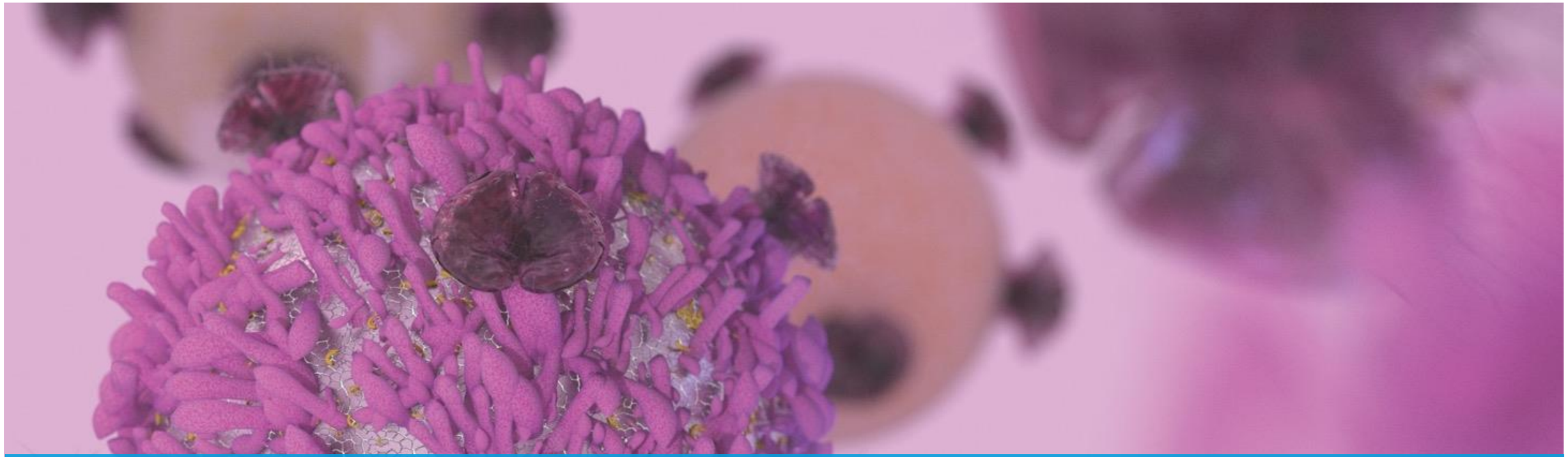

Evaluation of combination therapies using temporal data

Non-Clinical Statistics

Nicholas Hein
Principal Statistician
Janssen Research and Development
October 2022

T cell lymphocyte with receptors to kill cancer cell in cancer immunotherapy 3D render

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Imagine the start of a new collaboration…

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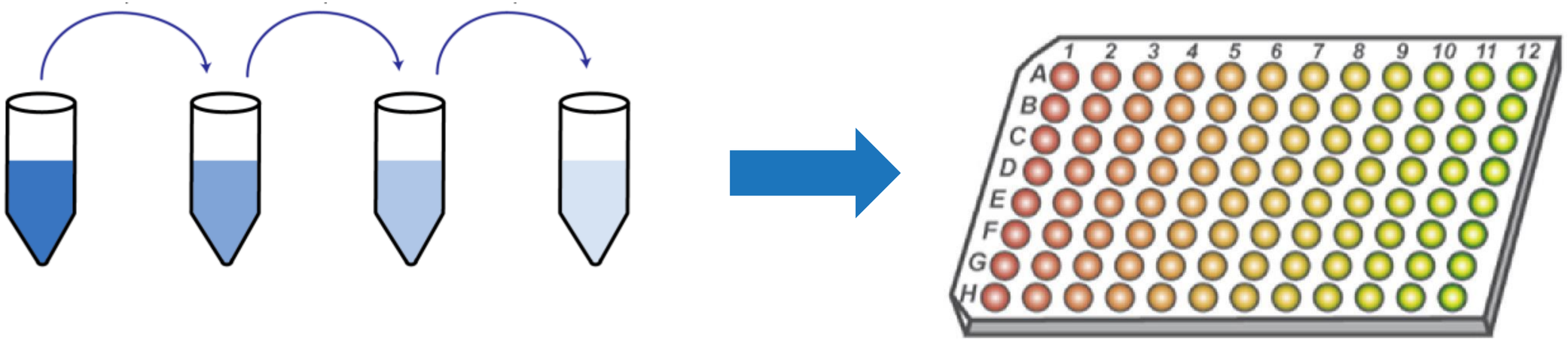
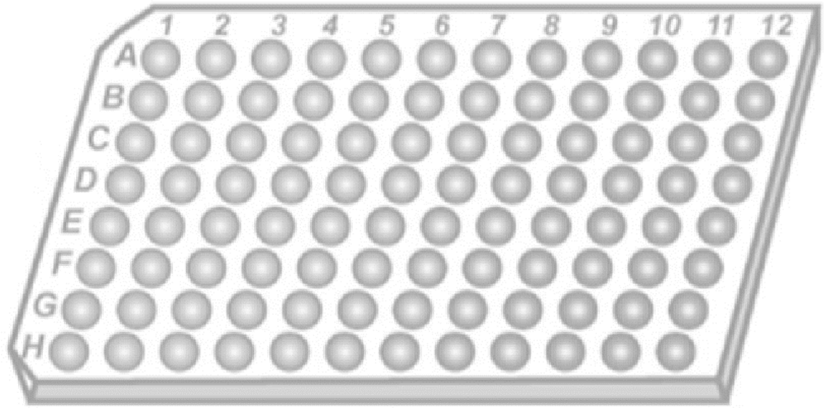
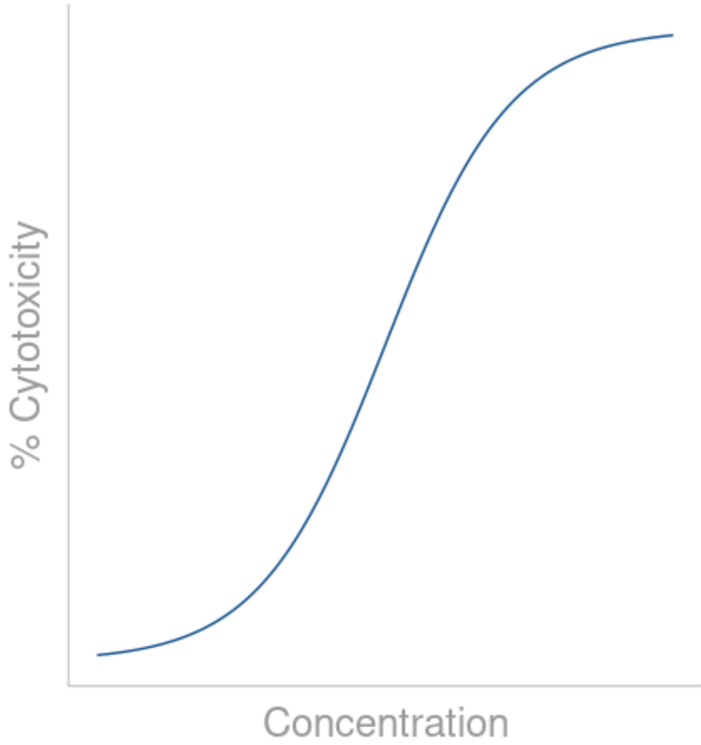
The scientist performed an in-vitro experiment and would like you to analyze the data.

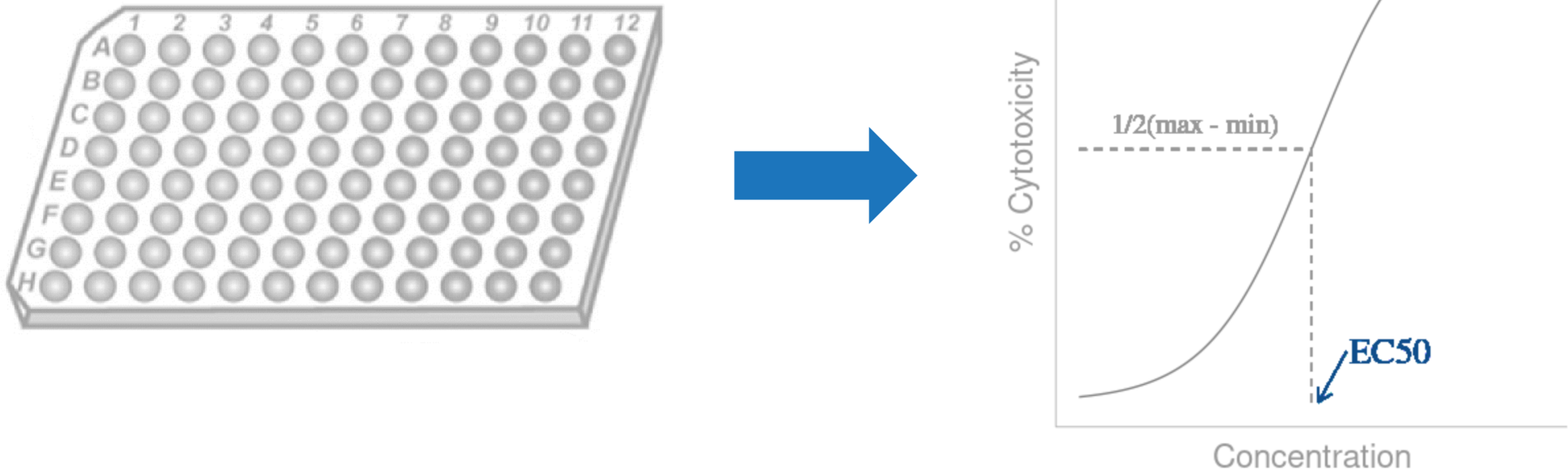


The scientists has asked you for a dose response analysis.



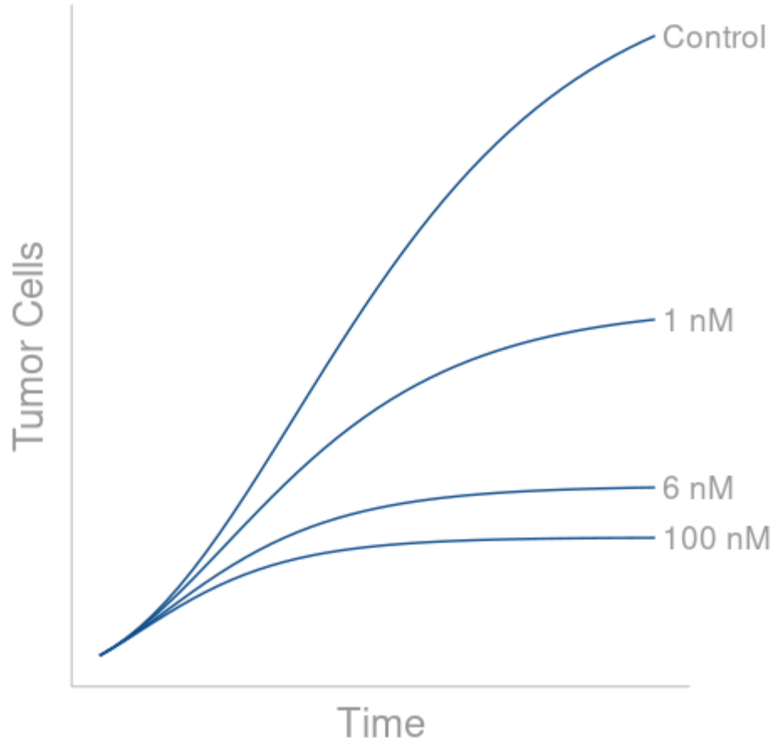


The scientist has asked you for some post-hoc estimates from the analysis.

