April 2016 **Article history** ▾

Assessing the Current State of Amber Force Field Modifications for DNA

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2016

1 seq. of 12 bp
100 x 10 µs / ~30K atoms

The latest and more complete study of DNA crystal simulations

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

All-atom crystal simulations of DNA and RNA duplexes☆

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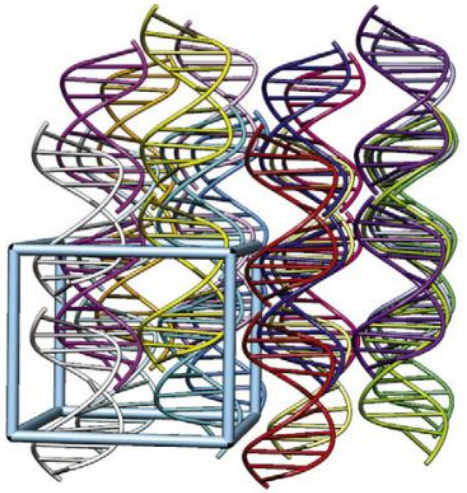
ABSTRACT

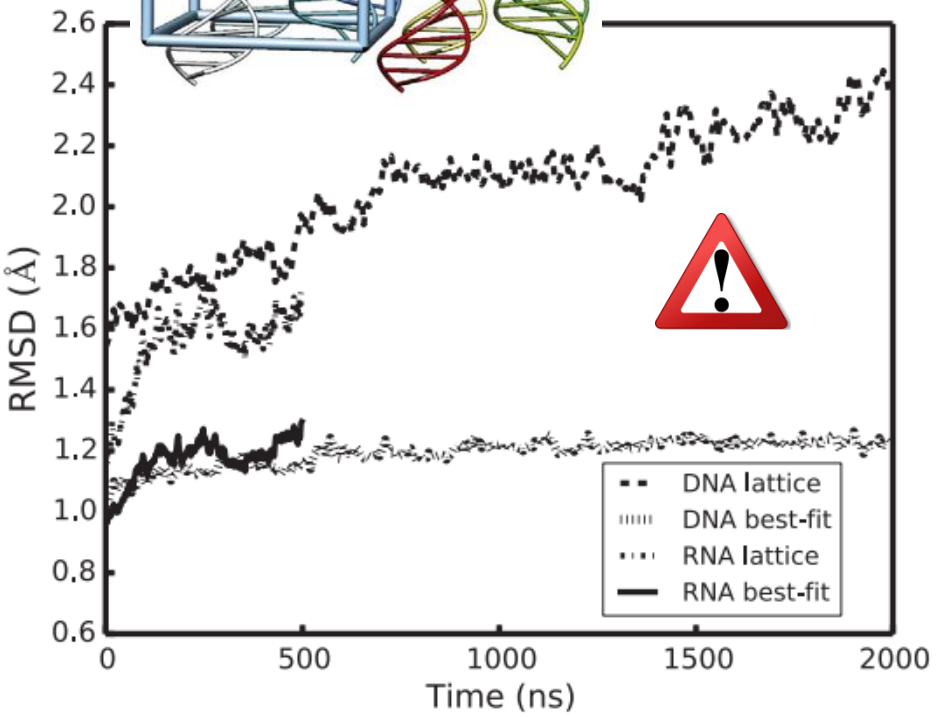
Background: Molecular dynamics simulations can complement experimental measures dynamics of biomolecules. The quality of such simulations can be tested by comparisons t against experimental crystallographic data.
Methods: We report simulations of DNA and RNA duplexes in their crystalline environment. mimic the conditions for PDB entries 1D23 [d(CGATCGATCG)2] and 1RNA [(UUAUAUAUAUAUA 8 unit cells, each with 4 copies of the Watson–Crick duplex; this yields in aggregate 64 μs of du DNA and 16 μs for RNA.
Results: The duplex structures conform much more closely to the average structure seen in th structures extracted from a solution simulation with the same force field. Sequence-depend helical parameters, and in groove widths, are largely maintained in the crystal structure, but a in solution. However, the integrity of the crystal lattice is slowly degraded in both simulation that the interfaces between chains become heterogeneous. This problem is more severe for which has fewer inter-chain hydrogen bond contacts than does the RNA crystal.
Conclusions: Crystal simulations using current force fields reproduce many features of observed but suffer from a gradual degradation of the integrity of the crystal lattice.
General significance: The results offer insights into force-field simulations that test their ability interactions between chains, which will be of importance also in non-crystalline applications tha and recognition.
This article is part of a Special Issue entitled Recent developments of molecular dynamics.

1. Introduction

RNA and DNA molecules play an important role in many biological processes, and an understanding of their structure and dynamics is indispensable for a complete understanding of their function. Molecular dynamics simulations can offer a detailed complement to experiment, and nucleic acid simulations in a crystal environment have long been used to test simulation methods [1,2]. A "modern" era began in the more closely resembles the experimental crystal stru simulations in a solution environment. Subsequent studie lattice employed longer time scales and different force broadly similar conclusions [8–13]. Advances in comput spurred a new round of biomolecular crystal simulati proteins [14–21]), that use larger simulation cells and attention to the properties of the crystal lattice, as well as characteristics of individual chains.



1D23 (10 bp)
2 μs /
192K atoms

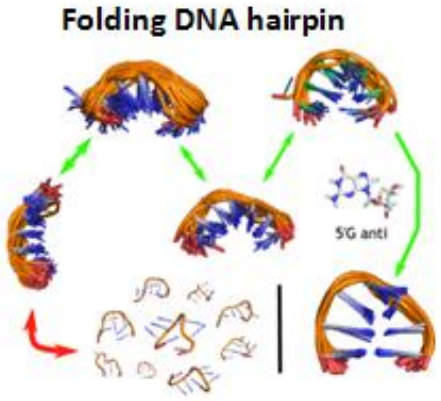


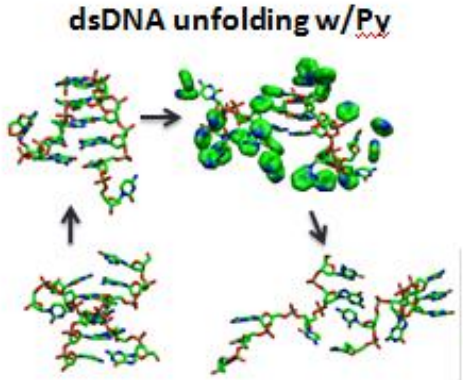
Conclusions: Crystal simulations using current force fields reproduce many features of observed crystal structures, but suffer from a gradual degradation of the integrity of the crystal lattice.

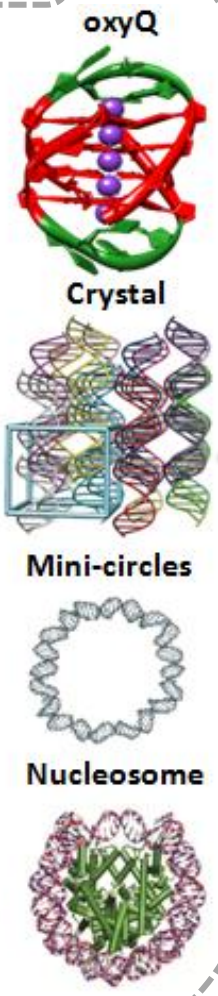
Refining the classical force field for DNA

From BSC0 (2007) to BSC1 (2016)

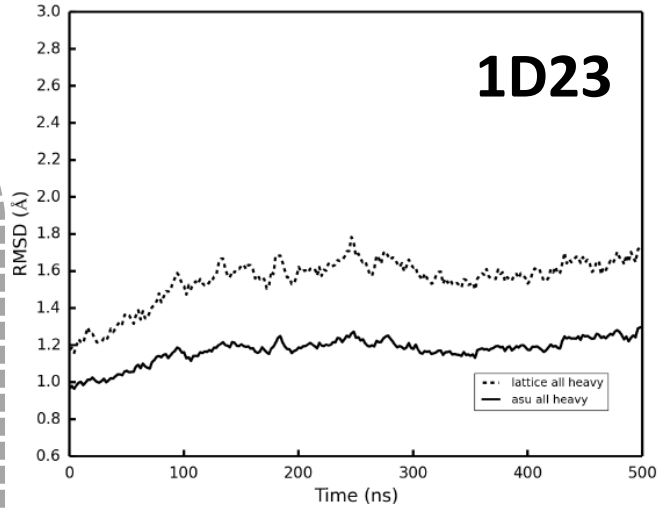
A new state-of-the-art
force field for DNA simulations PARMBSC1

