University of Strathclyde Science

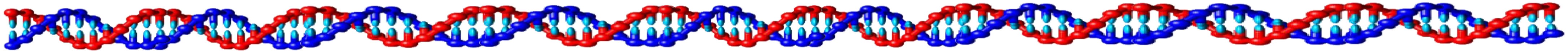
Coarse-Grain Modelling of DNA Triplet Repeat Slip-out Migration

Lewis M Russell | SN: 201817988

Supervisor | Dr Oliver Henrich

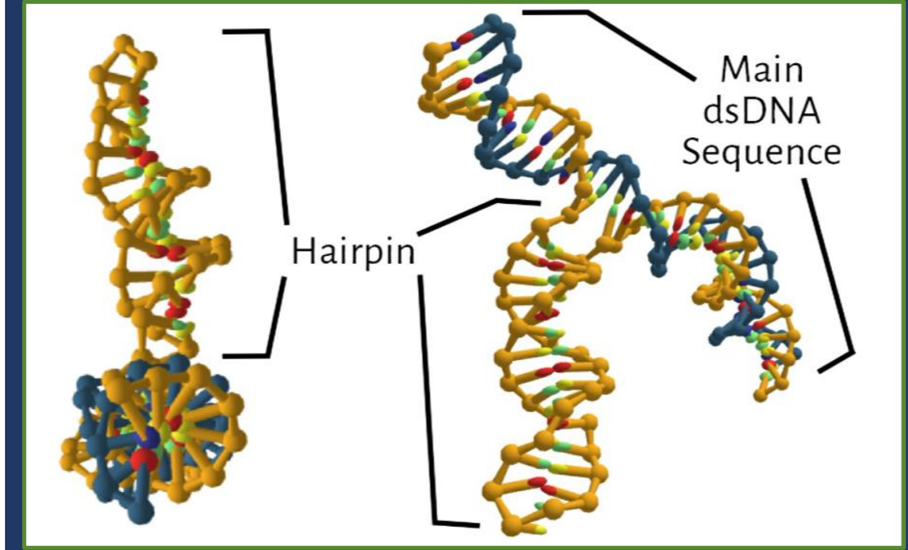
Date | 16/11/2022

Motivation for Triplet Repeat Slip-Out Research



- Triplet Repeat -> CAGCAG….. CTGCTG…..
- Attributed to Repeat-Expansion-Diseases* (REDs):
  - Huntington Disease (HD) – 1993
  - Spinocerebellar Ataxia (SCA) – 1993
  - Myotonic Dystrophy (DM) – 1992
- No therapy
- Little Understanding of Repeat-Sequence Mechanics

