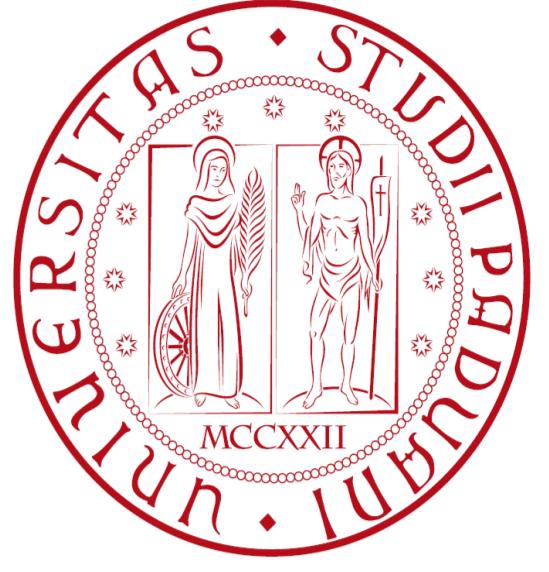


# Optimal Experimental Design for receptor drug development with PET studies

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## INTRODUCTION

**BACKGROUND:** To increase the efficiency of PK/PD experiments, optimal experimental design has been used to successfully optimize dose allocation and sampling schedule [1]. In PET receptor occupancy (PET-RO) [2] studies it has been demonstrated that adaptive optimal design (AOD) algorithms improve the assessment of drug kinetic time-courses [3].

However the value of applying adaptive or non-adaptive optimal design methodologies to PET-RO studies depends on several factors including drug affinity to the target as well as feasibility constraints such as sample size, number of scan per subjects and logistical constraints.

**AIM:** In this work we presented a simulation study to explore the potentialities of optimal design algorithms when applied to PET-RO, by evaluating the sensitivity of the results to experimental scanning times as well as misspecified drug kinetic assumptions.

## METHODS

### RECEPTOR-TIME COURSE MODEL USING BINDING POTENTIAL

A general representation of PK-occupancy time course model can be described as reported in Figure 1. However, in PET studies where only few PET scans per subject can be acquired, this model can not be applied and a simplified version needs to be considered. In our study, a  $k_{on}$ - $k_{off}$  model using the binding potential data derived from PET study was considered.

