Hormesis:
A Polynomial Fit Analysis

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Theme

"The broad generality of hormesis implies it is a characteristic of organisms rather than of the agents—such as toxic compounds or abused drugs—that perturb them."

Two Polynomial Analyses

Dose Hormesis:

NCI Yeast Cancer screen dataset

(polynomial curve fitting)

Temporal Hormesis:

i.v. Cocaine – substance abusers

i.v. Nicotine – smokers & nonsmokers

(ANOVA w/ polynomial contrasts)

NCI Yeast Dataset

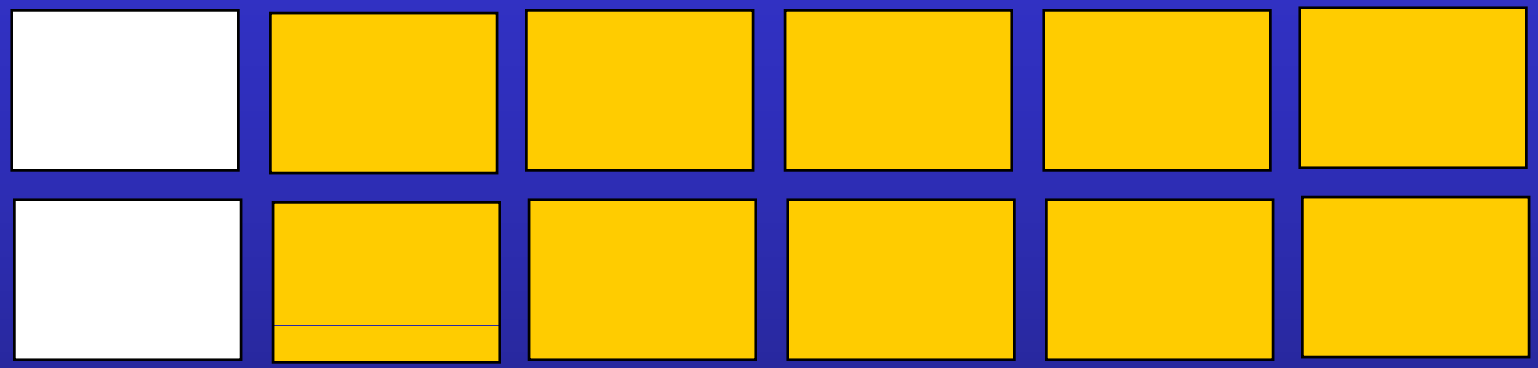
Calabrese, Staudenmayer, Stanek, and Hoffmann,
***Toxicological Sciences*, 94(2), 2006**

Growth inhibition (optical densities)

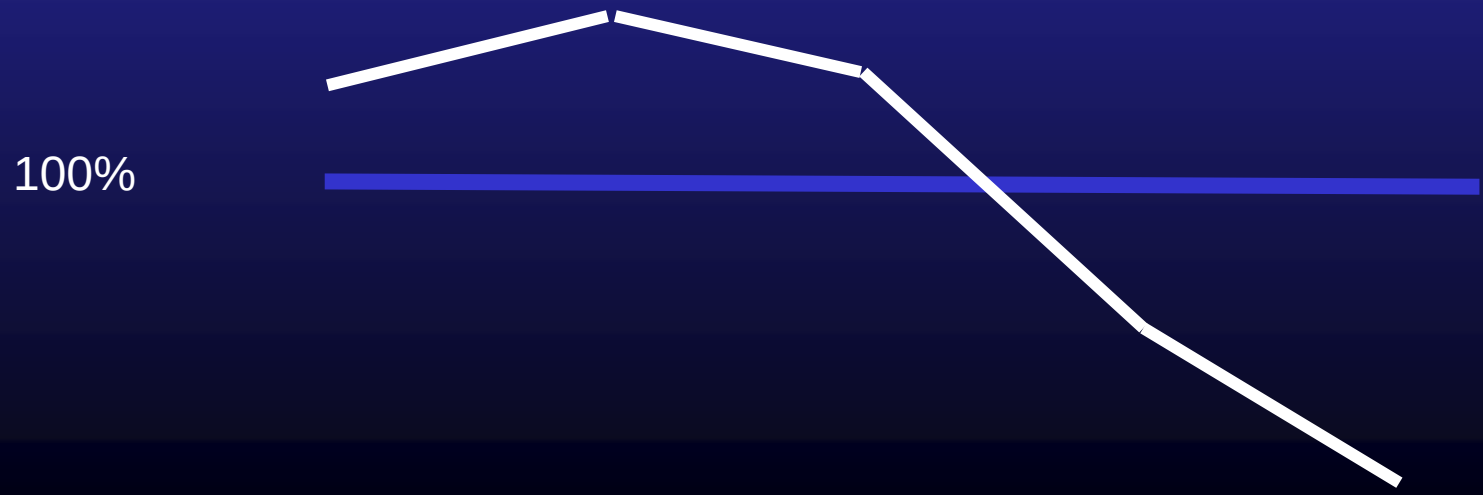
2189 putative toxic compounds
5 doses (plus control)
13 yeast strains

yields 28,457 dose-response curves

NCI Yeast Screening Design



Log-linear Dose of Toxic Compounds



Research Questions:

- **Is polynomial analysis useful for describing hormetic dose-response functions?**
- **Are there specific parameters that identify hormesis characteristics?**
- **Do the data support the hormesis model in this NCI dataset?**

