Willkommen
Welcome
Bienvenue

Machine learning and QSAR Meta-analysis of nanobiomaterials used as nanocarriers within a Safe by Design (SbD) context

Edgar Hernandez, Claudia Som, Bernd Nowack
Empa-Swiss Federal Laboratories for Materiasl Science and Technology
Technology and Society Laboratory
Environmental Risk Assessment and Management Group

Contact: Edgar.Hernandez@empa.ch

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Can machine learning and QSAR Meta-analysis of nanobiomaterials used as nanocarriers within a Safe by Design (SbD) context?

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PROJECT BACKGROUND AND RESEARCH GOAL

GoNanoBioMat

- GoNanoBioMat
  - Guidelines for polymeric nanobiomaterials for drug delivery systems
  - Aiding of SME and suppliers to implement Safe by design in an early phase of innovation

Safe by Design

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Need to understand the relationship between physico-chemical properties of NP and their effects, and see whether there is a way to relate these materials with toxicity.

If yes, this could be done

- by experimental research (in vitro, in vivo);
- by read-across
- by grouping NPs
- By QSAR modelling

Goal of research

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- Build a QSAR model that can predict cell viability as an output by using nanocarrier properties as an input
  - Apply a safe by design framework with new knowledge gained by the model output (Cell viability predictions)

How?

- Extract data from published papers that characterize nanocarriers
- Find intrinsic/extrinsic nanocarrier properties and their relationship to cell viability

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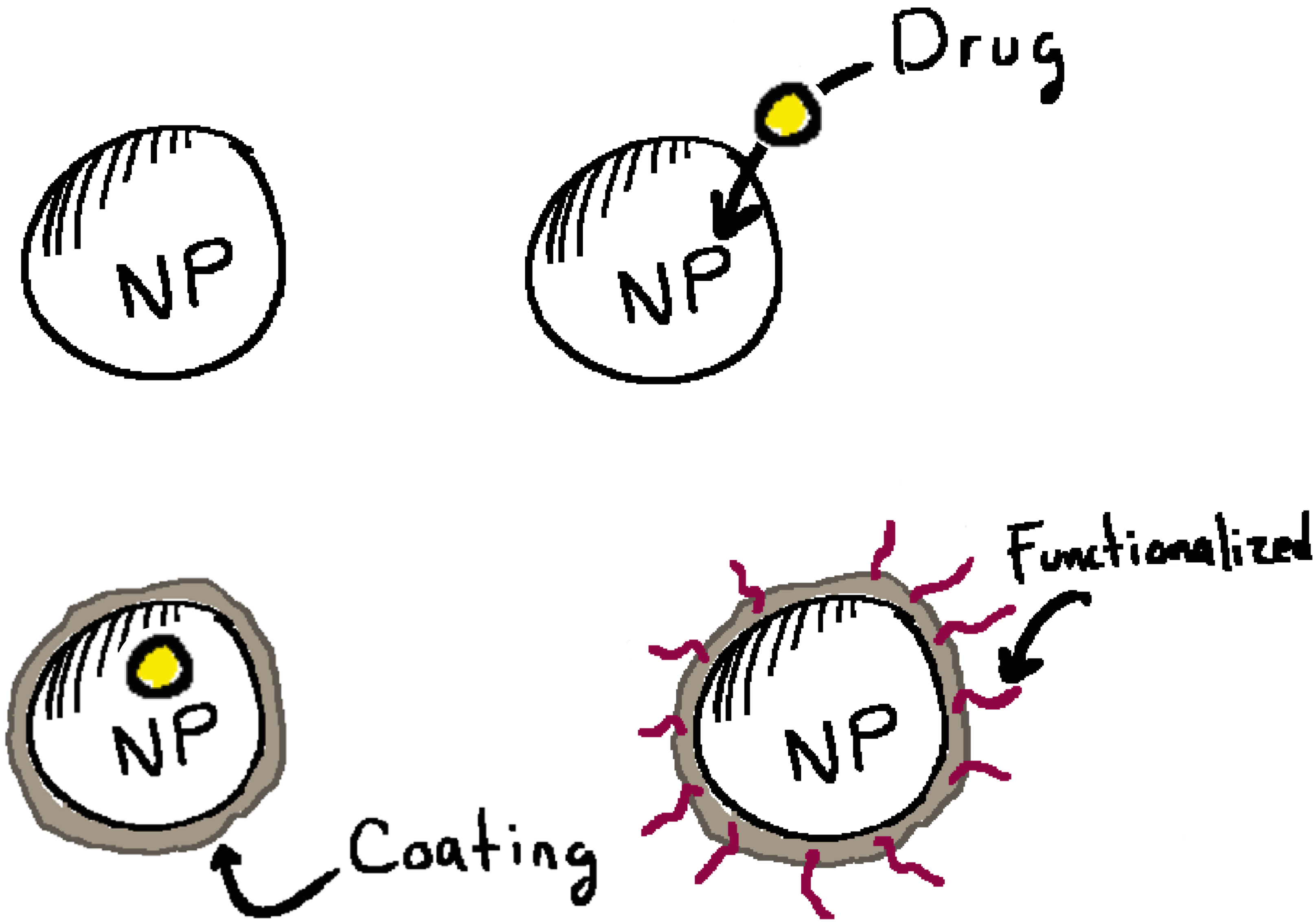
NANOCARRIER DESIGN

(in a SbD approach)

Nanocarrier design



QSAR APROACH

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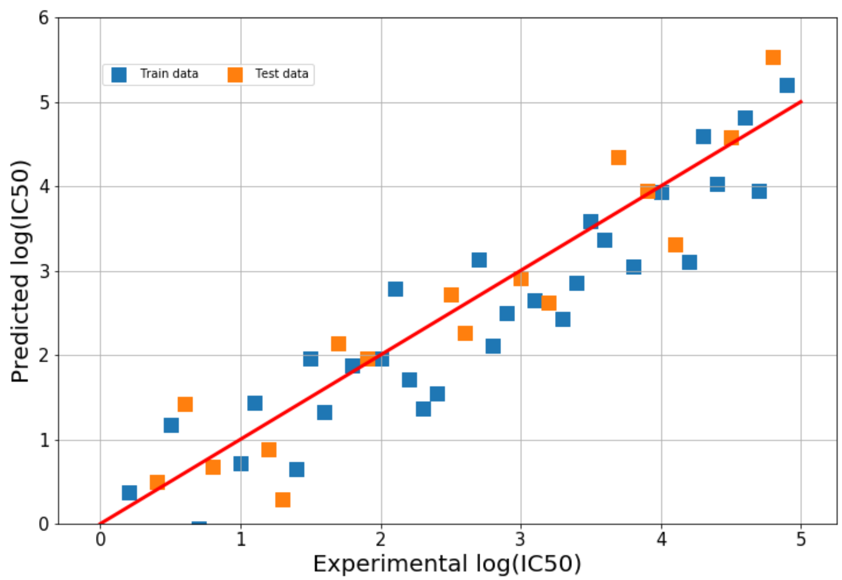
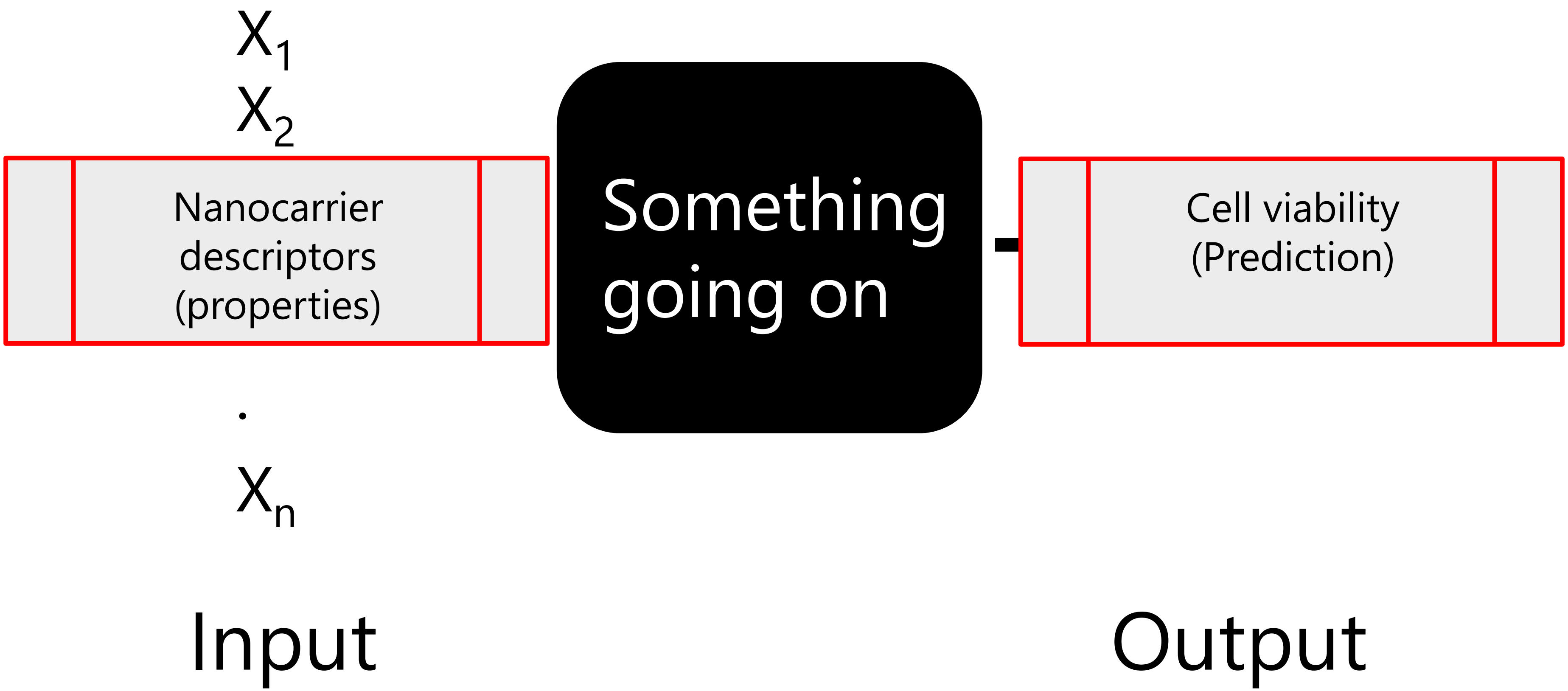
- Quantitative Structure (Property)-Activity Relationship
  - Regression analysis
  - Using chemical/structural descriptors (predictors)
  - To predict a desired activity