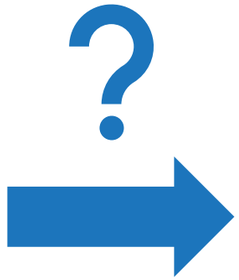


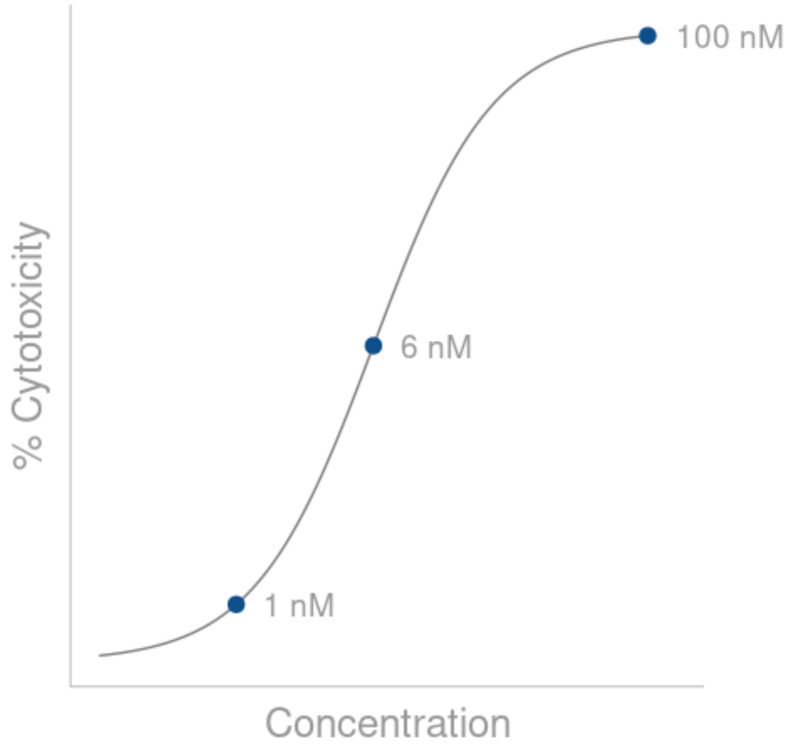
You’re thinking…

But wait, it is not as easy as you thought…



The data collected from the assay needs to be summarized ("flattened") for a dose response analysis.





In the next 10-12 minutes…

OUR GOAL:

1. Learn pragmatic approaches to “flatten” temporal assay data for dose response modeling.
2. Determine how these approaches perform in a simulation study.
3. Use this knowledge to recognize the upstream consequences of biases of these approaches.

We will end with a specific recommendation.

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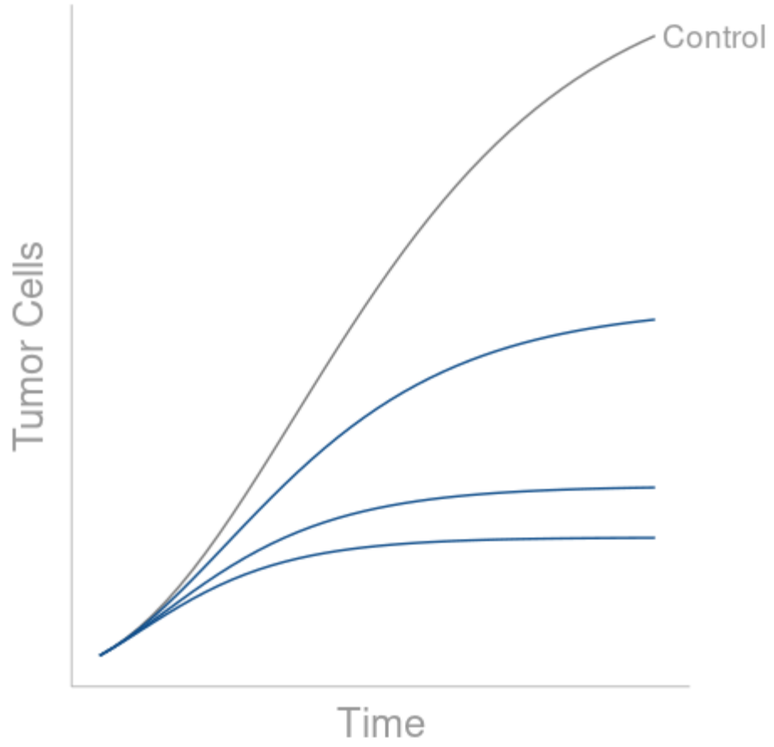
The data can be “flattened” by …

Cross-sectional



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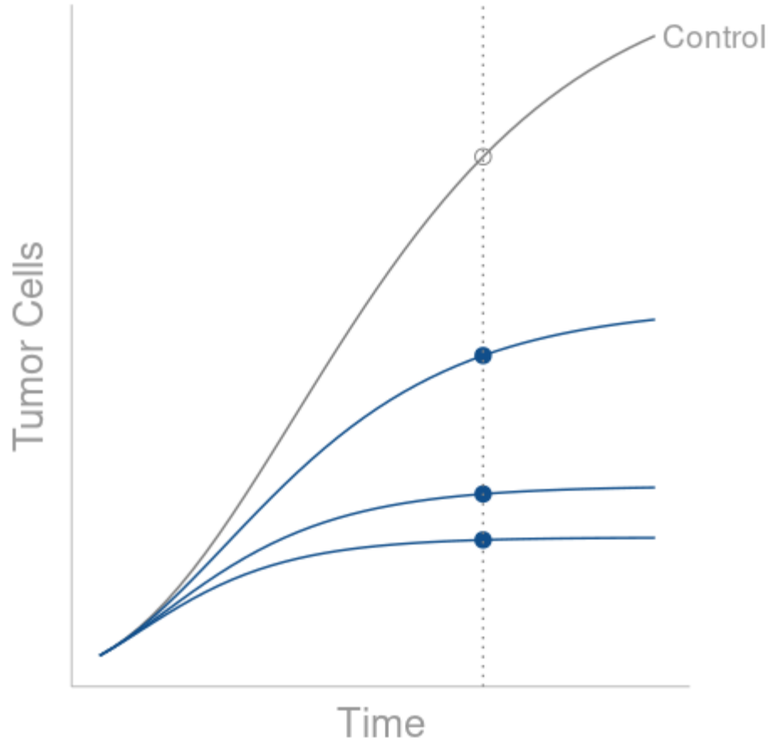
Cross-sectional



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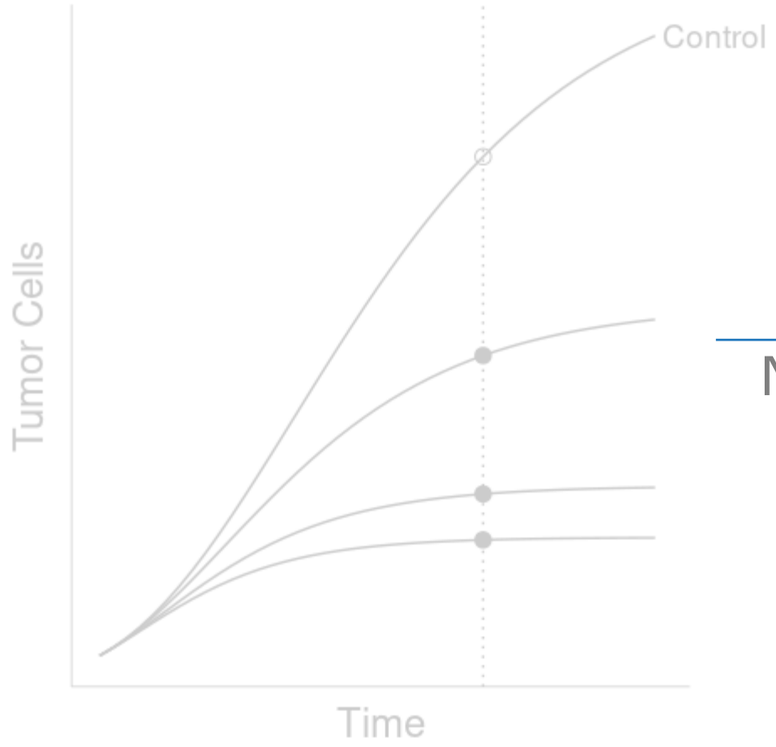

Normalize to control

$$1 - \frac{\textbf{Treatment}}{\textbf{Control}}$$

The data can be “flattened” by …

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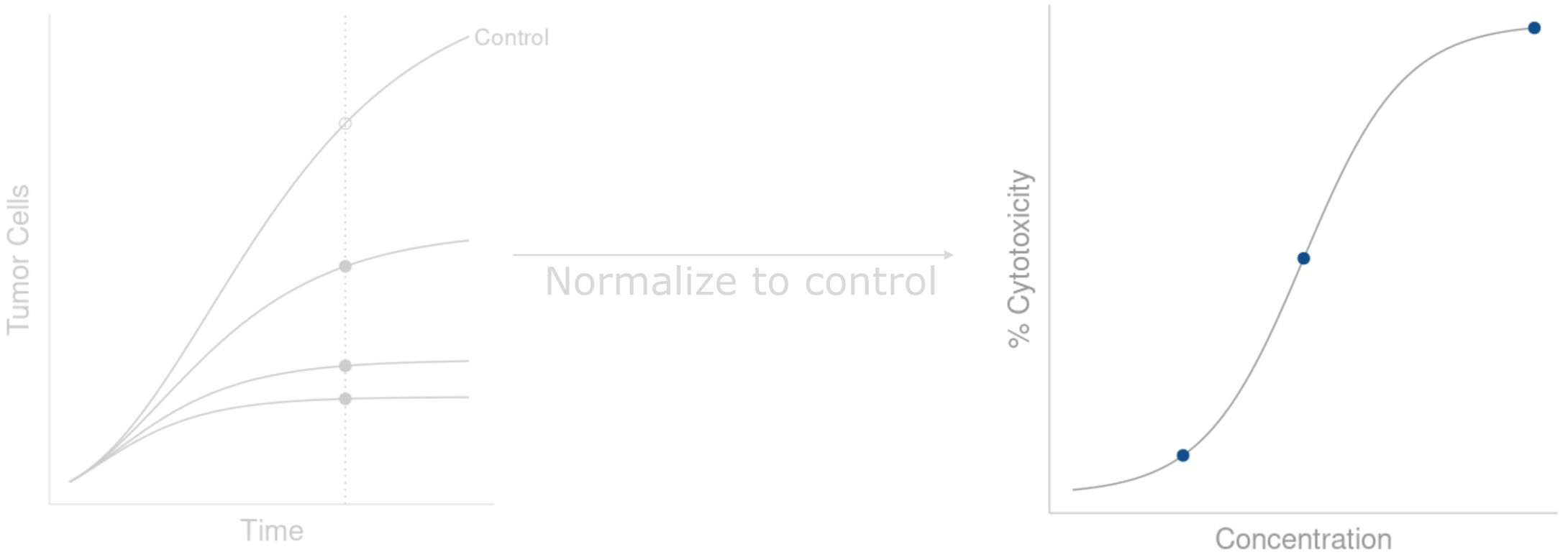

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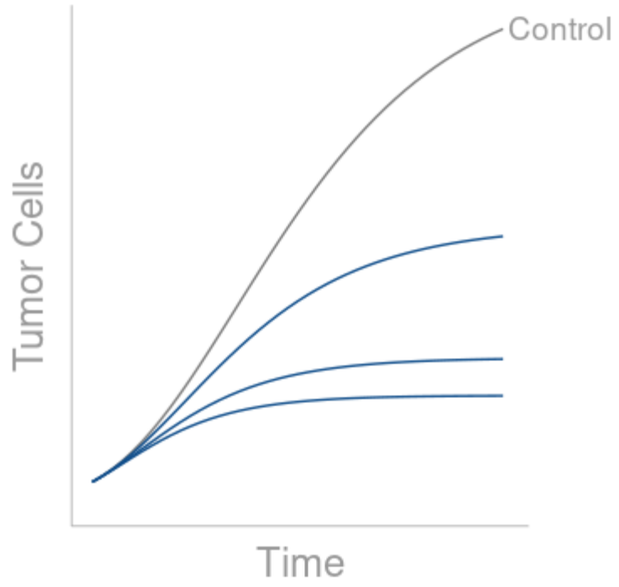
An alternative approach to “flatten” the data that does not discard data.

