

# Molecular Dynamics Simulations of DNA Minicircles

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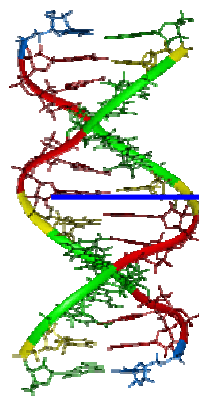
with thanks to Leesa Heffler for movie making

First insert brief re-visit to  $\alpha$  -  $\gamma$  flips. As reported earlier EPFL group extended poly(AT) ABC sequence out to 100 ns. With Schuette group did clustering analysis for identifying numbers of sub-states (article submitted).

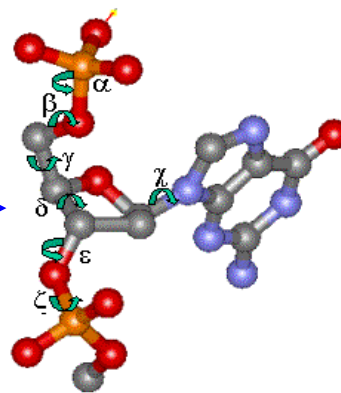
Were to have talk from Illya Horenko about this but US wouldn't give him a visa... So instead one slide from Christoff Schuette's talk earlier at the IMA

# Analysis of MD-data for DNA-segment

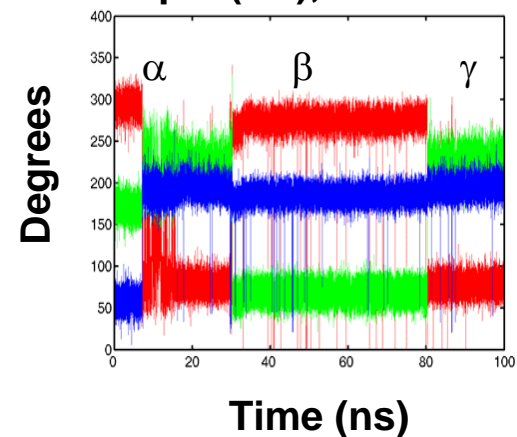
T-A-T-A-T-A-T-A-T-A-T-C  
 A-T-A-T-A-T-A-T-A-T-A-G  
 G C



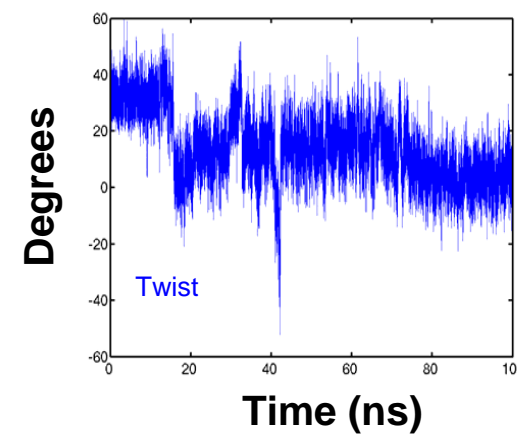
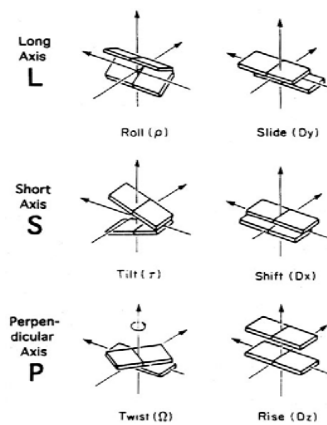
part of backbone



Step 9 (AT), 2<sup>nd</sup> strand



base-pair coordinates



Gonzalez and J.H.Maddocks:  
*Extracting parameters for base-pair  
 level models of DNA from molecular  
 dynamics simulations*  
 Theor.Chem.Acc. 106:76-82, 2001

And the flips have large scale consequences....

Clustering algorithms of the Almira visualizatio package

(almiraATAT15.mpg)

Back to Minicircles..

