Development of a Novel Computational Method to Identify Key Residues in Protein Structures

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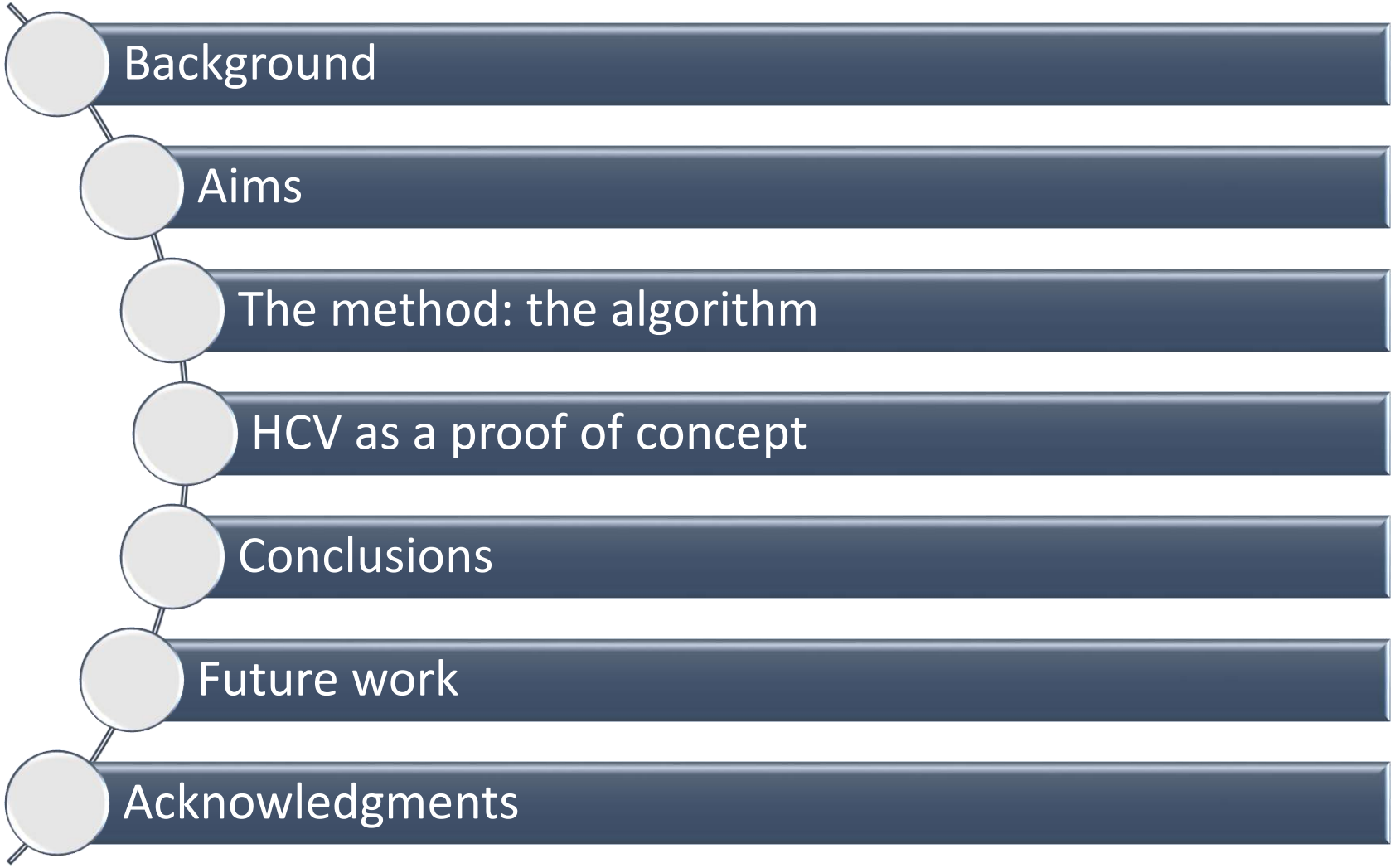
Summary


Background
Aims
The method: the algorithm
HCV as a proof of concept
Conclusions
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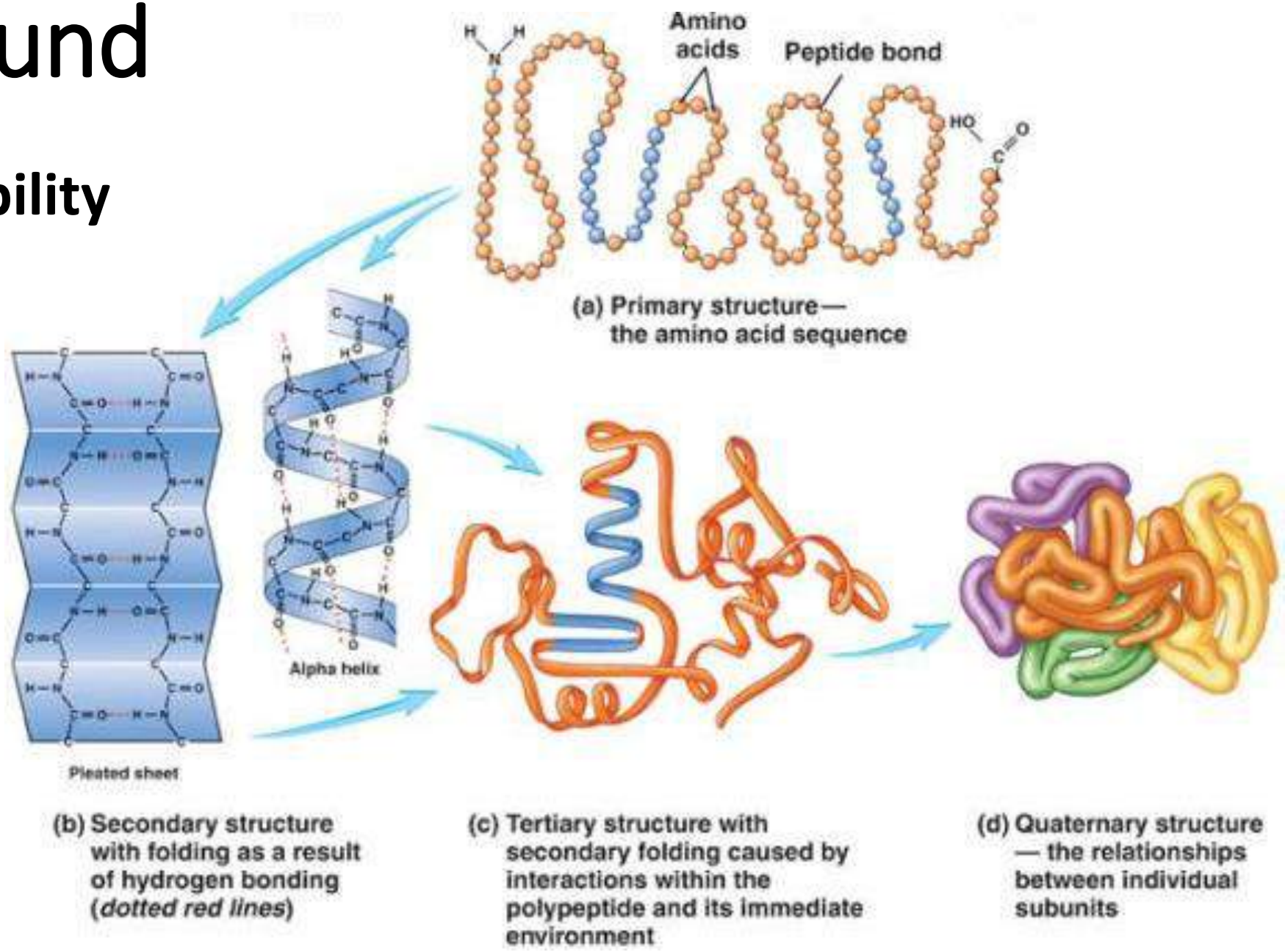
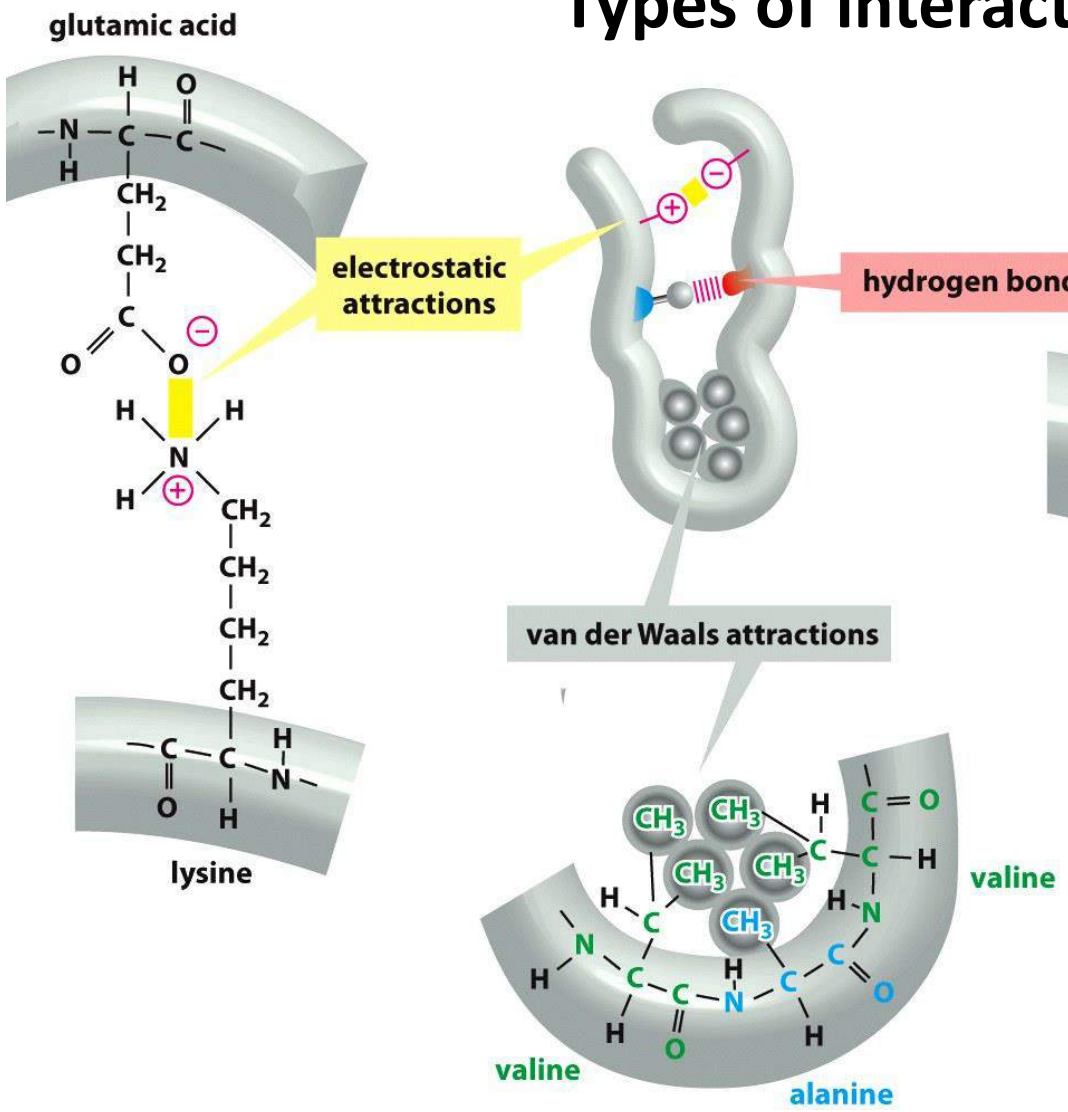
Acknowledgments

