

task2

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2025-11-14

Task 2: Tumor Models in Mice for Studying Treatment Effect

The dataset consists of 60 mice with repeated tumor volume measurements (for 90 days). Each mouse belongs to one of two disease models: induced tumors or xenograft mice, and is assigned either to a control or treatment group receiving the compound ATC10X.

set up

```
dat <- read.csv("Data_T2.csv")
```

```
str(dat)
```

```
## 'data.frame': 5460 obs. of 6 variables:
## $ X      : int 1 2 3 4 5 6 7 8 9 10 ...
## $ ID     : int 1 1 1 1 1 1 1 1 1 1 ...
## $ Time   : int 0 1 2 3 4 5 6 7 8 9 ...
## $ DV     : num 481 525 474 538 519 ...
## $ Treatment: int 0 0 0 0 0 0 0 0 0 0 ...
## $ Model  : int 1 1 1 1 1 1 1 1 1 1 ...
```

```
summary(dat)
```

	X	ID	Time	DV	Treatment
## Min.	1	Min. : 1.00	Min. : 0	Min. : 361.8	Min. : 0.0
## 1st Qu.	1366	1st Qu. : 15.75	1st Qu. : 22	1st Qu. : 559.2	1st Qu. : 0.0
## Median	2730	Median : 30.50	Median : 45	Median : 635.6	Median : 0.5
## Mean	2730	Mean : 30.50	Mean : 45	Mean : 673.2	Mean : 0.5
## 3rd Qu.	4095	3rd Qu. : 45.25	3rd Qu. : 68	3rd Qu. : 760.3	3rd Qu. : 1.0
## Max.	5460	Max. : 60.00	Max. : 90	Max. : 1381.5	Max. : 1.0
## Model					
## Min.		: 0.0			
## 1st Qu.		: 0.0			
## Median		: 1.0			
## Mean		: 0.6			
## 3rd Qu.		: 1.0			
## Max.		: 1.0			

```
dat <- dat %>%
  mutate(
    ID      = factor(ID),
    Treatment = factor(Treatment, levels = c(0, 1),
                        labels = c("Control", "Treatment")),
    Model   = factor(Model, levels = c(0, 1),
                      labels = c("Induced", "Xenograft")),
    logDV   = log(DV)
  )

summary(dat$DV)
```

```
##      Min. 1st Qu. Median     Mean 3rd Qu.     Max.
##  361.8   559.2  635.6   673.2   760.3  1381.5
```

```
summary(dat$logDV)
```

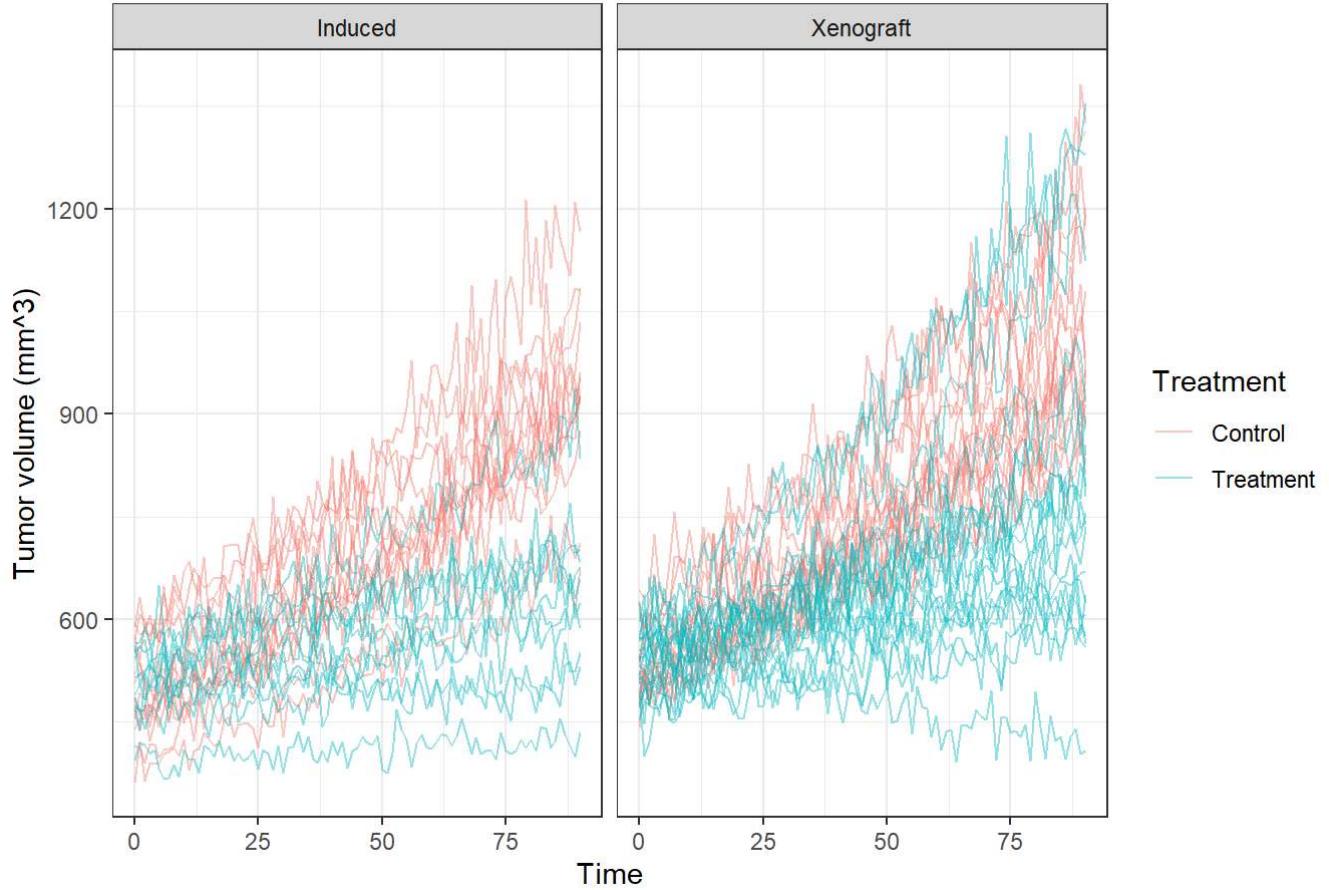
```
##      Min. 1st Qu. Median     Mean 3rd Qu.     Max.
##  5.891   6.327  6.455   6.485   6.634  7.231
```

visualization

Initial visualisations of raw DV and log-transformed DV showed that tumor growth is broadly exponential on the original scale but near-linear on the log scale. Average curves further suggested that tumors grew over time in all groups, with notably slower growth in the treatment group, and with broadly similar growth patterns across the two mouse models.

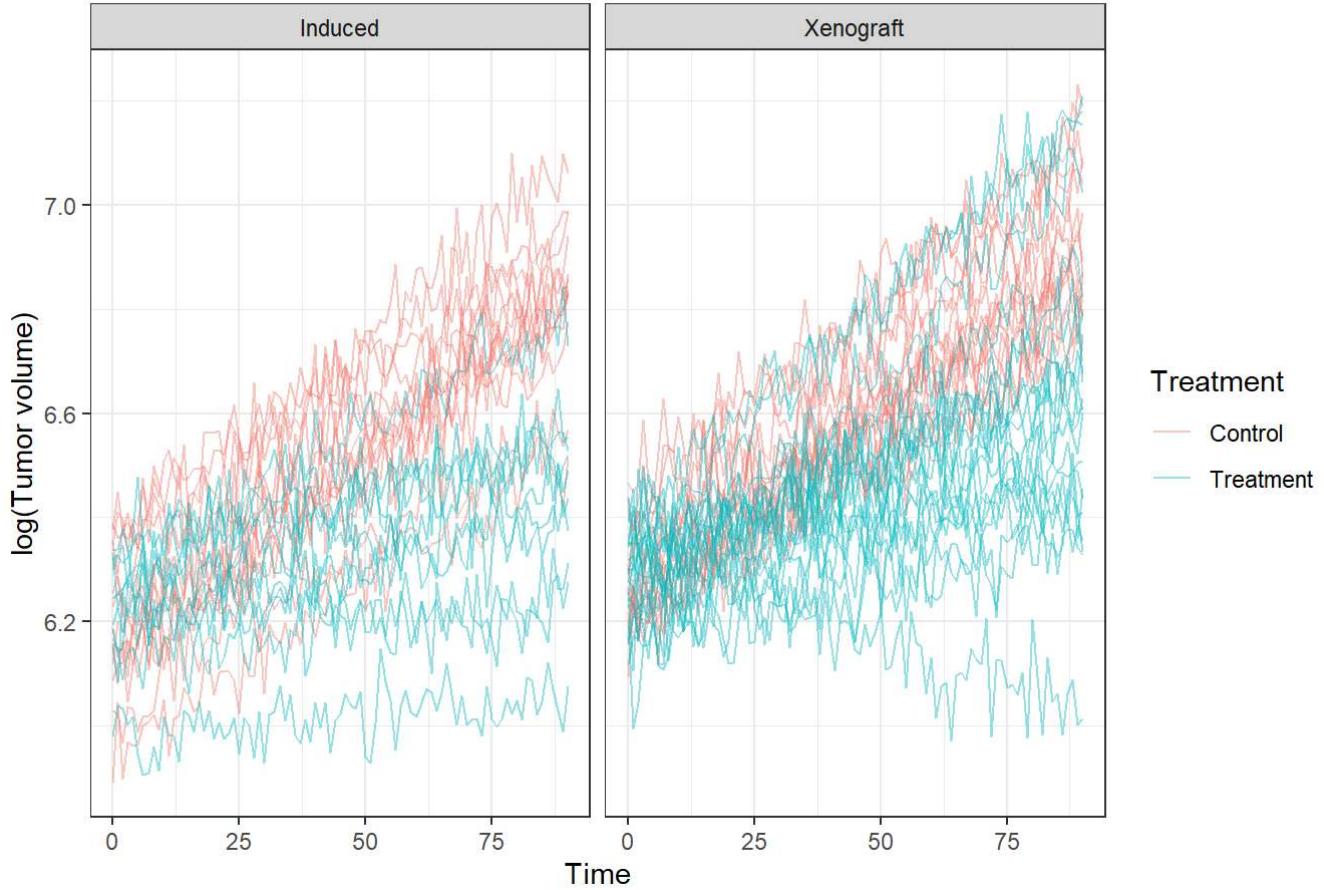
```
# raw DV
ggplot(dat, aes(x = Time, y = DV, group = ID,
                 colour = Treatment)) +
  geom_line(alpha = 0.4) +
  facet_wrap(~ Model) +
  scale_y_continuous("Tumor volume (mm^3)") +
  labs(title = "Individual tumor growth curves by treatment and model") +
  theme_bw()
```

