



Amorphous Blobs of Hope and Other Flights of Fancy

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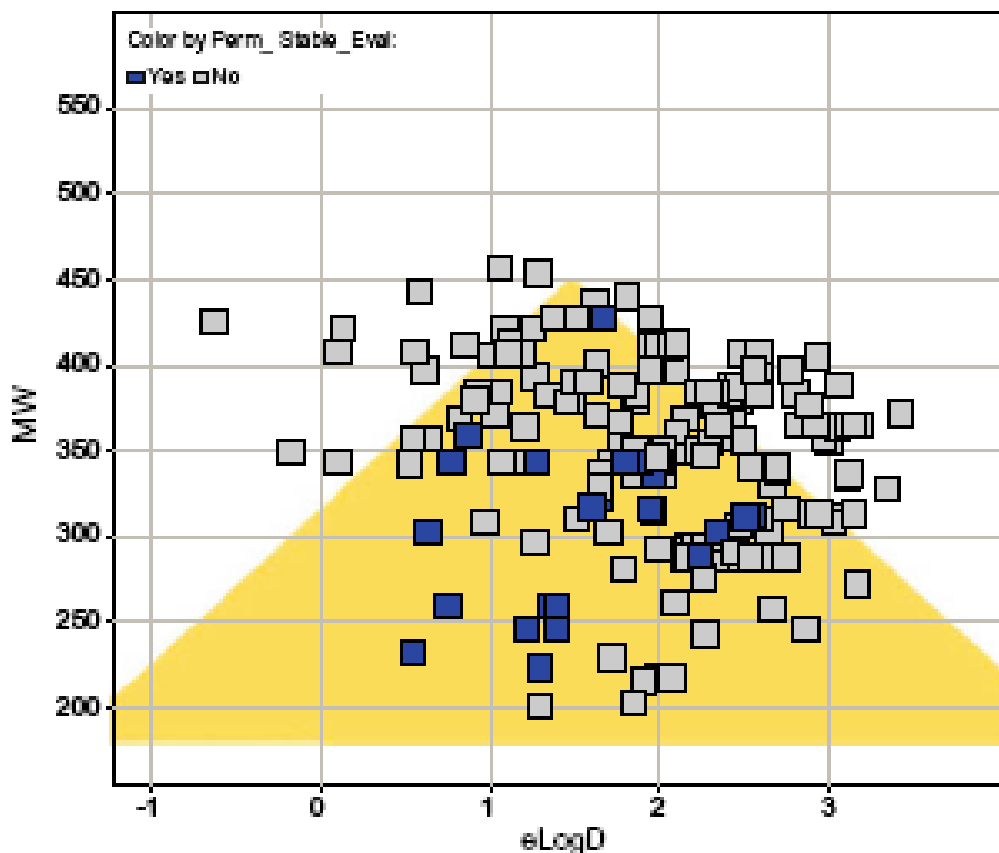
Rules of Thumb

- ...help folks make objective and informed decisions in the face of incomplete or inaccurate information.
- ... typically consist of information distilled down to minimum as a mnemonic (ie, the width of a carpenter's thumb is approximately 1 inch)
- ... and in today's usage, term implies "an imprecise but generally reliable and convenient standard"

Rules of Thumb—RO5

- Proposed by Lipinksy, etal in 1997 (Pfizer)
- Orally bioavailable compounds should have only one violation of the following molecular properties:
 - Molecular weight less than 500
 - logP less than 5
 - Hydrogen bond donors less than 5
 - Total number of nitrogen and oxygen atoms less than 10
- Have been implemented in many tools
- Generally considered harmless
- How Predictive?

Golden Triangle



- Published by Johnson, et al 2009 (Pfizer)
- Derived by analysis of PAMPA and HLM % remaining data
- Suggests that compounds with best oral absorbance and optimal clearance found in “golden triangle”
- Subset of ROF (MW \leq 500 and $\log P \leq$ 5)

Figure 5. Series A: combined in vitro permeability and clearance trends across MW and $\log D$.

3/75 Rule

- Published by Hughes, et al 2008 (Pfizer)
- Suggests that compounds with compounds with logP greater than three and tPSA less than 75, that you have a 2.5 times greater chance at being toxic
- Assumed to be due to the compounds promiscuity as measured by CEREP panel data

