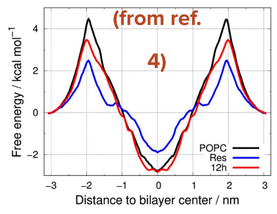
Umbrella sampling simulations of membrane PAINS

Pedro R. Magalhães, Pedro Reis, Diogo Vila-Viçosa, Miguel Machuqueiro, Bruno L. Victor ✉prmagalhaes@fc.ul.pt
BioISI: Biosystems and Integrative Sciences Institute; Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

PAINS · Pan assay interference compounds are molecules that show activity in multiple types of assays by interfering with the assay readout rather than through specific compound/target interactions.[1,2] **Membrane PAINS** are compounds that interact directly and nonspecifically with lipid membranes, promoting changes in their biophysical properties and affecting the function of mechanosensitive membrane proteins.[3]

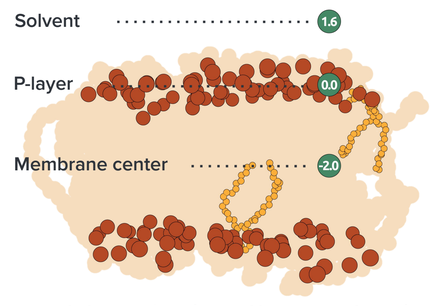
Membrane PAINS will shift the potential of mean force (**PMF**) profile of a bilayer as shown in previous coarse grained study,[3] which we adapted using an atomistic forcefield.[4] However, this atomistic approach was too computationally demanding and did not account for the inherent heterogeneity of a lipid bilayer.

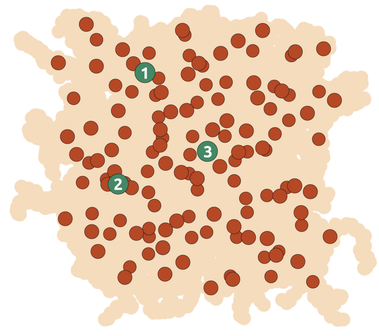


GOAL · Our goal is to establish a simple, fast and efficient computational protocol to accurately identify membrane PAINS. The first step in this process will be an extensive analysis of the control system (pure POPC).

SOFTWARE · GROMACS 2018.6[5] / GROMOS 54A7[6]

SETUP · We built a 128-POPC bilayer with a probe analogous to a benzene molecule.[4] The probe was placed in different positions relative to a P-layer (**0.0 nm**), from the solvent (**1.6 nm**) to the center of the membrane (**-2.0 nm**), spaced 0.1 nm.



