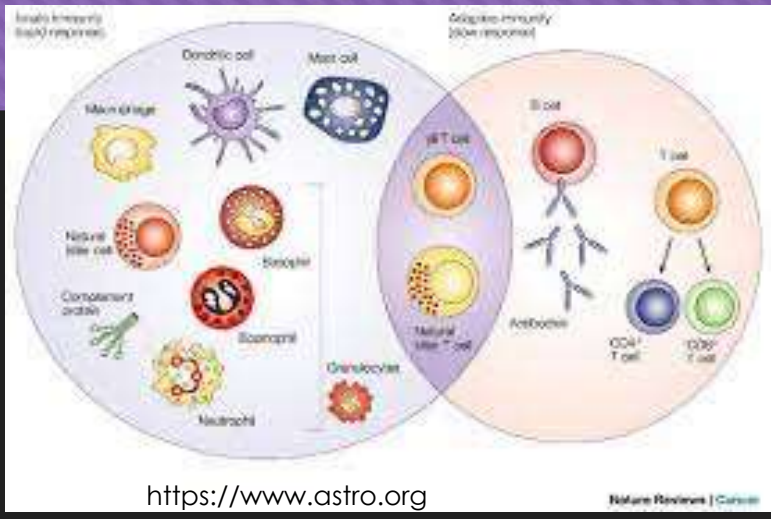
Modelling and computational approaches to investigate heterogeneous innate immune responses to cancers

Raluca Eftimie

University of Franche-Comté, France

Workshop: "NEW TRENDS IN BIOMATHEMATICS: Applications in Oncology and Immunology"

(Reggio Calabria, 21 June, 2024)



https://www.astro.org

Innate immunity in the context of cancer…

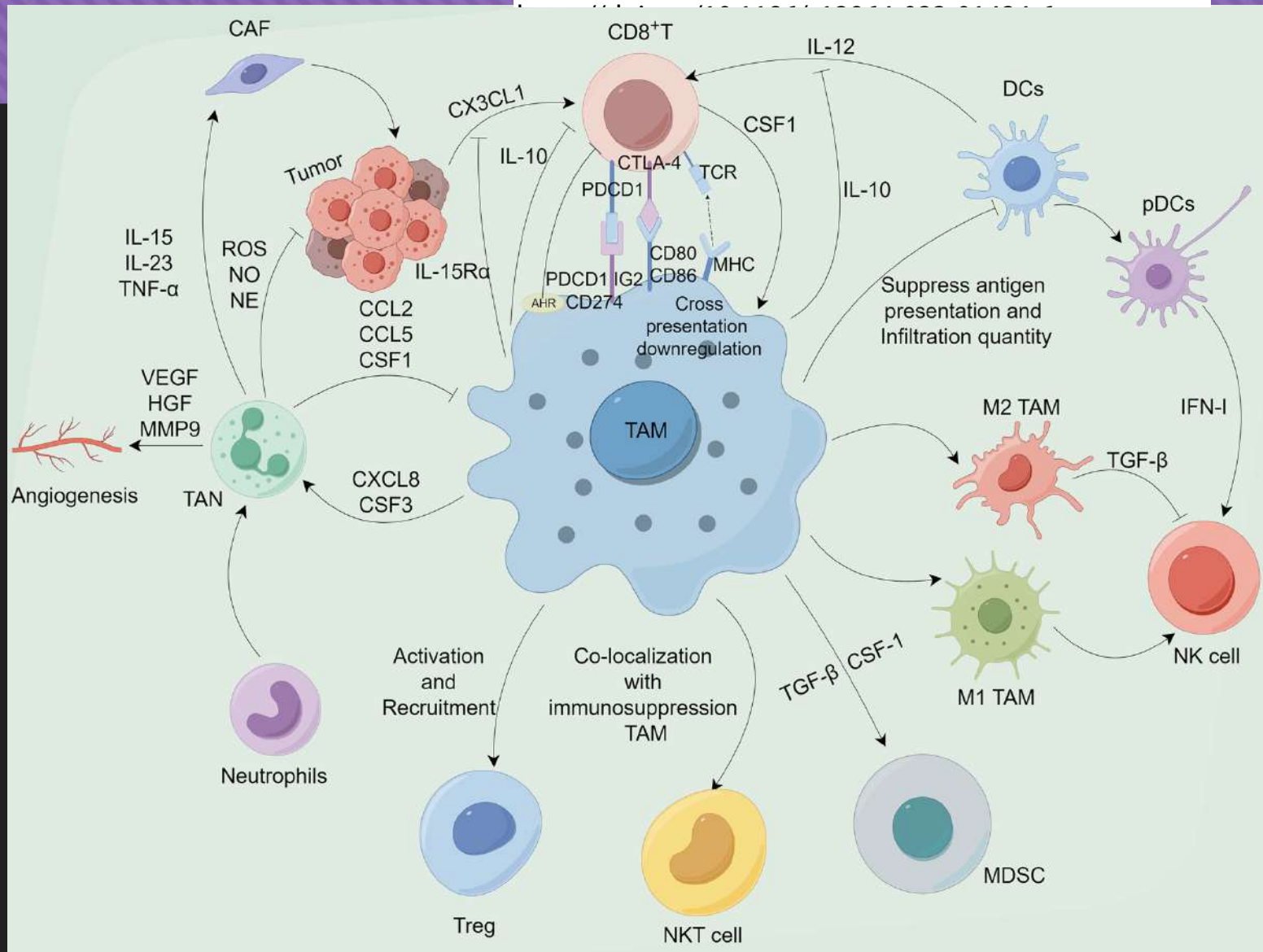
Most of the current immunotherapies for cancer focus on adaptive immune responses (immune checkpoint inhibitors, chimeric antigen receptors, …)

But innate immune cells infiltrating the Tumour Micro Environment (TME) can interfere with adaptive immune responses…

& macrophages play a central role in regulating both innate & adaptive immune responses (Th1&Th2 responses, modulate NK cells, ...)

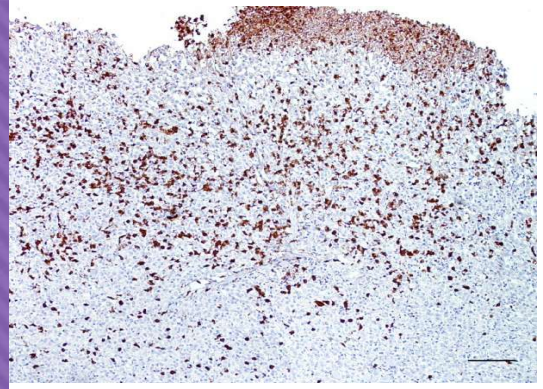
Macrophage barrier in the tumor microenvironment and potential clinical applications

Ji *et al. Cell Communication and Signaling* (2024) 22:74



- **Why focus on macrophages?**

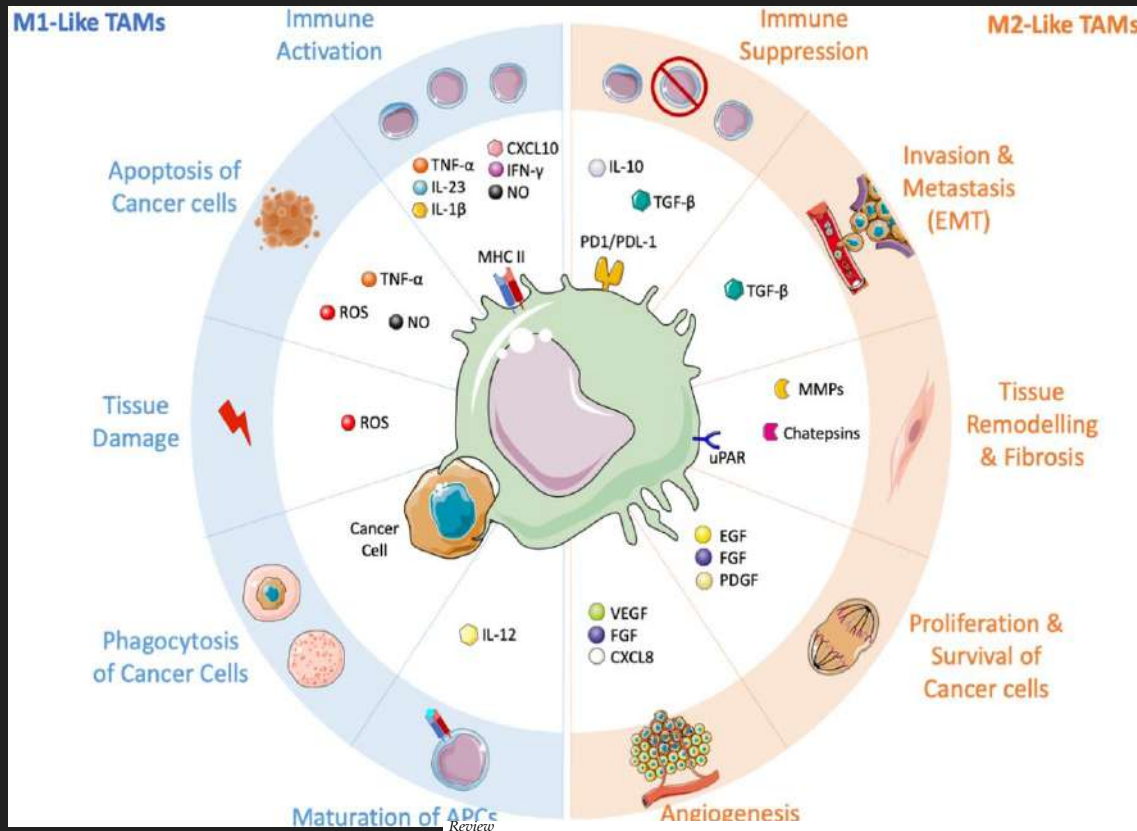
Macrophages are one of the most common cell types in solid tumours, sometimes forming up to 50% of total tumour mass (breast cancer, melanoma, …)

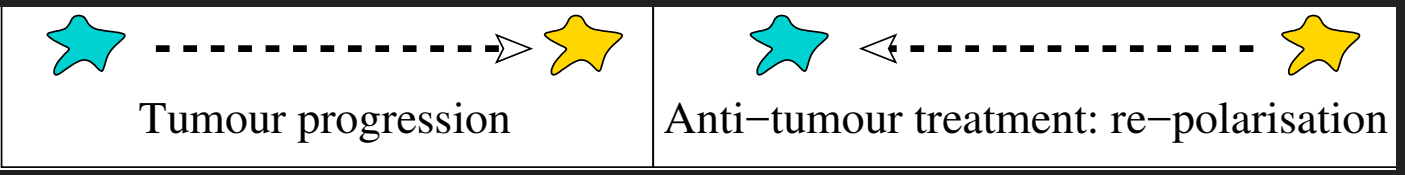


Pires et al, (2011). Ch. 10 in "Melanoma in the clinic: Diagnosis, management and complications of malignancy"

- Increased macrophage infiltration of tumours is generally associated with poor patient prognosis …

- **Heterogeneity** and plasticity of phenotypes (in response to environmental cues)
  - ➢ Anti-tumour M1-like cells
  - ➢ Pro-tumour M2-like cells





Review

Targeting Tumor-Associated Macrophages in Anti-Cancer Therapies: Convincing the Traitors to Do the Right Thing

Cristina Belgiovine [1,*], Elisabeth Digifico [1], Clément Anfray [1], Aldo Ummarino [2] and Fernando Torres Andón [1,3,*]

