Modelling Proteins with Coarse-Graining techniques

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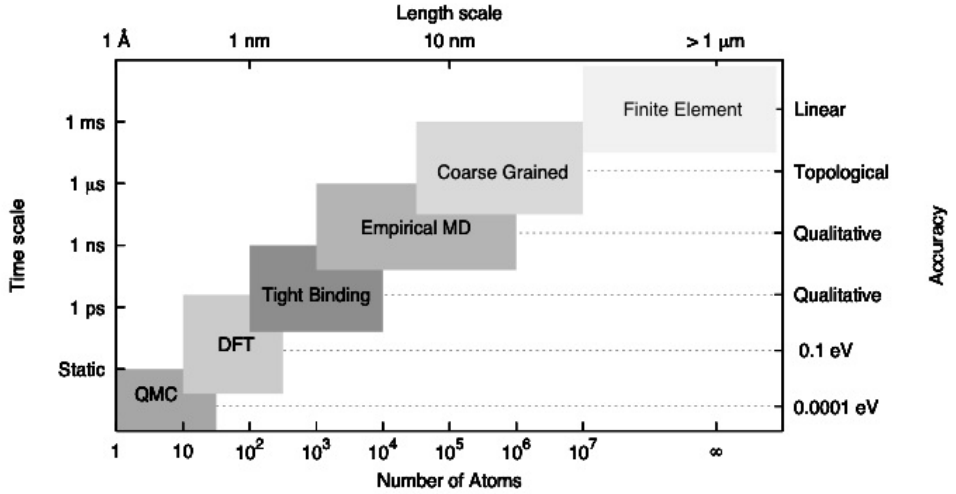
Motivation and Outline

- Ability of proteins to change conformation can be vitally important to their function
- Most widely used approach to computing protein motion is molecular dynamics (MD):

- Computationally expensive

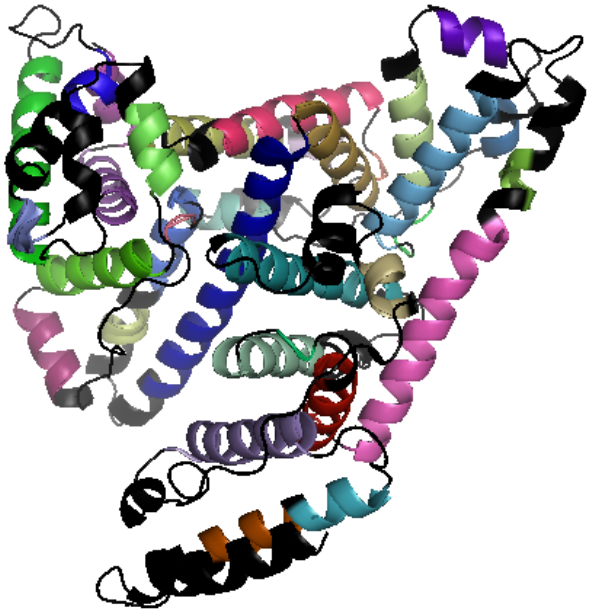
- Force-Field dependent

- High computational demand arises from need for a short timestep (~femtoseconds), whereas biological timescales of interest will be much longer (~ms)



Rigidity Analysis

- Alternative to a force based viewpoint is a constraint based one
- Protein is treated as a network In which all covalent bond lengths and angles are constrained
- Hydrophobic interactions and Hydrogen bonds are also constrained
- Rigidity then determined by balancing constraints against dof.
- Calculated using “pebble-game algorithm” - degrees of freedom (pebbles) being distributed over the constraints.

