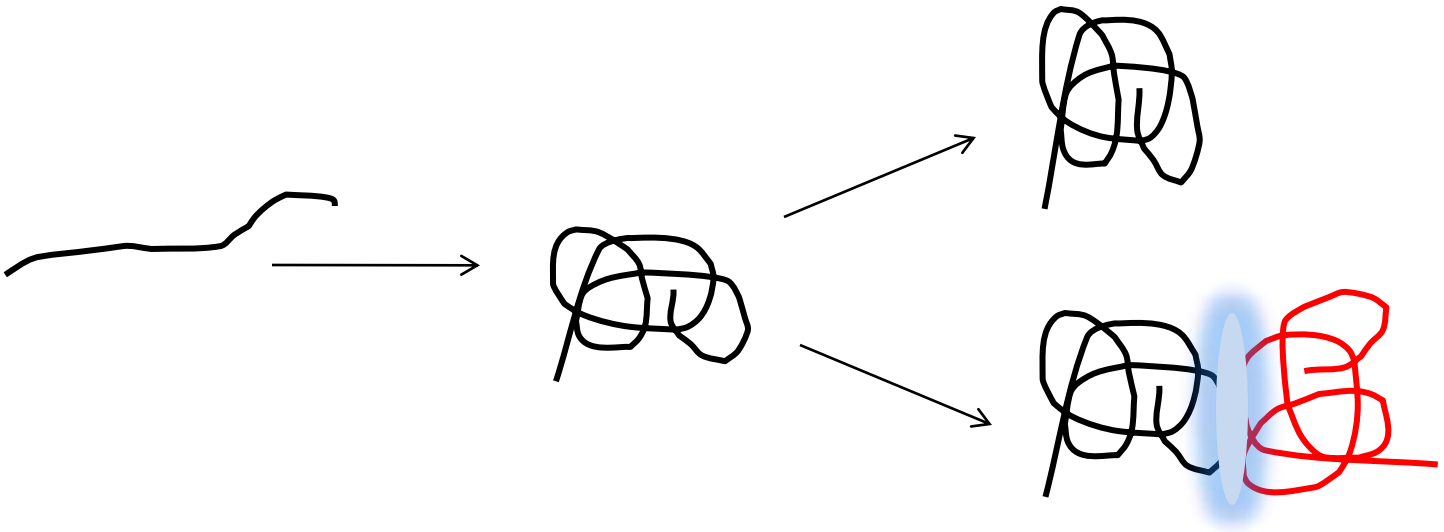
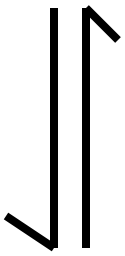
# Protein Function & Interactions

