Lecture 1:
Introduction to Proteins

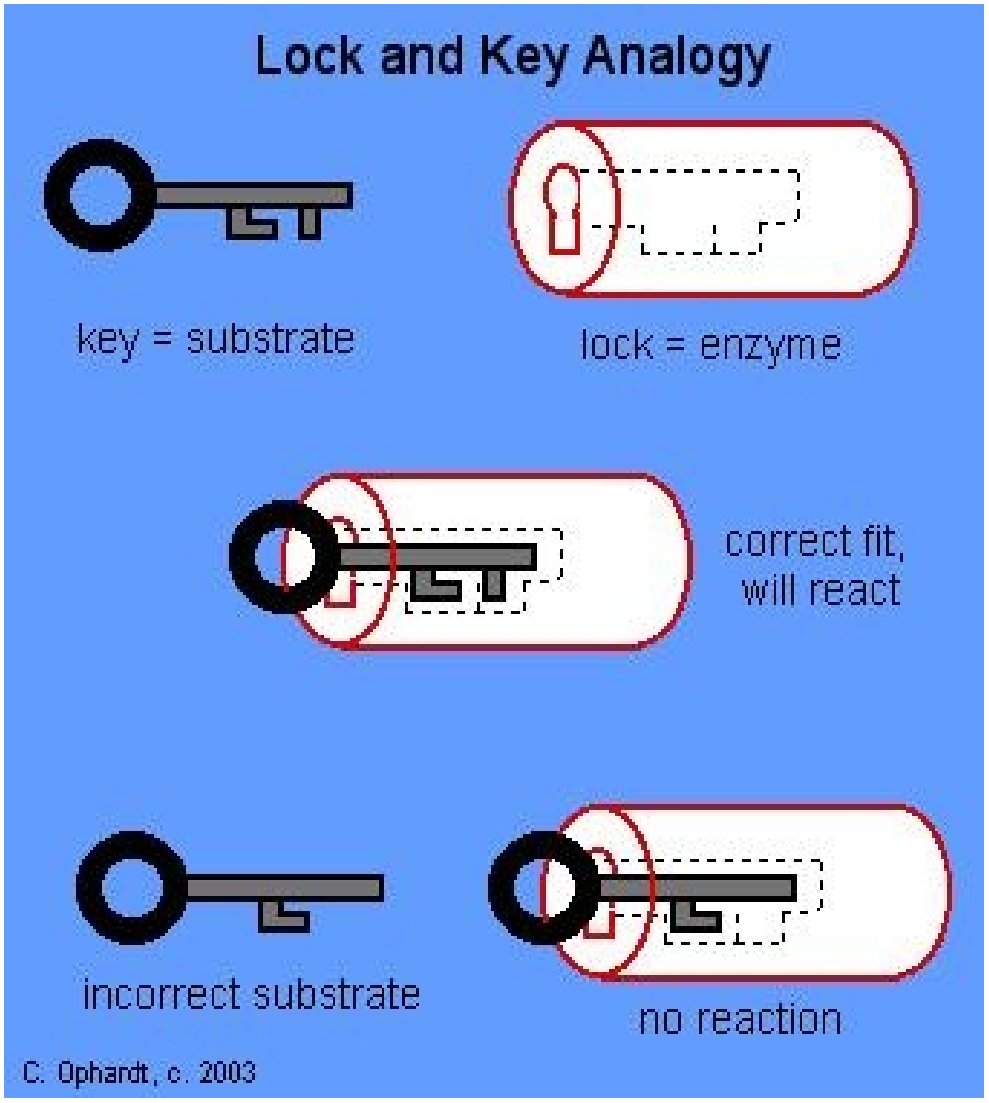
Lecturer:

Prof. Brigita Urbanc (brigita@drexel.edu)

