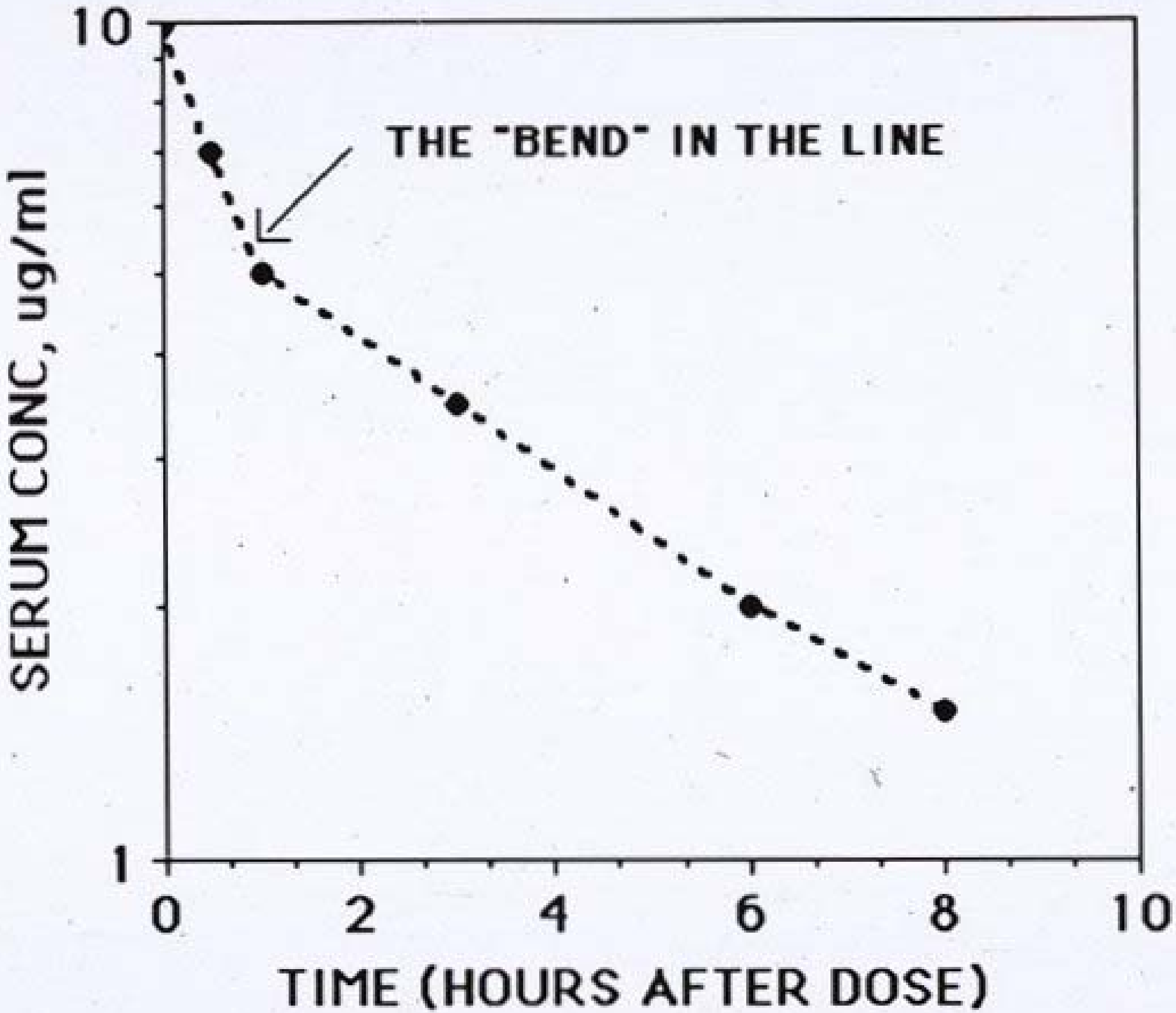
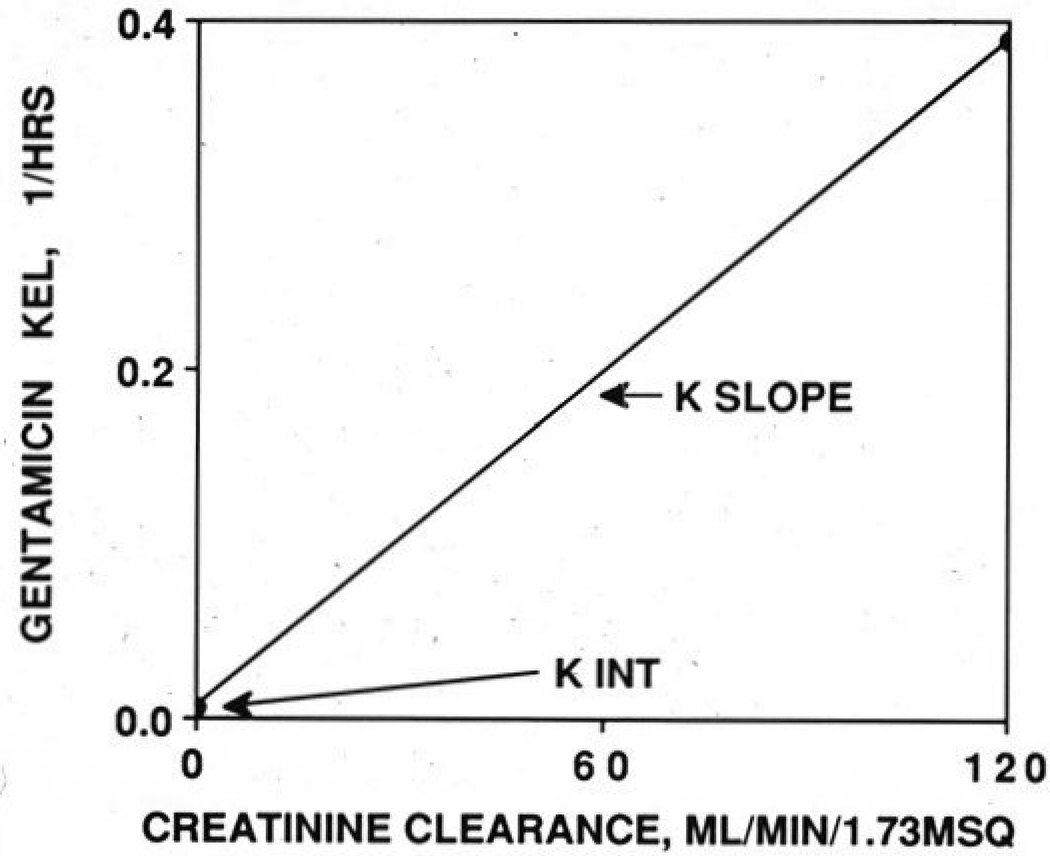
Bayes’ theorem

