Mathematical Modeling and Prediction of Clinical Metastasis
Sébastien Benzekry

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Mathematical Modeling and Prediction of Clinical Metastasis

S. Benzekry

BIRS - CMO workshop
Oaxaca, Mexico

November 27, 2018
Metastasis (μετά = beyond, στάσις = place)

- Metastases are the main cause of death (>90%) from solid cancers. 
  Lambert and Weinberg, Cell, 2017

  ![Graph showing localized and distant disease](image1.png)

- Breast
  - 94% of cases are local or regional at diagnosis but 30% will relapse 
  - Estimate the amount of residual distant disease at diagnosis in order to personalize the adjuvant (chemo)-therapy
  - Avoid unnecessary, heavy toxicities

- Lung
  - 57% of cases are metastatic
  - Decide whether to use whole brain radiation therapy or just (stereotactic) surgery
  - Avoid cognitive impairment of the patient


Institut Bergonié, Bordeaux
Some biological questions of interest to mathematical modeling

- **Minimal** model of metastatic dissemination and colonization able to reproduce the **systemic dynamics** of a solid cancer disease.

- Investigate the relevance of several processes:
  - (early VS late event *Klein, Nat Rev Cancer, 2009*)
  - (metastases of metastases *Gundem et al., Nature, 2015*)
  - (dormancy *Chambers and Groom, Nat Rev Cancer, 2002*)
  - **tumor-tumor interactions**
  - (cancer-immune interactions)
  - **differential effect of therapy** *Ebos et al. (Kerbel), Cancer Cell, 2009*
  - ((pre-)metastatic niche *Peinado et al. (Lyden), Nature, 2005*)
  - systemic inhibition of angiogenesis *O'Reilly et al. (Folkman), Cell, 1990s*
  - (self-seeding *Norton, Nat Med, 2001*)
Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) tumor growth
- Existing models are based on a statistical, biologically agnostic, prediction of survival

**Model**

**Individual biomarkers**
- PT size, lymph node status, histological grade, molecular factors, proliferation indices,…

**Black box**

![Graph showing Kaplan-Meier analysis of probability remaining metastasis-free and overall survival. The graph compares patients with good-prognosis and poor-prognosis signatures. The P value is less than 0.001.]
Metastasis: a forgotten major player in modeling

- The majority of mathematical modeling efforts in oncology are focused on (primary) tumor growth
- Existing models are based on a statistical, biologically agnostic, prediction of survival

**Clinical data**
PT size, lymph node status, histological grade, molecular factors, proliferation indices,…

**Imaging data (Radiomics)**

**Molecular data (-omics)**

Aerts et al., Nat Commun, 2014

van't Veer et al., Nature, 2002

**Biologically-based model**

\[
\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p)) V_p
\]

\[
\begin{align*}
\partial_t \rho(t, v) + \partial_v ((\alpha - \beta \ln(v)) \nu \rho(t, v)) &= 0 \\
g(V_0) \rho(t, V_0) &= \mu V_p(t)^\gamma \\
\rho(0, v) &= 0
\end{align*}
\]
1. Modeling the dynamics of metastatic burden in clinically relevant ortho-surgical animal systems

2. Clinical applications

3. Tumor-tumor interactions
1. Modeling the dynamics of metastatic burden in clinically relevant ortho-surgical animal systems
Experimental data and questions

Data
- Clinically relevant ortho-surgical animal models of metastasis
- Longitudinal measurements of primary tumor size and total metastatic burden
- n > 400 animals

Questions
- Minimal model of metastatic development. Dissemination law? Differences between mets and primary tumor growth?
- Quantify the inter-subject variability of metastatic development
- What is the impact of the primary tumor size at surgery on metastatic development and survival?
Injection (or first cell) → Pre-surgical → Post-surgical → Surgery

**Primary Tumor (PT)**

- PT growth law: \( g_p(V_p) = V_p(\alpha_p - \beta_p \ln(V_p)) \)

- Dissemination law: \( d(V_p) = \mu(V_p)^\gamma \)

**Metastases**

- Metastases growth law: \( g(V) = V(\alpha - \beta \ln(V)) \)
Mathematical formalism

- Primary tumor $V_p$ grows with rate $g_p$ [size.day$^{-1}$]
  \[ \frac{d}{dt} V_p = g_p(V_p), \quad V_p(t = 0) = V_i \]

