Optimizing Combination Therapy under a Bivariate Weibull Distribution, with Application to Toxicity and Efficacy Responses

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Nov,24 2011

1. Context
   - Two Dependent Binary Outcomes at dose x
   - Probabilities
2. Motivation
   - Motivation for Bivariate Weibull Distribution
   - Plots
3. Model Development
   - Methods for Constructing Bivariate Distributions
   - Bivariate Exponential Distribution
   - Bivariate Weibull Distribution
4. Information matrix
   - Likelihood
   - Information matrix
5. Rest of This Project
   - Rest of This Project

Two Dependent Binary Outcomes at dose x

Consider two dependent binary outcomes,* U for efficacy and V for toxicity. Outcome probabilities given the dose level x are defined as follow.

$$p_{uv} = Pr(U = u, V = v | X = x), u, v = 0, 1$$

		Toxicity 1	Toxicity 0	
Efficacy	1	p_{11}	p_{10}	$p_{1.}$
	0	p_{01}	p_{00}	$p_{0.}$
		$p_{.1}$	$p_{.0}$	1

*Motivated by Dragalin, Fedorov and Wu (2006).

Outcome Probabilities as function of dose

Outcome probabilities are

$$\begin{cases} p_{11} = \int_0^{y^*} \int_0^{z^*} f(y,z)dzdy \\ p_{10} = \int_0^{y^*} \int_{z^*}^{\infty} f(y,z)dzdy \\ p_{01} = \int_{y^*}^{\infty} \int_0^{z^*} f(y,z)dzdy \\ p_{00} = \int_{y^*}^{\infty} \int_{z^*}^{\infty} f(y,z)dydz \end{cases}$$

where $f(y,z)$ is the **bivariate Weibull density.**

Why the Bivariate Weibull Distribution?

1. Natural Dose Range
   $\Rightarrow 0 < \text{Dose} < \infty$

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1. Natural Dose Range
   $\Rightarrow 0 < \text{Dose} < \infty$
2. Flexibility
   $\Rightarrow$ 6 parameters to regress on one drug; can extend to multiple drugs and covariates.

