The IDEAS network: Training and research under one umbrella

29. November 2018
Thomas Jaki
Disclaimer

This project has received funding from the European Unions Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.
Current Statistics training

Traditional training in Statistics is often

- very general (MSc level)
- highly specialised (PhD level)
- completely isolated from practice
- neglecting transferable skills
What is IDEAS

• Pan-European training network
• Focus on early drug development
• Close interaction between academia
Objectives

a) train early-stage researchers in state of the art methods for designing, evaluating and analysing early phase studies

b) develop novel methodology for early phase studies through individually supervised, collaborative, research projects

c) provide an international, collaborative environment in which the academic research experience is paired with the challenges of undertaking drug development within the private sector

d) raise awareness about cutting edge methods for designing and analysing early phase studies among trialists and clinicians alike
Set-up

- 5 academic partners
- 3 industry partners
- Several associated partners (mostly industry)
- 14 early stage researchers (ESRs)
(i) individually supervised research projects
(ii) transnational, cross-sectorial secondments
(iii) network-wide training activities
(iv) individual training activities
Secondments

- Cross-sectorial
- Cross-national
- Minimum 3 months
- Research and daily work
Network-wide training

- A week-long kick-off event
- three week-long summer schools
- e-learning courses in statistical methodology
- a think tank
- surgery sessions
- dissemination workshop
Network-wide training

- Statistics
- Practical skills
- Networking
More on IDEAS

Website    www.ideas-itn.eu
email      ideas@lancaster.ac.uk
Twitter    @IDEAS_ITN
Motivation (I)

Consider a trial with **two arms** and **binary outcomes** which aims to find the **superior arm**.

- 10 outcomes observed for each arm
  - 4 successes on 1st arm
  - 6 successes on 2nd arm

Q: To which arm a next patient should be assigned?

We would like to
  - make a reliable recommendation (high statistical power)
  - maximize the proportion of the population on the superior arm

“Earn vs Learn” trade-off
Consider a trial with **two arms** and **binary outcomes** which aims to find the **superior arm**.

An example

- 10 outcomes observed for each arm
- 4 successes on 1st arm
- 6 successes on 2nd arm
Motivation (I)

Consider a trial with two arms and binary outcomes which aims to find the superior arm.

An example

- 10 outcomes observed for each arm
- 4 successes on 1st arm
- 6 successes on 2nd arm

Q: To which arm a next patient should be assigned?
Motivation (I)

Consider a trial with **two arms** and **binary outcomes** which aims to find the **superior arm**.

An example

- 10 outcomes observed for each arm
- 4 successes on 1st arm
- 6 successes on 2st arm

Q: To which arm a next patient should be assigned?

We would like to

- make a reliable recommendation (high statistical power)
- maximize the proportion of the population on the superior arm

“Earn vs Learn“ trade-off
1. **Option 1. Earn**
   Assign next patients to 2nd arm

**Challenges:**
- Selection can lock in the suboptimal arm
- Low statistical power
1. Option 1. Earn
   Assign next patients to 2nd arm

**Challenges:**
- Selection can lock in the suboptimal arm
- Low statistical power
1. **Option 1. Earn**
   Assign next patients to 2nd arm
   
   **Challenges:**
   
   - Selection can lock in the suboptimal arm
   - Low statistical power

2. **Option 2. Learn**
   Assign next patient to arm we know least about (e.g. the Shannon information)
1. **Option 1. Earn**
   Assign next patients to 2nd arm

   **Challenges:**
   - Selection can lock in the suboptimal arm
   - Low statistical power

2. **Option 2. Learn**
   Assign next patient to arm we know least about (e.g. the Shannon information)

   **Challenges:**
   - Unethical (low number of treated patients)
Current approaches

- Fixed randomization
- Randomized play the winner
- Current belief (maximum point estimate)
- Optimal multi-arm bandit (MAB) with dynamic programming
The Shannon information (entropy)

\[ h(f) = - \int_{\mathbb{R}} f(z) \log f(z) \, dz. \]
The Shannon information (entropy)

\[ h(f) = -\int_{\mathbb{R}} f(z) \log f(z) \, dz. \]

In the example above,

\[ h(\text{arm 1}) = h(\text{arm 2}). \]

This information \textbf{does not reflect} our specific interest in the superior arm.