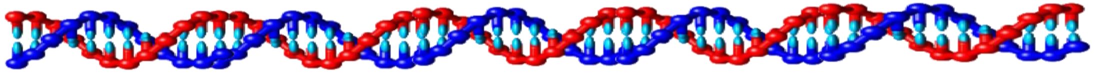
RED | Genetic Visualisation

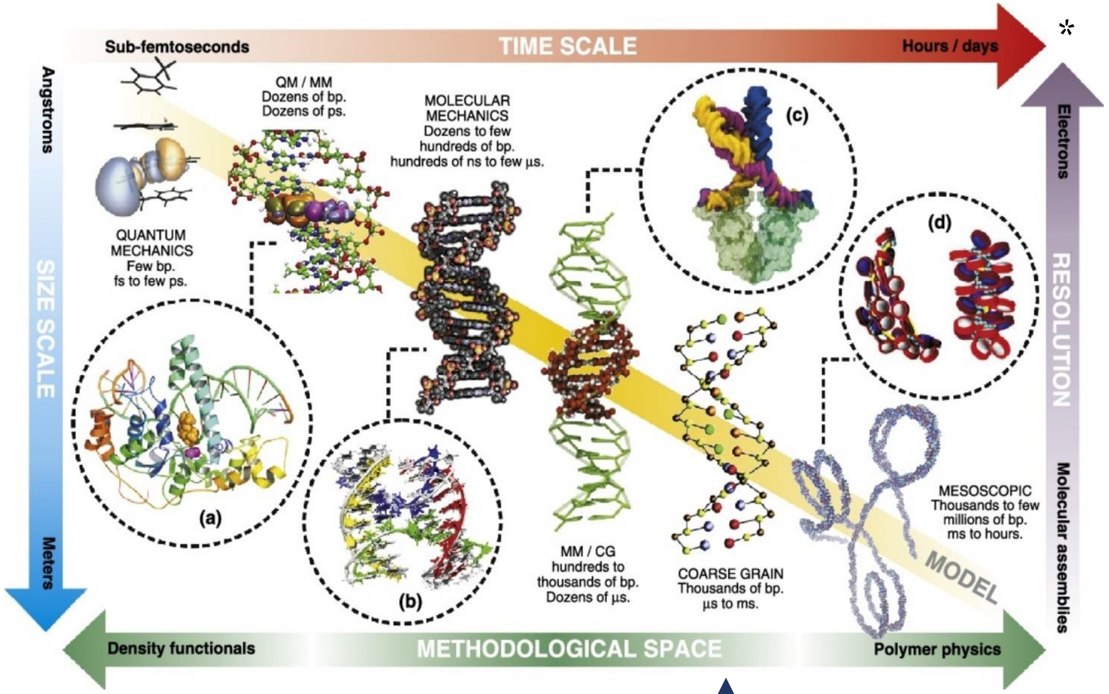


Hairpins contain undesirable repeat sequences of DNA bases, in our research case, CAG and CTG.

*Khristich, Mirkin.. J Biol Chem. 2020 Mar 27;295(13):4134-4170. doi: 10.1074/jbc.REV119.007678. Epub 2020 Feb 14.

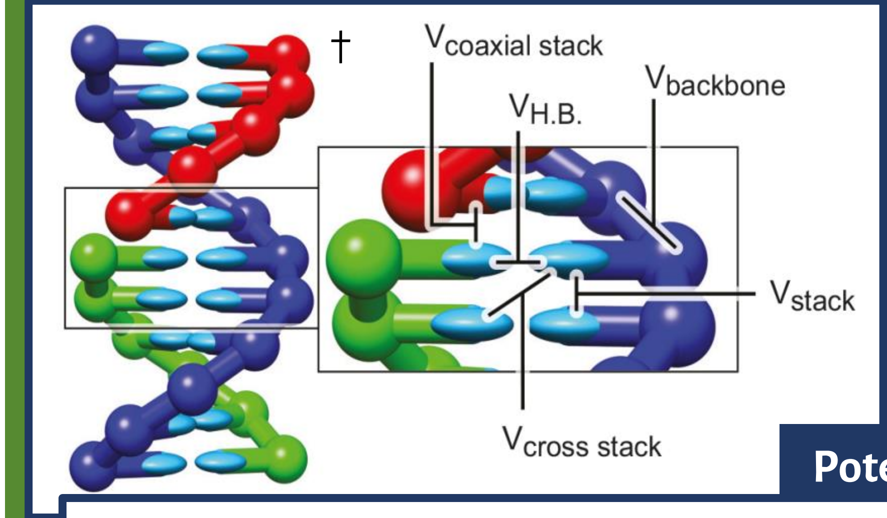
Coarse-Grain Modelling





oxDNA / CG-DNA

*Figure From: D Dans, Walther, G´omez, and Orozco. Current opinion in structural biology, 37:29–45, 2016.
†Figure From: Sulc, Romano, Ouldridge, Rovigatti, Doye, and Louis. The Journal of chemical physics, 137(13):135101, 2012.



Potentials

$$V = \sum_{\text{nn}} \left(V_{\text{backbone}} + V_{\text{stack}} + V'_{\text{exc}}\right) + \sum_{\text{other pairs}} \left(V_{\text{HB}} + V_{\text{cross\_stack}} + V_{\text{coaxial\_stack}} + V_{\text{exc}}\right).$$

Equ. of Motion

$$m\ddot{\boldsymbol{x}} = \boldsymbol{F}_c + \boldsymbol{F}_f + \boldsymbol{F}_r = -\frac{dV(\boldsymbol{r})}{d\boldsymbol{r}} - \gamma m \boldsymbol{v} + \sqrt{2m\gamma k_b T}\,\eta(t)$$

