From data production to hypothesis based project support

Extracting knowledge from data

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From data generation to hypothesis building

1990

2000

2010

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What is a hypothesis ?

10th PhysChem Forum
March 22-23 2011

a testable idea

which may evolve as additional information becomes available

The mission of the scientist is to formulate relevant questions and design experiments to test it

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What has happened ?

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Acknowledgments

- Giorgio Ottaviani
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Outline

- Getting started
- Multi dimensional optimization
- Local models to build hypotheses
- Extracting information in the absence of correlation
- Potential and limitations of in-vitro & in-silico approaches
- Conclusions/outlook

Target product profile

Defines the relevant assays and thresholds

- Dose, route of administration
- Target location
  - Periphery/central
  - Extracellular/intracellular
- PK/PD aspects
  - Cmax, free Cmax driven
  - AUC (free AUC) driven
  - Trough level
  - Duration of action

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Gathering and connecting data

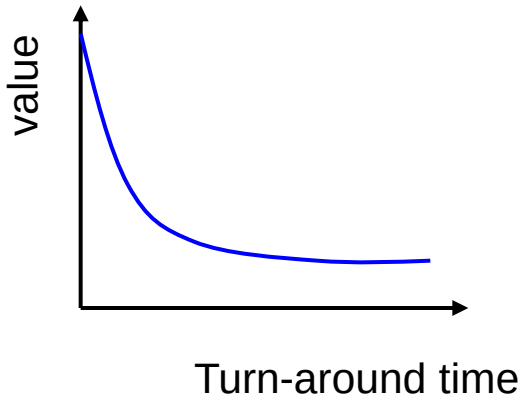
- Molecular Descriptor generators
  - Physicochemical properties
  - Structural
- Wet testing
  - In-vitro Primary – secondary – tertiary assays
  - Custom tailored assays to validate/invalidate a hypothesis
  - In-vivo PK (concentration vs. time profiles)
- Model building engine
  - Testing the “right” compounds
  - Generate hypotheses (PCA/PLS models, PBPK approaches)
  - Parameter sensitivity (PBPK, e-Numerics)

Assays packages and hierarchical testing

- Assay packages: addressing the same overall process
  - Solubility and permeability: absorption
  - Ionization and lipophilicity: logD
- Hierarchical testing
  - Primary assay: high-throughput, fast turn-around time
  - Follow-up assay: provides mechanistic understanding
    - Example of solubility: primary at pH6.8 followed by solubility pH-profile to separate solubility and ionization
    - Example of TDI: single concentration followed by K_i, K_{inact}

Properties of assay packages

- Primary assays
  - Thousands of compounds can be tested
  - “Undefined” compounds accepted
  - Need to spot check assay predictive power



- Secondary assays: build and test hypothesis
  - Question I want to answer and follow-up action need to be clear before I do the experiment

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Multidimensional optimization

