BIOCH 590: Biomacromolecules, Part I

Spring 2009

Introduction to Biological Macromolecules

General Principles and Key Concepts

General Introduction

- Course setup
  - Two parts: (I) physical biochemistry and (II) spectroscopy
  - Part I: from Jan 15 to Mar 6, by Jianhan Chen
- Lecture notes will be main study materials
- Textbooks:
  - two recommended
  - not required, but very useful resources for additional reading
  - Available from the Hale Library Reserve
- Two exams from Part I
  - Feb 9 and Mar 6 during lecture time (Mark these dates!)
- Grading
  - Both parts contribute equally
  - Part I: ~ 70% from exams and ~30% from homeworks

Course Overview

- Scope: physical properties of biological macromolecules
  - Basic principles of structure at multiple levels
  - Focus on the quantitative aspects
  - Theoretical frameworks: thermodynamics, statistical mechanics
  - Physical biochemistry: molecular interactions and interactions of macromolecules with environments
  - Experimental techniques to measure certain properties, which can be then used to infer about the structural organizations
- For this course
  - Emphasize a qualitative understanding of the quantitative nature
  - Build an appreciation of structural complexity and principles of theoretical and experimental studies of molecular structures
  - In Part II, a survey of basic and practical principles of common spectroscopic techniques for studying molecular structures

Tentative Topics

- Overview of macromolecular structure (1-2 lectures)
- Thermodynamics (4-5 lectures)
- Statistical Mechanics (3-4 lectures)
- Molecular interactions (3 lectures)
- Molecular motion and transport (3 lectures)
- Computer modeling (3 lectures)
- Inter-molecular interactions (3 lectures)

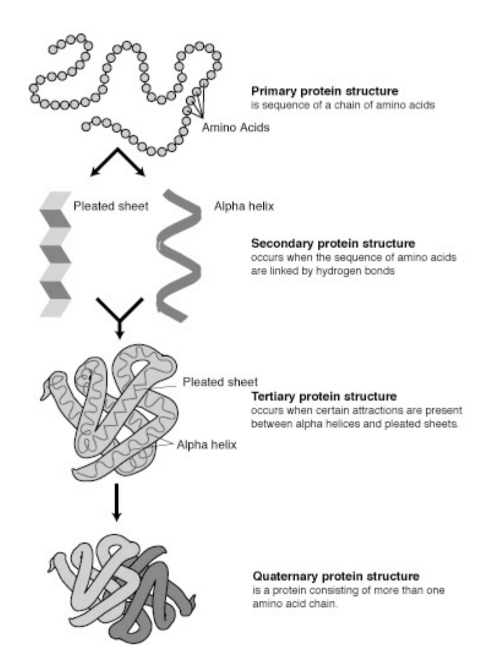
Topic 1

OVERVIEW OF BIOLOGICAL MACROMOLECULES

Reference: Chapter 1 of van Holde

Biological Macromolecules

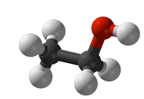
- Atom: smallest unit of an element (C, N, O, H etc)
- Molecule: smallest unit of an composite (H_2O, CO_2, C_6H_6 etc)
- Macromolecule: a large molecule
  - Smallest molecule: H_2
  - Largest molecules: DNAs (tens of billions of atoms!)
- Biological macromolecule: a large and complex molecule with specific biological functions
  - Typically biopolymers: monomers, oligomers
  - Hierarchical structures
    - Primary (1º): sequence of monomers (sugar, amino acid, nuclei acid, etc)
    - Secondary (2º): local regular structures (alpha helix, ect)
    - Tertiary (3º): global 3D fold
    - Quaternary (4º): organization of multiple subunits (polymers) in a functional complex



