The development of tumor resistance to chemotherapy: a population dynamics interpretation (V03)

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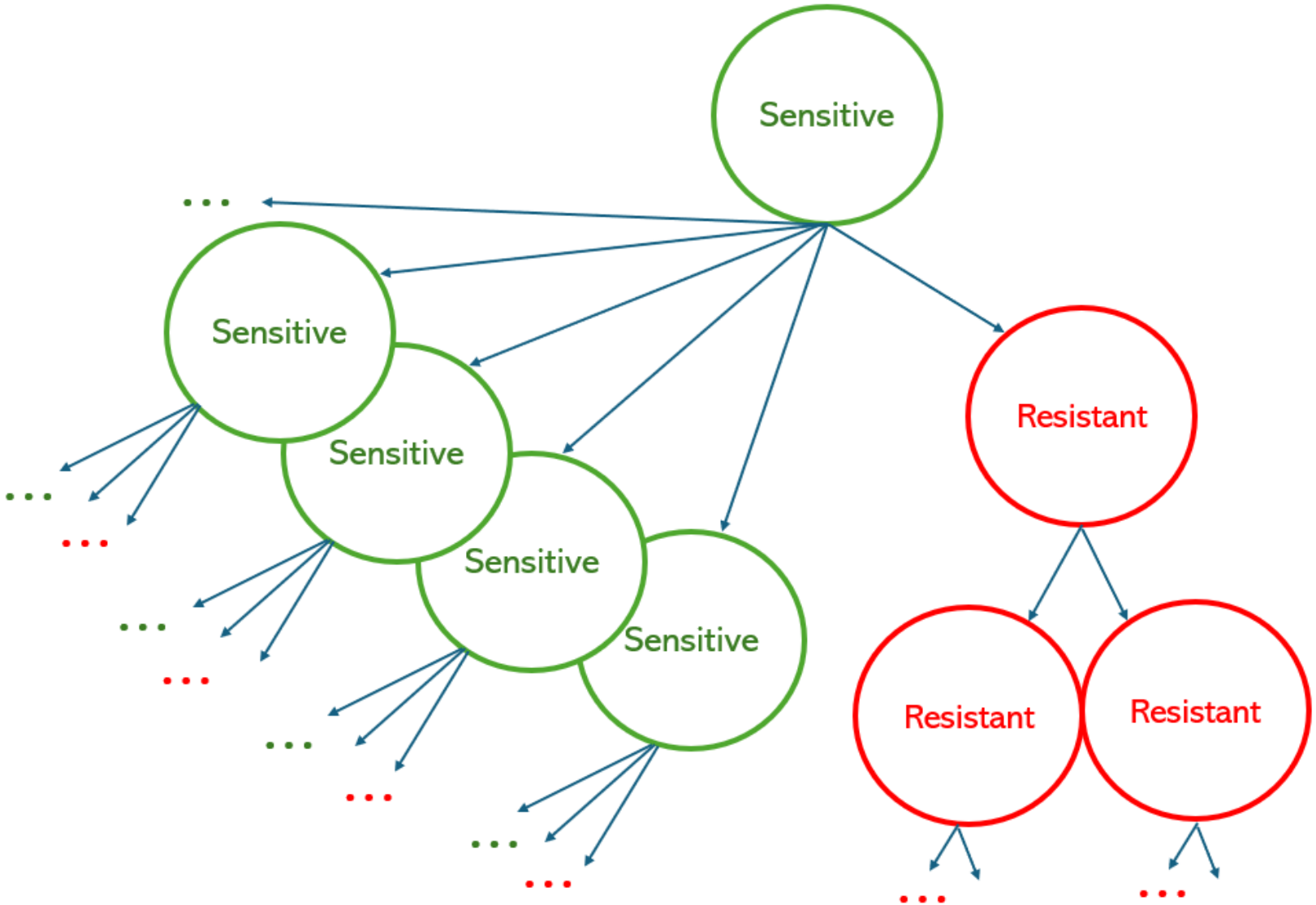
Abstract

