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Validation and refinement of the large molecule biodistribution model in PK-Sim.

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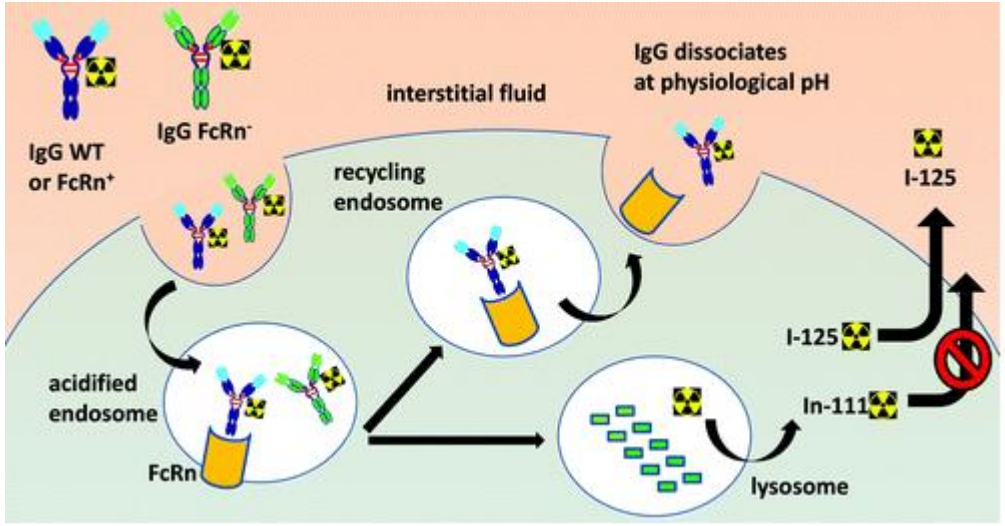
Outline

1. Opportunity
2. How we used it
3. What we found
4. What it means
5. What now?



Opportunity

- New radiolabeled large molecule biodistribution datasets are available in the literature with a wide range of modalities.
- The original large molecule publication paper included a limited number of molecules and modalities and only non-residualizing labels.
- The increasing number of large molecule modalities and their share in drug development grows the interest in the two-pore model and its validation.
- Combining residualizing and non-residualizing labels allow to refine the organ-specific catabolic clearances



Yip et al., mAbs 2014;6(3):689–696, Figure 4

How did we use this opportunity

- Reviewed the literature for radiolabeled biodistribution data for as many modalities as possible and digitized available date
- Limited the number of molecules per modality to prevent biased performance for mAbs
- Applied the default PK-Sim model for non-residualizing labels, and an extended model for residualizing labels
- Evaluated the model fits based on total error, GOF diagnostic plots and per tissue error calculations
- Compared the final model with alternative parameterizations

Modelling approach for the non-residualizing label model

- The default large molecule model
- Each molecule got its own MW, FcRn affinity start value (1.5 uM for Fc-containing modalities) and MW-dependent renal clearance as fraction of the GFR according to Li & Shah, *J Pharmacokinet Pharmacodyn* **46**, 305–318 (2019).
- For radiolabeled biodistribution studies, organ concentrations were multiplied with their densities to calculate volumetric concentrations, and lung density was set to 0.26 g/cm^3
- Estimated parameters: fraction interstitial and vascular, Kd FcRn, fraction of GFR, (dose)


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ORIGINAL PAPER

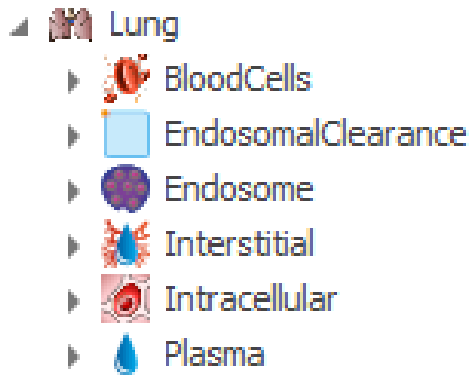
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A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim

Christoph Niederalt[1] · Lars Kuepfer[1] · Juri Solodenko[1] · Thomas Eissing[1] · Hans-Ulrich Siegmund[1] · Michael Block[1] · Stefan Willmann[2] · Jörg Lippert[2]

Modelling approach for the residualizing label model

- The same model and additions as for the non-residualizing label
- Addition of an EndosomalClearance compartment to all observed organs
- Reconnecting the endosome compartment to the organ-specific EndosomalClearance compartment
- Addition of first-order release from the Endosomal Clearance compartment
- Addition of a fraction of the EndosomalClearance compartment to the peripheral venous blood observer to represent blood residualisation
- Estimated parameters: fraction endosomal, Kd FcRn, fraction of GFR, (dose)



What did we find?

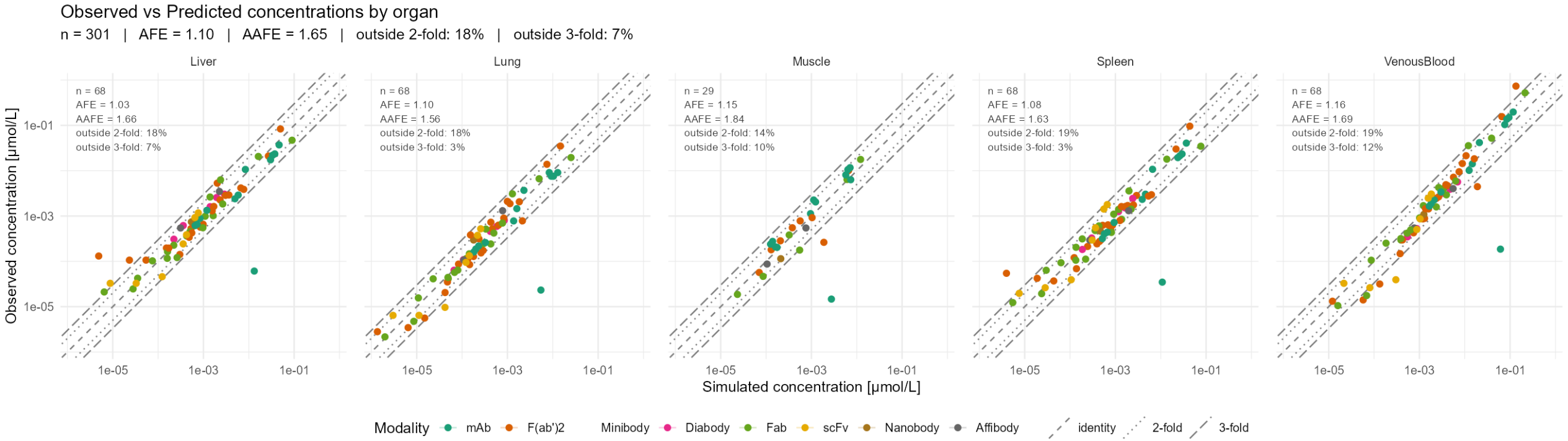
Lots of datasets

Modality	Residualizing	Nonresidualizing	Total
mAb	4	4	8
F(ab')2	3	5	8
Fab	3	4	7
Affibody	4	1	5
Nanobody	3	1	4
Diabody	1	1	2
Minibody	2	0	2
scFv	1	1	2

- Some datasets had only a single timepoint, the number of organs included varied significantly.
- Most data were available for blood, lung, muscle, spleen and liver.

What did we find?

The two-pore model performs well!