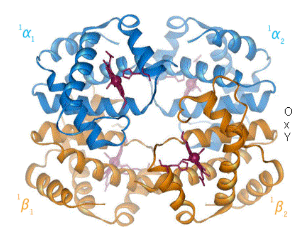
Stoichiometry and Geometry

- Stoichiometry: atomic composition
  - For biological macromolecules: compositions of (monomer) units
  - Relative easy to know
- Geometry: three-dimensional structure
  - More challenging to determine, especially for large, flexible ones
  - Protein folding problem

ethanol a.k.a. alcohol, biofuel — C_2H_6O

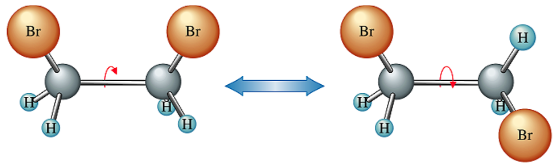


hemoglobin — $\alpha_2\beta_2$

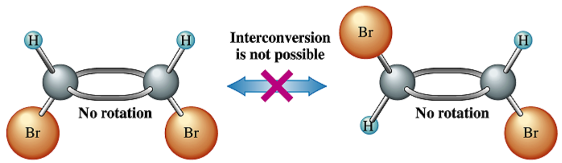


Configuration and Conformation

- Configuration: arrange of atoms around non-rotating bonds or around chiral centers
- Conformation: spatial arrange around rotatable bonds



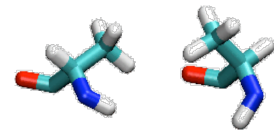
(a) The molecule 1,2-dibromoethane can rapidly interconvert between the two orientations shown, because a carbon–carbon single bond is not structurally rigid.



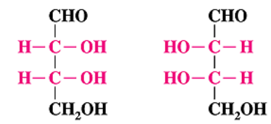
(b) The molecule 1,2-dibromoethene cannot interconvert between the two forms shown, because a carbon–carbon double bond is structurally rigid.

Chirality in Biology

- Most biomacromolecules consist of chiral monomers
- In biology, typically only one isomer is active
  - Virtually all sugars are D isomers
  - Most proteins are made of L amino acids



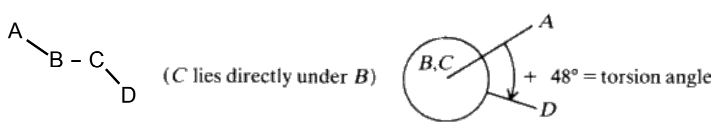
L- and D-alanine



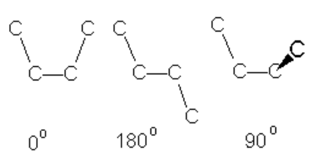
D- and L-erythrose

Conformation/Struture

- Mainly defined by torsion angles
  - Also referred to as dihedral angle: the angle between two groups on either side of a freely rotating chemical bond
  - Defined by four consecutively linked atoms: ϕ(A-B-C-D)



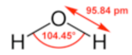
  - Right-hand rule: positive sense is clockwise



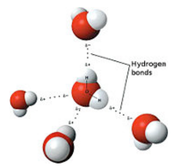
Determinant of Structure

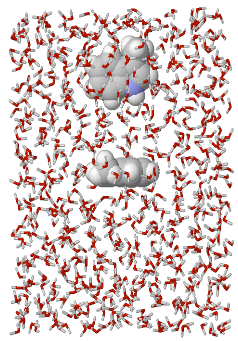
- Probability of observing a particular structure (conformation) is determined by its stability (as defined by the free energy)
  - Thermodynamics and statistical mechanics!
- The stability depends on a range of factors
  - Intramolecular interactions
    - Bonded: chemical bonds, angles, dihedrals etc
    - Nonbonded: "weak" interactions
      - Charged-charged, van der Waals (dispersion and repulsion)
  - Intermolecular interactions: nonbonded/weak interactions
    - Cellular environment: solvent (water), membrane, salt, pH etc
    - Association with other biomolecules, small molecules, ions, etc
- No single structure is *the* structure
  - It is all about probability (statistical mechanics!)
  - Motions and flexibility are important too

