

Multiple Model Adaptive Bayesian Dosing Control

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Professor of Pediatrics and Clinical Scholar

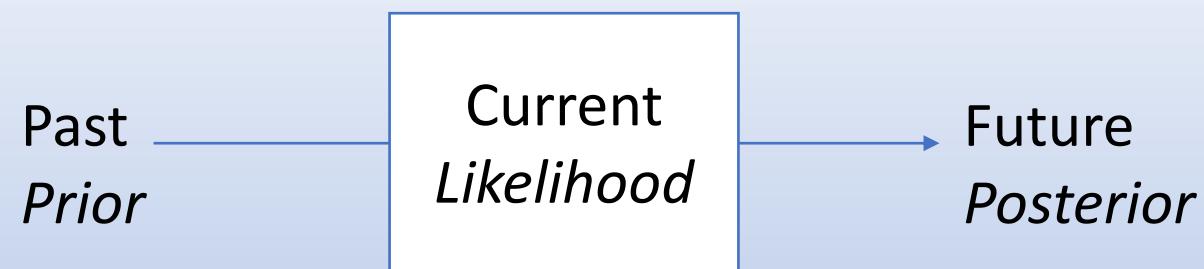
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Objectives

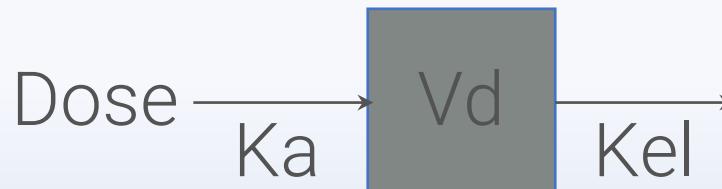
- To understand Multiple Model Bayesian adaptive control and differences from MAP Bayesian control
- To explore cases and studies with Multiple Model Bayesian Adaptive Control of dosing
- To be aware of different Multiple Model approaches to unstable or particularly unusual patients

Bayes' Theorem

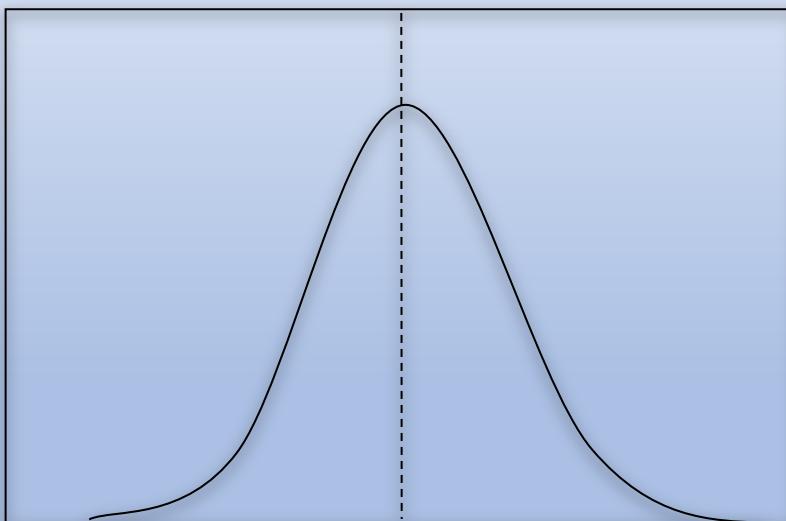


Bayesian Control

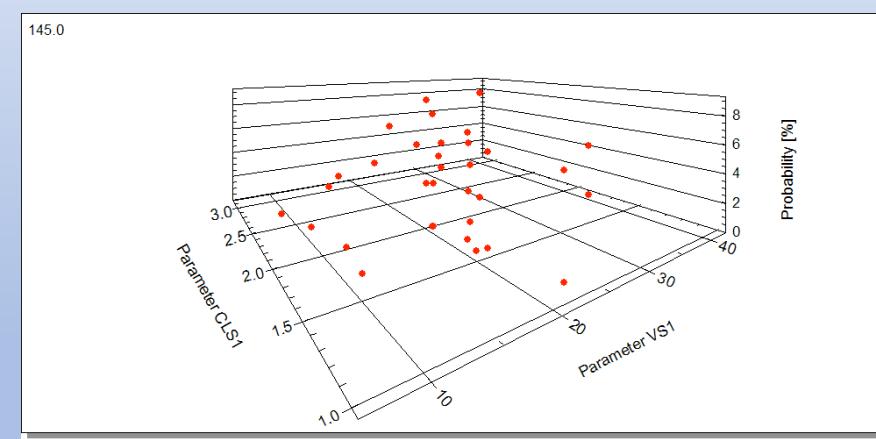
Begin with a model



Parametric

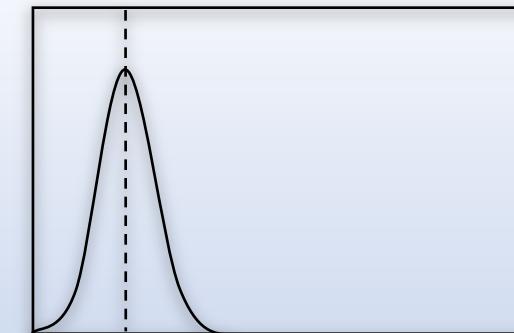
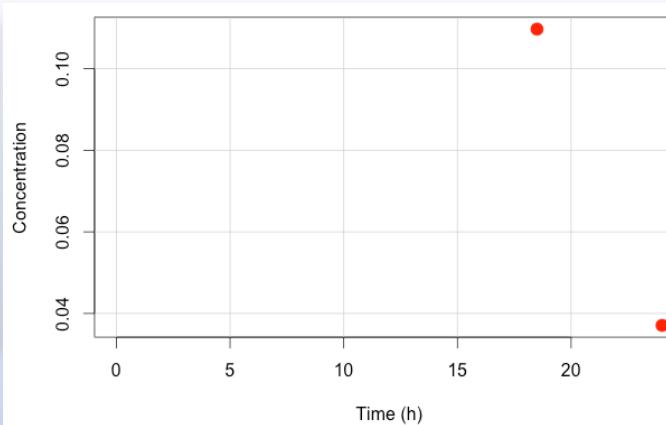
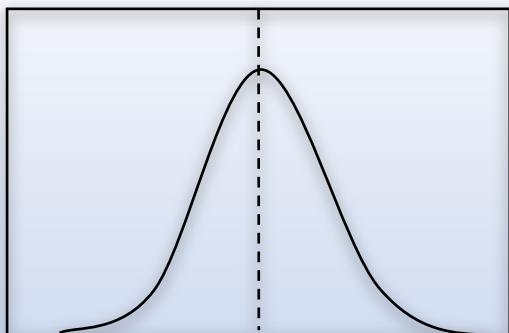


Nonparametric



Use the model

The parametric approach



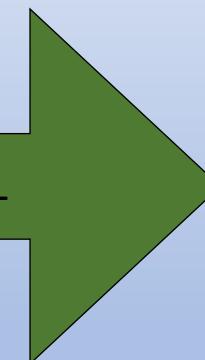
Population CL

Data

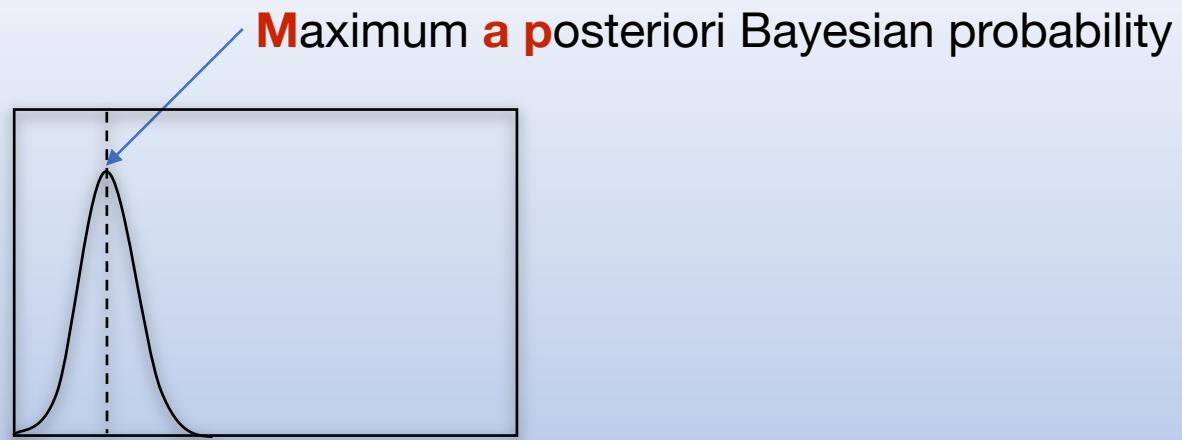
Individual CL

Bayesian Prior

Bayesian Posterior



MAP-Bayesian Parametric model



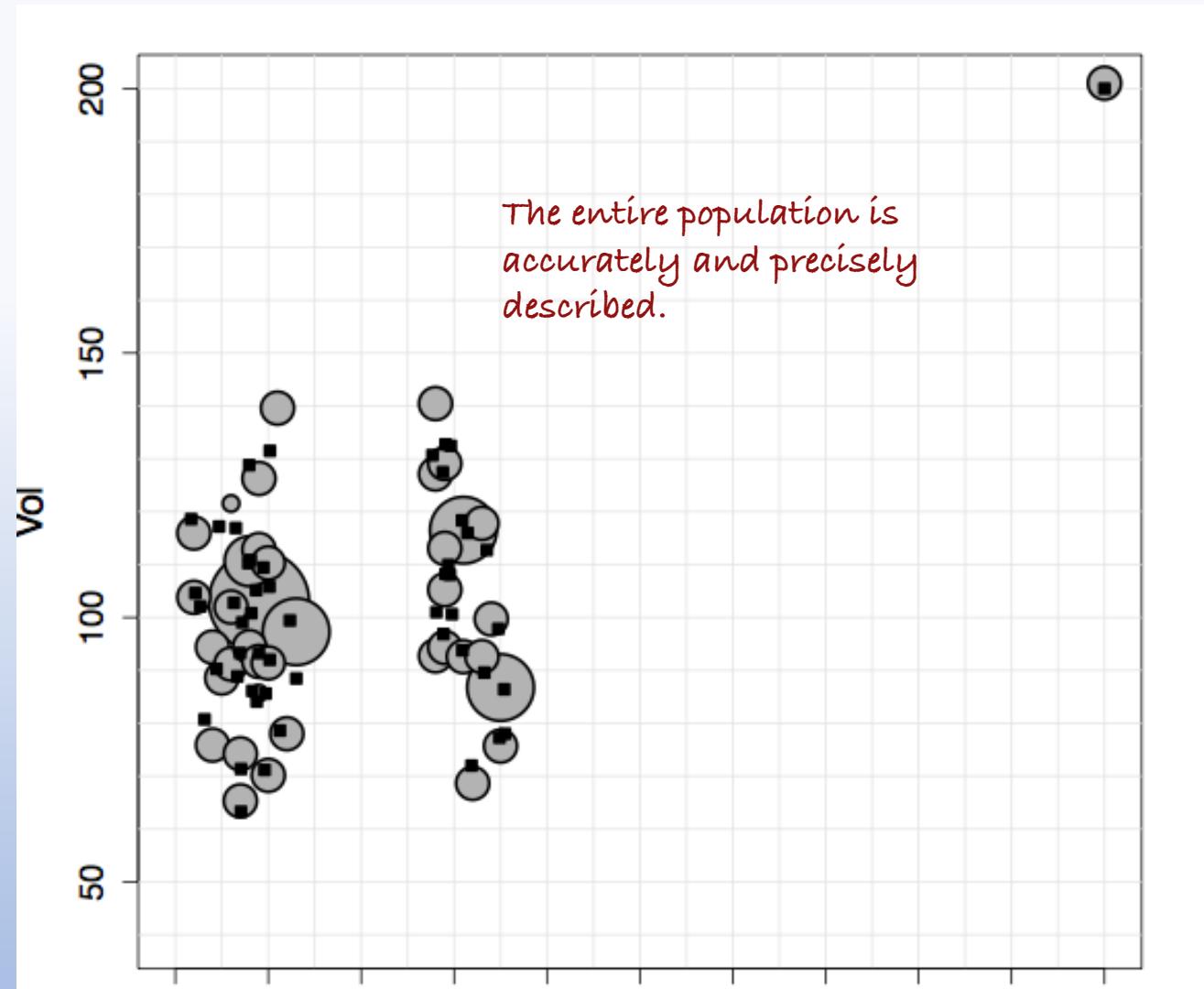
One version of the patient
Shrinkage towards population mean with sparse sampling
No probability of future success vs. failure

Non-Normal Populations

Simulated population (■)

Non-parametric estimation of population values (●)

Size proportional to probability

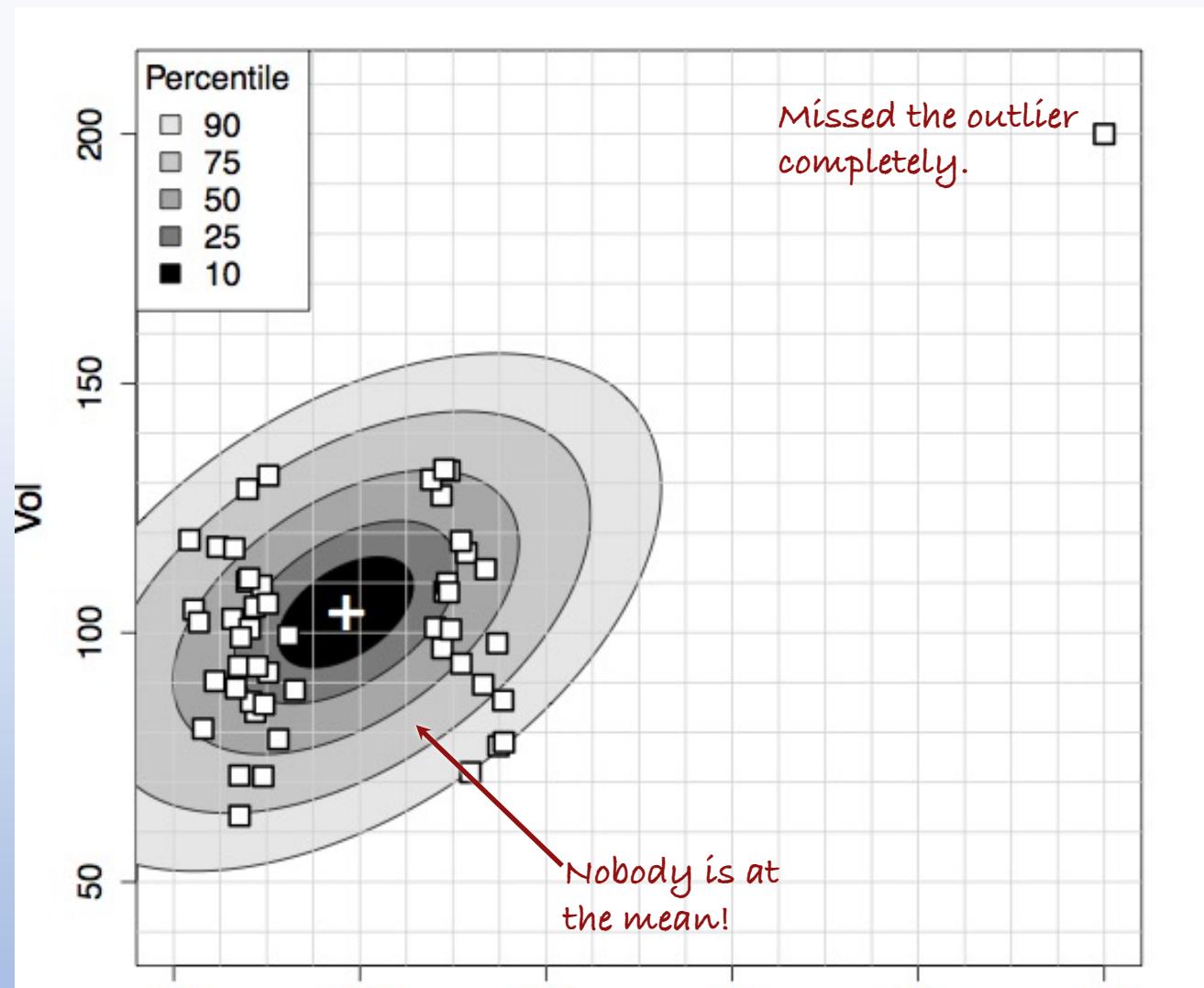


Neely MN, van Guilder MG, Yamada WM, Schmitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit. 2012;34(4):467–476.

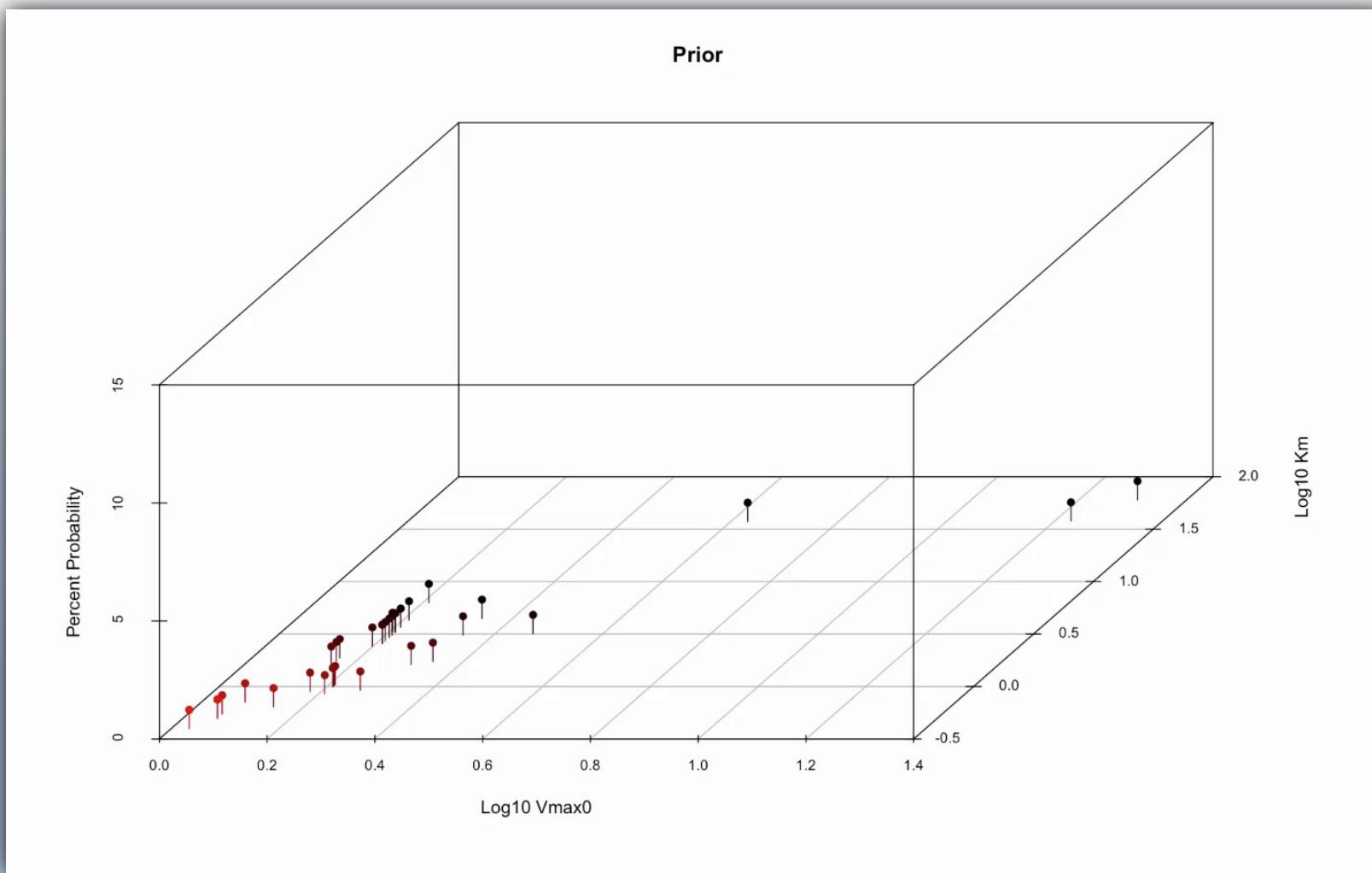
Non-Normal Populations

Simulated population ()

Mean (+) and percentile distributions of parametric population parameter estimates

