Novartis Mouse Clinical Trial: Data Analytics

Data & Clarity

Tao You, PhD

WHICH RATE LAW ACCURATELY RECAPITULATES TUMOUR GROWTH?

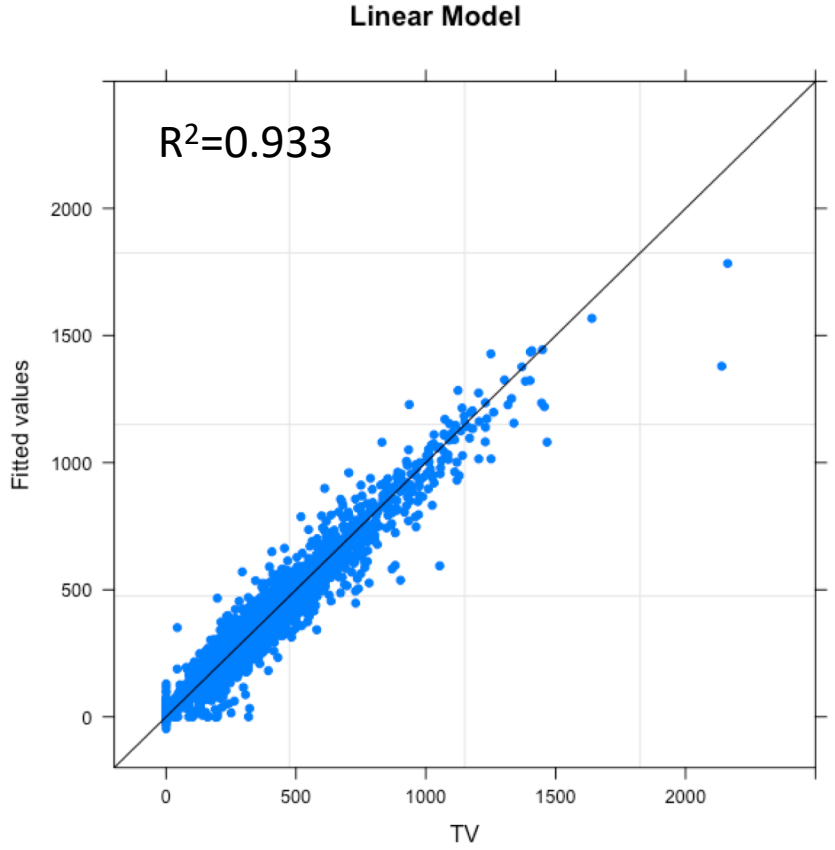
Linear model fits well

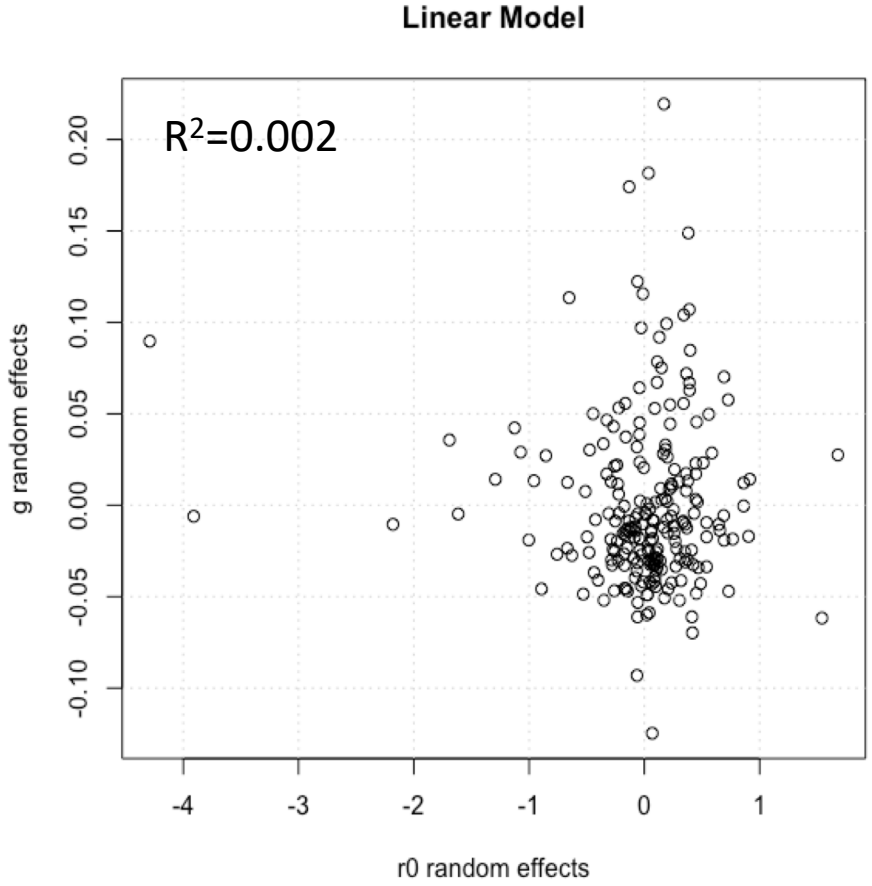
- Fixed: r_0, g; Random: diag(r_0, g)