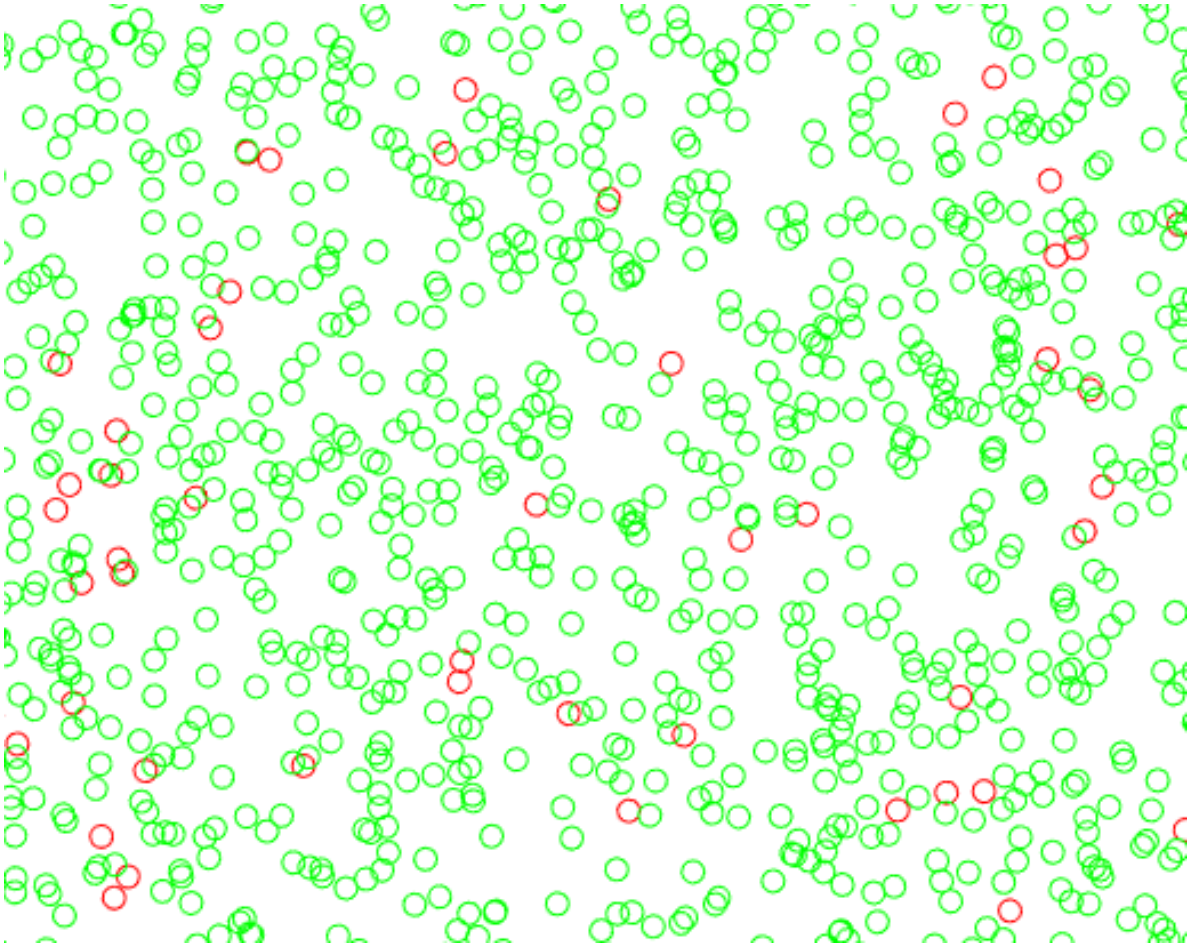
Cancer is a complex and constantly evolving disease: cancer cells can mutate and adapt to adverse conditions, making the tumor resistant to chemotherapy.
This phenomenon can be represented by a mathematical model that hypothesizes the ability of cells to randomly switch metabolic set-up, from a more efficient but drug-sensitive one to a less efficient, but drug-resistant one. The end result is the coexistence of two (or theoretically more) cell populations, potentially competing for resources.
The dynamics of the coexistence of these populations can explain why chemotherapy regimens, initially exhibiting marked effectiveness in reducing tumor mass, may eventually succeed or fail, depending on the drug-sensitivity and growth potential of the considered tumor cell populations.
A mathematical model incorporating such tumor cell population dynamics helps interpret the results of experiments of doxorubicin treatment of transplanted cancer in mice.

Not all tumor cells are created equal...



Schematic representation of the cell proliferation

... therefore cell populations are heterogeneous



Experimental setting

A genetically engineered **mouse model of breast cancer** (DNA repair gene, and p53, a regulator of cell cycle and genome stability, were knocked out in breast epithelial cells) is used to test new chemotherapy regimens.

The resulting mammary tumors highly **resemble** the Brca1-linked, triple-negative, **hereditary breast cancer in humans**: the molecular, immunohistochemical, morphological, and genetic characteristics are almost indistinguishable from their human counterpart.