Table 1
Observed odds for toxicity versus ClogP/TPSA

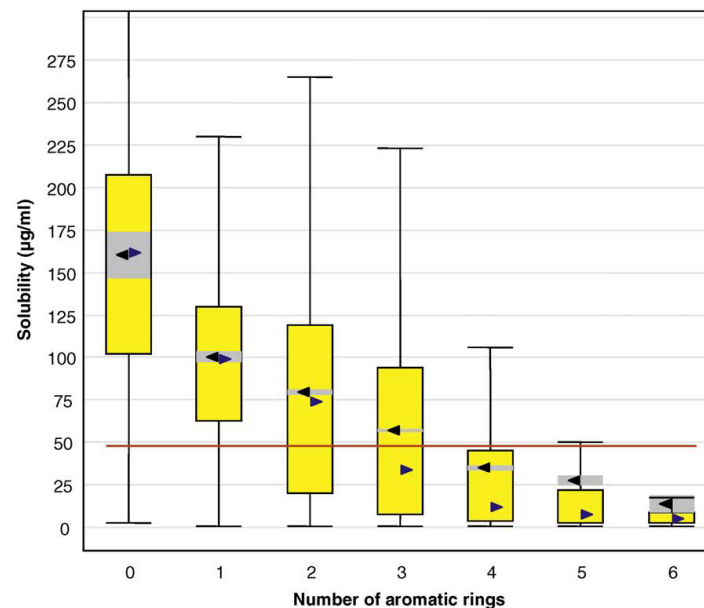
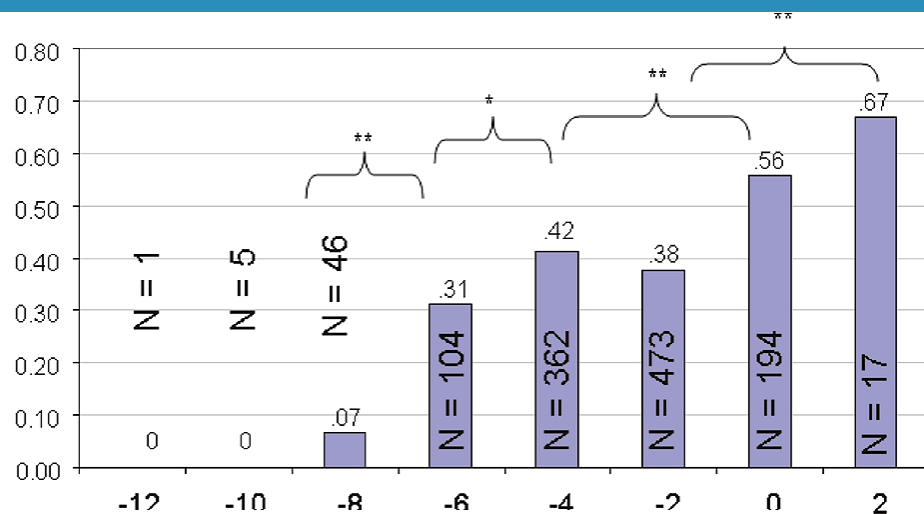
Toxicity	Total-drug		Free-drug	
	TPSA > 75	TPSA < 75	TPSA > 75	TPSA < 75
ClogP < 3	0.39 (57)	1.08 (27)	0.38 (44)	0.5 (27)
ClogP > 3	0.41 (38)	2.4 (85)	0.81 (29)	2.59 (61)

Table 2
Observed odds for promiscuity versus ClogP/TPSA

Promiscuity	TPSA > 75	TPSA < 75
ClogP < 3	0.25 (25)	0.80 (18)
ClogP > 3	0.44 (13)	6.25 (29)

Solubility and General Developability

- Lovering, 2009 (Wyeth) and Ritchie, 2009, GSK
- CLND solubility affected by two_{F_{sp3}} chemical features
- fSP3 less than 0.4 leads to poor solubility
- Number of Aromatic Rings gt 3 leads to poor solubility and formulation problems.



So, What's The Problem?

- Unnecessary reduction in information content
 - Potentially leads to miss-application and mis-understanding of the intent of the rule of thumb
 - Lipinsky "...deliberately emphasized enhanced educational effectiveness towards a well defined target audience at the expense of a loss of detail."
- "Hard" cutoffs in properties lead to discontinuities
 - Does a compound with a MW of 501 really have that different of a property than one that has a MW of 499? tPSA of 74 different from 76?
- Is this a problem that we've oversimplified? Do we need to take a harder look at the data?

If Not Rules of Thumb, Then What?

- Ideally like to have visualization and ranking tools that:
 - Are easy to interpret and remember
 - Are generally applicable
 - Information rich, heavily influenced by experimental results
 - Don't suffer from artificial data discontinuities (arbitrary cut-offs)
- Various ways to achieve goal:
 - Rules of Thumb
 - Hit to Lead tiering system
 - Aloha (Derek Debe)
 - PABOH visualization (this work)

What Do The Data Tell Us?

- What data do we have to examine whether or not these rules of thumb are useful?
- How well do the rules explain those data?

- Solubility: ~10,000 CLND data pts, pH 7.4
- PAMPA: ~6000 measurements
- HLM: ~5500 measurements
- CEREP data ~10000 data pts from 75 different targets

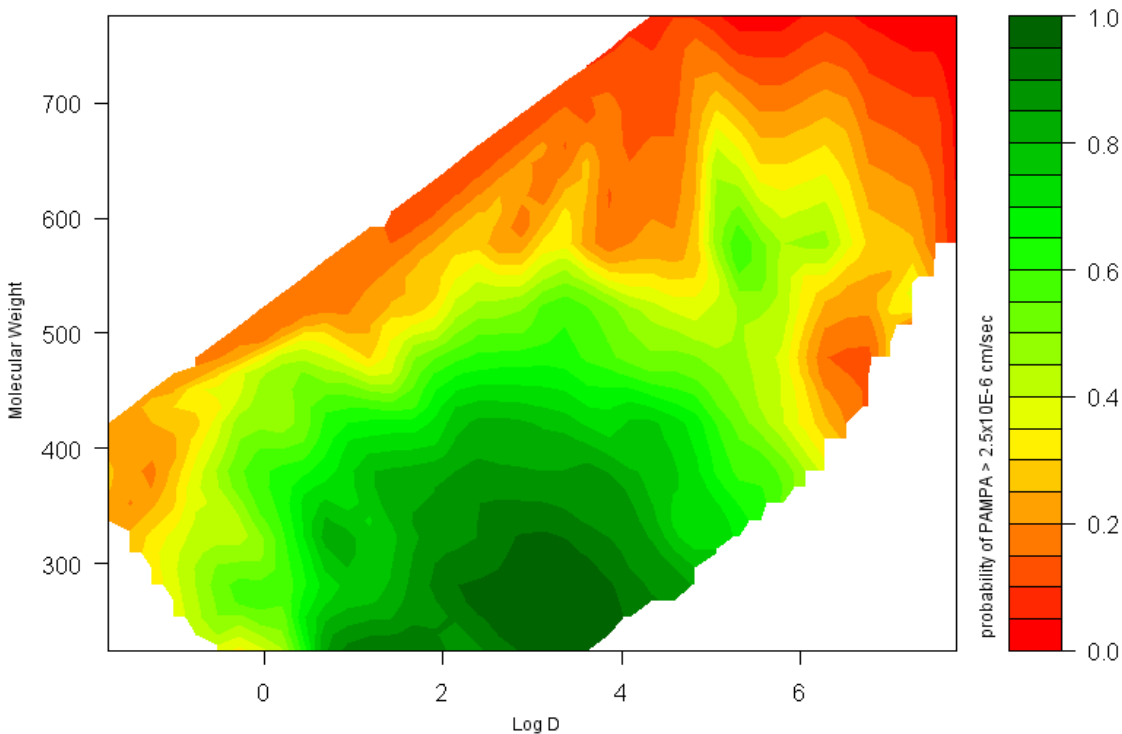
PABOH?? What the heck?

