Molecular Surface Property Graphs

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Summary

- Definition of MSPGs
- Molecular surfaces
- Molecular properties
- Calculation of MSPGs
- Potential Applications
- Future directions

Aim

Characterize the behaviour of a property

$$f : S \to \mathbb{R}$$

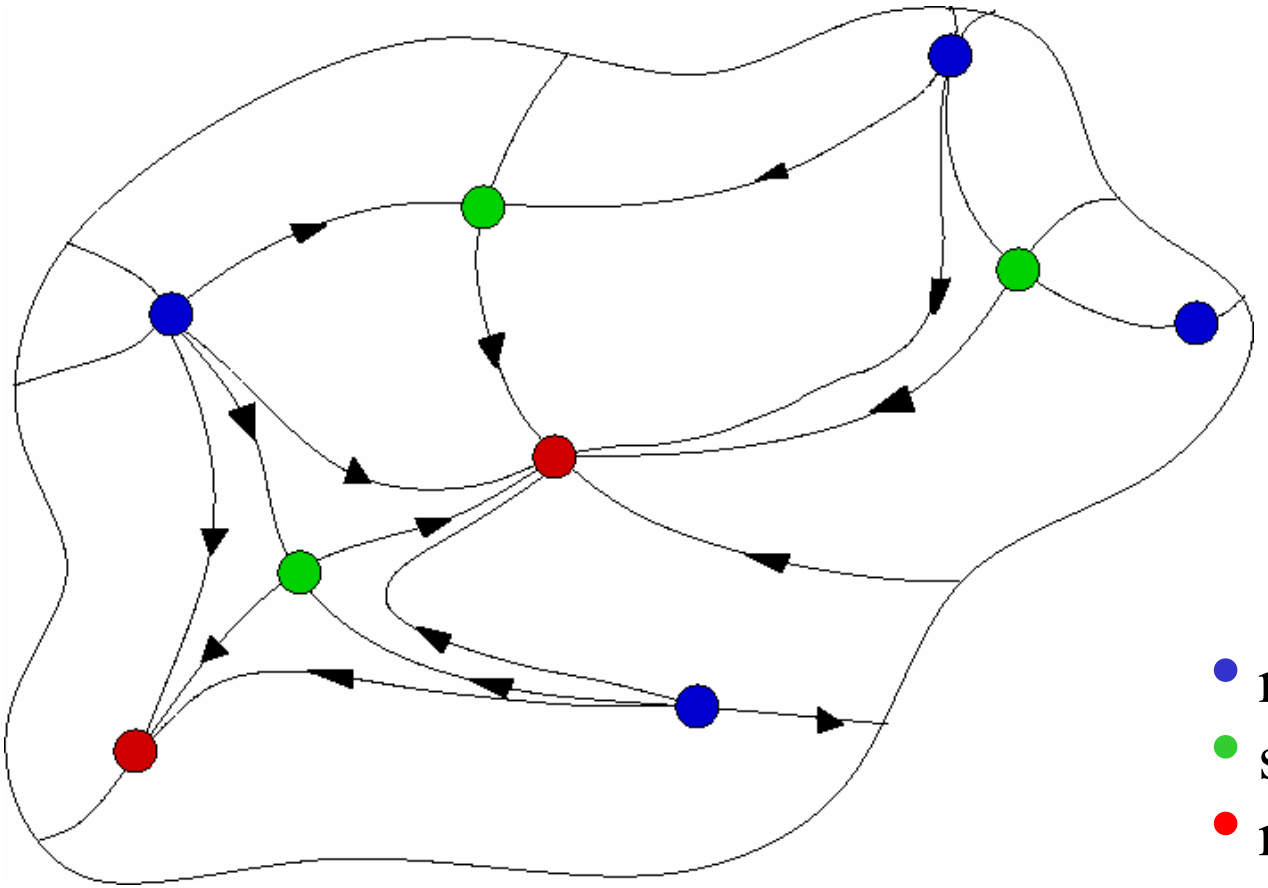
on a molecular surface S in terms of a graph G on S derived from the gradient vector field

