An ensemble approach to study association between metastasis and high interstitial fluid pressure in pancreatic cancer

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Fluid-sensitive migration mechanisms predict association between metastasis and high interstitial fluid pressure in pancreatic cancer

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Data + models = ♡

NORCE

- Data: From preclinical “models” of human pancreatic ductal adenocarcinoma (PDAC)
- Model: Mathematical model developed by Evje & co-workers
- Study done using an ensemble of in silico tumors

Pancreatic cancer

- Less than 8% survival rate after 5 years
- Number of new cases in Norway 2020: $\approx$ 1000
  - (of $\approx$ 36000 cancer cases)
- Most common form: Pancreatic ductal adenocarcinomas (PDAC)
- Treatment: Surgery

Numbers from
https://www.kreftregisteret.no/globalassets/cancer-in-norway/2021/cin_report.pdf

- https://kreftlex.no/Bukspyttkjertel

Preclinical data[1]

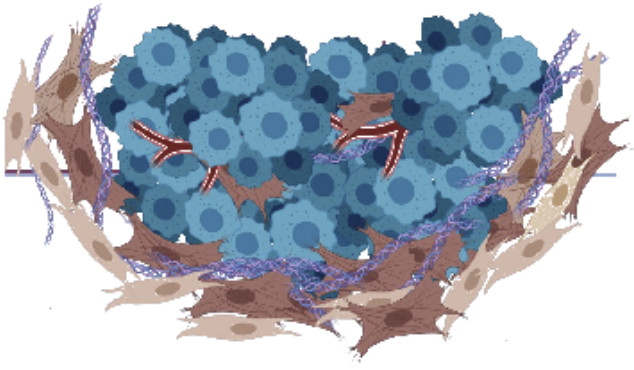
- Based on xenografts
  - Xeno: “stranger”, “guest”
  - Graft: “transplant”
- Intramuscular BxPC-3 & Capan-2 PDAC xenografts as preclinical tumor models
- Tumor grows to certain size before observations
  - Interstitial fluid pressure (IFP)
  - Microvascular density
  - Counting metastatic lymph nodes (of 6 pairs)
- 20 tumors of each model

[1] Lise Mari K. Andersen et al. “Lymph node metastasis and the physicochemical micro-environment of pancreatic ductal adenocarcinoma xenografts”. In: *Oncotarget* 8.29 (May 2017), pp. 48060–48074. DOI: 10.18632/oncotarget.18231.

In silico model

- Model developed by Evje and his former PhD student Waldeland
- Here: A version of the model being as simple as possible explaining the data

Tumor microenvironment
Mass balance



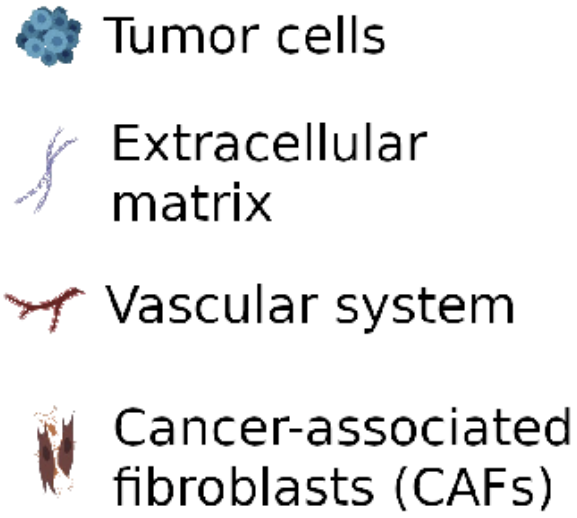


Figure based on Fig. 1 in Barrett & Purè [3].

