BIOMARKER-DRIVEN MODELS OF TUMOUR GROWTH INHIBITION IN PRECLINICAL ANIMAL STUDIES

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INTRODUCTION.

A biomarker – in the context of mechanism-based PK-PD modeling - is a measurement that defines quantitatively a process on the causal path between drug administration and clinical outcome [1]. The aim of this work is to investigate mathematical models that link biomarker modulation (due to the action of anticancer compounds) to tumour growth inhibition in preclinical experimental models. A major goal is the derivation of tumour growth inhibition models that are biomarker-driven rather than directly linked to drug pharmacokinetics. Being dependent on measurements that are likely to be more directly related to the mode of action to tumour response, this modeling approach should provide more accurate predictions of the antitumor treatment effects.

METHODS.

Models: To mathematically describe tumour growth, we propose two biomarker-driven version of the standard TGI Simeoni model [2,3], herein named B1-Simeoni and B2-Simeoni, where the input is not represented by the drug concentration but depends on the drug-induced biomarker modulation. Constraints on the potency parameter were derived to ensure consistency of the outcomes between the B-Simeoni models and the TGI-Simeoni. This was done by equating the steady-state tumour volumes predicted following constant drug concentrations. Herein we reported schematic representations and differential equations describing the three different models considered in this work, where c(t) and B(t) denote the drug concentration and biomarker concentration respectively.

A) TGI Simeoni model

$$\dot{x}_1(t) = \frac{\lambda_0 x_1(t)}{[1+(\frac{\lambda_0}{\lambda_1} w(t))^{\psi}]^{\psi^{-1}}} - k_2 c(t) x_1(t) \quad x_1(0) = w_0$$

$$\dot{x}_2(t) = k_2 c(t) x_1(t) - k_1 x_2(t) \quad x_2(0) = 0$$

$$\dot{x}_3(t) = k_1 x_2(t) - k_1 x_3(t) \quad x_3(0) = 0$$

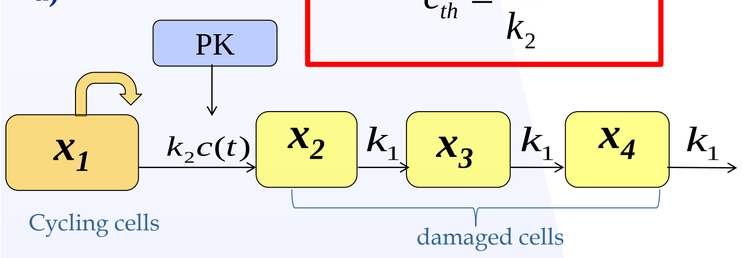
$$\dot{x}_4(t) = k_1 x_3(t) - k_1 x_4(t) \quad x_4(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$$

Threshold concentration

$$\bar{c}_{th} = \frac{\lambda_0}{k_2}$$

a)



B) B1-Simeoni model

$$\dot{B}(t) = k_{in}(1 - \frac{c(t)}{(IC_{50} + c(t))}) - k_{out} B(t) \quad B(0) = B_0 = \frac{k_{in}}{k_{out}}$$

$$\dot{x}_1(t) = \frac{\lambda_0 x_1(t)}{[1+(\frac{\lambda_0}{\lambda_1} w(t))^{\psi}]^{\psi^{-1}}} - \tilde{k}_2 I(t) x_1(t) \quad x_1(0) = w_0$$

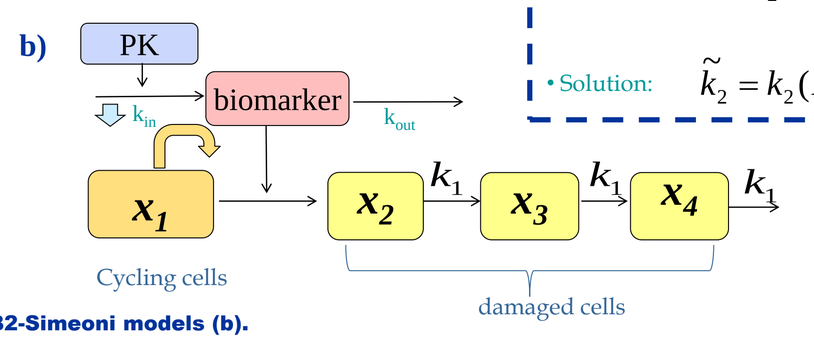
$$\dot{x}_2(t) = \tilde{k}_2 I(t) x_1(t) - k_1 x_2(t) \quad x_2(0) = 0$$

$$\dot{x}_3(t) = k_1 x_2(t) - k_1 x_3(t) \quad x_3(0) = 0$$

$$\dot{x}_4(t) = k_1 x_3(t) - k_1 x_4(t) \quad x_4(0) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$$

b)



