The Immune-Mediated Theory of Metastasis

Thomas Hillen and Adam Rhodes, University of Alberta

Metastasis

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Metastatic Curiosities

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- ... do metastasis occur at sites of injuries ?
- ... are metastasis related to chronic inflammations?
- ... do metastasis (sometimes) not react to immuno therapies?

Leili Shahriyari, Asst. Prof., U of Texas.

F1000Research F1000Research 2016, 5:175 Last updated: 25 DEC 2016

Check for updates

OPINION ARTICLE

A new hypothesis: some metastases are the result of inflammatory processes by adapted cells, especially adapted immune cells at sites of inflammation [version 1; referees: 3 approved]

Leili Shahriyari

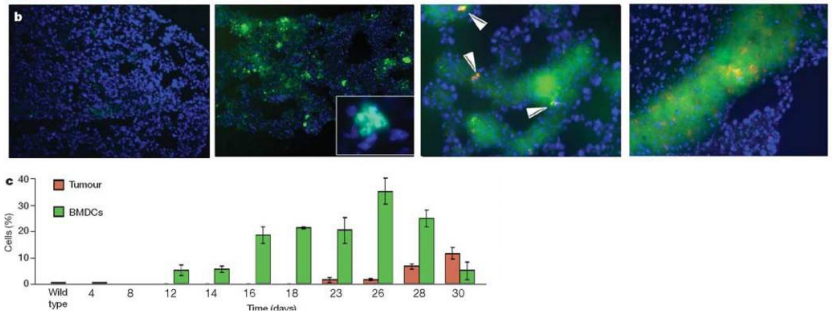
Mathematical Biosciences Institute, The Ohio State University, Columbus, OH, USA

Evidence of immune pro-tumor effects

Nature. 2005 Dec 8;438(7069):820-7.

VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche.

Kaplan RN[1], Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald DD, Jin DK, Shido K, Kerns SA, Zhu Z, Hicklin D, Wu Y, Port JL, Altorki N, Port ER, Ruggero D, Shmelkov SV, Jensen KK, Rafii S, Lyden D.



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PLoS One. 2015; 10(7): e0132710.
Published online 2015 Jul 24. doi: 10.1371/journal.pone.0132710

PMCID: PMC4514595
PMID: 26207636

Inflammation Mediated Metastasis: Immune Induced Epithelial-To-Mesenchymal Transition in Inflammatory Breast Cancer Cells

Evan N. Cohen, [1,5,6] Hui Gao, [1,5] Simone Anfossi, [1,5,6] Michal Mego, [7] Neelima G. Reddy, [1] Bisrat Debeb, [4,5] Antonio Giordano, [1,5] Sanda Tin, [1,5,6] Qiong Wu, [1,5] Raul J. Garza, [1,5] Massimo Cristofanilli, [8] Sendurai A. Mani, [3,6] Denise A. Croix, [9] Naoto T. Ueno, [2,5,6] Wendy A. Woodward, [4,5,6] Raja Luthra, [1] Savitri Krishnamurthy, [3,5] and James M. Reuben [1,5,6,*]

PLoS One

Nat Rev Immunol. 2015 Feb;15(2):73-86. doi: 10.1038/nri3789.

Immune cell promotion of metastasis.

Kitamura T[1], Qian BZ[1], Pollard JW[2].

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Immune cell promotion of metastasis.

Kitamura T[1], Qian BZ[1], Pollard JW[2].

☐ Immune Regulation of the Metastatic Process: Implications for Therapy.

(PMID:27613132 PMCID:PMC5364524)

Abstract | Citations | Related Articles | Data | BioEntities | External Links

de Mingo Pulido A[1], Ruffell B[2]

Affiliations

Advances in Cancer Research [17 Jun 2016, 132:139-163]

2019


The Oncologist®
Breast Cancer
Prediction of Bone Metastasis in Inflammatory Breast Cancer Using a Markov Chain Model
Takeo Fujii,[a,b,†] Jeremy Mason,[d,i,†] Angela Chen,[d] Peter Kuhn,[d,f,g,h,i] Wendy A. Woodward,[b,c] Debu Tripathy,[a] Paul K. Newton,[e,f,h] Naoto T. Ueno[a,b]

