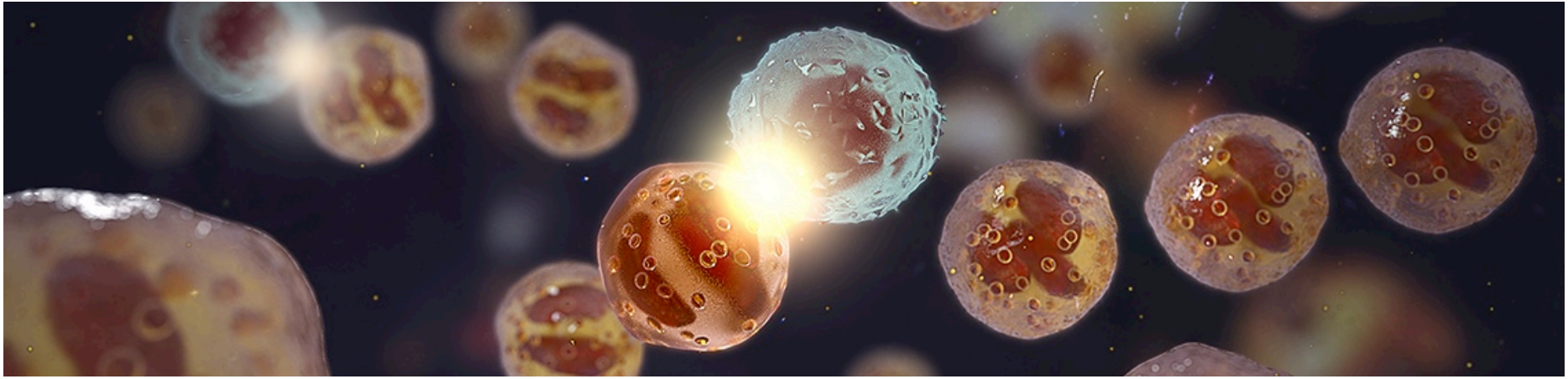
Dynamic predictions of survival in NSCLC, using tumor load measurements: A longitudinal joint modeling approach

Nidal Al-Huniti



Executive Summary

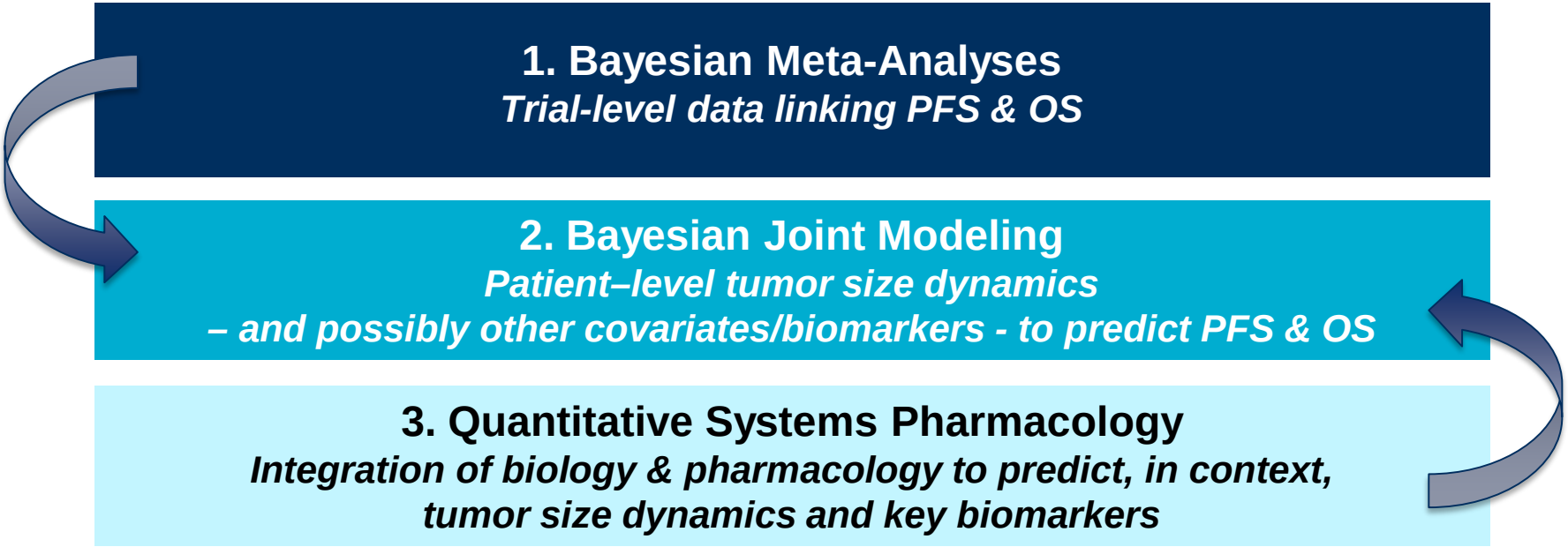
Problem Statement:

- Various endpoints are used at various stage of drug development in oncology but what is their predictive value?
- Multiple sources of data can be integrated using drug-disease modeling to predict clinical outcome and rationalize drug combinations

QCP Approach:

- A statistically valid basis for modeling and interpretation of longitudinal response dynamics, in the context of time-to-event (survival) has been developed and validated
- Modeling of trial-level survival data will inform individual-level joint models of tumor size and survival to make earlier trial prediction

Three Modelling Approaches Can Make Maximal Use of Data in Oncology



Context

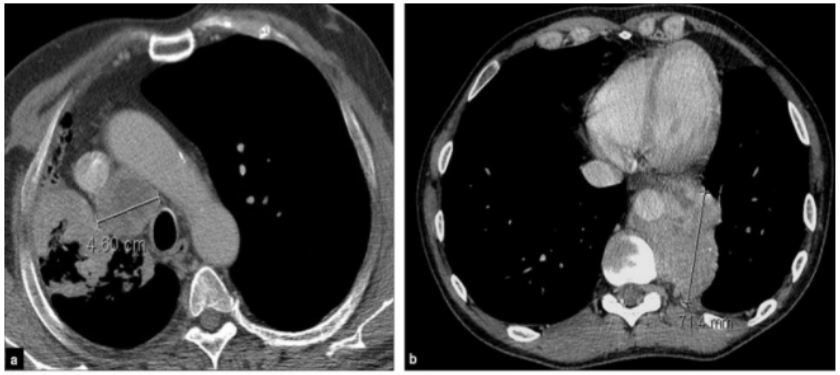
- Suppose we observe **repeated measurements** of a **clinical biomarker** on a group of individuals
- May be clinical trial patients or some observational cohort

Collection of **clinical biomarker** from patients

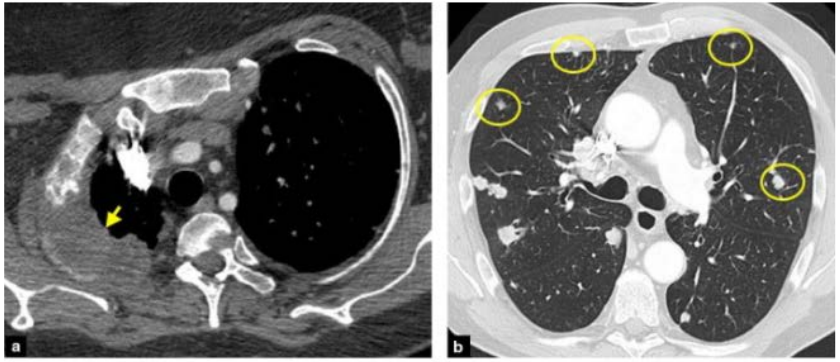
- In addition we observe the **time to some event** endpoint, e.g. death

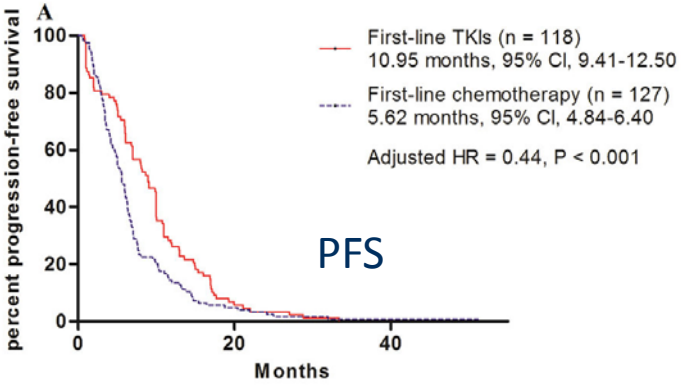
Example data measured in oncology

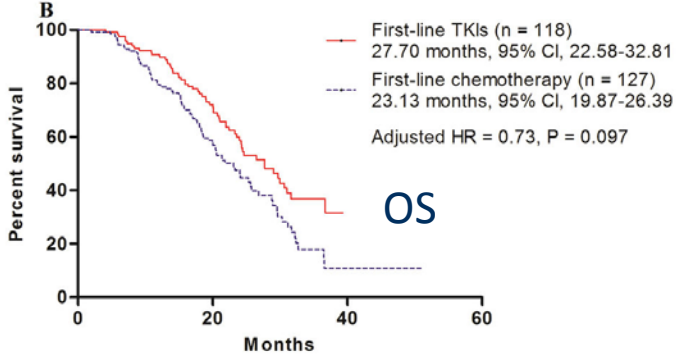
Target lesions



Non-target lesions

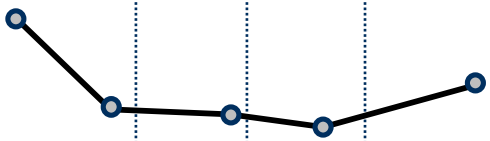






Images from Fournier L et al 2014
KM plots from Xu et al 2016

Problem: Rich longitudinal tumor dynamic data are reduced to categorical endpoints with a subsequent loss of information

RECIST[1] data					
Time (months)	0	2	5	7	10
Target Lesion SLD[2] (cm)	6 cm 4 cm 2 cm				
Non-target Lesion		SD	SD	SD	SD
New Lesion		No	No	No	**Yes**
Response		PR	PR	PR	**PD**

Reduction to Single Values:	
Time to Progression	10 mo.
Best Overall Response	PR
Best Percent Change in SLD	55%

1. RECIST = Response Evaluation Criteria In Solid Tumors
2. SLD = Sum of Longest Diameters of target lesions

CR = Complete Response
PR = Partial Response
SD = Stable Disease
PD = Progressive Disease

