Topological Methods for Exploring Low-density States on Biomolecular Folding Pathways

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Acknowledgements

Collaborators:

- Biology: Xuhui Huang, Greg Bowman, Vijay Pande
- Computer Science: Jian Sun, Leo Guibas
- Mathematics: Michael Lesnick, Gurjeet Singh, Gunnar Carlsson

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A motivating example: RNA Tetraloop

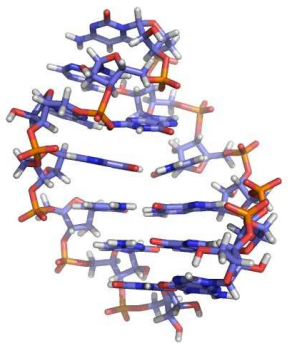


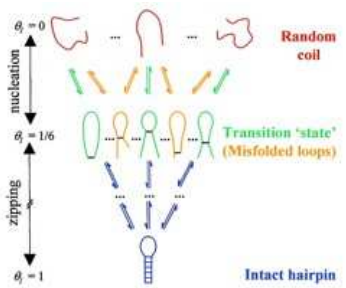
Figure: RNA GCAA-Tetraloop

Biological relevance:

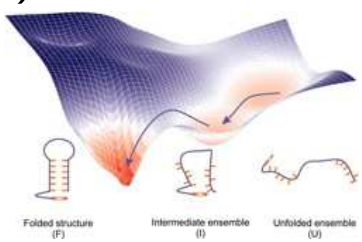
- serve as nucleation site for RNA folding
- form sequence specific tertiary interactions
- protein recognition sites
- certain Tetraloops can pause RNA transcription

Note: simple, but, biological debates over intermediate states on folding pathways

Debates: Two-state vs. Multi-state Models



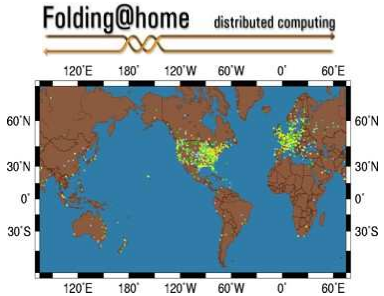
(a) 2-state model

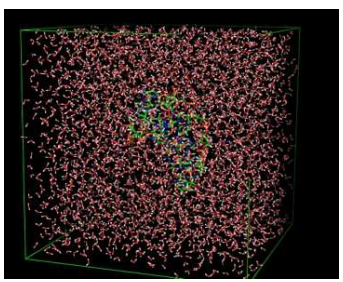


(b) multi-state model

- 2-state: transition state with any one stem base pair, from thermodynamic experiments [*Ansari A, et al. PNAS, 2001, 98: 7771-7776*]
- multi-state: there is a stable intermediate state, which contains collapsed structures, from kinetic measurements [*Ma H, et al. PNAS, 2007, 104:712-6*]
- experiments: no structural information
- computer simulations at full-atom resolution:
  - exisitence of intermediate states
  - if yes, what's the structure?

SREMD Simulations





Simulation Box.

[*Bowman, Huang, Y., Sun, ... Vijay. JACS, 2008, to appear*]

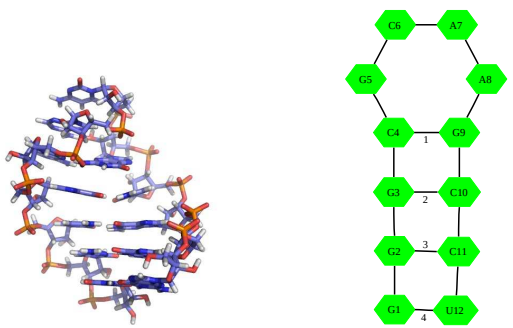
- 2800 SREMD (Serial Replica Exchange Molecular Dynamics) simulations with RNA hairpin (5'-GGGCGCAAGCCU-3')
- 389 RNA atoms, ∼4000 water and 11 Na^+
- SREMD random walks in temperature space (56 ladders from 285K to 646K) with molecular dynamic trajectories
- 210,000 ns simulations with ∼105,000,000 configurations
- Unfortunately, sampling still not converged!

