A Clinical Trial Simulation System, Its Applications, and Future Challenges

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- Miles Dunn, Amgen Pharmaceuticals
- Alin Tomoiaga, Texas Tech University

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- Vertex colleagues
- Merck colleagues and reviewers

PK/PD M&S

- Nick Holford (Univ. of Auckland, New Zealand)
- Ken Kowalski (A2PG)

Outline

- A CTS system
- CTS System overview
- Statistics in the system
- Examples of its applications
- Future challenges

Based on Westfall et al. (2008; CTS: A statistical approach, J Biopharma Stat)

Out of Scope

- The interface system
- Grid computation
- Details about PK/PD M&S
- Comparison to other CTS software

Why a CTS System? (I)

CTS on critical path

- Toward a better effectiveness toolkit
- Perform advanced clinical trial design and execution

Why a CTS System? (II)

Complicated clinical trial issues

- Biomarkers and surrogate endpoints
- Multiple correlated endpoints
- Combination therapies
- Subgroups
- Uncertain dose response relationship
- Dropouts
- Noncompliance
- Multiple treatment arms and patient allocation
- Approximate statistical methods (asymptotic not valid)
- How long to run the study?
- Which statistical test(s) to use?

Our Goal of a CTS System

To simulate ***realistic*** data sets

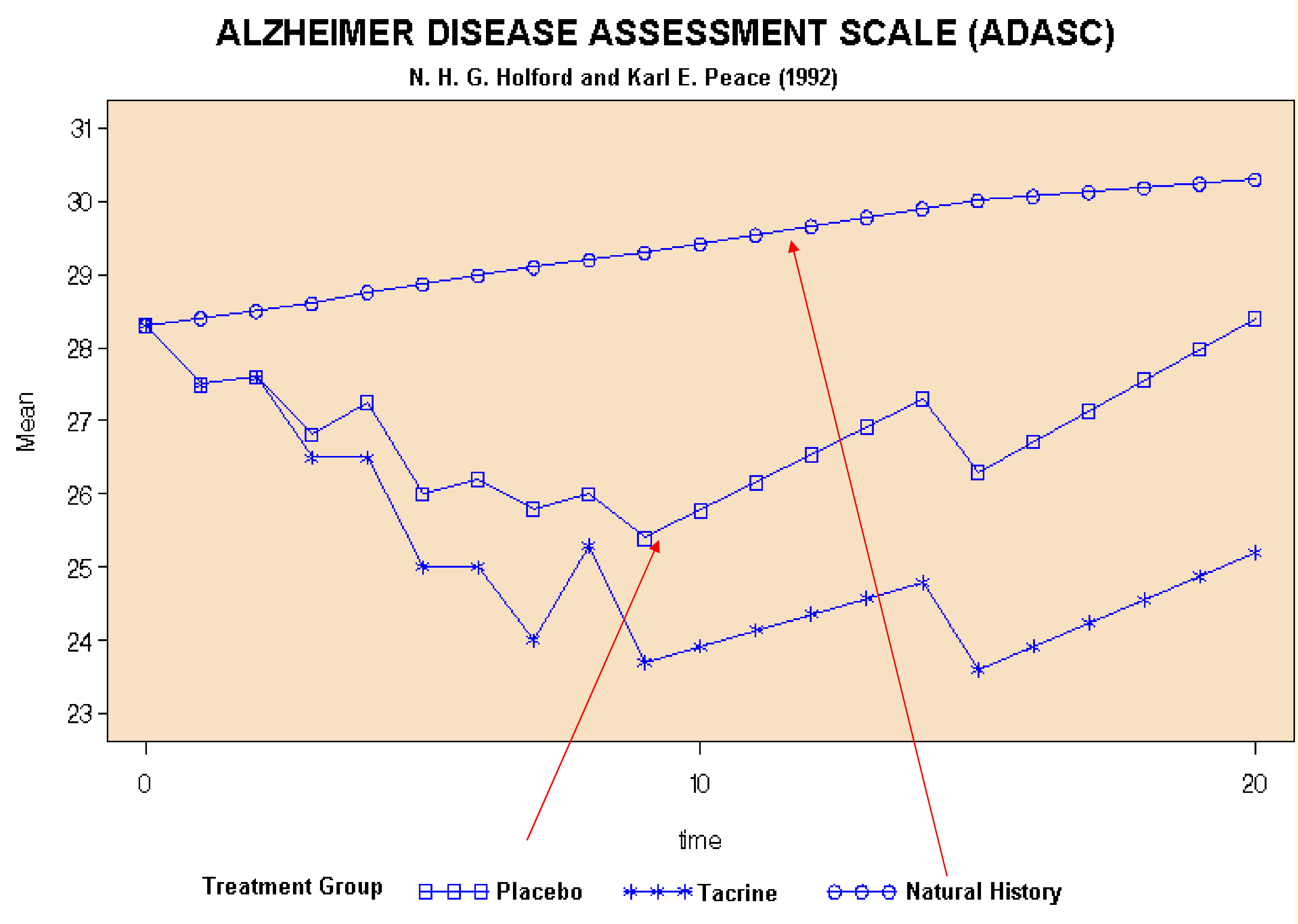
- Multiple timepoints/endpoints with flexible covariance structures
- Flexible mean structures and flexible distributions
- Complex compliance issues
- Informative dropout mechanisms

