Informative study designs: The value of within-subject dose-escalation in the “Espresso design”

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Objectives:

Evaluate information content and robustness of study designs
Drug development aims for most informative experimental designs while minimizing exposure of animals and patients to invasive procedures and potentially harmful drugs.

Standard design vs within-subject dose-escalation “Espresso design”
Dose-concentration-response information can be generated efficiently by investigating a range of exposures within individuals rather than relying on between subject analyses, either by following individuals’ responses as their drug concentrations decline or by applying within-individual dose escalation

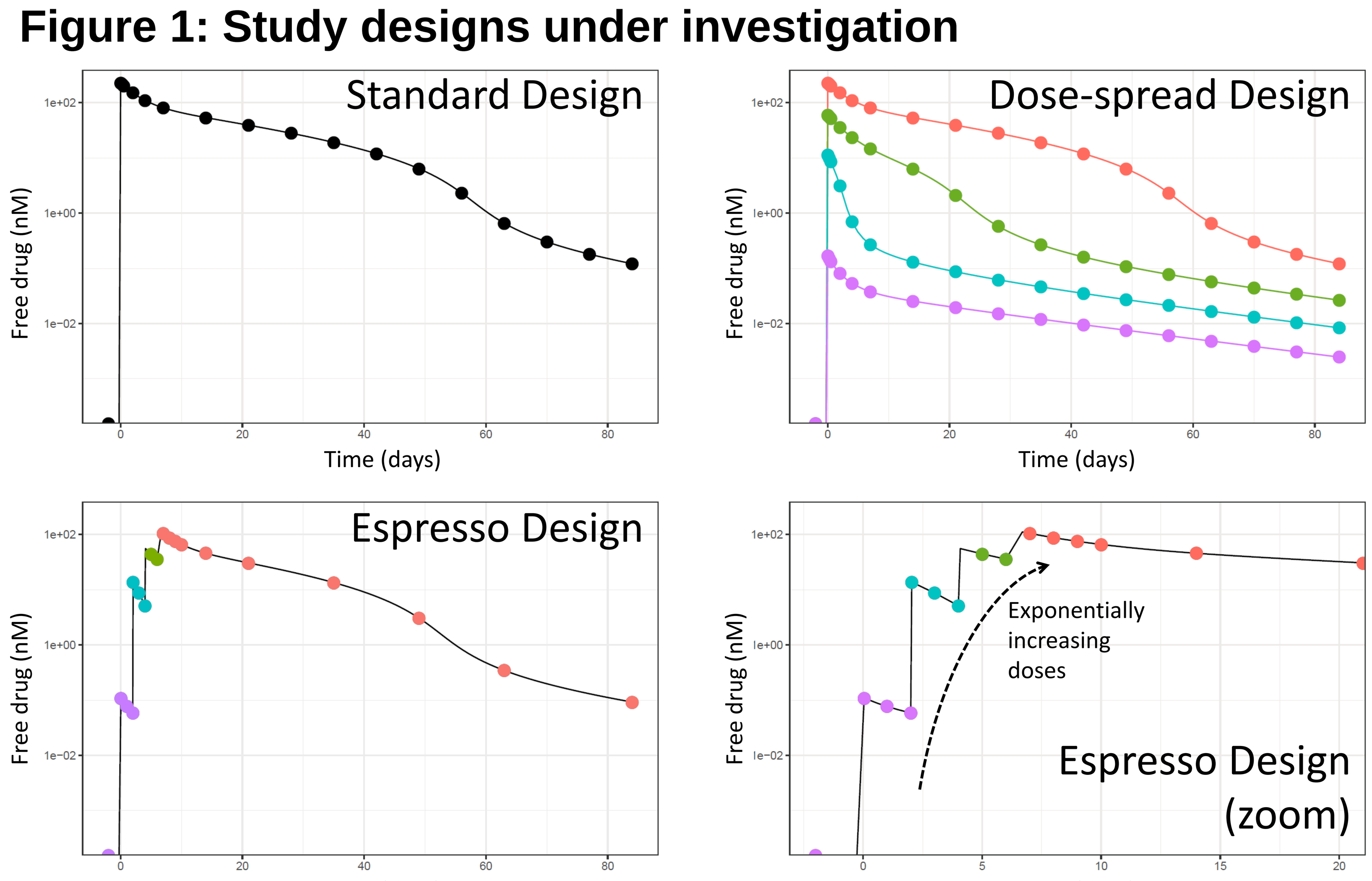
An Example of a pre-clinical study with 4 animals
Here, we evaluate the robustness of a within-individual dose escalation design (“Espresso design”) in a non-human primate study to inform the first-in-human dose for monoclonal antibodies with target-mediated drug disposition (TMDD).

Methods:

Optimal design software PopED [1] was used to evaluate 3 different study designs (see Figure 1) with 4 animals each

- “Standard design”: all administered a high dose
- “Dose-spread design”: spanning a dose range with 1 animal per dose
- “Espresso design”: within-individual dose escalation with increasing dose-amounts [2] (a similar approach has been published for an oncology Ph2-trial [3]).