Area under the curve (AUC)



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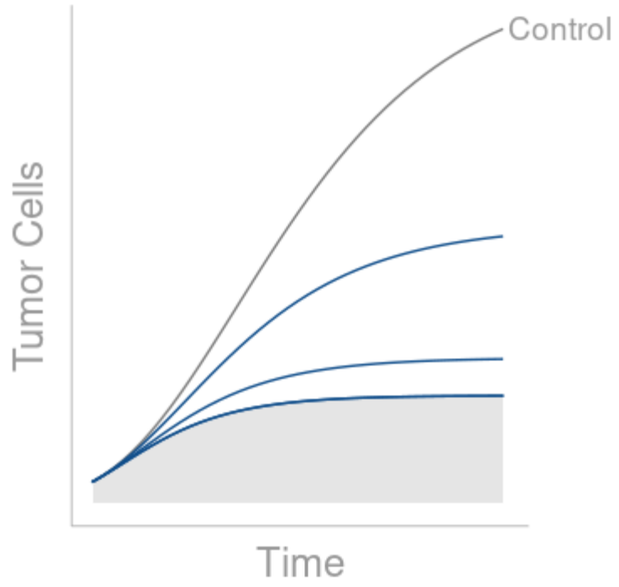

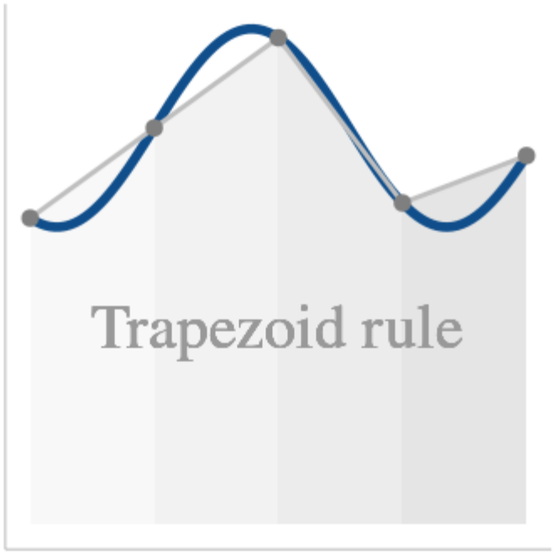

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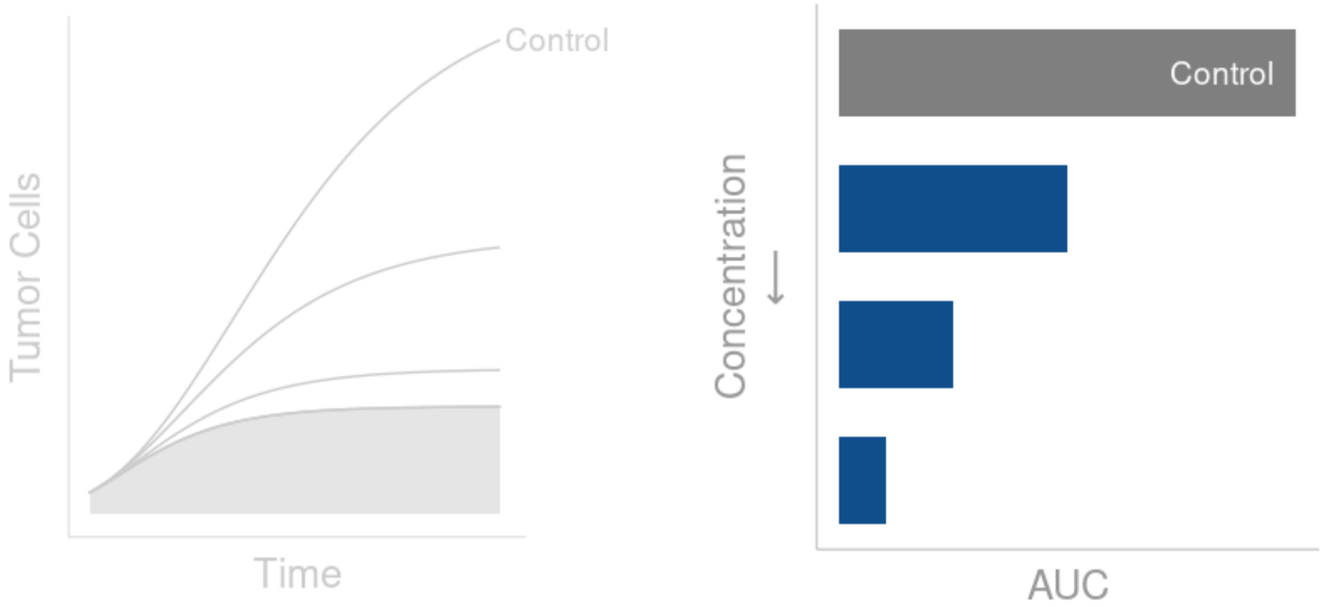

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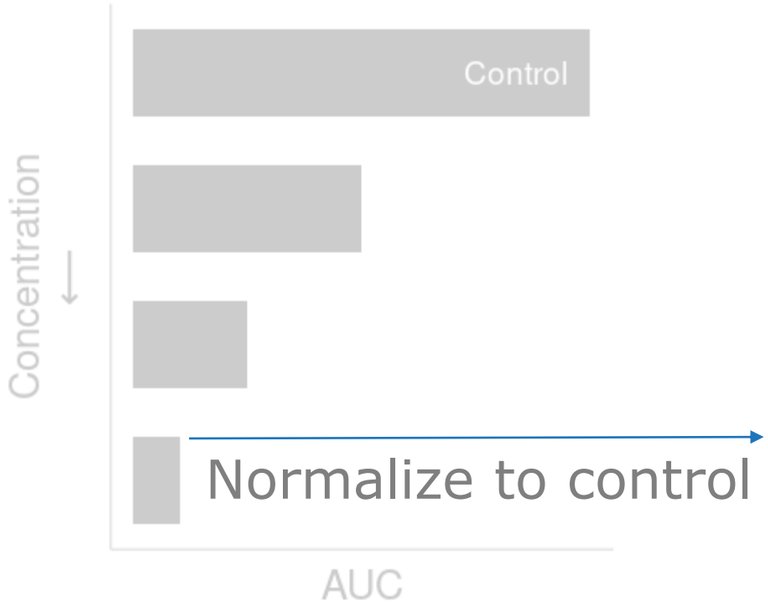

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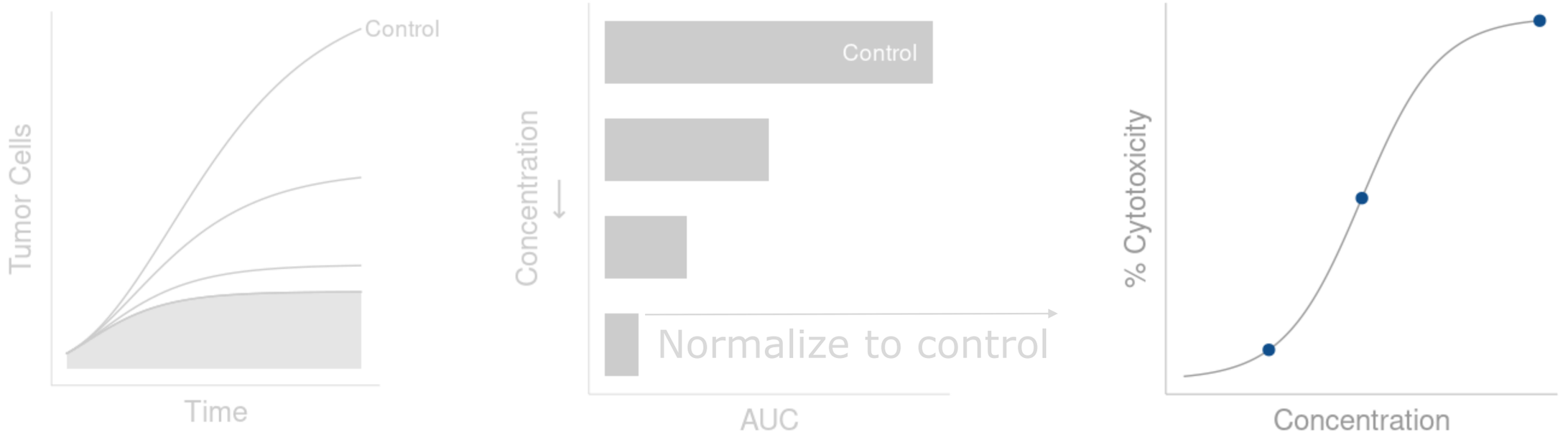
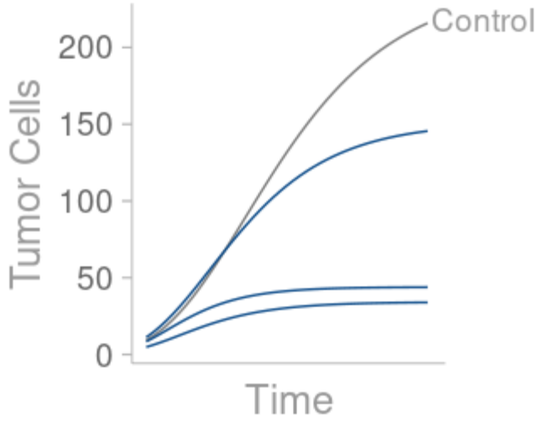


Extending the AUC method to handle baseline discrepancies.

Baseline adjusted AUC



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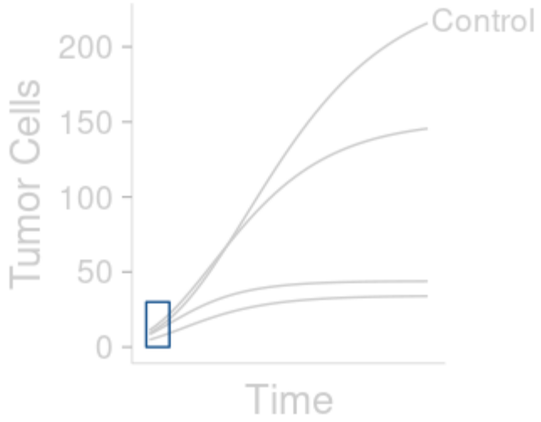

Adjust for baseline

$$\frac{\textbf{Tumor Cells}}{\textbf{Tumor Cells}_{\textbf{time=0}}}$$

Extending the AUC method to handle baseline discrepancies.

