Individualized, Maximally Precise Drug Therapy: A Physician's Bedside Viewpoint.

Listening to the patient,
Setting and hitting an individualized specific point target goal, at target time – NOT just being in a "therapeutic range",
in serum or a nonserum compartment, or an observable effect,
and a brief mention of some tools to do this best.

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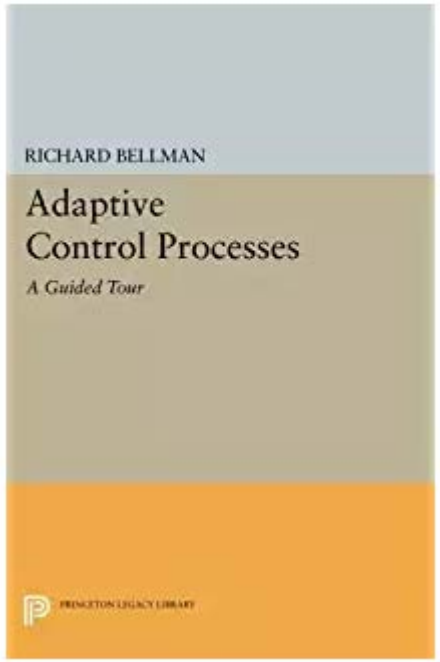
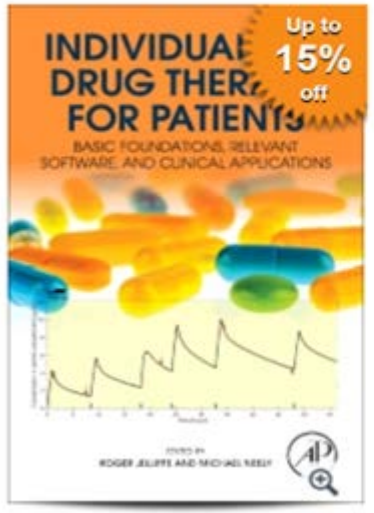
Sources for more info:

Control, not metrics.





Individualized Drug Therapy for Patients, 1st Edition

Basic Foundations, Relevant Software and Clinical Applications

Editor(s) :	Jelliffe & Neely
Expected Release Date:	17 Nov 2016
Imprint:	Academic Press
Print Book ISBN :	9780128033487
Pages:	434
Dimensions:	235 X 191

This practical guide provides clinical pharmacologists, pharmacists, and physicians with a valuable resource to help move traditional drug therapy beyond a memorized ritual to being a thoughtful quantitative process aimed at optimizing therapy for each individual patient

Dosage precision must be specifically maximized for each patient. But how?

Optimal modeling, tracking and control methods are needed.

What is the IDEAL Population PK/PD Model?

Given a data set from a patient population,

and the correct structural model, don't summarize yet!

Instead, find each individual patient's exact model parameter values.

- **The ideal popmodel is the collection of exact models of each patient studied.**
- **Multiple discrete support points, one for each patient, with any distribution!**
- **A finite, (NOT continuous!) collection, (no summary!) of each patient's**
- **exactly known parameter values.**

One can never do better than that. That is the unattainable ideal.
Nonparametric (NP) models approach this ideal pretty closely.

What do they look like?

Wikipedia: definition of "**Nonparametric Method**"

Nonparametric (NP) statistics do not **require** that the population data **meet the assumptions necessary** for parametric statistics.

NP statistics describe **unconstrained distributions** of **any** shape.

(Occam's razor fewest assumptions are best)

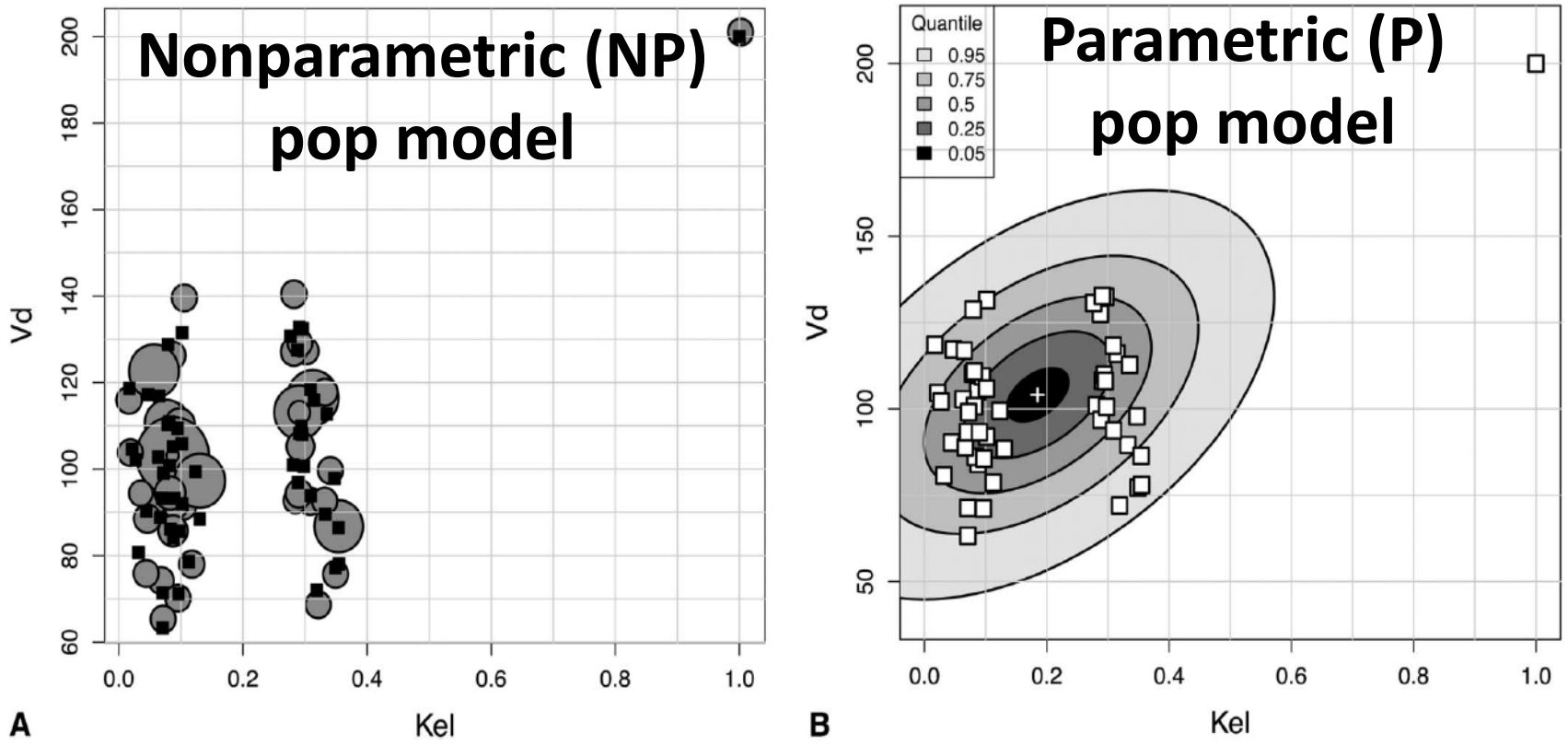


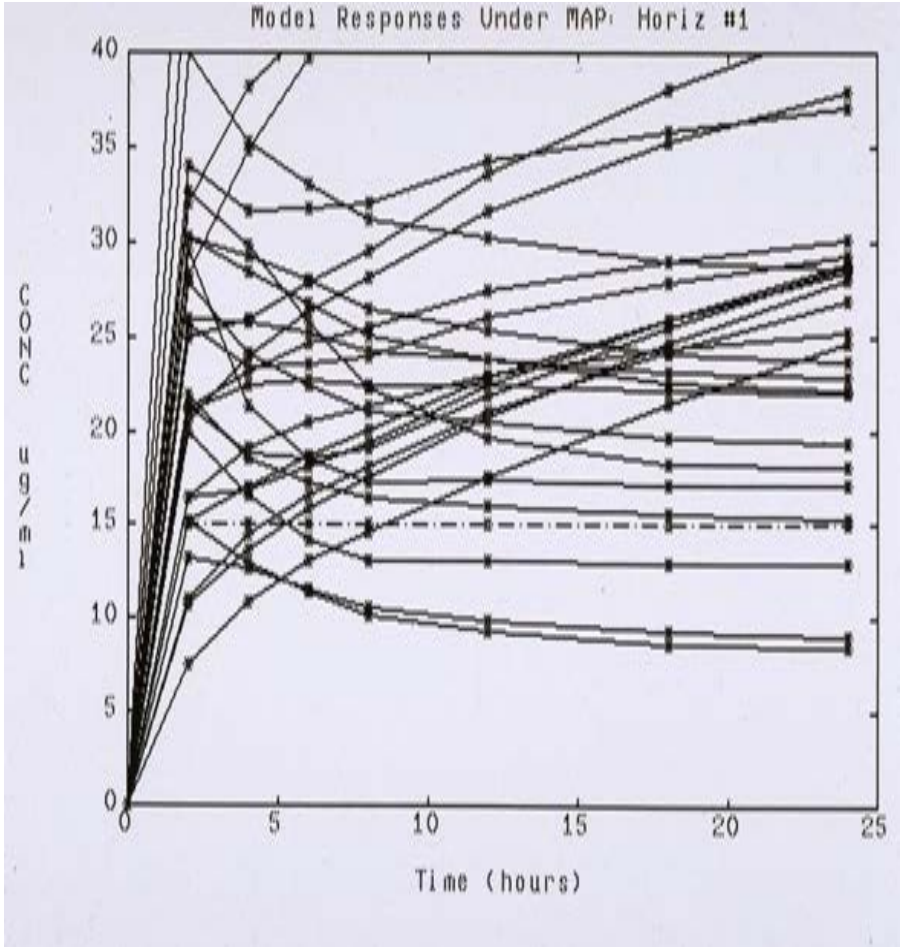
FIGURE 2. A, Results of the NPAG fit. True parameter values from the simulated population are shown as black squares, with NPAG support points shown as circles whose size is an approximate multiple of the size of 1 square, proportionally increased according to the probability of each NPAG point. B, Results of the IT2B fit. True parameter values are shown as white squares. Note the outlier in the upper right corner. The bivariate normal parameter distribution estimated by IT2B is depicted as ellipses of fading color corresponding to the percentile of the distribution. The white cross at the center is the mean.

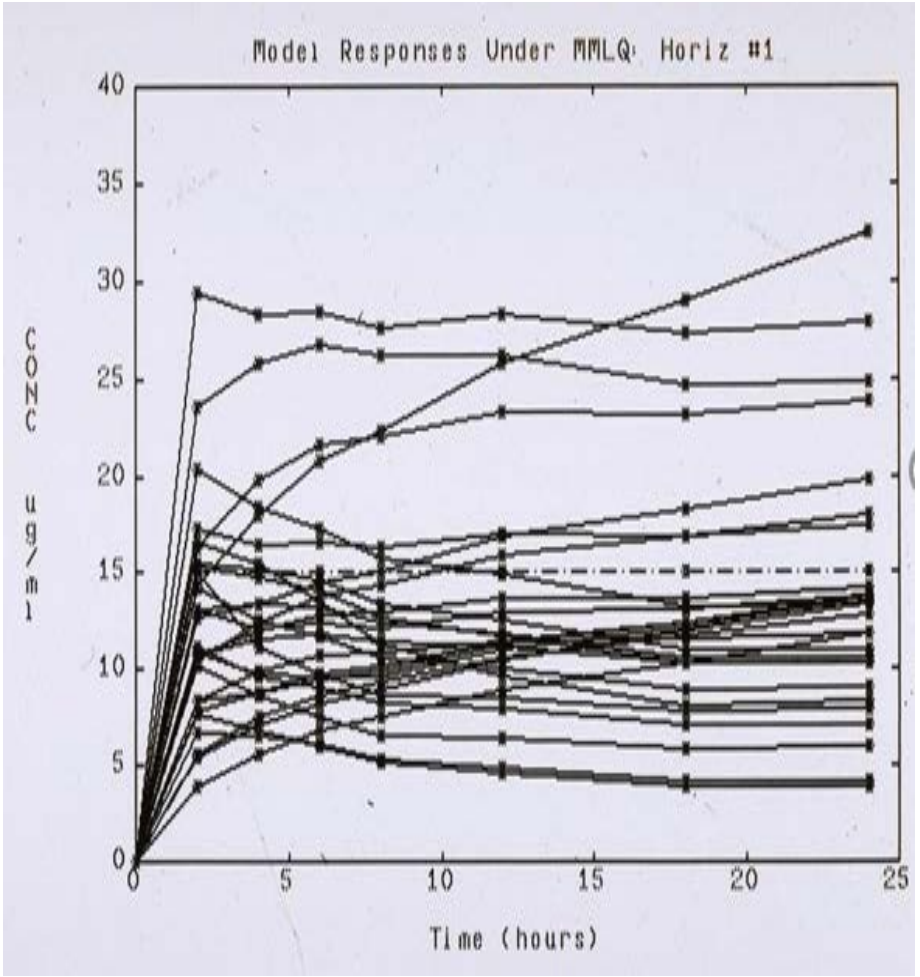
Visualize this without the true data points (black or white squares) which in real life you will never see. You will see the many small gray circles (left), the NP model support point estimates, but only a single ellipse cloud (right).

Which one (NP or P) is closer to the ideal? What will you do NOW?

Developing maximally precise dosage regimens using "Multiple Model" (MM) design.

1. The multiple models are all the support points in the NP popmodel.
   Each point has its own unique parameter values and probability.
2. Apply a candidate dosage regimen to all support points.
   Each point has its own unique response to that same dose.
3. Compare each response with your target goal. Calculate its weighted squared error (WSE) in failing to hit your target. Add these up.
4. Examine more candidate regimens - just like doing regression to minimize any weighted least squares cost function, and -
5. Find the regimen having the least overall total WSE in target goal achievement at target time. The maximally precise regimen.





Dosing on Means **Vanco** MM Dosing

MM dosing finds the regimen which hits target (15 ug/ml - dashes and dots) at target times (crosses) with minimal total WSE, thus hitting target most precisely.

Vertical axis = vancomycin concentration (ug/ml). Horizontal = time.

Doing TDM and getting NP Bayesian (NPB) posterior models for an individual patient's subsequent management and MM dosage adjustment.