$$x' = \text{grad } f(x)$$

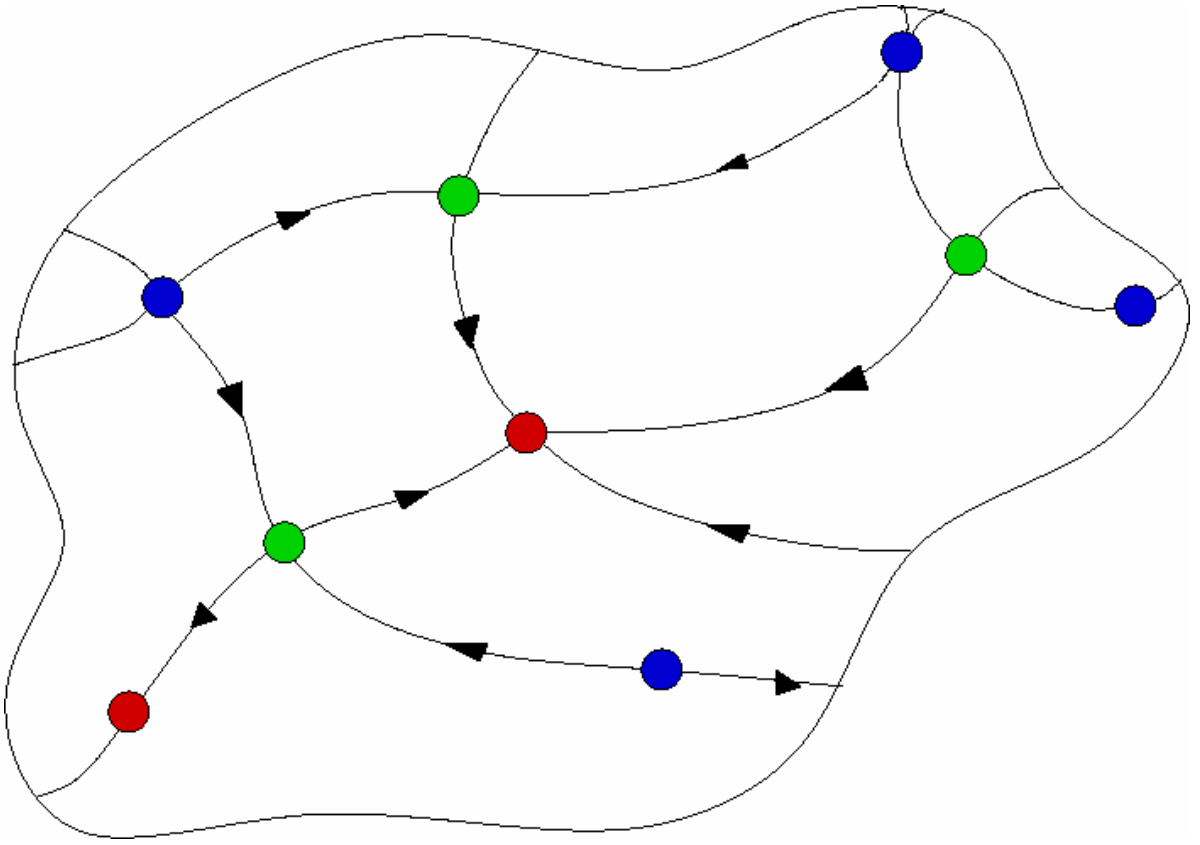
Gradient Vector Fields

- Orbits of grad f are orthogonal to the level sets of f
- Value of f increases along orbits of grad f
- There are no periodic orbits
- The fixed points of grad f are the critical points of f
  - attractors (sinks) of grad f are local maxima of f
  - repellors (sources) of grad f are local minima of f
  - saddles of grad f are saddles of f
- Through each saddle pass two invariant curves
  - the stable and unstable manifolds W^s and W^u