- Population of metastases represented by a density $\rho(t,v)$ [size$^{-1}$] structured in size $v$

- Secondary tumors grow in size with rate $g(v)$
  \[ \partial_t \rho(t, v) + \partial_v (g(v) \rho(t, v)) = 0 \]

- They are spread by the PT with dissemination rate $d(V_p(t))$ [day$^{-1}$]
  \[ g(V_0) \rho(t, V_0) = d(V_p(t)) \left( + \int_{V_0}^{+\infty} d(v) \rho(t, v) dv \right) \]

  --> fast computation of the metastatic burden

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

*Iwata, Kawasaki, Shigesada, J Theor Biol, 2000*
Statistical procedure: nonlinear mixed effects modeling

- Usual fitting methods consider each time series independently

\[
y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j
\]

MLE

\[
\hat{\theta}^j = \min_{\theta^j} \sum (y_i^j - M(t_i, \theta^j))^2
\]

Individual \(1 \leq j \leq N\)

Time \(t_i\)

- When only sparse data are available from subjects in the same population, one can fit parameters distribution all-in-once

\[
y_i^j = M(t_i^j, \theta^j) + \varepsilon_i^j
\]

\[\theta^1, \ldots, \theta^N \sim \mathcal{L} \mathcal{N}(\theta_\mu, \theta_\omega), \quad \theta_\mu \in \mathbb{R}^p, \ \theta_\omega \in \mathbb{R}^{p \times p}\]

- Reduces the number of parameters from \(pxN\) to \(p+p2\)

Lavielle, CRC press, 2014
The model fits at the individual and population levels

Nonlinear mixed-effects statistical model for inter-animal variability

\[ \theta^i = \theta_{pop} + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2) \]

⇒ model with same growth for PT and mets was the most parsimonious

⇒ good practical identifiability (all rse < 30%)

⇒ parameter \( \mu \) is a critical coefficient of inter-animal variability of metastatic potential (CV = 176%)

Benzekry et al. (Ebos), Cancer Res, 2016
Differential effects of anti-angiogenic therapies between primary tumor and metastases

Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy
Testing hypotheses for Sunitinib effect

Orthotopic implantation | Surgery
Pre-surgical | Post-surgical

Primary tumor size (cells)

Metastatic burden (cells)

0 20 40 60 80

Time (days)

10^2 10^4 10^6 10^8 10^10

Data PT, Data MB, Median PT, Median MB, 10th and 90th percentiles PT, 10th and 90th percentiles MB, simulation of therapy on metastases
A validated model of metastatic growth with neoadjuvant Sunitinib therapy

### Table 1: Parameter estimates of the KPD model obtained by likelihood maximization via the SAEM algorithm.

<table>
<thead>
<tr>
<th>Unit</th>
<th>Median value</th>
<th>CV (%)</th>
<th>r.s.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$ cell$^{-1}$·day$^{-1}$</td>
<td>2.12e-11</td>
<td>1.48e+03</td>
<td>17.3</td>
</tr>
<tr>
<td>$\alpha$ day$^{-1}$</td>
<td>1.94</td>
<td>18.1</td>
<td>2</td>
</tr>
<tr>
<td>$\beta$ day$^{-1}$</td>
<td>0.0911</td>
<td>19.7</td>
<td>2.21</td>
</tr>
<tr>
<td>$k$ (mg/kg)$^{-1}$</td>
<td>0.0372</td>
<td>32.1</td>
<td>6.34</td>
</tr>
<tr>
<td>$k_e$ day$^{-1}$</td>
<td>3.26 (fixed)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figures for data measurements**

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Orthotopic implantation</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-surgical</td>
<td>PT</td>
<td>MB</td>
</tr>
<tr>
<td>Post-surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su60(7D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su60(14D)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Survival model: $\mu$ as a covariate

Nonlinear mixed-effects survival model

\[
S^i(t) = \mathbb{P}(T^i \geq t) = e^{-\int_0^t h^i(s)ds}
\]

\[
h^i(t; T^i_e, s) = \frac{s}{T^i_e} \left( \frac{t}{T^i_e} \right)^s \frac{1}{1 + \left( \frac{t}{T^i_e} \right)^s}
\]

\[T^i_e = T^i_{e\text{\,pop}} + \beta \mu^i + \eta^i, \quad \eta^i \sim \mathcal{N}(0, \omega)\]
Trying to predict $\mu$ from biomarkers using machine learning

