A biologically-based mathematical model for prediction of metastatic relapse

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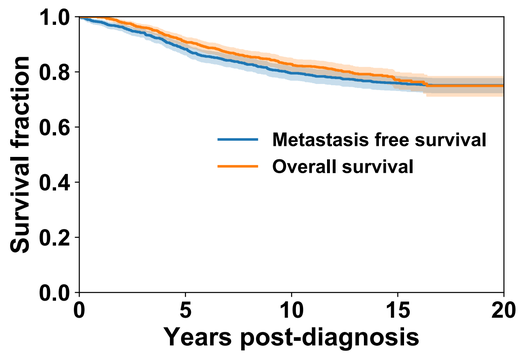
BACKGROUND & OBJECTIVES

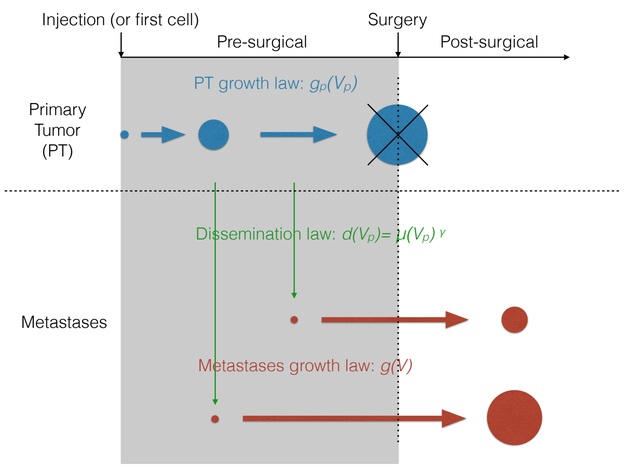
- Metastasis is the cause of **90% of deaths** from solid tumors *Chaffer and Weinberg, Science 2011*
- ~20-30% of breast cancer patients will relapse with distant metastases *EBCTG, Lancet, 2005*
- For breast cancer, the current factors influencing decision for **adjuvant therapy** are: tumor size, nodal involvement, molecular factors (hormonal receptors and HER2 status), histological type and grade.

Objective: establish a biologically-based mathematical model for individualised prediction of metastasis

Breast cancer data base (1057 patients), I. Bergonié



AN ELEMENTARY THEORY OF METASTATIC DYNAMICS: GROWTH + DISSEMINATION



Growth rates of primary and secondary tumors g_p and g

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

Poisson process for the dissemination with rate $d(V_p) = \mu V_p^\gamma$

Size distribution of the metastases $\rho(t,v)$
Iwata et al., J Theor Biol, 2000

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

Number of visible metastases

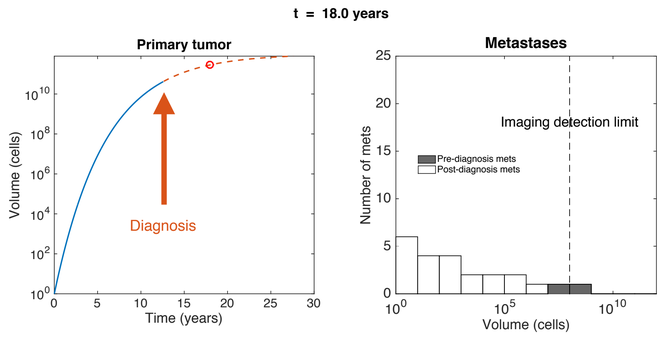
$$N_{vis}(t) = \int_0^{t-\tau_{vis}} d(V_p(t)) \mathbb{1}_{V_p(t) \leq V_d} dt$$

Time to relapse

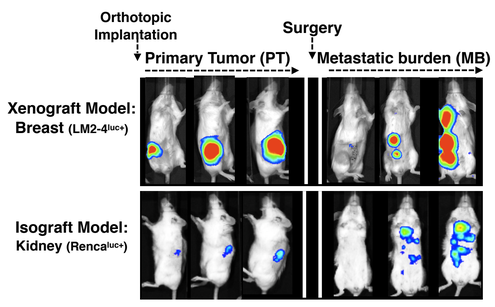
$$TTR = \inf\{t > 0; N_{vis}(t) > 1\}$$

Total metastatic mass

$$M(t) = \int_{V_0}^{+\infty} v\rho(t,v)dv = \int_0^t d\left(V_p(t-s)\right) V(s) ds$$



PRECLINICAL DATA AND POPULATION APPROACH



Data

$$M_j^i = M(t_j^i, \theta^i) + \sigma(M(t_j^i, \theta^i))\varepsilon_j^i, \quad \varepsilon_j^i \sim \mathcal{N}(0,1)$$

Structural model — Error model

Individual parameter θ^i

$$\theta^i = \theta_{pop} + \beta^T x^i + \eta_i$$

$$\eta_i \sim \mathcal{N}(0, \omega^2)$$

Population fits

(nonlinear mixed-effects)

CLINICAL DATA OF METASTATIC RELAPSE PROBABILITY

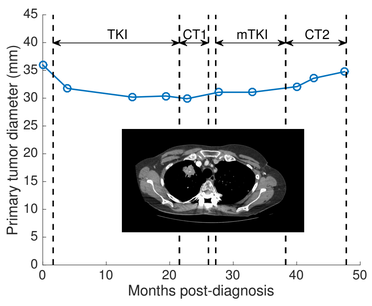
2648 breast cancer patients screened for 20 years after primary tumor resection (no adjuvant therapy)
Koscielny et al., Br J Cancer, 1984