- In the following plots, we illustrate the trends in our in-house data by plotting the probability of a positive result vs. two molecular properties
- The probability of positive result is defined as the ratio to good vs. bad results in each of the data bin. Each data bin required to have 5 or more measurements
- Plot smoothing was done same function often used in generating weather isobars

PABOH: Polychromatic Amorphous Blobs of Hope

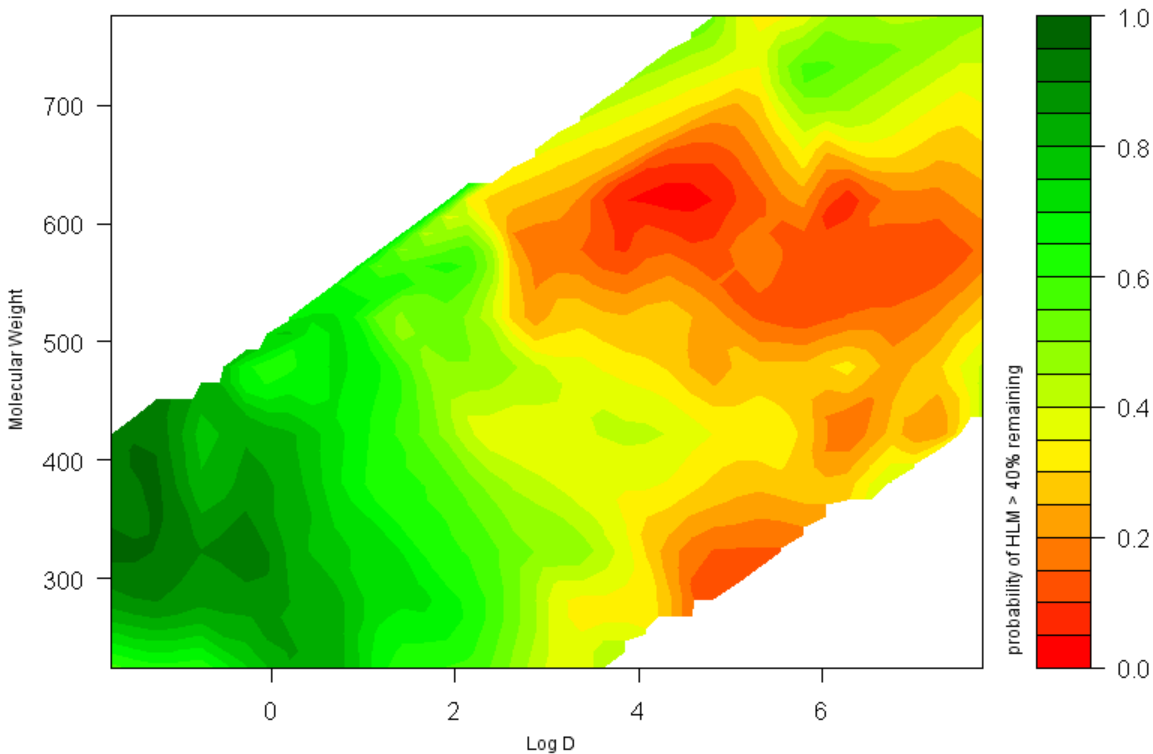
PABOH with PAMPA Data

- Probability of exhibiting PAMPA > 2.5×10^6 cm/sec measurement
- MW vs. calculated logD
- Green is highest probability
- Abbott in-house data