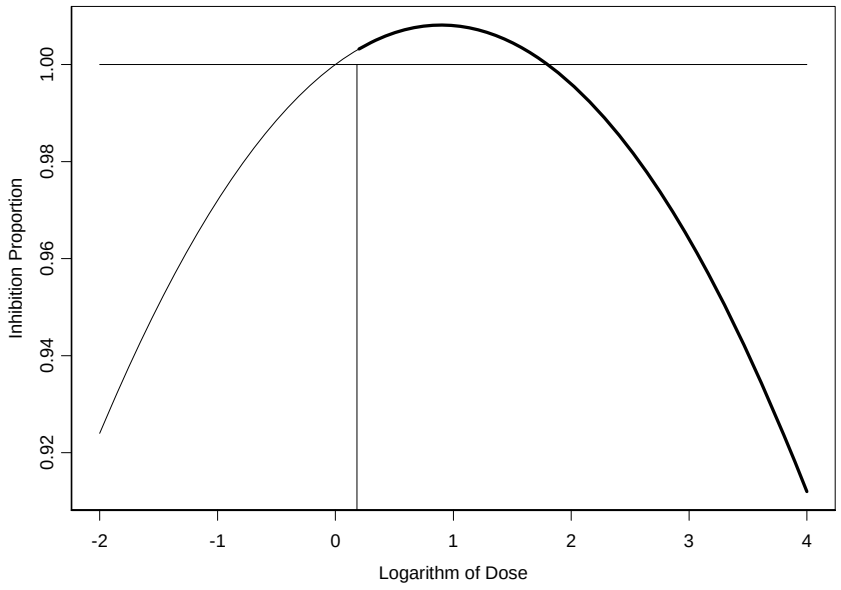
Quadratic Theoretical Functions

- Response=$A+BX+CX^2$

  $(A\text{-Response})+BX+CX^2 = 0$
- Determinant = $B^2-4(A\text{-Response})C$
- Number of solutions depends on whether Determinant >,=, or < than 0
- U-shape or inverse U depends on the sign of C

Determinant positive

Coefficient C negative

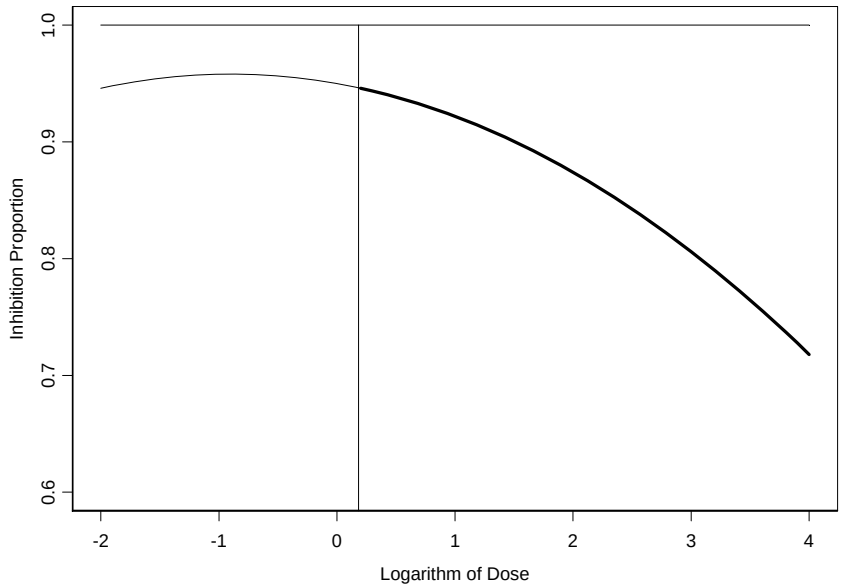


Determinant negative

Coefficient C negative

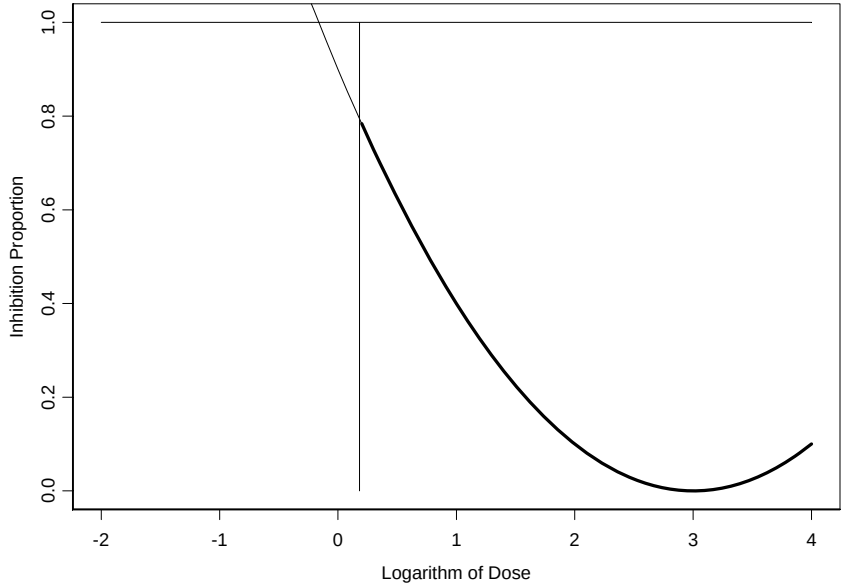
Determinant negative

Coefficient C negative



Determinant positive

Coefficient C positive



Summary of Quadratic Shapes

		Determinant	
		> 0	< 0
Coefficient C	C > 0	possible hormesis	rare case
	C < 0	**hormesis**	inverted “U”

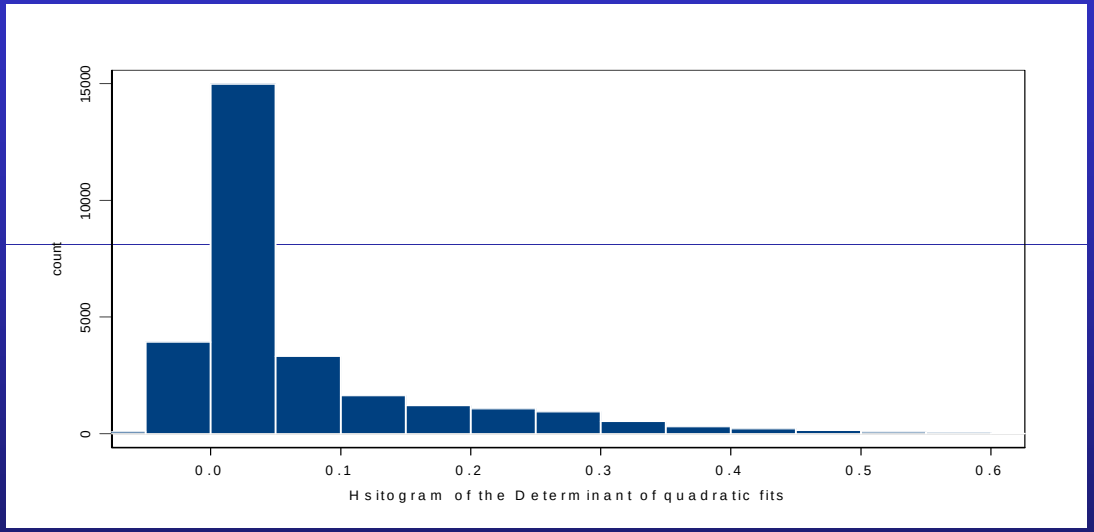
Individual or Averaged Curves?

