

PKPD model evaluating the ideal interplay between the PK and mechanism of activation of conditionally activated molecules

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Overview

Conditionally activated molecules are designed to deliver a targeted therapy or reduce the off-tumor activity by exploiting specific properties of the tumor micro-environment (TME), such as low pH or overexpression of specific proteases. These molecules are becoming increasingly present in clinical trials and are soon to reach the market. While most of the development focuses on the modality of activation of the molecules, **the interplay between these modalities and the PK properties of the molecule that ultimately lead to better efficacy with higher specificity remains elusive.**

Here, we aim to:

- to analyse the **interplay between the molecule half-life and activation kinetic;**
- show that there is a sweet spot within these properties which allows for the **best trade-off between molecule efficacy and locality of action.**

3-compartment model for PKPD simulations of conditional molecules

- Assumed molecules conditional by protease unmasking with PKPD properties same as [1]. (see Fig. 1)
- Only irreversible unmasking. Mask assumed otherwise “perfect”, i.e. no residual binding to target.
- IV administration in central compartment. Distribution occurs in a peripheral and tumor compartment (see Fig. 2).
- 10-fold increase in unmasking rate in tumor compared to the out of tumor rate κ (see Fig. 1).
- Base affinity, receptor expression and turnover rate remain unaffected by the properties of the molecules..

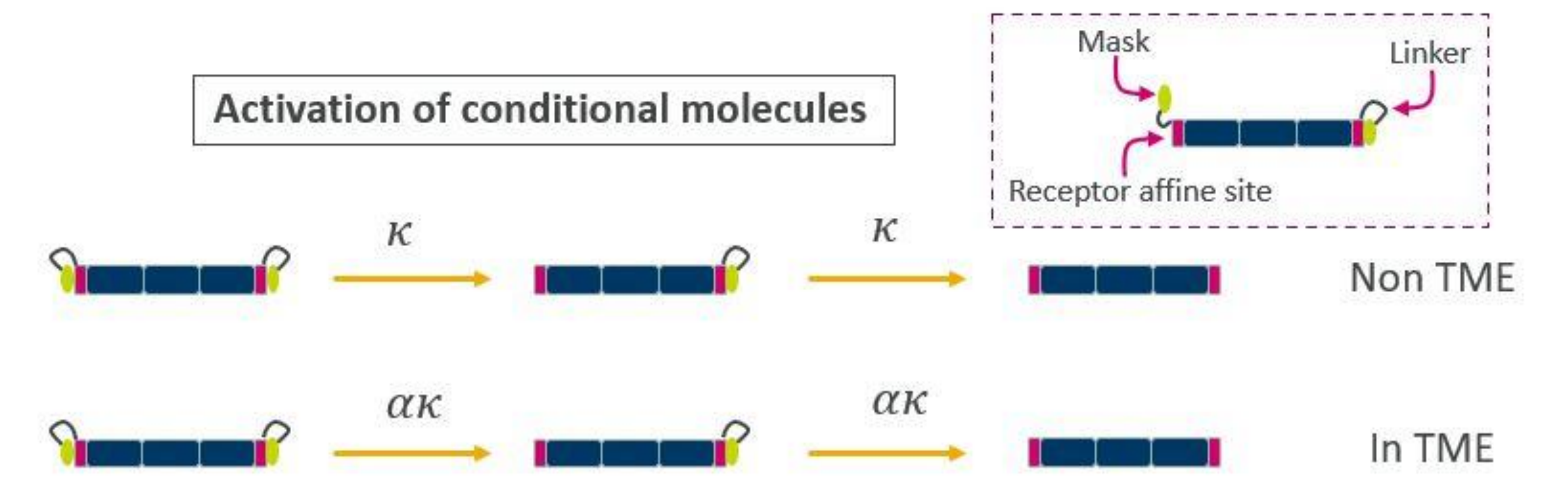


Figure 1: Schematic showing the mechanism of activation of the conditional molecules considered in this work.