	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

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

Fitting by NLME in R:
TV_0 = 200 mm^3
g = 0.041 mm/day





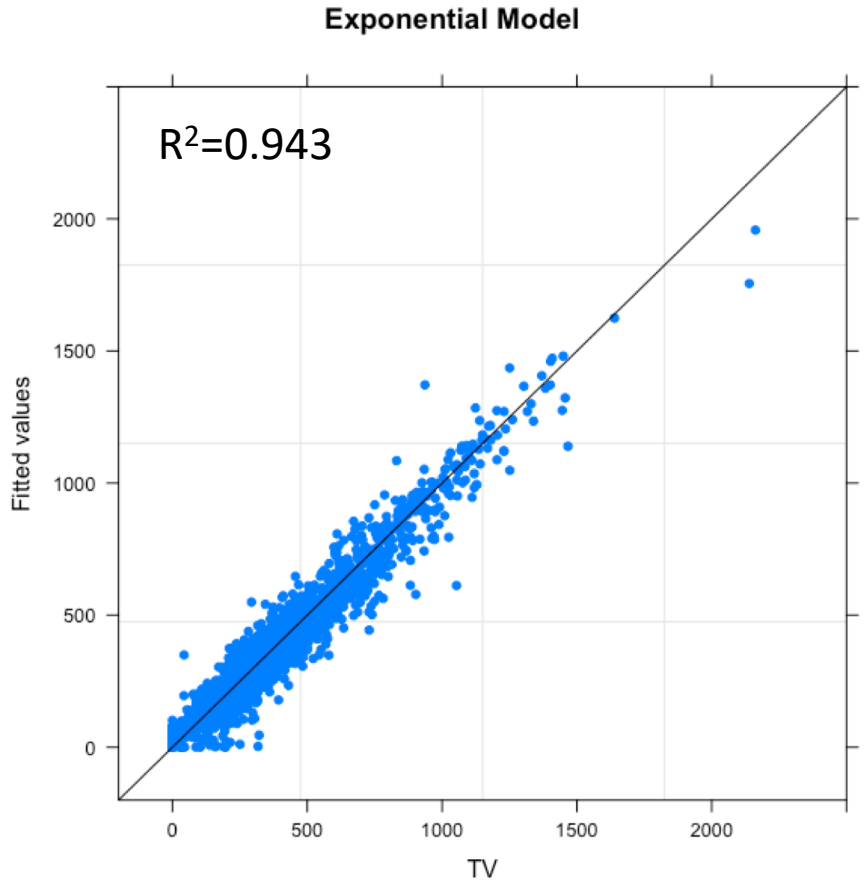
Exponential model fits well

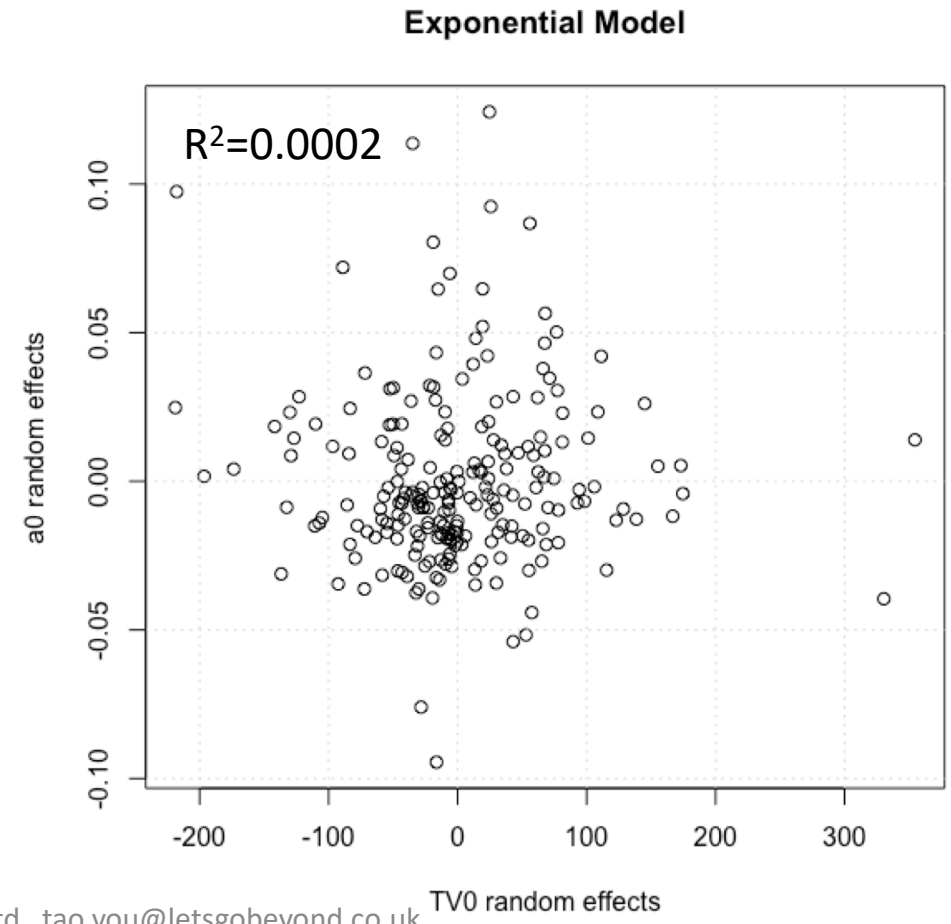
- Fixed: TV_0, a; Random: diag(TV_0, a)

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

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

Fitting by NLME in R:
TV_0 = 220 mm^3
a = 0.026





Exponential-linear model was actually just exponential

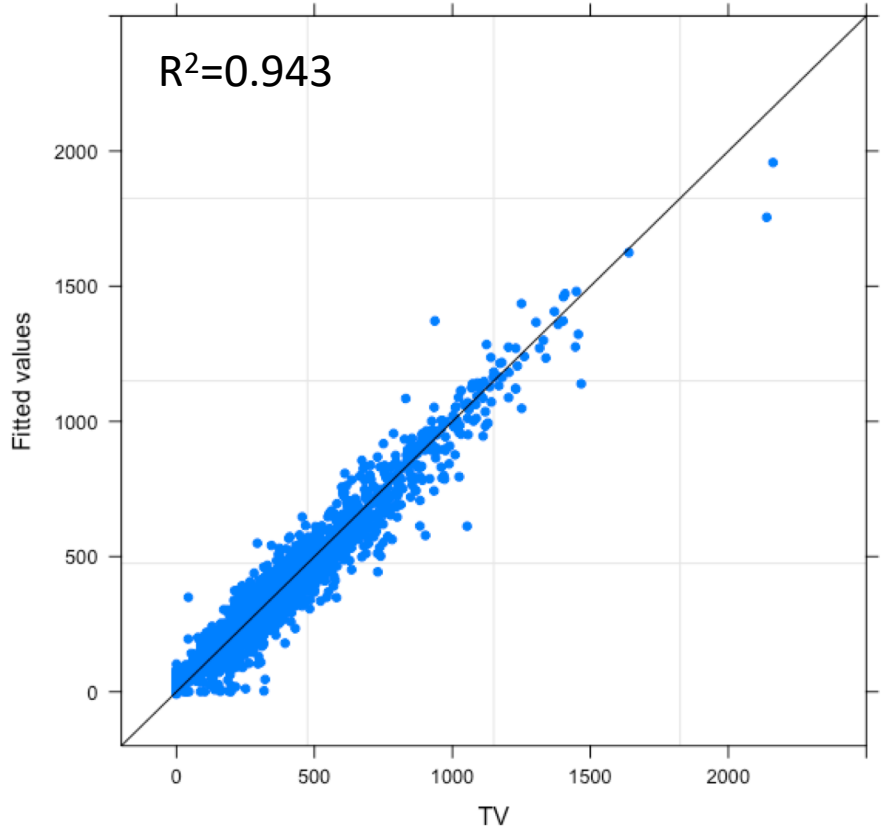
- Fixed: TV_0, a_0, $\boldsymbol{\tau}$; Random: diag(TV_0, a_0)