Background

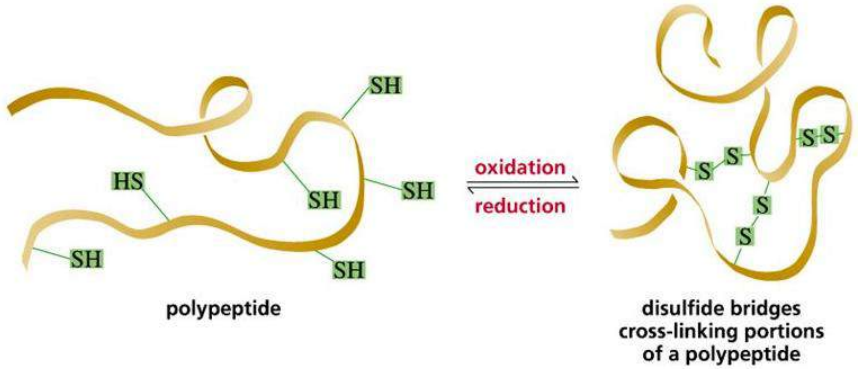
Protein stability



Types of interactions in a protein



The disulfide bridge in proteins contributes to the overall shape of a protein



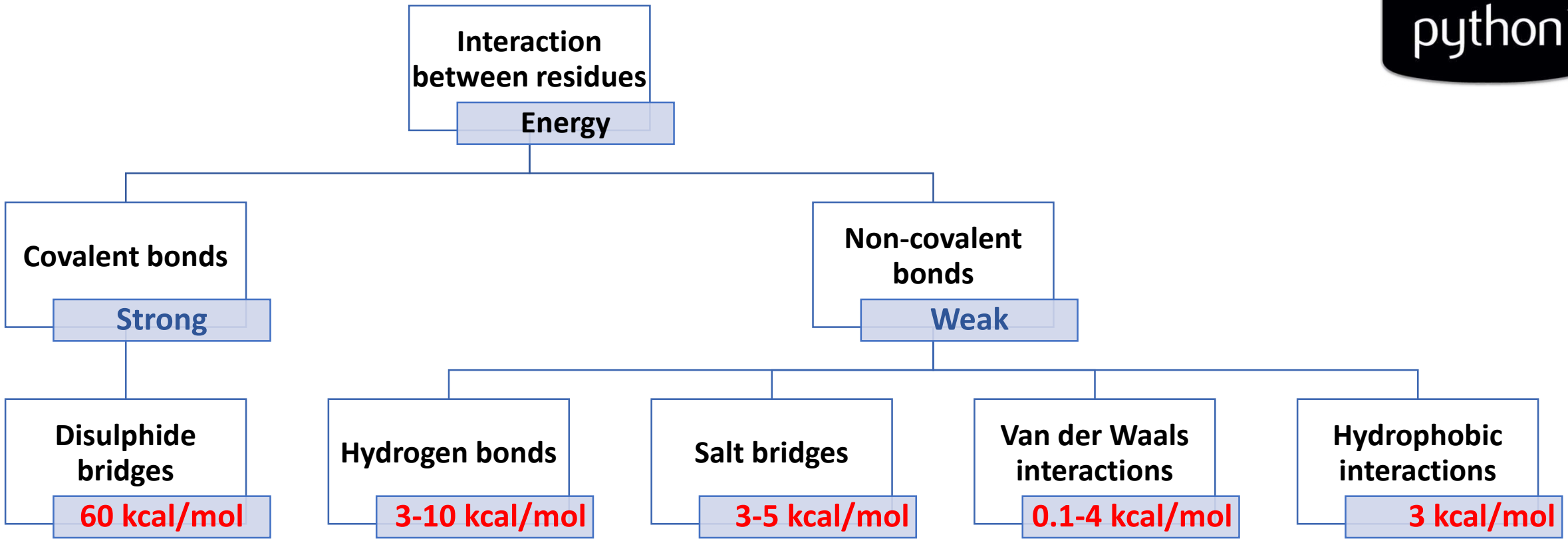
Aims

- Identify the key residues of protein that are essential for protein structure and function.
- Understand the contribution of each amino acid to the overall protein stability.
- Find viral epitopes with key residues and their role in immune escape!

