

# Modeling Targeted Therapies in Oncology: Incorporation of Cell Cycle Into a Tumor Growth Inhibition Model

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\*This work was done by Konstantinos Biliouris during his summer internship at Merck



## Motivation & Objectives

Macroscopic understanding of tumor growth is of high importance even though microscopic phenomena, such as signal transduction pathways, have received increasing interest.<sup>1</sup> A good understanding of tumor growth at the macroscopic level can bring immediate value to drug development and to the clinic in terms of optimized dosing schedule and improved prognosis.

An example of a macroscopic model for tumor growth is the model by Simeoni et al.,<sup>2</sup> which has been widely used to understand and characterize the drug effect observed in xenograft models. Simeoni model assumes that the drug affects all tumor cells regardless of their cell-cycle phases, resulting in a drug effect mostly determined by the total amount of administered drug. Such an assumption may be inappropriate for targeted therapeutics under development.

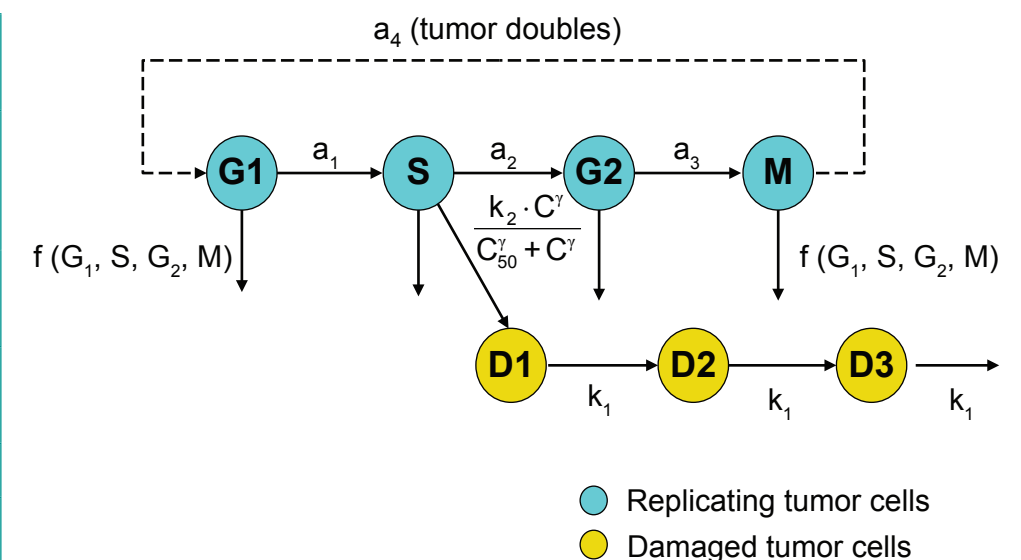
Two improvements to the Simeoni model are proposed to model the effects of targeted therapeutics, especially to explain possible dependency of efficacy on dosing schedule.

<sup>1</sup>P. Gerlee, Cancer Res., 73: 2407-2411 (2013)

<sup>2</sup>M. Simeoni et al., Cancer Res., 64: 1094-1101 (2004)

