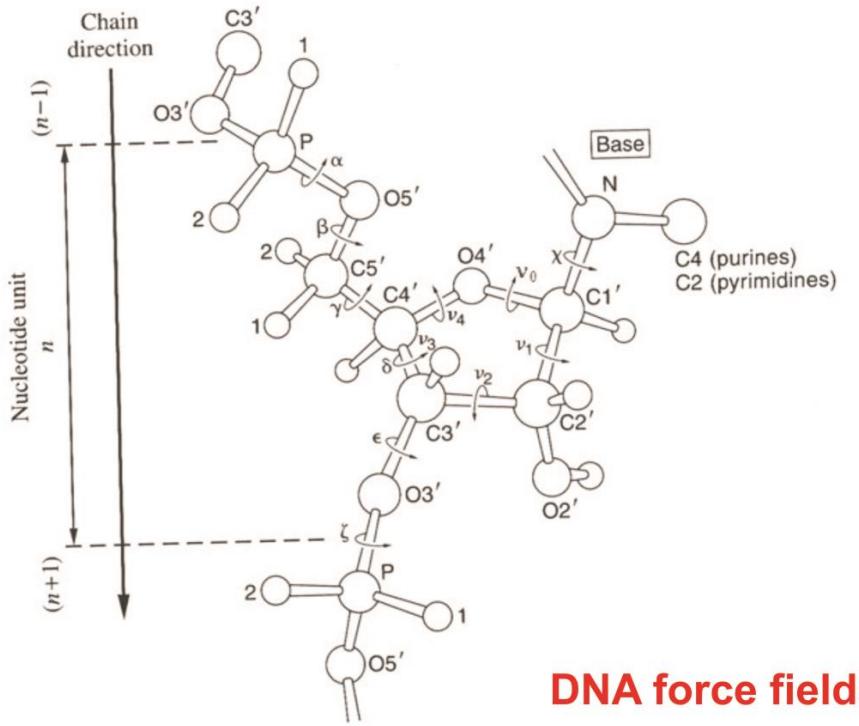
1. Models, sampling, time vs cost, the coarse-grain concept
2. All-atom Force Fields for DNA and RNA
3. Background on coarse-grain models for DNA/RNA
4. The Sirah Force Field for DNA
5. Background on coarse-grain models for Proteins
6. The Sirah Force Field for Prot/DNA/Lipids
7. Nucleosome dynamics & Chromosome modeling

All-atom Force Fields for DNA and RNA



Unified DNA/RNA force fields

- Weiner et al. 1984/1986
  - parm94 Cornell et al.
    - parm98 Cheatham et al.
      - parm99 Wang et al.
        - parm99+bsc0 Pérez et al. — 2007

- CHARMM27 MacKerell et al.
  - CHARMM36 MacKerell et al.

DNA force fields

- parm99+bsc0+χ+VdW Chen & García
- parm99+bsc0+χ_{OL4} Krepl et al.
  - parm99+bsc0+ε/ζ_{OL1} Zgarbova et al.
    - parm99+bsc0+β_{OL1} Zgarbova et al.
      - parm99+bsc0+OL15 χ_{OL4}+ε/ζ_{OL1}+β_{OL1} — 2015
- parm99+bsc0+bsc1 Ivani et al. χ+ε/ζ+puckering
  - **PARMBSC1** — 2015

RNA force fields

- parm99+bsc0+χ_{OL3} Zgarbova et al.
  - parm99+bsc0+χ_{OL3}+κ Darré et al. — 2016

Reviews

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Structural Biology

Multiscale simulation of DNA

Pablo D Dans[1,2], Jürgen Walther[1,2], Hansel Gómez[1,2] and Modesto Orozco[1,2,3]

DNA is not only among the most important molecules in life, but a meeting point for biology, physics and chemistry, being studied by numerous techniques. Theoretical methods can help in gaining a detailed understanding of DNA structure and function, but their practical use is hampered by the multiscale nature of this molecule. In this regard, the study of DNA covers a broad range of different topics, from sub-Angstrom details of the electronic distributions of nucleobases, to the mechanical properties of millimeter-long chromatin fibers. Some of the biological processes involving DNA occur in femtoseconds, while others require years. In this review, we describe the most recent theoretical methods that have been considered to study DNA, from the electron to the chromosome, enriching our knowledge on this fascinating molecule.

Addresses
[1] Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Baldiri Reixac 10-12, 08028 Barcelona, Spain
[2] Joint BSC-IRB Research Program in Computational Biology, Baldiri Reixac 10-12, 08028 Barcelona, Spain
[3] Department of Biochemistry and Molecular Biology, University of Barcelona, 08028 Barcelona, Spain

Corresponding author: Orozco, Modesto (modesto.orozco@irbbarcelona.org)

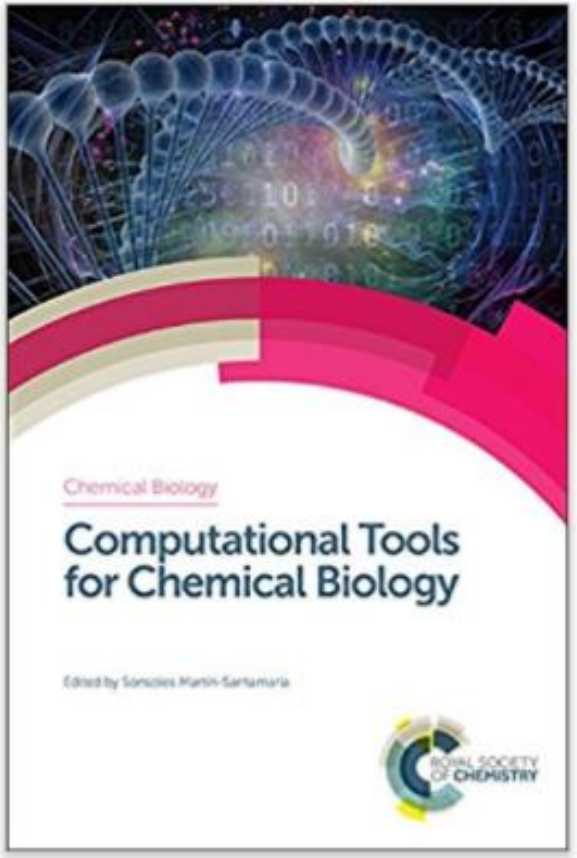
in the day time-scale (10^5 s); the local breathing of nucleobases occurs in the millisecond range (10^{-3} s), while electronic rearrangements take place in the sub-femtosecond time-scale ($<10^{-15}$ s).

During the last years we have witnessed the development of a wide repertoire of theoretical methods that aimed to reproduce the properties of DNA, either isolated or protein bound. Even if primitive, these methods allow researchers to consider the DNA at different resolution levels, and provide information of great value on the structure, dynamics, and interactions of this fascinating molecule. We will briefly summarize some of these most recent theoretical approaches, focusing our analysis on the contributions of the last three years, when the field has experienced a significant improvement.

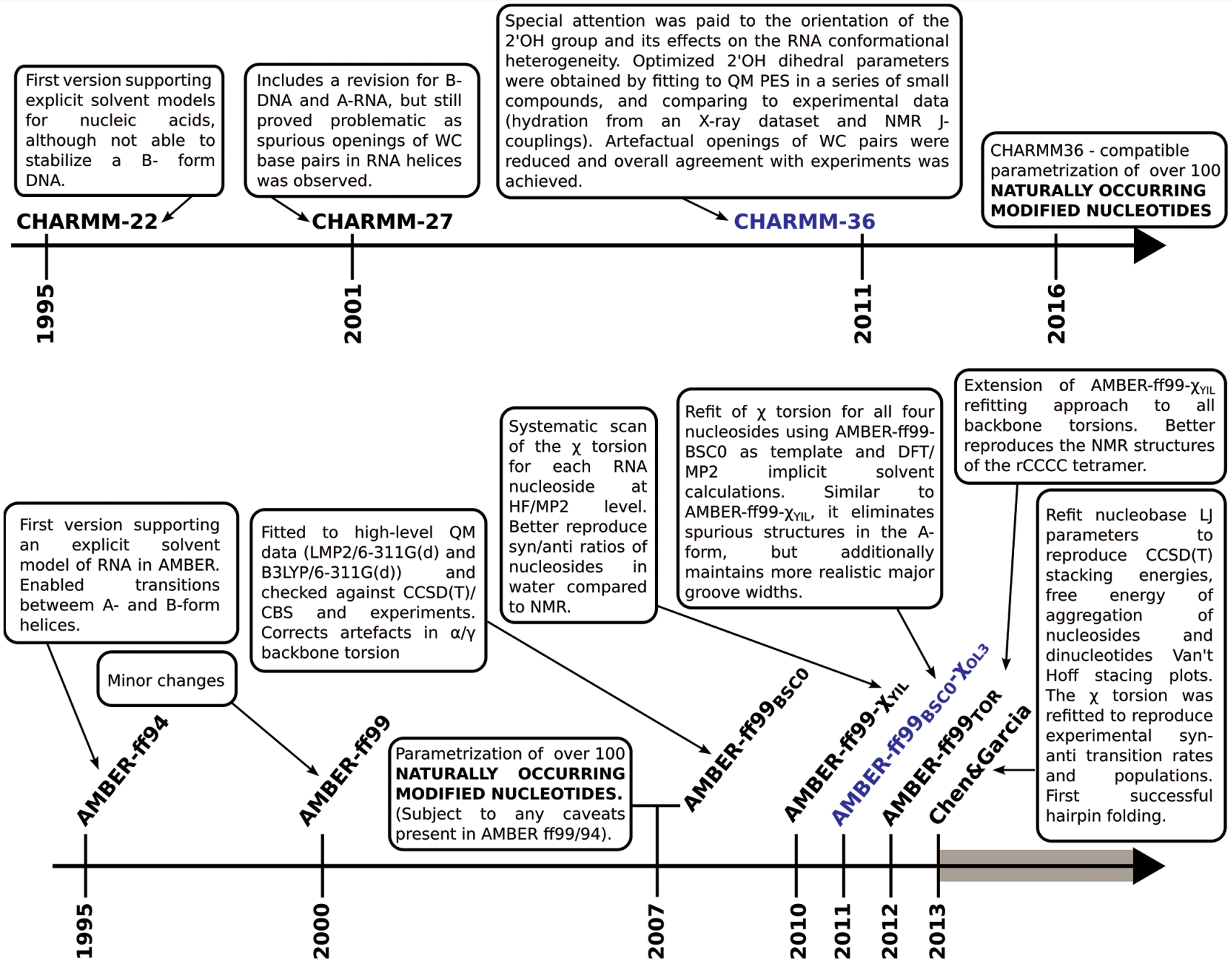
For the sake of simplicity, throughout this manuscript we will classify theoretical methods in four groups, according to their level of resolution (Figure 1): firstly, electronic, secondly, atomistic, thirdly, coarse grained, and lastly, mesoscopic. It is worth noting that moving in the resolution space means moving also in the methodological space, since the basic physical models underlying the

Multiscale simulation of DNA (2016)
PD Dans, J Walther, H Gómez, M Orozco
Current opinion in structural biology 37, 29-45