- 28457 individual response curves (already averaged over 2 measurements
- 2189 compounds, 13 strains
- Most of the variation is between the compounds, not between the strains
- Distributions of fitted parameters averaged over strains are similar to the distributions of the parameters of the individual curves.

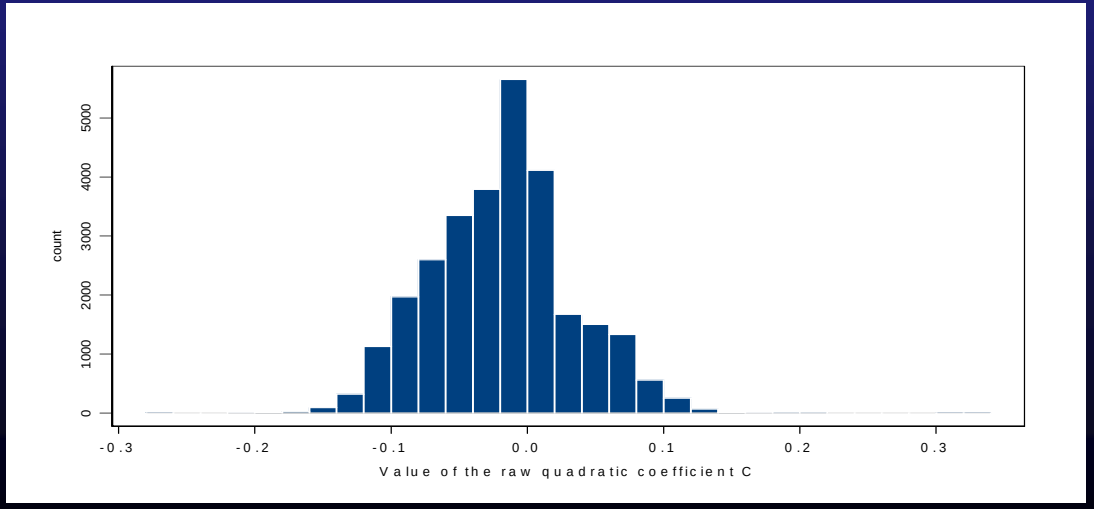
Individual or Average Curves?

