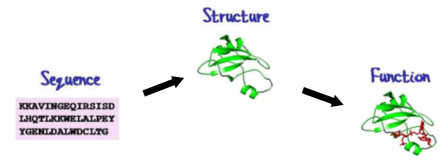
Algorithmic robotics and Motion Planing

Spring 2011

Dynamic Maintenance of Kinematic Chains

Itay Lotan

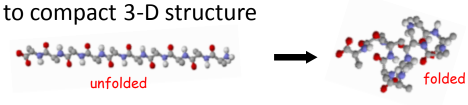
Central Dogma of Molecular Biology



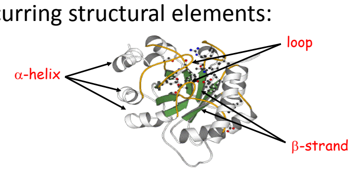
Understanding the 3-D structure of proteins is essential to understanding life

Protein Folding

- Protein chain spontaneously collapses (folds) to compact 3-D structure

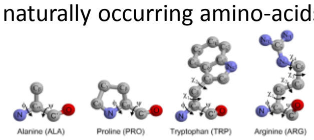


- Recurring structural elements:

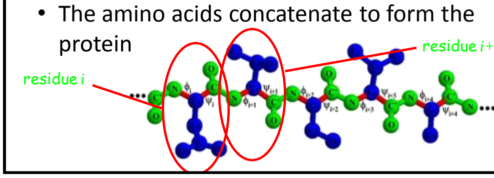


Chain of Amino-Acids

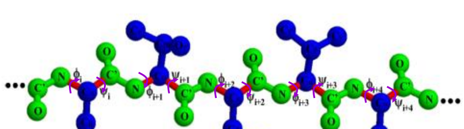
- 20 naturally occurring amino-acids



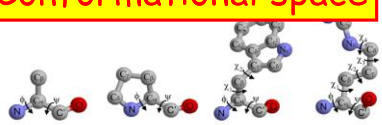
- The amino acids concatenate to form the protein



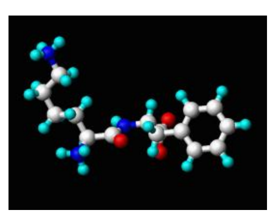
ϕ-ψ Kinematic Linkage Model

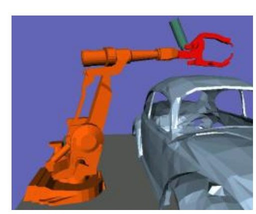


Conformational space



Molecule ≈ Robot



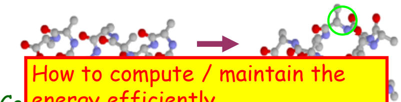


Monte Carlo Simulation (MCS)

- Popular method for sampling the conformation space of proteins
- Used for
  - estimating thermodynamic quantities
  - searching for low-energy conformations and the folded structure

MCS: How It Works

1. Perturb current conformation at random



How to compute / maintain the energy efficiently

2. Co
3. Accept with probability:

$$P(accept) = \min\left\{1, e^{-\Delta E / k_B T}\right\}$$

[E - energy, k_B - Boltzmann's constant, T - temperature]

Requires >>10^9 steps to sample adequately

Energy Function

- E = Σ bonded terms
  + Σ non-bonded terms
  + Σ solvation terms
- Bonded terms
  - *Bond-stretching, bending, rotating*
  - *O(n)*
- Non-bonded terms
  - E.g., Van der Waals and electrostatic
  - Depend on distances between pairs of atoms
  - $O(n^2)$ → Expensive to compute
- Solvation terms
  - May require computing molecular surface

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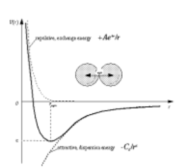
Non-Bonded Terms

- Energy terms go to 0 when distance increases
  - Cutoff distance (6 - 12Å)
- vdW forces prevent atoms from bunching up
  - Only *O(n)* interacting pairs

    [Halperin & Overmars, '98]



Challenge: find interacting pairs without enumerating all atom pairs?

