Molecular Dynamics Simulations of Peptides Interacting with Quartz Surfaces

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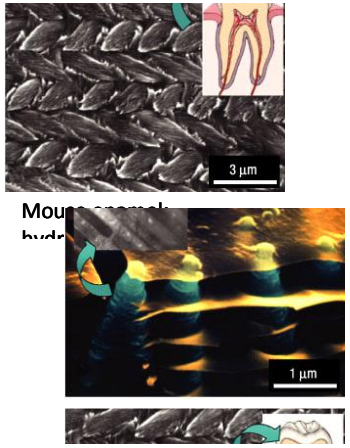
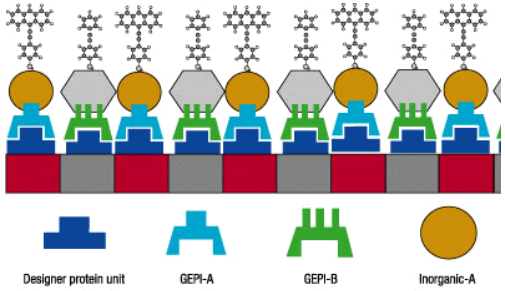
Workshop on Molecular Dynamics 5th June 2009

Peptide-inorganic interactions

- Proteins control the formation of natural hard materials.
- These proteins contain motifs that bind to the inorganic material.
- Understanding of peptide-inorganic recognition is necessary for exploitation.
- Diverse range of applications:
  - *E.g.* assembly of functional nanomaterials, biosensors.

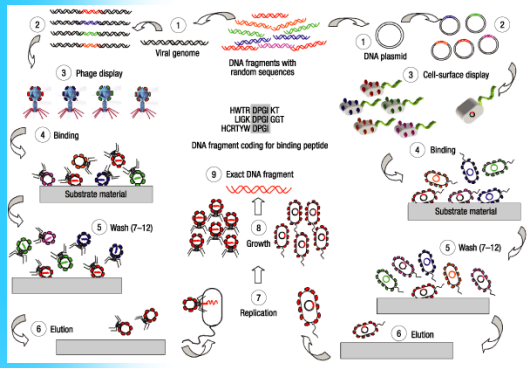


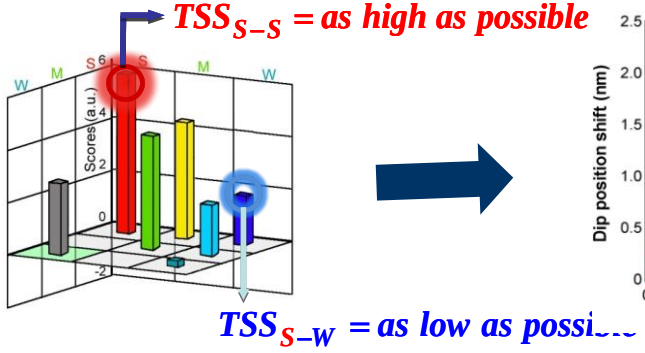


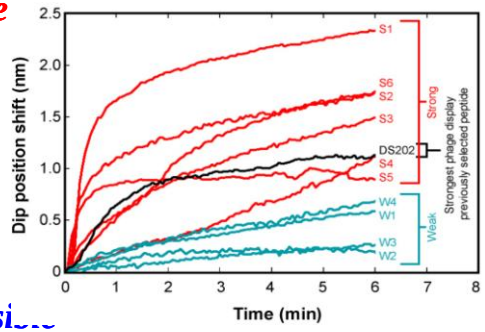
Sarikaya *et al. Nat. Mater.*, **2003**, 2, 577.

Design of quartz binding peptides

Phage Display → **Bioinformatics** → **Experimental Validation**







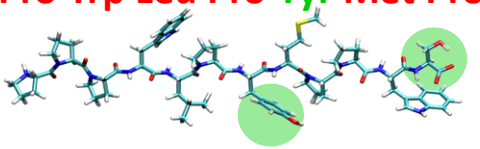
Oren *et al. Bioinformatics*, **2007**, 23, 2816.

Quartz binding peptides

- Amino acid content:
  - Non-polar, neutral residues;
  - Pro, trp, leu occur frequently.
- Key questions:
  - What are the mechanisms of binding?
  - What are the roles of the residue content and order?
  - What molecular level features give rise to a high binding affinity for quartz?

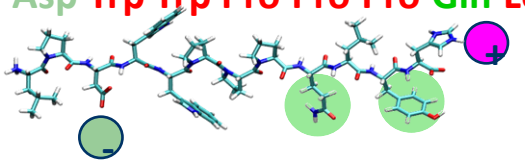
S1:

Pro Pro Pro Trp Leu Pro Tyr Met Pro Pro Trp Ser



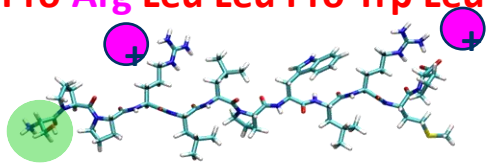
S2:

Leu Pro Asp Trp Trp Pro Pro Pro Gln Leu Tyr His



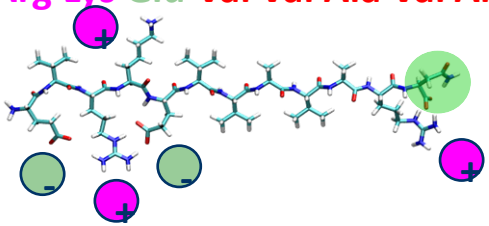
S3:

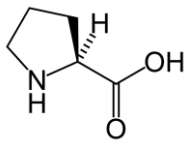
Ser Pro Pro Arg Leu Leu Pro Trp Leu Arg Met Pro



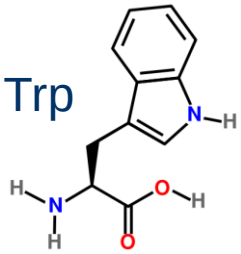
W1:

Glu Val Arg Lys Glu Val Val Ala Val Ala Arg Asn

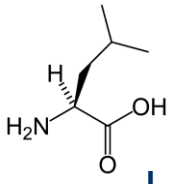




Pro



Trp

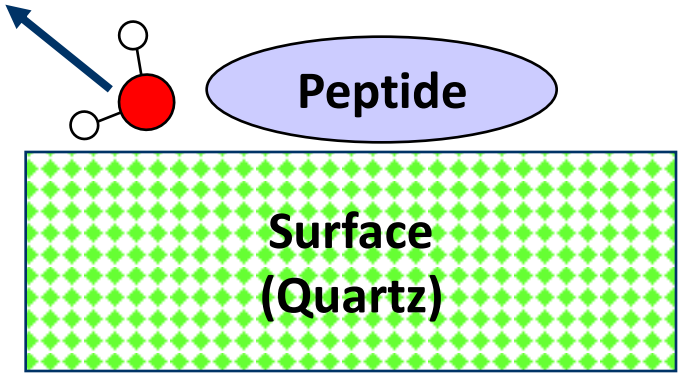


Leu

Our approach

Examine the nature of the surface and the role of water

- Structure and dynamics of water at the interface.
- Implications for binding.



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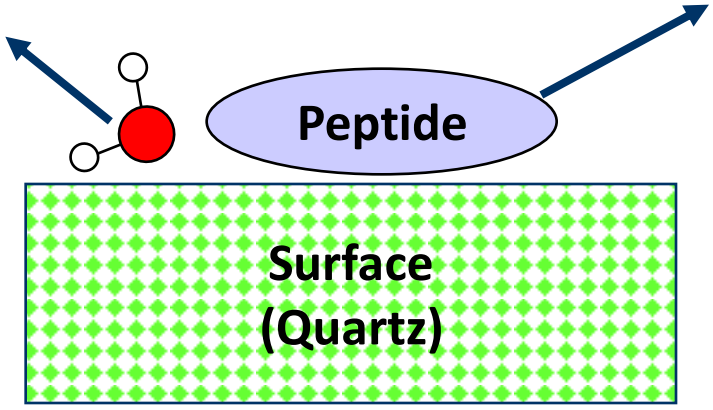

Characterise peptides in solution:

- Conformations of strong vs weak binders.
- Relationship between sequence → structure → function.