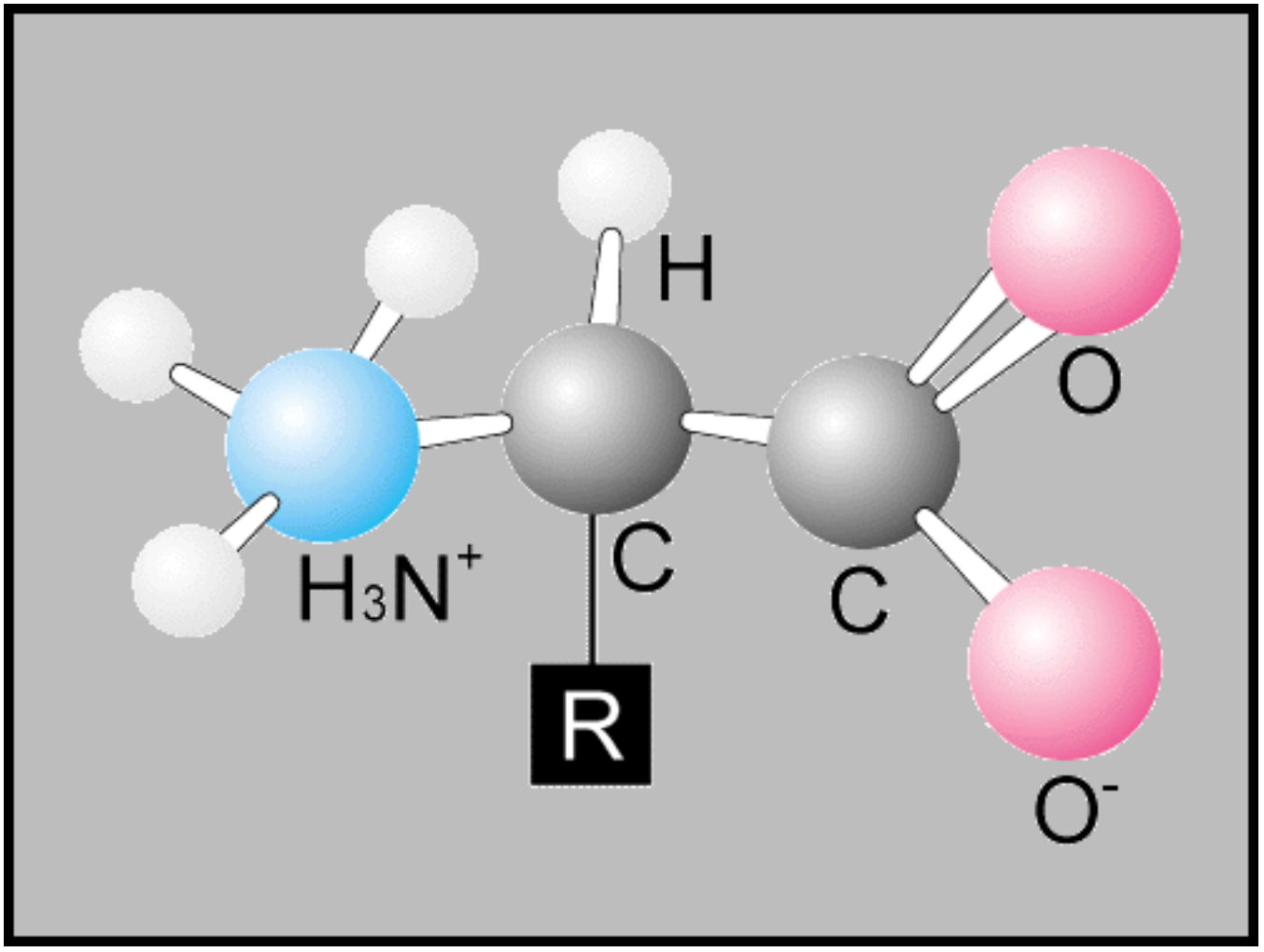
WHY ARE WE INTERESTED IN PROTEINS?

