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## ► To cite this version:

Antoine Moniot, Isaure Chauvot de Beauchêne, Yann Guermeur. Agglomerative clustering of fragment 3D structures based on pairwise RMSD. ISMB ECCB 2021, Jul 2021, Virtual, France. hal-03432682

**HAL Id: hal-03432682**

**<https://hal.science/hal-03432682>**

Submitted on 17 Nov 2021

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# Agglomerative clustering of fragment 3D structures based on pairwise RMSD



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## Introduction:

In structural biology, fragment-based 3D modeling methods make use of fragment libraries. The library associated with one fragment represents the whole set of possible 3D structures (conformations) that it can adopt (with a chosen precision). Given the computational constraints, deriving libraries of minimal cardinality appears as a strong requirement. This amounts to deriving  $\varepsilon$ -nets whose cardinalities are as close as possible to the corresponding *covering numbers*. A heuristic to derive such  $\varepsilon$ -nets is to cluster the observed conformations under appropriate constraints, and keep only the *representatives/prototypes*. In the framework of interest, the main difficulty encountered is to implement the clustering with the **RMSD** as dissimilarity measure. Indeed, the computation of this measure follows a superimposition, the nature of which has both biological and mathematical consequences.

We introduce such a method as a variant of the Hierarchical Agglomerative Clustering (HAC) algorithm. Compared to HAC, it makes it possible to reduce the number of prototypes, while maintaining an acceptable computation time.