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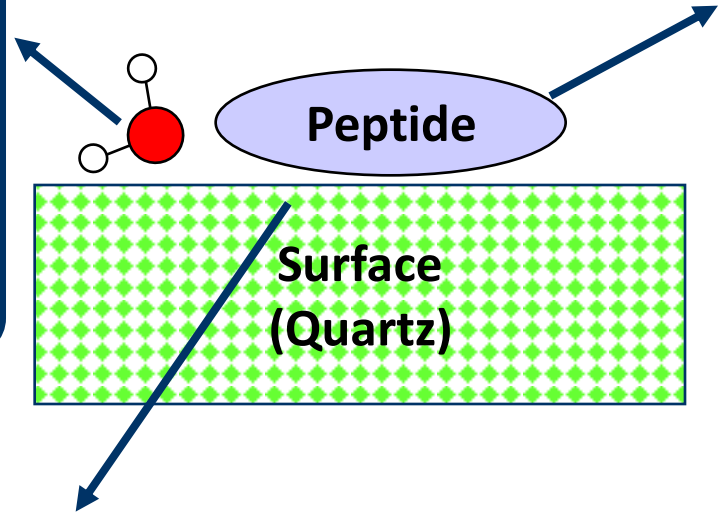

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Investigate the interactions of peptides with the surface

- Mechanisms of binding.
- Key amino acid residues.
- Structural motifs.

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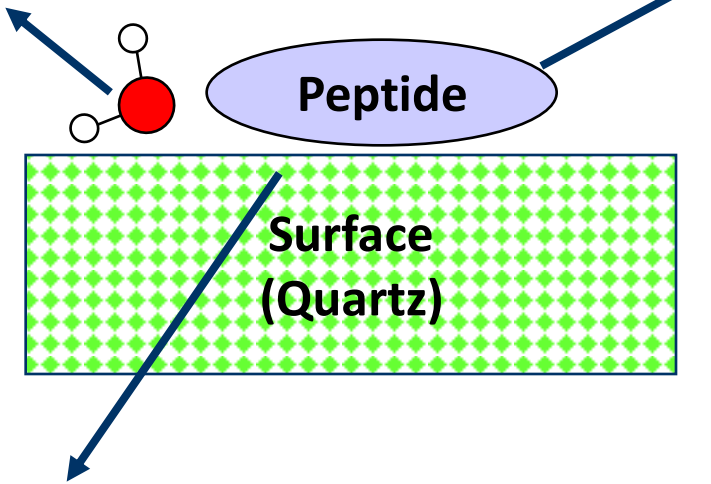

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- Conformations of strong vs weak binders.
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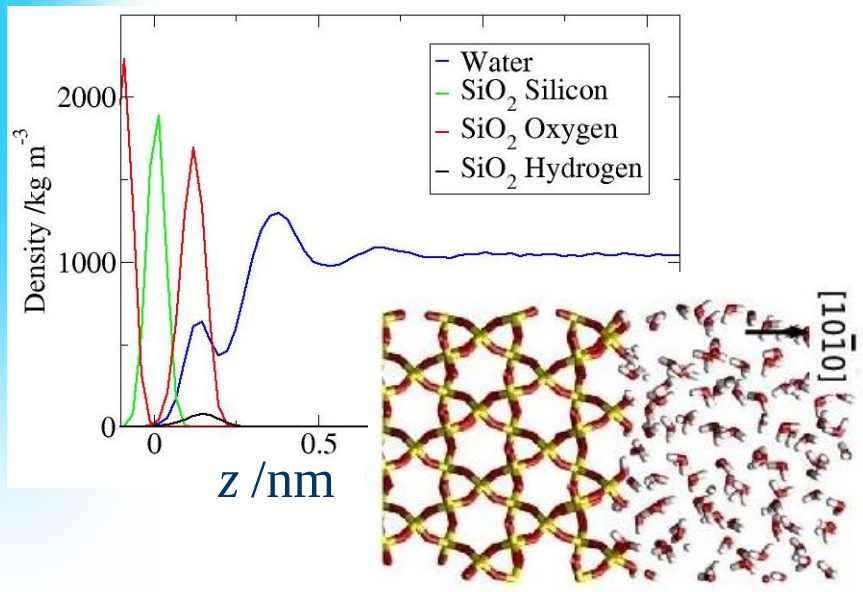
- Structural motifs.

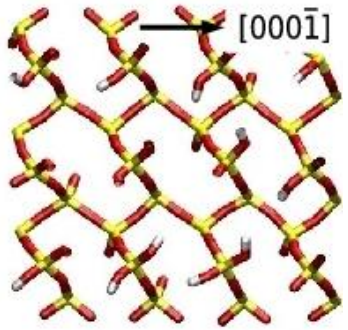
Molecular dynamics simulations

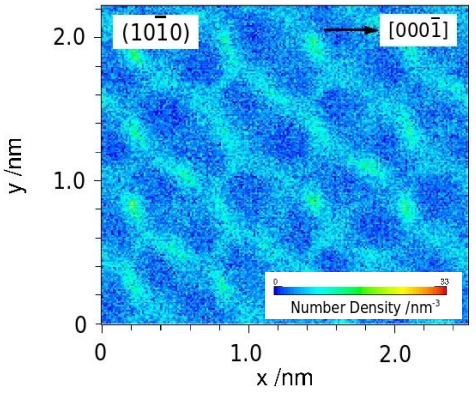
- Provide a molecular-level insight.
- CHARMM forcefield with silica parameters by Lopes *et al.* (bio and inorganic compatible), and TIP3P water (using Gromacs).

Interactions of water with the hydroxylated (100) surface

- Water forms weakly structured layers on the surface of quartz.
- Water penetrates small pockets on the surface.
- Within the first water layer, water is also ordered laterally.
  - May affect the mobility and aggregation of bound molecules/peptides.



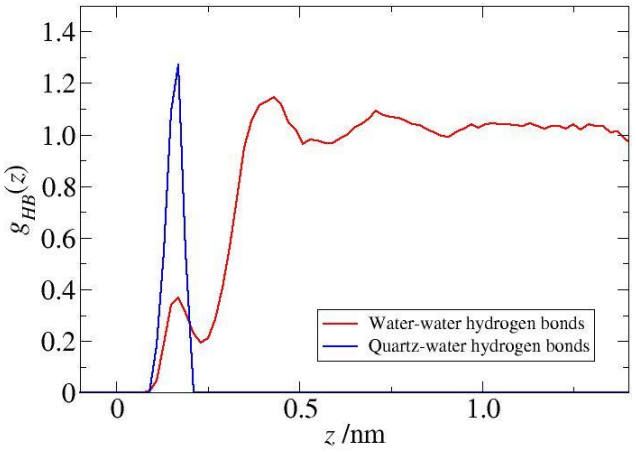


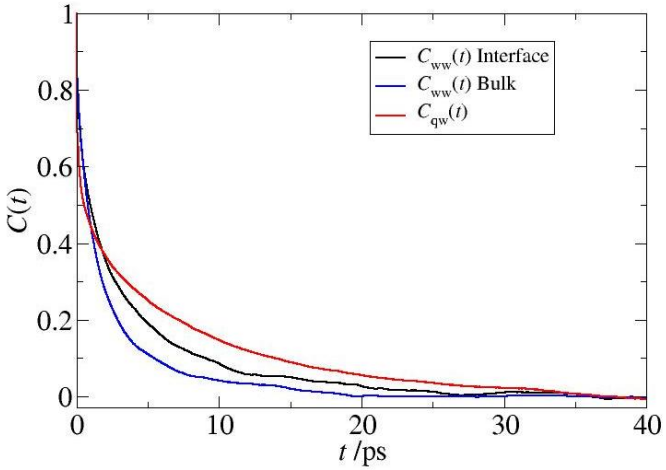


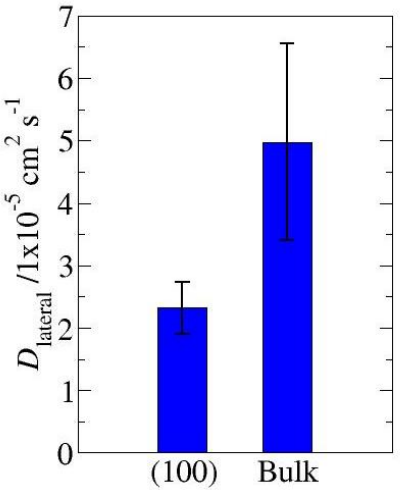
Notman & Walsh *Langmuir*, **2009**, 25, 1638.