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cancers

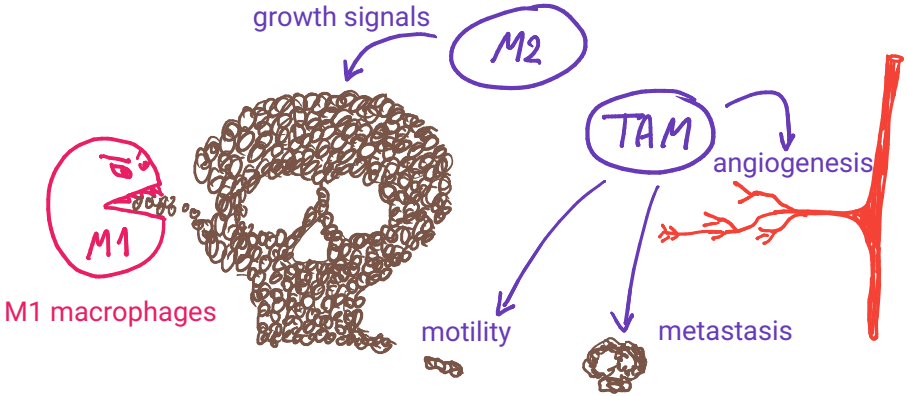
MDPI

Article

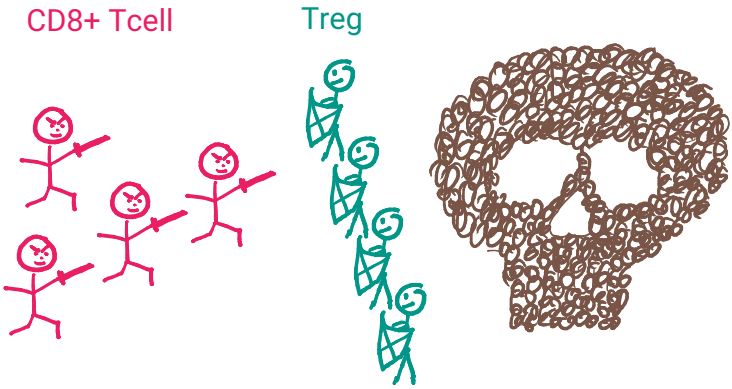
Latent Cytomegalovirus Infection in Female Mice Increases Breast Cancer Metastasis

Zelei Yang [1,2,3], Xiaoyun Tang [1,2,3], Guanmin Meng [1,2,3], Matthew G. K. Benesch [1,2,3,4], Martina Mackova [3,5], Ana Paula Belon [3,5], Jesus Serrano-Lomelin [3,5], Ing Swie Goping [1,2,3,6], David N. Brindley [1,2,3,*] and Denise G. Hemmings [2,3,5,7,*]

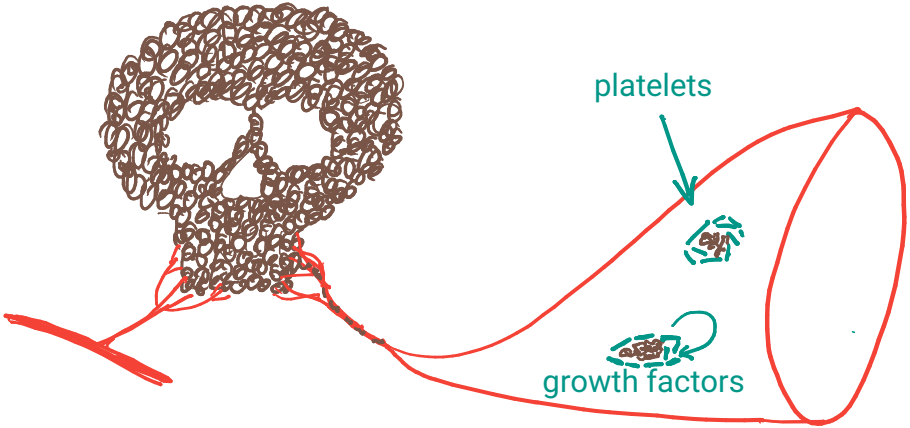
Macrophages



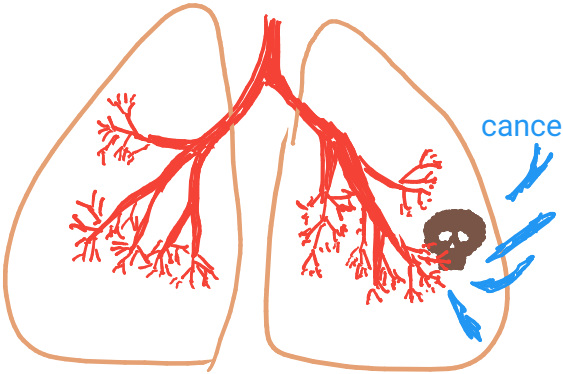
T lymphocytes



Platelets



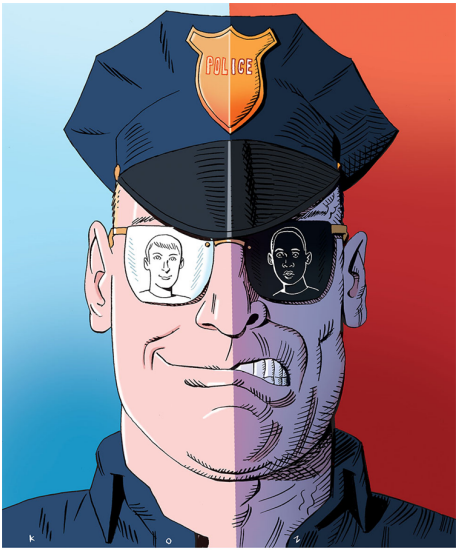
Fibroblasts



cancer associated fibroblasts

+ cancer growth
+ angiogenesis
+ invasion, metastasis
+ drug resistance

Good Cop - Bad Cop



Good Cop Bad Cop

Immune Education

All these transitions are gradual

- M1 $\rightarrow$ M2 $\rightarrow$ TAM
- fibroblasts $\rightarrow$ CAF
- Treg over expressions

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Shahriyari:

- The cancer actively interferes with the phenotypic make up of the immune response.
- chronic inflammations are a natural breeding ground for cancer metastasis.