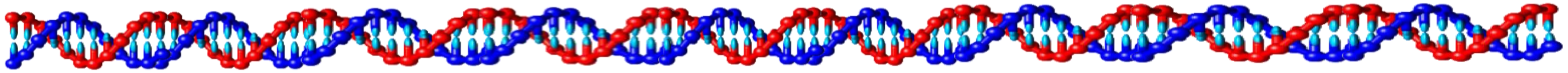
F_c | Potential-Dependent Conservative Force

F_f | Velocity-Dependent Frictional Force

F_r | Temperature-Dependent Random Force

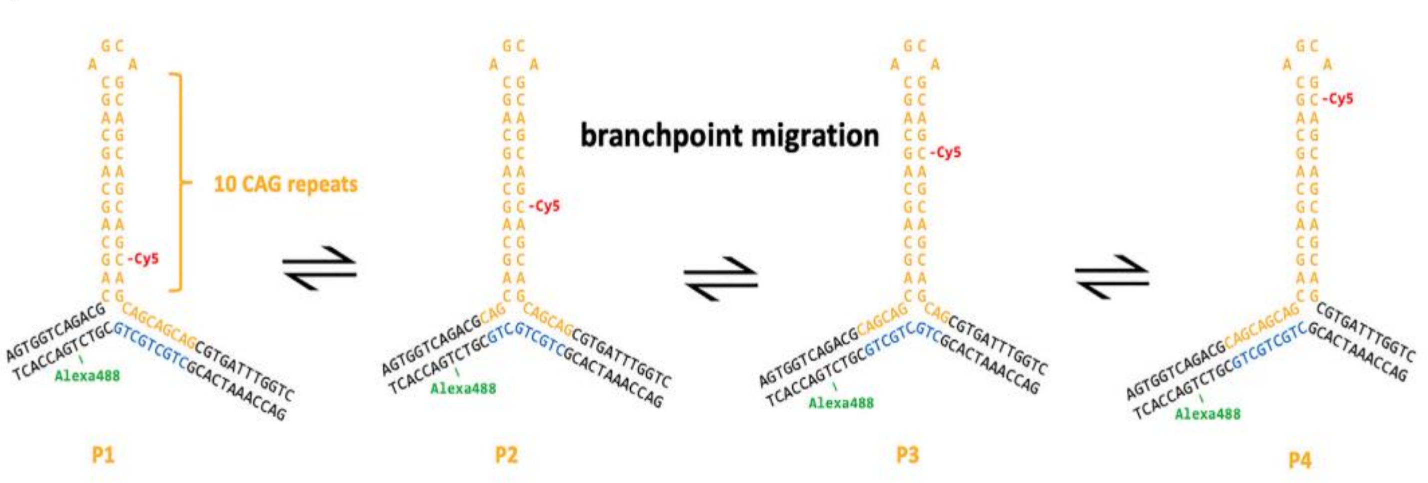
oxDNA | Our Molecular Dynamics Model

Rationale for Additional Modelling



- Paper* Investigates Hairpins:
  - CAG_10
  - CAG_40
  - CTG_30
- Hairpin Migrates Along Main dsDNA Strand

Hairpin Shown in Yellow

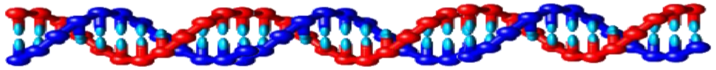


Main Finding | Triplet-Repeats Slip in and out of Main dsDNA Sequence -> branchpoint migration

- Regarding CG-Modelling, the Paper vs Project:
  1. Implement New "Metadynamics" Method
  2. Switch Directionality | 5'_GAC_3' -> 5'_CAG_3'
  3. Model CAG_40 and CTG_30 Hairpin Dynamics and Energies

*Bianco, Hu, Henrich, Magennis. Biophysical Reports, Volume 2, Issue 3, 2022, 100070, ISSN 2667-0747, https://doi.org/10.1016/j.bpr.2022.100070.

