Bayesian Copula Modeling for Clinical Trials

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Clinical Trials

- Clinical trials are controlled, randomized experiments of a medical intervention in human subjects

- Traditionally divided into 4 sequential phases

Phase I	first-in-human, dose-finding
Phase II	determine efficacy
Phase III	confirm efficacy, assess safety
Phase IV	long-term surveillance

Clinical Trials

- To gain regulatory approval, the benefits (efficacy) of an intervention must outweigh the risks (safety)
- Usually efficacy and safety outcomes are not modelled jointly
- Modelling outcomes together
  - Uses data more effectively
  - Provides better characterization of risk-benefit tradeoff

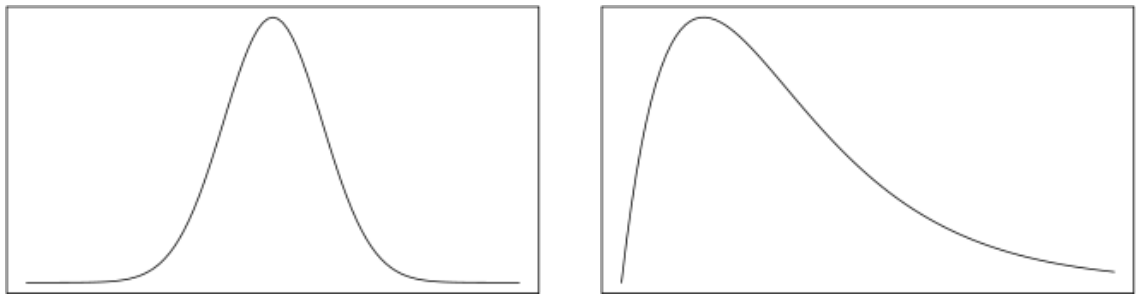
Copulas

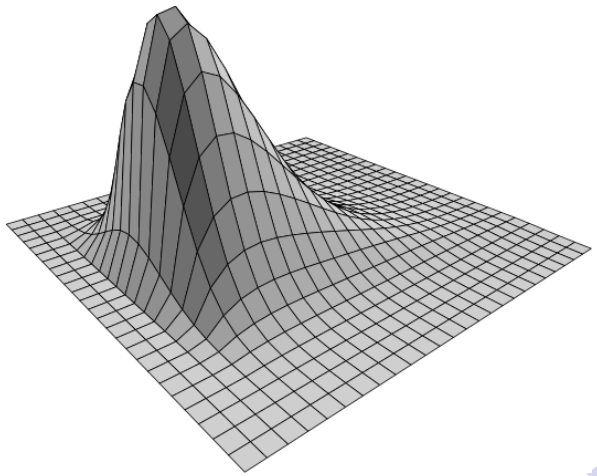
- Each outcome can be modelled by a univariate distribution function
- A *copula*, $C()$, is a mathematical function that combines univariate distributions to create a multivariate distribution
- *Sklar's Theorem*[1] guarantees that we can construct a proper multivariate distribution function from any univariate distributions with a given $C()$ function

[1] Sklar, A. (1959), "Fonctions de répartition à n dimensions et leurs marges", Publ. Inst. Statist. Univ. Paris, 8: 229231

Copulas

Ex. Combine $Normal(0, 1)$ and $Gamma(2, 1)$ distributions using a Gumbel copula $C_\theta(u, v) = \exp[-((-\log u)^\theta + (-\log v)^\theta)^{1/\theta}]$





Copulas

- We can study the resulting multivariate distribution function to determine how efficacy and safety are correlated
- In practice, the form of the univariate distributions and the type of copula are unknown and must be estimated from the observed data

Bayesian Inference

- Principled method of combining prior beliefs with newly collected data
- Provides a mechanism to incorporate information from animal models, previous studies, clinical expertise, etc.
- Simpler conceptual framework for adaptive designs
- Inference is based on posterior probabilities

EffTox design

Efficacy-Toxicity (EffTox)[2] is a study design which combines elements of Phase I and II trials

- A Bayesian copula model for the probabilities of Efficacy and Toxicity as a function of dose
- Criteria for dose acceptability
- Trade-off contours quantifying the desirability of each dose

[2] Thall, P. and Cook, J. (2004), "Dose-finding based on efficacy-toxicity trade-offs", Biometrics, 60:684-693.

