Statistical Methods in Pre- and Clinical Drug Development. Growth-Inhibition Model Example

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Cambridge Statistics Discussion Group

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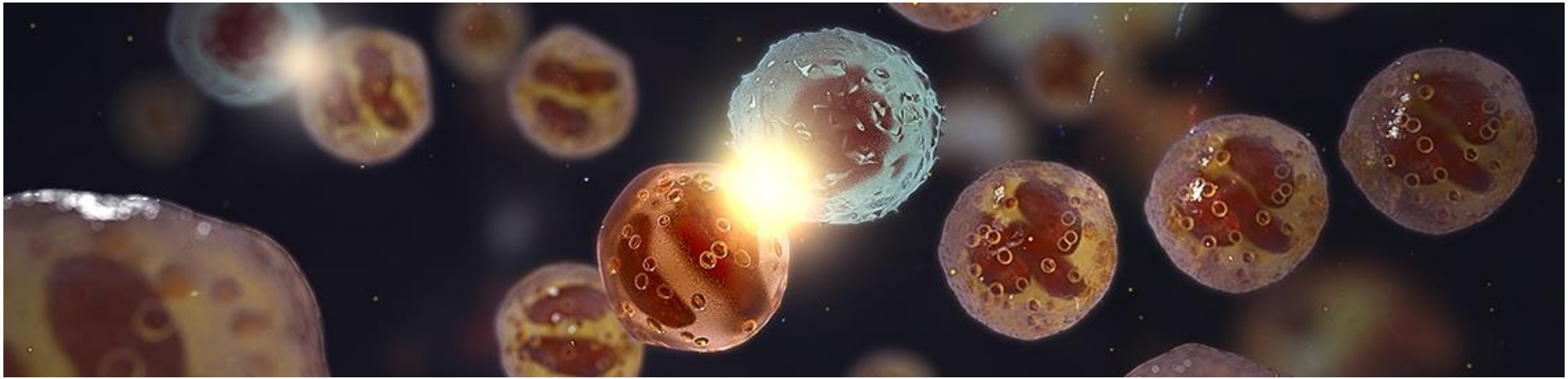
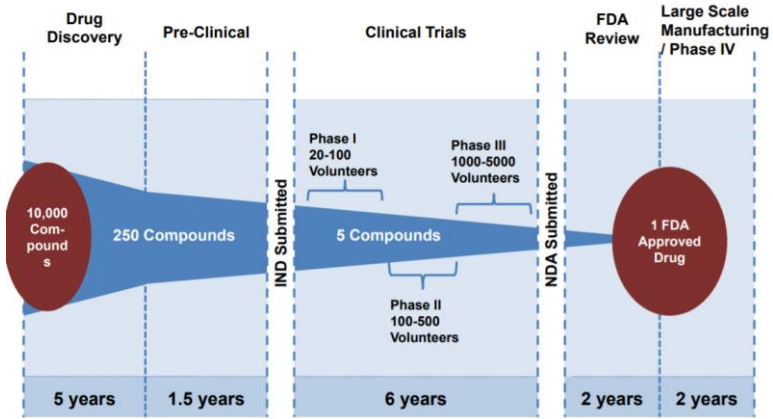


Introduction

- **Pre-clinical and clinical trials: safety and <u>efficacy</u> testing**
- **Clinical: more focus**
  - Less compounds
  - Bigger studies
  - Emphasis of robust designs, established endpoints
  - External evidence (meta-analysis)
  - Structured statistical analysis guidelines and standards
  - …
- **Pre-clinical: more diversity**
  - More compounds
  - Smaller studies (in-vivo 10 animals per arm)
  - Different types of experiments (in-vitro, in-vivo), exploratory character
  - Large amount of experimental data collected in-house
  - Lack of standardized statistical guidelines (in-house standards)



Source: Quelle (2006) Burrell Report Biotechnology Industry

Flexibility in choice and application of statistical models should serve the right purpose

Motivation

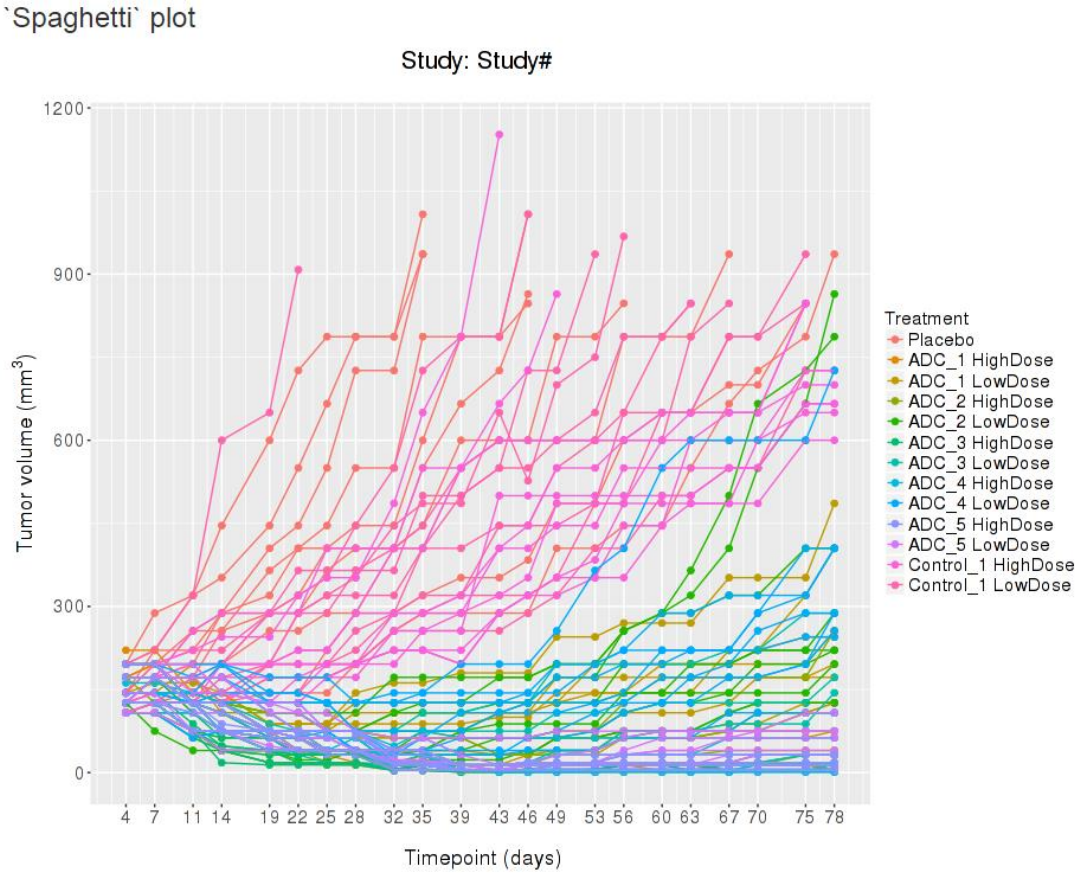
Statistical models in pre-clinical development: efficacy assessment

- Simplicity (non-statistical collaborators) and biological relevance
- Utilize richness of study data
- Applicable in study design: endpoint, effect size, simulations..
- Applicability for clinical data (translational purpose)

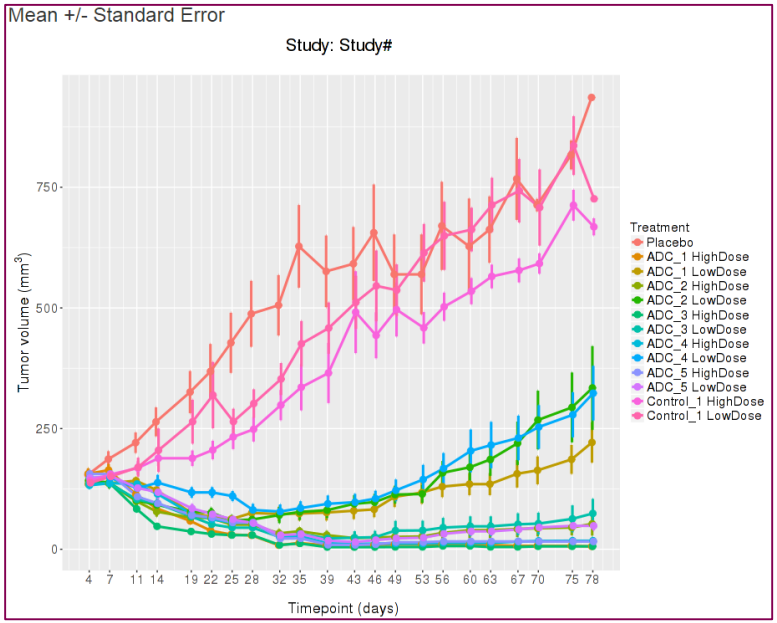
Novel methods or creative use of the existing ones

