Topology of Cyclo-Octane Energy Landscape

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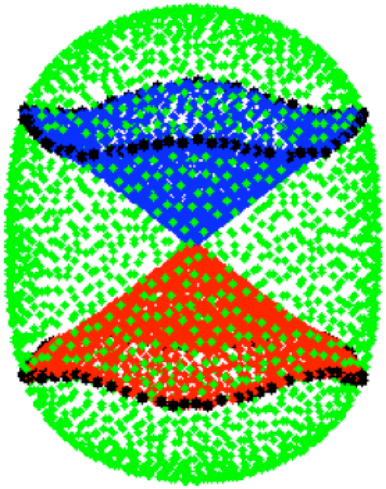

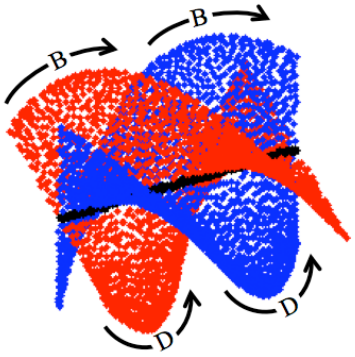

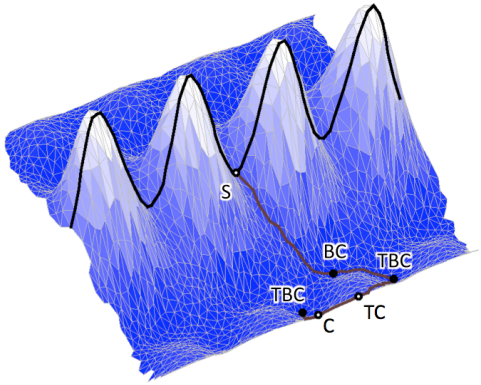

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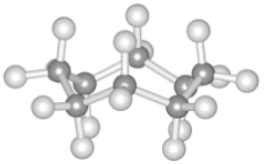
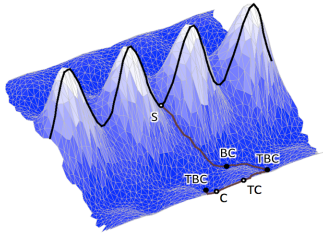
Overview of Work

- Cyclo-Octane has been studied as a model problem in computational chemistry for over 40 years.
  - Multiple conformations of similar energy.
  - Complex energy landscape.



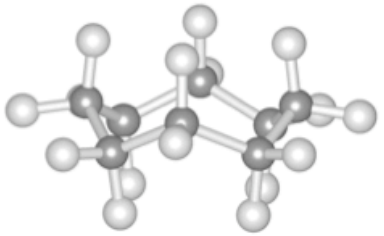
- We used/developed new methods from dimension reduction, computational algebraic geometry, and computational topology to better understand cyclo-octane.



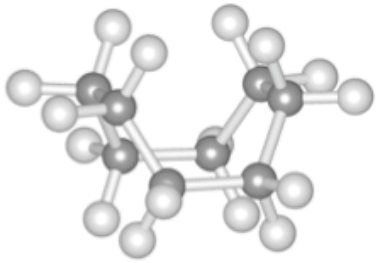
- As a result, we have completely characterized the conformation space of cyclo-octane:
  - The energy landscape, together with the topology of the conformation space, explains experimental observations that boat-chair is the dominant conformation of cyclo-octane.

Cyclo-Octane

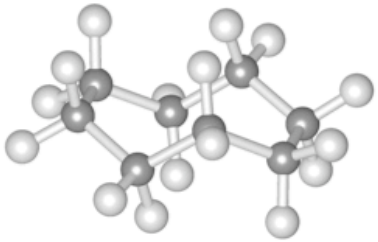
- Eight membered ring C_8H_{16} studied as a model problem for over 40 years in computational chemistry.
- "Cyclo-octane is unquestionably the conformationally most complex cycloalkane owing to the existence of so many forms of comparable energy." (Hendrickson, 1967).
- Three stable conformations: boat, boat-chair, and crown.
- Conformation space thought to be 2D due to ring closure constraint.



Crown



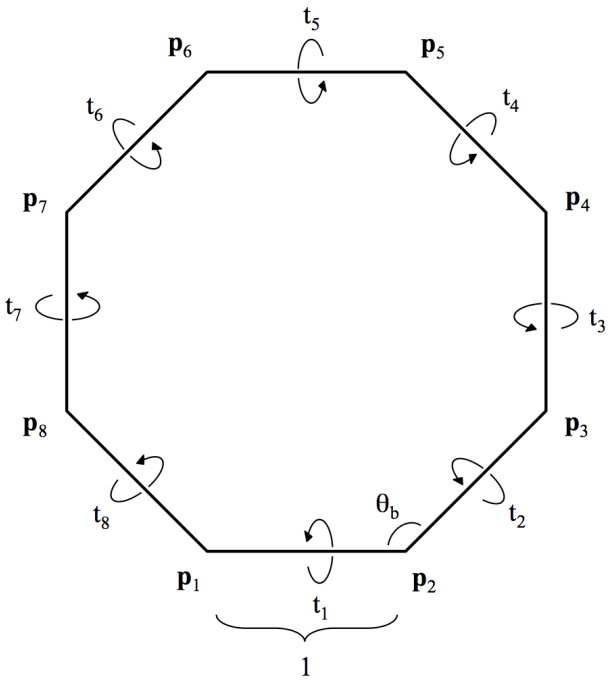
Boat



Chair

Enumerating Cyclo-Octane Conformations

- Cyclo-octane conformation can be described analytically using kinematic loop closure (Coutsias *et al*., 2005) or distance geometry (Portas *et al*. 2007).
  - Bond lengths and angles are fixed, while torsions are varied.
  - Algebraic equations (degree 16 for cyclo-octane) are solved to enumerate solutions.
  - At least 6 torsions are required, otherwise we have *s* – 6 degrees of freedom (*s* = 8 for cyclo-octane).