Moreover, these tumors **respond to chemotherapy** in a similar fashion: **initial** treatment with doxorubicin, docetaxel, or cisplatin significantly reduces tumor size and induces **remission**; however, **long-term** therapy often fails due to the emergence of drug **resistance**.

Experimental Protocol

Mammary tumors were transplanted into 49 mice, divided in two groups:

- G1: The mice received a first **4 mg/kg** dose of PLD (pegylated liposomal doxorubicin) when the tumor volume reached 200μL.
- G2: The mice received a first **6 mg/kg** dose of PLD when the tumor volume reached 200μL.

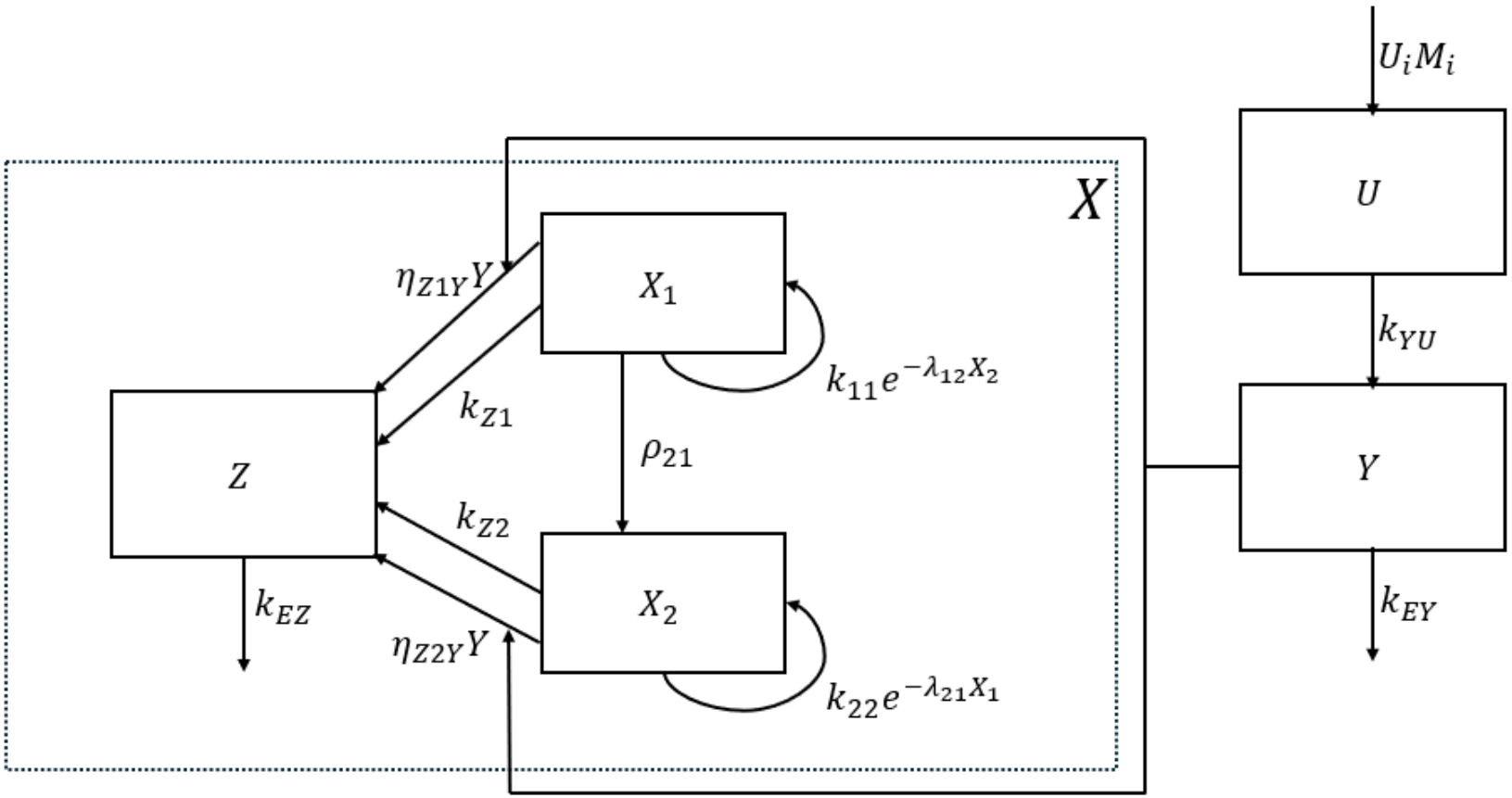
After the first dosage, the therapy was decided according to two different strategies:

- for the G1 group, chemotherapy doses were optimized by using an NMPC[1] (nonlinear model predictive controller);
- for the G2, a mixed-effect model was used for parameter identification, the doses were calculated using a two-compartment model for drug pharmacokinetics and a nonlinear pharmacodynamics and tumor dynamics model[2]. Therapy was tailored based on the model parameters, with the aim of obtaining a maximal effect with minimal dose.

