SPATIAL MODELING OF TUMOR DRUG RESISTANCE: THE CASE OF GIST LIVER METASTASES

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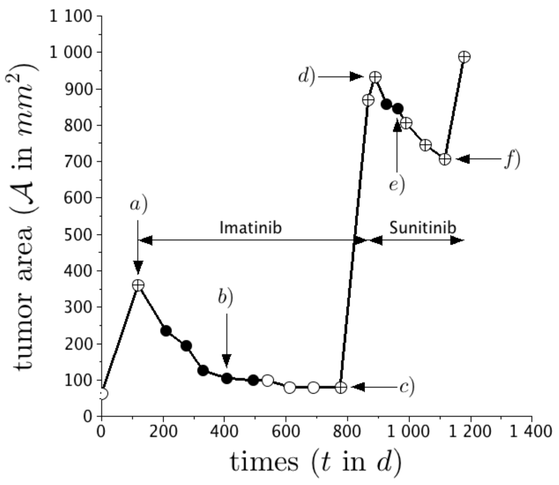
PROBLEM

The **liver** is one of the main target organs for distant spread and colonization of cancer cells (metastases). These secondary tumors are the major cause of patients death. In this context, monitoring **metastatic growth** is of crucial importance. Here, we focus on metastases to the liver from **gastro-intestinal tumors** (GIST). The usual scenario is the following:

1. At 1st line, the patient is treated with a targeted therapy: the imatinib (specific tyrosine kinase inhibitor). In 85% of cases, the metastases growth is controlled during several months before a **relapse**, due to development of resistance (see [4]).
2. After relapse detection, the standard 2nd line treatment is a multi-targeted inhibitor: the sunitinib. It has both **cytotoxic and antiangiogenic** effects. Once again, the growth of the metastases is controlled for some time before a new therapeutical failure occurs.

In Figure 1, a typical profile of growth of GIST metastases is shown.

Currently, the only kept information to clinically follow the cancer evolution is the diameter of the biggest lesion (RECIST criteria). Numerous studies (as in [5]) have already demonstrated the **deficiency of the RECIST criteria** to evaluate the treatment response. Our **mathematical model** suggests that tumor **heterogeneity** could precede the relapse.



Each point corresponds to a CT-scan:

- ⊕ : rather heterogeneous tumor
- ● : rather homogeneous tumor
- ○ : transitional case

