A FILTERING TECHNIQUE FOR FRAGMENT ASSEMBLY- BASED PROTEINS LOOP MODELING WITH CONSTRAINTS

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CP'12

Summary

Background

Joined Multibody Constraint

NP-completeness

Filtering

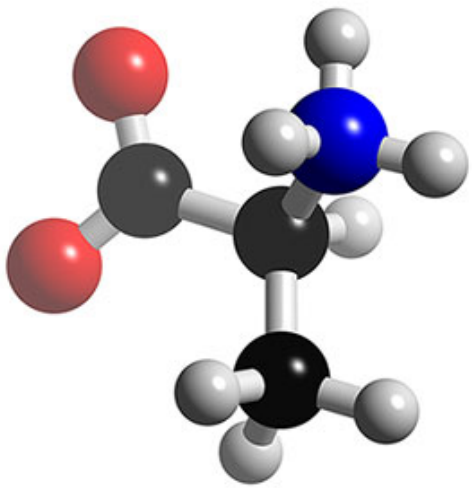
Results

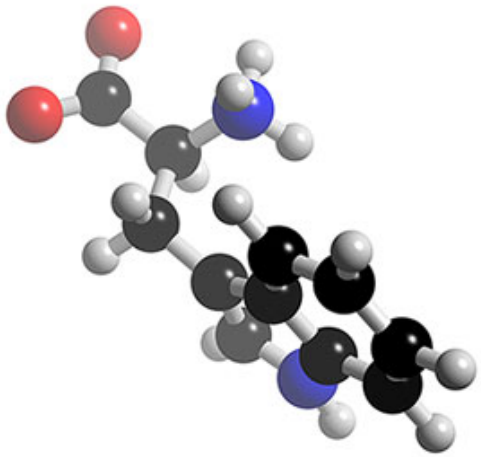
Conclusions

PROTEINS

AMINO ACIDS

- Proteins are molecules made of amino acids



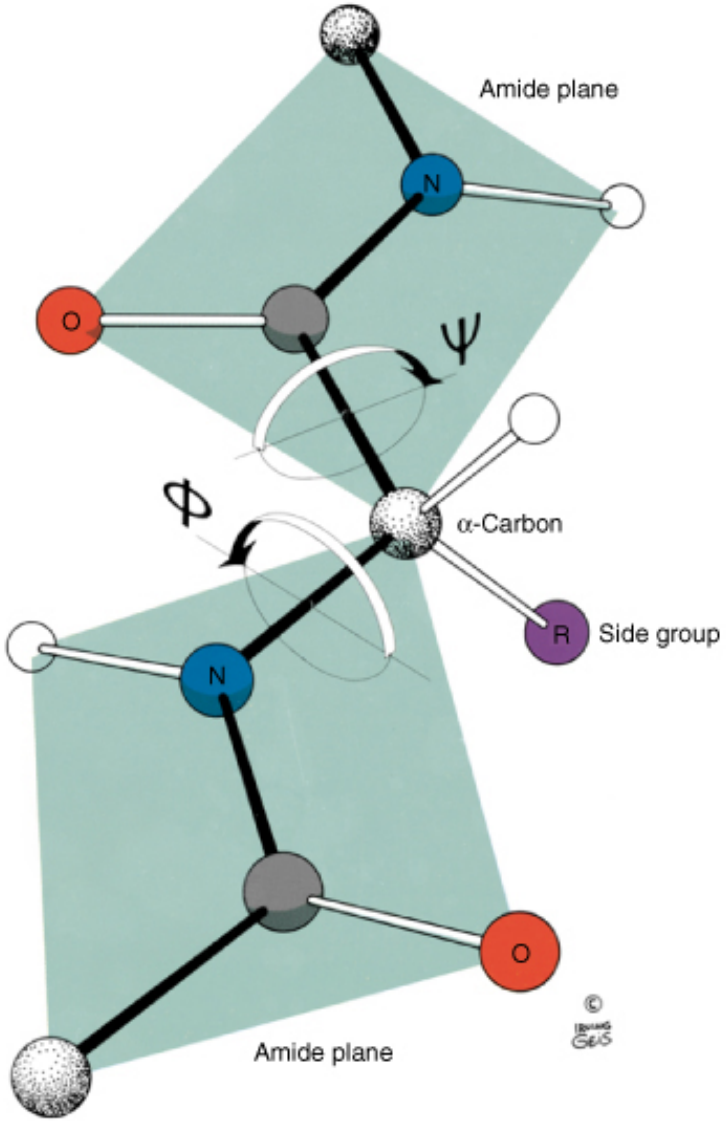


$C_3H_7NO_2 \rightarrow$ 13 atoms $\quad C_{11}H_{12}N_2O_2 \rightarrow$ 27 atoms

- Amino acids show different chemical properties depending on the specific atoms

PROTEINS

PEPTIDE BOND



- When connected together, amino acids can rotate along some bonds (Φ and Ψ angles).
- Rotation is rigid and the angles domains are continuous in nature.
- Some angles are forbidden because of atoms clashes

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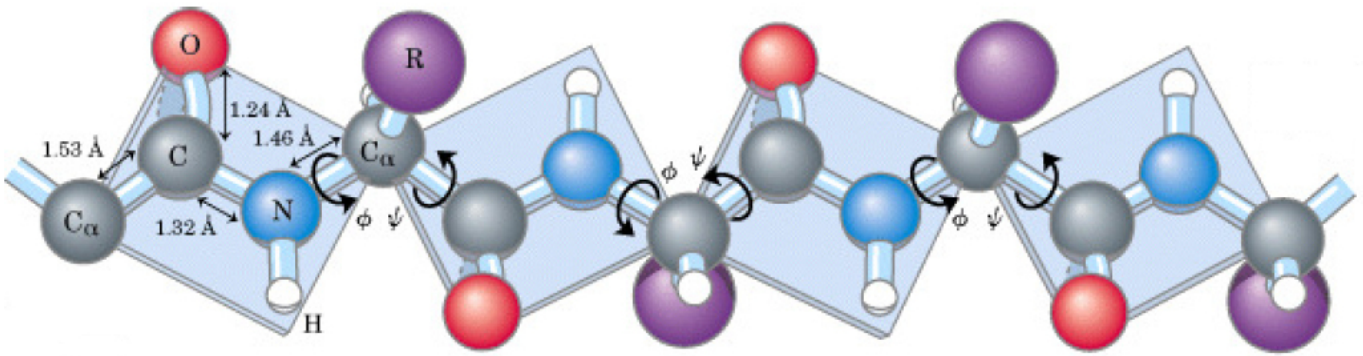
PROTEINS

BACKBONE

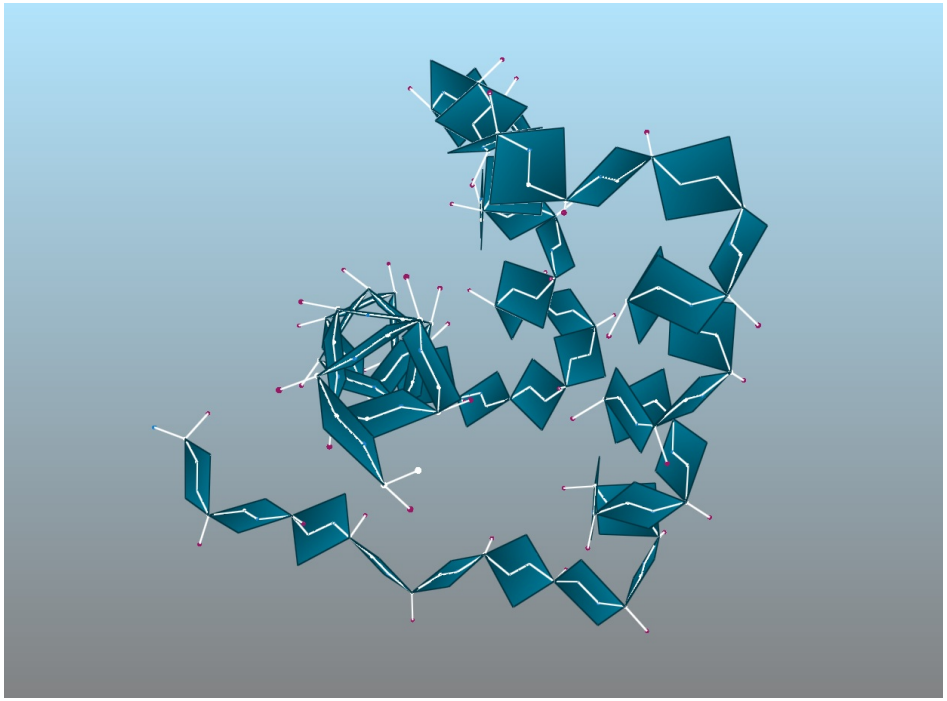
- Combining n amino acids gives at least $2n$ degrees of freedom molecule
- Constraints on angles *and* on atoms positions
- It can be modeled as an extension of a Self Avoiding Walk



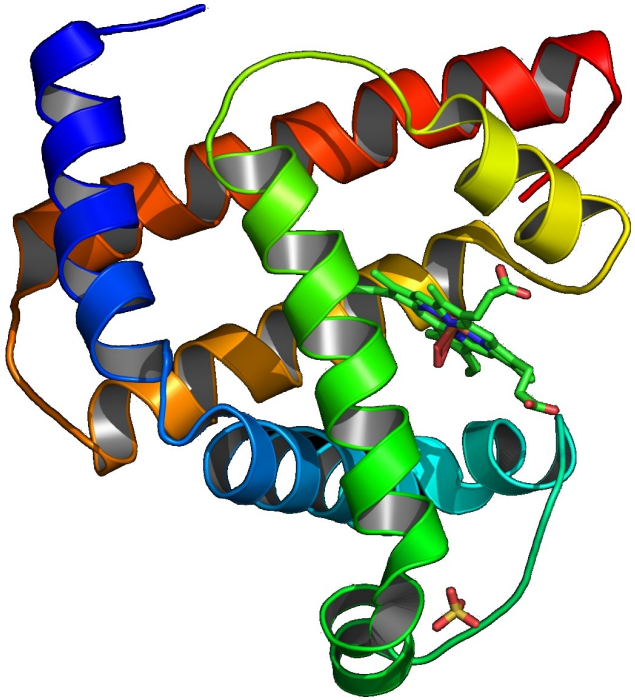
PROTEINS

TERTIARY STRUCTURE

Amino acid primary sequence:
GPEILCGAELVDALQFVCGDRGFYFNKPTGYGSSS...



planes...



