Mathematics & Statistics | Lancaster University

The IDEAS network: Training and research under one umbrella

29. November 2018

Thomas Jaki

Disclaimer

Mathematics & Statistics | Lancaster University

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

IDEAS Improving drug development

Current Statistics training

Mathematics & Statistics | Lancaster University

Traditional training in Statistics is often

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

IDEAS Improving drug development

What is IDEAS

Mathematics & Statistics | Lancaster University

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

IDEAS
Improving drug development

Objectives

Mathematics & Statistics | Lancaster University

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

IDEAS
Improving drug development

Set-up

Mathematics & Statistics | Lancaster University

- 5 academic partners
- 3 industry partners
- Several associated partners (mostly industry)
- 14 early stage researchers (ESRs)

IDEAS
Improving drug development

Training

Mathematics & Statistics | Lancaster University

(i) individually supervised research projects

(ii) transnational, cross-sectorial secondments

(iii) network-wide training activities

(iv) individual training activities

IDEAS Improving drug development

Secondments

Mathematics & Statistics | Lancaster University

- Cross-sectorial
- Cross-national
- Minimum 3 months
- Research and daily work

IDEAS
Improving drug development

Network-wide training

Mathematics & Statistics | Lancaster University

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

IDEAS Improving drug development

Network-wide training

Mathematics & Statistics | Lancaster University

- Statistics
- Practical skills
- Networking

IDEAS
Improving drug development

More on IDEAS

Mathematics & Statistics | Lancaster University

Website	www.ideas-itn.eu
email	ideas@lancaster.ac.uk
Twitter	@IDEAS_ITN

IDEAS
Improving drug development

Motivation (I)

Mathematics & Statistics | Lancaster University

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

IDEAS Improving drug development

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

Motivation (I)

Mathematics & Statistics | Lancaster University

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?

IDEAS Improving drug development

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

Motivation (II)

1. **Option 1. Earn**
   Assign next patients to 2nd arm

Motivation (II)

1. **Option 1. Earn**
   Assign next patients to 2nd arm

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

Motivation (II)

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)

Motivation (II)

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

Back to information measures

The Shannon information (entropy)

$$h(f) = -\int_{\mathbb{R}} f(z)\log f(z)\mathrm{d}z.$$

Back to information measures

The Shannon information (entropy)

$$h(f) = -\int_{\mathbb{R}} f(z)\log f(z)\mathrm{d}z.$$

In the example above,

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

This information **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?

Weighted information

Mathematics & Statistics | Lancaster University

Consider a two-fold experiment:

(i) what is the probability of success

(ii) is the probability of success close to a target, γ

IDEAS Improving drug development

Weighted information

Mathematics & Statistics | Lancaster University

Consider a two-fold experiment:

(i) what is the probability of success

(ii) is the probability of success close to a target, γ

A: The *weighted Shannon information*

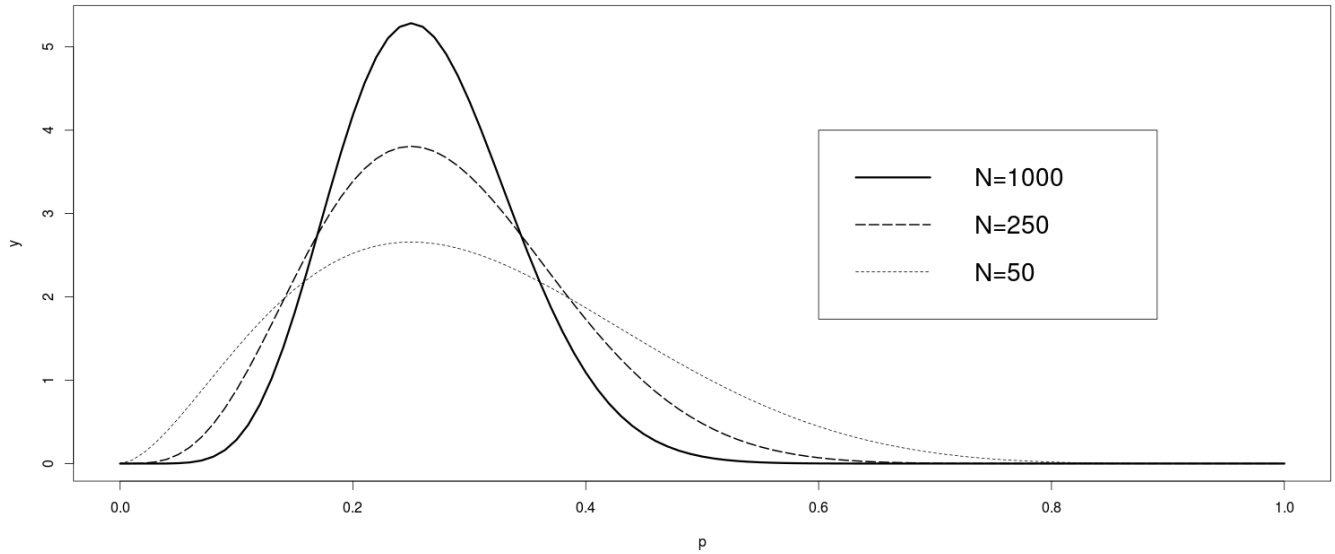
$$h_\phi(f) = -\int_{\mathbb{R}} \phi(z) f(z) \log f(z) \mathrm{d}z.$$