Assume the true patient is one of the NP pop support points. Each NP pop support point (with its parameter values) is a **candidate** to be the patient. But with what probability given the TDM data?

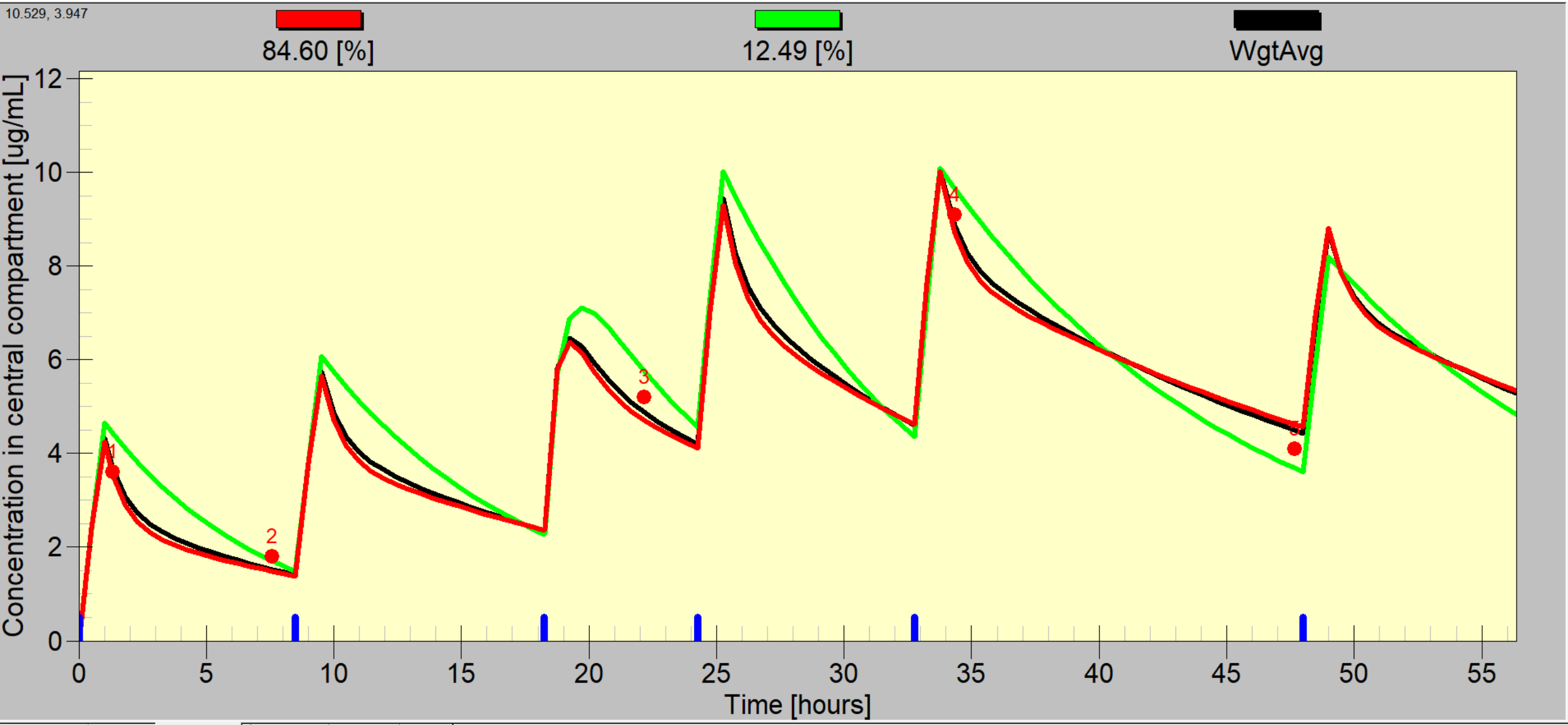
Those NP support points with parameter values predicting the TDM data well become more probable.

Those predicting poorly become less probable.

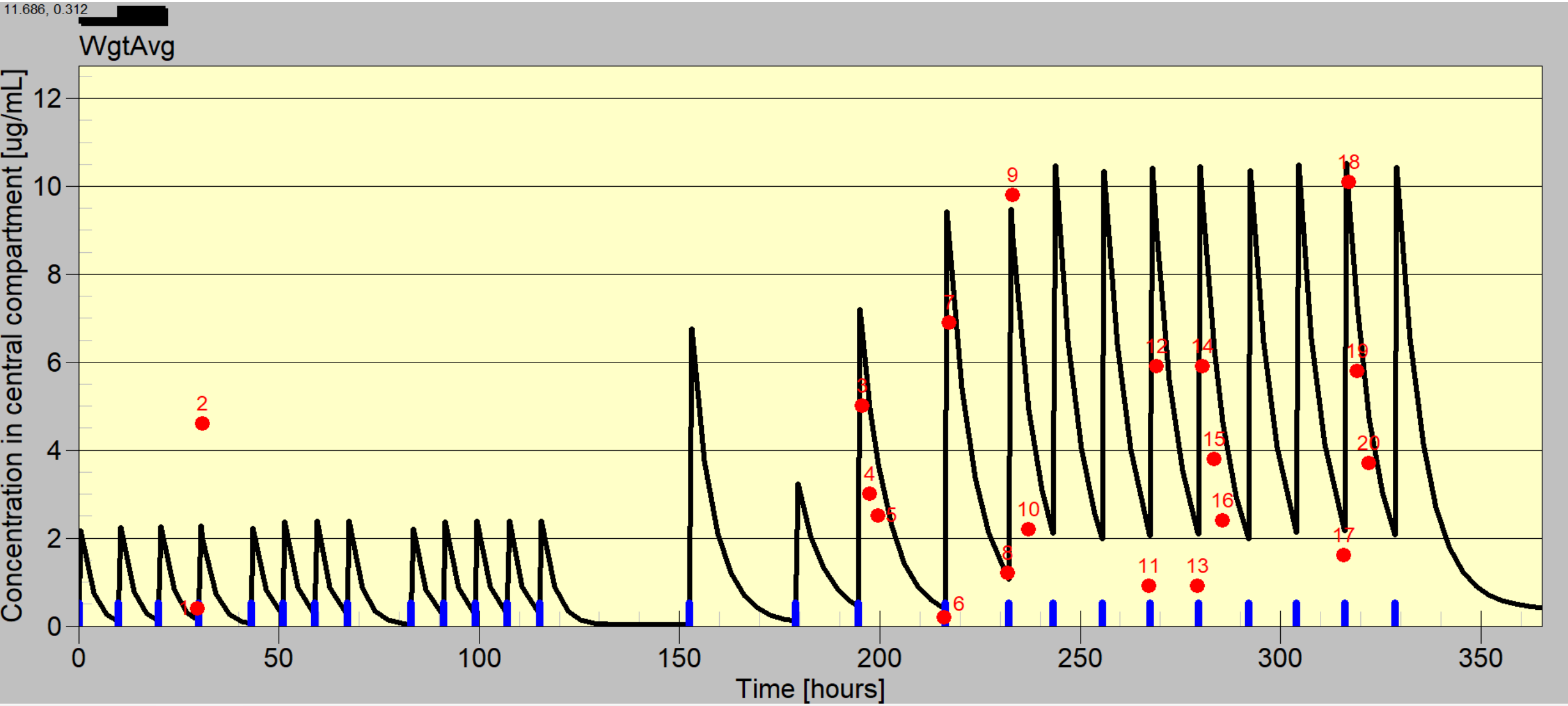
We get the revised Bayesian posterior probability of **all** the NP pop model support points given the pop model and that patient's TDM data.

Then do MM dosage again. TDM and MM control, cycle after cycle.

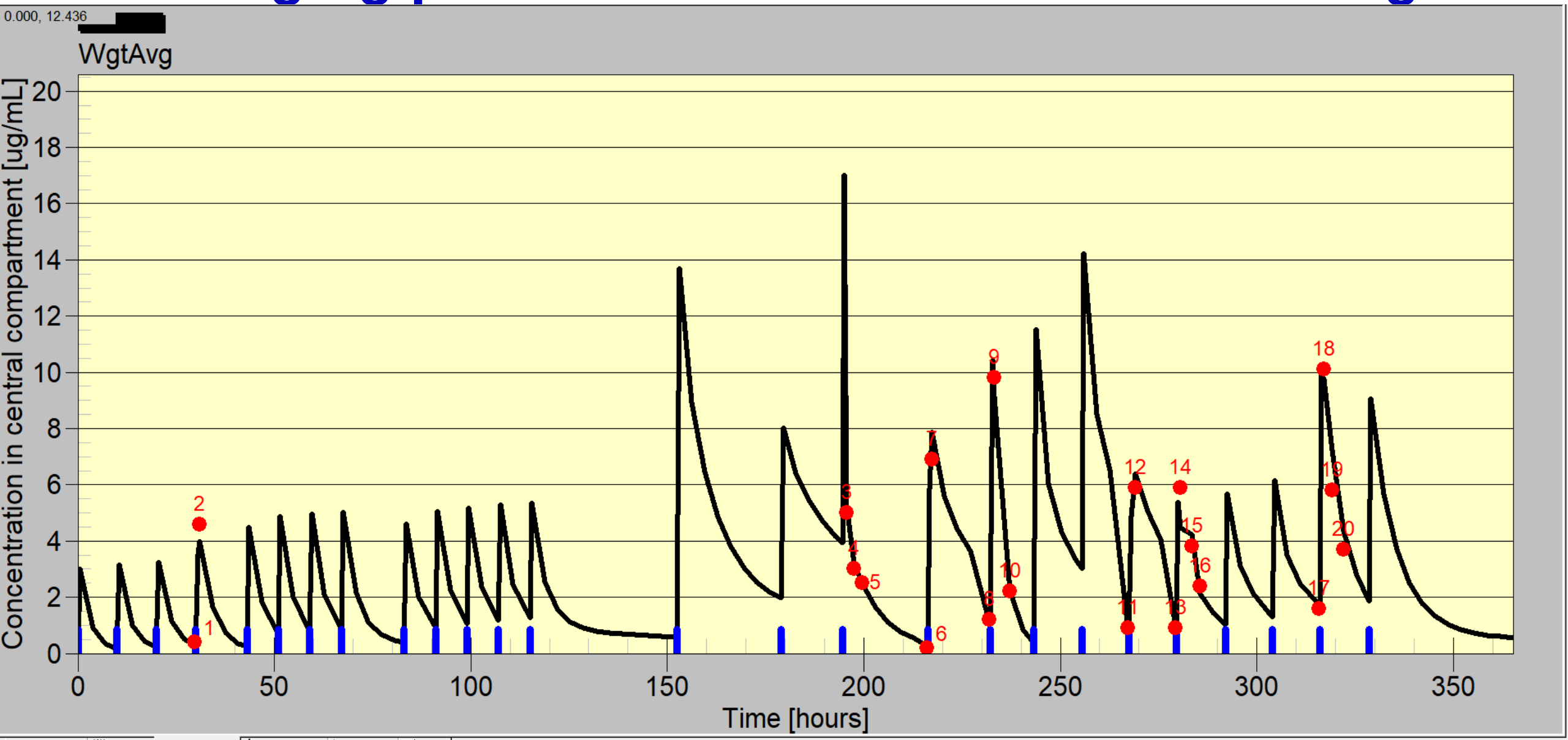
NPB posterior gent model estimates - significant posterior model support points, and overall weighted average

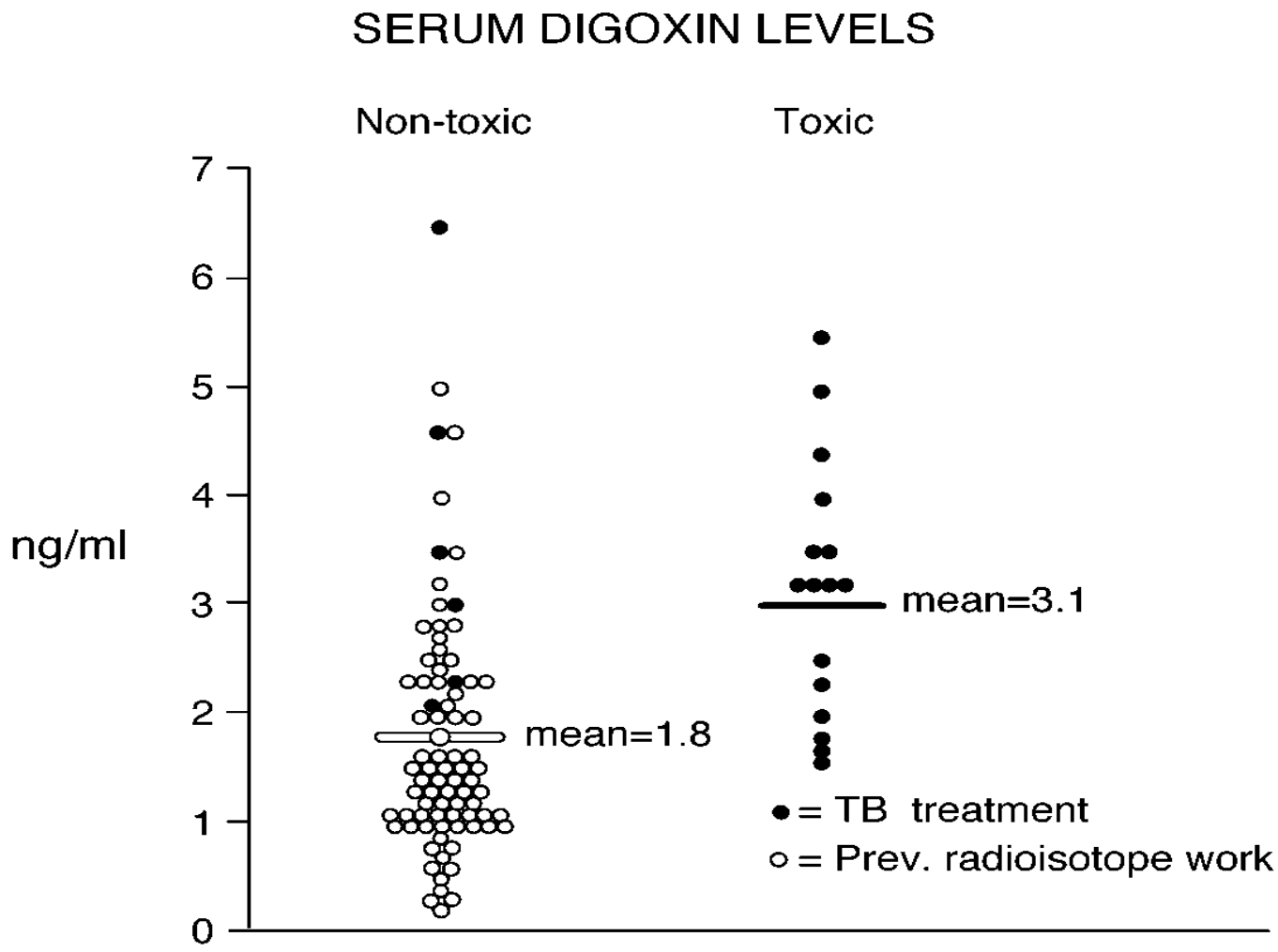


A highly unstable tobramycin patient, with high intra – individual variability. NP Bayesian weighted average fit, fixed parameter values throughout. A very poor fit!