QSAR APPROACH

- QSAR



QSAR

Dataset, our proposed descriptors!

Nanocarrier data set

IMPORTANT!!

- Papers with nanocarrier toxicity data: 115
- Data points: 420
- Extracted nanocarrier features: 16
  - Nanomaterial name

Nanocarrier data set

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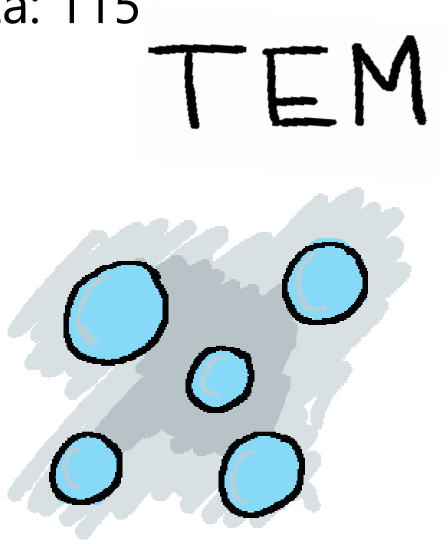
  - Diameter TEM (primary particle size)



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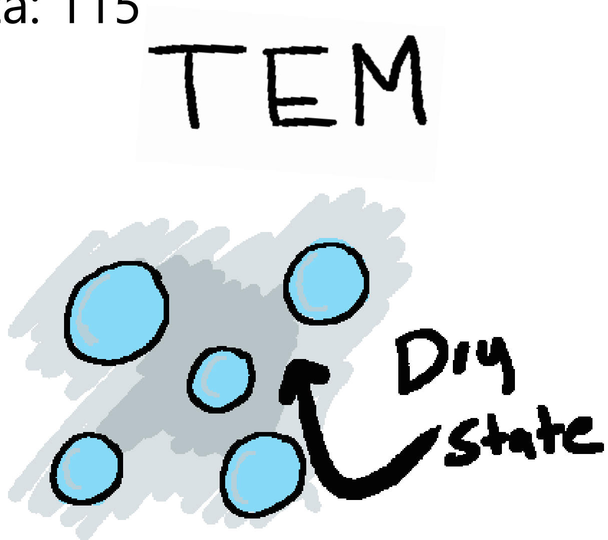

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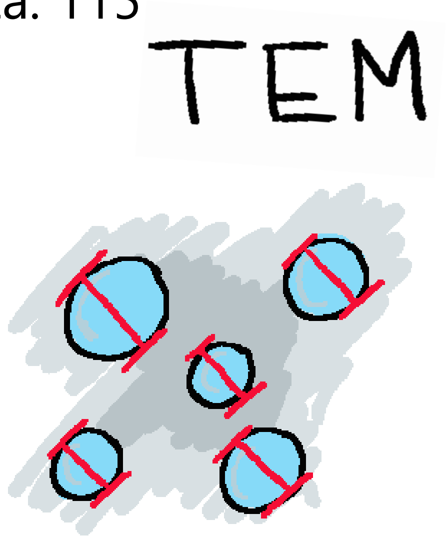

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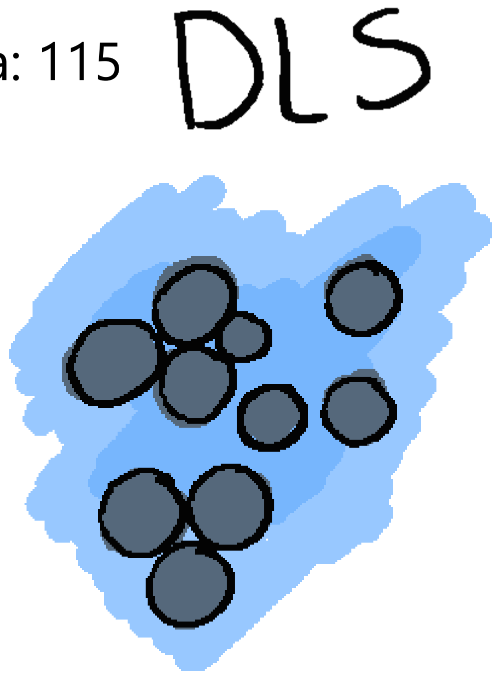

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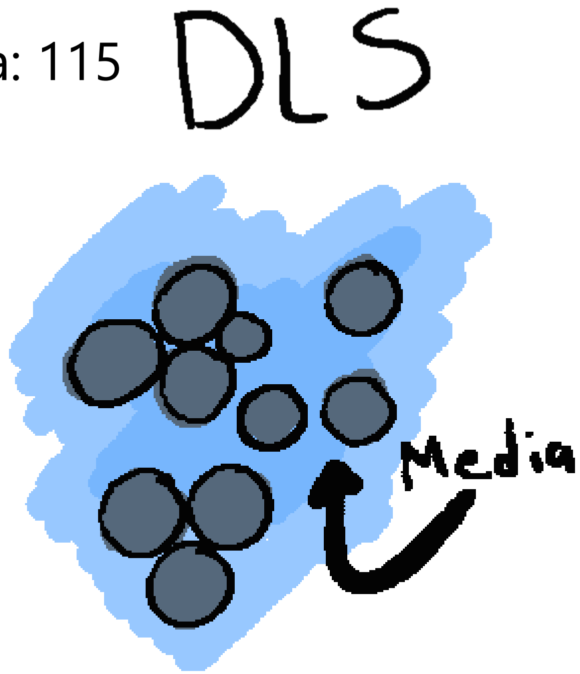

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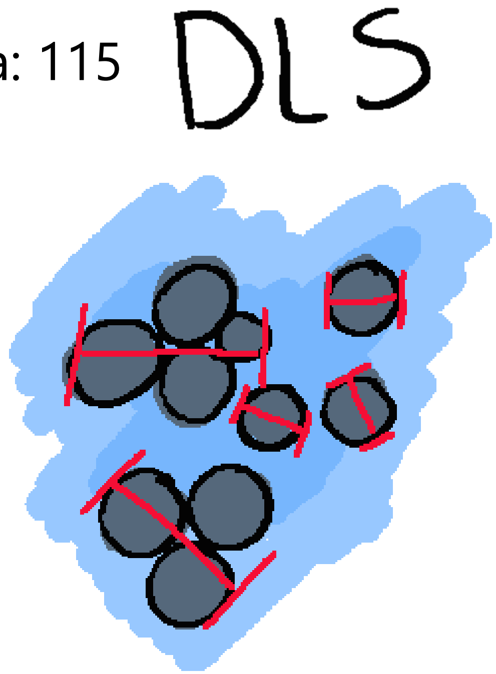