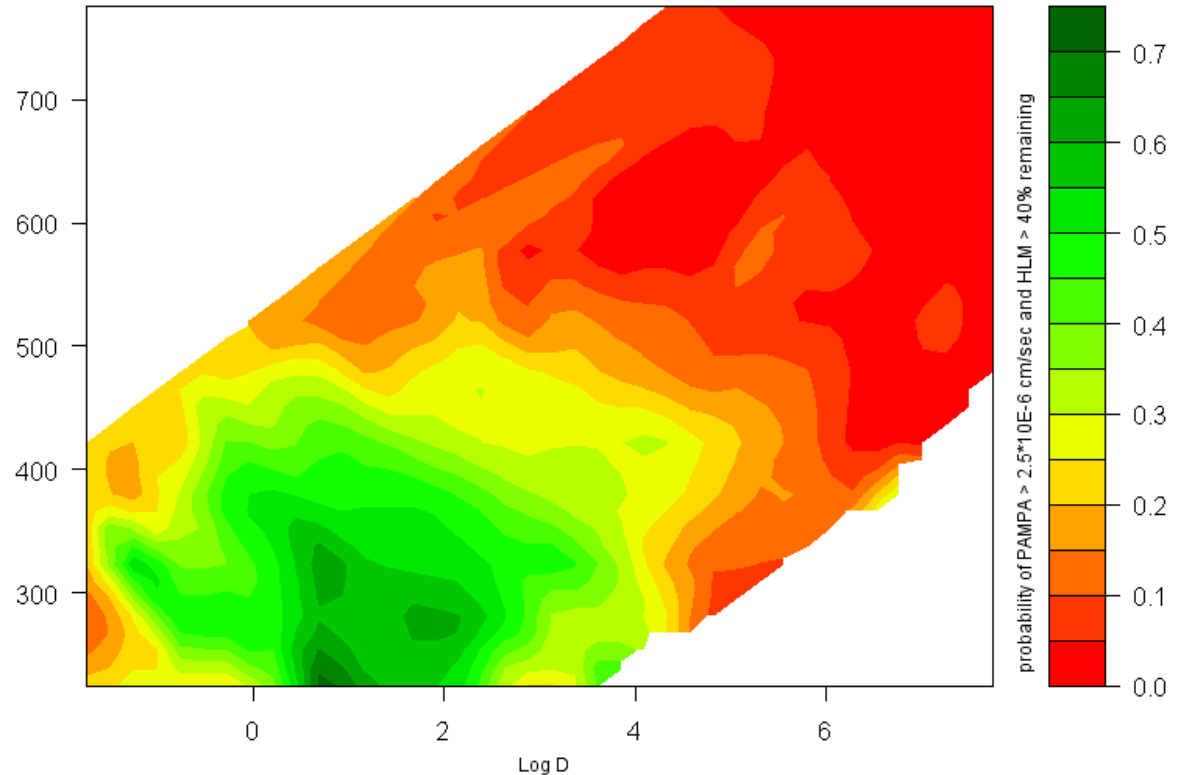
PABOH with HLM Data

- MW vs. LogD
- Probability of 40% remaining in Human Liver Microsome tests from HT-ADME