# Physical Laws

Protein Folding, Function and Interactions

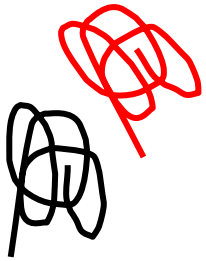


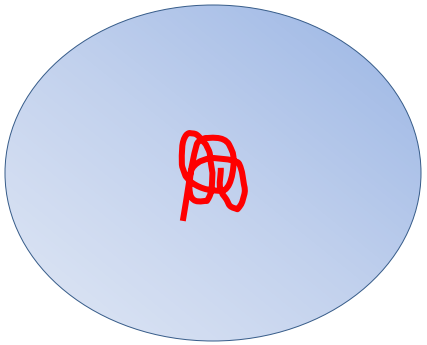
# Physical Laws



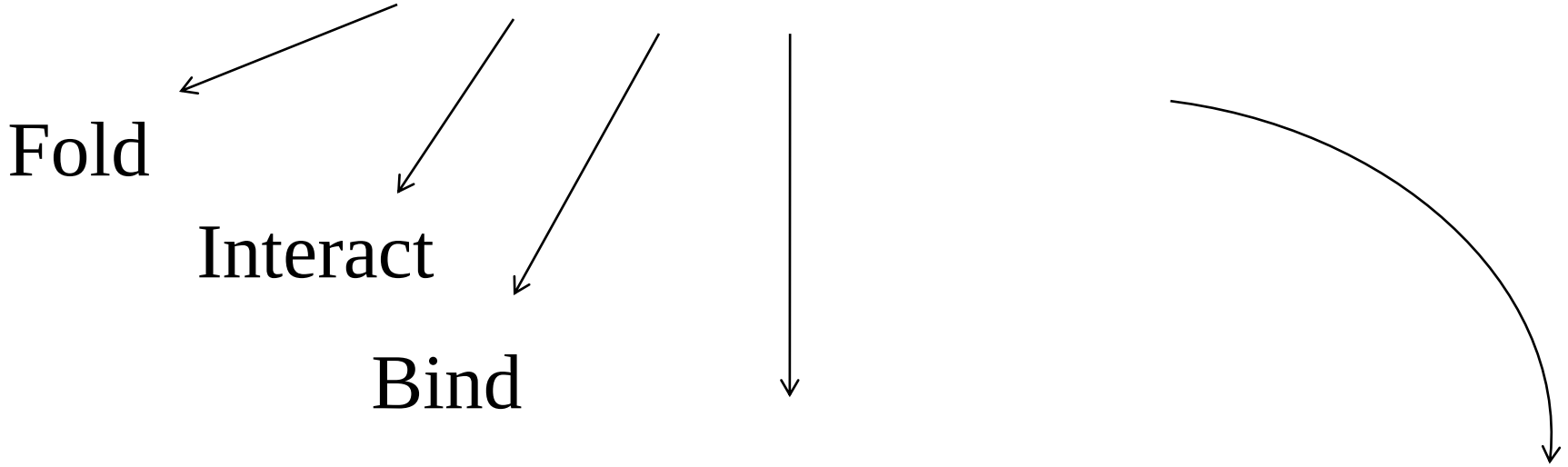
Energetics In a System

AGGLYWSGG

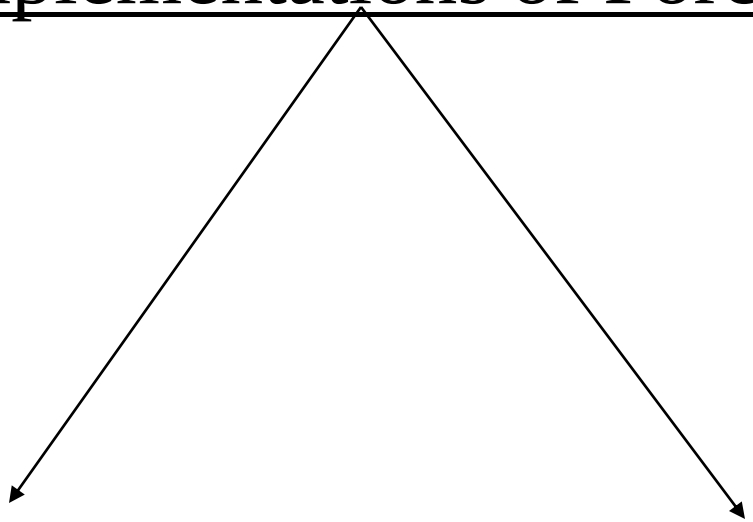




# Physical Laws

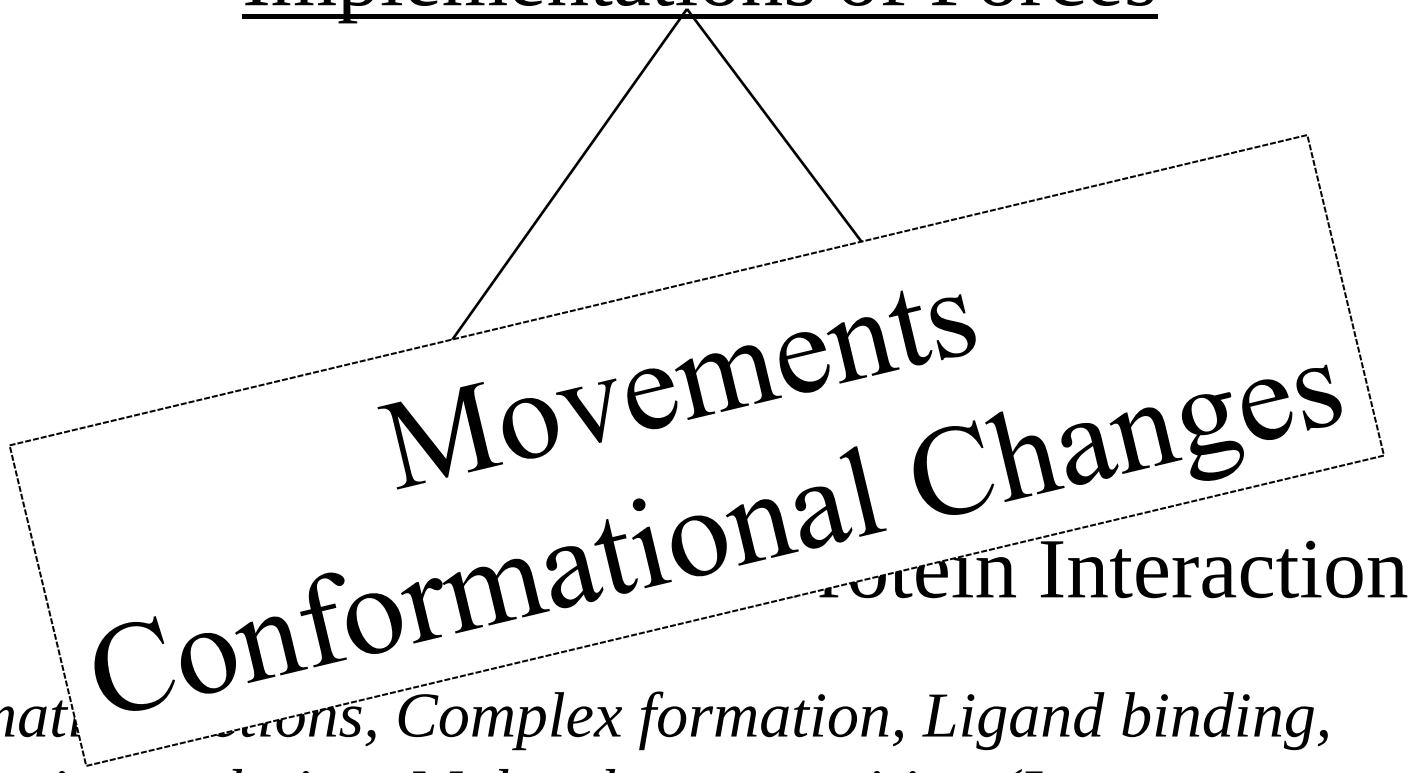


# Implementations of Forces



Protein Function $\longleftrightarrow$ Protein Interactions

# Implementations of Forces

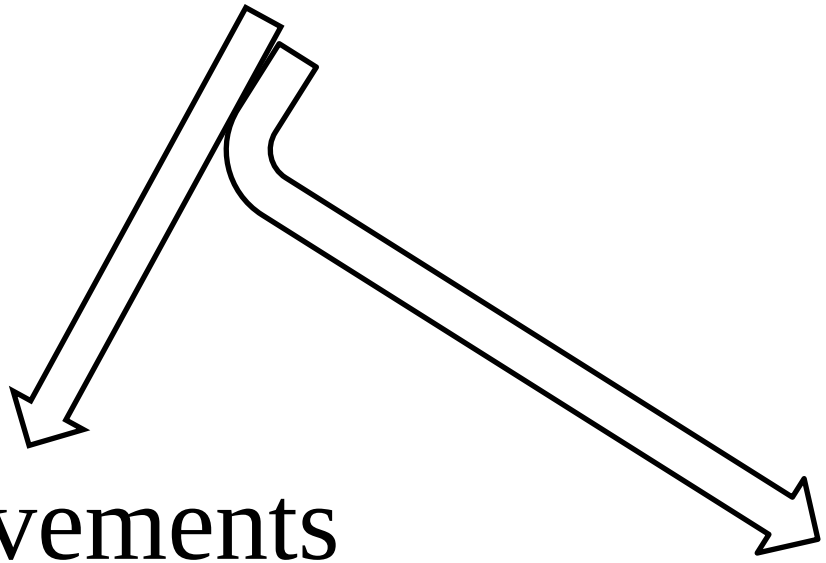



Protein Interactions

*Enzymat[illegible]ions, Complex formation, Ligand binding, Allosteric regulation, Molecular recognition (Immune response), Allosteric regulation, Signal transduction, Protein targeting or any cellular processes involving a protein molecule*

# *Protein Flexibilities*

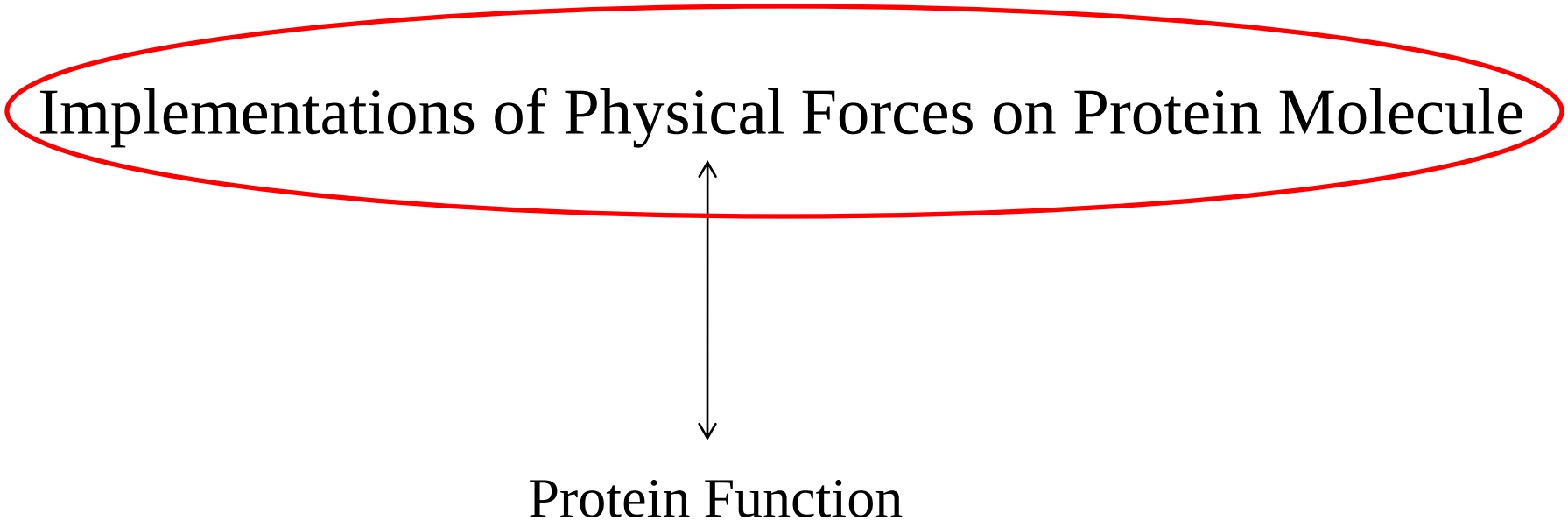
# Physical forces



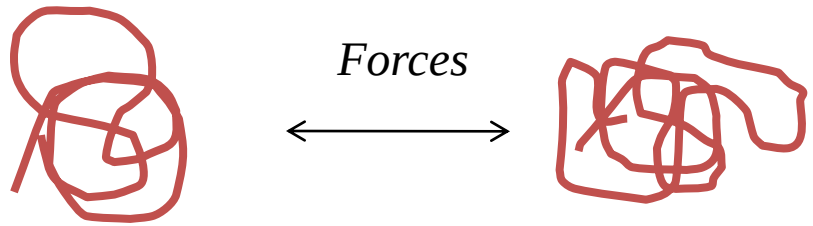
## Protein Movements

## Extents

| | |
|---|---|
| Ex.: Enzyme (coil) | 0.5 -2 Å |
| Allosteric regulation | 4-5 Å |
| Relative domain movements | larger |

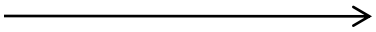

Implementations of Physical Forces on Protein Molecule
Protein Function

# Implementations of Physical Forces on Protein Molecule

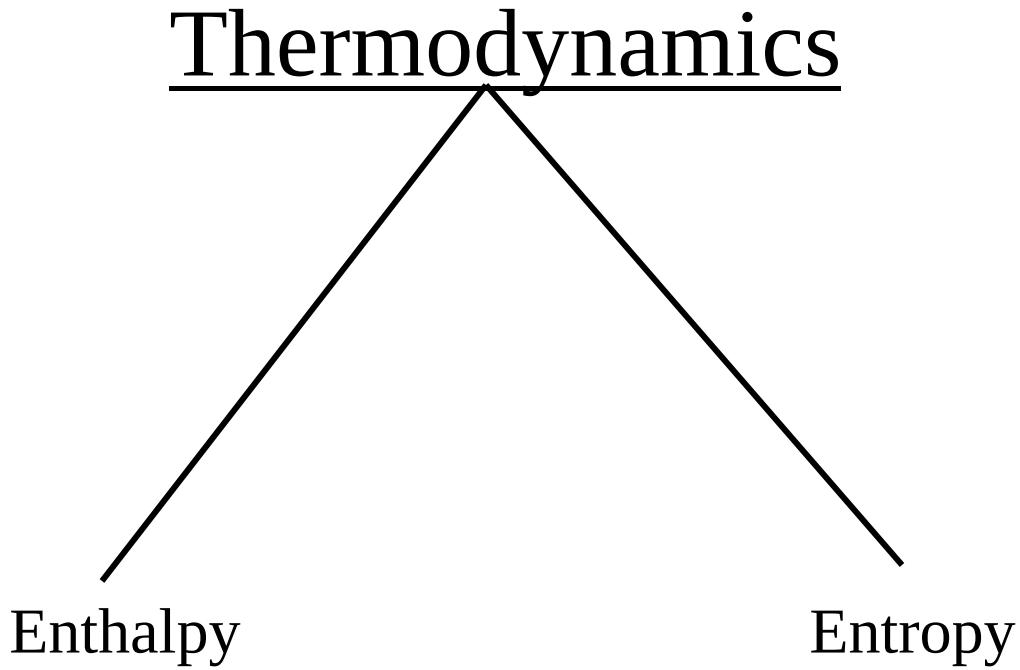



Structure Functional movements

***Reaction***



# Thermodynamics


Thermodynamics
Enthalpy
Entropy

# The Course

## How Protein Movements are Governed; Thermodynamic Implementations

# The Course

**Protein Fold to Function: Structural and Thermodynamic Parameters**

The course will have a general emphasis of how physical laws are implemented on biological molecules, in order to understand structure-function correlations. Protein folding, interaction and function are evolutionary implementation of the forces inherent in sequence. Protein function, for example, requires a precise local movement, is governed by the balances between these forces. This course will help us understand structural and functional aspect of protein molecule, covering fundamentals, scope of studies through experimental and computational approaches, their validity and applications. The thermodynamic forces, broadly electrostatics and hydrophobic, will be dissected to understand protein structure-function details at atomic levels. The course will also cover the current applications in protein targeting and drug design.

