Modèles géométriques pour la prédiction des interactions macro-moléculaires

Geometric models for the prediction of macro-molecular interactions

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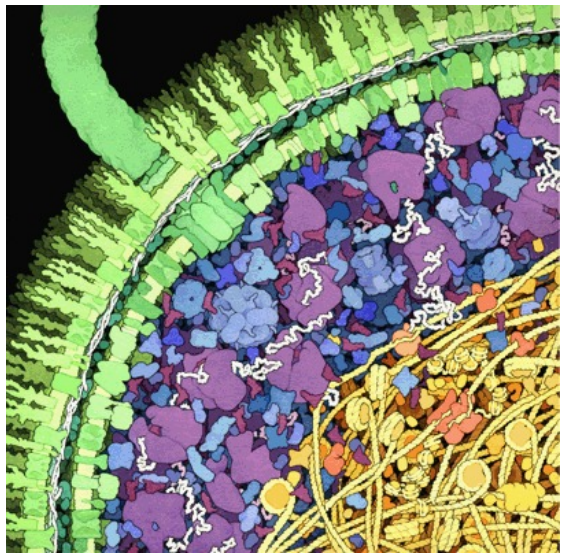

Inside Escherichia coli [D. Goodsell, The machinery of life]

Biological functions involve molecular structure (geometry) + dynamics

Protein complexes – physical chemistry 101

Modeling complexes: the machine learning approach

Modeling complexes: ab initio approaches

Outlook

Proteins and macro-molecular machines

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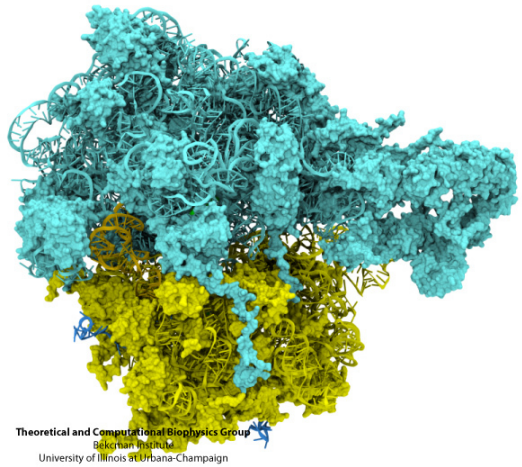
The machinery of life: protein synthesis by the ribosome

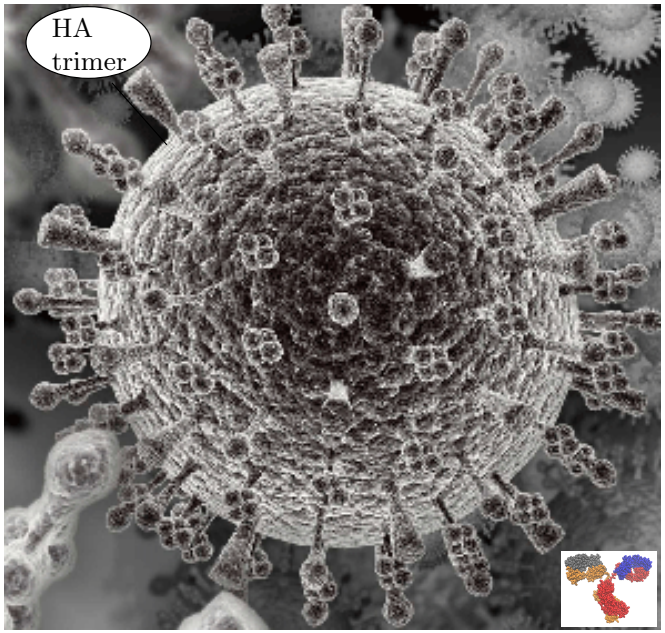
videos-science/video-ribosome-

youtube

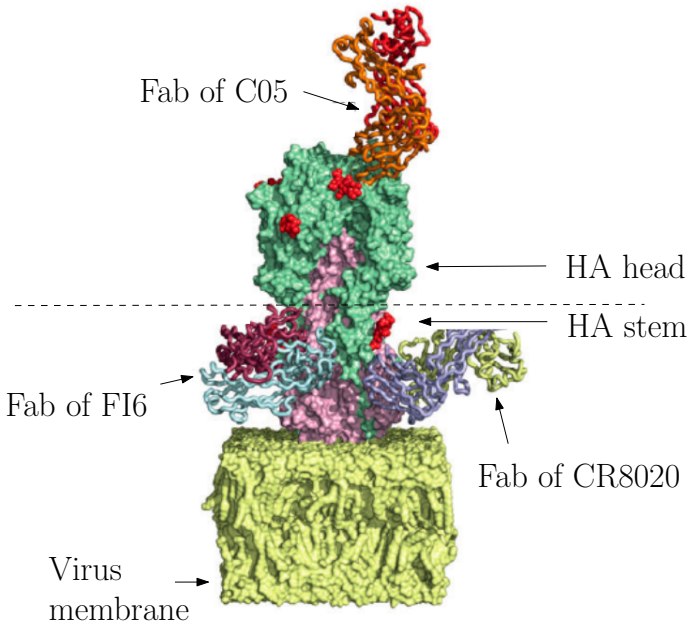


B-cell biology and antibody - antigen complexes

▷ Influenza



▷ (Broadly) neutralizing antibodies

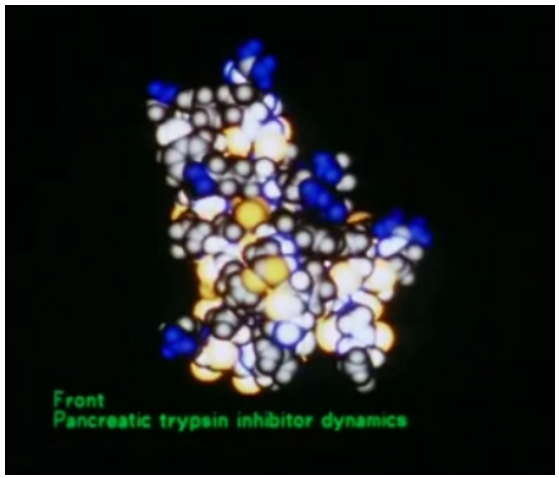


▷ Core questions on IG-Ag complexes

– Determinants of binding affinity
  relationship *affinity - avidity - virus entry inhibition*
– Role of complementarity determining regions (CDRs)
– Determinants of interaction specificity

Molecular dynamics: first simulation of a protein

videos-science/video-michael-levitt-first-MD–simulation



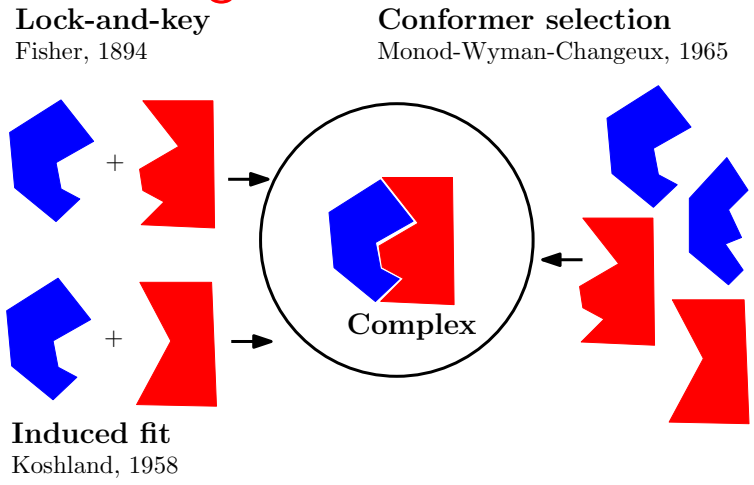
About the simulation duration, quoting M. Levitt "*Cannot remember, but likely less than 100 picoseconds*"

Dynamics...