Biological measurements on multiple biomarkers

- Circulating tumor cells
- Proliferative (Ki67+) and endothelial cells (CD31+)
- Myeloid Derived Suppressor Cells (MDSCs)

$$x_1 \rightarrow \cdots \rightarrow \mu$$

$X = [x_1, \ldots, x_N]$ (X-axis)

$Y = \mu$ (Y-axis)

$C_{TC} \% = 2^{log_2FC}$

$\text{Ki67} = \text{pl}$

$\text{MDSC}$

Nicolo et al. (Ebos, Benzekry), 2018, in preparation
Impact of treatment breaks

Mastri et al. (Benzekry, Ebos), 2018, in preparation
2. Clinical application
Metastatic relapse probability in a breast cancer clinical dataset

- 20 year follow-up of 2648 patients  
  Koscielny et al.,  
  Br J Cancer, 1984

- **Assumptions**
  
  - (lognormal) distribution of \( \mu \) for **inter-individual variability**
  
  - Doubling time from median values of the literature (7 months)  
    Coumans et al., BMC Cancer 2013
  
  - Maximal reachable size = \( 10^{12} \) cells \( \approx 1 \) kg  
    Klein, Nat Rev Cancer, 2009
  
  - Probability of developing a met = probability of having one at diagnosis

\[
\mathbb{P}(\text{Mets}) = \mathbb{P} \left( \mu \int_{0}^{T_1} V_p(t) > 1 \right)
\]

Benzekry et al. (Ebos), Cancer Res, 2016

<table>
<thead>
<tr>
<th>Diameter of PT (cm)</th>
<th>Prop. of relapse (Data)</th>
<th>Prop. of relapse (Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1 \leq D \leq 2.5 )</td>
<td>27.1</td>
<td>27.3</td>
</tr>
<tr>
<td>( 2.5 &lt; D \leq 3.5 )</td>
<td>42.0</td>
<td>43.1</td>
</tr>
<tr>
<td>( 3.5 &lt; D \leq 4.5 )</td>
<td>56.7</td>
<td>56.6</td>
</tr>
<tr>
<td>( 4.5 &lt; D \leq 5.5 )</td>
<td>66.5</td>
<td>65.6</td>
</tr>
<tr>
<td>( 5.5 &lt; D \leq 6.5 )</td>
<td>72.8</td>
<td>74.0</td>
</tr>
<tr>
<td>( 6.5 &lt; D \leq 7.5 )</td>
<td>83.8</td>
<td>80.1</td>
</tr>
<tr>
<td>( 7.5 &lt; D \leq 8.5 )</td>
<td>81.3</td>
<td>84.5</td>
</tr>
</tbody>
</table>
Diagnosis personalization

Virtual patient with median $\mu$

Nothing visible

Virtual patient with large $\mu$ (90th prct)

Breast cancer patient with primary tumor of 4.32 cm

Benzekry et al. (Ebos), Cancer Res, 2016
Data of a NSCLC patient with brain mets

**Primary tumor size**

**Metastases size**

**Number of visible mets**

**Lung CT**

**Brain CT scan**
Different biological scenarii

First cancer cell

Primary Tumor

Growth law: \( g_p(V_p) = V_p(\alpha_p - \beta_p \ln(V_p)) \)

Delay?

Dissemination law: \( d(V_p) = \mu(V_p)^\gamma \)

Brain Metastases

Growth law: \( g(V) = V(\alpha - \beta \ln(V)) \)

Same growth?

Dormancy?

Secondary dissemination?