IDEAS Improving drug development

Weight Function

The Beta-form weight function

$$\phi_n(p) = \Lambda(\gamma, x, n) p^{\gamma\sqrt{n}}(1-p)^{(1-\gamma)\sqrt{n}}. \quad (1)$$



Methods

- Model probability of success with a Beta distribution
- α is the true probability of success
- γ 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
- α is the true probability of success
- γ 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

Mathematics & Statistics | Lancaster University

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

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.

IDEAS Improving drug development

Illustration. Two arms trial

Mathematics & Statistics | Lancaster University

Consider the trial with $m = 2$ arms ($\alpha_1 = 0.5$ and $\alpha_2 = 0.7$), $n = 75$ patients

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

Alternative: Constrained rand. dynamic programming (Williamson et.al, 2016)

IDEAS Improving drug development

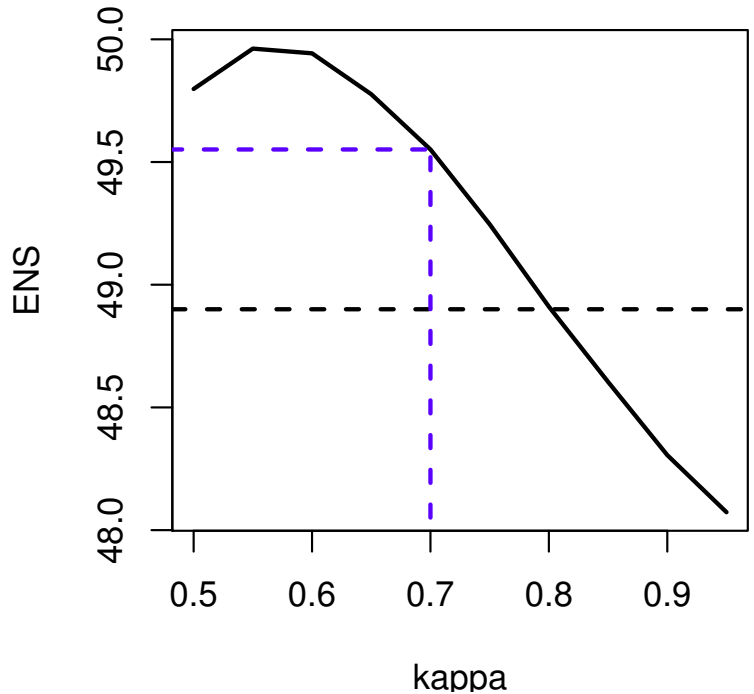
Illustration. Two arms trial

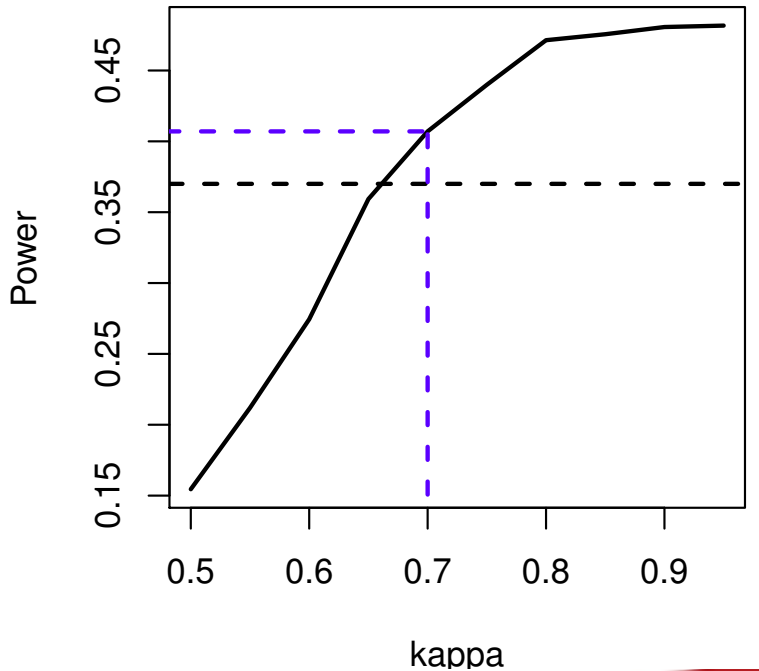
Mathematics & Statistics | Lancaster University

