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:

```
Input : $X := \{x_i : 1 \leq i \leq n\}$  # set of conformers
t > 0  # threshold value
Output: $P := \{p_i : 1 \leq i \leq \hat{s}\}$  # set of prototypes

Initialisation:
s := n  # number of prototypes
$P := X$  # set of prototypes
$R := (r_{i,j}) \in \mathbb{R}^{s \times s}$  # matrix of RMSD of prototypes after one-against-one superimposition
$R_{\text{mask}} := \{r_{i,j} \in \{0, 1\}^{s \times s}\}  \#$ set of clusters
$\varepsilon := \{x_i, 1 \leq i \leq s : 1 \leq i \leq n\}$  # set of clusters
$fusion := True$  
while fusion do
    fusion := False;
    $R_{\text{mask}} := False$;  # initialized at False
    tag := False;
    while (not tag and not fusion) do
        $i^*, j^* := \arg\min_{i \leq j \leq s} r_{i,j}^{\text{mask}}$ (False);
        mean := $(p_{i^*} + p_{j^*})/2$;
        $S_{\text{union}} := \varepsilon_{i^*} \cup \varepsilon_{j^*}$;  # superimposed on mean
        Compute the center of the smallest enclosing ball associated with $S_{\text{union}}$;
        if (max$_{x \in S_{\text{union}}} (\text{d superimposed}(x, \text{center})) \leq t$) then
            $P \setminus \{p_{i^*}, p_{j^*}\} \cup \{\text{center}\}$;
            Update $R$;
            Update $\varepsilon$;
            $s := s - 1$;
            $fusion := True$;
        else
            $r_{i^*,j^*}^{\text{mask}} := True$;
            if ($1 \leq i < j \leq s : r_{i,j}^{\text{mask}} = True$) then
                tag := True;
            end if
        end if
    end while
return $P$.
```

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.

Example:

```
$X = \{\}$
```

$P = \{\}$

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: