CompBioMed
A Centre of Excellence in Computational Biomedicine

e-Seminar #27
DNA Point Mutations in the Absence and Presence of Electric Fields

19 October 2022

The e-Seminar will start at 2pm CEST / 1pm BST

Presenter:
Dr. Alya A. Arabi
(United Arab Emirates University, University College London)

Moderator:
Tim Weaving
(University College London)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

INSILICO WORLD
https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with: VPH Institute – Building the Virtual Physiological Human

CompBioMed

A Centre of Excellence in Computational Biomedicine

e-Seminar #27

DNA Point Mutations in the Absence and Presence of Electric Fields

19 October 2022

Welcome!

Presenter:
Dr. Alya A. Arabi
(United Arab Emirates University, University College London)

Moderator:
Tim Weaving
(University College London)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

INSILICO WORLD

https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with: VPH Institute — Building the Virtual Physiological Human

Sharjah
الشارقة
Dubai International Airport
Khor Fakkan
خور فكان
Fujairah
الفجيرة
Kalba
كلباء
Hatta
حتا
Shinas
ولاية شناص
1 hr 19 min
143 km
Liwa
لوى
Sohar
ولاية صحار
Abu Dhabi
أبو ظبي
New Al Falah
الفلاح الجديدة
Sweihan
سويحان
Al Ain International Airport
Al Buraimi
البريمي
Al Ain
العين
E55
E88
E102
E84
E44
E11
E611
E14
E66
E16
E22
E30
E40
1
Layers
Google

Outline

Introduction: Point Mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields (*Interface Focus*, **2020**, 10: 20190120)

- GC
- AT

Results With Electric Fields (*Phys. Chem. Chem. Phys.*, **2021**, 23, 6252)

Biological Implications

Conclusions

Outline

Introduction: Point Mutations in DNA, Löwdin Mechanism

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

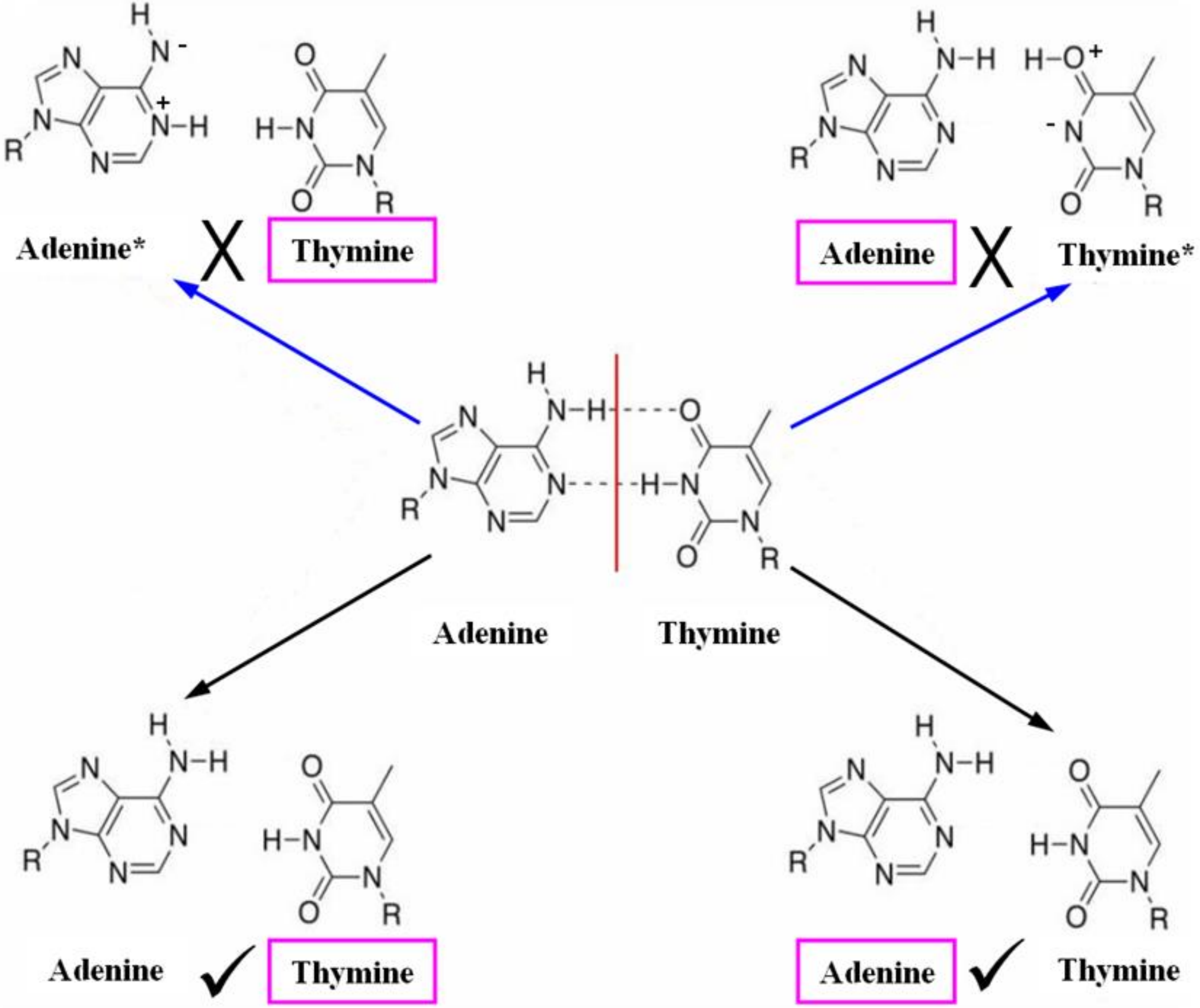
Results Without Electric Fields

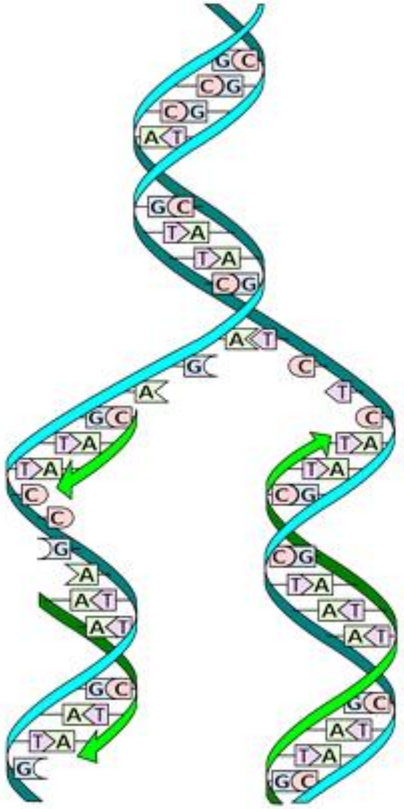
- GC
- AT

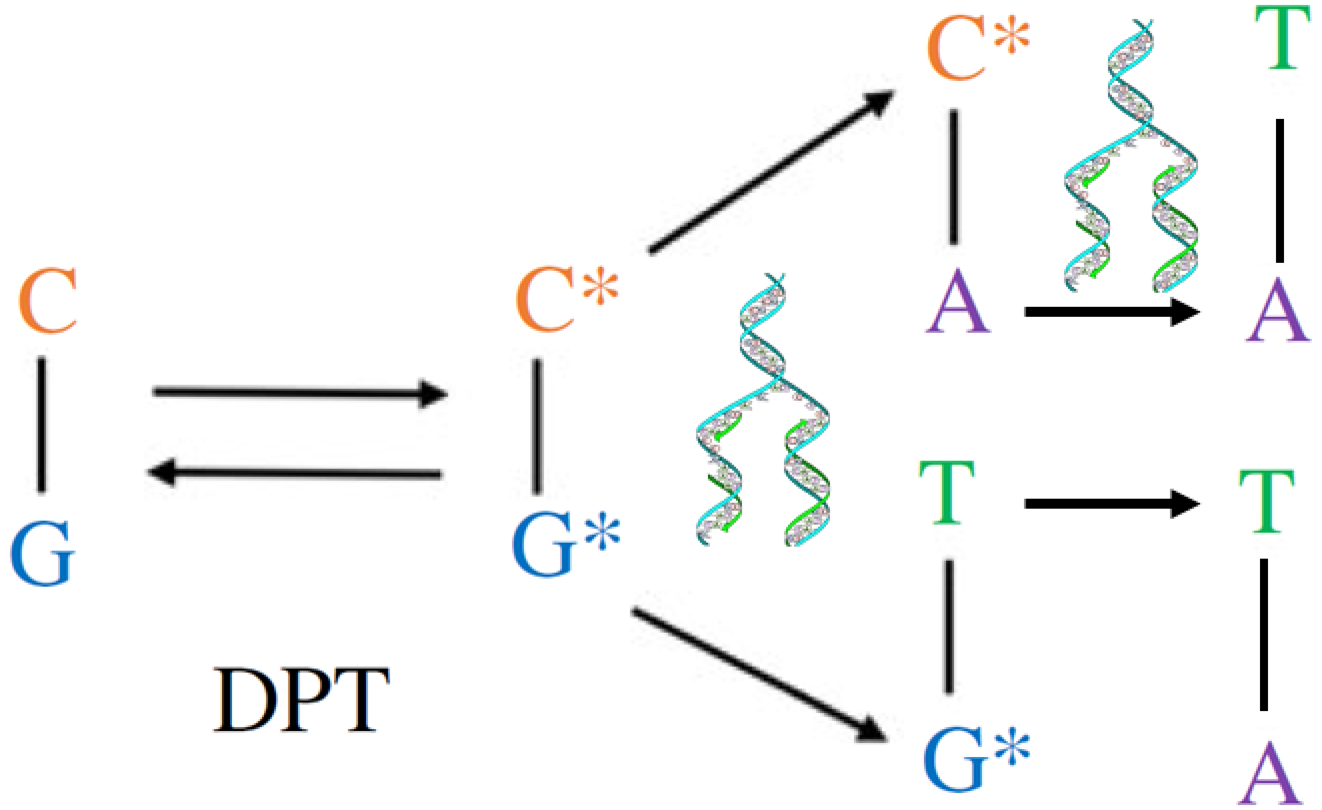
Results With Electric Fields

Biological Implications

Conclusions


Adenine*
X
Thymine
Adenine
X
Thymine*
Adenine
Thymine
Adenine
✓
Thymine
Adenine
✓
Thymine

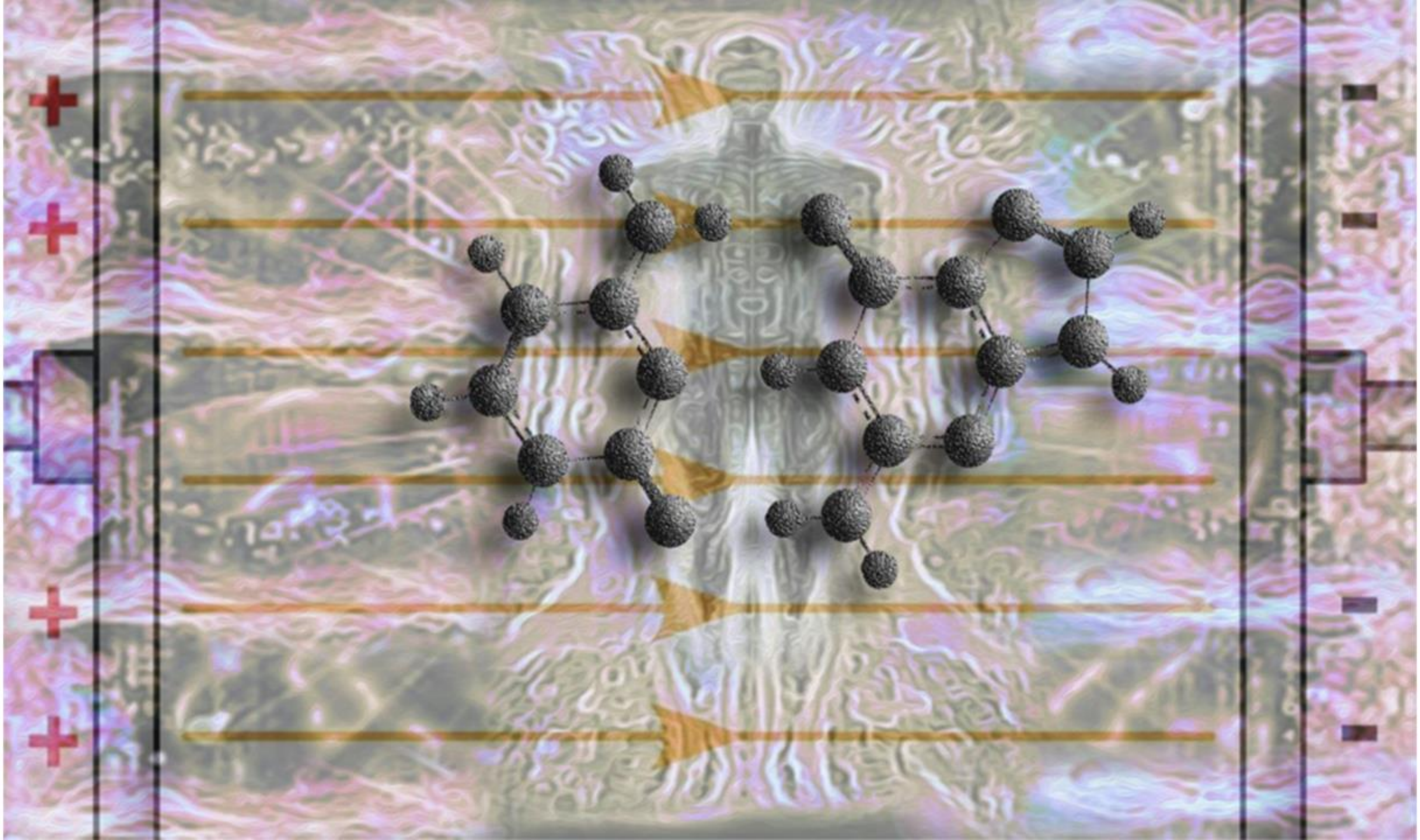




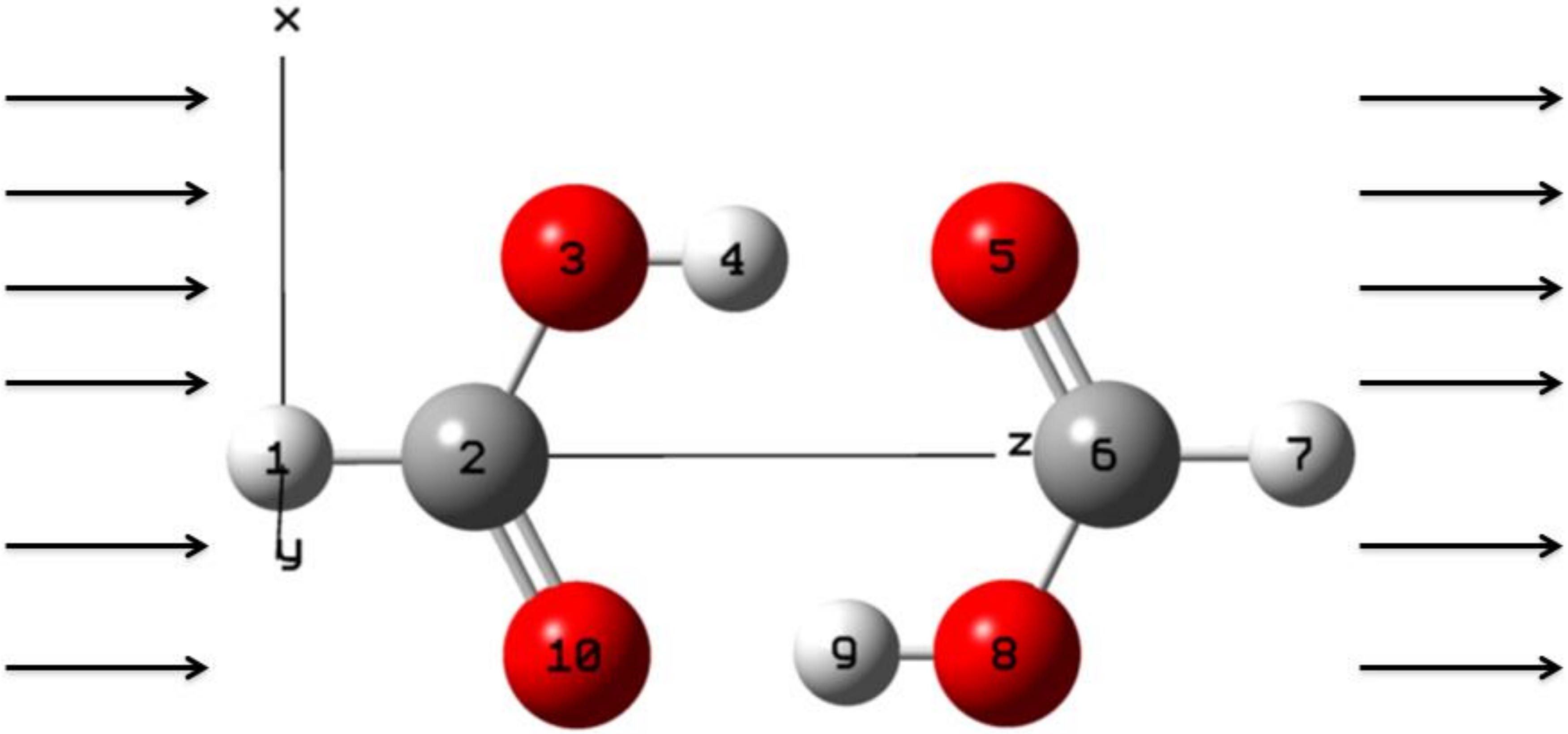
This hypothesis is supported by X-ray crystallography structures.

Rates of spontaneous mutations in humans: 10^{-8} to 10^{-11} base pairs per nucleotide replication or up to 30 base pairs per genome.