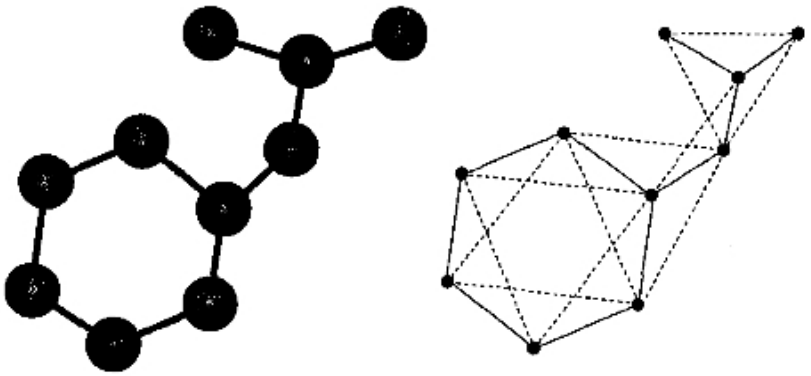


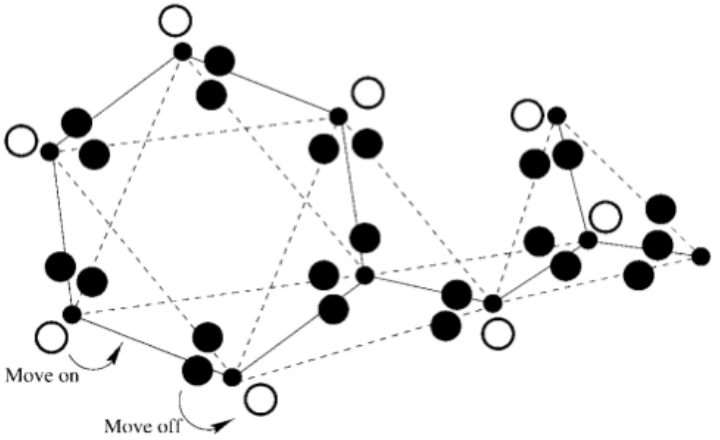
Pebble Game

Network is built up one distance constraint at a time.

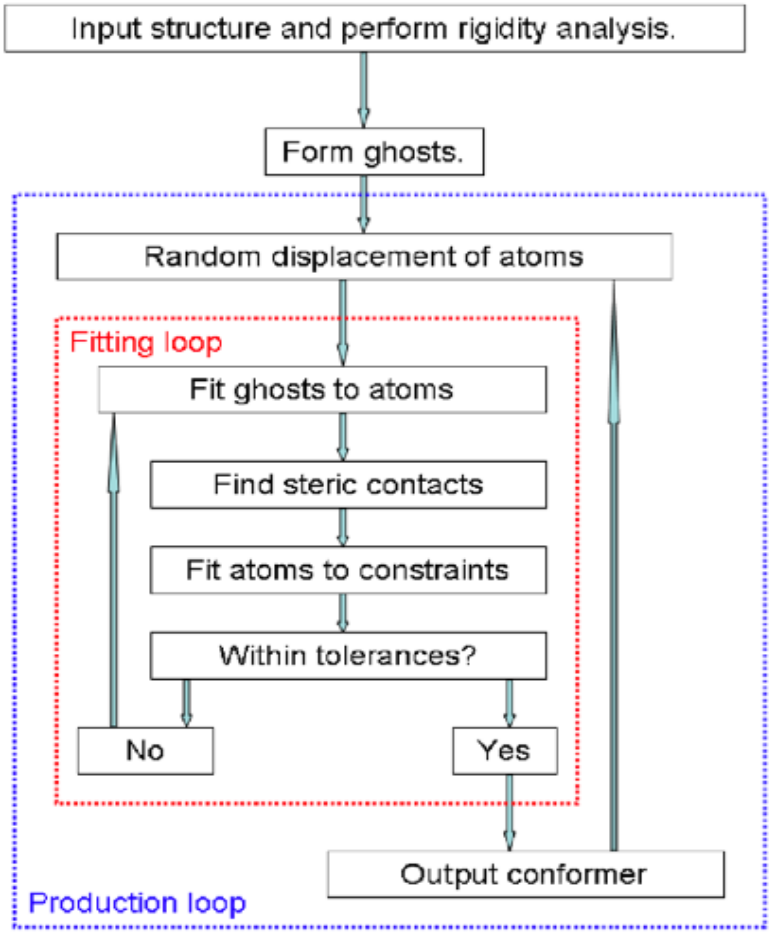
- Place constraint between vertices v1 and v2
- Rearrange pebbles to collect 3 on v1
- Whilst holding 3 pebbles on v1 maximise number on v2
- If number on v2 is 2 the constraint is redundant. Otherwise:
- Attempt to collect a pebble for each other neighbour of v2- if this cannot be done then that constraint is redundant
- Cover independent constraints with a pebble from v2