State Sampling



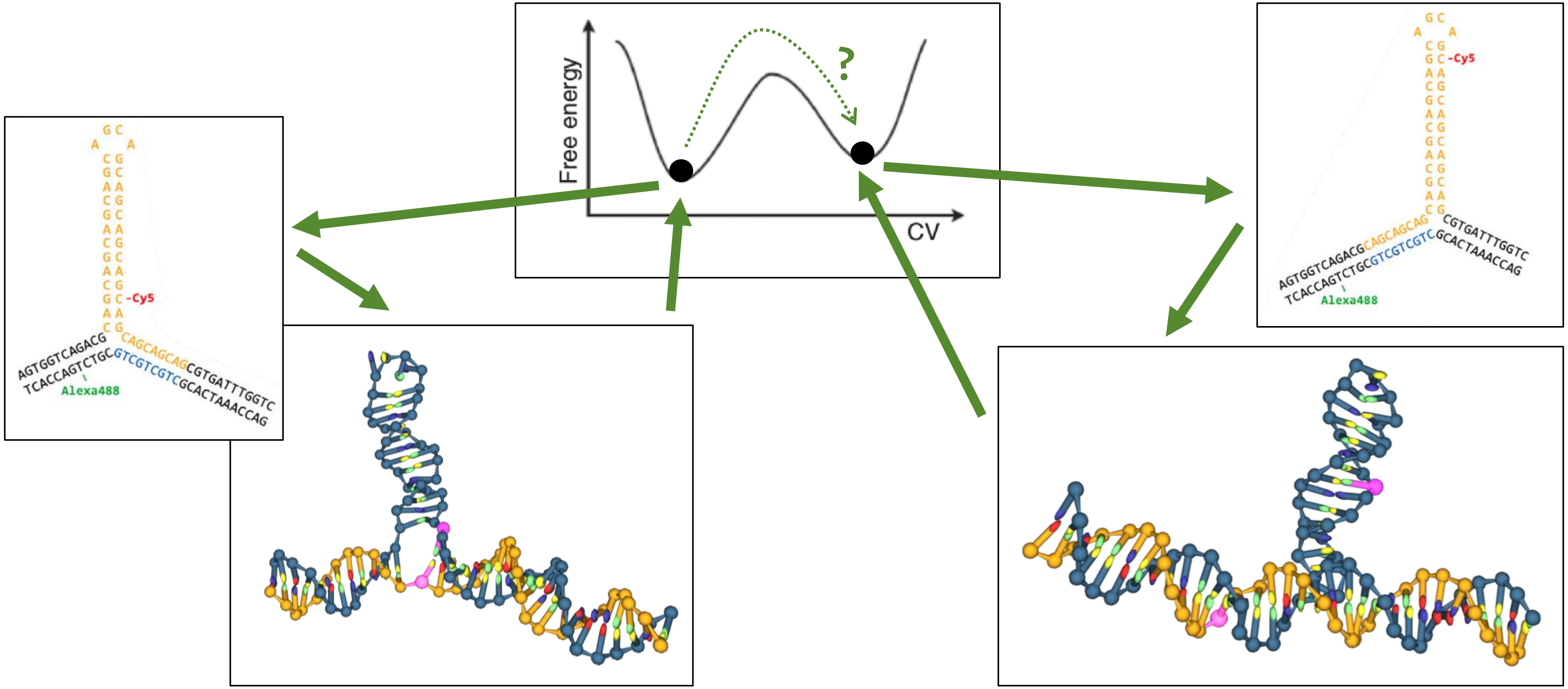
Reminder | Free Energy

$G = H - TS$

H | Enthalpy (U + pV)
T | System Temperature
S | Entropy

Maximum amount of work that a thermodynamic system can perform at **constant temperature**

