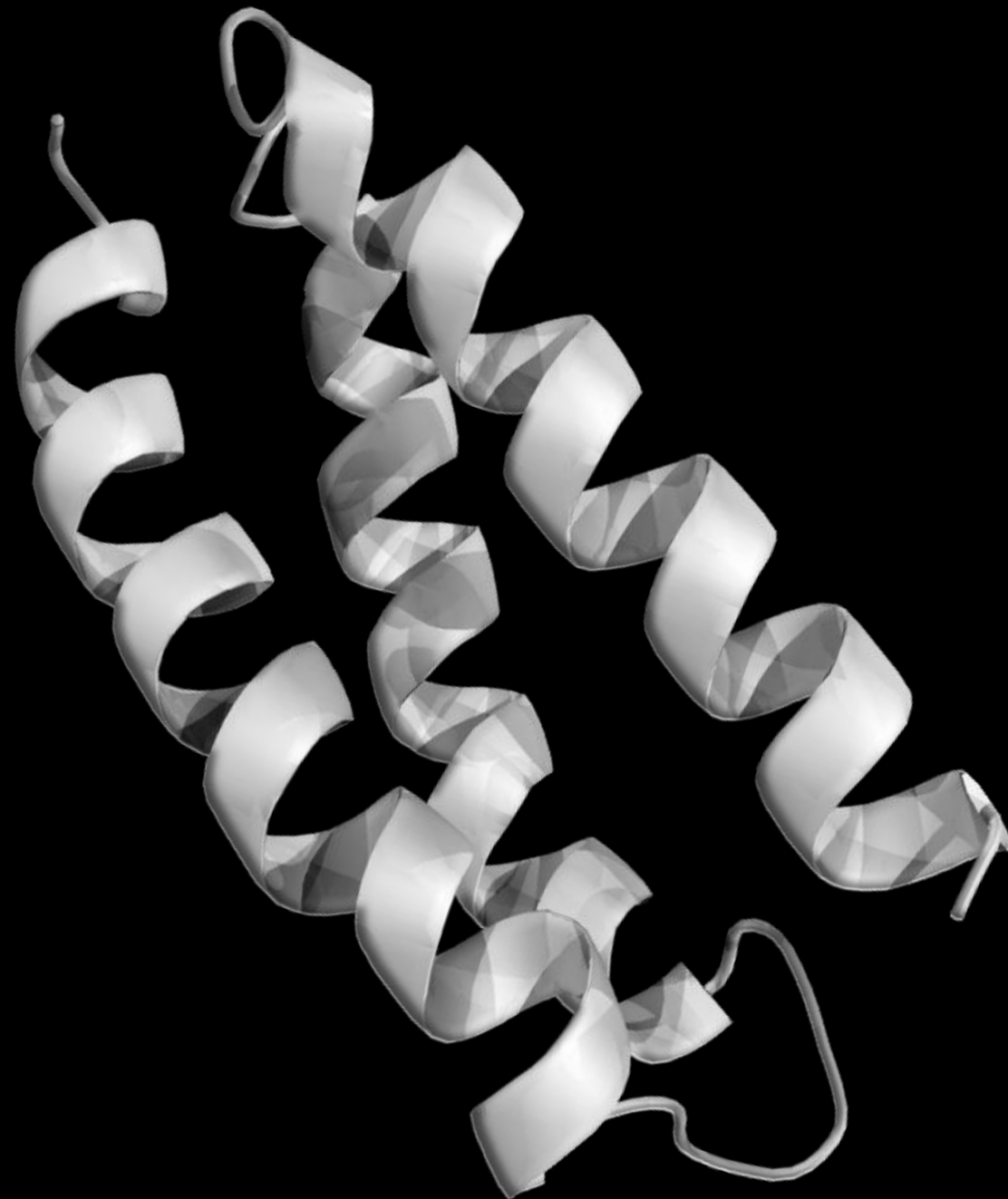# Computational design of peptides

Laboratório de Visualização e Computação Científica
Module 2

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2021-2022

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ProtoSyn

Program

Intro	Practical examples	Challenge
30 min	60 min	90 min

Break

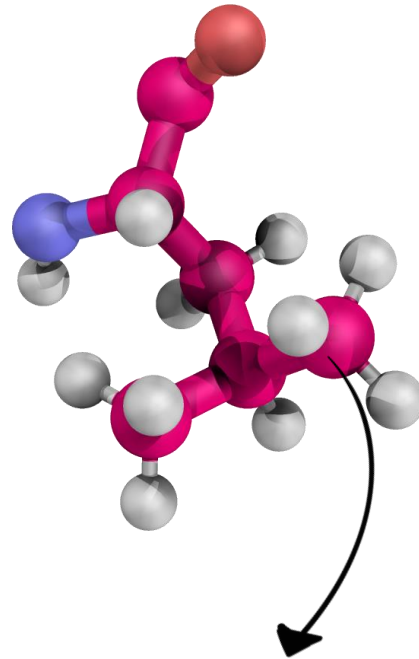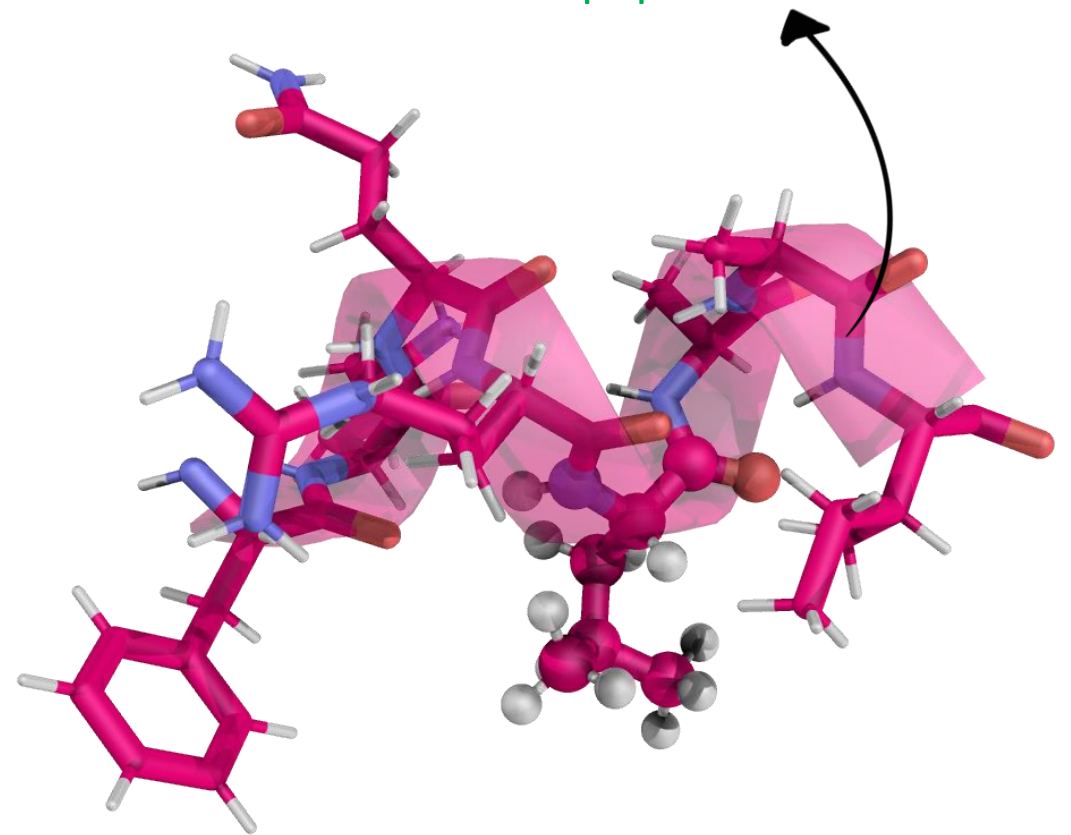# What's a peptide?

A group of aminoacids is called a protein.

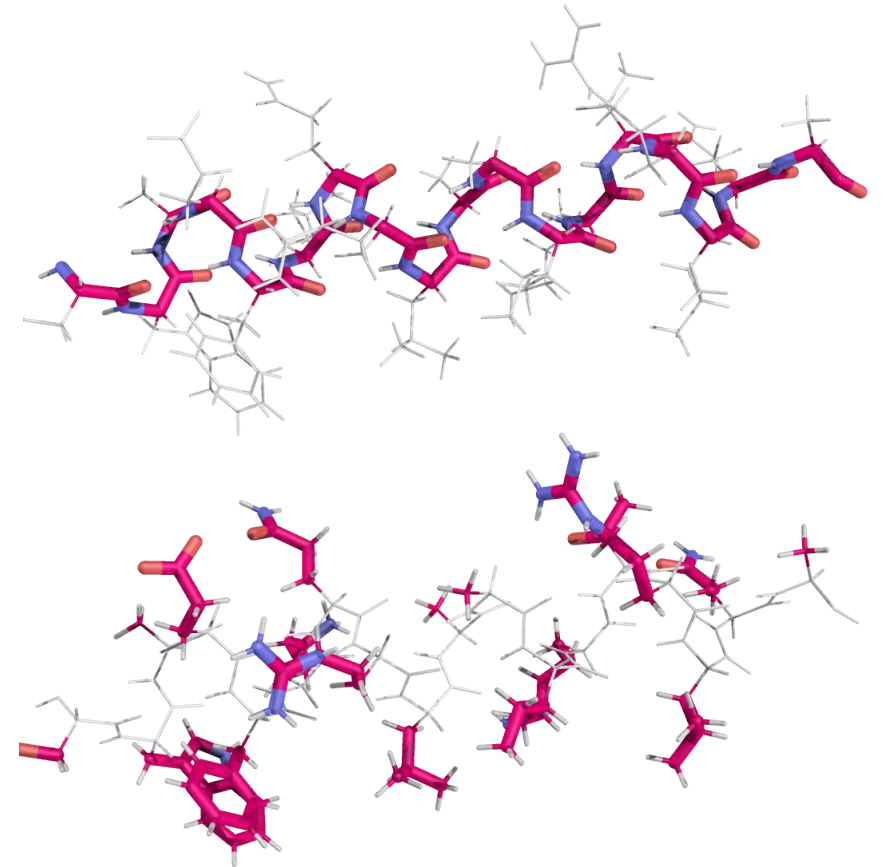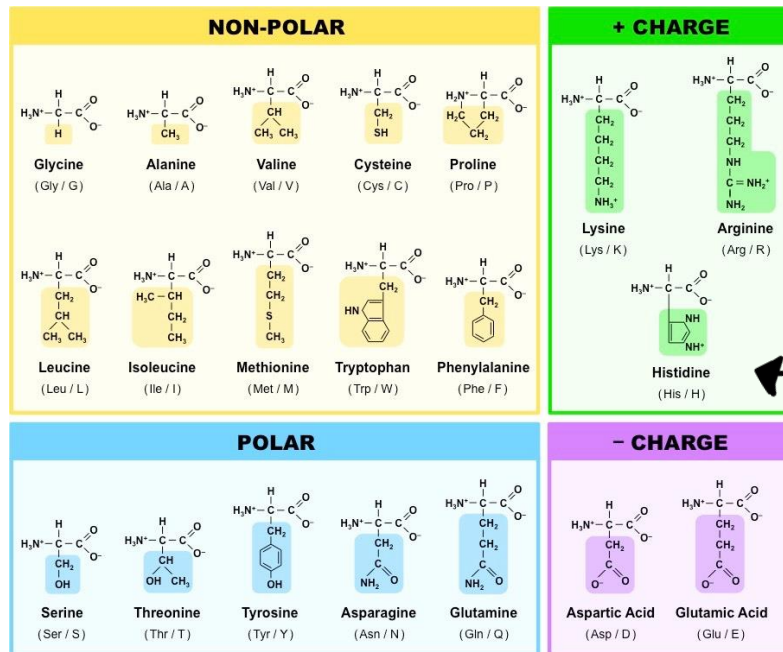A small protein (around 100 aminoacids) is called a peptide!

