

A Modular PBPK-QSP Platform in Julia for Optimizing the Therapeutic Window of Antibody-Drug Conjugates: ADC *In Silico* Design Engine (AIDE)

Yuezhe Li, Jimena Davis, Timothy Knab, Cole Zmurchok, and Daniel C. Kirouac
Metrum Research Group, Boston, MA, USA

Objectives

Antibody-drug conjugates (ADCs) are a rapidly evolving class of oncology therapeutics designed to expand the therapeutic index of potent cytotoxic payloads by leveraging the specificity of monoclonal antibodies. Despite clinical successes, many ADC candidates fail in late-stage development due to dose-limiting toxicities or insufficient efficacy. To support preclinical evaluation and de-risk ADC development, a modular, customizable PBPK-QSP platform using the open-source Julia [1] package **ModelingToolkit.jl** [2] was developed. This platform integrates a whole-body PBPK submodel to characterize ADC and payload biodistribution with a QSP submodel designed to predict both potential off-target toxicities and anti-tumor efficacy.

Methods

Model structure: A modular PBPK-QSP platform for ADCs was developed in Julia using **ModelingToolkit.jl** by integrating a whole-body PBPK model with a tumor QSP model through a mechanistic ADC tumor-penetration module. Systemic ADC disposition was characterized using a published PBPK framework [3]. The model accounted for ADC distribution into tissues through FcRn-mediated and FcRn-independent endothelial transport. ADC exchange between the systemic circulation and tumor was described using vascular and surface exchange mechanisms [4]. Within tissues and tumor, ADCs were transported into the interstitial space and subsequently internalized through receptor-mediated uptake [5]. Intracellular ADC degradation released the cytotoxic payload. These free payload molecules in plasma and non-tumoral tissues contributed to off-target toxicities, while those in tumor contributed to tumor cell killing.

Results

Does the model predict clinical PK of ADC and free-payload?

Cyno-to-human translation of ADC PK: The platform PBPK model captured ADC PK in cynomolgus macaques and translated to human systemic exposure for T-DM1 and T-DXd.

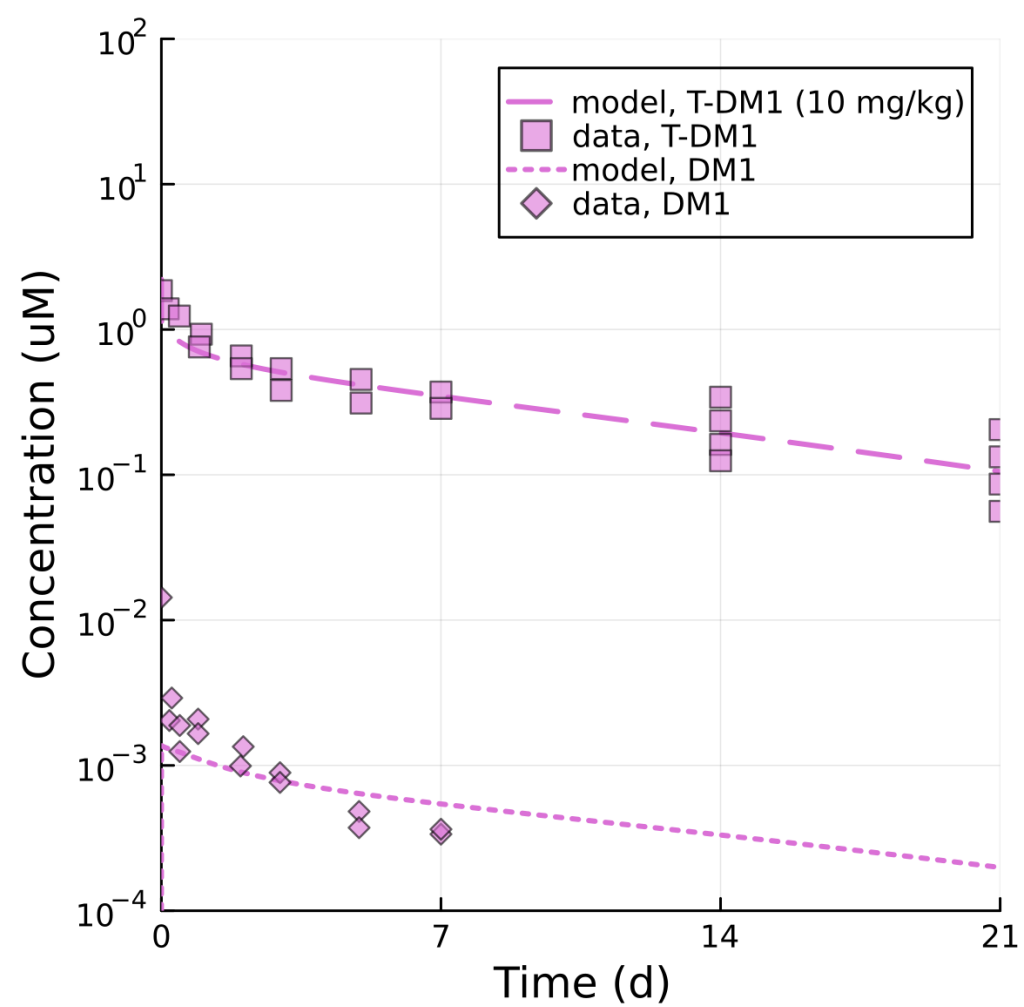


Figure 2A. T-DM1 plasma PK, cynomolgus macaque (data source [6])