Enumerating Cyclo-Octane Conformations (Example using Distance Constraints)

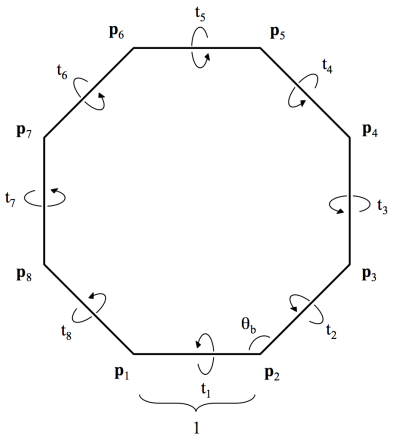
Define:

$$D(1,2,3,\ldots,k) = \begin{vmatrix} 0 & r_{1,2} & r_{1,3} & \cdots & r_{1,k} & 1 \\ r_{2,1} & 0 & r_{2,3} & \cdots & r_{1,k} & 1 \\ r_{3,1} & r_{3,2} & 0 & \cdots & r_{3,k} & 1 \\ \cdots & \cdots & \cdots & \cdots & \cdots & 1 \\ r_{k,1} & r_{k,2} & r_{k,3} & \cdots & 0 & 1 \\ 1 & 1 & 1 & \cdots & 1 & 0 \end{vmatrix}$$

where $r_{i,j} = \|\mathbf{p}_i - \mathbf{p}_j\|^2$. The constraints are given by

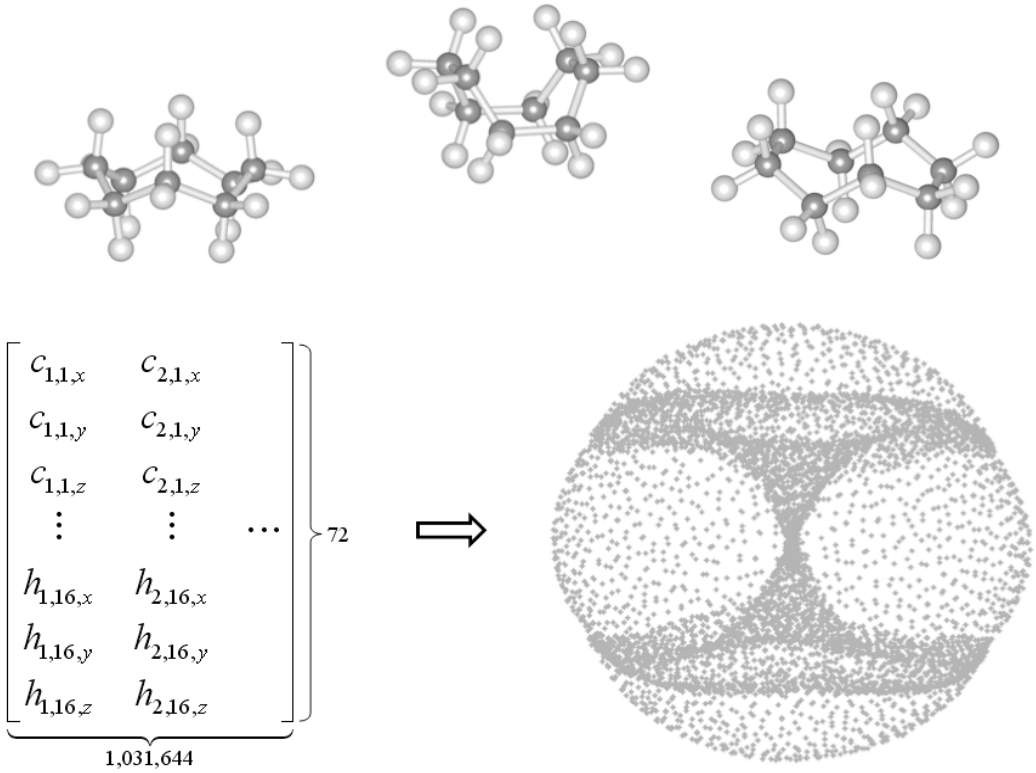
$$\begin{aligned} D(1,2) > 0 \qquad & D(\mathbf{R},i) = 0 \\ D(1,2,3) < 0 \qquad & D(\mathbf{R},j) = 0 \\ D(1,2,3,4) > 0 \qquad & D(\mathbf{R},i,j) = 0 \end{aligned}$$

where $\mathbf{R} = 1,\ldots,4$.



Dimension Reduction of Cyclo-Octane*

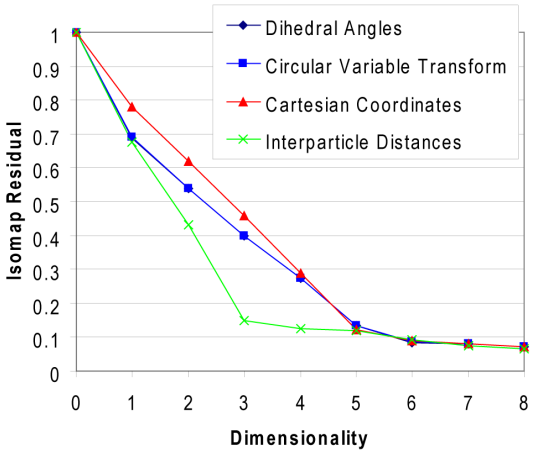
We applied nonlinear dimension reduction methods to the space of cyclo-octane conformations.