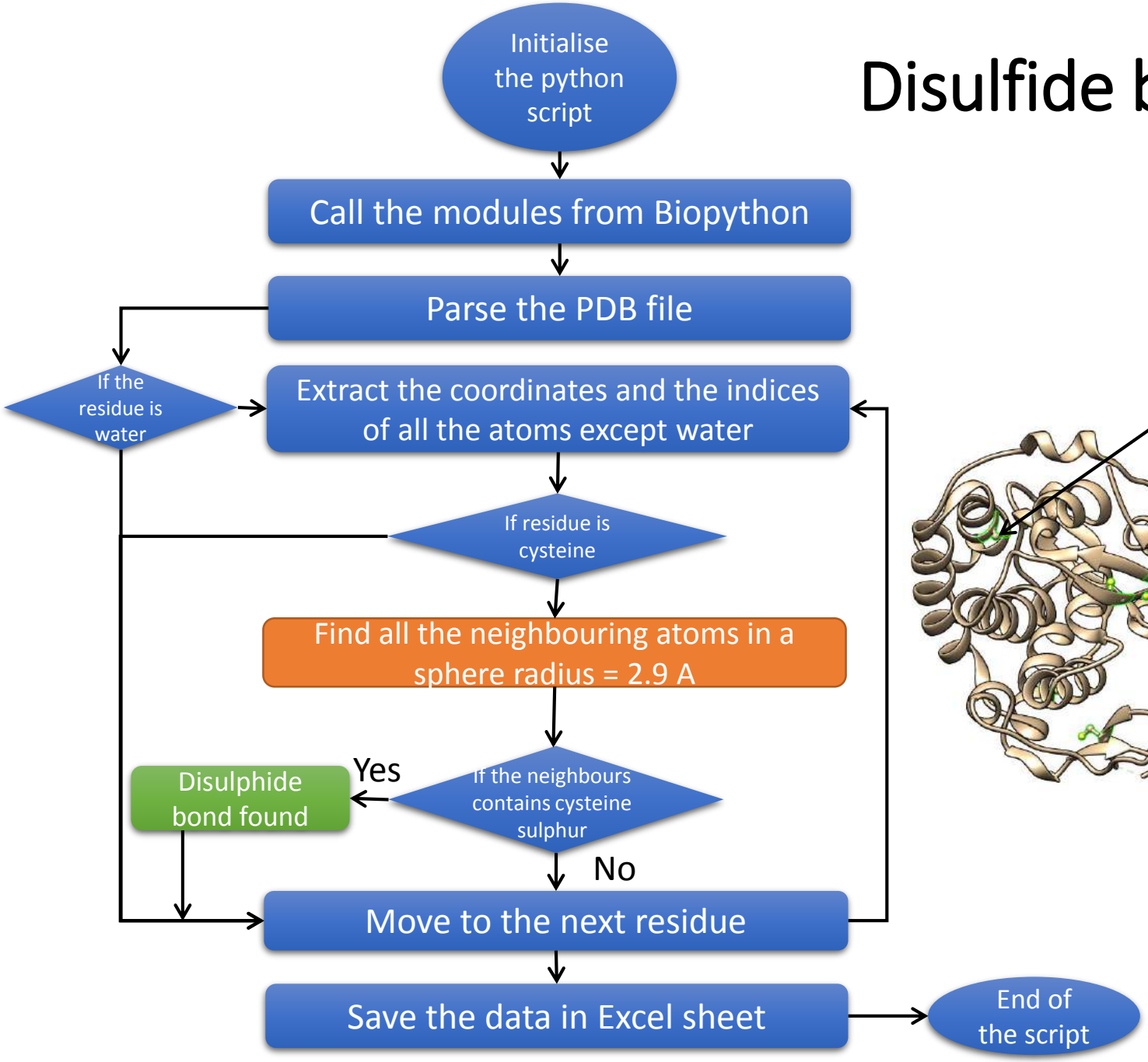
- **Key point:** A few amino acids are more important than the others in a protein stability.

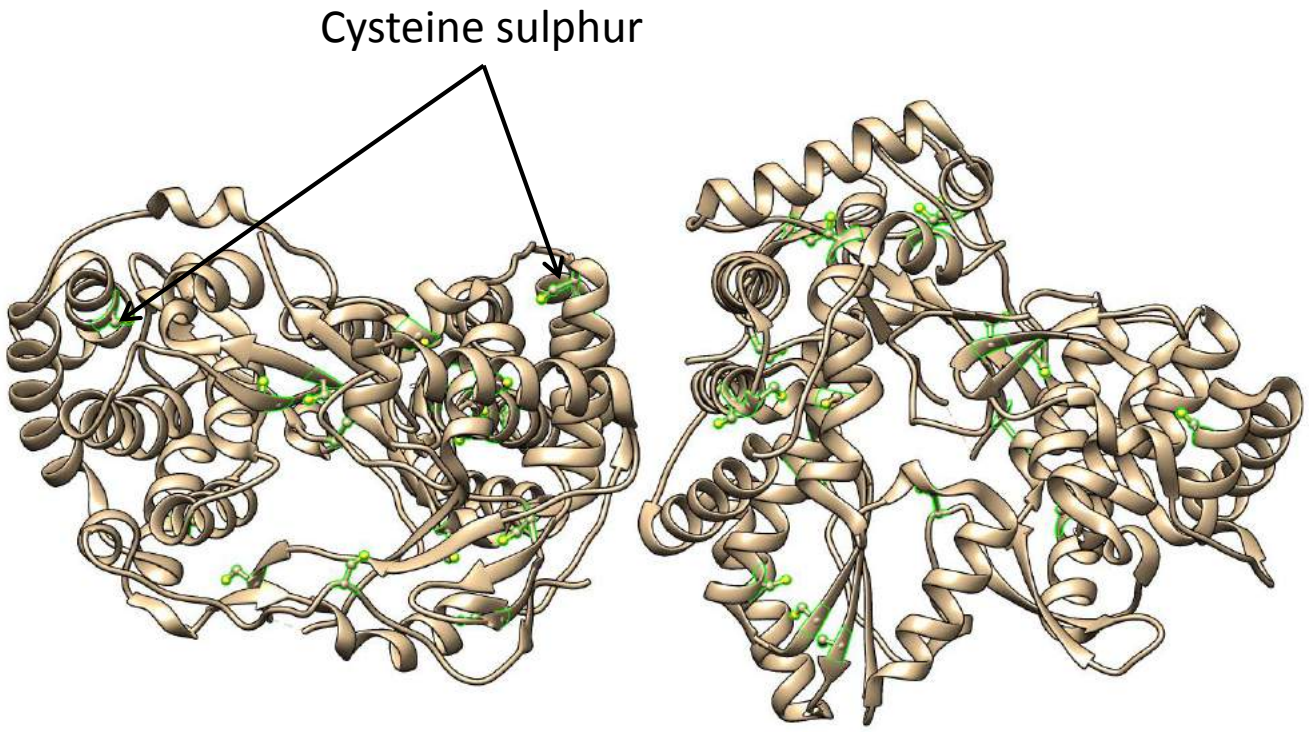
- **Our strategy:** We developed a method that assess quantitatively the importance of each amino acid in the protein based on their individual contribution to the overall stability.