Slide from Andy Stein, Novartis, PhUSE 2013

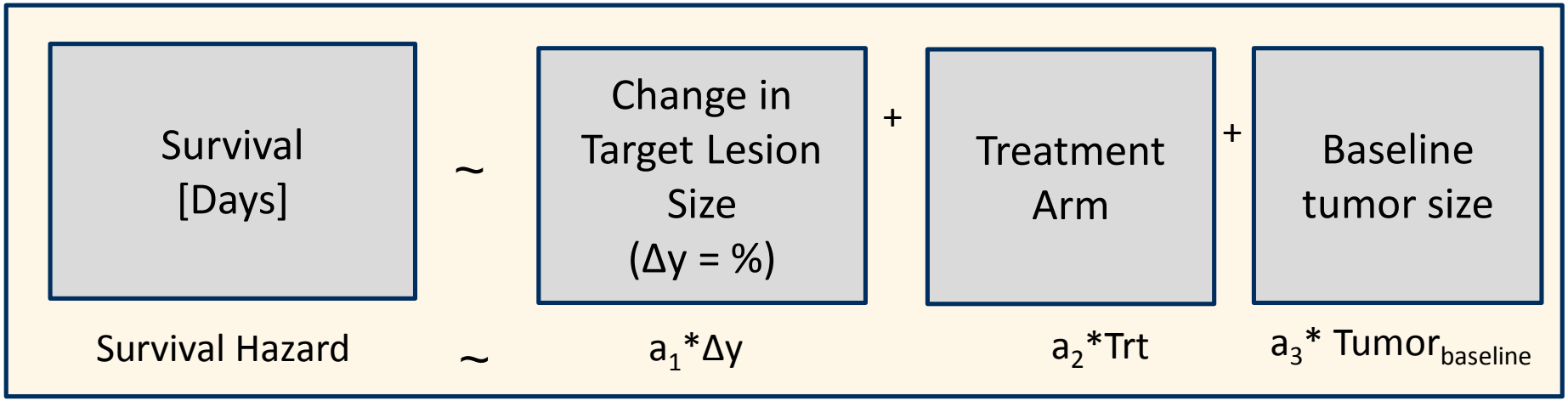
“Traditional” Sequential Approach : Longitudinal Modeling Provides Covariates to Event Model

Tumor Dynamics Longitudinal covariates,
Exponential decay rate, Response at 8 weeks, etc

Two-stage

Sequential approach

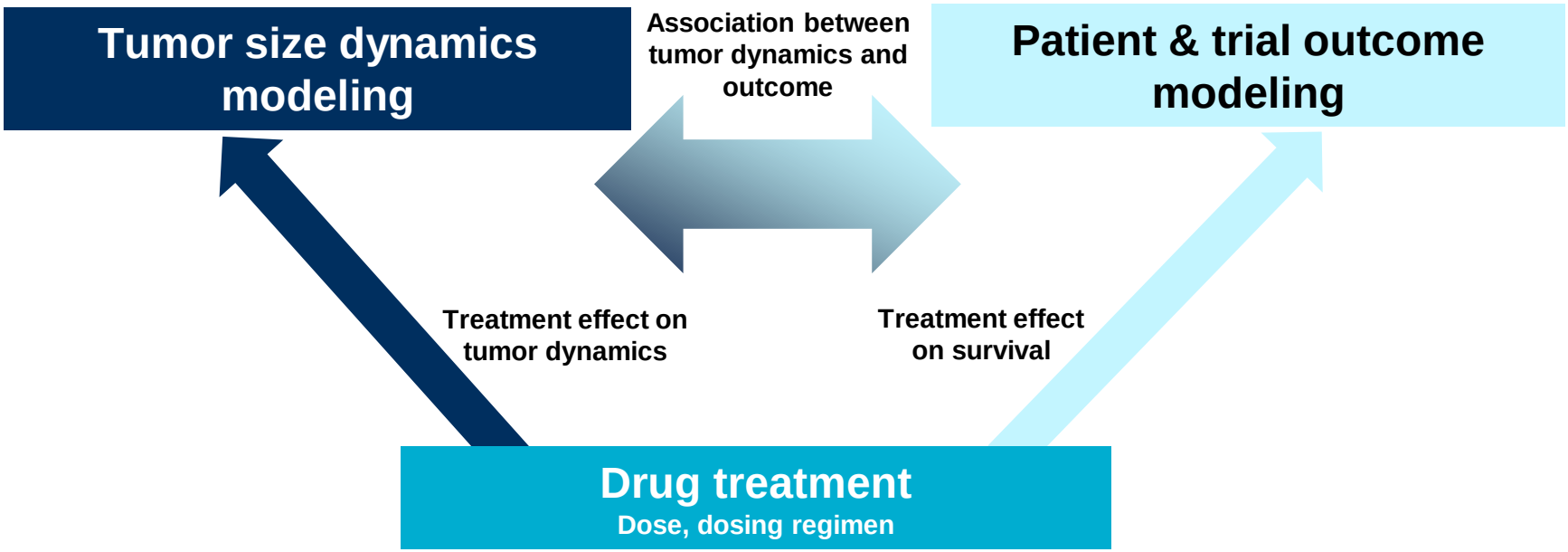
Event modeling (Cox Proportional Hazard)



{a1, a_2, a_3} are Cox coefficients linking each patient measurement to Survival

Wang Y et al.: Elucidation of Relationship between Tumor Size and Survival in NSCLC Patients Can Aid Early Decision Making in Clinical Drug Development. Clin Pharmacol Ther 2009; 86(2):167-174.

2. Joint Modeling of Tumor Size Dynamics, Biomarkers and Other Baseline Covariates to Improve Prediction of Outcome



Joint Modelling in the Literature (since 90s)

Appl. Statist. (1994)
43, *No.* 1, *pp.* 49–93

Informative Drop-out in Longitudinal Data Analysis

By P. DIGGLE†
Lancaster University, UK
and M. G. KENWARD
University of Reading, UK

SIMULTANEOUSLY MODELLING CENSORED SURVIVAL DATA AND REPEATEDLY MEASURED COVARIATES: A GIBBS SAMPLING APPROACH

CHERYL L. FAUCETT
Department of Biostatistics, University of California, Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90024, U.S.A.
AND
DUNCAN C. THOMAS
Department of Preventive Medicine, University of Southern California, 1540 Alcazar Street Suite 220, Los Angeles, CA 90033, U.S.A.

STATISTICS IN MEDICINE, VOL. 15, 1663–1685 (1996)

Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of posttreatment PSA: a joint modeling approach

CÉCILE PROUST-LIMA*
Institut National de la Santé et de la Recherche Médicale U897, Biostatistics Department and Université Victor Segalen Bordeaux 2, Bordeaux, F-33076, France
cecile.proust@isped.u-bordeaux2.fr
JEREMY M. G. TAYLOR
Department of Biostatistics and Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

Biostatistics (2009), **10**, 3, *pp.* 535–549
doi:10.1093/biostatistics/kxp009
Advance Access publication on April 15, 2009

Joint modeling of multivariate longitudinal measurements and survival data with applications to Parkinson's disease

Bo He and Sheng Luo Division of Biostatistics, The University of Texas Health Science Center at Houston

Statistical Methods in Medical Research
2016, Vol. 25(4) 1346–1358

DOI: 10.1177/0962280213480877
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Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Journal of Multivariate Analysis 91 (2004) 18–34
http://www.elsevier.com/locate/jmva

A new joint model for longitudinal and survival data with a cure fraction

Ming-Hui Chen,[a] Joseph G. Ibrahim,[b,*] and Debajyoti Sinha[c]
[a] *Department of Statistics, University of Connecticut, Storrs, CT 06269-4120, USA*
[b] *Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7420, USA*
[c] *Department of Biostatistics and Epidemiology Medical University of South Carolina, Charleston, SC 29425, USA*

Desmée *et al. BMC Medical Research Methodology* (2017) 17:105
DOI 10.1186/s12874-017-0382-9
BMC Medical Research Methodology
RESEARCH ARTICLE Open Access

Nonlinear joint models for individual dynamic prediction of risk of death using Hamiltonian Monte Carlo: application to metastatic prostate cancer

INSERM, Université Paris Diderot, Sorbonne Paris Cité
Solène Desmée[1*], France Mentré[1], Christine Veyrat-Follet[2], Bernard Sébastien[3] and Jérémie Guedj[1]

Biometrical Journal 53 (2011) 5, 750–763 DOI: 10.1002/bimj.201100052

Joint modelling of longitudinal and time-to-event data with application to predicting abdominal aortic aneurysm growth and rupture

Michael J. Sweeting* and Simon G. Thompson
MRC Biostatistics Unit, Institute of Public Health, Robinson Way, Cambridge, CB2 0SR, UK

What is “joint modelling” of longitudinal and time-to-event data?

- Treats both the longitudinal biomarker(s) and the event as outcome data
- Each outcome is modelled using a distinct regression submodel:
  - A (multivariate) **mixed effects model** for the longitudinal outcome(s)
  - A **proportional hazards model** for the time-to-event outcome
- The regression submodels are linked through **shared individual-specific parameters** and **estimated simultaneously** under a joint likelihood function

Why use “joint modelling”?

- Want to understand **whether (some function of) the longitudinal outcome is associated with the risk of the event** (i.e. epidemiological questions)
  - Joint models offer advantages over just using the biomarker as a time-varying covariate (described in the next slide!)
- Want to develop a **dynamic prognostic model**, where predictions of event risk can be updated as new longitudinal biomarker measurements become available (i.e. clinical risk prediction)
- Possibly other reasons:
  - e.g. adjusting for informative dropout, separating out “direct” and “indirect” effects of treatment

Joint model formulation

$y_{ijm}(t)$ is the value at time t of the
m^{th} longitudinal marker ($m = 1, \dots, M$)
for the i^{th} individual ($i = 1, \dots, N$)
at the j^{th} time point ($j = 1, \dots, n_{im}$)
T_i^* is "true" event time, C_i is the censoring time
$T_i = \min(T_i^*, C_i)$ and $d_i = I(T_i^* \leq C_i)$

- Longitudinal submodel

$y_{ijm}(t)$ follows a distribution in the exponential family with expected value $\mu_{ijm}(t)$ and

$$\eta_{ijm}(t) = g_m\left(\mu_{ijm}(t)\right) = \boldsymbol{x_{ijm}^T}(t)\boldsymbol{\beta_m} + \boldsymbol{z_{ijm}^T}(t)\boldsymbol{b_{im}}$$

$$\begin{bmatrix} \boldsymbol{b_{i1}} \\ \vdots \\ \boldsymbol{b_{iM}} \end{bmatrix} = \boldsymbol{b_i} \sim N(0, \boldsymbol{\Sigma})$$

- Event submodel

$$h_i(t) = h_0(t) \exp\left(\boldsymbol{w_i^T}(t)\boldsymbol{\gamma} + \sum_{m=1}^{M} \alpha_m \, \mu_{im}(t)\right)$$

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- Known as a **current value "association structure"**

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$$h_i(t) = h_0(t) \exp\left(\boldsymbol{w_i^T}(t)\boldsymbol{\gamma} + \sum_{m=1}^{M} \alpha_m \, \mu_{im}(t)\right)$$

$y_{ijm}(t)$ is both:
- error-prone
- measured at discrete times

Whereas $\mu_{im}(t)$ is both:
- error-free
- modelled in continuous time

Therefore less bias in α_m compared with a time-dependent Cox model.

- Known as a **current value "association structure"**

Joint modelling software

- An abundance of **methodological** developments in joint modelling
- But not all methods have been translated into **“user-friendly” software**

- Well established software for one longitudinal outcome
  - e.g. stjm (Stata); joineR, JM, JMbayes, frailtypack (R); JMFit (SAS)

- Recent software developments for **multiple longitudinal outcomes**
  - R packages: **rstanarm**, joineRML, JMbayes, survtd

- Each package has its strengths and limitations
  - e.g. (non-)normally distributed longitudinal outcomes, selected association structures, speed, etc.