Metastasis Modelling

- Stochastic models:
  - Liotta 1977: probability to be metastasis free
  - Michor 2006: metastatic phenotypes
  - Hanin 2016-18: natural history of metastasis
  - Frei, Hillen, Rhodes, 2019: branching stochastic process with settlement, metastatic reproduction number

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- PDE models:
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- PDE models:
  - Iwata 2000, Benzekry 2011-17: PDE model with moving boundaries
  - Hillen 2010, birth-jump processes
- Metastasis models including the immune system
  - Kuznetsov: basic model for tumor-immune interaction
  - Eikenberry 2009, PDE model with immune response
  - Enderling et al: dormancy, blow-up, abscopal effects
  - A. Friedman 2006-, Wilkie, Hahnfeldt 2017, Eftimie 2011-18, inclusion of pro-tumor effects of the immune system.
  - Rhodes, Hillen 2019 and 2020: Immune-mediated theory of metastasis.

Theories for metastatic blow-up

- Theory 1: Resource monopolization
- Theory 2: Immune surveillance
- Theory 3: Local promotion, global inhibition
- Theory 4: Immune-mediated theory of metastasis

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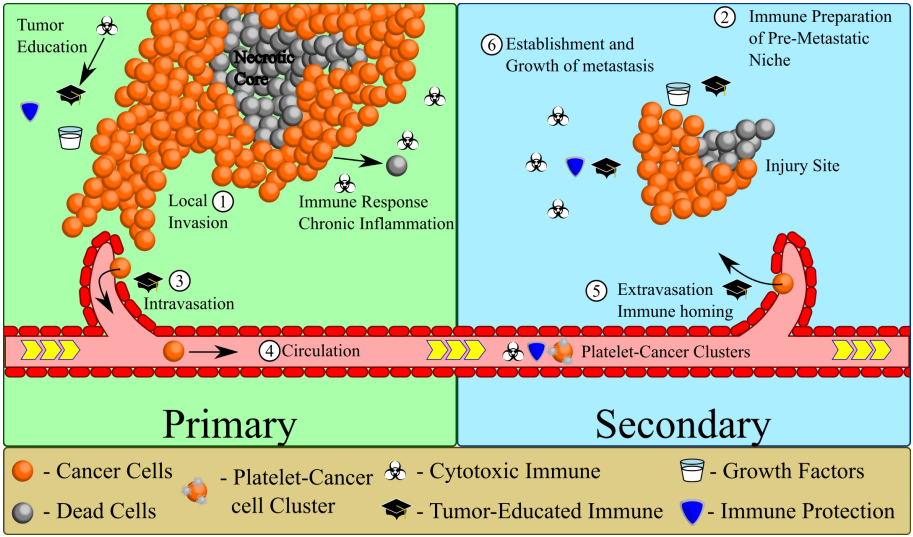
effect	Theory 1	2	3	4
metastatic dormancy	✓	✓	✓	✓
metastatic blow-up	✓	✓	✓	✓
mets at injuries				✓
mets at chronic inflammations				✓
immuno therapies				✓

The Model


Tumor Education
Necrotic Core
Local 1 Invasion
Immune Response Chronic Inflammation
3 Intravasation
4 Circulation
6 Establishment and Growth of metastasis
2 Immune Preparation of Pre-Metastatic Niche
Injury Site
5 Extravasation Immune homing
Platelet-Cancer Clusters
Primary
Secondary
- Cancer Cells
- Dead Cells
- Platelet-Cancer cell Cluster
- Cytotoxic Immune
- Tumor-Educated Immune
- Growth Factors
- Immune Protection

Analysis in three stages:

1. Stage 1: Full model (8 ODEs):
   - detailed inclusion of immune dynamics, recruitment and immune education
   - metastatic dormancy, blow-up, injuries, immune therapies

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   - parameter fitting and sensitivity analysis
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   - metastatic dormancy, blow-up
   - parameter fitting and sensitivity analysis
   - full bifurcation analysis
3. Stage 3: Minimal model (1 ODE):
   - singular perturbation reduction onto a slow manifold
   - systematic study of metastatic blow-up
   - risk assessment of biopsies
   - Immune cells as diagnostic tool for treatment response

Variables

- $i = 1, 2$, primary and secondary tumor sites
- $u_i(t)$: tumor cell density
- $v_i(t)$: necrotic cell density
- $x_i(t)$: cytotoxic immune cells (CT immune)
- $y_i(t)$: tumor educated, pro-tumor immune cells (TE immune).

