



Introduction

Many monoclonal antibodies (mAbs) display non-linear pharmacokinetic (PK) profiles that arise when target binding significantly alters the disposition of the therapeutic antibody. This is frequently called target mediated drug disposition (TMDD). [1] In this work, TMDD models combined with optimal design methods, were employed to evaluate the consequences of reduced sampling designs for trials with mAbs.

Methods

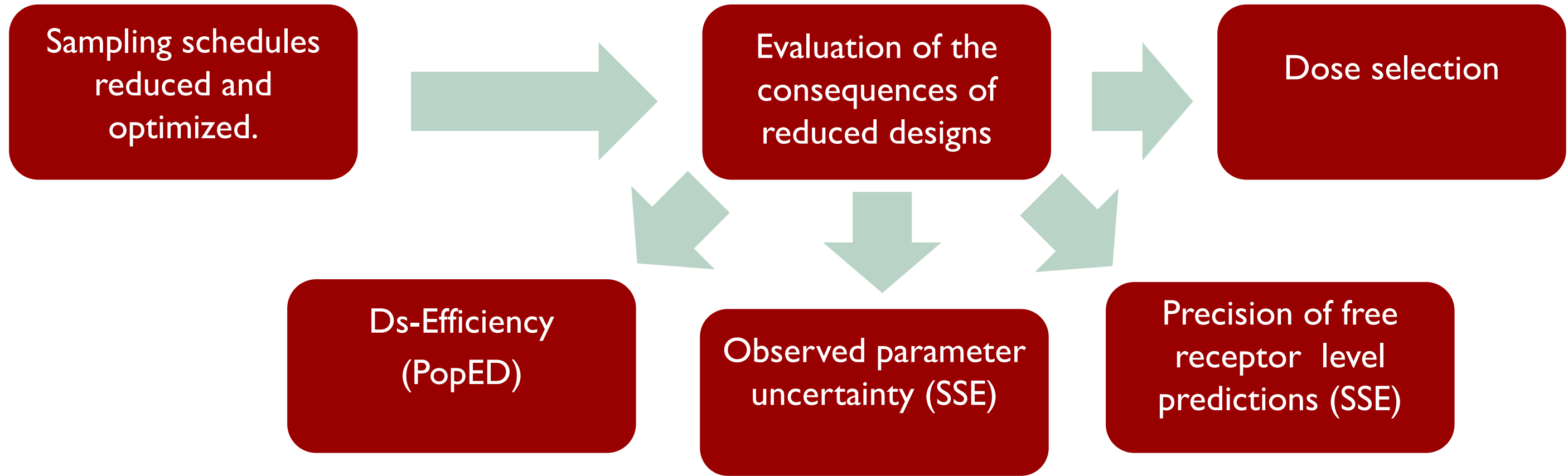


Figure 1: Work-flow of this project.

1) Models: Quasi-steady-state (QSS) and quasi-equilibrium (QE) approximations [2, 3, 4] of the full TMDD model were used to describe the interaction of a drug with a soluble receptor.

2) Design Optimization: Reference designs for sampling of mAbs and reduced designs (with respect to the number of samples, subjects in the trials and/or trial length) were evaluated and optimized using PopED [5]. In this work, the determinant of the fixed-effects portion of the model was maximized (Ds-criterion) because the focus was on population predictions.

3) Consequences of reducing designs: Reduced designs were compared to the reference designs with respect to Ds-efficiency (Eq. 1).

$$Eff_{DS} = \left[\frac{|FIM|_{\text{Interesting parameters}}/|FIM|_{\text{Uninteresting parameters}}}{|FIM|_{\text{Interesting parameters}}^*/|FIM|_{\text{Uninteresting parameters}}^*} \right]^{1/p} \quad (1)$$

* = reference design; p = number of interesting parameters in the model

The reference design for the QE model included 4 dose groups with 12 individuals receiving a subcutaneously administered mAb. The administered doses were 500, 1000, 2000 and 2500 nmols and 39 samples were available per individual (samples were available for total drug and total and free receptor). The reference design for the QSS model included 4 dose groups with 6 individuals. The administered doses were 100, 300 and 600 units given intravenously and 1000 units given subcutaneously. 28 samples of free drug and total receptor were available per individual.

Observed parameter imprecision, reported as relative root mean squared error (rRMSE%), was obtained using the stochastic simulation and estimation (SSE) functionality in PsN [6].