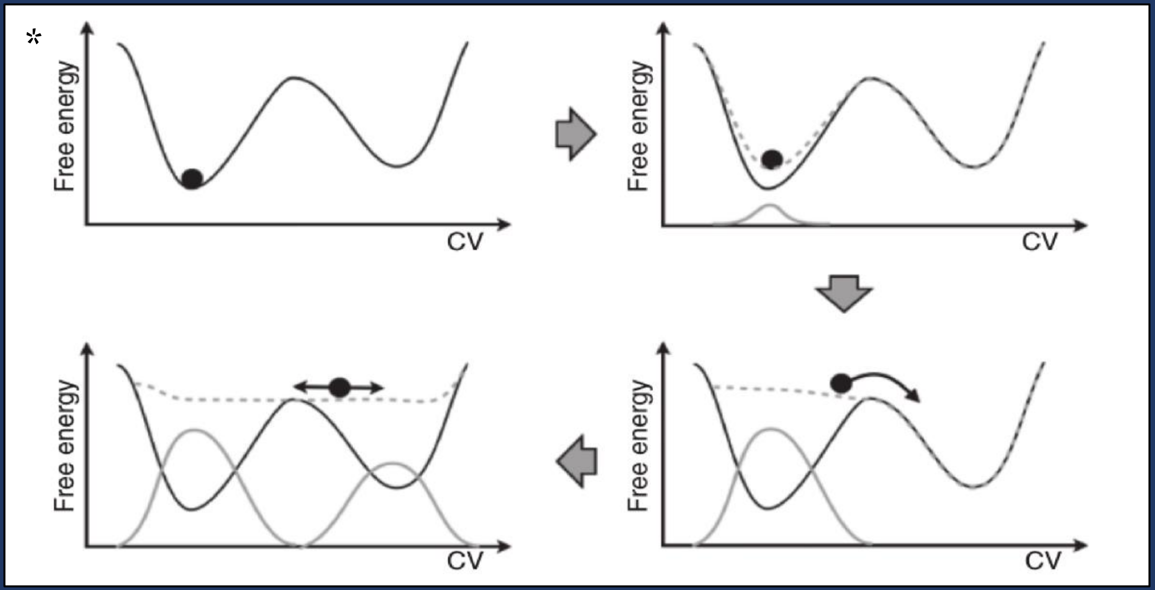
- Multiple Local Minima = Difficult to sample using conventional MD



Well-Tempered to Transition-Tempered MetaD

Principle of Metadynamics

Apply and Record Gaussian Energy Packets (HILLS)
-> Forces System into Rare Energy States
-> Allows for Complete Exploration of the
Free Energy Landscape



WTMetaD

- Reduces HILLS via exp decay
- HILLS only time-dependant
- Imprecise FES Convergence

TTMetaD

- Reduces HILLS based on FES and CV
- HILLS not time-dependant
- Complete Sampling of FES

*Figure From: Bussi and Branduardi. Free-energy calculations with metadynamics: Theory and practice. pages 1–49, 05 2015