Diagnosis

treatment
The model with dormancy could describe best the data

**Objective function**

<table>
<thead>
<tr>
<th>Model</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>5.51</td>
<td>2.53</td>
</tr>
<tr>
<td>Secondary</td>
<td>5.43</td>
<td>2.3</td>
</tr>
<tr>
<td>Delay</td>
<td>5.23</td>
<td>1.53</td>
</tr>
<tr>
<td>Dormancy</td>
<td>4.93</td>
<td>1.71</td>
</tr>
<tr>
<td>Diff. growth</td>
<td>4.95</td>
<td>1.79</td>
</tr>
</tbody>
</table>

Dormancy estimated to 133 days ± 4.2%
Years post diagnosis

-4 -3 -2 -1 0 1 2 3

-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

Years post-diagnosis

-6 -4 -2 0 2 4

Tumor size (cells)

Imaging detection limit

Number of metastases

Volume (cells)

$10^0$
$10^1$
$10^2$
$10^3$
$10^4$
$10^5$
$10^6$
$10^7$
$10^8$
$10^9$
$10^{10}$
$10^{11}$
$10^{12}$

Tumor size (cells)
Current work: implementing the mechanistic model into a biostatistical model at the population scale

- Use the model for predictions of time-to-relapse and survival
- Implement clinical variables and biomarkers as biologically meaningful covariates
- Predict metastasis for localized breast cancer patients (~10% relapse at 5 years) to advise for adjuvant therapy

```
<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>Accuracy</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random forest</td>
<td>0.727</td>
<td>87</td>
<td>91.7</td>
<td>22.5</td>
</tr>
<tr>
<td>Logistic regression</td>
<td>0.772</td>
<td>90.1</td>
<td>91</td>
<td>25</td>
</tr>
<tr>
<td>Cox regression</td>
<td>0.738</td>
<td>87.4</td>
<td>91.1</td>
<td>16.7</td>
</tr>
<tr>
<td>Bio-based</td>
<td>0.641</td>
<td>89.7</td>
<td>91.3</td>
<td>31.2</td>
</tr>
</tbody>
</table>
```

Notes: AUROC = Area Under the ROC curve, NPV = Negative Predictive Value, PPV = Positive Predictive Value.
3. Tumor-tumor interactions: a dynamical study of concomitant resistance
Concomitant tumor resistance

- **Inhibition** of secondary growth by a primary mass
- Critical clinical implications in terms of **post-surgery metastatic acceleration**

**Primary hypothesis:** athrepsia (deprivation of nutrients)

*Ehrlich, 1906*

- **Non-immunogenic systemic factors**
  *Dewys, Cancer Res 1972*

- **Cytostatic** circulating factor
  *Ruggiero et al., Br J Cancer 1985*

**Concomitant immunity**

*Bashford, 1908*

- CR occurs in **immune-deprived** mice
  *Gorelik, Int J Cancer 1981*

- Systemic inhibition of **angiogenesis**
  *O’Reilly et al. (Folkman), Cell 1994*
Questions and experiment

Questions

• Quantitatively distinguish between qualitatively valid theories of tumor-tumor interactions

• Establish and validate a minimal model able to simulate tumor-tumor interactions

Experiment

• Injection s.c. of two tumors of $10^6$ LLC cells in C57/BL6 mice

• Two groups
  
  – Control: only one tumor
  
  – Group S: simultaneous injection of cells in two different sites
A mouse with two tumors
One tumor has normal growth and the other is suppressed

Individual growth kinetics

Small/Large in two-tumor bearing animals VS artificially paired small/large controls

Benzekry et al. (Hahnfeldt), Cancer Res, 2017
Two-tumors models

• Requirements:

  • **Symmetry**: same parameters for tumor 1 and tumor 2
  
  • Should resume to **single tumor growth** in the absence of the other tumor

• Main assumption for the difference between the two tumors: difference in **the initial take** ($V_{0,1} = 1$, $V_{0,2} = 0.75$)

• Difference in the growth kinetics should not result from difference in $V_0$

• Model selection (rejection) criteria: goodness-of-fit + parameter identifiability

---

**Competition**

\[
\begin{align*}
\frac{dV_1}{dt} &= aV_1 \ln \left( \frac{K}{V_1 + V_2} \right), \quad V_1(t = 0) = V_{0,1} \\
\frac{dV_2}{dt} &= aV_2 \ln \left( \frac{K}{V_1 + V_2} \right), \quad V_2(t = 0) = V_{0,2}
\end{align*}
\]