**Other possible bivariate distributions considered

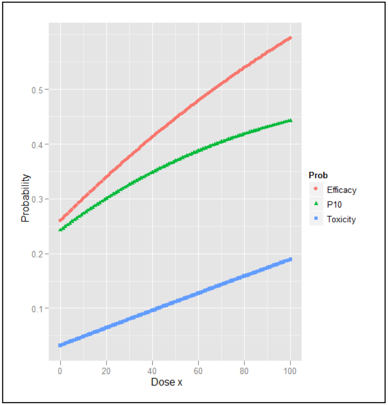
-Bivariate Gamma distribution

-Bivariate Beta distribution

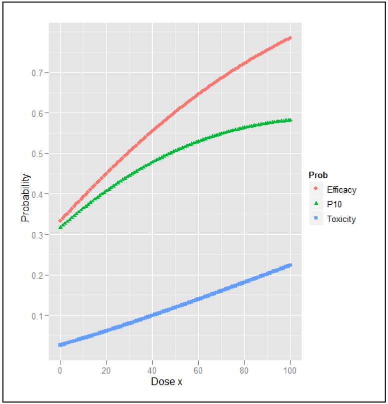
-Bivariate F-distribution

Plots

Bivariate Exponential Dist. $\sigma = 1$

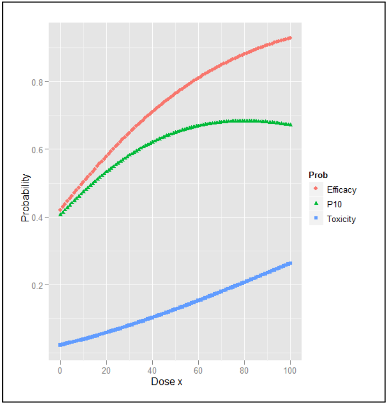


Bivariate Weibull Dist. $\sigma = 1.2$

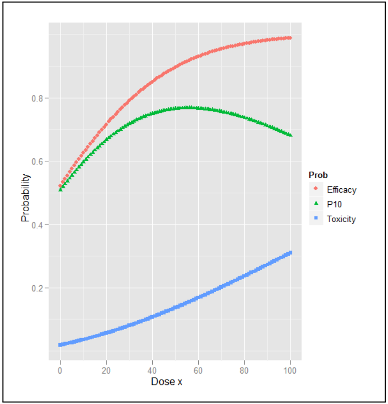


Plots

Bivariate Weibull Dist. $\sigma = 1.4$

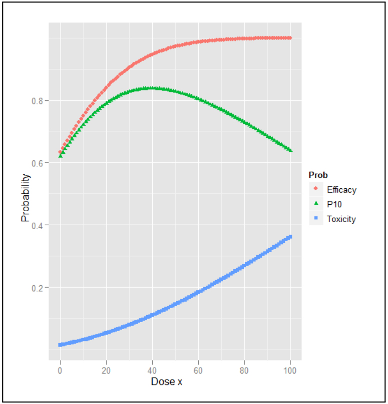


Bivariate Weibull Dist. $\sigma = 1.6$

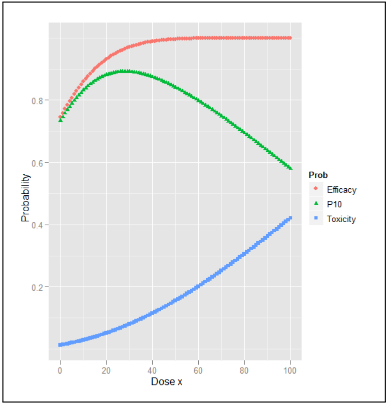


Plots

Bivariate Weibull Dist. $\sigma = 1.8$

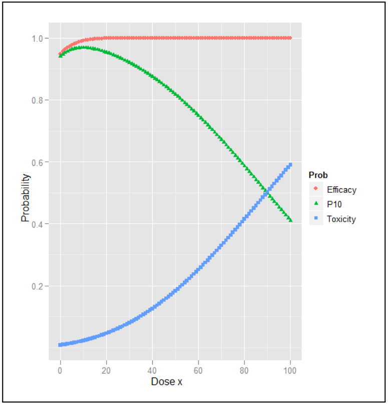


Bivariate Weibull Dist. $\sigma = 2$

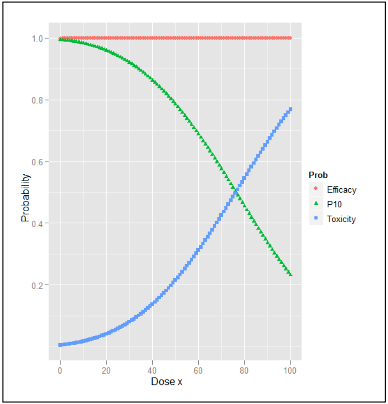


Plots

Bivariate Weibull Dist. $\sigma = 2.5$



Bivariate Weibull Dist. $\sigma = 3$



Methods for Constructing Bivariate Distribution

1. Combine a Conditional Distribution with a Marginal Distribution
$h(x, y) = f(x)g(y|x)$

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   $h(x, y) = f(x)g(y|x)$
2. Copula Methods
   - The Inversion Method
   - Geometric Methods
   - Algebraic Methods
   - Rüschendorf's Method
   - Distortion Function

Start with Independent Exponential Distribution, Freund (1961)

Let T_1 and T_2 have distributions

$$f(t_1) = \beta_1 exp(-\beta_1 t_1) \qquad for \quad t_1 > 0$$
$$f(t_2) = \beta_2 exp(-\beta_2 t_2) \qquad for \quad t_2 > 0.$$

Then the probability that T_1 fails (occurs) at t_1 and T_2 has not yet failed is

$$\frac{\partial}{\partial t} P(T_1 < t, T_2 > t_1)|_{t=t_1} = \beta_1 e^{-\beta_1 t_1} \times e^{-\beta_2 t_1} = \beta_1 e^{-(\beta_1+\beta_2)t_1}.$$

Freund (1961) uses Conditional Method Introduce to Dependency.

