FIM approximation, spreading of optimal sampling times and their effect on parameter bias and precision

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Background and Objectives

Optimizing designs for multiple individuals with the first order (FO) linearized Fisher Information Matrix (FIM) will produce the same optimal design (with potentially repeated samples) for all individuals given the same input and a rich enough individual design. However, it is natural to think that a first order conditional estimation (FOCE) approximation of the FIM will potentially spread the optimal sampling times for each individual due to the fact that the individual responses are different and these differences are acknowledged in the FOCE linearization. The purpose of this project is to investigate how the optimal design is affected by the FIM approximation and to investigate the bias and precision of parameter estimates in these designs. Moreover, the optimal designs' performances are compared to designs that are randomly spread from the optimal design points.

Methods and Materials

Sampling schedules with 5 samples $t_i \in (0,50)$, were optimized in PopED [1-2] for an EMAX model (*figure 1*) parameterized as shown in Table 1 with exponential inter individual variability IIV equal to 25% CV on Emax and EC50 amongst 100 individuals placed in one design group. The optimizations were performed using the determinants of the full FO-FIM, FOI-FIM, FOCE-FIM and FOCEI-FIM. The residual errors were fixed (RUV) in a combined additive and proportional residual error structure. The maximum magnitude of residual error was set to 10% of the model response for the two residual error structures. Three random designs were also applied to the optimal designs: for each individual, each optimal sample was uniformly spread ±2% (RN2) and ±6% (RN6). For comparison, a completely random design (RND) with all sampling points sampled from a uniform distribution U(0,50) was also generated.

Parameter	Value	
EMAX	100	
EC50	20	
γ	4.5	
ω^2_{EMAX}	0.0625	
ω^2_{EC50}	0.0625	
$\sigma^2_{add.}$:	25	FIX
$\sigma^2_{prop.}$:	0.0025	FIX

Table 1. Parameterization of sigmoidal Emax model used for optimization.

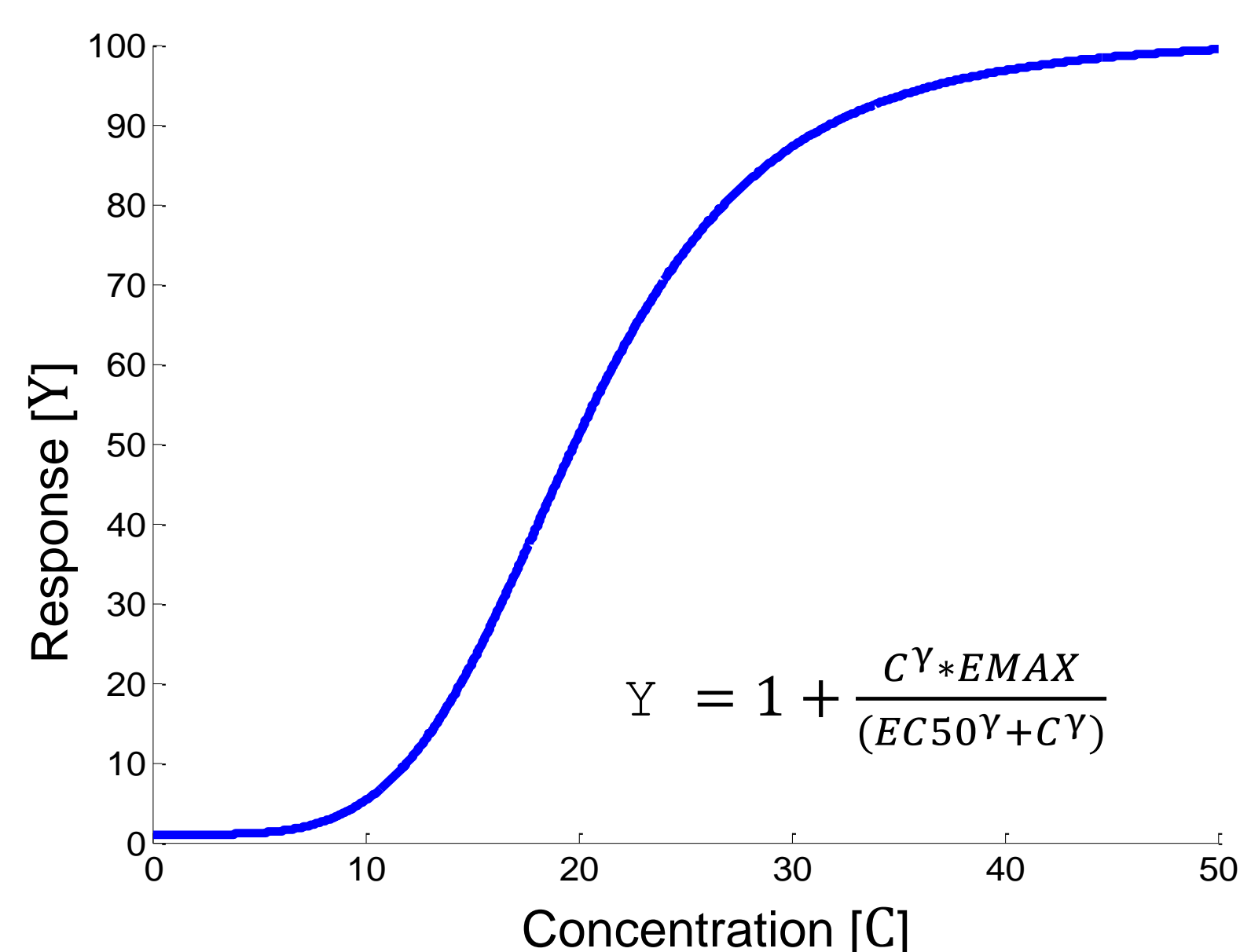$$Y = 1 + \frac{C^{\gamma} * EMAX}{(EC50^{\gamma} + C^{\gamma})}$$