Finding Pairs

	Update	Detection
Brute Force	$\Theta(n)$	$\Theta(n^2)$
Grid	$\Theta(n)$	$\Theta(n)$
Spatially-adapted hierarchy	$O(n \log n)$	$\Theta(n)$
Chain-aligned hierarchy	$O(n)$	$\Theta(n^{4/3})$
ChainTree	$O(k \log n/k)$	$\Theta(n^{4/3})$

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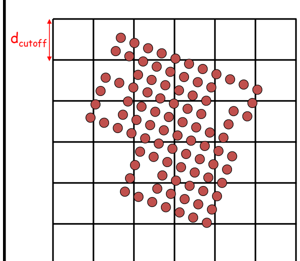
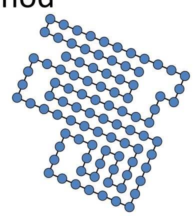
PARTITION THE SPACE

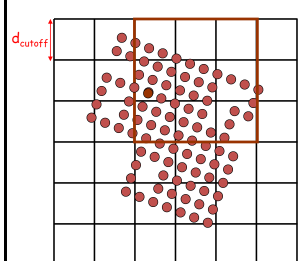
Grid Method





- Subdivide 3-space into cubic cells
- Compute cell that contains each atom center
- Represent grid as hash table

Grid Method



- $\Theta(n)$ time to build grid
- O(1) time to find interacting pairs for each atom
- $\Theta(n)$ to find all interacting pairs

Asymptotically optimal in worst-case

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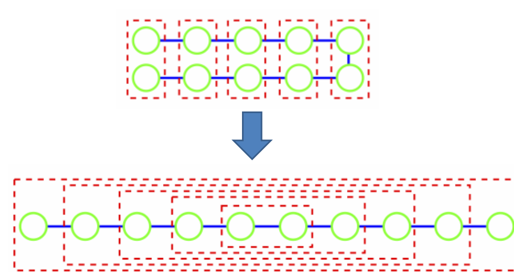
PARTITION THE OBJECT

Finding Pairs



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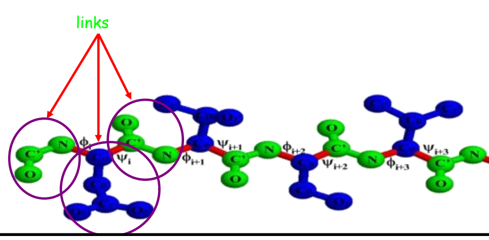
Protein as Kinematic Chain



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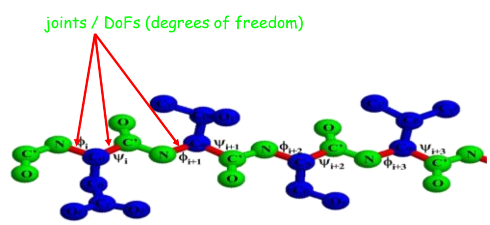
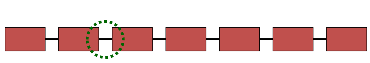


Properties of kinematic chains

- Small changes ⇒ large effects



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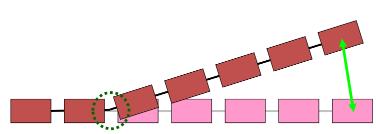
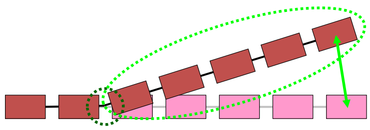


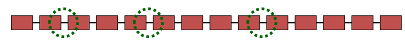
Properties of kinematic chains

- Small changes ⇒ large effects
- Local changes ⇒ global effects



Properties of kinematic chains

- Small changes ⇒ large effects
- Local changes ⇒ global effects
- Few DoF changes ⇒ long rigid sub-chains



