Mathematical modeling of differential effects of neo-adjuvant Sunitinib on primary tumor and metastatic growth

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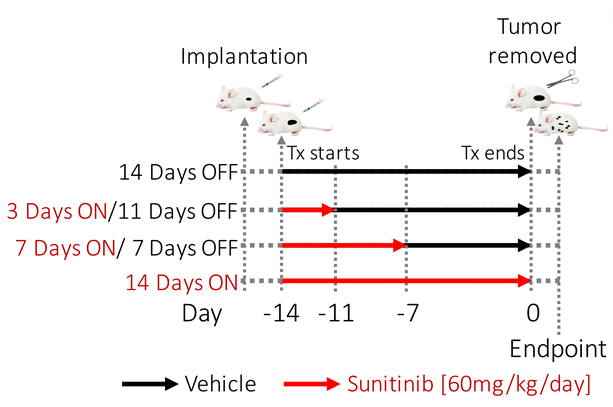
BACKGROUND

- **Sunitinib** is a drug with anti-angiogenic activity used in the treatment of patients with metastases from renal cell carcinoma or gastrointestinal tumors.
- It is currently evaluated in clinical trials in the neo-adjuvant setting.
- Despite clear efficacy in reducing established tumor growth, recent preclinical studies have shown **limited**, or even opposing, **efficacies in preventing metastatic spread**.
- In this work, we evaluated a **mathematical model of the metastatic process** to describe primary tumor and metastatic dynamics in response to sunitinib in a clinically relevant **ortho-surgical mouse model of spontaneous metastatic breast cancer**.

EXPERIMENTAL DATA

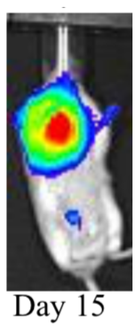


Measurements of

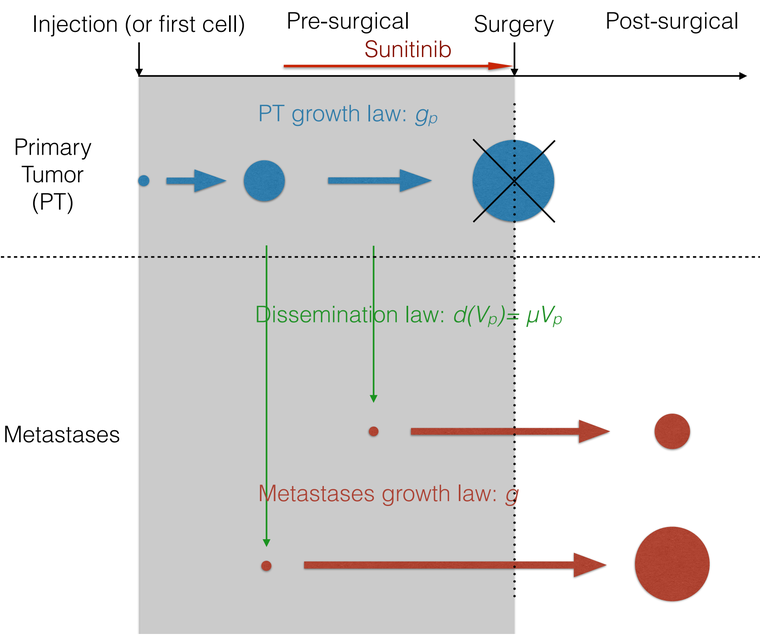
- primary tumor kinetics,
- metastatic burden (bioluminescence)
- pre-surgical molecular and cellular biomarkers, including Ki67 and CD31 expression, circulating tumor cells (CTCs) and myeloid derived suppressor cells (MDSCs).

Orthotopic xenograft breast model: LM2-4^{LUC+} human metastatic breast carcinoma cells.

