Chemical Space Networks using Tanimoto Coefficient

Subarna Palit

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Chemical Space

- Chemical space is of paramount importance in the field of Chemo-informatics and drug design
- To assess a set of target compounds for their molecular properties and associate chemical relationships with biological activities
- Distribution of all synthetically accessible molecules across a hypothetical multi-dimensional space
- Two major approaches

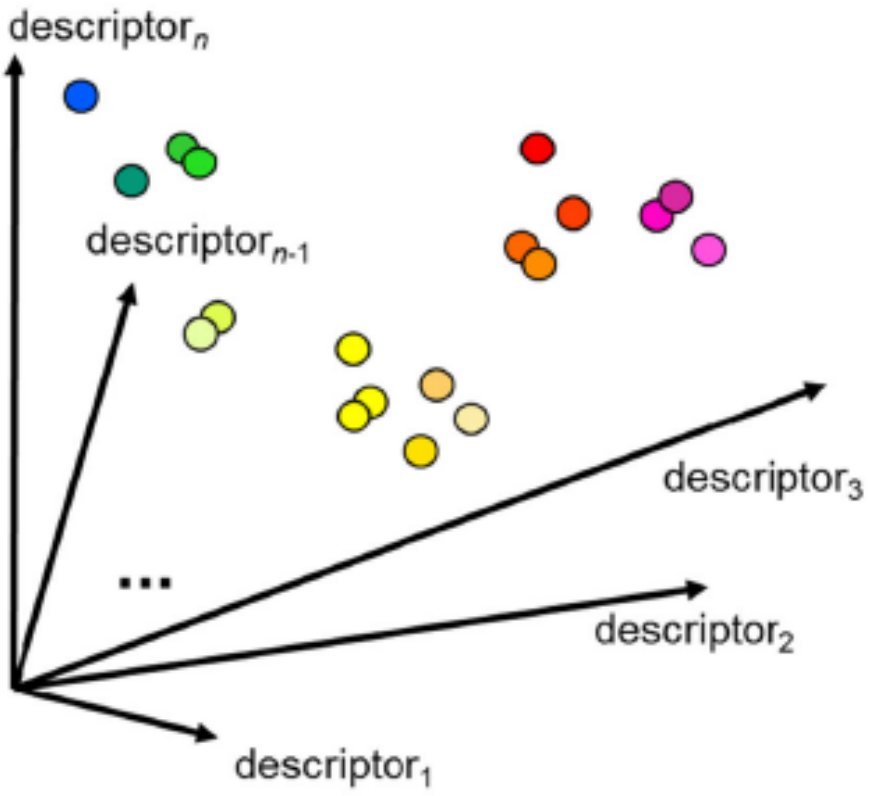
Coordinate-based	**Coordinate-free**

Vogt M, Stumpfe D, Maggiora GM, Bajorath J. Lessons learned from the design of chemical space networks and opportunities for new applications. J Comput Aided Mol Des. 2016 Mar;30(3):191-208 Accessed on 29.11.2016

Coordinate-based Chemical Space Representation

+ Traditionally molecular descriptors are used as coordinates
+ Increasing distance between molecules correlates with dissimilarity

– High-dimensional making it difficult to visualize; dimensionality reduction leading to loss of vital chemical information



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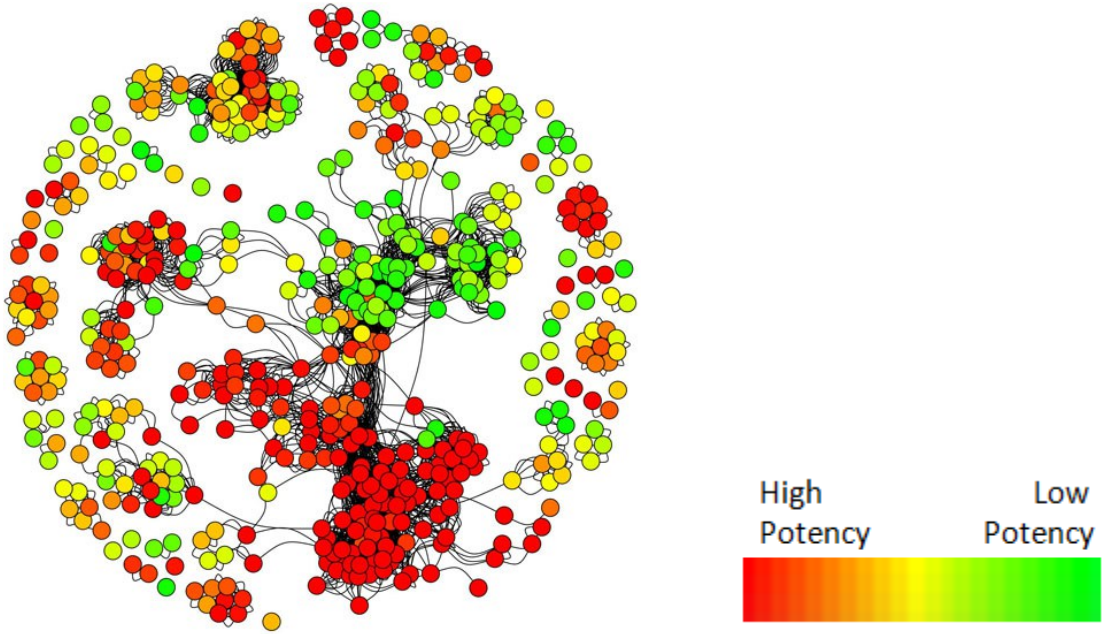
Coordinate-free Chemical Space Network

