Robust Designs for Random Effects Parameters

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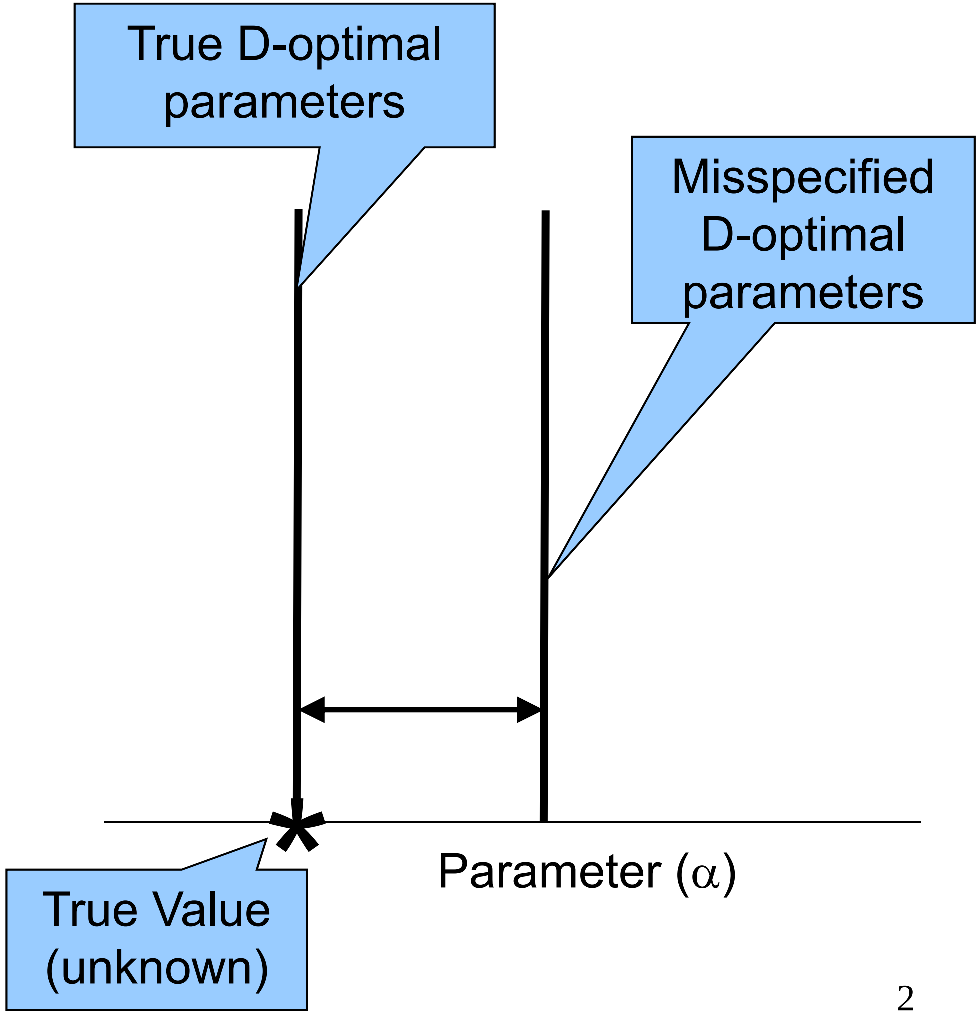
Typical assumptions made in optimal design calculations

- Model for system is known
- Assumed parameter values for model is a single value