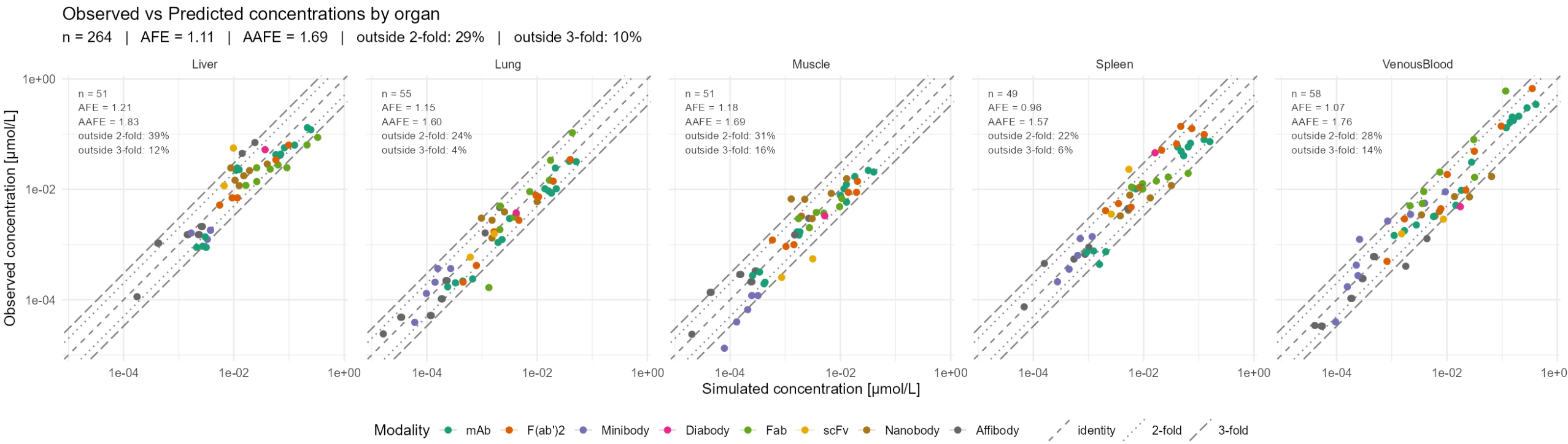
- RSE based on the covariance matrix estimate in MoBi <20% for all shared parameters and up to 250% for some of the individual Kd FcRn and GFR fraction estimates
- RSE of variation in parameter values after multistart with random start values that arrived at the lowest total error (8/10 runs) for all parameters below 5%

Tissue fractions, estimate ±95% CI (initial)

Organ	Vascular	Interstitial
Liver	0.172 ±0.094 (0.115)	0.132 ±0.062 (0.163)
Lung	0.408 ±0.093 (0.626)	0.075 ±0.125 (0.188)
Muscle	0.046 ±0.014 (0.026)	0.051 ±0.021 (0.120)
Spleen	0.136 ±0.120 (0.282)	0.123 ±0.084 (0.150)

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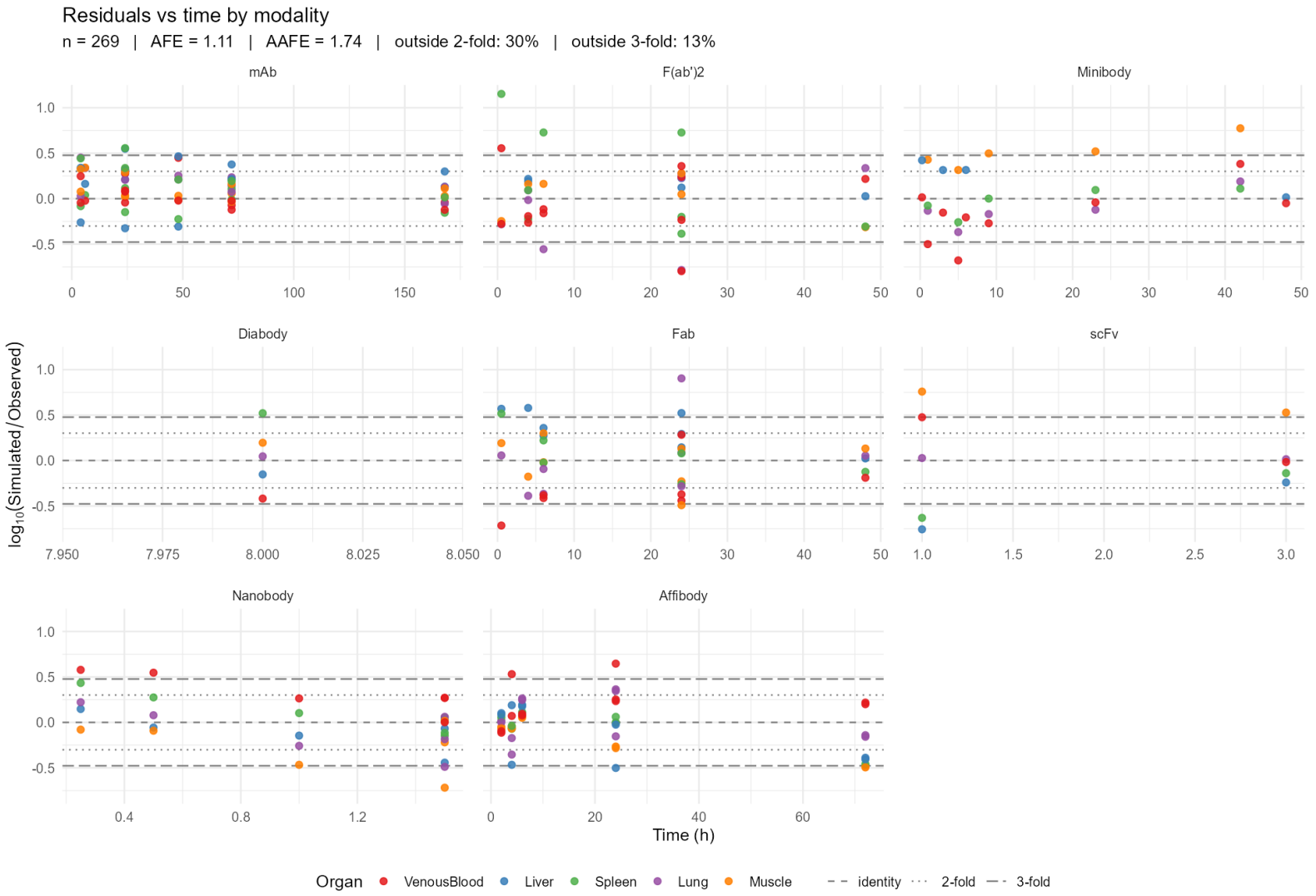
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Endosomal fractions, estimate ±95% CI (initial)

Organ	Endosomal
Liver	0.808 ±0.243 (0.200)
Lung	0.105 ±0.035 (0.200)
Muscle	0.317 ±0.105 (0.200)
Spleen	0.366 ±0.126 (0.200)