Individual tumor growth curves by treatment and model



```
# log(DV)
ggplot(dat, aes(x = Time, y = logDV, group = ID,
                 colour = Treatment)) +
  geom_line(alpha = 0.4) +
  facet_wrap(~ Model) +
  scale_y_continuous("log(Tumor volume)") +
  labs(title = "Individual log tumor growth curves by treatment and model") +
  theme_bw()
```

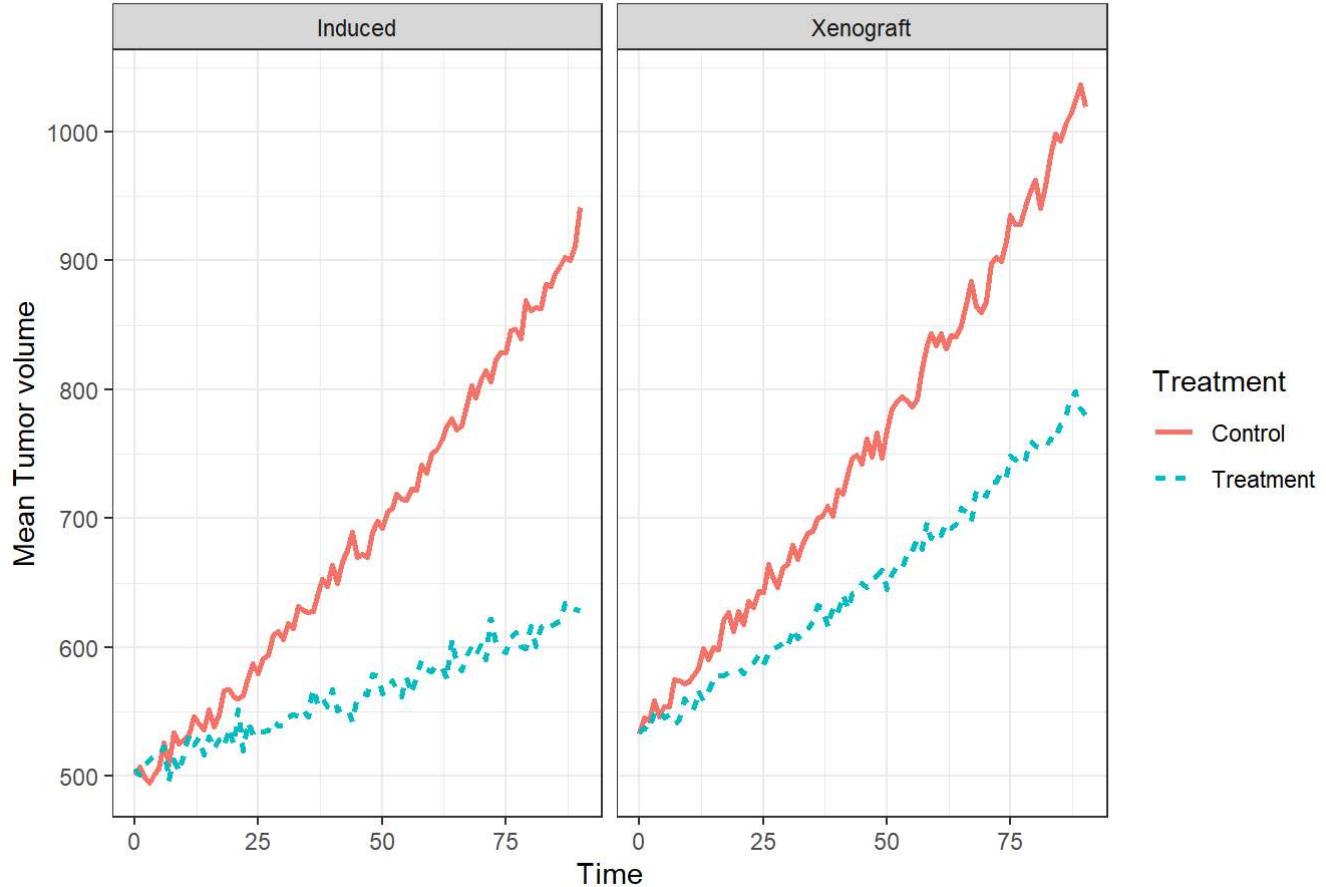
Individual log tumor growth curves by treatment and model



```
ggplot(dat, aes(x = Time, y = DV,
                 colour = Treatment, linetype = Treatment)) +
  stat_summary(fun = mean, geom = "line", size = 1) +
  facet_wrap(~ Model) +
  labs(y = "Mean Tumor volume",
       title = "Mean tumor growth by treatment and model") +
  theme_bw()
```

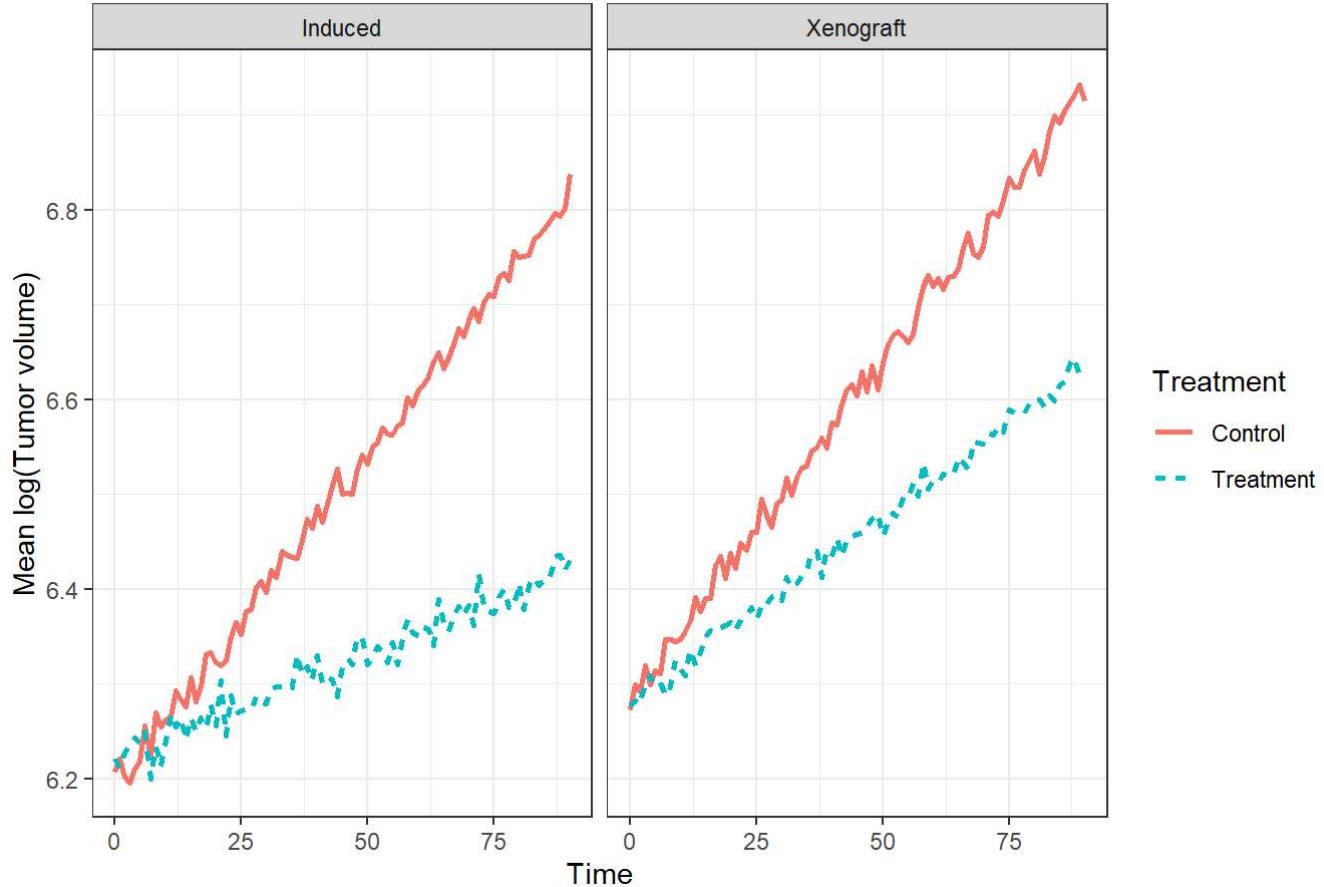
```
## Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
## i Please use `linewidth` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```

Mean tumor growth by treatment and model



