Kinetic trapping in alpha-helical crossovers -- the Phone Cord Effect

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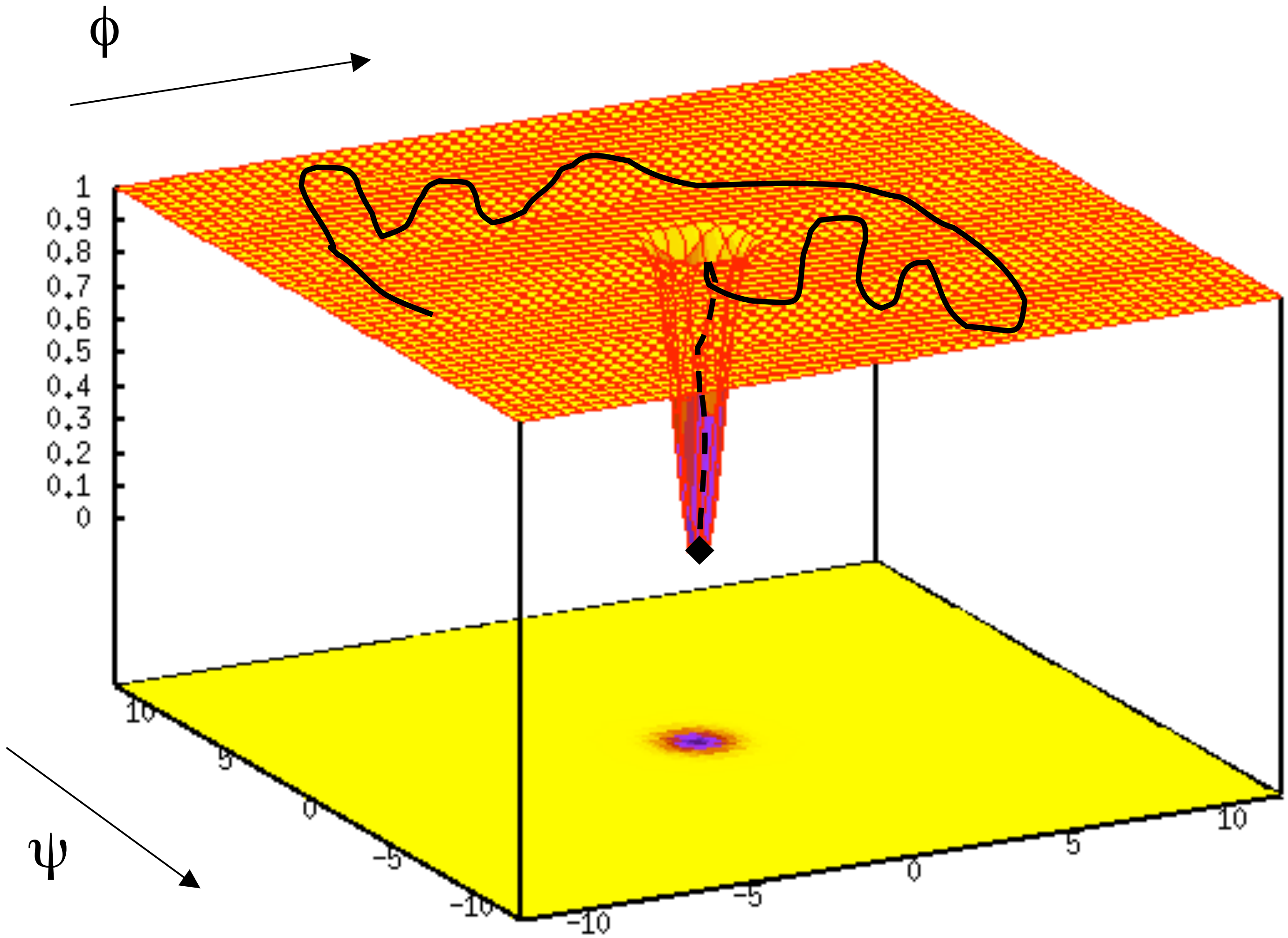
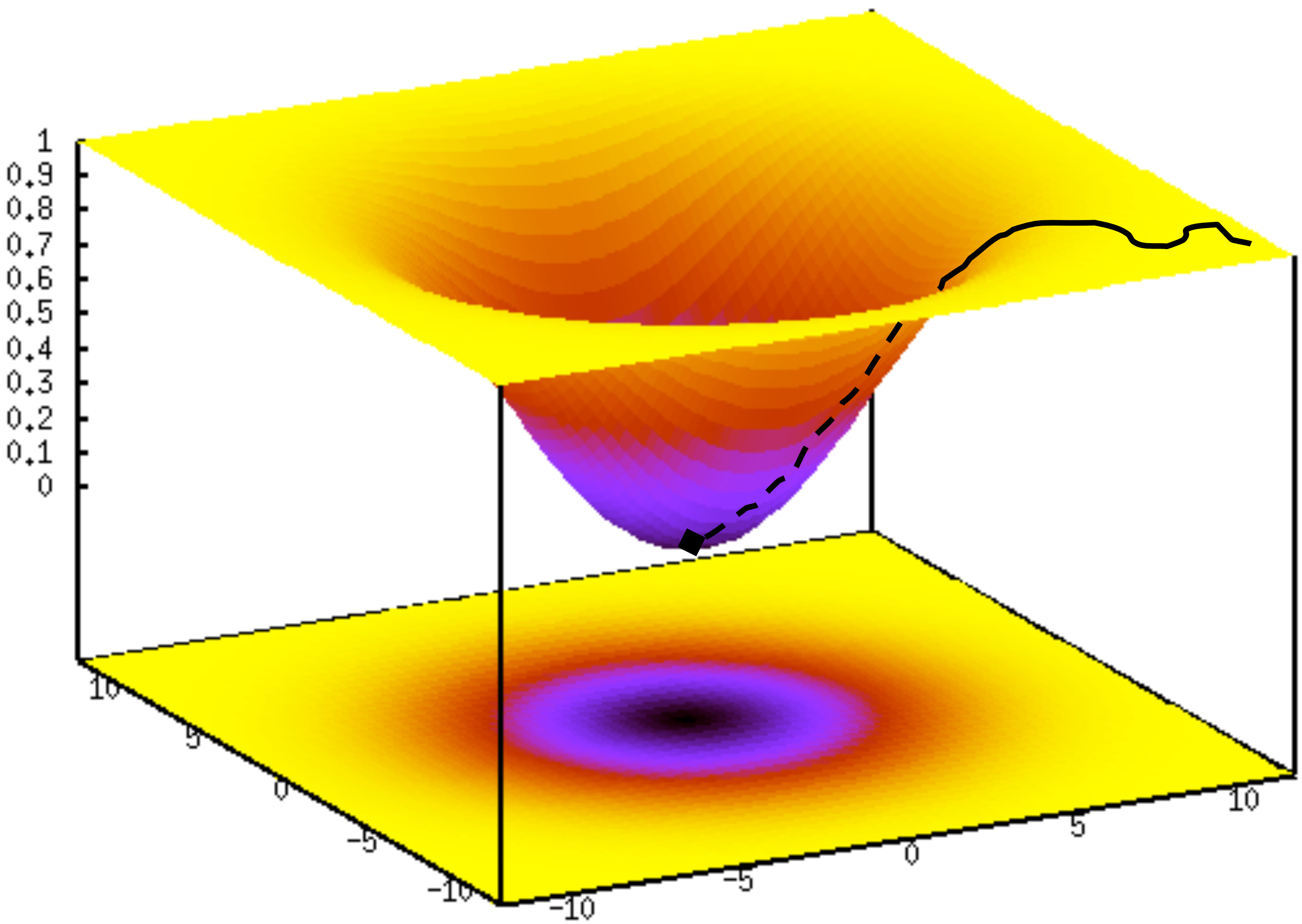
"All-or-nothing" energy landscape