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2. Specify, furthermore, that the probability density of T_2 given that T_1 fails *first* at t_1 is
$$\frac{\partial}{\partial t} P(T_2 < t | T_2 > t_1)|_{t=t_2>t_1} = \beta_2' e^{-\beta_2'(t_2-t_1)} \quad \textit{for } 0 < t_1 < t_2.$$

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3. $$f(T_1 = t_1, T_2 = t_2) = \beta_1 e^{-(\beta_1+\beta_2)t_1} \times \beta_2' e^{-\beta_2'(t_2-t_1)} \quad \textit{for } 0 < t_1 < t_2 < \infty$$

Freund (1961) Analogously

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$$f(T_1 = t_1, T_2 = t_2) = \beta_2 e^{-(\beta_1+\beta_2)t_2} \times \beta_1' e^{-\beta_1'(t_1-t_2)} \quad \textit{for } 0 < t_2 < t_1 < \infty$$

Freund (1961) In Summary

Bivariate Exponential Distribution

$$f(t_1,t_2)=\begin{cases}\beta_1 e^{-(\beta_1+\beta_2)t_1}\times\beta_2' e^{-\beta_2'(t_2-t_1)} & \text{for } 0<t_1<t_2<\infty\\ \beta_2 e^{-(\beta_1+\beta_2)t_2}\times\beta_1' e^{-\beta_1'(t_1-t_2)} & \text{for } 0<t_2<t_1<\infty\end{cases}$$

$$=\begin{cases}\beta_1(\beta_2')e^{-(\beta_2')t_2-(\beta_1+\beta_2-\beta_2')t_1} & \text{for } 0<t_1<t_2<\infty\\ \beta_2(\beta_1')e^{-(\beta_1')t_1-(\beta_1+\beta_2-\beta_1')t_2} & \text{for } 0<t_2<t_1<\infty\end{cases}$$

Marshall-Olkin (1967)

Introduced Dependency between Exponential Random Variables using Copula Methods

$$\bar{F}_M(t_1, t_2) = P[T_1 > t_1, T_2 > t_2]$$

$$= exp[-\beta_1 t_1 - \beta_2 t_2 - \beta_3 Max(t_1, t_2)], \qquad \beta_1, \beta_2, \beta_3 > 0.$$

Proschan-Sullo (1974) repeat steps taken by Freund, starting with marginal distribution T_1 and T_2 obtained from Marshall-Olkin to get bivariate exponential distribution with three parameters.

Proschan-Sullo (1974)

Bivariate Exponential Distribution

Proschan-Sullo proposed BVE which is the combination of both Freund (1961) and Marshall-Olkin (1967).

$$f(t_1, t_2) = \begin{cases} \beta_1(\beta_2^{'} + \beta_3)e^{-(\beta_2^{'}+\beta_3)t_2-(\beta_1+\beta_2-\beta_2^{'})t_1} & \text{for } 0 < t_1 < t_2 < \infty \\ \beta_2(\beta_1^{'} + \beta_3)e^{-(\beta_1^{'}+\beta_3)t_1-(\beta_1+\beta_2-\beta_1^{'})t_2} & \text{for } 0 < t_2 < t_1 < \infty \\ \beta_3 e^{-(\beta_1+\beta_2+\beta_3)t_1} & \text{for } 0 < t_1 = t_2 < \infty \end{cases}$$

Recall: Transformation from Exponential to Weibull

Using the transformation $Y = T_1^{\frac{1}{\sigma}}$ and $Z = T_2^{\frac{1}{\sigma}}$

If T_1 is distributed $\beta_1 e^{-\beta_1 t_1}$, then Y is distributed $\beta_1 \sigma y^{\sigma-1} e^{-\beta_1 y^{\sigma}}$.

If T_2 is distributed $\beta_2 e^{-\beta_2 t_2}$, then Z is distributed $\beta_2 \sigma z^{\sigma-1} e^{-\beta_2 z^{\sigma}}$.