Challenges for Data Analysis

- Massive data: $\sim 100M$ samples
- High dimensionality: $12K$ Cartesian coordinates
- Looking for a needle in a haystack:
  - intermediates/transition states of interests are of low-density
  - folded/unfolded states are dominant
- Samples are not in equilibrium distribution

Dimensionality reduction: Contact maps

- 12 residues for each conformation
- two nonadjacent residues are in contact if their nearest atoms are within $3\mathring{A}$
- every configuration as a undirected graph, described by 55-bit string



(a) (b)

Figure: (a) NMR structure of the GCAA tetraloop. (b) Contact map for the native state. Bases are numbered from 1 to 12 and native basepair contacts are numbered 1-4.

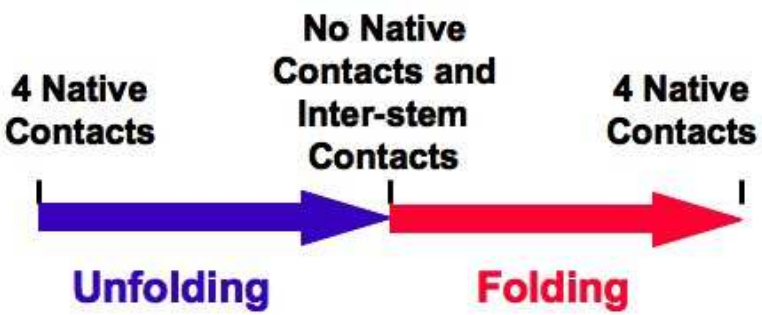
Further discussions on contact maps

- Contact maps faithfully represent the spatial relations between stem base-pairs
- Stem base-pair formation is crucial to characterize the structures of intermediate states
- Other representation like RMSD is too noisy due to the heterogeneity in loop shapes
- Distance metric between contact maps: Hamming distance
- Such a metric is too coarse for nonlinear dimensionality reduction methods (e.g. ISOMAP [*Das, et al. PNAS, 2006, 103:9885-9890*]) to find reaction coordinates

Needle through magnifying glasses: Conditional density functions

Conditioning on the region where intermediate states may host:

- folding/unfolding events



  - 760 unfolding events;
  - 550 folding events;

- biased toward the target states (folded/extended)

Note: applicable to non-equilibrium distributed data.

Our strategy

Problem: How to separate sparse intermediates from dense uninterested structures?

Solution

stratify data into density level sets, and

cluster on each level set

But, can we organize those clusters in a systematic way?

- Yes, Morse theory in mathematics provides an inspiration...

Morse Theory and Reeb graph

- a nice (Morse) function: $h : \mathcal{X} \to \mathbb{R}$, on a smooth manifold $\mathcal{X}$
- topology of $\mathcal{X}$ reconstructed from level sets $h^{-1}(t)$
- topological of $h^{-1}(t)$ only changes at 'critical values'
- Reeb graph: a simplified version, contracting into points the connected components in $h^{-1}(t)$

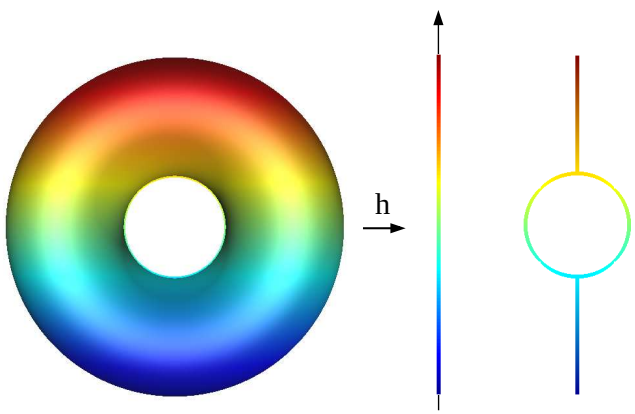
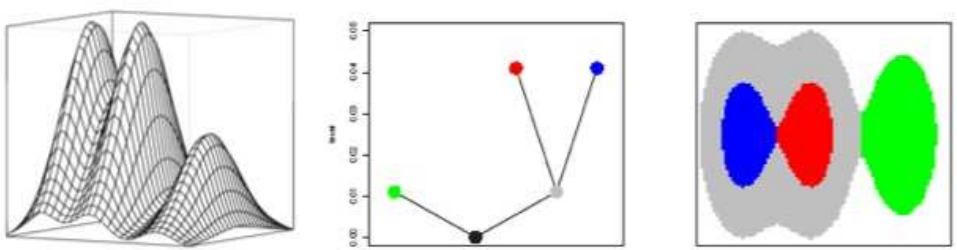


Figure: Construction of Reeb graph; h maps each point on torus to its height.