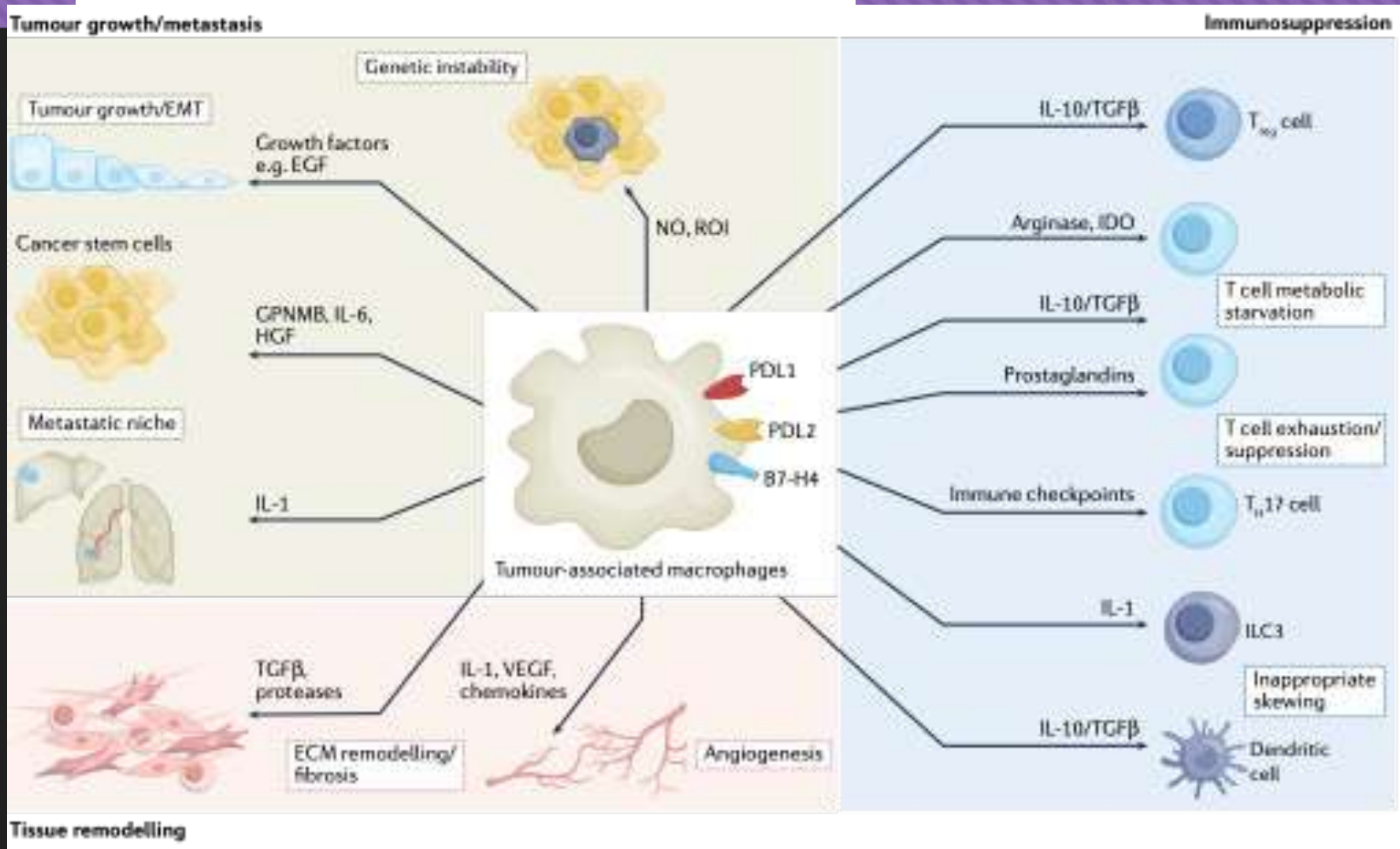
Why focus on macrophages?

- Tumour elimination (directly or through recruitment of T cells)
- Tumour growth
- Tumour cell migration and invasion
- Tumour metastasis
- Angiogenesis
- Suppression of innate and adaptive immune responses (T cell exhaustion/ suppression, …)

Macrophages as tools and targets in cancer therapy

Alberto Mantovani[1,2,3]✉, Paola Allavena[1,2], Federica Marchesi[2,4] and Cecilia Garlanda[1,2]

"…macrophages are double-edged swords with dual potential in cancer, a reflection of their plasticity in response to environmental cues…"



Tumor-Associated Macrophages in Human Breast, Colorectal, Lung, Ovarian and Prostate Cancers

Irina Larionova[1,2], Gulnara Tuguzbaeva[3], Anastasia Ponomaryova[2], Marina Stakheyeva[2], Nadezhda Cherdyntseva[1,2], Valentin Pavlov[4], Evgeniy Choinzonov[2] and Julia Kzhyshkowska[1,5,6]*

Macrophages distribution in various solid tumours:

2 markers are (usually) used to evaluate **T**umour-**A**ssociated **M**acrophages (TAM) correlation with cancer progression:

- **total amount of TAMs** (CD68)

…but:

CD68 Is Not a Macrophage-Specific Marker in Human BC.

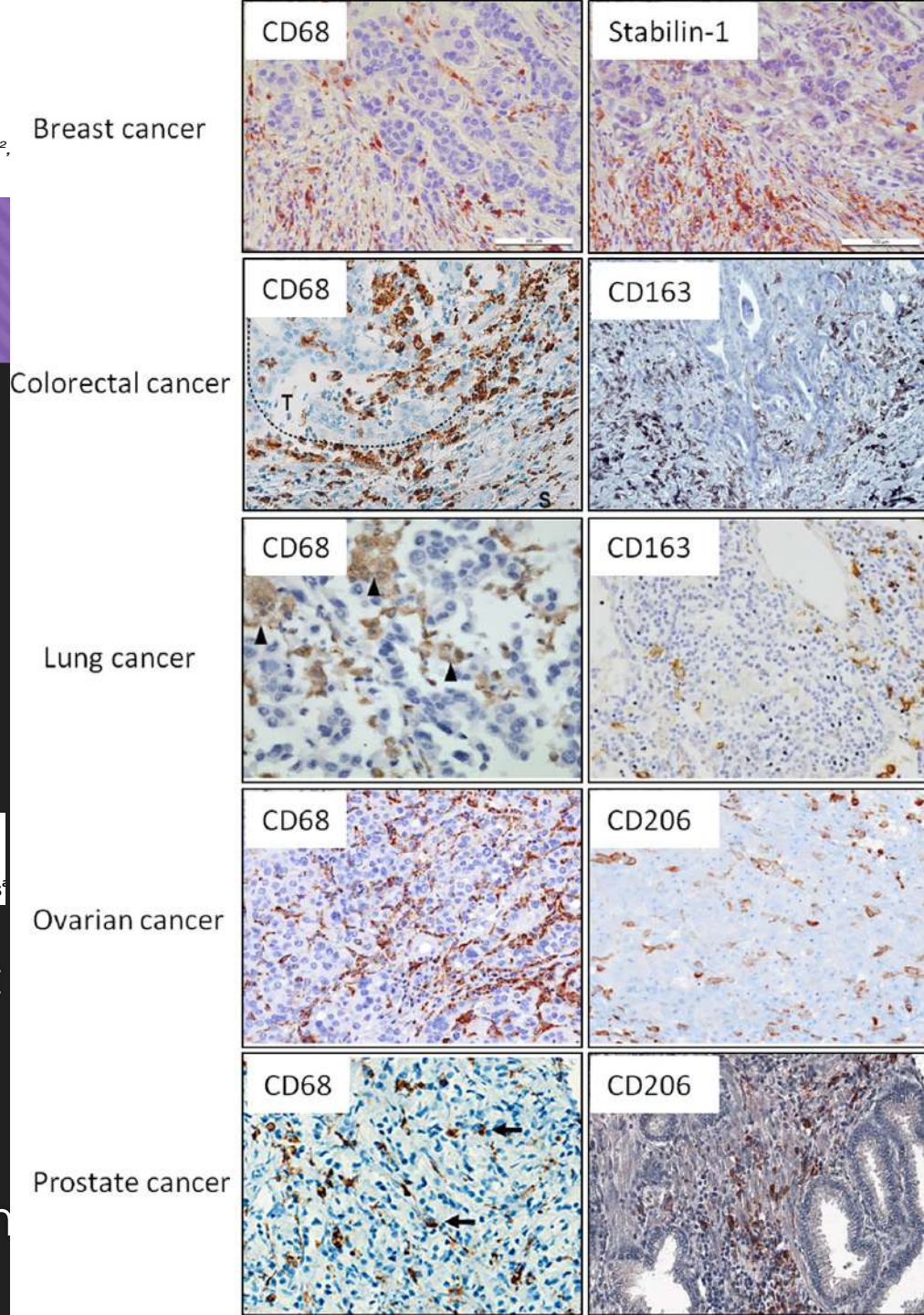
2796–2801 | PNAS | February 21, 2012 | vol. 109 | no. 8

Leukocyte composition of human breast cancer

Brian Ruffell[a], Alfred Au[a,b], Hope S. Rugo[b,c], Laura J. Esserman[b,d], E. Shelley Hwang[b,d], and Lisa M. Coussens[a]

- **phenotype of TAMs** (as identified by specific biomarkers:
(M1) HLA-DR, CD 80/86, iNOS …;
(M2) CD206, CD204, CD163, stabilin, …

- also the role of TAMs in tumour progression can depend on their localization inside the tumour…



Goal of this talk: review some mathematical models derived over the past few years to investigate the roles of various TAMs on tumour dynamics

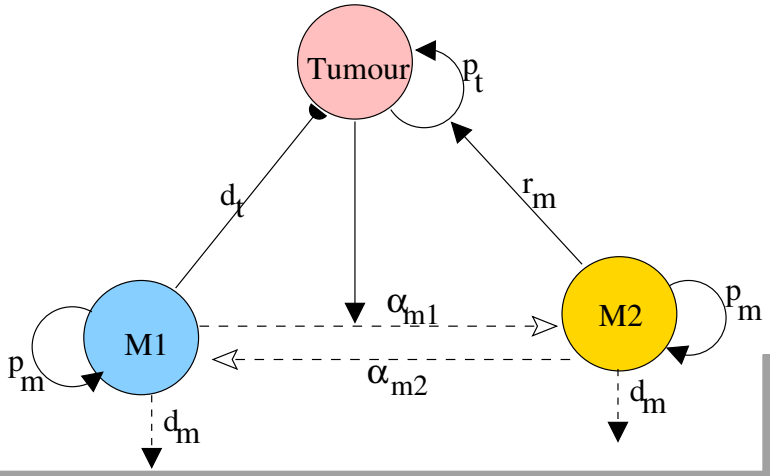
Single-scale models

- discrete macrophage populations: M1 vs M2

Multi-scale models

- phenotype heterogeneity (continuous phenotype variable)
- space heterogeneity (& discrete populations M1 vs M2)

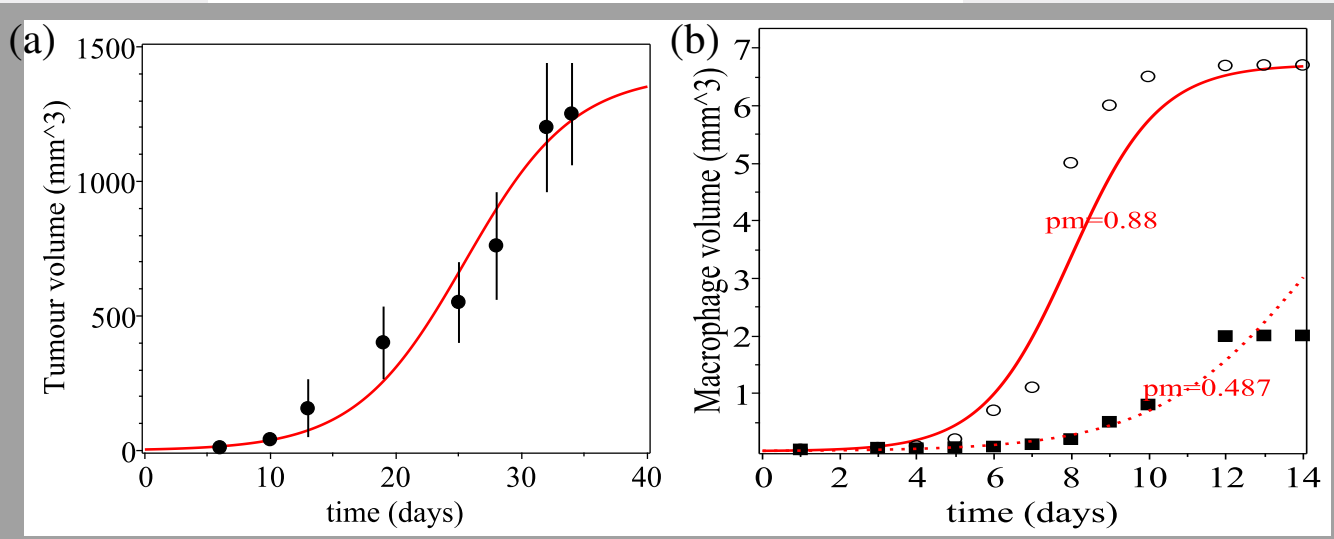
Single-scale models for cancer: ODE models for the anti-tumour & pro-tumour roles of 2 discrete macrophage populations: M1 and M2 cells



$$\text{Tumour:}\quad \frac{du_T}{dt} = p_t u_T\left(1-\frac{u_T}{K_T}\right)(1+r_m u_{M2}) - d_t u_T u_{M1},$$

$$\text{M1 cells:}\quad \frac{du_{M1}}{dt} = p_m u_{M1}\left(1-\frac{u_{M1}+u_{M2}}{K_M}\right) - d_m u_{M1} - \alpha_{m1} u_{M1}\frac{u_T}{K_T^*+u_T} + \alpha_{m2} u_{M2}$$

$$\text{M2 cells:}\quad \frac{du_{M2}}{dt} = p_m u_{M2}\left(1-\frac{u_{M1}+u_{M2}}{K_M}\right) - d_m u_{M2} + \alpha_{m1} u_{M1}\frac{u_T}{K_T^*+u_T} - \alpha_{m2} u_{M2}$$