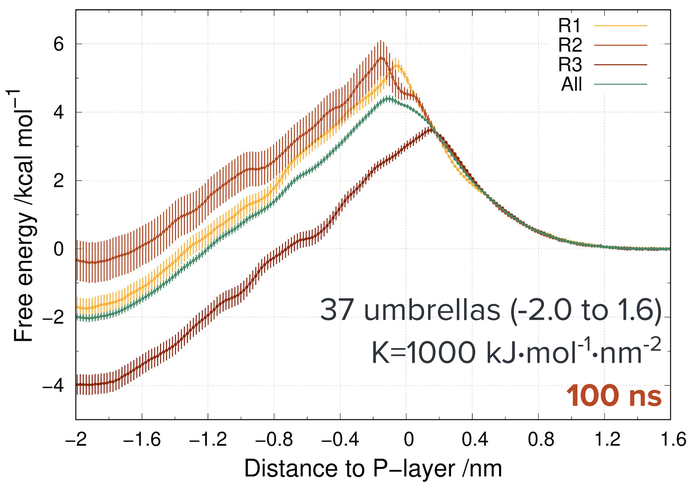


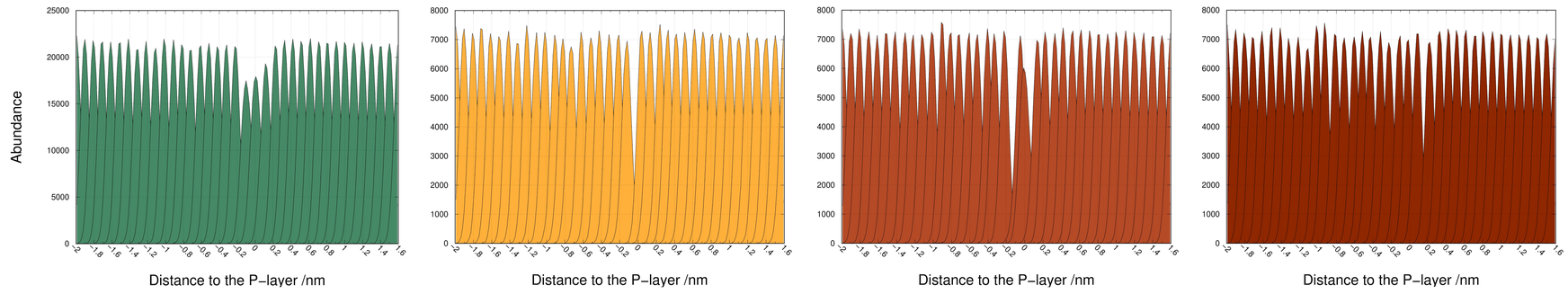
REPLICATES · were performed by placing the probe in different *xy* coordinates (*i.e.* in order to sample regions with different environments), *e.g.* probes **1**, **2** and **3**.

ANALYSIS · PMF profiles were calculated using the weighted histogram analysis method (**WHAM**)[7] and the Bayesian histogram bootstrapping was performed using 50 iterations.

Results

#1

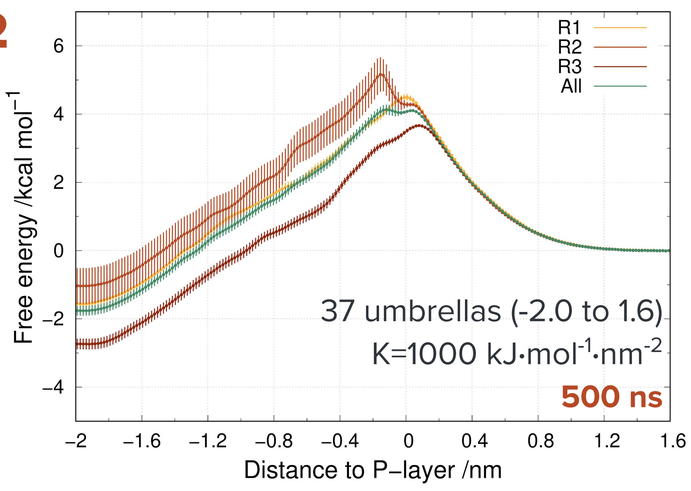


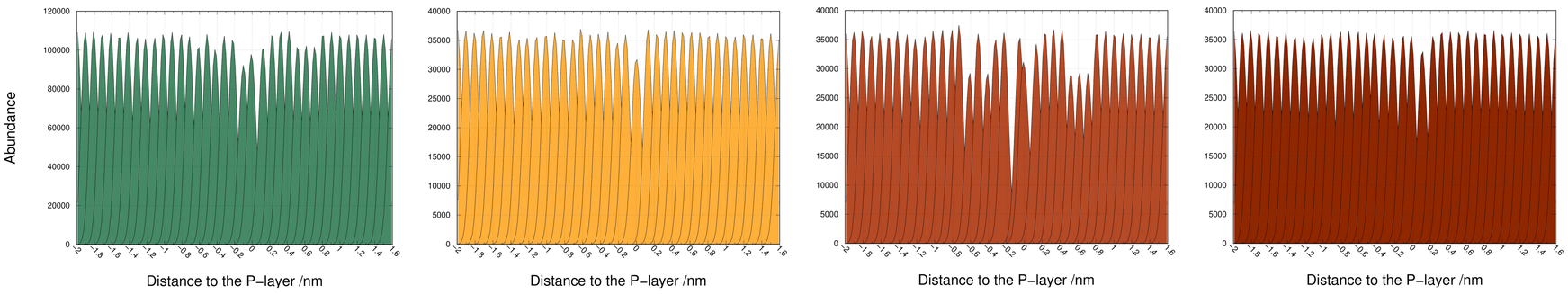


The different PMF profiles show the effect of membrane heterogeneity. The histograms show that the P-layer region may not be sampled properly with this combination of umbrellas/K.