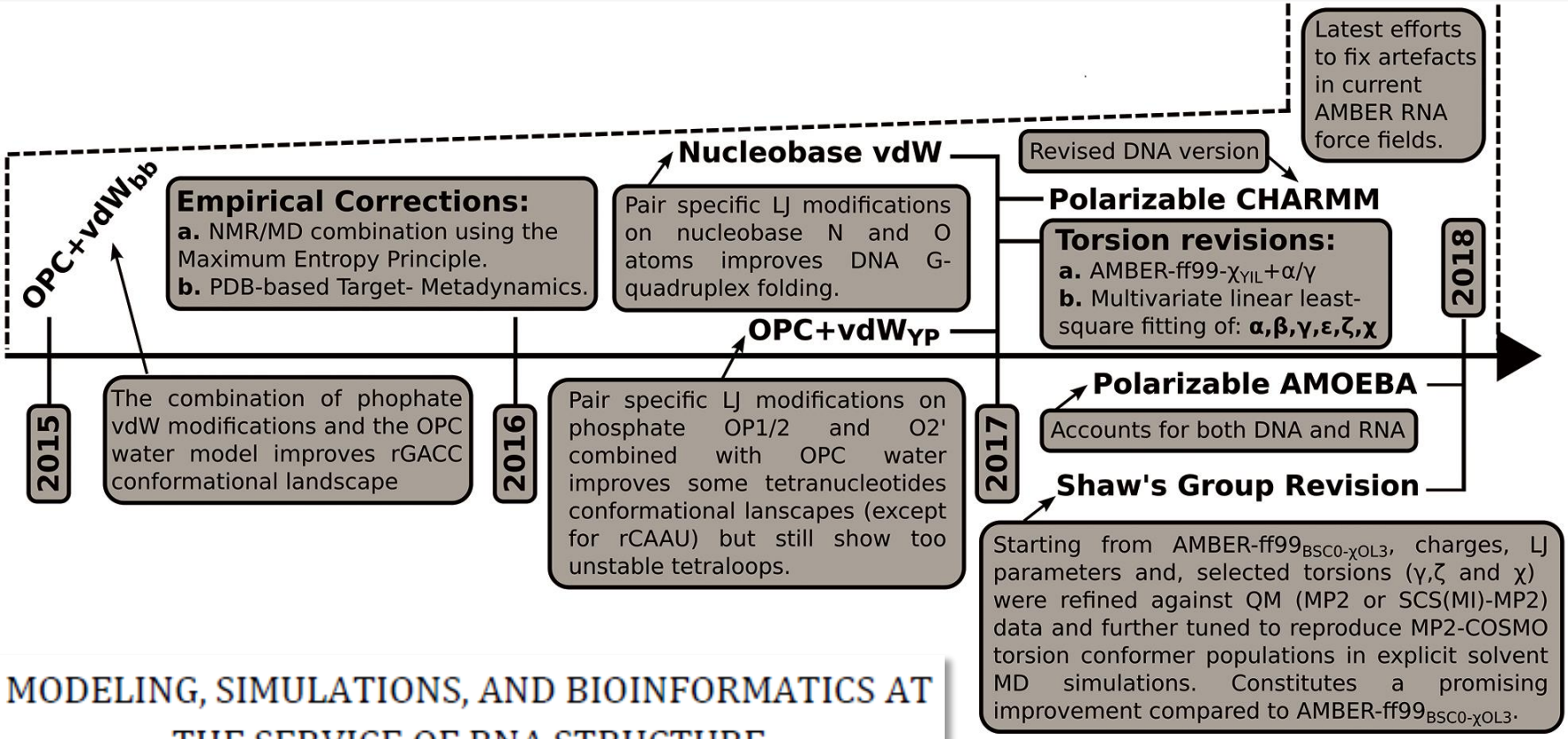
Molecular Modeling of Nucleic Acids (2017)
H Gómez, J Walther, L.Darré, I Ivani, PD Dans, M Orozco. In Computational Tools for Chemical Biology. RSC, ISBN: 1782627006



All-atom Force Fields for RNA (more details 1/2)



All-atom Force Fields for RNA (more details 2/2)



MODELING, SIMULATIONS, AND BIOINFORMATICS AT THE SERVICE OF RNA STRUCTURE

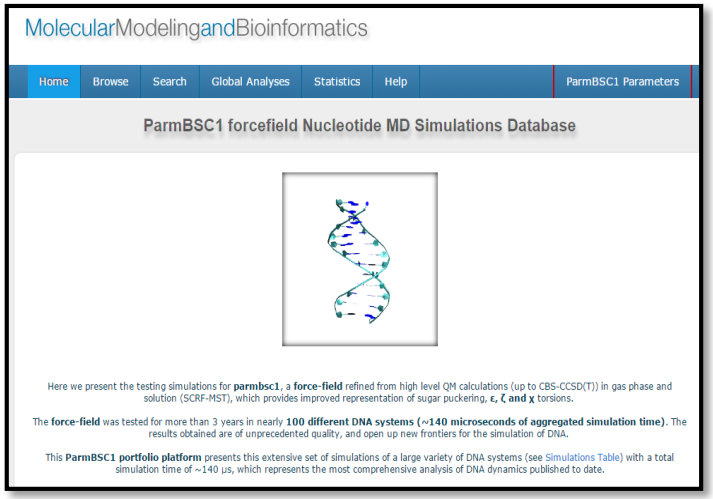
Pablo D. Dans,[1,2] Diego Gallego,[1,2,3] Alexandra Balaceanu,[1,2] Leonardo Darré,[1,2,4] Hansel Gómez,[1,2] and Modesto Orozco[1,2,3,*]

[1] Institute for Research in Biomedicine (IRB Barcelona), the Barcelona Institute of Science and Technology, 08028 Barcelona, Spain.
[2] Joint BSC-IRB Program in Computational Biology, Institute for Research in Biomedicine (IRB Barcelona), 08028 Barcelona, Spain.
[3] Department of Biochemistry and Biomedicine, Faculty of Biology, University of Barcelona, 08028 Barcelona, Spain.
[4] Functional Genomics Lab, Institut Pasteur of Montevideo, Montevideo, Uruguay.

Chem

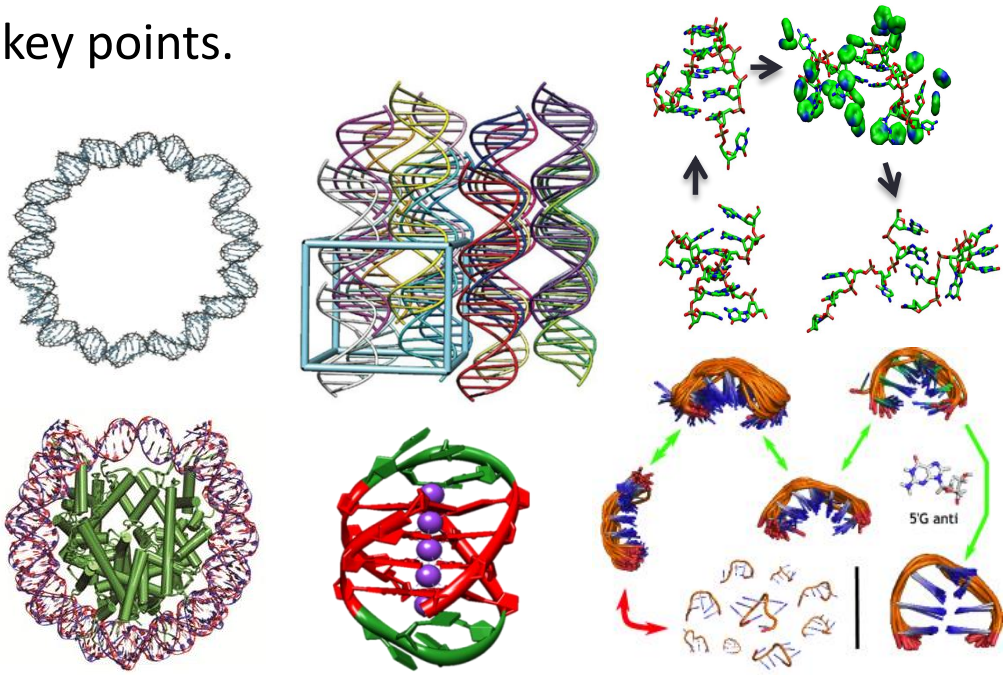
Cell Press

PARMBSC1 (parm99bsc1) for DNA



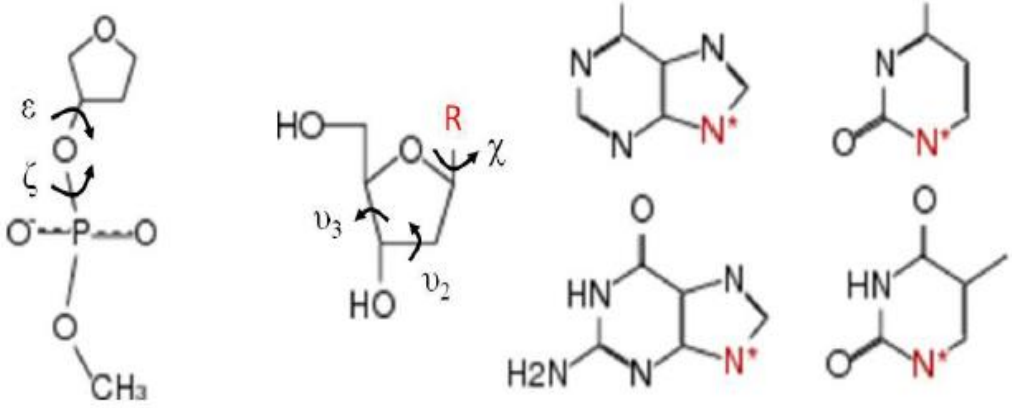
(http://mmb.irbarcelona.org/ParmBSC1)

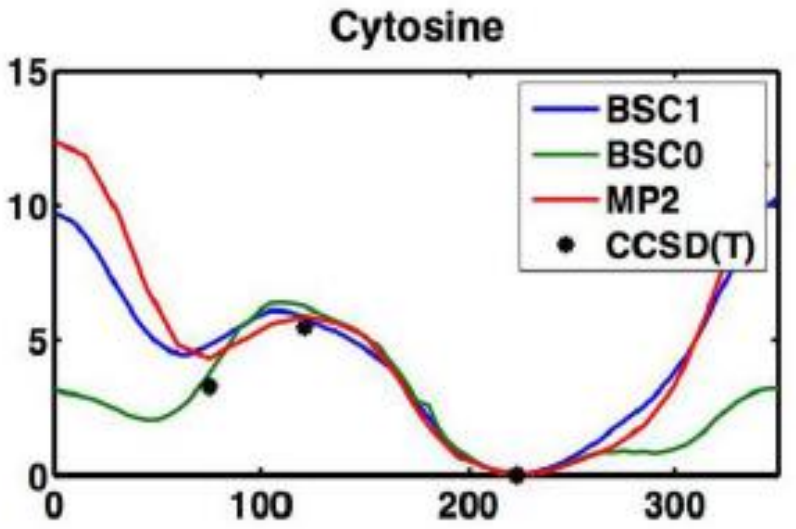
Parameterized on **ε/ζ, χ and puckering level** using MP2/aug-cc-pVDZ with CBS/CCST(Q) on key points.

