UNC
ESHELMAN
SCHOOL OF PHARMACY

Computer-Aided Design of Nanomaterials

with the Desired Bioactivity and Safety Profiles

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Research Objectives

Subtask 1

- To create, curate and maintain a specialized database incorporating all existing information on MNPs including their physical/chemical properties and associated biological data emerging from both ERC research teams and the scientific literature;

Subtask 2

- To develop statistically significant and externally validated QNAR models that can be used to prioritize MNPs for biological studies;

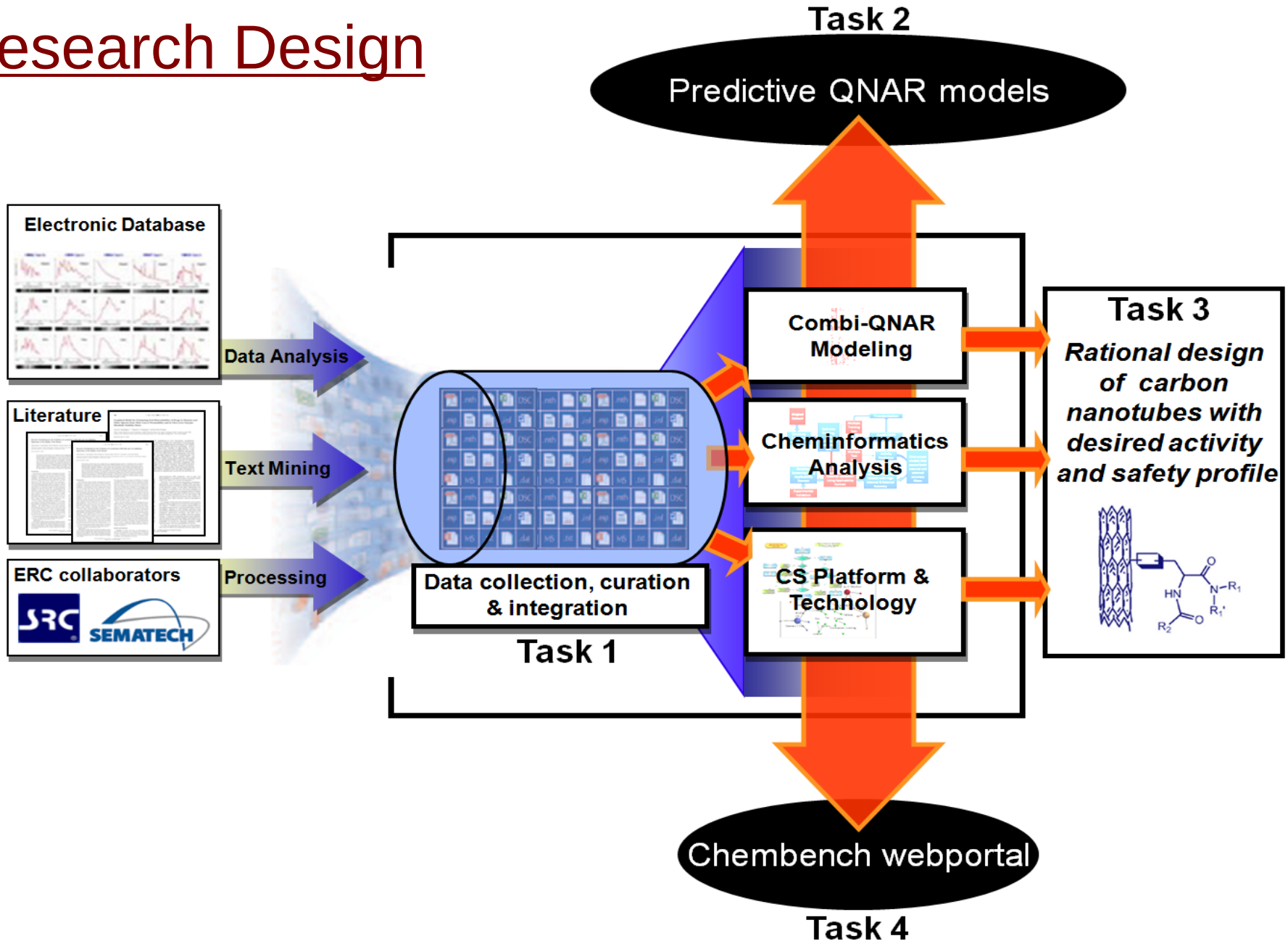
Subtask 3

- To design novel surface modified carbon nanotubes (CNTs) with the desired biocompatibility in collaboration with Dr. Bing Yan at St Jude Children's Research Hospital;

Subtask 4

- To make the database and all developed QNAR predictors accessible via our Chembench webportal (*http://chembench.mml.unc.edu*).

Research Design

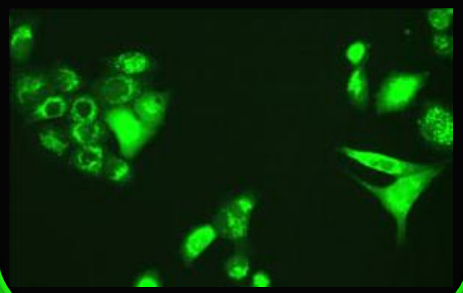


Challenges of data integration: an example of Lung A549 cells.

Pulskamp et al., Toxicol. Lett., 2007, 168, 58-74.

Several carbon MNPs (multi-walled, single-walled, carbon black, quartz) increased Reactive Oxygen Species (ROS) and decreased mitochondrial membrane potential in a dose- and time-dependent manner in rat macrophages and human **A549** lung cells.

Lung adenocarcinoma A549 cells



Liu et al., Nanotechnology, 2010, 21, 315106.

