# Safe and Sustainable Chemistry by Design

# WORLD4BUSINESS – July 4, 2023

**Prof. Santiago Aparicio**
**Department of Chemistry and ICCRAM**
**University of Burgos - Spain**

World Project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement nº 873005

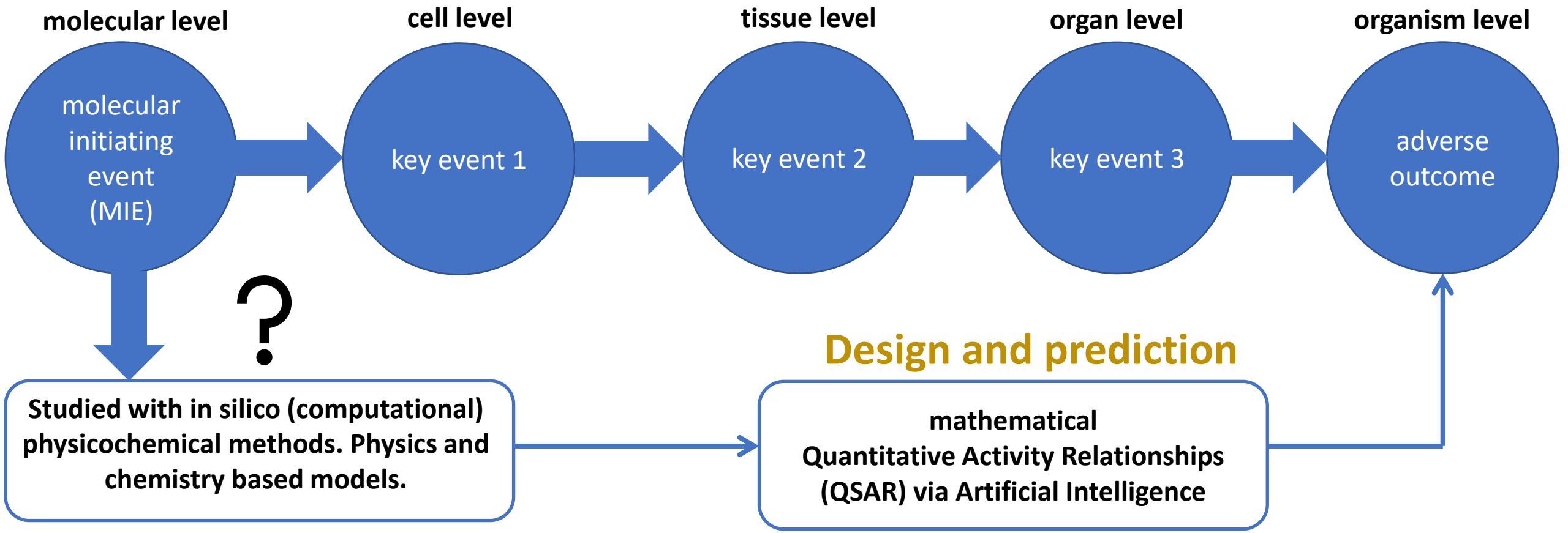
**Objectives:**

- Develop predictive methods and in silico tools for developing **Safe by Design** materials and chemicals (pure and multicomponent):

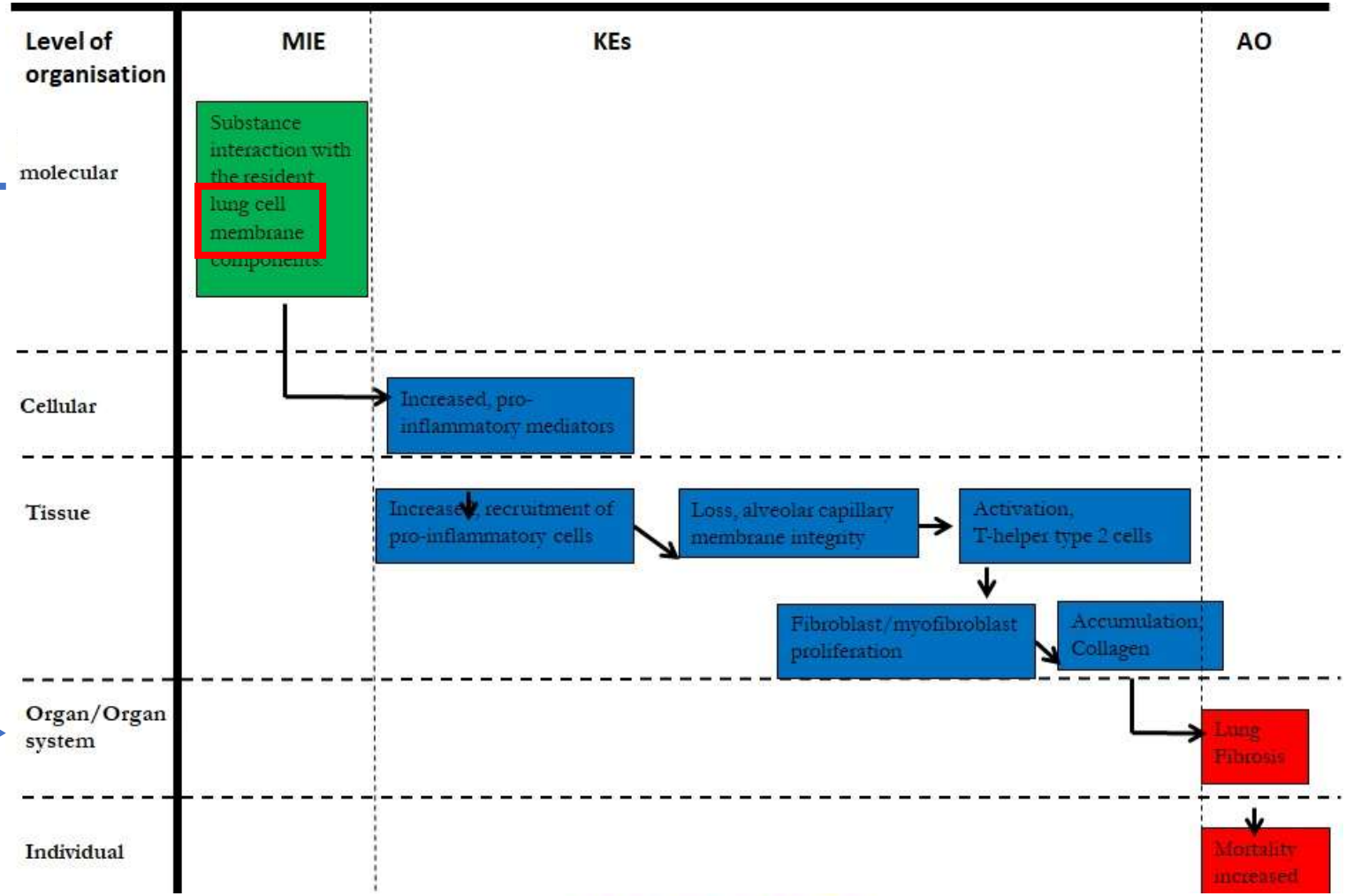
**How?**

- Understanding physicochemical properties of complex materials and chemicals and their relationship(s) with toxicity, safety and sustainability.
- Infer most relevant material and chemical molecular level descriptors.
- Understand interaction with relevant biosystems (plasma membranes).
- Develop mathematical simple predictive methods (QSAR – based and Artificial Intelligence approaches).

# Adverse Outcome Pathway (AOP) concept



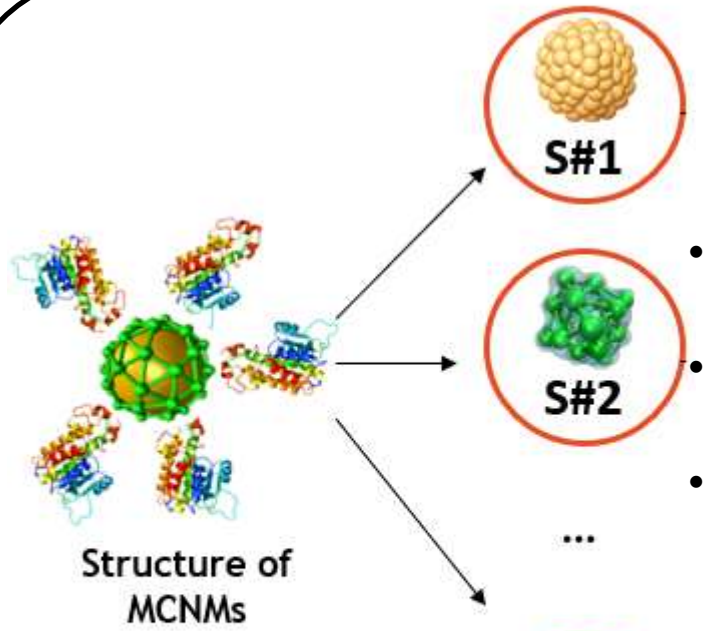
# Interaction of materials and chemicals with cell (plasma) membranes and key proteins as a key MIE



# CASE STUDIES

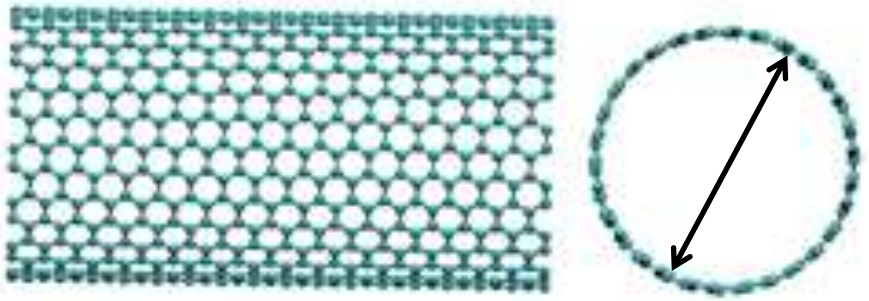
- **1.** Multicomponent nanomaterials (MCNMs). DIAGONAL HORIZON-2020 Project.
- **2.** High Aspect Ratio Nanomaterials (single and multiwalled nanotubes). DIAGONAL HORIZON-2020 Project.
- **3.** Deep Eutectic Solvents. DESforPFAS and NADESforNATURE projects.

## Properties and toxicological effects of a MCNM?




- Nature of the biological target
- Nanomaterial composition
- Interactions (additive, synergistic, antagonistic)

## Properties and toxicological effects of a HARN?




**Length to diameter ratio on properties and interaction with biological targets**

# Model membranes

**Nanomaterials exposure routes**

- respiratory (lung model membranes)
- dermal (epidermal model membrane)
- digestive (intestine model membrane)