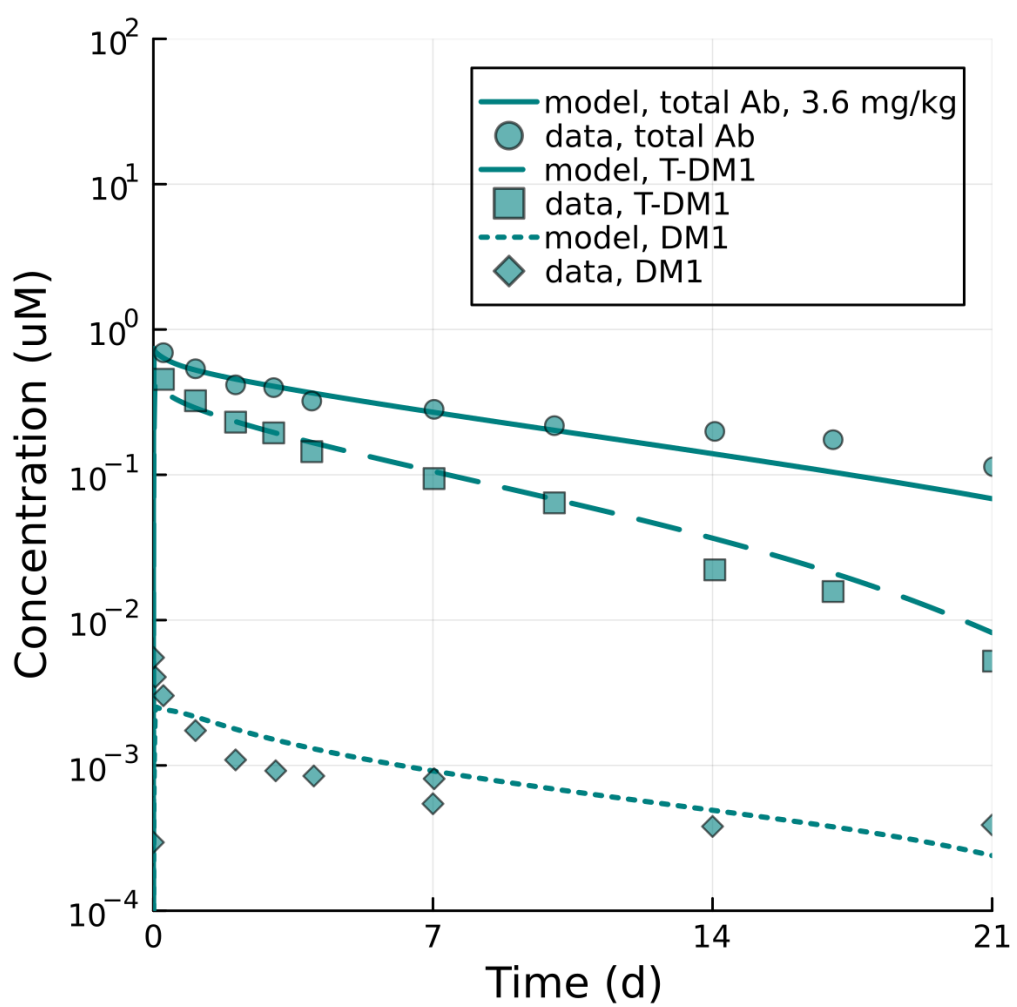


Figure 2B. T-DM1 plasma PK, human (data source [7])

PBPK backbone generalizes across ADCs with the same payload: DXd-related parameters calibrated to T-DXd were applied without re-estimation to Dato-DXd and I-DXd, capturing observed plasma PK profiles.