Proc. Natl. Acad. Sci. U. S. A., **2011**, 108, 17644

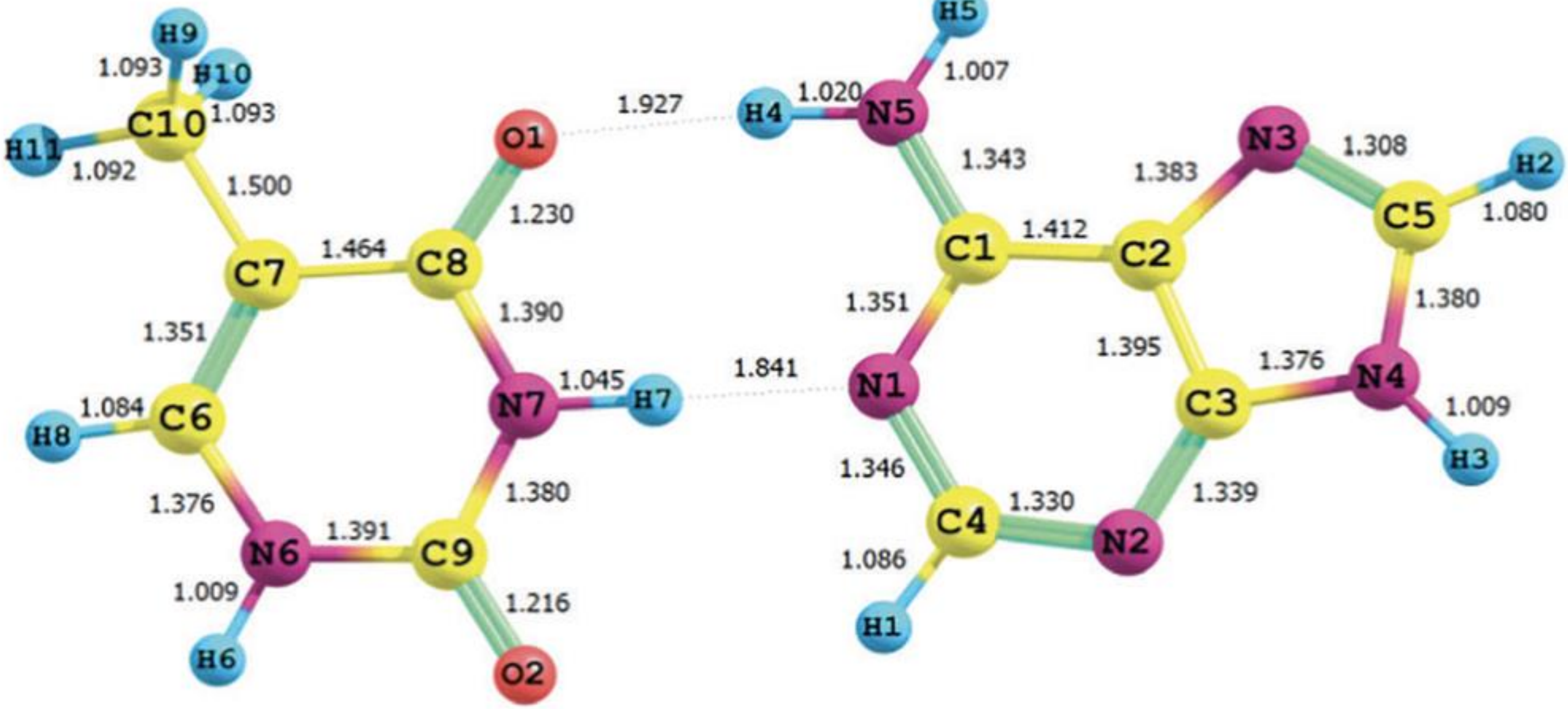


Simplified Symmetric Model



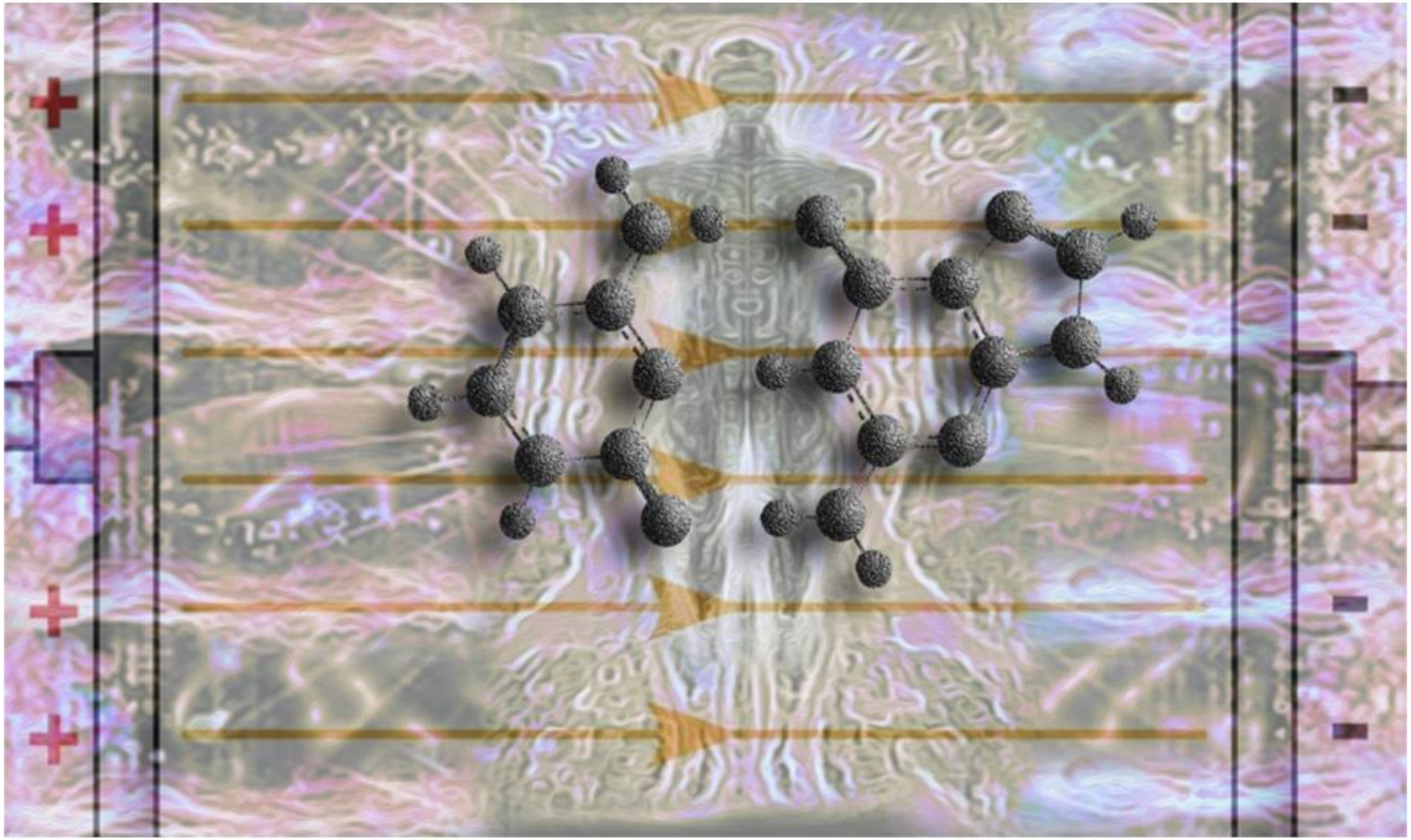
Phys. Chem. Chem. Phys., **2011**, 13, 13738

AT Base Pair



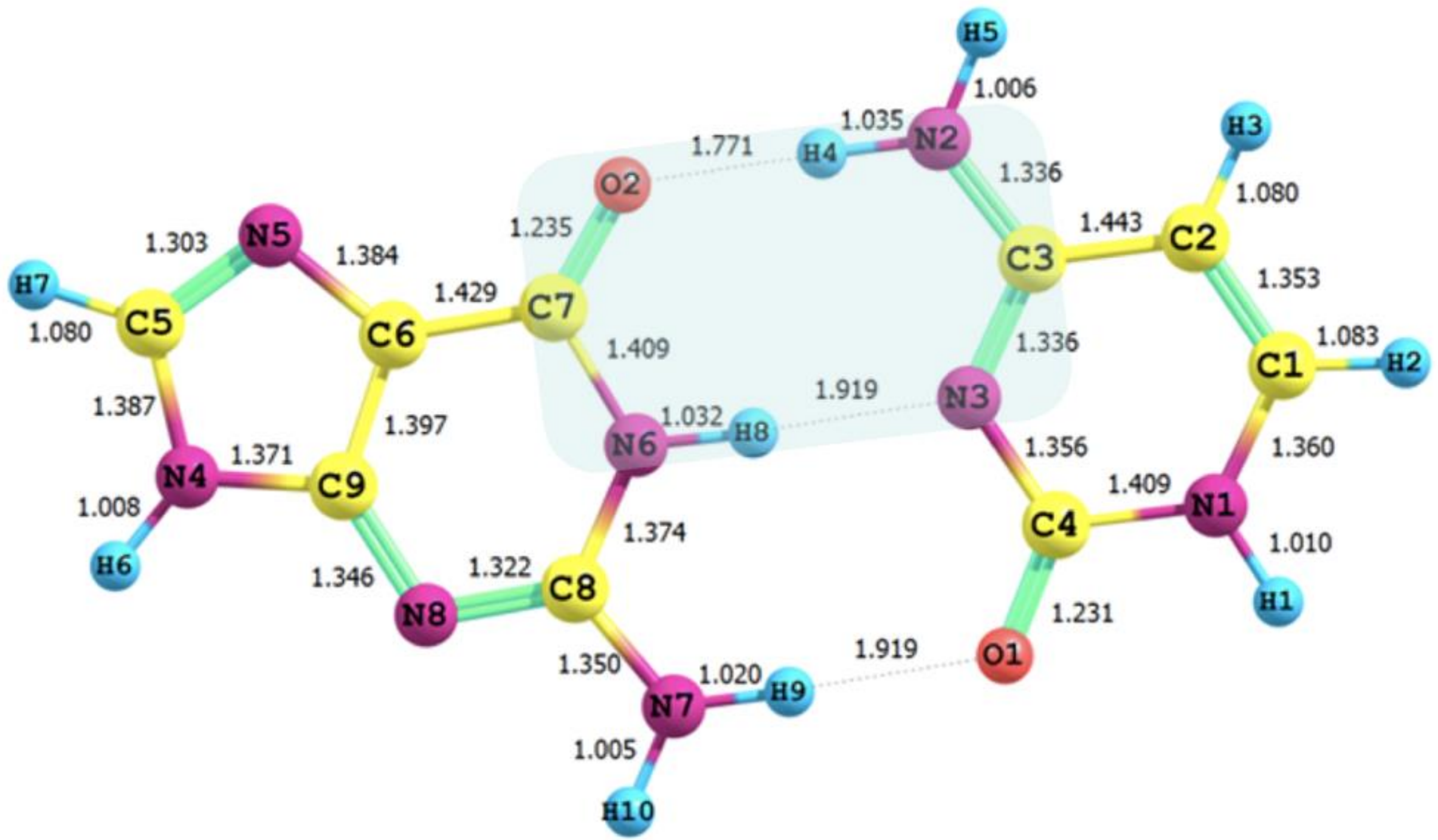
Phys. Chem. Chem. Phys., **2018**, 20 (18), 12406

GC Base Pair



J. Phys. Chem. B, **2018**, 122 (37), 8631

Three possible tautomerization reactions with zwitterion products



Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

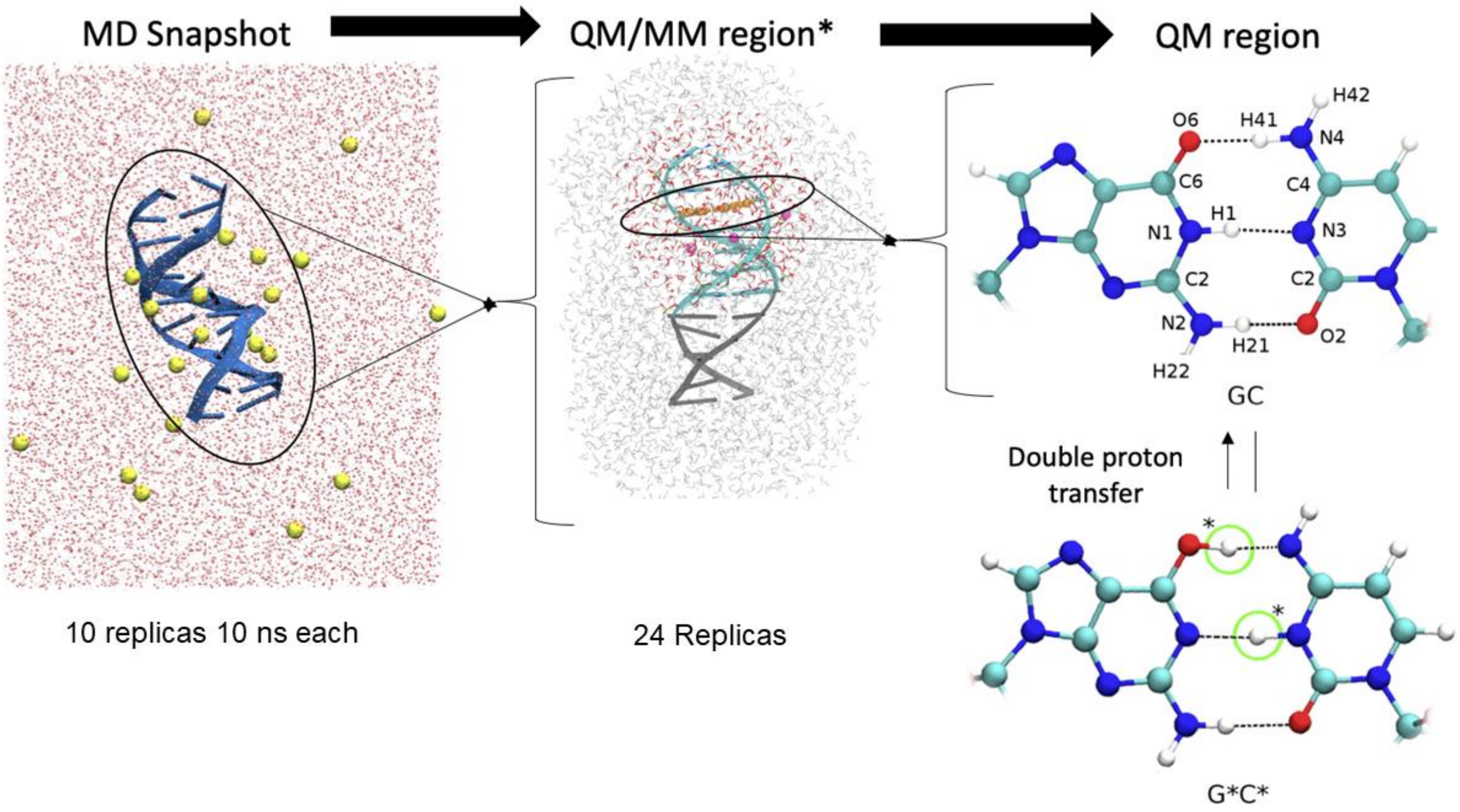
Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions


MD Snapshot
QM/MM region*
QM region
O6
H41
H42
N4
C6
C4
H1
N1
N3
C2
C2
N2
H21
O2
H22
GC
Double proton transfer
*
*
G*C*
10 replicas 10 ns each
24 Replicas

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

Ensemble Molecular Dynamics

Software used: NAMD 2.12
AMBER *parmbsc1* forcefield

PDB ID: 1BNA

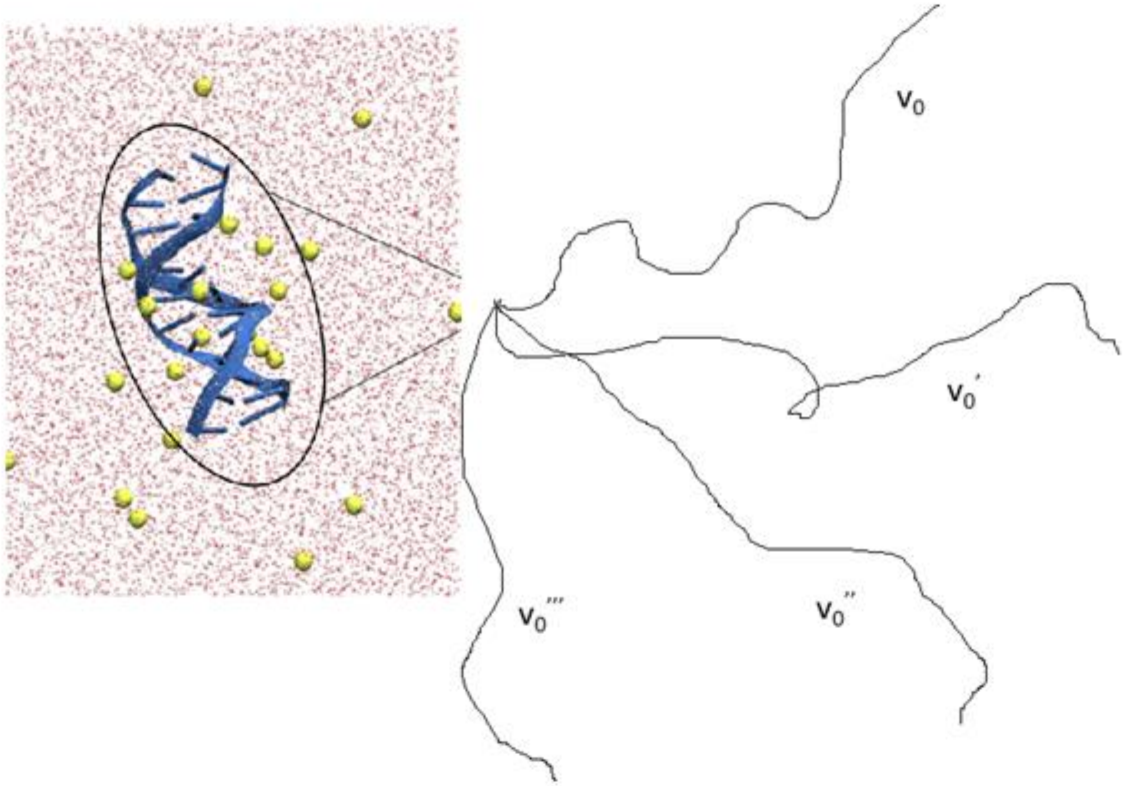
Neutralized it with 22 Na^+

Solvated in a 71 Å x 73 Å x 86 Å box using TIP3P water model.

Thermalized the dodecamer at 300 K and 1 atm.

10 replicas 10 ns each replica (starting with different initial
conditions - velocities), a total of 100 ns.

From a total of 10,000 frames, 24 frames were considered
(based on probabilistic distribution).



Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

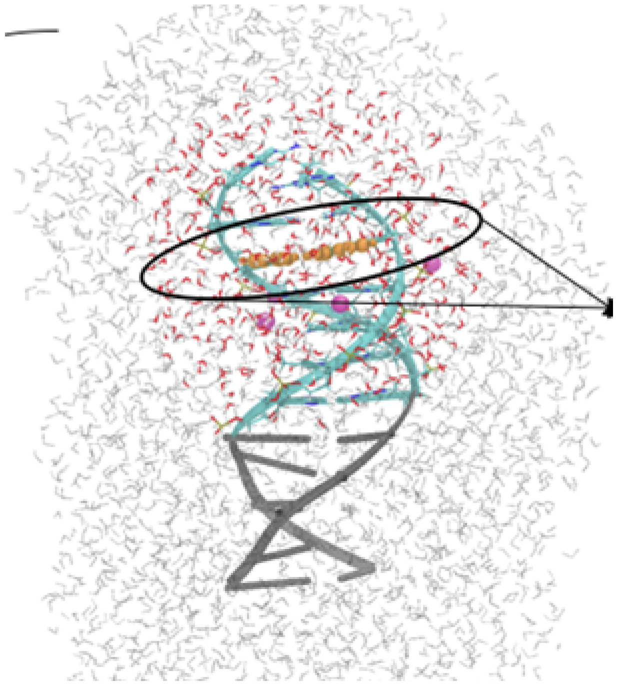
Biological Implications

Conclusions

QM Region

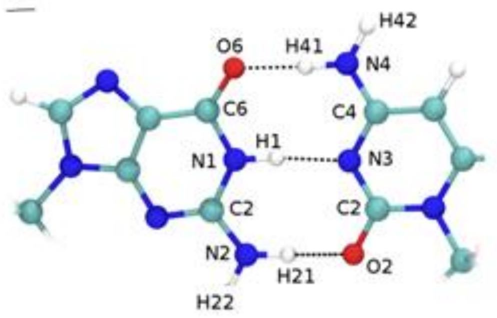
Software used: NWChem 6.6

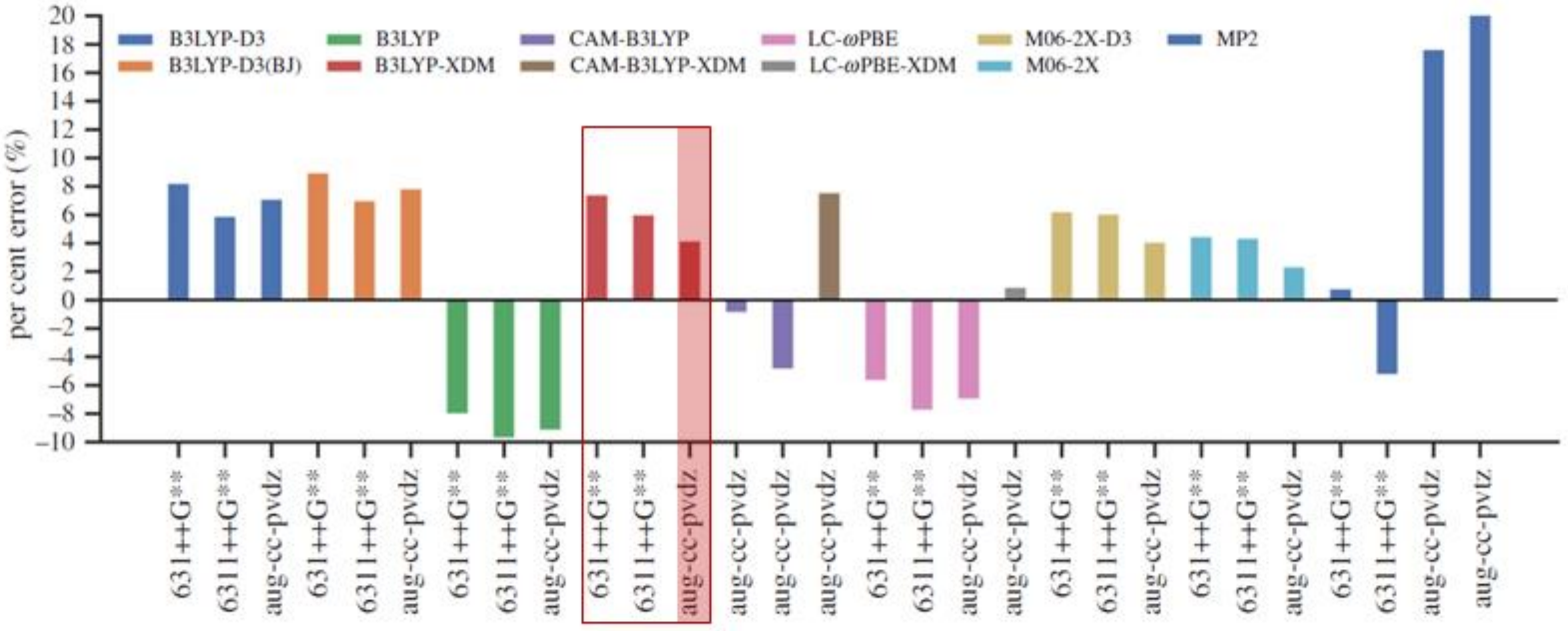
Benchmark (DFT, WFT) study for hydrogen-bonded and stacked PB.
Methods: B3LYP, cam-B3LYP, LC-*w*PBE, MP2;
With D3, D3(BJ), or XDM for dispersion;
With Pople and Dunning double and triple zeta basis sets.