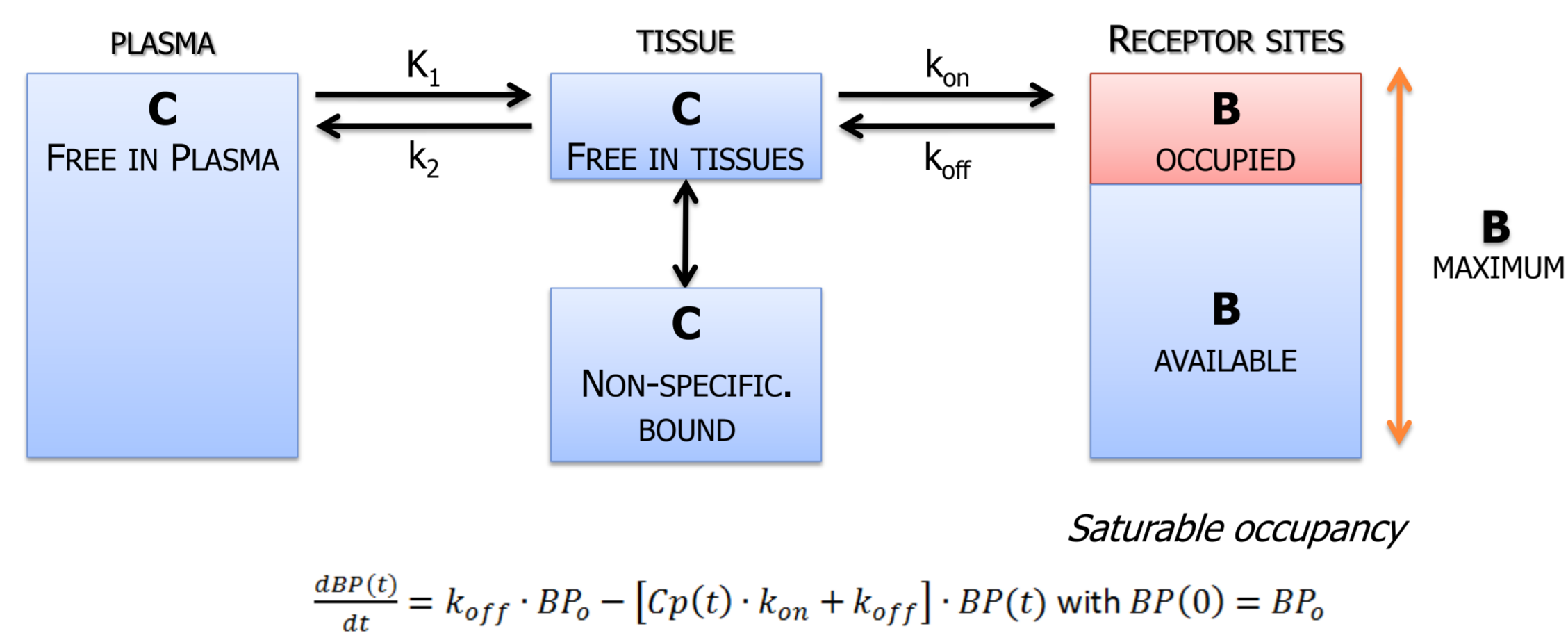


FIGURE 1. Schematic representation of PK-receptor binding model

### SIMULATION STUDIES

Simulated experimental designs were chosen according to adaptive, non-adaptive optimal designs and non optimized designs by using different levels of parameter misspecifications respect to the true simulated values (range: [-300%;+300%]). For each design, 100 populations each with 12 subjects were considered. Only two time points were assumed per subject, chosen in a time window of 0-36 hours (minimum distance 4 hours). Design optimization was identified using the D-optimality criterion [4]. Three simulated compounds with different brain affinities (Tab 1) were tested. The dose level was held constant for all the simulations.

Drug Affinity Scenario	$K_{on}$ [hours <sup>-1</sup> mol <sup>-1</sup> l]	$K_{off}$ [hours <sup>-1</sup> ]	$K_d$ [mol <sup>-1</sup> l]	Affinity (1/ $K_d$ ) [mol l <sup>-1</sup> ]	$BP_0$ [unitless]
Low	0.044	0.66	15.1	0.07	3
Medium	0.088	0.22	2.5	0.4	3
High	0.440	0.11	0.25	4.0	3

TABLE 1. Simulated compound kinetics

### SENSITIVITY ANALYSIS

Three different sections, each one focused to investigate a different issue concerning the experimental timing of PET occupancy studies, were organized as follow

#### THE EFFECTS OF GROUPING

- ✓ To show the impact of different designs to investigate a population of subjects;
- ✓ To show the impact of using D-optimality designs (*without misspecification*) for the definition of the scanning time in PET occupancy studies.
- ✓ To evaluate the performance of experimental design strategies in drug with different brain affinities.

#### THE EFFECTS OF MISSPECIFICATION

- ✓ To test D-optimality approaches when applied to RO studies and to evaluate the performance of the method in presence of misspecified parameter assumptions.

#### THE IMPACT OF ADAPTIVE OPTIMAL DESIGN

- ✓ To show how AOD can improve the population parameter quantification, even when prior parameter misspecification is present;
- ✓ To quantify the differences of AOD with D-optimal design in presence of misspecification.

