SNAPP: Unveiling the Inner Workings of a Class of Promising Antibacterial Polymers

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Next Pandemic - Antibiotic Resistance

BBC NEWS

Millions are dying from drug-resistant infections, global report says

By Philippa Roxby
Health reporter

20 January

More than 1.2 million people died worldwide in 2019 from infections caused by bacteria resistant to antibiotics, according to the largest study of the issue to date.

This is more than the annual death toll from malaria or Aids.

Antibiotics may no longer work because the bacteria they are intended to kill is becoming resistant

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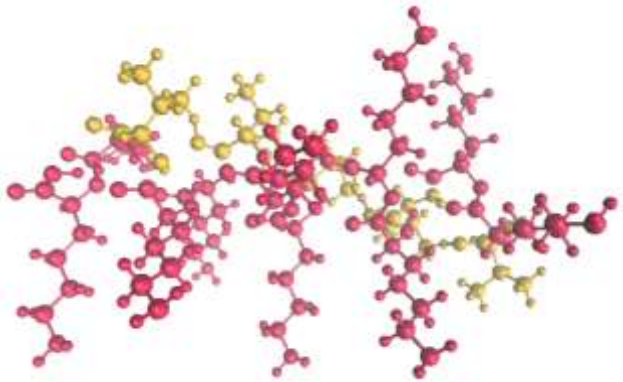
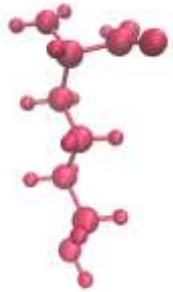
SNAPP – Structurally Nano Engineered Anti-Microbial Peptide Polymer



One arm
(KKVKKVKKVKKVKKV)

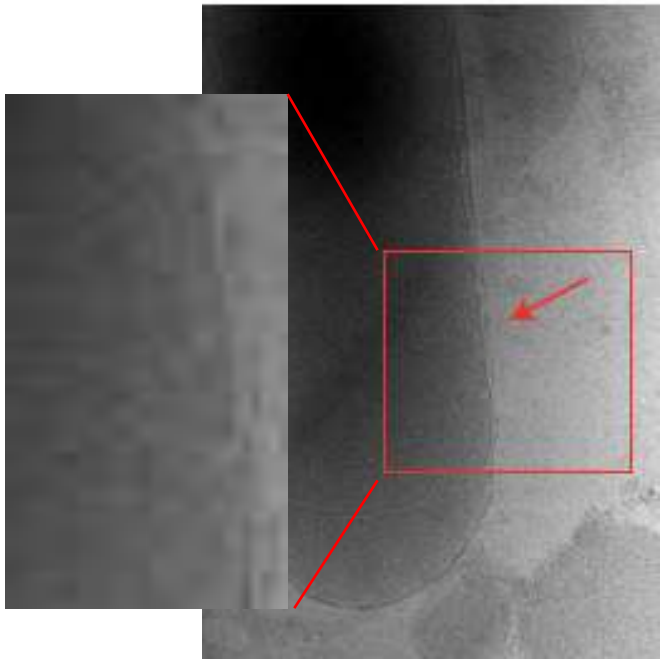


Lysine

Valine

2 : 1

Experimental Results

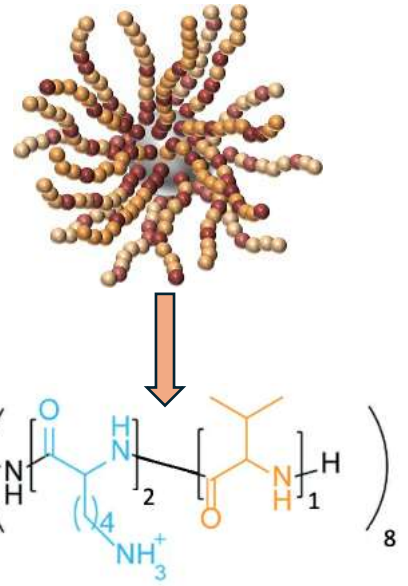


Cryo-TEM images of stripped cell walls and membranes of E-coli

Lam S.J. et.al, Nature Microbiology, 2016

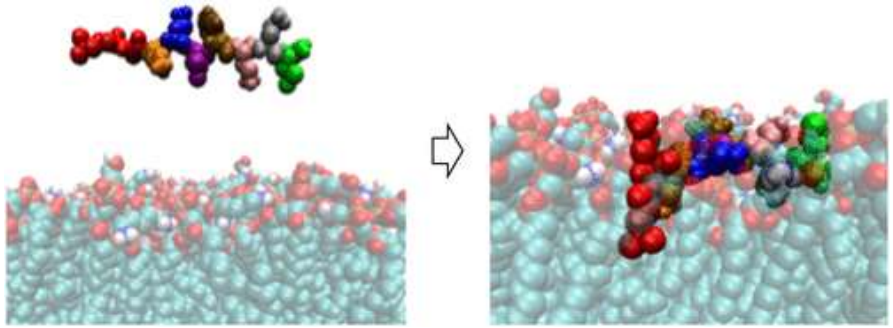
Why is SNAPP superior ?

- Stable unimolecular architectures up to infinite dilution
- Exhibit superior antibacterial activity against a range of clinically important Gram-negative and Gram-positive bacteria, including ESKAPE and colistin-resistant and MDR (CMDR) pathogens
- Low toxicity towards mammalian cells
- No resistant to SNAPPs in CMDR bacteria
- Destruct cell membranes and cell walls
- Low cost and effective antimicrobial agent

