

# Novartis Mouse Clinical Trial: Data Analytics

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Data & Clarity

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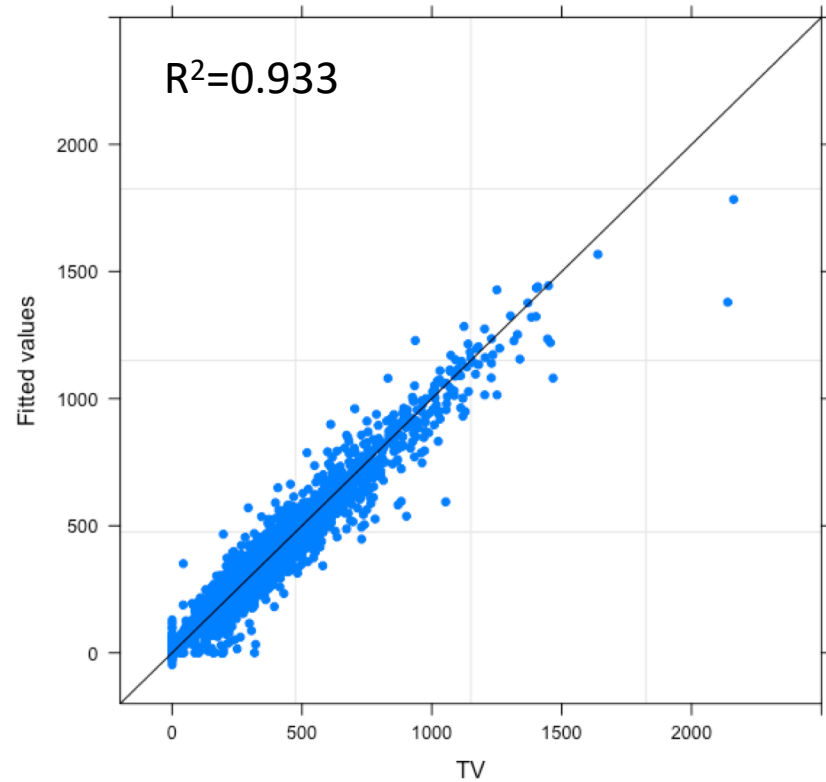
# WHICH RATE LAW ACCURATELY RECAPITULATES TUMOUR GROWTH?

# Linear model fits well

- Fixed:  $r_0$ ,  $g$ ; Random:  $\text{diag}(r_0, g)$

	Value	Std. Error	DoF	t-value	P-value
$r_0$	3.6	0.043	3160	84	0
$g$	0.041	0.0032	3160	13	0

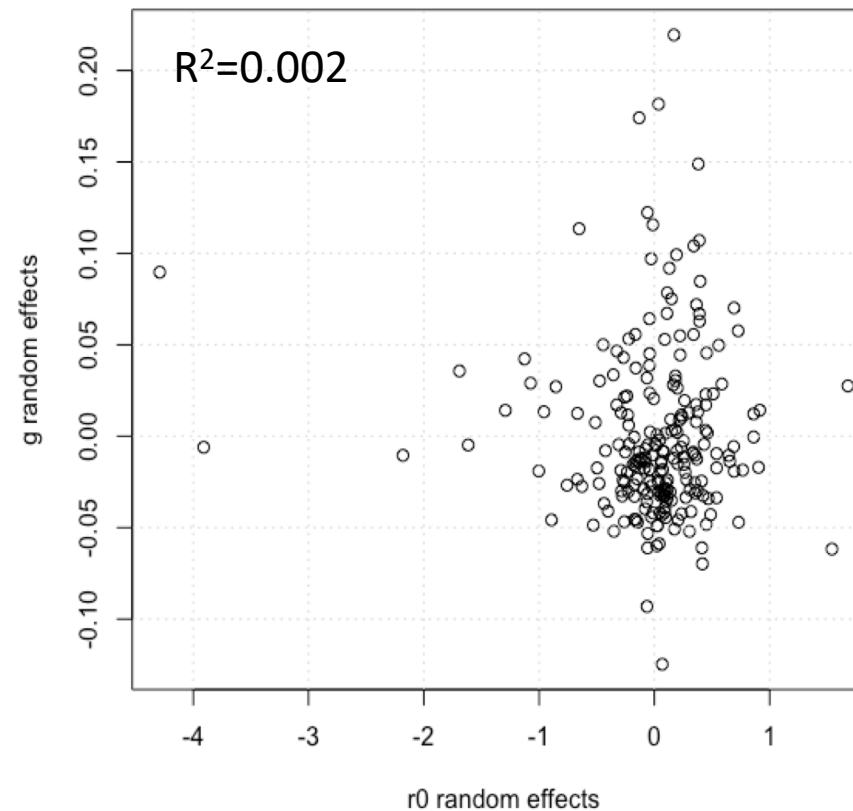
Linear Model



$$TV = \frac{4}{3} \pi (r_0 + g * t)^3$$

Fitting by NLME in R:  
 $TV_0 = 200 \text{ mm}^3$   
 $g = 0.041 \text{ mm/day}$