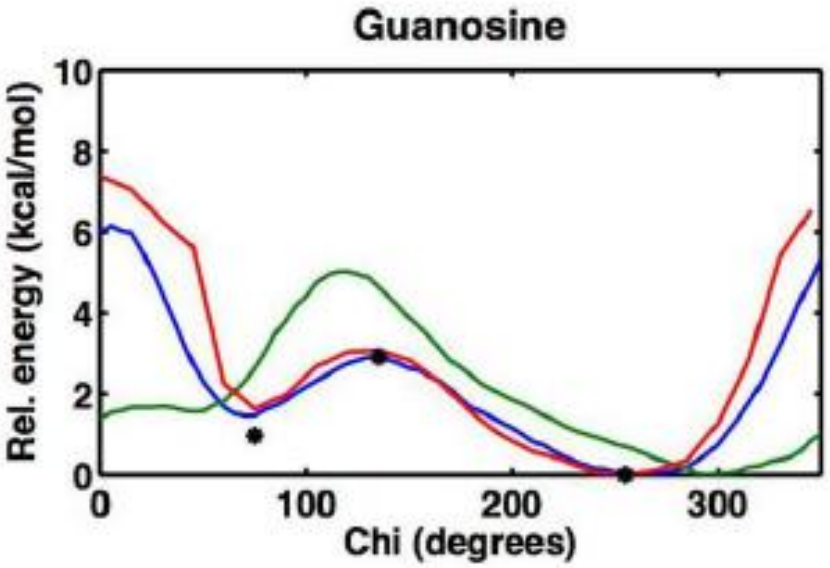


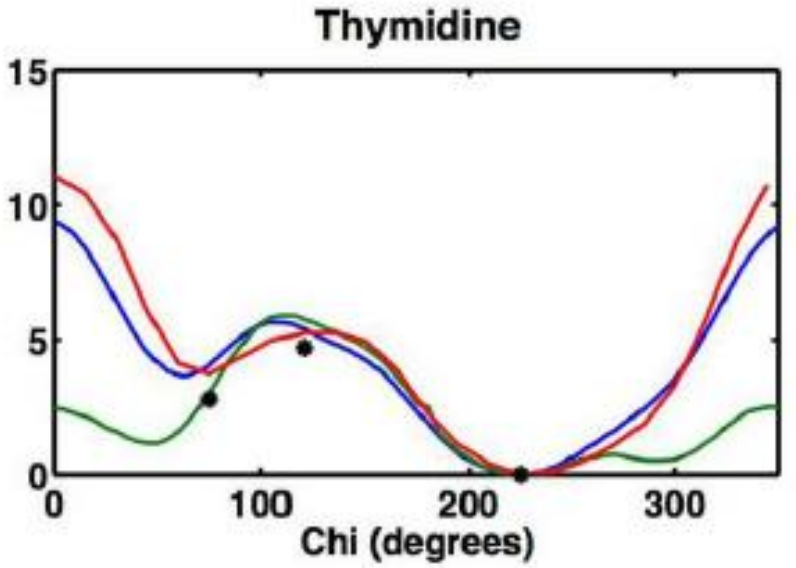
Tested on 100+ different systems (~140 µs) during 3 years, with significant improvements over other modern force fields for DNA simulations.

PARMBSC1: Models and the fitting of the Chi (χ) angle (classical vs QM profiles)