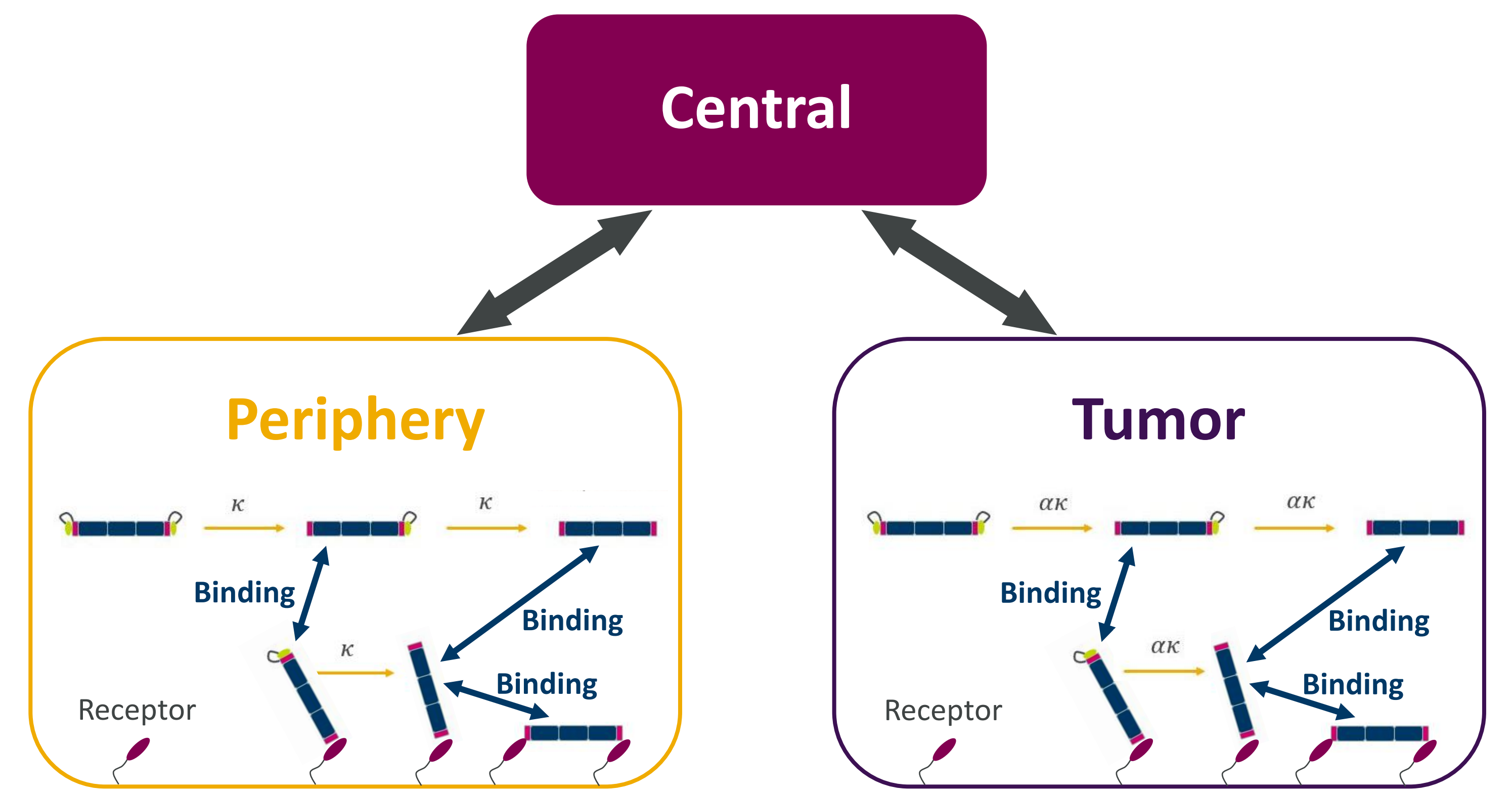


Figure 2: Schematic of the 3-compartment model detailing the PK and local activation kinetics.

- Efficacy** is measured by **receptor occupancy (RO)** in tumor.
- Locality of action** is measured by the **ratio between the RO in tumor and the RO in periphery.**
- All data used is based on a generic immune-checkpoint inhibitor (ICI) conditional molecule but the analysis is extendable independently of the specific mode of action.

Fast PK vs Fast activation kinetics

For a selected dose schedule and amount, we study the change in occupancy and specificity as a function of the molecule half-life and dynamics of activation.

- fast activation and a long half-life** are ideal for **maximizing target occupancy.**
- short half-life with a slow activation** are best for **improved locality of action.**
- This trend is maintained independent of the dose amount and the same result can be extended for different dosing schedules as well.