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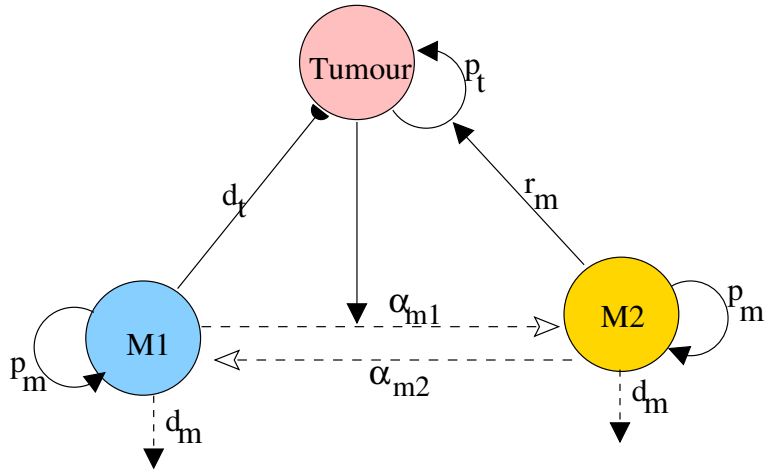

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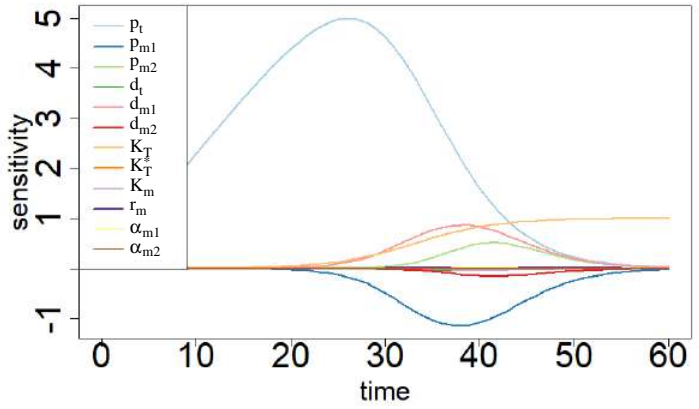
$$\text{M2 cells:}\quad \frac{du_{M2}}{dt} = p_m u_{M2}\left(1-\frac{u_{M1}+u_{M2}}{K_M}\right) - d_m u_{M2} + \alpha_{m1} u_{M1}\frac{u_T}{K_T^*+u_T} - \alpha_{m2} u_{M2}$$

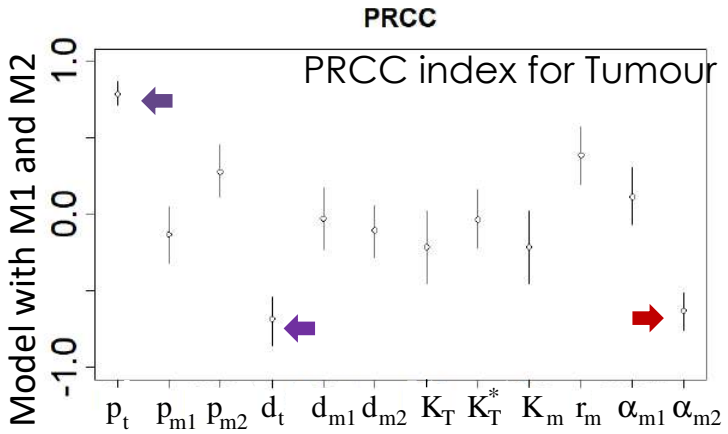
(a) Local sensitivity: vary each parameter at a time

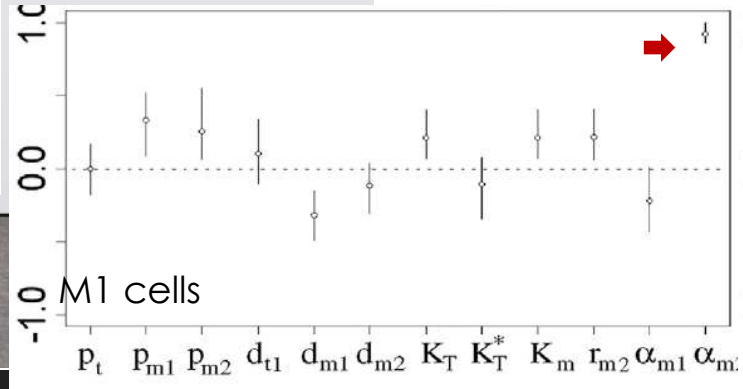
(i) Model with M1 and M2

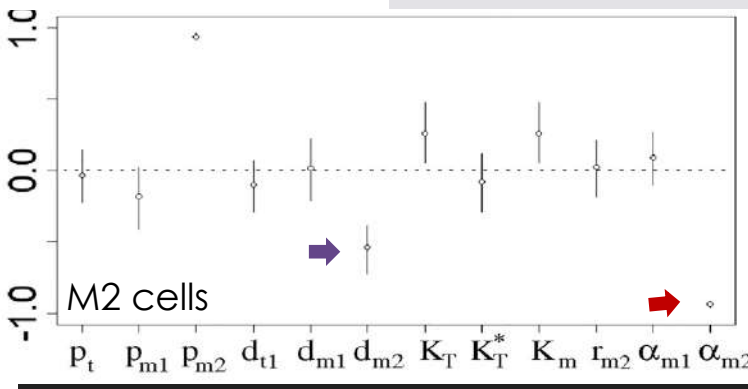


(b) Global sensitivity: vary all parameters

Important param: :
- Tumour cells: α_{m2}, d_{t1}, p_t

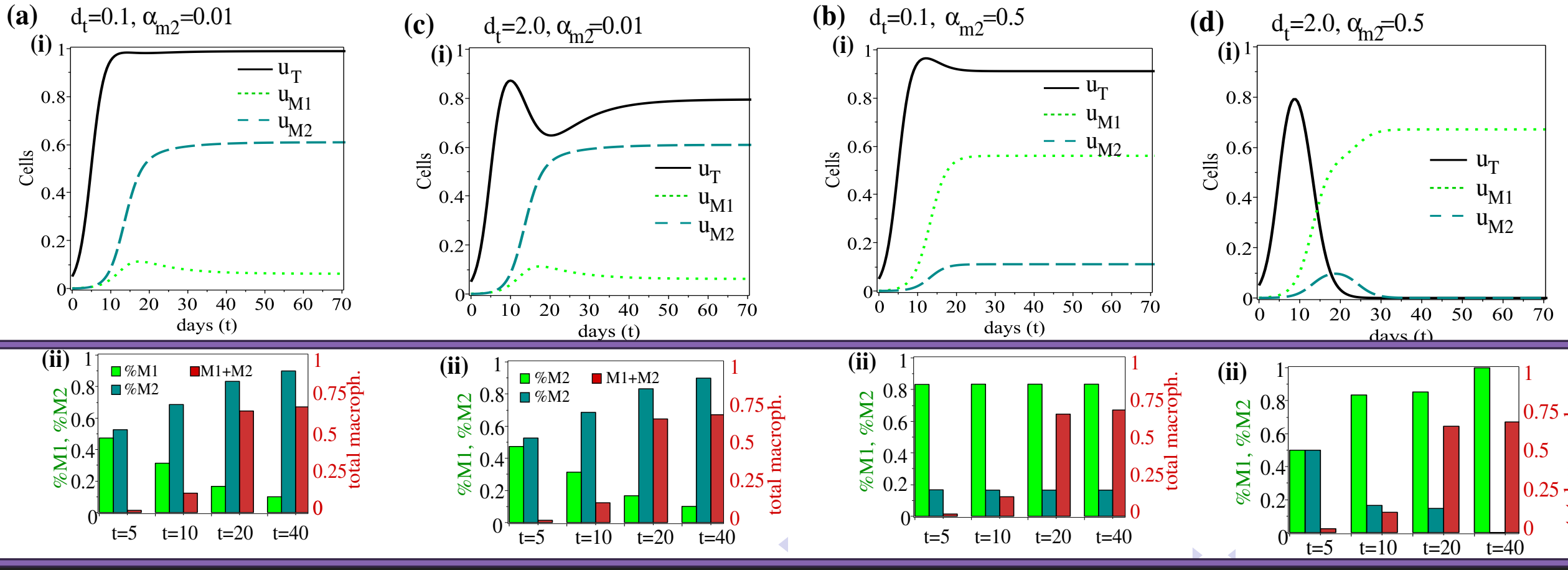






Important param:
- M1 cells: α_{m2};
- M2 cells: $\alpha_{m2}, d_{m2}, p_{m2}$

Single-scale models for cancer: ODE models for the anti-tumour & pro-tumour roles of 2 discrete macrophage populations: M1 and M2 cells: vary parameters identified as important



- Similar composition of infiltrating M1 & M2 cells, but different outcomes…
  (parameters related to functionality of the immune cells)

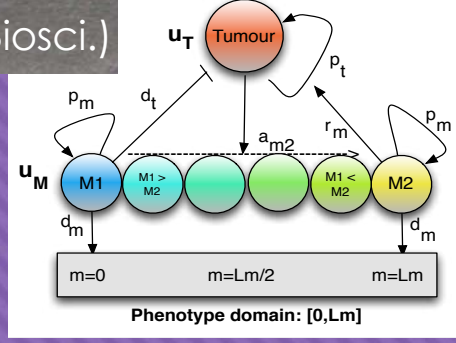
What are we missing?

The heterogeneity of macrophages:

- Phenotypic heterogeneity
- Spatial heterogeneity

Different cell functions?

Eftimie (2020; Math Biosci.)



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Different cell functions?

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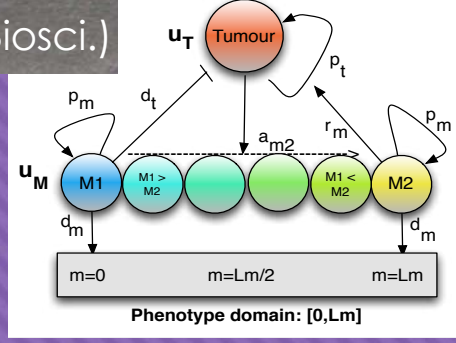