## RESULTS

### SIMULATED VALUES

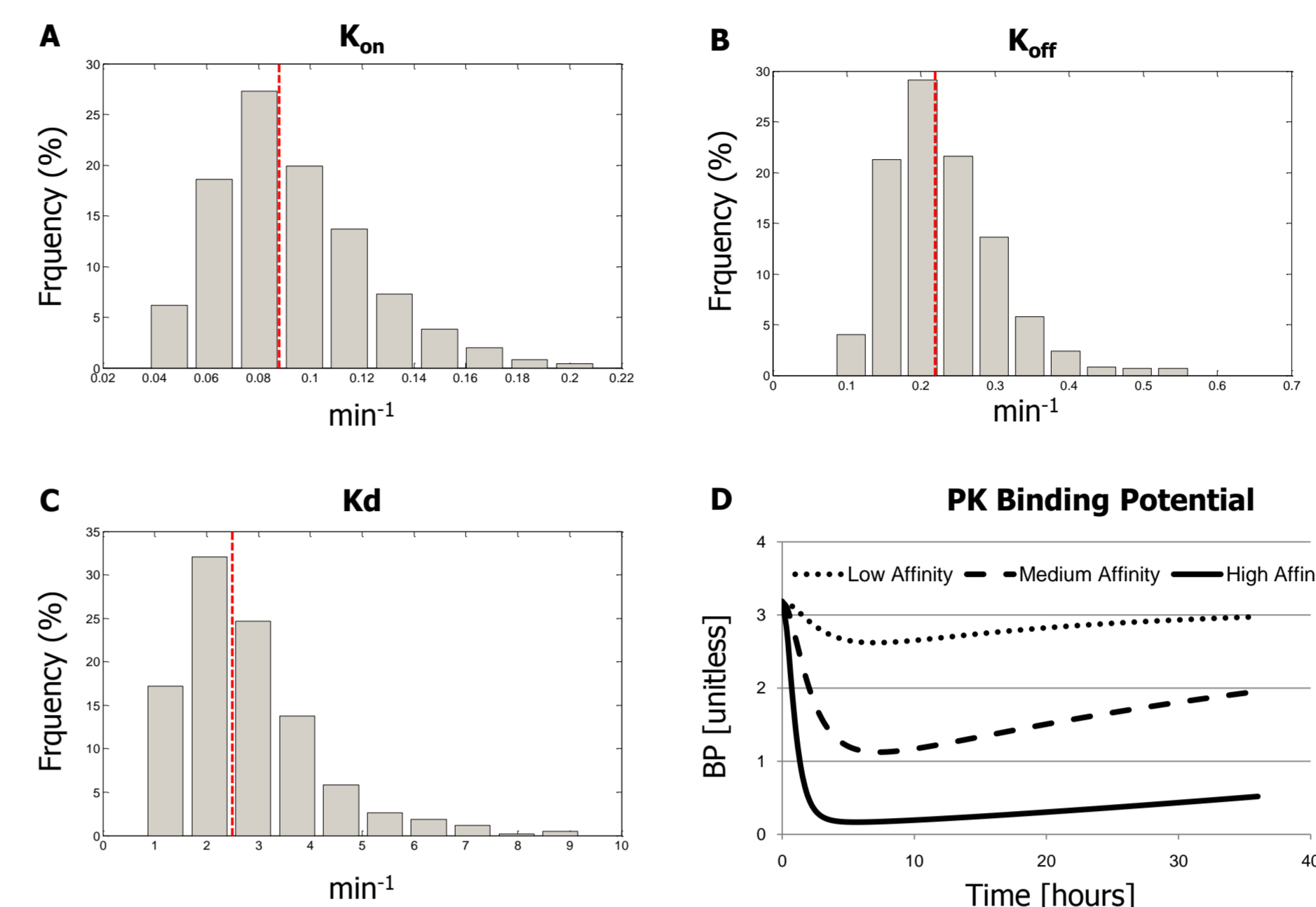


FIGURE 2. Panel A, B and C represent respectively the population variability for  $K_{on}$ ,  $K_{off}$  and  $K_d$  parameters, simulated for the medium affinity drug. For each parameter dashed line represents the mean population simulated value ( $\theta$ ). In Panel D the population mean of binding potential time courses is reported for all the three tested scenarios; dotted line represents low affinity drug; dashed line represents the medium affinity drug; continuous line represents the high affinity drug.