It shows the amount of information needed to answer the question:

What is the success probability?
Consider a two-fold experiment:
(i) what is the probability of success
(ii) is the probability of success close to a target, $\gamma$
Consider a two-fold experiment:
(i) what is the probability of success
(ii) is the probability of success close to a target, $\gamma$

A: The weighted Shannon information

$$h_{\phi}(f) = -\int_{\mathbb{R}} \phi(z)f(z)\log f(z)\,dz.$$
The Beta-form weight function

\[ \phi_n(p) = \Lambda(\gamma, x, n)p^{\gamma\sqrt{n}}(1 - p)^{(1-\gamma)\sqrt{n}}. \]
Methods

- Model probability of success with a Beta distribution
- $\alpha$ is the true probability of success
- $\gamma$ is the target probability (for instance, $\gamma = 0.999$)

Theorem

Let $h(f_n)$ and $h^{\phi_n}(f_n)$ be the standard and weighted differential entropies. Then,

$$\lim_{n \to \infty} \left( \left[ h^{\phi_n}(f_n) - h(f_n) \right] - \frac{1}{2} \left( \frac{(\alpha - \gamma)^2}{\alpha(1 - \alpha)} \right) n^{2\kappa-1} + \omega \right) = 0$$
Methods

• Model probability of success with a Beta distribution
• $\alpha$ is the true probability of success
• $\gamma$ is the target probability (for instance, $\gamma = 0.999$)

Theorem

Let $h(f_n)$ and $h^{\phi_n}(f_n)$ be the standard and weighted differential entropies. Then,

$$\lim_{n \to \infty} \left( \left[ h^{\phi_n}(f_n) - h(f_n) \right] - \frac{1}{2} \left( \frac{(\alpha - \gamma)^2}{\alpha(1 - \alpha)} \right) n^{2\kappa - 1} + \omega \right) = 0$$
Design

\[
\hat{\delta}_{n_j}^{(\kappa)} = \frac{(\hat{p}_{n_j} - \gamma)^2}{\hat{p}_{n_j}(1 - \hat{p}_{n_j})} n_j^{2\kappa - 1}
\]

Arm selection algorithm:
1. Start from \( \hat{\delta}_{\beta_i}^{(\kappa)} \), \( i = 1, \ldots, m \)
2. Observed \( n_i \) and \( x_i \) outcomes for the arm \( A_i \), \( i = 1, \ldots, m \)
3. Arm \( A_j \) is selected if it satisfies

\[
\hat{\delta}_{n_j}^{(\kappa)} = \inf_{i=1,\ldots,m} \hat{\delta}_{n_i}^{(\kappa)}.
\]

4. Repeat 2-3 until the total number of patients is reached.

Note: Randomize in case of tie.
Consider the trial with $m = 2$ arms ($\alpha_1 = 0.5$ and $\alpha_2 = 0.7$), $n = 75$ patients

Prior: $\hat{\rho} = (0.99, 0.99); \quad \beta = (2, 2)$

Alternative: Constrained rand. dynamic programming (Williamson et.al, 2016)
Consider the trial with $m = 2$ arms ($\alpha_1 = 0.5$ and $\alpha_2 = 0.7$), $n = 75$ patients

Prior: $\hat{p} = (0.99, 0.99); \quad \beta = (2, 2)$

Alternative: Constrained rand. dynamic programming (Williamson et.al, 2016)
We consider two trials with \( m = 4 \) treatments (Villar et.al, 2015)

Trial 1: \( N_1 = 423, \ p = [0.3, 0.3, 0.3, 0.5]^{\text{T}} \)

Trial 2: \( N_2 = 80, \ p = [0.3, 0.4, 0.5, 0.6]^{\text{T}}. \)

Hypothesis \( H_0 : p_0 \geq p_i \) for \( i = 1, 2, 3 \)

with the family-wise error rate calculated at \( p_0 = \ldots = p_3 = 0.3 \)

