Numerical investigation of the number of design points in Bayesian D-optimal designs in respect to prior uncertainty

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In D-optimal designs
Number of unique design points is limited by the “Equivalence Theorem”:

unique time points ≤ number of parameters

parameters also include random effects (?)

Also identifiability issues dictate that :

unique time points ≥ number of fixed effects parameters

Bayesian design, however may produce more unique design points
Theoretically an arbitrarily large number of points.

We investigate how this happens in respect to the magnitude of prior uncertainty starting from zero uncertainty which is the local design.

Methods

General form of a first order approximation for FIM:

$$M_{\alpha\beta}(\mathrm{X},\theta)=\frac{\partial f^{T}(X,\theta)}{\partial\theta_{a}}V^{-1}(X,\theta)\frac{\partial f(X,\theta)}{\partial\theta_{b}}+\frac{1}{2}Tr\left[V^{-1}(X,\theta)\frac{\partial V(X,\theta)}{\partial\theta_{a}}V^{-1}(X,\theta)\frac{\partial V(X,\theta)}{\partial\theta_{b}}\right]$$

Where
f: model, X: vector of sampling points, θ: parameters

and $V(\mathrm{X},\theta)=\frac{\partial f(X,\theta)}{\partial\theta_{a}}\Omega\frac{\partial f^{T}(X,\theta)}{\partial\theta_{b}}+\sigma_{1}^{2}Diag[f(X,\theta)f^{T}(X,\theta)]+\sigma_{2}^{2}\mathrm{I}$

Although simpler forms are available
e.g. considering fixed effects with additive error, FIM simplifies to

$$M_{\alpha\beta}(\mathrm{X},\theta)=\frac{\partial f^{T}(X,\theta)}{\partial\theta_{a}}\cdot\frac{\partial f(X,\theta)}{\partial\theta_{b}}$$

Methods

Bayesian optimal design:

ED $$\xi_{ED} = \arg\max \left\{ \underset{\theta}{E}(|M|) \right\}$$

θ ~ (prior distribution)

API $$\xi_{API} = \arg\max \left\{ \underset{\theta}{E}(\log|M|) \right\}$$

Optimisation algorithms:
Sequential quadratic programming (SQP) method. (MATLAB routine “fmincon”)
Simulated Annealing algorithm (much slower but more robust)

Sampling for averaging:
Monte Carlo sampling
Latin hypercube sampling, a stratified-random sampling procedure

API design (logged) fixed effects 4 points with additive error model

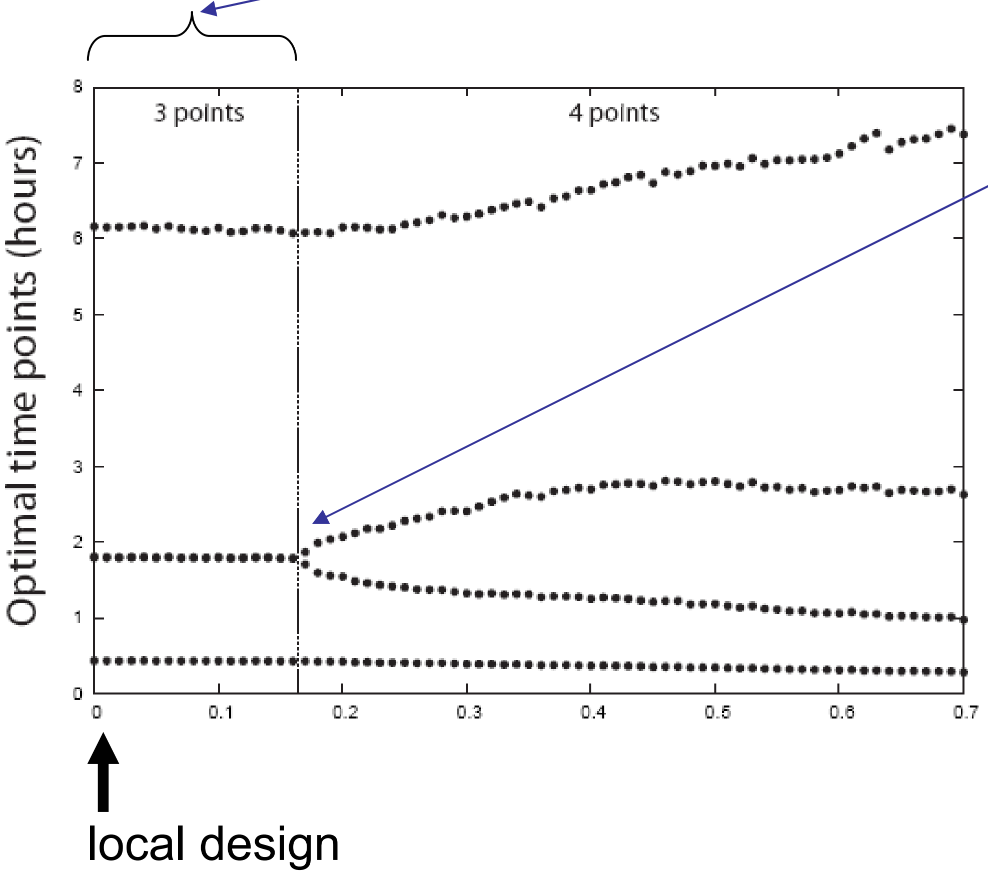
We use a 3 parameter first order absorption, one-compartment model with parameters (CL=3.75 L/h, V=15 L, k_a=2 h^{-1})

