

PBPK modeling approach to study the impact of lymph flow on biodistribution of therapeutic antibodies



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Introduction

Tissue specific blood flows (Q_{tis}) and lymph flows (L_{tis}) play a major role for the tissue distribution of therapeutic antibodies and are key parameters in physiologically-based pharmacokinetic (PBPK) models (1). L_{tis} are currently empirically fixed as percentage of Q_{tis} (2 and 4% for visceral and non-visceral organs, respectively) (2-4). Based on the PBPK model by Fronton et al. (5), we (i) characterized the impact of L_{tis} on the pharmacokinetics of monoclonal antibodies (mAbs); (ii) propose a range of probable L_{tis} values.

Methods:

Sensitivity analysis: Influence of L_{tis} alterations on mAb PK profiles was investigated by a sensitivity analysis implemented in MATLAB R2013b. The impact of L_{tis} on PK was evaluated (i) qualitatively by visual inspection of 3D plots of altered L_{tis} values, plasma and tissue mAb concentrations versus time; (ii) quantitatively with a gradient based scoring algorithm.

Log likelihood profiling: A probable range for L_{tis} values was defined using log-likelihood profiling (LLP) conducted in Monolix 4.3.3. L_{tis} values were sequentially altered and fixed and the model refitted to PK data after each alteration (3) to derive log-likelihood values (-2LL). A log-likelihood profile was generated for each tissue specific lymph flow. Derived and currently assumed L_{tis} values were compared.

Results: Qualitative assessment of impact of L_{tis} on mAb PK

Variations of L_{tis} in skin has an impact on PK of skin over the entire simulated timespan (21 days) whereas for liver solely early PK is affected (i.e. 48 first hours).

