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

Listening to the patient,

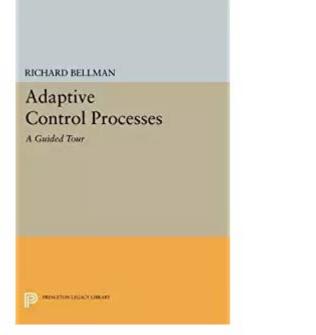
Setting and hitting an individualized specific point target goal,

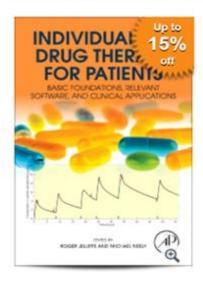
at target time - NOT just being in a "therapeutic range",

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.





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Individualized Drug Therapy for Patients, 1st Edition Basic Foundations, Relevant Software and Clinical Applications

> 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.
- <u>Multiple discrete support points, one for each patient, with any distribution!</u>
- A finite, (NOT continuous!) <u>collection, (no summary!)</u> of <u>each patient's</u>
- <u>exactly known</u> parameter values.

One can never do better than that. <u>That</u> is the unattainable ideal. Nonparametric (NP) models approach this ideal <u>pretty closely</u>. What do they look like?

Wikipedia: definition of "Nonparametric Method"

Nonparametric (NP) statistics do not <u>require</u> that the population data <u>meet the assumptions necessary</u>

for parametric statistics.

NP statistics describe <u>unconstrained distributions</u> of <u>any</u> shape.

(Occam's razor fewest assumptions are best)

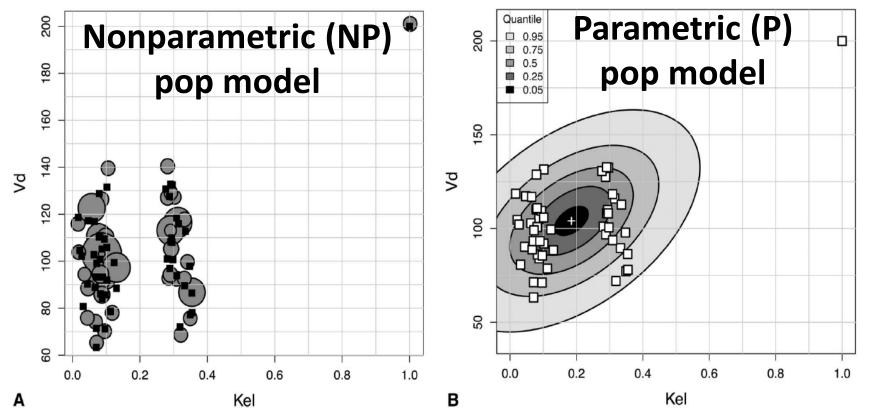
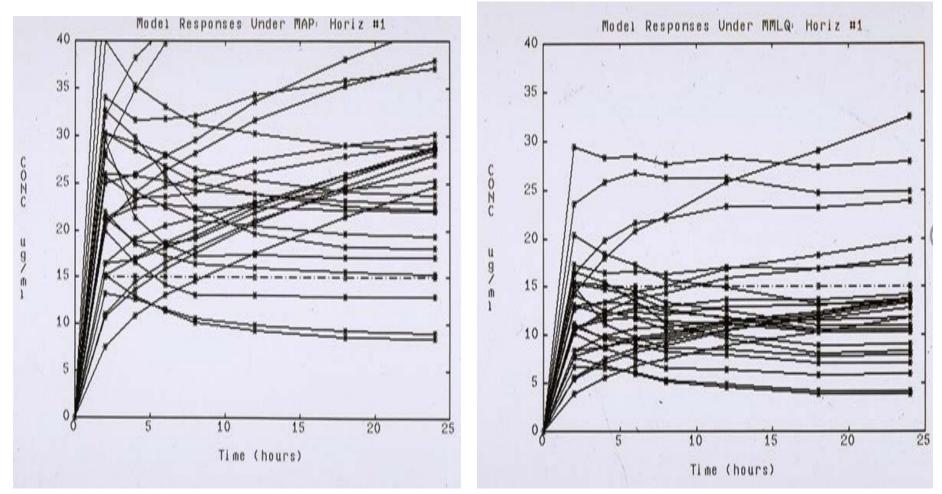


FIGURE 2. A, Results of the NPAG fit. True parameter values from the simulated population are shown as black squares, with NPAG support points shown as circles whose size is an approximate multiple of the size of 1 square, proportionally increased according to the probability of each NPAG point. B, Results 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 <u>multiple models</u> are all the <u>support points</u> in the NP popmodel. Each point has its own unique parameter values and probability.
- 2. Apply a <u>candidate</u> dosage regimen to all support points. Each point has its own unique response to that same dose.
- 3. <u>Compare each response with your target goal.</u> 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. <u>Find the regimen</u> 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 <u>NP Bayesian (NPB) posterior</u> <u>models</u> for an individual patient's subsequent management and <u>MM</u> <u>dosage adjustment.</u>

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

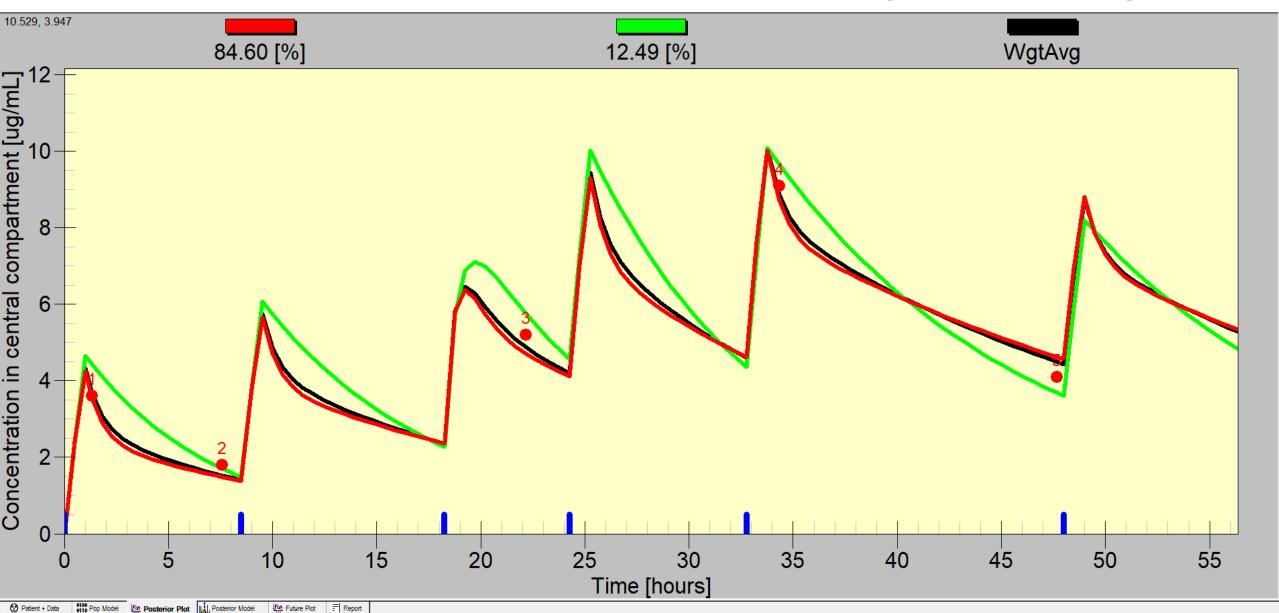
Those NP support points with parameter values predicting the TDM data well become more probable.