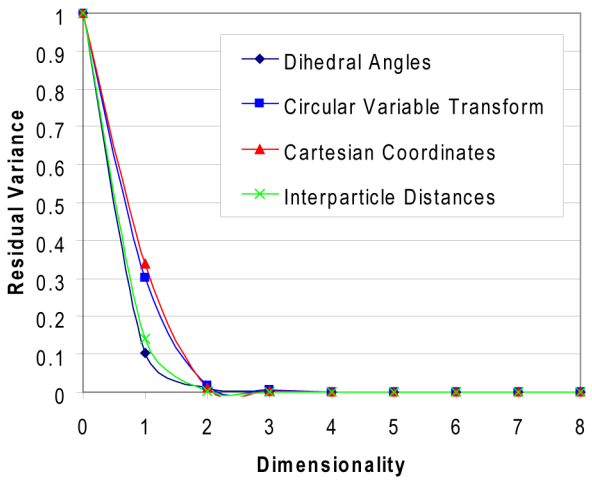


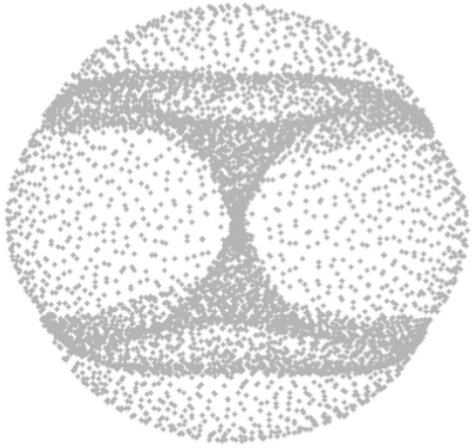
*W. M. Brown, S. Martin, S. N. Pollock, E. A. Coutsias, and J.-P. Watson (2008), "Algorithmic Dimensionality Reduction for Molecular Structure Analysis," *Journal of Chemical Physics* 129(6):064118.

Dimension Reduction of Cyclo-Octane

- In (Brown *et al.*, 2008), we applied Principal Component Analysis (PCA), IsoMap, Locally Linear Embedding, and an Autoencoder (neural network).
  - Best results were obtained using Isomap (Tenenbaum *et al.*, 2000).
  - Embedding dimension of conformation space was estimated to be 5.
  - Intrinsic dimension was estimated to be 2.

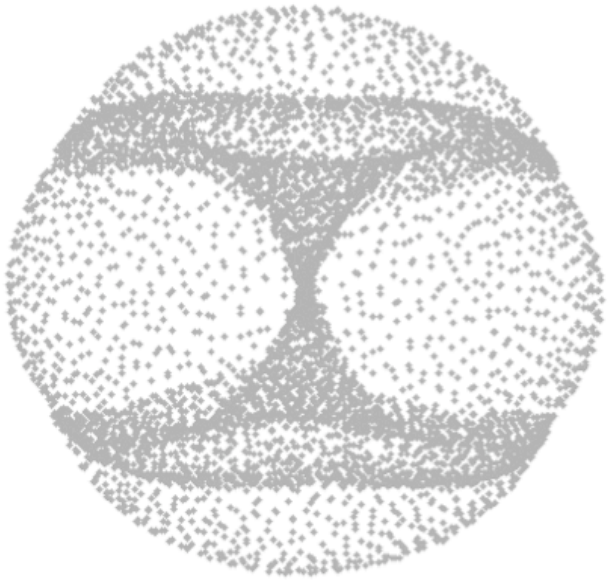






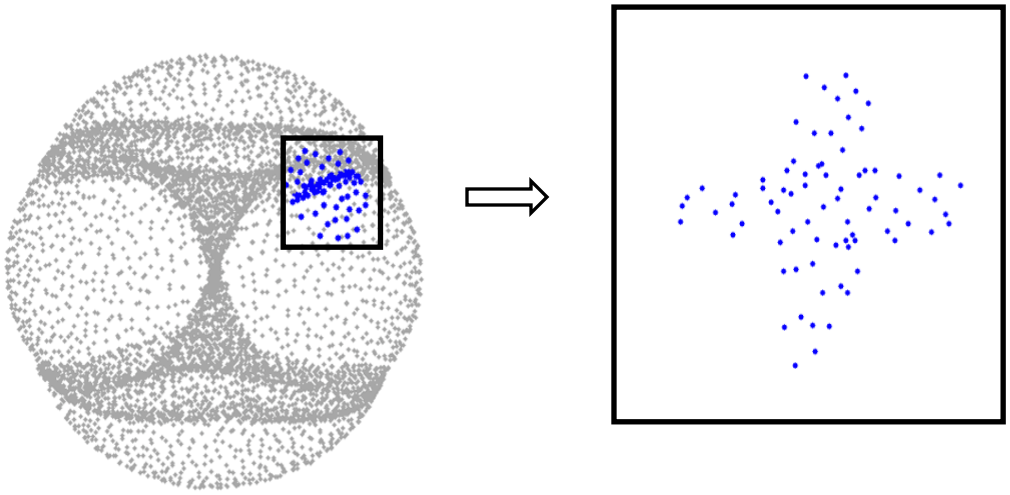
Questions Raised by Dimension Reduction of Cyclo-Octane

- This is a 3D visualization of a 5D object – what is in the other 2 dimensions?
- Are apparent intersections actually intersections (or just “singularities of projection”)?
- What is the topology of this object?
- What does this mean (in terms of molecular conformation)?



