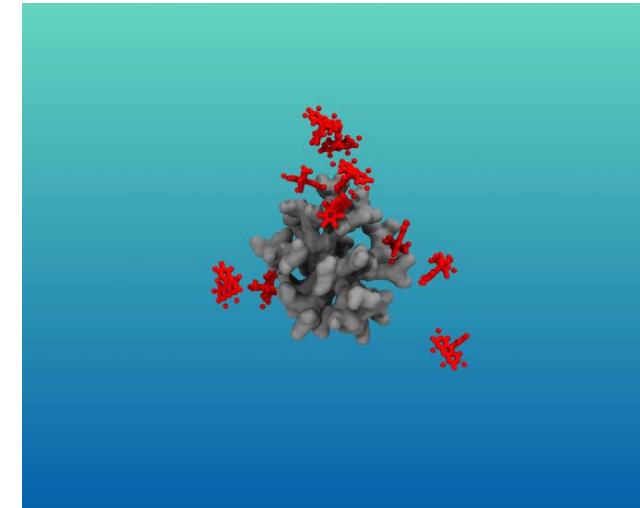
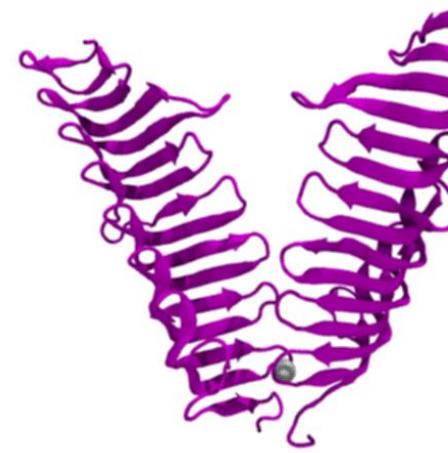
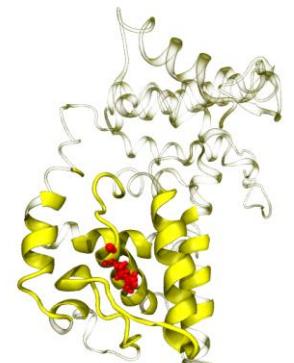
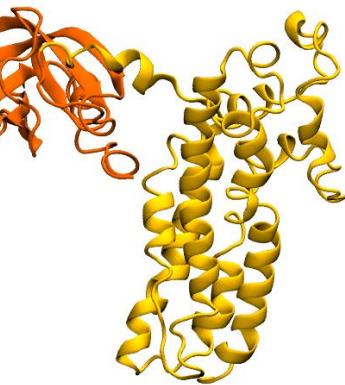
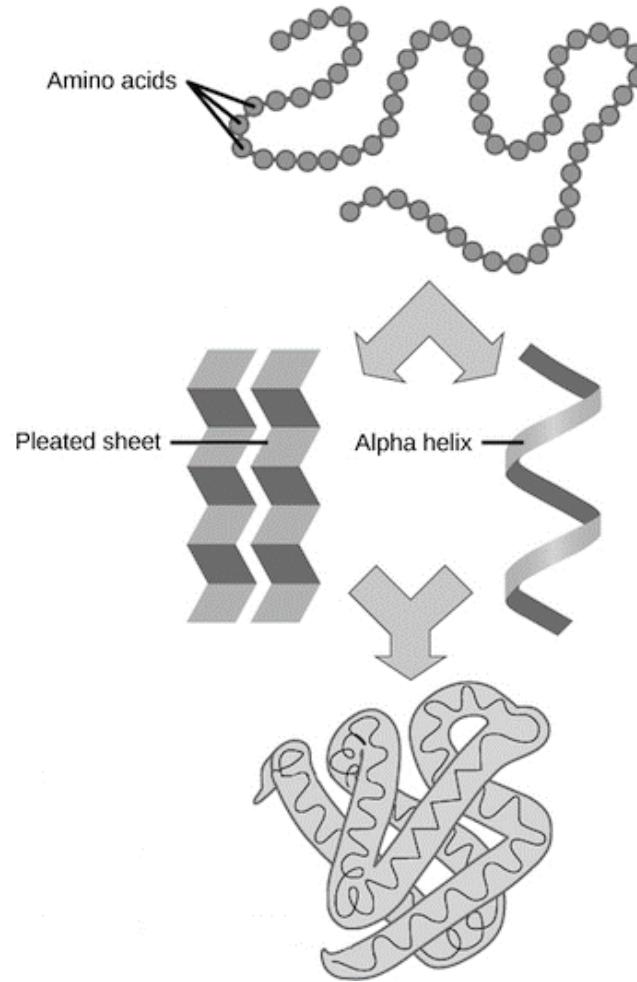




# Introduction to molecular modelling





# Order of Protein Structure

To understand how a protein gets its final shape or conformation, we need to understand the four levels of protein structure: primary, secondary, tertiary, and quaternary.



## Online databases

➤ Protein databases:

<https://www.rcsb.org/>



➤ Ligand databases:

<https://zinc.docking.org/>

<https://go.drugbank.com/>

<https://pubchem.ncbi.nlm.nih.gov/>

<https://www.ebi.ac.uk/chembl/>

<http://www.chemspider.com/>

ZINC15

PubChem

ChEMBL

DRUGBANK

ChemSpider  
The free chemical database

# Homology Modelling

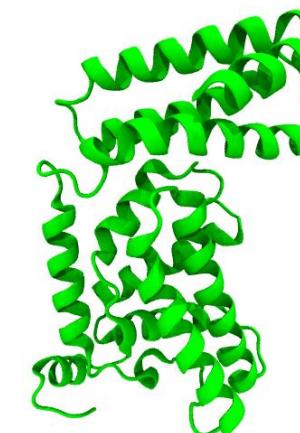
Homology modeling build the molecular model of a **target** protein from its amino acid sequence and an experimental 3D structure of a related homologous protein, the **template**

## Alignment

Query sequence Uniprot Q96Q42

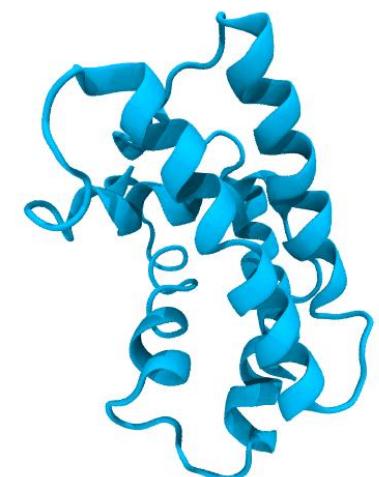
```
|DKLKVIQQTFFEEISQSVLASLHEDFLWSMDD
|...  
|DIIEMDSKRVPRDKLACITKCSKHIFNAIK
|PRODTKAGKTKESEIAHKFTVANIEPKASMEPASADDLPT
|...
|TPQMMLCVPVNEDIPEVSDMVVKAITDI
```