## Algorithm:

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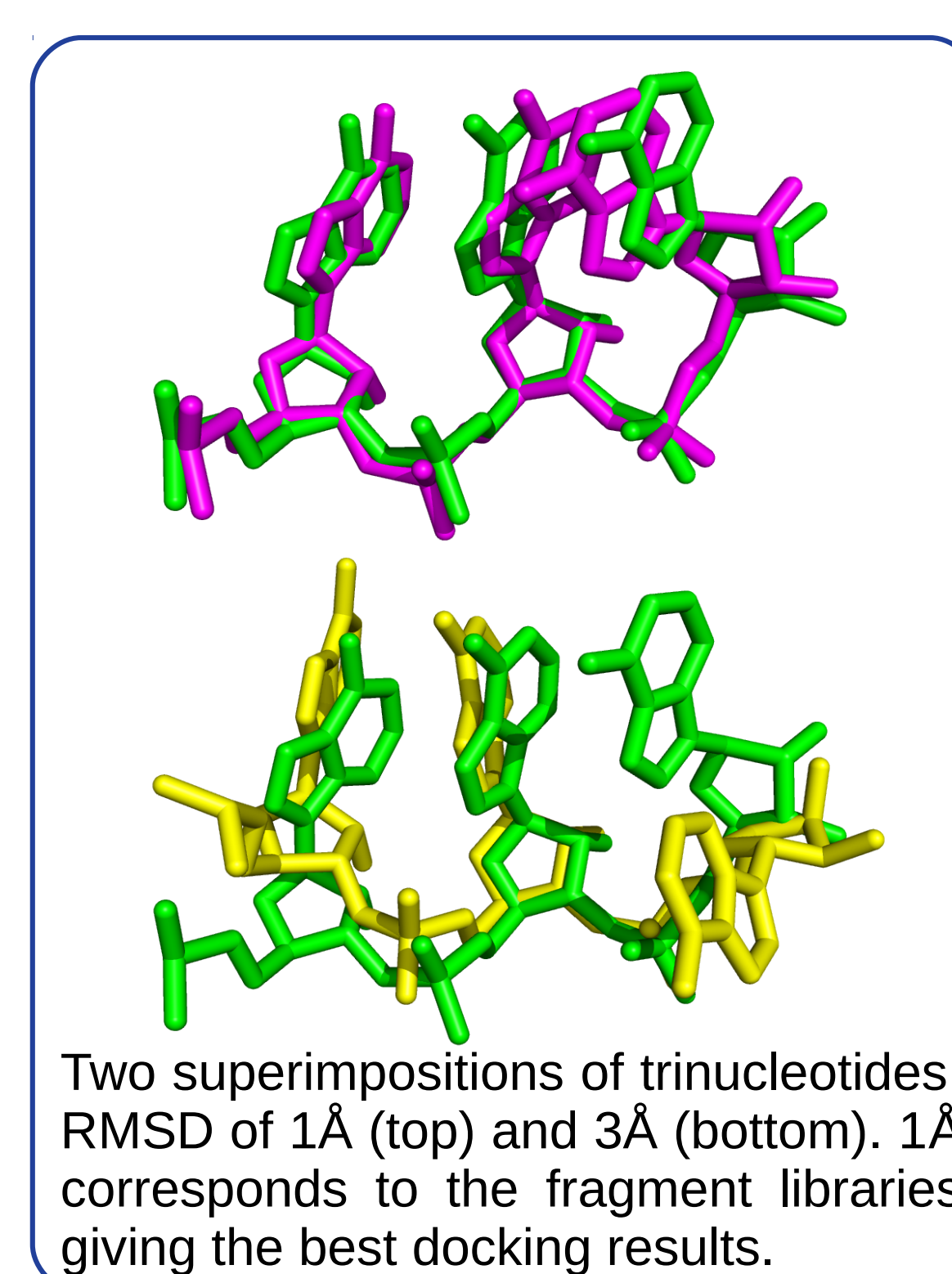
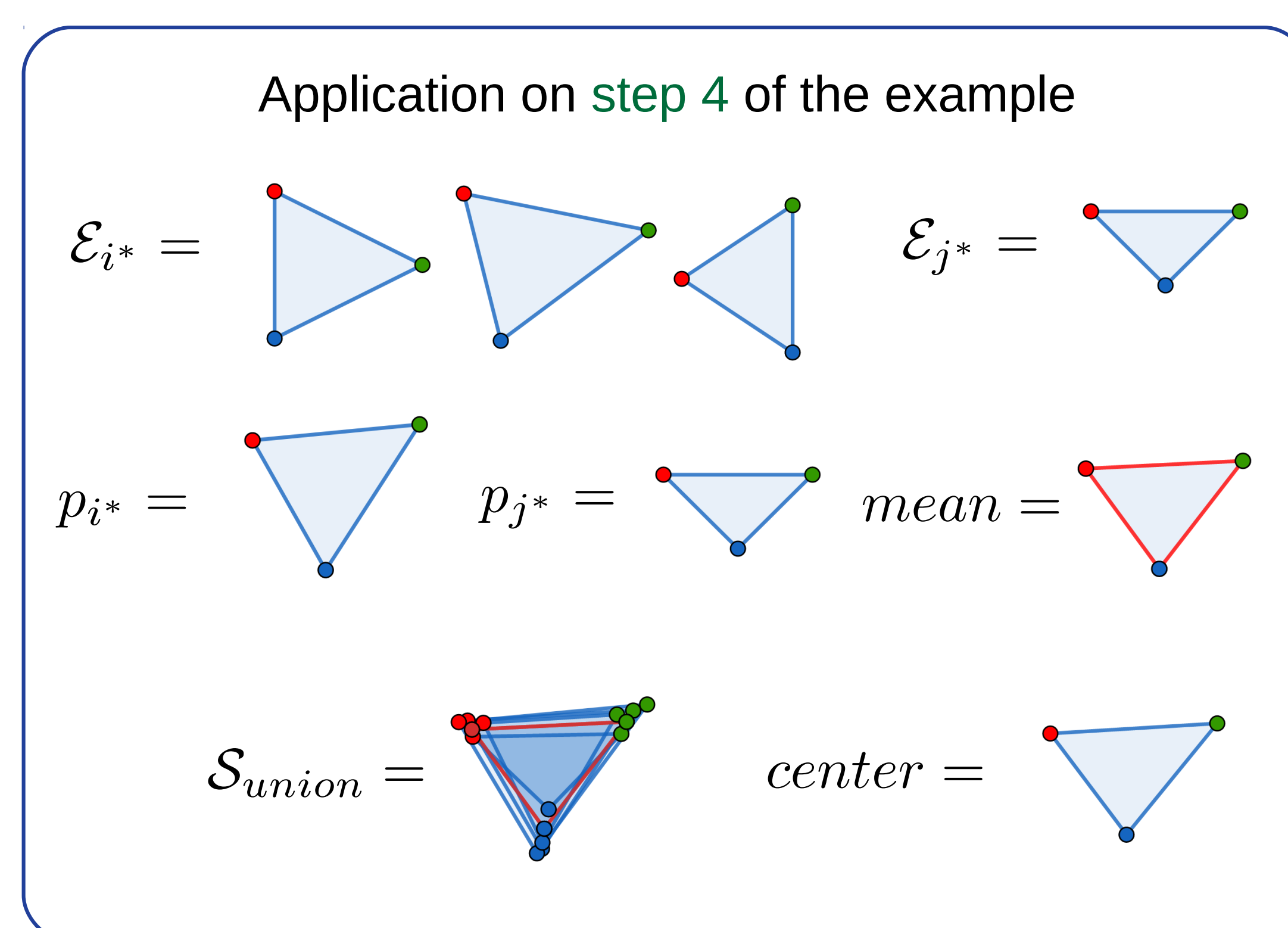
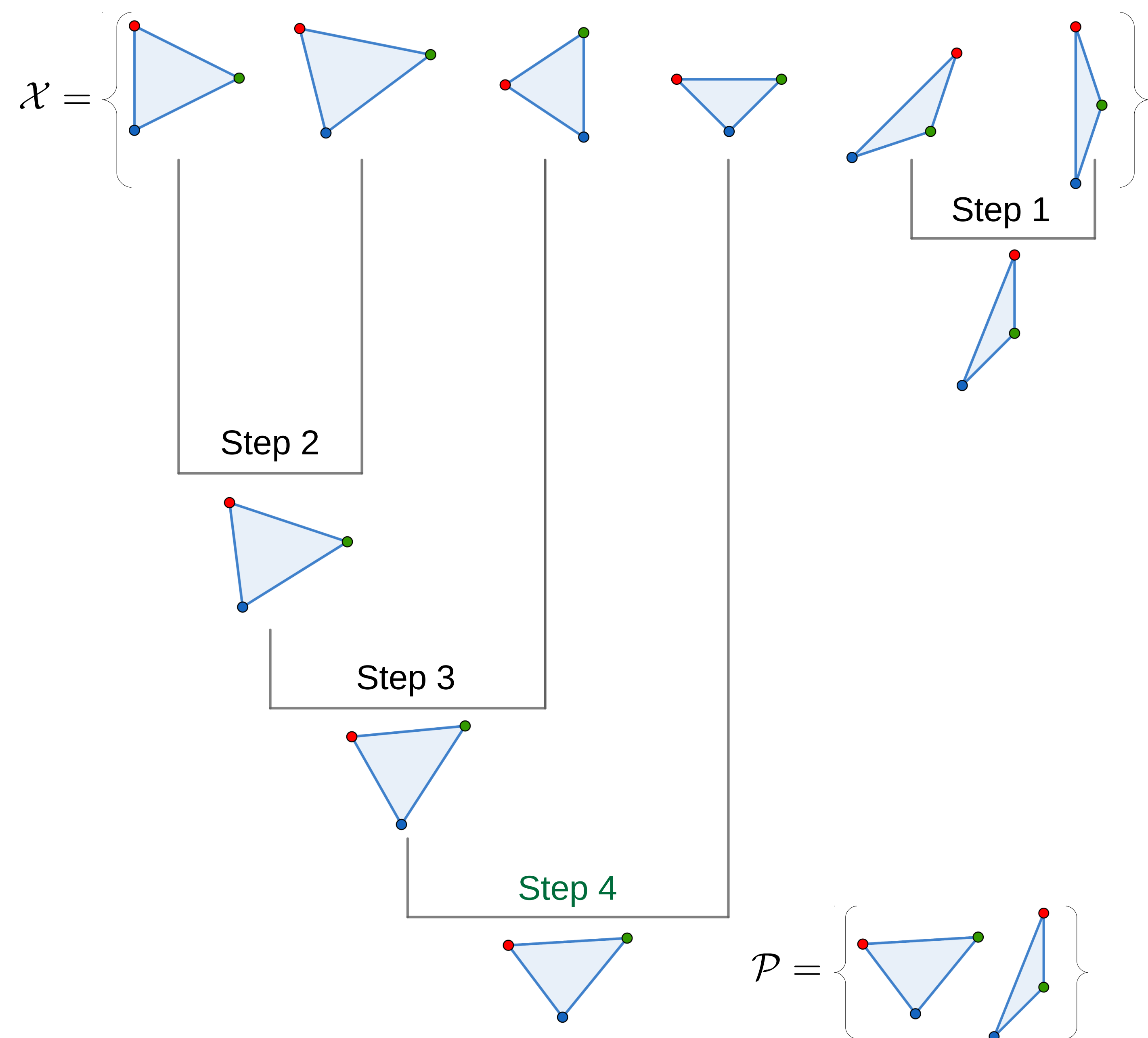
**Input** :  $\mathcal{X} := \{x_i : 1 \leq i \leq n\}$  # set of conformers  
 $t > 0$  # threshold value  
**Output**:  $\mathcal{P} := \{p_i : 1 \leq i \leq s\}$  # set of prototypes  
**Initialisation**:  
 $s := n$  # number of prototypes  
 $\mathcal{P} := \mathcal{X}$  # set of prototypes  
 $R := (r_{i,j}) \in \mathbb{R}^{s \times s}$  # matrix of RMSD of prototypes after **one-against-one superimposition**