Hydrogen bonding and lateral diffusion on quartz (100)

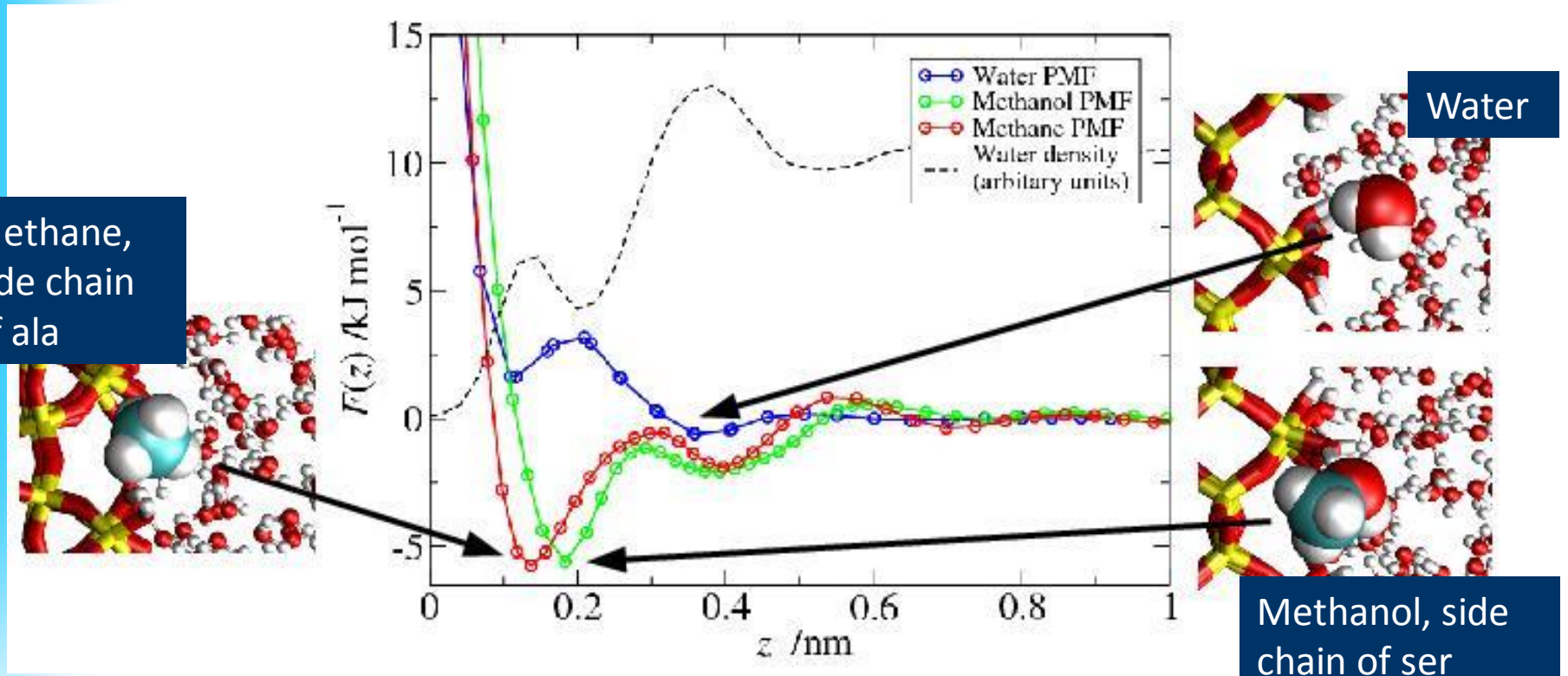
- Water h-bonds to the quartz surface.
- There is a peak in water-water h-bonds at the interface.
- H-bonds at the interface have a longer life time than h-bonds in the bulk (more stable).
- Leads to reduction in lateral diffusion of water on the surface.







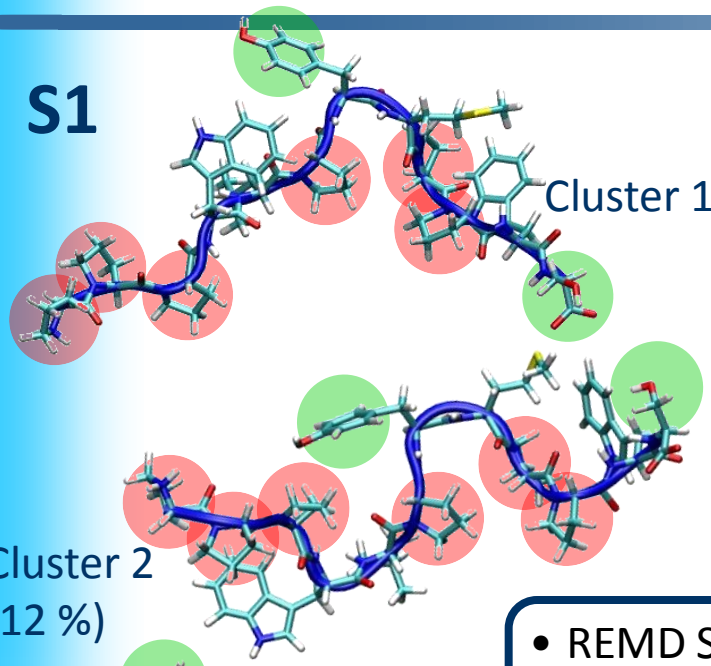
Free energy of small molecules as a function of distance to the (100) surface



$$\mathrm{PMF} = \int_z F_{\mathrm{constr}}(z)\, dz \,/\mathrm{kJ\ mol}^{-1}$$

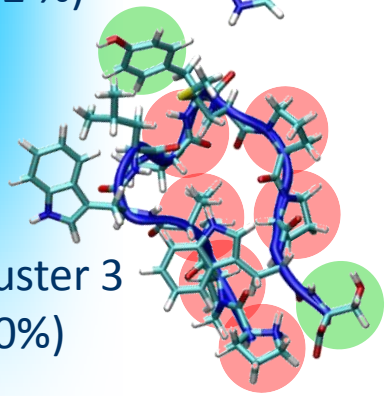
Solution structures of the peptides

S1



Cluster 1 (21%)

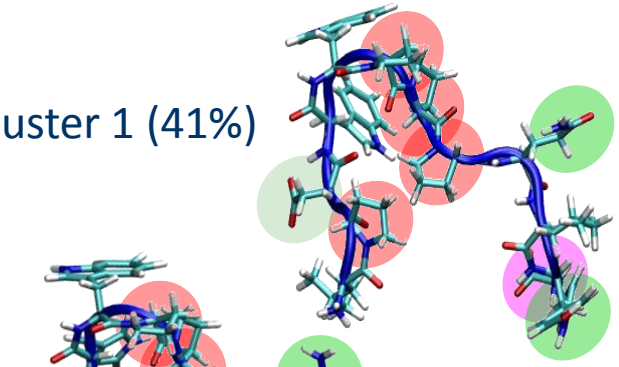
Cluster 2
(12 %)

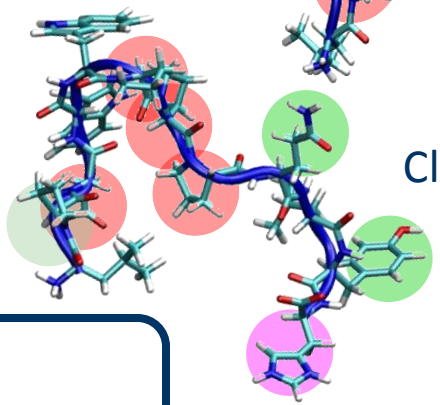


Cluster 3
(10%)