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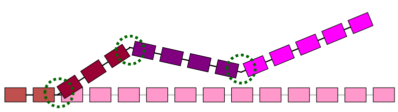
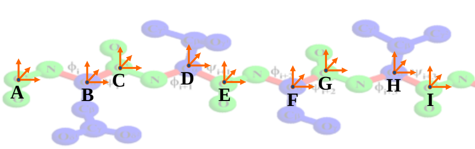


ChainTree: A tale of two hierarchies

- **Transform hierarchy:** approximates kinematics of protein backbone at successive resolutions
- **Bounding volume hierarchy:** approximates geometry of protein at successive resolutions

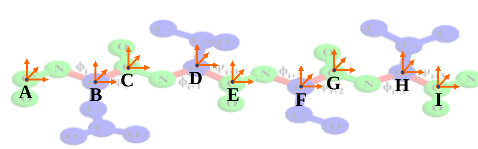
Hierarchy of Transforms



Hierarchy of Transforms

Rigid Body Transform = **T**ranslation + **R**otation

$$T = \begin{bmatrix} t_0 \\ t_1 \\ t_2 \end{bmatrix} \qquad R = \begin{bmatrix} r_{0,0} & r_{0,1} & r_{0,2} \\ r_{1,0} & r_{1,1} & r_{1,2} \\ r_{2,0} & r_{2,1} & r_{2,2} \end{bmatrix}$$



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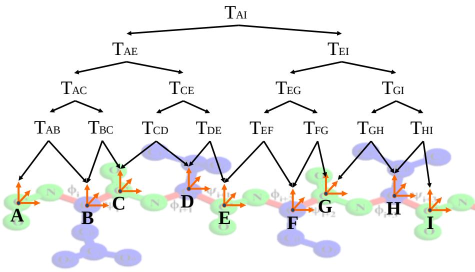
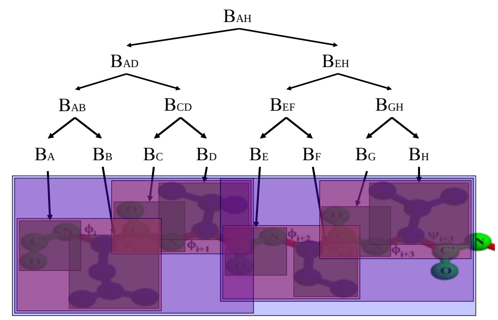
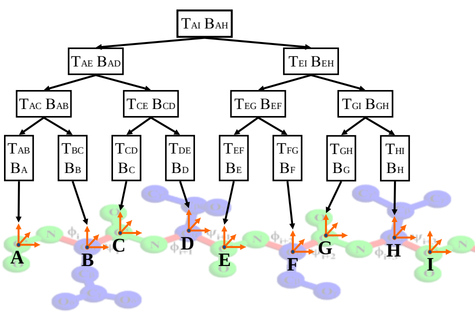


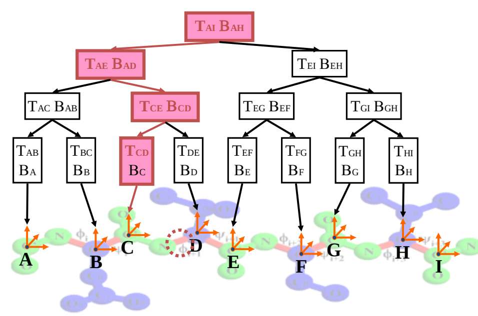
Hierarchy of Bounding Volumes (BVs)



The ChainTree



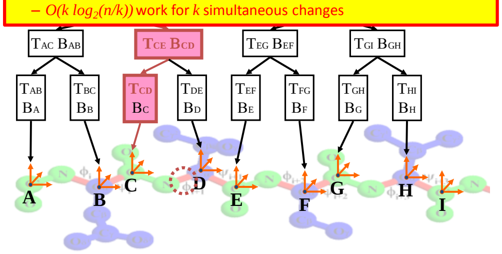
Updating the ChainTree



Updating the ChainTree

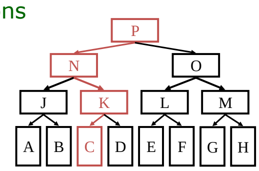
Update path to root:

- Recompute transforms that "shortcut" the DoF change
- Recompute BVs that contain the DoF change
- $O(k \log_2(n/k))$ work for k simultaneous changes



Detecting Interactions

Recursively search ChainTree for interactions



Pruning rules:

1. Prune search when distance between bounding volumes is more than cutoff distance
2. Do not search inside rigid sub-chains (no marked node between the tested nodes)

Computational complexity

- Updating:

$$O\left(k \log n/k\right)$$

- Searching:

$$\Theta\left(n^{4/3}\right)$$ worst case bound

Much faster in practice

Proof

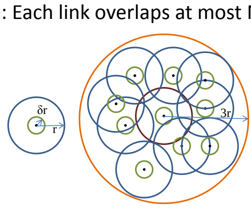
- Regularize the chain:
  - Replace all links by their bounding spheres
  - Make all sphere equal in size by growing smaller spheres
  - Further grow all links equally until each pair of consecutive links is in contact

No effect on complexity of the problem

Proof

Assumption: Distance between link centers > $\delta \cdot r$

Proposition: Each link overlaps at most M other links



At level i, replace r with $2^i \cdot r$

$M_i = 27 \cdot (2^i)^2 / q \quad 0 < q < 1$

Proof

M_i is bounded by number of BVs at level i

$$M_i \leq n/2^i$$

This bound is reached when $i > 1/3 \log n$

$$T = \sum_{i=0}^{\frac{1}{3}\log n} \left(\frac{27 \cdot 2^{2i}}{q}\right)\left(\frac{n}{2^i}\right) + \sum_{\frac{1}{3}\log n}^{\log n} \left(\frac{n}{2^i}\right)^2$$
$$= \frac{27n}{q}\left(2n^{1/3} - 1\right) + \frac{4}{3}\left(n^{4/3} - 1\right)$$
$$= O\left(n^{4/3}\right)$$

Proof

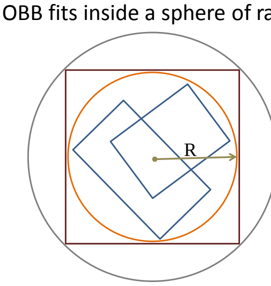
This bound holds as long as each BV at level i can be enclosed by sphere of radius $c \cdot 2^i r$

We still need to show this is true for the ChainTree BVs

We will prove the existence of c by induction

Proof

Lemma: given two OBBs inside sphere of radius R, their OBB fits inside a sphere of radius $\sqrt{3} \cdot R$



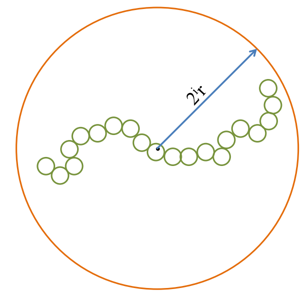
Proof

Base: for levels 0 through 4 choose an appropriate $c = c_1$

Induction step:

- Each BV at level i-5 fits inside a sphere of radius $c \cdot 2^{i-5} r$
- A sphere of radius $2^i r$ is enough to bound all links inside a BV at level i

Proof



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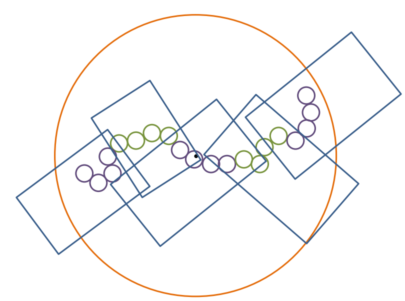
Base: for levels 0 through 4 choose an appropriate $c=c_1$

Induction step:

- Each BV at level i-5 fits inside sphere of radius $c \cdot 2^{i-5} r$
- A sphere of radius $2^i r$ is enough to bound all links inside a BV at level i
- No point in any of the 32 BVs at level i-5 is further than $2^i r + 2 \cdot c \cdot 2^{i-5} r$ from the center of this sphere