Bivariate Weibulll Distribution

Bivariate Weibulll Distribution

David D. Hanagal (2005) proposed a bivariate Weibull model by means of the transformations $T_1 = Y^\sigma$ and $T_2 = Z^\sigma$, $\sigma > 0$ from the bivariate exponential distribution proposed by Proschan and Sullo. (1974).

$$f(y,z) = \begin{cases} \beta_1(\beta_2' + \beta_3)\sigma^2 (yz)^{\sigma-1} e^{-(\beta_2'+\beta_3)z^\sigma - (\beta_1+\beta_2-\beta_2')y^\sigma} & \text{for } 0 < y < z < \infty \\ \beta_2(\beta_1' + \beta_3)\sigma^2 (yz)^{\sigma-1} e^{-(\beta_1'+\beta_3)y^\sigma - (\beta_1+\beta_2-\beta_1')z^\sigma} & \text{for } 0 < z < y < \infty \\ \beta_3 \sigma y^{\sigma-1} e^{-(\beta_1+\beta_2+\beta_3)y^\sigma} & \text{for } 0 < y = z < \infty \end{cases}$$

Bivariate Regression

$\theta_1 = (\theta_{11}, \theta_{12})$, $\theta_2 = (\theta_{21}, \theta_{22})$, $\mathbf{x}$=(1, x)

$T_1 = Y^\sigma e^{-\sigma\theta_1 \mathbf{x}}$, $T_2 = Z^\sigma e^{-\sigma\theta_2 \mathbf{x}}$

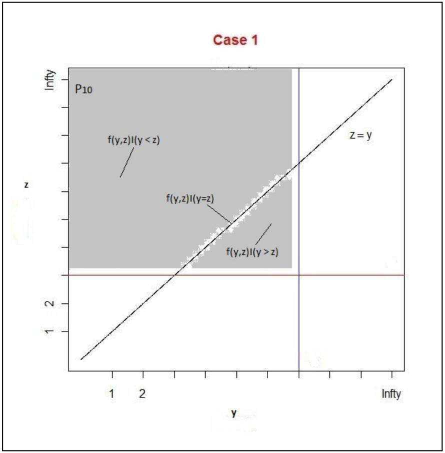
Outcome Probabilities as function of dose

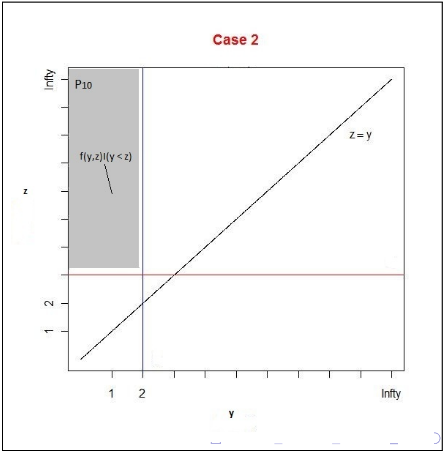
Outcome probabilities are

$$\begin{cases} p_{11} = \int_0^{y^*} \int_0^{z^*} f(y,z)dzdy \\ p_{10} = \int_0^{y^*} \int_{z^*}^{\infty} f(y,z)dzdy \\ p_{01} = \int_{y^*}^{\infty} \int_0^{z^*} f(y,z)dzdy \\ p_{00} = \int_{y^*}^{\infty} \int_{z^*}^{\infty} f(y,z)dydz \end{cases}$$

where $f(y,z)$ is the **bivariate Weibull density.**

Range of Integration for p_{10}: Case 1 ($y^* \geq z^*$) and Case 2 ($y^* < z^*$)





$p_{10} = P(U = 1, V = 0|X = x)$
where U= I(Efficacy), and V= I(Toxicity)

$$p_{10} = P(U = 1, V = 0|X = x) = \int_{z^*}^{\infty} \int_{0}^{y^*} f(y,z)dydz$$

$$= \left[\int_{0}^{z^*}\int_{z^*}^{\infty} f(y,z)I(y<z)dzdy + \int_{z^*}^{y^*}\int_{y}^{\infty} f(y,z)I(y<z)dzdy + \int_{z^*}^{y^*} f(y,z)I(z=y)dy + \int_{z^*}^{y^*}\int_{z^*}^{y} f(y,z)I(z<y)dzdy\right] I(y^* \geq z^*)$$

$$+ \left[\int_{0}^{y^*}\int_{z^*}^{\infty} f(y,z)I(y<z)dzdy\right] I(y^* < z^*).$$