Linear Model



# Exponential model fits well

- Fixed:  $TV_0$ ,  $a$ ; Random:  $\text{diag}(TV_0, a)$

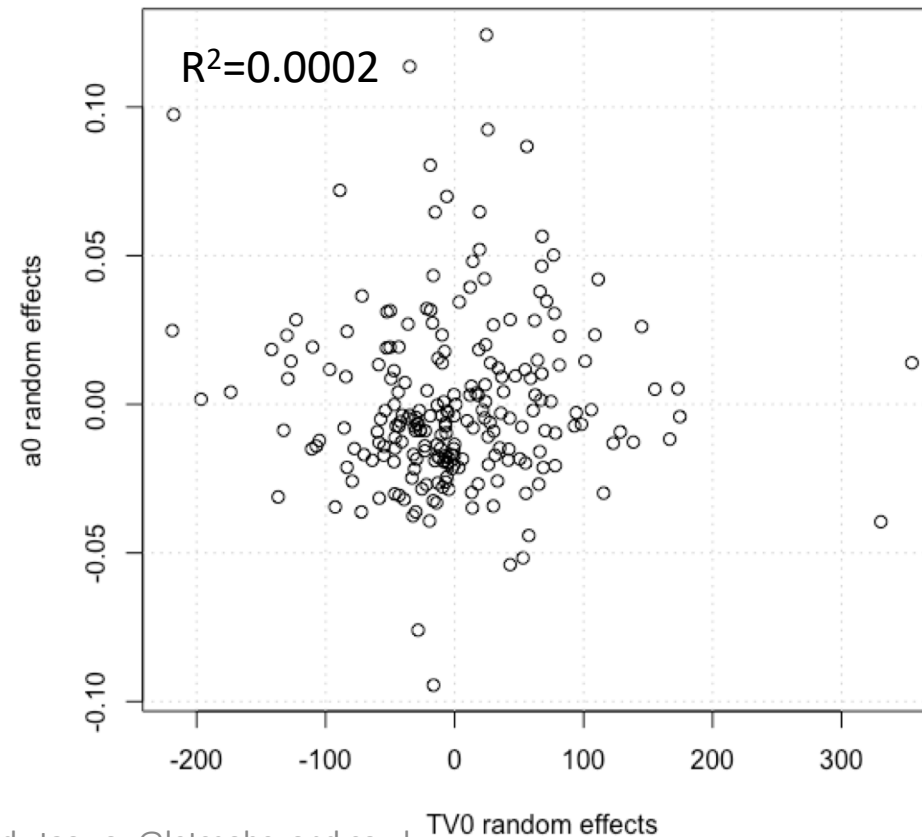
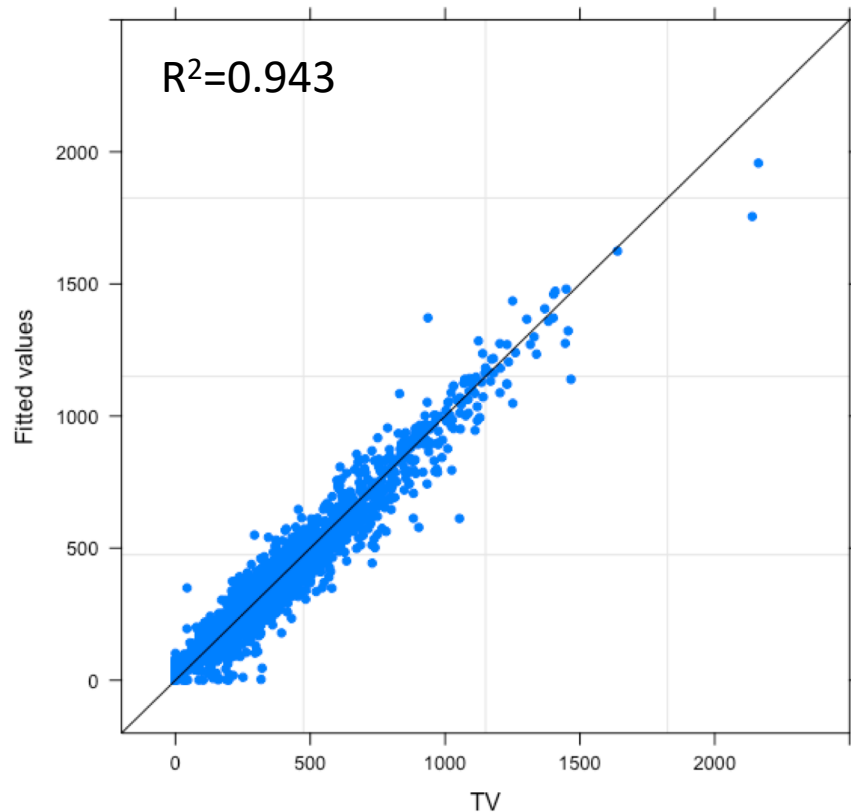
	Value	Std. Error	DoF	t-value	P-value
$TV_0$	220	5.4	3160	41	0
$a$	0.026	0.0020	3160	13	0

Exponential Model

$$TV = TV_0 e^{at}$$

Fitting by NLME in R:  
 $TV_0 = 220 \text{ mm}^3$   
 $a = 0.026$

Exponential Model





# Exponential-linear model was actually just exponential

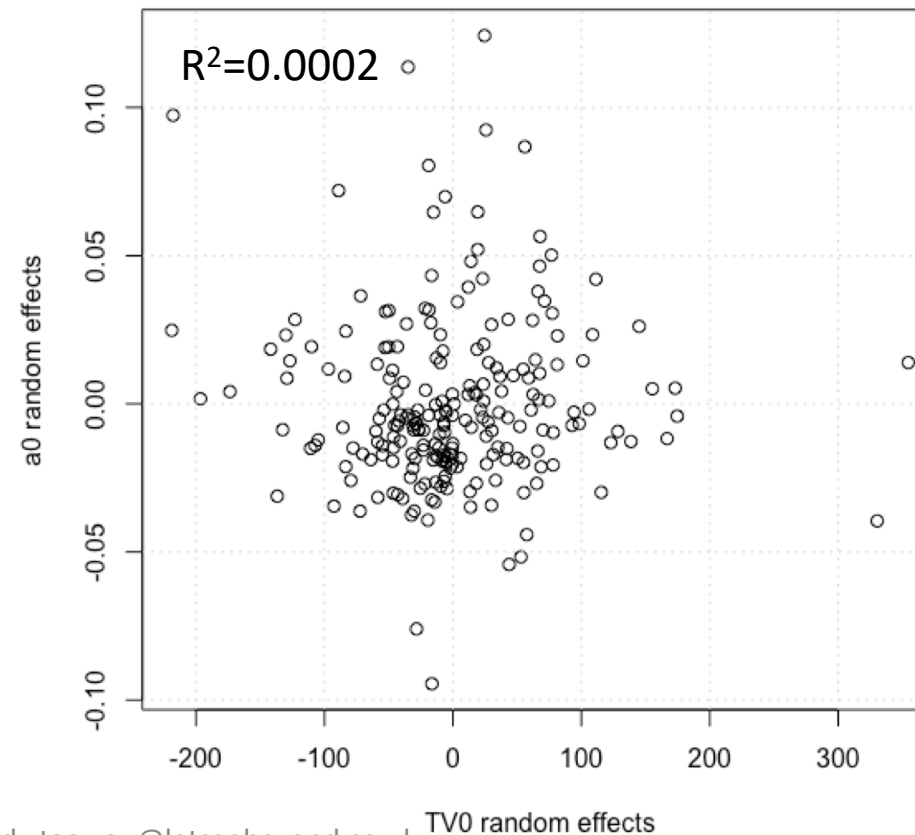
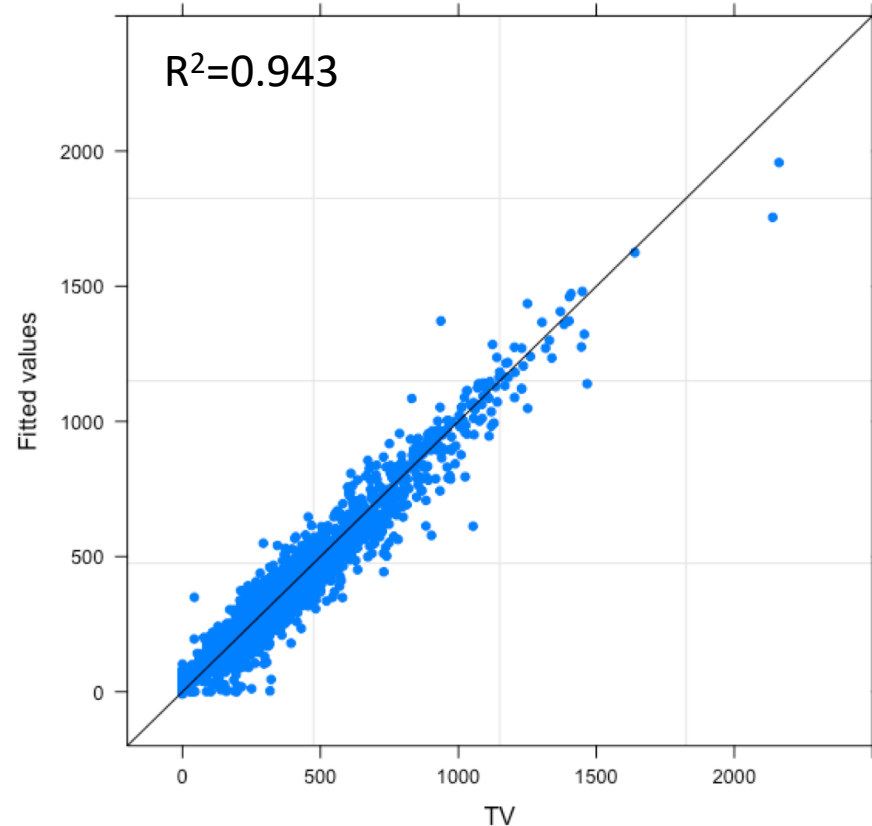
- Fixed:  $TV_0$ ,  $a_0$ ,  $\tau$ ; Random:  $\text{diag}(TV_0, a_0)$