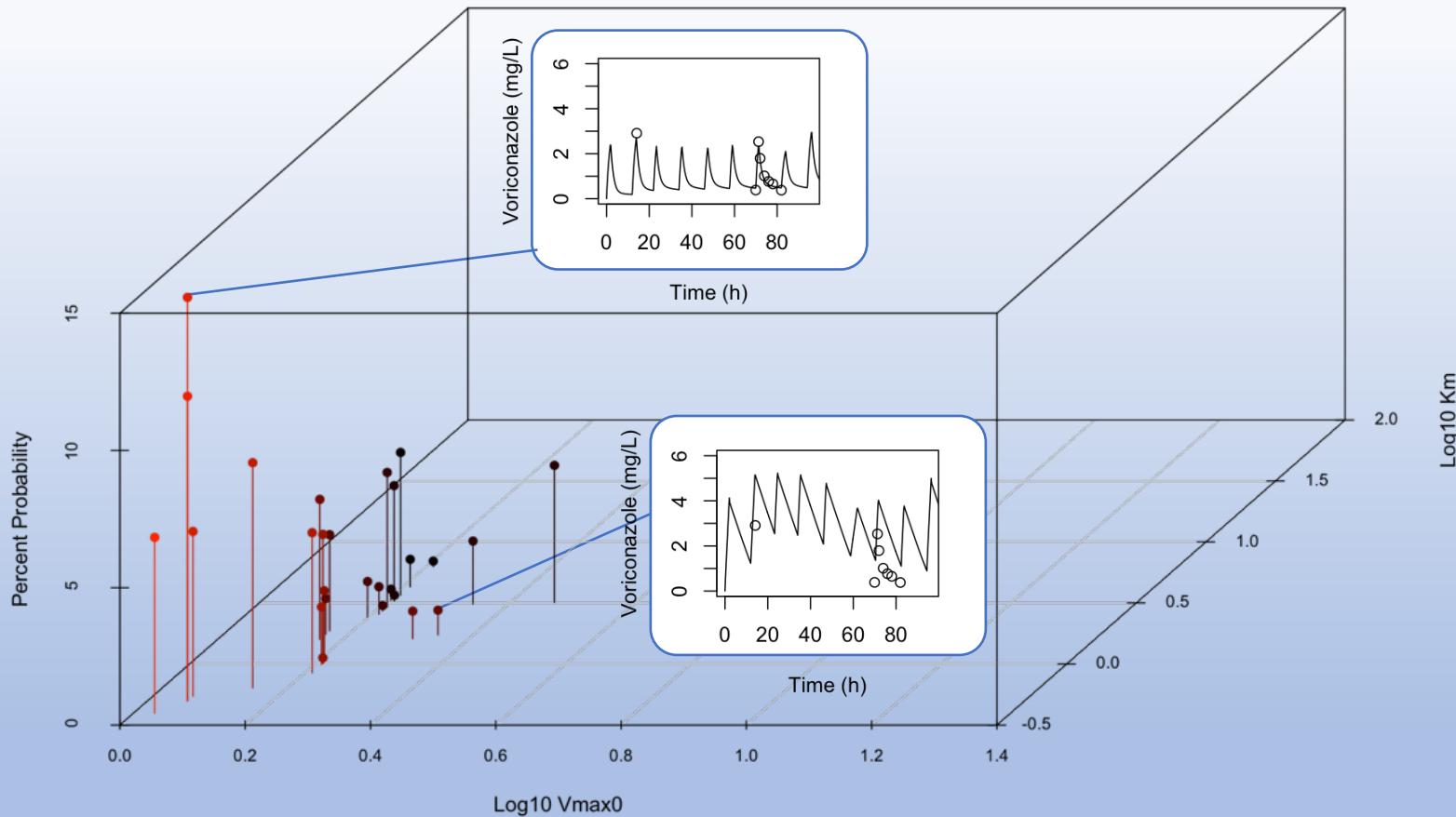


NP MM Approach

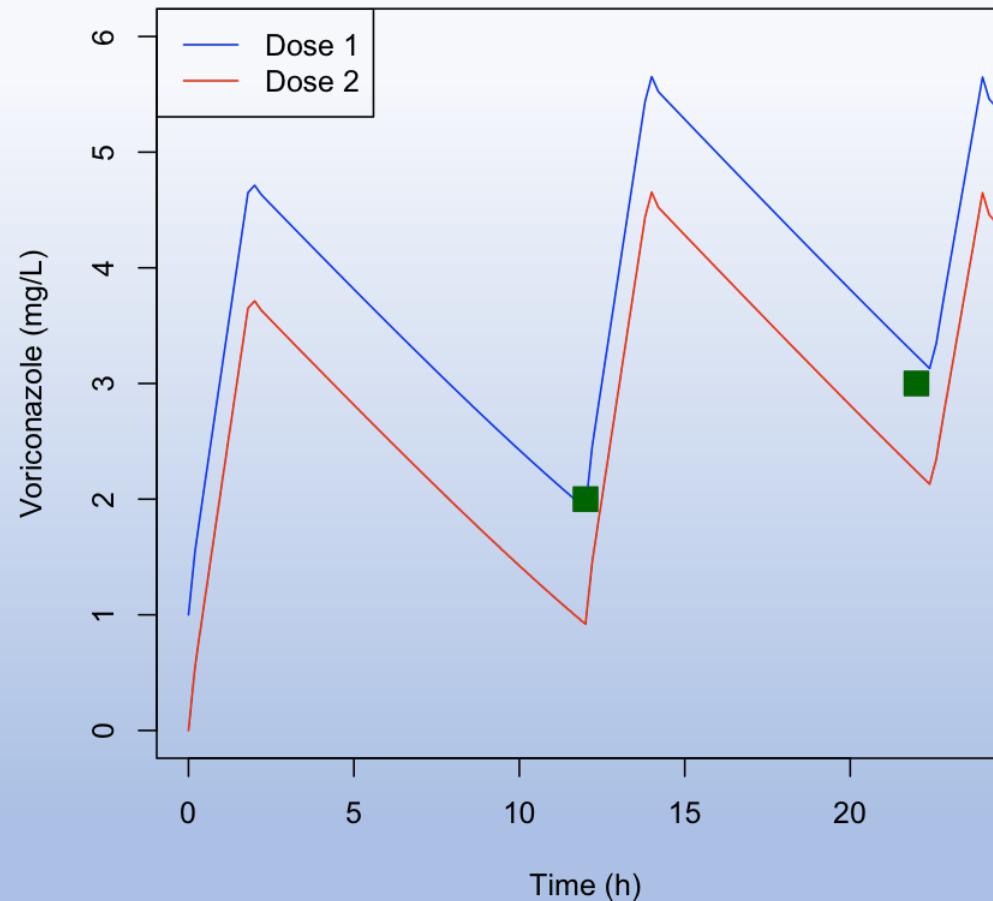


Multiple Models

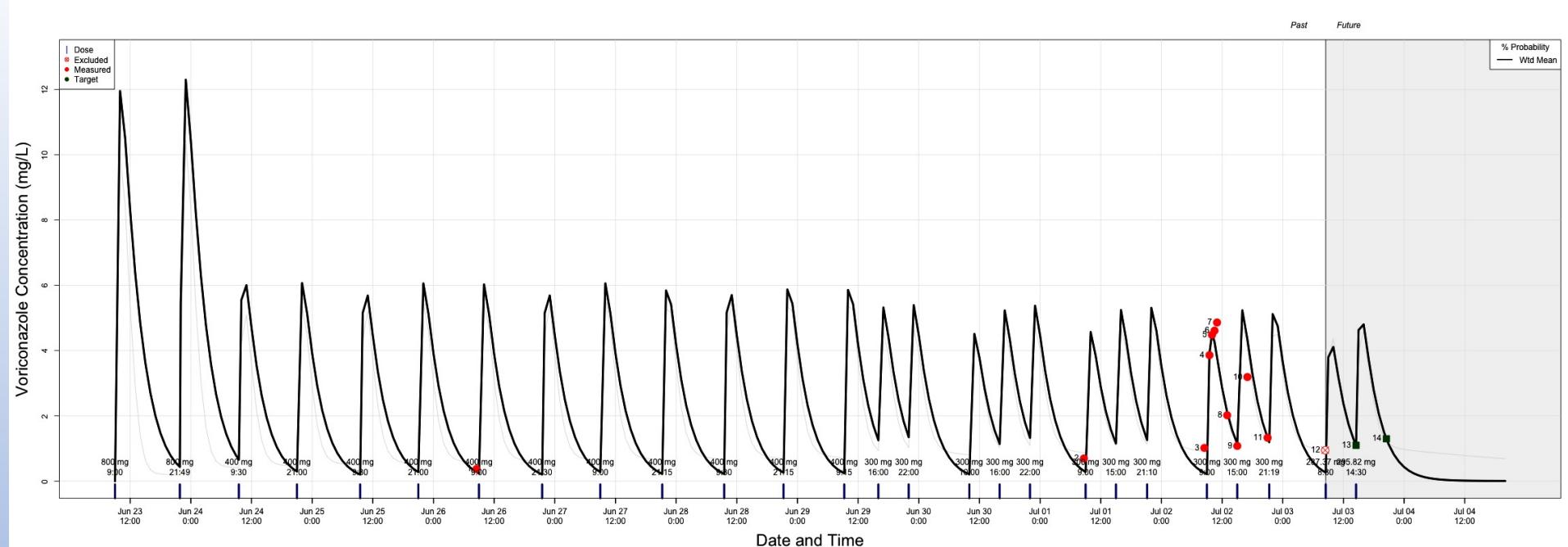
Posterior



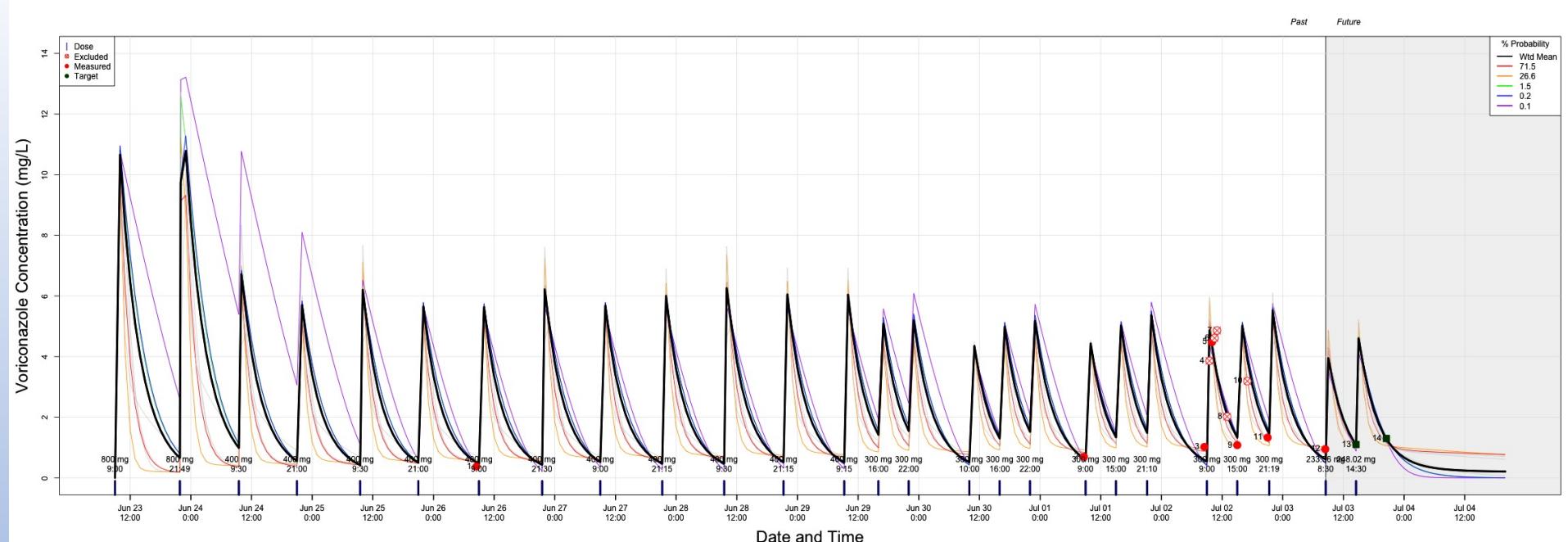
Multiple Models



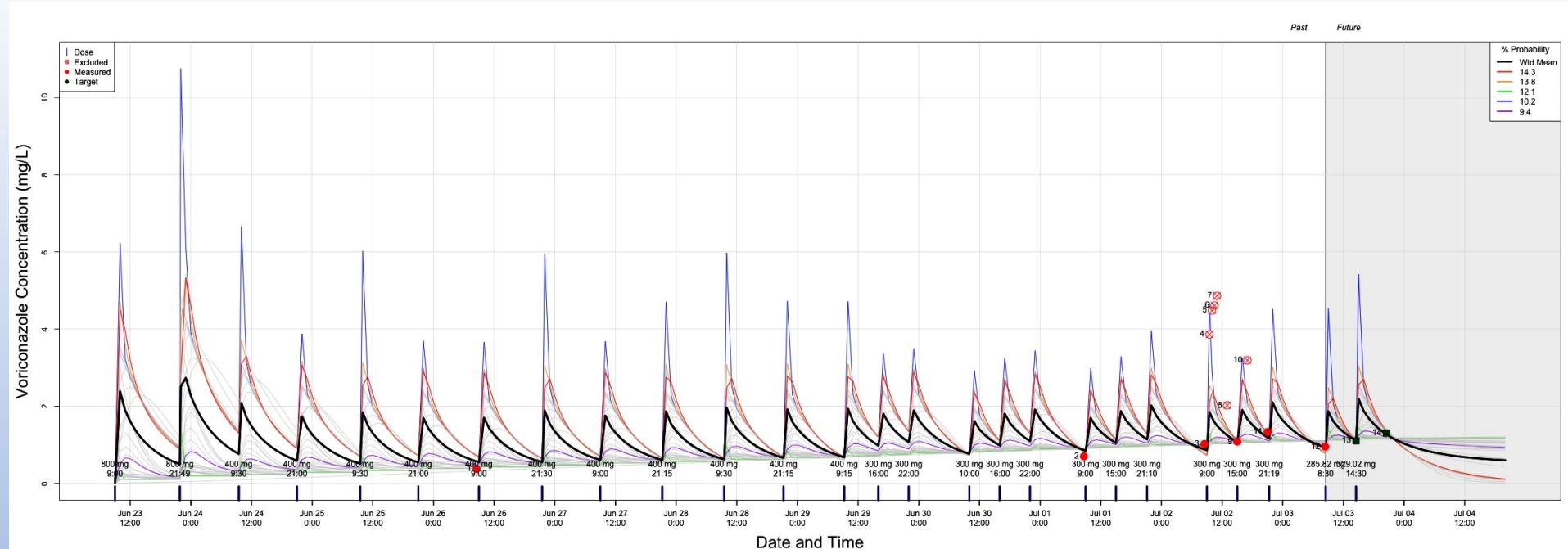
Very rich data



Moderate data



Very sparse data



Real Patients

Patient 1

- 45 year-old HIV+ woman
- Long history of medication intolerance
- Started a fos-amprnavir containing regimen (without ritonavir), 2 x 700 mg tablets twice daily (total 2800 mg/day).
 - Daytime fatigue, which she attributed to the morning dose
 - Enquired about taking the entire dose at night, otherwise does not wish to continue.

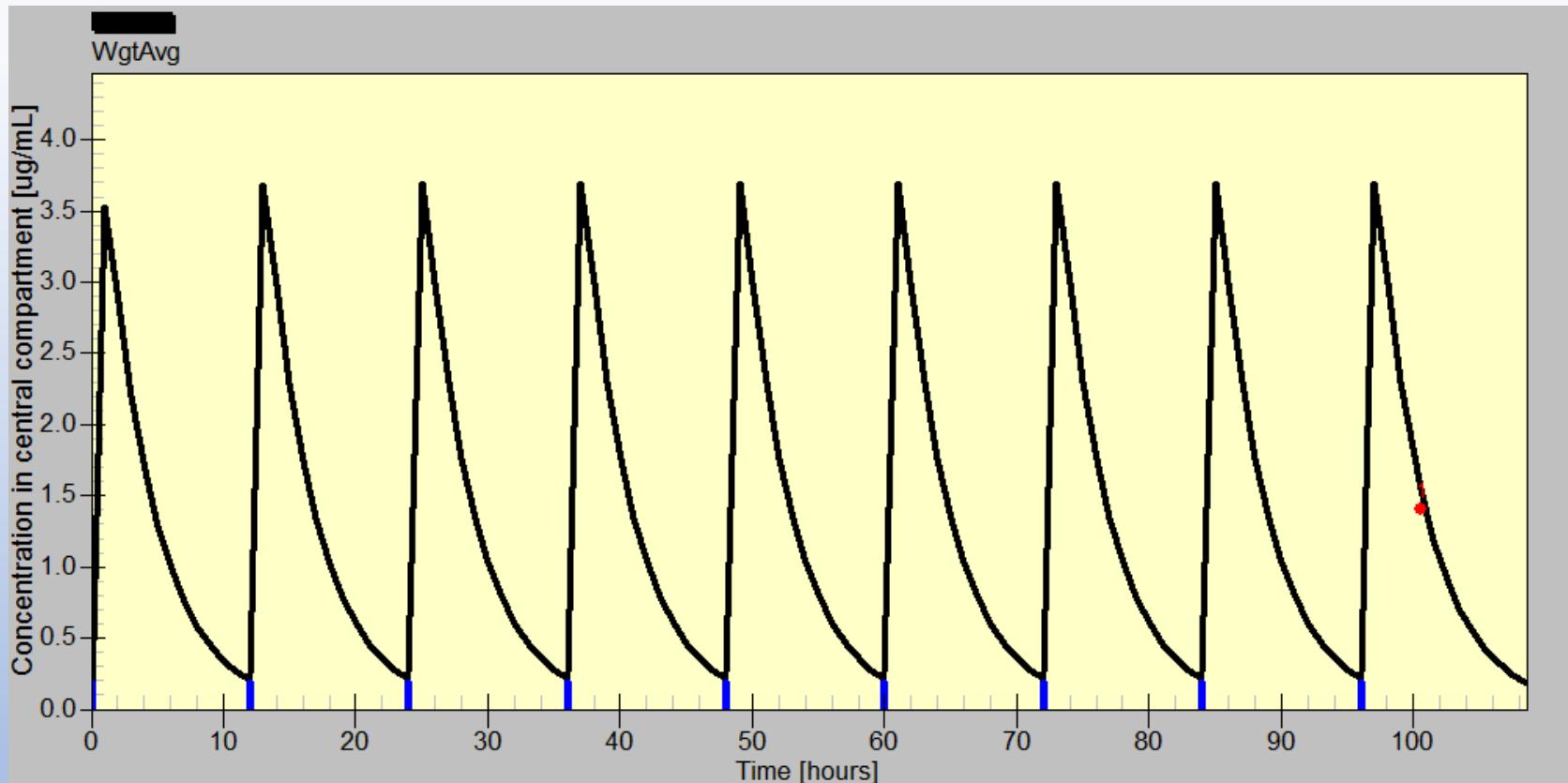
Patient 1 Options

- Tell her the problem is in her head and press on.
- Change to 4 tablets every evening, informing her that you hope it is sufficient to maintain virologic control without new (worse?) side effects.
- Change medications, yet again.
- Measure amprenavir concentration(s) and attempt rational drug management

Patient 1 Data

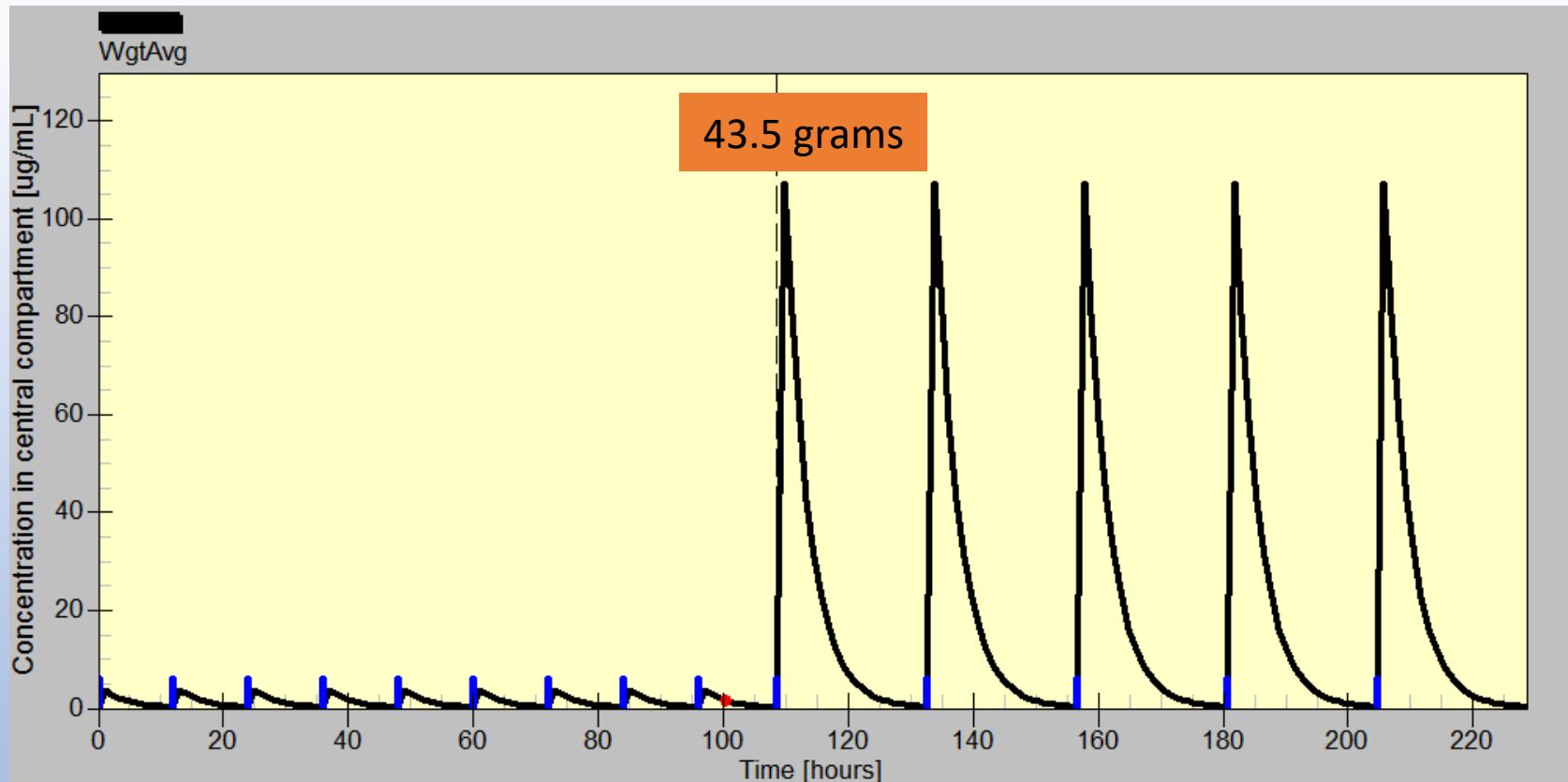
- On the standard dose of 1400 mg bid, a serum amprenavir concentration of 1.4 mg/L was measured 4.5 hours after her previous dose (1 week turnaround time).
- Resistance testing indicated no resistance to amprenavir
- Target amprenavir trough for wild-type virus suggested to be 0.23 to 0.4 mg/L
- Can she take all 4 pills at night???