[1] Kovács L., et al, Experimental Closed-Loop Control of Breast Cancer in Mice, https://www.hindawi.com/journals/complexity/2022/9348166/

[2] Kovács L., et al, Positive Impulsive Control of Tumor Therapy—A Cyber-Medical Approach, https://ieeexplore.ieee.org/document/10255720

The Mathematical Model



The model is structured into two sub-models, including 7 equations, 5 differential and 2 algebraic, for a total of 18 parameters

Sub-model for therapy administration

$$\frac{dU}{dt} = -k_{YU}U + \sum_{i=1}^{N} \delta(t - t_i)U_i M_i, U(t_0) = U_0 \quad (1)$$

$$\frac{dY}{dt} = k_{YU}U - k_{EY}Y, Y(t_0) = Y_0 \quad (2)$$

- U represents the kinetics of the administered drug
- U_i is the i-th dose of drug, administered at time t_i, with N is the total number of doses
- M_i is the mass of the mouse at time t_i
- Y represents the bioavailable drug that produces the effect on tumor cells

Sub-model for tumor growth:

$$\frac{dX_1}{dt} = k_{11} X_1 e^{-\lambda_{12} X_2} - \rho_{21} X_1 - k_{Z1} X_1 - \eta_{Z1Y} Y X_1 \ , \quad X_1(t_0) = X_{10} \tag{3}$$

$$\frac{dX_2}{dt} = \rho_{21} X_1 + k_{22} e^{-\lambda_{21} X_1} X_2 - k_{Z2} X_2 - \eta_{Z2Y} Y X_2 \ , \quad X_2(t_0) = X_{20} \tag{4}$$

$$\frac{dZ}{dt} = k_{Z1} X_1 + \eta_{Z1Y} Y X_1 + k_{Z2} X_2 + \eta_{Z2Y} Y X_2 - k_{EZ} Z \ , \quad Z(t_0) = Z_0 \tag{5}$$

$$X = X_1 + X_2 + Z \ , \ X(t_0) = X_0 = X_{10} + X_{20} + Z_0 \tag{6}$$

$$V = \rho_{VX} X \ , \ V(t_0) = \rho_{VX} X_0 \tag{7}$$

where:

- X_1 is the population of cells sensitive to the therapy
- X_2 is the population of cells resistant to the therapy
- Z represents dead cells
- X is the total amount of cells
- V represents the volume of the tumor mass