... tertiary structure

- Proteins FOLD spontaneously into their functional pose

PROTEINS

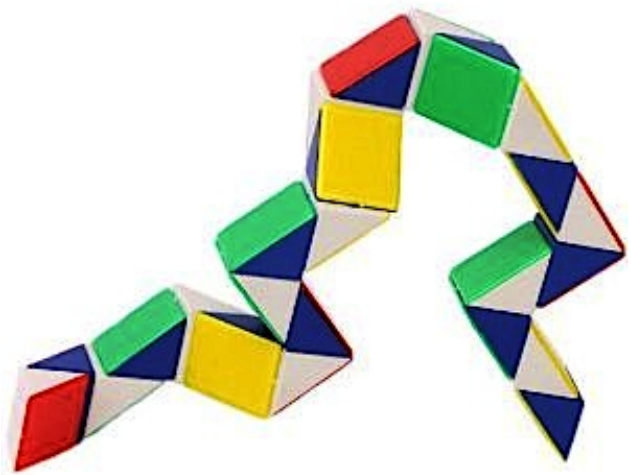
OUR CONTRIBUTION

- *Finite Domains* and *non linear* constraints model
- Goal: Fast geometrical exploration (independent of energy)
- Introduce *approximated propagators* for 3D points

PROTEINS

OUR MODEL

- Each torsional angle is associated to a discrete set of angles
- Chemists are happy with a large set ($\sim$ 100 sampled rotations per bond)
- Combinatorial explosion: 100^{2n}

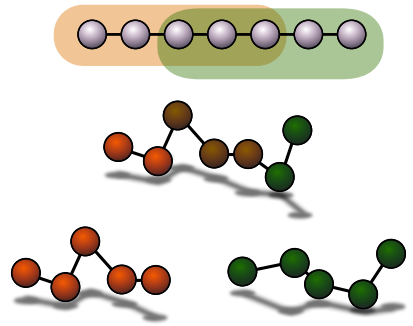


A simple instance of discretized angles

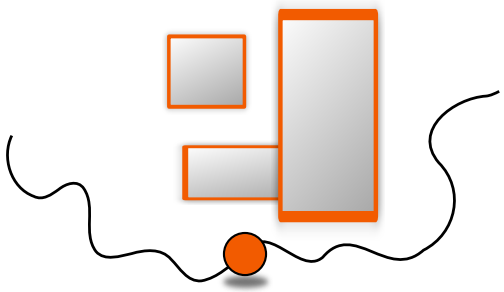
PROTEINS

CONSTRAINTS

1. Backbone structural constraints

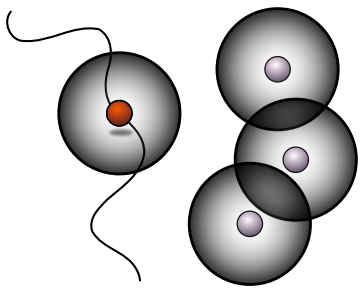


2. Amino acids local relationships



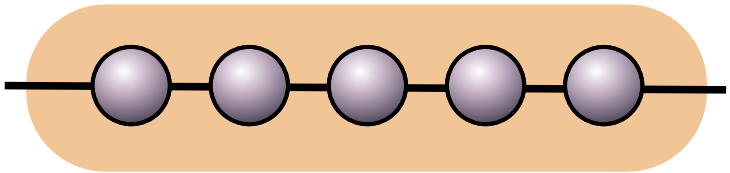
3. Spatial positions of atoms

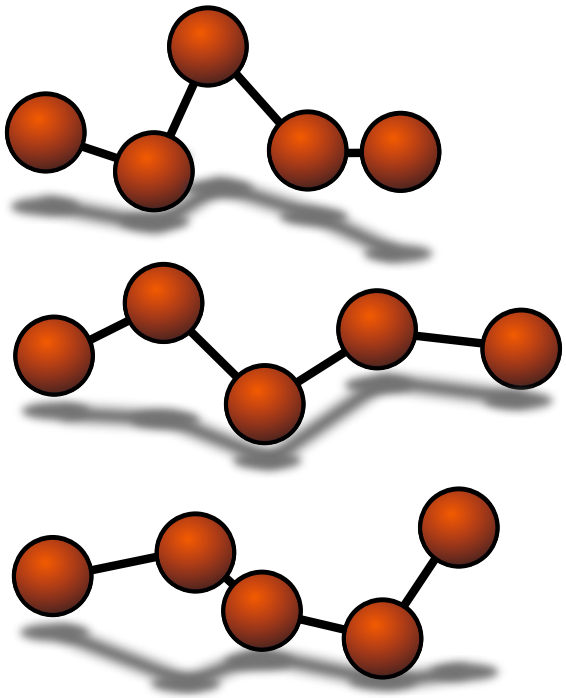
4. Non overlap of atoms



CONSTRAINTS

FRAGMENTS AND BODY





- Local structural behavior $\Rightarrow$ fragments
- A set of fragments (Body) is a *local spatial dictionary*

FRAGMENTS

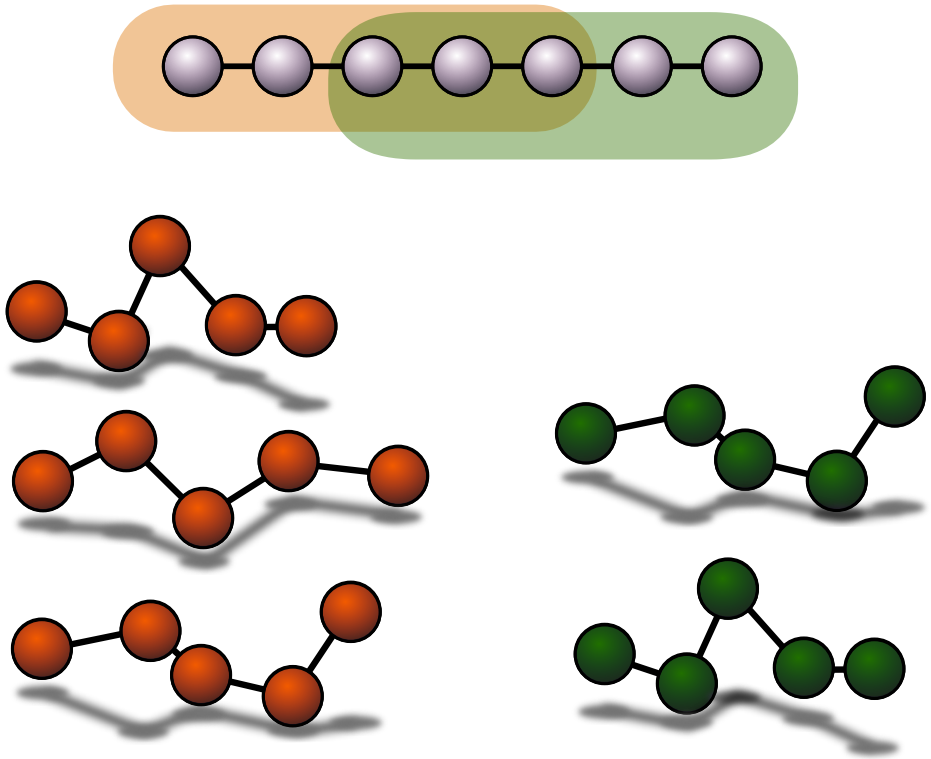
BODY

- Body = FD variable, Fragments = Domain
- A body can be associated to 1 .. n amino acids
- It can be seen as a constraint over Φ and Ψ angles
- It is similar to a `table` constraint over angles
- It affects 3D positions of atoms

FRAGMENT ASSEMBLY MODEL

BODY COMBINATION

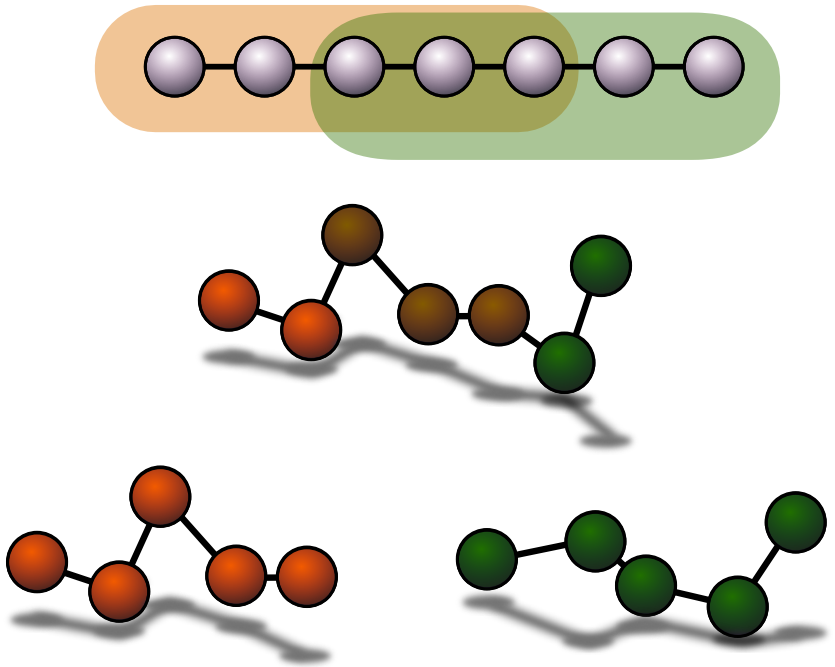
Example of domains for two overlapping bodies



FRAGMENT ASSEMBLY MODEL

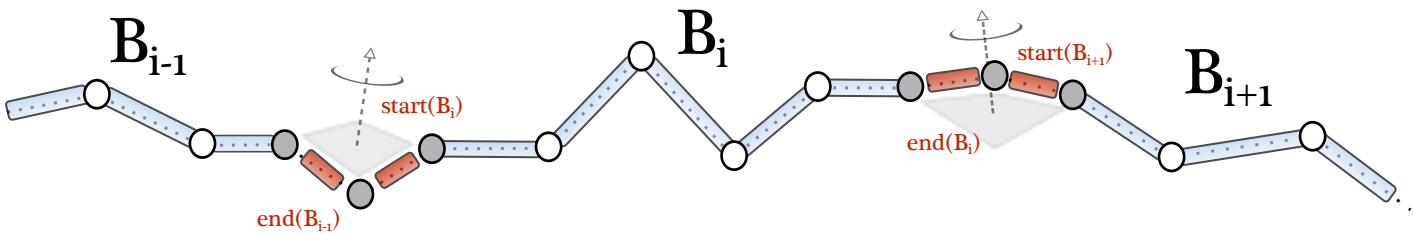
BODY COMBINATION

Constrain two selected fragments:
they must overlap in the space at anchors



MULTIBODY

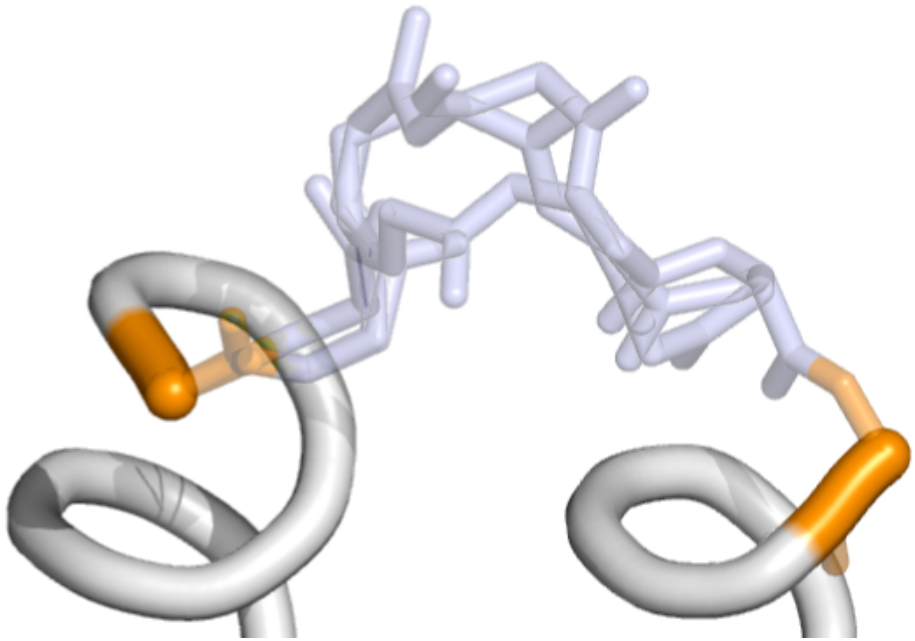
- A Multibody is a set of Bodies that covers a protein
- The protein is partitioned into Bodies that overlap at the anchors