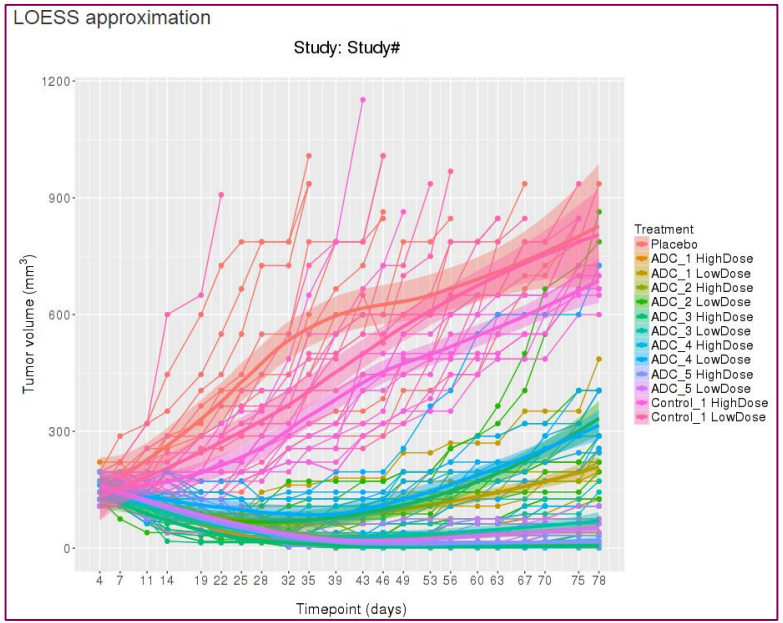
Oncology example

Example in-vivo efficacy study outcome



Example in-vivo efficacy analysis

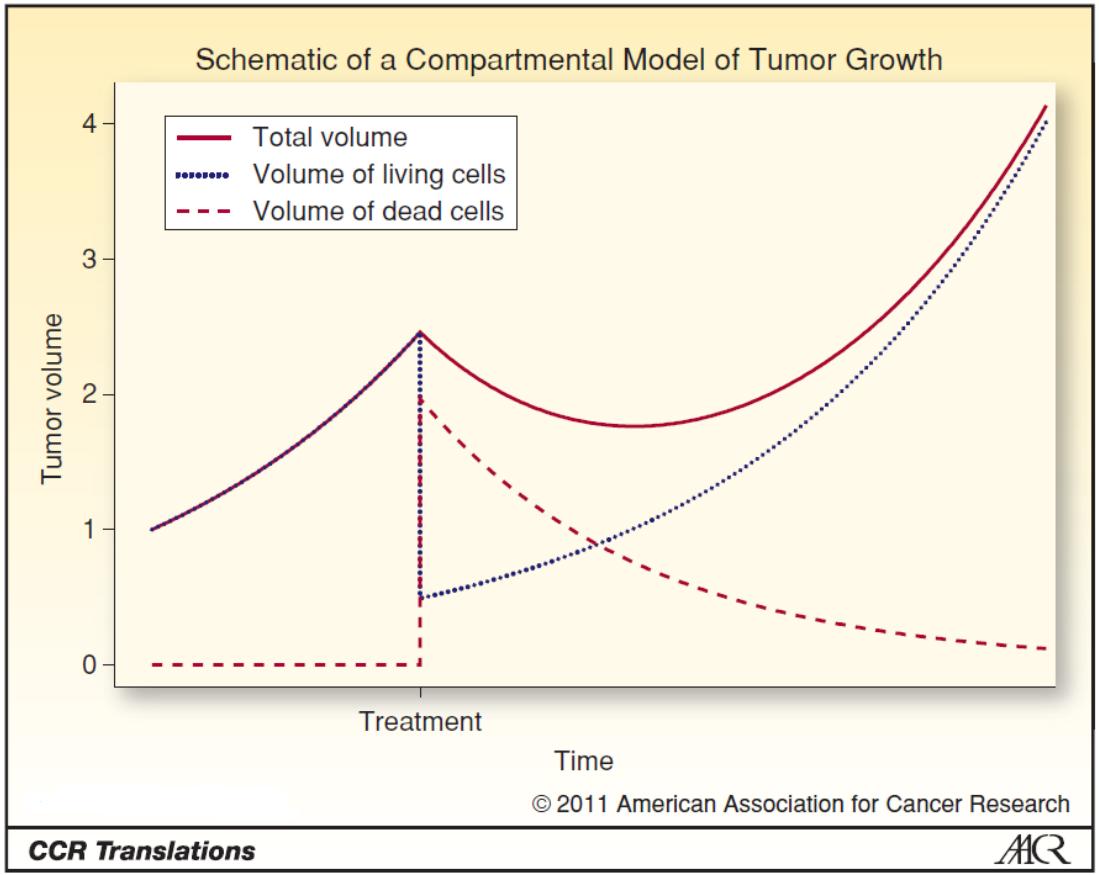




Methods (pros and cons):

1) TV difference at pre-specified timepoint (ANOVA, t-test, non-parametric)
2) Time to TV doubled/tripled since baseline, time to nadir (Kaplan-Meier, log-rank)
3) Curve fitting (linear / non-linear trend analysis, splines), LOESS

Heitjan 2011



The Model (*Stein et al. 2008, Looney et al.1975*)

f(t_i): Tumour Volume TV(t_i) normalized to its baseline TV(t_j), *i, j=0,1,…, T, i* ≥ *j*.

Growth-Inhibition (G-I) model:

$$f(t) = e^{-dt} + e^{gt} - 1$$

- $f(t) = e^{-dt}$ — *g*=0 inhibition model
- $f(t) = e^{gt}$ — *d*=0 growth model

Full (extended) G-I model:

$$f(t) = (\phi)e^{-dt} + (1-\phi)e^{gt}$$

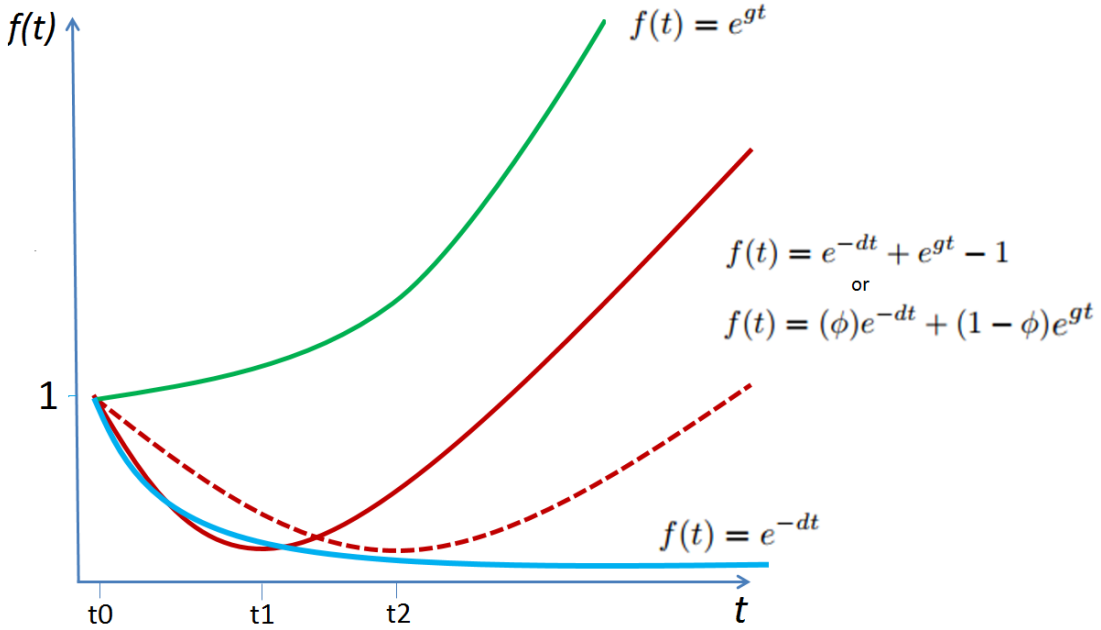
- $f(t) = e^{-dt}$ — ϕ =1 inhibition model
- $f(t) = e^{gt}$ — ϕ =0 growth model

g: exponential growth rate
d: exponential inhibition rate
ϕ: proportion of tumour cells sensitive to therapy

g, d, ϕ in [0,1]

Not a statistical model

The Model



Efficacy measures:

- Growth / re-growth rates between arms
- Time to regrowth (t_1, t_2)
- Inhibition rate
- Treatment sensitive cell fraction

Clinical applications

Therapeutic efficacy analysis:

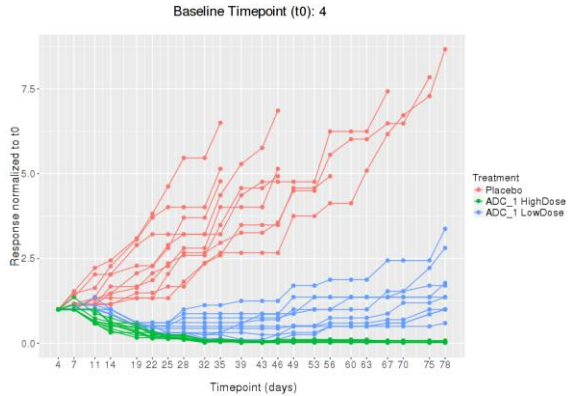
- TV or biomarker *g, d* rates as (secondary) endpoints
- *g, d* rates vs. Overall Survival (OS) correlation

Publication (selected)	Clin. Phase	TA*	Vars
Stein, Figg et al. 2008 (The Oncologist)	2	mCRPC	PSA, OS
Stein, Yang, et al. 2008 (The Oncologist)	2	RCC	TV, OS
Stein et al. 2010 (Clinical Caner Research)	2	mCRPC	PSA, OS
Blagolev et al. 2013 (Cell Reports)	3	mRCC	TV, OS
Burotto et al. 2015 (The Oncologist)	2	mCC	TV
Wilkerson et al. 2017 (Lancet Oncology)	2b, 3	mCRPC	PSA, OS

(*) metastatic(m), castration-resistant prostate cancer (CRPC), renal cell cancer (RCC), cervical cancer (CC)

Implementation: R package *tumgr (0.0.4, Wilkerson 2016)*

1) Four models get fitted to individual TV trajectories (Levenberg-Marquant)
2) Selected model: all significant params (p=0.05) and min AIC, or *'No model'*



$$f(t) = e^{-dt} + e^{gt} - 1$$

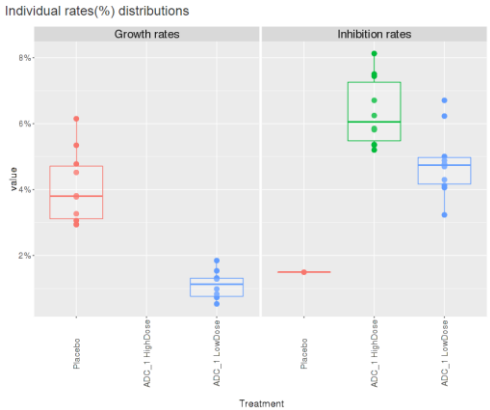
$$f(t) = e^{-dt}$$

$$f(t) = e^{gt}$$

$$f(t) = (\phi)e^{-dt} + (1-\phi)e^{gt}$$

or 'No model'

