SmartNanoTox

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Models and tools: statistical and physics-based modelling

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SmartNanoTox
Smart Tools for Gauging Nano Hazards

SmartNanoTox

is a project within Horizon2020 NMP-29 call:
"*Increasing the capacity to perform nano-safety assessment*"

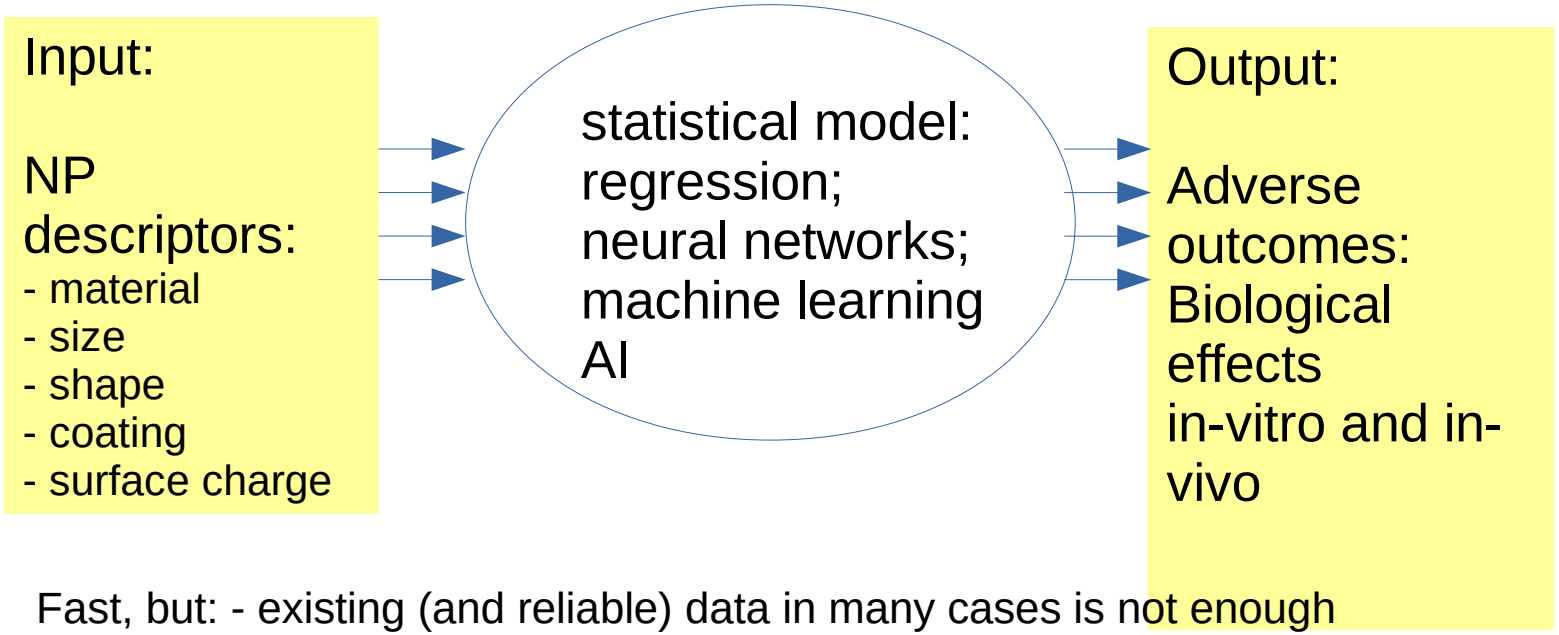
from the aims of the program:

- Develop and demonstrate a mechanism-based understanding of the toxicity
- Link the potential for adverse effects to specific physical or chemical nanoscale properties

Modeling and simulations are the tools to address these goals

"Statistical" toxicity modeling

QSAR : statistically derived relationships between NP descriptors and (known) adverse outcomes



