ENBIK 2016

Národní bioinformatická konference

Predikce toxicity nanočástic

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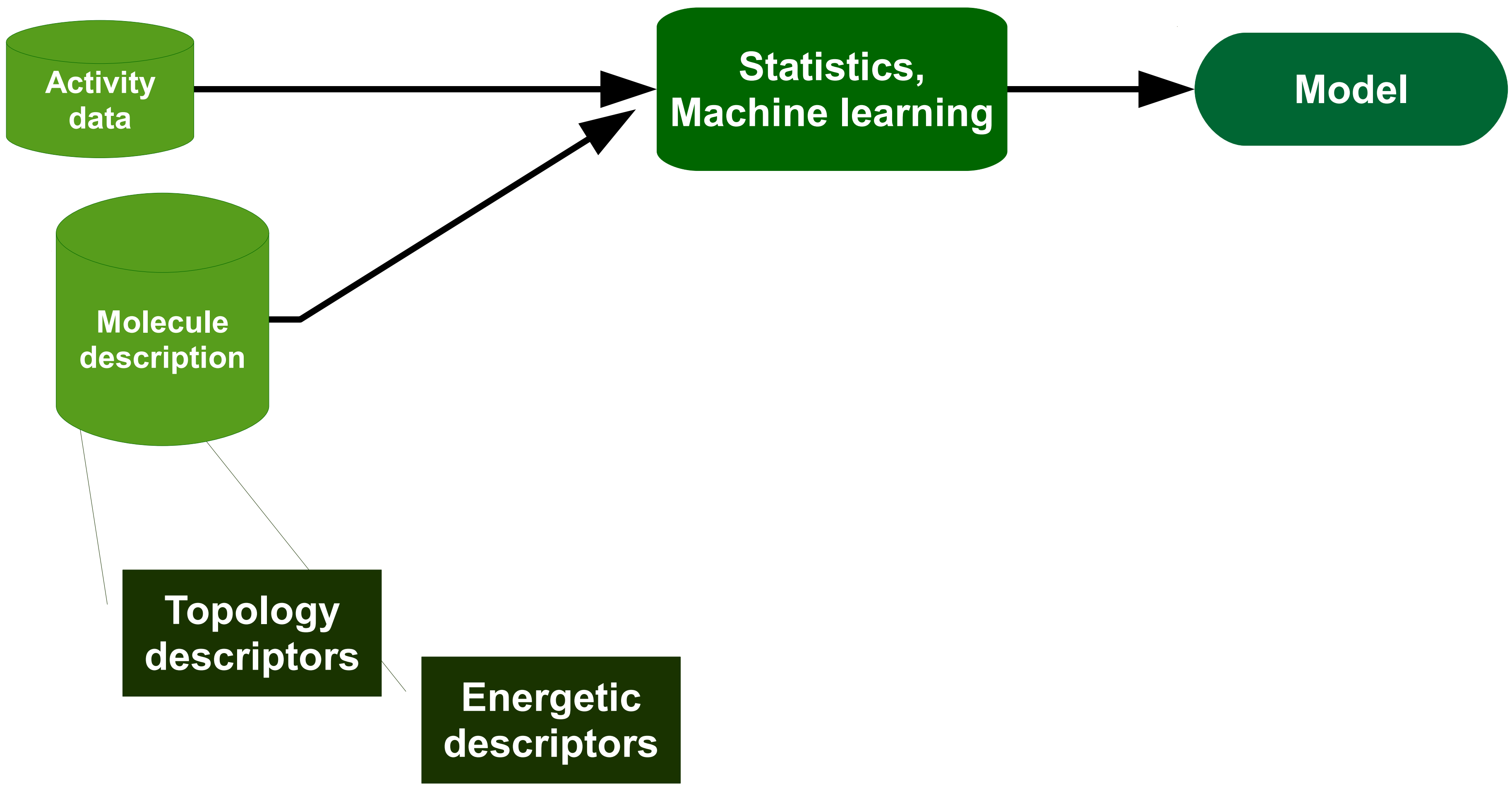
Outline

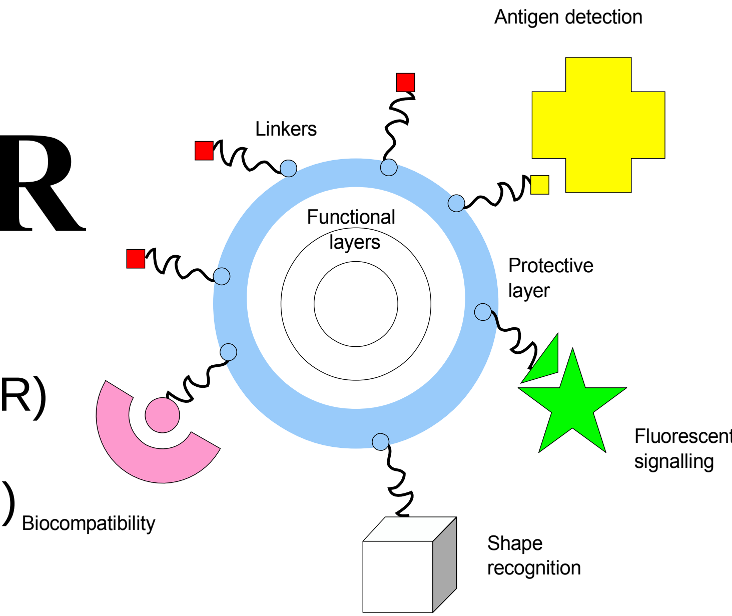
- **QSAR/nano-QSAR: state of the art**
- **Chalenges of current approaches**
- **Case study**
- **Proposal of new approaches based on relational learning**
- **Inductive logic programming (ILP)**
-

