

Elements of Biophysics

Saul Pierotti

October 30, 2019

21/10/19

- The course is made of elements, it is not a complete course
- We want to understand biomolecules
- Structure-function relationship
- The scale of things
- I don't know something if I cannot describe it with a model
 - A model is an equation
- Laser time dependent X ray cristallography allows to see a molecule “breathing”
- The deeper you go in resolution, the more you have to increase the perturbation
 - Bragg diffraction theorem
- Life makes sense only in the light of thermodynamics
- A cell is held together by London forces
- Freeze fracturing
- Atomic force microscope
- rita.casadio@unibo.it
- Complexity means that there are emergent proprieties
 - We do not have models that can predict a cell from its components
- Mitosis, meiosis, apoptosis, developmental biology
- Protein synthesis
- In a cell there are at least 240k different proteins
 - Their relative concentration is of paramount importance
- We are able to label all the neurons in a mouse brain

22/10/19

- I came late
- Bonds can be polar
- Ionic bonds are $2.7/3\text{\AA}$ long, and around -5 to -10 Kcal/mol
- Covalent bonds are around 100 Kcal/mol and they show an optimal nuclear distance, which is the bond lenght ($1 - 1.4\text{\AA}$)
 - The typical C-C bond is 1.4\AA
- Bond lenghts are calculated by X-ray diffraction studies, bond strenghts with calorimetry
- Disulphide bond are around -40 Kcal/mol, 2.07\AA
 - This bond is stable in an oxydized ambient
- Redox ambient potential describes the tendency of molecules in an environment to lose or acquire electrons
- Steric hindrance
- Bond resonance
- Peptide bond is around 1.5\AA (?) and is polar,
 - A long protein chain is highly polar end to end 2-4 Kcal/mol

- A Debye is the unit of measure of permanent dipoles
- A water molecule has a dipole
- The C-H bond is not polar (!)
- The OH_3^+ structure is called hydronium ion
 - One O atom generally interacts with 4 H, binding 2 at a time in a covalent way
- An H bond can be completely explained only with quantomechanics, it is 3-5 Kcal/mol and 1.5Å
- Cell membranes

23/10/19

- The dipolar interaction energy can be derived from the dipol moments
- The London force is the most dependent on distance
- The hydrophobic effect is the tendency of nonpolar molecules to aggregate in a polar solvent so to minimize the surface exposed to the solvent
- DNA
- We do not know the structure of mRNA
- The width of the DNA helix depends on salt concentration
 - The more salt the more compact it is
- The information content of DNA is in AT CG base pairing (so she wants)
- Transcribed regions are called loci
- Trascription is controlled by DNA methylation

24/10/19

- The relative dielectric constant comes from condensers
- A biological process is a series of chemical reactions catalized by enzymes
- Protein biosynthesis is a biological process that transfer information from DNA to ribosomes
- The receiver of information is the ribosome
- Every protein has an half-life: there is turnover
- The genetic code is redundant

28/10/19

- A protein is a biopolymer made of repeating peptide bonds, which form the backbone
- When an aminoacid enters in the structure of a protein, it becomes an amino-residue
- An aminoacid has a carboxil group and an aminic group bonded to a C_α
 - The side chain R can be one of 20 varieties
 - The carboxil group has a $pK_a \approx 4.2$
 - The amino group has a $pK_a \approx 9$
- The formation of the peptide bond is a condensation process where a water molecule is expelled
- The peptide bond is planar and has a dipole moment of around x debye
 - The bond is subjected to resonance because the C_α is bound to 2 electronegative atoms, O and N
 - It is shorter than a single bond, and the bond with O is longer than a double bond
 - The plane is defined by O, C_α and N
- Can every sequence be a protein?
 - A protein is long between 50 and 200-300 residues
 - If it is shorter usually it cannot fold in solution
- The bond between C_α and N is called Φ , the bond between C_α and COOH is called Ψ
 - Rotation is possible around these bonds
- Amino acids are zwitterionic, meaning that they have at phisiological pH both positive and negative charge
- The protein structure is the golden standard of proteomics