Water

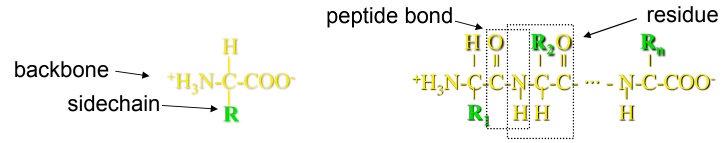


- Solvent of life
- Many unique properties
  - Maximum density at 4 ºC
    - Ice is lighter than liquid water
  - Polar molecule
    - hydrogen bonding network
    - High specific heat capacity
- Hydrophobicity and hydrophilicity
  - Solute polarity (carry partial charges or not)
  - Salts (e.g. NaCl) dissolve in water readily
  - Hydrocarbons (oil) do not mix with water
- Amphipathic molecules
  - Self-assembly to micelles, biological membranes

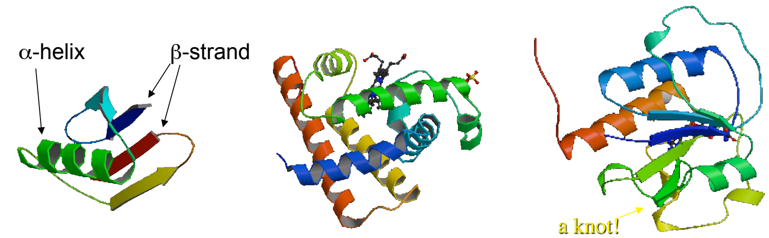




Hierarchical Organization of Proteins



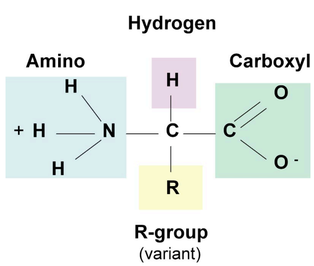
Primary Sequence: MTYKLILNGK TLKGETTTEA VDAATAEKVF KQYANDNGVD GEWTYDDATK TFTVTE

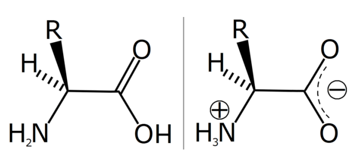


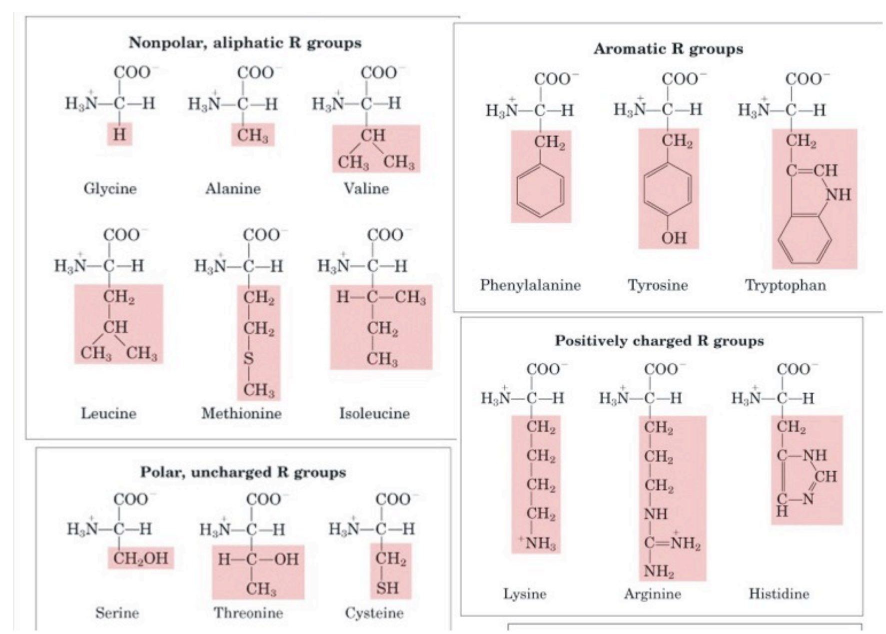
Protein G B1 (3gb1) **Myoglobin (1mbc)** **tRNA transferase (1mxi)**

