Slide 1

CLINICAL TRIAL SIMULATION & ANALYSIS

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland, New Zealand

Slide 2

SIMULATION

- Visualise the expected results
- Plan data layout
- Rehearse analysis method
- Optimise design

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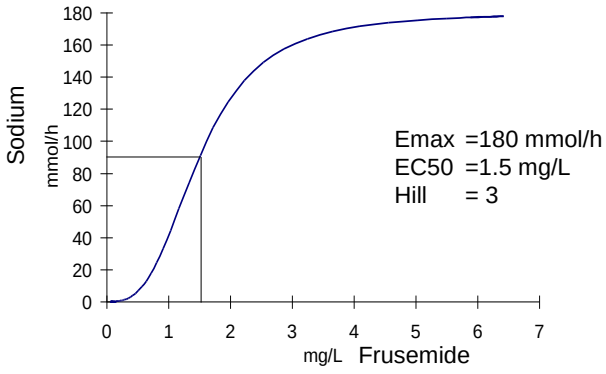
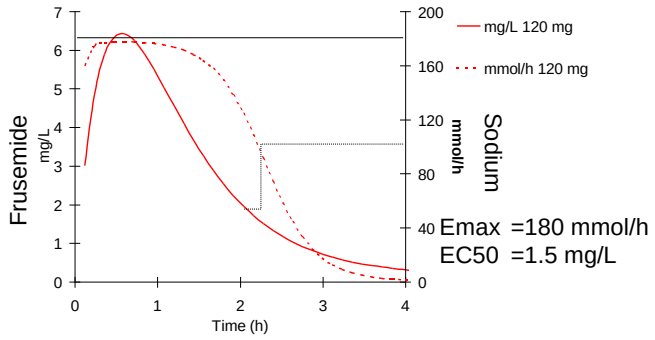
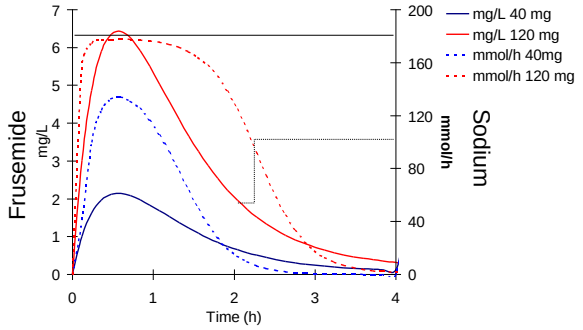
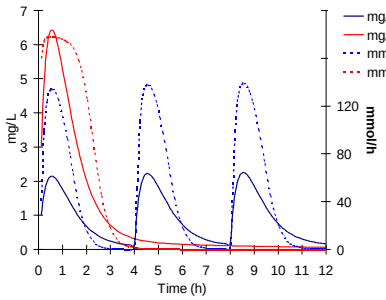
Pharmacometric Tools

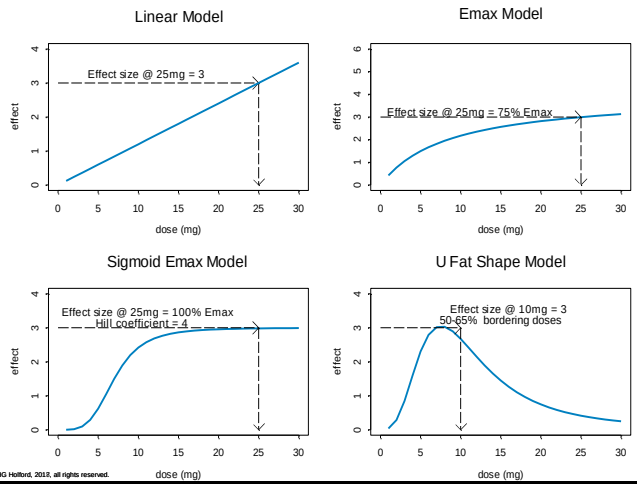
- Simulation
  - Excel
  - Berkeley Madonna
  - Pharsight Trial Simulator
- Individual Non-Linear Regression
  - WinNonLin / Adapt/Kinetica
- Population Non-Linear Regression
  - NONMEM / Monolix/Phoenix

Slide 4	**Using Simulation To Understand Dose, Concentration or AUC?** • Why use Dose? – Direct translation to prescription • Why not use Dose? – Ignores individual differences 	
Slide 5	**Dose, Concentration or AUC?** • Why use Concentration? – Learn about time course – Account for individual PK differences • Why not use Concentration? – May be hard to measure – Extra resources for PK analysis 	
Slide 6	**Dose, Concentration or AUC?** • Why use AUC? – Account for individual PK differences • Why not use AUC? – May be hard to measure – Extra resources for PK analysis – Ignores time course 	