Leads to locally optimal designs



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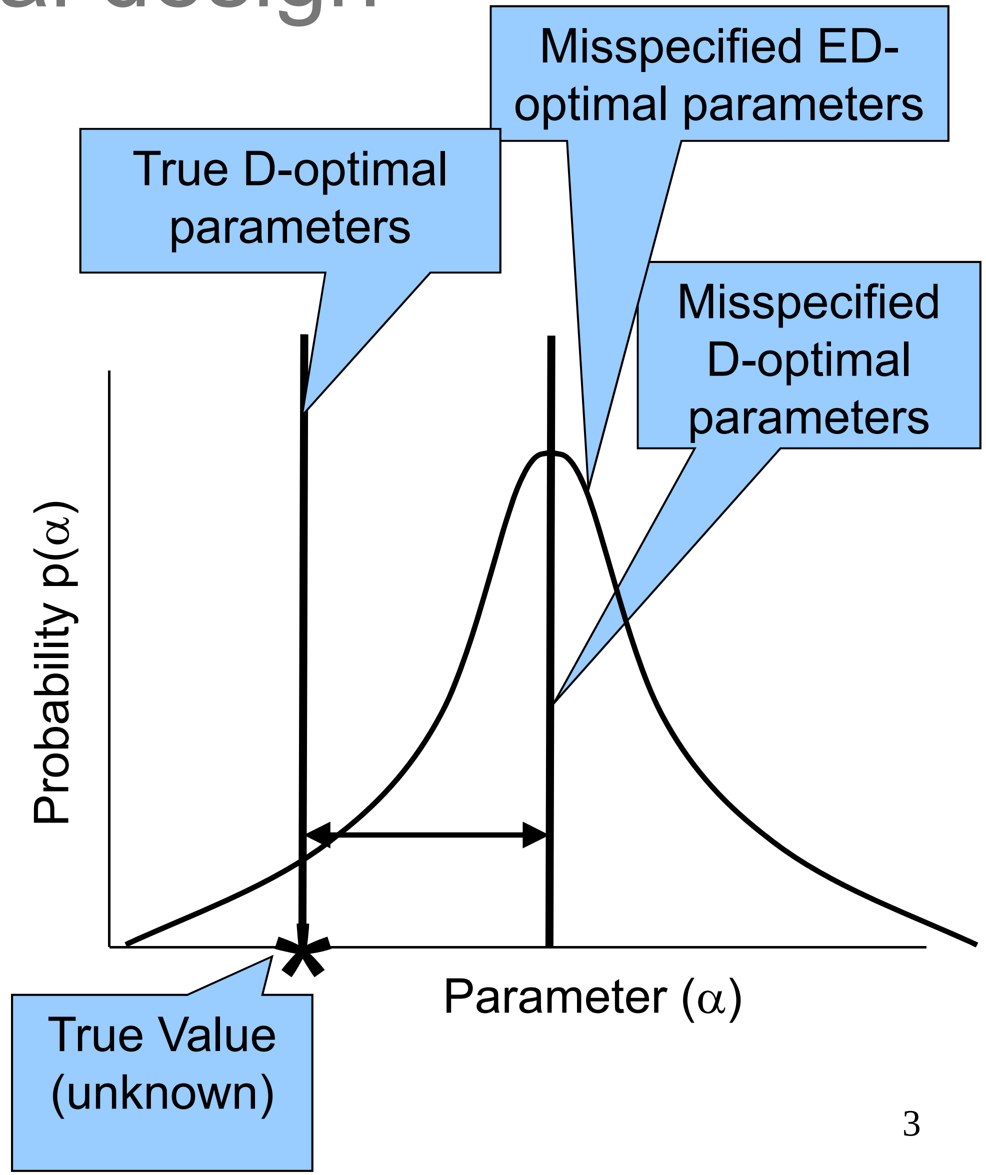
Robust optimal design

- Accounts for the possibility that your model parameters are incorrect when computing your design
  - Robust against misspecified priors
  - Only slightly less efficient than D-optimality when the parameters are not misspecified

M.G. Dodds, A. Hooker and P. Vicini. *J Pharmacokinet Pharmacodyn*, 32(1):33-64, 2005.



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Types of robust design

- API: $\arg\max_{\xi}\left(E_{\theta}[\log|M(\theta,\xi)|]\right)$
- EID: $\arg\min_{\xi}\left(E_{\theta}[|M(\theta,\xi)^{-1}|]\right)$
- ED: $\arg\max_{\xi}\left(E_{\theta}[|M(\theta,\xi)|]\right)$
- HClnD: $\arg\max_{\xi}\left(\sum_{i=1}^{n}\ln|M(\theta_i,\xi)|]\right),$

  $\theta_i \in$ various combinations of parameter percentiles

These calculations can be computationally costly!

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An observation

For ”standard” population optimal designs, incorporation of uncertainty around the variance parameters of the model seem to have low impact on the resulting optimal designs.