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$R^{mask} := (r_{i,j}^{mask}) \in \{0, 1\}^{s \times s}$   
 $\mathcal{E} := \{\{x_i\}_{1 \leq i \leq s} : 1 \leq i \leq n\}$  # set of clusters  
 $fusion := True;$   
**while**  $fusion$  **do**  
     $fusion := False;$   
     $R^{mask} := False;$  # initialized at *False*  
     $tag := False;$   
    **while** ( $not\ tag\ and\ not\ fusion$ ) **do**  
         $i^*, j^* := \operatorname{argmin}_{1 \leq i < j \leq s} (r_{i,j} : r_{i,j}^{mask} == False);$   
         $mean := (p_{i^*} + p_{j^*})/2;$   
         $\mathcal{S}_{union} := \mathcal{E}_{i^*} \cup \mathcal{E}_{j^*};$  # **superimposed on mean**  
        Compute the *center* of the smallest englobing ball associated with  $\mathcal{S}_{union}$ ;  
        **if** ( $\max_{x_i \in \mathcal{S}_{union}} (d_{superimposed}(x_i, center)) \leq t$ ) **then**  
             $\mathcal{P} \setminus \{p_{i^*}, p_{j^*}\} \cup \{center\};$   
            Update  $R$ ;  
            Update  $\mathcal{E}$ ;  
             $s := s - 1;$   
             $fusion := True;$   
        **else**  
             $r_{i_{min}, j_{min}}^{mask} := True;$   
            **if** ( $\forall 1 \leq i < j \leq s : r_{i,j}^{mask} == True$ ) **then**  
                 $tag := True;$   
            **end if**  
        **end if**  
    **end while**  
**end while**  
return  $\mathcal{P}$ ;