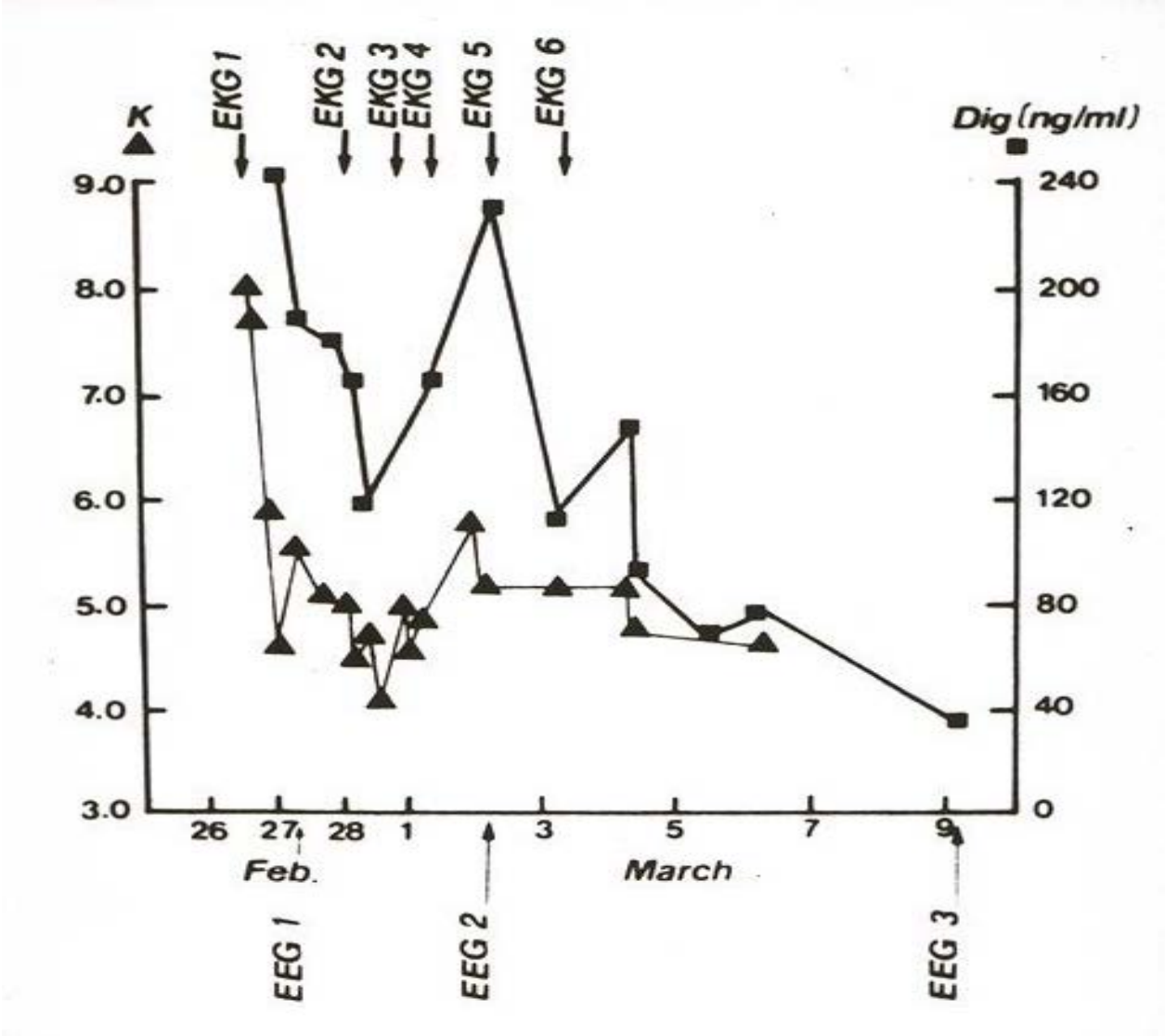


Tobramycin patient - IMM fitting – changing param values - much better tracking.

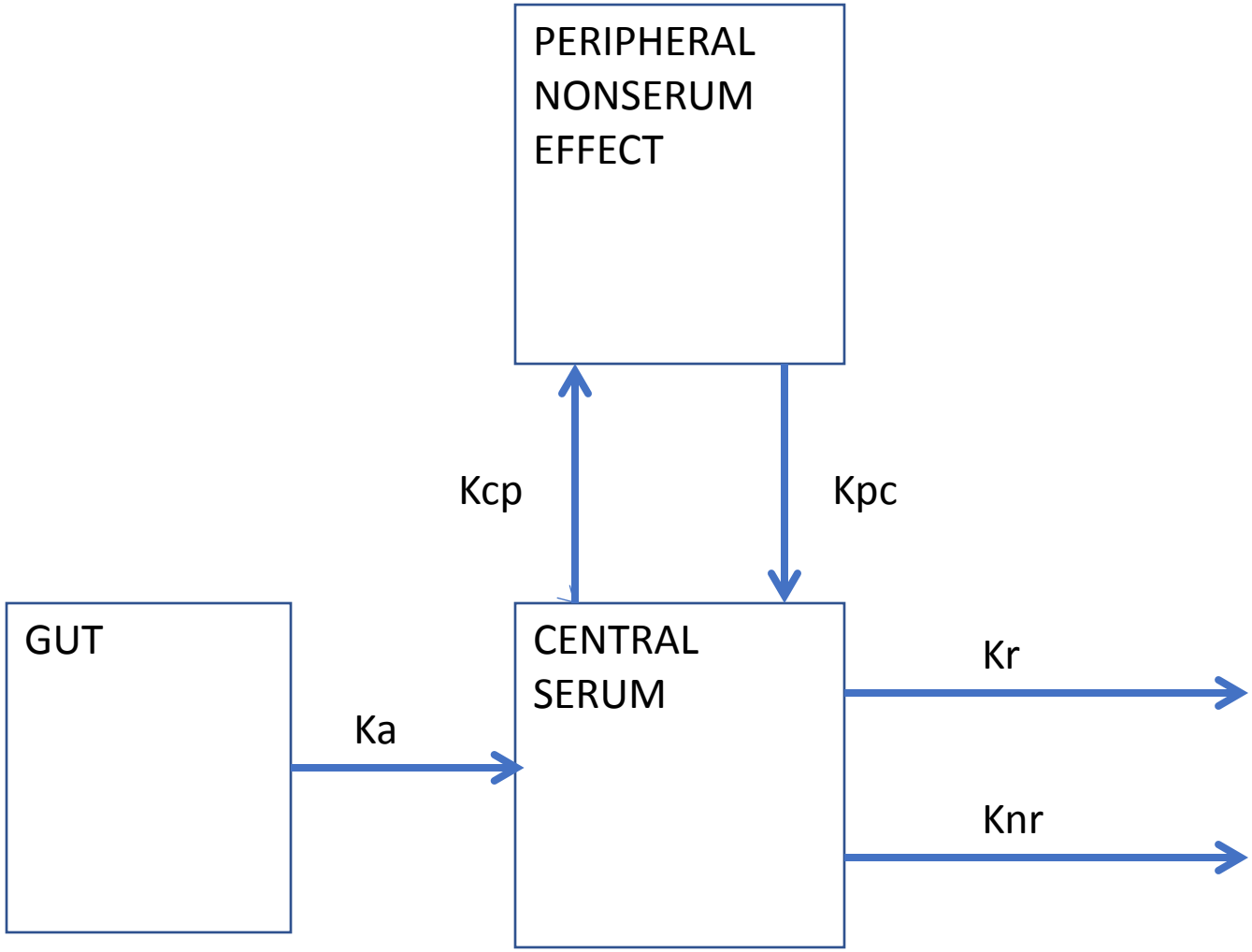


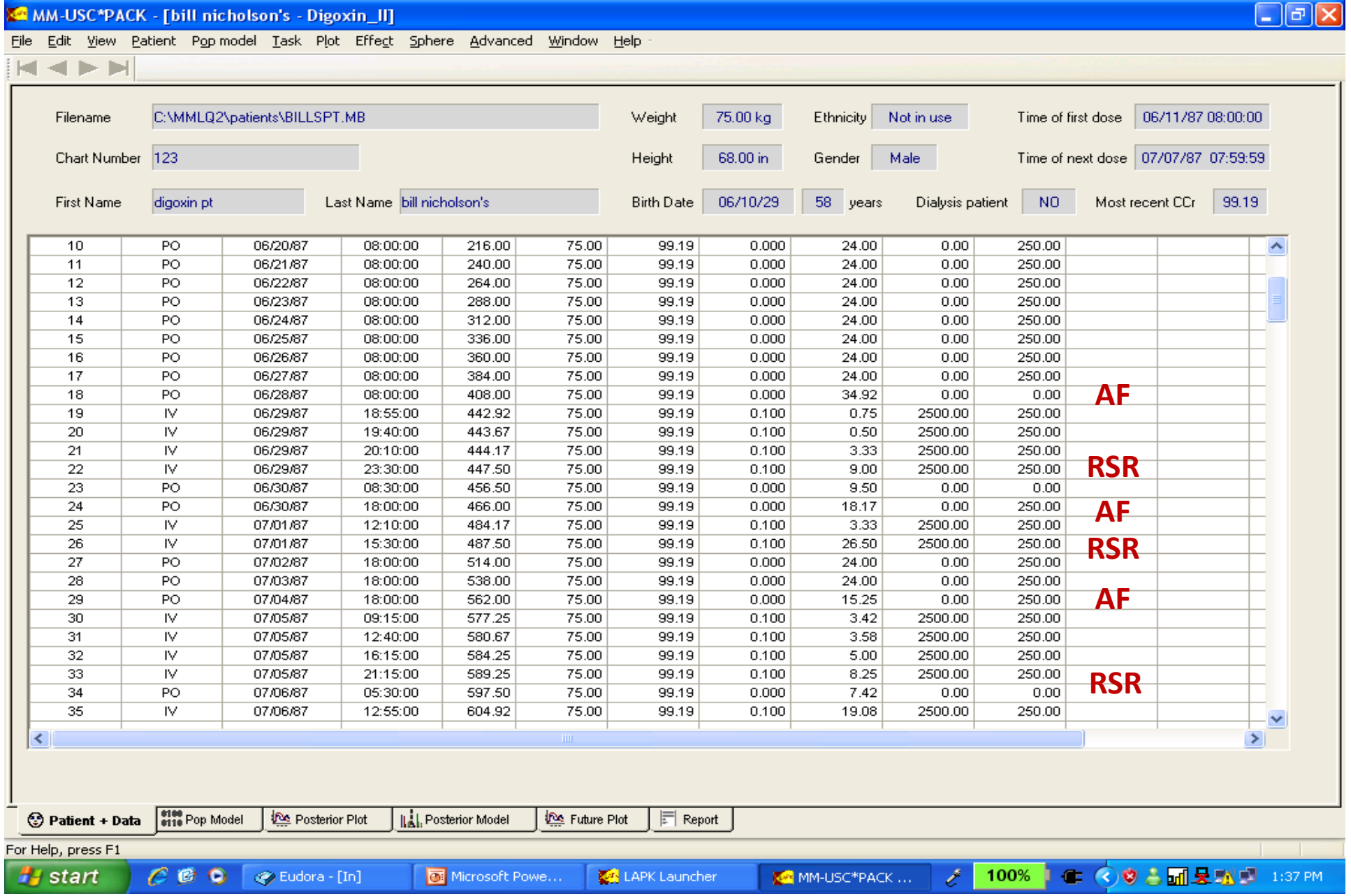


Serum digoxin concentrations in nontoxic and toxic patients found by Doherty [1]. Great overlap between therapeutic and toxic concentration. Half of these patients with serum levels of 3.0 ng/ml or more were NOT toxic.