- **enzymes of all chemical reactions;**
- **hormones;**
- **regulate/control gene expression;**
- **receptors in the membrane for intercellular signaling;**
- **immuno proteins (recognize good vs. bad cells);**
- **structural proteins (microfilaments, microtubules);**
- **transfer proteins.**

Protein function:
based on specific interactions with other molecules



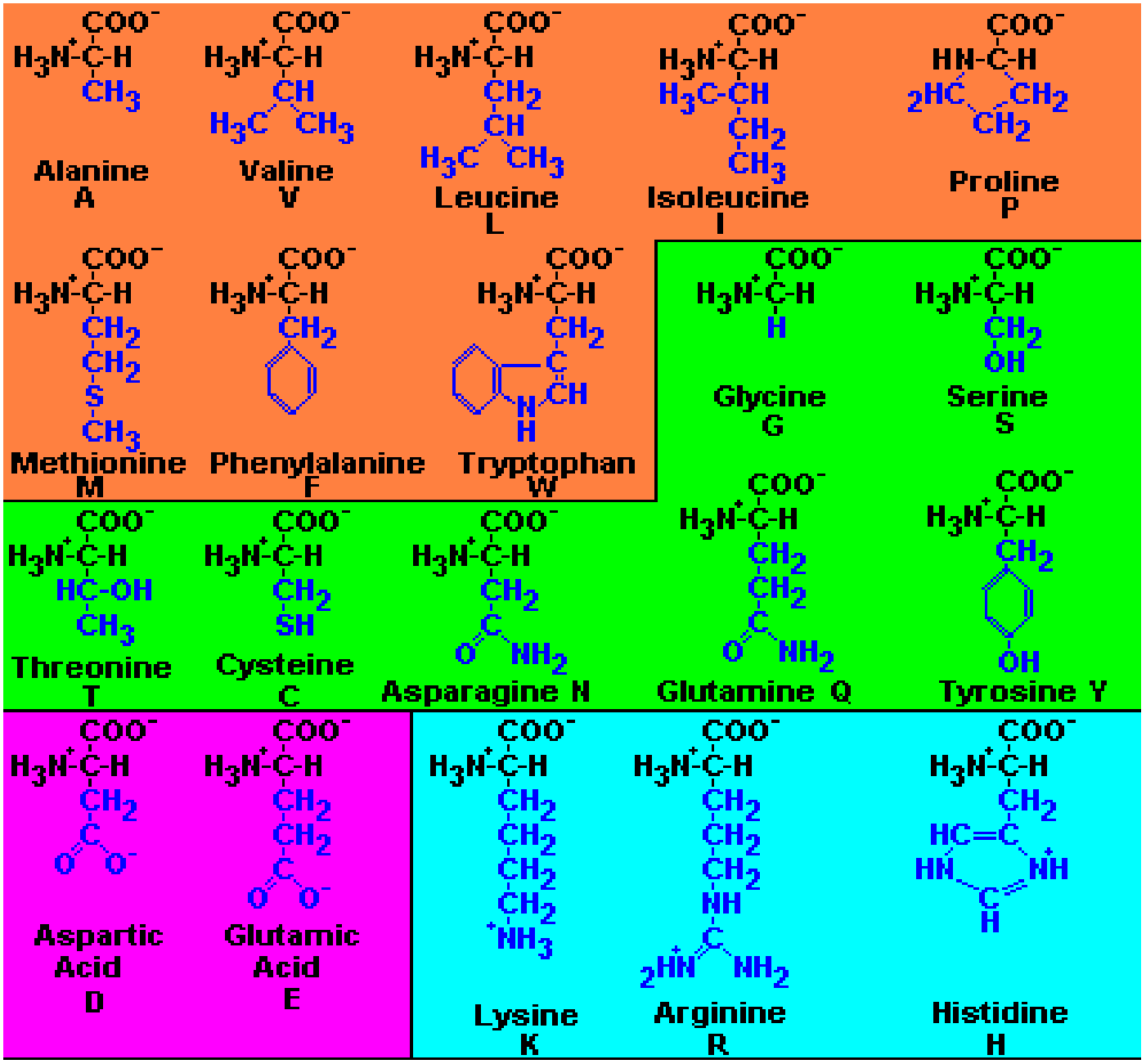
Amino acid is a building block of a protein.