95% prediction intervals (PI) of free receptor level were obtained from the SSEs. The difference in predictions between two designs was quantified with a prediction interval ratio (PIR) where the area of the PI of the reference design over a fixed time-span and a specific dose was divided by the same calculated area for the reduced design.

The ability of each design in selecting a dose resulting in a certain receptor level suppression at two weeks was investigated. The correct dose was calculated as the dose giving 95% target suppression in the typical individual given the true model. For each design, free receptor levels (given a range of doses and parameter uncertainty) were predicted. The probability of making a correct go/no-go decision for each of the doses was calculated (Figure 2).

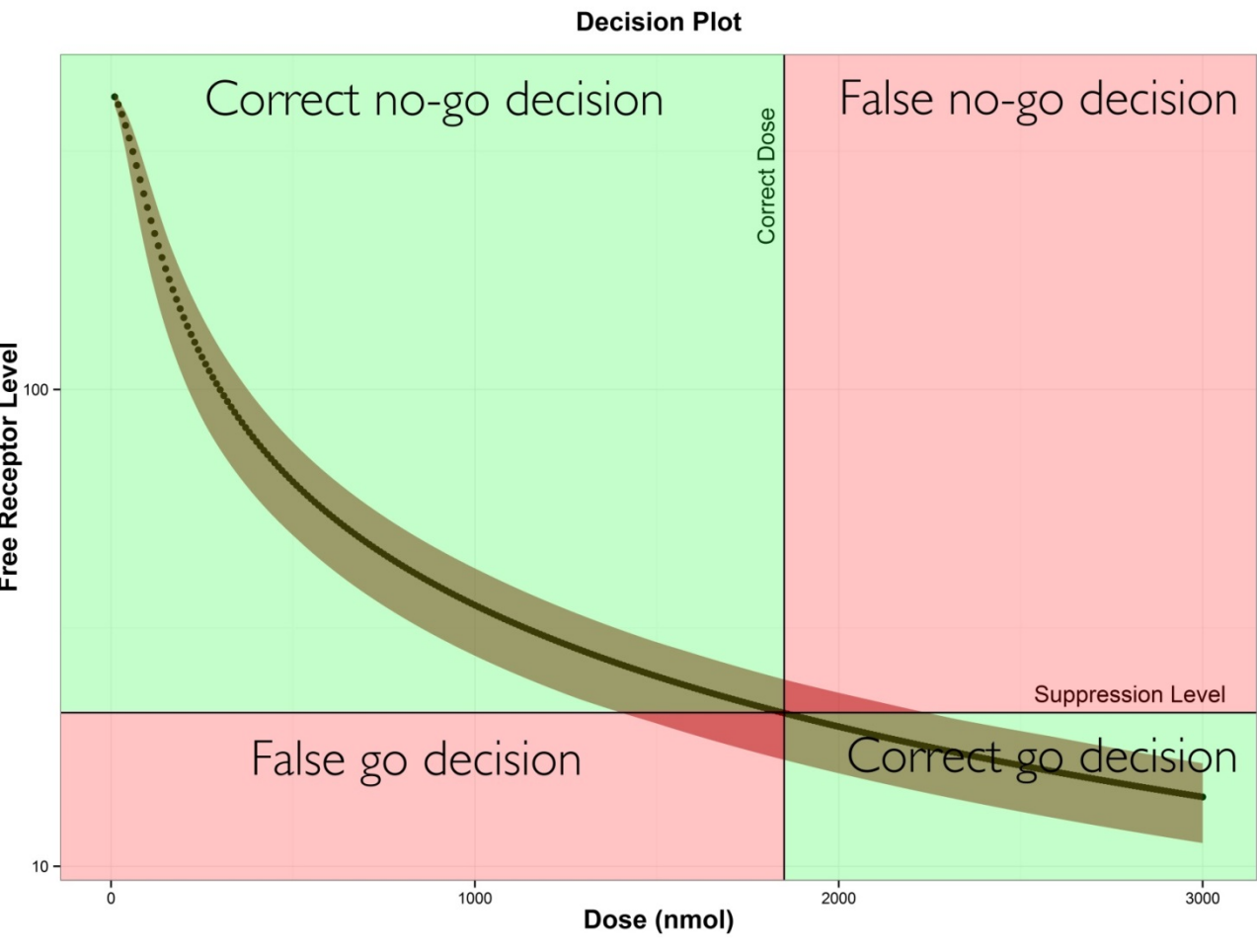


Figure 2: The black line shows the true free receptor level. The black vertical line represents the true dose resulting in the desired suppression level. The shaded region depicts the 95% free receptor PI for an investigated design. Thus, when a dose lower than the true dose yields a prediction (based on one of the designs) below the desired suppression, this would lead to a false decision, and conversely a dose higher than the true dose yielding a prediction above the desired suppression leads to a false decision.