**Angiogenesis inhibition**

\[
\begin{align*}
\frac{dV_1}{dt} &= aV_1 \ln \left( \frac{K_1}{V_1} \right), \quad V_1(t = 0) = V_{0,1} \\
\frac{dK_1}{dt} &= bV_1 - dV_1^2 K_1 - eV_1 V_2^{1.0,1.0} \quad K_1(t = 0) = K_0 \\
\frac{dV_2}{dt} &= aV_2 \ln \left( \frac{K_2}{V_2} \right), \quad V_2(t = 0) = V_{0,2} \\
\frac{dK_2}{dt} &= bV_2 - dV_2^2 K_2 - eV_1 V_2^{1.0,1.0} \quad K_2(t = 0) = K_0
\end{align*}
\]

**Proliferation inhibition**

\[
\begin{align*}
\frac{dP_1}{dt} &= \alpha P_1 - (\beta P_1 + \gamma (P_1 + P_2)) \quad P_1(t = 0) = V_{0,1} \\
\frac{dQ_1}{dt} &= \beta P_1 + \gamma (P_1 + P_2), \quad Q_1(t = 0) = 0 \\
\frac{dP_2}{dt} &= \alpha P_2 - (\beta P_2 + \gamma (P_1 + P_2)) \quad P_2(t = 0) = V_{0,2} \\
\frac{dQ_2}{dt} &= \beta P_2 + \gamma (P_1 + P_2), \quad Q_2(t = 0) = 0
\end{align*}
\]

_Benzekry et al. (Hahnfeldt), Cancer Res, 2017_
The competition model did not fit

\[
\begin{align*}
\frac{dV_1}{dt} &= a V_1 \ln \left( \frac{K}{V_1 + V_2} \right), & V_1(t = 0) = V_{0,1} \\
\frac{dV_2}{dt} &= a V_2 \ln \left( \frac{K}{V_1 + V_2} \right), & V_2(t = 0) = V_{0,2}
\end{align*}
\]

Benzekry et al. (Hahnfeldt), Cancer Res, 2017
The « inhibition of proliferation » model fitted best

<table>
<thead>
<tr>
<th>Model</th>
<th>Par.</th>
<th>Unit</th>
<th>Median value (CV)</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation inhibition</td>
<td>$\alpha$</td>
<td>day$^{-1}$</td>
<td>5.77 (67.4)</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td>$\beta$</td>
<td>day$^{-1}$</td>
<td>5.07 (49.3)</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>$\gamma$</td>
<td>-</td>
<td>0.074 (2.69e+03)</td>
<td>2.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>SSE</th>
<th>AIC</th>
<th>RMSE</th>
<th>R2</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation inhibition</td>
<td>0.204(0.0319 - 0.461)</td>
<td>-14.2(-54 - -8.28)</td>
<td>0.453(0.182 - 0.688)</td>
<td>0.961(0.902 - 0.987)</td>
<td>3</td>
</tr>
<tr>
<td>Angiogenesis inhibition</td>
<td>0.336(0.154 - 0.772)</td>
<td>-5.07(-27.5 - 5.67)</td>
<td>0.588(0.4 - 0.891)</td>
<td>0.957(0.645 - 0.986)</td>
<td>3</td>
</tr>
<tr>
<td>Competition</td>
<td>0.666(0.141 - 2.2)</td>
<td>-0.71(-33.2 - 13.1)</td>
<td>0.828(0.383 - 1.5)</td>
<td>0.694(-0.0757 - 0.964)</td>
<td>2</td>
</tr>
</tbody>
</table>
Conclusion

• A general modeling framework for **modeling metastases**

• Statistical nonliner **mixed-effects modeling** very useful for parameter estimations

• Simplified model (growth + dissemination) able to describe available clinically relevant **preclinical data** of dynamics of total metastatic burden

• **Same growth** for primary tumor and mets in breast animal model

• A **patient-specific key parameter \( \mu \)** is critical in the quantification of patient-specific metastatic aggressiveness

• Could be clinically useful for guiding **adjuvant therapy** (chemotherapy/WBRT)

• Application to clinical data of **number and size** of brain mets suggested **dormancy** in NSCLC

• **Quantitative** exploration of classical theories for metastatic colonization and **tumor-tumor interactions**
Acknowledgements

**Biology**

- Preclinical data of ortho-surgical animal models of metastases
  - J. Ebos
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  - L. Hlatky
  - P. Hahnfeldt
  - Center of Cancer and Systems Biology, Boston, MA, USA

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  - D. Barbolosi

Thank you for your attention!