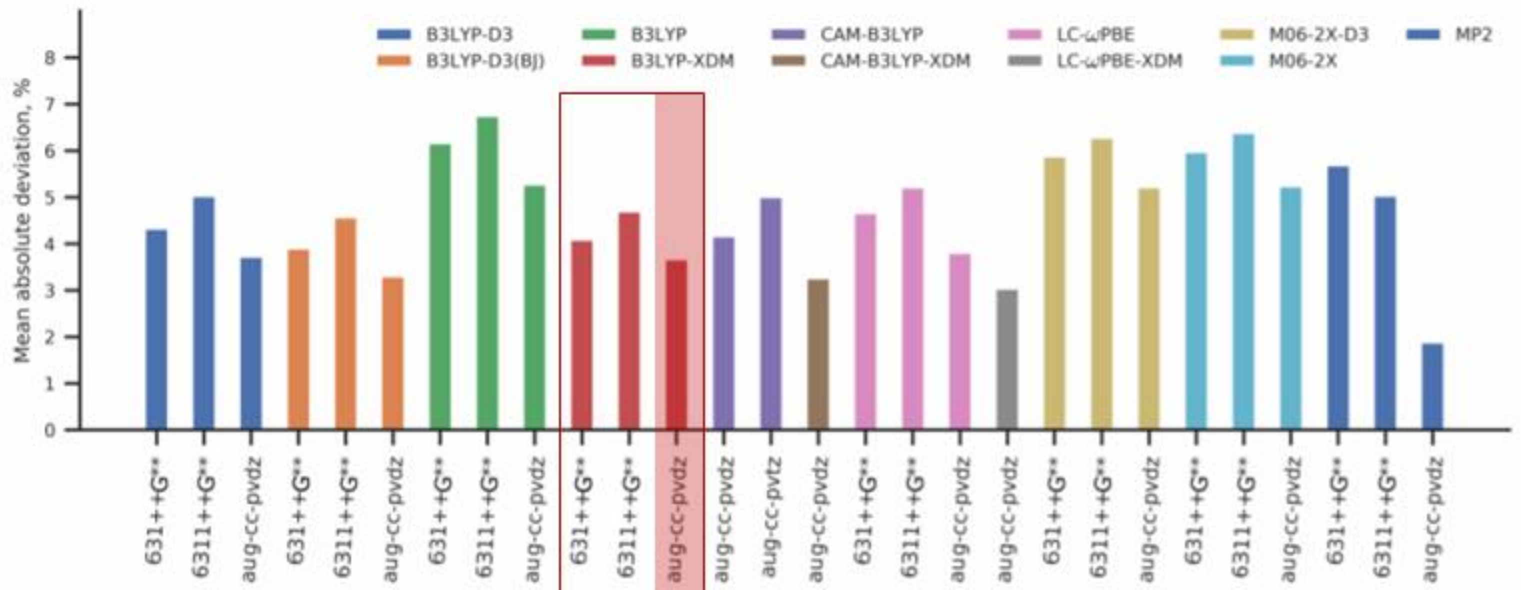
Reference geometries/energies: MP2(cc-pvtz)/CCSD(T)[CBS] (Hobza, 2006).
Stacked base pairs.

QM: H-Bonded GC



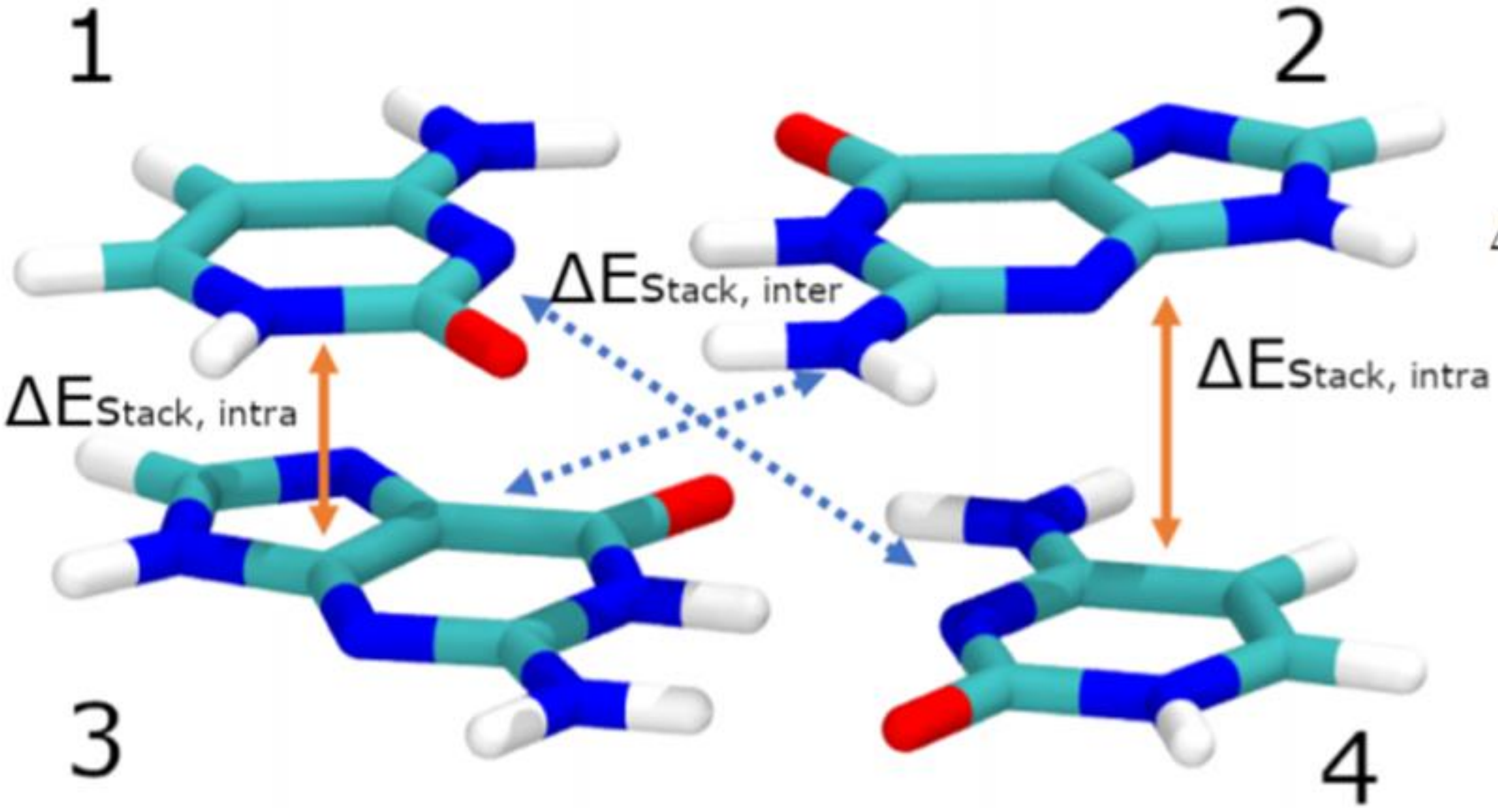


Energy



Geometry

QM: Stacked Base Pairs



$$\Delta E_{\text{stack}} = \Delta E_{13} + \Delta E_{24} + \Delta E_{14} + \Delta E_{23}$$

$$\Delta E_{XY} = E_{XY} - \sum_{i}^{X,Y} E_i$$

$$\Delta E_{4\text{stack}} = E_{1234} - E_{12} - E_{34}$$

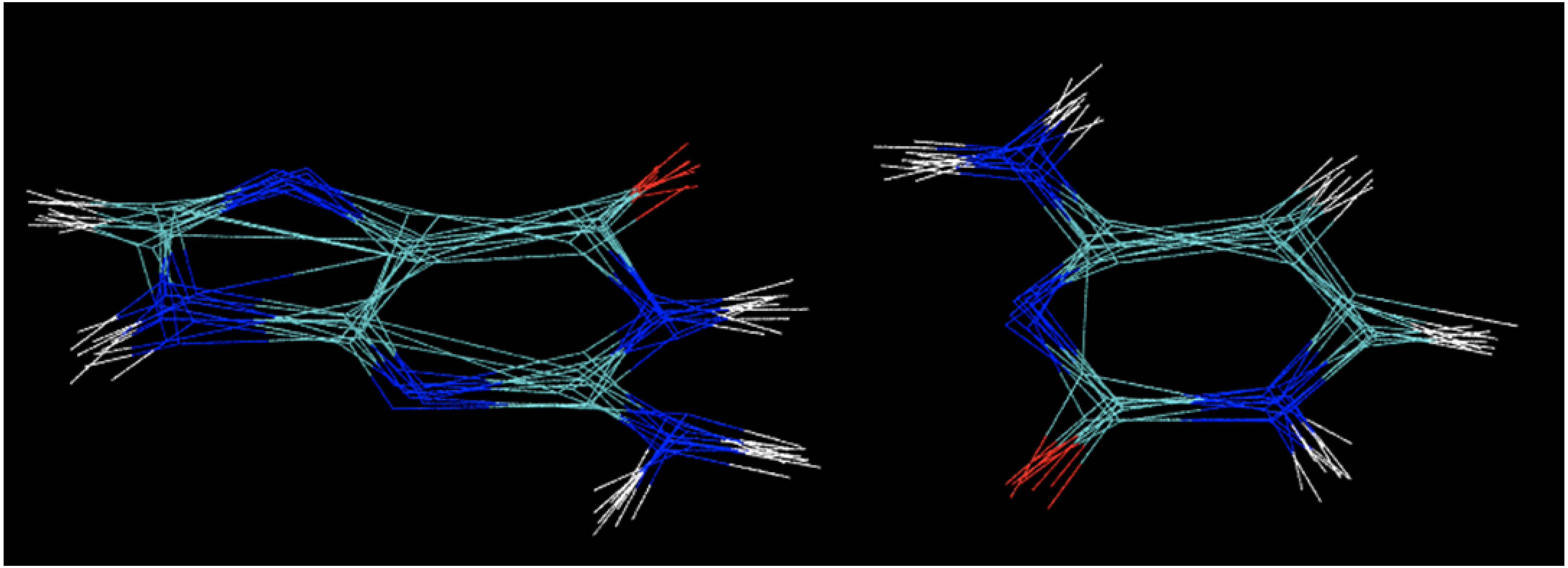
Phys. Chem. Chem. Phys., **2006**, 8, 1985

QM: Stacked Base Pairs

10 different combinations of stacked base pairs were considered:

method	basis sets	average error in ΔE_{stack} (kcal mol^{-1})	average error in ΔE_{4stack} (kcal mol^{-1})
B3LYP+D3	6-31++G**	−1.237	−2.000
	6-311++G**	−1.751	−2.462
	aug-cc-pvdz	−1.459	−2.144
B3LYP+D3(BJ)	6-31++G**	−1.889	−2.651
	6-311++G**	−2.402	−3.113
	aug-cc-pvdz	−2.111	−2.795
B3LYP+XDM	6-31++G**	−1.487	−1.867
	6-311++G**	−2.377	−2.520
	aug-cc-pvdz	0.782	0.345
CAM-B3LYP	6-31++G**	13.785	13.282
	6-311++G**	13.247	12.818
	aug-cc-pvdz	13.658	13.248

Dependence of QM on difference replicas



QM Region

B3LYP+XDM/aug-cc-pvdz

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

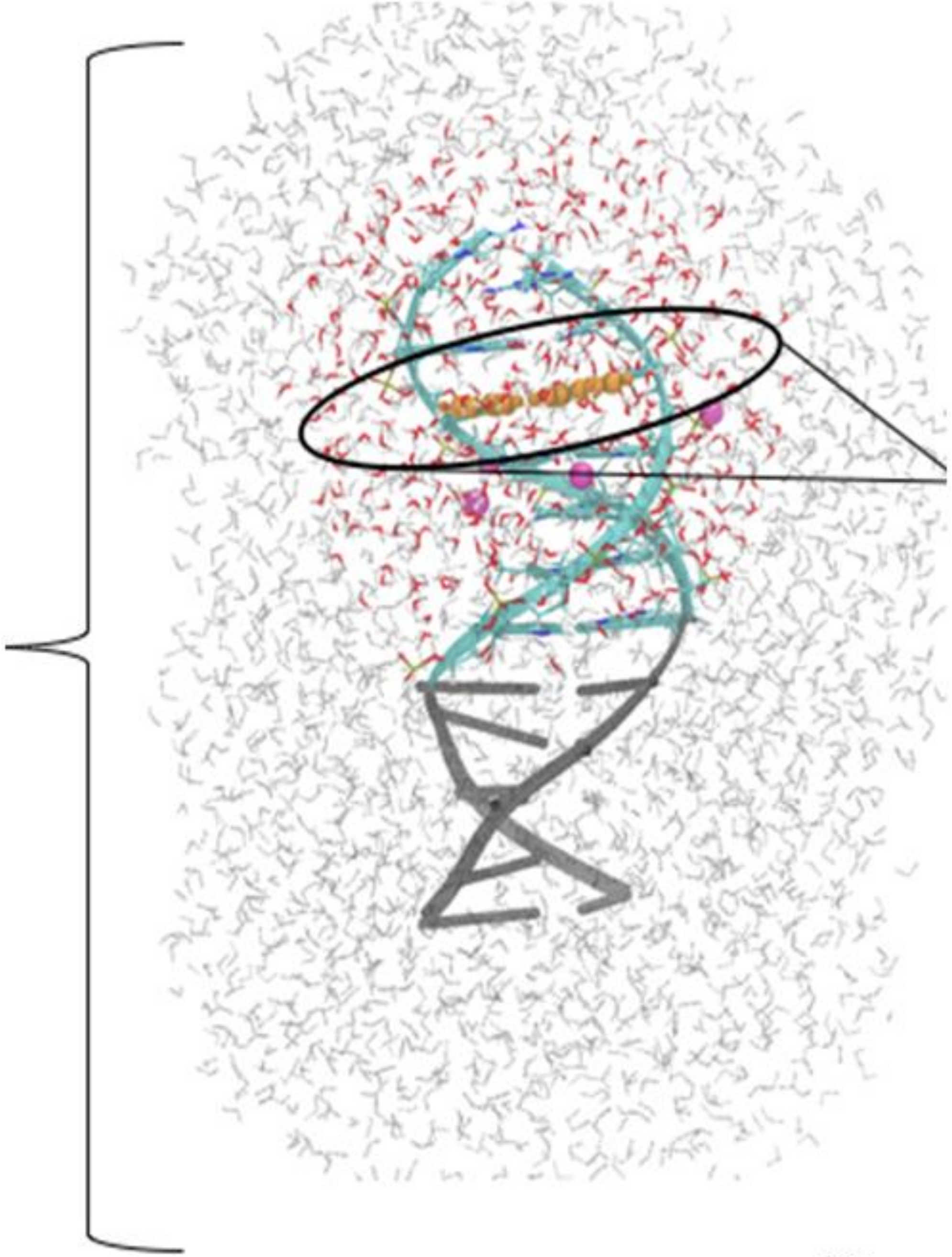
Conclusions

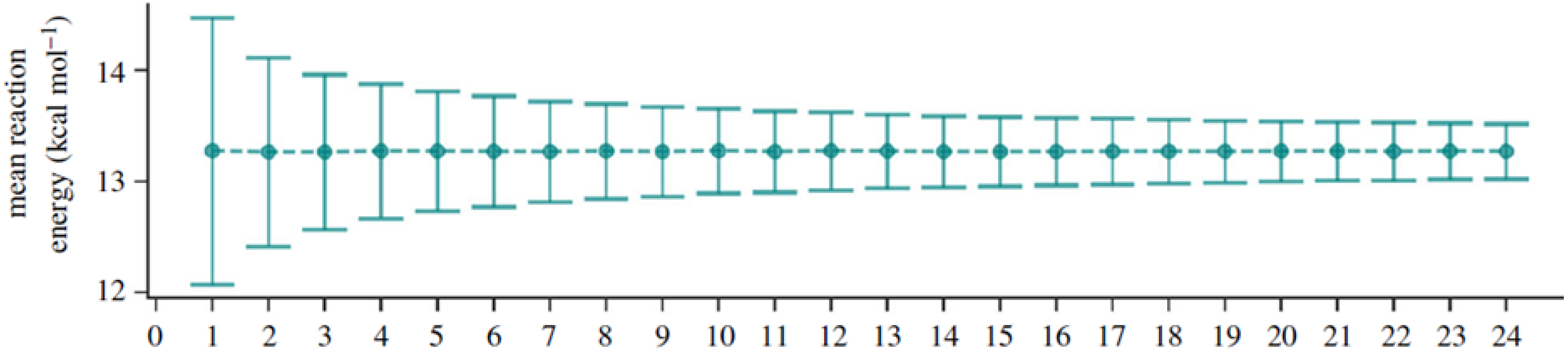
QM/MM

ChemShell 3.7 (DL-FIND module) to link NWChem 6.6 (QM) with DL-POLY (MM using AMBER parmbsc1 force field).

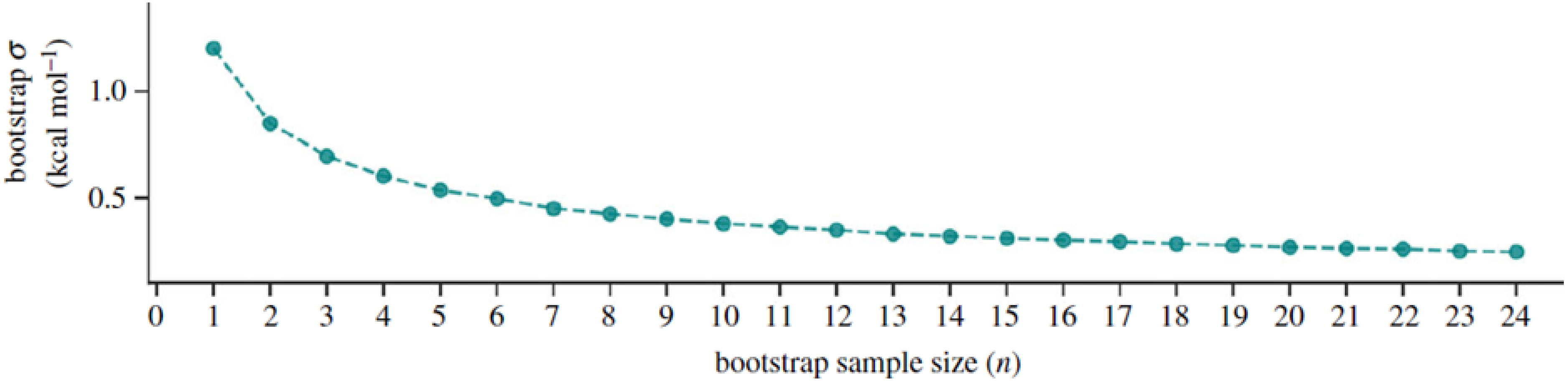
Relax the system in the MM region within 15 Å of the QM region (i.e. 6 out of 12 base pairs, i.e. ~9000 atoms, were relaxed) with solvation and counter ions.