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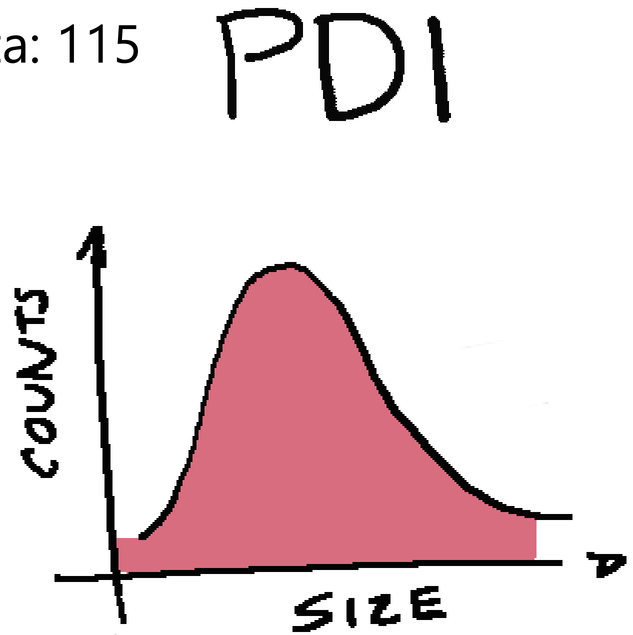
  - PDI (Polydispersity index)



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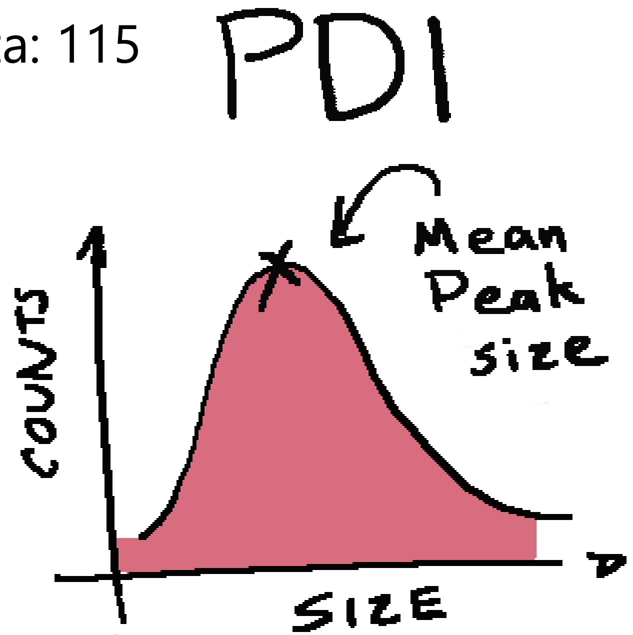

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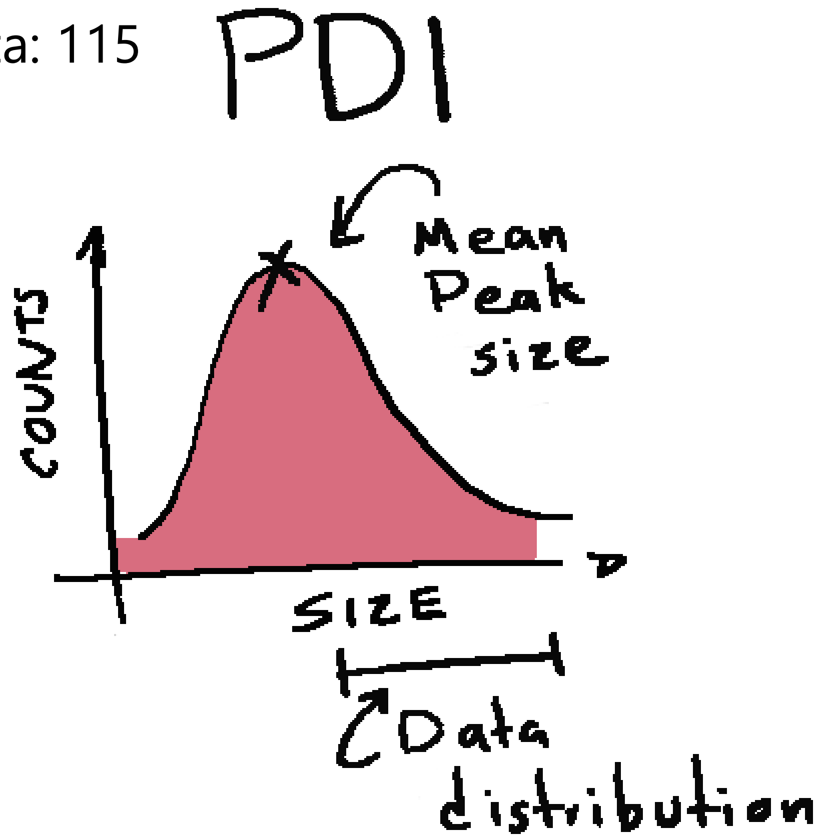

QSAR

Building the model

Nanocarrier Data Overview

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NPs	Size TEM	DLS	PDI	ZP	Exp Cond	Concentration [µg/ml]							Cell	Cell Media	Incubation Time
	[nm]	[nm]	[-]	[mV]	[-]	6	12	25	50	100	250	500	[-]	[-]	[hr]
PEG-PLA	121	137 ± 5	0.112 ± 0.034	−10.4 ± 2.4	Doube DI water	0.97	0.95	0.93	0.92	0.89	0.86	0.91	Caco-2	DMEM	24
SPIONs PEG-PLA	152	153 ± 1	0.162 ± 0.009	−21.2 ± 2.6	Doube DI water	0.95	0.92	0.93	0.91	0.92	0.88	0.85	Caco-2	DMEM	24
PLGA NPs	90	155.5±3.7	0.096±0.014	−31.20±4.16	Milli-Q water	1.00	0.98	0.97	0.96	0.95	0.94	–	U251	DMEM	72
CSNPs	161	175 ± 12.6	0.235	30 ± 1.15	PBS	1.00	1.00	1.00	0.96	0.98	0.97	–	HepG2	DMEM	48
PLA	200	215 ± 9	0.100 ± 0.02	−27.2 ± 6.2	DI Water	0.98	–	–	–	–	–	–	B16-F10	DMEM	24
CNPs	90	99.8 ± 2.15	0.072 ± 0.02	19.9 ± 1.27	TDW	0.98	0.98	0.97	–	–	–	–	HEK 293	DMEM	24
PS-CNPs	170	176.7 ± 2.21	0.124 ± 0.016	−19.9 ± 1.33	TDW	0.98	0.96	0.96	–	–	–	–	HEK 293	DMEM	24

Nanocarrier Data Overview: Cell viability

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NPs	Size TEM	DLS	PDI	ZP	Exp Cond	Concentration [µg/ml]							Cell	Cell Media	Incubation Time
	[nm]	[nm]	[-]	[mV]	[-]	6	12	25	50	100	250	500	[-]	[-]	[hr]
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Dose response curves