Bioluminescence monitoring of post-surgical metastasis



AN ELEMENTARY THEORY OF METASTATIC DYNAMICS: DISSEMINATION + GROWTH



Growth rates of primary and secondary tumors g_p and g

$$\frac{dV_p}{dt} = g_p(V_p(t), t)$$

Dissemination rate
$d(V_p) = \mu V_p$

Size distribution of the metastases $\rho(t,v)$

$$\begin{cases} \partial_t \rho(t,v) + \partial_v(g(v)\rho(t,v)) = 0 \\ g(V_0)\rho(t,V_0) = d(V_p(t)) \\ \rho(0,v) = \rho^0 \end{cases}$$

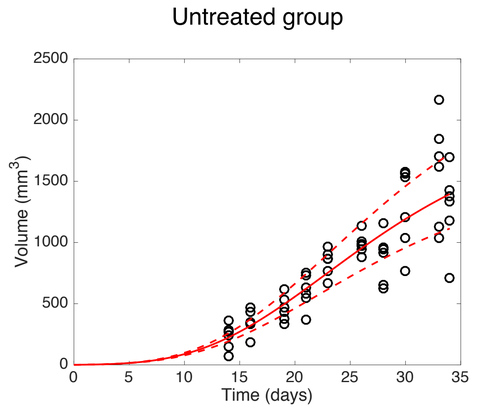
Metastatic burden (total metastatic number of cells)

$$M(t) = \int_0^t d(V_p(t-s))V(s)\,ds$$

DIFFERENTIAL EFFECTS OF SUNITINB ON PRIMARY TUMOR AND METASTASIS

Primary tumor growth:

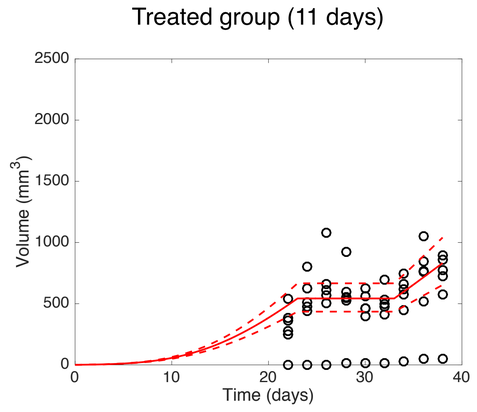
Untreated group



Gomp-Exp model

$$g_p(V) = \min\left(\lambda V, \left(\alpha_0 - \beta \ln\left(\frac{V}{V_c}\right)\right)V\right)$$

Treated group (11 days)

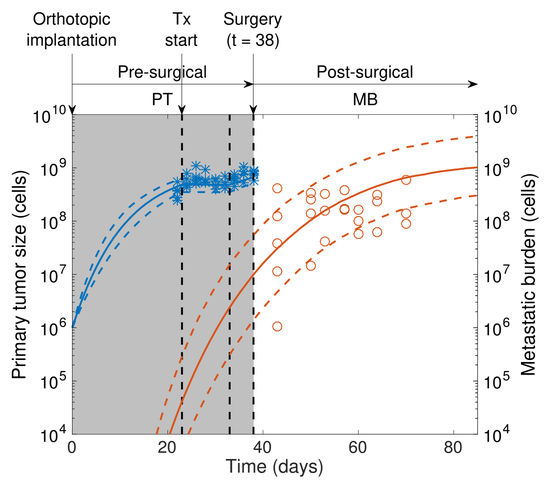


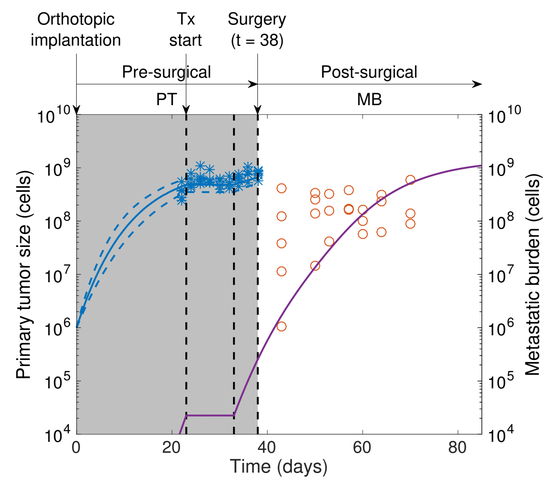
Gomp-Exp model with therapy

$g_p(V,t) = 0$ during the phase of treatment

Primary tumor - metastatic growth dynamics:

Treated group (11 days)





Population fit assuming **no effect of treatment on metastasis**

Simulation of **treatment also on metastasis**

Treatment acts differently on primary and secondary tumor growth

Mixed-effects population approach.

