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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 ε -nets whose cardinalities are as close as possible to the corresponding *covering numbers*. A heuristic to derive such ε -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.

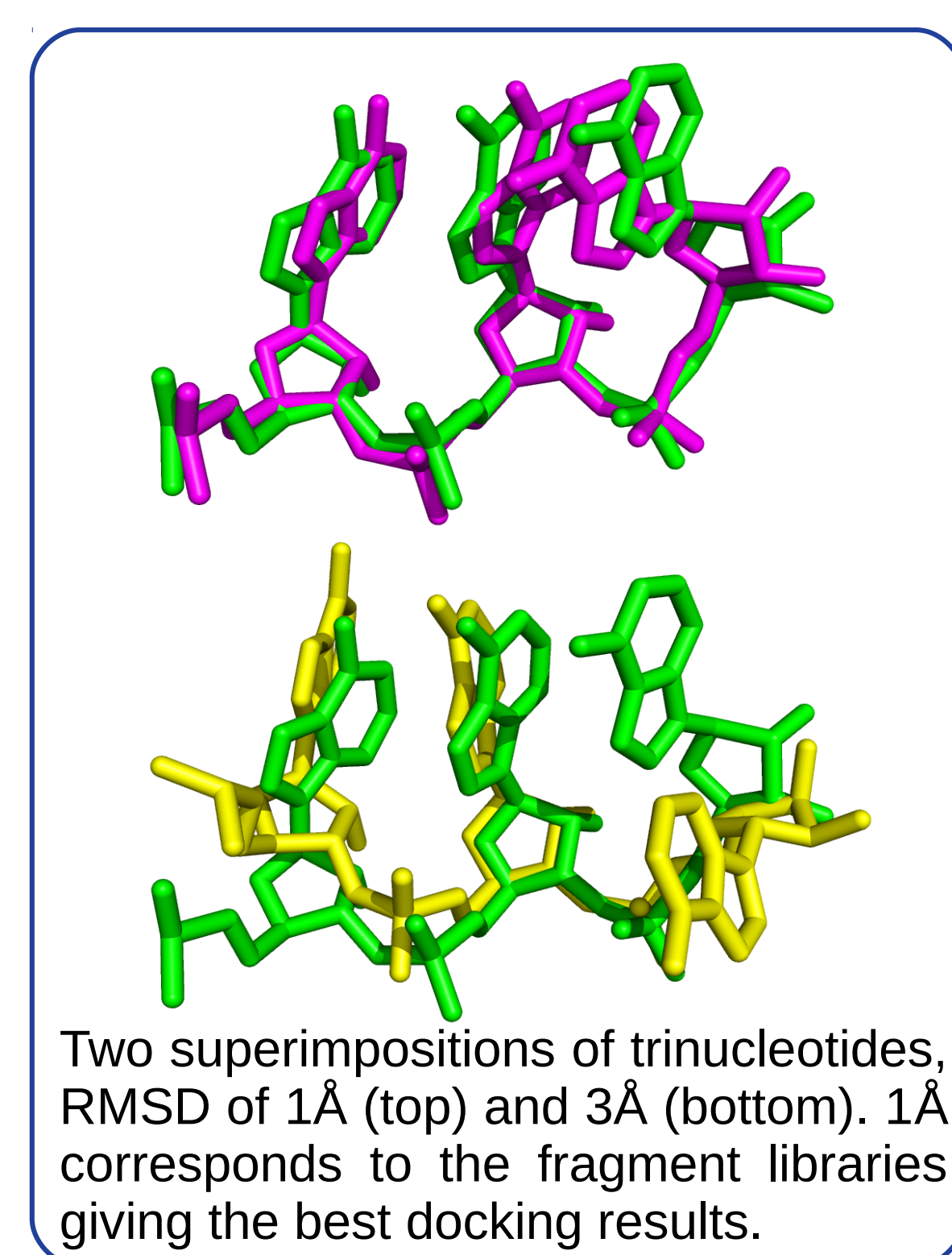
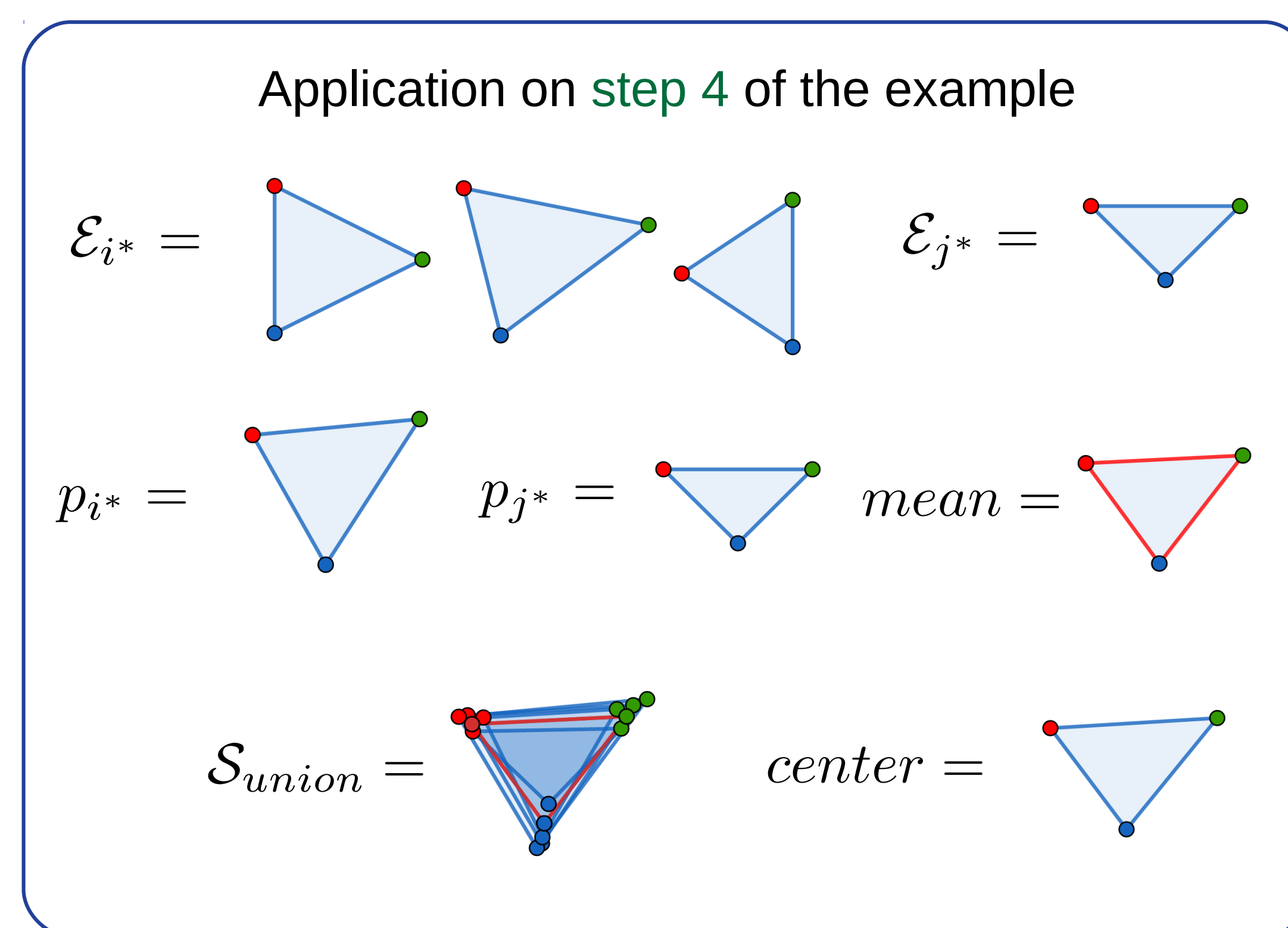
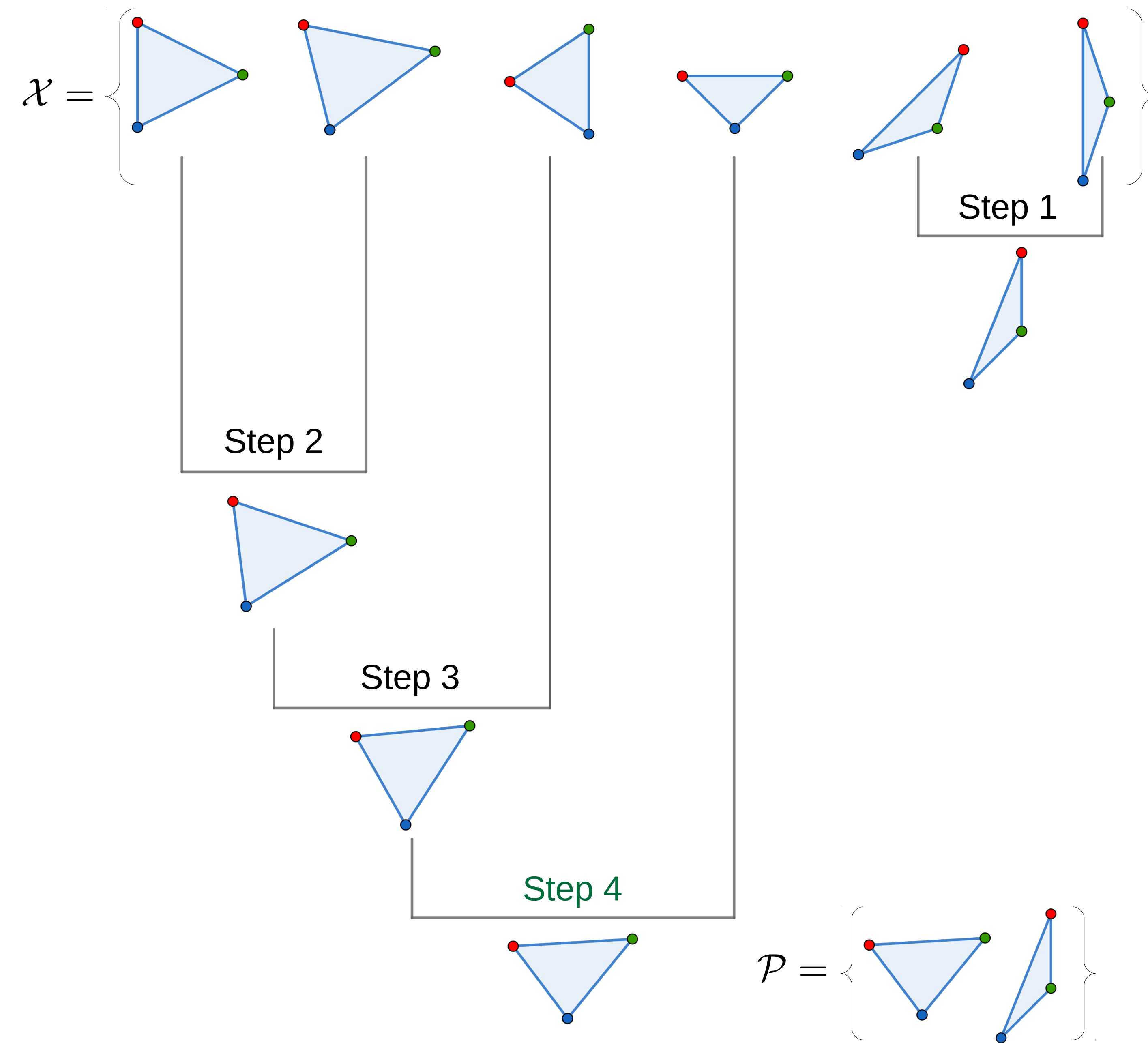
Algorithm:

```

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

 $R^{mask} := (r_{i,j}^{mask}) \in \{0,1\}^{s \times s}$ 
 $\mathcal{E} := \{\{x_i\}_{1 < j < s} : 1 \leq i \leq n\}$  # 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 ε -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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3. M. Frank, and P. Wolfe. An algorithm for quadratic programming. Naval Res. Logist. Quart., 3(1):95-110, 1956.