AN ADAPTIVE DOSE FINDING DESIGN (DOSEFIND) USING A NONLINEAR DOSE RESPONSE MODEL

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Thanks to
Dr. R. K. Elswick
Dr. Chris Gennings
Dr. Ramesh Ramakrishnan
For support and guidance
Objectives

- Motivation for the DOSEFIND
- How the DOSEFIND Works
- Simulation Plan/Results of DOSEFIND
- Conclusions
DOSEFIND Motivation

- Evaluate a pharmacodynamic (PD) marker that is indicator of efficacy in addition to safety considerations
- Describe a sigmoidal dose response curve using an adaptive approach with a non-linear methodology
- Quickly evaluate and eliminate dose levels below the no effect level (NOEL)
- Potential to provide significant time savings in later Phases of clinical trials development
Objectives

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How the DOSEFIND Works

The diagram shows the relationship between response and the number of tablets/capsules. The curve begins to level off at a certain point, indicating an optimal dosage range. Points A, B, and C represent different stages of the response curve.
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data

Response = \frac{0.6891}{exp(-2.286 + 0.5979 \times Dose)}
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data

Illustration (1st Iteration)
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data
Illustration (2nd Iteration)
How the DOSEFIND Works

An Illustration

Clinical Trials Example Data

Illustration (2nd Iteration)
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data

Illustration (3rd Iteration)

Response = 0.889 / \exp(-2.296 + 0.5979 \times \text{Dose})
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data

Illustration (4\textsuperscript{th} Iteration)
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data

Illustration (5th Iteration)
How the DOSEFIND Works
An Illustration

Clinical Trials Example Data

Illustration Final Curve
How the DOSEFIND Works
An Illustration

- Example Trial $n=20$, DOSEFIND $n=15$

- Target $T_D$ is $6.14$ at a threshold response of $0.55$

- DOSEFIND estimates $T_D$ as $5$ or $6$ ($5.27 \pm 0.44$)

- DOSEFIND puts all doses in the linear range
The general form of the non–linear model is:

\[ \mu = \alpha + \gamma F(D; \mathbf{B}) \]

where

\( D \) is the set of doses  \( D = \{d^{(1)}, \ldots, d^{(k)}\} \) and 
\( k \) is the number of dose steps

\( \mu \) denotes the unknown effect

\( \mathbf{B} \) denotes the vector of unknown parameters and 
\( \alpha \) is the minimum and 
\( \alpha + \gamma \) is the maximum unknown effect parameter
How the DOSEFIND Works

Illustrate DOSEFIND with the following 3 models:

Non-linear Logistic

\[ \mu = \alpha + \frac{\gamma}{1 + e^{-(\beta_0 + \beta_1 D)}} \]

Michaelis-Menten

\[ \mu = \alpha + \frac{\gamma \star D}{\phi + D} \]

Gompertz

\[ \mu = \alpha + \gamma e^{-e^{-(\beta_0 + \beta_1 D)}} \]
How the DOSEFIND Works

Calculation of \((T_D)\) for each model:

**Logistic:**

\[
T_D = \frac{\log \left( \frac{\mu_{T_D}}{\gamma - \mu_{T_D}} \right) - \beta_0}{\beta_1}
\]

**Gompertz:**

\[
T_D = \frac{-\log \left( \log \left( \frac{\gamma}{\mu_{T_D}} \right) \right) - \beta_0}{\beta_1}
\]

**Michaelis-Menten:**

\[
T_D = \phi \left( \frac{\mu_{T_D} - \alpha}{\gamma - \mu_{T_D} + \alpha} \right)
\]
Objectives

- Motivation for the DOSEFIND
- How the DOSEFIND Works
- Simulation Plan/Results of DOSEFIND
- Conclusions
## Simulation Plan

The four different assignment schemas are:

<table>
<thead>
<tr>
<th>Initial 3 Dose Levels</th>
<th>All Subsequent Dose levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
</tr>
<tr>
<td>(1, 1)</td>
<td>1</td>
</tr>
<tr>
<td>(3, 1)</td>
<td>3</td>
</tr>
<tr>
<td>(1, 1)</td>
<td>1</td>
</tr>
<tr>
<td>(3, 1)</td>
<td>3</td>
</tr>
</tbody>
</table>
Simulation Plan

The shape of the logistic model is modified by choosing different slopes and intercepts:

- $\beta_0 = -2.3$ and $\beta_1 = 0.60$, Base Model (SIM 1)
- $\beta_0 = -5$ and $\beta_1 = 1.8$, Steep slope (SIM 2)
- $\beta_0 = -2.3$ and $\beta_1 = 0.30$, Shallow slope (SIM 3)
Simulation Plan

Non-Linear Logistic Base Model (R1), Steep Slope (R2) and Shallow Slope (R3)

\[ R1 = \frac{0.6891}{1 + \exp(-2.296 + 0.5979 \times \text{Dose})} \]
\[ R2 = \frac{0.6891}{1 + \exp(-5 + 1.8 \times \text{Dose})} \]
\[ R3 = \frac{0.6891}{1 + \exp(-2.296 + 0.2969 \times \text{Dose})} \]
Simulation Plan

Gompertz (R1) and Michaelis-Menten (R2) Non-Linear Functions

\[
R_1 = 0.6891 \cdot (\exp(-\exp(-2.296+0.5979 \cdot \text{Dose})))
\]

\[
R_2 = 0.0592 + \frac{(0.7752 \cdot \text{Dose})}{(4.4556 + \text{Dose})}
\]
Simulation Plan

Expected Values of $T_D$ for the Target Threshold Effect

<table>
<thead>
<tr>
<th>Target Threshold Effect</th>
<th>SIM 1 Non-Linear Logistic</th>
<th>SIM 2 Steep $\beta_1$</th>
<th>SIM 3 Shallow $\beta_1$</th>
<th>SIM 4 Gompertz</th>
<th>SIM 5 Michaelis-Menten</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.55</td>
<td>6.14</td>
<td>3.54</td>
<td>12.36</td>
<td>6.83</td>
<td>7.69</td>
</tr>
</tbody>
</table>
Fixed Dose Simulations

FD1 = 0.6910/(1+exp(-(2.29+0.6014*Dose))
FD2 = 0.7218/(1+exp(-(2.31+0.2942*Dose))
FD3 = 0.6910/(1+exp(-(4.76+1.7050*Dose))

Response vs Dose Level
DOSEFIND Results

Results from SIM 1 (10 simulations of size n=100 each) for four sampling scenarios

<table>
<thead>
<tr>
<th>Run*</th>
<th>Mean Parameter Estimates and Standard Error</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$T_D$</td>
<td>$D_N$</td>
<td>$1/2$-width 95% CI</td>
<td>ARE</td>
<td></td>
</tr>
<tr>
<td>1-1, 1-1</td>
<td>6.18 (0.060)</td>
<td>9.00 (0.306)</td>
<td>0.639 (0.017)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>3-1, 1-1</td>
<td>6.09 (0.047)</td>
<td>7.98 (0.201)</td>
<td>0.583 (0.004)</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>1-1, 3-1</td>
<td>6.21 (0.035)</td>
<td>6.99 (0.108)</td>
<td>0.466 (0.017)</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>3-1, 3-1</td>
<td>6.15 (0.036)</td>
<td>6.40 (0.082)</td>
<td>0.435 (0.015)</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

ARE: Asymptotic Relative Efficiency WRT a “fixed dose” design
Fixed Dose “Base” model $\sigma^2=0.596$
DOSEFIND Results

Results from SIM 2 (10 simulations of size n=100 each) for four sampling scenarios

<table>
<thead>
<tr>
<th>Run*</th>
<th>Mean Parameter Estimates and Standard Error</th>
<th>½-width 95% CI</th>
<th>ARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$T_D$</td>
<td>$D_N$</td>
<td></td>
</tr>
<tr>
<td>1-1, 1-1</td>
<td>3.72 (0.052)</td>
<td>5.19 (0.031)</td>
<td>0.192 (0.006)</td>
</tr>
<tr>
<td>3-1, 1-1</td>
<td>3.67 (0.023)</td>
<td>5.02 (0.014)</td>
<td>0.150 (0.004)</td>
</tr>
<tr>
<td>1-1, 3-1</td>
<td>3.69 (0.038)</td>
<td>5.09 (0.040)</td>
<td>0.126 (0.006)</td>
</tr>
<tr>
<td>3-1, 3-1</td>
<td>3.71 (0.037)</td>
<td>5.01 (0.008)</td>
<td>0.089 (0.003)</td>
</tr>
</tbody>
</table>

Fixed Dose “Steep Slope” model $σ^2=0.236$
DOSEFIND Results

Results from SIM 3 (10 simulations of size \(n=100\) each) for four sampling scenarios