Currently much current interest in understanding the 94 (and shorter) bp minicircles of Cloutier & Widom (2004) that have been observed to cyclize much better (ie by a factor of  $10^6$  or so although some dispute over this) than they should, according to any of the standard theories.

A full atomistic resolution Molecular Dynamics simulations of an entire 94 bp minicircle in explicit solvent with counter ions is (just) feasible.

And it shows a possible mechanism for the enhanced cyclization via the formation of kinks associated with unstacking of certain base pairs through exceptionally large rolls or propellor twists.

For DNA, explicit solvent computations are generally considered to be necessary because DNA is so highly charged. Then the rate limiting step in the computation is the size of the solvent box, which in turn depends on the 'diameter' of the DNA fragment. In particular an MD simulation of a 94 bp circumference mini-circle in an octahedral box is roughly equivalent to the simulation of a 30 bp linear fragment because they require the same size solvent box.

Set up initial conditions at either Link 9 or Link 8 'low-energy' closed configuration constructed using the molecular mechanics code JUMNA by Lavery and collaborators. Solvate, and use as initial conditions for an AMBER run.

Wait (a long time) and see what happens.

## Simulation Protocol

- AMBER program
- PARM94 parameters
- Truncated octahedral box ( $\approx$  172K atoms)
- Potassium/chloride either minimal or physiological concentrations
- Particle mesh Ewald electrostatics
- 2 fs timestep (SHAKE on Hydrogen-X covalent bonds)
- equilibration, NVT  $\rightarrow$  NPT
- 30 ns trajectories, 48+ months of (alpha) CPU time a pop

First simulation: Link 9 and physiological salt

Show six movies (all made with the VMD visualization package)

First and Second Movies: details of the ‘final’ structure of a 30 ns simulation starting from a circular configuration. There is an almost straight segment between the base-pairs marked in yellow (can compute that the helical parameters take almost canonical B-form DNA values in this straight region), and a highly writhed S-shaped linking the two ends.

The straight segment appears to be being pulled in tension and twisted by the S-shaped portion. Heuristically compatible with two elastic segments joined at the yellow regions.

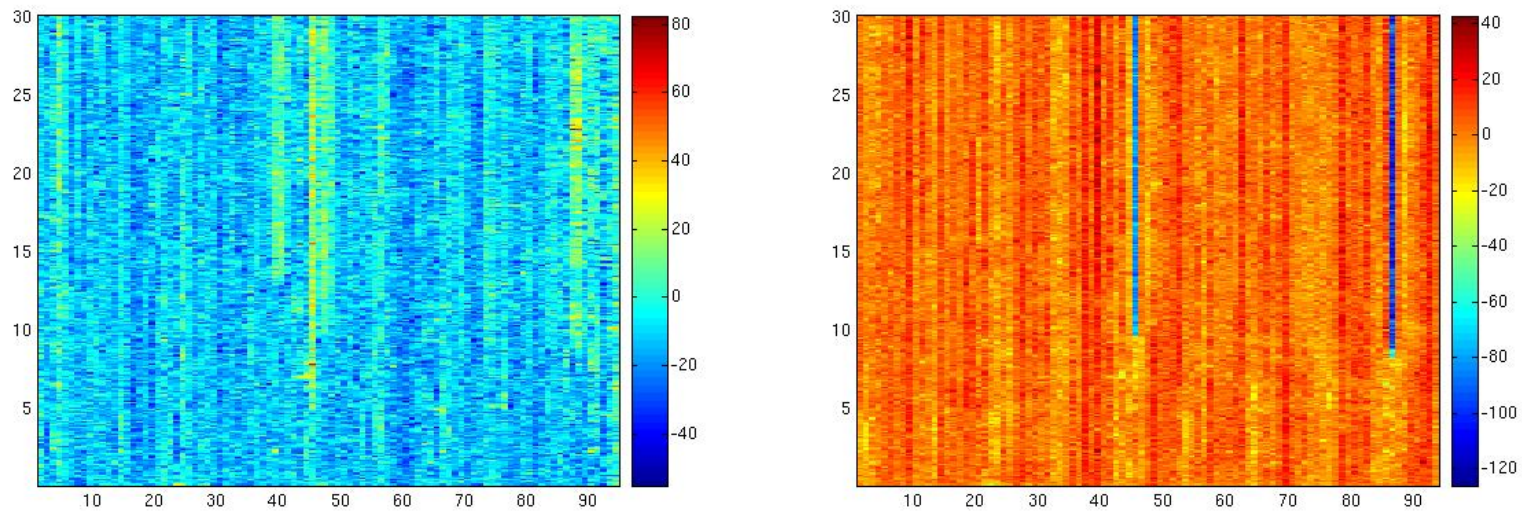
In both of the first two movies a static configuration is viewed from a moving eye-point. In the first movie there is a rotation with an axis close to the straight region and viewed from one side ([MOVmicROTATION.mpg](#)).

