Computer aided nanoparticles design through Enalos InSilicoNano Platform

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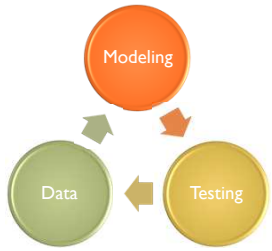
Abstract

Engineered nanoparticles (ENPs) are being extensively used in a great variety of application with a pace that is increasingly growing. The evaluation of the biological effects of ENPs is of outmost importance and for that experimental and most recently computational methods have been suggested. In an effort to computationally explore available datasets that will lead to ready-to-use applications we have developed and validated a QNAR model for the prediction of the cellular uptake of nanoparticles in pancreatic cancer cells. In this work we have tried to address the need of robust and predictive QNAR models for the assessment of the biological profile of ENPs and on top of that the proposed model has been made available online through Enalos InSilicoNano platform. In the proposed workflow all computational steps were incorporated in the platform and this complete line of operations was made feasible with the invaluable help of our in house made Enalos KNIME nodes, namely Enalos Mold2 node, Enalos Model Acceptability Criteria node and Enalos Domain – Similarity node. These nodes have been developed by Novamechanics Ltd and are publicly available through the KNIME Community and the company's website. The platform was used in a virtual screening framework to identify promising compounds within PubChem. Within this proposed strategy EnalosInSilicoNano platform emerges as a key component for evaluating novel nano-structures that have not been experimentally evaluated or even synthesized.



Enalos KNIME nodes

Enalos KNIME Nodes are designed and developed by Novamechanics Ltd with the aim to facilitate model development targeting lead identification and design for all KNIME users. The Nodes are freely available via the KNIME Community and the company's website (http://www.novamechanics.com/knime.php).

Enalos family nodes contain:

(i) Enalos Mold2 node for the calculation of Mold2 molecular descriptors
(ii) Enalos Model Acceptability Criteria node that can be used to validate the Quality of Fit and Predictive Ability of a continuous QSAR Model,
(iii) Enalos Domain – Similarity node that can be used to define Applicability Domain (APD) based on the Euclidean distances,
(iv) Enalos Domain – Leverages node that can be used to define Applicability Domain based on the Leverages.

PubChem Search

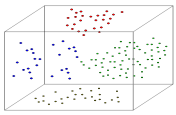
What are the most relevant compounds in terms of: structural, pharmacophore, or shape similarity or their scaffold?

PubChem database searched based on similarity measurements for the identification of the neighbours of the hit compound.

Molecules are considered as vectors in the space of descriptors (« chemical » space).

Dimensions of this space correspond to the number of descriptors.

Clustering methods are employed to analyze distances between compounds and identify clusters.



Scheme I. In silico identification of novel nanoparticles with desired properties

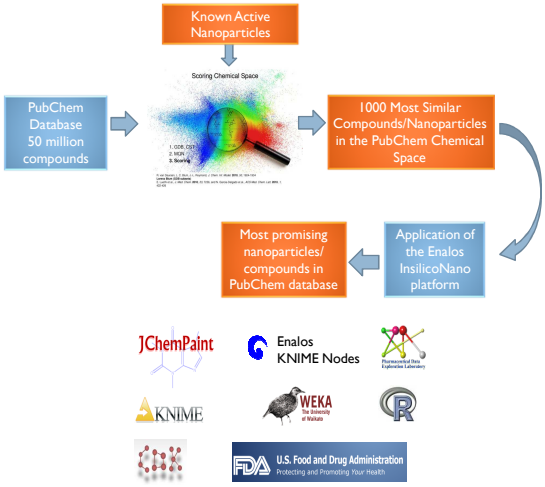
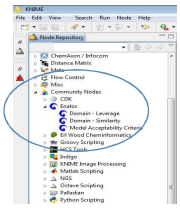


Figure 1. Enalos KNIME nodes and Enalos InSilicoNano Platform



Scheme II. Building Accurate and Robust Models using Enalos KNIME nodes

1. Data collection (nanoparticles) and integration in a single database
2. Descriptor Calculation (Enalos Mold2 KNIME node) – Variable Selection
3. Model Development (Enalos Model Acceptability Criteria KNIME node
4. Model Internal and External Validation
5. Define Domain of Applicability (Enalos Domain –Similarity and Domain – Leverage KNIME node)
6. Enalos KNIME workflows for the assessment of their cellular uptake

Computer aided nanoparticles design through Enalos InSilicoNano Platform

Novamechanics Ltd has recently launched Enalos InSilico Nano Platform, available at http://enalos.insilicotox.com/QNAR_PaCa2/ Enalos InSilico Nano Platform aims to address the need to reduce the amount of time spent by scientists in referencing disparate sources of data to aid decision making related to nanoparticles design and it offers an efficient and cost-effective response to the desire to reduce in vitro / in vivo testing. The available workflows are built based on diverse and reliable data sources and integrate advanced in silico tools to provide accurate predictions.

Through Enalos InSilicoNano Platform property predictions can be obtained for chemical structure provided by the user. Structures can be designed, entered as SMILES or imported in SDF format. The QNAR_PaCa2 model can be selected from the pull down menu of the available workflows already developed and provided by the Enalos InSilicNanoPlatform.

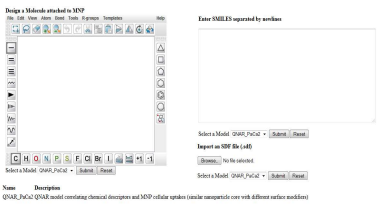


Figure 2. Enalos KNIME nodes: Model evaluation Results

Criterion	Assessment	Result
R^2 > 0.6	PASS	R^2 = 0.848
Rcvext^2 > 0.5	PASS	Rcvext^2 = 0.82
(R^2-R0^2)/R^2 < 0.1	PASS	(R^2-R0^2)/R^2 = 0.038
(R^2-R'0^2)/R^2 < 0.1	PASS	(R^2-R'0^2)/R^2 = 0.0
abs(R0^2-R'0^2) < 0.1	PASS	abs(R0^2-R'0^2) = 0.032
0.85 < k < 1.15	PASS	k = 1.019
0.85 < k' < 1.15	PASS	k' = 0.979
Model Predictive		

Acknowledgement

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References

• Enalos Drug Discovery Platform: www.insilicotox.com
• Enalos KNIME nodes: http://www.novamechanics.com/knime.php
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• Melagraki, G.,Afantitis,A Enalos InSilicoNano Platform:An online decision support tool for the design and virtual screening of nanoparticles, under publication