### THE EFFECTS OF GROUPING

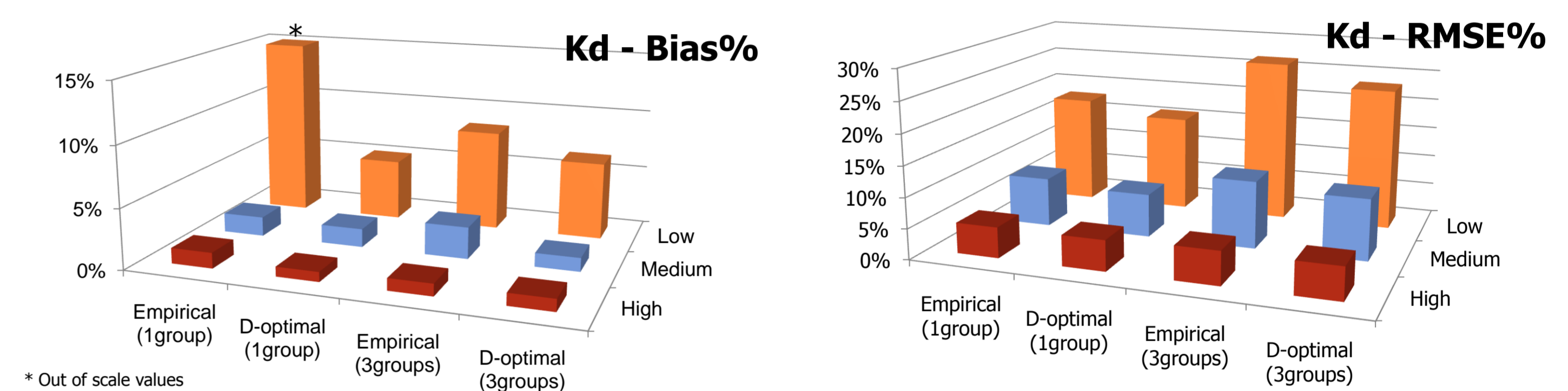


FIGURE 3. Optimal experimental designs applied *without* prior miss-specification.

### THE EFFECTS OF MISSPECIFICATION

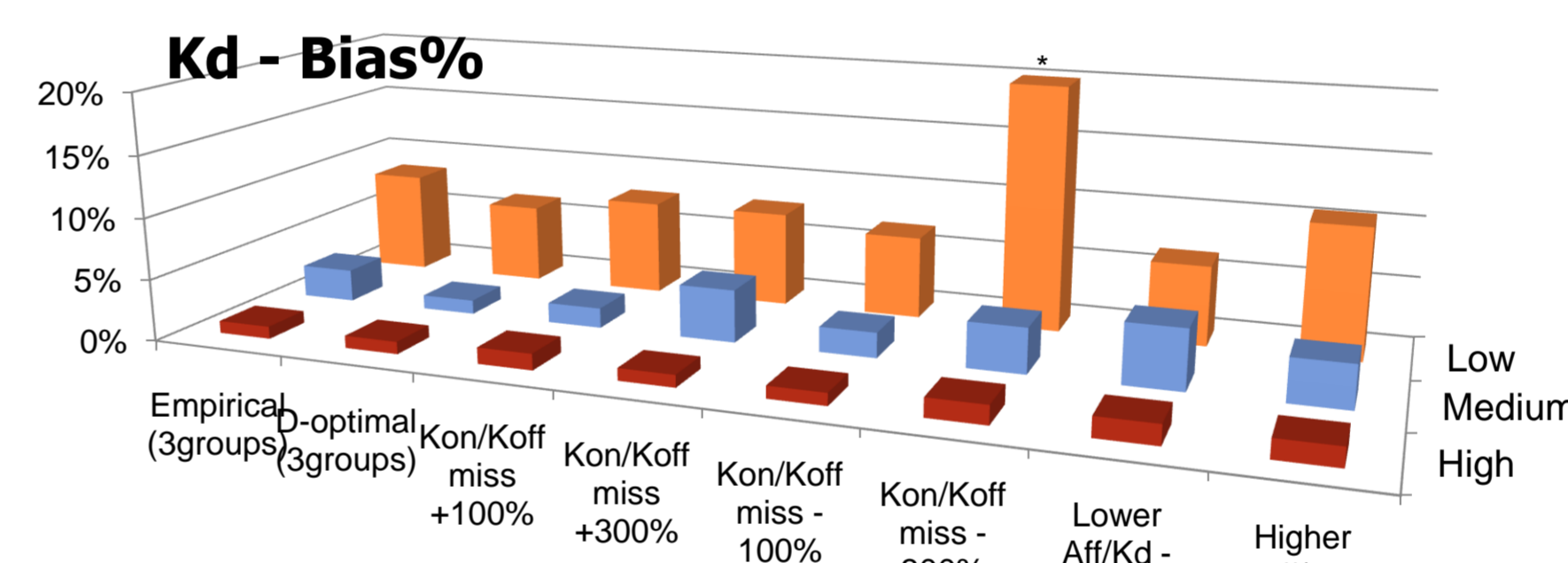


FIGURE 4. Optimal experimental designs applied *with* prior miss-specification.