- It allows the best predictions on function
- Functional genomics is the use of available data to infer information about unknown genes and proteins
- The secondary structure derives from the stabilisation of the protein by hydrogen bonding
- SCOP categorizes protein domains
 - The class of a protein is the way in which the backbone is organised (secondary structure)
 - * An all-alpha or all-beta protein have more than 90% of the residues in that conformation
 - * Alpha+beta proteins have a linker connecting the 2 domains
 - * Alpha/beta proteins have a mixing of the structures
 - A fold is the topological arrangement of a portion of secondary structure
 - A superfamily has a probable common ancestor
 - A family is a collection of proteins that have similar function and structure
 - * They can also have very different sequences (!)
- To categorize proteins, we have to do a structural alignment
- Proteins are a frustrated system because mainly hydrophobic
 - They tend to fold in solution
 - The ΔG associated with the folding process is around 0-50 kcal/mol and it is mostly independent from the protein itself

29/10/19

- A protein is stable because it is capable of auto-organization in a polar solvent, which gives rise to million of pairwise interaction
- Proteins form crystals when the solution is super-saturated
- Proteins are social entities
- The folding of a protein is defined hydrophobic collapse
- Chaperons help the folding process in vivo
- Folding in vitro happens in a binary system made of the protein and water
- It is better to say compute than predict
- What is protein function?
 - It can catalize a chemical reaction
- In bioinformatics, enzymes are classified in clusters by the Enzyme commission classification (ECC)
- The EC classification is a hierarchical system
 - EC1 are oxydoreductases
 - EC2 are transferases
 - * They transfer a functional group from a molecule to another
 - EC3 are hydrolases
 - EC4 are lyases
 - * A lyase is an enzyme that catalyzes the breaking of a covalent bond by a mean different from hydrolysis
 - EC5 are isomerases
 - * They promote intra-molecular rearrangement
 - EC6 are ligases
 - * A ligase forms new bonds using ATP
 - EC7 are translocases
 - * It is a fancy name for membrane transporter
 - Numbers after the first narrow down the activity of the enzyme
- The EC number does not consider isoforms (!)
 - It cannot differentiate
- GO terms are a big achievement of bioinformatics
- GO means gene ontology
 - An ontology is a vocabulary
- GO terms are standard words or phrases used for indexing or retrieving information
 - They are reviewed by experts in the respective fields

- GO defines relationships between terms
- Cellular component, Biological process and Molecular function are the 3 roots of Gene ontologies
 - From the roots, we can go down a hierarchical organization to find a specific term (es. cytosol)
 - Each term has a random number assigned to it
- The problem of protein validation: we can easily detect putative proteins, but it is difficult to experimentally validate them
- Computational biology is a field of bioinformatics involved in the development of tools for sequence analysis, functional genomics and proteomics
- Systems biology develops models for biological systems
- Thermodynamics dominates our life
 - U is the internal energy of the system, it is composed of a kinetic term and a potential term
 - W is mechanical work on the system
 - Q is heat added to the system
 - Most of the quantities in thermodynamics cannot be measured in an absolute way, only changes are measurable
- The enthalpy is the sum of internal energy and mechanical work done on the system
 - $H = U + pV$
 - The mechanical work is composed of the product of pressure and volume
 - A negative change in enthalpy means that the process is exothermic
- Entropy
- Gibbs free energy
 - If ΔG is 0 we are in an equilibrium condition
 - In life equilibrium means death
- Kinetics is a branch of thermodynamics

30/10/19

- The equilibrium constant of a reaction $A \rightleftharpoons B$ is $K_{eq} = \frac{[B]}{[A]}$
- ΔG is related to K_{eq} by $\Delta G^0 = -RT \ln(K_{eq}^0)$
- There is a relationship between the kinetic constants and the equilibrium constant
- Enzyme reactions can be modelled by the Michaelis-Menten equation
 - K_m and V_{max} are parameters of the equation
 - The relationship is hyperbolic
 - K_m is the $[S]$ at which $v = \frac{1}{2}V_{max}$
 - The enzymes that follow this kinetic are monomeric
- Multimeric enzymes are modelled by the Hill equation
 - The relationship is a sigmoid
 - There is an exponential term h
 - The parameters are the same of the MM, V_{max} and $[S]_{0.5}$
 - This takes into account the allosteric effect