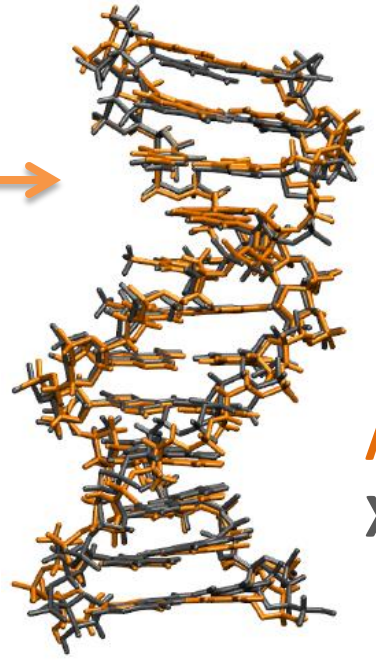






Ivani, Dans, et al. Nature Methods 2016

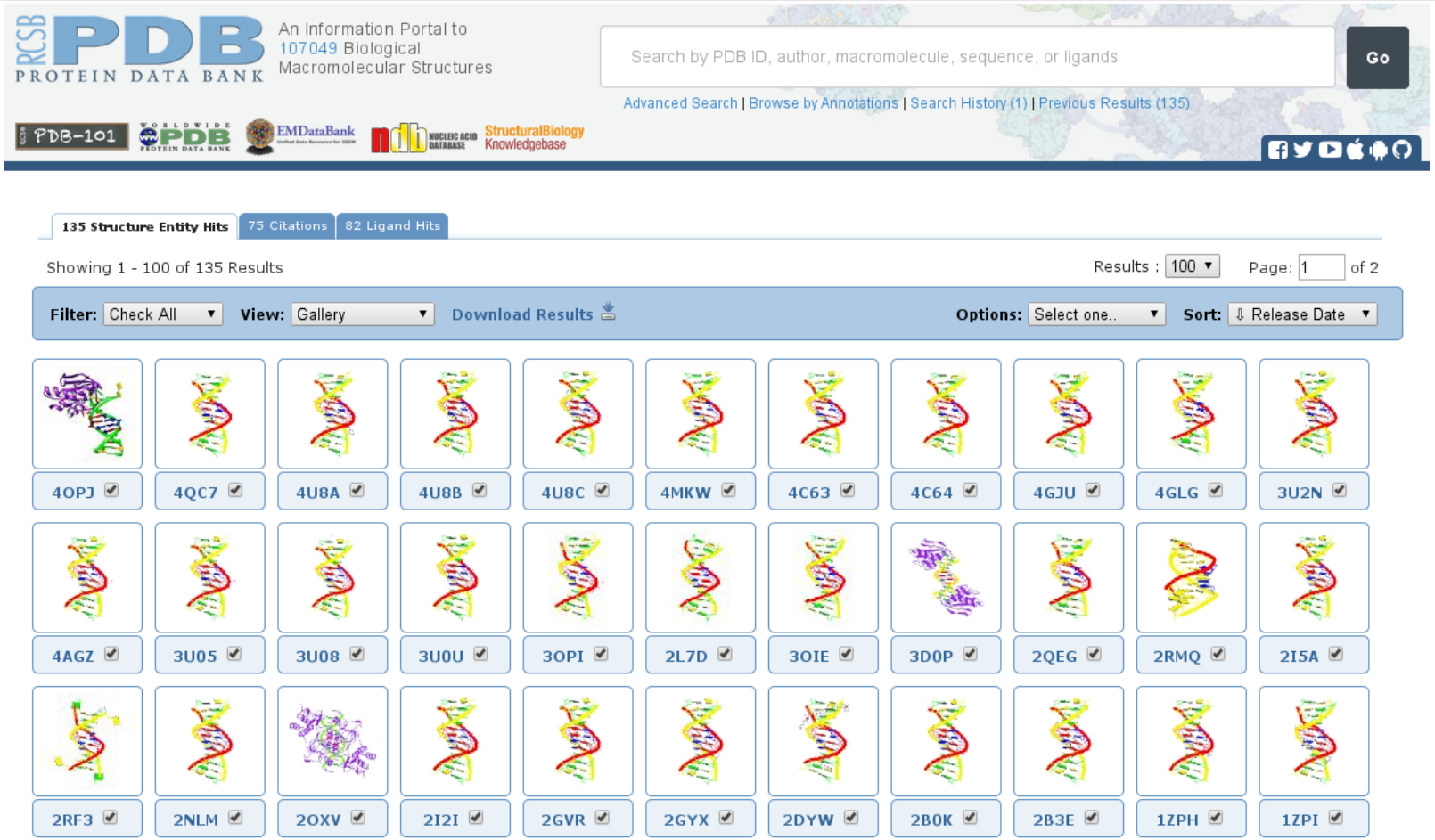




AVG/
X-ray

The paradigmatic Drew Dickerson Dodecamer

Three different space groups of the same sequence: CGCGAATTCGCG

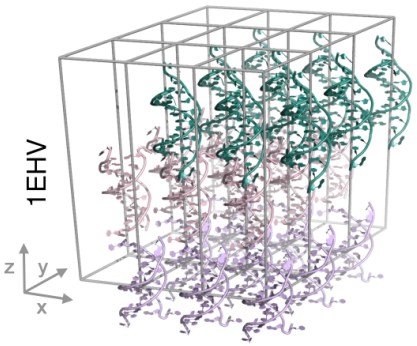


135 structures containing the DDD sequence in the PDB

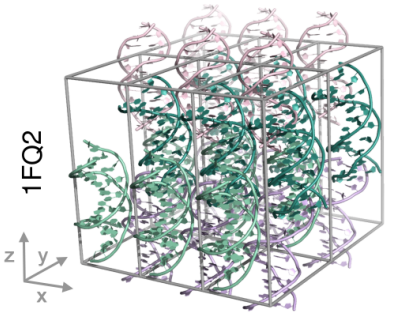
$P2_12_12_1$: 1FQ2 | $P3_221$: 1EHV | H3: 463D

Crystal simulation of DNA

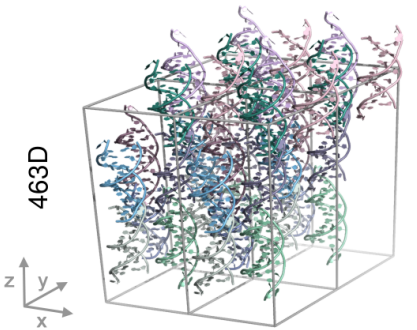
Extensive unbiased molecular dynamics simulations in the millisecond timescale



$P3_212$ - 3x3x1 cells



$P2_12_12_1$ - 3x2x1 cells



H3 - 2x2x1 cells

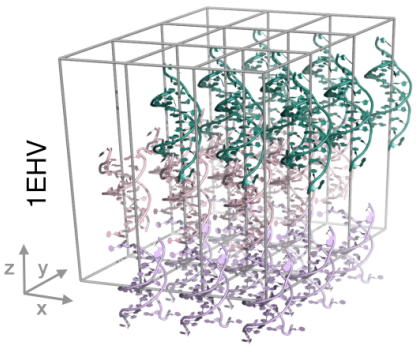
System name	PDB	Environment	Space group	Nº un cel			dsDNA to Spm ratio	Equilibration time (ps)	Simulation time (μs)
1EHV sol	1EHV	solution	---	---			/	600	1
15 mM	1EHV	crystal	$P3_212$	3x3x			/	600	1
200 mM	1EHV	crystal	$P3_212$	3x3x3		Na/KCl	200	/	600	1
400 mM	1EHV	crystal	$P3_212$	3x3x3		Na/KCl	400	/	600	4
600 mM	1EHV	crystal	$P3_212$	3x3x3	81	Na/KCl	600	/	600	1
800 mM	1EHV	crystal	$P3_212$	3x3x3	81	Na/KCl	800	/	600	1
1EHV Na/KCl	1EHV	crystal	$P3_212$	3x3x1	27	Na/KCl	400	/	600	4
1EHV Mg	1EHV	crystal	$P3_212$	3x3x1	27	$MgCl_2$	400	/	600	4
1EHV Mg CUFIX	1EHV	crystal	$P3_212$	3x3x1	27	$MgCl_2 \cdot 6H_2O$ CUFIX	400	/	600	4
1EHV 1:6	1EHV	crystal	$P3_212$	3x3x1	27	$SpmCl_4$	---	1:6	6000	1
1EHV 1:9	1EHV	crystal	$P3_212$	3x3x1	27	$SpmCl_4$	---	1:9	6000	1
1EHV 1:12	1EHV	crystal	$P3_212$	3x3x1	27	$SpmCl_4$	---	1:12	6000	1
1FQ2 sol	1FQ2	solution	---	---	1	Na/KCl	400	/	600	1
1FQ2 1:6 sol	1FQ2	solution	---	---	1	$SpmCl_4$	---	1:6	600	1
1FQ2 Na/KCl	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	Na/KCl	400	/	600	4
1FQ2 Na/KClequ	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	Na/KCl	400	/	6000	1
1FQ2 1:3	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	$SpmCl_4$	---	1:3	6000	1
1FQ2 1:6	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	$SpmCl_4$	---	1:6	6000	1
1FQ2 1:9	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	$SpmCl_4$	---	1:9	6000	1
1FQ2 1:9 CUFIX	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	$SpmCl_4$ CUFIX	---	1:9	6000	1
1FQ2 1:9 Mg	1FQ2	crystal	$P2_12_12_1$	3x2x1	24	$SpmCl_4$ + $MgCl_2 \cdot 6H_2O$	---			
463D sol			---	---	1	Na/KCl	40			
463D			H3	2x2x1	36	Na/KCl	40			