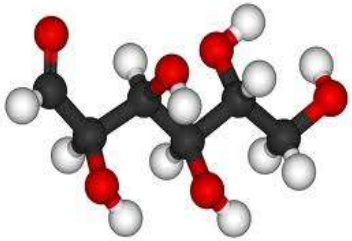
Fast, but: - existing (and reliable) data in many cases is not enough
- difficult to find correlations / relevant descriptors
- problem for new materials for which data absent

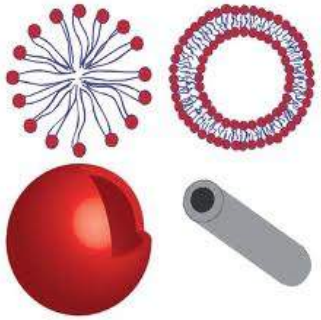
"Mechanisms aware "- approaches are wanted!

Physics-based modeling

Based on physical laws

$\Psi(x)$





ab-initio:
atoms,
electron
wave function

classical atomistic:
atoms,
molecules

coarse-grained:
molecular assemblies

$$\hat{H}\Psi = E\Psi \qquad \vec{a}_i = \vec{F}_i / m_i \qquad \vec{a} = \frac{d\vec{v}}{dt};\ \ \vec{v} = \frac{d\vec{x}}{dt}$$

- Rules of the game: physical laws:
  quantum (ab-initio) : Schrödinger equation
  classical (molecular dynamics): Newton laws of motion and/ or Statistical thermodynamics

Multiscale modeling

How to fill the gap between molecular level description and organism?
Molecular dynamics: scale ~10 nm time ~1 μs.

Output of a more detailed (more fundamental) model is plugged in into a more "coarse" model

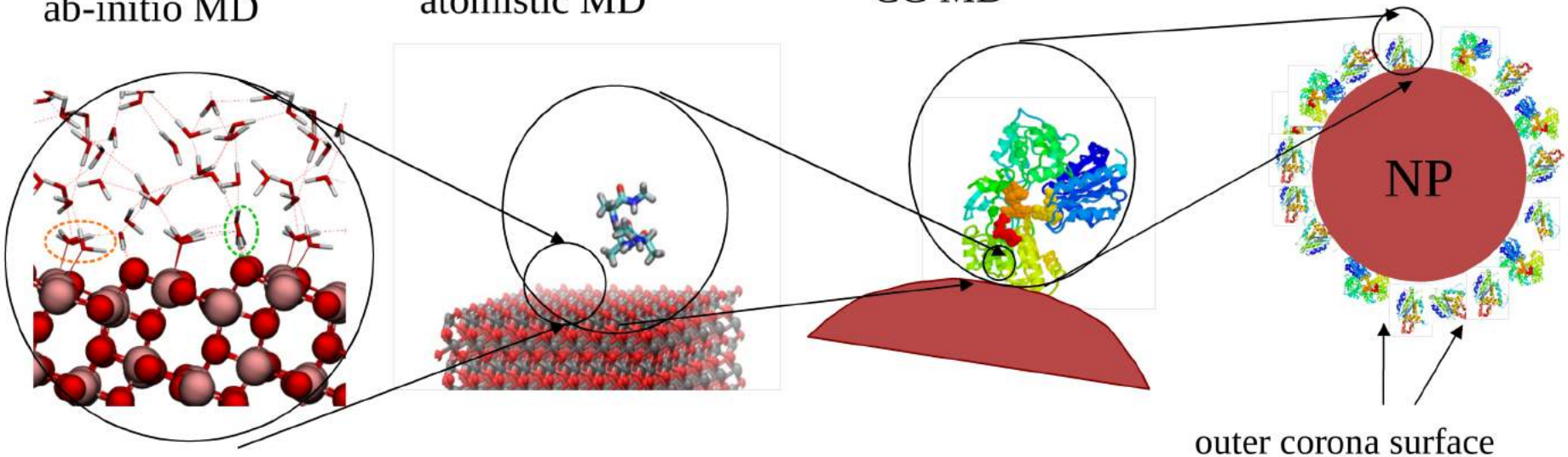
Multiscale modeling of NPs corona composition:

hydration pattern of the surface → interaction of AA with NP surface: → binding of blood plasma proteins → prediction of corona composition

ab-initio MD

atomistic MD

CG MD



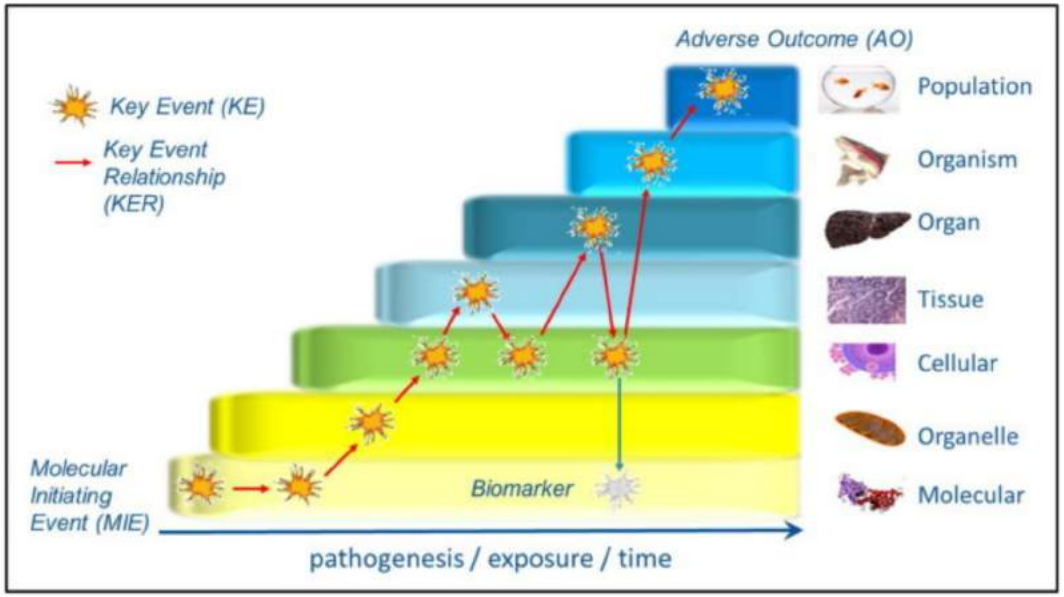
outer corona surface defines further fate of NP

Handshaking of molecular modeling and system biology

The idea here is to link "molecular properties" of NP, accessible by computer simulations, and "molecular initiating events" which are known (from the system biology) to lead to certain adverse outcomes.

Nanomaterial properties

multiscale molecular simulations



[Gerloff et al, Computat. Toxicology, 1,3 (2017)]

Fully mechanistic description of toxicity: but computationally very expensive

Combine statistical and physical-based modeling

Combination of statistical and physical-based modeling allows one to utilize advantages of each.

- Physical based modeling can provide new relevant descriptors which can provide higher predicting power

- Physical based modeling can be used for training of statistical models (machine learning, AI) which link computed physical-chemical descriptors and molecular initiating / key events leading to certain adverse outcomes

iQSAR: QSAR which is aware of molecular interactions

Binding free energies: "Bio-nano interactions" descriptors

"Conventional descriptors": Size and size distribution, shape, surface charge, ...

How to characterize a material quantitatively ?
TiO_2, Ag, CNT, $NiZnFe_4O_8$?