$$C = \frac{Dose \cdot k_a}{V \cdot k_a - CL}\left(e^{-\frac{CL}{V}t} - e^{-k_a t}\right)$$

We vary the common for all 3 parameters prior uncertainty from CV=0 to 0.7 with a small step, and we estimate and plot the API design for 4 points for each CV value.

For optimisation MATLAB routine “fmincon” was used, which uses a sequential quadratic programming (SQP) method. At each iteration a quadratic programming (QP) subproblem is solved.

API design (logged) fixed effects 4 points with additive error model

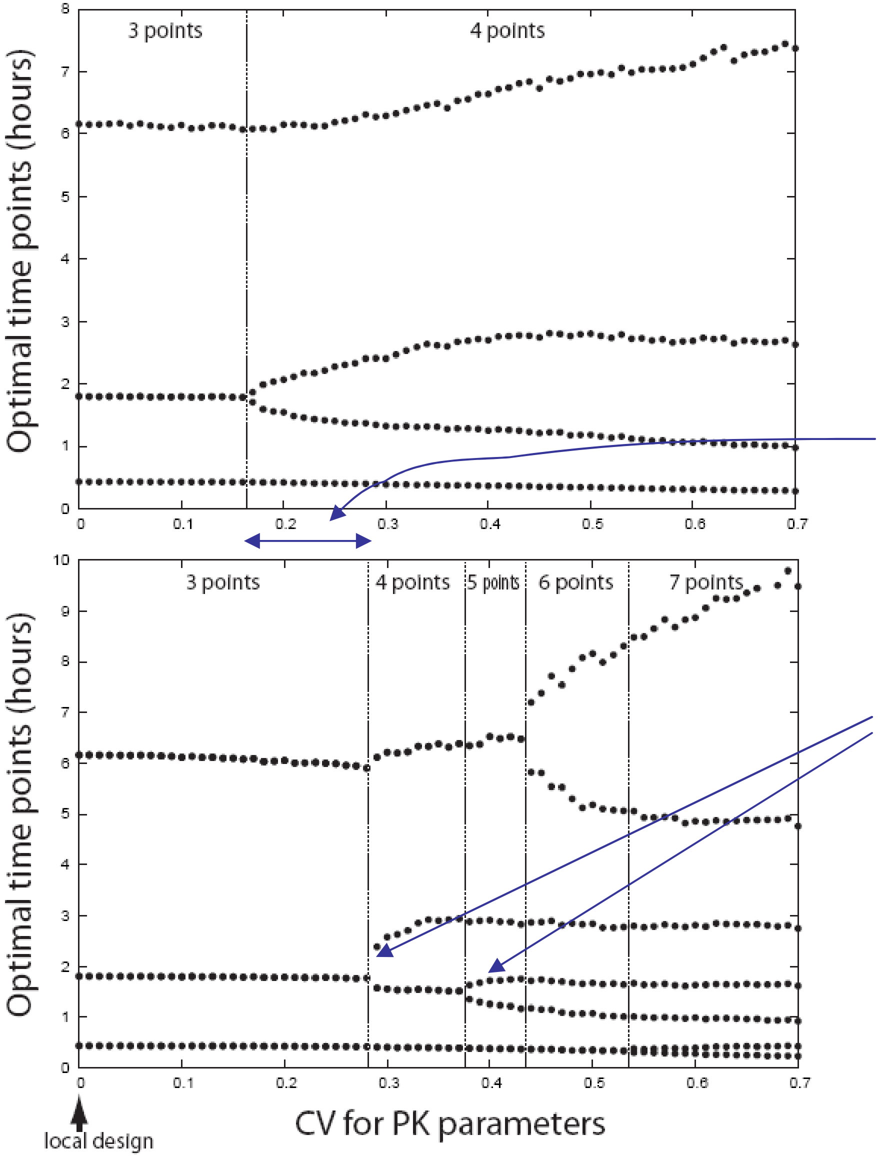


First region similar to local (only 3 points). But multifold computational effort

Extra point comes abruptly at CV=0.15

ED design (not logged) does not split the design at all (can be shown analytically) Pronzato and Walter. Math Biosci 75: 103 (1985).

API design fixed effects 7 points



Extra points appear gradually at CV=0.27, 0.37, 0.43 and 0.53