Gradient Flow



Molecular Surface Property Graph



$$\#\text{maxima} - \#\text{saddles} + \#\text{minima} = \chi(S) = 2$$

Molecular Surface Property Graphs

Define a directed graph G on S whose

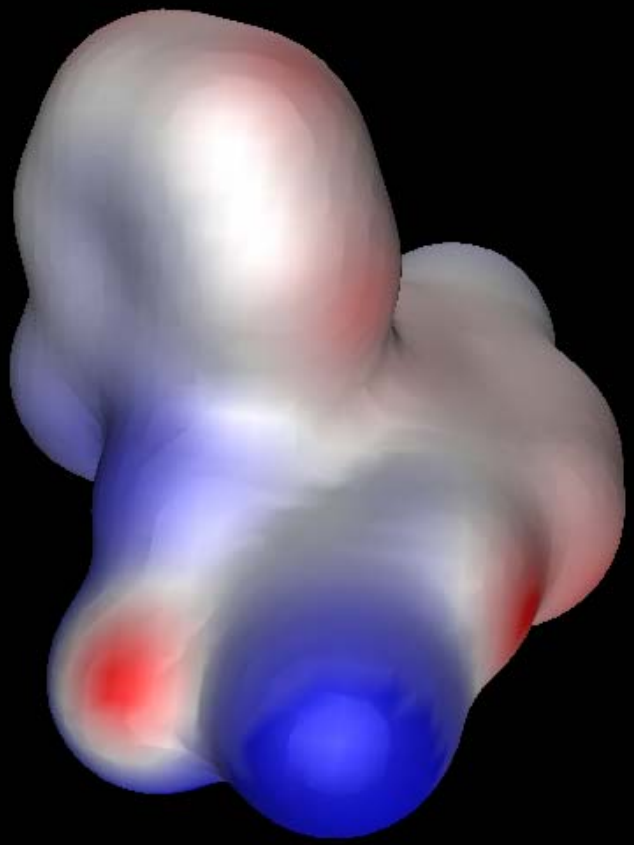
- vertices are the fixed points of grad f (*i.e.* the critical points of f)

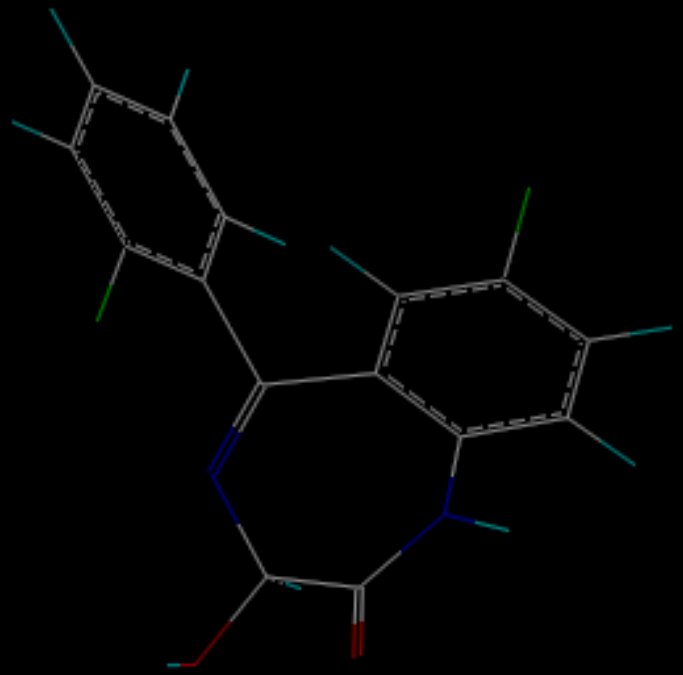
- edges are the stable and unstable manifolds of the saddle points of grad f

Label the vertices of G by the critical values of f and the eigenvalues of the Hessian(f) .