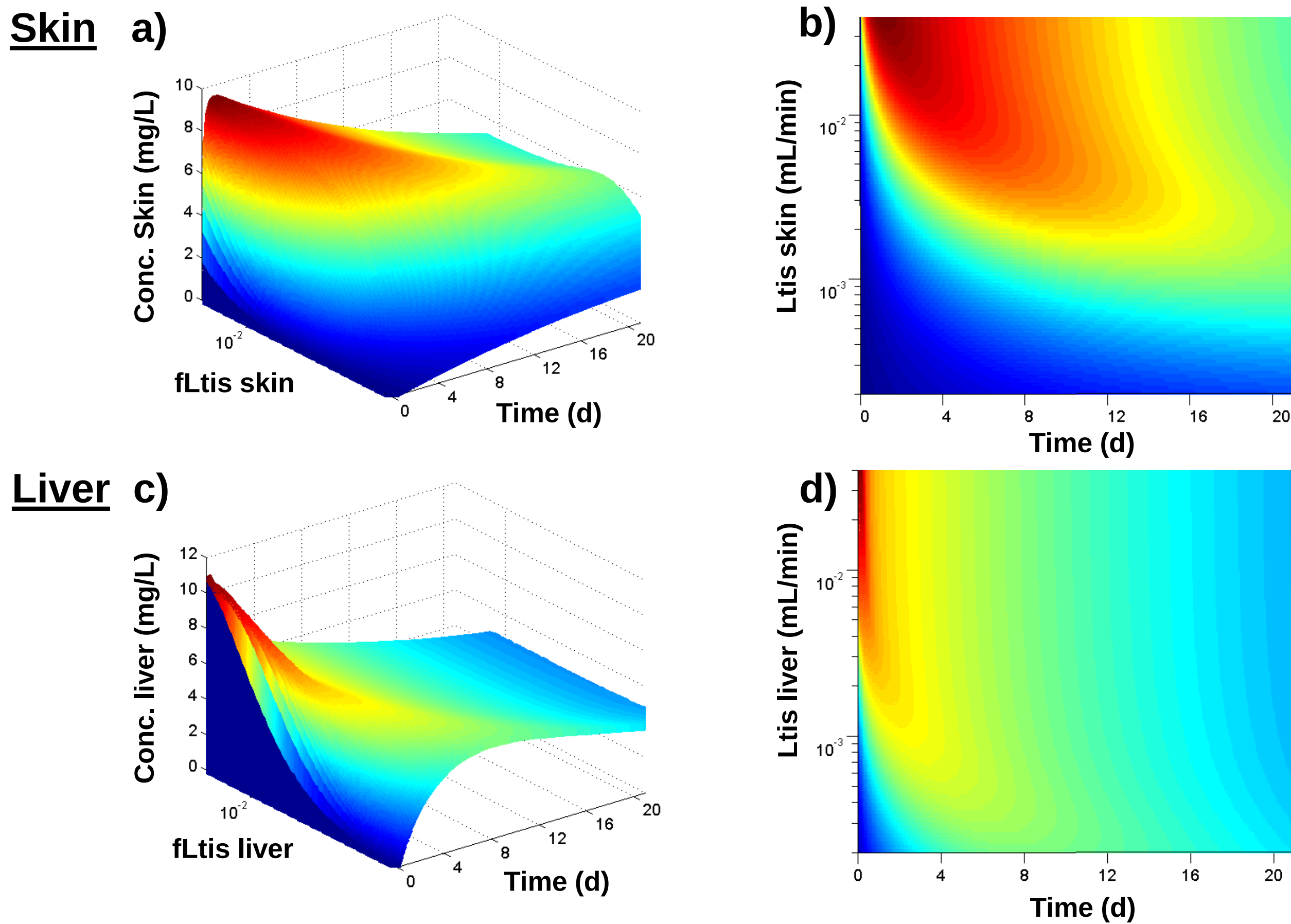


Figure 1: Impact of change of lymph flows on mAb concentration-time profile in the corresponding tissues. Simulations are based on the PBPK model from (5). Example is given for **a/b** skin, large/kinetically slow tissue and **c/d** liver, smaller/kinetically fast organ. Dark red indicates highest and dark blue lowest concentrations.

Results: Sensitivity score matrix

For each altered L_{tis} , PK profiles were simulated. Change in concentration corresponding to a specific L_{tis} alteration was derived at each time point as gradient $G(t_k, \Delta L_{tis}) = \frac{|\Delta Conc(t_k, \Delta L_{tis})|}{\Delta L_{tis}}$, with ΔL_{tis} the change in L_{tis} .

The sum of all gradients corresponding to a specific L_{tis} alteration affecting a specific PK output formed the entries into the sensitivity score matrix.

