The robustness of global optimal designs

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Background

A drawback with local optimal designs (OD), e.g. D-optimal, is that the parameters of the model are assumed known. This is a strong assumption and therefore robust (global) OD has been a suggested approach, i.e. without assuming that the parameters of the model are known but instead distributions of the parameters are known [1-5].

Objective

The objective is to compare different design criteria and to suggest an alternative criterion that overcomes some of the issues with other robust design criteria, such as overweighting certain parameter values.

Methods

Six different criteria were investigated; one local criterion D-optimal and five robust criteria ED-optimal (ED), API-optimal (API) , HCD-optimal (HCD), ED-EFF-optimal (ED_EFF) and B-API-optimal (BAPI). The BAPI is designed to spread the support point over the whole design region by splitting the expectation over the parameter distribution into n_i expectations over subsets of the parameter distribution (where n_i is e.g. the number of support points).

$$D = \left|\mathbf{FIM}(\theta,\ldots)\right|$$

$$ED = E_\theta\left[\left|\mathbf{FIM}\right|\right] \approx \frac{1}{n}\sum_{i=1}^{n}\left|\mathbf{FIM}(\theta_i,\ldots)\right|$$

$$API = E_\theta\left[\ln\left|\mathbf{FIM}\right|\right] \approx \frac{1}{n}\sum_{i=1}^{n}\ln\left|\mathbf{FIM}(\theta_i,\ldots)\right|$$

$$HCD = \ln\left|\mathbf{FIM}(\theta_{5\%},\ldots)\right| + \ln\left|\mathbf{FIM}(\theta_{95\%},\ldots)\right|$$

$$ED\_EFF = E_\theta\left[\frac{\left|\mathbf{FIM}\right|}{\left|\mathbf{FIM}^{D-opt}\right|}\right] \approx \frac{1}{n}\sum_{i=1}^{n}\frac{\left|\mathbf{FIM}(\theta_i,\ldots)\right|}{\left|\mathbf{FIM}^{D-opt}(\theta_i,\ldots)\right|}$$

$$BAPI = \sum_{j=1}^{n_i} E_{\theta_j}\left[\ln\left|\mathbf{FIM}_j\right|\right] \approx \frac{1}{n}\sum_{j=1}^{n_i}\sum_{i=1}^{n}\ln\left|\mathbf{FIM}(\theta_{j,i},\xi_j,\ldots)\right|$$