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An example: 1-compartment PK with linear absorption

$$y_{ij} = Dose_i \frac{ka_i}{V_i(ka_i - {CL_i}/{V_i})}\left(\exp(-{CL_i}/{V_i} \cdot t_{ij}) - \exp(-ka_i \cdot t_{ij})\right) \cdot (1+\varepsilon_{1ij}) + \varepsilon_{2ij} \quad (\mathrm{mg/L})$$

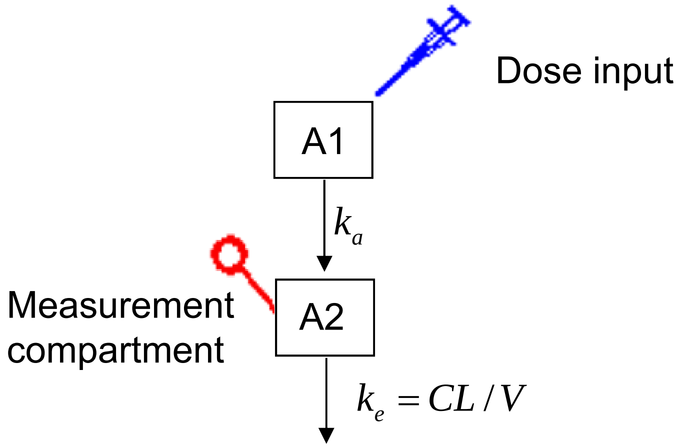
$$CL_i = \beta_{pop_1} e^{b_{1,i}} \quad (\mathrm{L/h}),$$

$$V_i = \beta_{pop_2} e^{b_{2,i}} \quad (L),$$

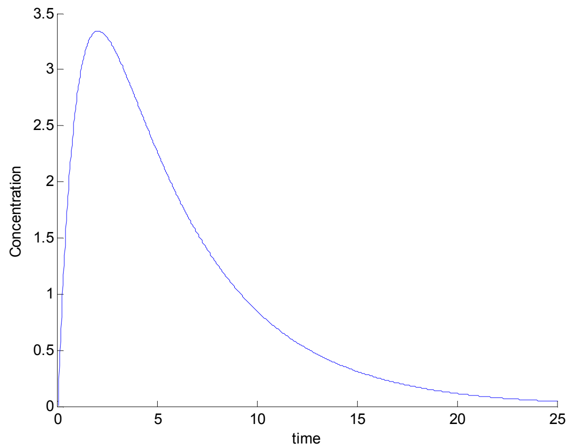
$$ka_i = \beta_{pop_3} e^{b_{3,i}} \quad (1/\mathrm{h}),$$

$$\varepsilon_{e,ij} \sim N(0, R), \qquad R = diag(r_1, r_2)$$

$$b_{b,i} \sim N(0, D), \qquad D = diag(d_1, d_2, d_3)$$



$$\theta = \left[\beta_{pop_1}, \beta_{pop_2}, \beta_{pop_3}, d_1, d_2, d_3, r_1, r_2\right]$$
$$= [4, 20, 1, 0.5, 0.1, 0.1, 0.01, 0.0001]$$
$$Dose = 100mg$$



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D-optimal design with different values of CL variability (d1)

- D-optimal design
  - 4 samples, same for each individual
  - Low CL variability (22 %CV)
  - High CL variability (70 %CV)

			Sample Times			
			S1	S2	S3	S4
Design calculation methods	FO reduced	Low varCL	0.0858	4.96	4.96	20.8
		High varCL	0.0831	4.89	4.89	21.9
	FO	Low varCL	0.0807	2.48	9.31	23.5
		High varCL	0.0813	2.39	9.20	24.0
	FOCEI	Low varCL	0.1036	2.95	7.44	17.6
		High varCL	0.0898	2.14	5.26	14.8

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So what is happening?

Investigate with two simple population examples with analytic expressions for the Fisher Information Matrix

- Linear model $y_{ij} = \exp(-at_{ij}) + b_i + \varepsilon_{ij}$

- Non-linear model $y_{ij} = \exp(-(a + b_i) \cdot t_{ij}) + \varepsilon_{ij}$

$$b_i \sim N(0, D) \qquad \varepsilon_{ij} \overset{iid}{\sim} N(0, R)$$

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FIM: computed from expectations and variances

$$M(\theta,\xi)=\frac{1}{2}\begin{bmatrix} A(\theta,\xi) & C'(\theta,\xi) \\ C(\theta,\xi) & B(\theta,\xi) \end{bmatrix}$$

$$A(\theta,\xi)=2\frac{dE}{da}V^{-1}\frac{dE}{da}+tr\left(\frac{dV}{da}V^{-1}\frac{dV}{da}V^{-1}\right) \qquad C(\theta,\xi)=tr\left(\frac{dV}{dD}V^{-1}\frac{dV}{da}V^{-1}\right)$$