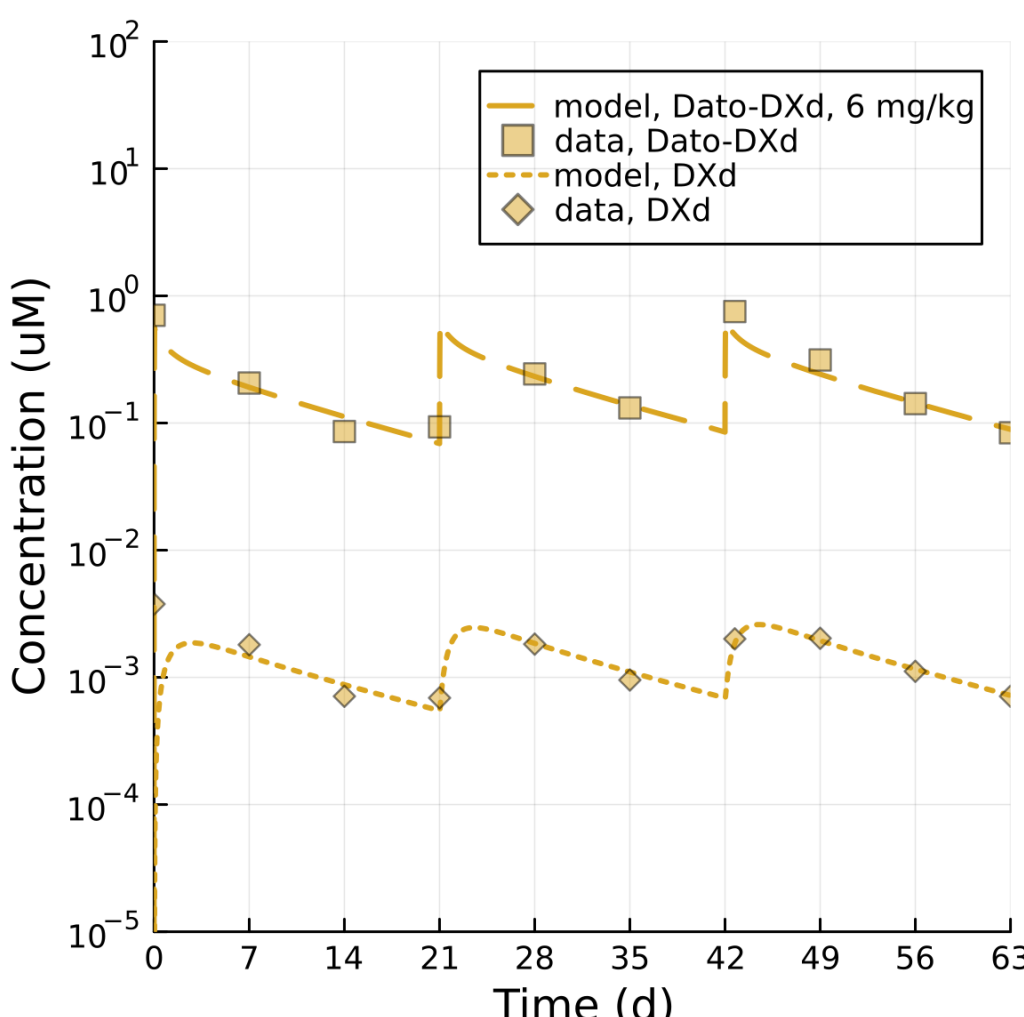


Figure 3A. Dato-DXd plasma PK, human (data source [10])

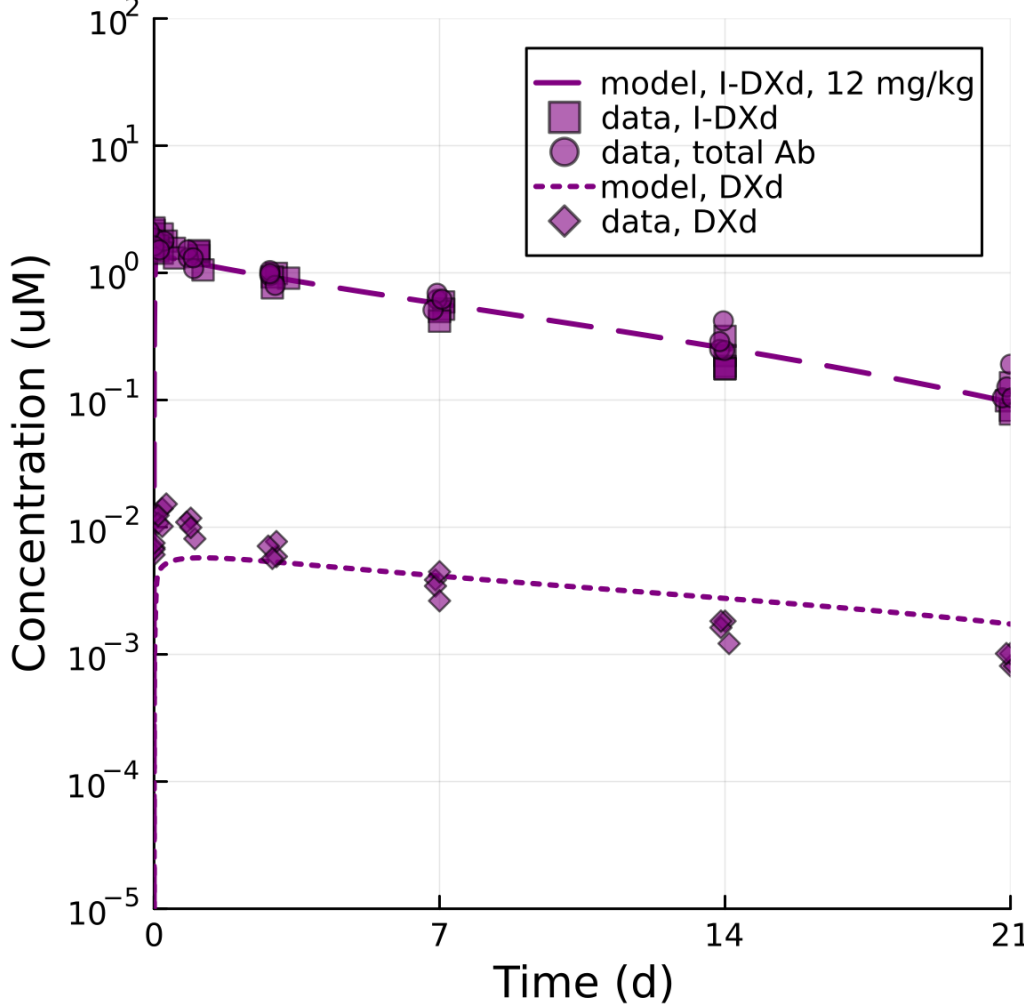


Figure 3B. I-DXd plasma PK, human (data source [11])

Where does the ADC and free-payload distribute?

