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MI205: R for Pharmacometrics

1. Getting Started
   (a) Course Introduction
   (b) Metrum Institute R Web Server
   (c) About the Course Materials
   (d) Licensing

2. Basic Mechanics in R
   (a) Objectives
   (b) Introduction to R
   (c) R Objects and Data Types
   (d) Getting Help Inside and Outside of R
   (e) Create R Objects and Perform Simple Operations
   (f) Import and Export Simple Data Sets with R
   (g) Load an R package
   (h) Write and Save an R Script and Execute Code from an R Script
   (i) Homework Problems

3. Basic Plotting
   (a) Objectives
   (b) Introduction
   (c) Graphics Devices
   (d) Traditional Graphics
   (e) Lattice Graphics
   (f) Homework
   (g) Basic Function Writing
   (h) Objectives
   (i) Introduction
   (j) Simple Functions
   (k) Exercises

4. Basic Plotting
   (a) Objectives
   (b) Introduction
   (c) Simple Functions
   (d) Exercises
   (e) Functions with Multiple Arguments
      i. Exercises
   (f) Default Argument Values
   (g) Arbitrary Arguments
      i. Exercises
(h) Variable Scope
   i. Additional Exercises

5. Data Summary
   (a) Objectives
   (b) Introduction
   (c) Simple Summaries Using table()
      i. Exercises
   (d) Applying Summary Functions Across Vectors and Dataframes
      i. Exercises
   (e) Subsetting a dataframe using a logical vector
      i. Homework

6. Data Assembly
   (a) Objectives
   (b) Introduction
   (c) Considerations
   (d) Source Management
      i. Column Management
      ii. Row Management
      iii. Imputations
      iv. Derived Variables
      v. Cell Management
      vi. Restrictions
      vii. Reorganization
   (e) Merge Management
      i. Order
      ii. Technique
      iii. Contextual Alterations
      iv. Characterization
   (f) Exercises

7. Modeling in R
   (a) Objectives
   (b) Introduction
   (c) Fitting a regression model with lm()
   (d) Generic methods for model objects
   (e) Fitting an "ANOVA model" with lm()
   (f) Fitting a nonlinear model with nls()
   (g) Fitting linear mixed-effects models with lme()
   (h) Fitting a nonlinear mixed effects model with nlme()
   (i) Homework
8. Modeling Outside of R
   (a) Objectives
   (b) Introduction
   (c) Usage of the metrumrg package
   (d) Preparing input files and data for modeling programs
   (e) Reading and plotting NONMEM output
   (f) Reading and plotting WinBUGS output
   (g) Summarizing a set of NONMEM runs
   (h) Fitting a nonlinear mixed effects model with nlme()
   (i) Homework

9. Advanced Function Writing
   (a) Objectives
   (b) Introduction
   (c) Debugging
   (d) Testing Input
   (e) Alerting the User
   (f) Branching
   (g) Looping
   (h) Controlling Visibility
   (i) Writing Methods
      i. Background
      ii. Implementation
   (j) Exercises

10. Advanced Exercises
    (a) Objectives
    (b) Introduction
    (c) The use of ifelse()
       i. Exercises
    (d) The use of do.call()
       i. Exercises
    (e) Usage of all () and any ()
    (f) Using/Choosing an R graphical user interface (GUI)
    (g) Homework

11. Advanced Data Assembly
    (a) Introduction
    (b) Irregular Extraction
    (c) Stratified Imputation
    (d) Dynamic Transformations
(e) Complex Criteria
(f) Table Reorganization
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   ii. cast
(g) Exercises
(h) Example Code

12. Advanced Graphics
   (a) Objectives
   (b) Introduction
   (c) Grid Basics
      i. Units
      ii. Viewports
   (d) Layouts
   (e) A Practical Example
MI210: Introduction to Population PKPD Modeling and Simulation

