Evaluation of a PK/PD DEB-based model for tumor-in-host growth kinetics under anticancer treatment

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INTRODUCTION: Mathematical models describing the tumor growth in animals often neglect the relationship between tumor and host organism. To overcome this limitation, a mechanistic PK/PD model combining the Dynamic Energy Budget (DEB) theory [2] with the Simeoni Tumor Growth Inhibition (TGI) model [3] and describing both the dynamics of the tumor-host interaction and the effect of anticancer treatments was developed [1].

OBJECTIVES: A new identification strategy for a slightly revised model formulation has been tested on data collected during 9 different experiments involving six novel anticancer candidates and six drugs already available on the market. Moreover, the tumor growth in control groups has been compared between the DEB-TGI model and the widely used Simeoni TGI model.

METHODS:

Datasets: Data for model validation refer to xenograft experiments conducted on Harlan Sprague Dawley mice. In these experiments the tumor and the net body weight of control and treated animals were collected at different doses; average data were considered. The PKs were derived from separate studies. The reported example involves male mice treated with vehicle (arm a) and three groups treated with drug A following different schedules and doses (arms b, c and d).

The model:

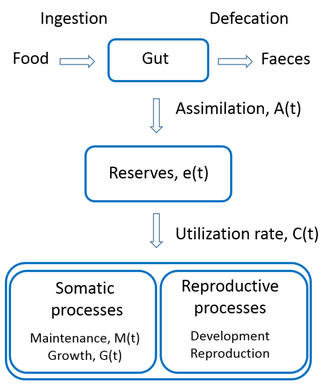
e: reserve amount

V: organism structural volume

V_{u1}: tumor volume of proliferating cells

V_{u2}, V_{u3}, V_{u4}: tumor volume of non-proliferating cells in the mortality chain

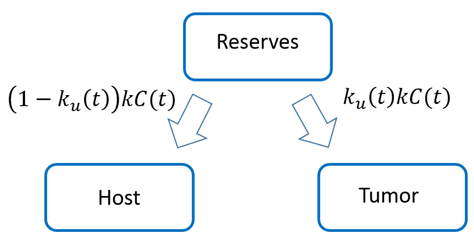
Tumor-free individual model:



Parameter	Dimension	Interpretation
ν	LT^{-1}	Energy conductance
ρ	-	Food-supply coefficient
$V_{1\infty}$	L^3	Maximum structural volume
g	-	Growth energy-investment ratio
m	T^{-1}	Maintenance-rate coefficient
ξ	-	Scaled reserve specific weight

Physiological parameters

Tumor-bearing individual model:



Parameter	Dimension	Interpretation
μ_u	-	Coefficient of gluttony
g_u	-	Tumor growth energy-investment ratio
m_u	T^{-1}	Tumor maintenance-rate coefficient
ω	-	Thermodynamic efficiency coefficient

Tumor growth parameters

Tumor-in-host DEB-based TGI model:

$$\frac{dV}{dt} > 0$$

$$\begin{cases} \frac{de(t)}{dt} = \frac{\nu}{V^{1/3}(t)}\left(\rho\left(\frac{V_{1\infty}}{V_{u1}(t)+V(t)}\right)^{2/3} - e(t)\right) \\ \frac{dV(t)}{dt} = \frac{(1-k_u(t))\nu e(t)V^{2/3}(t) - gmV(t)}{g+(1-k_u(t))e(t)} \\ \frac{dV_{u1}(t)}{dt} = \frac{(\nu V^{2/3}(t)+mV(t))gk_u(t)e(t)}{gg_u+(1-k_u(t))g_u e(t)} - (m_u - k_2 c(t))V_{u1}(t) \\ \frac{dV_{u2}(t)}{dt} = k_2 c(t)V_{u1}(t) - k_1 V_{u2}(t) \\ \frac{dV_{u3}(t)}{dt} = k_1 V_{u2}(t) - k_1 V_{u3}(t) \\ \frac{dV_{u4}(t)}{dt} = k_1 V_{u3}(t) - k_1 V_{u4}(t) \\ \rho(t) = \rho_b\left(1 - \frac{c(t)}{C_{50}+c(t)}\right) \\ W(t) = d_V(1+\xi e(t))V(t) \\ W_u(t) = d_{Vu}(V_{u1}(t)+V_{u2}(t)+V_{u3}(t)+V_{u4}(t)) \end{cases}$$

$$-\delta_{V_{Max}} < \frac{dV}{dt} < 0$$

$$\begin{cases} \frac{dV(t)}{dt} = \frac{(1-k_u(t))\nu e(t)V^{2/3}(t) - gmV(t)}{(1-k_u(t))(e(t)+\omega g)} \\ \frac{dV_{u1}(t)}{dt} = \left(\frac{mg\mu_u}{g_u} - m_u\right)V_{u1}(t) - k_2 c(t)V_{u1}(t) \end{cases}$$

$$\frac{dV}{dt} < -\delta_{V_{Max}}$$

$$\begin{cases} \frac{dV(t)}{dt} = -\delta_{V_{Max}} \\ \frac{dV_{u1}(t)}{dt} = \frac{k_u(t)}{g_u}\left(e(t)\nu V(t)^{2/3} + \delta_{V_{Max}}(e(t)+\omega g)\right) - (m_u + k_2 c(t))V_{u1}(t) \end{cases}$$

Parameter	Dimension	Interpretation
K_1	T^{-1}	First-order rate constant of transit
K_2	(ConcT^{-1}	Drug potency
C_{50}	$Conc$	Half maximal inhibitory concentration