Histograms of the Determinants and Quadratic Coefficients

Raw Responses

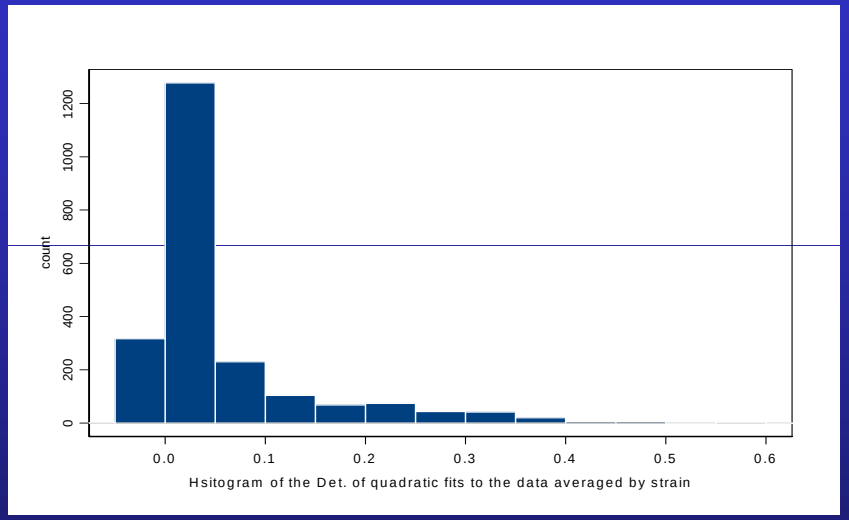


Determinant

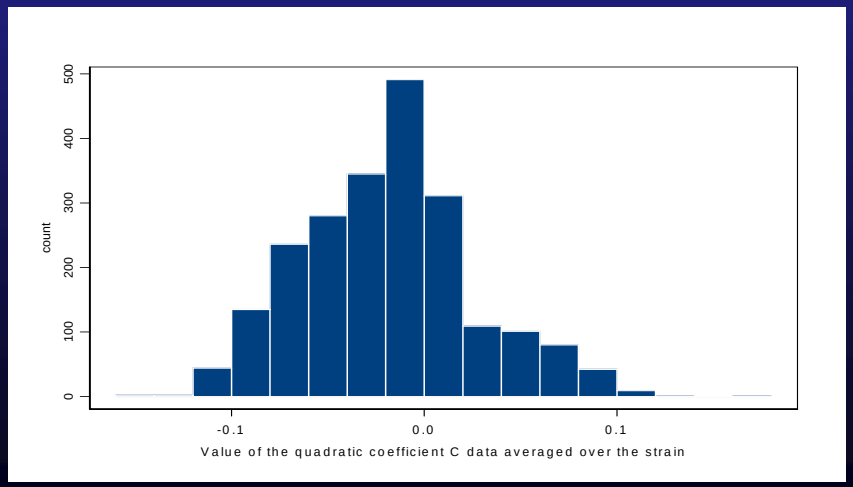


Quadratic Coefficient C

Averaged across Strains



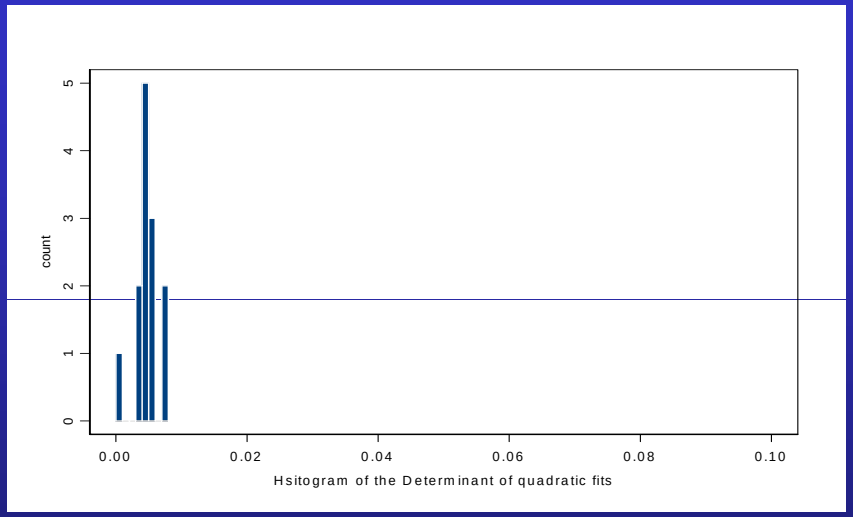
Determinant



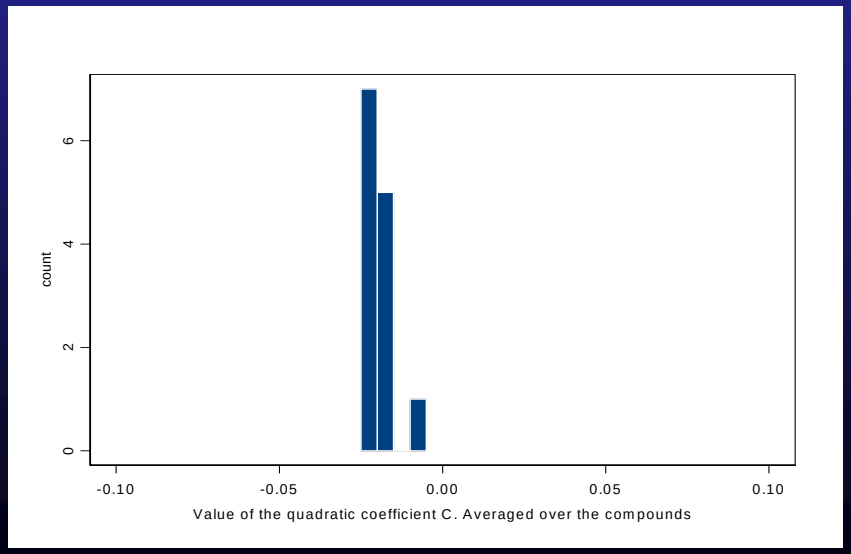
Quadratic