General Approach to CTS

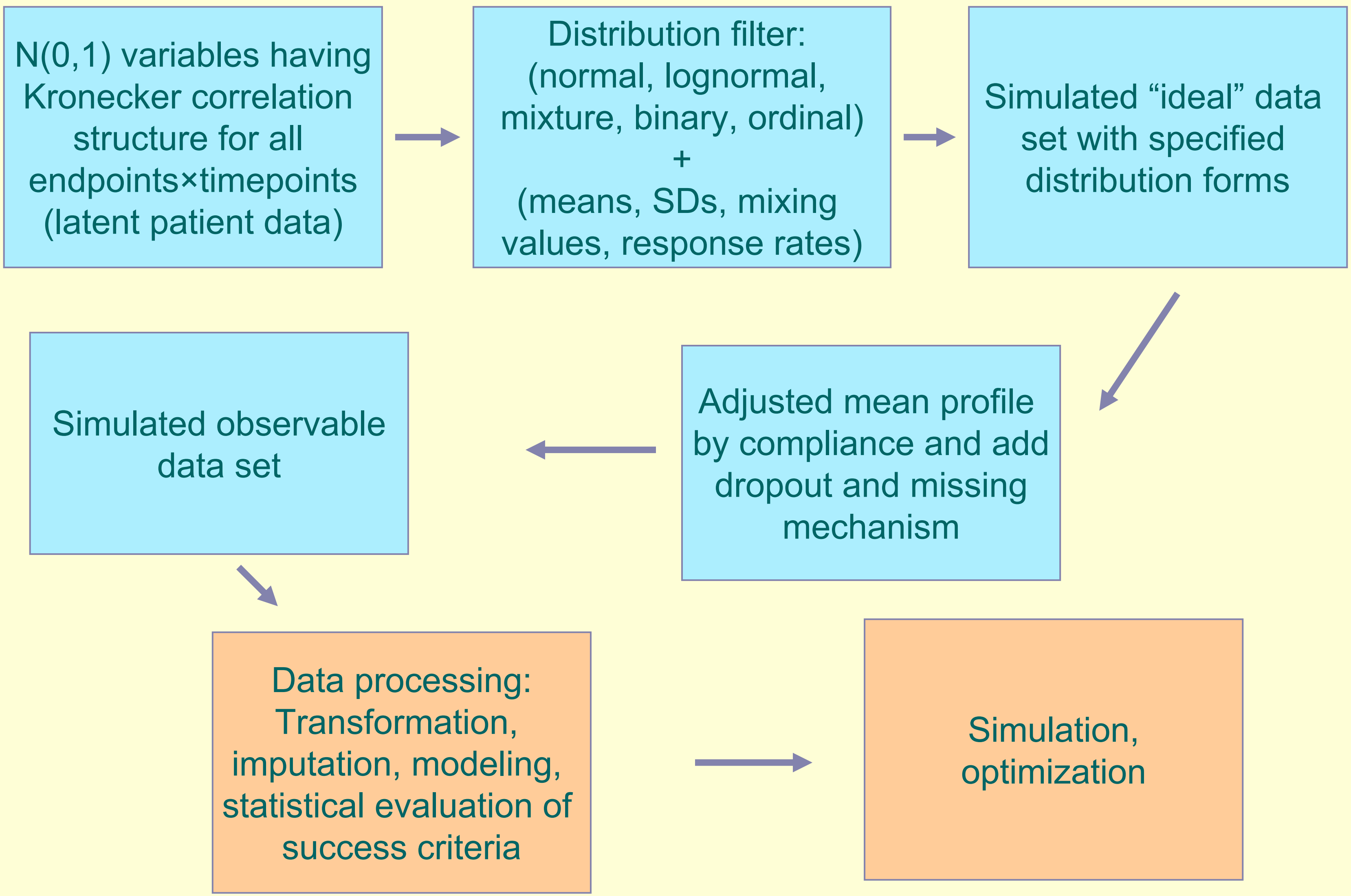
- Define model and model parameters
- Define decision outcomes
- Simulate success criteria
- Iterate, choose optimal design/analysis criteria

Our Approach

- Input: Historical/a priori inputs, specific on PD models, multiple endpoints
- Applications: emphasis on phase II/III design with noncompliance and dropout mechanisms, but can be for certain Phase I designs
- Statistical resolutions for complicated CTS
  - Flexible covariance structures
  - Flexible mean structures, including natural history and placebo effects, and filter
  - Statistical emphasis


ALZHEIMER DISEASE ASSESSMENT SCALE (ADASC)
N. H. G. Holford and Karl E. Peace (1992)
Mean
31
30
29
28
27
26
25
24
23
0
10
20
time
Treatment Group
Placebo
Tacrine
Natural History

Overview of CTS System



CTS System

N(0,1) variables having Kronecker correlation structure for all endpoints×timepoints (latent patient data)

→

Distribution filter:
(normal, lognormal, mixture, binary, ordinal)
+
(means, SDs, mixing values, response rates)

→

Simulated "ideal" data set with specified distribution forms

→

Adjusted mean profile by compliance and add dropout and missing mechanism

→

Simulated observable data set

→

Data processing: Transformation, imputation, modeling, statistical evaluation of success criteria