In applications.

Reeb graph has found various applications in computational geometry, statistics under different names.

- computer science: contour trees, reeb graphs
- statistics: density cluster trees, or Hartigan trees



Mapper: an extension for topological data analysis

[*Singh-Memoli-Carlsson. Eurograph-PBG, 2007*] Given a data set $\mathcal{X}$,

- choose a filter map $h : \mathcal{X} \to T$, where T is a topological space such as $\mathbb{R}$, S^1, $\mathbb{R}^d$, etc.
- choose a cover $T \subseteq \cup_\alpha U_\alpha$
- cluster/partite level sets $h^{-1}(U_\alpha)$ into $V_{\alpha,\beta}$
- graph representation: a node for each $V_{\alpha,\beta}$, an edge between $(V_{\alpha_1,\beta_1}, V_{\alpha_2,\beta_2})$ iff $U_{\alpha_1} \cap U_{\alpha_2} \neq \emptyset$ and $V_{\alpha_1,\beta_1} \cap V_{\alpha_2,\beta_2} \neq \emptyset$.
- extendable to simplicial complex representation.

Note: it extends Morse theory from $\mathbb{R}$ to general topological space T; may lead to a particular implementation of Nerve theorem through filter map h.

An example with real valued filter

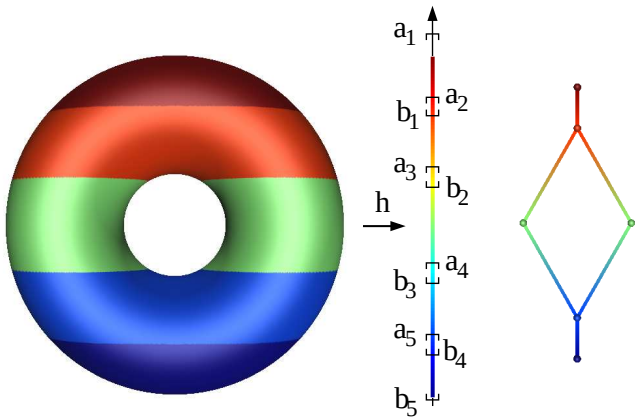


Figure: An illustration of Mapper.

Note:

- degree-one nodes contain local minima/maxima;
- degree-three nodes contain saddle points (critical points);
- degree-two nodes consist of regular points

Mapper with density filters in biomolecular folding

In biomolecular folding

- densest regions (energy basins) may correspond to metastates (e.g. folded, extended)
- intermediate/transition states on pathways connecting them are relatively sparse

Therefore with Mapper

- clustering on density level sets helps separate and identify metastates and intermediate/transition states
- graph representation reflects kinetic connectivity between states

A vanilla version

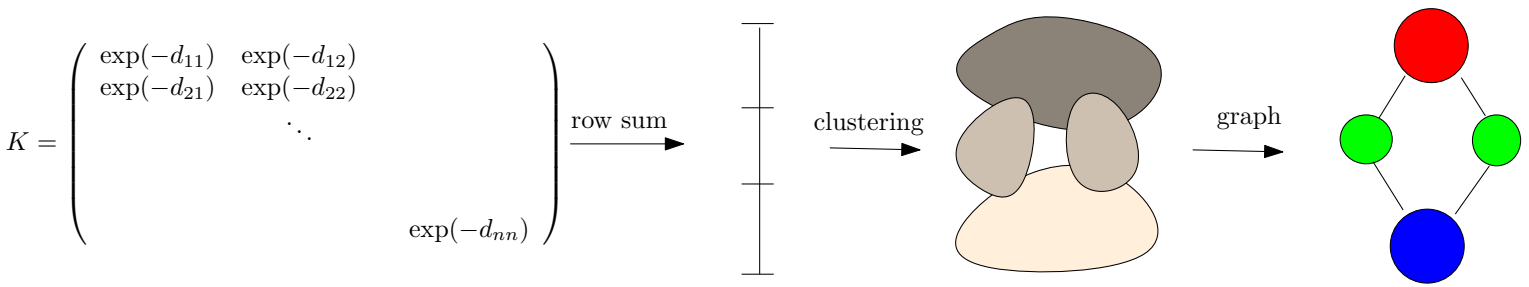


Figure: Mapper Flow Chart

1. Kernel density estimation $h(x) = \sum_i K(x, x_i)$ with Hamming distance for contact maps
2. Rank the data by h and divide the data into n overlapped sets
3. Single-linkage clustering on each level sets
4. Graphical representation