No	Treatment	g	d	phi
1	Placebo	0.029	0.015	
2	Placebo	0.029		
3	Placebo	0.045		
4	Placebo	0.038		
5	Placebo	0.038		
6	Placebo	0.048		
7	Placebo	0.061		
8	Placebo	0.031		
9	Placebo	0.033		
10	Placebo	0.053		
11	ADC_1 LowDose	0.013	0.062	
12	ADC_1 LowDose	0.007	0.067	
13	ADC_1 LowDose	0.005	0.047	0.994
14	ADC_1 LowDose	0.01	0.041	0.951
15	ADC_1 LowDose	0.015	0.049	
16	ADC_1 LowDose	0.007	0.048	0.955
17	ADC_1 LowDose	0.008	0.032	0.963
18	ADC_1 LowDose	0.013	0.05	
19	ADC_1 LowDose	0.013	0.041	0.845
20	ADC_1 LowDose	0.018	0.043	
21	ADC_1 HighDose		0.081	
22	ADC_1 HighDose		0.075	
23	ADC_1 HighDose		0.053	
24	ADC_1 HighDose		0.059	
25	ADC_1 HighDose		0.052	
26	ADC_1 HighDose		0.058	
27	ADC_1 HighDose		0.062	
28	ADC_1 HighDose		0.074	
29	ADC_1 HighDose		0.054	
30	ADC_1 HighDose		0.067	



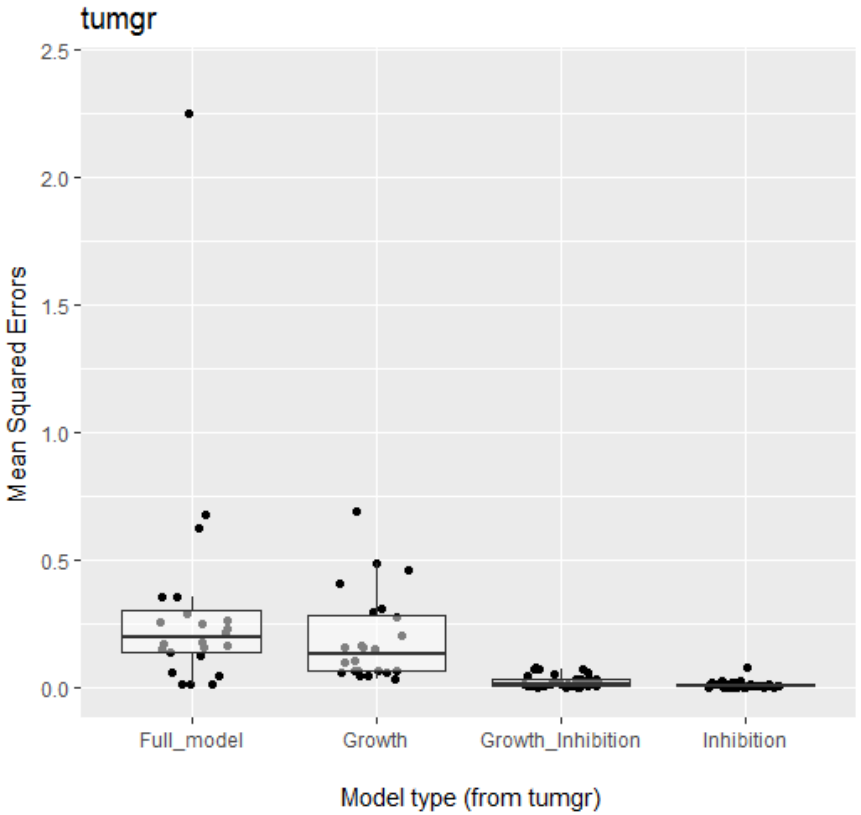
Model parameter value statistics

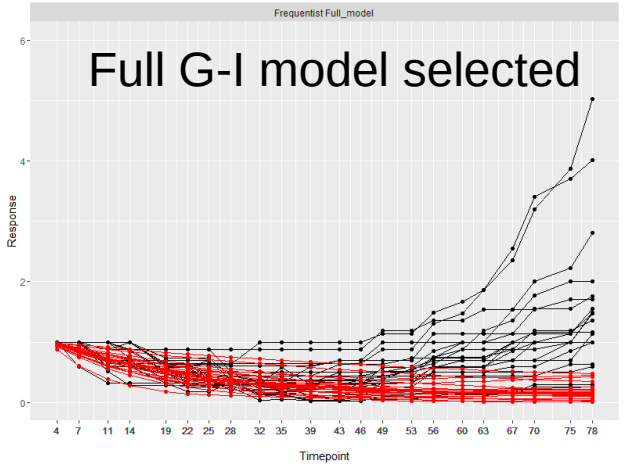
Treatment	Growth sample size	Median growth	p-value*	Inhibition sample size	Median inhibition	p-value*
Placebo	10	0.038	NA	1	0.015	NA
ADC_1 HighDose	0	NA	NA	10	0.061	0.182
ADC_1 LowDose	10	0.011	0.000	10	0.047	0.182

*p-value of Mann-Whitney test comparing investigated treatment growth / inhibition parameter outcomes with control group ones

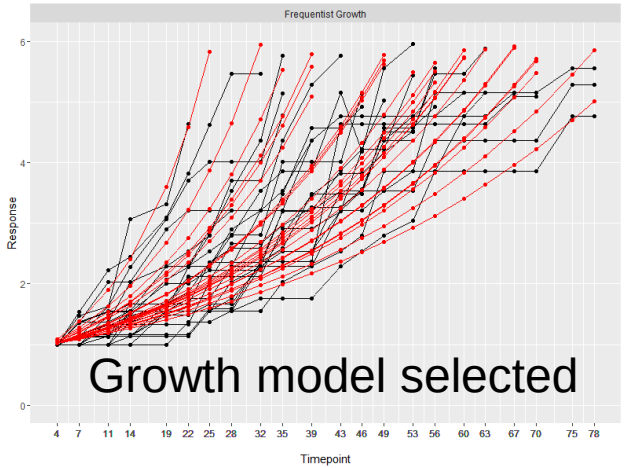
In-sample model fit

Study #: *tumgr*





Downsized re-growth rates



Non-exponential shape for growth

Comments (R solutions)

tumgr implementation

Pros:

1) Easy to implement: CRAN package with RShiny app
2) Short computational time

Cons:

1) 4 (+ '*No model*') competing models for each trajectory - no common modelling platform
2) Fits for individual tumor trajectories within treatment arm - longitudinal data structure
3) Numerical problems for particular model representations

Alternatives:

1) Mixed-effect model framework
2) One model for all studies - common modelling platform

Frequentist (nlme, gnls): convergence problems, good starting points required (tumgr ones failed)

Bayesian ?

Bayesian approach (in a nutshell)

1) In Bayesian statistics model parameters are considered as random variables
2) Parameter inference based on their distributions conditioned on the data called **posterior distribution**
3) Posterior distribution is a combination of **data distribution** and **prior distribution**

Data distribution

Prior distribution

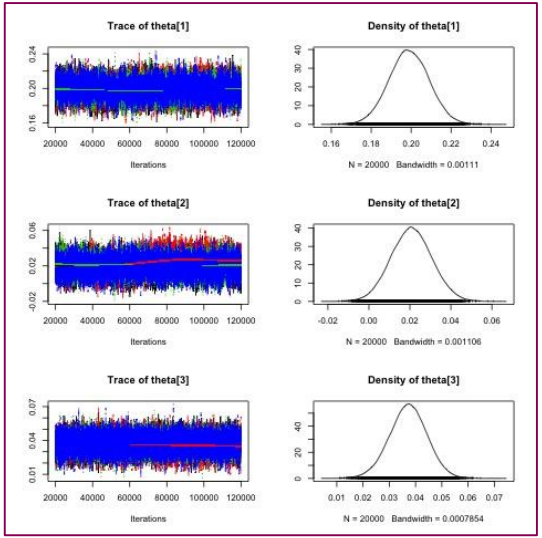
$$f(\boldsymbol{\theta}|\mathbf{y}) = \frac{f(\mathbf{y}|\boldsymbol{\theta})\pi(\boldsymbol{\theta})}{\int f(\mathbf{y}|\boldsymbol{\theta})\pi(\boldsymbol{\theta})d\boldsymbol{\theta}}$$

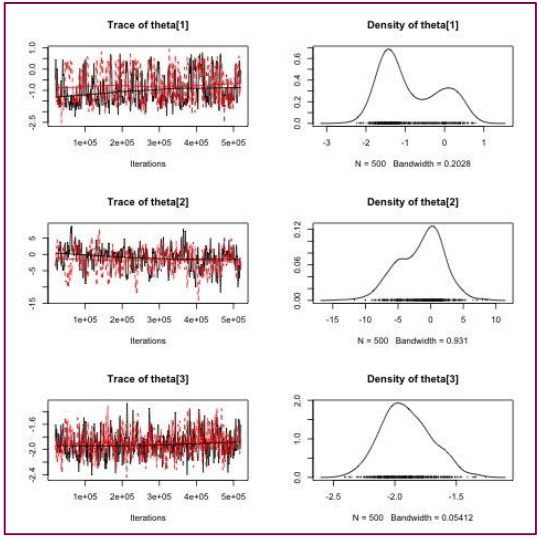
Posterior distribution

Normalizing constant

4) Posterior distributions are usually computed with Markov Chain Monte Carlo (MCMC) samplers
5) Subject to diagnostic criteria: convergence (good chain mixing) , effective sample size, autocorrelation

Typical MCMC samplers (Gibbs, Metropolis-Hastings) are implemented in computer software: WinBUGS, JAGS, Stan, SAS