Once the Pebble Game is finished Rigid Cluster Decomposition can occur





Geometric Simulation- FRODA algorithm



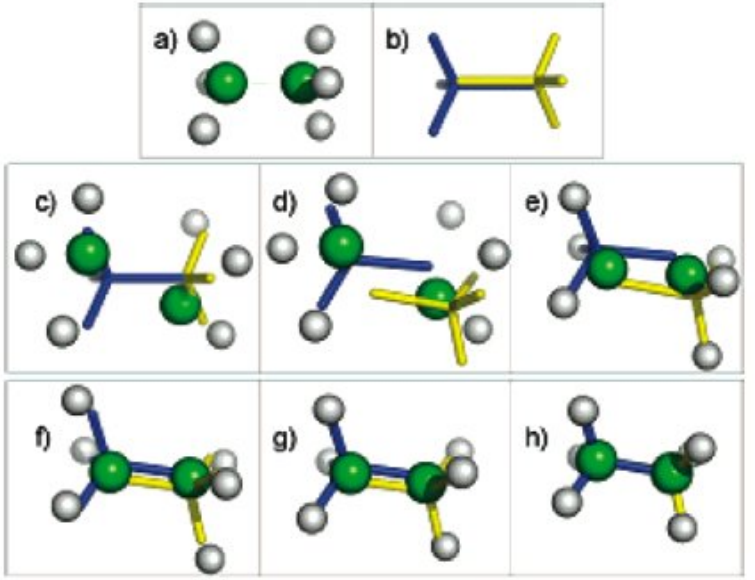
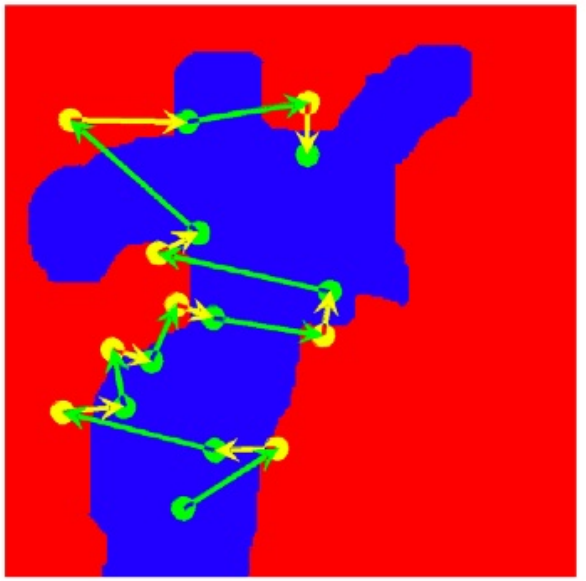
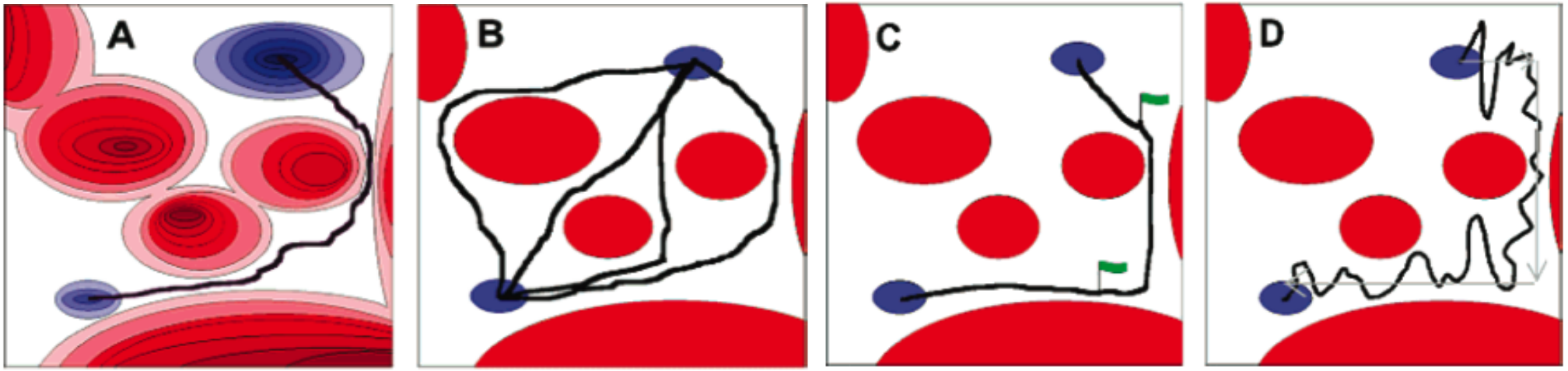