	Value	Std. Error	DoF	t-value	P-value
$TV_0$	220	5.4	3159	41	0
$a_0$	0.026	0.0020	3159	13	0
$\tau$	280	8600	3159	0.032	0.97

$$\frac{dV}{dt} = a_0 V, t \leq \tau; \frac{dV}{dt} = a_1, t > \tau. V \text{ is smooth: } \tau = \frac{1}{a_0} \log \left( \frac{a_1}{a_0 V_0} \right)$$

Fitting by NLME in R :  
 $TV_0 = 220 \text{ mm}^3$   
 $a = 0.026$   
 $\tau$ : Not sure

This fitting is based on all tumours. Looking at each histology may lead to different results.



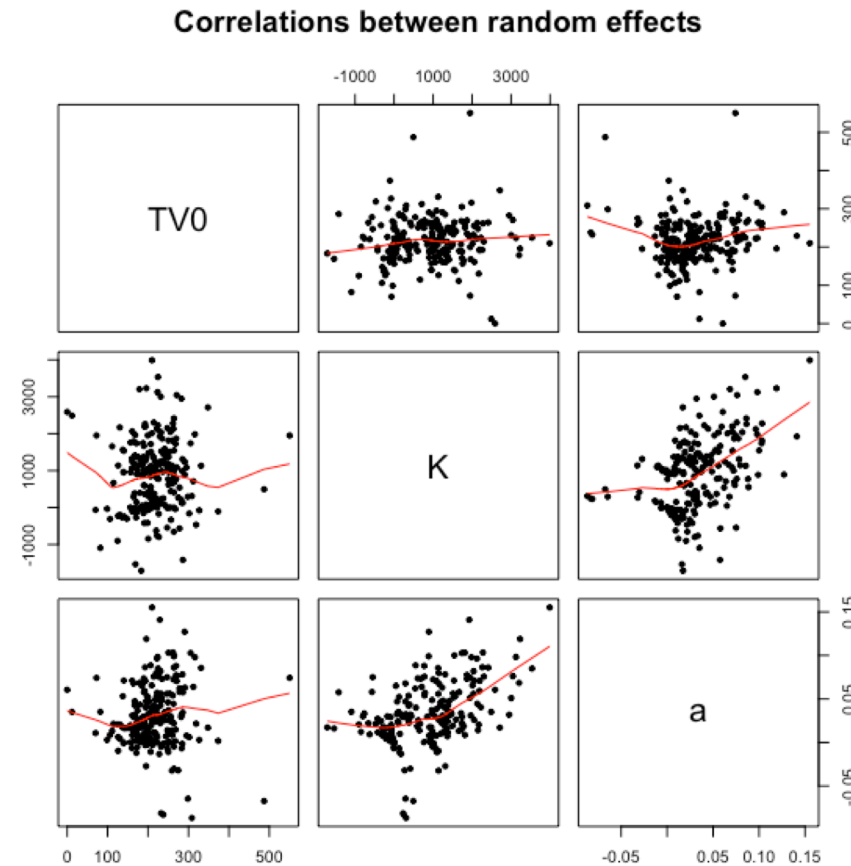
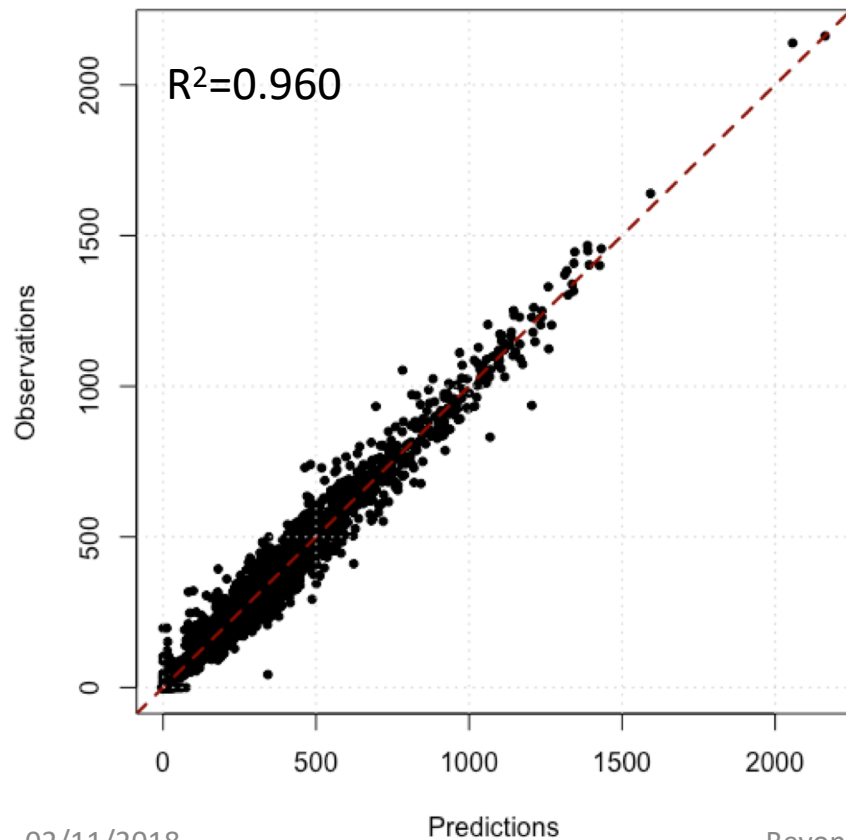
# Logistic model fits well using SAEMIX

- Fixed:  $TV_0$ ,  $K$ ,  $a$ ; Random:  $\text{diag}(TV_0, K, a)$

$$\frac{dV}{dt} = aV \left(1 - \frac{V}{K}\right) \quad a: \text{growth rate (/day)}; K: \text{carrying capacity (mm}^3\text{)}$$

	Value	Std. Error	CV(%)
$TV_0$	220	4.7	2.2
$K$	950	160	16
$a$	0.032	0.0029	9.0

Fitting looks OK. Random effects not correlated  
Logistic model can recapitulate all PDX's