Figure 1. Response and equation of sigmoidal Emax model.

The parameters for all designs were re-estimated (FOCEI) with NONMEM 7.2 [3] using MC simulations in PsN [4-5] (SSE) with unfixed RUV and the Empirical Covariance Matrix (empFIM) was calculated. All designs where also re-evaluated in PopED with unfixed RUV for direct comparison of the full D-optimal FIM (dFIM) and the reduced D-optimal FIM (redFIM) to the empFIM by utilizing the D-Criterion defined as $\det(FIM)^{1/p}$. Furthermore the total design bias was calculated as the sum of absolute relative biases for the parameters.

To investigate how sampling points cluster as the number of samples increase when using the FO and FOCE approximations of FIM, the FO-FIM and FOCE-FIM were optimized with different sampling schedules consisting of 5-10 samples.

Results

The OD differed between approximation methods and residual error models. The FO design showed clustering of individual samples and had 3 support points. The FOCE designs did not show the same clustering of sampling times as FO and showed 7 support points for 10 optimized samples.

The SSE-studies of the designs and re-evaluations in PopED revealed that the FOCE based design were generally better in terms of precision than FO based designs. The applied random spread around the OD support points did slightly lower bias with FO and FOI. In FO-RN2 and FOCE-RN2 the precision increased slightly, resulting in that the empFIM and total bias show to be the best overall designs for for the FO and FOCE FIM approximations, respectively.