Then in the second movie the view-point is close to being along the axis of the straight segment ([MOVmicSWISSROLL.mpg](#)).

Third Movie shows the circular initial configuration. The eye view-point evolves to show the planarity and uniformity of the initial shape ([miniROTATION.mpg](#))

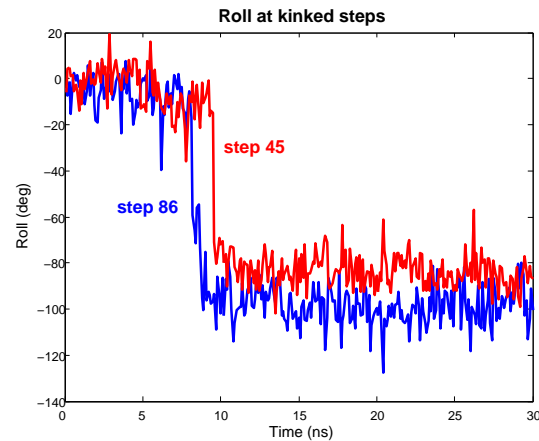
Fourth Movie shows the full 30 ns evolution from a fixed eye point. It is only after the fact that the particular base-pairs marked in yellow can be recognized to be special and be high-lighted. Beginning at around 9 ns the circle buckles and quite rapidly evolves to a highly deformed structure, which appears to be rather stable after around 20 ns. ([miniTRAJ.mpg](#))

The yellow base pairs separating the straight from S-shaped regions are unstacked. The 30 ns time series of the propellor twists (left) and rolls (right) at all 94 junctions are:



Time vertical, base-pair index horizontal, hot high, cold low.

Nothing much happens in propellor twists, but in rolls two junctions pop abruptly. (And nothing else dramatic in any other parameter.)