QSAR

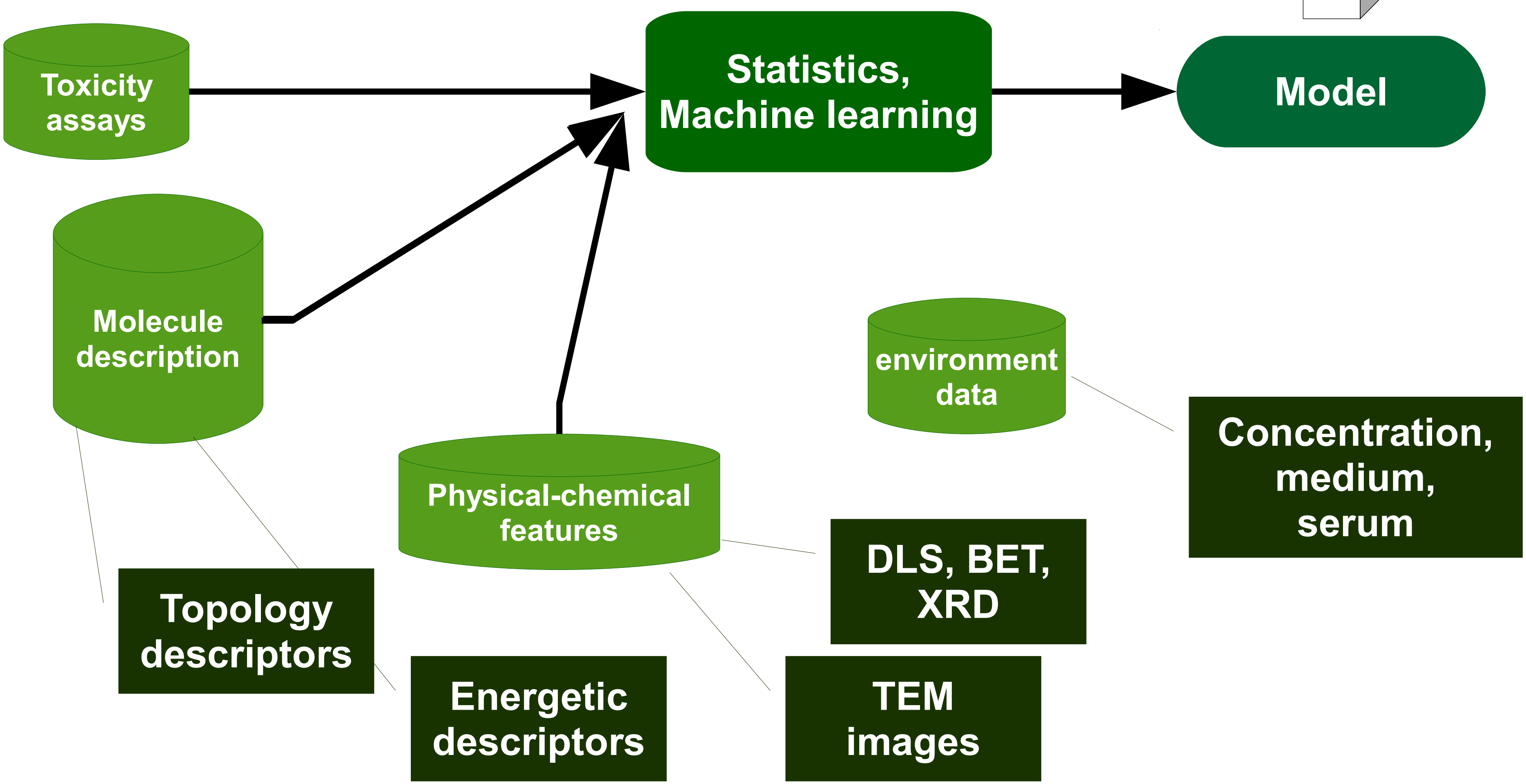
- Quantitative structure-activity relationship



nano-QSAR



- Quantitative **nanostructure**-activity relationship (QNAR)
- Quantitative nanostructure-**toxicity** relationship (QNTR)

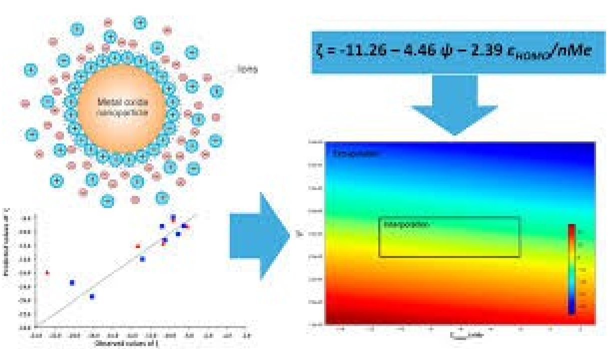


nano-QSAR: State of the Art

- **Degeneration to QSAR: fixing the core-composition, varying surface modifications or vice versa (Fourches 2011, Singh 2014, Ehret 2014)**
- **Building a model solely on the observabele physical-chemical characterization (Sayes 2010)**
  ← no safe-by-design
- **Well defined particles, fixed experimental conditions: modelling nano-specific descriptors (Puzyn 2011, Gajewicz 2015)**
  ← computationaly demanding
  ← unsuitable for current heterogeneous data

Puzyn et al. Nature 2011

- **18 MeOx**
- **12 quantum-chem. Descriptors (HOMO, LUMO, cluster energy…)**
- **Toxicity against bacteria cell**
- **Fitted by one feature: ΔH_{Me+} – enthalpy of formation of a gaseous cation**
- **Refers to a mechanism of toxicity ← detachment o metal cations**



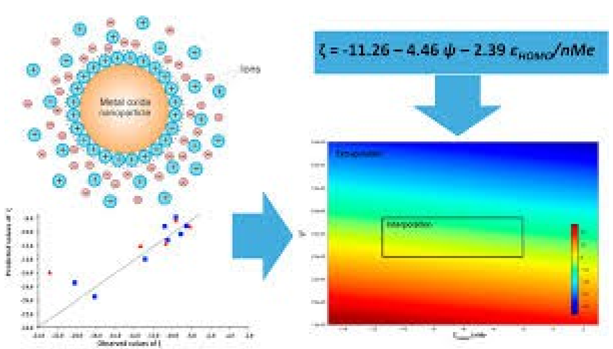
Puzyn, 2011

Gajewicz et al. Nanotox. 2015

- **18 MeOx… + 11 TEM image descriptors**
- **Toxicity against human HaCat cell line**
- **Fitted by TWO features**