# The Course

**Grading (A, B, C)**

| | |
|---|---|
| **Class Involvement** | **15%** |
| **Talks & Projects** | **25%** |
| **Mid-Term Tests (3)** | **30%** |
| **Final Exams (2 Sessions: a Class exam & a home work assignment)** | **30%** |

# Protein Fold to Function: Structural and Thermodynamic Parameters

## Classes

- Introduction, Basics, Strategies, Concepts, Books, References, Projects, Course layout, Scoring pattern

- A Protein Molecule

*Sequence, Structure and Fold Basics*

- Structural parameters in Folding & Function/ Project Assignments

*Functional Transformation: Structural input*

- Talks & Discussion

- Thermodynamic Parameters in Folding & Function

*Functional Transformation: Thermodynamic input*

- Electrostatics

  *Dissections, Implementations, Accuracies in functional transformations*

- Hydrophobic contributions and Entropies

  *Components and Their Implications, Roles and how it relates to enthalpy*

- Test & Discussion

- Conformational Distributions

  Barriers & Optimizations: *Conformational populations, conformational selections, population shifts, functional optimizations*

- Protein Flexibilities: Structural and Thermodynamic parameters

  *What is an optimum flexibility? Role of Geometry, Electrostatic and hydrophobic components, Functional Implementations of H-Bonds, Salt-bridges, van der waals term, Structural and thermodynamics of residue interactions*

- Protein Flexibilities: Microscopic and macroscopic implementations

  *Flexibilities in folding and associations, Electrostatic and Hydrophobic contributions and roles, relevant studies, Hydrophobic component, scopes and studies*

- Talks & Discussion

- Current Research Article / Project Assignments

  *Multiple current research articles on protein conformations, thermodynamics of folding and binding. Each student will be assigned with a specific project. Talks should be of 4-5 slides, stating the relevance and how information is helpful in current studies.*

- Biophysical Approaches: Structural, Kinetics and Thermodynamics

  *Validity and Scope. ITC, DSC, SPR, NMR & related Current approaches*

- Spring Break

- Spring Break

- Biophysical Approaches: Theoretical Analysis, Experimental correlations

  *Basics in theoretical approaches, algorithm, databases, knowledge based inputs*

- Biophysical Approaches: Theoretical Force Fields and their energetic components

  *Current approaches, Theoretical calculations, their scopes and limits, study examples*

- Test & Discussion

- Experimental Design: Questions and strategies

- Protein Movements

  *Extent of movements, Correlations with function*

- Protein-Protein Associations, Antibody-Antibody Recognition / Project Assignments

- Talks & Discussion

- Specificity of Molecular Recognition; Specificity *ver.* Flexibility: Roles

- Current Research Articles

- Protein in Medicine: Targeting & Disruptions

- Test & Discussion

- Current Strategies: Binding & Conformational Alterations

- Drugs, Leads and Chemical Compounds

  *Current approaches to drug development, small organic compounds ver a biological molecule, what to target and where to target, how to achieve binding specificity and affinity, how to avoid side effects.*

- Drug Evolution for Protein Target / Project Assignments

  *Enthalpy and entropy of drug binding*

- Talks & Discussion

- Summary (also on disorder, stability and pathological conformations)

  *Concepts in protein function.* Remaining-*Energetics of mis- folded conformations*

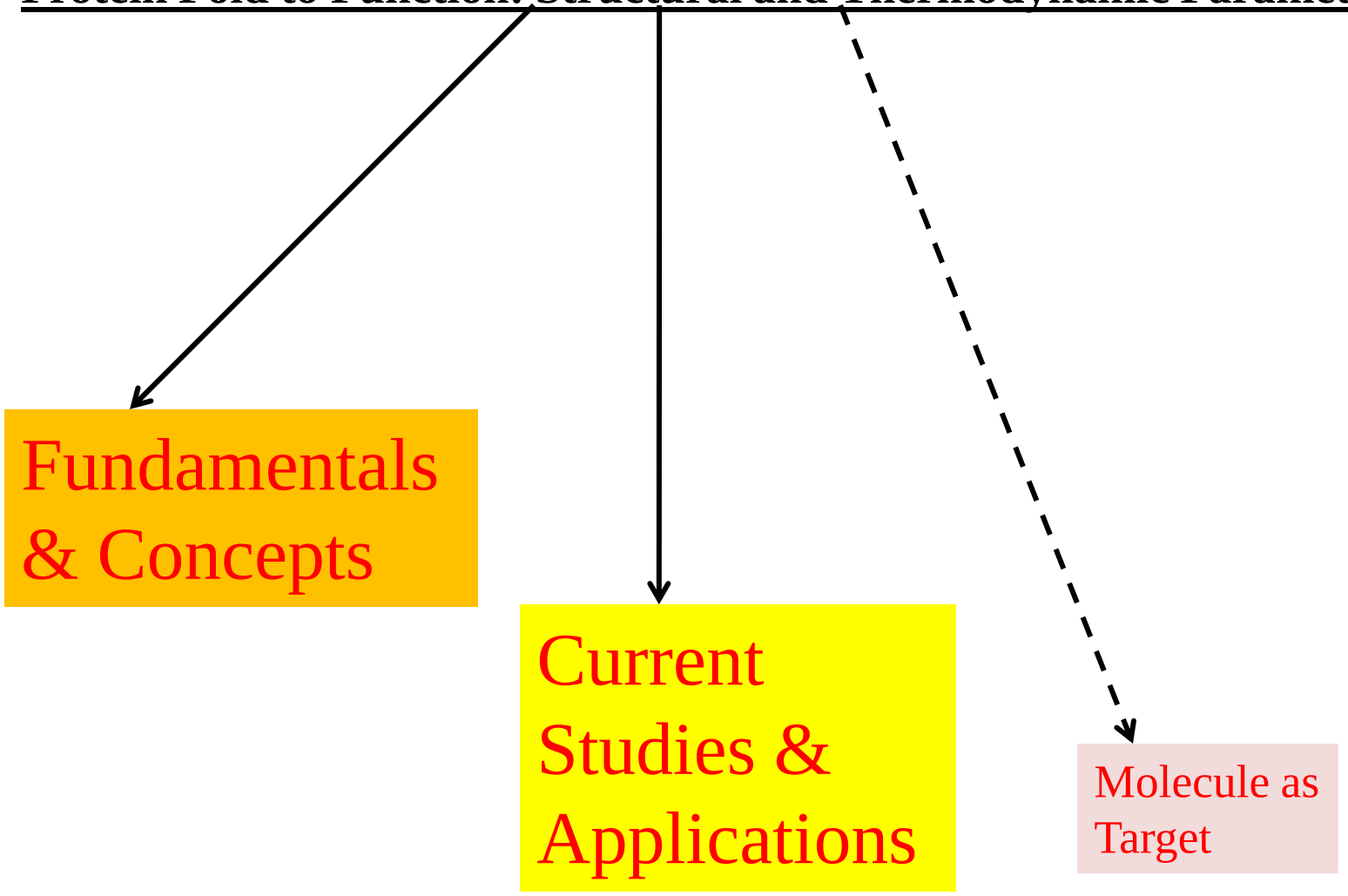
- BME 5620: Assignment Talks & Discussion (Assignments will be e-mailed to BME 5620 students a week before). BME 462 should be in this class too.

- Final Test I (4 descriptive and 10 Multiple Choice), Home work assignment

- Discussion, Questions, Scoring Patterns

# The Course

## Protein Fold to Function: Structural and Thermodynamic Parameters



Books (for Reference)

Introduction to Protein Structure, Branden & Tooze

Protein Structure and Molecular Properties, T. E. Creighton

Introduction to Protein Science, Arthur Lesk

Structure and Mechanism in Protein Science, Alan Fersht

Computer Simulations of Biomolecular Systems, Van Gunsteren, Weiner, A.J. Wilkinson

Protein Structure and Function (2004). Petsko and Ringe

*"Tests and Discussions will be based on what is discussed in the class, which may not be covered in any particular book."*

Advance level text/material will be referred as course progresses.