Stage 1: The Full Model

$$
\begin{aligned}
\frac{du_1}{dt} &= \underbrace{\gamma_1(y_1)g_1(u_1)u_1}_{\text{growth}} - \underbrace{\sigma_1(x_1,y_1)u_1}_{\text{death}} - \underbrace{s_1u_1}_{\text{shedding}} \\
\frac{dv_1}{dt} &= \underbrace{\theta_1\sigma_1(x_1,y_1)u_1}_{\text{dying cells}} - \underbrace{\mu_1v_1}_{\text{lysis}} \\
\frac{dx_1}{dt} &= \underbrace{\alpha_1}_{\text{natural influx}} + \underbrace{\lambda_1(u_1,v_1)x_1}_{\text{growth}} - \underbrace{\rho_1u_1x_1}_{\text{interaction with tumor}} - \underbrace{\omega_1x_1}_{\text{natrual death rate}} - \underbrace{ed_1(u_1)x_1}_{\text{tumor education}} \\
\frac{dy_1}{dt} &= \underbrace{ed_1(u_1)x_1}_{\text{tumor education}} - \underbrace{\tau_1y_1}_{\text{death}} - \underbrace{\tilde{s_1}y_1}_{\text{shedding}} + \underbrace{f_1(u_1)y_1}_{\text{tumor mediated expansion}} \\
\frac{du_2}{dt} &= \underbrace{\gamma_2(y_2)g_2(u_2)u_2}_{\text{growth}} - \underbrace{\sigma_2(x_2,y_2)u_2}_{\text{death}} + \underbrace{est(v_2,y_2,x_2)s_1mu_1}_{\text{establishment}} \\
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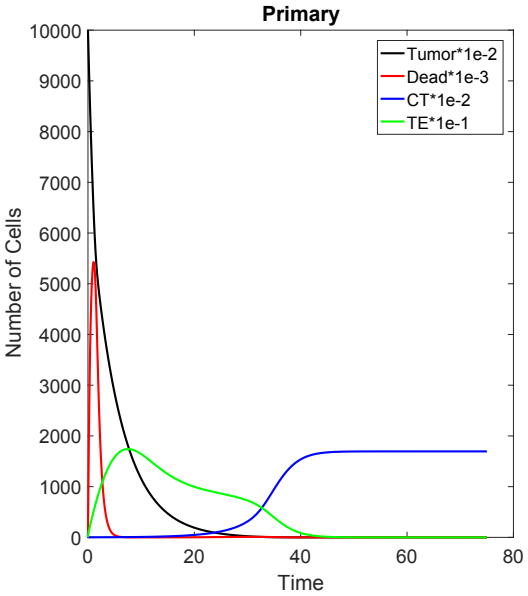
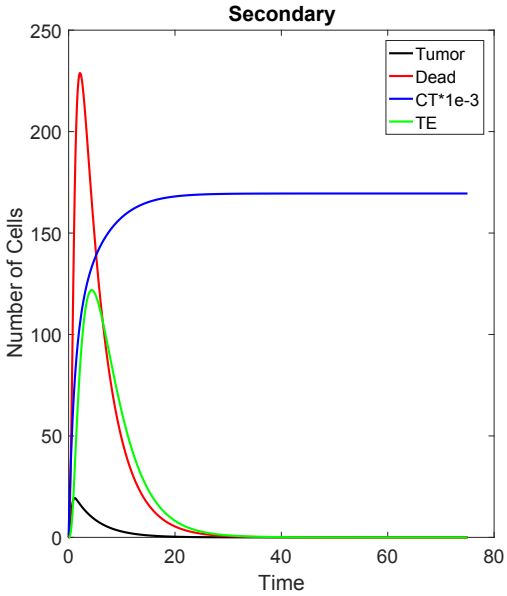
\frac{dy_2}{dt} &= \underbrace{ed_2(u_2)x_2}_{\text{tumor education}} - \underbrace{\tau_2y_2}_{\text{death}} + \underbrace{p\tilde{s_1}y_1}_{\text{arrival}} + \underbrace{f_2(u_2)y_2}_{\text{tumor mediated expansion}}
\end{aligned}
$$

Parameter Estimation

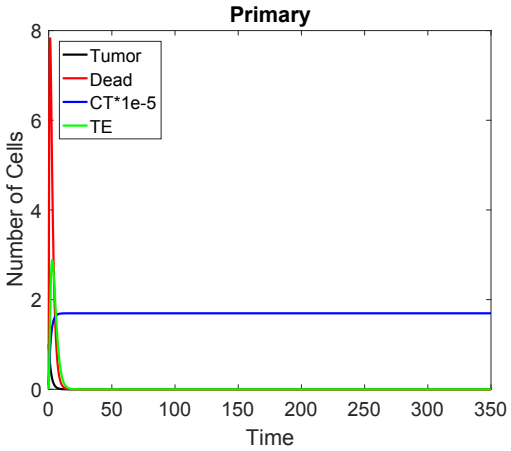
- Total of **70** parameters involved (including functional coefficients)
- Found $\approx$ **40** estimates from the literature.
- Leaves us with $\approx$ **30** unknowns, which are mostly threshold values in the functional coefficients.
- Consequently, we derive theoretical results and make (arbitrary) choices, and explore.