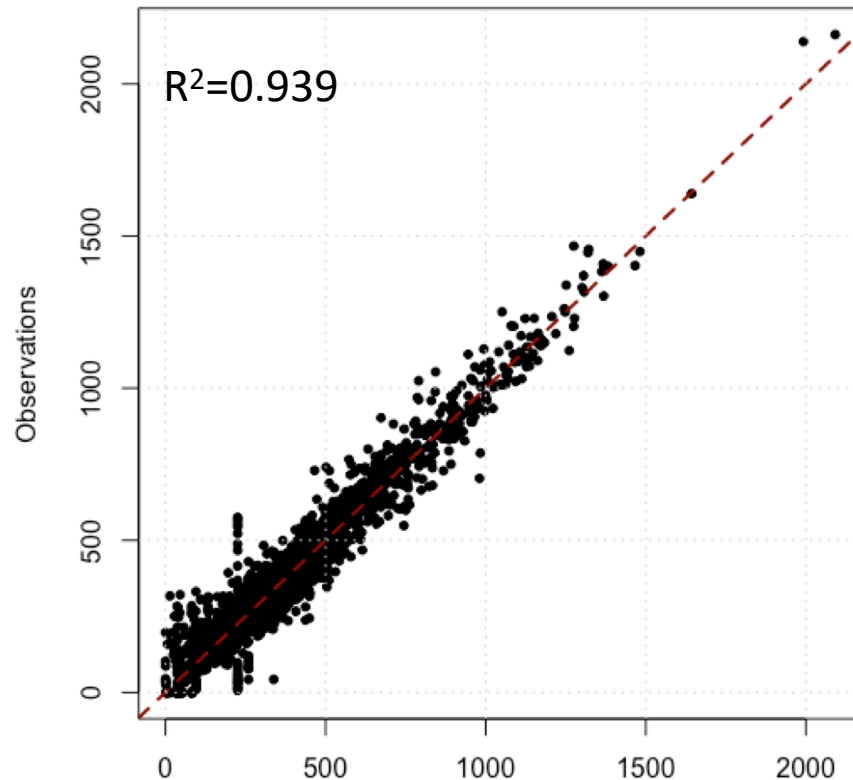


# Gompertz model was actually just exponential

- Fixed:  $TV_0$ ,  $\alpha$ ,  $\beta$ ; Random:  $\text{diag}(TV_0 + \alpha + \beta)$

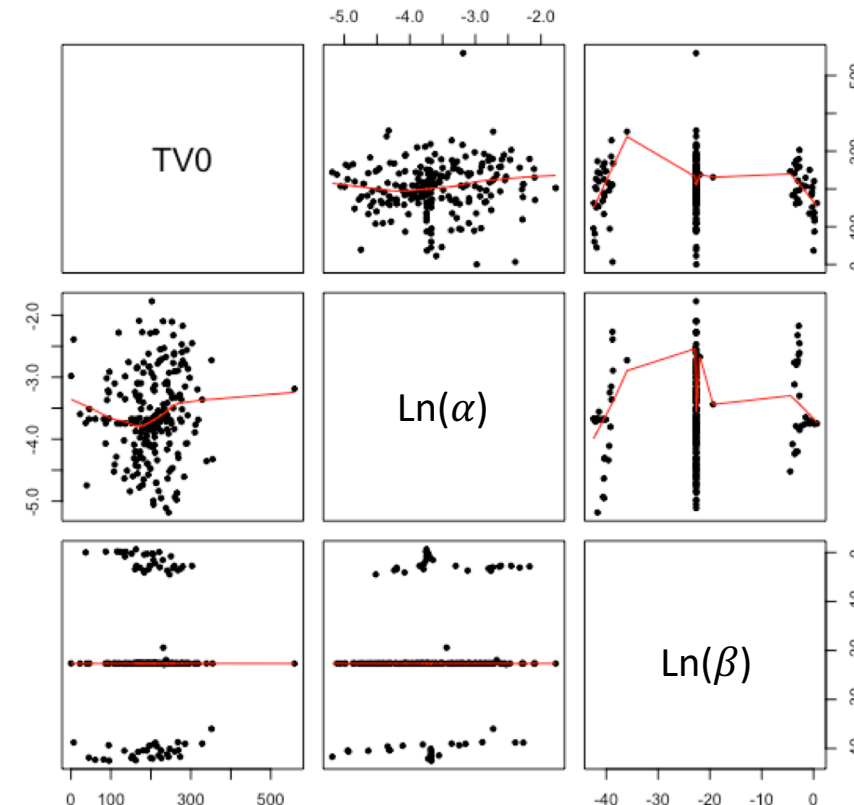
$$\frac{dV}{dt} = \alpha e^{-\beta t} V \quad \alpha: \text{growth rate (/day)}; \beta: \text{decay rate (/day)}$$

	Value	Std. Error	CV(%)
$TV_0$	210	5.0	2.4
$\ln(\alpha)$	-3.7	0.059	1.6
$\ln(\beta)$	-22.7	2.8	12



