AN ENERGY BASED MODEL ABLE TO DESCRIBE THE EFFECT OF ANTICANCER DRUGS ON TUMOR GROWTH AND HOST BODY WEIGHT

N. Terranova [1,5], F. Del Bene[2], M. Germani [3], M. Rocchetti [4] and P. Magni [1]

[1]*Dip. di Ingegneria Industriale e dell'Informazione, Università degli Studi di Pavia, Pavia, Italy,* [2]*Accelera srl, Nerviano, Italy,*
[3]*PKMS, Ablynx nv, Zwijnarde, Belgium,* [4] *Independent Consultant, Rho, Milan, Italy,*
[5]*Merck Institute for Pharmacometrics, Merck Serono S.A., Lausanne, Switzerland.*

MOTIVATION Cachexia is a complication responsible for around 20% of cancer deaths. For this reason, in preclinical pharmacological models, the decrease in the net body weight time course is considered a fundamental toxicological parameter to be evaluated. The energy loss caused by the tumor growth within the body is considered one of the causes of this side effect. Models based on dynamic energy budget (DEB) theory for describing the dynamics of the tumor host interaction are currently available [1]; however the effect of anticancer treatments should also be considered. For this purpose, we have developed a new PK/PD tumor-in-host DEB-based model that includes the Simeoni TGI model [2], able to describe the drug action on the tumor mass.

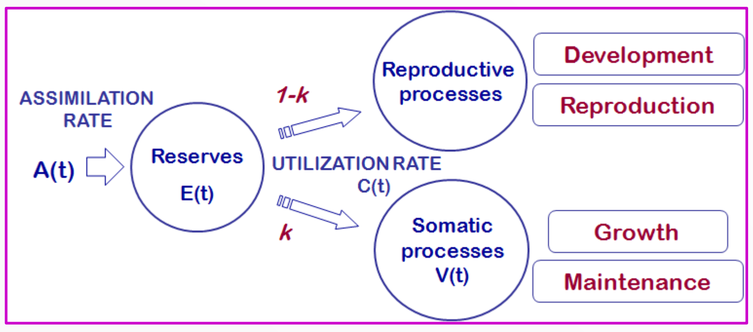
METHODS

Dataset

Pharmacological experiments in Harlan Sprague Dawley mice were performed in Nerviano Medical Sciences labs. In these experiments the tumor and the net weights of control and treated animals were recorded at different doses. The PK profiles were derived from separated studies.
The current example involves male mice treated with vehicle (arm a) and two groups treated with drug A following different schedules (arm b and c).

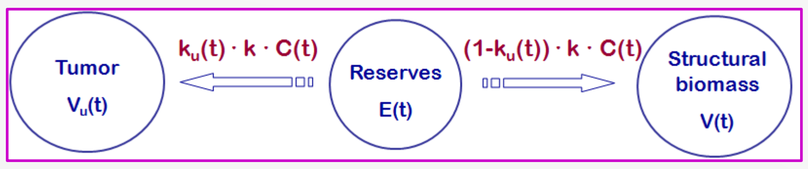
The model

The growth of an health organism and the growth of the tumor mass (in absence of a drug treatment – control group) can be described by using the model developed by Leeuwen et al. [1]. The model has been modified and extended for including the drug treatment following the strategy proposed by a largely used preclinical TGI model [2]. In particular, in the original tumor growth function the term representing the drug action on the proliferating cells, and the mortality chain have been included.



DEB theory: the physiological model

Tumor-bearing individual: energy allocation *k*-rule



Parameters of the 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

Tumor growth parameters

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

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

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

- 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

The differential equations that change in the two cases different from dV/dt>0 are respectively:

- Case $-a < \frac{dV}{dt} < 0$

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

- Case $\frac{dV}{dt} < -a$

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

Modifications of the model structure to describe other expected behaviors:
- **drug effect on host body weight**: food supply coefficient ρ modified to consider the reduced ability in introducing energy by food intake during treatment;
- **tumor growth saturation**: a maximum degradation rate decreasing to a threshold introduced into the model through a new parameter a.