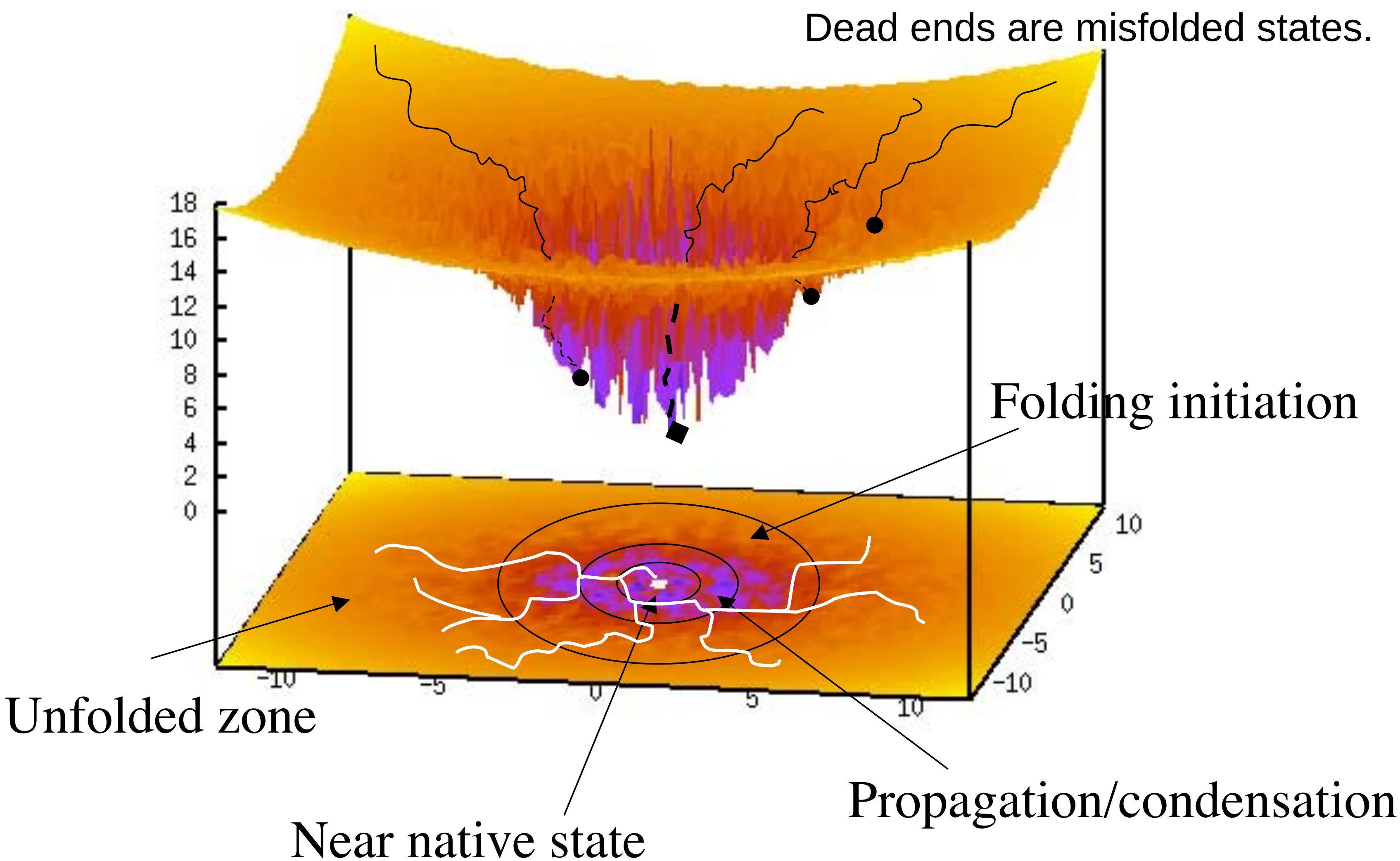
... like a golf course.

Folding funnel

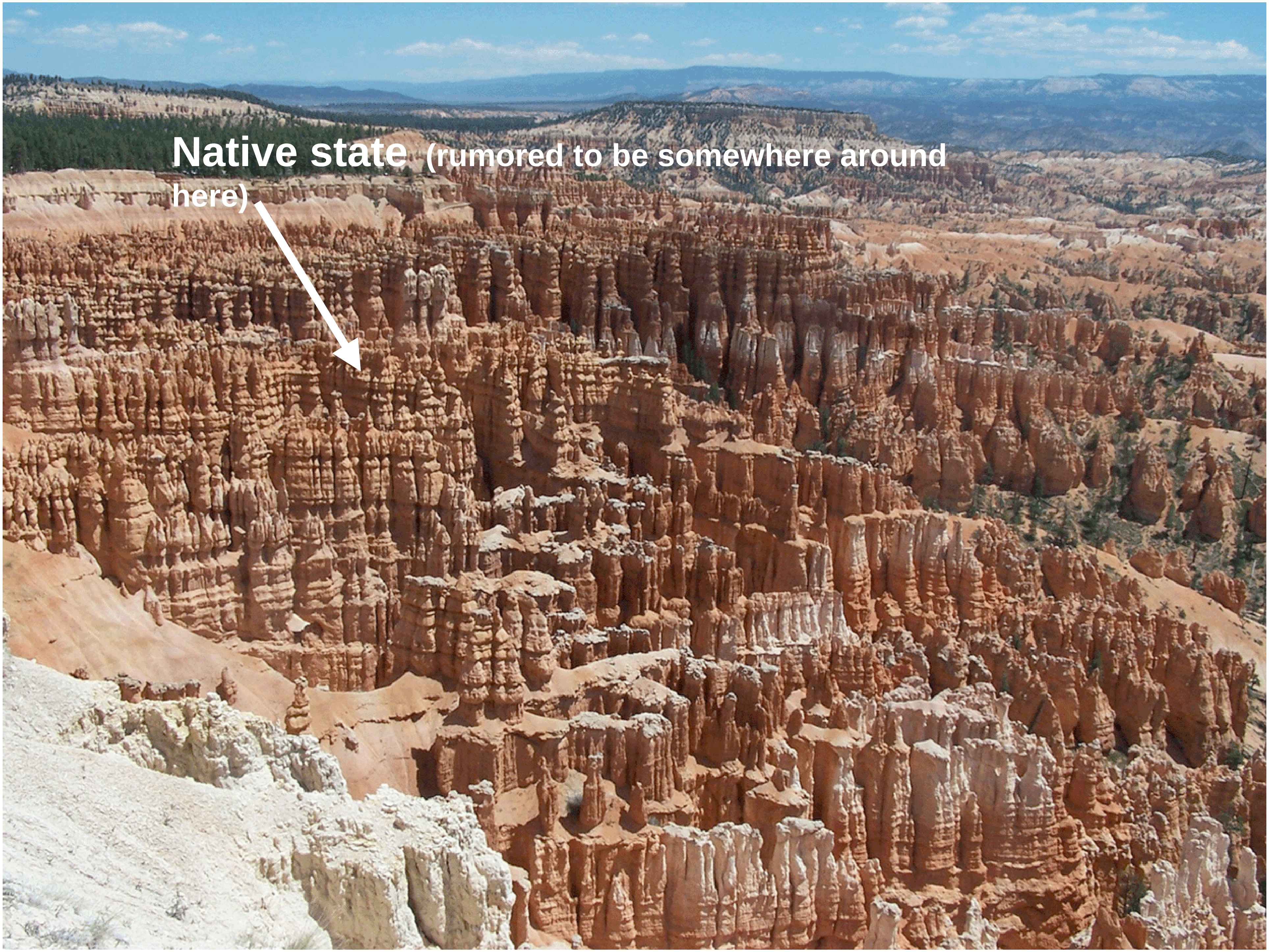


Energy goes down as structure approaches Native.

Folding funnel with chain crossing barriers



The folding pathway passes through zones, each can be characterized physically/informatically.

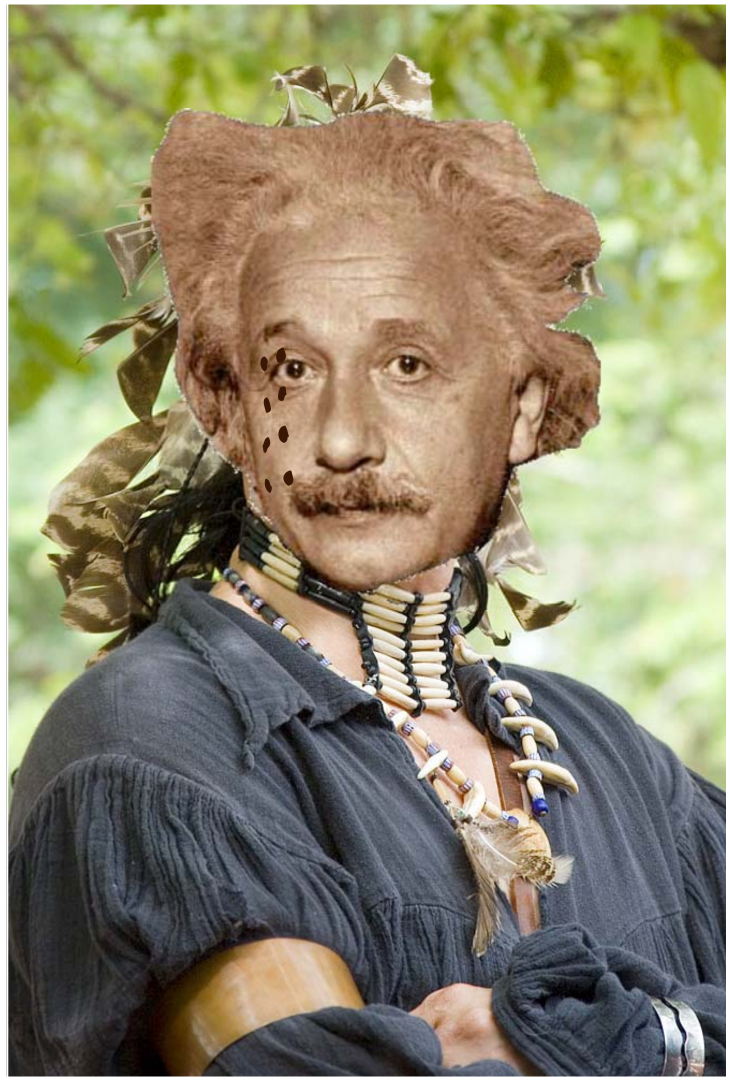

Native state (rumored to be somewhere around here)

“The Chain” just before folding, fully extended.

