Global, exact and fast group size optimization with corresponding efficiency translation in optimal design

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Background and Objectives

To increase the efficiency in various stages of drug development, optimal design has been used [1]. Group size optimization has been investigated previously by various techniques, e.g. within the Fedorov-Wynn algorithm [2], and implemented in software [2,3], however these search methods can be quite computationally intensive.

The aim of this investigation is to develop and explore fast and accurate methods for optimizing the number of individuals in different design groups. A secondary objective is to use the method to interpret efficiency using (the more understandable) number of individuals.

Methods

Group size optimization

Two different methods were developed, 1) an exhaustive global search (GS) and 2) a faster approximation (FA) method. The methods utilize the additive properties of the population Fisher Information Matrix (FIM), seen in eq. 1, to optimize the number of individuals per group in an experiment subject to eq. 2.

Eq. 1

$$FIM_{tot} = \sum_{q=1}^{\#\text{groups}} FIM_q$$

$$FIM_q = \sum_{i=1}^{\#\text{ind in q}} FIM_{i,q} = N_q \cdot FIM_{i,q}$$

Eq. 2

$$\arg\max_{N_q}\left(OFV\left(FIM_{tot}\right)\right) \quad \text{subject to} \quad \left\{\begin{array}{l} N_{q,\min} \le N_q \le N_{q,\max} \\ N_{tot,\min} \le \sum N_q \le N_{tot,\max} \end{array}\right\}$$

Assuming no other design variables change, the FIM can be optimized for group size using one $FIM_{i,q}$ calculated once per design group and then varying N_q given the restrictions in Eq. 2.

- The FA method begins from the lowest allowed N_q per group and iteratively adds one individual to the most informative group (within the given restrictions of Eq. 2) based on OFV.
- The GS method tests all combinations of group assignment to find the maximal OFV.

Efficiency translation

Efficiency (see eq. 3,4) is often used when comparing designs. Efficiency can be hard to interpret, e.g. a D-efficiency of 80% roughly means that the information with design A is 80% of the information with design B.

The efficiency can then be translated to number of individuals needed to get a certain efficiency using the same technique as in eq. 1 and 2. An efficiency curve (fig. 1) can be produced by translating the number of individuals to efficiency by distributing the individuals between design groups optimally (upper curve) or in the least informative way (lower curve).

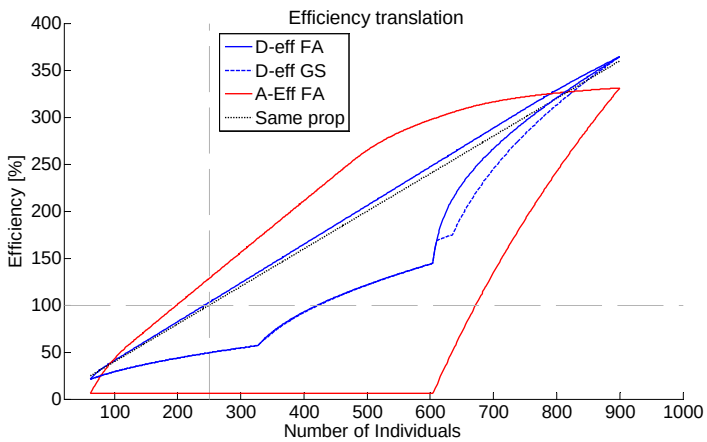

Fig 1. The translation of A - and D-efficiency to number of individuals for the Emax model. The lower red and blue lines represents the least amount of information that is possible with a given number of individuals while the upper lines represent the maximal information. The dotted blue line represents the true curve (GS) while the solid lines are approximations using the FA method (overlying the blue dotted upper curve). The black dotted line represents the D-efficiency where the number of individuals are split into the same proportions as the reference design. The reference design is located at the intersection of the dashed grey lines. Note that a black dotted line outside the blue region indicates that this proportion is not valid due to the restriction of the design groups.

$$A_{eff} = \frac{tr\left(FIM^{-1}(A)\right)}{tr\left(FIM^{-1}(B)\right)} \quad \text{Eq. 3}$$

$$D_{eff} = \left(\frac{|FIM(A)|}{|FIM(B)|}\right)^{1/p} \quad \text{Eq. 4}$$

Results

To investigate the group size optimization and efficiency translation a simple Emax model (E0, Emax and EC50 = 1) with exponential IIV (10% CV, fixed for EC50) and a proportional residual model (38% CV) was used. The concentrations were proportional to the dose and sample times ($c_{q,i}=A_q*t_{q,i}$). The study has 3 design groups with a placebo dose (0 units), a low dose (2.5 units) and a high dose (5 units). The groups had 5 sample times each (optimized within 0-1 time units). The group size restrictions [min, init, max] used were Placebo ~[23, 80, 300], Low ~ [4, 100, 300] and high ~ [35, 70, 300]. For optimization the total number of individuals in the study was restricted to 400, for efficiency translation (see fig. 1,2) no total restriction was used.

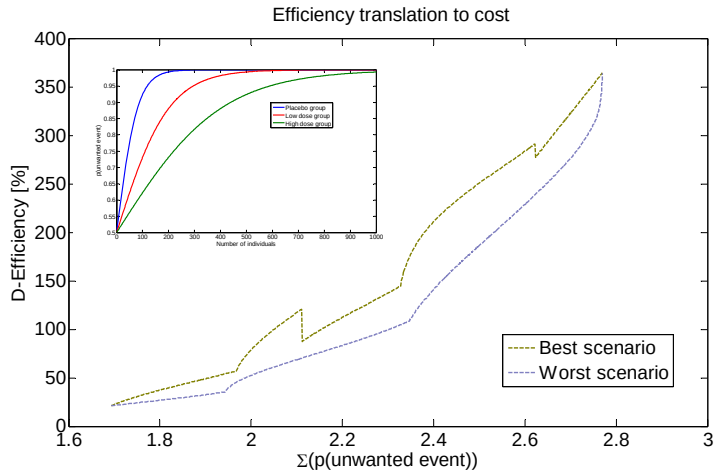

Fig 2. The D-efficiency calculated with the GS method translated to a cost function, i.e. the probability sum for all groups to have an unwanted event. The underlying model is the Emax-model but with the probability curves of having an event (small picture) as a cost function, depending on the number of individuals in each dose group.

- Optimizing the number of individuals in each group for D-optimal design gave [Placebo, Low, High] = [76,166,158] (both for GS and FA) and the run time was ~10 min (~22 million combinations tested) for the GS method and ~1 sec for the FA method.
- In figure 1 we illustrate how the efficiency could be translated to number of individuals.
- Figure 2 illustrates how the GA and FA methods could be used to translate the efficiency to even more complex functions, here a cost function depending on N_q.

Conclusions

- A global exact (GS) and a fast approximate (FA) group size optimization procedure was implemented in PopED 2.10
- A transformation tool for efficiency was implemented in PopED 2.10
- The methods allow an increased understanding of efficiency and is useful to compare different designs with each other and translate the information differences into e.g. number of individuals, power, money or more complex cost functions.

References

[1] Mentré, F., A. Mallet, and D. Baccar, *Optimal design in random-effects regression models.* Biometrika, 1997. **84**(2):429-442.

[2] Retout, S., et al., *Design in nonlinear mixed effects models: optimization using the Fedorov-Wynn algorithm and power of the Wald test for binary covariates.* Stat Med, 2007. **26**(28): p. 5162-79.

[3] *PopED, version 2.10 (2010) http://poped.sf.net*