First fit

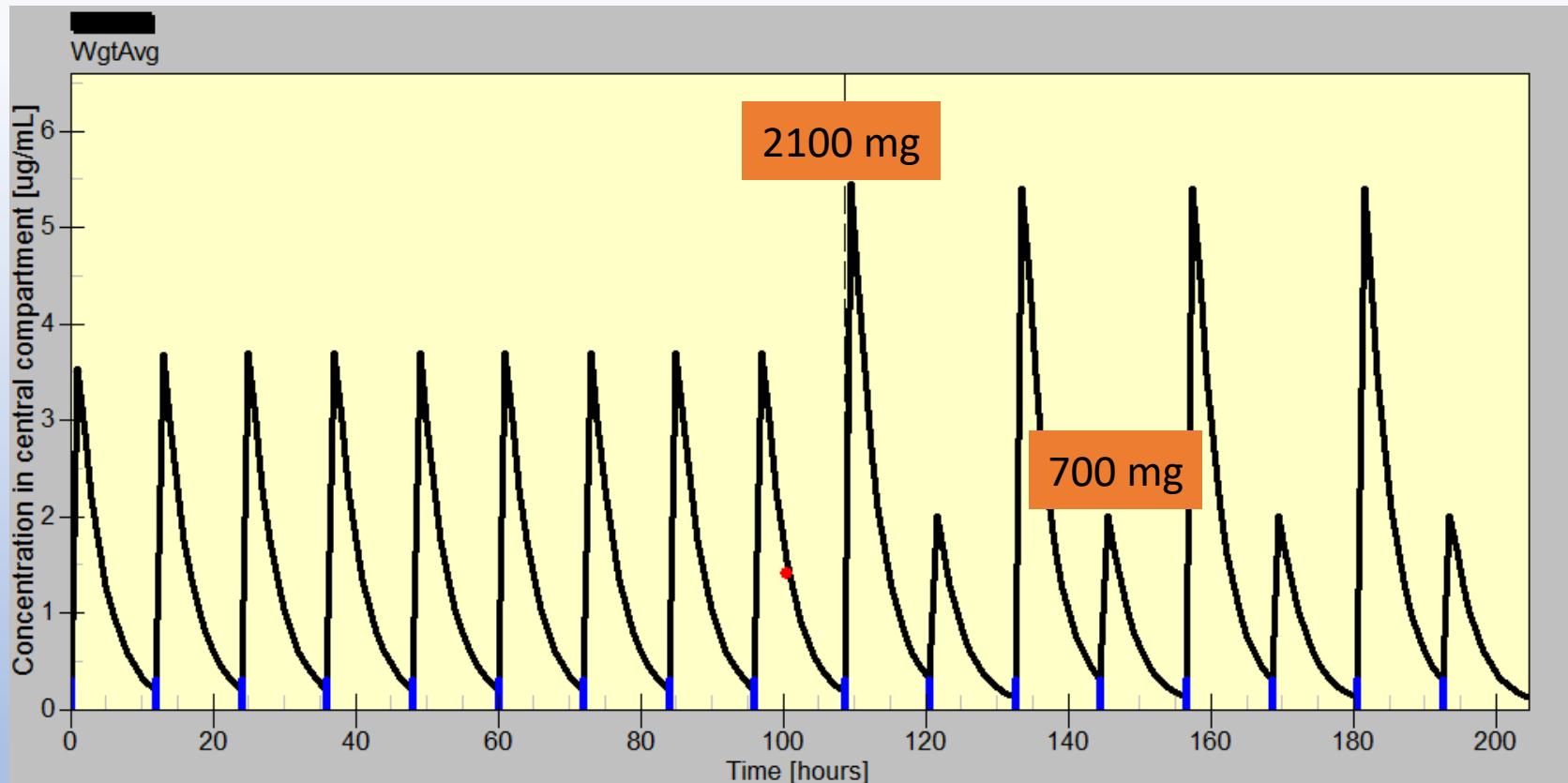


0.27 mg/L

Once daily dosing

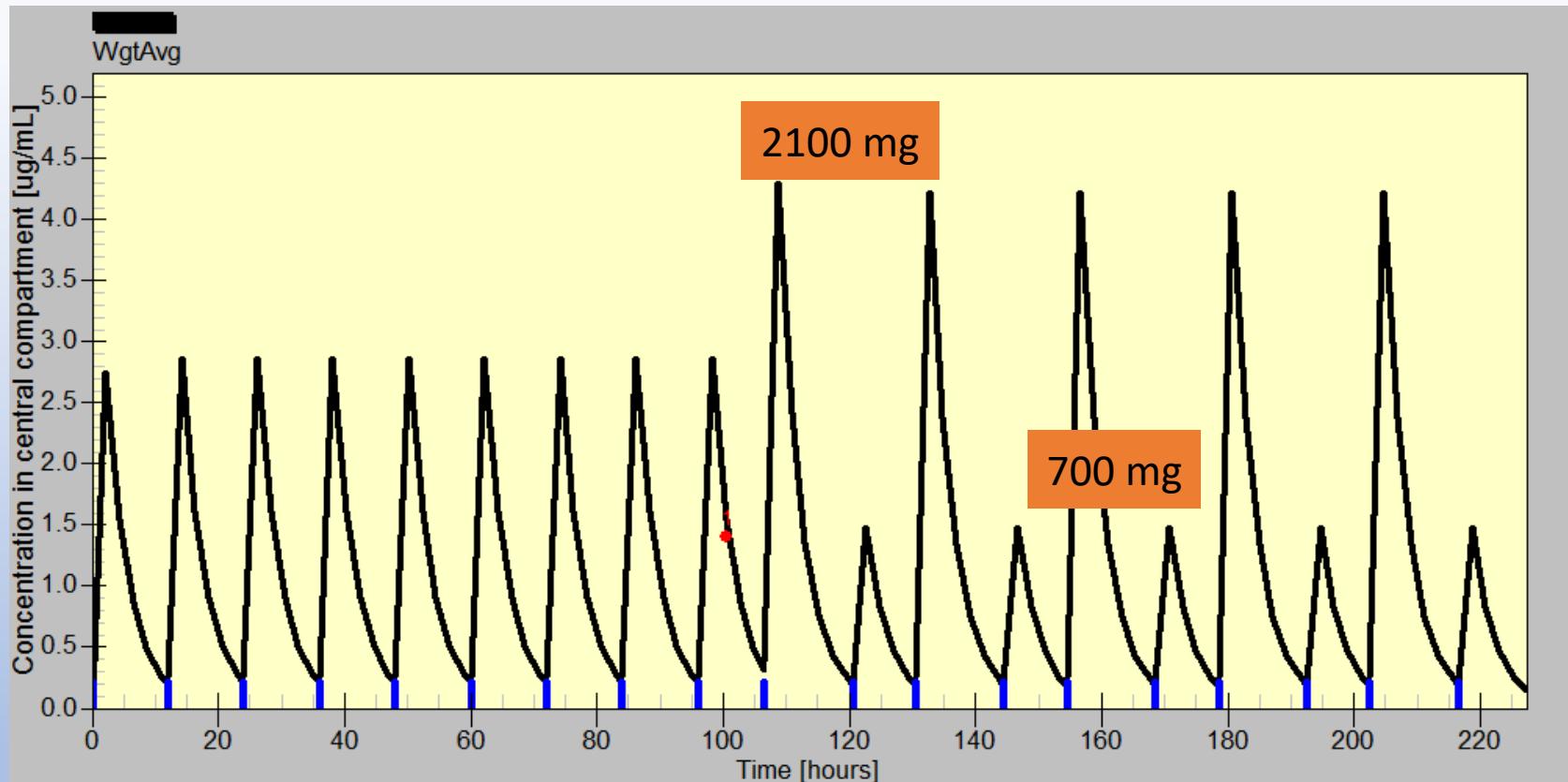


Every 12 h



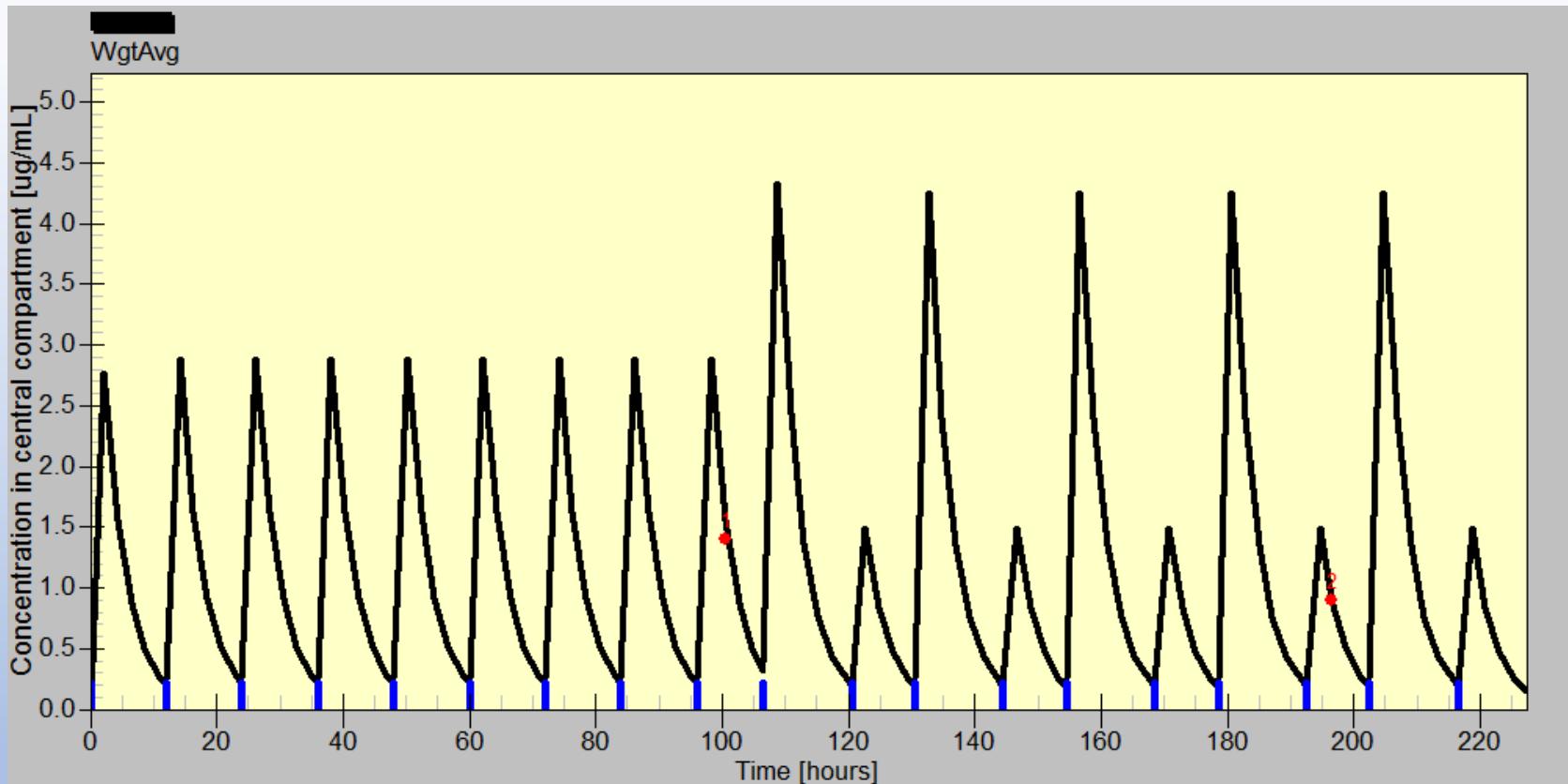
0.11 mg/L

Every 10, 14 h



0.26 mg/L

Results!



0.26 mg/L

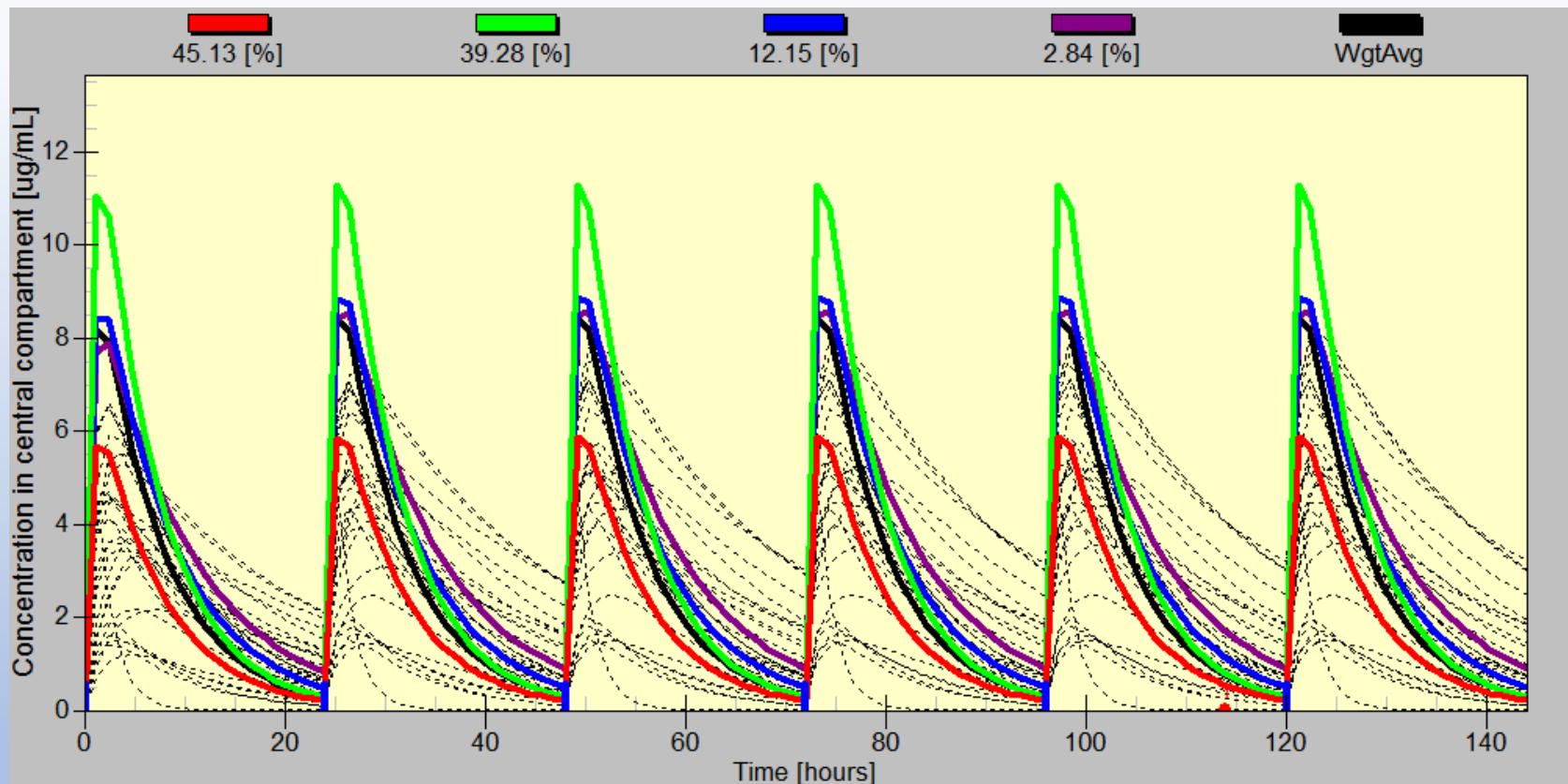
Patient 2

- 18 year old woman, taking atazanavir 400 mg once daily
- Repeatedly swears that she is taking it
- Yet bilirubin is normal, viral load is 30,000 copies/mL, CD4+ cell count is <20 cells/mL
- Level 18 hours after dose is <10 ng/mL. Could she have taken it?

The problem of adherence

- No gold standard
- How do you interpret a single low level?
- Do we really know what patients do with their medications?

No way!

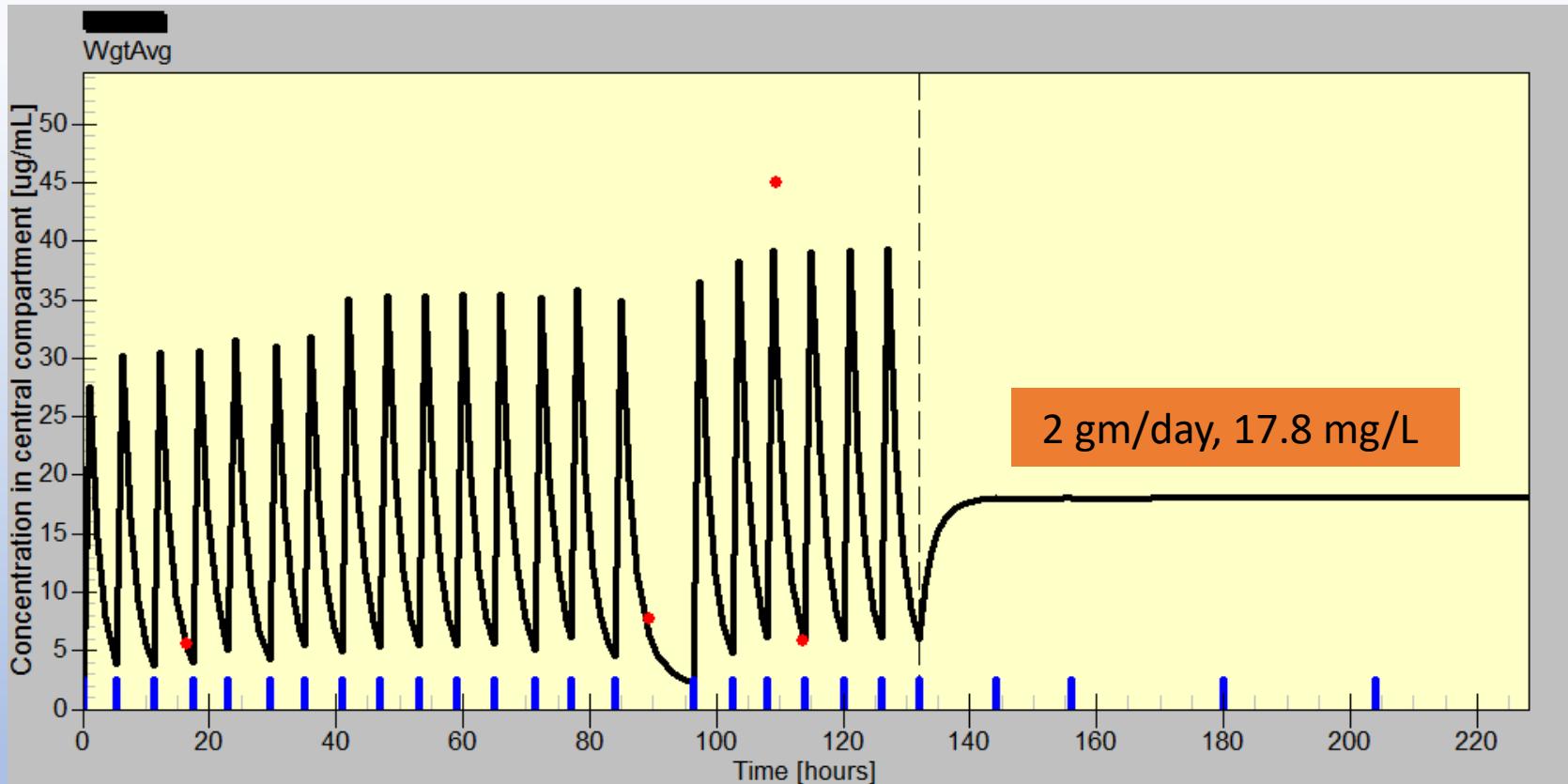


<0.6% chance

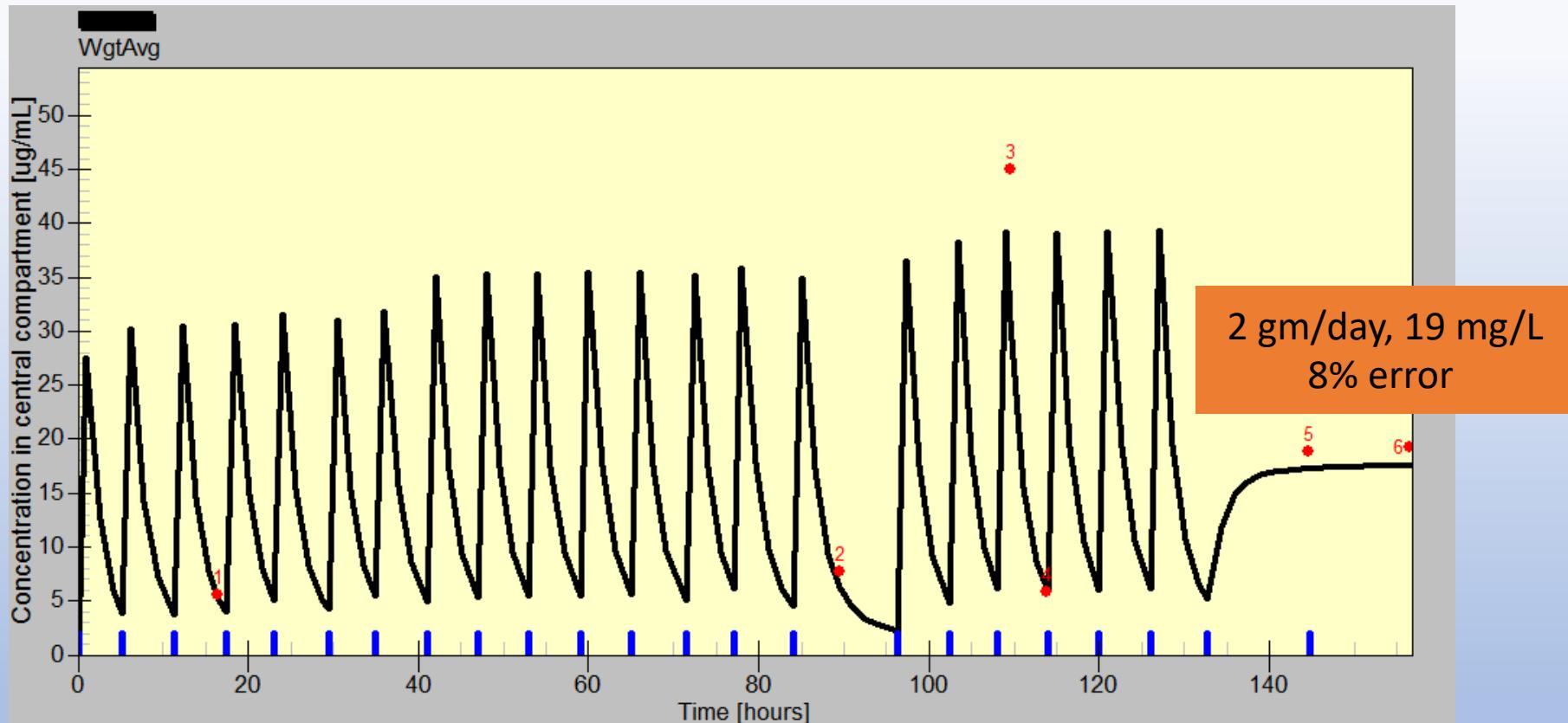
Patient 3

- 7 y/o who had a cerebellar brain tumor resected
- Developed an infection of the cavity with MRSA (vancomycin MIC 0.5 mg/L)
- Repeatedly culture positive and continually febrile for a week
- Primary team dosing vancomycin up to 80 mg/kg/day divided every 6 hours (500 mg/dose)
- Typical doses are 40-60 mg/kg/day
- Highest trough was 7.7 mg/L. Target was 15-20 mg/L

Fit and plan



Results



Retrospective Validations

MM Bias for Voriconazole

Basis for Bayesian Posterior Used to Calculate Predictions			
Bias	All Concentrations (Full Data)	Peak/Trough	Trough Only
Bias_target (mg/L)	0.08 (-0.02 to 0.42)	0.02 (-0.04 to 0.13)	0.04 (0.00 to 0.14)
%Bias_target	5.0 (-5.0 to 19.2)	1.5 (-10.3 to 7.0)	3.0 (-0.5 to 7.8)
Bias_total (mg/L)	0.04 (0.00 to 0.15)	0.00 (0.00 to 0.03)	0.02 (0.00 to 0.05)
%Bias_total	6.1 (0.3 to 22.2)	0.9 (0.1 to 5.1)	2.1 (0.2 to 9.8)
Bias_dose (mg)	-19 (-50 to 3)	-8 (-63 to 2)	-4 (-34 to 1)
%Bias_dose	-6.5 (-17.5 to 1.9)	-3.3 (-19.1 to 2.1)	-2.0 (-8.8 to 1.0)
AUC mg*h/L	58.5 (15.2 to 221.0)	64.3 (8.8 to 217.8)	41.3 (12.7 to 227.0)

Patient 4

- 7 year old girl with bone marrow transplant for AML
- Weight 28.2 kg
- Started on oral voriconazole for prophylaxis
- Enrolled in local study of the ontogeny of voriconazole pharmacokinetics*

*NIH-NICHD R01 HD070996 (PI: Neely)

Optimal Sampling

- Choose the times to sample that are the most informative
- Truly optimal sampling should be individualized, just as dosing should be individualized

MMopt

- Multiple-Model Optimal design
- Completely new optimal sampling paradigm in the PK world
- Shift focus from estimating parameters directly to correctly classifying which time-concentration profile among many matches a subject best