Log-normal distribution for the individual parameters:

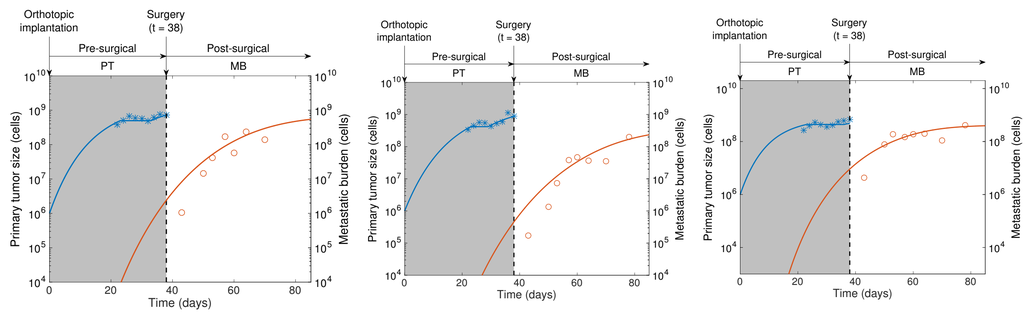
$$\log(\psi_i) \sim \log(\psi_{pop}) + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$

MLE of ψ_{pop} through the SAEM algorithm.

Table: Population parameters for the treated group.

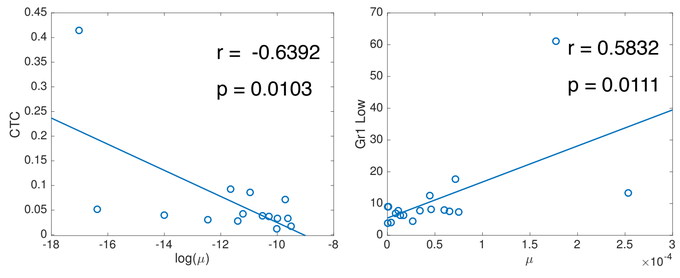
	estimate (CV %)	unit	r.s.e. (%)
μ_{pop}	1.009e-04 (117.476)	$mm^{-3}\cdot day^{-1}$	23.483
$\alpha_{0,pop}$	1.907 (22.919)	day^{-1}	6.208
β_{pop}	9.116e-02 (24.490)	day^{-1}	6.682

Individual dynamics



COVARIATES ANALYSIS

Biomarkers VS individual parameters



- Biomarkers can be included in the model as covariates in order to explain part of the variability in the individual parameters

x_i : individual covariate → $\log(\mu_i) = \log(\mu_{pop}) + \beta x_i + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$

REFERENCES

[1] Ebos, J. M. L., Mastri, M., Lee, C. R., Tracz, A., Hudson, J. M., Attwood, K., Cruz- Munoz, W. R., Jedeszko, C., Burns, P., and Kerbel, R. S. (2014). Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy. EMBO Mol Med, 6(12):1561–1576

[2] Benzekry, S., Tracz, A., Mastri, M., Corbelli, R., Barbolosi, D., and Ebos, J. M. L. (2016). Modeling spontaneous metastasis following surgery: an in vivo-in silico approach. Cancer Res, 76(3):535–547.

CONCLUSIONS

These results confirm a differential effect of sunitinib on primary (localized) tumors compared to secondary (metastatic) disease. Our results suggest that **Ki67+/CD31+, CTCs and MDSCs** measurements **might help in personalized prediction of** metastatic potential and thus aid in predicting benefit in overall **survival** for preoperative antiangiogenic treatments.