The remaining residues were frozen in space.





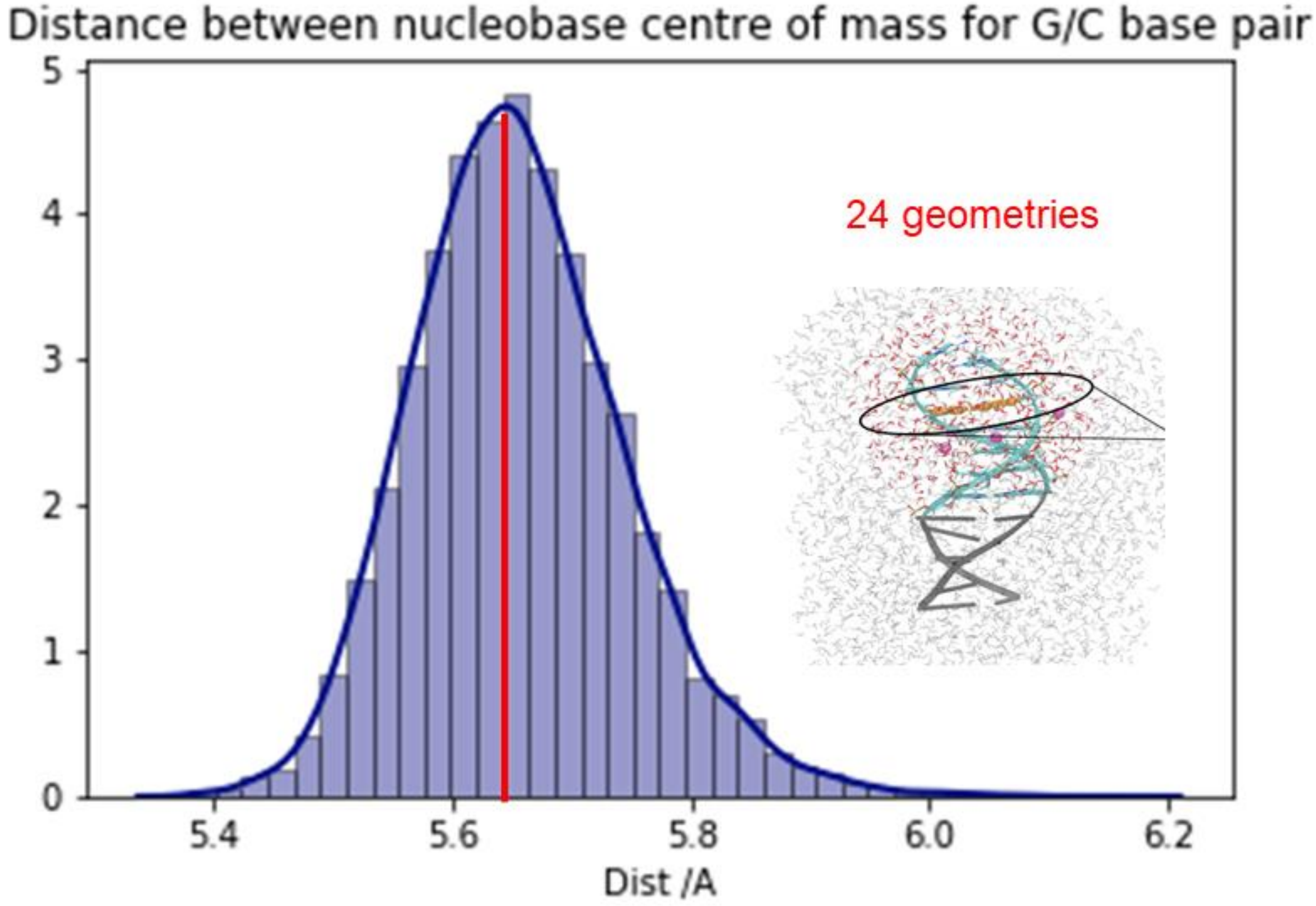
The mean G:C→G*:C* tautomerism reaction energy (ΔE_{rxn}) calculated using QM/MM (B3LYP+XDM/aug-cc-pvdz/AMBER). The error bars are the bootstrap standard deviation.



The bootstrap standard deviation (σ) of ΔE_{rxn}, plotted against the number of QM/MM replicas n.

A total of 24 different configurations associated with errors as low as 0.25 kcal mol^{-1}).

Molecular Dynamics



The distribution of average base pair distance, taken from 10,000 snapshots over 100 ns of MD simulations on dsDNA.

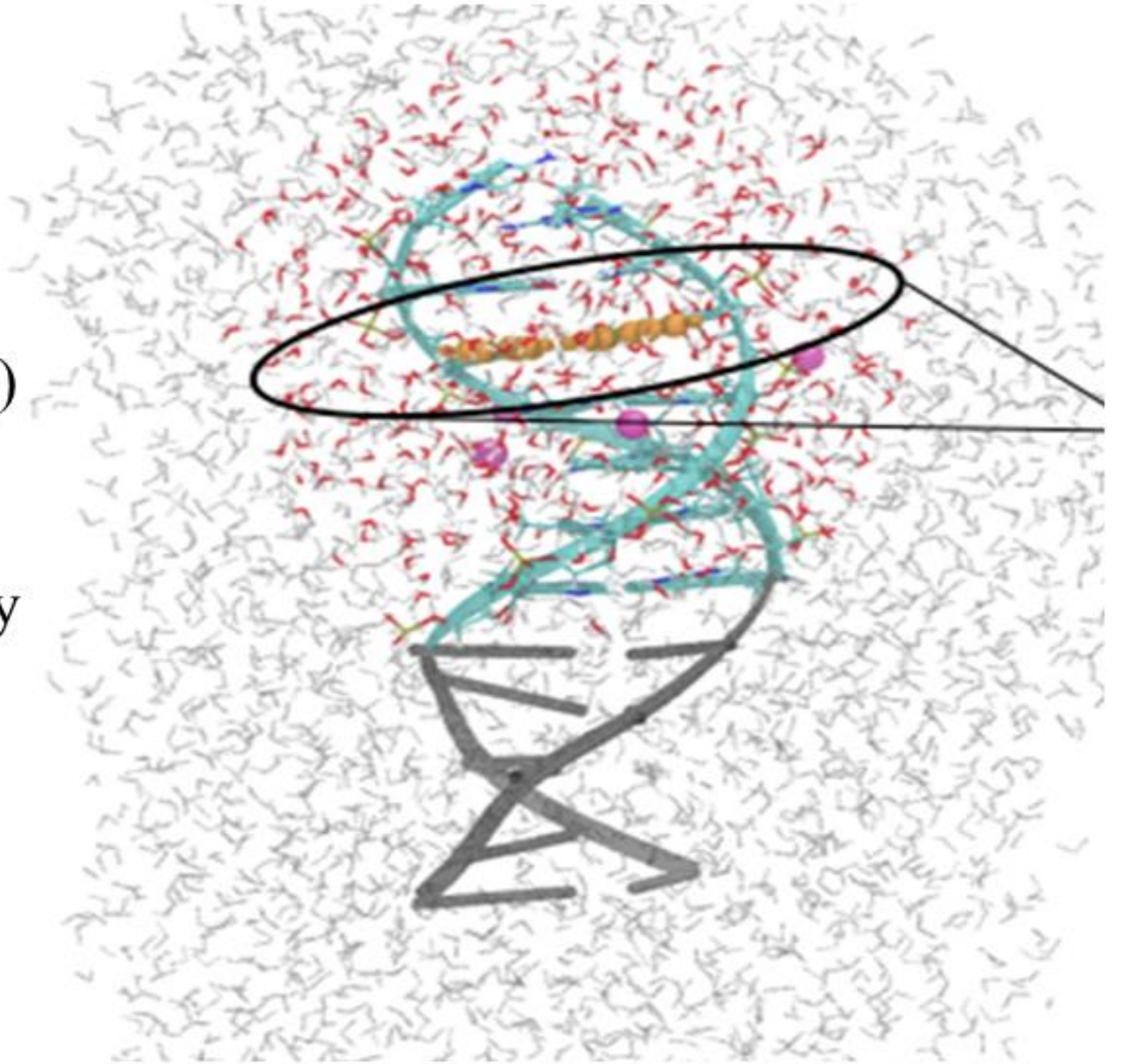
QM/MM

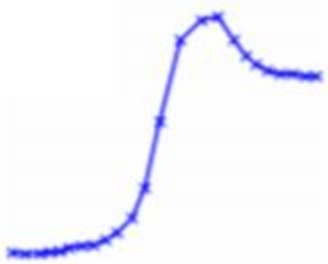
Solvation sphere of 15 Å around the DNA

IRC: ciNEB (climbing image nudged elastic band) using [XC]/6-311++G**/AMBER.

TS were verified by a single imaginary frequency in the Hessian.

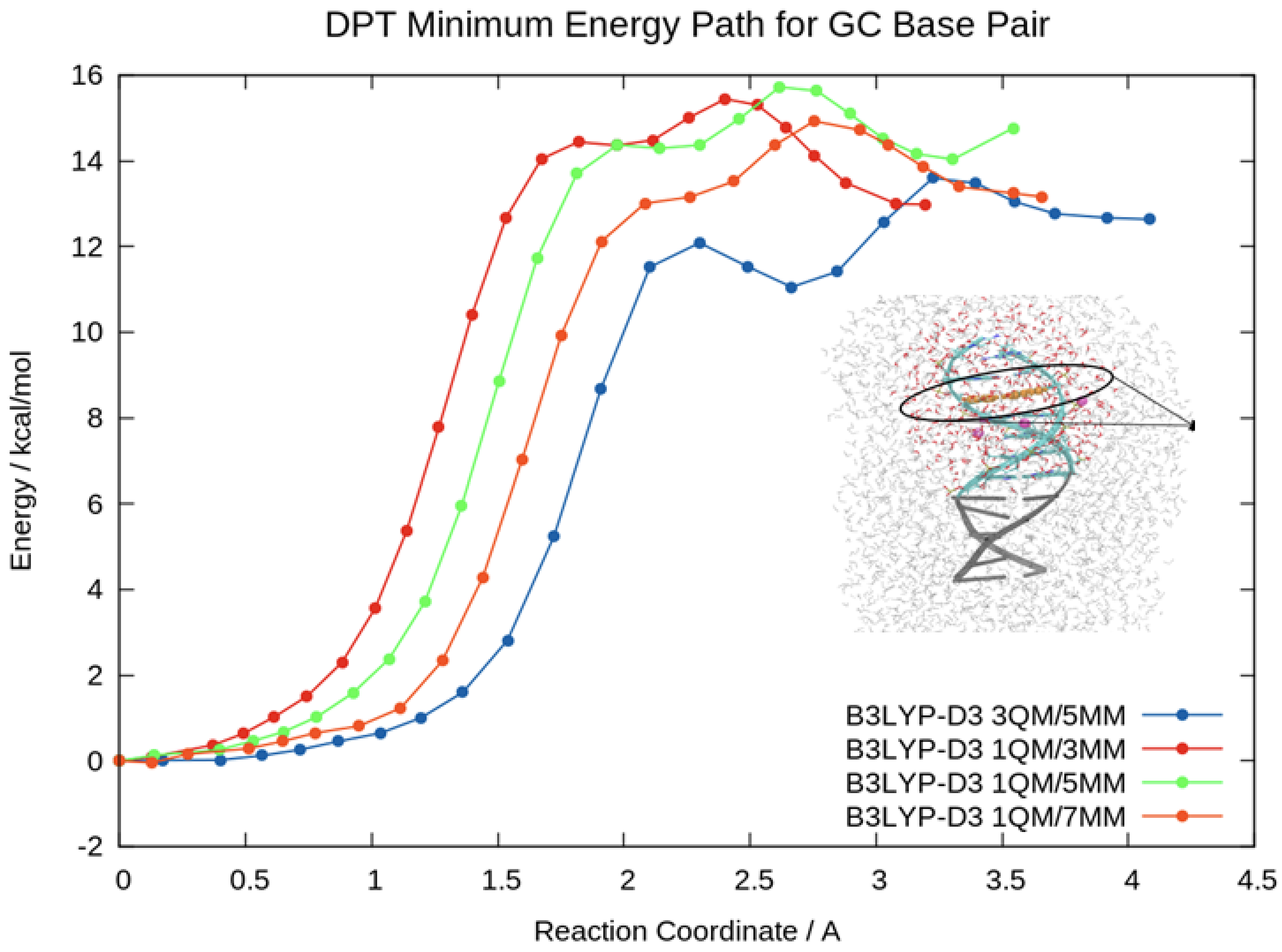
Size of the QM region?
1 base pair (starting from the third base pair).





QM/MM: IRC: size of QM and MM regions

ciNEB (climbing image nudge elastic band): B3LYP-D3/6-311++G**/AMBER



Barrier heights from 3 QM base pairs decrease, but only within the errors arising from ensemble averaging of single base pair QM regions.

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

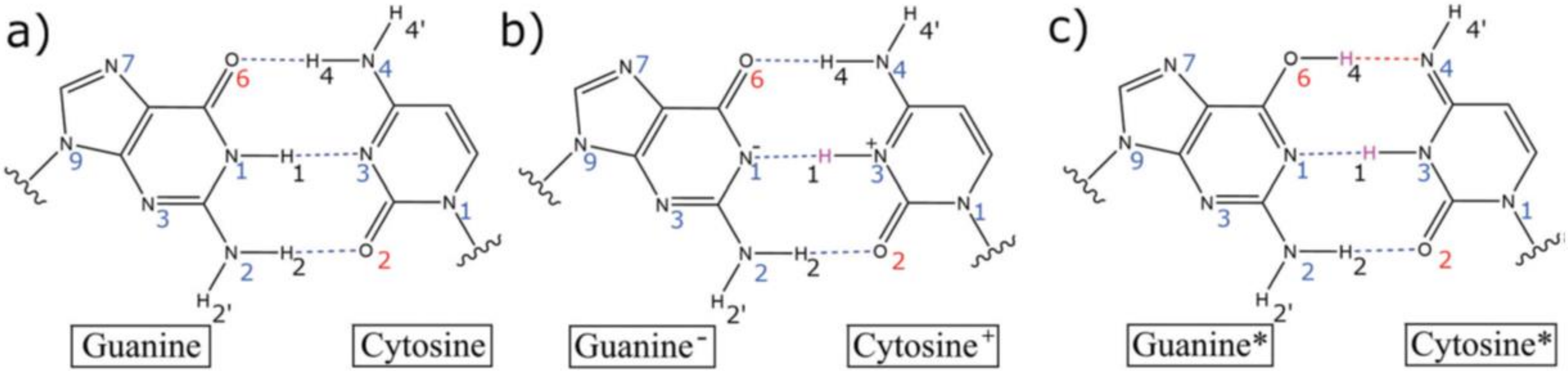
- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

Reactants and Products

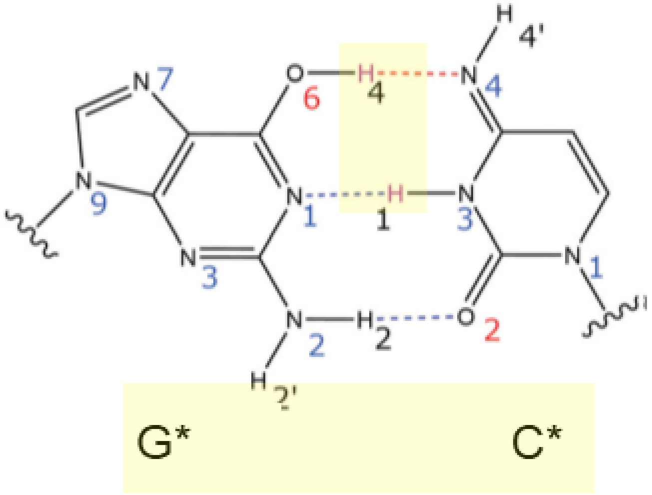


Canonical GC

G^-C^+ Zwitterion
Single Point Transfer

G*C* Tautomer
Double Proton Transfer

Three different base pair tautomerism pathways in GC:

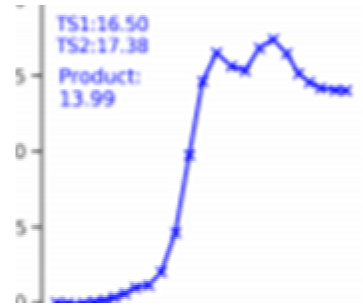


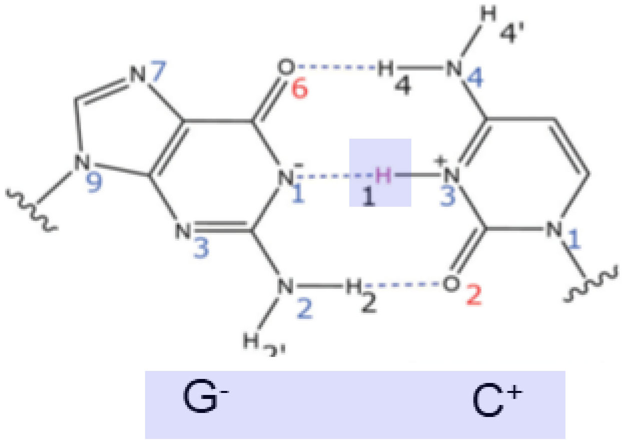
(1) ***Concerted*** double proton transfer

$$\mathrm{GC} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{G^*C^*}$$

(2) ***Stepwise*** double proton transfer

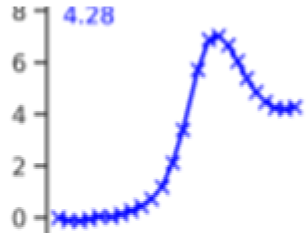
$$\mathrm{GC} \underset{k_a'}{\overset{k_a}{\rightleftharpoons}} \mathrm{(GC)_{Int}} \underset{k_b'}{\overset{k_b}{\rightleftharpoons}} \mathrm{G^*C^*}$$



