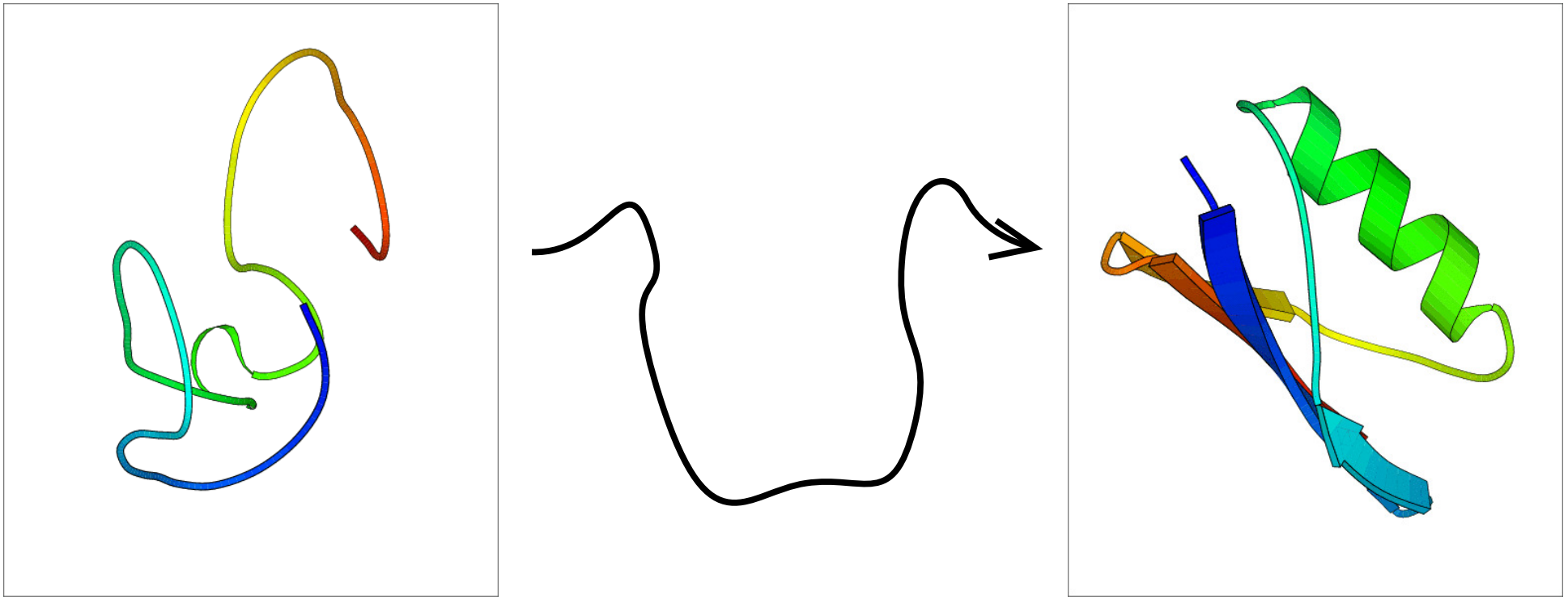
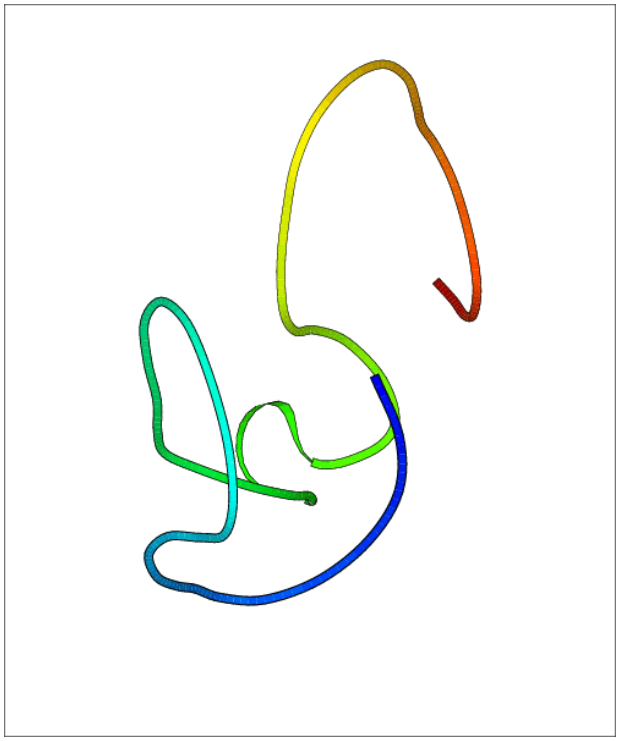
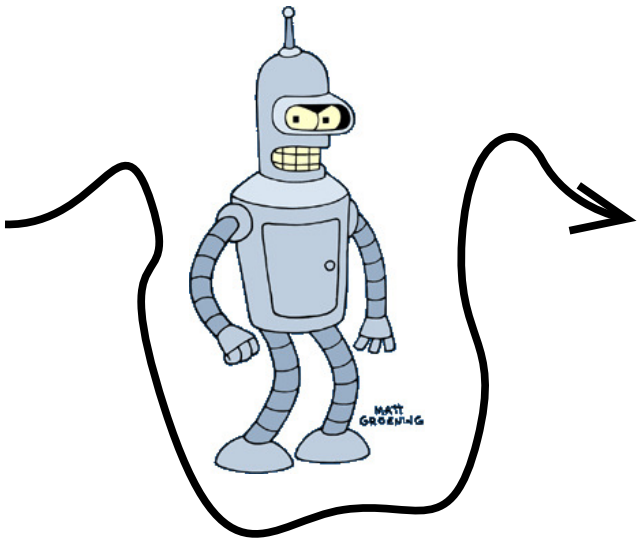
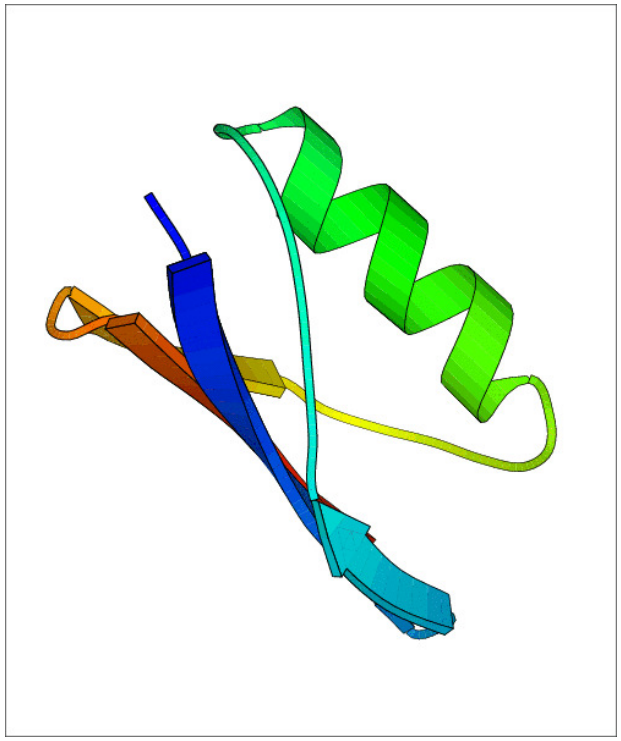
Predicting Protein Folding Paths



Protein Folding by Robotics





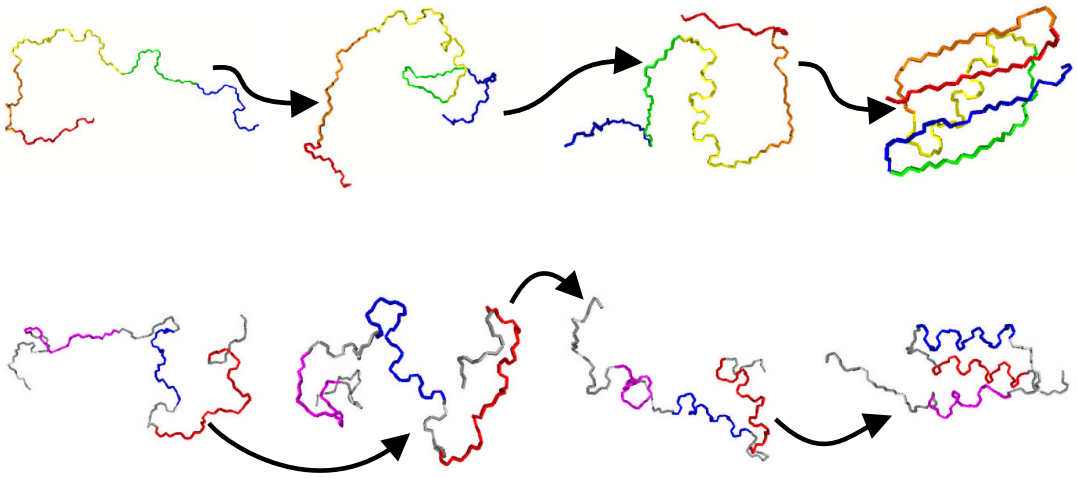


Probabilistic Roadmap Planning (PRM):