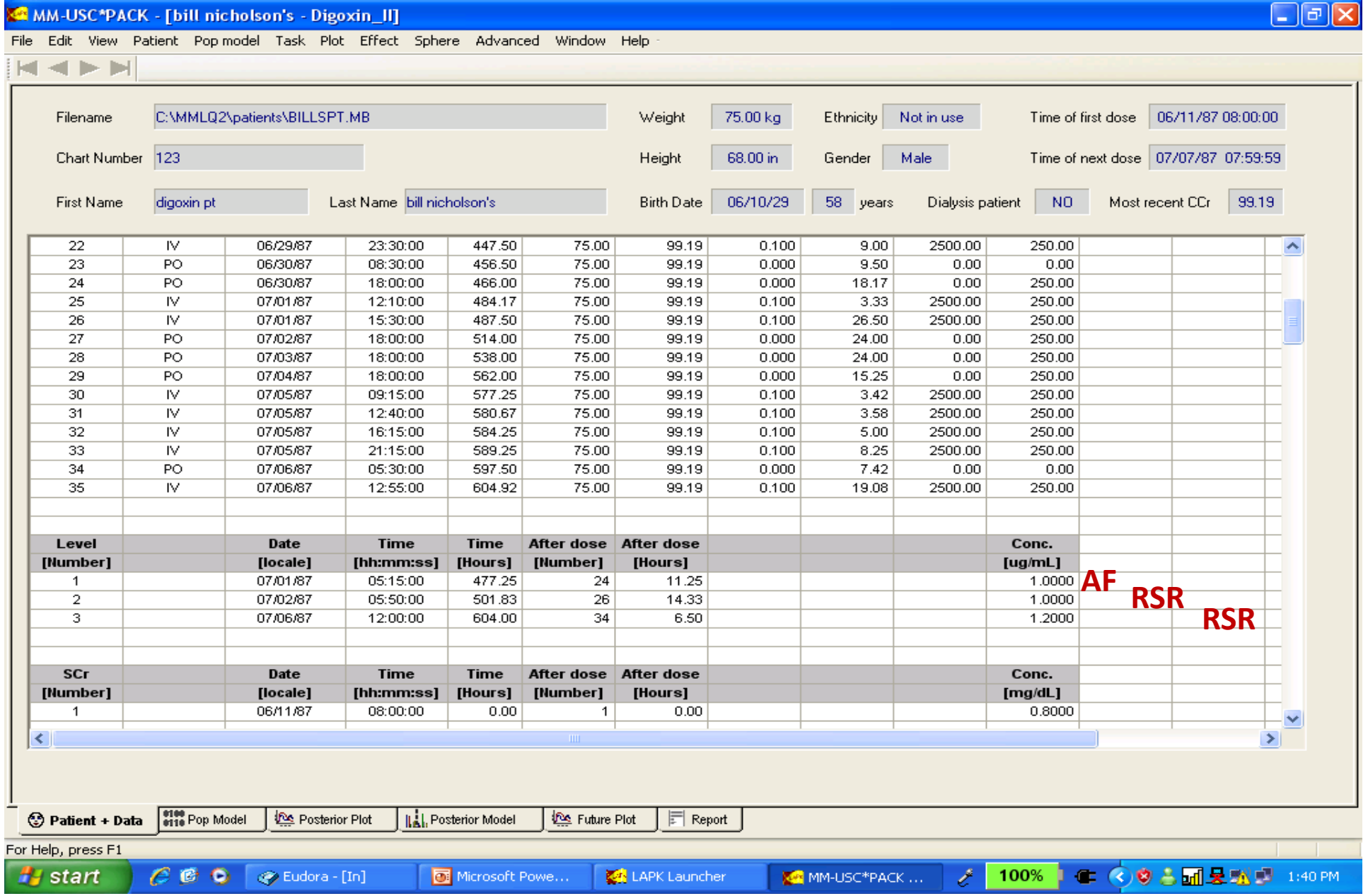


A suicide attempt – dig concs, K, and patient response

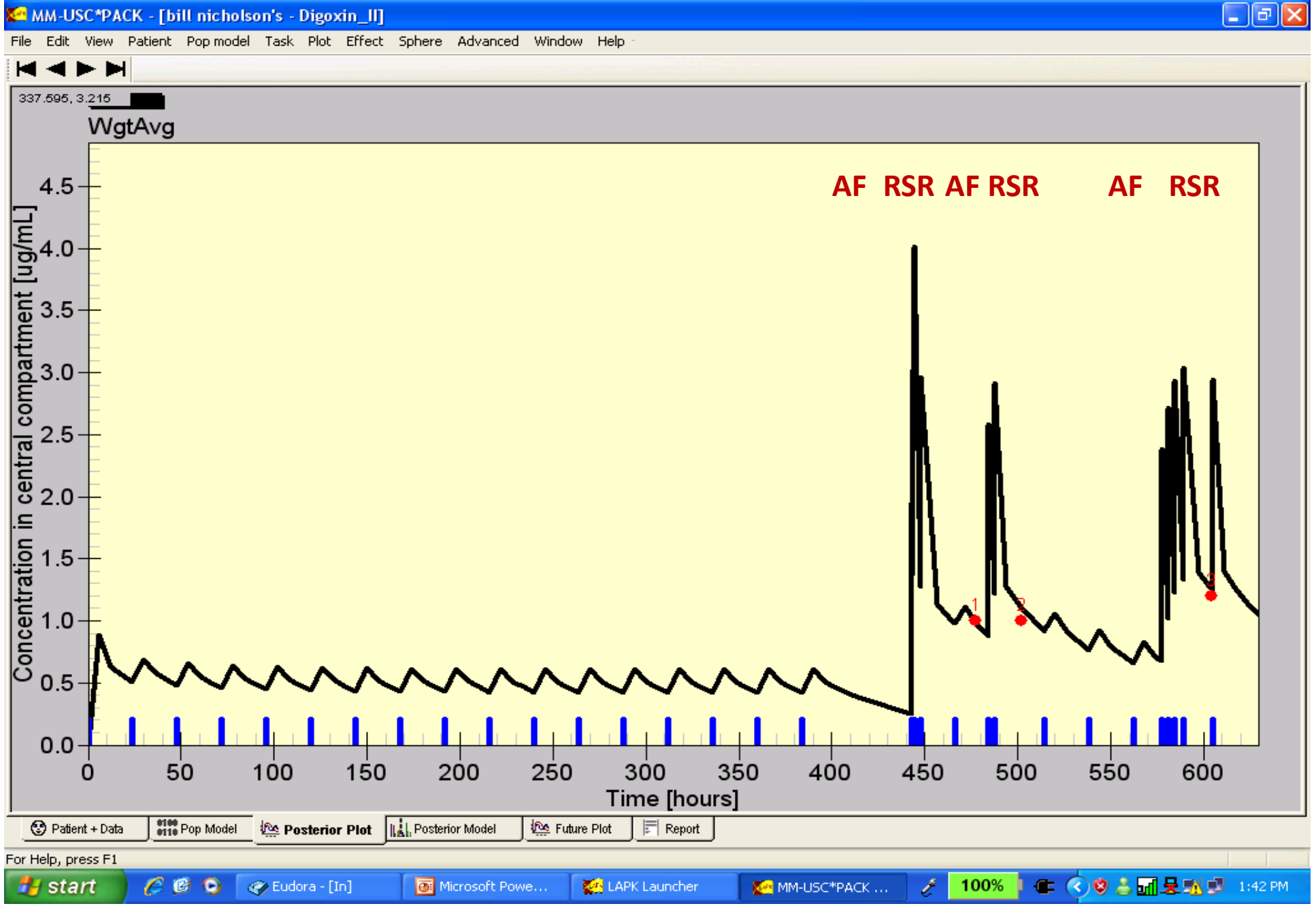

PERIPHERAL
NONSERUM
EFFECT
Kcp
Kpc
GUT
CENTRAL
SERUM
Ka
Kr
Knr



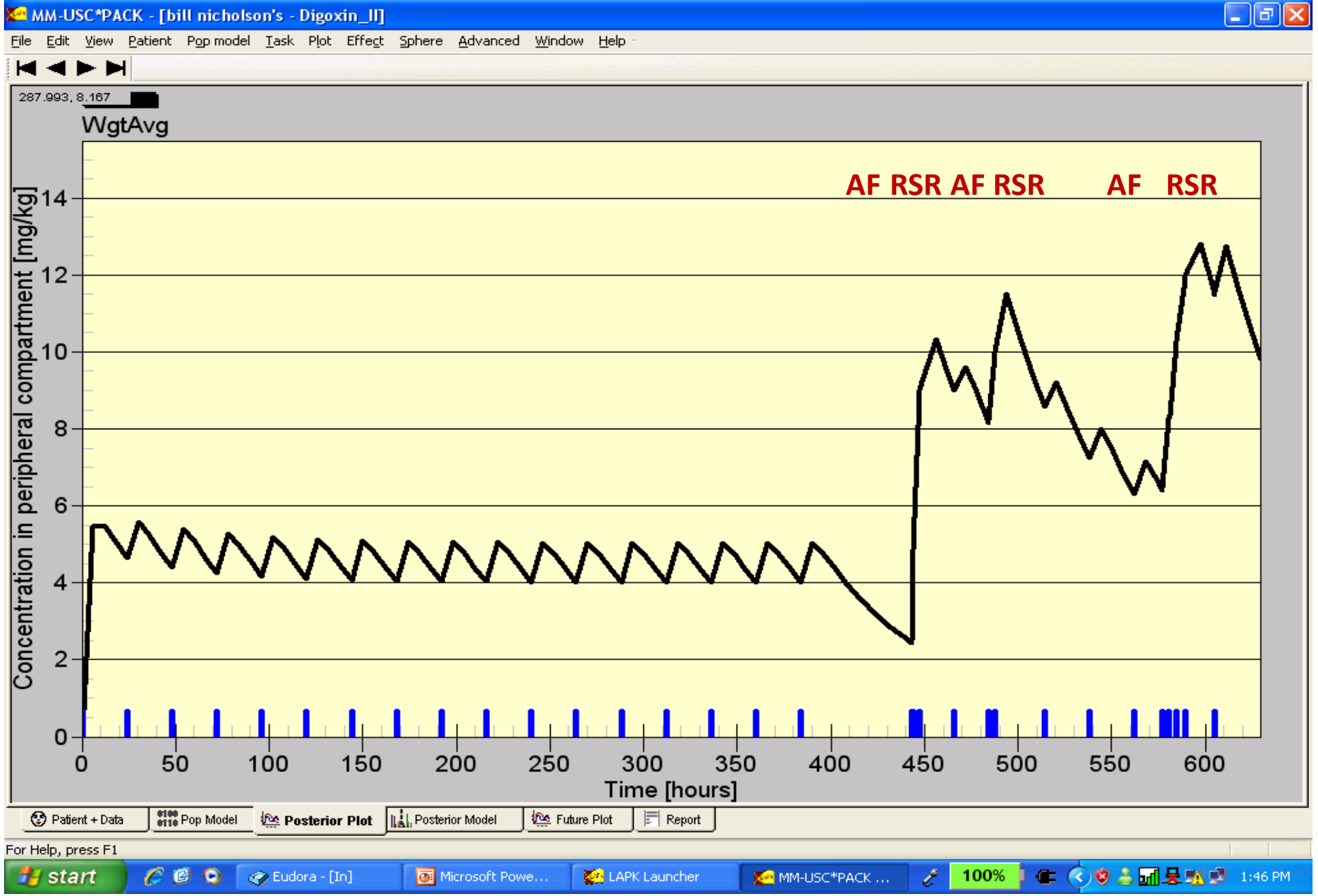
A phone consult – doses, history, response



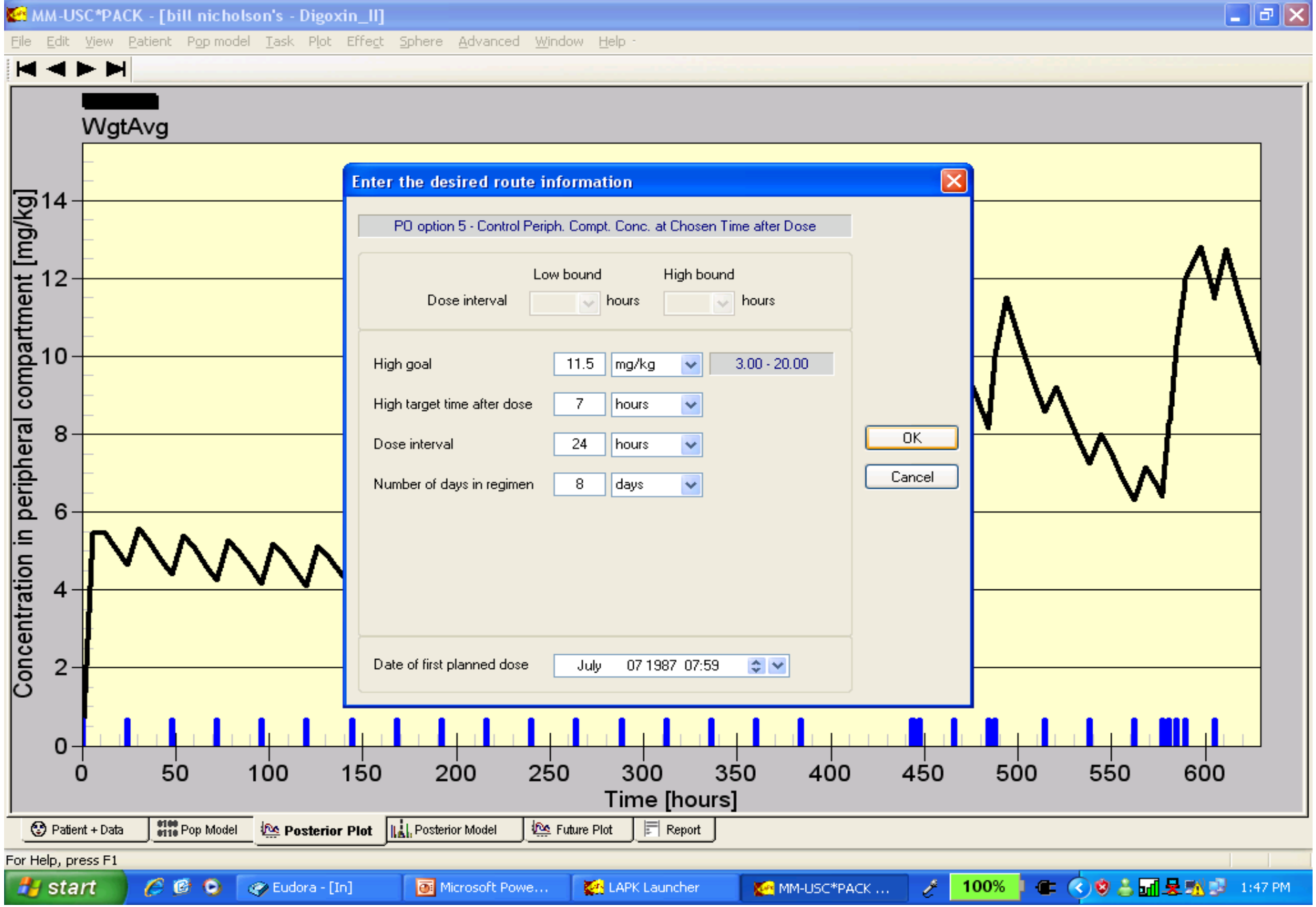
Phone consult – TDM serum concs., response