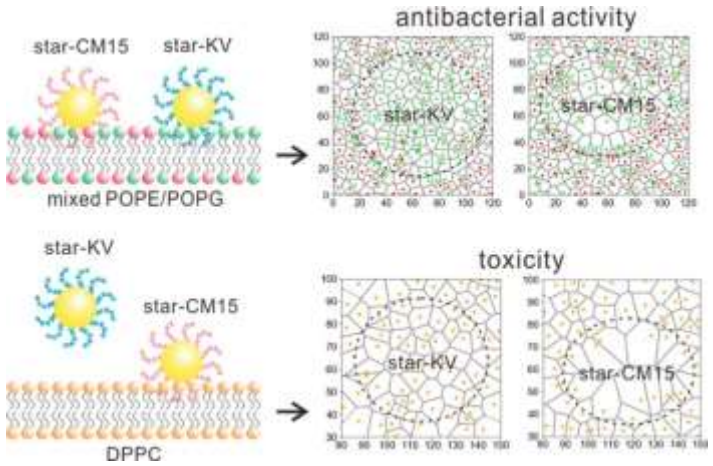


Molecular dynamics and Anti-Microbial Peptides

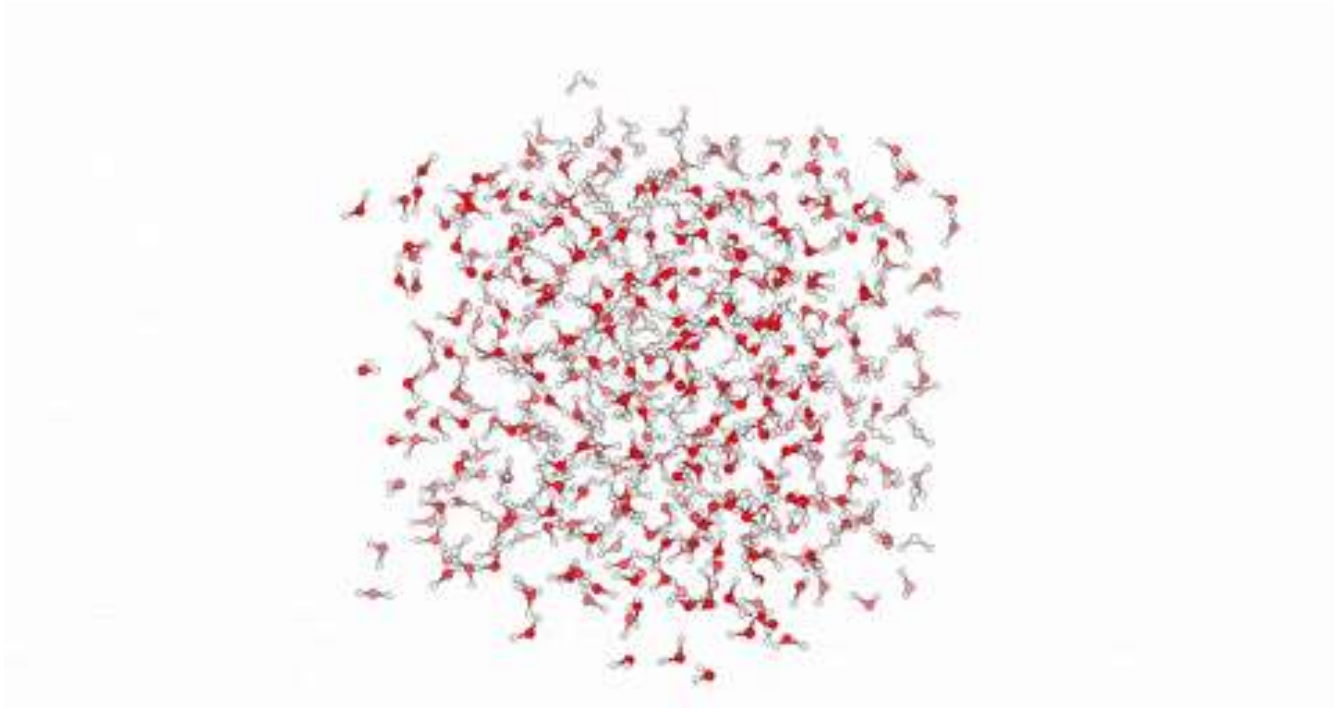
Chakraborty. A, et.al, ACS Omega, 2021



Yunhan Zhang, et.al, LANGMUIR, 2018



What is Molecular Dynamics ?



We follow the laws of classical mechanics, most notably Newton's law:

$$F_i = m_i a_i$$

$$a_i = d^2 r_i / dt^2$$

Power of computational tools

Reduce trial and error time in a lab setting

Once a model is created and validated, that model can be used to rerun repeatedly to collect data

This data can be used to train an AI algorithm, which can be used to identify complex patterns in the output data that can not be identified by human eye

Can create models and peptide sequences that cannot be controlled in an experimental setting

Mechanism of SNAPP – Computational Atomistic Study

Computational Models

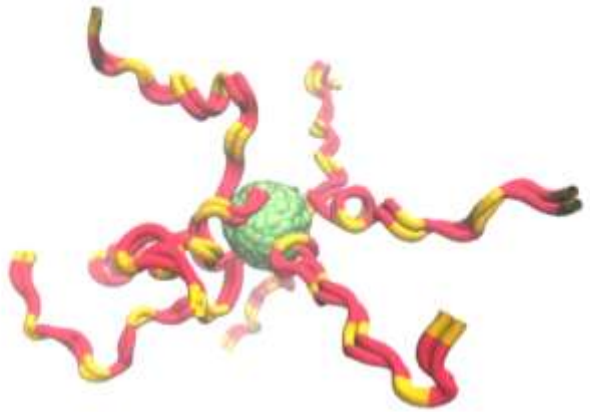
Alternating block SNAPP

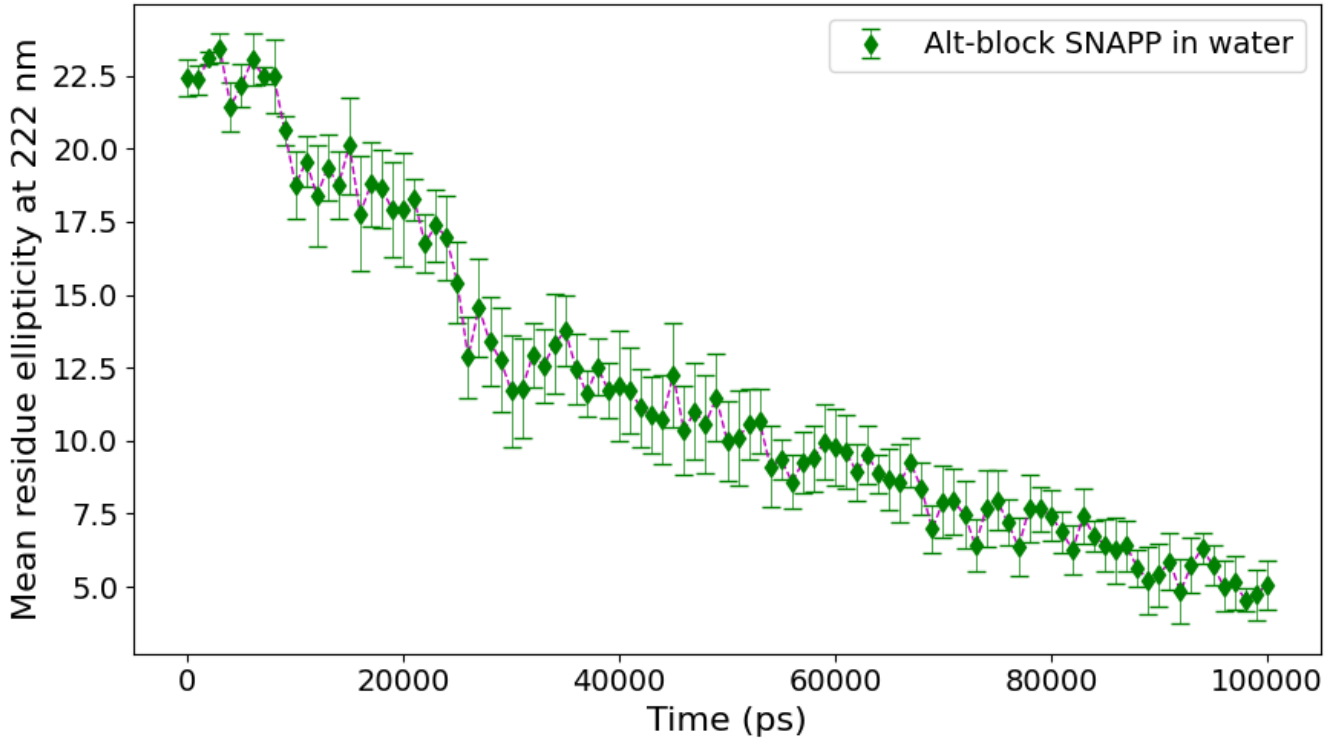
KKVKKVKKVKKVKKV

Verifying the computational SNAPP model via secondary structure analysis

	Hydrophilic environment	Hydrophobic environment
Experimental studies	Random Coil Shu J lam, Nature Microbiology, 2016, Steven Shirbin, Adv. Healthcare Materials, 2018, Wenyi Li, ACS, Applied Materials and Interfaces, 2022	Alpha Helix

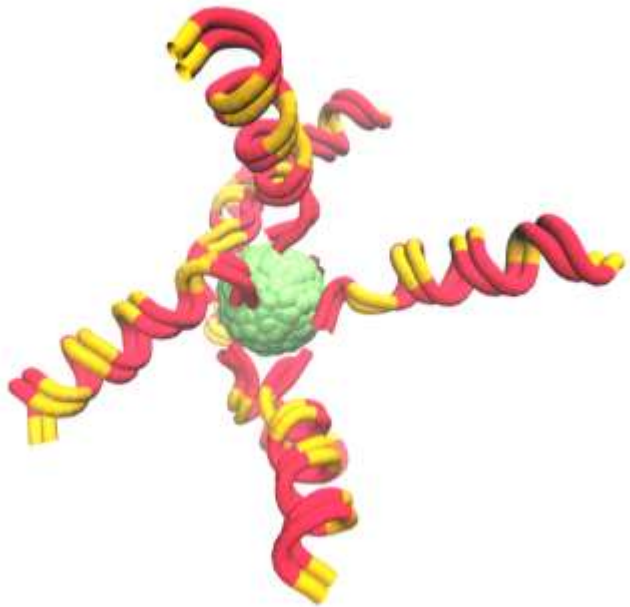
Secondary Structure - Alternating SNAPP in water