- Thomas, Song, Amato. *Protein folding by motion planning*. Phys. Biol., 2005

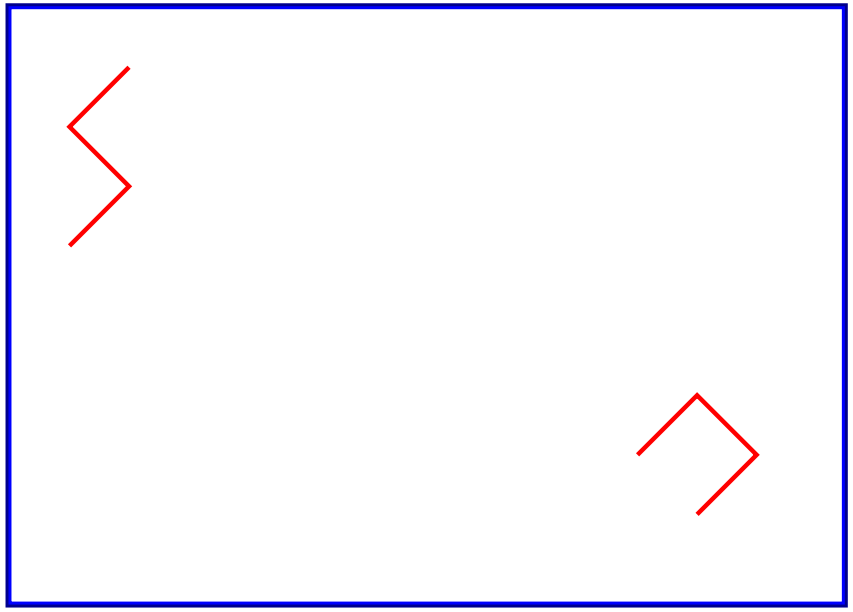
Aims

- Find good quality folding paths (into given native structure)
  - no structure prediction!
- Predict formation orders (of secondary structure)



Motion planning

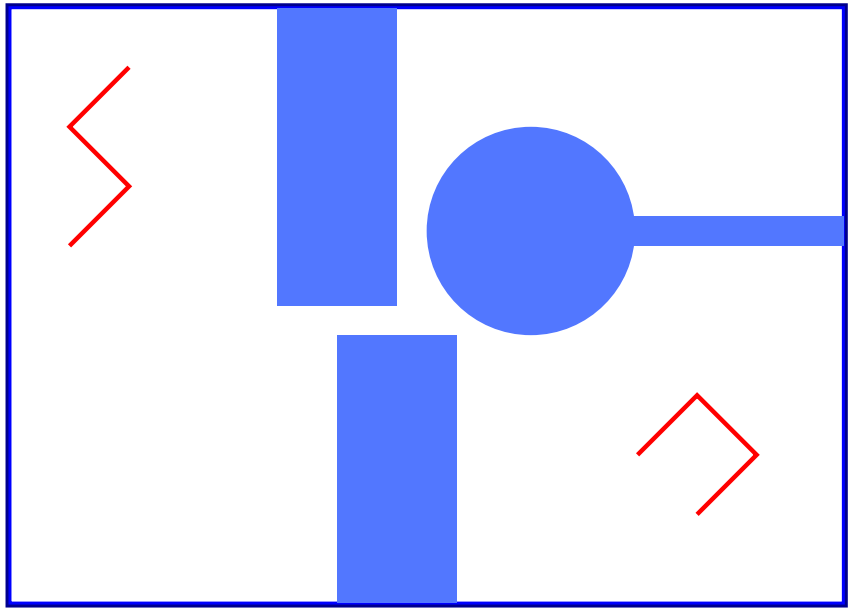
- Motion planning



- Probabilistic roadmap planing
  - Sampling of configuration space Q
  - Connect nearest configurations by (simple) *local planner*
  - Apply graph algorithms to "roadmap": Find shortest path

Motion planning

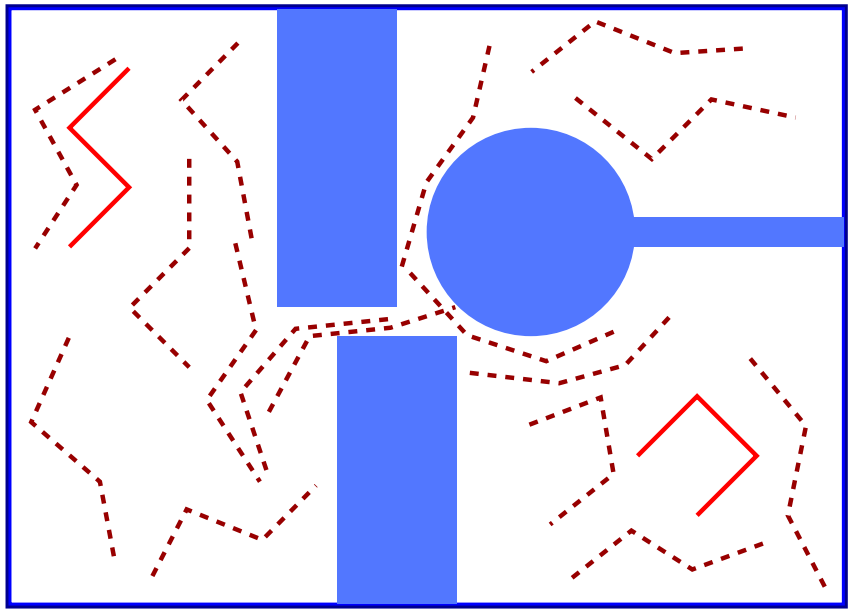
- Motion planning



- Probabilistic roadmap planing
  - Sampling of configuration space Q
  - Connect nearest configurations by (simple) *local planner*
  - Apply graph algorithms to "roadmap": Find shortest path

Motion planning

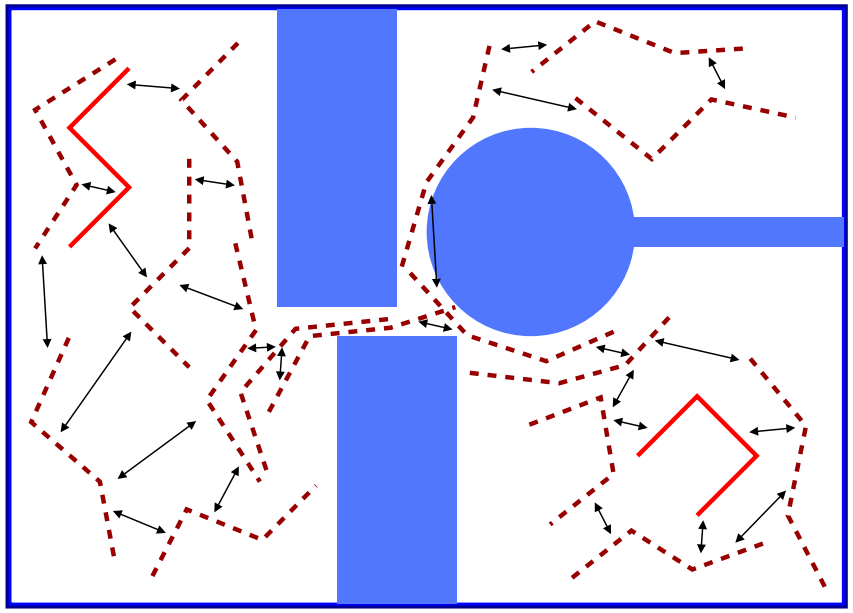
- Motion planning



- Probabilistic roadmap planing
  - Sampling of configuration space Q
  - Connect nearest configurations by (simple) *local planner*
  - Apply graph algorithms to "roadmap": Find shortest path