Physiological parameters of the tumor-free model

ξ -	g -	ν $[cm/day]$	$V_{1\infty}$ $[cm^3]$	m $[1/day]$	e_0 -	ρ -
0.59	16.06	1.15	20.97	0.026	1	1

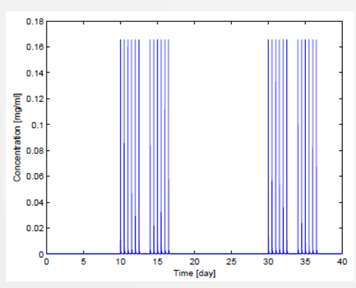
Tumor-related parameters estimates of the tumor-bearing model identified on the control arm

μ_u -	g_u -	m_u $[1/day]$	w_0 $[g]$	V_{u1_0} $[cm^3]$	a $[cm^3]$
4.14 (> 100%)	10.5 (> 100%)	$6e^{-10}$ (> 100%)	33 (3.4%)	0.018 (97%)	0.0027 (> 100%)

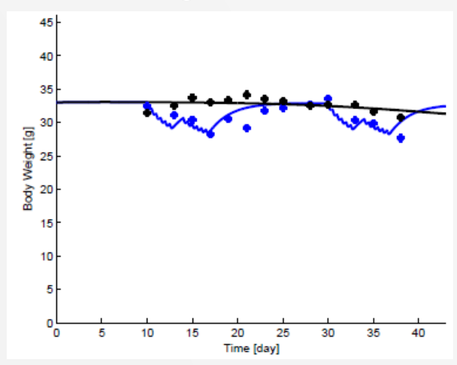
Drug-related parameter estimates of the new TGI DEB-based model identified on the treated groups

(b)			(c)		
k_1 $[1/day]$	k_2 $[microgml/day]$	k_{org} $[ml/mg]$	k_1 $[1/day]$	k_2 $[microgml/day]$	k_{org} $[ml/mg]$
2.93 (66%)	83.6 (5%)	1675 (11%)	$1e^{+3}$ (1.8%)	38.7 (9%)	2922 (3%)

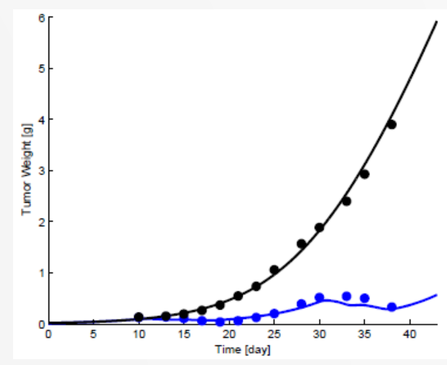
RESULTS



Mice growth curve

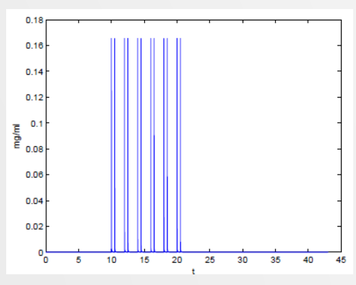


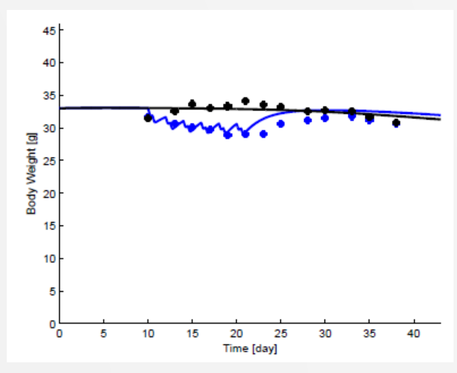
Tumor growth curve

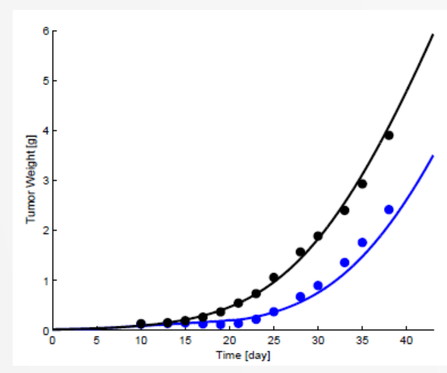


(b)

(c)







CONCLUSIONS: A physiological meaning has been given to the transition from the exponential to the linear phase for a specific weight threshold of tumor cells proposed by the Simeoni TGI model. The new tumor-in-host DEB-based model has been tested on different experiments showing good capability in describing tumor growth and host body growth even when an anticancer drug is administered. This allows to compare the efficacy and toxicity effects of different schedules providing an efficient tool for therapy optimization.

REFERENCES
[1] I. V. Leeuwen et al., *British Journal of Cancer, no. 89, pp. 2254–2263, 2003.*
[2] M. Simeoni et al., *Cancer Research, no. 64, pp.* 1094–11 101, 2004.

Acknowledgements: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Program (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also supported by financial contribution from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.