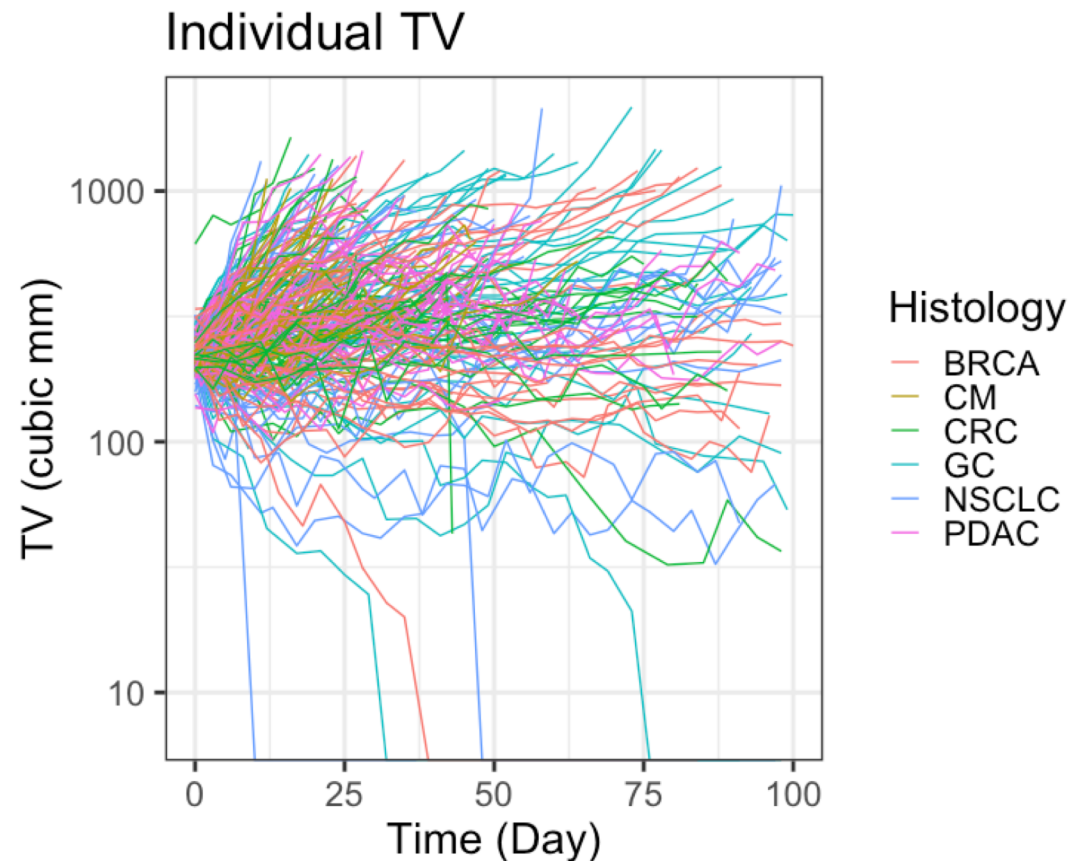
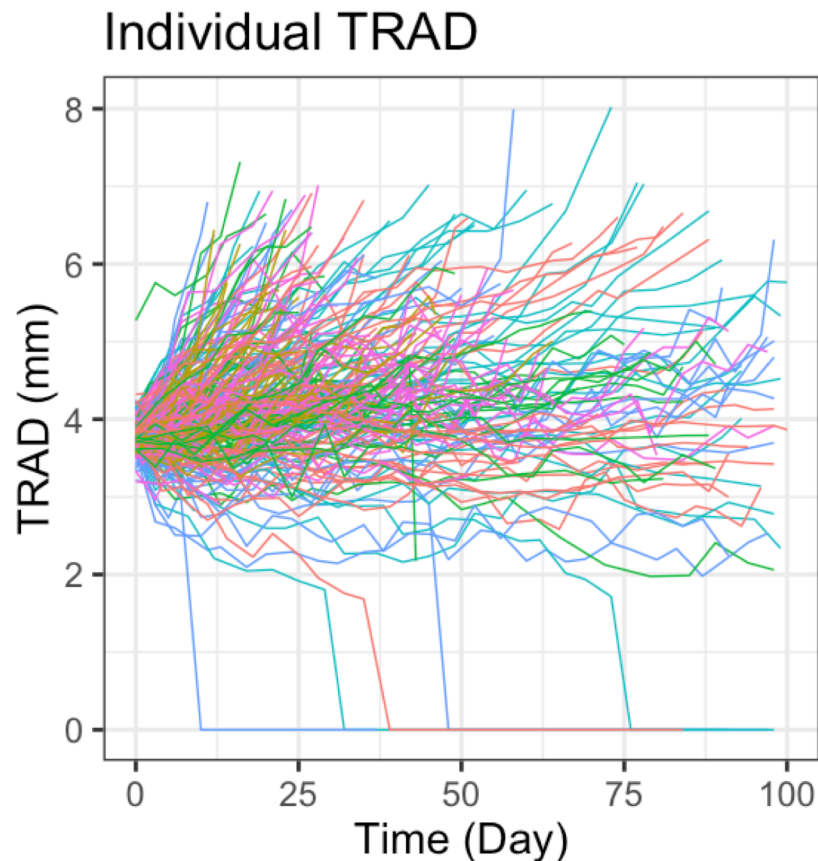
Fitting by SAEMIX:  $\beta$  is close to zero. Random effects not correlated. Gompertz reduced to exponential.

Correlations between random effects



# Which rate law accurately recapitulates tumour growth?

- All rate laws successfully recapitulate all PDX control growth
  - Parametric inferences were successful
  - Exponential-linear, logistic and Gompertz reduced to exponential model
  - Essentially only two types of dynamics: linear and exponential



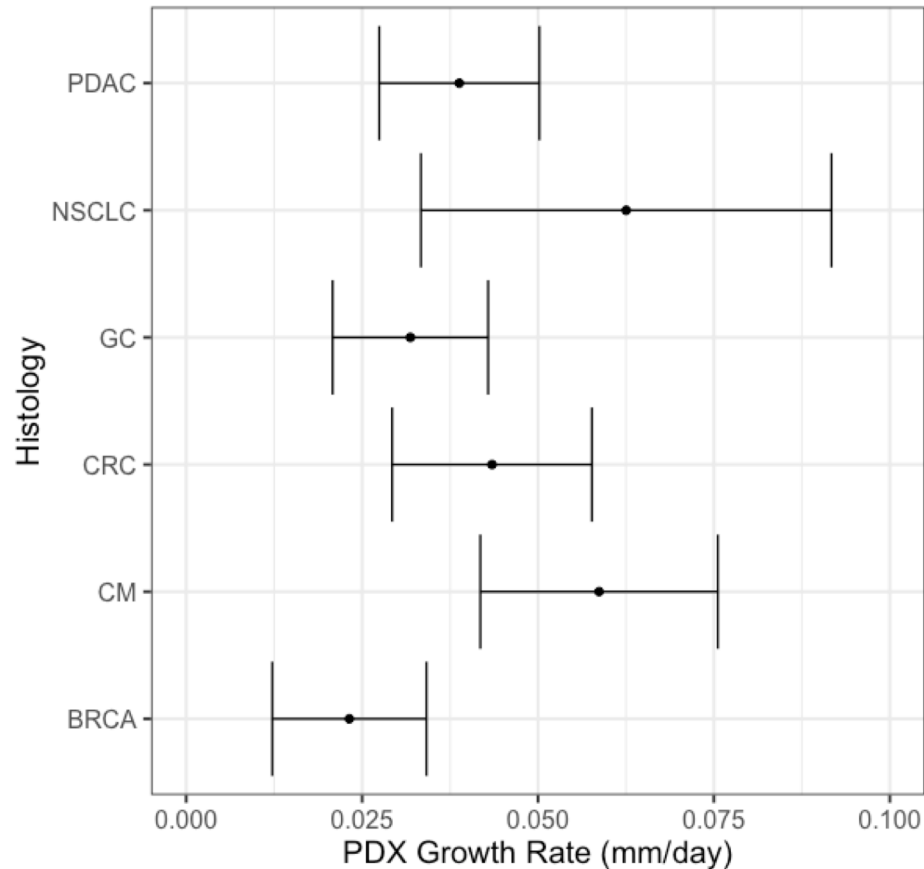
# Which rate law accurately recapitulates tumour growth?

- All rate laws successfully recapitulate all PDX control growth
  - Parametric inferences were successful
  - Exponential-linear, logistic and Gompertz reduced to exponential model
  - Essentially only two types of dynamics: linear and exponential
- Does growth rate vary by histology?
  - Inference using linear and exponential models
  - Are inference results consistent?