  1. ΔH_f^c **– enthalpy of a g**

  2. χ_f^c **– Mullliken electronegativity**

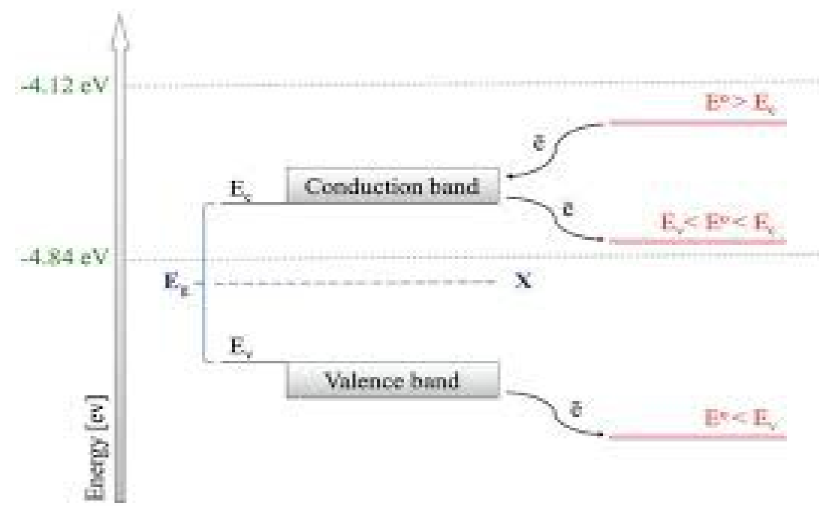


Puzyn, 2011

- **Refers to the TWO mechanism of toxicity:**

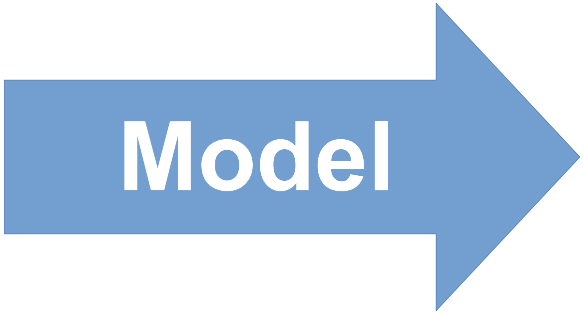
  I. Detachment of Me^+

  II. Redox properties of the metal oxides surfac



Gajewicz, 2015

ID	$descr_1$	$descr_2$	$descr_3$	...	...	$descr_N$
1	1	0	0			1
2	0	1	1			1
3	1	1	0			0
4	0	1	0			0



toxic
yes
no
yes
no

Current data

COST-MODENA consortium:

- 193 data examples
- 46 mostly metal/MeOx particles
- 13 features
- 11 cell-lines (epithelial, lung, embryonal...)
- 3 assay types: ATP, LDH, WST/ MTT
- 3 dispersion protocols: stirring, bath sonication, tip sonication

ANALYSIS

- Lasso, Regression Tree

Current data

COST-MODENA – Issues

i. **validity** of the models
<= limited data for independent models for each experimental configuration,

ii. **applicability** of the models
<= new experimental conditions,

iii. **Expressiveness**
<= great variability of particle or experiment design;
,,*a particle which has not coating*".

Results – extracted features

WST-1:

'Shape = round', 'Shape = elongated', 'Prim size 1', 'Prim size 2', 'Aspect ratio', 'potential', 'size in situ'

ATP:

'Shape = Heterogeneous', 'Prim size 2', 'Surface', 'potential', 'size in situ'

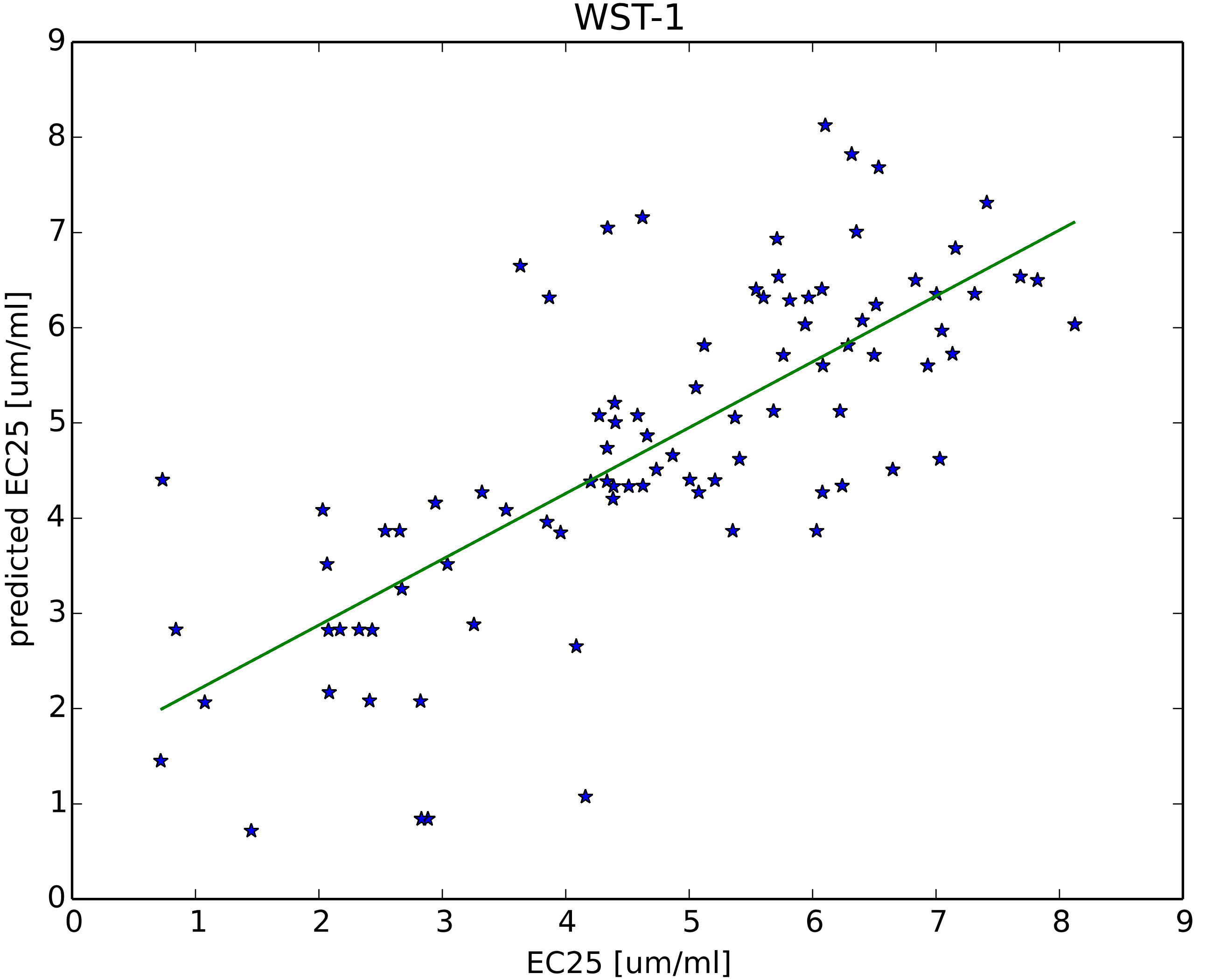
MTT:

'Shape = Mainly 2 euhedral morphologies: aspect ratio(20-250 nm and 400 nm) and 2:7,5 (50-350 nm)', 'Prim size 2', 'Surface' 'potential', 'size in situ'

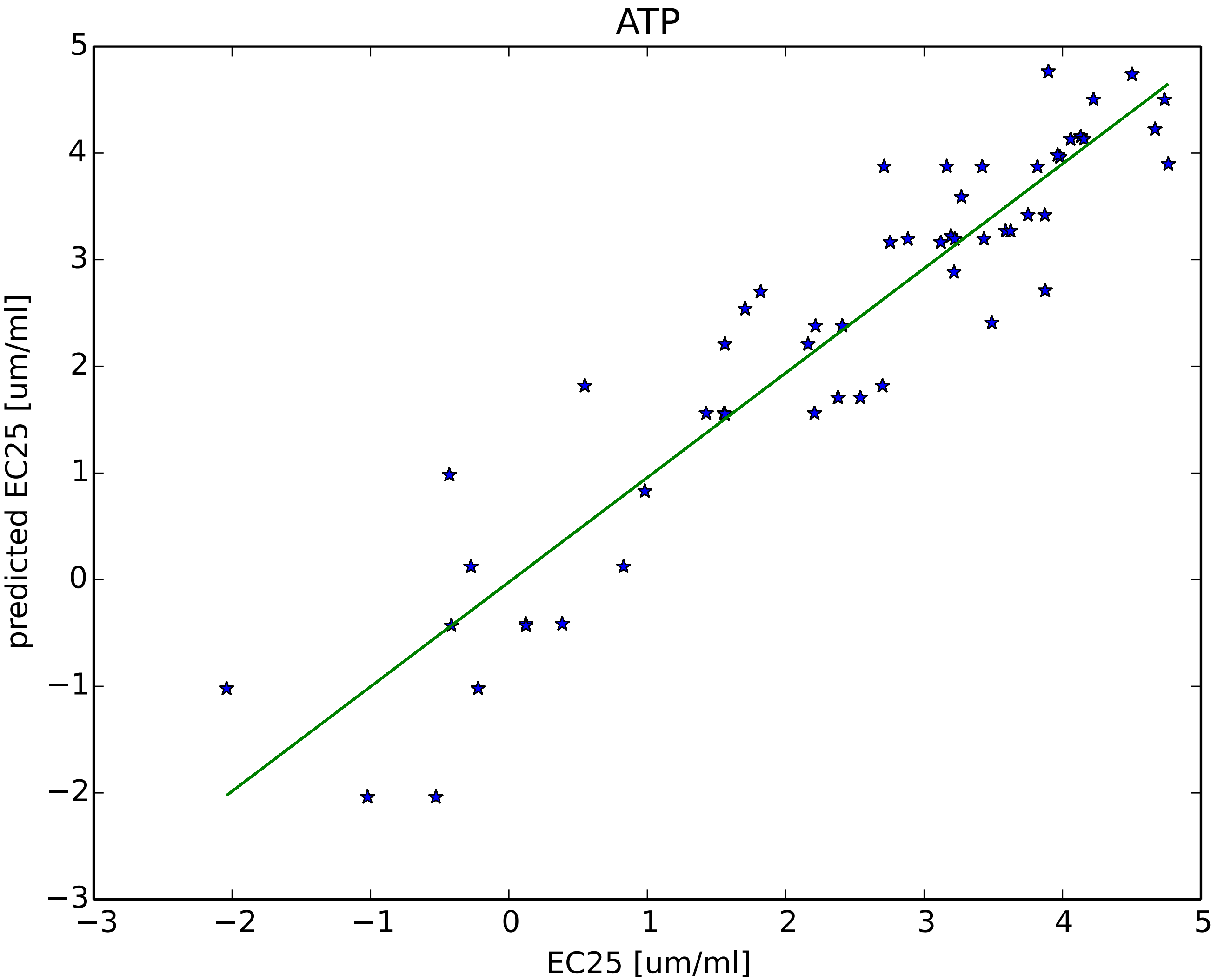
LDH:

'Shape = angular', 'Prim size 1', 'Surface', 'potential', 'size in situ'