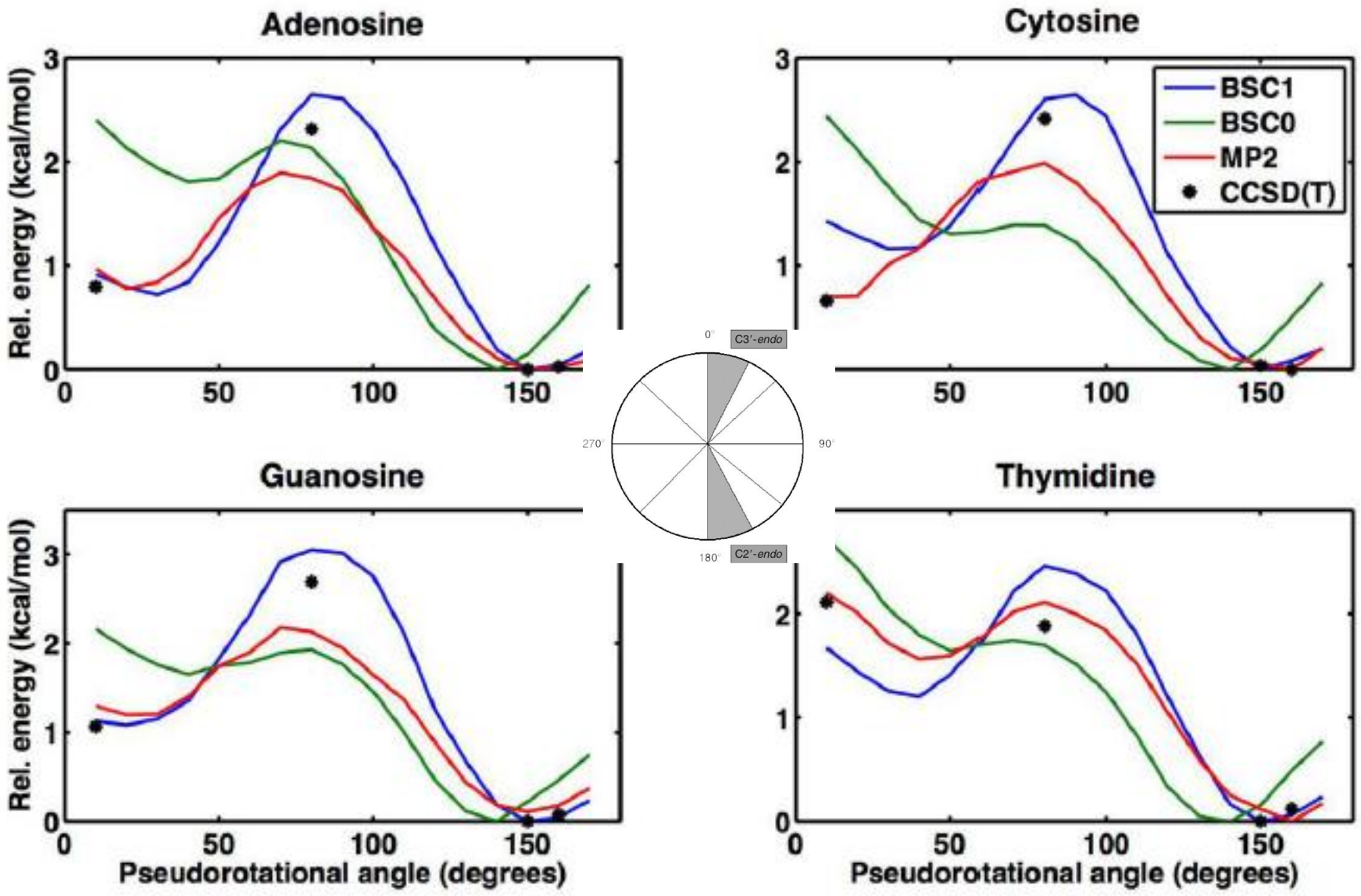




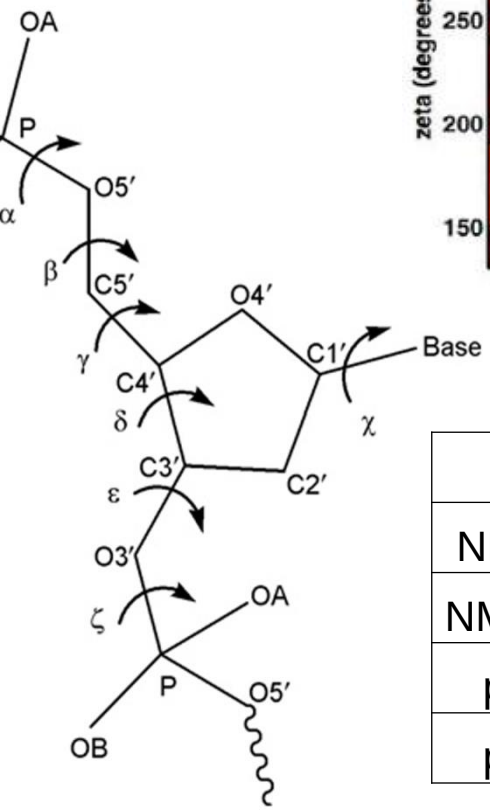


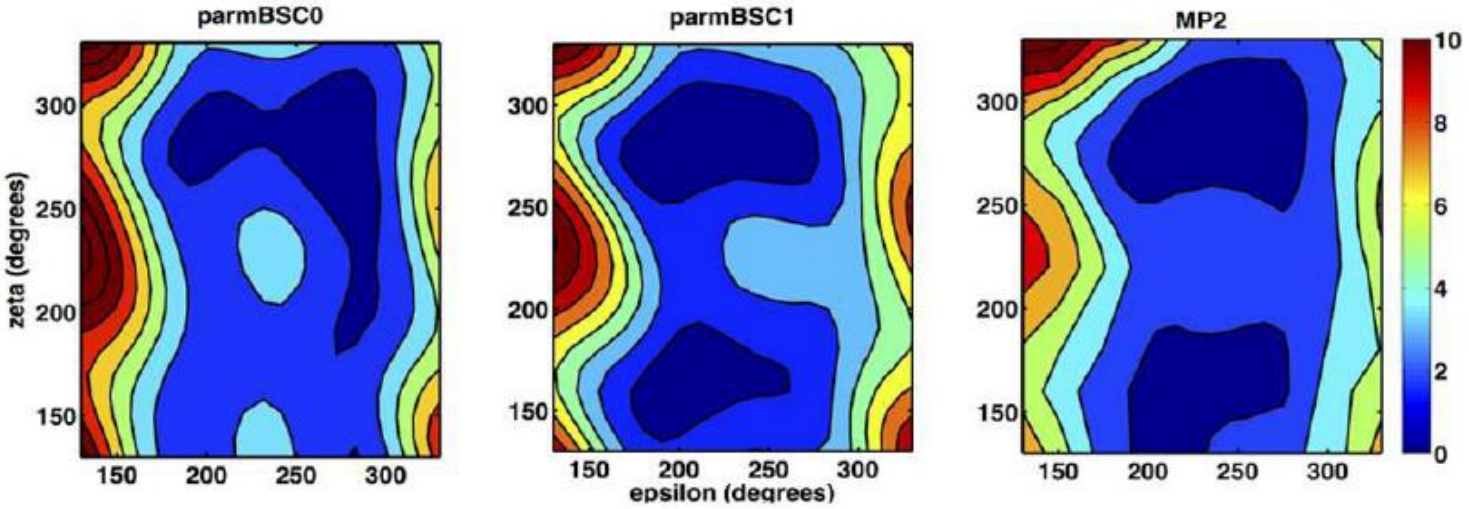


PARMBSC1: Fitting the torsion of the sugar moiety



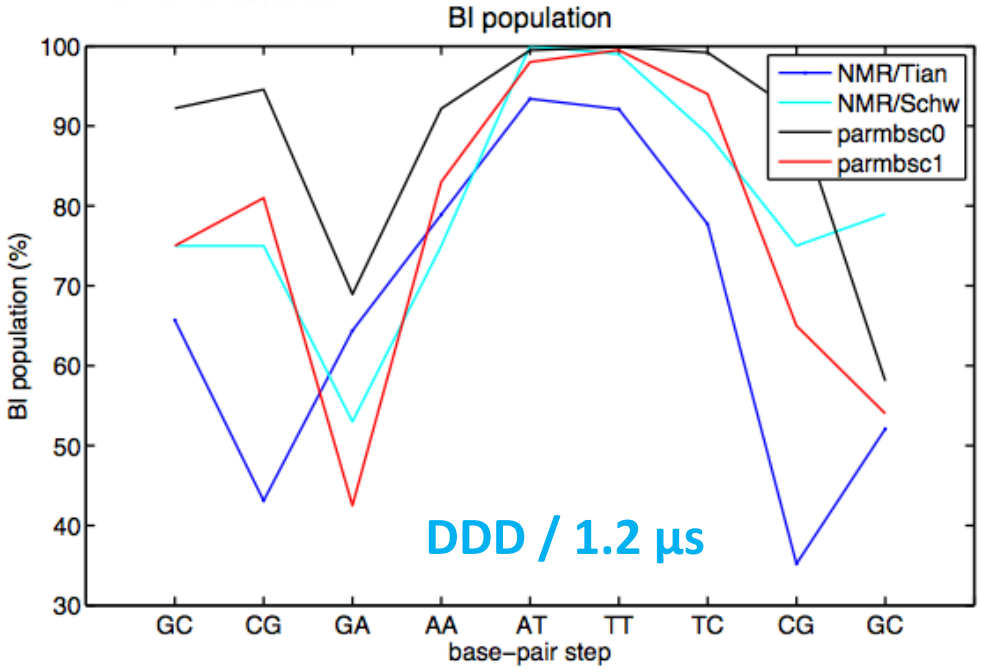
PARMBSC1: Fitting ε/ζ and BI/BII sequence-dependent propensities



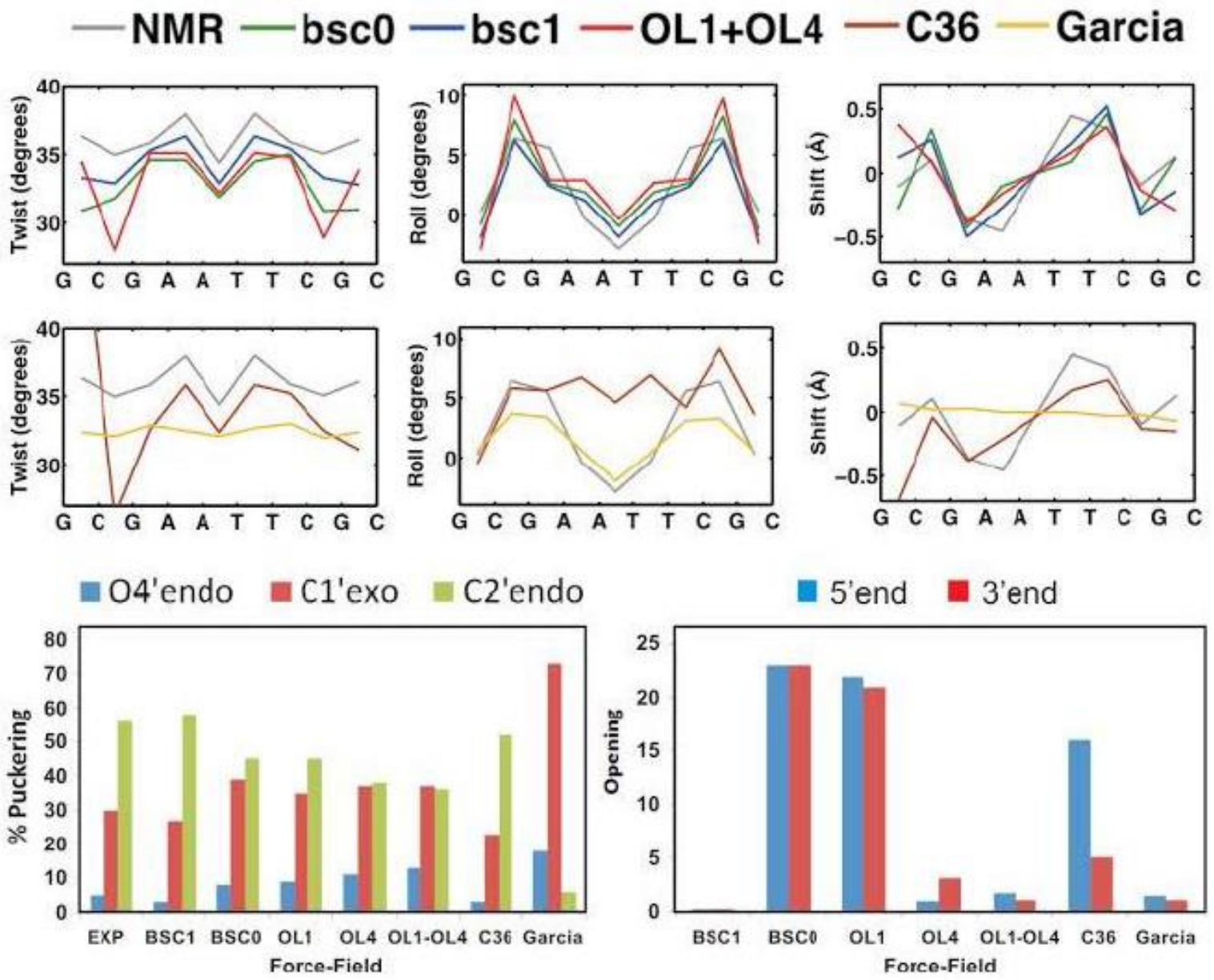


BI %	Aver.
NMR/Tian [1]	65.18
NMR/Schw [2]	80.00
parmbsc0	88.47
parmbsc1	76.89

[1] Tian et al, J. Phys. Chem. B 2009, 113 (9), 2596 | [2] Schwieters and Clore, Biochemistry 2007, 46 (5), 1152