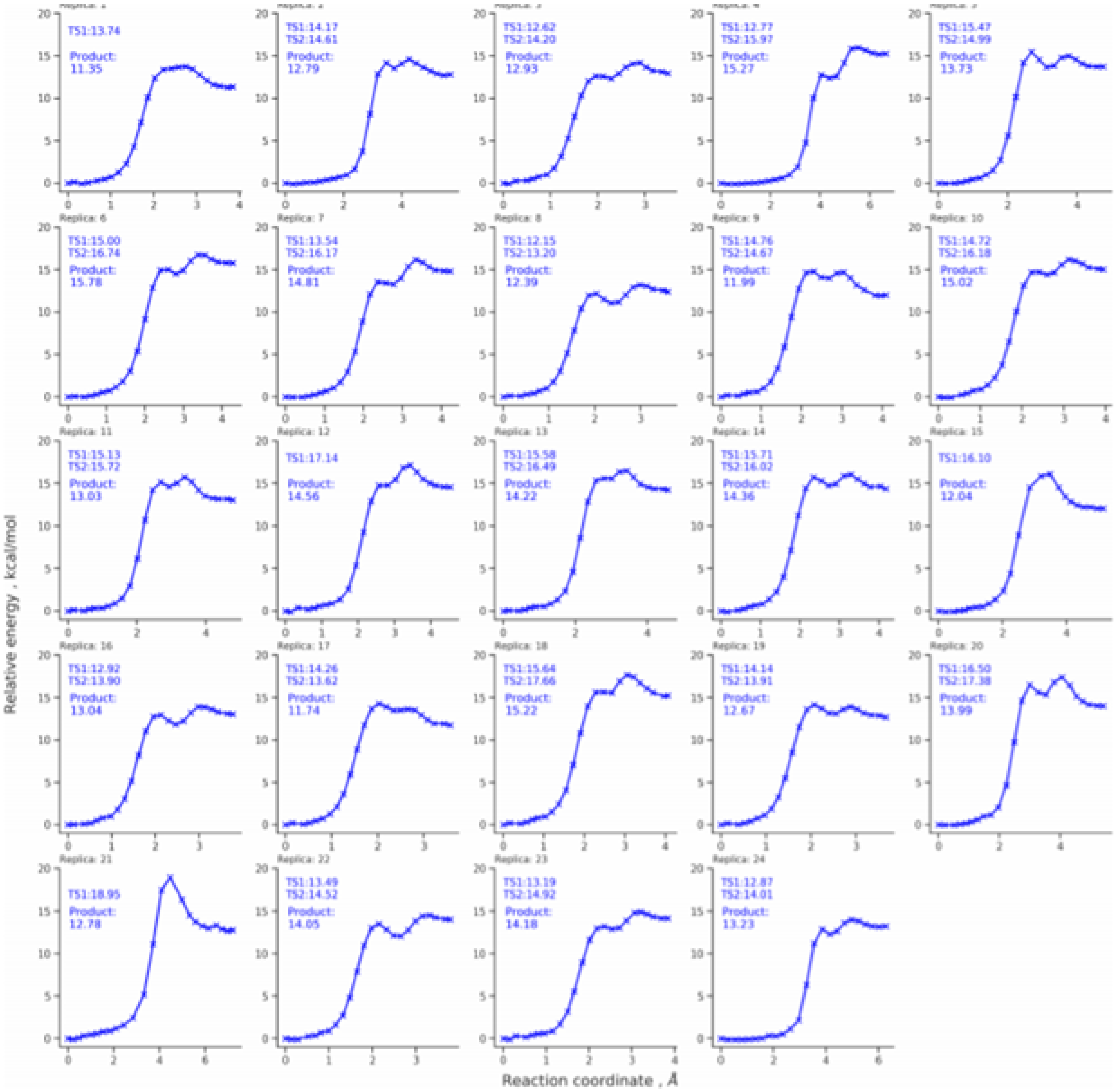


(3) Concerted single proton transfer

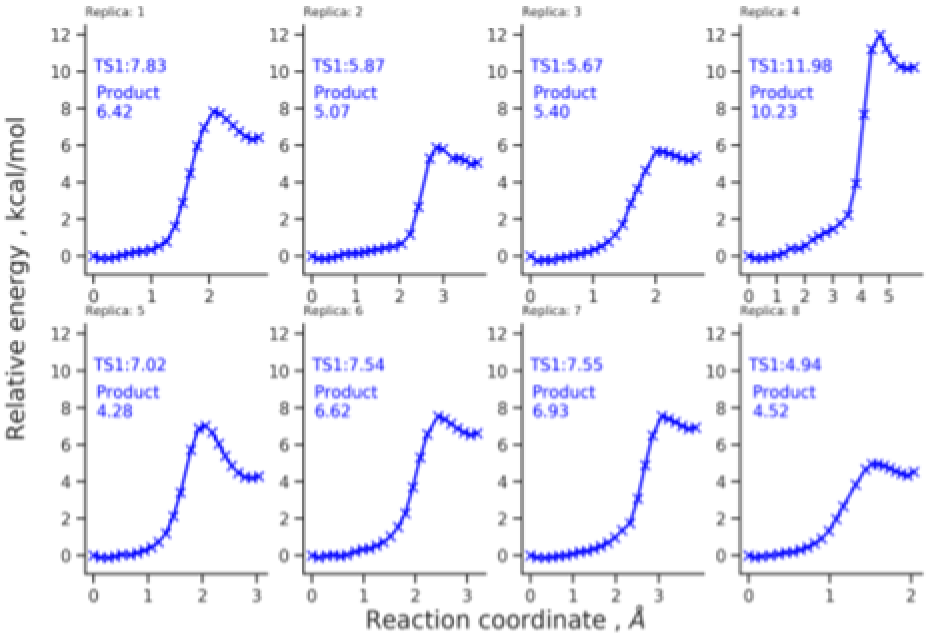
$$\mathrm{GC} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{G^-C^+}$$



Mechanism: ciNEB from QM/MM-ensemble: B3LYP+XDM/augcc-pvdz/AMBER

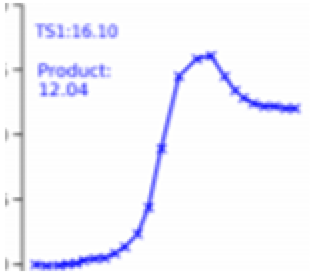
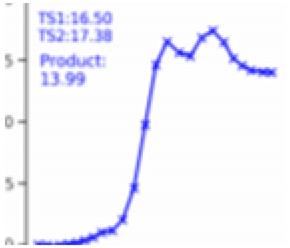
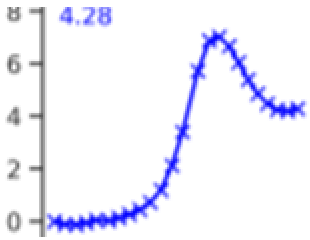


DPT of GC (24 out of 25 replicas).



SPT of AT (7 out of 25 replicas + 1 intra-A rearrangement)

Mechanism: probabilities based on 25 QM/MM replicas

		GC	AT
(1) ***Concerted*** double proton transfer (G*C* or A*T*)		12%	0%
(2) ***Stepwise*** double proton transfer (G*C* or A*T*)		84%	0%
(3) Concerted single proton transfer (G^-C^+ or A^+T^-)		4%	28%
(2) ***No*** reaction		0%	68%
			+4% Rearrangement

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

Thermodynamics

Gibbs Energy

$$\Delta G = \Delta E_{\mathrm{corr}} + k_{\mathrm{B}} T - \Delta S_{\mathrm{vib}} T,$$

$$E_{\mathrm{corr}} = \epsilon_0 + E_{\mathrm{vib}} + E_{\mathrm{ZPE}}.$$

Kinetics

Rate coefficient according to conventional transition state theory:

$$k(T) = \kappa(T)\frac{k_B T}{h}\exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right),$$

Wigner tunneling correction coefficient (quantum tunneling):

$$\kappa(T) = 1 + \frac{1}{24}(\beta\hbar\,\omega_b)^2;\ \beta = \frac{1}{k_B T},$$

ω_b is the imaginary frequency of the TS

Equilibrium constant and half life:

$$K = \frac{k_f}{k_r} \qquad t_{1/2} = \frac{\ln 2}{k_r}$$

Concentrations at time t:

$$[G^*C^*]_t = \frac{k_f[GC]_0 - k_r[G^*C^*]_0}{k_f + k_r}\{1 - \exp[-(k_f + k_r)t]\}$$

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

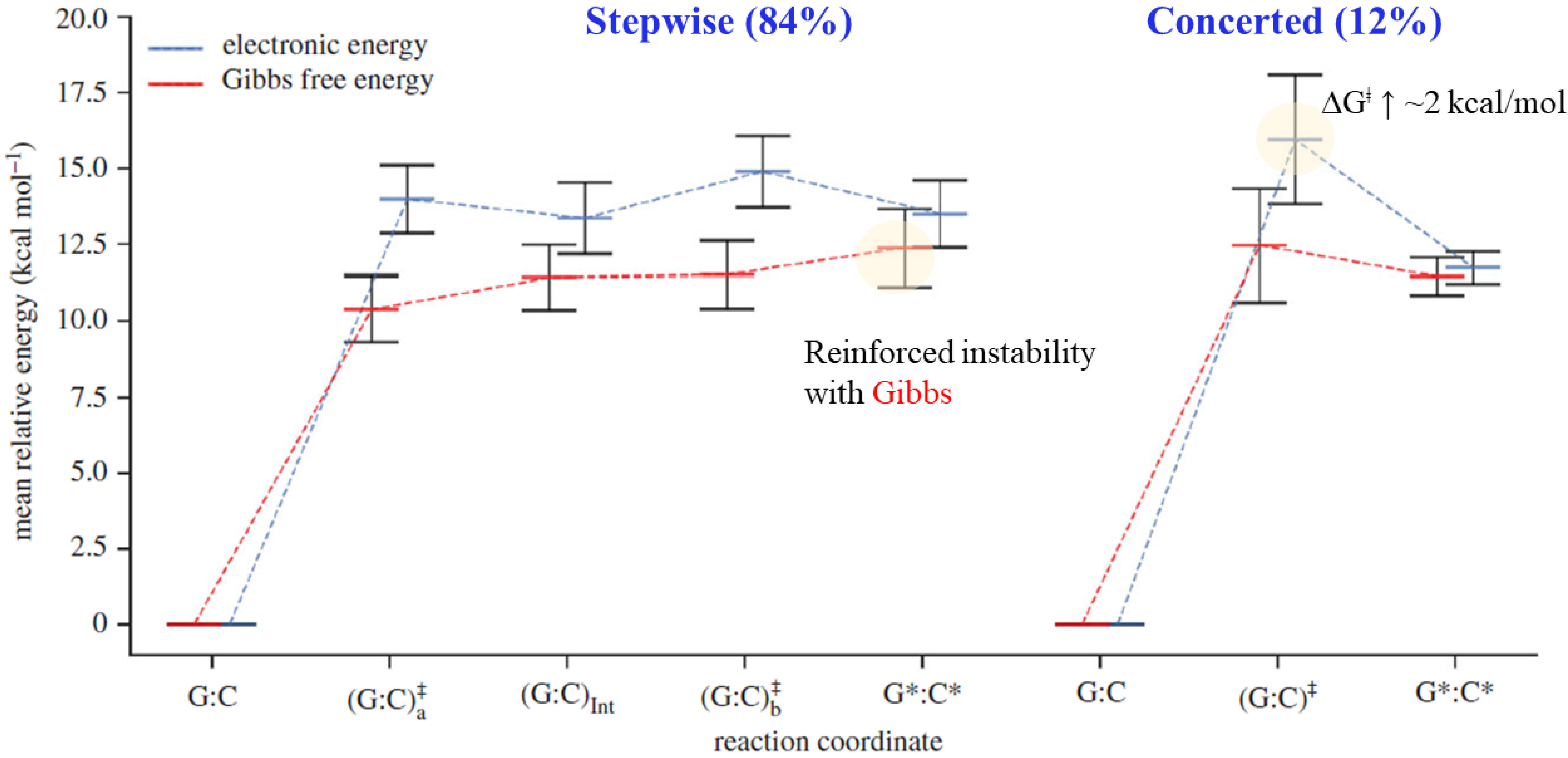
- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

DPT: GC to G*C*



Low reverse barriers help the DNA keep the fidelity to the canonical form.