## Template

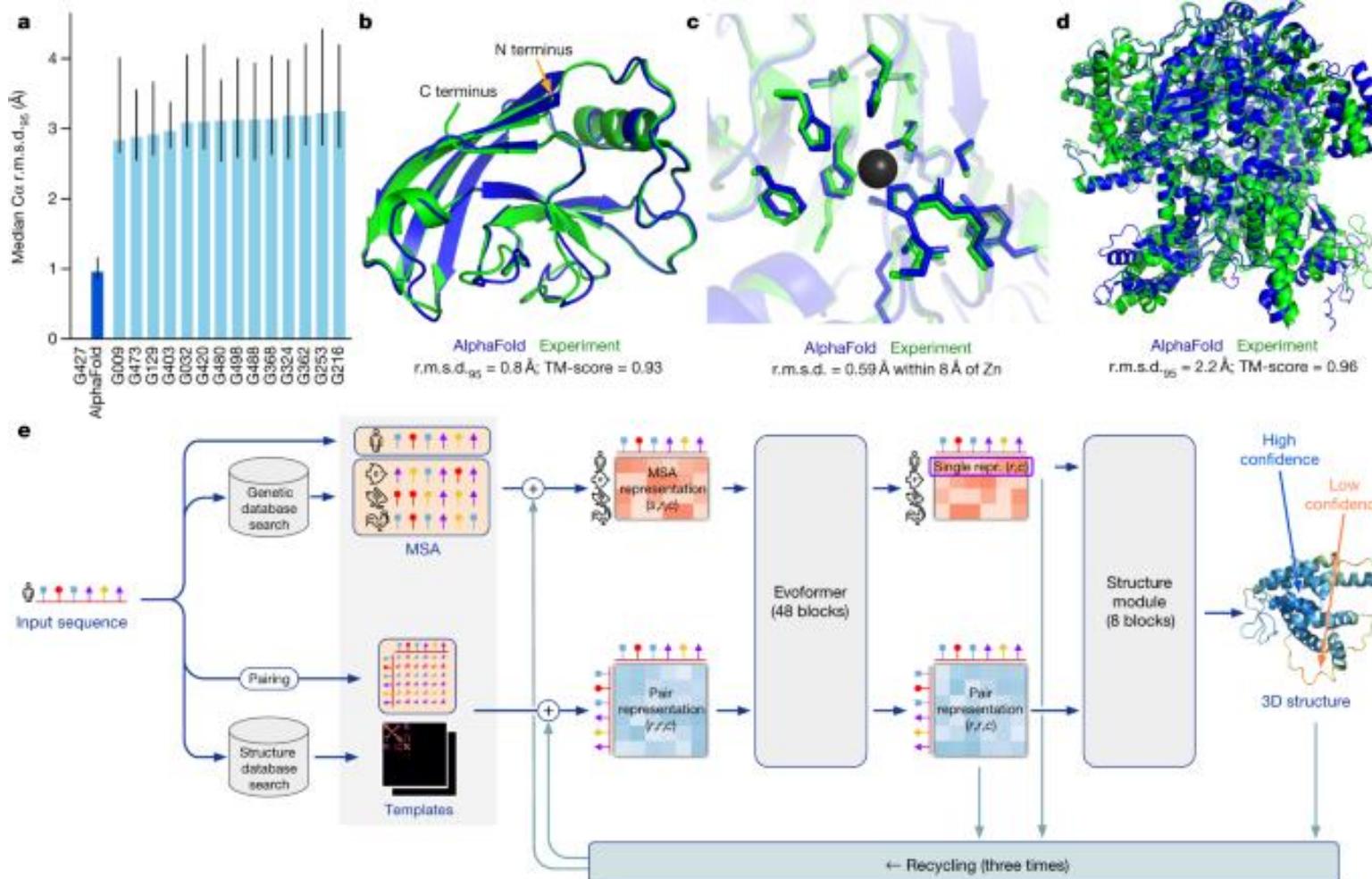


Modelling

## Homology model



# AlphaFold



AlphaFold is an AI system developed by DeepMind that predicts a protein's 3D structure from its amino acid sequence. It regularly achieves accuracy competitive with experiment.

DeepMind and EMBL's European Bioinformatics Institute (EMBL-EBI) have partnered to create AlphaFold DB to make these predictions freely available to the scientific community.

<https://alphafold.ebi.ac.uk/>

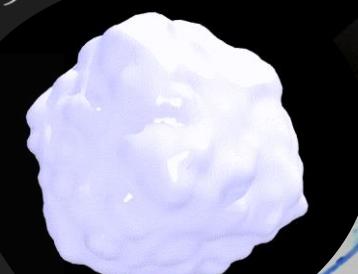
Play with alphafold2  
[Link](#)

<https://www.nature.com/articles/s41586-021-03819-2>

# MOLECULAR MODELLING AS A COMPUTATIONAL MICROSCOPE

$$\vec{F}_i = ma = m_i \frac{d^2 \vec{r}_i}{dt^2} = -\nabla U(\vec{R})$$

$$U(\vec{R}) = \sum_{bonds} k_i^{bond} (r_i - r_o)^2 + \sum_{angles} k_i^{angle} (\Theta_i - \Theta_o)^2 + \sum_{dihedrals} k_i^{dihed} (1 + \cos(n_i \phi_i + \delta_i)_+)$$
$$\sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}$$





Let's see an example



ACE2  
+  
Covid-19



# Equation of motion

The equations that describe the temporal evolution of a physical system is called **equation of motion**. There are different equations of motions, which characterize the motion with different levels of approximation:

- Time-dependent Schrödinger's Equation for quantum-mechanical system
- **Newton's Equation for classical-mechanical system**
- Langevin's Equation for stochastic system

$$i\hbar \frac{\partial \mathbf{m}}{\partial t}(r,t) = \hat{\mathcal{H}} \mathbf{m}(r,t)$$

$$m \frac{d^2 \mathbf{r}}{dt^2} = -\lambda \frac{d\mathbf{r}}{dt} + \boldsymbol{\eta}(t)$$



# Newton's Equation of motion

Molecules are quantum-mechanical systems whose motion should be described by Schrödinger's Equation. However, technical difficulties make solving Schrödinger's Equation for large systems impractical.

Therefore in classical molecular dynamics, the motion of a molecule is approximated by the laws of classical mechanics and by Newton's equation of motion. In its most simplistic form Newton's second law of motion states:

$$F_i = m_i a_i$$

where  $m_i$  is the mass of particle  $i$ ,  $a_i$  is its acceleration.

But the force  $f_i$  can also be written as the derivative of the potential energy function  $V$ :

$$F_i = - \frac{\partial V}{\partial r_i}$$

where  $r_i$  is the position of particle

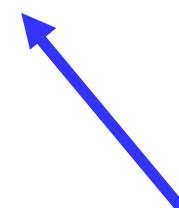
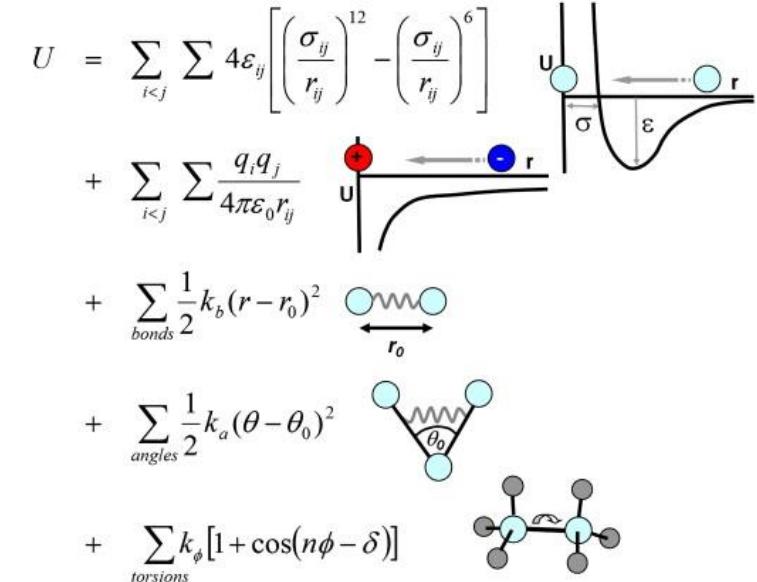
# Potential energy function

Therefore, we need to define the potential of our molecular system ..