- Can result is (large) conformational changes
- Account for the entropy of the system

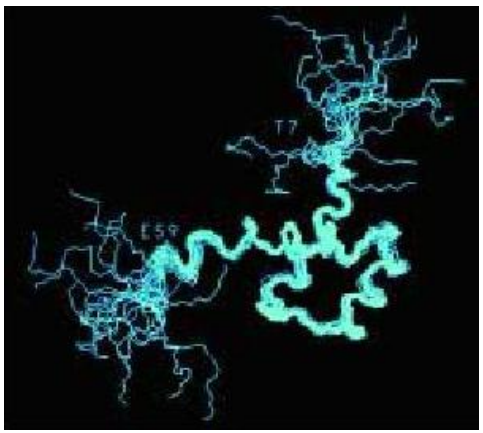
Protein interactions: docking, affinity, specificity

▷ Docking models:



- Lock-and-key: Fisher, 1894
- Induced fit: Koshland, 1958
- Conformer selection, Monod-Wyman-Changeux, 1965

▷ Flexibility matters



▷ Key ingredients:

– Geometry:
complementarity,conformations, flexibility

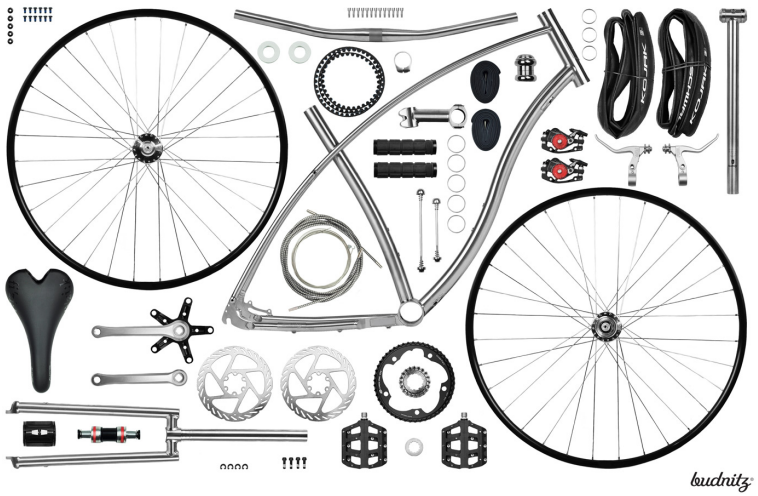
– Physics: enthalpy, entropy

▷ Major challenges (cf CAPRI):

geometry: large conformational changes

physics: entropy based affinity control

The lock and key metaphor is misleading: function is often about dynamics



$$\text{Information(spare parts)} < \text{Information(static bicycle)} \ll \text{Information(moving bicycle)}$$

Proteins and macro-molecular machines

Biological functions involve molecular structure (geometry) + dynamics

Protein complexes – physical chemistry 101

Modeling complexes: the machine learning approach

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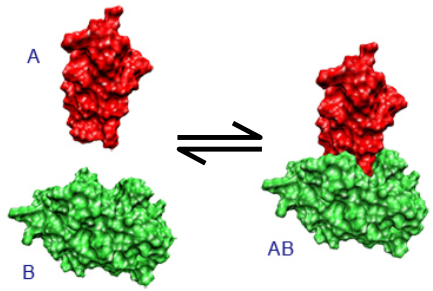
Outlook

Binding affinity: dissociation free energy

▷ Protein complexes rock back and forth



▷ Dissociation constant / free energy as a function of concentrations:

$$K_d = [A][B]/[AB]$$
$$\Delta G_d = -RT \ln K_d/c^\circ = \Delta H - T\Delta S.$$

▷ Binding affinities (thermodynamics):
– random complex: $K_d \sim 10^{-6}$
– high: $K_d \sim 10^{-9}$
– very high: $K_d \sim 10^{-12}$
– extreme: $K_d \sim 10^{-15}$

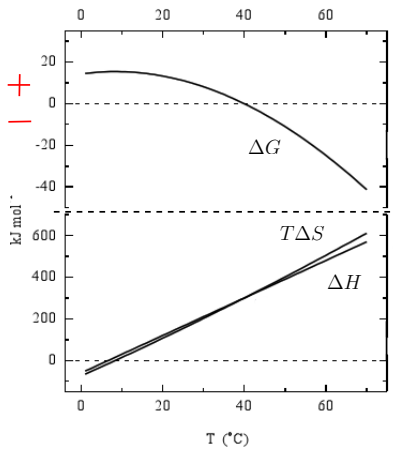
▷ Time scales (kinetics):
– short-lived complexes: $10^{-6}s$ (e.g. enzyme-substrate)
– stable complexes: $10^{3}s$ (e.g. antibody-antigen)
– permanent complexes: $10^{6}s$ (aggregates)

Binding affinity: thermodynamics

- Dissociation constant k_D for $C \leftrightharpoons A + B$:

$$K_d = \frac{[A][B]}{[C]}; \Delta G_d = -RT \ln K_d/c^\circ = \Delta H - T\Delta S. \quad (1)$$

- The enthalpy - entropy compensation:
  - enhanced packing of interface atoms due to attractive forces: $\Delta H < 0$
  - higher packing, restricted atomic motions: $T\Delta S < 0$
- Marginal stability of proteins and complexes:



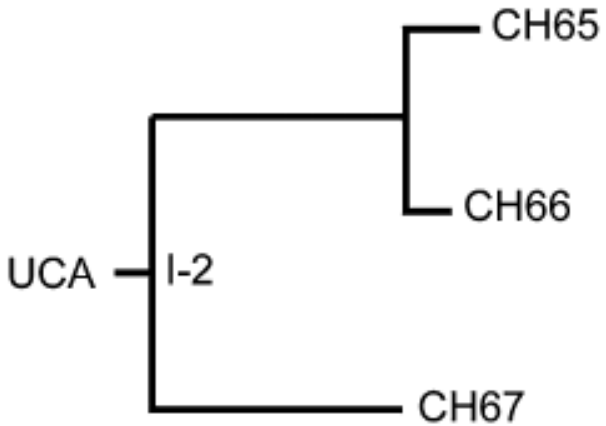
  - Large ΔH and $T\Delta S$ compensate
  - Crossing of curves difficult to predict
  - Marginals stability is key to regulation

Pict. courtesy of Alan Cooper (Thermodynamics of unfolding)

The immune response: affinity maturation

Rigidification of CDR loops limits the entropic penalty upon binding

▷ Antibodies: lineage

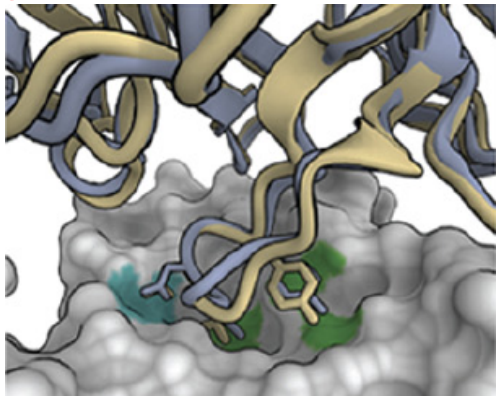


▷ Binding affinities: K_d analysis by SPR

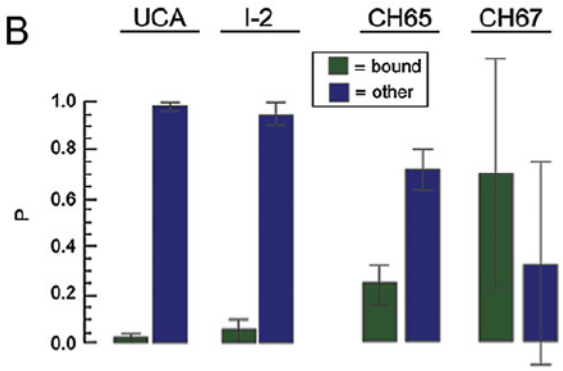
Fab	$K_d(\mu M)$
UCA	118 ± 14
I-2	142 ± 15
CH65	$0.49 \pm .10$
CH67	0.36 ± 0.04

CH65 $\sim$ CH67; wrt UCA:
$\Rightarrow \sim$ 200-fold improvement

▷ But UCA and CH65 have similar binding modes!!!