S2

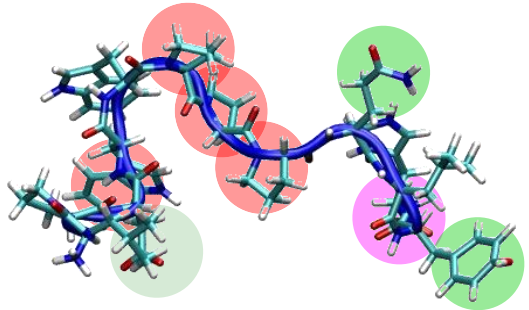
Cluster 1 (41%)





Cluster 2 (21%)

Cluster 3 (12%)



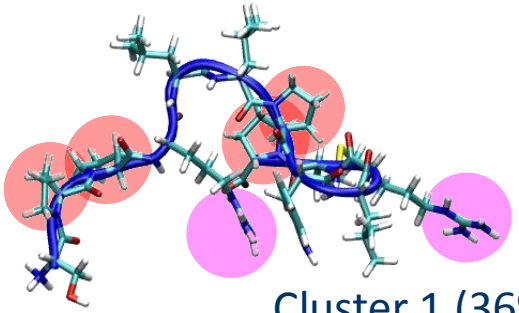
- REMD Simulations.
- Pro has significant influence on structure.
- Cluster analysis used to identify key conformations:
  - Strong binders have fewer clusters.

Pro Pro Pro Trp Leu Pro Tyr Met Pro Pro Trp Ser

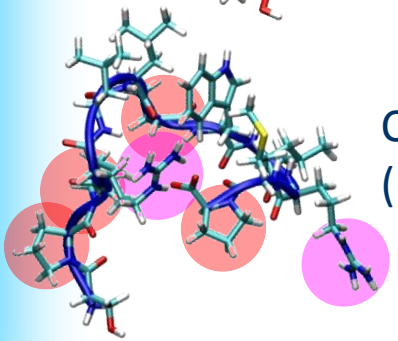
Leu Pro Asp Trp Trp Pro Pro Pro Gln Leu Tyr His

Solution structures of the peptides

S3

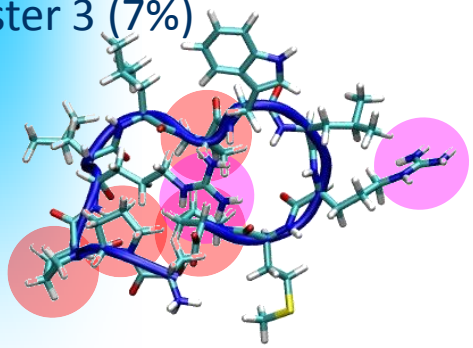


Cluster 1 (36%)

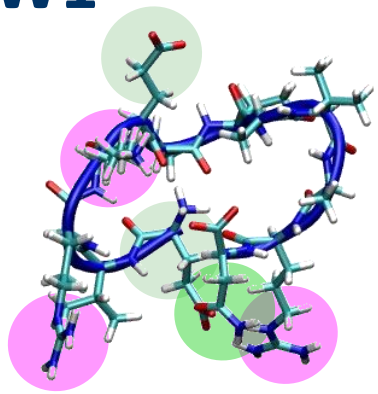


Cluster 2
(15 %)

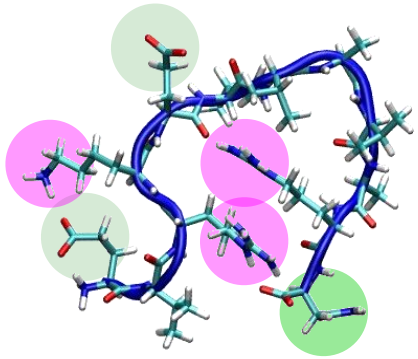
Cluster 3 (7%)



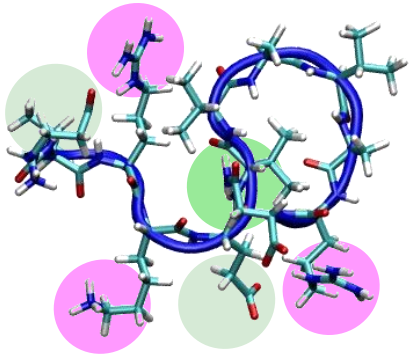
W1



Cluster 2 (8%)



Cluster 1 (9%)



Cluster 3 (7%)

- REMD Simulations.
- Pro has significant influence on structure.
- Cluster analysis used to identify key conformations:
  - Strong binders have fewer clusters.

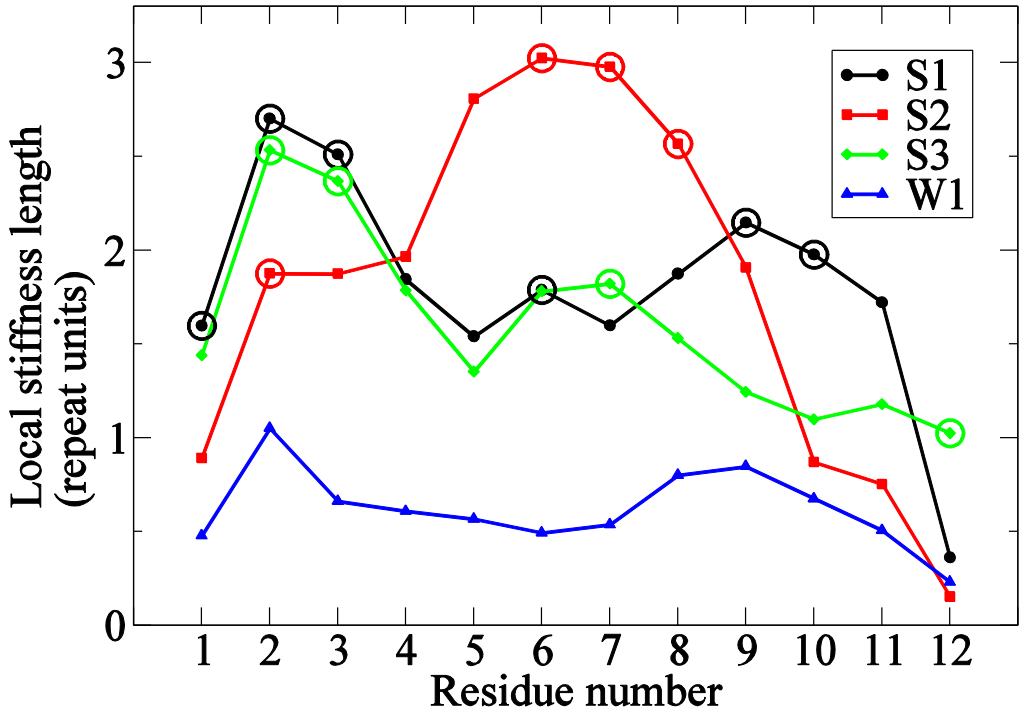
Ser Pro Pro Arg Leu Leu Pro Trp Leu Arg Met Pro

Glu Val Arg Lys Glu Val Val Ala Val Ala Arg Asn

Flexibility of the peptides

- Strong binders contain regions in the chain backbone that are locally, conformationally rigid.