Baseline adjusted AUC

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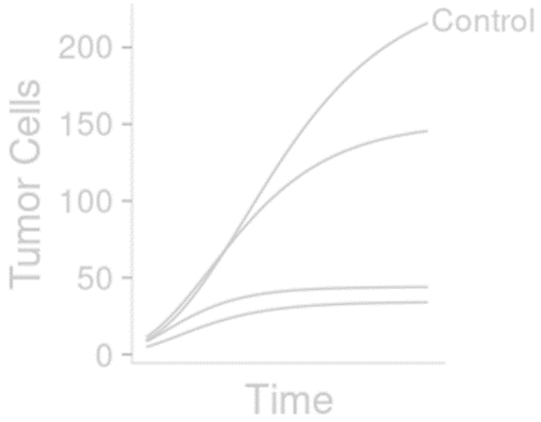
Baseline adjusted AUC



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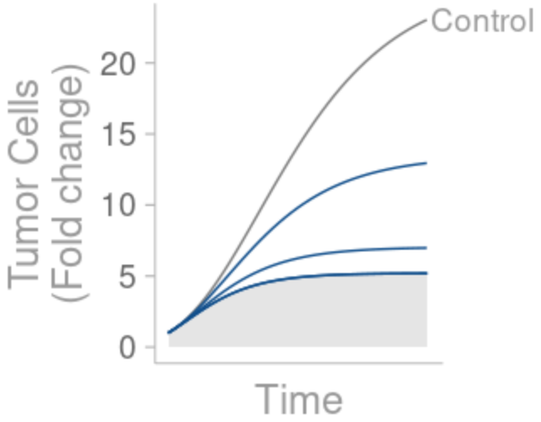
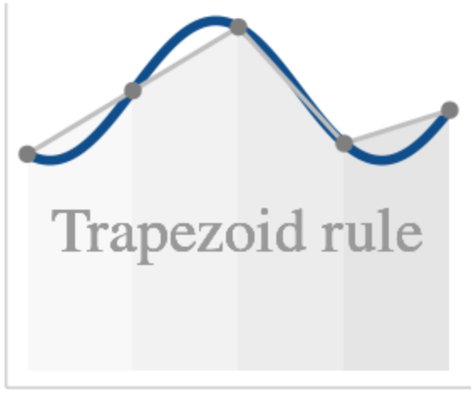


AUC



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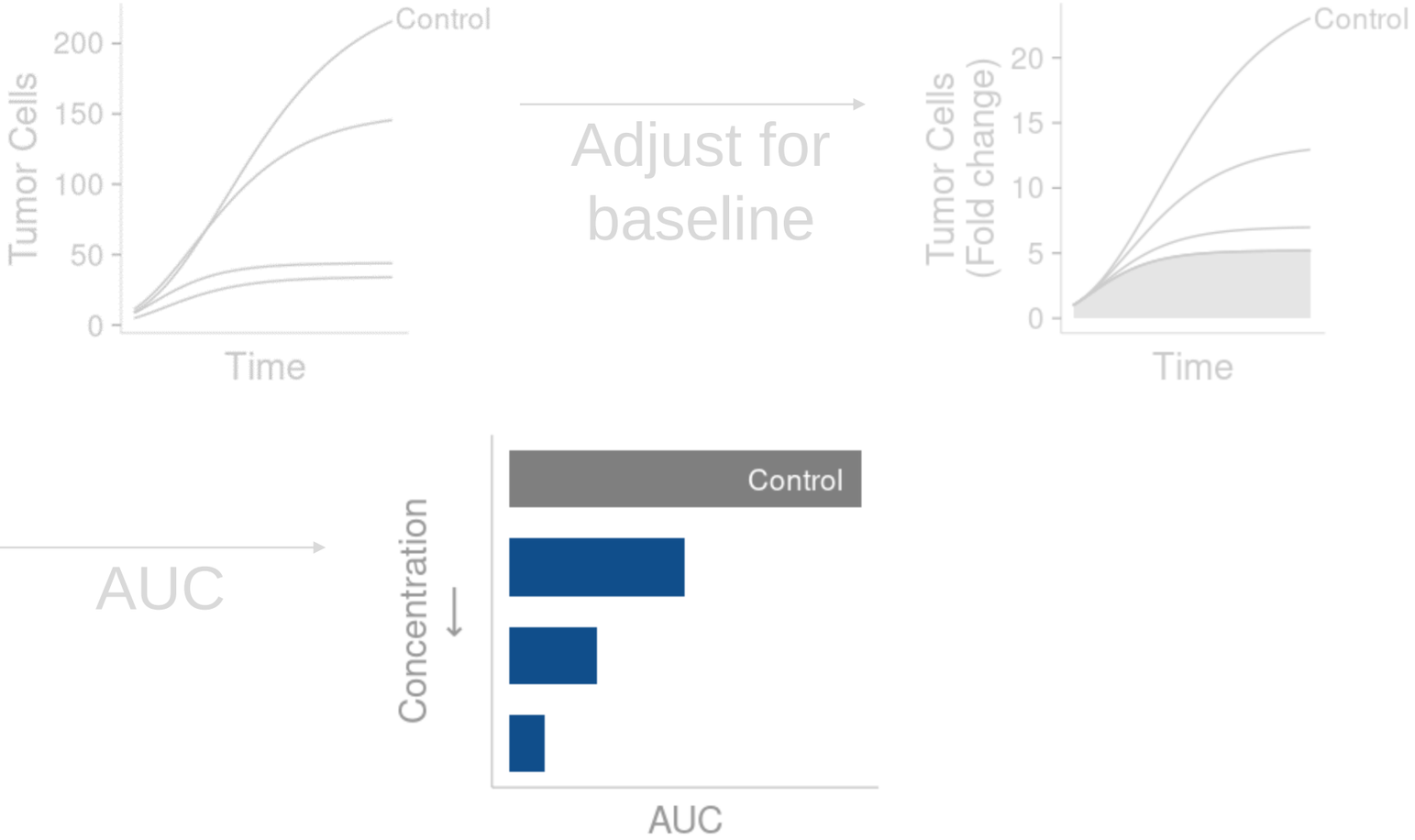

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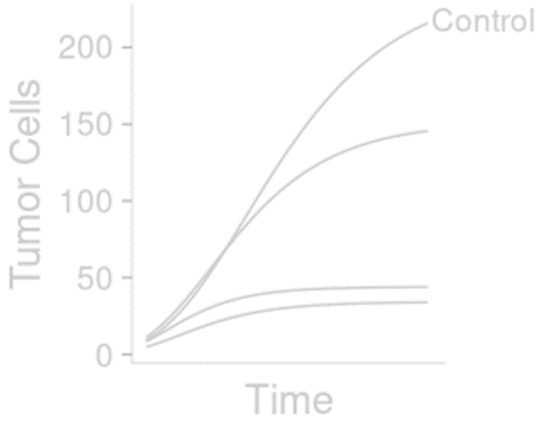

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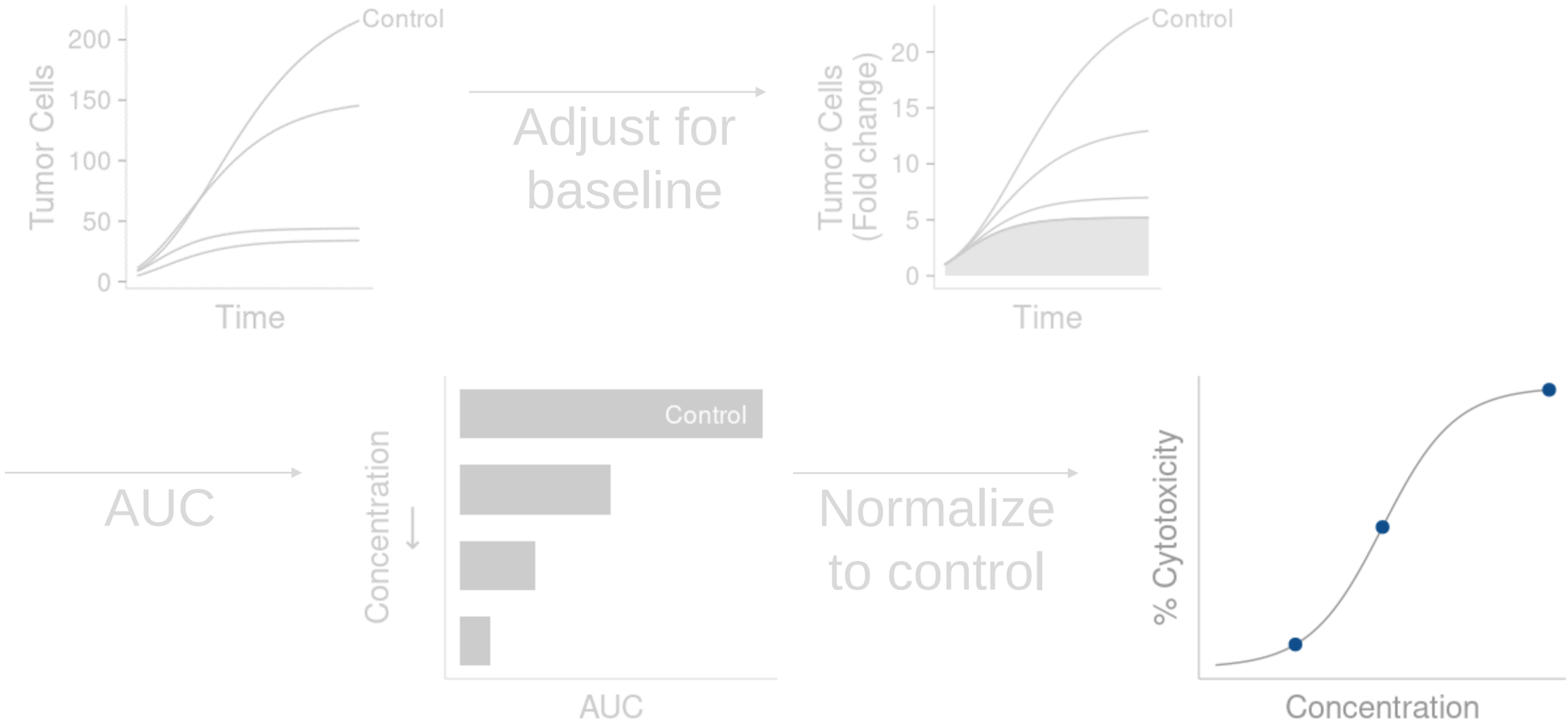

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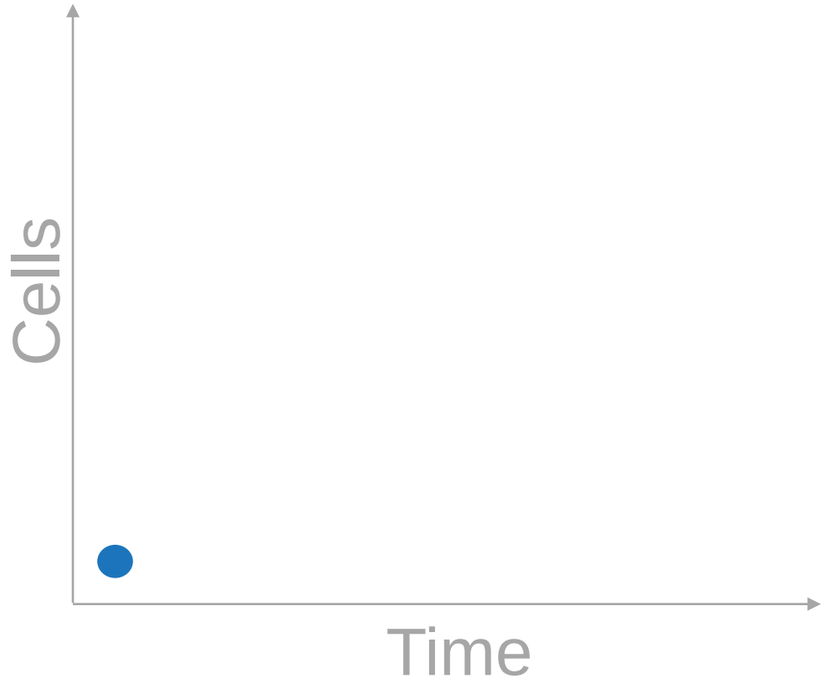
Simulating the control data using a biological model.



