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.

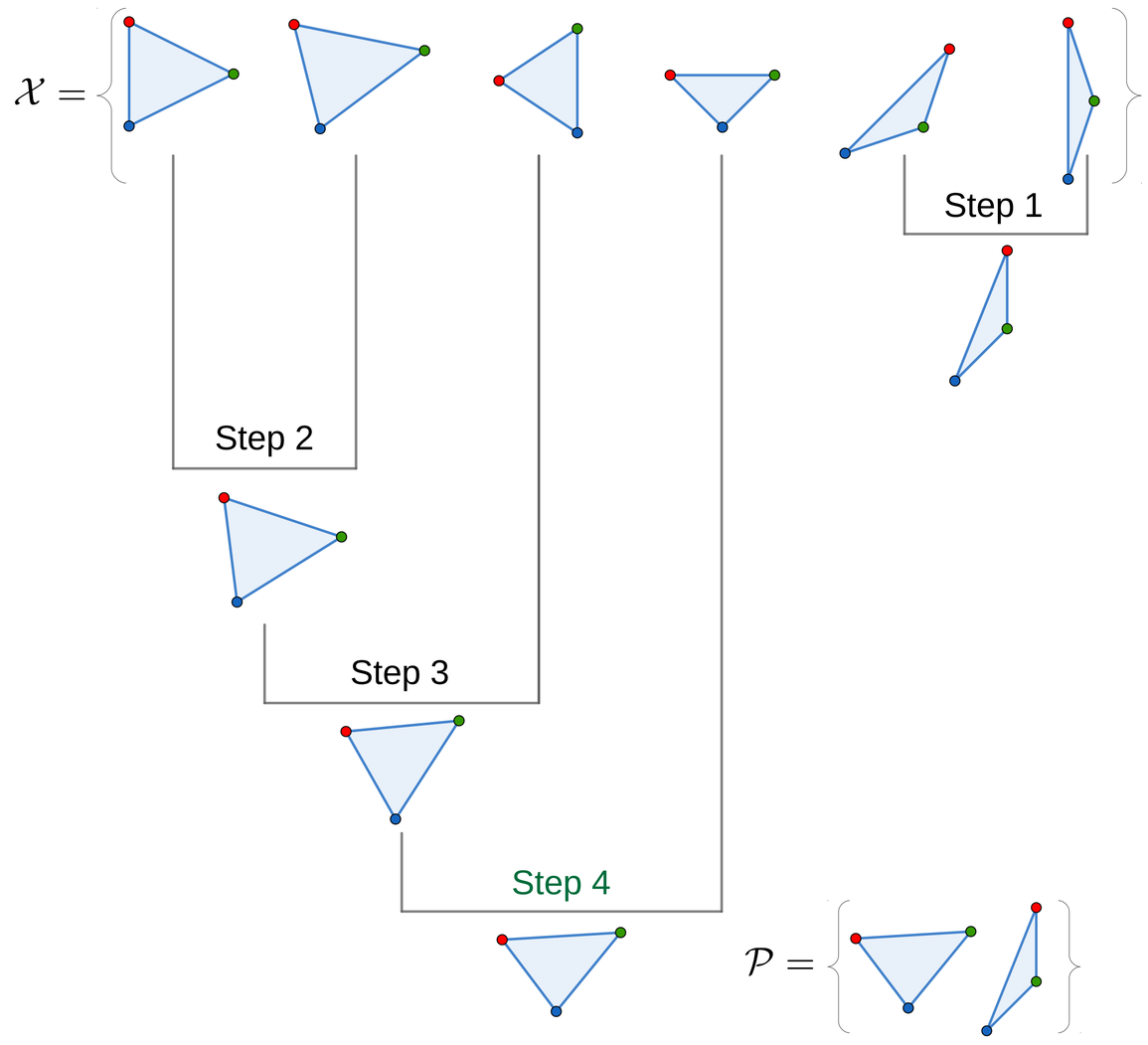
We introduce such a method as a variant of the Hierarchical Agglomerative Clustering (HAC) algorithm. Compared to HAC, it makes it possible to reduce the number of prototypes, while maintaining an acceptable computation time.