Coefficient C

Averaged across Compounds

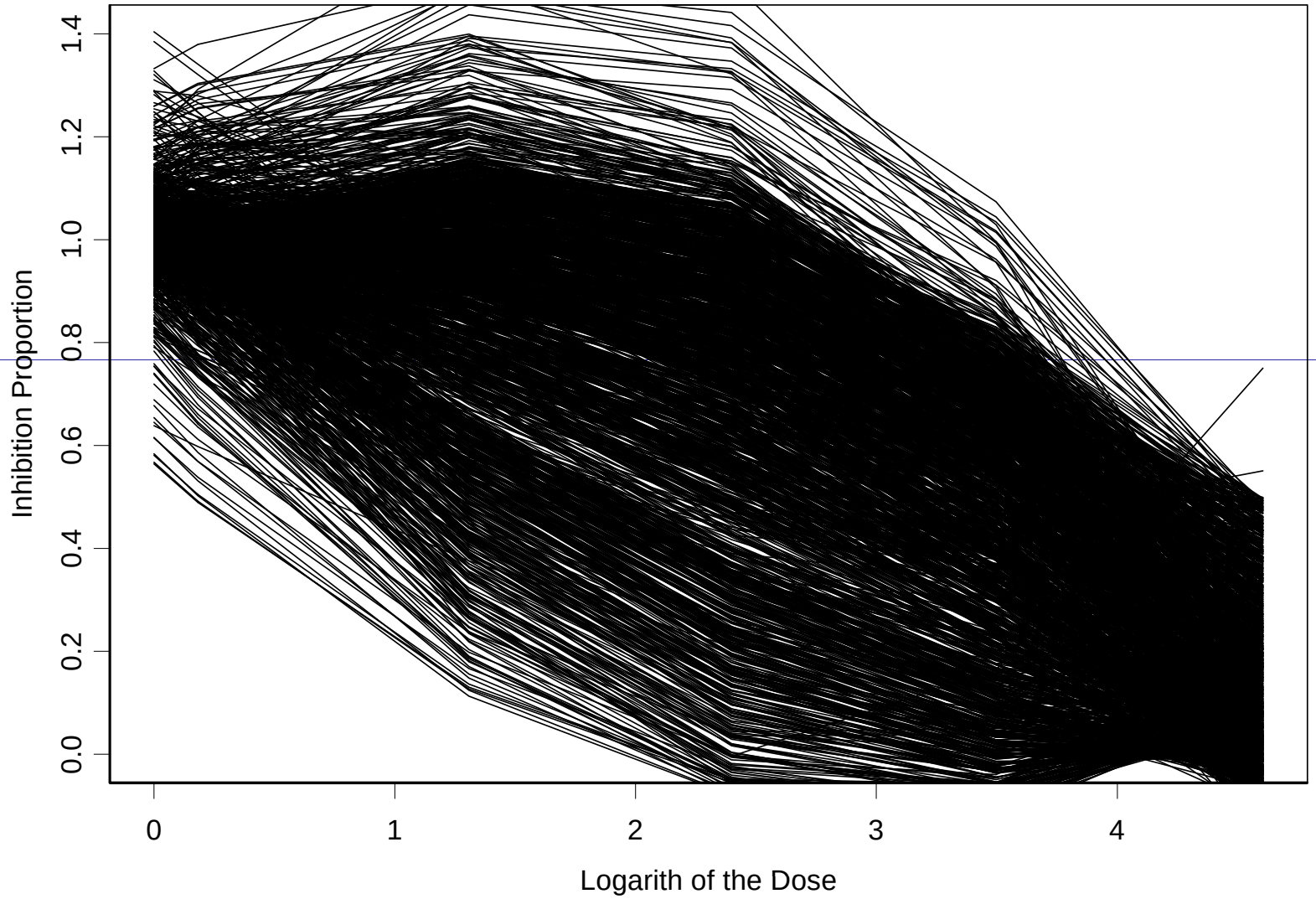


Determinant



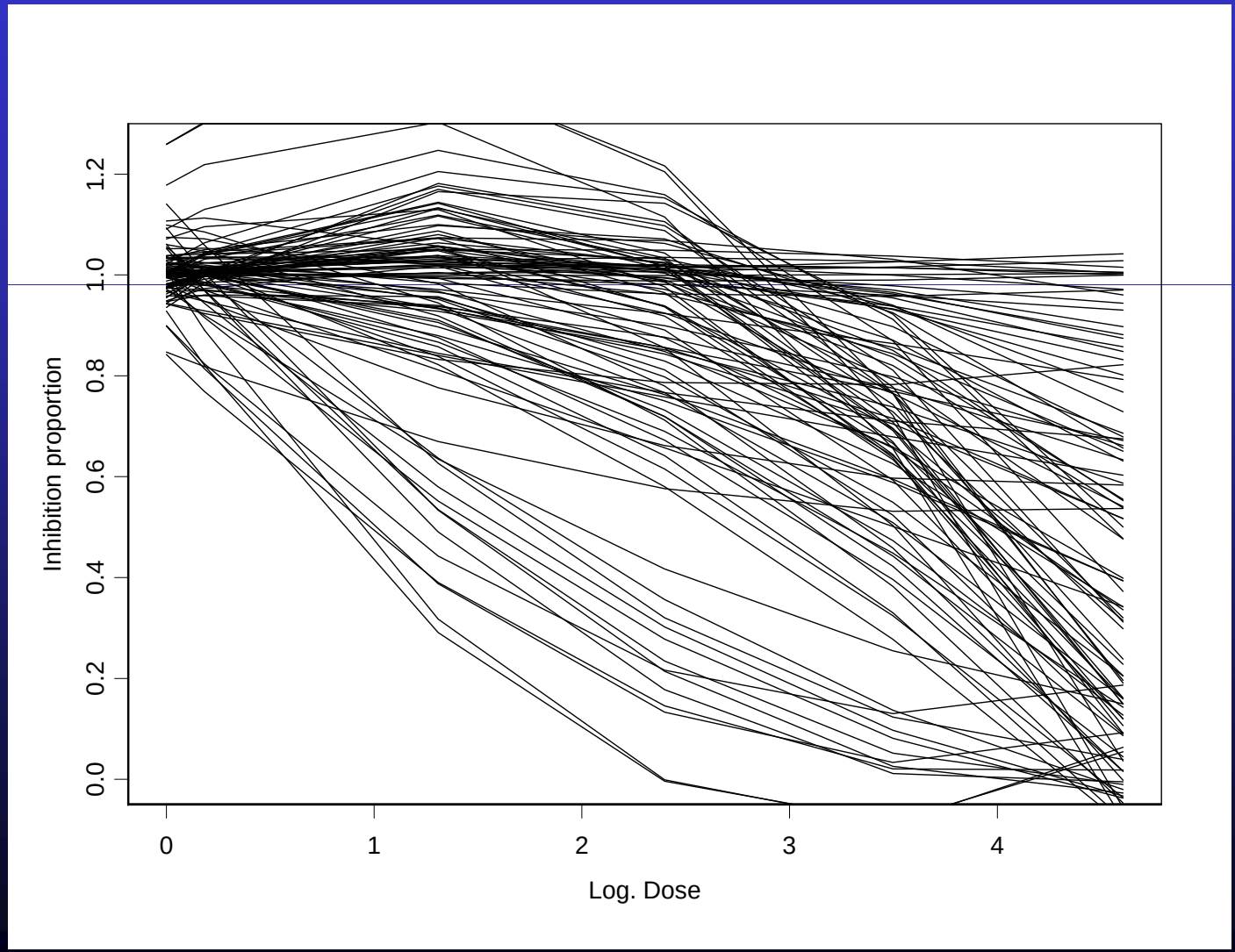
Quadratic

Coefficient C

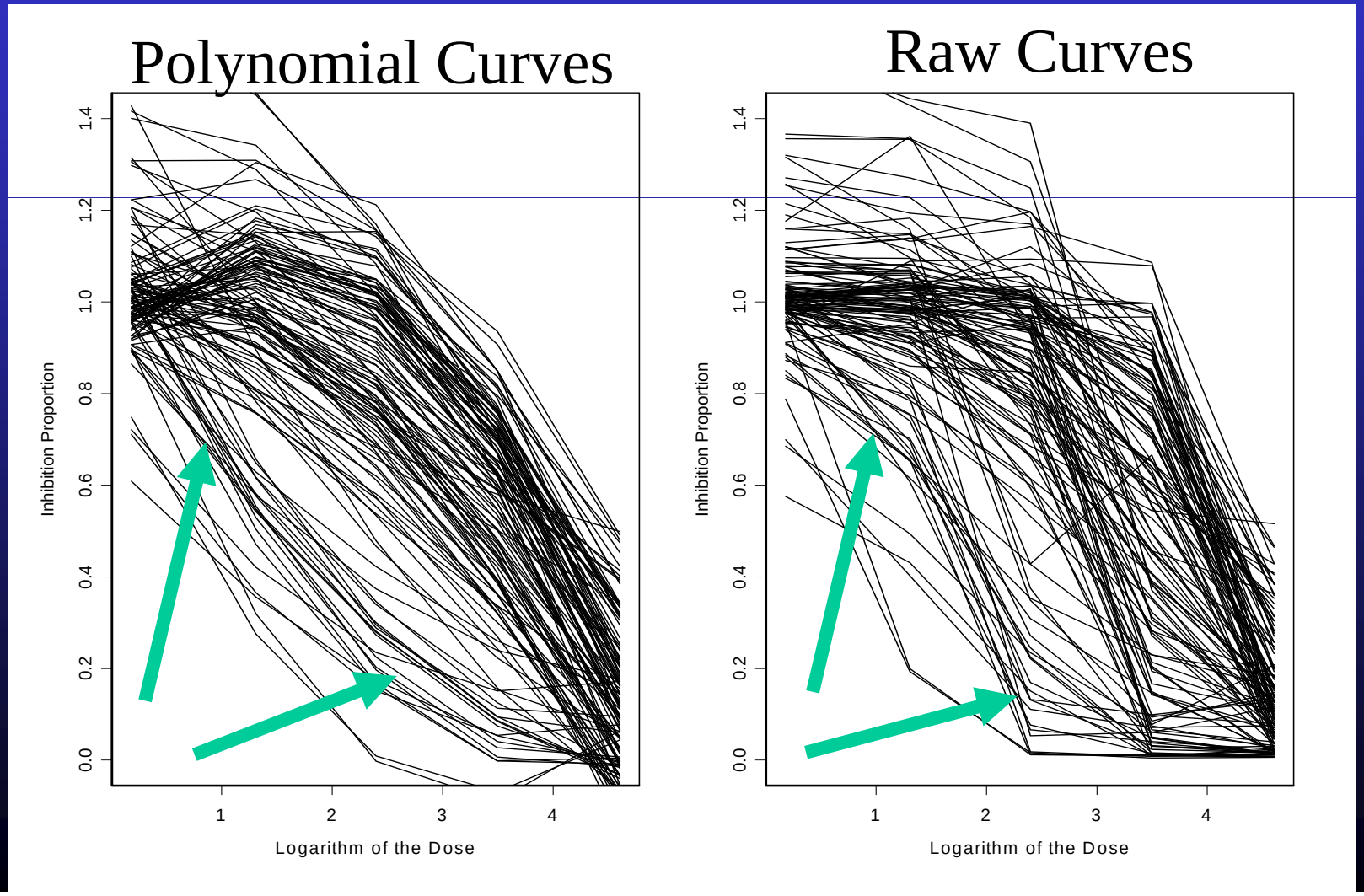


All 2189 compounds (averaged across yeast strains)

Quadratic Fits for 1st 100 Compounds (averaged across yeast strains)