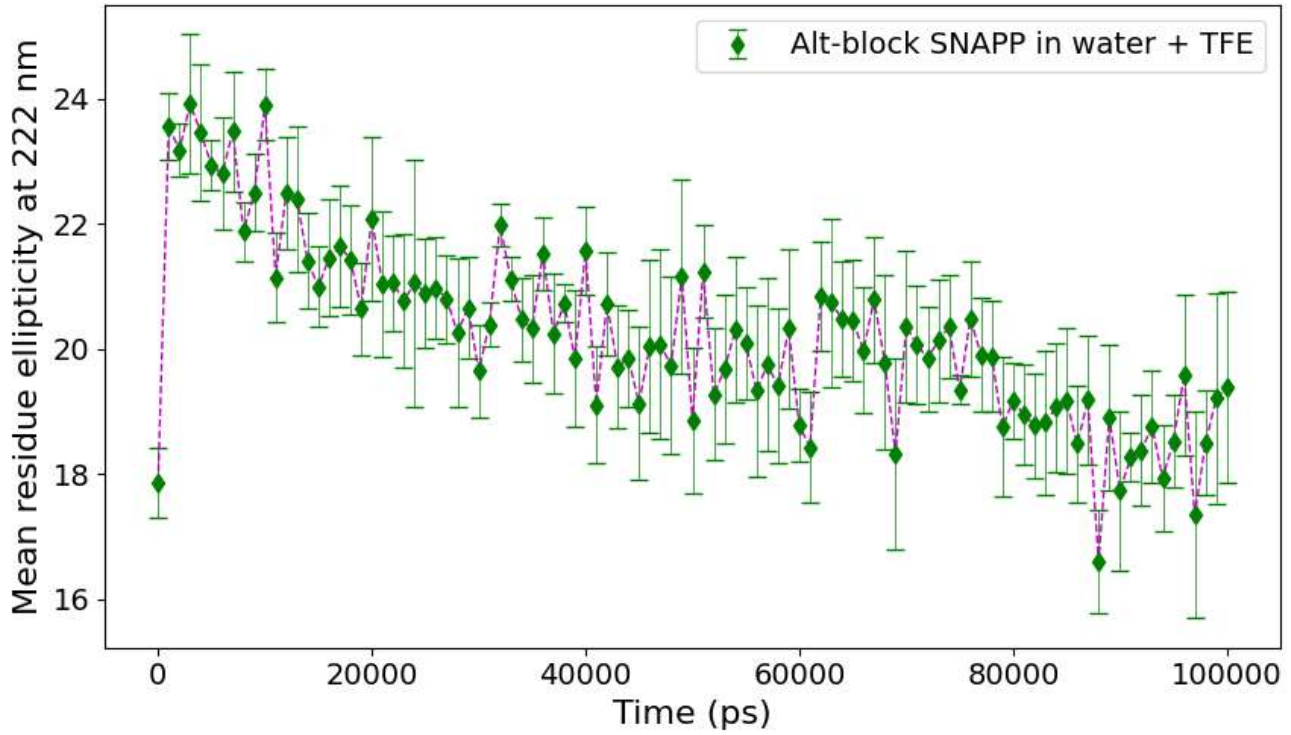




Mean residue ellipticity of alt-block SNAPP in water

Secondary Structure - Alternating SNAPP in water + TFE





Mean residue ellipticity of alt-block SNAPP in water and TFE

Mechanism of membrane disruption

Experimental data – (Lam, Shu Jie, (2016), *Structurally Nanoengineered Peptide Polymers for Combating Multidrug-Resistant Bacteria,* [PhD], The University of Melbourne)

	MDC (minimum polymer concentration that causes membrane destruction in all cells)
Alternating block SNAPP	0.8 +/- 0.1
Di-block SNAPP	17.3 +/- 1.3