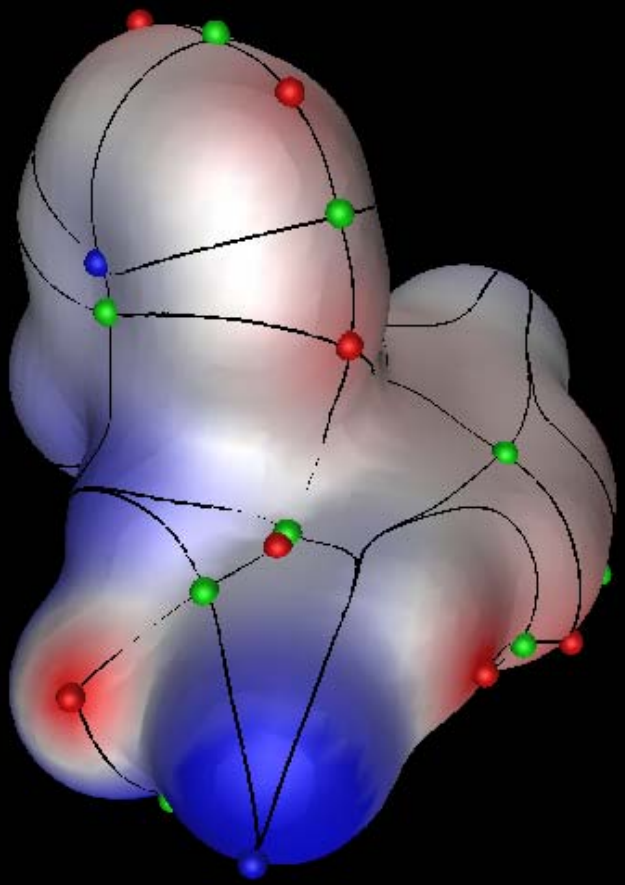
Label the edges of G by their length.