Those predicting poorly become less probable.

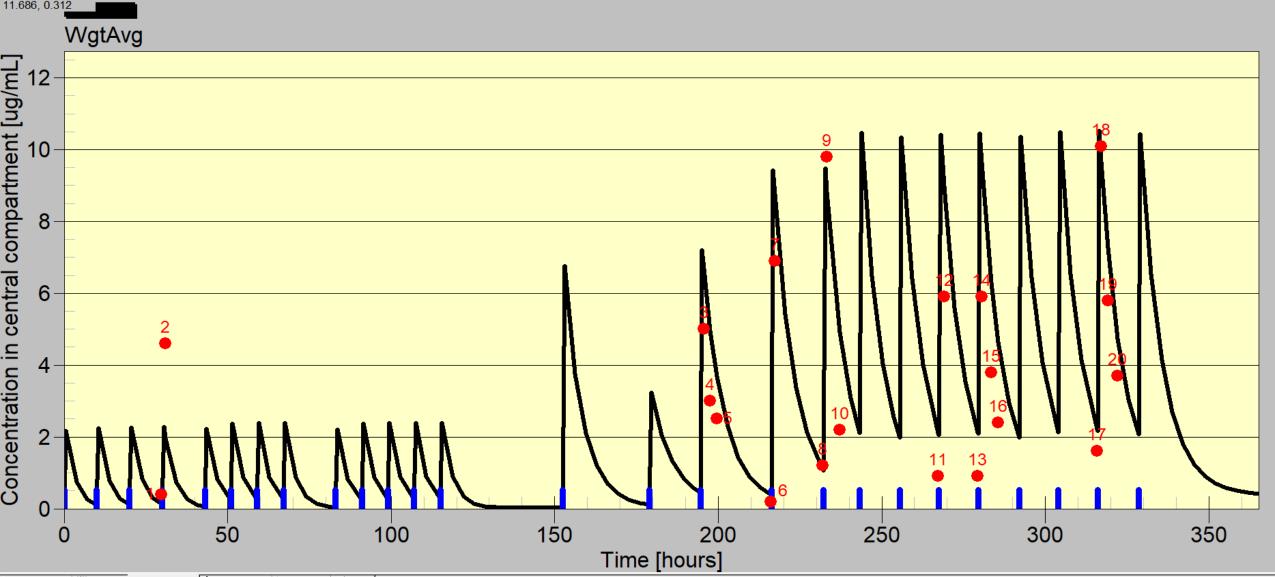
We get the revised Bayesian posterior probability of <u>all</u> the NP pop model support points given the pop model and that patient's TDM data.

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

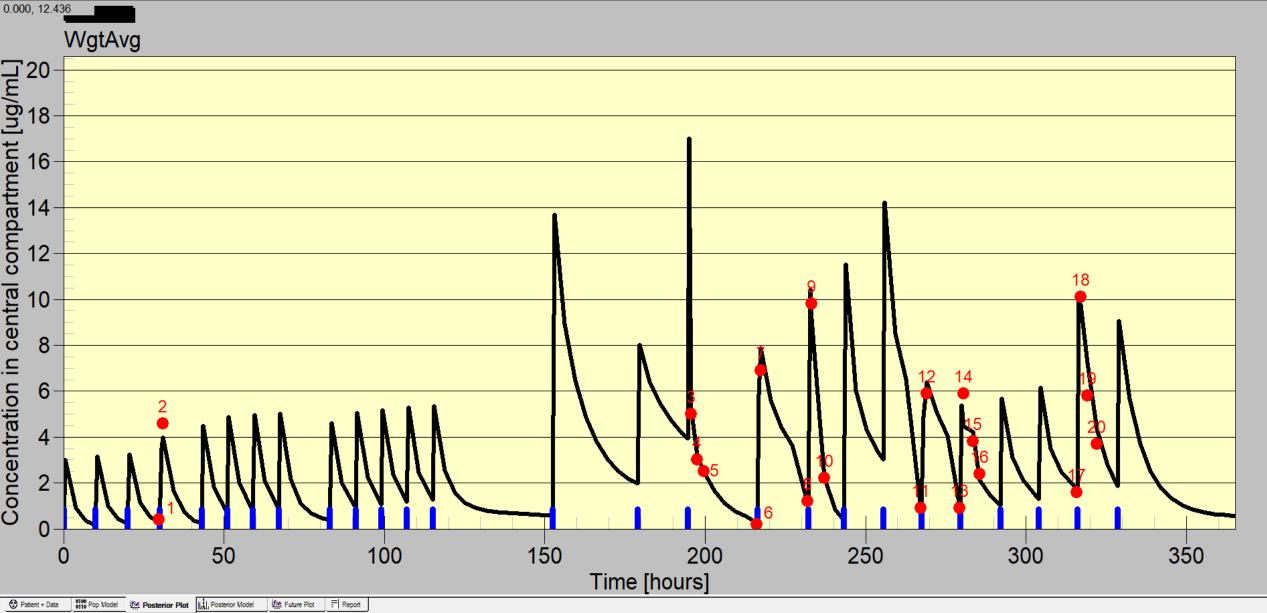
NPB posterior gent model estimates - significant posterior model support points, and overall weighted average



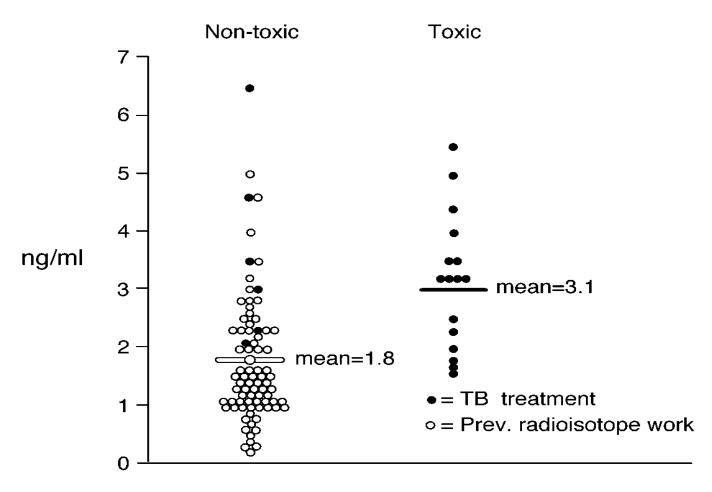
A highly unstable tobramycin patient, with high intra – individual variability. NP Bayesian weighted average fit, fixed parameter values throughout. <u>A very poor fit!</u>