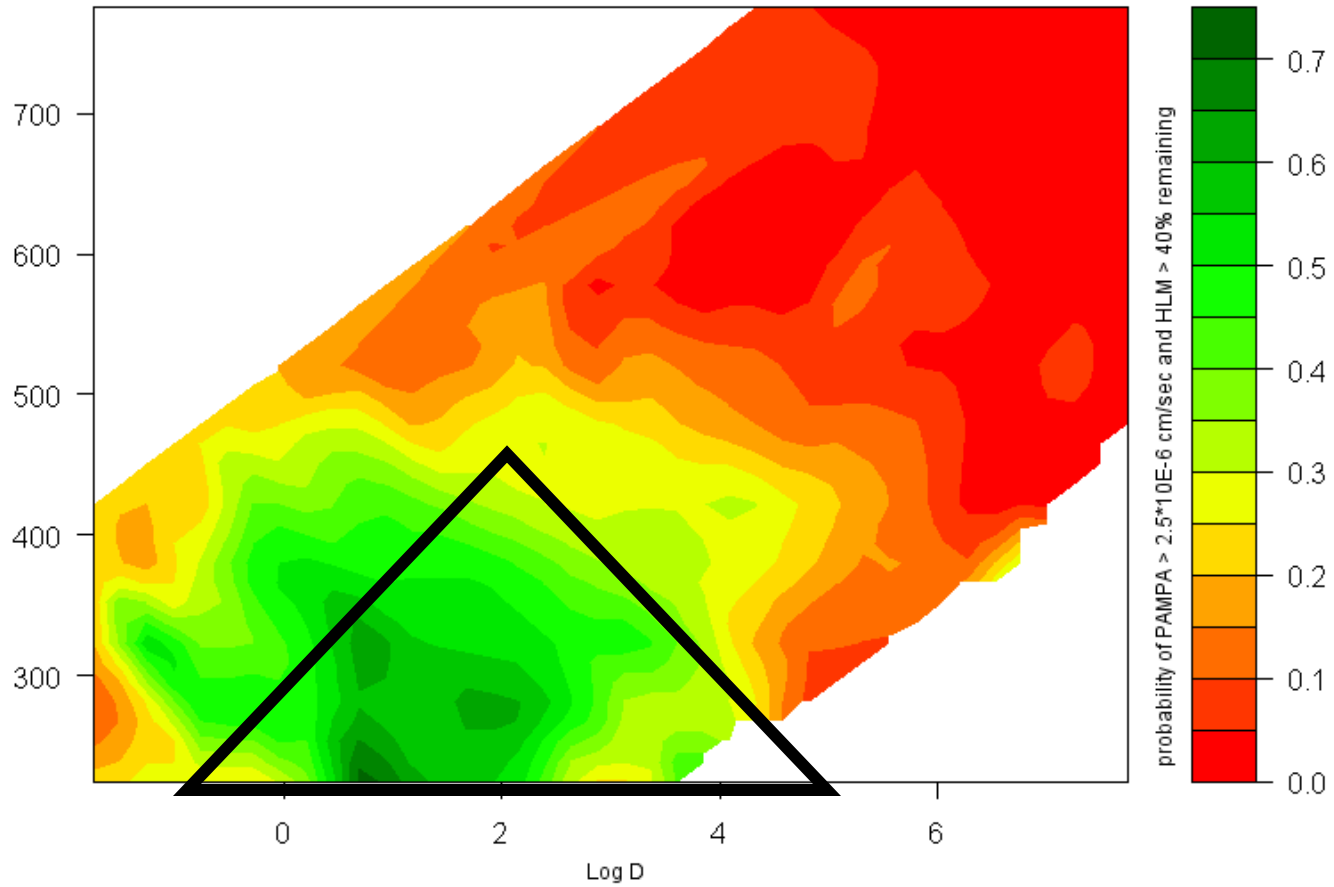


Combined HLM and PAMPA

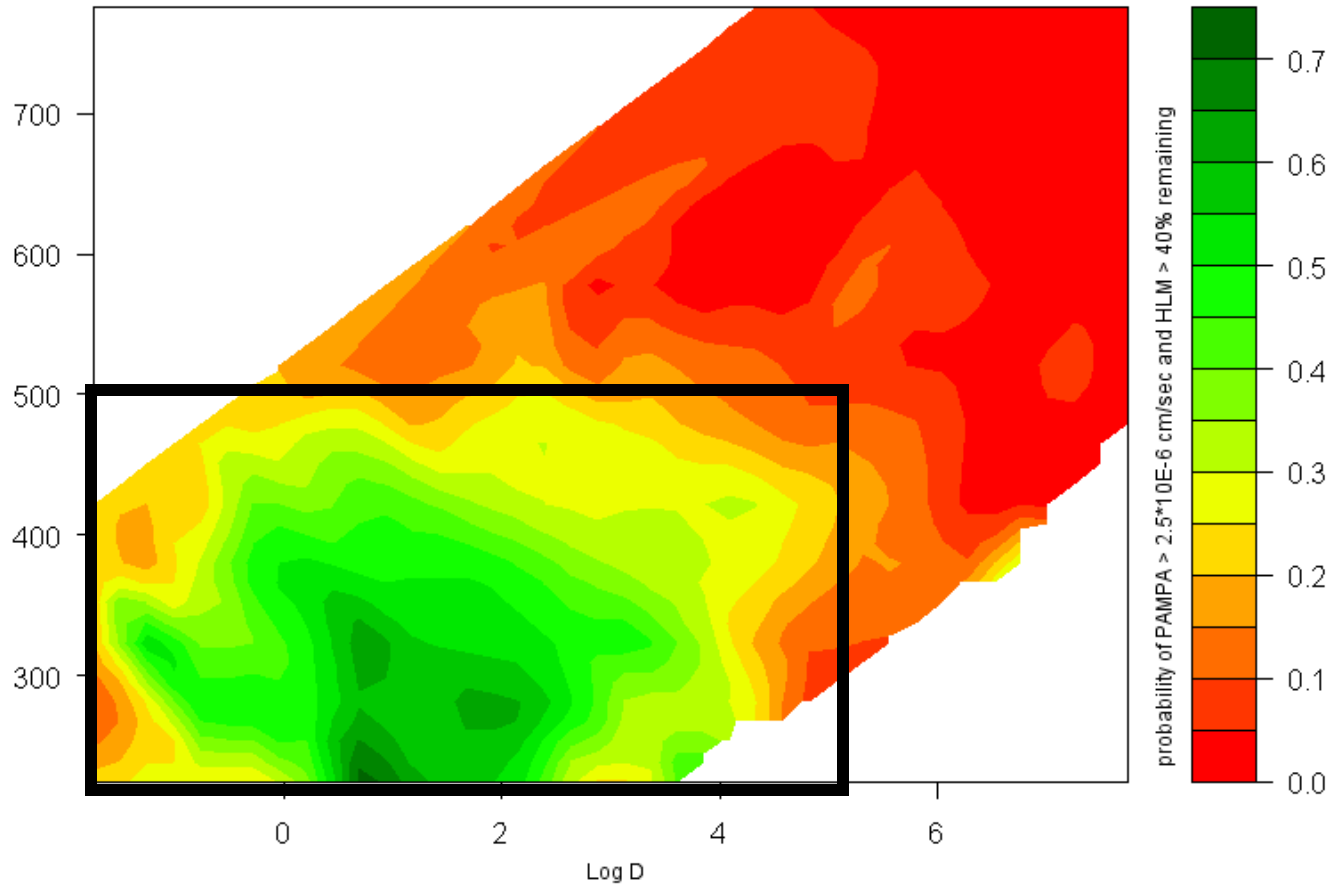
- Since PABOH plots are probabilities of success, if they are calculated using similar axes, they can be combined
- This plot is simple sum of HLM and PAMPA PABOH plots
- Equivalent to “Golden Triangle” or RO5 property space