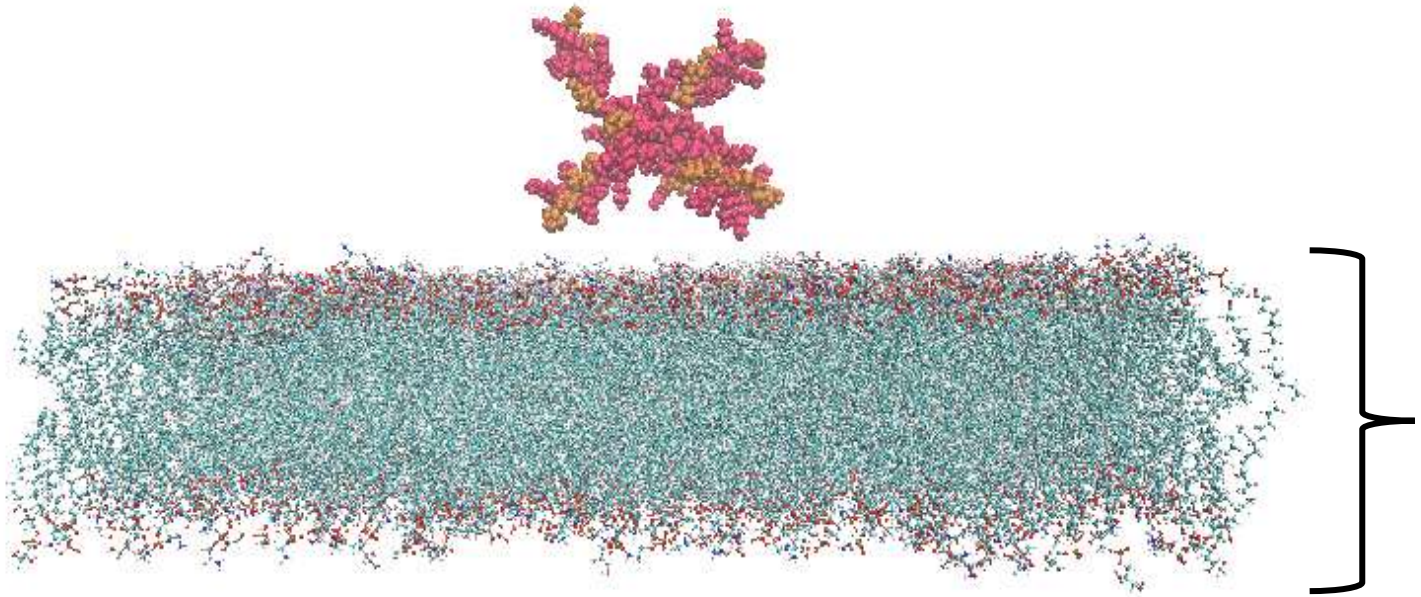
Alternating block SNAPP

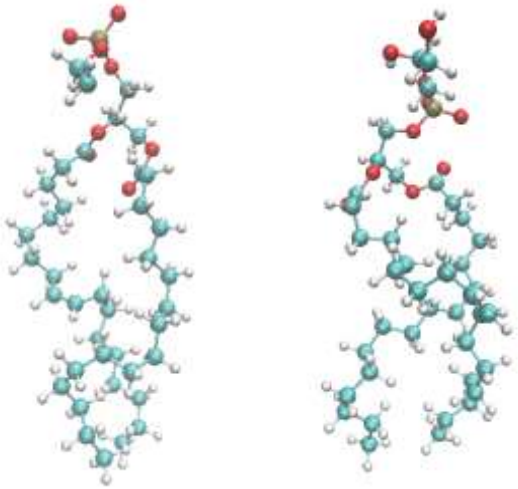
KKVKKVKKVKKVKKV

Di-block SNAPP

KKKKKKKKKKVVVVV

Alternating block SNAPP interaction with bilipid





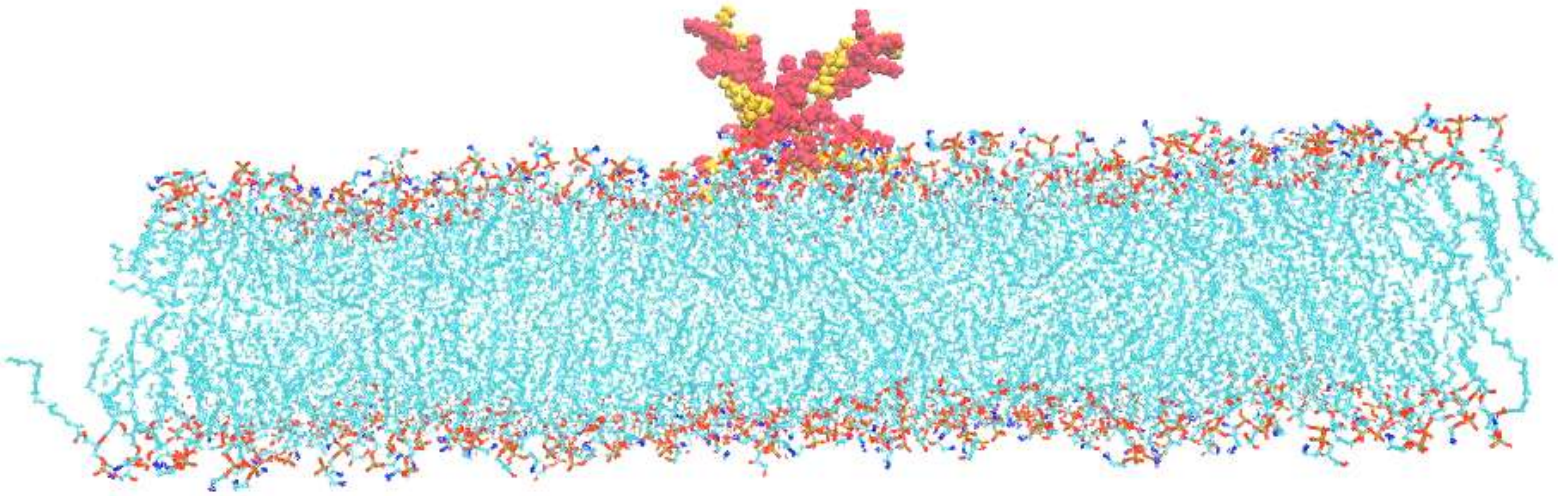
POPE: 1-Palmitoyl-2-oleoyl-sn-glycero-3 phosphatidylethanolamine

POPG: 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylglycerol

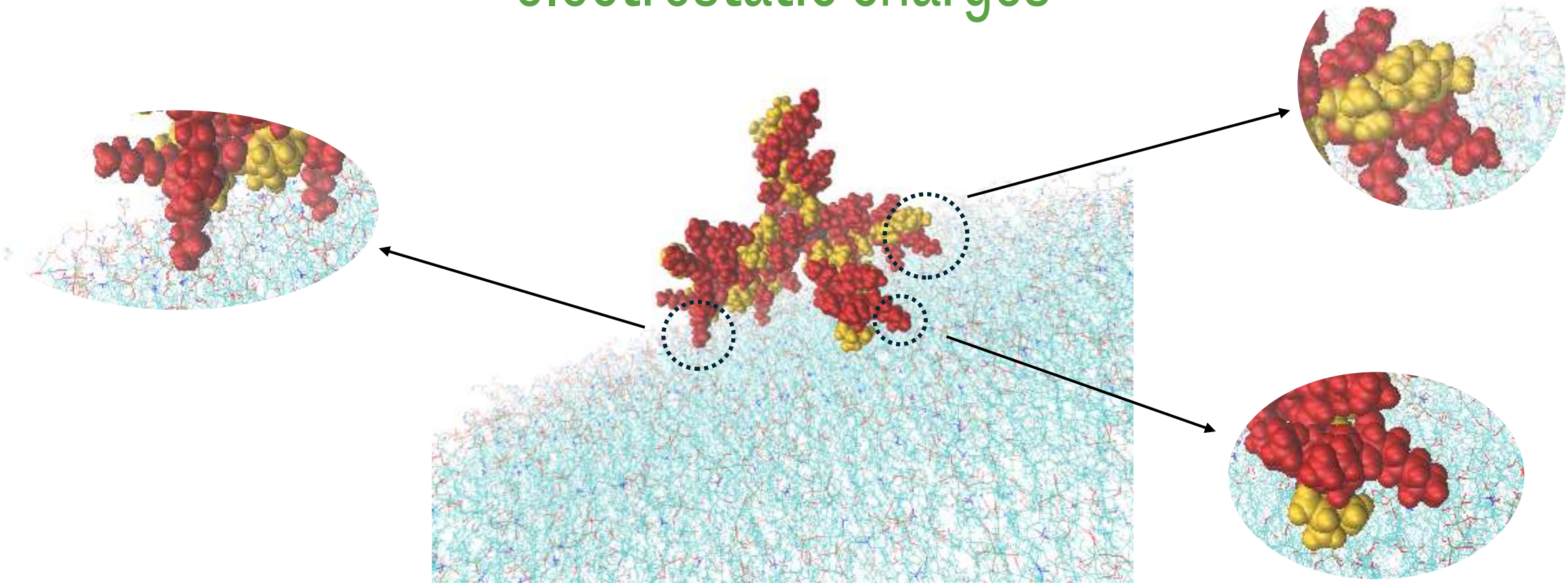
POPE : POPG

4 : 1

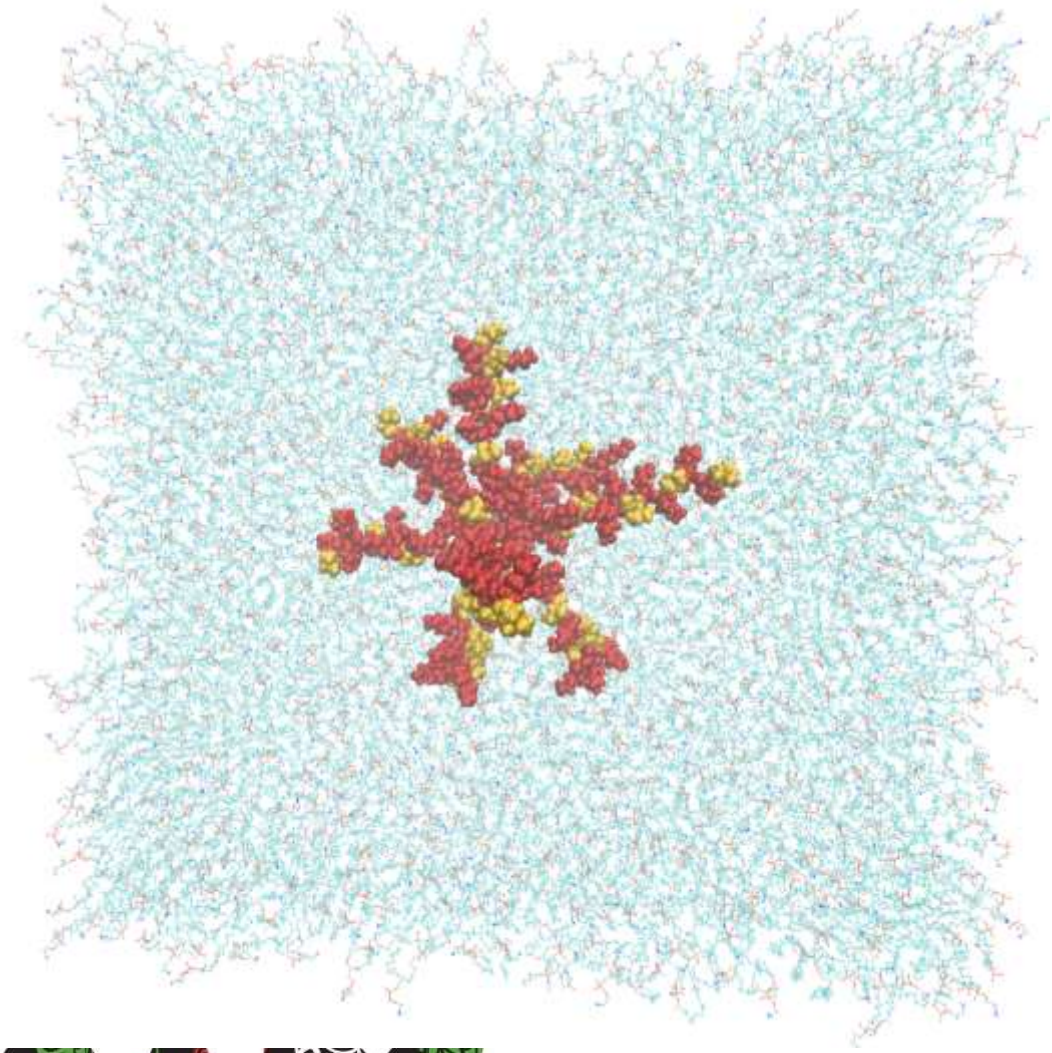
Alternating block SNAPP interaction with bilipid