We propose new type of descriptors (to be used alongside with conventional)
Not only characterize NPs, but also their interaction with biomatter:

Binding free energy of biomolecules to the material:

$$\Delta F_{bind} = -RTln\frac{C_{bound}}{C_{free}}$$

- free energy is a fundamental property determining direction of change
- directly measurable experimentally
- expresses strength of interaction of a biomolecule to the material
- directly relevant to phenomena such as corona formation, membrane permeation /disruption, other KE/MIEs

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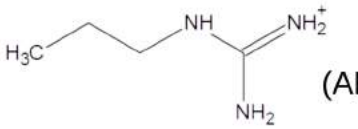
Choice of Biomolecules to describe bio-nano interactions

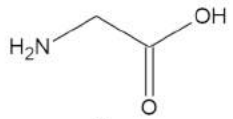
The aim is to cover typical fragments of biological molecules which can interact with NP in an organism:

- Aminoacids side chain analogues (18 st except Gly, Pro)



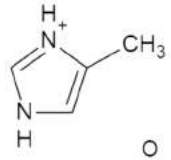
(ARG)

- Glycine and Proline with a backbone fragment



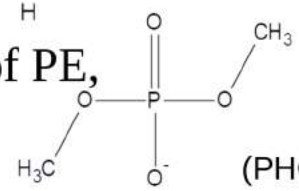
(GLY)

- for AA with 4 < pKa < 10: both protonated and deprotonated forms (His, Cys, Glu)



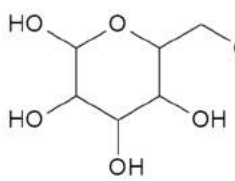
(HIS+)

- Fragments of lipid heads (choline and phosphate of PC; etanolamine of PE, ester fragment of PC/PE)



(PHO)

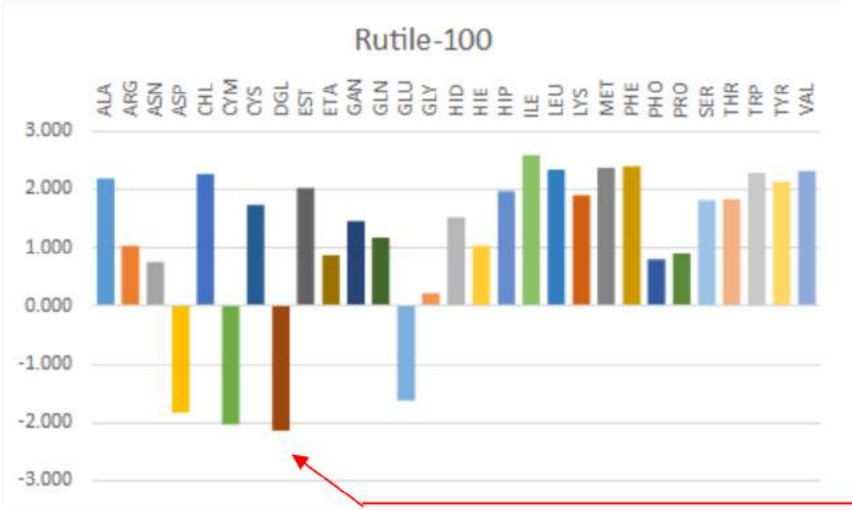
- glucose (component of sugars and glycolipids)



(DGL)

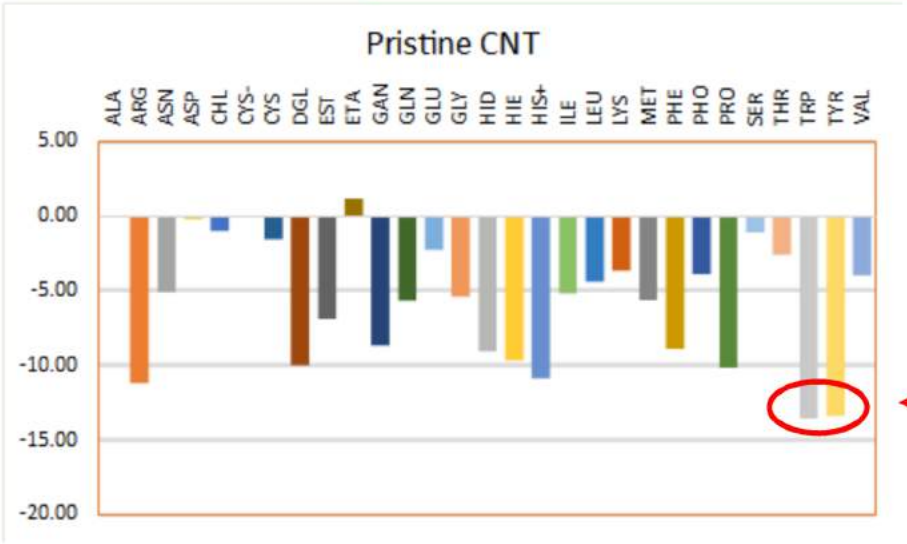
In total, 30 molecular fragments: 30 "binding free energy" descriptors