In this example, when no interaction was used, the RN2 designs did not significantly affect the predicted efficiencies (D-Criterion/D-criterion) in PopED. The D-Criteria of the reduced FIM is lower than the Full FIM and closer to the simulated empFIM for all but the FOI-RN2 and FOI-RN6 calculations.
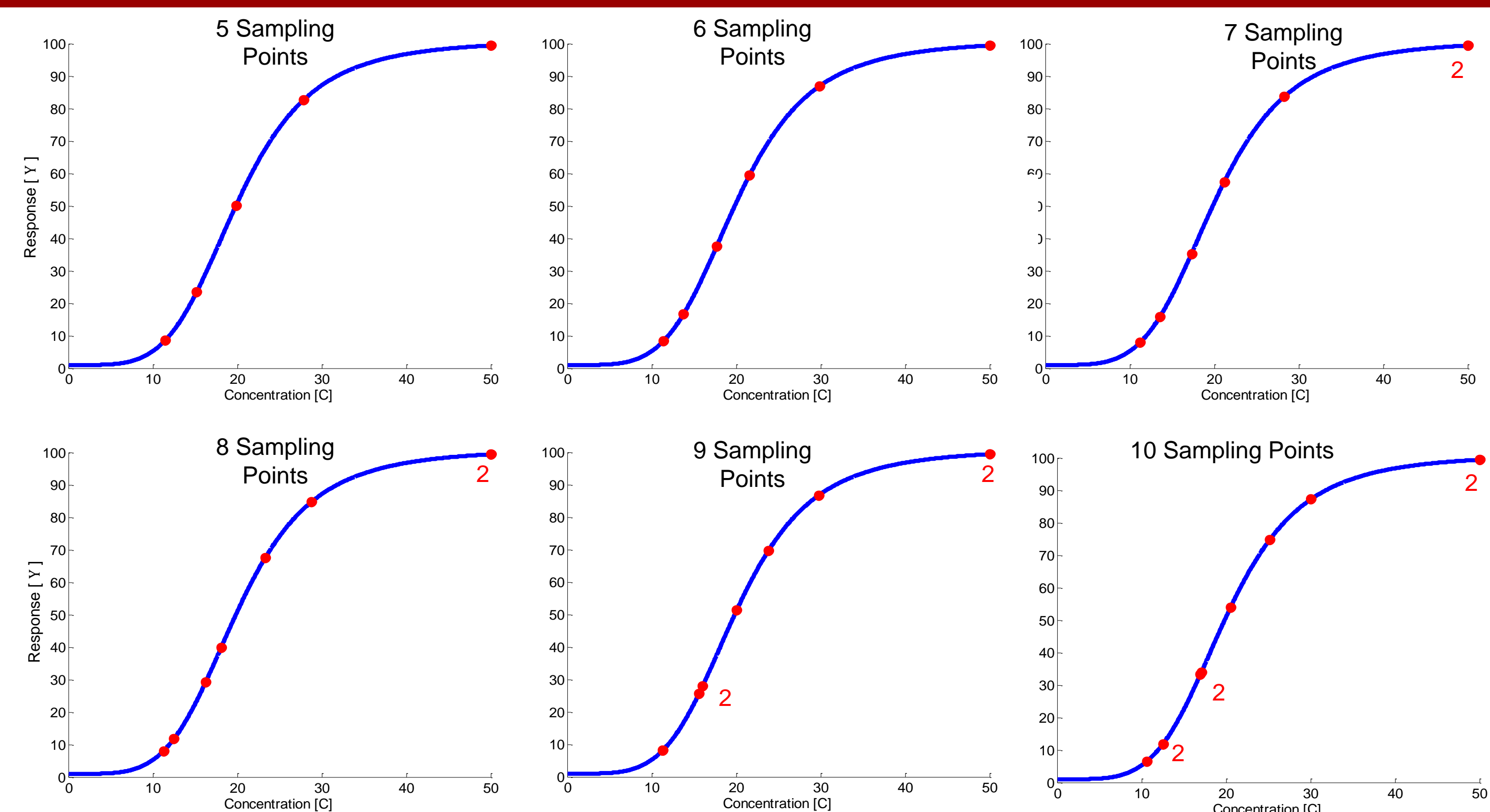
Email contact: eric.stromberg@farmbio.uu.se