- Describes quantitatively relationships between
- Prior probabilities
- New information
- Revised (posterior) probabilities


THE "BEND" IN THE LINE
SERUM CONC, ug/ml
10
1
0
2
4
6
8
10
TIME (HOURS AFTER DOSE)


0.4
0.2
0.0
GENTAMICIN KEL, 1/HRS
K SLOPE
K INT
0
60
120
CREATININE CLEARANCE, ML/MIN/1.73MSQ

Linear Regression on Logs of Levels

- Only fits data in a single dose interval.
- Cannot add new data. Must discard old data. Wasteful.
- Must be in steady state.
- Data must be post-distributional.
- Limited to a 1-compartment model.
- No population data considered to balance/augment patient data.
- Wrong error pattern assumed, of constant assay CV%

Nonlinear Least Squares Regression (1)

- Fits over all doses in history.
- No waiting for steady state any more.
- Can add new data as it becomes available.
- Not limited to 1-compartment models.
- Can handle correct weighting scheme, 1/var.
- Data can be at any time - not just post-distributional.

Nonlinear Least Squares Regression (2)

- BUT -
- No population data to augment patient data.
- Need at least 1 data point for each parameter fitted.

MAP Bayesian Regression (1)

- The best of the three methods.
- Fits over the entire dosage history.
- No waiting for steady state.
- Can add new data as it becomes available.
- Not limited to 1-compartment models.
- Can handle correct weighting scheme 1/var.
- Data can be at any time - not just post-distributional.

MAP Bayesian Regression (2)

- and <u>also</u>,
- Supplements with population data.
- Does not need 1 point per parameter fitted.
- Can fit with only 1 data point if needed.
- Tends to be best predictor. Most flight control systems are Bayesian controllers.