# Fundamentals & Concepts

$$S = -k_B \sum_{i=1}^{\Omega(E)} \left\{ \frac{1}{\Omega(E)} \ln \frac{1}{\Omega(E)} \right\} = k_B \ln(\Omega(E))$$

---

$$V(r) = \sum_{bonds} k_b (b - b_0)^2 + \sum_{angles} k_b (\theta - \theta_0)^2 + \sum_{torsions} k_\phi [\cos(n\phi + \delta) + 1]$$

$$+ \sum_{\substack{nonbond \\ pairs}} \left[ \frac{q_i q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^{6}} \right]$$

---

$$\frac{Ni}{N} = \frac{g_i \exp(-E_i / kT)}{\sum_j g_j \exp(-Ej / kT)}$$

$$\vec{\nabla} \cdot \left[ \varepsilon(\vec{r}) \vec{\nabla} \psi(\vec{r}) \right] = -4\pi p^f(\vec{r}) - 4\pi \sum_i c_i^{\infty} z_i q \lambda(\vec{r}) \cdot \exp\left[ \frac{-z_i q \Psi(\vec{r})}{k_B T} \right]$$

---

$$\Delta G = -RT \ln K_{eq}$$

---

$$\Delta G = \Delta H - T\Delta S$$

---

$$\phi_E = \frac{q}{4\pi\varepsilon_0 r}$$

$$\Delta\Delta G_{tot} = \Delta\Delta G_{desol} + \Delta\Delta G_{bridge} + \Delta\Delta G_{protein}$$

---

$$G_R = \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{m}\frac{\delta_i q_j}{\varepsilon_s r_{ij}}$$

---

$$\Delta G_E = \Delta G_R = G_R(\varepsilon_s, 80) - G_R(\varepsilon_s, 1)$$

---

$$\Delta\Delta G_{Bridge} = \sum_i \phi_i q_i$$

---

$$\Delta\Delta G_{\text{Protein}} = \sum_i \phi_i q_i$$

$$E_{bondstretch} = \sum_{1,2\,pairs} K_b(b - b0)^2$$

---

$$E_{bondbend} = \sum_{angles} K_\theta(\theta - \theta_0)^2$$

---

$$E_{rotate} = \sum_{1,4\,pairs} K_\varphi(1 - \cos(n\phi))$$

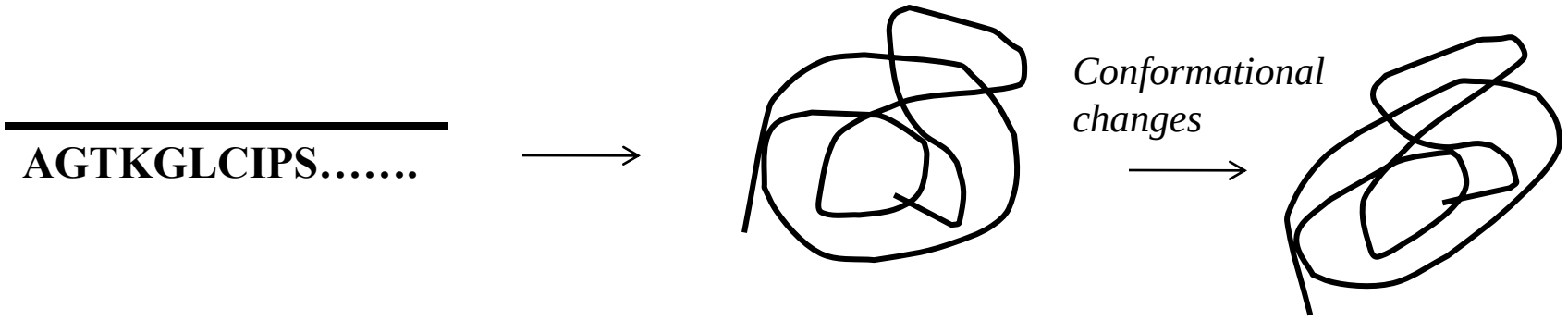
$$p_i = \frac{1}{Z} e^{-Ei/(kT)} = e^{-(Ei-A)/(kT)}$$

What is an equation ? A Formula ?

*Concept. How things work, or putting things together .*

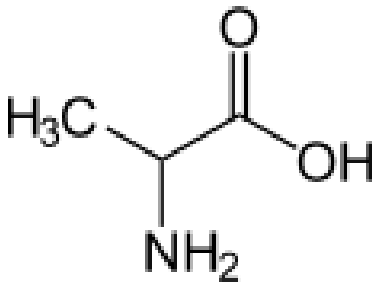
I. Basics
II. Fundamentals

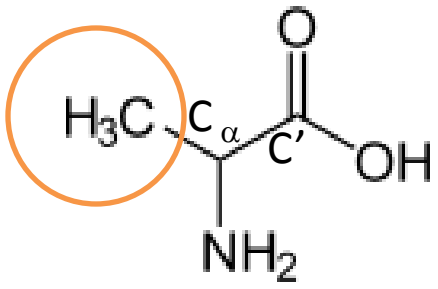
# A Protein Molecule



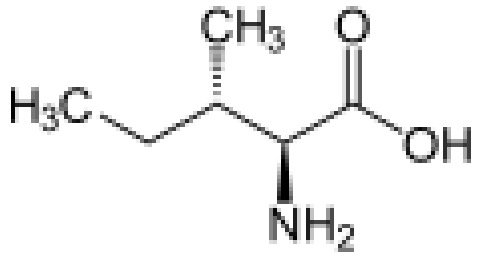

Sequence Fold Function

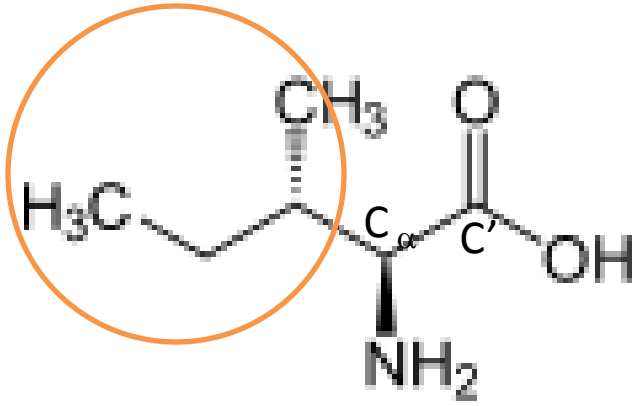
**ALA**




**ILE**



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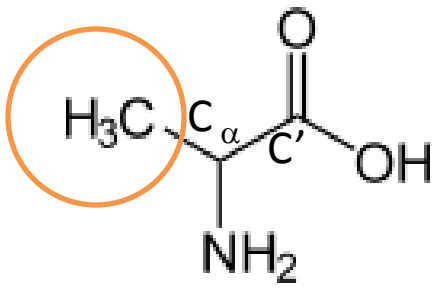
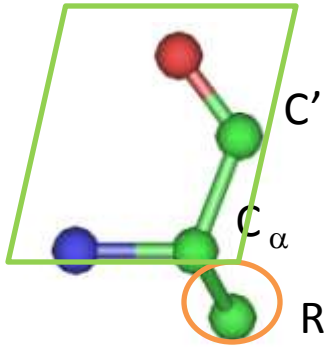
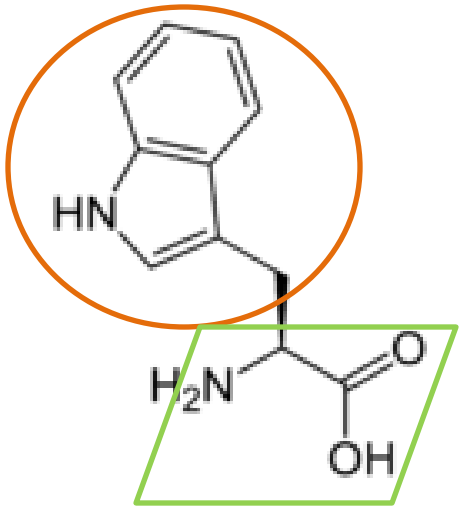
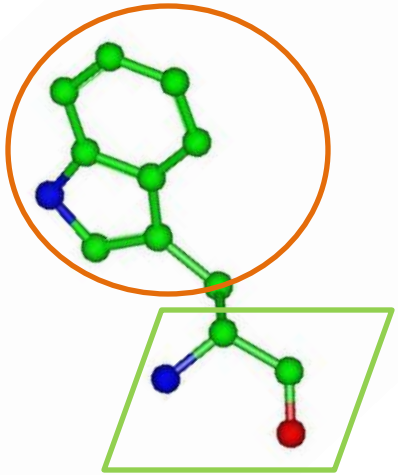


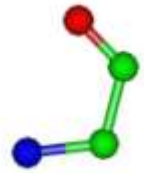




Residue

**TRP**





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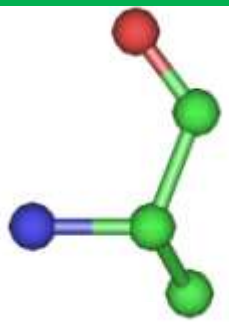
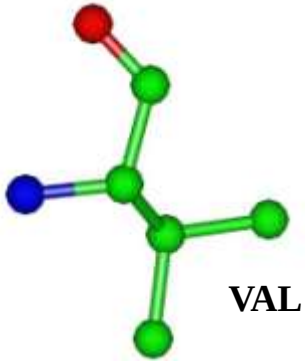


ALA



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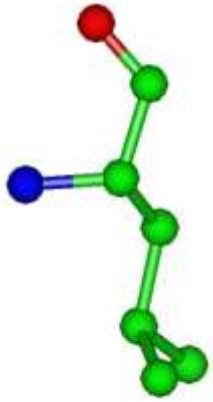

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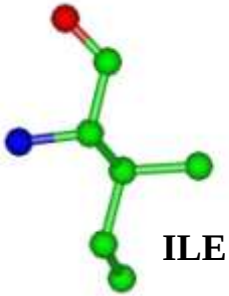