Figure 2. The motion of an ethane molecule as simulated by FRODA. (a) Initial atomic positions; (b) ghost templates; (c) random atomic displacement; (d) fitting of ghost templates to atoms; (e) refitting of atoms to ghost templates; (f) and (g) further iterations of (d) and (e); (h) until a valid new conformer is found.

- Constraints are enforced by iteratively fitting of ghost templates to atomic positions and each atom to the vertex of the appropriate template
- Interatomic potentials replaced by fictitious rigid bodies - “ghost templates”
- Scales roughly as O (N)

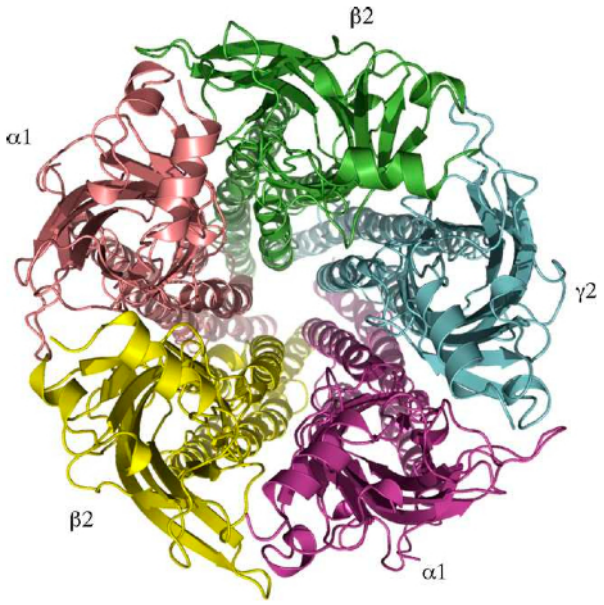
- Extreme speed up in generation of conformers
- Comes at cost of no energetic information for conformers beyond allowed or disallowed
- Causes a larger possible number of pathways
- Can be addressed with targeting – also increases ease of finding very large motions
- Nested Sampling