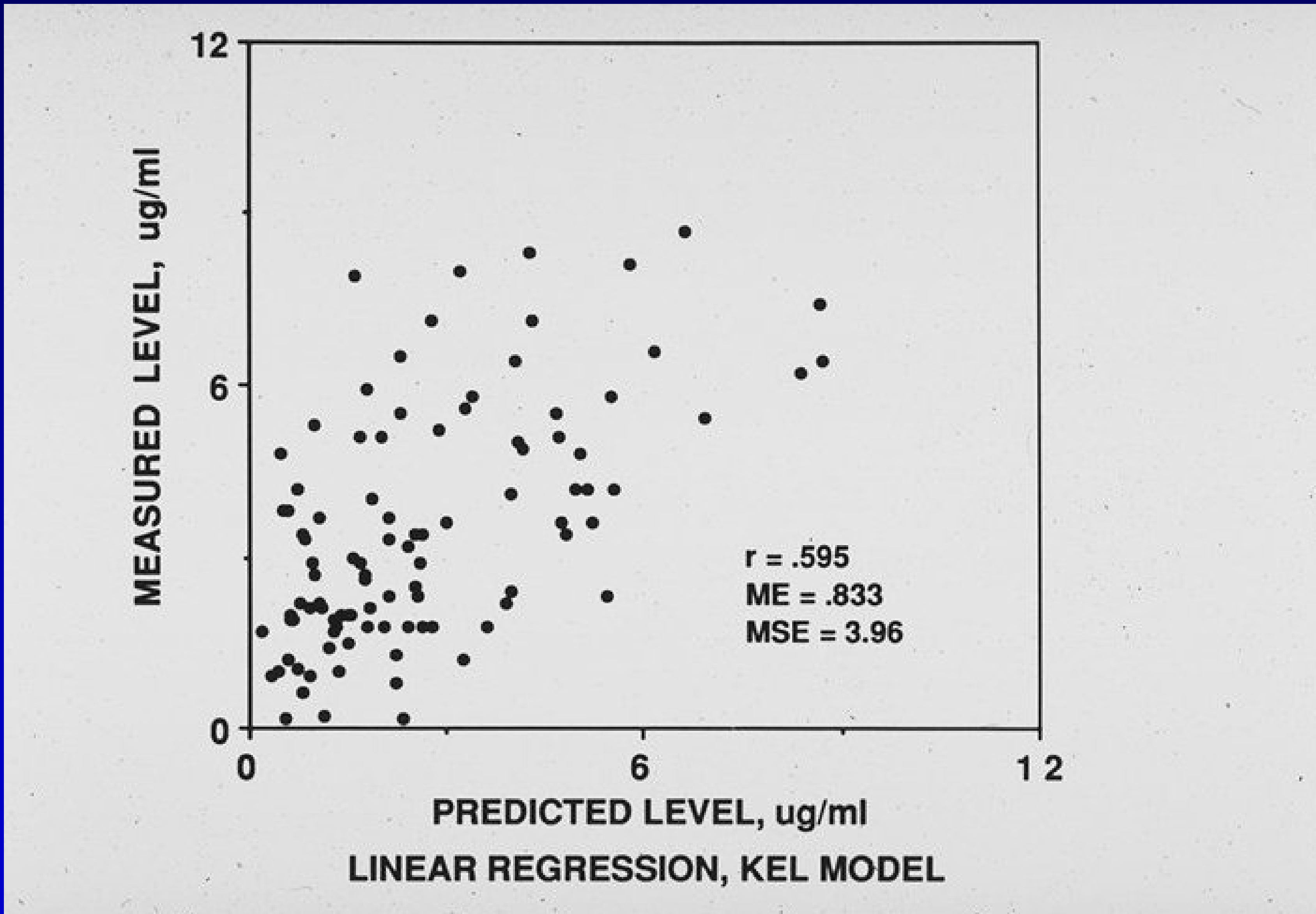
Rev. T. Bayes
(1702–1761)

QUANT BAYES' THEOREM:

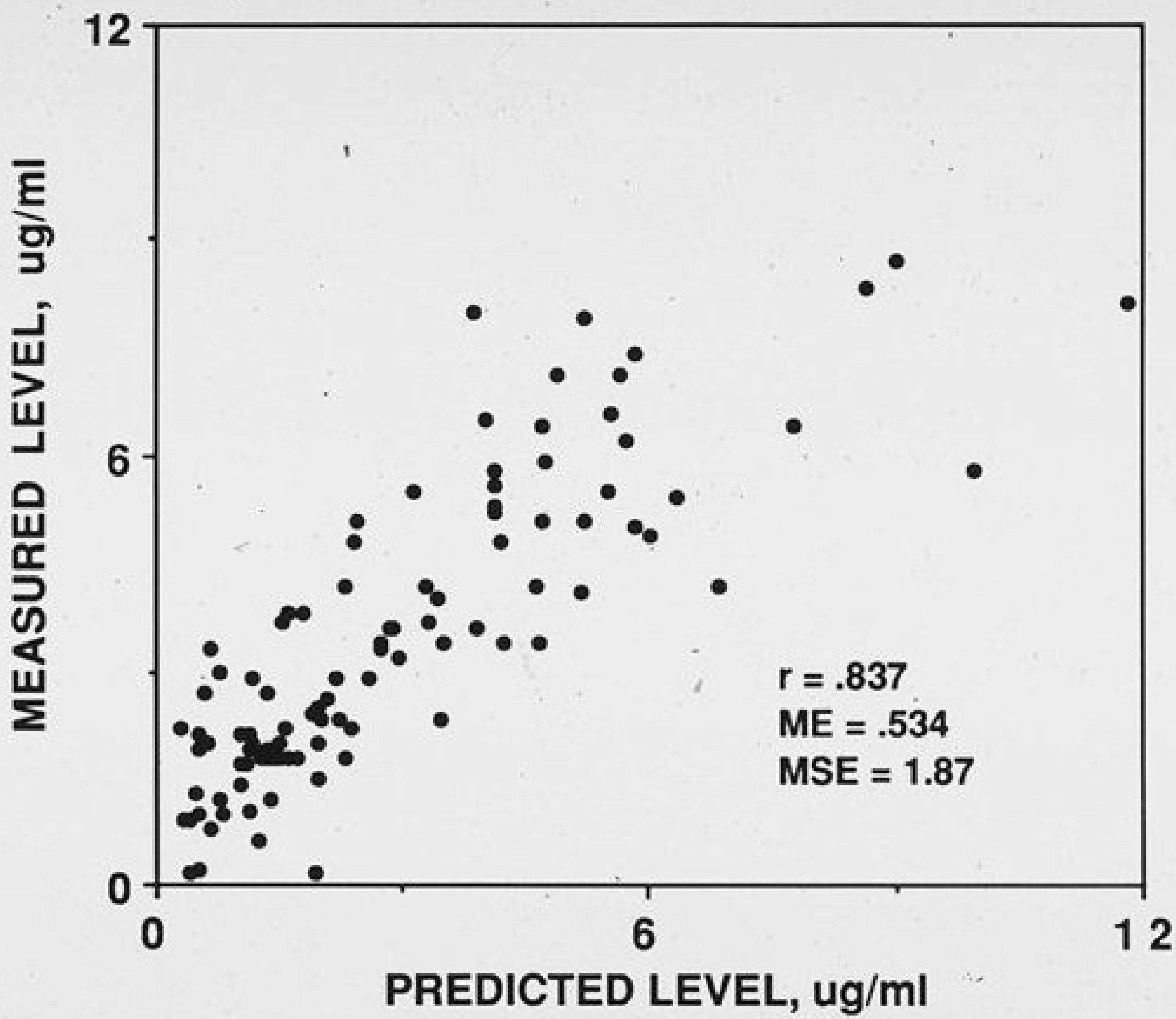
1. DETERMINE ASSAY ERROR EXPLICITLY.
2. USE IN CURRENT BAYESIAN OBJ FUNCTION

$$\text{MINIMIZE SUM } \frac{(\text{Cobs} - \text{Cmod})^2}{\text{SD}^2\ \text{Cobs}} + \text{SUM } \frac{(\text{Ppop} - \text{Pmod})^2}{\text{SD}^2\ \text{Ppop}}$$