→

Simulation, optimization

First Simulation Process

- Simulate repeated measures data for patient*endpoint data
  - Simulate correlated data with AR(1) as a carrying over effect for a patient endpoint data
  - Construct correlations between endpoints
  - Construct correlation for patient*endpoints
- Construct correlations for all patient data
- Efficiently simulate data with Kronecker covariance structure

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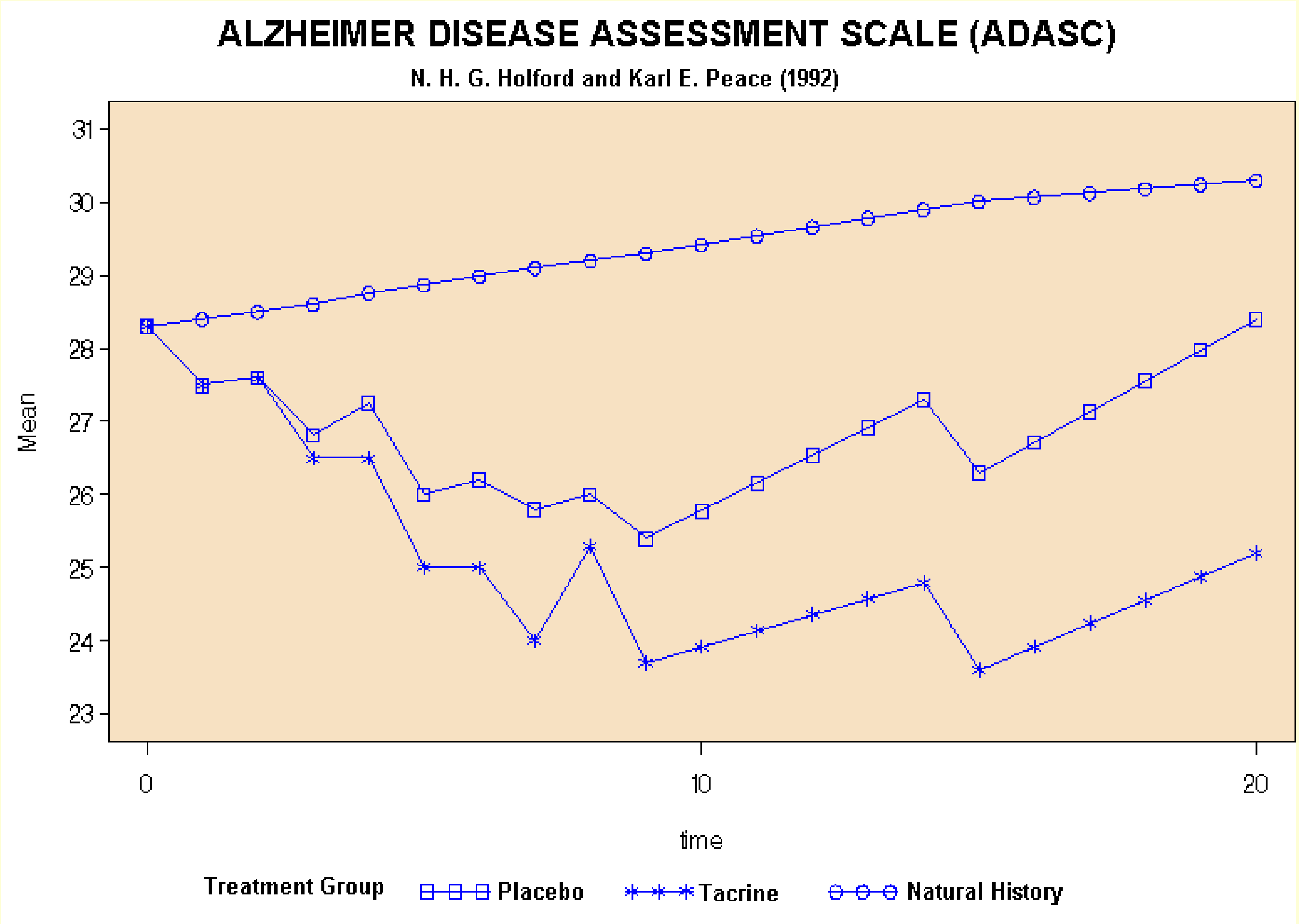
Mean Structure $M^{(g)}$ Specification

- Inputs come from
  - PD models
  - Early phase data
  - Studies on similar compounds
- To simplify input
  - specify a small number of x coordinates (time points)
  - specify means for each group, use piecewise linear interpolation



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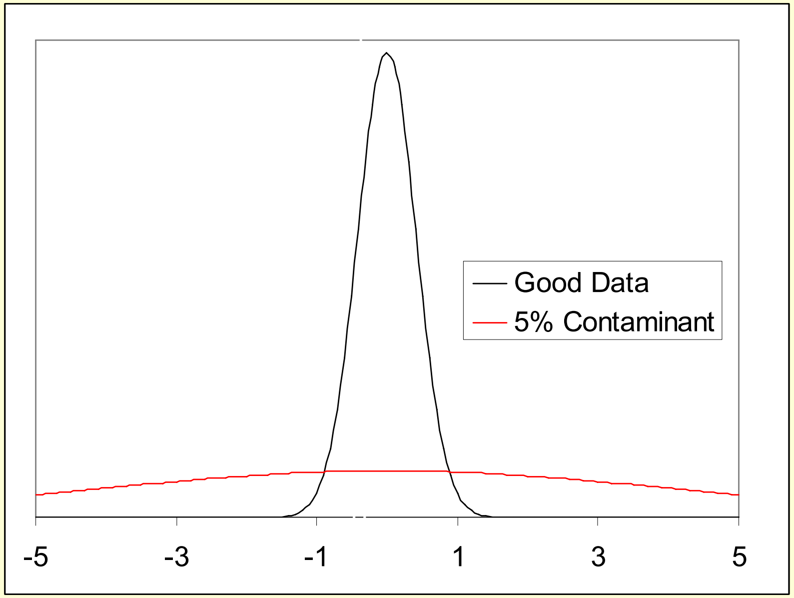
Distribution Filters