Scheme of the Python algorithm

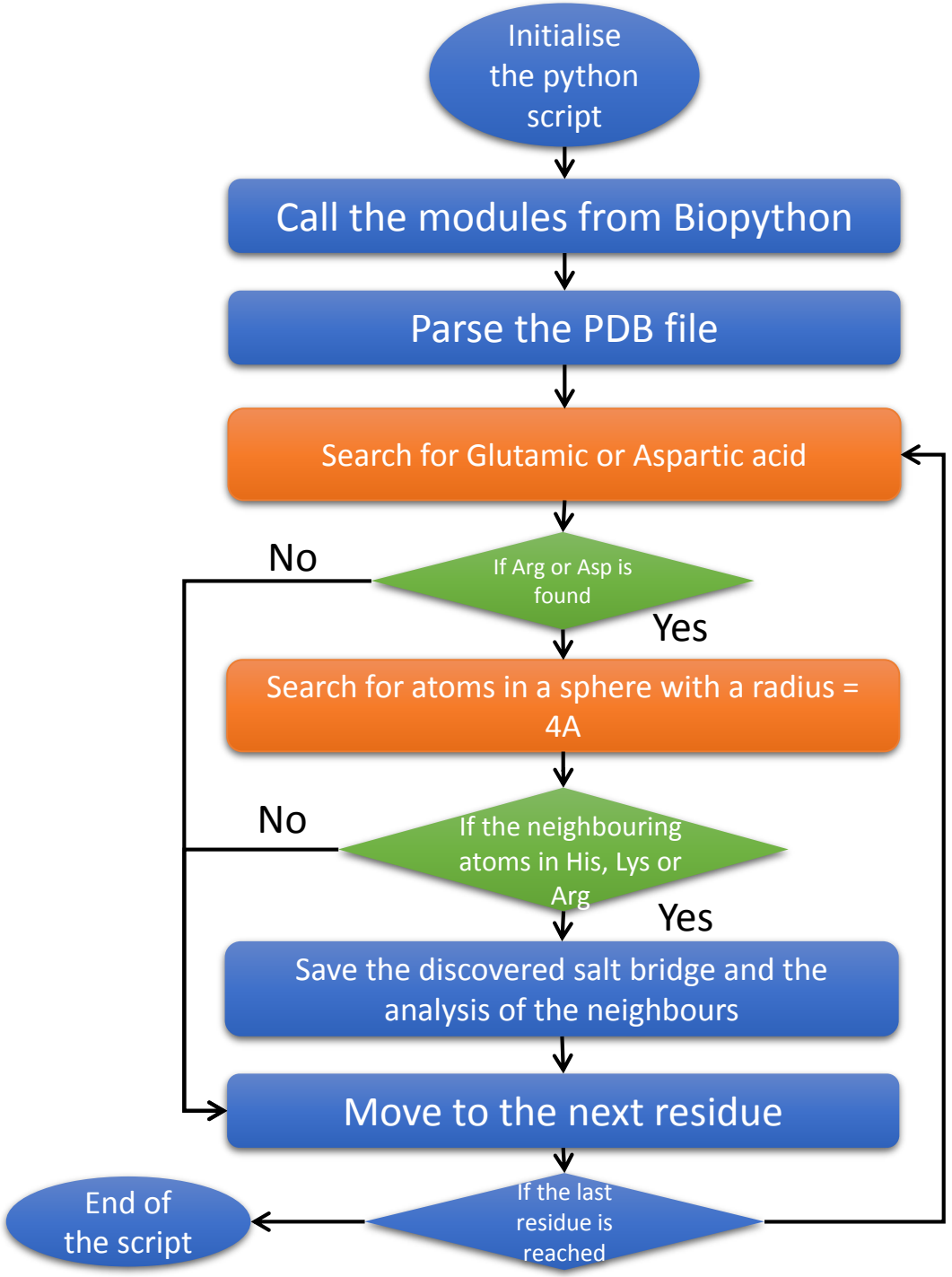


Disulfide bonds in Hydrogen bonds

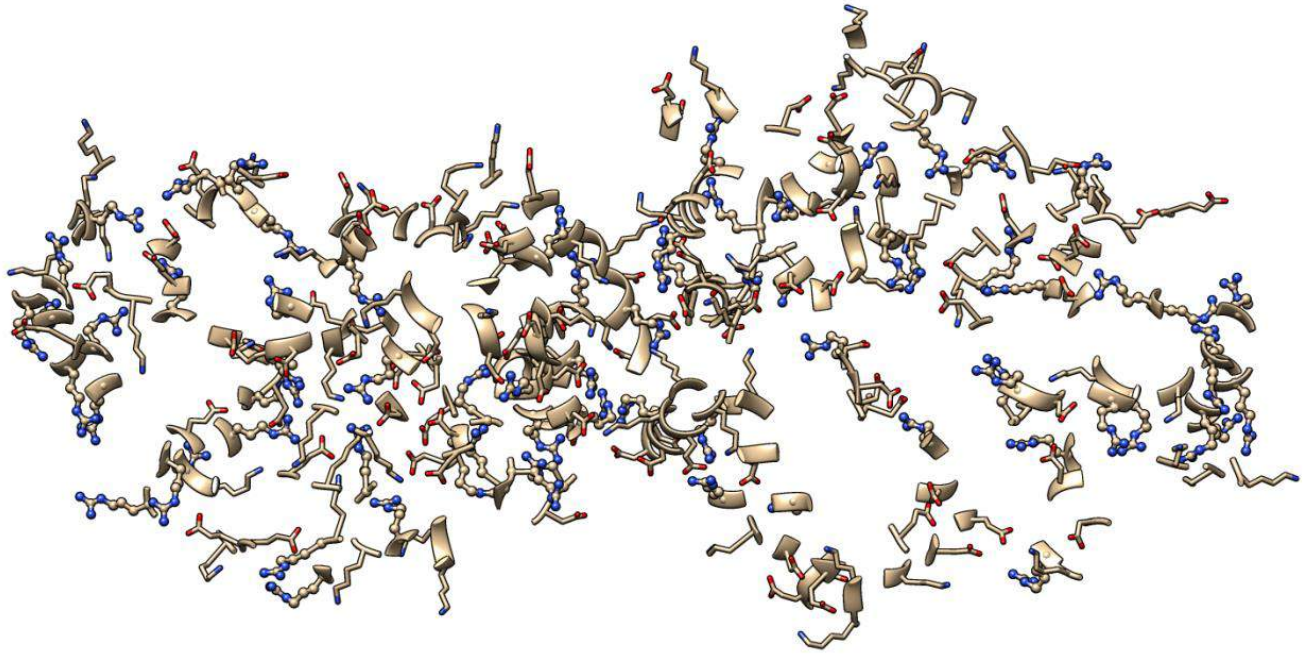




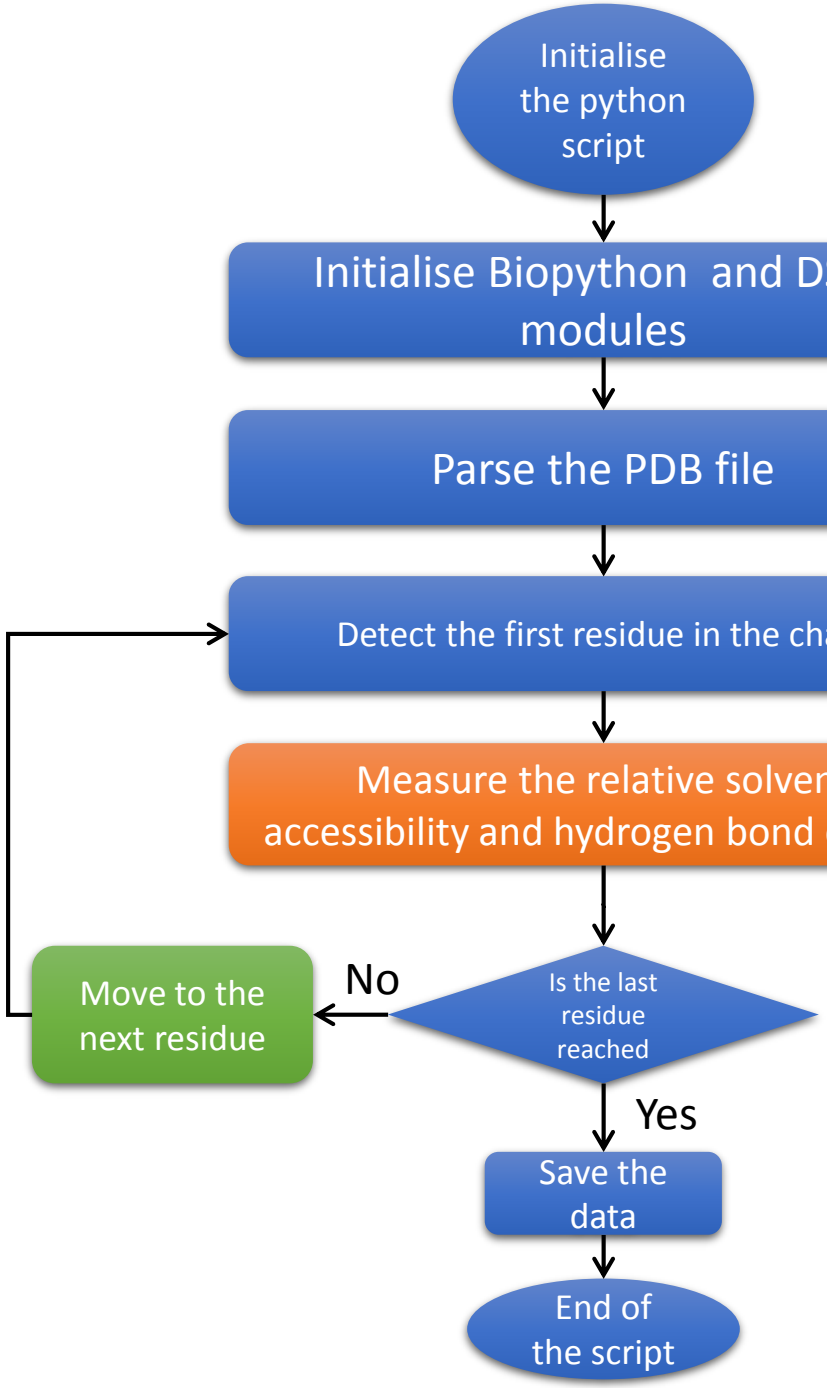
An example of a protein with scattered thiol groups