<table>
<thead>
<tr>
<th>Run*</th>
<th>Mean Parameter Estimates and Standard Error</th>
<th>½-width 95% CI</th>
<th>ARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(T_D)</td>
<td>(D_N)</td>
<td></td>
</tr>
<tr>
<td>1-1,1-1</td>
<td>12.34 (0.0878)</td>
<td>16.87 (0.4558)</td>
<td>0.847 (0.013)</td>
</tr>
<tr>
<td>3-1,1-1</td>
<td>12.23 (0.1000)</td>
<td>16.09 (0.4480)</td>
<td>0.833 (0.007)</td>
</tr>
<tr>
<td>1-1,3-1</td>
<td>12.38 (0.0644)</td>
<td>11.90 (0.4026)</td>
<td>0.728 (0.019)</td>
</tr>
<tr>
<td>3-1,3-1</td>
<td>12.31 (0.0506)</td>
<td>11.51 (0.4277)</td>
<td>0.704 (0.017)</td>
</tr>
</tbody>
</table>

Fixed Dose “Shallow Slope” model \(\sigma^2=1.639\)
Results from simulation (10 simulations of size n=100 each) for the Gompertz (SIM 4), the Michaelis-Menten Nonlinear (SIM 5) and the Non-Linear Logistic with Safety Adjustment (SIM 6) Models

<table>
<thead>
<tr>
<th>Run*</th>
<th>Mean Parameter Estimates and Standard Error</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T_D</td>
<td>½-width 95% CI</td>
</tr>
<tr>
<td>Gompertz</td>
<td>6.83 (0.031)</td>
<td>0.678 (0.019)</td>
</tr>
<tr>
<td>Michaelis-Menten</td>
<td>7.44 (0.058)</td>
<td>0.738 (0.02)</td>
</tr>
<tr>
<td>Non-linear Logistic + Safety</td>
<td>6.22 (0.055)</td>
<td>0.473 (0.02)</td>
</tr>
</tbody>
</table>

Sampling Schema (1-1,3-1)
DOSEFIND Results

Simulations that stopped prior to convergence of the confidence interval

<table>
<thead>
<tr>
<th>Run</th>
<th>SIM 1 Non-Linear Logistic</th>
<th>SIM 2 Steep $\beta_1$</th>
<th>SIM 3 Shallow $\beta_1$</th>
<th>SIM 4 Gompertz</th>
<th>SIM 5 Michaelis-Menten</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1, 1-1</td>
<td>1.6%</td>
<td>0%</td>
<td>24%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3-1, 1-1</td>
<td>0.4%</td>
<td>0%</td>
<td>24%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1-1, 3-1</td>
<td>0%</td>
<td>0%</td>
<td>1.5%</td>
<td>4.5%</td>
<td>3.3%</td>
</tr>
<tr>
<td>3-1, 3-1</td>
<td>0%</td>
<td>0%</td>
<td>1.4%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Percentage of runs that stopped due to an adverse event
Simulation including Probability of a DLT

Non-Linear Logistic (R1) with Adverse Event (AE) Probability Curve

\[ R1 = \frac{0.891}{1 + \exp(-2.296 + 0.5979 \times \text{Dose})} \]

\[ AE = \frac{1}{1 + \exp(-(\text{Dose} - 12.5)/3.413)} \]
DOSEFIND Results

Simulations that stopped prior to convergence of the confidence interval

<table>
<thead>
<tr>
<th>Run</th>
<th>SIM 1 Non-Linear Logistic</th>
<th>SIM 2 Steep $\beta_1$</th>
<th>SIM 3 Shallow $\beta_1$</th>
<th>SIM 4 Gompertz</th>
<th>SIM 5 Michaelis-Menten</th>
<th>SIM 6 Non-Linear Logistic + Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1, 1-1</td>
<td>1.6%</td>
<td>0%</td>
<td>24%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3-1, 1-1</td>
<td>0.4%</td>
<td>0%</td>
<td>24%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1-1, 3-1</td>
<td>0%</td>
<td>0%</td>
<td>1.5%</td>
<td>4.5%</td>
<td>3.3%</td>
<td>19.8%*</td>
</tr>
<tr>
<td>3-1, 3-1</td>
<td>0%</td>
<td>0%</td>
<td>1.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Percentage of runs that stopped due to an adverse event
DOSEFIND Results

Comparison of Relative Efficiency versus Relative Cost, for Base (SIM 1), Steep (SIM 2) and Shallow (SIM 3) Nonlinear Logistic Models
Conclusions