```
ggplot(dat, aes(x = Time, y = logDV,
                 colour = Treatment, linetype = Treatment)) +
  stat_summary(fun = mean, geom = "line", size = 1) +
  facet_wrap(~ Model) +
  labs(y = "Mean log(Tumor volume)",
       title = "Mean log tumor growth by treatment and model") +
  theme_bw()
```

Mean log tumor growth by treatment and model



linear mixed-effects model

To stabilize variance and linearize growth, tumor volume was log-transformed before modelling.

Linear mixed-effects models were appropriate here because the goal was to characterise tumor growth over time while accounting for repeated measurements.

Model 1: only time factor

This baseline model captures average growth over time while allowing each mouse to have its own intercept.

```
m1 <- lmer(logDV ~ Time + (1 | ID), data = dat)
summary(m1)
```

```

## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: logDV ~ Time + (1 | ID)
##   Data: dat
##
## REML criterion at convergence: -11011.2
##
## Scaled residuals:
##    Min     1Q Median     3Q    Max
## -4.7812 -0.6267 -0.0084  0.6217  4.9920
##
## Random effects:
##   Groups   Name        Variance Std. Dev.
##   ID       (Intercept) 0.026651 0.16325
##   Residual           0.007281 0.08533
## Number of obs: 5460, groups: ID, 60
##
## Fixed effects:
##             Estimate Std. Error      df t value Pr(>|t|)
## (Intercept) 6.251e+00 2.120e-02 6.004e+01 294.9 <2e-16 ***
## Time        5.205e-03 4.396e-05 5.399e+03 118.4 <2e-16 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##   (Intr) Time
## Time -0.093

```

Model 2: time x treatment

This model evaluates whether treatment affects baseline volume or growth rate.

```

m2 <- lmer(logDV ~ Time * Treatment + (1 | ID), data = dat)
summary(m2)

```

```

## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: logDV ~ Time * Treatment + (1 | ID)
##   Data: dat
##
## REML criterion at convergence: -13111.7
##
## Scaled residuals:
##    Min     1Q Median     3Q    Max
## -4.7869 -0.5578  0.0017  0.5414  5.0000
##
## Random effects:
##   Groups   Name        Variance Std. Dev.
##   ID       (Intercept) 0.021543 0.1468
##   Residual           0.004928 0.0702
## Number of obs: 5460, groups: ID, 60
##
## Fixed effects:
##                               Estimate Std. Error      df t value Pr(>|t|) 
## (Intercept)             6.242e+00 2.693e-02 5.886e+01 231.782 <2e-16 ***
## Time                  7.042e-03 5.115e-05 5.398e+03 137.676 <2e-16 ***
## TreatmentTreatment    1.822e-02 3.808e-02 5.886e+01  0.478   0.634
## Time:TreatmentTreatment -3.674e-03 7.233e-05 5.398e+03 -50.789 <2e-16 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##          (Intr) Time   TrtmntT
## Time      -0.085
## TrtmntTrtmn -0.707  0.060
## Tm:TrtmntTr  0.060 -0.707 -0.085

```

```
anova(m1, m2)
```

```
## refitting model(s) with ML (instead of REML)
```

```

## Data: dat
## Models:
## m1: logDV ~ Time + (1 | ID)
## m2: logDV ~ Time * Treatment + (1 | ID)
##   npar   AIC   BIC logLik -2*log(L) Chisq Df Pr(>Chisq)
## m1     4 -11027 -11001 5517.7    -11035
## m2     6 -13146 -13107 6579.2    -13158  2123  2 < 2.2e-16 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Model 3: time x treatment x model

This extends m2 by testing whether disease model influences growth or treatment effects.

```
m3 <- lmer(logDV ~ Time * Treatment * Model + (1 | ID), data = dat)
summary(m3)
```

```

## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: logDV ~ Time * Treatment * Model + (1 | ID)
##   Data: dat
##
## REML criterion at convergence: -13338.4
##
## Scaled residuals:
##    Min     1Q Median     3Q    Max
## -5.1913 -0.5747 -0.0055  0.5531  5.4582
##
## Random effects:
## Groups   Name        Variance Std. Dev.
## ID       (Intercept) 0.018788 0.13707
## Residual           0.004699 0.06855
## Number of obs: 5460, groups: ID, 60
##
## Fixed effects:
##                               Estimate Std. Error      df t value
## (Intercept)                6.193e+00  3.683e-02 5.690e+01 168.151
## Time                     6.938e-03  7.312e-05 5.396e+03  94.885
## TreatmentTreatment        2.747e-02  5.706e-02 5.690e+01   0.482
## ModelXenograft            9.107e-02  5.043e-02 5.690e+01   1.806
## Time:TreatmentTreatment  -4.709e-03  1.133e-04 5.396e+03 -41.576
## Time:ModelXenograft       1.949e-04  1.001e-04 5.396e+03   1.947
## TreatmentTreatment:ModelXenograft -3.209e-02  7.343e-02 5.690e+01  -0.437
## Time:TreatmentTreatment:ModelXenograft 1.515e-03  1.458e-04 5.396e+03  10.390
## Pr(>|t|)
## (Intercept) <2e-16 ***
## Time        <2e-16 ***
## TreatmentTreatment 0.6320
## ModelXenograft 0.0762 .
## Time:TreatmentTreatment <2e-16 ***
## Time:ModelXenograft 0.0516 .
## TreatmentTreatment:ModelXenograft 0.6637
## Time:TreatmentTreatment:ModelXenograft <2e-16 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
## (Intr) Time TrtmnT MdlXng Tm:TrT Tm:MdX TrT:MX
## Time      -0.089
## TrtmntTrtmn -0.645  0.058
## ModelXngrft -0.730  0.065  0.471
## Tm:TrtmntTr  0.058 -0.645 -0.089 -0.042
## Tm:MdlXngrf  0.065 -0.730 -0.042 -0.089  0.471
## TrtmntTr:MX  0.502 -0.045 -0.777 -0.687  0.069  0.061
## Tm:TrtmT:MX -0.045  0.502  0.069  0.061 -0.777 -0.687 -0.089

```

```
anova(m2, m3)
```

```
## refitting model(s) with ML (instead of REML)
```

```
## Data: dat
## Models:
## m2: logDV ~ Time * Treatment + (1 | ID)
## m3: logDV ~ Time * Treatment * Model + (1 | ID)
##   npar    AIC    BIC logLik -2*log(L)  Chisq Df Pr(>Chisq)
## m2     6 -13146 -13107 6579.2      -13158
## m3    10 -13407 -13341 6713.4      -13427 268.36  4 < 2.2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Model 4: Random slope model: time x treatment x model + (Time | ID))

This model further allows each mouse to have its own growth rate (random slope).

Anova tests demonstrated improvement across model steps, with a particularly large improvement from m3 to m4, confirming that individual-specific growth rates are essential for accurately modelling these data.