This is an atom
(trust me)

A group of atoms is a molecule.
This one in specific is called an **aminoacid**.

What's a peptide?

All aminoacids have the same backbone
but have different sidechains.

NON-POLAR					+ CHARGE	
Glycine (Gly / G)	Alanine (Ala / A)	Valine (Val / V)	Cysteine (Cys / C)	Proline (Pro / P)	Lysine (Lys / K)	Arginine (Arg / R)
Leucine (Leu / L)	Isoleucine (Ile / I)	Methionine (Met / M)	Tryptophan (Trp / W)	Phenylalanine (Phe / F)		Histidine (His / H)

POLAR					− CHARGE	
Serine (Ser / S)	Threonine (Thr / T)	Tyrosine (Tyr / Y)	Asparagine (Asn / N)	Glutamine (Gln / Q)	Aspartic Acid (Asp / D)	Glutamic Acid (Glu / E)

There are 20 different aminoacids,
each identified by a different letter.

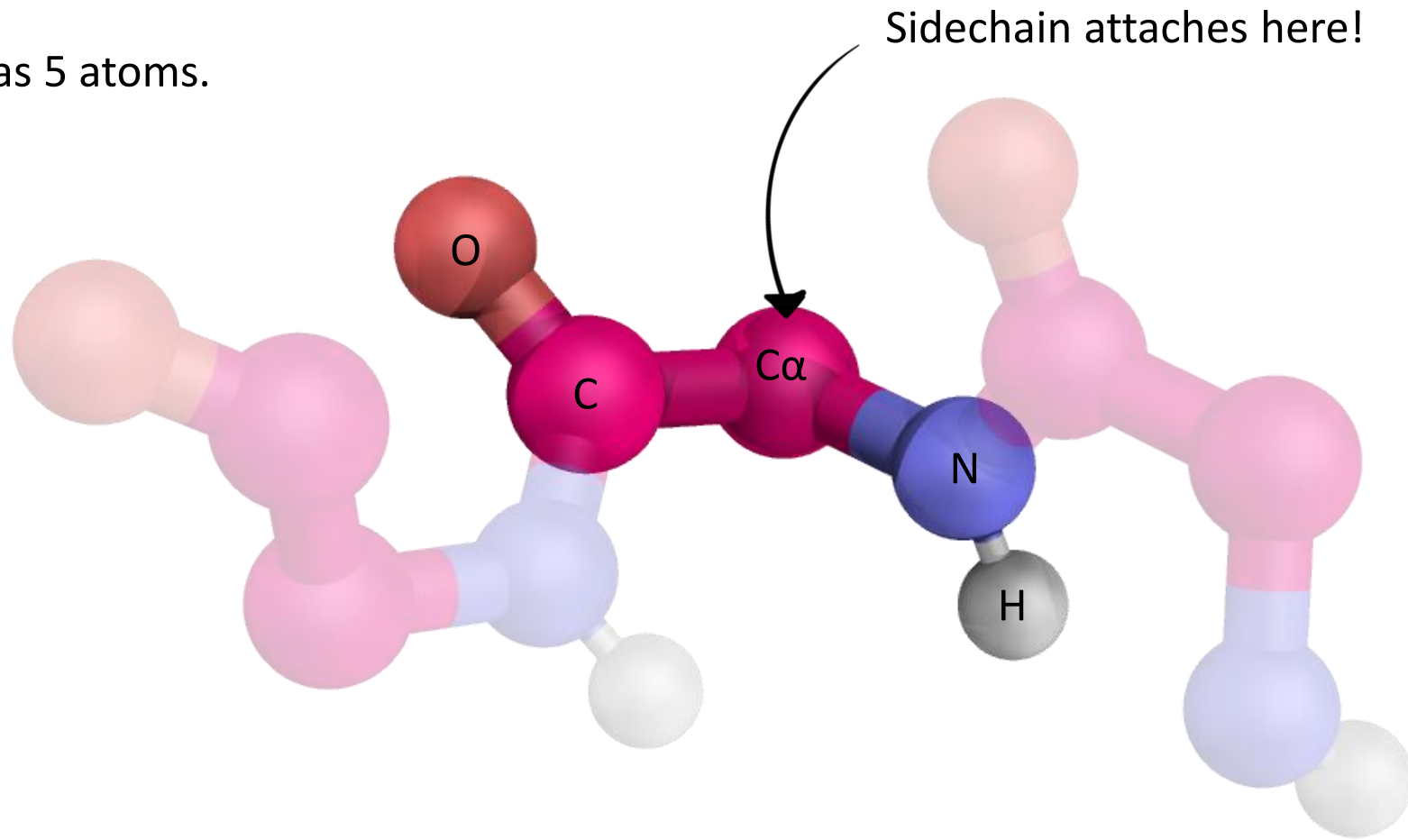# What's a peptide?
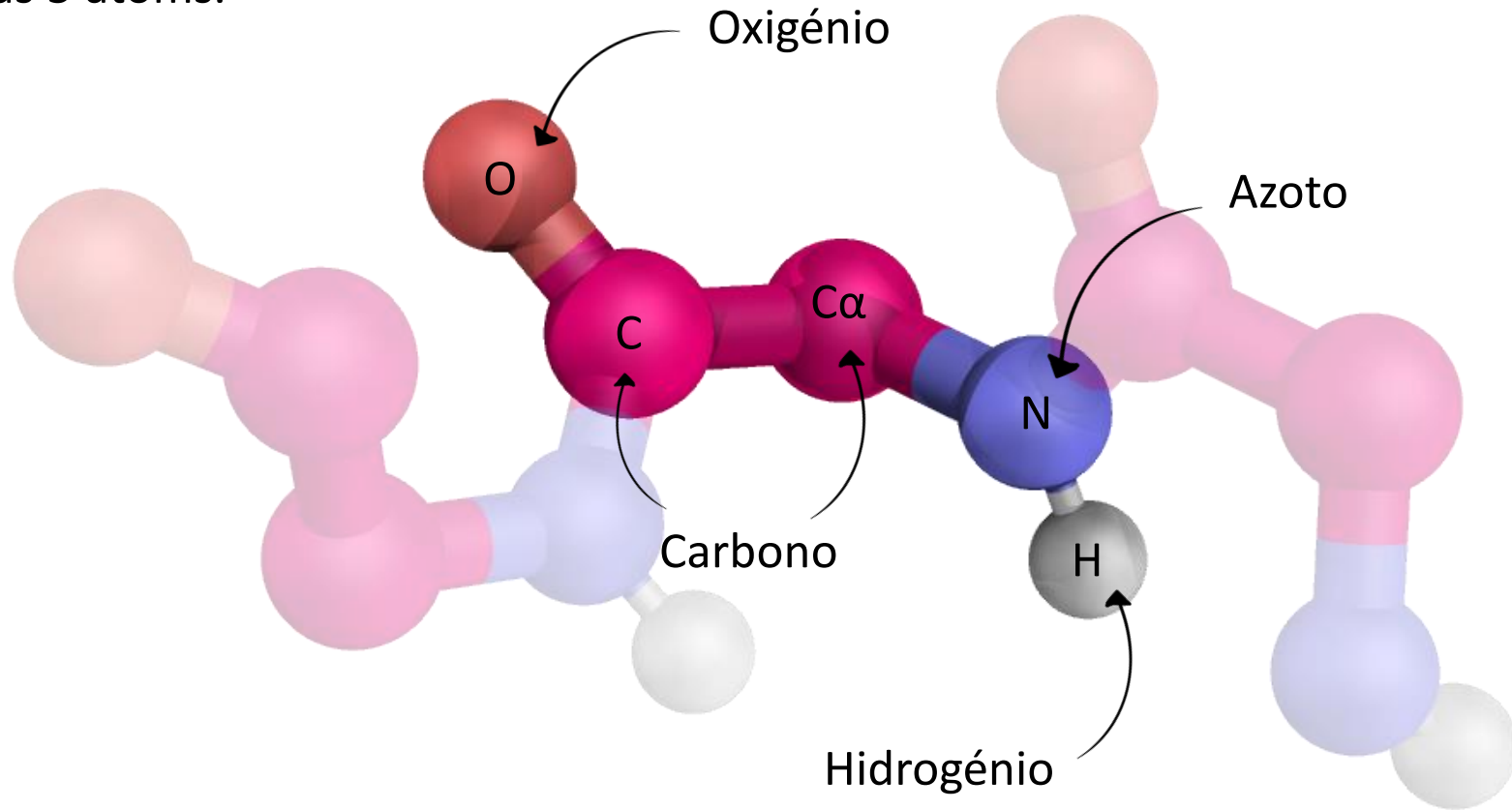
A backbone has 5 atoms.

What's a peptide?