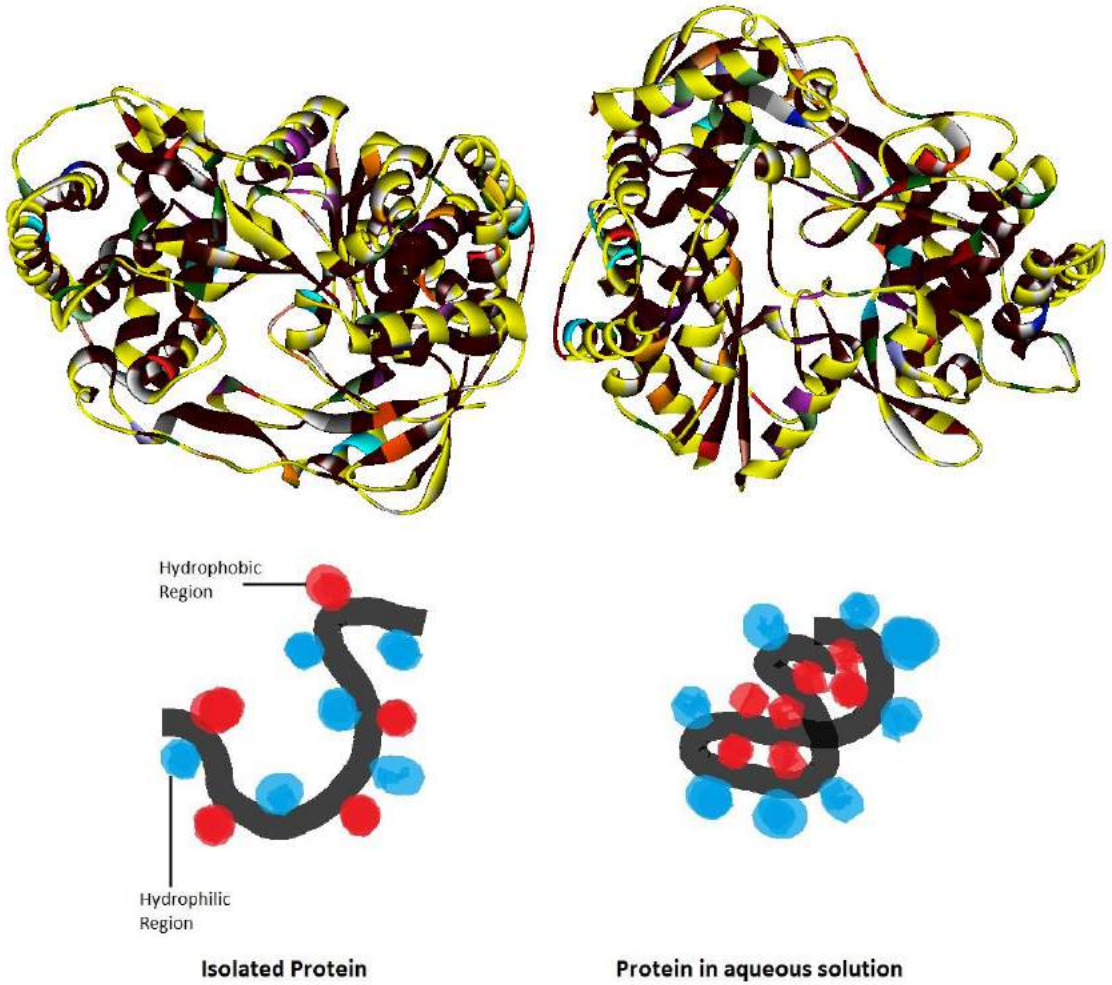
Salt bridges in Hydrogen bonds



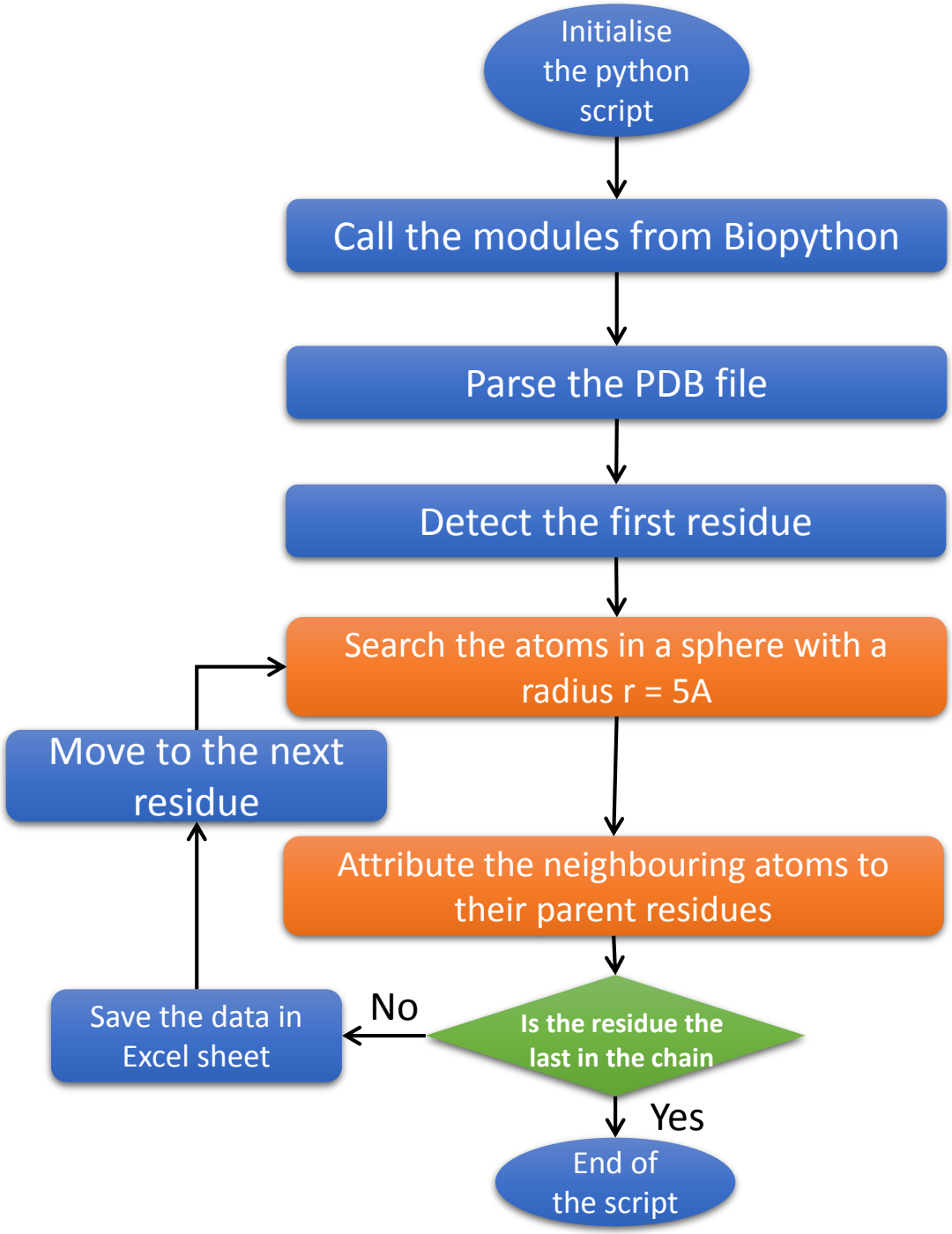
An example of salt bridges formed between oppositely charged amino acids