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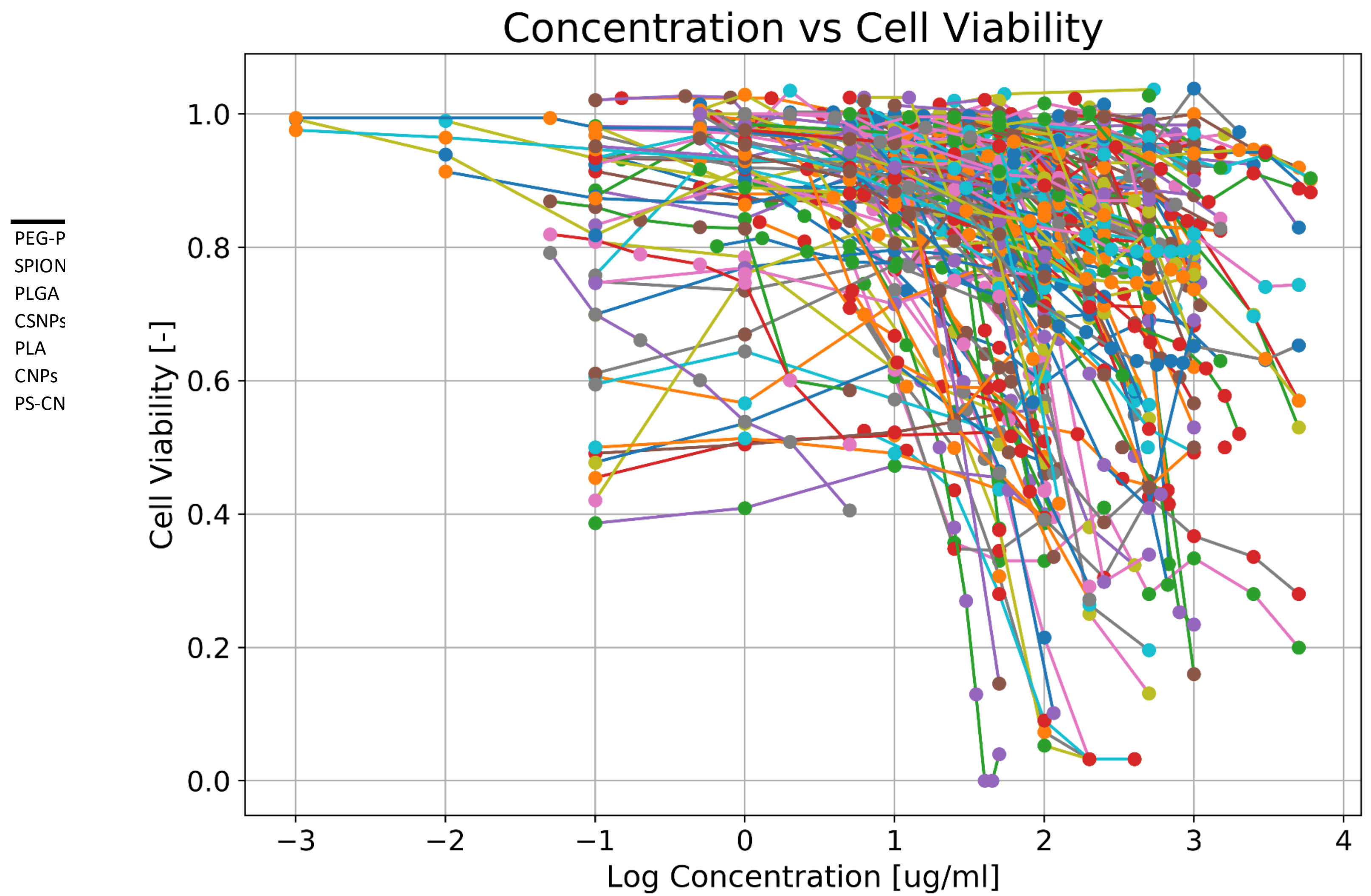
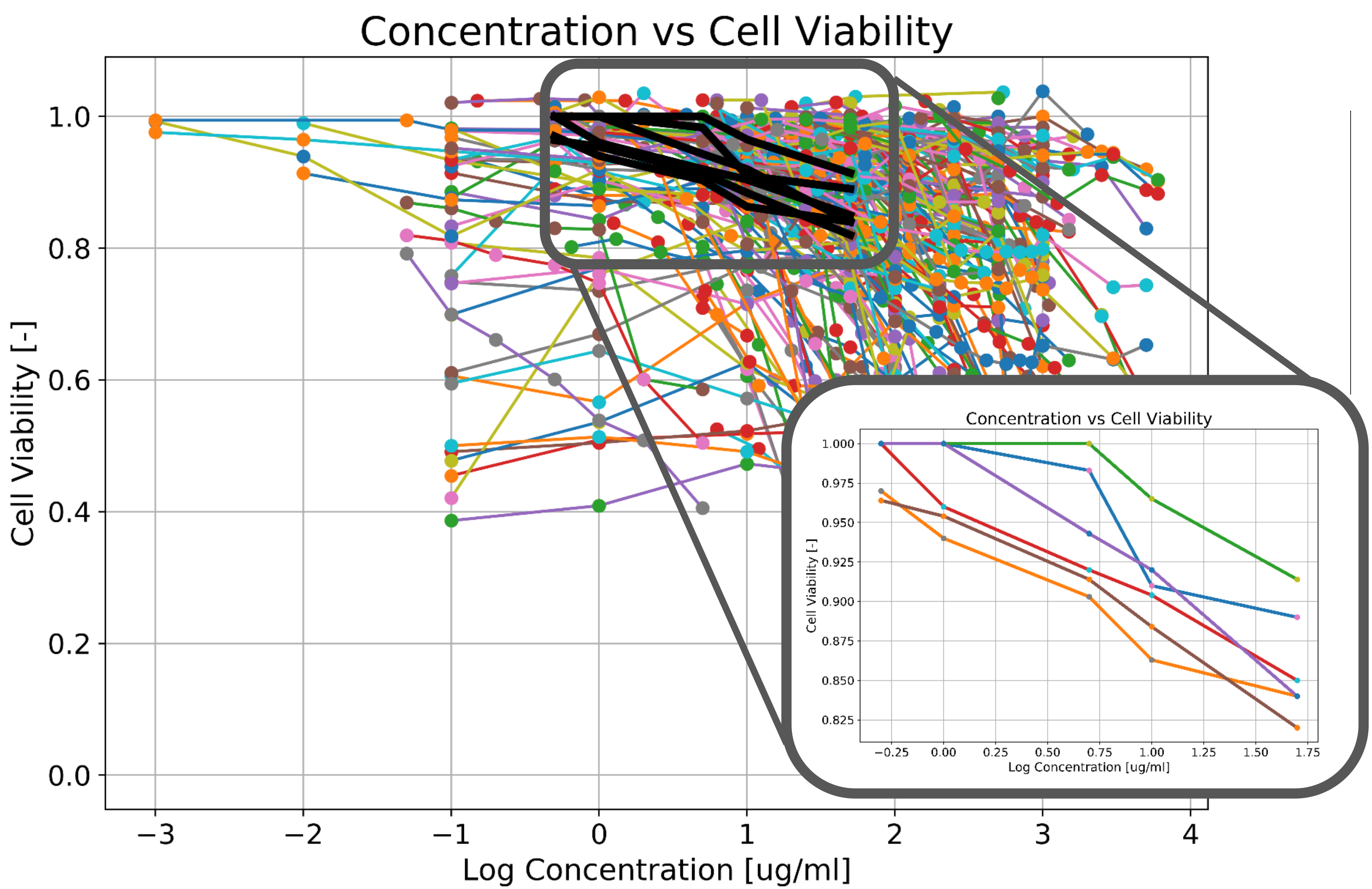