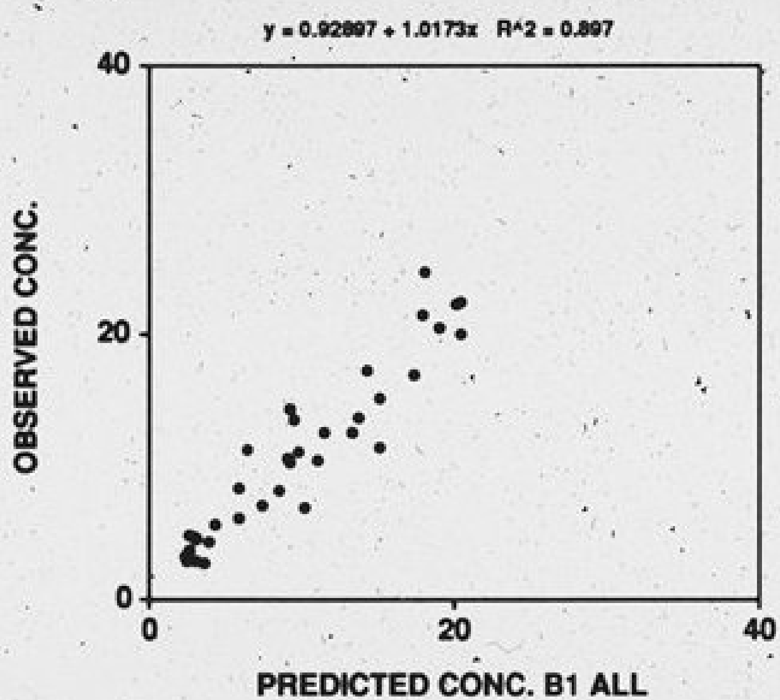
PRIOR PROB	NEW INFO	CONSIDER PRIOR+NEW	POST PROB	THERAPY GOALS	THERAPY CONTROL
POP MODEL	SERUM CONC'S	OBJ FUNCT	INDIV MODEL	LOOK AT PT, THINK	CALC DOSES



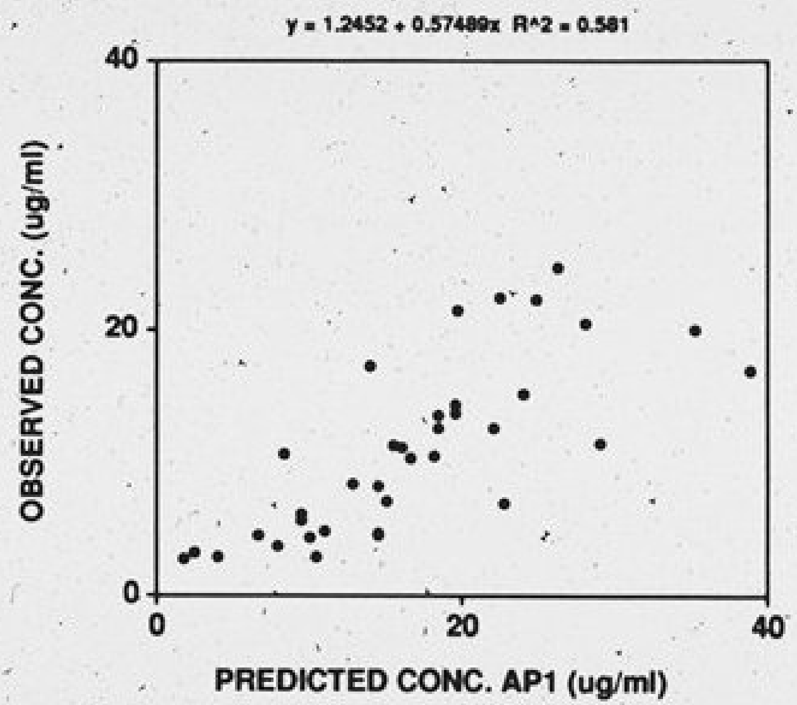
MEASURED LEVEL, ug/ml
12
6
0
0
6
1 2
PREDICTED LEVEL, ug/ml
r = .595
ME = .833
MSE = 3.96
LINEAR REGRESSION, KEL MODEL