(Note, residues distant along the chain

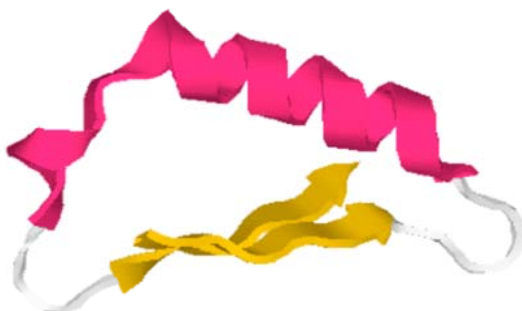
don’t know what the others are doing.)

(Note the flat energy landscape.)

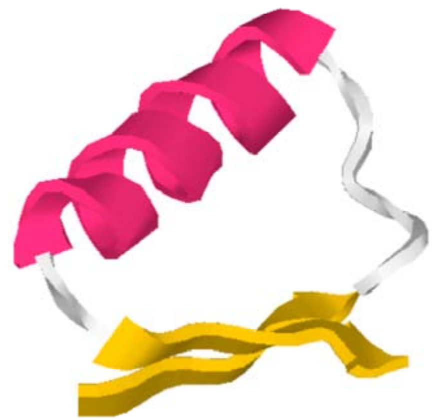


“Physics”, our folding guide.

βαβ supersecondary structure units are mostly right-handed



1J9L

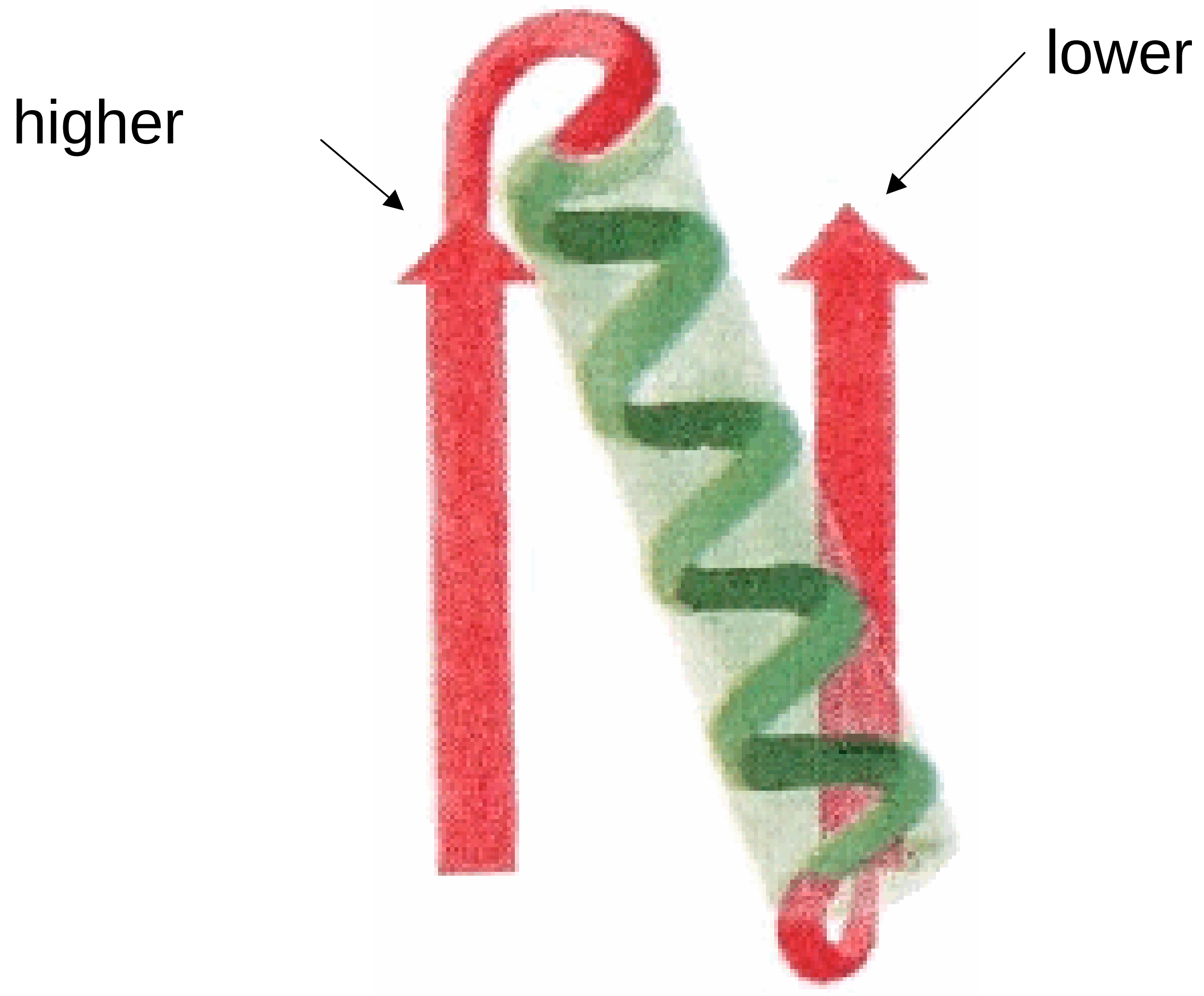


L-handed βαβ

1.5%

R-handed βαβ

98.5%



Sternberg & Thornton, JMB 1976: Twist of beta sheet makes right-handed crossover more probable.

Richardson, PNAS, 1976: Right-handed crossovers are trapped early in folding

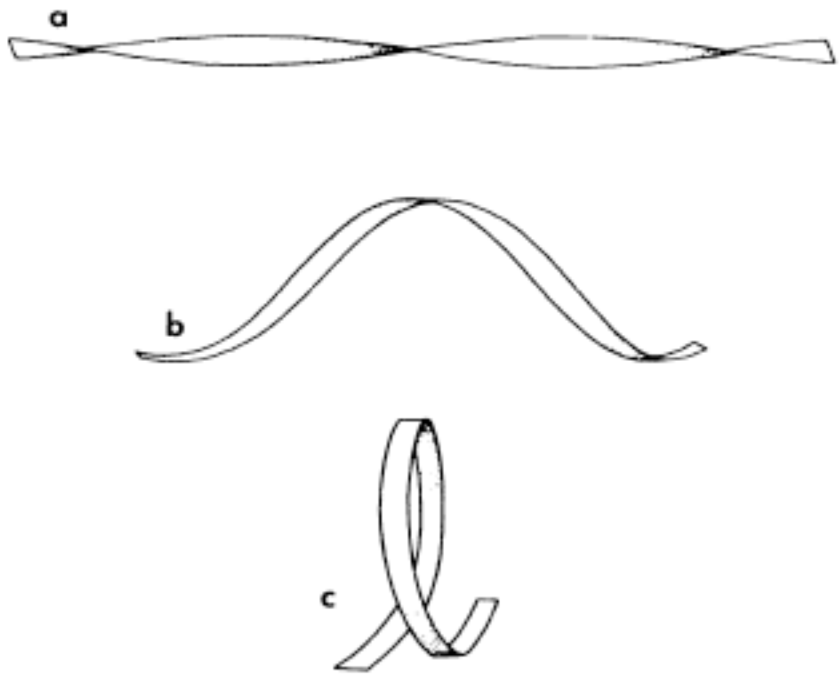


FIG. 4. A possible folding pathway which produces righthanded crossover loops from extended chain. In (a) the section of chain is extended, showing one full turn of the preferred righthanded twist for β strands. In (b) the two ends of this chain segment are moving toward one another, and the ribbon has started to buckle in a right-handed sense constrained by the chain twist. In (c) a complete righthanded loop is formed, with the two ends in position to form parallel β structure.