Motion planning

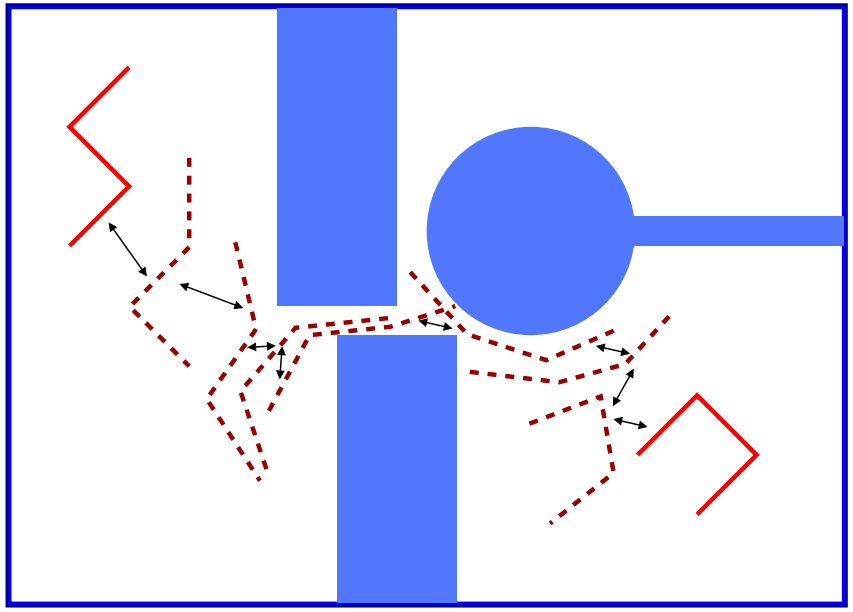
- Motion planning



- Probabilistic roadmap planing
  - Sampling of configuration space Q
  - Connect nearest configurations by (simple) *local planner*
  - Apply graph algorithms to "roadmap": Find shortest path

Motion planning

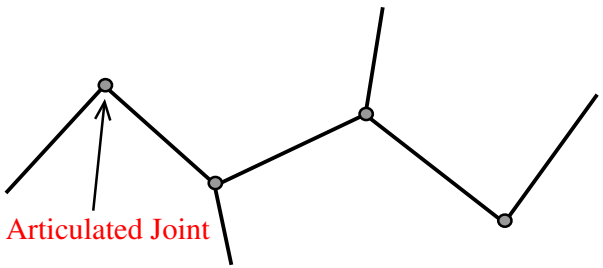
- Motion planning



- Probabilistic roadmap planing
  - Sampling of configuration space Q
  - Connect nearest configurations by (simple) *local planner*
  - Apply graph algorithms to "roadmap": Find shortest path

More on PRM for motion planning

- tree-like robots (*articulated robots*)



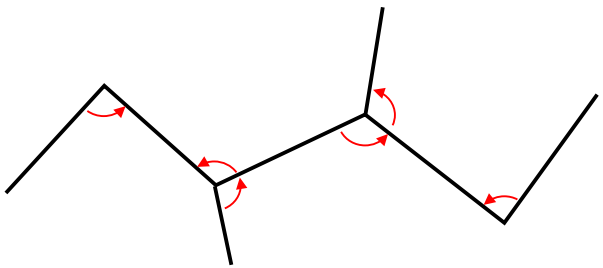
- configuration = vector of angles
- configuration space

$$Q = \{q \mid q \in S^n\}$$

  - S — set of angles
  - n — number of angles = degrees of freedom (dof)

More on PRM for motion planning

- tree-like robots (*articulated robots*)



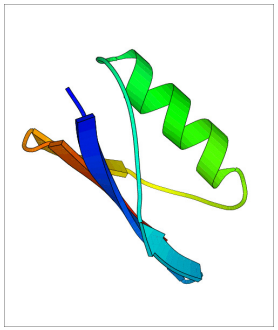
- configuration = vector of angles
- configuration space

$$Q = \{q \mid q \in S^n\}$$

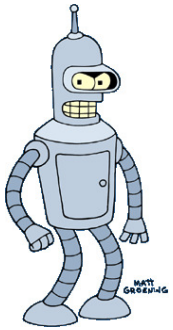
  - S — set of angles
  - n — number of angles = degrees of freedom (dof)

Proteins are Robots (aren't they?)

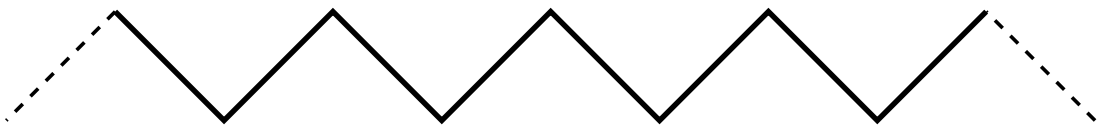
- Obvious similarity ;-)



==?



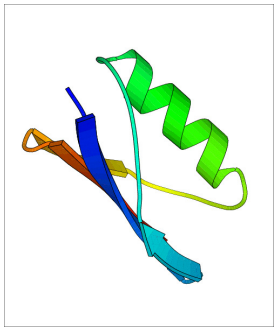
- Our model



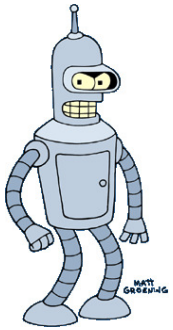
  - Protein == vector of phi and psi angles (treelike robot with 2n dof)
  - possible models range from only backbone up to full atom

Proteins are Robots (aren't they?)

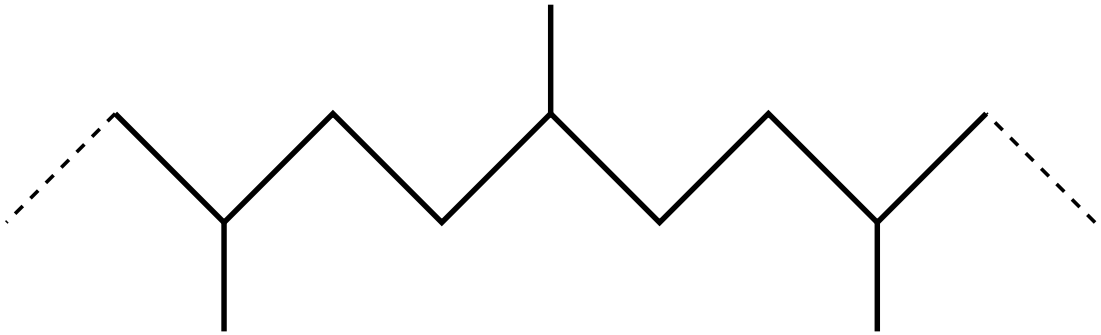
- Obvious similarity ;-)



==?



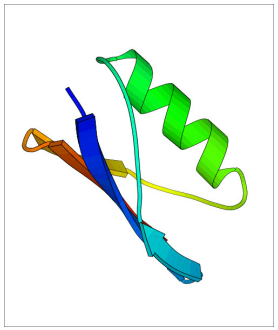
- Our model



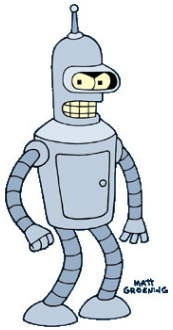
  - Protein == vector of phi and psi angles (treelike robot with 2n dof)
  - possible models range from only backbone up to full atom

Proteins are Robots (aren't they?)