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

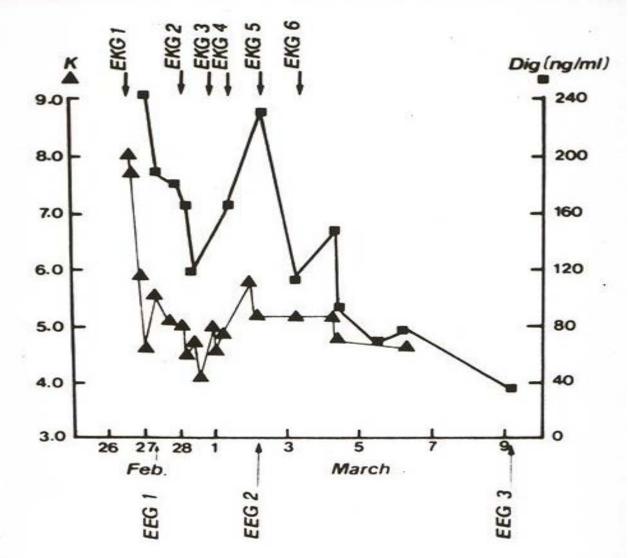


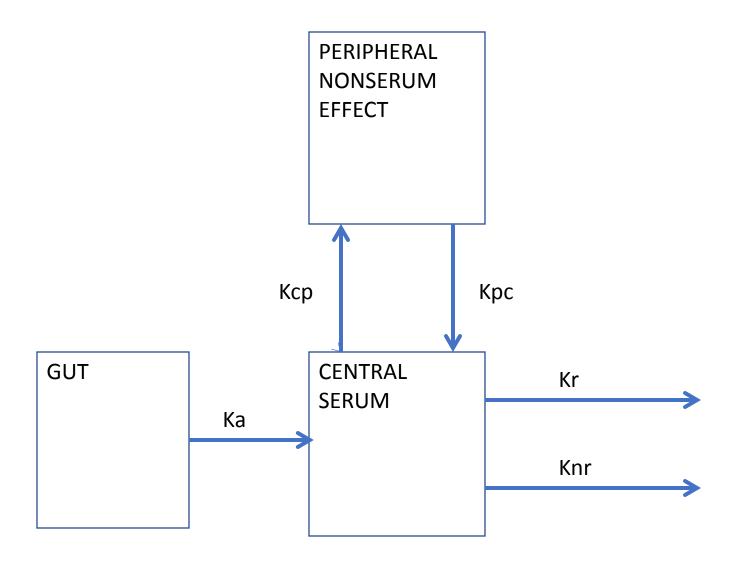
SERUM DIGOXIN LEVELS



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 <u>NOT</u> toxic.

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





🚾 MM-USC*PACK - [bill nicholson's - Digoxin_II]

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27 PO 07/02/87 18:00:00 514.00 75.00 99.19 0.000 24.00 0.00 250.00 260.00 28 PO 07/03/87 18:00:00 532.00 75.00 99.19 0.000 24.00 0.00 250.00 AF 29 PO 07/04/87 18:00:00 562.00 75.00 99.19 0.000 15.25 0.00 250.00 AF 30 IV 07/05/87 09.15:00 577.25 75.00 99.19 0.100 3.42 2500.00 250.00 31 IV 07/05/87 12:40:00 580.67 75.00 99.19 0.100 3.58 2500.00 250.00 32 IV 07/05/87 16:15:00 584.25 75.00 99.19 0.100 5.00 250.00 250.00 3.00 33 IV 07/05/87 21:15:00 589.25 75.00 99.19 0.100 8.25 2500.00 250.00 RSR 34 PO 07/06/87 12:55:00 604.92 75.00 99.19 0.100<	26	IV	07/01/87	15:30:00	487.50	75.00	99.19	0.100	26.50	2500.00	250.00	RSR		
29 PO 07/04/87 18:00:00 562.00 75.00 99.19 0.000 15.25 0.00 250.00 AF 1 30 IV 07/05/87 09:15:00 577.25 75.00 99.19 0.100 3.42 2500.00 250.00 4F 1 31 IV 07/05/87 12:40:00 580.67 75.00 99.19 0.100 3.58 2500.00 250.00 1 1 32 IV 07/05/87 16:15:00 584.25 75.00 99.19 0.100 5.00 250.00 250.00 1 1 33 IV 07/05/87 16:15:00 584.25 75.00 99.19 0.100 8.25 2500.00 250.00 RSR 1 34 PO 07/06/87 05:30:00 597.50 75.00 99.19 0.000 7.42 0.00 0.00 RSR 1 1 35 IV 07/06/87 12:55:00 604.92 75.00 99.19 0.100 19.08 2500.00 250.00 250.00 1 1 <td>27</td> <td>PO</td> <td>07/02/87</td> <td>18:00:00</td> <td></td> <td>75.00</td> <td>99.19</td> <td>0.000</td> <td>24.00</td> <td>0.00</td> <td>250.00</td> <td>Non</td> <td></td> <td></td>	27	PO	07/02/87	18:00:00		75.00	99.19	0.000	24.00	0.00	250.00	Non		
30 IV 07/05/87 09:15:00 577.25 75.00 99.19 0.100 3.42 2500.00 250.00 4 4 31 IV 07/05/87 12:40:00 580.67 75.00 99.19 0.100 3.58 2500.00 250.00 <t< td=""><td>28</td><td>PO</td><td>07/03/87</td><td>18:00:00</td><td></td><td>75.00</td><td>99.19</td><td>0.000</td><td>24.00</td><td>0.00</td><td></td><td></td><td></td><td></td></t<>	28	PO	07/03/87	18:00:00		75.00	99.19	0.000	24.00	0.00				
30 IV 07/05/87 09:15:00 577.25 75.00 99.19 0.100 3.42 2500.00 250.00 4 4 31 IV 07/05/87 12:40:00 580.67 75.00 99.19 0.100 3.58 2500.00 250.00 <t< td=""><td>29</td><td>PO</td><td>07/04/87</td><td>18:00:00</td><td></td><td></td><td>99.19</td><td>0.000</td><td>15.25</td><td>0.00</td><td>250.00</td><td>AF</td><td></td><td></td></t<>	29	PO	07/04/87	18:00:00			99.19	0.000	15.25	0.00	250.00	AF		
32 IV 07/05/87 16:15:00 584.25 75.00 99.19 0.100 5.00 2500.00 250.00 RSR 33 IV 07/05/87 21:15:00 589.25 75.00 99.19 0.100 8.25 2500.00 250.00 RSR 1 34 PO 07/06/87 05:30:00 597.50 75.00 99.19 0.000 7.42 0.00 0.00 RSR 1 35 IV 07/06/87 12:55:00 604.92 75.00 99.19 0.100 19.08 2500.00 250.00 1 1	30	IV	07/05/87	09:15:00		75.00	99.19	0.100	3.42	2500.00	250.00			
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35 IV 07/06/87 12:55:00 604.92 75.00 99.19 0.100 19.08 2500.00 250.00												RCP		
												N.SIN		
	35	IV	07/06/87	12:55:00	604.92	75.00	99.19	0.100	19.08	2500.00	250.00			~
				1				1		1 1	1			
Patient + Data 👬 Pop Model 💯 Posterior Plot 📊 Posterior Model 💯 Future Plot 📄 Report	Patient + Data	etee ette Pop Mor	del 🔯 Post	terior Plot	sterior Model	🖗 Future F	Plot 🗐 Rep	ort						

