Modeling of the metastatic variability in cancer disease

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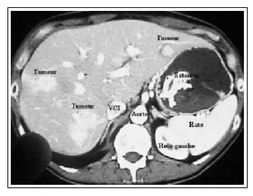
Problematics: who has to be treated ?

In spite of advances to precise the tumoral classification, it sometimes reveals to be insufficient to take into account the important variability in the tumoral aggressiveness. For example, in the breast cancer for a T1N0M0 classification which globally has an excellent forecast, a little fraction of patients still have a strong risk of death (see [KKN]).
In order to support the TNM classification we have developped a mathematical model which is able to describe at any time the **number of metastases** of a given size from a primary tumor since the origin of the cancer.
Moreover this model allows, for a given primary tumor, to estimate the potential number of **micrometastases**. We call this number the **MI** (Metastatic Index). We describe thereafter the important variability of the MI with respect to the tumoral parameters: a high value of the MI might be for an adjuvant chemotherapy on the contrary to a low MI.
Thus the MI computation could be an interesting additional indicator which could complete the traditional tools used to classify the tumoral aggressiveness.

Assessment

Primary tumors after reaching a critical volume may be at the origin of several metastatic tumors disseminated in the human body. At early stages, metastatic tumors are of small size and not detectable by medicinal apparatus, like in the case of the breast cancer, but evidence for the existence of occult micrometastases at diagnosis is overwhelming.



Liver metastases.

The micrometastases can grow rapidly and escape to any therapeutic treatment and often lead to the patient's death. The cancer has to be seen as a diffuse pathology [E] .
The aggressiveness of a cancer is far to be always the same, this **variability** seems to be determined as soon as the first tumoral cells appear and the biological diversity observed in the invasives cancers already exists in the localized forms.
In order to choose the appropriate treatment when a cancer is diagnosed, the tumor has to be classified according to some criteria as the tumor morphology (TNM or SBR classifications).

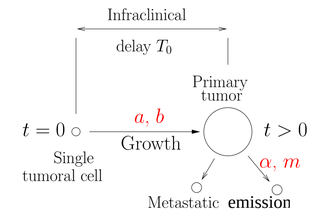
Description of the model

▶ **Mathematical model** (see [I-K-S])

Size structured population model: Evaluation of the metastatic colony size distribution $v(x,t)$ with cell number x at time t.

▶ We adopt a **Gompertzian** growth rate for the primary tumor and the metastases.

▶ This model allows to compute the **estimated origin time** of the cancer $\boldsymbol{T_0}$.



▶ **Model parameters**

- $\boldsymbol{a}$: Growth rate constant (day^{-1})
- $\boldsymbol{b}$: Maximum tumor size (in number of cells)
- $\boldsymbol{m}$: Colonization coefficient $(\text{cells/day})^{-1}$
- $\boldsymbol{\alpha}$: Fractal dimension of blood vessels infiltrating the tumor. It expresses how the blood vessels are geometrically distributed in or on the tumor.

Metastatic Index (MI)

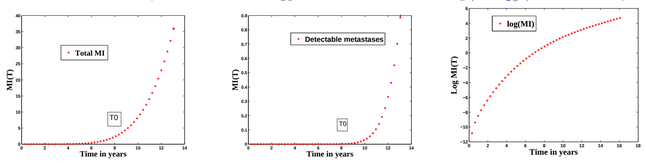
We define the **Metastatic Index** at time T by:

$$MI_{b_{min}}(T) = \int_{b_{min}}^{b} v(x,T)dx$$

▶ The **MI** represents the **total metastases number** whose size ranges from b_{min} and b.

Illustration: **The breast cancer**
A tumoral mass at the diagnosis of 1 gram (about 10^9 cells) corresponds to an origin time $T_0 = 2943$ days (about 8 years). The parameters are:
$a = 0.000471$ day^{-1}, $b = 10^{12}$ cells, $m = 2.5 \times 10^{-7}$ cells/day^{-1} and $\alpha = 0.48$.

MI_1 at $T_0 + 5$ y. MI_{10^8} at $T_0 + 5$ y. $\log(MI_{10^8})$ at $T_0 + 8$ y.



▶ The total **MI** is equal to 40 but we see that there is **only one detectable metastasis** at time $T_0 + 5$ years.