Reduced M() calculated with dV/da=0

$$B(\theta,\xi)=tr\left(\frac{dV}{dD}V^{-1}\frac{dV}{dD}V^{-1}\right)$$

Retout et. al, JBS, 2003

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Expectations and variances

- Linear model $y_{ij} = \exp(-at_{ij}) + b_i + \varepsilon_{ij}$
- Non-linear model $y_{ij} = \exp(-(a + b_i) \cdot t_{ij}) + \varepsilon_{ij}$

	Linear model	Non-linear model
True	$E[y_{ij}] = \exp(-at_{ij})$ $V[y_{ij}] = D + R$	$E[y_{ij}] = \exp\left(-at_{ij} + \frac{t_{ij}{}^2 D}{2}\right)$ $V[y_{ij}] = \exp(-2t_{ij}a + 2t_{ij}{}^2 D) - \exp(-2at_{ij} + t_{ij}{}^2 D) + R$
FO approximation	NA	$E[y_{ij}] \approx \exp(-at_{ij})$ $V[y_{ij}] \approx \exp(-2at_{ij})\, t_{ij}{}^2 D + R$

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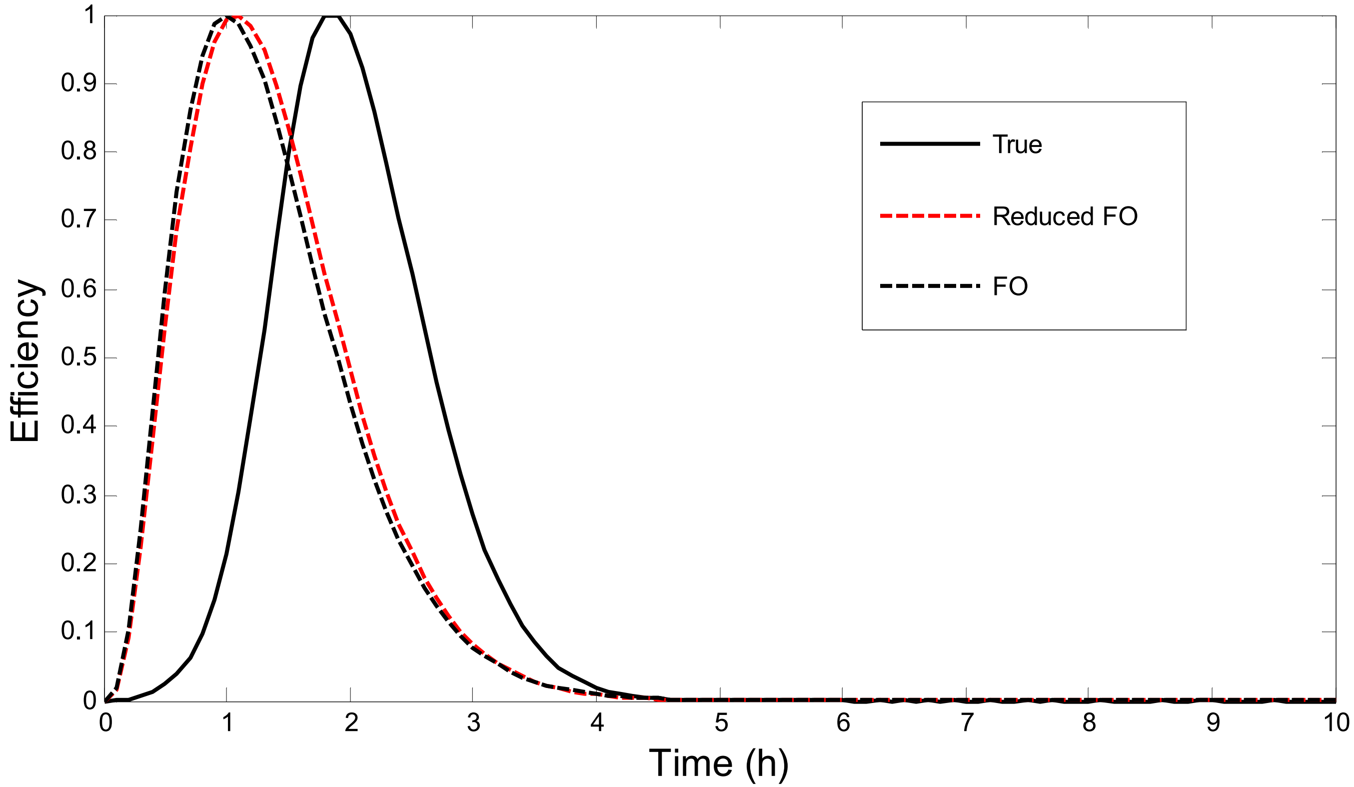
D-optimal design for linear model