Bio-Nano descriptors: Binding free energies



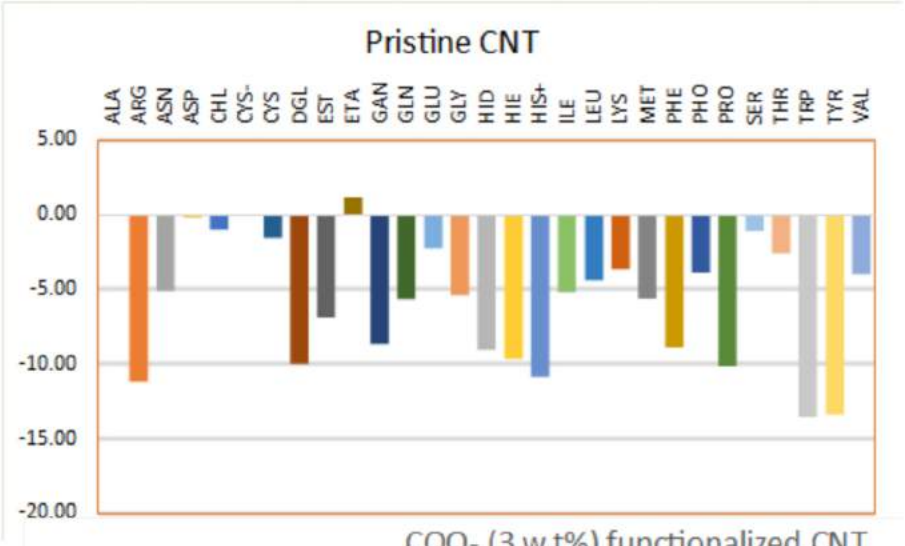
NM fingerprints:
Comparison of nanomaterials on equal footing

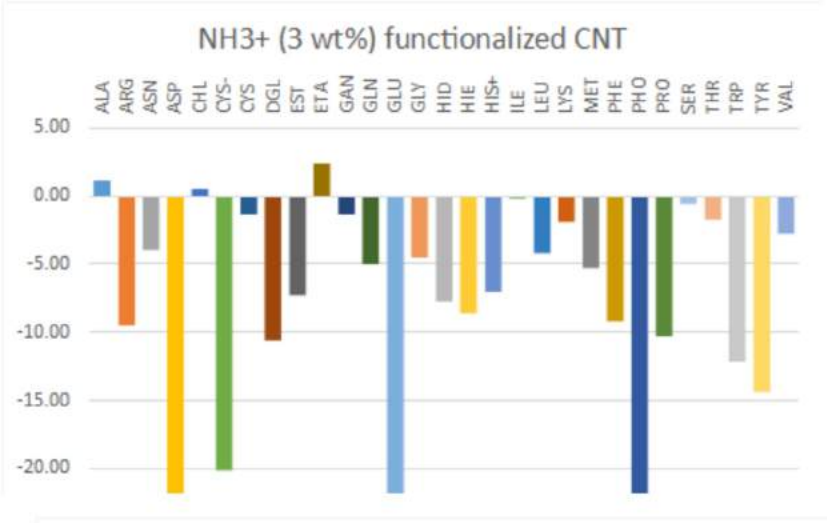
Strongest binding: glucose – many h-bonds