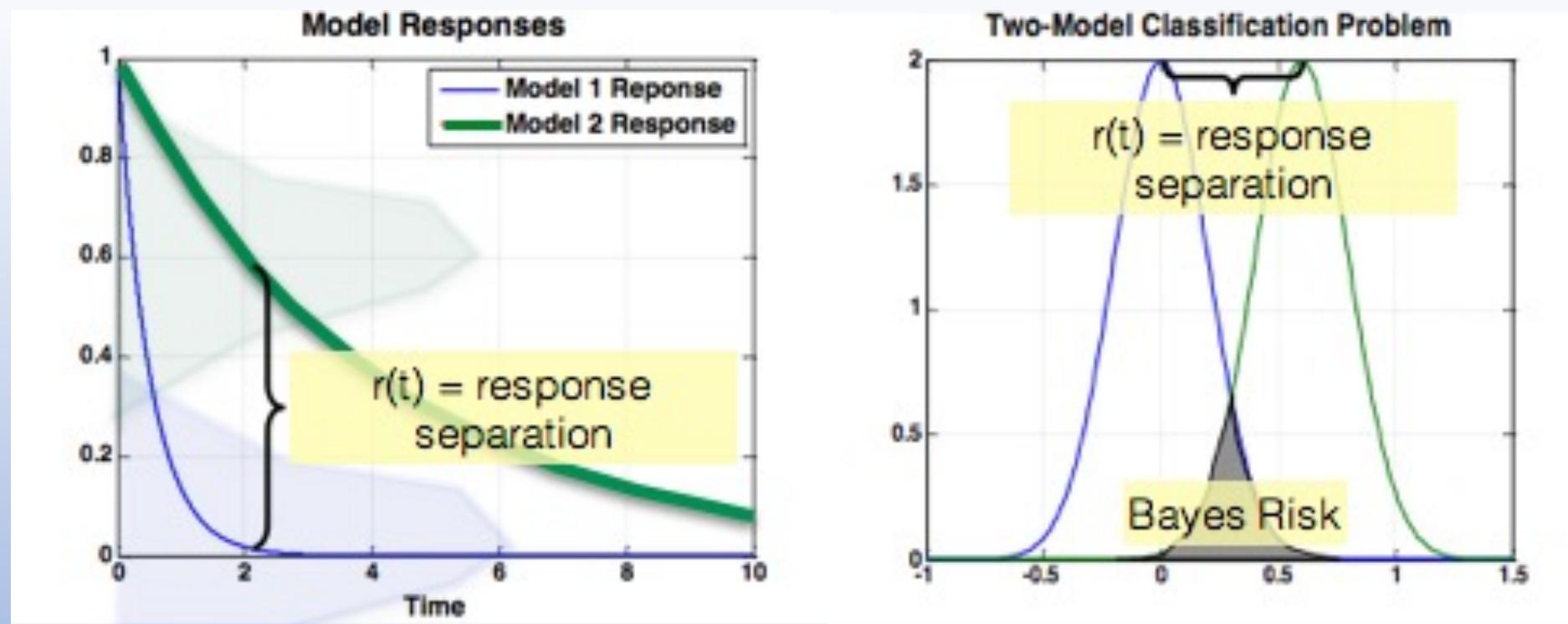
D-optimal



MMopt

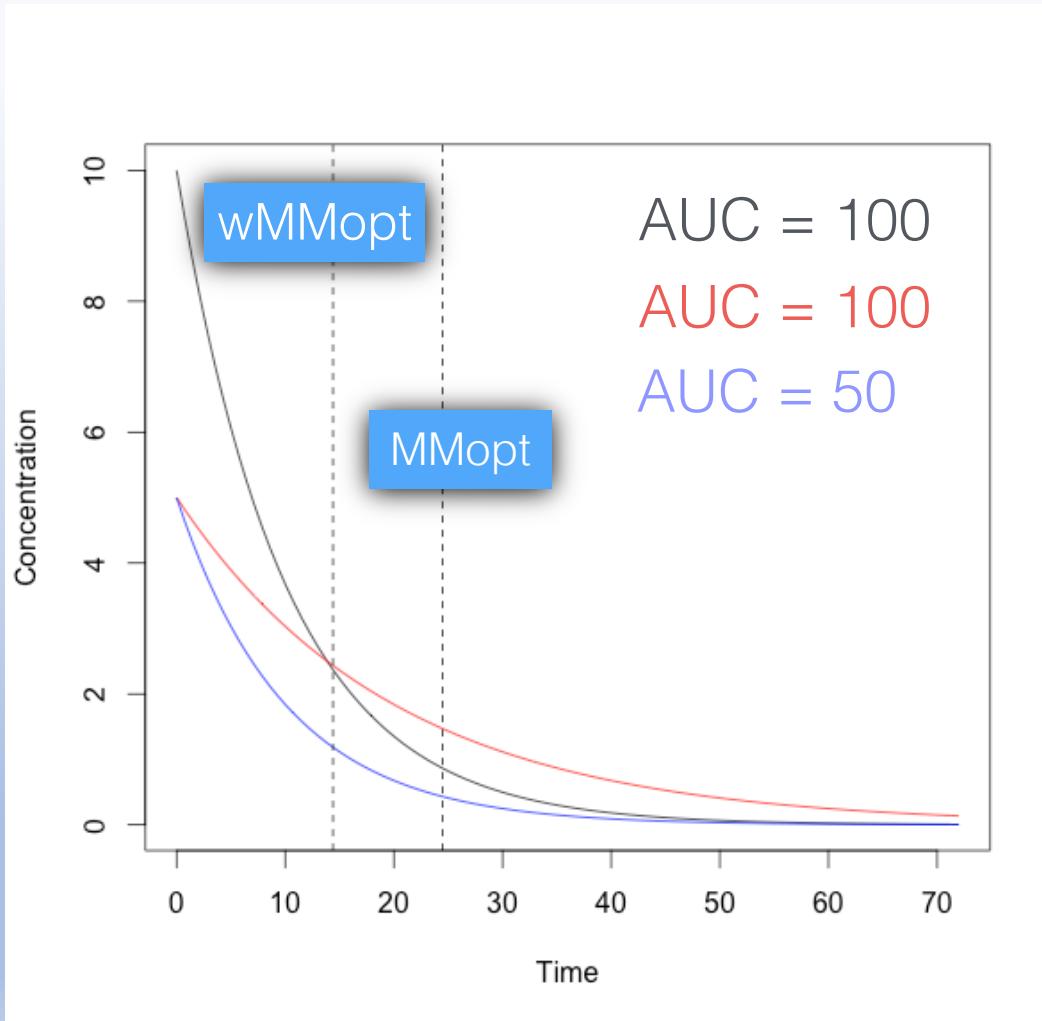


Minimize misclassification

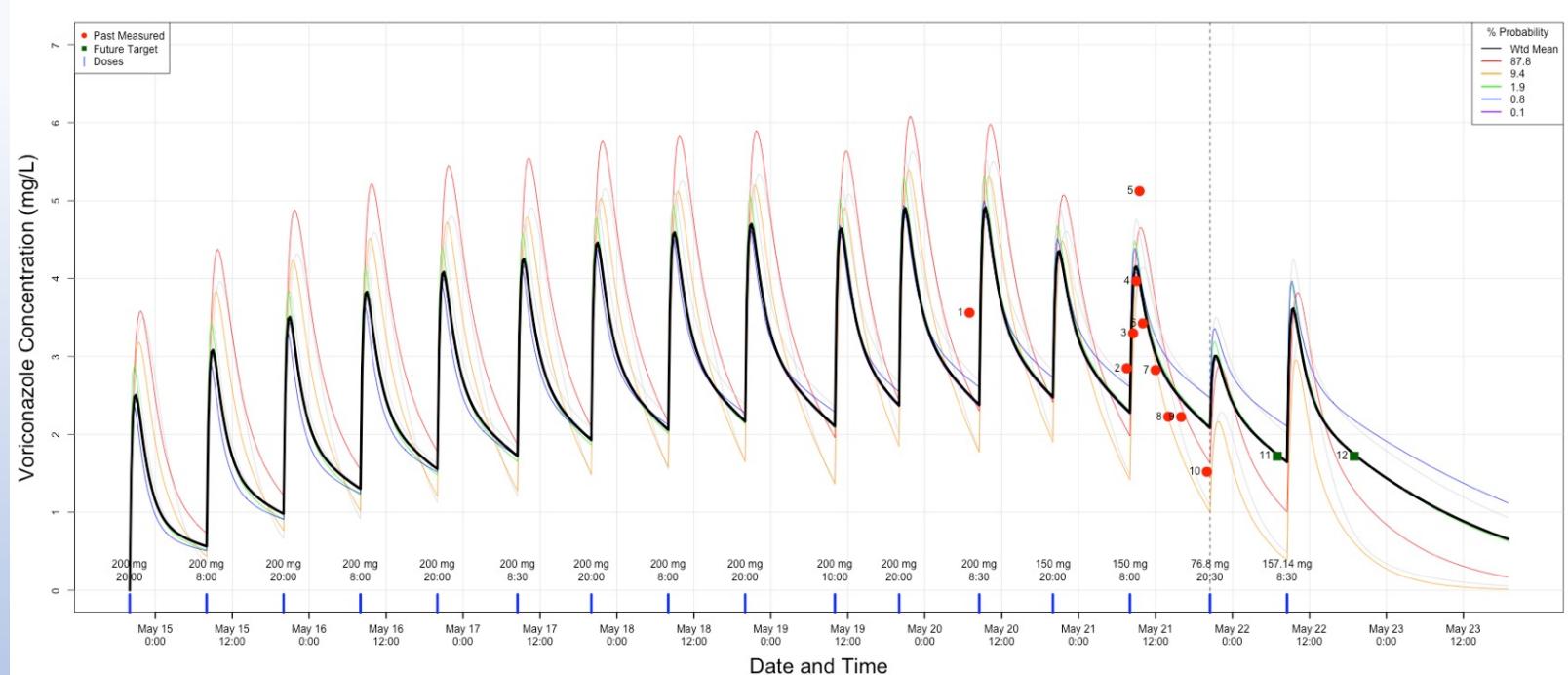


Choose Time t to maximize $r(t)$

Weighted MMopt

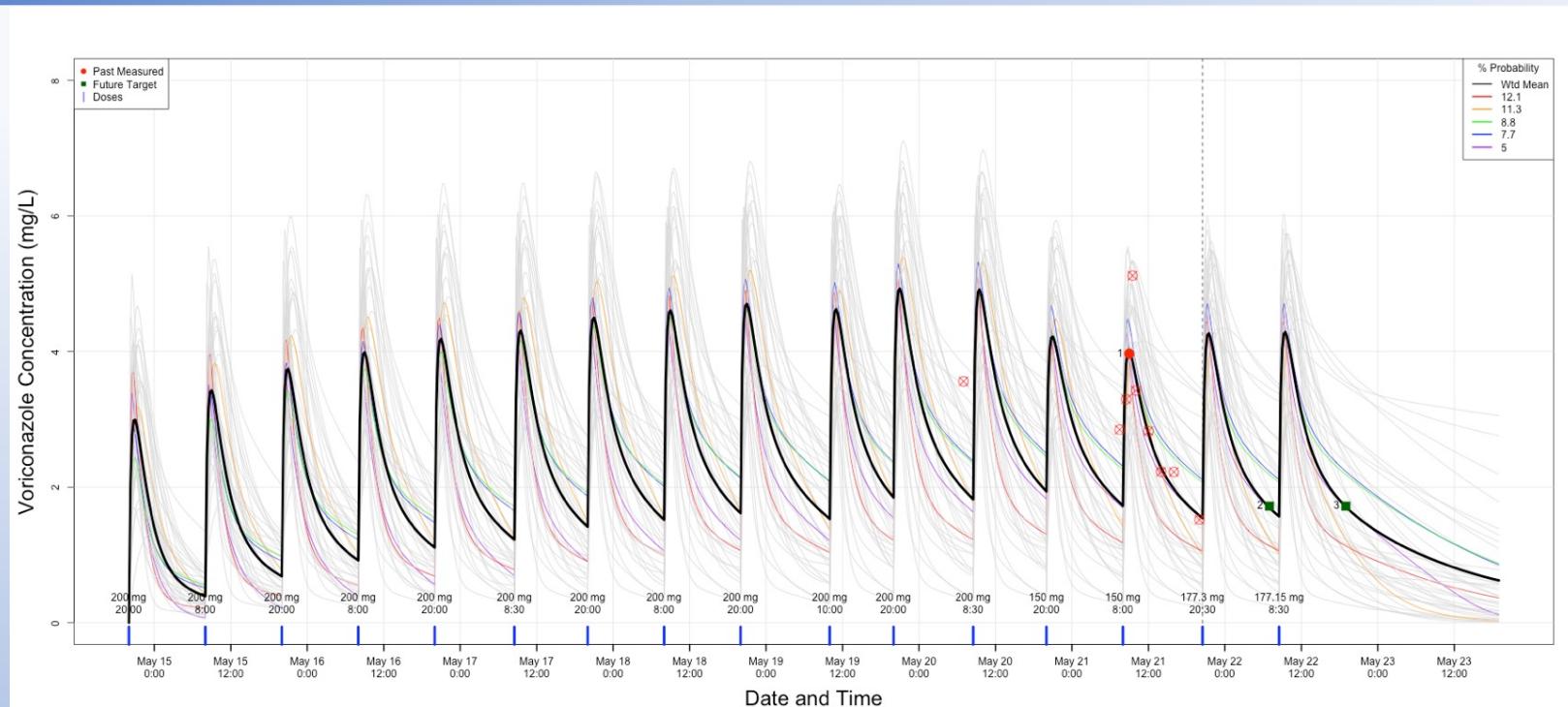


All the Data



	Date	Time	Dose	Units	%Err
1	5/21/13	20:30	76.8	mg	-48.8%
2	5/22/13	8:30	157.14	mg	4.8%

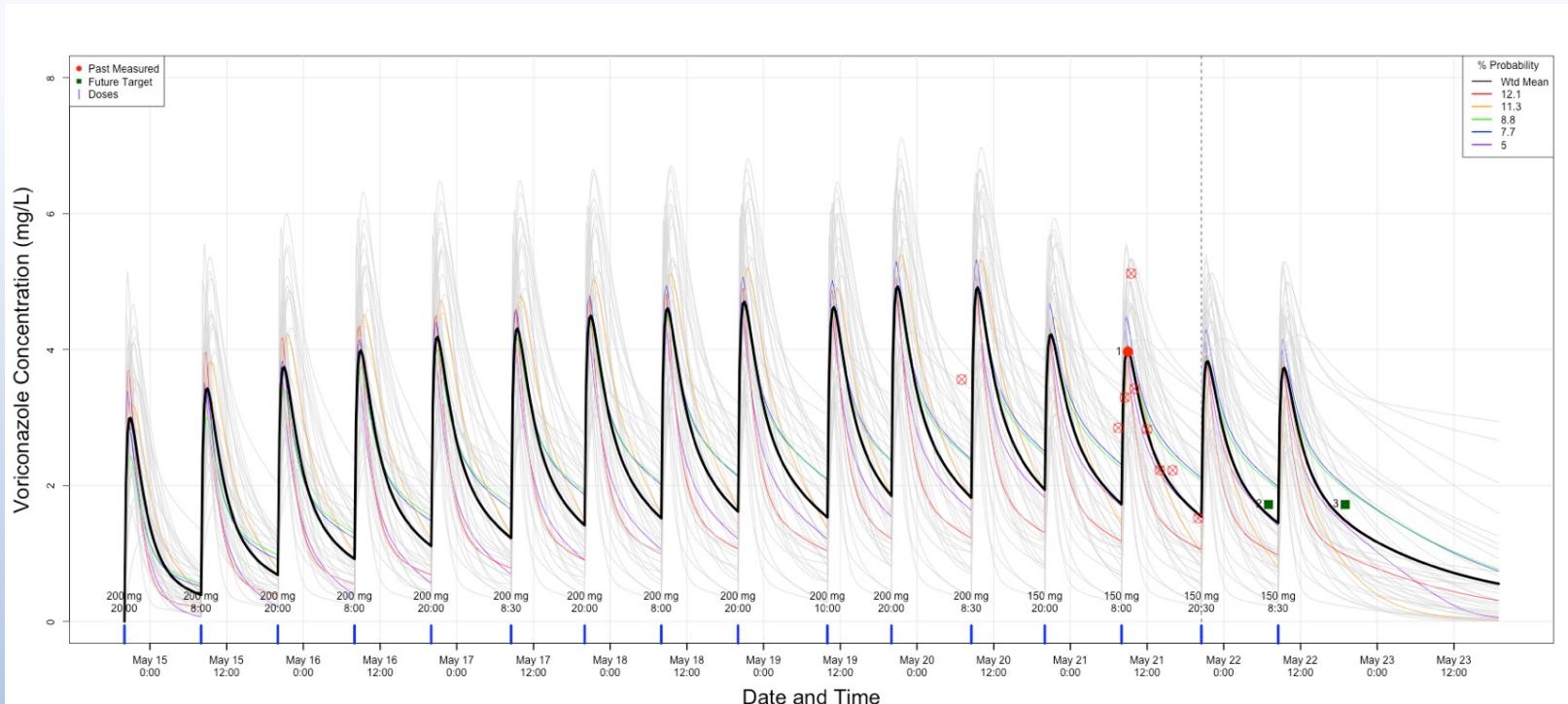
Optimal Sampling*



	Date	Time	Dose	Units	%Err
1	5/21/13	20:30	177.3	mg	18.2%
2	5/22/13	8:30	177.15	mg	18.2%

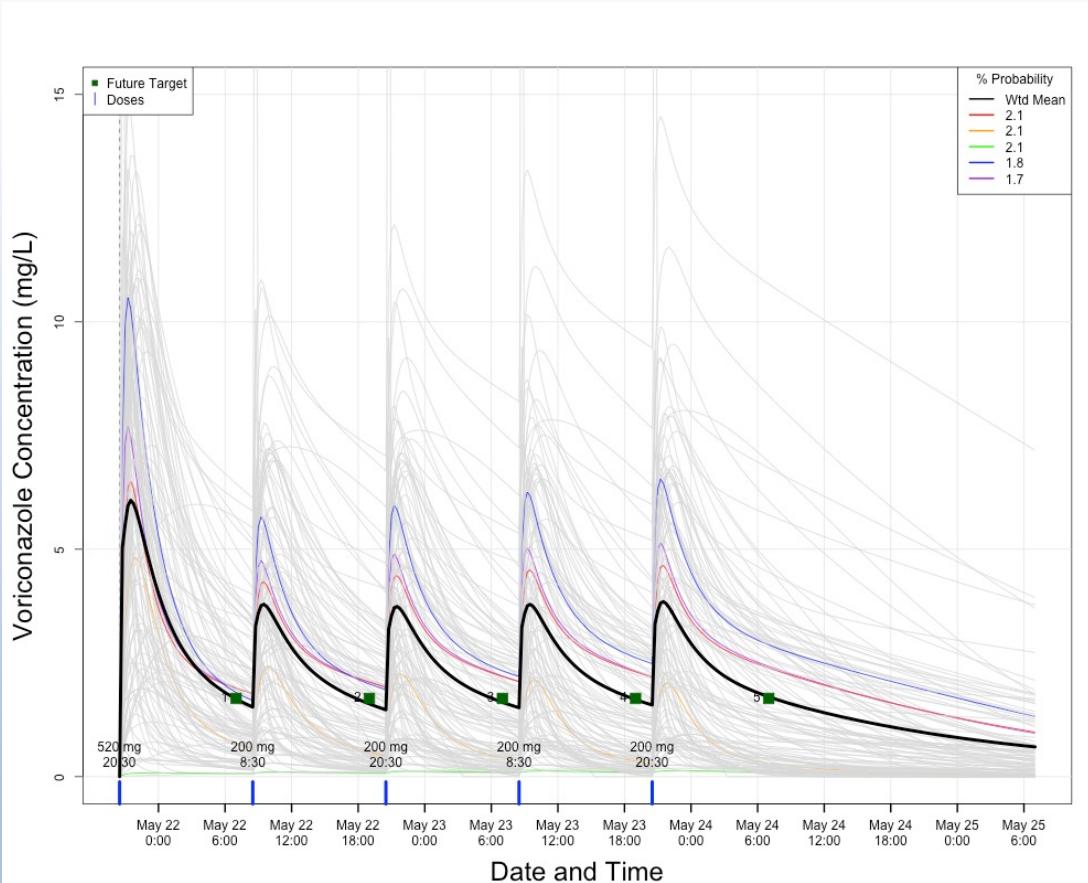
*Neely MN , Bayard DS, Hope WW . Multiple Model Optimal (MMopt) Sampling for First Dose Oral Voriconazole TDM in Children, IATDMCT,
Salt Lake City, September 22-26, 2013

Optimal Sampling, Fixed Dose



	Date	Time	Conc	Pred	%Err
1	5/22/13	7:00	1.72	1.56	-9.3%
2	5/22/13	19:00	1.72	1.48	-14.9%

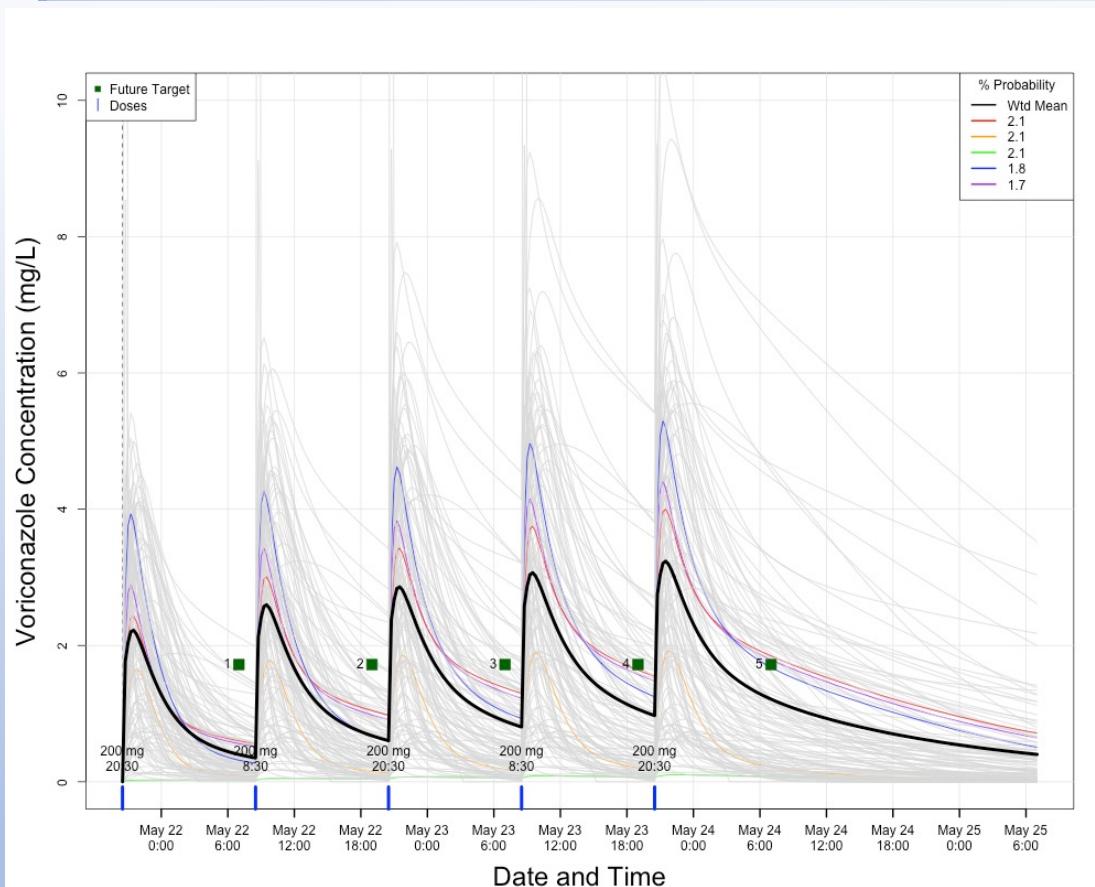
Initial Dosing



Loading: 520 mg (~19 mg/kg) x 1
Maintenance: 200 mg (~7 mg/kg) q12 h

	Date	Time	Conc	Pred	%Err
1	5/22/13	7:00	1.72	1.71	-0.6%
2	5/22/13	19:00	1.72	1.6	-7%
3	5/23/13	7:00	1.72	1.64	-4.7%
4	5/23/13	19:00	1.72	1.69	-1.7%
5	5/24/13	7:00	1.72	1.76	2.3%

Initial Dosing, No Load



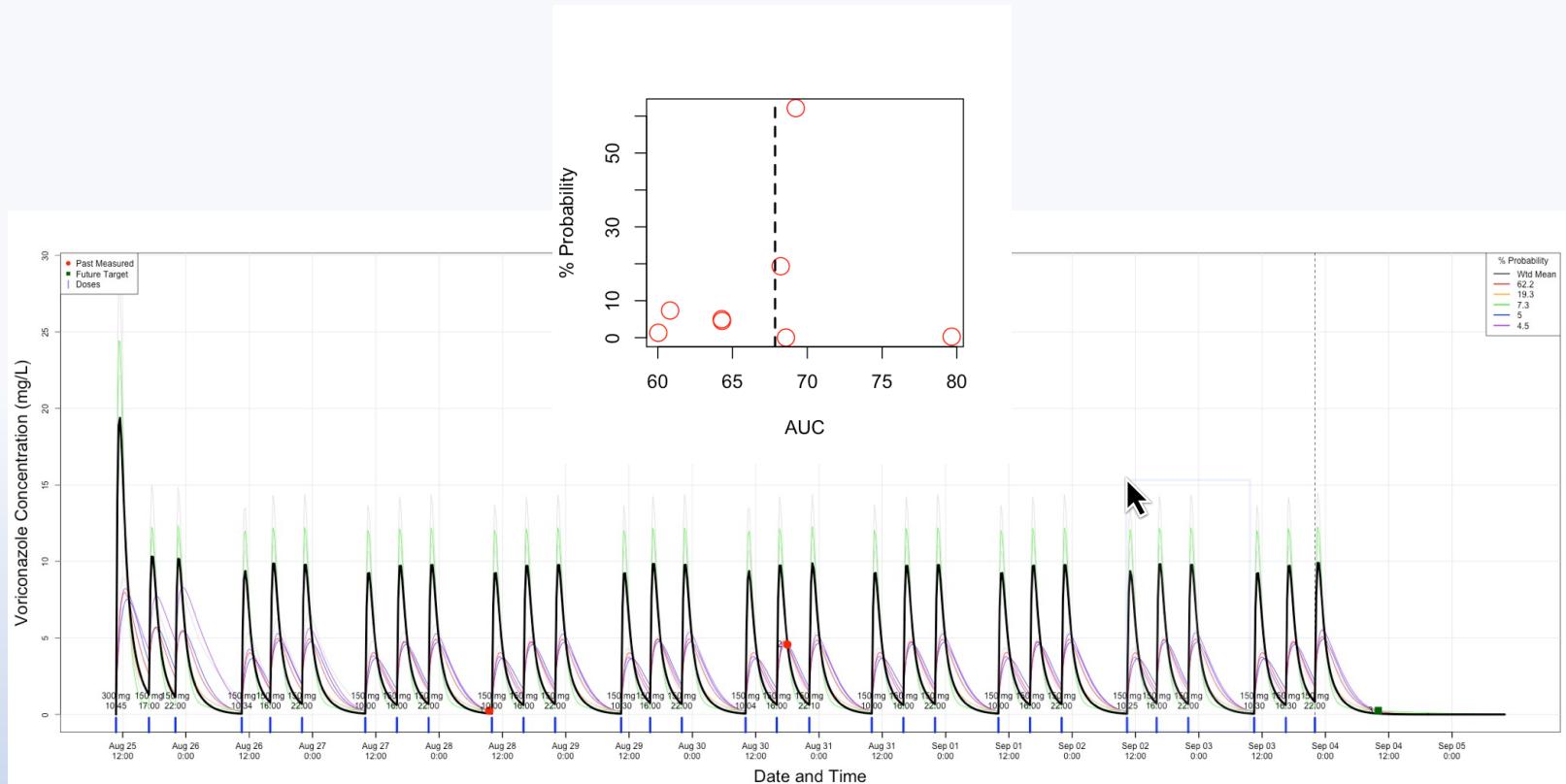
Loading: none

Maintenance: 200 mg (~7 mg/kg) q12 h

	Date	Time	Conc	Pred	%Err
1	5/22/13	7:00	1.72	0.4	-76.7%
2	5/22/13	19:00	1.72	0.68	-60.4%
3	5/23/13	7:00	1.72	0.89	-48.2%
4	5/23/13	19:00	1.72	1.06	-38.4%
5	5/24/13	7:00	1.72	1.21	-30%

Patient 5

- 13 month old bone marrow transplant patient on long-term oral voriconazole for pulmonary nodules with +Galactomannan
- Weight 8.76 kg
- Voriconazole trough concentration repeatedly <0.5 mg/L. Dose gradually increased to 17 mg/kg/dose PO tid (51 mg/kg/day).
- A 75 kg adult at this dose would be getting 3825 mg/day compared to usual dose of 400 mg/day.