- Can be analytically derived to be t_{ij}=1/a
- i.e. **<u>NOT</u>** dependent on variance parameter
- Note: the ***<u>size</u>*** of the parameter uncertainty is dependent on the variance parameter

D-optimal design for the non-linear model

$$y_{ij} = \exp(-(a + b_i) \cdot t_{ij}) + \varepsilon_{ij} \qquad [a = 1, D = 1, R = 1]$$



Optimal design is shifted for the FO methods

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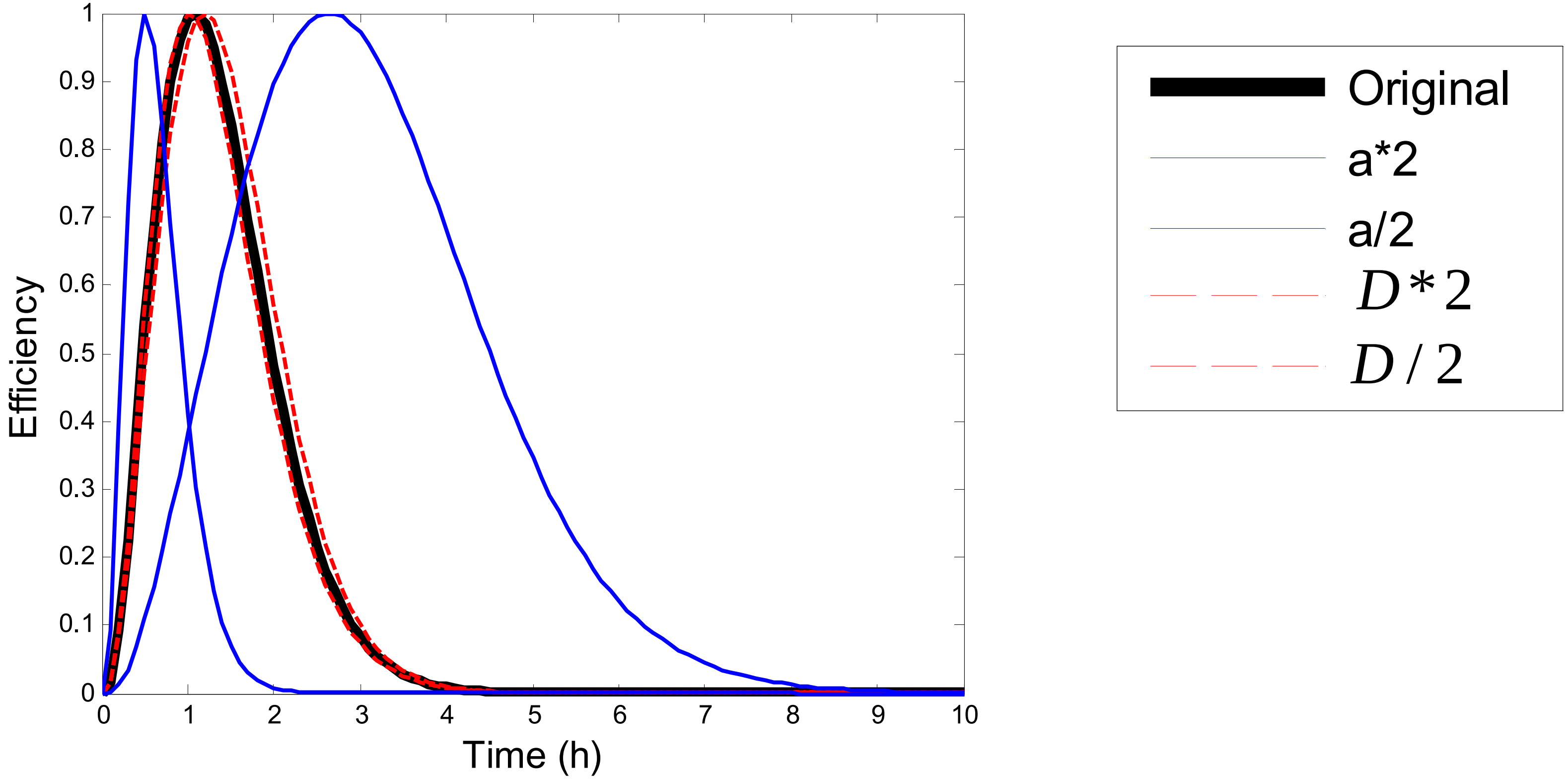
Reduced FO D-optimal