- Developed an Adaptive Method that:
  - produces a dose response curve profile of a desired PD parameter
  - the choice of the functional form is not sensitive to the estimation of the $T_D$
  - is more efficient as measured by ARE to a "fixed dose" design
  - is more cost effective as measured by sample size to a "fixed dose" design
Conclusions

- Uses general non-linear 3 and 4 parameter models
- General structure for variance
- Use early trials in humans to assess efficacy as well as safety
Background: Modified CRM Design

Piantadosi et.al. 1997

- Model: \[ \Pr[\text{toxicity}] = \frac{1}{1 + e^{-\beta(d-d_{50})}} \]

- Logistic regression
- Not using fixed set of dose levels
- Assigns patients based on new d30
- Does not estimate the variance of the target dose
- Based on observance of toxicity
How the DOSEFIND Works

The variance of \( Y \) is assumed to be a function of the mean, that is,

\[
\text{Var}(Y) = \tau V(\mu)
\]

Under the premise that the observed variance is larger in the “linear” portion of the dose response curve for responses between zero and one, \( V(\mu) \) is assumed to follow \( \mu (1 - \mu) \)
How the DOSEFIND Works

Let \( G_i = \alpha + \gamma F\left( d^{(i)}, \beta \right) \) and let \( H \) be the partial derivatives from the \( (T_D) \) equations, then \( \hat{\Sigma} \) and \( \text{Var}(T_D) = H\Sigma H' \) are derived using the quasi-likelihood approach found in Seber and Wild (1989).
How the DOSEFIND Works

The estimate of the target dose ($T_D$) for the general nonlinear form is:

$$T_D = \frac{F^{-1}\left(\left(\frac{\mu_{T_D} - \alpha}{\gamma}\right) - \beta_0\right)}{\beta_1}$$
How the DOSEFIND Works
An Illustration

Illustration Results for the DOSEFIND Method

<table>
<thead>
<tr>
<th>Steps</th>
<th>$\beta_0$</th>
<th>$\beta_1$</th>
<th>$\gamma$</th>
<th>Actual Dose</th>
<th>Target Dose</th>
<th>Variance</th>
<th>$\frac{1}{2}$ 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.0698</td>
<td>1.1054</td>
<td>0.33145</td>
<td>-</td>
<td>10.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-2.07356</td>
<td>0.40014</td>
<td>0.81388</td>
<td>7.0176</td>
<td>7.0</td>
<td>0.7612</td>
<td>1.800</td>
</tr>
<tr>
<td>3</td>
<td>-2.05163</td>
<td>0.49431</td>
<td>0.76334</td>
<td>6.0664</td>
<td>6.0</td>
<td>0.5695</td>
<td>1.254</td>
</tr>
<tr>
<td>4</td>
<td>-2.10020</td>
<td>0.55409</td>
<td>0.74503</td>
<td>5.6615</td>
<td>6.0</td>
<td>0.2968</td>
<td>0.633</td>
</tr>
<tr>
<td>5</td>
<td>-2.1183</td>
<td>0.60724</td>
<td>0.73635</td>
<td>5.2707</td>
<td>5.0</td>
<td>0.2121</td>
<td>0.444</td>
</tr>
</tbody>
</table>
DOSEFIND Results

Results from SIM 7 (10 simulations of size n=100 each) for fixed dose levels

Desired Response: 0.55 and Desired Target Dose: 6.14, 3.54 and 12.36

<table>
<thead>
<tr>
<th>Run</th>
<th>Mean Parameter Estimates and Standard Error</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run Parameter Estimates</td>
<td>$T_D$</td>
<td>1.2-width 95% CI</td>
</tr>
<tr>
<td>Logistic</td>
<td>6.21 (0.0319)</td>
<td>1.212 (0.0108)</td>
<td>0.596 (0.0053)</td>
</tr>
<tr>
<td>Steep $\beta 1$</td>
<td>3.62 (0.0101)</td>
<td>0.481 (0.0035)</td>
<td>0.236 (0.0017)</td>
</tr>
<tr>
<td>Shallow $\beta 1$</td>
<td>12.62 (0.0588)</td>
<td>3.335 (0.9366)</td>
<td>1.639 (0.4603)</td>
</tr>
</tbody>
</table>
DOSEFIND Results

Comparison of Bias-Squared versus Mean Square Error for Nonlinear Logistic Models

![Graph showing comparison of Bias-Squared versus Mean Square Error for different models.](image-url)