$$V(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n) = \sum_{bond} \frac{1}{2} k_{b_n} (b_n - b_{0_n})^2 + \sum_{angle} \frac{1}{2} k_{\theta_n} (\theta_n - \theta_{0_n})^2 + \\ + \sum_{improper dihedral} \frac{1}{2} k_{\xi_n} (\xi_n - \xi_{0_n})^2 + \sum_{dihedral} k_{\phi_n} [1 + \cos(m_n \phi_n - \delta_n)] +$$

$$+ \sum_{nonbonded pairs(ij)} \left( \left( \frac{C_{ij}^{(12)}}{r_{ij}^{12}} - \frac{C_{ij}^{(6)}}{r_{ij}^6} \right) + \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{\epsilon_r r_{ij}} \right)$$

non bonded interactions



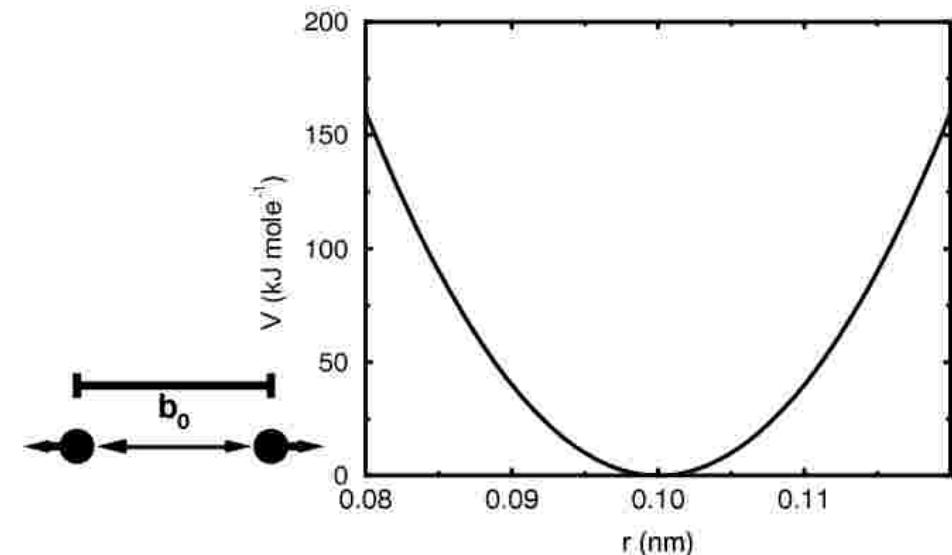
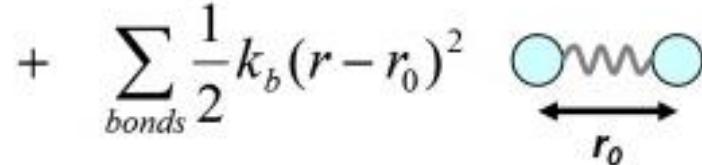
bonded interactions

# Bond Stretching Energy

$$\sum_{bond} \frac{1}{2} k_{b_n} (b_n - b_{0n})^2$$

$k_b$  is the spring constant of the bond    $b_0$  is the bond length at equilibrium

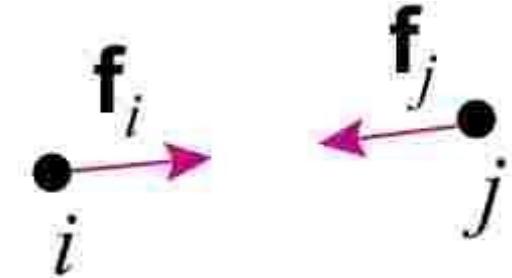
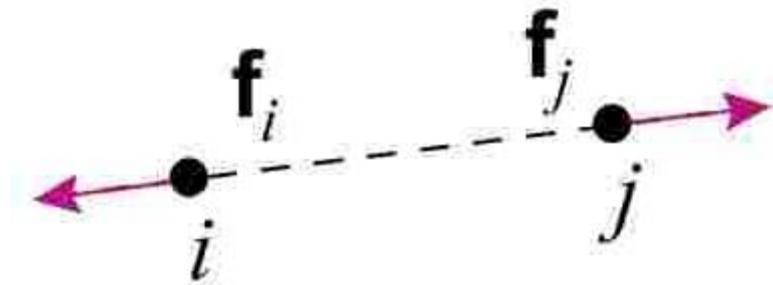
Unique  $k_b$  and  $b_0$  assigned for each bond pair, i.e. C-C, O-H



Principle of bond stretching (left), and the bond stretching potential (right).

# Bond Stretching Force

If atom  $i$  and  $j$  are closer than  $b_0$ , the bond force separates them

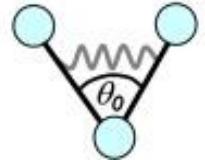


If atom  $i$  and  $j$  are farther than  $b_0$ , the bond force draws them nearer

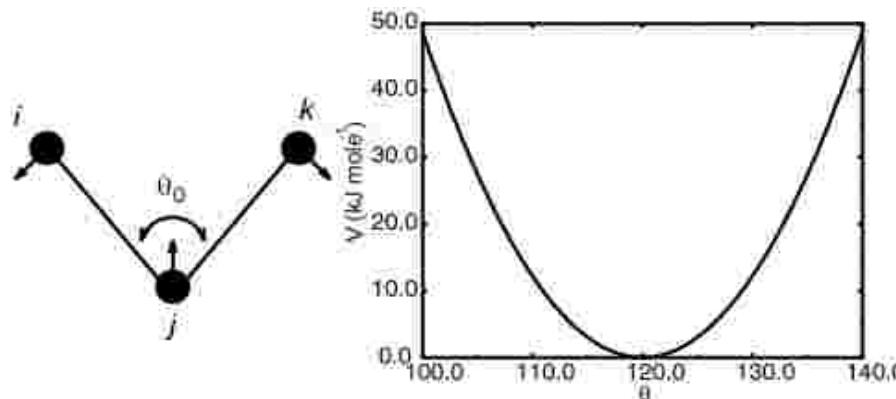
# Bending Energy

$$+ \sum_{angle} \frac{1}{2} k_{\theta_n} (\theta_n - \theta_{0_n})^2$$

$$+ \sum_{angles} \frac{1}{2} k_a (\theta - \theta_0)^2$$



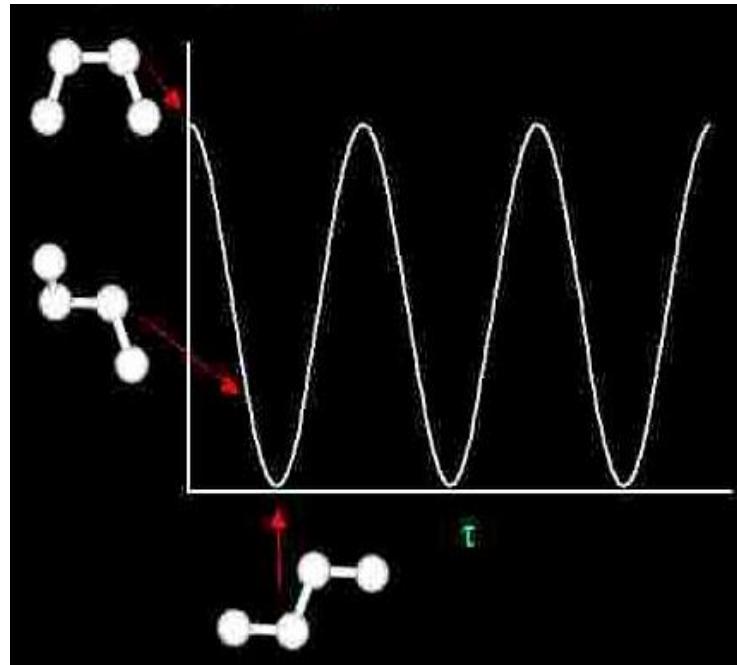
$k_\theta$  is the spring constant of the bending  
 $\theta_0$  is the angle bending at equilibrium



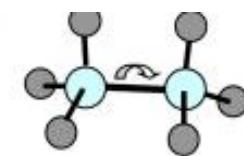
Principle of angle vibration (left) and the bond angle potential (right).

Unique parameters for angle bending are assigned to each bonded triplet of atoms based on their types (e.g. C-C-C, C-O-C, C-C-H, etc.)