```
m4 <- lmer(logDV ~ Time * Treatment * Model + (Time | ID), data = dat)
```

```
## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control$checkConv, :
## Model failed to converge with max|grad| = 0.00704387 (tol = 0.002, component 1)
```

```
summary(m4)
```

```

## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: logDV ~ Time * Treatment * Model + (Time | ID)
##   Data: dat
##
## REML criterion at convergence: -17631.9
##
## Scaled residuals:
##    Min     1Q Median     3Q    Max
## -4.2265 -0.6684  0.0051  0.6463  3.8377
##
## Random effects:
##   Groups   Name        Variance Std. Dev. Corr
##   ID       (Intercept) 1.031e-02 0.101516
##          Time         4.099e-06 0.002025 0.01
##   Residual           2.029e-03 0.045045
## Number of obs: 5460, groups: ID, 60
##
## Fixed effects:
##                               Estimate Std. Error      df t value
## (Intercept)                6.1931944  0.0272466 56.0881214 227.301
## Time                      0.0069376  0.0005432 55.9830698 12.772
## TreatmentTreatment         0.0274739  0.0422103 56.0881151  0.651
## ModelXenograft            0.0910747  0.0373090 56.0881165  2.441
## Time:TreatmentTreatment   -0.0047094  0.0008415 55.9830728 -5.596
## Time:ModelXenograft       0.0001949  0.0007438 55.9830723  0.262
## TreatmentTreatment:ModelXenograft -0.0320936  0.0543227 56.0881133 -0.591
## Time:TreatmentTreatment:ModelXenograft 0.0015147  0.0010830 55.9830739  1.399
## Pr(>|t|)
## (Intercept) < 2e-16 ***
## Time        < 2e-16 ***
## TreatmentTreatment 0.5178
## ModelXenograft 0.0178 *
## Time:TreatmentTreatment 6.84e-07 ***
## Time:ModelXenograft 0.7942
## TreatmentTreatment:ModelXenograft 0.5570
## Time:TreatmentTreatment:ModelXenograft 0.1675
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
## (Intr) Time TrtmnT MdlXng Tm:TrT Tm:MdX TrT:MX
## Time 0.004
## TrtmntTrtmn -0.645 -0.002
## ModelXngrft -0.730 -0.003  0.471
## Tm:TrtmntTr -0.002 -0.645  0.004  0.002
## Tm:MdlXngrf -0.003 -0.730  0.002  0.004  0.471
## TrtmntTr:MX  0.502  0.002 -0.777 -0.687 -0.003 -0.003
## Tm:TrtmT:MX  0.002  0.502 -0.003 -0.003 -0.777 -0.687  0.004
## optimizer (nloptwrap) convergence code: 0 (OK)
## Model failed to converge with max|grad| = 0.00704387 (tol = 0.002, component 1)

```

anova(m3, m4)

```
## refitting model(s) with ML (instead of REML)
```

```
## Data: dat
## Models:
## m3: logDV ~ Time * Treatment * Model + (1 | ID)
## m4: logDV ~ Time * Treatment * Model + (Time | ID)
##   npar    AIC    BIC logLik -2*log(L) Chisq Df Pr(>Chisq)
## m3     10 -13407 -13341  6713.4      -13427
## m4     12 -17683 -17604  8853.4      -17707  4280   2 < 2.2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

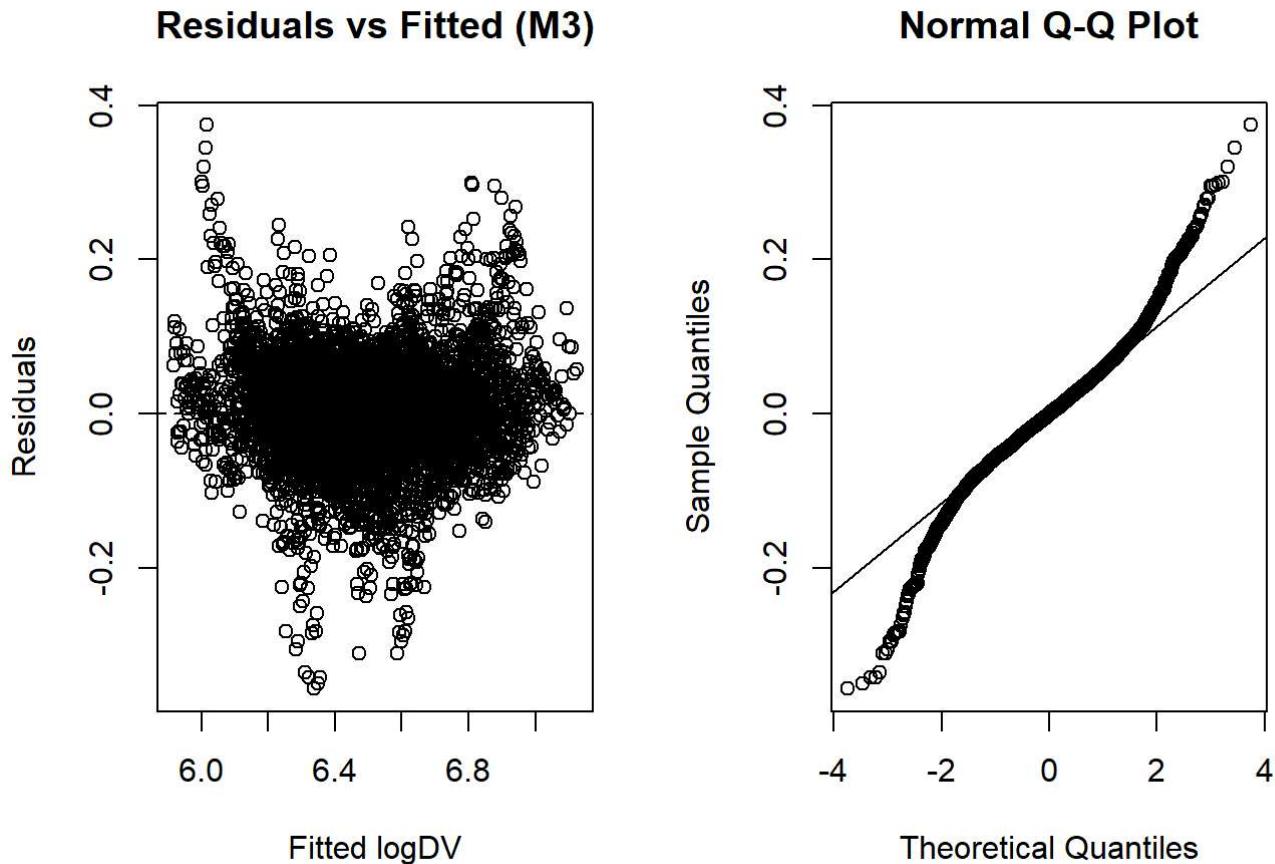
Residual diagnostics showed clear differences between m3 and m4.

For m3, the residuals-fitted plot showed systematic structure, and the Q–Q plot showed significant deviations in both tails, indicating poor adherence to model assumptions.

By contrast, m4 yielded centred, approximately homoscedastic residuals forming a symmetric cloud and a Q–Q plot closely following the reference line. This indicates that random slopes successfully captured within-mouse variability, leaving residuals that behave approximately as assumed (independent and normally distributed).

```
# residual vs fitted & qq plot
# m3
par(mfrow = c(1, 2))
plot(resid(m3) ~ fitted(m3),
     main = "Residuals vs Fitted (M3)", xlab = "Fitted logDV", ylab = "Residuals")
abline(h = 0, lty = 2)

qqnorm(resid(m3))
qqline(resid(m3))
```



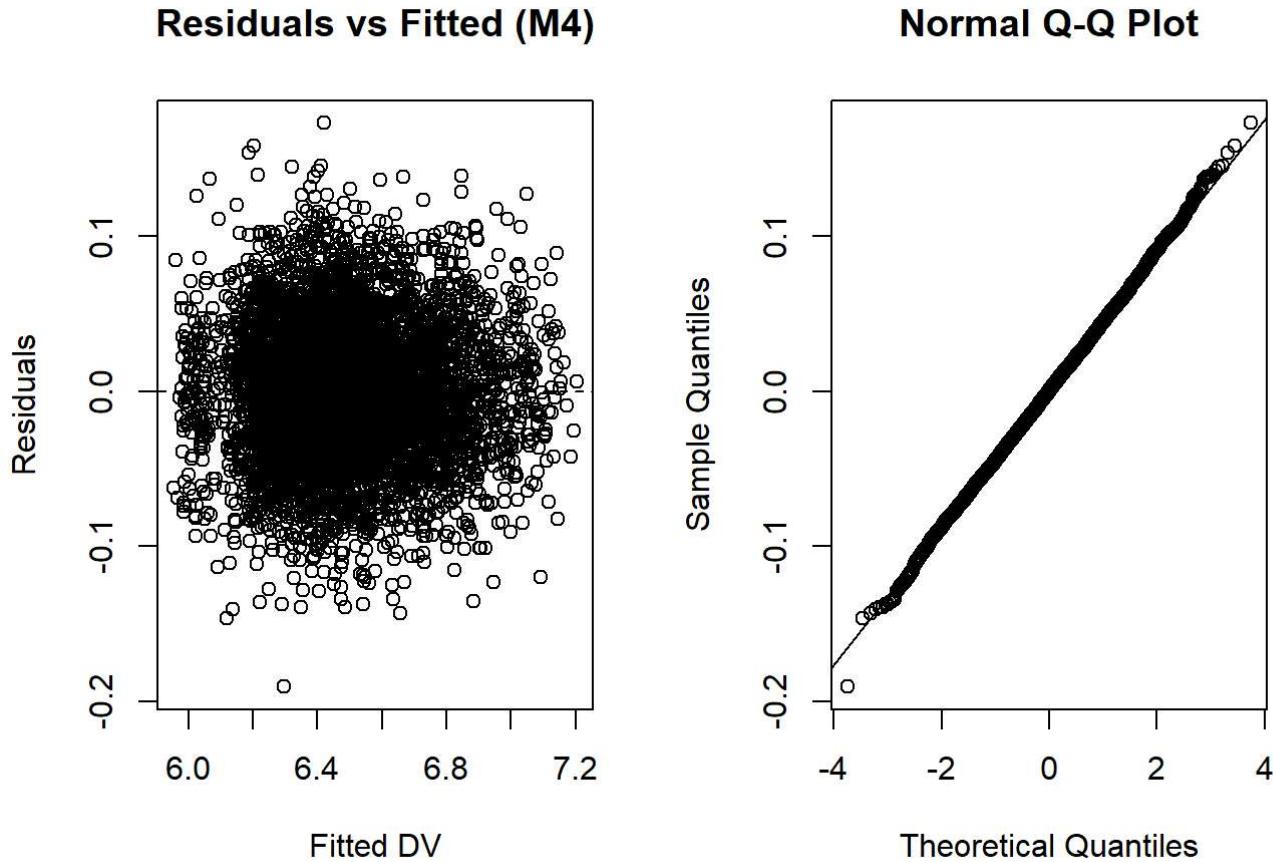
```

par(mfrow = c(1, 1))

# m4
par(mfrow = c(1, 2))
plot(resid(m4) ~ fitted(m4),
     main = "Residuals vs Fitted (M4)", xlab = "Fitted DV", ylab = "Residuals")
abline(h = 0, lty = 2)

qqnorm(resid(m4))
qqline(resid(m4))

