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

1. Bayesian Meta-Analyses
   *Trial-level data linking PFS & OS*

2. Bayesian Joint Modeling
   *Patient–level tumor size dynamics – and possibly other covariates/biomarkers - to predict PFS & OS*

3. Quantitative Systems Pharmacology
   *Integration of biology & pharmacology to predict, in context, tumor size dynamics and key biomarkers*
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

PFS

OS

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

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>2</th>
<th>5</th>
<th>7</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Lesion SLD</strong> (cm)</td>
<td>6 cm</td>
<td>4 cm</td>
<td>2 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-target Lesion</strong></td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td><strong>New Lesion</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

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

**Reduction to Single Values:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Progression</td>
<td>10 mo.</td>
</tr>
<tr>
<td>Best Overall Response</td>
<td>PR</td>
</tr>
<tr>
<td>Best Percent Change in SLD</td>
<td>55%</td>
</tr>
</tbody>
</table>

**Notes:**
- 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

Event modeling (Cox Proportional Hazard)

Survival [Days] ~ Survival Hazard

Change in Target Lesion Size ($\Delta y = \%$) ~ $a_1 \cdot \Delta y$

Treatment Arm $\sim a_2 \cdot \text{Trt}$

Baseline tumor size $\sim a_3 \cdot \text{Tumor}_{\text{baseline}}$

{$a_1, a_2, a_3$} are Cox coefficients linking each patient measurement to Survival

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

- Tumor size dynamics modeling
- Drug treatment: Dose, dosing regimen
- Association between tumor dynamics and outcome
- Treatment effect on tumor dynamics
- Treatment effect on survival
- Patient & trial outcome modeling
Joint Modelling in the Literature (since 90s)

Informative Drop-out in Longitudinal Data Analysis

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

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

Ming-Hui Chen, Joseph G. Ibrahim, and Debajyoti Sinha

Available online at www.sciencedirect.com


http://www.elsevier.com/locate/jmva

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 U987, Biomathematics Department and Université Victor Segalen Bordeaux 2, Bordeaux, F-33076, France
cécile.proust@inserm.fr

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

Soéline Desmée, France Mentel, Christine Veyrat-Follet, Bernard Sébastien, and Jérémie Guédj

BMC Medical Research Methodology

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

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

• Longitudinal submodel

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

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

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

• Event submodel

\[
h_i(t) = h_0(t) \exp \left( w_i^T(t) \gamma + \sum_{m=1}^{M} \alpha_m \mu_{im}(t) \right)
\]
Joint model formulation

• Longitudinal submodel

\[ y_{ijm}(t) \text{ is the value at time } t \text{ of the } \]
\[ m^{th} \text{ longitudinal marker } (m = 1, \ldots, M) \]
\[ \text{for the } i^{th} \text{ individual } (i = 1, \ldots, N) \]
\[ \text{at the } j^{th} \text{ time point } (j = 1, \ldots, n_{im}) \]
\[ T_{i}^{*} \text{ is “true” event time, } C_{i} \text{ is the censoring} \]
\[ \text{time} \]
\[ T_{i} = \min(T_{i}^{*}, C_{i}) \text{ and } d_{i} = I(T_{i}^{*} \leq C_{i}) \]

\[ y_{ijm}(t) \text{ follows a distribution in the exponential family with expected value } \mu_{ijm}(t) \text{ and } \]
\[ \eta_{ijm}(t) = g_{m}\left(\mu_{ijm}(t)\right) = x_{ijm}(t)^{T}\beta_{m} + z_{ijm}(t)^{T}b_{im} \]
\[ \begin{bmatrix} b_{i1} \\ \vdots \\ b_{iM} \end{bmatrix} = b_{i} \sim N(0, \Sigma) \]

• Event submodel

\[ h_{i}(t) \]
\[ = h_{0}(t) \exp\left( w_{i}^{T}(t)\gamma + \sum_{m=1}^{M} \alpha_{m} \mu_{im}(t) \right) \]

• Known as a current value “association structure”
Joint model formulation

• Longitudinal submodel

\[ y_{ijm}(t) = h_0(t) \exp \left( w_i^T(t) \gamma + \sum_{m=1}^{M} \alpha_m \mu_{im}(t) \right) \]

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\[ \begin{bmatrix} b_{i1} \\ \vdots \\ b_{iM} \end{bmatrix} = \mathbf{b}_i \sim N(0, \Sigma) \]