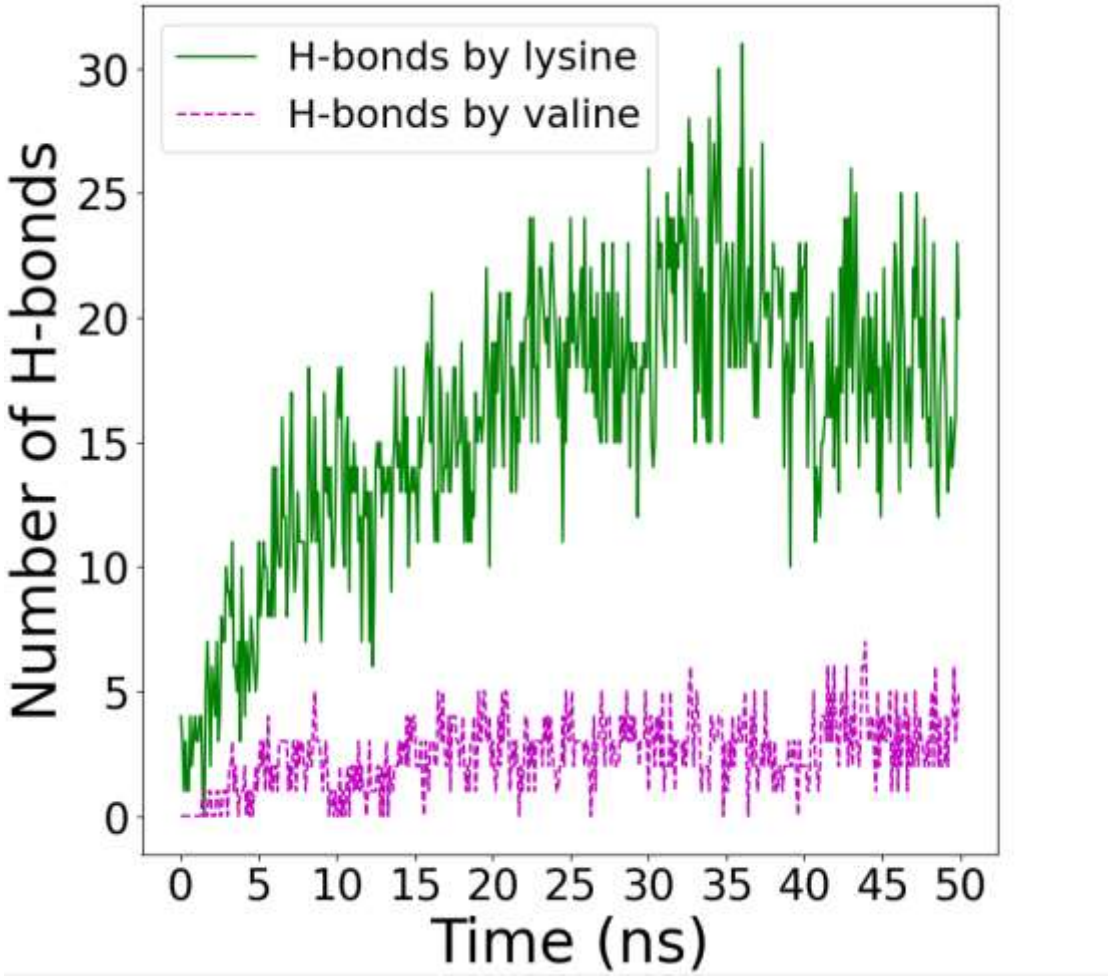


Step 1 – Initial binding of SNAPP into the bilayer via electrostatic charges

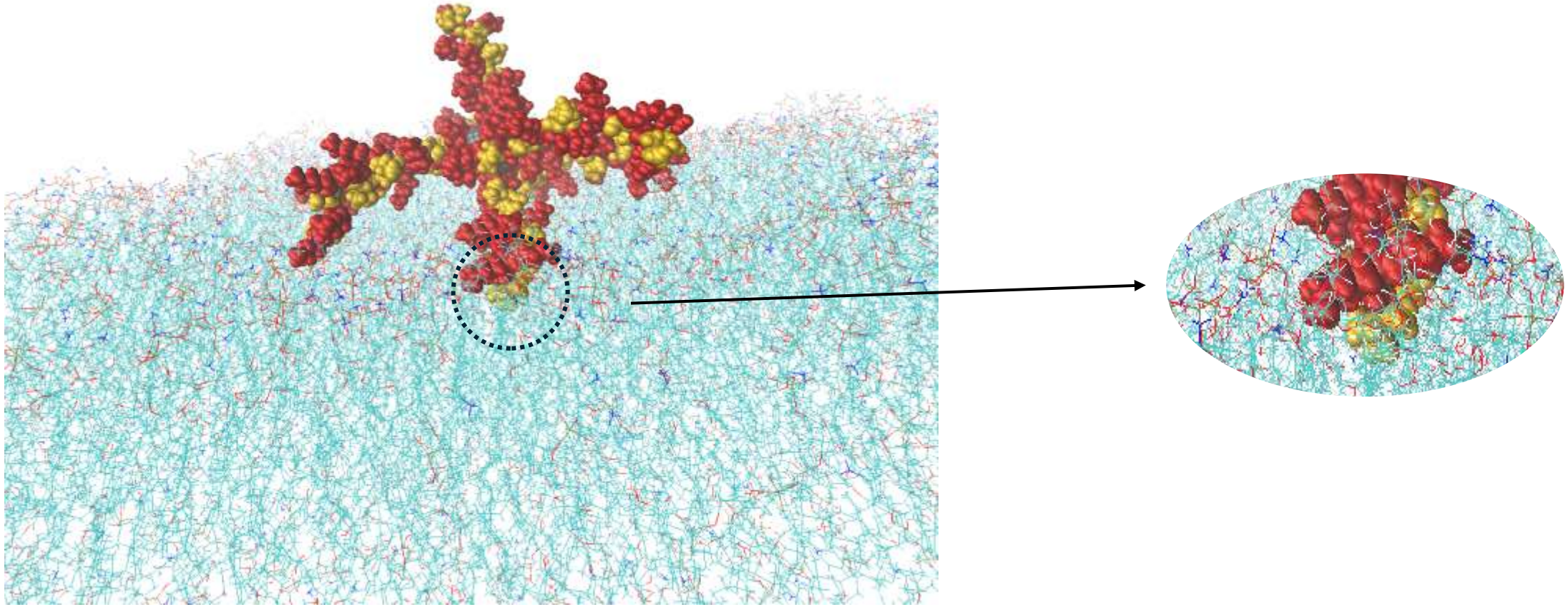


Step 2 – Widening SNAPP arms

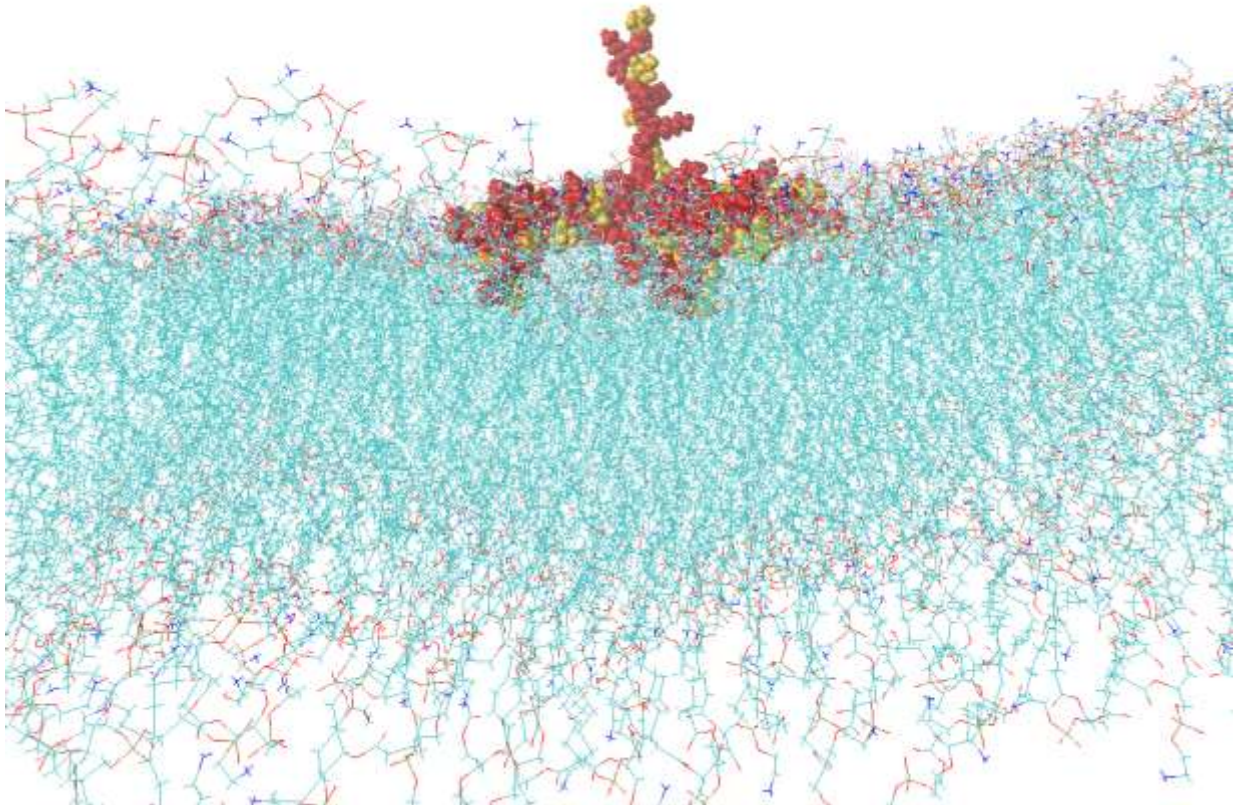