The authors demonstrated the efficiency for lung cancer treatment of nanodiamond NPs carrying paclitaxel on their surface: these NPs were found *(i)* to reduce the **A549** cell viability *in vitro* by inducing both mitotic arrest and apoptosis, and *(ii)* blocked the tumor growth in mice.

Tahara et al., Int. J. Pharm., 2009, 382, 198-204.

The A549 cell uptake of chitosan-modified PLGA nanospheres is time-, temperature-, and concentration-dependent, regulated by clathrin-mediated endocytosis. Low cytotoxicity was reported for these modified, surface decorated nanospheres, suggesting them as preferable drug carriers for **A549** cells.

Deng et al., Nanotoxicology., 2010, 4, 186-195.

Foldbjerg et al., Arch. Toxicol., 2010, In Press.

PVP coated silver nanoparticles were reported to induce ROS and damage DNA in **A549** cells depending on their doses, as well as increase gap junctional intercellular communication.

Round Robin Effort

CeO2 toxicity & aggregation

Johnston et al. *Environmental science & technology* **2010**, *44*, 1144-51.

Significant uptake found in zebrafish liver. Formation of large NP aggregates (up to 3 µm). Unlikely to be a major ecotoxicological hazard for many nonbenthic fish

Para, R. **2011**. Thesis manuscript

Important decreases of rat heart weights proportionally to the number of instillation days. Inhalation of CeO_2 NPs can cause increased cardiac oxidative stress and autophagy

Eom, H.-J.; Choi, J. *Toxicology letters* **2009**, *187*, 77-83.

Oxidative stress induced by CeO_2 NPs in human bronchial epithelial Beas-2B cells is caused by an increase of the cellular reactive oxygen species (ROS) concentrations.

Lin, W.; Huang, Y.-W.; Zhou, X.-D.; Ma, Y. *International journal of toxicology* **2006**, *25*, 451-7.
Lin, W.; Stayton, I.; Huang, Y.-wern; Zhou, X.-D.; Ma, Y. *Toxicological & Environmental Chemistry* **2008**, 90, 983-996.

Cytotoxicity of CeO_2 NPs is directly related to an oxidative stress and lipid peroxidation mechanism. CeO_2 NPs (20 nm) are significantly more cytotoxic than Al_2O_3 NPs (13 and 22 nm).

Van Hoecke et al. *Environmental pollution (Barking, Essex : 1987)* 2011, *159*, 970-6.

Increasing pH and IS enhanced aggregation, while increasing NOM decreased mean aggregate sizes. The NOM was found to adsorb to the CeO_2 NP surface. => reduction in NP toxicity

Van Hoecke et al. *Environmental science & technology* **2009**, *43*, 4537-46.

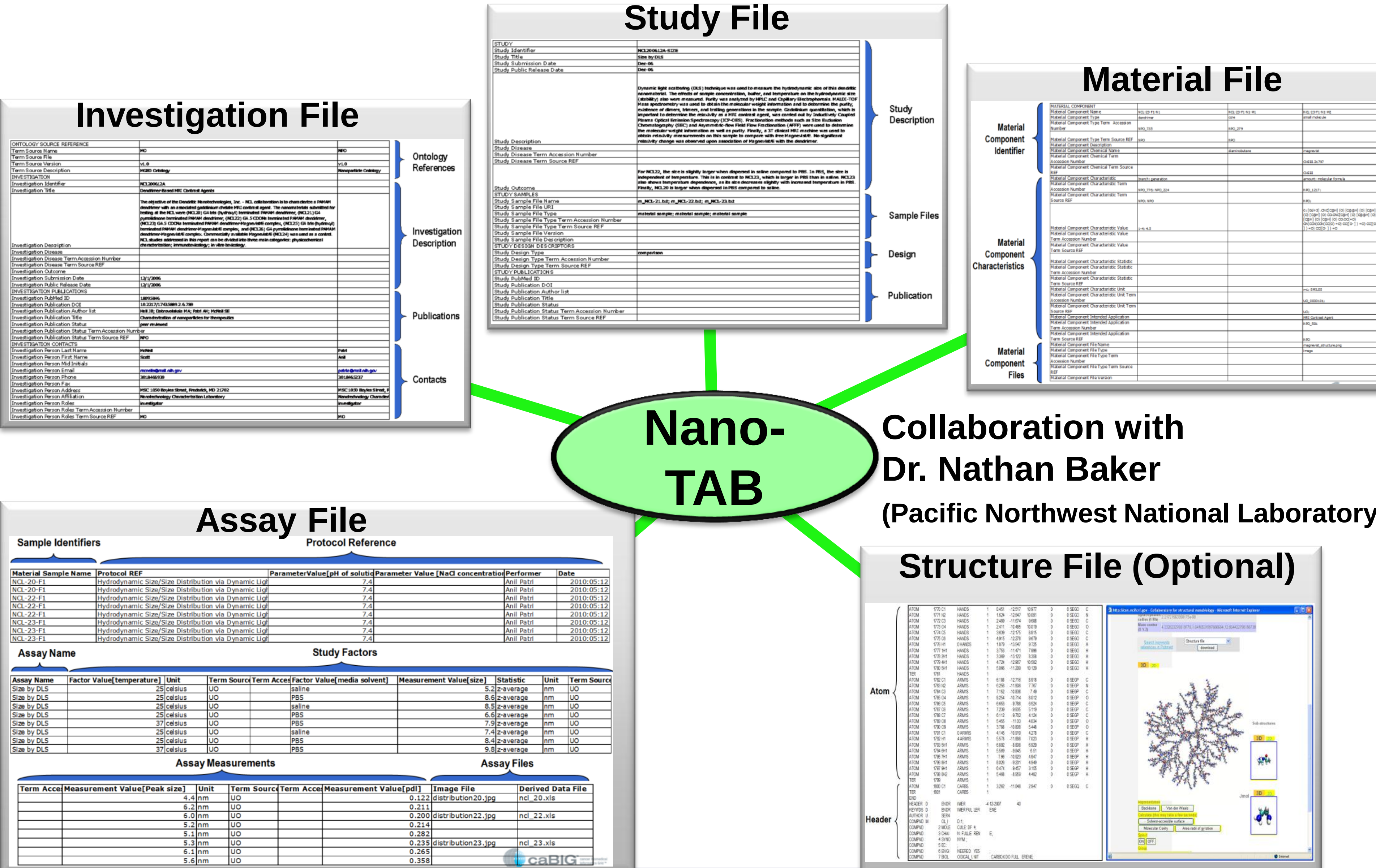
Aquatic toxicity of CeO2 NPs with different sizes (14, 20, and 29 nm; pH=7.4; mean aggregate size = 400 nm). No acute toxicity for two crustaceans (*Daphnia magna* and *Thamnocephalus platyurus*) up to test concentrations of 1000 and 5000mg/L respectively. Significant chronic toxicity to unicellular green alga *P.subcapitata* with EC_{10} between 2.6 and 5.4 mg/L. Chronic toxicity was found to increase with decreasing nominal particle diameter.