Figure 1: Study designs under investigation



The “Espresso Design” can be seen as collecting information at different concentration levels (similar to the Dose-spread Design).

Results:

“Espresso design” allows for early estimate of Kd

The information on Kd in the Standard design peaks during the washout phase. The information peak occurs at a much earlier timepoint for the “Espresso design”. This allows estimation of Kd even when anti-drug antibodies (ADAs) appear after Day 10 – or to detect possible time-dependent changes comparing “Espresso” and washout phase.

Figure 2: Sensitivity of PK to Kd (Partial Derivatives)

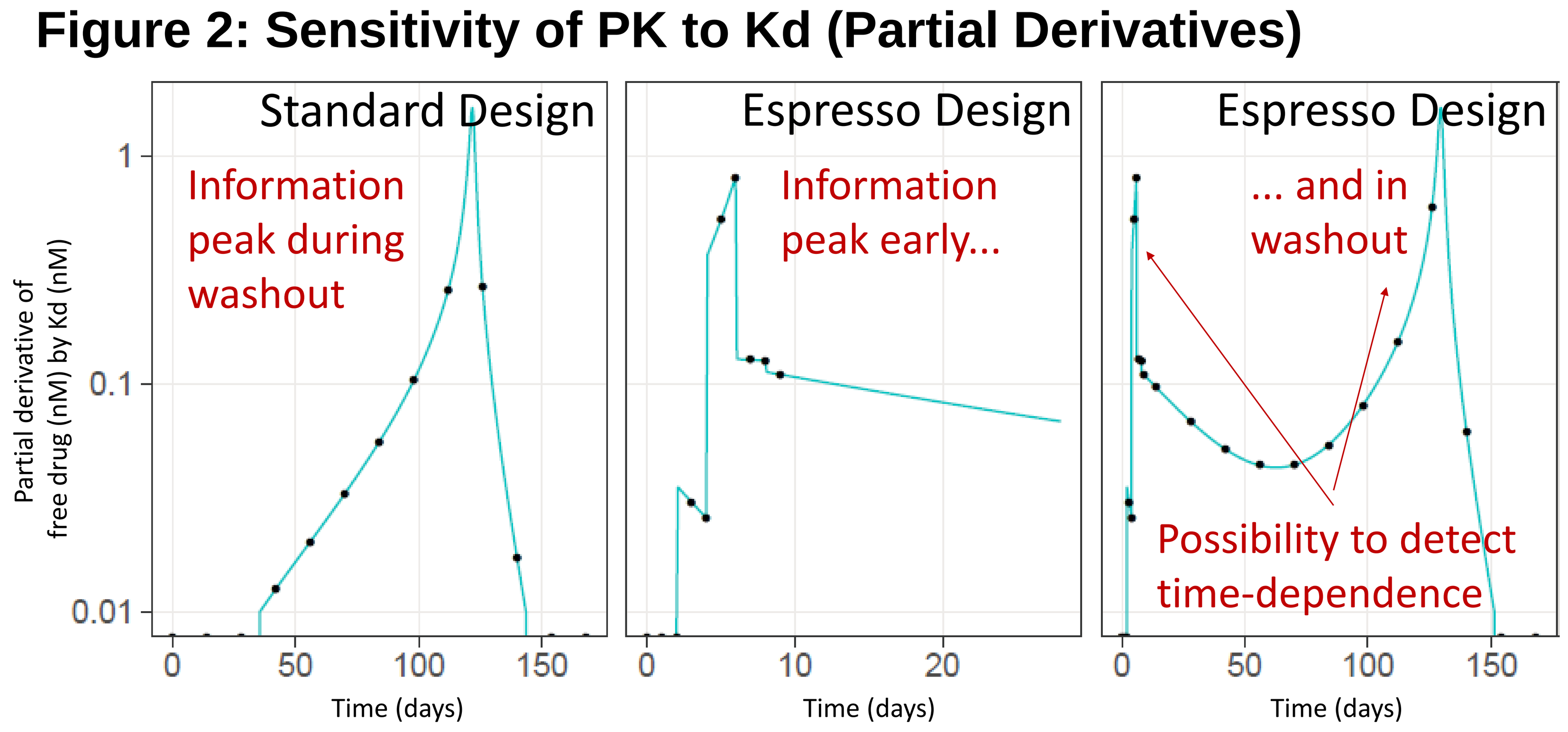
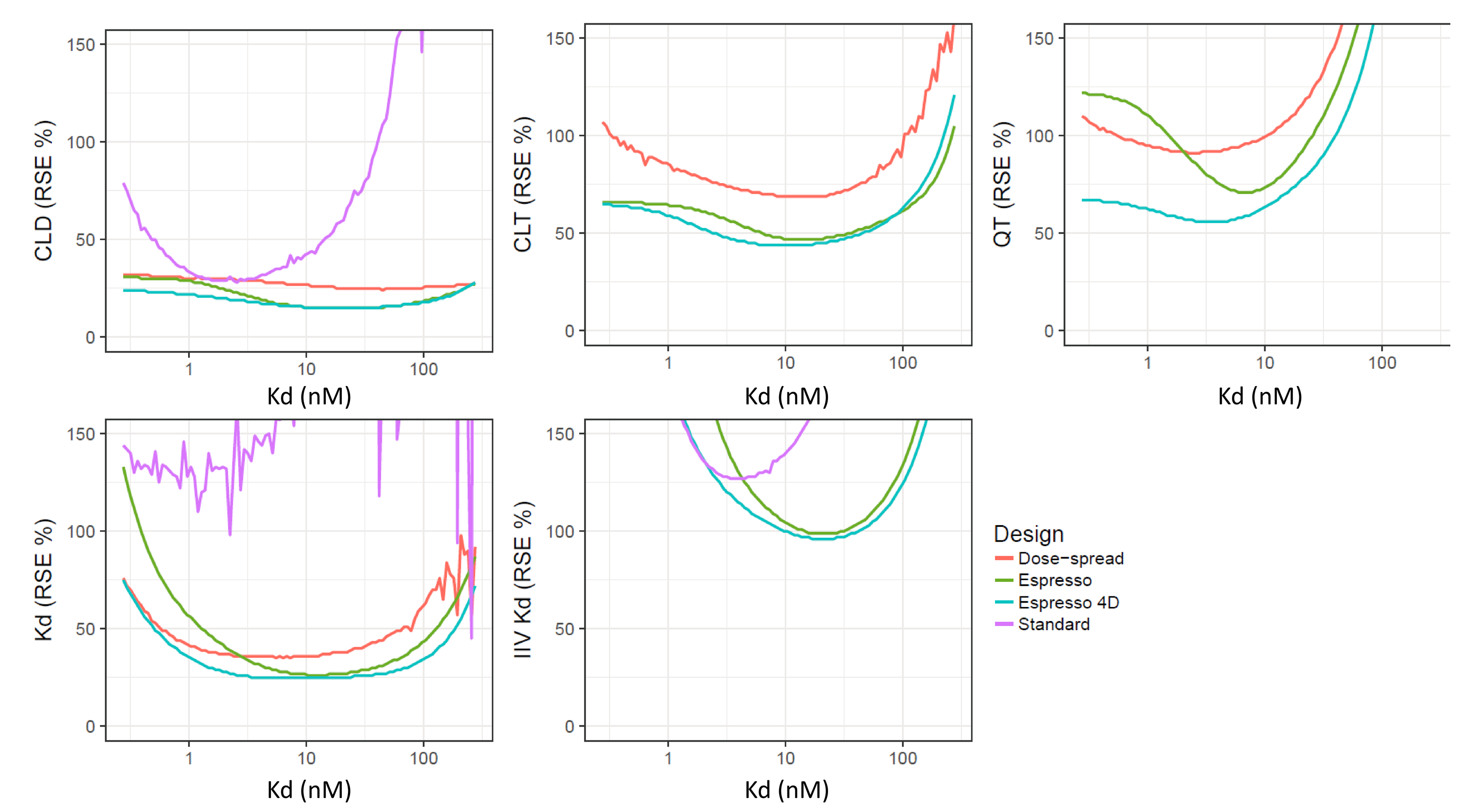