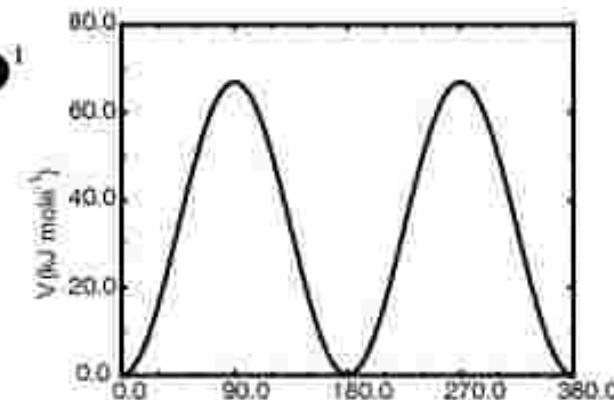
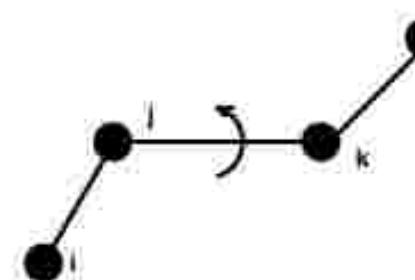
# Torsional or Dihedral Energy



$$+ \sum_{torsions} k_\phi [1 + \cos(n\phi - \delta)]$$



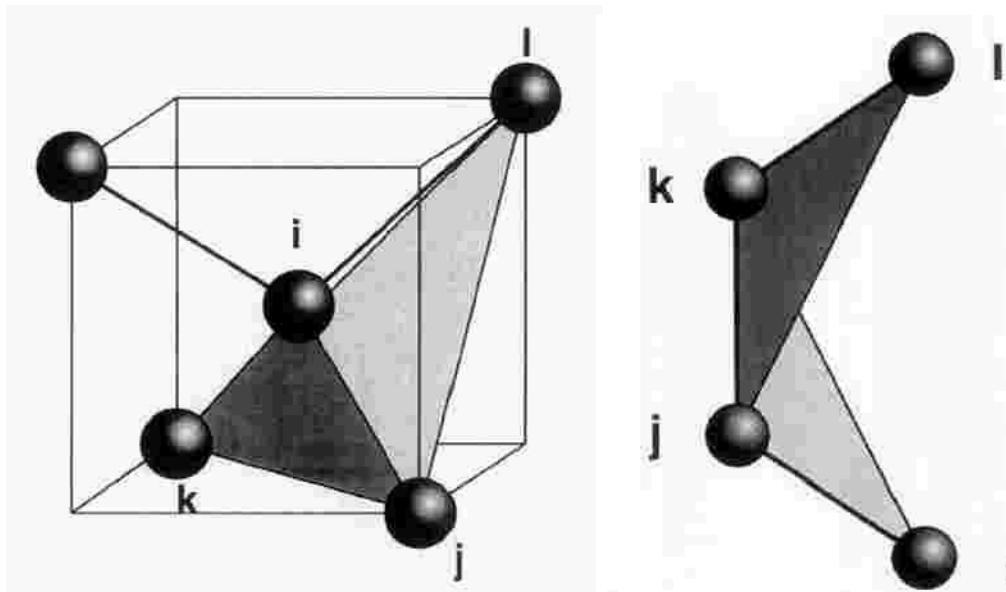
$$+ \sum_{improper\ dihedral} \frac{1}{2} k_{\xi_n} (\xi_n - \xi_{0_n})^2 + \sum_{dihedral} k_{\phi_n} [1 + \cos(m_n \phi_n - \delta_n)]$$



Principle of proper dihedral angle (left, in *trans* form) and the dihedral angle potential (right).

# Improper Dihedral Energy

The energy required to deform a group of atoms from its equilibrium angle,  $x_0$ . Used for tetrahedral or planar groups

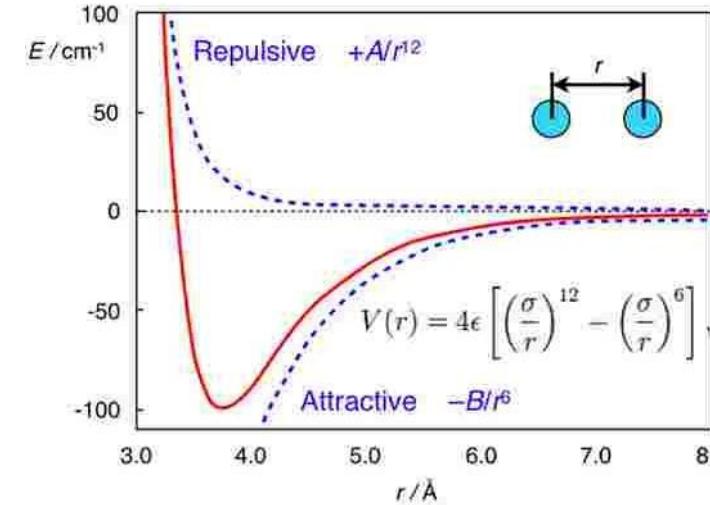


$$+ \sum_{improper \ dihedral} \frac{1}{2} k_{\xi_n} (\xi_n - \xi_{0_n})^2$$

Again this system can be modeled by a spring, and the energy is given by the Hookean potential with respect to the planar angle

# Lennard Jones (Van der Waals) interactions

Sir John Lennard Jones

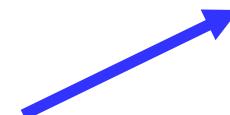


Johannes Diderik Van der Waals

## LJ interactions

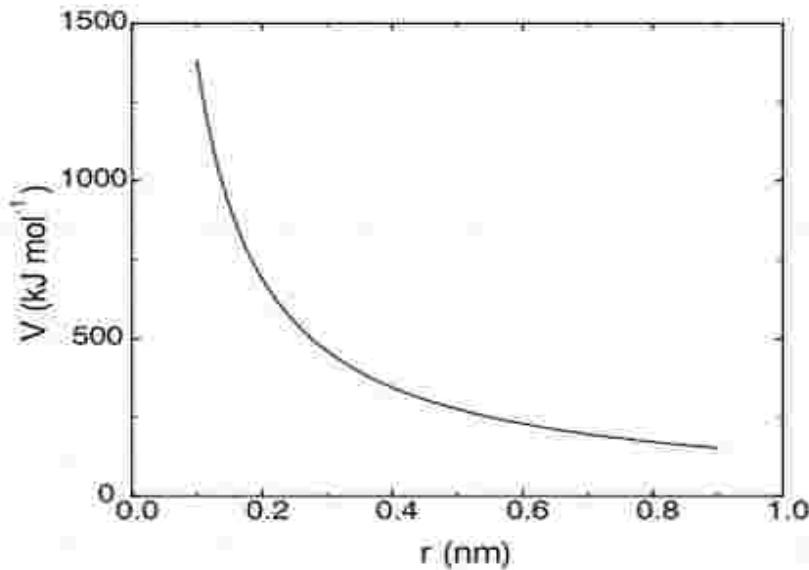
$$\sum_{\substack{\text{nonbonded} \\ \text{pairs}(ij)}} \left( \left( \frac{C_{ij}^{(12)}}{r_{ij}^{12}} - \frac{C_{ij}^{(6)}}{r_{ij}^6} \right) \right)$$

non bonded interactions



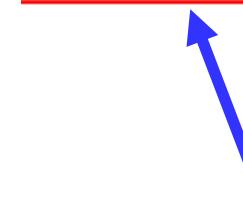
# Electrostatic interactions

$q_i$  and  $q_j$  are the partial atomic charges for atoms  $i$  and  $j$ , separated by a distance  $r_{ij}$  and  $\epsilon_r$  is the relative dielectric constant:

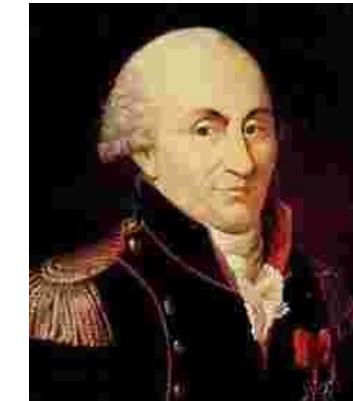


## Electrostatic

$$\left. + \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{\epsilon_r r_{ij}} \right)$$