• Event submodel

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

- error-prone
- measured at discrete times

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

Therefore less bias in \( \alpha_m \) 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

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)

\[ \frac{dy}{dt} = \text{net\_growth} - \text{drug\_induced\_decay} \]

**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):

$$\begin{align*}
\{ h_i(t|M_i(t)) &= h_0(t)\exp\{\gamma^T w_i + \eta_{1..p}^T m_{1..p}(t) + \eta_0 m_{0i}(t)\} \\
y_{0i}(t) &= m_{0i}(t) + \varepsilon_{0i}(t)
\end{align*}$$

With tumour diameter defined by:

- **Baseline covariates**
- **Other biomarkers** (new lesion, etc)
- **Tumour burden** (sum-of-diameters)

$$\begin{align*}
\beta_{i\times gef} &\sim \mathcal{N}(\lambda_0 + \lambda_{1b} gef + (\lambda_{2b} + \lambda_{3b} gef) base. sld, \sigma_\beta^2) \\
\alpha_{i\times gef} &\sim \mathcal{N}(\lambda_0 + \lambda_{1a} gef, \sigma_\alpha^2) \\
TS_{0i\times gef} &\sim \mathcal{N}(\lambda_0 + \lambda_{1t} gef, \sigma_{TS0}^2)
\end{align*}$$

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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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

- **EGFR**+ patients
  - Geftinib 250 mg
  
- **EGFR**- patients
  - Geftinib 250 mg

- **EGFR**+ patients
  - Carboplatin / Paclitaxel

- **EGFR**- patients
  - Carboplatin / Paclitaxel

**Model data**

- Blue line: Trial data
- Red line: Model data

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

Probability of OS

Observed survival

Model simulations

Model predicts IFUM OS using baseline data cut-off

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

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
We thank numerous collaborators at AZ, who have contributed to data & development of these models, including:

- **Quantitative Clinical Pharmacology:**
  - David Carlile, Lulu Chu, Bishoy Hanna, Kaitlyn Minchella, Ganesh Mugundu, Hongmei Xu, Xiao Tong, Diansong Zhou, James Dunyak, Helen Tomkinson, Sergey Aksenov, Gabriel Helmlinger and Don Stanski

- **M&S Decisions, Moscow:** Yuri Kosinsky, Boris Shulgin and Dmitry Onishchenko

- Stan Group: Eric Novik and Daniel Lee in collaboration with Jacki Buros from Hammer Lab / Dept of Genetics and Genomics, Icahn School of Medicine at Mt Sinai and Sam Brillman from Monash University.
Selected further reads

- Brown ER, Ibrahim JG. A Bayesian semiparametric joint hierarchical model for longitudinal and survival data. Biometrics. 2003;59:221–228
- 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
Back up
Association structures

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

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

• 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:

\[
\eta_{im}(t) \quad \rightarrow \quad \text{Linear predictor (or expected value of the biomarker) at time } t
\]

\[
\frac{d\eta_{im}(t)}{dt} \quad \rightarrow \quad \text{Rate of change in the linear predictor (or biomarker) at time } t
\]

\[
\int_0^t \eta_{im}(s) \, ds \quad \rightarrow \quad \text{Area under linear predictor (or biomarker trajectory), up to time } t
\]

\[
\eta_{im}(t - u) \quad \rightarrow \quad \text{Lagged value (for some lag time } u)
\]
Association structures

• A more general form for the event submodel is

\[
h_i(t) = h_0(t) \exp \left( \sum_{m=1}^{M} \sum_{q=1}^{Q_m} \alpha_{mq} f_{mq}(\beta_m, b_{im}; t) \right)
\]
Joint Modeling to Predict Survival

Time-dependent mixed-effects model informs hazard

Joint model (first-order):

\[
\begin{align*}
    h_i(t|\mathcal{M}_i(t)) &= h_0(t) \cdot \exp \left( \gamma^T w_i + \alpha_0 \cdot m_i(t) + \alpha_1 \cdot m'_i(t) \right) \\
    y_i(t) &= m_i(t) + \varepsilon_i(t) = x_i^T(t) \cdot \beta + z_i^T(t) \cdot b_i + \varepsilon_i(t)
\end{align*}
\]

Survival submodel updated:

\[
m'_i(t) = \frac{d}{dt} \left\{ x_i^T(t) \cdot \beta + z_i^T(t) \cdot b_i \right\}
\]