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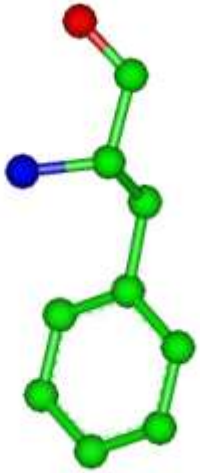

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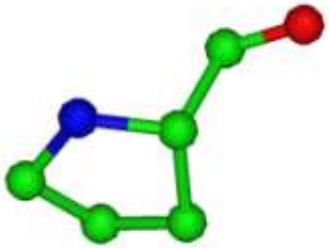

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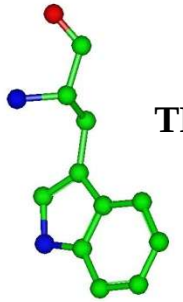

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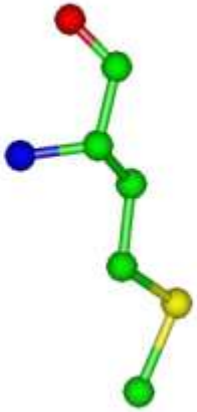

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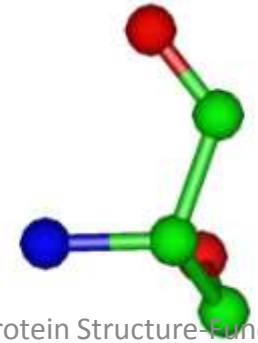

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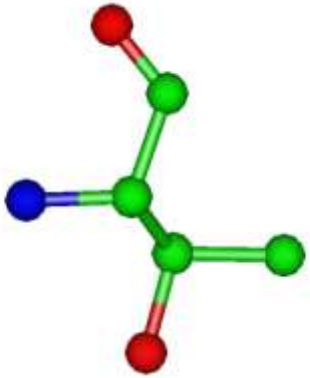

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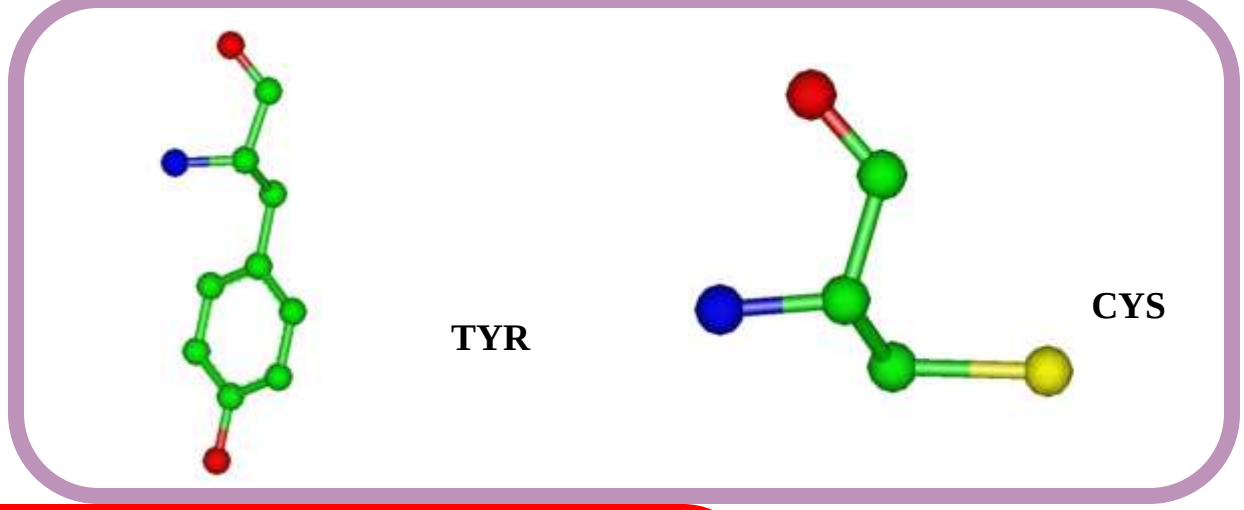
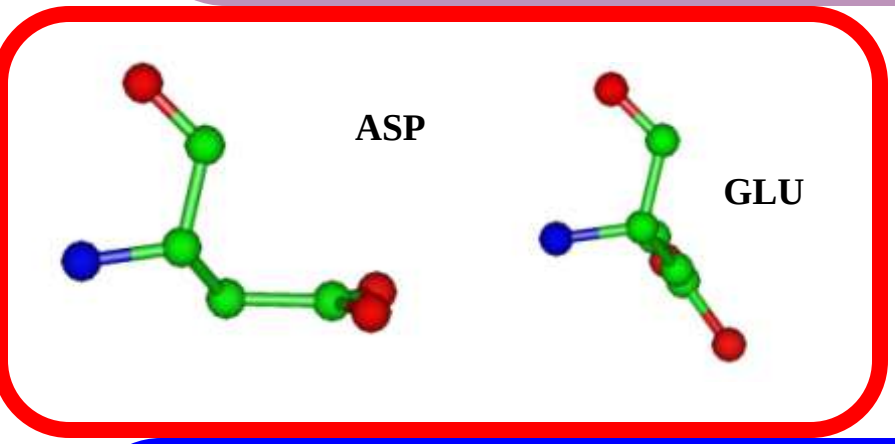

TYR
CYS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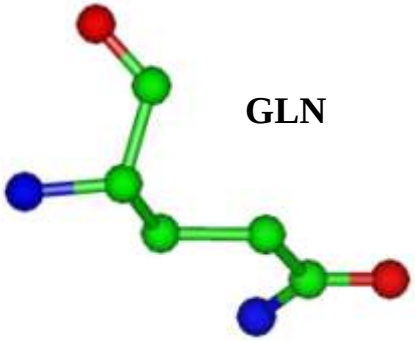
GLU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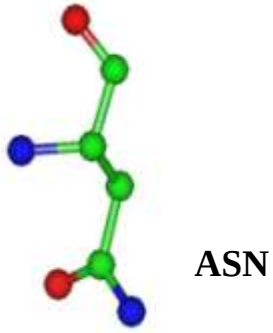
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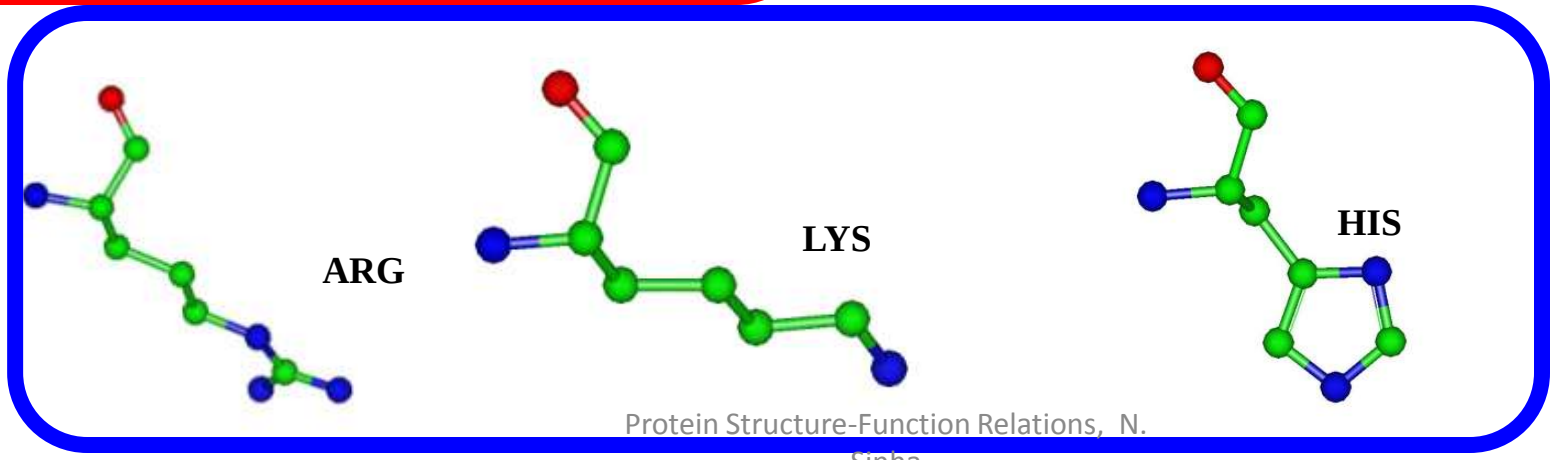
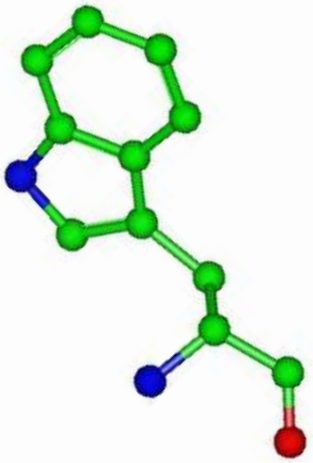
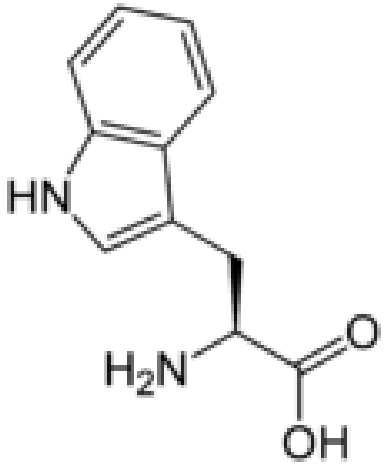
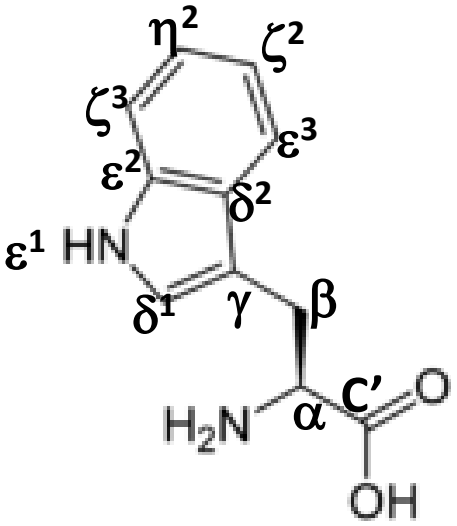