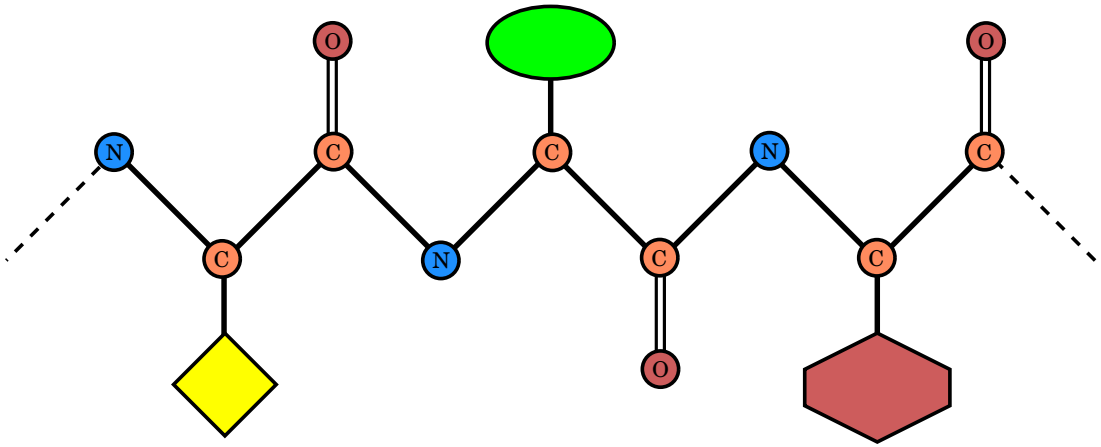
- Obvious similarity ;-)



==?



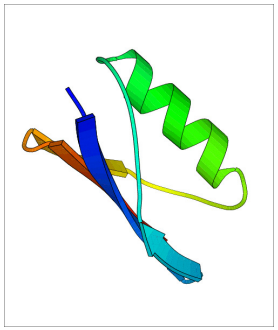
- Our model



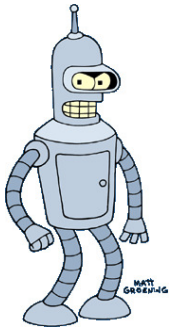
  - Protein == vector of phi and psi angles (treelike robot with 2n dof)
  - possible models range from only backbone up to full atom

Proteins are Robots (aren't they?)

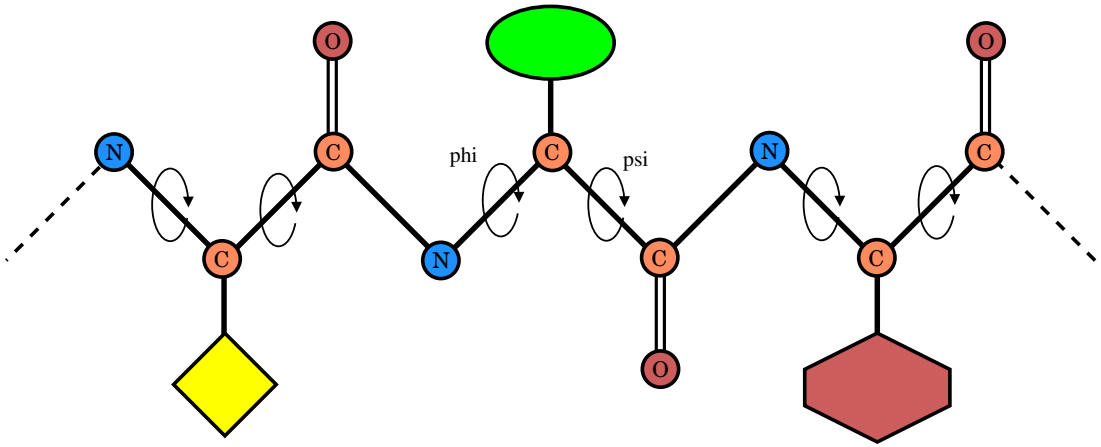
- Obvious similarity ;-)



==?



- Our model



  - Protein == vector of phi and psi angles (treelike robot with 2n dof)
  - possible models range from only backbone up to full atom

Differences to usual PRM

- no external obstacles, but
  - self-avoidingness
  - torsion angles
- quality of paths
  - low energy intermediate states
  - kinetically prefered paths
  - highly probable paths

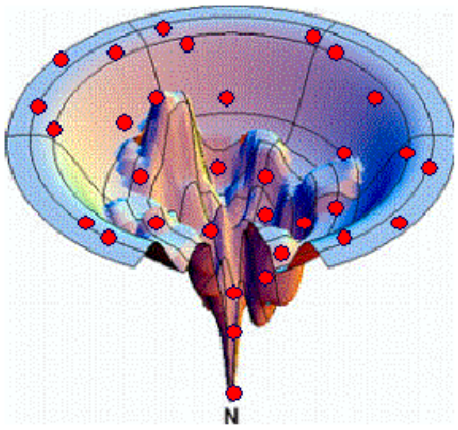
Energy Function

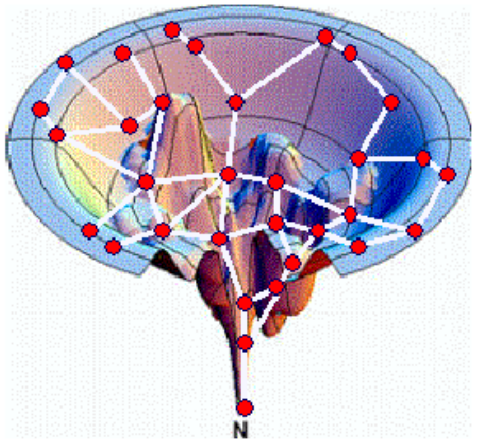
- method can use any potential
- Our coarse potential
  [Levitt. J.Mol.Biol., 1983.]
  - each sidechain by only one "atom" (zero dof)

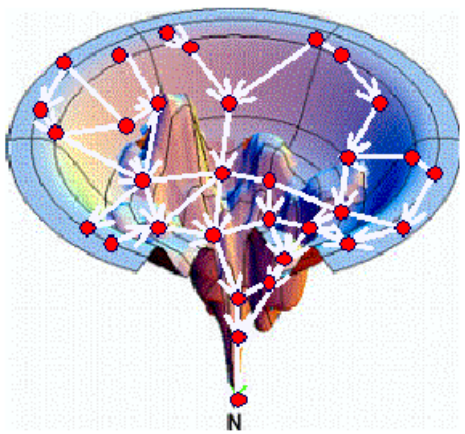
$$U_{tot} = \sum_{\text{restraints}} K_d\{[(d_i - d_0)^2 + d_c^2]^{\frac{1}{2}} - d_c\} + E_{hp}$$

  - first term favors known secondary structure through main chain hydrogen bonds and disulphide bonds
  - second term hydrophobic effect
  - Van der Waals interaction modeled by step function
- All-atom potential: EEF1
  [Lazaridis, Karplus. Proteins, 1999.]