Dose response curves



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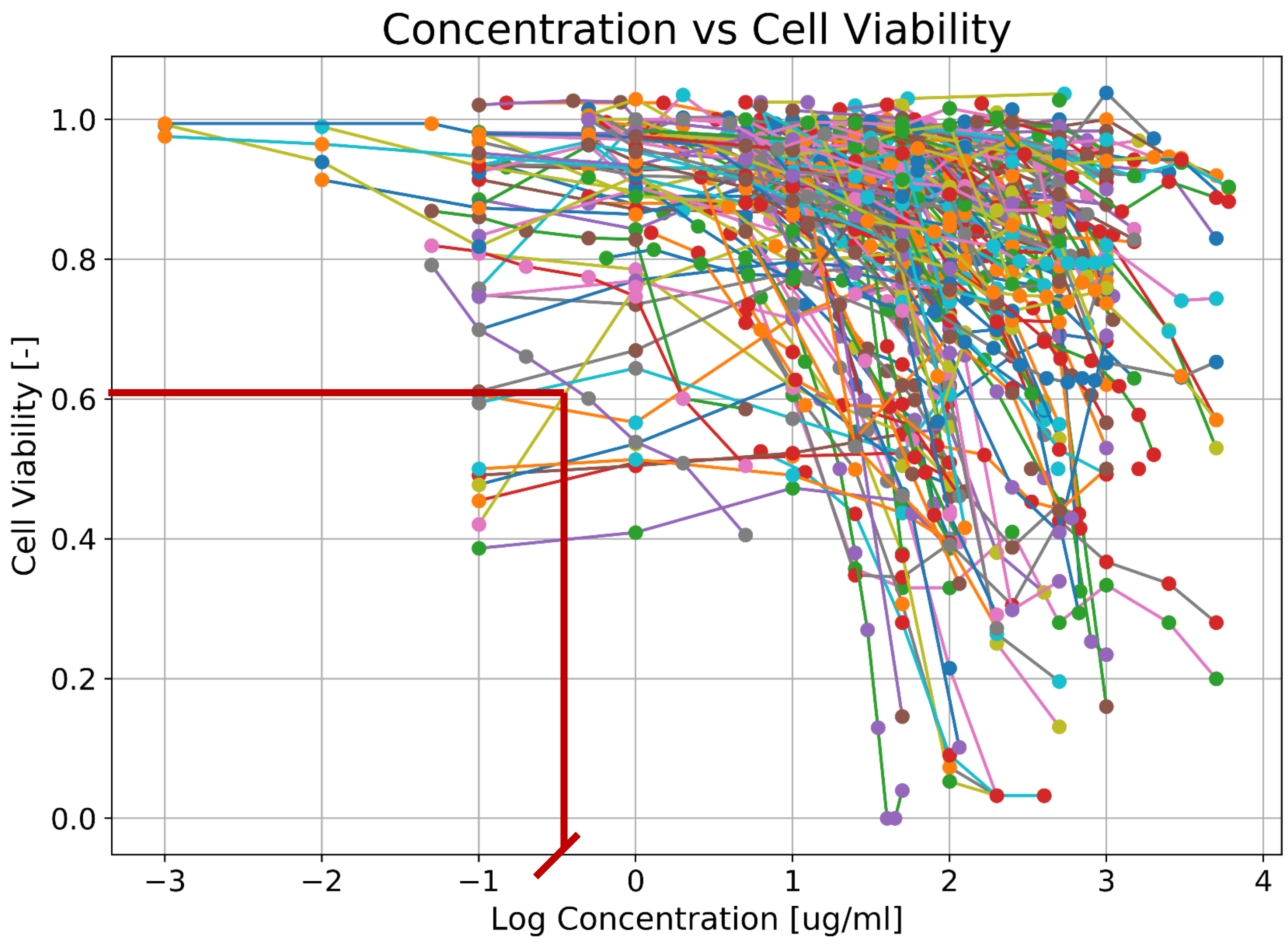
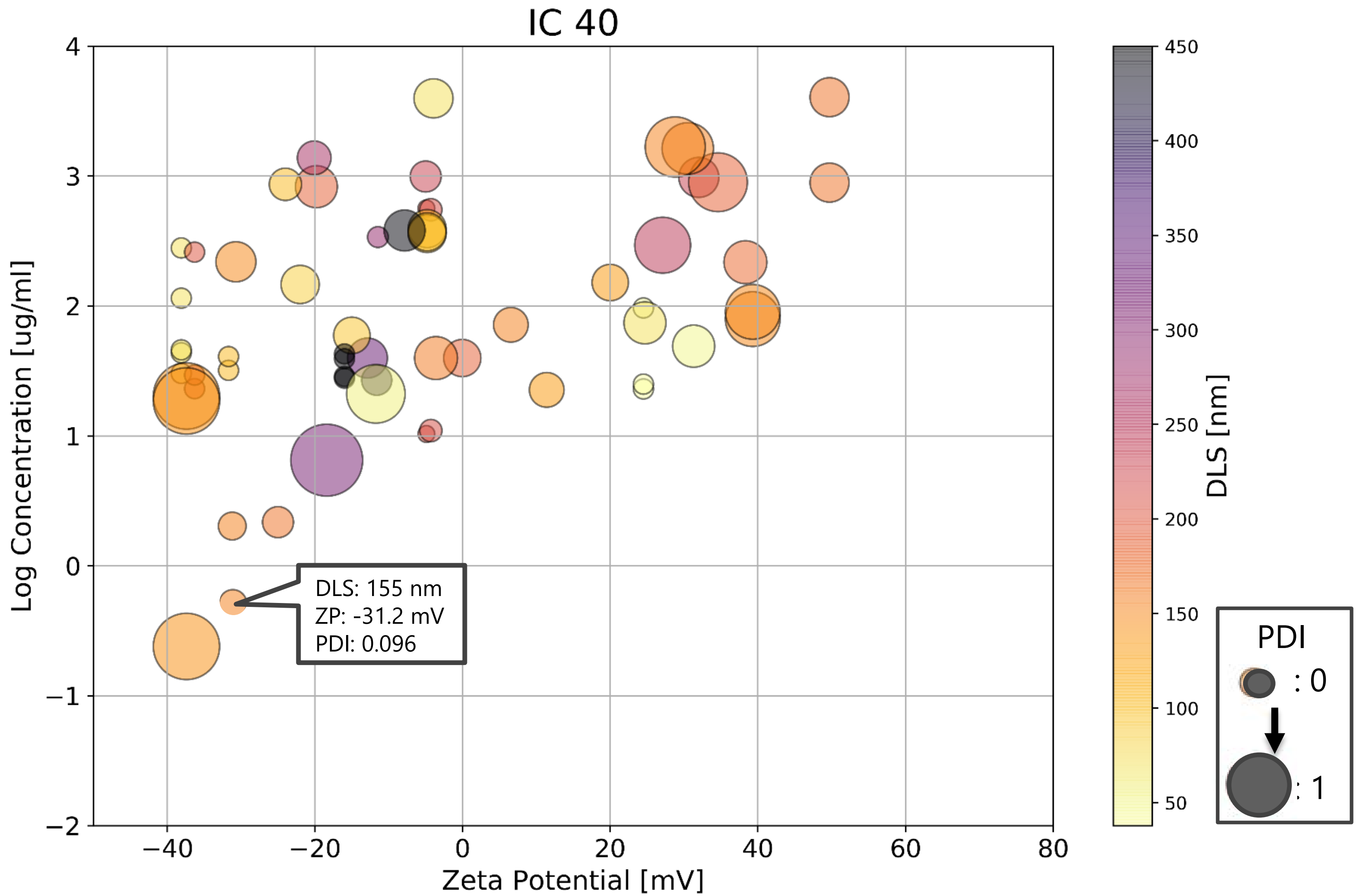
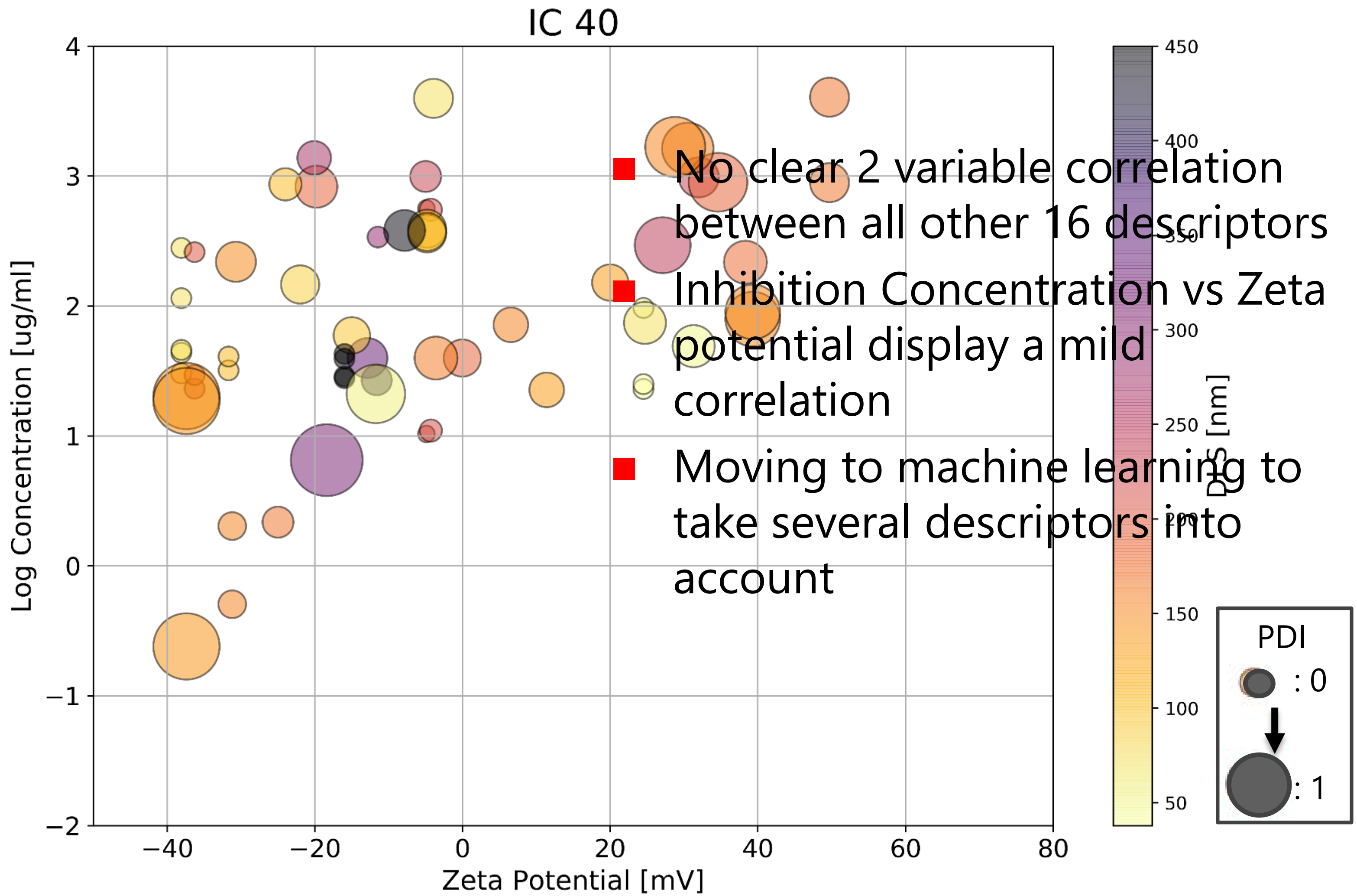