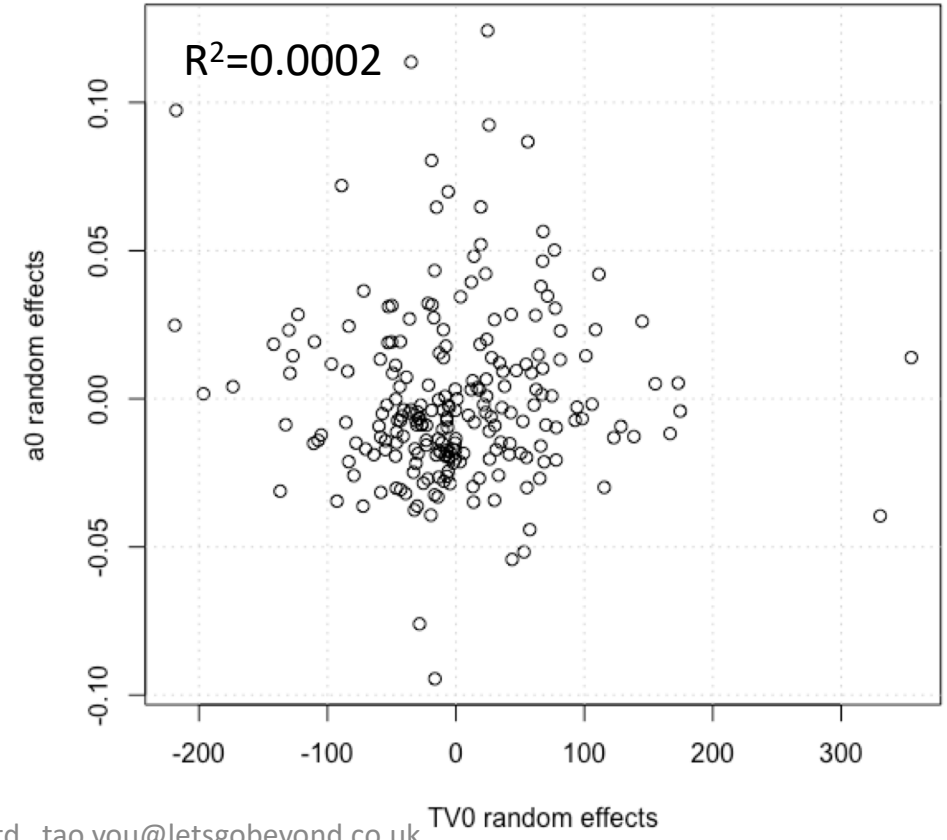
	Value	Std. Error	DoF	t-value	P-value
TV_0	220	5.4	3159	41	0
a_0	0.026	0.0020	3159	13	0
$\boldsymbol{\tau}$	280	8600	3159	0.032	0.97

$\frac{dV}{dt} = a_0 V, t \leq \tau; \frac{dV}{dt} = a_1, t > \tau$. V 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 mm^3
a = 0.026
$\boldsymbol{\tau}$: Not sure

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





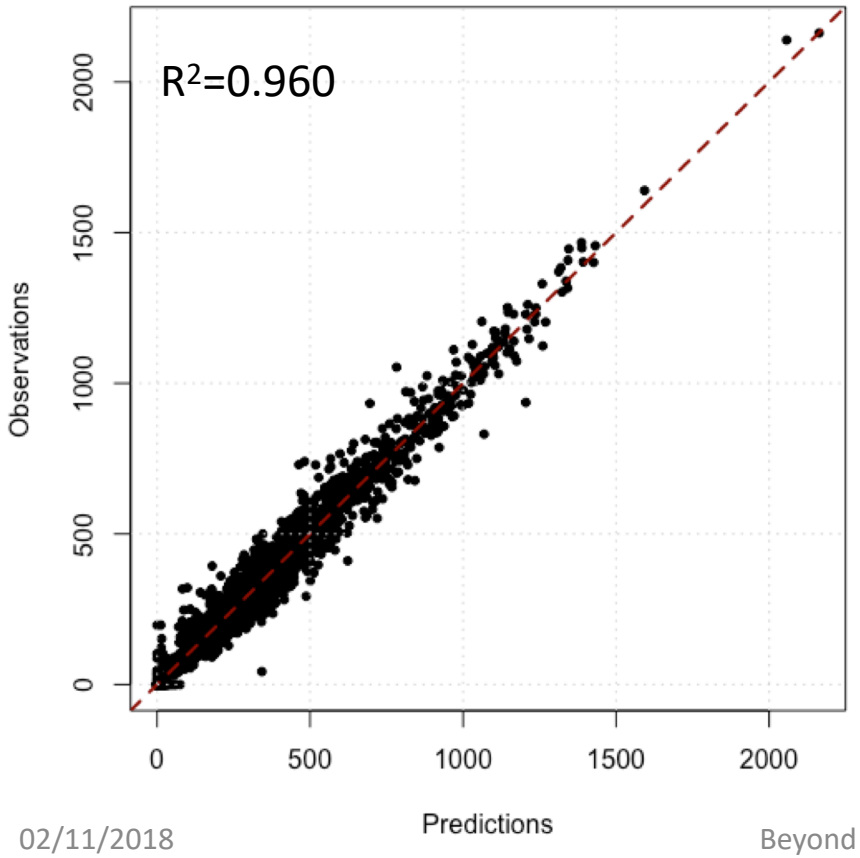
Logistic model fits well using SAEMIX

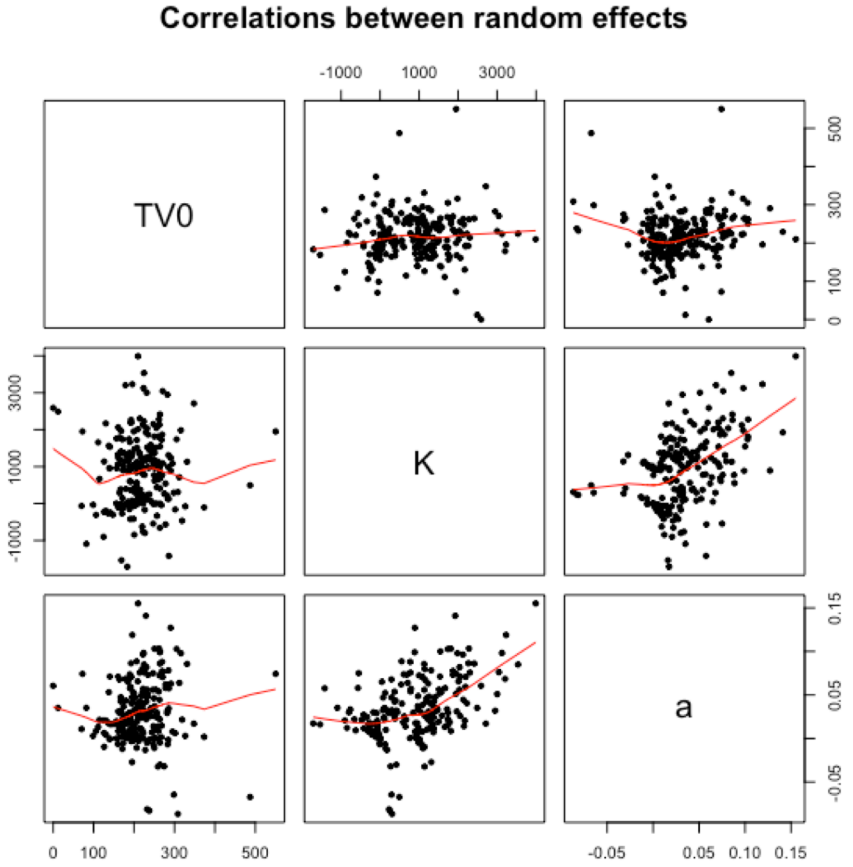
- Fixed: TV_0, K, a; Random: diag(TV_0 , K, a)