Additionally, the correct dose combined with the resulting parameter uncertainty of the different designs was used to calculate the deviation of the predicted receptor suppression level from the correct receptor suppression level.

Conclusions

- ✓ For TMDD models evaluated, between 23-58% reductions in the number of samples was possible without decreasing the efficiency of the design below 90%.
- ✓ Even with large parameter uncertainty, population predictions can still be relatively accurate.
- ✓ Designs with low efficiency may still result in correct dose decisions

Objectives

The objectives of this work were twofold:

- Optimize reduced sampling schedules for two TMDD models.
- Determine the consequences of reduced designs on parameter precision, precision of free target level predictions at certain time-points and on dose selection.

Results

The effects on average and maximum parameter imprecision of selected reduced trial designs are summarized in Table 1. It was possible to reduce the amount of samples by 23.1% and by 53.8% for the QE and QSS models respectively without decreasing efficiency below 90%. Although efficiency suffered in all of the reduced trial designs, predictions of free receptor remained fairly accurate in some cases indicating that the influential parameters for the predictions are relatively less affected (Figure 3, Table 1).

Table 1: Summary of selected reduced trial designs. * = V2 rRMSE% > 10000

Design	Description	Total Samples	Optimization	Sampling Times (days)	Ave. rRMSE%	Max. rRMSE%	Eff _{DS}	PIR
QE Model								
Reference	Reference design	1872	NA	0, 0.5, 1, 2, 4, 7, 10, 14, 28, 42, 56, 70, 84	5.50	8.92	1.00	1.00
2	Optimized reference design with 3 fewer samples	1440	Dis-optimization of sample times	0,0.0.38,0.38,4.5,8.8, 8.50,84	6.37	12.24	0.92	0.81
3	6 hour sampling for 48h	1296	NA	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2	61.41	>200	0.060	0.034
3	Last sample taken at 48h, 27 samples per id.	1296	Dis-optimization of sample times	0,0.083,0.083,1,1,1.2,2.2	47.08	151.32	0.074	0.035
4	4 samples per id and analyte	576	NA	0, 0.25, 1.84	15.73	18.68	0.34	0.81
4	4 samples per id and analyte	576	Dis-Optimization of sample times	0, 0.38, 9.73	8.73	20.67	0.57	0.89
QSS Model								
Reference	Reference design	624	NA	0.0417,0.25,0.5,1,3.7,14,21,28,35,42,49,56	11.54	23.90	1.00	1.00
2	Optimized reference design with 7 fewer samples	288	Dis-optimization of sample times	0.05,6.72,10.08,28.56	14.47	27.51	0.91	0.78
3	4 lds per group and 5 samples taken per id and analyte	160	NA	0.04017, 1, 2, 7, 56	20.25	36.35	0.32	0.50
4	6 hour sampling for 48h	384	NA	0.0417,0.25,0.5,1,3.7,14,21,28,35,42,49,56	>1000	>1000	0.020	0.16
5	3 lds per group and 4 samples taken per id and analyte	96	NA	0.0,25,1,56	>1000*	>1000*	0.12	0.33
5	3 lds per group and 4 samples taken per id and analyte	96	Dis-optimization of sample times	0.7,8.28,56	25.20	45.06	0.39	0.57