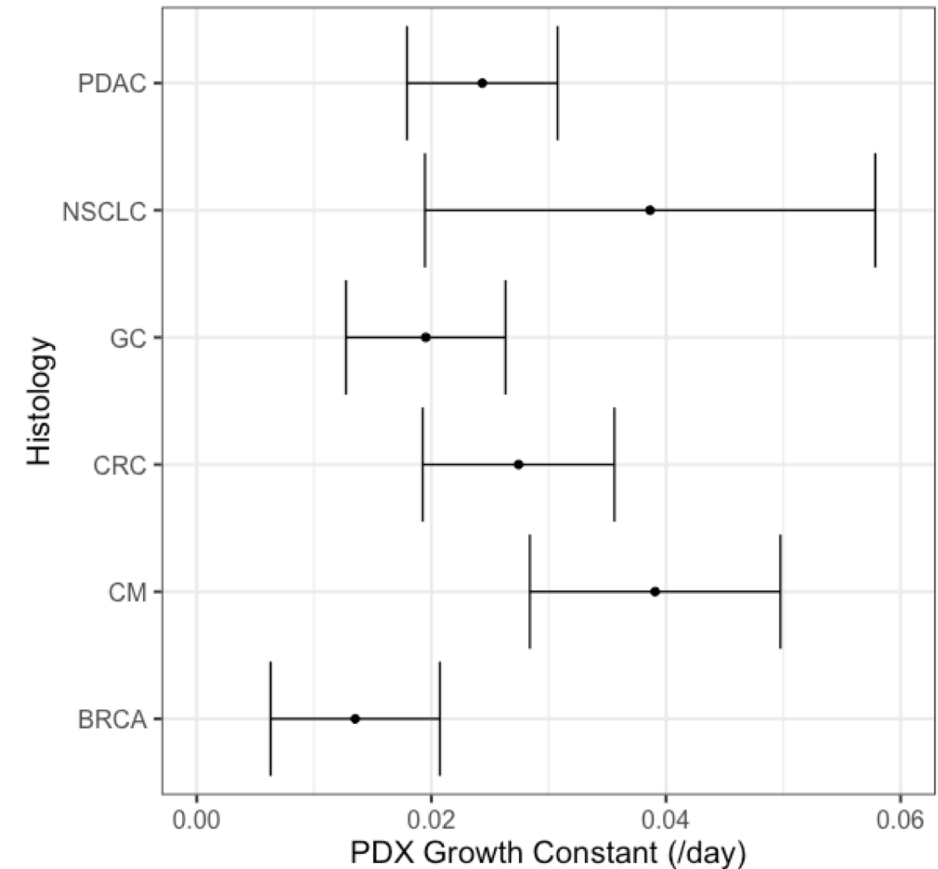
# Growth rate varies by histology

- Inferences by both models are largely consistent
  - Linear: NSCLC and CM grow significantly faster than BRCA
  - Exponential: PDAC, NSCLC, CM grow significantly faster than BRCA

PDX growth by histology (linear model)



PDX growth by histology (exponential model)





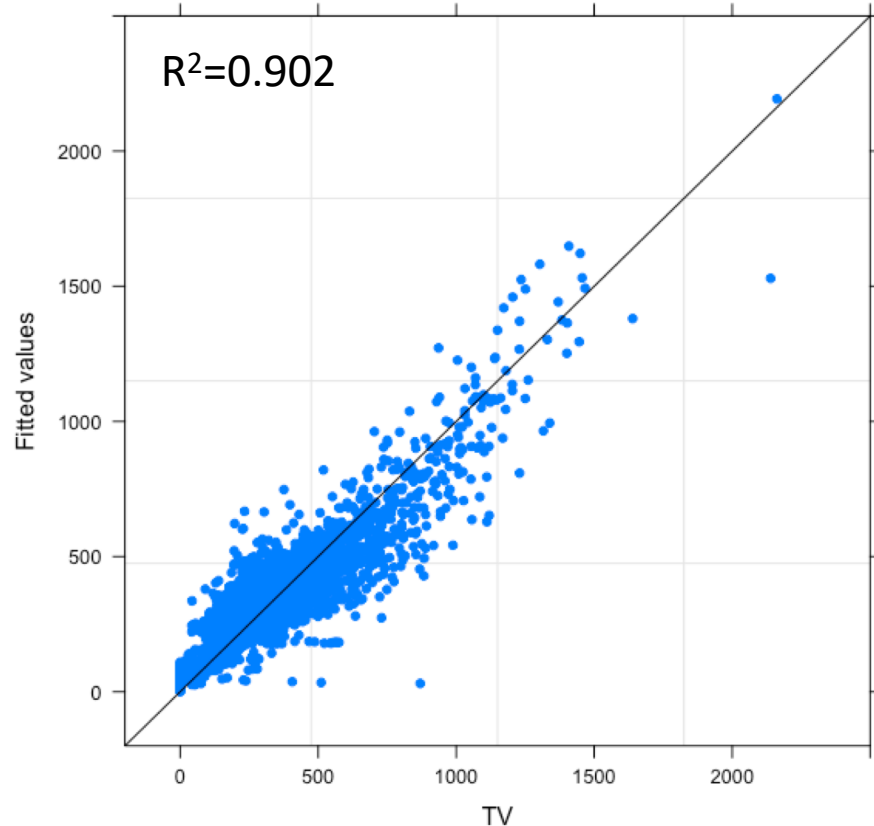
# Supporting slides



# Logistic model could not be fitted by NLME

- Fixed:  $TV_0$ ,  $K$ ,  $\alpha$ ; Random:  $TV_0$

	Value	Std. Error	DoF	t-value	P-value
$TV_0$	290	6.6	3159	44	0
$K$	200	5.7	3159	35	0
$\alpha$	-0.015	7.6e-4	3159	-20	0



$$\frac{dV}{dt} = aV \left(1 - \frac{V}{K}\right)$$

$a$ : growth rate (/day);  $K$ : carrying capacity ( $\text{mm}^3$ )

Ideally random effects should include  $K$  and  $\alpha$   
 Unfortunately, NLME can only handle  $TV_0$  as a random effect  
 Other configurations leads to computational errors

The results were not good:  
 $TV_0 = 290 \text{ mm}^3$   
 $K = 200 \text{ mm}^3$  This looks really suspicious  
 $\alpha$ : Negative This violates the assumption of the model

An alternative optimisation algorithm was used for model fitting  
 Stochastic Approximation Expectation Maximisation (SAEM) for mixed effects models – SAEMIX R library



# Gompertz model could not be fitted by NLME

- Fixed:  $TV_0$ ,  $\alpha$ ,  $\beta$ ; Random:  $TV_0 + \alpha + \beta \sim 1$

	Value	Std. Error	DoF	t-value	P-value
$TV_0$	230	4.4	3159	51	0
$\alpha$	0.022	0.0020	3159	11	0
$\beta$	-0.018	0.0033	3159	-5.3	0