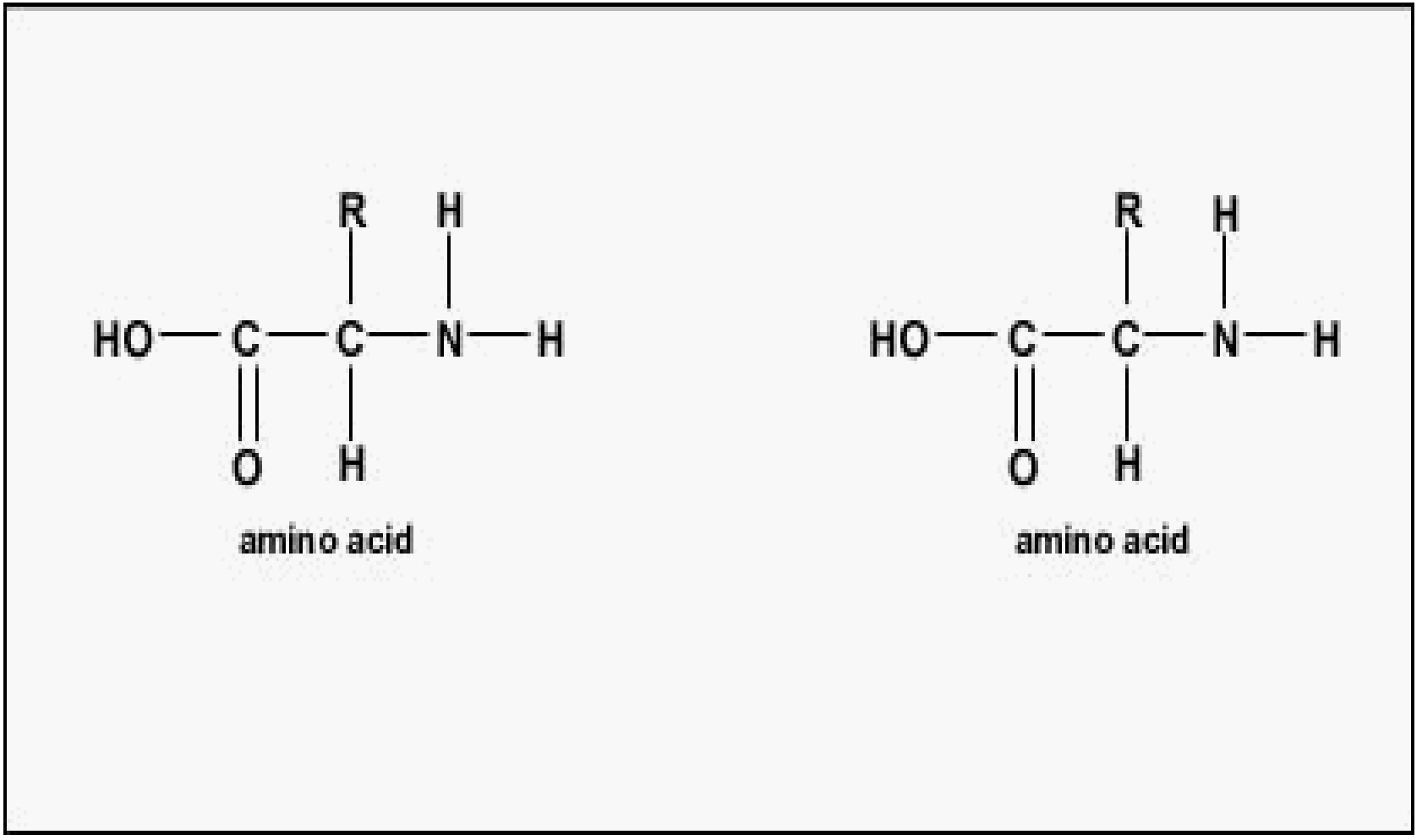
20 AAs

hydrophobic
("hate" water)

hydrophilic
("love" water)