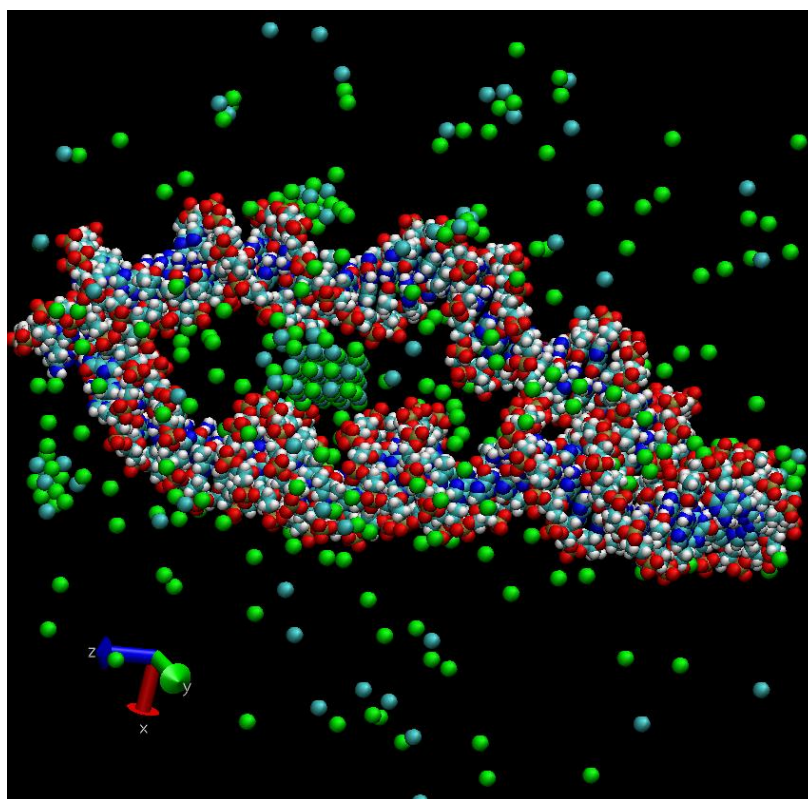


The two critical steps are the junction between base pairs 45 and 46 with local sequence cgCGct, and between 86-87 with sequence ctAGtc. Observe the nearly 90 degree jumps over rather short time scales. The length of the straight segment between kinks is 41 base pairs.

Fifth and Sixth Movies: details of the yellow base-pairs.

These two movies are each 300 ps long, close-up visualizations of the two critical base-pair steps at the time of the transitions in the rolls. Unstacking of each of the two base-pair steps at junctions 45 ([MOVmic-kink45.mpg](#)) and junction 86 ([MOVmic-kink86.mpg](#)) can be seen. However the base pairs stay paired. In junction 45 the unstacking is preceded by a very high propellor twist within a pair and then the bases snap to a configuration with an almost 90 degree angle between the planes of two successive base-pairs. There is a similar evolution in the 86 unstacking, but slightly less sharp in time. The resulting unstackings are very similar to the kinks proposed by Crick and Klug (Nature, 1975)

So far so good except that at the end of the above simulation much of the excess salt has formed a crystal.