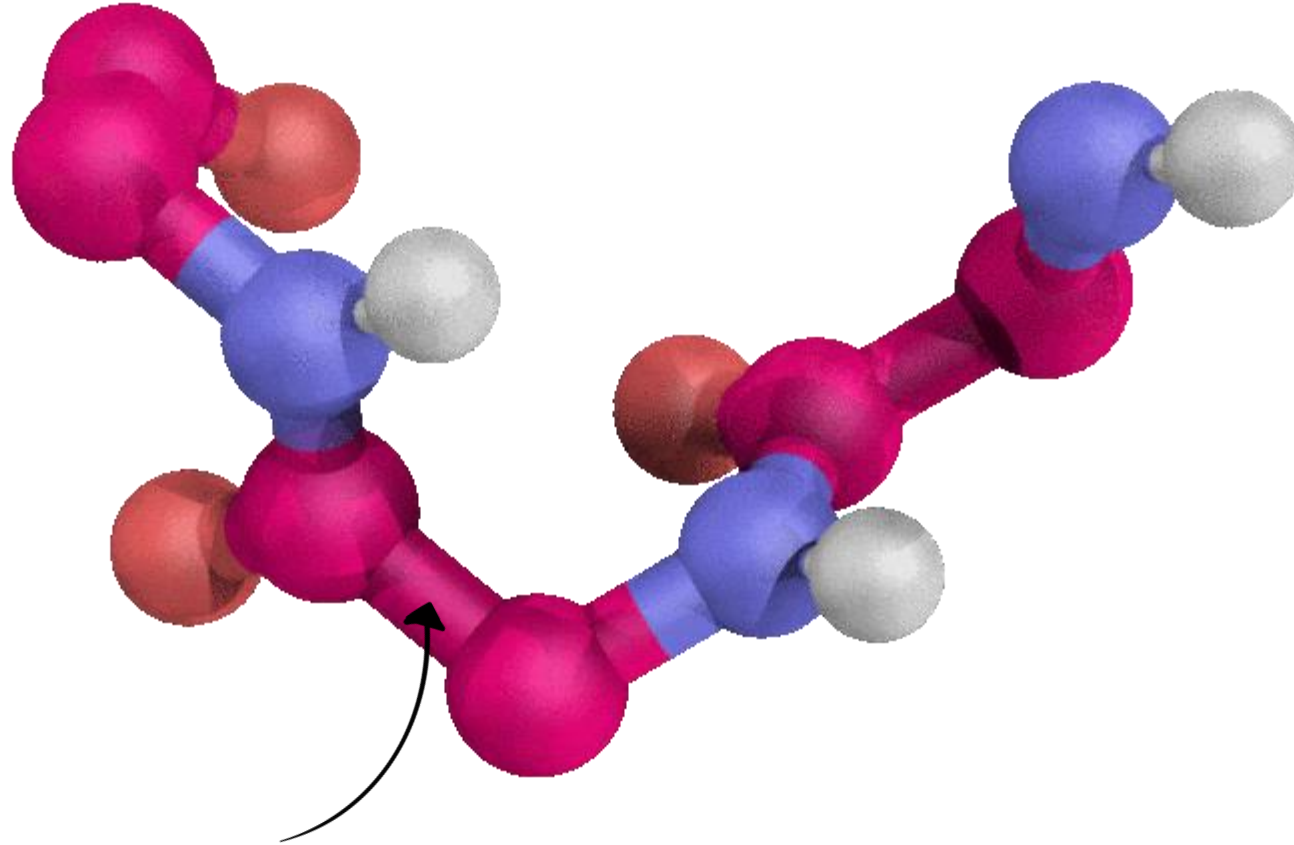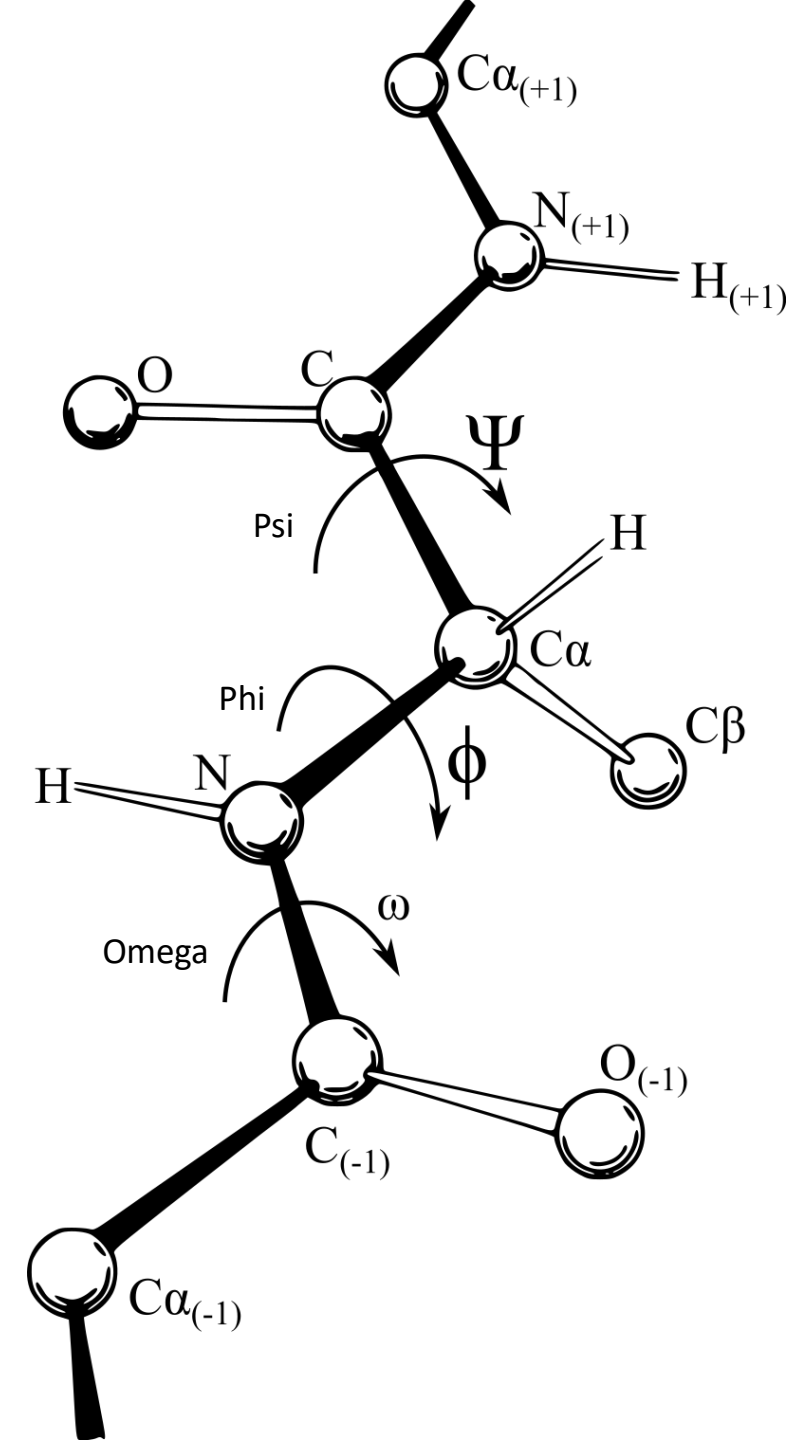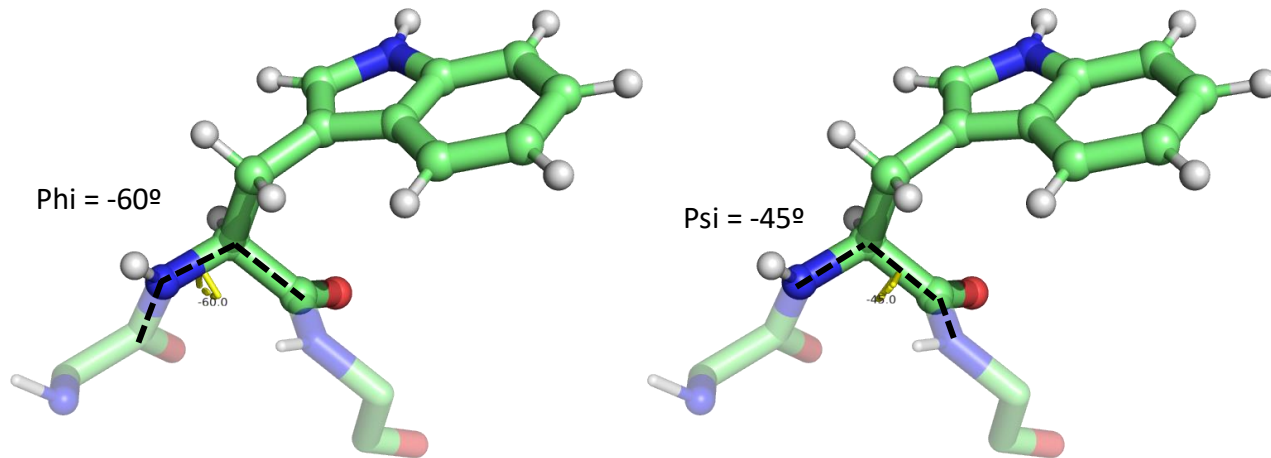A backbone has 5 atoms.

Sidechain attaches here!

What's a peptide?

A backbone has 5 atoms.

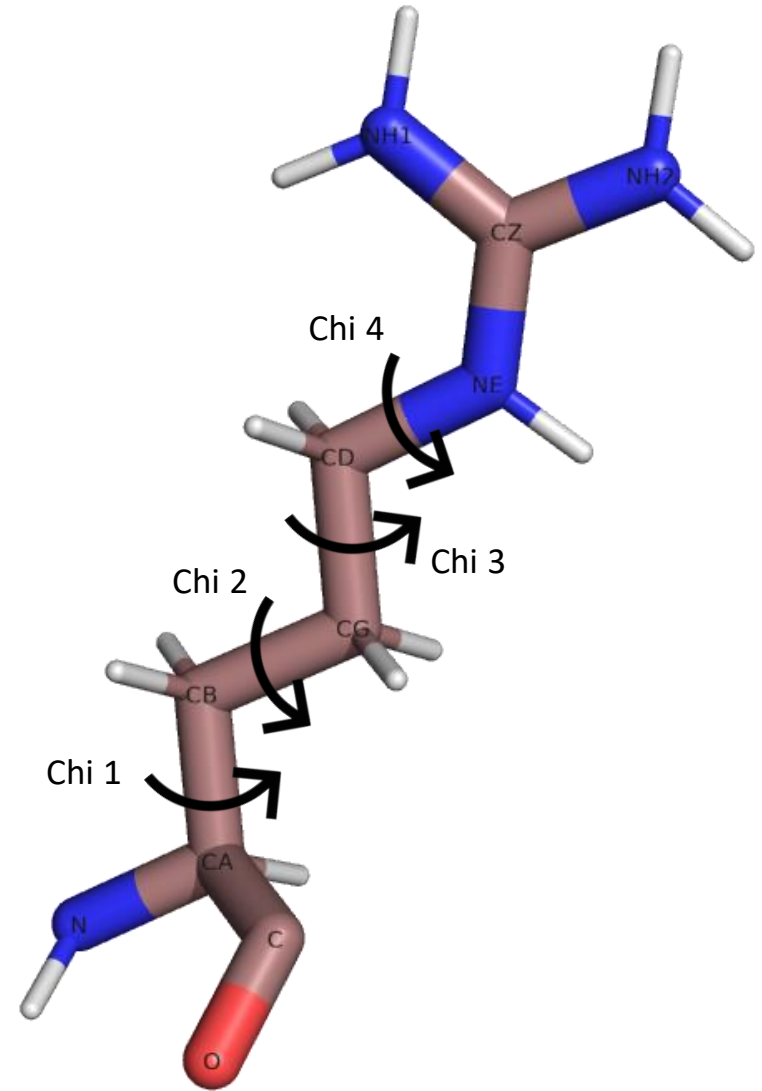Bonds connect two atoms and can be rotated.