PARMBSC1: Benchmarks 1

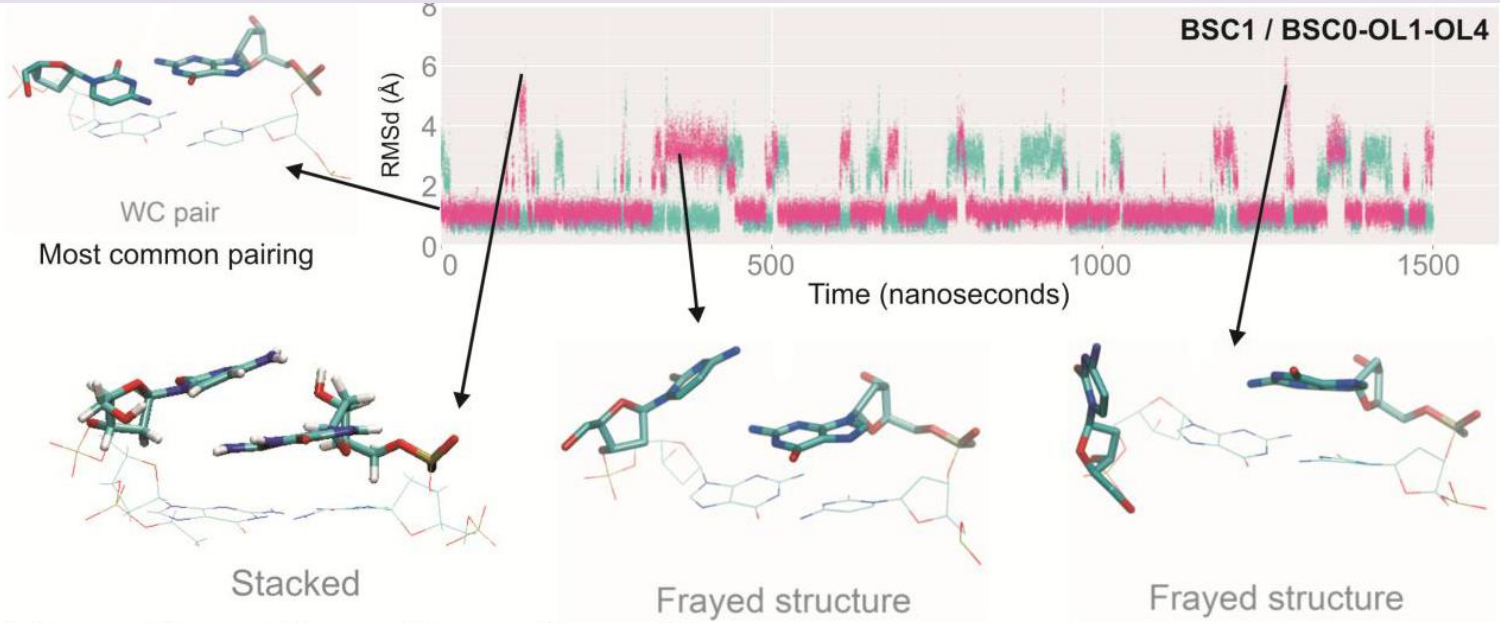


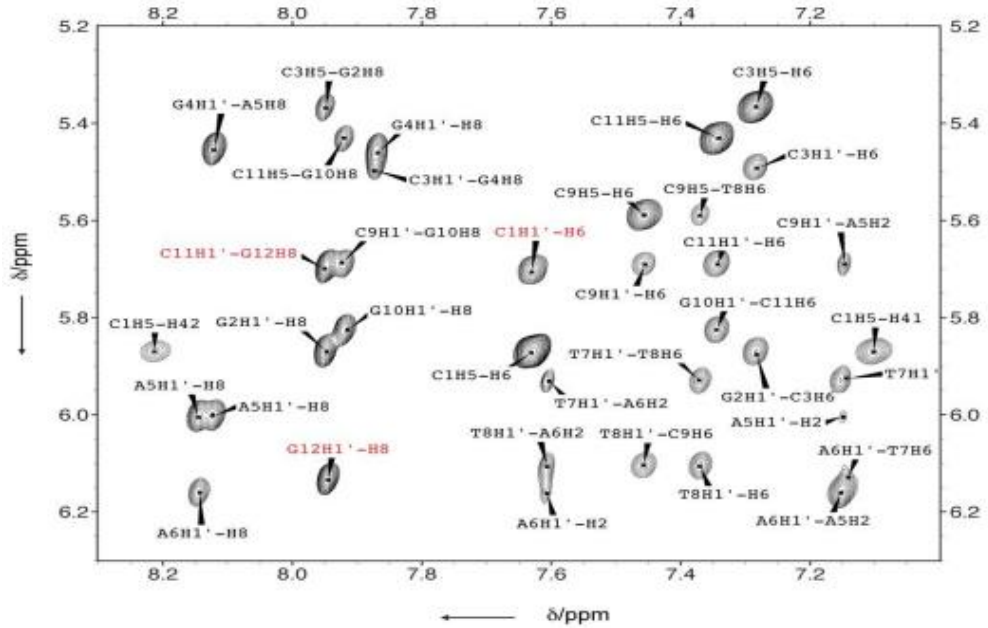
PARMBSC1: Benchmarks 2

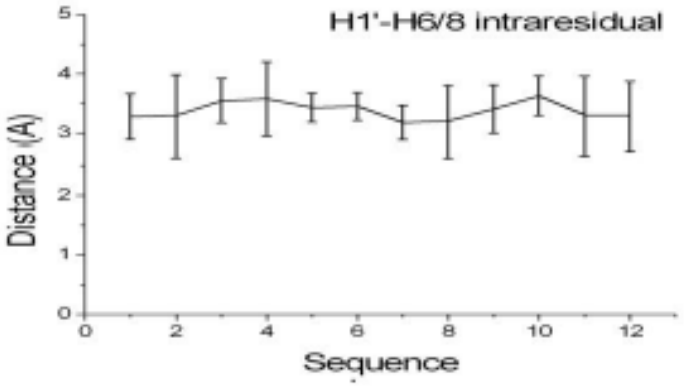
	Twist	Roll	Slide	Rise	Shift	Tilt	BI(%)	Major groove width	Minor groove width
Parmbsc1	**34.3±5.4**	**1.5±5.4**	**-0.3±0.5**	**3.3±0.3**	**0.0±0.8**	**0.0±4.5**	**77**	**11.9±1.7**	**5.4±1.2**
Parmbsc0	32.8±5.8	2.7±5.8	-0.4±0.6	3.3±0.3	0.0±0.7	0.0±4.3	84	12.9±1.8	3.9±1.2
OL1	33.3±5.7	2.7±5.9	-0.2±0.6	3.3±0.3	0.0±0.7	0.0±4.4	83	12.2±1.4	6.1±1.3
OL4	33.3±6.4	2.6±5.9	-0.1±0.6	3.3±0.3	0.0±0.7	0.0±4.5	85	12.1±1.4	6.5±1.3
OL1+OL4	33.0±6.1	2.8±5.7	-0.3±0.6	3.3±0.3	0.0±0.7	0.0±4.3	86	12.4±1.5	6.0±1.2
C36 [d]	34.5±11	5.1±8.8	0.8±1.0	3.6±0.8	-0.1±1.1	0.9±8.0	66	10.5±1.5	8.3±1.7
Cheng-Garcia(CG)	32.5±3.4	1.5±5.2	-1.7±0.5	3.4±0.3	0.0±0.4	0.0±4.3	100	15.3±1.6	5.5±0.9
X-ray [b]	**35.2±0.6**	**-0.7±1.1**	**0.1±0.1**	**3.3±0.1**	**-0.1±0.1**	**-0.4±0.9**		**11.2±0.1**	**4.6±0.3**
NMR [c]	**35.6±0.8**	**1.6±1.0**	**-0.3±0.1**	**3.2±0.1**	**0.0±0.1**	**0.0±0.7**	**73[e]**	**11.9±0.3**	**4.7±0.3**

All-atom Force Fields for DNA and RNA

PARMBSC1: Benchmarks 3







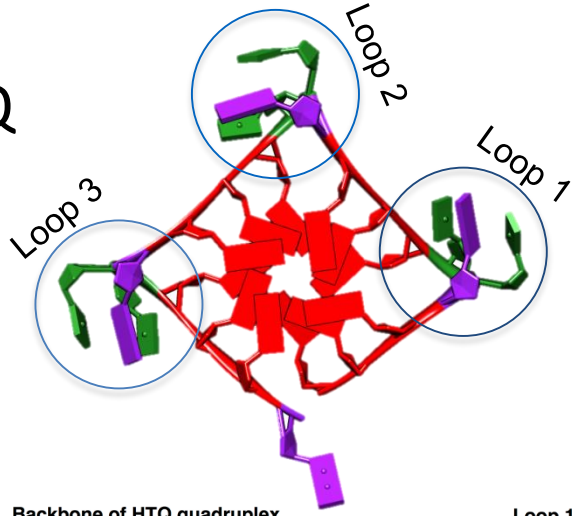
PARMBSC1: Benchmarks 4

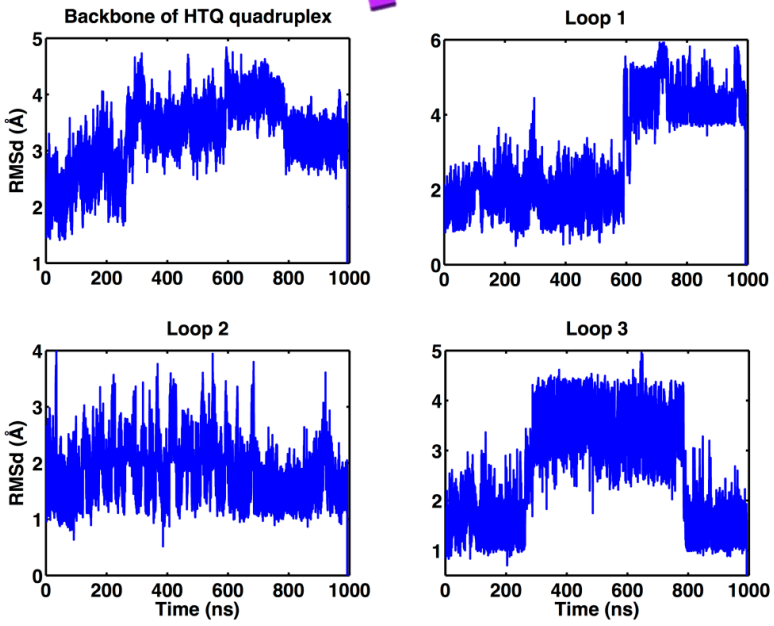
Table S3. Ability of MD-ensembles obtained from parmbsc0 and parmbsc1 force fields to reproduce NMR observables for Drew-Dickerson dodecamer. The first block correspond to residual dipolar couplings Q-factor, $q = \sqrt{\sum (RDC_{calc} - RDC_{exp})^2} \Big/ \sqrt{\sum RDC_{exp}^2}$, where RDC_{exp} has been determined using PALES [2], and the second block to NOEs (146 restraints).

	NMR	X-ray	Fiber model B-DNA	Fiber model A-DNA	BSC1	BSC0
Bicelles, 1NAJ [a], 129 RDCs	0.17	0.49	0.51	0.87	0.32	0.36
Bicelles, 1DUF [b], 204 RDCs	0.23	0.53	0.66	0.92	0.34	0.38
Sum of violations (A)	0.01	10.0	7.6	42.01	0.4	2.6
Largest violation (A)	0.01	1.0	0.4	1.3	0.2	1.3
Num. of violated restraints	1	35	36	84	2	5

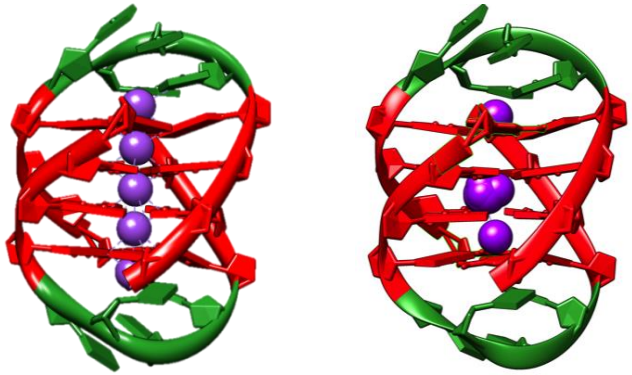
PARMBSC1: Reproducing complex DNA structures 1