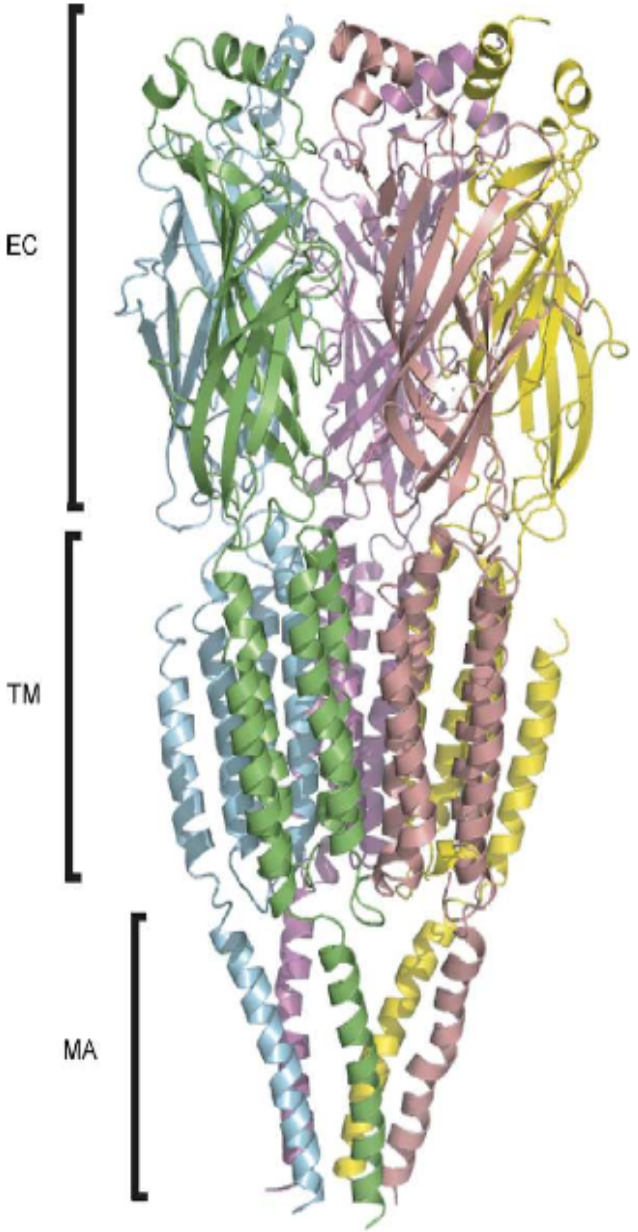




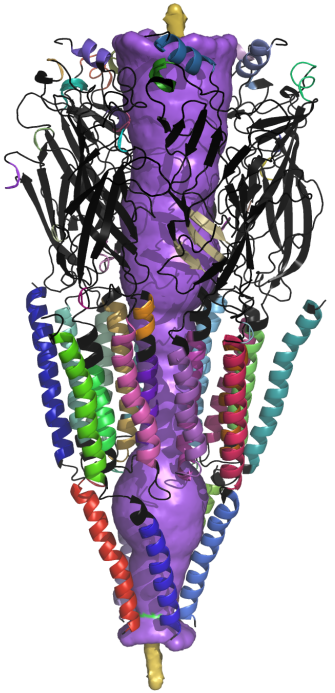
GABA_A Receptor

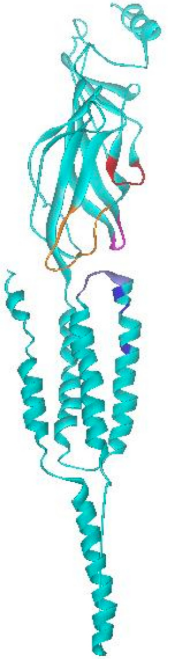
- Ligand Gated Ion Channel
- Responsible for fast neuronal inhibition
- 5 protein subunits
- Member of cys-loop family
- Binds 2 GABA molecules between subunits