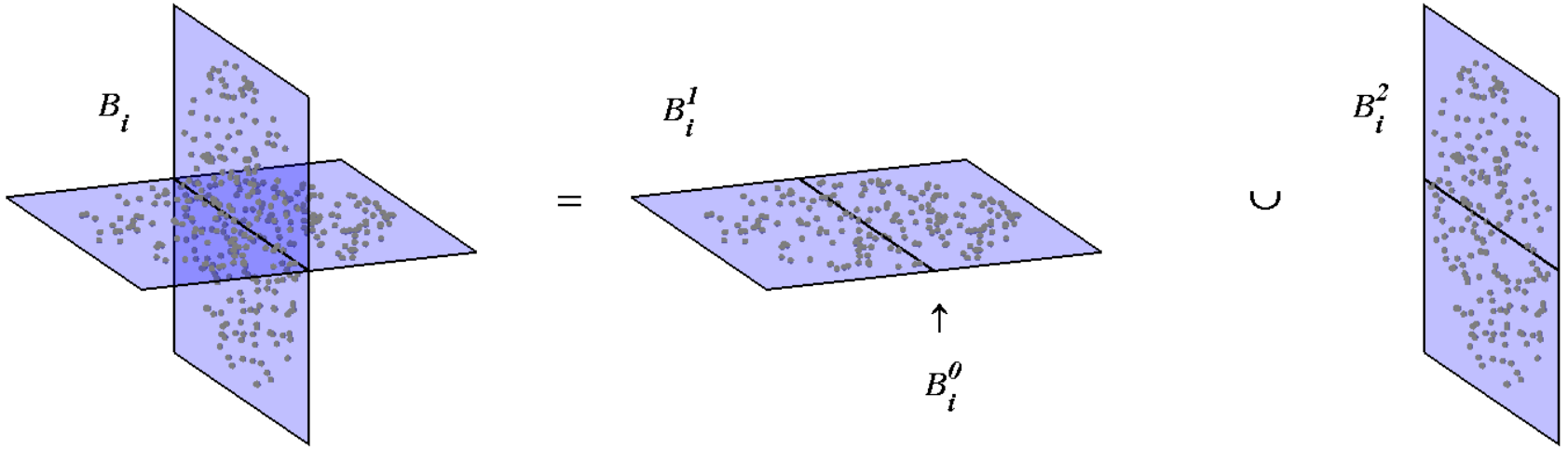
Triangulation of Cyclo-Octane

- Need triangulation to compute topological invariants such as homology (more later).
- Problems:
  - Existing surface reconstruction methods are limited to 3D, except incremental projection algorithm (Freedman, 2007).
  - (Freedman, 2007) assumes manifold surface.
  - We have non-manifold surface in 24 (ring atoms) or 72 (all atoms) dimensions.



Triangulation of Cyclo-Octane*

- Solution:
  - Model non-manifold neighborhoods as two intersecting planes in 3D.
  - Decompose non-manifold neighborhood into an intersecting line and two isolated planes
  - Triangulate intersections then use (Freedman, 2007) to triangulate surface.



*S. Martin and J.-P. Watson (2010), "Non-Manifold Surface Reconstruction from High Dimensional Point Cloud Data," accepted in *Computational Geometry: Theory and Applications.*

Fitting Two Intersecting Planes

- Overview:
  - We use PCA to project a non-manifold neighborhood into xyz coordinates.
  - We fit a quadratic polynomial to the data using a least squares fit subject to the constraint that it must factor.
  - We factor the polynomial, find the intersection of the two planes, and split the neighborhood accordingly.

- Details:
  - Denote a polynomial by

$$\begin{aligned} f(x,y,z) &= a_{11}x^2 + 2a_{12}xy + 2a_{13}xz + 2a_{14}x + a_{22}y^2 + \\ &\quad 2a_{23}yz + 2a_{24}y + a_{33}z^2 + 2a_{34}z + a44 = 0. \end{aligned}$$

  - Write $A = (a_{ij})$, denote by A_3 the 3x3 upper left submatrix of A, and let

$$T_2 = (a_{11}a_{22} - a_{12}^2) + (a_{11}a_{33} - a_{13}^2) + (a_{22}a_{33} - a_{23}^2)$$

  - Let $\mathbf{m}_j = [x_j^2 \;\; 2x_jy_j \;\; 2x_jz_j \;\; 2x_j \;\; y_j^2 \;\; 2y_jz_j \;\; 2y_j \;\; z_j^2 \;\; 2z_j \;\; 1]$ and $M = [\mathbf{m}_j]$.
  - We must solve

$$\begin{aligned} \min_{\mathbf{a}} \quad & \mathbf{a}^T M^T M \mathbf{a} \\ \text{s.t.} \quad & \operatorname{rank}(A) = \operatorname{rank}(A_3) = 2, \\ & T_2 \le 0, \;\; \|A_3\|_F = 1. \end{aligned}$$

Fitting Two Intersecting Planes (More Details)

We re-write the minimization

$$\begin{array}{rl} \min_{\mathbf{a}} & \mathbf{a}^T M^T M \mathbf{a} \\ \text{s.t.} & \text{rank}(A) = \text{rank}(A_3) = 2, \\ & T_2 \leq 0, \ \|A_3\|_F = 1. \end{array}$$

By observing that

$$\left\{ A \;\middle|\; \begin{array}{l} \text{rank}(A) = 2, \\ \text{rank}(A_3) = 2, \\ \|A_3\|_F = 1 \end{array} \right\} = \left\{ \lambda_1 \mathbf{q}_1 \mathbf{q}_1^T + \lambda_2 \mathbf{q}_2 \mathbf{q}_2^T \;\middle|\; \begin{array}{l} \lambda_1, \lambda_2 \neq 0, \\ \lambda_1^2 + \lambda_2^2 = 1, \\ \|\tilde{\mathbf{q}}_1\| = \|\tilde{\mathbf{q}}_2\| = 1, \\ \tilde{\mathbf{q}}_1^T \tilde{\mathbf{q}}_2 = 0 \end{array} \right\}$$

so that we can minimize the following equivalent problem

$$\begin{array}{rl} \min_{\mathbf{q}_1, \mathbf{q}_2, \lambda_1, \lambda_2} & \sum_j (\lambda_1 \mathbf{q}_1^T X_j \mathbf{q}_1 + \lambda_2 \mathbf{q}_2^T X_j \mathbf{q}_2)^2 \\ \text{s.t.} & \|\tilde{\mathbf{q}}_1\| = \|\tilde{\mathbf{q}}_2\| = 1, \tilde{\mathbf{q}}_1^T \tilde{\mathbf{q}}_2 = 0, \\ & \lambda_1, \lambda_2 \neq 0, \lambda_1^2 + \lambda_2^2 = 1, \\ & T_2 = \sum_{j<k\leq 3} \det([\lambda_1 \mathbf{q}_1 \mathbf{q}_1^T + \lambda_2 \mathbf{q}_2 \mathbf{q}_2^T]_{jk}) \leq 0, \end{array}$$

where X_j is a matrix of quadratic monomials in *xyz* coordinates for data point *j*.