Data depositories

Studies on MNP of different core structure, size, shape, and with various surface modifications have been reported but all published data are diverse, non-searchable, and spread among numerous sources of information.

- Lack of centralized data repository
- Limits our capability to develop predictive tools to assess nanotoxicity in advance of manufacturing
- Severely limits the design of novel nanomaterials that are environmentally benign and safe for human exposure

Data sharing/storing format for nanomaterials

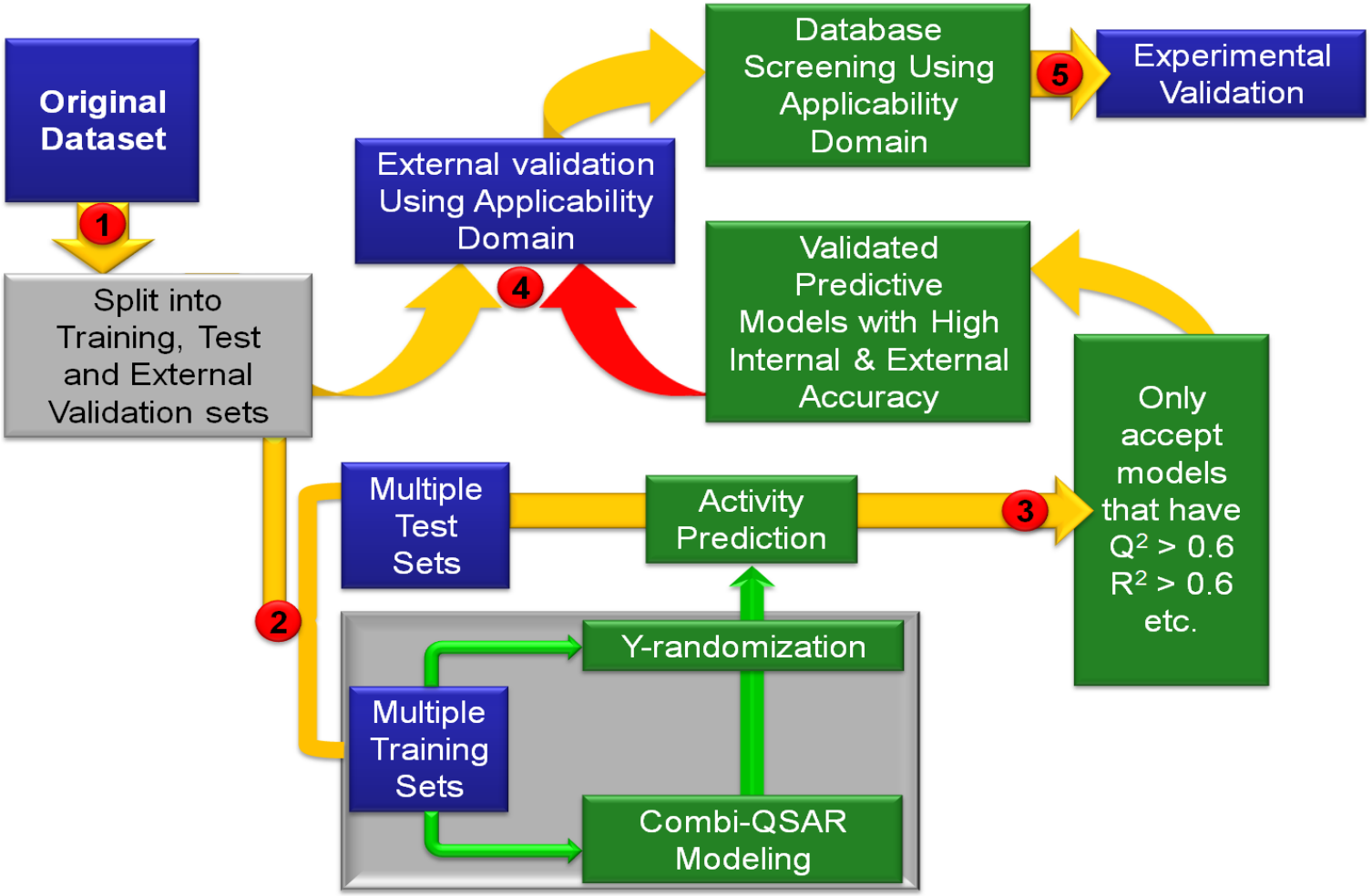


Material Sample Name	Protocol REF	ParameterValue[pH of solutio	Parameter Value [NaCl concentratio	Performer	Date
NCL-20-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-20-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-22-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-22-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-22-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-22-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-23-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-23-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12
NCL-23-F1	Hydrodynamic Size/Size Distribution via Dynamic Ligh	7.4		Anil Patri	2010:05:12