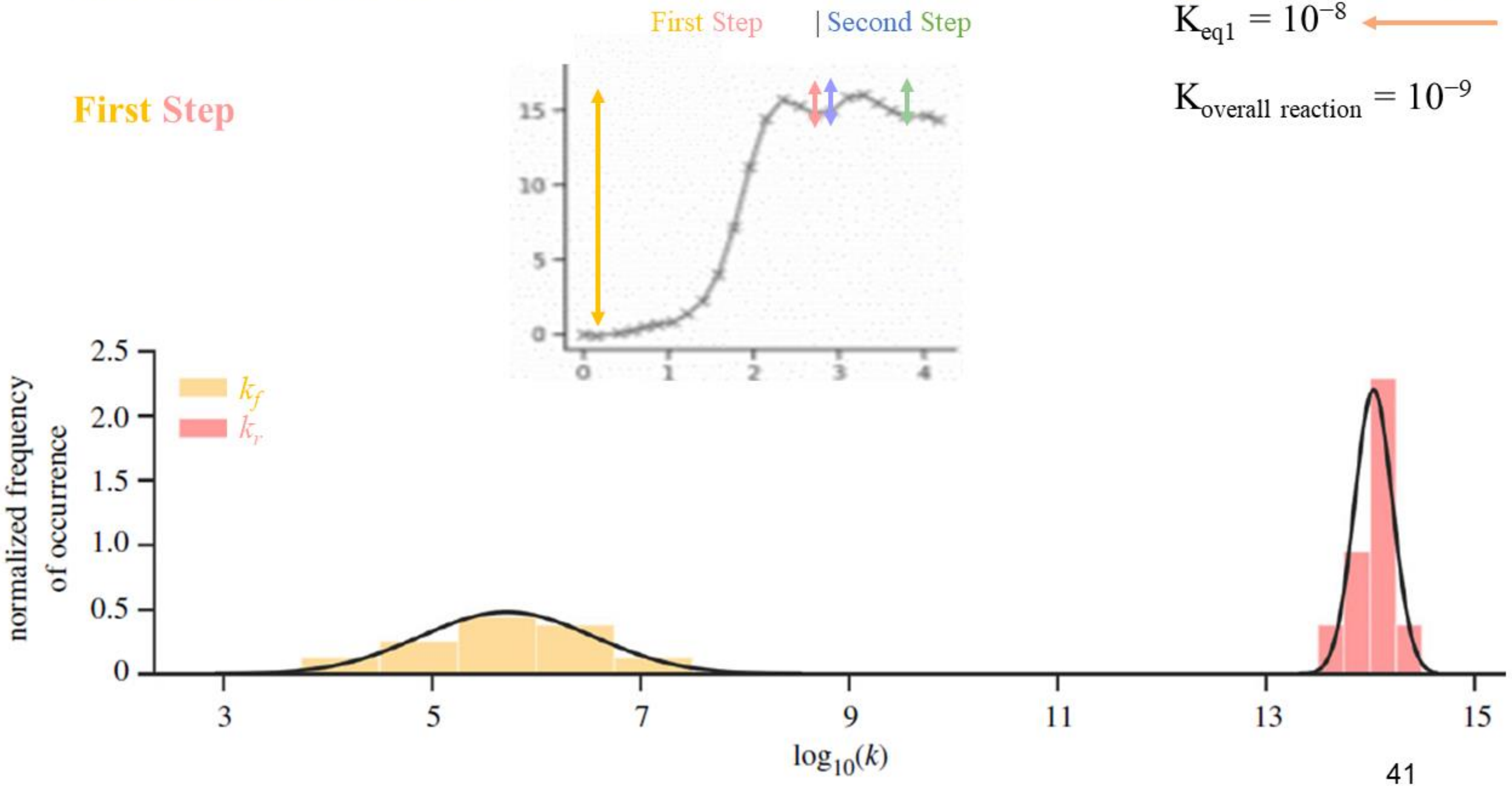
Stepwise DPT: GC to G*C*

k_f is ~10^8 times < k_r

$K_{eq1} = 10^{-8}$

$K_{overall\ reaction} = 10^{-9}$

First Step

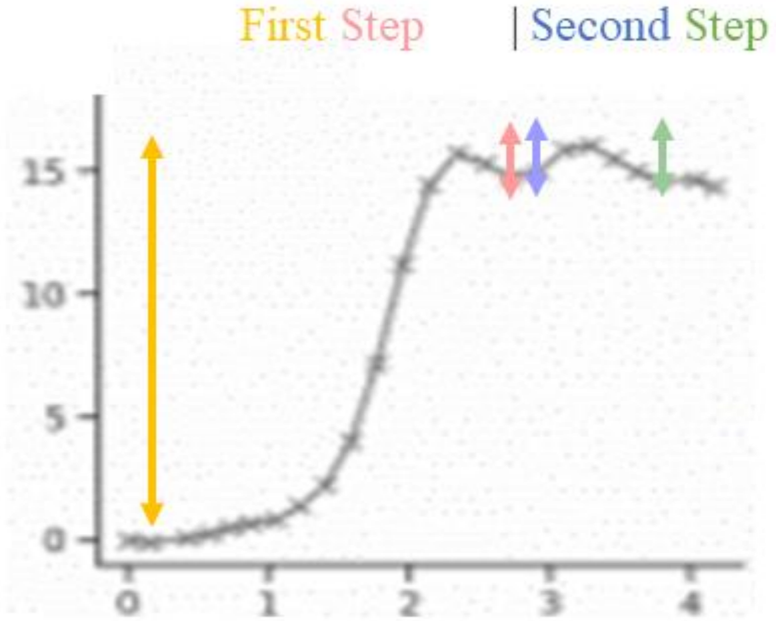


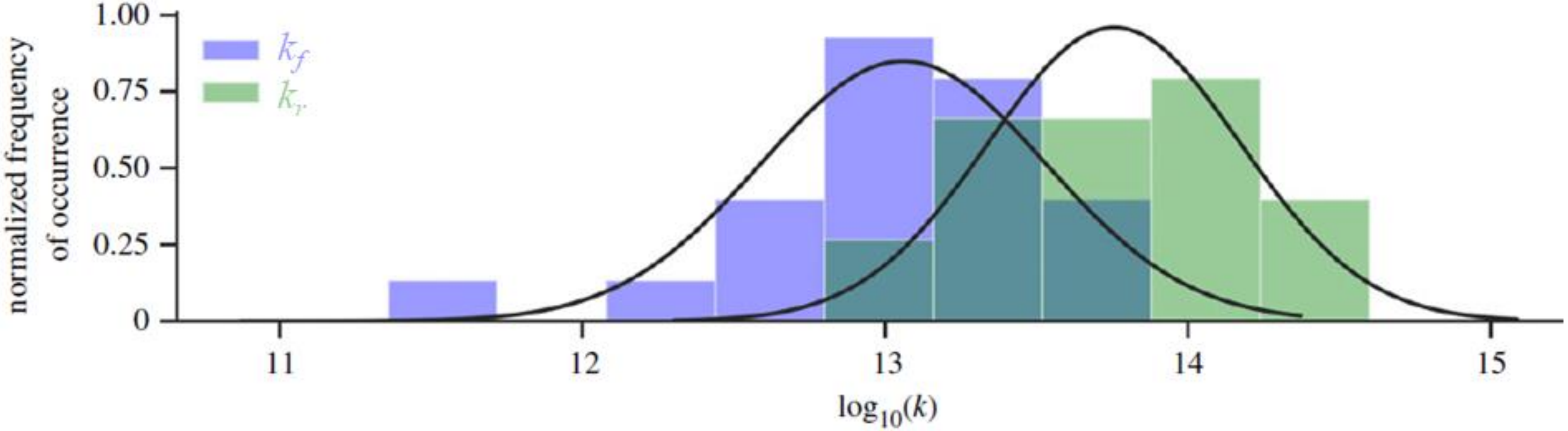
Stepwise DPT: GC to G*C*

k_f and k_r overlap at 10^{13} s^{-1}

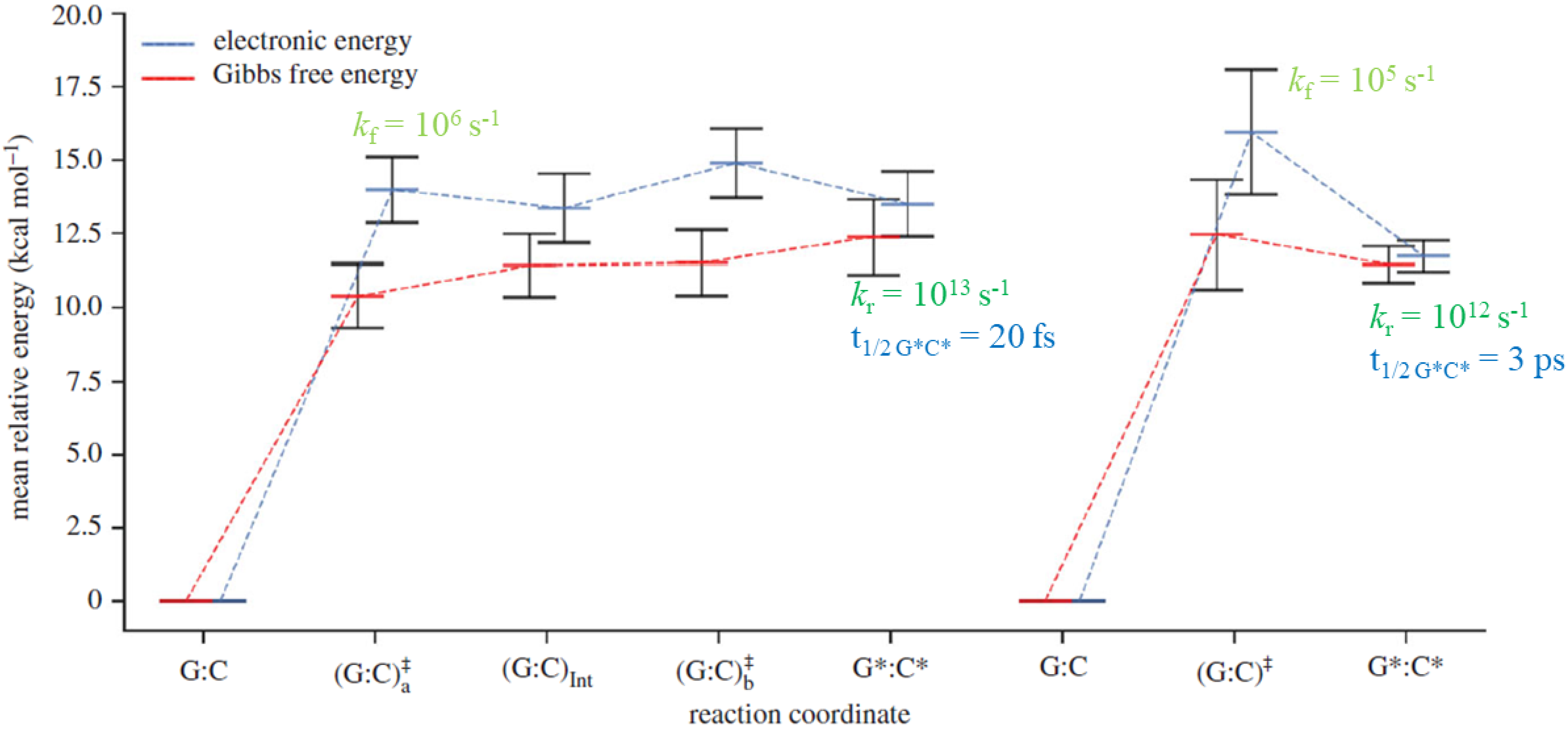
K_{eq2} = 0.6

Second Step





Stepwise DPT in GC   Concerted DPT in GC



Experimental NMR of k_f is $10^5\ s^{-1}$

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

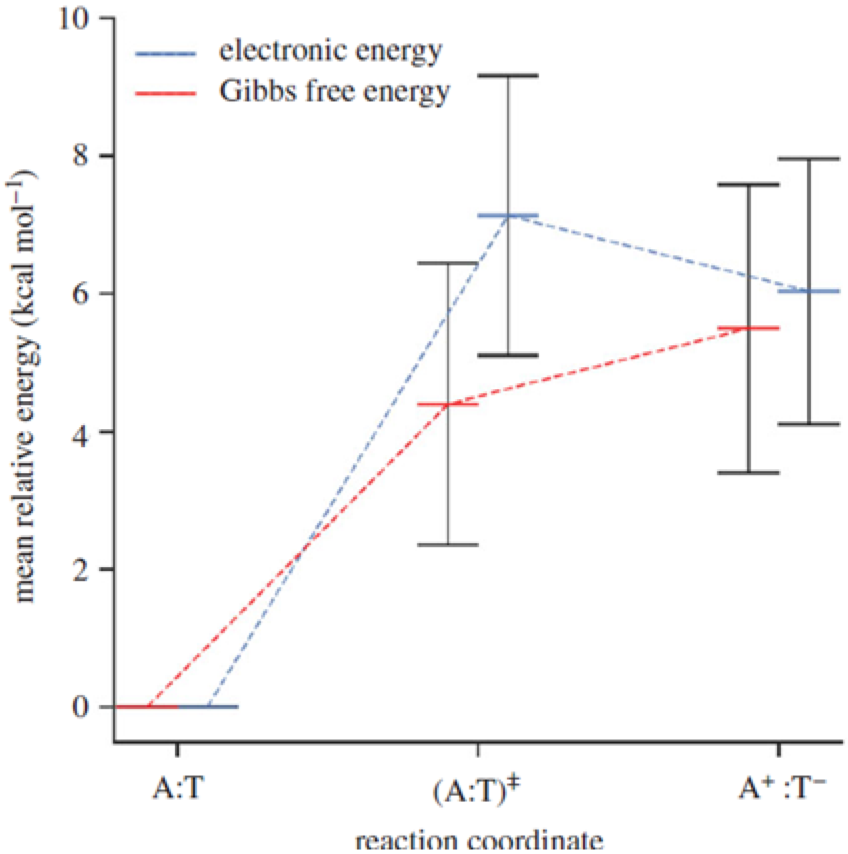
Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions



Concerted SPT of AT (28%) to $A^{+}T^{-}$

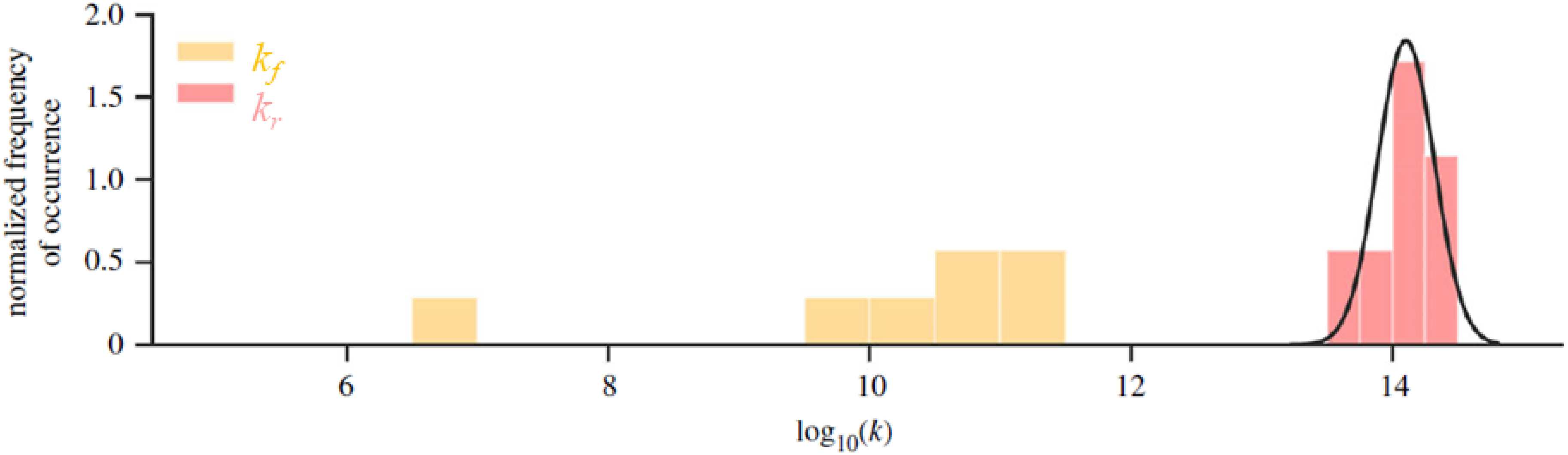
$A^{+}T^{-}$ is not stable

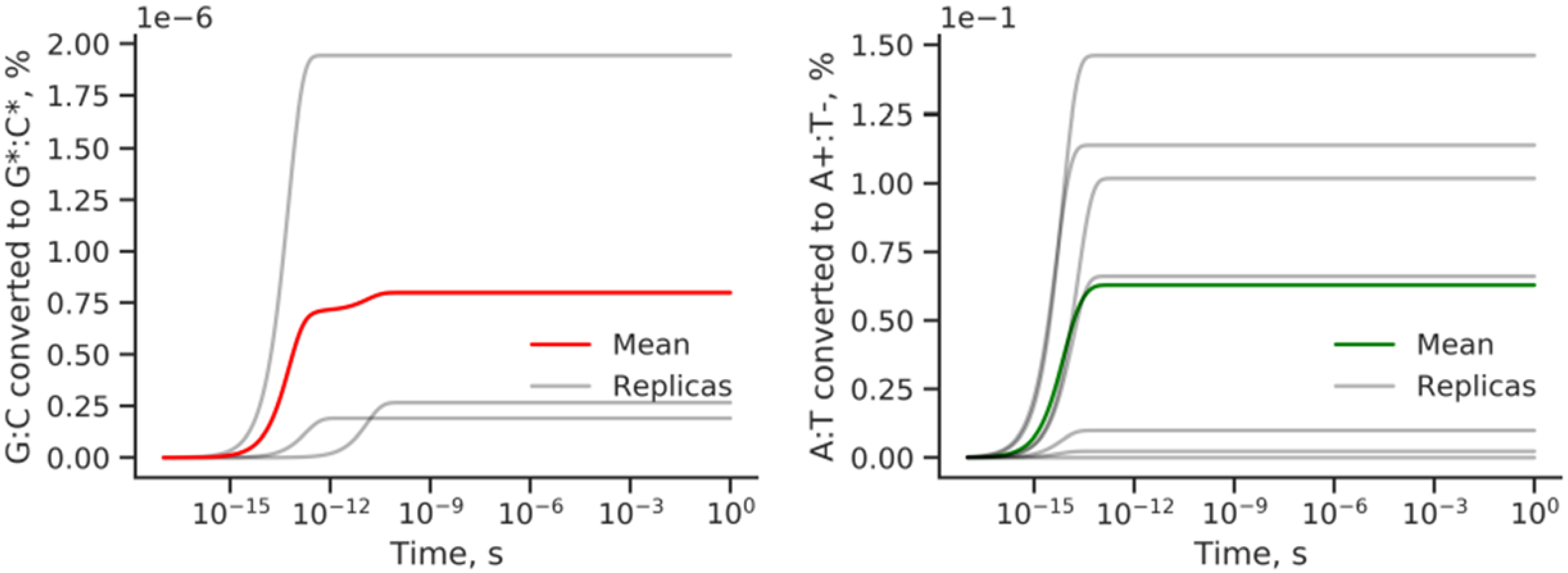
$k_f = 10^{10}\ s^{-1}$

$k_r = 10^{14}\ s^{-1}$

$K_{eq} = 10^{-4}$

$t_{1/2\,A^{+}T^{-}} = 6.3 \pm 4.0$ fs





(a) G:C→G*:C*, Concerted

(b) A:T→A^+:T^-, Concerted

It takes ~10^{-10} s for [G*C*] to reach equilibrium.
The A^+T^- zwitterion reaches equilibrium faster, at 10^{-13}s.
$[A^+T^-]_{eq}$ (6×10^{-2} %) >> [G*C*] (8×10^{-7}%).

After 1 s, the following are produced:
8 G^+C^-
12 G*C*
9.4×10^5 A^+T^- (i.e. 0.06% of the AT content in the genome)

•Assuming:

1) human genome size (3×10^9 bp) is 50:50 of GC:AT

2) the reverse barrier > 3 kcal mol^{-1} for a permanent mutation to occur

and

3) given that DNA opening during replication is ~1 billion times slower than $t_{1/2}$ of the G*C* tautomer (~3 ps),

< 1 base pair of the 12 G*C* may lead to a permanent GC→AT mutation during DNA replication.

Experimentally 30 base pairs per genome

A^+T^- are assumed not to contribute to the mutation in DNA because of the barrierless (or even the negative) reverse reaction.

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields (Summary)

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

First study to report statistically robust rate coefficients for the various mechanisms of proton transfer mechanisms in GC and AT.

The model built was realistic enough to reproduce NMR experimental data better than previous approximate models.

GC

Both the stepwise (84%) and concerted (12%) DPT pathways in GC occur with similar equilibrium constant, $K \sim 10^{-9}$.

The stepwise forward and reverse rates are faster than the concerted pathways.

At equilibrium, a total of 20 G*C* tautomers are present in the human genome. However, they swiftly revert to GC.

G*C* do not last long enough to impact point mutations in DNA, < 1 G*C* in the context of human genome replication.

AT

No A^*T^* tautomerism is not observed in any ensemble QM/MM replicas.

A^*T^* tautomers in the human genome, at equilibrium, $\ll$ G^*C^*, which is in agreement with experimental observations.

A^+T^- zwitterion is 1000 times more likely to occur than the G^*C^* tautomer.

However, A^+T^- is very unstable ($t_{1/2} = \sim 6$ fs), it reverts quickly to AT.

A^+T^- is not likely to contribute to point mutations in DNA.

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

Choice of Field Strengths

Electric field strength at the middle of two opposite charges (+0.5 e and -0.5 e) separated by:

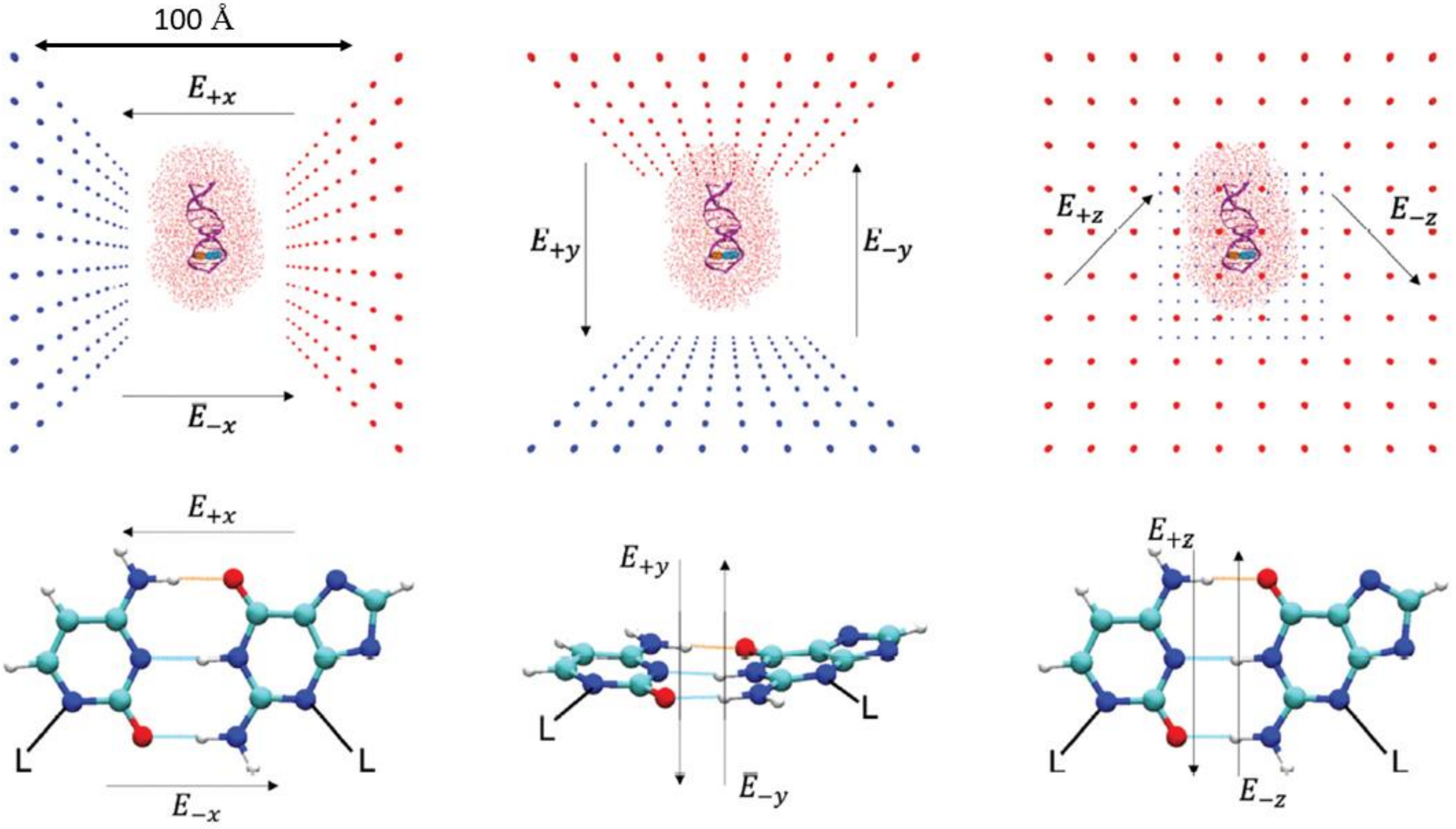
- 10 Å is ~10^9 V m^{-1} (0.010 au).
- 34 Å is ~10^8 V m^{-1} (0.001 au).

These distances (10-35Å) are typical between charges in the microenvironment of DNA.

Therapeutic medical properties of electric fields:

- ~10^1 V m^{-1}: enhancing/speeds wound healing by 25%
- 10^3 V m^{-1}: permeabilize tumor cells for the targeted delivery of non-permeable drugs
- 10^3-10^5 V m^{-1} over microseconds: electrochemotherapy
- ~10^6-10^7 V m^{-1} over nanoseconds: gene therapy via electroporation to pass DNA through the phospholipid bilayer of a cell.

Scanning tunnelling microscope (STM) during the imaging process ($> 10^9$ V m^{-1}).



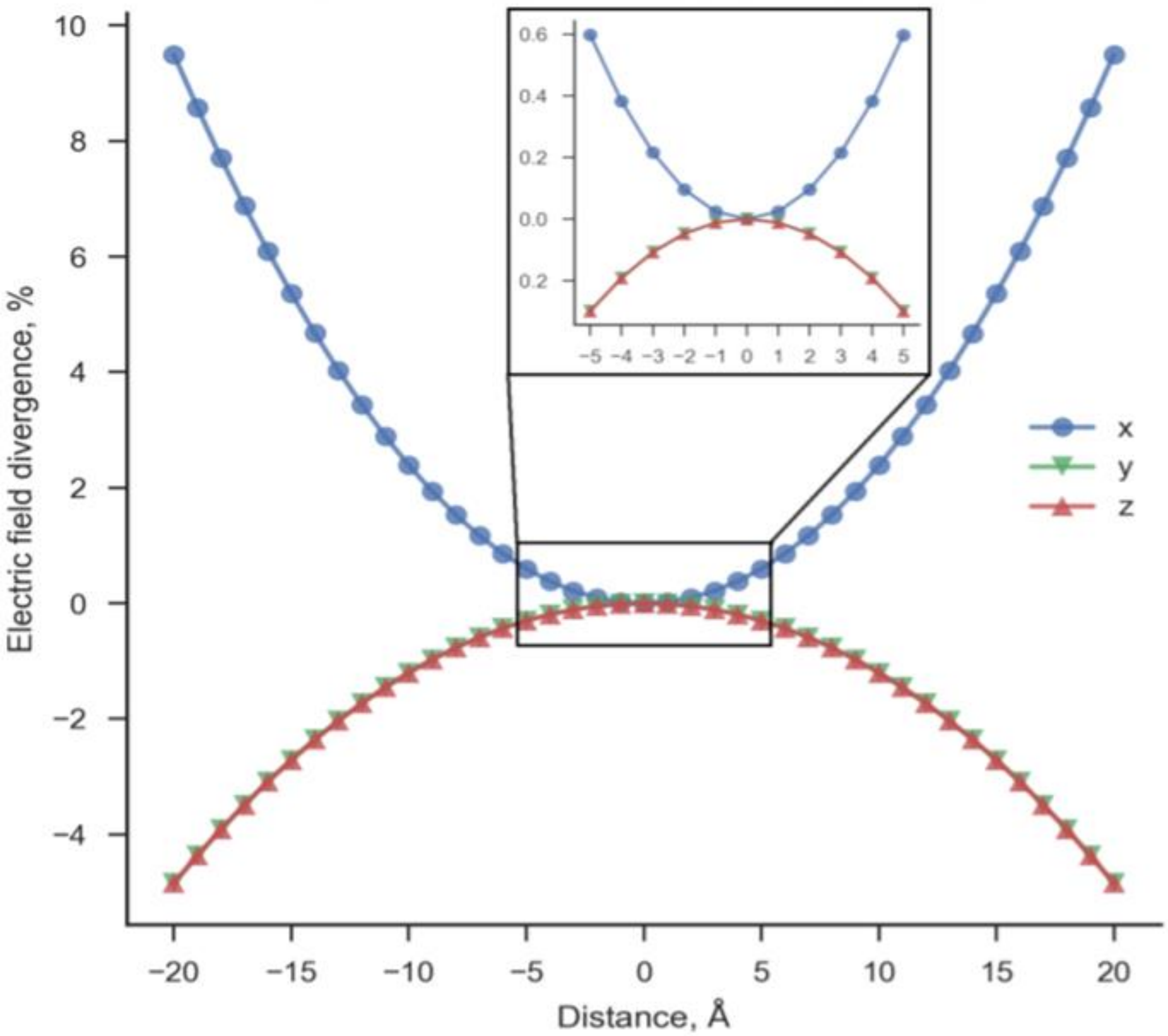
100 Å x 100 Å grid of 100 charged dummy atoms

Charge on each point: 1.82×10^{-6} to 0.182 a.u.