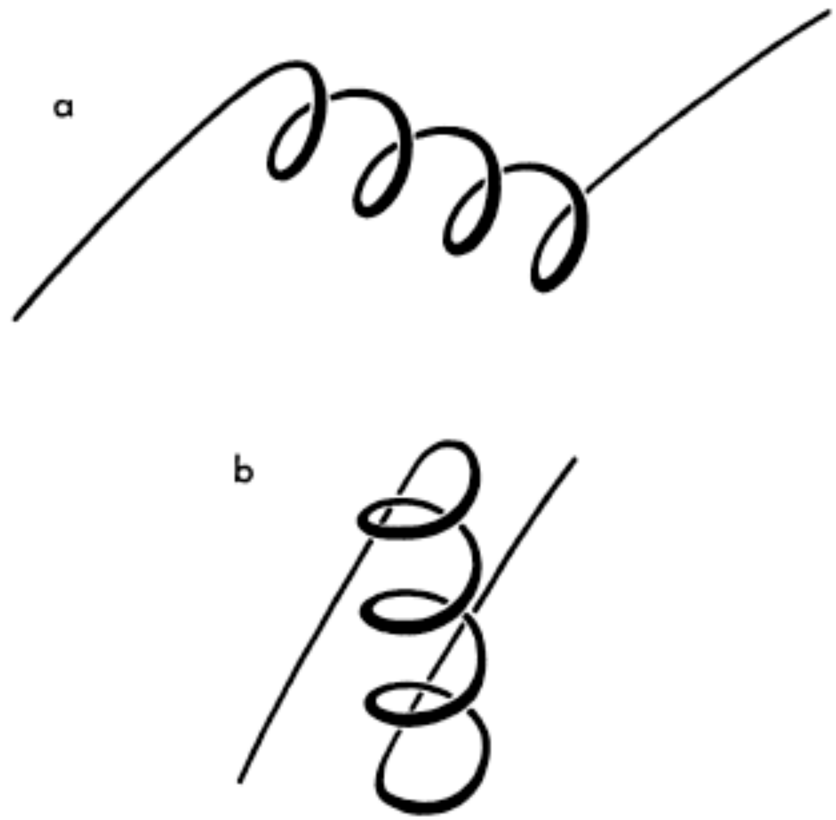
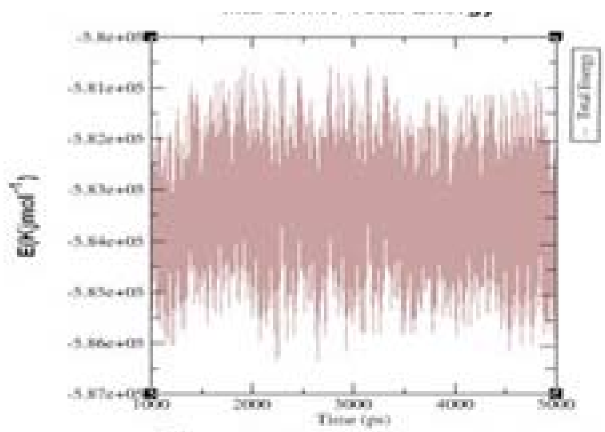
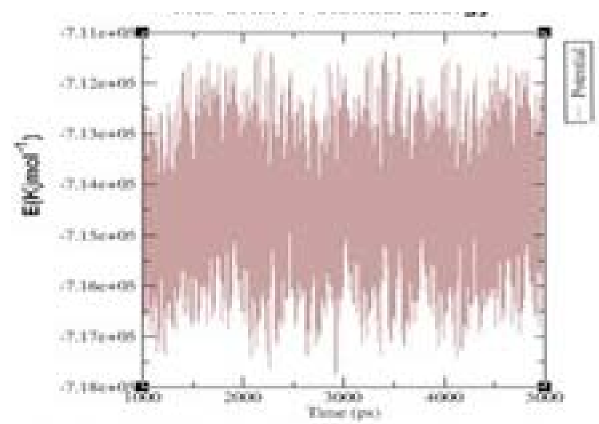


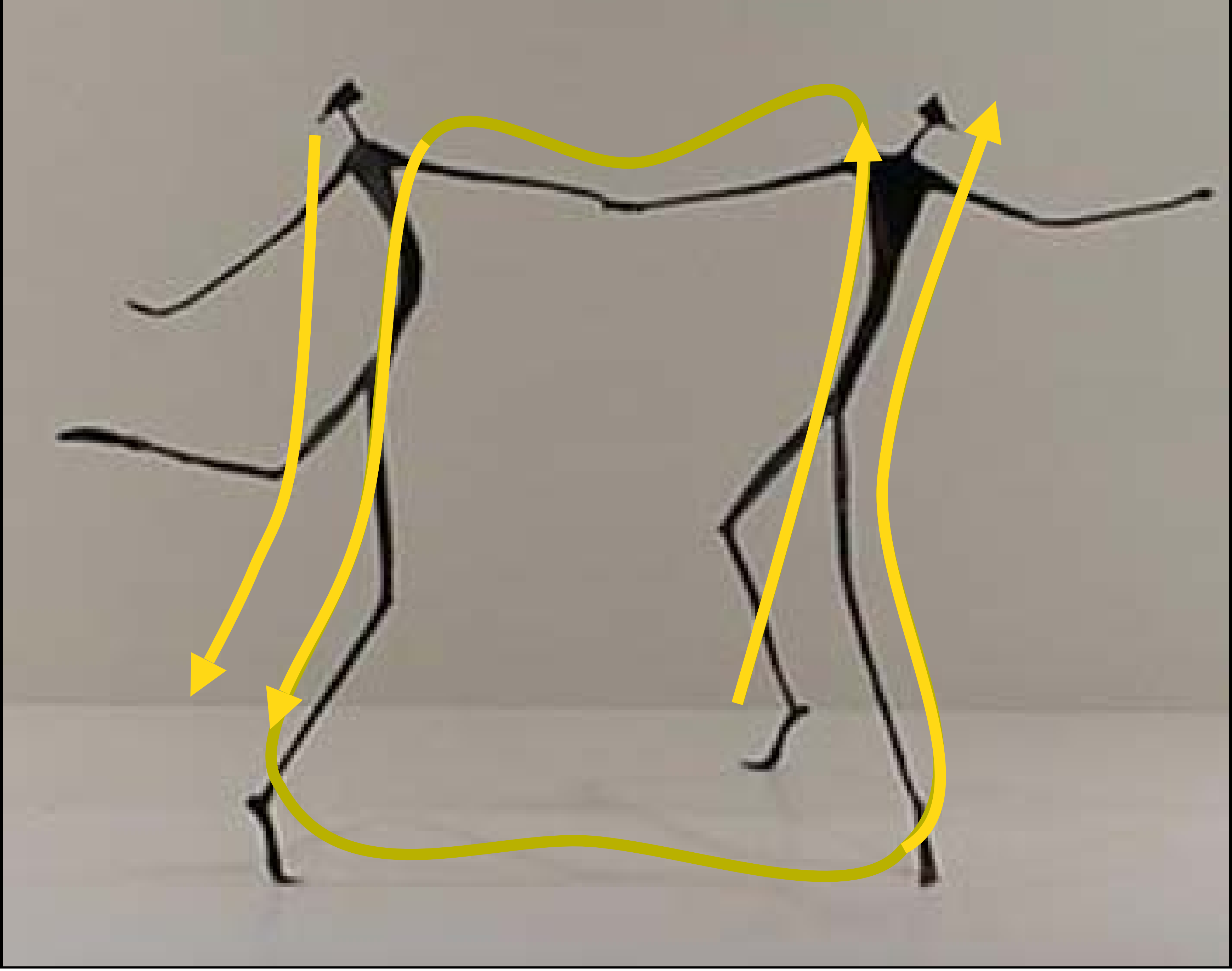
FIG. 5. A possible folding pathway which forms righthanded crossover loops from a righthanded α-helix with a β strand at each end of it.

Scheraga, JMB 1989: Potential energy of R-handed lower than L-handed because of loops.



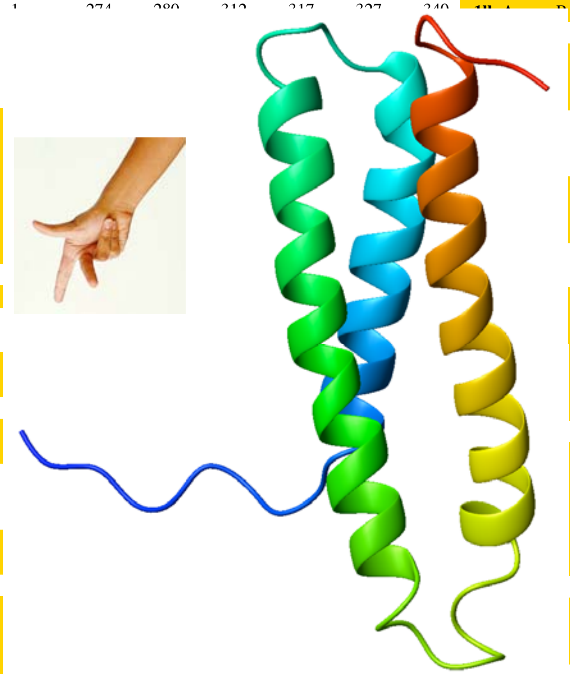


β-sheet twisting leads to R-handedness in 2-layer β-sandwichs.



B. Cole: Handedness of all 3-helix bundles

PDB code/chain	R/L	frac R	Contacts	Helix residue ranges: Helix 1		Helix 2		Helix 3	
1a26A	R	1.00	14	703	721	726	739	755	778
1a9xA	R	1.00	6	420	429	433	445	449	456
1a9xA	R	1.00	7	433	445	449	456	460	479
1a9xA	R	1.00	8	460	479	486	494	499	506
1a9xA	R	1.00	1	486	494	499	506	510	519
1aa7A	R	0.89	28	109	117	121	132	140	157
1aa7A	R	1.00	3	19	33	39	47	54	67
1aa7A	R	1.00	1	39	47	54	67	78	83
1aa7A	R	1.00	18	90	105	109	117	121	132
1abvA	L	0.00	3	23	39	41	47	53	64
1adtA	L	0.00	4	180	194	200	203	212	224
1aepA	L	0.00	9	34	65	69	86	94	121
1aepA	R	1.00	2	69	86	94	121	126	129
1aepA	R	1.00	1	94	121	126	129	131	154
1af7A	R	0.80	5	47	61	66	75	80	88
1agrE	R	1.00	2	53	61	63	68	70	82
1ah7A	L	0.00	3	13	27	34	42	44	54
1ah7A	L	0.00	6	187	190	193	204	206	241
1ah7A	L	0.10	10	106	124	141	151	172	185
1ailA	R	0.86	29	3	24	30	50	54	69
1aorA	L	0.00	1	237	240	243	253	274	280
1aorA	L	0.00							
1aorA	L	0.00							
1aorA	L	0.00							
1aorA	L	0.14							
1aorA	L	0.20							
1aorA	R	1.00							
1aorA	R	1.00							
1b79A	R	1.00							
1b79A	R	1.00							
1b79A	R	1.00							
1bf5A	R	1.00							
1bf5A	R	1.00							
1bgfA	L	0.00							
1bgfA	R	1.00							
1bmtA	L	0.00							
1bouA	L	0.00							
1bouA	R	1.00							
1bvp1	R	0.90							
1c1kA	L	0.00							
1c1kA	R	1.00							
1c75A	R	1.00							
1cktA	L	0.18							
1crkA	L	0.17							
1cshA	L	0.00							
1cshA	R	1.00							
1cshA	R	1.00							
1cukA	L	0.08							
1d2tA	R	0.96							
1d2tA	R	1.00							
1dbhA	R	1.00							
1dbhA	R	1.00							
1dbhA	R	1.00	2	331	363	367	379	381	392
1dj8A	L	0.14	7	29	39	52	68	74	82
1dj8A	R	1.00	7	18	23	29	39	52	68
1dlwA	R	1.00	1	2	6	9	25	38	52
1dnpA	L	0.00	3	310	318	324	335	341	355
1dnpA	R	0.88	8	204	224	238	243	248	258
1dnpA	R	1.00	2	324	335	341	355	359	369