Assay Name	Factor Value[temperature]	Unit	Term Source	Term Acces	Factor Value[media solvent]	Measurement Value[size]	Statistic	Unit	Term Source
Size by DLS	25	celsius	UO		saline	5.2	z-average	nm	UO
Size by DLS	25	celsius	UO		PBS	8.6	z-average	nm	UO
Size by DLS	25	celsius	UO		saline	8.5	z-average	nm	UO
Size by DLS	25	celsius	UO		PBS	6.6	z-average	nm	UO
Size by DLS	37	celsius	UO		PBS	7.9	z-average	nm	UO
Size by DLS	25	celsius	UO		saline	7.4	z-average	nm	UO
Size by DLS	25	celsius	UO		PBS	8.4	z-average	nm	UO
Size by DLS	37	celsius	UO		PBS	9.8	z-average	nm	UO

Term Acce	Measurement Value[Peak size]	Unit	Term Source	Term Acce	Measurement Value[pdI]	Image File	Derived Data File
	4.4	nm	UO		0.122	distribution20.jpg	ncl_20.xls
	6.2	nm	UO		0.211		
	6.0	nm	UO		0.200	distribution22.jpg	ncl_22.xls
	5.2	nm	UO		0.214		
	5.1	nm	UO		0.282		
	5.3	nm	UO		0.235	distribution23.jpg	ncl_23.xls
	6.1	nm	UO		0.265		
	5.6	nm	UO		0.358		

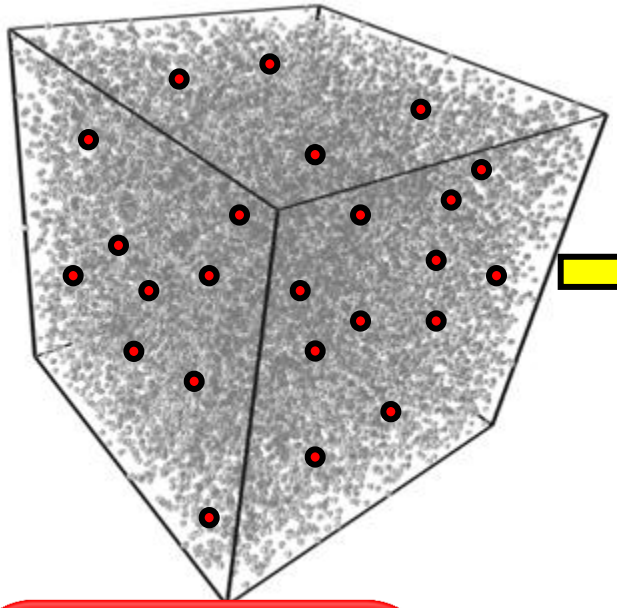
Predictive QNAR Workflow



** Tropsha, A. Best Practices for QSAR Model Development, Validation, and Exploitation Mol. Inf., 2010, 29, 476 – 488).*

Computer-aided design of novel carbon nanotubes with desired biological properties

(in collaboration with Dr. Bing Yan, St. Jude Children's Research Hospital)



Similarity Search

Consensus QSAR models

VIRTUAL SCREENING

~10^2 molecules

240,000 *in silico* designed small molecules which are considered attachable to CNTs