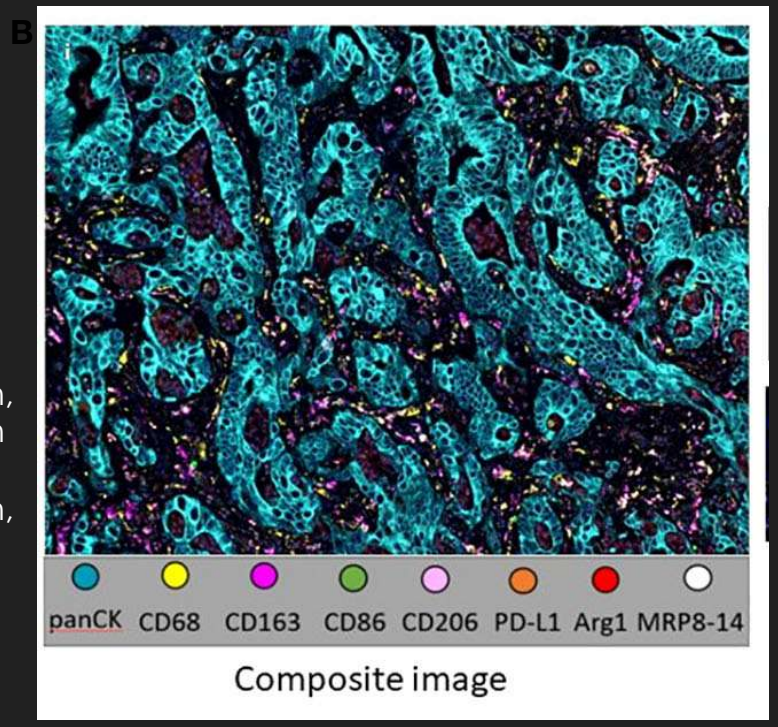
PUBLISHED 10 August 2023

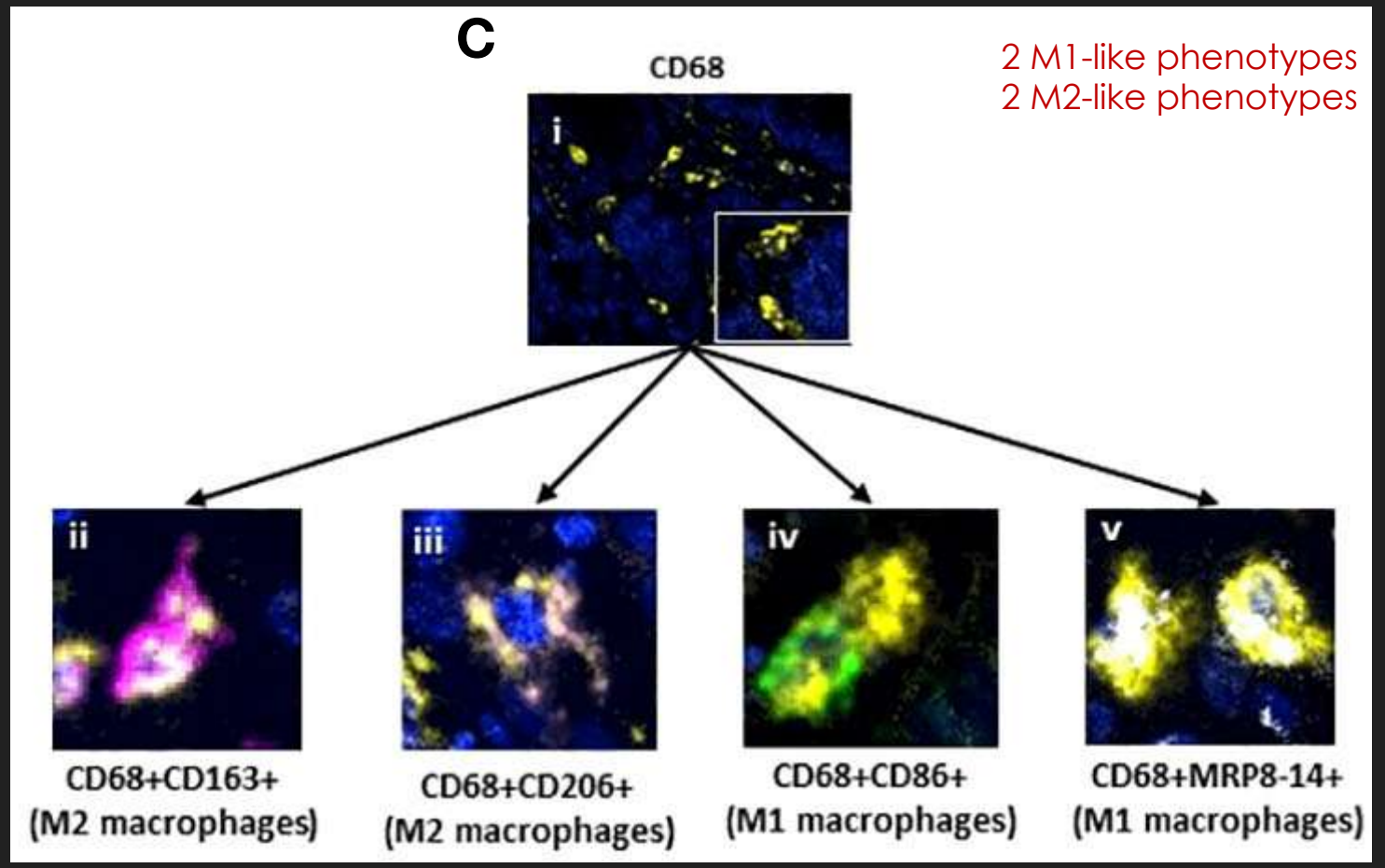
Exploratory study of macrophage polarization and spatial distribution in colorectal cancer liver metastasis: a pilot study

Isha Khanduri[1], Dipen M. Maru[2] and Edwin R. Parra

Digital Image Analysis:

raw image scanning & preparation, tissue segmentation, cell detection & segmentation, phenotyping





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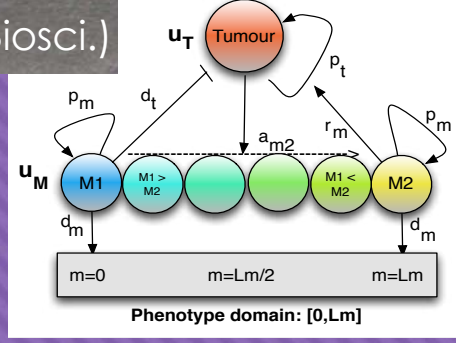
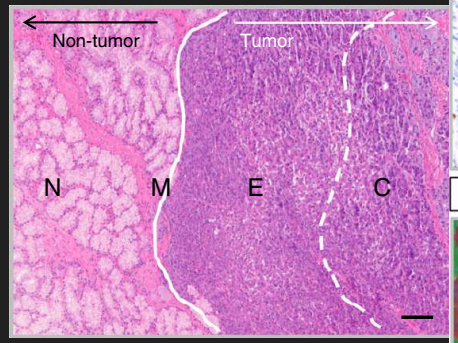
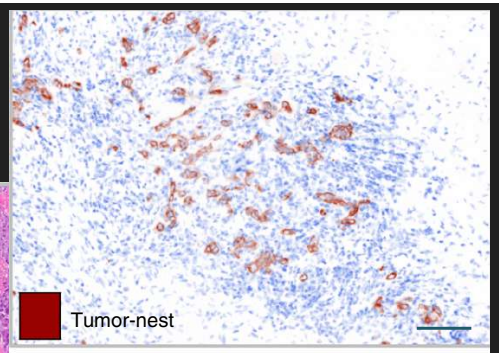


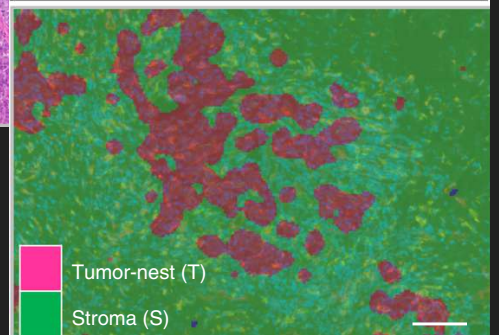
NATURE COMMUNICATIONS | (2019)10:3928

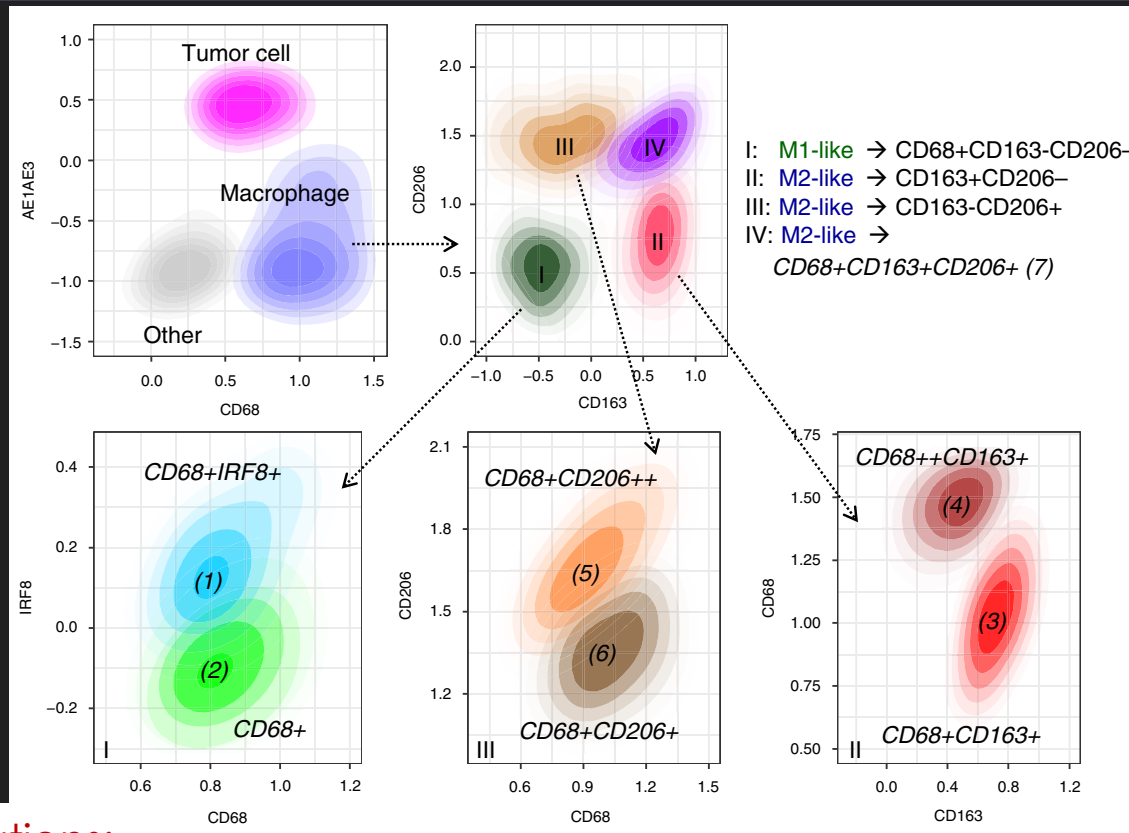
Macrophage spatial heterogeneity in gastric cancer defined by multiplex immunohistochemistry

Yu-Kuan Huang [1,2,3], Minyu Wang [1,2,3], Yu Sun [2,3], Natasha Di Costanzo[1], Catherine Mitchell[4] Adrian Achuthan [3], John A. Hamilton [3,5], Rita A. Busuttil [1,2,3] & Alex Boussioutas[1,2,3]



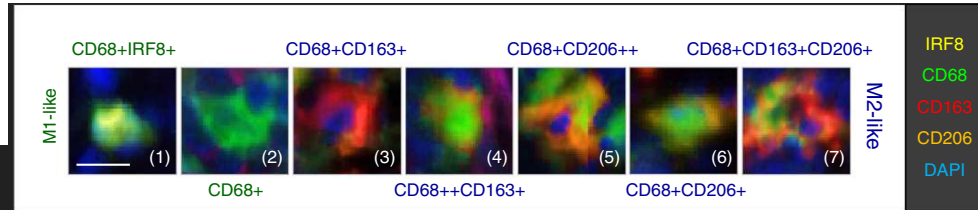






7 TAM sub-populations:

- 2 M1-like phenotypes
- 5 M2-like phenotypes



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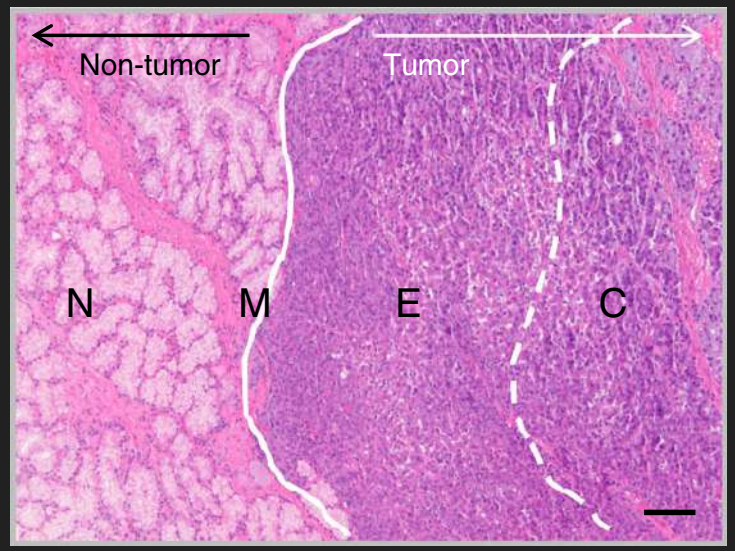
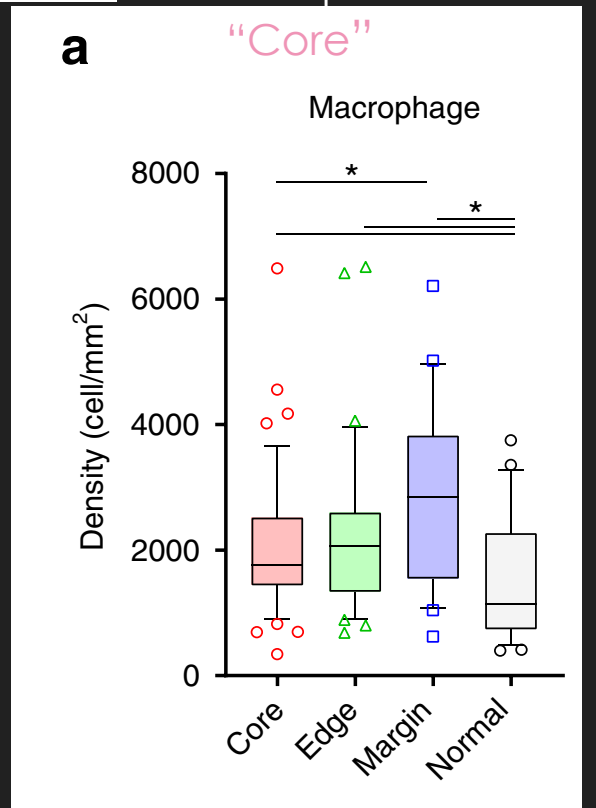
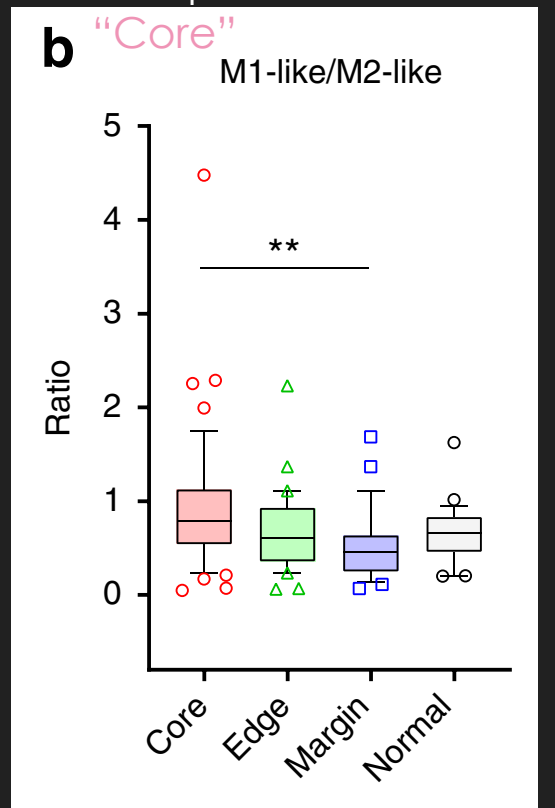