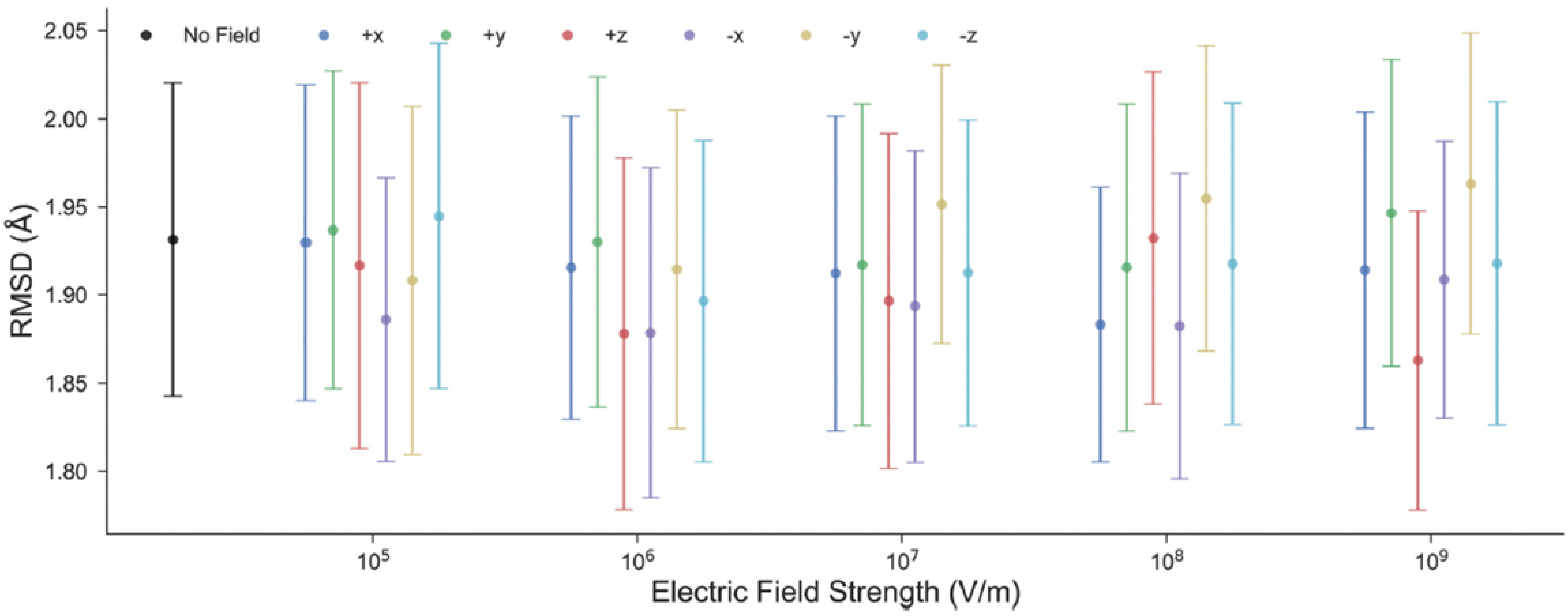
Field strengths: 1.0×10^{4} to 1.0×10^{9} V m^{-1}.

Alignment: the base pair HB at the cell origin

Electric Field Homogeneity



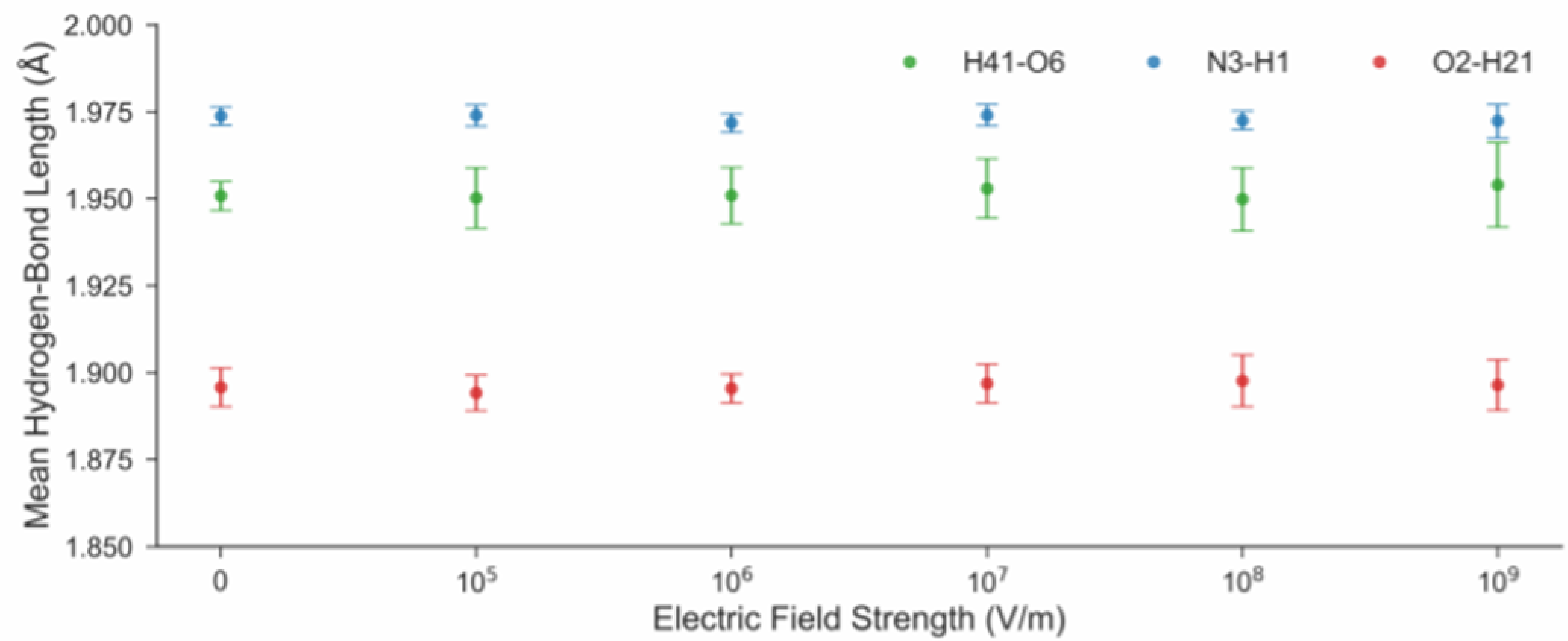
MD with vs. without E



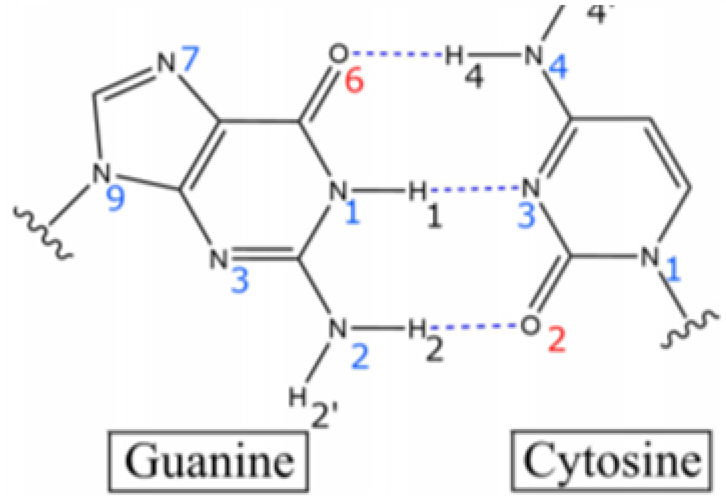
RMSD of the non-hydrogen atoms with respect to the X-ray structure.

After 10 ns MD simulations without or with E up to 1.00 x 10^9 V m^1, RMSD is the same (< 2 Å)

Thus, QM/MM simulations will use geometries taken from MD trajectories in the absence of E



Average ± sd of H-bonds distances are basically the same up to 10^7 vm^{-1}

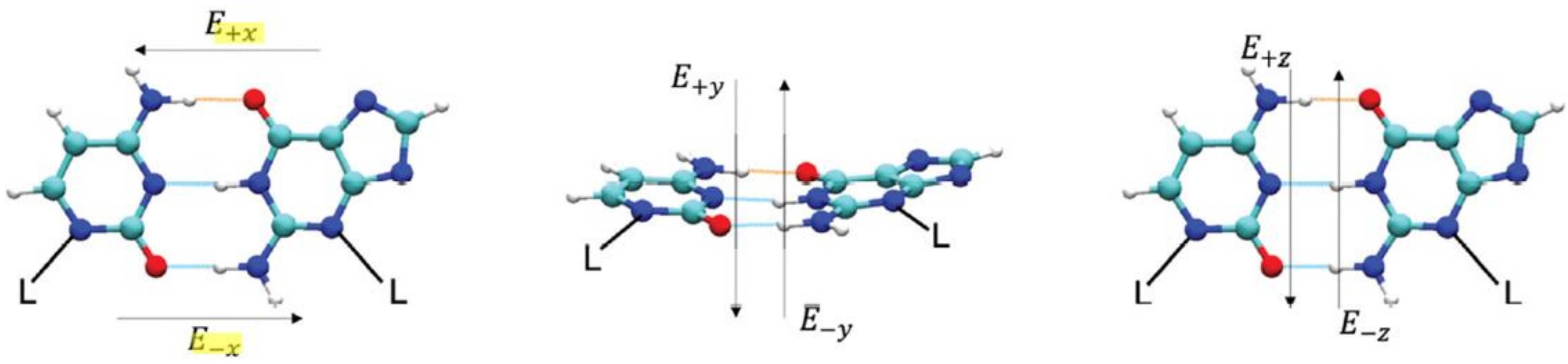


Mutations via base pair PT do not occur more readily in the context of therapeutic medical treatments (10^7 V m^{-1}).

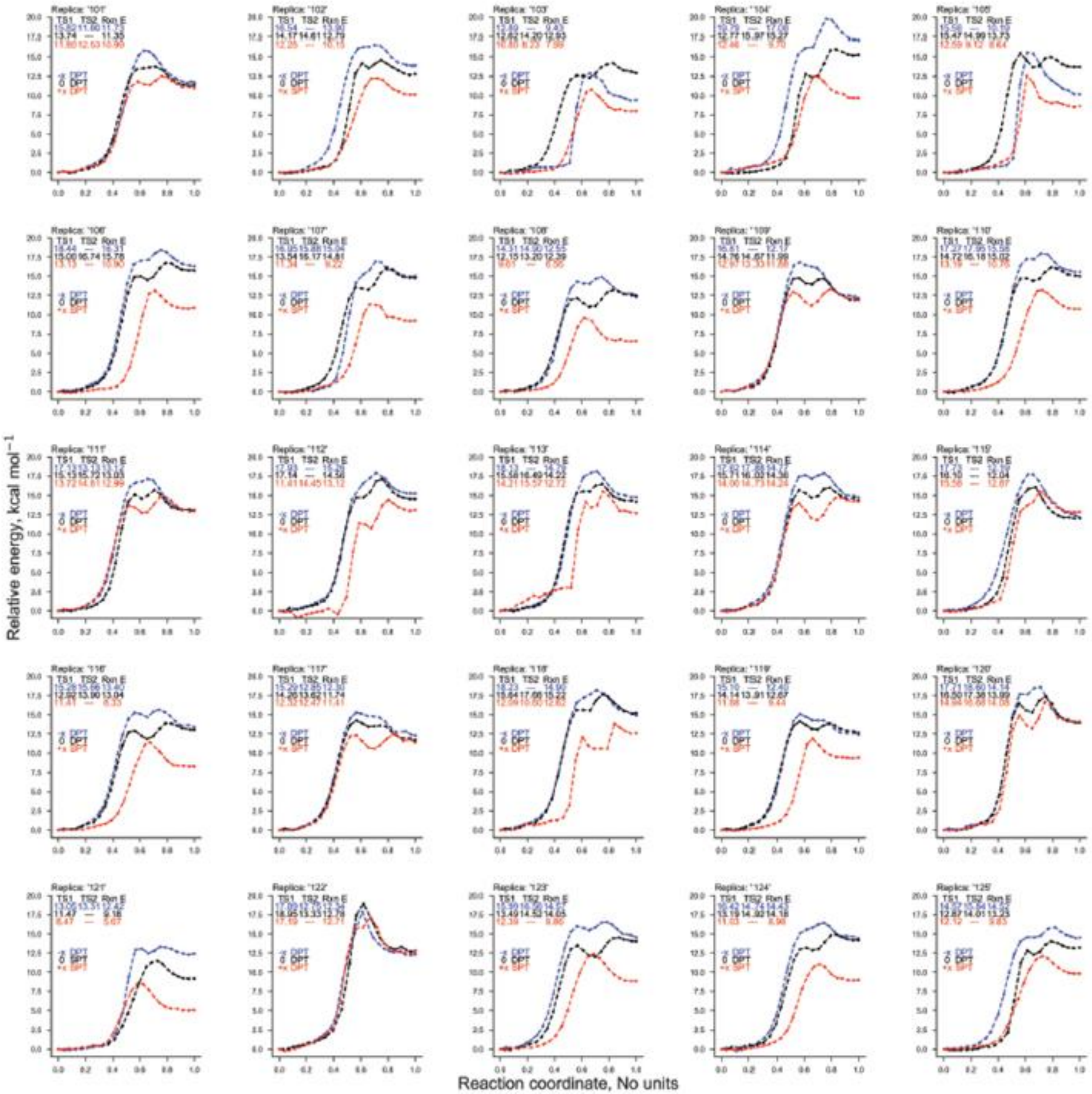
Only E > 5 x 10^8 V m^{-1} influence the energetics of PT reactions.

GC under electric fields of 1.0×10^9 V m^{-1}

Electric field direction	Single proton transfer G⁻C⁺	Double proton transfer G*C*		
		Total	Stepwise	Concerted
E_{-x}	0	25	8	17
E_0 [a]	1	24	21	3
E_{+x}	14	11	10	1



E_{+y}, E_{-y}, E_{+z}, E_{-z}, with $E < 10^7$ Vm^{-1} have same ratios as the E_0 case



Electronic energies of GC

$\mathbf{E_0}$ $\mathbf{E_{+x}}$ $\mathbf{E_{-x}}$

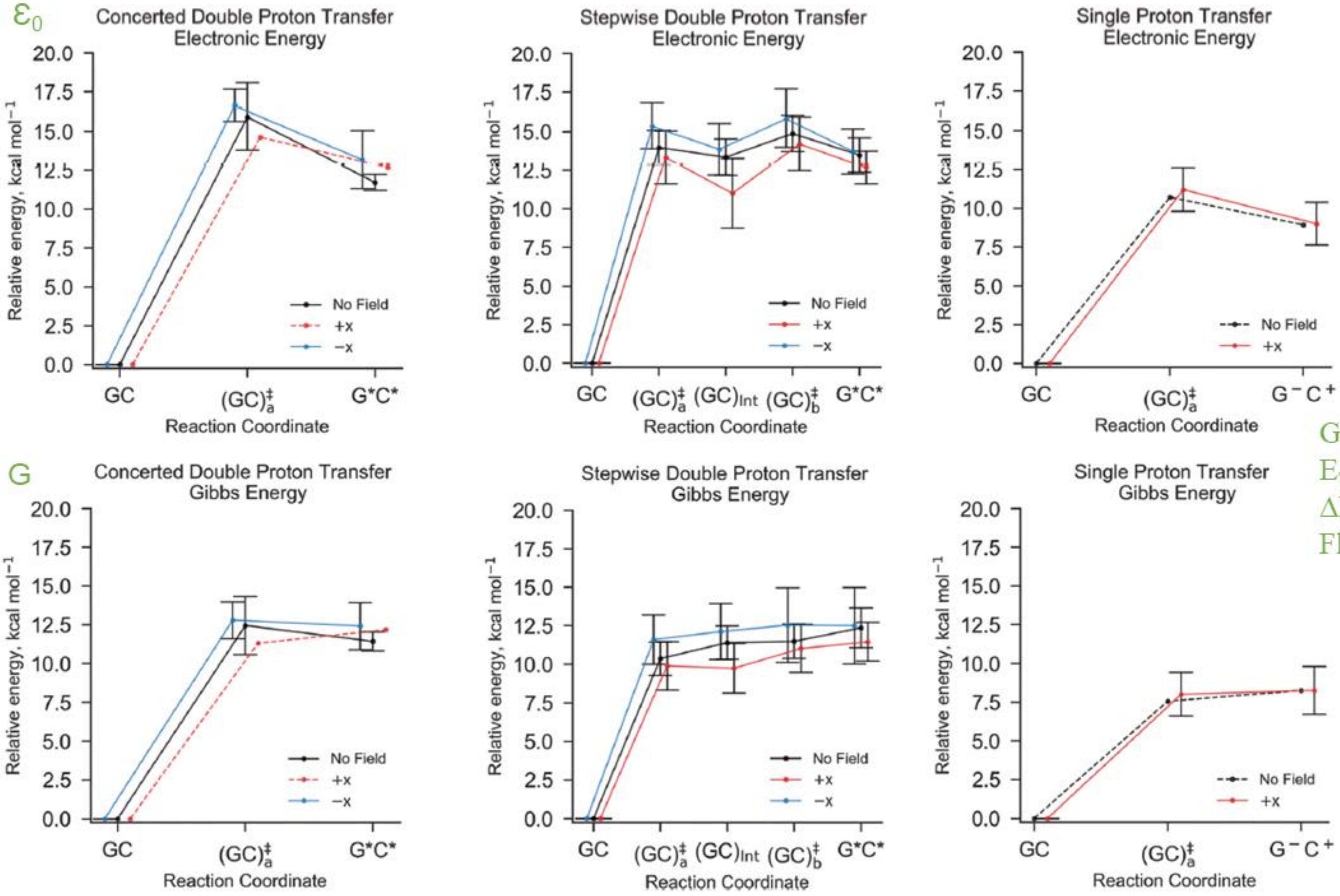
1.0×10^9 V m^{-1}

Compared to ΔE_0

E_{+x} decreases ΔE

E_{-x} increases ΔE

$E_{-x} > E_0 > E_{+x}$



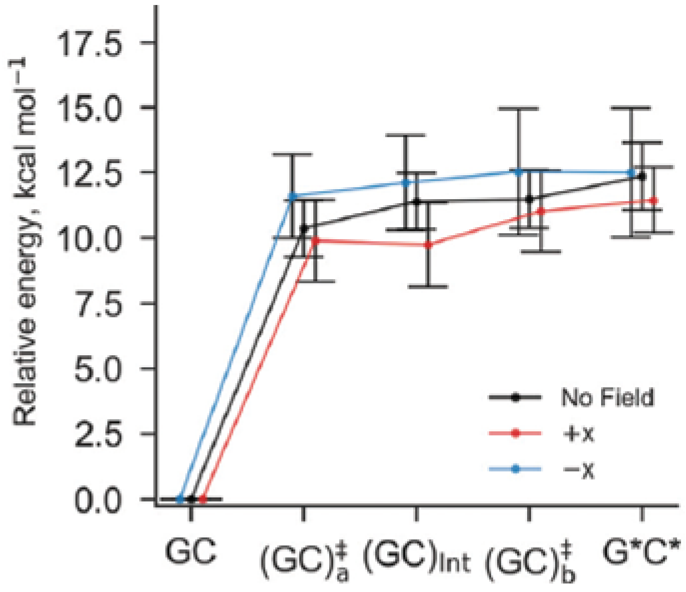
Gibbs vs. $\mathcal{E}_0$:

E_{TS} ↓ ~2.5 kcal mol^{-1}

ΔE ↓ $_{max}$ 0.5 kcal mol^{-1}

Flattened curves

Stepwise DPT (to G*C*)



$\Delta G^{\ddagger}$ ↑

$\Delta G^{\ddagger}$ ↓

Overall, $E_{-x} \uparrow \langle \Delta G^{\ddagger} \rangle_{f\ \&\ r}$ of 1st step by ~1 kcal/mol

$E_{-x} \uparrow \langle \Delta G^{\ddagger} \rangle_{f\ \&\ r}$ of 2nd step by 0.5 kcal/mol

$E_{-x} \downarrow \langle \Delta G^{\ddagger} \rangle$

Consequently

$K_{(-x)} = 8.86 \times 10^{-9} < K_{(+x)} = 1.96 \times 10^{-10}$,

and

$t_{1/2\ G^*C^*\ (-x)} = \sim 10 \times 10^{-13}$ s $> t_{1/2\ G^*C^*\ (+x)} = \sim 1 \times 10^{-13}$ s

$t_{1/2\ G^*C^*\ (\text{no field})}$ < picoseconds $(E_{\pm x})$.