Similarity Search

462 molecules

QNAR Predictions

CA non-binders

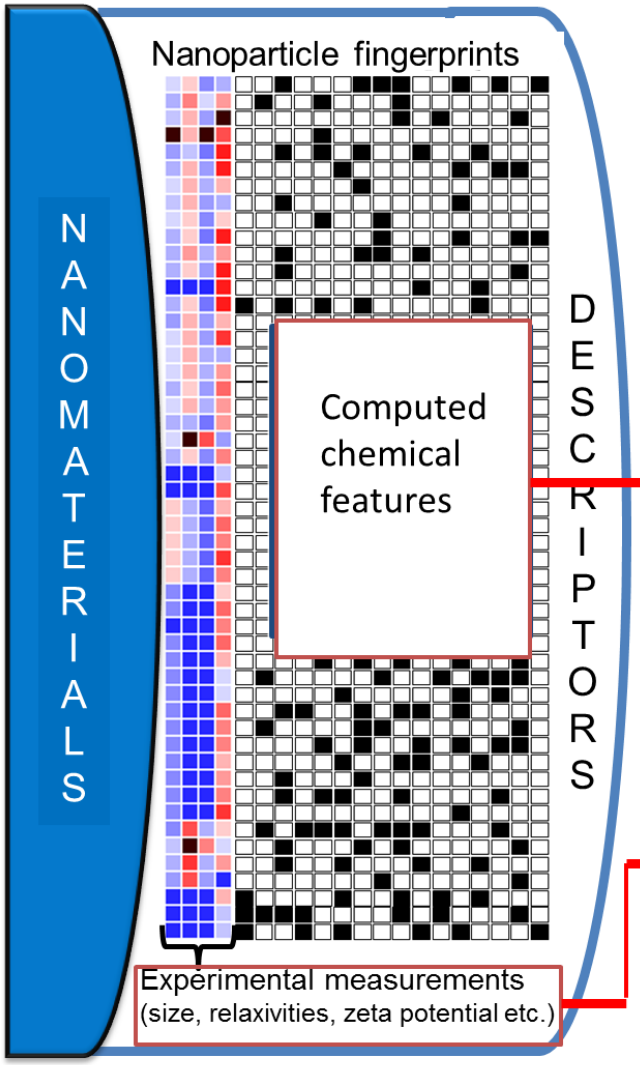
110 molecules

Non-toxic

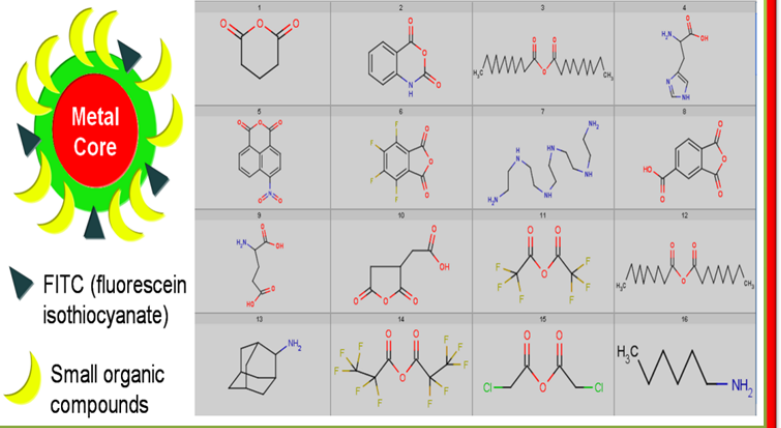
189 molecules

Experimental Validation

MNP Types and Descriptors



ALL PARTICLES HAVE THE SAME CORE BUT DIFFERENT SURFACE MODIFIERS



Classical molecular descriptors can be computed for a molecule representing surface modifier.

ALL PARTICLES HAVE DIFFERENT CORES/ARCHITECTURES

MNP	CLIO	PNP	MION	QD	Feridex IV	Ferrum Hausmann
#. particle	23	19	4	3	1	1

In the absence of defined three-dimensional structure only experimentally mesured properties could be used as descriptors

New theoretical MNP descriptors: Computed characteristics of materials*

Index	▲ Name	Atom Number	Fit Band Gap (eV)	me(m0)	mmine(m0)	mh(m0)	mminh(m0)	Mass ratio	Valence Band Width (eV)	Core Valence Gap (eV)	Density (g/cm3)
1	Al1La1O3	5	5.13	0.45	0.36	1.81	0.56	4.06	7.46	6.06	6.42
2	As1Ca3Cl3	7	3.39	0.64	0.34	0.52	0.24	1.24	1.36	1.62	2.63
3	As1Cl1Hg3O4	9	3.67	1.21	1.21	2.6	2.42	2.15	6.21	0.18	8.76
4	Ba1Ce1O3	5	4.9	2.54	1.81	3.69	0.3	1.45	3.15	8.17	6.44
5	Ba1F3Li1	5	9.68	0.63	0.51	12.87	0.8	20.52	2.31	6.27	5.25
6	Ba1O3Pr1	5	3.63	2.9	1.9	4.75	0.3	1.63	3.07	8.07	6.52
7	Ba1O3Zr1	5	5.01	0.69	0.37	2.92	0.9	4.2	3.64	6.75	6.28
8	Ba1Se1	2	2.55	0.55	0.23	0.67	0.19	1.23	3.06	7.49	6.57
9	Be1H3Na1	5	2.15	0.51	0.49	0.41	0.23	1.25	9.63	14.17	1.67
10	Bi1In1O3	5	1.22	0.26	0.22	11.71	0.35	44.78	7.13	2.87	8.37
11	Br1K3O1	5	2.11	0.38	0.37	2.35	0.55	6.27	0.92	2.62	2.5
12	Br1O1Rb3	5	1.46	0.34	0.33	2.13	0.41	6.35	1.07	2.66	3.58
13	Br3Cd1Cs1	5	2.35	0.19	0.18	6.39	0.28	34.39	5.55	0.78	5.32
14	C1K4O4	9	3.96	0.5	0.5	8.74	6.45	17.55	0.13	0.69	2.65
15	C1Li4O4	9	6.53	0.8	0.79	3.45	1.84	4.28	4.28	1.66	2.63
16	C1Na4O4	9	3.67	0.48	0.48	5.38	3.89	11.21	0.68	0.33	2.97

*data from aflowlib.org (collaboration with Prof. Stefano Curtarolo, Duke University)