reconciling different properties within ONE molecule

stability

selectivity

solubility

potency

h-ERG

reactive metabolites

permeability

Half-life

metabolic CL

VdSS

PPB

CYP-450 inhibition

PKPD

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Metadata mask information

Getting started

Multidimensional optimization

Local models to build hypotheses

Extracting information
In the absence of correlation

Potential and limitations

Conclusions

	In-vivo				In-vitro								In-silico						
cmpd	**VSS (L/kg)**	Cl	t1/2	exp %FU 7.4	HTSol6.8	logPAMPA	logPGI	FA%	logPe4	logPe6.8	logPe8	RLM	mw	psa	clogp	flex_index	AlphaH2 (A)	BetaH2 (B)	Pi2 (S)
1	4.4	157.7	0.99	100	0.004	-4.2	-4.2	96	-4.2	-4.3	-4.6	21.8	452.5	97.8	4.3	17.7	0.13	1.9	3.9
2	2.29	157	0.28	95	0.004	-5.1	-5.3	50	-5.3	-6.1	-6.4	27.7	547.7	106.1	4.7	14.6	0.13	2.6	4.6
3	23.69	116.2	4.88	1	0.42	-4.2	-4.2	96	-7.1	-5.4	-4.2		461.6	82.6	4.3	10.8	0.13	2.0	3.5
4	1.25	17.9	1.12	5	0.805	-4	-4	98	-6.2	-4.6	-4	248.5	462.6	85.8	3.7	10.8	0.13	2.2	3.8
5	4.8	35	1.69	5	0.014	-4.3	-4.3	95	-9.3	-4.9	-4.3	48.7	462.6	85.8	3.7	10.8	0.13	2.3	3.8
6	0.63	12.6	1.23	100	0.015	-5.2	-5.4	46	-5.6	-5.4	-5.7	129.8	477.6	108.9	2.3	10.5	0.13	2.3	4.4
7	1.97	51.6	0.51	69	0.004	-4.2	-4.2	96	-6.2	-4.4	-4.2	513.3	493.6	101.1	3.7	16.2	0.13	2.4	3.9
8	9.64	67.6	2.02	2	0.284	-4.5	-4.6	88	-5.9	-5.3	-4.6		476.6	85.8	4.0	12.6	0.13	2.5	3.7
9	25.96	108.7	1.81	5	0.004	-4.9	-5.1	66	-6	-5.7	-5.1	214.8	509.7	102.5	5.8	15.7	0.62	2.5	3.4
10	3.64	64	0.89	20								331.9	490.6	102.9	2.9	10.2	0.13	2.6	4.4
11	2.91	21.8	1.57	100	0.004	-3.8	-3.8	99	-3.8	-3.9	-4.1		427.5	74.8	4.8	11.7	0.13	1.8	3.5
12	22.36	121.3	1.14	100	0.004	-3.9	-3.9	99	-7.3	-3.9	-4	334.2	463.6	91.8	3.4	12.9	0.13	2.2	3.7
13	1.38	40.6	0.6	100	0.004	-3.9	-3.9	99	-3.9	-3.9	-4	826.2	461.5	84.0	4.3	13.0	0.18	1.9	3.6
14	7.84	62.2	2.5	6	0.825	-5.3	-5.9	35	-6.2	-7.2	-5.9	75.2	478.6	111.7	2.8	16.7	0.4	2.5	4.3
15	9.09	66.3	2.34	100	0.004	-4.5	-4.5	91	-4.5	-4.5	-4.8	373.4	481.5	74.8	5.3	12.5	0.18	1.6	3.3
16	6.13	80.5	1.57	100	0.007	-4.6	-4.7	85	-4.7	-4.9	-5.2	107.5	422.5	88.6	4.4	14.2	0.13	1.7	3.4
17	3.97	69.2	1.26	100	0.004	-4	-4	98	-4.1	-4	-4.2	124.8	401.5	65.5	4.5	10.0	0.18	1.5	3.3
18	11.23	111.6	2.51	100	0.004	-4.6	-4.7	86	-4.7	-5.1	-5.3	108.9	346.4	62.3	4.9	11.6	0.18	1.2	2.9
19	7.02	73	2.51	94	0.046	-3.9	-3.9	99	-3.9	-4.1	-4.3		473.6	76.1	5.6	19.0	0.13	2.0	3.4
20	4.51	66.1	1.3	25	0.023	-4	-4	98	-6.9	-4.1	-4	604.1	474.5	78.0	4.7	12.6	0.18	2.2	3.6
21	8.5	54	2.9	24	0.004							4.6	454.6	68.8	5.8	11.0	0.13	2.0	3.4
22	4.72	34	1.94	100	0.005	-4	-4	98	-4.1	-4	-4.1	196.6	465.5	84.0	4.0	10.7	0.18	1.9	3.6
23	6.1	22	4.3	100	0.004	-4.5	-4.5	91	-4.5	-4.7	-5	100.1	445.5	74.8	5.0	9.0	0.13	1.8	3.4
24	13.7	35		99	0.004	-3.8	-3.8	99	-3.8	-5	-5.2	163.6	446.5	81.5	4.8	11.2	0.18	1.7	3.2
25	6	49		100	0.007	-3.6	-3.6	99	-3.6	-4.6	-4.8		494.5	68.8	5.5	10.1	0.18	2.0	3.4
26	2.7	18		98	0.019	-4	-4	98	-5.5	-4	-4.2	59.9	414.5	87.6	3.0	9.7	0.13	2.0	3.6
27	2.6	66		100	0.004	-4.3	-4.3	95	-4.4	-4.3	-4.3	202.5	439.4	95.0	2.4	9.1	0.13	2.0	3.6
28	5	91		16	0.01	-4.6	-4.7	85	-6.5	-5.1	-4.7	924	550.6	97.3	3.9	14.5	0.36	3.0	3.5
29	12.1	49		1	0.054	-4.5	-4.6	88	-6.1	-5.5	-4.6	364.7	534.6	85.8	4.9	11.2	0.29	2.6	3.3
30	4.2	16	2.7	99	0.004	-4.4	-4.4	93	-4.6	-4.4	-4.4	110.9	551.6	90.9	3.8	16.3	0	2.5	4.0
31	2.9	31	1.5	98	0.004	-4.1	-4.1	97	-4.8	-4.1	-4.4	185.2	506.6	70.8	4.9	11.8	0.13	2.0	3.4
32	4	18	3.5	97	0.004	-4	-4	98	-4	-4	-4.1	155.6	528.6	58.6	5.0	9.5	0	2.0	3.3
33	8	27	5.1	5	0.093	-4.7	-4.8	79	-5.8	-5.5	-4.8	115.5	597.7	91.2	4.7	11.7	0.13	2.7	4.0
34	8.8	18	7.2	2	0.605	-4.5	-4.6	88	-6.3	-5	-4.6	199.7	490.6	70.6	3.1	10.2	0.13	2.4	2.3
35	8.9	32	3.9	14	0.006	-4.8	-4.9	75	-5.9	-5.9	-4.9	39.2	549.6	82.9	5.2	16.4	0.4	2.5	3.6
36	5.4	39	2.6	100	0.004	-4.3	-4.3	95	-4.3	-4.5	-4.5	254.4	509.6	91.8	4.9	13.7	0.13	2.2	3.7
37	8.3	42	5.5	98	0.006	-3.5	-3.5	100	-4.5	-3.5	-3.8	520.9	422.4	70.6	3.9	11.8	0.13	1.9	2.9
38	7.2	87	2.1	45	0.004	-4.6	-4.7	85	-6.2	-4.9	-4.7	70.9	484.6	89.0	5.2	14.4	0.36	2.4	3.6
39	3.4	31	1.5	100	0.008	-3.9	-3.9	99	-4.6	-3.9	-4.2	94.2	436.4	87.6	2.8	9.2	0.13	2.0	3.6
40	6.7	101	1.5	99	0.004	-3.9	-3.9	99	-3.9	-5.6	-6	46.7	479.5	66.9	6.0	14.6	0.13	1.8	2.9
41	8.5	42	2.2	98	0.004	-3.9	-3.9	99	-3.9	-5.3	-5.9	152.3	449.5	57.7	6.2	11.1	0.13	1.6	2.6
42	26.7	46	9.8	4	0.036	-4.5	-4.5	90	-7.6	-5	-4.5	165	547.7	73.0	6.0	12.8	0.29	2.6	3.1
43	2.2	54	0.5	99	0.032	-5.2	-5.6	44	-6	-5.6	-5.9	200.9	533.6	90.0	4.7	13.1	0.4	2.7	3.6
44	15.9	58	5.2	9	0.893	-3.9	-3.9	99	-7.3	-4.6	-3.9	309.9	534.6	85.8	4.9	11.2	0.29	2.6	3.3
45	9.5	46	3.7	7	0.004	-5.1	-5.6	49	-6.2	-7.3	-5.6	95.5	477.6	107.5	3.3	10.5	0.29	2.5	3.9
46	2.4	31	1.3	100	0.036	-5.5	-6.6	19	-7.9	-6.6	-6.8	124.1	543.6	107.1	3.9	11.0	0.4	2.9	4.3
47	12.3	46	4.4	1	0.118	-4.4	-4.4	93	-5.8	-5.1	-4.4	50.8	533.6	73.0	5.5	13.1	0.29	2.5	3.1
48	3.4	16	3	98	0.27	-4.6	-4.7	85	-6	-4.7	-5	330.4	547.6	90.0	5.1	12.8	0.4	2.7	3.6
49	11.9	50	3.7	1	0.766	-5.3	-5.6	37	-5.6	-6.8	-7.2		547.6	105.7	4.6	11.0	0.56	3.0	3.9
50	60.9	70	13.2	1	0.807	-5	-5.2	56	-6.3	-6.5	-5.2	154	524.7	108.5	6.5	21.0	0.62	2.3	3.3
51	9.6	45	3.6	1	0.004	-5	-5.2	60	-6.7	-7.2	-5.2	130.8	534.7	119.5	5.2	13.1	0.65	2.8	3.8
52	10.8	47	2.7	61	0.877	-4	-4	98	-5.3	-4.3	-4	577.5	575.7	90.0	5.5	10.4	0.29	2.7	3.8
53	24.4	32	10.7	0	1	-4.3	-4.3	95	-7.3	-4.4	-4.3	49.5	561.7	73.0	6.5	12.5	0.29	2.6	3.1
54	7.5	38	3.4	11	0.036	-3.3	-3.3	100	-5.9	-3.3	-3.4	91.2	435.5	73.4	5.2	9.2	0.29	1.9	2.9
55	9.3	39	4.3	0	1	-4.7	-4.7	83	-5.6	-5.7	-4.7	96.9	557.7	90.0	5.3	10.8	0.29	2.7	3.8
56	9.5	44	4.4	9	1	-5	-5.2	60	-5.2	-5.9	-5.2	554.4	532.6	93.7	4.1	11.3	0.29	2.6	3.7
57	15.2	10	18.2	0	0.988	-5.3	-5.9	37	-5.9	-6.9	-7	19.4	520.6	85.8	3.6	13.5	0.29	2.8	3.3
58	12.9	93	2.8	0	0.425	-4.6	-4.7	83	-5.3	-6.5	-4.7	171.1	545.6	80.8	5.2	12.8	0.29	2.6	3.5
59	1.7	22	2.2	1	0.966	-4.9	-5	68	-5.1	-5.3	-5	213.2	531.6	80.8	4.6	13.2	0.29	2.5	3.4
60	17.5	28	9.8	0	0.01	-4.6	-4.6	87	-6.6	-6	-4.6	97.6	533.7	106.7	5.7	15.0	0.65	2.7	3.5
61	8.4	50	2	0	0.372	-4.3	-4.3	95	-7.1	-5.7	-4.3	68.6	577.7	80.3	4.8	15.6	0.13	3.1	3.5
62	4.6	78	1.5	86	0.004	-5	-5.2	60	-6.4	-5.6	-5.2	213.2	548.6	94.1	3.4	10.9	0.13	3.0	4.0
63	18.8	63	5.2	80	1	-4	-4	98	-5.1	-4.8	-4	171.1	548.7	85.8	5.4	10.9	0.29	2.6	3.3
64	11	54	6.5	97	0.004	-3.6	-3.6	99	-3.6	-4.8	-5	61.6	540.6	60.9	6.0	13.0	0.13	2.0	2.8
65	35.6	20	27.3	2	0.035	-5.4	-9.1	31	-9.1	-9.1	-9.2	144.4	505.6	81.7	4.3	11.9	0.42	2.5	3.1
66	13.7	72	3.2	28	0.209	-4.8	-5	72	-7.1	-5.2	-5	101.2	520.6	81.2	5.2	13.5	0.33	2.5	3.1
67	5.2	55	1.7	98	0.031	-4.1	-4.1	97	-4.7	-4.1	-4.1	195.2	561.6	81.2	5.8	12.5	0.13	2.8	3.6
68	2.7	63	1.1	67	1	-5.2	-5.5	46	-7	-5.8	-5.5	3.4	548.6	94.1	4.0	12.8	0.13	3.1	3.8
69	17.1	58	5	7	0.016	-3.8	-3.8	99	-5	-3.8	-3.9	69	569.1	85.8	5.7	10.5	0.36	2.5	3.4
70	22.2	66	5	17	1	-4	-4	98	-6	-4.2	-4	374.6	559.6	109.6	4.4	10.7	0.36	2.7	3.8
71	7.5	134	1.3	64	0.013	-4.5	-4.6	88	-5.6	-4.6	-4.8	198	547.6	90.0	5.0	12.8	0.28	2.7	3.6
72	1.8	43	0.8	70	0.037	-4.3	-4.3	95	-6.4	-4.5	-4.3	195.2	548.6	102.9	4.5	10.9	0.28	2.9	3.6
73	3.5	112	0.7	80	1	-5.4	-6.9	28	-6.9	-7.8	-7.5	75.7	534.6	102.9	3.6	11.2	0.28	2.9	3.6

Extracting value from data

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Different dimensions, different dynamic range...

