



OBJECTIVES: Our objective is to model the time course of an imaging biomarker in malignant tumors following a single dose of bevacizumab. The biomarker, K^{trans} , is monitored by Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) and reflects vascular permeability, surface area and rate of perfusion within each lesion. Patients underwent DCE-MRI at two timepoints before treatment and four time points after treatment; we subsequently used a mixed-effects model to describe true individual baseline values [1,2] and response to treatment [3]. Assessment of intra-patient variability via multiple baseline scans is important when comparing pre-treatment levels to a single post-treatment scan. Here, we assess the impact of multiple baseline scans when not one, but four, post-treatment scans are obtained, by fitting the model to simulated data with either one or two pretreatment timepoints.

METHODS: DCE-MRI data was collected from 10 patients with liver metastasis from primary colorectal cancer, where each patient received two pretreatment scans and four additional scans subsequent to a single dose of the anti-VEGF antibody bevacizumab [4]. K^{trans} , a PD parameter that reflects vascular permeability, surface area and rate of perfusion within each lesion was estimated for each imaging time point.

We developed a modified indirect response, mixed-effects model to describe the population change in K^{trans} after treatment.

1000 data sets were simulated in NONMEM using population parameters estimated by fitting our modified indirect response model to the full data set. The mixed effects model was then fitted to two variations of the 1000 simulated data sets, where: 1) each patient received 2 baseline scans (each simulated data set is unmodified) and 2) each patient received only a single baseline scan (the first baseline scan from each simulated data set was removed).

RESULTS: The model that was fitted to the original data and was used to generate the simulated data is characterized by three structural parameters [k_{out} (time^{-1}), k_{tol} (time^{-1}) and $loss$ (dimensionless)], three interindividual variance parameters, and one overall residual variance parameter. The parameter estimates obtained from the simulated data varied widely, likely due to data sparsity in the presence of large residual variability. The quality of the parameter estimates obtained from the simulated data was slightly improved in the two-baseline scenario as shown by the following root mean square errors (RMSE): where

Root Mean Square Errors			
	k_{out}	k_{tol}	$loss$
mean	111 (133)	43 (45)	14 (15)
%CV	155 (225)	78 (108)	105 (113)

RMSE's are expressed as percentages of the true parameter values underlying the simulation and numbers in parentheses are for the one-baseline scenario. %CV refers to variability of each parameter between individuals.