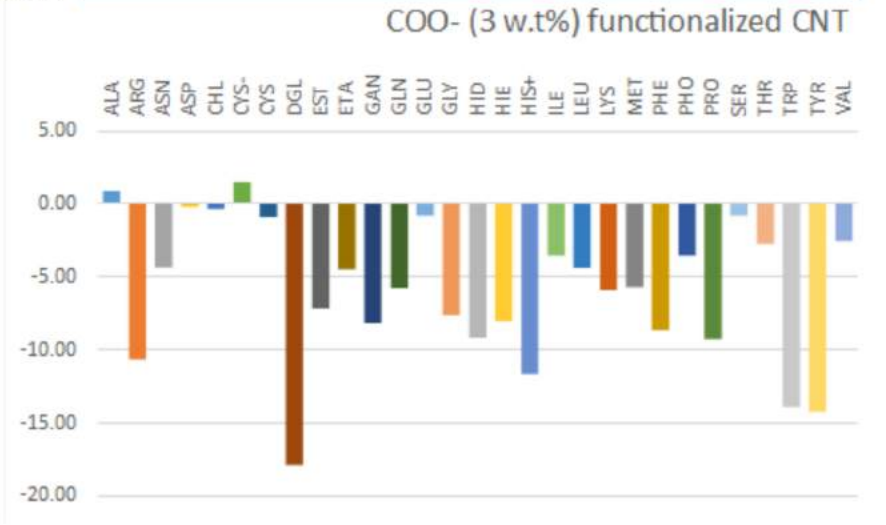


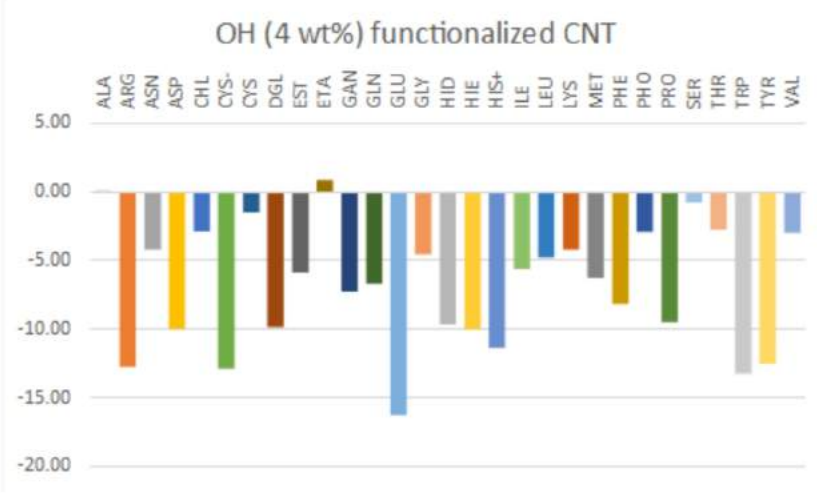
Strongest binding: aromatic AA

Binding free energies at CNTs different functionalization









Different functionalization of CNT gives different ”fingerprints”

Prediction of inflammation response

Neural network trained by data on adsorption energies and on
CNT inflammation (neutrophil influx into the lungs of mice after the inhalation)