Models for Bayesian application

$$f(t) = e^{-dt} + e^{gt} - 1$$

- $f(t) = e^{-dt}$ — *g*=0 inhibition model
- $f(t) = e^{gt}$ — *d*=0 growth model

$$f(t) = (\phi)e^{-dt} + (1-\phi)e^{gt}$$

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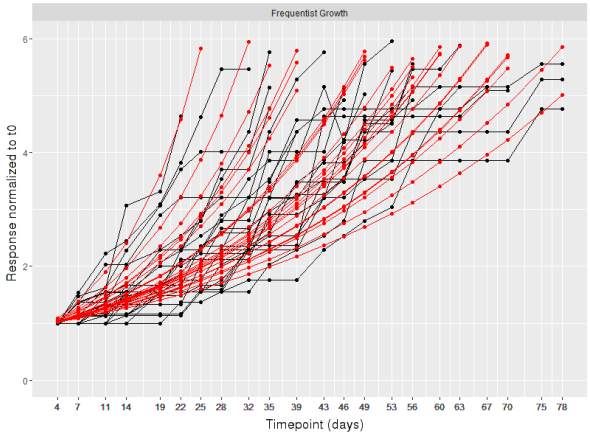
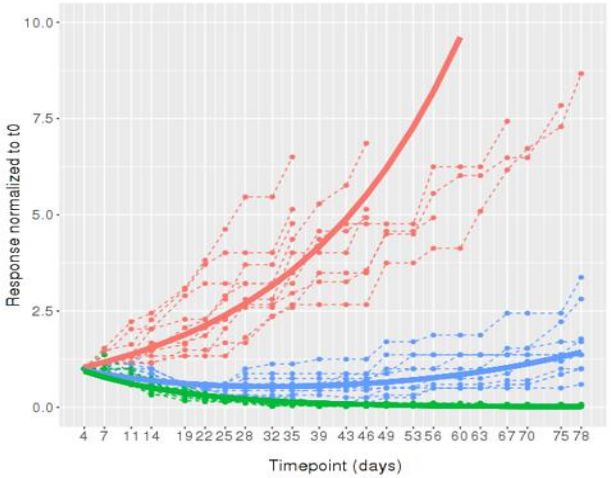
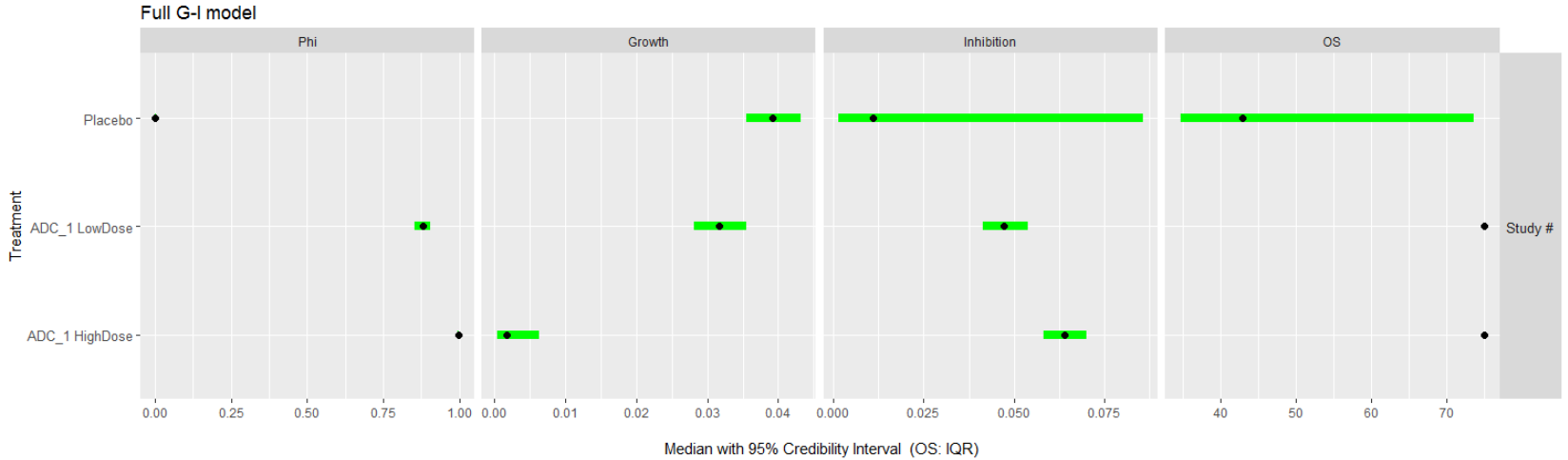


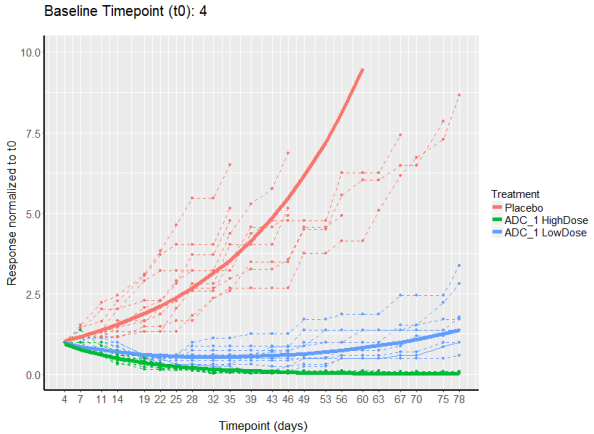


Considered on:

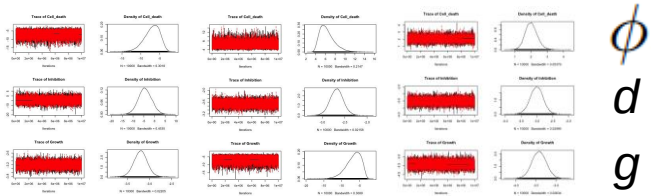
- Tumour level (alternative for *tumgr*)
- Treatment level (mixed-effect model)

Bayesian model fit: Study # selected treatments

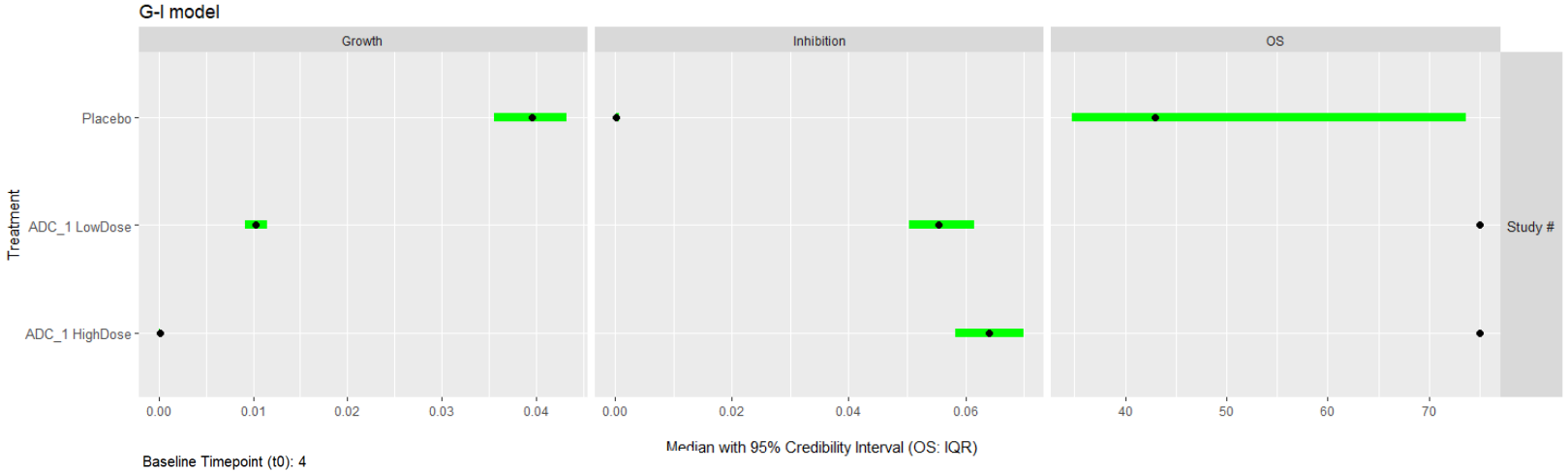


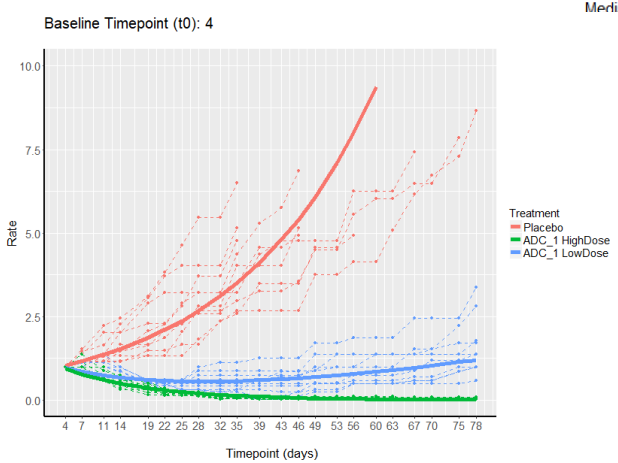


Full G-I model				
Treatment	*g*	*d*	*ϕ*	*T2R*
Placebo	0.039	0.011	0.001	0
ADC_1 LowDose	0.032	0.047	0.881	30
ADC_1 HighDose	0.002	0.064	0.998	147

