Development of the Drude Polarizable Force Field for DNA and RNA and Applications to Investigations of Nucleic Acid Structure and Dynamics

Justin A. Lemkul

Department of Biochemistry, Virginia Tech

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The Classical Drude Oscillator Model

Response to electric field
and molecular polarizability

$$\alpha = \frac{q_D^2}{k_D}$$

Neighboring
dipole screening

DNA Stability with Drude-2013

Goals of refinement

1. Improve A-/B-DNA base stacking
2. Stabilize Z-DNA

Drude Nucleic Acid Force Field Development

DNA base refinement
Stacking interactions
Water interactions

DNA dihedral refinement
 χ (base changes)
 $\alpha, \beta, \gamma, \epsilon, \zeta$ (BI/BII, Z)
Sugar pucker

DNA validation
B-DNA, including A-tracts
A-DNA and Z-DNA

RNA base development
Uracil stacking interactions
Water/ion interactions

RNA dihedrals
 $\alpha, \beta, \gamma, \epsilon, \zeta$ /2'-OH 2-D surfaces

RNA validation
dsRNA, stem-loops,
tertiary folds

DNA Refinement: Base Stacking

$$U_{inter} = U_{stack} - U_{mono1} - U_{mono2}$$

	A-DNA			B-DNA			$\Delta U_{inter}(B-A)$		
	C36	Drude-2013	Drude-2017	C36	Drude-2013	Drude-2017	C36	Drude-2013	Drude-2017
Avg. Err.	-0.41	0.95	-0.11	0.18	1.34	-0.12	0.64	0.40	-0.01
AUE	1.44	1.23	0.79	1.41	1.44	0.61	1.12	0.69	0.70
RMSE	1.67	1.45	0.95	1.34	1.21	0.75	1.39	0.94	0.86

DNA Refinement: Sugar Puckering

DNA Refinement: Backbone Dihedrals

Drude-2017 B-DNA

Drude-2017 B-DNA

	experiment		MD simulation	
	assignment ^a	first derivative ^b	Drude-2013 ^c	Drude-new
EcoRI (12 bp)				
P1	0.48	0.46	0.51	0.49
P2 ^d		0.76	0.79	0.76
P3	1.14	1.12	1.12	1.07
P4	1.54	1.51	1.49	1.50
P5	1.87	1.83	1.80	1.88
1DCV (8 bp)				
P1		0.51	0.52	0.52
P2 ^d		0.76	0.82	0.81
P3		1.18	1.11	1.09
P4		1.53	1.50	1.47
P5		1.79	1.80	1.86

Drude-2017 A-DNA

A $\rightarrow$ B conversion in water
A-DNA stable in 75% EtOH

Drude-2017 Z-DNA

RNA 2'-OH and Conformational Energetics

Drude-2017 dsRNA

Drude-2017 dsRNA

UUCG Stem-Loop

r(GGCACUUCGGUGCC)

2KOC Heavy Atom RMSD

UUCG Stem-Loop

Base Dipole Moments in Stem-Loops

Ade and Ura very sensitive to environment
Gua and Cyt less sensitive

A Brief Foray into Mg^{2+}

The Drude-2017 Nucleic Acid Force Field

JCTC (2017) 13: 2053-2071

JCTC (2017) 13: 2072-2085

JPCB (2016) 120: 11436-11448

JCC (2018) 39: 2624-2646

G-Quadruplexes in Biology

Specific helicases

Telomeres

Promoters

G-Quadruplex Structure

S. Balasubramanian et al. (2011) *Nat. Rev. Drug Discov.* 10: 261-275.

The challenge:
ion-ion interactions

Stability of *c-kit* with Drude-2017

K⁺ Binding is Cooperative

Electronic Structure of *c-kit1* Stem

	with solvent		
	2 K ⁺	3 K ⁺	ΔE_{INT}
tetrad 1	-29.7 ± 4.5	-36.2 ± 2.6	-6.5 ± 2.7
tetrad 2	-64.8 ± 3.8	-65.9 ± 4.2	-1.1 ± 2.8
tetrad 3	-28.3 ± 3.9	-28.7 ± 4.3	-0.4 ± 2.9

Nucleobase Dipole Moments in DNA

Canonical B-form dsDNA (6 μ s)

1BNA (EcoRI/DD 12mer)
2L8Q (11mer)
1S2R (12mer, A-tract)
1DCV (10mer)
1AXP (purine-rich 10mer)
1ZF1 (10mer)

DNA G-Quadruplexes (20 μ s)

c-kit1: PDB 2O3M
c-kit2: PDB 2KYP
bcl-2: PDB 2F8U
c-myc: PDB 1XAV
telomere: PDB 1K8P

JCTC (2017) 13: 2072-2085

Telomeric GQ Base Dipole Moments

RNA Folding: gc(UUCG)gc Tetraloop

Conclusions

- Drude-2017 force field accurately models a wide range of nucleic acid structures, improvement over Drude-2013 in base stacking and conformational energetics
- Explicit electronic polarization improves K^+ retention in GQs
 - Coordination of K^+ from bulk solution to open tetrad faces is a common feature but varies in affinity
- Base dipole moments in GQ stems are sensitive to K^+ coordination
- RNA base dipole moments in stems and loops vary as a function of environment and folding state

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