Parameter Estimation

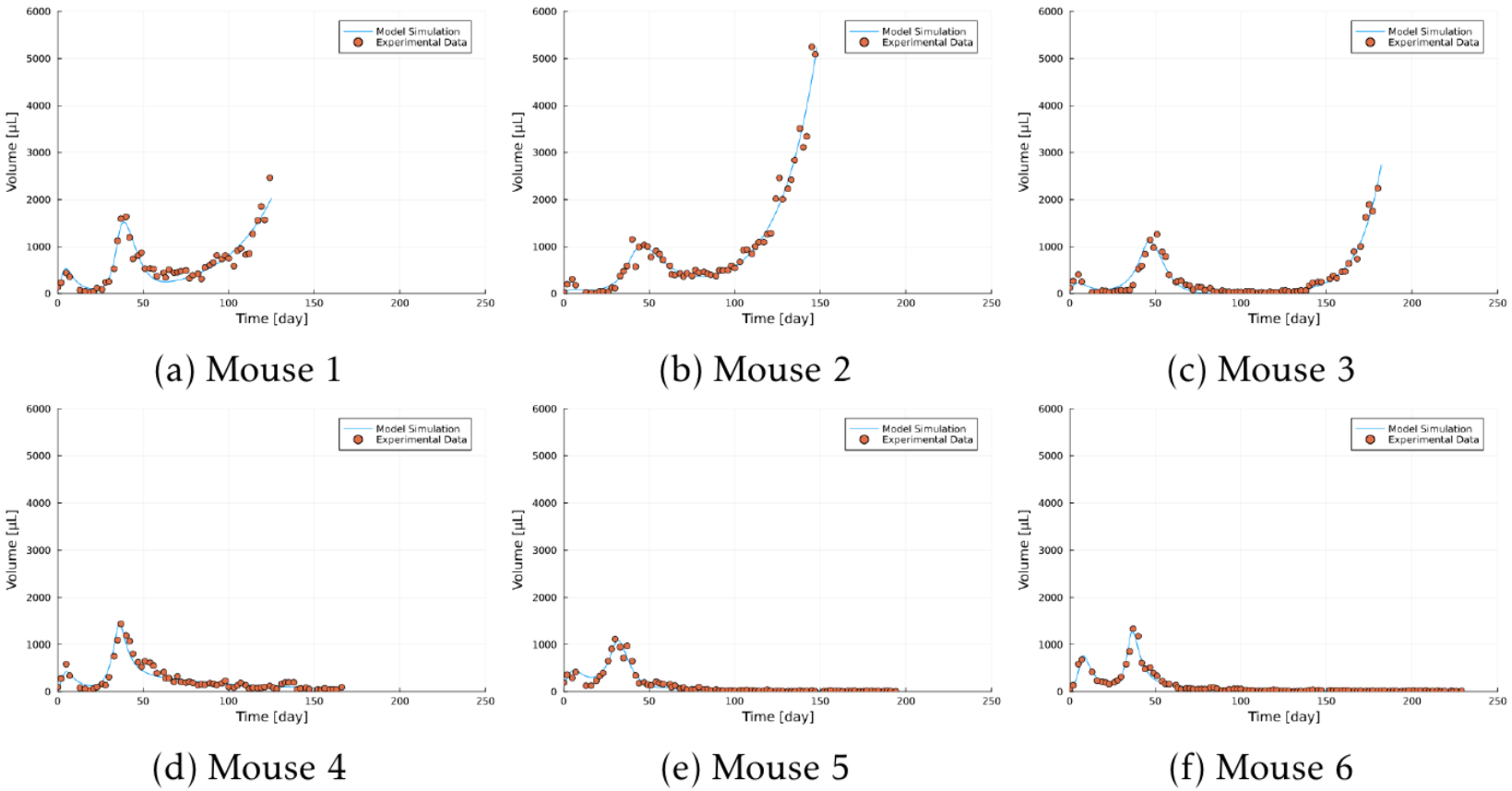
The model was adapted on data obtained from the experimental procedure described above.

Data over time (observed tumor volume for about 150 days) from six mice of the G1 group were used to obtain mouse-specific parameter estimates. Each mouse presented about 50 experimental time-points and the parameter vector consisted of 6 free parameters.

The mice were chosen so that three of them (“Resistant”) eventually developed uncontrollable, expanding tumor size, while the other three (“Non-resistant”) showed reduction of tumor size until eventual disappearance (within the time-frame of the experiment). The model was **identical** for the two groups.

The algorithm used for optimizing the Ordinary Least Squares (OLS) loss function was the Nelder-Mead method.