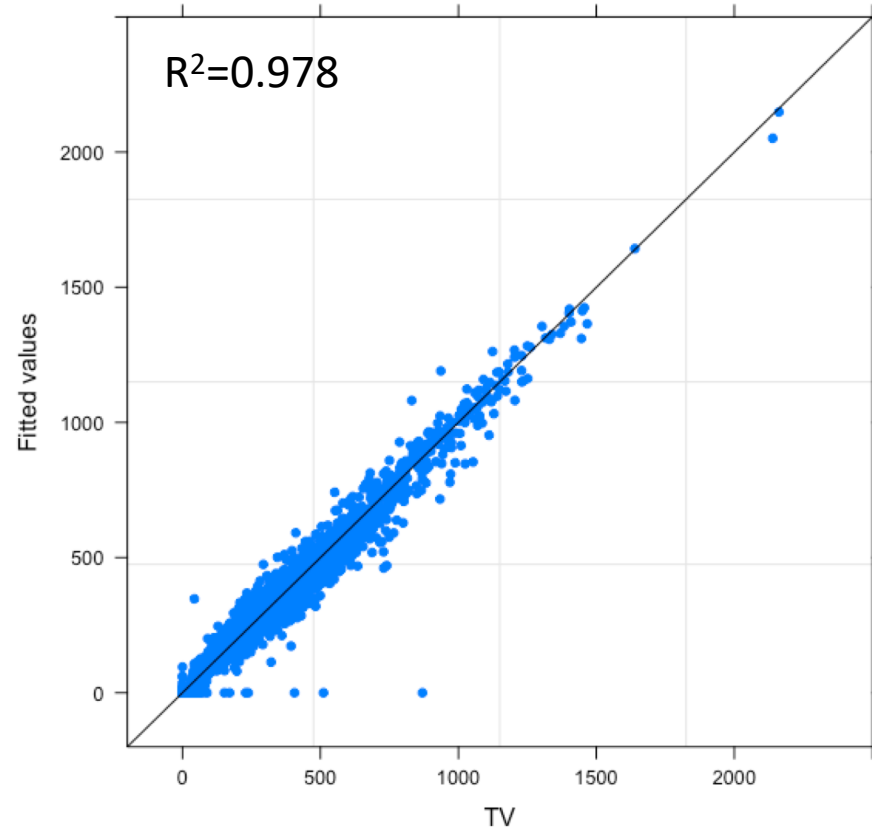


$$\frac{dV}{dt} = \alpha e^{-\beta t} V \quad \alpha: \text{growth rate (/day)}; \beta: \text{decay rate (/day)}$$

The best model allow random effects to be correlated



The fitted  $\beta$  was supposed to be larger than 0 to indicate decay in growth rate – this violates the assumption.



# Growth rate varies by histology

- Linear model

WALD

	Value	Std. Error	DoF	t-value	P-value
$r_0$	3.6	0.043	3155	84	<b>0</b>
$g(\text{BRCA})$	0.022	0.0075	3155	3.1	<b>0.0023</b>
$g(\text{CM})$	0.036	0.011	3155	3.2	<b>0.0013</b>
$g(\text{CRC})$	0.021	0.010	3155	2.0	<b>0.0458</b>
$g(\text{GC})$	0.0089	0.010	3155	0.87	0.3844
$g(\text{NSCLC})$	0.038	0.011	3155	3.3	<b>0.0008</b>
$g(\text{PDAC})$	0.016	0.011	3155	1.5	0.1320

ANOVA

	numDF	DoF	F-value	P-value
$r_0$	1	3155	7099	<b>&lt;0.0001</b>
$g(\text{BRCA})$	1	3155	172	<b>&lt;0.0001</b>
$g(\text{CM})$	1	3155	5.13	<b>0.0236</b>
$g(\text{CRC})$	1	3155	0.670	0.4133
$g(\text{GC})$	1	3155	0.744	0.3884
$g(\text{NSCLC})$	1	3155	8.92	<b>0.0028</b>
$g(\text{PDAC})$	1	3155	2.27	0.1320

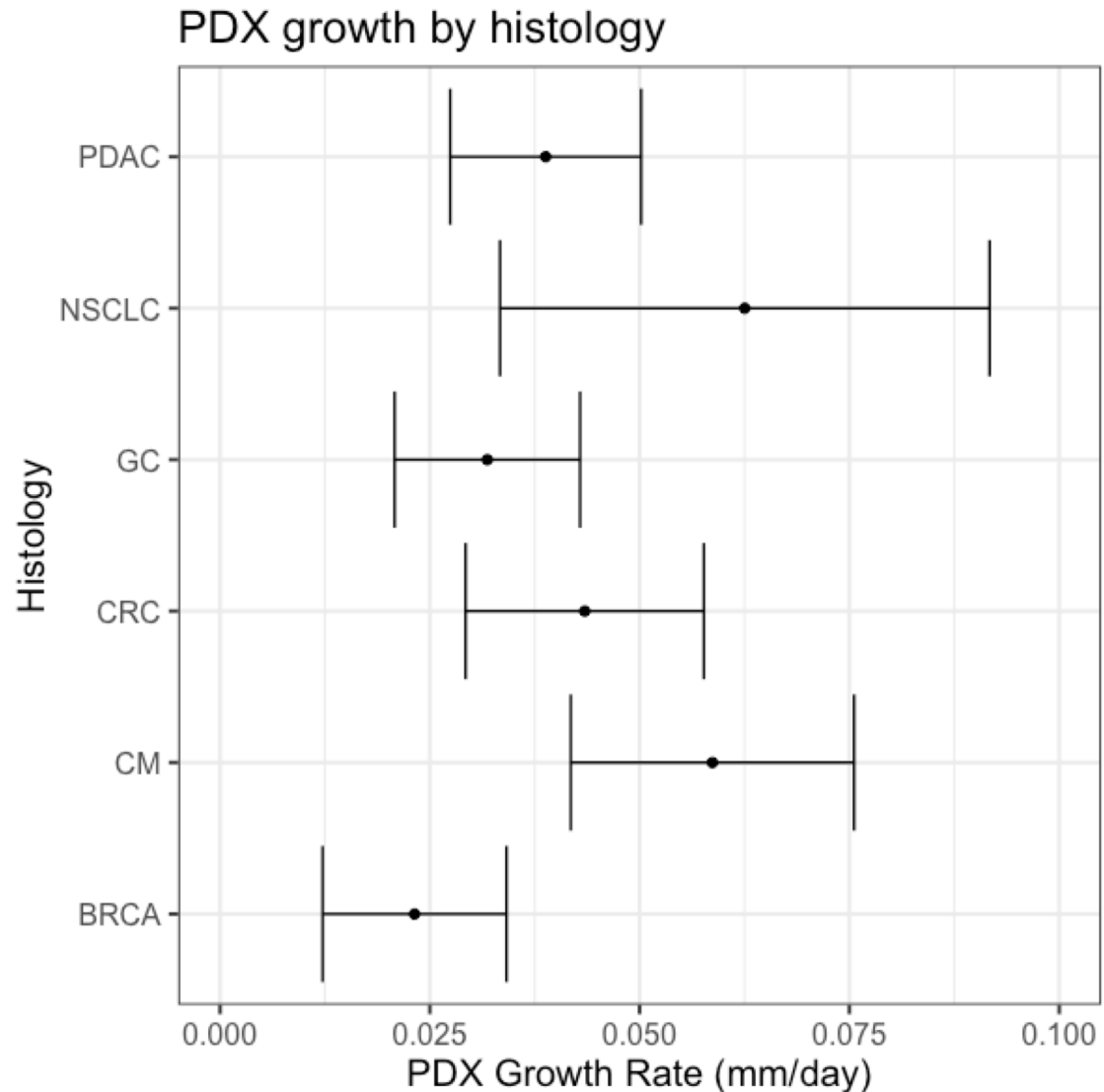
- $g(\text{BRCA})$  is chosen as baseline
- To recover growth for other histology, e.g. CM:  $g(\text{BRCA}) + g(\text{CM})$
- Significantly faster than BRCA baseline: CM and NSCLC

# Growth rate varies by histology

- Linear model
  - A different specification:
    - No baseline
    - Each histology has its own growth rate

```
nlme(TV~4/3*pi*(r0+(TYPE=="BRCA")*g_BRCA*TIME+
              (TYPE=="CM")*g_CM*TIME+
              (TYPE=="CRC")*g_CRC*TIME+
              (TYPE=="GC")*g_GC*TIME+
              (TYPE=="NSCLC")*g_NSCLC*TIME+
              (TYPE=="PDAC")*g_PDAC*TIME)^3,
      fixed = r0+g_BRCA+g_CM+g_CRC+g_GC+g_NSCLC+g_PDAC~1,
      random = pdDiag(r0+g_BRCA+g_CM+g_CRC+g_GC+g_NSCLC+g_PDAC~1),
      data = dat.ctrl.grp,
      start = c(3,0.1,0.1,0.1,0.1,0.1,0.1),
      method='ML',
      control = nlmeControl(
        pnlsMaxIter=10,
        msMaxIter=100,
        tolerance=1e-3)
      )
```