Fitting Two Intersecting Planes (Still More Details)

- We can obtain a very good initial estimate for the minimization using the following procedure:
  - Get unconstrained solution by setting a^* to be the right singular vector of M.
  - Form matrix $A^* = (a_{ij}^*)$ and normalize such that $\|A_3^*\|_F = 1$.
  - Decompose $A_3^* = \lambda_1 \tilde{\mathbf{q}}_1 \tilde{\mathbf{q}}_1^T + \lambda_2 \tilde{\mathbf{q}}_2 \tilde{\mathbf{q}}_2^T$
  - Solve for $\mathbf{q}_1 = [\tilde{\mathbf{q}}_1 \ r]^T, \mathbf{q}_2 = [\tilde{\mathbf{q}}_2 \ s]^T$

$$[\lambda_1 \tilde{\mathbf{q}}_1 \ \lambda_2 \tilde{\mathbf{q}}_2] \begin{bmatrix} r \\ s \end{bmatrix} = \begin{bmatrix} a_{14}^* \\ a_{24}^* \\ a_{34}^* \end{bmatrix}$$

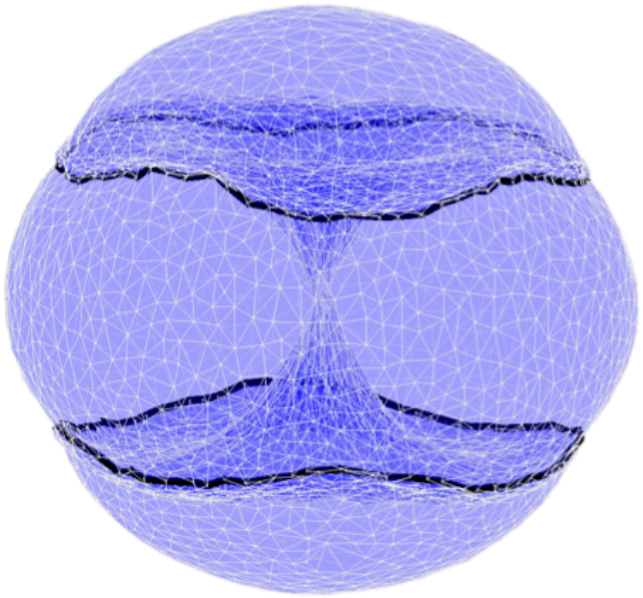
  - Now re-set $a^* = \lambda_1 \mathbf{q}_1 \mathbf{q}_1^T + \lambda_2 \mathbf{q}_2 \mathbf{q}_2^T$

- This estimate works without further optimization for cyclo-octane!

- Not shown: how to factor a^*.

Triangulation of Cyclo-Octane

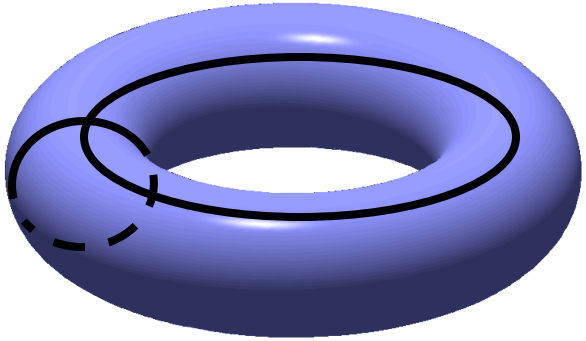
- Performed surface reconstruction 5 times using randomly selected subsamples (at least ε distance apart) of 24 dimensional (ring atom only) cyclo-octane data.
  - 6,040 samples (ε = .12)
  - 7,114 samples (ε = .11)
  - 8,577 samples (ε = .10)
  - 10,503 samples (ε = .9)
  - 13,144 samples (ε = .8)



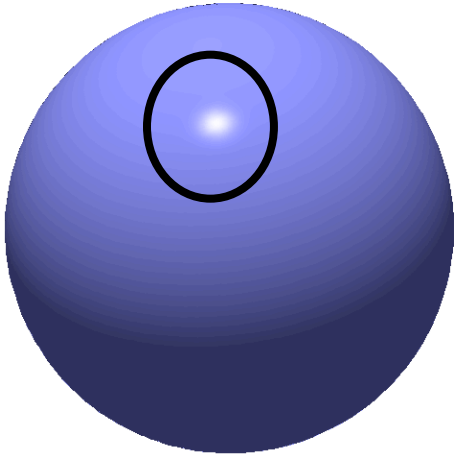
- Verified local topology in each case as homotopic to a point.

Primer on Algebraic Topology

- Recent development in computational algebraic topology allow us to investigate the topology of triangulated/point set data.
  - Available tools such as Plex (comptop.stanford.edu) and Chomp (chomp.rutgers.edu) can compute topological invariants known as Betti numbers.
  - Betti numbers count number of connected components (β_0), number of loops (β_1), number of voids (β_2), etc. using algebraic homology.