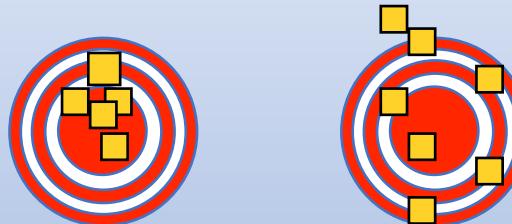
1. Vfend package insert mean (CV%) adult AUC 200 mg PO q12h, <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=dac26bcd-7a59-401f-9f66-a0649767cece> (accessed 9/10/13)

2. Vfend package insert mean (CV%) adult AUC 300 mg PO q12h

3. Siopi M, Mavridou E, Mouton JW, Verweij PE, Zerva L, Meletiadis J. 2014. Susceptibility breakpoints and target values for therapeutic drug monitoring of voriconazole and Aspergillus fumigatus in an in vitro pharmacokinetic/pharmacodynamic model. *J Antimicrob Chemo* dku023.

Vancomycin MM

	Bias	Imprecision
BestDose ¹	-0.11 mg/L	2.8 mg/L
Nomogram ²	-3 mg/L	8 m/L



1. Nunn, M. O., Corallo, C. E., Aubron, C., Poole, S., Dooley, M. J., & Cheng, A. C. (2011). Vancomycin dosing: assessment of time to therapeutic concentration and predictive accuracy of pharmacokinetic modeling software. *The Annals of Pharmacotherapy*, 45(6), 757–763.
2. Lee, E., Winter, M. E., & Boro, M. S. (2006). Comparing two predictive methods for determining serum vancomycin concentrations at a Veterans Affairs Medical Center. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*, 63(19), 1872–1875.

Piperacillin MM

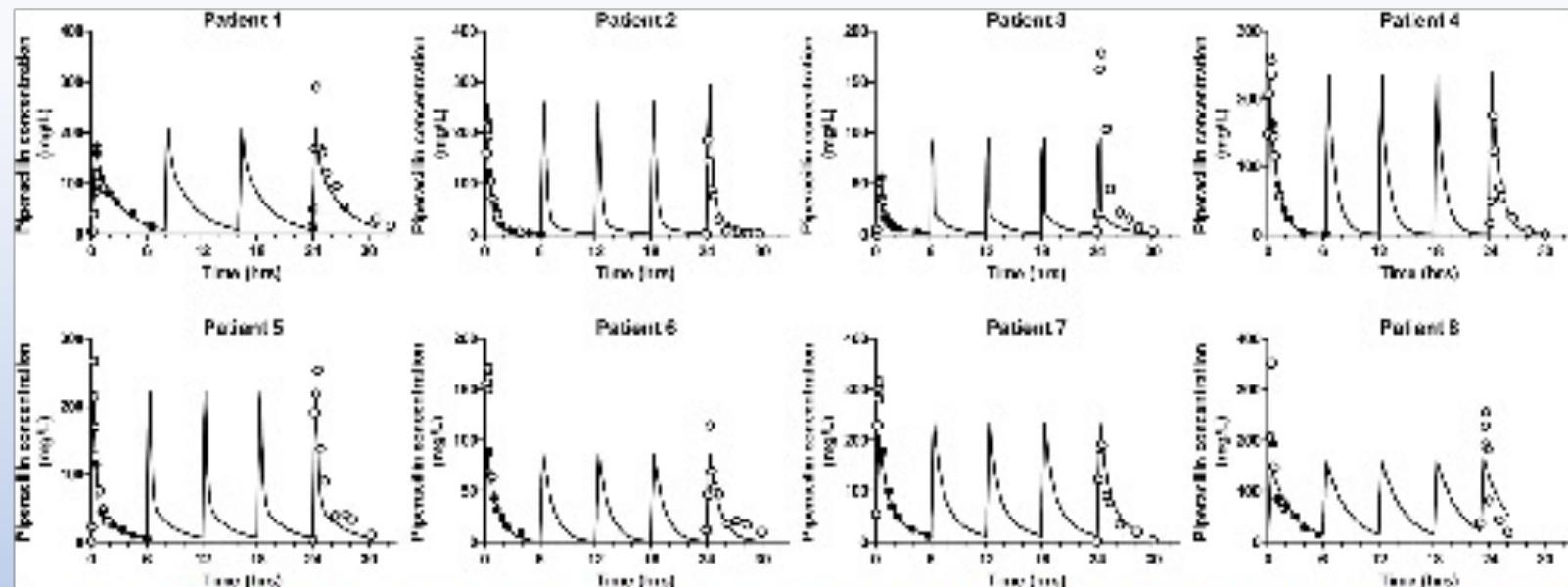


FIG 4 Piperacillin concentration-time profiles for eight validation patients generated from six observed piperacillin concentrations during the first dosing interval. Observed data entered into the software package (●) and observed data unknown to the software package (○) are shown. The predicted piperacillin concentration-time profiles are indicated by the solid lines.

Piperacillin MM

- With at least two measured concentrations, mean dose predicted by Bestdose was 4.02 g in patients given an actual mean dose of 4.00 g

Prospective Validations

Vancomycin: Primary Hypothesis

More patients are therapeutic by vancomycin AUC than by trough.

Neely, M. N., Youn, G., Jones, B., Jelliffe, R. W., Drusano, G. L., Rodvold, K. A., & Lodise, T. P. (2014). Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrobial Agents and Chemotherapy*, 58(1), 309–316. doi:10.1128/AAC.01653-13

Neely MN, Kato L, Youn G, Kraler L, Bayard D, Van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. *Antimicrob Agents Chemother*. 2018 Feb;62(2):e02042–17.

Study Design



Target Exposures



Year 1
IDSA Troughs

Year 2
 $AUC:\text{MIC} \geq 400$ (MRSA)
 $AUC \geq 400$ (others)
 $AUC < 800$ (toxicity)

Year 3
 $AUC:\text{MIC} \geq 400$ (MRSA)
 $AUC \geq 400$ (others)
 $AUC < 800$ (toxicity)

Study Population

	Year 1 Control N=75	Year 2 MM N=88	Year 3 MMopt N=89	P-value
Age, years	47.7 (19.0 – 71.0)	48.0 (18.0 – 93.0)	50.3 (22.0 – 81.0)	0.42
Male sex	61 (81%)	67 (76%)	67 (75%)	0.57
Weight, kg	82.4 (47.7 – 150.9)	81.0 (46.4 – 193.6)	78.8 (30.3 – 180.0)	0.64

Neely MN, Kato L, Youn G, Kraler L, Bayard D, Van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. *Antimicrob Agents Chemother*. 2018 Feb;62(2):e02042–17.

Baseline Renal Function

	Year 1 Control	Year 2 MM	Year 3 MMopt	P-value
Scr (mg/dl)	0.82 (0.36 – 1.63)	0.84 (0.33 – 2.71)	0.83 (0.39 – 2.21)	0.92
CrCl (ml/min)	146.9 (36.0 – 665.5)	131.1 (31.7 – 281.0)	126.8 (27.8 – 286.8)	0.14

Subjects with ≥ 1 sample after enrollment

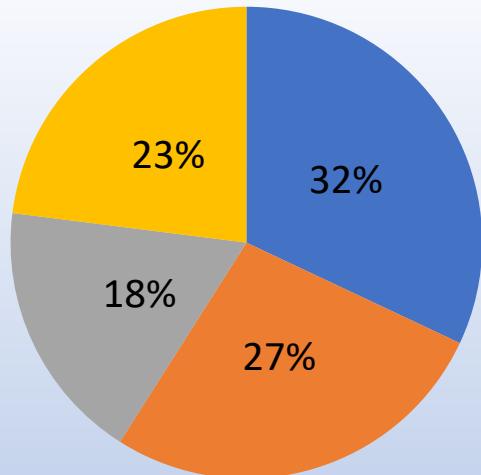
	Year 1 N=44	Year 2 N=51	Year 3 N=56	P-value
Days of vancomycin	7.8 (4.1, 14.3)	5.4 (4.0, 8.6)	4.7 (3.2, 8.7)	0.05
Days until discharge	9.0 (6.0, 21.0)	8.0 (4.0, 15.0)	7.0 (5.0, 16.0)	0.37
Samples per patient	3.6 (1 - 15)	2.1 (1 – 8)	2.4 (1 – 12)	0.007
Trough concentration (mg/L)	14.4 (3.8 – 27.2)	9.7 (4.5 – 29.6)	10.9 (3.5 – 25.8)	0.005
Daily AUC mg*h/L	510 (160 – 1050)	459 (154 – 975)	459 (194 – 890)	0.29

Primary Outcome

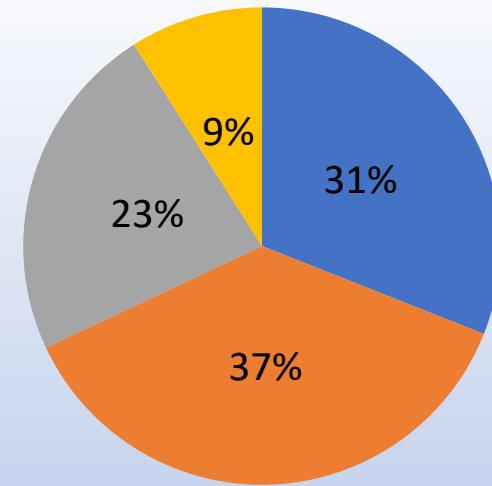
70% of AUCs vs. 19% of troughs were therapeutic ($P<0.0001$)

Predictions vs. Reality

Simulated AUC $\geq 400^*$



Measured AUC ≥ 400



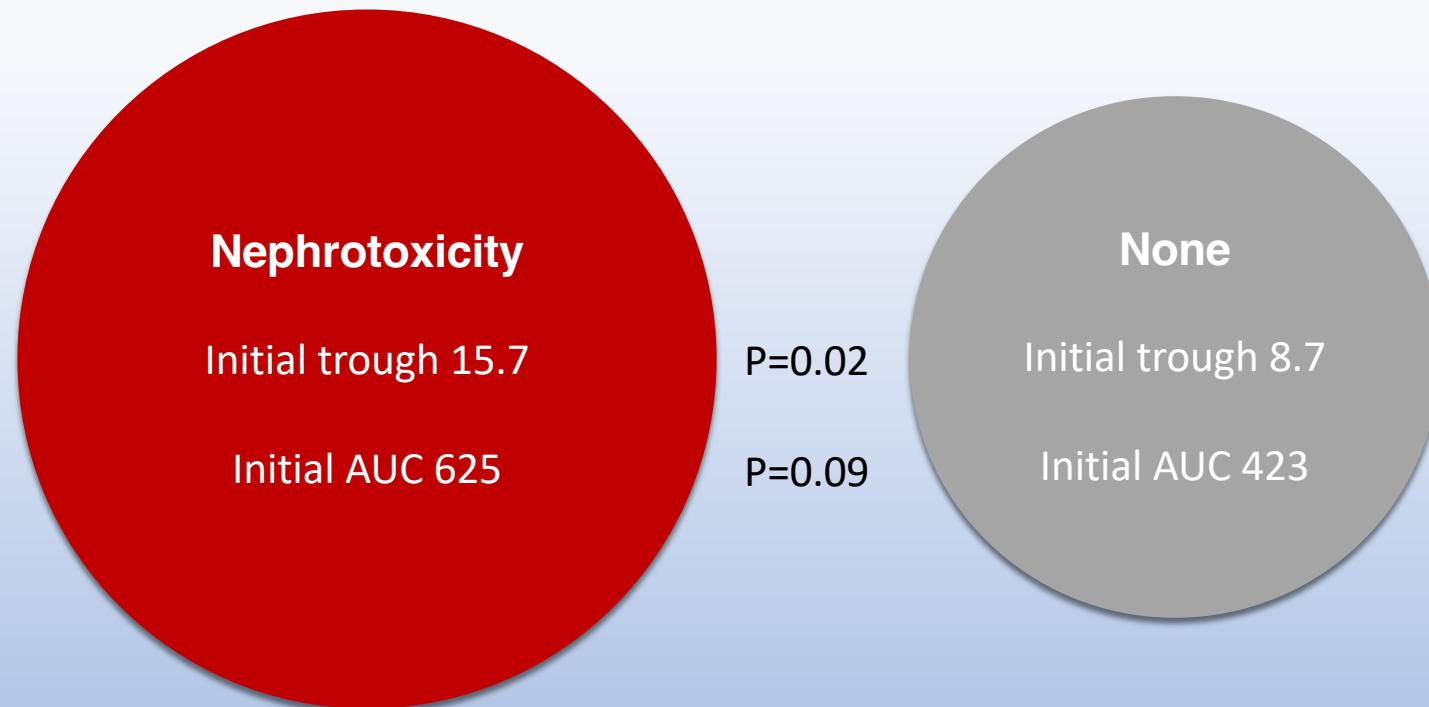
■ <10 ■ 10 to <15 ■ 15 to <20 ■ ≥ 20

End of vancomycin therapy

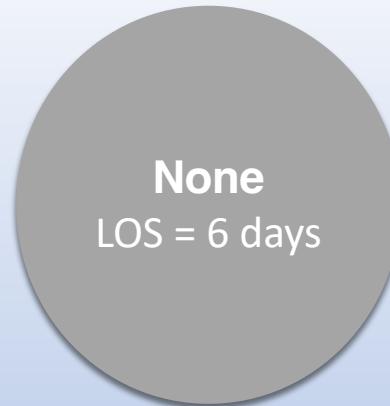
	Year 1 (n=75)	Year 2 (n=88)	Year 3 (n=89)
Resolved	59 (71%)	60 (67%)	66 (74%)
Relapsed	1 (1%)	0	0
Failure	0	0	0
Death	0	0	0
Toxicity	2 (2%)	0	0
De-escalation	7 (8%)	5 (6%)	6 (7%)
Not indicated	8 (10%)	9 (10%)	9 (10%)
Transferred	6 (7%)	16 (18%)	9 (10%)
Nephrotoxicity	6 (7%)	0	2 (2%)

P=0.01

PK-Pharmacotoxicity



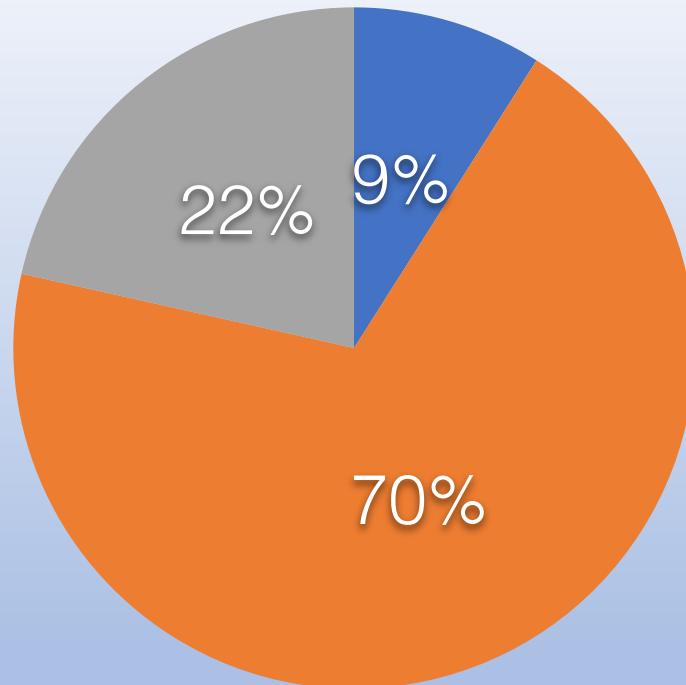
Pharmacoconomics



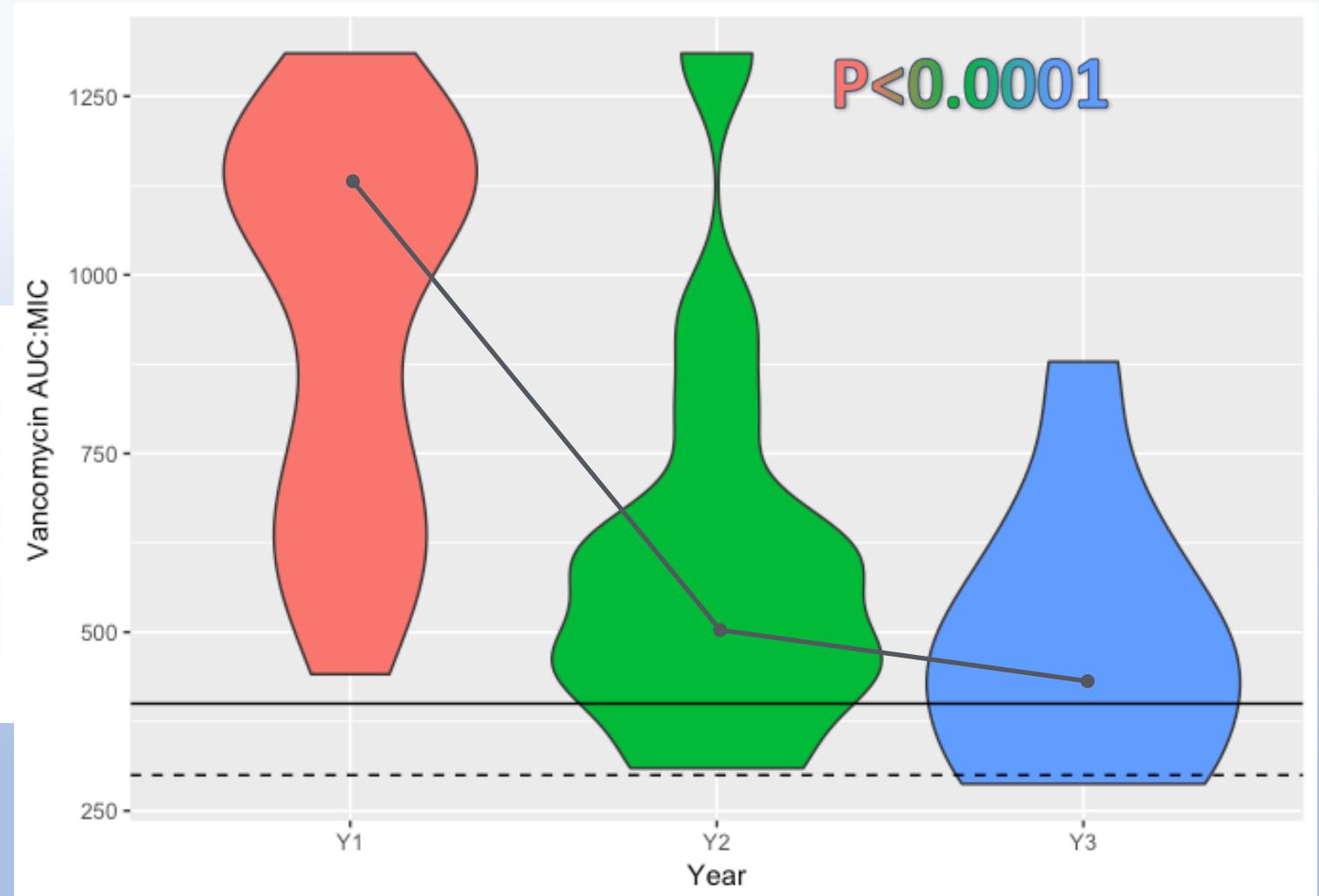
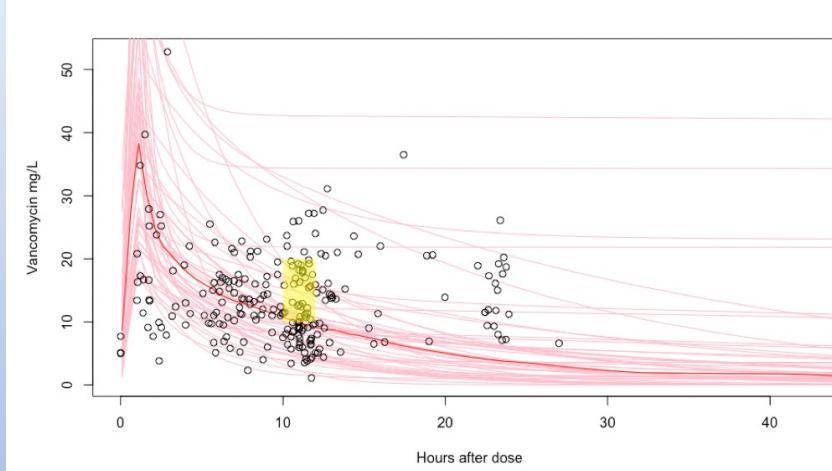
P=0.002
\$146,400 per patient
\$1,171,200 in the study