- Little dependence on variance parameter, D
- High dependence on mean parameter, a

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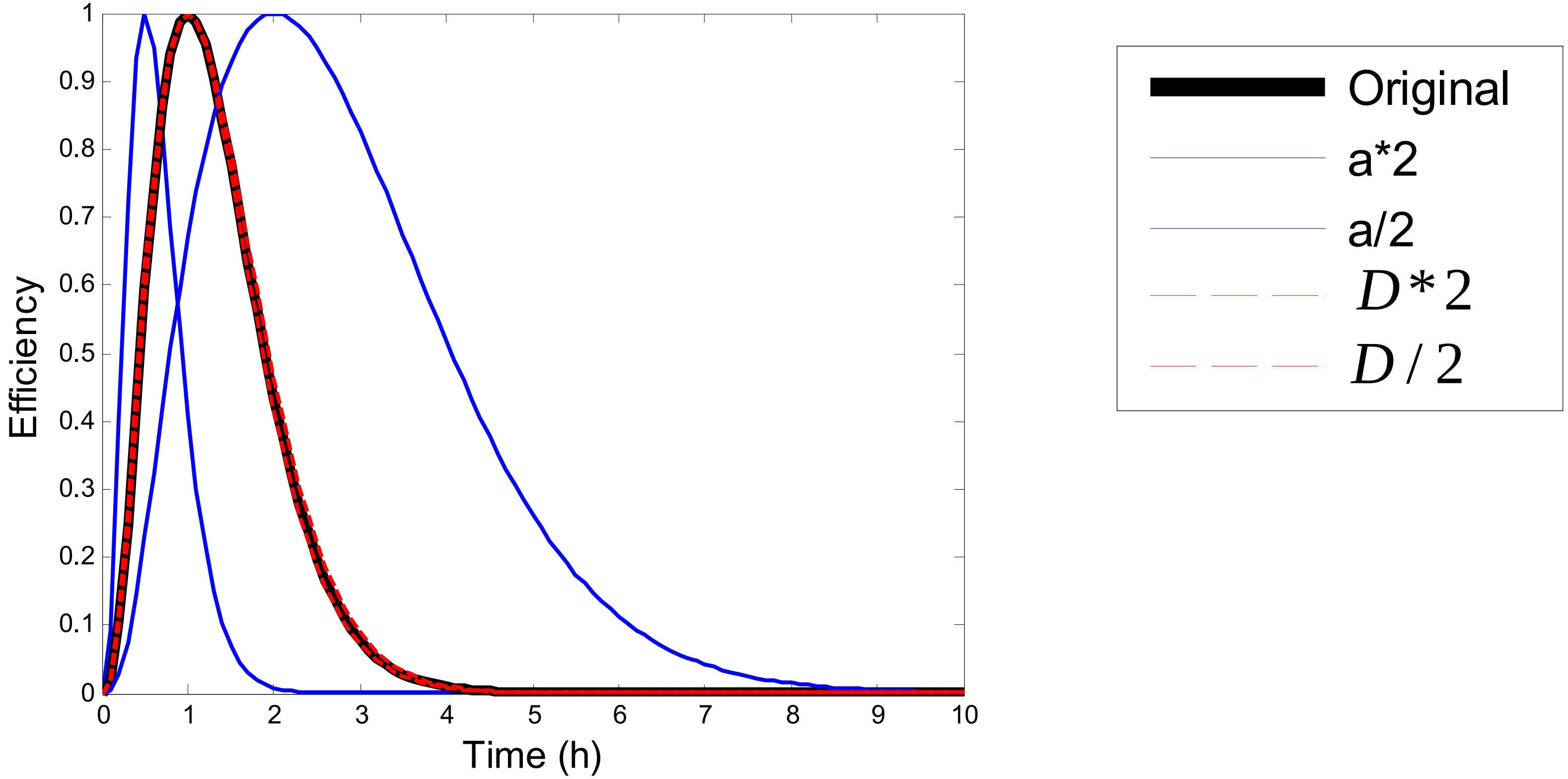
FO, D-optimal



- Little dependence on variance parameter, D
- High dependence on mean parameter, a