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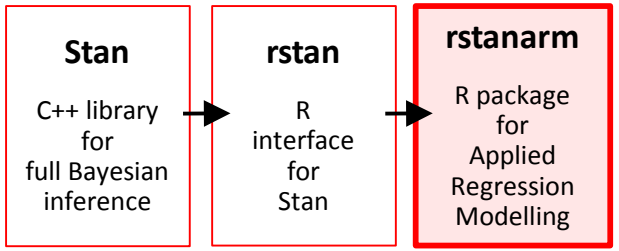
Bayesian joint models via Stan

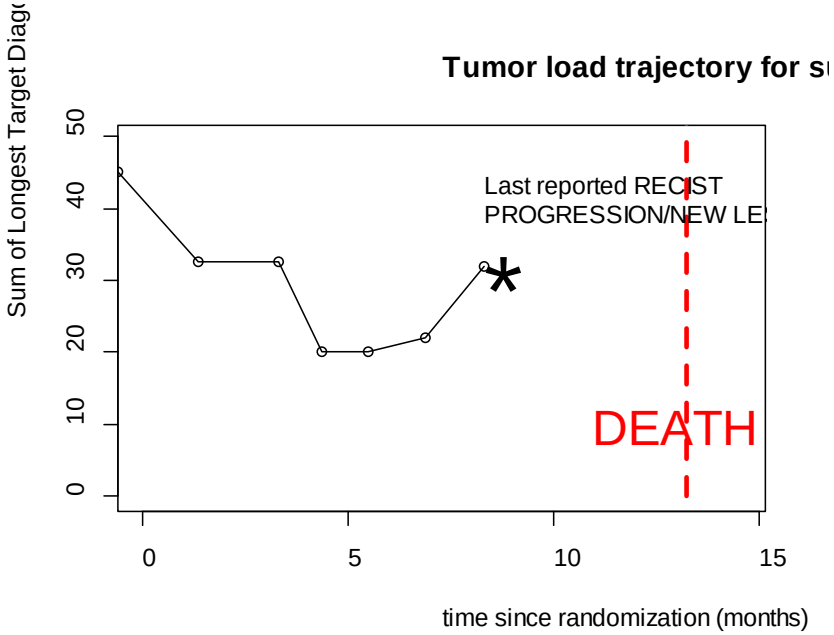


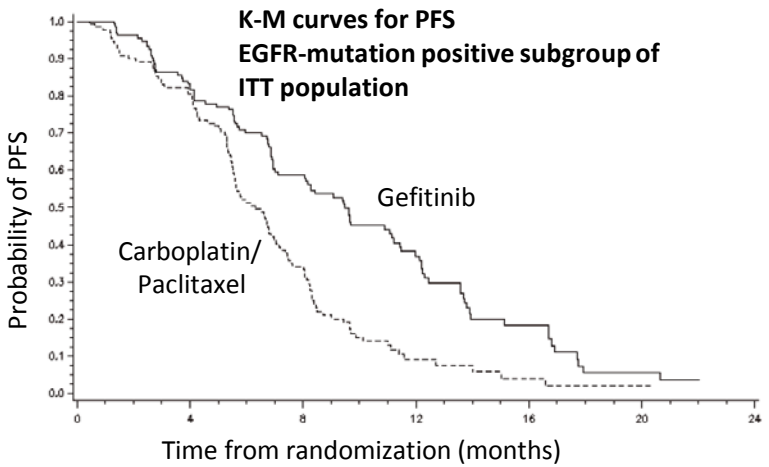
- Included in **rstanarm** version ≥ 2.17.2
  - https://cran.r-project.org/package=rstanarm
  - https://github.com/stan-dev/rstanarm
- Can specify **multiple longitudinal outcomes**
- Allows for **multilevel** clustering in longitudinal submodels (e.g. time < patients < clinics)
- Variety of **families** (and link functions) for the longitudinal outcomes
  - e.g. normal, binomial, Poisson, negative binomial, Gamma, inverse Gaussian
- Variety of **association structures**
- Variety of **prior distributions**
  - Regression coefficients: normal, student t, Cauchy, shrinkage priors (horseshoe, lasso)
- **Posterior predictions** – including "dynamic predictions" of event outcome
- Baseline hazard
  - B-splines regression, Weibull, piecewise constant

Iressa IPASS Study Was Used to Investigate the Relationship Between Tumor Dynamics and Survival

Gefitinib (N=609) or Carboplatin + Paclitaxel (N=608)
Hazard ratio for progression or death

- **Overall:** **0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001**
- **In EGFR-mutant (N=261): 0.48; 95% CI, 0.36 to 0.64**
- **In EGFR-wild type (N=176):** **2.85; 95% CI, 2.05 to 3.98**





Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med. 2009 Sep 3;361(10):947-57*

Modeling of Tumor Size Dynamics in Humans

Comparison of approaches

More 'empirical'

$$y(t) = y_0 e^{-dt} + gt$$

Advantages

- *Simple structure but cannot capture all types of treatment response patterns*
- *Minimal number of parameters; can obtain identifiable parameter estimates across different, even small datasets*

Limitations

- *Does not account for varying dose information (e.g., dose de-escalation and modification)*
- *Cannot be used to extrapolate tumor dynamics to different dosing regimens (incl. discontinuation) within a study or across studies*

More 'mechanistic' (ODEs)

$$\frac{dy}{dt} = net\_growth \quad - drug\_induced\_decay$$

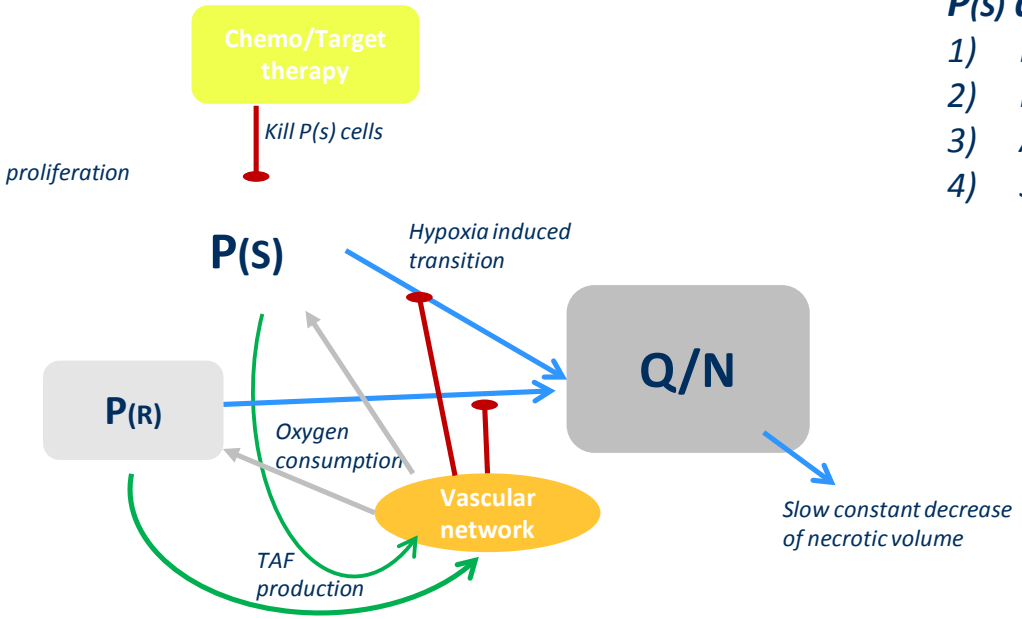
Advantages

- *Various characteristics of drug effects can be flexibly modeled:*
  - *Dose dependence*
  - *Drugs only acting on a fraction of cells*
  - *Delay in drug action*
  - *Drug resistance, drug discontinuation*

Limitations

- *Models have more parameters than empirical models; more information needed need to identify parameter values*

The model with two tumor cell clones (drug-sensitive and drug-resistant)



P(S) and P(R) might differ in:

1) *Intrinsic proliferation rate;*
2) *Resistance to hypoxia;*
3) *Angiogenesis capability;*
4) *Sensitivity to CTLs attack and/or immunogenicity*

P(S) and P(R)– drug-sensitive and drug-resistant clones of tumor cells;
Q/N - quiescent/necrotic tumor regions;
TAF - tumor angiogenesis factors

Modeling of Tumor Size Dynamics in Humans

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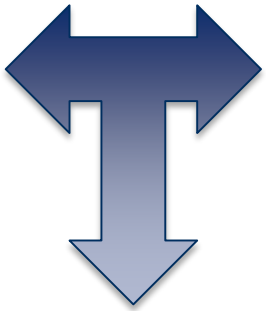


Middle ground

Use inference from mechanistic modelling to guide priors on parameters after progression

Joint Model with an Empirical Mean-Shift Longitudinal Submodel for Tumour Burden

Basic Joint Model structure for survival and longitudinal biomarker(s):

$$\begin{cases} h_i(t|\mathcal{M}_i(t)) = h_0(t)exp\{\gamma^\top w_i + \eta_{1..p}^\top m_{1..pi}(t) + \eta_0 m_{0i}(t)\} \\ y_{0i}(t) = m_{0i}(t) + \varepsilon_{0i}(t) \end{cases}$$

Baseline covariates

Other biomarkers (new lesion, etc)

Tumour burden (sum-of-diameters)

With tumour diameter defined by:

$$\beta_{i\times\texttt{gef}} \sim \mathcal{N}(\lambda_{0b} + \lambda_{1b}\texttt{gef} + (\lambda_{2b} + \lambda_{3b}\texttt{gef})\texttt{base.sld}, \sigma_\beta^2)$$

$$\alpha_{i\times\texttt{gef}} \sim \mathcal{N}(\lambda_{0a} + \lambda_{1a}\texttt{gef}, \sigma_\alpha^2)$$