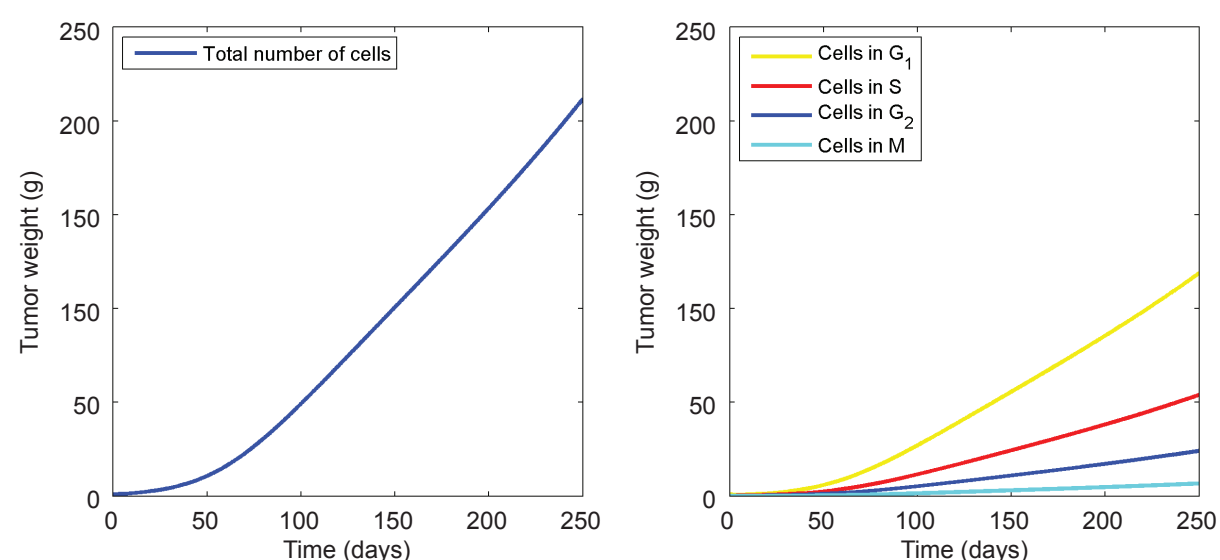
## Model Structure

$a_k$	Transition rates between phases
$f(\cdot)$	(Natural) death rate as a function of $G_1$ , S, $G_2$ , and M
$k_1$	Rate for delay in tumor death
$k_2$	Maximum rate of tumor elimination
$\gamma$	Hill coefficient
$C_{50}$	Concentration for 50% efficacy
$C$	Drug concentration