- Significantly faster than BRCA:
  - NSCLC, CM



# Growth rate varies by histology

- Exponential model

WALD

	Value	Std. Error	DoF	t-value	P-value
$TV_0$	220	5.4	3155	40	<b>0.0000</b>
$\alpha(\text{BRCA})$	0.014	0.0034	3155	4.0	<b>0.0001</b>
$\alpha(\text{CM})$	0.025	0.0064	3155	3.9	<b>0.0001</b>
$\alpha(\text{CRC})$	0.014	0.0054	3155	2.6	<b>0.0108</b>
$\alpha(\text{GC})$	0.0059	0.0049	3155	1.2	0.2293
$\alpha(\text{NSCLC})$	0.025	0.010	3155	2.4	<b>0.0161</b>
$\alpha(\text{PDAC})$	0.011	0.0049	3155	2.2	<b>0.0300</b>

ANOVA

	numDF	DoF	F-value	P-value
$r_0$	1	3155	1695	<b>&lt;0.0001</b>
$\alpha(\text{BRCA})$	1	3155	184	<b>&lt;0.0001</b>
$\alpha(\text{CM})$	1	3155	9.66	<b>0.0019</b>
$\alpha(\text{CRC})$	1	3155	2.69	0.1011
$\alpha(\text{GC})$	1	3155	0.0146	0.9037
$\alpha(\text{NSCLC})$	1	3155	3.84	<b>0.0502</b>
$\alpha(\text{PDAC})$	1	3155	4.71	<b>0.0300</b>

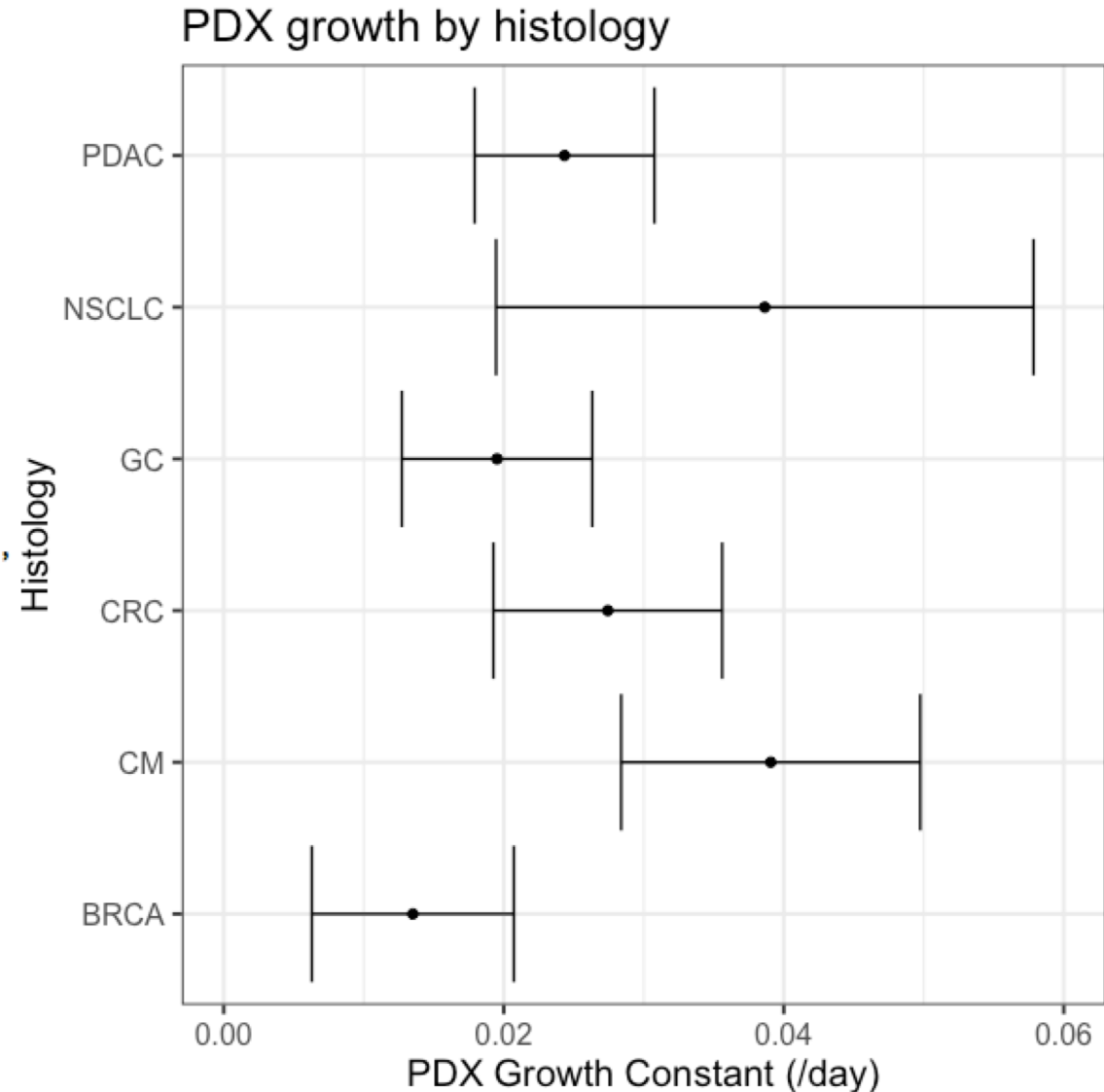
- $\alpha(\text{BRCA})$  is chosen as baseline
- To recover growth for other histology, e.g. CM:  $\alpha(\text{BRCA}) + \alpha(\text{CM})$
- Significantly faster than BRCA baseline: CM, NSCLC and PDAC

# Growth rate varies by histology

- Exponential model
  - A different specification:
    - No baseline
    - Each histology has its own growth rate

```
nlme(TV~TV0*exp((TYPE=="BRCA")*a_BRCA*TIME+
  (TYPE=="CM")*a_CM*TIME+
  (TYPE=="CRC")*a_CRC*TIME+
  (TYPE=="GC")*a_GC*TIME+
  (TYPE=="NSCLC")*a_NSCLC*TIME+
  (TYPE=="PDAC")*a_PDAC*TIME),
fixed = TV0+a_BRCA+a_CM+a_CRC+a_GC+a_NSCLC+a_PDAC~1,
random = pdDiag(TV0+a_BRCA+a_CM+a_CRC+a_GC+a_NSCLC+a_PDAC~1),
data = dat.ctrl.grp,
start = c(150,0.01,0.01,0.01,0.01,0.01,0.01),
method='ML',
control = nlmeControl(
  pnlsMaxIter=10,
  msMaxIter=100,
  tolerance=1e-3)
)
```

- Significantly faster than BRCA:
  - PDAC, NSCLC, CM



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