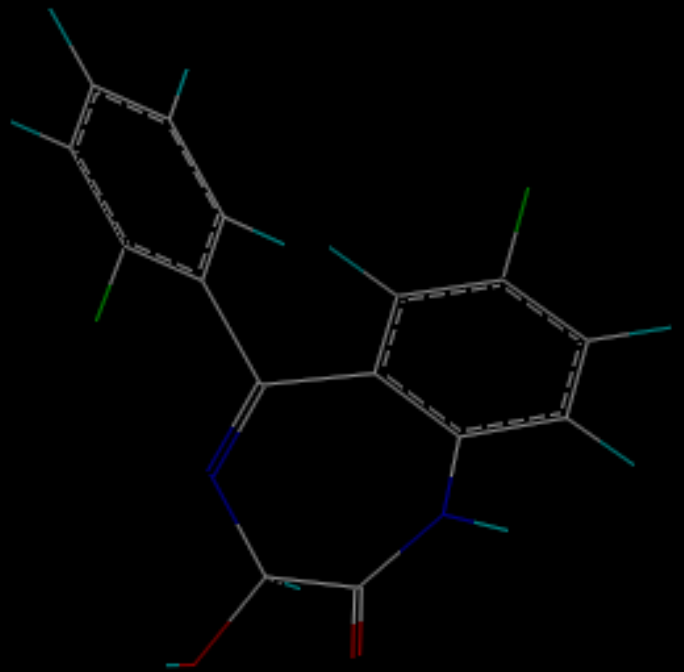
Lorazepam – electrostatic potential





Lorazepam – electrostatic potential





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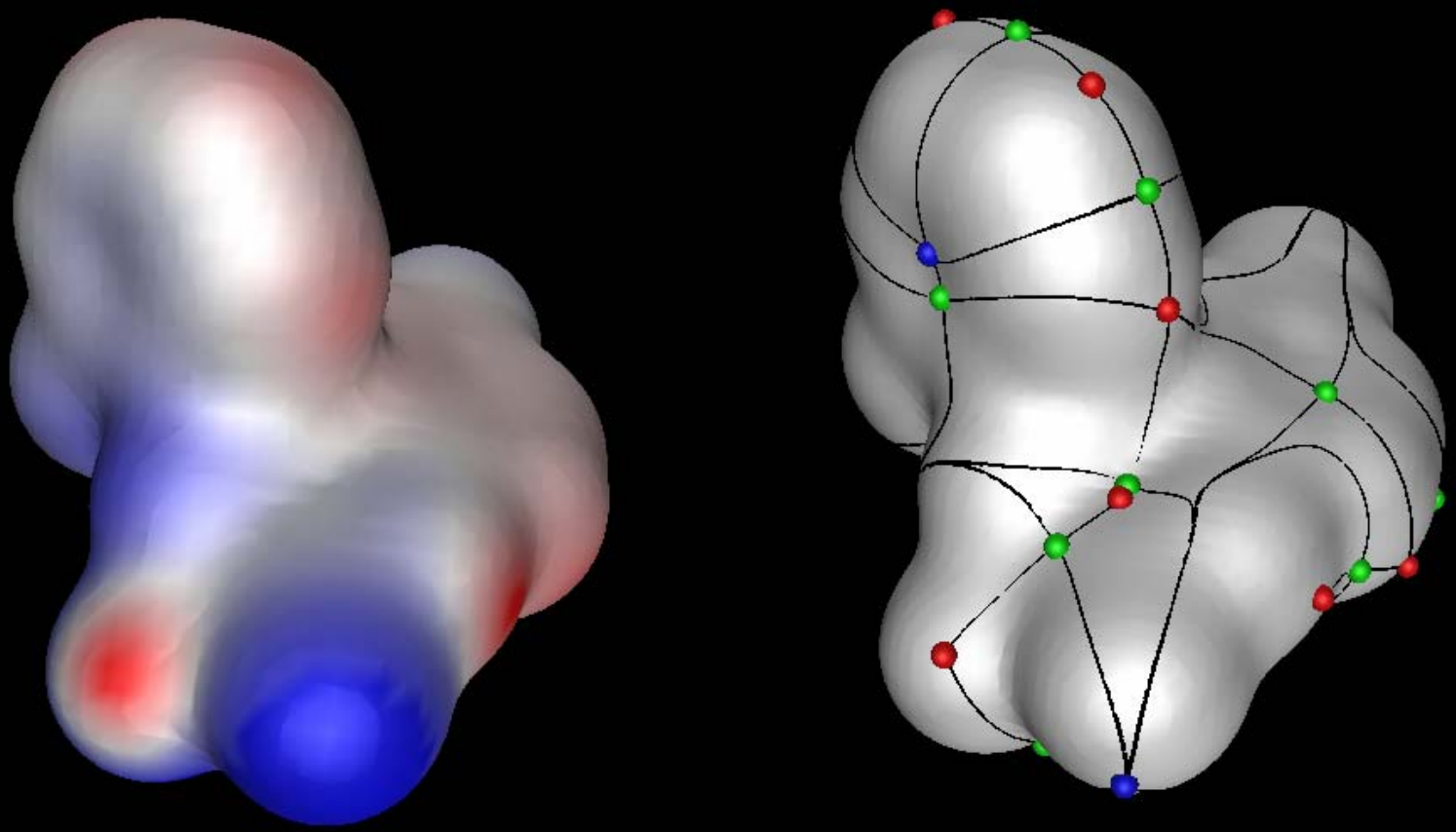
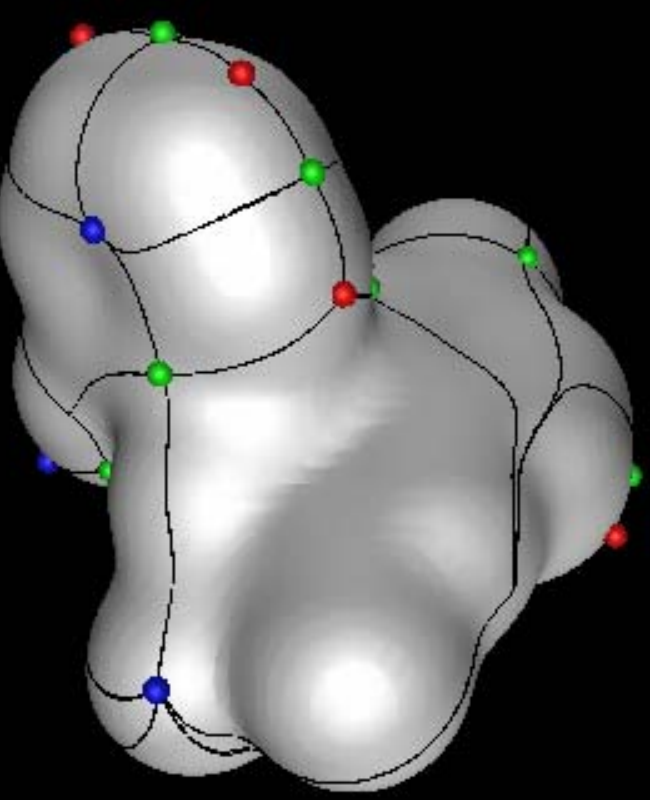
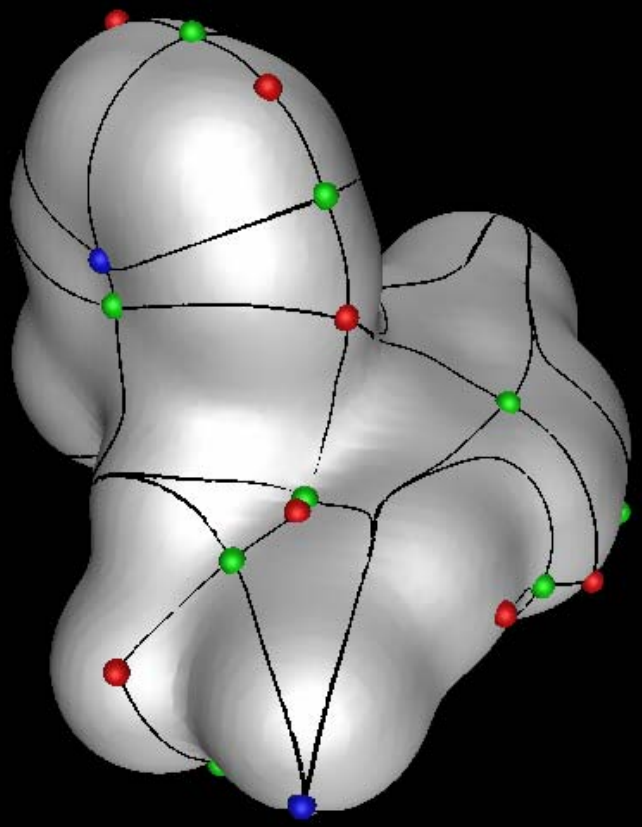


