Xenograft experiments: assessing consistency between a drug-driven and a biomarker-driven tumor growth inhibition model

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BACKGROUND. Integrating biomarker dynamics to describe the effect of antitumoral drugs provides a deeper insight in the mechanistic aspects of tumor progression [1, 2]. When the dynamics of a selective biomarker causally and quantitatively related to the inhibition of an associated tumor is considered [3], it is worth asking what structures should have a biomarker-to-tumor model and a drug-to-tumor one, in order to produce consistent predictions. In this work we resort to steady-state conditions to check the consistency between some PK/PD models published in the literature [4].

METHODS. All PK/PD data used in this work were simulated according to models and parameters reported in [4], using NONMEM version 7.2. We focused the analysis on three models: i) drug-to-biomarker (effect compartment model, model I, see scheme on the right), ii) drug-to-tumor model driven by the concentration in the effect compartment (model III, see scheme on the right), iii) tumor growth inhibition model driven from the effect of AKT biomarker (model IV, see scheme on the right). To assess whether model III and the cascade of model I with model IV describe consistent behaviors, a steady-state analysis was performed. In analogy with the method proposed in [5, 6], the so-called characteristic curves were computed. Moreover, resorting to the reverse engineering approach, a new model structurally matched with the reference drug-to-tumor one (model III) was proposed.

DRUG-TO-TUMOR REFERENCE MODEL

D → T

$$\frac{dT}{dt} = k_{ng} \cdot T(1 - T/T_{SS}) - K_4 \cdot T$$
$$\frac{dK_1}{dt} = \left(\frac{k_{\max} \cdot C_e}{KC_{50} + C_e} - K_1 \right) / \tau$$
$$\frac{dK_2}{dt} = (K_1 - K_2)/\tau$$
$$\frac{dK_3}{dt} = (K_2 - K_3)/\tau$$
$$\frac{dK_4}{dt} = (K_3 - K_4)/\tau$$

model III

Drug-to-tumor (model III) Characteristic curve

$$\bar{T} = T_{SS}\left(1 - \frac{k_{\max}\bar{C}_e}{KC_{50} + \bar{C}_e}\right) / k_{ng}$$

DRUG-TO-TUMOR CASCADED YAMAZAKI MODEL

Drug-to-biomarker model

$$\frac{dC_e}{dt} = k_{e0}(C_p - C_e)$$
$$E = E_0 \times \left(1 - \frac{E_{\max} \times C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}}\right)$$

model I

D → B → T

Biomarker-to-tumor TGI model

$$\frac{dT}{dt} = k_{ng} \cdot T(1 - T/T_{SS}) - K_4 \cdot T$$
$$\frac{dK_1}{dt} = \left(\frac{k_{\max} \cdot (1/E - 1)}{KC_{50} + (1/E - 1)} - K_1 \right) / \tau$$
$$\frac{dK_2}{dt} = (K_1 - K_2)/\tau$$
$$\frac{dK_3}{dt} = (K_2 - K_3)/\tau$$
$$\frac{dK_4}{dt} = (K_3 - K_4)/\tau$$

model IV

Cascaded Yamazaki (model I + model I) Characteristic curve

$$\bar{T} = T_{SS}\left(1 - \left(\frac{k_{\max}(1/\bar{E} - 1)}{KE_{50} + (1/\bar{E} - 1)}\right)\right) / k_{ng}$$

DRUG-TO-TUMOR CASCADED NEW MATCHED MODEL

Drug-to-biomarker model

$$\frac{dC_e}{dt} = k_{e0}(C_p - C_e)$$
$$E = E_0 \times \left(1 - \frac{E_{\max} \times C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}}\right)$$

model I

D → B → T

Biomarker-to-tumor TGI model

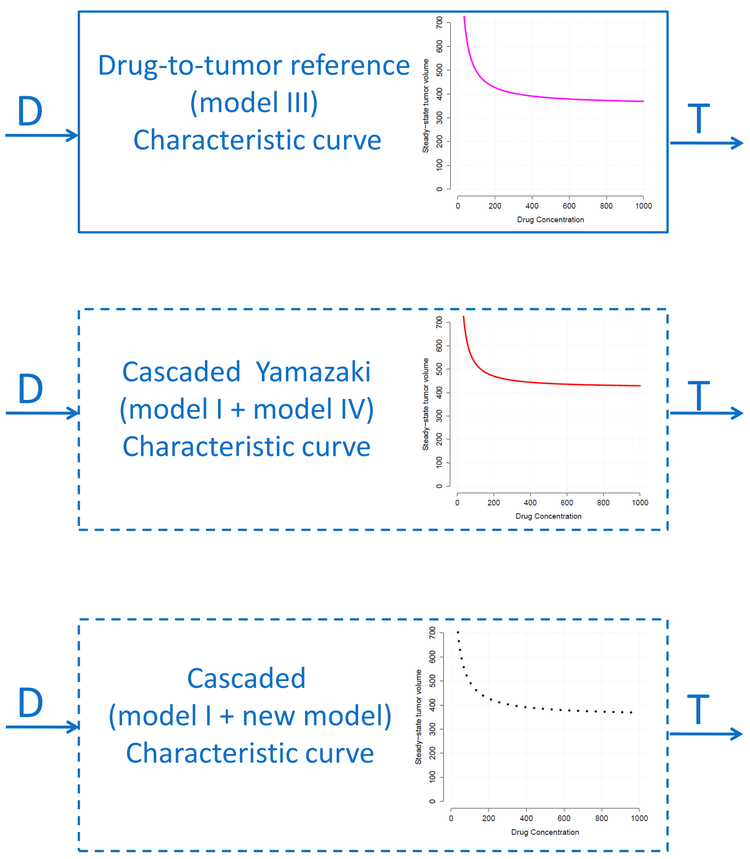
$$\frac{dT}{dt} = k_{ng} \cdot T(1 - T/T_{SS}) - K_4 \cdot T$$
$$\frac{dK_1}{dt} = \left(\frac{k_{\max} \cdot EC_{50}}{R + 1} - K_1 \right) / \tau$$
$$R = \frac{KC_{50}}{\sqrt[\gamma]{(1 - E)/(E + 1 - E_{\max})}}$$
$$\frac{dK_2}{dt} = (K_1 - K_2)/\tau$$
$$\frac{dK_3}{dt} = (K_2 - K_3)/\tau$$
$$\frac{dK_4}{dt} = (K_3 - K_4)/\tau$$