Drug related parameters

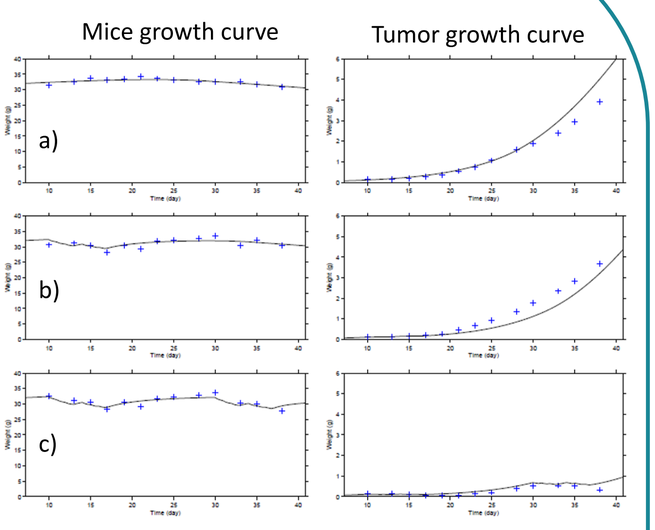
RESULTS

Identification strategy:

1.Tumor-free model were identified on growth data.

2. Obtained values were used to find e_0 at the beginning of the experiment.

3. Keeping fixed the tumor-free model parameters and e_0 to the values previously estimated, the tumor-related and the drug-related parameters were simultaneously estimated on the control and the treated groups.



Physiological parameters

ξ	g	ν	$V_{1\infty}$	m	e_0	w_0	ρ
-	-	$[cm/week]$	$[cm^3]$	$[1/day]$	-	g	-
0.2116	15	8.82	31.2	0.0267	0	1	1
-	(6%)	(4%)	(3%)	-	-	-	-

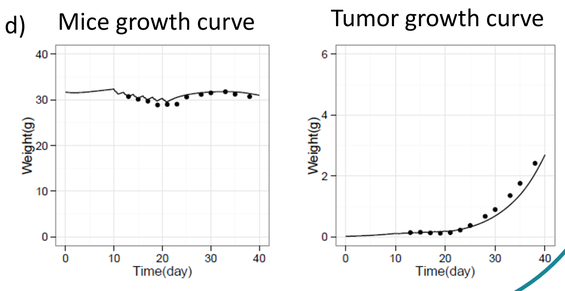
Tumor-related and drug-related parameters

μ_u	g_u	m_u	$\delta_{V_{max}}$	V_{u10}	W_0	ρ_b
-	-	$[1/day]$ -	$[cm^3]$	g	-	
4.11	12.1	0.000258	0.131	0.0202	31.7	-
(28%)	(26%)	(> 100%)	(48%)	(30%)	(2%)	-

k_1	k_2	C_{50}
$[1/day]$	$[ml/mgday]$	$[mg/ml]$
55.5	68.3	0.000127
(> 100%)	(14%)	(55%)

DEB-TGI predictive power

Estimated parameters were used to obtain the body weight and the tumor weight predictions for arm d involving drug A administered in a different schedule and dose.



Comparative study: DEB-TGI and Simeoni TGI model:

A dynamic system analysis showed that, as the Simeoni model, the DEB-TGI model predicts an exponential growth of the tumor in the early phases of its development.

The parameter combination describing the exponential growth rate is independent of the structural biomass and the energy reserve and shows that both tumor characteristics and host conditions lead the tumor growth.

$$\tilde{\lambda_0} = \frac{mg\mu_u}{g_u} - m_u$$

Tumor weights for 9 datasets were simulated by using estimates obtained from the DEB-TGI model identification on the control groups. Then, the Simeoni model was identified on the simulated datasets.

Control group	Tumor line	λ_0	$\tilde{\lambda_0}$
Exp 1	A2780	0.497	0.487
Exp 2	A2780	0.354	0.478
Exp 3	A2780	0.464	0.481
Exp 4	A2780	0.373	0.441
Exp 5	A2780	0.432	0.467
Exp 6	HTC116	0.216	0.27
Exp 7	A375	0.221	0.21
Exp 8	A375	0.148	0.152
Exp 9	A375	0.139	0.134

The two exponential growth rates have always comparable values.

Tumor weight threshold W_{th} characterizing the switch between the exponential and the linear growth in the Simeoni model was calculated: it occurs always when the tumor slows down its growth, while the host degrades its structural biomass with a constant maximum rate and the energy demand remains unfulfilled.

CONCLUSIONS: The tumor-in-host DEB-based model confirmed its good capability in describing tumor and host body growth even when an anticancer drug is administered; it also provides a quantitative measurement of the drug potency (K_2) and of the drug side effect (C_{50}). Moreover, from the comparative analysis a physiological meaning has been given to the transition from the exponential to the linear phase for a specific threshold weight of tumor cells, enforcing the robustness and the validity of the Simeoni TGI empirical function.

REFERENCES:[1] Terranova N., Del Bene F., Germani M., Rocchetti M., Magni P. An energy based model able to describe the effect of anticancer drugs on tumor growth and host body weight. PAGE 23 (2014) Abstr 3176.

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[3] M. Simeoni, P. Magni, C. Cammia, G. De Nicolao, V. Croci, E. Pesenti, M. Germani, I. Poggesi, and M. Rocchetti. Predictive pharmacokinetic pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Research, no. 64, pp. 1094–11 101, 2004.