What's a peptide?

A dihedral angle is the angle between two planes.

Phi = -60º

Psi = -45º

What's a peptide?

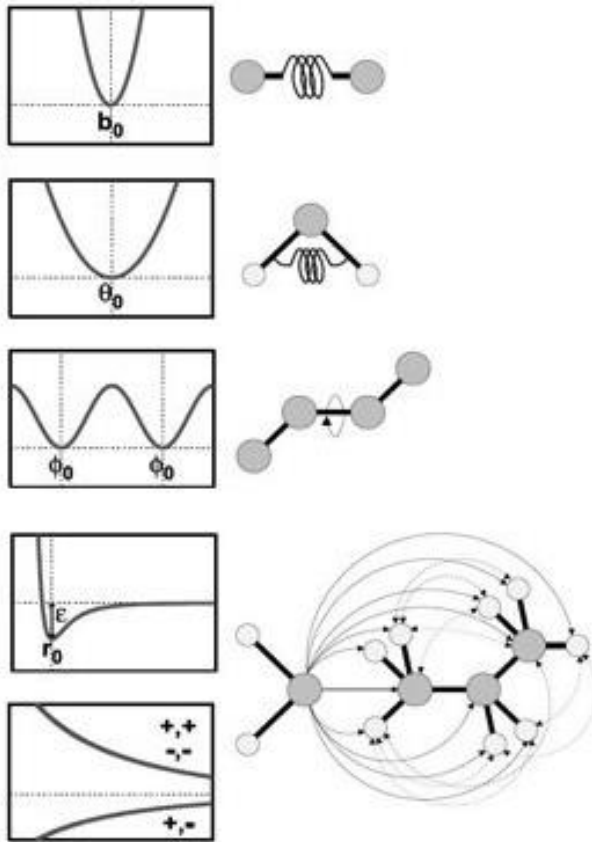A dihedral angle is the angle between two planes.

What's a peptide?

Atoms interact with the environment (hydrophobic effect, water molecules packaging, etc).

This is known as entropy.
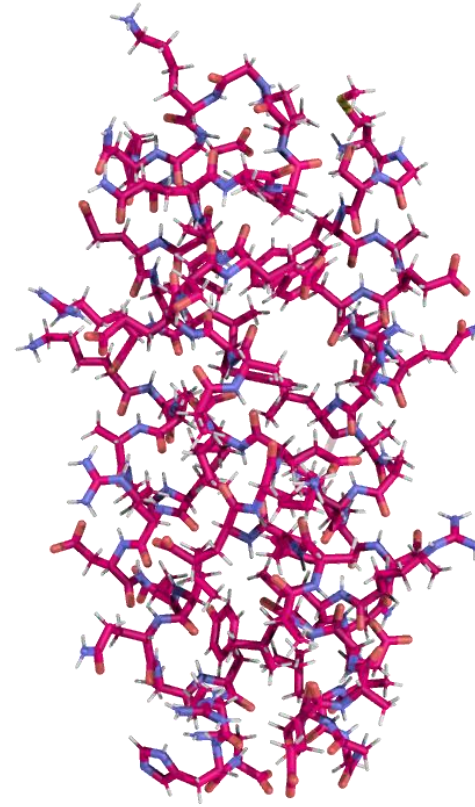
$$\Delta G = \Delta H_{system} - T\Delta S_{system}$$

Atoms interact with each other in many ways and impose certain positions/rotations.

This phenomenon is known as enthalpy.

What's a peptide?

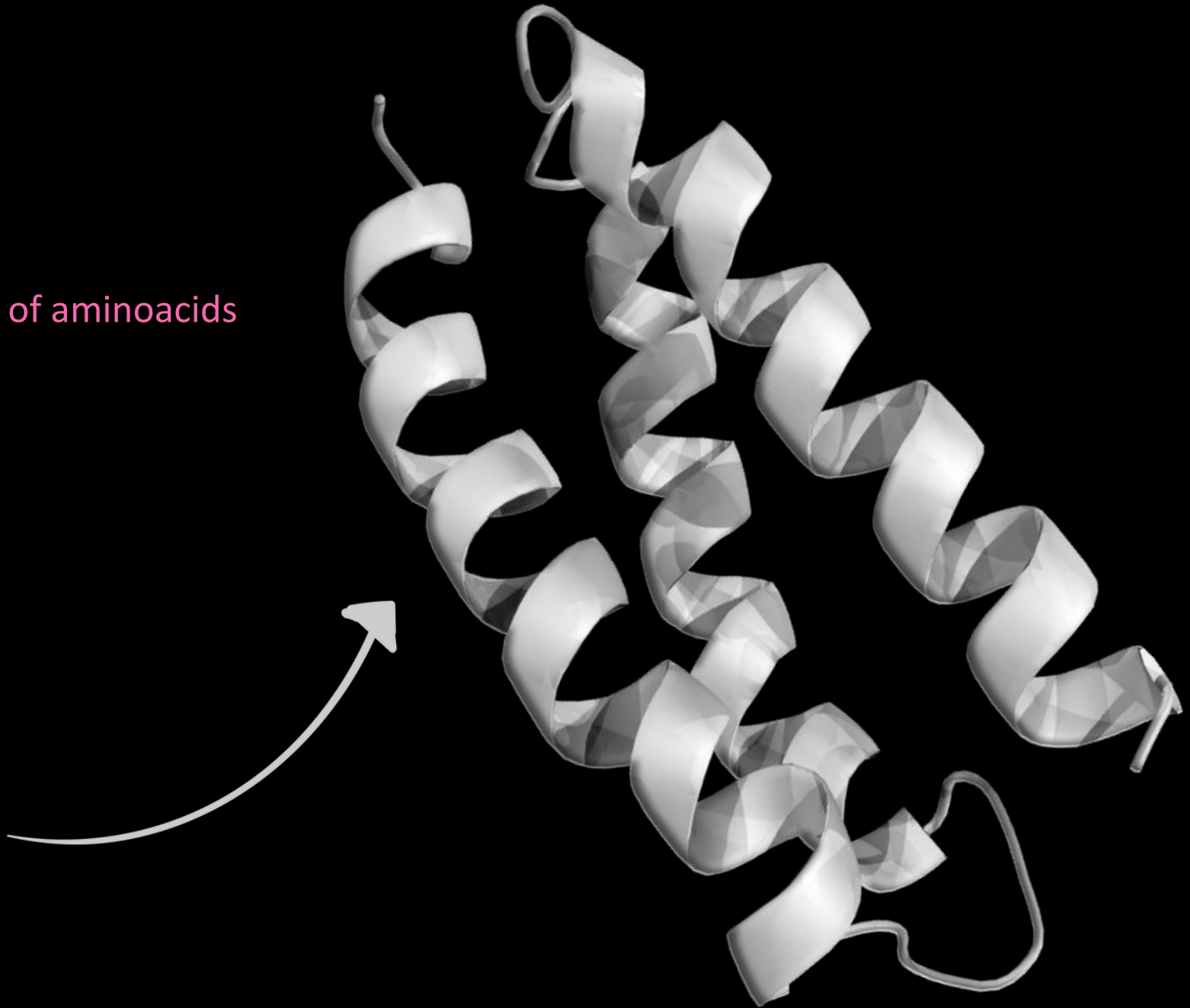Atoms interact with each other and the environment in many ways and impose certain positions/rotations.

Naturally, this effects causes the emergence of secondary structures, such as the alpha helix.

Ok ...

The peptide structure therefore is a
physical expression of the sequence of aminoacids
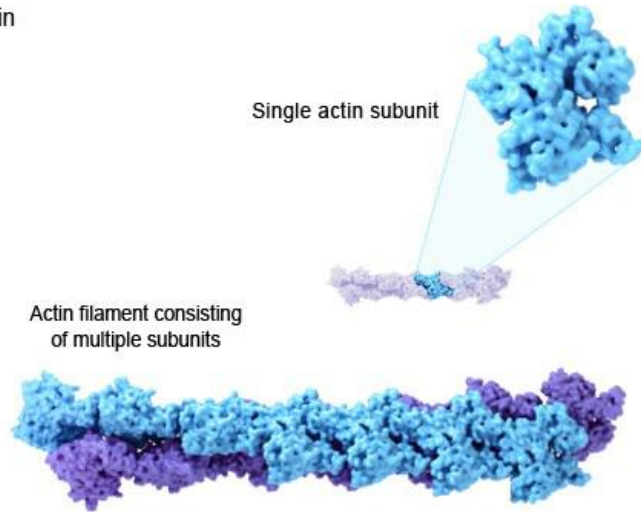that compose the peptide.

MGSWAEFKQRLA ...

Why design peptides?

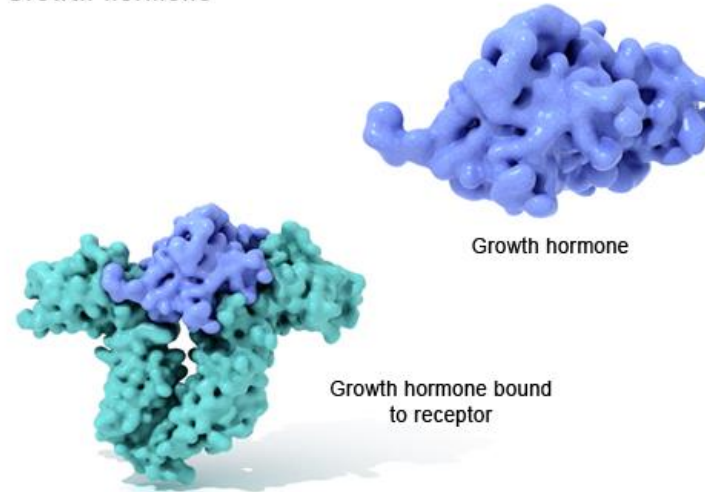Proteins and peptides are the machines of our cells.

Structural

Messenger

Enzimes

Why design peptides?

Proteins and peptides are the machines of our cells.