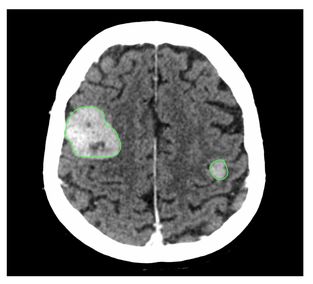
Cancer inception time can be inferred from PT volume V1 at diagnosis time T1 (Gompertz growth).
Lognormal distribution of **metastatic parameter μ** for inter-individual variability (2 degrees of freedom)

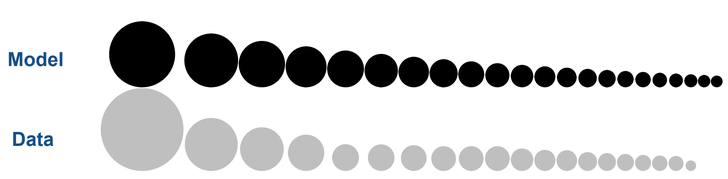
$$\mathbb{P}(\text{Mets}) = \mathbb{P}\left(\mu \int_0^{T_1} V_p(t)dt > 1\right)$$

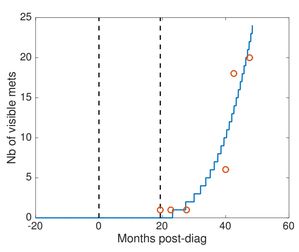
Diameter of primary tumor at diagnosis (cm)	Proportion of patients developing metastasis (%)	Model fit
$1 \leq D \leq 2.5$	27.1	25.5
$2.5 < D \leq 3.5$	42.0	42.4
$3.5 < D \leq 4.5$	56.7	56.3
$4.5 < D \leq 5.5$	66.5	65.9
$5.5 < D \leq 6.5$	72.8	74.3
$6.5 < D \leq 7.5$	83.8	80.8
$7.5 < D \leq 8.5$	81.3	85.7

PERSONALIZED SIMULATIONS FOR DIAGNOSIS AND PROGNOSIS OF BRAIN METASTASES IN LUNG CANCER

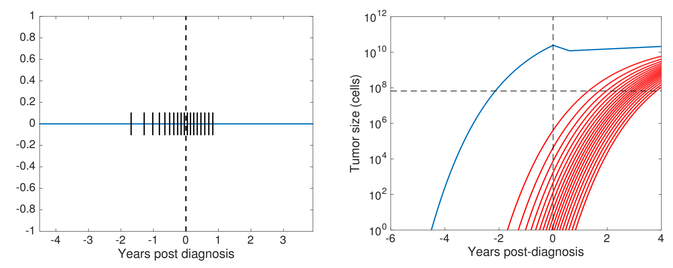








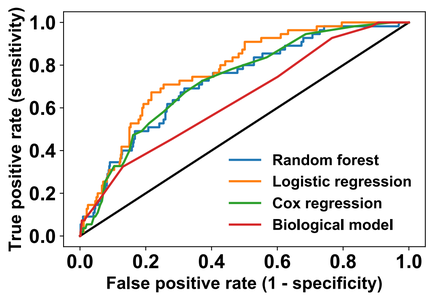
Simulations of the natural history



PREDICTIVE PERFORMANCES FOR 5-YEARS METASTATIC RELAPSE FROM BREAST

	AUROC	Accuracy	NPV	PPV
Random forest	0.727	87	91.7	22.5
Logistic regression	0.772	90.1	91	25
Cox regression	0.728	87.4	91.1	16.7
Bio-based	0.641	89.7	91.3	31.2

AUROC = Area Under the ROC curve, NPV = Negative Predictive Value
PPV = Positive Predictive Value



	p
tumor_size_clinical	0.00165
tumor_size_histological	0.4
grade	0.358
histology	0.0041
TNM_T	0.146
TNM_N	0.599
nb_invaded_ganglions	0.619
menopausal_status	0.000471
ER	0.543
PR	0.34
Ki67	3.09e-05
HER2	0.17
HER2_intensity	0.482
CK56	0.793
EGFR	0.016
VIM	0.226
ALDH1	0.674
CD24	0.894
CD44	0.397
E_cadherin	0.207
TRIO	0.0646
BCL2	0.727
age_at_diagnosis	0.0599
diagnosis_year	0.101
radio	0.276

Features selection based on Cox regression

CONCLUSION AND FUTURE DIRECTIONS

- A **biologically-based** mathematical model was able to **describe preclinical and clinical data** of metastatic development in breast, lung and kidney cancer
- Machine learning algorithms used here don't account for censored data + limited to prediction of relapse event at a fixed horizon
- The biological model accounts for these and could give predictions of the metastatic state at diagnosis and future evolution in order to **guide therapeutic intervention**
- Predictive power is **only modest so far** but only the primary tumor size was considered here as a feature with only other source of inter-subject variability being the dissemination parameter μ

==> include **more features** and link parameter μ and others to clinical features and biomarkers in a **biologically relevant way**

S. Benzekry, A. Tracz, M. Mastri, R. Corbelli, D. Barbolosi, J.M.L. Ebos , Modeling spontaneous metastasis following surgery: an in vivo-in silico approach. Cancer Research, 76(3), 4931-40, 2016