MMopt Samples

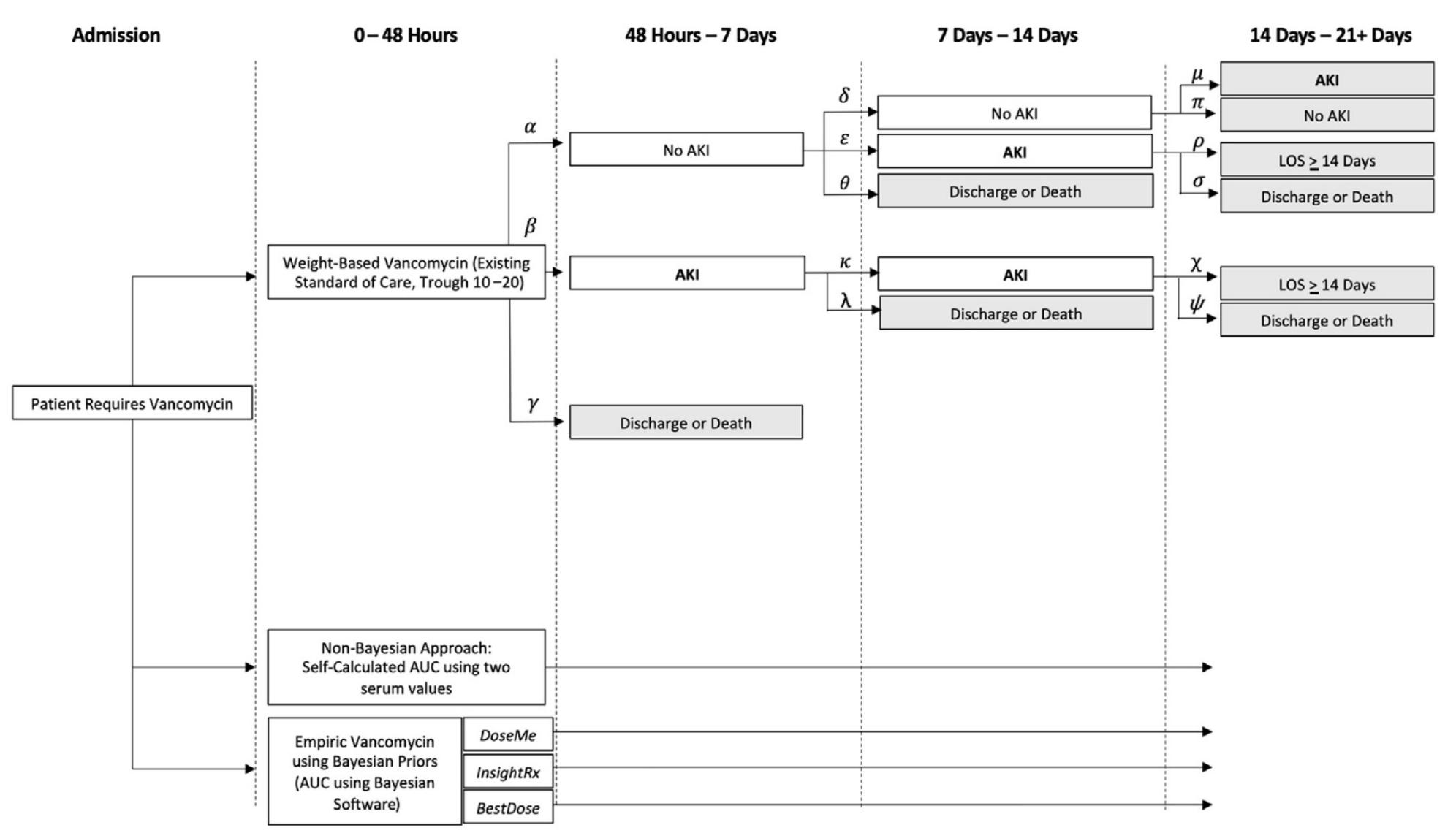
■ Peak ■ Random ■ Trough



Better Control with Bayes



Cost-benefit analysis



Lee, Brian V., Gary Fong, Michael Bolaris, Michael Neely, Emi Minejima, Amy Kang, Grace Lee, and Cynthia L. Gong. "Cost–Benefit Analysis Comparing Trough, Two-Level AUC and Bayesian AUC Dosing for Vancomycin." *Clinical Microbiology and Infection* 27, no. 9 (September 2021): 1346.e1-1346.e7

Table 3

Base case outcomes

Dosing method	Trough (US\$)	Two-sample AUC (US\$)	Bayesian (US\$)
Additional AKI treatment cost per patient	2982	2136	917
Incremental cost benefit vs trough per patient	—	846	2065
Incremental cost benefit for 500 vancomycin patients/year vs trough	—	423 000	1 032 500
Incremental cost benefit for 1000 vancomycin patients/year vs trough	—	846 810	2 065 720
Bayesian AUC program thresholds (no. of patients needed to break-even program cost)			
BESTDOSE	—	0	0
PRECISEPK	—	12	5
INSIGHTRX	—	99	41
DOSEMeRx Year 1	—	15	6
DOSEMeRx Year 2	—	29	12
DOSEMeRx Year 3	—	36	15

Abbreviation: AKI, acute kidney injury.

Busulfan

Existing Busulfan TDM

CHLA	Seattle Cancer Center (SCA)*
First Dose (2 hour infusion)	First Dose (2 hour infusion)
16 doses over 4 days	16 doses over 4 days
9 samples: 0, 2, 2.25, 2.5, 3, 3.5, 4.5, 5.5, and 6 hours	7 samples: 2, 2.25, 2.5, 3, 4, 5, and 6 hours
Excel	WinNonLin
C _{ave} 700-900 ng/mL	C _{ave} 600-700 ng/mL

*Maheshwari S, Kassim A, Yeh RF, Domm J, Calder C, Evans M, Manes B, Bruce K, Brown V, Ho R, Frangoul H, Yang E. 2013. Targeted Busulfan therapy with a steady-state concentration of 600–700 ng/mL in patients with sickle cell disease receiving HLA-identical sibling bone marrow transplant. Bone Marrow Transplant 49:366–369.

Project Goal

Reduce blood sampling



Compare dose calculations

SCA
(NCA)

CHLA
(NCA)

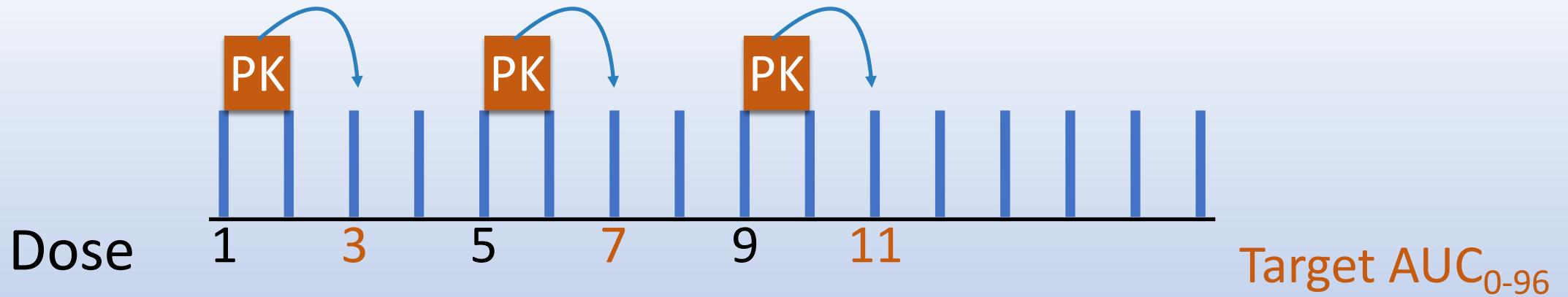
BestDose
(Bayesian)

BestDose
Optimal
(Bayesian)

GOLD STANDARD

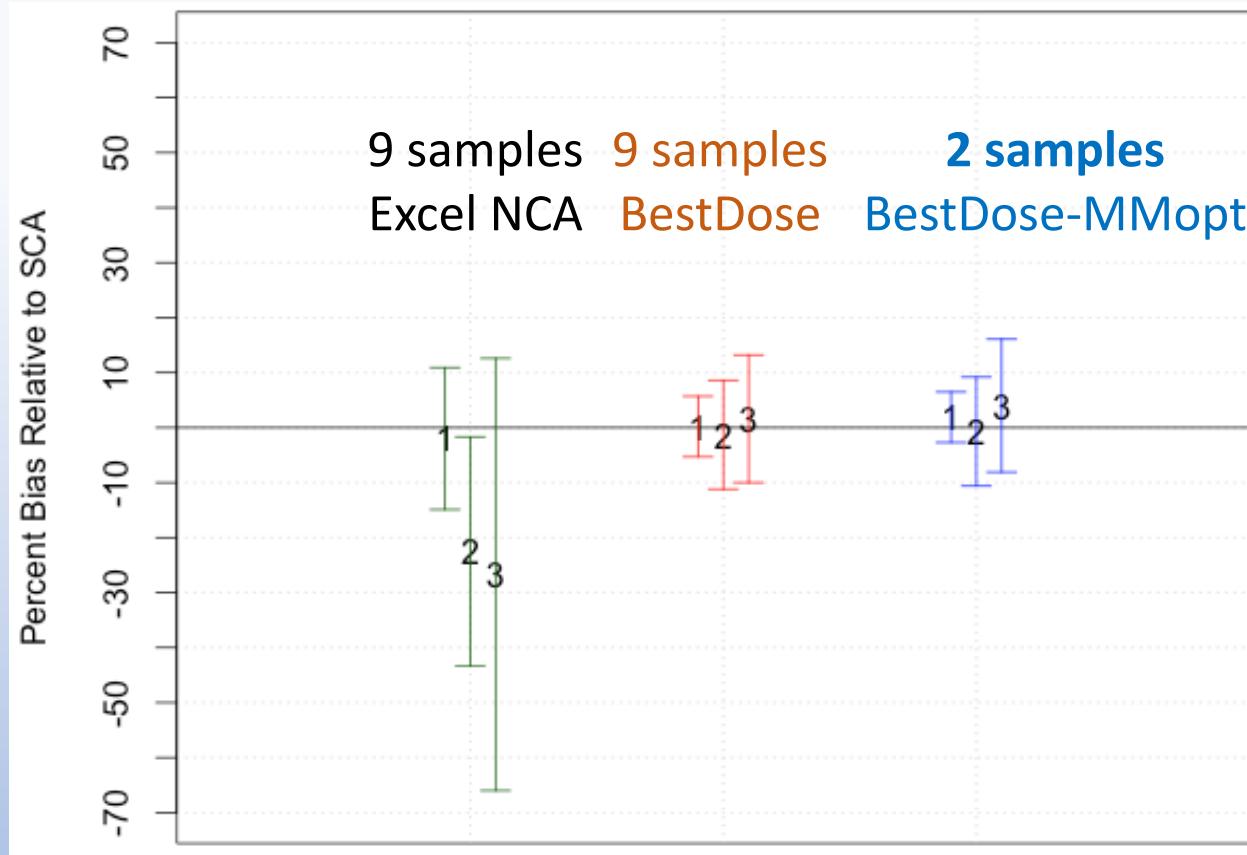
Blinded

Plan



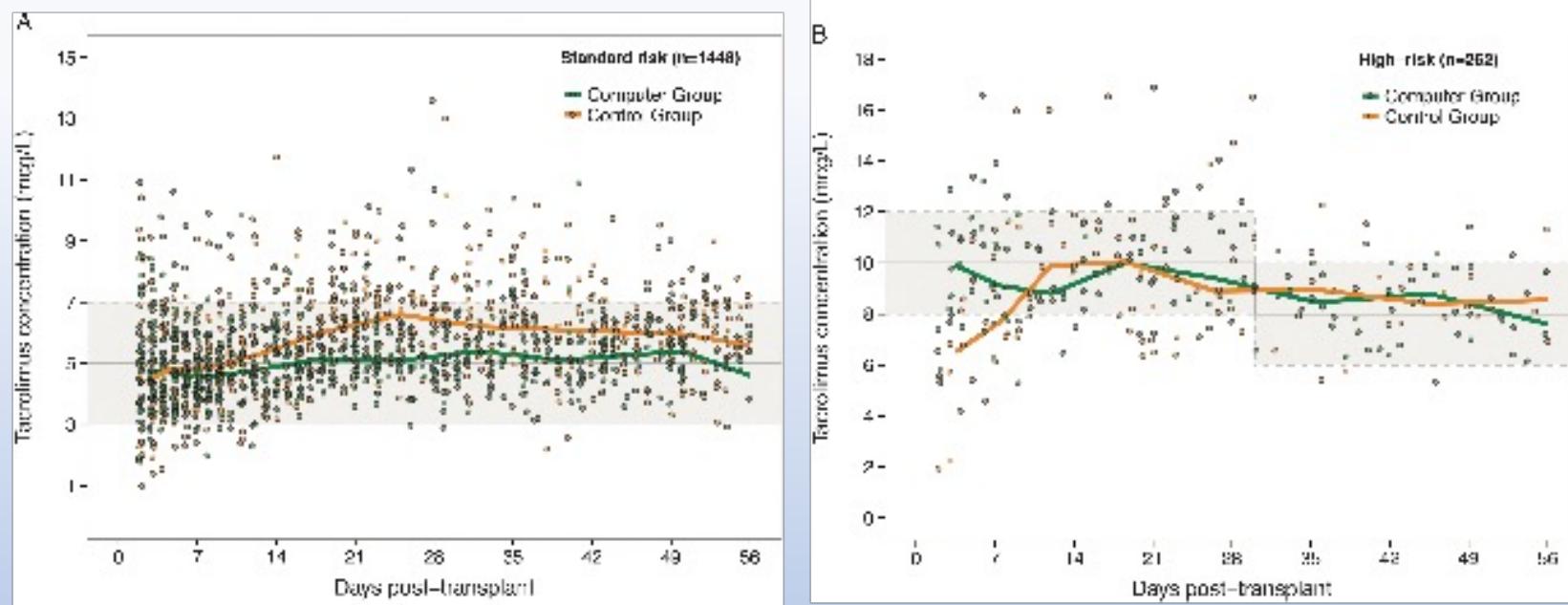
20 patients

Results: Dose Calculation Bias



Neely M, Philippe M, Rushing T, Fu X, Van Guilder M, Bayard D, et al. Accurately Achieving Target Busulfan Exposure in Children and Adolescents With Very Limited Sampling and the BestDose Software. Ther Drug Monit. 2016 Jun;38(3):332–42.

Prospective: Tacrolimus



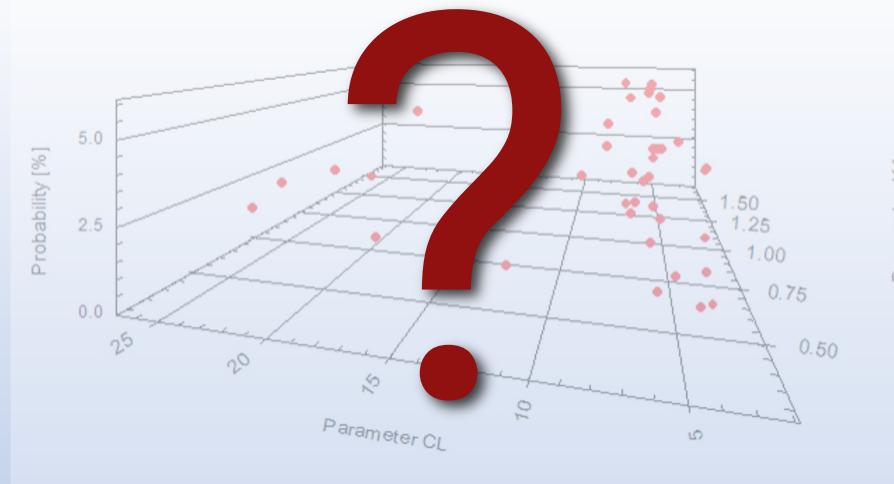
- BestDose – 90% (95% CI 84-95%) therapeutic
28% fewer samples!
- Expert TDM – 78% (75%-82%) therapeutic

(P<0.001)

Tacrolimus-BD outcomes

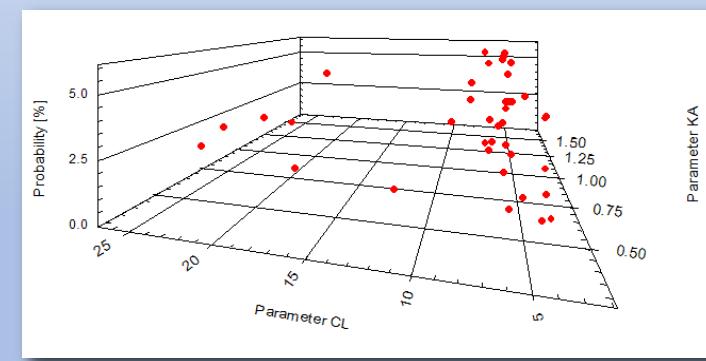
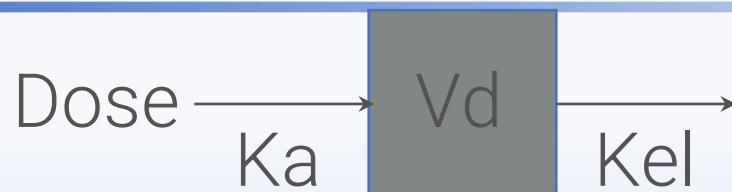
- 2-hour post oral glucose challenge lower in BD group (5.9 vs. 6.8 mmol/L, P=0.008)
- GFR higher in BD group (59 vs. 53 ml/min/1.73m², P=0.046)

A problem



What if you do not have a population model?

Making the priors



Making the priors

- Assume one compartment, absorptive model
- Generate model parameter distributions from literature: k_a , V_d , CL
- Simulate 50 “patients” from these distributions (Monte Carlo)
- Use population modeling software, e.g. Pmetrics, to generate a model from the simulated data

The package insert

351 **Table 7. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic
352 Parameters in Adults**

Regimen	C _{max} (mcg/mL)	T _{max} (hours) [*]	AUC ₂₄ (mcg•hr/mL)	C _{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 1,400 mg q.d. plus Ritonavir 100 mg q.d.	7.93 (7.25-8.68)	1.5 (0.75-5.0)	66.4 (61.1-72.1)	0.86 (0.74-1.01)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

353 ^{*}Data shown are median (range).

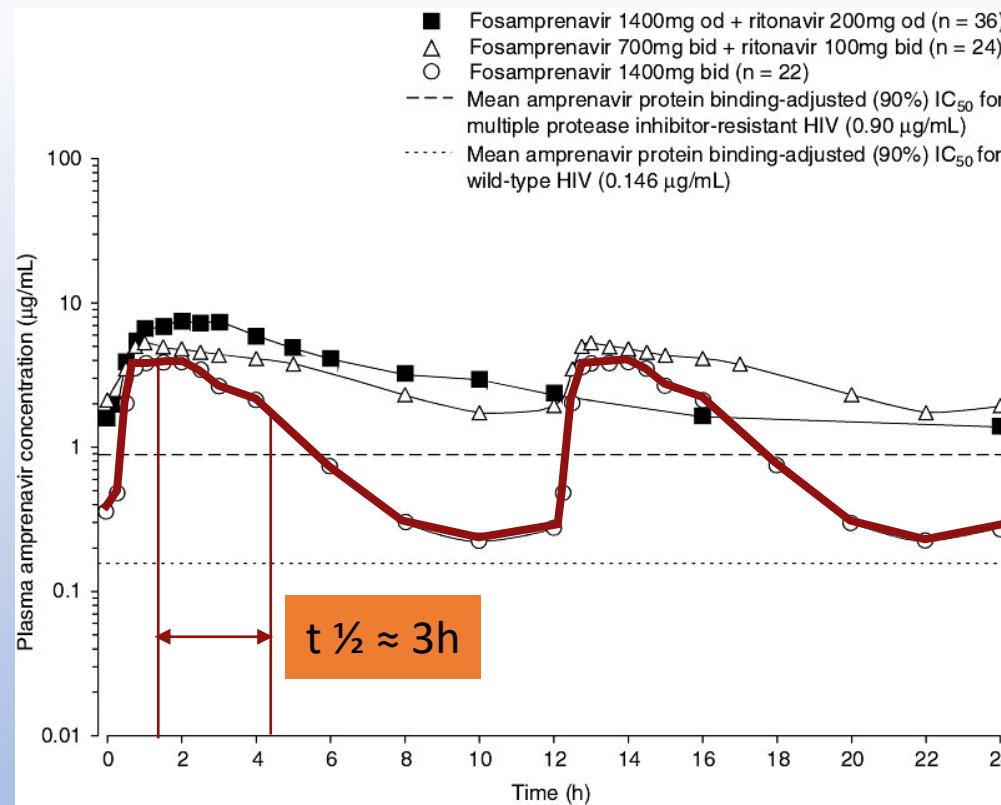
354

The package insert

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single dose of 14C-amprenavir can be accounted for as metabolites in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. **The plasma elimination half-life of amprenavir is approximately 7.7 hours.**

Special Populations: *Hepatic Impairment:* The pharmacokinetics of amprenavir have been studied after the administration of LEXIVA in combination with ritonavir to adult HIV-1-infected patients with mild and moderate hepatic impairment. Following 2 weeks of dosing

The package insert



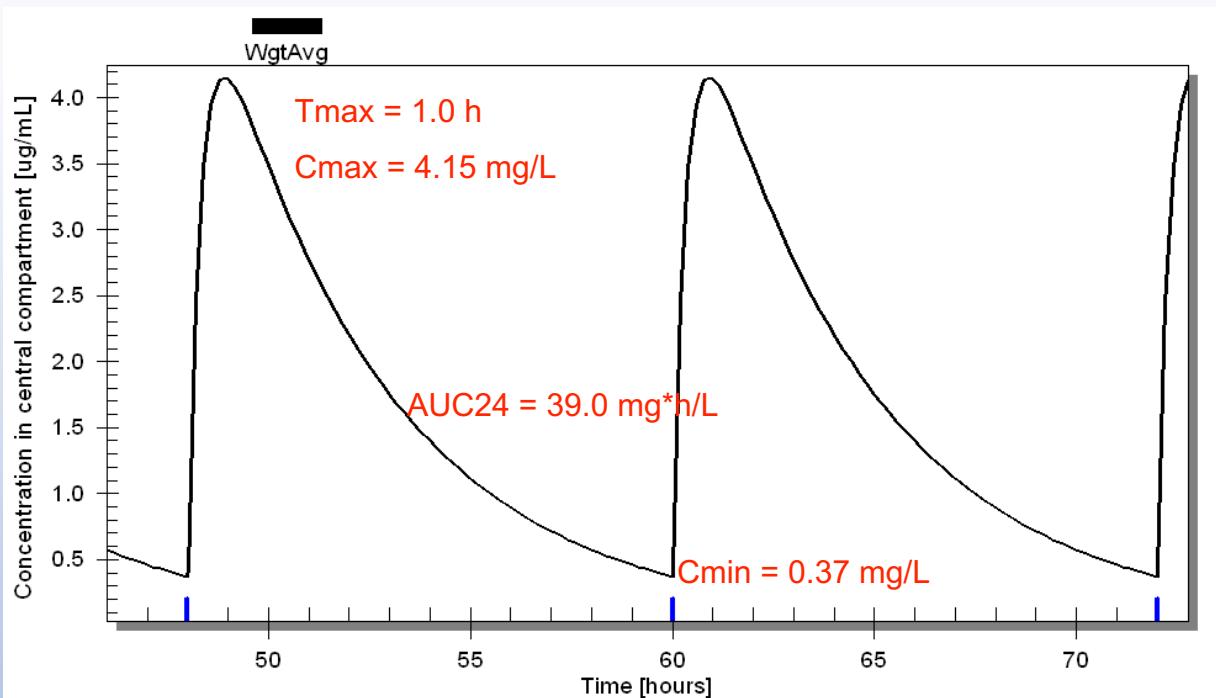
Useful equations

- $\text{Dose} = \text{AUC}_{\text{ss},0-\tau} * \text{CL}$
- $V_d = t_{1/2} * \text{CL} / \ln(2)$
- $k_e = \text{CL}/V$ and $\ln(2) / t_{1/2}$
- $C_{\max} = \text{Dose} * \exp(-k_e * T_{\max}) / V_d$
- $T_{\max} = \ln(k_a) - \ln(k_e) / (k_a - k_e)$

Building the prior

- For fos-amprenavir (derived from package insert)
 - $K_a = 3.0 \text{ (0.38) } h^{-1}$
 - $V_d = 297 \text{ (41) L}$
 - $CL = 68 \text{ (9.4) L/h}$
 - $t_{\frac{1}{2}} = 0.693 * V_d / CL \approx 3 \text{ h}$

Simulating from the model



Regimen	C_{max} (mcg/mL)	T_{max} (hours) [*]	AUC_{24} (mcg•hr/mL)	C_{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)

Points for consideration

- Is the reference from a relevant population?
- Are there multiple references for the same drug? Should parameter estimates be composites?
- You must validate your simulation in some way by comparing it to observed data (e.g. does the simulated AUC agree with the reported AUC)