▶ We observe an **exponential** growth rate characterized by the **Malthusian** parameter $\boldsymbol{\lambda_0}$.

Variability of the MI with respect to the parameters α and m

▶ We present the variability of $\boldsymbol{m}$ and $\boldsymbol{\alpha}$ in the case of the breast cancer using the following parameters:

$a = 0.000471$ day^{-1}, $b = 10^{12}$ cells, $m = 1.2 \times 10^{-8}$ cells/day^{-1}, which give that the approximate origin time of cancer is $T_0 = 2943$ days.

▶ Estimate of the **detectable metastases number** (more than 10^8 cells):

m	$MI_{10^8}(T_0)$	$MI_{10^8}(T_0+3)$	$MI_{10^8}(T_0+5)$
2.5×10^{-9}	0	0	0
2.6×10^{-8}	0	0	0
2.4×10^{-7}	0	0	2
2.3×10^{-6}	0	3	20

▶ The parameter $\boldsymbol{m}$ is linked to the **migration potential** of the metastases. We can use the parameter $\boldsymbol{m}$ to describe the **angiogenic capacity** of the tumor.

α	$MI_{10^8}(T_0)$	$MI_{10^8}(T_0+3)$	$MI_{10^8}(T_0+5)$
0.2	0	0	0
0.48	0	0	0
0.66	0	0	4
0.8	0	3	53

▶ The parameter $\boldsymbol{\alpha}$ is linked to the aggressiveness of the tumor.

The previous tabulars shows a virtual example of four patients who have no detectable metastasis at time $\boldsymbol{T_0}$ of diagnosis, however following the value of $\boldsymbol{m}$ and $\boldsymbol{\alpha}$, the model predicts that 3 or 5 years later the first two patients will not have any detectable metastasis contrary to the two other patients who have an important metastatic risk. Consenquently in the case of two patients in T1N0M0 classification, the identification of the parameters $\boldsymbol{m}$ and $\boldsymbol{\alpha}$ would allow to differentiate them in precising their respective metastatic risk.

Validation of the MI

▶ In a retrospective trial involving 2648 patients with a breast cancer treated at the Gustave Roussy institute between 1954 and 1972, Koscielny et al. have defined in [TK] the risk to develop metastases with respect to the initial tumor mass $\boldsymbol{x_0}$. These data have been compared to those computed by the model.

▶ For each initial tumor size 100 random draws have been done following a two dimensional normal distribution for the parameters $\boldsymbol{\alpha}$ and $\boldsymbol{m}$ with mean value and standard deviation respectively of $\boldsymbol{\mu_m = 2.5 \times 10^{-8}}$ and $\boldsymbol{\sigma_m = 1.8 \cdot 10^{-8}}$ for $\boldsymbol{m}$ and $\boldsymbol{\mu_\alpha = 0.48}$ and $\boldsymbol{\sigma_\alpha = 0.3}$ for α. The other parameters are $\boldsymbol{a = 0.000471}$ and $\boldsymbol{b = 10^{12}}$.

▶ We compute the ratio of patients with **at least one metastasis** (detectable or not) at the diagnosis with respect to the initial tumoral mass. The results are:

Initial size $\boldsymbol{x_0}$	Computed %	Observed % ([TK])
1.5 – 2.5 cm	**25.6%**	**25%**
4.5 – 5.5 cm	**67.25%**	**65%**
6.5 – 7.5 cm	**79.5%**	**78%**
9.5 – 10.5 cm	**84%**	**85%**

▶ The similarity of the computed results and the observed ones could confirm the ability of the model in predicting the risk of metastatic extension.

Infulence of m on the choice of the treatment

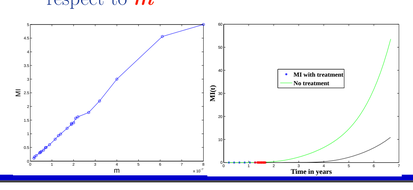
▶ The treatment takes place in the Gompertzian growth rate as a **loss term**. We use a 3 compartment PK-PD model [M].