Gompertz Model

$$y = y_0 exp\left\{\frac{A}{r}(1 - exp\{-rt\})\right\}$$

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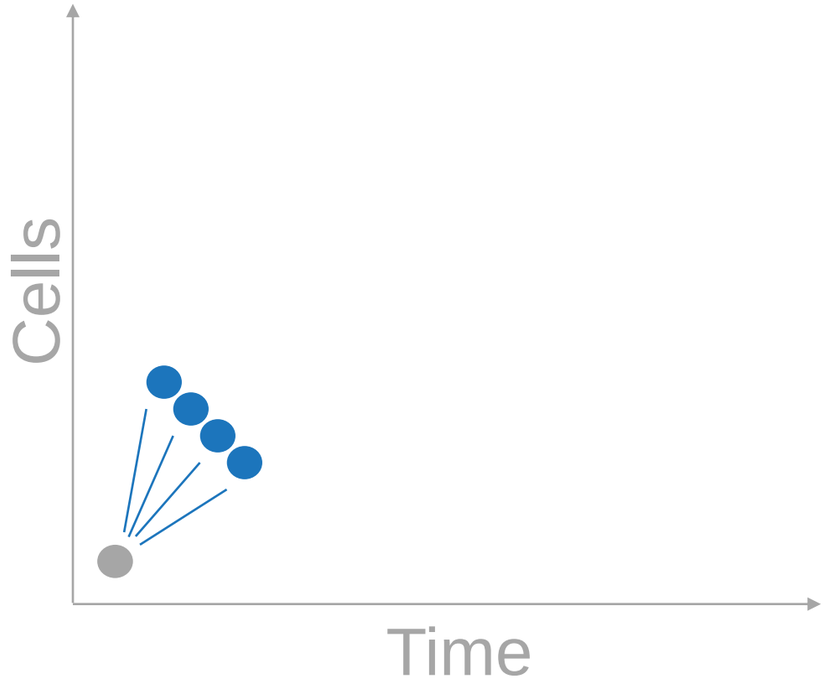

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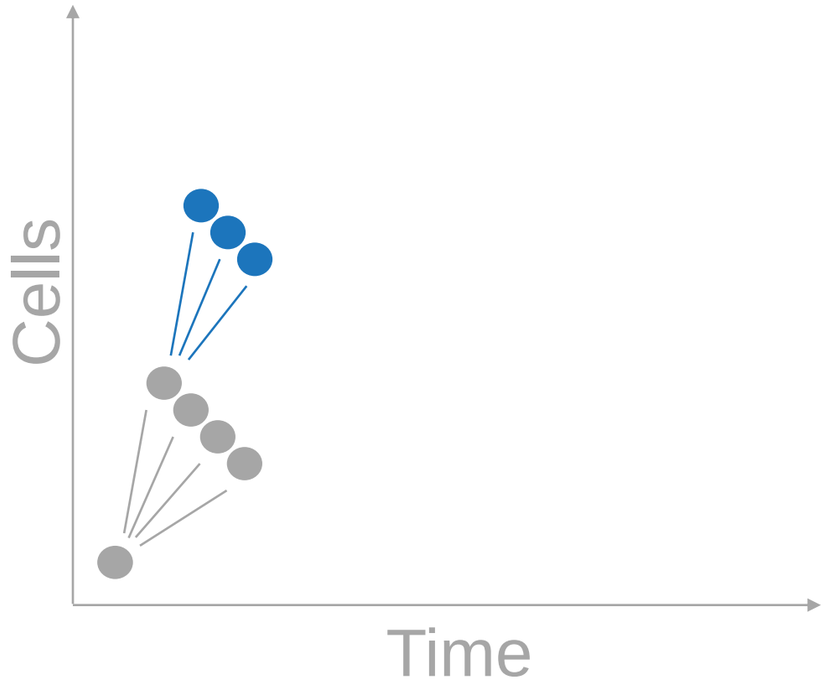

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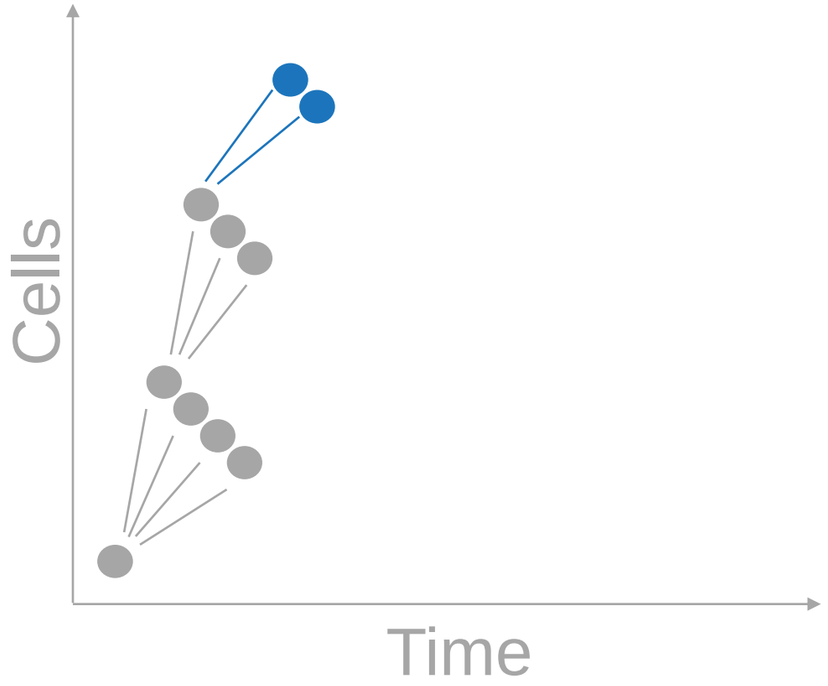

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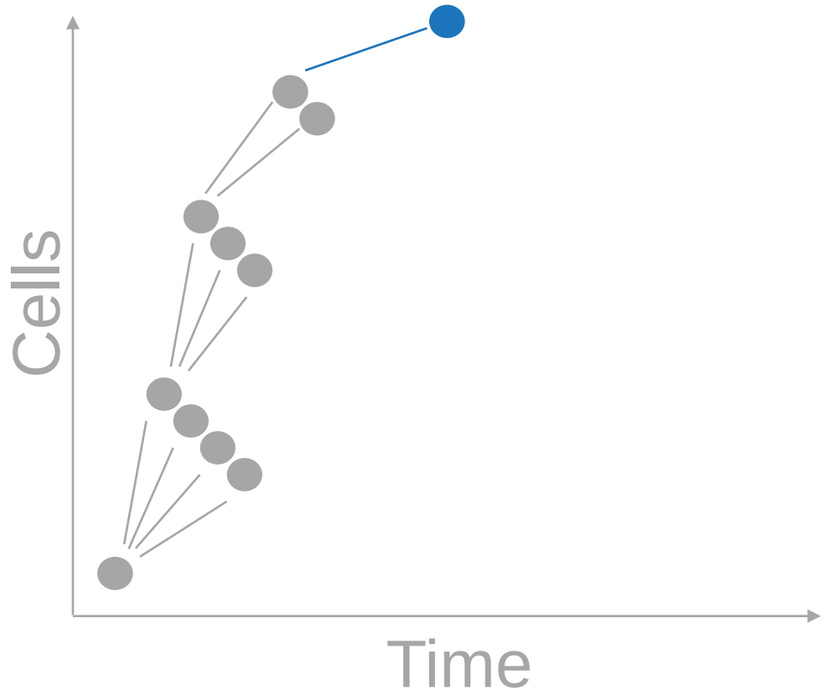

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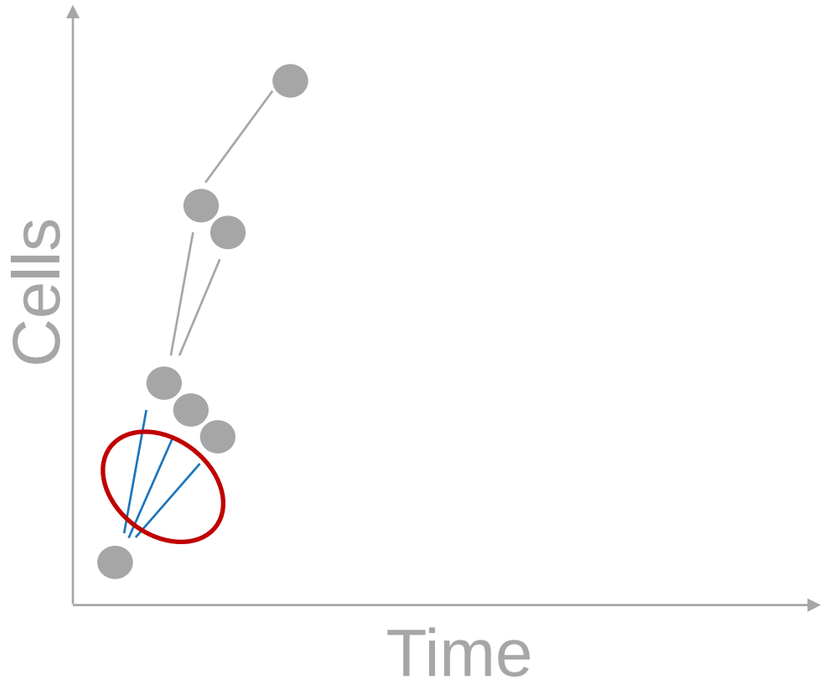
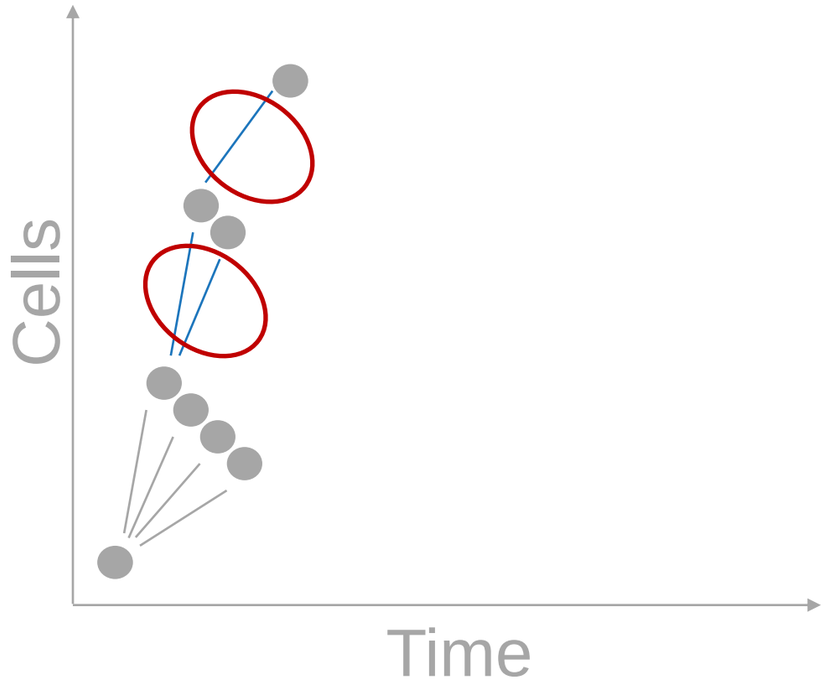
Introducing a drug into the system through a link with the Gompertz model parameters.