- Network-based representation of biologically relevant chemical space
  - nodes represent molecules, edges represent pair-wise molecular similarity relationships
- CSN for a set of active compounds



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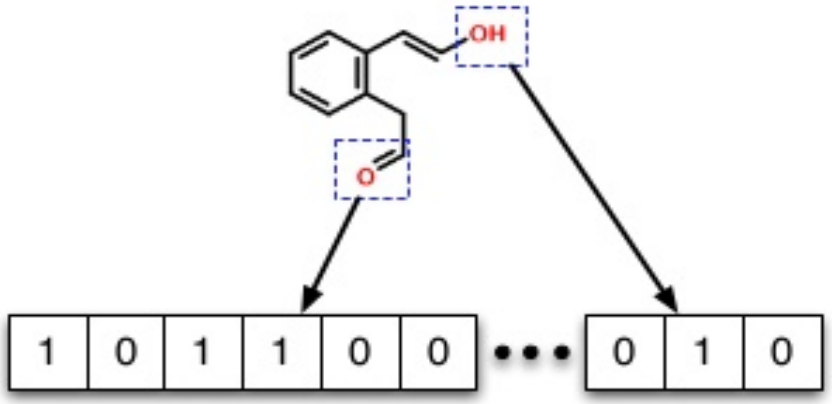
Fingerprint-based similarity

- Fingerprints are a way of encoding the structure of a molecule
- Most common being a series of bits representing the presence (1) or absence (0) of particular substructures in the molecule
- Tanimoto coefficient is most widely used for binary fingerprints



Tanimoto Coefficient

A	1	0	1	1	0	1
B	1	1	0	1	0	0
C	1	0	0	1	0	0

$$Tc = \frac{C}{A+B-C}$$

A = bits set to 1 in structure A, B = bits set to 1 in structure B, C = number of 1 bits common to both
Range is 0 to 1

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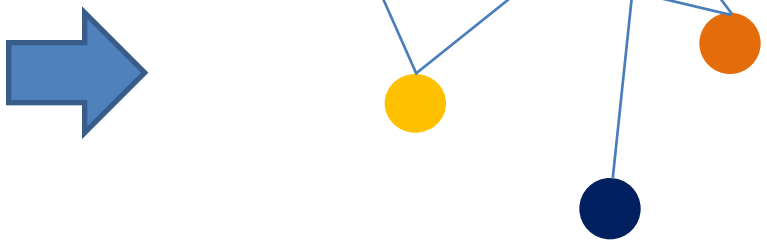
Tanimoto similarity threshold values (THR-CSN)

	A	B	C	D	E
A	1	T_{AB}	T_{AC}	T_{AD}	T_{AE}
B		1	T_{BC}	T_{BD}	T_{BE}
C			1	T_{CD}	T_{CE}
D				1	T_{DE}
E					1



As threshold values are varied each value yields a different so-called threshold CSN (THR-CSN)

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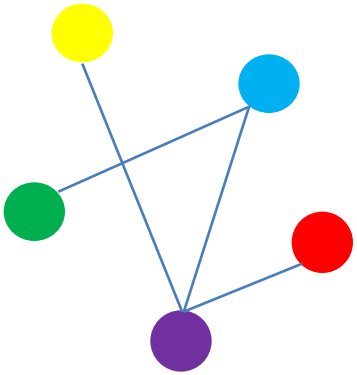
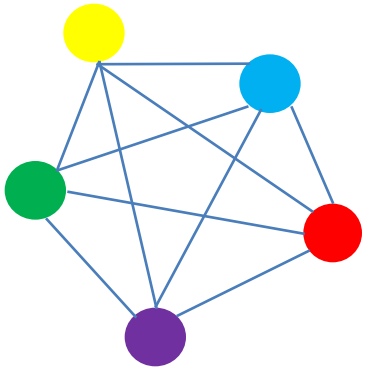
Edge Density

- Network density is defined as the ratio of actual edges in a network over all potential edges
- While a low density network with many singletons is not very informative, highly dense network get more difficult to interpret

LOW



HIGH



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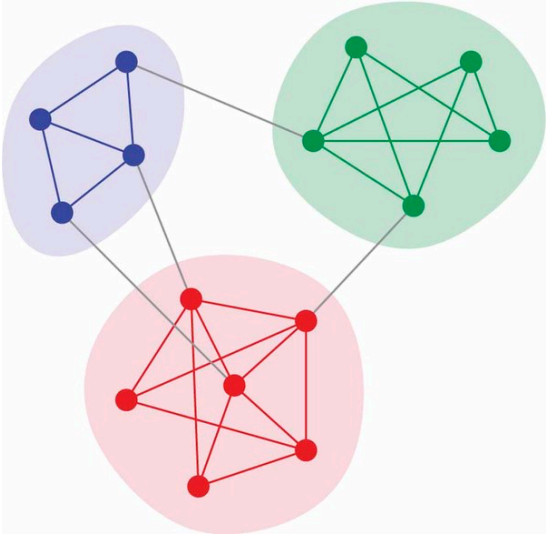
Community Structure and Modularity