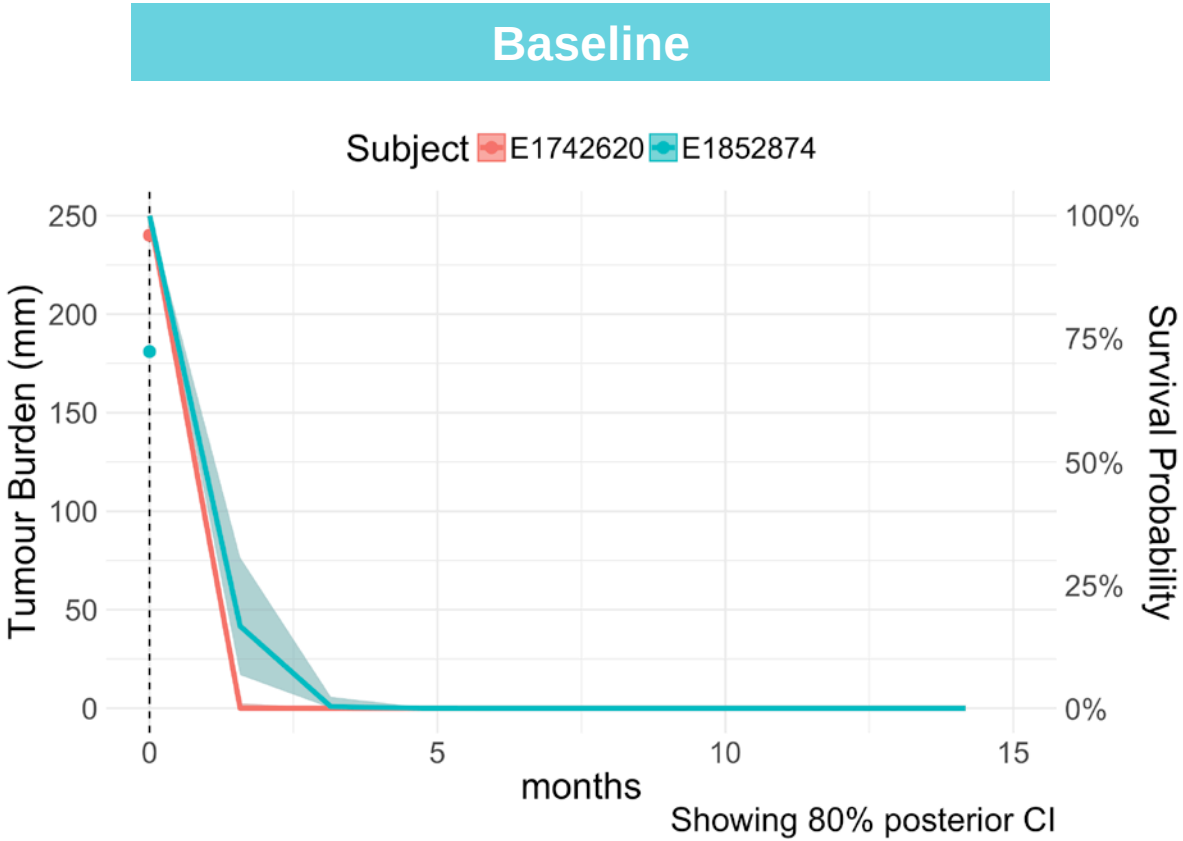
$$TS_{0i\times\texttt{gef}} \sim \mathcal{N}(\lambda_{0t} + \lambda_{1t}\texttt{gef}, \sigma_{TS0}^2)$$

Mean shift: `gef` terms set to 0 after progression events

Stan and a branch of the R package rstanarm were used to fit this model. Many thanks to Sam Brilleman, the Stan developers, and the authors of rstanarm.

2. Joint Modeling: Example from Iressa IPASS Study

- Consider 2 patients
- Same baseline covariates (same dosing, EGFR status, WHO performance status)



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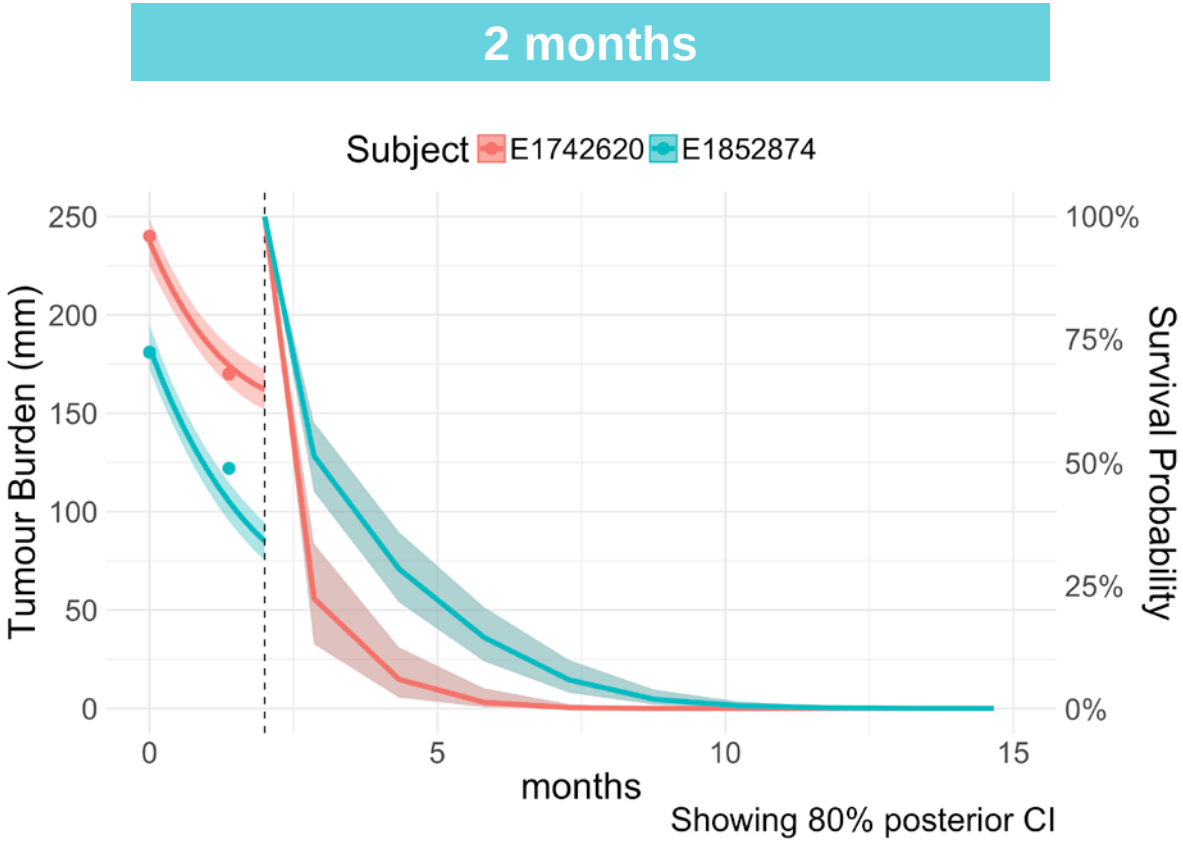

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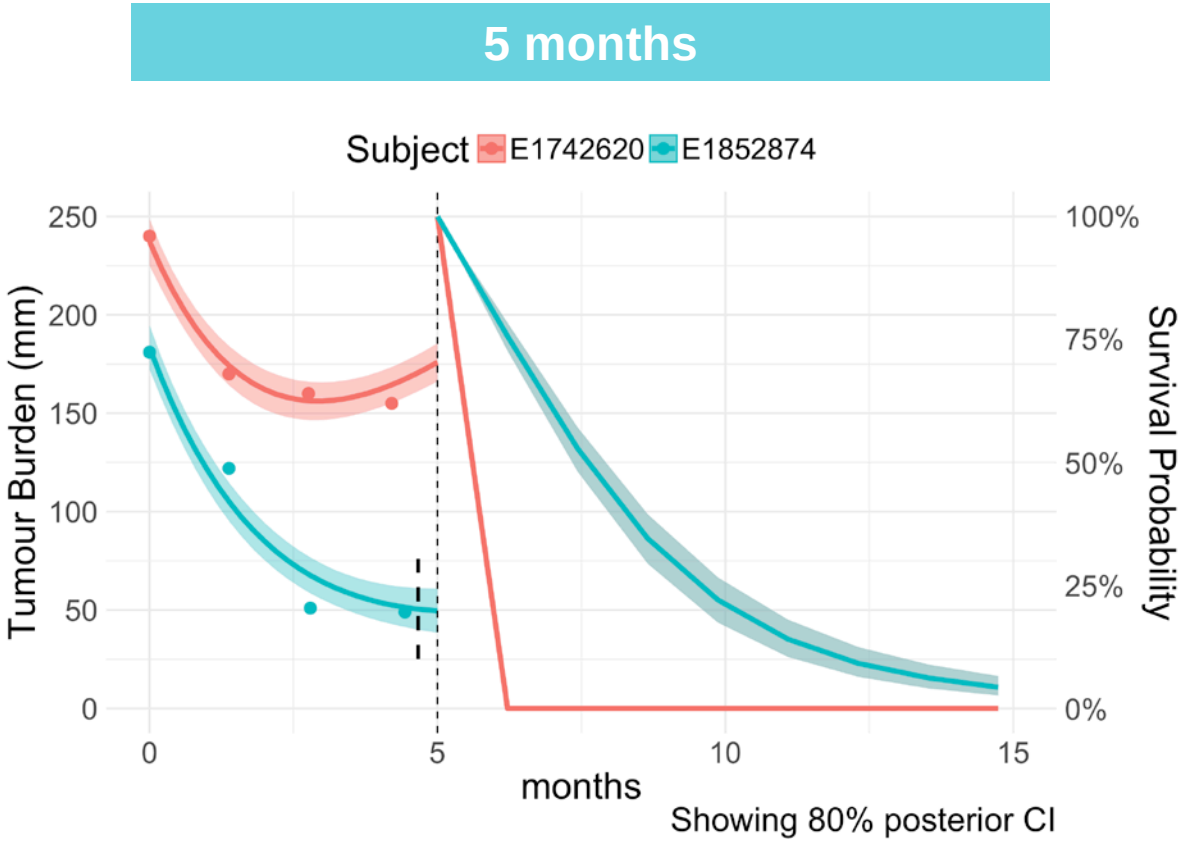