PDB code/chain	R/L	frac R	Contacts	Helix residue ranges: Helix 1		Helix 2		Helix 3	
1j0tA	L	0.06	16	16	31	37	40	49	56
1jj2O	L	0.00	9	4	14	28	33	37	45
1jj2O	L	0.00	5	90	111	116	127	134	141
1jr3A	R	0.78	9	278	297	304	308	310	319
1jr3A	R	1.00	11	246	258	261	273	278	297
1jswA	L	0.00	6	47	65	70	83	104	121
1jswA	L	0.00	18	201	226	246	257	275	302
1jswA	L	0.00	6	275	302	331	355	365	388
1jswA	R	1.00	1	147	182	201	226	246	257
1k6kA	R	1.00	2	4	20	27	35	38	46
1k6kA	R	1.00	8	27	35	38	46	51	64
1k8kE	R	1.00	8	63	83	88	100	123	148
1kjsA	R	0.76	38	16	26	34	38	45	62
1kp8A	L	0.00	4	53	59	65	84	89	109
1kp8A	R	0.82	28	10	29	53	59	65	84
1l8wA	L	0.00	11	228	240	255	260	277	289
1lbuA	R	1.00	1	17	25	44	56	67	76
1lkpA	R	1.00	1	56	63	83	112	115	144
1llaA	L	0.00	6	266	282	300	309	317	320
1llaA	R	1.00	5	300	309	317	320	323	332
1llpA	L	0.00	1	166	177	203	209	236	242
		1.00	3	70	73	75	80	87	101
		0.00							
		0.86							
		1.00							
		1.00							
		0.00							
		0.00							
		0.11							
		1.00							
		1.00							
		1.00							
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		0.79							
		1.00							
		0.95							
		1.00							
		0.00							
		1.00	4	66	76	80	83	86	92
		1.00	3	120	129	131	145	151	169
		1.00	4	2	19	22	39	43	63
		0.00	15	33	55	62	67	70	83
1n81A	L	0.00	13	116	142	146	153	156	169
1n81A	R	1.00	3	62	67	70	83	91	108
1n81A	R	1.00	5	146	153	156	169	176	193
1n93X	L	0.00	3	130	149	152	156	159	172
1n93X	L	0.00	2	256	276	278	281	289	293
1n93X	L	0.12	8	71	82	86	93	130	149
1n93X	R	1.00	9	53	59	63	68	71	82

61% R,

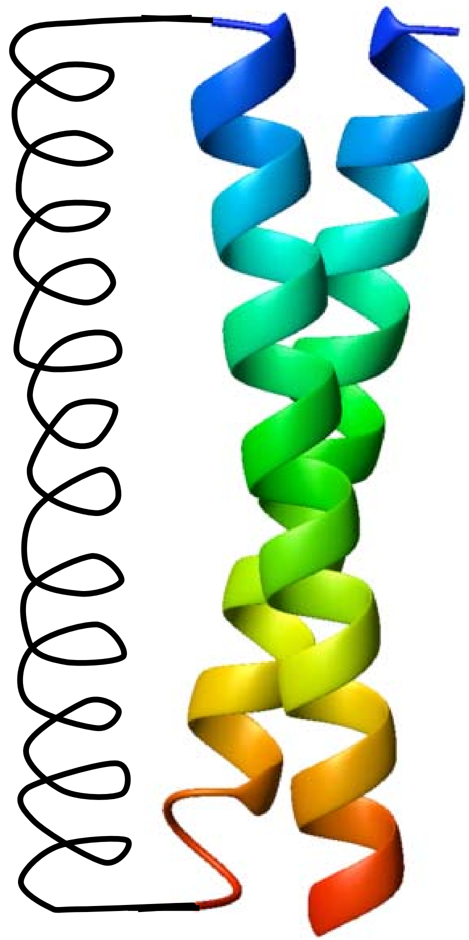
39% L,

n=431,

p(R=0.50)<0.01

PDB code/chain	R/L	frac R	Contacts	Helix residue rang: Helix 1		Helix 2	
1tm9A	R	0.83	6	57	74	92	106
1tx4A	L	0.10	21	192	203	209	214
1tx4A	R	0.86	14	64	75	90	102
1tx4A	R	1.00	5	165	183	185	188
1tx9A	L	0.00	11	88	97	104	109
1tx9A	R	1.00	2	75	85	88	97
1tzyA	L	0.00	3	17	21	26	37
1u84A	R	1.00	2	28	38	44	58
1ubyA	L	0.00	5	53	67	73	85
1ubyA	L	0.00	13	167	191	204	214
1ubyA	L	0.00	6	204	214	216	231
1ubyA	L	0.00	4	283	291	294	303
1un8A	R	1.00	24	356	371	373	382
1un8A	R	1.00	5	388	404	413	427
1un8A	R	1.00	16	477	490	495	511
1us7B	L	0.00	8	203	226	234	242
1us7B	R	1.00	4	156	164	168	177
1us7B	R	1.00	6	294	300	317	321
1utgA	R	1.00	5	4	14	18	27
1uujA	R	1.00	2	5	21	25	35
1v2zA	R	1.00	7	186	203	211	225
1v2zA	R	1.00	9	211	225	229	246
			1	26	45	50	63
			9	9	18	22	38
			20	22	38	50	63
			11	68	77	87	93
			8	135	150	160	178
			3	67	78	84	97
			17	43	57	60	72
			10	60	72	77	91
			2	102	116	123	132
			6	17	23	25	45
			14	381	402	412	428
			9	412	428	438	450
			5	438	450	458	475
			2	458	475	477	485
			5	263	297	304	321
			8	364	377	381	390
			2	289	301	305	322
			4	11	44	49	71
			1	92	128	138	161
			5	6	12	16	20
			5	23	41	55	70
			5	16	20	23	41
			1	105	120	132	137
			3	28	36	46	60
			2	242	252	260	281
			14	316	326	332	336
1yfsA	R	0.80	10	260	281	291	309
1yfsA	R	1.00	3	338	370	380	389
1yfsA	R	1.00	14	380	389	394	403
1yfsA	R	1.00	3	394	403	410	423
1ygeA	L	0.00	3	636	640	643	656
1ygeA	L	0.12	8	255	276	286	292
1ygeA	R	1.00	1	410	415	417	422
1ygeA	R	1.00	6	474	516	523	530
1yozA	R	0.77	13	65	81	83	95
1z67A	L	0.00	7	32	41	45	52
1zt2B	L	0.00	2	27	33	35	50

Does the twisting argument apply to helices?