A phone consult – doses, history, response

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MM-USC*PACK - [bill nicholson's - Digoxin_II]

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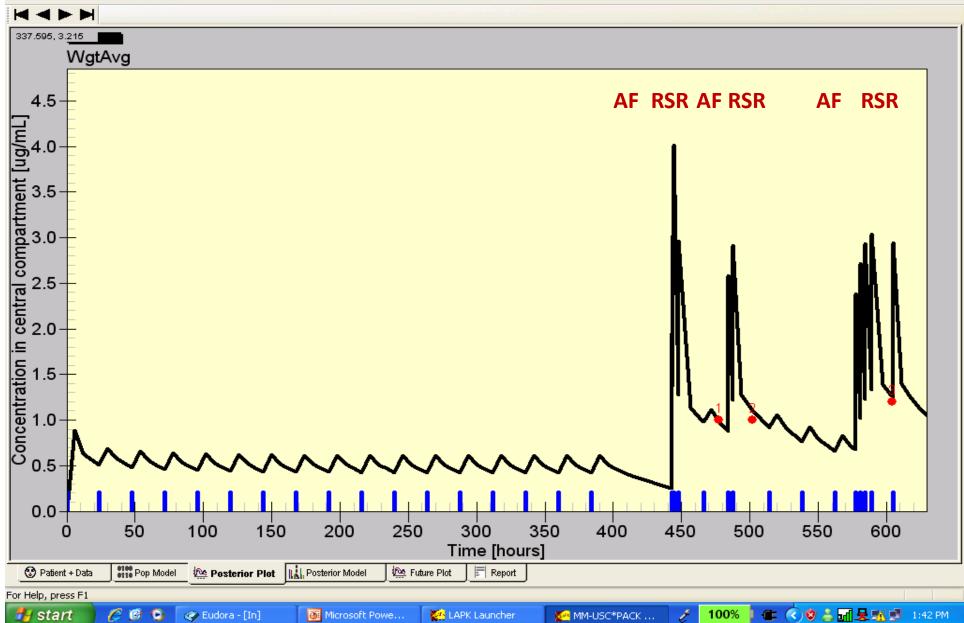
Filename	C:\MMLQ2\patients\BILLSPT.MB						75.00 kg	Ethnicity N	Not in use	Time of I	first dose 06/	/11/87 08:00:	00
Chart Number 123					Height	68.00 in	Gender	Male	Time of	next dose 07/	/07/87 07:59:	59	
First Name	digoxin pt		Last Name bill nic	holson's		Birth Date	06/10/29	58 years	Dialysis pa	itient NO	Most recer	nt CCr 99.1	9
22	IV	06/29/87	23:30:00	447.50	75.00	99.19	0.100	9.00	2500.00	250.00			
23	PO	06/30/87	08:30:00	456.50	75.00	99.19	0.000	9.50	0.00	0.00			
24	PO	06/30/87	18:00:00	466.00	75.00	99.19	0.000	18.17	0.00	250.00			
25	IV	07/01/87	12:10:00	484.17	75.00	99.19	0.100	3.33	2500.00	250.00			
26	IV	07/01/87	15:30:00	487.50	75.00	99.19	0.100	26.50	2500.00	250.00			
27	PO	07/02/87	18:00:00	514.00	75.00	99.19	0.000	24.00	0.00	250.00			
28	PO	07/03/87	18:00:00	538.00	75.00	99.19	0.000	24.00	0.00	250.00			
29	PO	07/04/87	18:00:00	562.00	75.00	99.19	0.000	15.25	0.00	250.00			
30	IV	07/05/87	09:15:00	577.25	75.00	99.19	0.100	3.42	2500.00	250.00			
31	IV	07/05/87	12:40:00	580.67	75.00	99.19	0.100	3.58	2500.00	250.00			
32	IV	07/05/87	16:15:00	584.25	75.00	99.19	0.100	5.00	2500.00	250.00			
33	IV	07/05/87	21:15:00	589.25	75.00	99.19	0.100	8.25	2500.00	250.00			
34	PO	07/06/87	05:30:00	597.50	75.00	99.19	0.000	7.42	0.00	0.00			
35	IV	07/06/87	12:55:00	604.92	75.00	99.19	0.100	19.08	2500.00	250.00			
Level		Date	Time	Time	After dose	After dose				Conc.			\square
Number]		[locale]	[hh:mm:ss]	[Hours]	[Number]	[Hours]				[ug/mL]			
1		07/01/87	05:15:00	477.25	24	11.25				1.0000			
2		07/02/87	05:50:00	501.83	26	14.33				1.0000	RSF	X	
3		07/06/87	12:00:00	604.00	34	6.50				1.2000		RSR	
SCr		Date	Time	Time	After dose	After dose				Conc.			
Number]		[locale]	[hh:mm:ss]	[Hours]	[Number]	[Hours]				[mg/dL]			
1		06/11/87	08:00:00	0.00	1	0.00				0.8000			~
)[1	1	1111							l	>
Patient + Dat	ta 0100 Pop Mo	del 💆 Poste	rior Plot	sterior Model	Euture 🗠	Plot 📕 Reg	ort						

Phone consult – TDM serum concs., response

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🎦 MM-USC*PACK - [bill nicholson's - Digoxin_II]

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

🎦 MM-USC*PACK - [bill nicholson's - Digoxin_II]

