Alpha helical crossovers favor right-handed supersecondary structures by kinetic trapping. The Coriolis force in protein folding.

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ABSTRACT

The remarkable predominance of right-handedness in beta-alpha-beta helical crossovers has been explained in terms of equilibrium stability, but a kinetic control mechanism may also play a role. If the beta-sheet contacts are made before the crossover helix is fully formed, and if the helix formation generally follows the energetic pathway of least resistance, then the folding helix would impart a torque on the ends of the two strands. Such a torque would tear apart a left-handed conformation but not a right-handed one. Right-handed helical crossovers predominate even among all-alpha proteins, where the equilibrium stability of the beta sheet twist does not apply. Using simple molecular simulations, we can reproduce the right-handed preference in beta-alpha-beta units, without imposing specific beta strand geometry. This kinetic trapping mechanism is dubbed the "Coriolis effect" because psi angles going "south" on the Ramachandran plot lead to a left-handed spin of the helix ends, while psi angles going "north" lead to a right-handed spin. Kinetic trapping explains the presence of a right-handed superhelical preference in alpha helical crossovers.

Brownian Dynamics simulations reproduce handedness given Coriolis force

Torsion space Brownian molecular dynamics simulations (Bystroff, 2001) were carried out to demonstrate the effect of a preferred route to helix on the superhelical handedness of a 3-part helical crossover unit such as a βαβ unit. No beta-strand specific forces were used, thus the packing of the terminal β strands played no role in defining the handedness.

A chain of alanines, length 29, was divided five segments, B1, L1, H, L2, and B2, with segment lengths 7,3,9,3, and 7 respectively.

Each simulation was carried out in two steps:
1) COLLAPSE. The chain was initialized in an extended conformation (psi=100±10, phi=-120±10). Strands B1-L1 and L2-B2 were "*collapsed*" by forcing the terminal atoms to cross to the opposite ends of the frozen H segment. A collapsed state was detected by measuring the distance and direction of the terminal atoms projected onto to the long axis of the H segment.

2) FOLD. Once collapsed, torsion angles within the H segment were unfixed and a helix was allowed to form. Energies were assigned to backbone Psi angles in H according to

Hypothesis 1: South) the energy barrier at phi=0 is lower, or
Hypothesis 2: North) the energy barrier at phi=180 is lower.

A high energy barrier was assigned to the phi angle, but full 360° rotations of both angles were possible and were observed.

At the end of each simulation, several values are reported:
- The overall handedness : Right, Left or ambiguous.
- The percent of Psi angles in H that went South versus North.
- Collapsed status: Collapsed or Not Collapsed.
- Status of the H segment: Helical or Not Helical.

Result
Hypothesis 1: South) **61% R-handed** (n=155)
Hypothesis 2: North) **39% R-handed** (n=395)

Probability either of these results could be the result of chance, p=0.01

Database statistics of three-helix bundles show R-handed preference

Three helix bundles are defined as protein substructures containing three consecutive helices, with no intervening beta strands, and where the first and third helix are in close contact. These are the helical analogs of beta-alpha-beta units and can be either right- or left-handed. Three-helix bundles were extracted from the SCOP database (version 1.73), taking one representative from each all-alpha super-family.

Three-helix units were identified in SCOP database (version 1.73) all-alpha proteins using backbone angles. The handedness was determined by calculating a vector between contacting residues and comparing it to the axis of the middle helix. This method rarely fails to identify the true handedness, but to be sure, we averaged the handedness value over all contacts and kept only those cases where the handedness was unambiguously assigned. The 499 three-helix bundles are reported below. **61.5% are right-handed**.

Each example on this list is from a different fold, and thus cannot be considered as related by homology, even remotely. As such, they represent independent counts of three-helix bundle topology. If no energy difference existed then the counts should partition themselves evenly, within statistical limits. The probability of getting 61.5% right-handed three-helix bundles by chance, given the null model of equally likely right and left-handed forms, was determined using the resampling method to be p=0.0001.

Folding a helix:

a rope

a ball-chain

- Coiling a rope torques the ends.
- Coiling a ball-chain doesn't.
- Does folding a helix torque the ends?

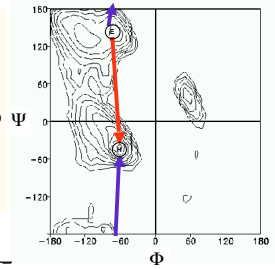
Anyone who has ever coiled a **rope** knows that you have to twist the ends to get it to coil and stay flat. Depending on which way you twist the ends, you get either a right-handed or a left handed rope coil, or helix. Coiling a **ball-chain**, on the other hand, does not require twisting the ends since each link can pivot to relieve accumulating torque.

The backbone of a polypeptide can pivot but *does not* pivot freely. There are energy barriers in both the φ and ψ backbone angles, adding resistance to bond rotation. As a result, a nature of a polypeptide chain is perhaps more like a rope than a ball-chain. If so, then the formation of a helix should torque the ends.

Extended to helical: traveling North versus South

An unfolded polypeptide exists mostly in the upper-left corner of Ramachandran plot, the extended (E) conformation. When folding from extended to helical (H), the ψ angle can go either "**North**" through 180°, or "**South**" through 0°.

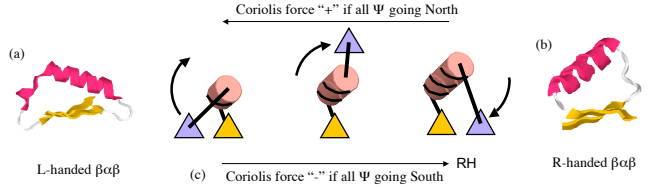
Both energy calculations and backbone statistics (contours) show that South (red arrow) has a lower energy barrier than North (blue arrow). South angle changes can be concerted over several consecutive residues. A concerted South pathway passes through 3-10 helix. North cannot be concerted, as it would cause the chain to cross itself.