HTQ

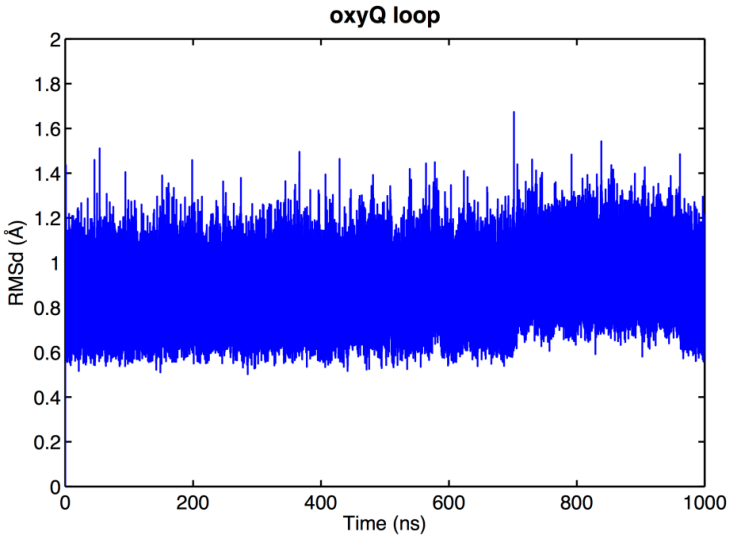




oxyQ

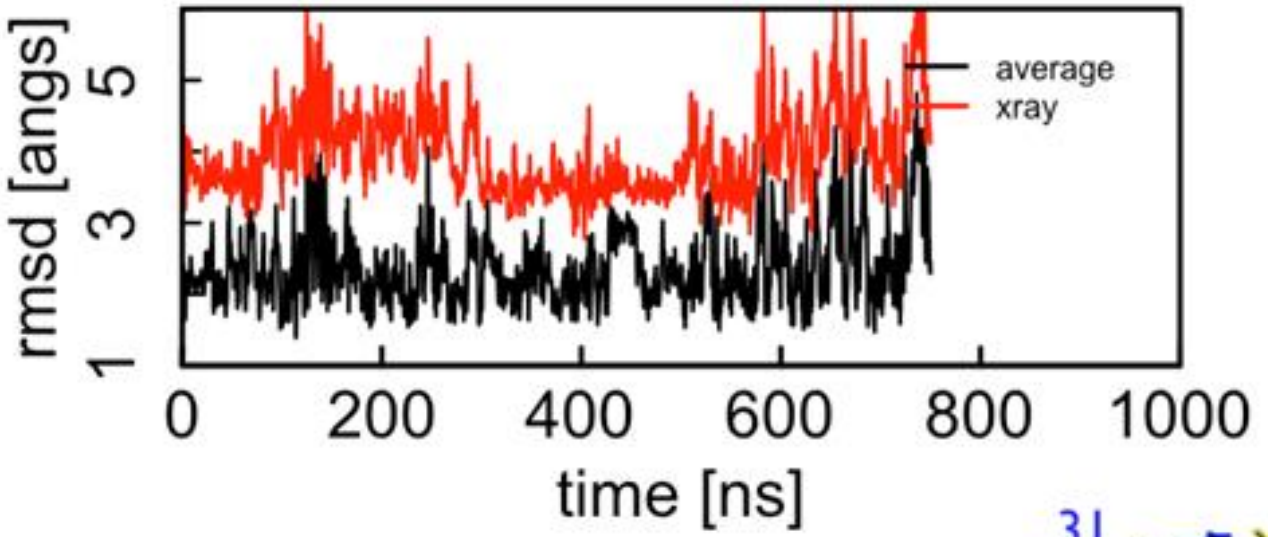


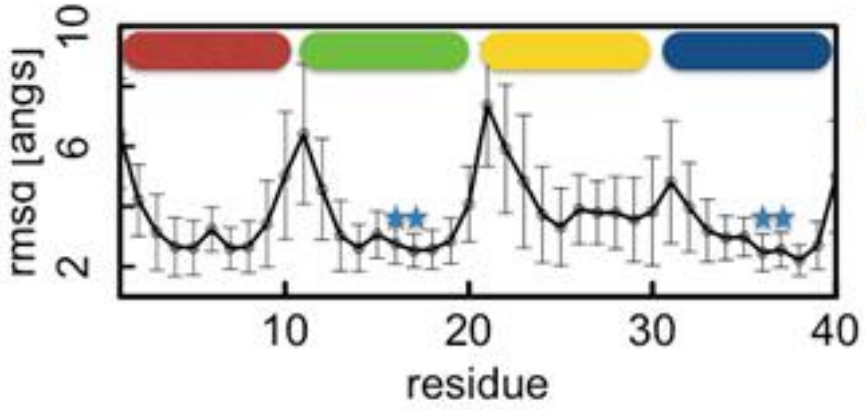
X-ray Average structure



Fadrna et al, *JCTC,* (2009), *5,* 2514

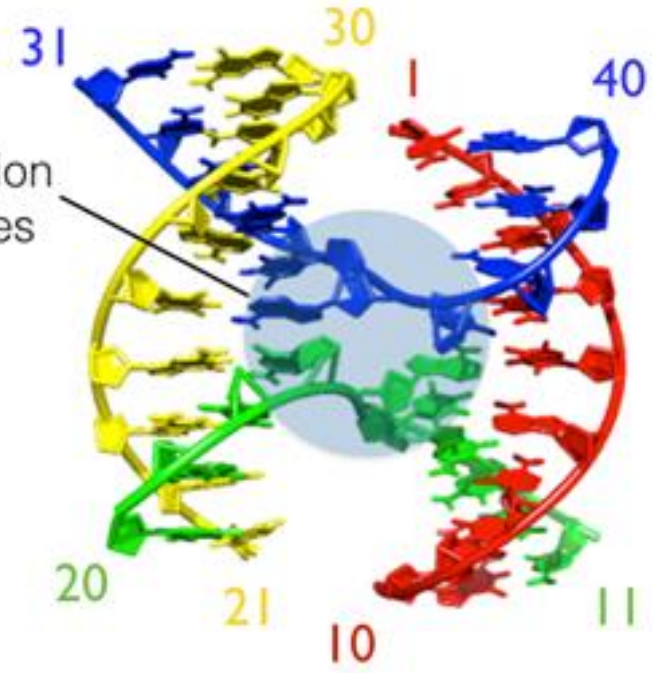
PARMBSC1: Reproducing complex DNA structures 2





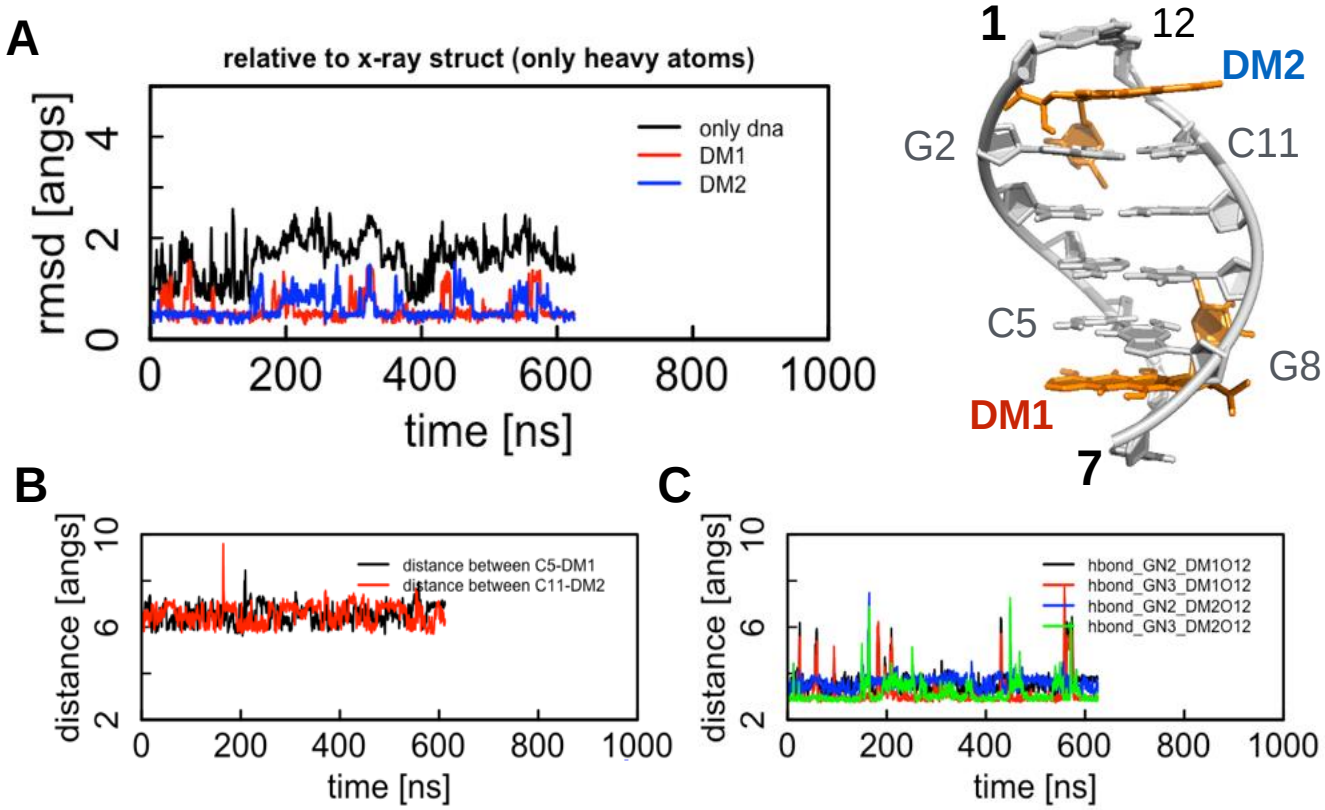
All heavy atoms RMSD (top) and per-residue RMSD (bottom). X-ray structure was taken as reference in the per-residue RMSD calculation. Note the higher RMSD values correspond to end strand bases.