MULTIBODY

MORE CONSTRAINTS

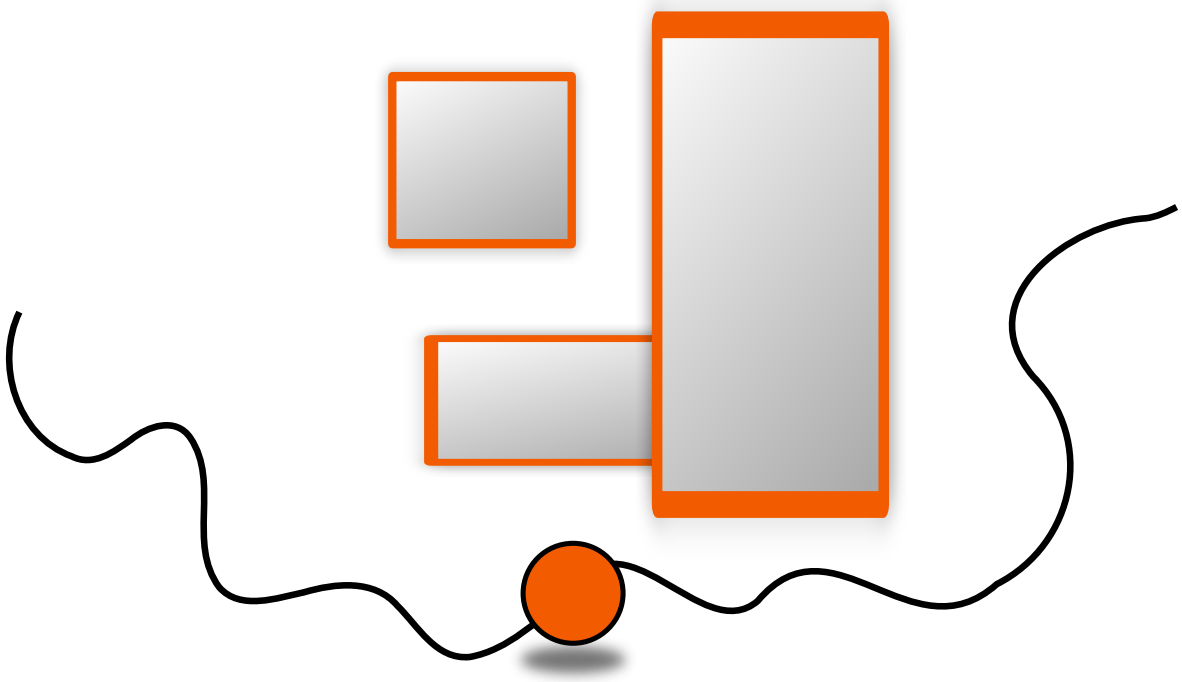
- Restricted spatial positions for some anchors
- Convenient modelling of accurate mobility (eg. loops, flexibility, ligand interactions, typical subunits arrangements)



MULTIBODY

SPATIAL CONSTRAINTS

Each atom can be constrained to a specific region



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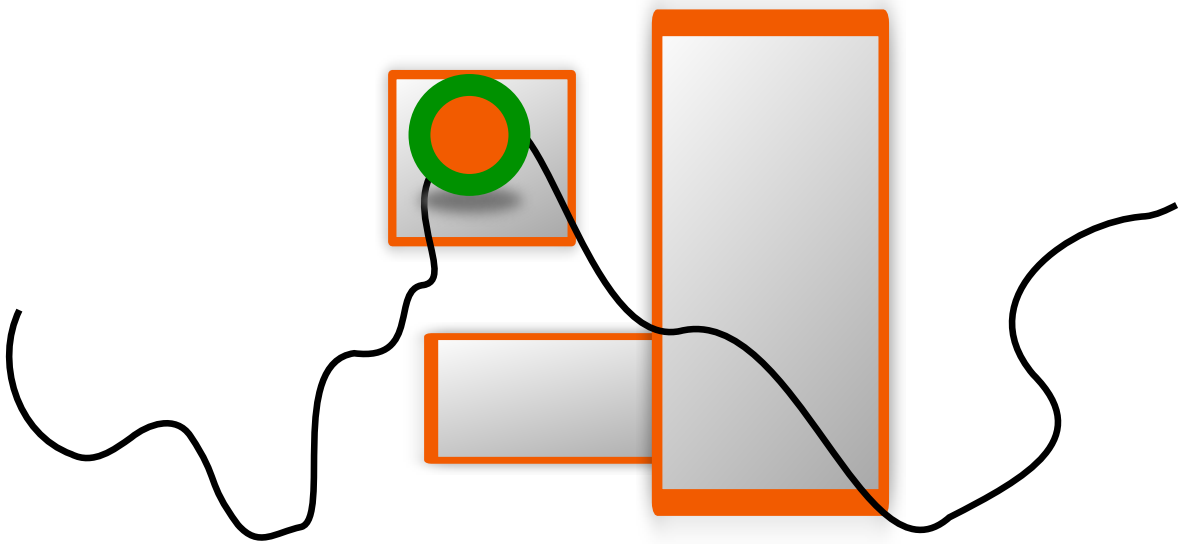

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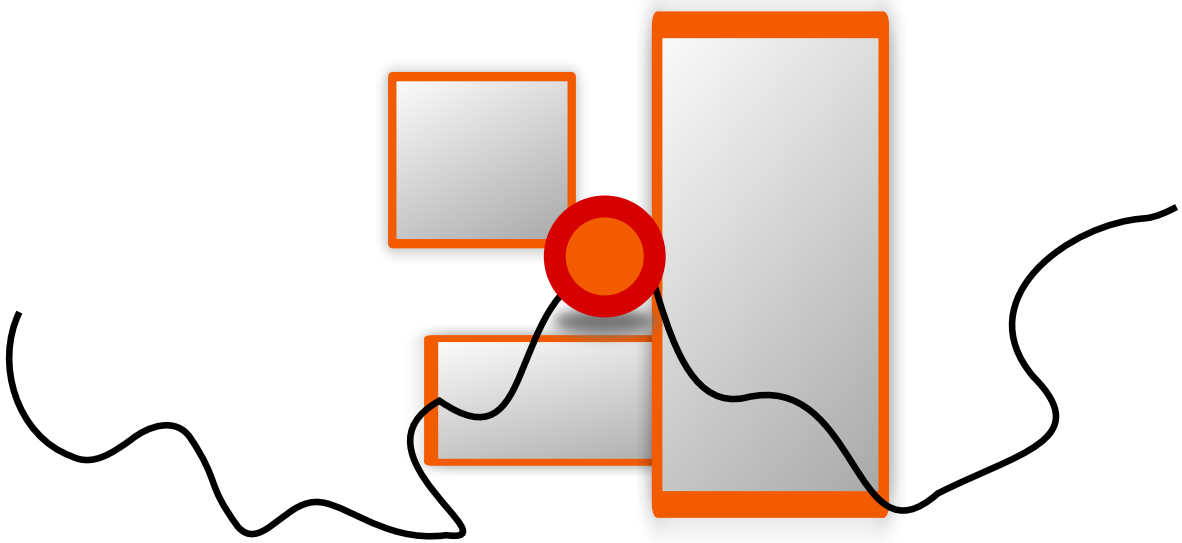
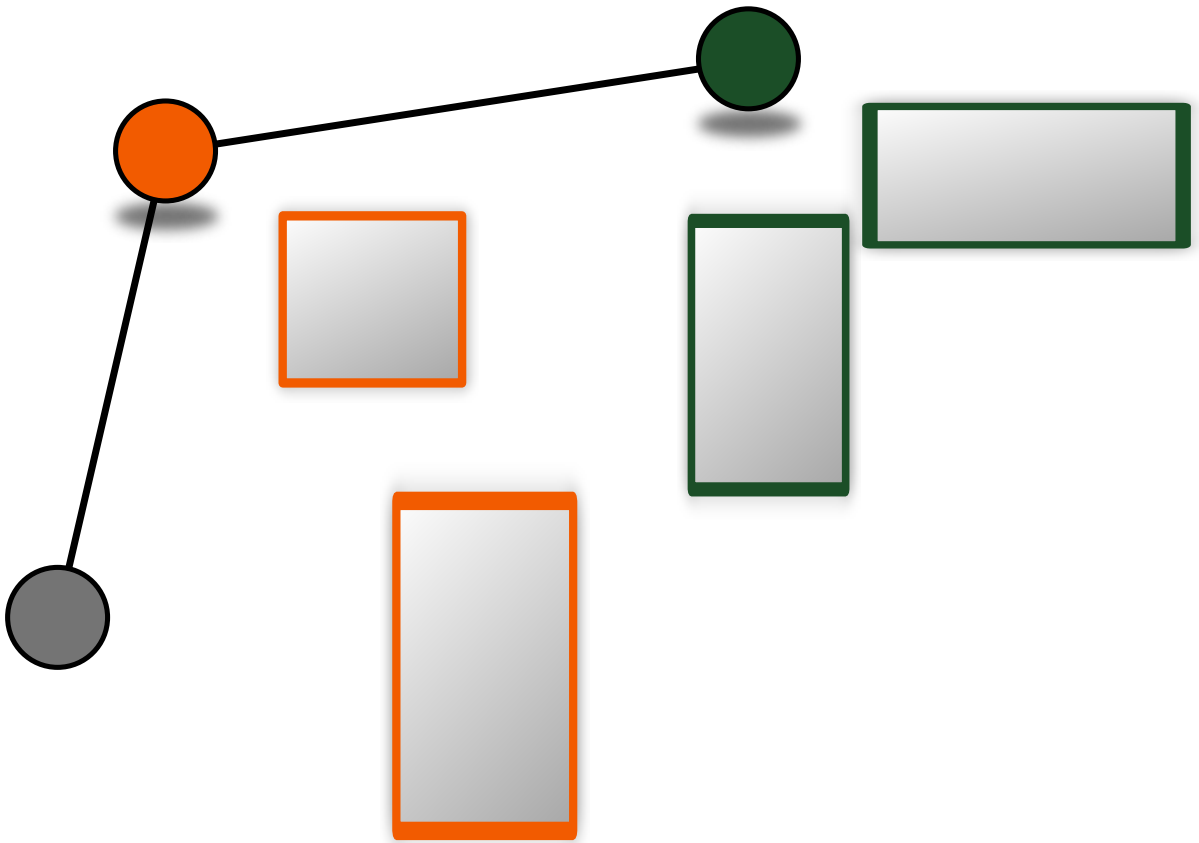