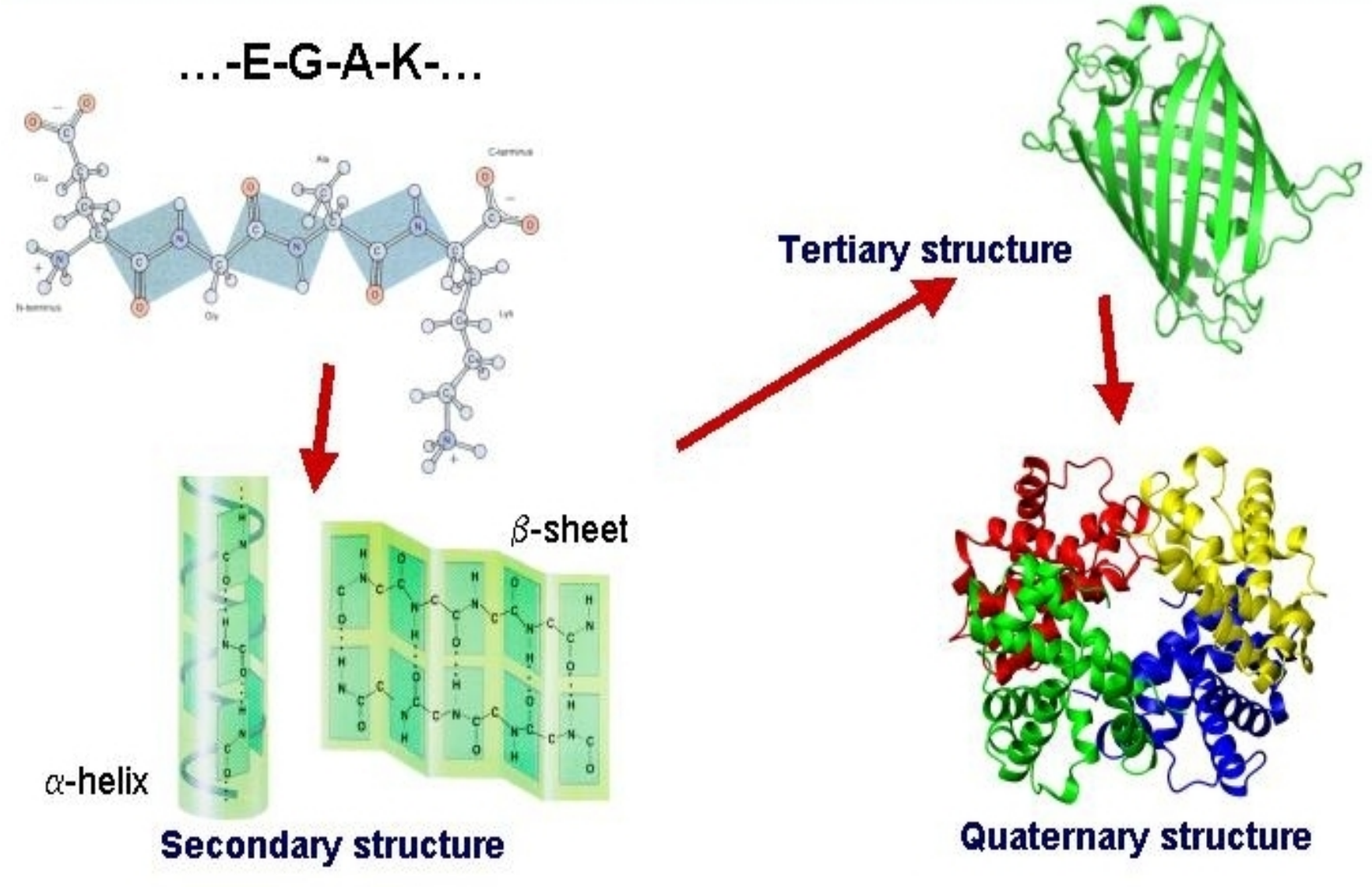


Two AAs Form a Peptide Bond



- **a protein is made of a specific sequence of aas;**
- **an "operating" protein is folded into a specific 3D structure;**
- **protein structure in a crystal or in solution was shown to be practically the same;**
- **protein structure depends on the presence/ absence of water in environment!**

Protein Structure



Classes of proteins with respect to "environmental" conditions:

(1) fibrous proteins (high degree of regular structure due to HBs);

(2) membrane proteins (HBs inside the membrane);

(3) water-soluble globular proteins (less regular structure, hydrophobic effect).

Protein Data Bank*:

www.pdb.org

*Repository of information about the 3D structures of large biological molecules, including proteins and nucleic acids.

Terminology:

- ***in vivo:*** **in a living organism**

- ***in vitro:*** **in an "artificial" environment outside a living organism**

- ***in silico:*** **in a computer-generated environment**

- **native structure: biologically active protein structure**

In vivo **formation of the native tertiary structure happens during biosynthesis or immediately after.**

If protein structure unfolded, the protein refolds back into the native tertiary structure *in vitro* spontaneously (Christian B. Anfinsen).