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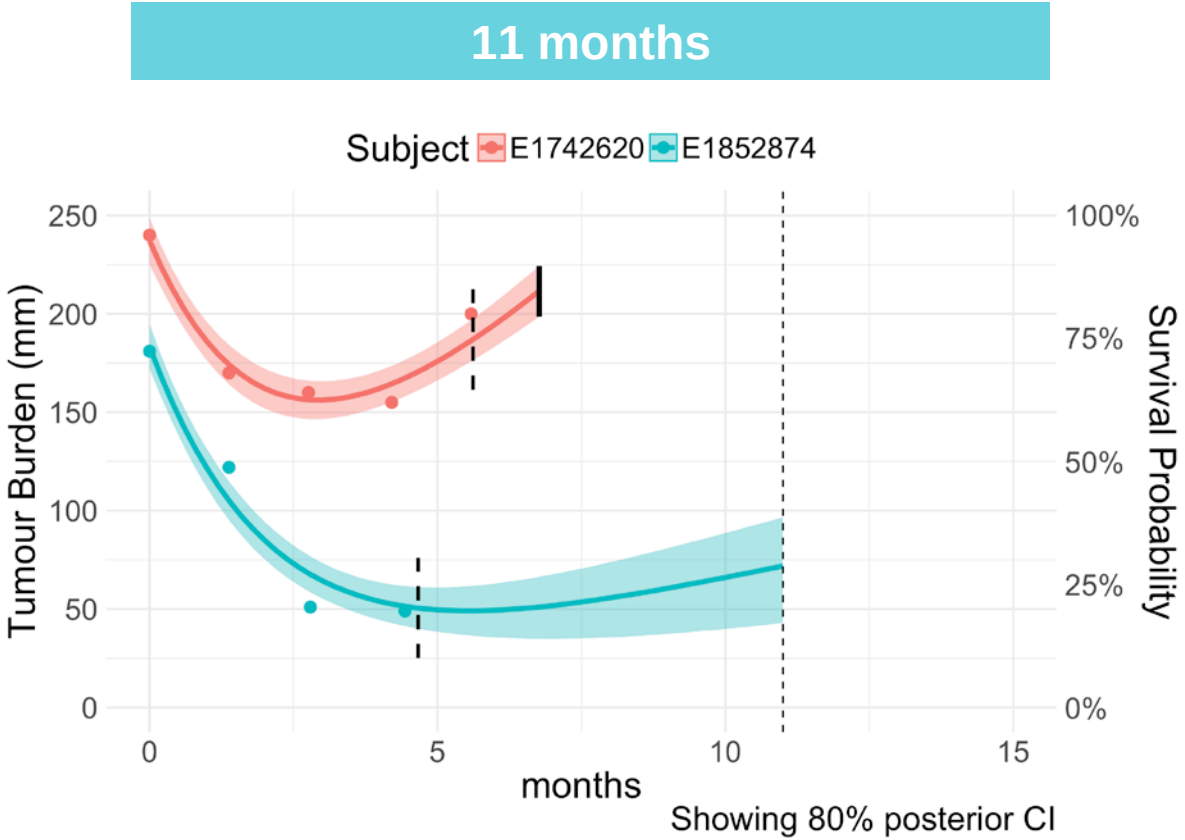
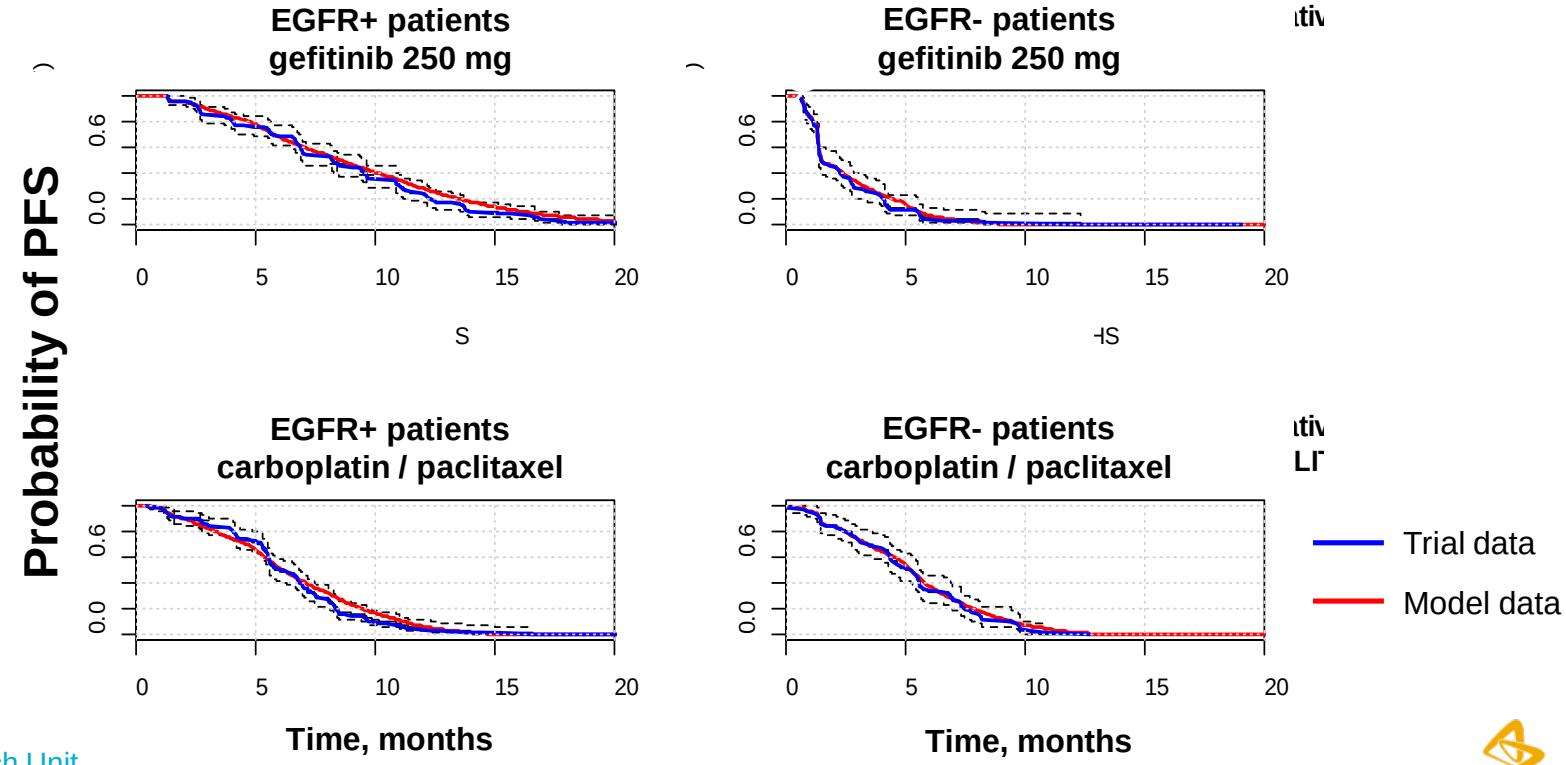


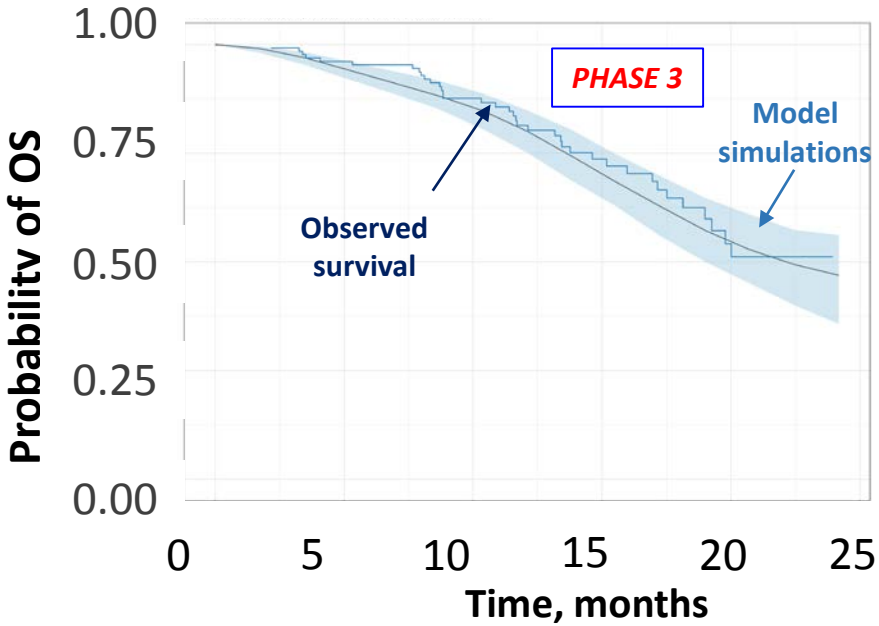
2. Joint Modeling: Example, gefitinib (EGFR inh) & chemotherapy

2-month tumor size data predict 2-year PFS outcome
for both an EGF-R inhibitor & chemotherapy, in NSCLC patients

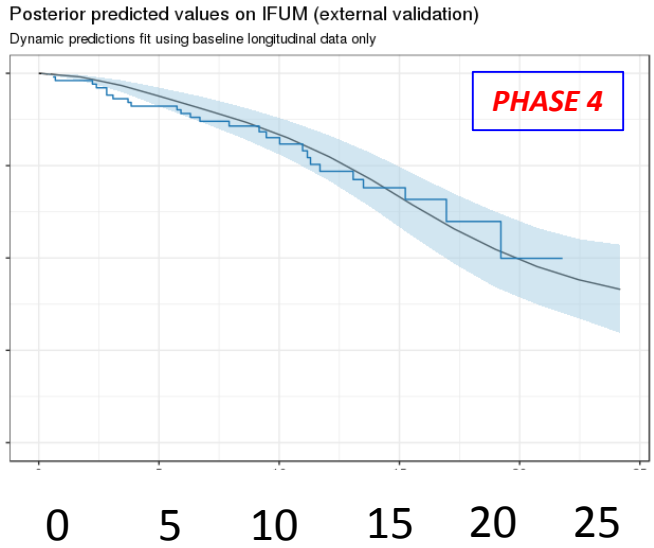


Bayesian Joint modeling in Stan using b-spline and no lag time

Joint model validated on IPASS data



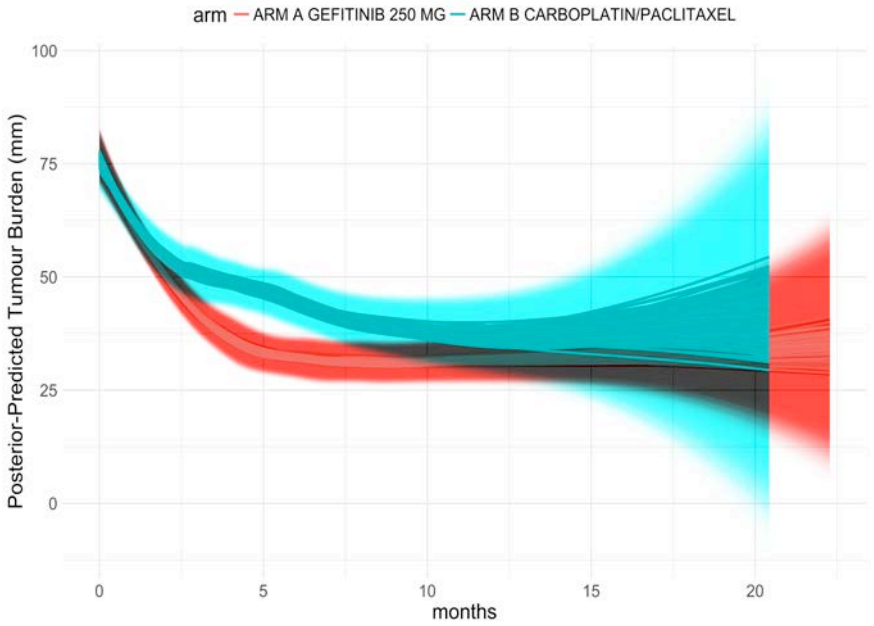
Model predicts IFUM OS using baseline data cut-of1f



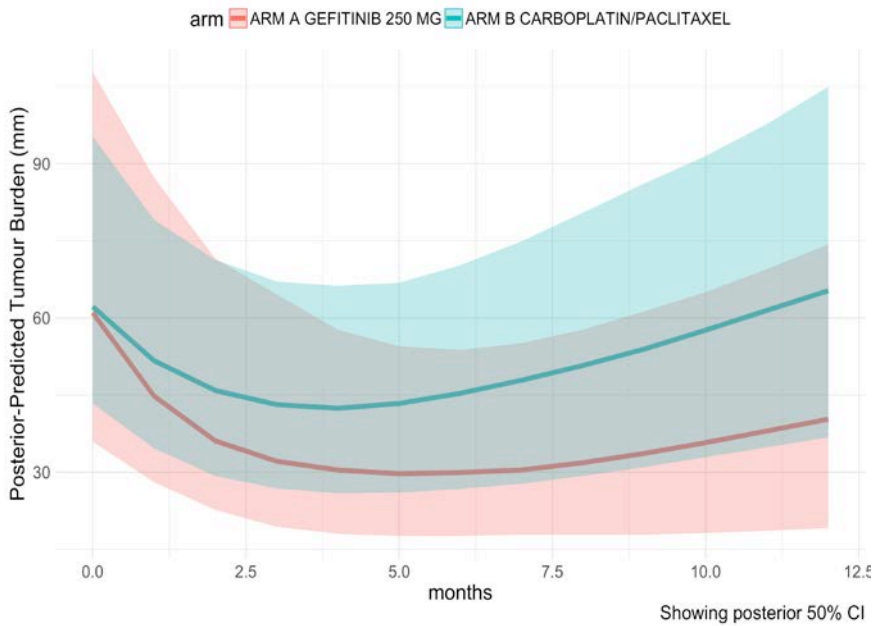
Rizopoulos, D. (2011). Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data. *Biometrics* **67**, 819–829.