- All random variables are constructed from the correlated N(0,1) W's:
  - Normal
  - Mixture
  - Lognormal
  - Binary
  - Ordinal
  - Survival
- The W's are "latent" patient values
- Specific input issues for these variables

Mixture Distribution

- For each endpoint i, input contamination fraction p_i, and ratio r_i of contaminated to normal stddevs.

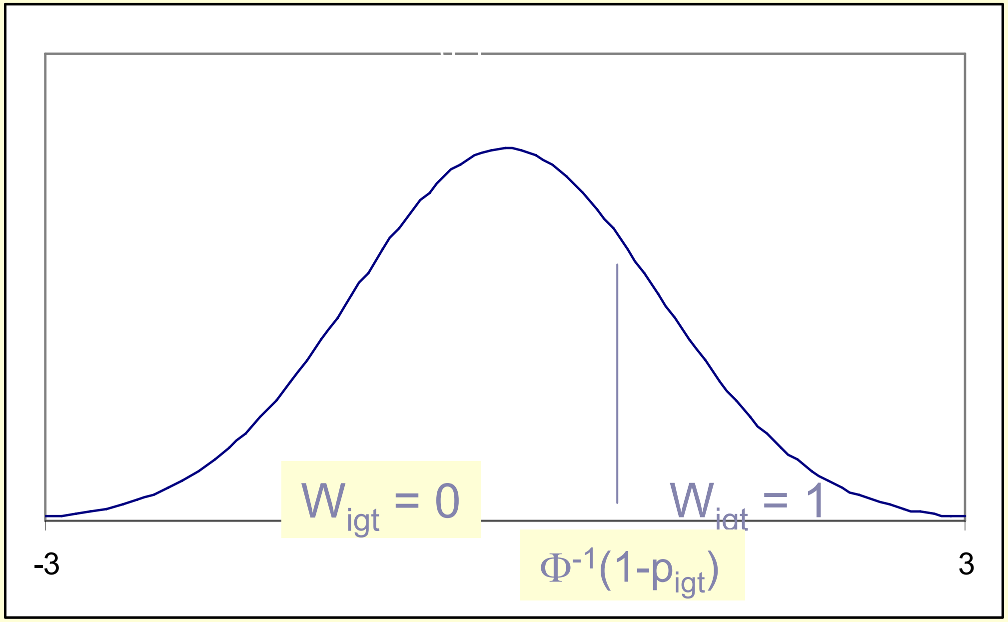
$$W_{igt} \rightarrow I(U \geq p_i) W_{igt} / (1-p_i+p_i r_i^2)^{½} + I(U < p_i) r_i W_{igt} / (1-p_i+p_i r_i^2)^{½}$$