▶ Clinical example: Association of **Docetaxel** and **Epirubicine** in the metastatic breast cancer: **Standard protocol** of **21** days per cycle.
→ We have done $n = 30$ random draws of $\boldsymbol{m}$ with $\boldsymbol{\sigma_m = 1.8 \cdot 10^{-8}}$ and $\boldsymbol{\mu_m = 2.5 \cdot 10^{-7}}$ and then we compute $\boldsymbol{MI(T_0 + 5)}$ including **6** chemotherapy cycles for each patient.
→ Parameters: $\boldsymbol{a}$ = 0.00871, $\boldsymbol{b}$= 10^{12}, T_0 = 1591 days, $\boldsymbol{\alpha}$= 0.48.

$\boldsymbol{m}$	$MI_{10^8}(T_0+5)$	$\boldsymbol{m}$	$MI_{10^8}(T_0+5)$
$1.7 \cdot 10^{-8}$	**0**	$7.0 \cdot 10^{-8}$	**0**
$1.9 \cdot 10^{-8}$	**0**	$1.3 \cdot 10^{-7}$	**1**
$2.7 \cdot 10^{-8}$	**0**	$2.7 \cdot 10^{-7}$	**2**
$5.0 \cdot 10^{-8}$	**0**	$4.0 \cdot 10^{-7}$	**3**
$6.1 \cdot 10^{-8}$	**0**	$6.1 \cdot 10^{-7}$	**5**

▶ We observe an important variability on the **MI**. This inter-individual variability could confirm the fact that the treatment can not be the same for all the patients.

Evolution of **MI** with respect to $\boldsymbol{m}$ MI_{10^8} at $T_0 + 5$ years



Optimization of the treatment taking into account the inter-individual variability

▶ We consider here the "limit cases" in **blue** presented in the previous table. They represent the cases where the treatment is not adapted and the therapeutic response can be improved. We consider two possibilities to optimize the treatment.

(1) Increasing of the cycles number for the standard protocol.

$\boldsymbol{m}$	6 cycles	9 cycles	12 cycles
$1.3 \cdot 10^{-7}$	1	**0**	OK
$2.7 \cdot 10^{-7}$	2	1	**0**
$4.0 \cdot 10^{-7}$	3	2	1
$6.1 \cdot 10^{-7}$	5	4	3

(2) We use a **densified protocol** of **14** days per cycle using the Model I methodology [B-I].

$\boldsymbol{m}$	9 cycles	13 cycles	18 cycles
$1.3 \cdot 10^{-7}$	**0**	OK	OK
$2.7 \cdot 10^{-7}$	2	**0**	OK
$4.0 \cdot 10^{-7}$	3	1	**0**
$6.1 \cdot 10^{-7}$	4	3	1

▶ This modeling and the **identification** of $\boldsymbol{m}$ could be useful in order to optmize the therapeutic protocols.

Perspectives and references

▶ **Protocols optimization** Identification of the parameters $\boldsymbol{\alpha}$ and $\boldsymbol{m}$ in order to optimize the number of chemotherapy cycles and to prevent the apparition of micrometastases using the value of the MI.

[BBHV] **D. Barbolosi, A. Benabdallah, F. Hubert, F. Verga** (2009) "Mathematical and numerical analysis for a model of growing metastatic tumors", *Mathematical Biosciences* **208, pages 1-14.**

[B-I] **D. Barbolosi, A. Iliadis (2001) "Optimizing drug regimens in cancer chemotherapy: a simulation study using a PK-PD model", *Computers in Biology and medicine*, pages 157-172.**

[I-K-S] **K. Iwata, K. Kawasaki and N. Shigesada (2000) "A dynamical Model for the Growth and Size Distribution of Multiple Metastatic Tumors", *J. Theor. Biol*, 203, pages 177-186.**

[KKN] **P. Kronqvist et al. (2004) "Predicting aggressive outcome in TIN0M0 breast cancer", *British Journal of Cancer*, 91, pages 277-281.**

[TK] **Koscielny S, Tubiana M, Le MG, (1984) "Breast cancer: Relationship between the size of the primary tumor and the probability of metastatic dissemination", *British Journal of Cancer*, 49, pages 709-715.**

[E] **D. Elias (2006) "Rationnels de la chirurgie oncologique au sein d'un traitement multimodal des cancers", *Bull. Cancer*, 93, pages 775-781.**

[M] **C. Meille, D. Barbolosi, N. Frances, A. Iliadis (2008) "An interface model for dosage adjustment connects hematotoxicity to pharmacokinetics", *J. Pharmacokinetics Pharmacodynamics*, 35, pages 619-633.**