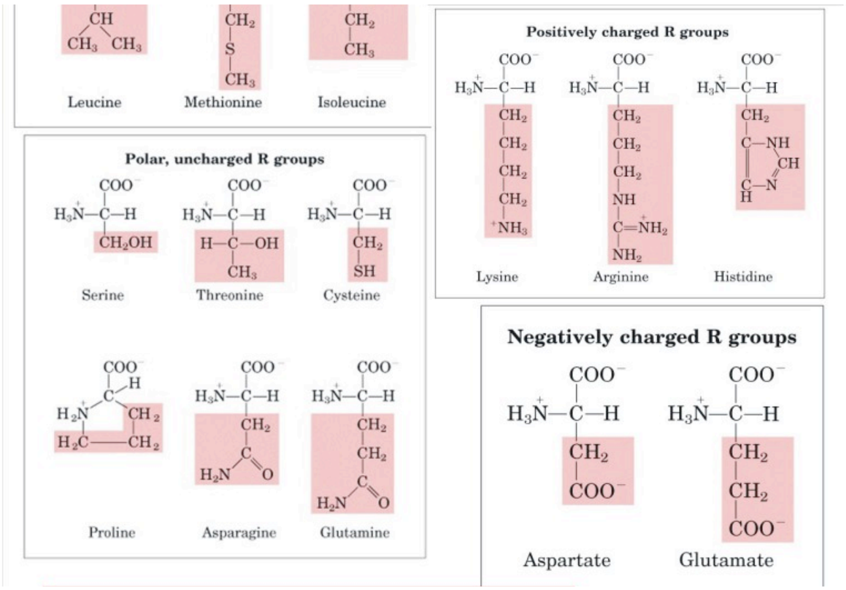
Natural Amino Acids

- All α-amino acids in L-configuration
- Essential vs non-essential ones
- Co-exist in two forms
  - Ionic (zwitterionic form) and unionized
- Side chains vary







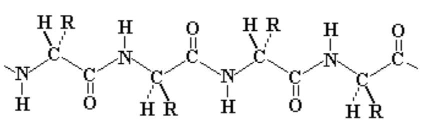


Three-Letter and Single-Letter Codes

Amino Acid	3-Letter	1-Letter	Amino Acid	3-Letter	1-Letter
Alanine	Ala	A	Leucine	Leu	L
Arginine	Arg	R	Lysine	Lys	K
Asparagine	Asn	N	Methionine	Met	M
Aspartate	Asp	D	Phenylalanine	Phe	F
Cysteine	Cys	C	Proline	Pro	P
Histidine	His	H	Serine	Ser	S
Isoleucine	Ile	I	Threonine	Thr	T
Glutamine	Gln	Q	Tryptophan	Trp	W
Glutamate	Glu	E	Tyrosine	Tyr	Y
Glycine	Gly	G	Valine	Val	V

Foldable Sequence Space is Limited

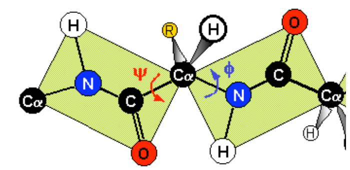
- Huge number of possible sequences: 20^N

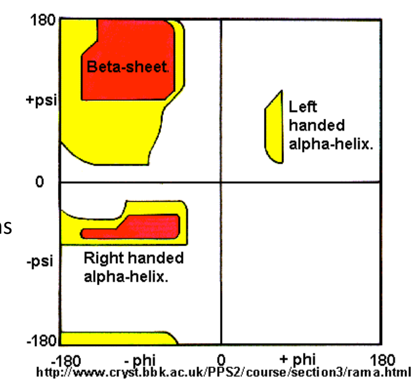


- Only a small subset are explored in biology and most of them give rise to specific 3D structures under the proper conditions
  - Sequence determines structure (or lack or structure)
  - Protein structure-function paradigm: enzymes
  - Some sequences are "intrinsically disordered"! They play very important roles in signaling and regulation.