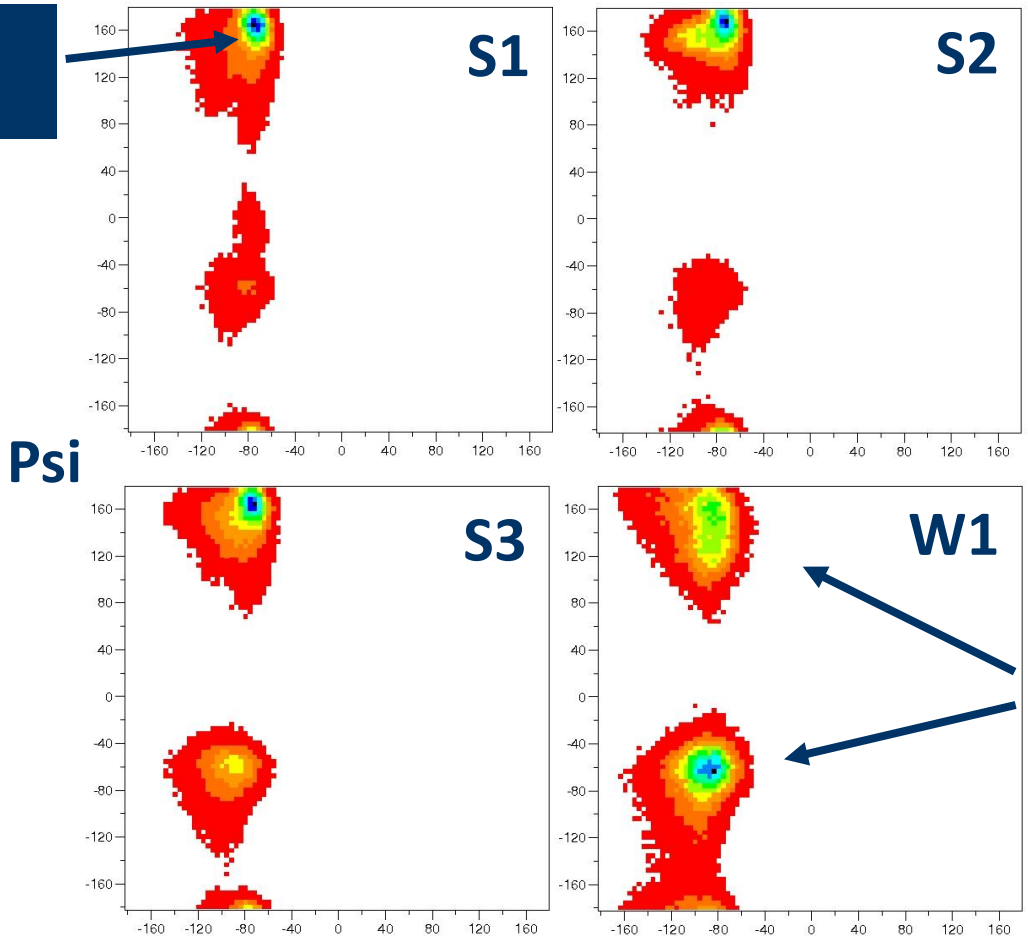
S1: two proline-rich regions connected by a semi-flexible spacer.



S2: central proline-rich region flanked by semi-flexible chains at either end.

Secondary structure

Polyproline character

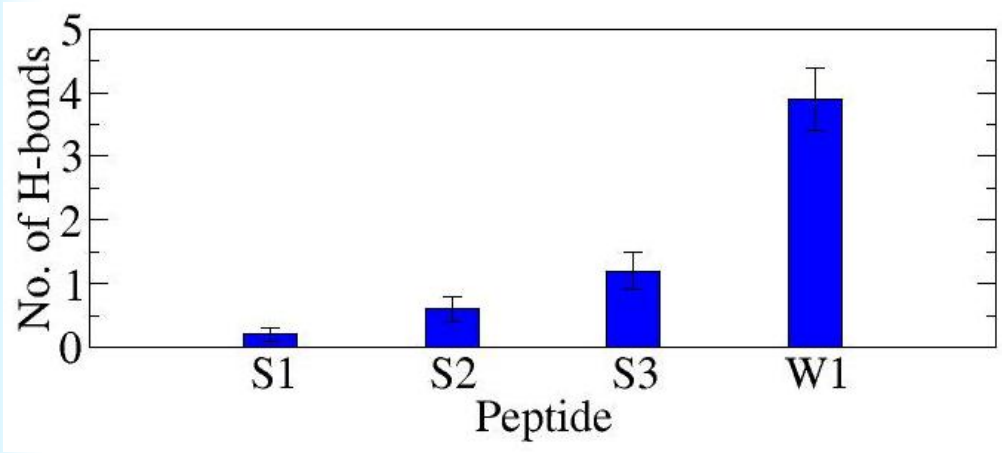


Random coil configuration

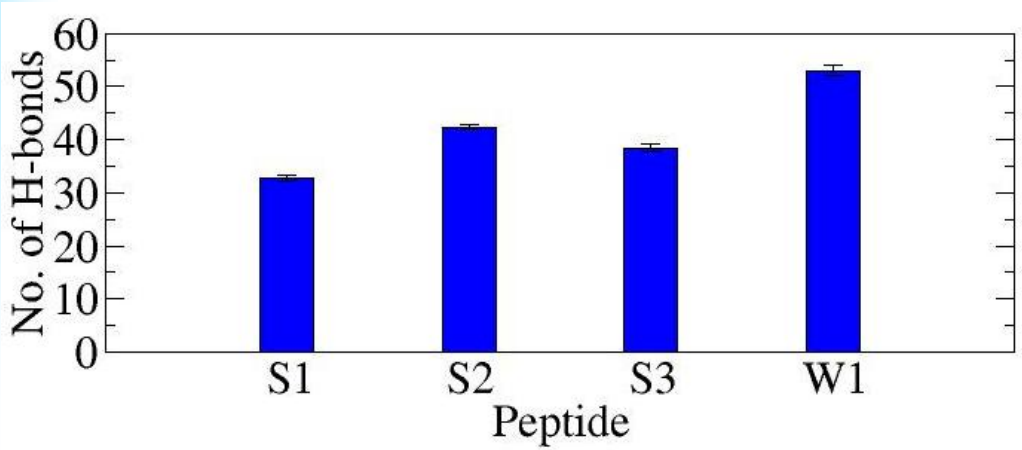
Results are in agreement with CD spectra (Evans *et al*).