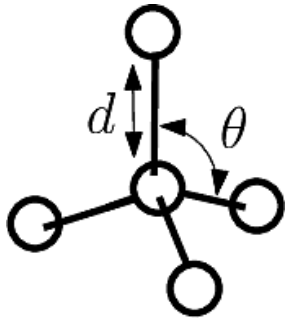
▷ Solution: time spent bound conformations – long MD simulations



▷Ref: Harisson et al; PNAS 110, 2013

Force fields: the potential energy of a (bio-)molecular system

- The $3n-6$ degrees of freedom of a molecule:



  - types for atoms (element, bonds)
  - covalent: bond lengths, angles
  - non covalent: pairwise distances
  - solvent model

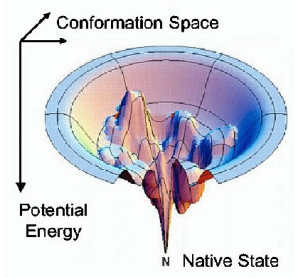
- Potential energy:

$$U_{\text{total}} = E_{\text{bond}} + E_{\text{angle}} + (E_{\text{proper}} + E_{\text{improper}}) + (E_{\text{vdw}} + E_{\text{electro}}) \qquad (2)$$

E_{bond}: bonds
E_{angle}: covalent angles
E_{proper}: proper dihedrals
E_{improper}: improper dihedrals
E_{vdw}: van der Walls
E_{electro}: electrostatics

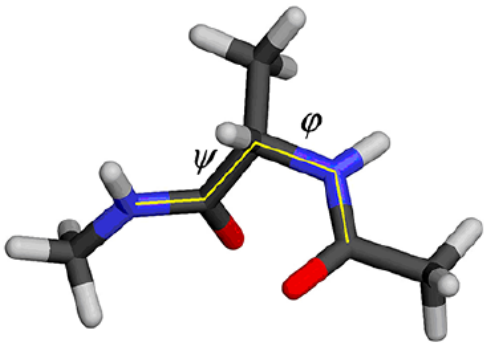
- Examples:

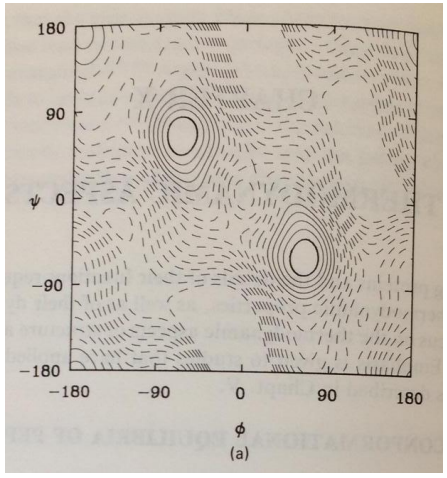
  - AMBER: $S_u = (73, 133, 112, 3, 14, 758)$
    1093 unique parameters
  - CHARMM: $S_u = (85, 152, 209, 13, 33, 1)$
    493 unique parameters
  - MARTINI: $S_u = (16, 4, 0, 2, 21, 3)$
    46 unique parameters

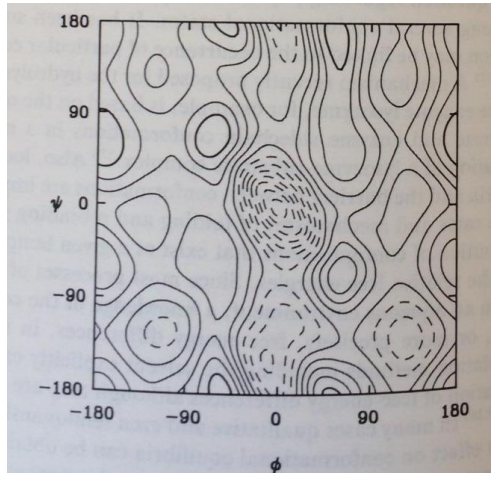


Potential energy landscapes: illustration

- Potential energy map: vacuum (PE) versus solvated (PMF):

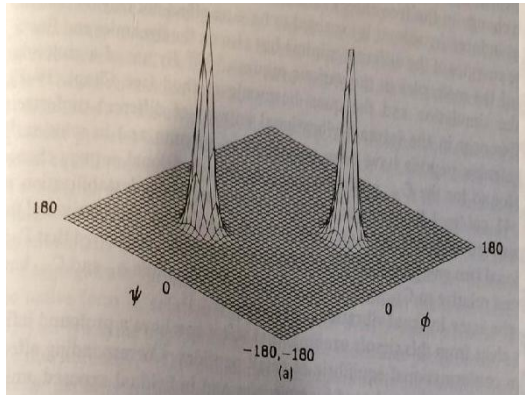


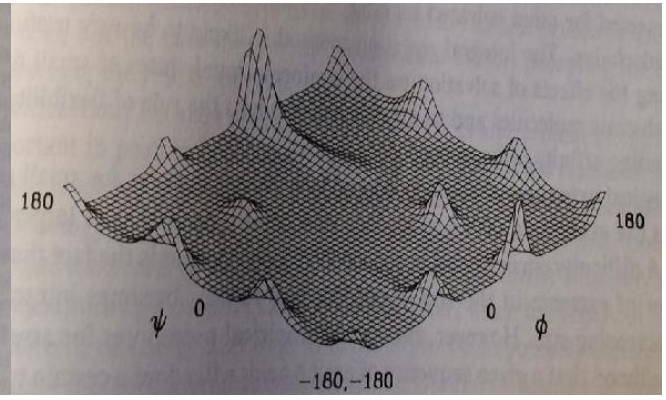




- Corresponding Boltzmann-weighted probability maps:

Solvent stabilizes many more conformers–hydrogen bonding.

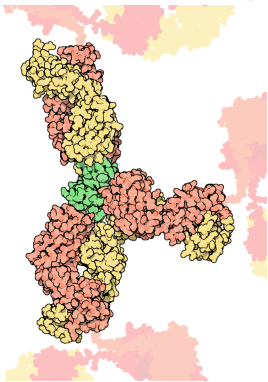




- Ref: Petitt, Karplus, Chem. Phys. Lett., 121, 1985

Binding affinity: direct calculation

- A standard antibody-antigen complex:



- Model without solvent:
  - FAB of antibody $\sim$ 3000 atoms
  - Antigen (lysozyme) $\sim$ 1000 atoms
  - One conformation: 1 point in $\mathbb{R}^{3\times 4000}$

- ΔG_d as a multidimensional integral with U the PE and W the solvent PMF:

$$\Delta G_d = -\frac{1}{\beta} \ln \left(\frac{8\pi^2}{c^\circ} \frac{\int e^{-\beta(U(r_A)+W(r_A))} dr_A \times \int e^{-\beta(U(r_B)+W(r_B))} dr_B}{\int e^{-\beta(U(r_C)+W(r_C))} dr_C} \right)$$

- Ref: Woo ad Roux, PNAS 102 (19), 2005
- Ref: Gilson and Zhou, Ann. Rev. Biophys. Biomol. Struct., 36, 2007

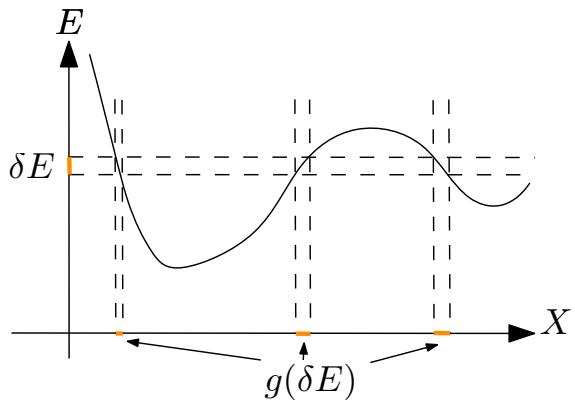
Free energy, density of states, and volume calculations:

why are these questions so difficult?

▷ Partition function and density of states:

$$Z = \sum_{x_i:\text{state}} e^{-\beta E(x_i)}$$

$$= \sum_{j:\text{energy level}} g(E_j) e^{-\beta E_j}$$



▷ Volume of polytopes, hardness: (Thm.) The volume of a polytope $K \subset \mathbb{R}^d$ can be approximated within a relative error ε with probability $1 - \delta$ using $O^*(d^4)$ oracle calls.

▷ Fundamental issues:

- regions (catchment) basins in conformational space are not polytopes
- Boltzmann's distribution *concentrates* the mass (probability)... how i.e. yielding which kind of entropy based stabilization?