Lorazepam





lipophilicity potential

electrostatic potential

Surfaces

- Connolly Surface
- Level surface $F^{-1}(0)$ where

$$F(r) = \sum \exp\left[\left(\left|r - c_i\right| - r_i\right)/d\right]$$

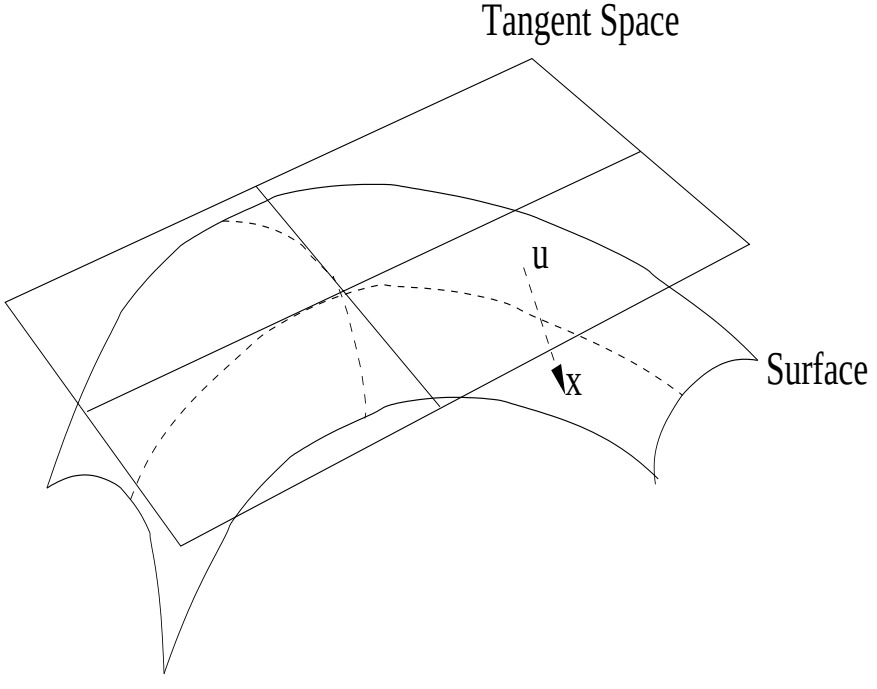
Properties

- Electrostatic Potential $f(x) = \sum q(i) / d(x,i)$
- Lipophilicity Potential $f(x) = \sum l(i)/ (1 + d(x,i))$