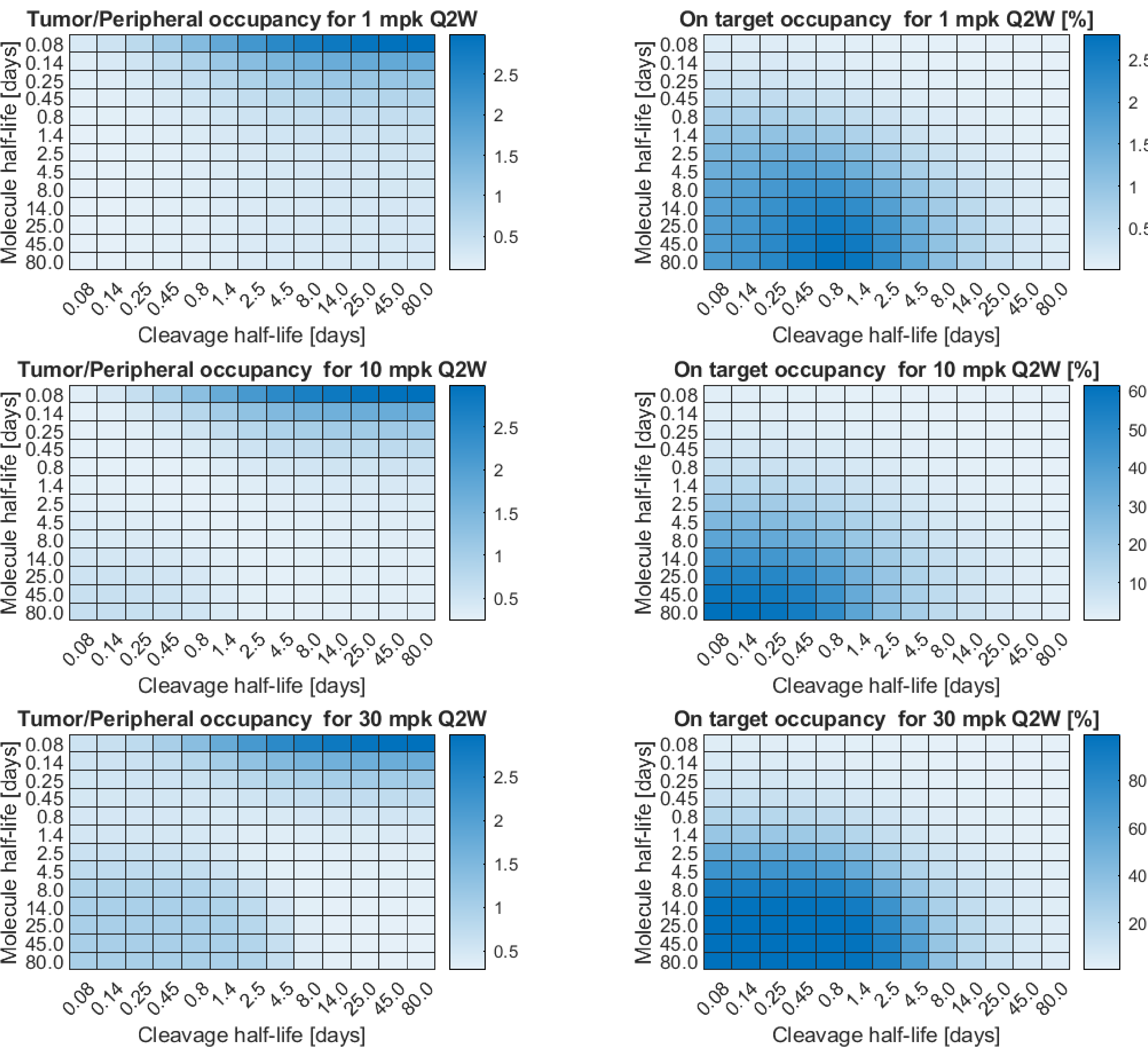


Figure 3: Contour plots showing the specificity and efficacy of the conditional molecules as a function of the molecule half-life and cleavage rate for dose ranges 1, 10, 30 mpk for Q2W.

- Fast activation rate** entails that all the **molecules** are in their active state and therefore can **occupy all the receptors but indiscriminately.**
- Since the activation rate in the tumor is higher than off-tumor, **short half-life molecules** tend to **activate mostly in the tumor and are cleared before they can travel to the rest of the body**, leading to high specificity.
- However, since this differential in activation requires a relatively low activation rate, most molecules remain inactive and thus the efficacy is low.

Concluding thoughts

- Here, we have shown the interplay between the mechanism of activation and the PK of conditionally activated molecules using a simple 3-compartment PKPD model.
- The simulated results suggest that maximizing molecule **efficacy requires slow clearance with fast activation while the polar opposite molecule properties are required to maximize specificity of action.**
- Efficacy is obtained not only by the receptor occupancy but also by the potency of the molecule. Therefore, this simple framework suggests that **very potent molecules should be designed as short half-life with a moderate to slow activation rate.** On the other hand,. **less potent molecules that require higher occupancies should ideally be designed with a moderate to long half-life and a fast activation mechanism**

References

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