Parameter	Unit	Range (for drug like molecules)
MW	$g.mol^{-1}$	100-1000
PSA	A^2	10 to 200
Potency	M	10^{-10} to 10^{-6}
Dose	$g.kg^{-1}$	0.0001 to 1
Solubility	M	10^{-9} to 10^{-2}
Tm	K	320-580
ΔHf,m	$kJ.mol^{-1}$	10-100
LogP		-2 to +8
pKa*		0 to 12
permeability	$cm.s^{-1}$	10^{-7} to 10^{-2}
ER		0 to 10 (Caco), 0 to 100 (MDCK)
Vss	$L.kg^{-1}$	0.1 to 100
CL (int)	$\mu l.min^{-1}.mg^{-1}$	20-200
PPB	%	0-100

*: requires transformation to FI

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...and its consequence

- Different dimension and dynamic range
  - Normalization required before statistical analysis
- Parameters of similar dimension can be +, -, x or /
  - Potency + solubility (M)
  - Potency / solubility (dimensionless)
- Parameters of different dimension can only be x or /
  - Solubility x permeability (flux factor) M. $cm.s^{-1}$
  - $\log P_o = \log P_{mem} + \log(D/h)$
  - $P_o = P_{mem} \times D/h$

    $cm.s^{-1}$ $cm^2.s^{-1}/cm$

P_o = intrinsic membrane permeability, P_{mem} = membrane partition coefficient , D = diffusion coefficient within the membrane, h = membrane thickness

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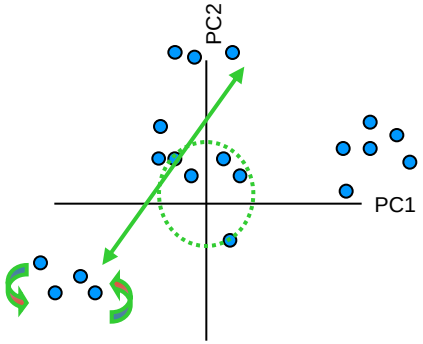
Compressing information

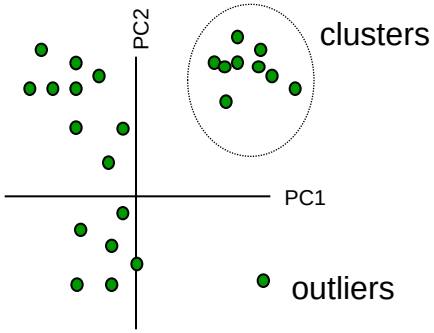
PCA produces two useful and straightforward diagrams

• The loading plot contains information about the variables: it is composed of few vectors (Principal Components, PCs) which are obtained as linear combinations of the original X-variables



to highlight the variables
which contain
similar/independent information

• The score plot contains information about the objects: each object is described in terms of its projection onto the PCs, (instead of the original variables)



to understand the
distribution of the objects

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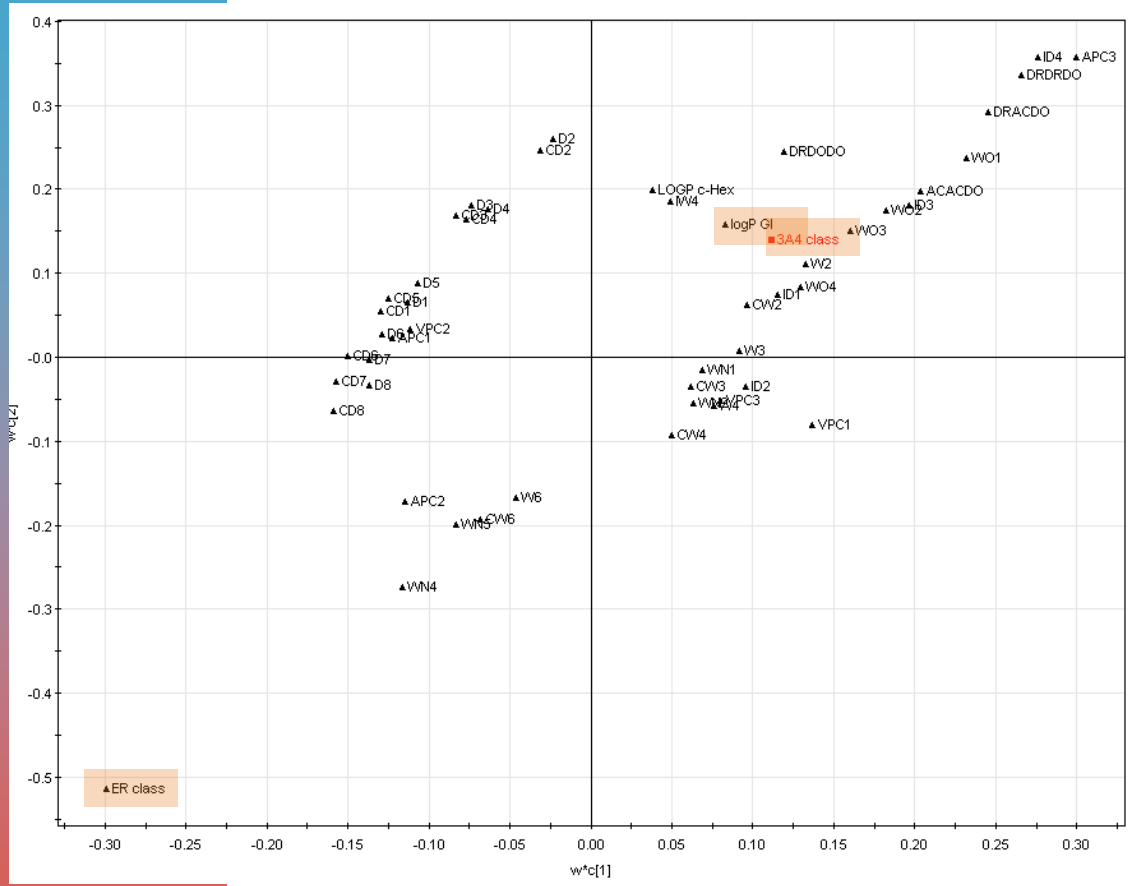
Going beyond plotting X vs. Y

Analysis of chemotype A



- Difficult to reconcile 3A4 activity and brain exposure with this chemotype
- Need to find optimal balance/compromise

- 3A4 activity and ER and negatively correlated
- 3A4 and Passive perm. are positively correlated

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What are models good for ?

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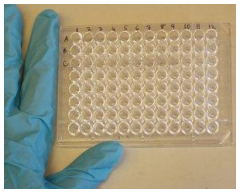

- Prediction of in-vivo response
- Link readout with chemical descriptors and...
- ...Formulate hypothesis
- **Global models**: to get started
  - Useful to manipulate large number of compounds
  - Rarely going beyond text book knowledge
- **Local models**: more information rich but restricted to local chemical space

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The power of local models

- Prioritize wet testing
- Uncover local opportunities

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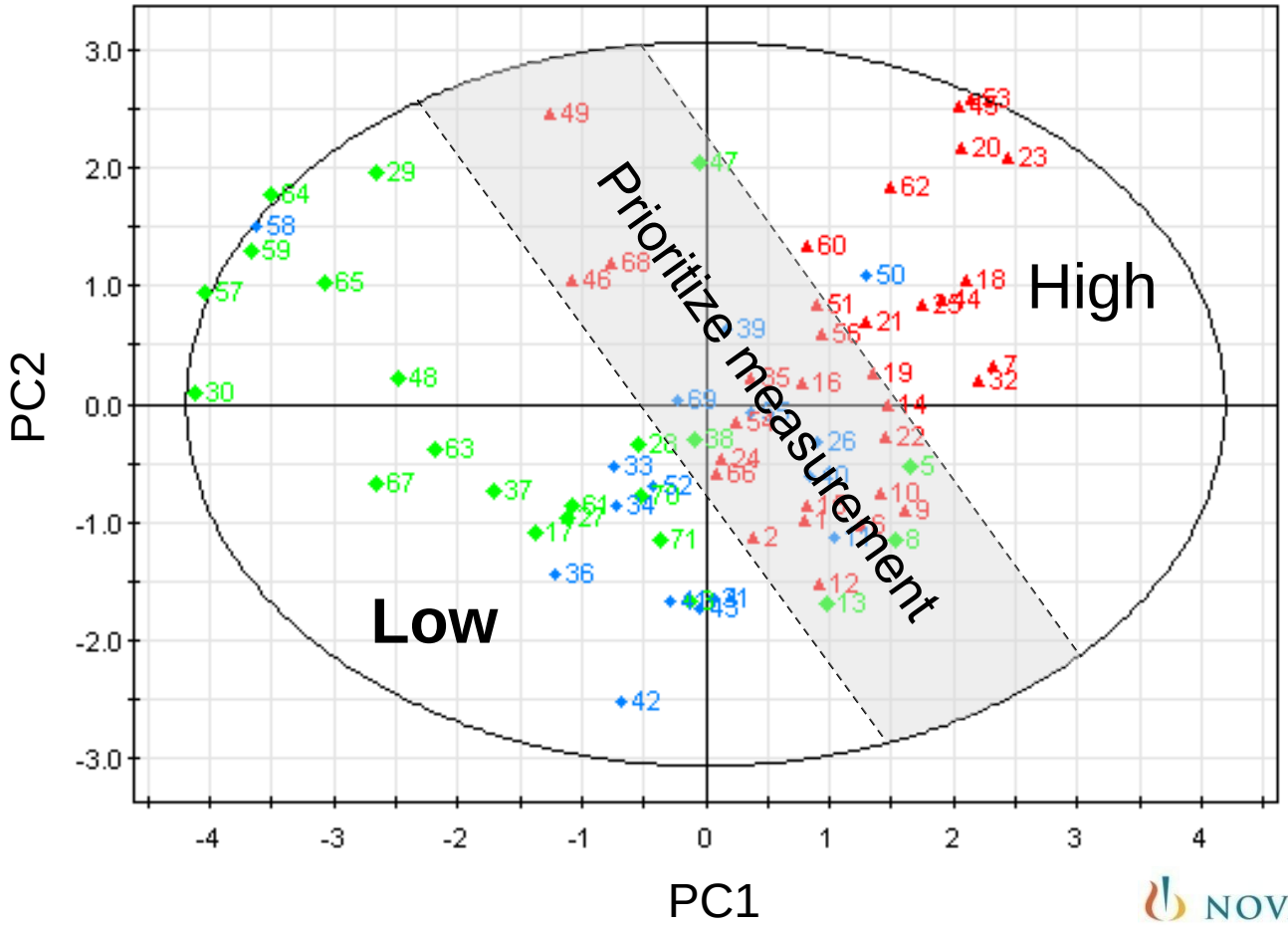
Targeting the right compounds for wet testing