ARG
LYS
HIS

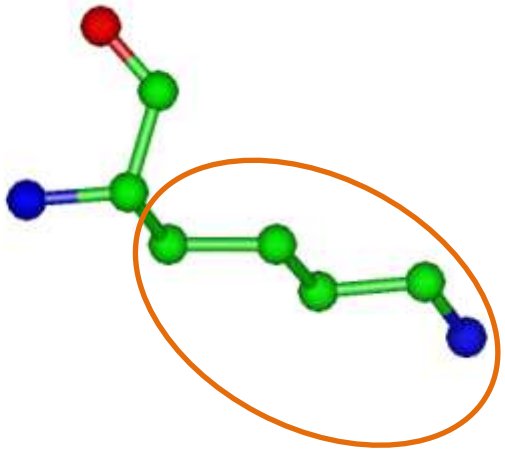
# TRP

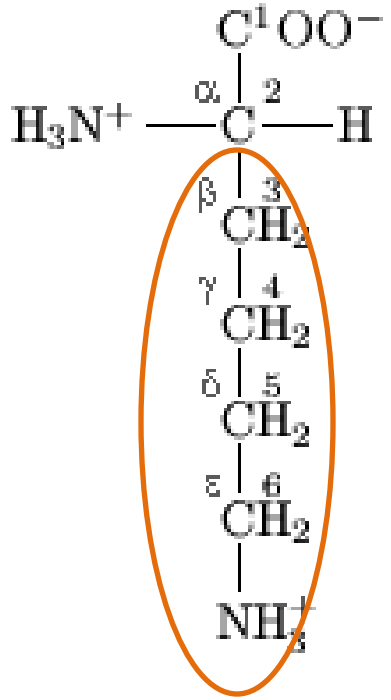




# LYS



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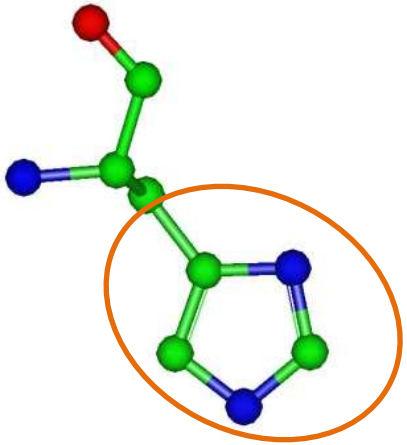
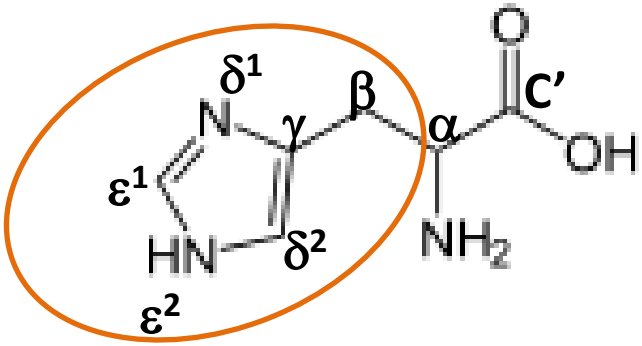
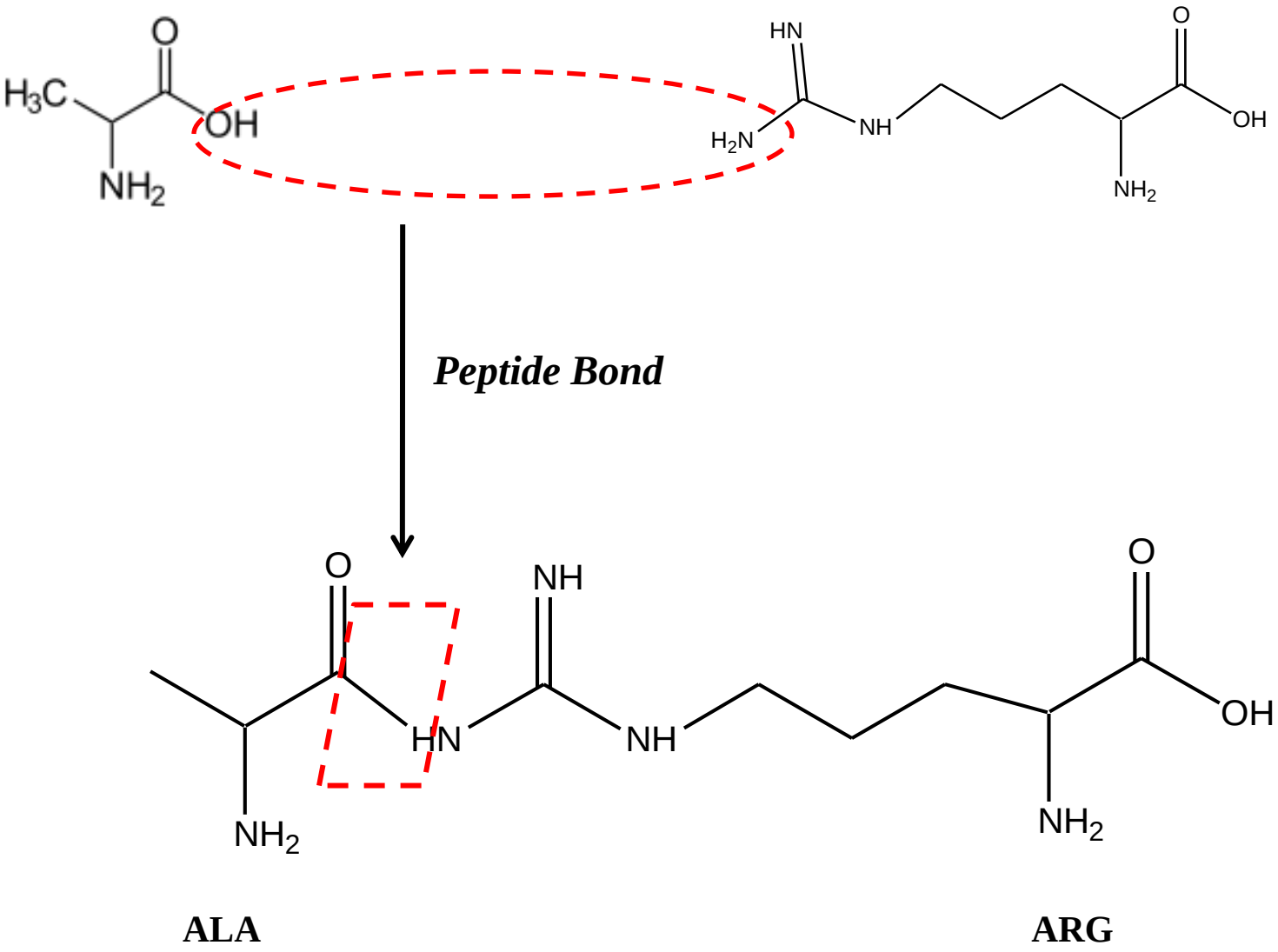


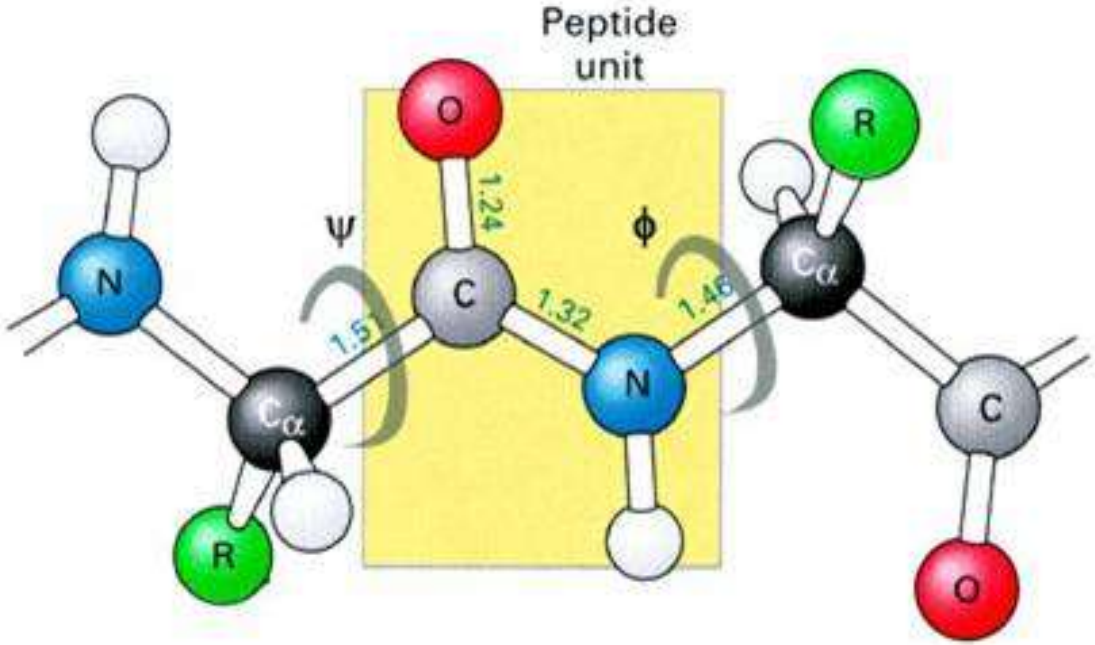



[Nomenclature: Protein Structure and Molecular Properties: T. E. Creighton]