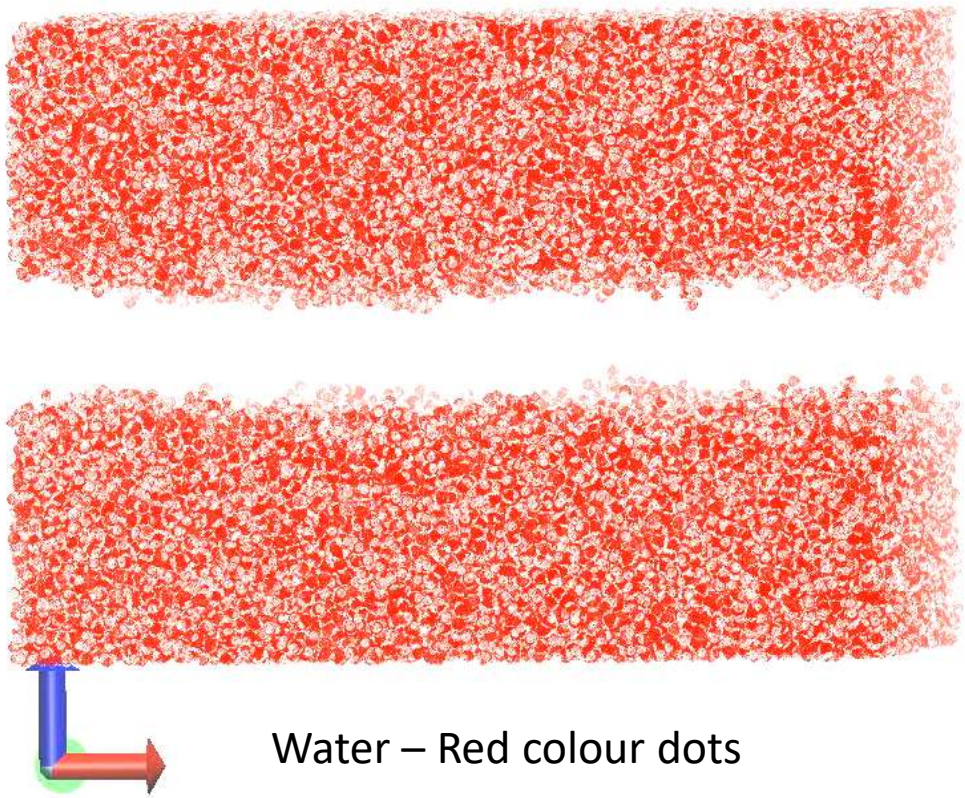
Step 3 – Hydrophobic – Hydrophobic interaction of Valine and lipid tails



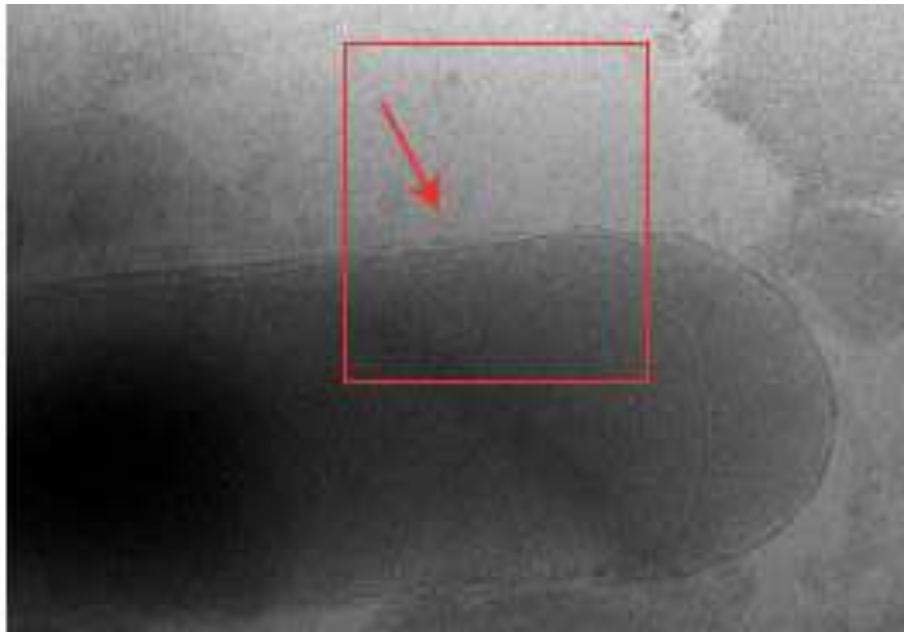
Step 4 – SNAPP emersed into the bilipid layer