Algorithm

- Locate critical points of f (Newton-Raphson).
- Linearize at saddles, find eigenvectors of Hessian(f).
- Integrate gradient vector field forward in time from 2 points on unstable eigenvector, backward in time from 2 points on stable eigenvector (Runge-Kutta).
- Integrate to boundary of surface patch, then continue on adjacent patch until reaching another critical point.
- Requires local co-ordinates on surface
  - Connolly surface – spheres and tori
  - Implicit surface – ?

Local Co-ordinates for Implicit Surfaces



n general, $F^{-1}(0)$ is a 2-dimensional submanifold of $\mathbb{R}^3$, so we can

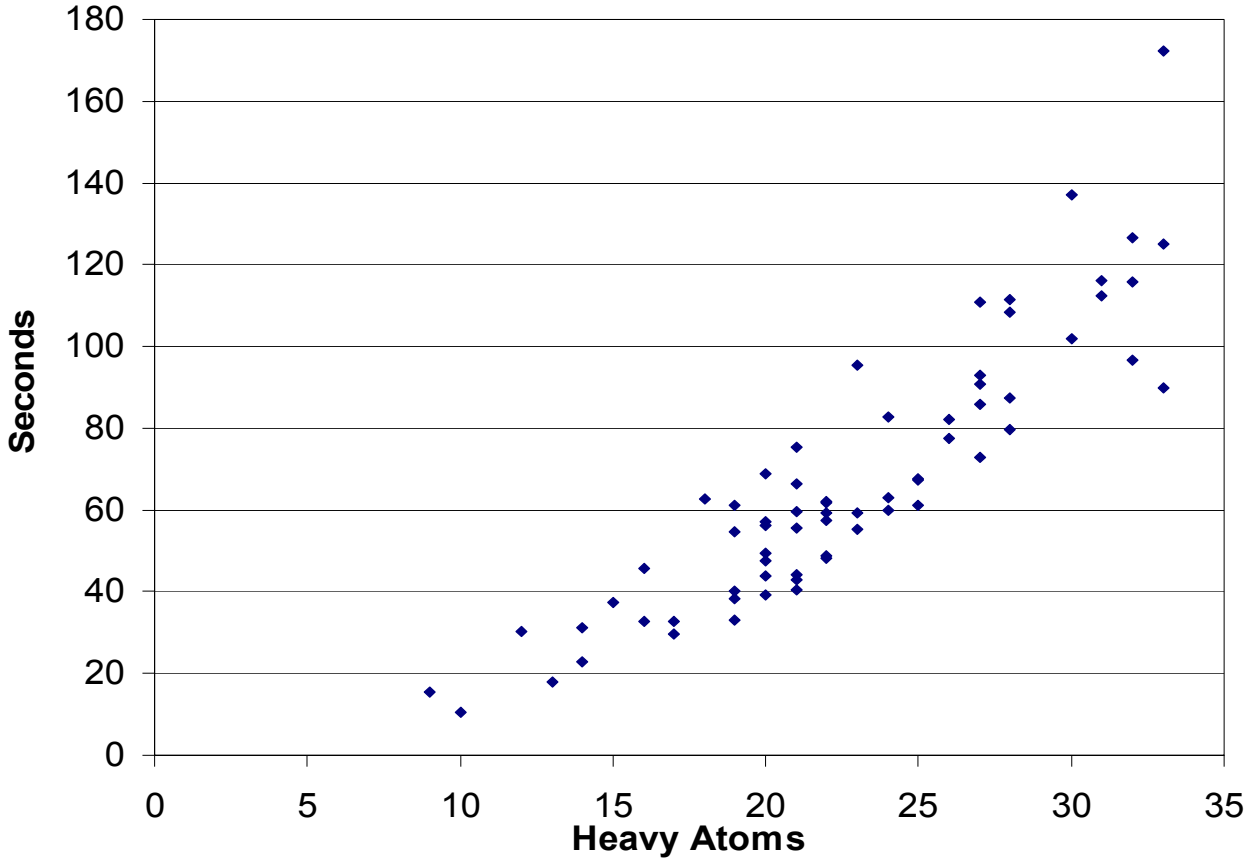
- cover surface with co-ordinate patches
- project co-ordinates from tangent space onto surface
- use existing software
  - Multifario (Henderson), MANPAK (Rheinboldt)