How torque from helix formation can manifest in superhelical right-handedness:

A crossover unit such as a βαβ unit in proteins may be right-handed (helix direction aligns with the fingers of the right hand when the thumb is played along the contacts between the terminal groups) or left-handed.

If the non-local contacts form before the helix is fully folded, and if the helix formation produces a clockwise (negative) torque on the ends, then the resulting rotation will pull apart contacts in a left-handed crossover, but it will push together contacts in a right-handed crossover.

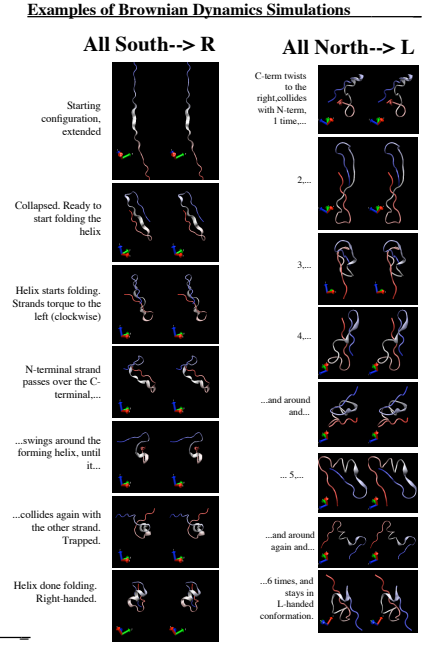


a) 1J9L:123-165 -- A left-handed βαβ unit. Only about 1.5% of all βαβ units are left-handed.

b) 1BYS:57-87 -- A right-handed βαβ unit.

c) A left-handed torque, generated by the Ψ angles going South on the Ramachandran plot, converts left-handed to right-handed

Examples of Brownian Dynamics Simulations

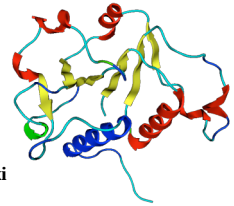


Coriolis force may explain knotted proteins

Topological knots are rare in proteins, and the possible pathways for knot formation remains a mystery. The existence of an intrinsically local Coriolis force provides an explanation for how helices could burrow through a loop or roll around a terminal strand.

We studied the structure of HAEMOPHILUS INFLUENZAE METHYLTRANSFERASE (1mxi), a protein with an overhand knot near its C-terminus. The C-terminal helix is long and very hydrophobic.

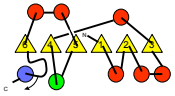
It is not hard to imagine how applying torque to the C-terminal helix could cause it to tunnel through the 4-5 crossover loop (which contains a single turn of helix). The C-terminal helix (blue) initially packs against strand 6. Twisting clockwise as it forms, it forces the 4-5 crossover away from the beta-sheet, then around the forming helix to the other side, as shown here in TOPS cartoons.



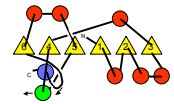
1mxi

How Coriolis force might form a knot in *1mxi*

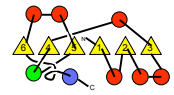
Hypothetical intermediate state with helices 5 and 8 switched. Helix 5 (green) is short and loose. Helix 8 (blue) is hydrophobic and long.



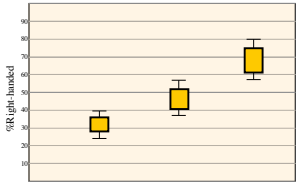
As helix 8 forms, the ends twist to the left. If the loop N-terminal to helix 8 finds its way under the loop, it pushes helix 5 to the left.



As helix 8 continues to fold, it rolls against helix 5 until the whole terminal segment passes through.

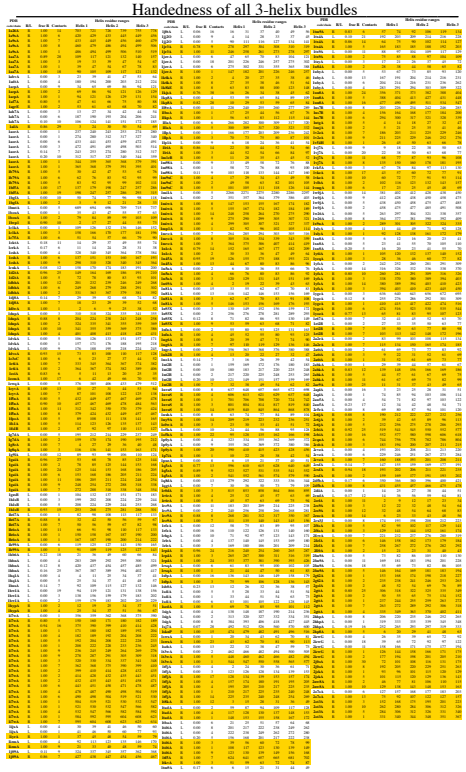


Summary of Brownian Dynamics Simulations



ΔΨ	0% South	50% South	100% South
Trials	2738	1164	501
Collapsed	2540	1066	418
Helical	851	578	286
Ambiguous	456	299	131
Right-handed	124	130	107
Left-handed	271	149	48
%R-handed	31%	47%	69%

Handedness of all 3-helix bundles



61% R, 39% L, n=431, p(R=0.50)<0.01

Selected Bibliography

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