New theoretical MNP descriptors: Materials fingerprints

Index	Name	Atom Number	Fit Band Gap (eV)	me(m0)	mmine(m0)	mh(m0)	mminh(m0)	Mass ratio	Valence Band Width (eV)	Core Valence Gap (eV)	Density (g/cm3)
1	Al1La1O3	5	5.13	0.45	0.36	1.81	0.56	4.06	7.46	6.06	6.42
2	As1Ca3Cl3	7	3.39	0.64	0.34	0.52	0.24	1.24	1.36	1.62	2.63
3	As1Cl[illegible]3O4	9	3.67	1.21	1.21	2.6	2.42	2.15	6.21	0.18	8.76
4	Ba1C[illegible]1O3	5	4.9	2.54	1.81	3.69	0.3	1.45	3.15	8.17	6.44
5	Ba1[illegible]Li1										
6	Ba1C[illegible]Pr1										
7	Ba1O3Zr1										
8	Ba1Se1										
9	Be1H3Na1	5	2.15	0.51	0.49	0.41	0.23	1.25	9.63	14.17	1.67
10	Bi1In1O3	5	1.22	0.26	0.22	11.71	0.35	44.78	7.13	2.87	8.37
11	Br1K3O1	5	2.11	0.38	0.37	2.35	0.55	6.27	0.92	2.62	2.5
12	Br1O1Rb3	5	1.46	0.34	0.33	2.13	0.41	6.35	1.07	2.66	3.58
13	Br3Cd1Cs1	5	2.35	0.19	0.18	6.39	0.28	34.39	5.55	0.78	5.32
14	C1K4O4	9	3.96	0.5	0.5	8.74	6.45	17.55	0.13	0.69	2.65
15	C1Li4O4	9	6.53	0.8	0.79	3.45	1.84	4.28	4.28	1.66	2.63
16	C1Na4O4	9	3.67	0.48	0.48	5.38	3.89	11.21	0.68	0.33	2.97
17	C2Ca1	3	3.28	1.33	0.33	1.56	0.59	1.17	1.81	0.49	2.25
18	Ca1O3Ti1	5	4.1	1	0.45	2.66	0.82	2.65			
19	Ca1O3Zr1	5	5.25	0.7	0.39	3.09	0.93	4.39			
20	Ca3Cl3P1	7	3.4	0.63	0.34	0.56	0.27	1.13			
21	Cd1F3Rb1	5	5.58	0.44	0.44	40.03	0.52				
22	Cl1Rb1	2	7.33	0.39	0.39	3.31	0.7				
23	Cl3Cs1Sn1	5	1.75	0.47	0.08	0.11	0.1				
24	Cr1La1O3	5	3.33	0.72	0.36	1.69	1.45				
25	Cs1F3Hg1	5	1.89	0.34	0.33	325.67	0.43	968.99			
26	Cs1F3Mg1	5	9.98	0.45	0.44	7.73	0.54	17.32			
27	Cs3O3Sb1	7	5.18	1.96	0.32	2.23	1.63	1.14			
28	Cs3Sb1Se3	7	4.05	5.49	1.76	3.68	0.9	1.49			
29	Cu2O1	3	1.79	0.82	0.82	1.87	0.22	2.28	6.84	11.98	6.14
30	Cu3S4Ta1	8	3.84	1.31	0.97	1.24	0.62	1.06	5.3	6.82	4.93
31	F3Mg1Na1	5	8.9	0.56	0.56	11.78	1.83	21.02	3.94	15.54	2.97
32	F3Rb1V1	5	3.86	0.49	0.49	12.81	1.98	26.01	7.49	3.25	4.39
33	F3Rb1Yb1	5	2.39	0.49	0.49	9.59	3.96	19.35	0.19	4.86	5.63
34	F3Sc1	4	9.1	4.35	1.17	23.29	2.35	5.36	3.03	16.02	2.62
35	Fe1La1O3	5	1.63	1.11	0.53	11.35	0.36	10.23	9.02	6.58	6.85
36	Ge1I3Rb1	5	1.66	0.38	0.06	0.12	0.1	3.12	4.43	2.4	4.15
37	I1K3O1	5									
38	Ir1S1Sb1	3									
39	N2O1	3									
40	O2Si1	3									
41	O3Pb1Ti1	5									
42	O3Sn1Sr1	5									
43	O3Sr1Tc1	5									
44	O3Sr1Ti1	5									
45	O6Se2Sn1	9									
46	Os1Se2	3									

Etc.

46 materials (*e.g.*, CaO_3Zr, BaSe, etc.)

Data Curation Normalization and Selection of Descriptors

Descriptors derived from quantum mechanics calculations (DFT)
In collaboration with Dr. Curtarolo (Duke University)