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

	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





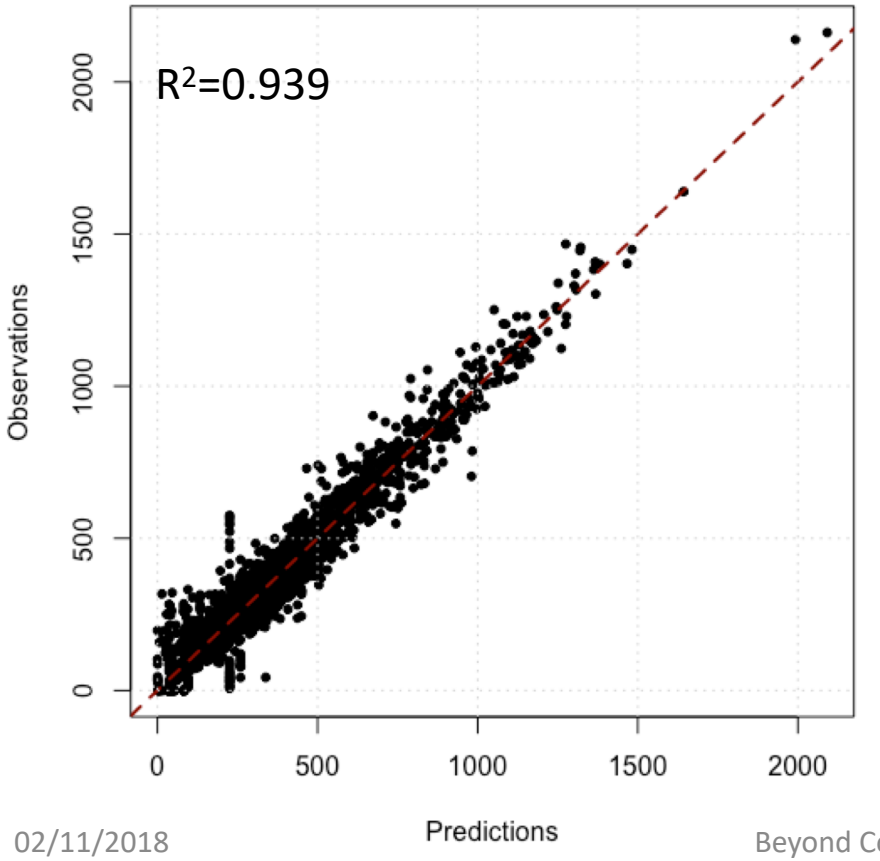
Gompertz model was actually just exponential

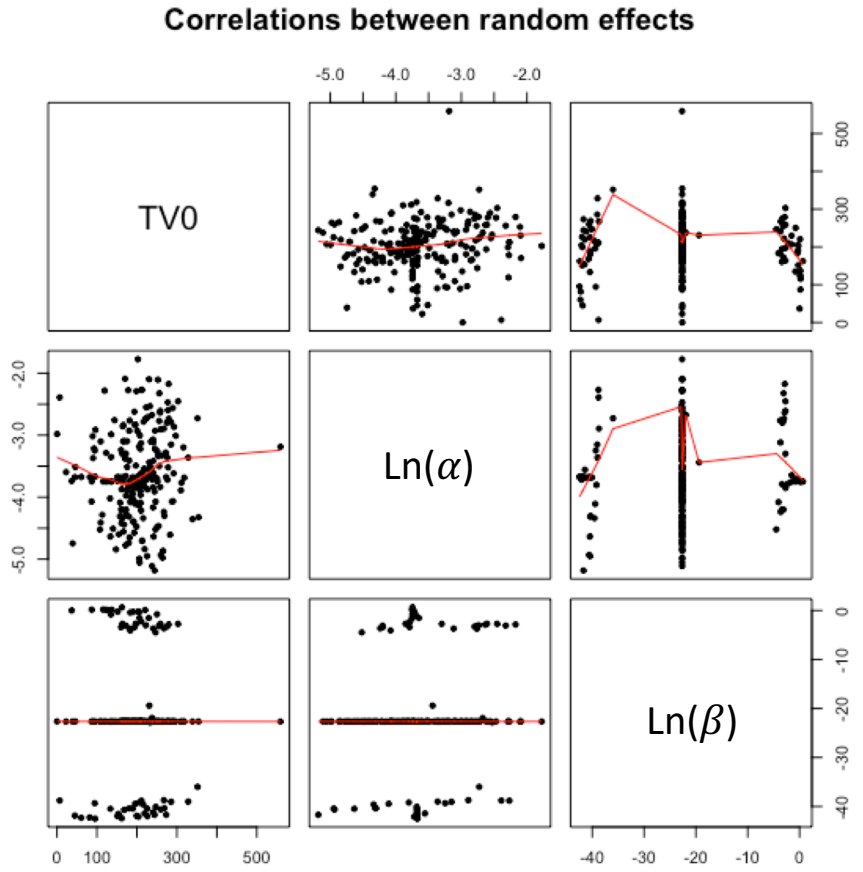
- Fixed: TV_0, α, β; Random: diag(TV_0+α+β)