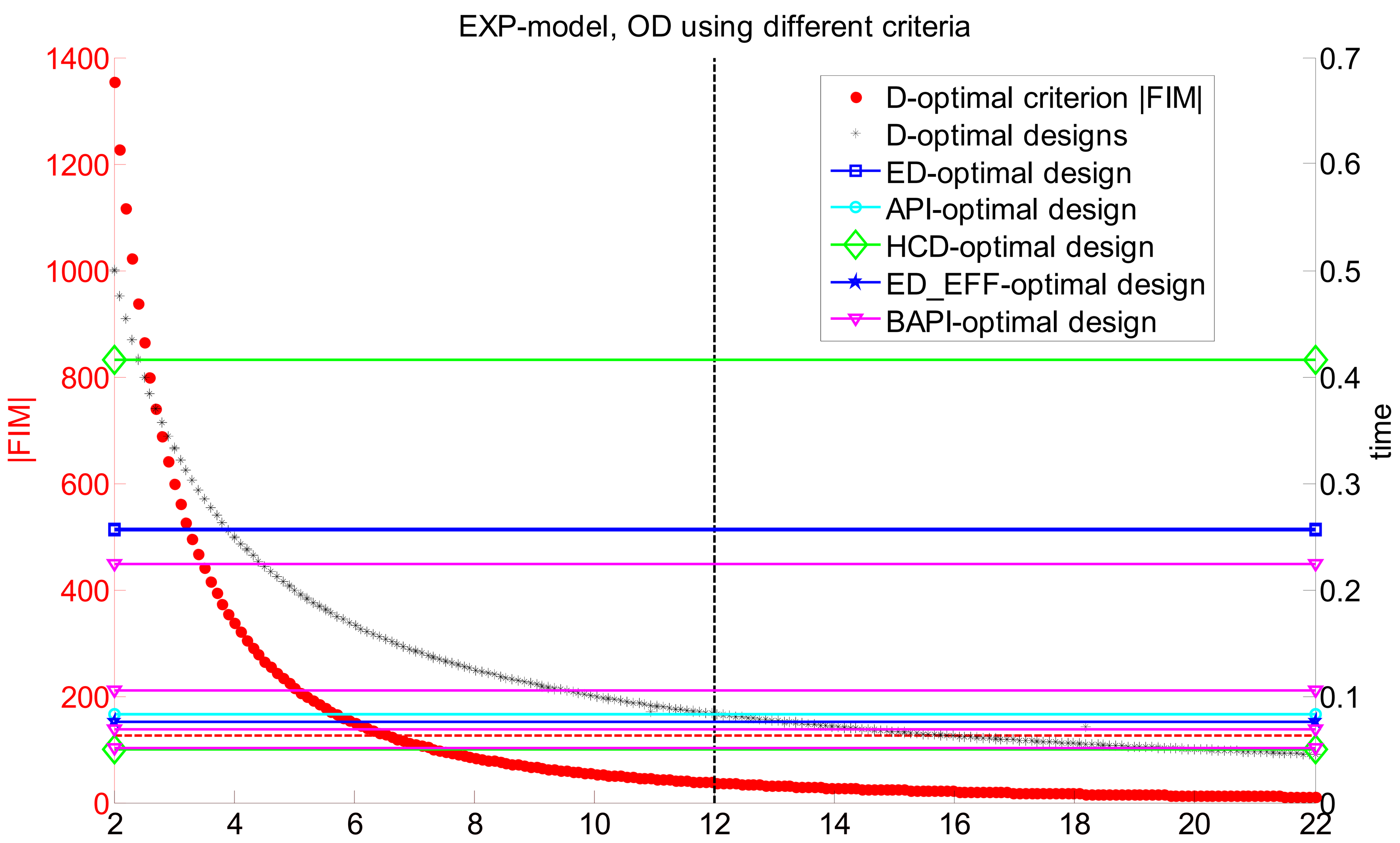

Figure 1. Optimal designs using different criteria. The red dots are the |FIM| for D-optimal designs with 200 different θ_k values (over the entire parameter uncertainty distribution). The dotted lines are the median of the θ_k distribution (black) and the median of the D-optimal |FIM| (red). Note that all designs have 4 cluster points except BAPI and HCD (HCD has 2 cluster points). Standard D-optimal design at θ_k=12 is close to most of the robust criteria except ED which matches the D-optimal design at θ_k=4.

Two models were investigated; A one-parameter fixed effect (4 samples between 0-2 & 100 ind), exp decay model (EXP) and a two-parameter mixed effect (3 doses between 0-6 & 100 ind), Emax model (EMAX) were θ_{D50} and ω^2_{D50} (exp IIV of 30%) were the parameters to estimate. A uniform parameter distribution was assumed for EXP, θ_k=[2,22] and for EMAX, θ_{D50} = [0.1,6.1]. 200 uniformly spread samples from the parameter distribution were used for the robust criteria and a D-optimal design was found for each sample. Multiple (n=1000) simulations and estimations (SSE) were used to check the performance of the designs. Figure 1 and 2 shows the optimal designs using the different criteria.