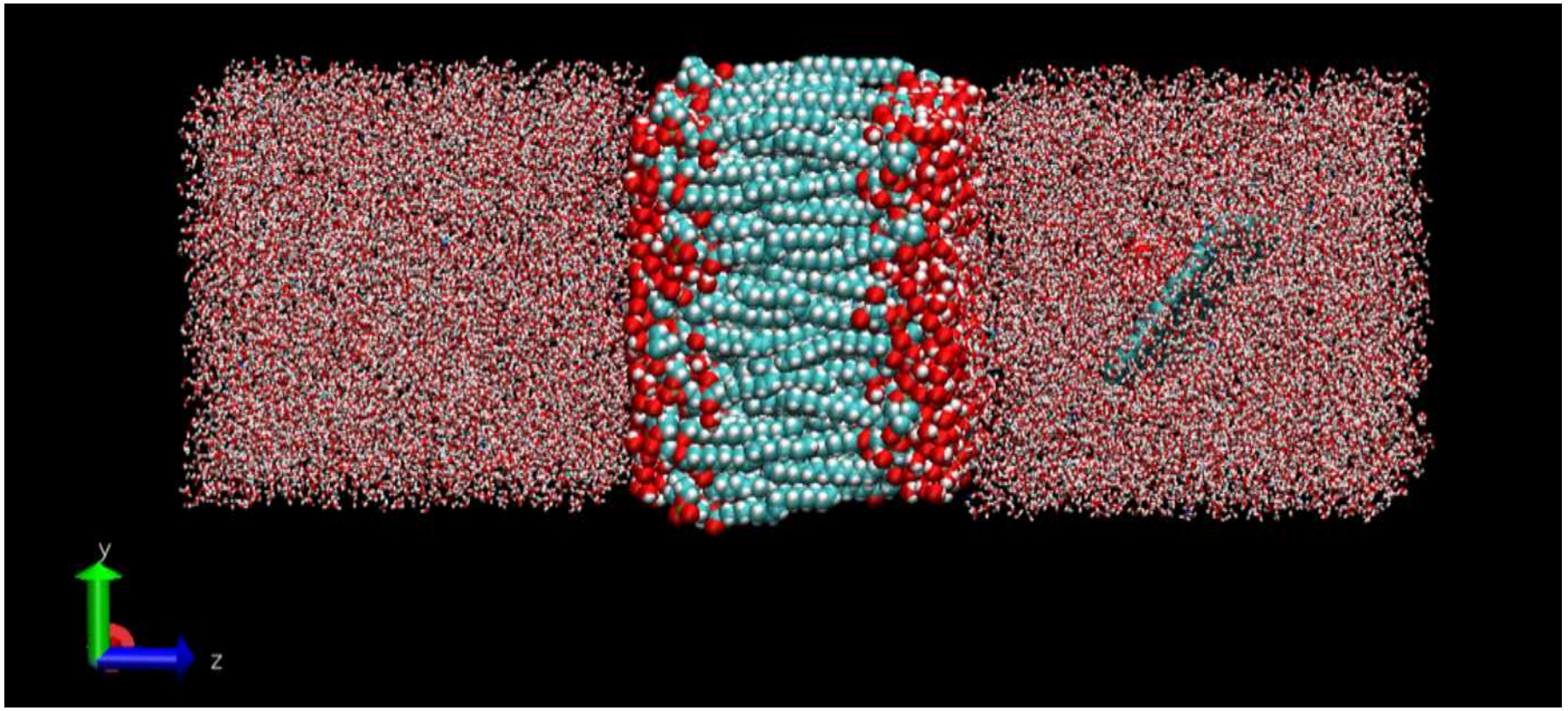
| lipid | lung | intestine | epidermal |
|---|---|---|---|
| Phosphatidylcholine (lecithin) | 50.3 | 44.9 | 46 |
| Phosphatidylcholine (lecithin) eter | | | |
| Suma PC + PC eter (sólo Szlasa 2020) | 50.3 | 44.9 | 46 |
| Sphingomyelin | 11.8 | 11.1 | 10.5 |
| Phosphatidylcholine + Sphingomyelin | 62.1 | 56 | 56.5 |
| Phosphatidylethanolamine | 18.5 | 25.1 | 28 |
| Alkenyl phosphatidylethanolamine | | 5.4 | |
| PE eter | | | |
| Suma (PE + PE eter OR PE + PE-P) | 18.5 | 30.5 | 28 |
| Lysophosphatidylcholine (lysolecithin) | 2.1 | | trace |
| Lysobisphosphatidic acid | 1.6 | | |
| Phosphatidylglycerol | 2.6 | | 2.1 |
| Cardiolipin (diphosphatidylglycerol) | 1.1 | | |
| Phosphatidylglycerol & cardiolipin | 3.7 | | |
| Phosphatidylserine | 7.4 | 7.4 | 6.8 |
| Phosphatydilinositol | | 4.8 | 6.6 |
| Phosphatidyl serine & phosphatidyl inositol | 7.4 | 12.2 | 13.4 |
| Diacylglycerol | | | |
| Others | 1.2 | | |
| Ceramide | | 1.4 | |

# MCNMs and HARNs under study

- Carbon based: Graphene, Graphene oxide, decorated Graphene.
- Metal oxide nanoparticles (Zn,Co, Pd,Rh) decorated and on ceramic surfaces ($CeO_2$,$ZrO_2$).
- Ti alloys with TiC nanoparticles.
- $TiO_2$ nanoparticles decorated with metallic atoms.
- Quantum dots: alloyed and core-shell structures

- Carbon nanotubes (single walled and multiwalled)
- Silver nanowires.

# Interaction of nanomaterials with cell membranas as a key MIE

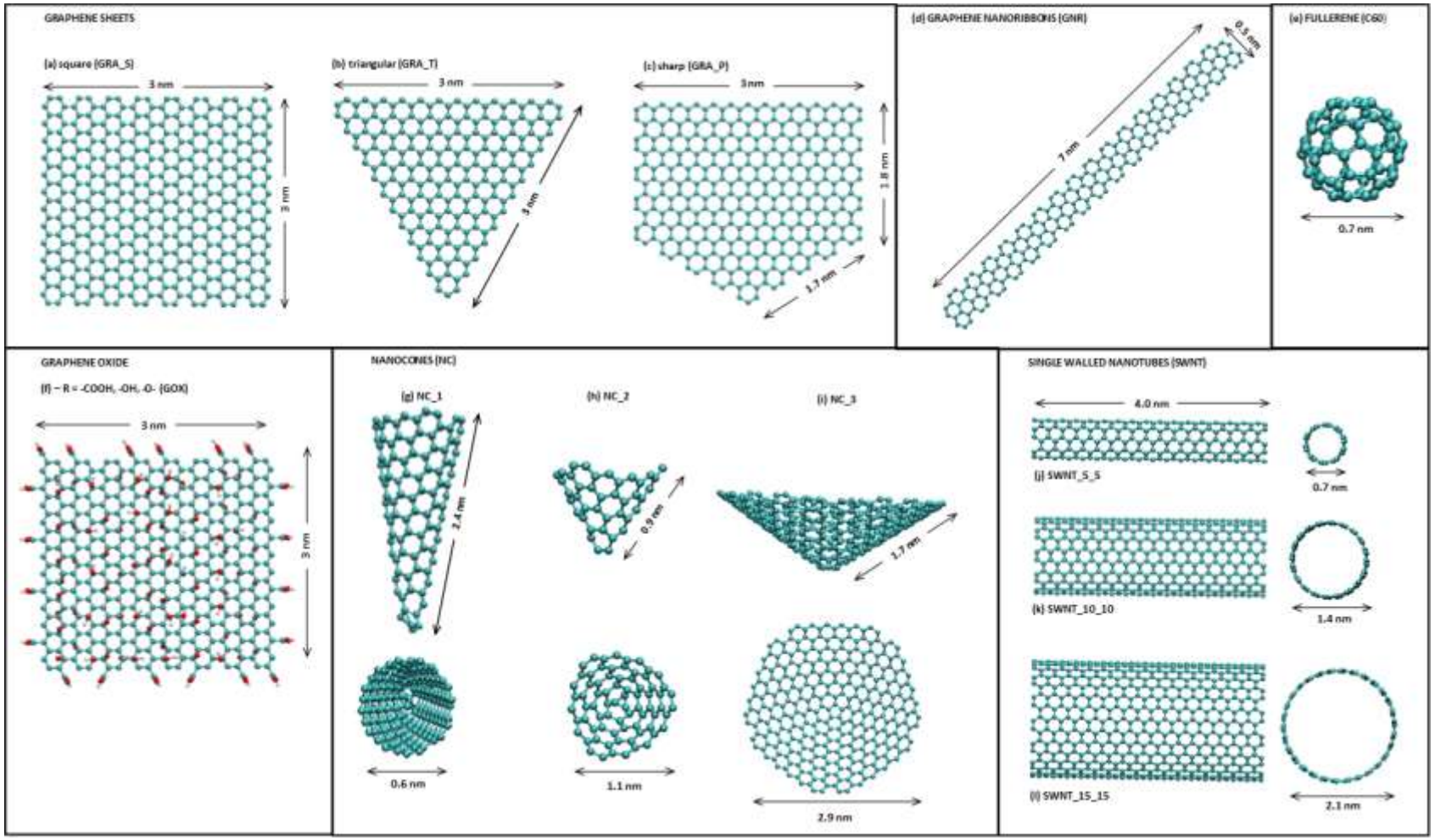



**Molecular Dynamics analysis of interaction with biomembranes**

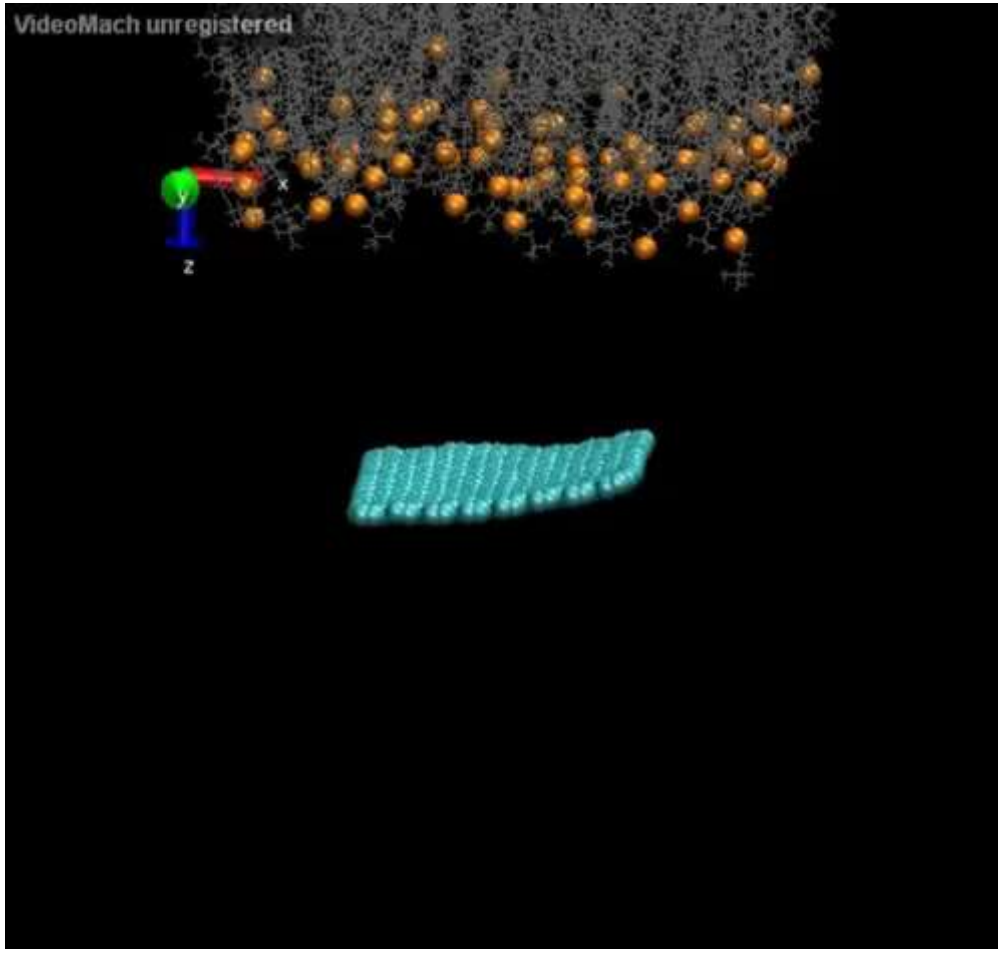
**Toxicity?**
**Safety?**
**Reverse design.**

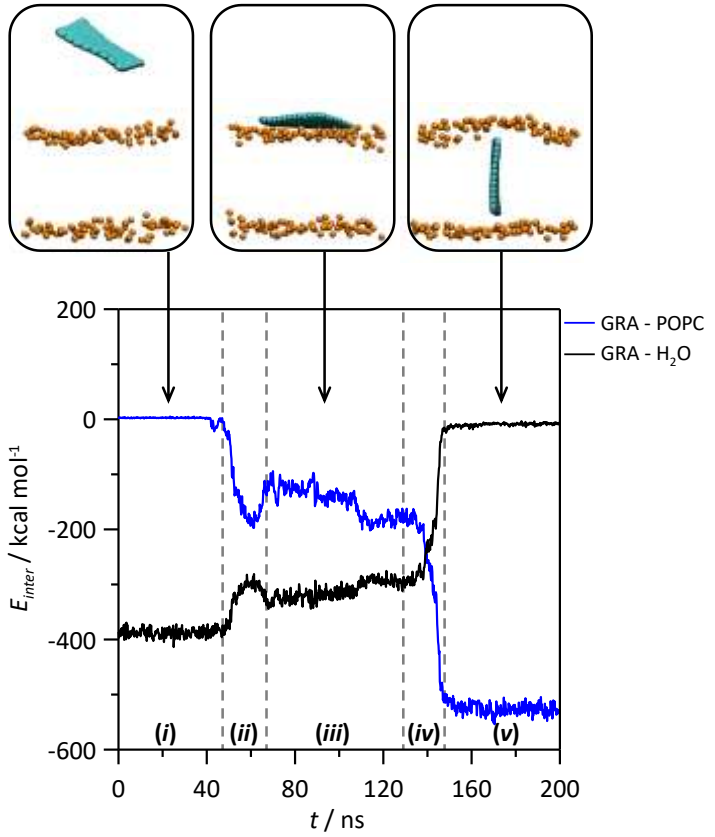
**model membranes in contact with a system formed by nanomaterials of**