▷Ref: Dyer, Freeze, Kannan, J. ACM 38(1), 1991

▷Ref: Lovász, Vempala, J. Comput. Syst. Sci., 71(2), 2006

▷Ref: Lelièvre, Stoltz, Rousset, Free energy computations, World Sc., 2010

Estimating Kd: two routes

- Learning: regression
  - Databases of crystal structures + affinity measurements
  - Regression models involving relevant variables
- From first principles
  - Atomic models of the partners
  - A force field and a thermodynamic sampling algorithm

Proteins and macro-molecular machines

Biological functions involve molecular structure (geometry) + dynamics

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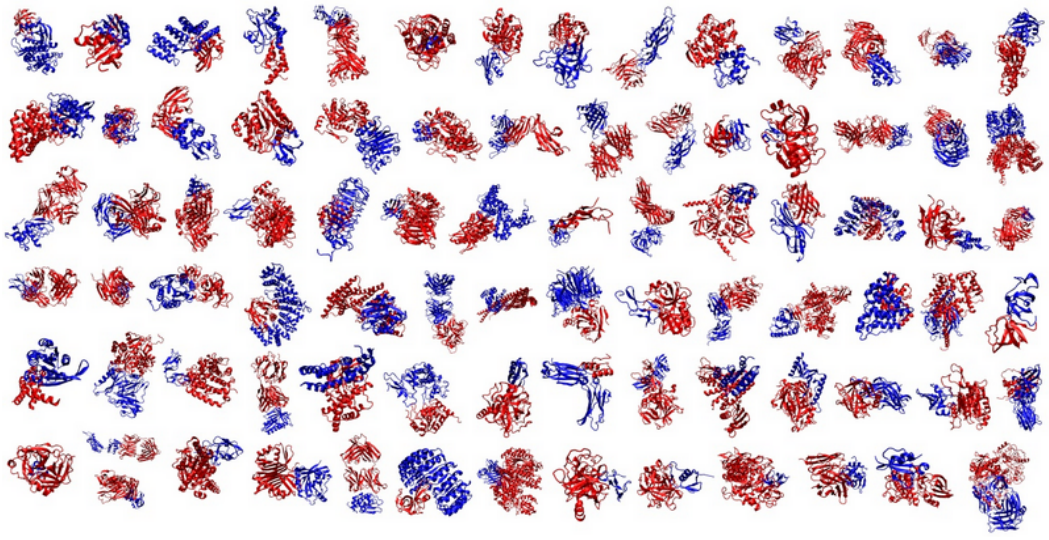
Modeling complexes: ab initio approaches

Outlook

Protein interactions: the structure affinity benchmark

http://bmm.cancerresearchuk.org/~bmmadmin/Affinity/



▷ Dissociation constant vs affinity

$$\Delta G_d = -RT \ln K_d/c^\circ$$

▷ NB: in general, bound partners only do not suffice to get accurate predictions

- ▷ 144 protein complexes
  - 17 IG - Ag complexes
- ▷ Binding affinity known: ITC, SPR
  - caveat: order of magnitude matter (pH, ion strength, . . .)
- ▷ Three crystal structures known: bound complex + 2 unbound partners

▷Ref: Kastritis et al; Protein Science (20), 2011

Binding affinity estimation as a regression problem

- Regression:
  - Regression: predicting the value of a continuous (dependent) variable from the values of other (independent) variables.
  - ΔG is the dependent variable
  - Many types of regressors: least squares, regularized least squares, k nearest neighbours, regression trees, multivariate adaptive splines, ...
- Adequate variables: two classes of methods
  - Large collections of parameters coding distances, biochemical properties (H-bonds, properties of a.a.), conservation of a.a., etc.

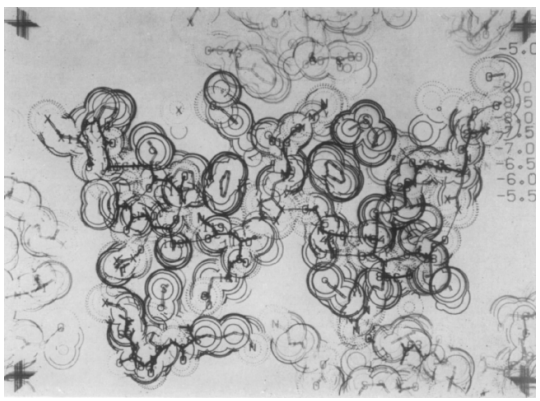
    NB: requires a close monitoring to avoid overfitting.
  - A small number of them: more precise encoding of enthalpy and entropy related quantities.
- Overfitting and sparsity
  - Variable selection and regularization via the LASSO
  - Sparse model enumeration + cross validation

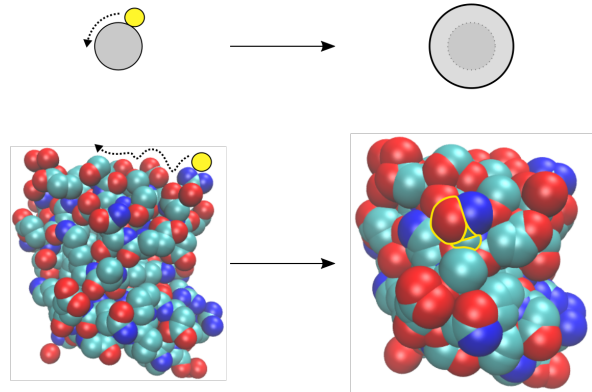
Solvent Accessible Models: the birth

From Lee-Richards, *The interpretation of protein structures: Estimation of static accessibility*:

"*The successful elucidation of the structure of a protein by single-crystal diffraction procedures provides a list of atomic co-ordinates whose reliability will vary in different parts of the molecule.*"

"*The topology of the surface of a protein is intimately related to its function; parts of the surface are directly involved in interactions with other molecules; the solvent- protein interface is almost certainly related to the structure of the native molecule; and the chemical reactivity of the various functional groups will depend on their relation to this interface.*"





▷Ref: Lee and Richards, JMB, 3 (55), 1971

▷Ref: Connolly, J. Appl. Crystallography, 1983

▷Ref: Akkiraju and Edelsbrunner, Discrete Appl. Math., 1996

Solvent Accessible Models: the rise

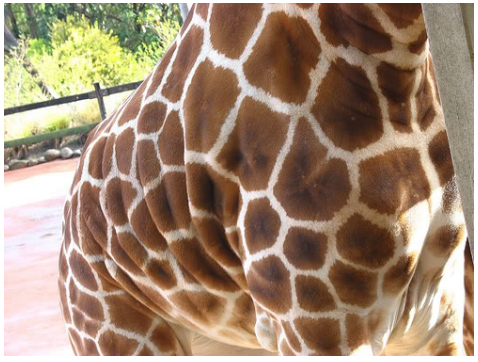
From Chotia, *Structural invariants in protein folding*:
"*An analysis of 15 protein structures indicates: First, the loss of accessible surface area by monomeric proteins on folding–proportional to hydrophobic energy–is a simple function of molecular weight; second, the proportion of polar groups forming intramolecular hydrogen bonds is constant; and third, protein interiors are closely packed, each residue occupying the same volume as it does in crystals of amino acids.*"

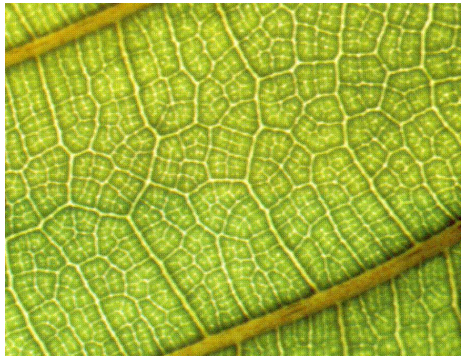
From Janin, *Principles of protein–protein recognition*:
"*The formation of the protein–protein interface by the insulin dimer, the trypsin-PTI complex and the* $\alpha\beta$ *oxyhaemoghbin dimer removes 1,130–1,720* $\AA^2$ *of accessible surface from contact with water. The residues forming the interface are close packed: each occupies the same volume as it does in crystals of amino acids. These results indicate that hydrophobicity is the major factor stabilising protein–protein association, while complementarity plays a selective role in deciding which proteins may associate.*"