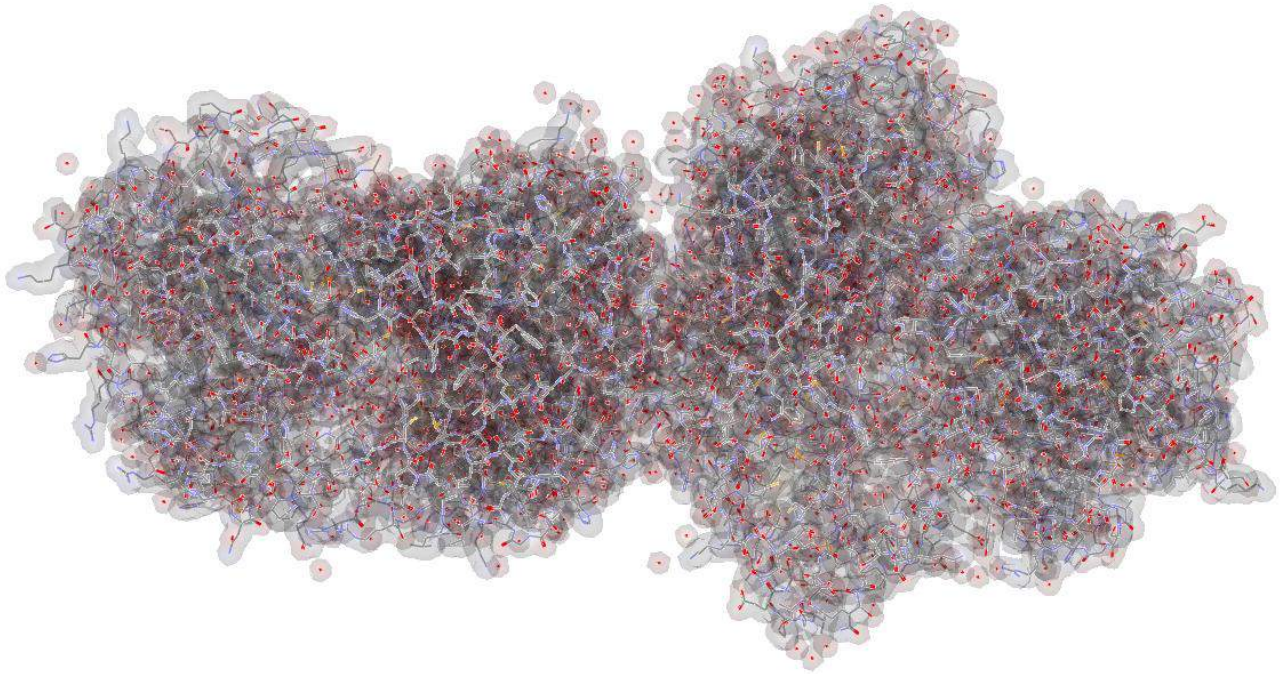
Hydrophobic Interactions and Hydrogen bonds



Illustrations of how protein changes shape to allow polar regions (blue and yellow) to interact with water while non-polar hydrophobic regions (red and brown) do not interact with the water.

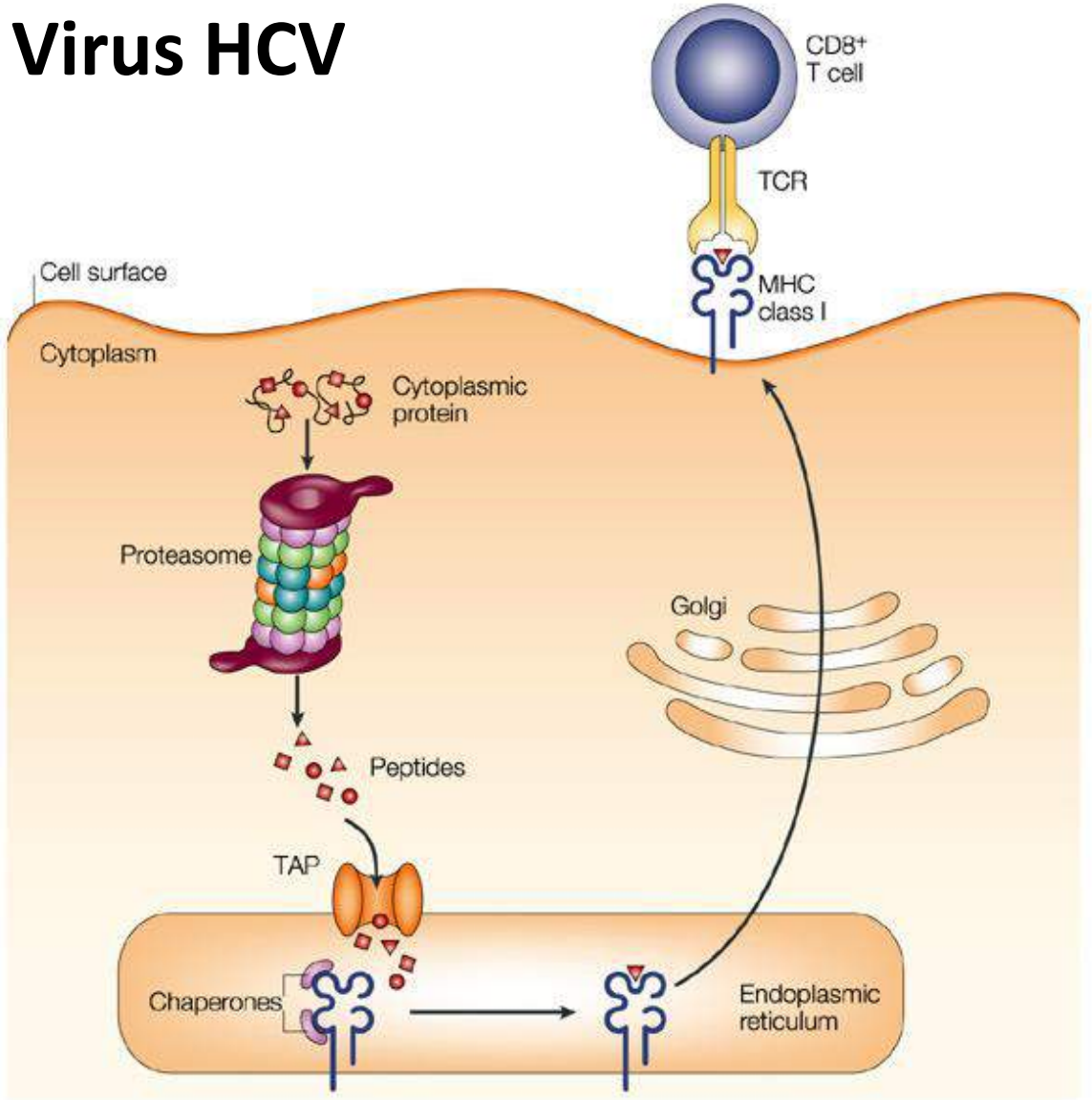


Van der Waals forces



The proof of concept: the Hepatitis C Virus HCV

- In hosts, viruses are controlled by innate immune system by recognising the presence of fragments of the viral protein (epitopes) on cell surfaces.
- Viruses escape the immune attack by mutating the epitope amino acids
- Some people can eliminate the virus better by presenting epitopes that are important for the virus.
- Our method can find epitopes that have crucial importance.