# Carbon based nanomaterials and HARNs

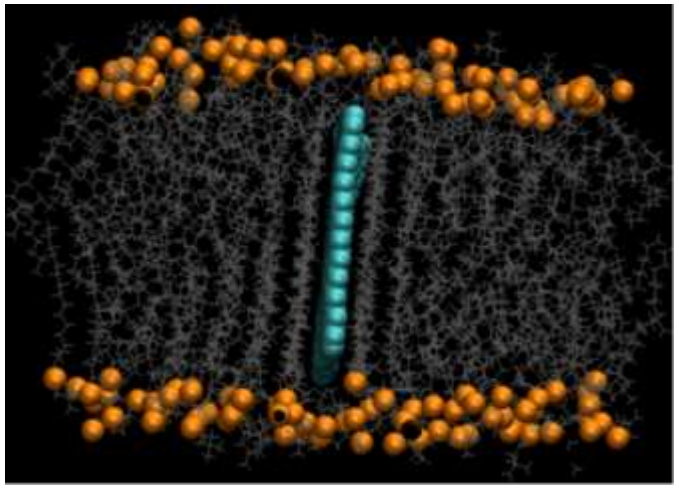


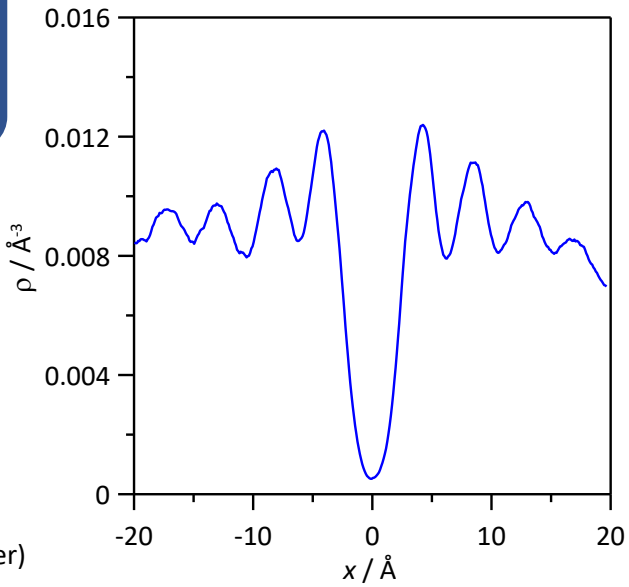
# Graphene nanoplatelets

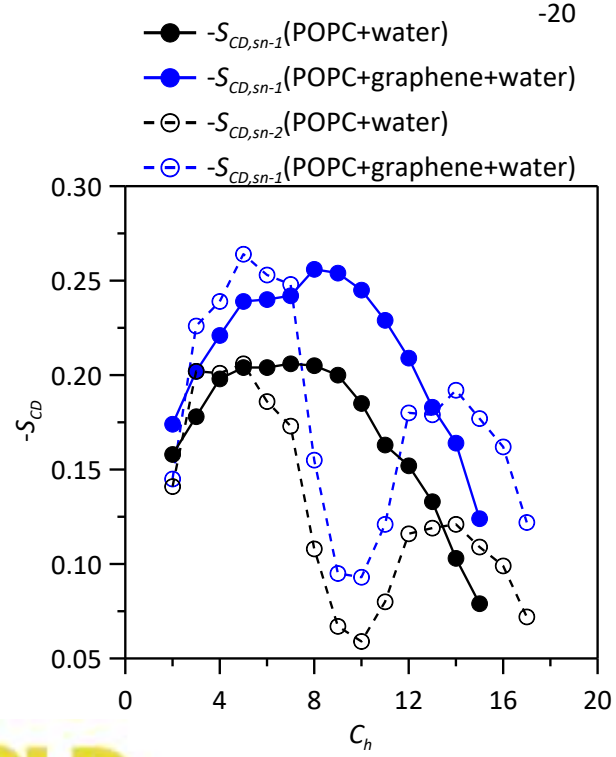


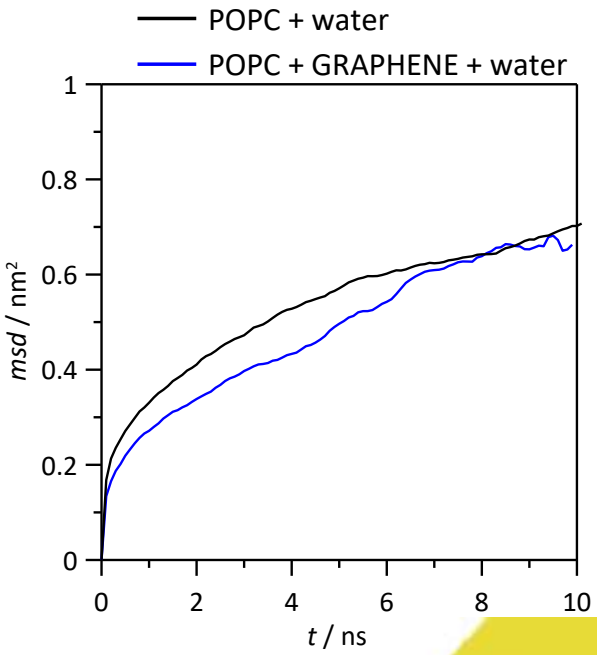



# Graphene nanoplatelets



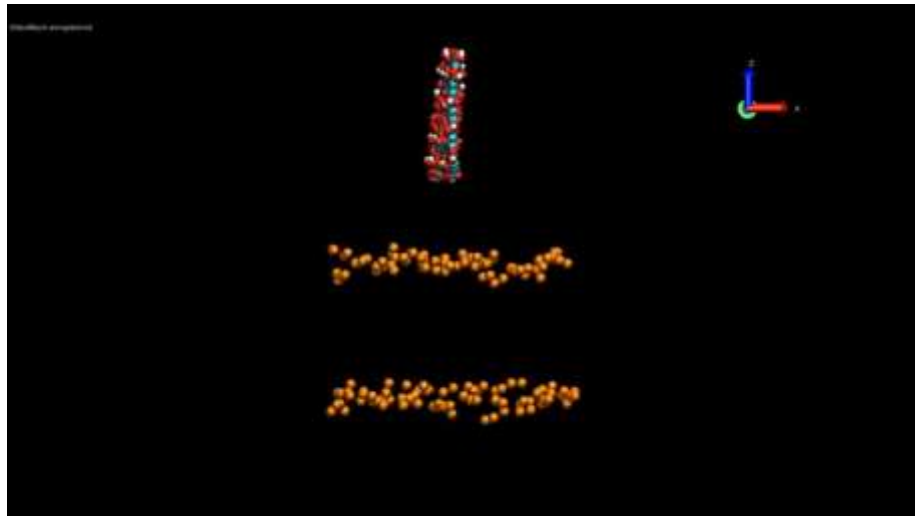


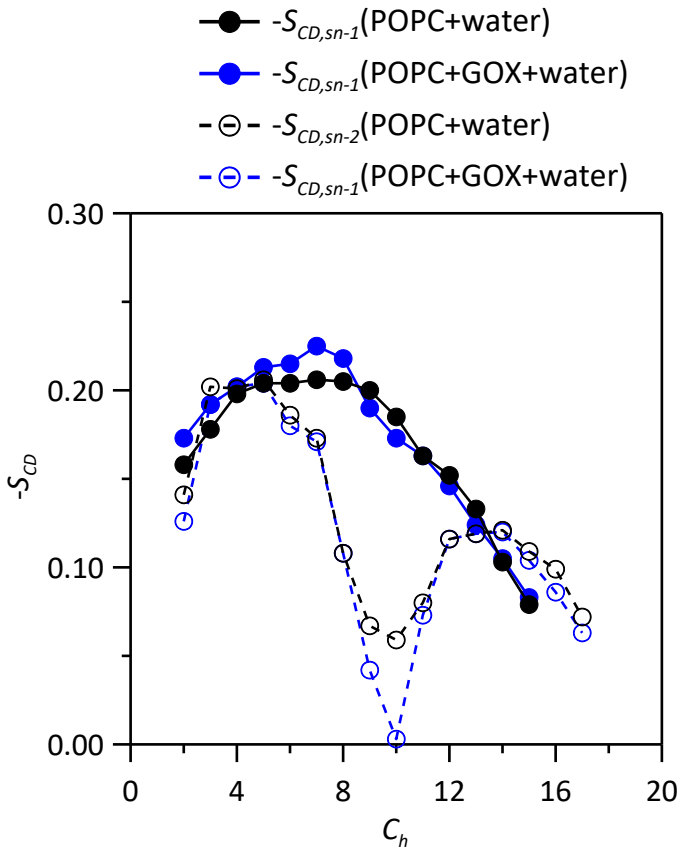



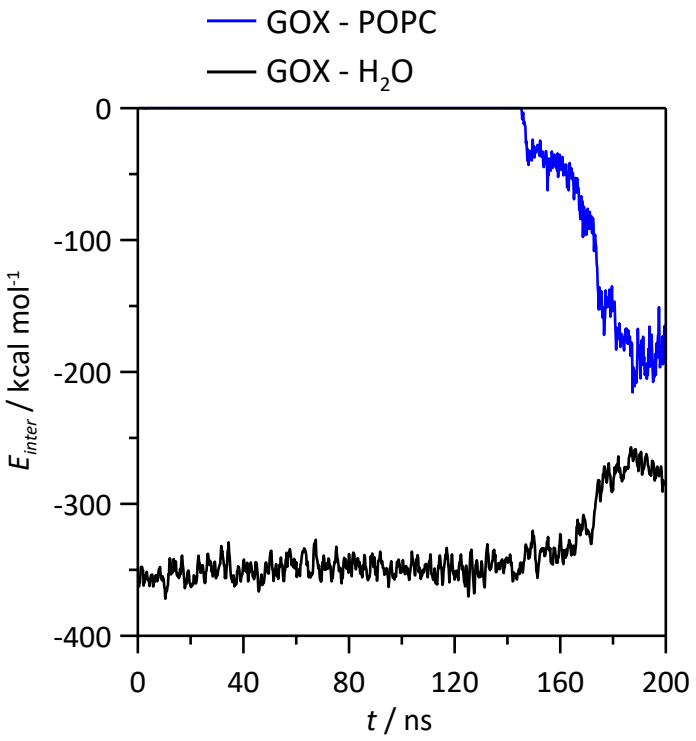




**Large disruption of lipid membrane structuring**

# Graphene oxide nanoplatelets

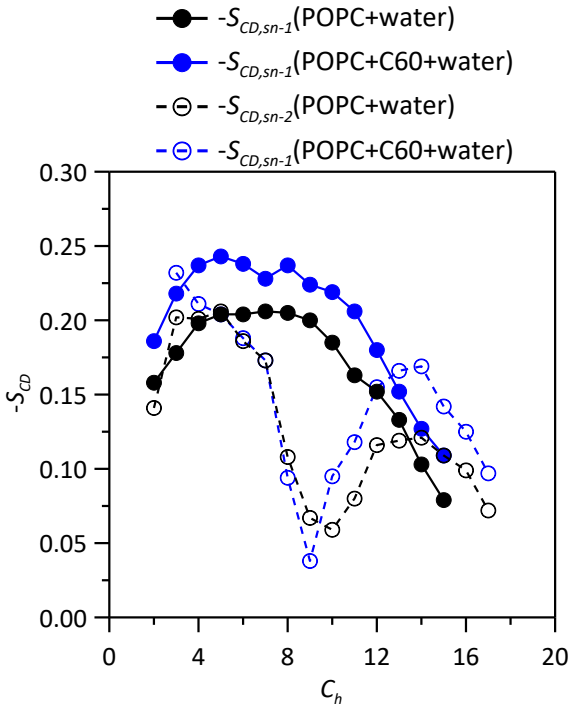


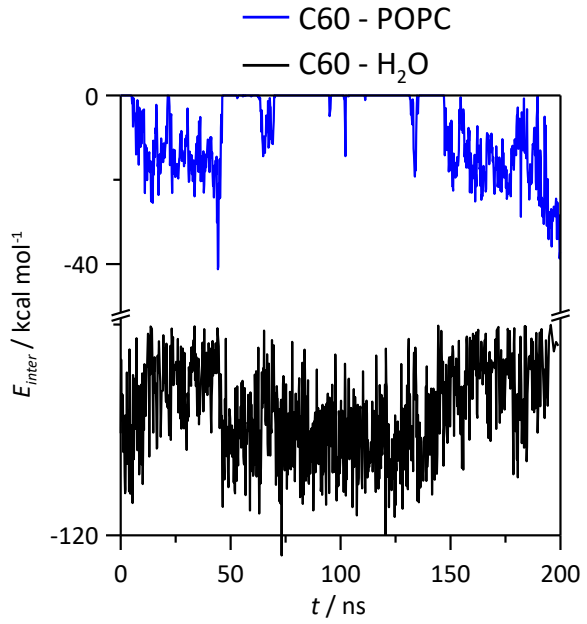



**Nanoplatelets adsorbed on outer side of the membrane**
**Lower membrane disruption**

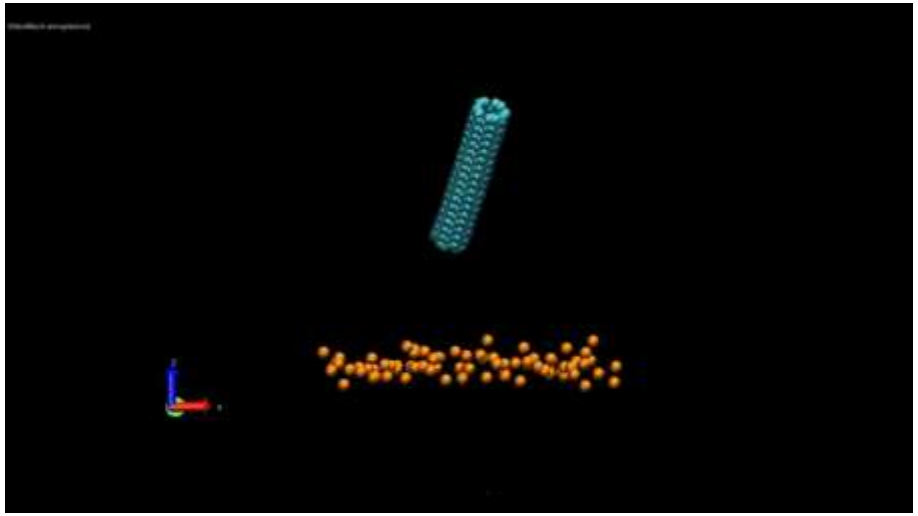
# Fullerenes

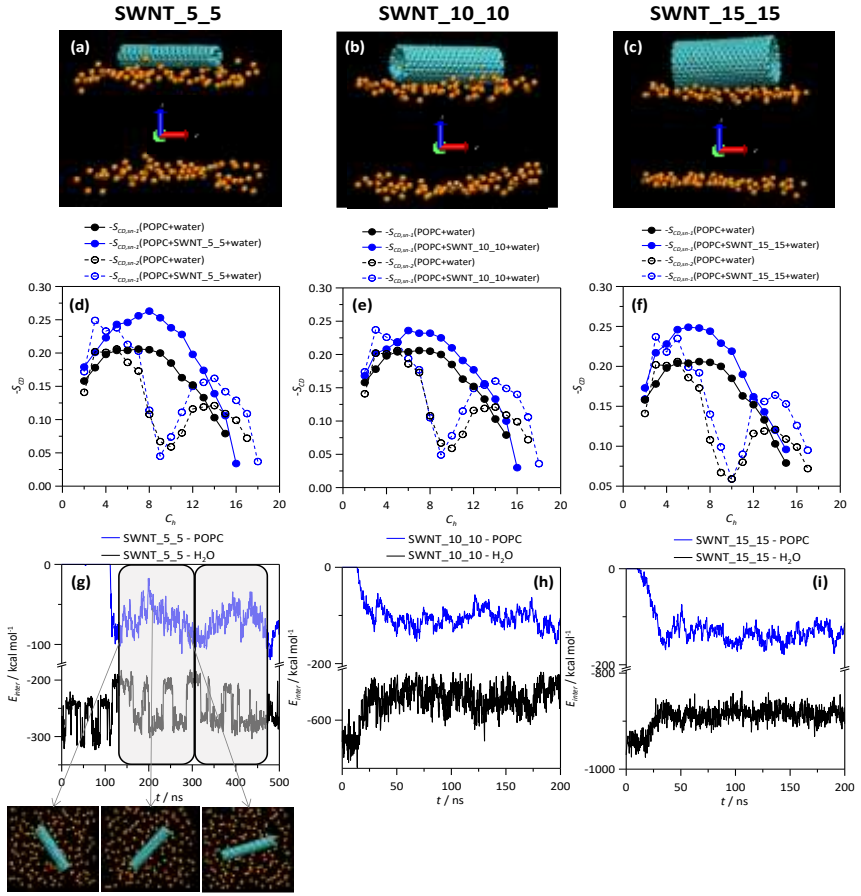



**Nanoparticle adsorbed and rolling on polar side of the membrane**

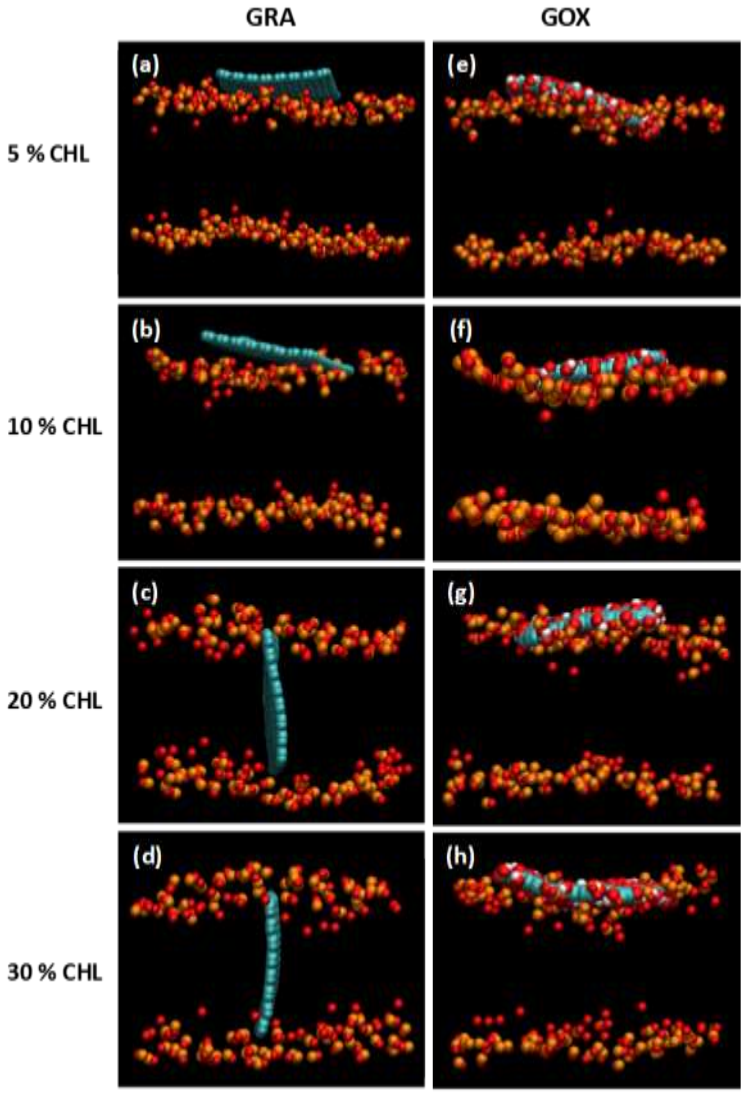
# Carbon nanotubes






**Nanotubes adsorbed on outer side of the membrane**
**Lower membrane disruption**

# Membrane composition effect



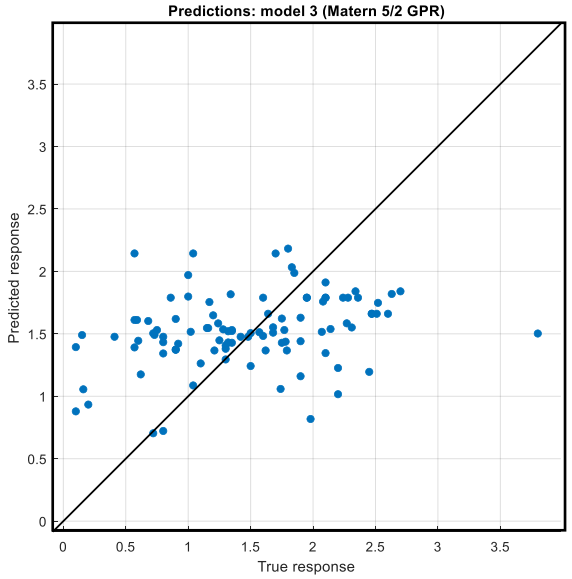
# Parameters for membrane disruption quantification

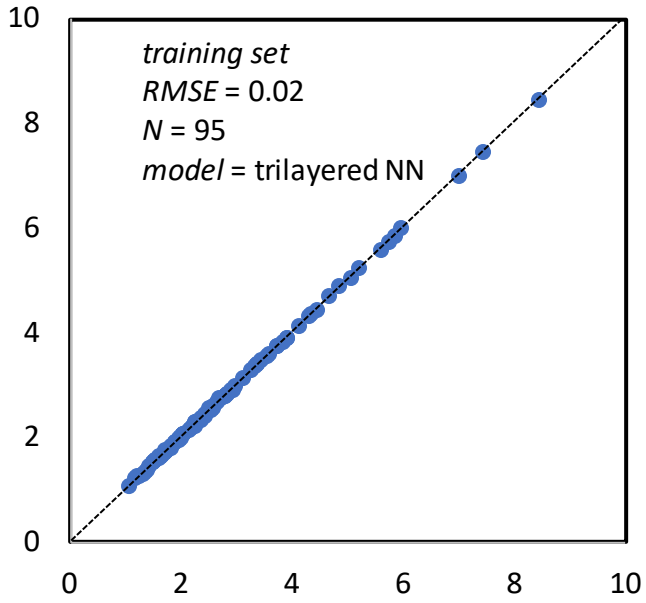
| System | FINAL | $A_{POPC}$ / nm$^2$ | h / nm | $-\langle S_{CD}\rangle_{sn-1}$ | $-\langle S_{CD}\rangle_{sn-2}$ | $\omega_\rho$ / nm | $\Theta_{PN}$ / deg | $\Theta_{sn-1}$ / deg | $\Theta_{sn-2}$ / deg |
|---|---|---|---|---|---|---|---|---|---|
| POPC-water | – | 0.644±0.017 | 3.940±0.196 | 0.160±0.054 | 0.123±0.055 | 0.464±0.044 | 74.3±1.9 | 148.5±1.5 | 146.3±1.6 |