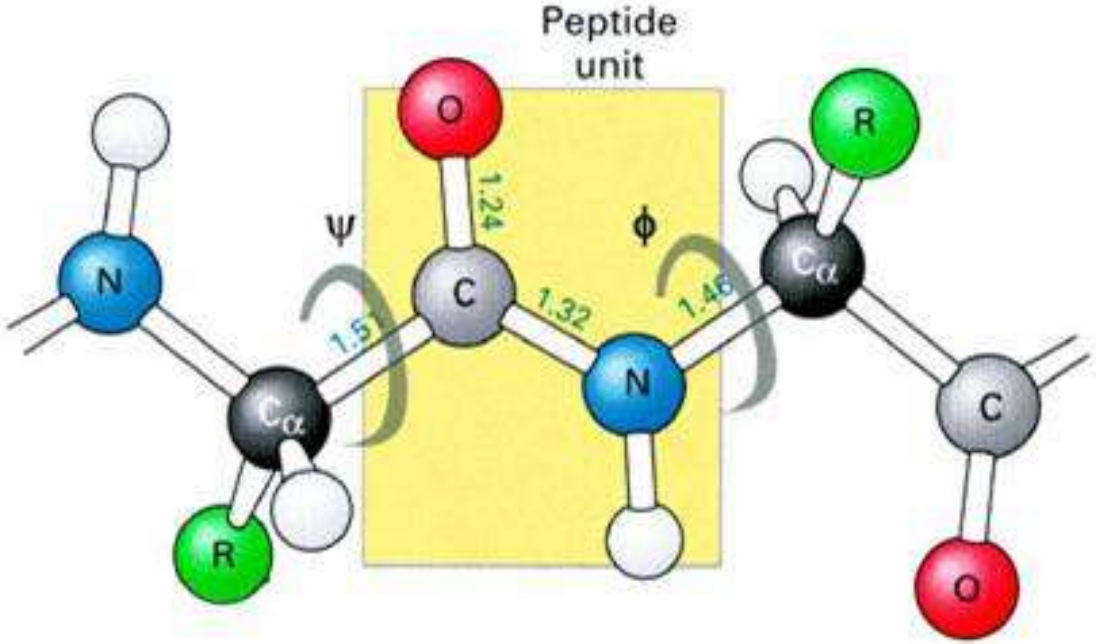
## *Functional transformation*



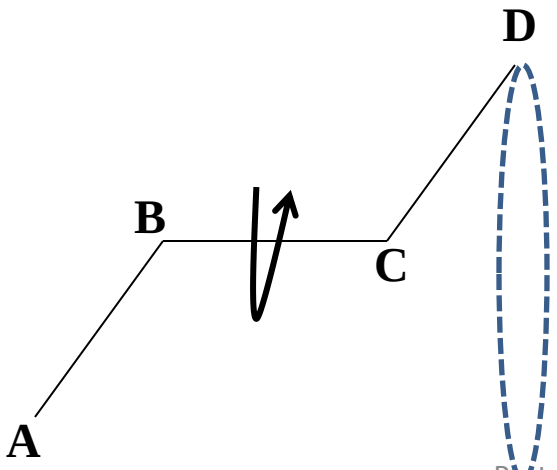
## *Functional transformation*



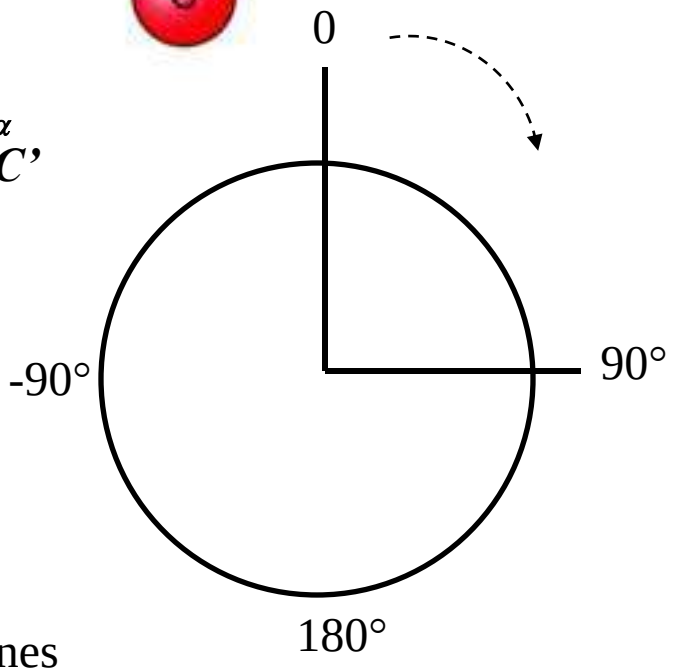

***Phi ($\phi$)-torsion angle N-$C_\alpha$***
***Psi ($\Psi$)-torsion angle $C_\alpha$-C'***



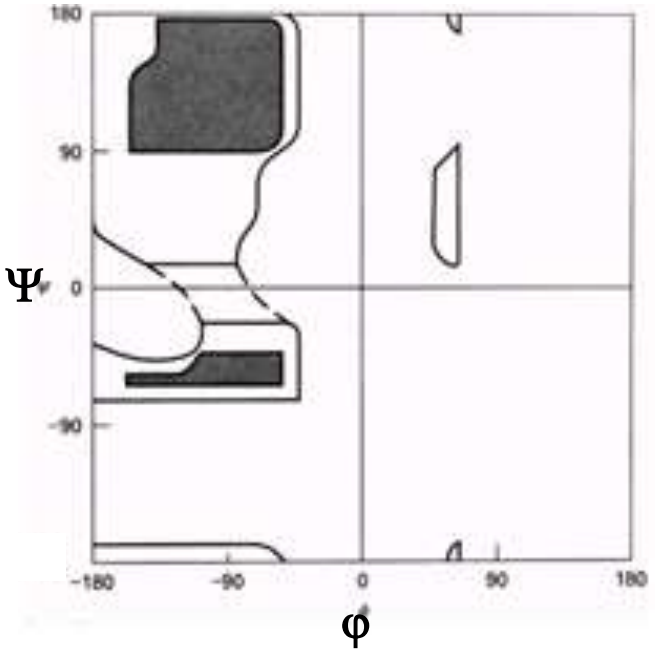

***Phi (ϕ)-torsion angle N-$C_\alpha$***
***Psi (Ψ)-torsion angle $C_\alpha$-C'***



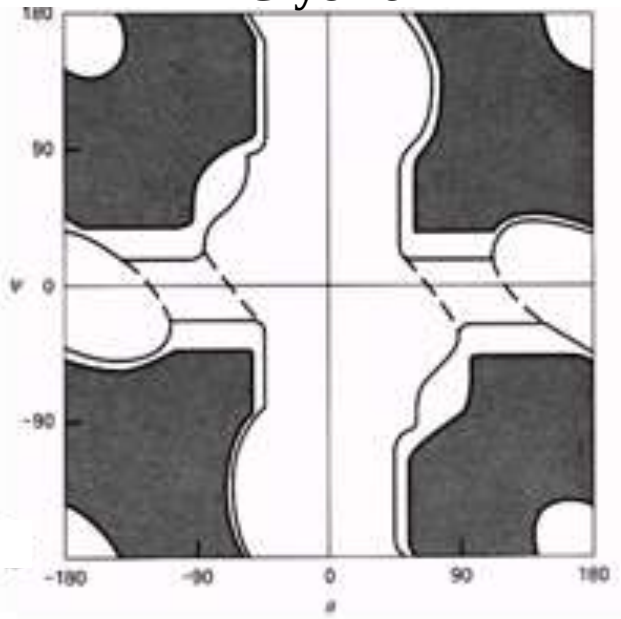

Comparing two planes



**Alanine**

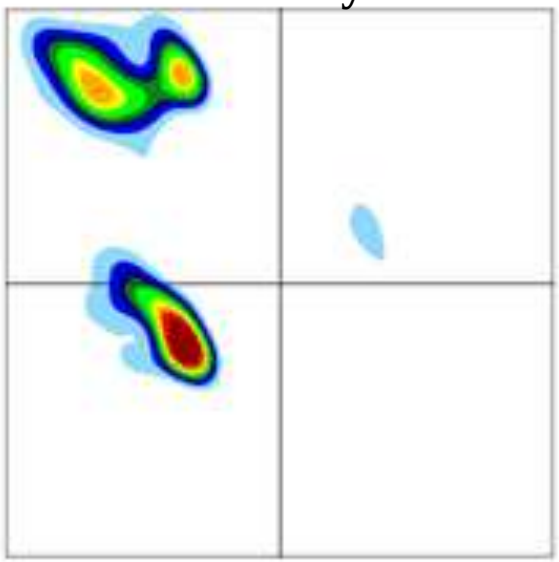