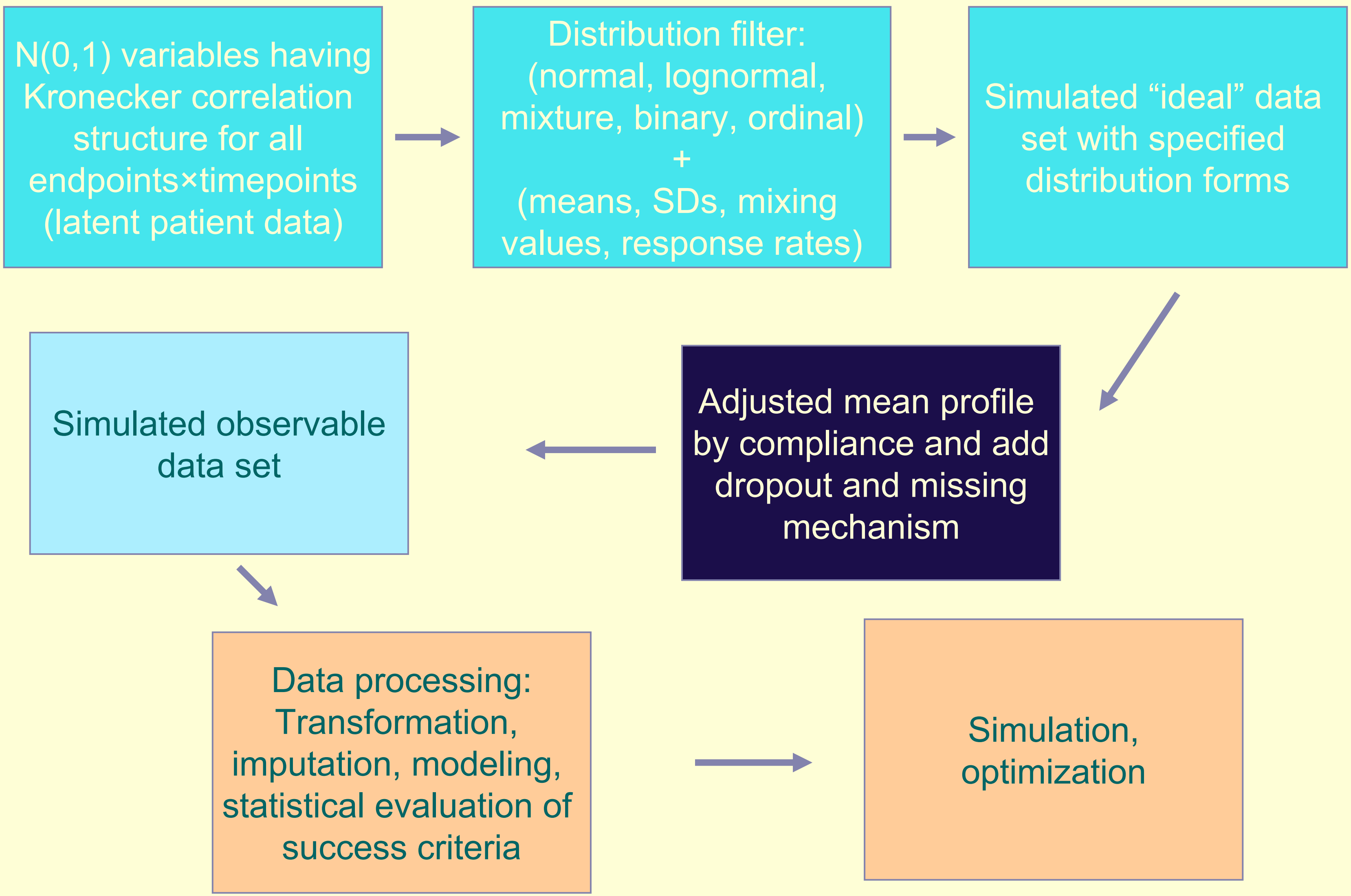
- Otherwise same as for normal
- Correlations maintained among contaminated variables with common fractions, otherwise attenuated; means and stddevs identical

Binary Distribution

- Input probabilities p_{igt} ; thresholds are $t_{igt} = \Phi^{-1}(1 - p_{igt})$
- $W_{igt} \rightarrow I(W_{igt} > t_{igt})$
- Correlations refer to tetrachoric correlations



CTS System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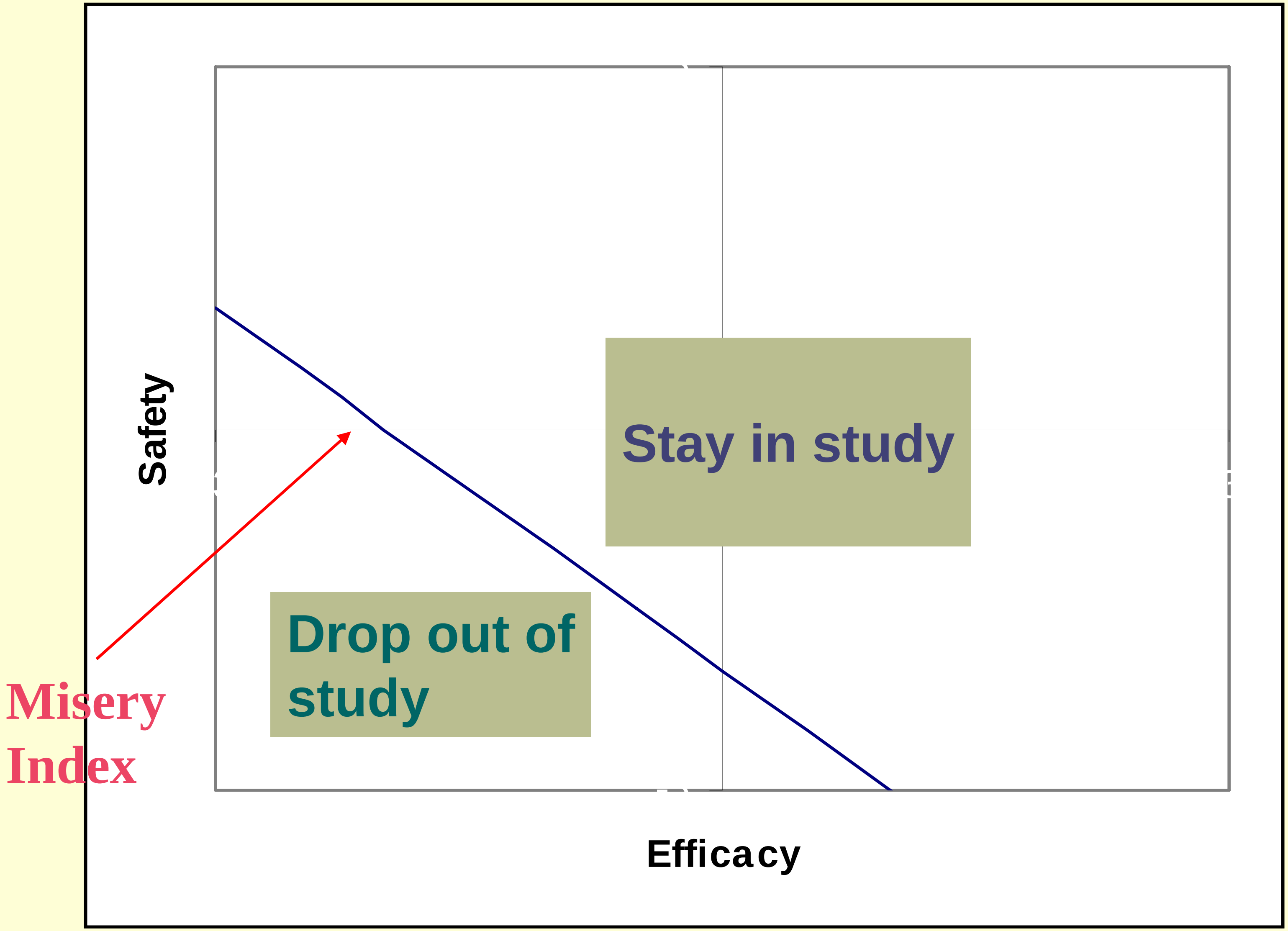
Dropout Mechanism