Average Tumor Load Trajectory Varies According to Treatment among EGFR+ Patients

Population average values, limited to observed occasions



Population average values, adjusted for censoring & survivorship bias



Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** ***N Engl J Med. 2009 Sep 3;361(10):947-57***

Conclusion

- A statistically valid basis for modeling and interpretation of longitudinal response dynamics, in the context of time-to-event (survival) censoring, through development of a joint longitudinal/event model has been developed and validated.

- Modeling of trial-level survival data will inform individual-level joint models of tumor size and survival to make earlier trial prediction

- The modeling approach can be applied to:
  - Predict outcome for early clinical results
  - Support ranking of drug combinations
  - Optimize late-phase trial designs and/or project survival outcome from early-phase data

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Selected further reads

- Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. Biometrics. 1997;53:330–9
- Brown ER, Ibrahim JG. A Bayesian semiparametric joint hierarchical model for longitudinal and survival data. Biometrics. 2003;59:221–228
- Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, Fagerberg J, Bruno R. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics JCO 2009;27:4103-4108
- Rizopoulos D. **JM**: an R package for the joint modelling of longitudinal and time-to-event data. Journal of Statistical Software 2010; 35(9):1–33.
- Hansson EK, Westwood P, Amantea M, Miligan PA, Karlsson, MO, Friberg, LE, PKPD modelling of VEGF, sVEGF-2, sVEGFR-3 and sKIT as biomarker of tumor response following sunitinib treatment in GIST. ACoP 2011
- Sweeting MJ, Thompson SG. Joint modelling of longitudinal and time-to-event data with application to predicting abdominal aortic aneurysm growth and rupture. Biometrical Journal 2011; 53(5):750–763.
- Rizopoulos D. Joint Models for Longitudinal and Time-to-event Data with Applications in R. Chapman & Hall: London, 2012.
- Gould AL, Boye ME, Crowther MJ, Ibrahim JG, Quartey G, Micallef S, Bois FY. Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian joint modeling working group. Statistics in Medicine 2015; 34(14):2181–2195.
- Philipson P, Sousa I, Diggle P, Williamson P, Kolamunnage-Dona R, Henderson R. **joineR** – joint modelling of repeated measurements and time-to-event data. 2012. https://cran.r-project.org/web/packages/joineR/vignettes/joineR.pdf.
- Crowther MJ, Abrams KR, Lambert PC. Joint modeling of longitudinal and survival data. Stata Journa 2013; 13(1):165–184.
  Zhang D, Chen MH, Ibrahim JG, Boye ME, Shen W. 2015JMFit: a SAS macro for assessing model fit in joint models of longitudinal and survival data.
- Bender BC, Schindler E, Friberg LE. Population pharmacokinetic–pharmacodynamic modelling in oncology: a tool for predicting clinical response. British Journal of Clinical Pharmacology. 2015;79(1):56-71. doi:10.1111/bcp.12258.
- Desmée S, Mentré F, Veyrat-Follet C, Sébastien B, Guedj J, Nonlinear joint models for individual dynamic prediction of risk of death using Hamiltonian Monte Carlo: application to metastatic prostate cancer. 2017 BMC Medical Research Methodology
- Desmée S, Mentré F, Veyrat-Follet C, Sébastien B, Guedj J, Using SAEM Algorithm for Mechanistic Joint Models characterizing their relationship between nonlinear PSA kinetics and survival in prostate cancer patients. 2017 Biometrics 73, 305-312
- Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. J Clin Oncol. 2010;28:2796–801
- Chen T, Wang Y, Variable selection for joint models of multivariate longitudinal measurements and event time data. 2017 Stats Med Vol 36 24 3820-3829
- …

Back up

Association structures

- A more **general form** for the event submodel is

$$h_i(t) = h_0(t) \exp\left(\boldsymbol{w_i^T}(t)\boldsymbol{\gamma} + \sum_{m=1}^{M} \sum_{q=1}^{Q_m} \alpha_{mq} f_{mq}(\boldsymbol{\beta_m}, \boldsymbol{b_{im}}; t) \right)$$

- This posits an **association** between the **log hazard of the event** and **any function of the longitudinal submodel parameters**; for example, defining $f_{mq}(.)$ as:

$\eta_{im}(t)$ ⟶ Linear predictor (or expected value of the biomarker) at time t

$\frac{d\eta_{im}(t)}{dt}$ ⟶ Rate of change in the linear predictor (or biomarker) at time t

$\int_0^t \eta_{im}(s)\, ds$ ⟶ Area under linear predictor (or biomarker trajectory), up to time t

$\eta_{im}(t-u)$ ⟶ Lagged value (for some lag time u)

Association structures

- A more **general form** for the event submodel is

$$h_i(t) = h_0(t) \exp\left(\boldsymbol{w_i^T}(t)\boldsymbol{\gamma} + \sum_{m=1}^{M} \sum_{q=1}^{Q_m} \alpha_{mq} f_{mq}(\boldsymbol{\beta_m}, \boldsymbol{b_{im}}; t) \right)$$

Joint Modeling to Predict Survival

Time-dependent mixed-effects model informs hazard

Joint model (first-order):

$$\begin{cases} h_i(t|\mathcal{M}_i(t)) = h_0(t) \cdot \exp\left(\gamma^{\mathrm{T}} w_i + \alpha_0 \cdot m_i(t) + \alpha_1 \cdot m_i'(t)\right) \\ y_i(t) = m_i(t) + \varepsilon_i(t) = \\ \quad = x_i^{\mathrm{T}}(t) \cdot \beta + z_i^{\mathrm{T}}(t) \cdot b_i + \varepsilon_i(t) \end{cases}$$

- Survival model may be dependent on the *rate-of-change* of tumor size
- Also, *delay term* may be implemented

Survival submodel updated:

$$m_i'(t) = \frac{d}{dt}\{x_i^{\mathrm{T}}(t) \cdot \beta + z_i^{\mathrm{T}}(t) \cdot b_i\}$$

Longitudinal submodel:

$y_i(t)$ – measurements of $m_i(t)$ (with error)

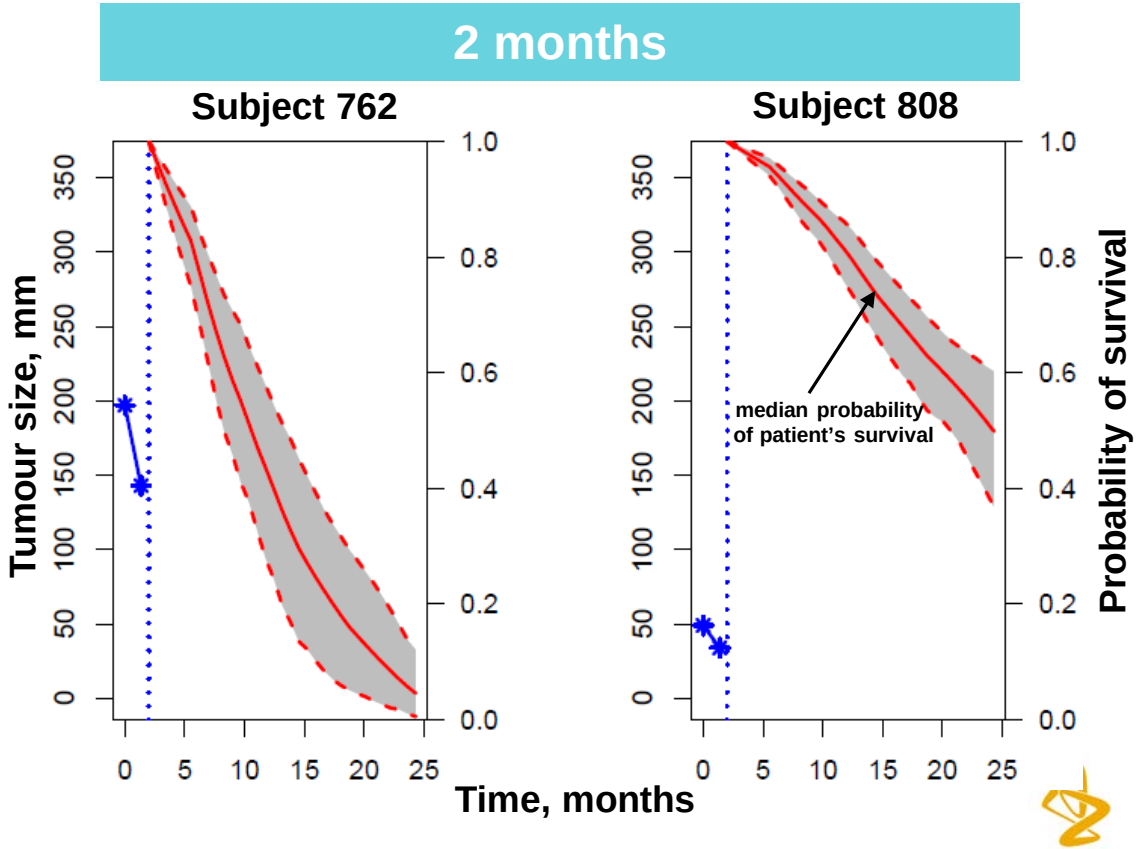
$x_i(t)$ and β – fixed-effects design matrix and coefficients

$z_i(t)$ and b_i – random-effects design matrix and coefficients, $b_i \sim \mathcal{N}(0, D)$

rstanarm was used to jointly model the relationship between tumor dynamics (size) measurements and PFS /OS

2. Joint Modeling: Example, gefitinib (EGFR inh)

- Consider 2 patients with same baseline covariates (same dosing, EGFR status, WHO performance status)