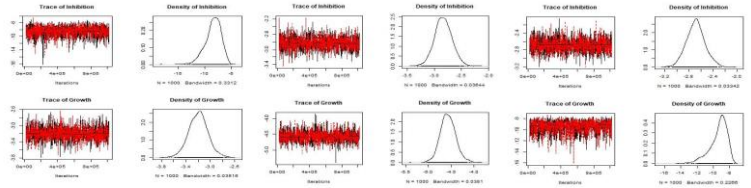


Bayesian model fit: Study # selected treatments





G-I model				
Treatment	*g*	*d*	*ϕ*	*T2R*
Placebo	0.039	0.000	-	0
ADC_1 LowDose	0.010	0.055	-	26
ADC_1 HighDose	0.000	0.064	-	99



d

g

Bayesian model fit: Study # selected treatments

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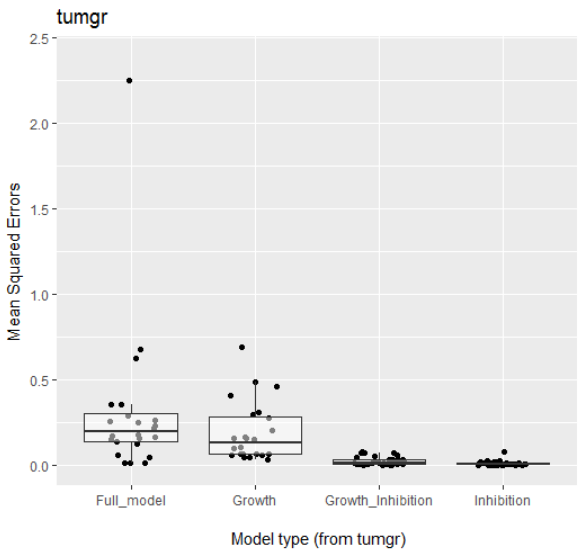
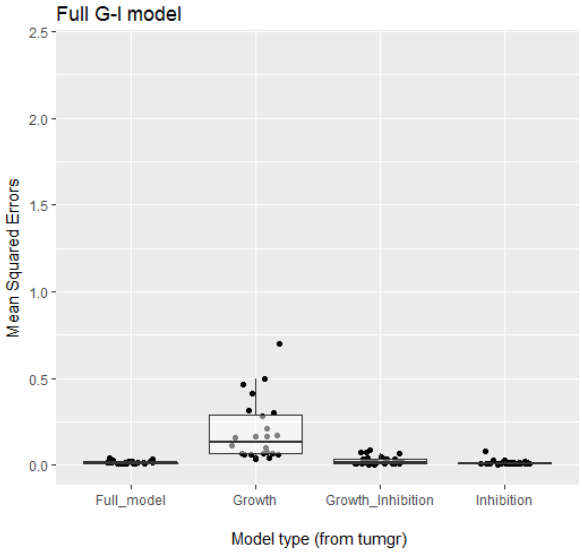
G-I model				
Treatment	*g*	*d*	*ϕ*	*T2R*
Placebo	0.039	0.000	-	0
ADC_1 LowDose	0.010	0.055	-	26
ADC_1 HighDose	0.000	0.064	-	99

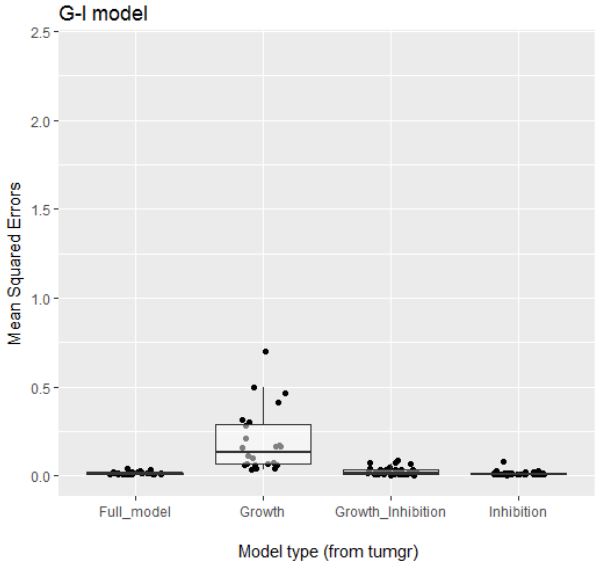
tumgr				
Treatment	*g*	*d*	*ϕ*	*T2R*
Placebo	0.038	0.015	-	-
ADC_1 LowDose	0.011	0.047	-	-
ADC_1 HighDose	0.000	0.061	-	-

In-sample model fit

Study #: Tumour level

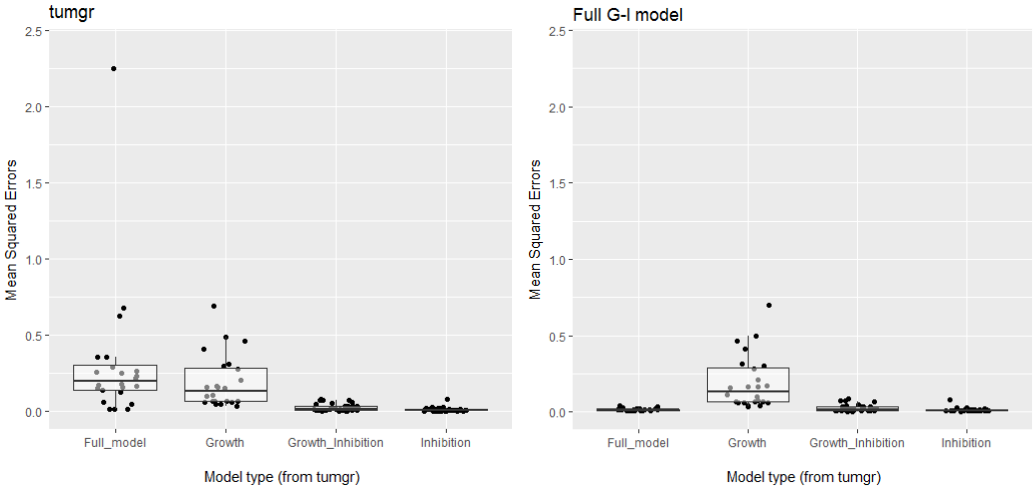


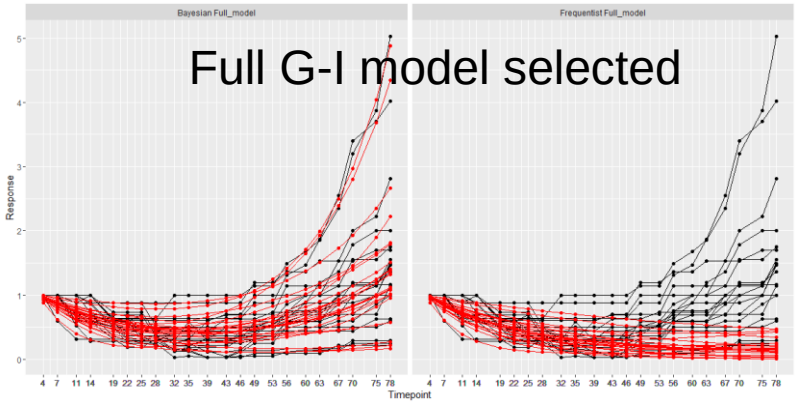




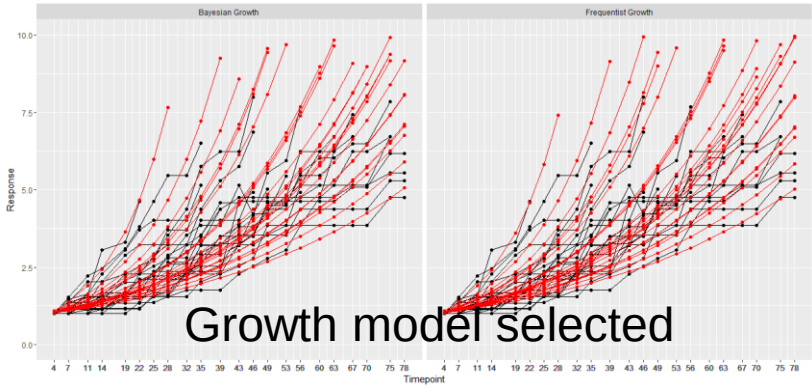
In-sample model fit

Study #: Tumour level





Full G-I model selected

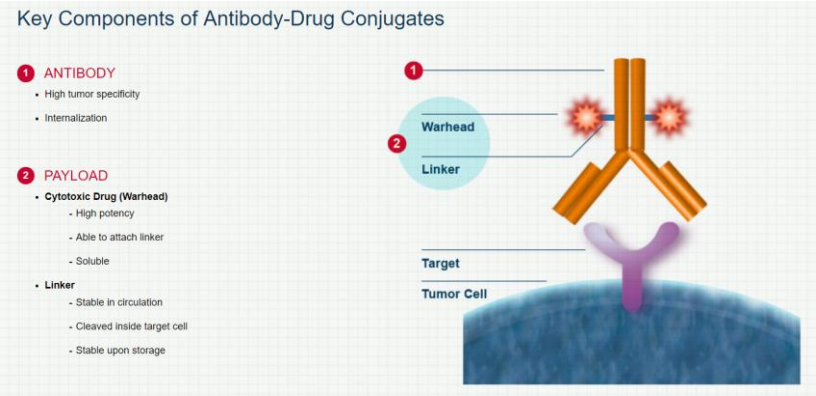


Growth model selected

- Bayesian solution improved Full G-I model fit
- Similar performance for Growth model

Example database: Antibody Drug Conjugates (ADC)