MDCK-MDR1 efflux within a chemical series

ER >10 **ER 5-10** **ER <5**



Uncover local opportunities

Reducing Vss w/o compromising solubility

- General guideline: reduce logP and basicity
- Problem
  - Lowering logP may lead to poor potency
  - Reducing basicity leads to low soluble compounds
- Are there other opportunities within the local chemistry space ?

73 compounds, 16 dimensions

Reducing Vss w/o compromising solubility

Getting started

Multidimensional optimization

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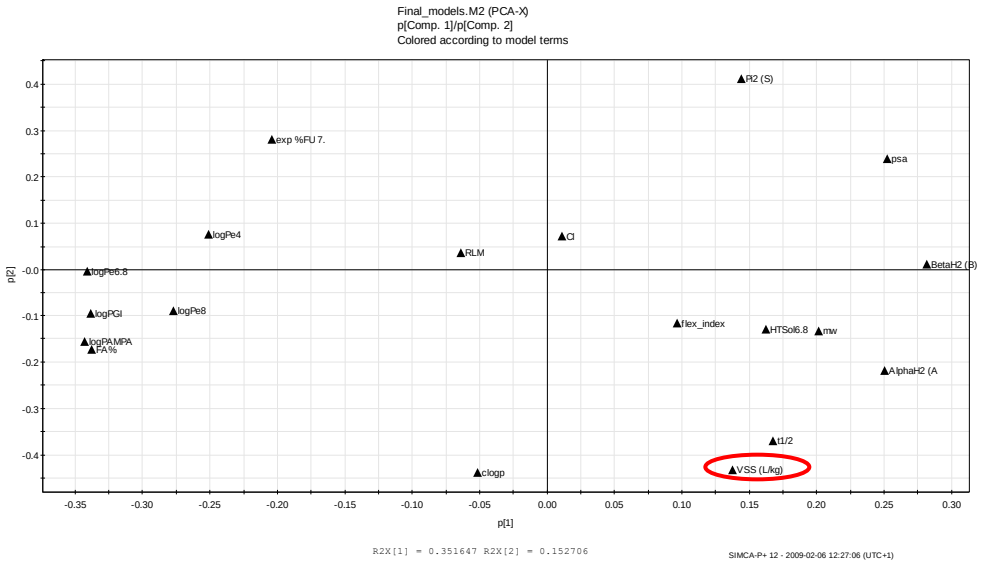
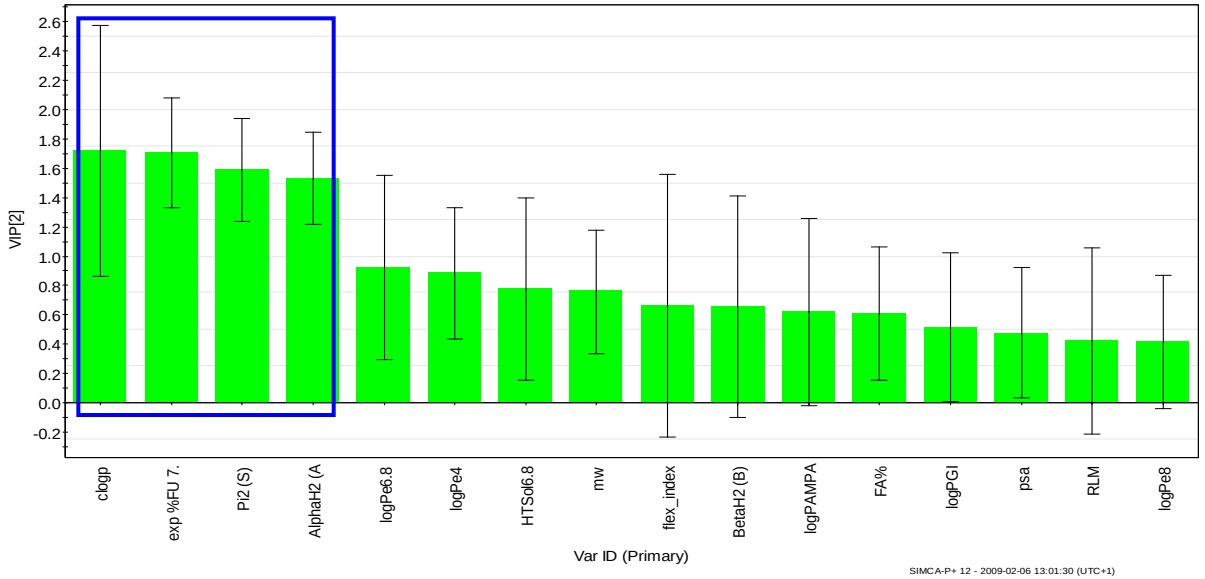
In the absence of correlation

Potential and limitations

Conclusions





N=73

- 2PCs model
- R^2= 0.53
- Q^2 = 0.42

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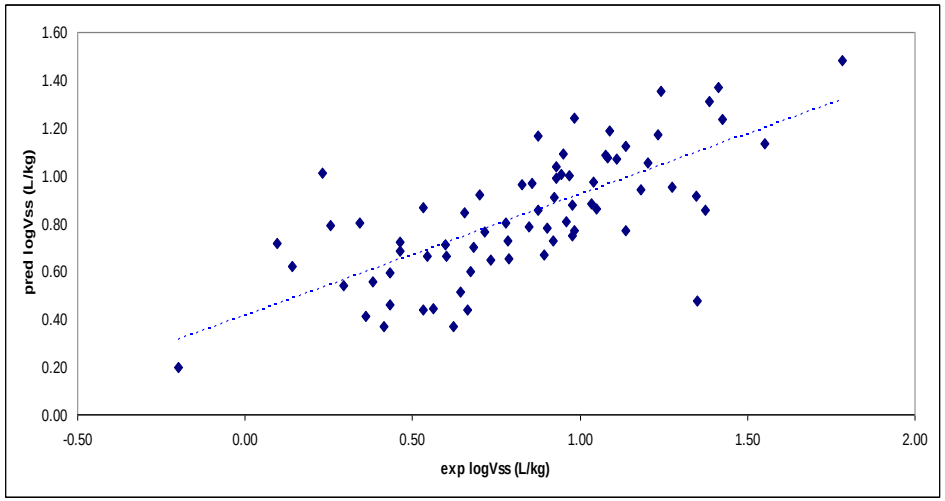
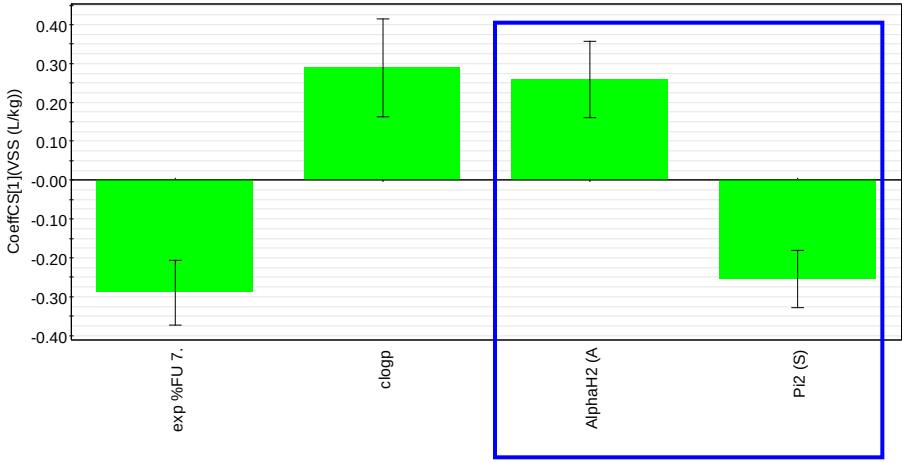
Local model for Vss: going beyond generic rules