PABOH vs. Golden Triangle

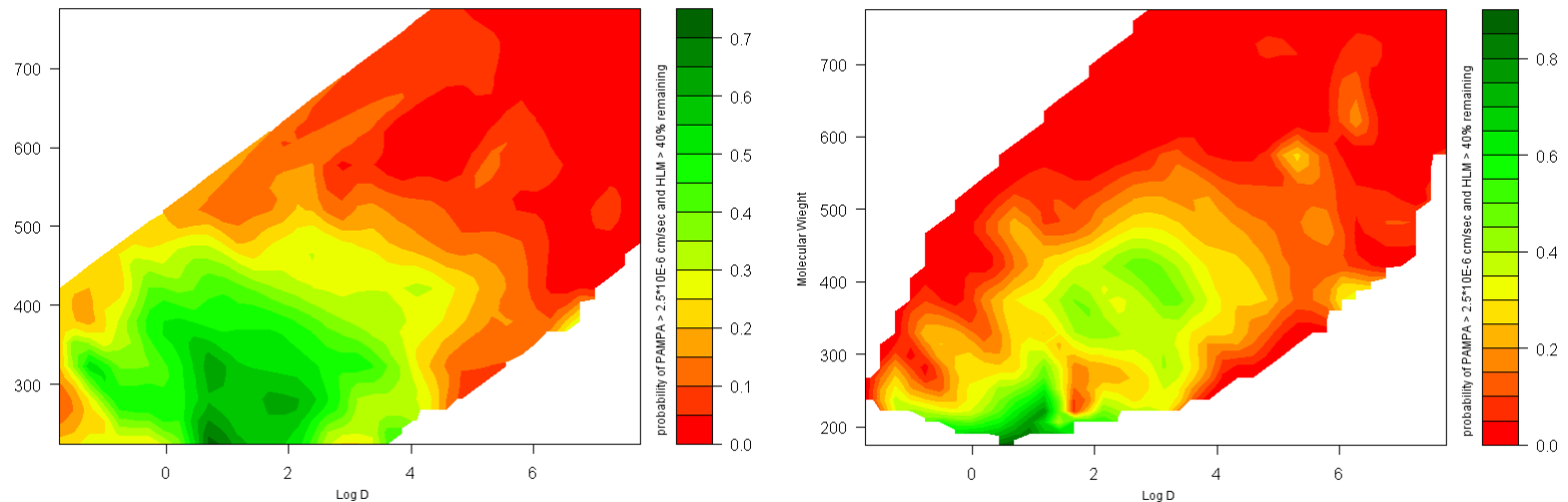


PABOH vs. RO5

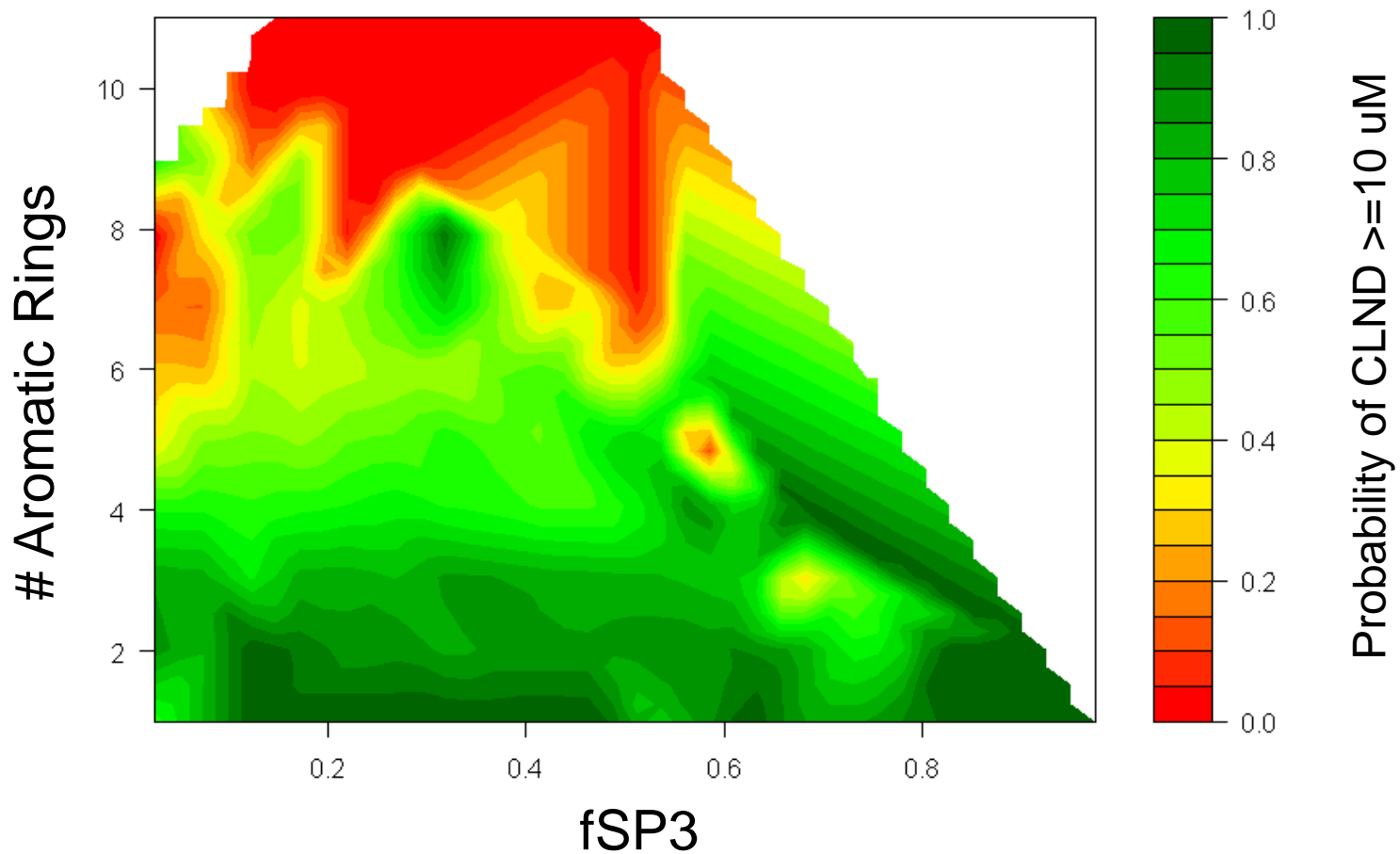


Comparison of Combined HLM and PAMPA to Rat PO

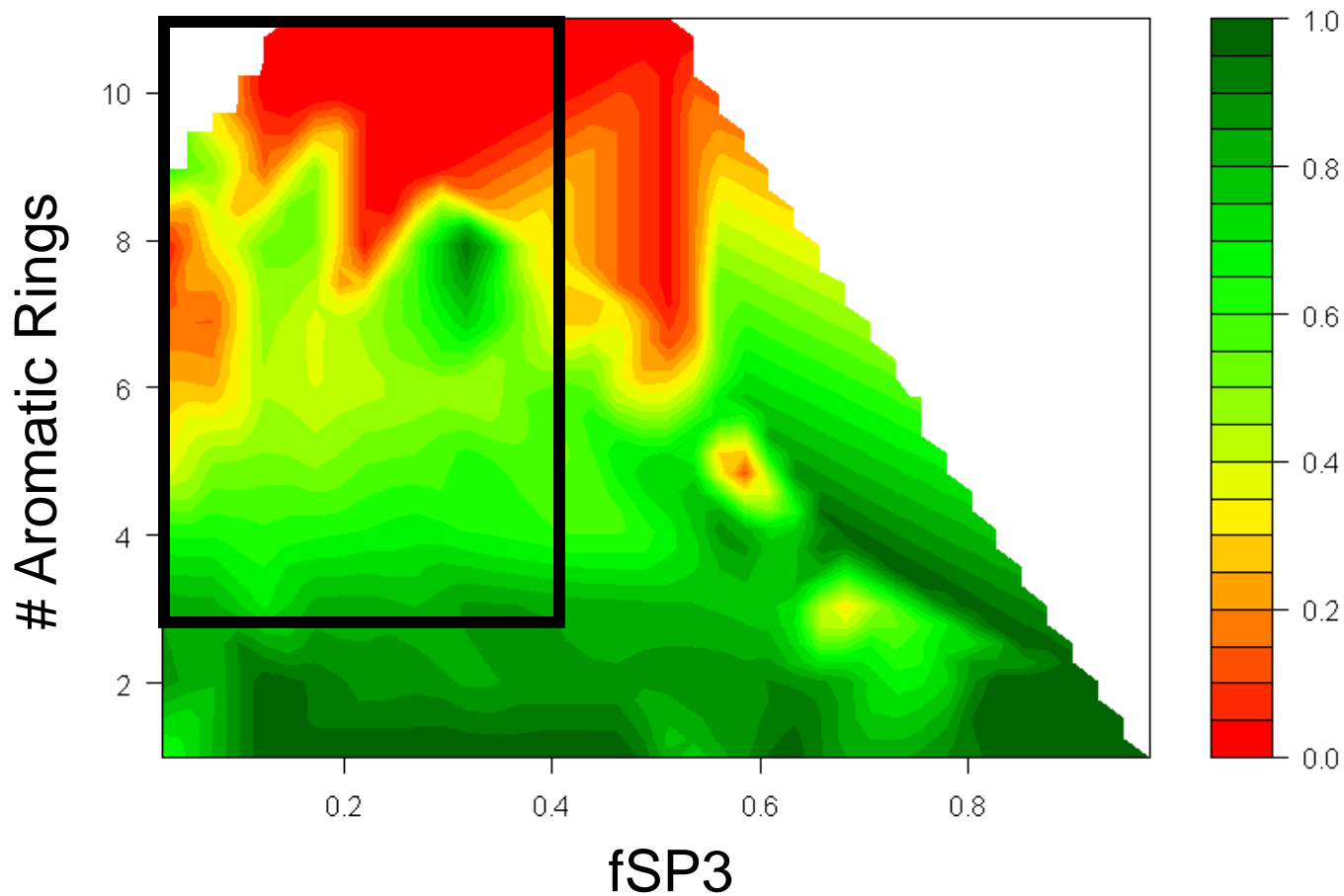
- How well does PABOH for combined HLM and PAMPA data predict bioavailability?