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

	Value	Std. Error	CV(%)
TV_0	210	5.0	2.4
Ln(α)	-3.7	0.059	1.6
Ln(β)	-22.7	2.8	12

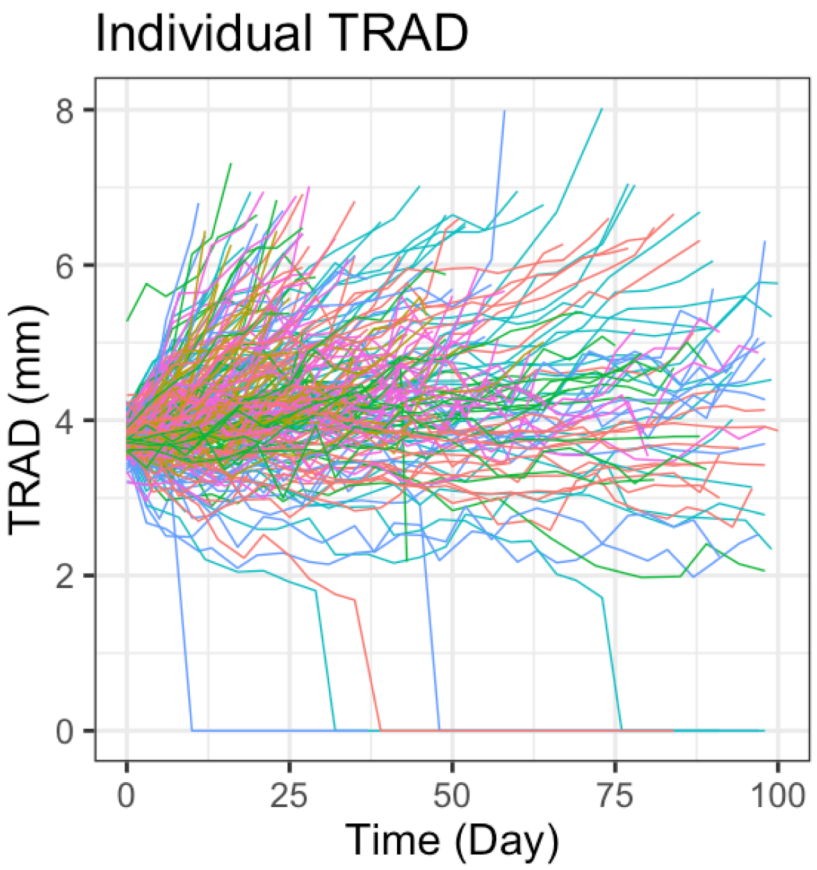
Fitting by SAEMIX: β is close to zero. Random effects not correlated. Gompertz reduced to exponential.

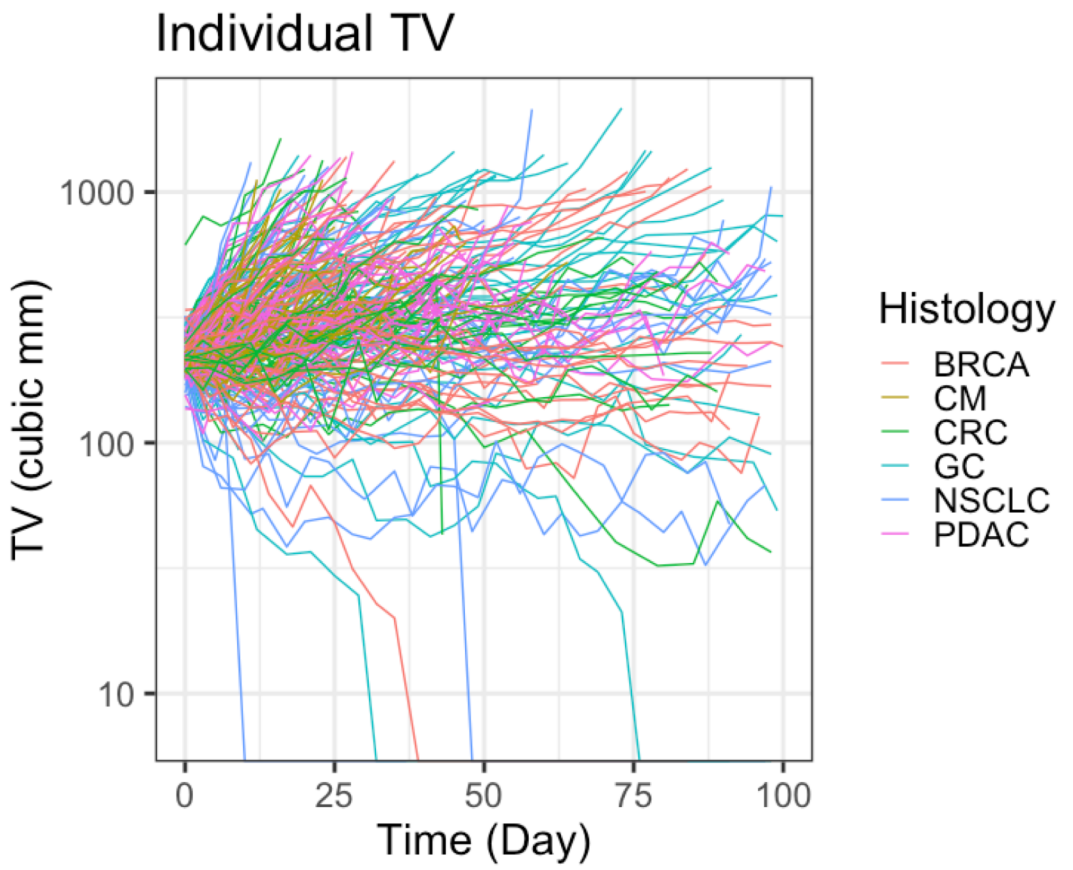




Which rate law accurately recapitulates tumour growth?