Consider the trial with $m = 2$ arms ($\alpha_1 = 0.5$ and $\alpha_2 = 0.7$), $n = 75$ patients

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

Alternative: Constrained rand. dynamic programming (Williamson et.al, 2016)





IDEAS Improving drug development

Numerical study

Mathematics & Statistics | Lancaster University

We consider two trials with $m = 4$ treatments (Villar et.al, 2015)
Trial 1: $N_1 = 423$, $p = [0.3, 0.3, 0.3, 0.5]^{\mathrm{T}}$
Trial 2: $N_2 = 80$, $p = [0.3, 0.4, 0.5, 0.6]^{\mathrm{T}}$.

$$\text{Hypothesis} \quad H_0 : \; p_0 \geq p_i \text{ for } i = 1, 2, 3$$

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

$$\text{Prior :} \qquad \hat{p} = (0.99, 0.99, 0.99, 0.99); \quad \beta = (5, 2, 2, 2)$$

We study:

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

Comparators:

- MAB approach based on the Gittins index
- Fixed randomization

IDEAS Improving drug development

Numerical study. Results

Mathematics & Statistics | Lancaster University

Trial 1

Method	$H_0 : p_0 = p_1 = p_2 = p_3 = 0.3$			$H_1 : p_0 = p_1 = p_2 = 0.3, p_3 = 0.5$		
	α	$p^*(s.e)$	ENS(s.e.)	$(1-\eta)$	$p^*(s.e.)$	ENS (s.e.)
MAB	0.05	0.25 (0.18)	126.7 (9.4)	0.43	0.83 (0.10)	198.3 (13.7)
WE ($\kappa = 0.55$)	0.05	0.22 (0.20)	126.9 (9.4)	0.55	0.83 (0.18)	197.1 (17.8)

IDEAS Improving drug development

Numerical study. Results

Mathematics & Statistics | Lancaster University

Trial 1

Method	$H_0 : p_0 = p_1 = p_2 = p_3 = 0.3$			$H_1 : p_0 = p_1 = p_2 = 0.3, p_3 = 0.5$		
	α	$p^*(s.e)$	ENS(s.e.)	$(1-\eta)$	$p^*(s.e.)$	ENS (s.e.)
MAB	0.05	0.25 (0.18)	126.7 (9.4)	0.43	0.83 (0.10)	198.3 (13.7)
WE ($\kappa = 0.55$)	0.05	0.22 (0.20)	126.9 (9.4)	0.55	0.83 (0.18)	197.1 (17.8)
FR	0.05	0.25 (0.02)	126.9 (9.4)	0.82	0.25 (0.02)	147.9 (9.6)
WE ($\kappa = 0.65$)	0.05	0.23 (0.13)	126.9 (9.4)	0.87	0.74 (0.10)	189.3 (13.7)

IDEAS Improving drug development

Numerical study. Results

Mathematics & Statistics | Lancaster University

Trial 2

Method	$p_0 = p_1 = p_2 = p_3 = 0.3$			$p_0 = 0.3, p_1 = 0.4, p_2 = 0.5, p_3 = 0.6$		
	α	$p^*(s.e)$	ENS(s.e.)	$(1-\eta)$	$p^*(s.e.)$	ENS (s.e.)
MAB	0.00	0.25 (0.13)	24.0 (4.10)	0.00	0.49 (0.21)	41.6 (5.4)
WE ($\kappa = 0.55$)	0.01	0.20 (0.15)	24.0 (4.10)	0.11	0.50 (0.27)	40.7 (5.9)

IDEAS Improving drug development

Numerical study. Results

Mathematics & Statistics | Lancaster University

Trial 2

Method	$p_0 = p_1 = p_2 = p_3 = 0.3$			$p_0 = 0.3, p_1 = 0.4, p_2 = 0.5, p_3 = 0.6$		
	α	$p^*(s.e)$	ENS(s.e.)	$(1-\eta)$	$p^*(s.e.)$	ENS (s.e.)
MAB	0.00	0.25 (0.13)	24.0 (4.10)	0.00	0.49 (0.21)	41.6 (5.4)
WE ($\kappa = 0.55$)	0.01	0.20 (0.15)	24.0 (4.10)	0.11	0.50 (0.27)	40.7 (5.9)
FR	0.05	0.25 (0.04)	24.0 (4.10)	0.50	0.25 (0.04)	36.0 (4.3)
WE ($\kappa = 0.65$)	0.05	0.24 (0.07)	24.0 (4.05)	0.52	0.47 (0.21)	40.2 (4.8)

IDEAS Improving drug development

Conclusion

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

	MAB	FR
Power	higher	same
ENS	same	higher

- 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