Targeted cancer therapy: mAb – linker (conjugation side) – warhead



Source: www.spirogen.com

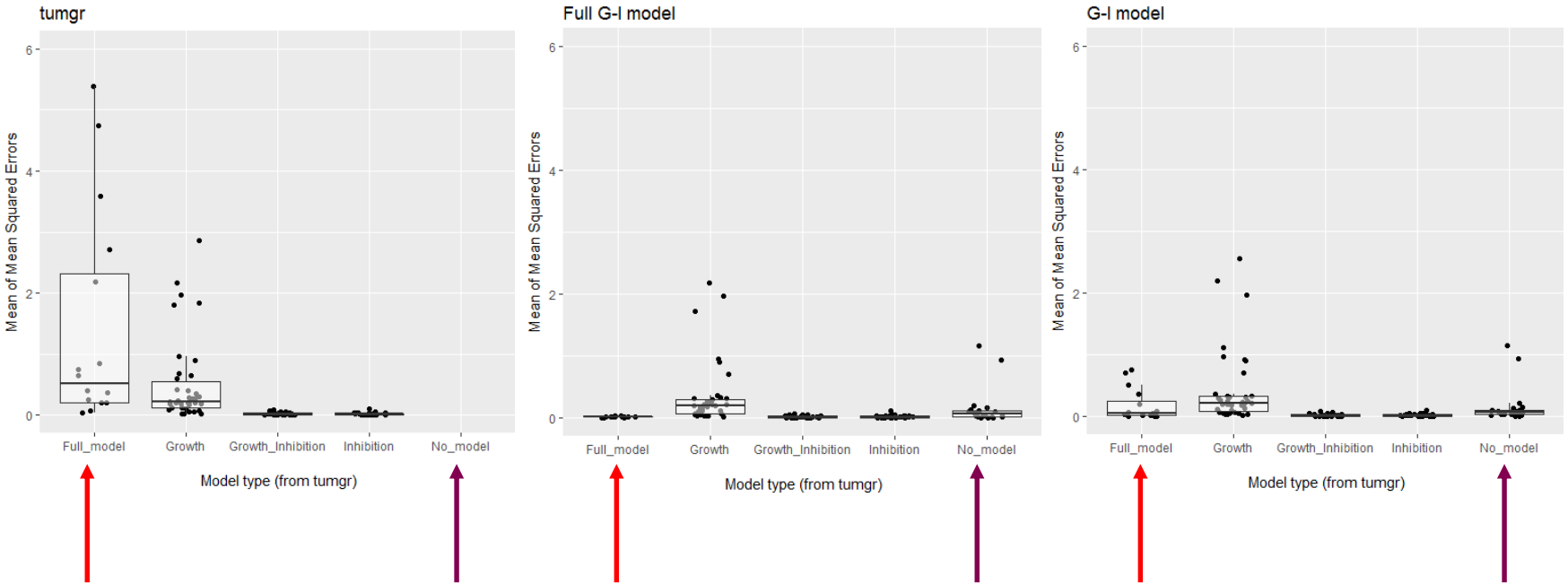
17 mAbs, 30 payloads, 8 conjugation sides: **4080** possible combinations (not all feasible)

Database: 38 in-vivo efficacy studies:

- **66** different ADCs administered at different dosing levels
- 147 different treatment lines (+38 controls)
- 2300+ individual efficacy (Tumor Volume) outcomes
- 28 cancer cell lines

In-sample model fit

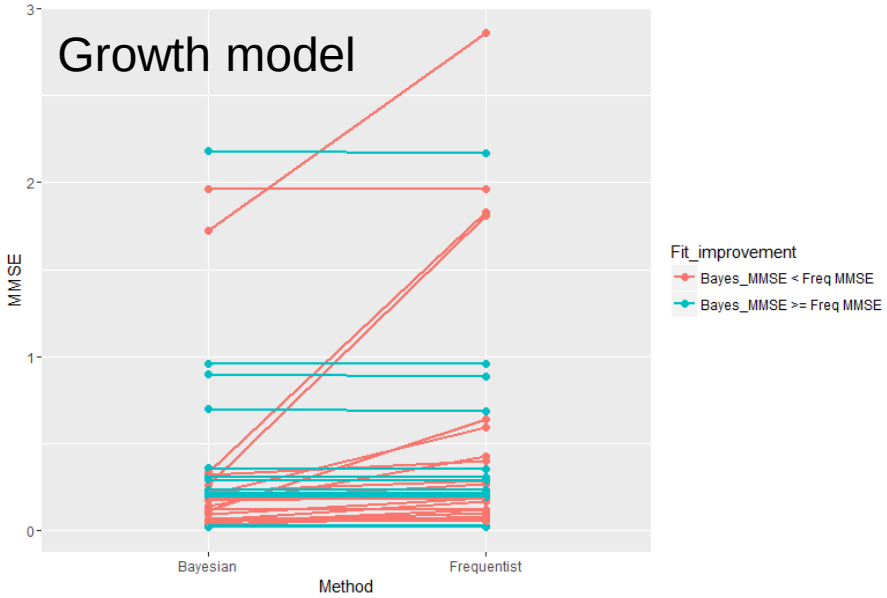
ADC database: Tumour level

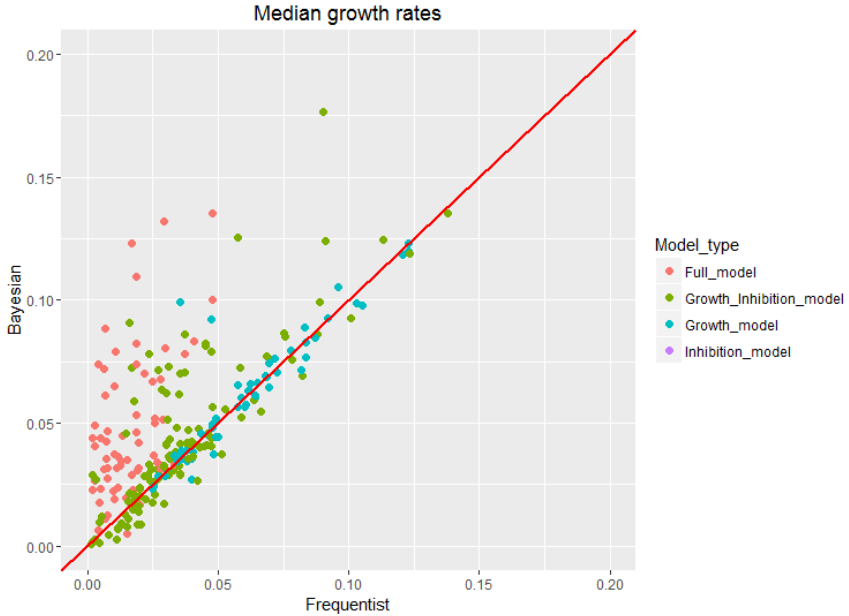


(richer than G-I parametric form?)

In-sample model fit

ADC database: *tumgr* vs. Bayesian Full G-I model (Tumour level)

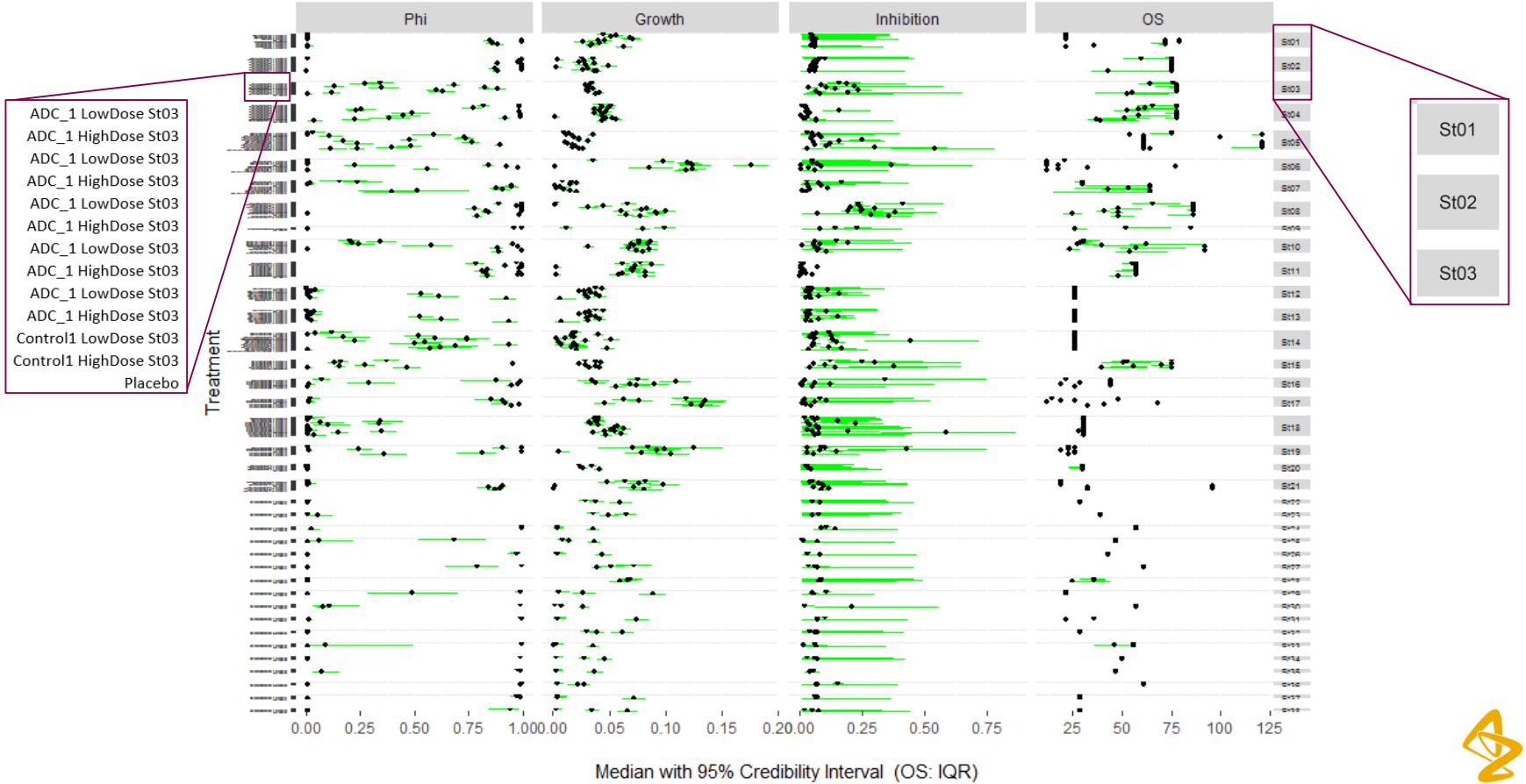




Bayesian model (usually) improves the Growth model fit.
Frequentist growth rates in Full model are downsized.