- Y = log(Vss)
- Xs: %FU 7.4, clogP, HBD, polarizability
- 1PC model
- R^2= 0.51
- Q^2 (LOO) = 0.49
- 85% within 2-fold

scaled



Vss

log(Vss) = 1.13 - 0.24Fu7.4 + 0.11clogP + 0.67alpha - 0.24Pi2

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Extracting information in absence of correlation

- The value of orthogonal assays
- In-vivo/in-vitro Clearance

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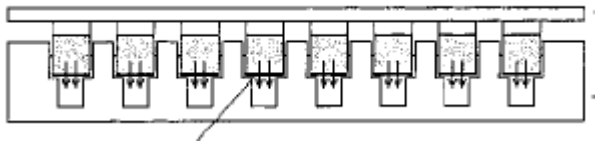
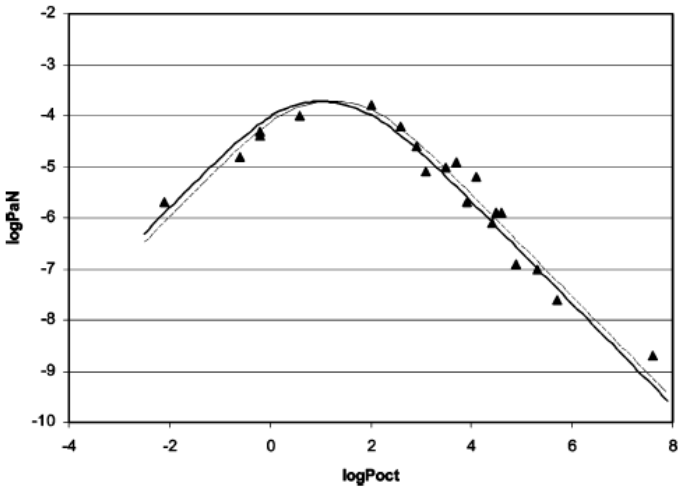
Low [C] logP > high [C] logP: what does it mean?

Example 1

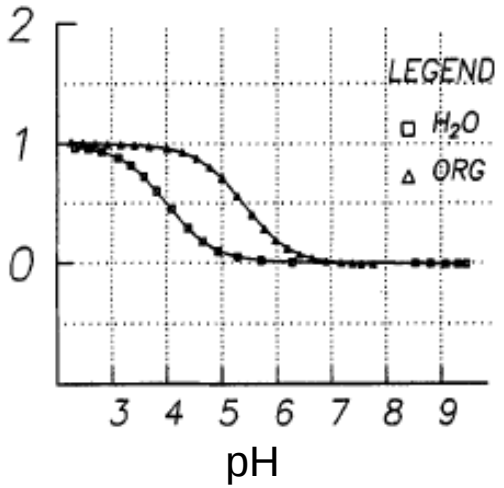


Octanol layer



from Faller-B et al , J. Med. Chem, 2005, 48(7), 2571

Compound 218



from Avdeef-A , J. Pharm. Sci, 1993, 82(2), 183

Loading [C]: 5 uM

Compound 218 : logP = 5.8

Loading [C]: 500 uM

Compound 218 : logP = 4.2

Are both assays measuring the same thing?

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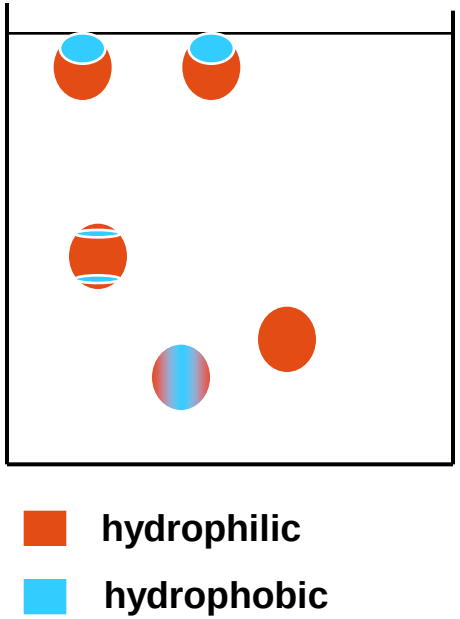
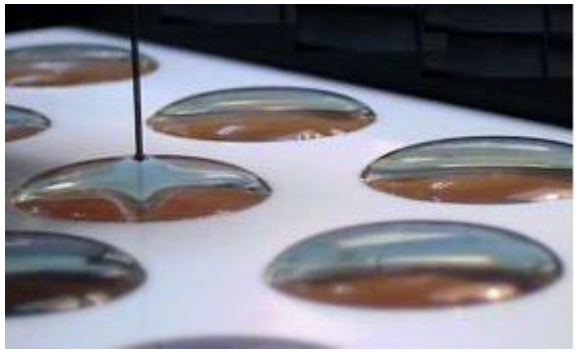
Surface pressure and amphiphilicity

- Amphiphilic molecules accumulate at the surface (air-water interface)
- Causes a drop in surface tension (this is what is measured)
- At higher concentrations, micelles are being formed in the solution





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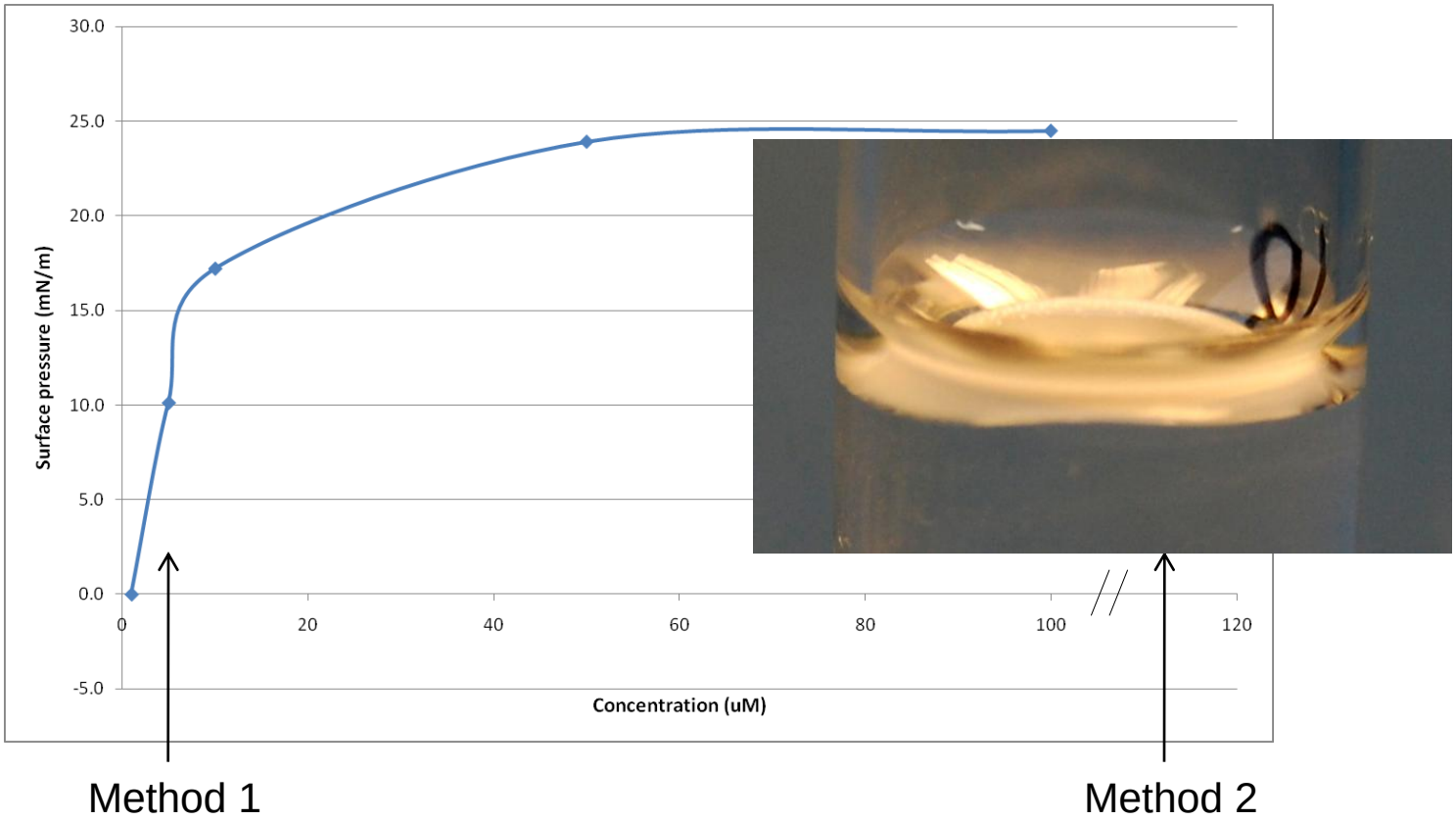
logP below and above the CMC