“Consensus” Data Set

74 compounds – intersection of

- RX List top 200 prescription drugs, 2002
- Harvard Chembank database

Timings (Connolly – Electrostatic)

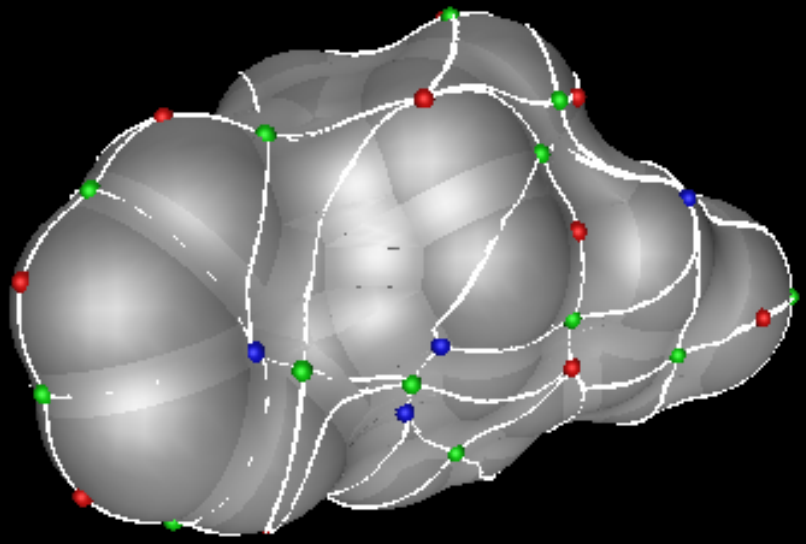


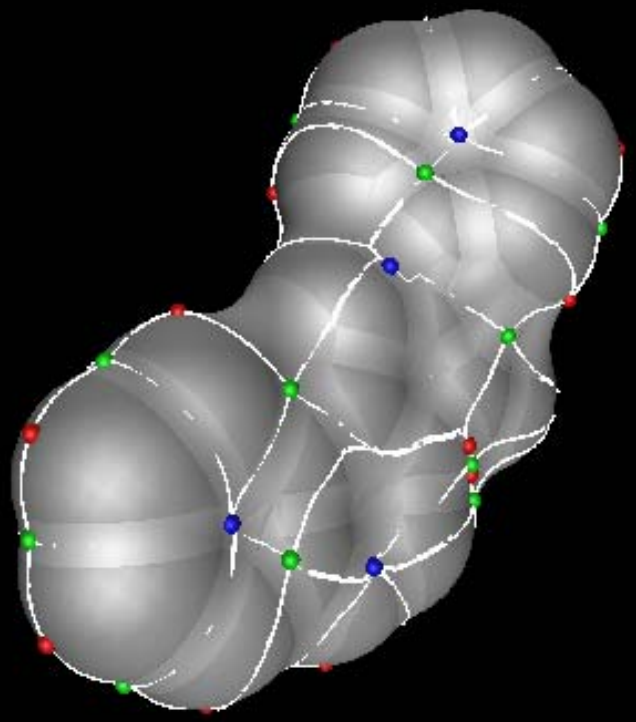
Potential Applications

- Similarity
  - Pattern recognition methods
  - Maximal common subgraphs
- Complementarity
  - Compare ligand graph with graph induced on ligand by receptor
- QSAR
  - Topological indices

Ro15-1788

CGS-8216





Lebuta, J. CGC, 1999

Future Directions

- Spherical Harmonic Surfaces
  - global co-ordinate system
  - star-shaped surfaces

- QM Properties (Clark)
  - molecular electrostatic potential
  - local ionization energy
  - local electron affinity
  - local polarizability

Acknowledgements

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