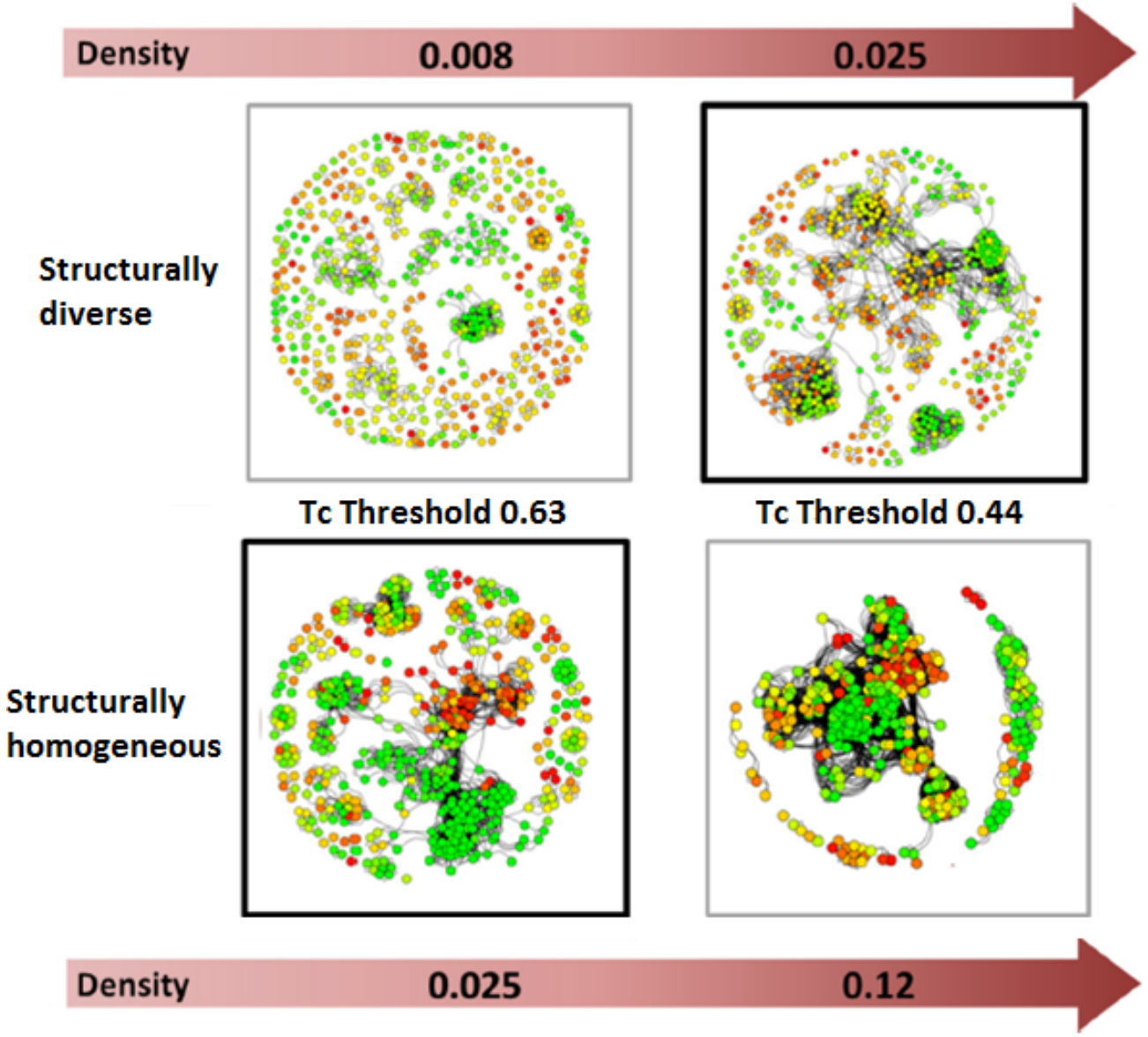
- Communities are groups of nodes in a network
  - more links between nodes within the same community
  - lesser links between nodes in different communities
- Network modularity generally correlates with community structures accounting for the nodes separated into well-defined modules



https://data.graphstream-project.org/talks/CSSS2012/gs-communities.html#/home Accessed on 29.11.2016

THR-CSNs

At low edge densities, CSNs have been found to display well-resolved topologies which can be compared



Zwierzyna M, Vogt M, Maggiora GM, Bajorath J (2015) Design and characterization of chemical space networks for different compound data sets. J Comput Aided Mol Des 29:113–125 Accessed on 29.11.2016

Discussion

- Useful in SAR exploration – community structures leading to differences between similarity relationships
- Display and analysis of only moderately sized and biologically relevant compound sets

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THANK YOU !