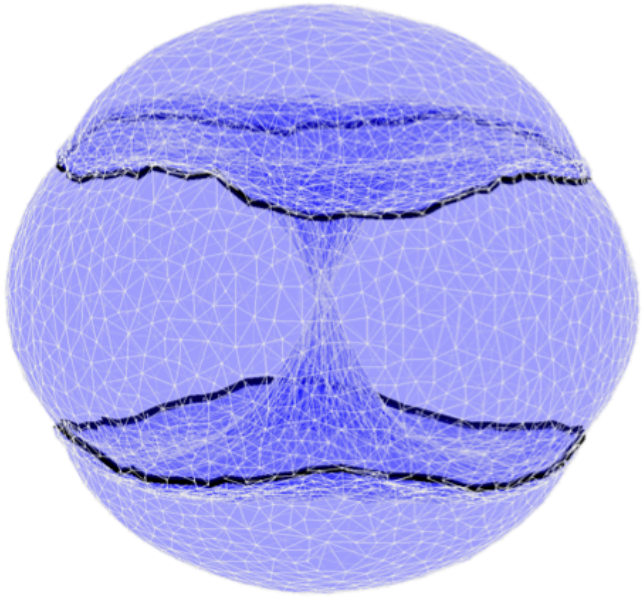
Torus Betti Numbers: 1,2,1



Sphere Betti Numbers: 1,0,1

Topology of Cyclo-Octane*

- We used computational topology tools to compute Betti numbers of cyclo-octane conformations.
  - Plex (comptop.stanford.edu) to compute boundary maps and Laplacian operators.
  - Linbox (www.linalg.org) to compute ranks of Laplacians.
  - Afra Zomordian's persistence codes (not publicly available).

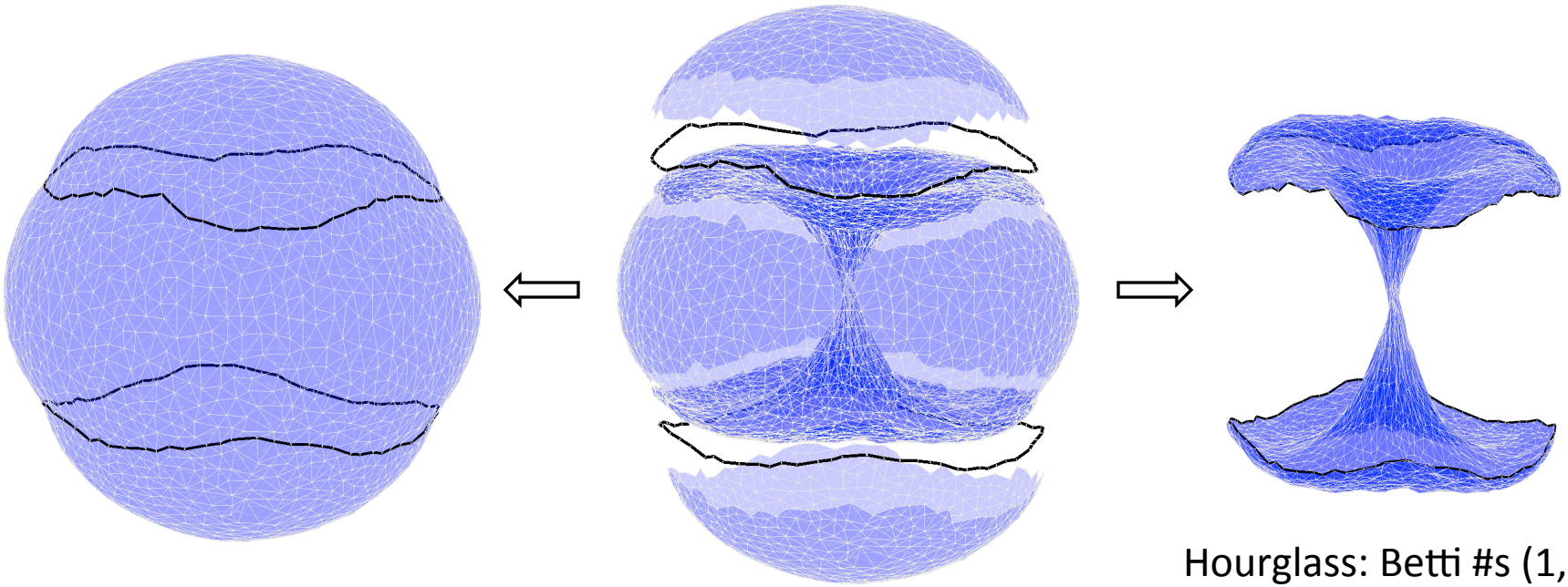


- We computed the Betti numbers for each of the 5 triangulations.
  - $\beta_0 = 1, \beta_1 = 1, \beta_2 = 2$.

*S. Martin, A. Thompson, E. A. Coutsias, and J.-P. Watson (2010), "Topology of Cyclo-Octane Energy Landscape," *J. Chem. Phys.* 132(23):234115.

Decomposition of Cyclo-Octane

- Betti numbers (1,1,2) are uninformative, due to the non-manifold nature of the conformation space.
- However, we can use our triangulation to decompose the space into two components via the self-intersections.



Sphere: Betti #s (1,0,1)

Hourglass: Betti #s (1,1,0)

Cyclo-Octane Canonical Basis

- To resolve the identity of the hourglass, we derived a canonical basis from the distance constraints which gives an analytical version of the Isomap coordinates.

  – The canonical basis in torsion coordinates is given by

$$\mathbf{c}_r = (u, -u, u, -u, u, -u, u, -u)^T$$

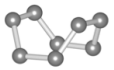
$$\mathbf{b}_1 = (0, v, 0, -v, 0, v, 0, -v)^T$$

$$\mathbf{b}_2 = (v, 0, -v, 0, v, 0, -v, 0)^T$$

$$\mathbf{c}_1 = (v, 0, -v, w, -v, 0, v, -w)^T$$

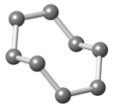
$$\mathbf{c}_2 = (v, -w, v, 0, -v, w, -v, 0)^T,$$