Misery Indices for Dropout

Local Misery indices from t-1 to t:

<u>Safety Misery Index</u>

S_t = average of safety endpoints at time t

<u>Efficacy Misery Index</u>

E_t = average of efficacy endpoints at time t

<u>Combined Index</u>

I_t = (Safety weight)*S_t + (1 – Safety weight)*E_t

Cumulative Misery Index and Dropout

- Cumulative misery index is determined by an exponential smoothing parameter (recency)
- Dropout rate is control by the threshold determined by each group
- Also allow non-informative dropout

Noncompliance

- A continuous measurement on the [0,1] scale
- Subject-specific and carryover effects
- Group specific
- Specified by median and 10th percentile of compliance

Noncompliance Effect

- Noncompliance regresses the patient response <u>toward natural history or placebo</u>
- Allow local and global effects via an exponential smooth
- Allow local compliance values related to the misery index

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Simulated observable data set and some outputs

→

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The Simulated Data

	Endpoints->	1				2				…	p			
	Timepoints->	1	2	…	t	1	2	…	t	…	1	2	…	t
PAT	Dose													
0001	Pbo	9.7	8.7	…	11.3	11.7	7.8	…	11.1	…	9.3	8.3	…	9.2
0002	Pbo	9.7	9.6	…	9.9	9.5	12.0	…	12.4	…	11.7	8.4	…	11.9
…	…	8.6	9.2	…	9.6	10.0	9.7	…	8.3	…	7.4	11.4	…	10.8
0200	High	10.7	10.3	…	9.8	10.6	10.1	…	11.9	…	10.1	10.8	…	9.1

Outputs

- **Analysis**
  - Jonckheere-Terpstra trend analysis
  - Chi-square
  - Cochran-Armitage
  - Cox proportional hazard analysis
  - ANOVA or ANCOVA followed by LS means pair-wise comparison with different multiple comparison adjustments
  - Logistics regression
- **Display**
  - Summary of rejecting and accepting the null hypotheses
  - Graph of power function using a series of sample sizes
  - Summary of basic statistics
  - Summary of simulation conditions

Example 1: Non-Compliance Effect

- Investigate the non-compliance impact on treatment effect on 3 different diseases based on published PD models or data
- Definition: failure of patients to take medicines in their prescribed manner

Characteristics and Simulation Designs of 3 Diseases

- Alzheimer: fast progressing disease; 2 groups (placebo and treatment), regress to natural disease, same compliance rates
- Rheumatoid Arthritis: slow progressing disease and strong placebo effect; 2 groups (placebo and treatment), regress to placebo, same compliance rates
- HIV: fast progressing and possible resistance to drug; 2 groups (QD and BID), regress to natural disease, different compliance rates

Results

- Non-compliance affects the power, but in different levels depending upon the disease progress and sample size
- When two groups with the same non-compliance rates, the power is reduced. Analyzing these data with the compliance as a covariate cannot reach the same power
- When two groups with different compliance rates and the same response rates, analyzing the data with the compliance as a covariate can reach the same power

Example 2: Choice of Test (O'Brien or ACR20)

- O'Brien's Test: Average-like composite of
  1. Tender Joint Count
  2. Swollen Joint Count
  3. Patient Global Assessment
  4. Investigator Global Assessment
  5. Grip Strength
  6. Pain
  7. Erythrocyte Sedimentation Rate
- ACR20 = 1 if 20% improvement in (1. and 2.) and
  20% improvement in $\geq$ 3 of (3.-7.)
  = 0 otherwise

Power Comparison

Parameter settings from historical arthritis studies reported in Anderson, Bolognese, and Felson (2003), "Comparison of Rheumatoid Arthritis Clinical Trial Outcome Measures, *Arthritis and Rheumatism* 48, 3031-3038.

Design	O'Brien	ACR20
50,50	.60	.41
70,70	.86	.40
100,100	.98	.58

Example 3: Dose-Response Arthritis Study

- Primary Endpoint: ACR20
- Control, low, mid, and high doses
- Expectations (control → high):
  - ACR20 Response rates: 30%, 50%, 60%, 70%
  - Dropout rates: 5%, 10%, 15%, 20%
- Dose/placebo tests
  - Chi-Square
  - Fixed-sequence (H →M →L)
- Total number of patients = 200; how to allocate?