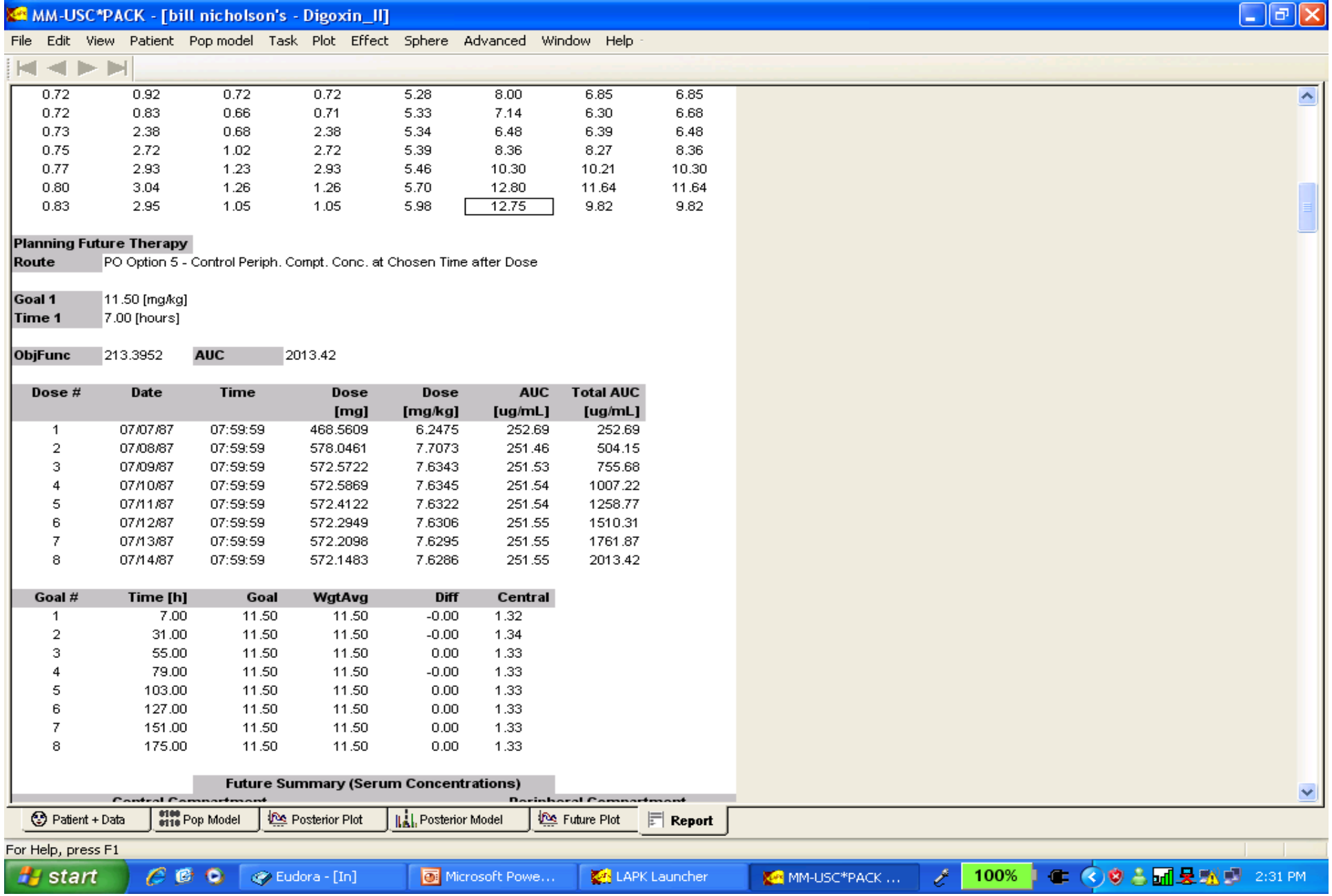
Phone consult – NP Bayesian posterior – TDM plot of serum concentrations



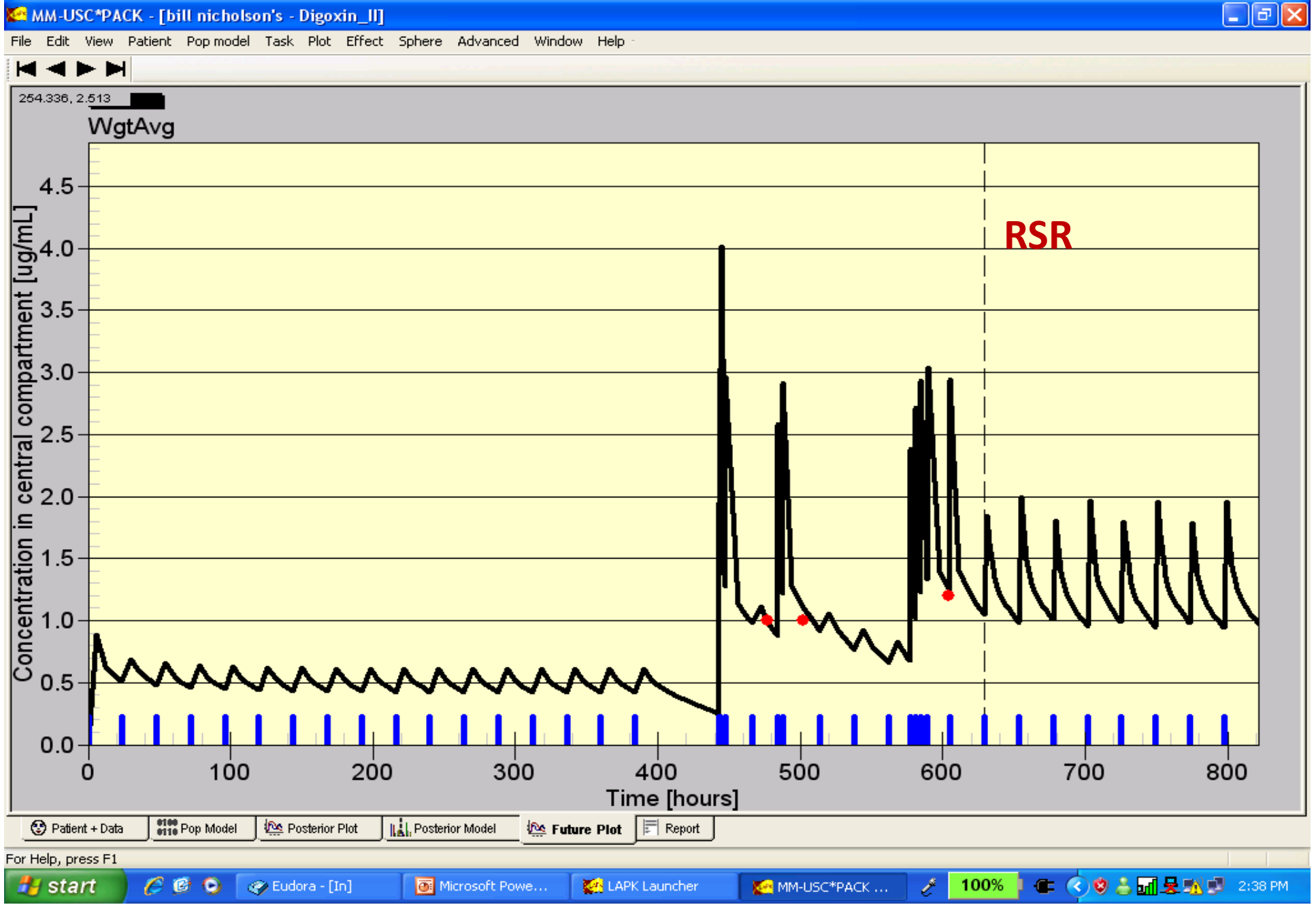
Phone consult – NP Bayesian posterior – periph. concentrations, response.



Setting target goals and regimen format



Ideal PO regimen = 572 ug/day – OK, how about 562.5, or 500 and 625 on alt days?



Predicted serum compartment concentrations – new regimen

Predicted peripheral compartment concentrations – new regimen

Things the industry and the FDA can do to educate and encourage clinicians to treat patients as individuals, and with maximal precision.

1. **Use, and publish or make available, NP pop models for clinical use and MM dosage.** Advocate individualized therapy in package inserts, with general method and drug - specific references.

2. **Don't be vague any more. Advocate setting a specific point target for each patient. Evaluate need for the drug versus a risk of toxicity above which you will not go for that patient.**

3. **Individualized therapy is more than therapy for subpopulations. Knowing genetics and other factors is good, but many factors will always remain undiscovered. Track the drug!**

4. **Advocate using NP bedside** software. Been here **for years. Use the new industry NP models** for maximally precise **individualized therapy and safety.**

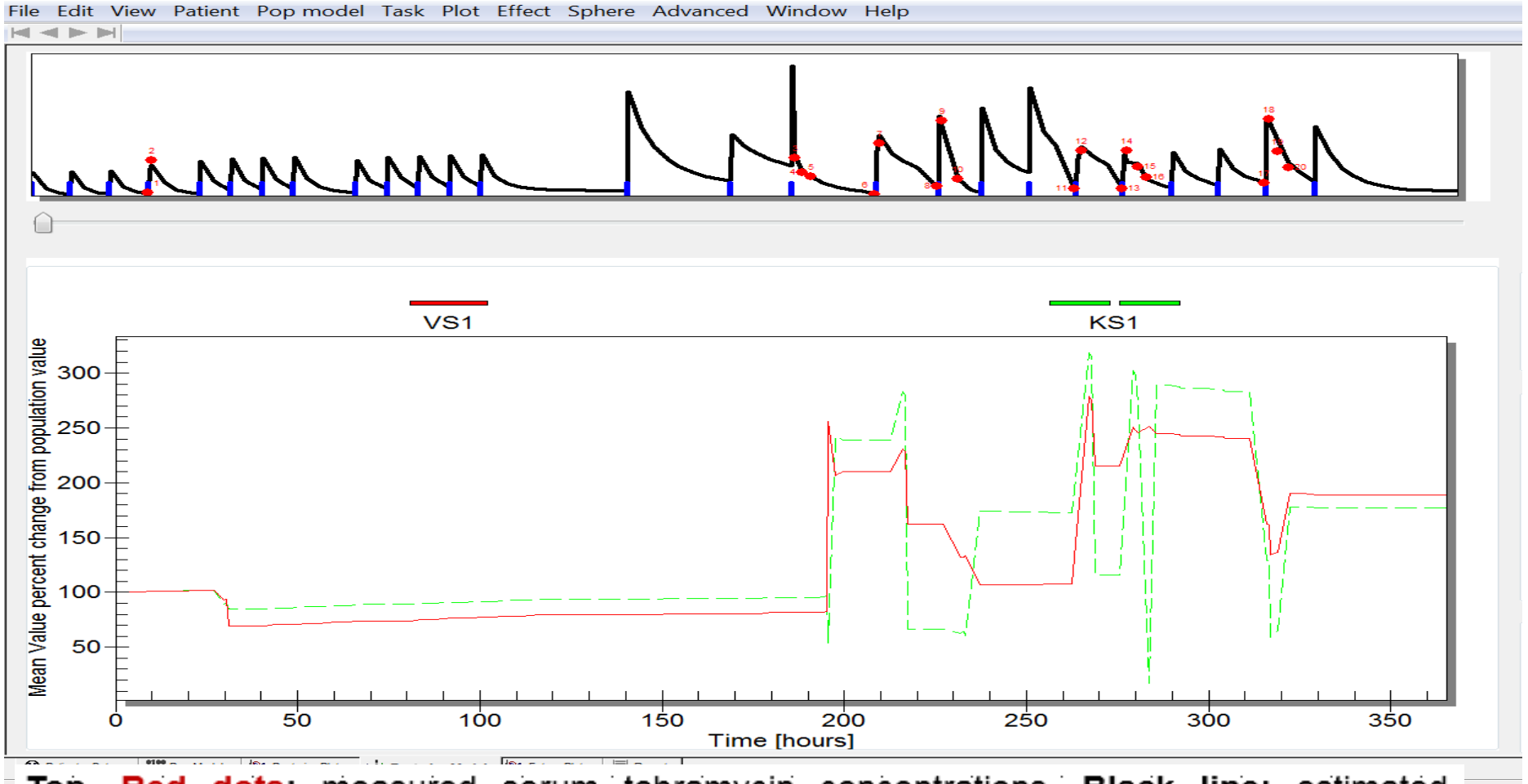
5. **Advocate tracking drugs in acutely ill, highly variable patients having changing model parameters over time, using interacting multiple model (IMM) tracking and analysis.**

6. **Form an FDA Individualized therapy advisory group, as Dr. Neely suggests.**

7. **Listen to the patient. S/he tells you the target - everything! Can you, will you, listen?**

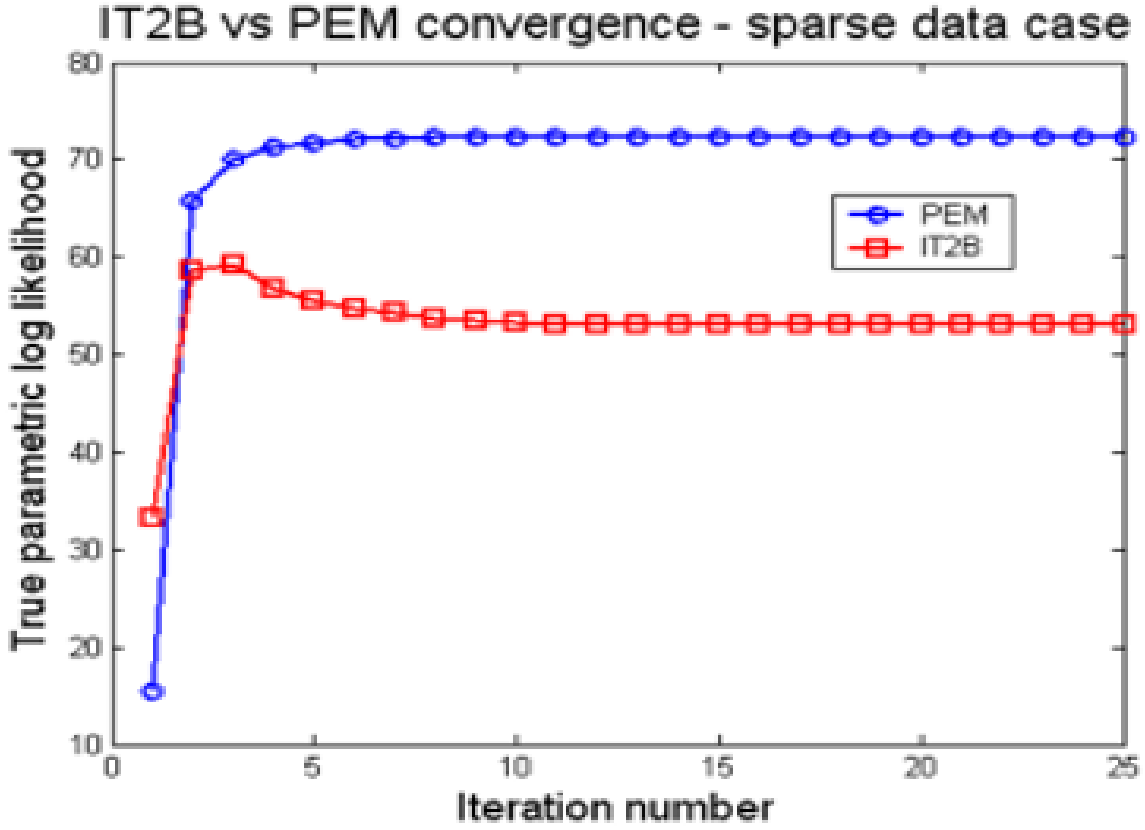
Our sweet dog Diamond would have said,
“Thanks so much, FDA, for organizing this needed and provocative workshop, and thanks, all of you, for coming, and for your thoughtful attention!”

