Modeling Primary Tumor Dynamics of Human-to-Mouse Xenografted Non-Small Cell Cancer in Response to Administration of Bevacizumab and Pemetrexed-Cisplatin

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Background

- **Situation:** Bevacizumab is an anti-angiogenic drug commonly administered contaminantly with chemotherapeutic drugs for advanced non-squamous non-small cell lung cancer (NSCLC). Bevacizumab administration transiently enhances chemotherapeutic drug delivery, resulting in increased efficacy of chemotherapeutic drugs [1].

- **Objective:** This analysis attempts to characterize tumor growth dynamics as measured by fluorescence in response to concurrent vs. sequential administration of pemetrexed-cisplatin and bevacizumab in NSCLC tumor carrying mice.

Methods

- **Experiment:** Data comes from previous experiment [2] where 77 mice were randomized into 5 treatment groups:
  i) control (saline, N=15),
  ii) beva then pemetrexed-cisplatan after 3 days
  iii) beva then pemetrexed-cisplatan after 8 days
  iv) concomitant beva + pemetrexed-cisplatan
  v) pemetrexed cisplatin alone

- **Statistical Analysis:** Tumor size was evaluated by fluorescence and the resulting data were analyzed using the stochastic approximation expectation maximization algorithm implemented in Monolix 2018 R1. Standard model diagnostics were completed using various R packages as well as other components of the Monolix Suite.

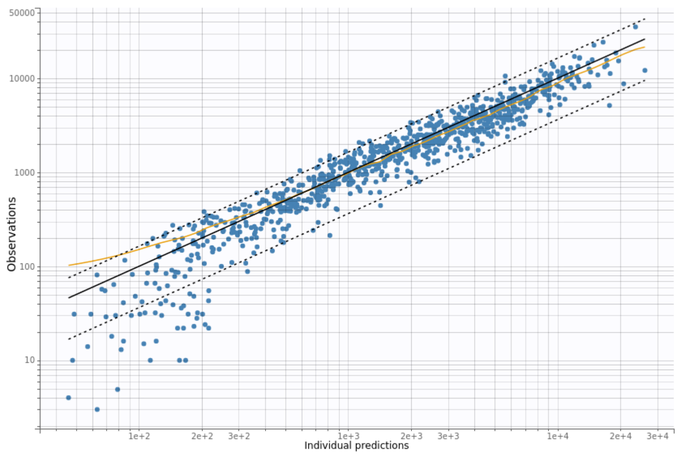
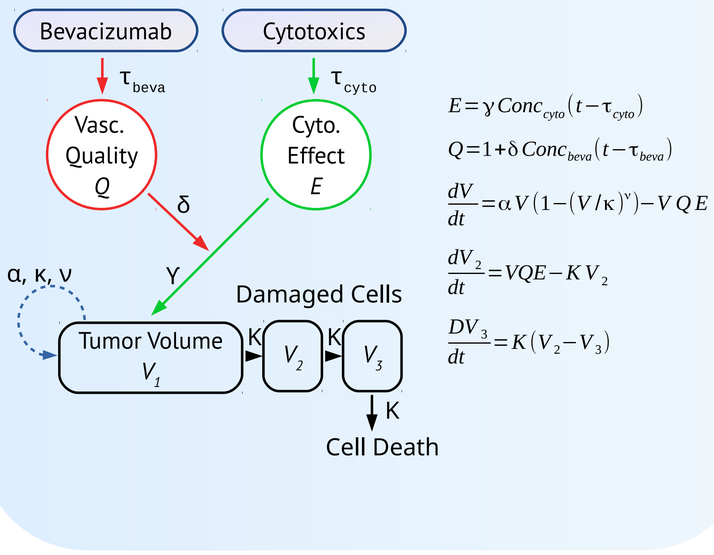


Fig 1: Log-10 observed vs. log-10 individual predictions (spline in yellow). The model least accurately predicts the dynamics of larger tumors. This is in part due to the structure of the measurement error (proportional) but is also due to the relative richness of the data set in smaller tumors.

Results

Fig 2: Adapted Generalized Logistic Growth Model



$$E = \gamma\, Conc_{cyto}(t-\tau_{cyto})$$

$$Q = 1+\delta\, Conc_{beva}(t-\tau_{beva})$$

$$\frac{dV}{dt} = \alpha V\left(1-(V/\kappa)^{\nu}\right) - V\,Q\,E$$

$$\frac{dV_2}{dt} = VQE - K\,V_2$$

$$\frac{DV_3}{dt} = K\,(V_2 - V_3)$$

Fig 3: Control (No Treatment Adm Post Xenograft)