$p_{1.} = P(U = 1|X = x)$ where U= I(Efficacy)

$$p_{1.} = P(U = 1|X = x) = \int_0^\infty \int_0^{y^*} f(y,z)dydz$$

$$= \int_0^{y^*} \int_0^{y} f(y,z)I(z < y)dzdy + \int_0^{y^*} \int_y^{\infty} f(y,z)I(y < z)dzdy + \int_0^{y^*} f(y,z)I(y = z)dy$$

$$= \frac{\beta_2(\beta_1' + \beta_3)}{\beta_1 + \beta_2 - \beta_1'} \left(\frac{1}{(\beta_1' + \beta_3)} \left(1 - e^{-(\beta_1' + \beta_3){y^*}^\sigma}\right) - \frac{1}{(\beta_1 + \beta_2 + \beta_3)} \left(1 - e^{-(\beta_1+\beta_2+\beta_3){y^*}^\sigma}\right) \right)$$

$$+ \frac{\beta_1}{\beta_1 + \beta_2 + \beta_3} \left(1 - e^{-(\beta_1+\beta_2+\beta_3){y^*}^\sigma}\right) + \frac{\beta_1}{\beta_1 + \beta_2 + \beta_3} \left(1 - e^{-(\beta_1+\beta_2+\beta_3){y^*}^\sigma}\right).$$

$p_{.1} = P(V = 1|X = x)$ where V= I(Toxicity)

$$p_{.1} = P(V = 1|X = x) = \int_0^{\infty} \int_0^{z^*} f(y,z)dzdy$$

$$= \int_0^{z^*} \int_0^{z} f(y,z)I(y < z)dydz + \int_0^{z^*} \int_z^{\infty} f(y,z)I(z < y)dydz + \int_0^{z^*} f(y,z)I(y = z)dz$$

$$= \frac{\beta_1(\beta_2' + \beta_3)}{\beta_1 + \beta_2 - \beta_2'} \left(\frac{1}{(\beta_2' + \beta_3)} \left(1 - e^{-(\beta_2'+\beta_3)z^{*\sigma}}\right) - \frac{1}{(\beta_1 + \beta_2 + \beta_3)} \left(1 - e^{-(\beta_1+\beta_2+\beta_3)z^{*\sigma}}\right) \right)$$

$$+ \frac{\beta_2}{\beta_1 + \beta_2 + \beta_3} \left(1 - e^{-(\beta_1+\beta_2+\beta_3)z^{*\sigma}}\right) + \frac{\beta_3}{\beta_1 + \beta_2 + \beta_3} \left(1 - e^{-(\beta_1+\beta_2+\beta_3)z^{*\sigma}}\right).$$

Likelihood

$$L(\Theta|u,v;x) = p_{11}^{uv} \times p_{10}^{u(1-v)} \times p_{01}^{(1-u)v} \times p_{00}^{(1-u)(1-v)}$$

$$\Rightarrow l(\Theta|u,v;x)$$

$$= (u)(v)ln(p_{11}) + (u)(1-v)ln(p_{10}) + (1-u)(v)ln(p_{01}) + (1-u)(1-v)ln(p_{00})$$

$(**p_{11} = 1 - p_{10} - p_{01} - p_{00})$

Partial derivative (Tentative)

$\frac{\partial l(\Theta|u,v;x)}{\partial \Theta} = ABC;$

where

$\Theta = \{\theta_{11}, \theta_{12}, \theta_{21}, \theta_{22}, \beta_1, \beta_2, \beta_3, \beta_1', \beta_2', \sigma\}$

$$A = diag(\frac{\partial \theta_1}{\partial \theta_{11}}, \frac{\partial \theta_1}{\partial \theta_{12}}, \frac{\partial \theta_2}{\partial \theta_{21}}, \frac{\partial \theta_2}{\partial \theta_{22}}, 1, 1, 1, 1, 1, 1)$$