Change the initial proliferation rate

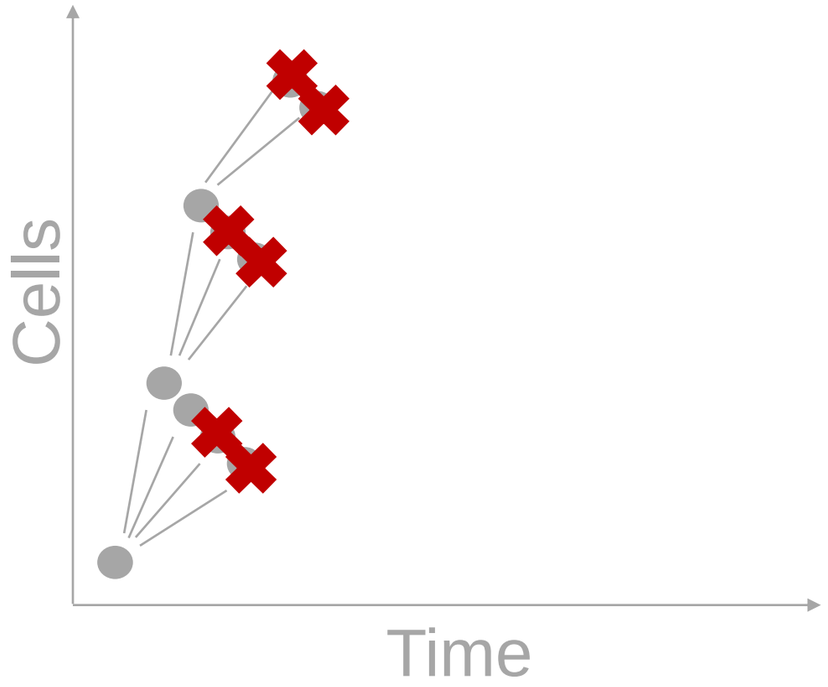
Introducing a drug into the system through a link with the Gompertz model parameters.



Change the rate of decay of the proliferation rate

Introducing a drug into the system through a link with the Gompertz model parameters.

Kill cells



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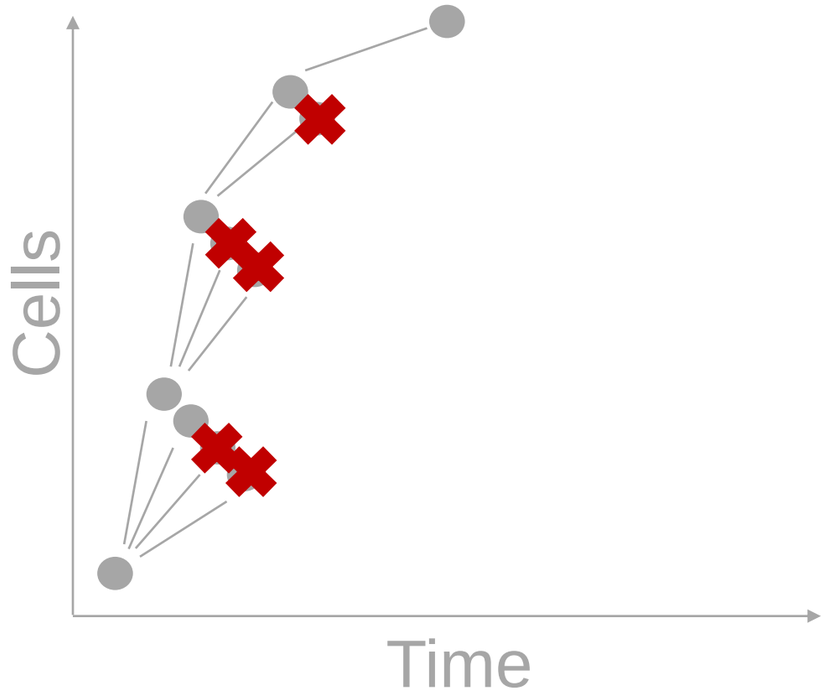
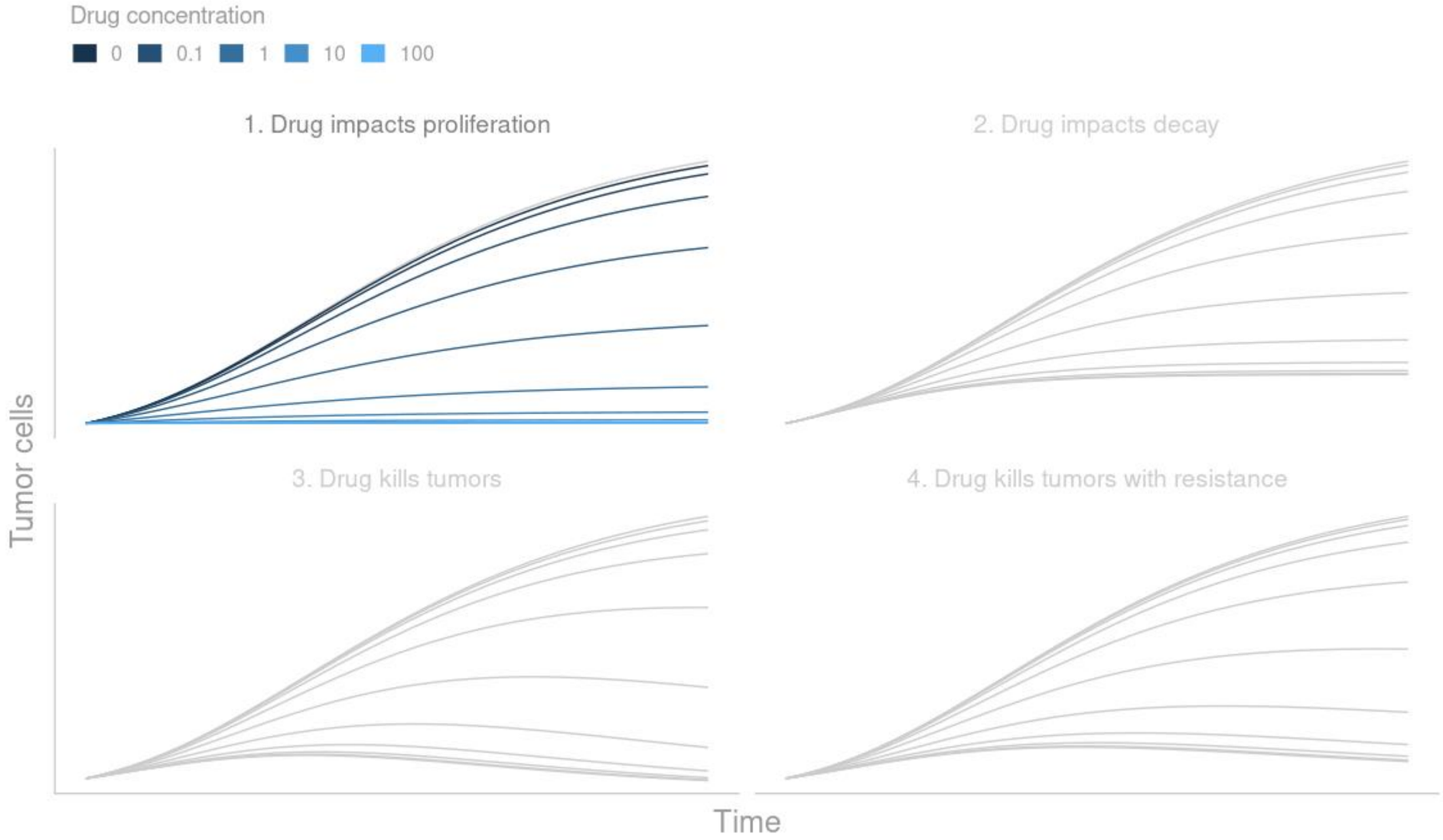


Kill cells with drug resistance over time

Some examples of simulated data.



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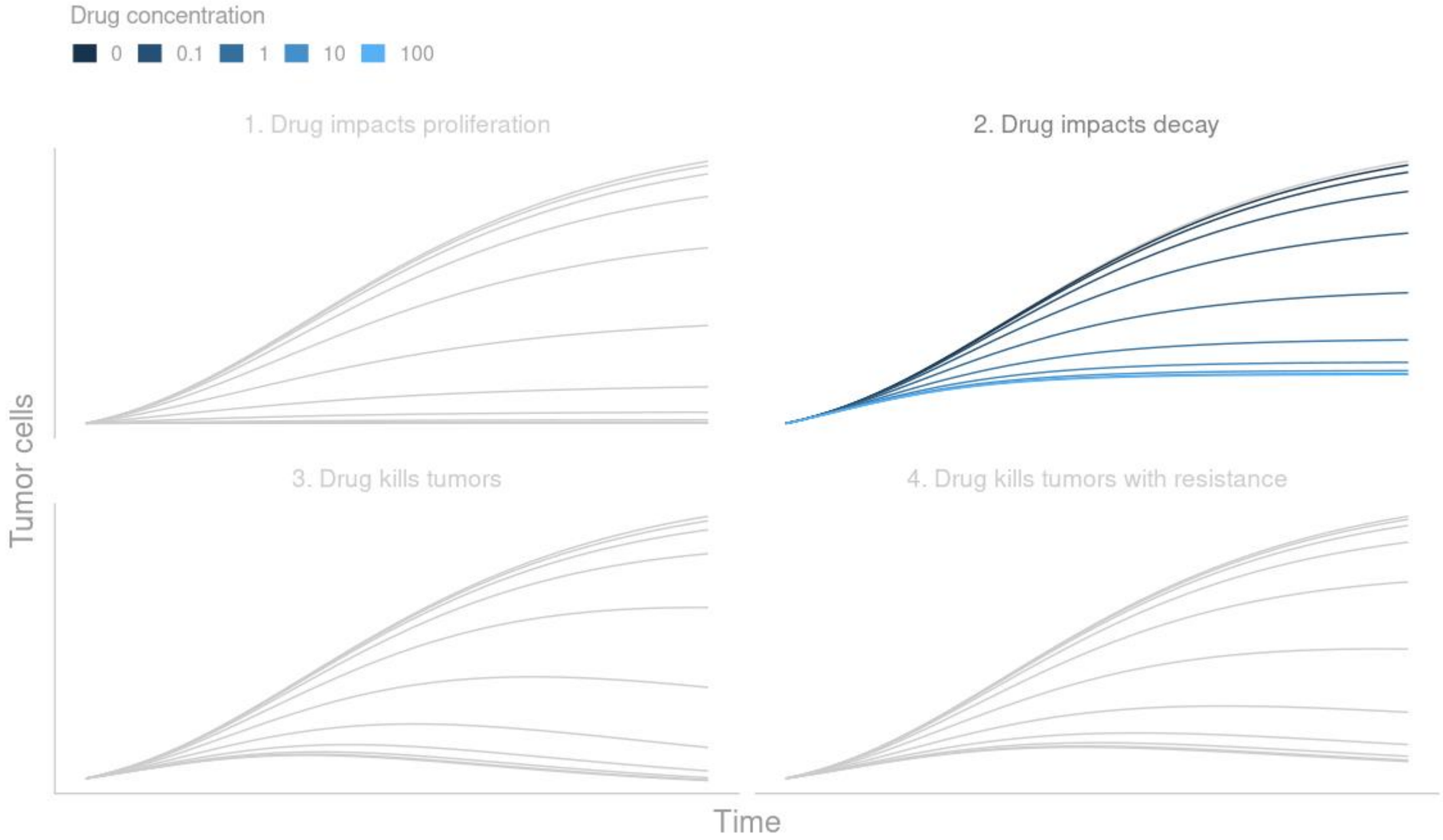