| POPC-water-GRA-S | P | 0.615±0.008 | 4.218±0.216 | 0.201±0.059 | 0.170±0.064 | 0.422±0.030 | 74.2±0.8 | 154.8±0.5 | 154.0±0.7 |
| POPC-water-GNR | A | 0.601±0.009 | 4.176±0.158 | 0.197±0.060 | 0.148±0.077 | 0.391±0.031 | 75.1±0.8 | 153.6±0.5 | 151.0±1.4 |
| POPC-water-GRA-T | A | 0.603±0.010 | 4.179±0.017 | 0.197±0.059 | 0.147±0.071 | 0.421±0.036 | 75.0±0.9 | 154.0±0.8 | 151.2±1.1 |
| POPC-water-GRA-P | A | 0.603±0.008 | 4.180±0.181 | 0.195±0.056 | 0.144±0.061 | 0.492±0.034 | 74.8±0.7 | 154.1±0.9 | 151.4±0.7 |
| POPC-water-GOX | A | 0.646±0.009 | 3.948±0.153 | 0.163±0.057 | 0.163±0.061 | 0.446±0.037 | 75.4±0.8 | 148.8±0.6 | 145.0±1.0 |
| POPC-water-SWNT_5_5 | A | 0.597±0.008 | 4.191±0.184 | 0.199±0.064 | 0.149±0.064 | 0.412±0.026 | 73.5±0.8 | 155.2±0.6 | 151.4±0.8 |
| POPC-water-SWNT_10_10 | A | 0.606±0.008 | 4.123±0.156 | 0.181±0.057 | 0.145±0.058 | 0.437±0.042 | 74.3±0.9 | 151.5±0.7 | 151.5±0.7 |
| POPC-water-SWNT_15_15 | A | 0.608±0.008 | 4.144±0.145 | 0.186±0.066 | 0.148±0.060 | 0.445±0.036 | 75.1±0.9 | 152.9±1.0 | 150.6±0.7 |
| POPC-water-NC1 | P | 0.651±0.009 | 4.000±0.191 | 0.172±0.058 | 0.128±0.060 | 0.484±0.037 | 74.0±1.0 | 149.9±0.8 | 149.5±0.7 |
| POPC-water-NC2 | A | 0.640±0.010 | 4.001±0.180 | 0.165±0.060 | 0.134±0.058 | 0.460±0.050 | 74.0±1.2 | 148.8±0.7 | 146.5±0.6 |
| POPC-water-NC3 | P | 0.653±0.009 | 4.002±0.142 | 0.164±0.051 | 0.135±0.060 | 0.517±0.039 | 73.8±0.9 | 149.9±0.7 | 146.7±0.7 |
| POPC-water-C60 | A | 0.614±0.008 | 4.131±0.153 | 0.189±0.060 | 0.140±0.059 | 0.456±0.037 | 74.0±1.1 | 152.5±0.7 | 150.7±0.6 |