Partial derivative (Tentative)

$$BC = \begin{bmatrix} \frac{\partial p_{10}}{\partial \theta_1} & \frac{\partial p_{01}}{\partial \theta_1} & \frac{\partial p_{00}}{\partial \theta_1} \\ \frac{\partial p_{10}}{\partial \theta_1} & \frac{\partial p_{01}}{\partial \theta_1} & \frac{\partial p_{00}}{\partial \theta_1} \\ \frac{\partial p_{10}}{\partial \theta_2} & \frac{\partial p_{01}}{\partial \theta_2} & \frac{\partial p_{00}}{\partial \theta_2} \\ \frac{\partial p_{10}}{\partial \theta_2} & \frac{\partial p_{01}}{\partial \theta_2} & \frac{\partial p_{00}}{\partial \theta_2} \\ \frac{\partial p_{10}}{\partial \beta_1} & \frac{\partial p_{01}}{\partial \beta_1} & \frac{\partial p_{00}}{\partial \beta_1} \\ \frac{\partial p_{10}}{\partial \beta_2} & \frac{\partial p_{01}}{\partial \beta_2} & \frac{\partial p_{00}}{\partial \beta_2} \\ \frac{\partial p_{10}}{\partial \beta_3} & \frac{\partial p_{01}}{\partial \beta_3} & \frac{\partial p_{00}}{\partial \beta_3} \\ \frac{\partial p_{10}}{\partial \beta_1'} & \frac{\partial p_{01}}{\partial \beta_1'} & \frac{\partial p_{00}}{\partial \beta_1'} \\ \frac{\partial p_{10}}{\partial \beta_2'} & \frac{\partial p_{01}}{\partial \beta_2'} & \frac{\partial p_{00}}{\partial \beta_2'} \\ \frac{\partial p_{10}}{\partial \sigma} & \frac{\partial p_{01}}{\partial \sigma} & \frac{\partial p_{00}}{\partial \sigma} \end{bmatrix} \begin{bmatrix} \frac{u(1-v)}{p_{10}} - \frac{uv}{1-p_{10}-p_{01}-p_{00}} \\ \frac{(1-u)(v)}{p_{01}} - \frac{uv}{1-p_{10}-p_{01}-p_{00}} \\ \frac{(1-u)(1-v)}{p_{00}} - \frac{uv}{1-p_{10}-p_{01}-p_{00}} \end{bmatrix}$$

Information matrix (Tentative)

Since, $\frac{\partial l(\Theta|u,v;x)}{\partial\Theta} = ABC$;

$$I(\Theta) = E\left[\left(\frac{\partial l(\Theta|u,v;x)}{\partial\Theta}\right)\left(\frac{\partial l(\Theta|u,v;x)}{\partial\Theta}\right)^T\right] = E\left((ABC)(ABC)^T\right)$$

$$= E\left(ABCC^TB^TA^T\right) = AB\left[E\left(CC^T\right)\right](AB)^T.$$

Information matrix (Tentative)

$$\Rightarrow E\left(CC^T\right) = \underbrace{\begin{bmatrix} \frac{1}{p_{10}} + \frac{1}{1-p_{10}-p_{01}-p_{00}} & \frac{1}{1-p_{10}-p_{01}-p_{00}} & \frac{1}{1-p_{10}-p_{01}-p_{00}} \\ \frac{1}{1-p_{10}-p_{01}-p_{00}} & \frac{1}{p_{01}} + \frac{1}{1-p_{10}-p_{01}-p_{00}} & \frac{1}{1-p_{10}-p_{01}-p_{00}} \\ \frac{1}{1-p_{10}-p_{01}-p_{00}} & \frac{1}{1-p_{10}-p_{01}-p_{00}} & \frac{1}{p_{00}} + \frac{1}{1-p_{10}-p_{01}-p_{00}} \end{bmatrix}}_{D}$$

$$= \underbrace{\begin{bmatrix} \frac{1}{p_{10}} & 0 & 0 \\ 0 & \frac{1}{p_{01}} & 0 \\ 0 & 0 & \frac{1}{p_{00}} \end{bmatrix} + \left(\frac{1}{1 - p_{10} - p_{01} - p_{00}}\right) \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix}}_{D}$$

(Because U is distributed *Bernoulli*$(p_{1.})$, and V is distributed *Bernoulli*$(p_{.1})$ and U and V are dependent.)

Rest of This Project

1 Canonical Form

Rest of This Project

1. Canonical Form
2. Compute Optimal Design

Rest of This Project

1. Canonical Form
2. Compute Optimal Design
3. Penalty Function

Fin

Thank you for your attention!