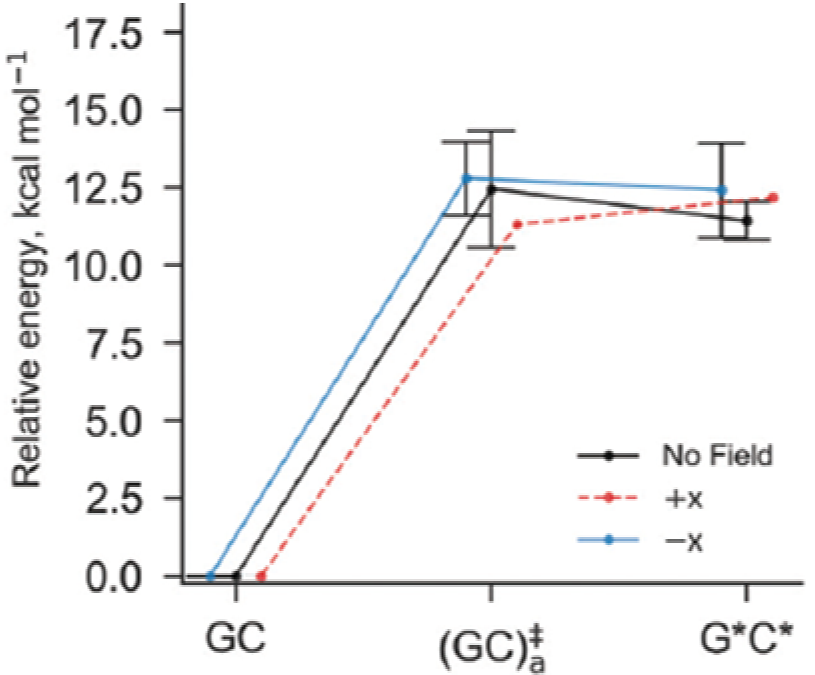
Thus, at E_0, G*C* tautomer is more likely to revert back to GC.

Concerted DPT (to G*C*)

Concerted DPT	$\Delta G_f^\ddagger$ Mean	σ	$\Delta G_r^\ddagger$ Mean	σ	ΔG Mean	σ	$K \times 10^{-9}$ Mean	σ	$t_{1/2} \times 10^{-12}$ Mean	σ	$k_f \times 10^4$ Mean	σ	$k_r \times 10^{12}$ Mean	σ
E_{-x}	12.79	1.18	0.38	1.08	12.42	1.52	26.2	68.3	1.42	1.68	6.81	11.2	2.41	2.07
E_0	12.46	1.86	1.01	1.45	11.44	0.61	7.99	8.09	4.57	6.29	0.53	0.71	2.75	3.78
E_{+x}	11.33	—	−0.86	—	12.19	—	1.32	—	—	—	—	—	—	—

Almost no concerted DPT in the presence of E_{+x}.

Basically all the concerted DPT reactions occur only in the presence of E_{-x}.



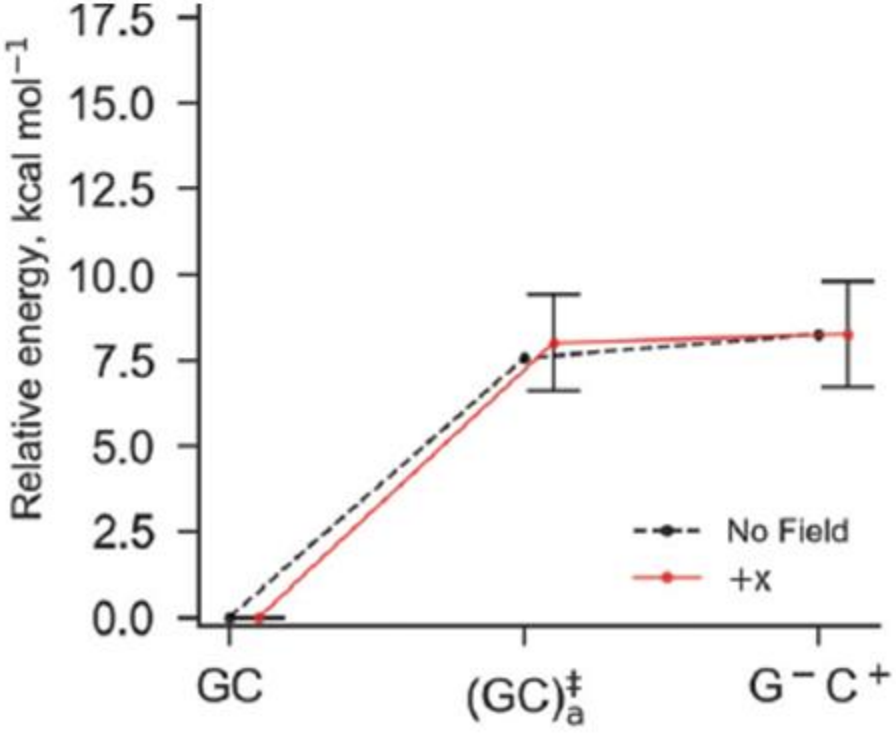
SPT Reaction (to G^-C^+)

	$\Delta G_f^\ddagger$		$\Delta G_r^\ddagger$		ΔG		$K \times 10^{-6}$		$t_{1/2} \times 10^{-15}$		$k_f \times 10^{10}$		$k_r \times 10^{14}$	
SPT	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ
E_{-x}	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E_0	7.56	—	−0.71	—	8.27	—	0.95	—	—	—	—	—	—	—
E_{+x}	8.18	1.45	−0.14	0.42	8.32	1.64	25.3	73.6	6.97	8.26	8.23	14.1	4.05	4.06

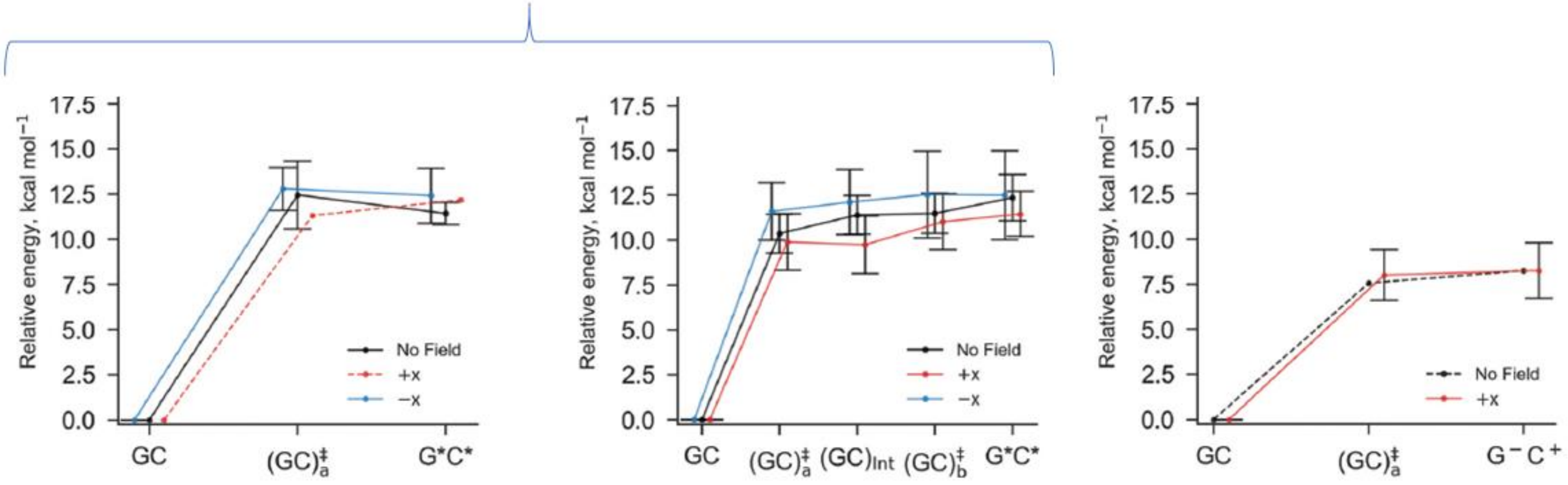
No reactions with E_{-x}.

Reverse $\Delta G^\ddagger$ for SPT remains negative with E_{+x}

E_{+x} increases the thermodynamic population of the G^-C^+ compared to E_0



DPT vs. SPT Reactions



$\Delta G^{\ddagger}{}_{SPT} < \Delta G^{\ddagger}{}_{DPT}$ (either pathway)

SPT reaction has a lower forward $\Delta G^{\ddagger}$ than either DPT pathways.

K ($G^{-}C^{+}$) ($\sim 10^{-6}$) > K (G*C*) ($\sim 10^{-9}$) fidelity is more conserved with the formation of G*C* as opposed to $G^{+}C^{-}$

Point mutation is more favored and faster with SPT than DPT.

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

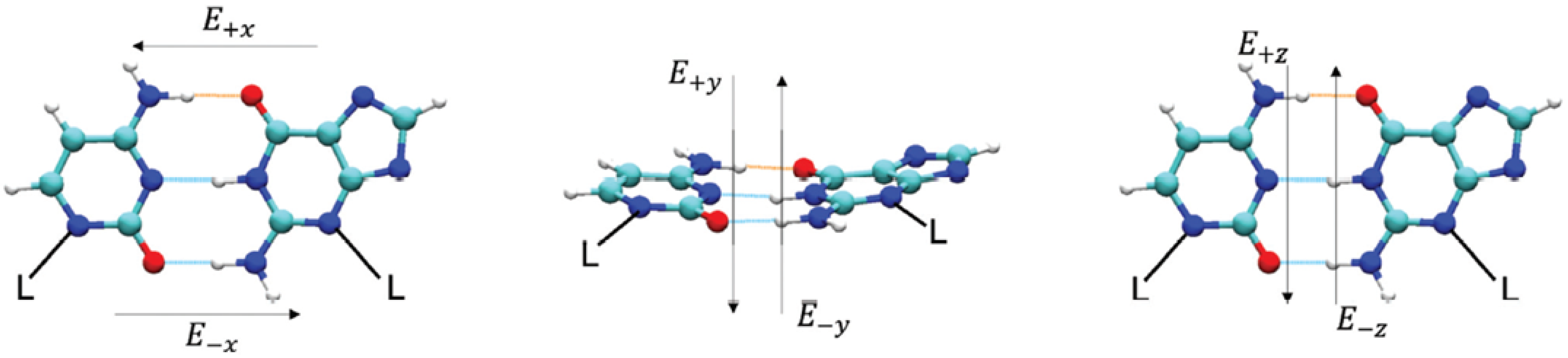
Conclusions

MD simulations: electric fields (1.00×10^9 V m^{-1}) in 10 ns pulses have a negligible effect on the *structural* properties of DNA, they will not break down or fragment aqueous DNA in ambient conditions.

QM/MM: weaker electric fields ($<1.00 \times 10^7$ V m^{-1}) have no effect on the proton transfer mechanisms in GC.

Thus, E applied in medical practices (10^7 V m^{-1}) will unlikely affect the onset of genetic diseases.

Only E_x >1.00 x 10^9 Vm^{-1} alter the kinetics and thermodynamics of the proton transfer.
Even then, $t_{1/2}$ G*C* is ~ps, and $t_{1/2}$ G^-C^+ ~fs.



E > ~3.00 x 10^9 V m^{-1} stabilize G*C*.

E in phospholipid bilayer (10^8–10^9 V m^{-1}) are just short of stabilizing the otherwise transient mutagenic tautomers.

Outline

Introduction: Point mutations in DNA

Methodology: Multiscale Model

- Ensemble MD Simulations
- QM Model
- QM/MM Model

Results Without Electric Fields

- GC
- AT

Results With Electric Fields

Biological Implications

Conclusions

First study to report statistically robust rate coefficients for the various mechanisms of proton transfer mechanisms in GC and AT, in the absence and presence of electric fields.

At equilibrium, a total of 20 G*C* tautomers are present but do not last long enough to impact point mutations in DNA, only < 1 G*C* remains in the context of human genome replication.

No A*T* tautomerism is not observed in any ensemble QM/MM replicas.

$A^{+}T^{-}$ zwitterion is 1000 times more likely to occur than the G*C* tautomer, but does not likely to contribute to point mutations in DNA.

$E < 10^7$ V m^{-1} do not affect the stability of the GC and will likely not induce errors in DNA replication via the Löwdin mutation mechanism.

Oriented external electric fields (E_x =1.00 x 10^9 V m^{-1}) increase the likelihood of mutation occurrence:
E_{+x} promotes the formation of the G^-C^+ zwitterion,
E_{-x} promotes the formation of the G*C* tautomer.

However, G^-C^+ and G*C* are still transient species with $t_{1/2}$ < several ps, i.e. ~3 to 5 orders of magnitude < ns timescale for DNA replication. Thus point mutations still have very low probabilities of occurrence, even under the effect of fields up to 1.00 x10^9 V m^{-1}.

Sara ElGengehi
Taabeer Fatima
Alaa Osman
Ghufran Salloum

Tiyyaba Furqan
AbdelRahman Atef
Anju Choorakottayil
Alexander Gheorghiu

Acknowledgements

Peter V. Coveney (UCL)

$$$

Cherif F. Matta (MSVU)

You Lu
Thomas Keal
ChemShell on ARCHER

UAEU جامعة الإمارات العربية المتحدة United Arab Emirates University

جامعة زايد ZAYED UNIVERSITY

NSERC CRSNG

CompBioMed

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

INNOVATION Canada Foundation for Innovation Fondation canadienne pour l'innovation

Funded by the Horizon 2020 Framework Programme of the European Union

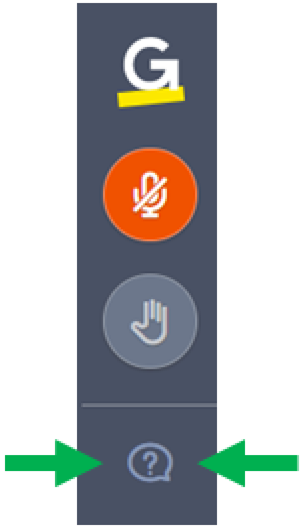
UCL

Mount Saint Vincent University

Dalhousie University

Q&A

To pose a question, please click on the symbol and send your question via the 'Ask the staff a question' panel



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

Thank you for participating!

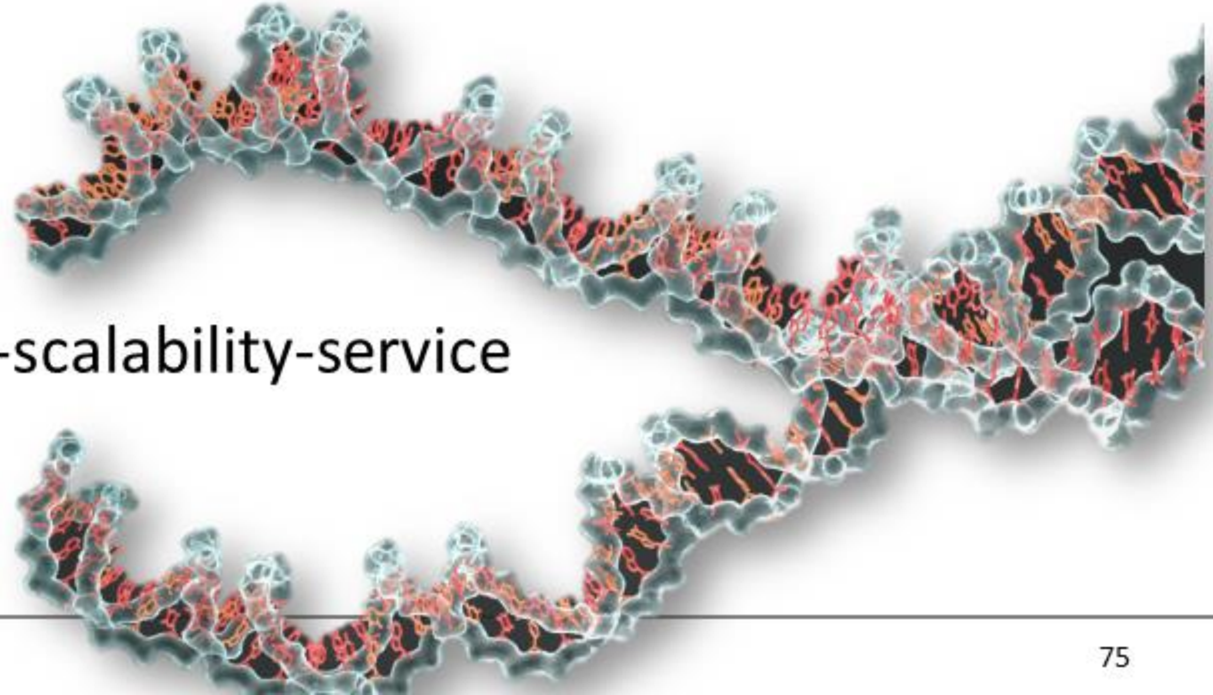
…don't forget to fill in our feedback questionnaire…

Visit the CompBioMed website (www.compbiomed.eu/training)
for a full recording of this and other e-Seminars,
to download the slides
and to keep updated on our upcoming trainings

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

CompBioMed's *Free* Scalability Service

- Improves performance of your biomedicine applications on high performance computers
  - Experts in both biomedical applications and high performance computers
  - Make your biomedicine applications run in parallel
  - Improving the scalability of those already parallelised



- www.compbiomed.eu/compbiomed-scalability-service

www.compbiomed.eu/compbiomed-scalability-service

- Contact for *Free* Service
  - General technical questions
    - Slack: #scalability channel of ***the InSilicoWorld Community of Practice***
    - Email: compbiomed-support@ucl.ac.uk
  - Full service
    - Application Form or light-weight web form
      - Formal collaborative relationship with CompBioMed Centre of Excellence

- Application and Data Security
  - Great care when adapting your applications and managing your data
    - Our Data Policies cover Data Privacy, Data Security and Research Data Management

InSilicoWorld Community of Practice

The first community entirely on *in silico* medicine on Slack

www.insilico.world/community

Expertise	• The community is invitation only: in this way we ensure only interested experts have access
Collaboration	• Join teams and collaboratively work on shared goals, projects, concerns, problems or topics
Safe space	• A pre-competitive space where experts from academia, industry, and regulatory agencies can ask for and exchange advices

More than 500 experts have already joined the community and its channels

InSilicoWorld Members

CompBioMed

- **Large Biomedical Companies**

  Medtronic, Smith & Nephew, Pfizer, Johnson and Johnson, Innovative Medicine Initiative, CSL Behring, Ambu, RS-Scan, Corwave EN, Zimmer Biomet, Novartis, Bayer, ATOS, Biogen, Agfa, Icon PLC, Amgen, ERT, Exponent, etc.

- **Biomedical SMEs**

  Nova Discovery, Lynkeus, Obsidian Biomedical, Quibim, Mediolanum Cardio Research, Voisin Consulting, CRM-Microport, Mimesis srl, H. M. Pharmacon, MCHCE, etc.

- **Independent Software Vendors**

  Ansys, In Silico Trials Technologies, 3DS, KIT, ASD Advanced Simulation & Design GmbH, Kuano-AI, Aparito, Chemotargets, Digital Orthopaedics, ExactCure, Materialise, Bio-CFD, Matical, FEOPS, 4RealSim, Exploristics, Synopsis, Virtonomy, Cad-Fem Medical, etc.

- **Regulators and Standardisation Bodies**

  FDA, DIN, BSCI China, NICE, Critical Path Institute, ACQUAS, etc.

- **Clinical Research Institutions**

  Istituto Ortopedico Rizzoli, Sloan Kettering Cancer Center, Royal College of Surgeons Ireland, Gratz University Hospital, Charite Berlin, Centre Nacional Invesigaciones Oncologicas, Aspirus Health, Universitätsklinikum des Saarlandes, European Society for Paediatric Oncology, etc.

Medtronic Pfizer BAYER InSilicoTrials Mimesis In Silico Medicine Istituto Ortopedico Rizzoli 125 nova DISCOVERY ZIMMER BIOMET CHARITÉ DIN Virtonomy.io ASPIRUS HEALTH FDA DIGITAL ORTHOPAEDICS Ansys