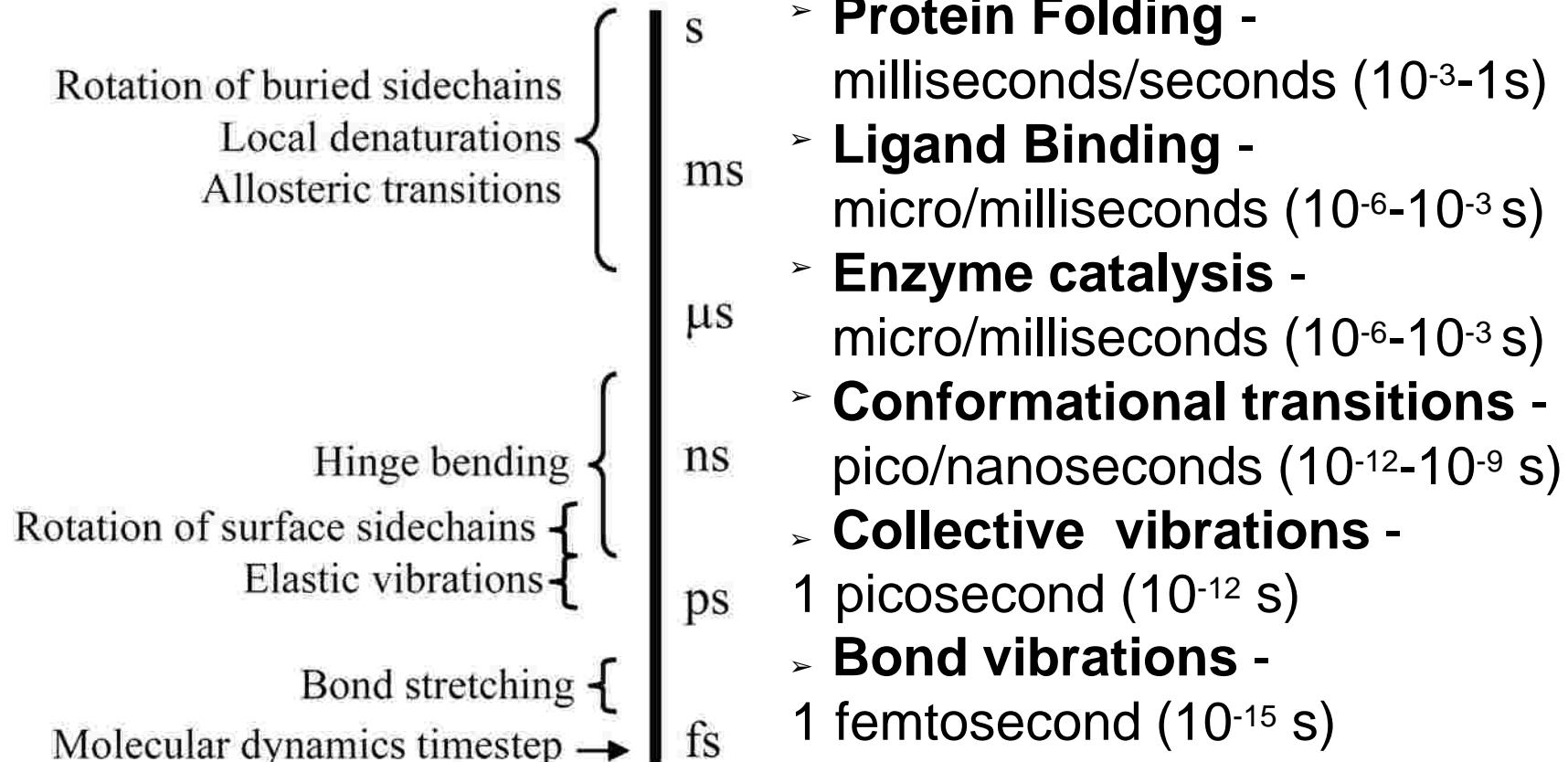
non bonded interactions



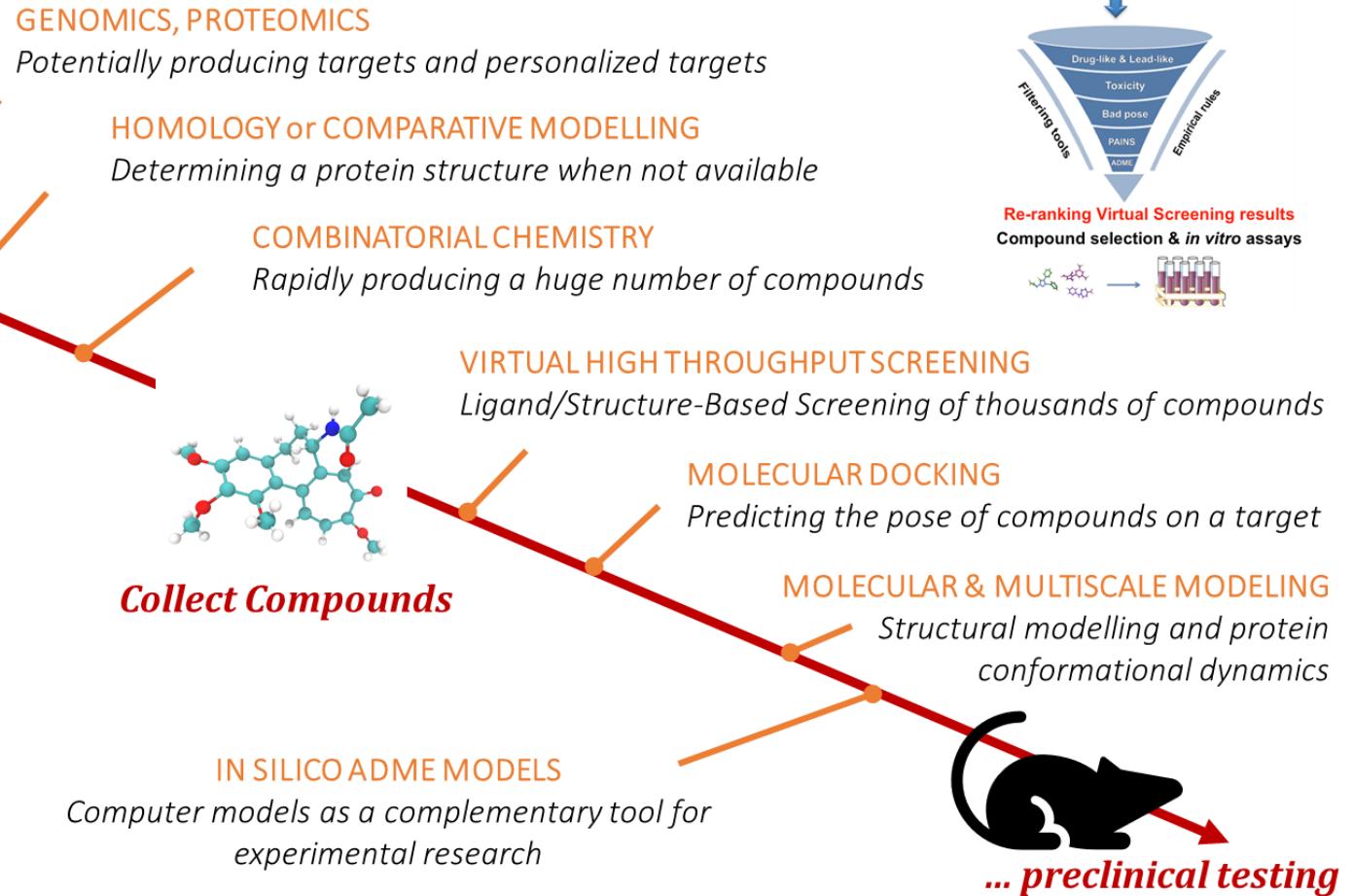
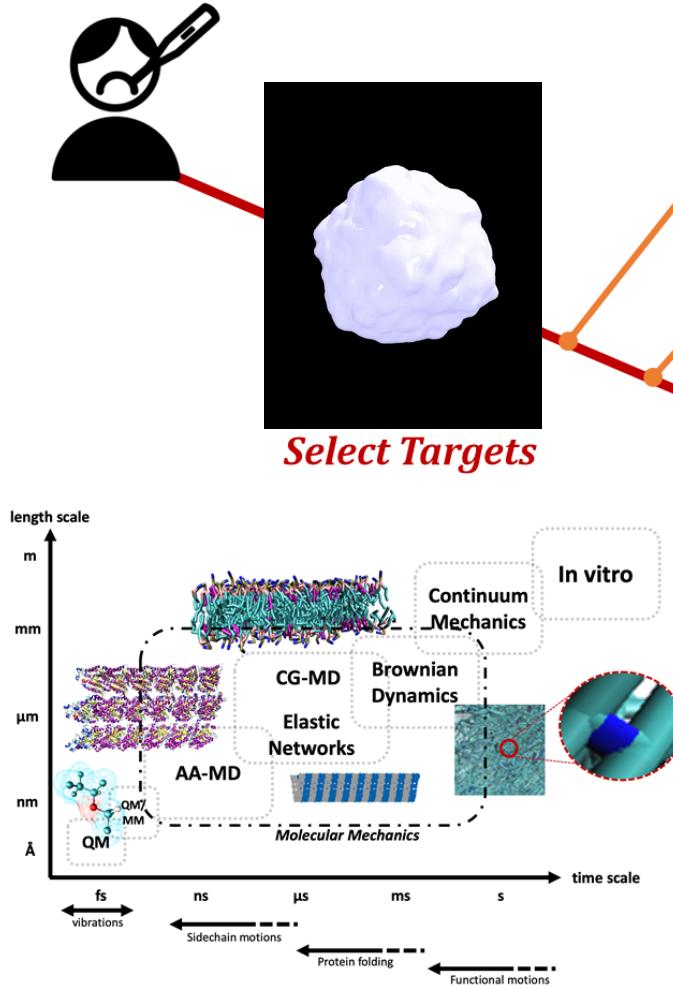
Charles Augustin de Coulomb