Hydrogen bonding

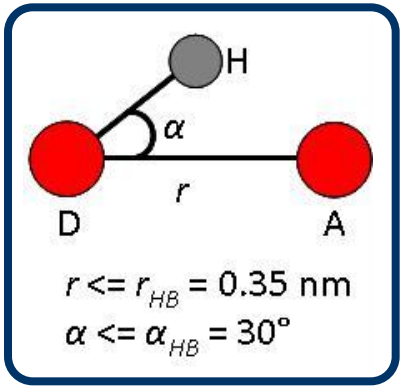
Intra-peptide hydrogen bonds



Peptide-water hydrogen bonds

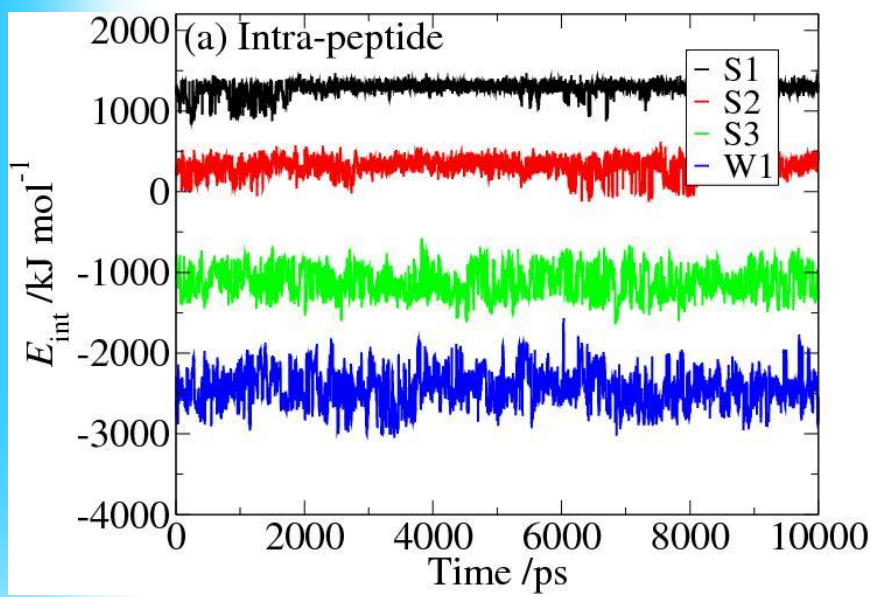


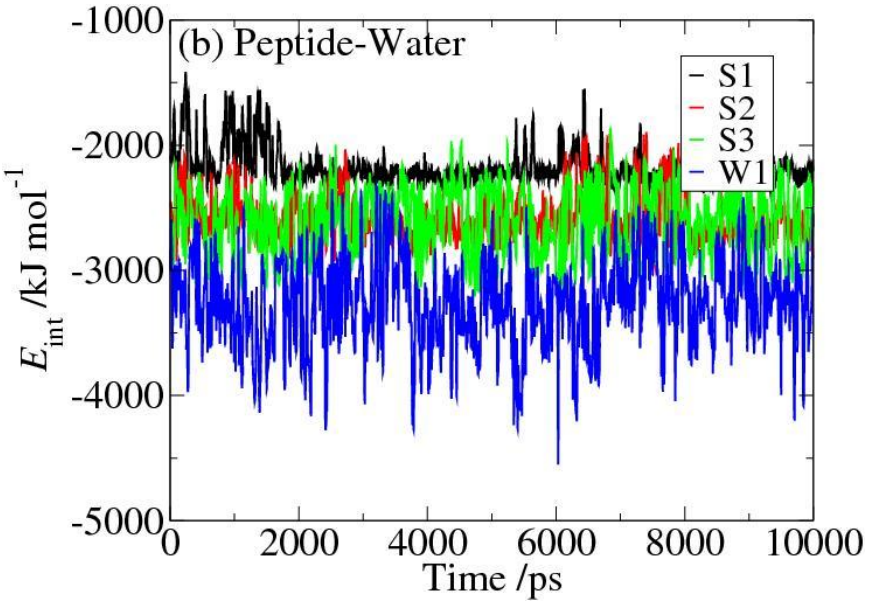
- Indicates that W1 has a greater intrinsic stability due to internal hydrogen bonds.
- Strong binders achieve stability via interactions with the surface?



Interaction energy

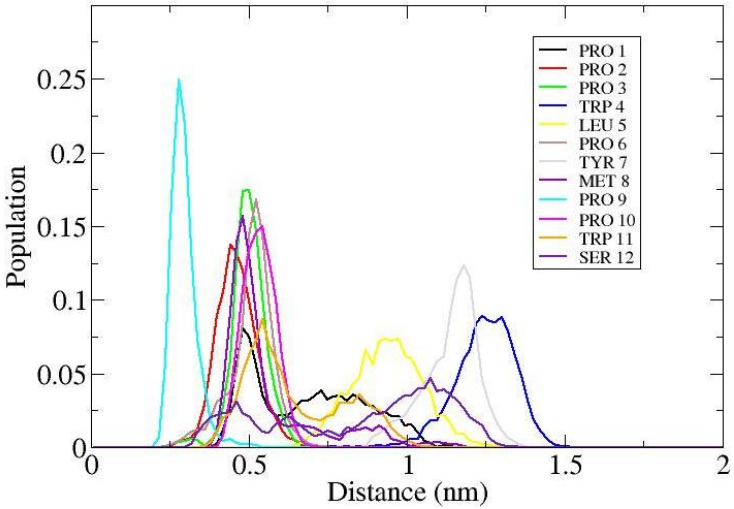
- Strong binders are less stable in solution than weak binders.

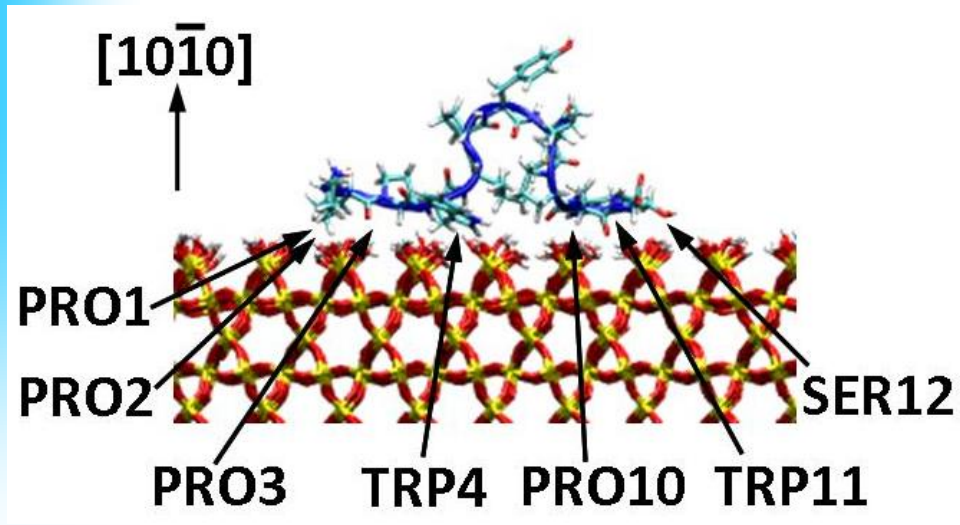


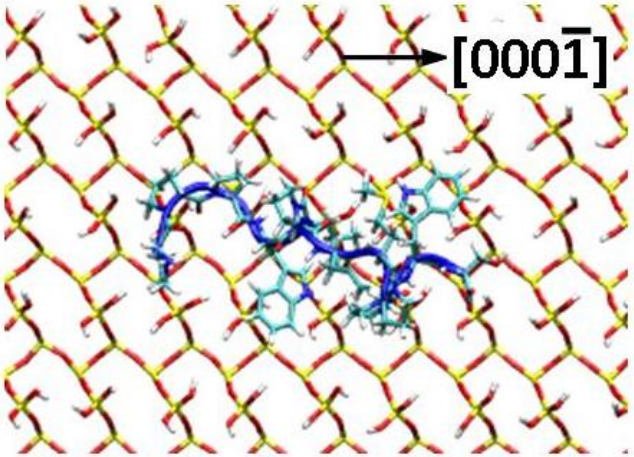


S1 on quartz (100) surface

- S1 has many different bound configurations.
- This is the lowest energy configuration found so far.
- Pro 1, 2, 3, and 10 bind directly to the surface. Trp lies flat on the surface.

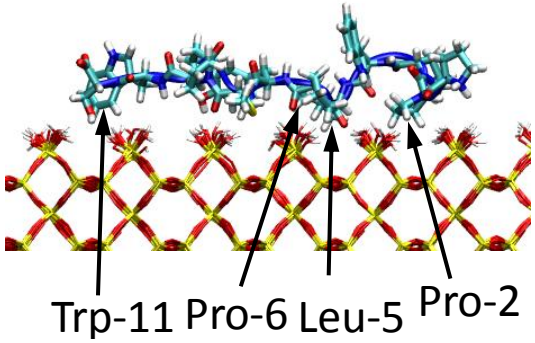


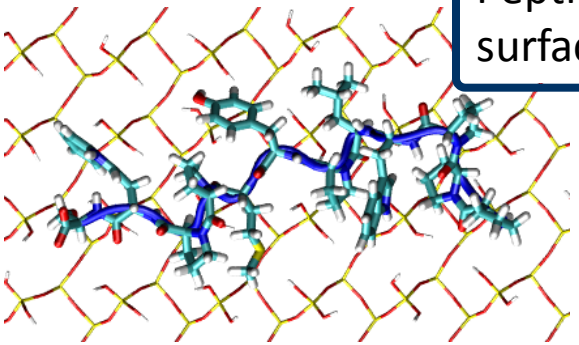




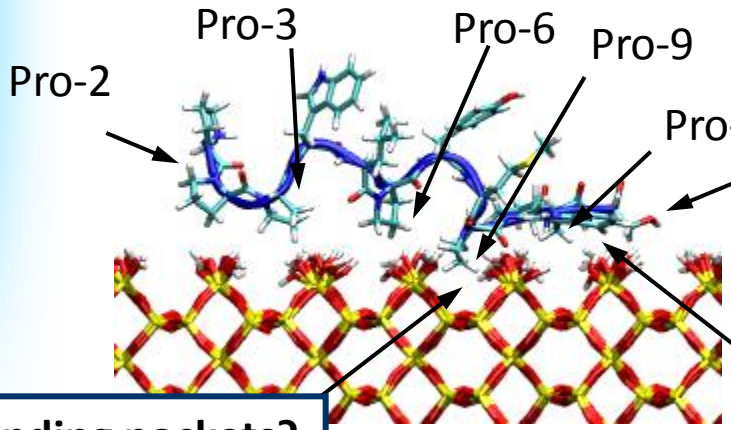
S1 on quartz (100) surface

- S1 has many bound configurations.
- Common binding motifs.