Mapper output for Unfolding Pathways

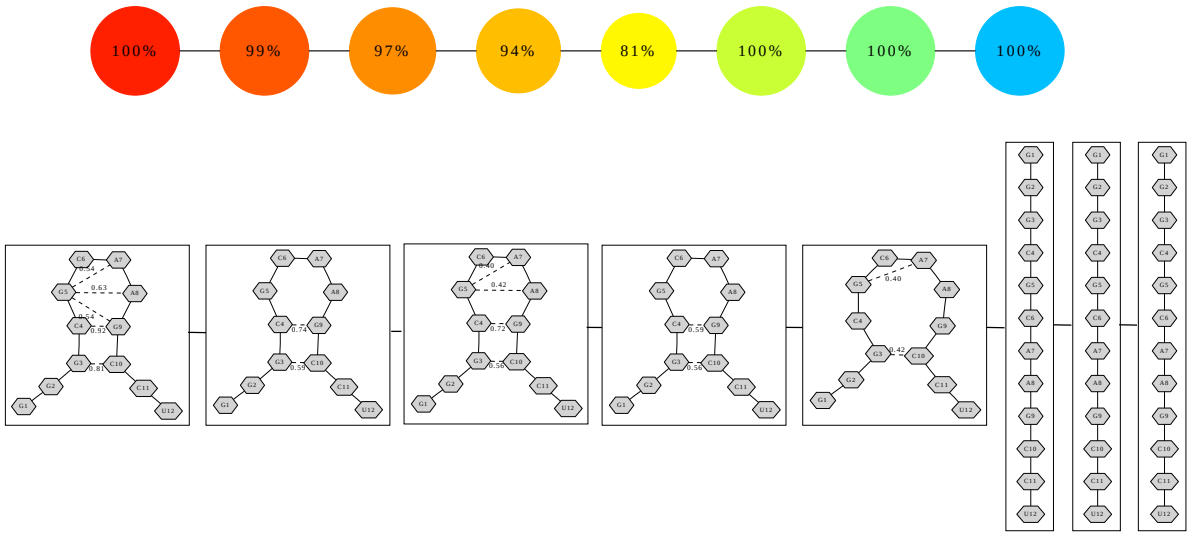


Figure: Unfolding pathway

Mapper output for Refolding Pathways

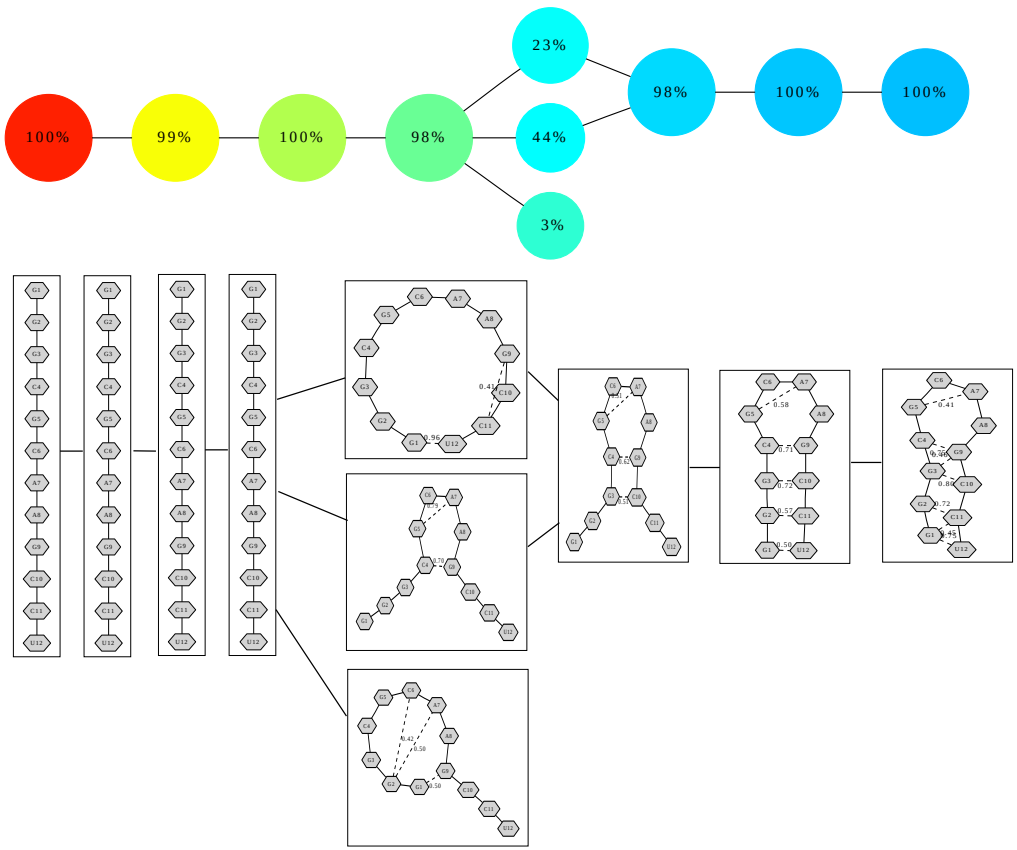
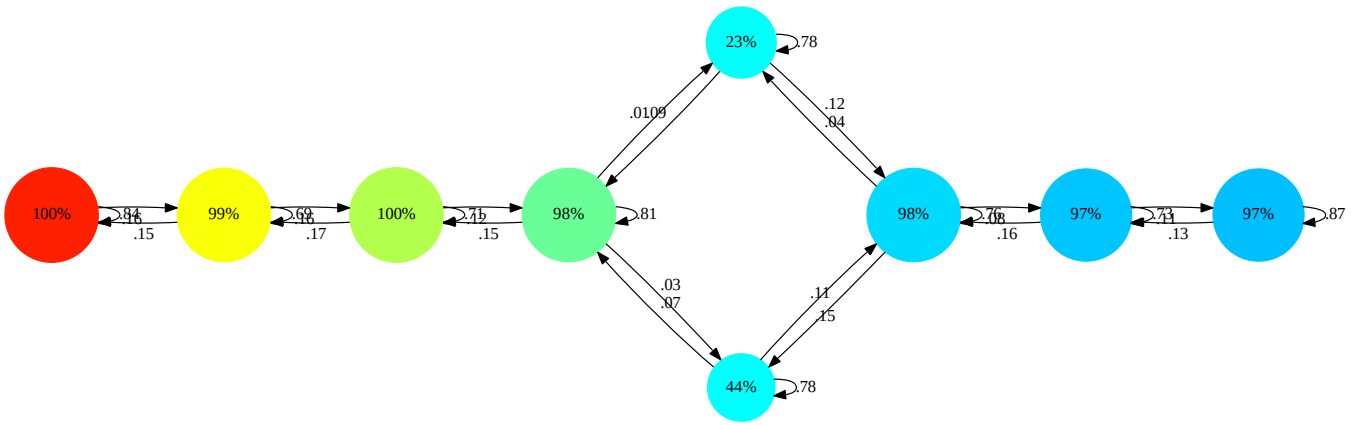


Figure: Refolding pathway

Transition Counts: 2ps lag time



- The two intermediate states, are on-pathways; the inner base-pair formation is easier in proceeding than backing (.15/.07), while the end base-pair formed more reluctant (.12/.09)
- Note that this is not a Markov State Model.

Biological Suggestions from Mapper Results

[*Bowman, et al. JACS 2008, to appear*]

- Folding and unfolding follows different pathways
- For folding pathways, there are multiple intermediate states
  - a dominant one with inner/closing stem base-pair formed
  - a less dominant one with outer/end stem base-pair formed
- This in the first time provides structural evidence in support of multistate hypothesis on folding pathways

Open problems and future directions

- Only static information is used, how to incorporate kinetic information?
- Combine geometric embedding with topological methods for better characterization of reaction coordinates?
- Toward a new generation of transition networks (Markov State Models)?
  - Mapper may characterize both metastable states and intermediate/transition states on different density/energy level sets
  - Traditional transition networks are based on metastates, which can be inferred from Mapper results