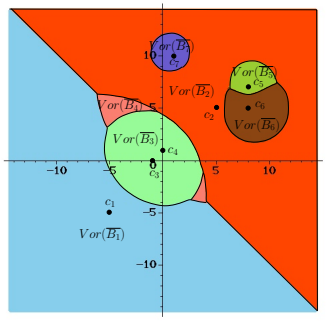
▷`Ref: Chothia, Nature 254, 1975`

▷`Ref: Janin, Nature 256, 1975`

Voronoi diagrams in Biology, Geology, Engineering

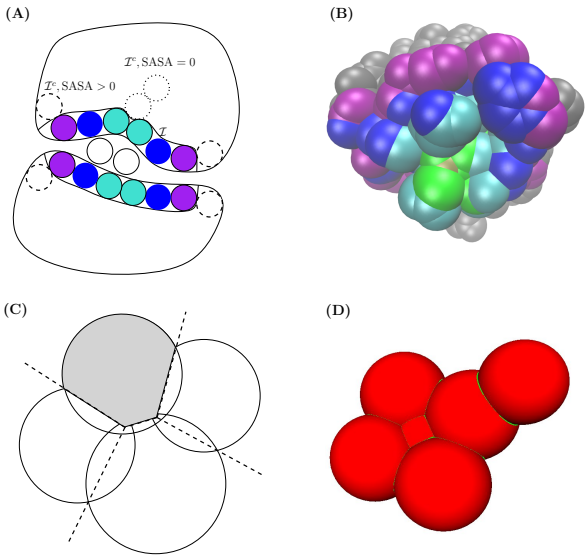






Our parameters: overview

▷ Our variables: proxys for enthalpy and (vibrational) entropy variations upon binding, the latter based on packing properties



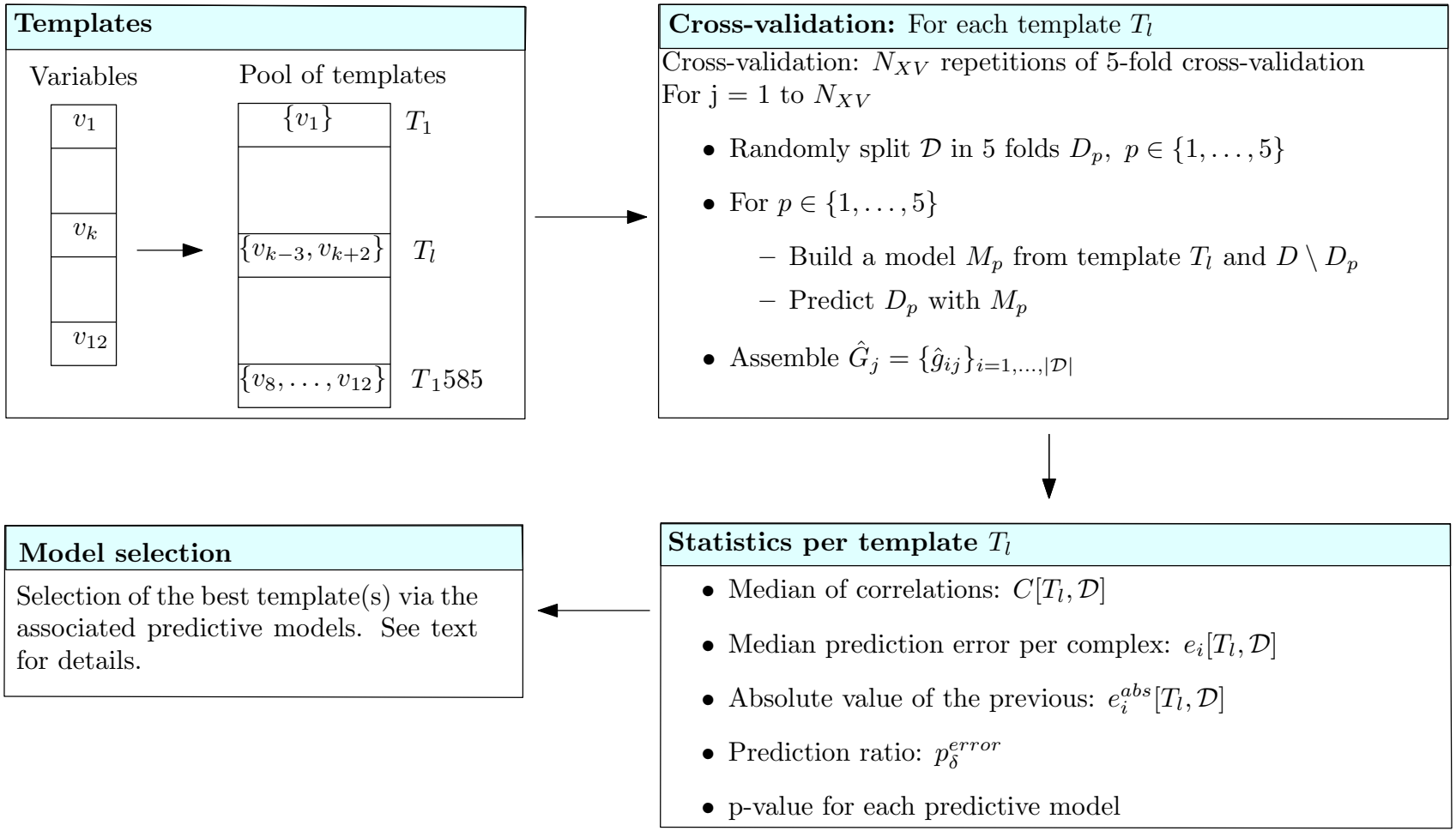
▷ Or particular interest

- IVW-IPL: inverse volume-weighted internal path length
- $\text{NIS}^{charged}$: fraction of charged residues on the non-interacting surface (NIS)

- **(A)** Binding patch and labeling of interface atoms The non interface atoms ($\mathcal{I}^c$) are split into those which retain solvent accessibility (SASA > 0, dashed balls), and those which do not (SASA $= 0$, dotted balls)

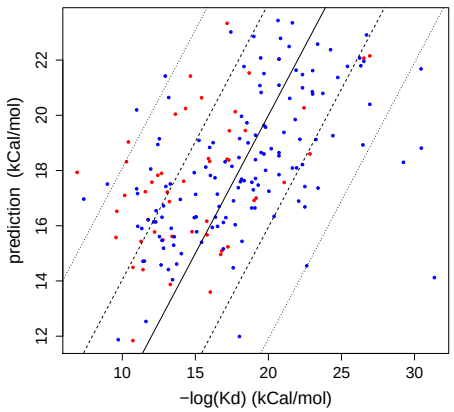
  NB: **Buried Surface Area** or **BSA**: area of colored spherical caps
- **(B)** Shelling order of an atom: smallest number of atoms traveled to reach an exposed non interface atom, i.e. an atom belonging to $\mathcal{I}^c$ and with SASA > 0 (in grey)
- **(C,D)** Atomic packing: via Voronoi volumes

Statistical methodology

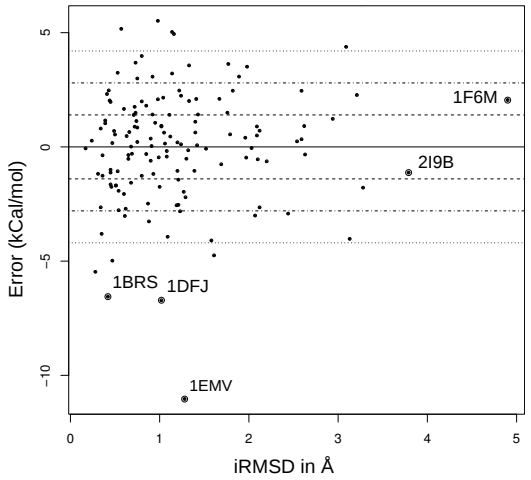


Results on the structure affinity benchmark

▷ Predictions vs measurements



▷ Hardness vs flexibility



▷ State-of-the-art binding affinity estimates on the SAB:

– Whole SAB: K_d within one and two *OOM* in 48% and 79% of cases
  high resolution (2.5Å): K_d within one and two *OOM* in 62% and 89%
– Absence of correlation between prediction hardness and protein flexibility

▷ Landmarks:

– 1 OOM (order of magnitude): 1.4 kcal/mol
– kT per molecule, or RT per mole at room temperature: 0.6 kcal/mol
– ΔG_d, exp. errors $\sim$ 0.3 kcal/mol