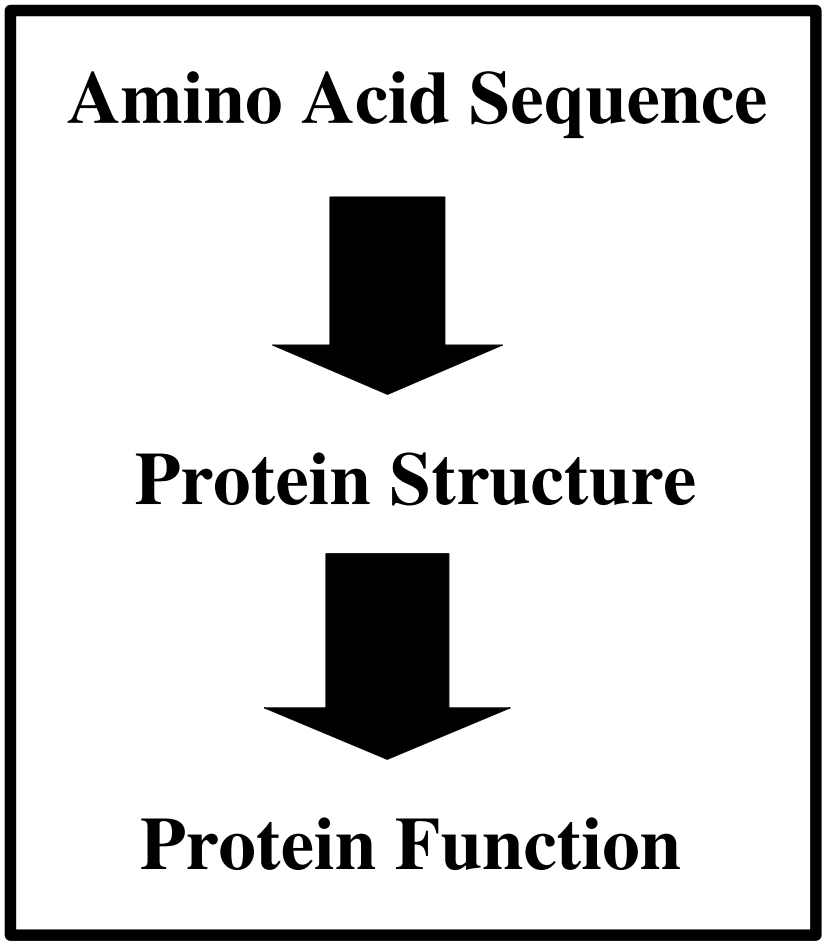
The native state is unique, stable, & kinetically accessible (thermodynamic hypothesis).

Unfolding **RNase enzyme** under extreme chemical conditions, followed by refolding of the enzyme's amino acid structure refolded spontaneously back into its origin.

"The native conformation is determined by the totality of interatomic interactions and hence by the amino acid sequence, in a given environment."

(Christian B. Anfinsen, Nobel Prize , Acceptance Speech, 1972)

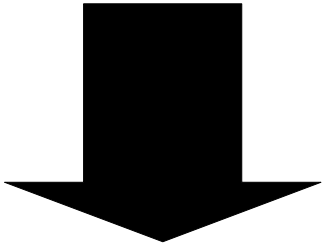
Causal Relationship*:



***valid for small, up to 300 amino acids sequences**

Reverse NOT true:

Same function can be performed by proteins of very different structure/architecture.



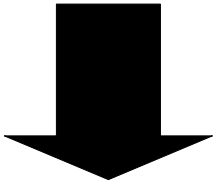
Protein function has no effect on its structure.

Levinthal Paradox:

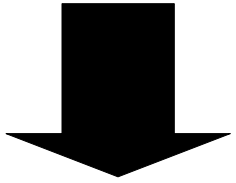
How does a protein manage to find its native structure within seconds (ms to minutes of folding time)?

Where is the paradox?

