Data-driven computational simulation of tumor progression: Characterization of tumor microenvironment using ES-MDA

Geir Nævdal

gena@norceresearch.no

NORCE

Steinar Evje and Jahn Otto Waldeland

University of Stavanger

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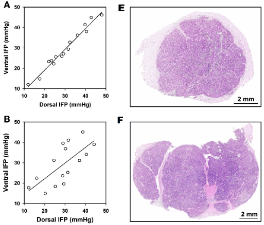
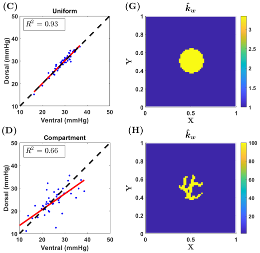
Introduction

- Preclinical studies have shown that interstitial fluid pressure (IFP) within tumors can be heterogeneous
- In-silico model is built that can mimic this behavior
- Model has been trained to comply with experimental in vitro results
- By varying parameters of the model spatially the behavior of preclinical study can be matched
- Can these parameters be tuned by images of the tumor?
- How to use information from images without getting ensemble collapse

Motivation





Left from Hansem et al., 2019.[1]. Right from Waldeland et al., 2021.[2]

Tumor microenvironment – Mass balance

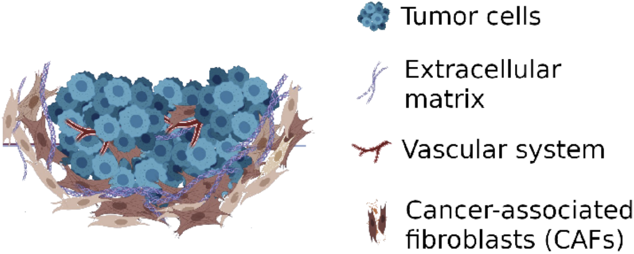


Figure based on Fig. 1 in Barrett & Purè [3].

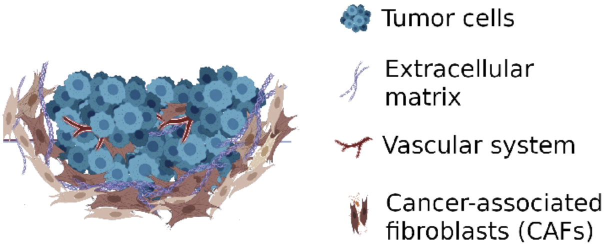
α_c,α_f,α_w: volume fraction of cell, fibroblast and fluid

u_c,u_f,u_w: interstitial cell, fibroblast and fluid velocity

Q_v, Q_l: transvascular flux related to blood and lymphatic vessels

$$(\alpha_c)_t + \nabla \cdot (\alpha_c \mathrm{u}_c) = 0$$
$$(\alpha_f)_t + \nabla \cdot (\alpha_f \mathrm{u}_f) = 0$$
$$(\alpha_w)_t + \nabla \cdot (\alpha_w \mathrm{u}_w) = Q$$
$$Q = Q_v - Q_l$$
$$\alpha_c + \alpha_f + \alpha_w = 1$$

Tumor microenvironment – Momentum balance



$$
\begin{aligned}
\alpha_c \nabla (P_w + \Delta P_{cw} + \Lambda_C) &= -\zeta_c \mathrm{u}_c + \zeta_{cf}(\mathrm{u}_f - \mathrm{u}_c) \\
\alpha_f \nabla (P_w + \Delta P_{fw} + \Lambda_H) &= -\zeta_f \mathrm{u}_f - \zeta_{cf}(\mathrm{u}_f - \mathrm{u}_c) \\
\alpha_w \nabla P_w &= -\zeta_w \mathrm{u}_w
\end{aligned}
$$

P_w:	interstitial fluid pressure
ΔP_{cw},ΔP_{fw}:	cell-cell stress, CAF-CAF stress
Λ_C,Λ_H:	chemotaxis stress
ζ_c,ζ_f,ζ_w,ζ_{cf}:	cell-ECM, fibroblast-ECM, fluid-ECM and cell-fibroblast interaction coefficients

Summary of model

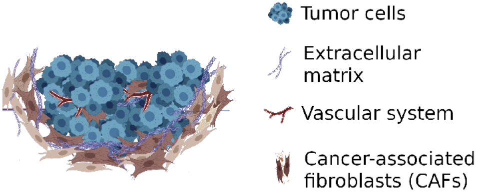
- Flow from vascular system close to tumor periphery to lymphatic system outside tumor.
- Interaction coefficients are specified as follows:

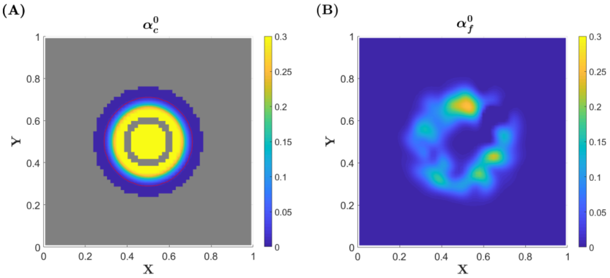
$$\zeta_w = l_w k_w \alpha_w^{r_w}, \quad \zeta_c = l_c k_c \alpha_c^{r_c}, \quad \zeta_f = l_f k_f \alpha_f^{r_f}, \quad \zeta_{cf} = l_{cf} \alpha_c^{r_c f} \alpha_f^{r_f c}$$

- Four additional equations for transportation of chemical components
- Chemotaxis drives migration towards lymphatic system
- Fibroblasts much more mobile than cancer cells, but cancer cells can be attached to fibroblasts

See Waldeland et al., 2021 [2] for more about the model.

Mathematical tumor





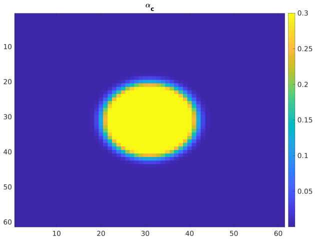
A: (Tumor) cell concentration B: Fibroblast concentration

A: Inner gray ring: Vascular system

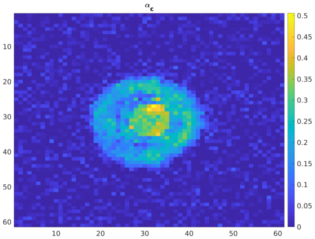
A: Outer gray area: Lymphatic system

Available images

- Assume information about α_c is available from images (time, T, is dimensionless).



$T = 0$



$T = 1/2$

- Update model at $T = 1/2$ and predict to $T = 1$

Unknown parameters

Unknown parameters:

- α_f^0 (initial fibroblast concentration.)
- T_v (used for calculating $Q_v = T_v\big(\widetilde{P}_v^* - P_w\big)$ where P_v^* is the vascular fluid pressure.)
- $\log(k_w)$ (part of $\zeta_w = I_w k_w \alpha_w^{r_w}$.)

α_f^0 and $\log(k_k)$ varies spatially, T_v is set as a constant.

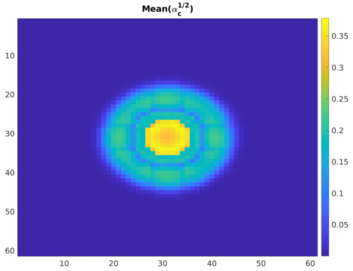
$$
\begin{aligned}
&(\alpha_c)_t + \nabla \cdot (\alpha_c \mathrm{u}_c) = 0 \\
&(\alpha_f)_t + \nabla \cdot (\alpha_f \mathrm{u}_f) = 0 \\
&(\alpha_w)_t + \nabla \cdot (\alpha_w \mathrm{u}_w) = Q \\
&Q = Q_v - Q_l \\
&\alpha_c + \alpha_f + \alpha_w = 1 \\
&\alpha_w \nabla P_w = -\zeta_w \mathrm{u}_w
\end{aligned}
$$

Data assimilation: ES-MDA

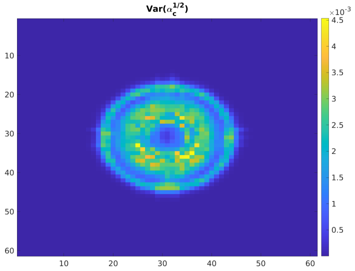
- Using a modified ES-MDA (Emerick & Reynolds, 2013). [4]
- Using (L)ETKF to calculate the update steps (Hunt, Kostelich, Szunyogh, 2007). [5]
- The ES-MDA is performed with 4 update steps with equal weights.
- Ensemble size is 100.

Extracting information from the image

- To avoid ensemble collapse the information used from the image is reduced.
- Heuristic approach:
  - Calculate the variance of the forecast of $\alpha_c^{1/2}$ with the initial ensemble.
  - Use the K points with highest variance as data.

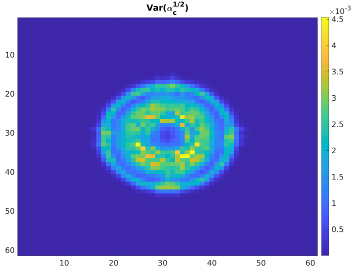


Mean forecast α_c



Variance of forecast α_c

Results with $K = 200$ points: Selection of measurements



Variance of forecast α_c

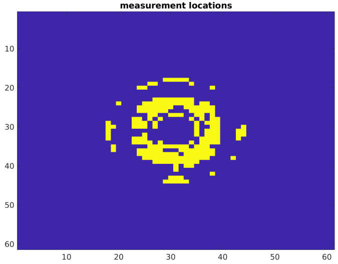
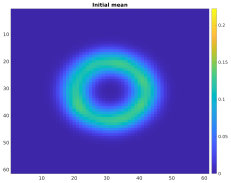
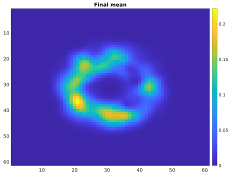