MULTIBODY

SPATIAL CONSTRAINTS

Spatial constraints on different atoms may interact through fragments



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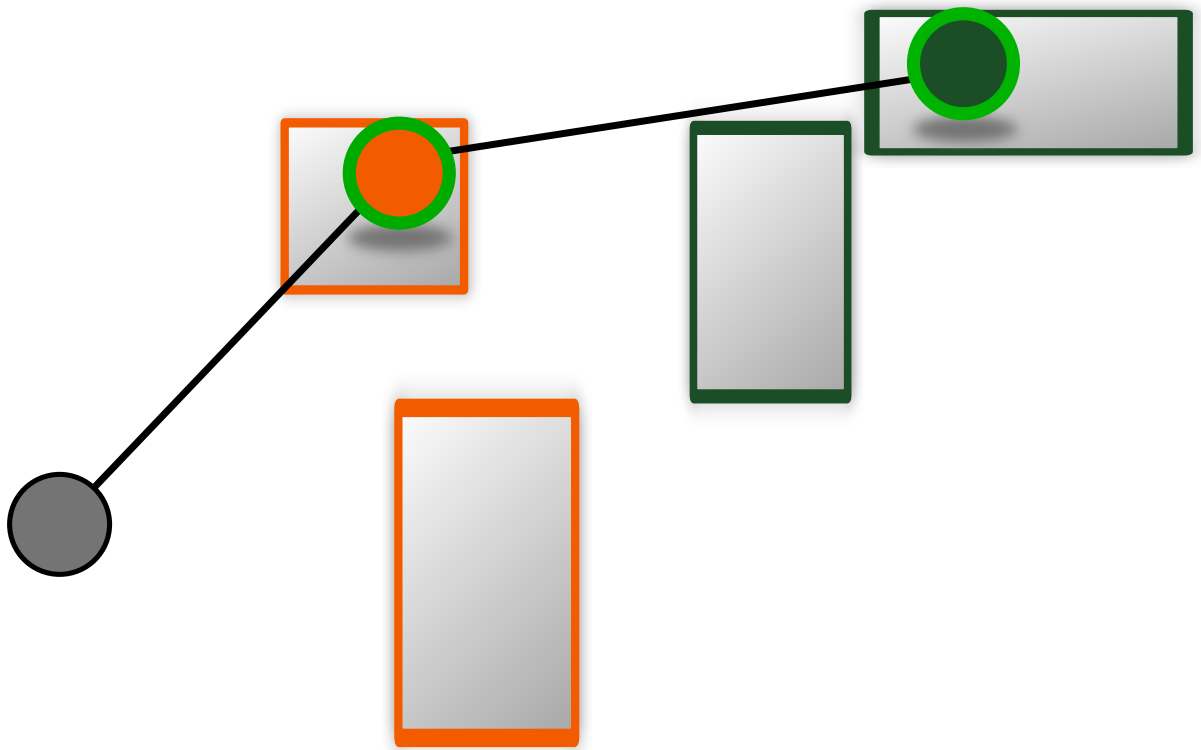

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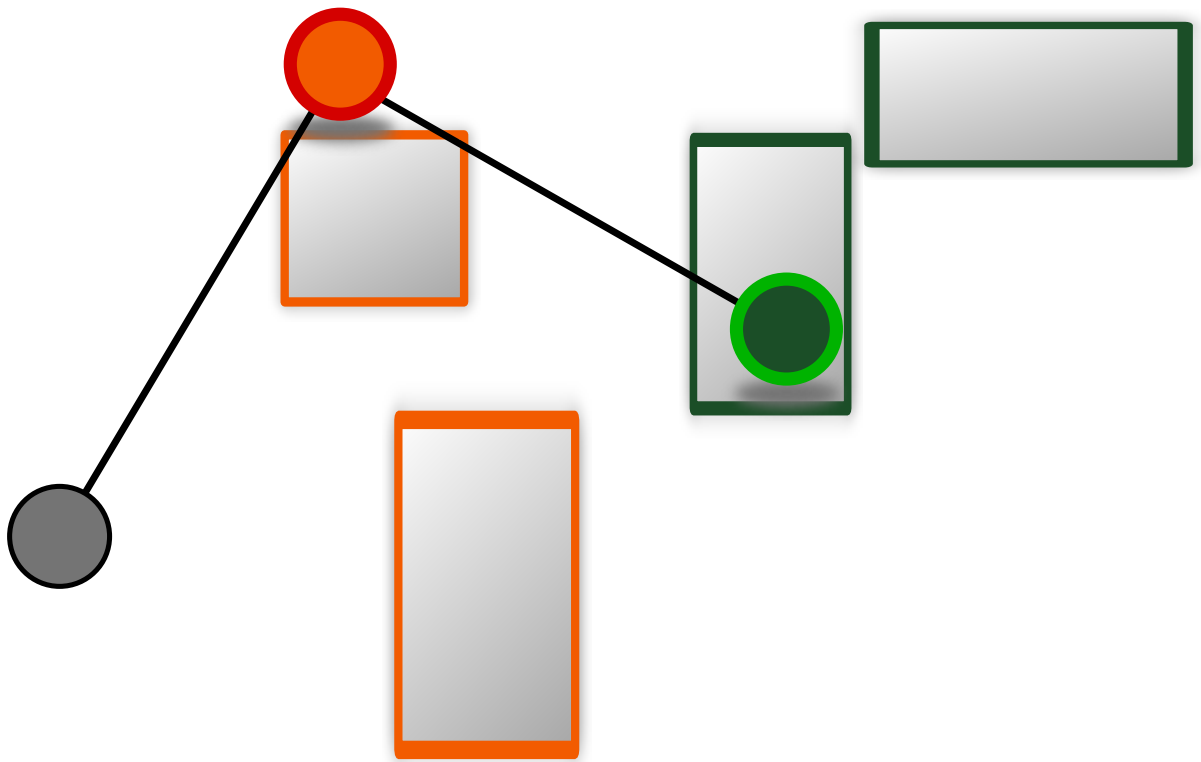
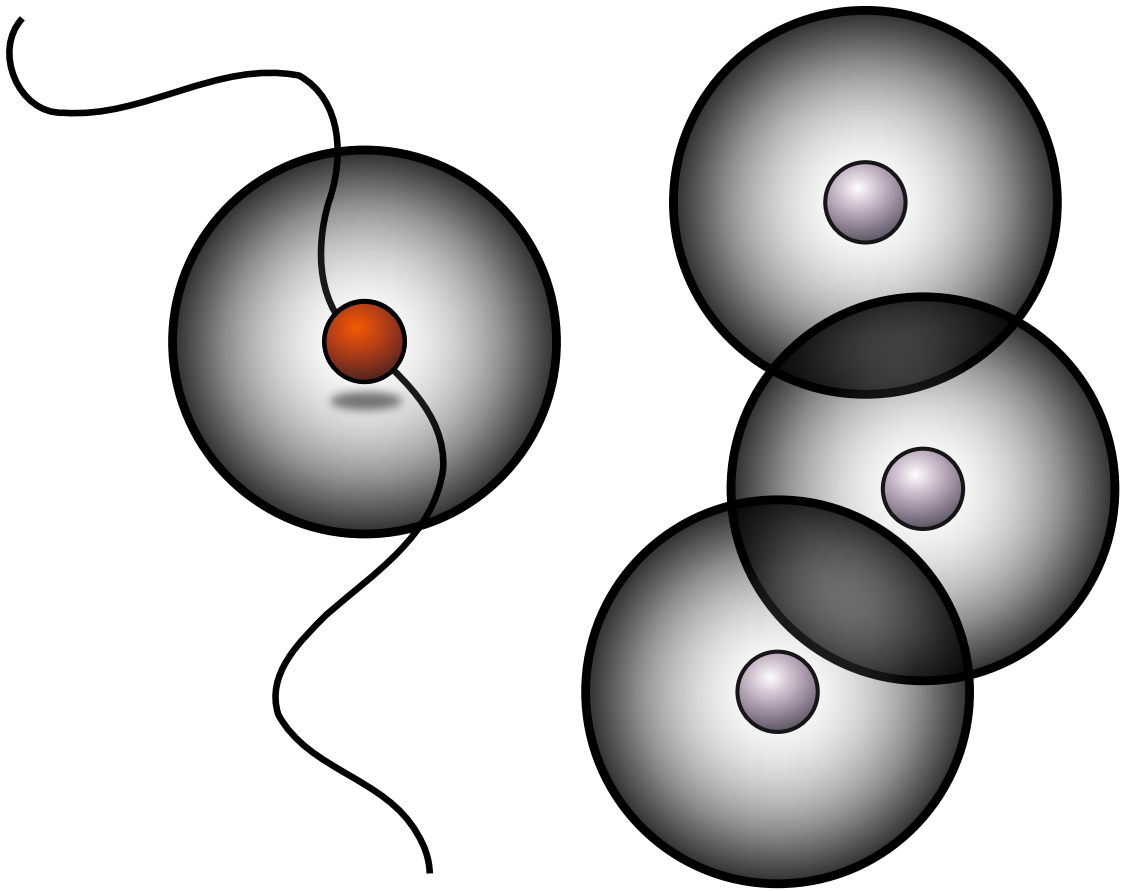