81 copies of DDD + water + ions ~ **1 million atoms**

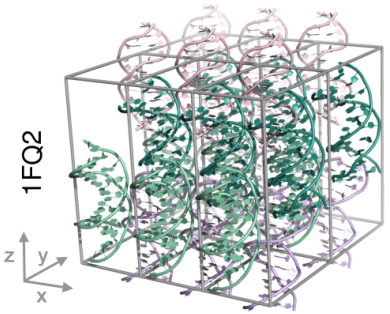
28 different systems

+ 40 μs Milisecond duplex dynamics

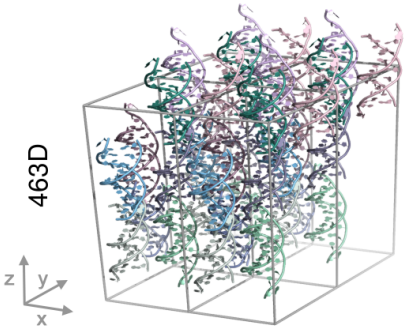
Molecular Dynamics: limitations



$P3_212$ - 3x3x1 cells



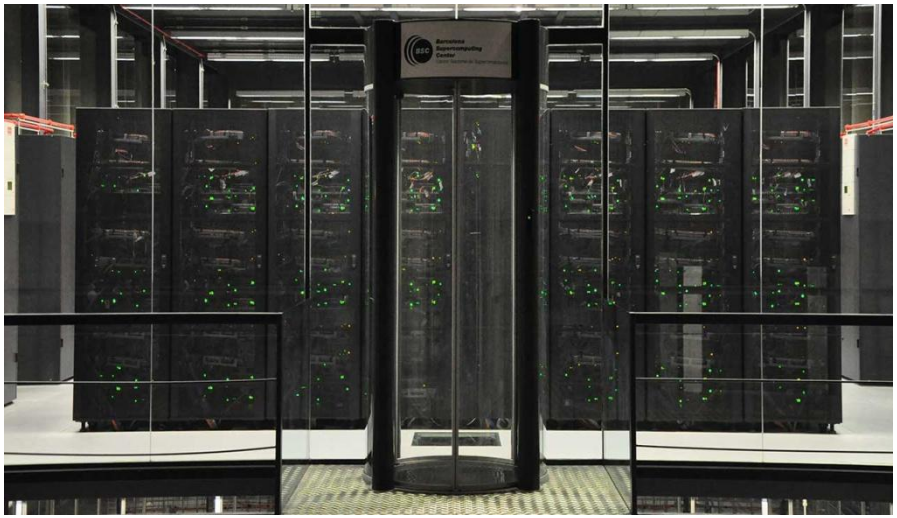
$P2_12_12_1$ - 3x2x1 cells



H3 - 2x2x1 cells

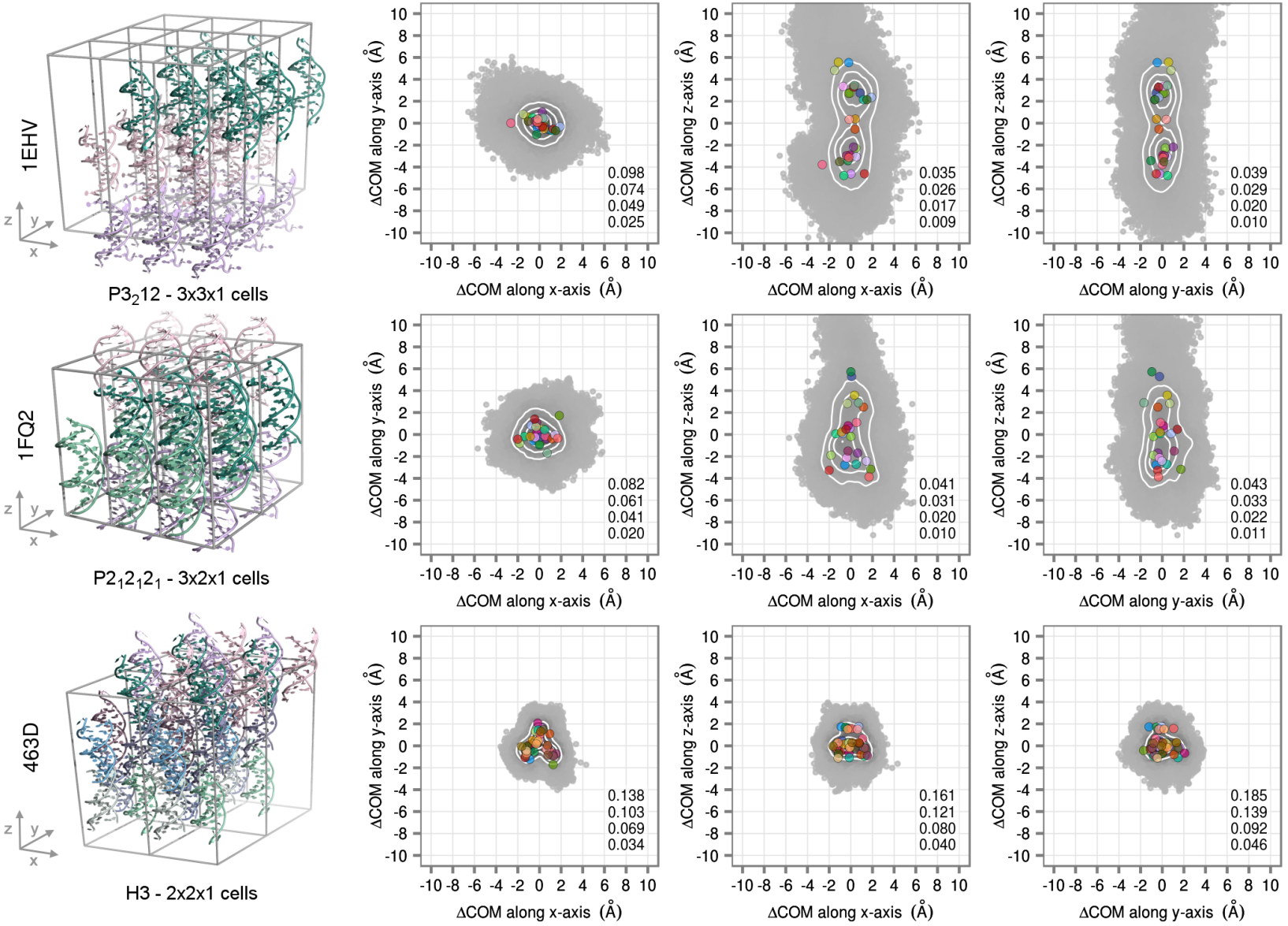
1EHV (81 copies of DDD): 512 cores, 7 runs, 72 h each
= 260,000 hs for 1 µs