Biomarker steady-state relationships

$$I(t) = 1 - \frac{B(t)}{B_0}$$

$$c(t) = \bar{c} \Rightarrow \bar{I} = \bar{I}(\bar{c}) = \frac{\bar{c}}{IC_{50} + \bar{c}}$$

$$\Rightarrow \bar{c} = \bar{c}(\bar{I}) = \frac{IC_{50}\bar{I}}{1 - \bar{I}}$$

Remark: connection between TGI and B1-Simeoni Steady-state consistency:

- Requirement: $\tilde{k}_2 I(\bar{c}_{th}) = k_2 \bar{c}_{th}$
- Solution: $\tilde{k}_2 = k_2(IC_{50} + \bar{c}_{th})$

C) B2-Simeoni model

$$\dot{B}(t) = k_{in}(1 - \frac{c(t)}{(IC_{50} + c(t))}) - k_{out} B(t) \quad B(0) = B_0 = \frac{k_{in}}{k_{out}}$$

$$\dot{x}_1(t) = \frac{\lambda_0 x_1(t)}{[1+(\frac{\lambda_0}{\lambda_1} w(t))^{\psi}]^{\psi^{-1}}} - k_2 f(I(t)) x_1(t) \quad x_1(0) = w_0$$

$$\dot{x}_2(t) = k_2 f(I(t)) x_1(t) - k_1 x_2(t) \quad x_2(0) = 0$$

$$\dot{x}_3(t) = k_1 x_2(t) - k_1 x_3(t) \quad x_3(t) = 0$$

$$\dot{x}_4(t) = k_1 x_3(t) - k_1 x_4(t) \quad x_4(t) = 0$$

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$$

B2 Steady-state TGI consistency

How to choose *f(I)*?

When $c(t) = \bar{c}$ it should be

$$f(\bar{I}(\bar{c})) = \bar{c}$$

Solution: $f(I) = \bar{c}(I) = \frac{IC_{50} I}{1 - I}$

Figure 1: block diagrams of TGI–Simeoni model (a), and B1-Simeoni and B2-Simeoni models (b).

Data: Literature [4] data of tumour growth inhibition and and biomarker concentration were used.

Approach: The model were fitted to the data. Exponential IIV was included on all parameters. Proportional residual variability was adopted. To test the performance of the models, a simulation-based approach was also considered: data sets were generated using the three models A), B), and C), using the same experimental design, assuming a administration time window of 480 hours [120;600] and the model parameters obtained in the previous step. All datasets were analysed using each of the models.

Software: Both simulation and fitting of data were performed with NONMEM version VI.

RESULTS-Fitting Experimental data.

The new models and the standard TGI model were fitted to the data. Fittings are reported in Fig. 2, while Tab.1 reports estimated parameters. All the models performed satisfactorily.

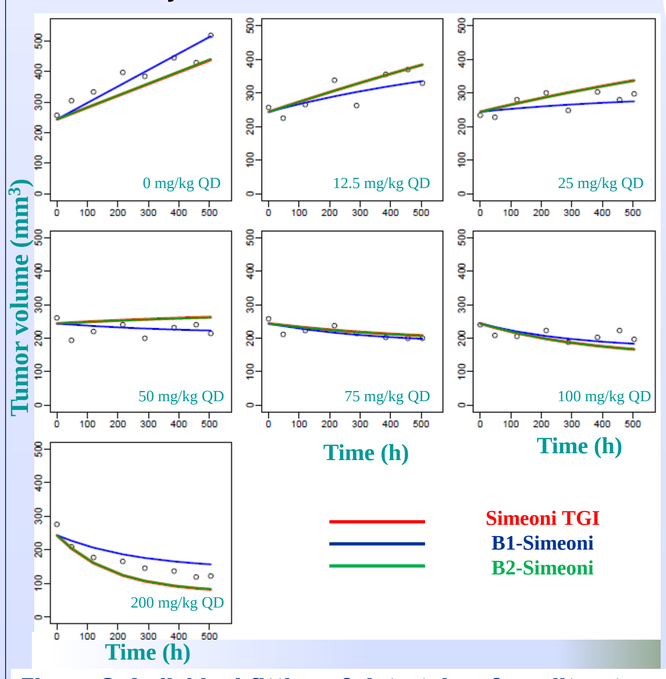


Figure 2: Individual fitting of data taken from literature [4] performed by the proposed three models. The damage rate constant k_1 was fixed to 5 h^{-1}.