Prior: \( \hat{\rho} = (0.99, 0.99, 0.99, 0.99); \ \beta = (5, 2, 2, 2) \)

We study:

- the type-I error rate \((\alpha)\)
- statistical power \((1 - \eta)\)
- expected number of successes (ENS)

Comparators:

- MAB approach based on the Gittins index
- Fixed randomization
Numerical study. Results

### Trial 1

<table>
<thead>
<tr>
<th>Method</th>
<th>( H_0: p_0 = p_1 = p_2 = p_3 = 0.3 )</th>
<th>( H_1: p_0 = p_1 = p_2 = 0.3, p_3 = 0.5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \alpha )</td>
<td>( p^* ) (s.e.)</td>
</tr>
<tr>
<td>MAB</td>
<td>0.05</td>
<td>0.25 (0.18)</td>
</tr>
<tr>
<td>WE (( \kappa = 0.55 ))</td>
<td>0.05</td>
<td>0.22 (0.20)</td>
</tr>
</tbody>
</table>
## Trial 1

<table>
<thead>
<tr>
<th>Method</th>
<th>$H_0: p_0 = p_1 = p_2 = p_3 = 0.3$</th>
<th>$H_1: p_0 = p_1 = p_2 = 0.3, p_3 = 0.5$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>$p^*(s.e.)$</td>
</tr>
<tr>
<td>MAB</td>
<td>0.05</td>
<td>0.25 (0.18)</td>
</tr>
<tr>
<td>WE ($\kappa = 0.55$)</td>
<td>0.05</td>
<td>0.22 (0.20)</td>
</tr>
<tr>
<td>FR</td>
<td>0.05</td>
<td>0.25 (0.02)</td>
</tr>
<tr>
<td>WE ($\kappa = 0.65$)</td>
<td>0.05</td>
<td>0.23 (0.13)</td>
</tr>
</tbody>
</table>
Numerical study. Results

Trial 2

<table>
<thead>
<tr>
<th>Method</th>
<th>$p_0 = p_1 = p_2 = p_3 = 0.3$</th>
<th>$p_0 = 0.3, p_1 = 0.4, p_2 = 0.5, p_3 = 0.6$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>$p^*(s.e.)$</td>
</tr>
<tr>
<td>MAB</td>
<td>0.00</td>
<td>0.25 (0.13)</td>
</tr>
<tr>
<td>WE ($\kappa = 0.55$)</td>
<td>0.01</td>
<td>0.20 (0.15)</td>
</tr>
</tbody>
</table>
Trial 2

<table>
<thead>
<tr>
<th>Method</th>
<th>$p_0 = p_1 = p_2 = p_3 = 0.3$</th>
<th>$p_0 = 0.3, p_1 = 0.4, p_2 = 0.5, p_3 = 0.6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>$p^*(s.e.)$</td>
<td>ENS(s.e.)</td>
</tr>
<tr>
<td>MAB</td>
<td>0.00</td>
<td>0.25 (0.13)</td>
</tr>
<tr>
<td>WE ($\tilde{\kappa} = 0.55$)</td>
<td>0.01</td>
<td>0.20 (0.15)</td>
</tr>
<tr>
<td>FR</td>
<td>0.05</td>
<td>0.25 (0.04)</td>
</tr>
<tr>
<td>WE ($\tilde{\kappa} = 0.65$)</td>
<td>0.05</td>
<td>0.24 (0.07)</td>
</tr>
</tbody>
</table>
Conclusion

- Simple, intuitively clear, can be computed by non-statisticians
- Penalty parameter $\kappa$ reflects the trade-off between ENS and Power
- Performs better than currently used approaches

<table>
<thead>
<tr>
<th></th>
<th>MAB</th>
<th>FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>higher</td>
<td>same</td>
</tr>
<tr>
<td>ENS</td>
<td>same</td>
<td>higher</td>
</tr>
</tbody>
</table>

- Can be applied to any trial with the target $\gamma \in (0, 1)$
- Theoretical result: the design is consistent
- The criterion can be generalized for multinomial outcomes