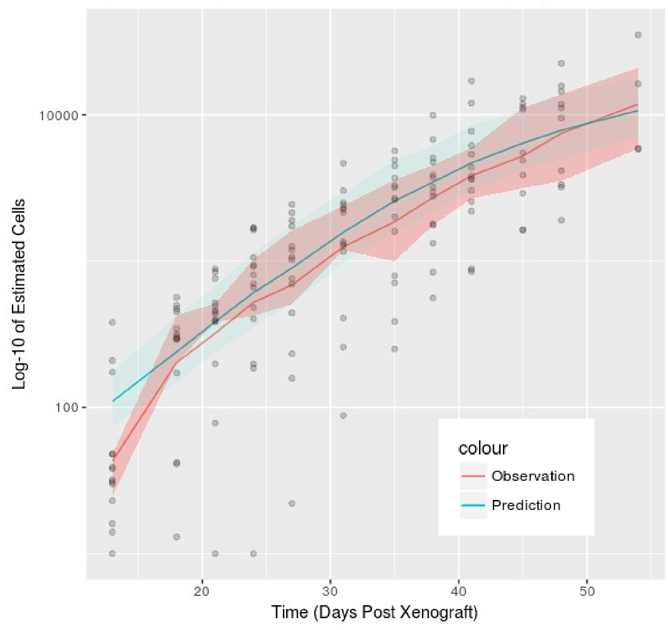


Fig 4: Chemotherapy Only (Bevacizumab Control)