The initial region is wider than before, CV=0.30 instead of CV=0.15. So one can go for more points and get less instead.

A point can split twice

Fixed effects for proportional error model

Both API (shown) and ED (not shown) designs in fixed effects for proportional error model, do not split the design.

CV	t_1	t_2	t_3	t_4
0	0	0	2.96	24
0.5	0	0	3.71	24

Fixed effects for combined error model

API fixed effects with combined error model behaves similarly to additive (not shown). ED in this case splits the design but for much higher CV.

However, the exact behaviour for combined error depends on the relation between additive and proportional portions.

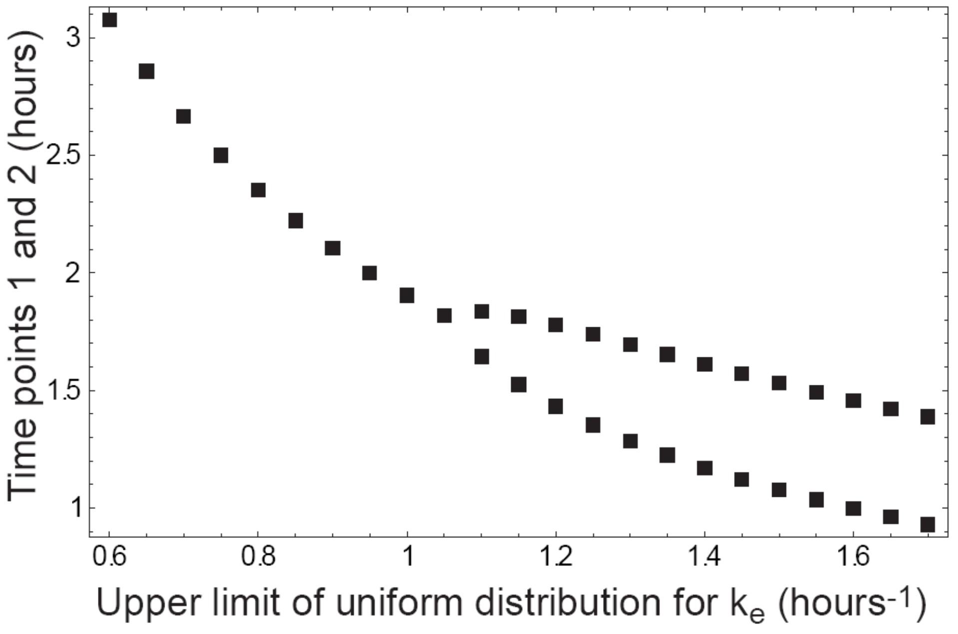
Detailed investigation

Model used (2 param.) $f(t) = \frac{Dose}{V} e^{-k_e t} + \varepsilon_i$ where $\varepsilon_i \sim N(0, \sigma)$

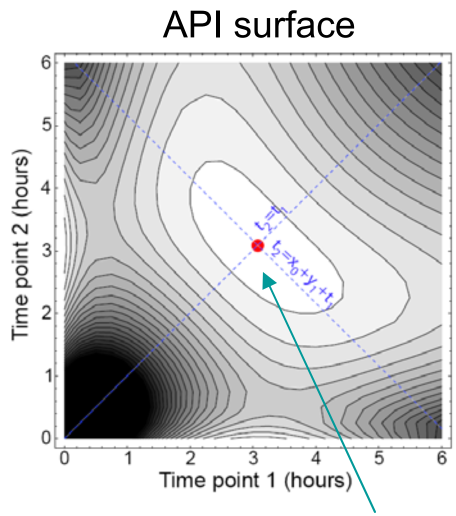
Uniform prior $k_e \sim U(a, b)$, where $a=0.05\ h^{-1}$ and b varies