**Glycine**

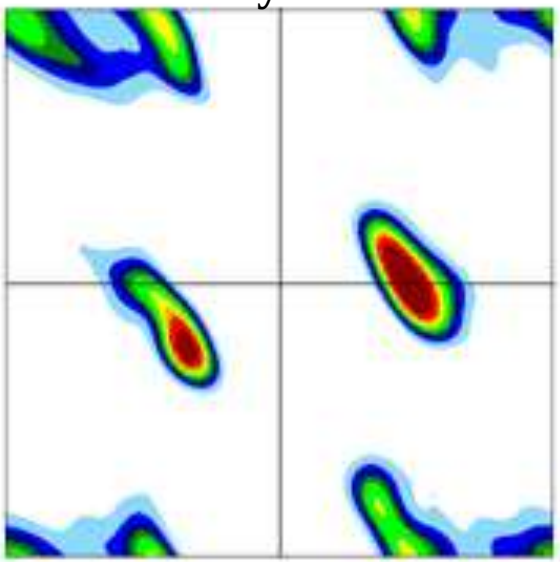



**Allowed regions (Ramachandran & Sasisekharan, 1968)**

**Non-Glycine**

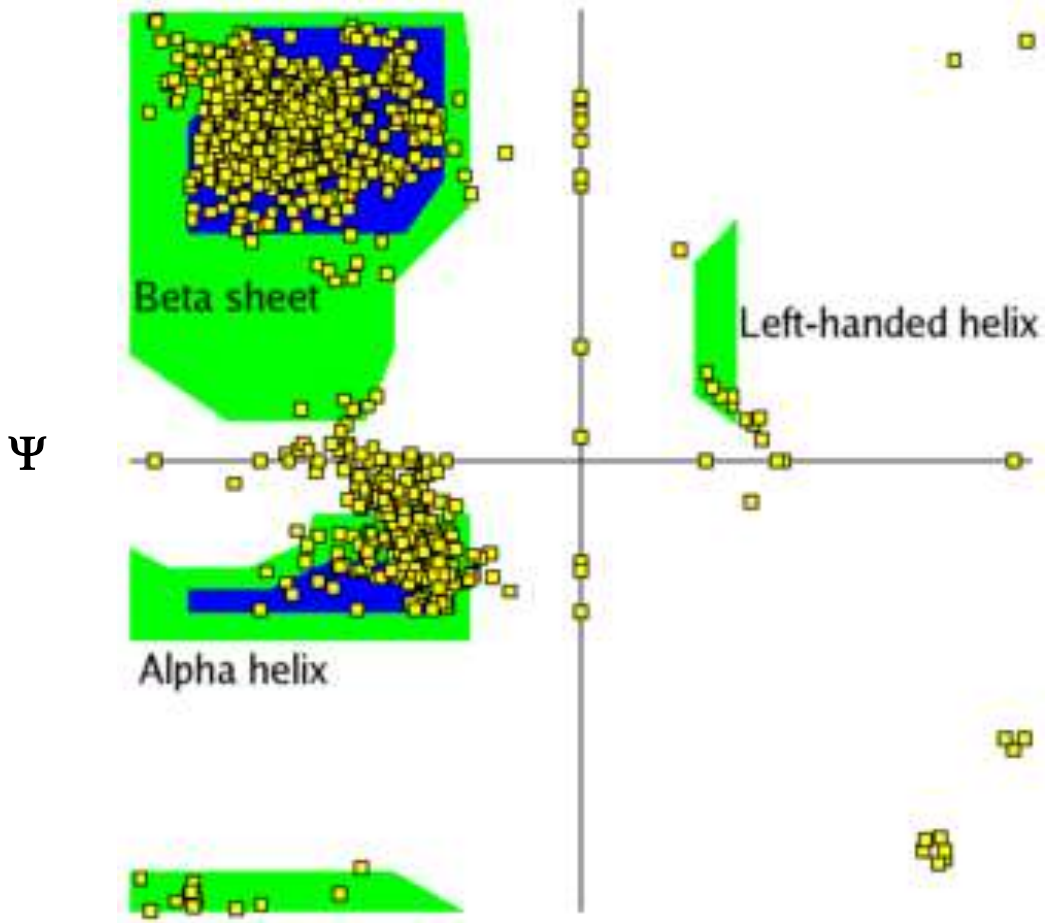


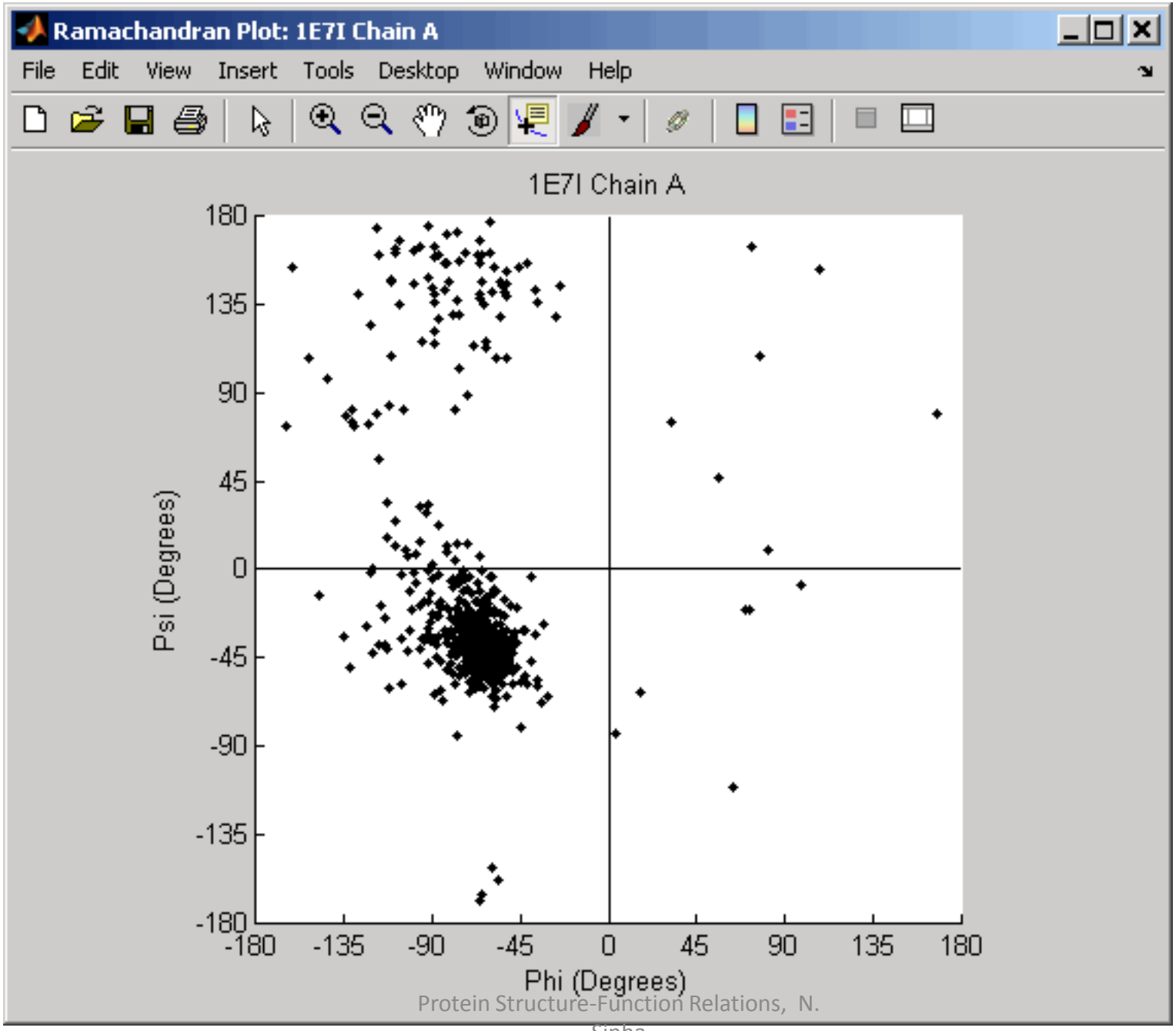
**Glycine**

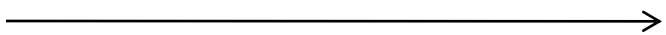


[Hovmöller *et al.* (2002) Acta. Cryst. D58, 768-776]

# Ramachandran Plot




Ramachandran Plot: 1E7I Chain A
File Edit View Insert Tools Desktop Window Help
1E7I Chain A
Psi (Degrees)
Phi (Degrees)
180
135
90
45
0
-45
-90
-135
-180
-180 -135 -90 -45 0 45 90 135 180

Sequence  Structure