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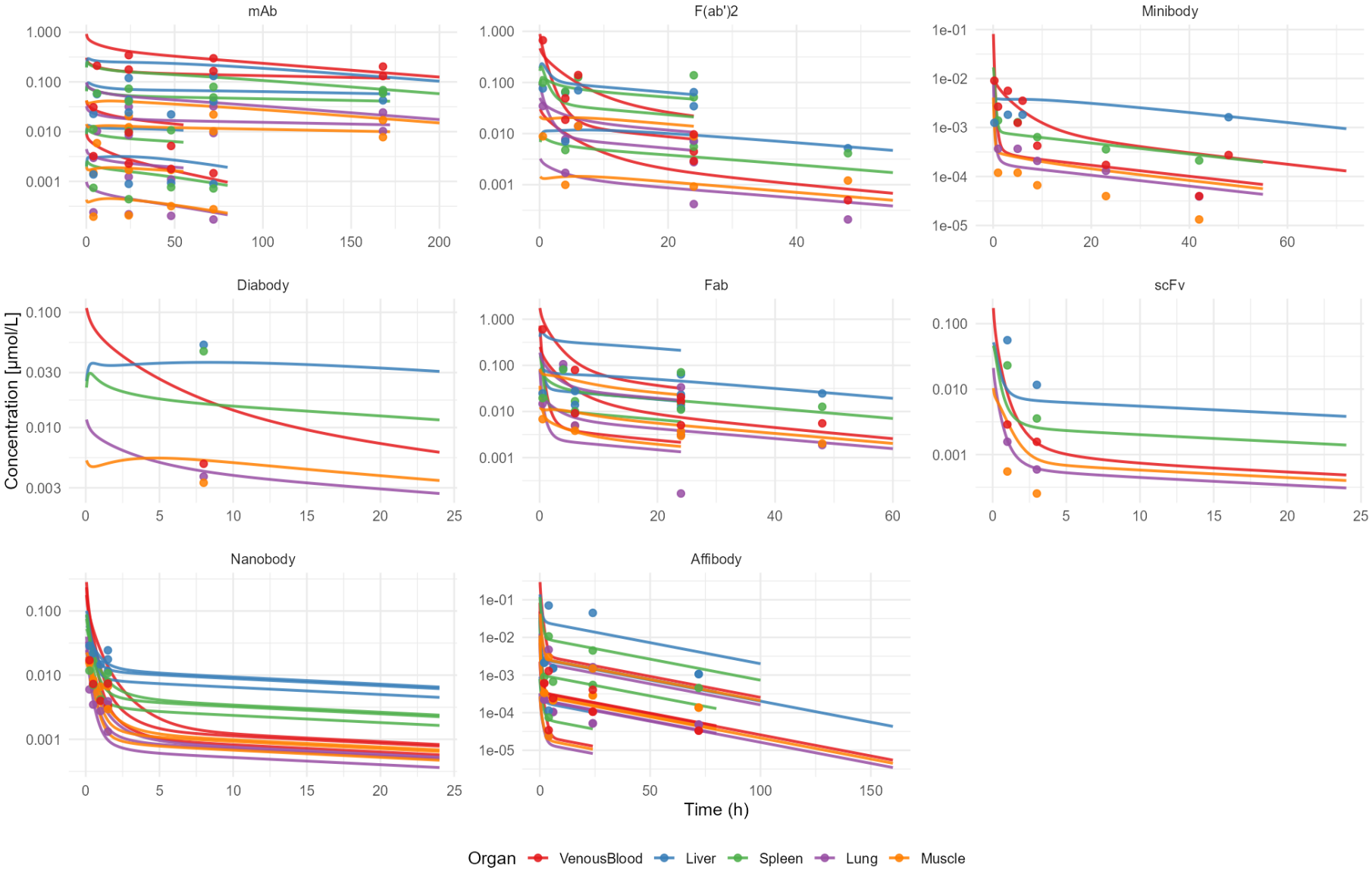
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What did we find?

Time profiles by modality

lines = simulated, points = observed

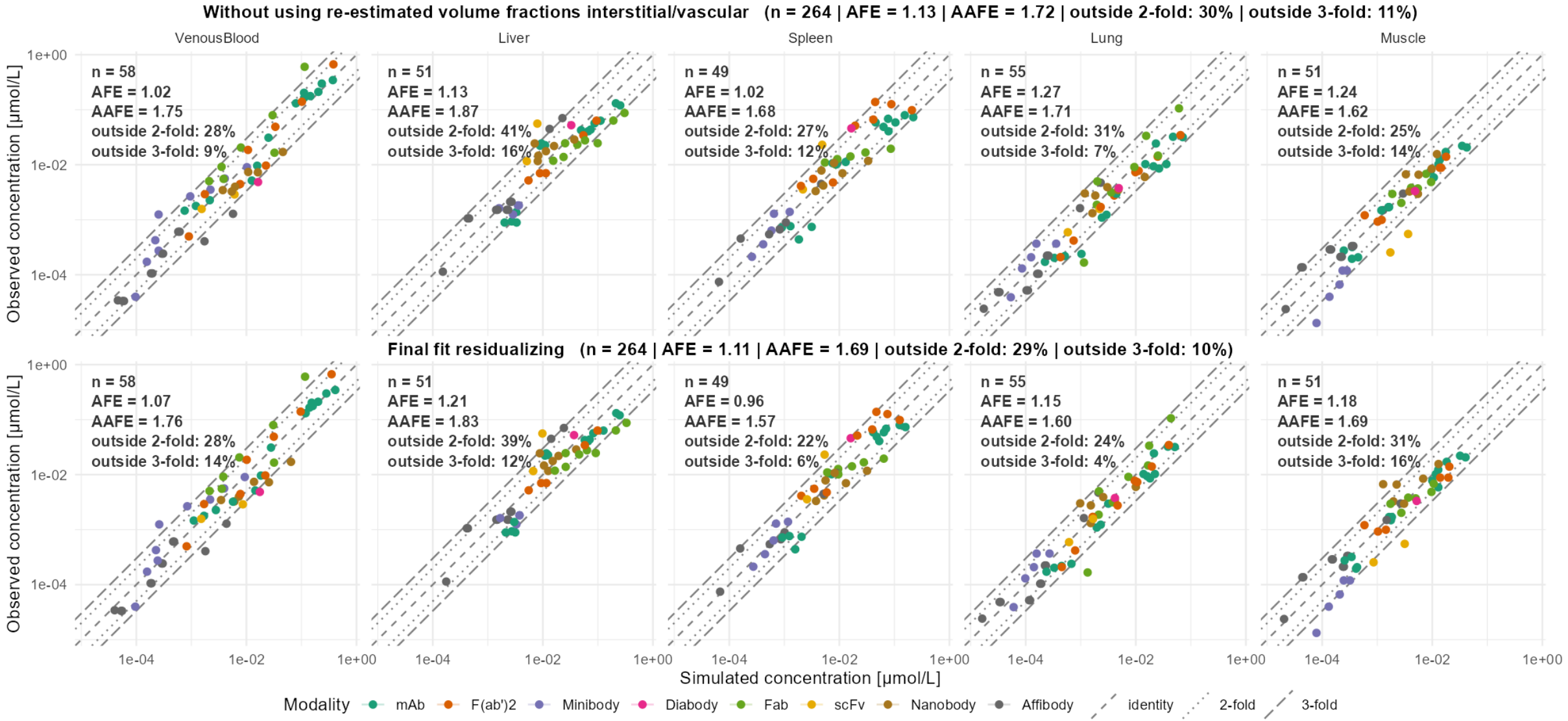


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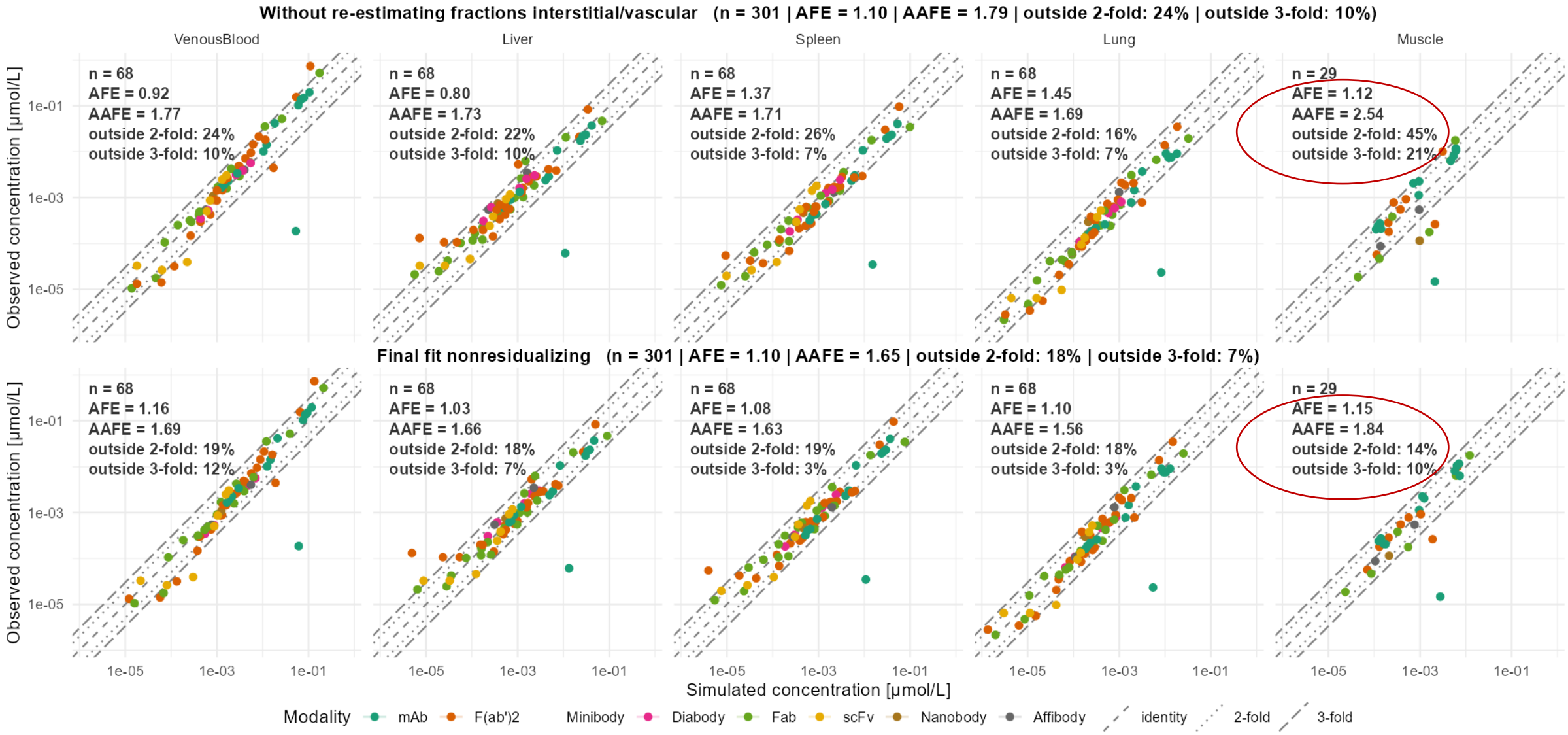
What did we find?