More macrophages in the "Margin" compared to "Core"



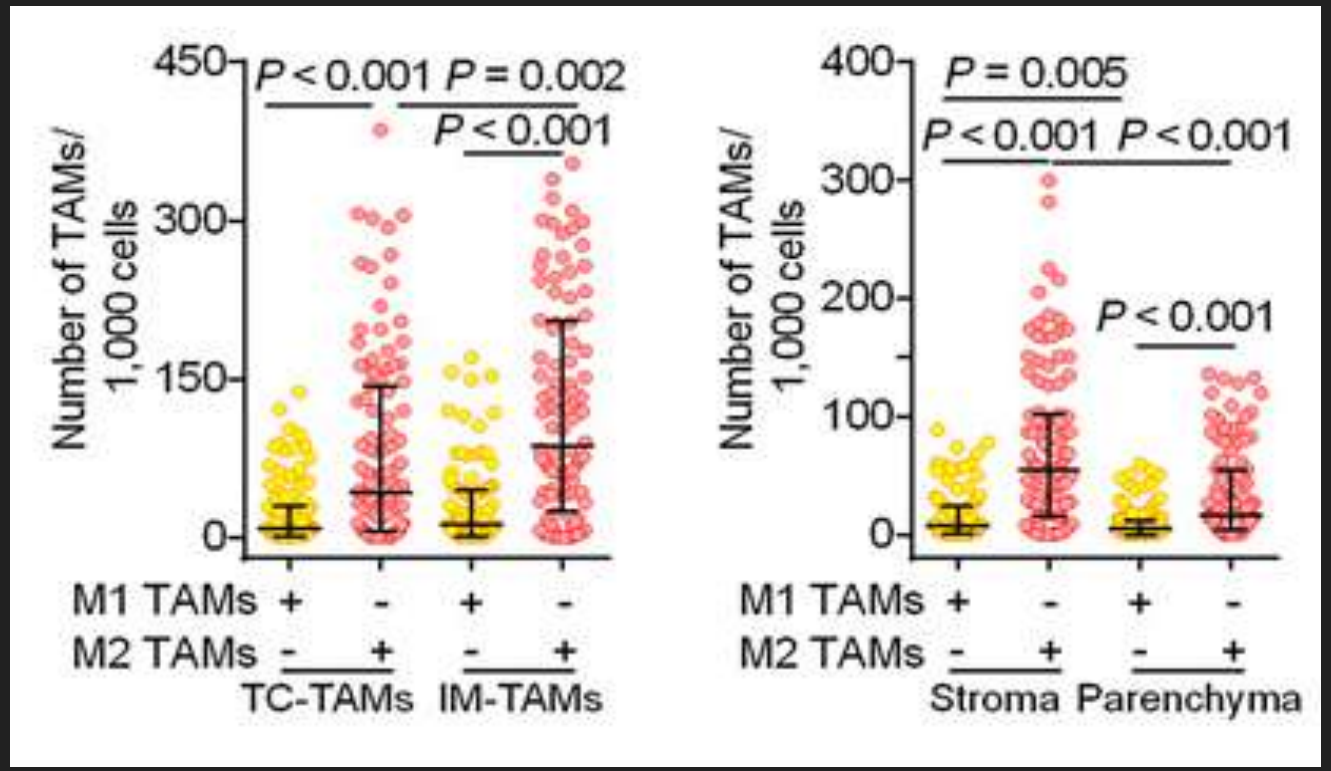
More M2 cells than M1cells in the "Margin" compared to "Core"



CANCER RESEARCH | TUMOR BIOLOGY AND IMMUNOLOGY
Cancer Res 2020;80:4414–25

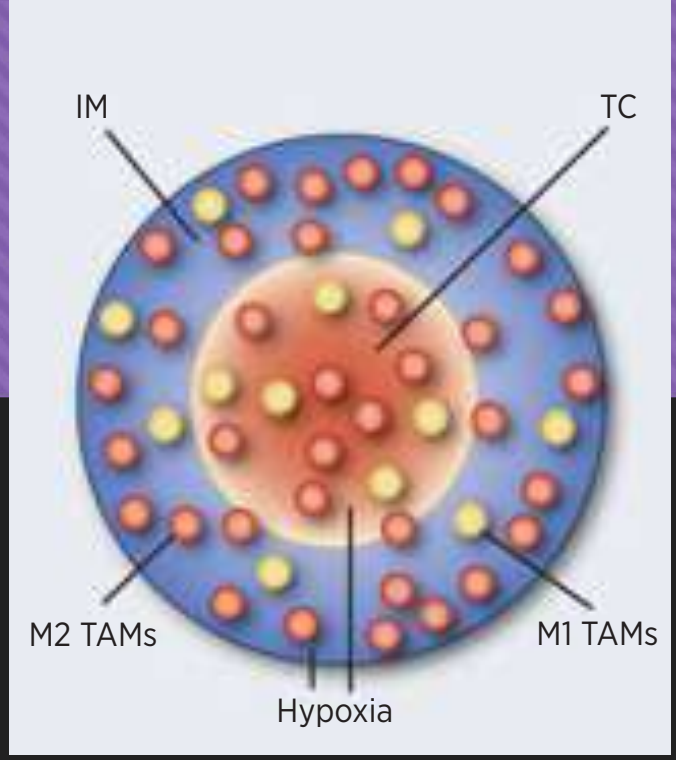
Spatial Density and Distribution of Tumor-Associated Macrophages Predict Survival in Non–Small Cell Lung Carcinoma

Xiang Zheng[1], Andreas Weigert[2], Simone Reu[3], Stefan Guenther[1], Siavash Mansouri[1], Birgit Bassaly[4], Stefan Gattenlöhner[4], Friedrich Grimminger[5], Soni Savai Pullamsetti[1,5], Werner Seeger[1,5,6], Hauke Winter[7], and Rajkumar Savai[1,5,6,8]



Tumour Center

Invasive Margin



Multiplex staining showed that spatial density and distribution of TAMs are independent predictors of lung cancer survival

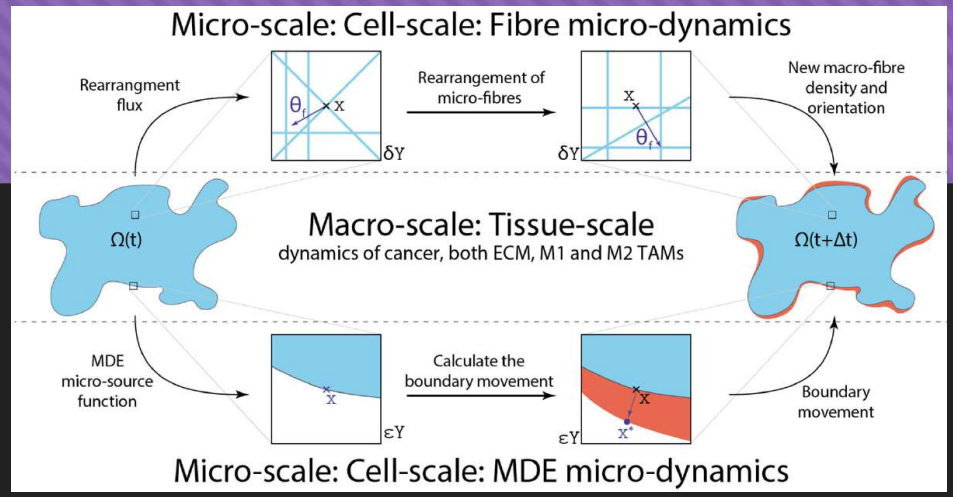
Multi-scale models for cancer: integro-partial-differential equations for the spatial distribution of macrophages inside tumours

D. Trucu

S. Suveges

Re-polarisation of Macrophages Within Collective Tumour Cell Migration: A Multiscale Moving Boundary Approach

*Szabolcs Suveges[1], Raluca Eftimie[2] and Dumitru Trucu[1]**



Macroscale model

$$\frac{\partial c}{\partial t} = \nabla\cdot[D^c(\mathbf{u})\nabla c - c\mathcal{A}_c(x,t,\mathbf{u},\theta_f)] + P_c(\mathbf{u}) - Q_c(\mathbf{u}), \tag{23a}$$

$$\frac{\partial M_1}{\partial t} = \nabla\cdot[D^M(\mathbf{u})\nabla M_1 - M_1\mathcal{A}_M(x,t,\mathbf{u},\mathbf{S}_{M_1M})] + P_{M_1}(\mathbf{u}) - Q_{M_1}(\mathbf{u}) - T_{12}(\mathbf{u}) + T_{21}(\mathbf{u}) + M_I, \tag{23b}$$

$$\frac{\partial M_2}{\partial t} = \nabla\cdot[D^M(\mathbf{u})\nabla M_2 - M_2\mathcal{A}_M(x,t,\mathbf{u},\mathbf{S}_{M_2M})] + P_{M_2}(\mathbf{u}) - Q_{M_2}(\mathbf{u}) + T_{12}(\mathbf{u}) - T_{21}(\mathbf{u}), \tag{23c}$$

$$\frac{\partial l}{\partial t} = -l(\beta_{lc}c + \beta_{lM_1}M_1 + \beta_{lM_2}M_2) + (\gamma_0 + \gamma_{M_2}M_2)(1-\rho(\mathbf{u})), \tag{23d}$$

Non-fibrous

$$\frac{\partial F}{\partial t} = -F(\beta_{Fc}c + \beta_{FM_1}M_1 + \beta_{FM_2}M_2), \tag{23e}$$

Fibrous

components of ECM

$$0 = D_\sigma\Delta\sigma - d_\sigma(c + M_1 + M_2), \tag{23f}$$

M2->M1 re-polarization domain: tumour core (due to lack of nutrients)

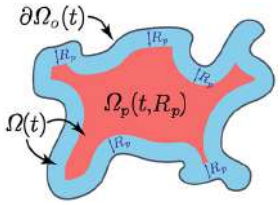


FIGURE 2 | Schematic of the re-polarisation domain $\Omega_p(t,R_p)$ that is highlighted with red.

$$\mathcal{A}_c(x,t,\mathbf{u},\theta_f) := \frac{1}{R}\int_{\mathbf{B}(0,R)}\mathcal{K}(y)\Big[n(y)\big(\mathbf{S}_{cc}c(x+y,t) + \mathbf{S}_{cl}l(x+y,t) + \mathbf{S}_{cM}(M_1(x+y,t) + M_2(x+y,t))\big) + \widehat{n}(y,\theta_f(x+y,t))\mathbf{S}_{cF}F(x+y,t)\Big]\big[1-\rho(\mathbf{u})\big]^+,$$

Microscale model:

$$\frac{\partial m}{\partial \tau} = D_m\Delta m + h(y,\tau),$$
$$m(y,0) = 0,$$
$$\frac{\partial m}{\partial n} = 0,$$

$$h(y,\tau) = \begin{cases} \dfrac{\int_{\mathbf{B}(y,\gamma_h)\cap\Omega(t_0)} h_\Sigma(x,\tau)\,dx}{\lambda(\mathbf{B}(y,\gamma_h)\cap\Omega(t_0))} & y \in \epsilon Y \cap \Omega(t_0), \\ 0 & y \notin \epsilon Y \setminus (\Omega(t_0) + \{z \in Y \mid \|z\|_2 < \rho\}), \end{cases} \tag{26}$$

$$h_\Sigma(x,\tau) := \alpha_c c(x,t_0+\tau) + \alpha_{M_1}M_1(x,t_0+\tau) + \alpha_{M_2}M_2(x,t_0+\tau),$$

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$$\frac{\partial c}{\partial t} = \nabla\cdot[D^c(\mathbf{u})\nabla c - c\,\mathcal{A}_c(x,t,\mathbf{u},\theta_f)] + P_c(\mathbf{u}) - Q_c(\mathbf{u}), \tag{23a}$$

$$\frac{\partial M_1}{\partial t} = \nabla\cdot[D^M(\mathbf{u})\nabla M_1 - M_1\,\mathcal{A}_M(x,t,\mathbf{u},\mathbf{S}_{M_1M})] + P_{M_1}(\mathbf{u}) - Q_{M_1}(\mathbf{u}) - T_{12}(\mathbf{u}) + T_{21}(\mathbf{u}) + M_I, \tag{23b}$$

$$\frac{\partial M_2}{\partial t} = \nabla\cdot[D^M(\mathbf{u})\nabla M_2 - M_2\,\mathcal{A}_M(x,t,\mathbf{u},\mathbf{S}_{M_2M})] + P_{M_2}(\mathbf{u}) - Q_{M_2}(\mathbf{u}) + T_{12}(\mathbf{u}) - T_{21}(\mathbf{u}), \tag{23c}$$

$$\frac{\partial l}{\partial t} = -l(\beta_{lc}c + \beta_{lM_1}M_1 + \beta_{lM_2}M_2) + (\gamma_0 + \gamma_{M_2}M_2)(1-\rho(\mathbf{u})), \tag{23d}$$

$$\frac{\partial F}{\partial t} = -F(\beta_{Fc}c + \beta_{FM_1}M_1 + \beta_{FM_2}M_2), \tag{23e}$$

$$0 = D_\sigma\Delta\sigma - d_\sigma(c + M_1 + M_2), \tag{23f}$$

K(y) : kernel for the spatial ranges of cell-cell and cell-matrix interactions

S_{cc}, S_{cl}, S_{cF}... : strength of cell-cell and cell-matrix adhesive interactions

$$\mathcal{A}_c(x,t,\mathbf{u},\theta_f) := \frac{1}{R}\int_{\mathbf{B}(0,R)} \mathcal{K}(y)\,n(y)\Big(\mathbf{S}_{cc}c(x+y,t) + \mathbf{S}_{cl}l(x+y,t) + \mathbf{S}_{cM}(M_1(x+y,t)+M_2(x+y,t))\Big) + \widehat{n}(y,\theta_f(x+y,t))\mathbf{S}_{cF}F(x+y,t)\Big]\big[1-\rho(\mathbf{u})\big]^+,$$

Why non-local cell-cell and cell-matrix interactions?