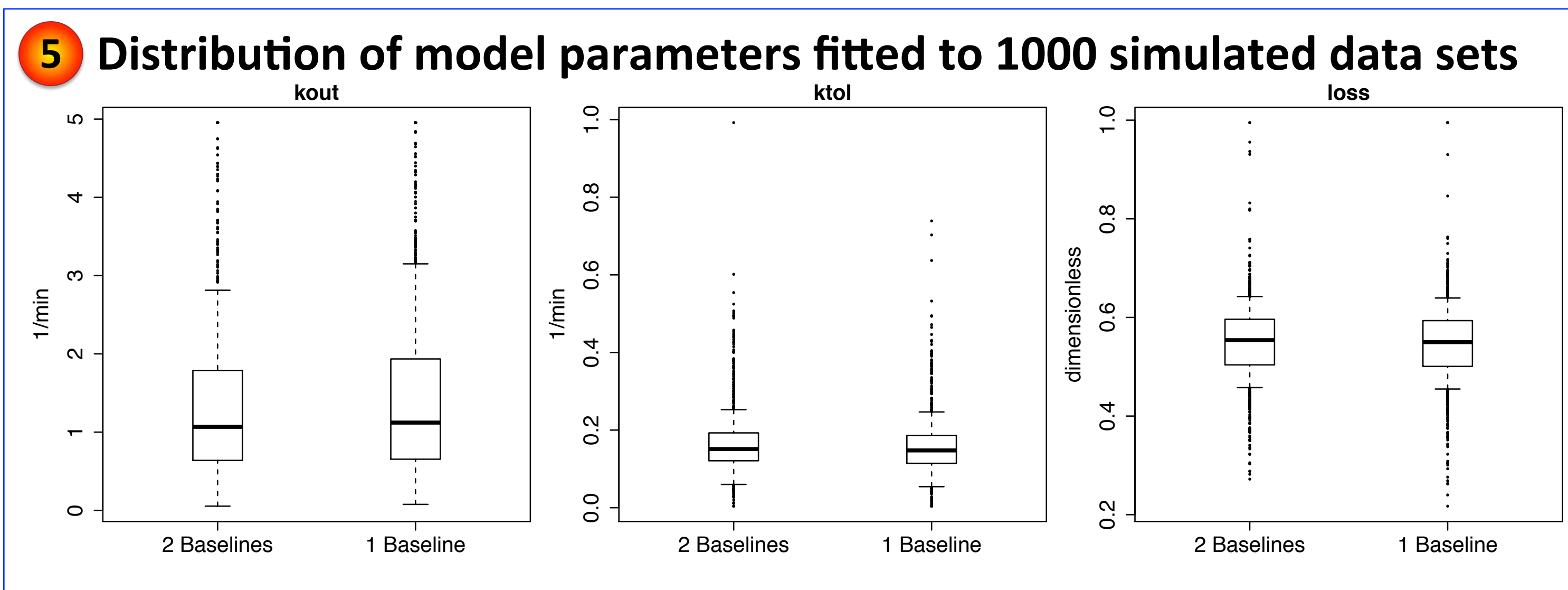
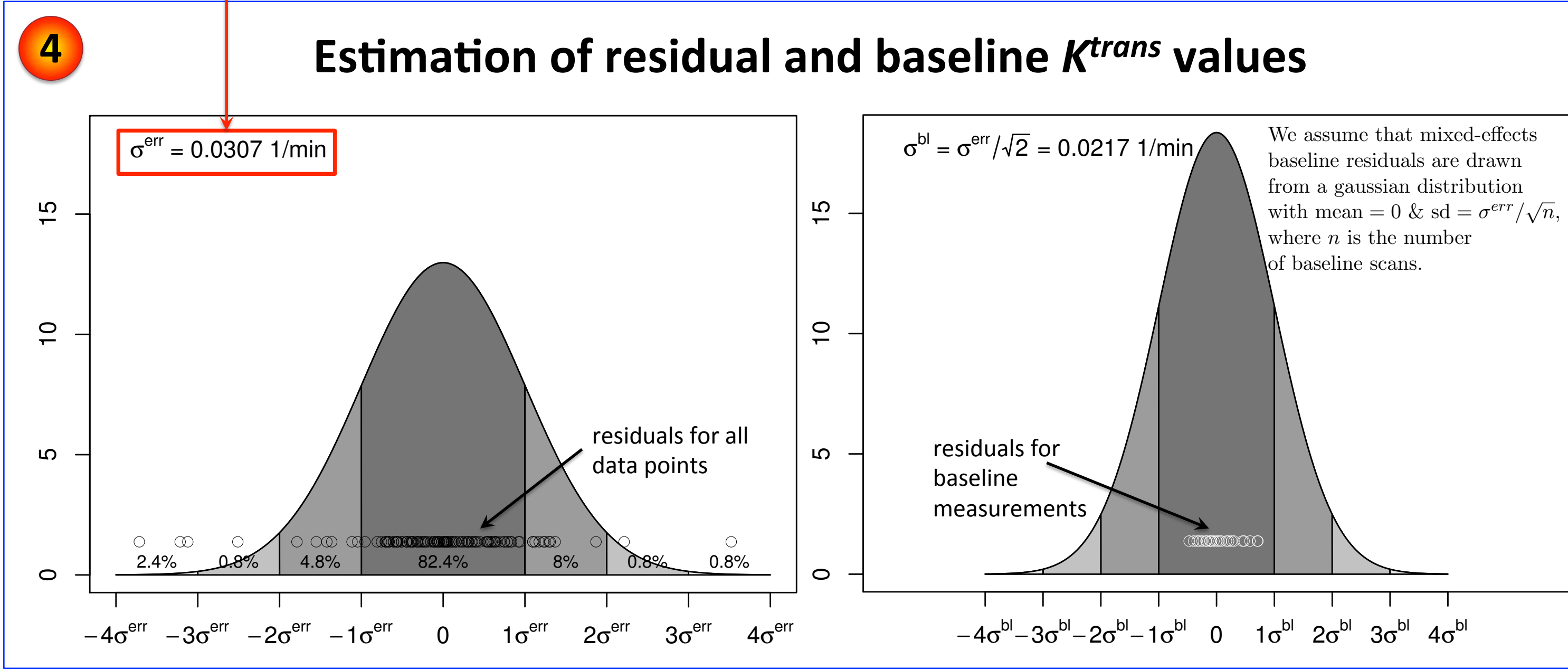
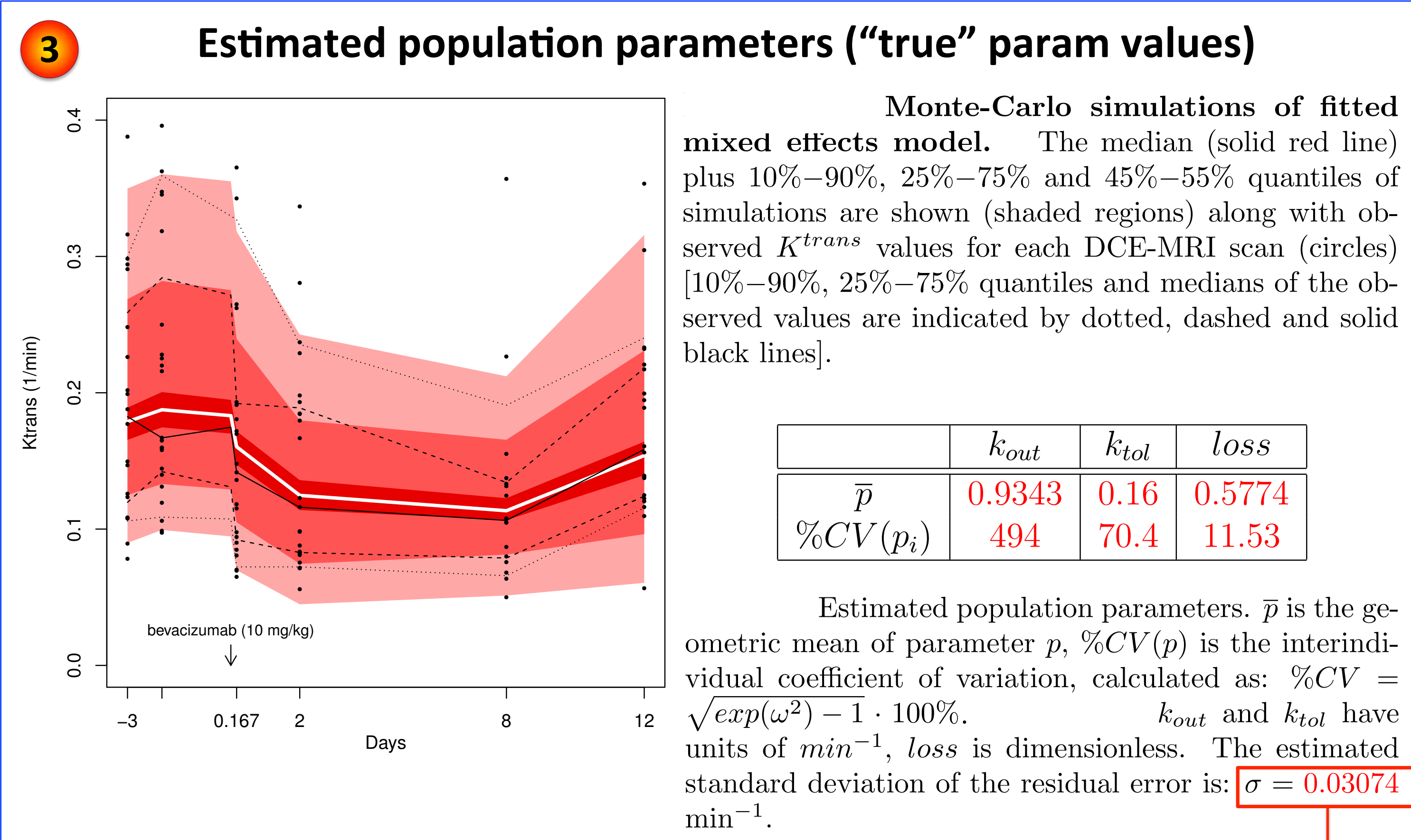
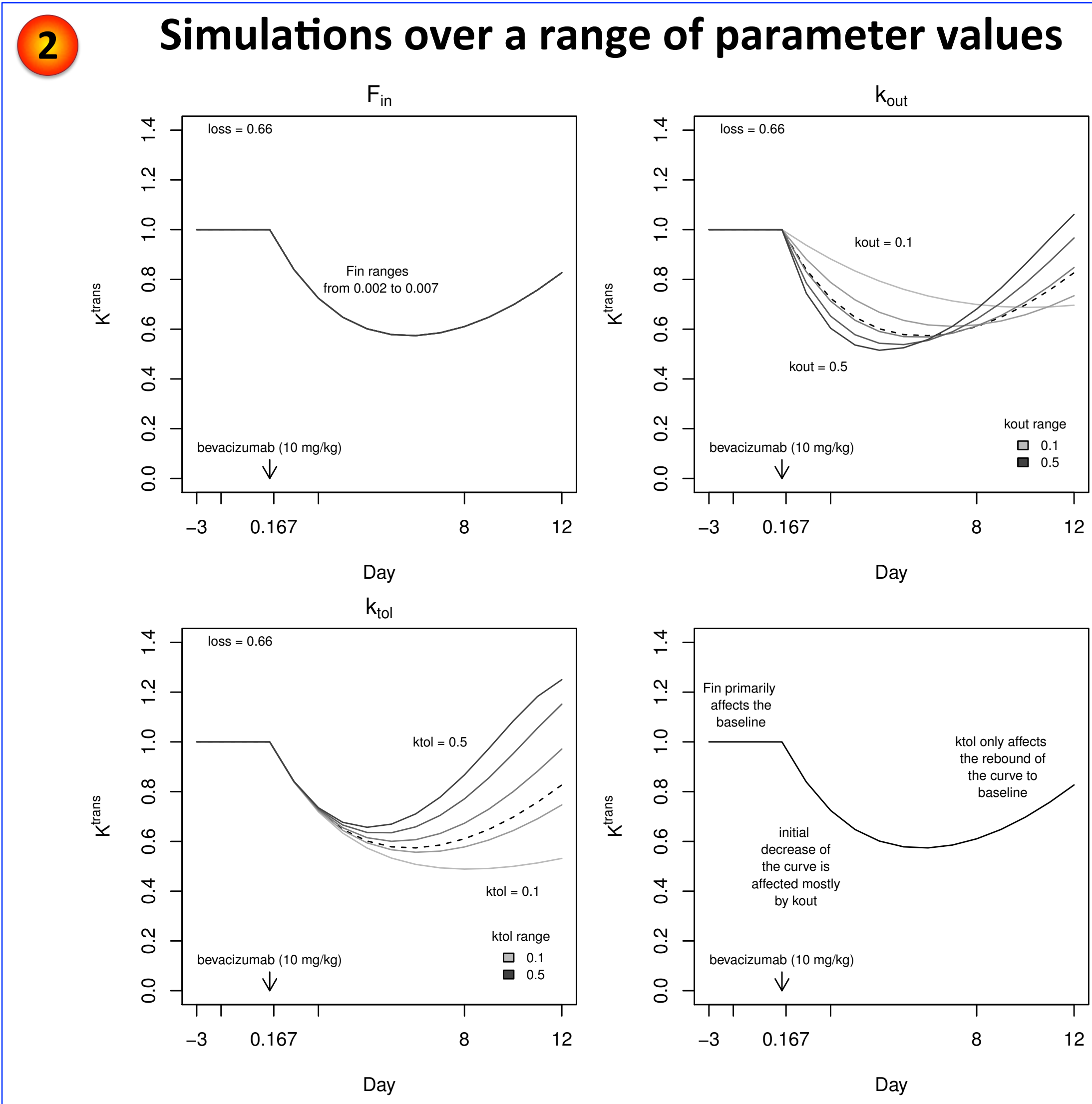
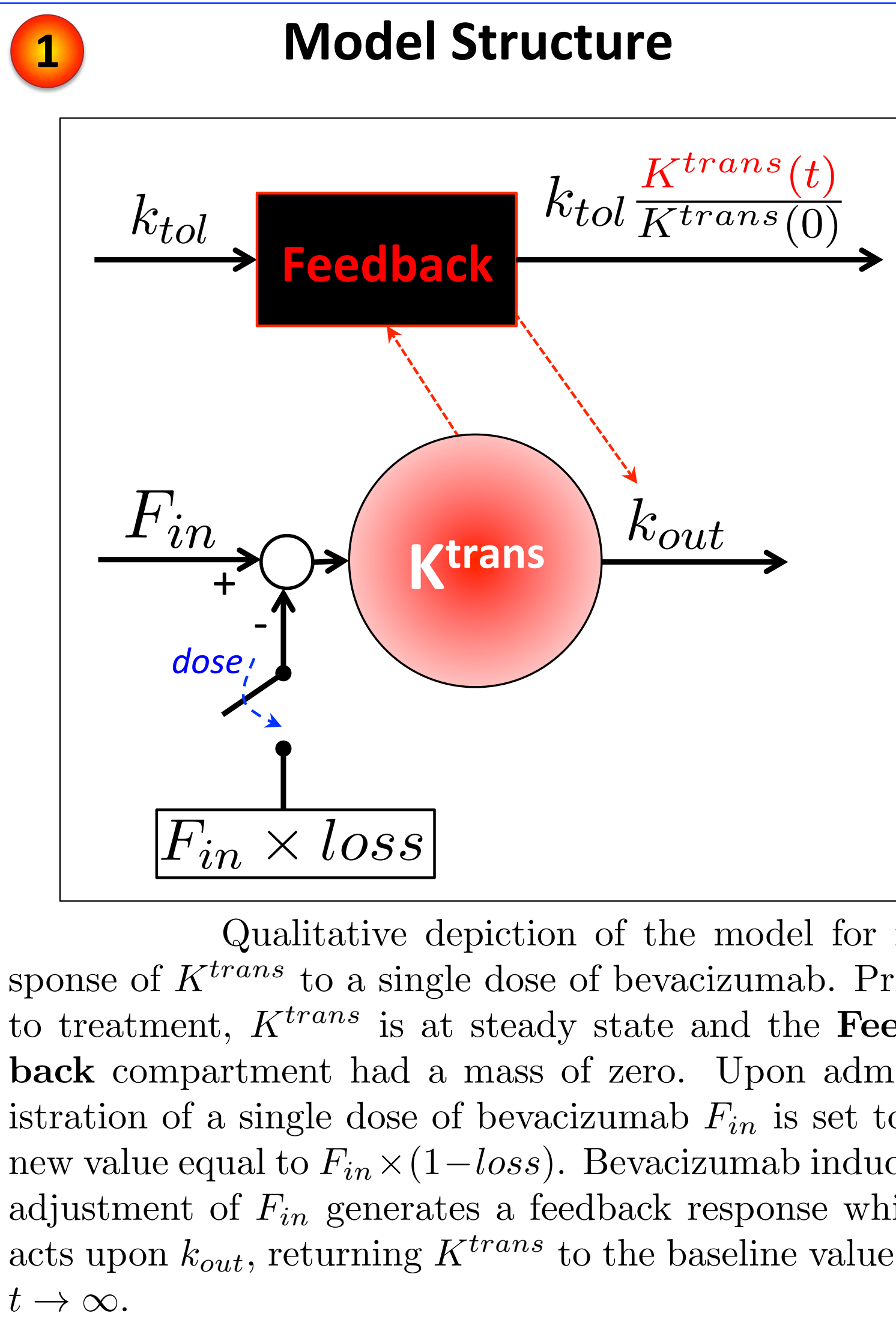
CONCLUSION: The results observed here suggest that double baseline scans, which are costly and a burden to patients, may not be required for everyone enrolled in the study if multiple (≥ 4) post treatment scans are obtained.

REFERENCES

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ACKNOWLEDGEMENTS: The authors thank Michel Friesenhahn, Ph.D. (Genentech) for statistical guidance.

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1 Indirect response model with feedback element describes changes in K^{trans} during treatment.

2 Model simulations across a range of parameters illustrate relationship between each parameter and the K^{trans} time course.

3 The model is first fitted to all patient data; mean population parameters are estimated along with variability of each parameter within the population; Monte Carlo simulations are generated and compared to the actual measured data.

4 Distribution of residuals for each estimated data point (left-hand panel) superimposed on the estimated gaussian distribution with mean = 0 and sd = σ^{err} compared to distribution of estimated mixed-effects baseline values (right-hand panel).

5 Summary of parameter estimates based on 1000 simulated data sets (with 1 or 2 baselines) based on the parameters shown in **Box 3**