Important Torsions of Proteins

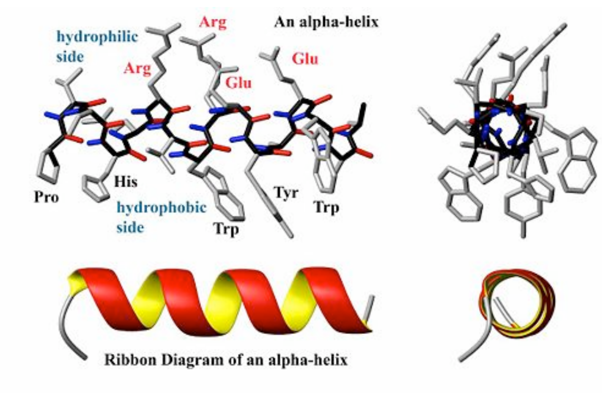
- Backbone torsions
  - ϕ: C(O)-N-Cα-C(O))
  - ψ: N-Cα-C(O)-N
  - ω: H-N-C(O)-O
    - Mostly 180º (trans)
- Ramachandran plot
  - 2D plot of (ϕ,ψ) distribution
  - Allow assignment of secondary structures
  - Statistics of known protein structures reveal common regions of (ϕ,ψ) distributions
  - An important way of structural evaluation





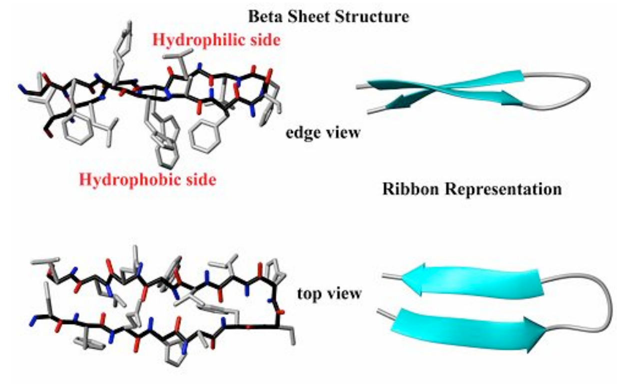
Secondary Structures of Proteins

- α-helix: (i,i+4) hydrogen bonds, 3.6 residues/1.8 Å per turn

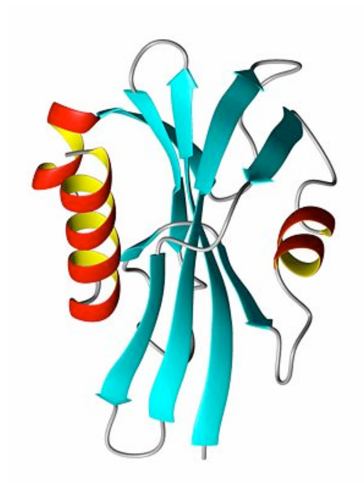


Secondary Structures of Proteins

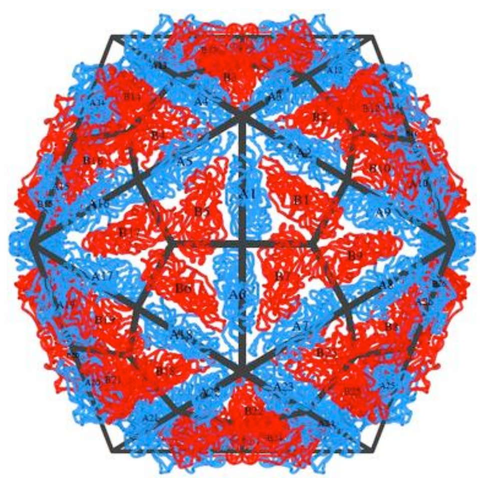
- β-strands: trans- backbone torsions, multiple hydrogen bonds