PRM method for Proteins

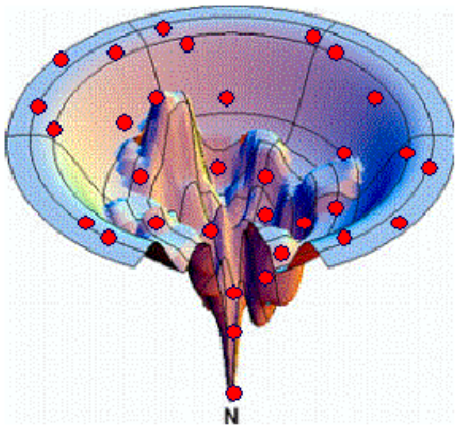


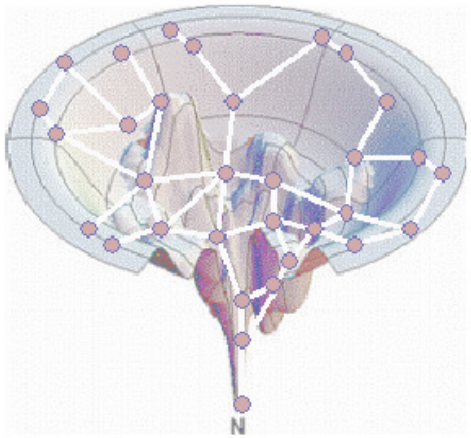


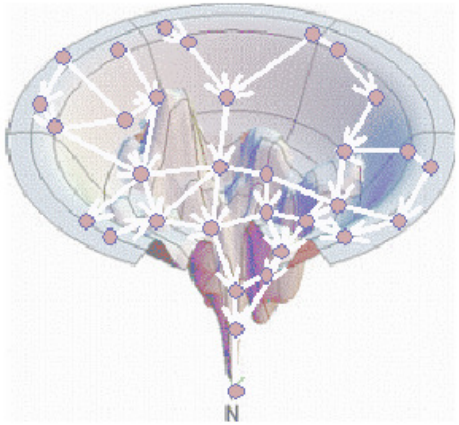


- Sampling
- Connecting
- Extracting

Sampling — Node Generation







Sampling

Connecting

Extracting

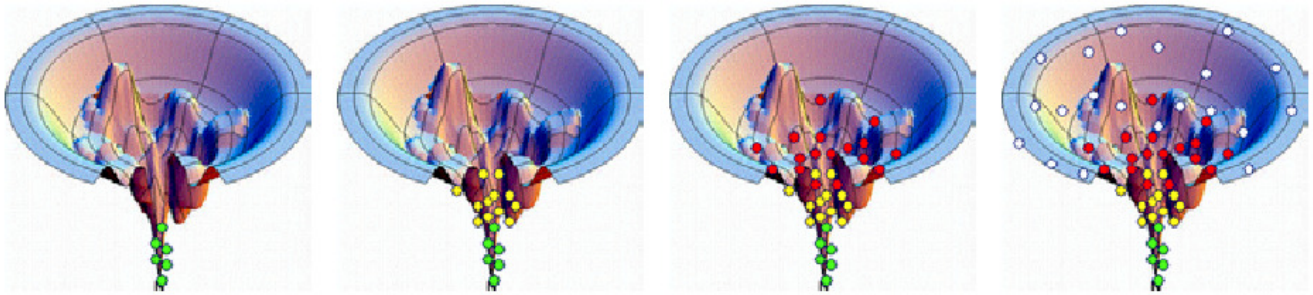
Node Generation

- No uniform sampling
  - configuration space too large
  - $\Rightarrow$ need biased sampling strategy
- Gaussian sampling
  - centered around native conformation
  - with different STDs $5^\circ, 10^\circ, \ldots, 160^\circ$
  - ensure representants for different numbers of native contacts
- Selection by energy

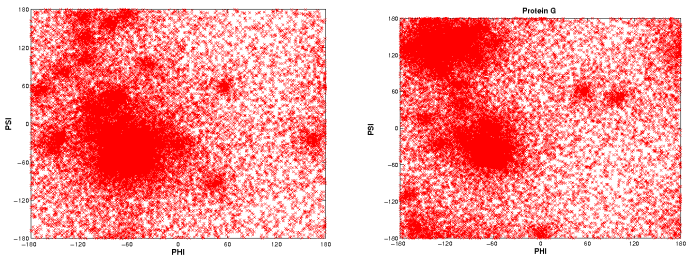
$$P(\text{accept } q) = \begin{cases} 1 & \text{if } E(q) < E_{\text{min}} \\ \frac{E_{\text{max}} - E(q)}{E_{\text{max}} - E_{\text{min}}} & \text{if } E_{\text{min}} \leq E(q) \leq E_{\text{max}} \\ 0 & \text{if } E(q) > E_{\text{max}} \end{cases}$$

More on Node Generation

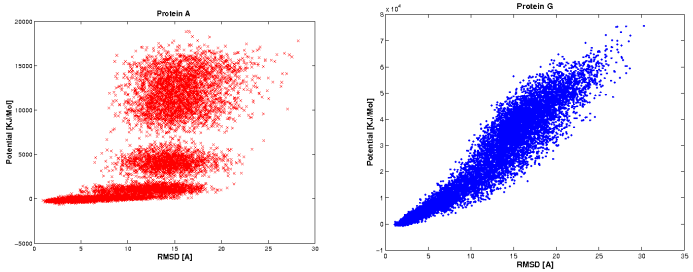
- Visualization of Sampling Strategy



- Distribution

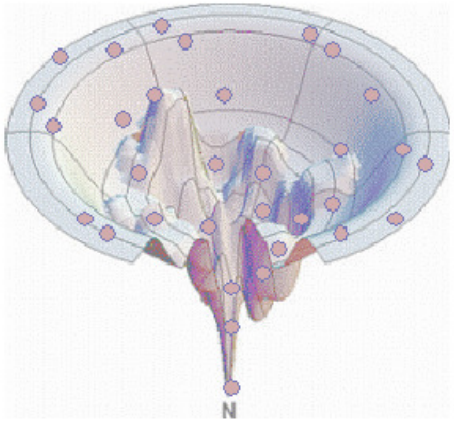


Psi and Phi angles

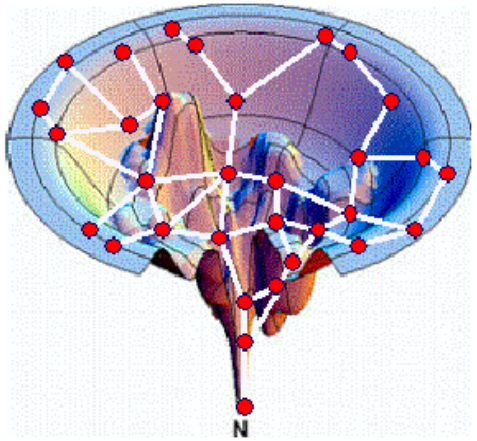


RMSD vs. Energy

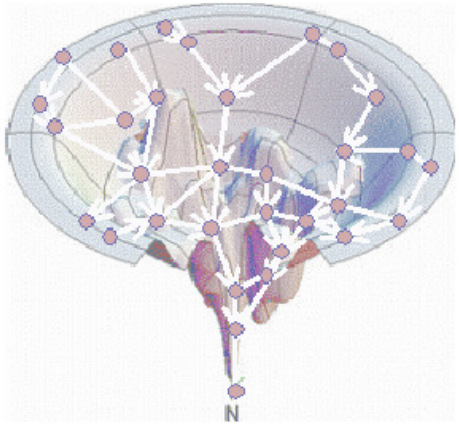
Node Connection



Sampling



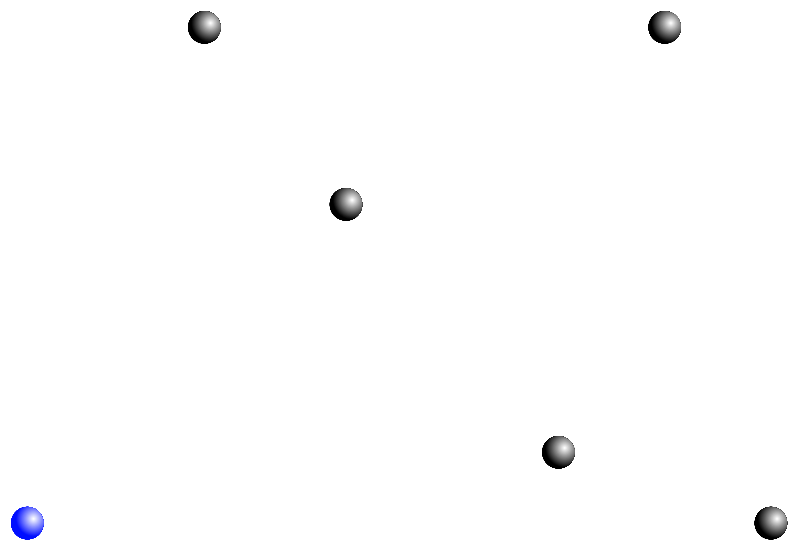
Connecting



Extracting

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



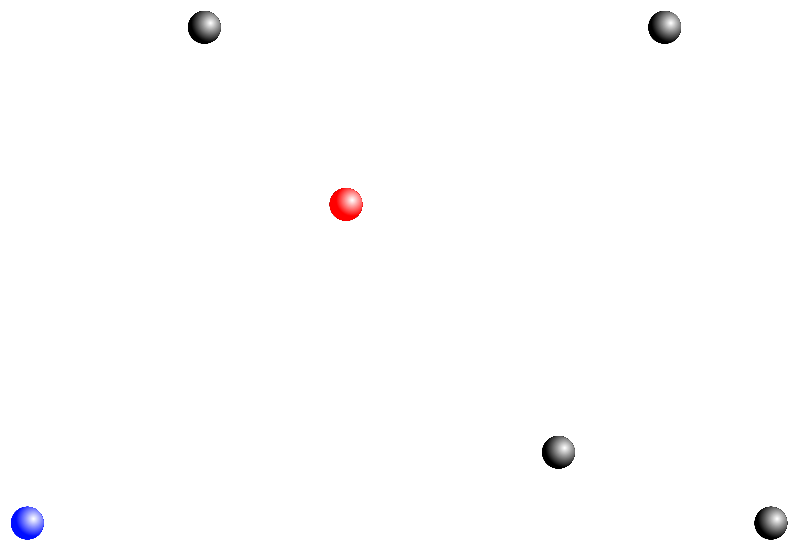
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