Figure 3: Precision of selected parameters for 2-cmt TMDD model for different Kd values (robustness to Kd uncertainty)



“Espresso” refers to up-titration every 2 days, “Espresso 4D” has a 4-day interval between doses.

Higher parameter precision for “Espresso design” – independent of actual Kd value

1-cmt TMDD model (not shown)
“Espresso design” provides minor improvement over the other designs for the drug clearance, but is substantially better for estimating clearance of the target (50% RSE versus more than 100% RSE for most Kd values investigated). Of note, the “Dose-spread design” also out-performs the “Standard design”.

2-cmt TMDD model (Figure 3)
The “Standard design” allows only drug clearance to be estimated with less than 100% RSE. Both the “Dose-spread design” and the “Espresso design” give good precision of most parameters (<100% RSE), except for inter-individual variability of Kd, which the “Dose-spread design” cannot estimate.

When including the 2nd compartment an up-titration interval of 4 days (“Espresso 4D”) was slightly better than an interval of 2 days (“Espresso”).

Appearance of anti-drug antibodies
When simulating appearance of anti-drug antibodies at Day 10 none of the clearance parameters for drug and target were identifiable with precision in any of the designs. The remaining parameters were however estimated with good precision with the Espresso design, as well as the Dose-spread design, but not the Standard design with only a high-dose.

Conclusions:

- The “Espresso design” with within-subject dose escalation
  - Provides good estimates of all parameters (except for clearances) in the first 10 days and thus allows for assessment of possible time-dependent changes of the underlying physiological system
  - Achieves high exposure levels in all subjects (for safety investigations) compared with a design which spreads subjects across dose-levels
- Innovative study designs can provide more robust information than “Standard designs”. Varying the dosing-regimen can provide much more gain than optimizing sampling times or just dose levels
- For assessing additional study objectives a mix of different design types will need to be applied

References:

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