Conclusions

Non-parametric, multiple-model, Bayesian adaptive control of therapeutic drugs:

- Accurate and precise
- Flexible
- Associated with better outcomes

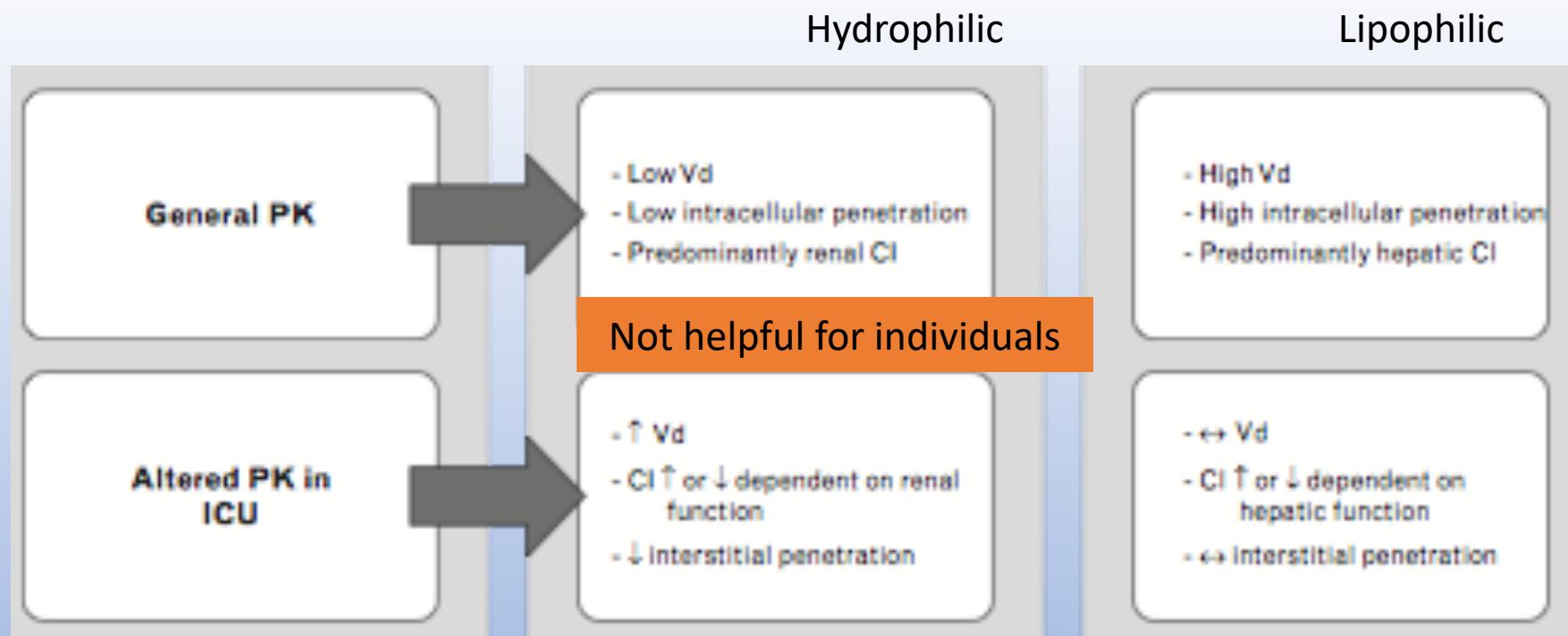
Acknowledgements

- Support from ACCP, NIH-NICHD R01 HD070996 and NIH-NIGMS R01 GM068968
- LAPKB - Mike van Guilder, Alan Schumitzky, David Bayard, Jay Bartroff, Alona Kryshchenko, Tatiana Tatarinova, Walter Yamada, Elliott Keeter, Roger Jelliffe, Bob Leary, Julián Otálvaro, Rong Chen

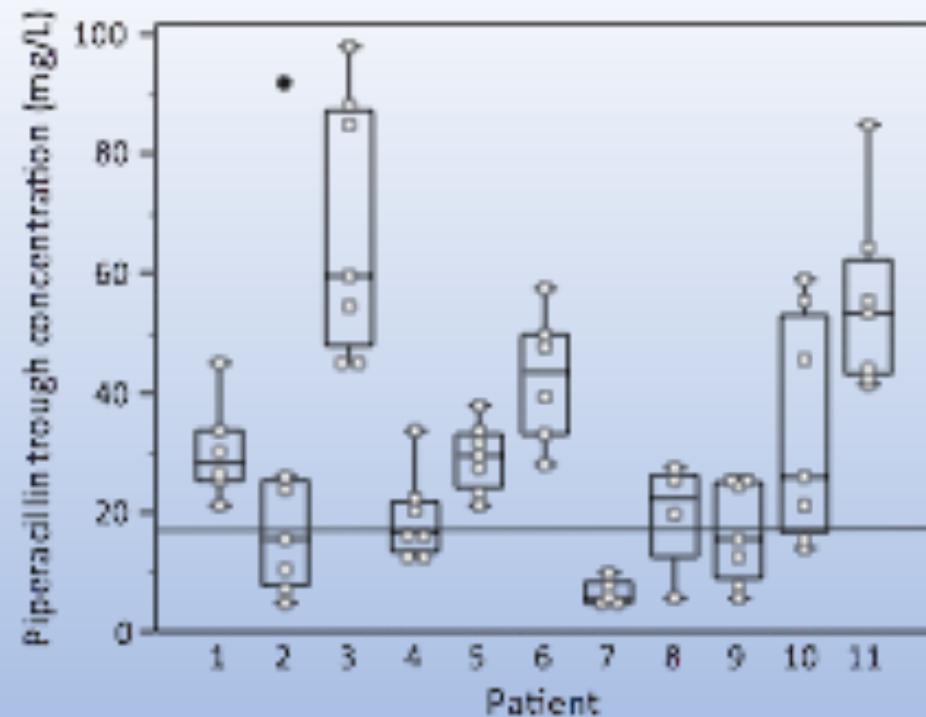
Backup

Critically ill patients are highly variable and unstable.

General principles

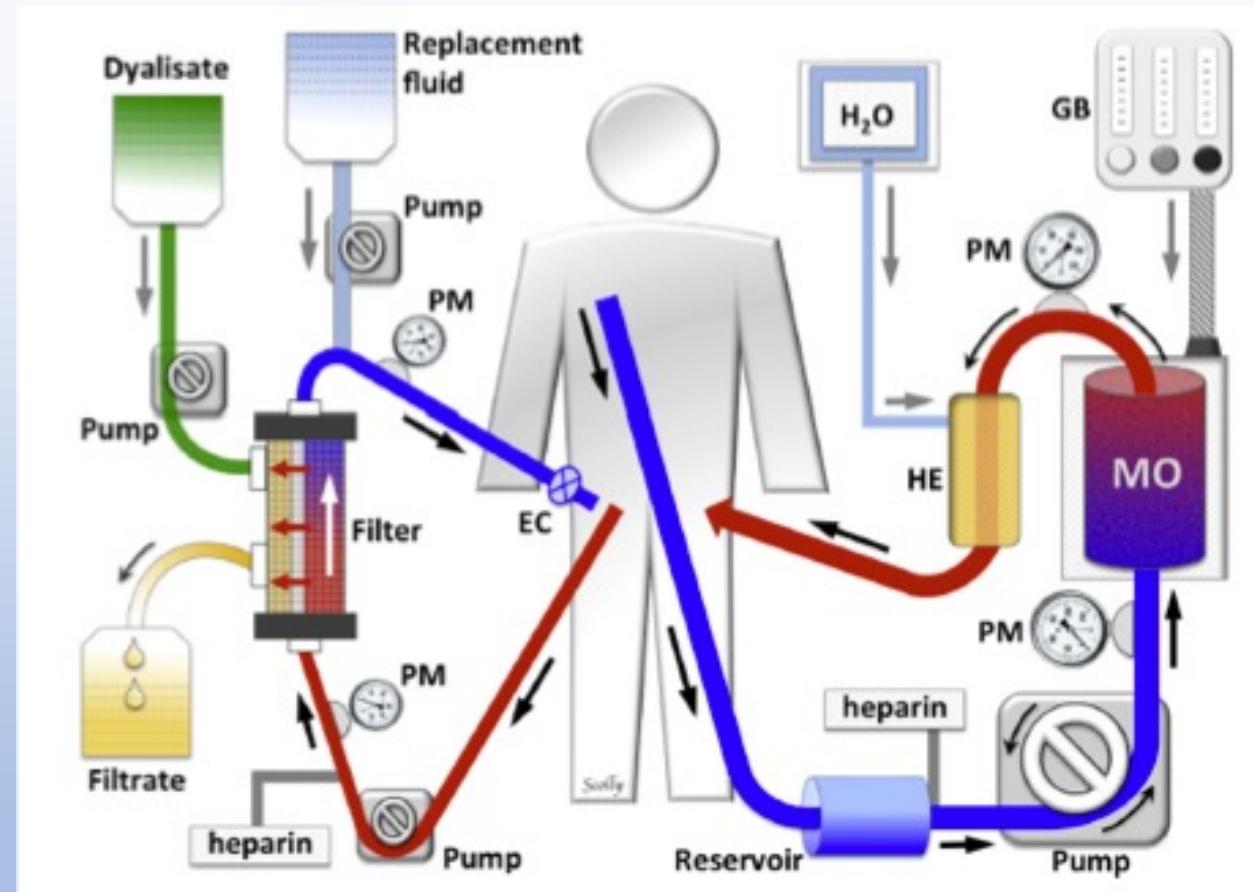


Inter- and intra-individual variability



Carlier, M., Carrette, S., Stove, V., Verstraete, A. G. & De Waele, J. J. Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? A longitudinal study over an entire antibiotic course. *Int J Antimicrob Agents* 43, 470–473 (2014).

More complexity



Graphic courtesy of Jason Roberts, PharmD

IMM - track changing parameters

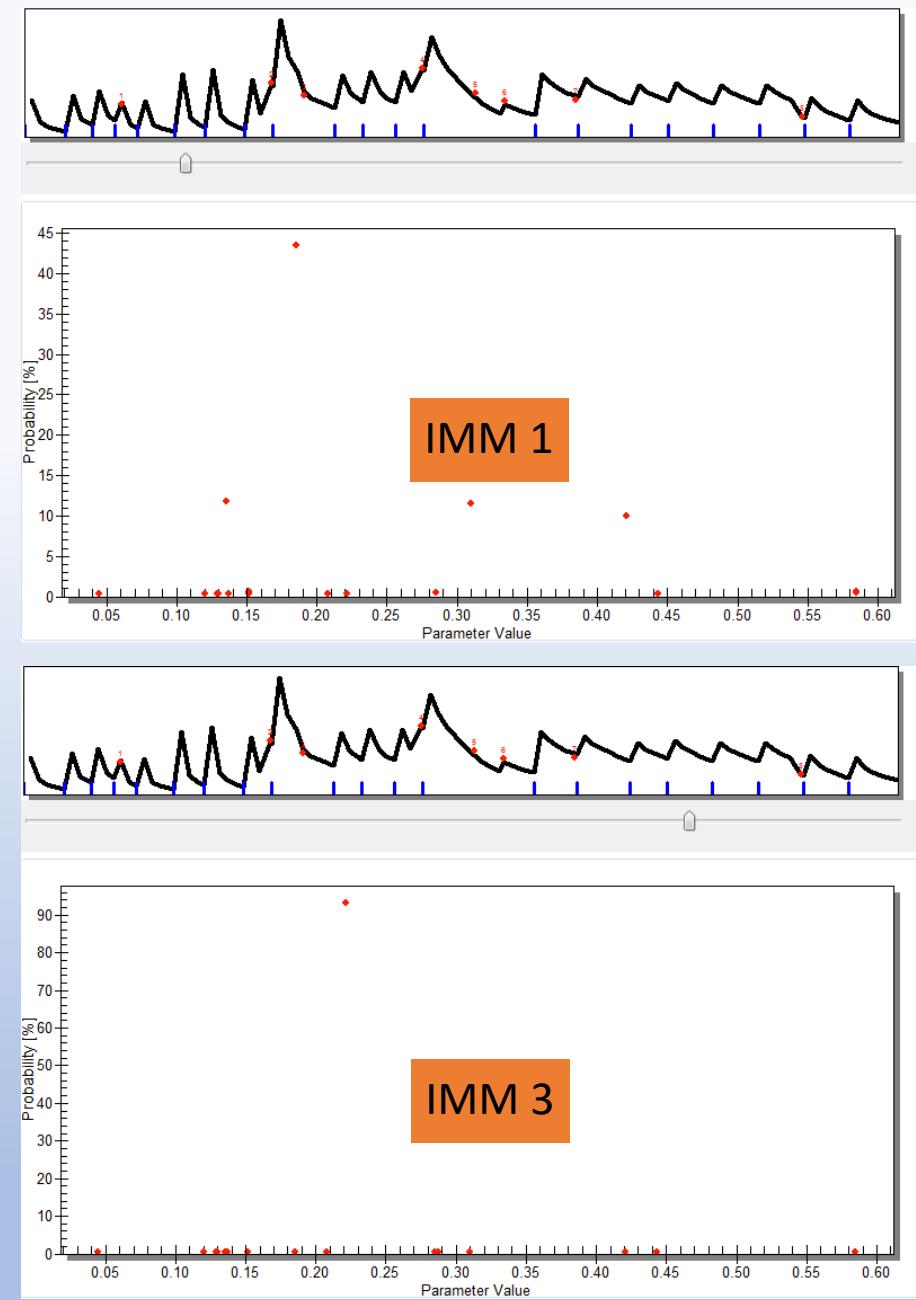
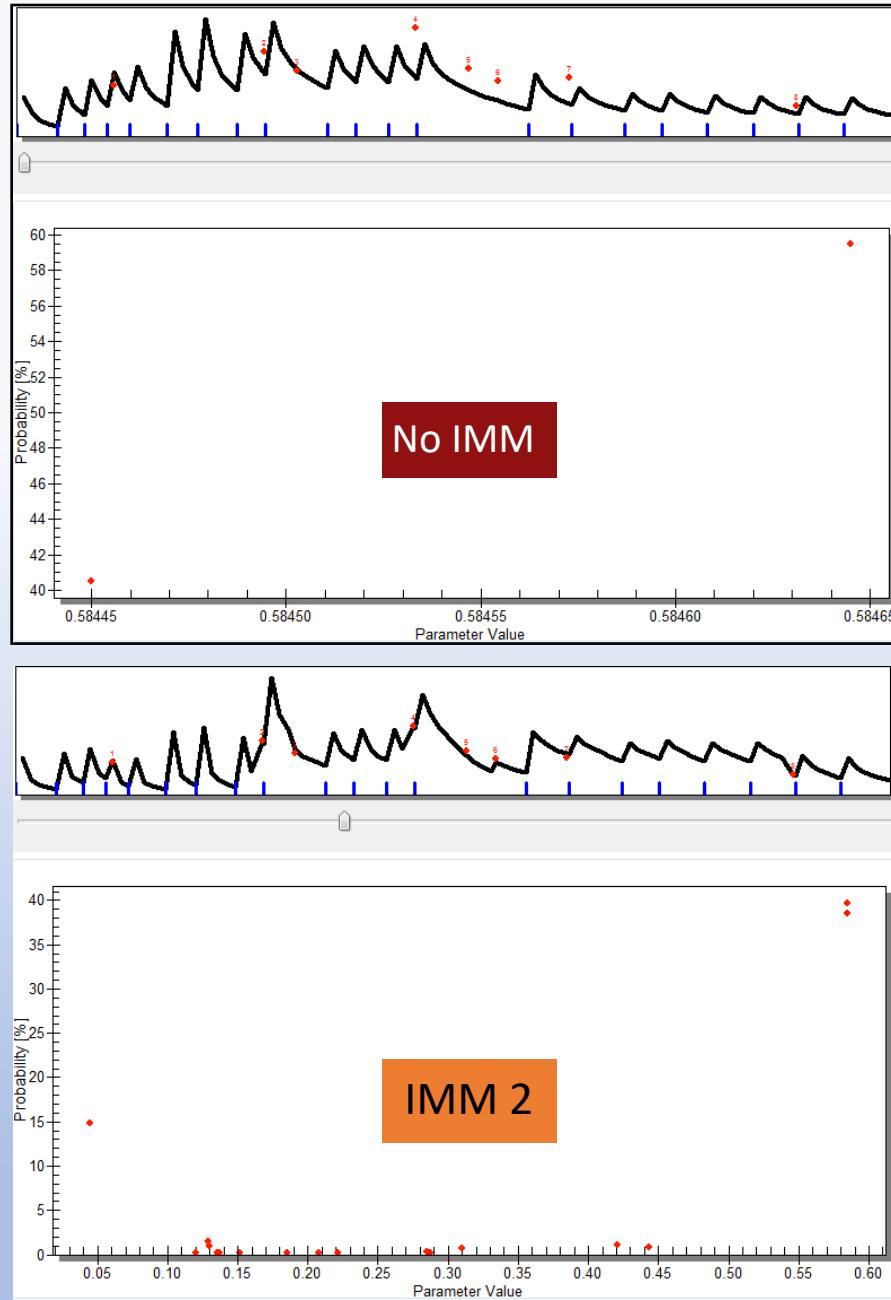
At each measured serum concentration, with a specified probability (usually 3-10%), the model can be refit to the new data to generate a new Bayesian posterior

The points in the model don't change their values, only their probabilities



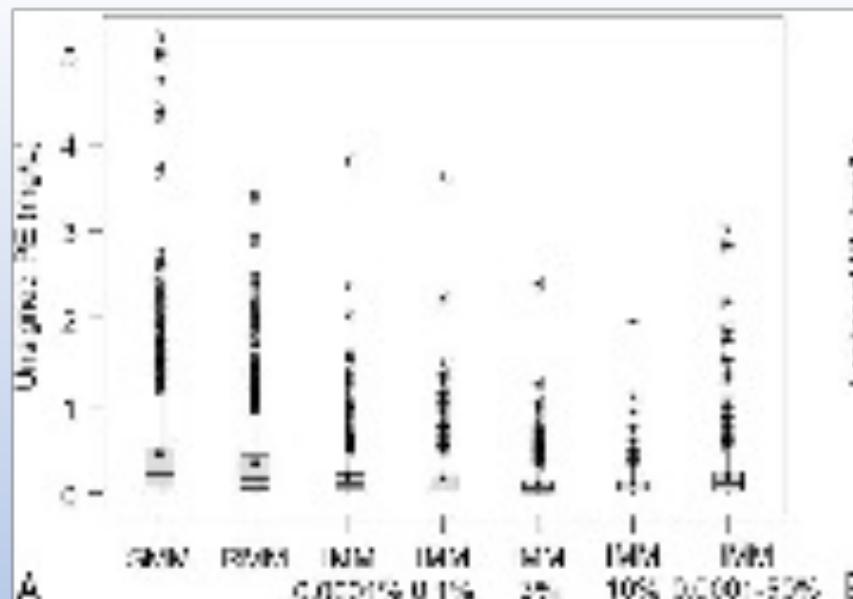
Interacting MM (IMM)

- Useful when one set of parameter estimates does not capture a single patient over time, i.e. the patient is changing
 - For example, development or recovery from septic shock and changes in volume of distribution and/or clearance