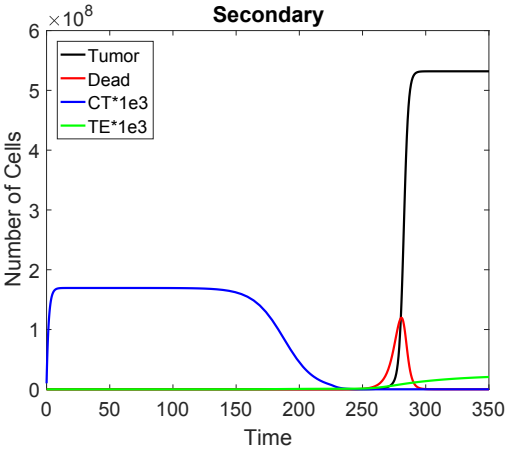
Steady States: Disease-Free



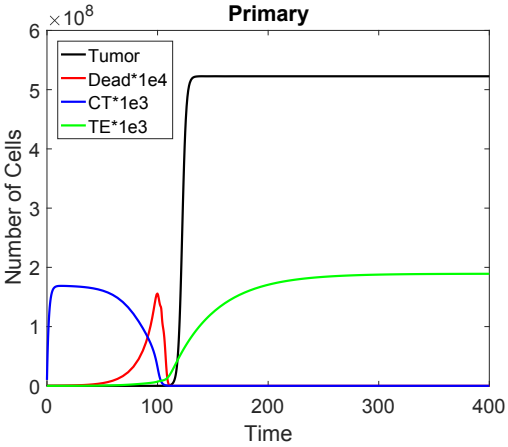


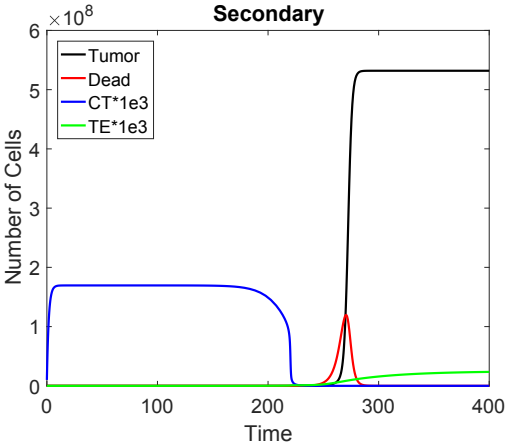
Steady States: Metastatic Only





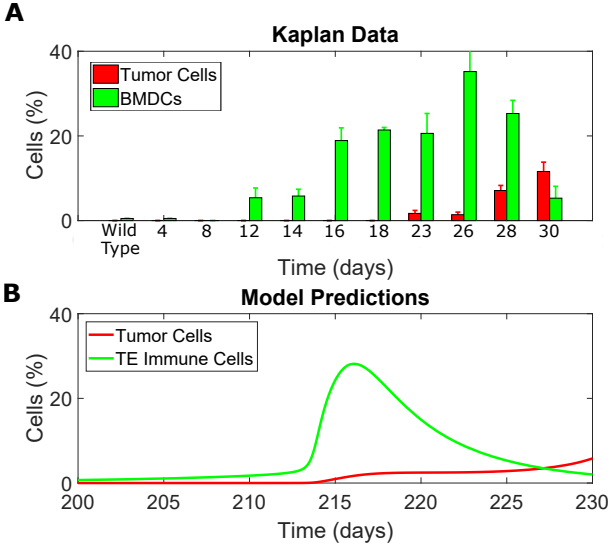
Steady States: Full Disease



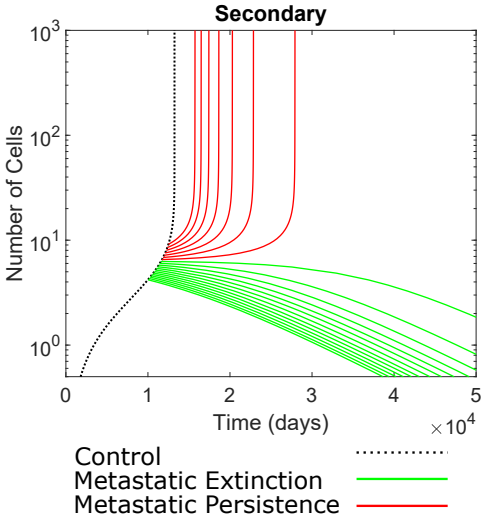


Result 1: Early Seeding

Kaplan et al., Nature 2005, A: Data, B: ODE model.