ADC biodistribution: The platform PBPK model predicted dose-dependent whole-body distribution of T-DM1 across tissues.

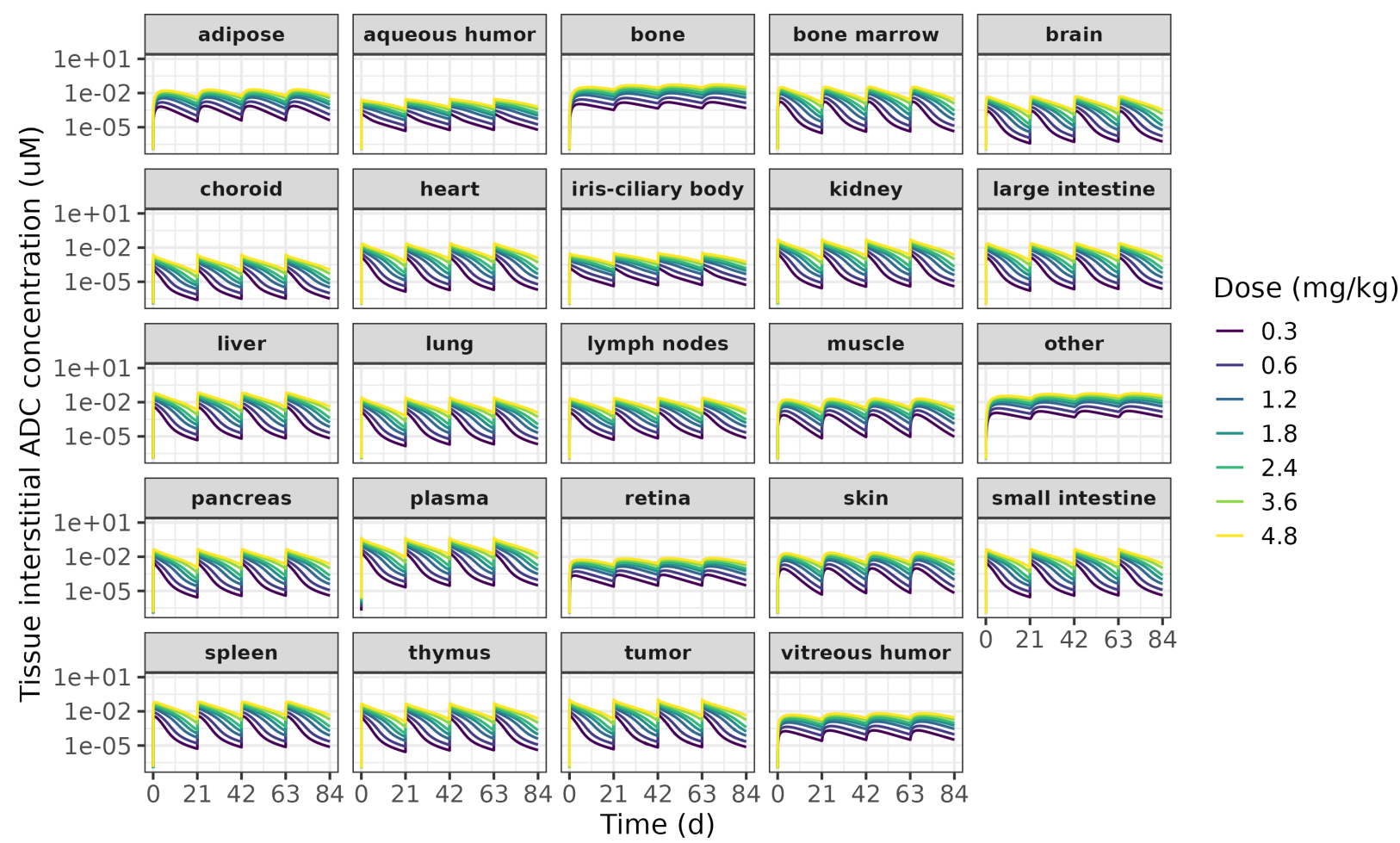


Figure 4. Predicted T-DM1 distribution across the whole body

Mechanistic prediction of liver payload exposure: The model predicted higher free payload concentrations in liver endothelial cells for T-DM1 than T-DXd at both approved and DAR-adjusted equivalent doses, consistent with the observed difference in hepatotoxicity [12].