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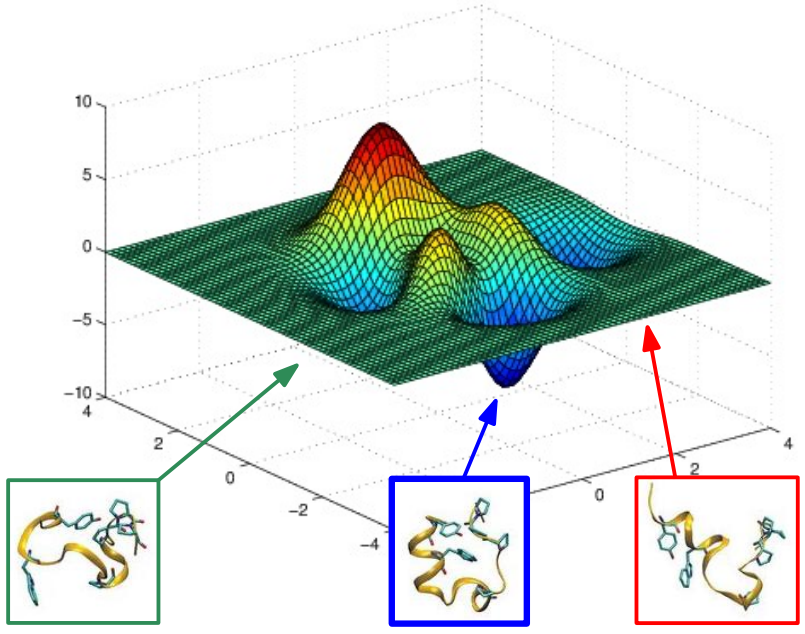
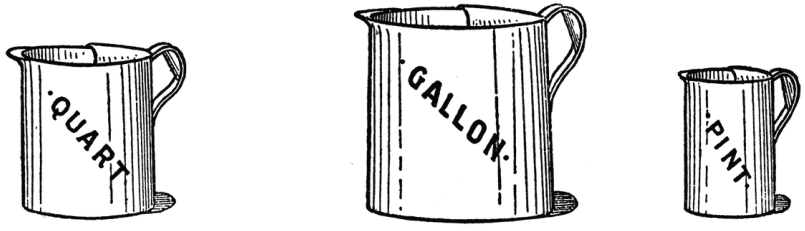
Outlook

Emergence of function from Structure – Thermodynamics – Dynamics



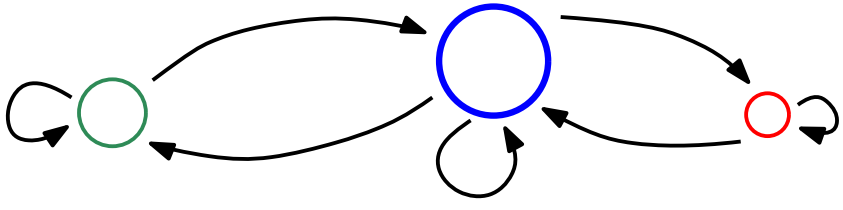
Potential Energy Landscape

- large number of local minima
- enthalpic barriers
- entropic barriers



Structure: stable conformations i.e. local minima of the PEL

Thermodynamics: meta-stable conformations i.e. ensemble of conformations easily inter-convertible into one - another.



Dynamics: transitions between meta-stable conformations e.g. Markov state model

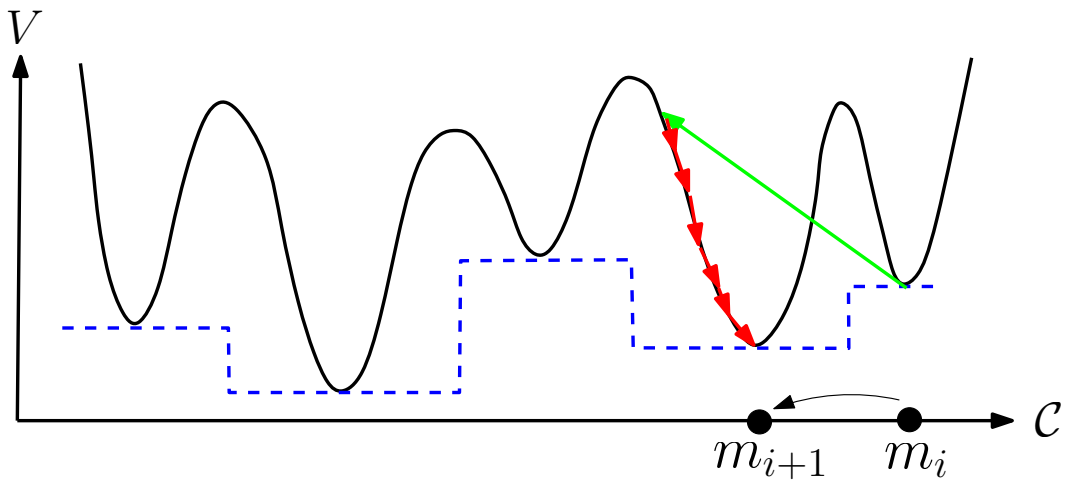
Contributions discussed

- (Structure) Sampling potential energy landscapes
- (Thermodynamics) Simplifying potential energy landscapes

Exploring Potential Energy Landscapes:

basin hopping

- ▷ Goal: enumerating low energy local minima
- ▷ Basin-hopping and the basin hopping transform
  - Random walk in the space of local minima
  - Requires a *move set* and an *acceptance test* (cf Metropolis)
    and the ability to descend the gradient (*quenching*)
    aka energy minizations
- ▷ Limitation: no built-in mechanism to avoid staying trapped

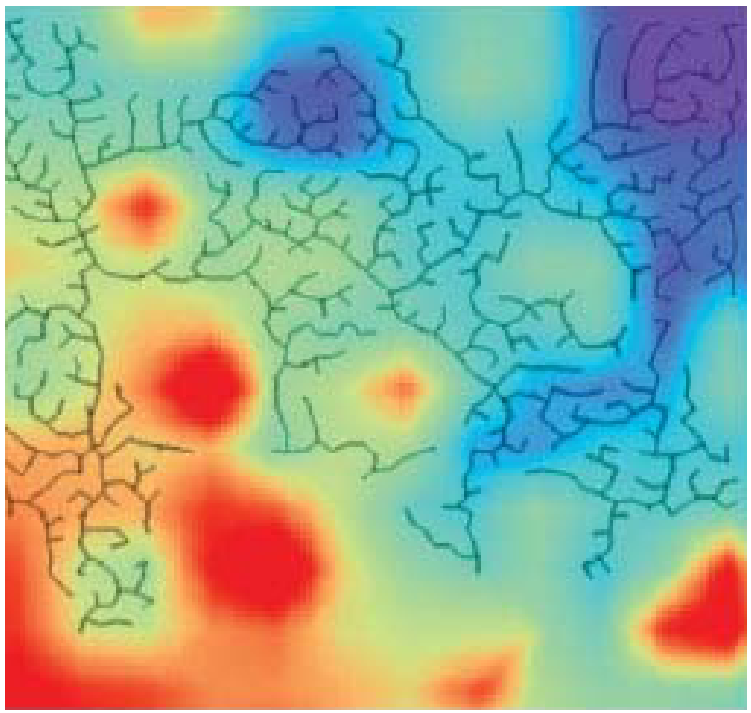


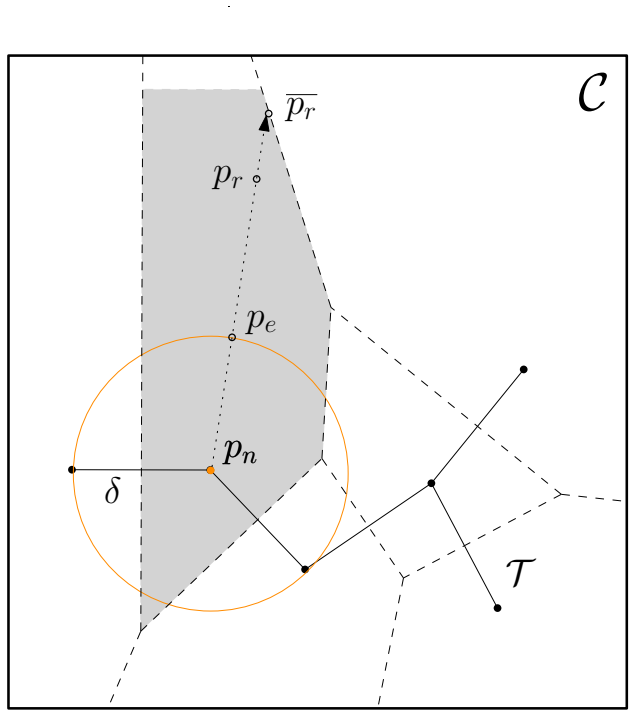
▷Ref: Li and Scheraga, PNAS, 1987

Exploring Potential Energy Landscapes:

transition based rapidly exploring random trees (T-RRT)