1. Introduction to Population PKPD Modeling
   (a) Overview
   (b) Introduction to Population PKPD Modeling and Simulation
      i. Population PKPD Definition
      ii. History and Rationale
      iii. Software
      iv. Modeling and Simulation in Drug Development
   (c) Introduction to Nonlinear Regression Concepts
      i. Phase 1 Exposure-Response Examples
      ii. The Method of Maximum Likelihood
      iii. MaximumLikelihoodApproach
      iv. Least-Squares Objective Functions
      v. Diagnostics for Regression Models (Individual or Naive-Pooled Data)
   (d) Examples (Excel Workbook)
   (e) Problems
      i. Problem 1.1
      ii. Problem 1.2
   (f) Maximum Likelihood for Population Repeated Measures Data
      i. Data for Population Analyses
      ii. Hierarchical Population Mixed-Effects Models
      iii. Population NLMEM Objective Functions
      iv. Diagnostics for Population Models
   (g) Study Guide Questions

2. Population PK-PD Data Requirements and Formatting
   (a) Overview
   (b) Data Terminology
   (c) Data Specification for the NONMEM System
      i. General Data Requirements for NMTRAN
      ii. Data Requirements for NMTRAN with PREDPP
      iii. Data Item Names
      iv. NMTRAN Control Records: $DATA and $INPUT
   (d) Data Assembly Points to Consider and Best Practices
   (e) Practice Problems
   (f) Study Guide Questions

3. Covariate Model Building
   (a) Objectives of Covariate Model Development
   (b) Common Covariate Model Parameterizations
      i. Covariate-Parameter Models for Continuous Covariates
ii. Covariate-Parameter Models for Categorical Covariates
iii. Combining Continuous & Categorical Covariates
iv. Desirable Properties of Covariate Model Parameterizations
(c) Data Reduction: Before You Start Covariate Model Building
(d) Covariate Modeling Methods
   i. Traditional Covariate Screening Methods in Population PKPD
   ii. Other Covariate Modeling Methods
(e) Inferences about Covariate Effects
(f) Other Statistical Considerations
(g) Aligning Methods with Modeling Purpose
(h) Practice Problems
(i) References
(j) Study Guide Questions

4. Simulation
   (a) Topics
   (b) Calling Random Number Routines
   (c) Simulation Problem

5. Model Qualification
   (a) Can We Agree on a Name?
   (b) A Risk-Based Approach to Model Qualification
   (c) What to Evaluate or Qualify?
   (d) Model Qualification Methods
      i. Assumption Checking
      ii. Test Data Sets for Model Qualification
      iii. Log-Likelihood Profile: Qualification of Parameter Estimates
      iv. Bootstrap: Qualification of Parameter Estimates
      v. Leverage Analysis
      vi. Qualification Based on Predictive Performance
      vii. Posterior Predictive Check
      viii. When is Evaluation Less Important?
   (e) Sensitivity Analysis

6. Direct and Indirect Continuous Pop PK-PD Models
   (a) Background
   (b) Basic PD Models
   (c) SPRED Example
   (d) Linking PK and PD
   (e) PK-PD Modeling Steps
   (f) Direct PKPD
   (g) Effect Compartment PK-PD
7. Regulatory Guidance and Best Practices

(a) Overview

(b) Regulatory Support for M&S
   i. Regulatory Meetings/Interactions: End of Phase IIa Meeting
   ii. Regulatory Review and Analysis
   iii. Regulatory Guidance Documents
   iv. FDA Population Pharmacokinetics Guidance
   v. EMEA Guidance on Pop PK

(c) Review of Best Practices

(d) Systems and Procedures
   i. Data Preparation
   ii. Modeling and Simulation
   iii. Reporting and Communication

(e) References
MI212: Advanced Topics in Population PK-PD Modeling & Simulation

1. Getting Started
   (a) Course Introduction
   (b) Metrum Institute R Web Server
   (c) About the Course Materials

2. Inter-Occasion Variability and Mixture Models
   (a) Overview
   (b) Inter-occasion variability
   (c) Mixture Model
   (d) Problem

3. BQL data
   (a) Overview
   (b) BQL data
   (c) Potential Approaches to Treating BQL Data
      i. Likelihood Function
   (d) NONMEM CODE
   (e) Dealing with BQL (censored) data in WinBUGS
   (f) Model checking with BQL data
   (g) Problem
   (h) Study Guide Questions

4. Advanced Pharmacokinetic Topics I
   (a) Overview
   (b) Parameter Identifiability
   (c) Nonlinear Pharmacokinetics
      i. Example: two-compartment IV infusion input with parallel nonlinear and linear clearance pathways
      ii. Example: one-compartment IV infusion input with autoinduction of clearance
   (d) Target-mediated drug disposition
      i. Example: full target-mediated drug disposition model with IV bolus input
   (e) Problems
   (f) Study Guide Questions