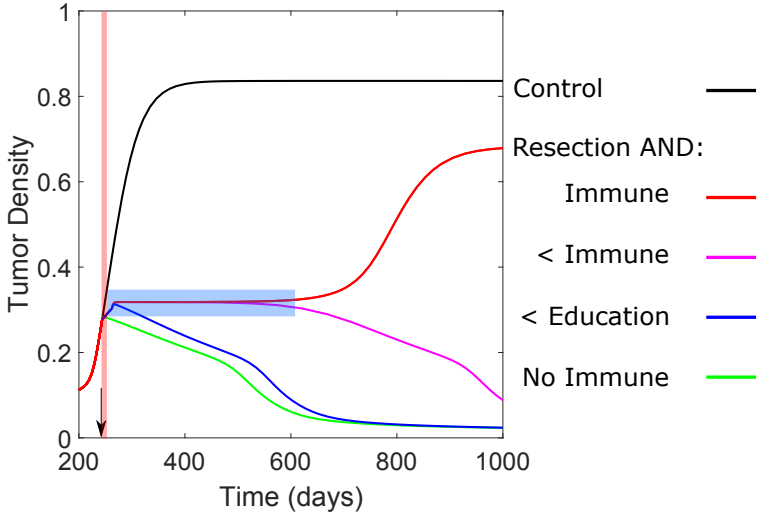


Result 2: Primary Resection



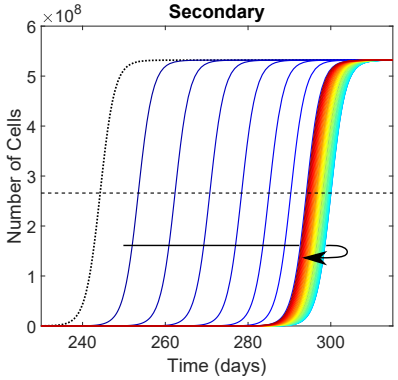
- Early resection leads to slow decline in the secondary (green curves)
- Late resection leads to quick-growth in the secondary site (red curves, metastatic blow-up).

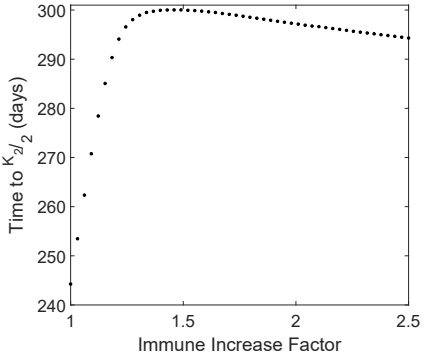
Result 3: Primary Resection and increased Immune Response



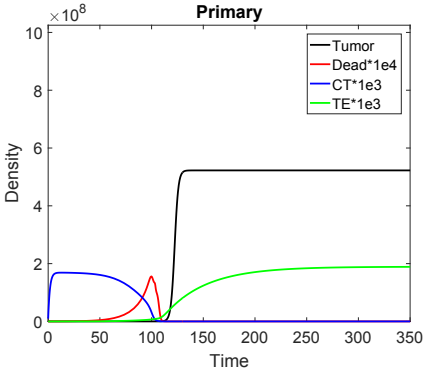
Result 4: Immuno-Therapy

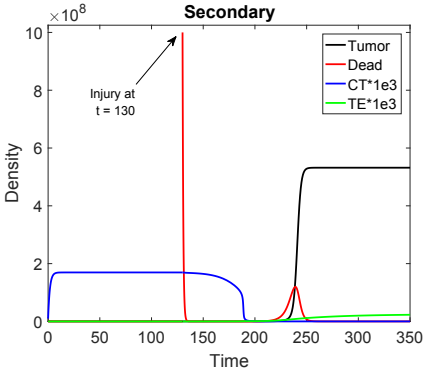
- The effect of immuno-therapies is less than expected.
- The wrong dosage can increase tumor growth (dose is increasing from blue to red).
- Immune education can turn good cops into bad cops.



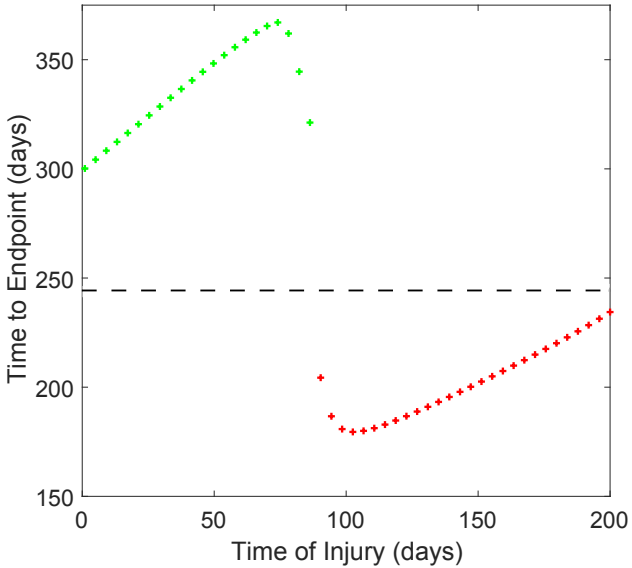


Result 5: Site of Injury





Result 5: Time to reach 1/2 K at injury site



Stage 2: Reduced Model

- Primary reaches steady state before dynamics *really* start at secondary site.
- Treat primary as a source term.