Is the re-estimation of vascular/interstitial fractions really needed?



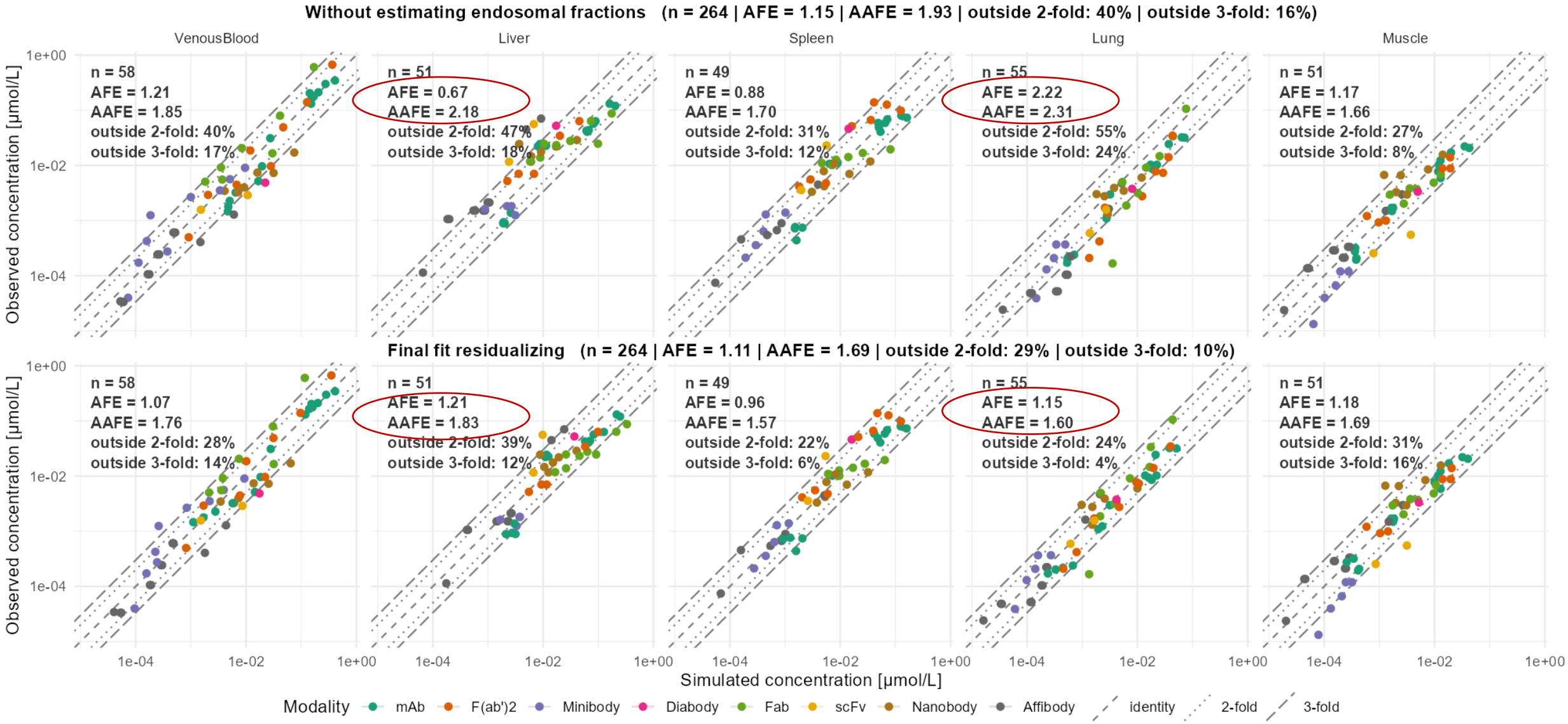
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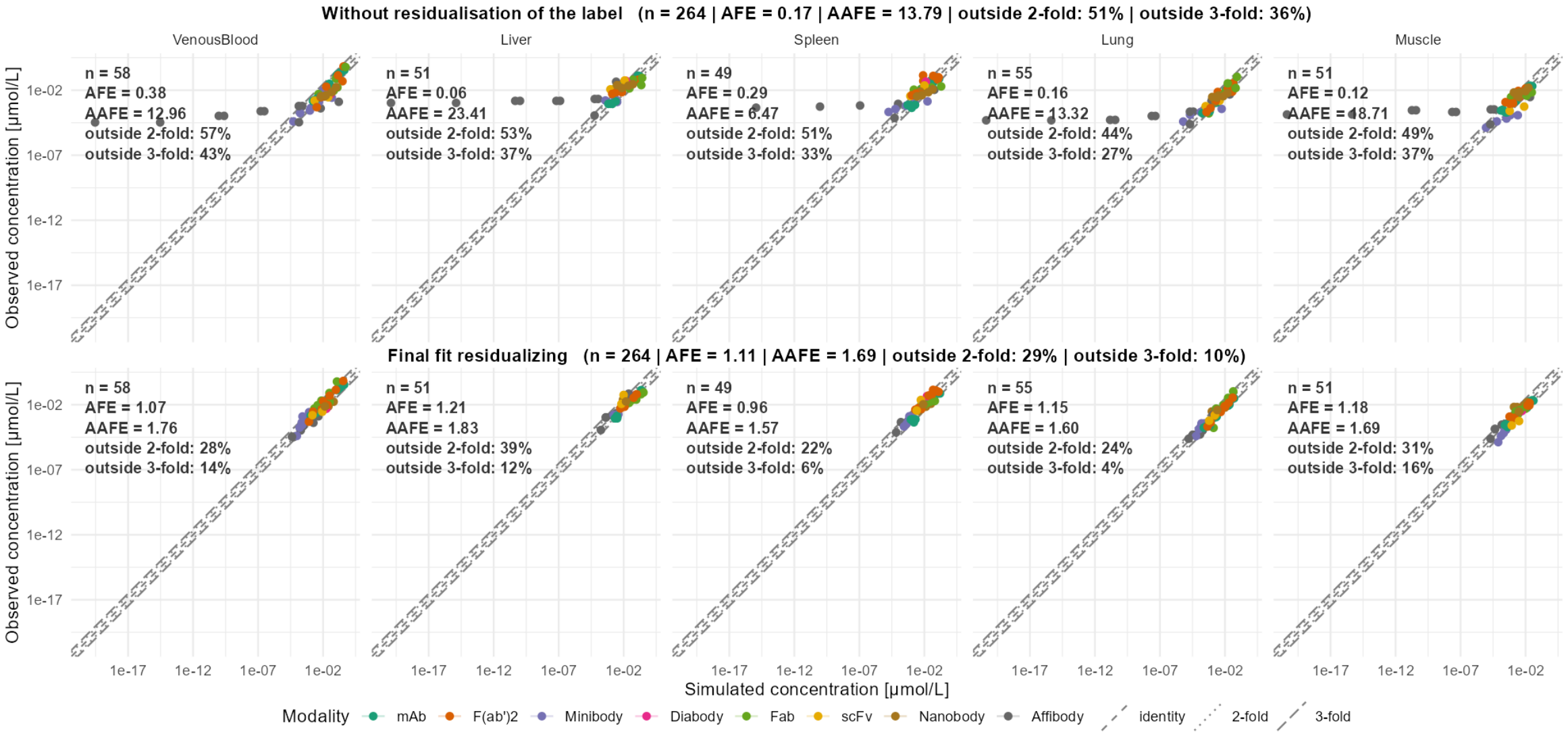
What did we find?

