R-NN Curves: A Method for Diversity Analysis and Cluster Identification

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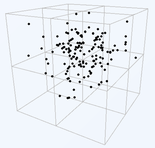
1 Diversity Analysis

- *What is it?*
  - *Understand the distribution of chemical structures in a chemical space as well as with respect to themselves*
- *Why is it useful?*
  - *Compound acquisition*
  - *Lead hopping*
  - *Enhancing local regression techniques*

2 Approaches to Diversity Analysis

Cell based

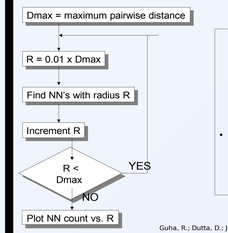


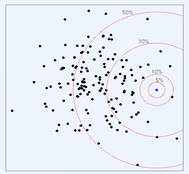
- Not useful for high dimensional data
- Choice of bin size is tricky

Distance based

- Generally requires pair-wise distance calculations
- Can be sped up using kD-trees

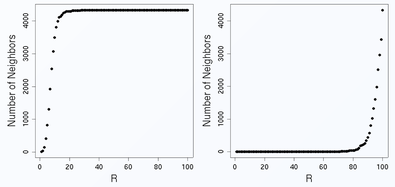
3 Generating R-NN Curves





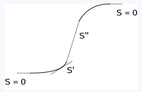
Guha, R.; Dutta, D.; Jurs, P.C.; Chen, T.; *J. Chem. Inf. Model.*, **2006**, *ASAP*

4 R-NN Curve Examples



5 Characterizing R-NN Curves

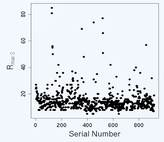
- Rigorous Approach
  - Fit a sigmoid curve and use the fit parameters
- Simpler Approach
  - Determine the value of R where the lower tail transitions to the linear portion of the curve



- Determine slope at varying R
- Slope is maximal on the linearly increasing portion
- Find R for first occurrence of the *maximal* slope - $R_{max(S)}$
- Rapidly performed using a finite difference approach

6 Summarizing R-NN Curves

- Visual inspection is reasonable for a few curves $R_{max(S)}$
- Inspecting hundreds of curves is painful
- Summarize large datasets using $R_{max(S)}$ values



- *Points towards the top are located in sparse regions*
- *Points towards the bottom are located in dense regions*
- *Significant outliers are easily detected*

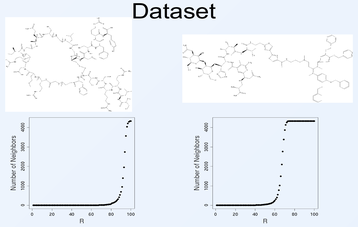
7 R-NN Curves : Kazius Dataset

- Dataset
  - *4337 molecules*
  - *Avg. MW = 240*
  - *Avg. Tanimoto = 0.21*
  - *Calculated MOE descriptors*
- Two significant outliers
- Descriptor space
  - Random 5-descriptor space was selected

- Defined outliers as
  - *R = 0.5 x Dmax*
  - *NN count < 10% of the dataset*
- Resulted in 2 outliers
  - *3904 had 2 NN's*
  - *1861 had 41 NN's*
- ***Subjective procedure***

Kazius, J.; McGuire, R.; Bursi, R.; *J. Med. Chem.*, **2005**, *48*, 312–320

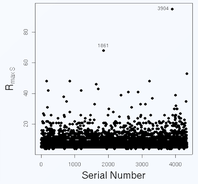
8 Outliers in the Kazius Dataset



9 Outliers in the Kazius Dataset

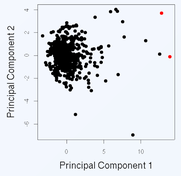
- 1861 & 3904 are immediately identifiable as outliers
- Not many significant outliers

One plot summarizes the location characteristics of all the molecules in the dataset



10 Alternative Methods?

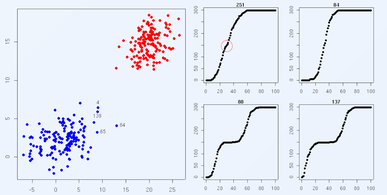
- R-NN curves essentially perform dimension reduction
- Alternative approach is to use PCA
- *Problem*
  - *Eigendecomposition via SVD is O(mn²)*
  - *Difficult to visualize more than 2 or 3 PC's at the same time*



11 R-NN Curves & Clusters?

- When clusters are present R-NN curves in general exhibit a *stepped* appearance
- Counting the number of steps identifies the number of clusters
- Problems
  - Steps may not be distinct
  - All the points in a dataset may not exhibit stepping

12 R-NN Curves for Clustered Data



Simulated Data

13 Counting the Steps

- Essentially a curve matching problem
- Start with a set of *canonical* sigmoid curves
- Match R-NN curves to the canonical set
  - How many R-NN curves do we look at?

- Standardize R-NN Curves
  - Procrustes transformation
- *Matching approaches*
  - Slope analysis
  - Hausdorff / Frechet distance
  - RMSE from distance matrix

14 Curve Matching – Distance Metrics

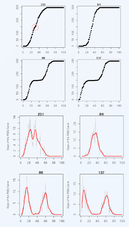
- Use techniques from the field of object recognition
- Hausdorff distance is a measure of the maximum distance between curves represented as *sets of points*
- Frechet distance takes into account the location and *ordering* of the points on the curves

Two dissimilar curves with small Hausdorff distance

Frechet, M., *Sur quelques points du calcul fonctionnel. Rendiconti del Circolo Mathematico di Palermo*, **1906**, *22*, 1–74.
http://www.cim.mcgill.ca/~stephane/cs507/Project.html

15 Curve Matching - Slopes

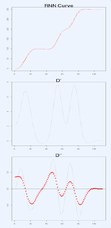
- The slope on a step is a minima
- Plotting slope vs. R generates peaks
  - 1 step : 2 peaks
  - 2 steps : 3 peaks
  - ……
- Identify the peaks
- Automated identification can select spurious peaks



16 Slope Analysis

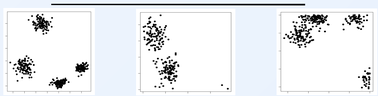
- Generate an R-NN curve and smooth it
- Evaluate the second derivative and smooth it
- Determine the number of roots of the second derivative, N_{root}

$$N_{peak} = [max(N_{root}) + 1]/2$$



17 Preliminary Results

- Simulated 2D data
- Predicted *k*, followed by k-means clustering
- Investigated similar values of *k*



k	ASW
4	0.61
3	0.74
5	0.70

k	ASW
3	0.44
2	0.65
4	0.47

k	ASW
4	0.64
3	0.48
5	0.56

ASW – average silhouette width, higher is better

18 Conclusions

- Applicable to arbitrary dimensions
- Can be extended to handle large datasets
- Summarizing a dataset does not require user-defined parameters
- Simple and intuitive approach to visualizing molecules in a chemical space
- Useful approach to identifying number of clusters
  - A number of techniques for curve matching are available
  - Need to achieve balance between specificity and speed
  - Not necessarily automatic