Slide 7	**When is Time Course Important?** • Dose vs AUC is linear • C vs Effect is non-linear • Outcome is related to cumulative effect **Almost all drugs!** 	
Slide 8	**Frusemide Diuretic Effect**  	
Slide 9	**Frusemide Diuretic Effect**  	

Slide 10	**Frusemide Diuretic Effect**  	
Slide 11	**Frusemide Response**  40 mg x 3 » AUCe = 540 mmol Na^+/12h 120 mg x 1 » AUCe = 400 mmol Na^+ /12h **Response is increased 35% using 40 mg x 3** 	
Slide 12	**What Questions does CTS help to Answer?** • **Learning Trials** – How big an effect? – Effect Size Estimates – **Bias and Precision** • **Confirming Trials** – Does the drug work? – YES/NO Answer – **Power** 	

Slide 13	**Simulation Models** • Covariate Distribution – Variability and covariance – Predicts Subject characteristics (age, weight, sex, renal function) • Input-Output – Structural, fixed and random effects – Predicts protocol observations • Execution – Deviations from nominal protocol – Predicts actual observations 	
Slide 14	**Exposure-Response Relationship** • Exposure – Dose – Area under the Conc-Time Curve – Concentration(Time) • Response – Biomarker – Clinical Outcome 	
Slide 15	**Clinical Trial Simulation (CTS) Process** 1. Predict time course of response in patient 2. Add variability (subject, execution) 3. Analyse single clinical trial 4. Replicate Steps 1-3 multiple times (100+) 5. Meta-analysis of multiple replicates 6. Evaluate design performance (e.g. power) 7. Replicate Steps 4-6 over design space 8. Construct design-performance surface 	

Slide 16	**Monte-Carlo Simulation** • Developed for atomic bomb research • Based on using random numbers to generate simulated data • Very powerful tool for modern statistics 	
Slide 17	**Why Use Simulation for Exposure Response?** • **Between subject variability** – Covariate Distribution model • **Complex time varying responses** – Input Output model • **Nominal protocol never happens** – Execution model 	
Slide 18	**Exposure Response Shape**  	

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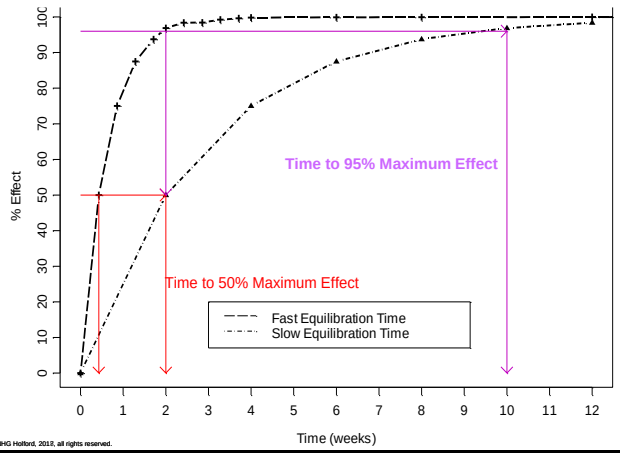
Speed of Onset



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Parameter Sensitivity

- Always uncertainty about key parameters
- Consider two cases compared to existing therapy:
  - **Standard**: New drug similar Emax
  - **Super**: New drug has greater Emax

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Does The Drug Work?

Power to Detect One or More Significant Dose Levels

Assumption	No Effect	Lin	Emax	SEmax	Ushape
Slow Std		63	53	80	21
Fast Std		97	97	100	69
Slow Super		97	98	100	62
Fast Super	1	100	100	100	100

- Sensitive to magnitude of effect
- Poor power for slow onset
- Poor power for U Shape DR pattern
- Type 1 error (no effect column) is acceptable (1%)

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How Big an Effect?

Estimation Bias in Size of Treatment Effect

DR Pattern	Best effect dose	Standard		Super	
		slow onset	fast onset	slow onset	fast onset
Linear	25	45	98	46	98
SEMax	25	68	103	68	104
Emax	25	49	91	50	92
Ushape	10	39	99	41	100

% of true value at 2 weeks for best effect dose

• Slow onset has **biased** (under) estimate of true treatment effect

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Conclusion

Why Do Simulation?

- Deterministic
  - Complex questions
  - Often simple graphs (e.g. frusemide)
- Stochastic
  - To answer a statistical question
  - Power, Precision

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Slide 25	ANALYSIS • Descriptive • Comparison – Means – Proportions • Regression – Linear – Non-linear 		
Slide 26	Descriptive Statistics • Mean • Standard Deviation • Standard Error • etc 		
Slide 27	Means • Two Samples – t-test • ANOVA – one factor – two factor – etc • Parametric/Non-Parametric • Repeated Measures 		

Slide 28	## Proportions • Chi-square 	
Slide 29	## Regression • Correlation • Linear regression – simple – multiple • Non-linear regression – individual – population 	
Slide 30	## Regression • Parameters and Models – Test hypotheses with different models – Estimate parameters 	