Apparent logP drops as compound does not homogeneously distribute in the water phase

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Power and limitations of in-silico molecular descriptors

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When in-silico does better than in-vitro

Example of clearance ivivc

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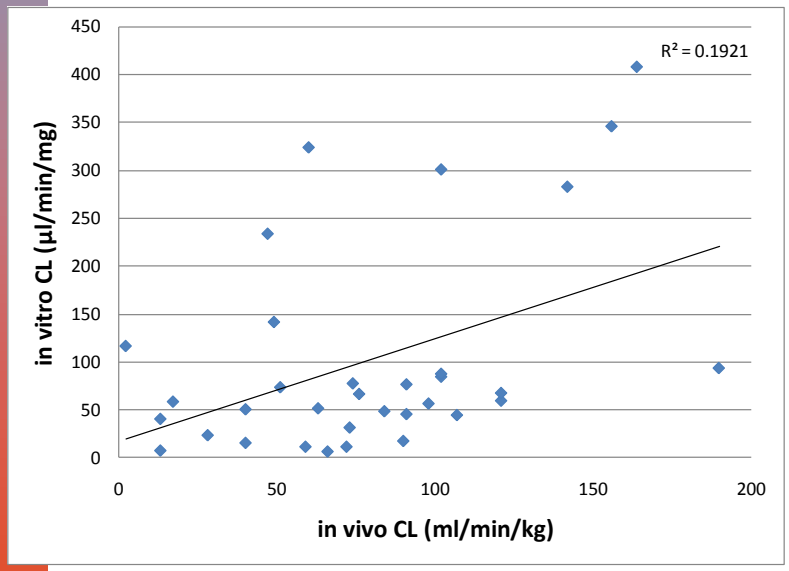
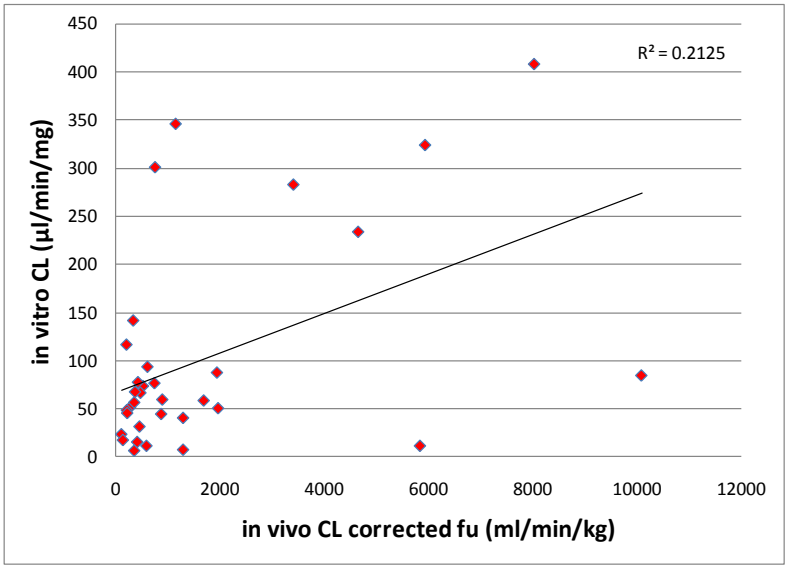
When in-silico does better than in-vitro

Example of clearance ivivc

- Poor ivivc (RLM, in-vivo CL)
- Correction by fraction unbound (f_u) did not improve correlation





PLS model and hypothesis building

The addition of 3 in silico descriptors led to a fairly predictive PLS model

CL in vivo decreases

- The most important descriptors related to in vivo CL are in vitro CL (CL_{int}), hydrophobic descriptors (D4, D5) and neutral fraction at pH 7.4 (AUS7.4).
- plasma fraction unbound (f_u) had a low coefficient.

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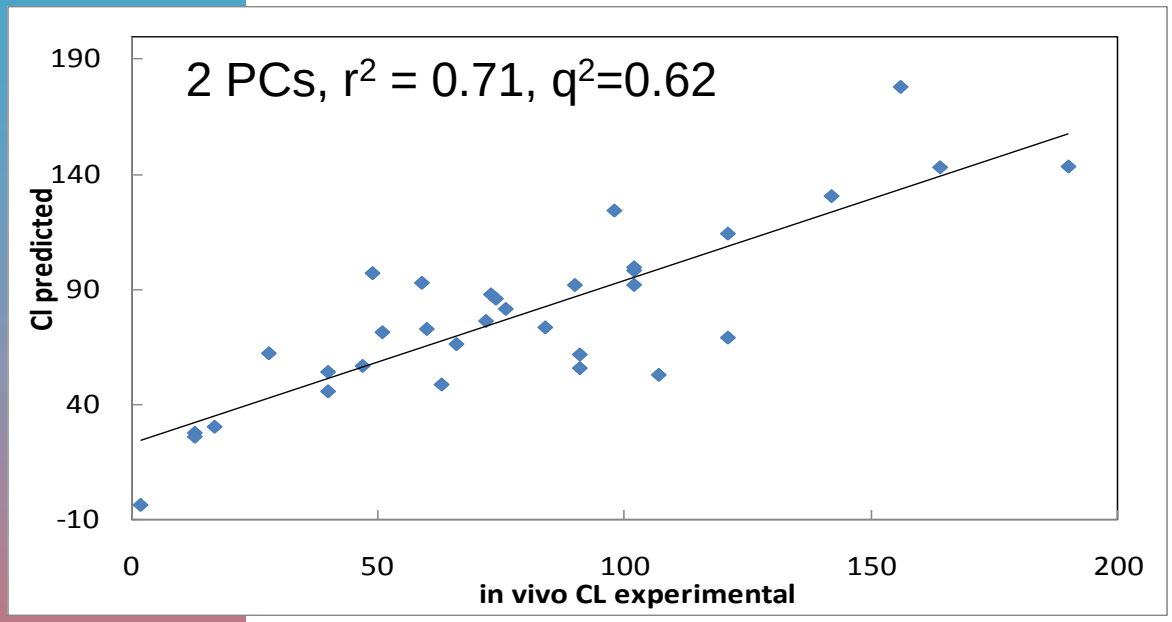
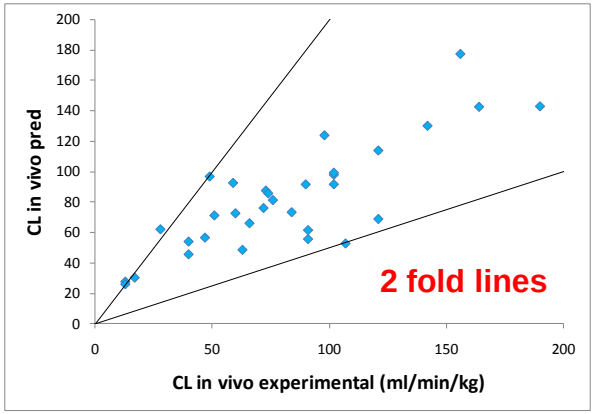
Hybrid model to reconcile in vitro and in-vivo data





GMFE = 1.36

$$CL_{invivo} = 274 + 0.19CL_{int} - 2.1D4 - 2.4D5 - 32AUS7.4$$

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When in-vitro does better than in-silico