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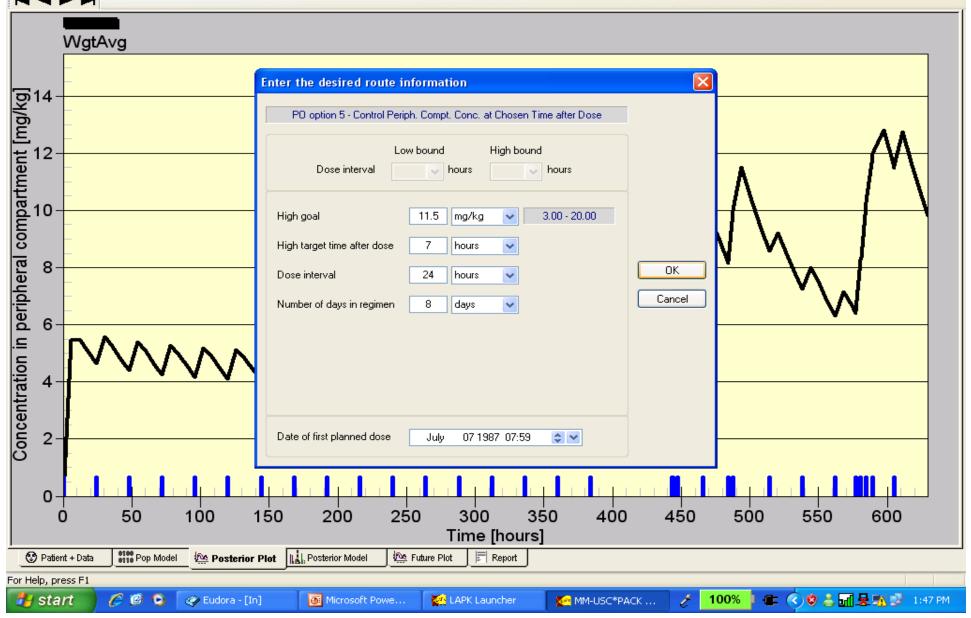
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Phone consult – NP Bayesian posterior – periph. concentrations, response.

🔄 MM-USC*PACK - [bill nicholson's - Digoxin_II]

<u>File Edit Vi</u>ew Patient Popmodel <u>T</u>ask Plot Effe<u>c</u>t <u>Sphere A</u>dvanced <u>Wi</u>ndow <u>H</u>elp





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Setting target goals and regimen format

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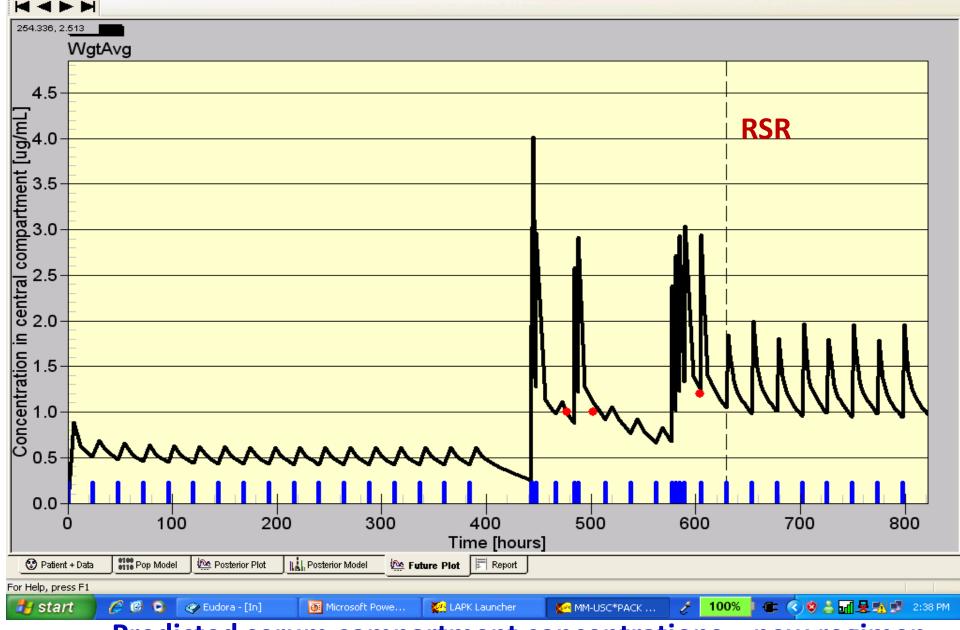
🕑 Patient		op Model 🛛 🖾	Posterior Plot	Posterior I		Future Plot		
	Control Co	Future Su	ummary (Seru	ım Concentr	-	ral Comparts	nont	
8	175.00	11.50	11.50	0.00	1.33			
7	151.00		11.50	0.00	1.33			
6	127.00		11.50	0.00	1.33			
5	103.00		11.50	0.00	1.33			
4	79.00		11.50	-0.00	1.33			
3	55.00		11.50	0.00	1.33			
2	31.00		11.50	-0.00	1.34			
1	7.00		11.50	-0.00	1.32			
Goal #	Time [h]		WgtAvg	Diff	Central			
8	07/14/87	07:59:59	572.1483	7.6286	251.55	2013.42		
	07/13/87	07:59:59	572.2098 573.4492	7.6295	251.55	1761.87		
6 7	07/12/87 07/12/87	07:59:59	572.2949 572.2009	7.6306	251.55	1510.31		
5	07/11/87	07:59:59	572.4122	7.6322	251.54	1258.77		
4	07/10/87	07:59:59	572,5869	7.6345	251.54	1007.22		
3	07/09/87 07/09/87	07:59:59	572.5722	7.6343	251.53	755.68		
2	07/08/87	07:59:59	578.0461	7.7073	251.46	504.15		
1	07/07/87	07:59:59	468.5609	6.2475	252.69	252.69		
	070707	07.50.50	[mg]	[mg/kg]	[ug/mL]	[ug/mL]		
Dose #	Date	Time	Dose	Dose	AUC	Total AUC		
ojFunc	213.3952	AUC 2	2013.42					
oal 1 ime 1	11.50 [mg/kg] 7.00 [hours]							
lanning Fi oute	Iture Therapy PO Option 5 -	Control Periph. (Compt. Conc. at	Chosen Time	after Dose			
			1.00	0.00	12.10	0.02	0.02	
0.83	2.95	1.05	1.20	5.98	12.00	9.82	9.82	
0.80	3.04	1.25	1.26	5.70	12.80	11.64	10.50	
0.75	2.72	1.02	2.72	5.39 5.46	0.30 10.30	10.27	0.30 10.30	
0.73 0.75	2.38 2.72	0.68 1.02	2.38 2.72	5.34 5.39	6.48 8.36	6.39 8.27	6.48 8.36	
0.70		0.66	0.71	5.33	7.14	6.30	6.68	
0.72	0.83	LLEE						

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

🚰 MM-USC*PACK - [bill nicholson's - Digoxin_II]

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Predicted serum compartment concentrations – new regimen

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🚰 MM-USC*PACK - [bill nicholson's - Digoxin_II]