- consider a protein of 100 amino acids (residues);
- assume 2 conformations possible for each residue;



- the number of possible conformations is 2^{100} !
- each conformational change ~ picosecond

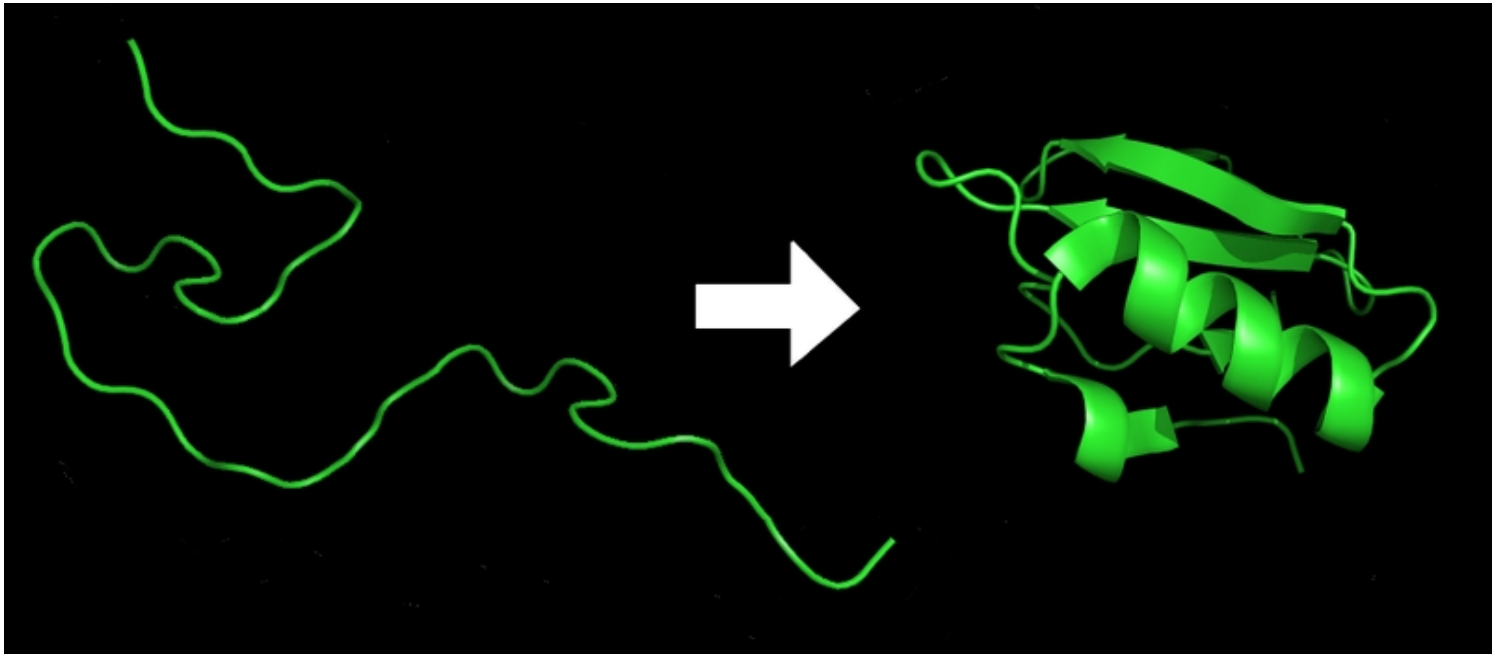


- 2^{100} ps or 10^{10} years needed for folding!

Levinthal's solution to the paradox:

The native structure is endpoint of some specific folding pathway, independent of whether this structure is the most stable or not. The native state corresponds to the most accessible local minimum of the free energy (driven by kinetics) rather than to the global free energy minimum (driven by stability).

CURRENT EXPLANATION:
Free energy (F = E – TS) changes upon folding:
$\Delta F = \Delta E - T\,\Delta S$



Thermodynamic quantities:

- **temperature T;**
- **internal energy of protein conformation E;**
- **conformational entropy S;**

What happens upon folding?

(1) S decreases (loss of conformational "freedom");

(2) E decreases (intramolecular interactions);

(1) $\Delta F > 0$ & (2) $\Delta F < 0$

TO BE CONTINUED ...