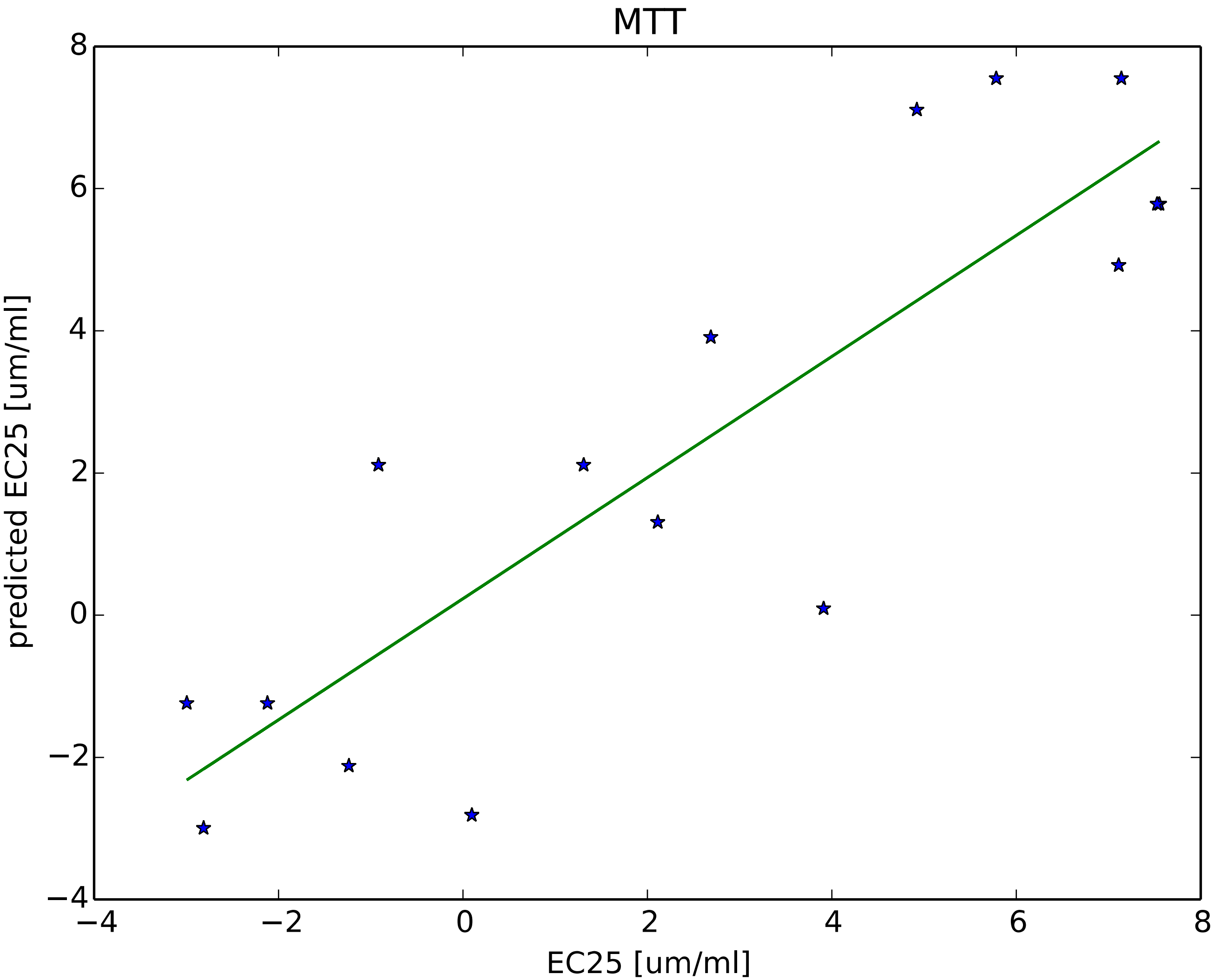
Results – performance



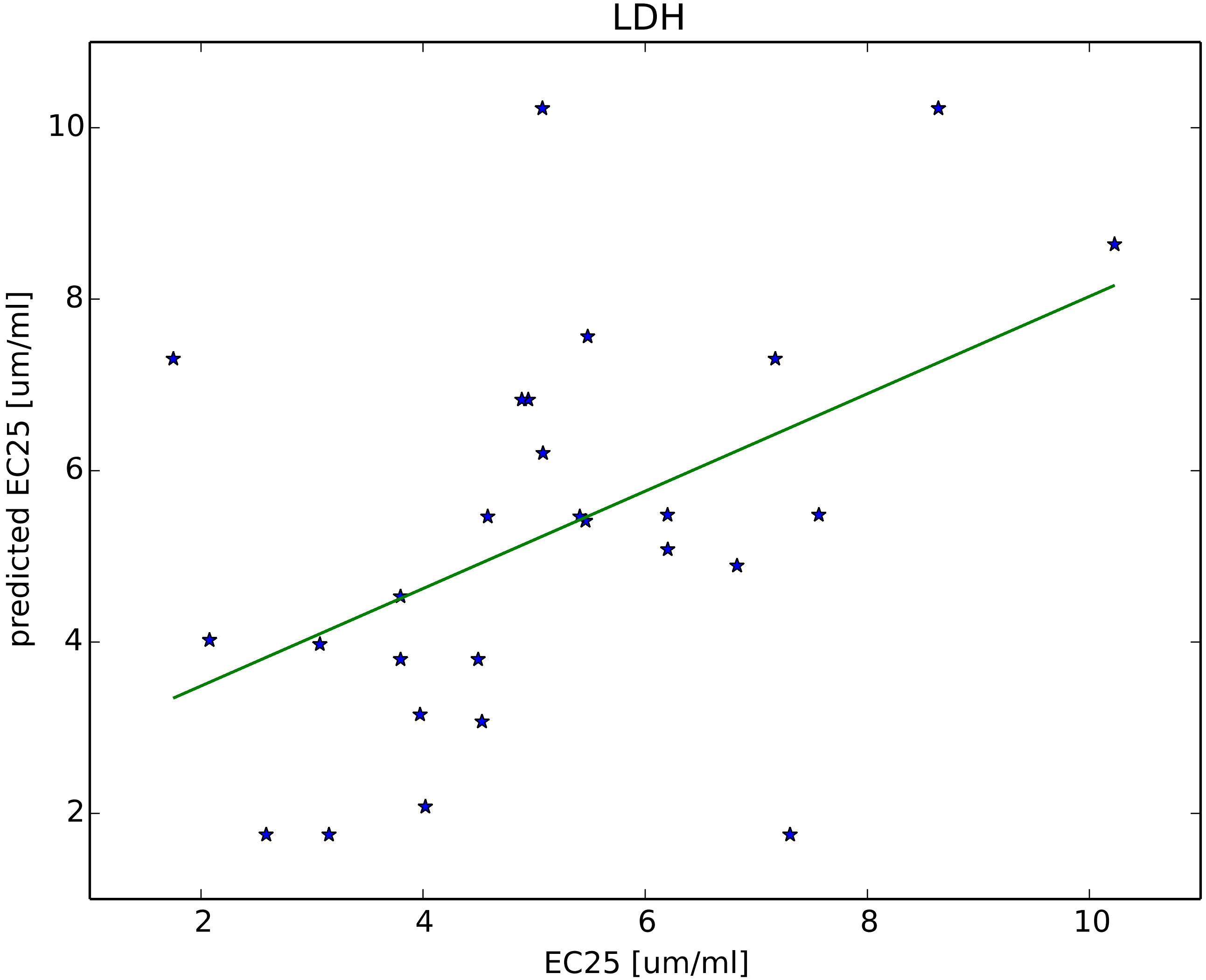
Results – performance



Results – performance

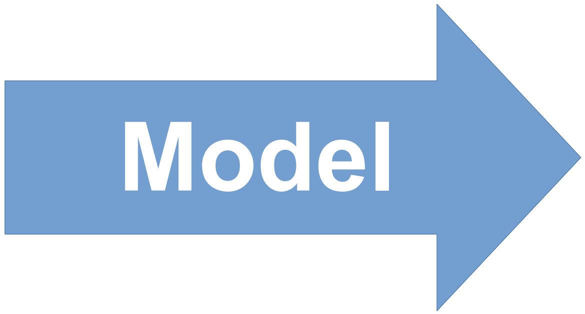


Results – performance



Propositional Interpretation

ID	$descr_1$	$descr_2$	$descr_3$	...	...	$descr_N$
1	1	0	0			1
2	0	1	1			1
3	1	1	0			0
4	0	1	0			0



toxic
yes
no
yes
no

(Multi) relational Interpretation

particle

particle	core	size	shape	ζ–pot	...
part1	cor1	...	...	...	
part2	cor2	...	...	...	
part3	cor2	...	...	...	

coating

coat	chemical	descr1	...	descrN
coat1	chem1	0		1
coat2	chem2	1		1

has_coat

particle	coat
part1	coat1
part2	coat2

experiment

ID	particle	medium	conc.	response
ex1	part1	med1	high	low
ex2	part1	med2	middle	high
ex3	part2	med1	low	low
ex4	part2	med2	middle	high
ex5	part3	med1	middle	high
ex6	part3	med2	middle	high

core_composition

core	chemical	descr1	...	descrN
cor1	ZnO	0		1
cor2	TiO	1		1

Propositional Representation

Standard, *propositional*, representation of particle/data:

part1 =

<hasCore_Au=**True**, hasCore_Si=**False,** hasCore_ZnO=**False,...**>

– redundant features
– what about a new core-material?

part1 = <hasCore_Au=**True,...**hasCoat_Si=**True**>

part2 = <hasCore_Si=**True,...,**hasCoat_Si=**False**>