The Coulomb interaction (for particles with equal signed charge)

# Timescale



# The role of Molecular modelling

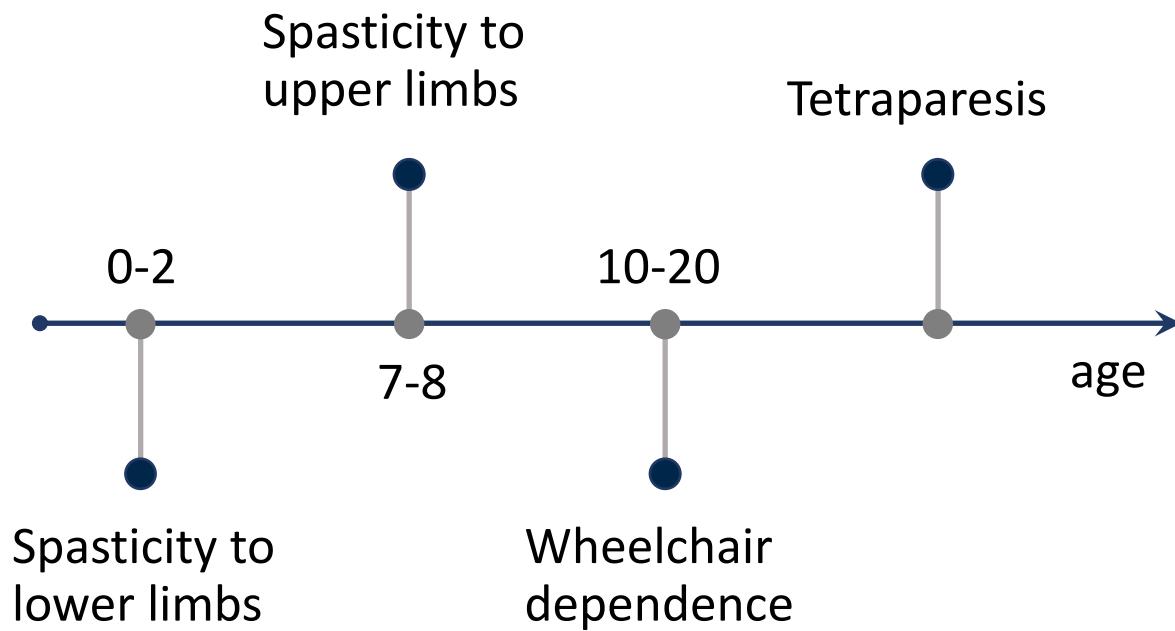




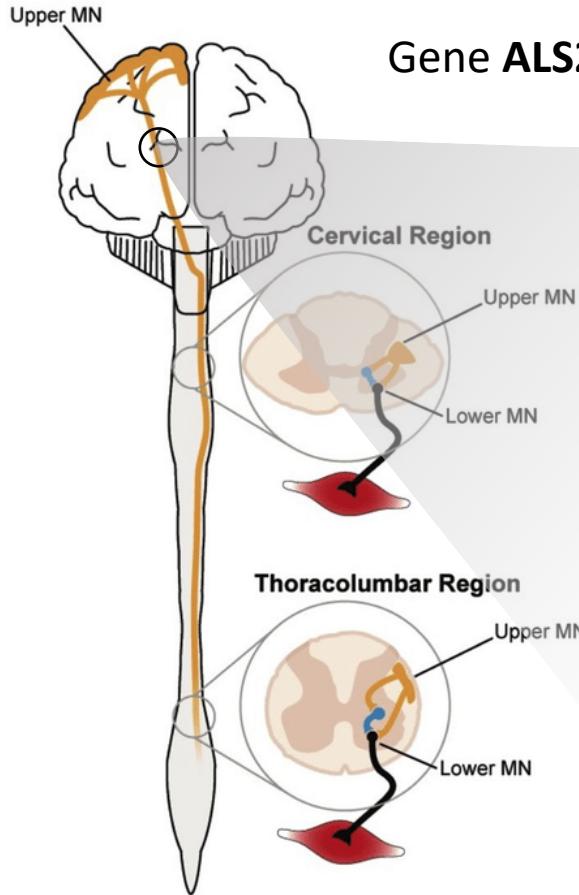
# A real world application

**IAHSP:** Infantile onset Ascending hereditary spastic paraplegia

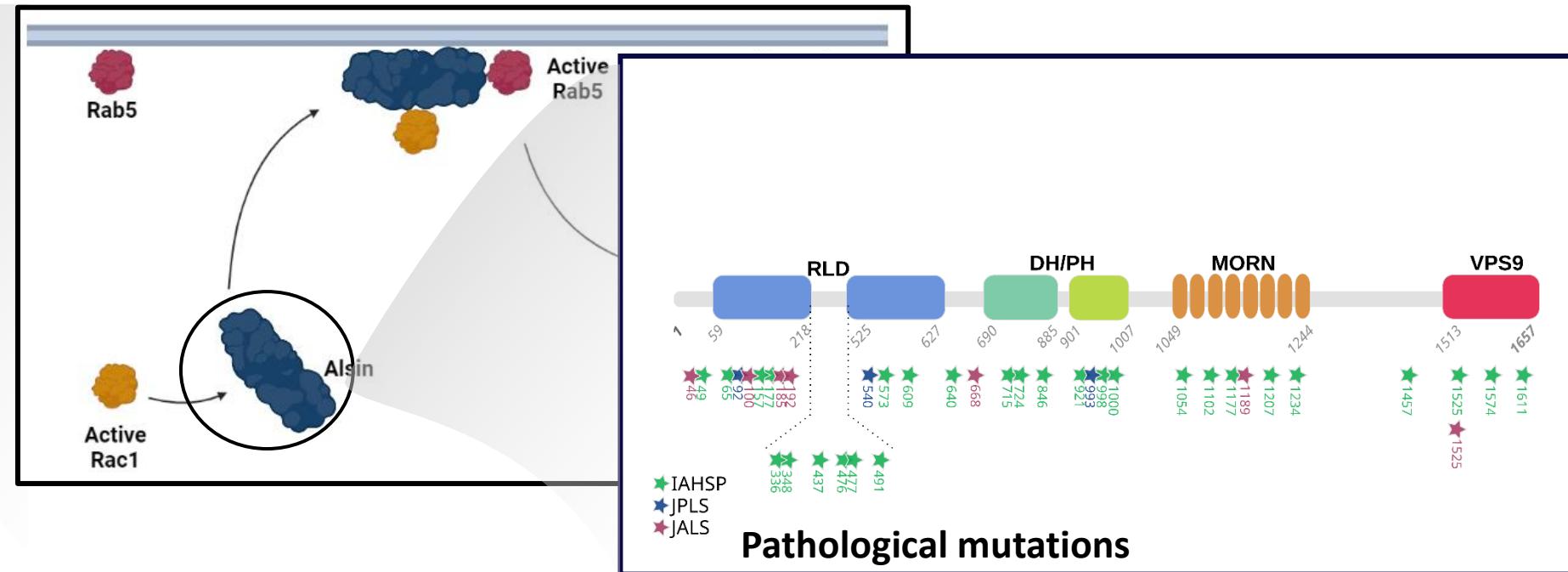
Rare neurodegenerative disease related to **mutation** on gene **ALS2**