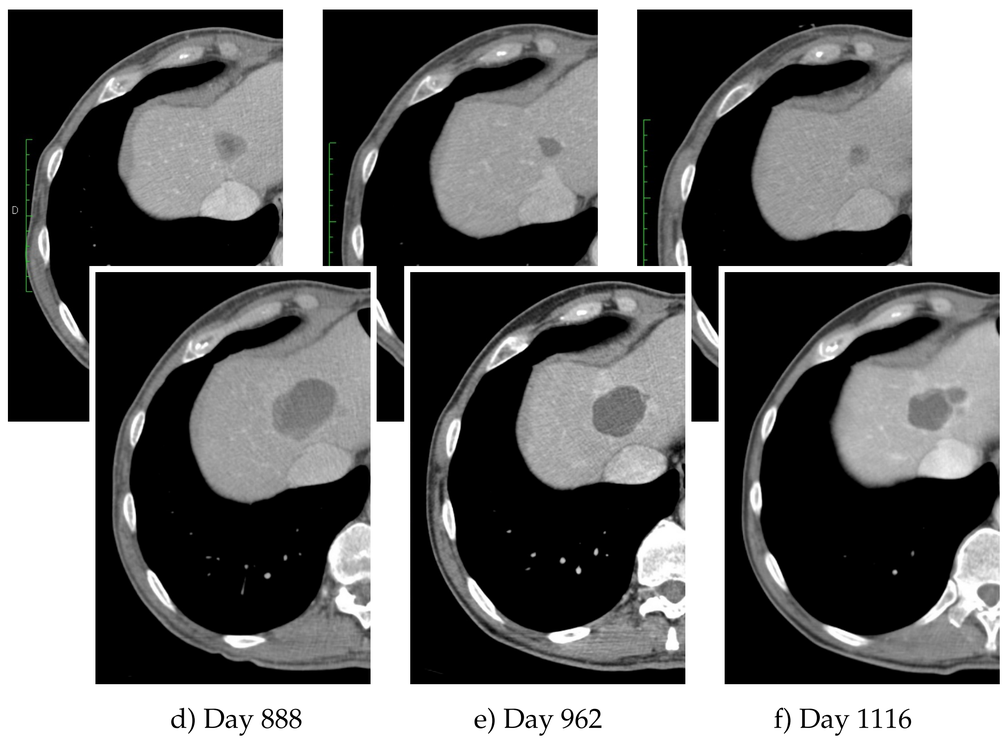


Figure 1: Evolution of the tumor area followed by a series of CT-scans of a patient affected by two successive relapses.

MODEL

- 2 treatments with different effects: imatinib (cytotoxic, $\mathcal{T}_1$) and sunitinib (cytotoxic and antiangiogenic, $\mathcal{T}_2$).
- 5 different cell populations: 3 proliferating (P_i), one necrotic population (N) and healthy cells population (S) (see. [2, 3])

$$\partial_t P_i+\nabla\cdot(\mathbf{v}P_i)=\gamma_P P_i-(I_i(\mathcal{T}_1)+I_i(\mathcal{T}_2))(1+M)P_i \qquad i=1,2,3$$

$$\partial_t N+\nabla\cdot(\mathbf{v}N)=\gamma_P^- \textstyle\sum_i P_i+\gamma_S^- S-\mu(1+M)N +\sum_i(I_i(\mathcal{T}_1)+I_i(\mathcal{T}_2))(1+M)P_i$$

$$\partial_t S+\nabla\cdot(\mathbf{v}S)=\gamma_S S \qquad \text{with} \qquad P_1+P_2+P_3+N+S=1$$

- Passive motion (velocity $\mathbf{v}$) of cells, due to cancer cells proliferation

$$\nabla\cdot\mathbf{v}=\gamma_P^+ \textstyle\sum_i P_i-\mu(1+M)N$$

closed by a Darcy law (Π: medium pressure)

$$\mathbf{v}(t,\mathbf{x})=-k\nabla\Pi(t,\mathbf{x})$$

- Coupling with the angiogenic signal (ξ) and the vascularization (M) (see. [1])

$$\partial_t\xi=\alpha\textstyle\int(1+\epsilon_\xi-[\gamma_P^+])(A(\mathcal{T}_2)(P_1+P_2)+P_3)\,\mathrm{d}\mathbf{x}-\lambda\xi$$

$$\partial_t M-\xi\tfrac{\nabla S}{\|\nabla S\|}\nabla M=C_0 S\left(1-\tfrac{M}{2M_{th}}\right)-\eta\textstyle\sum_i P_i M+\psi\Delta M$$

- Numerical simulations on 2D staggered grid, finite volumes method
- Reconstitution of CT-scan view: interpolation of the gray levels of the different cells population.

CONCLUSIONS

Our model is able

1. To quantitatively the evolution of the tumor area.
2. To report functional structure of the lesion.
3. To reproduce a large spectrum of behaviors (total control of the tumor, control before a relapse or even straightaway treatments resistance) for the two kinds of treatments (see. Figure 5).

RESULTS

Our model is able to reproduce

- the time evolution of tumor area (see. Figure 2)
- the metastasis structure during the different phases of control and relapse.

Indeed, on the CT-scans as well as in our simulations (see Figure 3), we can notice the following elements:

1. Imatinib (administrated from day 119) homogenizes the tumor. Moreover, the lesion becomes darker that means a larger necrosis rate.
2. Just before the first relapse (day 776), a heterogeneity appears. It reflects the recovery of cellular activity, even if the tumor area has not yet increased.
3. The sunitinib is administrated from the day 867. We note again a general darkening of the tumor during the first months.
4. Just before the sunitinib resistance occurs (day 1116), tumor becomes again very heterogeneous.