Antibodies   Transport

Immunoglobulin G (IgG)

Foreign particle
binding site

Foreign particle
binding site

U.S. National Library of Medicine

Ferritin

Single ferritin subunit

Ferritin protein consisting
of 24 subunits
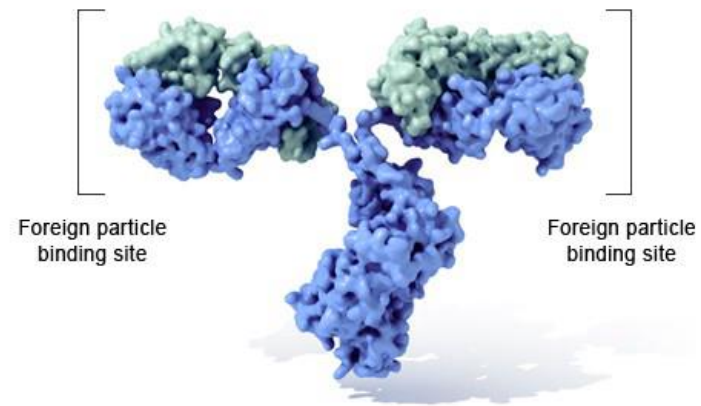
Cross section
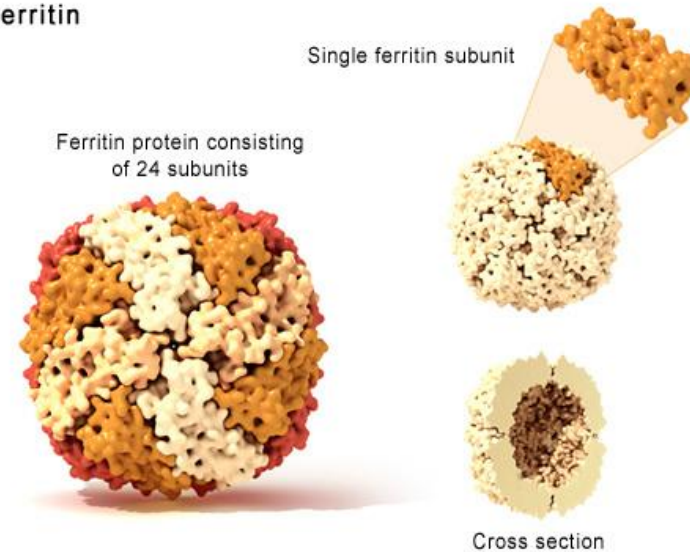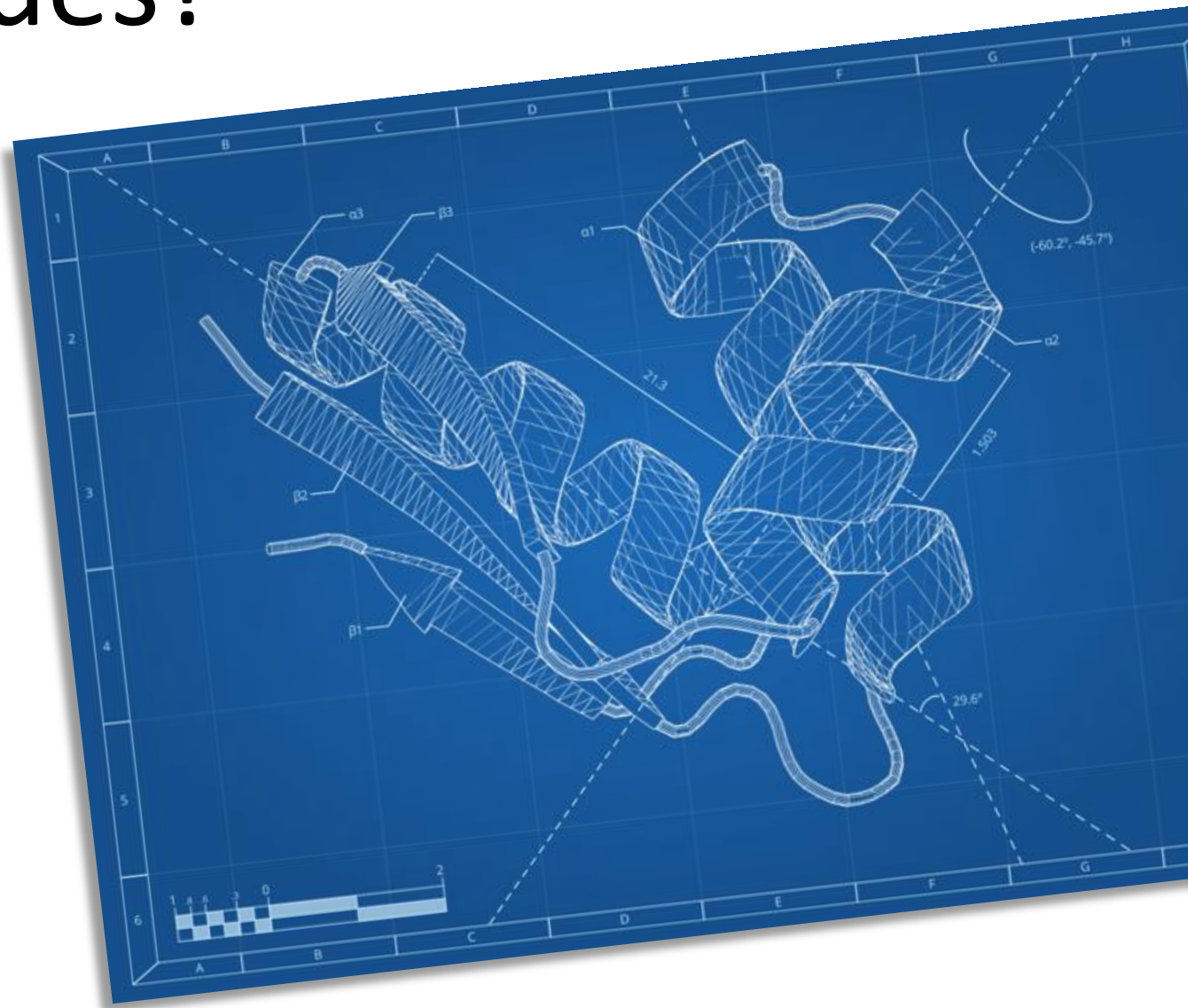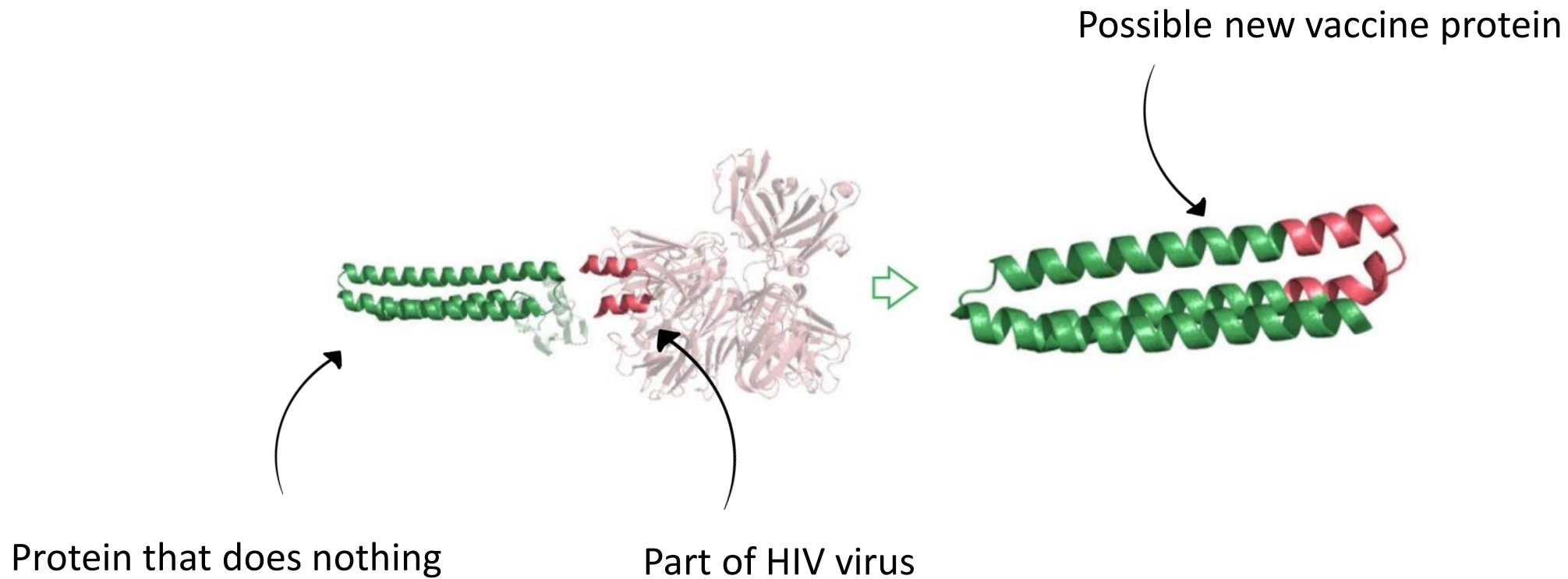
U.S. National Library of Medicine

Why design peptides?

Designing a peptide means trading, removing or adding one or more aminoacids of a peptide to obtain a new structure.

Structure

=

Function

Why design peptides?

Some examples:

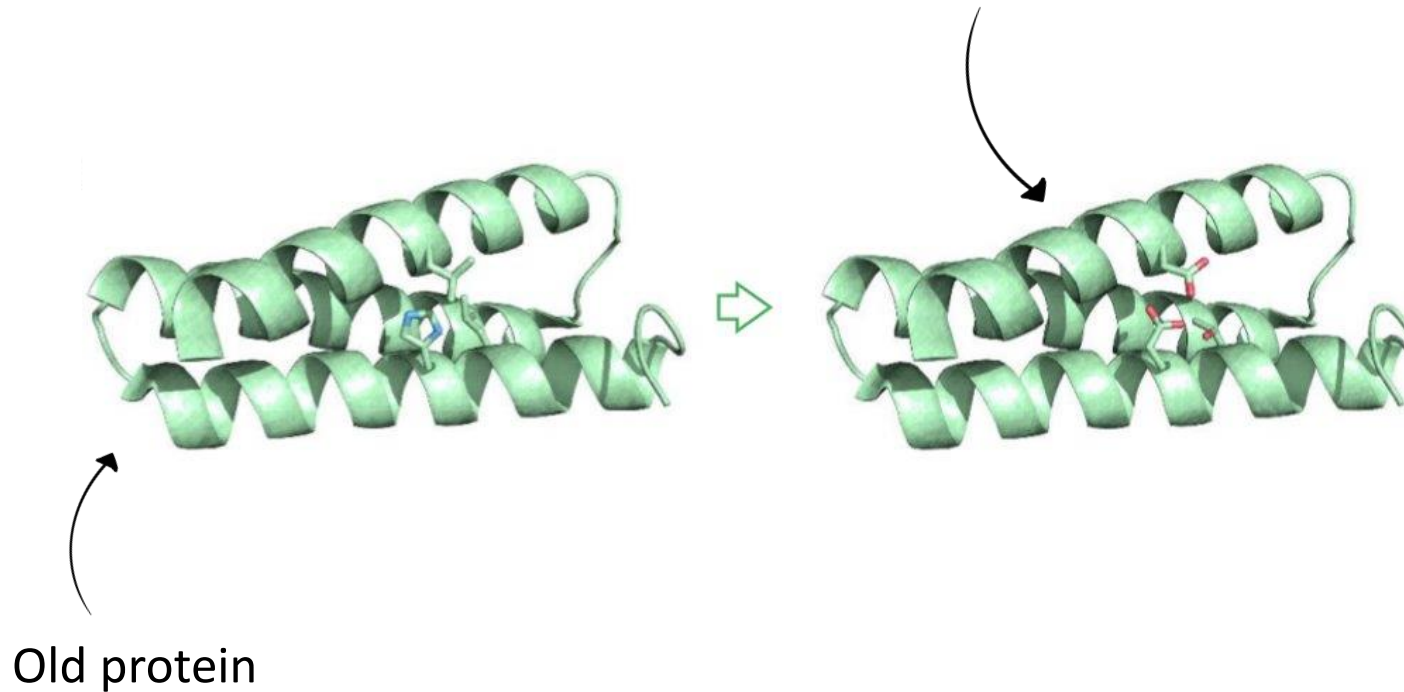Possible new vaccine protein

Protein that does nothing

Part of HIV virus

Correia et al. (2010, 2014)
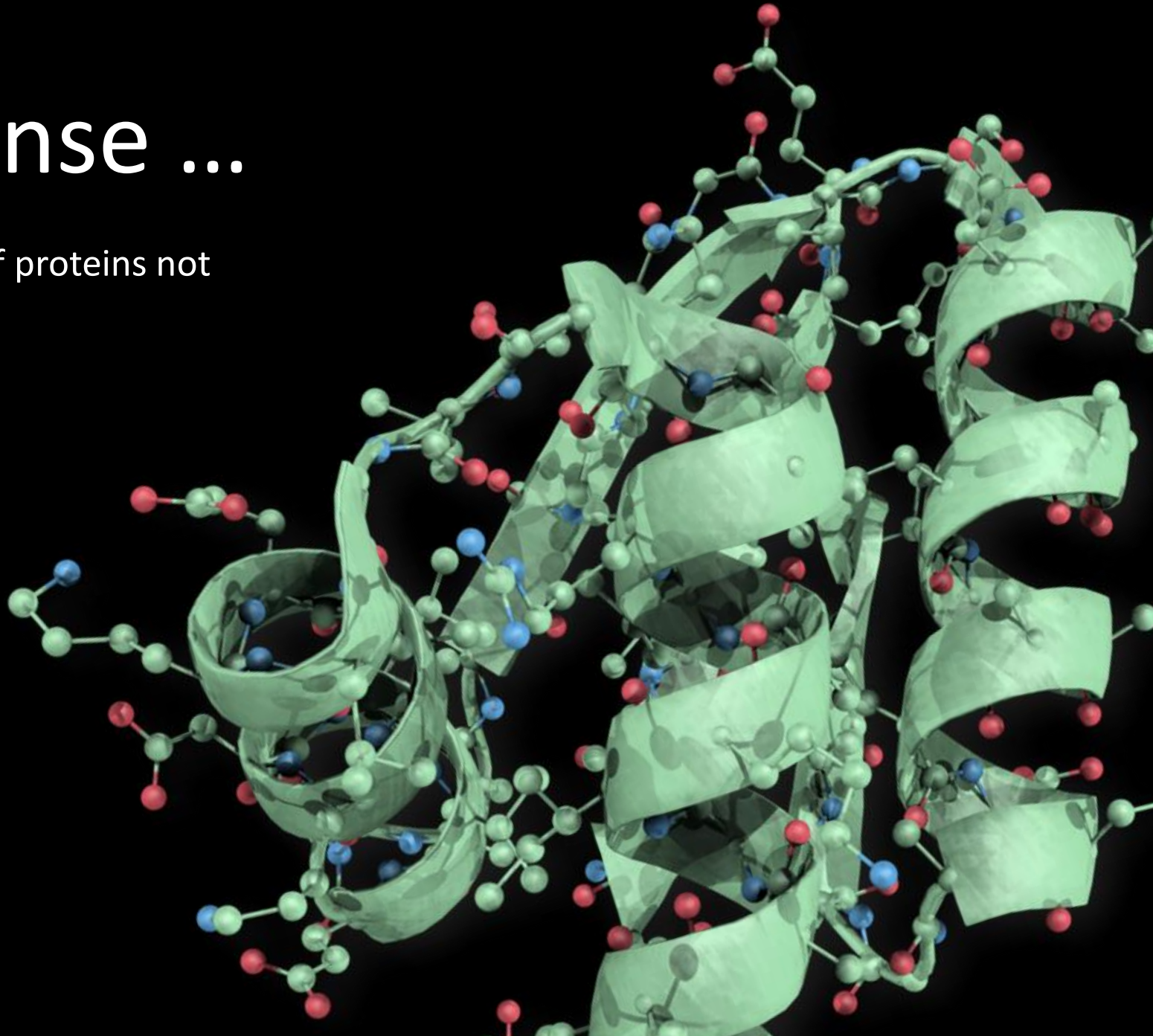
Why design peptides?

Some examples:

New protein was mutated and is now able to grab uranium from sea water
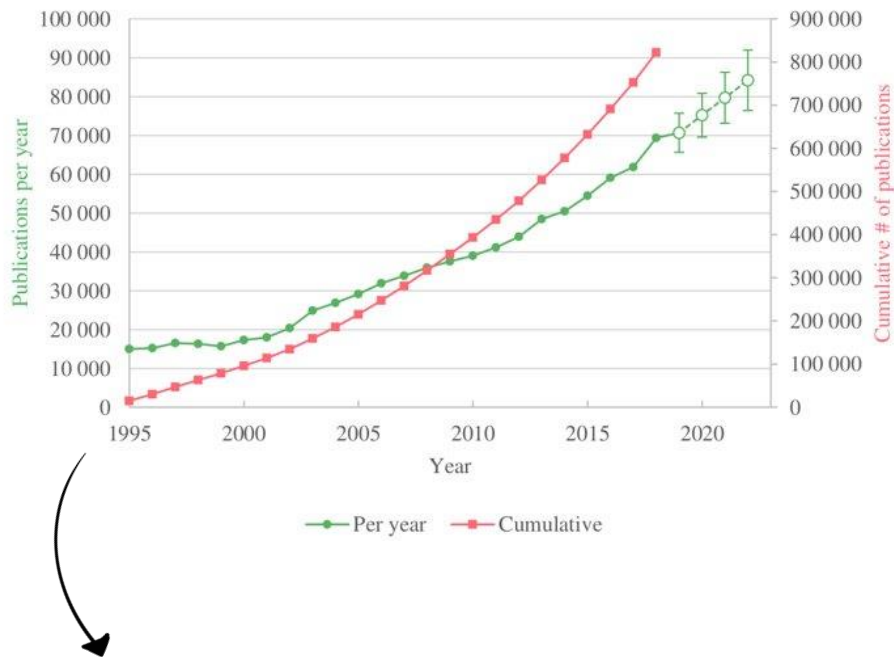
Old protein

Zhou at al. (2014)

That makes sense …

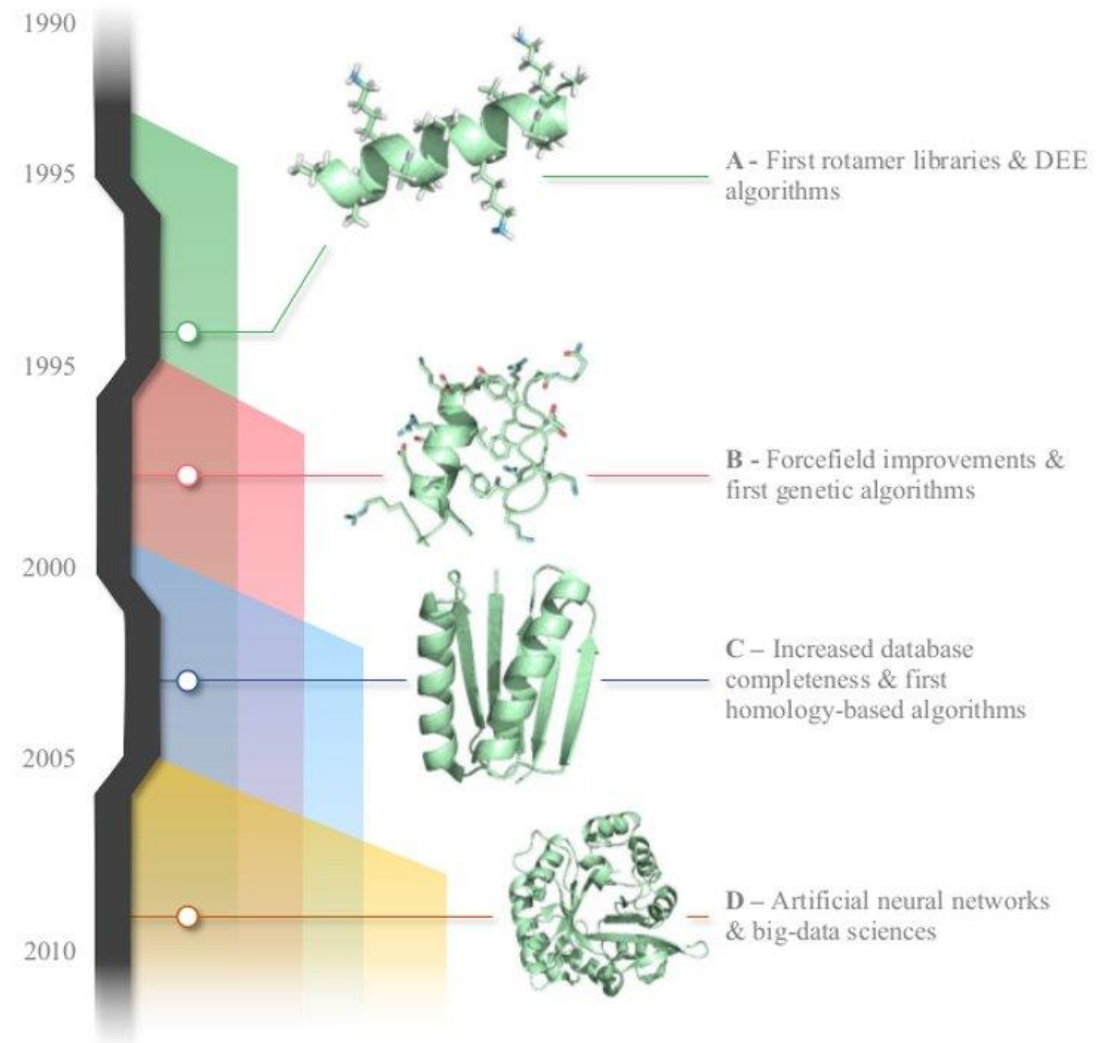Protein design unlocks the potential of proteins not yet explored by nature.