1FQ2 (24 copies of DDD): 480 cores, 9 runs, 72 h each
= 300,000 hs for 4 µs

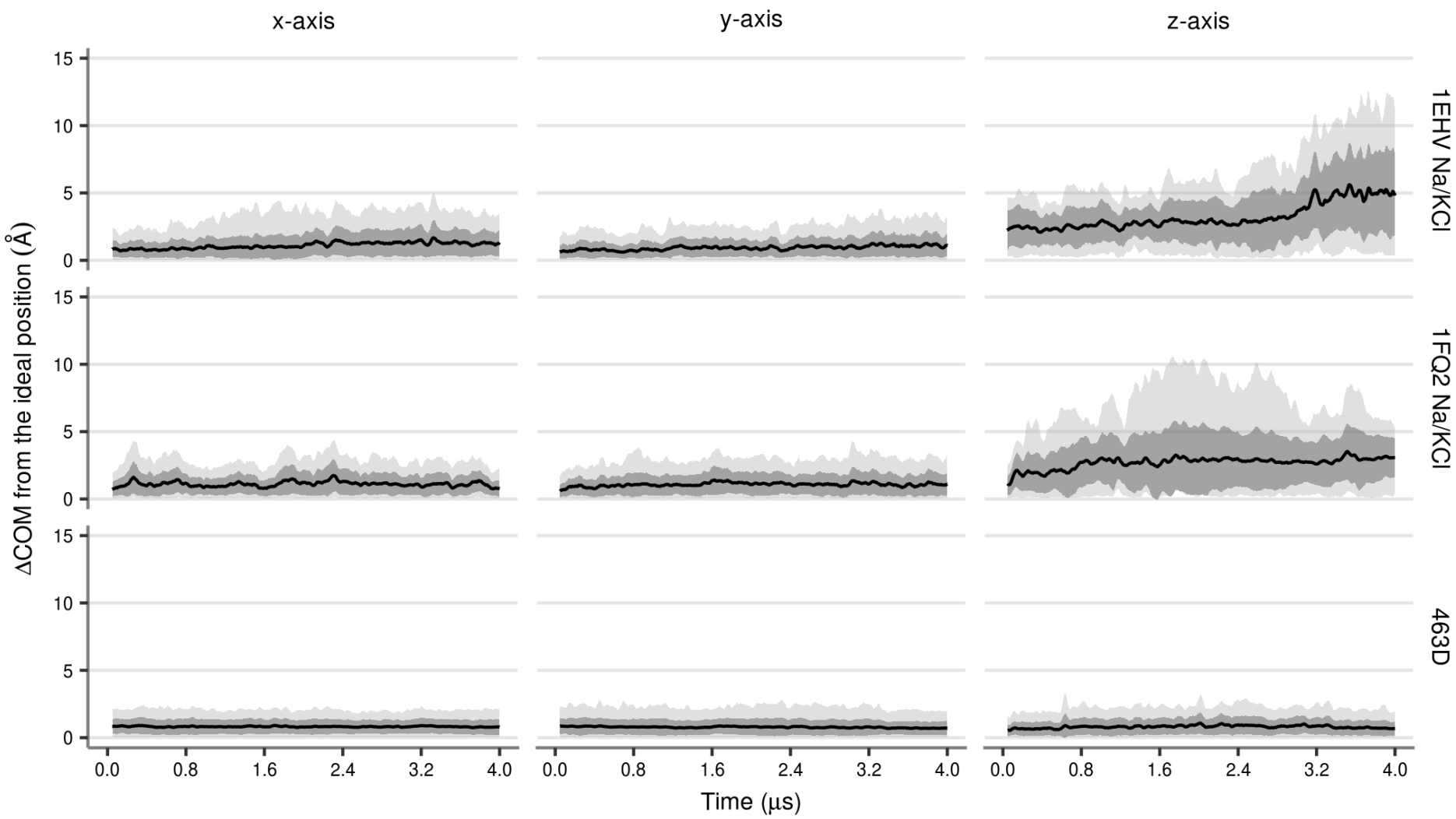


MareNostrum

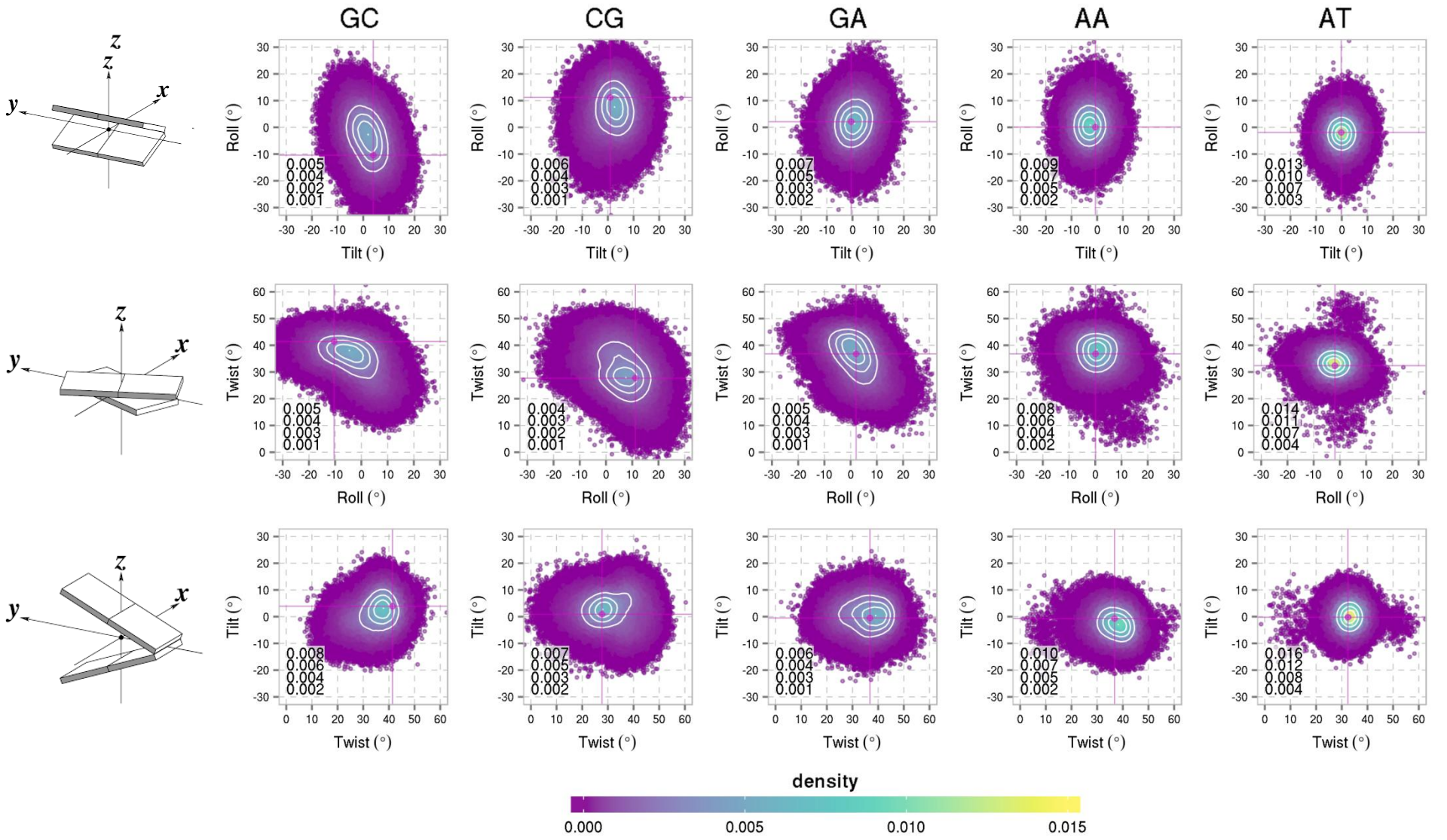
Results: Center of mass displacement



Results: Center of mass displacement along time

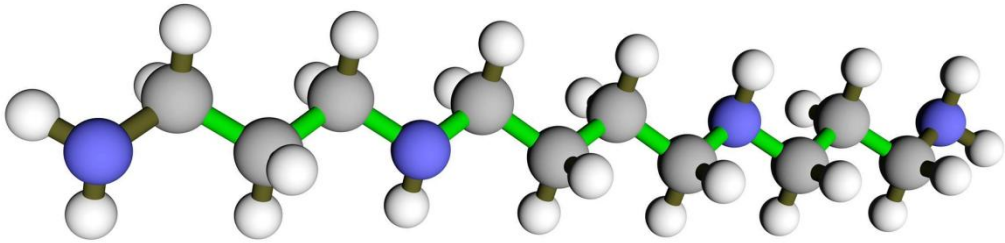


Results: Helical parameters of failed systems 1FQ2

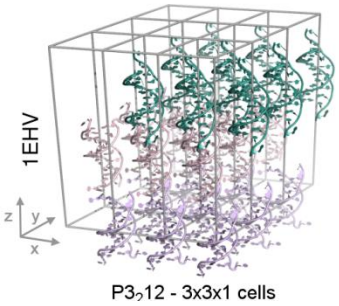


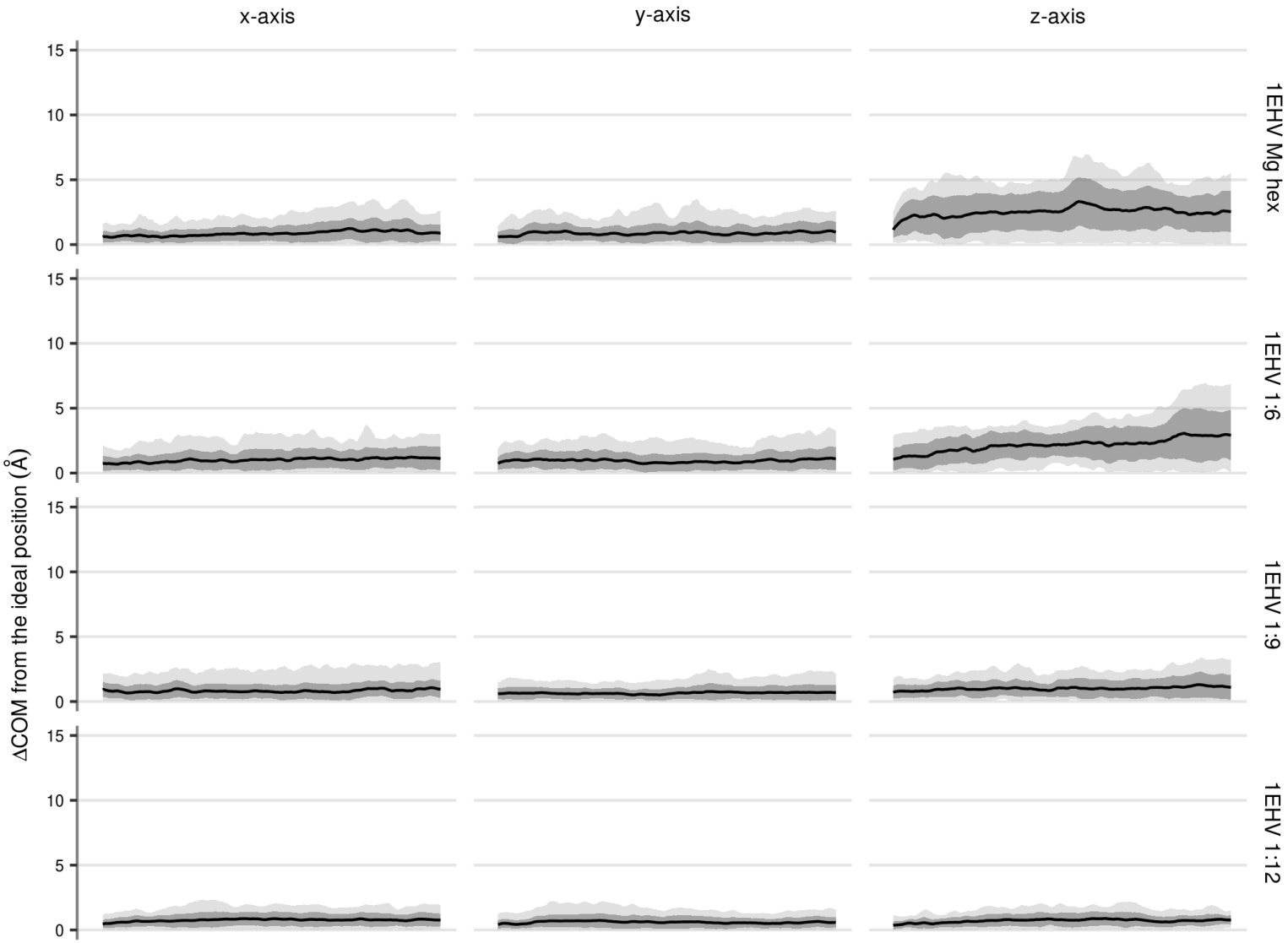
Learning from failure

I. Is this due to a specific space group not properly handled by MD simulations?
II. Is this due to the size (number of DNA copies) of the unit cell?
III. Is this due to internal pressure issues?
IV. Is this due to equilibration issues?
V. Is this due to the salt concentration?
VI. Is this an effect of the type of salt used?
VII. Is this due to distortions in the internal structure of the DNA molecules?
VIII. Is this due to ends artifacts (fraying, opening, stacking between DNA molecules)?
IX. Is this an effect of specific 3D orientations between DNA copies (packing, effect of unbalanced DNA-DNA interactions, etc)?
X. Is this fixed by adding small organic compounds present in the experimental buffer to the crystal simulations?