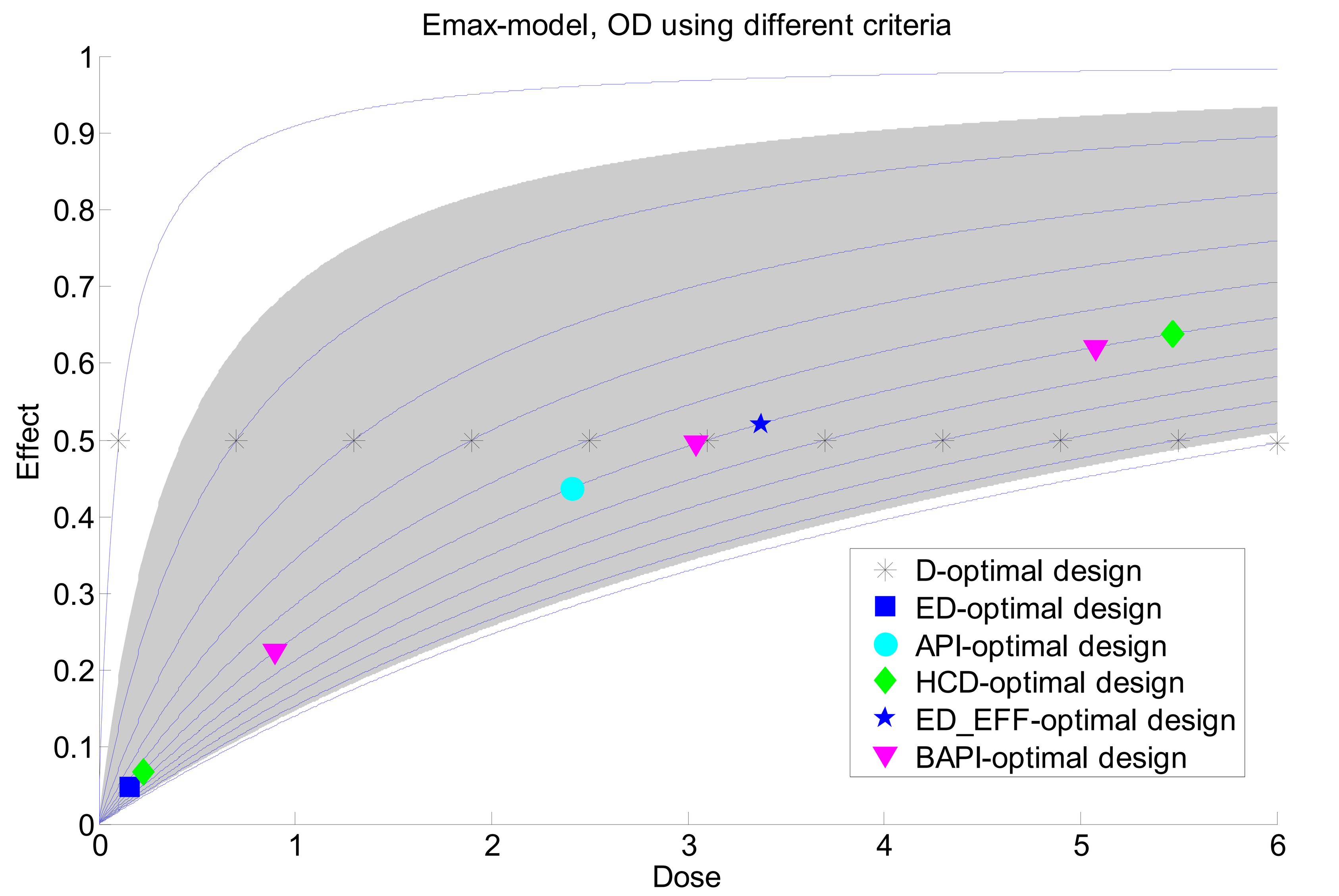

Figure 2. The shaded area represents the 95% prediction interval from the θ_{D50} parameter uncertainty distribution. The thin blue lines are the corresponding θ_{D50} values used in the SSE. The D-optimal design for the values used in SSE are present as well as the robust criteria designs. All the design points in the figure are clustered except the BAPI samples and the low HCD sample. BAPI and HCD spread the design points as opposed to the other robust criteria which is similar to a D-optimal design for a specific θ_{D50} value.

Results

As expected, the D-optimal designs (which use the optimal design in each SSE) is slightly better (bias and precision, fig. 3 and table1) than the robust criteria for both models. All the robust designs except ED perform well for the EXP model, while HCD and BAPI perform best for the EMAX model.

