Geometry & Physics of Proteins

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Acknowledgement: George Rose

Creation of universe: 13.8 billion years
Formation of earth: 4.5 billion years
Life on earth: 3.5 billion years

What gives the cell its life and personality are enzymes. They govern all body processes; malfunction of even one enzyme can be fatal. Nothing in nature is so tangible and vital to our lives as proteins, and yet so poorly understood and appreciated by all but a few scientists.

Arthur Kornberg
Compactness-Hydrophobicity
Difficult Problem

• Formidable complexity: 20 types of amino acids, role of water, huge number of degrees of freedom, steric constraints, chain connectivity
• Finite size
• Role of evolution

Standard approach: one protein at a time
Hints of Simplicity

Biological function appears to be more a correlate of macromolecular geometry than of chemical detail.

Anfinsen

Any effective picture of protein structure must provide at the same time for the common character of all proteins as exemplified by their many chemical and physical similarities, and for the highly specific nature of each protein type.

Bernal
(1939)
Common Character of Proteins

• Rapid and reproducible folding
• Ability to expel water from interior of structure
• Cooperative transition to folded state with few intermediates
• Flexible and versatile
• ~ 100,000 proteins => ~1000 folds
• Pretty building blocks – helices and sheets
• Form determines function
• Amyloid formation – Alzheimer’s & mad cow diseases
Are these similarities an accident or is there a deeper underlying reason why proteins share these amazing attributes?

What is the phase of matter employed by nature to house these protein native state structures?

What are the essential ingredients that one must incorporate in order to develop a unified framework for understanding proteins?
Helices and sheets: Periodically repeatable structures for which hydrogen bonds provide the scaffolding

“The precise geometrical relationships among the atoms and molecules and the rigorous application of the new structural principles”  
Linus Pauling  
(1954)

Ramachandran, Ramakrishnan & Sasisekharan; Rose: Importance of steric constraints
Compact Phases of Standard Polymers:

String and beads model

all pairs

Crystalline phase: Hamiltonian walks

Compact disordered phase

Swollen
“Synthetic analogs of globular proteins are unknown. The capability of adopting a dense globular configuration stabilized by self interactions and of transforming reversibly to the random coil are peculiar to the chain molecules of globular proteins alone.”

Paul Flory
Continuum description

Potential energy of self interaction

\[ \int_0^L ds_1 \int_0^L ds_2 \delta(\vec{r}(s_1) - \vec{r}(s_2)) \]

Edwards

I. Renormalization group theory: artificial cut-off length for regularizing the theory

II. Closed chain – fixed number of knots
Ideal close-packed helix
Tube

- Mutual distance between pair of particles: no contextual information
- Continuum limit: Pair wise interaction must be discarded
- Three body interaction: Characteristic length scale is the radius of a circle passing through the three points
- Sheet of paper of non zero thickness: 4 body interaction

Gonzalez & Maddocks
Tube

- Two length scales
- Self-tuning of length scales
- Inherent anisotropy
- Marginally compact phase
- Relatively few putative native state structures
- Vicinity of a new type of phase transition
- Long tubes – amyloid type structures

Backbone of protein: Approximately uniform tube of radius 2.7 Angstroms
Ground State Phase Diagram For Short Tubes

Protein Structures
(A1)  (B1)  (C1)  (D1)

Thick Tube Ground States
(A2)  (B2)  (C2)  (D2)
(A3)  (D3)
Homopolymer model

Hydrogen bonds: Geometrical constraints on mutual orientation of local coordinate systems – local bonds, non-local bonds and cooperativity

Hydrophobicity

Local bending energy penalty
Ground State Phase Diagram

HOMOPOLYMER

-5    -4    -3    -2     -1     0     +1  +2   +3   +4

$b_w$

$e_R$

bending energy

attraction energy

-0.6    -0.4    -0.2     0     0.2    0.4

e_w

coil

3-stranded
β-sheet

β-helix

single
α-helix

2-helix bundle

β-barrel
Consequences of the tube picture

Pre-sculpted free energy landscape

Molecular evolution

Amyloid formation

Few folds: easy design
Summary

• Tube picture: Bridge polymer science and protein science

• Continuum description of tube or sheet of non-zero thickness

• Marginally compact phase: Expel water from core, Flexible and versatile, Few folds, Helices and zig zag strands of correct geometry, Almost immediate ordering on lowering temperature, Amyloid-like phase

• Pre-sculpted free energy landscape

• Folds and evolution
strong α-helix formers
(LEU, ALA, GLU)

strong β-strand formers
(VAL, TYR, ILE)
Consecutive residues along a strand
$T = 0$ Phase Diagram of Tube

$L =$ Tube Length

$\Delta =$ Tube Thickness

$R =$ Range of attraction