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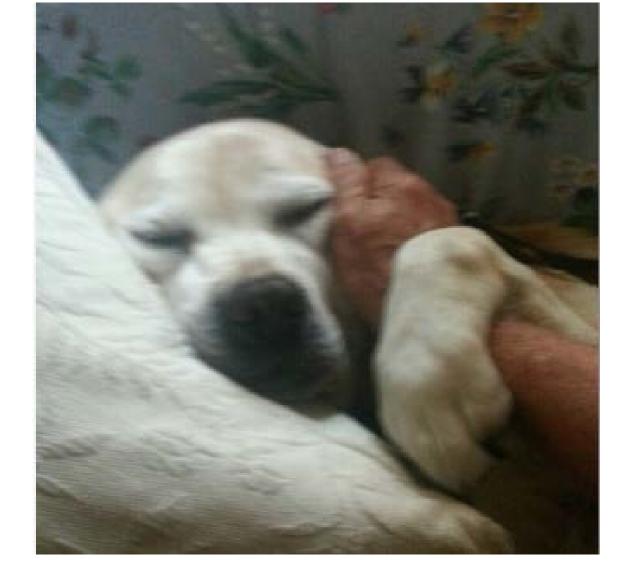


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Predicted peripheral compartment concentrations – new regimen

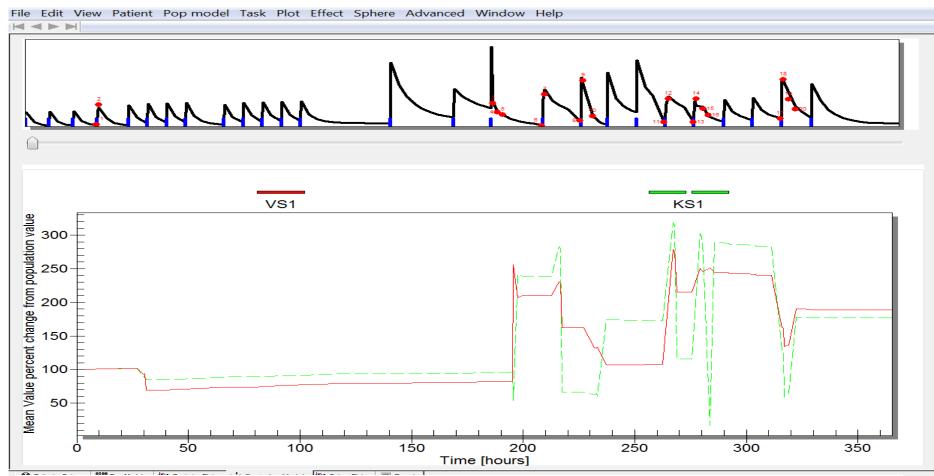
Things the industry and the FDA can do to educate and encourage clinicians to treat patients as individuals, and with maximal precision.

- 1. Use, and publish or make available, <u>NP</u> 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. <u>Advocate setting a specific point target for each patient</u>. 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 <u>bedside</u> software. Been here <u>for years.</u> Use the new industry NP models for maximally precise <u>individualized therapy and safety.</u>
- 5. Advocate <u>tracking drugs in acutely ill, highly variable patients having changing model</u> <u>parameters over time, using interacting multiple model (IMM) tracking and analysis.</u>
- 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?



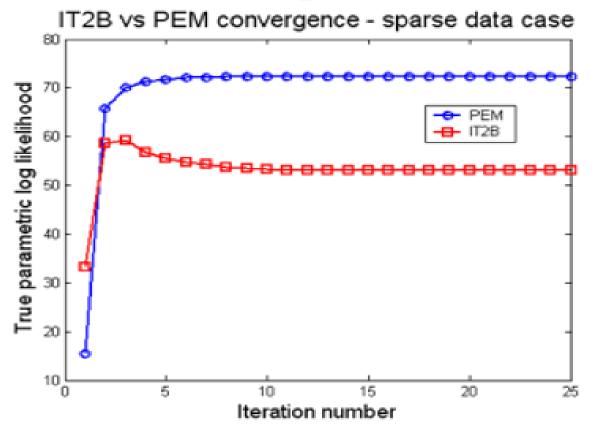
Our sweet dog Diamond would have said, "Thanks so much, FDA, for organizing this needed and provocative workshop, and thanks, all of you, for coming, and for your thoughtful attention!"

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 (interoccasional) 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 <u>estimation of target</u> <u>trajectories</u> in the controlled area and their prediction into the near future".*

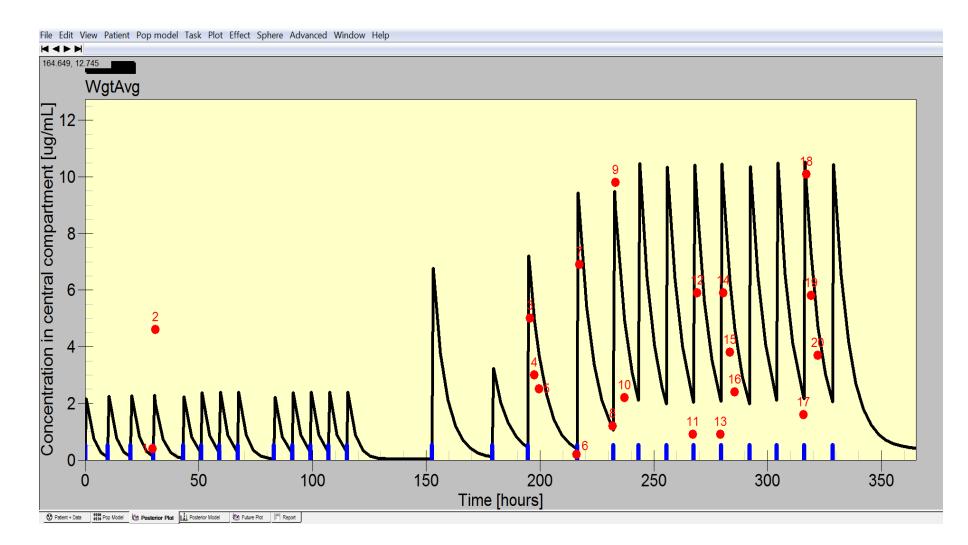
* E. MAZOR Technion, Israel Institute of Technology, A. AVERBUCH Tel Aviv University, Y. BAR-SHALOM, Fellow, IEEE University of Connecticut, J. DAYAN Technion, Israel Institute of Technology

Interacting Multiple Model Methods in Target Tracking: A Survey.