```



```
par(mfrow = c(1, 1))
```

Results and predictions & Impact of treatment and disease model

The anova(m4) table evaluates the significance of each fixed effect. The effect of Time, Model and interaction Time x Treatment were highly significant. And there was no significant difference in treatment effect among different models. Also, the treatment slows down the growth rate of the tumor, but this change doesn't depend on the model.

```
anova(m4)
```

```
## Type III Analysis of Variance Table with Satterthwaite's method
##          Sum Sq Mean Sq NumDF DenDF F value    Pr(>F)
## Time      0.70840 0.70840     1 55.983 349.1299 < 2.2e-16 ***
## Treatment 0.00036 0.00036     1 56.088   0.1770  0.675573
## Model     0.01548 0.01548     1 56.088   7.6303  0.007746 **
## Time:Treatment 0.10808 0.10808     1 55.983  53.2640 1.114e-09 ***
## Time:Model   0.00627 0.00627     1 55.983   3.0925  0.084121 .
## Treatment:Model 0.00071 0.00071     1 56.088   0.3490  0.557031
## Time:Treatment:Model 0.00397 0.00397     1 55.983   1.9560  0.167462
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

We did interpolation and extrapolation up to 120 days to predict results of models. The predicted tumor growth from m3 and m4 produced same results because both models have the same fixed-effects structure. They differ only in how they model specific variability. It is obvious to see that the increase rate of tumor volume in the treatment group of the induced tumor mouse model is much lower than that in the xenograft mouse model.

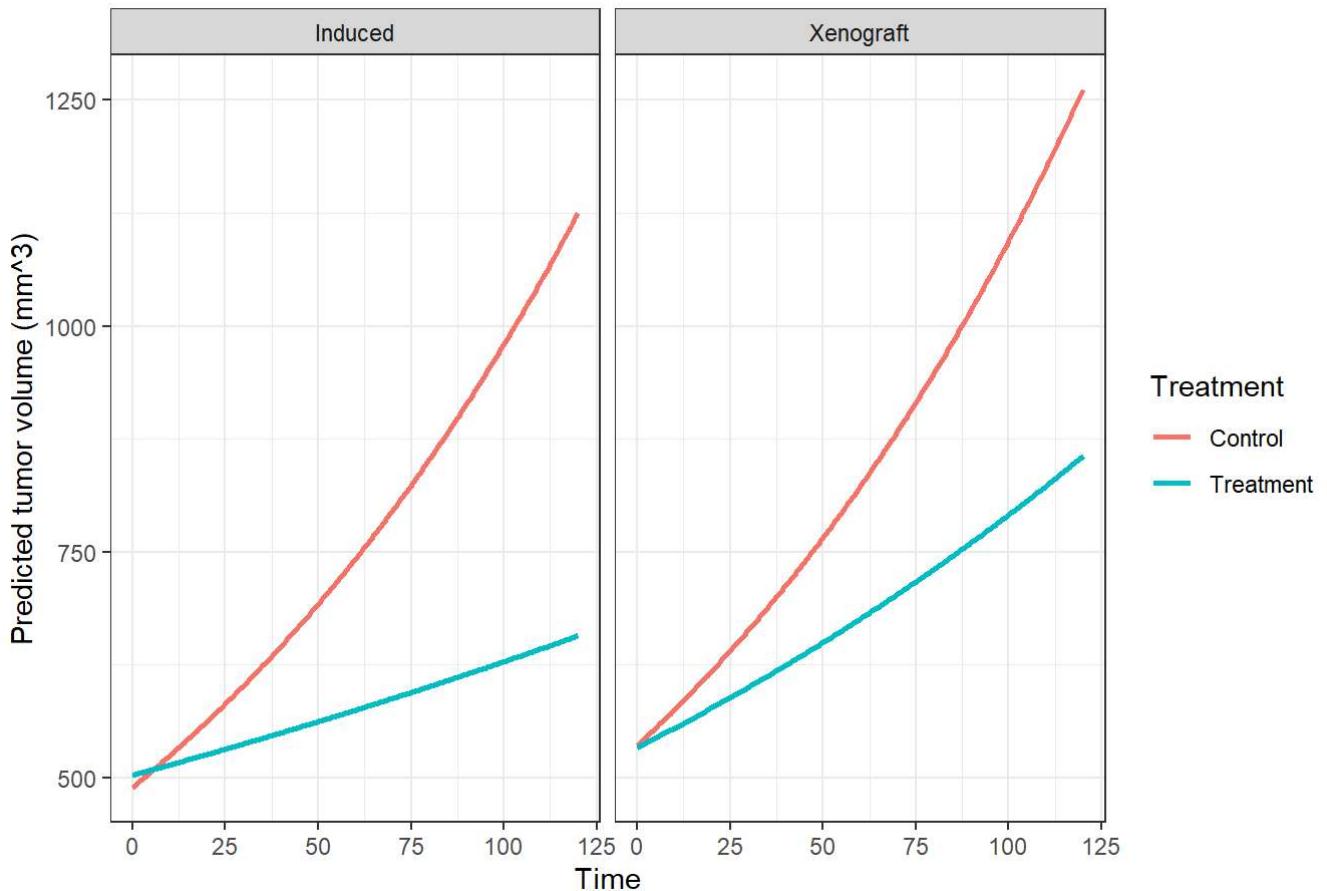
```
# interpolation & extrapolation
time_seq <- seq(from = min(dat$Time), to = 120, by = 0.5)

newdat <- expand.grid(
  Time      = time_seq,
  Treatment = levels(dat$Treatment),
  Model     = levels(dat$Model)
)

newdat$pred_logDV <- predict(m3, newdata = newdat, re.form = NA)
newdat$pred_DV <- exp(newdat$pred_logDV)

ggplot(newdat, aes(Time, pred_DV, colour = Treatment)) +
  geom_line(size = 1) +
  facet_wrap(~ Model) +
  labs(y = "Predicted tumor volume (mm^3)",
       title = "Predicted tumor growth by treatment (M3)") +
  theme_bw()
```

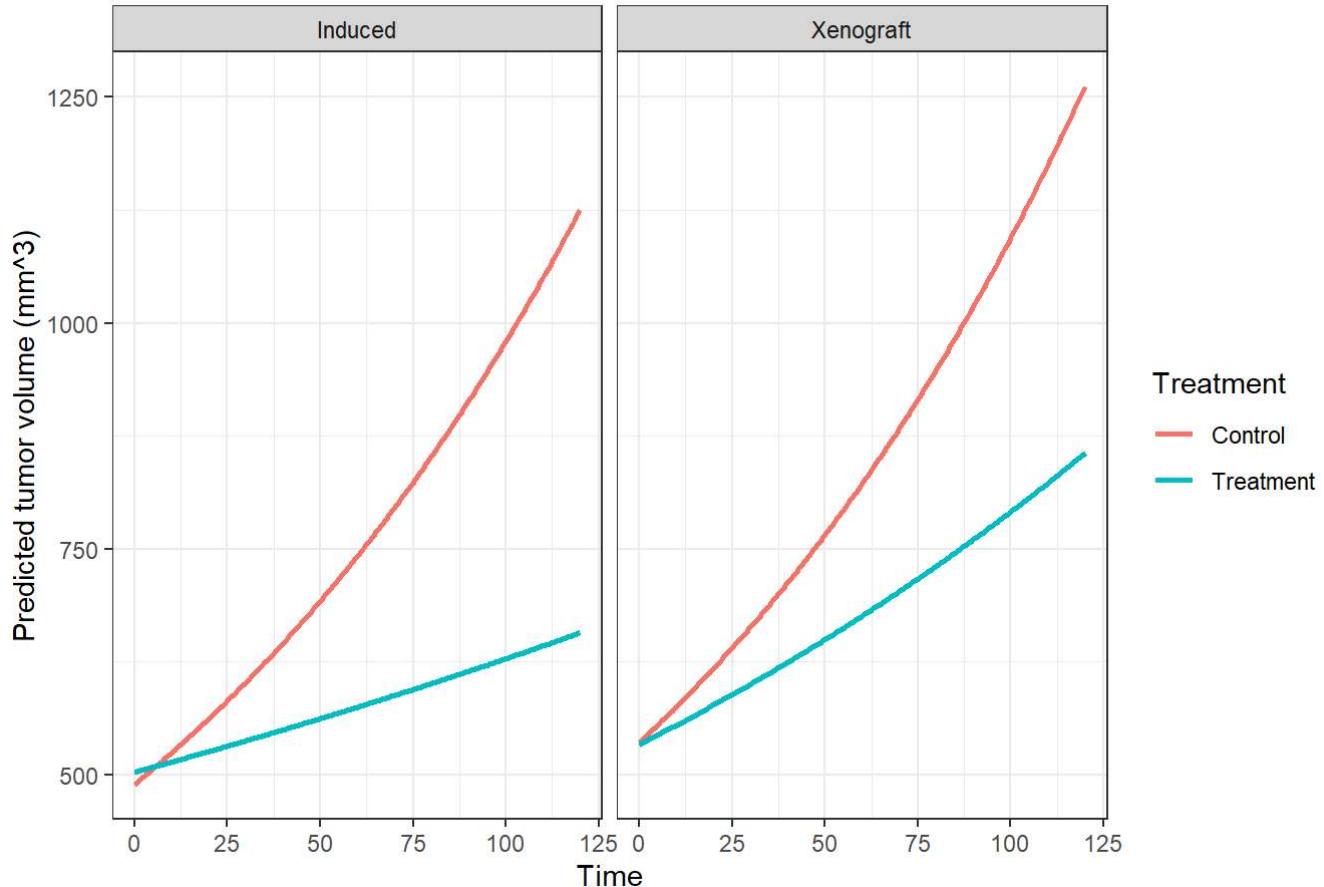
Predicted tumor growth by treatment (M3)



```
newdat$pred_logDV <- predict(m4, newdata = newdat, re.form = NA)
newdat$pred_DV <- exp(newdat$pred_logDV)
```

```
ggplot(newdat, aes(Time, pred_DV, colour = Treatment)) +
  geom_line(size = 1) +
  facet_wrap(~ Model) +
  labs(y = "Predicted tumor volume (mm^3)",
       title = "Predicted tumor growth by treatment (M4)") +
  theme_bw()
```

Predicted tumor growth by treatment (M4)



To illustrate how m3 and m4 differ in their handling of individual mice, predictions were generated for new data with 60 subjects. Under m3, all mice shared the same growth rate and differed only in their intercepts, resulting in parallel trajectories. In contrast, m4 produced curves with differing slopes as well as intercepts, reflecting its random-slope structure. This more flexible pattern can align better with the observed variability in tumor progression.

```
# new data with ID
newdat_id <- dat %>%
  group_by(ID, Treatment, Model) %>%
  summarise(Time = seq(min(Time), 120, length.out = 20),
            .groups = "drop")
```

```
## Warning: Returning more (or less) than 1 row per `summarise()` group was deprecated in
## dplyr 1.1.0.
## i Please use `reframe()` instead.
## i When switching from `summarise()` to `reframe()`, remember that `reframe()`
##   always returns an ungrouped data frame and adjust accordingly.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```

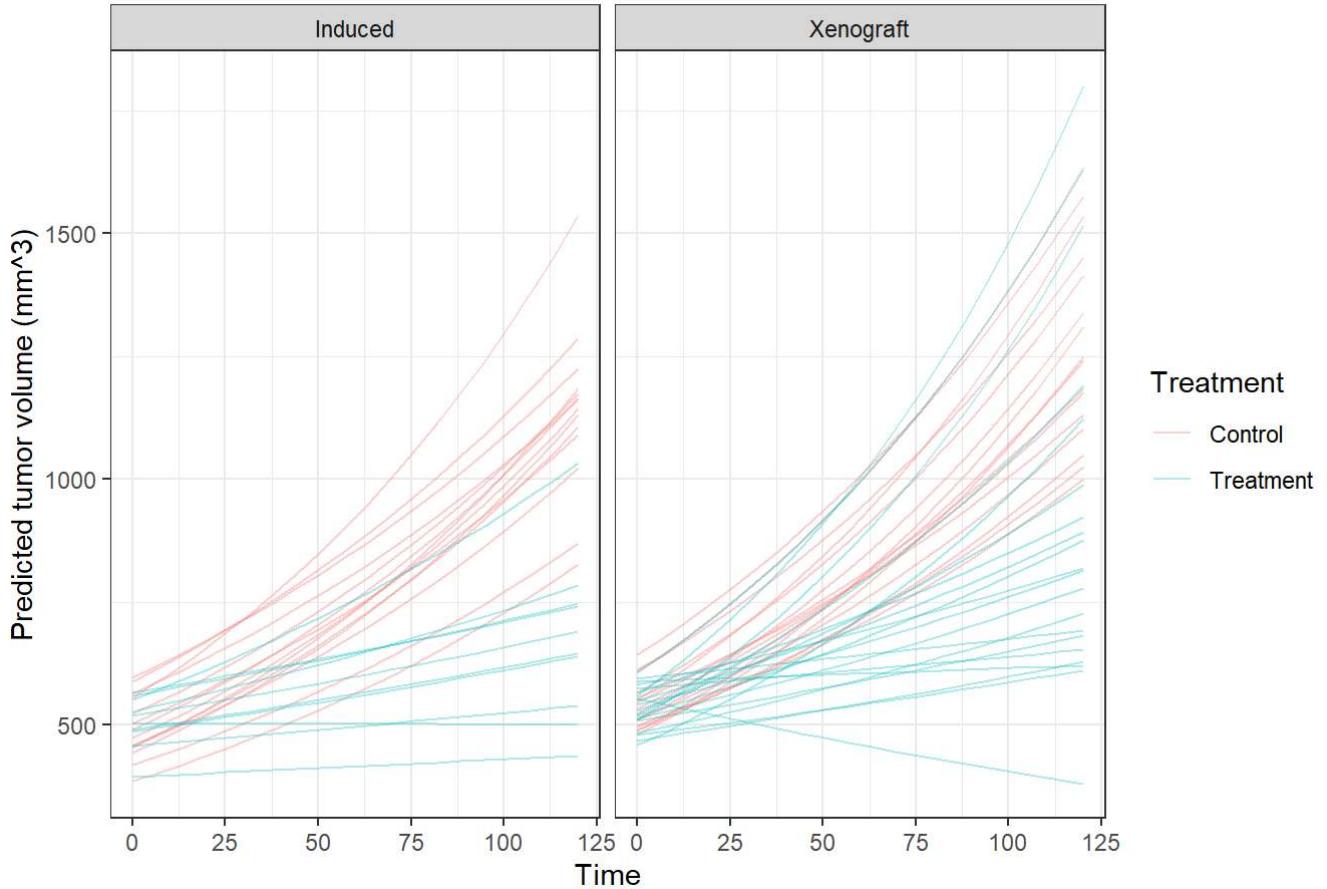
```

newdat_id$pred_logDV <- predict(m4, newdata = newdat_id, re.form = NULL)
newdat_id$pred_DV <- exp(newdat_id$pred_logDV)

ggplot(newdat_id, aes(Time, pred_DV, group = ID, colour = Treatment)) +
  geom_line(alpha = 0.3) +
  facet_wrap(~ Model) +
  labs(y = "Predicted tumor volume (mm^3)",
       title = "Individual-level predictions including random effects (M4)") +
  theme_bw()

```

Individual-level predictions including random effects (M4)