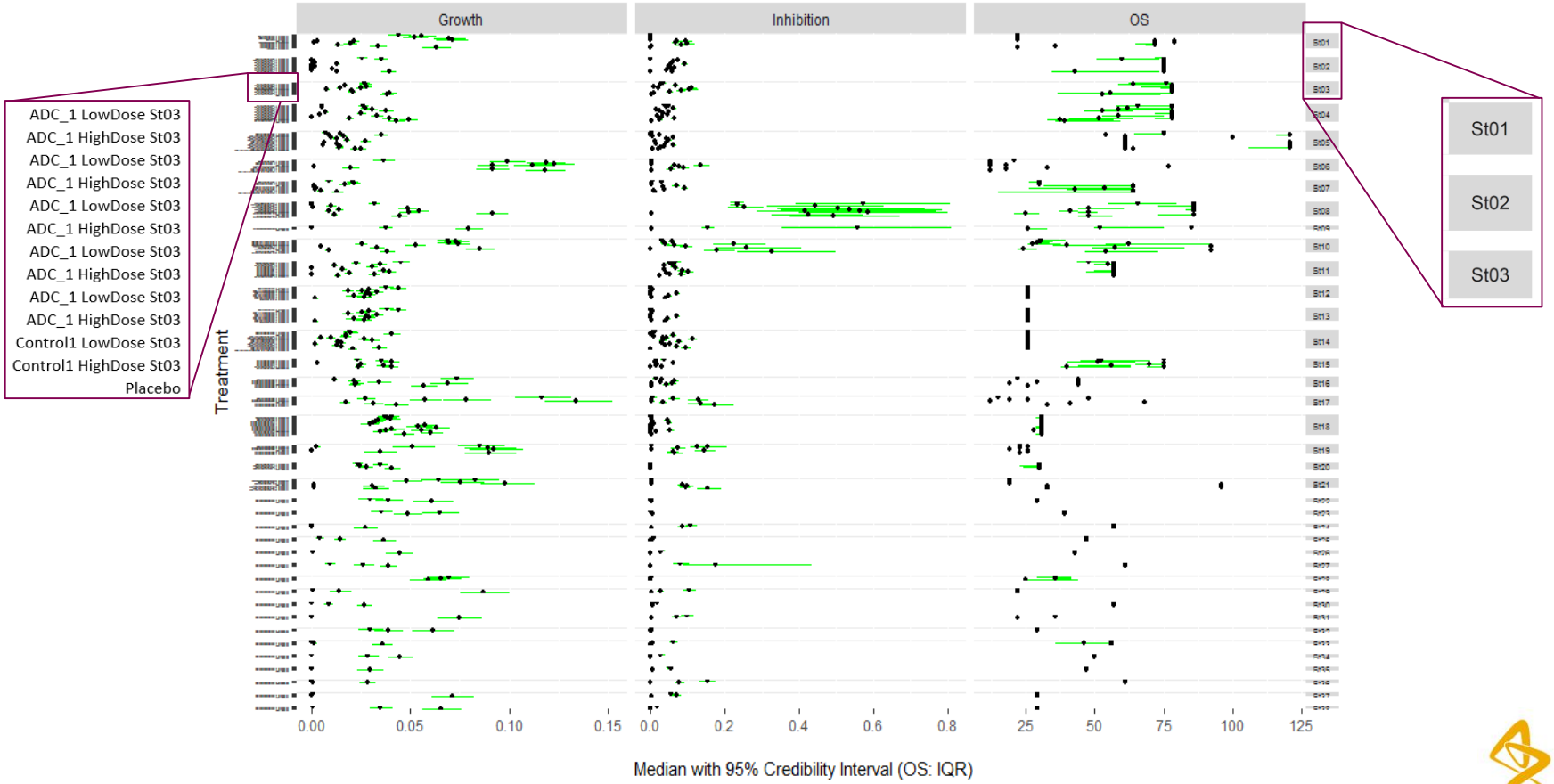
Model parameters (Bayesian)

$$f(t) = (\phi)e^{-dt} + (1-\phi)e^{gt}$$



Model parameters (Bayesian)

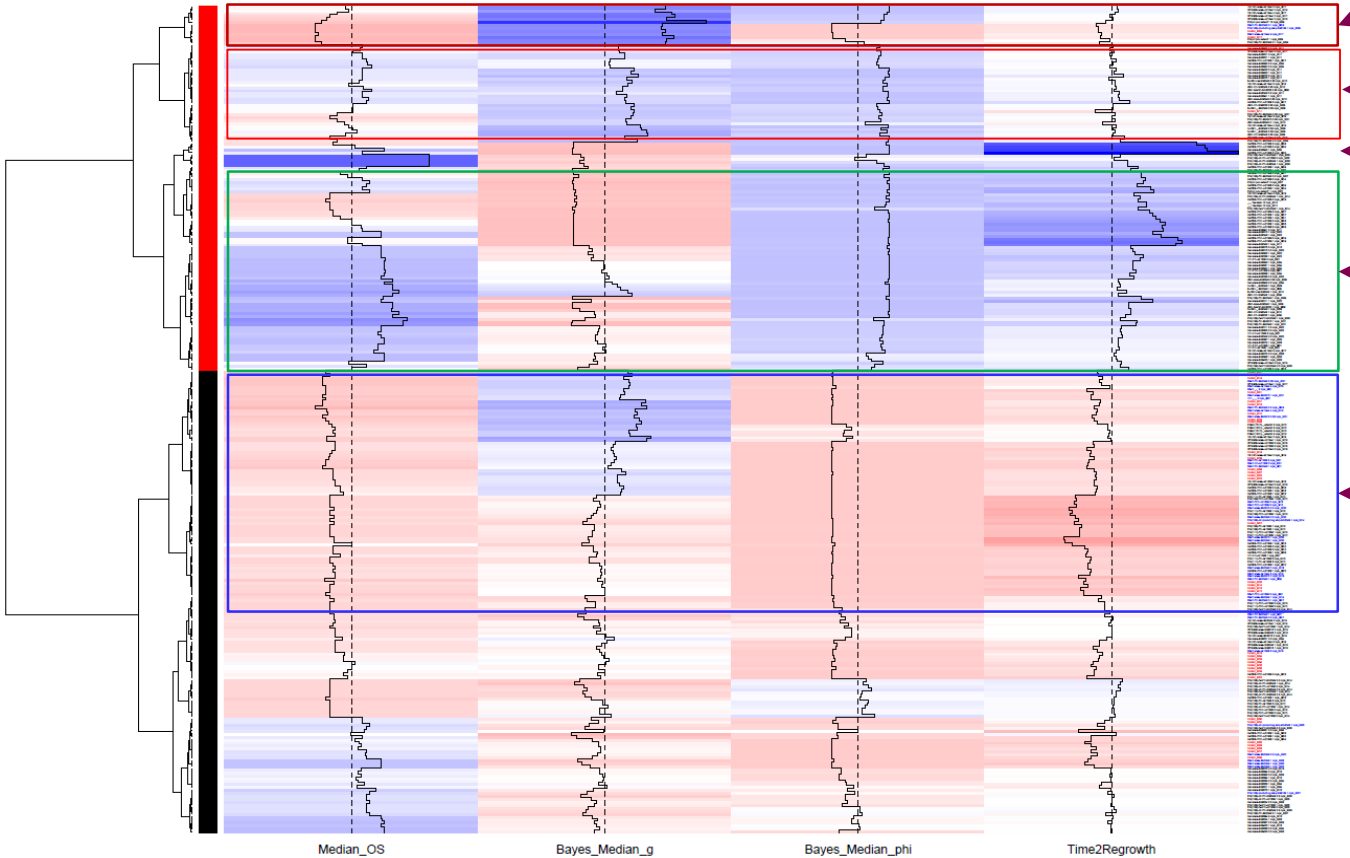
$$f(t) = e^{-dt} + e^{gt} - 1$$



Cluster analysis on Bayesian model outcomes

Controls,
Control Treatments

$$f(t) = (\phi)e^{-dt} + (1-\phi)e^{gt}$$



Control-like treatments:
- Highly growing TV
- Short OS
- Mixed trt sensitive cell fraction