- 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



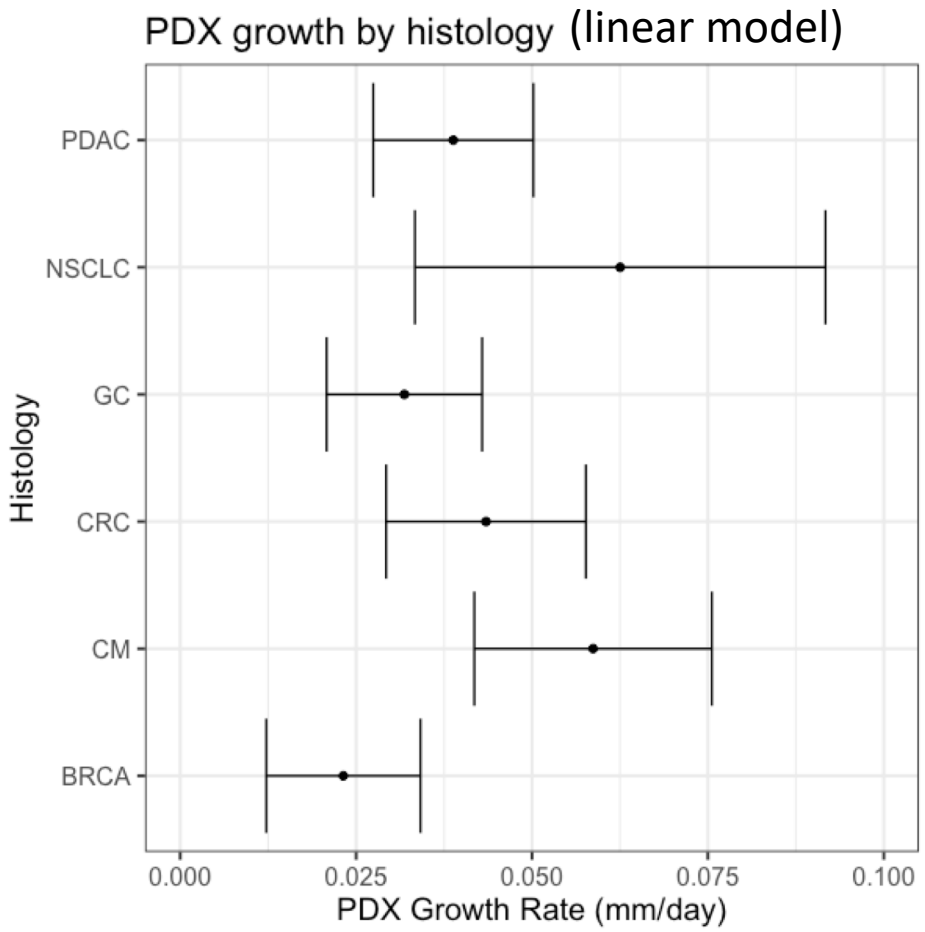


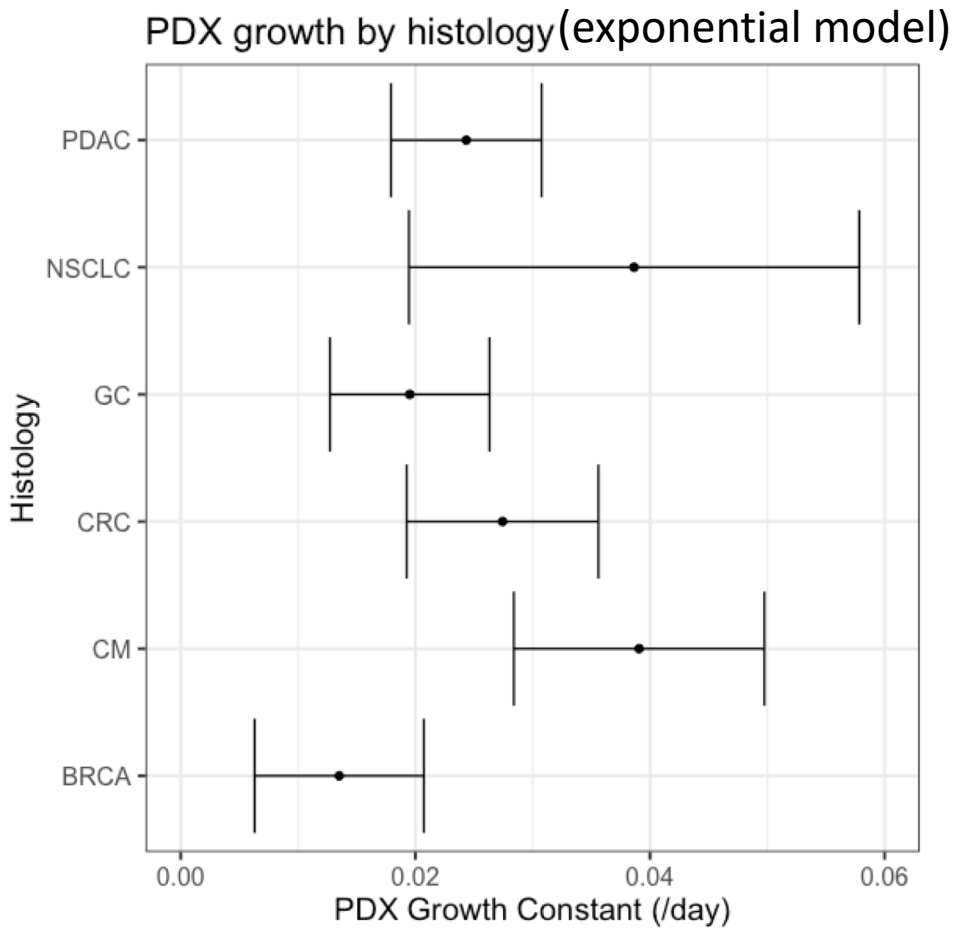
Which rate law accurately recapitulates tumour growth?

- 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



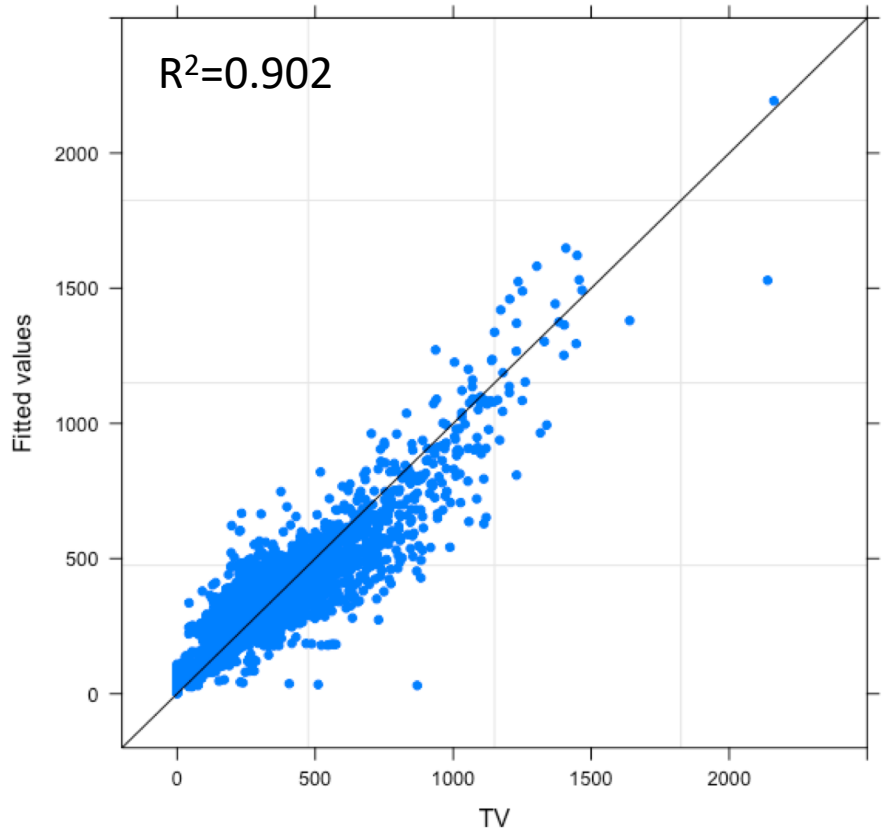


Supporting slides

Logistic model could not be fitted by NLME

- Fixed: TV_0, K, α; 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
α	-0.015	7.6e-4	3159	-20	0