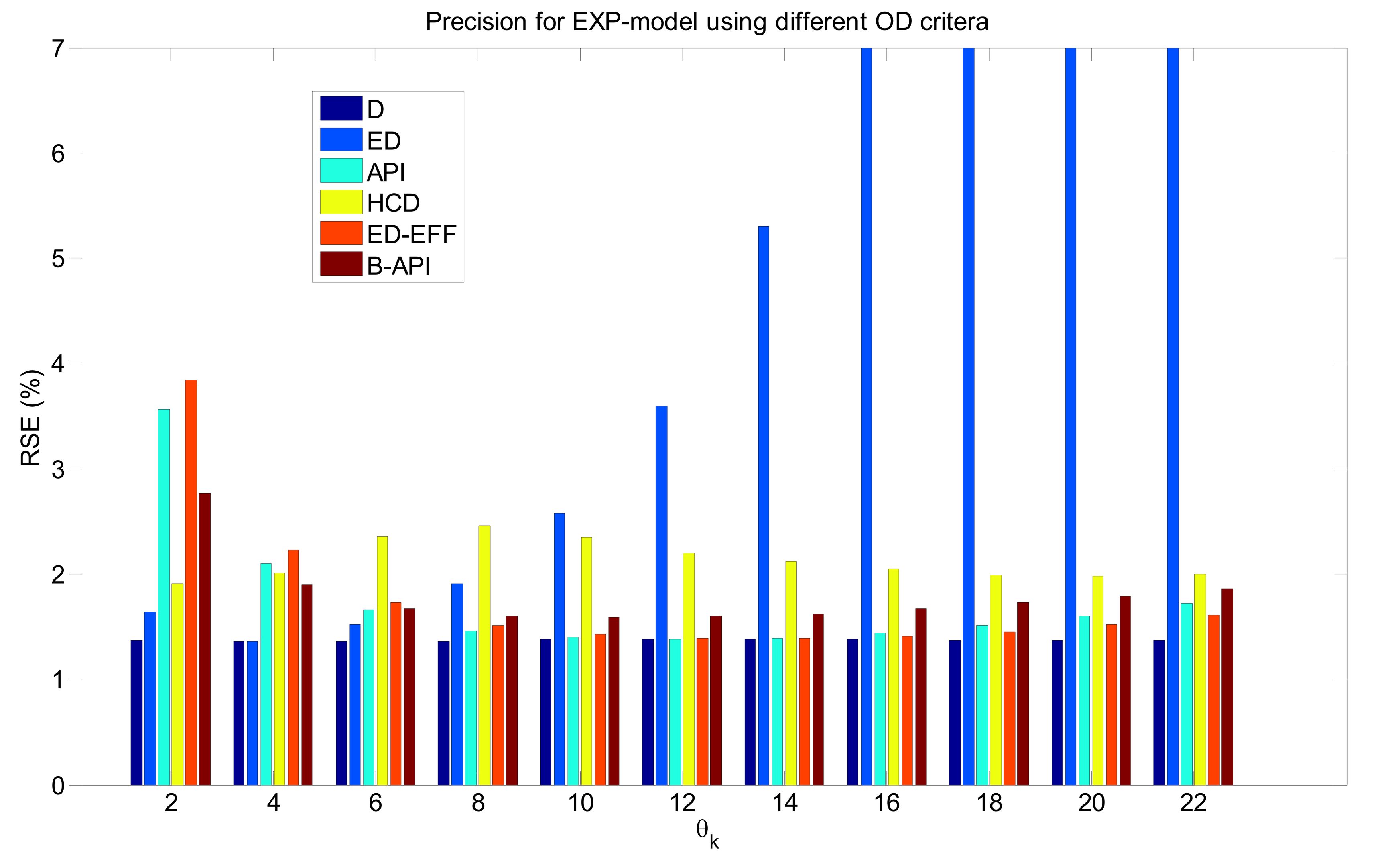

Figure 3. The RSE(%) from the SSE using the optimal designs from the different criteria. The RSE(%) for ED (with θ_k>14) is not visible in the plot but goes up to a maximum of 226% for θ_k=22. Note that the D-optimal designs are the only designs that are changing between θ_k values.