Proof



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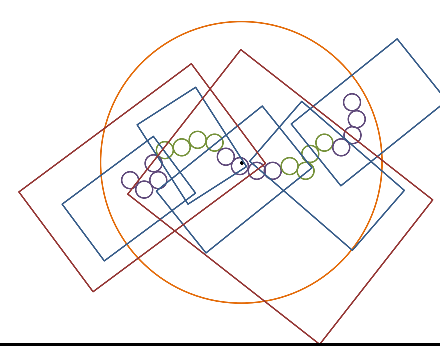
Induction step:

- Each BV at level i-5 fits inside sphere of radius $c \cdot 2^{i-5} r$
- A sphere of radius $2^i r$ is enough to bound all links inside a BV at level i
- No point in any of the 32 BVs at level i-5 is further than $2^i r + 2 \cdot c \cdot 2^{i-5} r$ from the center of this sphere
- No point in any of the 16 BVs at level i-4 is further than $\sqrt{3}(2^i r + 2 \cdot c \cdot 2^{i-5} r)$ from the center of this sphere

Proof



Proof

$$\left(2^i r + 2c \cdot 2^{i-5} r\right) \cdot \sqrt{3}^5 \le c \cdot 2^i r$$

$$\left(\frac{1}{\sqrt{3}^5} - \frac{1}{16}\right)^{-1} \le c$$

$$c = \max\left\{\left(\frac{1}{\sqrt{3}^5} - \frac{1}{16}\right)^{-1}, c_1\right\}$$

Proof

- We have shown $O(n^{4/3})$
- Still need to prove $\Omega(n^{4/3})$
- Construct a chain configuration where bound is achieved

Proof

Each ***link*** is a sphere of radius r

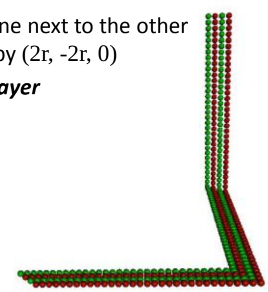
- Place d ***links*** along x-axis (starting at origin)
- Place d ***links*** parallel to y-axis
- Place d ***links*** parallel to z-axis

This constitutes a ***unit***

Proof

- Place d/8 ***units*** one next to the other each translated by (2r, -2r, 0)

This constitutes a ***layer***

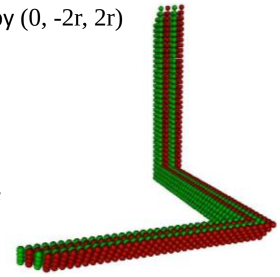


Proof

- Place d/8 ***layers*** one on top of the other translated by (0, -2r, 2r)

This is the ***chain***

$$n = d/8 \ \textit{layers} = d^2/64 \ \textit{units} = 3d^3/64 \ \textit{links} = O(d^3)$$



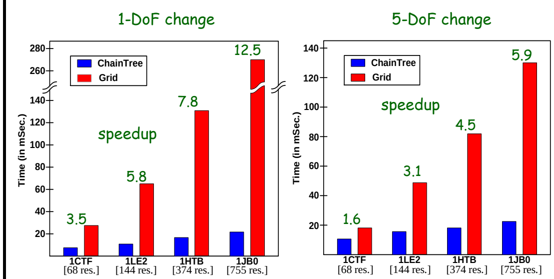
Proof

- The point $\left(2(d-1)r, (d-1)r, \tfrac{1}{4}(d-1)r\right)$ is contained inside convex hull of each ***unit***
- There is a level in BVH where each ***unit*** has its own BV
- At this level all BV pairs intersect
- We have $\frac{1}{2}\left(d^2/64\right)\left(d^2/64 - 1\right)$ overlaps: $\Omega(n^{4/3})$