How?

Traditionally done by blind mutations in a lab.
Computational tools save time and money.

When searching ScienceDirect for "Protein Design"
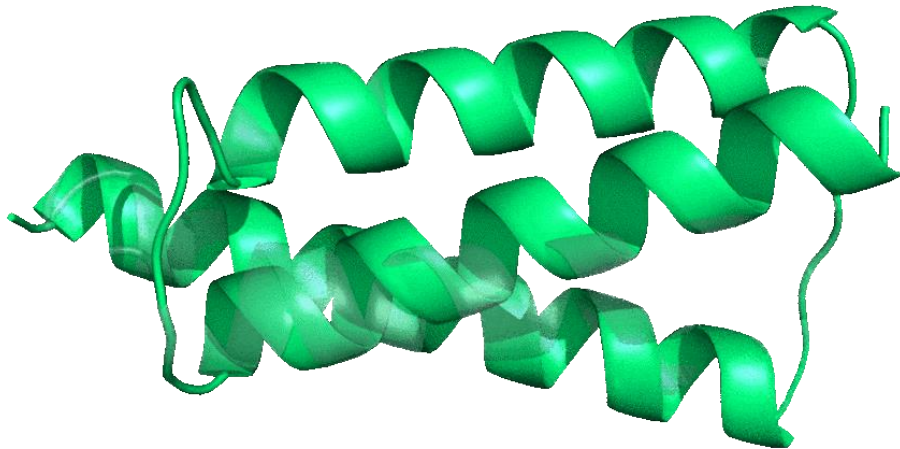

A - First rotamer libraries & DEE algorithms

B - Forcefield improvements & first genetic algorithms

C – Increased database completeness & first homology-based algorithms

D – Artificial neural networks & big-data sciences

How?

Conformational search engine   +   Energy function

Changes the structure (and sometimes sequence) of a peptide

Evaluates the energy (or fitness) of a given structure
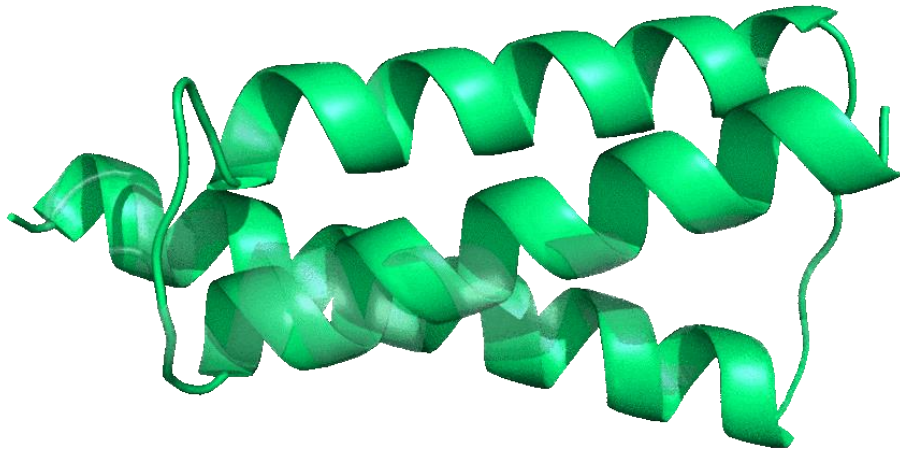

System energy

How?
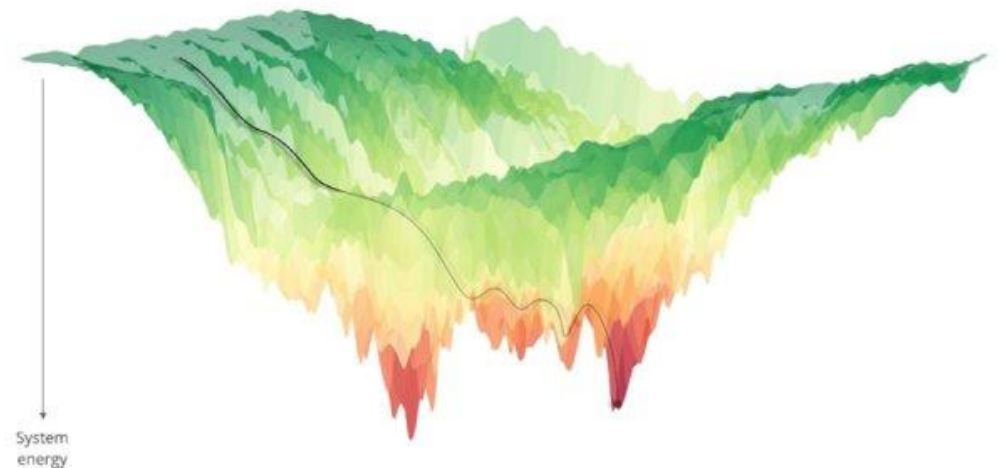
Conformational search engine + Energy function
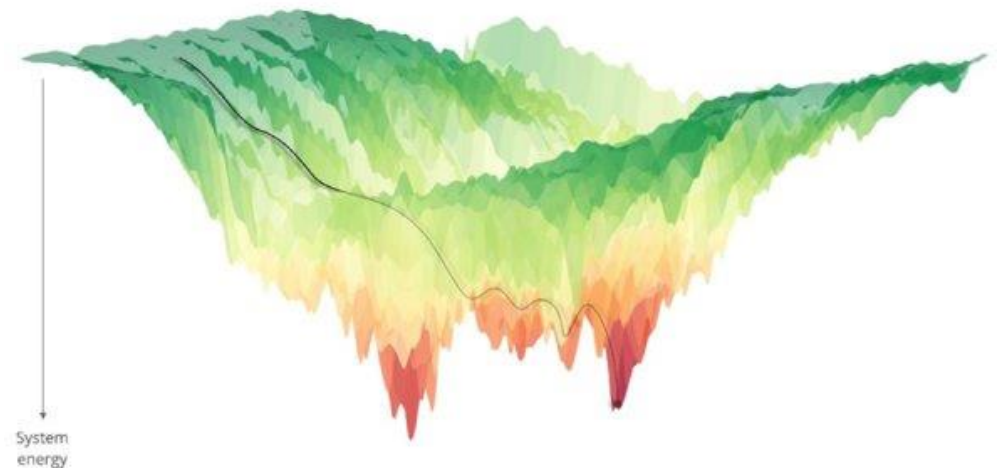
Monte-Carlo
Steepest Descent
Molecular Dynamics

Forcefields
Density Functional Theory (DFT)
Machine Learning and AI

System energy

Alright, I get it now.

Computational manipulation of proteins requires a conformational search engine that exhaustively samples the conformational space in search for the structure that mimics reality with the highest possible affinity (highest energy function score).
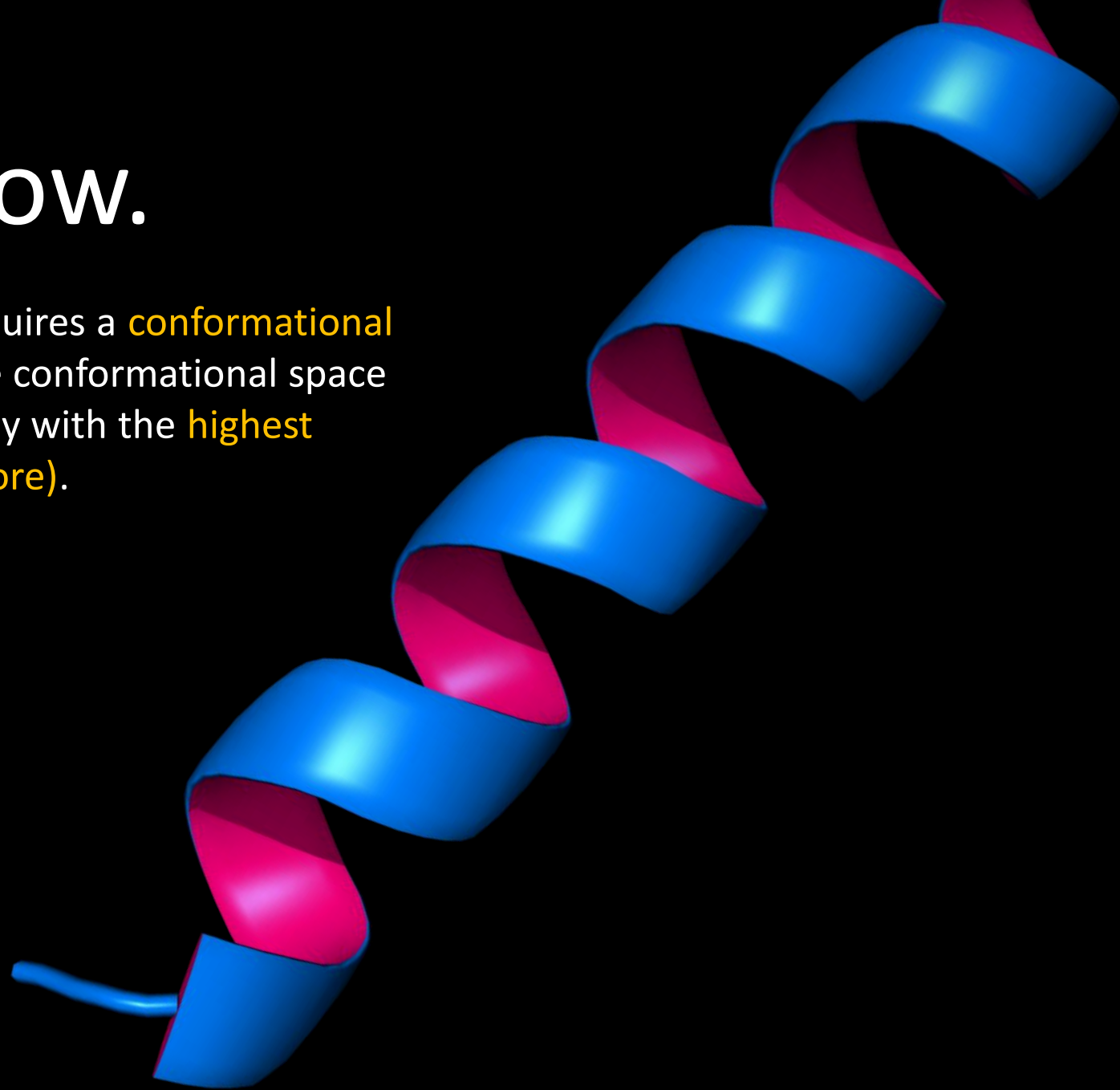
Some practical exercises

In the first class we'll focus on the conformational manipulation.