MULTIBODY

DISTANCE CONSTRAINTS

Minimal distance between pairs of atoms



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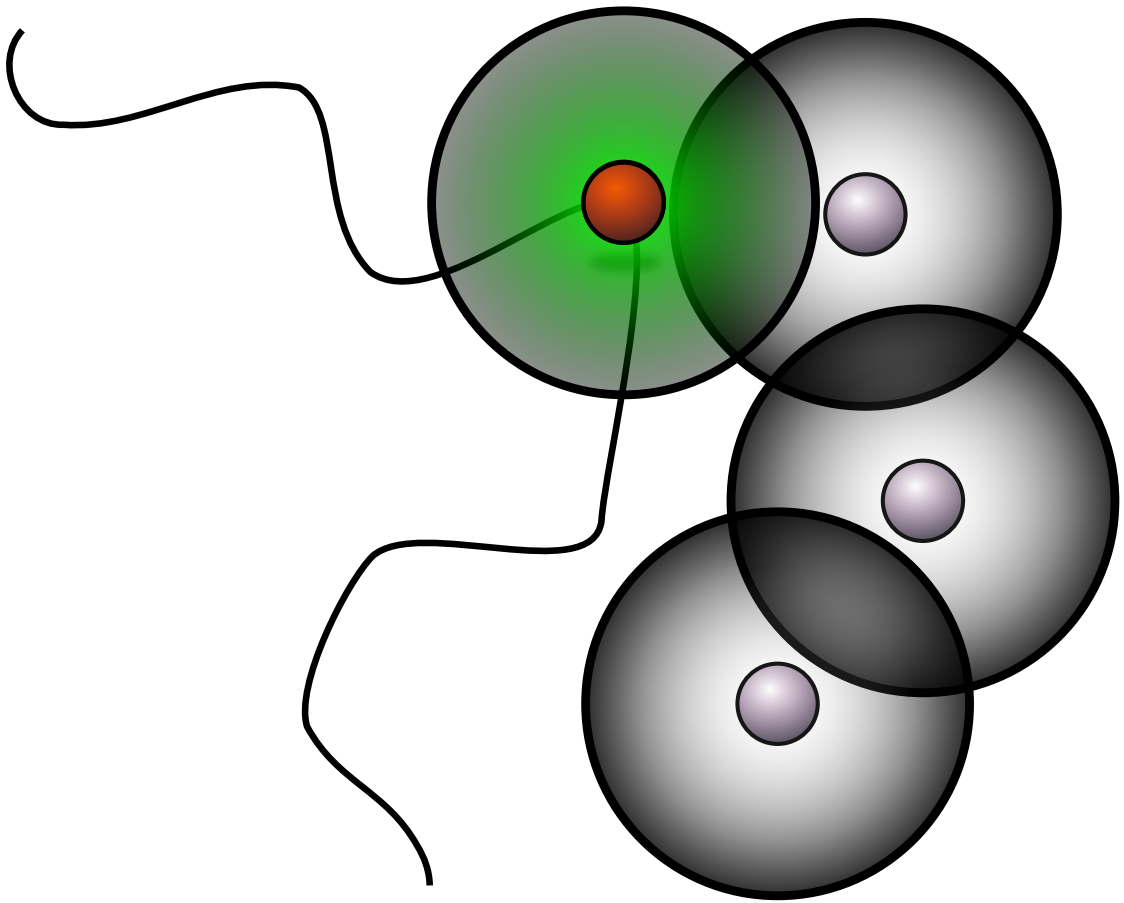

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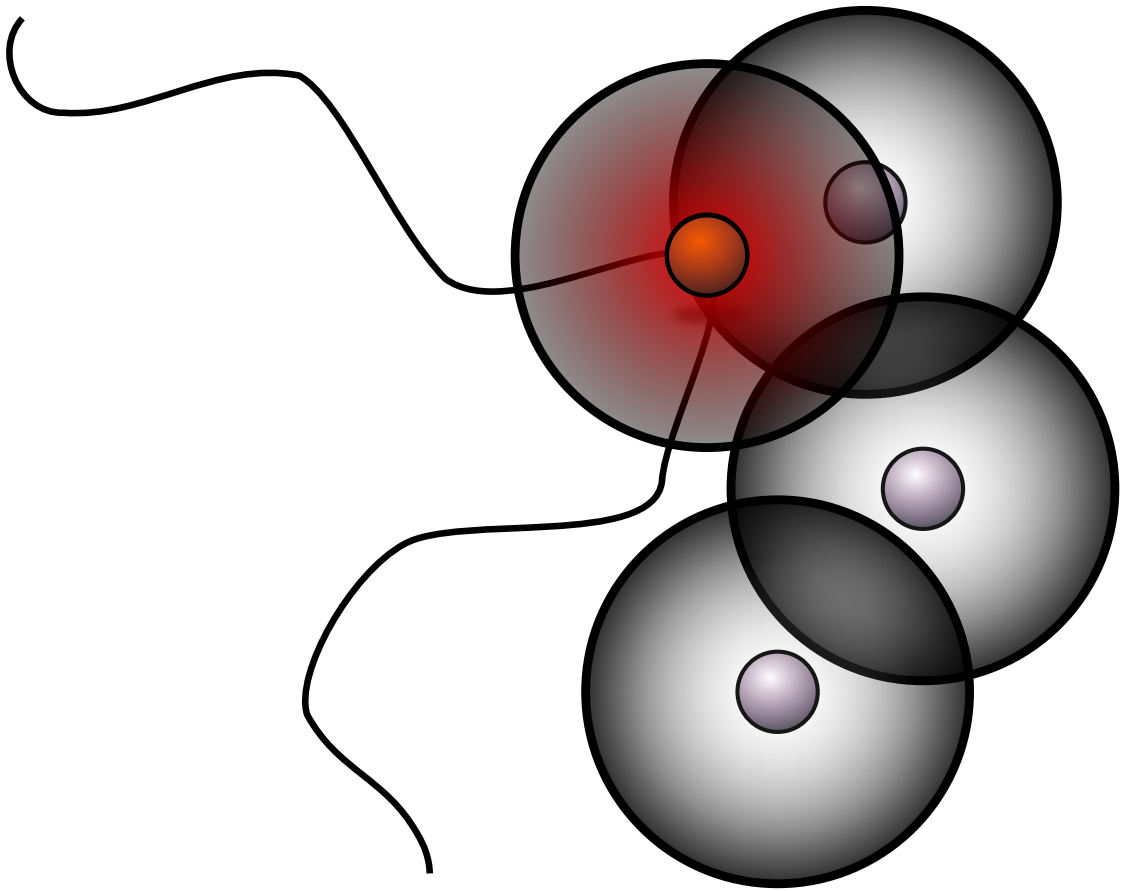
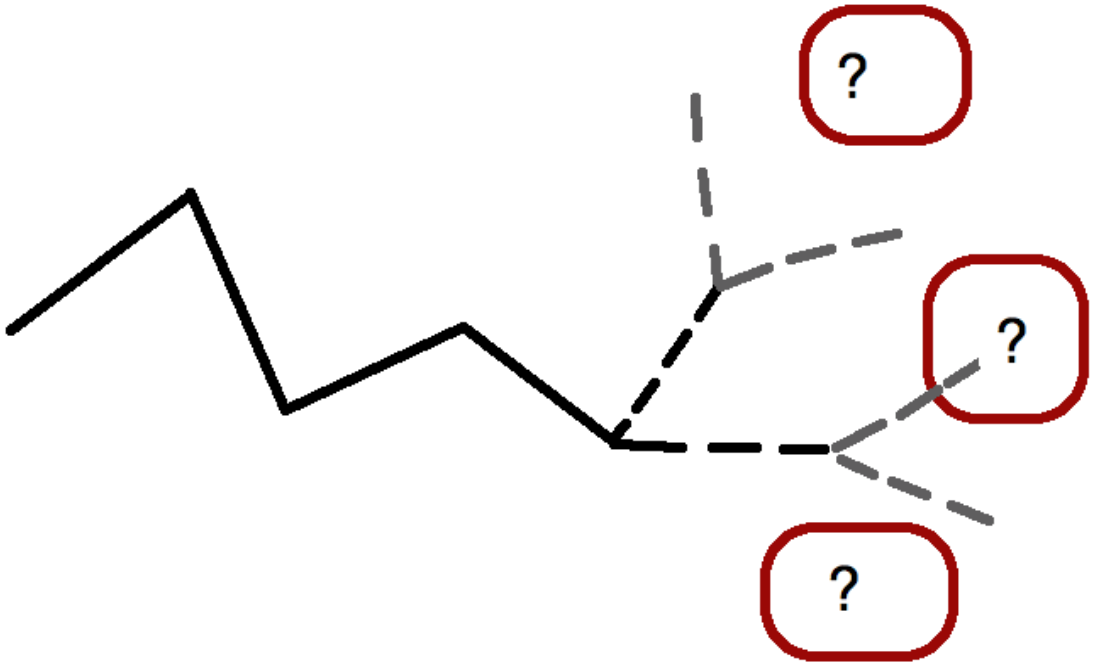


THE JOINED-MULTIBODY (JM) CONSTRAINT

INTUITION

- Given a set of fragments for each body
- Given a set of admissible atom volumes
- Given a minimal inter-atomic distance
- We want to identify the fragments combinations that satisfy all the constraints



THE JOINED-MULTIBODY (JM) CONSTRAINT

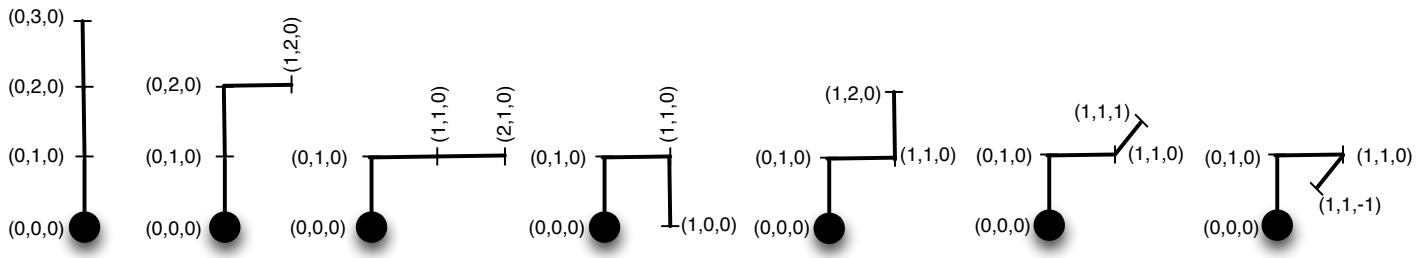
COMPLEXITY

THEOREM

The problem of determining consistency of JM constraints (i.e., the existence of a solution) is NP-complete.

PROOF.

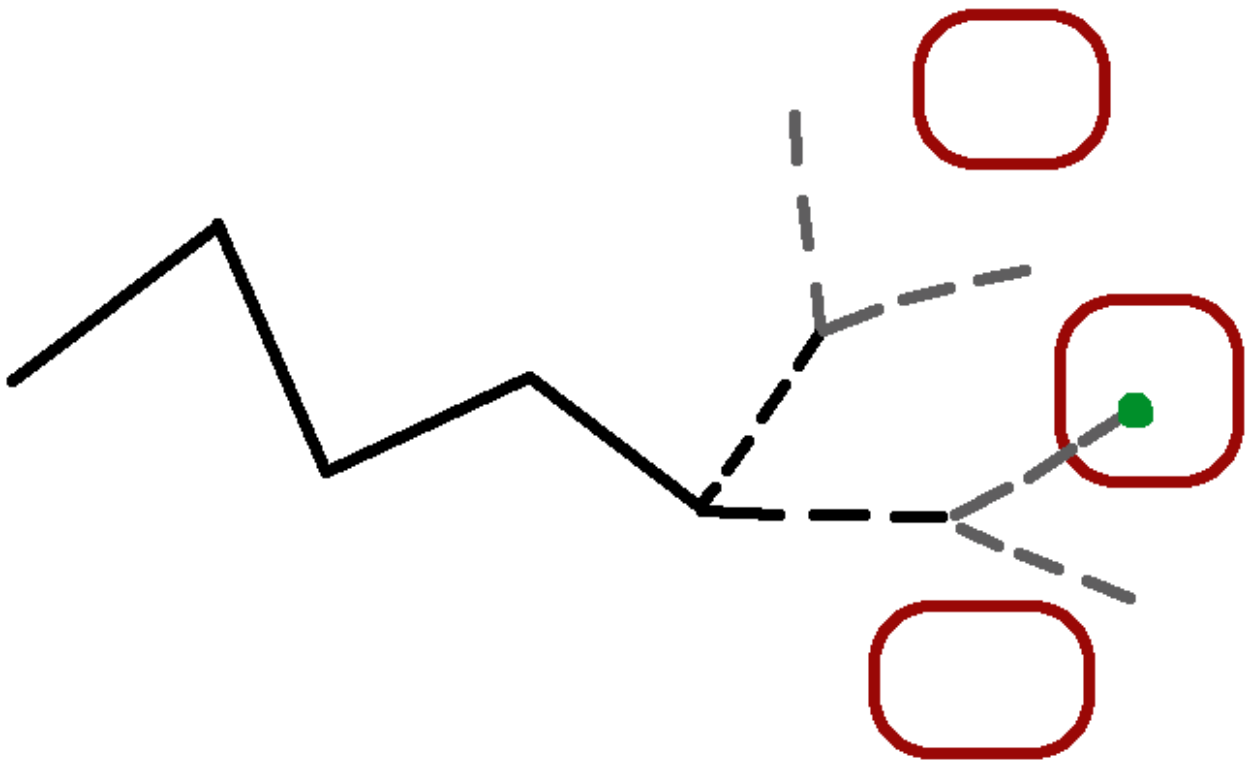
Sketch: reduction from Self Avoiding Walk on 3D cubic lattices. Idea: create a set of discrete fragments and force them on a lattice. □