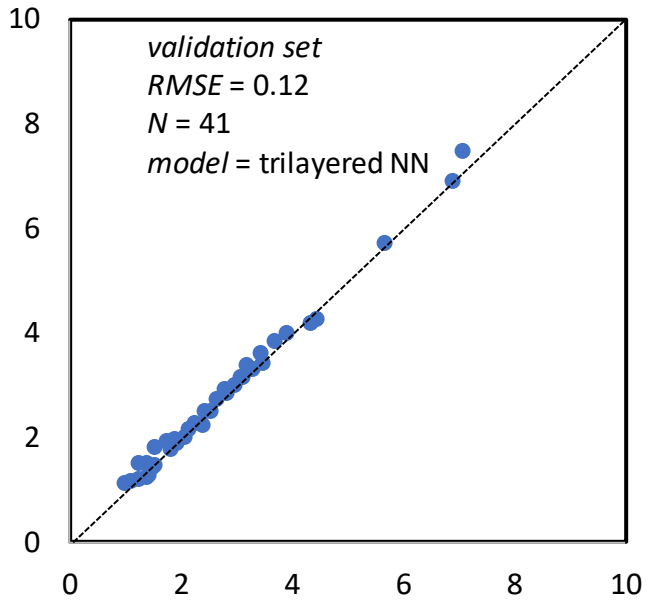
# Quantitative – structure – activity relationships
# &
# Machine learning (Artificial Intelligence)

- Neural Networks
- Supported Vector Machines
- Decission trees

**Response quantified as Adverse Outcomes (experimental toxicity data on model organisms)**



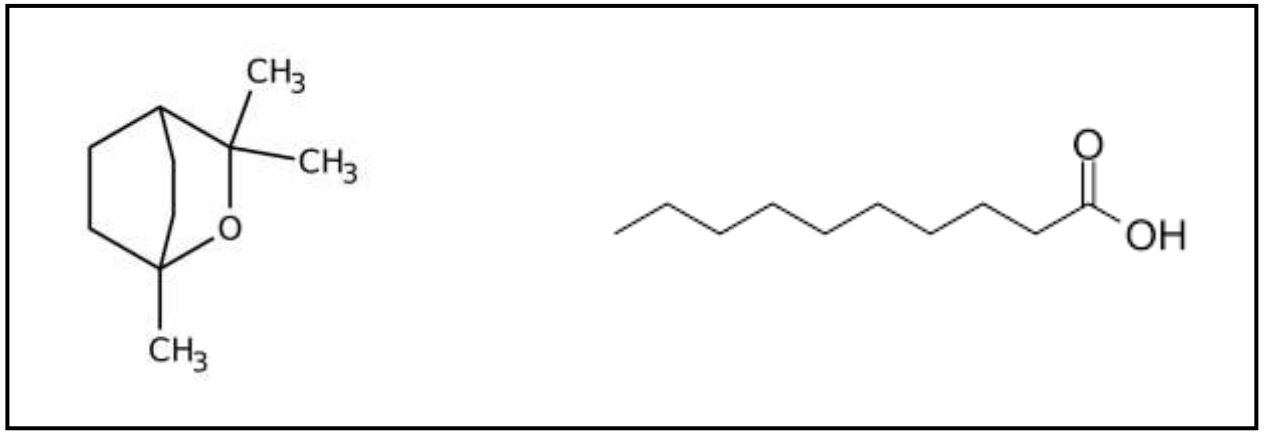



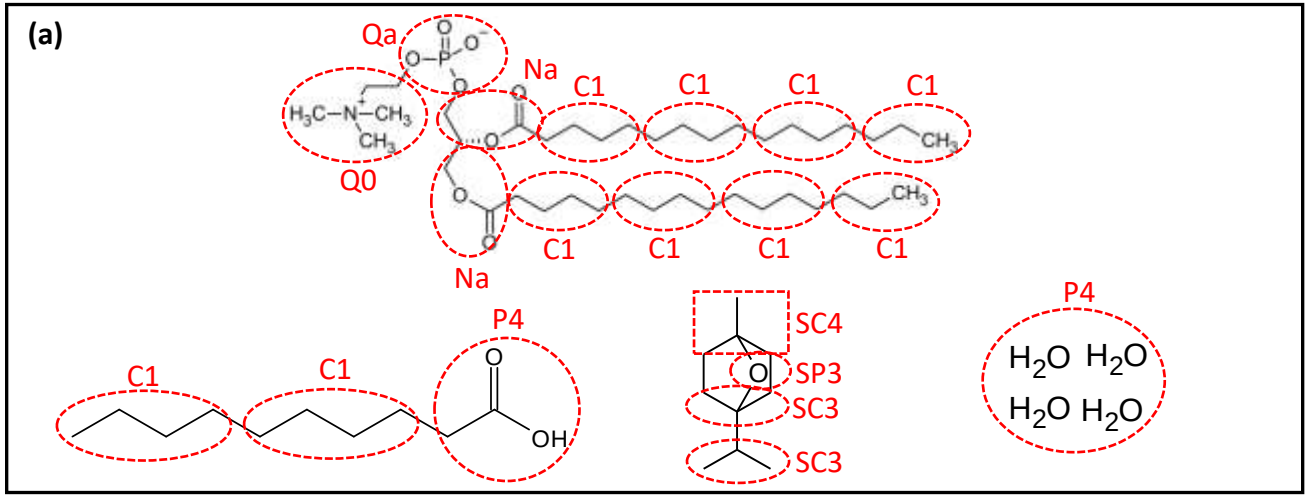



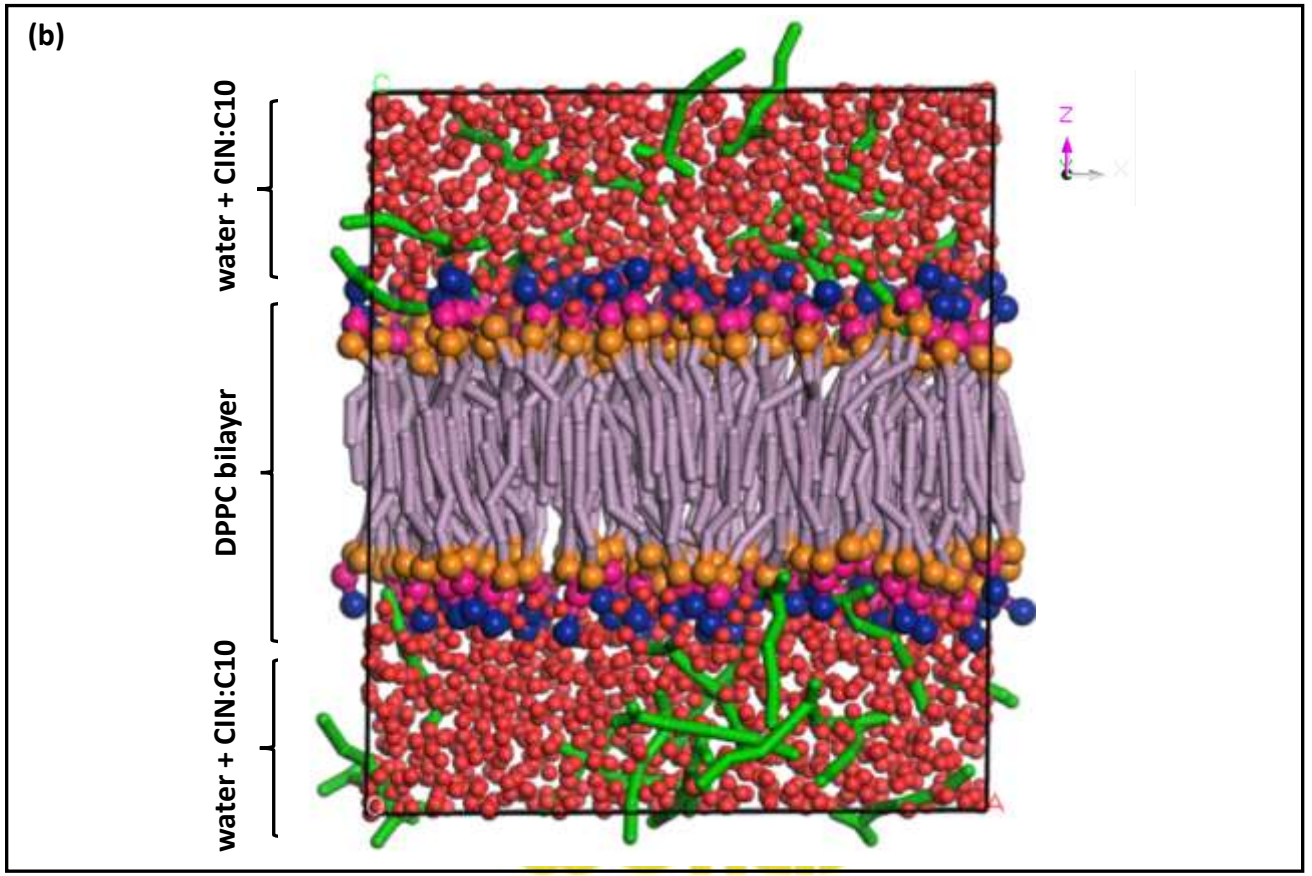

**Simple monoparametric model (qualitative descriptor penetration / no penetration)**

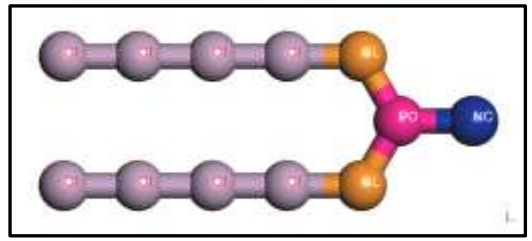
**trained multiparametric model (quantitative descriptors)**