- ▷ Goal: sample basins and transitions
- ▷ Algorithm growing a random tree favoring yet unexplored regions
  - node to be extended selection: *Voronoi* bias
  - node extension: interpolation + Metropolis criterion (+temperature tuning)
- ▷ Limitation: oblivious to local minima



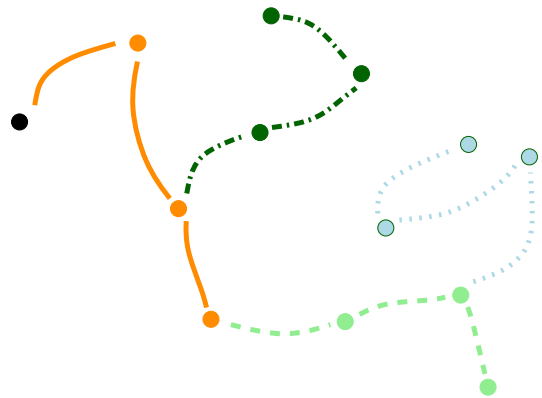


▷Ref: LaValle, Kuffner, IEEE ICRA 2000

▷Ref: Jaillet, Corcho, Pérez, Cortés, J. Comp. Chem, 2011

Exploring energy landscapes:
a generic approach yielding BH, T-RRT,...

- Input: potential energy function with million, billion, trillion of local minima
- Goal: enumerate low energy + persistent local minima
- Hybrid algorithm: alternate BH and T-RRT extensions



- Key ingredients:
  - Boosting the exploration of yet-unexplored regions – Voronoi bias
  - Managing distances while alleviating concentration phenomena
  - Favoring spatial adaptation – local Metropolis-Hasting tests

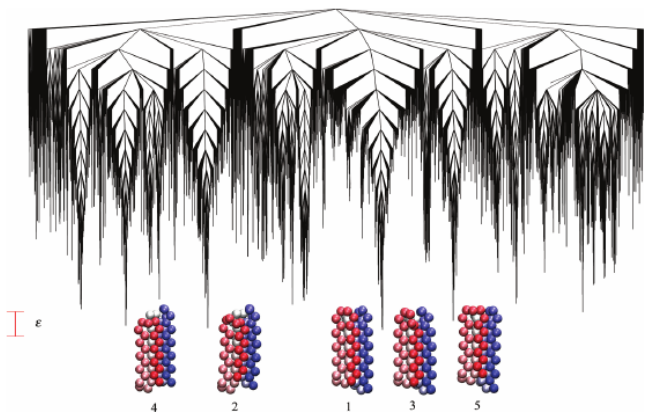
Ref: Roth, Dreyfus, Robert, Cazals; J. Comp. Chem.; 2015

Protein model BLN69: model and force field

- Description:
  - Three types of Beads: : hydrophobic(B), hydrophylic(L) and neutral(N)
  - Configuration space of intermediate dimension: 207
  - Challenging: frustrated system
  - Exhaustively studied: DB of $\sim 450k$ critical points (Industry)

$$V_{BLN} = \frac{1}{2} \cdot K_r \sum_{i=1}^{N-1} (R_{i,i+1} - R_e)^2 + \frac{1}{2} K_0 \sum_{i=1}^{N-2} (\theta_i - \theta_e)^2 + \epsilon \cdot \sum_{i=1}^{N-3} [A_i(1 + \cos\phi_i) + B_i(1 + 3\cos\phi_i)]$$
$$+4\epsilon \sum_{i=1}^{N-2} \sum_{j=i+2}^{N} \cdot C_{ij}[(\frac{\sigma}{R_{i,j}})^{12} - D_{ij}(\frac{\sigma}{R_{i,j}})^{6}]$$

- Disconnectivity graph: describes merge events between basins

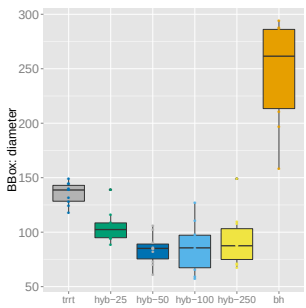


- Ref: Honeycutt, Thirumalai, PNAS, 1990
- Ref: Oakley, Wales, Johnston, J. Phys. Chem., 2011

Exploring energy landscapes: performances of Hybrid

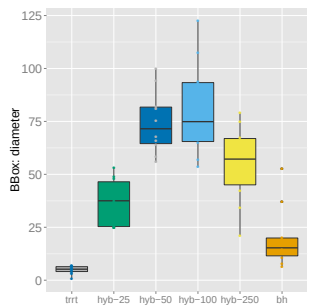
- ▷ Contributions: enhanced exploration of low lying regions of a complex landscape
- ▷ Protocol:
  - Contenders: BH, T-RRT, Hybrid for various parameter values b
  - Count and assess the local minima reported from two reference databases:
    $BLN69 - min - all$: 458,082 minima
    BLN69-min-E_{-100}: 5932 minima.

- Bounding box $\emptyset$: all mins



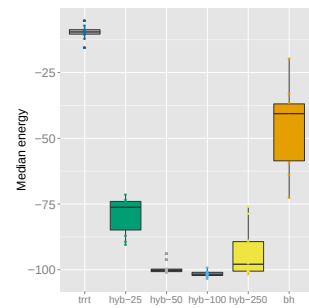
$BLN69 - min - all$

vs low lying



$BLN69 - min - E_{-100}$

- Median energies



$BLN69 - min - all$

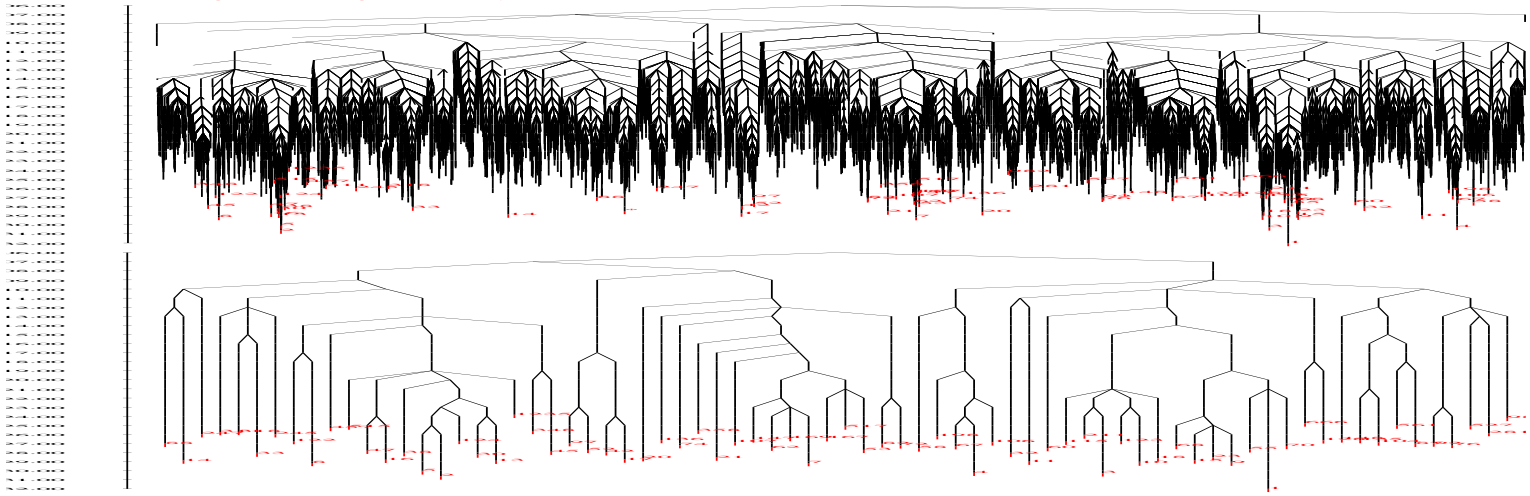
- ▷ Assessment:
  - Combines critical building blocks:
    minimization, spatial exploration boosting, nearest neighbor searches
  - Bridging the gap to thermodynamics