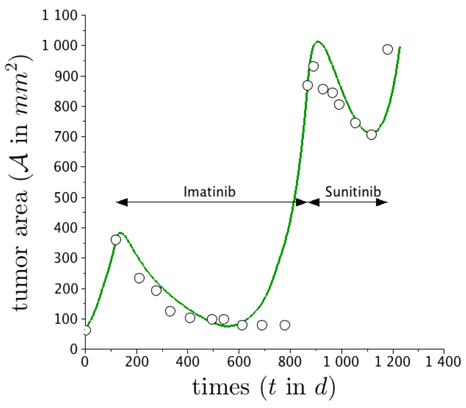


Figure 2: Comparison between the area evolution measured on CT-scans and the one given by numerical simulation.

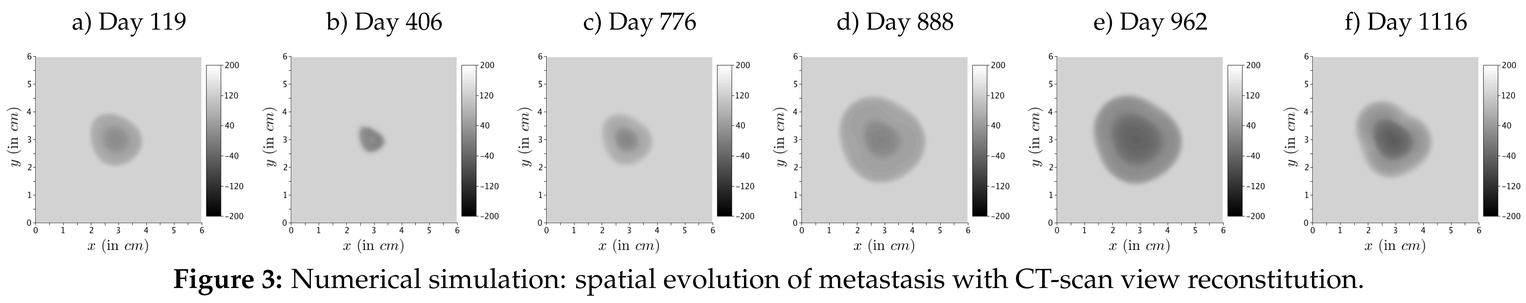


Figure 3: Numerical simulation: spatial evolution of metastasis with CT-scan view reconstitution.

We continue our simulations by varying the parameter of the imatinib dose administrated to the patient. As we can see on the Figure 4, it exists a threshold dose: below it, the treatment does not control the tumor (it continues to growth) and above it, the progression free survival time ($\mathrm{T_{PFS}}$, time during which the lesion stays smaller than at the treatment beginning) is constant, independently of the dose, even if the minimum lesion size ($\mathcal{A}_{\min}$) varies with respect to the dose. Thus, according to the model, a reduction of the tumor area is not synonymous with increasing of survival time and doubling time ($\mathrm{T_{double}}$). However, this model can not be used to optimize treatment.