			RSE(%)						Absolute PE(%)					
			D	ED	API	HCD	ED_EFF	BAPI	D	ED	API	HCD	ED_EFF	BAPI
EXP	θ_k	2	1.4	1.6	3.6	1.9	3.8	2.8	0.037	0.044	0.071	0.058	0.081	0.035
		4	1.4	1.4	2.1	2.0	2.2	1.9	0.032	0.032	0.045	0.063	0.047	0.029
		6	1.4	1.5	1.7	2.4	1.7	1.7	0.031	0.045	0.036	0.079	0.036	0.034
		8	1.4	1.9	1.5	2.5	1.5	1.6	0.030	0.070	0.030	0.061	0.032	0.040
		10	1.4	2.6	1.4	2.3	1.4	1.6	0.019	0.13	0.019	0.033	0.022	0.032
		12	1.4	3.6	1.4	2.2	1.4	1.6	0.018	0.26	0.018	0.038	0.018	0.051
		14	1.4	5.3	1.4	2.1	1.4	1.6	0.024	0.58	0.026	0.037	0.024	0.051
		16	1.4	9.1	1.4	2.0	1.4	1.7	0.036	1.53	0.051	0.034	0.043	0.063
		18	1.4	105.6	1.5	2.0	1.5	1.7	0.044	19.96	0.051	0.040	0.049	0.058
		20	1.4	193.2	1.6	2.0	1.5	1.8	0.037	73.57	0.054	0.036	0.049	0.063
		22	1.4	226.1	1.7	2.0	1.6	1.9	0.035	109.46	0.060	0.033	0.049	0.073
EMAX	θ_{D50}	0.1	5.7	5.88805	30.4	10.0	41.3	21.2	0.2	0.9	4.4	2.2	5.0	4.2
		0.7	5.6	8.28274	7.5	9.4	8.9	7.4	0.2	1.6	2.2	0.7	2.7	1.5
		1.3	5.7	12.4769	6.1	8.8	6.7	6.5	0.2	1.3	1.2	1.4	1.7	0.9
		1.9	5.6	17.2772	5.7	7.8	6.0	6.3	0.2	0.2	0.6	1.4	1.1	0.6
		2.5	5.6	22.9668	5.6	7.3	5.8	6.2	0.2	1.5	0.2	1.2	0.7	0.4
		3.1	5.6	30.4445	5.7	6.9	5.7	6.2	0.2	3.8	0.1	0.9	0.4	0.2
		3.7	5.7	247.262	5.8	6.7	5.6	6.2	0.2	17.4	0.4	0.7	0.1	0.0
		4.3	5.6	239.265	5.9	6.6	5.7	6.3	0.2	23.2	0.6	0.5	0.1	0.2
		4.9	5.6	490.782	6.1	6.5	5.8	6.3	0.2	64.4	0.8	0.3	0.3	0.3
		5.5	5.6	2.5E+13	6.3	6.5	5.8	6.4	0.2	1E+12	0.9	0.1	0.5	0.4
		6.1	5.6	5.6E+14	6.5	6.5	6.0	6.6	0.2	3.1E+13	1.0	0.0	0.6	0.6
	ω^2_{D50}	0.1	45.4	47.9	1597.2	117.8	3030.2	295.3	9.1	9.3	236.6	6.2	508.9	110.9
		0.7	45.4	81.3	67.6	98.5	84.6	68.6	9.1	7.7	9.5	2.0	6.1	8.1
		1.3	45.4	136.3	50.4	88.7	57.9	57.1	9.1	15.6	9.6	1.9	10.0	8.3
		1.9	45.4	199.9	46.1	76.3	49.6	54.0	9.1	52.9	9.1	5.8	9.5	8.3
		2.5	45.4	266.6	45.5	68.7	46.5	53.2	9.1	95.2	9.1	7.3	9.2	8.4
		3.1	45.4	334.1	46.3	64.4	45.5	53.3	9.1	136.8	9.3	7.8	9.1	8.6
		3.7	45.4	1465.4	47.9	61.9	45.6	54.1	9.1	231.0	9.5	8.0	9.1	8.7
		4.3	45.4	1416.5	50.0	60.6	46.2	55.3	9.1	272.0	9.7	8.1	9.2	8.9
		4.9	45.4	2807.7	52.3	60.0	47.3	56.7	9.1	494.7	10.0	8.1	9.4	9.0
		5.5	45.4	3475.6	54.9	59.9	48.7	58.3	9.1	658.6	10.2	8.1	9.6	9.1
		6.1	45.4	3829.9	57.7	60.1	50.2	60.0	9.1	742.5	10.3	8.1	9.7	9.1

Table 1. The RSE(%) and absolute PE(%) for EXP and EMAX from the SSE. The values in the table are color scaled, i.e. a green value indicates a more precise or accurate value and a value going towards red indicated a less precise or accurate value.

Conclusions

- ✓ HCD performs very well and is fast to compute. However, likely to have problems if optimal information vs. the parameter distribution is non-monotonic
- ✓ BAPI performs in general very well with low bias but is slower than HCD
- ✓ ED_EFF performs good in general but very slow
- ✓ API performs good in general but worse than BAPI in the border of the parameter distribution
- ✓ ED **not** robust, overweighs the most informative region

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