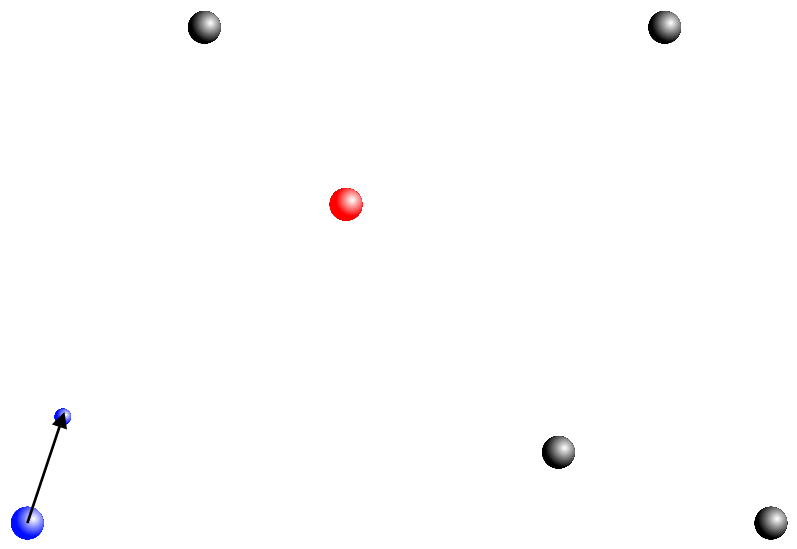
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



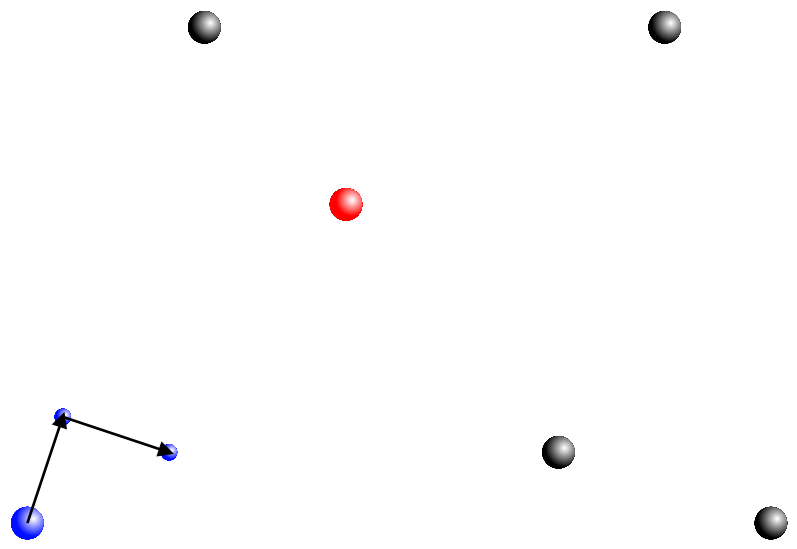
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



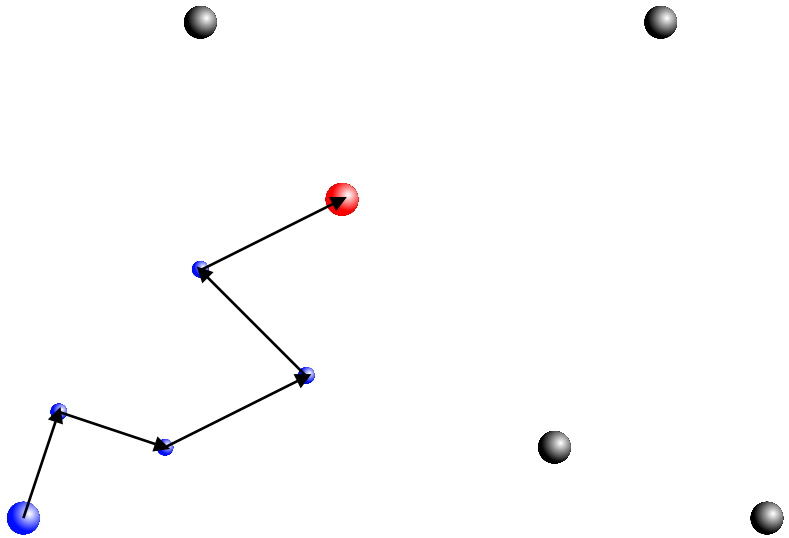
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



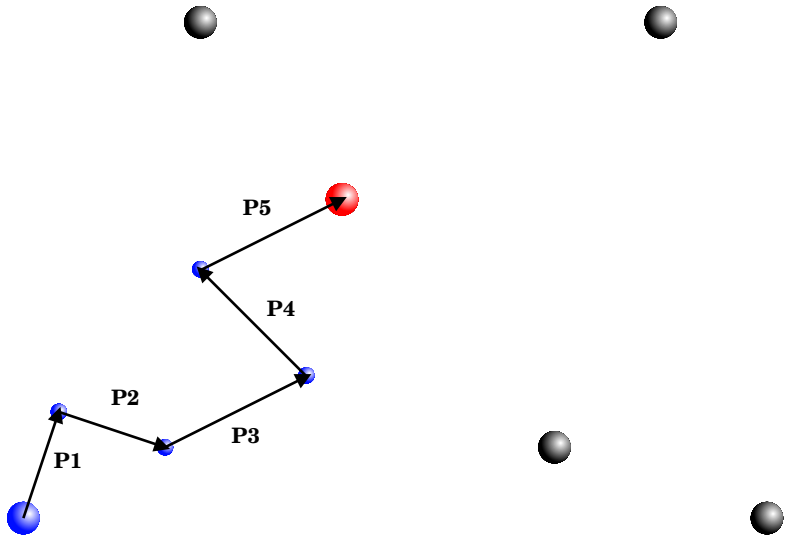
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



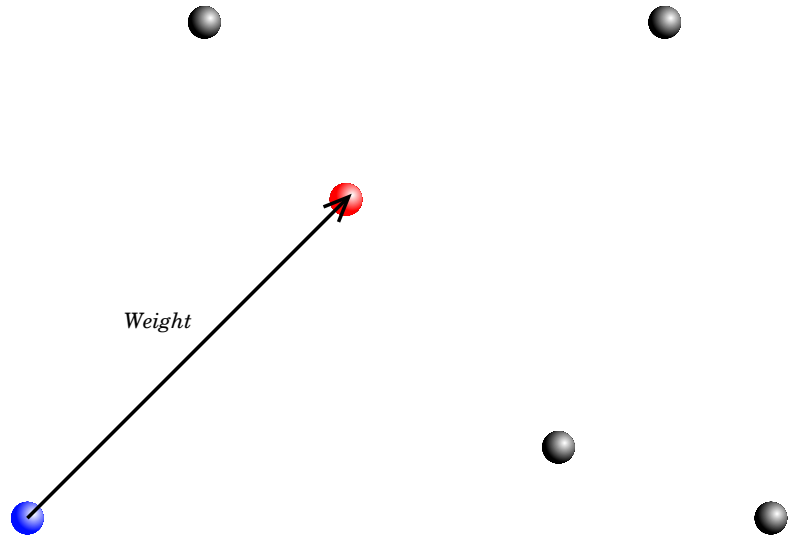
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner



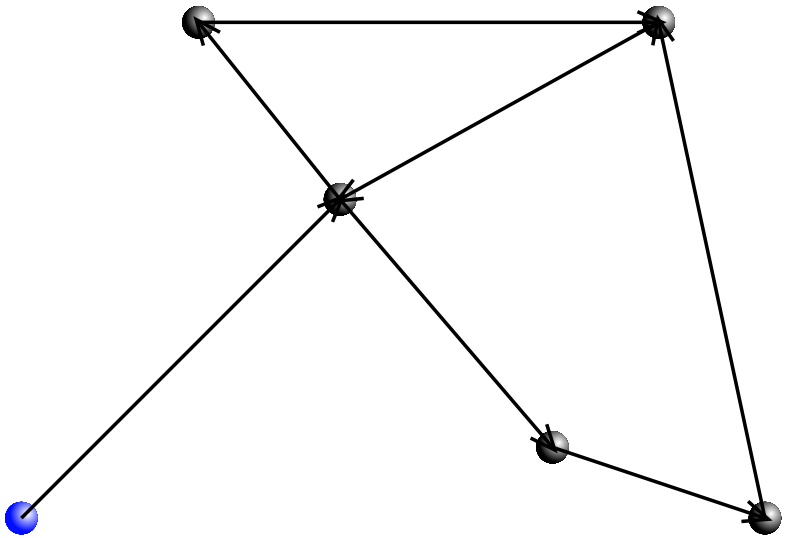
- assign weights to edges

$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

Connecting Nodes by Local Planner

- connect configurations in close distance
- generate N intermediary nodes by local planner