FILTERING ALGORITHM

APPROXIMATED POLYNOMIAL TIME ALGORITHM

- Identify those fragments in each body that are of no support
  1. Need a fast approximation of reachable volumes
  2. Intersect it with JM spatial domains
  3. Filter non supported fragments



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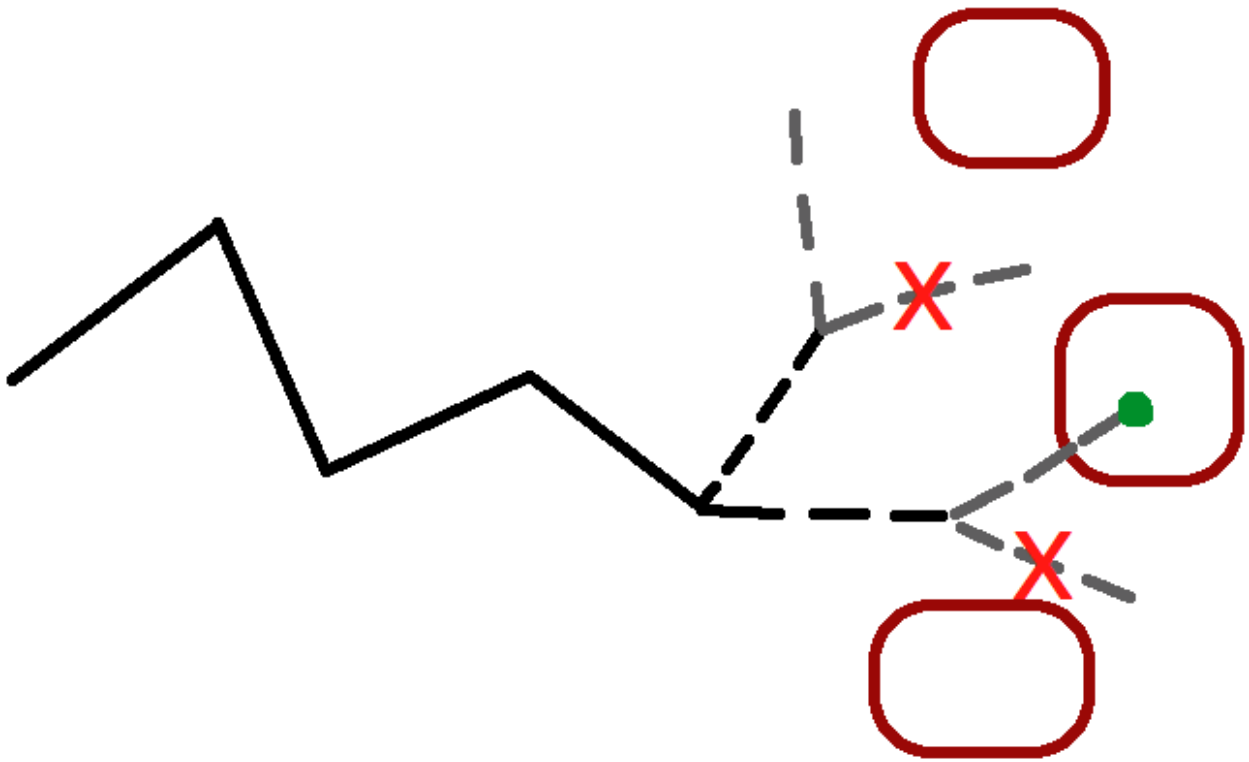

FILTERING ALGORITHM

BOUNDS CONSISTENCY?

- Compute spatial bounding box for end points of assembled bodies
- Simple bounds consistency degenerates into a large box
- The bounds degenerate immediately

ALMOST NO FILTERING

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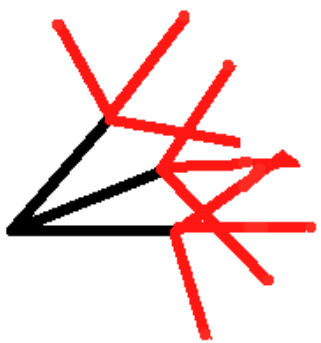

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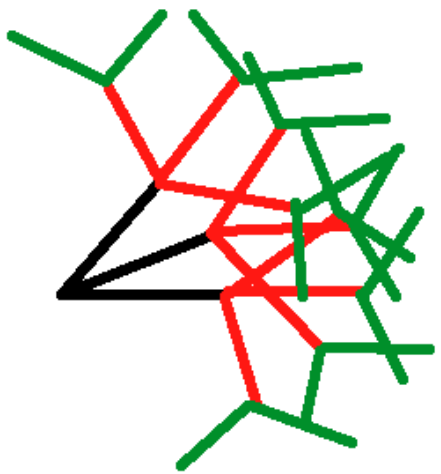

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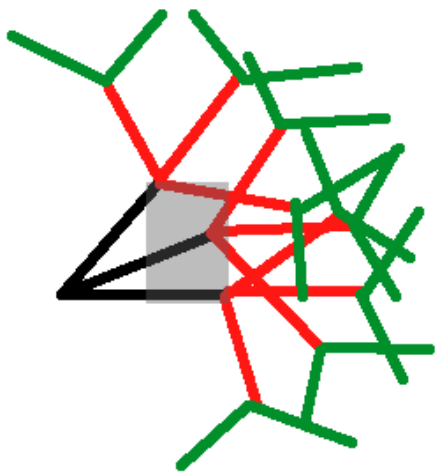

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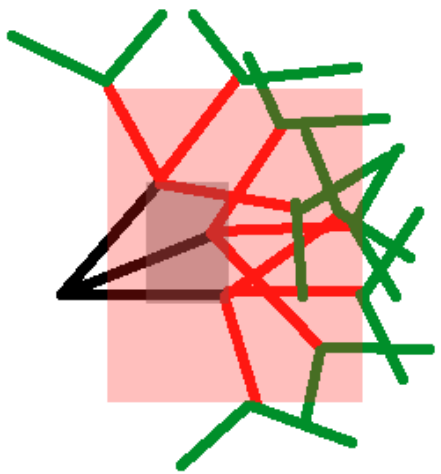

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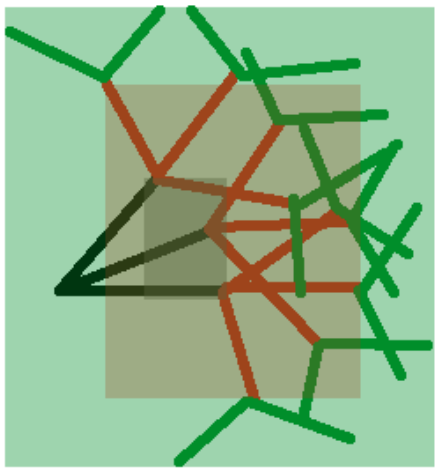
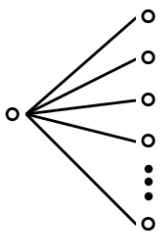


FILTERING ALGORITHM

CLUSTERING: MORE ACCURATE DESCRIPTION

- Clustering both in space and angle
- Each fragment in a body is assembled and clustered
- Number of clusters and errors are controlled
- Balance between simple bounds consistency and complete explosion
- Clusters are intersected with JM spatial domains



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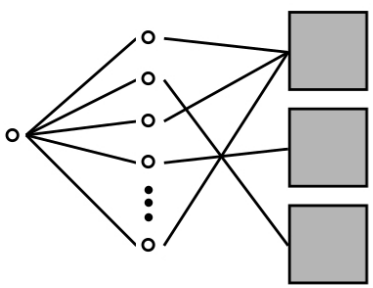

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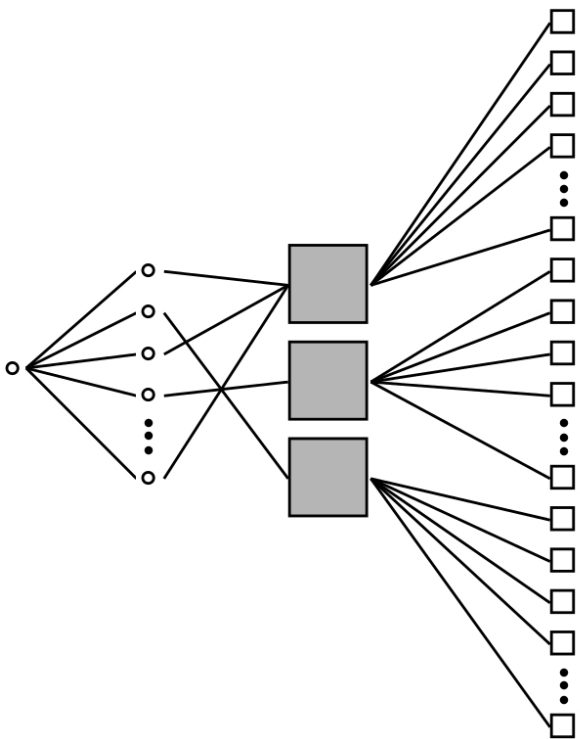