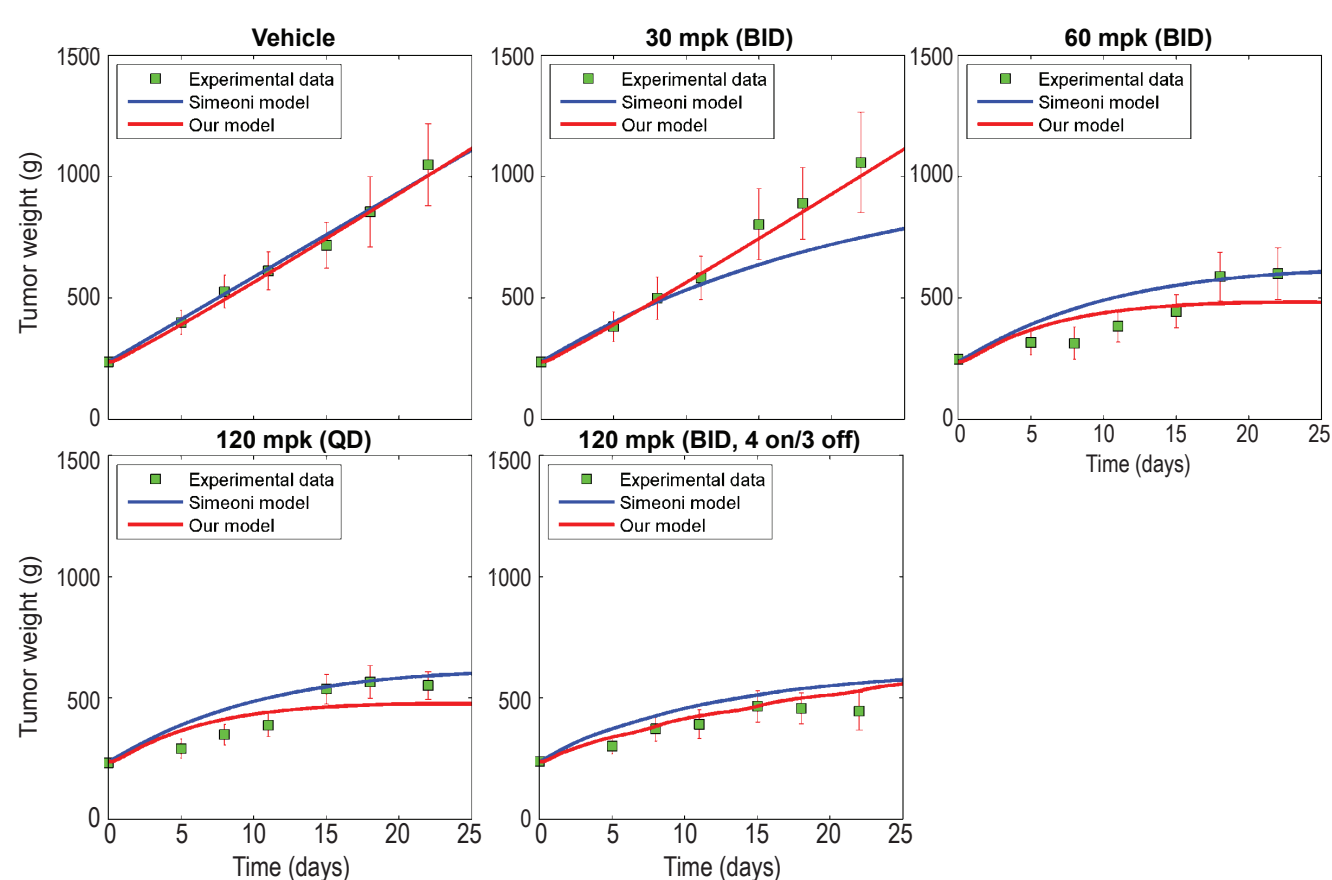
## Results

### Tumor Growth Model Behavior



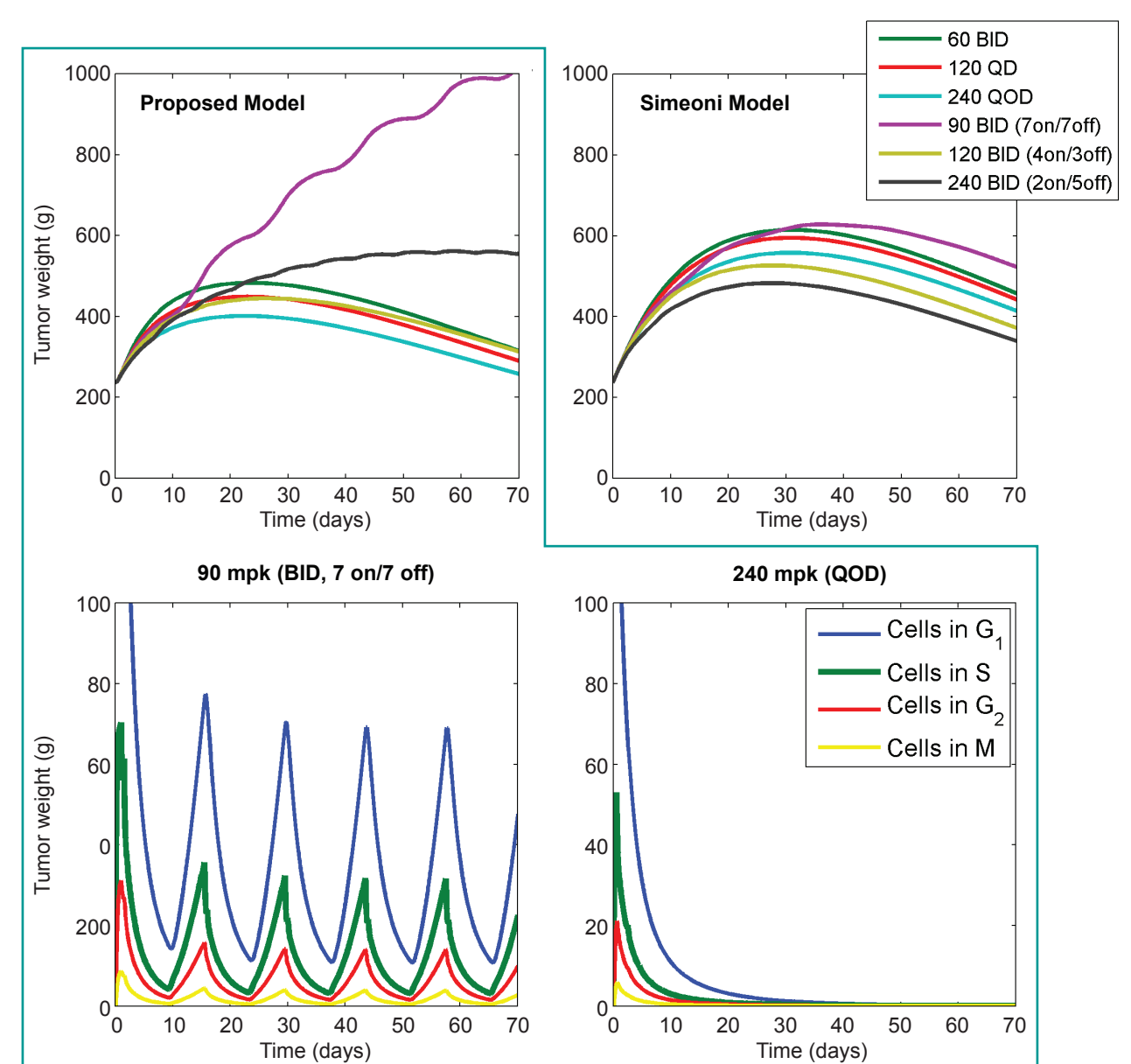
The proposed model can reproduce the “exponential-to-linear” tumor growth pattern as the Simeoni model. In addition, it can capture how many cells are in each cell-cycle phase.