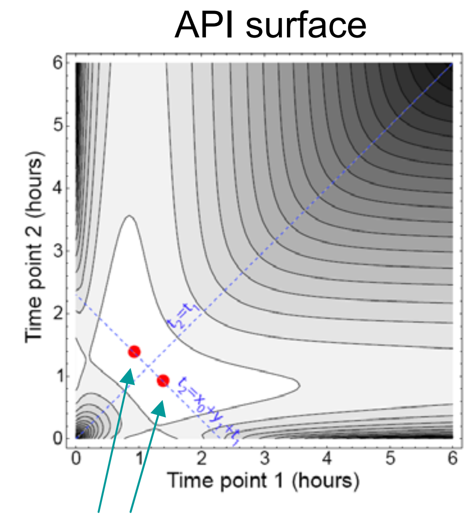
We design for 3 points but $t_3=0$ always so we are interested in the other 2 points

$$API(t_1, t_2) = \frac{1}{b-a} \int_a^b \log\left(\frac{e^{-2k_e(t_1+t_2)}((t_1 - t_2)^2 + e^{2k_e t_2} t_1{}^2 + e^{2k_e t_1} t_2{}^2}{V^6} \right) dk_e$$



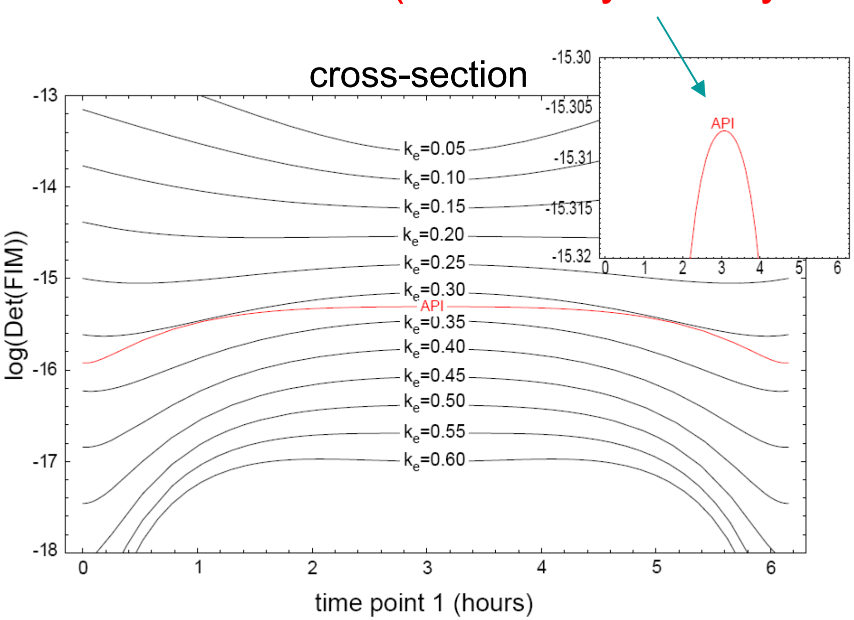
The bifurcation is a result of the features of the averaged surface which become more pronounced as the uncertainty increases.