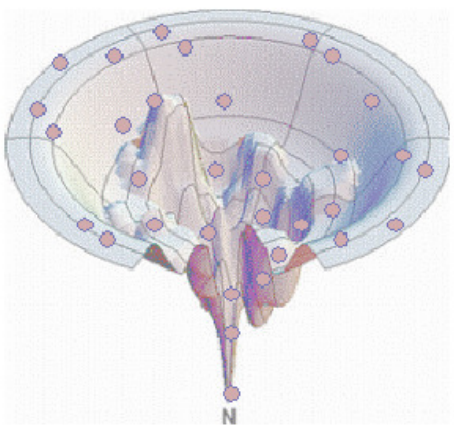


- assign weights to edges

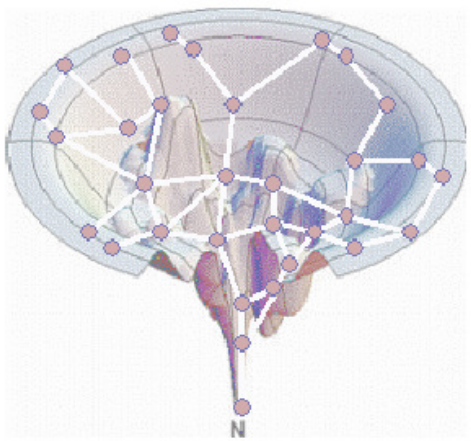
$$P_i = \begin{cases} e^{-\frac{\Delta E}{kT}} & \text{if } \Delta E > 0 \\ 1 & \text{if } \Delta E \leq 0 \end{cases}$$

$$Weight = \sum_{i=0}^{N} -log(P_i)$$

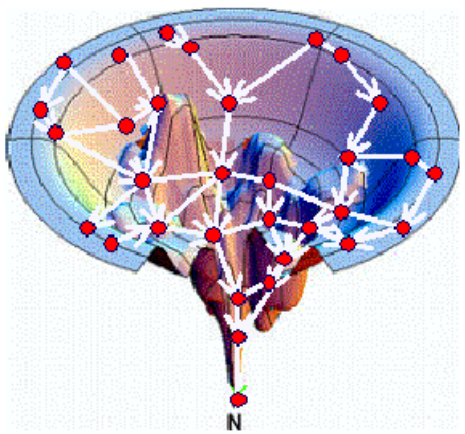
Extracting Paths



Sampling



Connecting

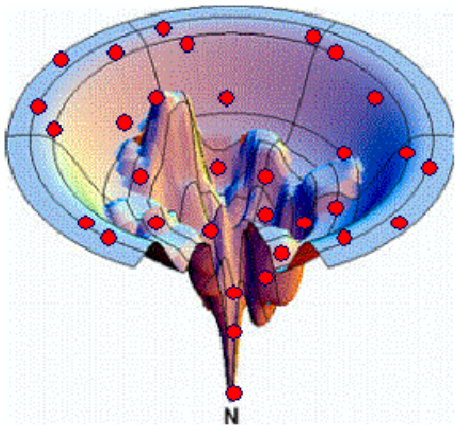


Extracting

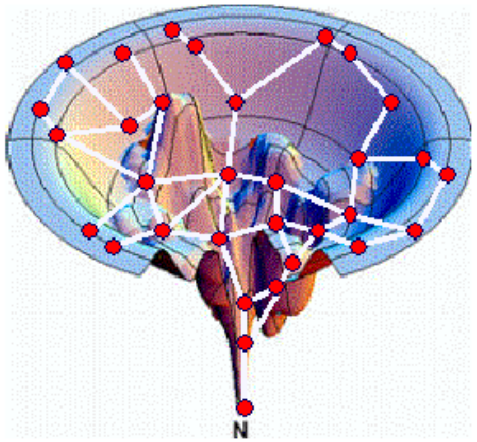
Extracting Paths

- Shortest Path
  - extract one shortest path
  - from some starting conformation, one path at a time
- Single Source Shortest Paths (SSSP)
  - extract shortest paths from all starting conformation
  - compute paths simultaneously
  - generate tree of shortest paths (SSSP tree)

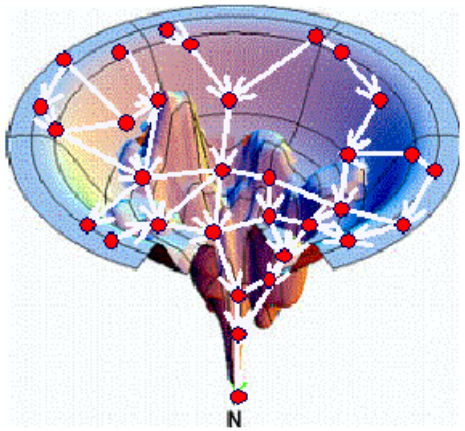
Big Picture



- Sampling



- Connecting



- Extracting

Studied Proteins

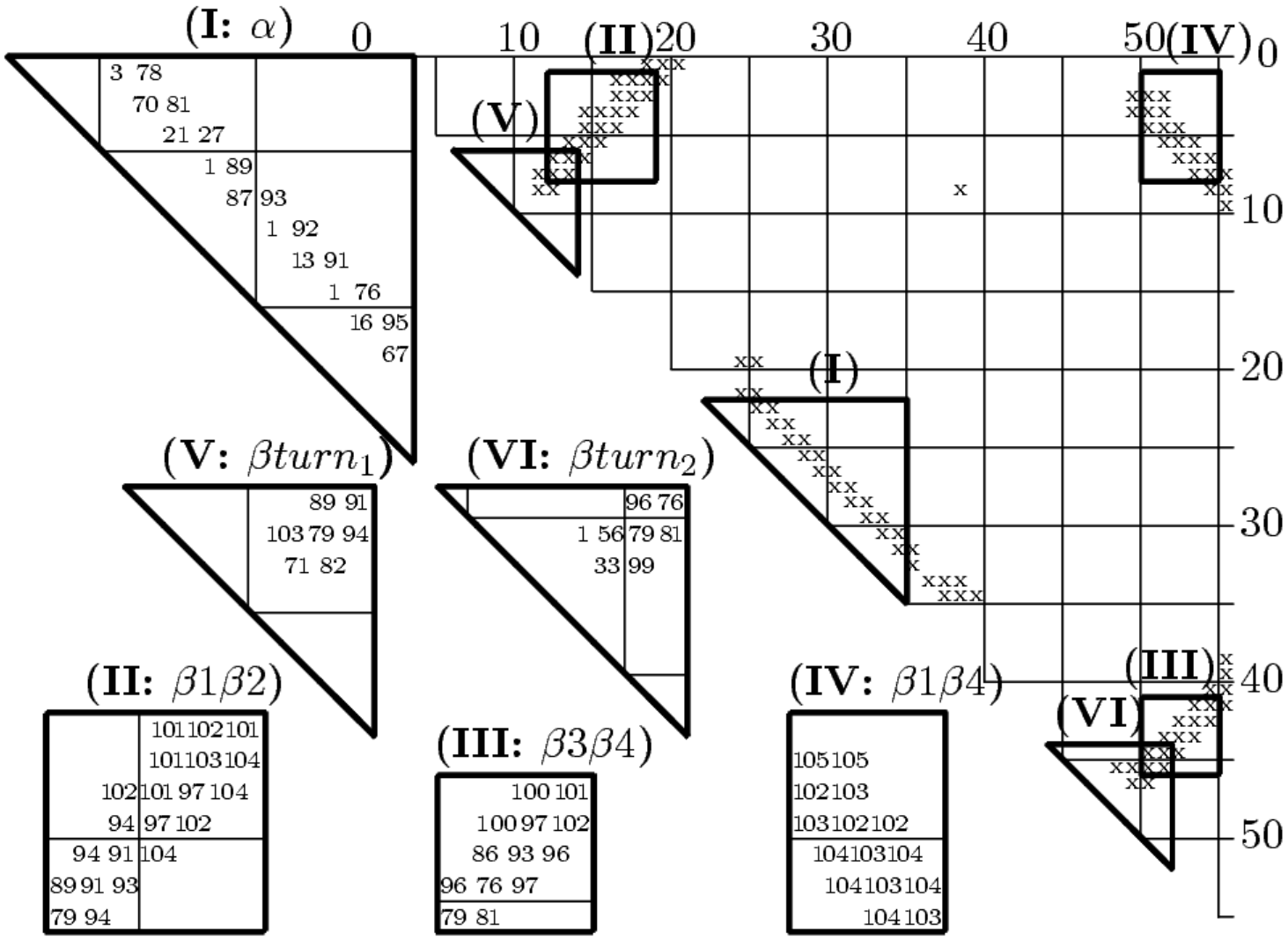
- Overview of studied proteins, roadmap size, and construction times