IMM – V and K can change now over time.



Top. Red dots: measured serum tobramycin concentrations. **Black line:** estimated weighted average serum tobramycin concentrations. Vertical axis: serum tobramycin concentrations up to 12 ug/ml. **Bottom:** percent changes in estimated mean Vs1 (red, V in L/kg) and Ks1 (green, K in 1/hr per unit of creatinine clearance). Some changes appear volatile, perhaps from errors recording times of dosing and drawing samples. There are also clear changes in V and K not discoverable by other methods. **Changes in K are separated from changes in V. Each parameter reflects a distinct and separate therapeutic issue.**

Likelihood convergence – FOCE vs PEM



PEM, with exact likelihood, increases it monotonically. IT2B, using the FOCE likelihood approximation, wanders off course, and will therefore obtain erroneous parameter estimates.

Interacting Multiple Model (IMM) Tracking

How to track drug behavior and individualize therapy in these unstable, acutely ill patients?

High intra - patient (inter-occasional) variability has been a big obstacle to TDM and individualized therapy.

Some say TDM not useful here!

“The main purpose of a tracking system for air traffic control or air defense is the estimation of target trajectories in the controlled area and their prediction into the near future”.*

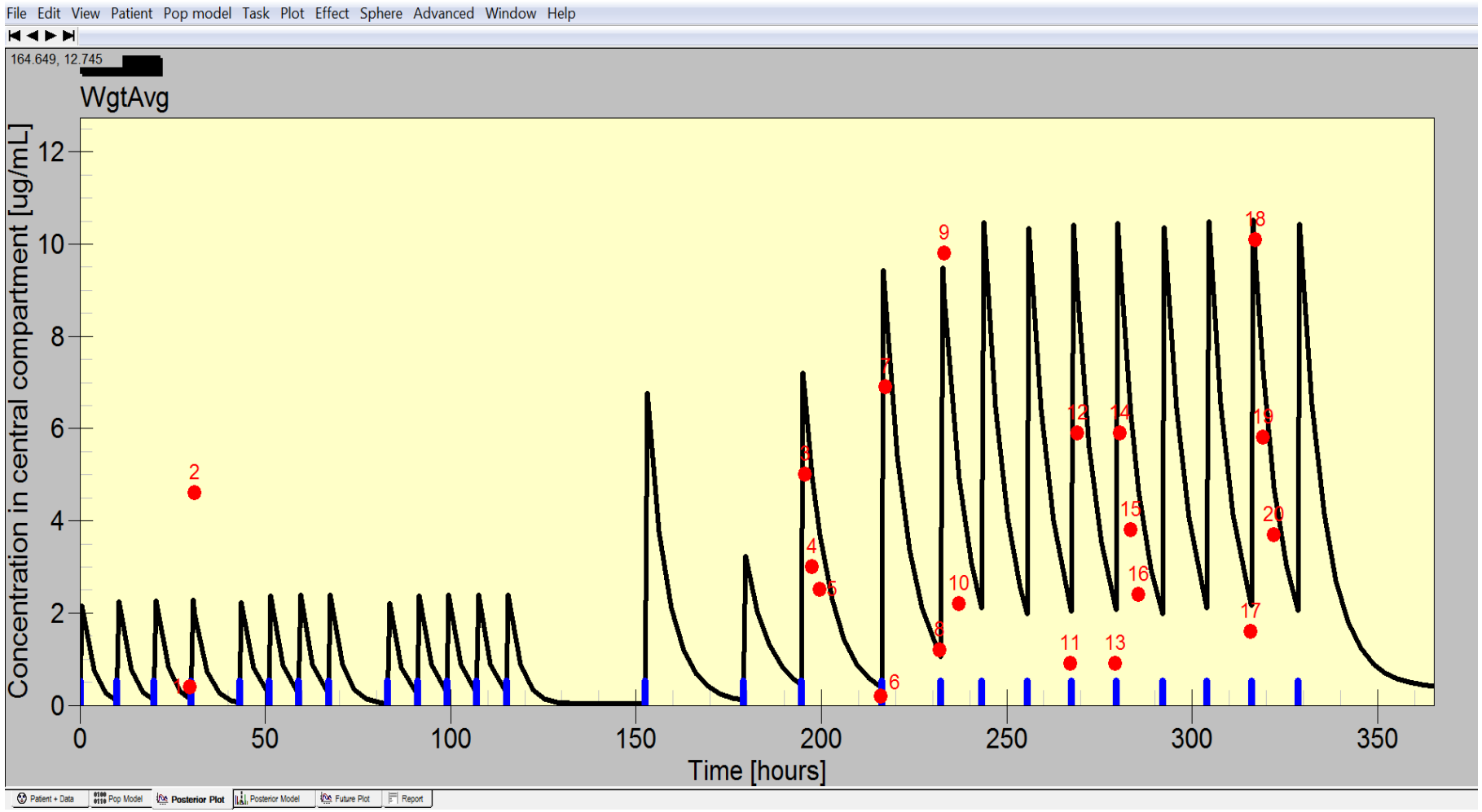
* **E. MAZOR** Technion, Israel Institute of Technology, **A. AVERBUCH** Tel Aviv University, **Y. BAR-SHALOM,** Fellow, IEEE University of Connecticut, **J. DAYAN** Technion, Israel Institute of Technology

Interacting Multiple Model Methods in Target Tracking: A Survey.

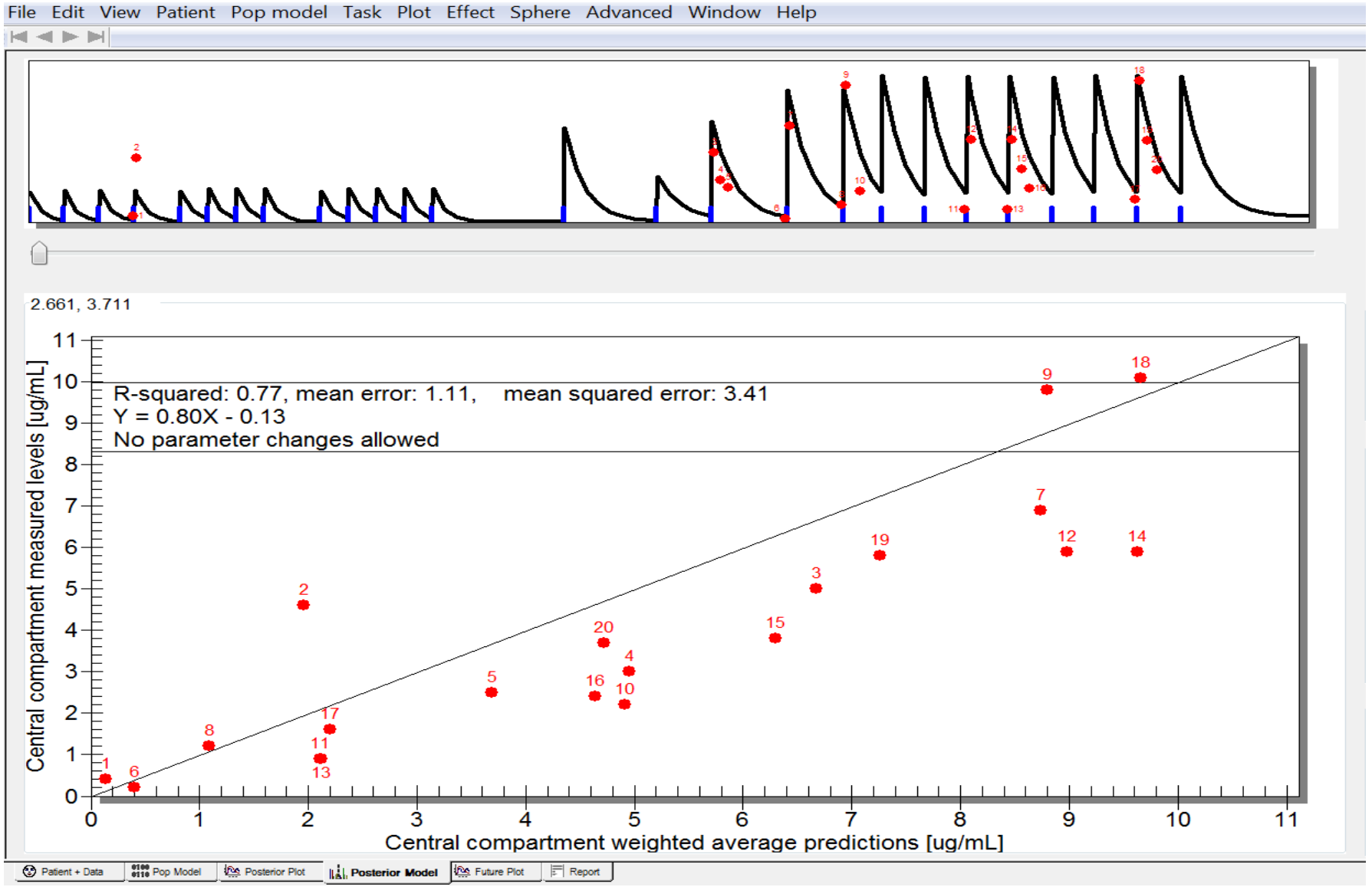
IEEE TRANSACTIONS ON AEROSPACE AND ELECTRONIC SYSTEMS VOL. 34, NO. **1** JANUARY 1998.

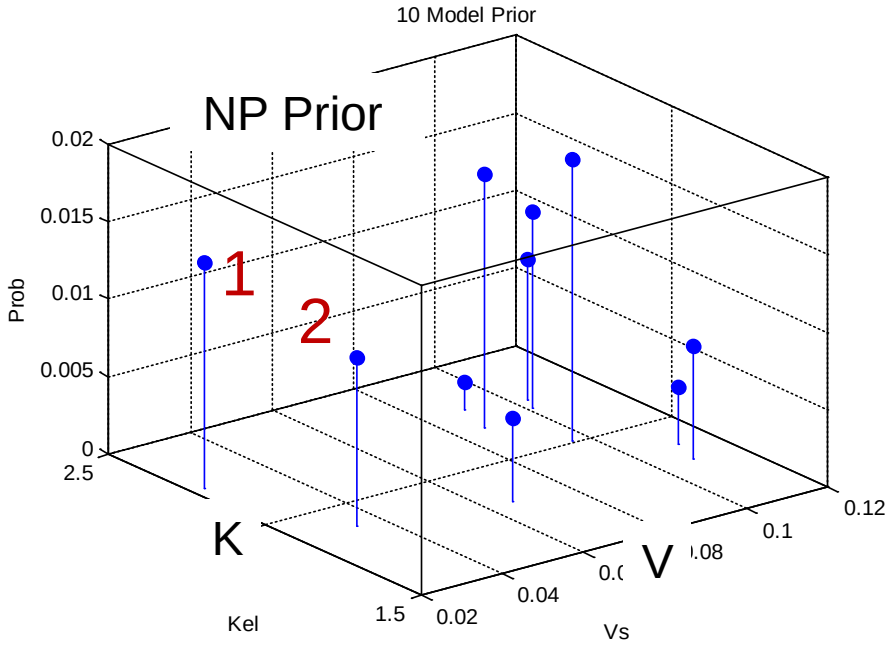
Bayard D, and Jelliffe R**:** A Bayesian Approach to Tracking Patients Having Changing Pharmacokinetic Parameters. J. Pharmacokin. Pharmacodyn. 31 (1): 75-107, 2004.

A highly unstable patient, regular NP Bayesian fit, unchanged parameter values throughout, giving a very poor fit.



Predicted versus measured levels





A swap (exchange) between points 1 and 2.
Before swap,
Point 1 always has parameters V1, K1, conc is Amt 1/V1
Point 2 always has parameters V2, K2, conc is Amt 2/V2

The swap – Amt 1 passes to Point 2, Amt 2 goes to Point 1.