What if we increase the sampling?

#2

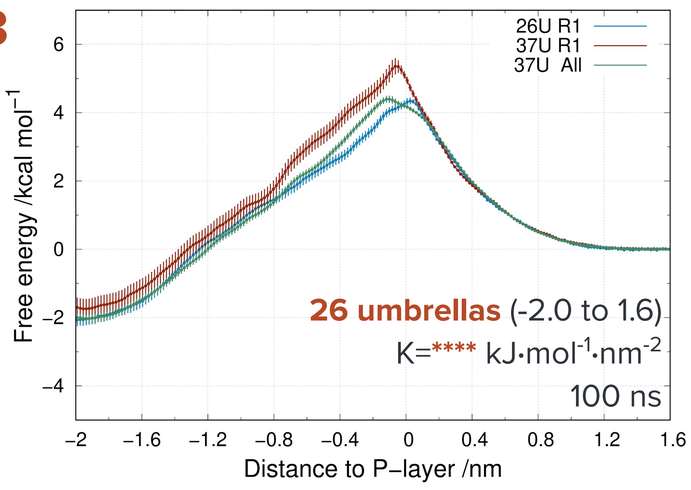


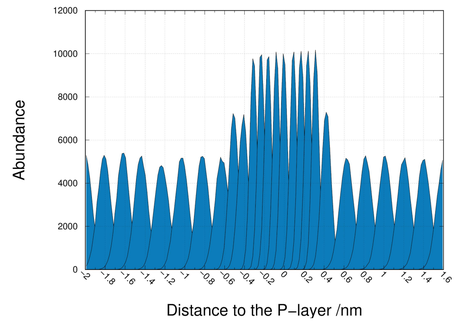


Increasing the simulation time helps the PMFs converge, but the lack of sampling in the P-layer region remains. The computational cost becomes prohibitive.

What if we adjust the number of umbrellas?

#3



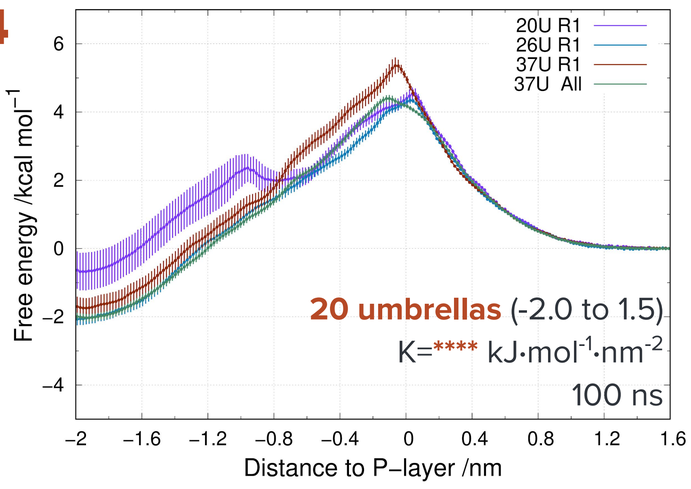


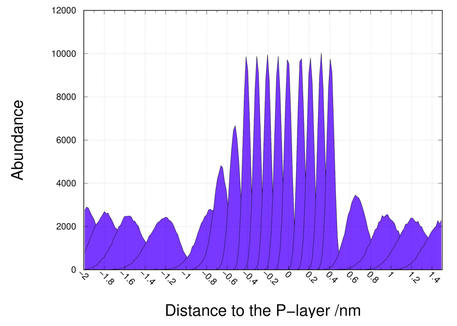
Umbrellas and K constants (K=500, 1000 or 2000)
-2.0, -1.8, -1.6, -1.4, -1.2, -1.0, -0.8, -0.6
-0.5, -0.4
-0.3, -0.225, -0.15, -0.075, 0.0, 0.075, 0.15, 0.225, 0.3
0.4
0.6, 0.8, 1.0, 1.2, 1.4, 1.6

Some issues persist in the region of interest, but the PMF profile looks very similar to the one with 37 umbrellas, at a reduced computational cost.