Algorithm:

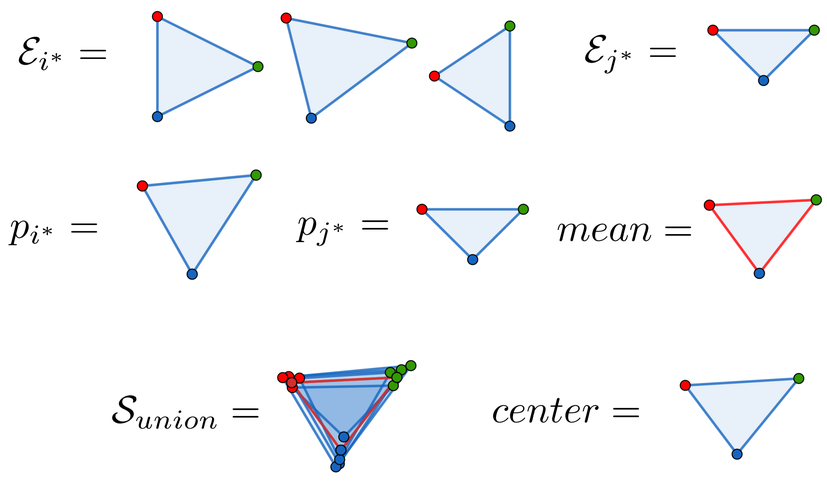
Input : $\mathcal{X} := \{x_i : 1 \leqslant i \leqslant n\}$ # set of conformers
$t > 0$ # threshold value
Output: $\mathcal{P} := \{p_i : 1 \leqslant i \leqslant s\}$ # set of prototypes
Initialisation:
$s := n$ # number of prototypes
$\mathcal{P} := \mathcal{X}$ # set of prototypes
$R := (r_{i,j})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

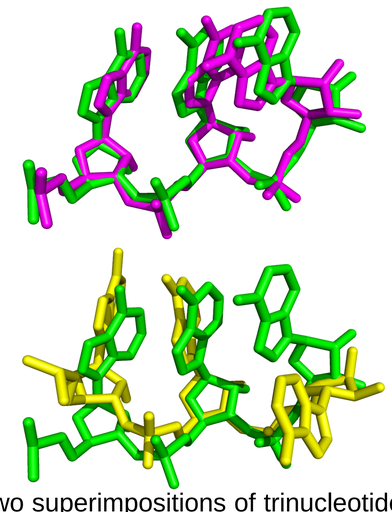
$fusion := True$;
while $fusion$ **do**
  $fusion := False$;
  $R^{mask} := False$; # initialized at $False$
  $tag := False$;
  while *(not tag* ***and*** *not* $fusion$*)* **do**
    $i^*, j^* := \underset{1 \leqslant i < j \leqslant s}{\operatorname{argmin}} (r_{i,j} : r_{i,j}^{mask} == False)$;
    $mean := (p_{i^*} + p_{j^*})/2$;
    $\mathcal{S}_{union} := \mathcal{E}_{i^*} \cup \mathcal{E}_{j^*}$; # **superimposed on** mean
    Compute the *center* of the smallest englobing ball associated with $\mathcal{S}_{union}$;
    if $\left(\max_{x_i \in \mathcal{S}_{union}} (d_{superimposed}(x_i, center)) \leqslant t \right)$ **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 $(\forall\ 1 \leqslant i < j \leqslant s : r_{i,j}^{mask} == True)$ **then**
        $tag := True$;
      end if
    end if
  end while
end while
return $\mathcal{P}$;

Example:



Application on step 4 of the example





Two superimpositions of trinucleotides, RMSD of 1Å (top) and 3Å (bottom). 1Å corresponds to the fragment libraries giving the best docking results.

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.