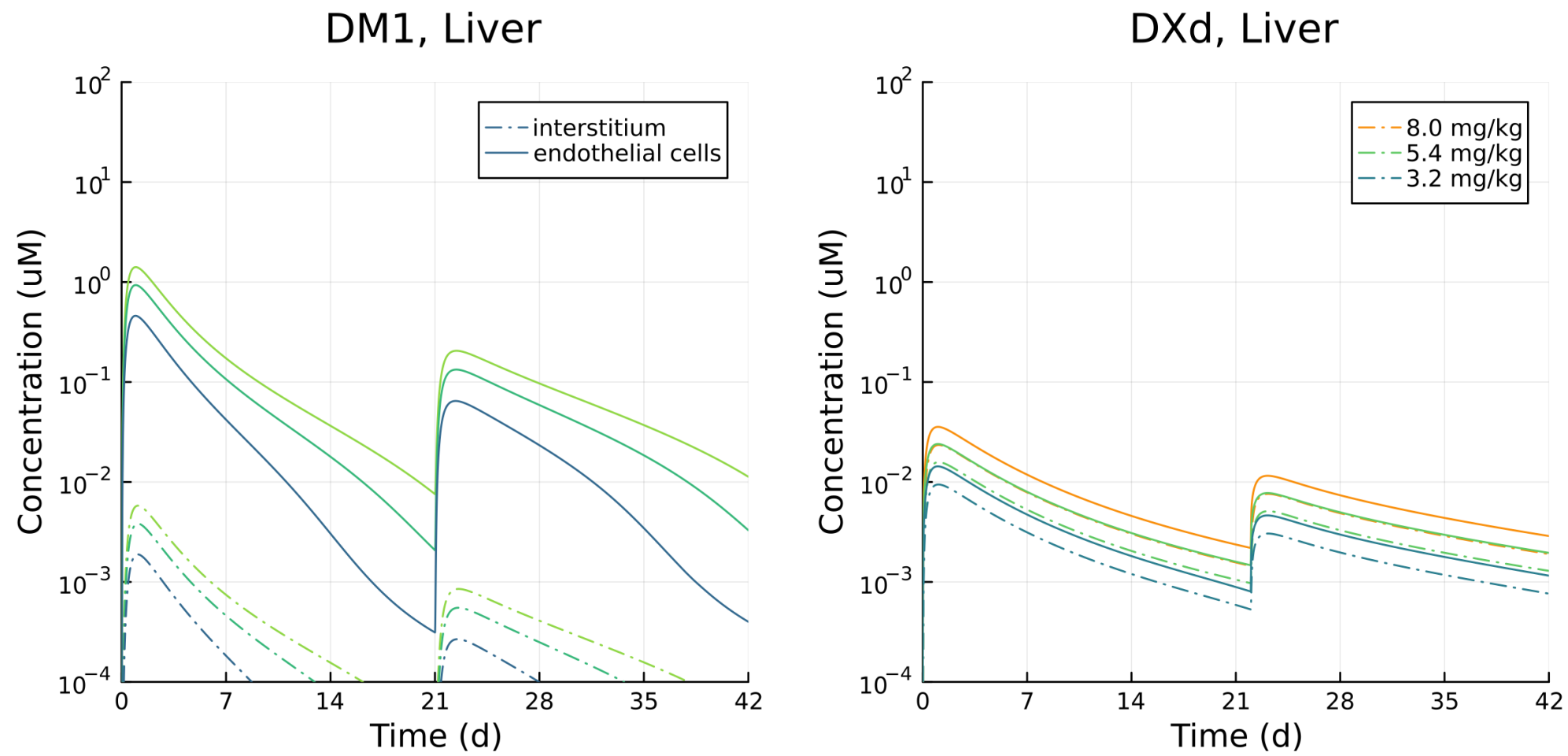


Figure 5A. Predicted DM1 exposure in liver Figure 5B. Predicted DXd exposure in liver

What ADC properties affect the therapeutic window?

Faster payload diffusion widens the therapeutic window: Increasing payload diffusion decreases liver endothelial exposure while enhancing tumor exposure, resulting in a wider predicted therapeutic window.