Do tissue-specific endosomal fractions improve the fit significantly?



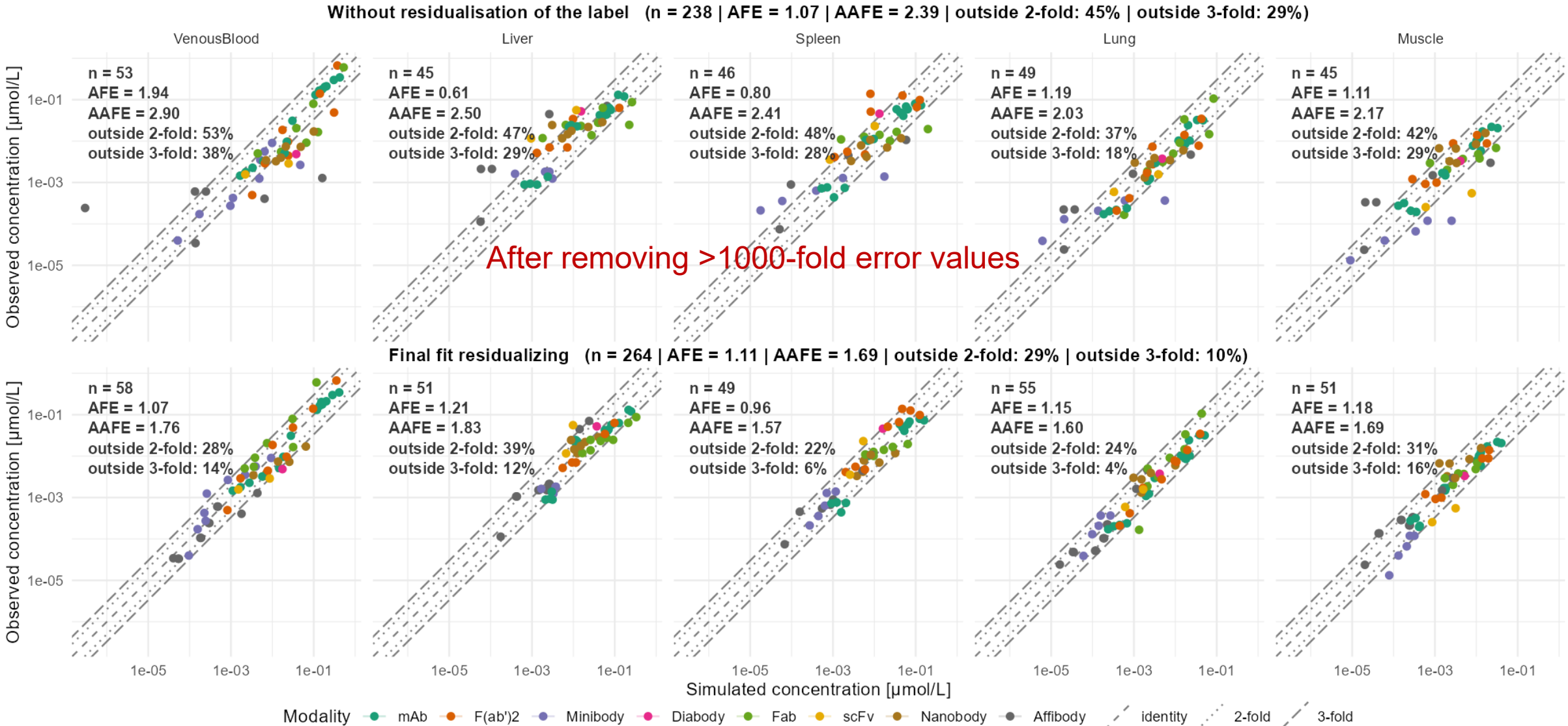
What did we find?

What is the impact of residualisation in the model?