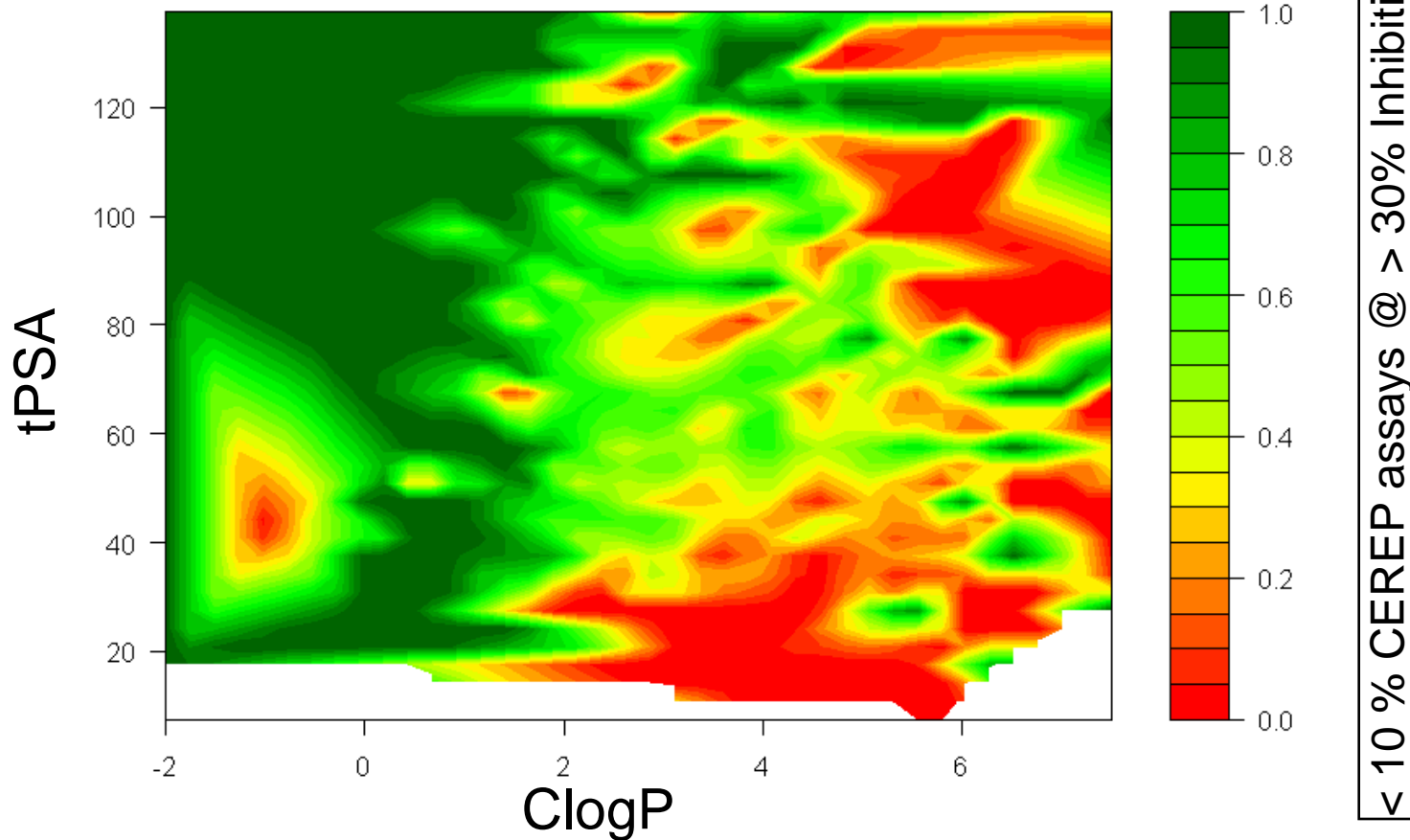
PABOH Plots for Solubility



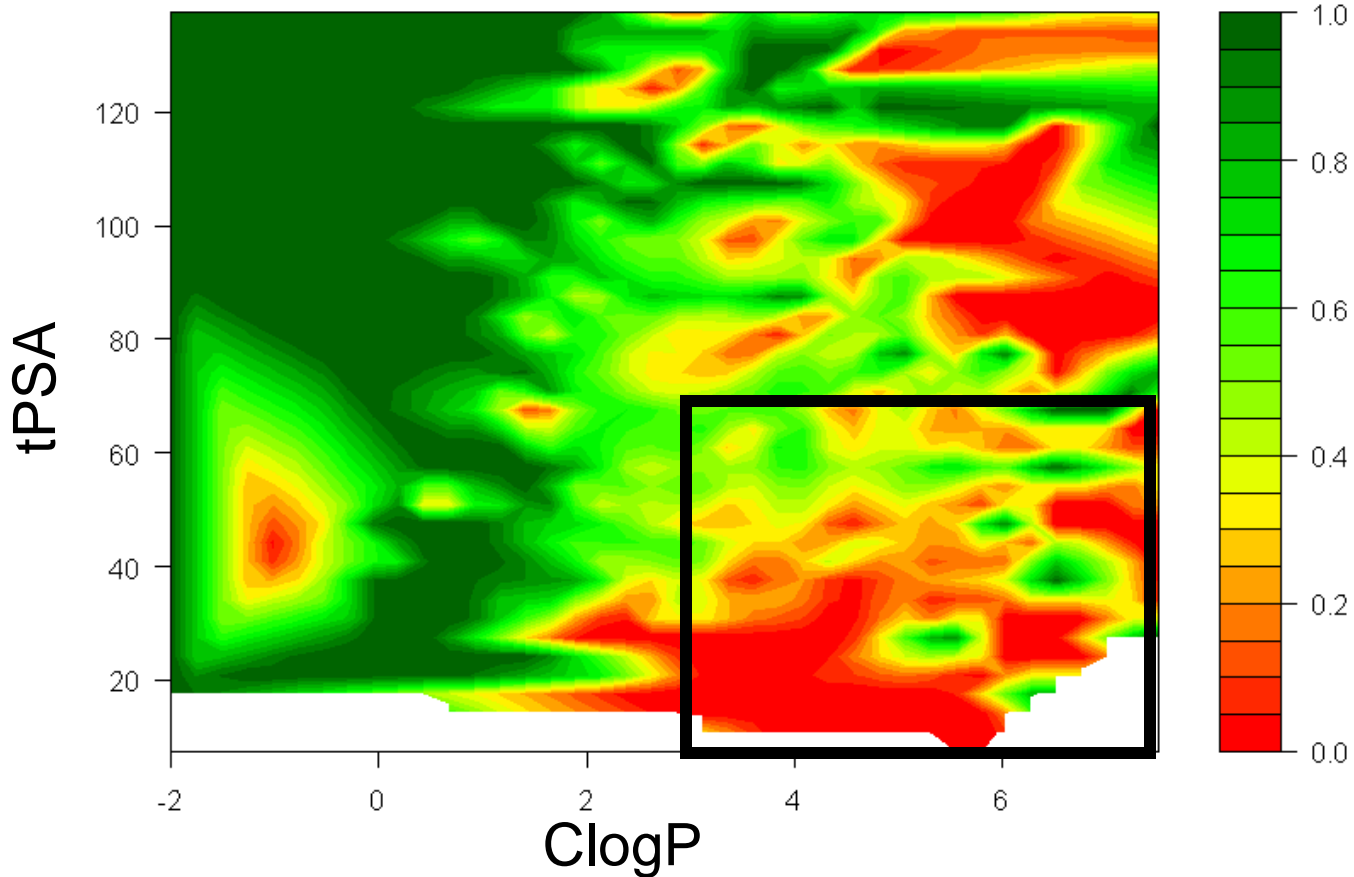
PABOH Plots vs. nAR < 3, fSP3 > 0.4



PABOH Toxicity/Promiscuity



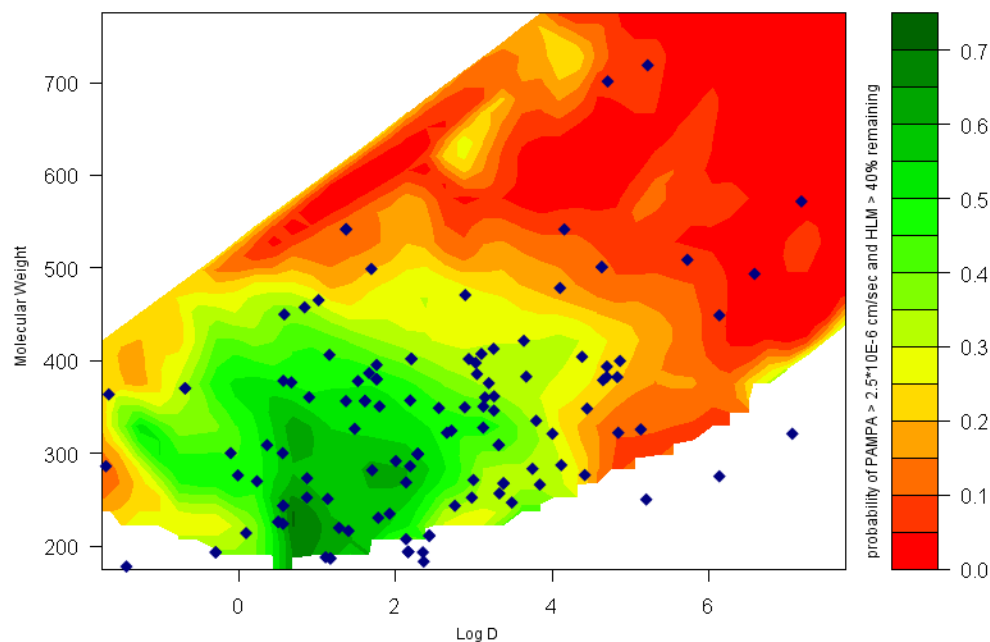
PABOH vs. 3/75 rule



< 10 % CEREP assays @ > 30% Inhibition

Orally Administered Drugs

- 117 orally available, marketed drugs
- Guess which two are Abbott Drugs?



Conclusions

- Simple rules of thumb are of limited use in careful data analysis
 - Discontinuities in cutoffs
 - Inaccurate representation of data
- Large amounts of data are available in corporate collections to allow more detailed analyses
- Continuous functions that describe trends in data can be useful
- Probability space allows for combination of data from disparate sources

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