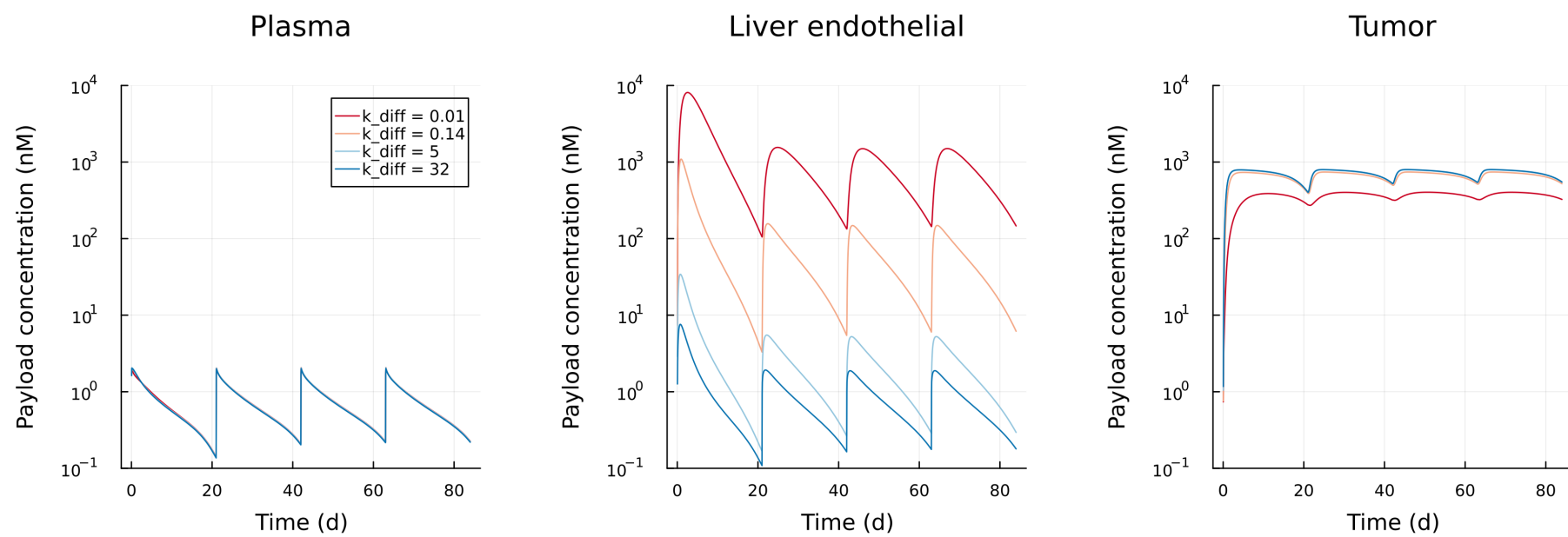


Figure 6A. Effect of payload diffusion on systemic, tissue, and tumor exposure. Predicted free payload concentrations in plasma, liver endothelial cells, and tumor at increasing diffusion rates. Higher diffusion rates shift payload exposure toward the tumor while reducing exposure in liver endothelial cells.

Linker stability shapes the therapeutic window: Faster payload deconjugation, reflecting reduced linker stability, decreases liver and tumor payload accumulation and widens predicted therapeutic window.

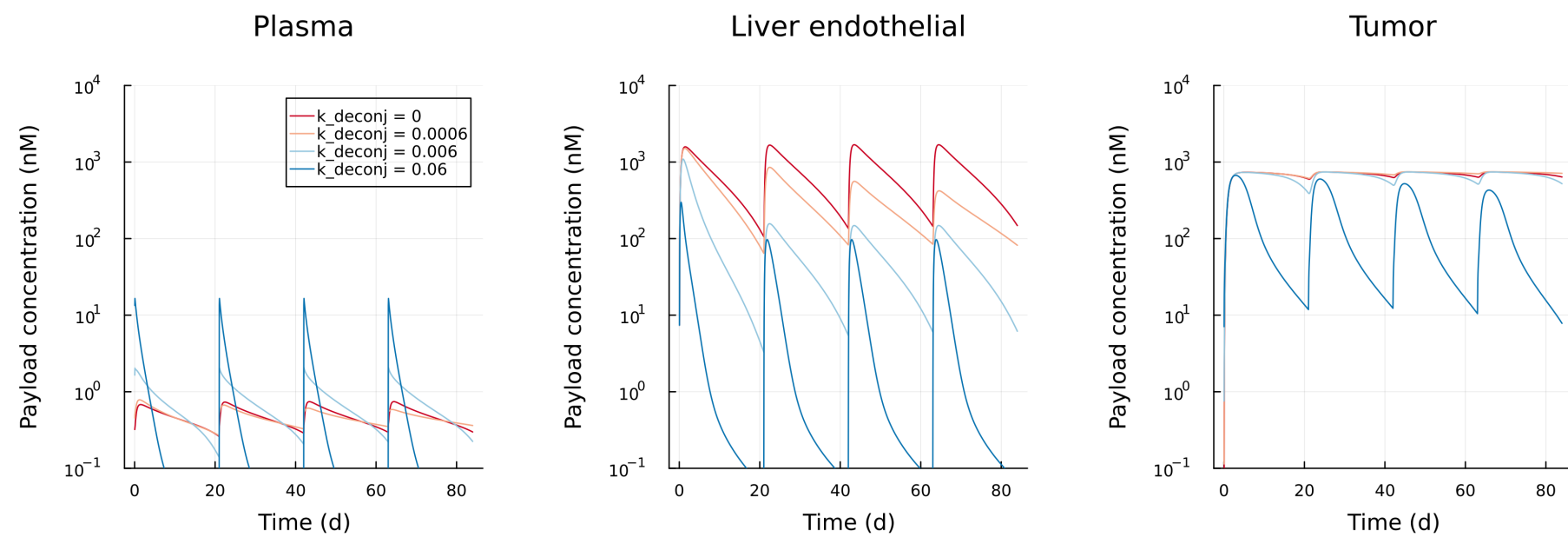


Figure 7A. Effect of payload deconjugation rate on systemic, tissue, and tumor exposure. Predicted free payload concentrations in plasma, liver endothelial cells, and tumor at increasing deconjugation rates. Faster deconjugation reduces payload accumulation in liver and tumor.