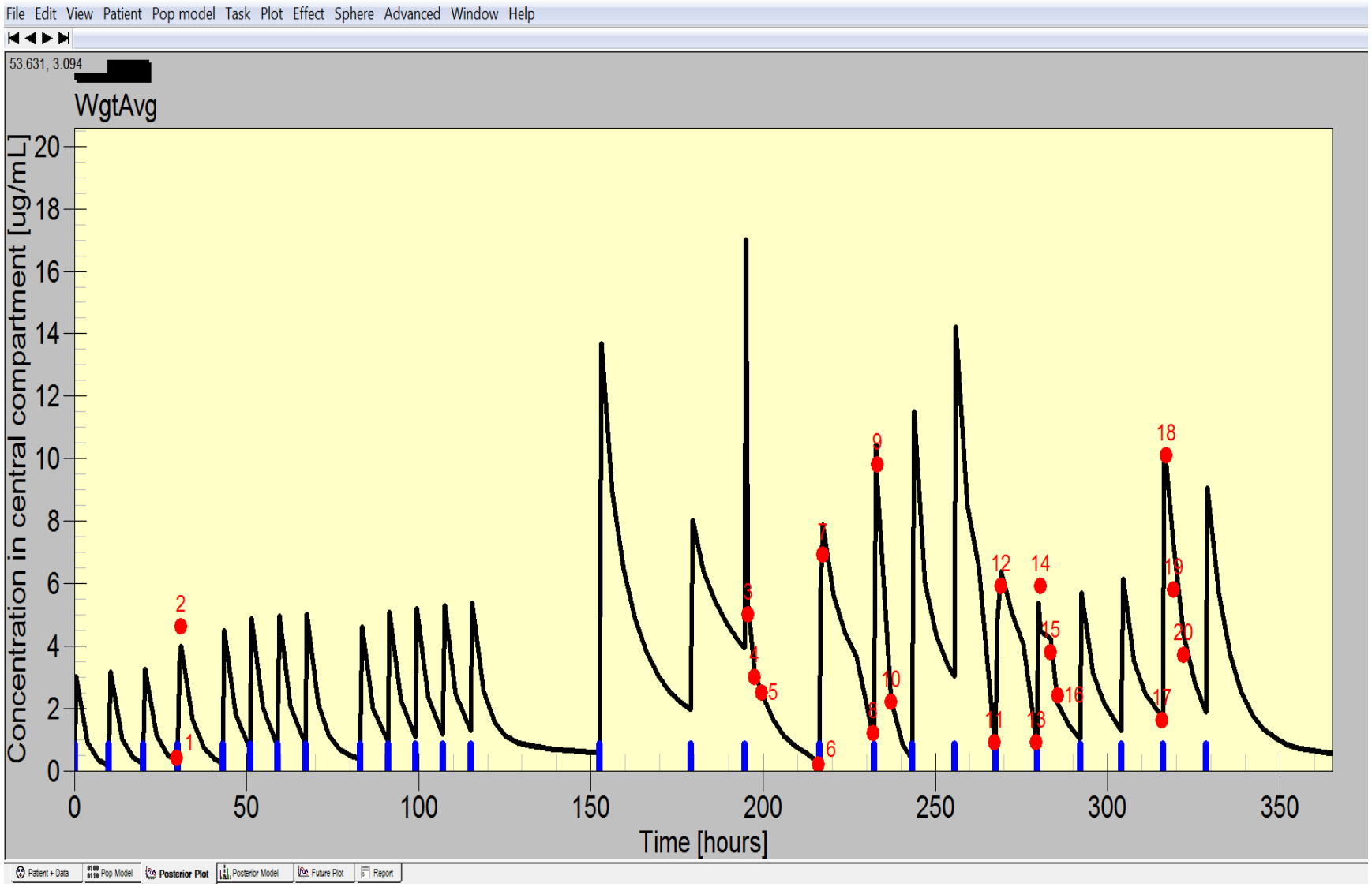
After swap, Conc 1 is now Amt 2/V1, eliminated by K1, and

Conc 2 is now Amt 1/V2, eliminated by K2.

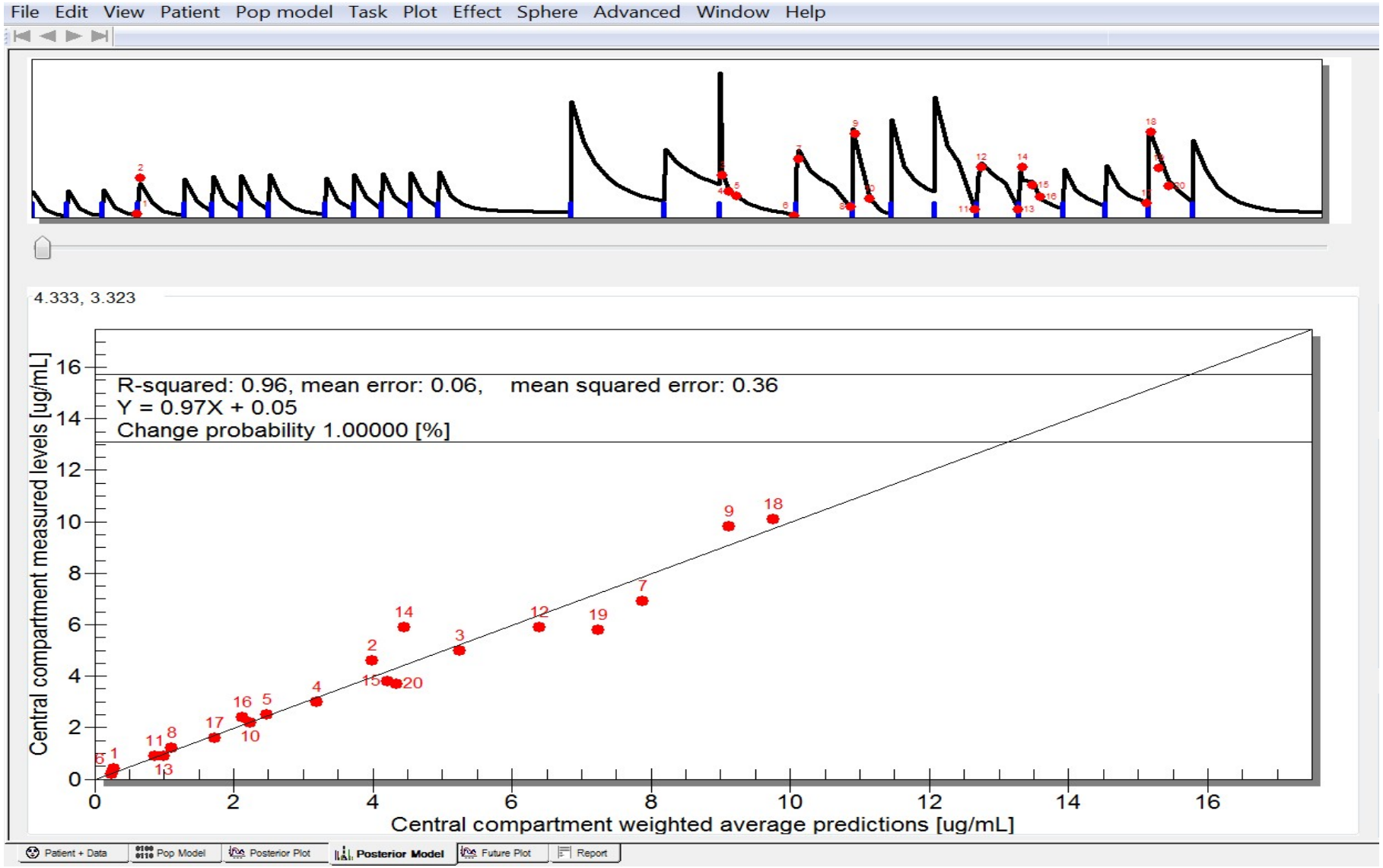
This is how **drug amounts** can **change their parameter values** over time.

Does the swap fit the data better? **IMM looks at all combinations of pairs like this**, finds most probable sequences of interacting swaps that fit the changing data best. Gets the **changing** NP Bayesian posterior joint density over time, tracks unstable patients best.

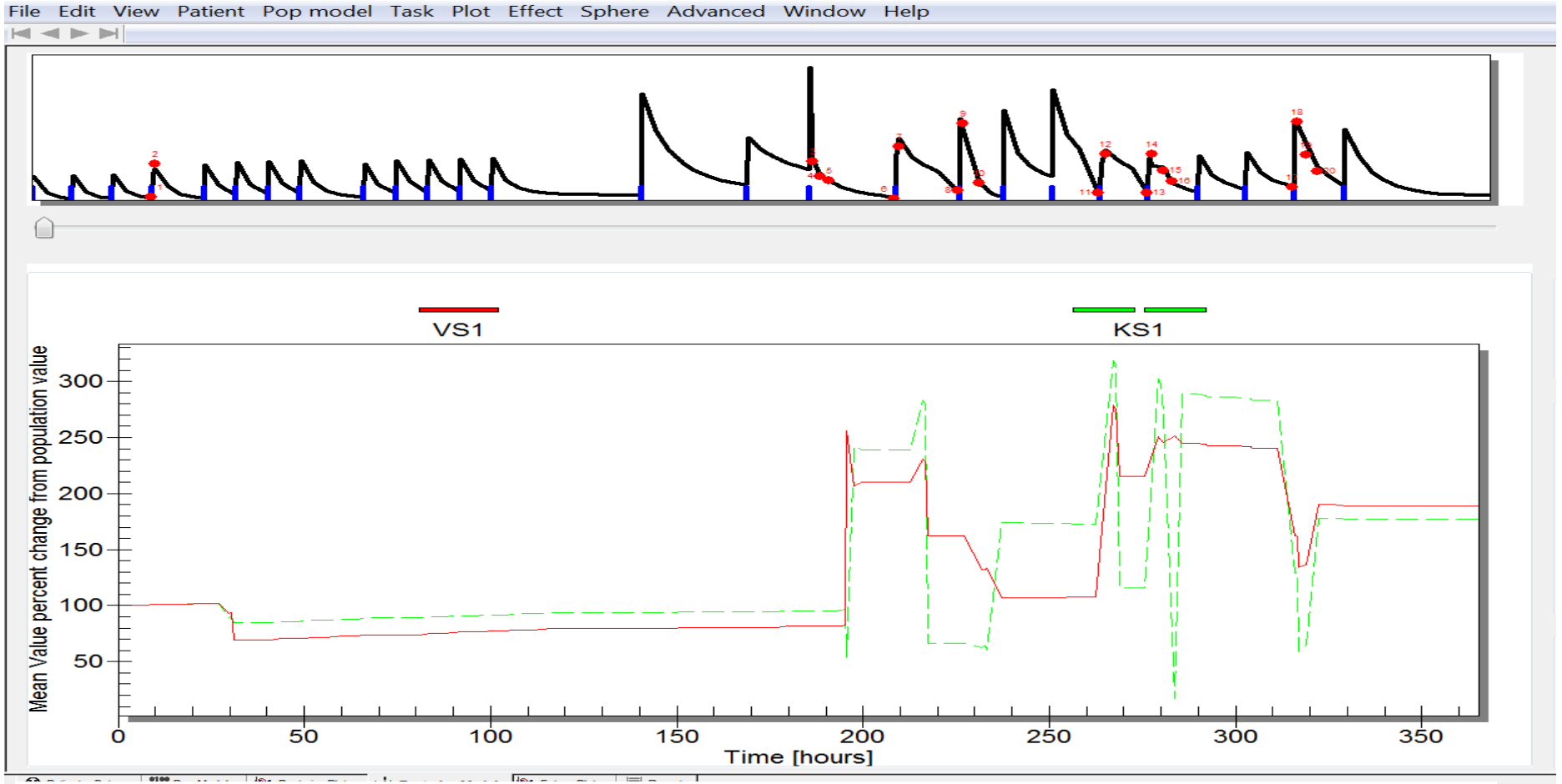
IMM – much better tracking



IMM - better estimated vs measured



IMM – V and K change over time



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Optimize TDM sampling protocols

Don’t just spot check or get steady state troughs. Sample to learn drug behavior best, and as soon as possible. Plan before you sample.

Do NOT wait to get steady state troughs, leaving the patient at risk by not knowing for too long!

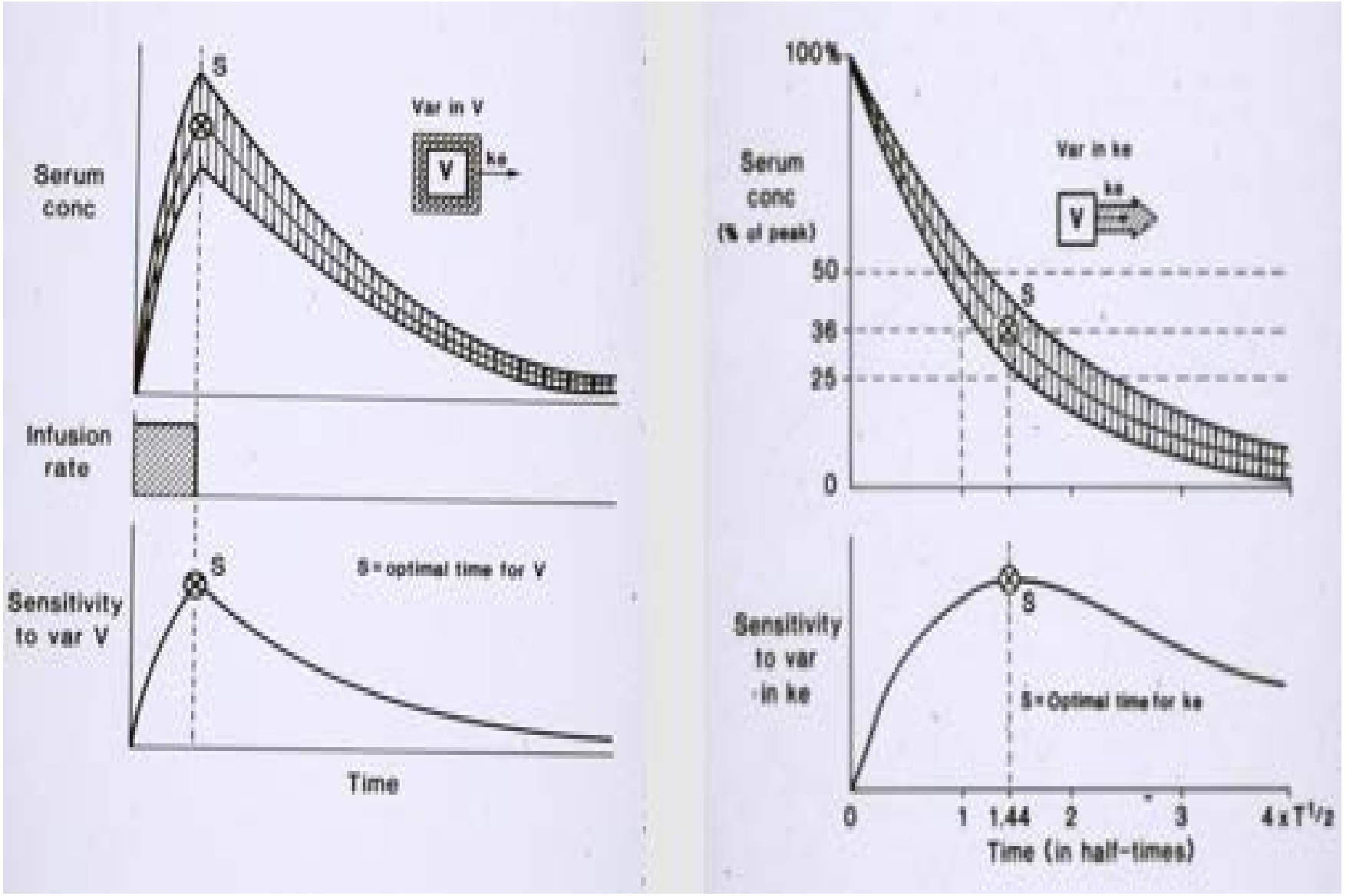
Start TDM right with the very first dose!