# The case of Deep Eutectic Solvents
# Coarse Grained Approach

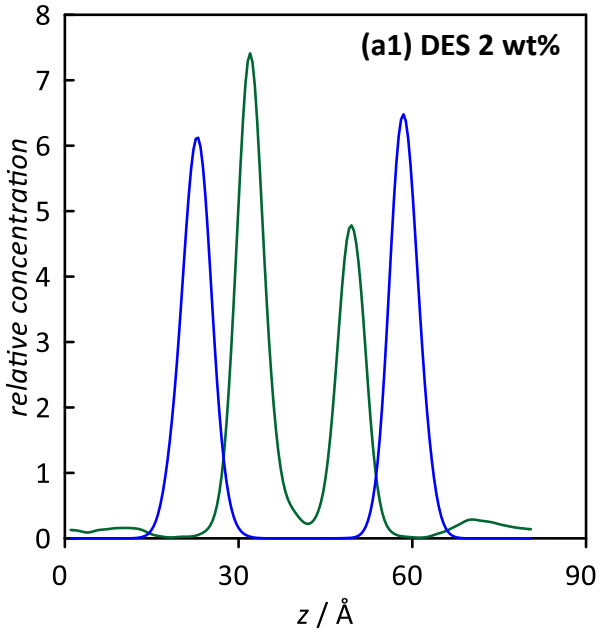


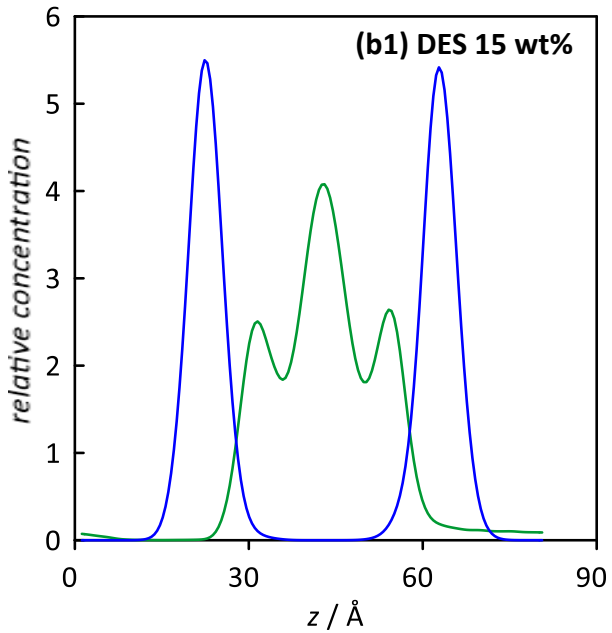

(a)
Qa
Na
C1
C1
C1
C1
Q0
C1
C1
C1
C1
Na
P4
C1
C1
OH
SC4
SP3
SC3
SC3
P4
H2O H2O
H2O H2O

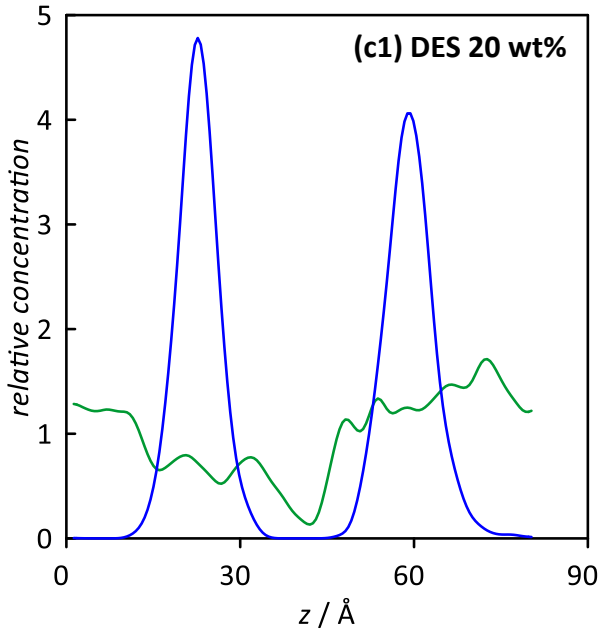

(b)
water + ClN:C10
DPPC bilayer
water + ClN:C10
Z

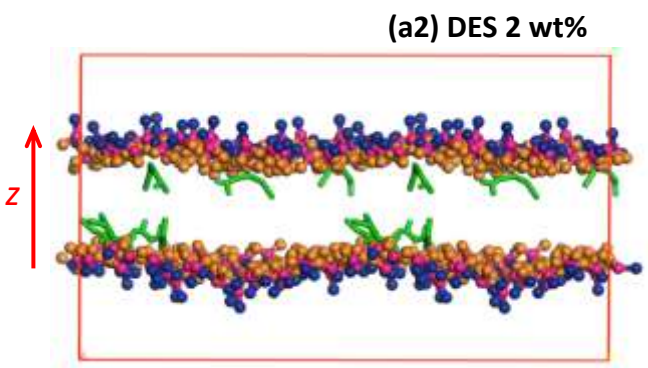


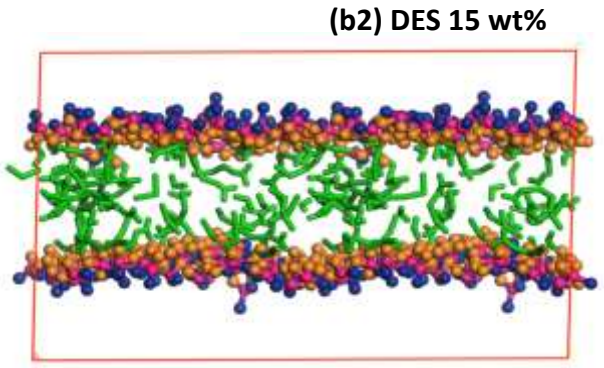
NC(DPPC)
O(CIN@DES)