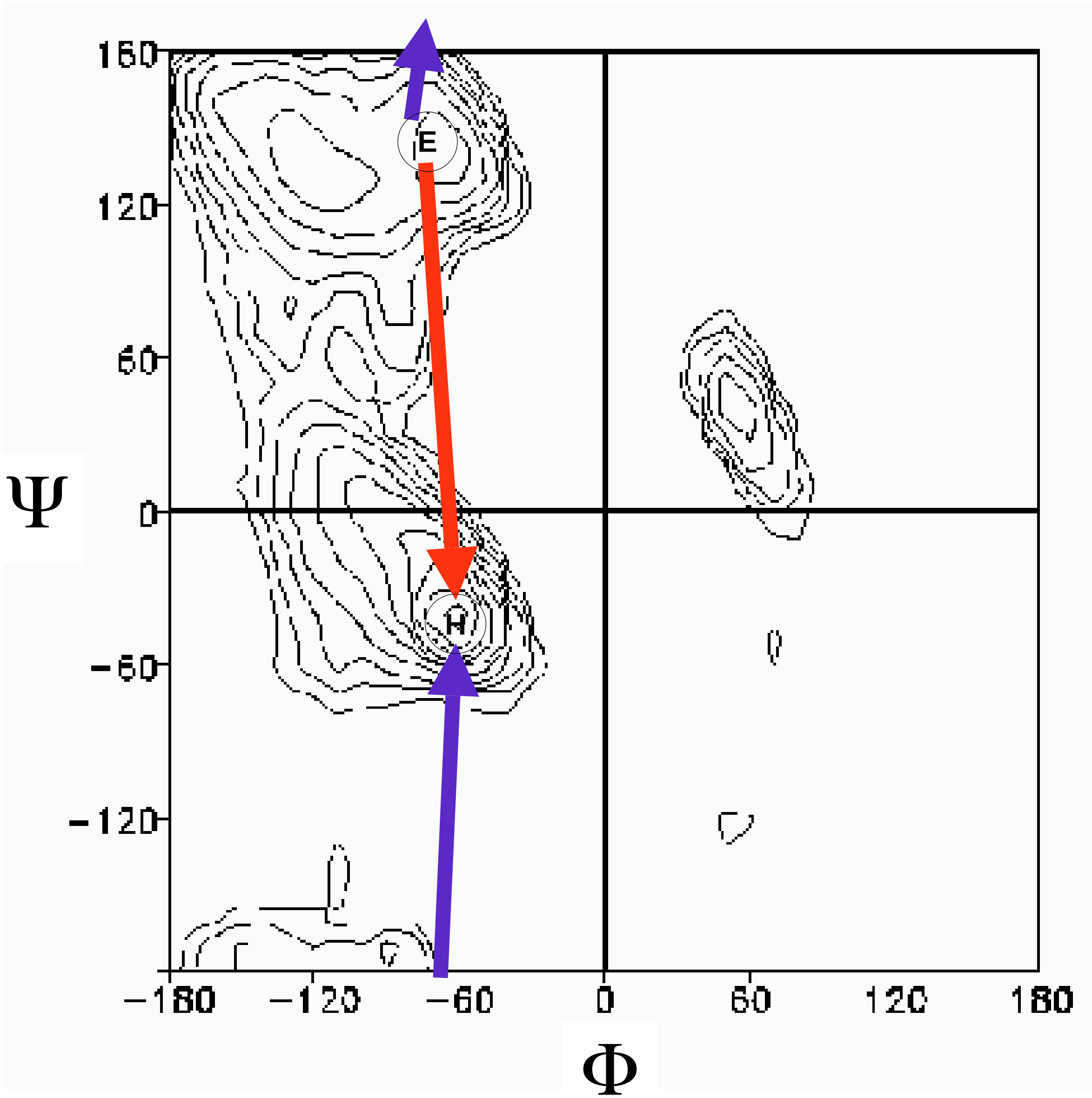


Coiled-coil helix packing would argue for left handed crossovers!

Unanswered questions

- Even $\beta\alpha\beta$ with *long loops* containing multiple helices are mostly R-handed.
- Both R-handed and L-handed β helices exist.
- 3-helix bundles, containing no beta, are predominantly R-handed.

The path from Extended to Helical: Northern versus Southern route



South

http://www.bioinfo.rpi.edu/bystrc/pub/mpeg/south.gif

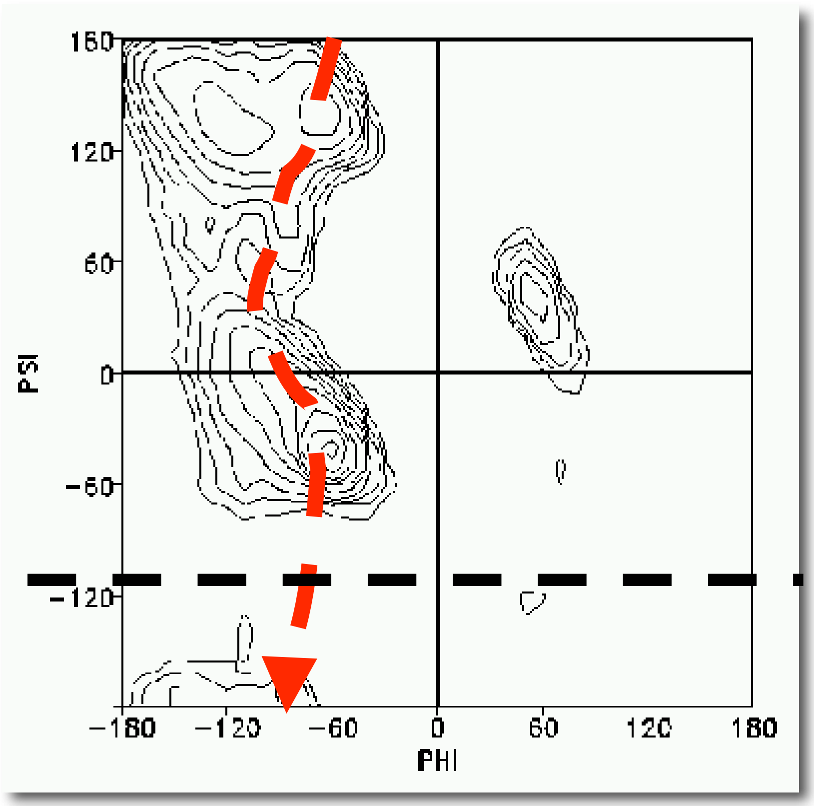
North

http://www.bioinfo.rpi.edu/bystrc/pub/mpeg/north.gif

How does a polypeptide chain behave under torsion?

a rope

a ball-chain



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

An experiment: the phone cord effect

Start with extended chain.