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

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

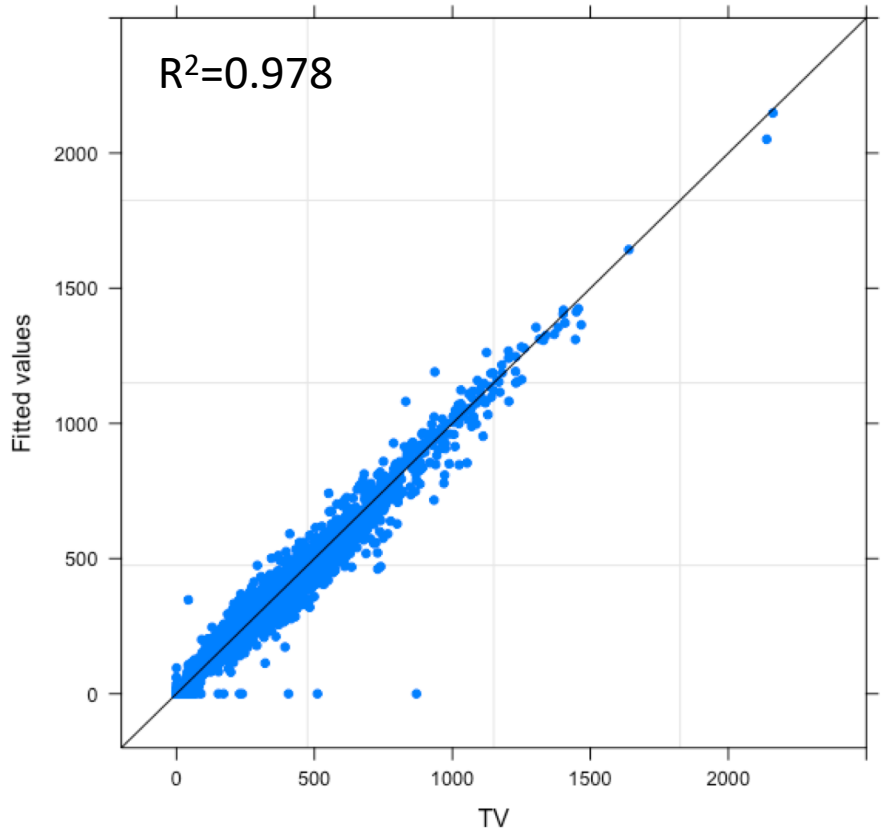
The results were not good:
TV_0 = 290 mm^3
K = 200 mm^3 This looks really suspicious
α: Negative This violates the assumption of the model

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

Gompterz model could not be fitted by NLME

- Fixed: TV_0, α, β; Random: $TV_0+\alpha+\beta$~1

	Value	Std. Error	DoF	t-value	P-value
TV_0	230	4.4	3159	51	0
α	0.022	0.0020	3159	11	0
β	-0.018	0.0033	3159	-5.3	0



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

The best model allow random effects to be correlated

The fitted β 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	**0**
***g*(BRCA)**	0.022	0.0075	3155	3.1	**0.0023**
***g*(CM)**	0.036	0.011	3155	3.2	**0.0013**
***g*(CRC)**	0.021	0.010	3155	2.0	**0.0458**
g(GC)	0.0089	0.010	3155	0.87	0.3844
***g*(NSCLC)**	0.038	0.011	3155	3.3	**0.0008**
g(PDAC)	0.016	0.011	3155	1.5	0.1320

ANOVA

	numDF	DoF	F-value	P-value
r_0	1	3155	7099	**<0.0001**
***g*(BRCA)**	1	3155	172	**<0.0001**
***g*(CM)**	1	3155	5.13	**0.0236**
g(CRC)	1	3155	0.670	0.4133
g(GC)	1	3155	0.744	0.3884
***g*(NSCLC)**	1	3155	8.92	**0.0028**
g(PDAC)	1	3155	2.27	0.1320

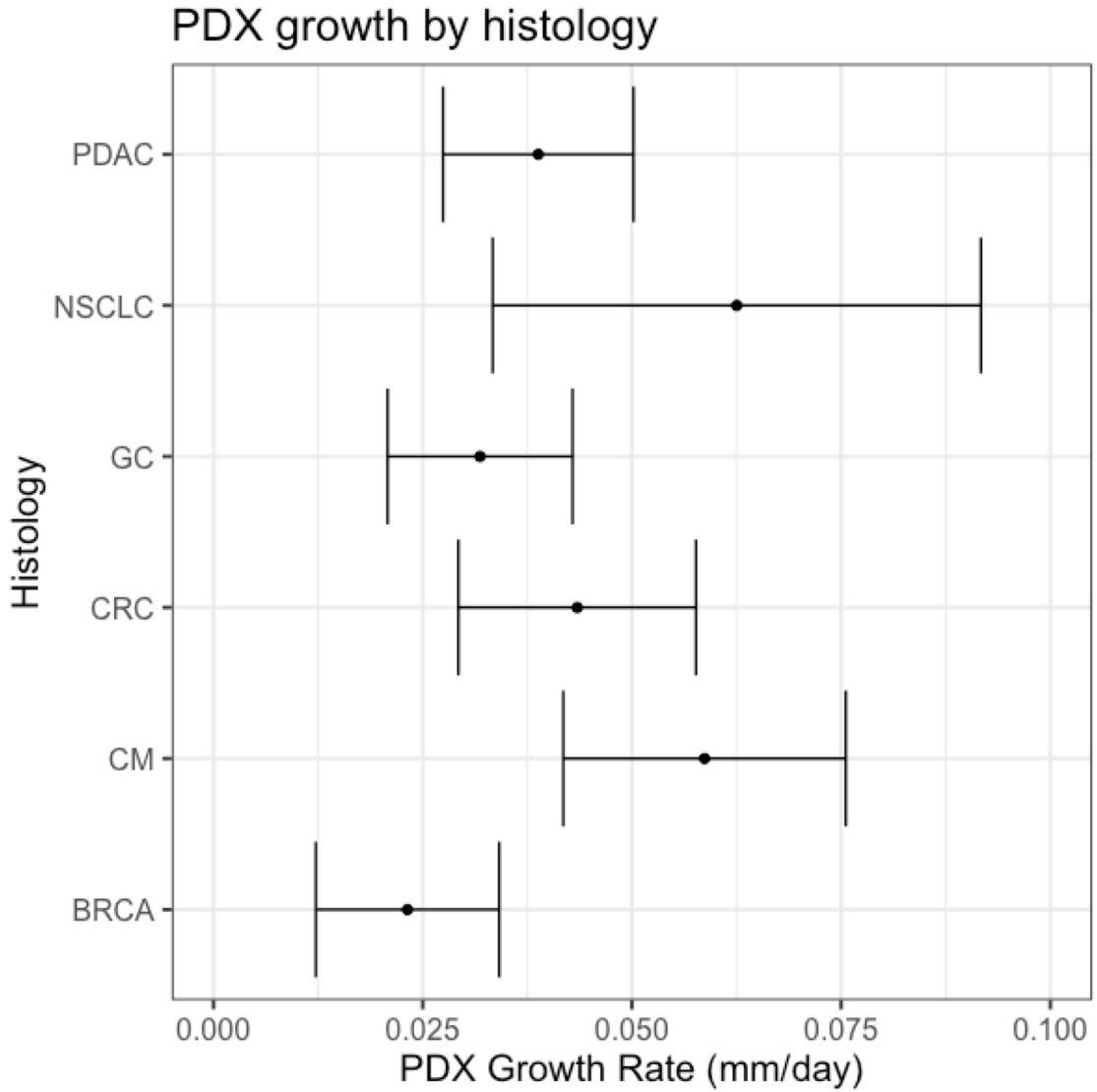
- g(BRCA) is chosen as baseline
- To recover growth for other histology, e.g. CM: *g*(BRCA) + *g*(CM)
- Significantly faster than BRCA baseline: CM and NSCLC