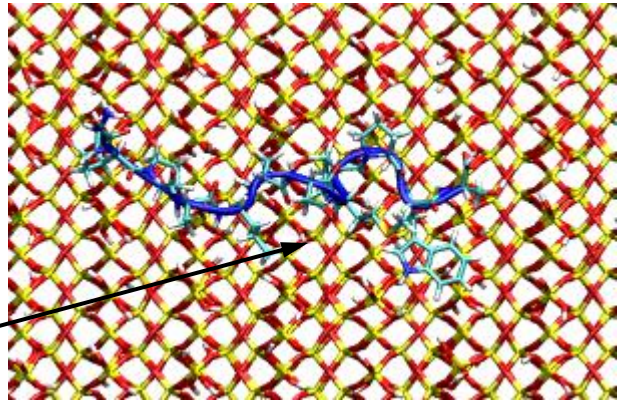




Peptide flat on surface

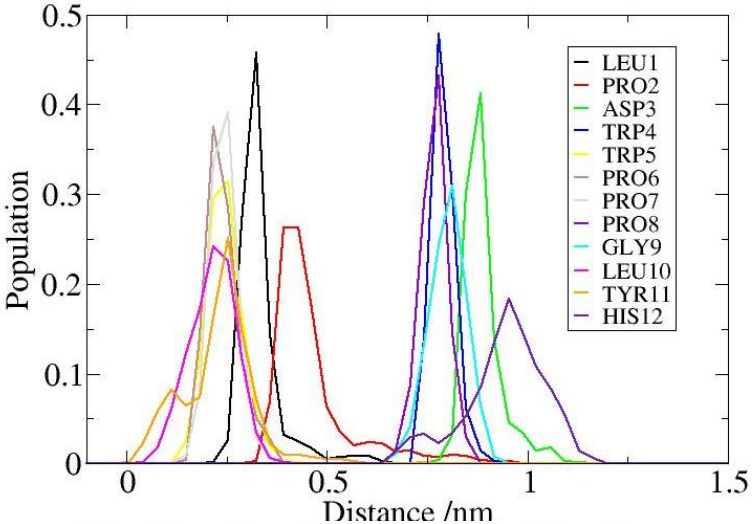


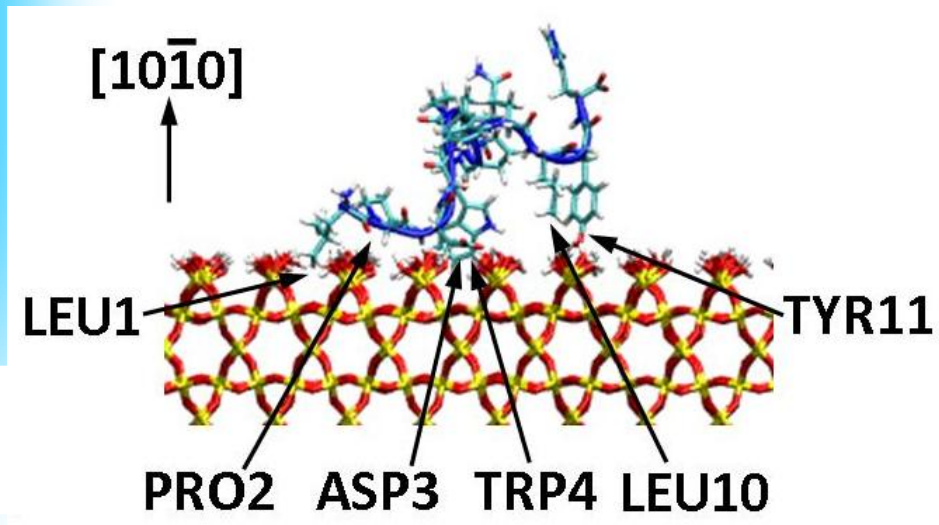
Binding pockets?

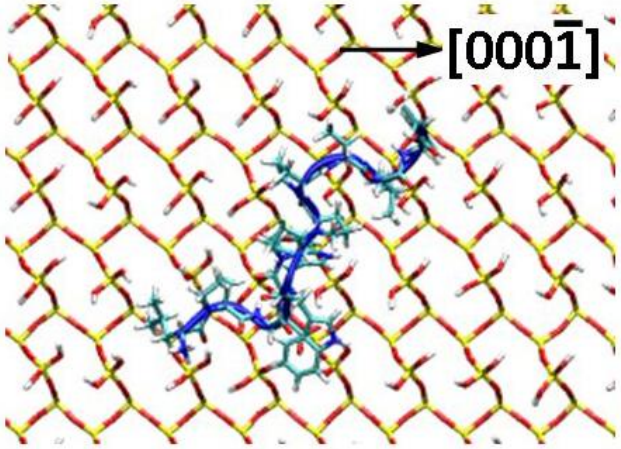


S2 on quartz (100) surface

- As with S1, pro binds directly to the surface.
- Leu and trp also bind.
- Trp binds either flat or perpendicular to the surface.