Force the ends to cross-over

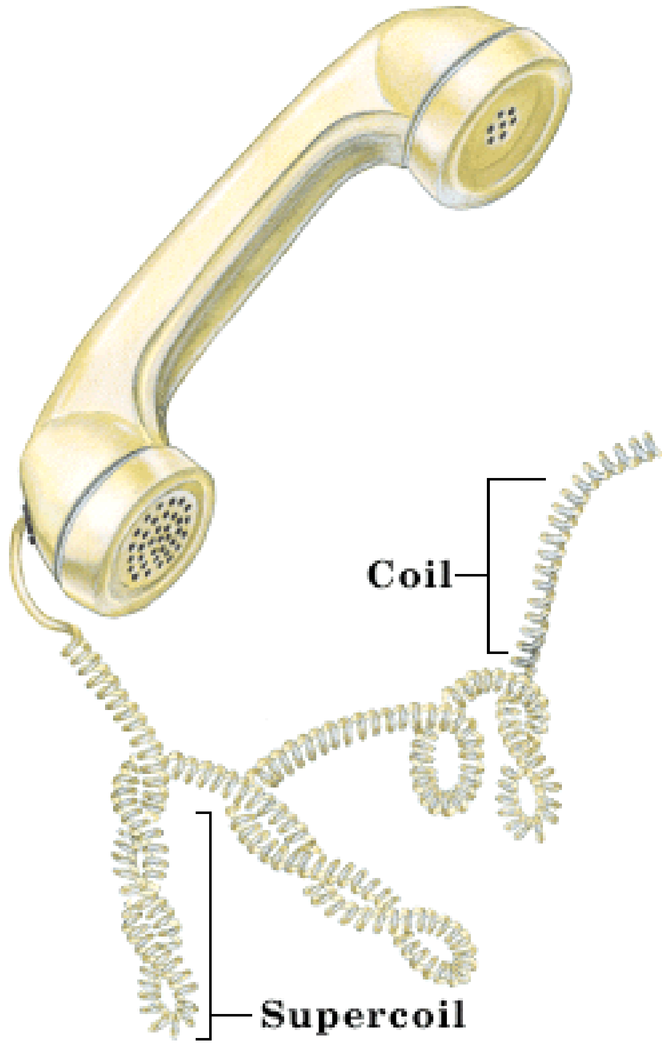
Form a helix in the middle, using

(1) all “South” moves

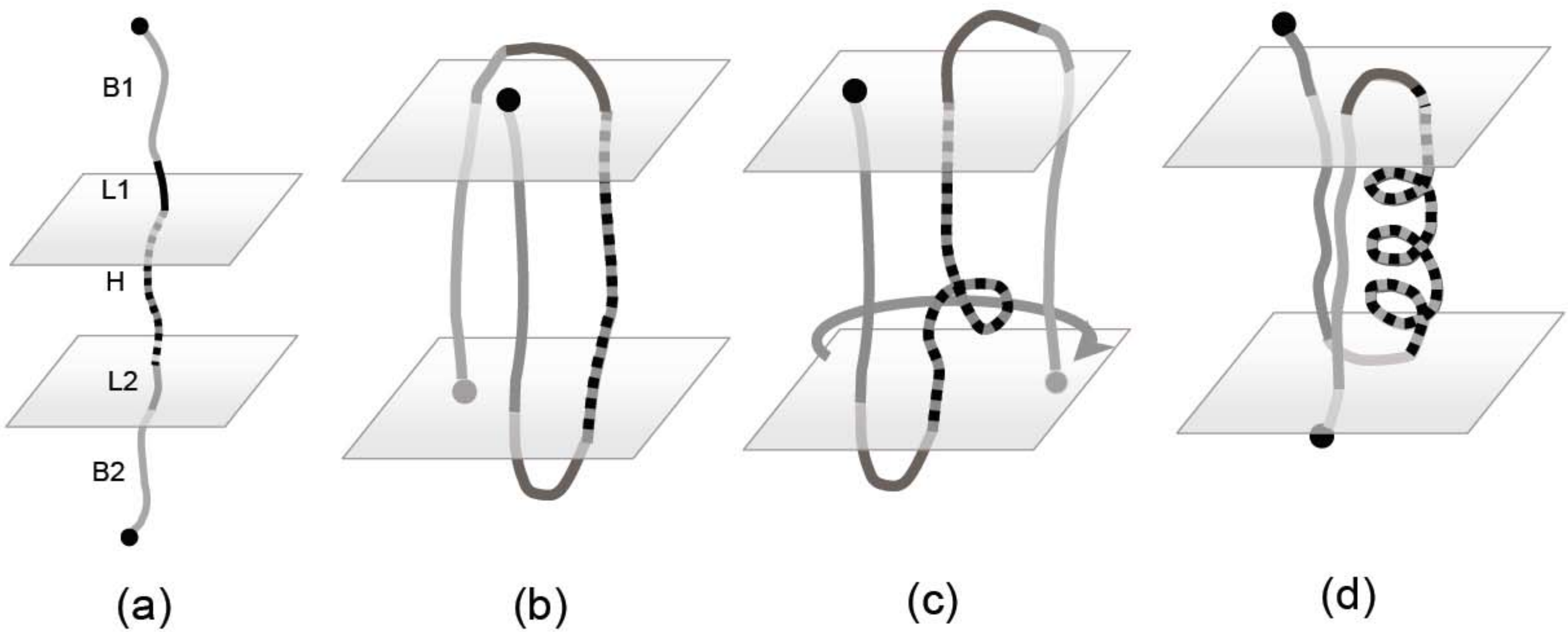
(2) all “north” moves

(3) no preference

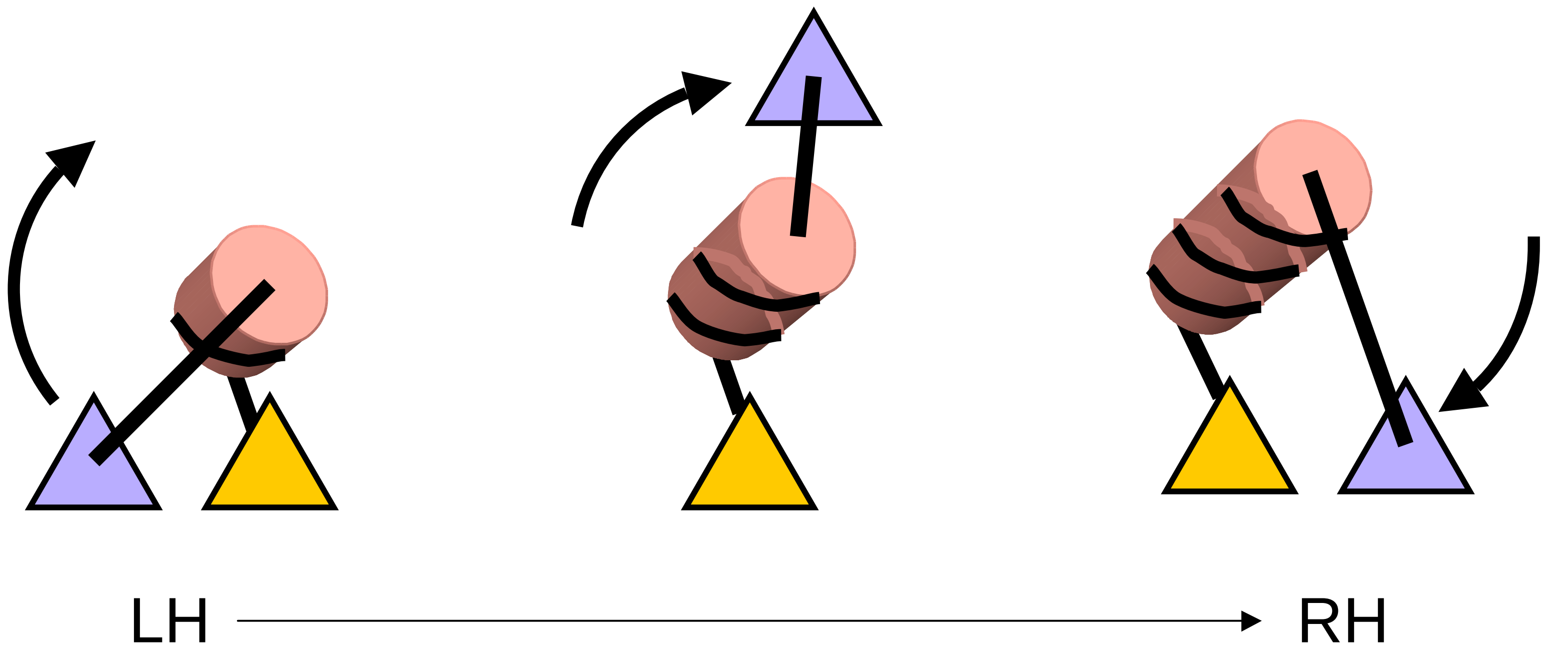
Look at the resulting handedness.