Inhibition concentration from dose response curves



ICx% represents decrease in cell viability by x%
IC 40 means that cells viability is inhibited by 40%

Inhibition concentration from dose response curves



- No clear 2 variable correlation between all other 16 descriptors
- Inhibition Concentration vs Zeta potential display a mild correlation
- Moving to machine learning to take several descriptors into account

ICx% represents decrease in cell viability by x%
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QSAR Machine learning

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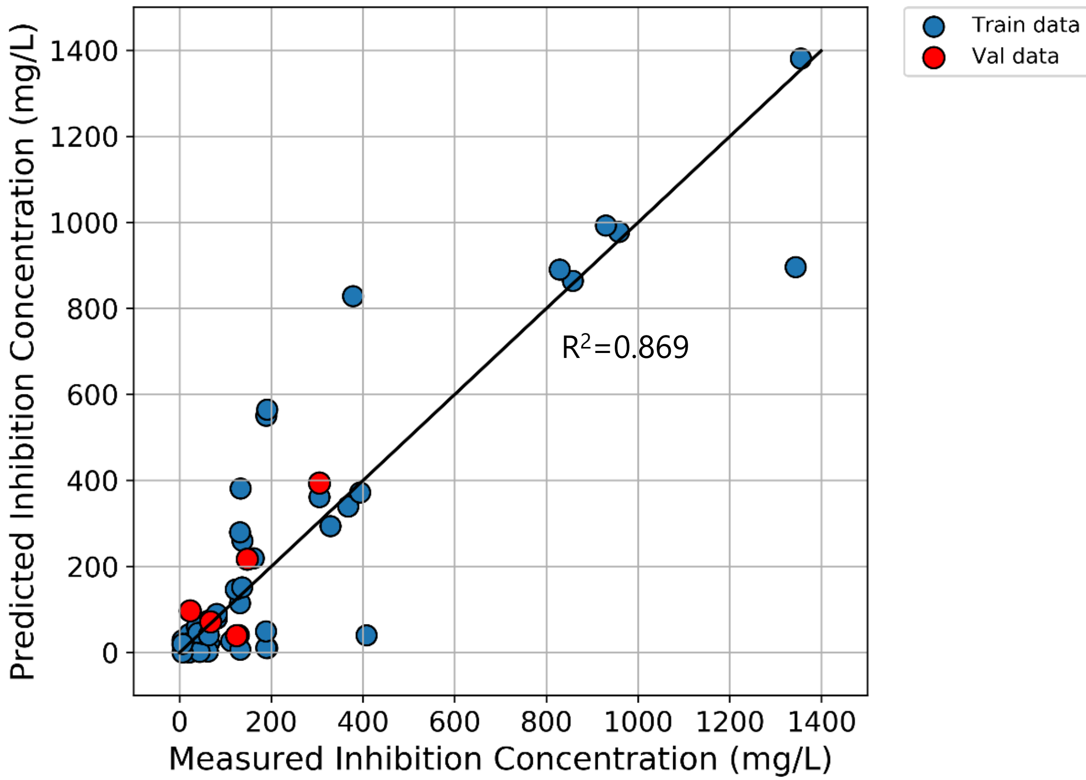
- Using the processed data with IC 40 as our desired output
- 6 out of 16 descriptors used:
  - DLS, Zeta Potential, PDI, as numerical inputs and
  - Incubation time, cell line tissue, and experimental conditions as categorical inputs
- Different parameter permutations can be applied to find best model
- Using cross validation with each to estimate the best model performance

Results

- For IC 40 (Inhibition concentration 40%) as our predicted value
  - Using 6 out of 16 features



- Problems:
  - Data size
  - Small validation set
  - Small model domain

Conclusions

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- Get more data
- Improve methods to extract data (We need more data!)

- More complex and heterogeneous materials than atoms or simple compounds
- Not all papers describe well the intrinsic and extrinsic properties
- Material for nanocarriers are not expected to be toxic

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Thanks!

Acknowledgments

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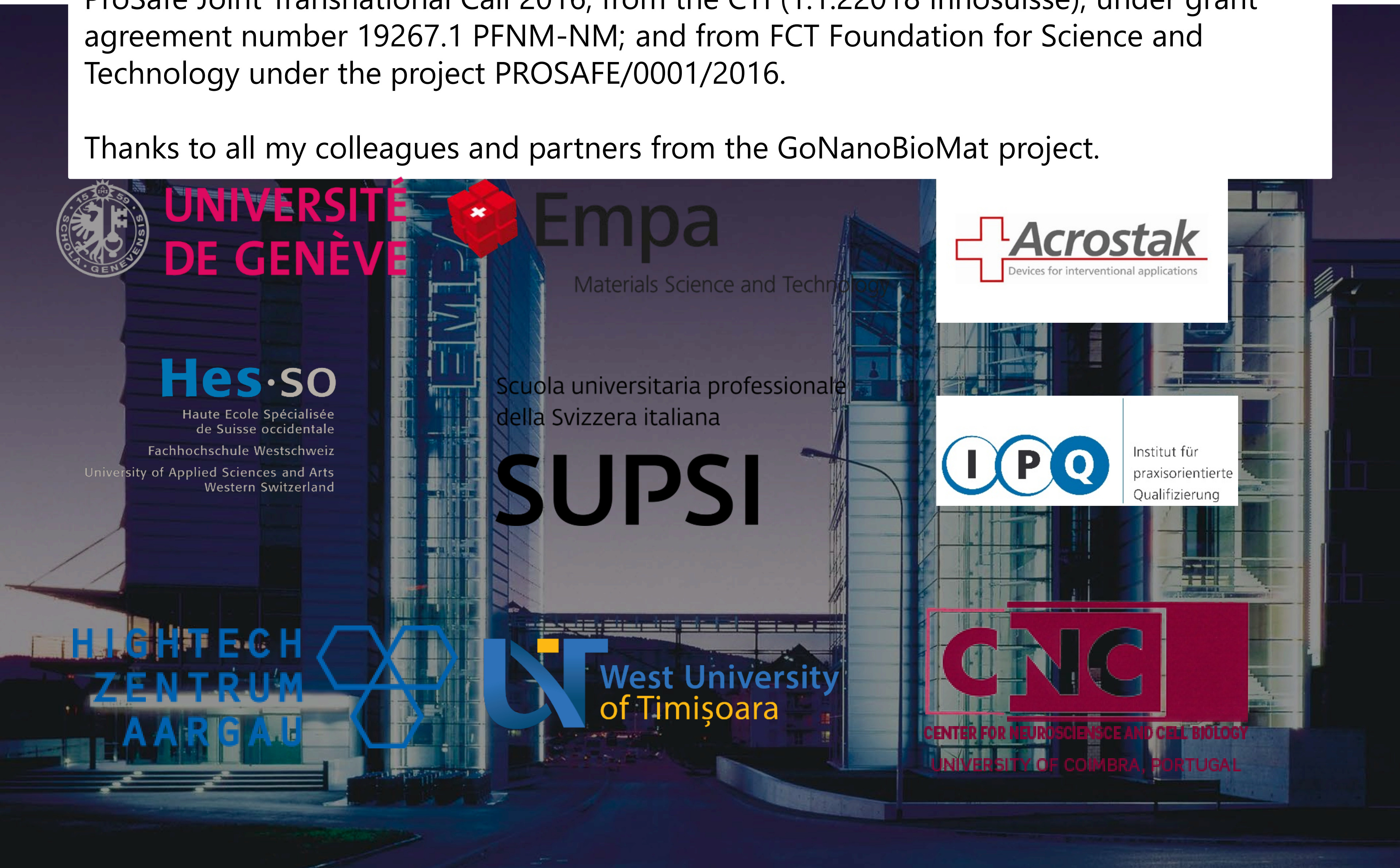
Thanks to all my colleagues and partners from the GoNanoBioMat project.