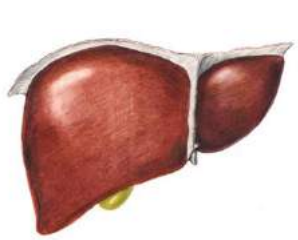


Mechanism of interaction between a virus and the immune system.

Nature Reviews Immunology 3, 952-961 (December 2003)

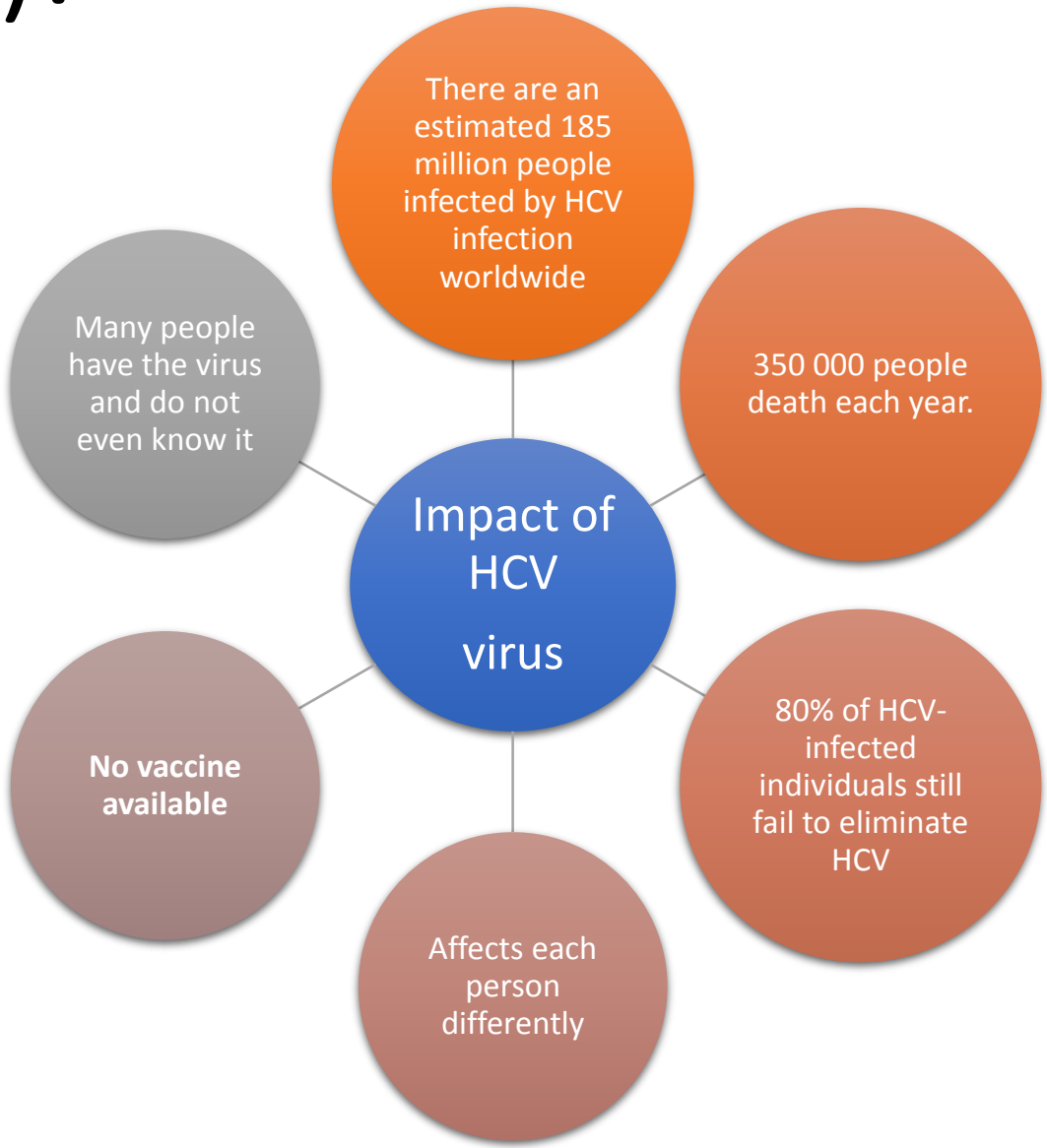
What Is Hepatitis C Virus (HCV)?

- Hepatitis means inflammation of the liver
  - Hepat (liver) + itis (inflammation)= Hepatitis
- there is a specific virus that is causing a liver to inflame (swell or become larger than normal)