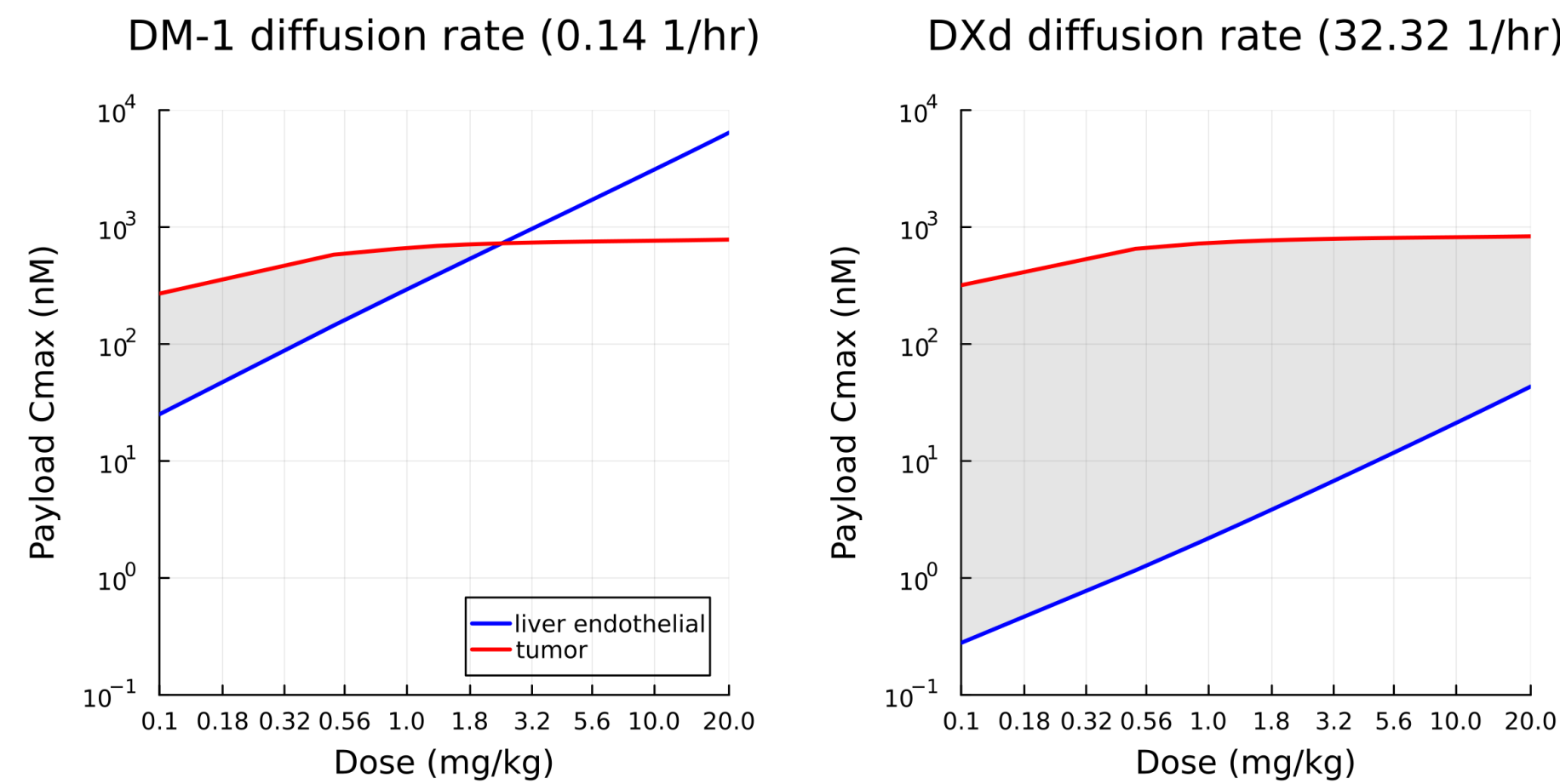


Figure 6B. Faster payload diffusion widens the predicted therapeutic window. Predicted free payload Cmax in liver endothelial cells (blue) and tumor (red) for DM1 and DXd diffusion rates [5]. Shading indicates the separation between tumor and liver endothelial exposure. Faster DXd diffusion decreases liver endothelial exposure while increasing tumor exposure, widening the separation between predicted toxicity- and efficacy-relevant exposures.