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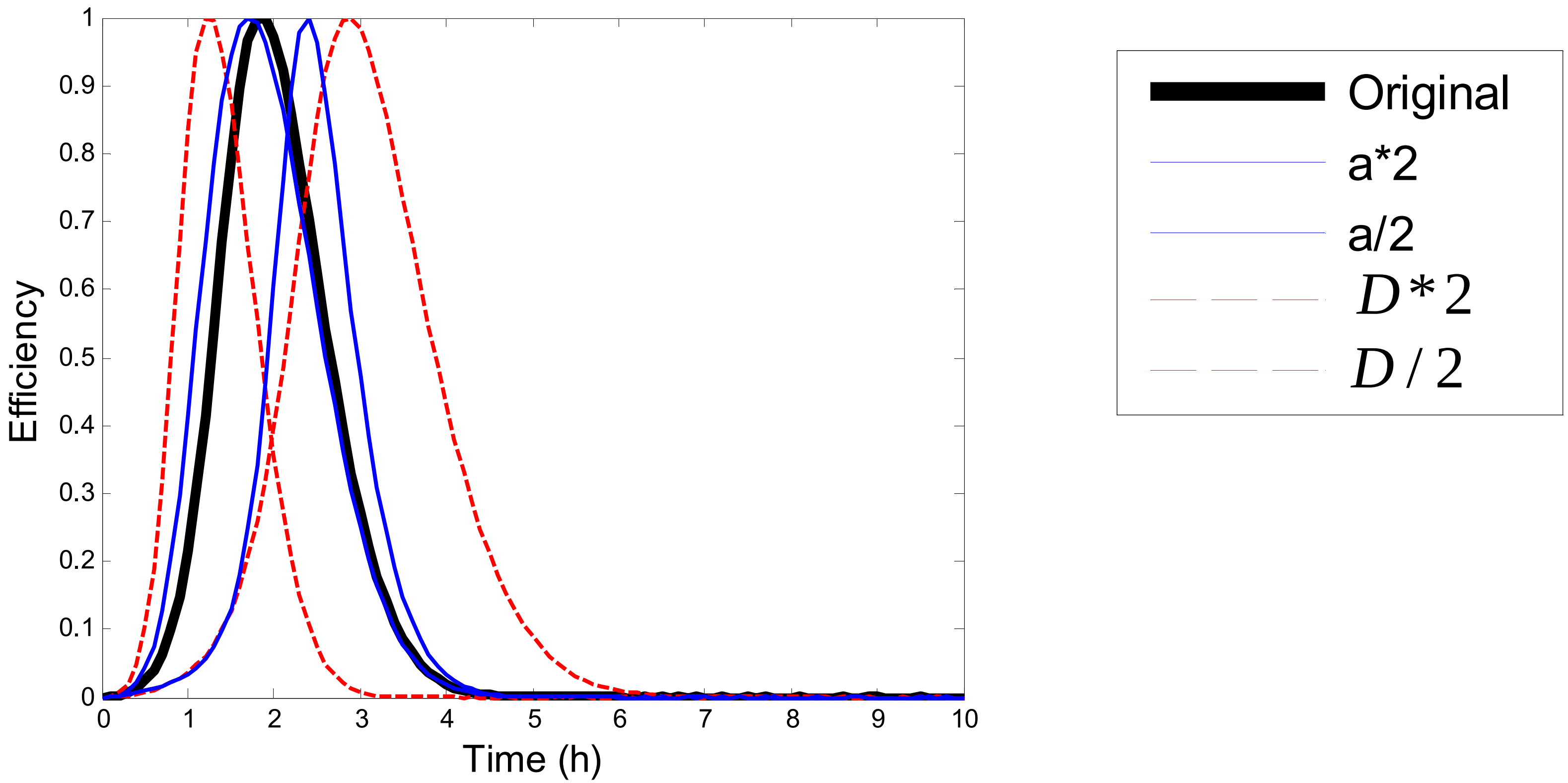
Full, D-optimal



- Higher dependence on variance parameter, D
- lower dependence on mean parameter, a