– one material in multiple attributes

Propositional Representation

part3 =
<hasCore_Si=**True,...,**hasCoat_Si=**False**, hasCoat_Cit=**False**,
hasCoat_PEP=**False,** hasCoat_PEG=**False**>

– exhaustive representation of a **bare** particle

– what about multiple, „chained“, surface modifications??

Relational Representation

First-Order Logic representation:

IF part1 **hasCore** c1 & c1 **isAg** & part1 **hasCoat** ct1 & ct1 **isSi**
THEN part1 **isTox**

IF part2 **hasCore** c1 & c1 **isAg** **&** part2 **hasCoat** ct2 **&** ct2 **isCit**
THEN part2 **isTox**

IF part3 **hasCore** c2 **&** c2 **isSi** **THEN** part3 **NOT isTox**

- Facta = {part1, part2, c1, c2, ct1}
- Realtions = {**hasCore, isAg, isTox, isTox**}

Learning the hypothesis – ILP

First-Order Logic representation:

IF part1 **hasCore** c1 & c1 **isAg** & part1 **hasCoat** ct1 & ct1 **isSi**
THEN part1 **isTox**

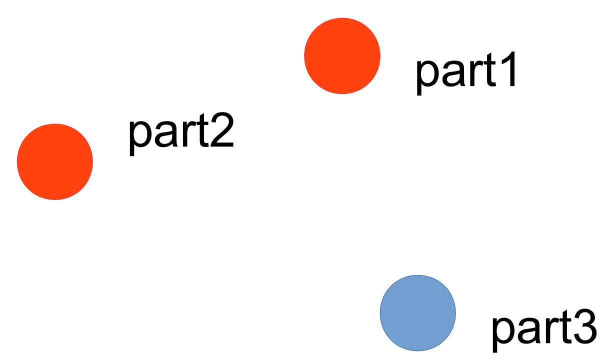
IF part2 **hasCore** c1 & c1 **isAg & ** part2 **hasCoat** ct2 **&** ct2 **isCit**
THEN part2 **isTox**

IF part3 **hasCore** c2 **&** c2 **isSi** **THEN** part3 **NOT isTox**

Induction of a Hypothesis *H*:

H |= {ex+}

H |/= {ex-}



Learning the hypothesis – ILP

First-Order Logic representation:

IF part1 **hasCore** c1 & c1 **isAg** & part1 **hasCoat** ct1 & ct1 **isSi**
THEN part1 **isTox**

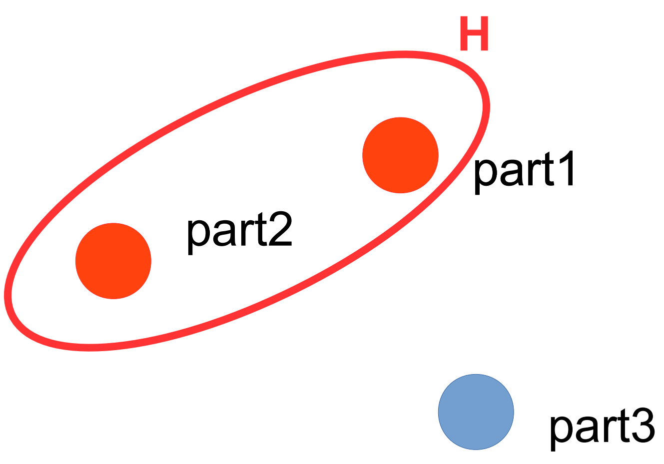
IF part2 **hasCore** c1 & c1 **isAg** **&** part2 **hasCoat** ct2 **&** ct2 **isCit**
THEN part2 **isTox**

IF part3 **hasCore** c2 **&** c2 **isSi** **THEN** part3 **NOT isTox**

Induction of a Hypothesis *H*:

H = part **hasCore** c & c **isAg** |= {ex+}

H = part **hasCore** c & c **isAg** |/= {ex-}



Learning the hypothesis – ILP

First-Order Logic representation:

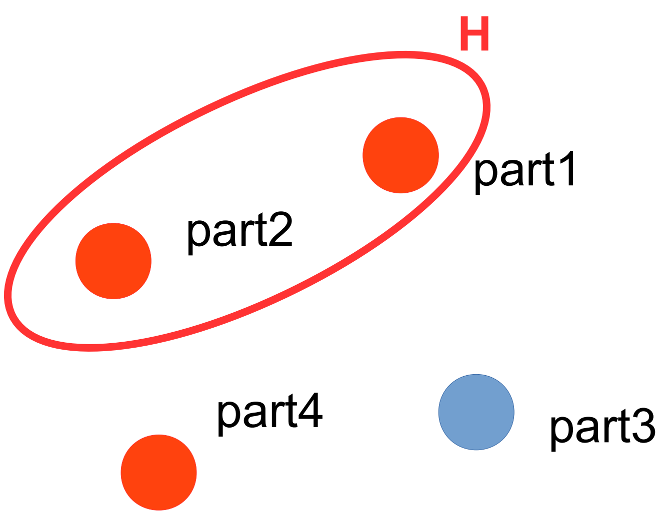
IF part1 **hasCore** c1 & c1 **isAg** & part1 **hasCoat** ct1 & ct1 **isSi**
THEN part1 **isTox**

IF part2 **hasCore** c1 & c1 **isAg** **&** part2 **hasCoat** ct2 **&** ct2 **isCit**
THEN part2 **isTox**

IF part4 **hasCore** c3 **&** c3 **isX**
THEN part4 **isTox**

Induction of a Hypothesis *H*:

H = part **hasCore** c & c **isAg** |/= {ex+}



Learning the hypothesis – ILP

First-Order Logic representation:

IF part1 **hasCore** c1 & c1 **isAg** & c1 **hasDescr** d1, d2, …
THEN part1 **isTox**

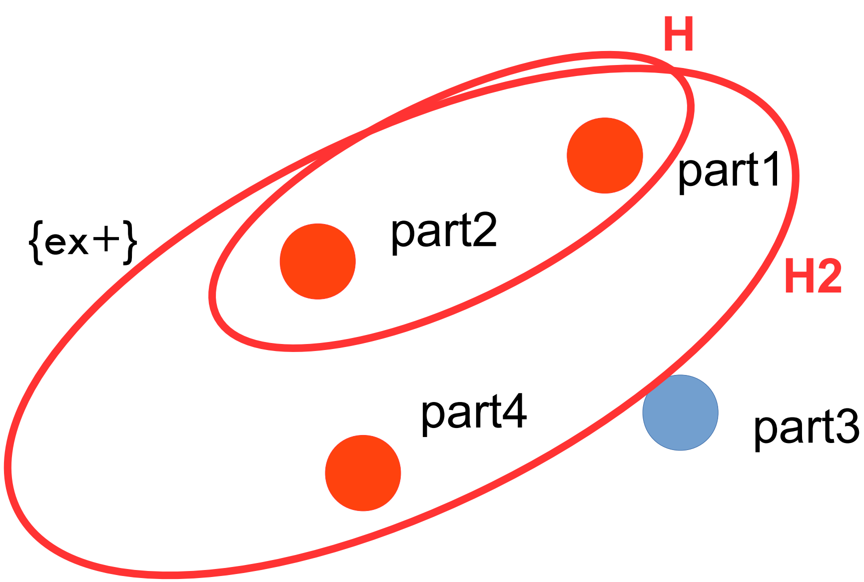
IF part2 **hasCore** c1 & c1 **isAg** & c1 **hasDescr** d1, d2, …
THEN part2 **isTox**

IF part4 **hasCore** c3 **&** c3 **isX** & c1 **hasDescr** d1, d2, …
THEN part4 **isTox**

Induction of a Hypothesis *H*:

H = part **hasCore** c & c **isAg** |/= {ex+}

H2 = part **hasCore** c & c **hasDescr** d1, d2 |= {ex+}



Relational Representation

Unknown experimental condition:

… part1 **uptakenBy** cell1 & cell1 **is16hbe** …
… part2 **upatakenBy** cell2 & cell2 **isNCI-h292** …

Adding a ***knowledge***:

IF cell **is16HBE THEN** cell **isBronchEpithel**

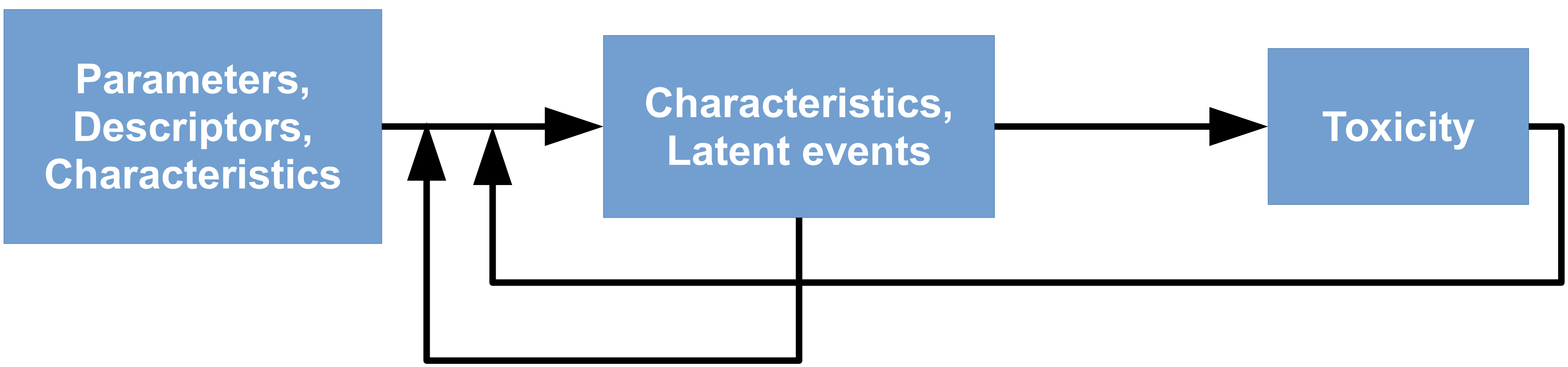
IF cell **isNCI-h292 THEN** cell **isBronchEpithel**

Deducing:

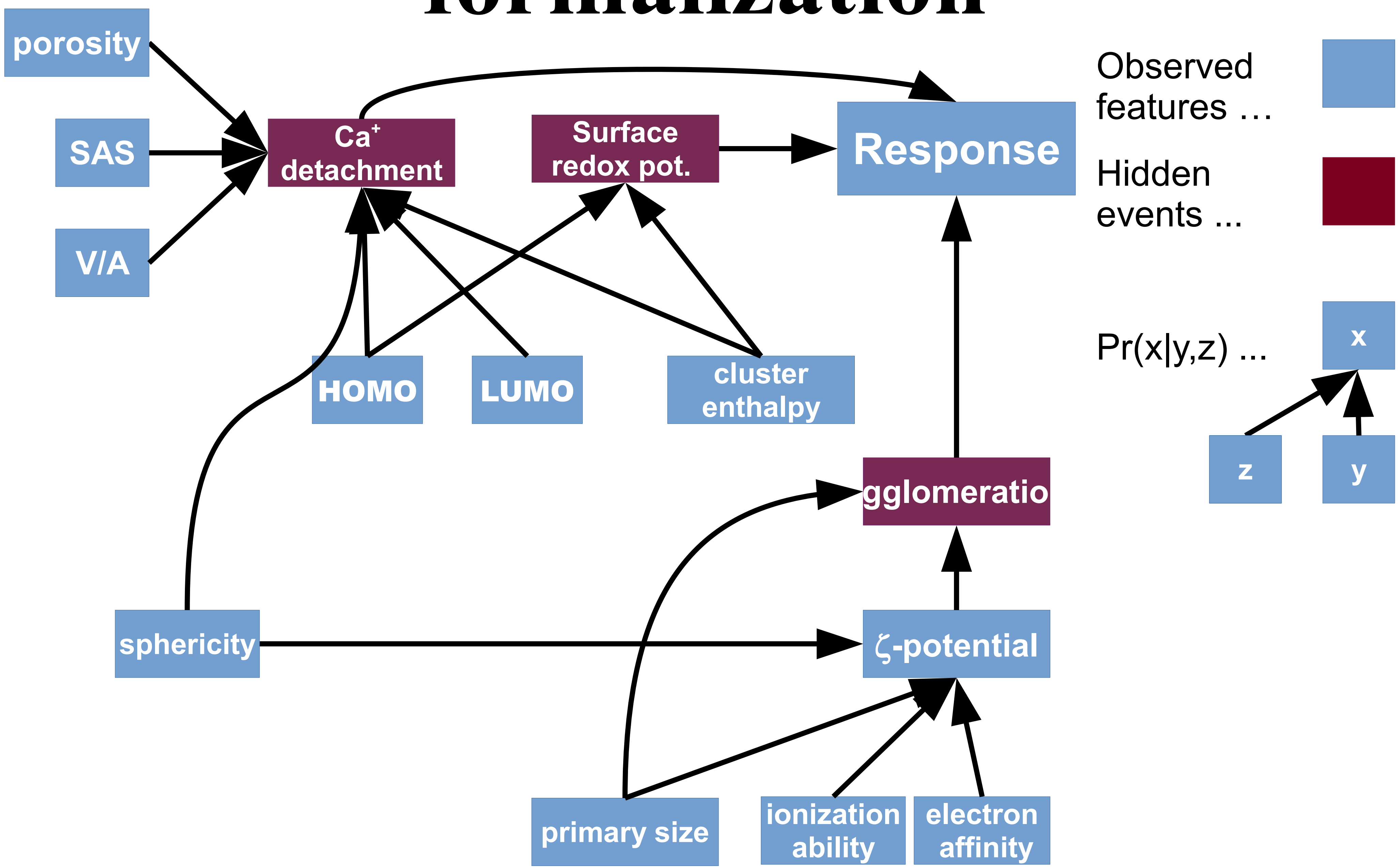
part1 **uptakenBy** cell1 & cell1 **isBronchEpithel**

Hidden Topics

Idea of Deep Learning:



Gajewicz, 2015 – Domain formalization



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References

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