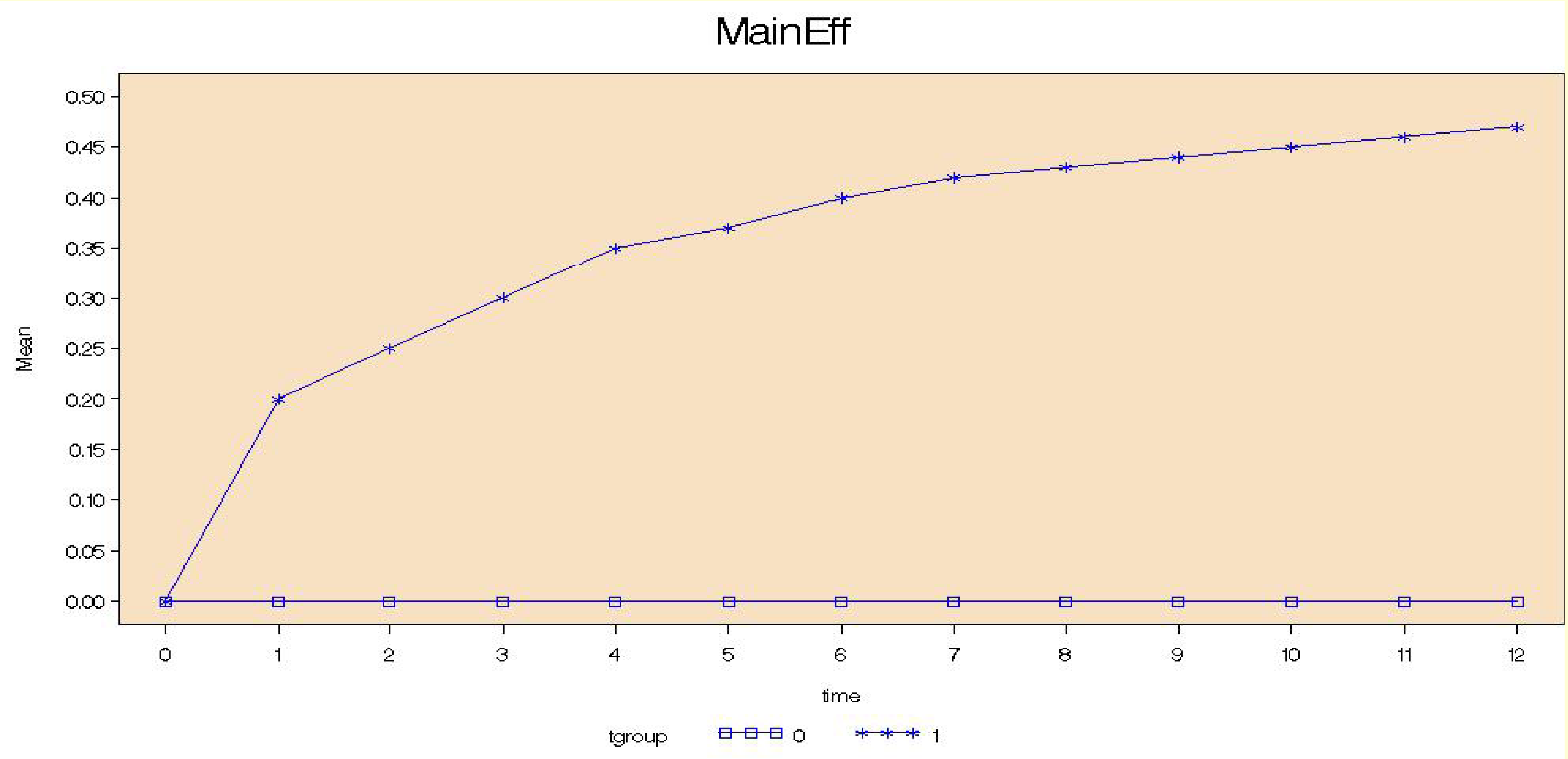
Fixed Sequence Power

Design (High to control)	High Dose	Med Dose	Low Dose
50,50,50,50	.973	.816	.465
101,33,33,33	.966	.800	.448
95,30,35,40	.981	.822	.426
80,40,40,40	.977	.835	.480
80,35,40,45	.985	.837	.452
74,42,42,42	.976	.834	.484

Example 4: Choice of Design, Test, and Duration of Study

- Outlier-prone mixture distributions
- Want to select the appropriate test
- Want to select the sample size allocation
- Want to investigate the length of study

Input Response Curves



Power Results

	Type of Analysis							
Design	AOV	ANCOVA Mean	ANCOVA Median	Difference Mean	Difference Median	K-W	K-W Diff Mean	K-W Diff Median
12 wks/ 30,30	0.41	0.55	0.54	0.48	0.47	0.58	0.67	0.65
12 wks/ 50,50	0.57	0.73	0.72	0.67	0.64	0.80	0.87	0.86
12 wks/ 100,100	0.83	0.94	0.93	0.90	0.89	0.97	0.99	0.99
8 wks/ 30,30	0.36	0.49	0.48	0.43	0.41	0.51	0.59	0.57
8 wks/ 50,50	0.51	0.67	0.66	0.59	0.58	0.73	0.82	0.80
8 wks/ 100,100	0.78	0.90	0.90	0.86	0.84	0.95	0.98	0.98

Clinical Trial Simulations?