# IAHSP disease and the Alsin protein



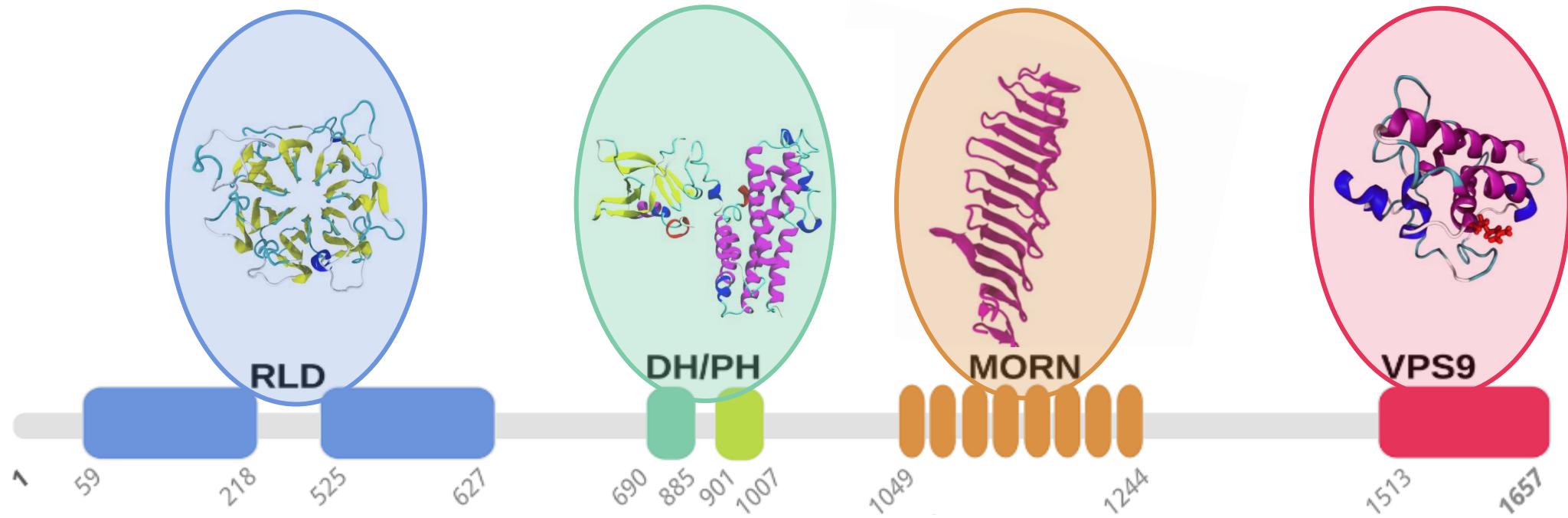
Gene **ALS2** encodes for Alsin Protein



Hadano, S. et al. *Nat. Genet.* 29, 166–173 (2001)

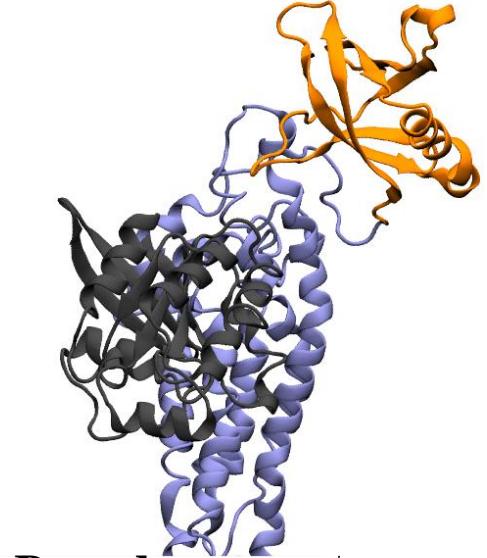
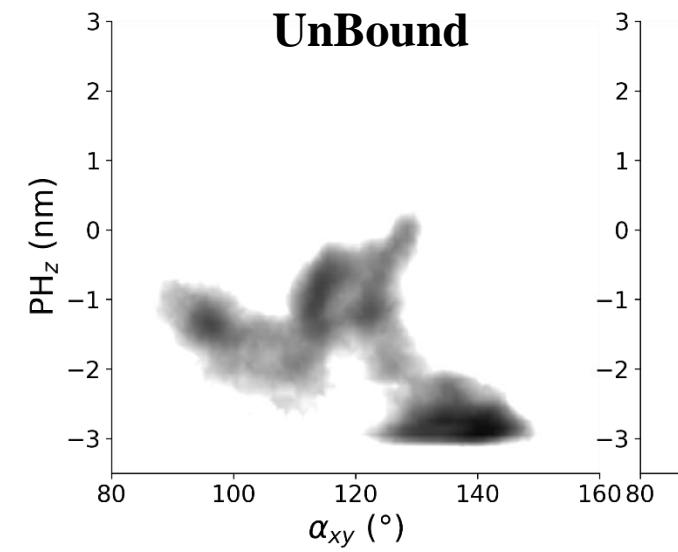
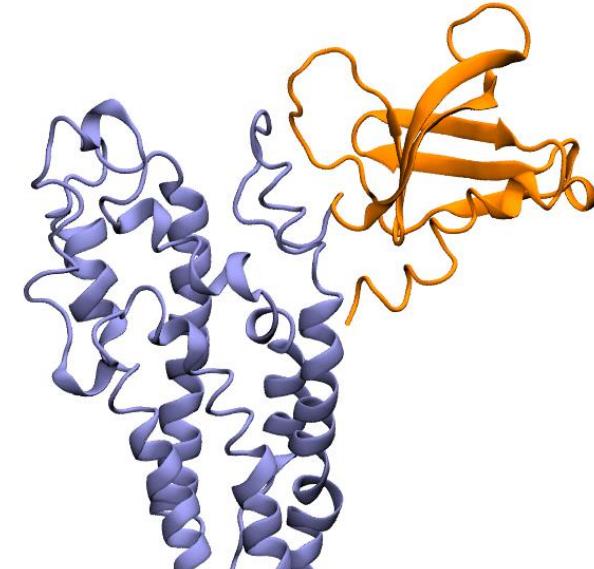
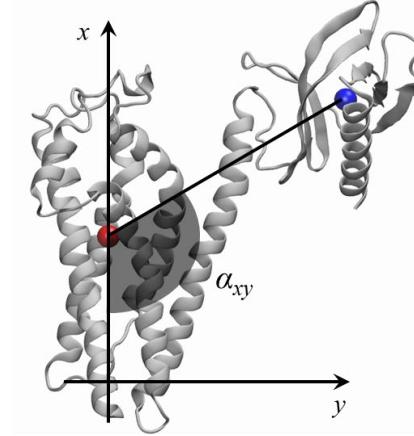
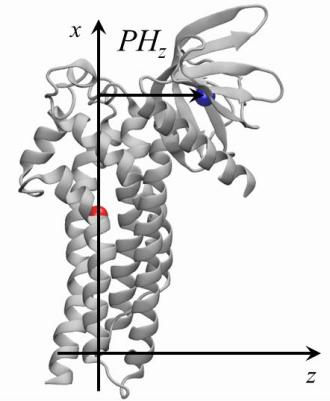