Longitudinal submodel:

- \( y_i(t) \) – measurements of \( m_i(t) \) (with error)
- \( x_i(t) \) and \( \beta \) – fixed-effects design matrix and coefficients
- \( z_i(t) \) and \( b_i \) – random-effects design matrix and coefficients, \( b_i \sim \mathcal{N}(0, D) \)

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

rstanarm was used to jointly model the relationship between tumor dynamics (size) measurements and PFS / OS
Consider 2 patients with same baseline covariates (same dosing, EGFR status, WHO performance status)
Consider 2 patients with same baseline covariates (same dosing, EGFR status, WHO performance status)

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:
  \[ S_i(t|M_i(t)) = \exp \left\{ - \int_0^t h_i(s|M_i(s)) \, ds \right\} \]

- Log-likelihood is maximized for \( \{T_i, \delta_i, y_i\} \)
  - \( T_i \) is the time to event
  - \( \delta_i \) is the censoring indicator
  - \( y_i(t) \) is the longitudinal evolution

- Maximization is conditional on baseline covariates

*measured with error!*

*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?

<table>
<thead>
<tr>
<th>PRECLINICAL</th>
<th>PHASE I, II</th>
<th>PHASE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Growth Inhibition (TGI)</td>
<td>Tumor Dynamics Overall Response Rate (ORR)</td>
<td>Progression Free Survival (PFS) Overall survival (OS)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Repeatedly measured tumor size (RECIST(^1)) data</th>
<th>Reduction to Single Values:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 mo.</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>7</td>
<td>Maximum change in SLD</td>
</tr>
<tr>
<td>10</td>
<td>- 55%</td>
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<tr>
<td>Target Lesion SLD(^2) (cm)</td>
<td></td>
</tr>
<tr>
<td>6 cm</td>
<td></td>
</tr>
<tr>
<td>4 cm</td>
<td></td>
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<td>2 cm</td>
<td></td>
</tr>
<tr>
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<td>No</td>
</tr>
<tr>
<td>Response</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>PD</td>
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### More ‘empirical’

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**Limitations**
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### More ‘mechanistic’ (ODEs)

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- 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

\[
\begin{align*}
  h_i(t|\mathcal{M}_i(t)) &= h_0(t)\exp\left\{\gamma^T w_i + \alpha m_i(t)\right\} \\
  y_i(t) &= m_i(t) + \varepsilon_i(t) \\
  m_i(t) &= \beta_i t + T S_{0i} e^{-\alpha_i t}
\end{align*}
\]

Where

\[
\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}
\]

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

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

One clone model
Tumor volume: $TV = P + Q$
Tumor diameter: $TD = 2(3/4\pi \cdot TV)^{1/3}$
Tumor surface: $TS = 4\pi \cdot (TD/2)^{1/2}$

Blood vessels amount: $va = dP_{max} \cdot TS$
Vascular density: $vd = va/\{P\}$

P cells survival function: $Surv_P = vd/(vd + K_P)$

\[
\frac{dP}{dt} = kp \cdot P - k_{pq} \cdot (1 - Surv_P) \cdot P
\]
\[
\frac{dQ}{dt} = k_{pq} \cdot (1 - Surv_P) \cdot P - k_Q \cdot Q
\]

Two clones model
Tumor volume: $TV = P_1 + P_2 + Q$
Tumor diameter: $TD = 2(3/4\pi \cdot TV)^{1/3}$
Tumor surface: $TS = 4\pi \cdot (TD/2)^{1/2}$

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

P1 cells survival function: $Surv_{P1} = vd/(vd + K_{P1})$
P2 cells survival function: $Surv_{P2} = vd/(vd + K_{P2})$

\[
\frac{dP_1}{dt} = kp \cdot P_1 - k_{pq} \cdot (1 - Surv_{P1}) \cdot P_1
\]
\[
\frac{dP_2}{dt} = kp \cdot P_2 - k_{pq} \cdot (1 - Surv_{P2}) \cdot P_2
\]
\[
\frac{dQ}{dt} = k_{pq} \cdot \{(1 - Surv_{P1}) \cdot P_1 + (1 - Surv_{P2}) \cdot P_2\} - k_Q \cdot Q
\]

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.

Q

P

tumor growth

Q

P

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;

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Individual Risks Estimated Dynamically

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

Longitudinal tumor modeling for $i$th subject

- 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

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

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