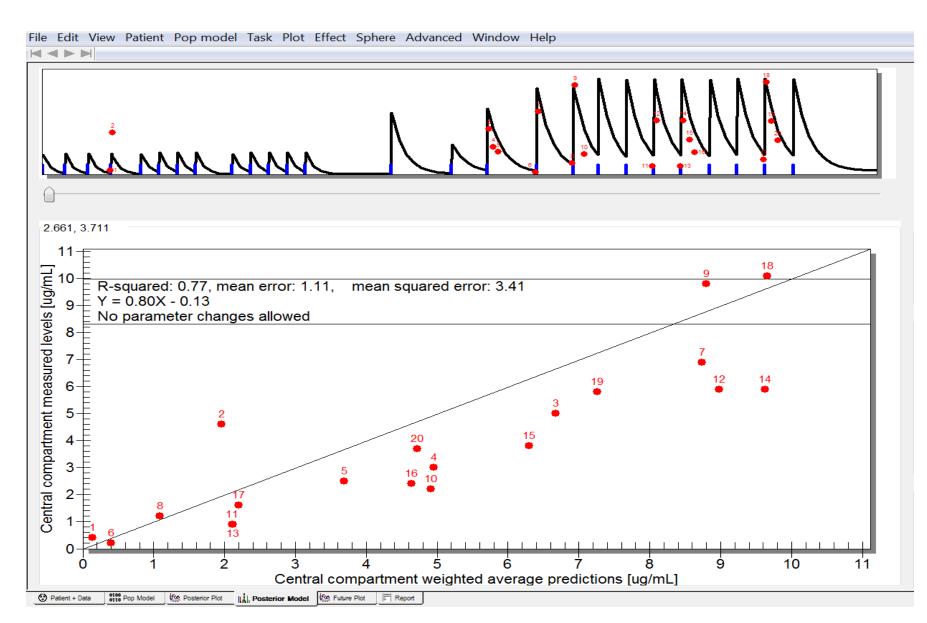
IEEE TRANSACTIONS ON AEROSPACE AND ELECTRONIC SYSTEMS VOL. 34, NO. 1 JANUARY 1998.

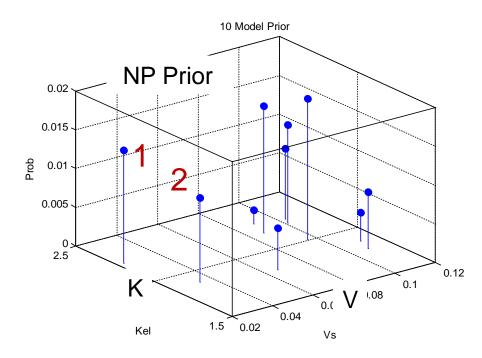
Bayard D, and Jelliffe R: A Bayesian Approach to Tracking Patients Having Changing Pharmacokinetic Parameters. J. Pharmacokin. Pharmacodyn. 31 (1): 75-107, 2004.

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.

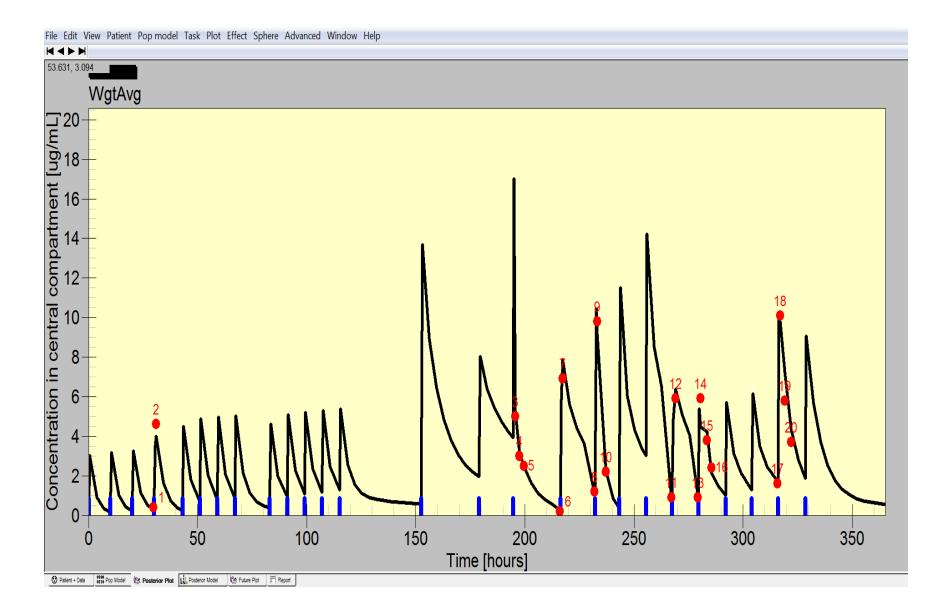
Before swap, Point 1 always has parameters V1, K1, conc is Amt 1/V1 Point 2 always has parameters V2, K2, conc is Amt 2/V2

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.

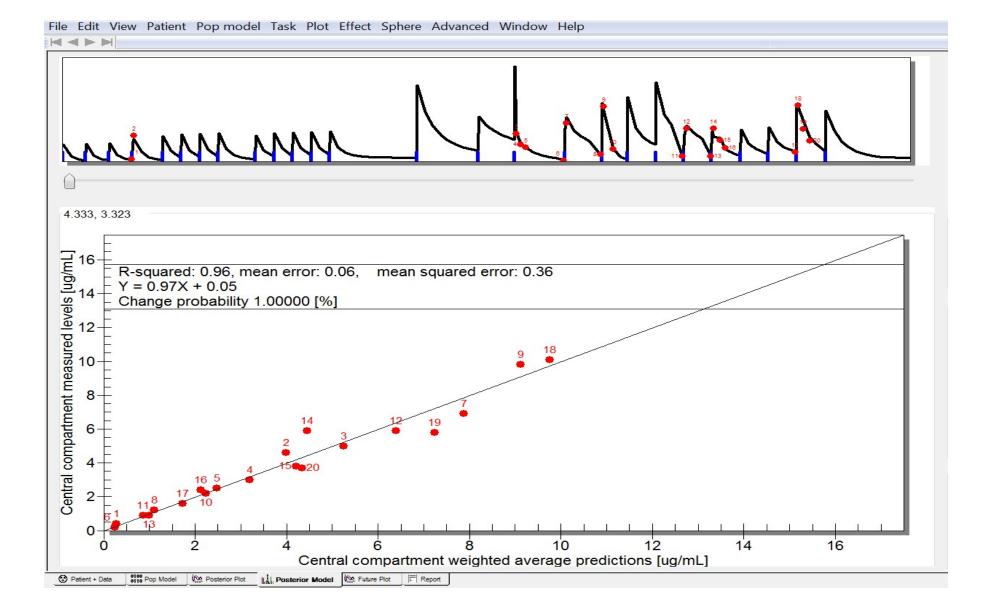
This is how drug amounts can change their parameter values over time.