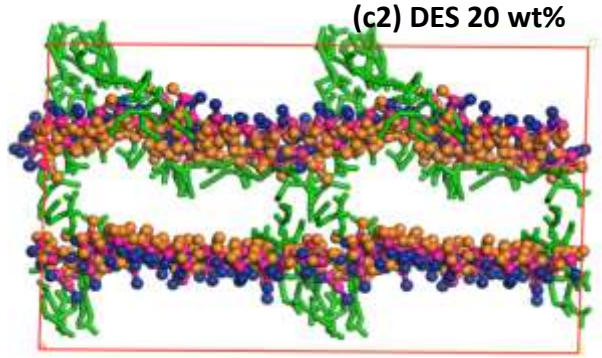


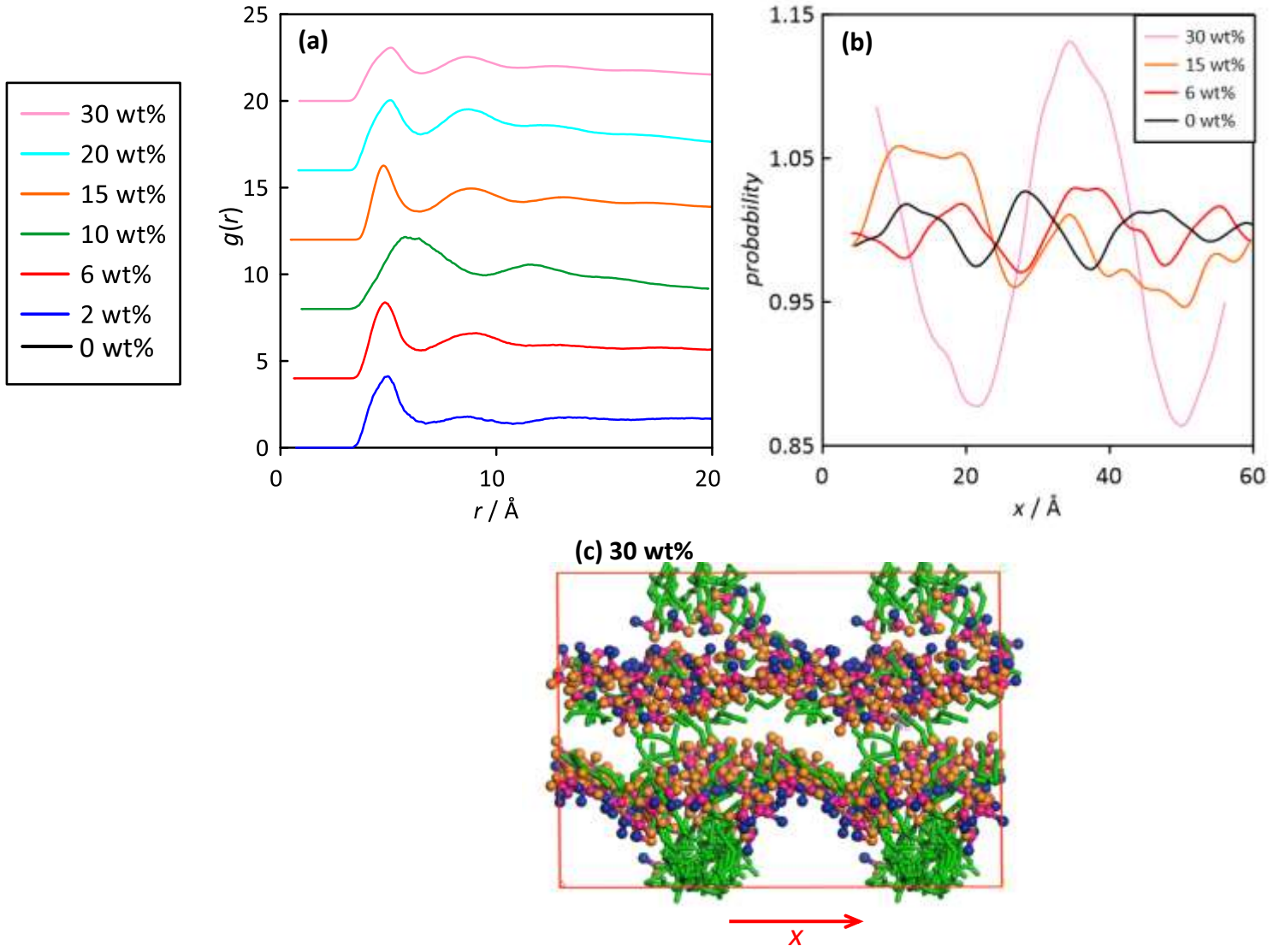



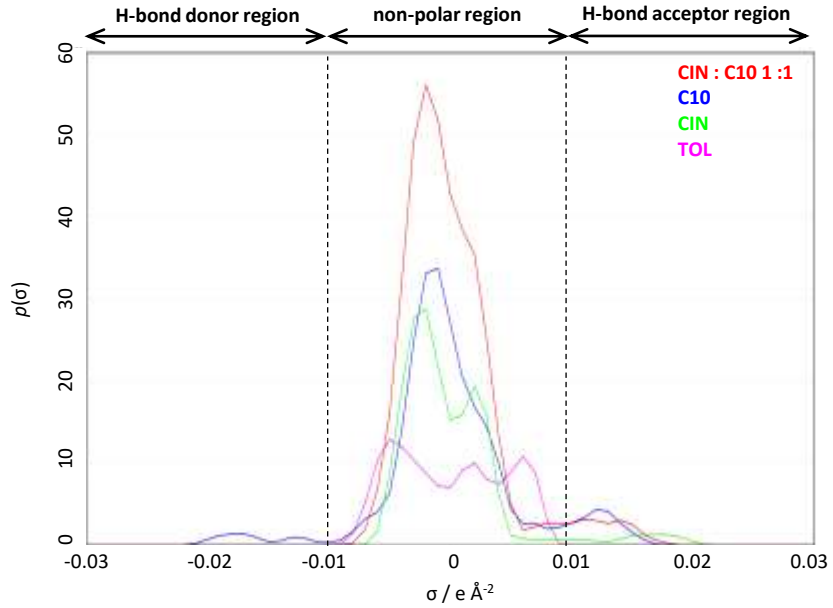



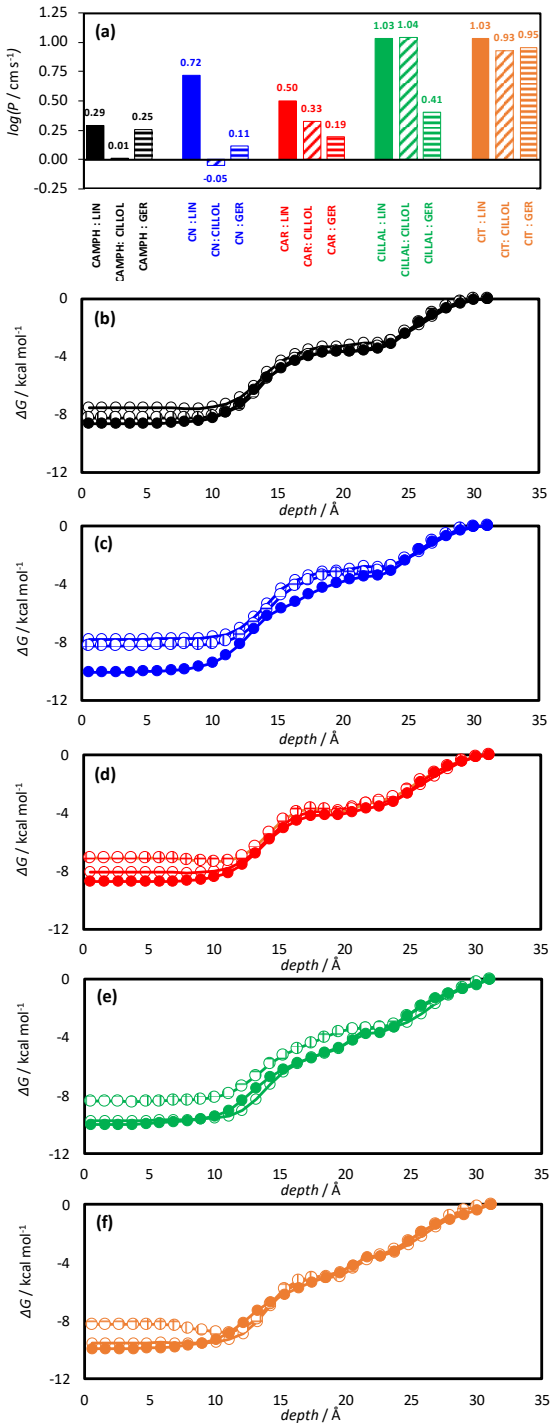



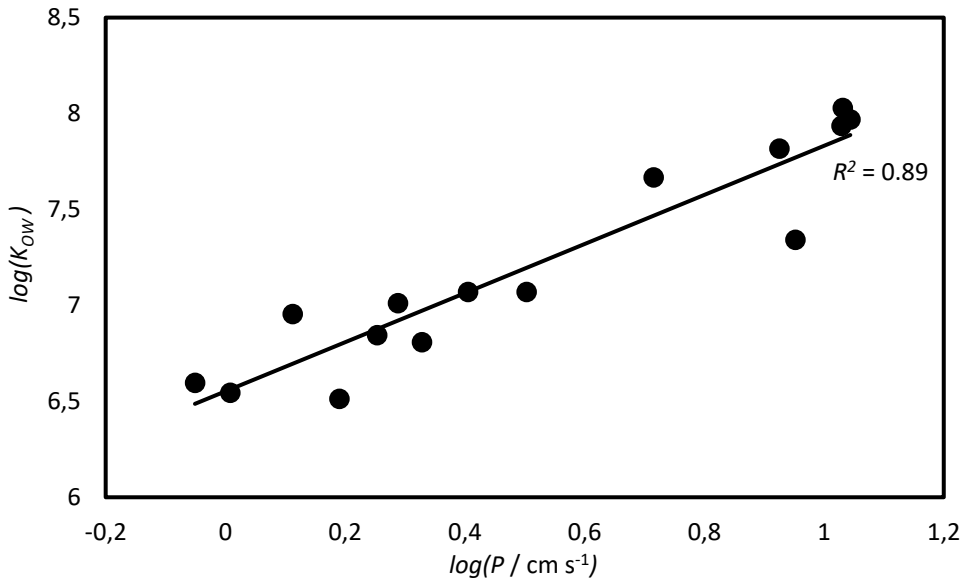

30 wt%
20 wt%
15 wt%
10 wt%
6 wt%
2 wt%
0 wt%
(a)
g(r)
r / Å
(b)
probability
x / Å
(c) 30 wt%
x

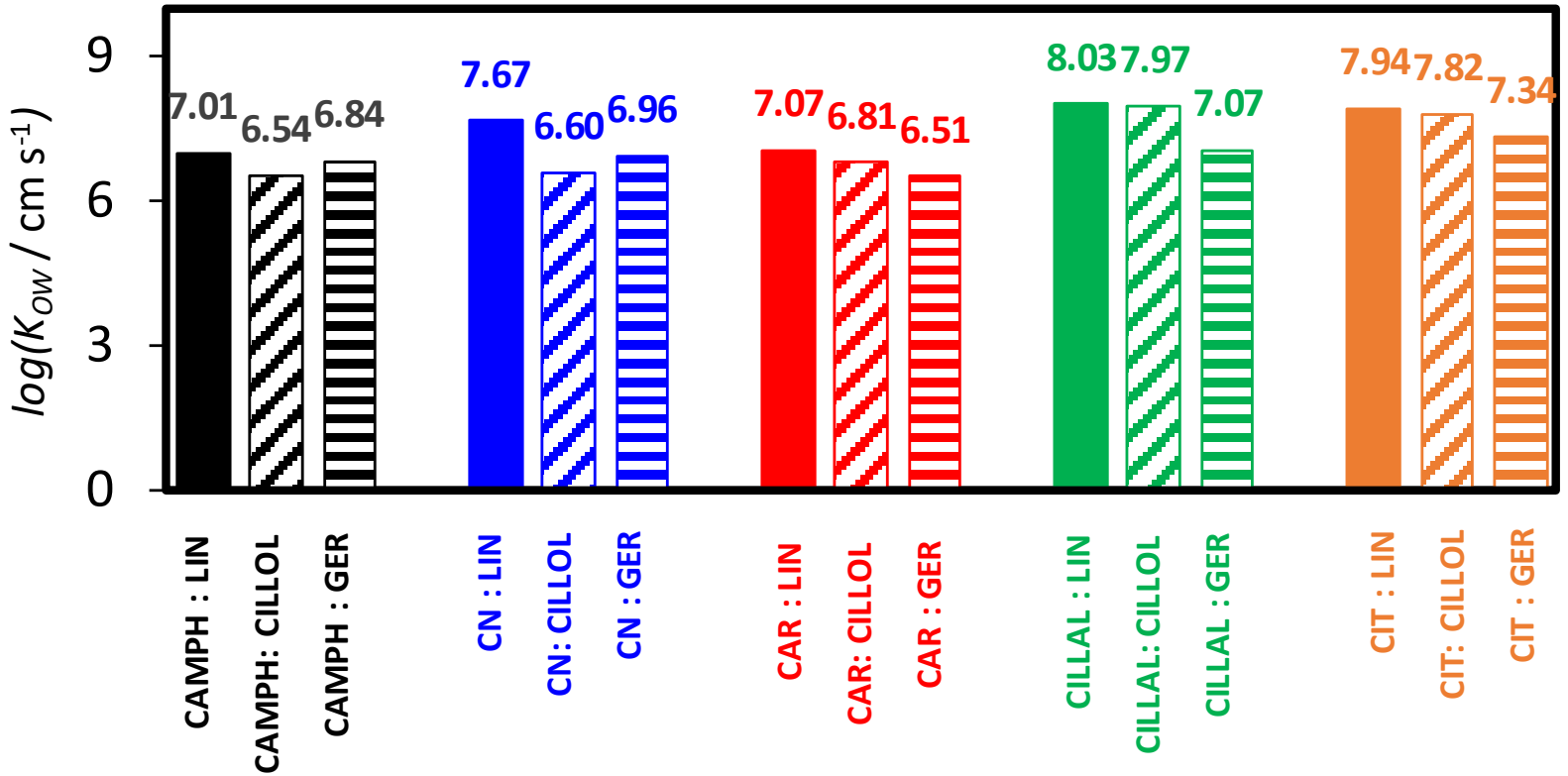
# COSMO-RS APPROACH FOR DEEP EUTECTIC SOLVENTS

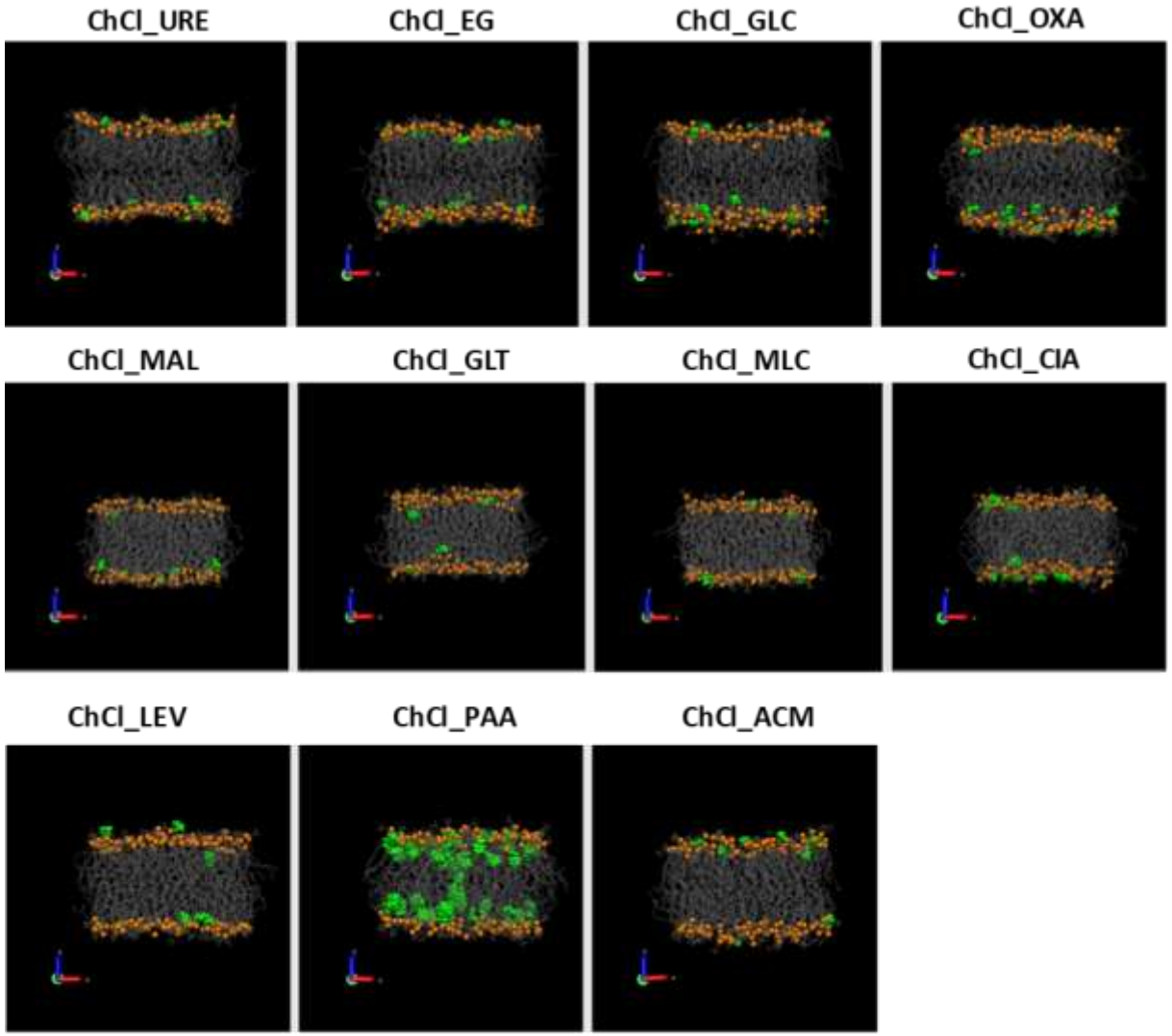



- Combination of quantum chemistry + thermodynamics modelling
- Computationally fast and efficient
- Accurate for thermophysical properties, phase equilibria and environmental properties (octanol-water partition coefficients, permeability, interfacial properties…)


(a)
log(P / cm s-1)
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
0.29
0.01
0.25
0.72
-0.05
0.11
0.50
0.33
0.19
1.03
1.04
0.41
1.03
0.93
0.95
CAMPH : LIN
CAMPH: CILLOL
CAMPH : GER
CN : LIN
CN :CILLOL
CN : GER
CAR : LIN
CAR: CILLOL
CAR : GER
CILLAL : LIN
CILLAL: CILLOL
CILLAL : GER
CIT : LIN
CIT: CILLOL
CIT : GER
(b)
(c)
(d)
(e)
(f)
ΔG / kcal mol-1
0
-4
-8
-12
0
5
10
15
20
25
30
35
depth / Å

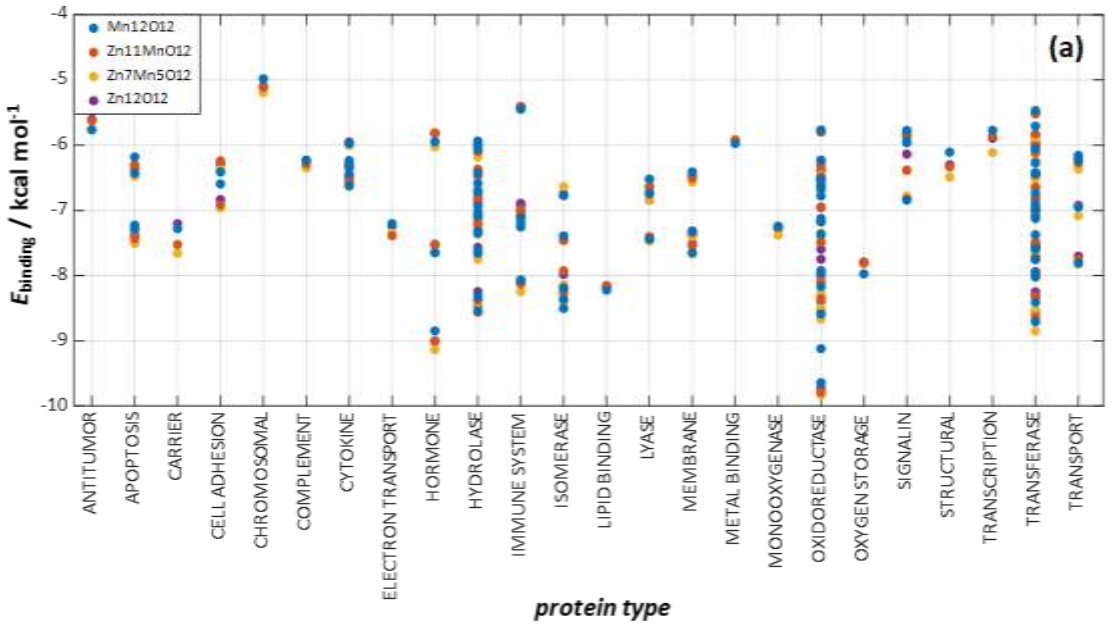

8,5
8
7,5
7
6,5
6
log(K_OW)
R² = 0.89
-0,2
0
0,2
0,4
0,6
0,8
1
1,2
log(P / cm s⁻¹)