Review

Tunneling Nanotubes and Tumor Microtubes in Cancer

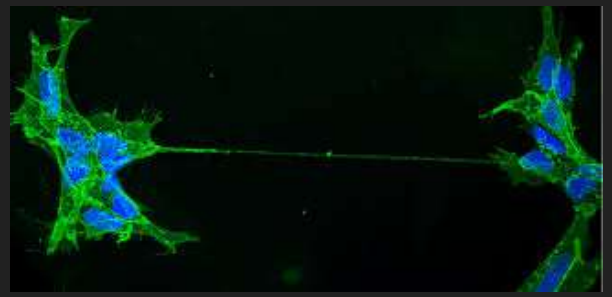
Cora Roehlecke [1,*] and Mirko H. H. Schmidt [1,2,3]

Specialized intercellular communications via cytonemes and nanotubes.

Yukiko M. Yamashita[1], **Mayu Inaba**[2], and **Michael Buszczak**[3]

Thin, long membrane protrusions:

- Tunneling nanotubes (TNT): up to 100 μm
- Cytonemes: up to 700 μm
- Average cell diameter: 10-40 μm



$$\mathcal{A}_c(x,t,\mathbf{u},\theta_f) := \frac{1}{R}\int_{\mathbf{B}(0,R)} \mathcal{K}(y)\Big[n(y)\big(\mathbf{S}_{cc}c(x+y,t)+\mathbf{S}_{cl}l(x+y,t) +\mathbf{S}_{cM}(M_1(x+y,t)+M_2(x+y,t))\big) +\widehat{n}(y,\theta_f(x+y,t))\mathbf{S}_{cF}F(x+y,t)\Big]\big[1-\rho(\mathbf{u})\big]^+,$$

$$\mathbf{S}_{cc}(x,t) := \mathbf{S}_{min} + (\mathbf{S}_{max}-\mathbf{S}_{min})\exp\left[1-\frac{1}{1-(1-l(x,t))^2}\right]$$

Why non-local cell-cell and cell-matrix interactions?

Review

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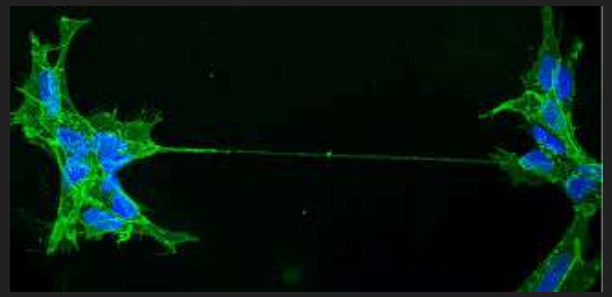
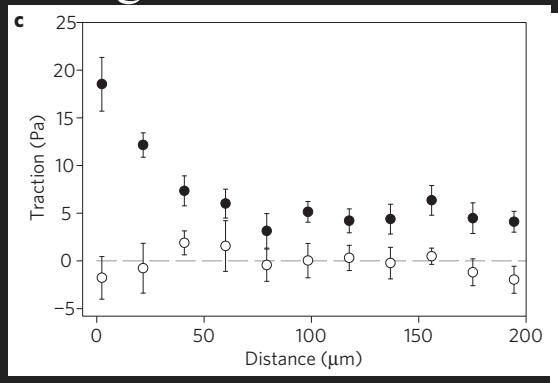
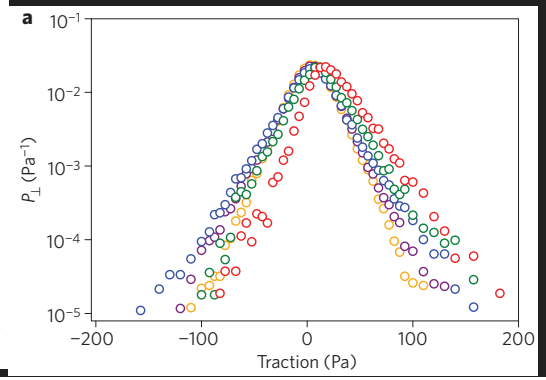


Long-distance traction forces:





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$$\mathbf{S}_{cc}(x,t) := \mathbf{S}_{min} + (\mathbf{S}_{max} - \mathbf{S}_{min}) \exp\left[1 - \frac{1}{1-(1-l(x,t))^2}\right]$$

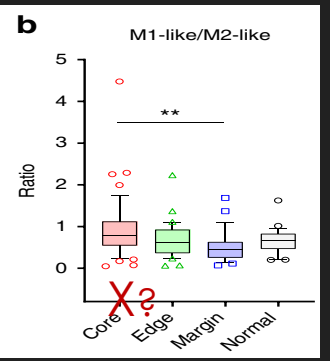
Physical forces during collective cell migration

Xavier Trepat[1,2★], **Michael R. Wasserman**[1], **Thomas E. Angelini**[3], **Emil Millet**[1], **David A. Weitz**[3], **James P. Butler**[1,4] and **Jeffrey J. Fredberg**[1★]

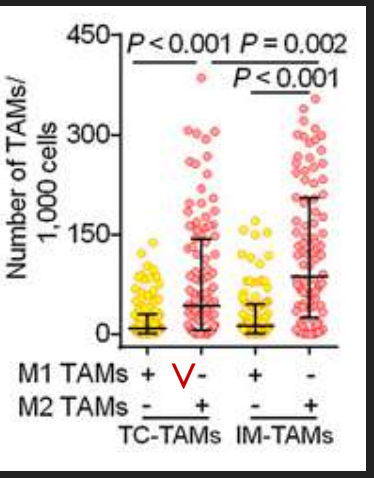
Multi-scale models for cancer: integro-differential equations for the spatial distribution of macrophages inside tumours (& random parameters)

D. Trucu

S. Suveges



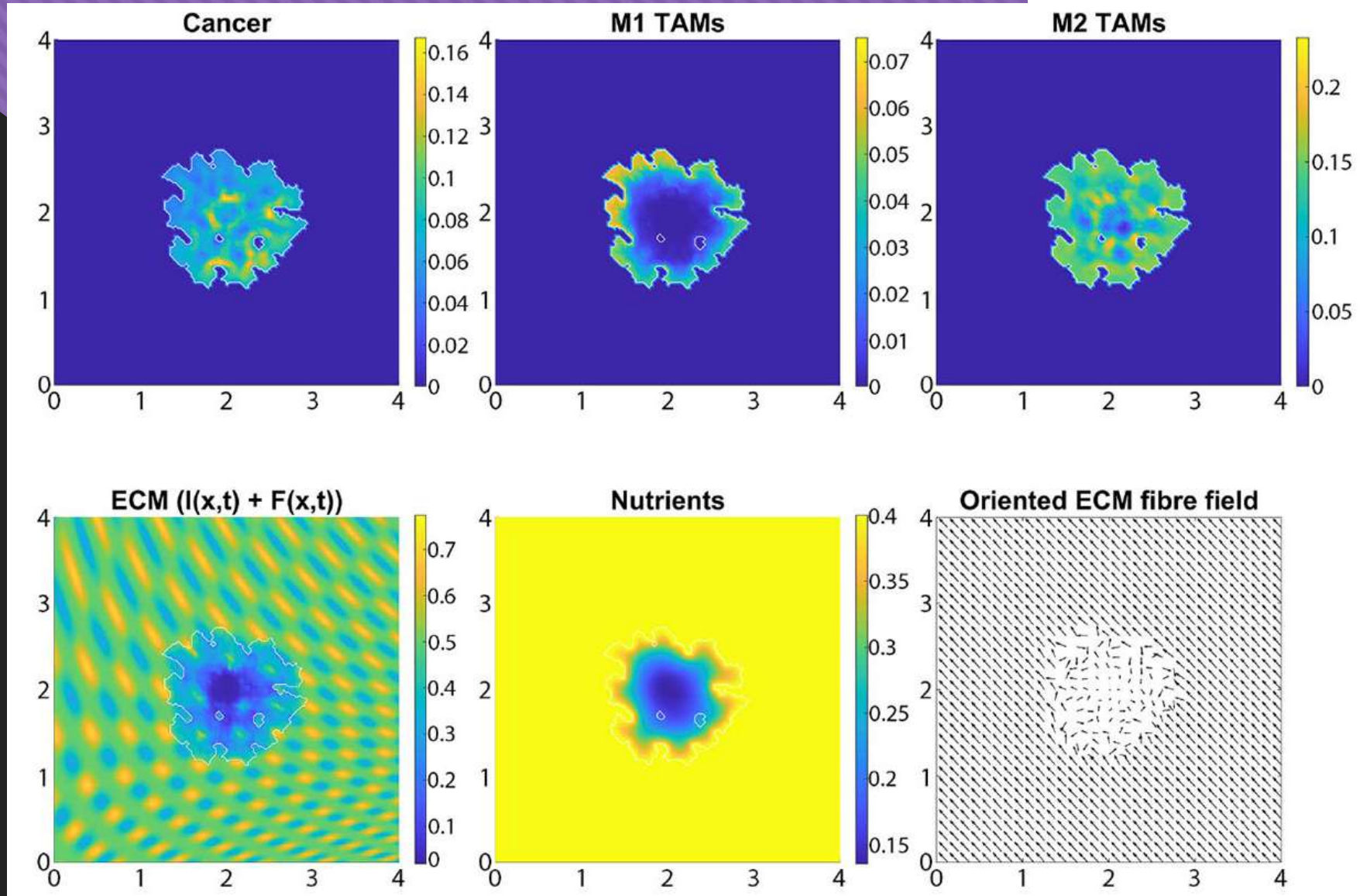
NATURE COMMUNICATIONS | (2019)10:3928



Cancer Res 2020;80:4414-25

Re-polarisation of Macrophages Within Collective Tumour Cell Migration: A Multiscale Moving Boundary Approach

*Szabolcs Suveges[1], Raluca Eftimie[2] and Dumitru Trucu[1]**



M1: at the boundary (but low levels!)