Step 5 – Water enters the bilipid



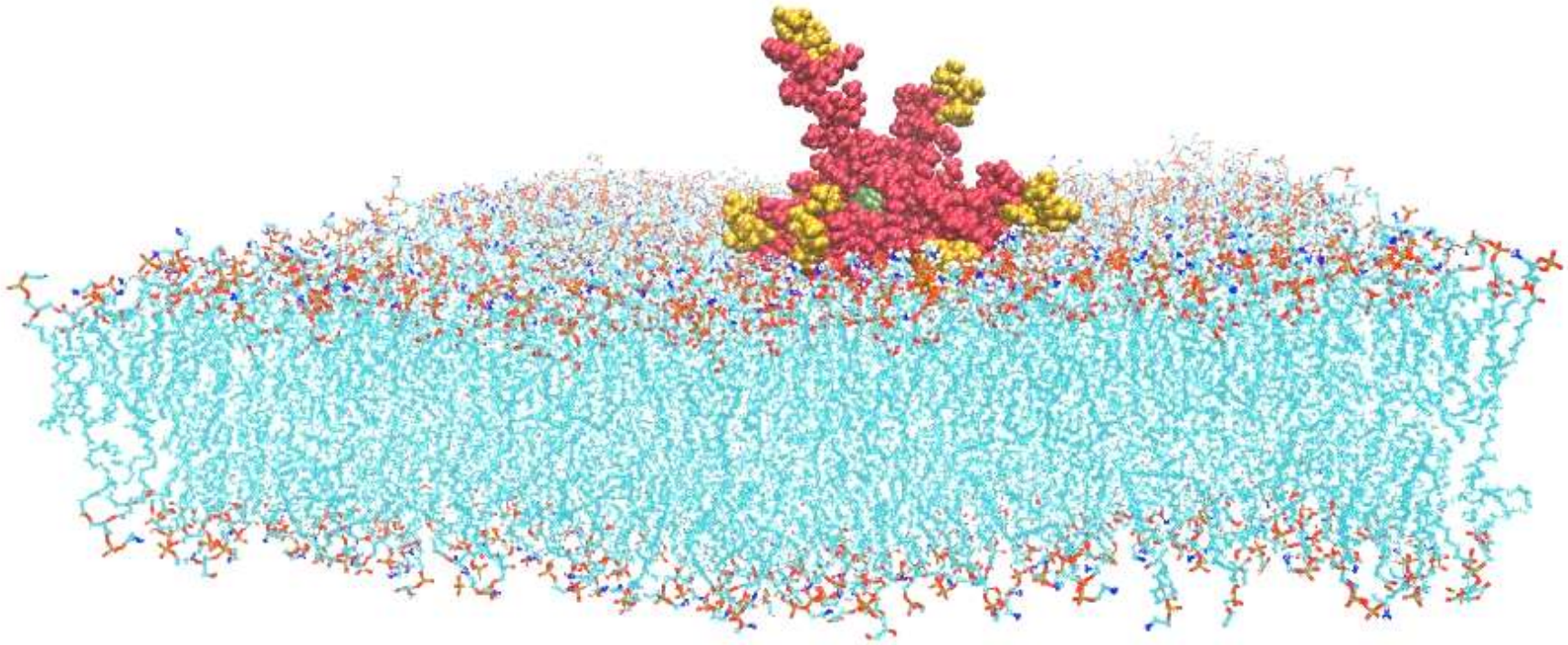
Water – Red colour dots



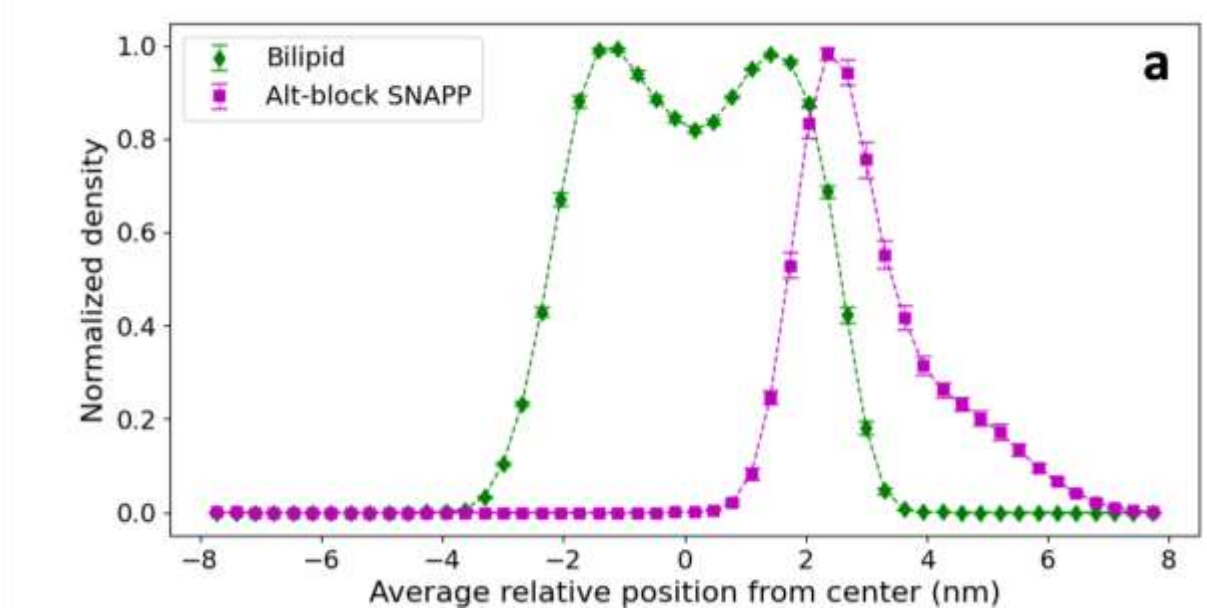
Cryo-TEM images of stripped cell walls and membranes of E-coli