NM-400
NM-401
NM-402
NM-403
NRCWE-001
NRCWE-002
NRCWE-025
NRCWE-026
NRCWE-030
NRCWE-040
NRCWE-041
NRCWE-042
NRCWE-043
NRCWE-044
NRCWE-045
NRCWE-046
NRCWE-047
NRCWE-048
NRCWE-049
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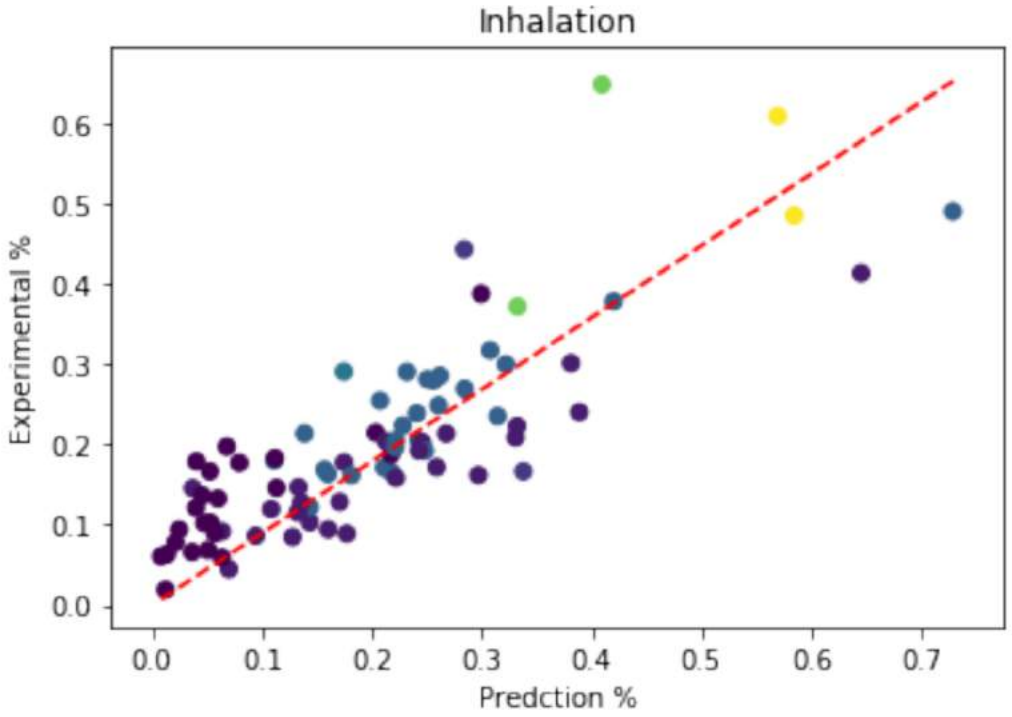


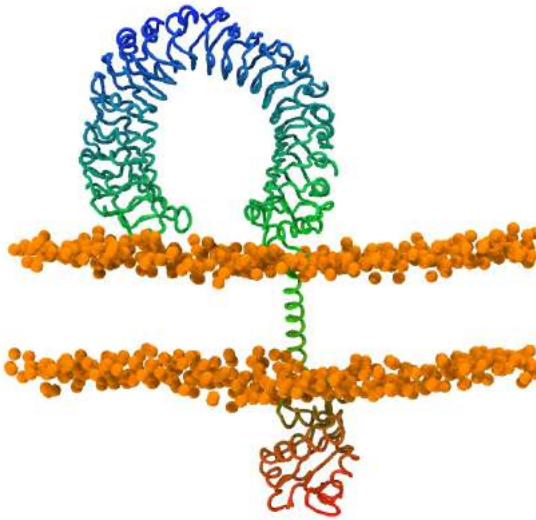
Predicted vs experimental data for the change in
percentage of neutrophil influx when exposed to CNT

Simulations of Molecular Initiating Events

Sensing of NP by cell receptors is one of possible molecular initiating / key events in AOP

Tool Like Receptor 4 (TLR4) is a part of immune system

Responsible for recognizing microbial components (LPS) and initiating intracellular signaling cascade leading to immune response to microbial invaders.



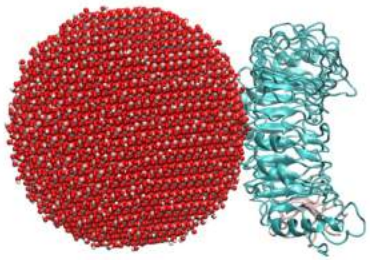
Activated through ligand-induced dimerization.