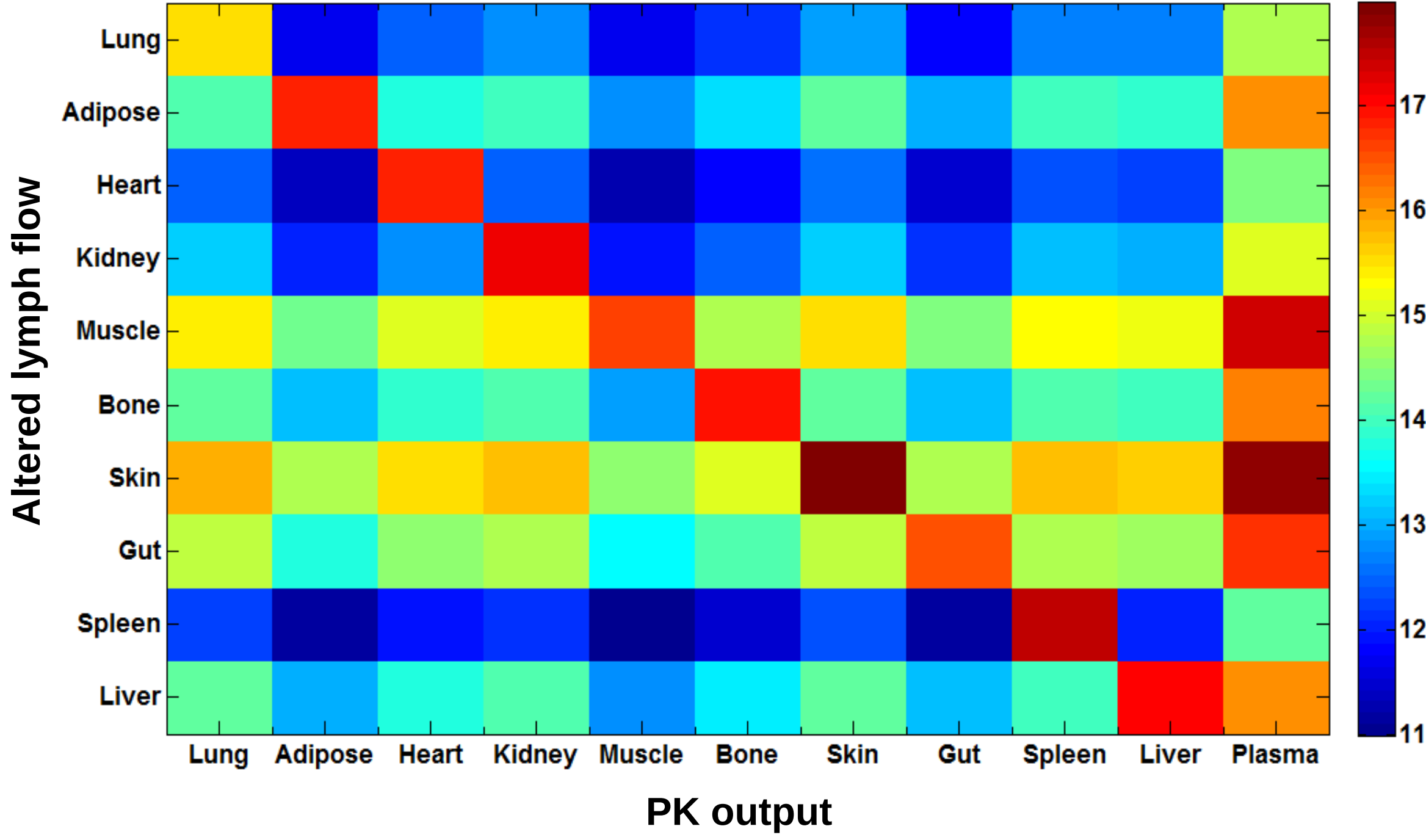


Figure 2: Heat map of the sensitivity score matrix displaying the impact that a tissue specific lymph flow has on the PK profile. Dark red indicating highest, dark blue lowest impact score.

Most impact was seen on the organ itself where L_{tis} was altered. Impact on PK in plasma and other tissues is mainly observed for skin and muscle, the largest organs.

Results: Log-likelihood profiling

L_{tis} were sequentially fixed to a range of values and the PBPK model was fitted to mAb 7E3 biodistribution data in mice (3). For each fixed L_{tis} , remaining lymph flows and partition coefficients were estimated. The -2LL value was derived and the log-likelihood profile was established accordingly.