1) Learn how to use PyMOL;

2) Explore the basics of ProtoSyn;
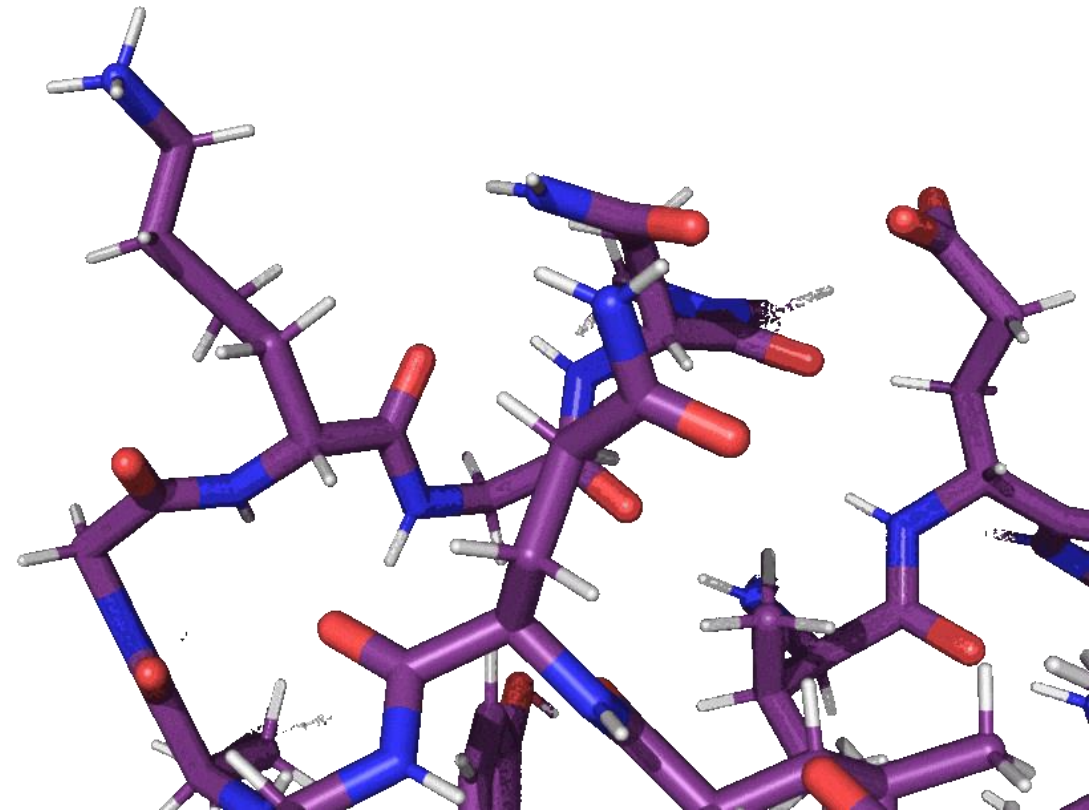
3) Visualize some quick molecular manipulations;

The challenge

The first step to any design effort is the ability to change the nature of aminoacids in the structure. In other words, we must be able to perform mutations!

Changing the nature of aminoacids introduces new properties to the overall protein/peptide.

The first part, we'll attempt to mutate a residue.

The challenge

A sub-problem of computational design of proteins is the correct placement of sidechains.

It is the sidechain interaction with each other and the environment that mostly provides the functionality to proteins (for example, enzymatic or catalytic activity).

Each sidechain can have multiple conformations (called rotamers). Which is the correct combination of rotamers of all sidechains that stabilizes the structure?
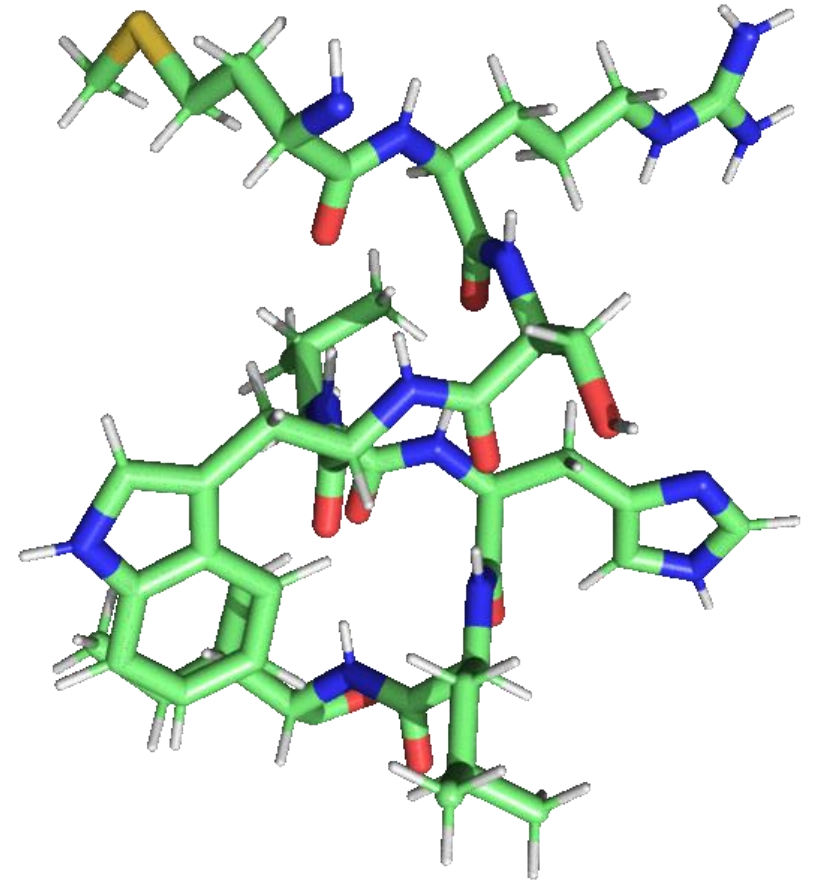
The challenge

The backbone angles greatly influence what rotamers are possible. This restrictions have been compiled in Rotamer Libraries.

Phi = -60º

Psi = -45º
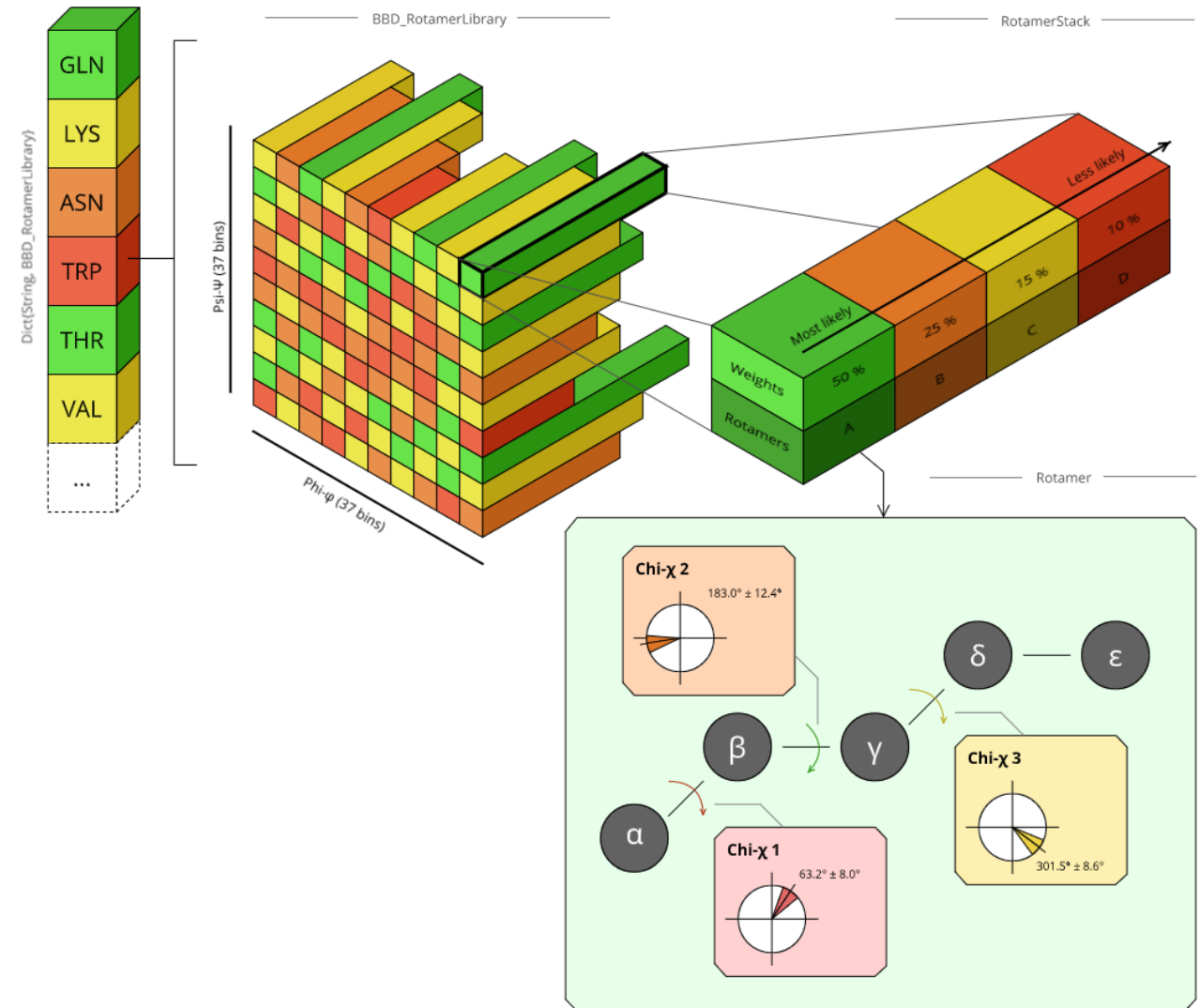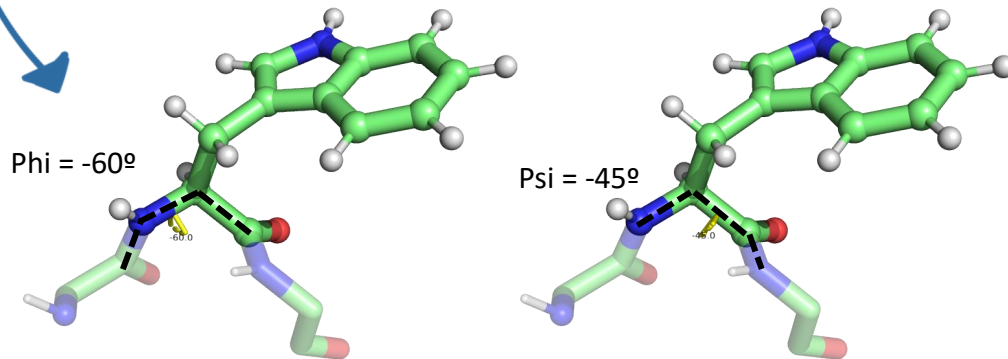
In the second part we'll attempt to load a Rotamer Library and apply different rotamers.