$\mathbf{c}_r$

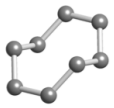


$\mathbf{b}_1$

$\mathbf{b}_2$



$\mathbf{c}_1$



$\mathbf{c}_2$

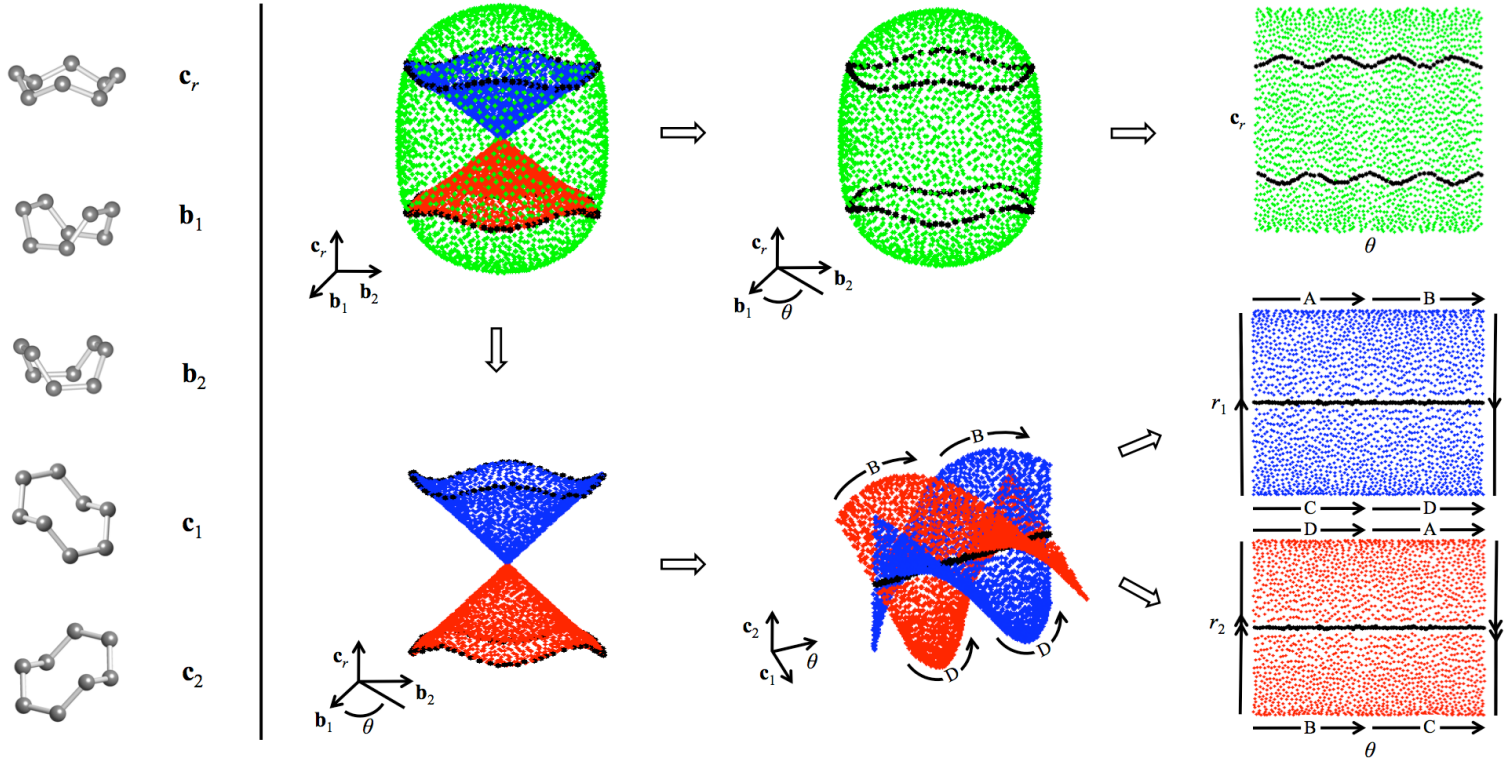
where

$$\cos u = (1 - \sqrt{2} - \cos\theta_b)/(1 + \cos\theta_b)$$

$$\cos v = \cos^2\theta_b / \sin^2\theta_b$$

$$\cos w = (3\cos^2\theta_b - 1)/\sin^2\theta_b\,.$$

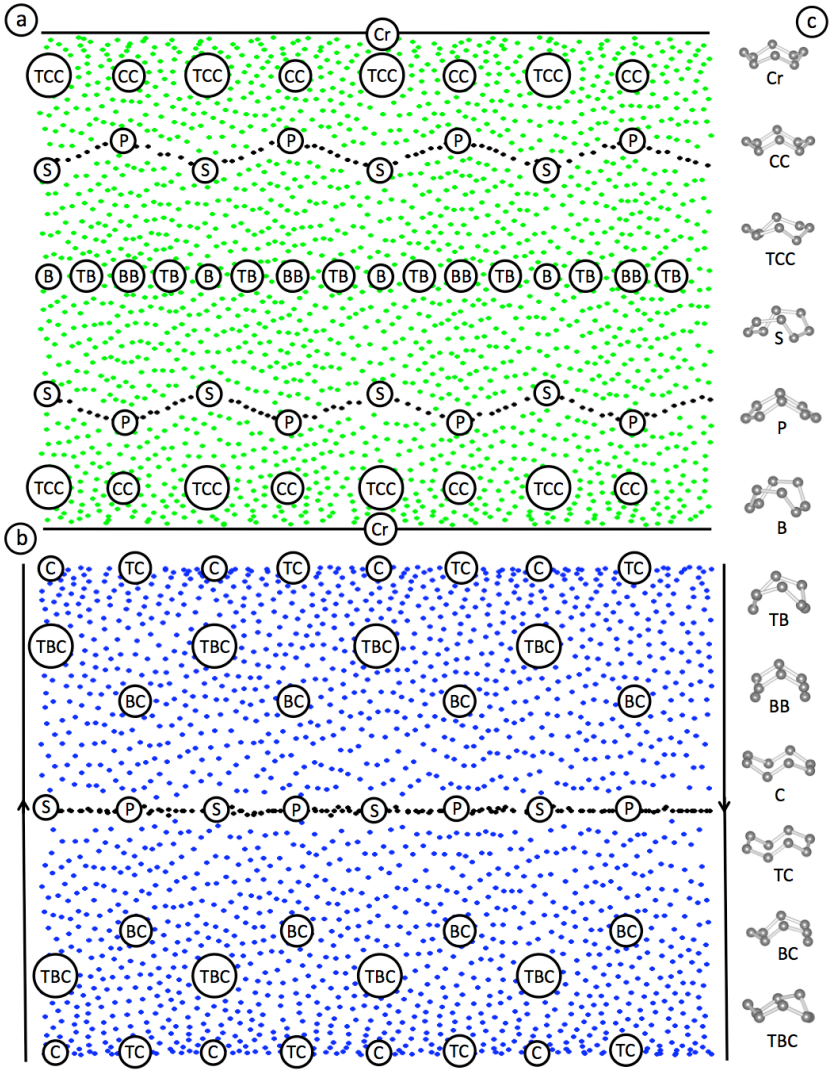
Analytic Cyclo-Octane Decomposition



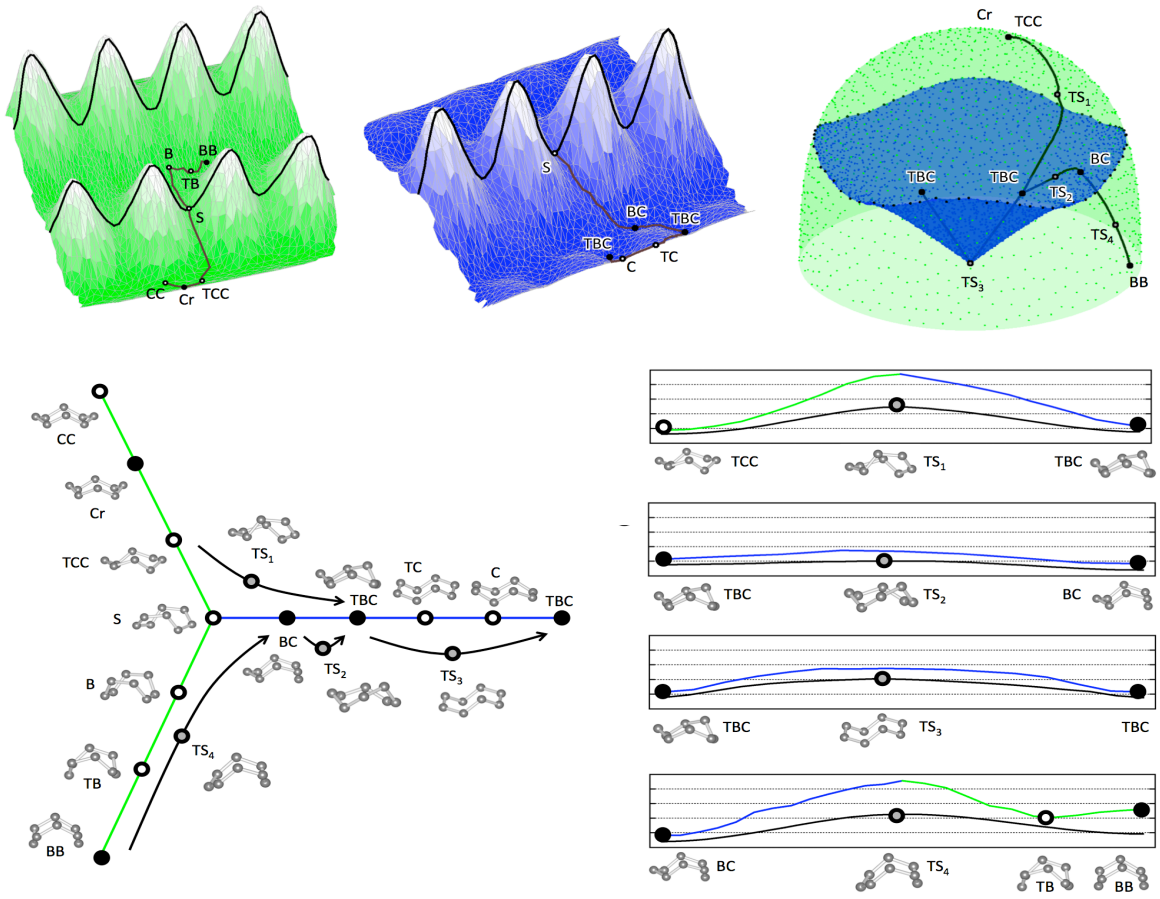
- Triangulation allowed decomposition of conformation space into a sphere and a Klein bottle intersecting in two rings.
- Klein bottle is a unique discovery in the field of molecular conformation.

Understanding Cyclo-Octane Conformations

- Structure of conformation space can be explained by the geometry of the cyclooctane molecule.
- There are ten “canonical conformations” which can be grouped into three families: Crown (Cr), Boat (B), and Boat-Chair (BC).
- There are twice as many BC conformations as there are Cr conformations, which causes a twist in the conformation space.
- The twist forms a Mobius strip.
- The Klein bottle forms because there are two Mobius strips (due to symmetry by reflection) joined at their edges.



Cyclo-Octane Energy Landscape



- The energy landscape, together with the topology of the conformation space, explains experimental observations that BC is the dominant conformation of cyclooctane.

Conclusions

- Our work on cyclo-octane has revealed novel discoveries in field of molecular motion.
  - We have used new tools from computational algebraic geometry/topology to complete characterize a 40 year old model problem.
  - Algebraic singularities are evidence of previously unsuspected mathematical complexity.
  - Klein bottle evidence of previously unassumed non-orientable structure.

- In addition, the cyclo-octane data has motivated the need for better data analysis algorithms.
  - Previous algorithms assume a manifold structure. For certain datasets this assumption is inadequate, and such algorithms will fail.
  - We need a new class of algorithms that can handle algebraic structure, including singularities.
  - The algorithms that we developed to analyze cyclo-octane are just one small step towards this new class of algorithms.
  - Future challenges include data set size, dimension of structure, different types of singularities, etc.