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

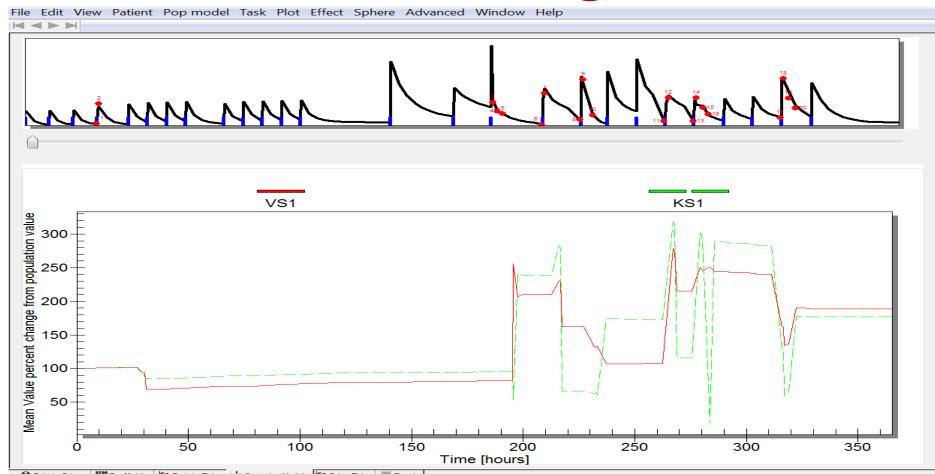
IMM – much better tracking



IMM - better estimated vs measured



IMM – V and K change over time



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 <u>distinct and separate therapeutic</u> issue.**

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. <u>Plan</u> 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!

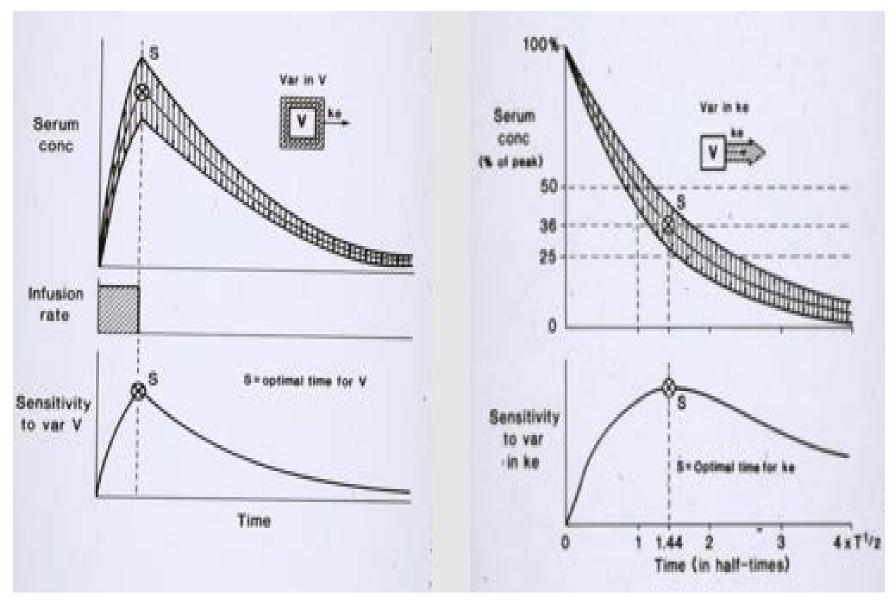
Use D-optimal or MM-opt design. There is an optimal sampling time to

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.

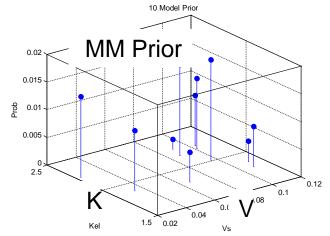
D and MM Optimal Sampling



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 classification theory.
 - 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</u> <u>missclassification</u> (Duda et. al.).

Model Response Separation r(t)

0.8

0.6

0.4

0.2

Model Responses

r(t) = response separation

Model 1 Reponse

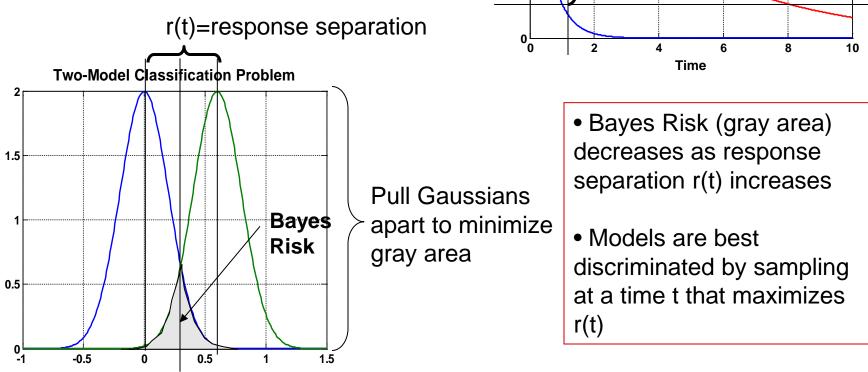
Model 2 Response

• 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



Unweighted MMOpt for PK Estimation

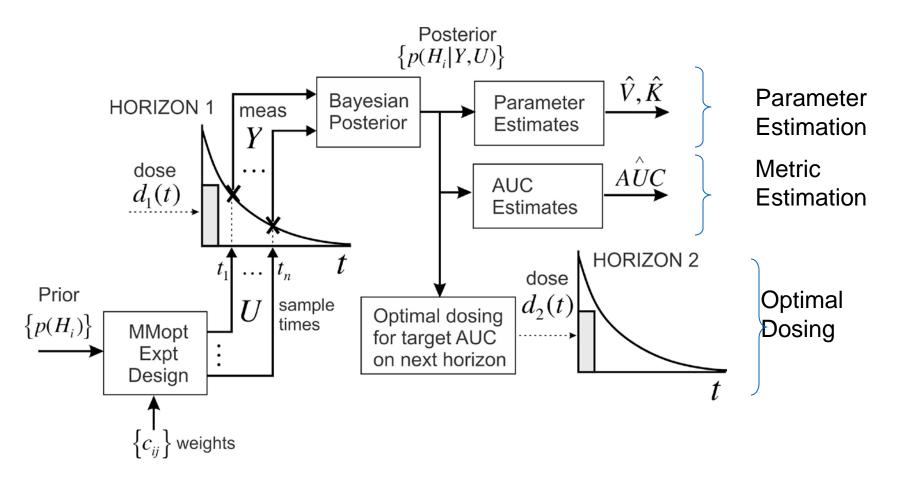
• Summary of optimal 1,2 and 3 sample designs applied to PK parameter estimation

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

- <u>1 Sample Design</u>: 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
 - <u>2 Sample Design</u>: Bayes Risk of 0.29 versus 0.33
 - <u>3 Sample Design</u>: 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			RMS Error	99% conf
	(hr)			(AUC units)	(AUC units)
	1-Se	ample D	esign		
$Bopt_C_1$	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-Sc	ample D	Pesign		
$MMopt_C_1$	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

- <u>1 Sample Design</u>: 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
 - <u>2 Sample Design</u>: RMS error of 2.11 versus 2.62 (units of AUC)
 - <u>3 Sample Design</u>: 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

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

#	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

=	Squared AUC error incurred if j 'th subject's
	ideal dose D_j is given to <i>i</i> 'th subject

	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

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

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