Example of passive permeability

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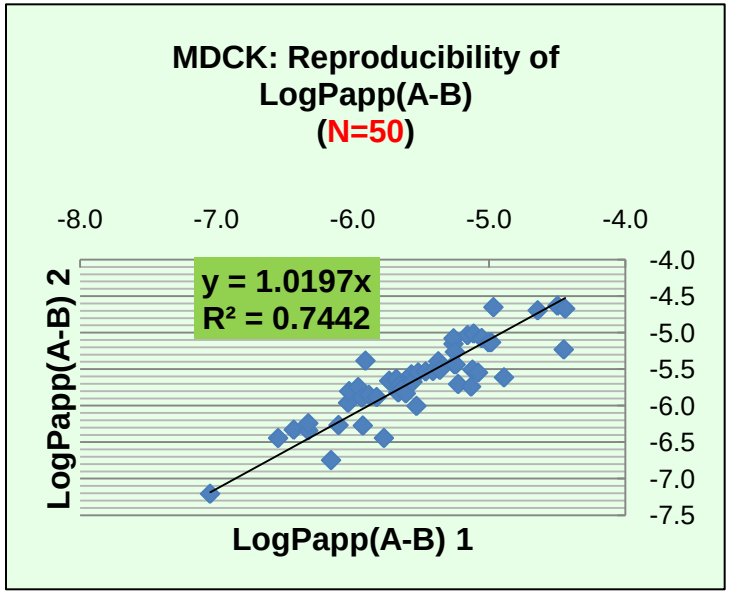
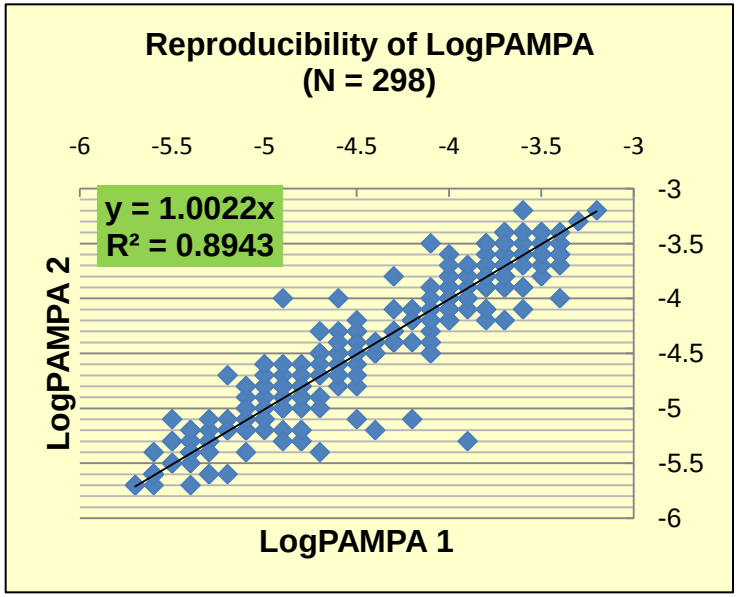
Step 1: setting the expectations right

Correlation cannot be better than assay robustness





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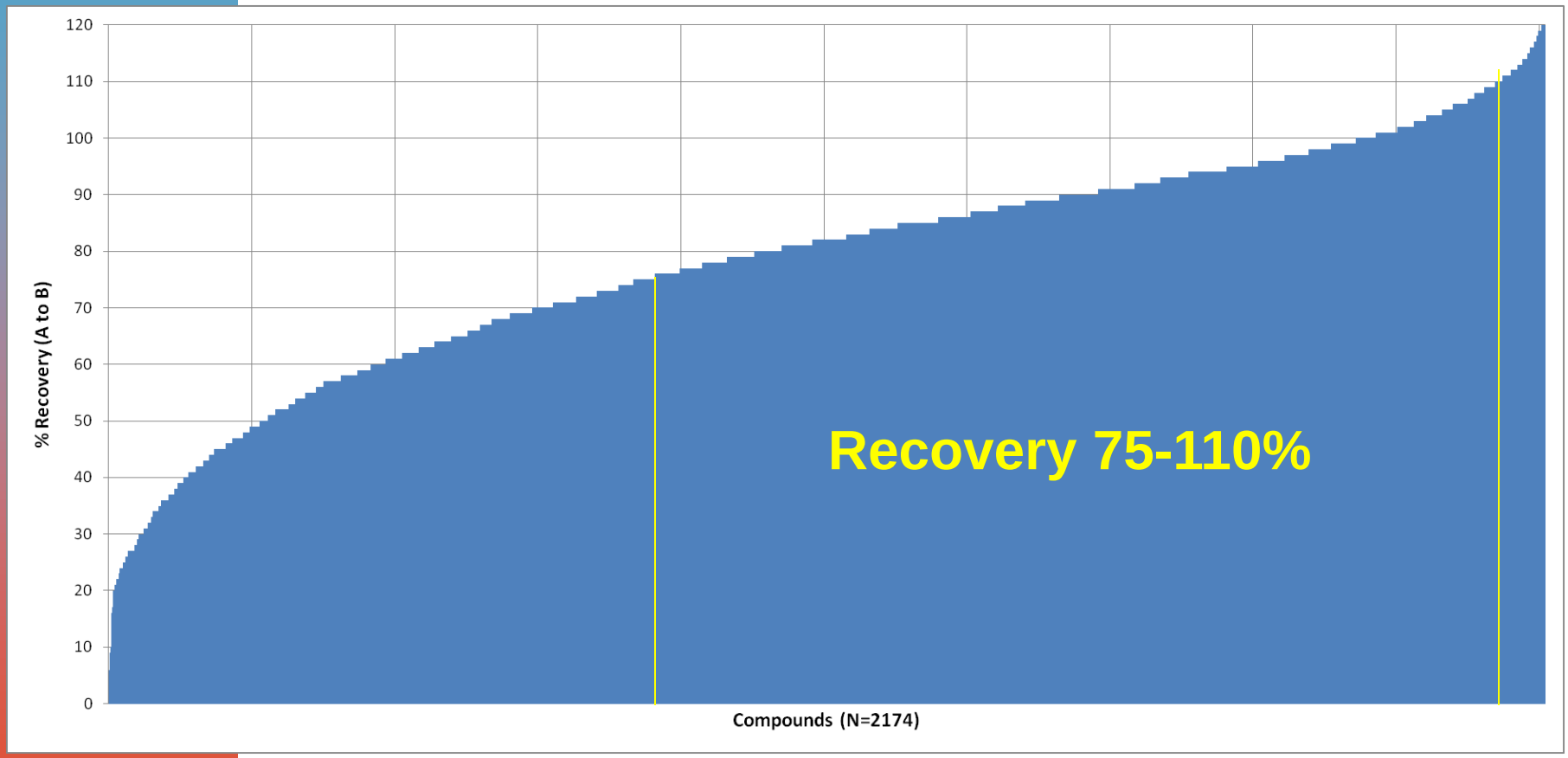
Filtering by recovery