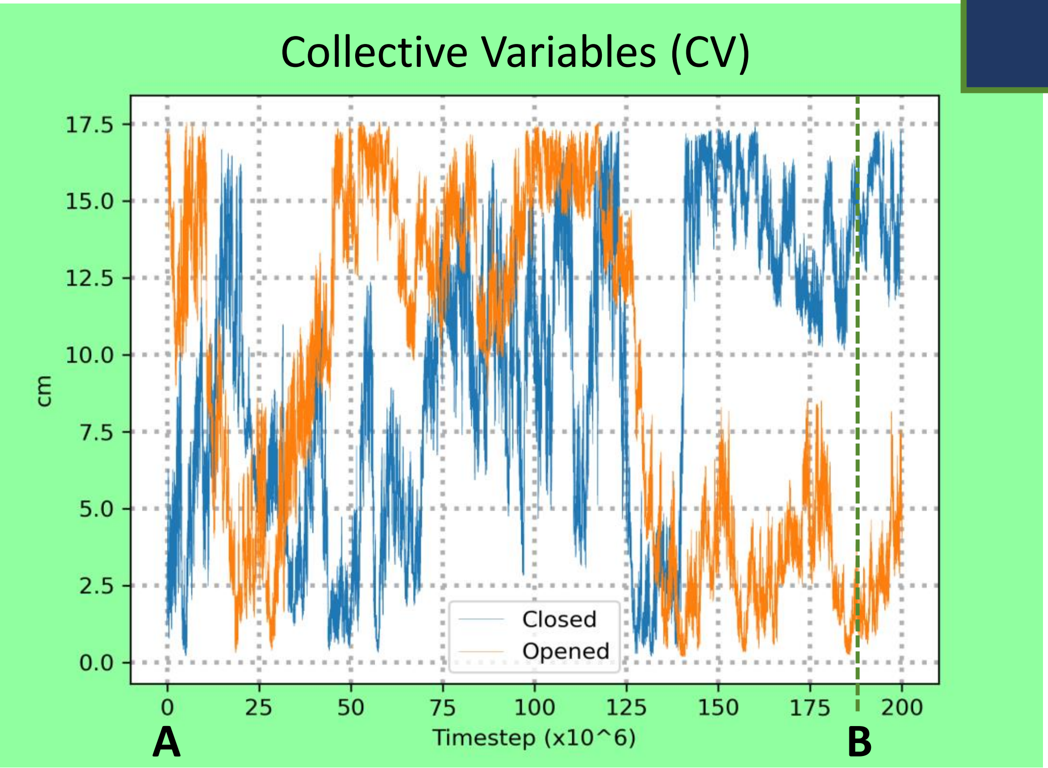
Contact Maps and Collective Variables

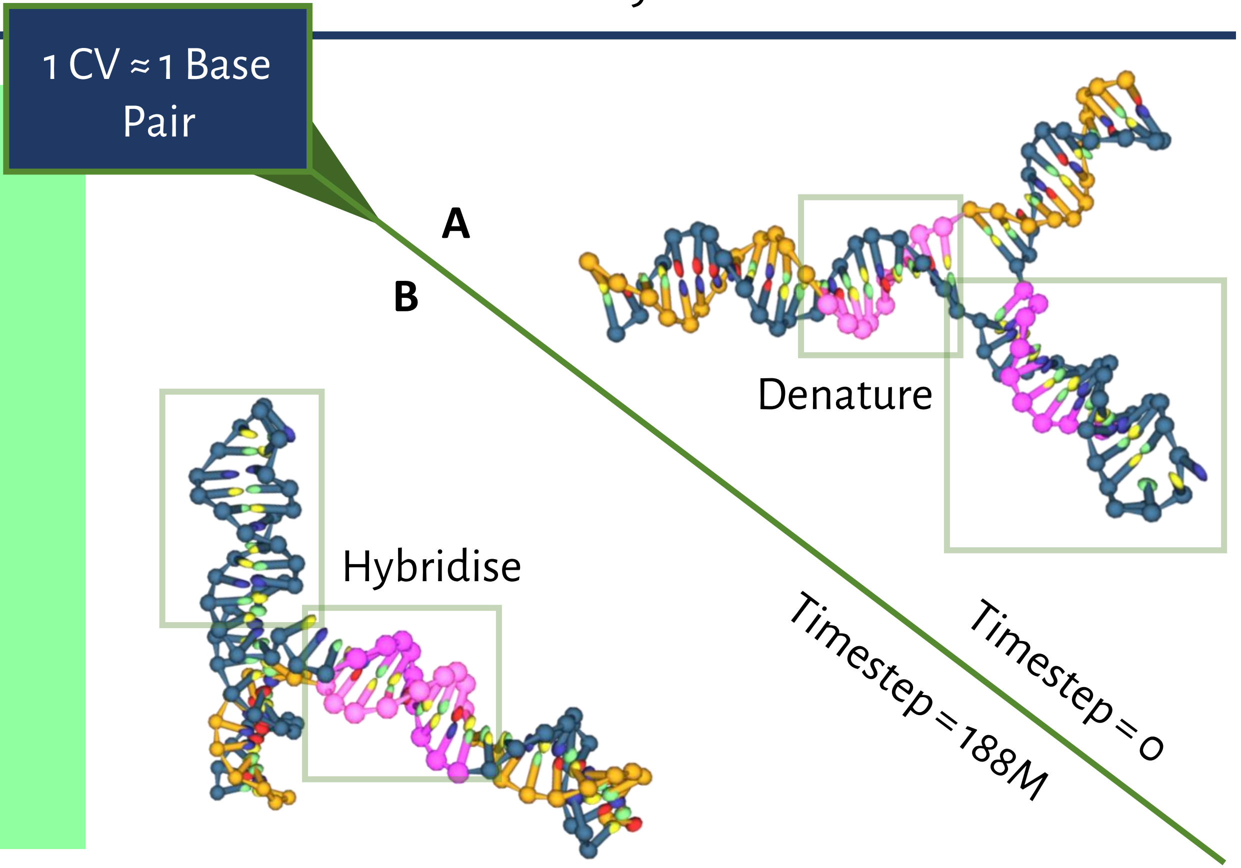
Contact Maps:

- Calculate distances between a number of pairs of atoms
- Transform each distance by a switching function (outputs CVs)

Switching Function:

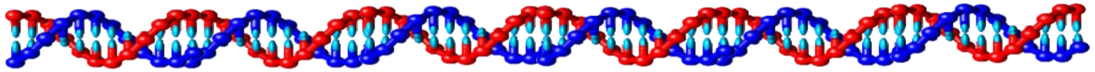
- For $r \leq d_0, s(r) = 1.0$
- While for $r > d_0$ the function decays smoothly to 0



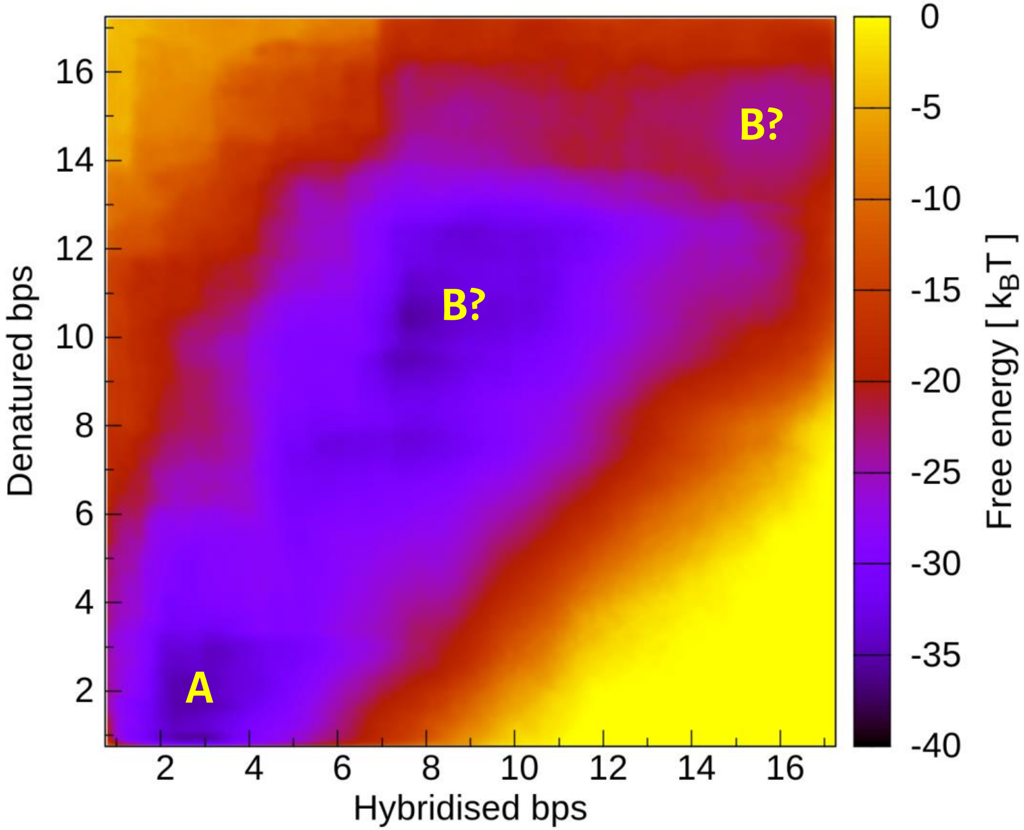


Documentation | https://www.plumed.org/doc-v2.7/user-doc/html/_c_o_n_t_a_c_t_m_a_p.html