Cluster re-growing after a short time with slightly lower than Control rate

The same ADC over three different cell lines

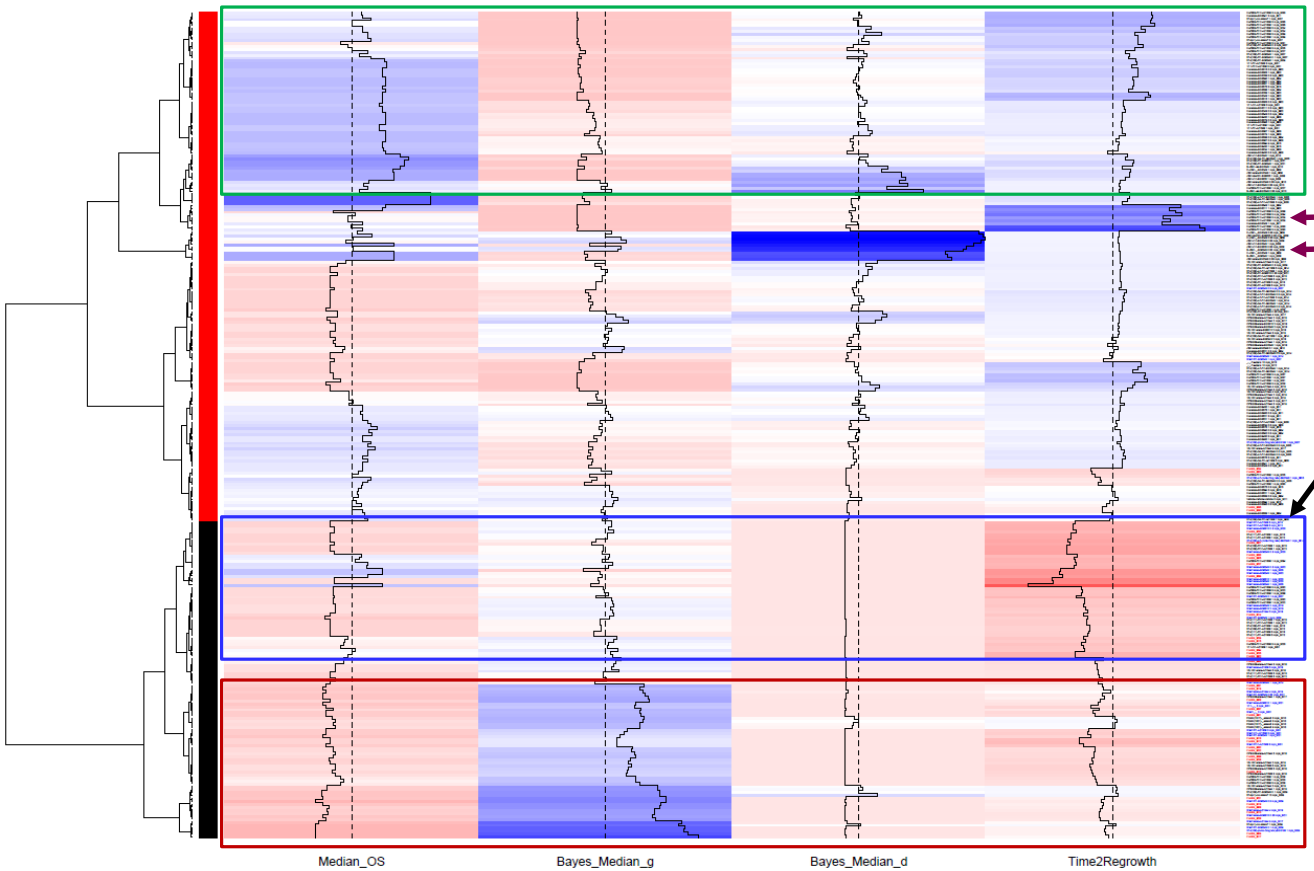
Strongest responders:
- High trt sensitive cell fraction
- Extended time-to-regrowth
- Extended OS
- Small growth

Weakest responders:
- Short(est) time to regrowth
- Low trt sensitive cell fraction

Cluster analysis on Bayesian model outcomes

Controls,
Control Treatments

$$f(t) = e^{-dt} + e^{gt} - 1$$



Prolonged overall survival

Highly responding: long time2regrowth, low growth

Highly responding: strong inhibition, small regrowth

Time to regrowth strong indicator of the cluster border

?? short but weaker regrowth

Strong growth with short overall survival

Summary

1) Growth-Inhibition model applied in pre-clinical in-vivo efficacy analysis

2) Existing (frequentist) approach was presented, and extended to Bayesian framework

3) Bayesian framework: pooled analysis, successful progression to hierarchical model setup

4) Cluster analysis of the model outcomes for Antibody Drug Conjugates studies

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Appendix

Full G-I model Bayesian application

$$y_{ij} = \varphi_i \exp(-d_i t_{ij}) + (1-\varphi_i) \exp(g_i t_{ij}),$$

where: i is for subject level, j is timepoint index

$$\varphi_i = \varphi_0 + u_{1i}$$
$$d_i = d_0 + u_{2i}$$
$$g_i = g_0 + u_{3i}$$

$$\begin{bmatrix} u_{1i} \\ u_{2i} \\ u_{3i} \end{bmatrix} \sim Norm\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau_{11} & 0 & 0 \\ 0 & \tau_{22} & 0 \\ 0 & 0 & \tau_{33} \end{bmatrix} \right)$$

JAGS (4.2.0) Full G-I implementation (Treatment level)

```
modelJAGS.txt="
  model{
  ## Likelihood:
  for(i in 1:N){
  ## Constrain value to [0,1]
  Phi[i] <- 1/(1+exp(-thetaNo[no[i],1]))
  d[i] <- 1/(1+exp(-thetaNo[no[i],2]))
  g[i] <- 1/(1+exp(-thetaNo[no[i],3]))
  ##------------------------
  mu[i] <- Phi[i] * exp(-d[i] * t[i]) + (1- Phi[i]) * exp(g[i] * t[i])
  y[i] ~ dnorm(mu[i], tauErr)
  }

  sigmaErr ~ dunif(0, 2)
  tauErr <- pow(sigmaErr, -2)

  ## Priors on random effects
  for(j in 1:nSubj){
  thetaNo[j, 1:3] ~ dmnorm(theta, Tau.B)
  ## theta comes as prior knowledge about parameters:
  }

  ## Priors on fixed effects:
  for(k in 1:3){
  # Exp[k] <- -log((1-fixed[k])/fixed[k]) ## staring values come from tumgr
  Exp[k] <- -2.2 ## implies that solution will be 0.099 (~.1) for all the parameters
  theta[k] ~ dnorm(Exp[k], .1) ## less than 0.1 increases autocorrelation
  }

  ##------------------------
  Phi <- theta[1]
  Inhibition <- theta[2]
  Growth <- theta[3]
  ##------------------------

  Tau.B[1:3, 1:3]  <- inverse(Omega[,])
  Omega[1,1] <- pow(tau11,-1/2)
  Omega[2,2] <- pow(tau22,-1/2)
  Omega[3,3] <- pow(tau33,-1/2)
  Omega[1,2]  = Omega[1,3]  = Omega[2,1]  = Omega[2,3]  = Omega[3,1] = Omega[3,2] <- 0
  tau11 ~ dgamma(1, .1) ## less than 0.1 increases autocorrelation
  tau22 ~ dgamma(1, .1) ## less than 0.1 increases autocorrelation
  tau33 ~ dgamma(1, .1) ## less than 0.1 increases autocorrelation
  }
  "
```

```
Data1 <- list(N=nrow(Data0),
              nSubj=length(levels(Data0 $ No)),
              no=Data0 $ No,          ## ID
              t=Data0 $ Timepoint,  ## Original scale transformed baseline = 1st timepoint
              y=Data0 $ Response, ## TV rate wrt baseline level
               fixed=fixed                ## starting points for fixed effects
              )
```

```
theta.jags <- run.jags(model=modelJAGS.txt,
                       monitor=c('Phi', 'Inhibition', 'Growth'),
                       data=Data1,
                        adapt=1e4,
                        burnin=1e4,
                       sample=1e4,
                       thin=1e3, module=c("glm", "lecuyer"),
                       method="parallel")
```

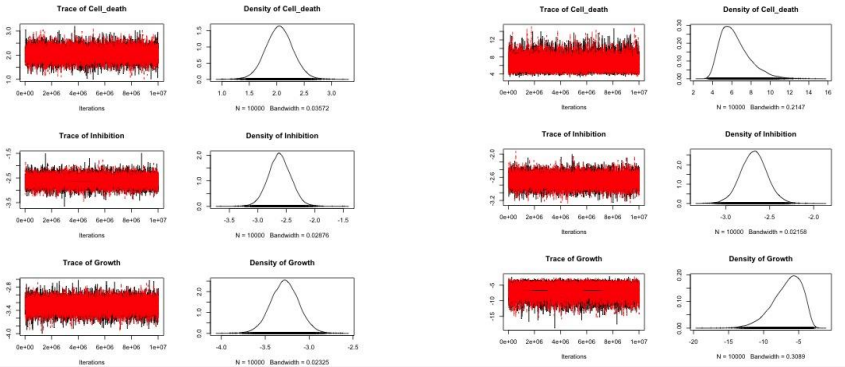
```
## inhibition only:
    ## fixed comes from the tumgr fit, then it becomes transformed to the Full model prior
   if(is.na(fixed $ Median_phi) & !is.na(fixed $ Median_d) & is.na(fixed $ Median_g)){
     ## only inhibition then phi gest elevated to 0.8
     fixed $ Median_phi <- 0.8 ## large trt sensitive cell fraction
     fixed $ Median_g <- 0.01 ## small growth
   }
## inhibition and growth (no trt sensitive cells)
   if(is.na(fixed $ Median_phi) & !is.na(fixed $ Median_d) & !is.na(fixed $ Median_g)){
     ## composite model then phi becomes 0.01
     fixed $ Median_phi <- 0.01 ## medium trt sensitive cell fraction (next to observed inhibition)
   }
## growth only
   if(is.na(fixed $ Median_phi) & is.na(fixed $ Median_d) & !is.na(fixed $ Median_g)){
     fixed $ Median_phi <- 0.01 ## negligible trt sensitive cell fraction
     fixed $ Median_d <- 0.01 ## negligible inhibition
   }
```

MCMC diagnostics

Chain convergence / mixing:

- Visual analysis
- Effective sample size
- Geweke statistics

Typical chain shapes

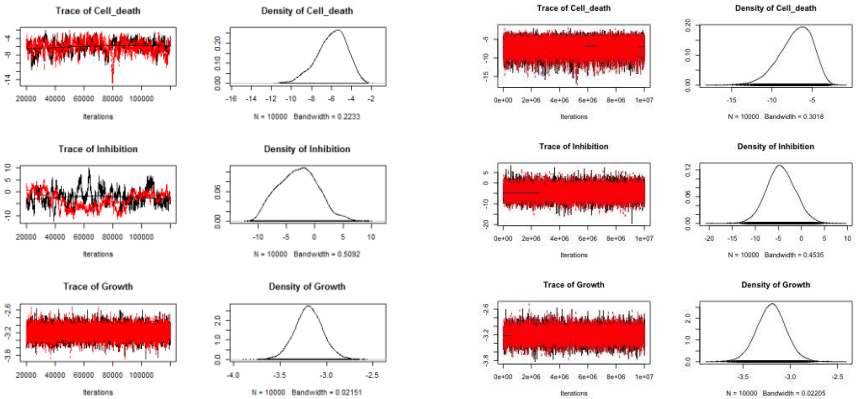


Autocorrelation was a problem:

- High thinning (1e3)
- Migrate to Stan (HMC, NUTS)

thin = 1e1

thin = 1e3



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