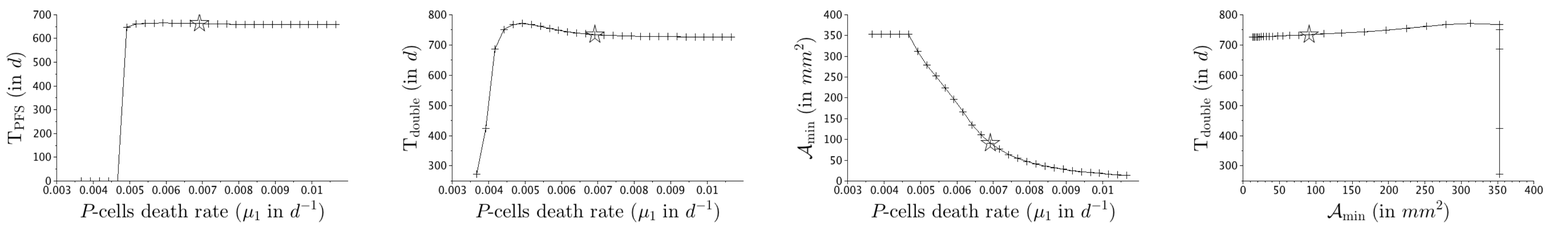
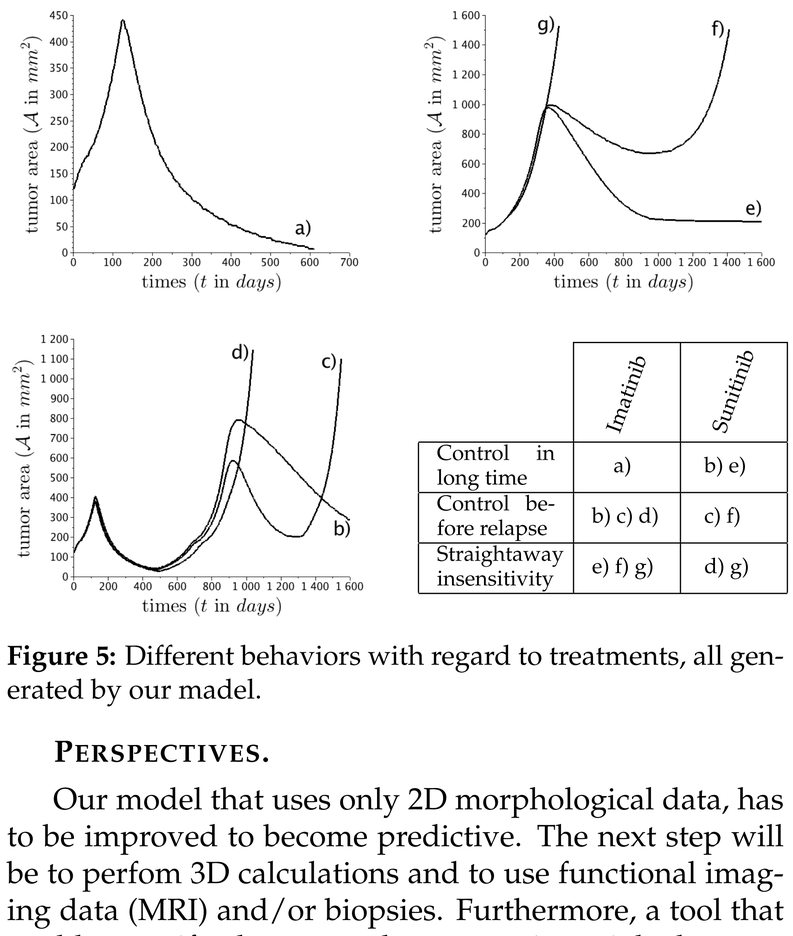


Figure 4: Treatment efficiency in term of progression free survival time ($\mathrm{T_{PFS}}$), of doubling time ($\mathrm{T_{double}}$) and of the minimum area reached by the tumor ($\mathcal{A}_{\min}$). The star corresponds to the parameter used for the simulation presented in Fgures 2 and 3.



	Imatinib	Sunitinib
Control in long time	a)	b) e)
Control before relapse	b) c) d)	c) f)
Straightaway insensitivity	e) f) g)	d) g)

Figure 5: Different behaviors with regard to treatments, all generated by our madel.

PERSPECTIVES.

Our model that uses only 2D morphological data, has to be improved to become predictive. The next step will be to perfom 3D calculations and to use functional imaging data (MRI) and/or biopsies. Furthermore, a tool that could quantify the tumor heterogeneity might be very usefull to improve the relapse diagnosis.

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