Holliday junction

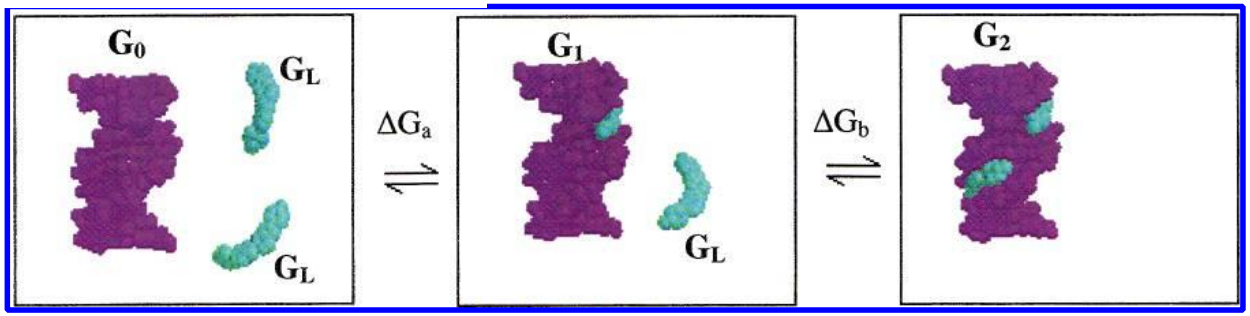


PARMBSC1: Drug intercalation & cooperativity

Daunomycin intercalation

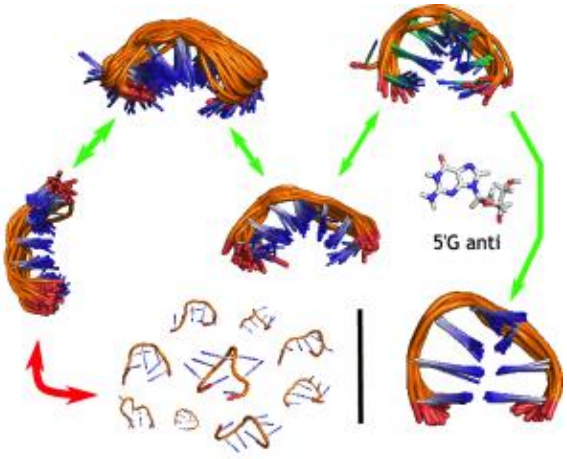


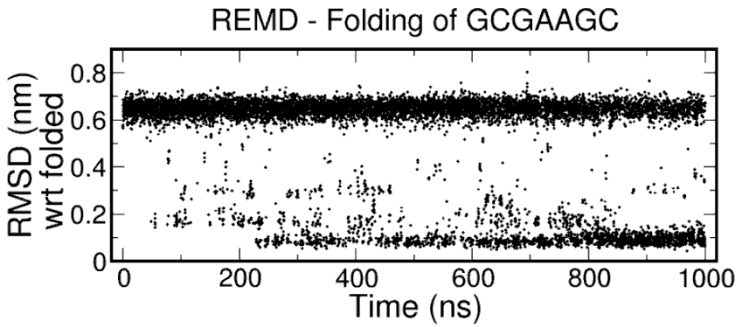
Drug cooperativity

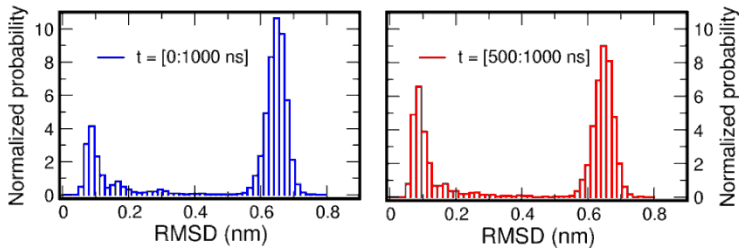


PARMBSC1: Folding and unfolding

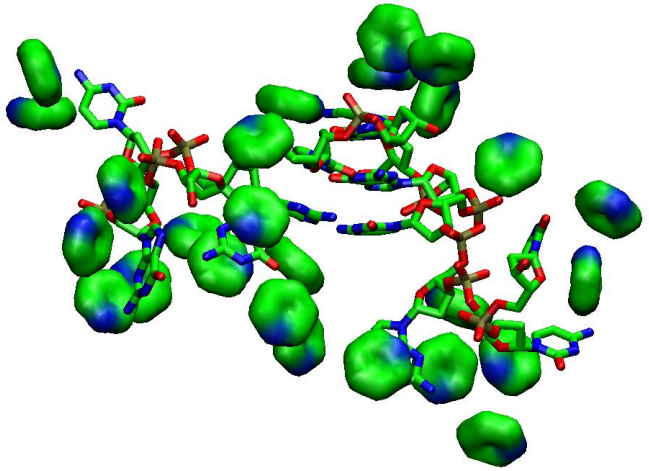
DNA hairpin folding

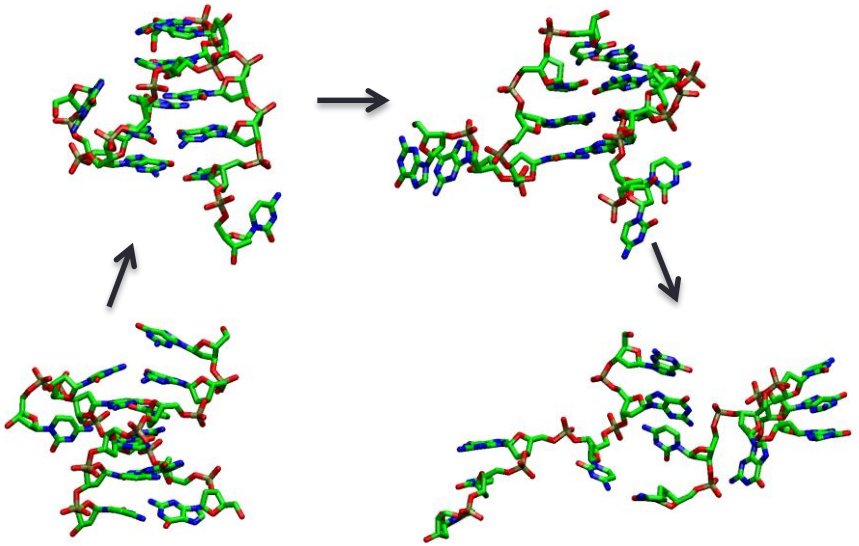






DNA unfolding





PARMBSC1… a state of the art force field for DNA simulations

- ✓ Clear improvements of helical parameters of B-DNA.
- ✓ Increase of BII population, by ~10%.
- ✓ Good agreement with NMR data (RDCs and NOEs).
- ✓ Bimodality of CpG steps converges after 200 ns (DDD).
- ✓ Reproduce all previous results done with BSC0.
- ✓ Simulation of huge variety of systems and properties with clear improvements, if not comparable results, with one universal force-field.
- ✓ Duplexes, Triplexes, Quadruplexes, G-DNA loops, Z-DNA, mini-circles, crystal simulations, intercalators, folding/unfolding, long oligomers, holliday-junctions, hairpins, drug intercalation, drug cooperativity, A-tracks, dielectric properties, stiffness, protein-DNA, etc.

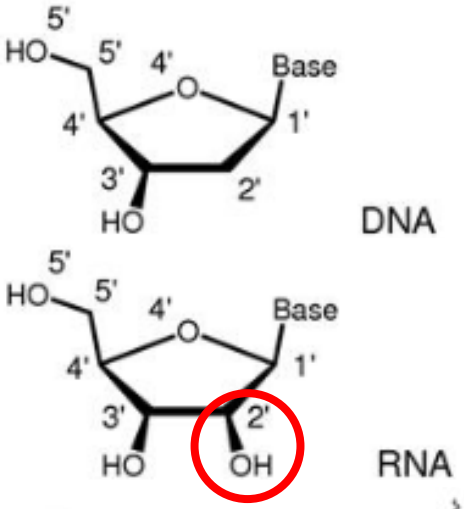
Parm99+BSC0-χ_{OL3}-Kappa

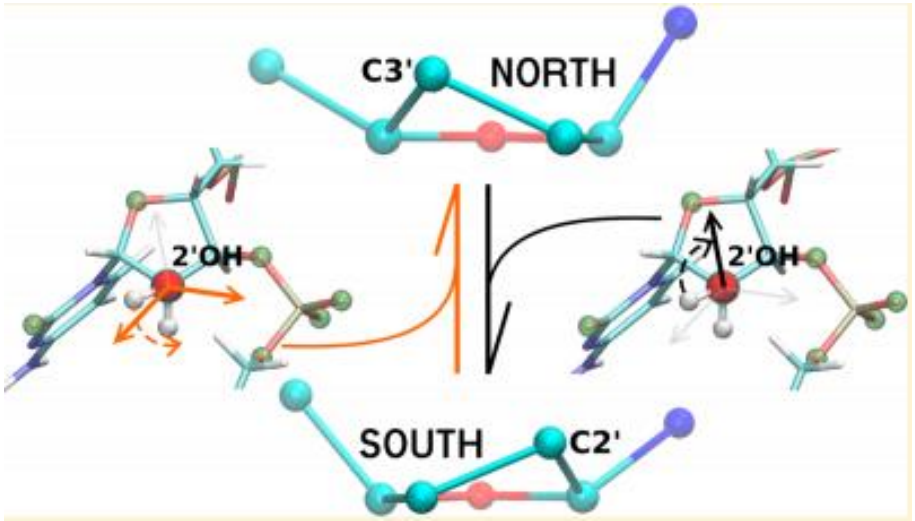
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

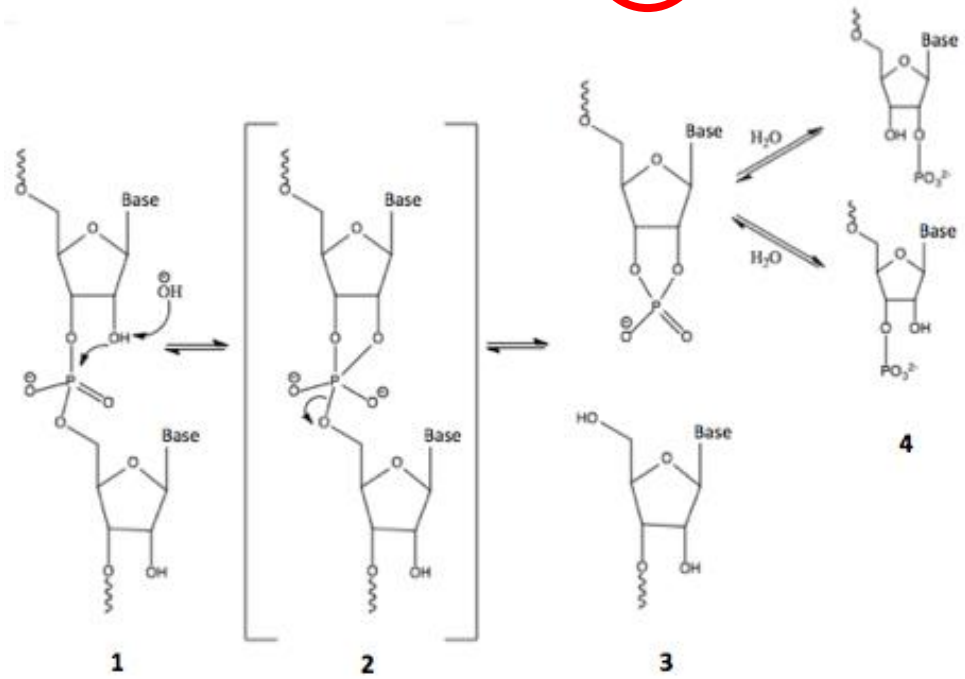
Small Details Matter: The 2′-Hydroxyl as a Conformational Switch in RNA

Leonardo Darré,[†,‡] Ivan Ivani,[†,‡] Pablo D. Dans,[†,‡] Hansel Gómez,[†,‡] Adam Hospital,[†,‡] and Modesto Orozco*[,†,‡,§]

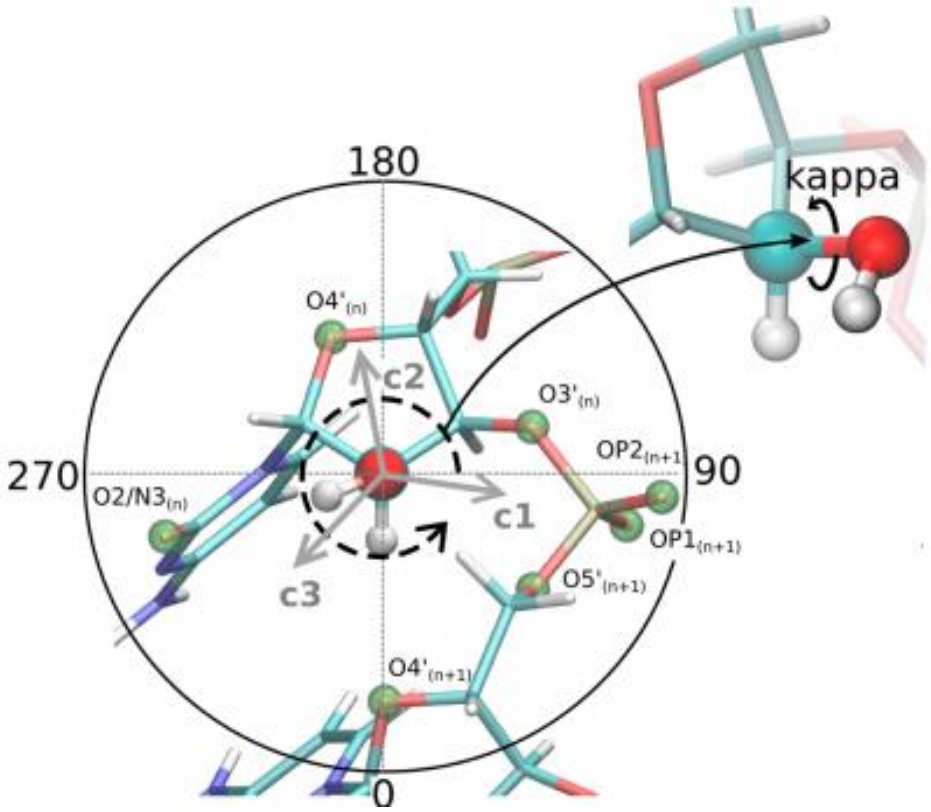
[†]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, 08028 Barcelona, Spain
[‡]Joint BSC-IRB Program in Computational Biology, Institute for Research in Biomedicine, 08028 Barcelona, Spain
[§]Department of Biochemistry and Biomedicine, Faculty of Biology, University of Barcelona, 08028 Barcelona, Spain