2. Joint Modeling: Example, gefitinib (EGFR inh)

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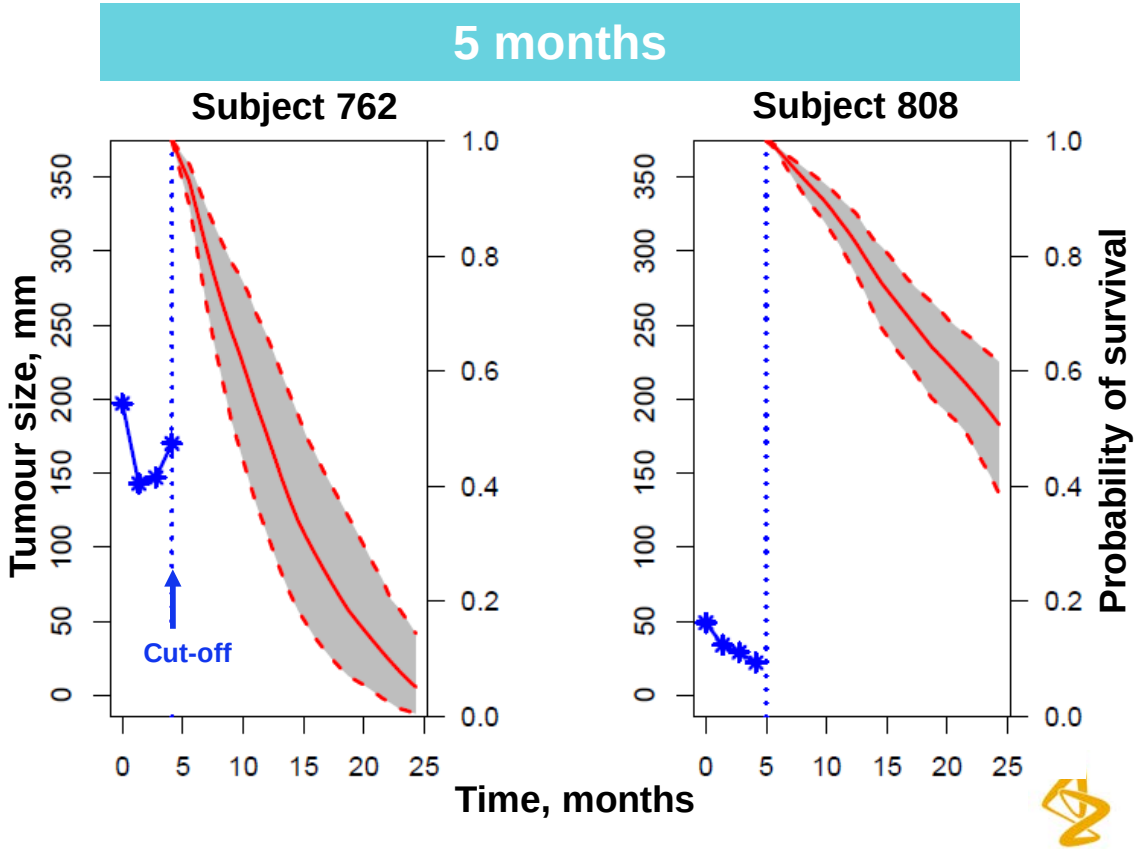
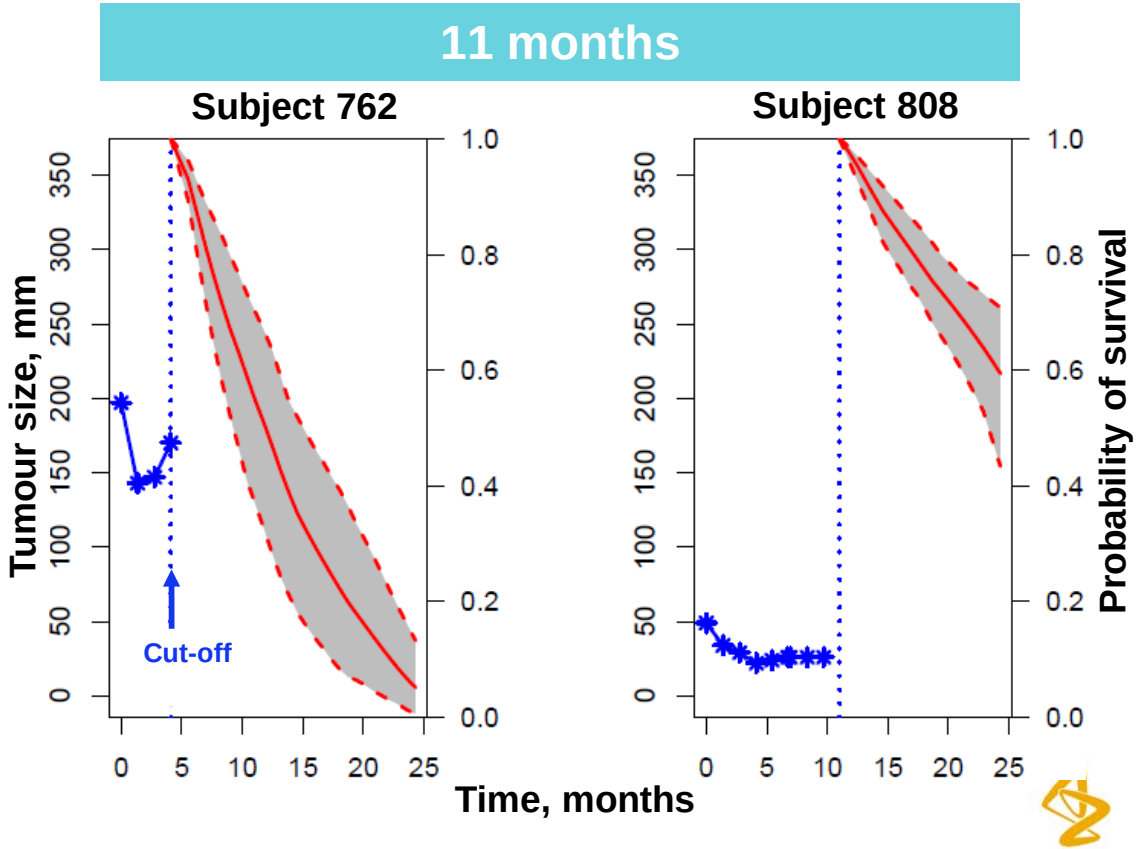
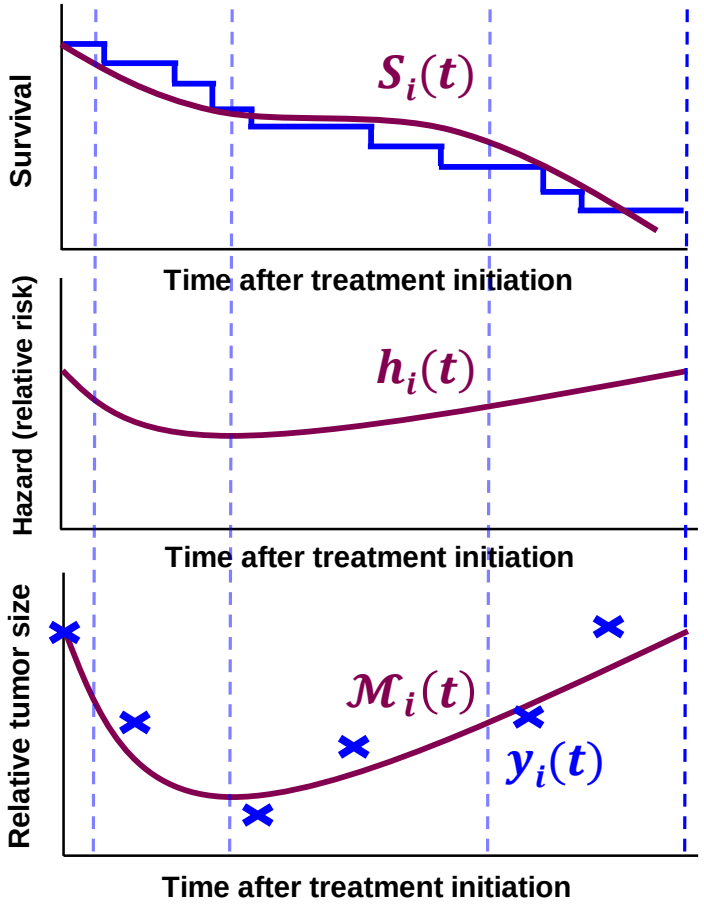


2. Joint Modeling: Example, gefitinib (EGFR inh)

- Consider 2 patients with same baseline covariates (same dosing, EGFR status, WHO performance status)
- Their therapeutic prognoses differ only because of differences in tumour dynamics (baseline & trajectory)



Continuous modeling of endpoints: Joint approach



► Individual survival function:

$$S_i(t|\mathcal{M}_i(t)) = \exp\left\{-\int_0^t h_i(s|\mathcal{M}_i(s))\,ds\right\}$$

► Log-likelihood is maximized for $\{T_i, \delta_i, yi\}$

- T_i is the time to event
- δ_i is the censoring indicator
- $y_i(t)$ is the longitudinal evolution

} for *i*th subj.

measured with error!

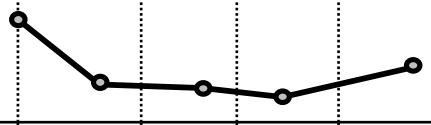
► Maximization is conditional on baseline covariates

Ibrahim 2010, J Clin Oncol 28:2796-2801
Rizopoulos 2010, J Stat Soft 35:1-33

Problem: Different clinical endpoints are used in each phase, but are they correlated and predictive of the next phase?

PRECLINICAL	PHASE I, II	PHASE III
Tumor Growth Inhibition (TGI)	Tumor Dynamics Overall Response Rate (ORR)	Progression Free Survival (PFS) Overall survival (OS)

PROBLEM: **Rich longitudinal tumor dynamic data are reduced to categorical endpoints with a subsequent loss of information**

Repeatedly measured tumor size (RECIST[1]) data					
Time (months)	0	2	5	7	10
Target Lesion SLD[2] (cm)	6 cm 4 cm 2 cm				
New Lesion		No	No	No	**Yes**
Response		PR	PR	PR	**PD**

Reduction to Single Values:	
PFS	10 mo.
Best Overall Response	PR
Maximum change in SLD	- 55%

Slide adapted from Andy Stein, Novartis, PhUSE 2013

Modeling of Tumor Size Dynamics in Humans

Comparison of approaches

More 'empirical'

$$y(t) = y_0 e^{-dt} + gt$$

Advantages

- *Simple structure but cannot capture all types of treatment response patterns*
- *Minimal number of parameters; can obtain identifiable parameter estimates across different, even small datasets*

Limitations

- *Does not account for varying dose information (e.g., dose de-escalation and modification)*
- *Cannot be used to extrapolate tumor dynamics to different dosing regimens (incl. discontinuation) within a study or across studies*

More 'mechanistic' (ODEs)

$$\frac{dy}{dt} = net\_growth \quad - drug\_induced\_decay$$

Advantages

- *Various characteristics of drug effects can be flexibly modeled:*
  - *Dose dependence*
  - *Drugs only acting on a fraction of cells*
  - *Delay in drug action*
  - *Drug resistance, drug discontinuation*

Limitations

- *Models have more parameters than empirical models; more information needed need to identify parameter values*

Joint Model with an Empirical Mean-Shift Longitudinal Submodel for Tumor Burden

$$\begin{cases} h_i(t|\mathcal{M}_i(t)) = h_0(t)exp\left\{\gamma^\top w_i + \alpha m_i(t)\right\} \\ y_i(t) = m_i(t) + \varepsilon_i(t) \\ m_i(t) = \beta_i t + TS_{0i}e^{-\alpha_i t} \end{cases}$$

