nlmixr^2: data specifications and exploration

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Current nlmixr² team is composed of many companies collaborating for a common goal

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Vision of nlmixr²

nlmixr^2 or rxode^2 model data define both the observations and dosing events; the basics are described below

Observations

TIME

Independent Variable (sometimes called **x**), often TIME since pharmacometrics models describe drug concentrations and effects over time

DV

Dependent Variable (sometimes called **y**), which often describes the observed drug response or concentration

CMT

Compartment/Effect Location. The parsed nlmixr2 model describes this for a specific model

EVID

The event id, in this case EVID=0 for observations

DVID

Dependent Variable ID. The parsed nlmixr2 model describes this for a specific model

Dosing Events

AMT

Amount of Drug or Amount of Event at the time.

CMT

ODE compartment name or number where dosing occurs

EVID

Nlmixr2 event type (0: Observation, 1: Dose, 2: Other, 3: Reset, 4: Reset+Dose, 5: Replace; 6: Multiply; 7: Phantom/Transit compartment)

RATE or DUR

Rate (RATE) or Duration (DUR) of an infusion

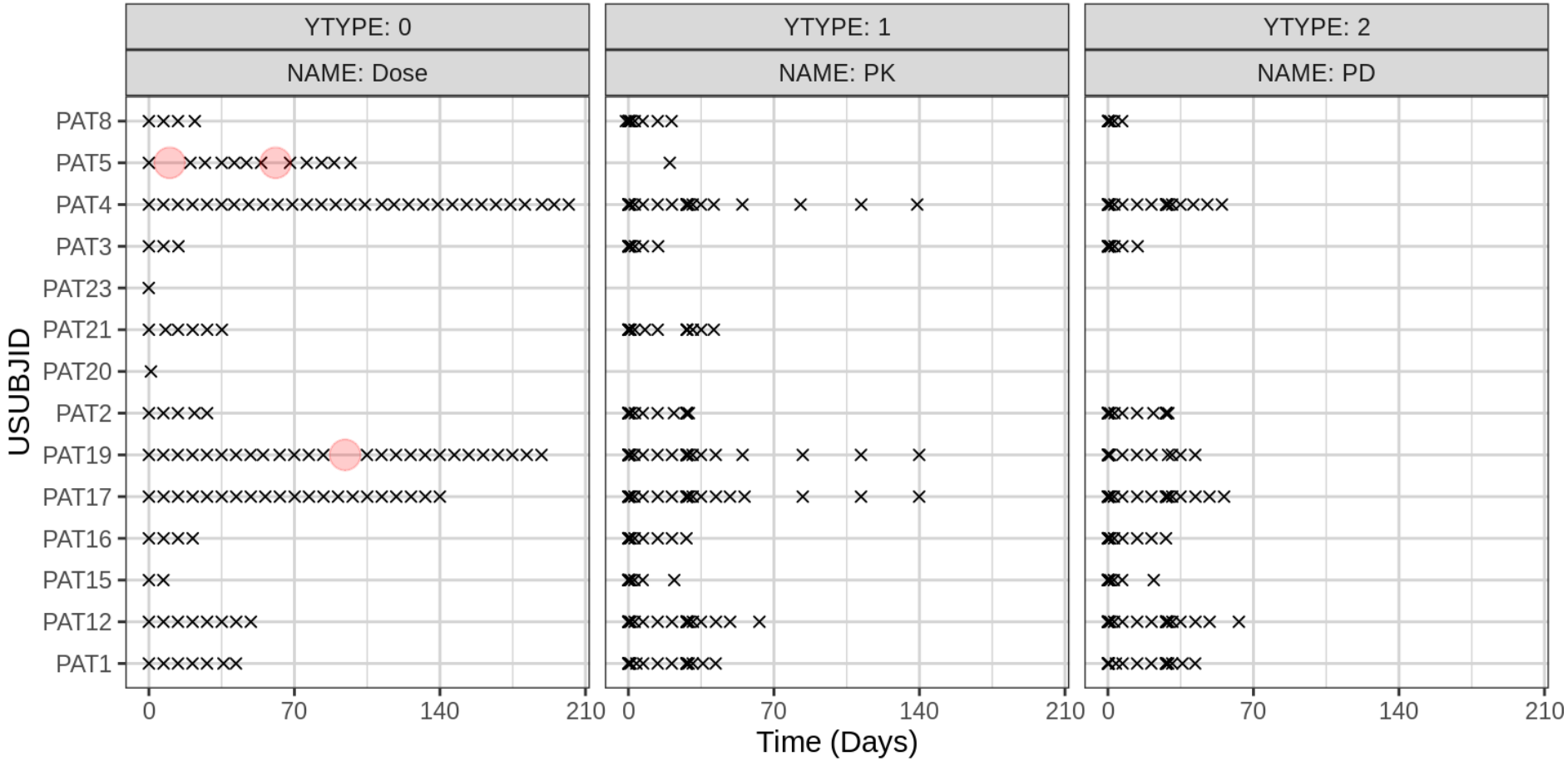
Subject Identifier (ID) text/numeric

First step in any analysis is to make sure your data are correct (from xgx)

Some common checks are:

- Patient Information
  - Number of Patients per Treatment Arm? More or less than expected?
  - Number of Observations/Doses per Treatment Arm? More or less than expected?
- Dosing:
  - Patients that received a dose of 0?
  - Patients that never received a dose?
- Observations:
  - Duplicate, or missing times or observations?
  - Summary statistics of observations per time point?
- Demographics
  - Summary of key demographic covariates (Number in category or mean/sd/range median)

This includes graphical exploration of subject dosing/observation history (and perhaps missing values too)



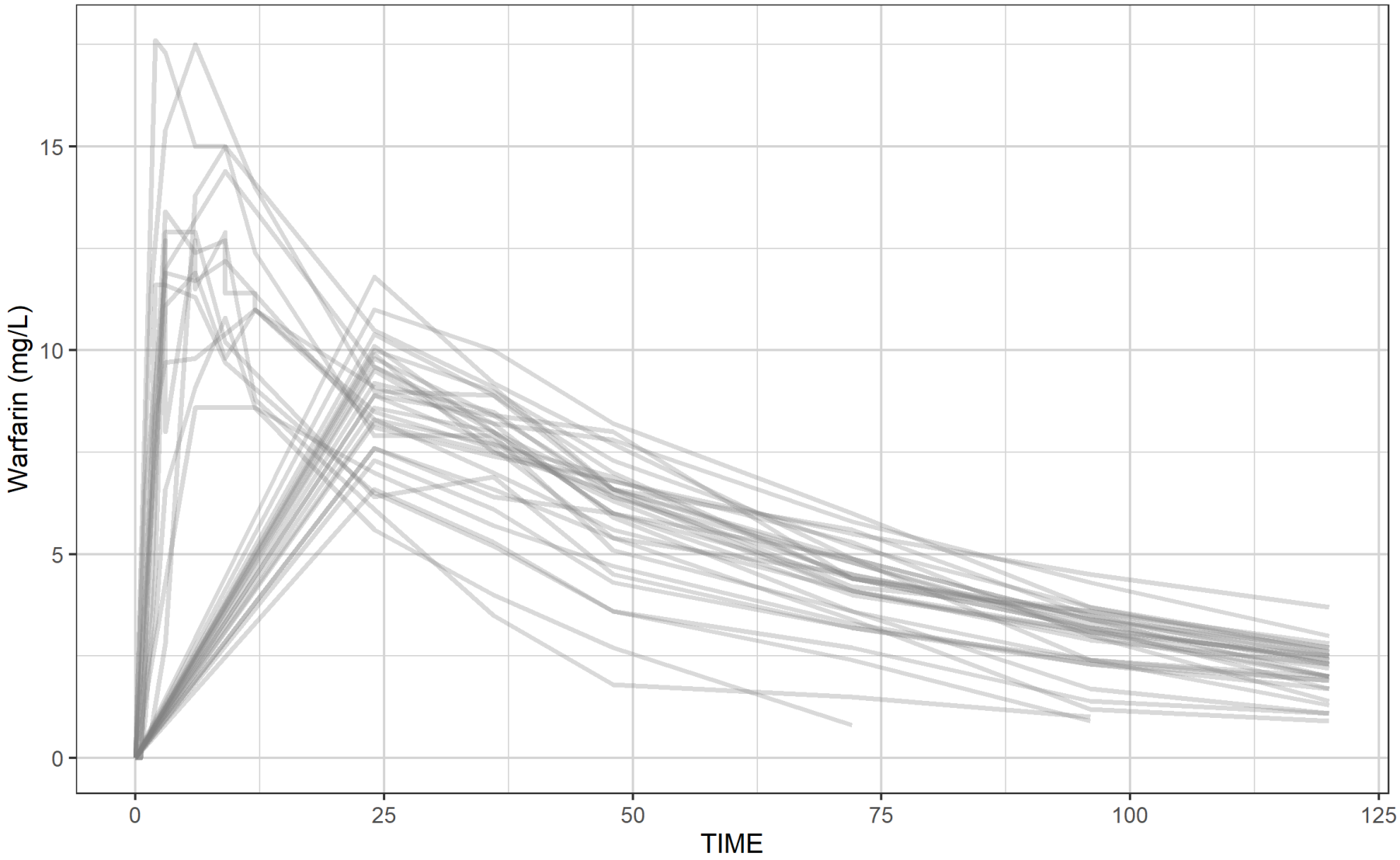
Code available at http://opensource.nibr.com/xgx/Data_Checking.html

Assess the data before you start analysis (from PopSim Course)

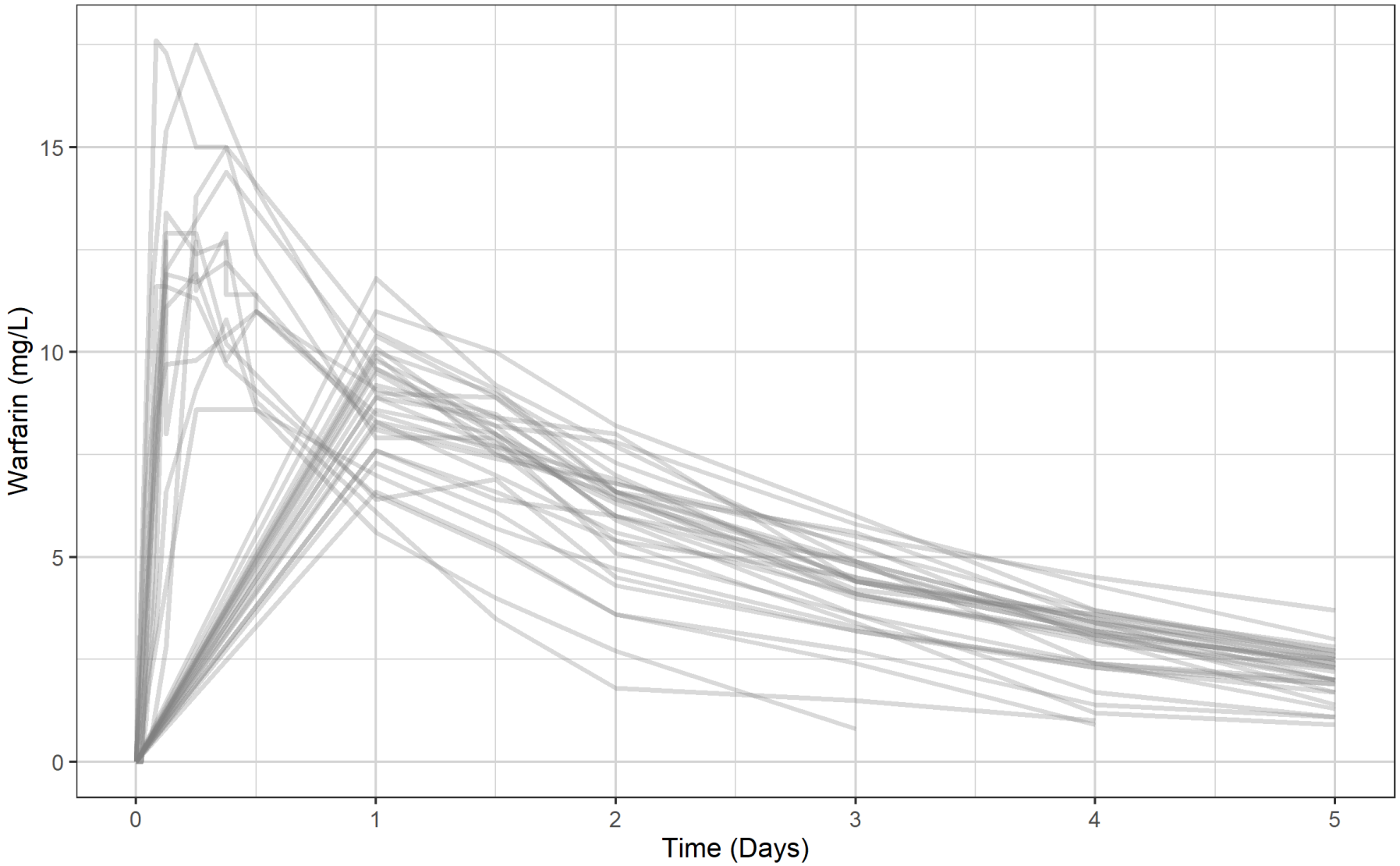
- Classic data sets used by Nick Holford in his courses:
  - O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs initiation of warfarin therapy without a loading dose. Circulation 1968;38:169-177
  - O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963;42(10):1542-1551

- Some simple plots to get a feel of the data
- Additional xgxr functionality to improve and summarize the profiles

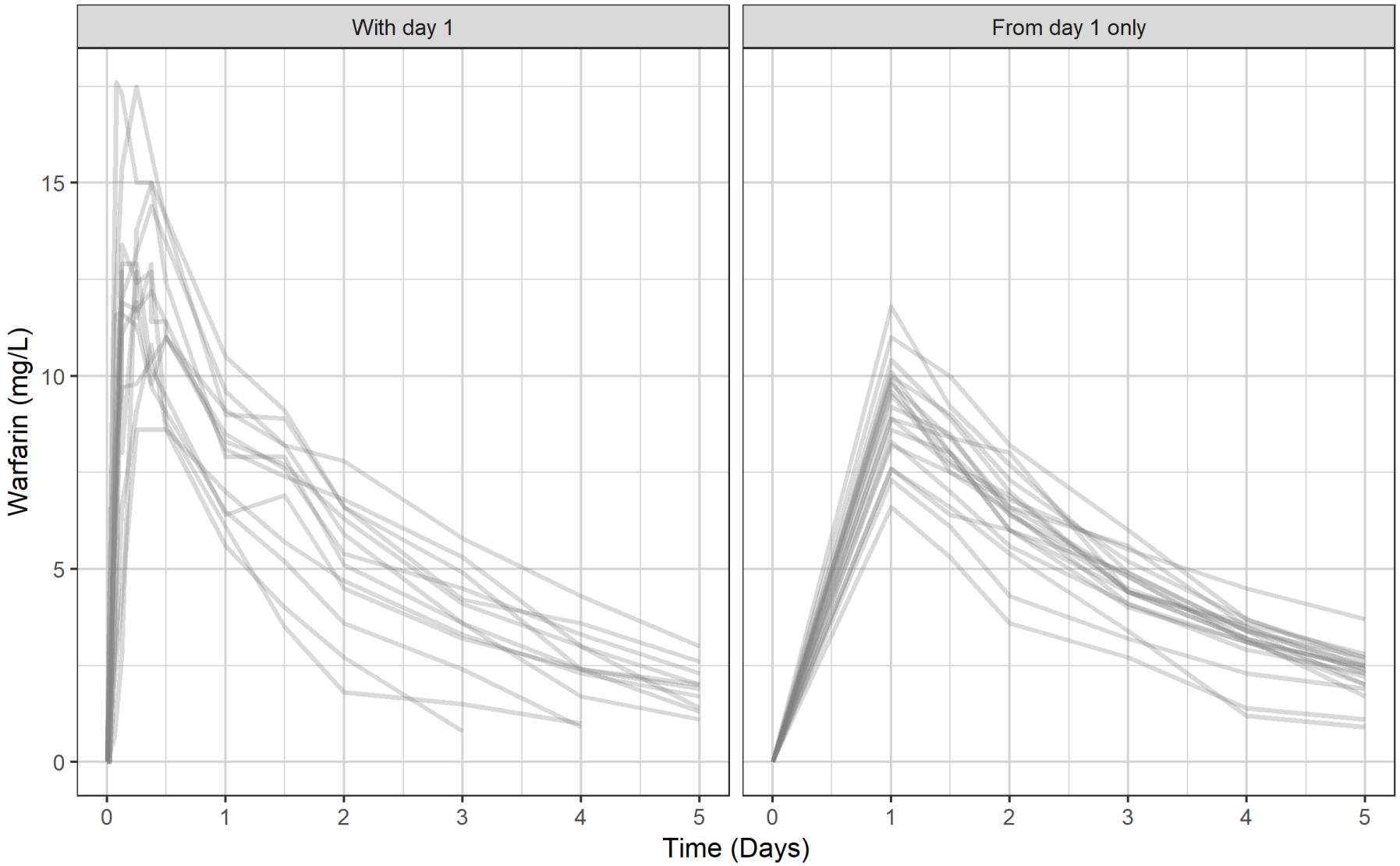
Our warfarin data file: a simple ggplot to provide an impression



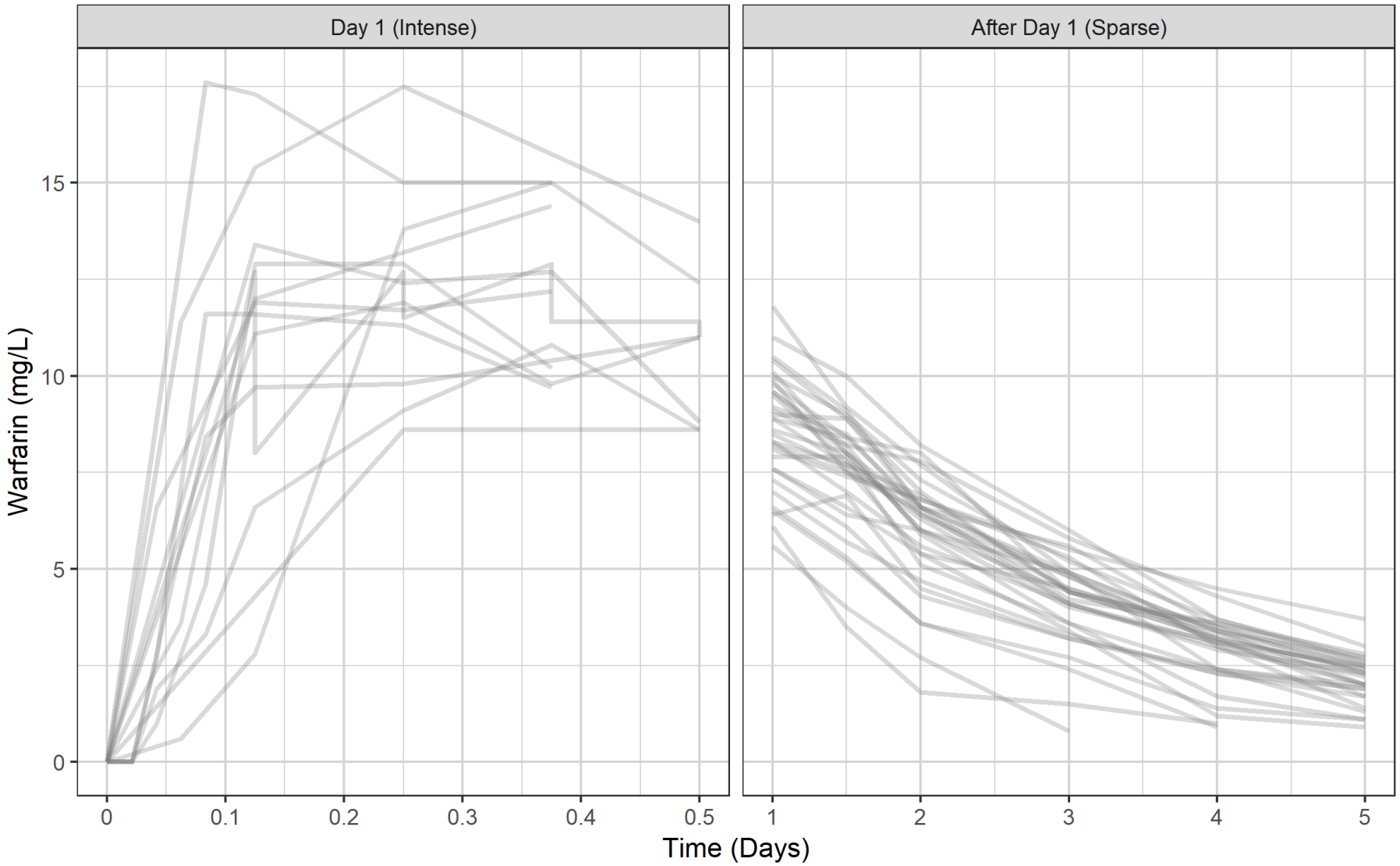
Change the x-axis from hours to days and add a proper label using the xgx helper `xgx_scale_x_time_units(units_dataset = "hours", units_plot = "days")`



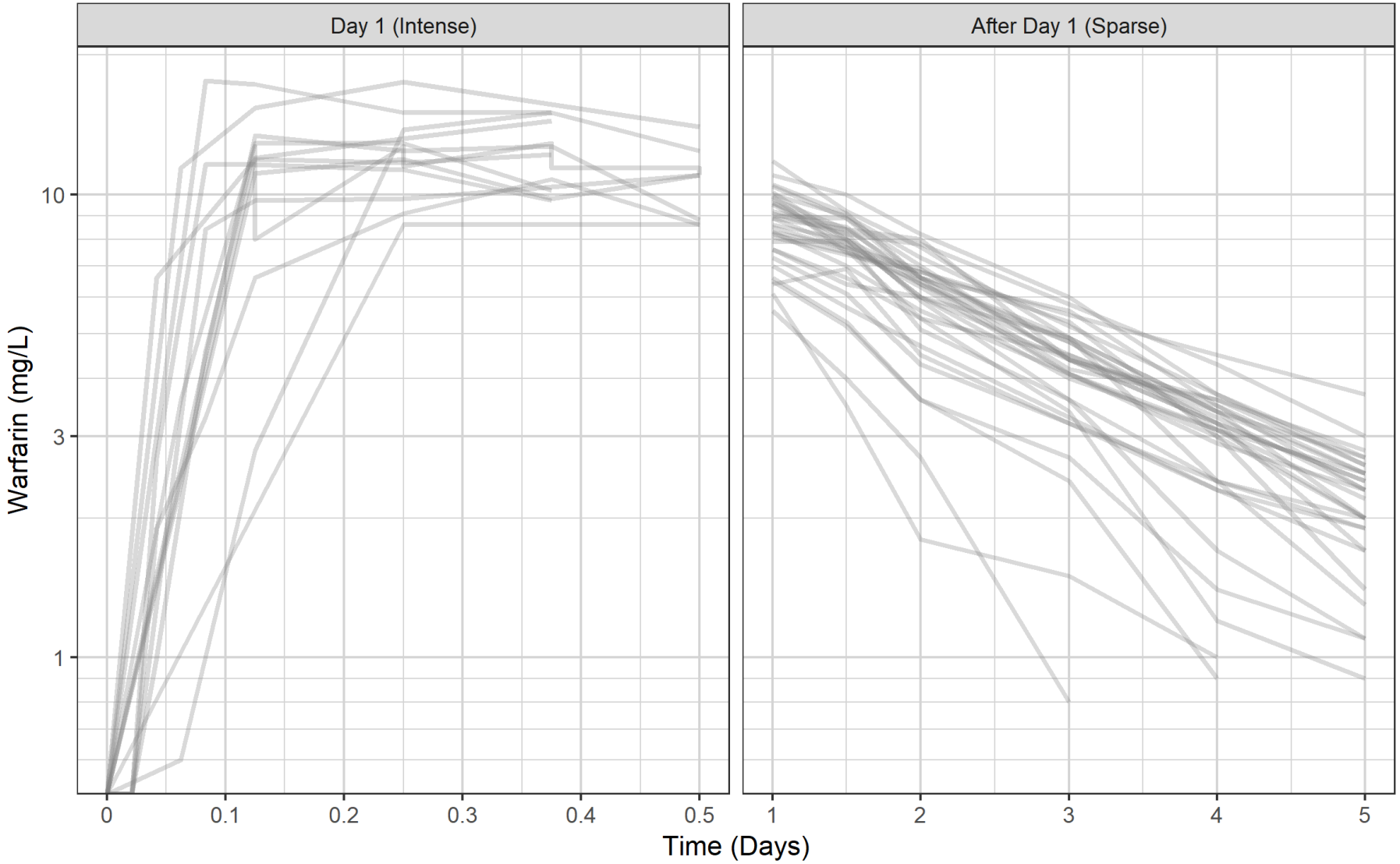
The data set has two types of profiles…



...but you can also group by rich day 1 and sparse later days...



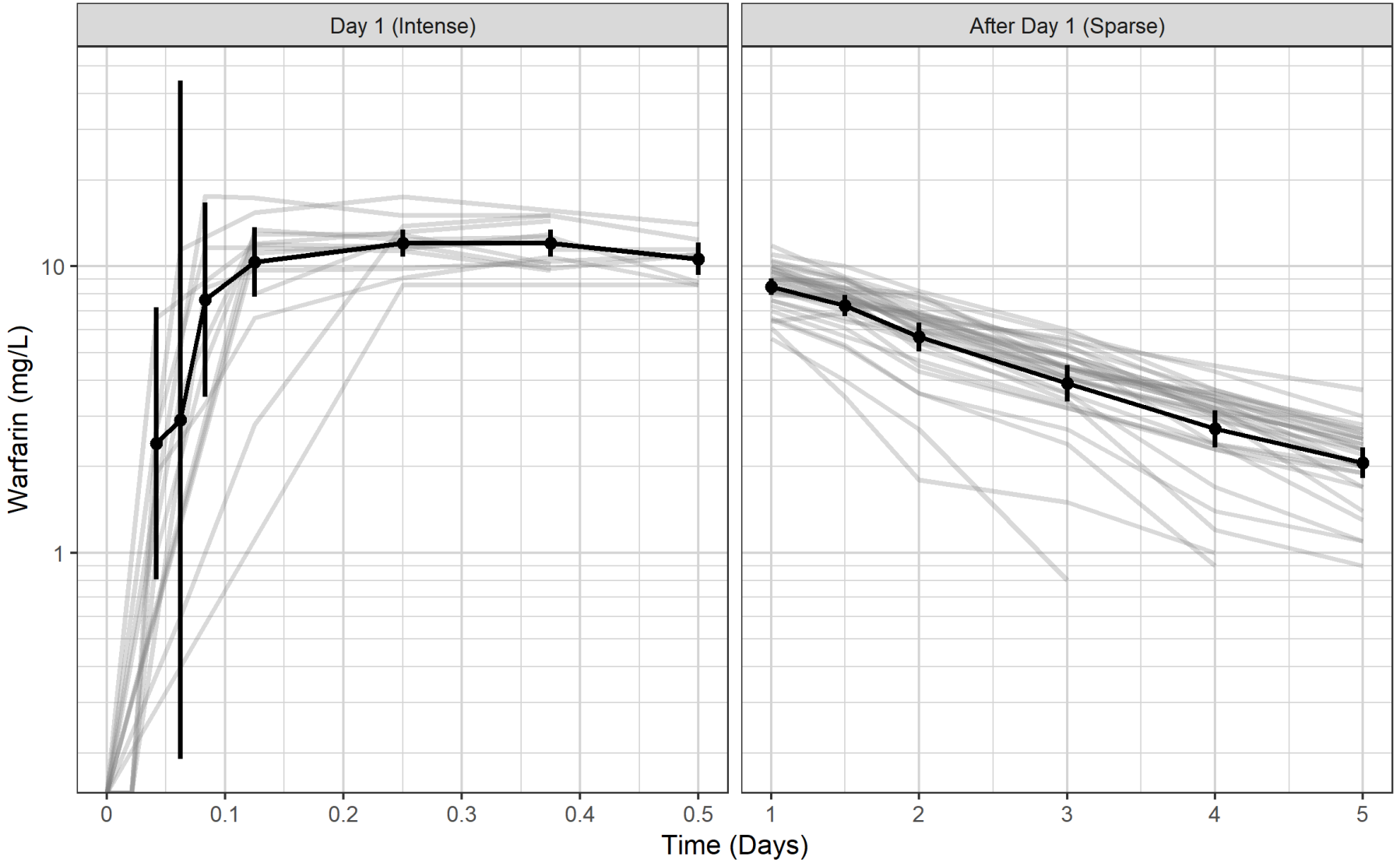
Switch to semi-log scale using xgx helper `xgx_scale_y_log10()`
Any clues to what model we should use?



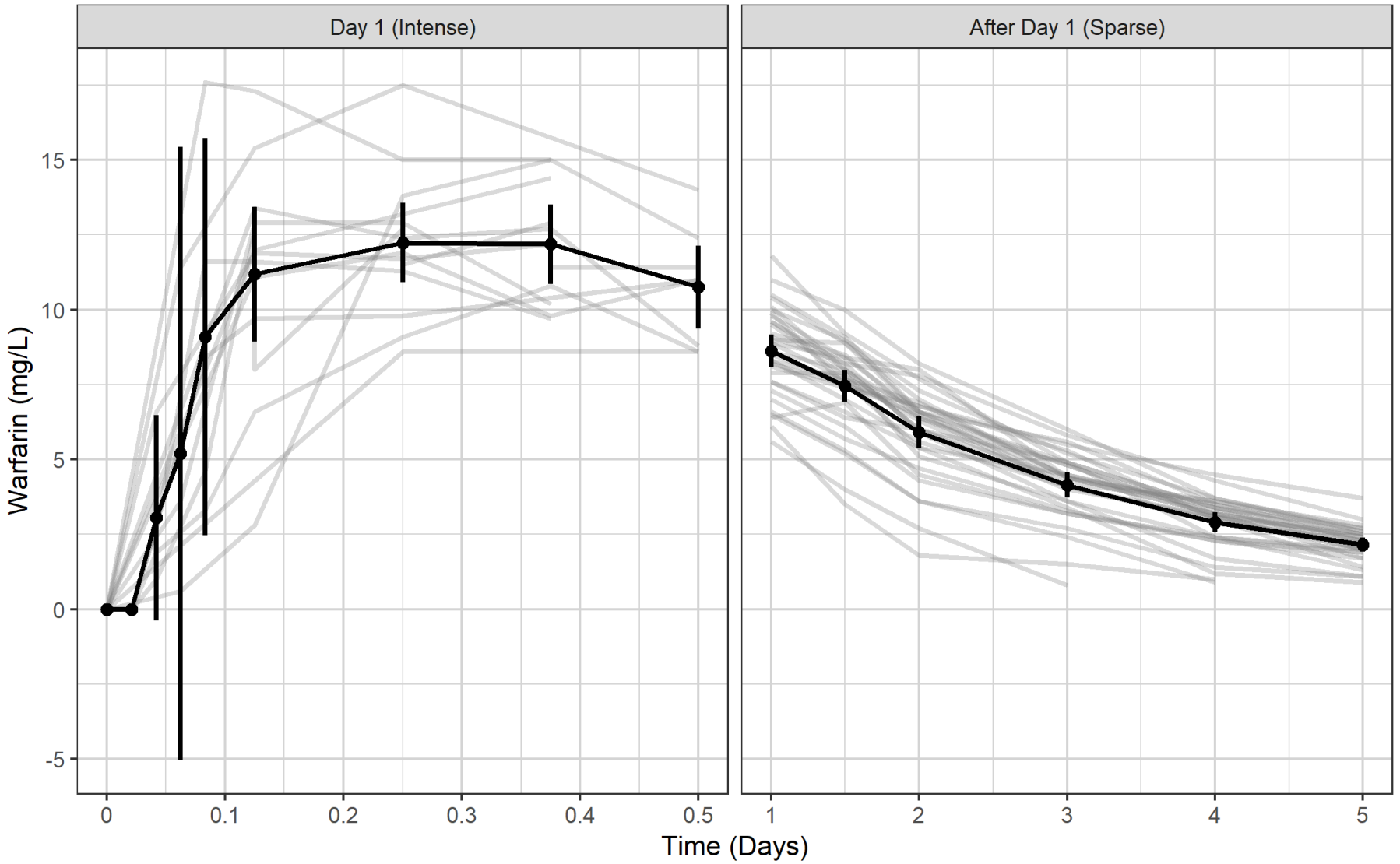
nlmixr²

xgx can also add nice summary information if data has nominal times: summaries of mean plus 95% CI

```
xgx_geom_ci(aes(x = TIME, color = NULL, group = NULL, shape = NULL), conf level = 0.95)
```

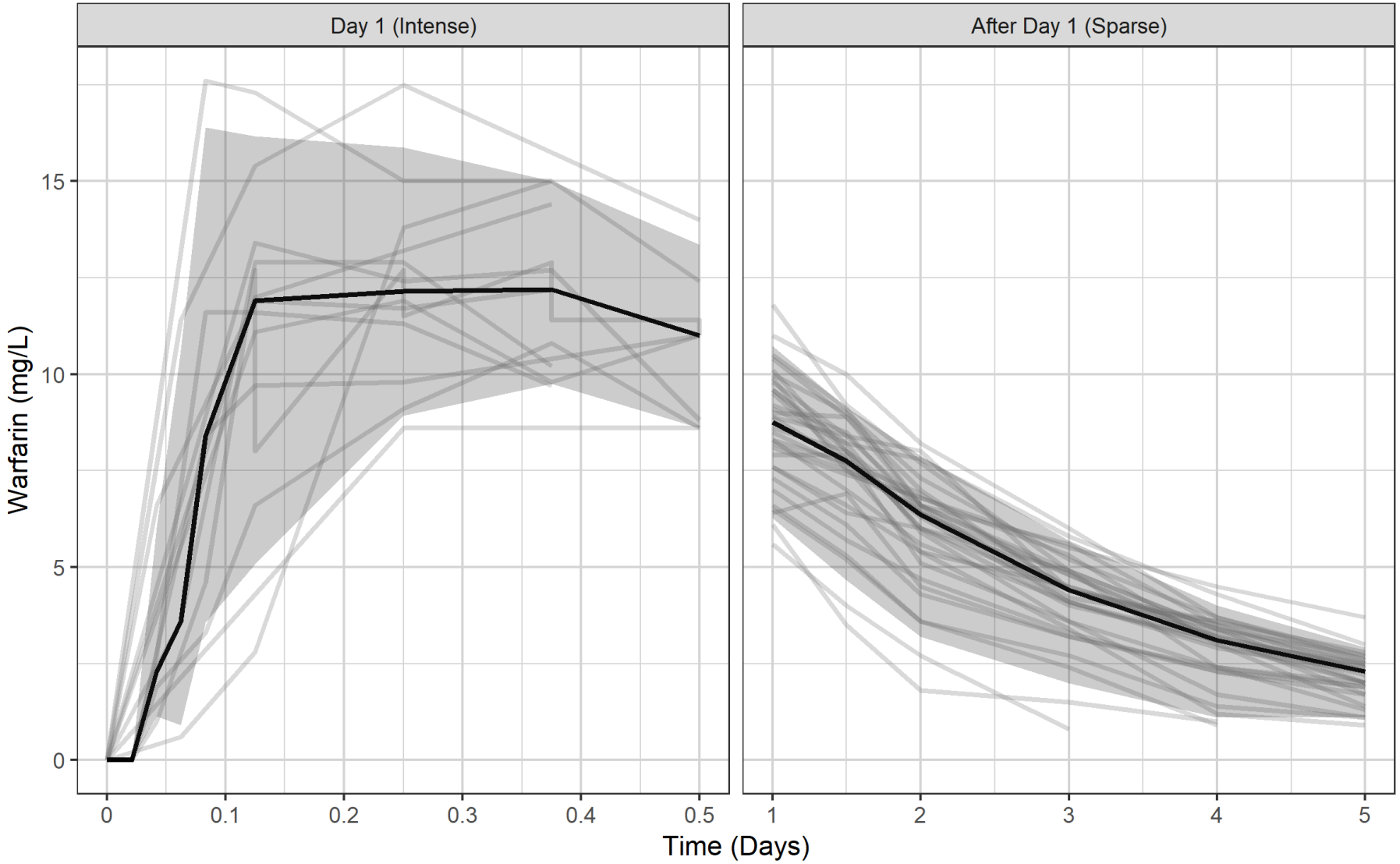


On linear scale this would result in a CI crossing zero because CIs are assumed symmetrical