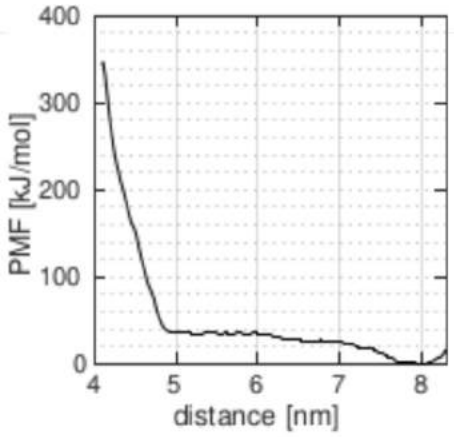
Can NP cause signaling event?

We performed molecular dynamics simulations of full TLR4 in membrane; as well as of extracellular domain in contact with nanoparticles

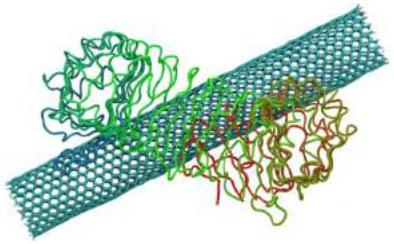
TLR4 interaction with nanoparticles

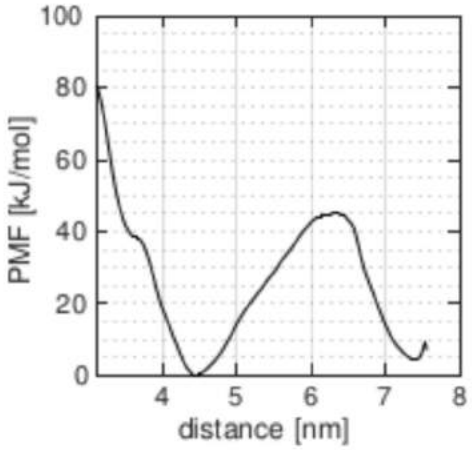
TiO_2



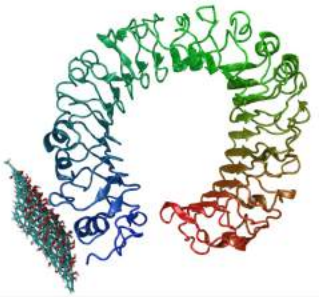


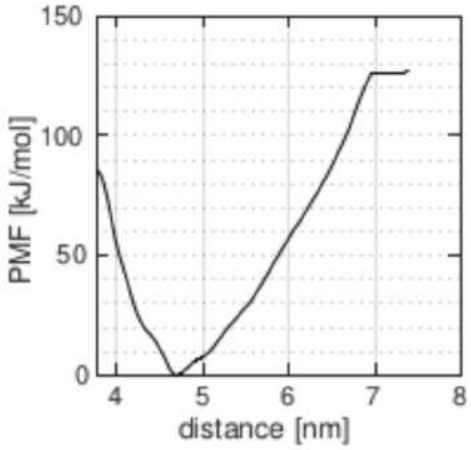
CNT





Graphene oxide





MD (metadynamics) simulations of the potential of mean force (PMF) between extracellular domain of TLR4 and NP. Atomistic simulations in explicit water, ~1μs.

Conclusions & Take Home Messages

- Physics-based simulations provide molecular insight into biomolecular-nanomaterial interactions thus contributing to mechanism-based understanding of the toxicity
- Physical-based modeling can provide relevant descriptors to statistical models with potential to improve predictivity, facilitate grouping and read-across
- We introduced new type of descriptors based of biomolecular-nanomaterial interactions (binding free energies) which characterize different types of NM on equal footing, and demonstrated their predictive character
- We demonstrated possibility to directly model MIE of specific AOP by molecular simulations

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