Can we further optimize this?

#4



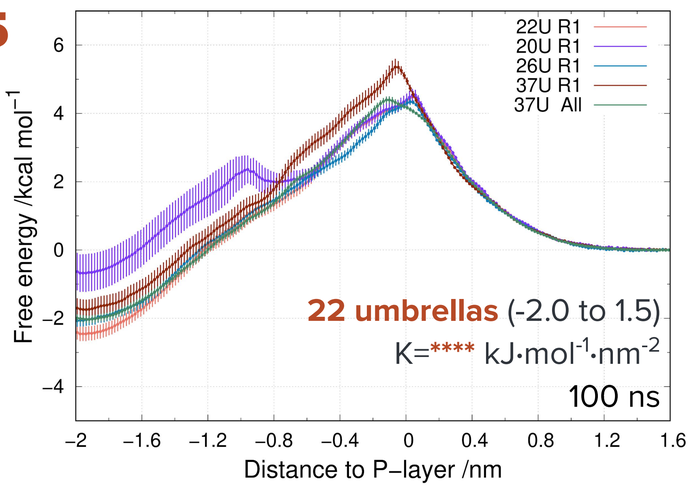


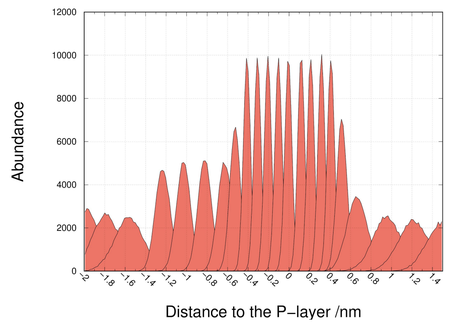
Umbrellas and K constants (K=100, 200, 500, 1000 or 2000)
-2.0, -1.7, -1.4, -1.1, -0.8
-0.65
-0.5
-0.4, -0.3, -0.2, -0.1, 0.0, 0.1, 0.2, 0.3, 0.4
0.6
0.9, 1.2, 1.5

Several regions (not just in the center of interest) now lack sampling, which greatly impacts the PMF profile.

Can we fix this by using umbrellas from previous runs to fill in the gaps?

#5





Umbrellas and K constants (K=100, 200, 500, 1000 or 2000)
-2.0, -1.7, -1.4
-1.2, -1.0, -0.8, -0.6
-0.5
-0.4, -0.3, -0.2, -0.1, 0.0, 0.1, 0.2, 0.3, 0.4
0.5
0.6
0.9, 1.2, 1.5

CONCLUSION · The number of umbrellas can be optimized. However, this is no substitute for replicates (or longer simulation times). We theorize that a **replica-exchange umbrella sampling** protocol should give us the best of both worlds (⬆ sampling of different bilayer regions & ⬇ computational cost). Now all we need is to implement it.

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR
Grants: PTDC/BIA-BFS/28419/2017, SFRH/BD/136226/2018, UID/MULTI/00612/2019, UID/Multi/04046/2019

Refs. 1 Nelson, K.M. *et al.* (2017) *JMC* 60:1620
2 Baell, J.B. *et al.* (2010) *JMC* 53:2719
3 Ingólfsson, H.I. *et al.* (2014) *ACSCB* 9:1788
4 Jesus, A.R. *et al.* (2017) *JMC* 60, 568
5 Abraham, M.J. *et al.* (2015) *S* 1:19
6 Schmid, N. *et al.* (2011) *EBJ* 40:843
7 Hub, J.S. *et al.* (2010) *JCTC* 6:3713