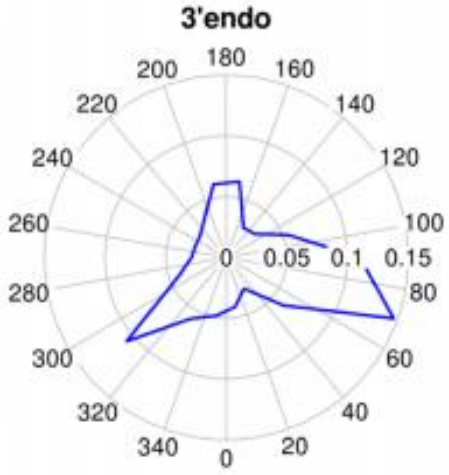




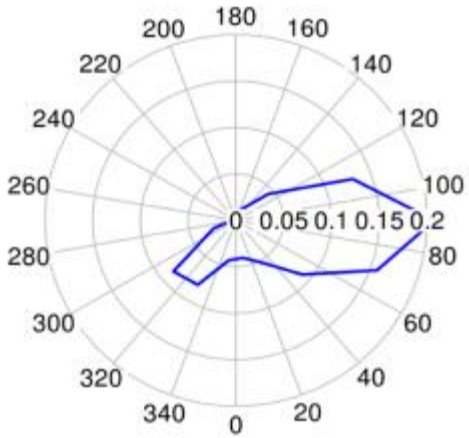


Parm99+BSC0-χ_{OL3}-Kappa



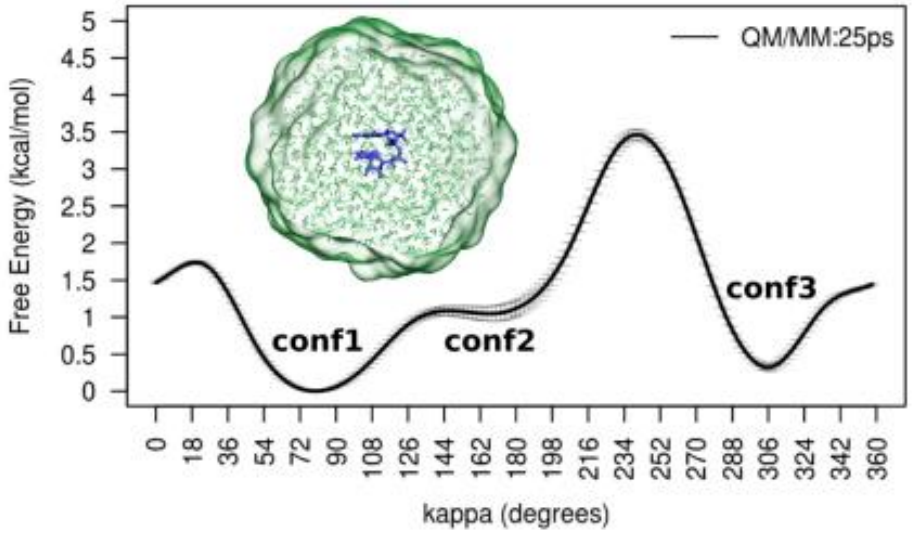


Protein Data Bank



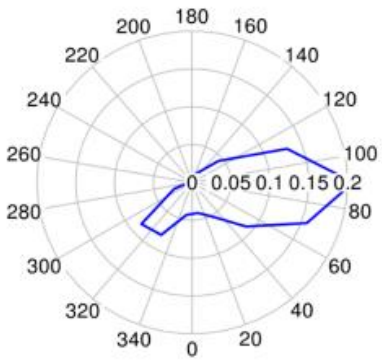
Parm99bsc0+χ_{OL3}

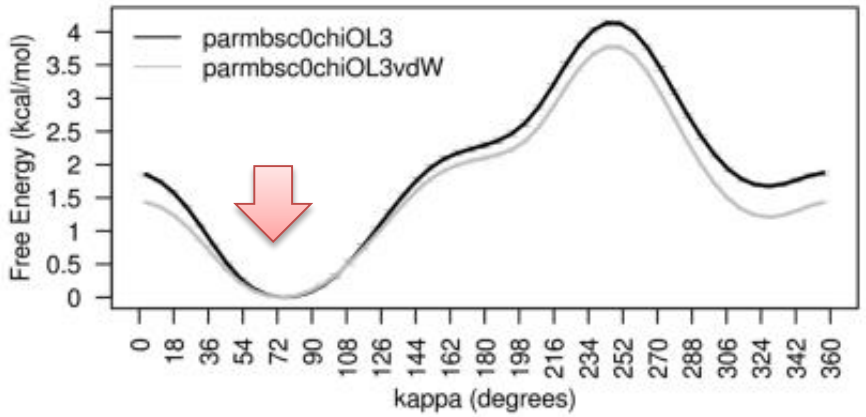
QM/MM
Umbrella Sampling
at the dinucleotide level



Parm99+BSC0-χ_{OL3}-Kappa

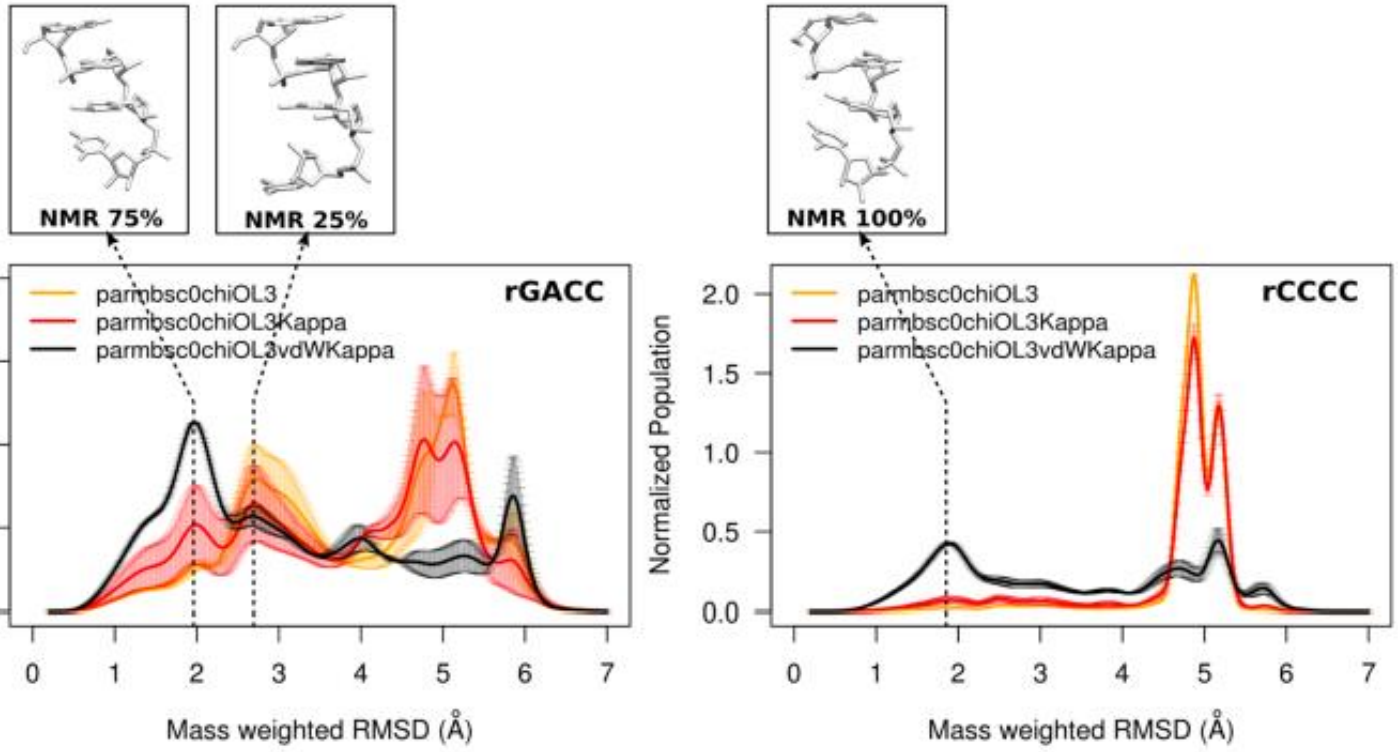
Parm99bsc0+χ_{OL3}





Parm99bsc0+χ_{OL3}+Kappa

Folding of tetranucleotides



Force fields for DNA: Benchmarking published

Nucleic Acids Research, 2017 1–14
doi: 10.1093/nar/gkw1355

How accurate are accurate force-fields for B-DNA?

Pablo D. Dans[1,2,†], Ivan Ivani[1,2,†], Adam Hospital[1,2], Guillem Portella[1,2,3], Carlos González[4,*] and Modesto Orozco[1,2,5,*]

[1]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, 08028 Barcelona, Spain, [2]Joint BSC-IRB Program in Computational Biology, Institute for Res Reixac 10-12, 08028 Barcelona, Spain, [3]Department of Chemistry, University of Camb 1EW Cambridge, UK, [4]Instituto Química Física Rocasolano. Consejo Superior de Inve Serrano 119, 28006 Madrid, Spain and [5]Department of Biochemistry and Biomedicine of Barcelona, 08028 Barcelona, Spain

Received November 5, 2016; Revised December 13, 2016; Editorial Decision December 22, 2016; Accepte

ABSTRACT

Last generation of force-fields are raising expectations on the quality of molecular dynamics (MD) simulations of DNA, as well as to the belief that theoretical models can substitute experimental ones in several cases. However these claims are based on limited benchmarks, where MD simulations have shown the ability to reproduce already existing 'experimental models', which in turn, have an unclear accuracy to represent DNA conformation in solution. In this work we explore the ability of different force-fields to predict the structure of two new B-DNA dodecamers, determined herein by means of ^{1}H nuclear magnetic resonance (NMR). The study allowed us to check directly for experimental NMR observables on duplexes previously not solved, and also to assess the reliability of 'experimental structures'. We observed that technical details in the annealing procedures can induce non-negligible local changes in the final structures. We also found that while not all theoretical simulations are equally reliable, those obtained using last generation of AMBER force-fields

ence data for force-field re
hind the improvement of
uum increase in hardware
as a new generation of ha
access to larger trajectory
field emerged, forcing a co
this sense, problems in tw
scale parm94 (7) simulati
parm99 (8), which was the
nanosecond trajectories re
α/γ transitions, which acc
entire duplex (9). These iss
(BSC0 from now on) revis
standard' for almost a dec
jectories highlighted the ex
quired further recalibratio
to parmbsc1 (BSC1 from
family of force-fields (12–1
of error-driven refinement
family of force-fields leadi
two-body (15) and polariz

There is little doubt th
provides improved picture
2,10–11). However, how ac

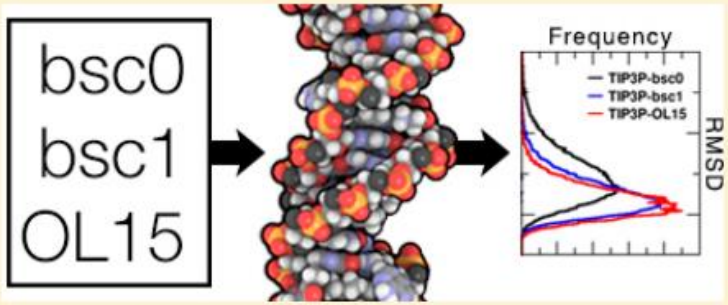
JCTC Journal of Chemical Theory and Computation
Article
pubs.acs.org/JCTC

Assessing the Current State of Amber Force Field Modifications for DNA

Rodrigo Galindo-Murillo,[†,∥] James C. Robertson,[†,∥] Marie Zgarbová,[‡] Jiří Šponer,[‡,§] Michal Otyepka,[‡] Petr Jurečka,[‡] and Thomas E. Cheatham, III*[,†]

[†]Department of Medicinal Chemistry, University of Utah, 2000 East 30 South, Skaggs 105, Salt Lake City, Utah 84112, United States
[‡]Regional Centre of Advanced Technologies and Materials, Department of Physical Chemistry, Faculty of Science, Palacky University, 17 Listopadu 12, 771 46 Olomouc, Czech Republic
[§]Institute of Biophysics, Academy of Sciences of the Czech Republic, Královopolská 135, 612 65 Brno, Czech Republic

Supporting Information



ABSTRACT: The utility of molecular dynamics (MD) simulations to model biomolecular structure, dynamics, and interactions has witnessed enormous advances in recent years due to the availability of optimized MD software and access to significant computational power, including GPU multicore computing engines and other specialized hardware. This has led researchers to routinely extend conformational sampling times to the microsecond level and beyond. The extended sampling time has allowed