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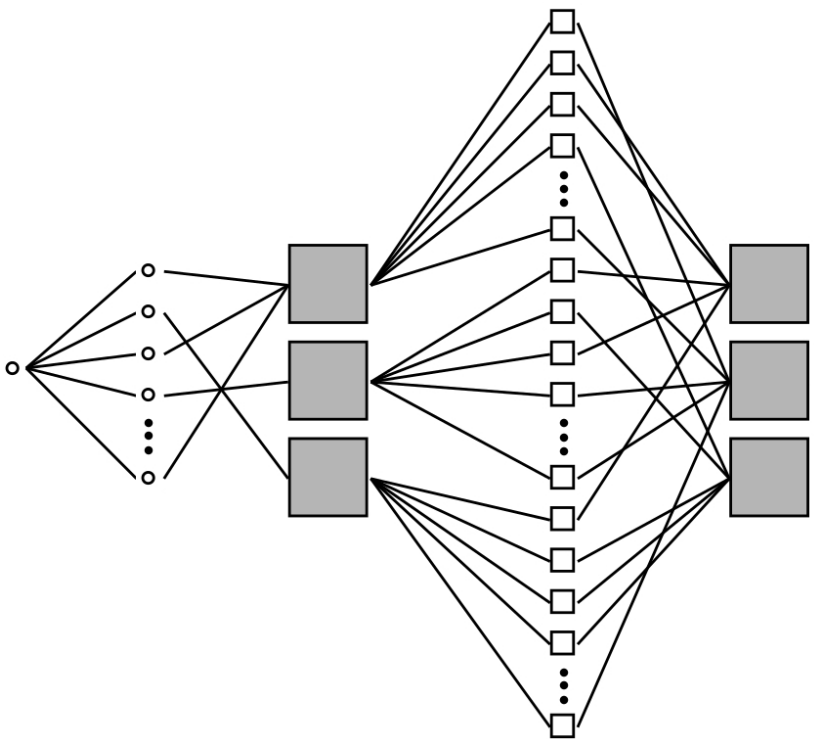

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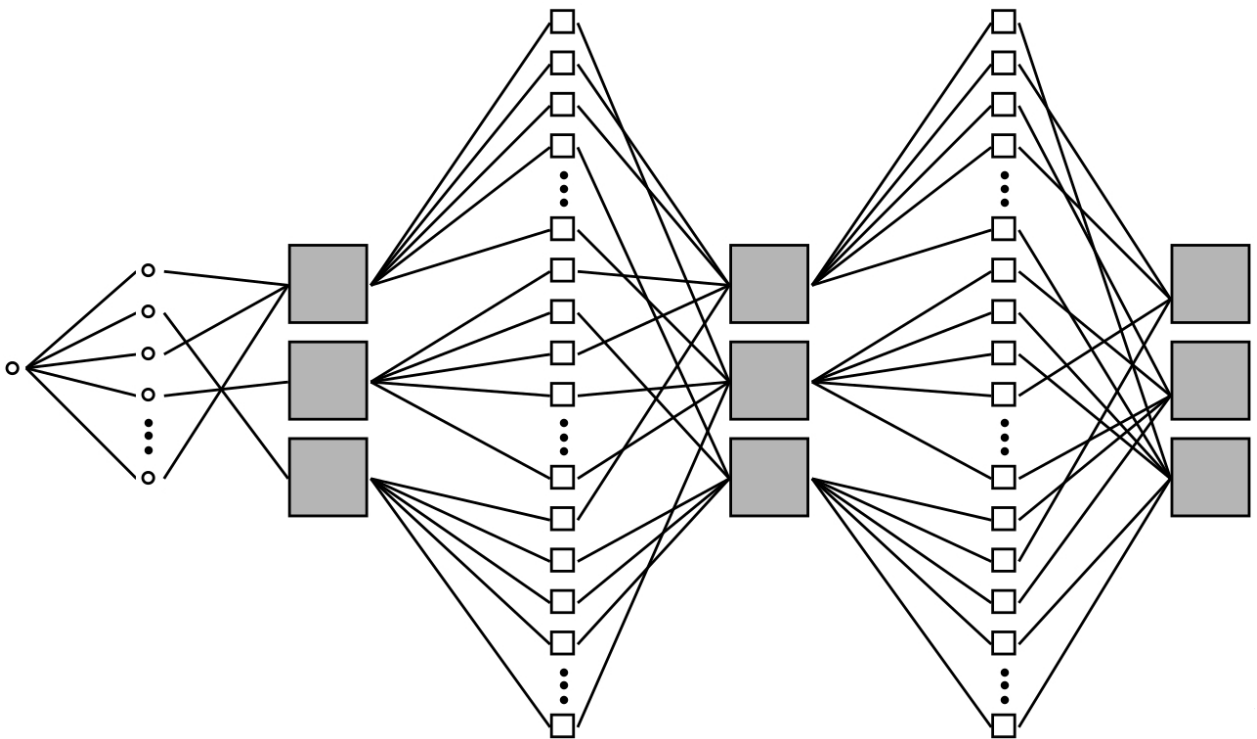
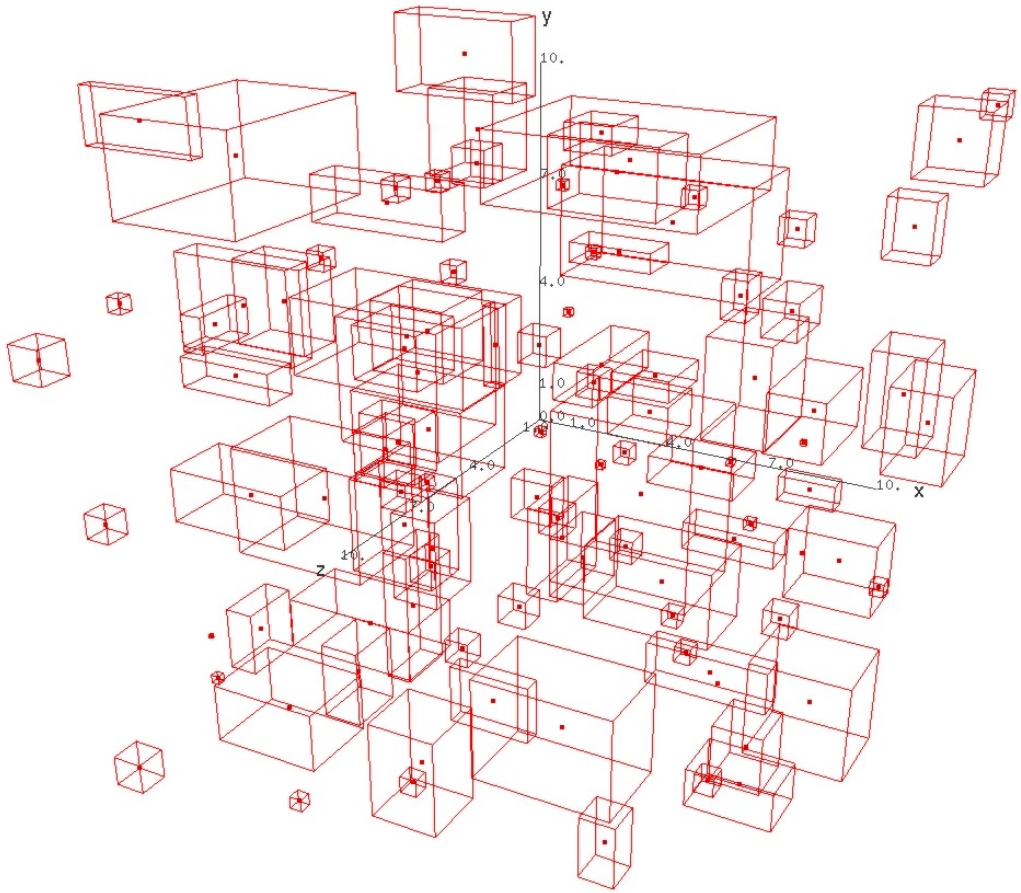


FILTERING ALGORITHM

APPROXIMATED POLYNOMIAL TIME ALGORITHM

- Example of 3D clusters for a JM with a few bodies



FILTERING ALGORITHM

APPROXIMATED POLYNOMIAL TIME ALGORITHM

- Each cluster contains similar fragments
- Select a representative for each cluster
- Filter out non representatives (controlled error)
- Keep significantly different arrangements
- It can be seen as approximated direct kinematics

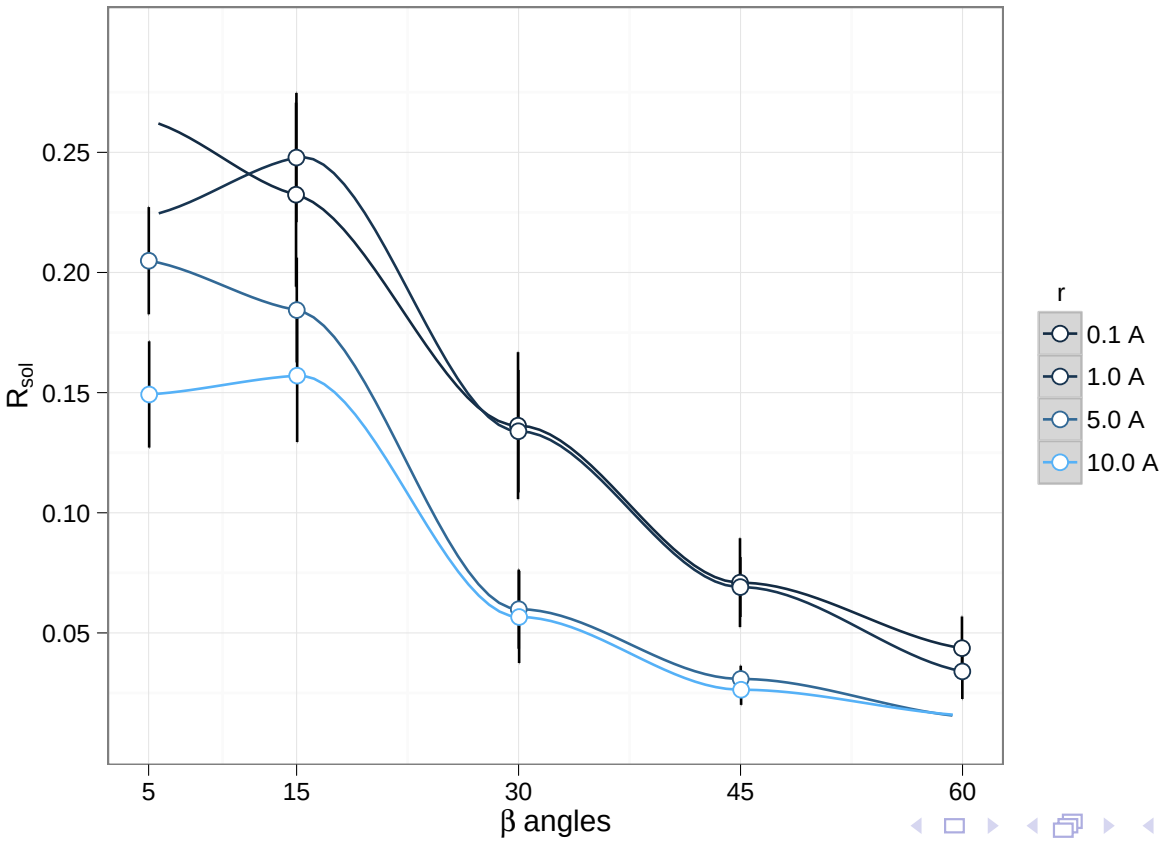
EXPERIMENTS

- We implemented the JM propagator in FIASCO (Fragment-based Interactive Assembly for protein Structure prediction with COnstraints)
- C++ constraint solver
- Host: Linux Intel Core i7 860, 2.5 GHz, 8 GB