Bayesian Copula model

- Consider a binary bivariate outcome $Y = (Y_E, Y_T)$ where $Y_k \in \{0, 1\}$, $k = E, T$
- The marginal probability at dose x_j for outcome k is modelled as $\pi_{k,j} = \text{logit}^{-1}(\eta_{k,j})$ where $\eta_{k,j}$ is a linear function of dose
- The joint probability of both outcomes given dose and $\eta_{k,j}$ parameters θ is $Pr(Y_E = a, Y_T = b|x_j, \theta) = \pi(a, b|x_j, \theta)$ for $(a, b) = (1, 1), (1, 0), (0, 1), (0, 0)$

Bayesian Copula model

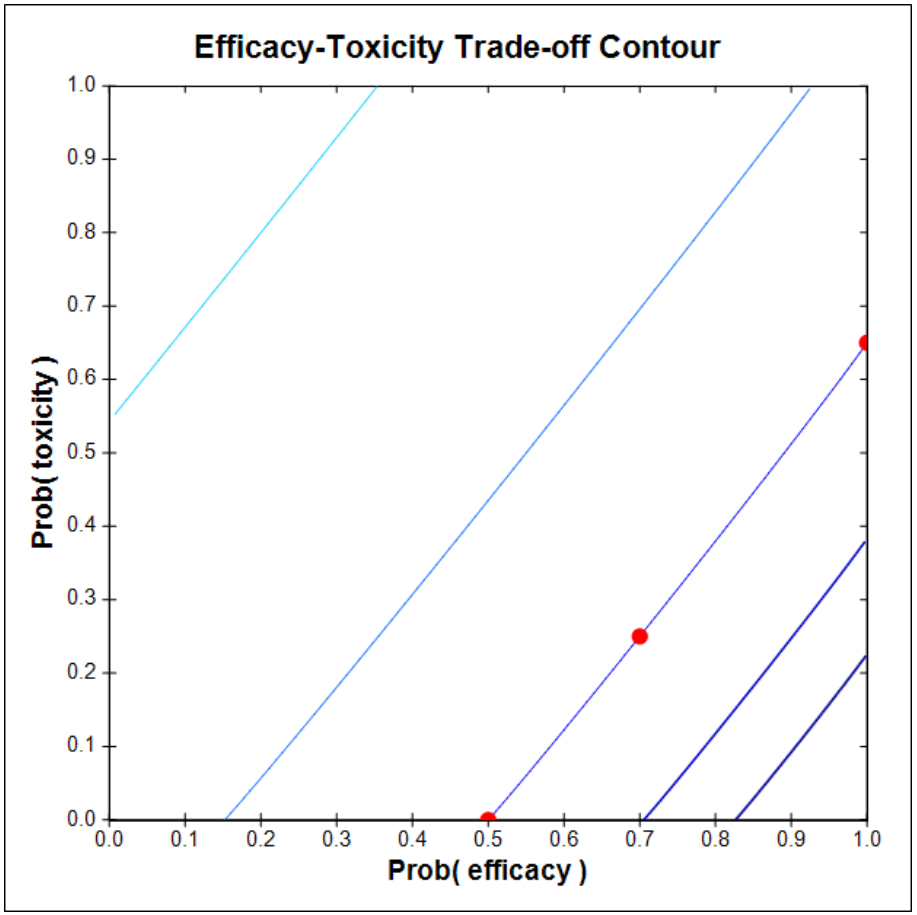
- The joint probability, $\pi(a, b|x_j, \theta)$, is modelled with a Farlie-Gumbel-Morgenstern (FGM) copula
- For subject i, let $(Y_{i,E}, Y_{i,T})$ be the observed outcome and $x_{[i]}$ the assigned dose, the likelihood of the data $\mathcal{D}_n$ for all n subjects is $\mathcal{L}(\mathcal{D}_n|\theta) = \prod_{i=1}^{n} \pi(Y_{i,E}, Y_{i,T}|x_{[i]}, \theta)$
- Finally, the posterior is $p(\theta|\mathcal{D}_n) \propto \mathcal{L}(\mathcal{D}_n|\theta) \times p(\theta)$

Dose Acceptability

- Using information elicited from physicians, bounds are established to prevent assigning a dose which is likely to be ineffective or too toxic
- The trial is stopped if no dose is acceptable based on estimates from the Bayesian model

Trade-off contours

- Trade-off contours represent equally desirable pairs of efficacy/toxicity probabilities (Prob(efficacy),Prob(toxicity))
- (0.5,0), (0.7,0.25), (1,0.6) equally desirable
- Dose desirability calculated from model estimates and used to assign dose in next cohort



Simulations

Comparison to classical designs

- How to elicit and incorporate non-standard prior distributions
- More flexible modelling of copula (copula conditional regression, nonparametric estimation)
- Implementation of more efficient, flexible, and easy to use software

- Copula models
  - Use data more effectively
  - Formally quantify risk-benefit tradeoff
- Bayesian paradigm
  - Easier to interpret inference
  - More flexible designs