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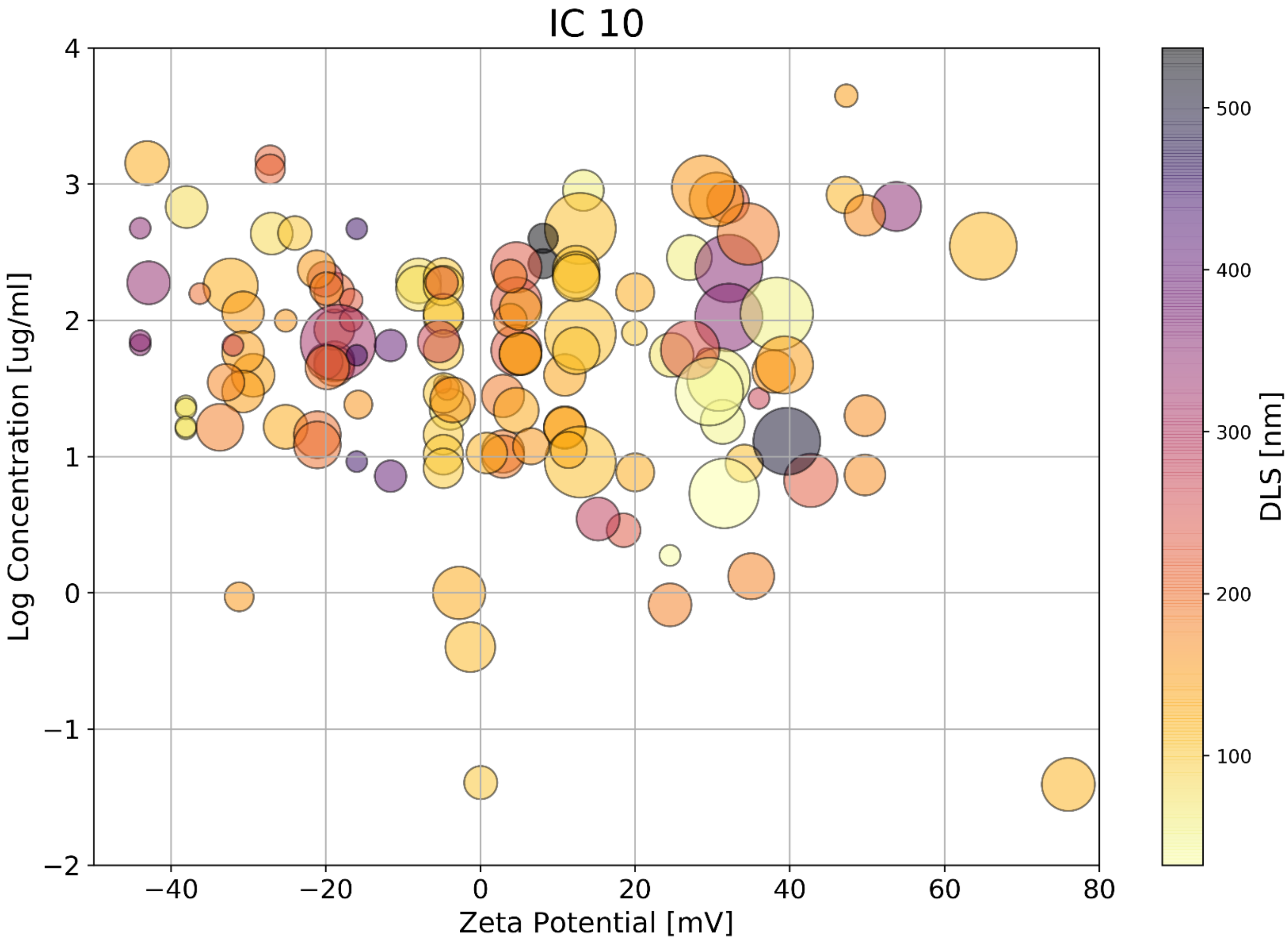
Inhibition concentration from dose response curves



ICx% represents decrease in cell viability by x%
IC 10 means that cells viability is inhibited by 10%