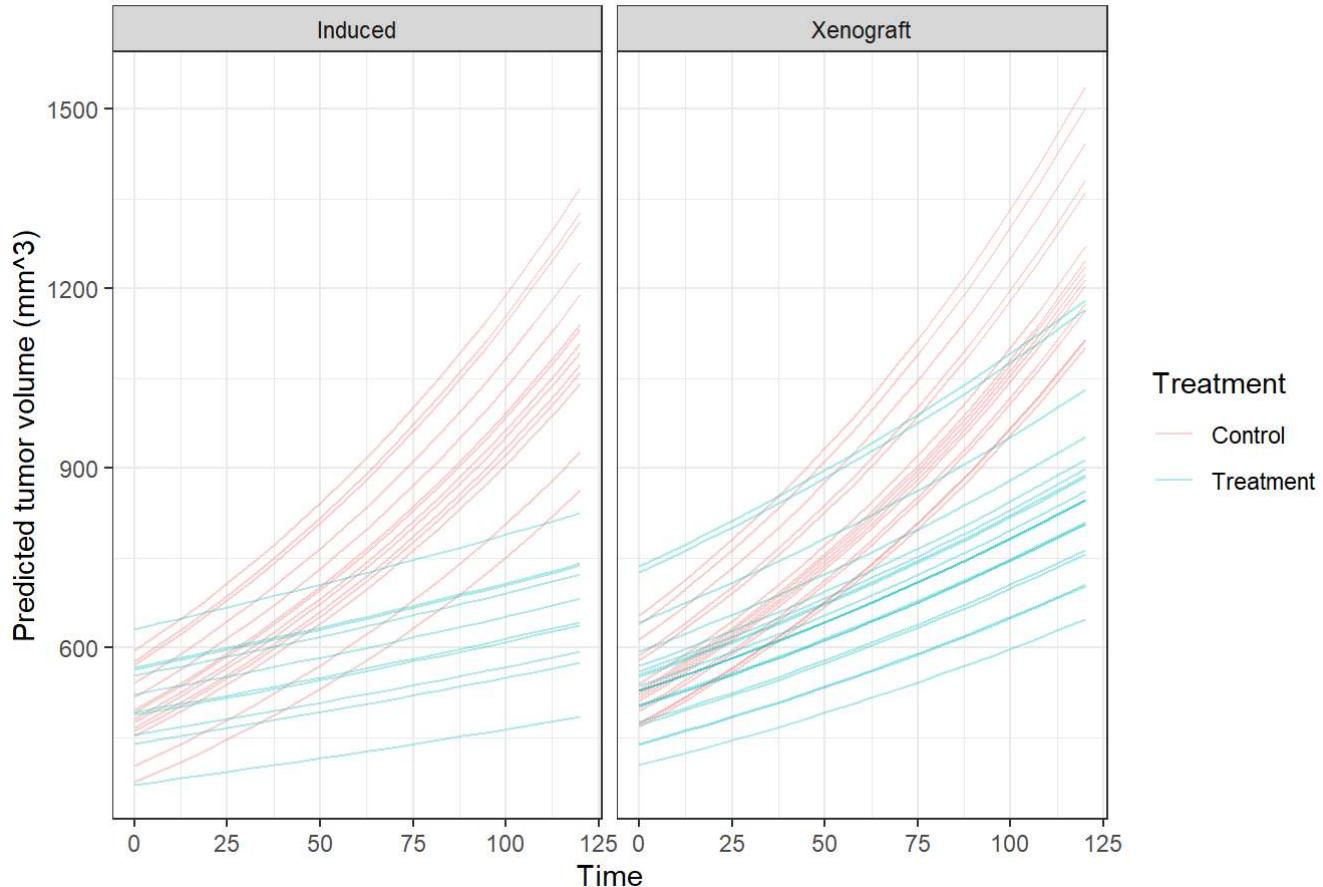
```

newdat_id$pred_logDV <- predict(m3, newdata = newdat_id, re.form = NULL)
newdat_id$pred_DV <- exp(newdat_id$pred_logDV)

ggplot(newdat_id, aes(Time, pred_DV, group = ID, colour = Treatment)) +
  geom_line(alpha = 0.3) +
  facet_wrap(~ Model) +
  labs(y = "Predicted tumor volume (mm^3)",
       title = "Individual-level predictions including random effects (M3)") +
  theme_bw()

```

Individual-level predictions including random effects (M3)



The estimated trends from emtrends(m4) further quantified these differences. Treated mice showed a consistently smaller Time slope than controls, confirming that ATC10X slows tumor growth on the log scale. The two tumor models exhibited slightly different slopes, with induced tumors growing marginally slower than xenografts in the absence of treatment and displaying a slightly larger reduction under treatment.

Overall, ATC10X suppresses the growth of tumors, and the two disease models differ slightly in both baseline size and growth dynamics. The fixed effects reveal similar conclusions across models, while the random-slope structure of m4 provides a more realistic representation of the heterogeneous growth rates observed in individual mice.

```
emtrends(m4, ~ Treatment | Model, var = "Time")
```

```
## Note: D. f. calculations have been disabled because the number of observations exceeds 3000.
## To enable adjustments, add the argument 'pbkrtest.limit = 5460' (or larger)
## [or, globally, 'set emm_options(pbkrtest.limit = 5460)' or larger];
## but be warned that this may result in large computation time and memory use.
```

```
## Note: D. f. calculations have been disabled because the number of observations exceeds 3000.
## To enable adjustments, add the argument 'lmerTest.limit = 5460' (or larger)
## [or, globally, 'set emm_options(lmerTest.limit = 5460)' or larger];
## but be warned that this may result in large computation time and memory use.
```

```

## Model = Induced:
##   Treatment Time.trend      SE  df asympt.LCL asympt.UCL
##   Control      0.00694 0.000543 Inf  0.005873  0.00800
##   Treatment     0.00223 0.000643 Inf  0.000968  0.00349
##
## Model = Xenograft:
##   Treatment Time.trend      SE  df asympt.LCL asympt.UCL
##   Control      0.00713 0.000508 Inf  0.006137  0.00813
##   Treatment     0.00394 0.000454 Inf  0.003047  0.00483
##
## Degrees-of-freedom method: asymptotic
## Confidence level used: 0.95

```

The ability to carry out predictions, within and beyond the ranges of the data

To evaluate predictive performance within the observed data range, overall predictions were generated using the fixed effects of m3 and m4. For both m3 and m4, the root-mean-square error on the log scale was approximately 0.15, corresponding to an average prediction error of around 16% on the original tumor volume scale. This indicates that both models capture the main growth dynamics of the data reasonably well at the population level.

```

# RMSE
# m4
dat$pred_logDV <- predict(m4, re.form = NA)
dat$resid_logDV <- dat$logDV - dat$pred_logDV

rmse <- sqrt(mean(dat$resid_logDV^2))
rmse

```

```
## [1] 0.1490912
```

```
p = exp(rmse)-1
p
```

```
## [1] 0.1607788
```

```

# m3
dat$pred_logDV <- predict(m3, re.form = NA)
dat$resid_logDV <- dat$logDV - dat$pred_logDV

rmse <- sqrt(mean(dat$resid_logDV^2))
rmse

```

```
## [1] 0.1490912
```

```
p = exp(rmse)-1
p
```

```
## [1] 0.1607788
```

The marginal R² was around 0.56 for both models, showing that the fixed effects explained more than half of the systematic variation in tumor growth. The conditional R² reached 0.96 for m4 and 0.91 for m3, reflecting the substantial contribution of random effects in capturing individual differences. The higher R^{2c} of m4 indicates that allowing each mouse to have its own growth rate provides a better overall representation of data.

```
library(MuMIn)
```

```
## Warning: package 'MuMIn' was built under R version 4.5.2
```

```
r.squaredGLMM(m4)
```

```
##          R2m          R2c
## [1, ] 0.558666 0.9621573
```

```
r.squaredGLMM(m3)
```

```
##          R2m          R2c
## [1, ] 0.5605041 0.9120662
```

When examining prediction intervals over time, the random-intercept model (m3) showed almost constant 95% interval widths, with only a very slight U-shaped pattern and values remaining around 0.14 on the log scale. This behaviour is typical for a model that assumes a common growth rate across mice and therefore does not allow uncertainty to accumulate strongly with time.