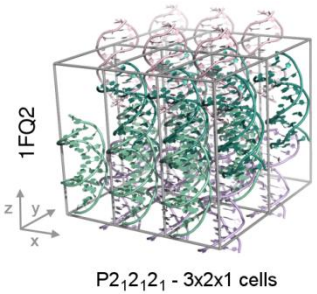


Results: Center of mass displacement using SPM for 1EHV

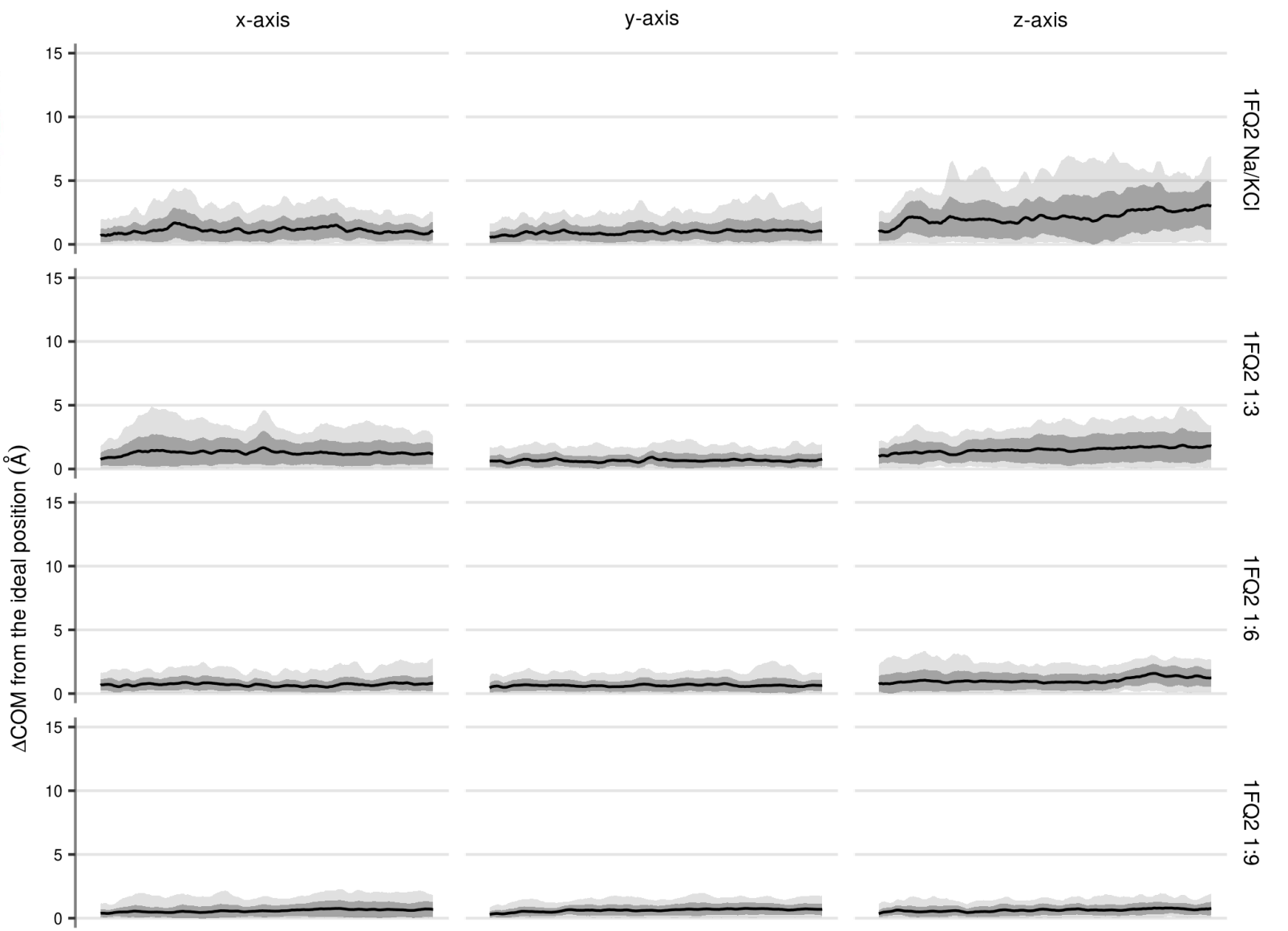




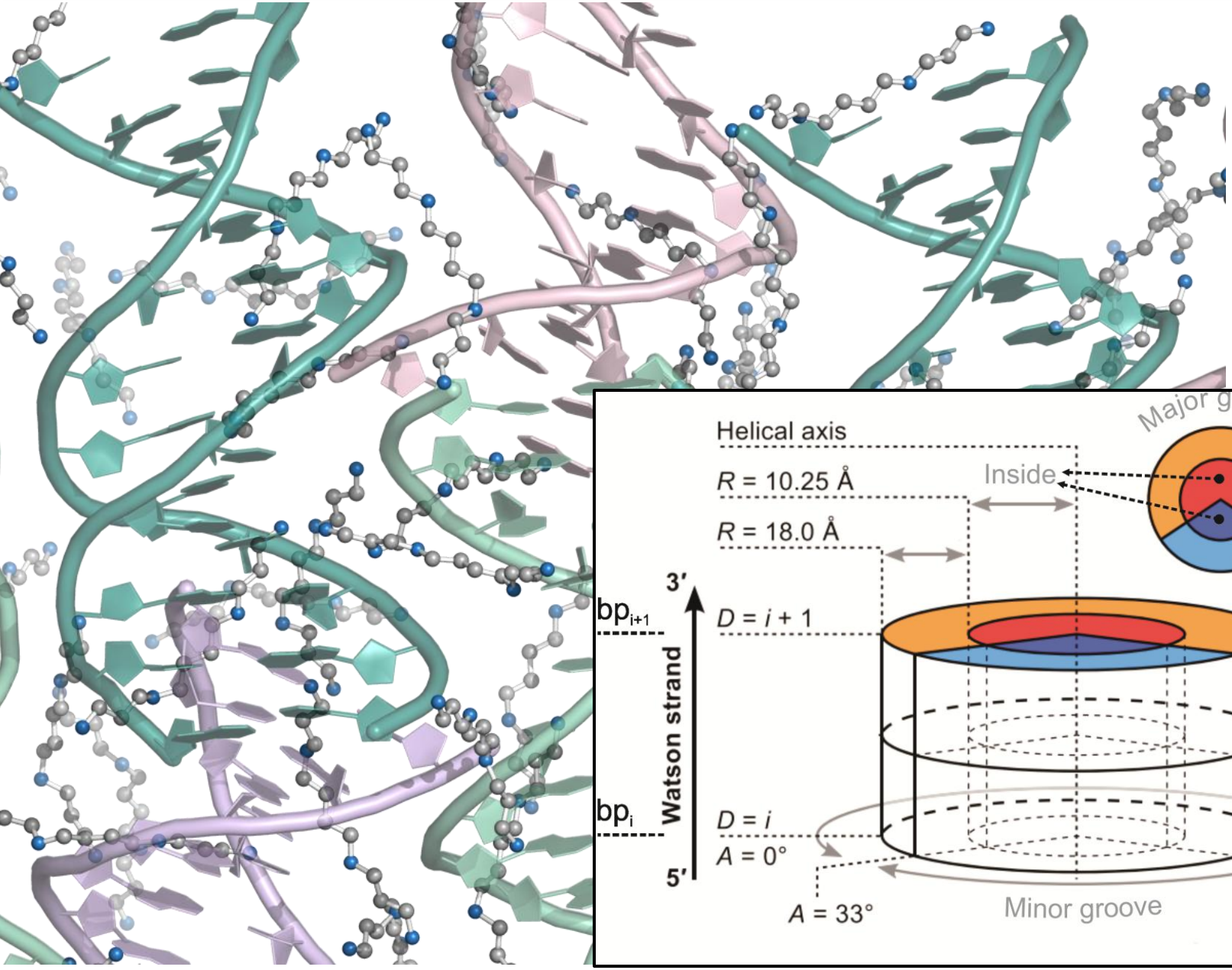
Results: Center of mass displacement using SPM for 1FQ2