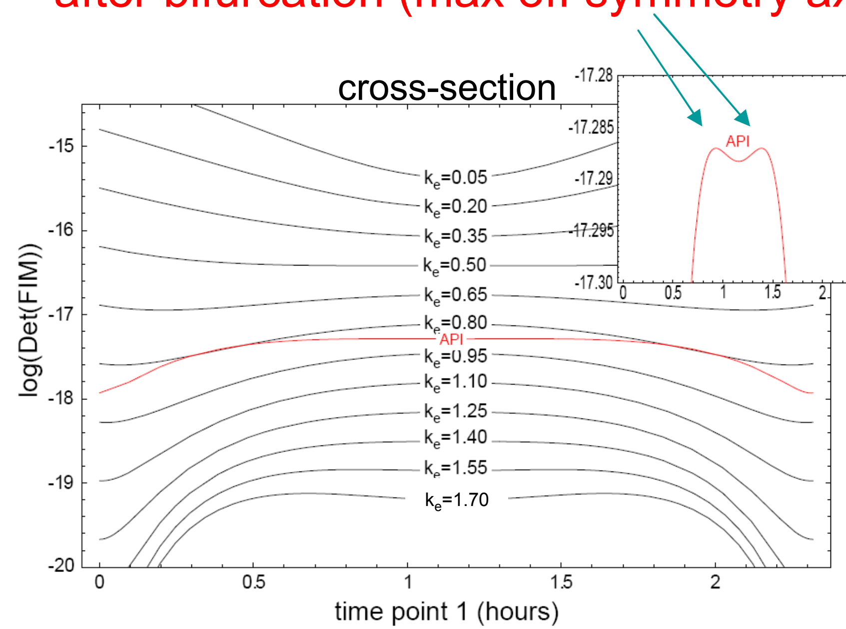




before bifurcation (max on symmetry axis)

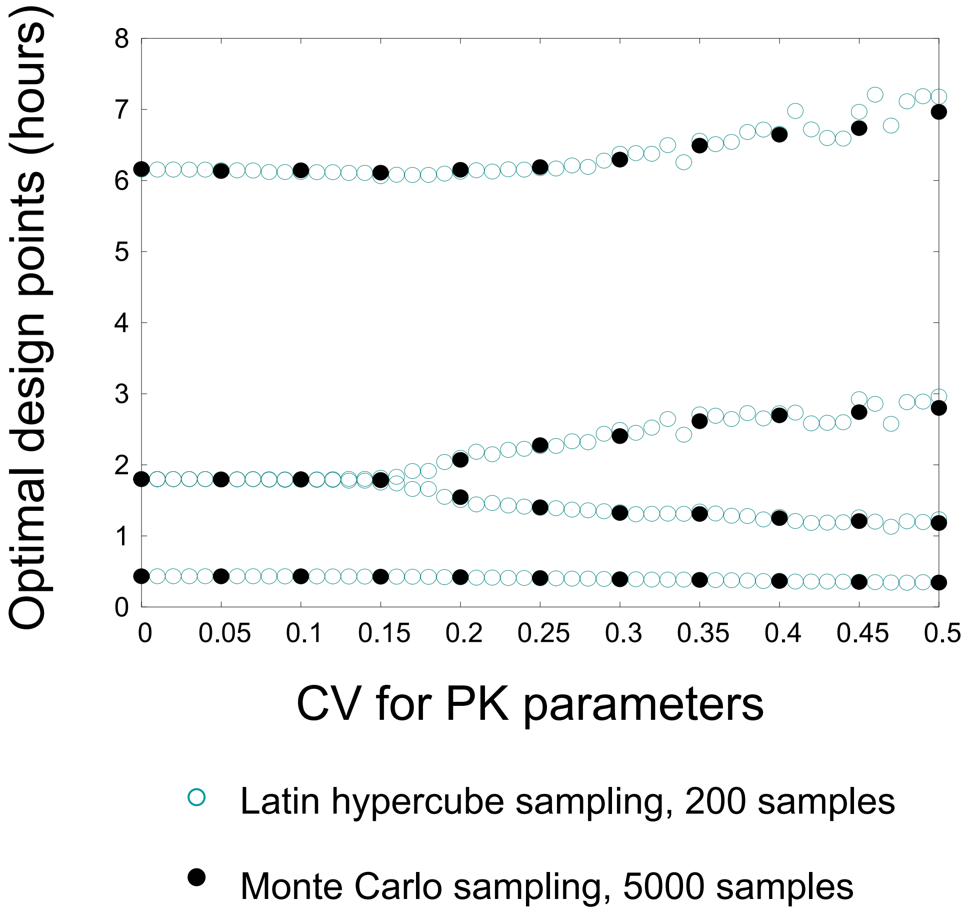
after bifurcation (max off symmetry axis)