### Validation Against Mouse Xenograft Data for Drug X



The proposed model fits the mouse xenograft data for drug X better due to the saturating drug effect modeled by a sigmoidal  $E_{max}$  function.

### Simulated Tumor Burden Over Longer Treatment Period



The proposed model shows treatment-schedule dependent efficacy under a simulation study (top panels). Further investigation shows that 90 mpk BID 7 on/7 off dosing schedule, for instance, does not show comparable efficacy to 240 mpk QOD because the tumor cells in the S phase are not sufficiently suppressed during treatment and let to regrow (bottom panels).

## Conclusions

- The proposed model can successfully
  - Reproduce slowing of tumor growth rate as Simeoni model does
  - Fit preclinical data better
  - Exhibit treatment-schedule dependency for targeted therapeutics
- The model predicts that the dosing schedule has to be chosen more carefully for targeted therapeutics
  - Too much or too frequent dosing (e.g. 240 mpk BID) does not improve efficacy
  - Each dose has to be large enough to suppress the tumor during off-treatment or eradicate it
- The proposed model is practical for drug development since the number of fitted parameters can be kept to a minimum using literature information or data from in vitro experiments
- Future work
  - Model refinement to enable biological interpretation of model parameters
  - Validation of the model with longer-term mouse xenograft data

## Model Details

- Tumor growth model for  $G_1$  and M

– Note that the natural death rates are the same for all the phases

$$\frac{dG_1}{dt} = \underbrace{2 \cdot a_4 \cdot M}_{\text{from Mitosis}} - \underbrace{a_1 \cdot G_1}_{\text{flowing into Synthesis}} - \underbrace{d_1 \cdot G_1 \cdot \left[ \frac{M}{k + G_1 + S + G_2 + M} \right]}_{\text{Natural death (empirical)}}$$

$$\frac{dM}{dt} = \underbrace{a_3 \cdot G_2}_{\text{from } G_2} - \underbrace{a_4 \cdot M}_{\text{flowing into } G_1} - \underbrace{d_1 \cdot M \cdot \left[ \frac{M}{k + G_1 + S + G_2 + M} \right]}_{\text{Natural death (empirical)}}$$

- Strategies to reduce number of parameters to fit

- Relative size of  $a_k$ 's are fixed by literature data.
- $d_1$  is set to be equal to  $a_4$  to maintain “exponential-to-linear” growth characteristics