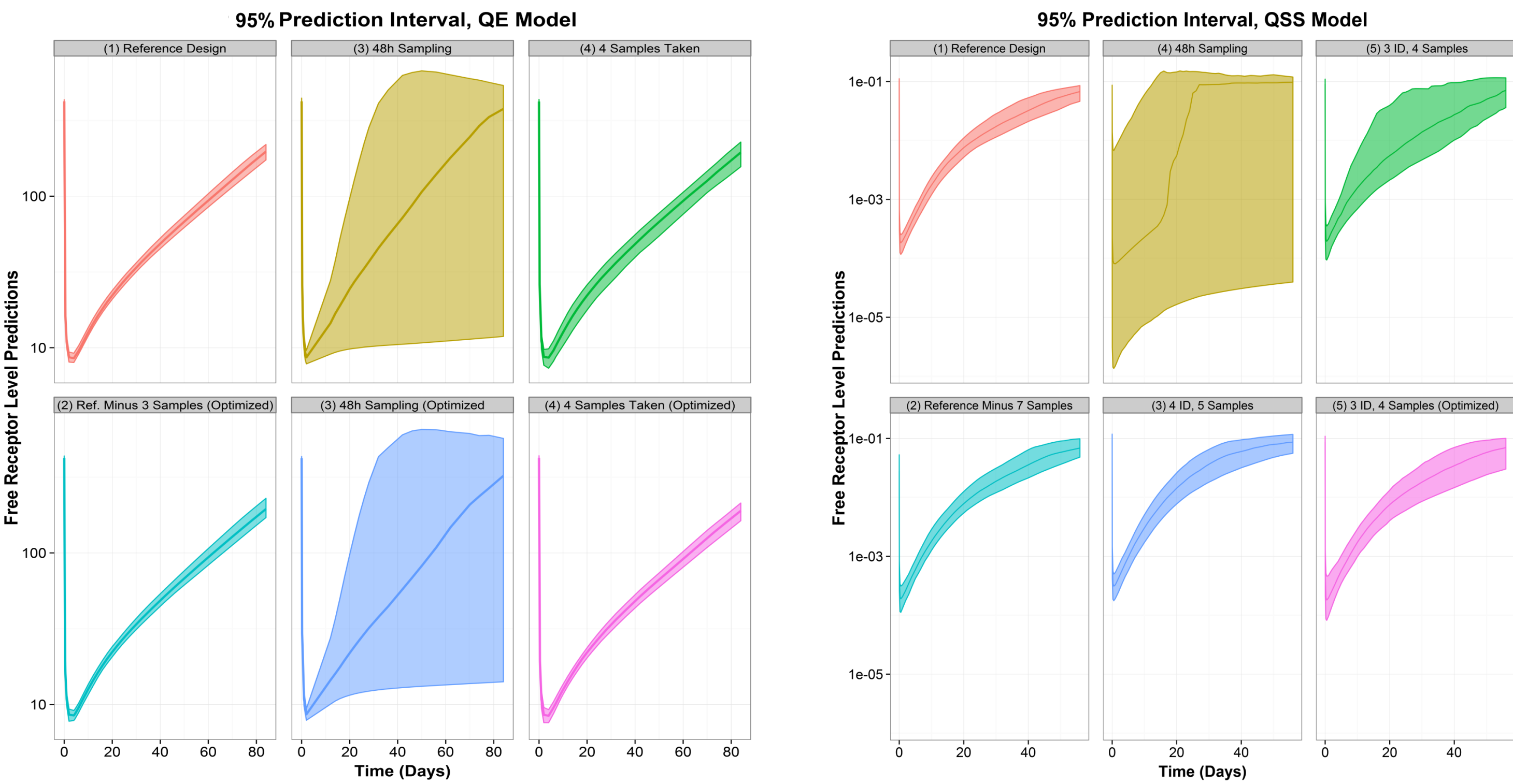


Figure 3: Pls of selected designs in the QE (left) and QSS (right) models. The subcutaneous dose is shown for the QSS model and the highest dose is shown for the QE model. Designs 4 and 5 in the QE and QSS models respectively feature low efficiency yet the imprecision in free receptor prediction does not appear to be highly affected. Sampling for a short period of time (designs 3 and 4 in the QE and QSS models respectively) results in very poor predictions as indicated by both efficiency and PIR. Visually, it is difficult in most cases to distinguish optimized from unoptimized designs.

The probability of making a correct go/no-go decision with the QE model and with the various designs can be seen in Figure 4. The probability of making a correct decision based on Design 3 is low for all doses apart from the least informative lowest doses.