	Simeoni TGI Θ (CV %)	B1-Simeoni Θ (CV %)	B2-Simeoni Θ (CV%)
w_0 (mm^3)	243 (2.8)	243 (2.72)	243 (2.8)
λ_1 $(mm^3 h^{-1})$	0.388 (19.38)	0.54 (7.38)	0.392 (18.67)
k_2 *	0.00114 (22.92)	0.00499 (7.71)	0.00119 (17)
SIGMA	1140 (20.35)	634 (17.66)	1110 (19.9)

Table 1: Estimated parameters of the three models. *The units of k_2 are *(L μmol⁻¹h⁻¹)* both for TGI Simeoni and B2-Simeoni models, and *(h^{-1})* for the B1-Simeoni model.

	Biomarker Θ (CV %)
k_{in}(*fluorescence intensity* h^{-1})	68100 (28.5)
k_{out} (h^{-1})	4.05 (27.9)
IC_{50} $(\mu mol\ l^{-1})$	0.768 (24.2)

Table 2: Estimated parameters of the biomarker model.

RESULTS-Fitting of Simulated data.

Simulation parameters, inspired by those estimated on the experimental data are reported in Tab. 3 together with associated estimates. A constant CV error model was adopted both in simulation and fitting. Parameter estimates were satisfactory both in terms of data fitting and CV values.