# Alsin homology models

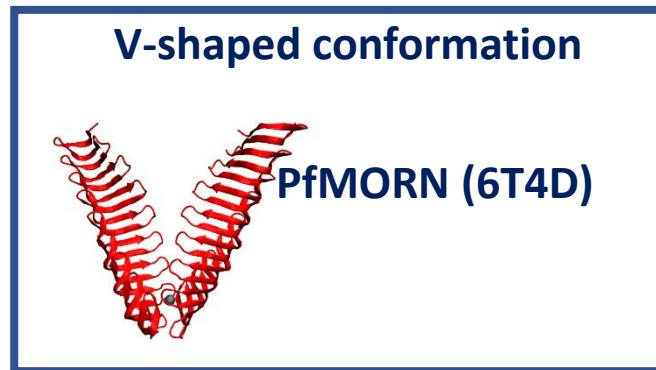




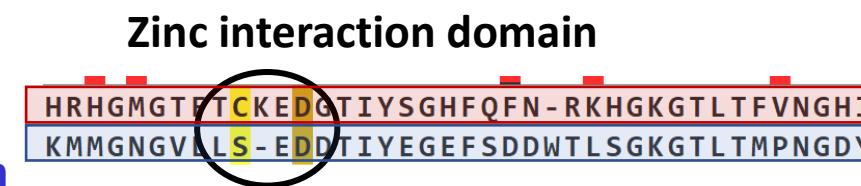
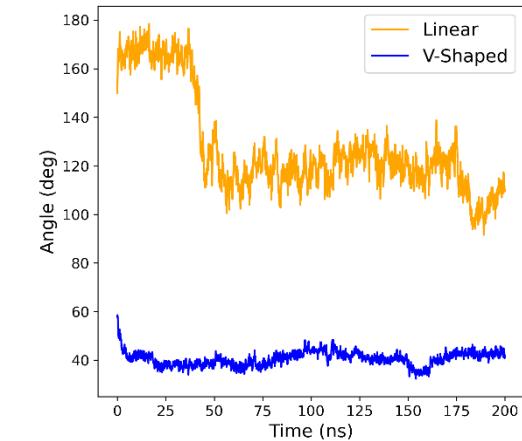
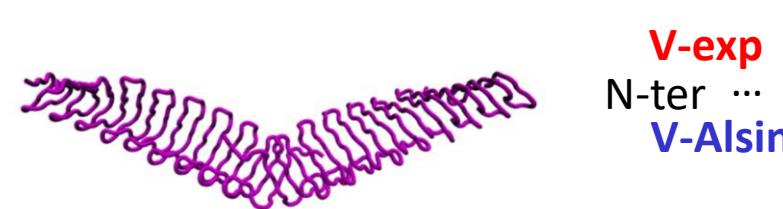
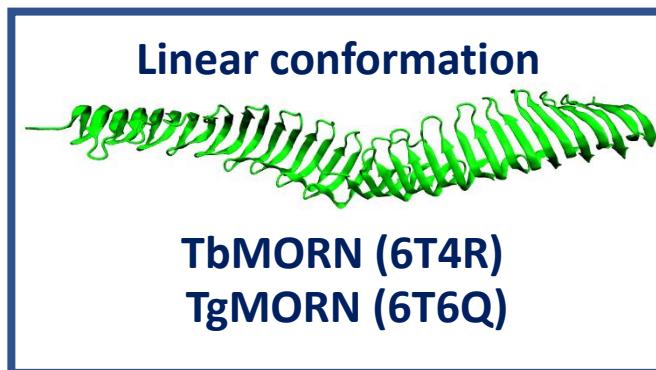
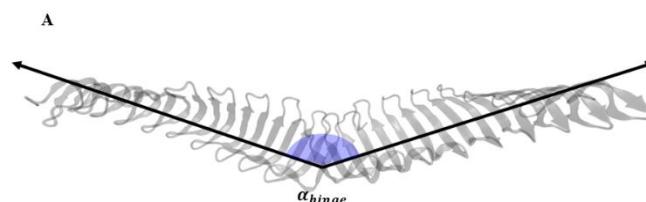
# DH/PH-rac1 interaction



# Dimerization of MORN Domain



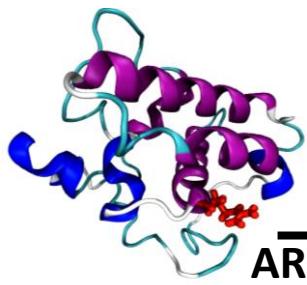
- Linear assembly → C-termini
- V-shaped assembly → C-termini + Zn ion



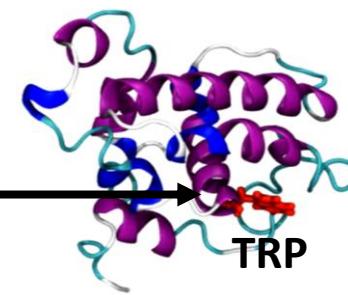
- ✓ Asp 309 → Asp 1217
- ✓ Glu 308 → Glu 1216
- ✗ Cys 307 → Ser 1215

# VPS9 WT vs MUT

Wild type

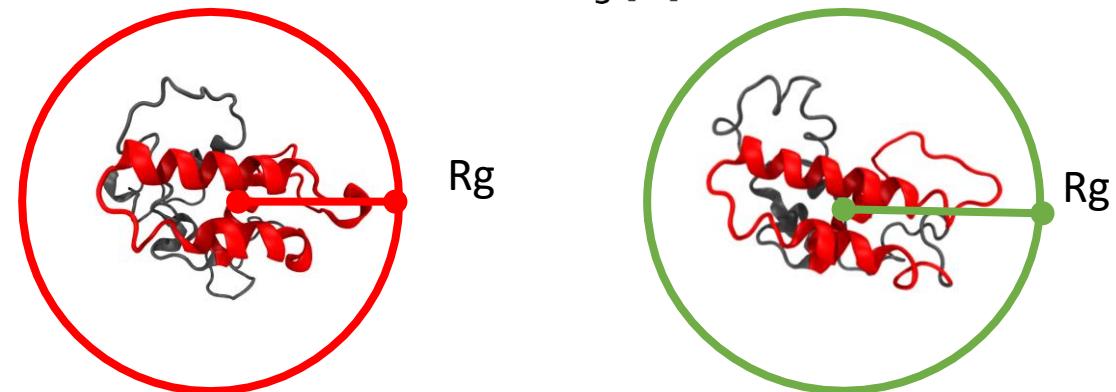
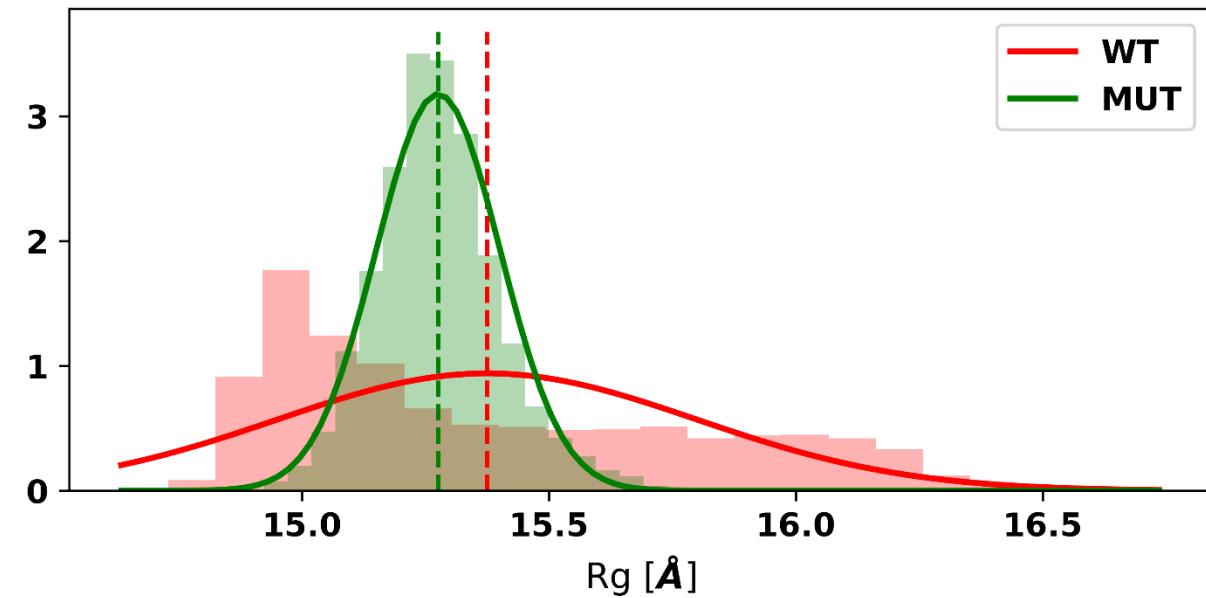


Mutated



Radius of gyration ( $R_g$ ) has been employed as a measure of the compactness of the structure.

$$R_g = \left( \frac{\sum_i ||r_i||^2 m_i}{\sum_i m_i} \right)^{\frac{1}{2}}$$





<https://crystal.m3b.it/>



November 2020

November 2021