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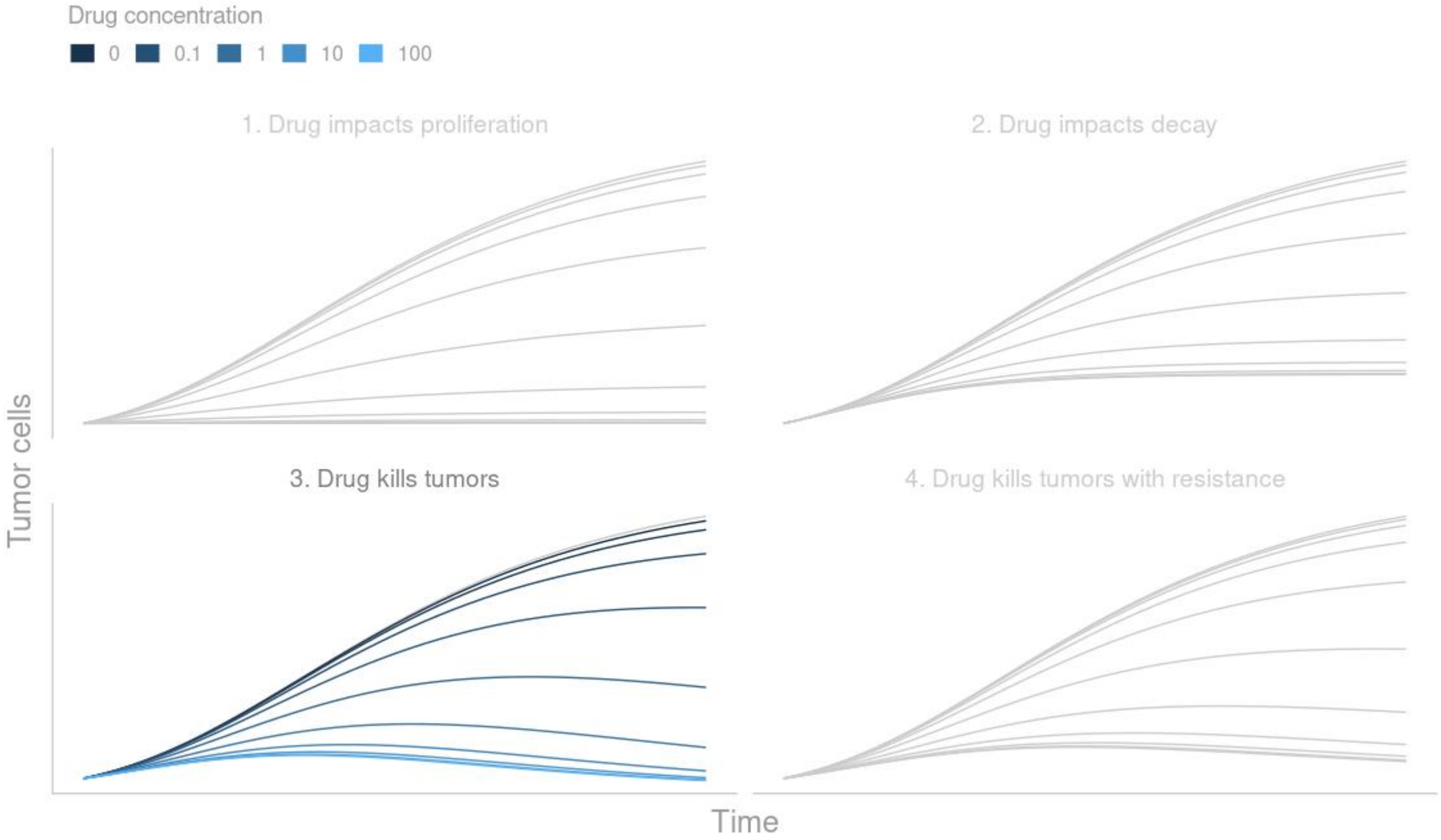

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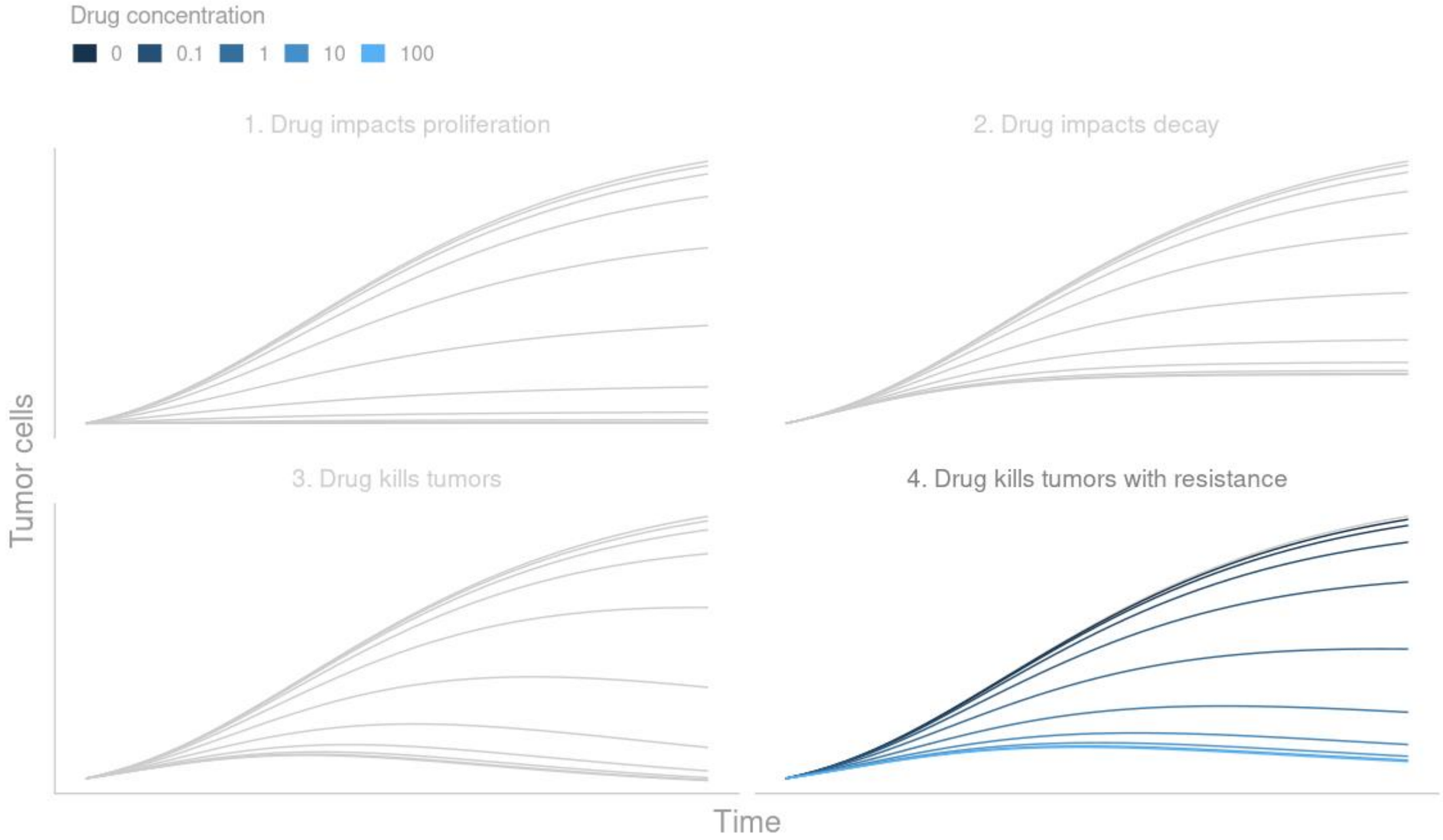

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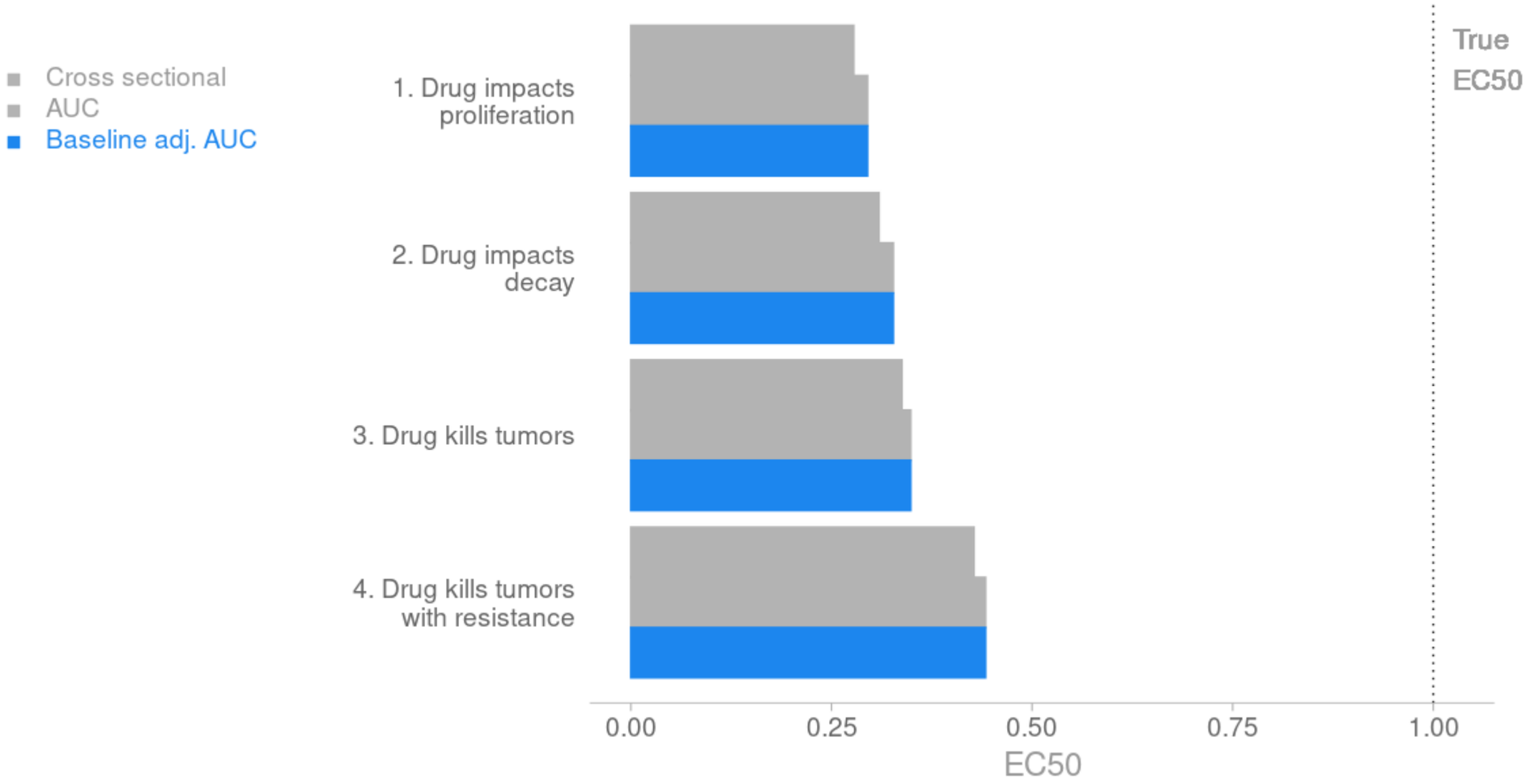
All methods resulted in biased EC50 estimates.



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Can we modify the different “flattening” methods to decrease the bias of the EC50 estimate?

Cross sectional – log transform the measured responses.

AUC/Baseline adj. AUC – log transform AUC prior to normalization.