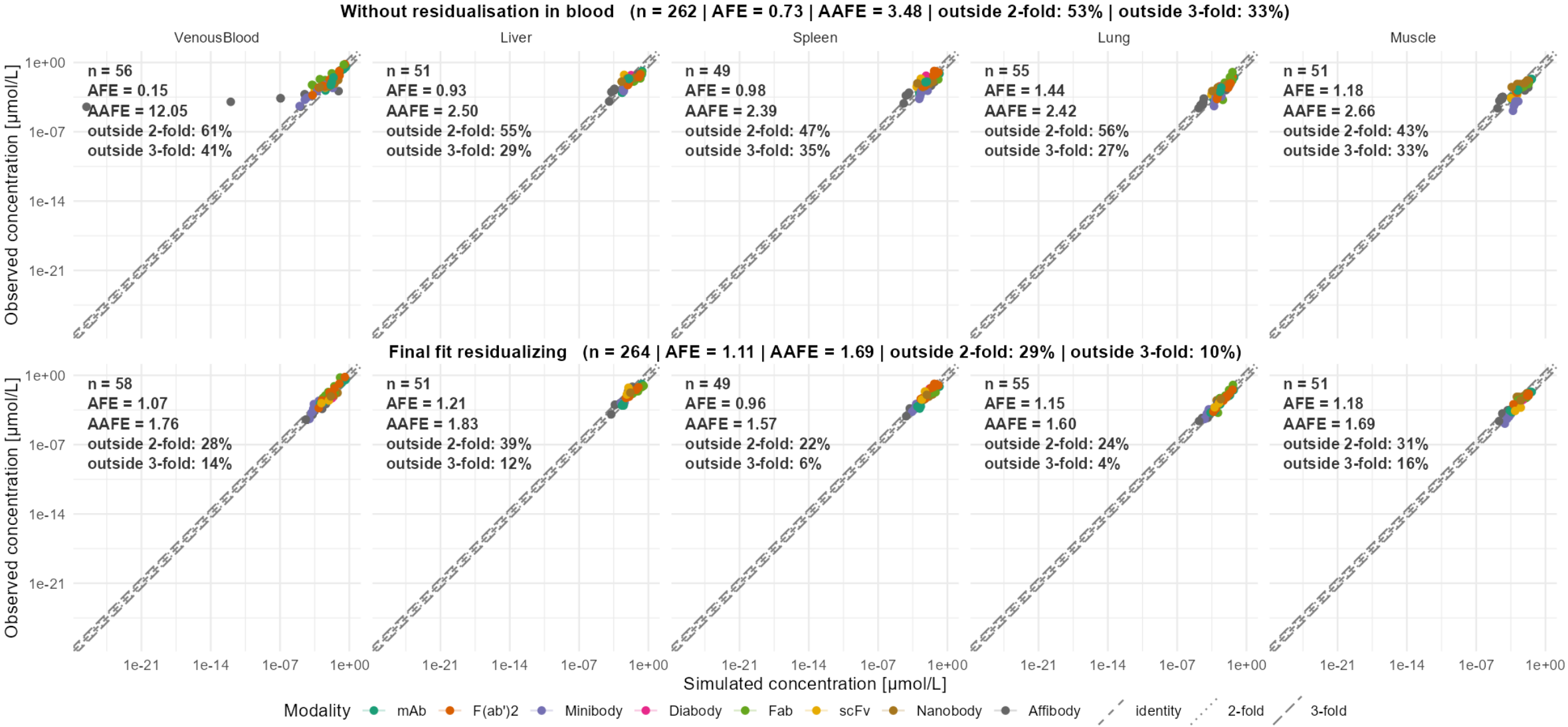
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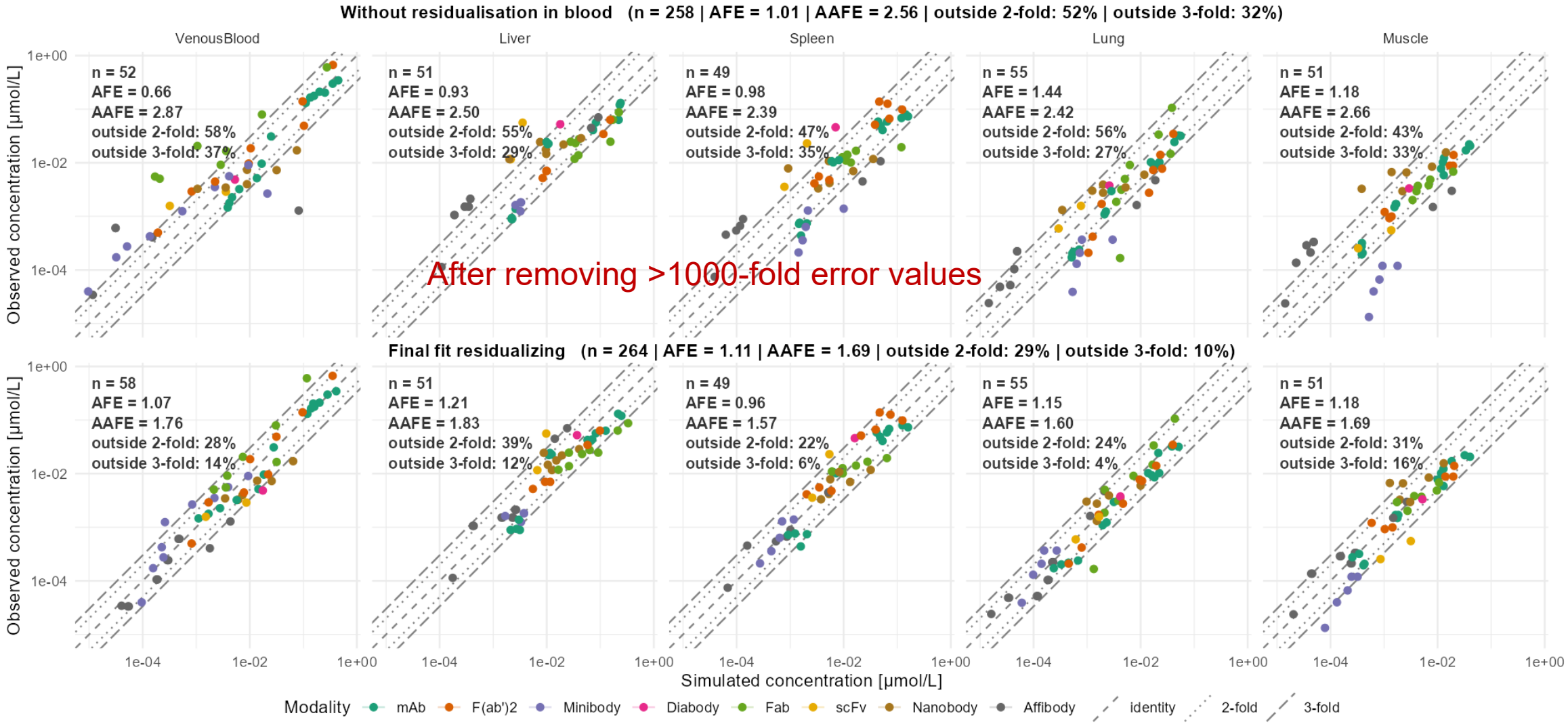
What did we find?

Is the residualisation in whole blood also critical for the model fit?



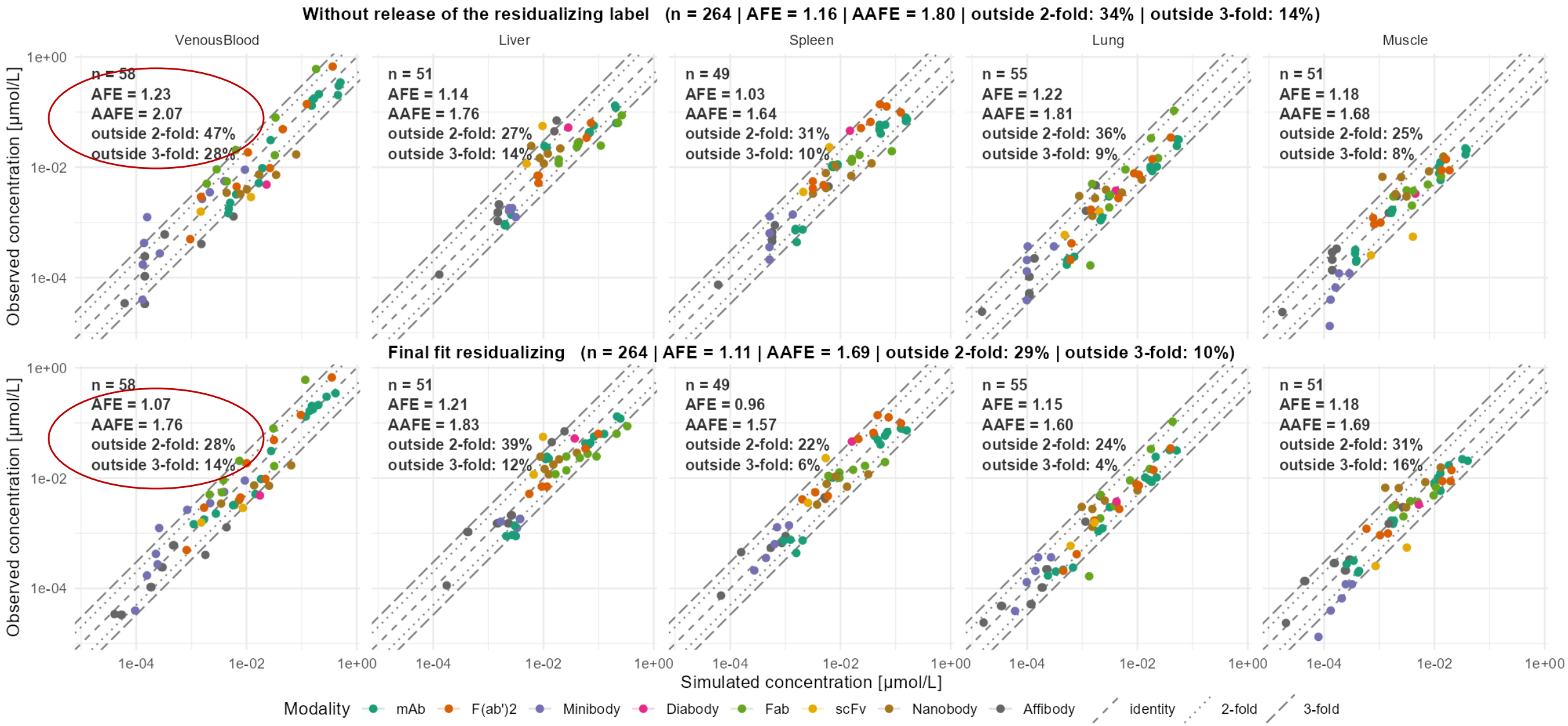
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What did we find?

Is the release of the radiolabel identifiable?



What does all of this mean?

- The two-pore model can describe protein biodistribution and residualizing labels for a wide range of modalities and molecules
- Resdiualizing labels require inclusion of catabolized protein!!
- If sufficient data are available, interstitial and vascular fractions can be refined, but residualizing label data are less informative for this
- Endosomal fraction or other tissue-specific clearance parameters need refinement for residualizing labels
- Residualisation also occurs in whole blood
- Release of residualizing labels is visible on the 1-week timescale in mice

What now?