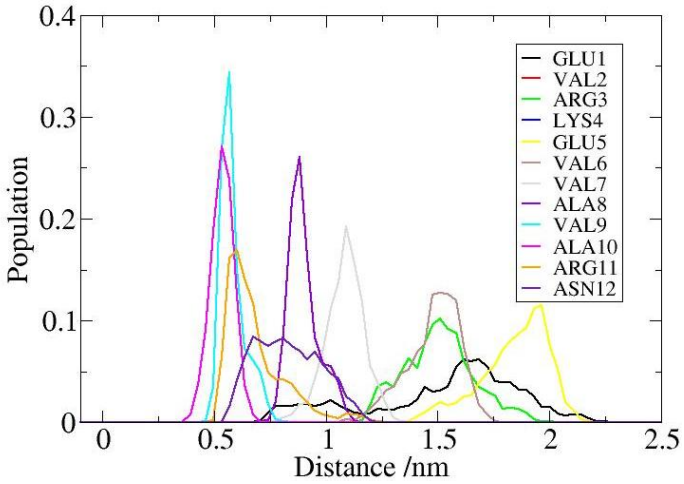


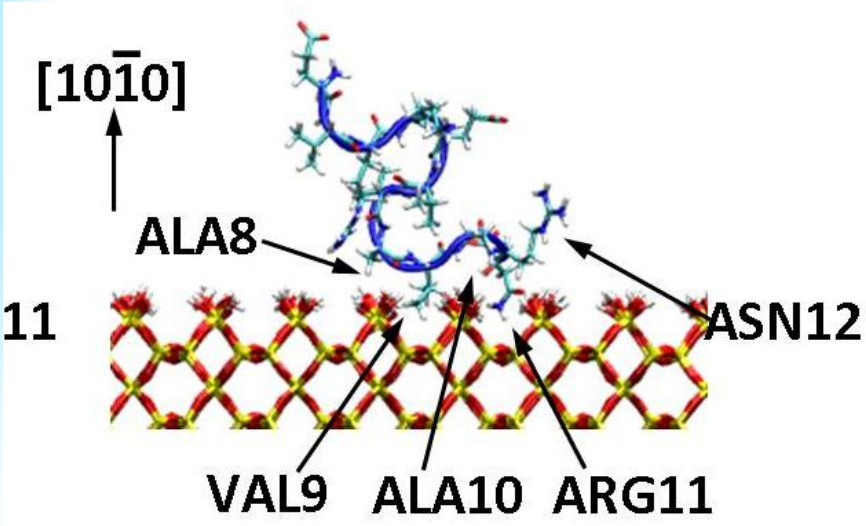


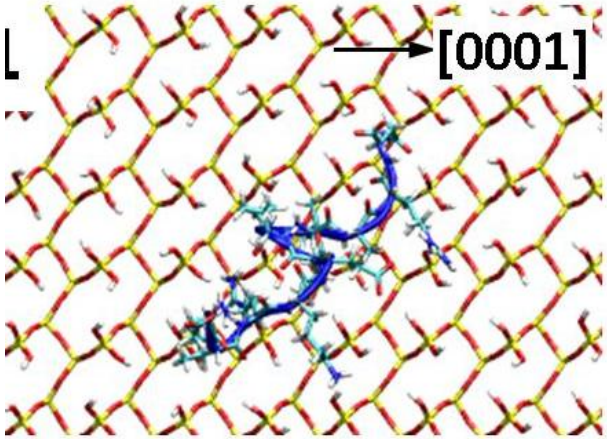


W1 on quartz (100) surface

- W1 is bound *via* ala and val (nonpolar, neutral) and arg (basic).
- Fewer residues interact with the surface *c.f.* strong binders (lower surface coverage.



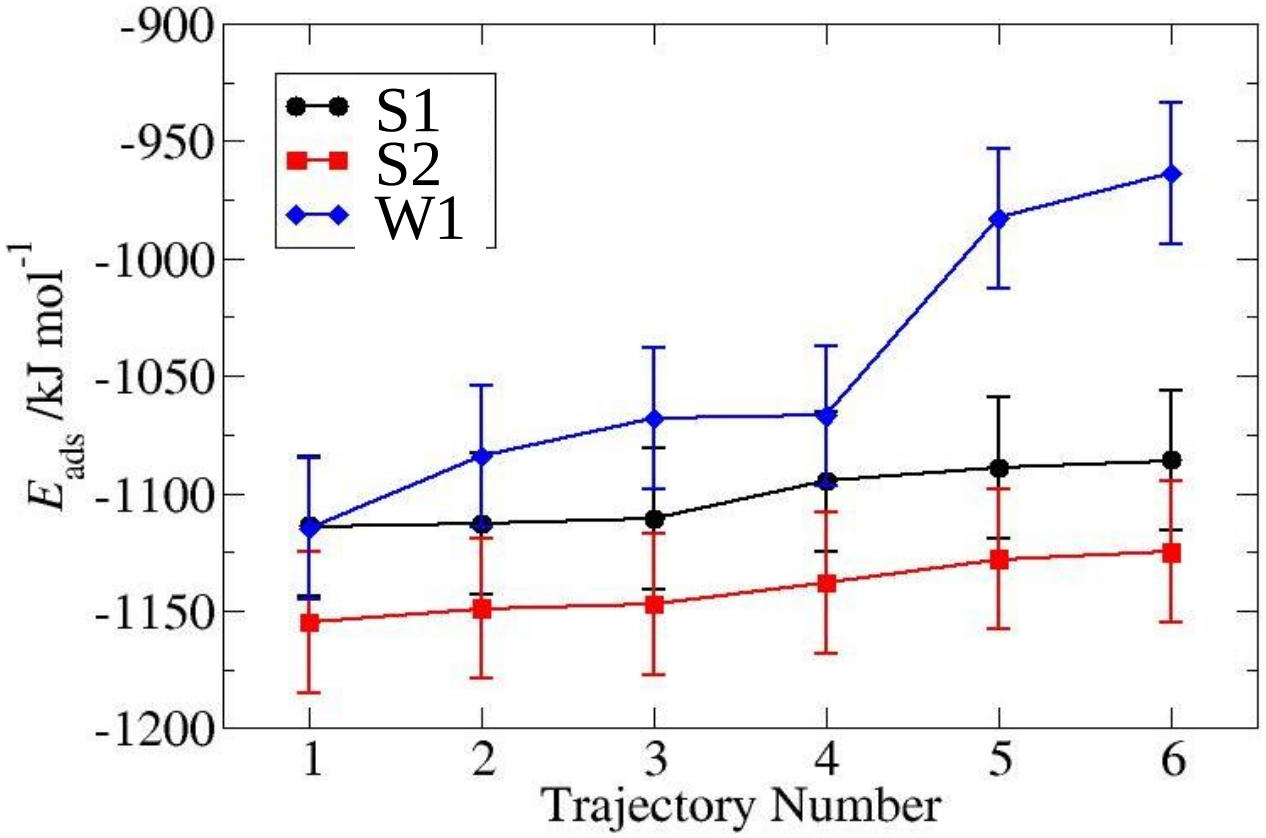




Summary of interacting residues

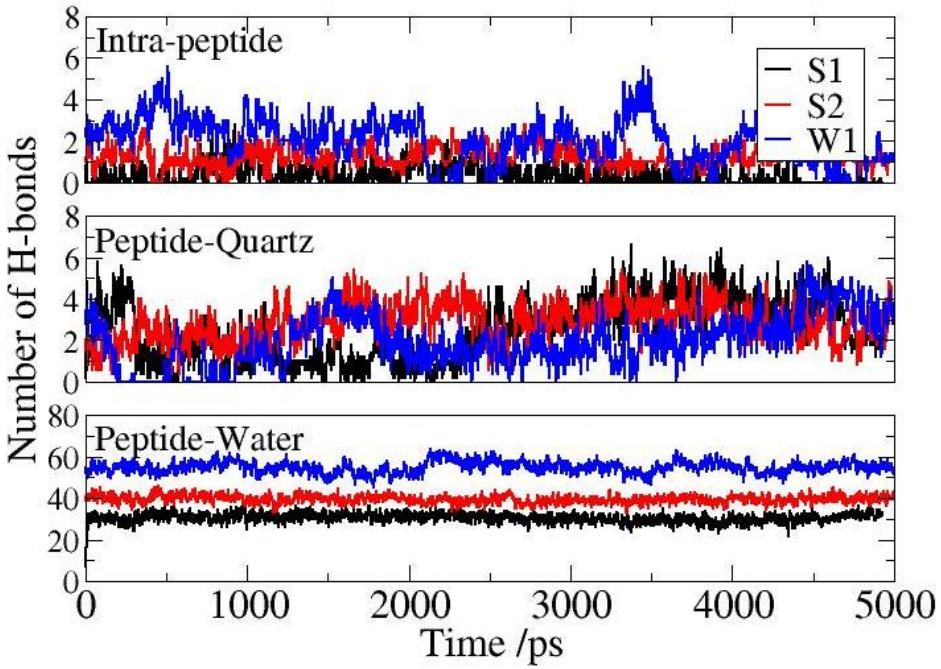
Peptide	Contact Point Residues
S1	PPPWLPYMPPWS
	PPPWLPYMPPWS
	PPPWLPYMPPWS
	PPPWLPYMPPWS
	PPPWLPYMPPWS
S2	LPDWWPPPQLYH
	LPDWWPPPQLYH
	LPDWWPPPQLYH
	LPDWWPPPQLYH
	LPDWWPPPQLYH
W1	EVRKEVVAVARN
	EVRKEVVAVARN
	EVRKEVVAVARN
	EVRKEVVAVARN
	EVRKEVVAVARN

Adsorption Energies



Hydrogen bonding

- Strong binders form hydrogen bonds with the quartz surface.
- Weak binders h-bond to the surface at the expense of intramolecular h-bonds.



Summary

- Adsorption of small hydrophobic moieties is favourable.
- Hydrogen bond formation may be a key driving force for interactions of biomolecules with quartz surfaces.
- The relative stability of a peptide in solution compared to the interface is likely to be a contributing factor.
- Proline is a key residue:
  - Plays a conformational role and binds directly to the surface.
- Our results support the idea that a peptide with a high binding affinity has many bound configurations.

- Current/future work:
  - Effects of mutating key residues on the binding free energy.

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