Image points used (yellow)

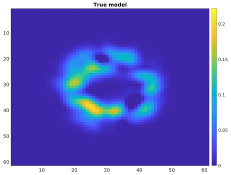
Initial fibroblast concentration (α_f^0)



Initial mean

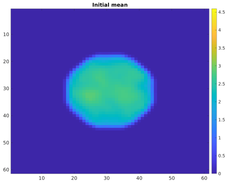


Final mean

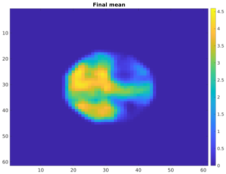


True field

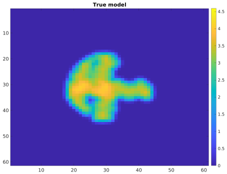
$\log(k_w)$



Initial mean



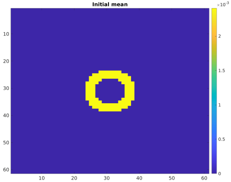
Final mean



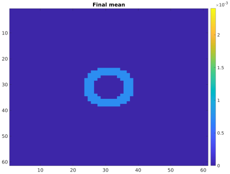
True field

$T_v T^*$

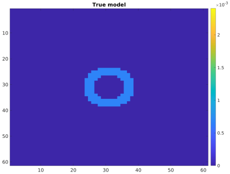
(T^* is a normalization constant.)



Initial mean

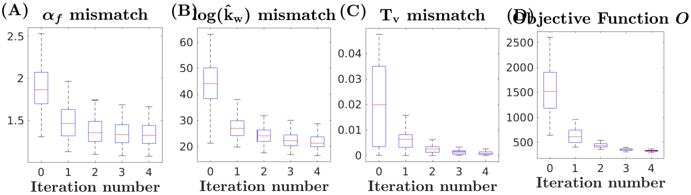


Final mean

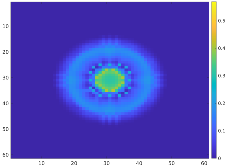


True field

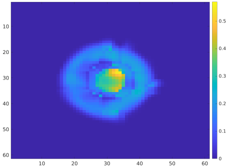
Match to variables and data



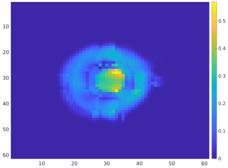
Forecast of α_c at $T = 1$



From initial mean

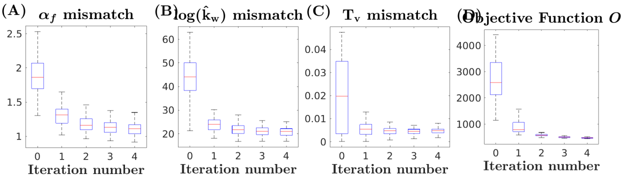


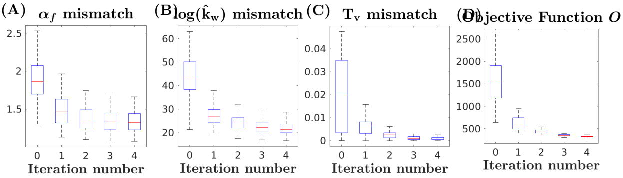
From final mean



True field

Effect of $K = 400$ versus $K = 200$





Summary

Conclusions:

- Possible to estimate parameters from the images using ES-MDA
- Possible to extract information about tumor micro-environment

Further work:

- Add birth & death of cells
- Take into account different phenotypes of cells
- Use in treatment planning?

References I

- Lise Mari K. Hansem et al. "Intratumor Heterogeneity in Interstitial Fluid Pressure in Cervical and Pancreatic Carcinoma Xenografts". In: *Translational Oncology* (2019). DOI: 10.1016/j.tranon.2019.05.012.
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- Richard Lee Barrett and Ellen Puré. "Cancer-associated fibroblasts and their influence on tumor immunity and immunotherapy". In: *eLife* (2020). DOI: 10.7554/eLife.57243.
- Alexandre A Emerick and Albert C Reynolds. "Ensemble smoother with multiple data assimilation". In: *Computers & Geosciences* 55 (2013), pp. 3–15. DOI: 10.1016/j.cageo.2012.03.011.

References II

Brian R. Hunt, Eric J. Kostelich, and Istvan Szunyogh. "Efficient data assimilation for spatiotemporal chaos: A local ensemble transform Kalman filter". In: *Physica D* 230 (2007), pp. 112–126. DOI: 10.1016/j.physd.2006.11.008.