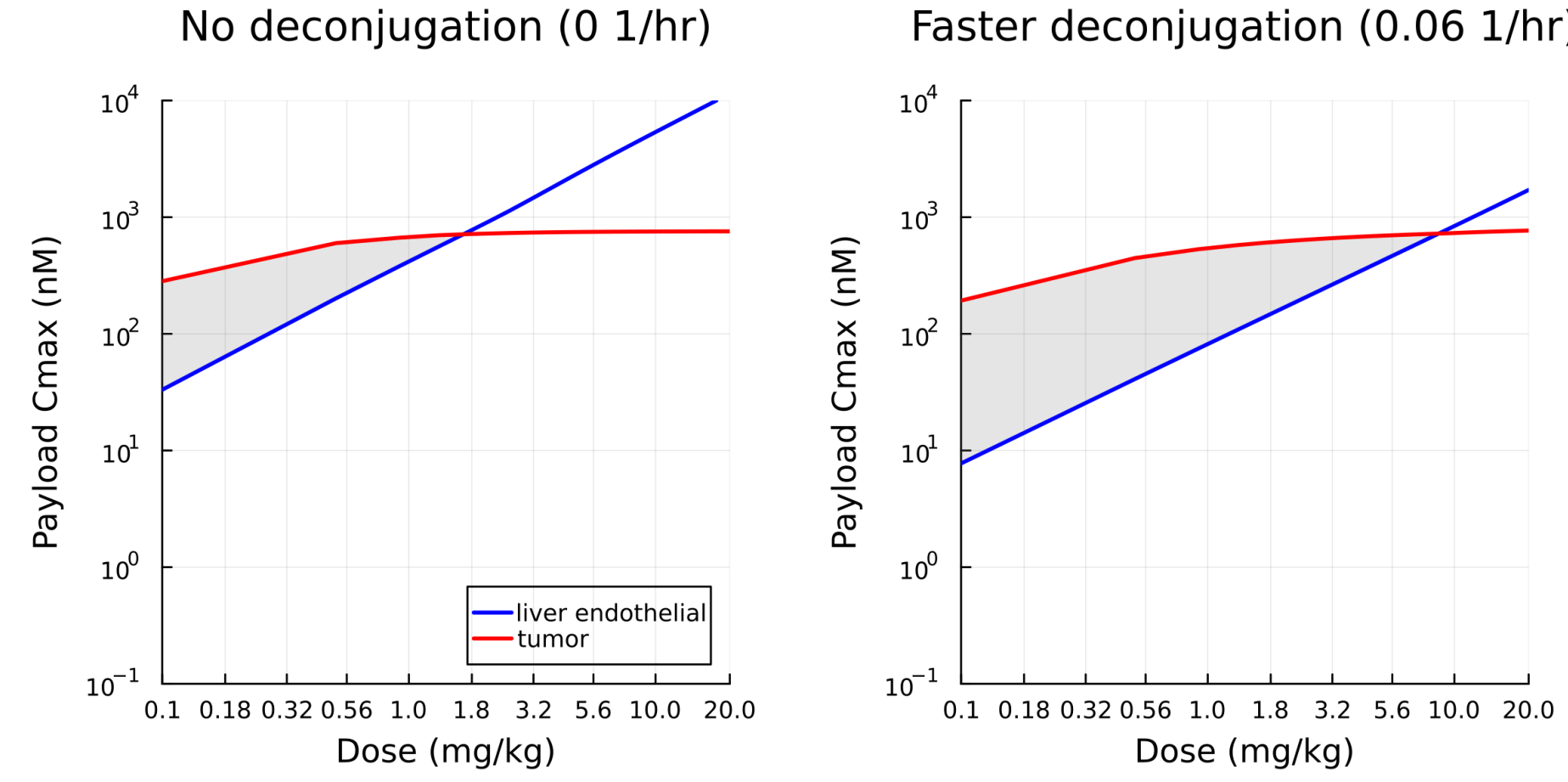


Figure 7B. Faster payload deconjugation widens the predicted therapeutic window. Predicted free payload Cmax in liver endothelial cells (blue) and tumor (red) with no deconjugation versus faster deconjugation. Shading highlights the exposure differences between scenarios. Faster deconjugation reduces payload accumulation and increases the separation between toxicity- and efficacy-relevant exposures.

References

- Bezanon *et al.* SIAM Rev. 59 (2017):65–98.
- Ma *et al.* ModelingToolkit (2021).
- Jones *et al.* CPT Pharmacometrics Syst. Pharmacol. 8 (2019):738–747.
- Singh *et al.* AAPS J. 18 (2016):861–875.
- Scheuher *et al.* J. Pharmacokinet. Pharmacodyn. 51 (2024):429–447.
- US FDA. Kadcyla BLA 125427 Review (2013).
- Girish *et al.* Cancer Chemother. Pharmacol. 69 (2012):1229–1240.
- Nakada T. Transl. Reg. Sci. 3 (2021):65–71.
- Doi *et al.* Lancet Oncol. 18 (2017):1512–1522.
- Hong *et al.* CPT Pharmacometrics Syst. Pharmacol. 14 (2025):2149–2160.
- Tran *et al.* ACCP Annual Meeting Poster (2024).
- Dong *et al.* Sci. Rep. 15 (2025):28790.

MetrumRG Publications/Posters

Conclusions: A predictive, mechanism-based platform model to support ADC design

- Predictive:** Captured ADC PK across species and molecules, including cyno-to-human translation for T-DM1 and T-DXd and plasma PK for Dato-DXd and I-DXd.
- Mechanistic:** Characterized ADC biodistribution; predicted higher liver endothelial payload exposure for T-DM1 than T-DXd, aligning with clinical data.
- Design-relevant:** Payload diffusion and linker stability produced distinct exposure-response tradeoffs, illustrating how design parameters shift the efficacy-toxicity balance.

Summary: The modular PBPK-QSP platform provides a mechanistic framework connecting ADC design to PK, tissue exposure, efficacy, and toxicity to support candidate selection and optimization.