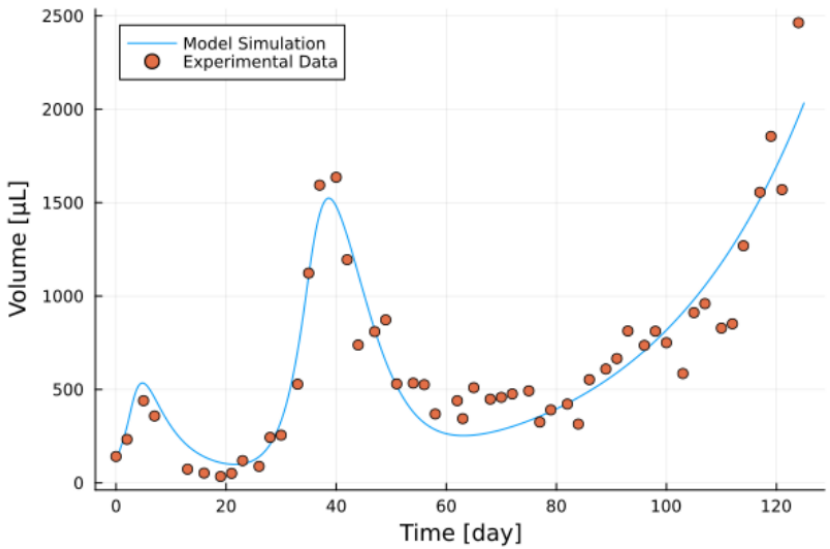
Results



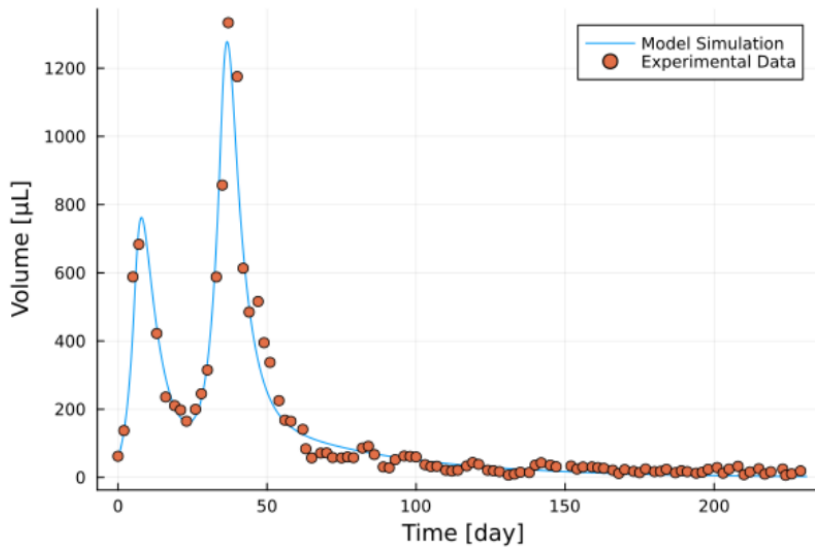
(a) Mouse 1 (b) Mouse 2 (c) Mouse 3

(d) Mouse 4 (e) Mouse 5 (f) Mouse 6

Fitting from the estimation procedure. Volume-time model predictions (continuous blue lines) together with observed data (red circles) for the "Resistant" group (mice 1, 2 and 3) and for the "Non-resistant" group (mice 4, 5 and 6).



(a) Mouse 1



(b) Mouse 6

Enlargement of the observed (red circles) and predicted (continuous blue lines) volume-time graphs for mouse 1 ("Resistant") and mouse 6 ("Non-resistant").

Parameter estimates

Table: Model parameter estimates of the "Resistant" group.

Parameters	Mouse 1	Mouse 2	Mouse 3	Mean	Standard Deviations
k_{11}	0.475583	0.273432	0.191653	0.31356	0.14615614
ρ_{21}	0.054943	0.029465	0.000106	0.02817	0.02744105
k_{22}	0.096442	0.106717	0.137548	0.11357	0.02139278
λ_{21}	0.044887	0.001539	0.007941	0.01812	0.02339861
η_{Z1Y}	22.92304	8.355523	10.54997	13.9428	7.85409636
η_{Z2Y}	6.91E-14	0.007749	0.046335	0.01803	0.02481878

Table: Model parameter estimates of the "Non-resistant" group.

Parameters	Mouse 4	Mouse 5	Mouse 6	Mean	Standard Deviations
k_{11}	0.499719	0.252323	0.472718	0.408254	0.135712754
ρ_{21}	0.056246	0.008369	0.02918	0.031265	0.024006644
k_{22}	0.047043	0.051064	0.038818	0.045642	0.00624229
λ_{21}	5.19E-08	3.69E-16	2.92E-12	1.73E-08	2.99599E-08
η_{Z1Y}	22.43253	9.369059	24.22907	18.67689	8.110711154
η_{Z2Y}	0.034729	0.113285	0.034136	0.060717	0.045526682

Comments on the results

- k_{11} and ρ_{21} values are approximately the same in "Resistant" and "Non-resistant" mice: same X_1 dynamics
- similarly, η_{Z1Y} is large in both groups: same chemiotoxic effect on sensitive cells
- k_{22} is almost three times smaller and η_{Z2Y} is more than three times larger in the "Non-resistant" WRT the "Resistant" group: in "Non-resistant" mice X_2 cells replicate slower and are more sensitive to chemiotherapy!
- a substantial λ_{21} in the "Resistant" group points to visible suppression of the "resistant" cells by the "sensitive" cells.
- λ_{21} approximates zero in the "Non-resistant" mice: we are unable to discriminate a two-cell-population from a single-cell-population model.

Future developments

- Extend the parameter estimation procedure to the whole set of the experimental units;
- Parameter estimation with a Non Linear Mixed-Effects approach;

Thank you!

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