Example of Fitted and Raw Curves. Effect of Saturation



Compounds
(averaged across yeast strains)

Two basic inhibition response shapes:

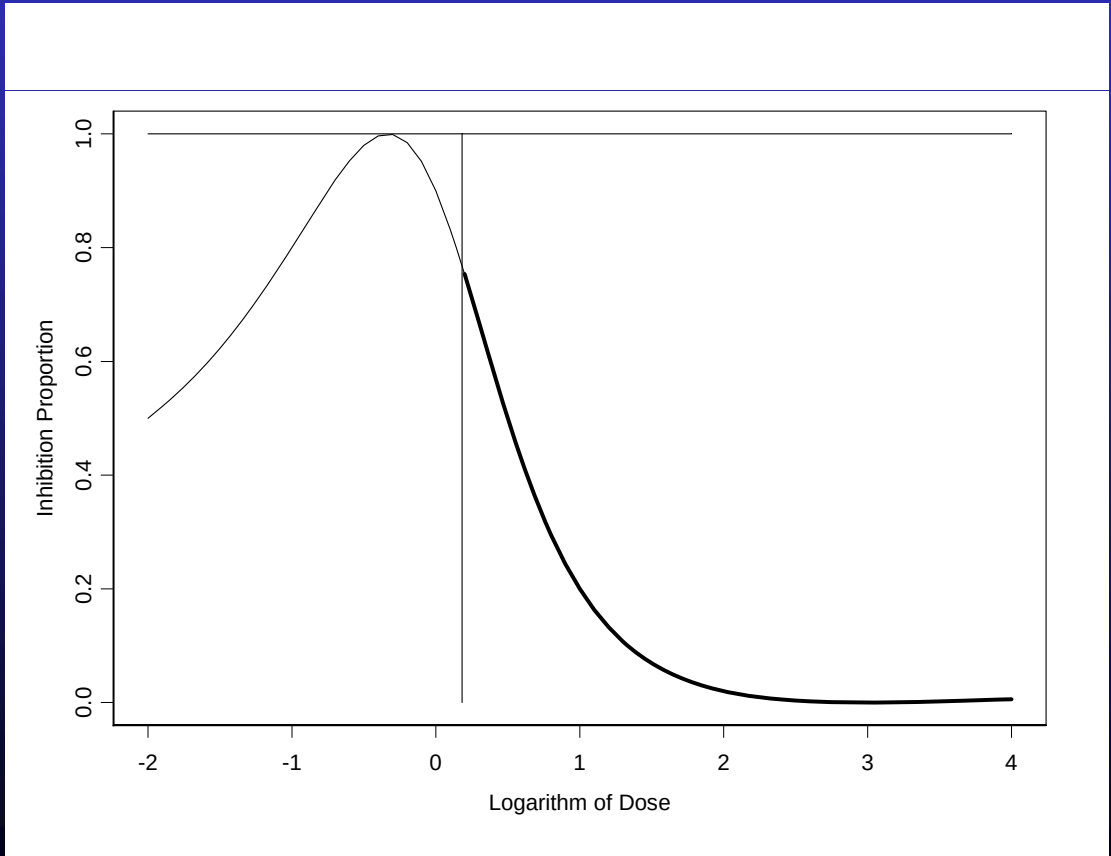
1. **U-shaped**
2. **Inverted U-shaped (usually hormetic)**

(or no response – flat)

Saturation effects can lead to wrongful fit (Inverted U vs. U)