M2: at the boundary & inside tumour

ECM degraded

Nutrients consumed in the tumour core area

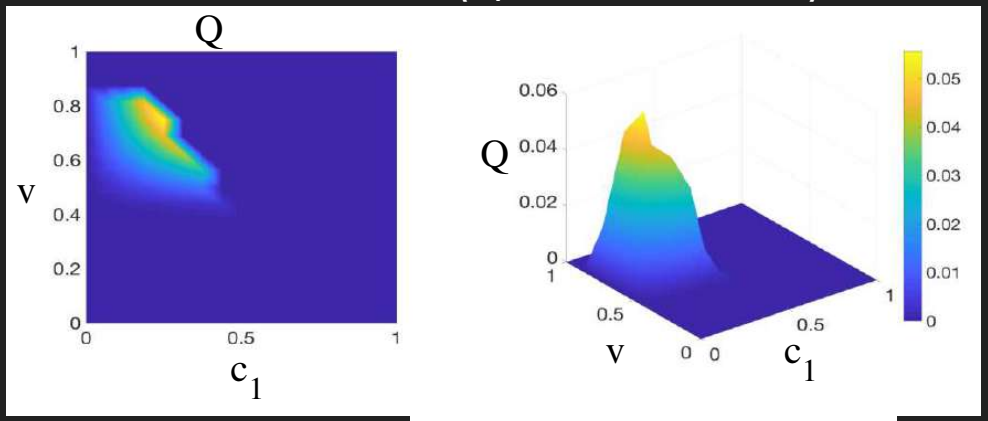
Many parameters & functions need to be estimated from data…

Identification of an unknown function: only for tumour-ECM interactions…

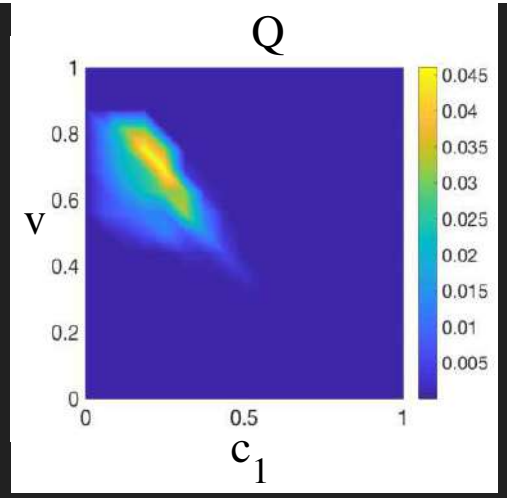
Inverse problem approaches for mutation laws in heterogeneous tumours with local and nonlocal dynamics

Maher Alwuthaynani[1], Raluca Eftimie[2] and Dumitru Trucu[1,*]

True mutation law (synthetic data)



Reconstructed mutation law (3% noise in measured data)



Only tumour & ECM:

$$\frac{\partial c_1}{\partial t} = \underbrace{D_1 \Delta c_1}_{\text{random motility}} - \underbrace{\nabla \cdot [c_1 \mathcal{A}_1(x,t,\mathbf{u}(\cdot,t))]}_{\text{adhesion}} + \underbrace{\mu_c c_1 \left(1 - \frac{c_1 + c_2 + v}{K_c}\right)}_{\text{logistic proliferation}} - \underbrace{\omega(t)}_{\substack{\text{mutation} \\ \text{switch}}} \underbrace{Q(\cdot,\cdot)}_{\substack{\text{unknown} \\ \text{mutation}}},$$

$$\frac{\partial c_2}{\partial t} = \underbrace{D_2 \Delta c_2}_{\text{random motility}} - \underbrace{\nabla \cdot [c_2 \mathcal{A}_2(x,t,\mathbf{u}(\cdot,t))]}_{\text{adhesion}} + \underbrace{\mu_c c_2 \left(1 - \frac{c_1 + c_2 + v}{K_c}\right)}_{\text{logistic proliferation}} + \underbrace{\omega(t)}_{\substack{\text{mutation} \\ \text{switch}}} \underbrace{Q(\cdot,\cdot)}_{\substack{\text{unknown} \\ \text{mutation}}},$$

$$\frac{\partial v}{\partial t} = \underbrace{-\rho(c_1 + c_2)v}_{\text{degradation}} + \underbrace{\mu_v (K_c - c_1 - c_2 - v)^+}_{\text{ECM remodelling}}.$$

$$\omega(t) := \frac{\left(1 + tanh\left(\frac{t - t_{1,2}}{t_s}\right)\right)}{2}.$$

$$\mathcal{A}_p(x,t,\mathbf{u}(\cdot,t)) := \frac{1}{R} \int_{\mathbf{B}((0,0),R)} n(y) \cdot \mathcal{K}(\|y\|_2) \cdot g_p(\mathbf{u}(x+y,t),t) \chi_\Omega(x+y)\, dy.$$

- Tikhonov regularization with K=forward operator: minimization of functionals J_α to identify the unknown function $m^{c1,c2,v}$

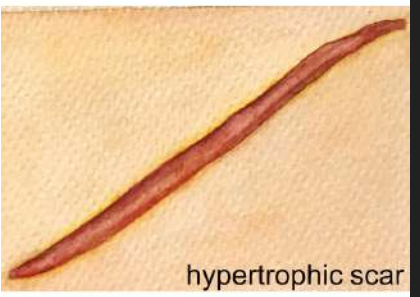
$$J_\alpha : \mathfrak{M}^1 \to \mathbb{R}, \quad \forall \alpha > 0,$$

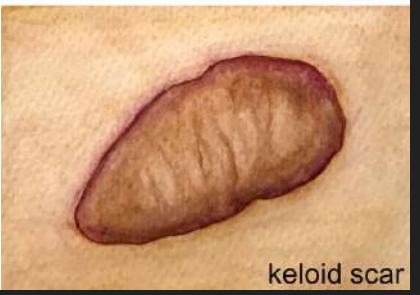
defined by

$$J_\alpha(m) := \left\| K(m) - \begin{bmatrix} \tilde{c}_1^* \\ \tilde{c}_2^* \\ \tilde{v}^* \end{bmatrix} \right\|_2^2 + \alpha \|m\|_2^2, \quad \forall m \in \mathfrak{M}^1.$$

Many more disorders where macrophages play important roles…

Work in progress: keloids = abnormal wounds or benign tumours?





Hypertrophic scars and keloids: Overview of the evidence and practical guide for differentiating between these abnormal scars

Grace C. Limandjaja[1] | Frank B. Niessen[2] | Rik J. Scheper[3] | Susan Gibbs[1,4]

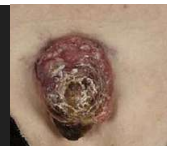
Abnormal wound healing

- Hypertrophic scars (raised scars)
- Keloid scars (raised scars that invade the surrounding tissue, beyond the primary injured area)

Nicholas RS, *et al*. *BMJ Case Rep* 2014. doi:10.1136/bcr-2014-203600

An important case of misdiagnosis: keloid scar or high-grade soft-tissue sarcoma?

Rebecca Spenser Nicholas,[1] Matthew Stodell[2]



Figures 1–3 show a lesion on the anterior chest of a 49-year-old woman which was originally misdiagnosed as a keloid scar.

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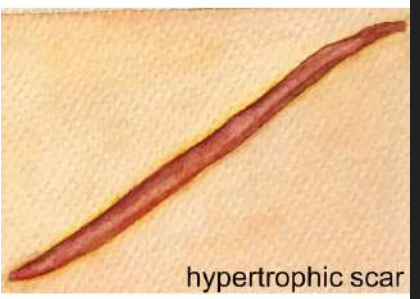
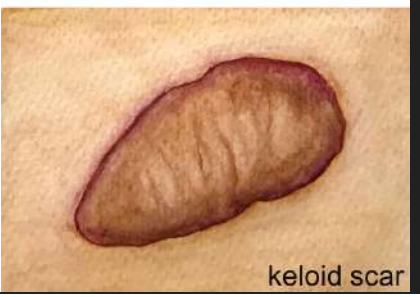
Work in progress: keloids = abnormal wounds or benign tumours?





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Abnormal wound healing

- Hypertrophic scars (raised scars)
- Keloid scars (raised scars that invade the surrounding tissue, beyond the primary injured area)

The epigenetics of keloids

Experimental Dermatology. 2021;30:1099–111

Andrew W. Stevenson[1] | Zhenjun Deng[1] | Amira Allahham[1] | Cecilia M. Prêle[2] |
Fiona M. Wood[1,3] | Mark W. Fear[1,4]

"Keloid scars are unique to humans, and thus an accurate animal model is not easily available, making studying the disease difficult. Existing models have succeeded in inducing hypertrophic (but not keloid) scar in wild-type and immune-deficient mice, rabbits and red duroc pigs, but although similar in appearance to keloids, they don't grow beyond the wound boundary. "

"Other models use implantation of human keloid scar or tissue-engineered keloid cells on immune-deficient mice. While these models have found success in replicating a 'keloid-like' wound that grows beyond the wound boundary, there are inherent issues. Firstly, with immune-deficient mice, the role of the immune system in keloids cannot be explored …"

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Single-scale models for wound healing: normal vs abnormal wounds & tumours


D. Trucu


O Adebayo


G. Rolin

Research article

Mathematical investigation of normal and abnormal wound healing dynamics: local and non-local models

O. E. Adebayo[1], S. Urcun[2], G. Rolin[3,4], S. P. A. Bordas[2], D. Trucu[5] and R. Eftimie[1,5,*]

- Growth factor (TGFβ): $\frac{\partial g}{\partial t} = D_g \Delta g + F_g(f, m)$
- Fibroblasts: $\frac{\partial f}{\partial t} = \nabla \cdot \left(D_f \nabla f - \mu_f f A_f[g, f, m, e]\right) + F_f(g, f, m, e)$
- Macrophages: $\frac{\partial m}{\partial t} = \nabla \cdot (D_m \nabla m - \mu_m m A_m[g, f, m, e]) + F_m(g, f, m, e)$
- ECM (collagen): $\frac{\partial e}{\partial t} = F_e(g, f, m, e)$

Nonlocal flux due to adhesive cell-cell & cell-matrix interactions:

$$A_{f,m}[g, f, m, e] = \frac{1}{R} \int_{B(0,R)} K\left(||y||_2\right) \iota(y)(1 - \rho(u))^{+} \Gamma_{f,m}(x + y, t) dy$$

- Focus on the role of inflammation : macrophages & TGFβ
- Biomechanical forces: considered implicitly through nonlocal flux terms for cell-cell and cell-ECM adhesion (same as for solid tumours)

$$K(||\mathbf{y}||_2) = \frac{||\mathbf{y}||_2}{2\pi\sigma^2} e^{-||\mathbf{y}||_2^2 / 2\sigma^2}$$

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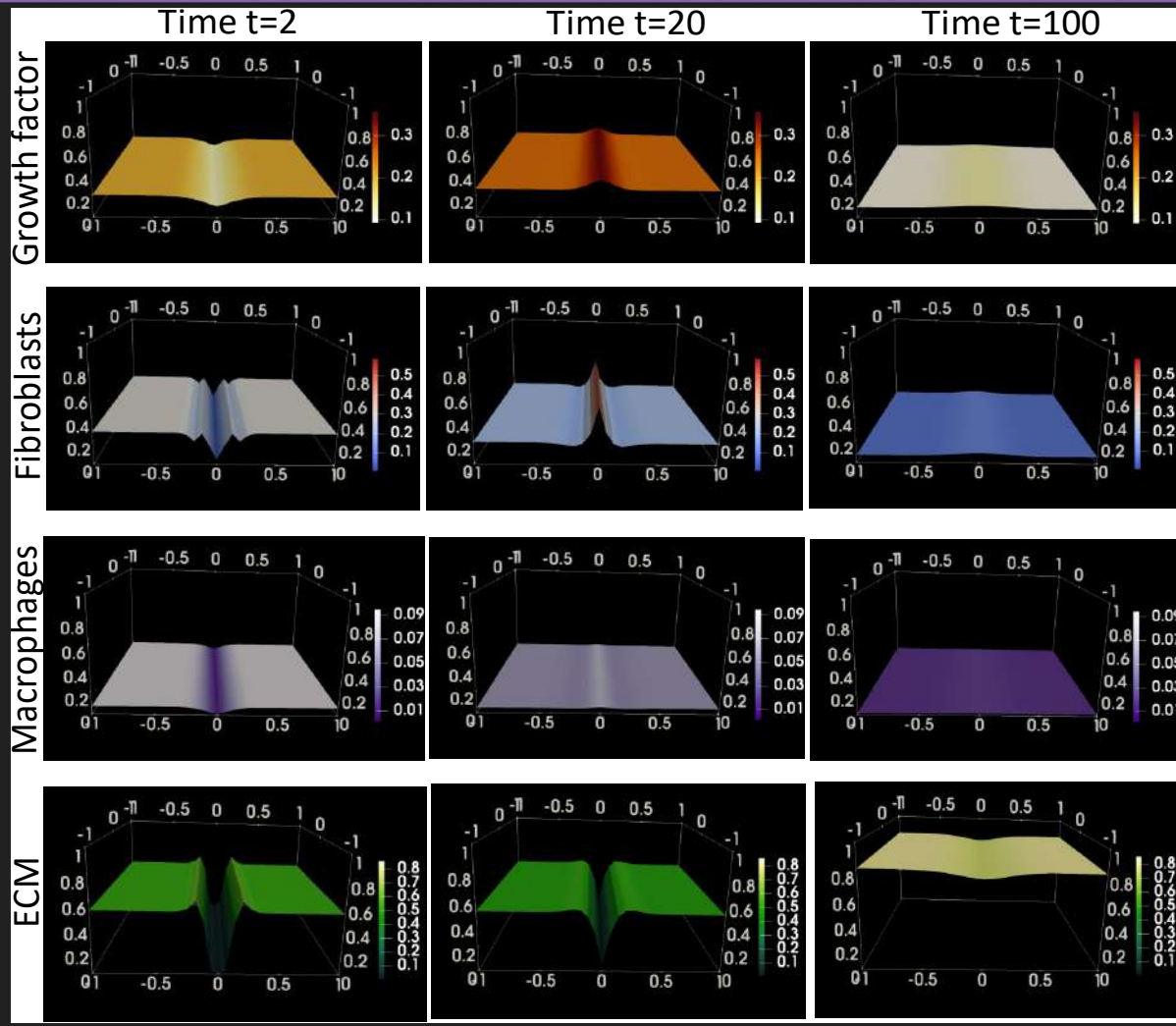
O. E. Adebayo[1], S. Urcun[2], G. Rolin[3,4], S. P. A. Bordas[2], D. Trucu[5] and R. Eftimie[1,5,*]