Figure 2. FOCE-FIM D-optimal designs for increasing number of sampling events (dots). A number marks where multiple sampling points are clustered on top of each other.
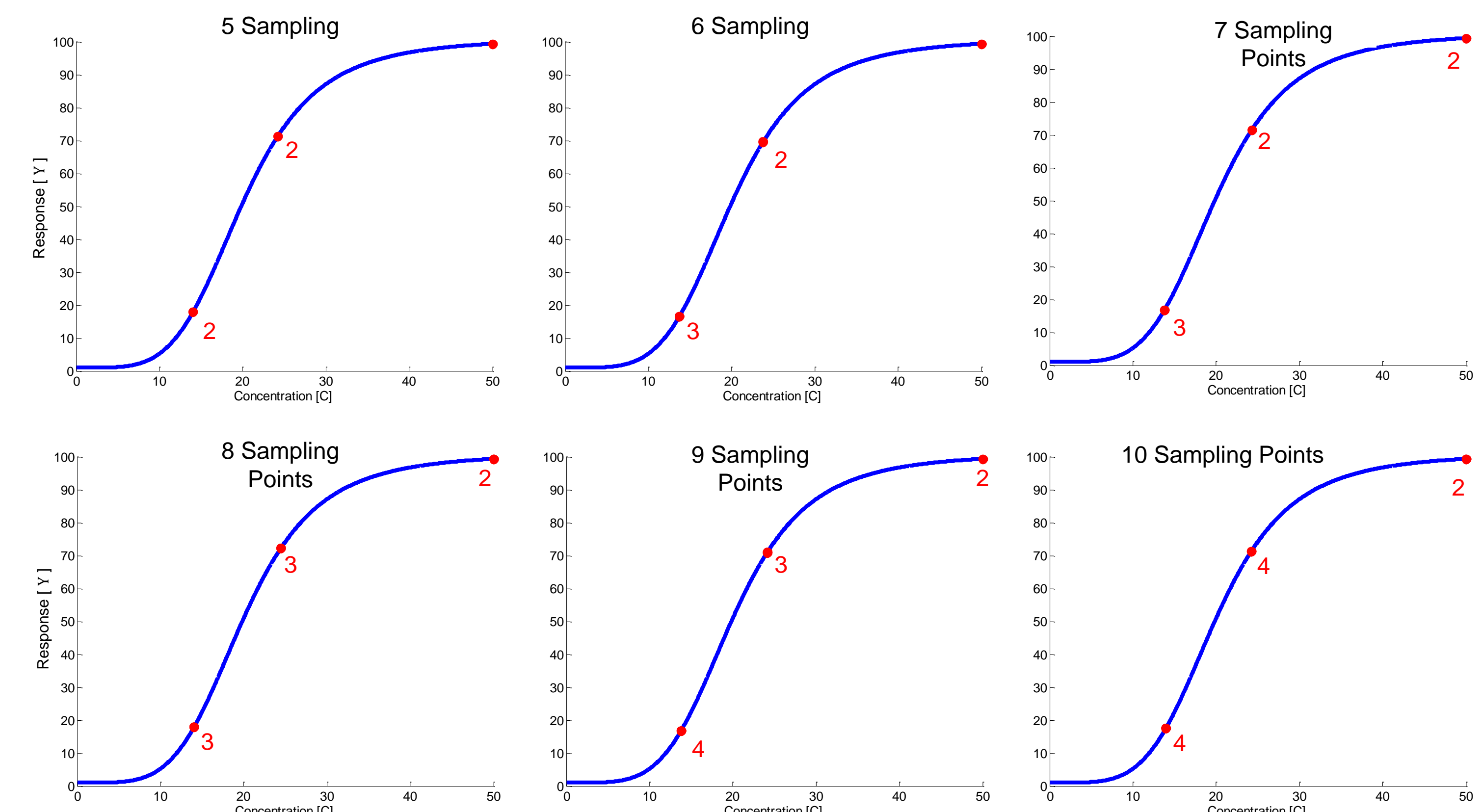
Figure 3. FO-FIM D-optimal designs for increasing number of sampling events (dots). A number marks where multiple sampling points are clustered on top of each other.
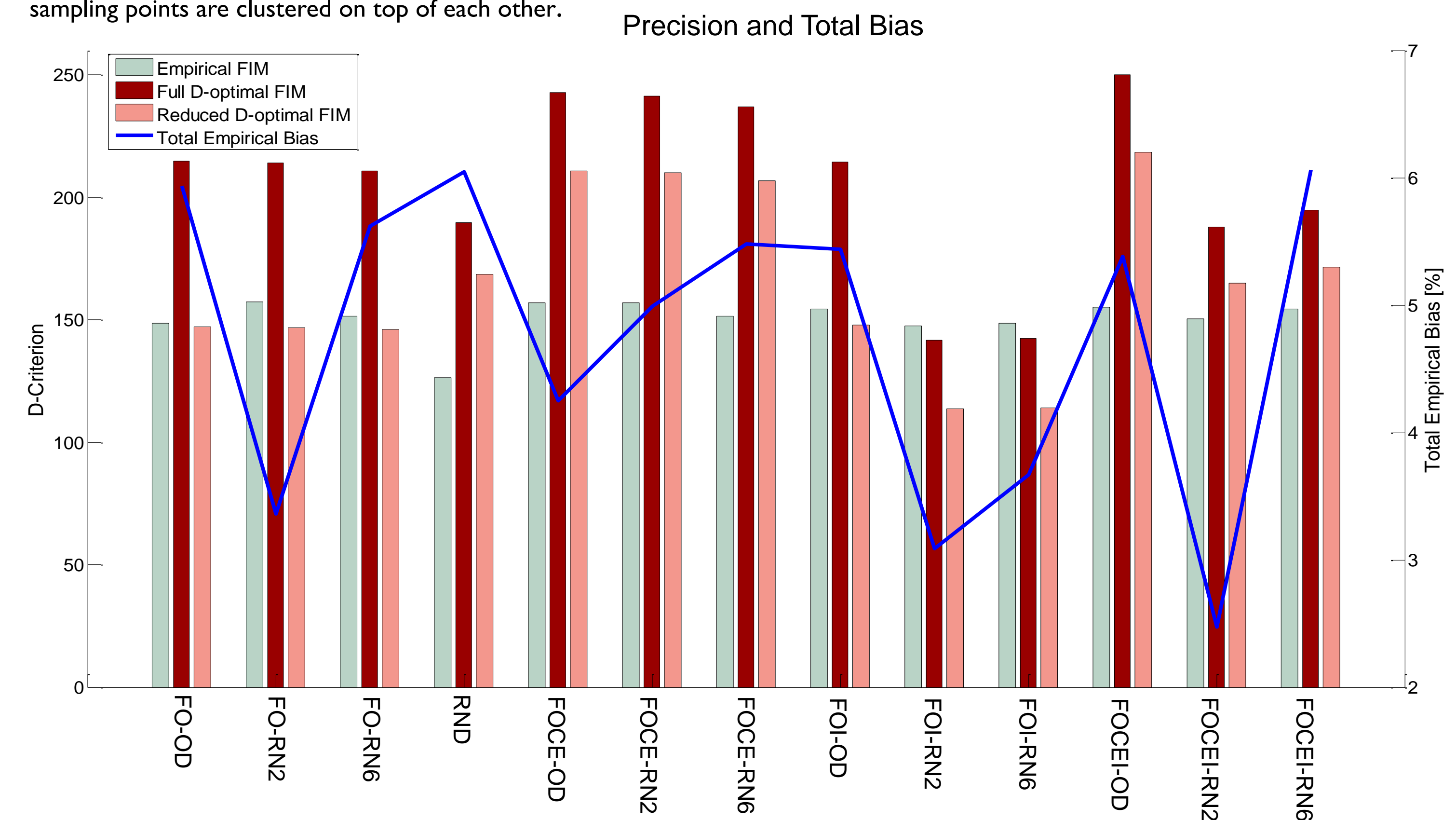
Figure 4. D-Criterion of re-estimated empFIM, dFIM and redFIM with and without applied spread around optimal sampling times. The total absolute relative biases is represented as the blue line.

Conclusions

- Using the FOCE approximation of the FIM increases the number of support points in a design and gives slightly better estimation properties, in this example, compared to FO.

- In this example spreading sampling times gave designs nearly as efficient as the optimal designs and in a few cases, spreading slightly improved precision.

- D-Criteria of reduced FIM is in this example lower than its Full FIM equivalent and closer to the empirical information, for all but the FOI-RN2 and FOI RN6 calculations.

- The differences in precision and bias between the designs in this example are to small to give clear results, further studies of different models and/or designs is required.

References

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[4] Lindbom, L., Ribbing, J., Jonsson, E.N., "Perl-speaks-NONMEM (PsN) - A Perl module for NONMEM related programming", 2004 Computer Methods and Programs in Biomedicine 75 (2), pp. 85-94. [5] Lindbom, L., Pihlgren, P., Jonsson, N., "PsN-Toolkit - A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM", 2005 Computer Methods and Programs in Biomedicine 79 (3), pp. 241-257