Probability of Making Correct Decision

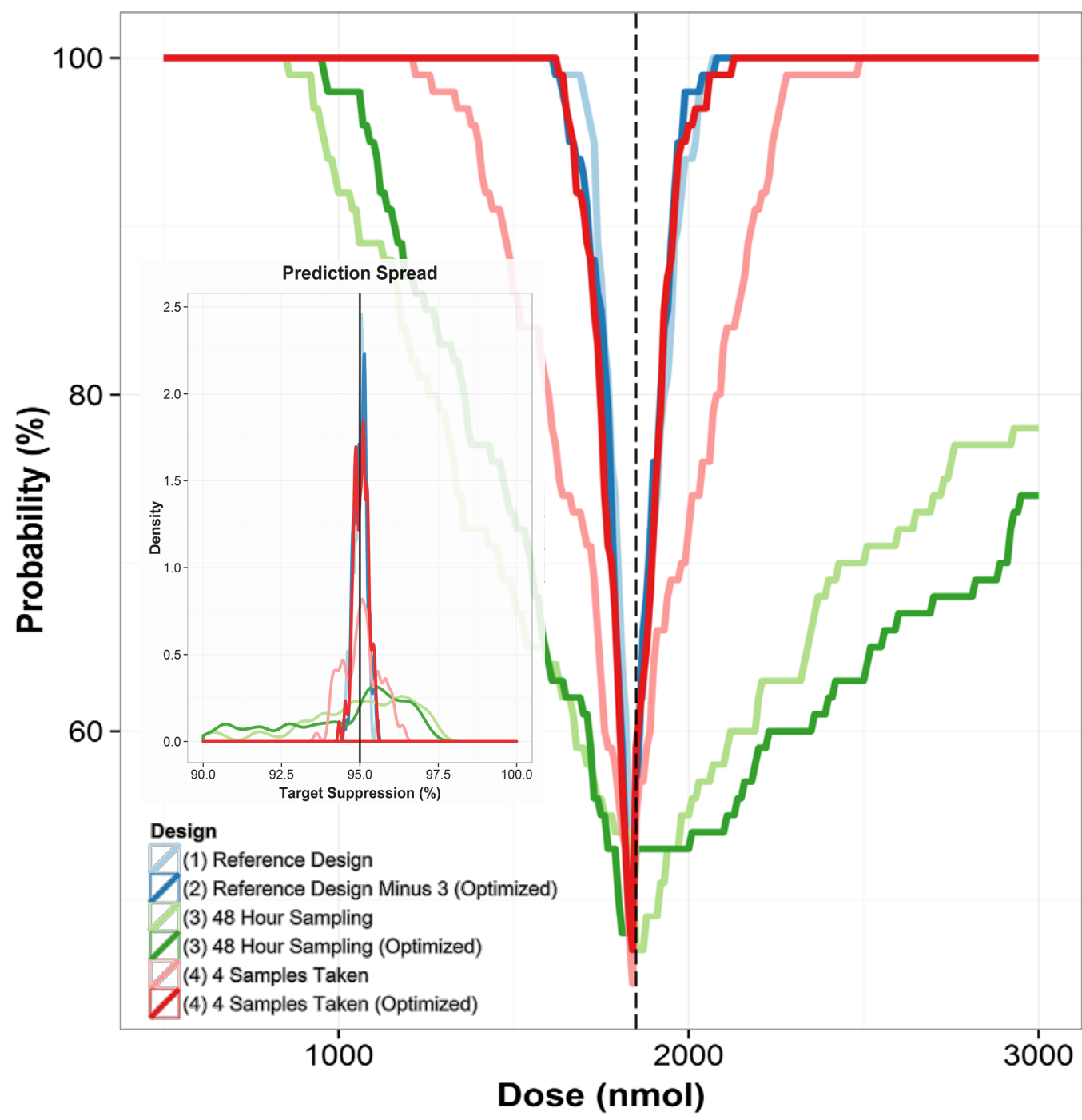


Figure 4: shows the probability of making a correct decision based on the evaluated designs. The reference design had an 80% probability of making a correct go/no-go decision in ~95% of the evaluated doses. An 80% probability of making a correct go/no-go decision was made in ~83% of the evaluated doses with design 4 and was increased to ~94% when design 4 was optimized.

The true dose resulting in adequate receptor suppression in the QE model was 1850 nmol. Table 2 shows the required doses in the different designs of the QE model to maintain 95% confidence in making a correct go decision.

Table 2: Dose for 95% Confidence in go-decision

Design	True	(1)	(2)	(3)	(3 opt)	(4)	(4 opt)
Dose (nmol)	1850	2020	1970	>3000	>3000	2240	1980
Difference from true dose (%)	0	9.19	6.49	NA	NA	21.08	7.03

The spread of the prediction of free receptor with the evaluated designs given the true dose mirrors the results from the probability of making a correct decision evaluation (Figure 4). Poor designs (design 3) fail to hit the correct target with any precision while design 4, when optimized, hits the target with a similar frequency as the reference design despite having inferior efficiency.

References

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