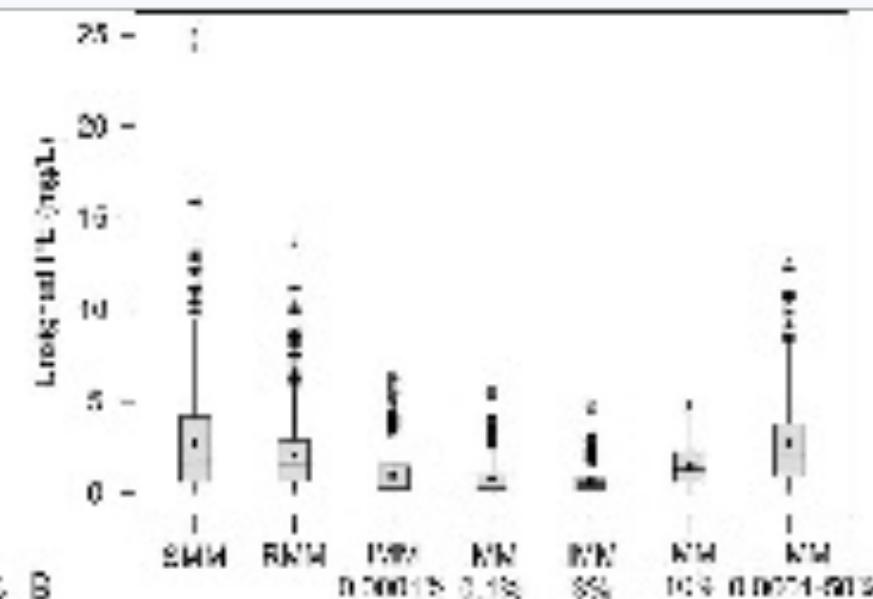


IMM in CTICU Patients

Gentamicin

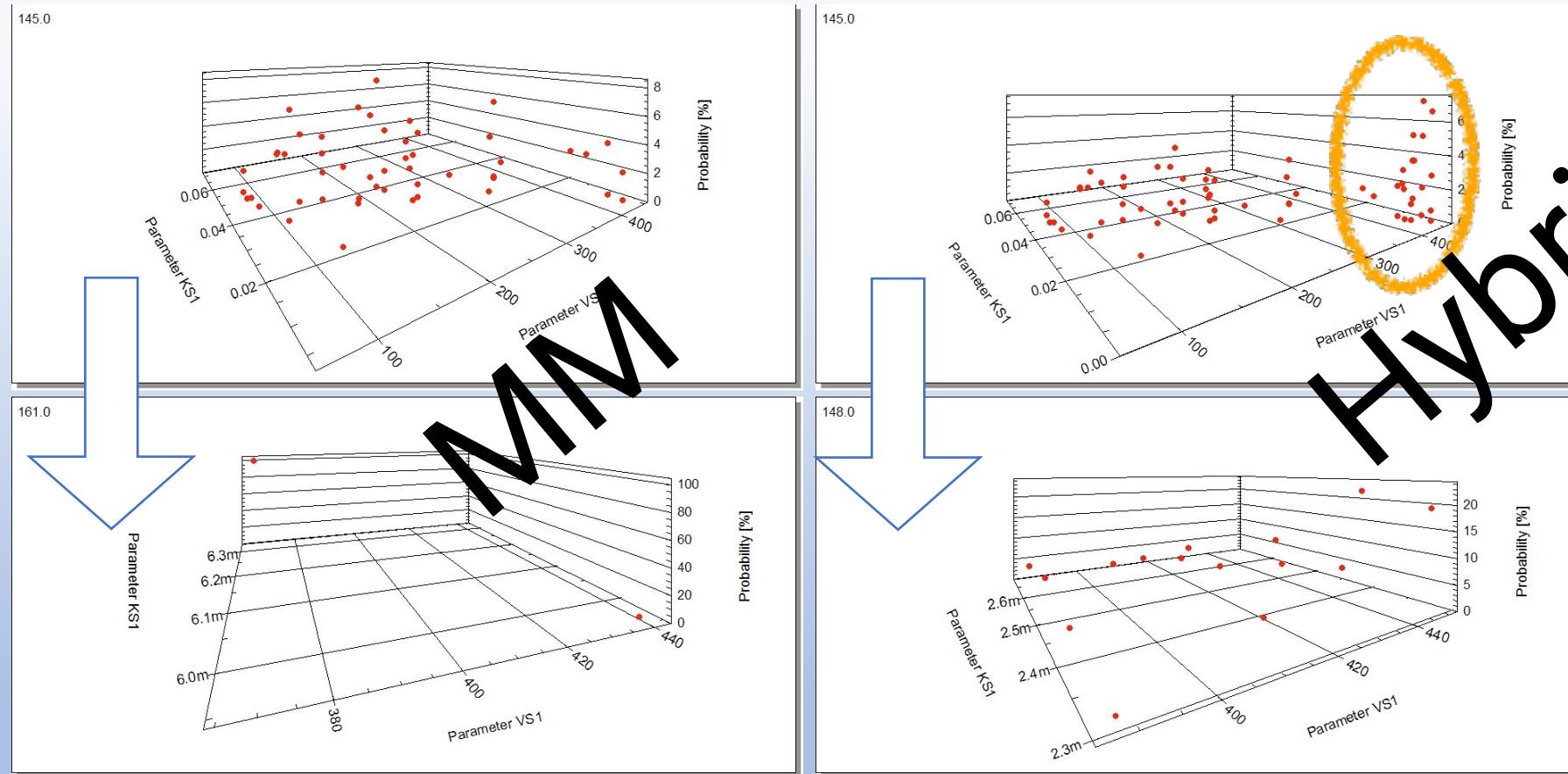


Vancomycin

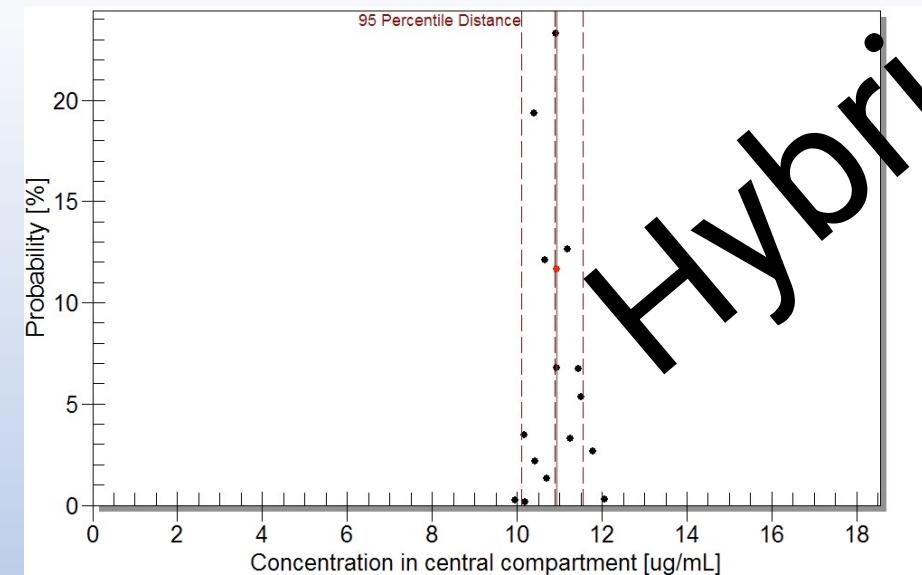
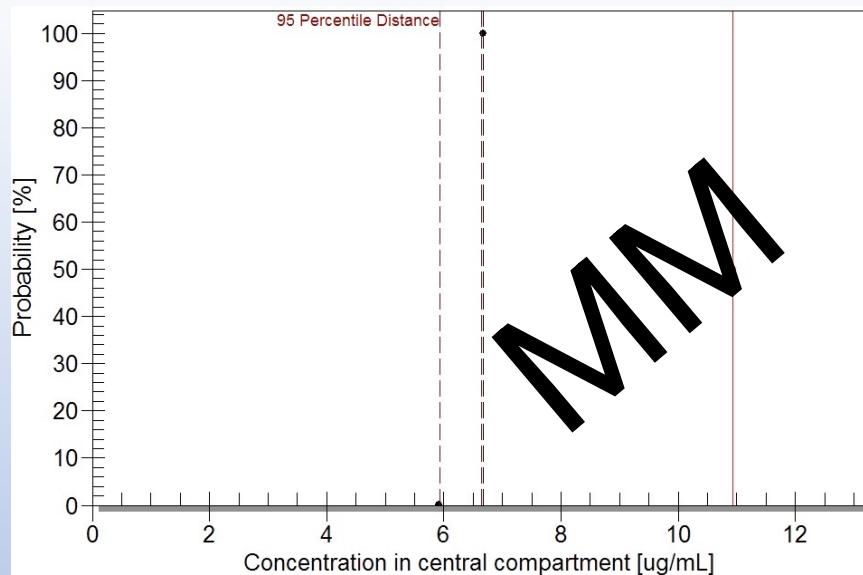


Macdonald, I., Staatz, C. E., Jelliffe, R. W. & Thomson, A. H. Evaluation and comparison of simple multiple model, richer data multiple model, and sequential interacting multiple model (IMM) Bayesian analyses of gentamicin and vancomycin data collected from patients undergoing cardiothoracic surgery. *Ther Drug Monit* 30, 67–74 (2008).

Hybrid MAP Bayesian MM



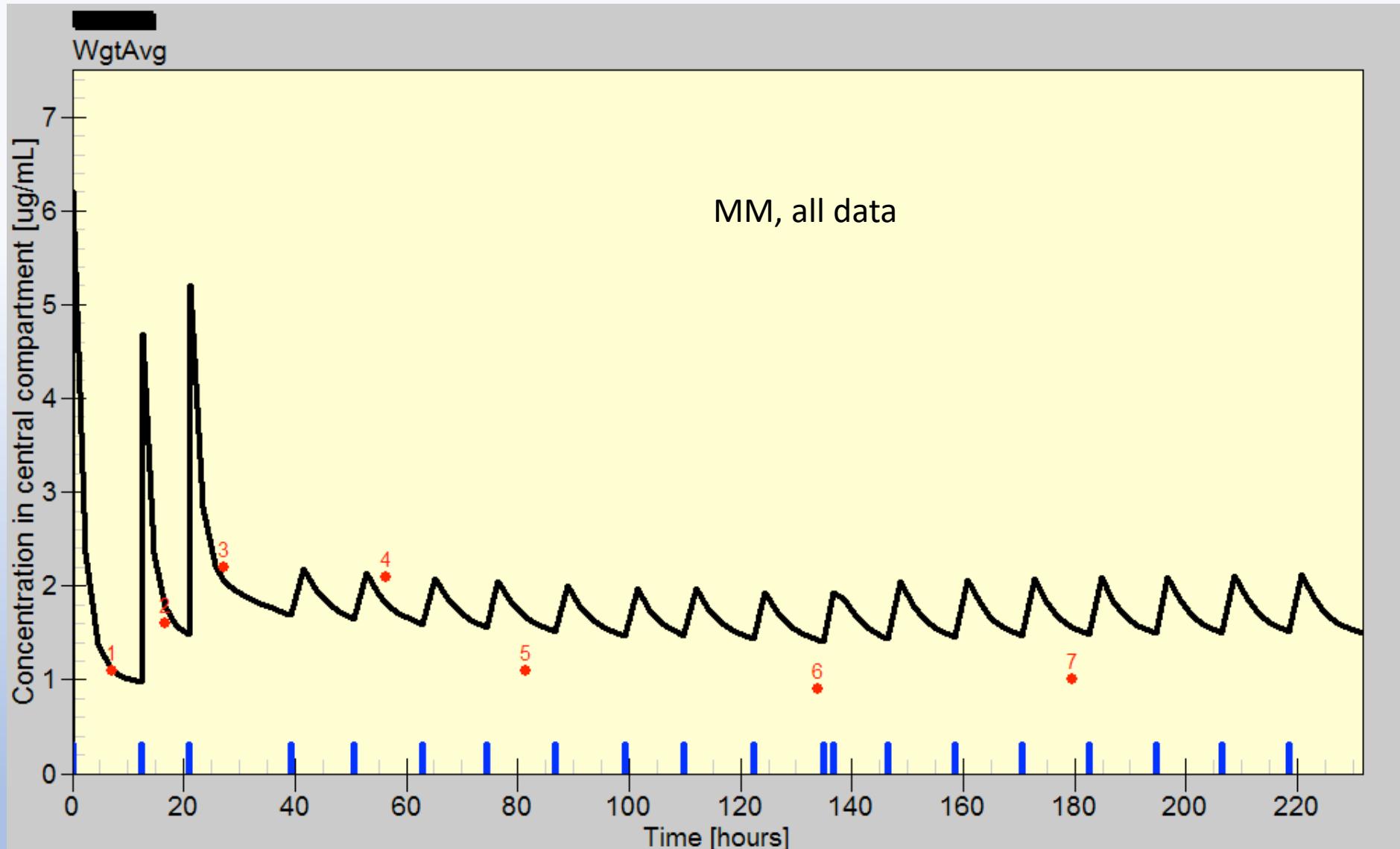
Hybrid MAP Bayesian MM

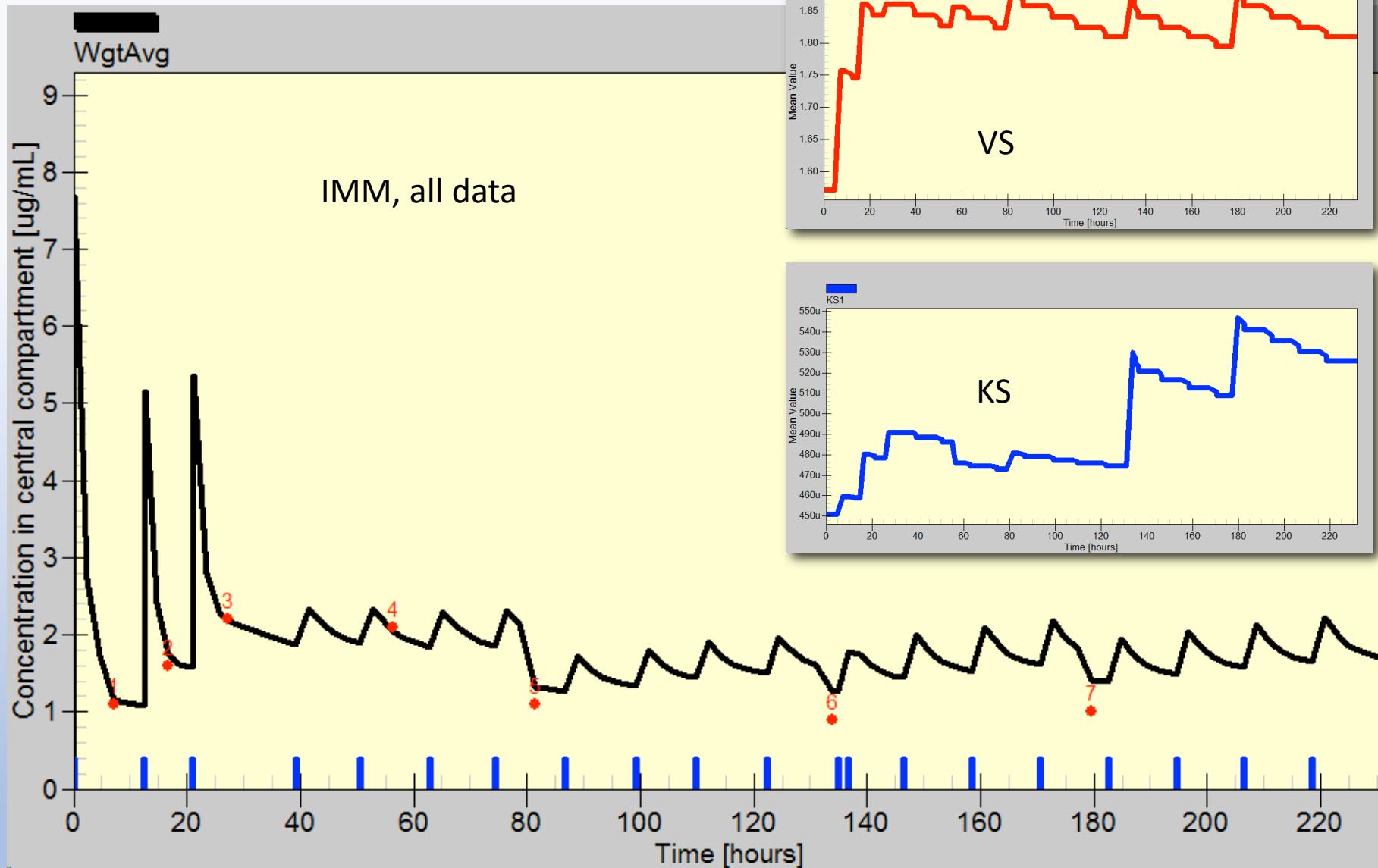


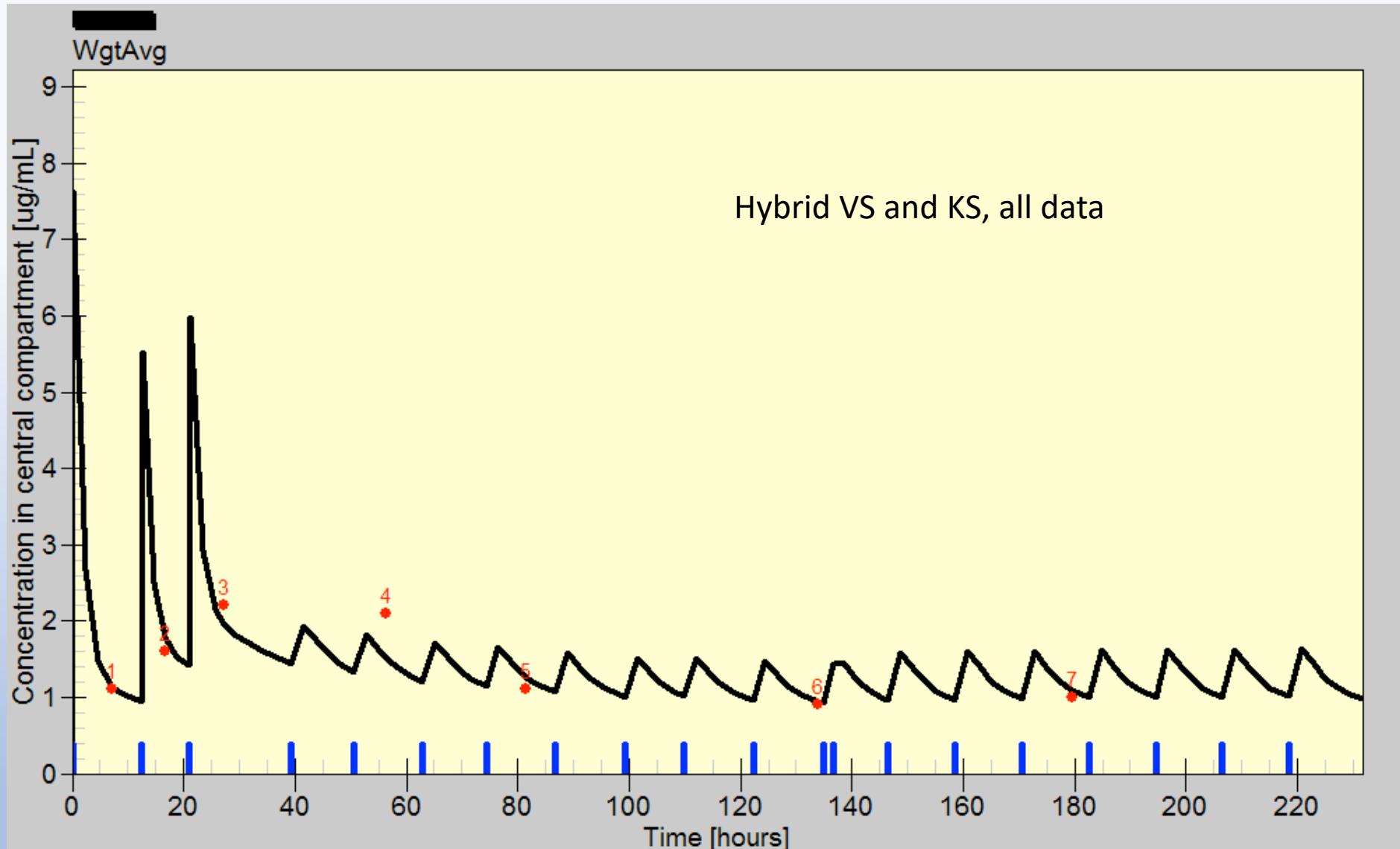
Much better precision!

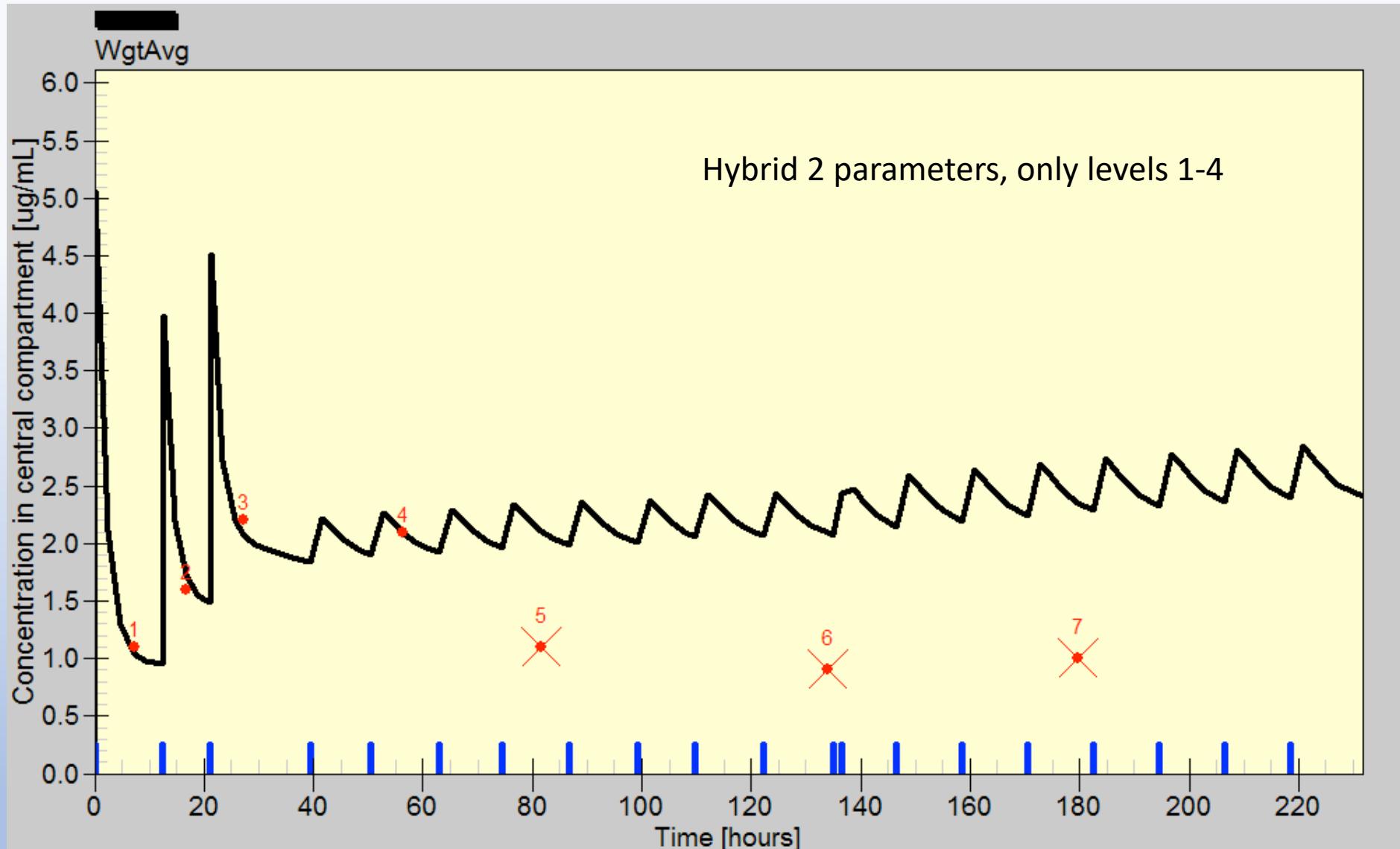
Patient 6

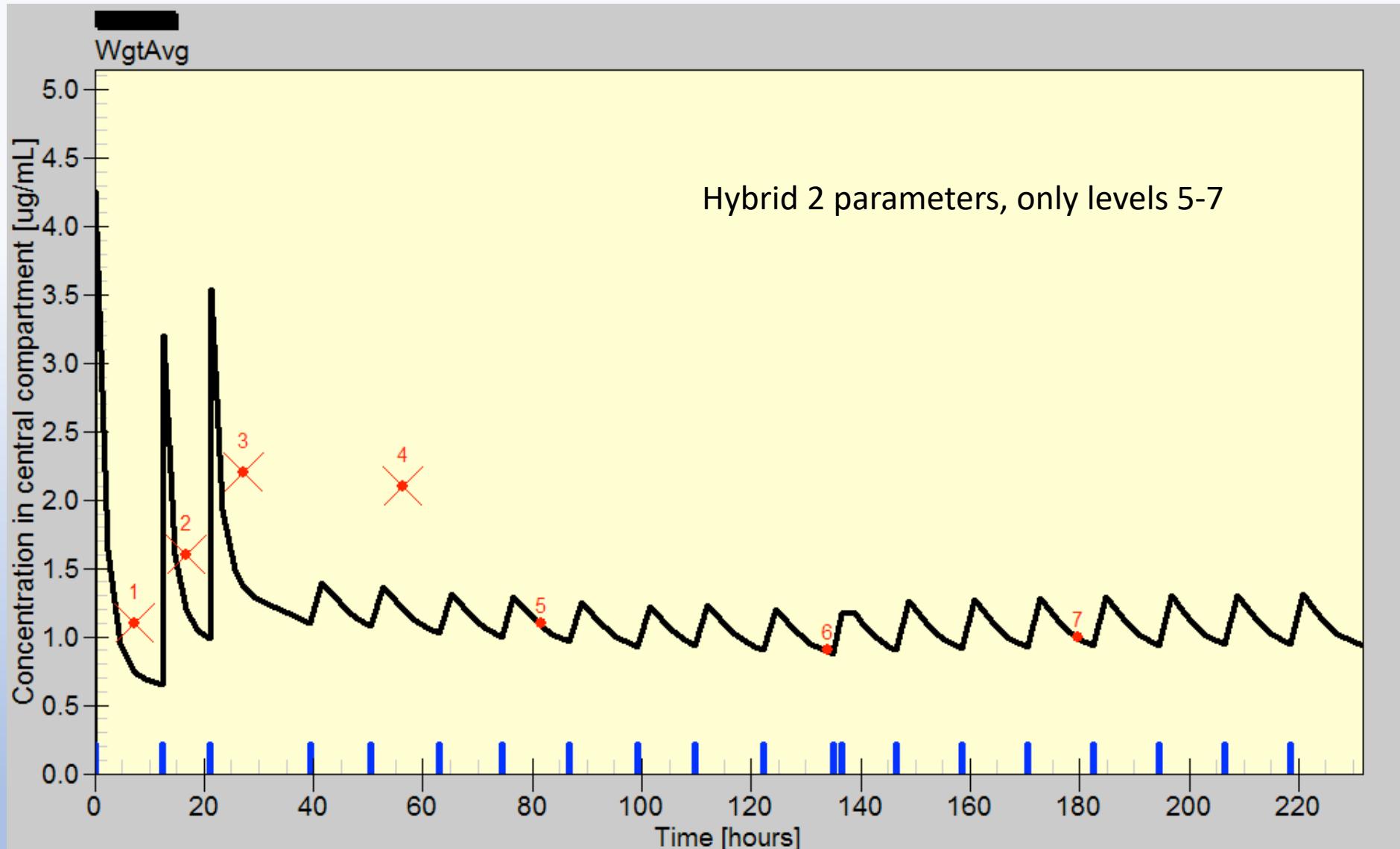
- 5 week old infant presents with supra-ventricular tachycardia (SVT) and a heart rate of >200 beats per minute
- He is in cardiac failure with pulmonary edema
- Team converts him to sinus rhythm with adenosine and begins therapy with digoxin - target is 1 mcg/L
- Over time his maintenance dose requirement increases from 15 to 18 mcg every 12 hours











Changing PK Parameters

	<48 hours	>48 hours	All
VS	2.33	2.76	1.53
KS	0.00018	0.000827	0.0015
KCP	0.45	0.448	0.448
KPC	0.121	0.12	0.12
KA	0.489	0.487	0.487
KI	0.023	0.023	0.023