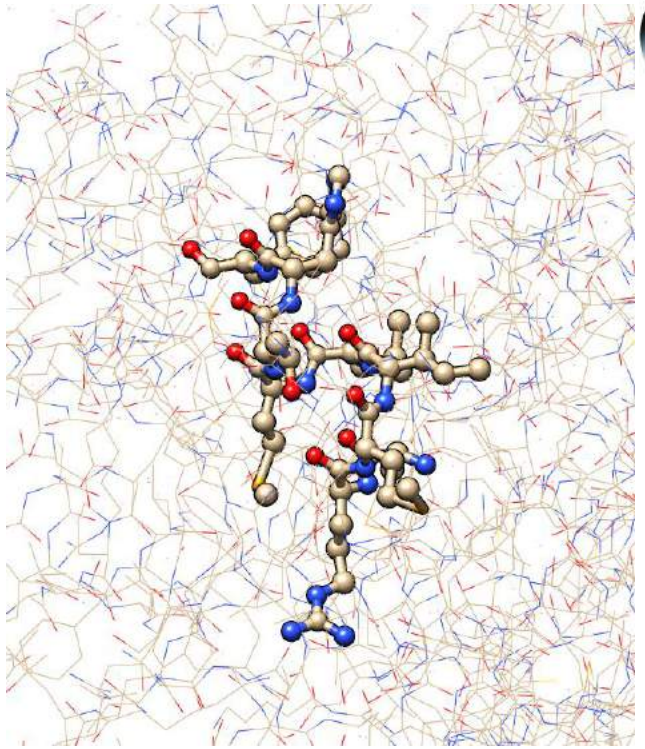


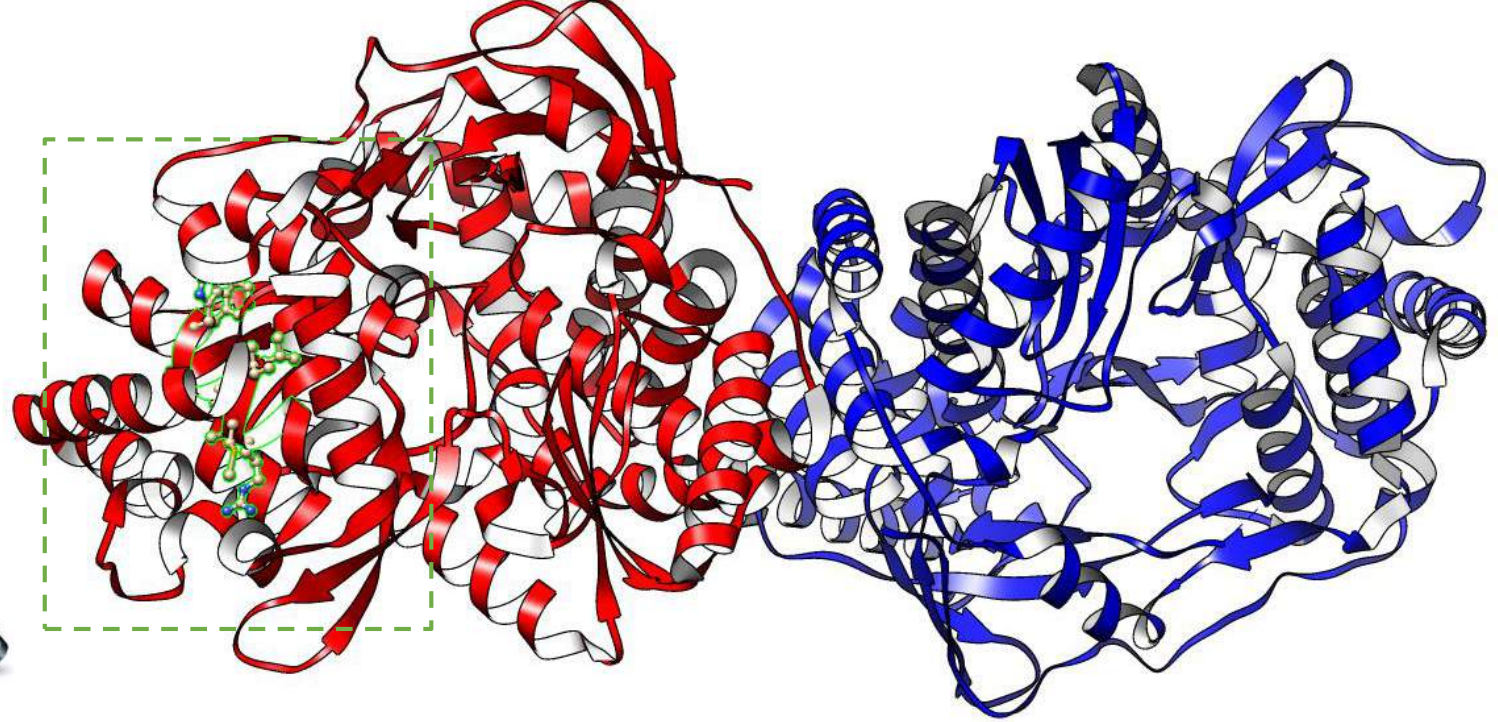
Structure of Hepatitis C Virus

Transmission electron–micrograph of positively-stained particles that resemble the flaviviruses that cause hepatitis C infections



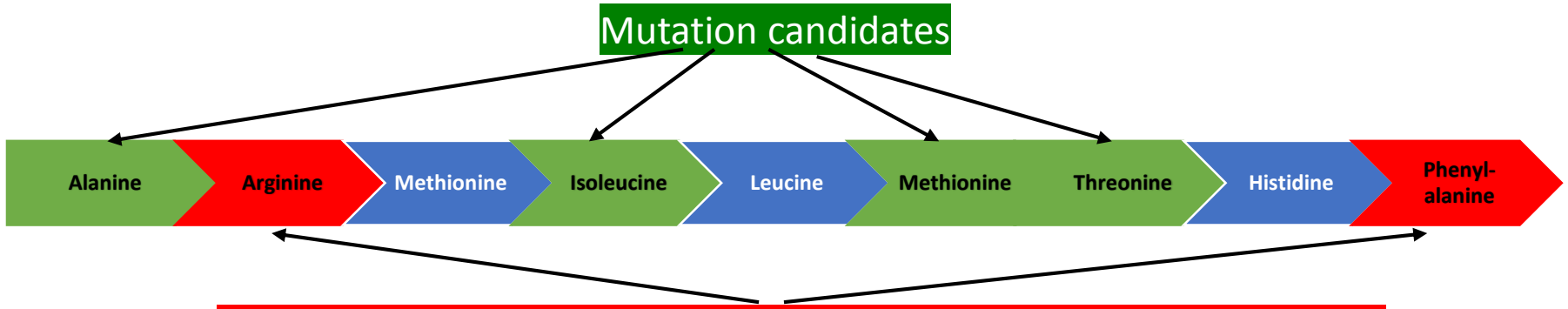
Results



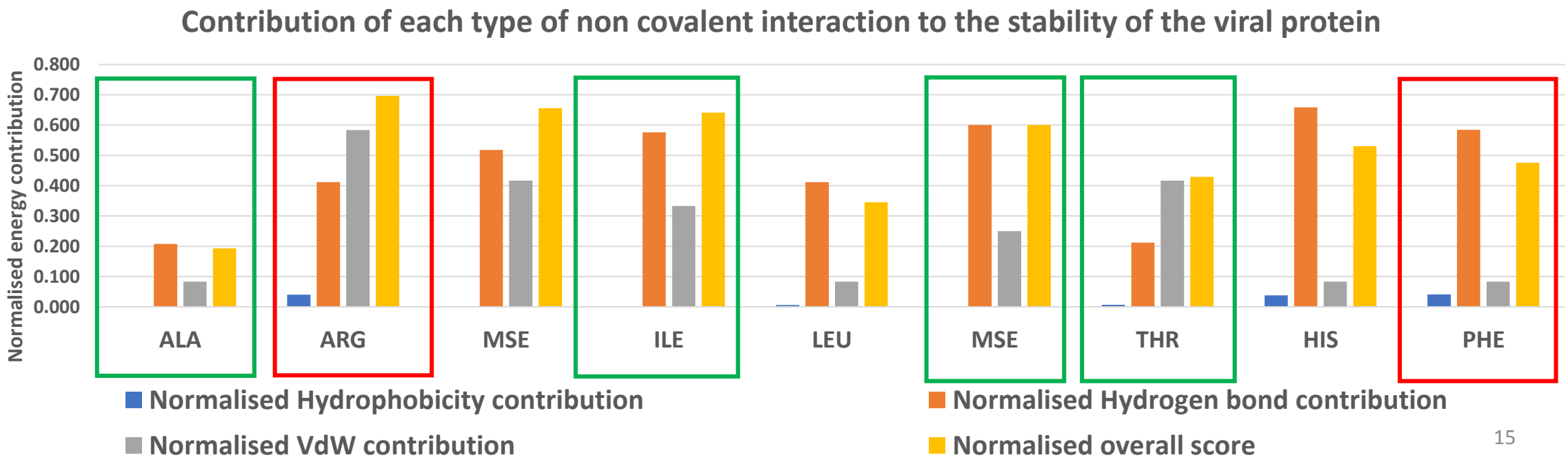


The epitope NS5B$_{421–429}$ = [ARMILMTHF]

The sequence = Alanine-Arginine-Methionine-Isoleucine-Leucine-Methionine-Threonine-Histidine-Phenylalanine



Amino acid of the epitope	Epitope index	Normalised Hydrophobicity contribution	Normalised Hydrogen bond contribution	Normalised vdW contribution	Normalised overall score	Function of residue
ALA	421	0.000	0.208	0.083	0.193	Mutate
ARG	422	0.040	0.412	0.583	0.696	HLA-B27 binder
MSE	423	0.000	0.518	0.417	0.656	
ILE	424	0.000	0.576	0.333	0.641	mutate
LEU	425	0.006	0.412	0.083	0.345	
MSE	426	0.000	0.600	0.250	0.600	mutate
THR	427	0.007	0.212	0.417	0.429	mutate
HIS	428	0.038	0.659	0.083	0.530	
PHE	429	0.041	0.584	0.083	0.475	HLA-B27 binder



Conclusions

- The selected epitope that is a part of one of the viral protein can be mutated according to the HLA system of the host.
- This Python code is the first to assess individual stabilising energy for each amino acid of the protein.
- It is restricted to viral protein and can be applicable to any protein with an available PDB file.
- This algorithm is open-source and can be used and improved by anyone.

Future work

- Apply the implemented algorithm to more proteins.
- Improve the precision of the Hydrogen bonds energy by including quantum mechanics calculations.
- Make this algorithm available as an online service.
- Test other method to calculate the relative solvent accessibility.

Acknowledgments

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CVR
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University of Glasgow
Centre for Virus Research

Thank you for your attention.

Questions?