9
6
3
0
log(K_OW / cm s-1)
7.01
6.54
6.84
7.67
6.60
6.96
7.07
6.81
6.51
8.03
7.97
7.07
7.94
7.82
7.34
CAMPH : LIN
CAMPH: CILLOL
CAMPH : GER
CN : LIN
CN: CILLOL
CN : GER
CAR : LIN
CAR: CILLOL
CAR : GER
CILLAL : LIN
CILLAL: CILLOL
CILLAL : GER
CIT : LIN
CIT: CILLOL
CIT : GER

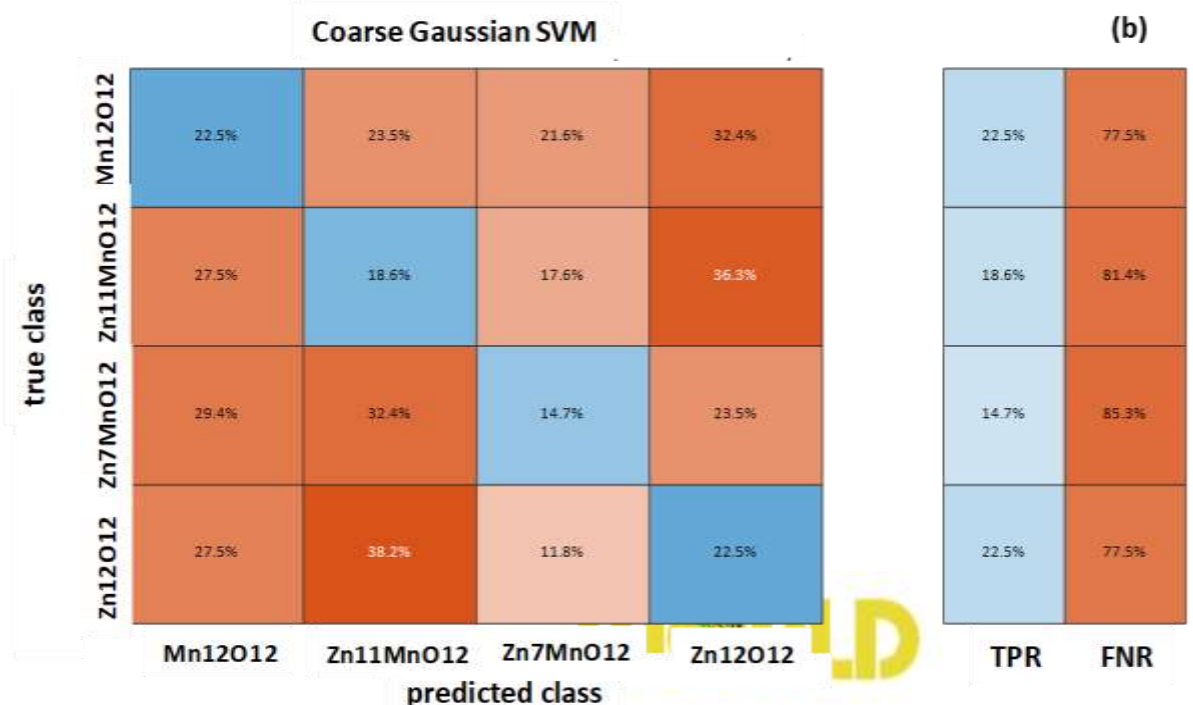

ChCl_URE
ChCl_EG
ChCl_GLC
ChCl_OXA
ChCl_MAL
ChCl_GLT
ChCl_MLC
ChCl_ClA
ChCl_LEV
ChCl_PAA
ChCl_ACM

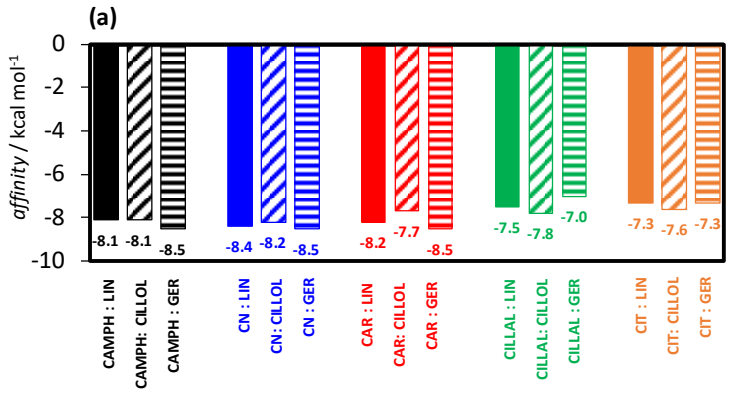
# PROTEIN DOCKING AND INTERACTION

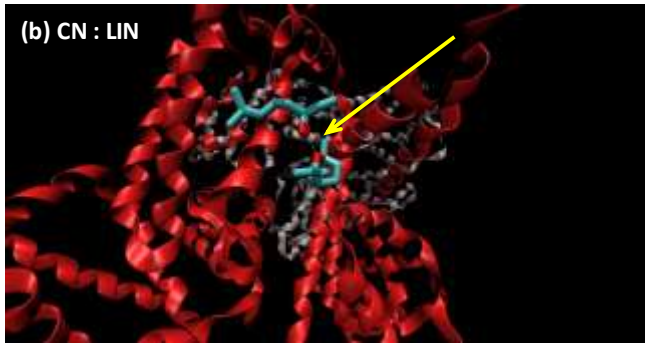
chemical / material – protein interaction strength

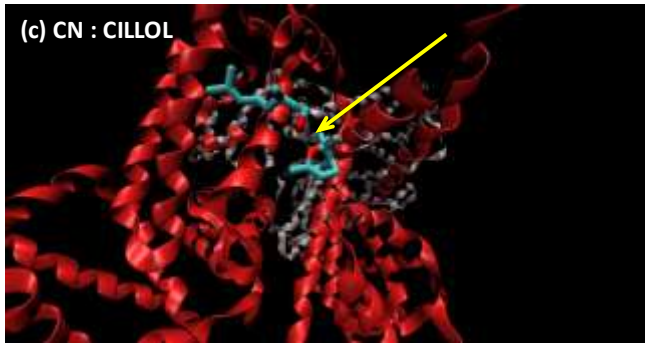


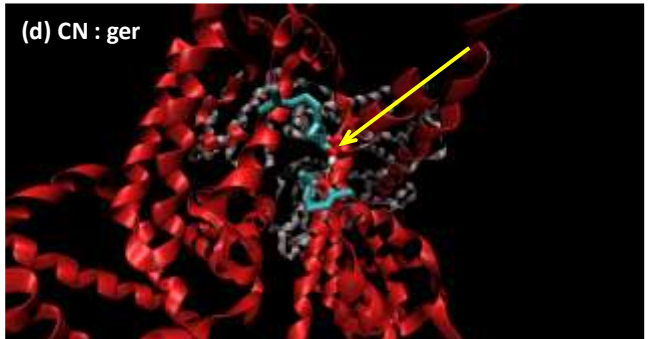

collection of $10^3$ human target proteins



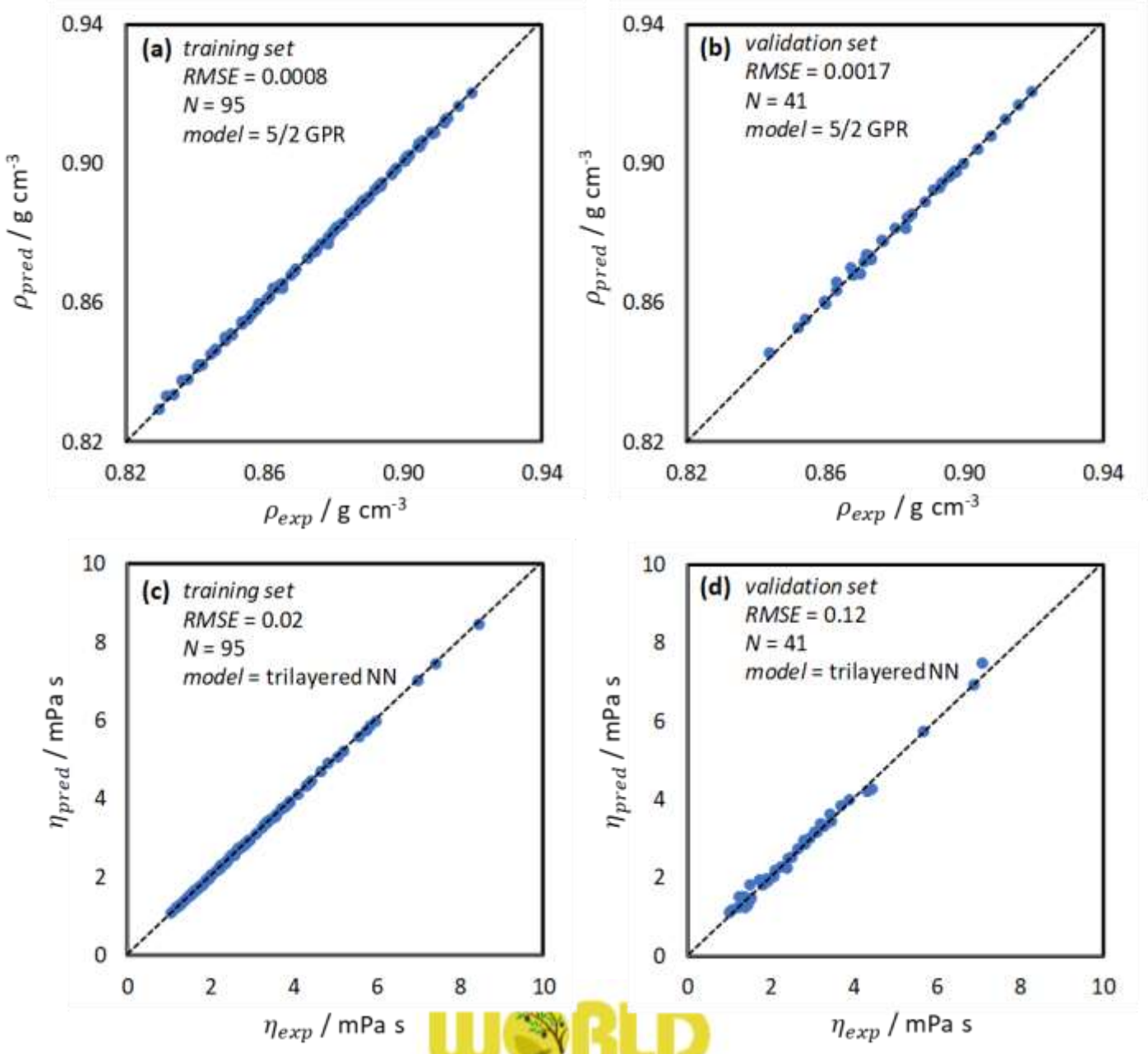

(a)
affinity / kcal mol-1
0
-2
-4
-6
-8
-10
-8.1
-8.1
-8.5
-8.4
-8.2
-8.5
-8.2
-7.7
-8.5
-7.5
-7.8
-7.0
-7.3
-7.6
-7.3
CAMPH : LIN
CAMPH: CILLOL
CAMPH : GER
CN : LIN
CN: CILLOL
CN : GER
CAR : LIN
CAR: CILLOL
CAR : GER
CILLAL : LIN
CILLAL: CILLOL
CILLAL : GER
CIT : LIN
CIT: CILLOL
CIT : GER


(b) CN : LIN


(c) CN : CILLOL


(d) CN : ger

# PREDICTION OF PROPERTIES: FUNCTIONALITY AND PERFORMANCE



UNIVERSIDAD DE BURGOS | ICCRAM

https://www.diagonalproject.eu/

NANOCOMP

https://www.ubu.es/nanocomp-project


# Questions?

WORLD