Tertiary and Quaternary Structures



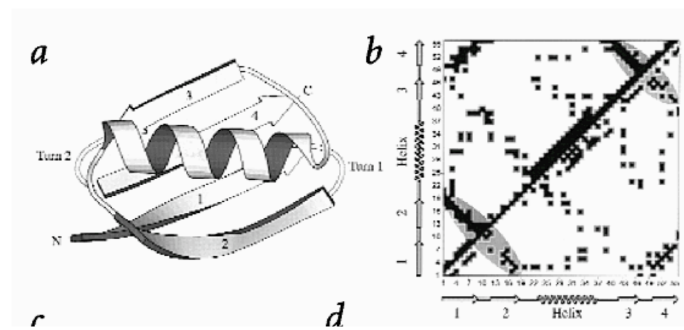
p13 protein from GB virus-B



Structure of the L-A virus Capsid

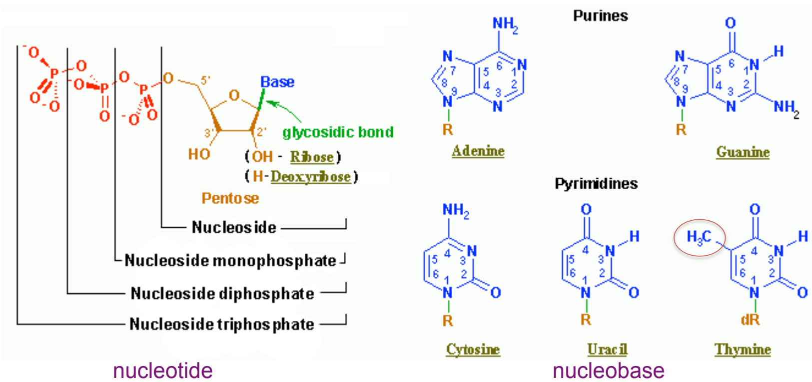
Contact Map

- A simple way of representing protein folds



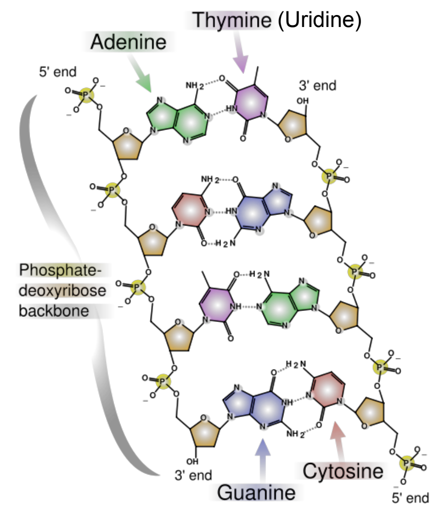
Nuclei Acids

- Polymer of nucleotides: highly flexible (compared to peptides)
- Deoxyribonucleic acid (DNA): A/G/C/T
- Ribonuclei acid (RNA): A/G/C/U



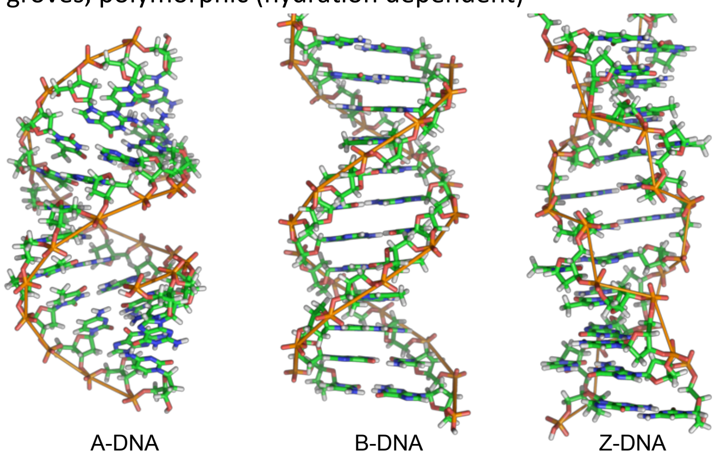
Watson-Crick Base Pairs

- G-C and A-T(U)
- DNA almost exclusively exist as duplex held together by forming Watson-Crick base pairs
- A robust mechanism for faithful replication and translation
- Other pairings possible but mostly in RNA to give rise to non-trivial structures