▷Ref: Oakley et al; J. of Physical Chemistry B; 2011

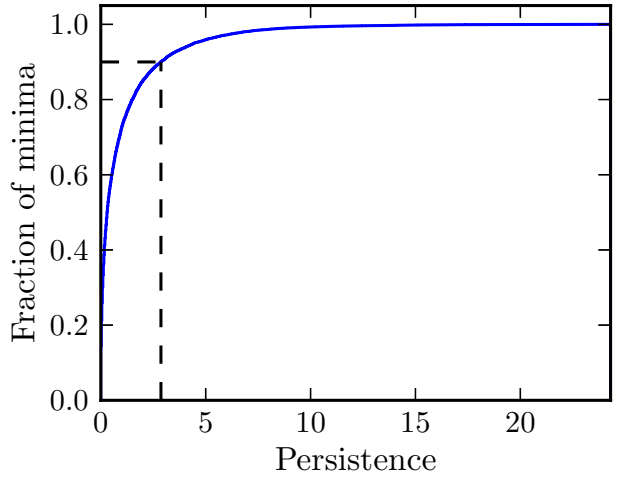
▷Ref: Roth, Dreyfus, Robert, Cazals; J. Comp. Chem.; 2015

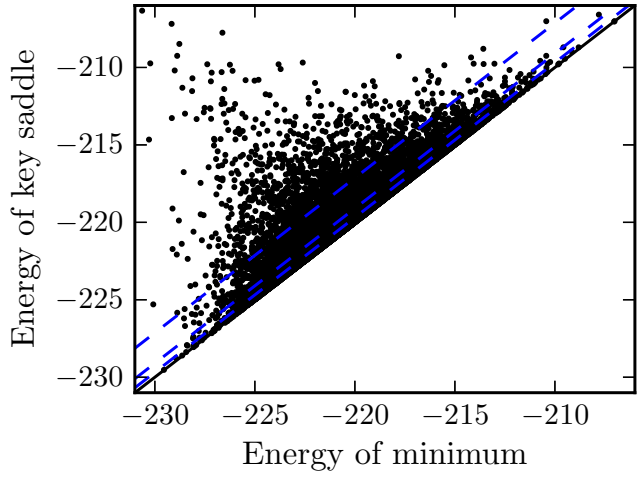
Binary Lennard-Jonnes LJ_{60}

- Coarse graining the system:



- Using the distribution of barriers' heights:





- Ref: Carr, Mazauric, Cazals, Wales; J. Chem. Phys.; 2016

Proteins and macro-molecular machines

Biological functions involve molecular structure (geometry) + dynamics

Protein complexes – physical chemistry 101

Modeling complexes: the machine learning approach

Modeling complexes: ab initio approaches

Outlook

Learning vs ab-initio approaches: different philosophy? No...it's rather a matter of *resolution*

- Force field development:
  - Tuning parameters so as to match experimental data (heat capacity, density, viscosity, T for state changes, surface tension, etc) using (small) organic molecules, then extrapolating to bio-molecules
- Affinity predictions:
  - Tuning parameters yielding faithful affinity estimates
- Main difference: microscopic versus macroscopic modeling
- Commonalities: model optimization using regression, cross-validation, Bayesian models, etc

Ref: Pande et al, The J. Phys. Chem. letters, 5 (11), 2014

Ref: Horta et al, J. of Chem. Theory and Computation, 12(8), 2016

What are we critically missing to enter the era of atomic level engineering?

- Fundamental insights into equilibrium thermodynamics require:
  - Potential energy: enhanced exploration algorithms
    akin to shape / model learning
  - Free energy: enhanced multicanonical sampling algorithms
    akin to high dimensional volume calculations
  - Dynamics: multi-scale Markov state models

- Countless breakthroughs in terms of applications:
  - Biology: understanding processes; understanding evolution
    coding sequences $\sim$ 80 millions in `UniProt/TrEMBL`
    structures: $125,000$ in the Protein Data Bank
  - Medicine: immunology, cancer, neurosciences,...
  - Synthetic biology
  - Material sciences

▷Ref: UniProt/Trembl: http://www.ebi.ac.uk/uniprot/TrEMBLstats
▷Ref: PDB: http://www.rcsb.org/pdb/static.do?p=general_information/pdb_statistics/index.html

Hall of fame

- More than 20 structural biology-related Nobel Prizes in 50 years:
  - J. Kendrew and M. Perutz, chemistry 1962: *for their studies of the structures of globular proteins*
  - F. Crick, J. Watson and M. Wilkins, medecine 1962: *for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material*
  - C. Anfinsen, chemistry 1972: *for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation*
  - K. Wutricht and J. Fenn, chemistry 2002: *for the development of methods for identification and structure analyses of biological macromolecules*
  - R. Kornberg, chemistry 2006: *for his studies of the molecular basis of eukaryotic transcription*
  - V. Ramakrishnan, T. Steitz, A. Yonath, chemistry 2009: *for studies of the structure and function of the ribosome*
  - M. Karplus, M. Levitt, A. Warshell, chemistry 2013: *for the development of multiscale models for complex chemical systems*

Methods: molecular simulation

The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

The Nobel Prize in Chemistry 2013

© Harvard University
Martin Karplus

Photo: © S. Fisch
Michael Levitt

Photo: Wikimedia Commons
Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

Connexions between my talk and Prof. Boissonnat's course

C1: Modèles géométriques discrets
→ Voronoi models in various guises

C2: La puissance de l'aléa
→ Randomized constructions, Monte Carlo algorithms

C3: Le calcul géométrique
→ Robust geometric predicates and constructions
The Computational Geometry Algorithms Library – code and spirit!

C4. Génération de maillages
→ The Poisson-Boltzmann equation

C5: Courbes et surfaces
→ Surface / shape reconstruction
→ Convergence of regressors

C6: Espaces de configurations
→ Conformational spaces: exploration, planning

C7. Structures de données géométriques
→ Geometric approximation theory, geometric optimization

C8: Analyse géométrique et topologique des données
→ Topological persistence, geometric/topological data analysis

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The Structural Bioinformatics Library

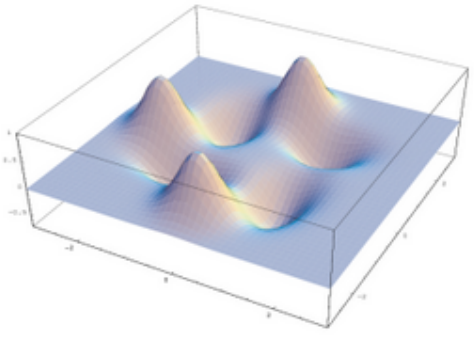
HOME WHAT IS THE SBL ? APPLICATIONS GETTING THE SBL DOCUMENTATION SBL COMMUNITY F.A.Q

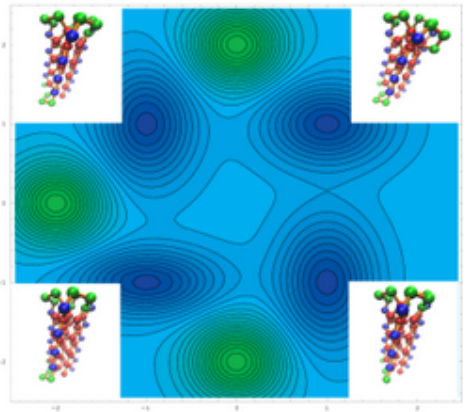
Structural Bioinformatics Library

A C++/Python API for solving structural biology problems.

Conformational analysis:

modeling energy landscapes





Why adopt the SBL ?

For Biologists:

- comprehensive in silico environment providing applications,
- answering complex bio-physical problems,
- in a robust, fast and reproducible way.

For Developers:

- broad C++/python toolbox,
- with modular design and carefull specifications,
- fostering the development of complex applications.

http://sbl.inria.fr

▷Ref: Cazals and Dreyfus; Bioinformatics, 2016

Acknowledgments

- Former Inria director and mentor
  - Gilles Kahn (†)
- Colleagues and students
  - Jean-Daniel Boissonnat
  - Joël Janin
  - Sylvain Pion (software engineering), Dorian Mazauric (algorithms), Juan Cortés (sampling, AlgoSB)
  - Charles Robert (biophysics, AlgoSB), Pierre Boudinot (immunology), Félix Rey (virology)
  - PhD students: Sébastien Loriot, Tom Dreyfus, Andrea Roth, Simon Marillet, Augustin Chevallier, Romain Tetley
- Inria ... Algorithms-Biology-Structure is already 10 years old