$P2_12_12_1$ - 3x2x1 cells

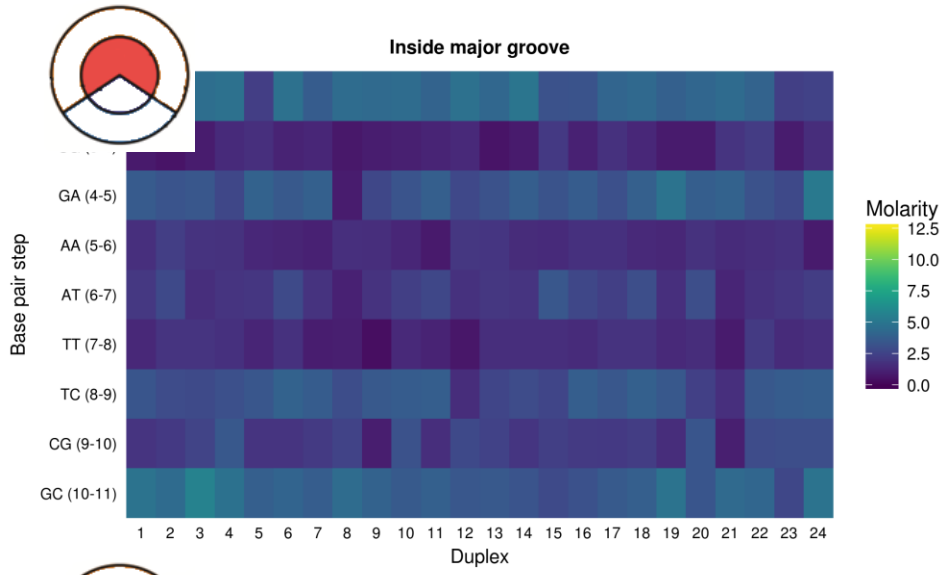


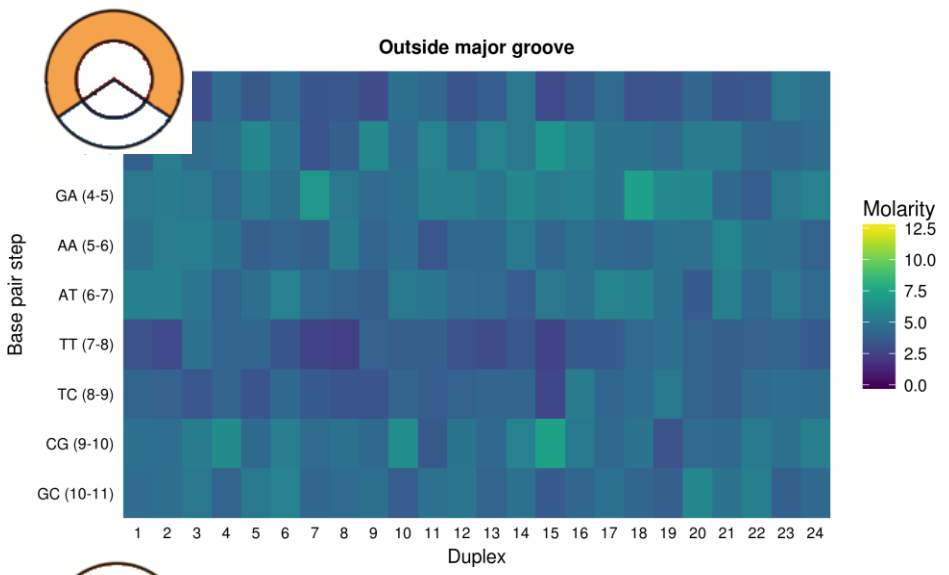
Biomolecular simulation of DNA crystals

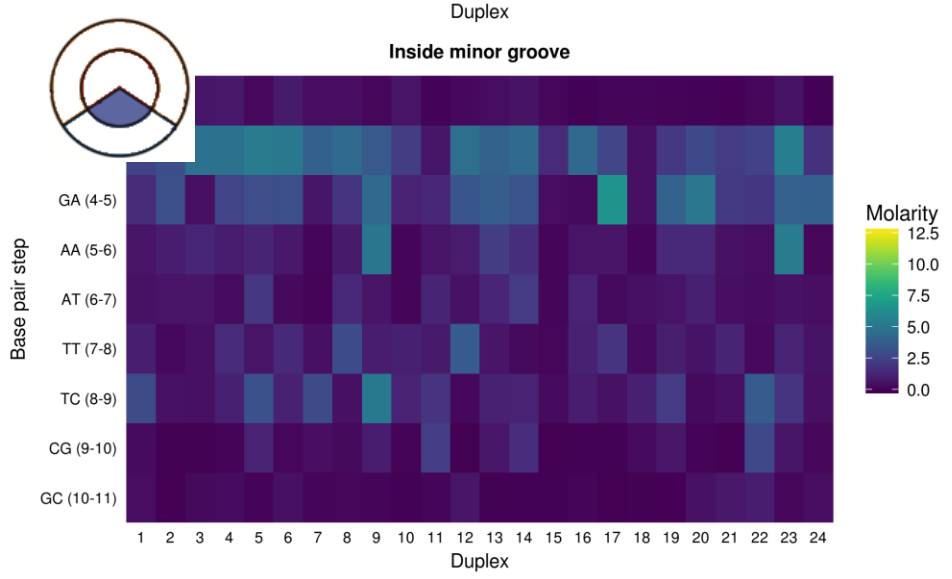


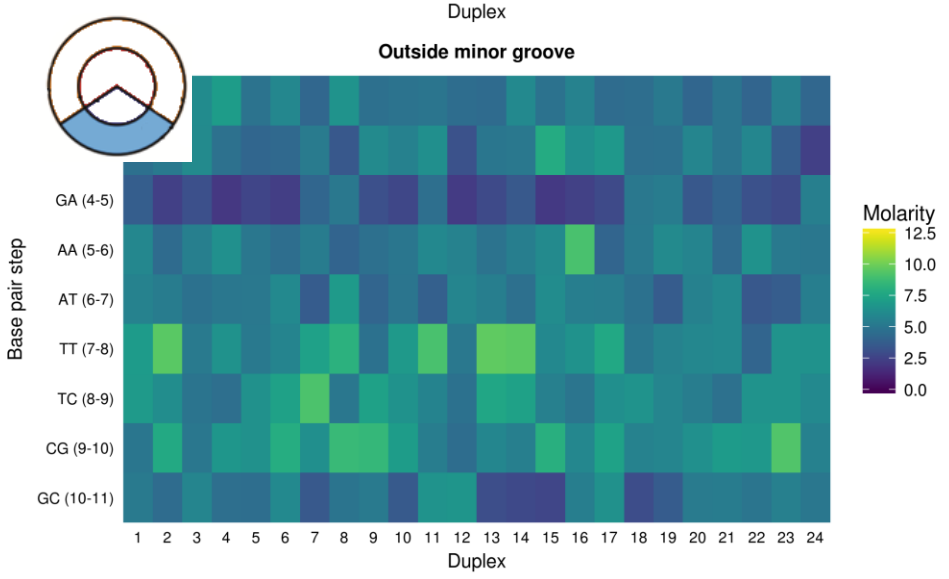
1FQ2

Average helical parameters along the sequence of 1FQ2

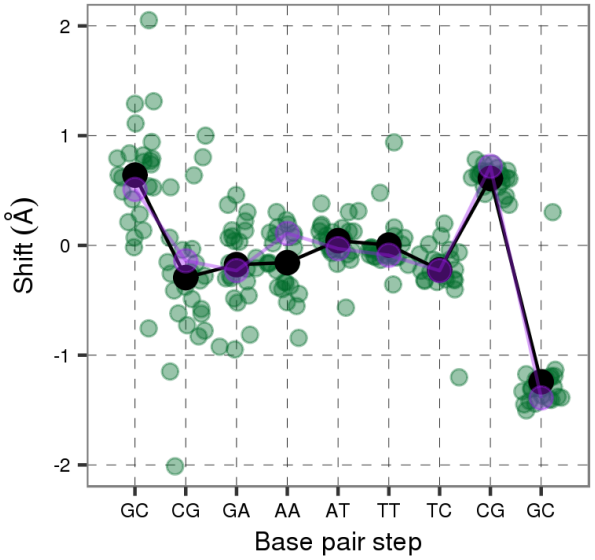


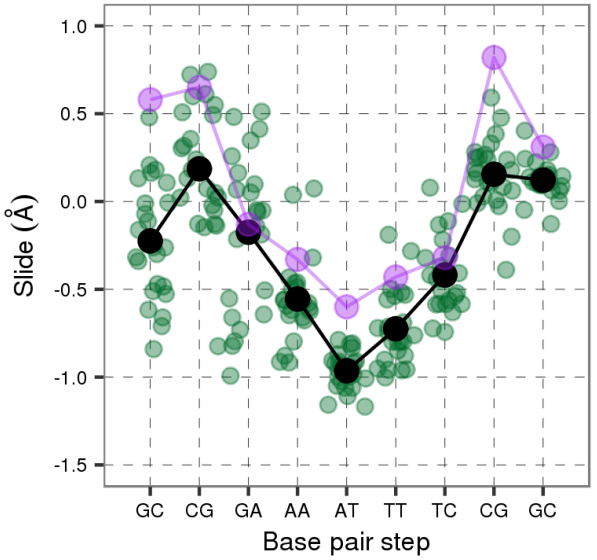


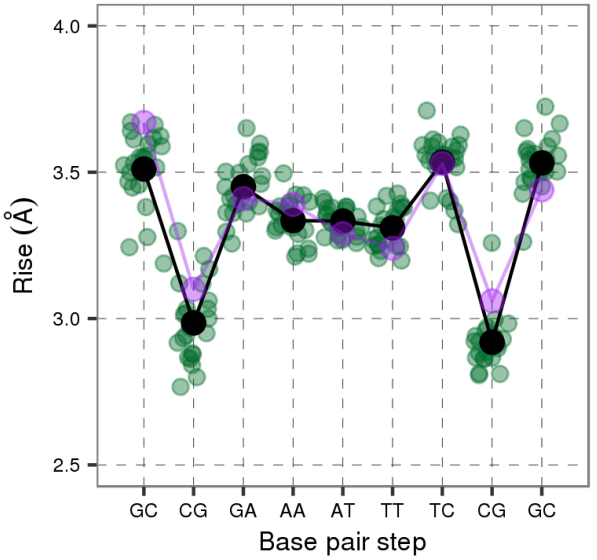


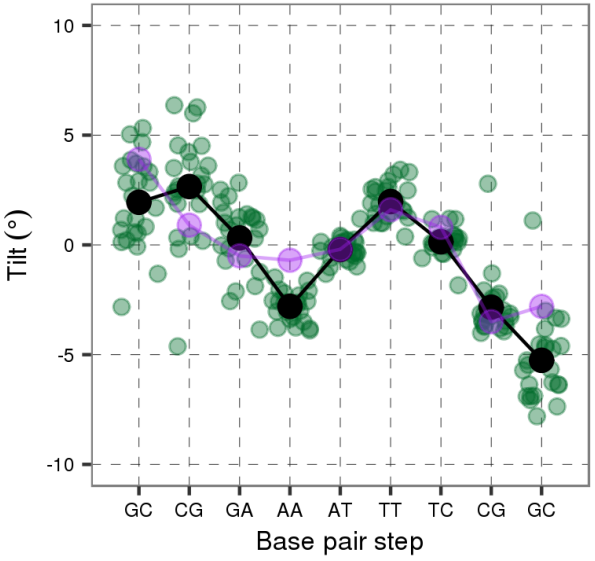


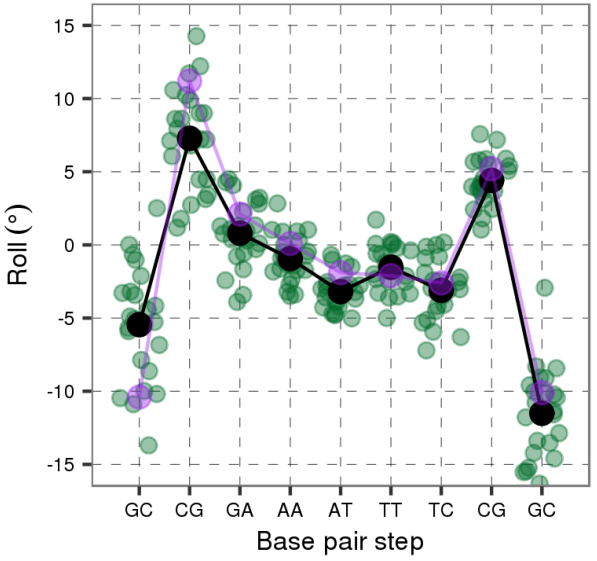
Average helical parameters along the sequence of 1FQ2