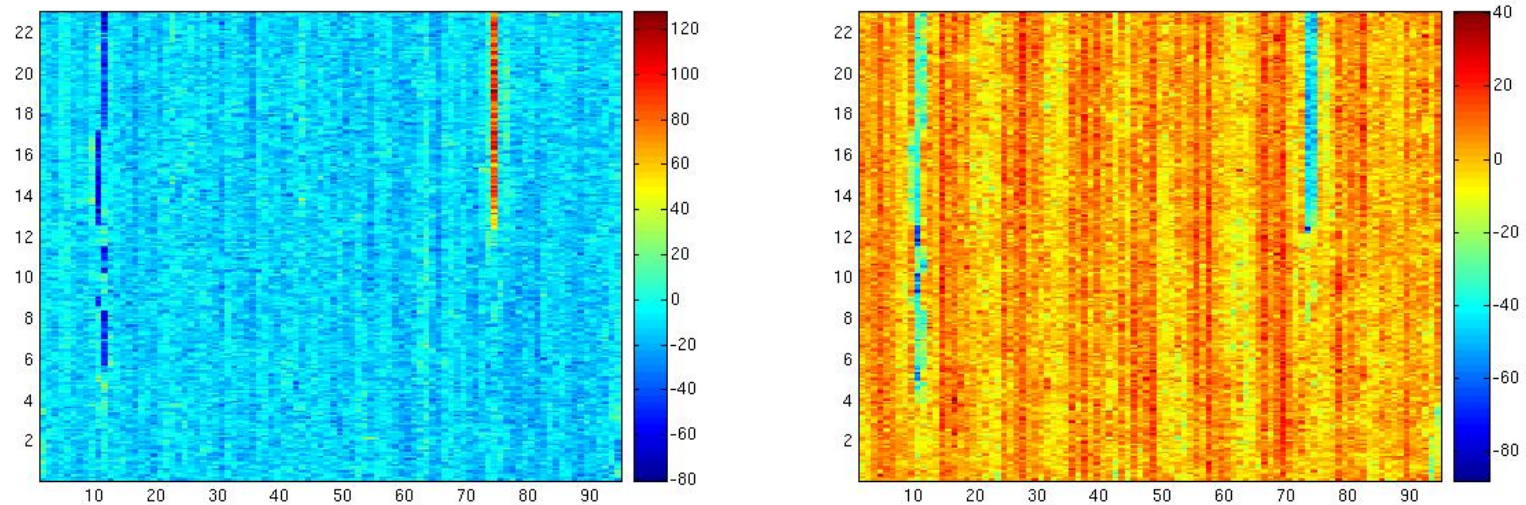


The salt crystal forms definitively several nanoseconds later than the kinks, so there is some reason to hope that the simulation may not be so bad.

Nevertheless started two more simulations at minimal salt, namely Link 9 at Link 8.

## Link 9 Minimal Salt:

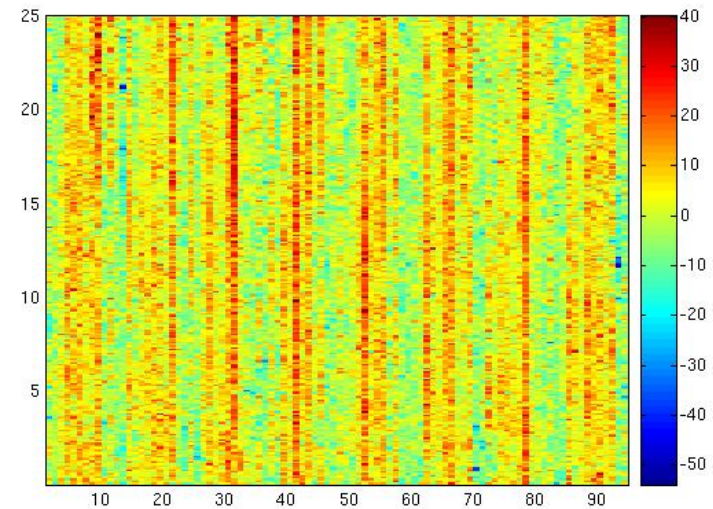
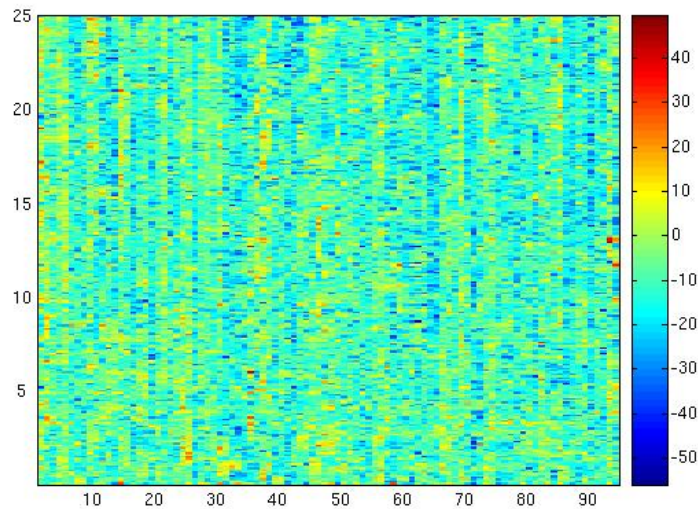
The time series of the propellor twists (left) and rolls (right) at all junctions are:



Now there is action in both propellor twist, and rolls around step 11 (at the end of the trajectory), with sequence `tcgTagc`, and around 74 with sequence `ataGgat`. And now straight segment is 31 base pairs.

## Link 8 Minimal Salt:

The time series of the propellor twists (left) and rolls (right) at all junctions are:



Now there is no abrupt action in anything. Circle stays more or less circular. Link 8 is the 'Amber'  $Lk_0$  torsionally unstressed link. Rolls display an approximate period eight behaviour, higher when register is phased outward.

The time series of the average twists for Link 8 (left) and Link 9 (right)