New model

Cascaded (model I + new model) Characteristic curve

$$\bar{T} = T_{SS}\left(1 - \frac{k_{\max}EC_{50}}{R + 1}\right) / k_{ng}$$
$$R = \frac{KC_{50}}{\sqrt[\gamma]{(1 - \bar{E})/(\bar{E} + 1 - E_{\max})}}$$

RESULTS. Steady-state behaviors described by the characteristic curves of model III and the cascade of model I and model IV differ especially for higher concentrations (Fig.1). In particular, the cascade of model I and model IV predicted higher tumor volumes than model III. The novel biomarker-to-tumor model was able to recover consistency between these models: indeed, tumor growth modulation induced by biomarker inhibition is compatible with that induced by drug-concentration. The new model eases the comparison and understanding of the relationships between parameters of drug-to-biomarker and biomarker-to-tumor submodels. This paves the way to more precise predictions of tumor growth inhibition resulting from different protocols, but also from administration of different drugs, provided that they act on the same causal pathway. In order to investigate the differences between models predictions, the tumor growth profiles were simulated with two experiments: Example 1 (reproduction of study 3 in [4], see Fig.2) and Example 2 (1 daily dose for 150 days, in order to reach steady-state, see Fig.3) referring to low and high levels of concentrations, respectively.



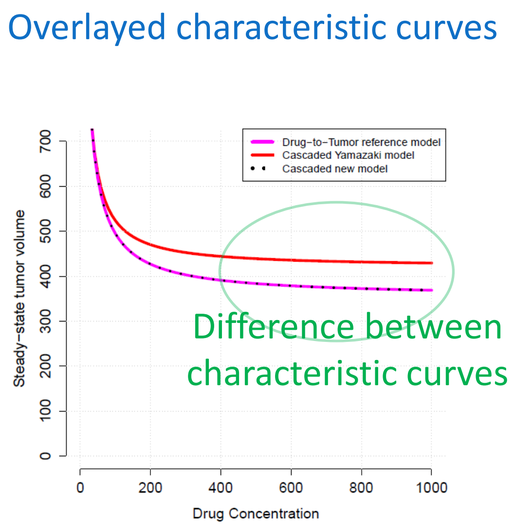


Fig.1 Overlay plot of the characteristic curves of the three models.

Findings: at high steady-state concentration the reference drug-to-tumor model and the cascade drug-to-biomarker-to-tumor model behave differently.
Solutions: introduce new matched drug-to-biomarker-to-tumor model.

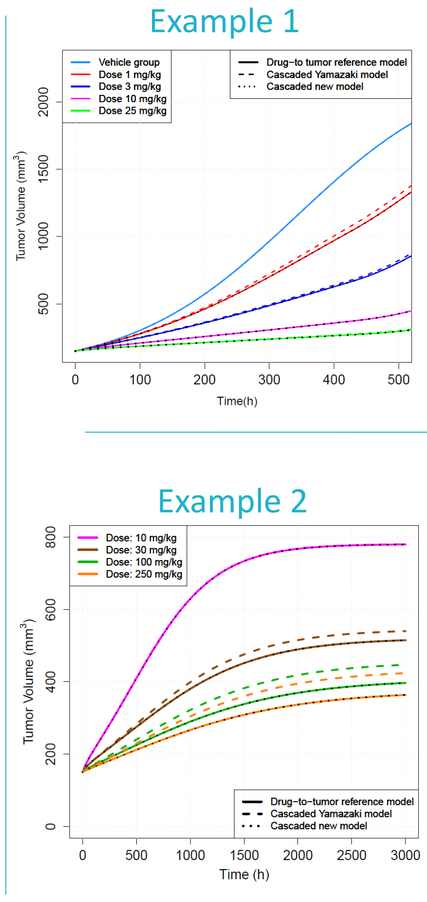


Fig.2 Reproduction of Study 3 reported in [4], simulated with model III (drug-driven Y. model), the cascaded of model I with model IV (cascaded Y. model), and the new matched biomarker-to-tumor model (cascaded matched model).

Findings: In Example 1, all models yields quite consistent predictions (low levels of drug concentration).

Fig.3 Simulated new experiment at higher doses corresponding to the concentration in the discrepancy characteristic curves ranges.

Findings: In Example 2, the Yamazaki-cascaded model behaves differently from the reference drug-to-tumor model which is in fact consistent with the new "matched" (i.e. reverse-engineered to comply with the steady state consistency requirement) cascaded model. The discrepancy is more evident when the drug-to-biomarker model is working near to saturation conditions ($C > EC_{50}$).

CONCLUSIONS With reference to xenograft experiments, we analysed the steady-state consistency between a drug-to-tumor model and a biomarker-to-tumor one taken from [4]. Since a discernible discrepancy was highlighted, we proposed a novel biomarker-to-tumor model that ensures steady-state consistency. The proposed model was validated on both steady-state characteristic curves and simulated PK/PD experiments.

This work was supported by the DDMoRe project (www.ddmore.eu).

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