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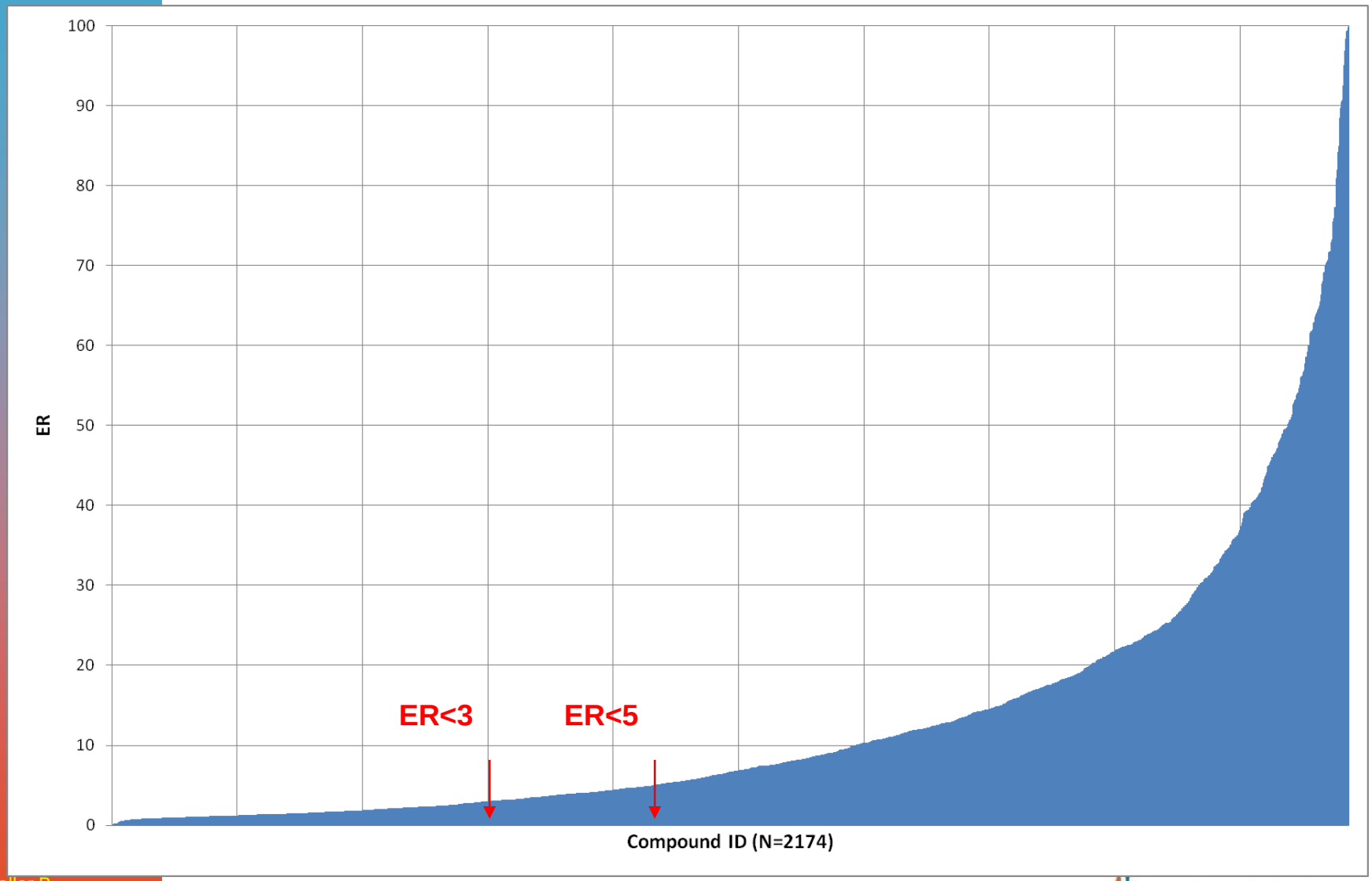
Filtering by ER



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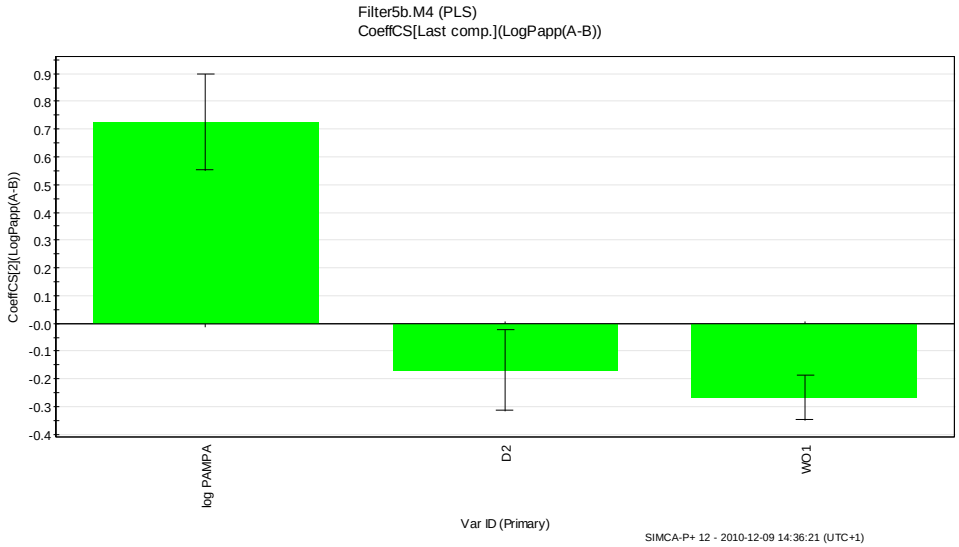
Impact of data filtering on correlation

Criteria	N	R2 PAMPA-MDCK	slope	R2 hyPLS	Q2 hyPLS
ER <5	535	0.38	0.55	0.51	0.5
ER<5, Rec >50%	436	0.43	0.65	0.60	0.57
ER<5 Rec.75-110%	207	0.51	0.73	0.70	0.66
ER<3 Rec.75-110%	116	0.68	0.95	0.72	0.67

hyPLS: hybrid PLS model based on VS+ descriptors **and** experimental PAMPA



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Prediction without experimental data

- Exp. PAMPA came as a major descriptor in the hyPLS model
- Can we predict MDCK permeability based on calculated properties alone ?

Criteria	N	R2 PAMPA-MDCK	R2 PLS	Q2 PLS
ER<3 Rec.75-110%	116	0.68	0.40	0.30

- Calculated molecular properties fail to replace exp. PAMPA in predicting MDCK passive permeability

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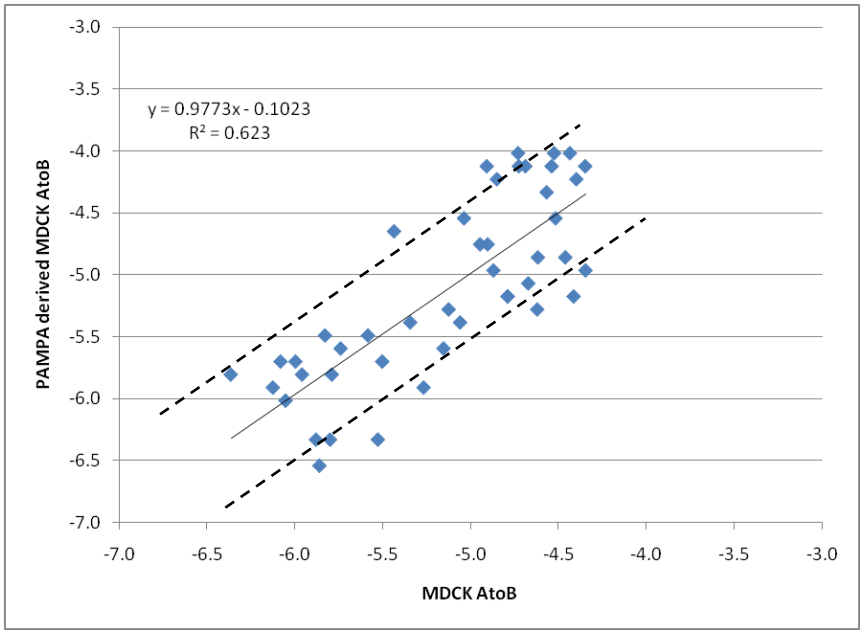
External test set: 45 generic drugs

- Selection criteria
  - Rec. 75-110%
  - ER <3
- R2 = 0.62, slope = 0.97
- 70% predicted within 0.5 log unit



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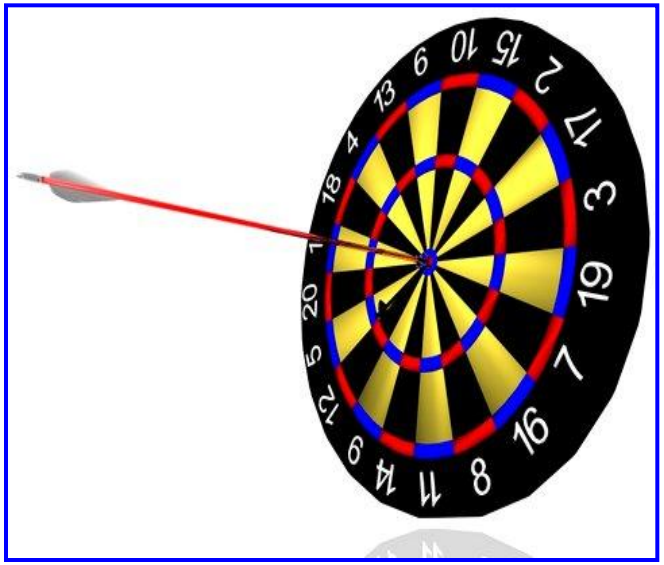
Conclusions -1

- Define clearly what you need to achieve
  - What is critically important
  - Where can I compromise
- Assay packages: science based as opposed to technology driven
- Mechanistic understanding needed for correct data interpretation
  - No variance, no information
  - Synthesize model compounds outside the potency race

Conclusions -2

- Different readout for same property: information rich
- What it takes to extract knowledge from data
  - Quality data
  - Reformatting / normalization
  - Build model
  - Use descriptors that are interpretable in MedChem terms
- Local models help to find opportunities within a chemical series and prioritize wet testing
- Models are best used to formulate and test hypothesis
- Go beyond plotting X vs. Y

Outlook



Fishing expedition

Hypothesis testing

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