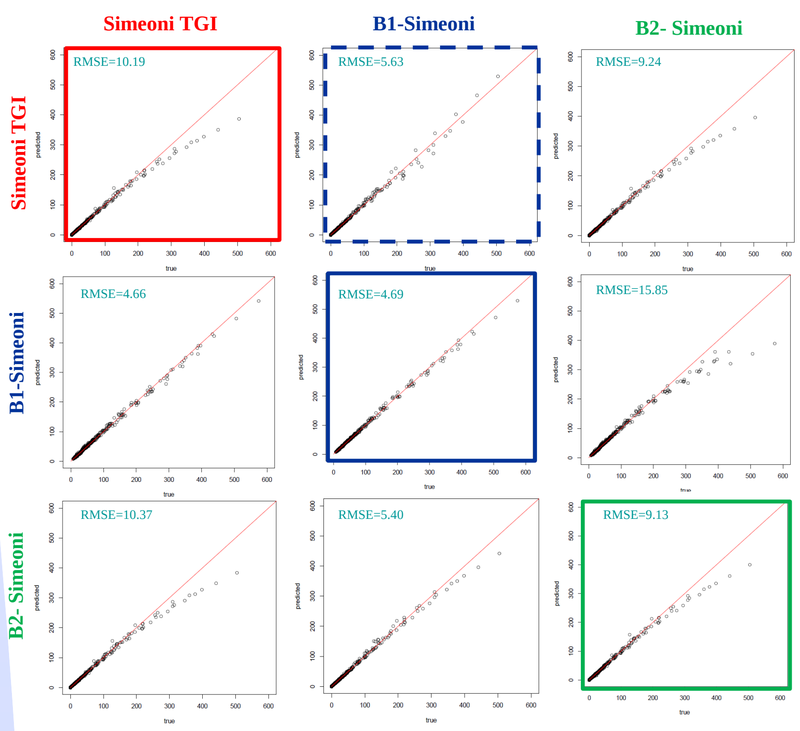


Figure 3: Goodness of fit of data simulated and fitted by the three models

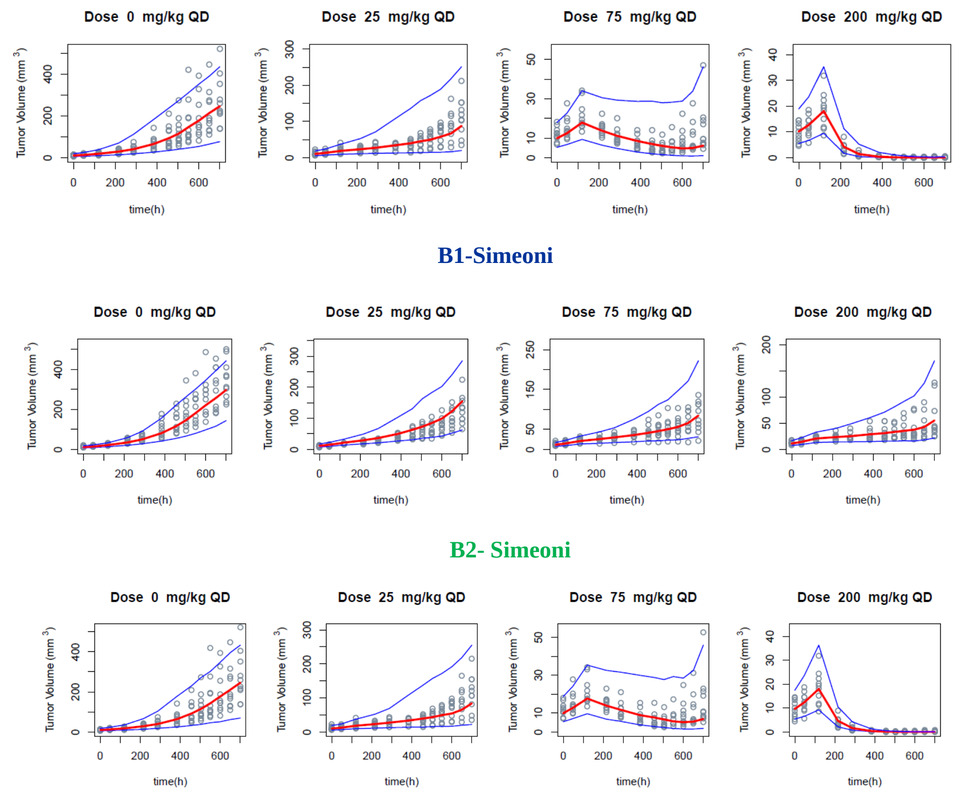


Figure 4: VPC of the three models corresponding to the cases on the main diagonal of Fig.3. Median (red), 5th (blue),95th (blue) are shown.

	Simulation Θ	Simulation Ω	Simeoni TGI Θ (CV %)	Simeoni TGI Ω (CV %)	B1-Simeoni Θ (CV %)	B1-Simeoni Ω (CV %)	B2-Simeoni Θ(CV%)	B2-Simeoni Ω (CV%)
w_0 (mm^3)	10	0.0861	10 (6.2)	0.349 (11.4)	11.4 (4.4)	0.0551 (21.4)	10 (6.45)	0.122 (23.7)
λ_0 (h^{-1})	0.005	0.0222	0.00480 (1.36)	0.273 (15.5)	0.00508 (3.64)	0.0274 (26.97)	0.00487 (3.26)	0.0718 (20.9)
λ_1 $(mm^3 h^{-1})$	1	0.0222	0.727 (8.33)	0 FIX	0.805 (7)	0.0171 (140)	0.754 (8)	0.000127 (122)
k_2 $(L\ \mu mol^{-1} h^{-1})$	0.00499	0.0222	0.00412 (0.4)	0.177 (7.7)			0.00420 (3.4)	0 FIX
$\tilde{k}_2$ (h^{-1})	0.00499	0.0222			0.00511 (7.25)	0 FIX		
SIGMA	0.0095		0.0146 (19.3)		0.0121 (11.9)		0.0185 (12.3)	

Table 3: Simulation and Estimated parameters of the three models corresponding to the cases on the main diagonal of Fig.3.

CONCLUSIONS

Building on the Simeoni TGI model, different mathematical models linking tumor growth inhibition and biomarker modulation have been proposed. Steady-state relationships were used to ensure consistency between the steady-state response of the new models and the standard TGI. This made possible to express the potency parameters of the newly proposed B-Simeoni models as a function of the potency parameter of the standard Simeoni model, thus reducing unnecessary redundancy. Both experimental individual data and simulated population ones confirmed model suitability.

REFERENCES

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