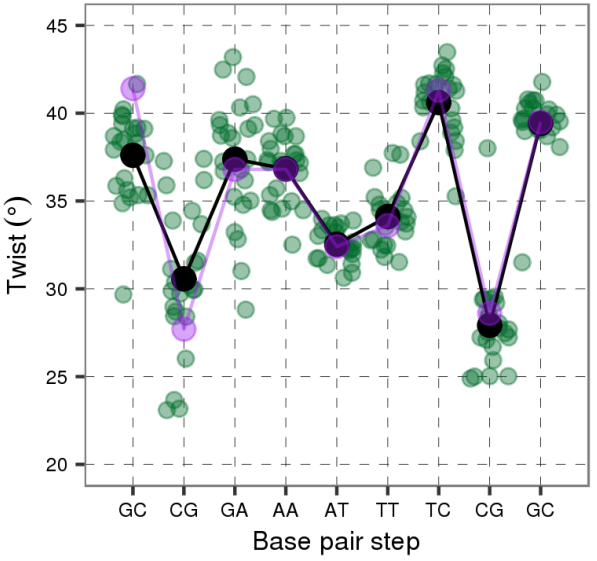




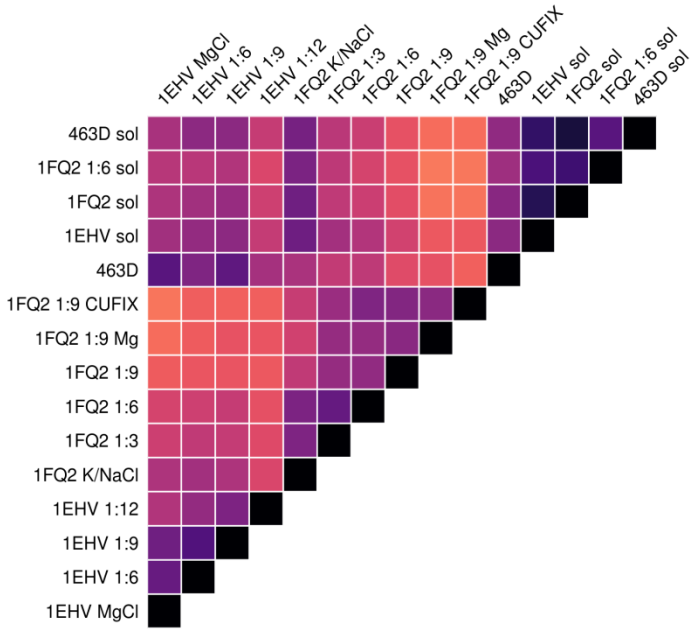




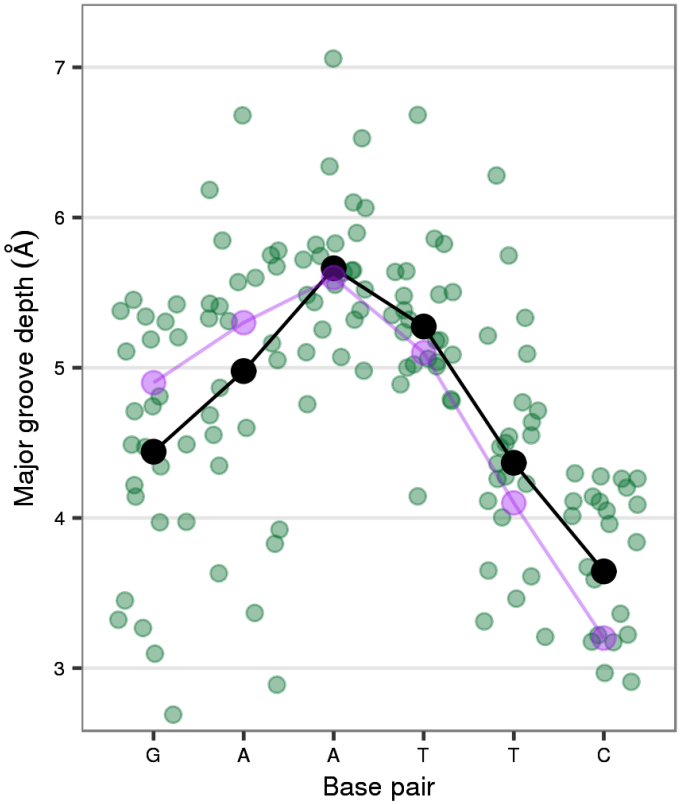


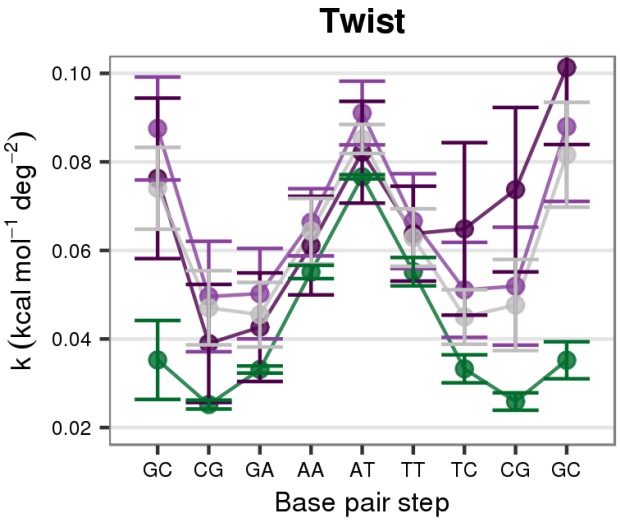


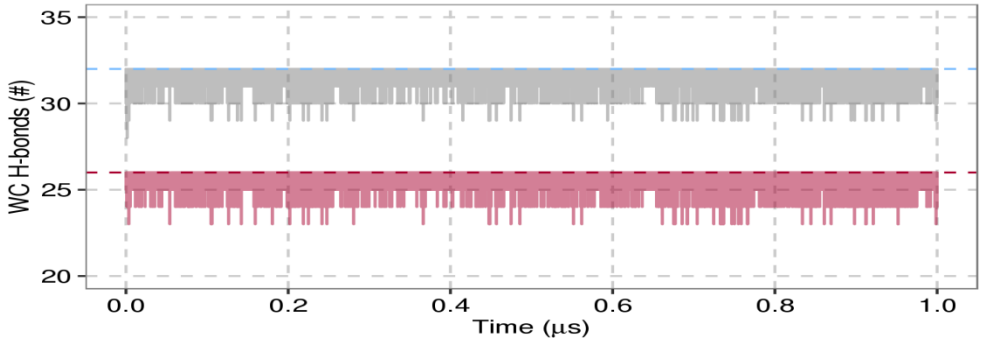
Global and local descriptors



- Backbone torsional space
- Global and local Flexibility
- WC hbonds
- Diffusion
- Effective Temp.
- Fraying
- Essential dynamics
- Groove dimensions







Conclusions

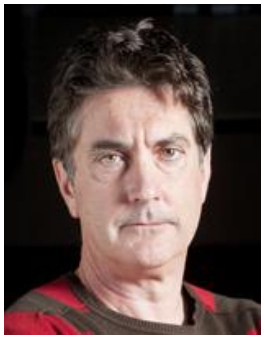
- For the first time, we obtained stable simulations of DNA crystals in various symmetry groups and under different solvent environments allowing us to understand with unprecedented level of detail the nature of the intermolecular interactions that guarantee the stability of crystals.

- Our results are a proof of concept that expand the actual limits of the field, opening the door to anticipate the specific need or effect of an additive prior to the wet lab, and enabling, with a high probability of success, the all-atom simulation of crowded cellular environments, where one-meter-long DNA has to pack into a nucleus of 5 µm in diameter.

- Through extensive unbiased MD simulations on the millisecond timescale, here we demonstrate how the stability of DNA crystals depends on subtle interactions between the packed DNA molecules and the components of the buffer used to reach crystallization conditions.

Submitted to Nature Chemistry, in revision

Expanding the boundaries of DNA crystal simulations



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