---

## Example:



## Analysis:

The algorithm is based on the HAC [1], the main difference is the linkage method. We defined a linkage method which is the “**smallest enclosing balls**”. The computation of those balls is a quadratic problem and to solve it we are using the Frank-Wolfe algorithm [3].

The algorithm was applied to trinucleotides of RNA. We compared the results obtained, for the sequence AAA, to a classic HAC with the “complete” linkage method. For the “complete” linkage we obtain **2817 clusters**, and with our “smallest enclosing balls” we obtain **2421 prototypes** (coming from a set of 11,813 conformations). The difference is that the “complete” linkage is not adapted to calculate  $\varepsilon$ -nets, it is merging clusters when all members are at maximum 1Å from other members, and it does not give any prototypes.

In the fragment-based method for the docking of RNA on protein [2], the docking of the conformers is proportional to the number of prototypes.

## Conclusion and ongoing research:

- Our method performs better than the state-of-the-art one;
- On the application of trinucleotides, the cardinality directly translate into a gain in computation time;
- We are planning to apply our method to other biological problems;
- Statistical analysis is in progress to derive generalization error bounds and excess risk bounds.

## References:

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2. I. Chauvot de Beauchene, S. de Vries, and M. Zacharias. Fragment-based modelling of single stranded RNA bound to RNA recognition motif containing proteins. NucleicAcidsResearch, 44(10):4565-4580, 2016.
3. M. Frank, and P. Wolfe. An algorithm for quadratic programming. Naval Res. Logist. Quart., 3(1):95-110, 1956.