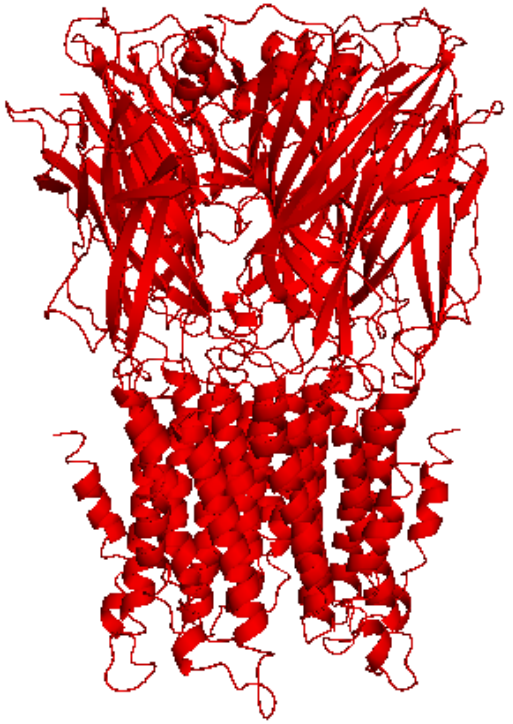
- No Crystallography Data
- What is available?
- Experimental Data of structurally similar nAChR (Closed-state structure of related LGIC, REFER analysis)
- NMA
- Open Structure?





Torpedo nAChR: α subunit

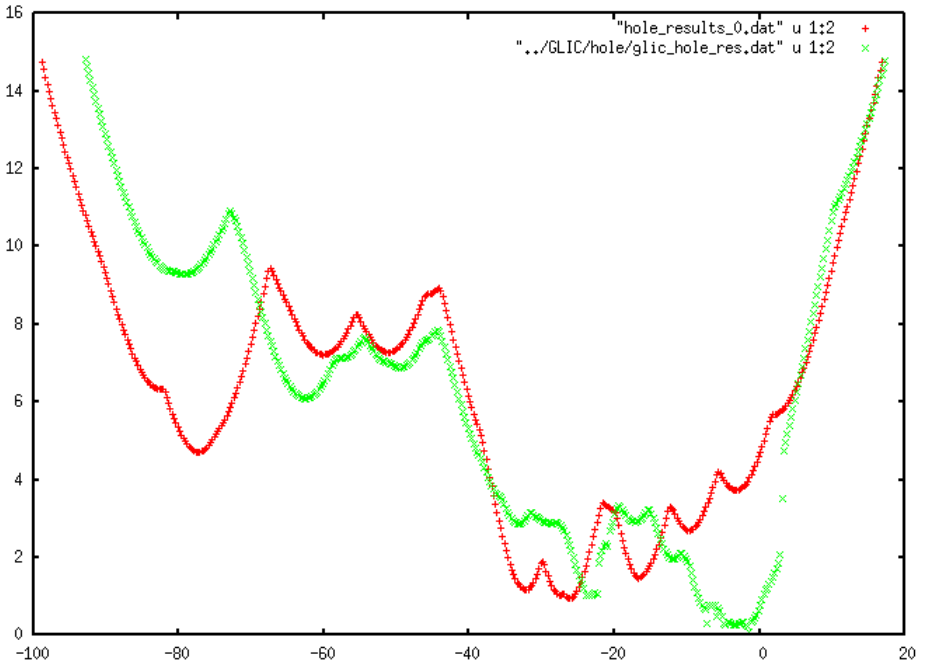
block	aa numbers	sequence	Φ
Loop 2 (purple)	44 - 49	DEVNQI	0.81
Loop 5 (red)	92 - 100	LYNNADGDF	0.93
Loop 7 (C – C, orange)	128 - 142	CEIIVTHFPFDQQNC	0.77
M2 – M3 linker (light blue)	270 - 276	AVPLIGK	0.64
M2 cap (blue)	260, 265, 268	I, P, S	0.89, 0.9, 0.97
M4	408 -	HILLCVF	0.54



- ELIC and GLIC
- Less than 20% amino acid sequence alignment
- But .. very similar structurally and in different states
- NMA and direct targeting available

Summary and Future Work

- Computationally cheap method of deriving stereochemically valid conformers
- Used to examine ion channel pore openings
- Validating methodology by examining Elic to Glic (see right)
- Extend method to nAChR/GABA



Acknowledgements and References

Danny Cole, Mike Payne

Stephen Wells, Mike Thorpe, Emilio Jiminez

P.L. Chau, Ian Martin

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