Mixed effects

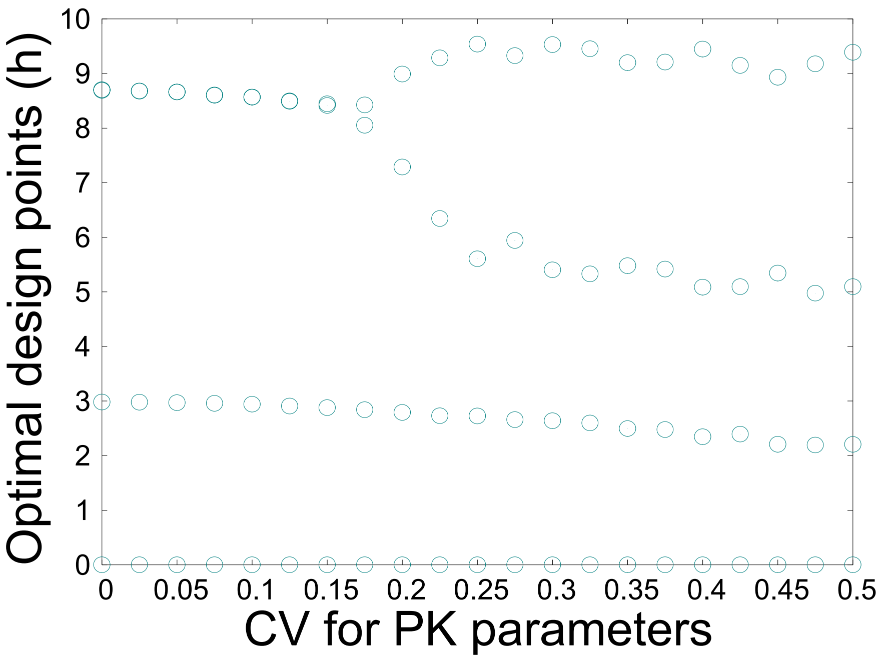
Calculation of the FIM is more expensive so we use Latin hypercube sampling instead of Monte Carlo to save time. It is a stratified-random sampling procedure.
Example shown before comparing LHS and MC and showing agreement



Mixed effects

In mixed effects with **additive error** both API (shown) and ED behave similarly to the fixed effects additive case.

Application to a 2-parameter model f=50/V*exp(-k*t), where k=0.25, V=15, BSV=20%, σ=0.1



For optimisation, a Simulated Annealing algorithm was used

For **proportional error** again both API (shown) and ED behave similarly to the fixed effects and do not split the design

CV	t_1	t_2	t_3	t_4
0	0	10.97	10.97	24
0.5	0	10.78	10.78	24

For **combined error** again both API and ED behave similarly to the fixed effects and split the design (not shown) but this also depends on the weight between additive and proportional error.

Elementary designs with weights

more than one sampling schemes, weight w_i corresponds to the proportion of subjects for this elementary design

$$FIM = \sum_i w_i \cdot FIM_i \quad \text{where} \quad \sum_i w_i = 1$$

2 design points

CV	***t_1***	***t_2***
0	2.513	5.725

2 elementary designs of 2 points each

CV	***w_1***	***t_1***	***t_2***	***w_2***	***t_1***	***t_2***
0	0.799	0	4.411	0.201	24	24
0.5	0.783	0	3.672	0.217	24	24

2 elementary designs of 3 points each

CV	***w_1***	***t_1***	***t_2***	***t_3***	***w_2***	***t_1***	***t_2***	***t_3***
0	1	0	3.406	7.745	0	0.558	6.082	22.874
0.5	1	0	2.102	6.655	0	3.467	17.095	21.81

Conclusions

- In Bayesian optimal design, the number of design points is not always larger than the number of model parameters.
- The extra points appear under certain conditions that depend on a lot of factors, namely the choice of the type of the prior distribution, the magnitude of the uncertainty, the central values of the parameters the number of design points and the weighting scheme.
- In respect to the magnitude of the uncertainty, and everything else kept the same, the extra points appear gradually as the uncertainty increases, for API criterion with additive error. This has certain implications:
  - A considerable region of small uncertainty gives results almost identical to the local design but with multifold computational effort.
  - Each extra point appears abruptly after a critical value of the uncertainty like a bifurcation.
- We have shown graphically that these features are geometrical particularities of the algebraic manipulation involved with the Bayesian criterion used and are quite sensitive from a lot of factors.

Conclusions

- Proportional error does not seem to have the same behaviour and times points do not split, while the behaviour with combined error depends on the relation between additive and proportional.
- For mixed effects the behaviour is similar to the fixed effects
- If the ED criterion is used instead of the API, the splitting of time points occurs again, but for higher uncertainty and especially for additive error in fixed effects does not occur at all. Summarising all the cases:

	Fixed		**Mixed**	
	API	ED	API	ED
add	yes	no	yes	yes
prop	no	no	no	no
comb	yes	yes	yes	yes

- If elementary designs with weights are used to account for the number of subjects for each design, these weights do not change a lot with uncertainty.