Experimental Setup

- Energy function:
  - Van der Waals
  - Electrostatic
  - Attraction between folded-state contacts
  - Cutoff at 12Å
- 300,000 steps MCS with Grid and ChainTree
- **Steps are the same with both methods**
- Early rejection for large vdW terms

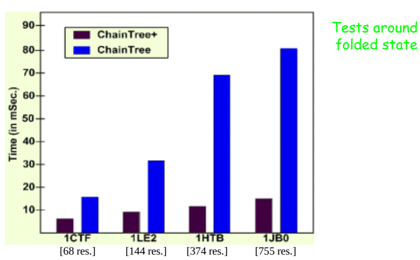
Test



Two-Pass ChainTree

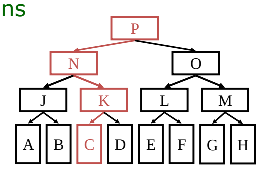
(ChainTree+)

1st pass: small cutoff distance to detect steric clashes
2nd pass: normal cutoff distance



Computing the Energy

Recursively search ChainTree for interactions



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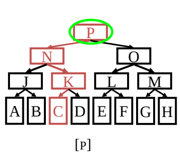

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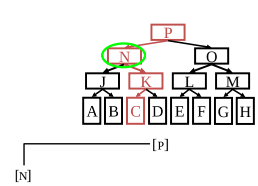

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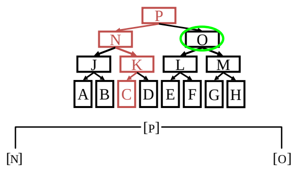

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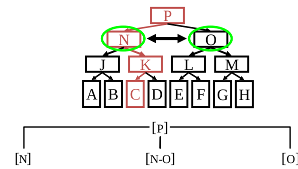

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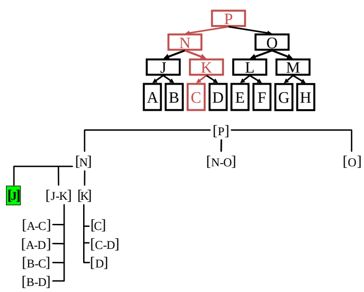
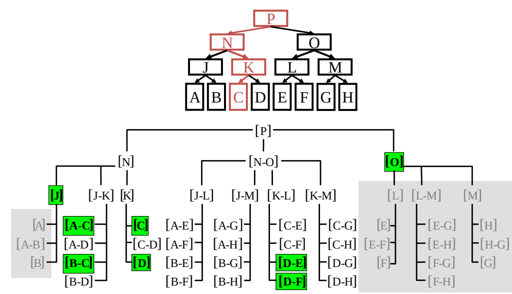
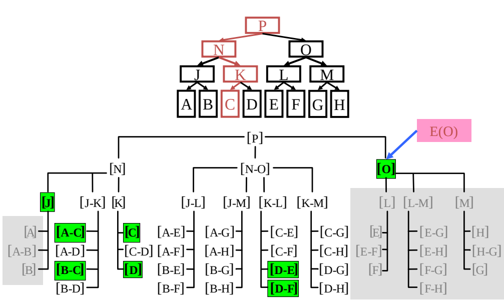


Computing the Energy

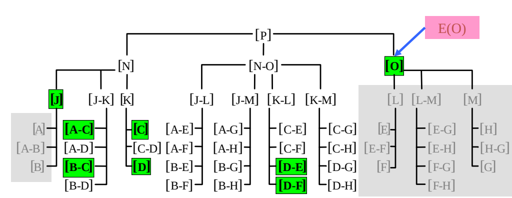


Computing the Energy

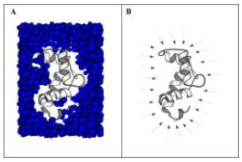


Computing the Energy

The Energy Tree



Extension: Interaction with Solvent



- Implicit solvent model: solvent as continuous medium, interface is solvent-accessible surface

E. Eyal, D. Halperin. Dynamic Maintenance of Molecular Surfaces under Conformational Changes. Proc. 21st ACM Symposium on Computational Geometry (SoCG05) 2005