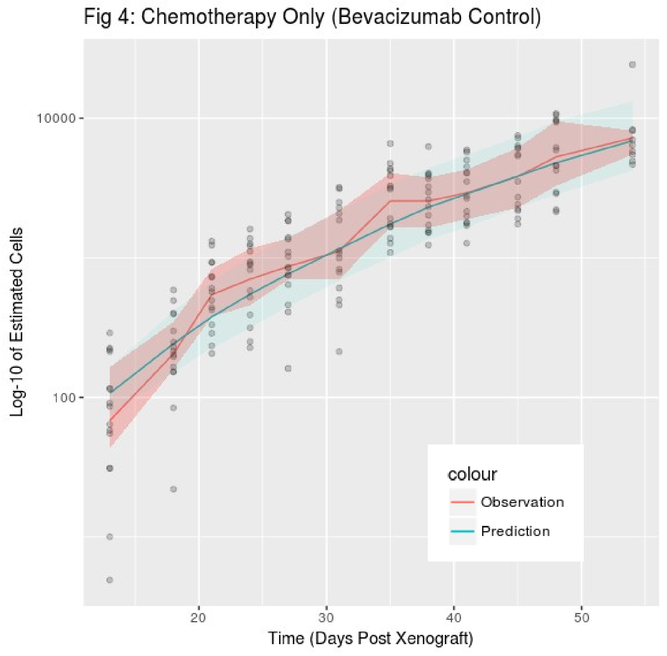


Fig 5: Concomitant Scheduling

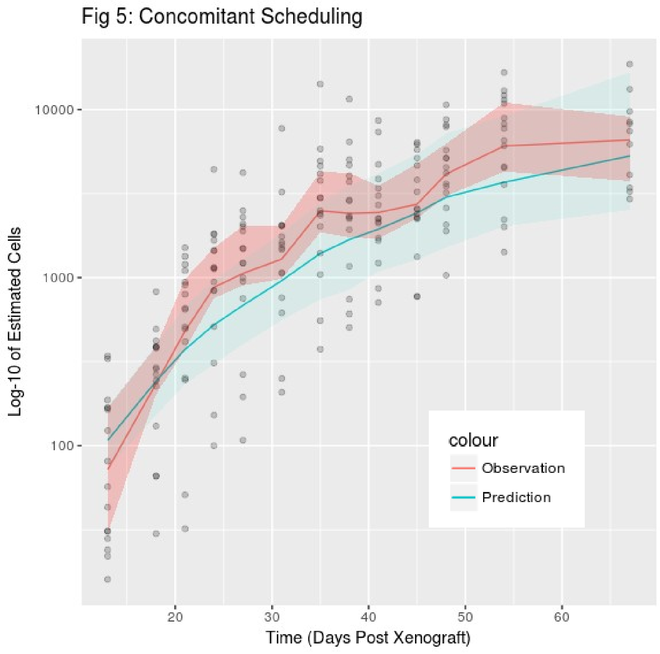


Fig 7: Eight Day Scheduling Gap

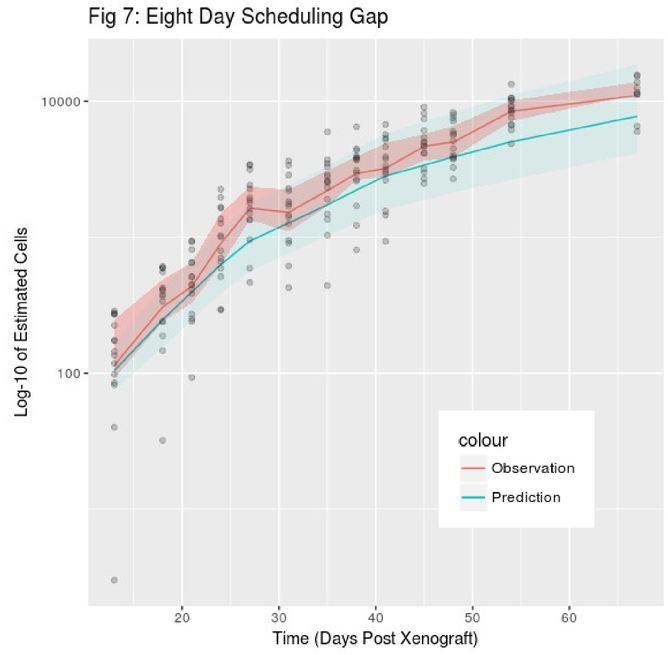
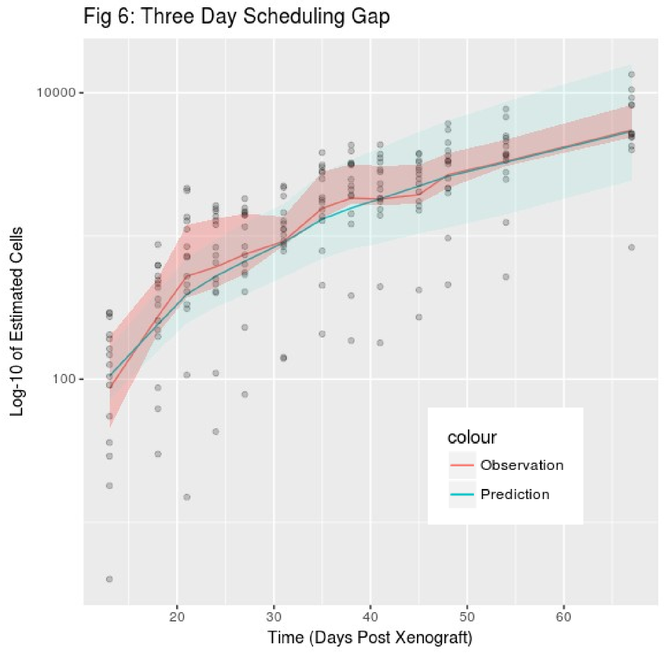


Fig 6: Three Day Scheduling Gap



In Figure 2, the underlying structural model is depicted. Bevacizumab and the chemotherapeutics are both delayed by parameters τ_A and τ_C respectively before exerting their various effects. The chemotherapeutics inhibit the growth of the tumor while Bevacizumab enhances the action of the chemotherapeutics by transiently increasing vascular quality. The Tumor volume grows at a generalized logistic rate parameterized by α, κ, and ν . The death of the cells damaged by the cytotoxics are modeled via two cell death compartments parameterized by coefficient K.

In Figures 3 through 7 the resulting fit of the model vs the observations for the various treatments on log-10 scale. The vertical error bars are the 50%-IQR on the predictions the model provides (Monte-Carlo simulation wit h N = 1000) while the pink area is the 50%-IQR on the observations. The individual paths of the two data sets are produced by taking the geometric mean of the data at the various time points.

Conclusions and Perspectives

- Our model-based analysis showed that a revisited Logistic (Gompertzian) growth function was predictive for modeling the effect of various scheduling of pemetrexed-cisplatin and bevacizumab in NSCLC tumor carrying mice. The model will further be refined and then used to anticipate the optimal delay between anti-angiogenesis therapy and chemotherapy, and its dependence on the therapeutic dosing schedule.
- Structural identifiability of the model parameters was further confirmed using sensitivity analyses, the estimated correlation of the random effects (<0.10 for most parameters) and the accurate precision of the final model parameters (RSE<20%). To get this low RSE, some parameters such as ν were fixed to reasonable values. The validity of final model parameter estimates was further confirmed through visual predictive checks using 1000 Monte-Carlo simulations although before publication the numerical value of the estimates will be precisely analyzed.

References **[1]** Zhao S, Gao F, Zhang Y, Zhang Z, Zhang L. Bevacizumab in combination with different platinum-based doublets in the first-line treatment for advanced nonsquamous non-small-cell lung cancer: A network meta-analysis. Int J Cancer. 2018 Apr 15;142(8):1676-1688.

[2] S. Mollard, J. Ciccolini, D.C. Imbs, R. El Cheikh, D. Barbolosi, S. Benzekry Oncotarget, Volume 5, 10.18632/oncotarget.15484, 2017