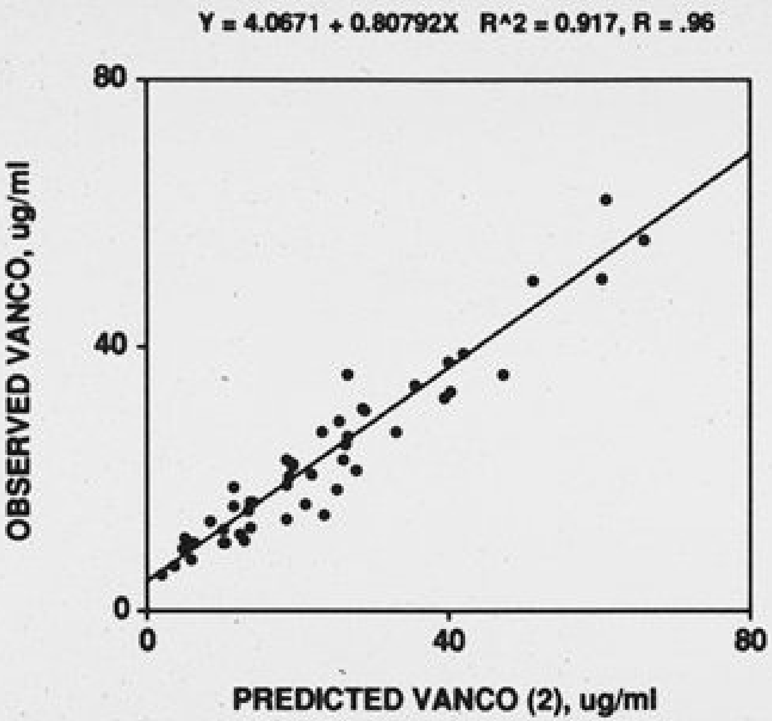
BAYESIAN FITTING, KSLOPE MODEL



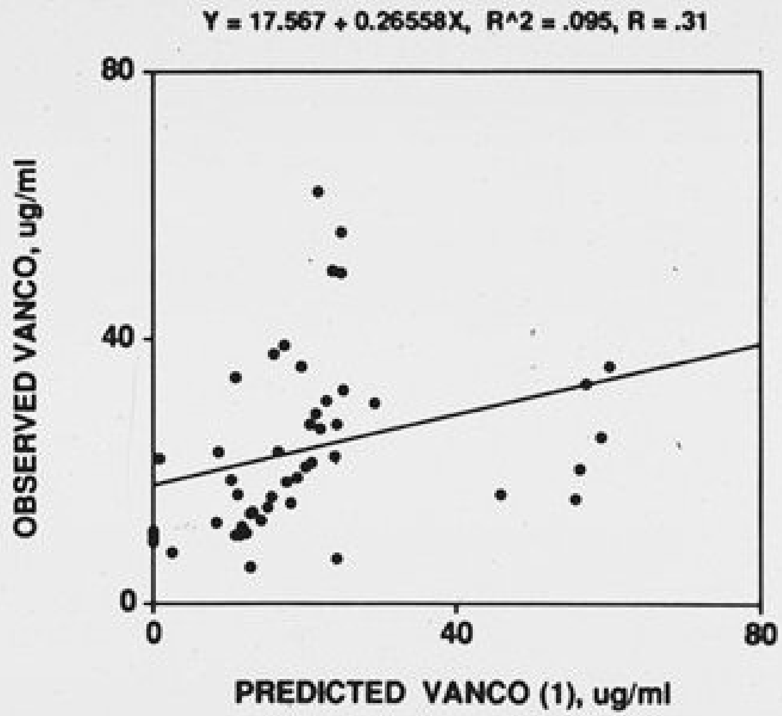
y = 0.92897 + 1.0173x R^2 = 0.897
OBSERVED CONC.
PREDICTED CONC. B1 ALL
0
20
40



y = 1.2452 + 0.57489x R^2 = 0.581
OBSERVED CONC. (ug/ml)
PREDICTED CONC. AP1 (ug/ml)
0
20
40



Y = 4.0671 + 0.80792X R^2 = 0.917, R = .96
80
40
0
0
40
80
OBSERVED VANCO, ug/ml
PREDICTED VANCO (2), ug/ml



Y = 17.567 + 0.26558X, R^2 = .095, R = .31
80
40
0
0
40
80
OBSERVED VANCO, ug/ml
PREDICTED VANCO (1), ug/ml

Limitations of Current Bayesian PK and Dosage

- Assume Gaussian, Lognormal Distributions
- The Separation Principle

The Separation Principle

- Whenever you separate the process of controlling the behavior of a system into
- First, getting the best single point parameter estimates, and then
- Second, using these values to control the system to achieve target goals,
- The control job is usually done **suboptimally**.
- No performance criterion (precision, etc.) is optimized.