Demonstrative simulations



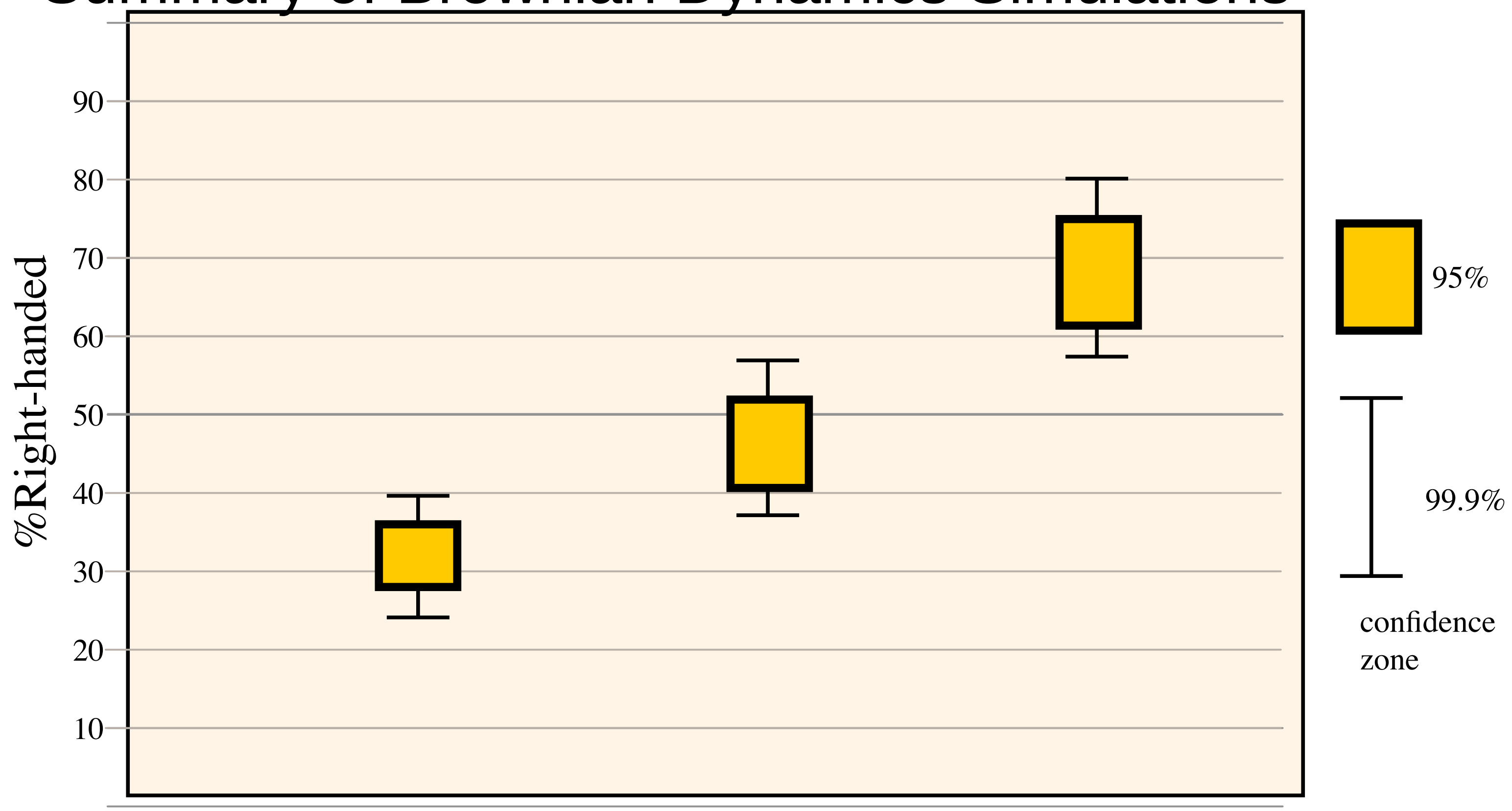
left-handed βαβ turns to right-handed



phone cord videos

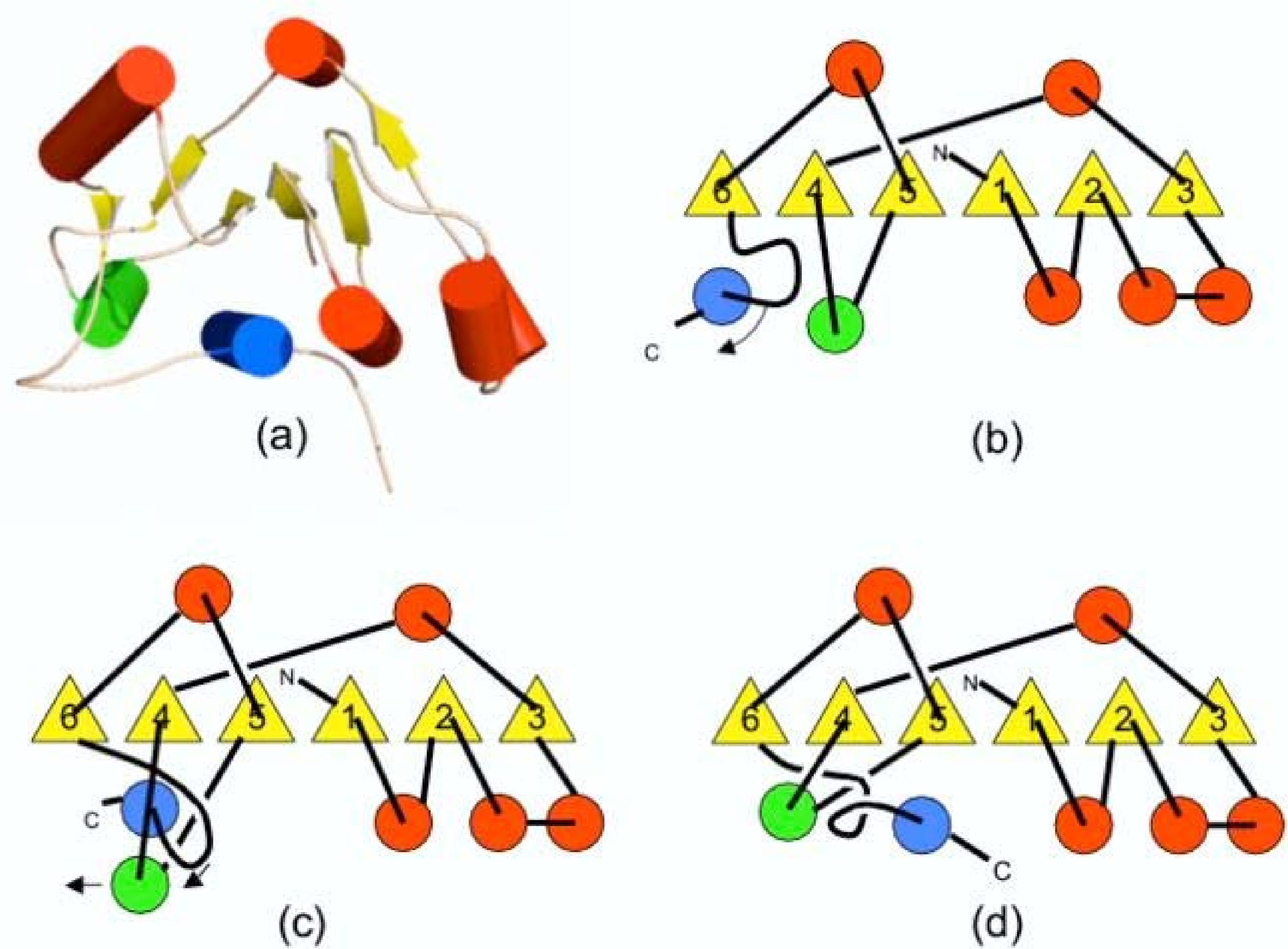
- http://www.youtube.com/watch?v=6hQYjtmU6E0
- http://www.youtube.com/watch?v=hYunWX7Sllg&eurl=http%3A%2F%2Fwww.bioinfo.rpi.edu%2Fbystrc%2Fphonecord%2F&feature=player_embedded

Summary of Brownian Dynamics Simulations



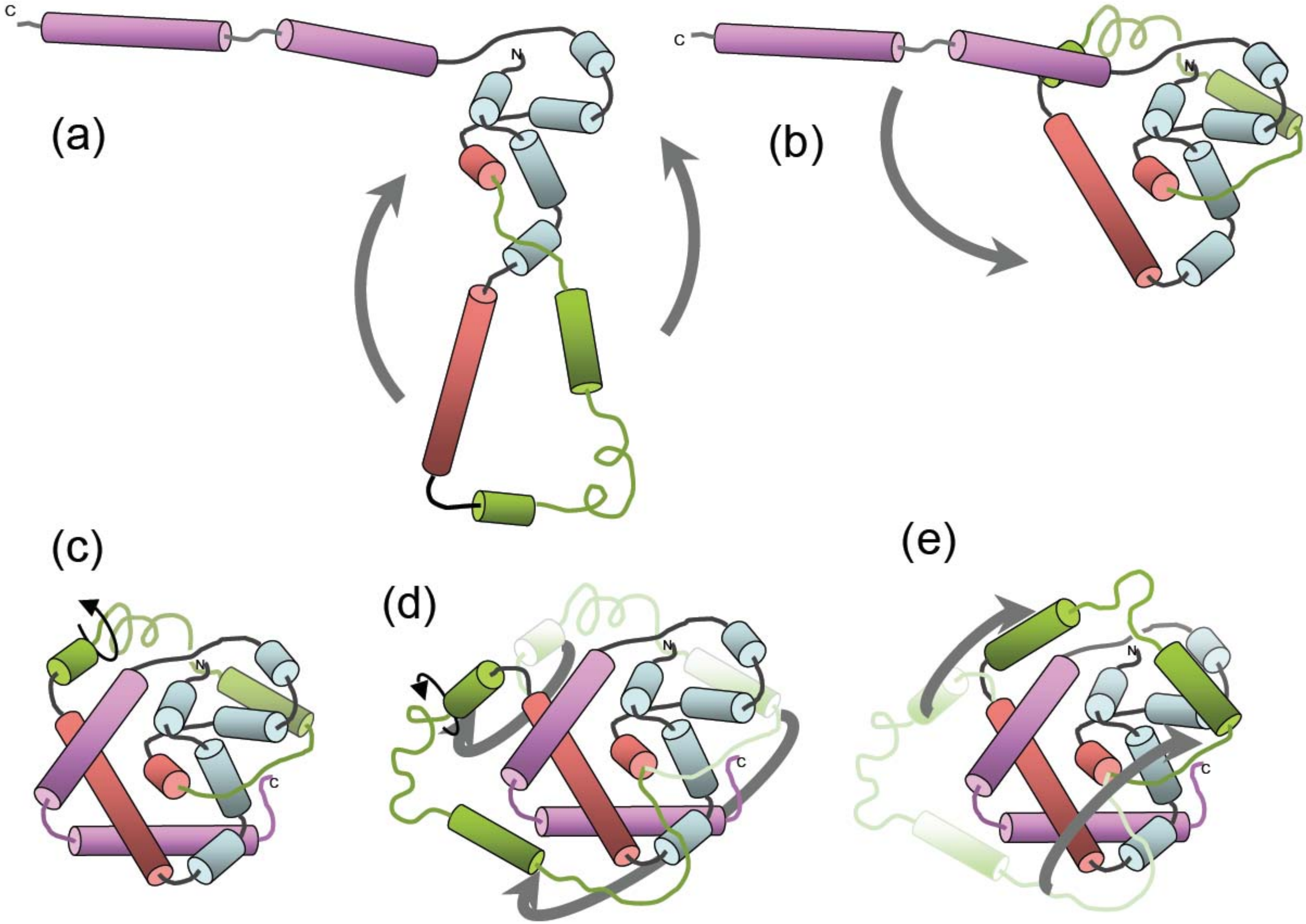
ΔΨ	**0% South**	**50% South**	**100% South**
Trials	2738	1164	501
Collapsed	2540	1066	418
Helical	851	578	286
Ambiguous	456	299	131
Right-handed	124	130	107
Left-handed	271	149	48

1mxi, a knotted protein: does the C-terminal helix screw itself through a loop?



(a) (b) (c) (d)

1yva, another knotted protein. Can a loop roll over the surface?



Maybe we will do this...

- Fold a cyclized $\beta\alpha\beta$ peptide
- *Fold a $\beta\alpha\beta$ in the microscope*
- Design a knot

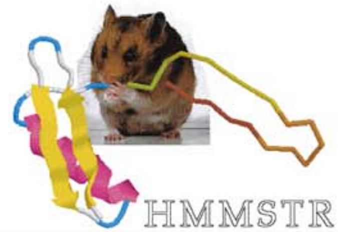
Reference

- Cole BJ & Bystroff C. (2009) Alpha helical crossovers favor right-handed supersecondary structures by a kinetic trapping mechanism. The phone cord effect in protein folding. Protein Science 18(8) 1602 - 1608

- Supplementary data:
- http://www.bioinfo.rpi.edu/bystrc/phonecord/

Bystroff Lab

www.bioinfo.rpi.edu/bystrc/



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HMMSUM: **Yao-ming Huang**

CALF: **Patrick Buck**

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ƒ Wilfredo Colón (RPI-Chemistry)
* Jon Dordick (RPI-Chem Eng.)

Think Globally,
Act Locally.