Peter Bonate (2007; Clinical trial simulation: theory. Phamacometrics. Edited by Ette and Williams)

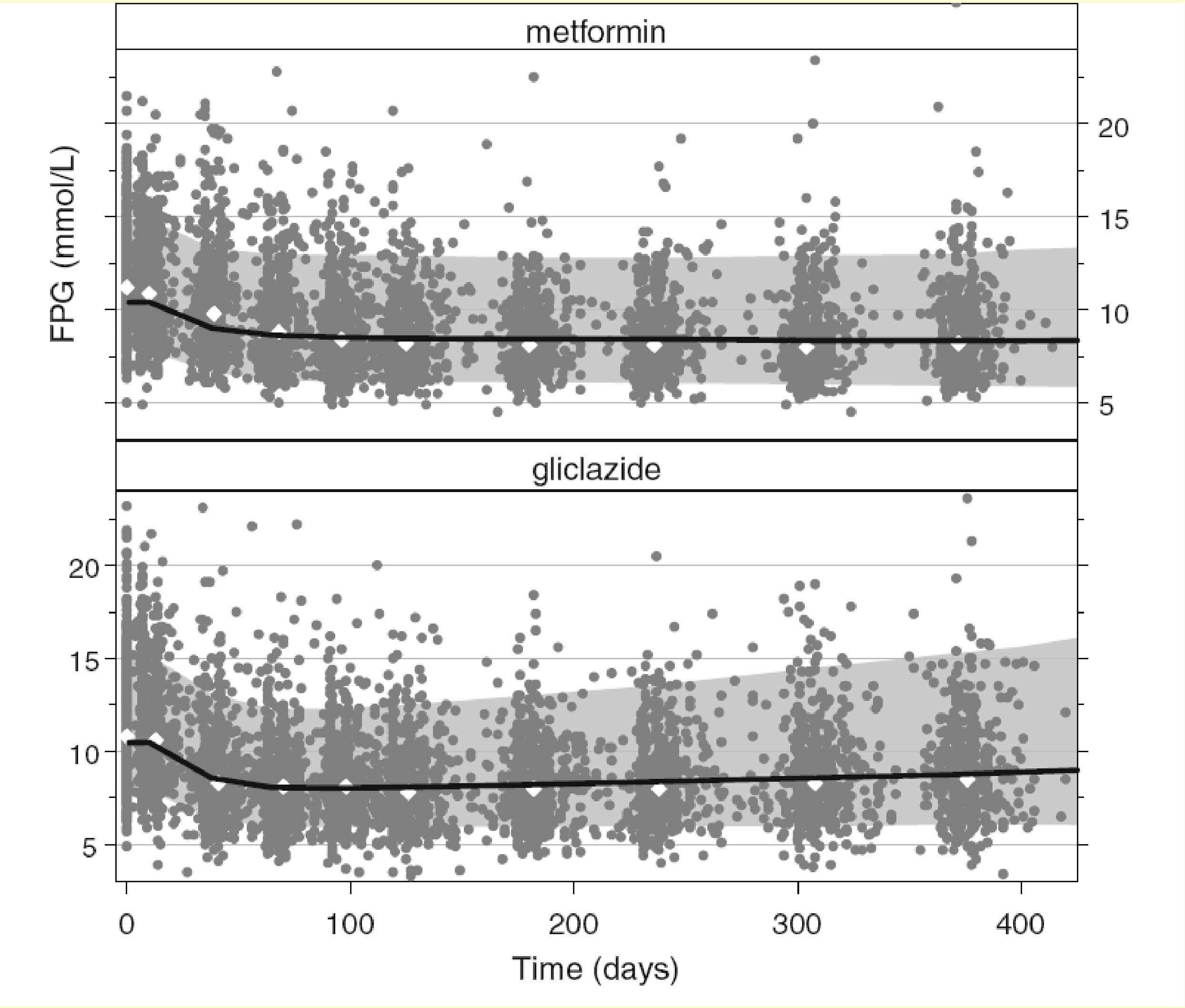
- To think that you can simulate a process as complicated as a clinical trial simply sound crazy
- Simulation is nothing more than applied modeling. The principals:
  - A model is needed
  - Sources of variability in the model must be understood as does how those parameters are correlated
  - Once the system is defined, an input design must be defined

Future Challenges

- Needs additional inputs from clinicians project managers, and pharmacokineticists
  - Test misery index
  - Incorporate complex noncompliance issues
- Limited by piece wise linear models
  - Increase segments for continuous models

Future Challenges

- Constrained by PD empirical inputs
  - Required good PD models
  - Early stage trial simulations may rely on PK/PD models
  - May use confirmed covariates and its associated variation from PopPK to construct the input model Hu and Zhou (2008; J Clin Pharmacol)
- Constant standard deviation input may not be held



Fast plasma glucose vs time (Winter et al 2006; J PK PD)

Future Challenges

- Input information has to be well estimated before entering the simulations
  - May be hard to get good estimations for all the correlations

Conclusions

- Illustrate complex statistical considerations and their resolutions in CTS
- Demonstrate wide applications with a CTS system
- Face future challenges