5. Advanced Pharmacokinetic Modeling Topics 2
   (a) Overview
   (b) Parent-Metabolite Models with Plasma Data Only
      i. Parameter Identifiability of the Parent-Metabolite Model with Plasma Data
      ii. Modeling Urine Drug Data
iii. Modeling Covariance of Residual Random Effects
iv. Problem

6. Advanced PK-PD Modeling Topics 1
   (a) Overview
   (b) Direct and Indirect Continuous Pop PK-PD Models
   (c) Background
   (d) Basic PD Models
   (e) PRED Example
   (f) Linking PK and PD
   (g) PK-PD Modeling Steps
   (h) Direct PK-PD Models
   (i) Effect Compartment PK-PD
   (j) Semi-Parametric Effect Compartment
   (k) PK-PD Model with Tolerance*
   (l) Indirect PD Response Models
   (m) Circadian Baseline Models
   (n) Overview
   (o) Example
   (p) NMTRAN Control Stream
   (q) References

7. Advanced PK-PD Modeling Topics 2 - Precursor Pool, Transit Compartment and Lifespan Models
   (a) Overview
   (b) Precursor Pool Models
   (c) Transit Compartment PD Models
   (d) PK Models with Transit Compartments for Oral Absorption
   (e) Lifespan Models
   (f) Problem
   (g) Study Guide Questions

8. Advanced PK-PD Modeling Topics 3 - Multiple Endpoint Turnover and Mechanistic (Multi-scale) Models
   (a) Overview
   (b) Mechanistic / Systems biology / Multiscale Models
   (c) Definitions and Introduction
   (d) Bone and Calcium Model
   (e) Mechanistic / Systems Biology / Multiscale Model Summary
   (f) Points to Consider
   (g) Problem

9. Disease Progression Model
(a) Markers of Disease Progression
(b) Application of Disease Progression Models
(c) NONMEM Data Setup for Disease Progression Models
(d) Types of Disease Progression Models
(e) Disease Progression Models for Capped Scales
(f) Disease Progression Models: Room for Improvement
(g) Problem
(h) Study Guide Questions

10. Simulation Basics

(a) Overview

(b) Implementation of Simulation in NONMEM
   i. Simple Fixed-Value Simulations
   ii. Deterministic Simulation Based on Individual Conditional Estimates
   iii. SIMULATION
   iv. Simulating Data for One Individual
   v. Simulating Population Data
   vi. Simulating Covariate Distributions
   vii. Simulation with Uncertainty
MI250: Introduction to Bayesian PK-PD Modeling & Simulation

1. Overview of the current and potential role of Bayesian methods in clinical drug development

2. Introduction to Bayesian statistical principles and methods
   (a) Bayes Rule
   (b) Bayesian modeling & inference process
   (c) Likelihood principle

3. Computation for Bayesian modeling
   (a) Key challenge of Bayesian modeling and inference: high-dimensional multiple integration
   (b) General computational approach: posterior simulation
   (c) Brief intro to Markov chain Monte Carlo simulation

4. WinBUGS basics
   (a) What is it? How do I get it? How do I run it?
   (b) WinBUGS demo: Linear regression

5. Introduce PK/PD modeling case study to be used throughout the course

6. Hands-on example 1: Simple nonlinear regression, e.g., a PK/PD model relating a single exposure metric to a single continuous PD outcome

7. Topics in Bayesian model development using WinBUGS I
   (a) Using WinBUGS scripts
   (b) R tools for running WinBUGS and analyzing MCMC simulations
   (c) Assessing convergence
   (d) Programming hierarchical models (aka mixed effect or population models)

8. Hands-on example 2: Nonlinear mixed effects, e.g., a PK/PD model relating observed drug concentrations to continuous PD measurements at the same time.

9. Topics in Bayesian model development using WinBUGS II
   (a) Model evaluation and comparison
   (b) BUGSModelLibrary for pharmacometric modeling: Introduction & demonstration
   (c) Dealing with censored data in WinBUGS
      i. BQL data

10. Hands-on example 3: Population PK

11. Topics in Bayesian model development using WinBUGS III
    (a) Informative prior distributions in clinical pharmacology applications
    (b) Using the cut function in WinBUGS
    (c) Programming models in terms of differential equations

13. Additional topics & closing discussion

(a) Selected published examples of Bayesian applications

(b) Considerations in deciding whether to use:
   i. Bayesian or maximum likelihood methods
   ii. WinBUGS or NONMEM or ?