- Next step: repeat for human data
- Raise awareness for the nature of residualizing labels
- Apply the two-pore model with increased confidence
- Implement endosomal clearance in blood cells?

Acknowledgements



Pieter-Jan de Sutter

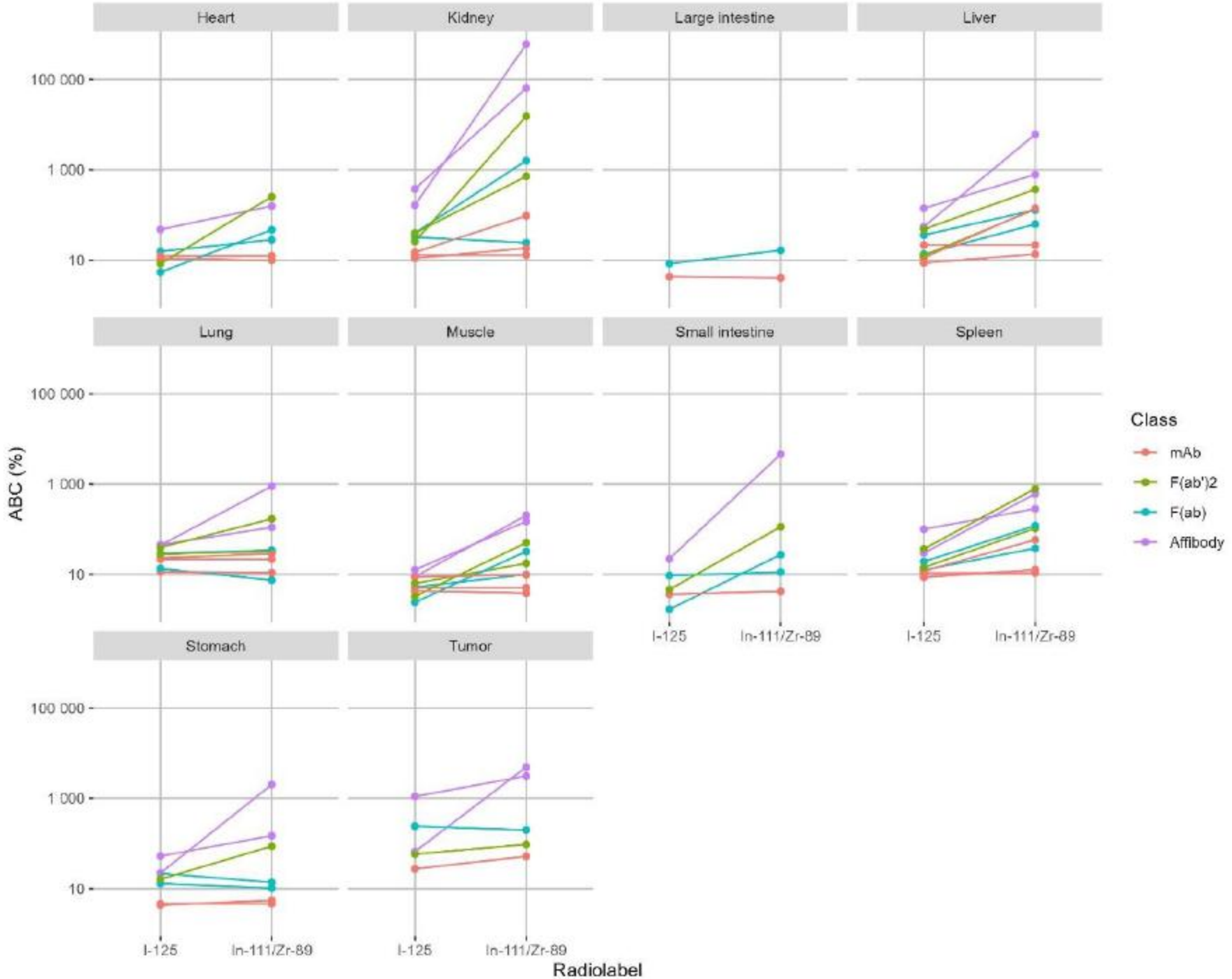


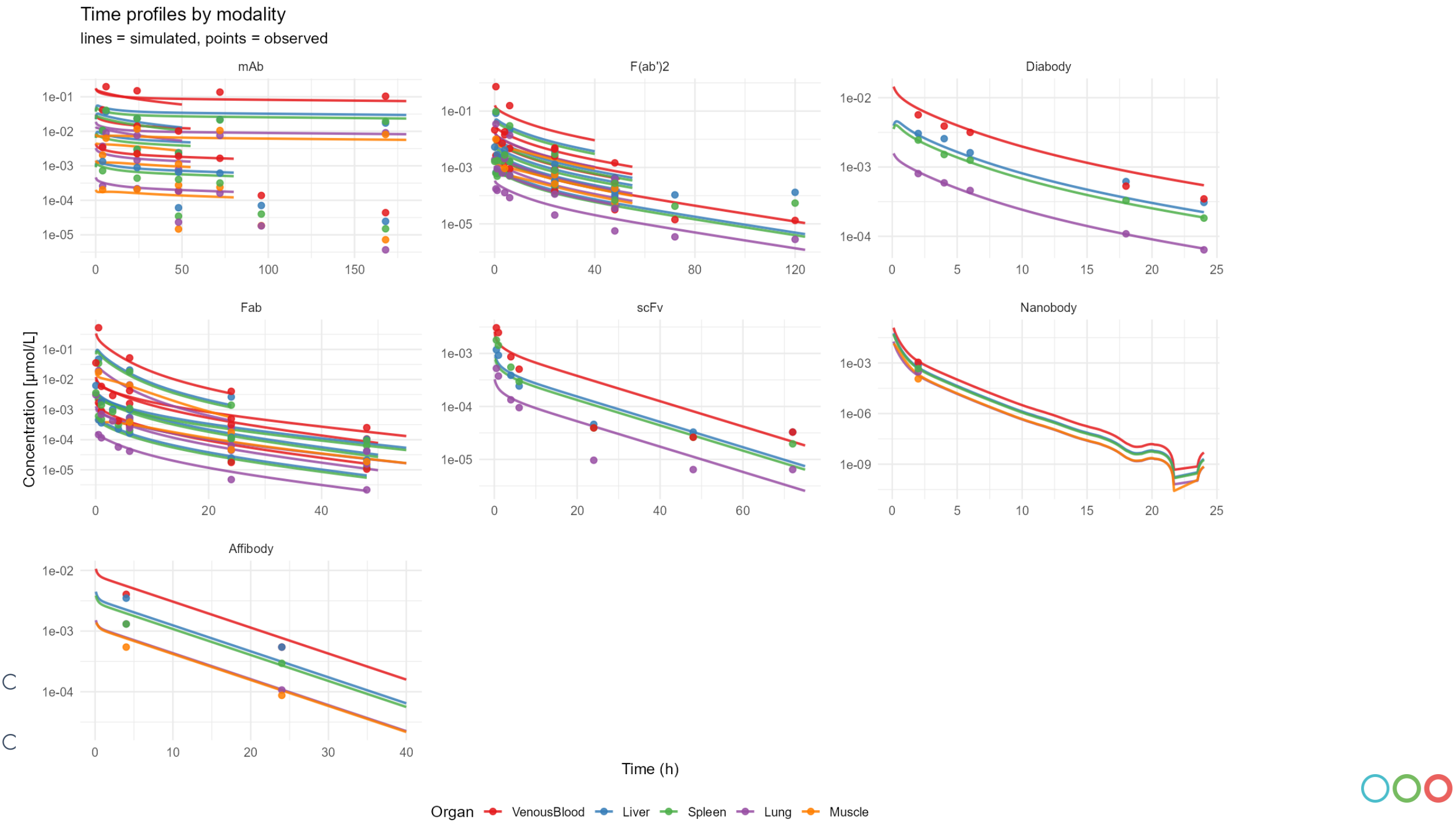
Hannah Rakers

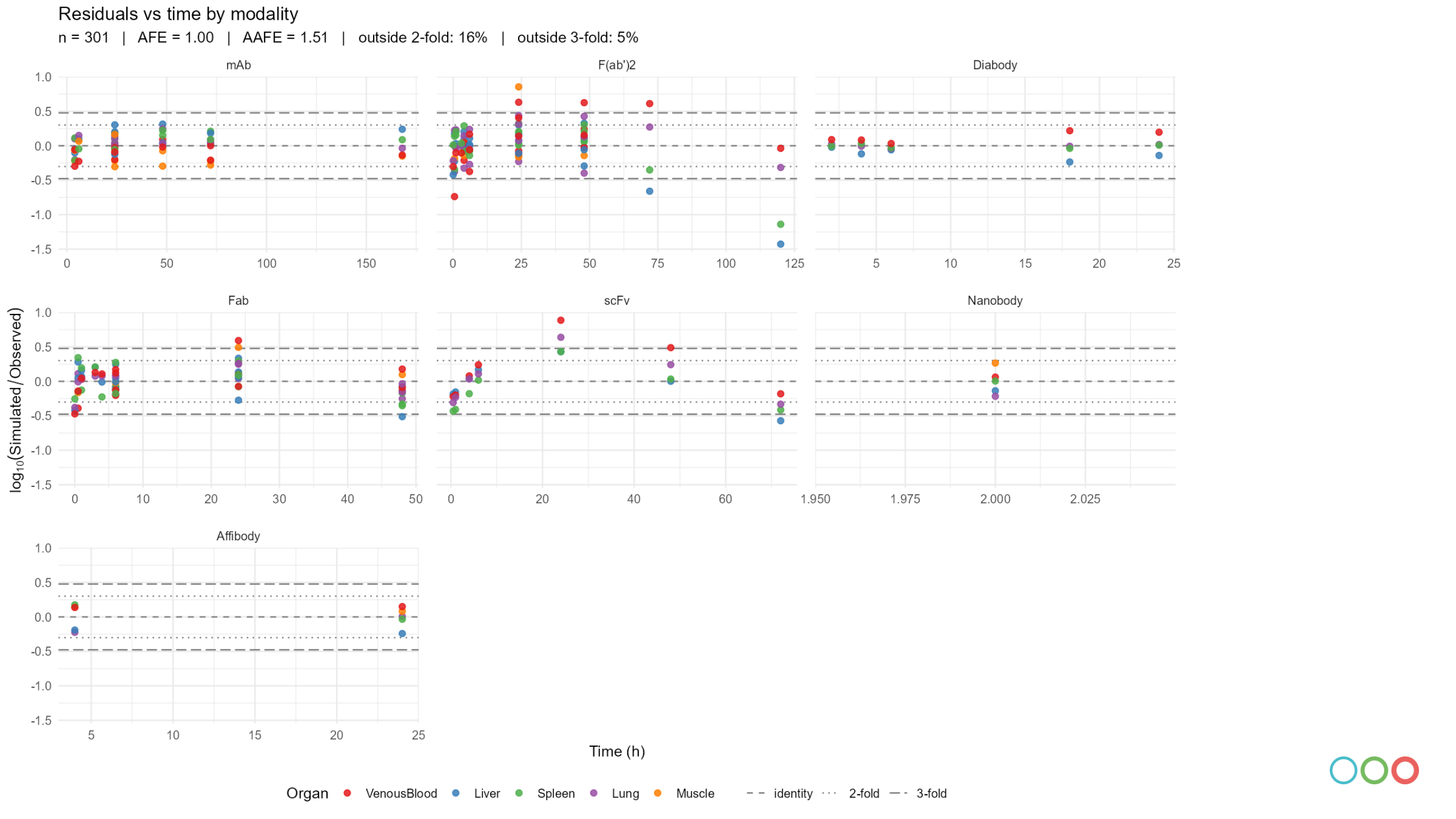


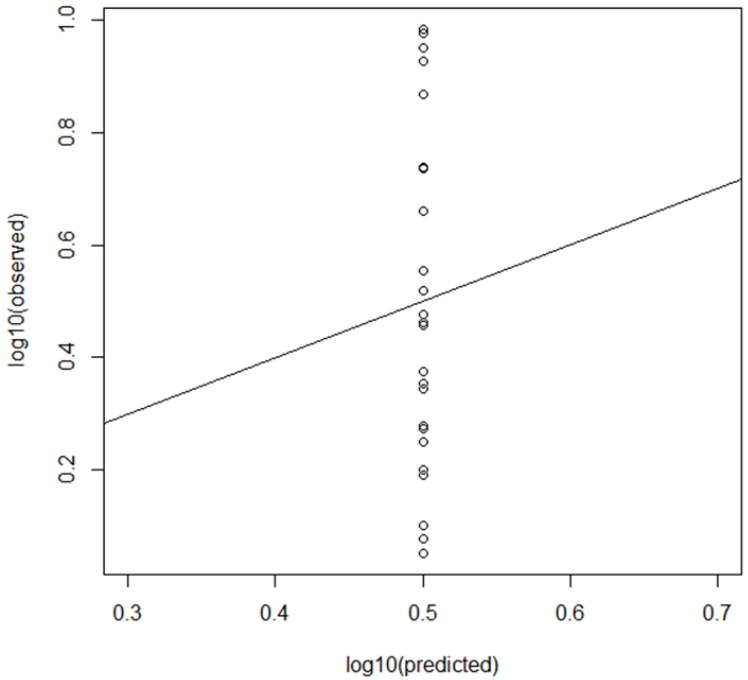
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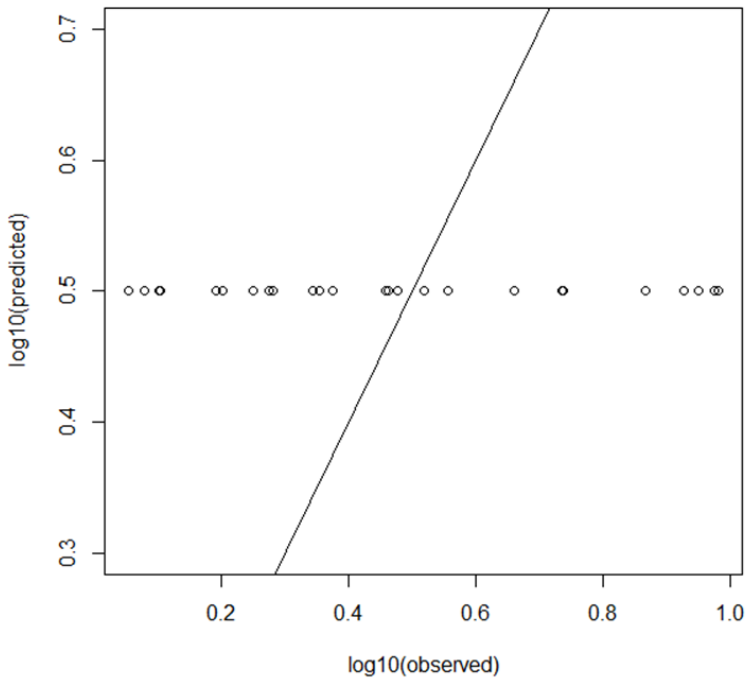
Amber Vandeputte


Heart
Kidney
Large intestine
Liver
Lung
Muscle
Small intestine
Spleen
Stomach
Tumor
100 000
1 000
10
ABC (%)
I-125
In-111/Zr-89
Radiolabel
Class
mAb
F(ab')2
F(ab)
Affibody


Time profiles by modality
lines = simulated, points = observed
mAb
F(ab')2
Diabody
Fab
scFv
Nanobody
Affibody
Concentration [µmol/L]
Time (h)
Organ
VenousBlood
Liver
Spleen
Lung
Muscle


Residuals vs time by modality
n = 301 | AFE = 1.00 | AAFE = 1.51 | outside 2-fold: 16% | outside 3-fold: 5%
mAb
F(ab')2
Diabody
Fab
scFv
Nanobody
Affibody
log10(Simulated/Observed)
Time (h)
Organ
VenousBlood
Liver
Spleen
Lung
Muscle
identity
2-fold
3-fold





https://github.com/Open-Systems-Pharmacology/Forum/discussions/1460