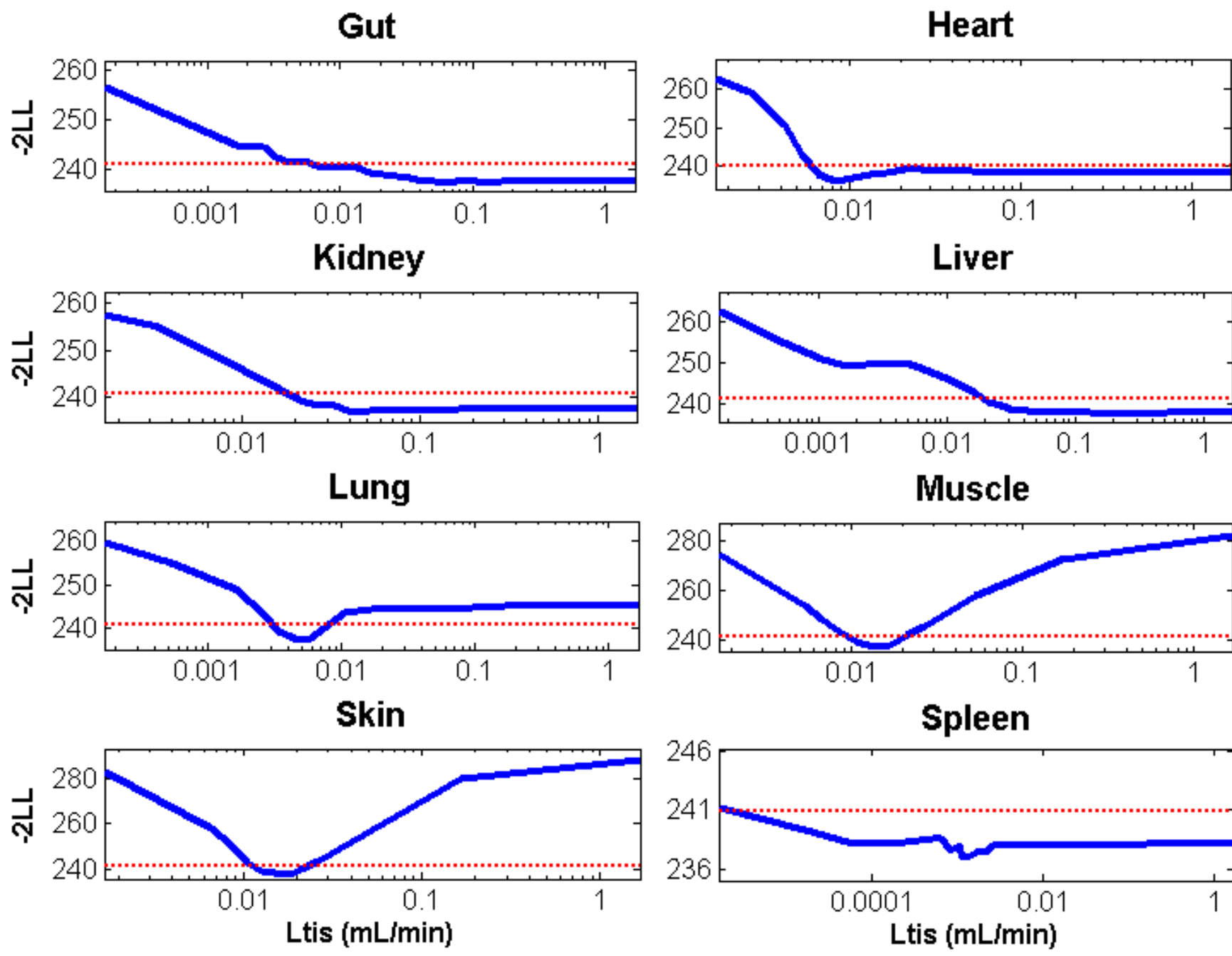


Figure 3: Log likelihood profile to derive the most probable tissue specific L_{tis} values. Red dashed line indicates the 95th percentile of the confidence interval around the L_{tis} value leading to the minimal -2LL value. This corresponds to an increase in -2LL of 3.84. L_{tis} values resulting in -2LL values higher than this threshold result in significantly worse fitting.

Results: Assumed vs. LLP derived lymph flow values

Tissue	Assumed L_{tis} (mL/min)	LLP derived L_{tis} (mL/min)
Gut	0.018	0.042 (>0.008)
Heart	0.011	0.008 (>0.005)
Kidney	0.032	0.042 (>0.017)
Liver	0.022	0.053 (>0.017)
Lung	0.175	0.005
Muscle	0.032	0.013
Skin	0.048	0.017
Spleen	0.001	0.0017 (>0.0000017)
-2LL	348	237

Table 1: Assumed and LLP derived L_{tis} values. -2LL denotes the log-likelihood value to assess the goodness of fit of the PBPK model to 7E3 mAb biodistribution data using corresponding L_{tis} values.

- Probable lymph flow values derived by log likelihood profiling for lung, muscle and skin are lower than currently assumed values in the PBPK model (2 and 4% of blood flow for visceral and non-visceral organs, respectively).

- Only broad ranges of L_{tis} values could be defined for kinetically-fast tissues (early T_{max}). Biodistribution data with earlier sampling times are required to define a narrower range.

- Typically assumed lymph flow values resulted in a significantly higher log-likelihood value than the newly derived parameter values when fixed and fitted to the data.

Conclusion

L_{tis} affect several aspects of mAb PK: lowering L_{tis} leads to lowering C_{max} and increasing T_{max} . The influence on the tissue itself is high while the impact on other organs is dampened by the interconnecting plasma compartment. This sensitivity analysis provides new insight into the potential impact of altered lymph flow on the PK profile in patients (e.g. due to immobility or inflammation).

Log-Likelihood profiling allowed us to define probable lymph flow values for lung, muscle and skin that drastically differ from currently assumed L_{tis} values in PBPK models for therapeutic antibodies and suggests lower L_{tis} values for big/slow tissues and higher L_{tis} values for small/fast tissues. However, LLP approach is currently restrained to some tissues due to lack of early time points in biodistribution data.

References

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