(c) What didn’t we cover?
MI255: Exposure-Response Modeling of Categorical, Count, and Time-to-Event Data

1. Some general theory/background:
   (a) Modeling from a probabilistic point of view: the likelihood function
   (b) Maximum likelihood for continuous data
   (c) Extending ML to odd-type data
   (d) Hierarchical (mixed effects) modeling of odd-type data
   (e) Bayesian modeling of odd-type data

2. Modeling binary data
   (a) Logistic regression models
   (b) Bernoulli model for individual binary data
   (c) Binomial model for summary data
   (d) Mixed effects modeling of binary data

3. Hands-on Problem 1: Logistic regression for binary data

4. Model evaluation, esp. simulation-based methods for categorical data models

5. Hands-on Problem 2: Longitudinal binary data

6. Modeling ordered categorical (ordinal) data
   (a) Cumulative logit models
   (b) Modeling longitudinal ordinal data: Comparative performance of approximate ML (e.g., NONMEM) and MCMC (e.g., WinBUGS)

7. Hands-on Problem 3: Longitudinal ordinal data

8. Modeling count data
   (a) The Poisson model
   (b) Variations on the Poisson model to deal with over-dispersion or zero inflation

9. Hands-on Problem 4: Count data

10. Modeling time-to-event data for a single event per individual
    (a) Principles and methods of survival analysis for modeling censored data

11. Hands-on Problem 5: Time-to-event data: Constant hazard model

12. Models with time-varying hazard

13. Miscellaneous topics:
    (a) Modeling repeated time-to-event data
    (b) Modeling of inter-event time intervals

14. Hands-on Problem 6: Repeated time-to-event data

15. Closing discussion
MI260: Model-based Meta-analysis to Support Decision-Making in Clinical Drug Development

1. Introduction
   (a) Rationale and role of model-based meta-analysis in clinical drug development
   (b) Why do it?
   (c) What decisions benefit from meta-analysis and model-based meta-analysis in particular?
   (d) Motivating examples

2. The systematic review and planning your meta-analysis
   (a) Analysis plan
   (b) Database construction
      i. Data sources
      ii. Data types, e.g., mean, mean change from baseline, percent change from baseline, standard deviation, standard error

3. Traditional meta-analysis
   (a) What is it?
   (b) Fixed effects meta-analysis

4. Random effects meta-analysis and meta-regression
   (a) Measures of heterogeneity
   (b) What the traditional random effects model is and how it differs from fixed effects
   (c) Meta-regression

5. Selection bias and missing data

6. Combining different types of data

7. Network Meta-analysis
   (a) Relationship to random effects meta-analysis
   (b) Assumptions
   (c) Fitting the models

8. Model-based meta-analysis (MBMA)
   (a) What is it?
   (b) Role of MBMA: Objectives not adequately addressed by traditional meta-analysis
   (c) Why Bayesian? / Why BUGS?

9. Modeling sample mean data

10. Modeling sample standard deviations: why and how

11. Population simulations
    (a) Simulating probable ranges of population estimands, e.g., population mean, probability of an event, etc.
(b) Using simulation results to support decision-making in a competitive market environment

12. Issues arising from analysis of summary data
   (a) Applying models developed to describe responses in individuals to summary data
   (b) Analysis of longitudinal data
      i. Pitfalls of treating treatment arms as “super-patients”
      ii. Within-arm correlation
      iii. Approaches for addressing these issues

13. Modeling other types of summary statistics:
   (a) Number or fraction of patients with a particular outcome or that experience an event
   (b) Number or fraction of patients within each level of an ordinal scale
   (c) Number of events per patient
   (d) Summary statistics for time-to-event measurements

14. Issues arising from use of LOCF and OC data

15. Combining summary and individual data

16. Incorporating a broader range of data and knowledge
   (a) Leveraging the Bayesian framework to incorporate additional quantitative knowledge via informative prior distributions
   (b) Integrating preclinical, biomarker and clinical outcome data to improve prediction and decision-making in early clinical development

17. Miscellaneous topics

18. Closing discussion