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Model for three quantities:

- u: tumor cell density,
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\end{aligned}$$

Multiscale analysis

- slow tumor dynamics: $\dot{u} = f(u, x, y)$
- fast immune response

$$\begin{aligned} \varepsilon \dot{x} &= g_1(u, x, y) \\ \varepsilon \dot{y} &= g_2(u, x, y) \end{aligned}$$

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- fast immune response

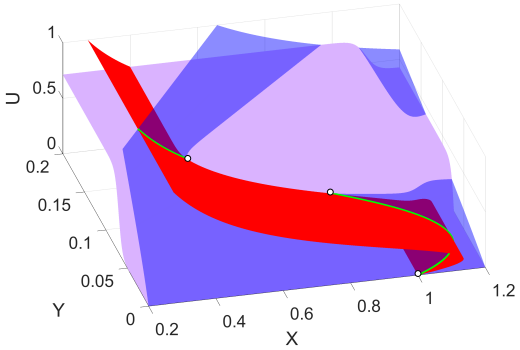
$$\begin{aligned} \varepsilon \dot{x} &= g_1(u, x, y) \\ \varepsilon \dot{y} &= g_2(u, x, y) \end{aligned}$$

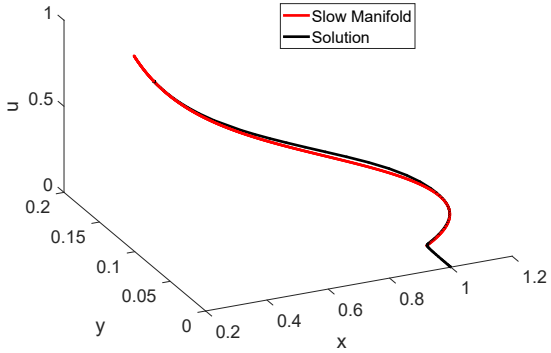
For $\varepsilon \to 0$ use geometric singular perturbation theory

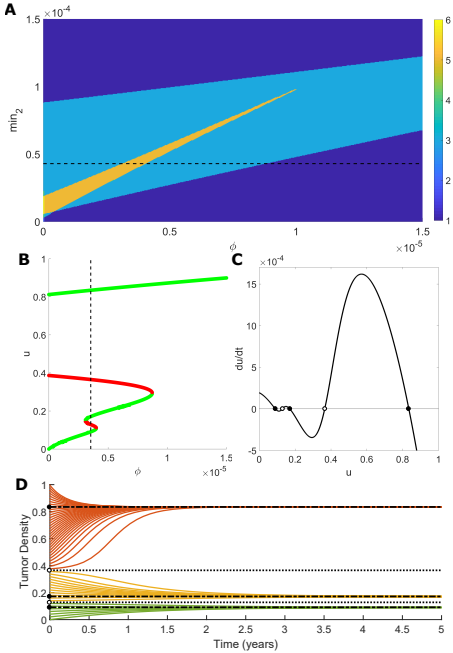
- The dynamics $\dot{u} = f(u, x, y)$ lifes on the slow manifold

$$M := \{(u, x, y) : g_1(u, x, y) = 0, g_2(u, x, y) = 0\}.$$

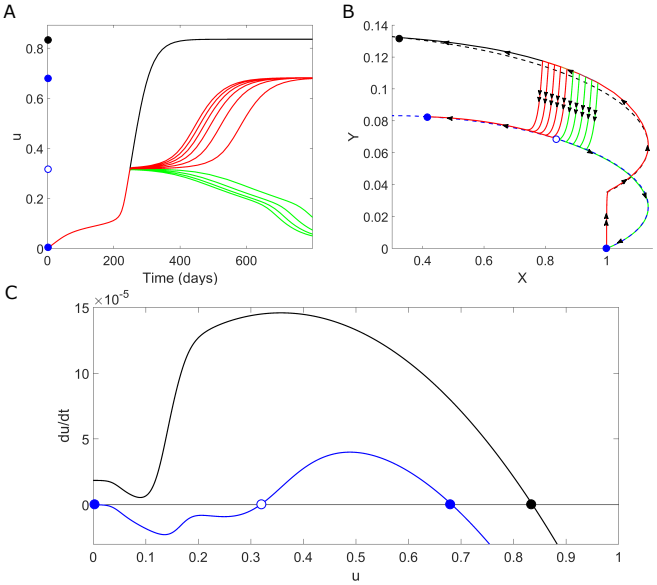
Slow manifold






A
B
C
D
min2
ϕ
u
du/dt
Tumor Density
Time (years)

Result 6: Primary resection



Result 7: Systematic study of metastatic blow-up

	primary removal	inflammation	increased education	metastatic dormancy	metasatic blow-up
case 1	100%				
case 2	100%	yes		✓	
case 3	100%	yes	yes	✓	✓
case 4	small %	yes			(✓)

Biopsies

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Breast Cancer Res Treat. 2013 June ; 139(2): 391–401. doi:10.1007/s10549-013-2575-1.