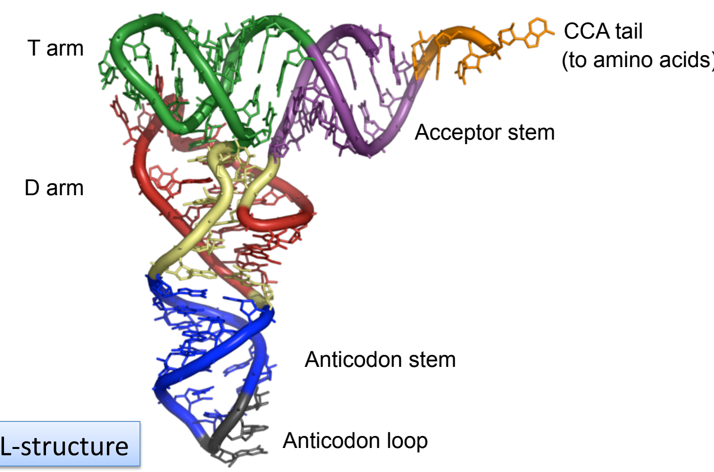
Helical Structures of DNA (RNA)

- Famous DNA double helix: stacking of base pairs, minor/major groves, polymorphic (hydration dependent)



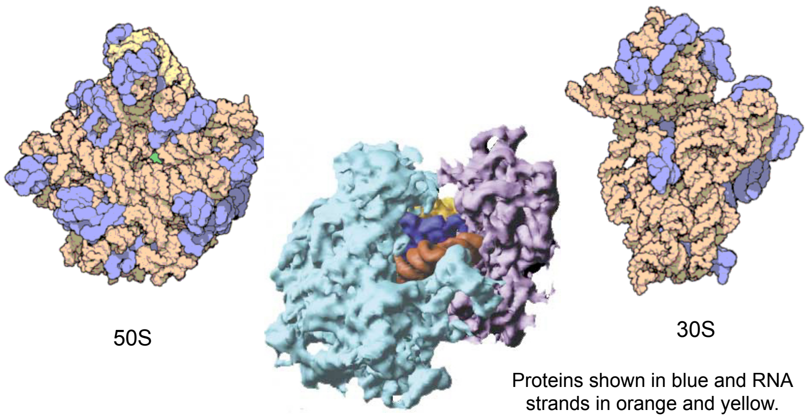
Tertiary Structure of RNA

- Single-strand RNA often fold into tertiary structures



Ribosome: the Protein Factory

- Prokaryotic ribosome consists of 42 proteins (~35% weight) and 3 ribosomal RNAs (rRNA) (~65% weight) and measures about 200 Å across.

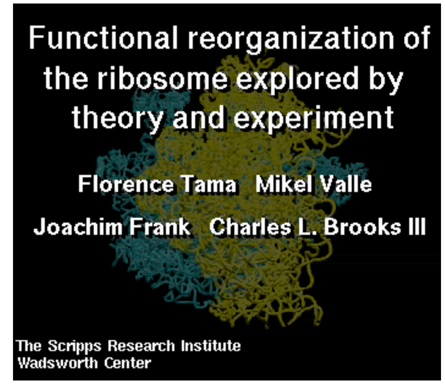


Proteins shown in blue and RNA strands in orange and yellow.

Functional Motions of Ribosome

"This movie depicts a ratchet-like rearrangement of the 70S ribosome. The rotation of the 30S ribosomal subunit relative to the 50S subunit shows high correspondence to motion captured in cryo-EM maps of the ribosome and postulated to be a key mechanical step in the translocation of the mRNA•tRNAs complex. "

http://brooks.chem.lsa.umich.edu/



Tama et al. Proc Nat Acad Sci, **100** 9319 (2003).

Homework Assignment 1

- 1. hand draw the backbone conformation of Alanine Dipeptide in (1) right-hand helx (phi,psi)=(-60,-60) and (2) left-hand helix (+60, 60)
- 2. hand draw a schematic contact map of the following beta-sheet protein fold.