In contrast, the random-slope model (m4) produced intervals that widened more substantially, from about 0.10 within the observed range to over 0.25 by day 120. This reflects the fact that m4 explicitly models between-mouse variability in growth rates, so uncertainty about the population mean naturally increases as predictions are pushed further away from the data. Thus, m4 does not perform worse. Instead, it provides a more realistic representation of long-term uncertainty, whereas m3 may underestimate extrapolation uncertainty by assuming identical slopes for all animals.

```
# prediction intervals
time_grid <- seq(0, 120, by = 5)
# m4
emm_long <- emmeans(
  m4,
  ~ Treatment * Model | Time,
  at = list(Time = time_grid)
)
```

```
## Note: D.f. calculations have been disabled because the number of observations exceeds 3000.
## To enable adjustments, add the argument 'pbkrtest.limit = 5460' (or larger)
## [or, globally, 'set emm_options(pbkrtest.limit = 5460)' or larger];
## but be warned that this may result in large computation time and memory use.
```

```
## Note: D.f. calculations have been disabled because the number of observations exceeds 3000.
## To enable adjustments, add the argument 'lmerTest.limit = 5460' (or larger)
## [or, globally, 'set emm_options(lmerTest.limit = 5460)' or larger];
## but be warned that this may result in large computation time and memory use.
```

```

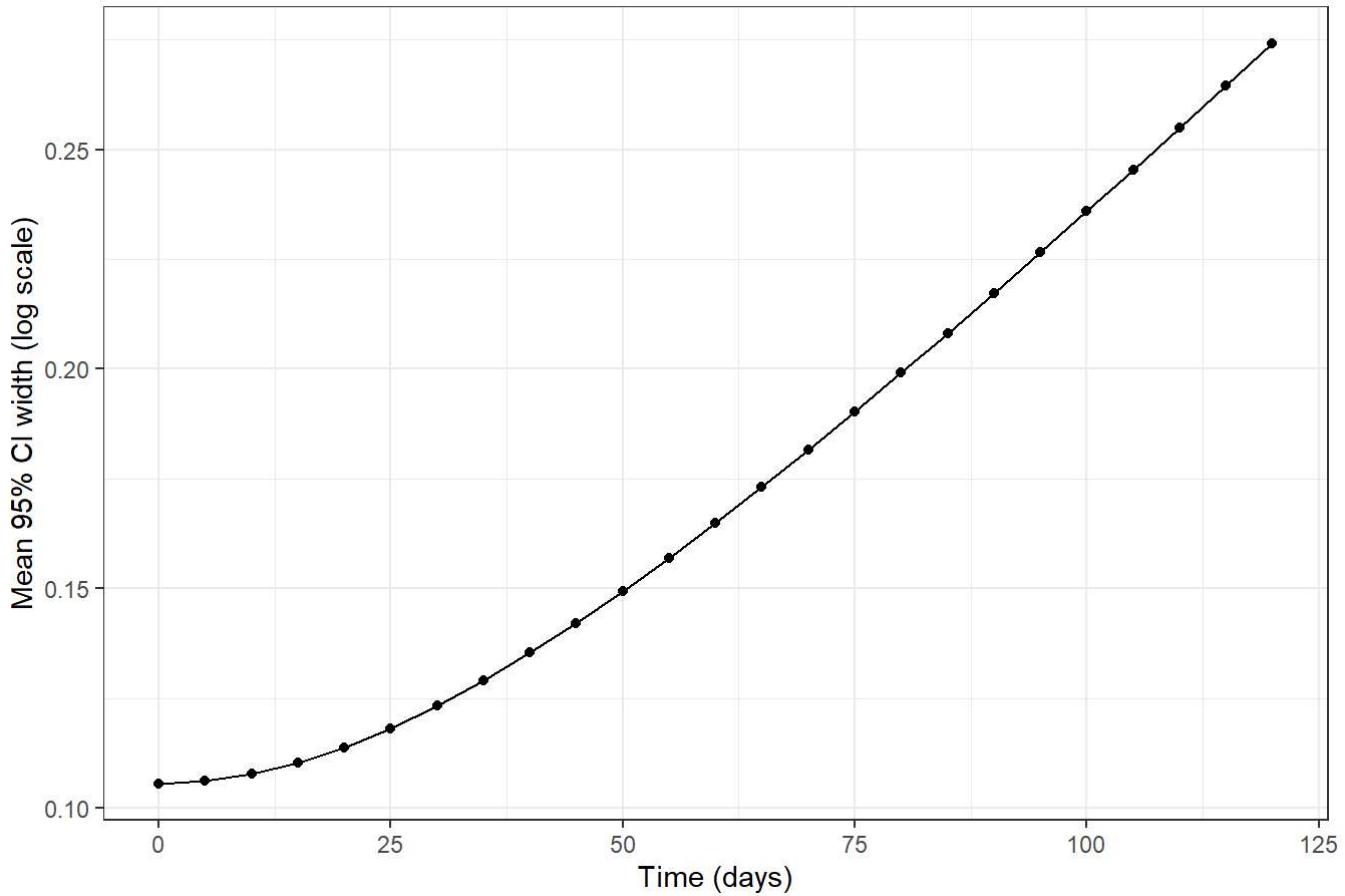
emm_df <- as.data.frame(emm_long)
emm_df$CI_width <- emm_df$asym.UCL - emm_df$asym.LCL

ci_by_time <- emm_df %>%
  group_by(Time) %>%
  summarise(mean_CI_width = mean(CI_width), .groups = "drop")

ggplot(ci_by_time, aes(x = Time, y = mean_CI_width)) +
  geom_line() +
  geom_point() +
  labs(
    x = "Time (days)",
    y = "Mean 95% CI width (log scale)",
    title = "Change in prediction interval width over time (M4)"
  ) +
  theme_bw()

```

Change in prediction interval width over time (M4)



```

# m3
emm_long <- emmeans(
  m3,
  ~ Treatment * Model | Time,
  at = list(Time = time_grid)
)

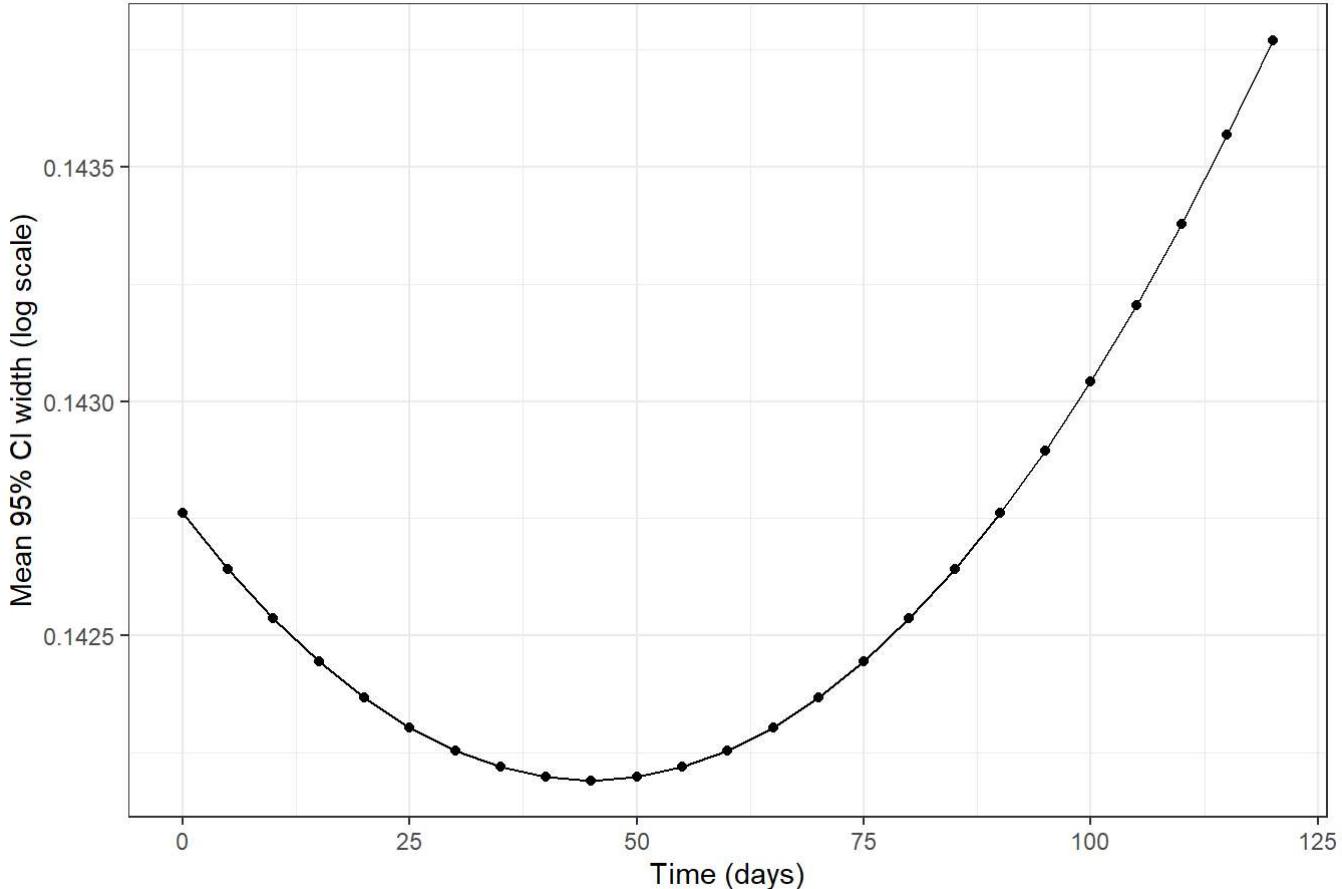
```

```
## Note: D.f. calculations have been disabled because the number of observations exceeds 3000.
## To enable adjustments, add the argument 'pbkrtest.limit = 5460' (or larger)
## [or, globally, 'set emm_options(pbkrtest.limit = 5460)' or larger];
## but be warned that this may result in large computation time and memory use.
## Note: D.f. calculations have been disabled because the number of observations exceeds 3000.
## To enable adjustments, add the argument 'lmerTest.limit = 5460' (or larger)
## [or, globally, 'set emm_options(lmerTest.limit = 5460)' or larger];
## but be warned that this may result in large computation time and memory use.
```

```
emm_df <- as.data.frame(emm_long)
emm_df$CI_width <- emm_df$asymp.UCL - emm_df$asymp.LCL

ci_by_time <- emm_df %>%
  group_by(Time) %>%
  summarise(mean_CI_width = mean(CI_width), .groups = "drop")
ggplot(ci_by_time, aes(x = Time, y = mean_CI_width)) +
  geom_line() +
  geom_point() +
  labs(
    x = "Time (days)",
    y = "Mean 95% CI width (log scale)",
    title = "Change in prediction interval width over time (M3)"
  ) +
  theme_bw()
```

Change in prediction interval width over time (M3)



Because the model is linear in time on the log scale, the predicted growth rate remains constant. This reflects a structural feature of the model rather than biological reality. Real tumors are unlikely to follow such sustained exponential expansion due to biological constraints such as limited resource. Therefore, while the model

provides reliable interpolation within the observed time range, predictions far outside the data should be interpreted cautiously and viewed as illustrative rather than biologically realistic.