Free Energy Landscapes



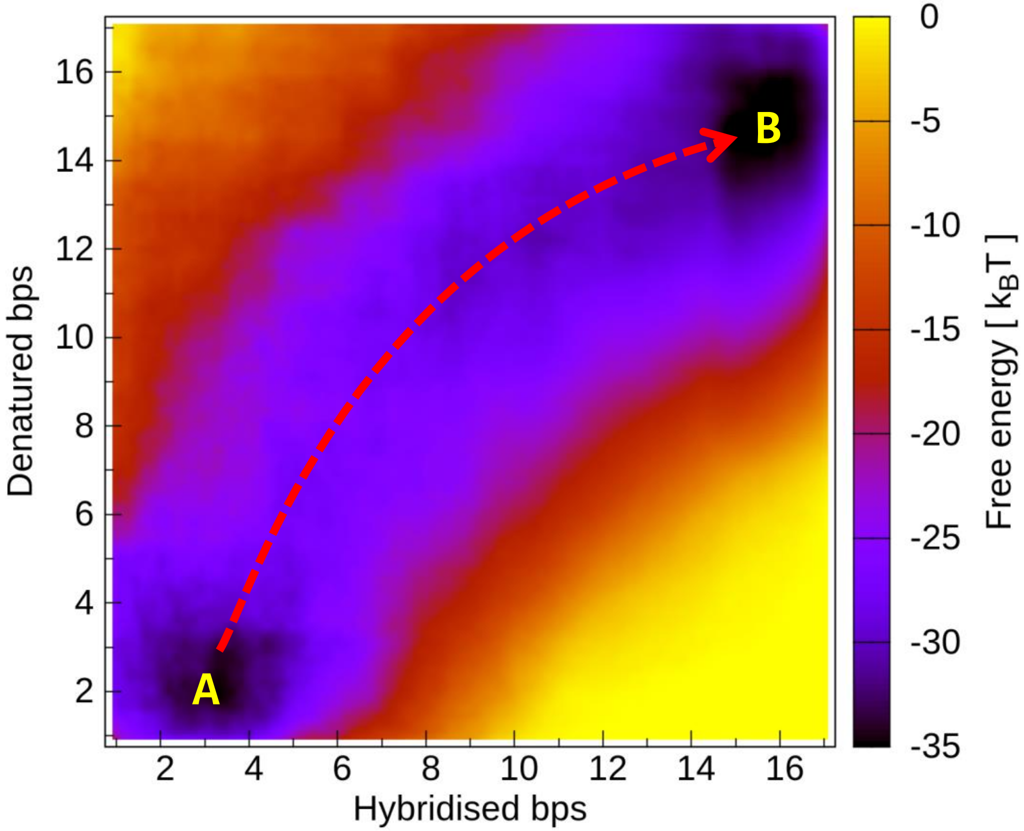
Initial State = A
Final State = B



WTMetaD, CTG_10

- Initial State well-defined, but Final State lacks definition -> not yet fully converged

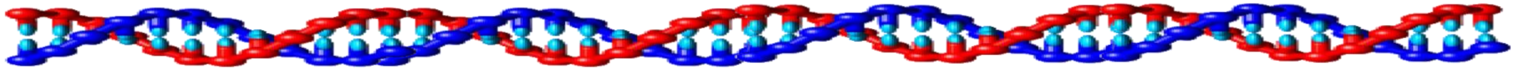
Initial State = A
Final State = B



TTMetaD, CTG_10

- Both Initial and Final State Well-Defined
- Clear Transitional Mechanics (Path -->)

Conclusion and Remaining Work



- TTMetaD over WTMetaD for Hairpin Migration Simulations:
  - Removes Dependence on Tuneable Parameters,
  - Faster Convergence with Greater Accuracy.
- CG-Modelling matching Experimental Findings*
- Results so far for CTG/CAG_10
- CAG_40 and CTG_30 ?

A Few Useful Links:

https://www.lammps.org/ | https://docs.lammps.org/Packages_details.html#pkg-cg-dna

https://dna.physics.ox.ac.uk/index.php/Main_Page | https://www.plumed.org/

.ppt here on my GitHub | https://github.com/lrussell676/Public_Yr_5_Files

*Bianco, Hu, Henrich, Magennis. Biophysical Reports, Volume 2, Issue 3, 2022, 100070, ISSN 2667-0747, https://doi.org/10.1016/j.bpr.2022.100070.

THE PLACE OF USEFUL LEARNING

University of Strathclyde
Science