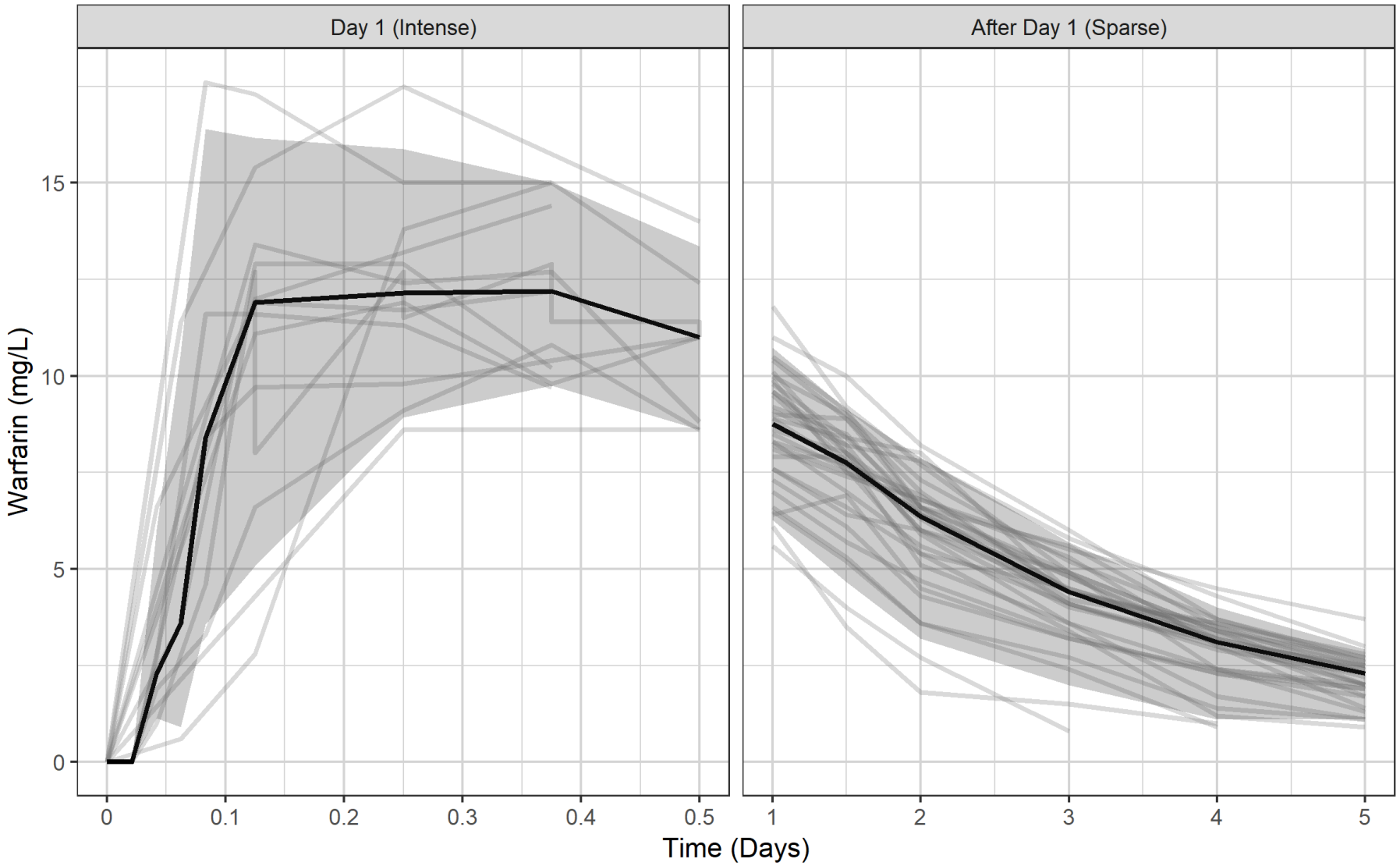


...so perhaps a median and 95% of the data would be more suitable

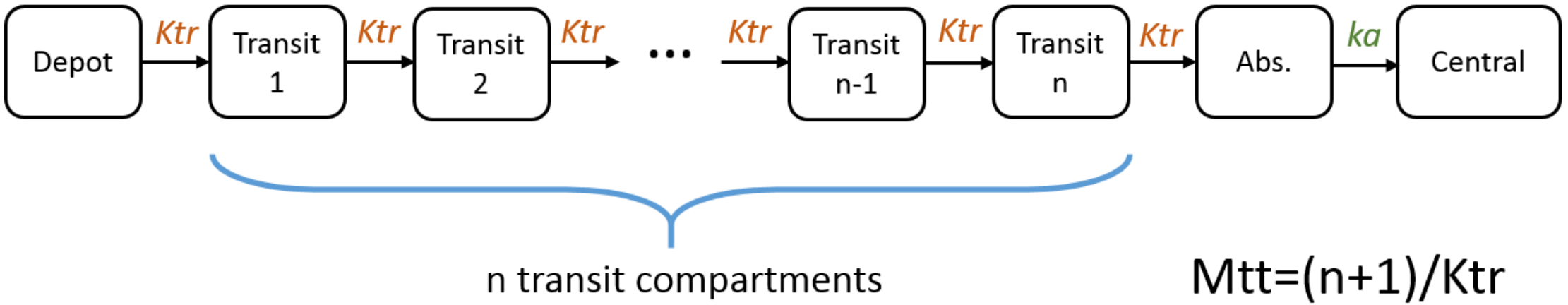
```
xgx_geom_pi(aes(x = TIME, color = NULL, group = NULL, shape = NULL)
```



There appears to be a delay in absorption…



One way to model delayed absorption is through ODE compartments that must be crossed first (transit compartment)



- Transit compartments take more time to enter the system because they have to go through n transit compartments before entering the blood
- Transit compartments and any arbitrary ODE can be fit with nlmixr2
- (Image from https://mlxtran.lixoft.com/examples/transit-compartments-weibull-absorption/)