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	**0.0000**
***a*(BRCA)**	0.014	0.0034	3155	4.0	**0.0001**
***a*(CM)**	0.025	0.0064	3155	3.9	**0.0001**
***a*(CRC)**	0.014	0.0054	3155	2.6	**0.0108**
a(GC)	0.0059	0.0049	3155	1.2	0.2293
***a*(NSCLC)**	0.025	0.010	3155	2.4	**0.0161**
***a*(PDAC)**	0.011	0.0049	3155	2.2	**0.0300**

ANOVA

	numDF	DoF	F-value	P-value
r_0	1	3155	1695	**<0.0001**
***a*(BRCA)**	1	3155	184	**<0.0001**
***a*(CM)**	1	3155	9.66	**0.0019**
a(CRC)	1	3155	2.69	0.1011
a(GC)	1	3155	0.0146	0.9037
***a*(NSCLC)**	1	3155	3.84	**0.0502**
***a*(PDAC)**	1	3155	4.71	**0.0300**

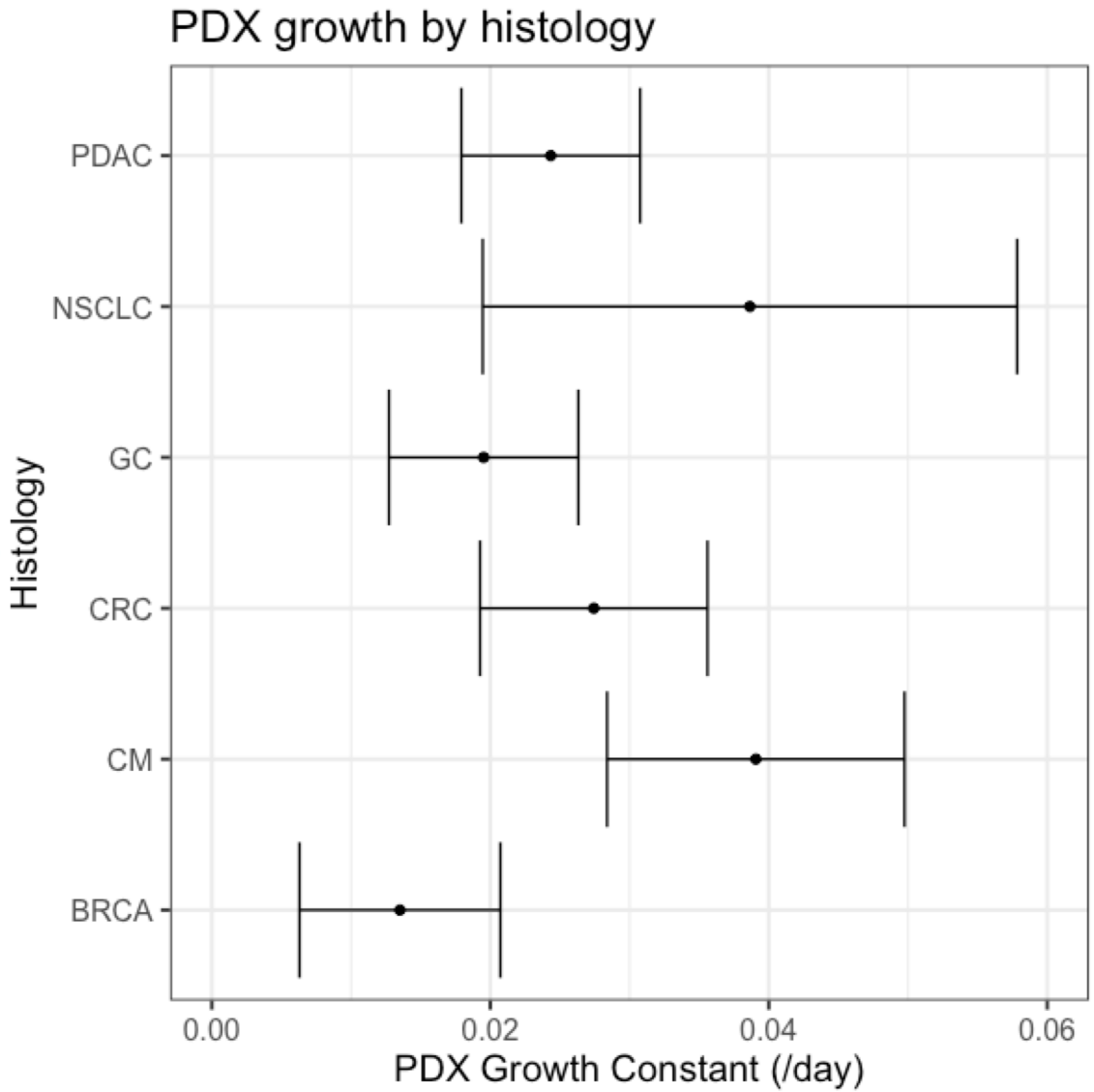
- *a*(BRCA) is chosen as baseline
- To recover growth for other histology, e.g. CM: *a*(BRCA) + *a*(CM)
- Significantly faster than BRCA baseline: CM, NSCLC and PDAC

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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- Contact Information:
  Please contact Tao You: Email: tao.you@letsgobeyond.co.uk or visit www.letsgobeyond.co.uk.
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