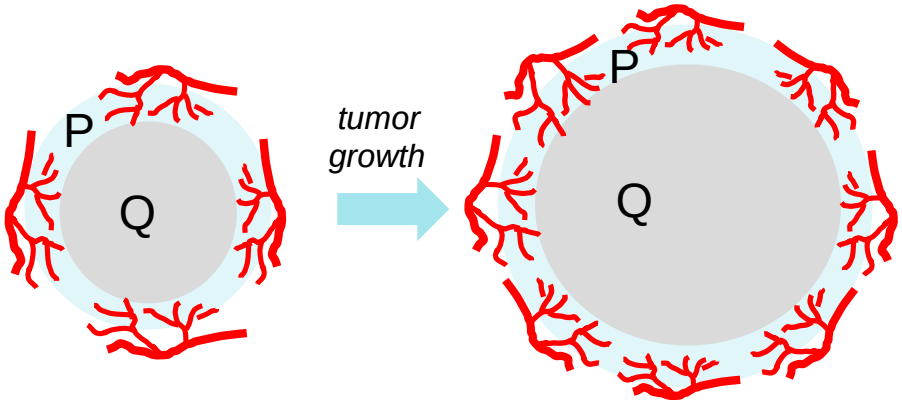
Where

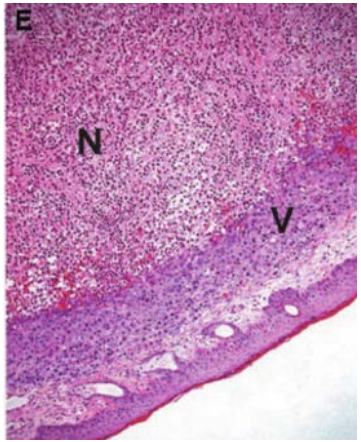
$$\mathcal{M}_i(t) = \left\{m_i(s), 0 \leq s < t\right\}$$

$$\alpha \sim \mathcal{N}(0, \sigma_\alpha^2)$$

$$\varepsilon_i(t) \sim \mathcal{N}(0, \sigma_\varepsilon^2)$$

Spherical model of tumor lesion





The model assumptions:

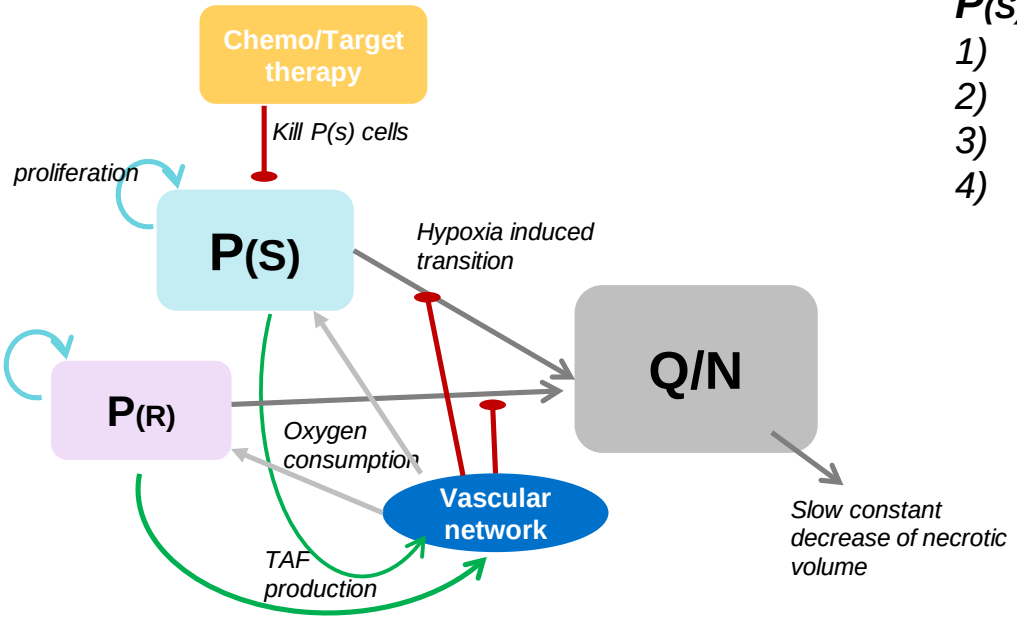
1) Spherical geometry of tumor lesion is assumed. Proliferative (P) cells form external “viable rim” of tumor, and Quiescent (Q) cells form internal core of tumor;

2) P -> Q transition rate is driven by hypoxia and depends on current value of vascular density in P-zone. Q cells elimination rate is constant and relatively slow;

3) Equilibrium thickness of “viable rim” is independent on tumor diameter, and depends on tumor ***angiogenesis capability*** and P cells ***resistance-to-hypoxia*** parameter values;

4) Chemo or target drug kills P cells, not Q cells.

Step 2: The model with two tumor cell clones (drug-sensitive and drug-resistant)

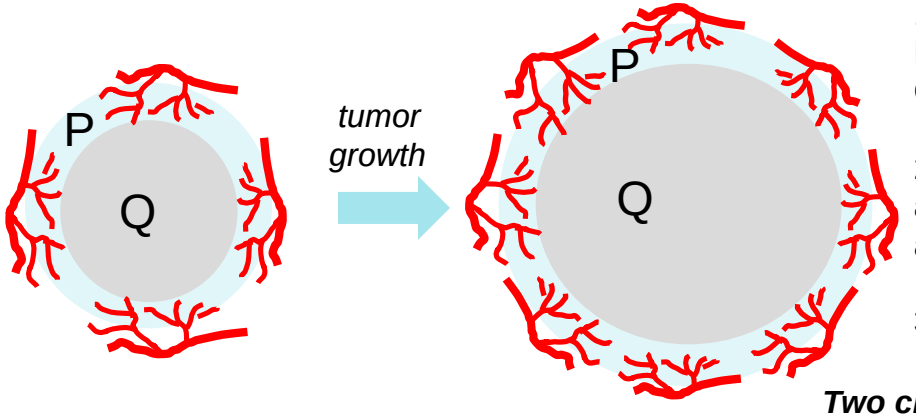


P(S) and P(R) might differ in:

1) *Intrinsic proliferation rate;*
2) *Resistance to hypoxia;*
3) *Angiogenesis capability;*
4) *Sensitivity to CTLs attack and/or immunogenicity*

P(S) and P(R)– drug-sensitive and drug-resistant clones of tumor cells;
Q/N - quiescent/necrotic tumor regions;
TAF - tumor angiogenesis factors

The model structure and assumptions made



1) Spherical geometry of tumor lesion is assumed.
P (proliferative) cells form external “viable rim” of tumor;
Q (quiescent) cells form internal core of tumor;

2) Thickness of “viable rim” is independent on tumor diameter, and depends mainly on dP_{max} (tumor angiogenesis capability) and K_p (hypoxia-dependent resistance) parameter values.

3) Chemo drug kills P cells, not Q cells

One clone model

Tumor volume: TV = P+Q
Tumor diameter: TD = 2*(3/4π * TV)^1/3
Tumor surface: TS = 4 π * (TD/2)^1/2

Blood vessels amount: va= dP_{max}*TS;
Vascular density: vd= va/P;

P cells survival function: $Surv_p$ = vd/(vd + K_p)

dP/dt = k_p*P – k_{pq} * (1 – $Surv_p$) * P
dQ/dt = k_{pq} * (1 – $Surv_p$) * P – k_q* Q

Two clones model

Tumor volume: TV = P_1+P_2+Q
Tumor diameter: TD = 2*(3/4π * TV)^1/3
Tumor surface: TS = 4 π * (TD/2)^1/2

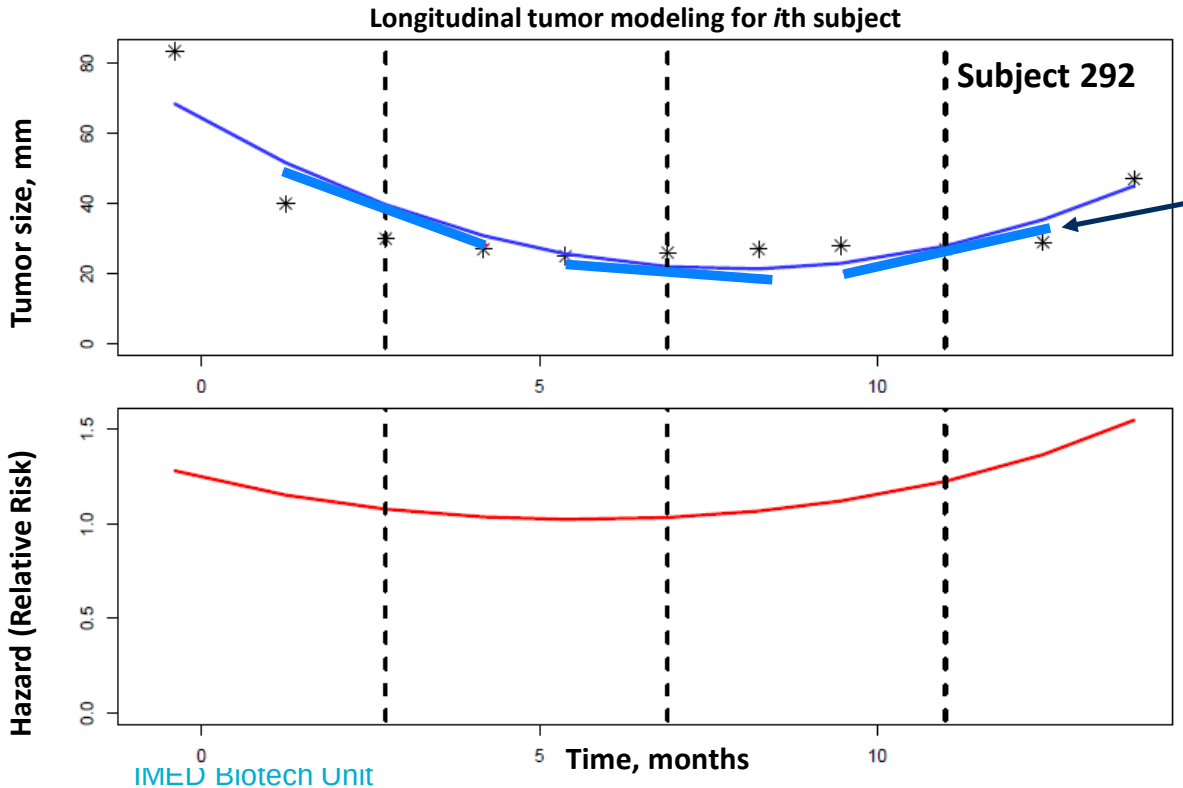
Blood vessels amount: va= dP_{max}*TS,
where dP_{max} = {dP_{max1}*P_1+ dP_{max2}*P_2}/(P_1+P_2)
Vascular density: vd= va/(P_1+P_2);

P_1 cells survival function: $Surv_{p1}$ = vd/(vd + K_{p1})
P_2 cells survival function: $Surv_{p2}$ = vd/(vd + K_{p2})

dP_1/dt = k_p*P_1– k_{pq} * (1 – $Surv_{p1}$)*P_1
dP_2/dt = k_p*P_2– k_{pq} * (1 – $Surv_{p2}$)*P_2
dQ/dt = k_{pq}*{(1 – $Surv_{p1}$)*P_1 + (1 – $Surv_{p2}$)*P_2} – k_q*Q

Individual Risks Estimated Dynamically

The longitudinal and survival components of the joint model are typically linked (joined) through the relative risk function



Individual patient time-dependent slopes are incorporated in the model

Cumulative hazard updated as longitudinal history is accumulated

Subject-specific odds change with every new response record

Association structures

- A more **general form** for the event submodel is

$$h_i(t) = h_0(t) \exp\left(\boldsymbol{w_i^T}(t)\boldsymbol{\gamma} + \sum_{m=1}^{M} \sum_{q=1}^{Q_m} \alpha_{mq} f_{mq}(\boldsymbol{\beta_m}, \boldsymbol{b_{im}}; t) \right)$$

- This posits an **association** between the **log hazard of the event** and **any function of the longitudinal submodel parameters**