Use D-optimal or MM-opt design. There is an optimal sampling time to get best info about each patient, given a certain dosage regimen format.

Often, get a peak and a sample at about 1/3 of peak.

Do NOT waste money, effort, and compromise patient care with poor TDM designs. The TDM community can do a MUCH BETTER job here. Better info, better care, shorter stays, less cost.

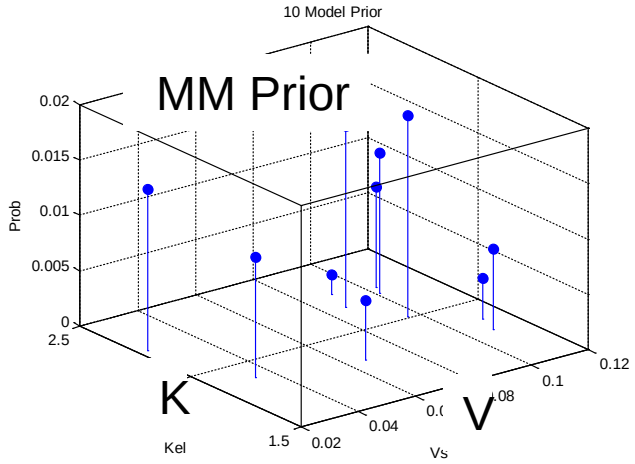
D and MM Optimal Sampling



D-optimal design – best time to sample for V is at the peak. Best for K is at 36% of peak.

Multiple Model Optimal Design

- **USC *BestDose* optimal sampling software is based on the discrete support points in the <u>nonparametric</u> population model.**
  - **Nonparametric Maximum Likelihood (NPML) estimation of a population model has the form of a MM prior (Mallet, and Lindsay).**
  - **Software for population NPML modeling is available, e.g., NPEM (Schumitzky, NPAG (Leary, Baek , USC*PACK (Jelliffe, and Pmetrics (Neely) and clinical Bestdose.**



- **Experiment design for MM (i.e., discrete) models is a subject found in <u>classification theory.</u>**
  - **How do we sample the patient to find out which support point he corresponds to most closely?**
  - **Classifying patients is fundamentally different from trying to estimate a patient's model parameter values.**
- **Treating MM experiment design in the context of classification theory leads to the mathematical problem of <u>minimizing Bayes risk of missclassification</u> (Duda et. al.).**

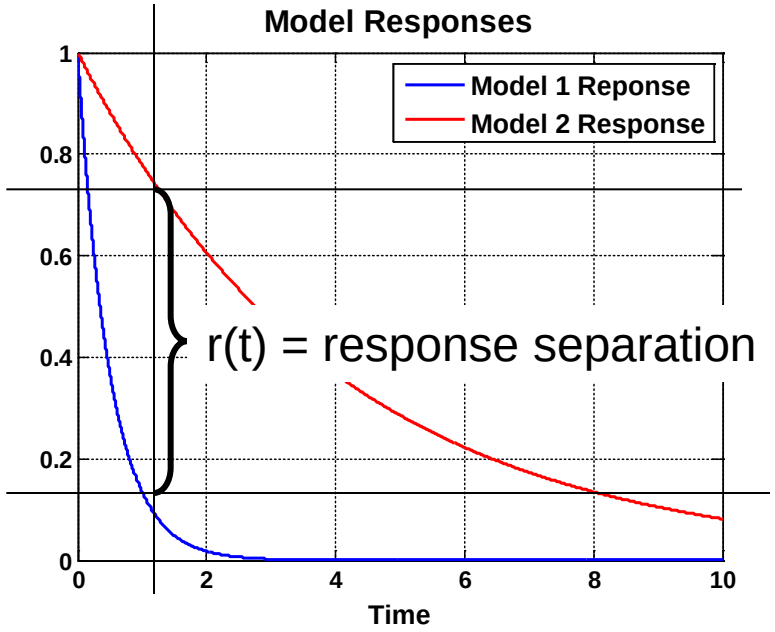
Model Response Separation r(t)

- **Model Response Separation r(t) is the separation between two model responses at a given time t**

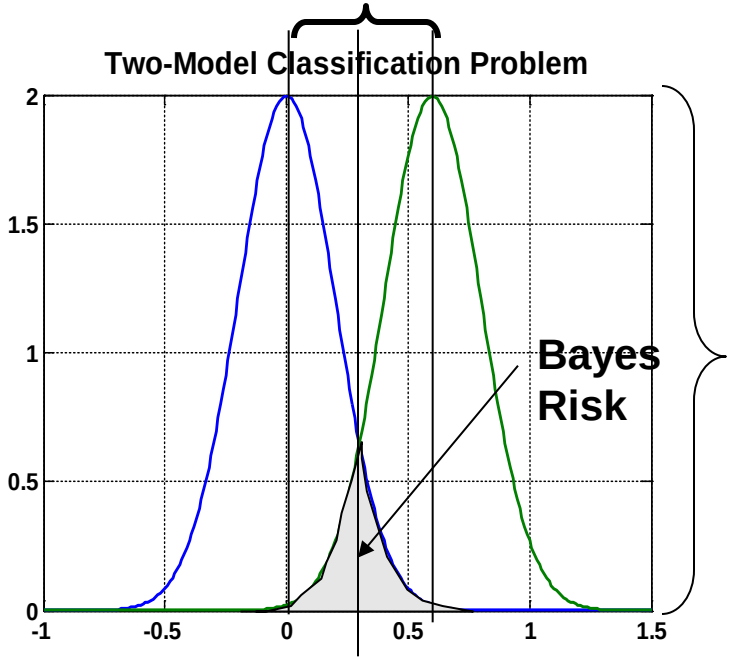
$$r(t) = |\eta(t, a_1) - \eta(t, a_2)|$$

- **Defines natural statistic for discriminating between two models**

- **Bayes Risk is shown in gray area below**



r(t)=response separation



Pull Gaussians apart to minimize gray area

- Bayes Risk (gray area) decreases as response separation r(t) increases

- Models are best discriminated by sampling at a time t that maximizes r(t)

Unweighted MMOpt for PK Estimation

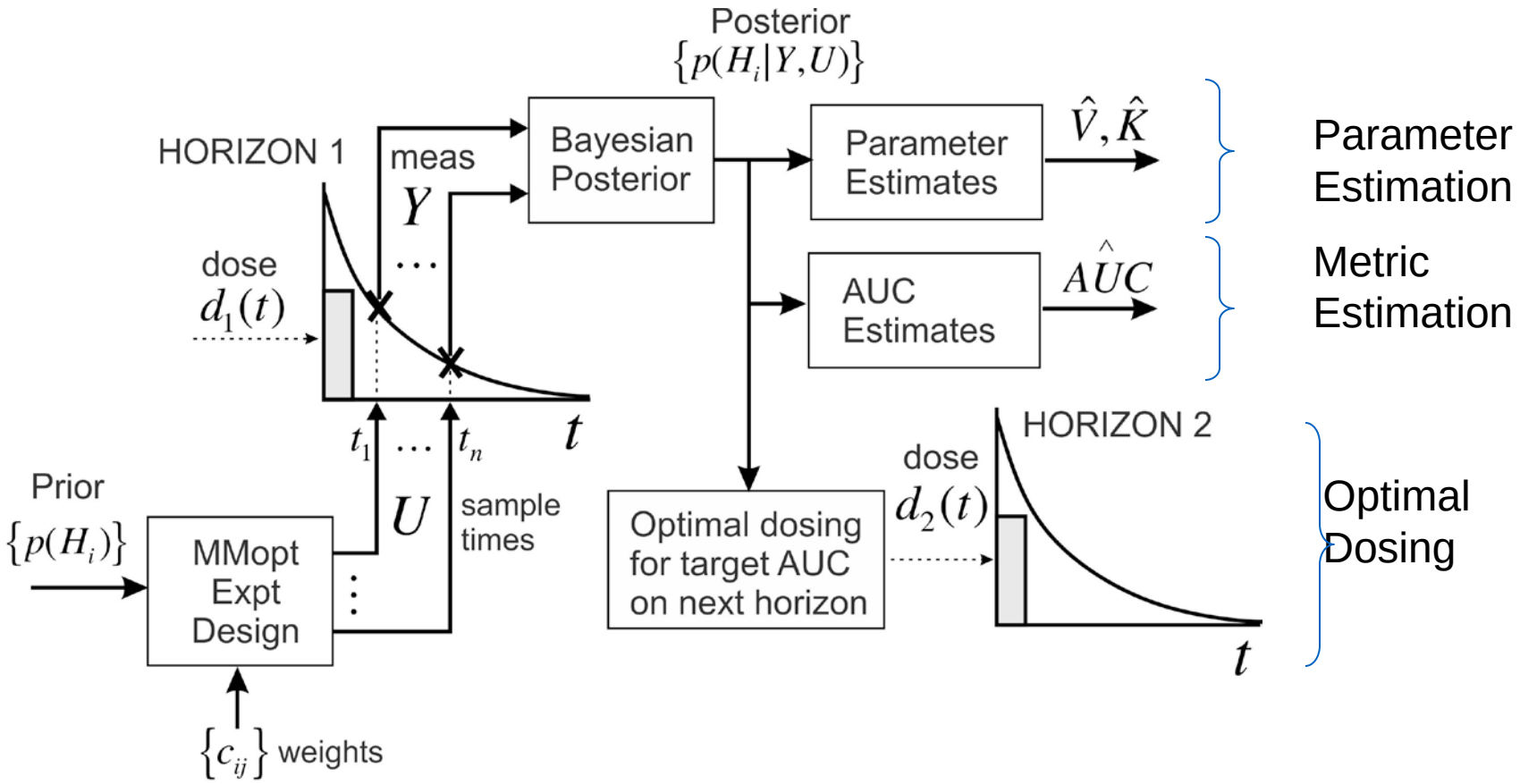
- Summary of optimal 1,2 and 3 sample designs applied to PK parameter estimation

Design Metric	Samples (hr)			Bayes Risk (prob)	99% conf (prob)
	1-Sample Design				
Bopt	4.25			0.5474	±0.0015
MMopt	4.25			0.5474	±0.0015
	2-Sample Design				
MMopt	1	9.5		0.2947	±0.0014
EDopt	1	24		0.3272	±0.0014
	3-Sample Design				
MMopt	1	1	10.5	0.2325	±0.0013
EDopt	1	1	24	0.2617	±0.0013

- **1 Sample Design: MMOpt performance equals Bayesian optimal design (both have Bayes Risk of 0.5474).**
- **MMOpt performance improves on EDopt design for 2 and 3 sample designs**
  - **2 Sample Design: Bayes Risk of 0.29 versus 0.33**
  - **3 Sample Design: Bayes Risk of 0.23 versus 0.26**
- **All results are statistically significant to p<0.0001**

Weighted MMOpt for AUC control

- Introduce weights $\{c_{ij}\}$ to specify a cost for each type of classification error
- Assign c_{ij} as the cost of mistaking truth subject i for subject j $(j \neq i)$
- Choice of weights tailors experiment design to desired applications of interest



Weighted MMOpt for AUC Control (2)

- Summary of optimal 1,2 and 3 sample designs applied to AUC control

Design Metric	Samples (hr)			RMS Error (AUC units)	99% conf (AUC units)
	1-Sample Design				
Bopt_C_1	12.5			3.6194	±0.0273
MMopt_C_1	14			3.7729	±0.0166
MMopt	4.25			16.7924	±0.1145
	2-Sample Design				
MMopt_C_1	1	13		2.1102	±0.0125
MMopt	1	9.5		2.2575	±0.0232
EDopt	1	24		2.6159	±0.0174
	3-Sample Design				
MMopt_C_1	1	10.25	10.25	1.6967	±0.0078
MMopt	1	1	10.5	1.9991	±0.0192
EDopt	1	1	24	2.4194	±0.0174

- **1 Sample Design: weighted MMOpt performance approximates that of the weighted Bayesian optimal design (RMS error of 3.62 versus 3.77 AUC units)**
- **MMOpt performance improves on EDopt design for 2 and 3 sample designs**
  - **2 Sample Design: RMS error of 2.11 versus 2.62 (units of AUC)**
  - **3 Sample Design: RMS error of 1.70 versus 2.42 (units of AUC)**
- **All results are statistically significant to p<0.0001**

Weighted MMOpt for AUC Control (3)

- **OBJECTIVE: Design an experiment most informative about next dose needed for patient to achieve a specified AUC of $\alpha_{des} = 40$**
  - **In this case MMopt weights are chosen as**

$$c_{ij} = \left(\frac{D_j}{V_i K_i} - \alpha_{des}\right)^2$$

$$= \text{Squared AUC error incurred if } j\text{'th subject's ideal dose } D_j \text{ is given to } i\text{'th subject}$$

#	Ideal Dose
1	409.8827
2	417.1242
3	238.6149
4	387.6442
5	462.1011
6	128.2311
7	443.2281
8	103.6267
9	378.3394
10	385.2965
Mean	335.4089
STD	35.8470

Ideal Doses $\{D_j\}$ to achieve desired AUC of $\alpha_{des} = 40$

	$j=1$	$j=2$	$j=3$	$j=4$	$j=5$	$j=6$	$j=7$	$j=8$	$j=9$	$j=10$
$i=1$	0	0.499	279	4.70	25.9	755	10.5	893	9.47	5.75
$i=2$	0.482	0	293	7.99	18.6	767	6.26	903	13.8	9.31
$i=3$	824	895	0	624	1403	342	1176	512	548	604
$i=4$	5.26	9.25	236	0	59.0	716	32.8	858	0.921	0.0586
$i=5$	20.4	15.1	374	41.5	0	835	2.66	962	52.5	44.2
$i=6$	771	8121	1185	6548	10846	0	9654	58.9	6086	6430
$i=7$	9.05	5.54	340	25.1	2.90	808	0	939	34.2	27.3
$i=8$	13975	14643	2715	12019	19147	90.1	17184	0	11244	11821
$i=9$	11.1	16.8	218	0.967	78.4	699	47.0	843	0	0.541
$i=10$	6.51	10.9	231	0.0594	63.5	712	36.1	855	0.521	0

Matrix of Weights $\{c_{ij}\}$