#### Most evident results

- The presence of different groups with different designs increases the information extract from the experiments (reducing both bias and variability);
- D-optimality without misspecification provides similar performance using both unique or multi-group designs;
- $K_{on}$  and  $K_{off}$  estimates are much more sensitive to the change of time schedule than  $K_d$  and  $BP_0$
- The higher the affinity the better the performance of the design are.

### THE IMPACT OF ADAPTIVE OPTIMAL DESIGN

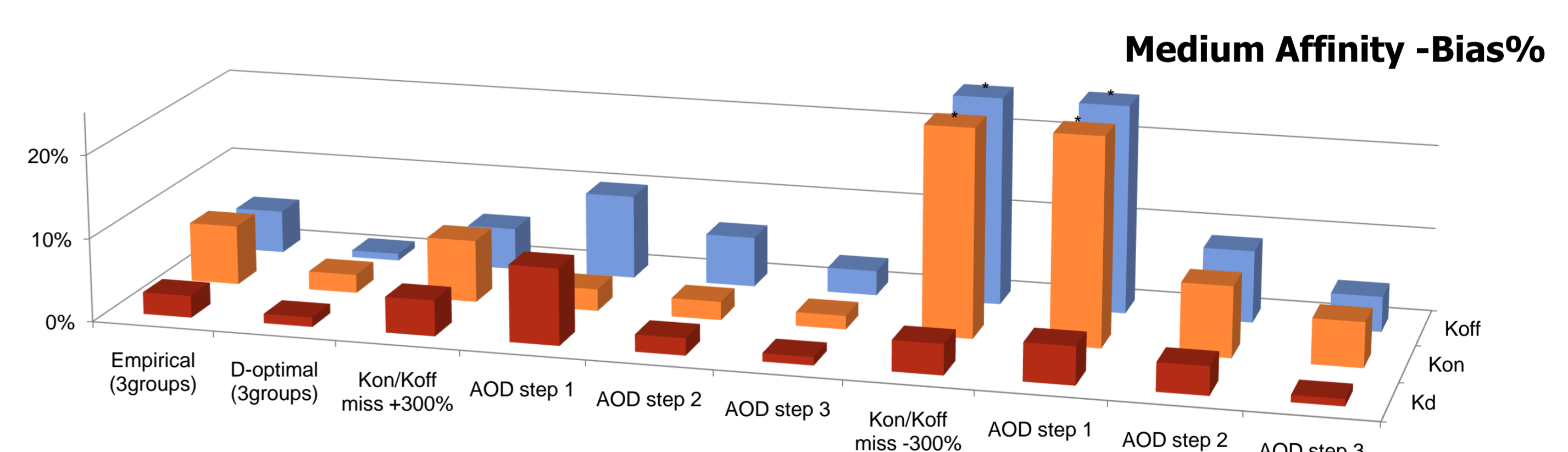


FIGURE 5. Adaptive Optimal Design in presence of prior parameter miss-specification.

#### Most evident results

- The use of AOD improves precision and accuracy, by reducing both bias and RMSE values of parameter estimates compared to the misspecified design used as starting point; In particular, the quality of the final estimates is comparable to those provided by design without misspecification.
- With AOD all the parameters of interest reported bias% <10% and RMSE <30% in all the tested conditions while D-optimality produced estimate performance with larger variability (bias% range: 0% - 47%; RMSE% range: 10%-309%).

## CONCLUSIONS

A rational management of the PET scan time, defined according to the characteristics of the tested compounds (kinetics, dynamic and inter-subjects variability) can greatly ameliorate the quality of the estimates in PET receptor occupancy studies. This result can be achieved by organizing the studied population in cohorts with different experimental designs and by applying the available methods for experimental design optimization. In particular if the initial misspecification is limited (<100%) D-optimality provided reliable results. In case of greater parameters misspecification, AOD represents a valid tool to guide experimental design settings.

## REFERENCES

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