Alternative Model
Modified Sigmoid

Response = $(A+BX+CX^2)/(1+FX^2)$



Temporal Hormesis

i.v. Cocaine

- PET study of cocaine
- N=10 cocaine users

- placebo, 20 mg, 40 mg
- 30 min recording

i.v. Nicotine

- PET study of nicotine
- N=9 smokers & nonsmokers
- placebo, .75 mg, 1.5 mg
- 26 min recording

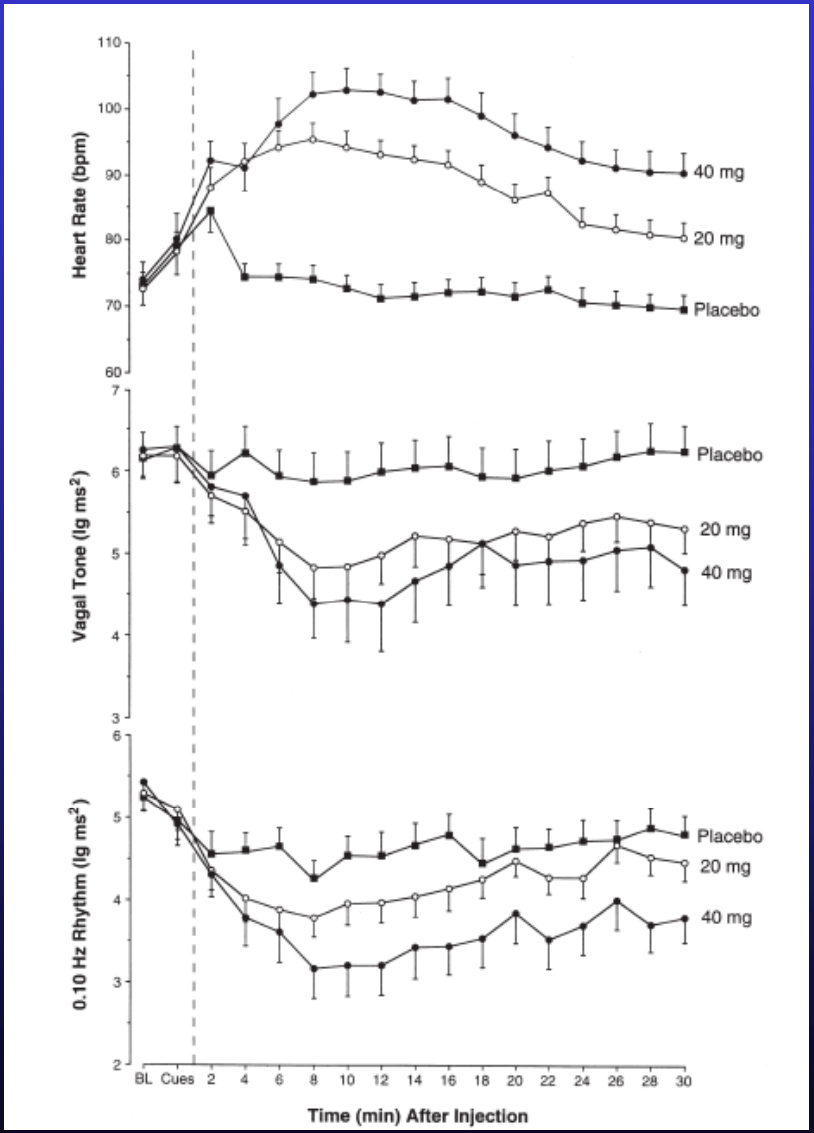
Statistical Analyses

Repeated-measures Analysis of Variance (ANOVA)

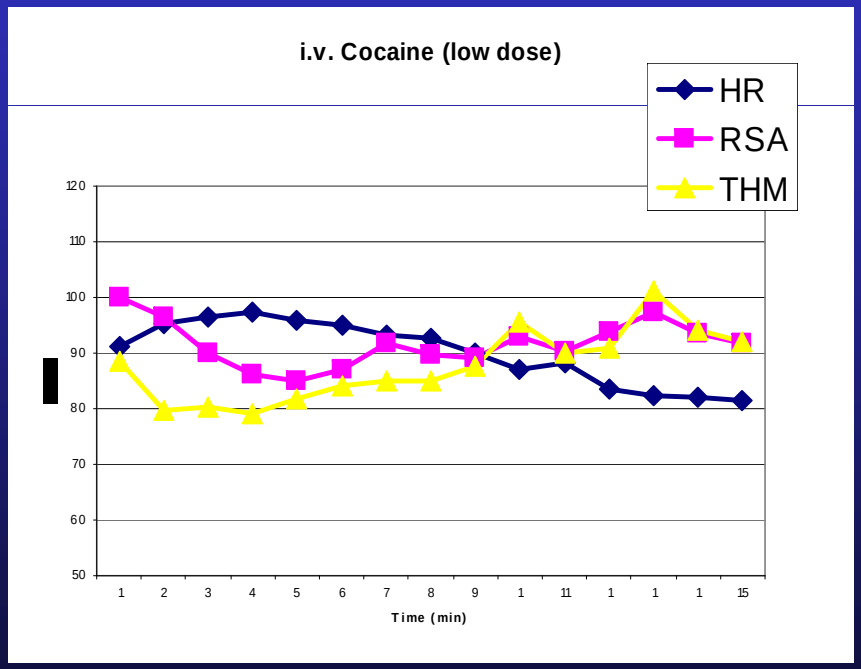
Within-subject factors:

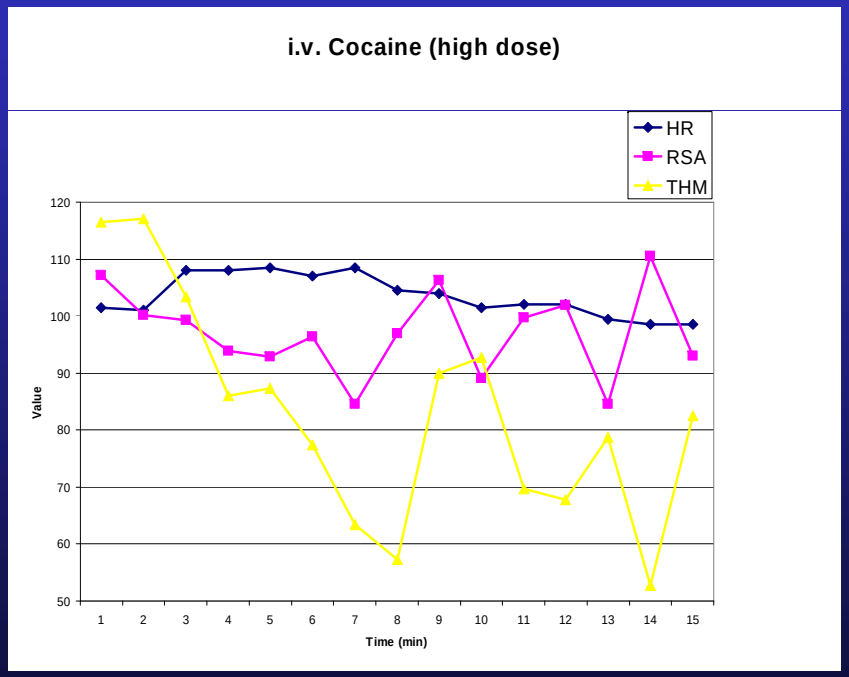
- **Dose** (placebo, low, high)
- **Cardiovascular Measure** (HR, RSA, THM)
- **Time** (polynomial trends)

i.v. Cocaine


Heart Rate (bpm)
110
100
90
80
70
60
40 mg
20 mg
Placebo
Vagal Tone (lg ms²)
7
6
5
4
3
Placebo
20 mg
40 mg
0.10 Hz Rhythm (lg ms²)
6
5
4
3
2
Placebo
20 mg
40 mg
BL Cues 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time (min) After Injection

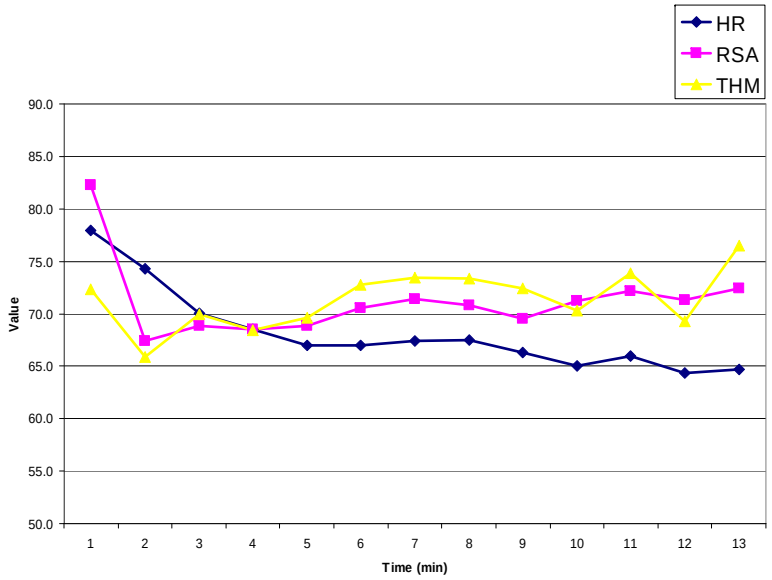
i.v. Cocaine


i.v. Cocaine (low dose)
HR
RSA
THM
120
110
100
90
80
70
60
50
1
2
3
4
5
6
7
8
9
1
11
1
1
1
15
Time (min)

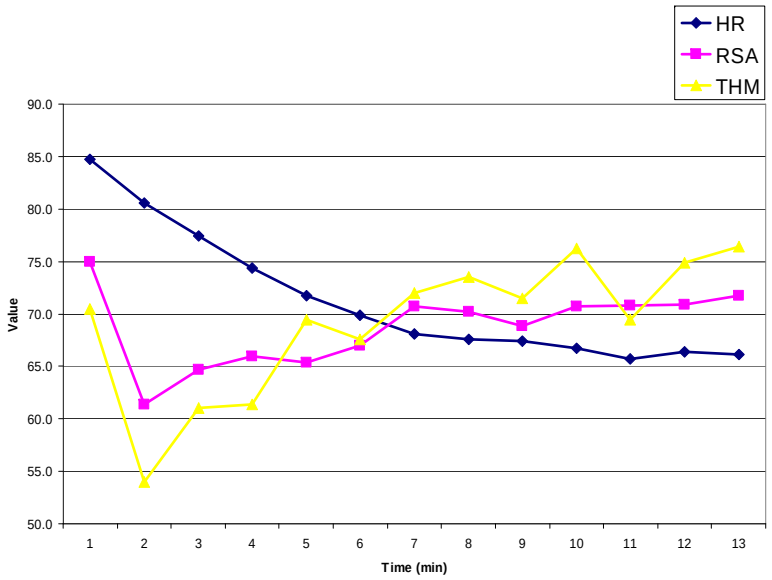

i.v. Cocaine (high dose)
HR
RSA
THM
Value
120
110
100
90
80
70
60
50
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Time (min)

i.v. Nicotine

i.v. Nicotine (low dose)



i.v. Nicotine (high dose)



Dose * Measure * Time
polynomial cubic interaction

	Cocaine		Nicotine	
	F(1,9)	**p**	**F(1,8)**	**p**
Lo - RSA	13.2	.005	6.1	.038
Lo - THM	14.2	.004	.04	ns
Hi - RSA	28.4	.0001	9.3	.016
Hi - THM	13.1	.006	2.2	ns

Summary

- it would be difficult to improve upon Calabrese et al. (2006)
- polynomial analysis appears appropriate for testing hormesis
  - both “dose” and “temporal” hormesis
- we hope that nonlinear sigmoid modeling will improve this further
  - particularly for dealing with saturation effects at very low and very high doses

Plausible Hypothetical Assumptions

- Hormetic (biphasic) drug response has both a psychostimulant and a psychosedative component.
- The psychostimulant component is recruited rapidly and is roughly linear with dose.
- The psychosedative component is recruited slowly and is exponentially related to dose.
- These two components are nonadditive.
- Do these assumptions “generate” dose-hormesis and temporal-hormesis?