Lam S.J. et.al, Nature Microbiology, 2016

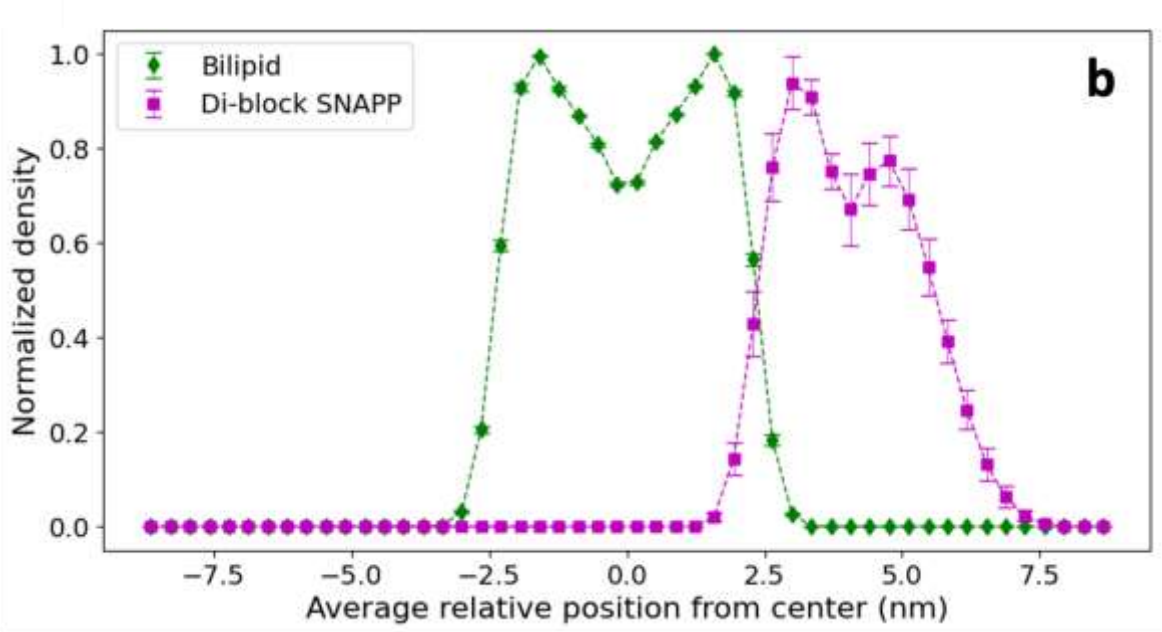
Di-block SNAPP interaction with bilipid



Alt block and Di-block SNAPPs comparison
Partial density Analysis

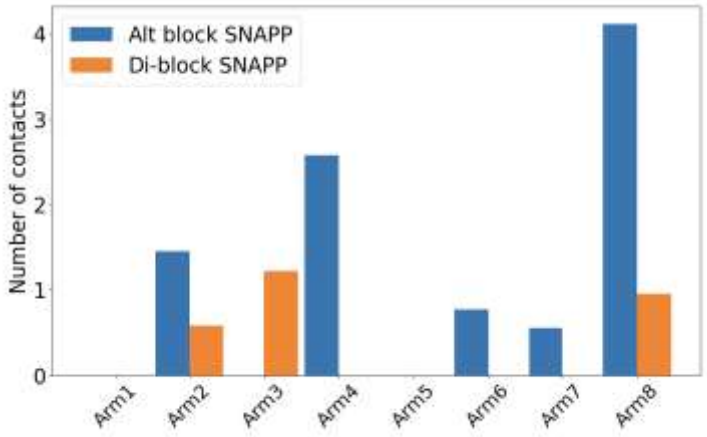


Partial density distribution of alt-block SNAPP with bilipid

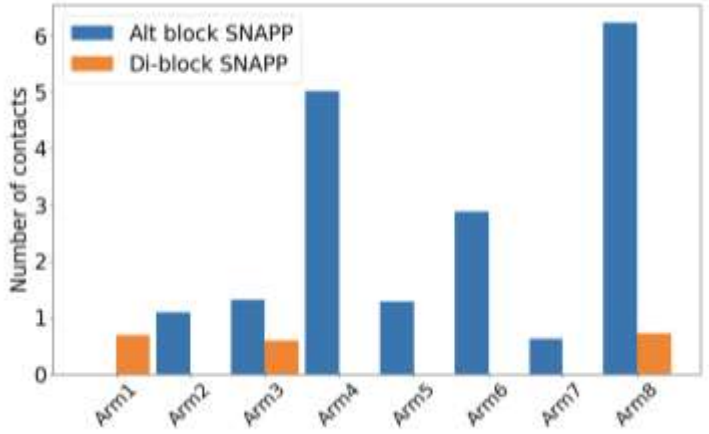


Partial density distribution of di-block SNAPP with bilipid

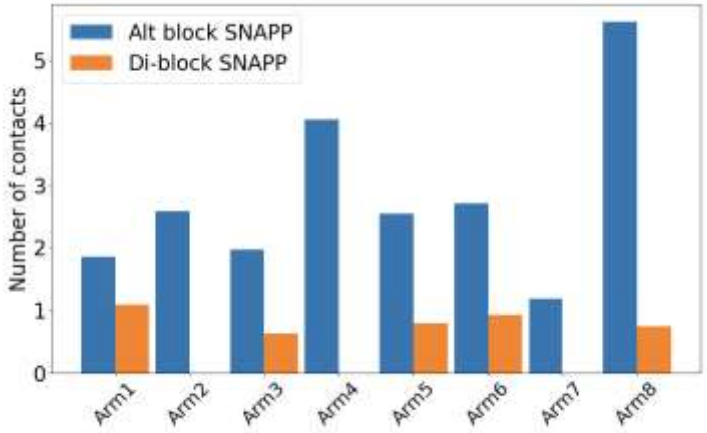
Alt block and Di-block SNAPPs comparison
Contact Analysis



0-10 ns

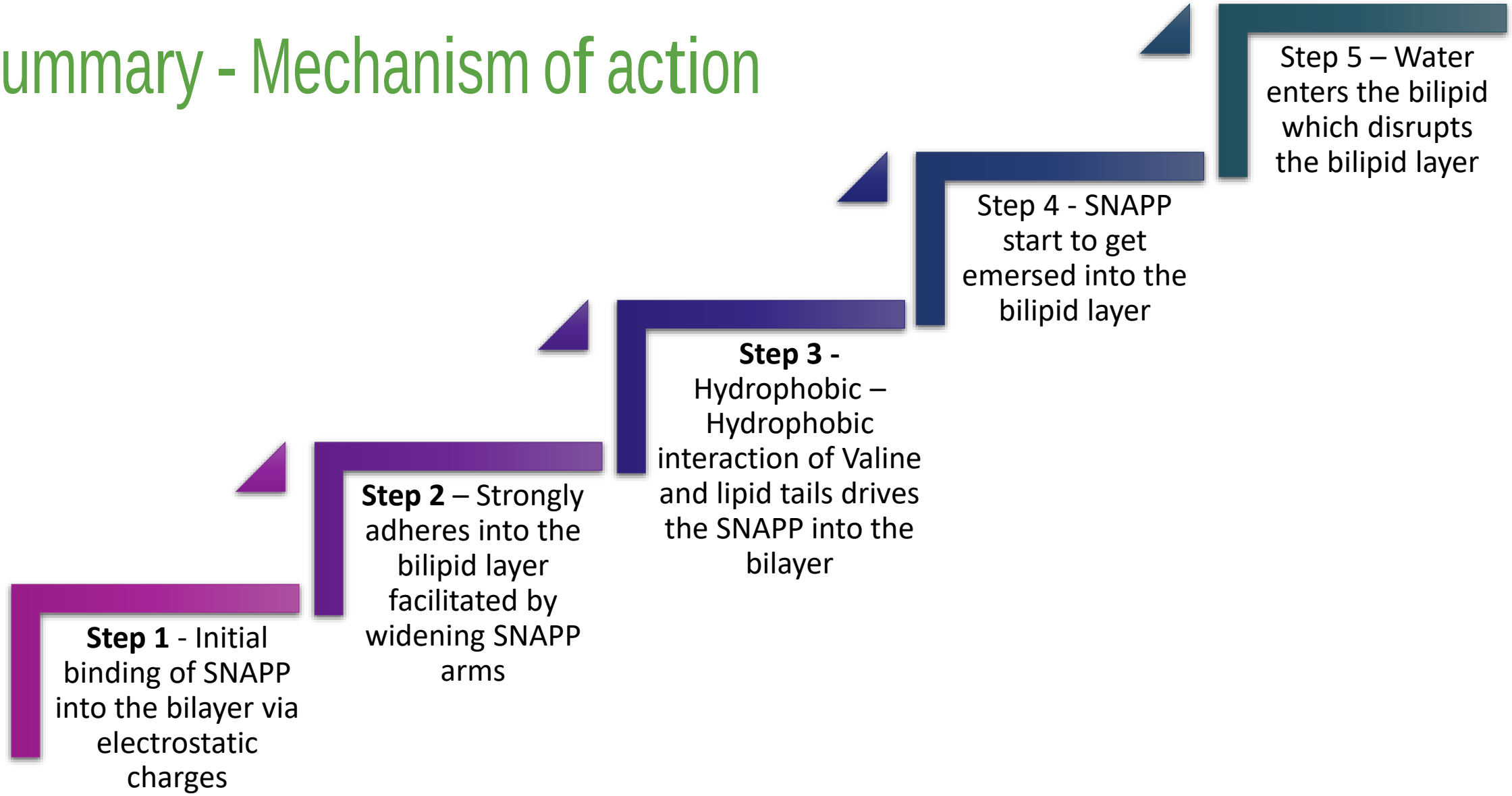


10-25 ns



25-50 ns

Summary - Mechanism of action



Acknowledgement

My PhD supervisors –

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Members of the Soft Matter Informatics Research Group
Members of the Polymer Science Group


Any Questions