Normal wound healing:



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ANALYTICAL INVESTIGATION OF A NON-LOCAL MATHEMATICAL MODEL FOR NORMAL AND ABNORMAL WOUND HEALING

O.E. Adebayo[1], D. Trucu[2*] and R. Eftimie

Single-scale models for wound healing: normal vs abnormal wounds & tumours


Abnormal wound healing: hypertrophic scars/keloids (high fibroblast densities in the wound area @t=20)

- Growth factor (TGFβ): $\frac{\partial g}{\partial t} = D_g \Delta g + F_g(f,m)$
- Fibroblasts: $\frac{\partial f}{\partial t} = \nabla \cdot \left(D_f \nabla f - \mu_f f A_f[g,f,m,e]\right)\right) + F_f\,(g,f,m,e)$
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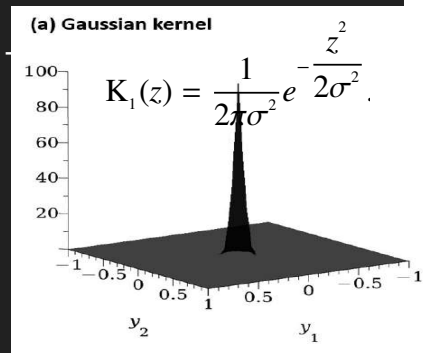

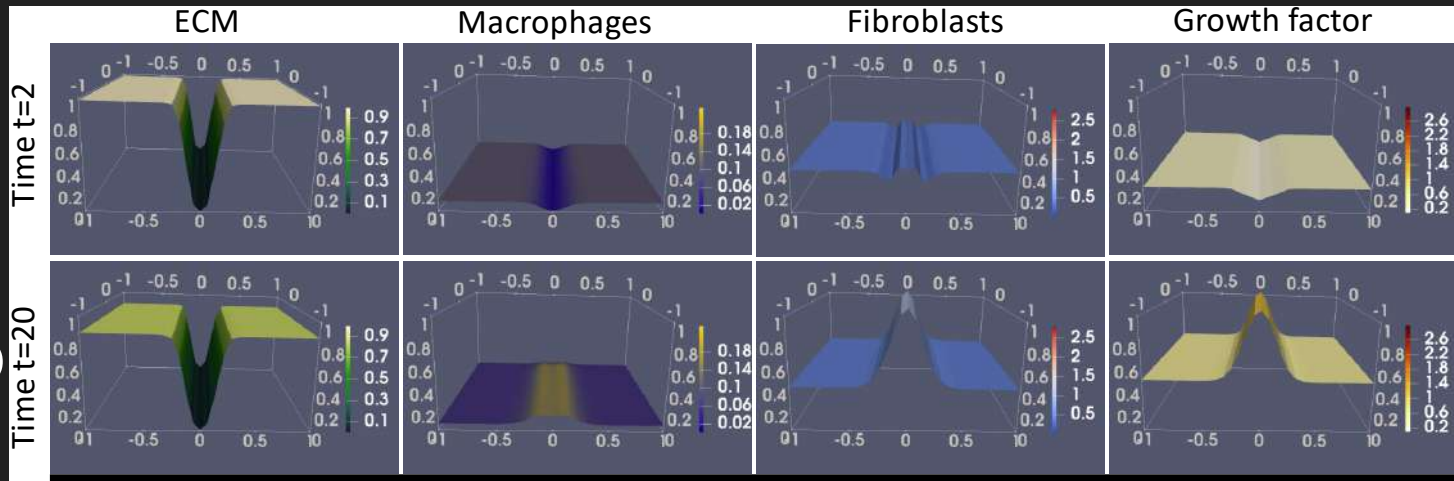

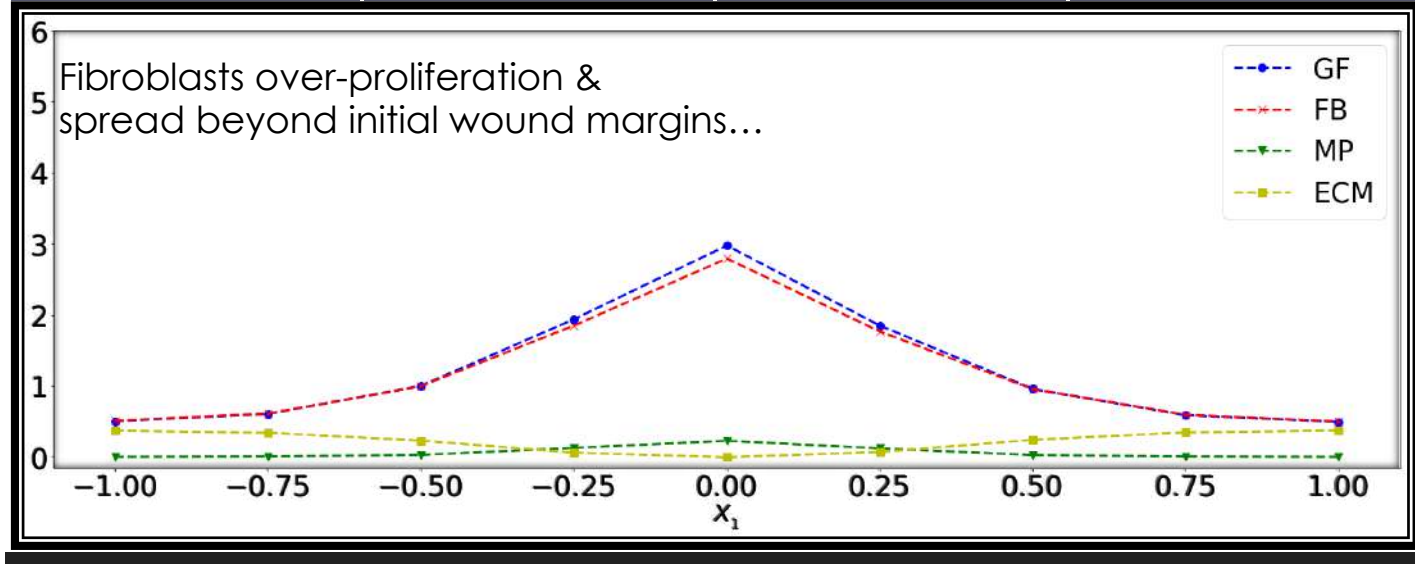

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Summary and open questions:

- Building models in steps (single-scale =>multi-scale) to address various questions related to complex biological interactions

- Local/Non-local spatial interactions between TAMs & tumour cells (& other types of cells) seem to be important

- Spatial data is being generated and can be used for model parametrization
  - Dynamic **spatio-temporal** changes in cells distributions and their phenotype (=>their functionality) => spatio-temporal data available…?

Perspective

A temporal perspective for tumor-associated macrophage identities and functions

Camille Blériot,[1,2] Garett Dunsmore,[1] Direna Alonso-Curbelo,[3,*] and Florent Ginhoux[1,4,5,6,*]

Cancer Cell 42, May 13, 2024

"Clinical observations and experimental systems support that their heterogeneity, plasticity, and pleiotropic functions are influenced by multiple parameters, including ontogeny, spatial context, and several temporal determinants -- from macrophage individual experience and lifespan to the organism's age and exposome. Herein, we propose to integrate the dimension of time into the current framework to better understand the roles of macrophages inter-connecting inflammation and cancer and their dynamism within developing and evolving tumoral niches."

Summary and open questions:

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$$A_{f,m}[g,f,m,e](\mathbf{x},t) = \frac{1}{R}\int_{\mathbf{B}(0,R)} \mathrm{K}(\|\mathbf{y}\|_2)\mathbf{n}(\mathbf{y})(1-\rho(u))^{+}\boldsymbol{\Gamma}_{f,m}(\mathbf{x}+\mathbf{y},t)\,\mathrm{d}\mathbf{y}.$$

$$\boldsymbol{\Gamma}_f(\mathbf{x}+\mathbf{y},t) := \mathbf{S}_{ff} f(\mathbf{x}+\mathbf{y},t) + \mathbf{S}_{fm} m(\mathbf{x}+\mathbf{y},t) + \mathbf{S}_{fe} e(\mathbf{x}+\mathbf{y},t)$$

$$\mathbf{S}_j := \mathbf{S}_j^{\max}\frac{e+g}{1+e+g}, \quad j \in \{ff, fm, mm, mf, fe, me\}.$$

Summary and open questions:

- New **mathematical/computational approaches** need to be developed for estimating parameters & functions/functionals in multi-scale local/nonlocal models …

Quantifying tissue growth, shape and collision via continuum models and Bayesian inference

Carles Falcó[1], Daniel J. Cohen[2,3], José A. Carrillo[1] and Ruth E. Baker[1]

Bayesian Parameter Identification for Turing Systems on Stationary and Evolving Domains

Eduard Campillo-Funollet[1] · Chandrasekhar Venkataraman[1] Anotida Madzvamuse[1]

$$\begin{cases} \partial_t \mu = \nabla \cdot [\mu \nabla (H'(\mu) + V(\mathbf{x}) + W * \mu)] \\ \mu(\mathbf{x}, 0) = \mu_0(\mathbf{x}) \ , \end{cases}$$

(2024 ArXiV preprint)

Variational approach to estimate "W" from synthetic data

$$\widehat{W} \in \underset{\Psi \in \mathcal{H}}{\arg\min}\, \tilde{\mathcal{E}}_\infty(\Psi) \ ,$$

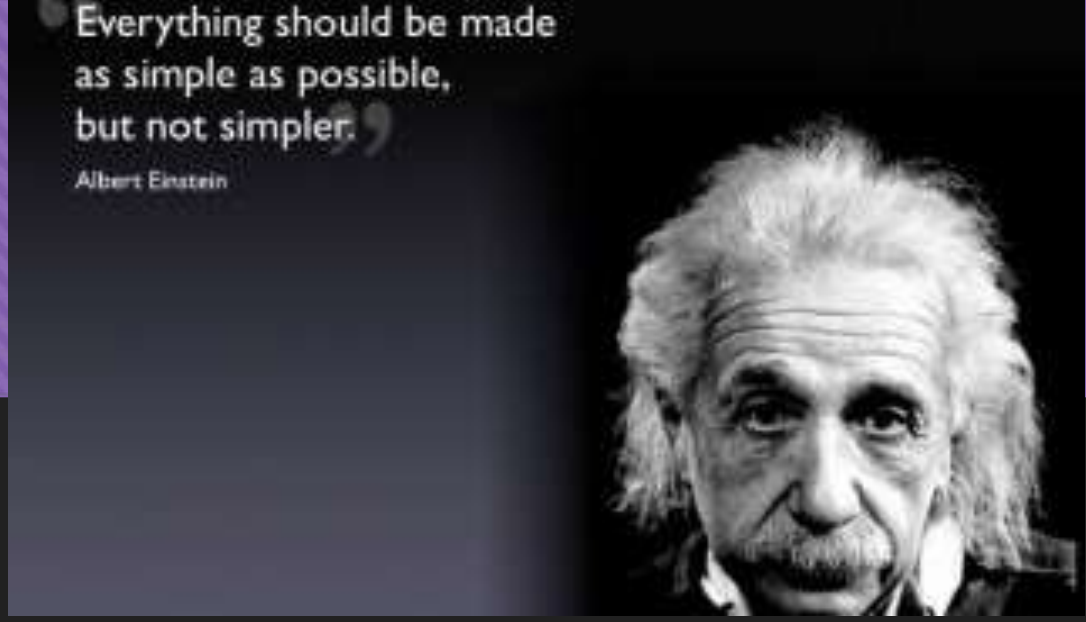
with

$$\tilde{\mathcal{E}}_\infty(\Psi) = \frac{1}{T} \int_0^T \int_{\mathbb{R}^d} \|\nabla \Psi * \rho - \nabla W * \rho\|^2 \rho(t, \boldsymbol{x}) \mathrm{d}\boldsymbol{x}\, \mathrm{d}t$$

Sparse identification of nonlocal interaction kernels in nonlinear gradient flow equations via partial inversion

José A. Carrillo[1], Gissell Estrada-Rodriguez[2], László Mikolás[1] and Sui Tang[3]

Thank you !



- ANR-PRCI (2022-2025)
- Region Bourgogne Franche-Comté (2022-2025)
- Chrysalides (UBFC; 2022)

1 Postdoc position (18 months) available

- Param. Identification for non-local PDEs
- Adaptive mesh refinement for invading fronts (keloids)…