pdb	Description	Length	SS	# Nodes	Time (h)
1gb1	Protein G domain B1	56	$1\alpha + 4\beta$	8 000	6.400
2crt	Cardiotoxin III	60	5β	8 000	6.430
1bdd	Staphylococcus protein A	60	3α	10 000	10.400
1shg	SH3 domain α-spectrin	62	5β	10 000	8.344
2ptl	Protein L, B1 domain	62	$1\alpha + 4\beta$	4 000	3.104
1coa	CI2	64	$1\alpha + 4\beta$	10 000	9.984
1srl	SH3 domain src	64	5β	8 000	5.990
1nyf	SH3 domain fyn	67	5β	10 000	8.418
2ait	Tendamistat	74	7β	10 000	13.327
1ubq	Ubiquitin	76	$1\alpha + 5\beta$	8 000	10.381
1pks	SH3 domain PI3 kinase	79	$1\alpha + 5\beta$	10 000	14.446
1pba	Procarboxypeptidase A2	81	$3\alpha + 3\beta$	8 000	10.845

Formation orders

- formation order of secondary structure for verifying method
- formation orders can be determined experimentally [Li, Woodward. Protein Science, 1999.]
  - Pulse labeling
  - Out-exchange
- prediction of formation orders
  - single paths
  - averaging over multiple paths (SSSP-tree)

Timed Contact Maps



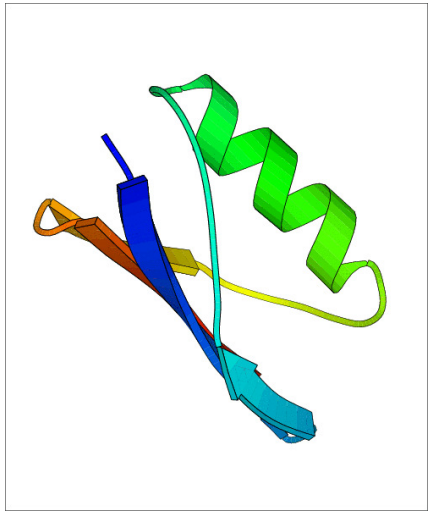
Formation Order

pdb	Out exchange	Pulse labeling	Our SS formation order	Comp.
1gb1	[α, $\beta1$, $\beta3$, $\beta4$], $\beta2$	[α, $\beta4$], [$\beta1$, $\beta2$, $\beta3$]	α, $\beta3$–$\beta4$, $\beta1$–$\beta2$, $\beta1$–$\beta4$	Agreed
2crt	[$\beta3$, $\beta4$, $\beta5$], [$\beta1$, $\beta2$]	$\beta5$, $\beta3$, $\beta4$, [$\beta1$, $\beta2$]	$\beta1$–$\beta2$, $\beta3$–$\beta4$, $\beta3$–$\beta5$	Not sure
1bdd	[$\alpha2$, $\alpha3$], $\alpha1$	[$\alpha1$, $\alpha2$, $\alpha3$]	[$\alpha2$, $\alpha3$], $\alpha1$, $\alpha2$–$\alpha3$, $\alpha1$–$\alpha3$	Agreed
1shg	N/A	N/A	$\beta3$–$\beta4$, $\beta2$–$\beta3$, $\beta1$–$\beta5$, $\beta1$–$\beta2$	N/A
2ptl	[α, $\beta1$, $\beta2$, $\beta4$], $\beta3$	[α, $\beta1$], [$\beta2$, $\beta3$, $\beta4$]	α, $\beta1$–$\beta2$, $\beta3$–$\beta4$, $\beta1$–$\beta4$	Agreed
1coa	[α, $\beta2$, $\beta3$], [$\beta1$, $\beta4$]	N/A	α, $\beta3$–$\beta4$, $\beta2$–$\beta3$, $\beta1$–$\beta4$	Agreed
1srl	N/A	N/A	$\beta3$–$\beta4$, $\beta2$–$\beta3$, $\beta1$–$\beta5$, $\beta1$–$\beta2$	N/A
1nyf	N/A	N/A	$\beta3$–$\beta4$, $\beta2$–$\beta3$, $\beta1$–$\beta2$, $\beta1$–$\beta5$	N/A
2ait	[$\beta1$, $\beta2$], [$\beta3$, $\beta4$, $\beta5$, $\beta6$, $\beta7$]	N/A	$\beta1$–$\beta2$, $\beta3$–$\beta4$, [$\beta2$–$\beta5$, $\beta3$–$\beta6$], $\beta3$–$\beta5$	Agreed
1ubq	[α, $\beta1$, $\beta2$], [$\beta3$, $\beta5$], $\beta4$	N/A	α, $\beta3$–$\beta4$, $\beta1$–$\beta2$, $\beta3$–$\beta5$, $\beta1$–$\beta5$	Agreed
1pks	N/A	N/A	$\beta3$–$\beta4$, $\beta1$–$\beta5$, [$\beta1$–$\beta2$, $\beta2$–$\beta3$]	N/A
1pba	N/A	N/A	[$\alpha1$, $\alpha3$], [$\beta1$–$\beta2$, $\beta1$–$\beta3$]	N/A

- no (reported) contradictions between prediction and validation
- different kind of information from experiment and prediction

The Proteins G and L

- Studied in more detail
- good test case
- structurally similar: $1\alpha + 4\beta$



- fold differently
  - Protein G: β-turn 2 forms first
  - Protein L: β-turn 1 forms first

Comparison of Analysis Techniques
β-Turn Formation

Name	Contacts considered	Energy function	Secondary structure formation order	Analyze first x% contacts				
				20	40	60	80	100
Protein G	All	Our	α, turn 2, turn 1	53	52	52	50	50
			turn 2, α, turn 1	15	9	17	22	22
			α, turn 1, turn 2	25	33	26	23	24
		All-atom	α, turn 2, turn 1	36	37	55	55	57
			turn 2, α, turn 1	3	0	0	0	0
			α, turn 1, turn 2	50	63	45	45	43
			turn 1, α, turn 2	12	0	0	0	0
	Hydrophobic	Our	α, turn 2, turn 1	96	96	85	96	87
			α, turn 1, turn 2	4	4	12	2	11
		All-atom	α, turn 2, turn 1	76	78	78	92	69
			α, turn 1, turn 2	24	22	22	8	31
Protein L	All	Our	α, turn 1, turn 2	24	30	37	38	41
			turn 1, α, turn 2	3	4	4	4	6
			α, turn 2, turn 1	73	63	60	48	39
		All-atom	α, turn 1, turn 2	25	25	48	43	41
			α, turn 2, turn 1	75	75	52	57	59
	Hydrophobic	Our	α, turn 1, turn 2	72	68	72	70	69
			turn 1, α, turn 2	5	9	5	7	15
			α, turn 2, turn 1	23	22	22	23	15
		All-atom	α, turn 1, turn 2	66	76	78	95	97
			turn 1, α, turn 2	3	0	0	0	0
			α, turn 2, turn 1	31	24	22	5	3

Conclusion

- PRM can be applied to "realistic" protein models
- Introduced method makes verifiable prediction
- Coarse potential is sufficient
- Predictions in good accordance to experimental data