Inhibition concentration from dose response curves

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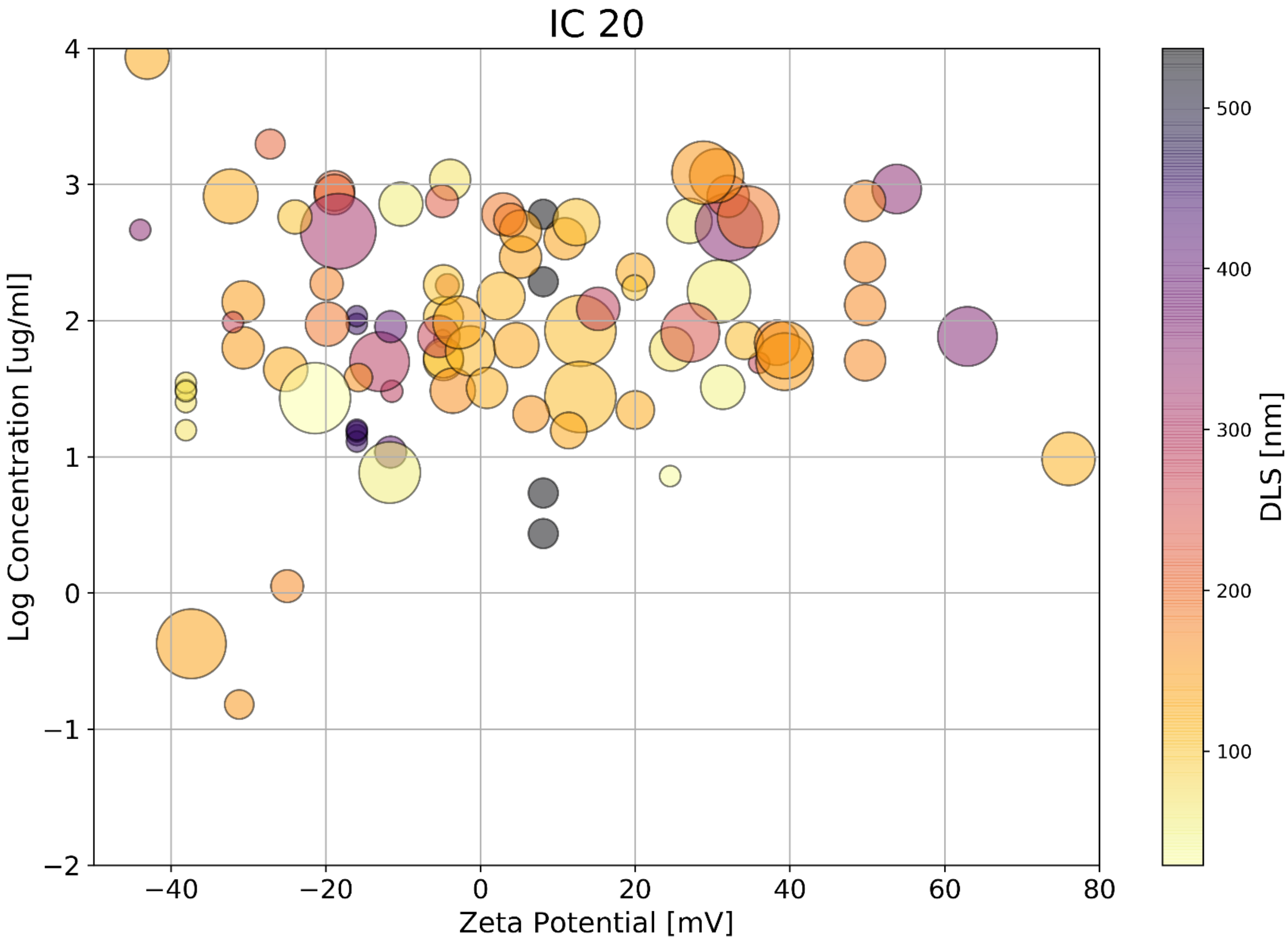
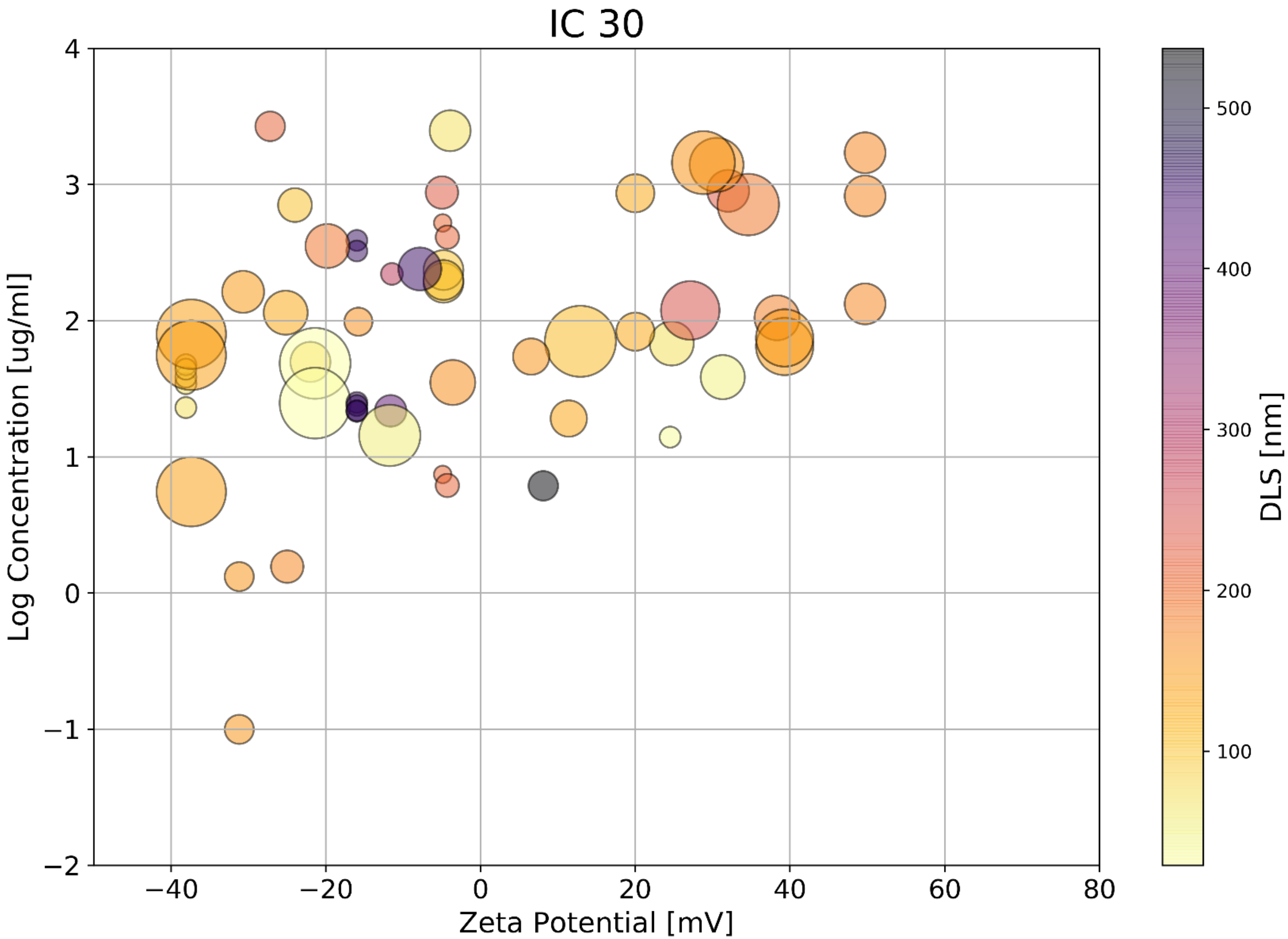


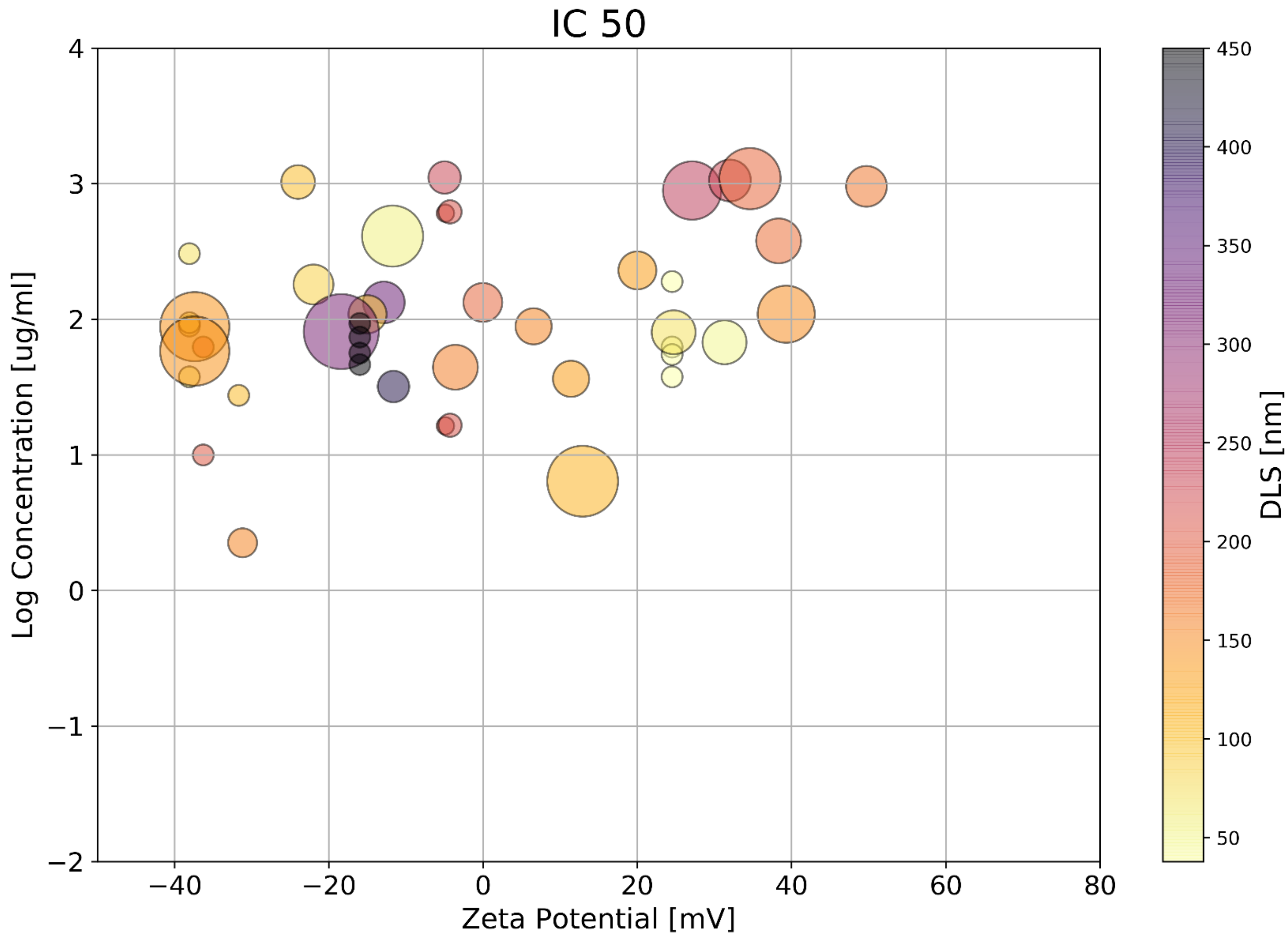
ICx% represents decrease in cell viability by x%
IC 20 means that cells viability is inhibited by 20%

Inhibition concentration from dose response curves



ICx% represents decrease in cell viability by x%
IC 30 means that cells viability is inhibited by 30%

Inhibition concentration from dose response curves



ICx% represents decrease in cell viability by x%
IC 50 means that cells viability is inhibited by 50%