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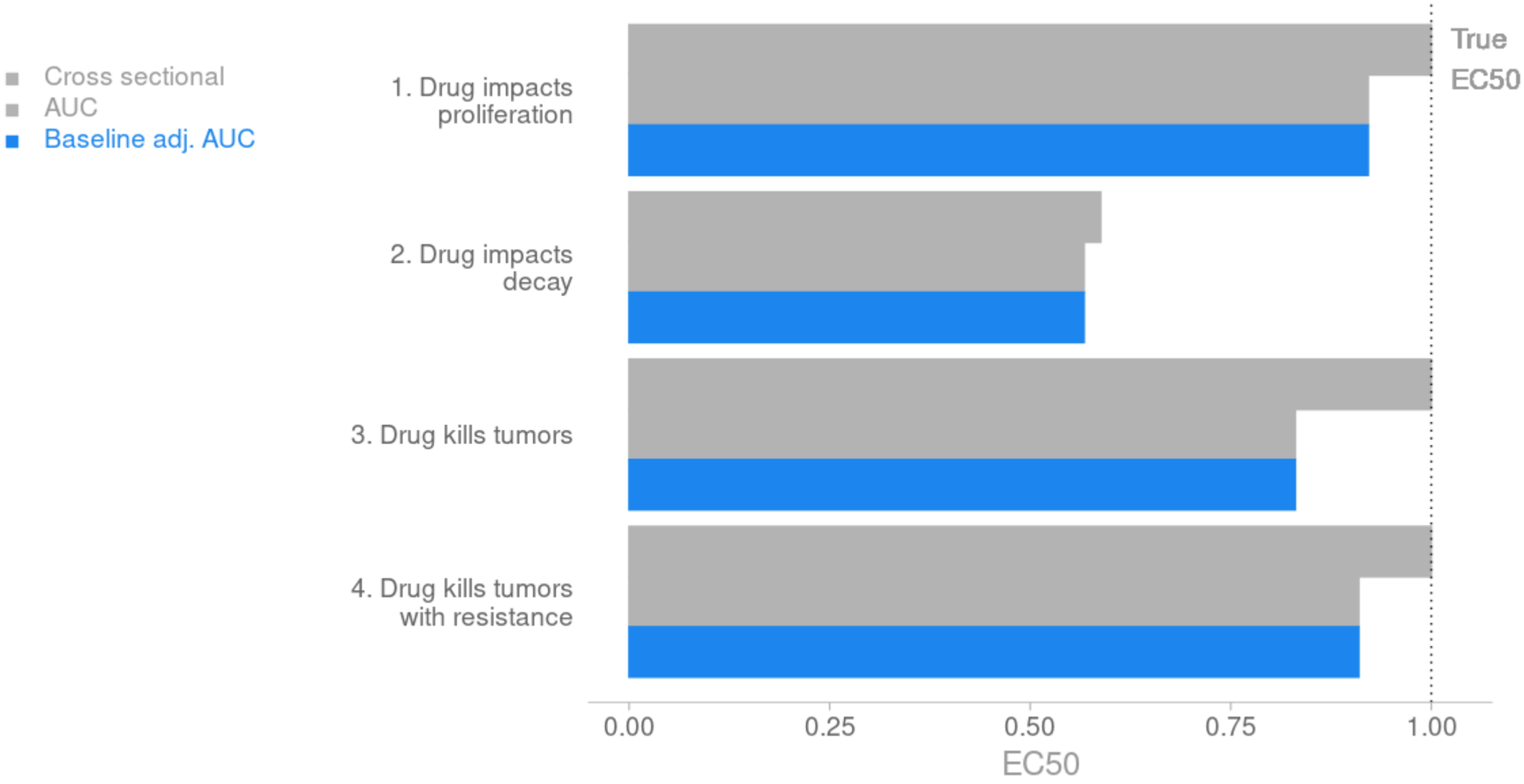
Cross sectional – log transform the measured responses.

AUC/Baseline adj. AUC – log transform AUC prior to normalization.

Does including a logarithmic transformation decrease the bias of the EC50 estimate?



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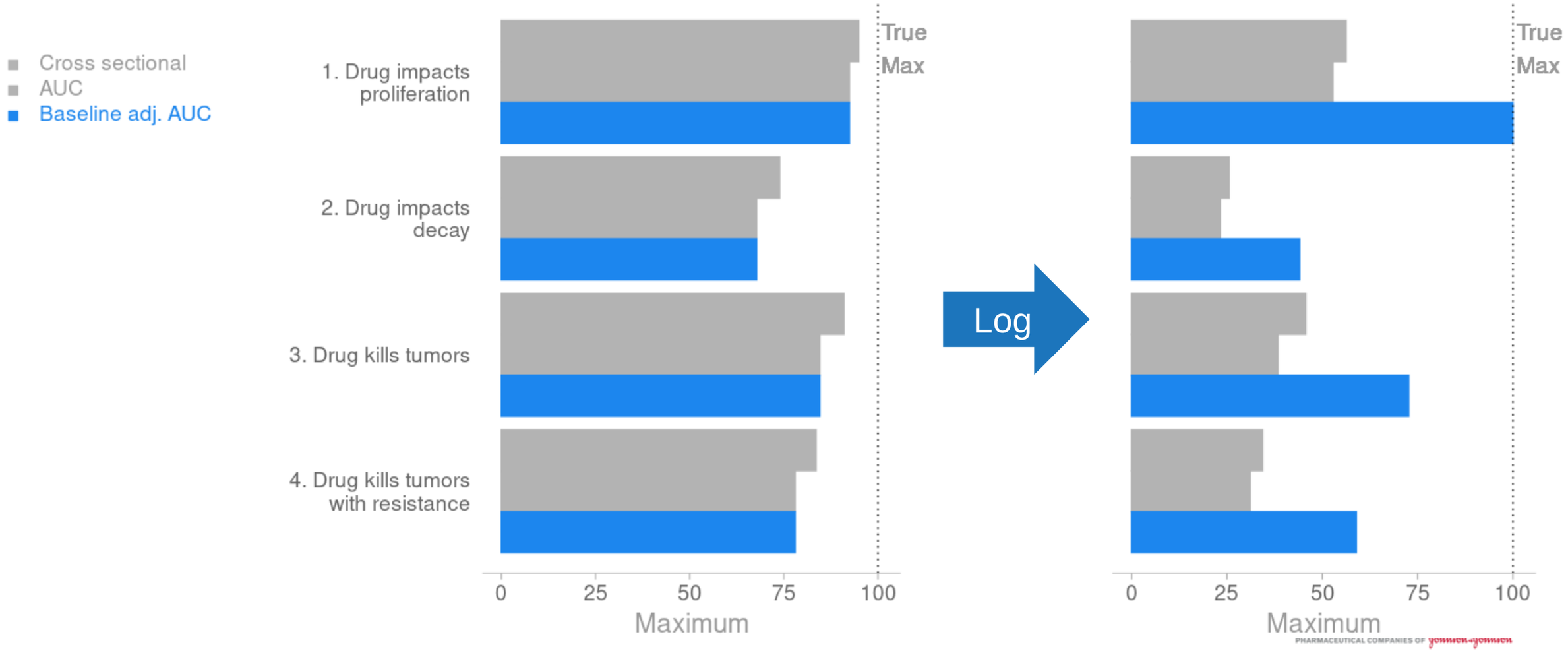
What is the impact of the logarithmic transformation on the estimation of the upper asymptote?



There are trade-offs when using the logarithmic transformation.

All methods biased (EC50) on **original** data scale.

Cross sectional and AUC estimated of EC50 less biased on logarithmic scale; however, max cytotoxicity extremely biased.

Baseline adj. AUC (with log-transformed AUC) balances the biases of EC50 and max cytotoxicity.

Results hold when data simulated with random error.

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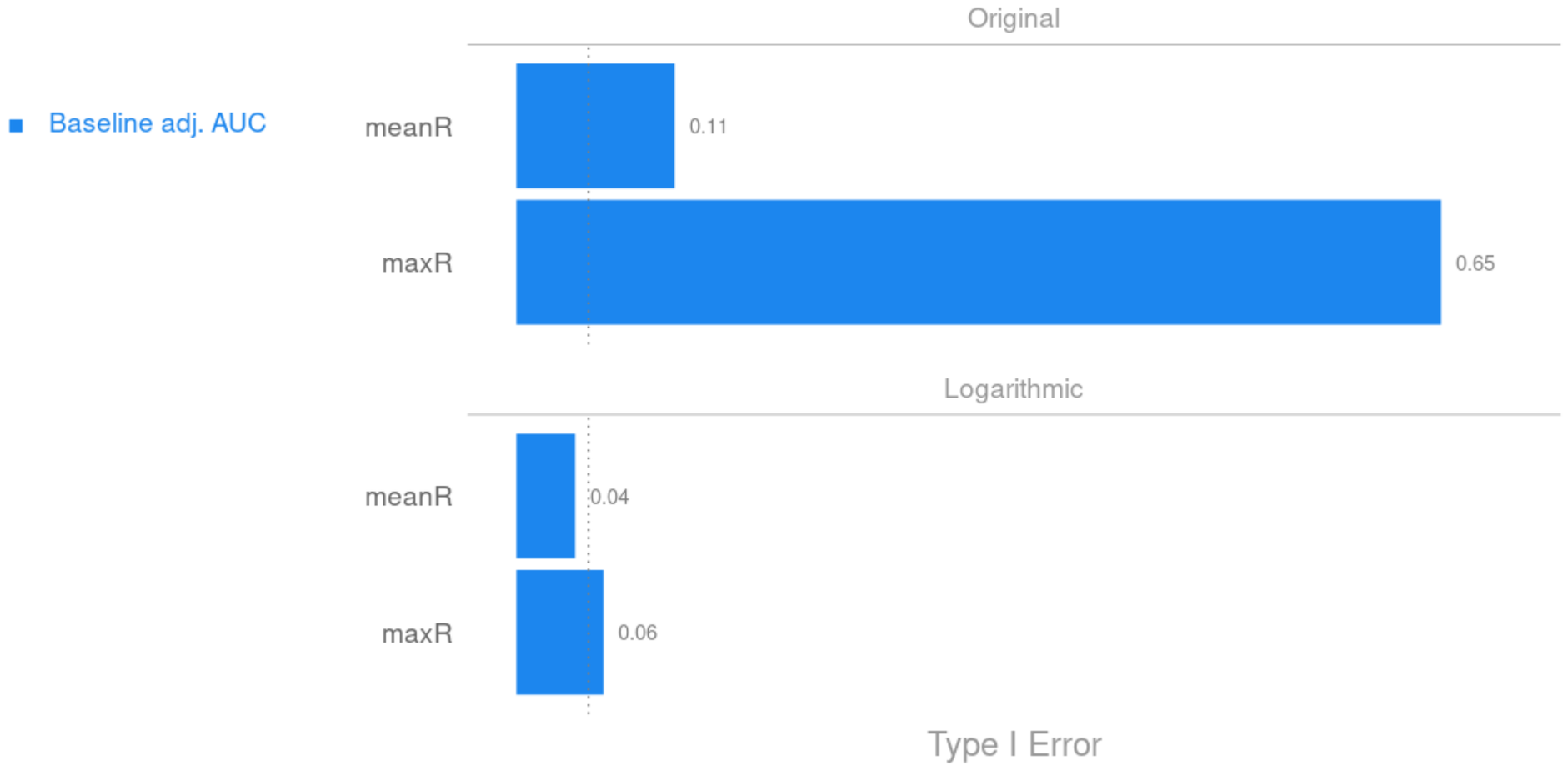
Reducing the bias of EC50 estimate is important for upstream analyses.



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Take home messages…

Under simulation, log transformed AUC (**adjusted for baseline**) is the best (as measured by EC50 and max cytotoxicity) method to use for "flattening" temporal assay data in order to estimate dose response.

Bias in the EC50 estimate inflates type I error of meanR and maxR statistic.


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