EXPERIMENTS

SEARCH SPACE EXPLORED

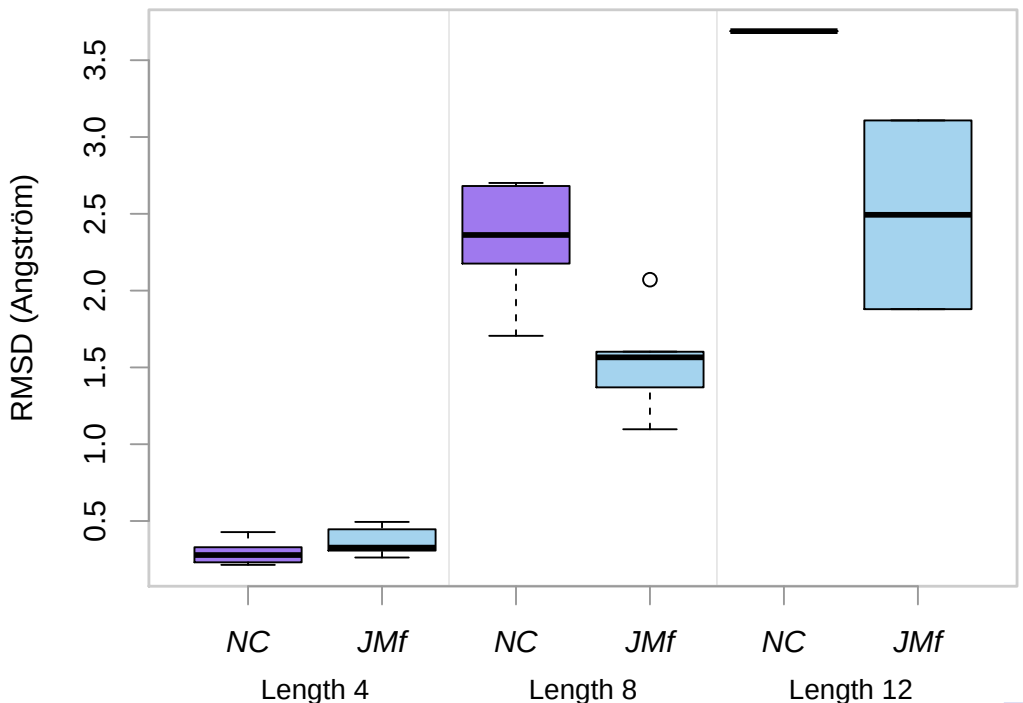
- Loop length 4, 60 fragments per amino acid, at most 100 clusters per anchor
- JM filtered solutions vs unconstrained solutions
- Increasing space and angle clusters size, $\Rightarrow$ less solutions



EXPERIMENTS

QUALITY OF FILTERED SOLUTIONS

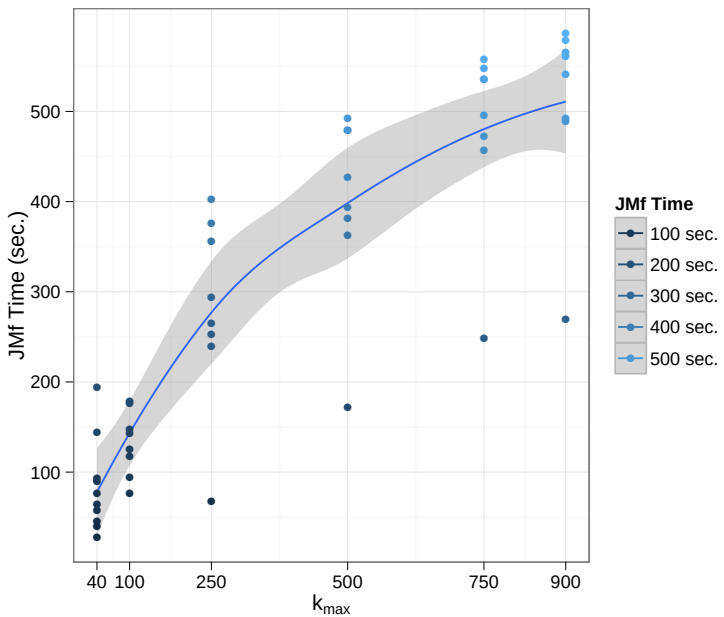
- Can you guarantee that filtered solutions do not deviate from optimal?
- Length 4: 1.0 Å and 15°; Length 8,12: 2.5 Å and 60°
- Comparing best RMSD from original found

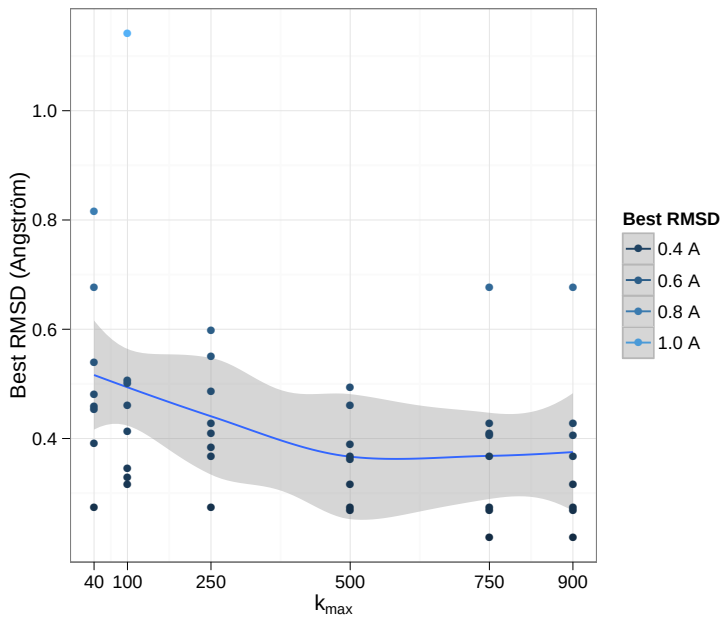


EXPERIMENTS

QUALITY VS EFFICIENCY

- Number of clusters affects quality and computational times
- Clusters features: 1.0 Å and 30°
- After 500 clusters no relevant benefits





EXPERIMENTS

LOOP PREDICTOR COMPARISON

- We compared our tool against other 3 popular predictors
- We used a general fragment database
- Our results are on the same order of magnitude

Loop Length	**Average RMSD**			
	CCD	SOS	FALCm	JMf
4	0.56	0.20	0.22	0.30
8	1.59	1.19	0.72	1.31
12	3.05	2.25	1.81	1.97

CONCLUSIONS

The paper contains:

- Novel constraint to model rigid bodies with degrees of freedom
- NP-completeness proof
- Approximated propagator (directional)
- Experimental validation

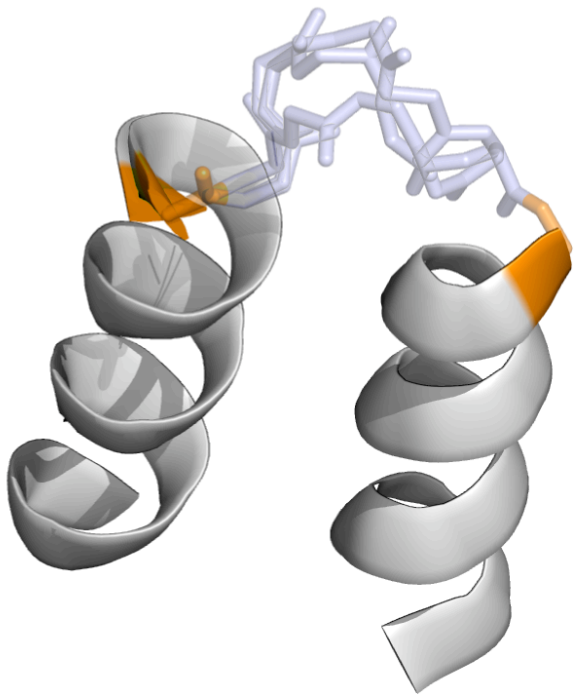
Future work:

- Bidirectional propagator
- Loop fragment databases
- Uniform spatial conformation sampling based on JM
- Interactive feedback (FIASCO GUI)

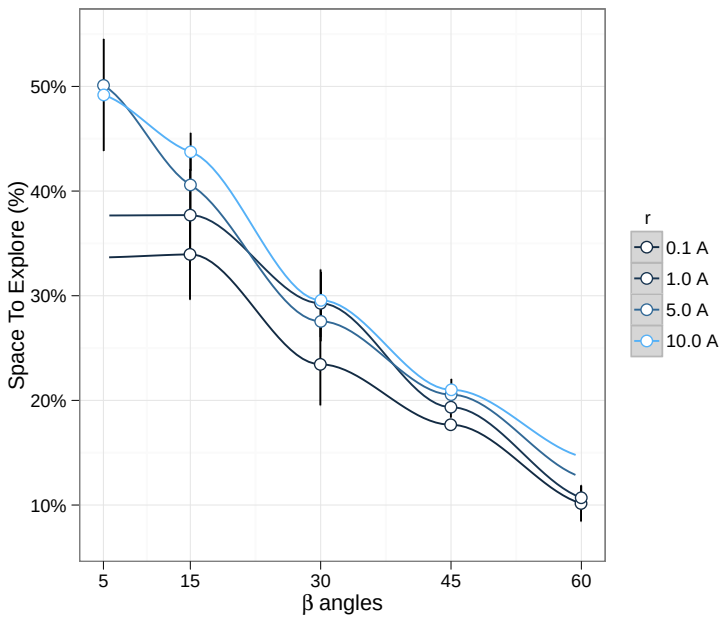
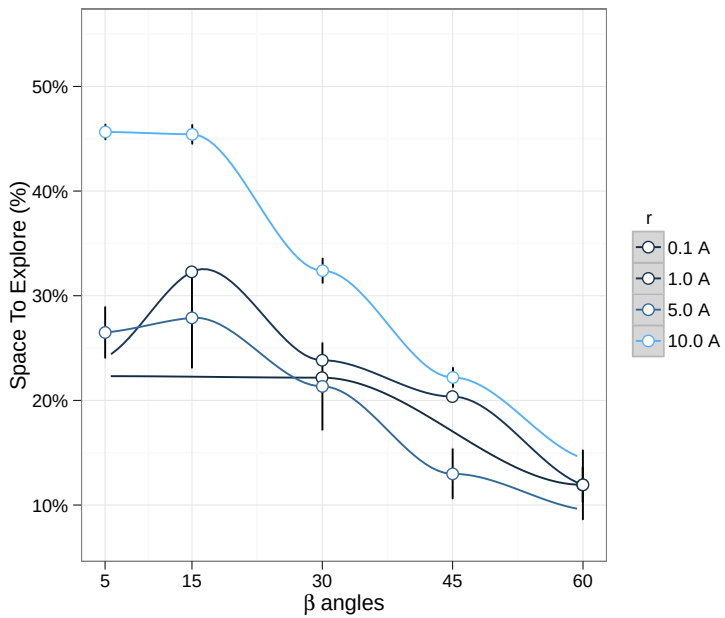
CONCLUSIONS

Thank you!

Please visit `www.cs.nmsu.edu/fiasco/`



EXPERIMENTS

SEARCH SPACE EXPLORED

- Larger loops length (8 and 12), can't do exhaustive search
- Lower bound to the filtering ratio