Acute Inflammation induced by the biopsy of mouse mammary tumors promotes the development of metastasis

Julia Hobson[1], **Phani Gummadidala**[1], **Brian Silverstrim**[1], **Dore Grier**[1], **Janice Bunn**[2], **Ted James**[3], and **Mercedes Rincon**[1,*]

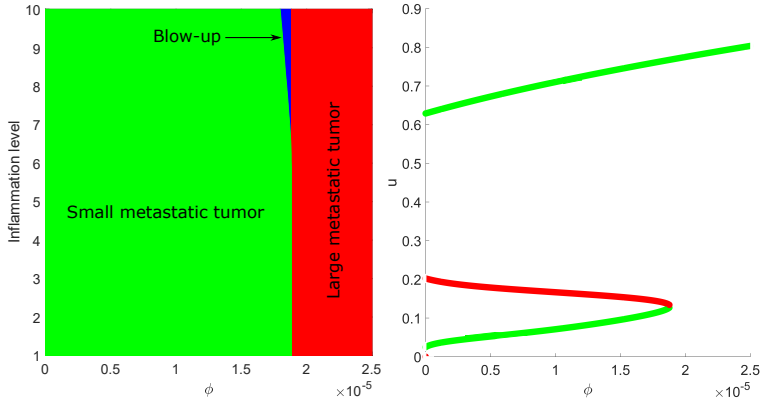
Biopsies

By Kevin Punsky

Mayo Researchers Find Cancer Biopsies Do Not Promote Cancer Spread

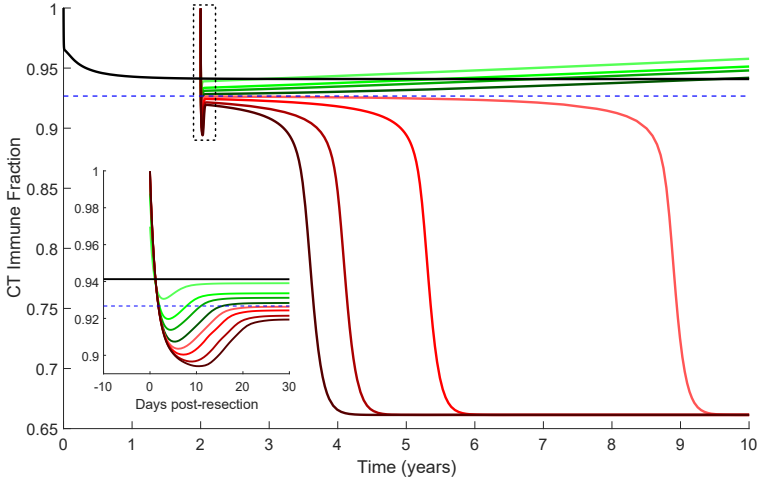
JACKSONVILLE, Fla. — A study of more than 2,000 patients by researchers at Mayo Clinic's campus in Jacksonville, Florida, has dispelled the myth that cancer biopsies cause cancer to spread. In the Jan. 9 online issue of Gut, they show that patients who received a biopsy had a better outcome and longer survival than patients who did not have a biopsy.

Result 8: Biopsies

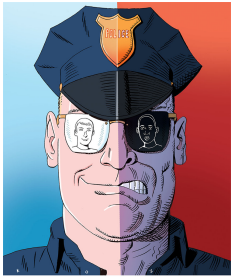


Result 9: Immune response as diagnostic tool

Model for case 4 (resection, inflammation and increased education).



Conclusions 1



- The pro-tumor effects of the immune system are well established and more evidence is gained every day.
- The exact process how tumors influence the immune cells and change their phenotype is largely unknown and more research is needed.

Conclusion 2

- The inclusion of tumor education into a mathematical model can explain
  1. metastatic dormancy
  2. metastatic blow-up upon resection of the primary
  3. metastasis at sites of injuries
  4. metastasis to sites of chronic inflammations
  5. metastasis in bone, lung, and liver
  6. reduced response to immuno-therapies

Conclusion 2

- The inclusion of tumor education into a mathematical model can explain
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  2. metastatic blow-up upon resection of the primary
  3. metastasis at sites of injuries
  4. metastasis to sites of chronic inflammations
  5. metastasis in bone, lung, and liver
  6. reduced response to immuno-therapies
- It would not have been possible to generate these insights without mathematical modelling.

Conclusions 3

- It is likely that pro-tumor immune effects are different from cancer to cancer and from patient to patient. This is not a one-fits-all approach.
- Patient-specific treatment design will not only require a genetic fingerprint of the cancer but also a genetic and phenotypic characterization of the immune system.
- This is a worthwhile idea for future research.

Thank You!

Adam Rhodes:

- A. Rhodes, T. Hillen. A Mathematical Model for the Immune-Mediated Theory of Metastasis. J. Theoretical Biology, Vol 482, 2019.
- A. Rhodes, T. Hillen. The Immune-Mediated Theory of Metastasis Can Explain Metastatic Dormancy and Blow-Up, to appear 2020, bioRxiv.