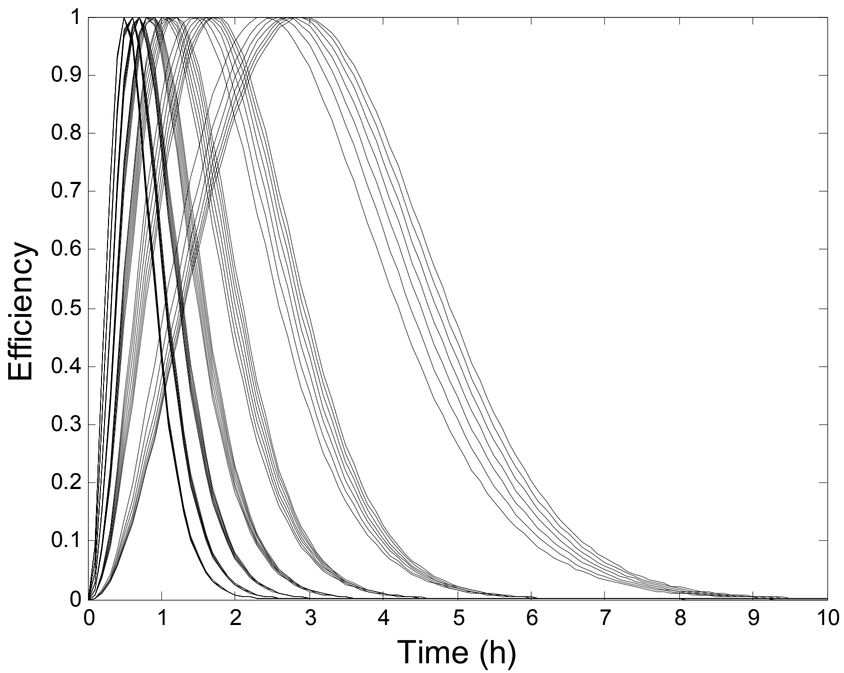
Coverage of design space, reduced FO vs. Full

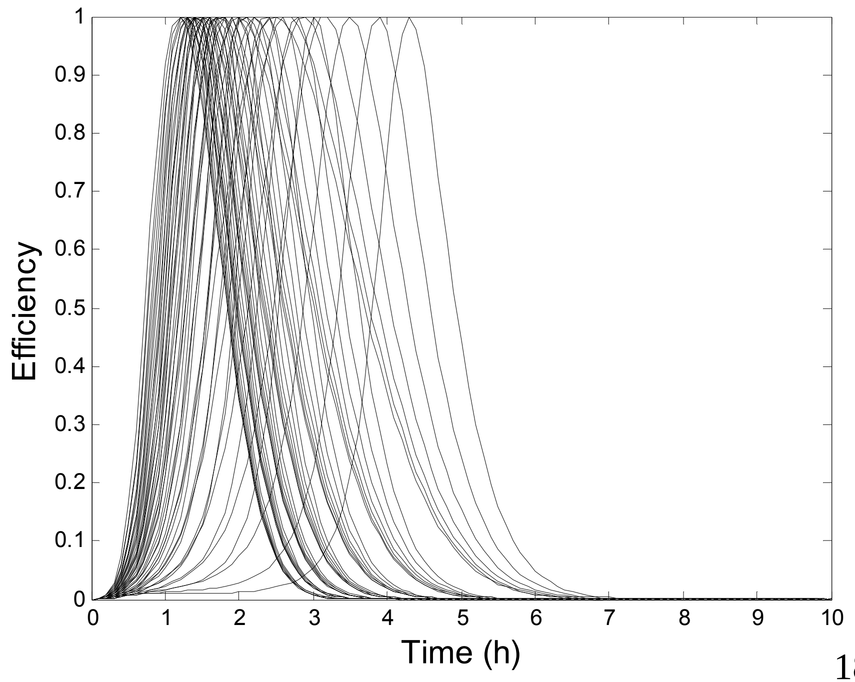
Reduced FO

- [0.5, 2.9] Variability in a and D
- [0.5, 2.6] Only on a

Full

- [1.2, 4.3] Variability in a and D





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Discussion

- Exact solutions to nonlinear models with linear and nonlinear random effects perform differently in terms of the optimal design and the dependence of this design on the assumed parameters.

- FO methods used to approximate the expectation and variance of non-linear models may result in a shift of the D-optimal design compared to the exact solution.

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Discussion (2)

- Optimal designs with exact solutions and FO approximations to the non-linear model have different sensitivity to model parameters
  - Exact solution appear more sensitive to variance components
  - FO approach appears more sensitive to mean value parameters.
  - Higher order approximations (FOCE/Laplace) appear to be more dependent on variance components

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Discussion (3)

Can we ignore uncertainty on variance parameters in design calculations when using FO approximations?

- Ignoring uncertainty on variance parameters with FO methods will have significantly less impact on final designs than uncertainty on mean value parameters given the same magnitude of parameter and parameter uncertainty.