Materials Fingerprints

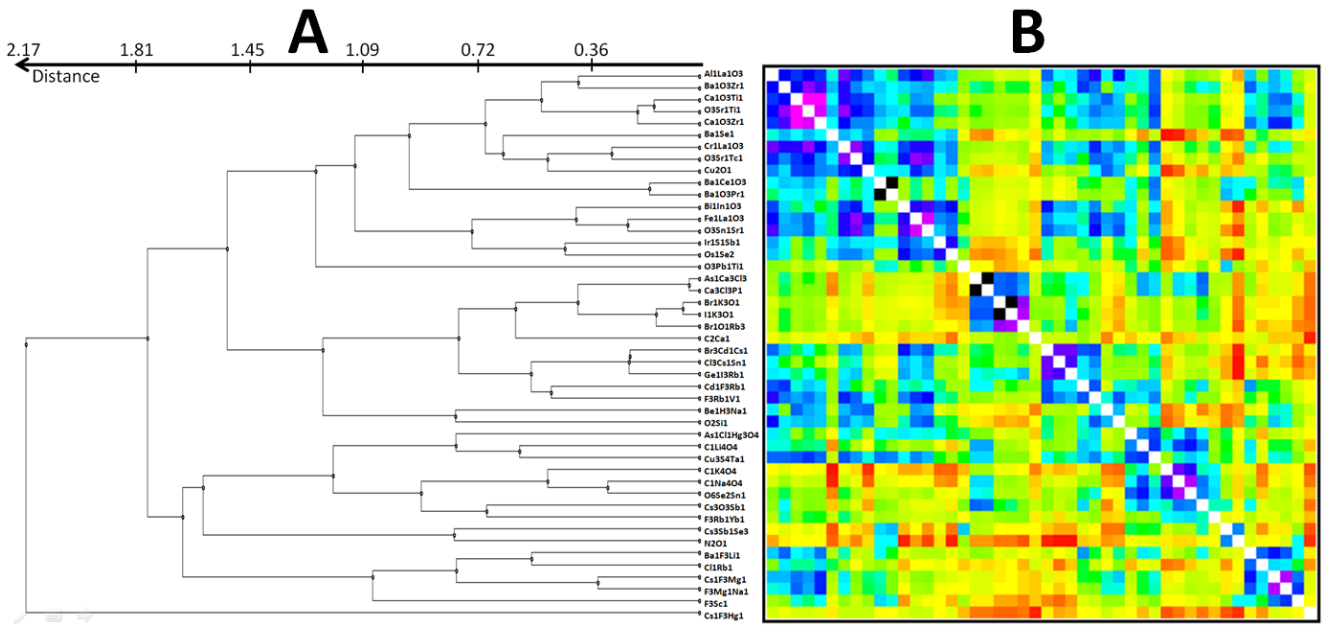
0.429	0.456	0.044	0.129	0.005	0.072	0.003	0.732	0.376	0.515
0.714	0.260	0.076	0.121	0.001	0.022	0.000	0.123	0.098	0.113
1.000	0.292	0.173	0.496	0.008	0.365	0.001	0.607	0.008	0.763
0.429	0.430	0.398	0.754	0.011	0.032	0.000	0.301	0.508	0.517
0.429	0.966	0.075	0.194	0.039	0.110	0.020	0.218	0.389	0.391
0.429	0.287	0.459	0.793	0.014	0.032	0.001	0.293	0.502	0.525
0.429	0.442	0.085	0.134	0.009	0.126	0.003	0.350	0.419	0.500
0.000	0.166	0.061	0.073	0.002	0.014	0.000	0.292	0.466	0.531
0.429	0.121	0.054	0.185	0.001	0.021	0.000	0.948	0.884	0.012
0.429	0.017	0.012	0.069	0.036	0.039	0.045	0.699	0.176	0.721
0.429	0.117	0.032	0.134	0.007	0.071	0.005	0.079	0.160	0.100
0.429	0.044	0.025	0.116	0.006	0.049	0.006	0.094	0.163	0.214
0.429	0.144	0.000	0.052	0.019	0.028	0.034	0.541	0.045	0.398
1.000	0.324	0.053	0.190	0.027	1.000	0.017	0.000	0.040	0.116
1.000	0.613	0.103	0.315	0.010	0.274	0.003	0.414	0.100	0.113
1.000	0.292	0.049	0.181	0.016	0.597	0.011	0.055	0.017	0.149
0.143	0.248	0.193	0.116	0.005	0.077	0.000	0.168	0.027	0.073
0.429	0.340	0.137	0.168	0.008	0.113	0.002	0.468	0.702	0.272
0.429	0.469	0.086	0.142	0.009	0.131	0.003	0.395	0.689	0.320
0.714	0.262	0.075	0.121	0.001	0.027	0.000	0.117	0.103	0.082
		0.042	0.164	0.123	0.066	0.092	0.412	0.063	0.361
		0.034	0.142	0.010	0.095	0.008	0.128	0.439	0.238
		0.047	0.009	0.000	0.000	0.003	0.589	0.000	0.212
		0.090	0.129	0.005	0.213	0.001	0.604	0.540	0.543
0.429	0.092	0.025	0.116	1.000	0.052	1.000	0.606	0.788	0.554
0.429	1.000	0.044	0.164	0.023	0.069	0.017	0.476	0.898	0.333
0.714	0.461	0.300	0.112	0.007	0.241	0.000	0.021	0.013	0.359
0.714	0.335	0.897	0.733	0.011	0.126	0.000	0.001	0.002	0.283
0.143	0.081	0.107	0.328	0.005	0.019	0.001	0.670	0.747	0.485
0.857	0.311	0.190	0.392	0.004	0.082	0.000	0.516	0.424	0.357
0.429	0.879	0.063	0.216	0.036	0.272	0.021	0.380	0.970	0.149
0.429	0.313	0.051	0.185	0.039	0.296	0.026	0.735	0.200	0.300
0.429	0.148	0.051	0.185	0.029	0.608	0.019	0.006	0.301	0.431
0.286	0.901	0.704	0.478	0.071	0.354	0.004	0.289	1.000	0.112
0.429	0.063	0.156	0.203	0.035	0.041	0.010	0.887	0.409	0.560
0.429	0.066	0.032	0.000	0.000	0.000	0.002	0.429	0.147	0.274
0.429	0.137	0.025	0.121	0.007	0.074	0.006	0.072	0.150	0.145
0.143	0.199	0.164	0.392	0.001	0.057	0.002	0.594	0.149	0.951
0.143	0.487	0.880	1.000	0.013	0.370	0.000	0.067	0.246	0.000
0.143	0.589	0.029	0.125	0.009	0.088	0.008	1.000	0.424	0.321
0.429	0.312	1.000	0.207	0.002	0.025	0.007	0.487	0.035	0.686
0.429	0.125	0.007	0.060	0.009	0.098	0.012	0.877	0.367	0.520
0.429	0.000	0.117	0.108	0.004	0.145	0.001	0.691	0.558	0.504
0.429	0.329	0.149	0.172	0.008	0.112	0.002	0.460	0.602	0.377
1.000	0.370	0.036	0.147	0.018	0.652	0.014	0.271	0.071	0.315
0.143	0.019	0.014	0.086	0.003	0.153	0.003	0.622	0.313	1.000

Materials Similarity based on their Fingerprints

Tanimoto similarity coefficient S between materials A and B is calculated as follows:

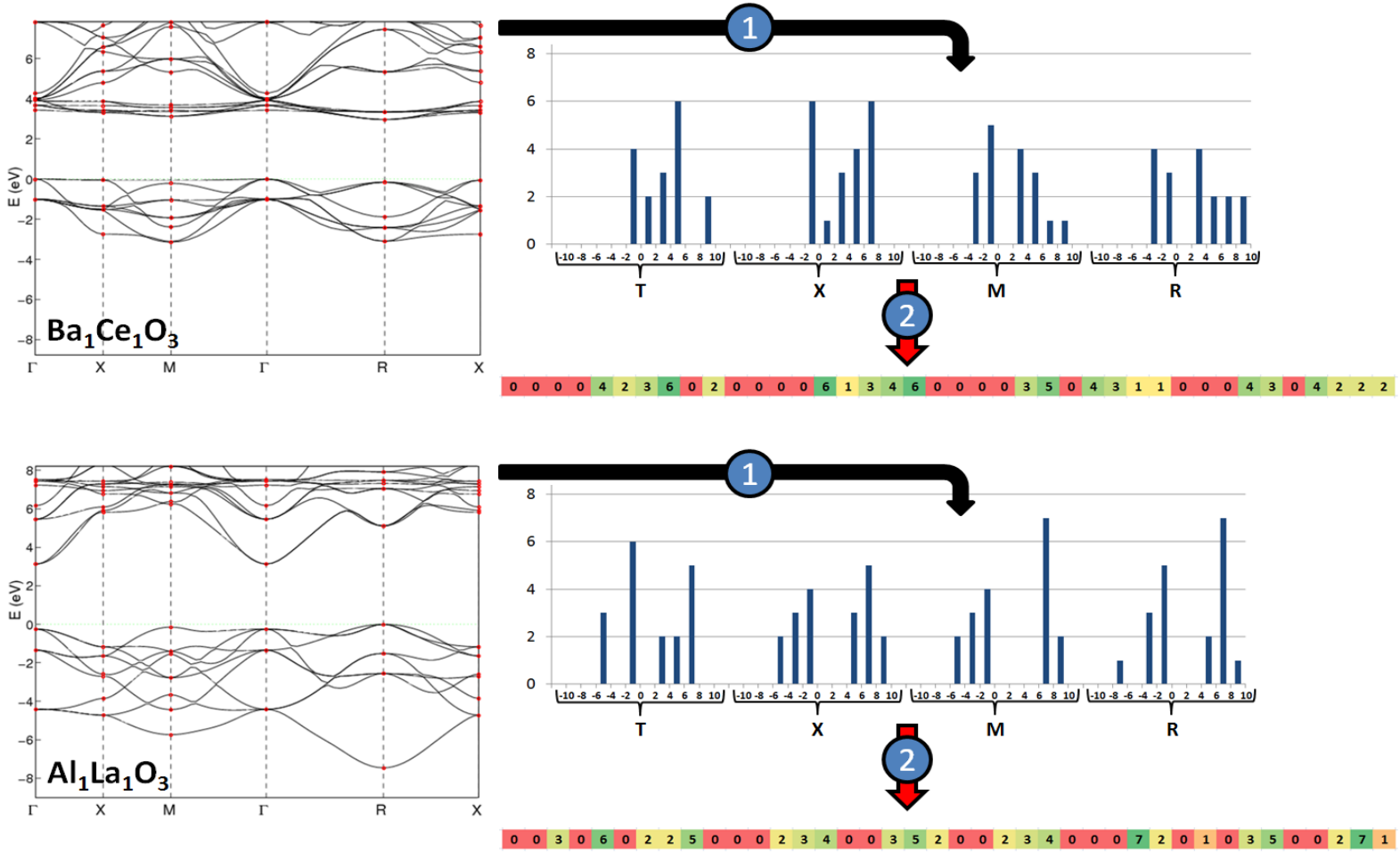
$$S_{A,B} = [\sum_{j=1}^{j=n} x_{jA}x_{jB}]/[\sum_{j=1}^{j=n}(x_{jA})^2 + \sum_{j=1}^{j=n}(x_{jB})^2 - \sum_{j=1}^{j=n} x_{jA}x_{jB}]$$

with x_j is the value of the j^{th} descriptor and *n* the total number of descriptors in the fingerprints. Tanimoto similarities are ranging from 0 (no similarity between materials A and B) to 1 (A and B are identical).



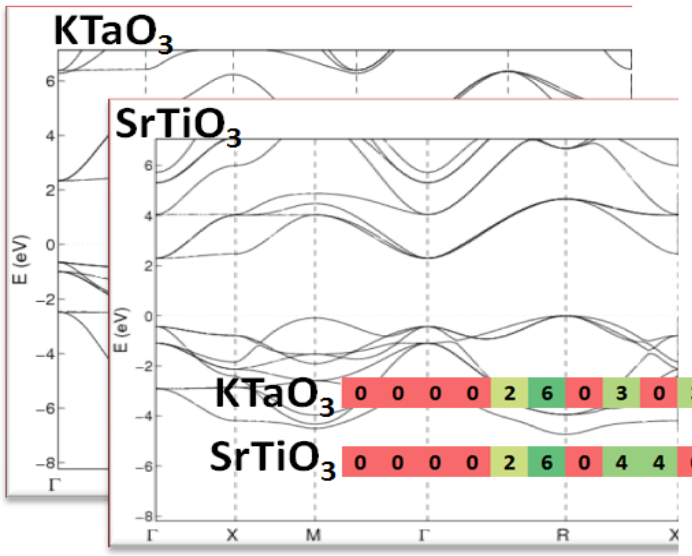
Hierarchical clustering of 46 materials according to their fingerprints.

Material Fingerprints



Materials fingerprints generated from electronic band structures computed with DFT. Band structures are transformed into band distribution plots **(1)** and then converted into materials fingerprints **(2)**.

Reprofiling materials with desired properties



KTaO$_3$ 0 0 0 0 2 6 0 3 0 3 0 0 0 0 0 0 1 3 5 0 1 2 1 2 0 0 0 0 3 2 4 0 0 3 1 2 0 0 0 0 3

SrTiO$_3$ 0 0 0 0 2 6 0 4 4 0 0 0 0 0 0 1 3 5 0 4 1 2 1 0 0 0 0 2 3 4 0 2 2 2 2 0 0 0 0 1

TANIMOTO_SIMILARITY (KTaO$_3$, SrTiO$_3$) = 0.74

BOTH COMPOUNDS ARE SIMILAR BASED ON THEIR BAND STRUCTURES

"KTaO$_3$ is a promising candidate for superconductivity induced by electrostatic doping because it is similar to the superconductor SrTiO$_3$: [...] have similar band structures, and both exhibit quantum para-electricity"

Ueno et al. Nature Nanotechnology, May 2011, Online Epub.

Summary and future studies

- Our results demonstrate that QNAR models can successfully predict the biological effects of MNPs from their descriptors that are either experimentally measured or calculated.
- Further progress of QNAR modelling requires new data: collection, curation, and ontology.
- New approaches to theoretical descriptor calculations help extending QNAR modeling to diverse MNPs with different cores enabling model development in the absence of experimentally measured MNPs properties.

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