α_c,α_w: volume fraction of cell and fluid

$\mathbf{u}_c$,$\mathbf{u}_w$: interstitial cell and fluid velocity

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

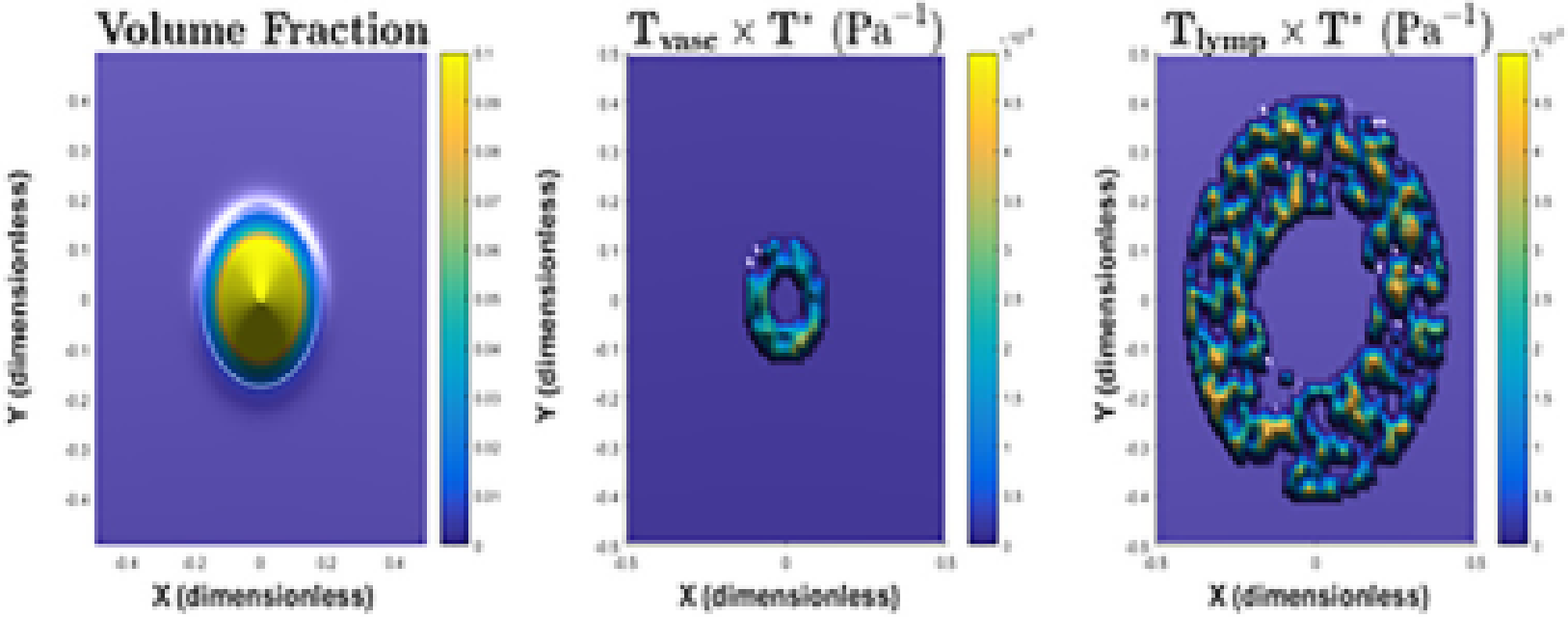
$$(\alpha_c)_t + \nabla \cdot (\alpha_c \mathbf{u}_c) = 0$$

$$(\alpha_w)_t + \nabla \cdot (\alpha_w \mathbf{u}_w) = Q$$

$$Q = Q_v - Q_l$$

$$\alpha_c + \alpha_w = 1$$

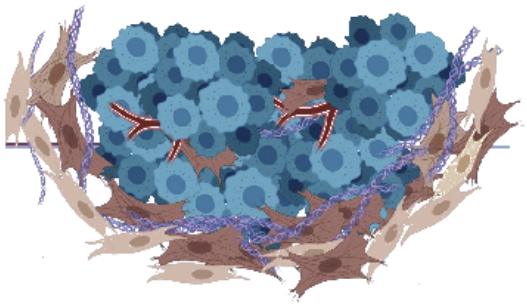
Physiochemical microenvironment



$$Q_v = T_v(\tilde{P}_v^* - P_w)$$

$$Q_l = T_l(P_w - \tilde{P}_l^*)$$

Tumor microenvironment
Momentum balance



Tumor cells

Extracellular matrix

Vascular system

Cancer-associated fibroblasts (CAFs)

$$\alpha_c \nabla(P_w + \Delta P_{cw} + \Lambda_C) = -\zeta_c \mathbf{u}_c + \zeta_{cw}(\mathbf{u}_w - \mathbf{u}_c)$$
$$\alpha_w \nabla P_w = -\zeta_w \mathbf{u}_w + \zeta_{cw}(\mathbf{u}_c - \mathbf{u}_w)$$

P_w:	interstitial fluid pressure
$\Delta P_{cw}(\alpha_c)$:	effect of elevated cell phase pressure
Λ_C:	chemotaxis
$\zeta_w(= l_w k_w \alpha_w^{r_w}), \zeta_c, \zeta_{cw}$:	fluid-ECM and cell-ECM resistance and cell-fluid interaction

Summary of model

$$\mathbf{u}_c = \frac{f_c(\alpha_c)}{\alpha_c}\mathbf{U}_T - \frac{h(\alpha_c)}{\alpha_c}\nabla(\Delta P_{cw}) - \frac{h_c(\alpha_c)}{\alpha_c}\nabla\Lambda_c$$

$$\mathbf{U}_T = \alpha_c\mathbf{u}_c + \alpha_w\mathbf{u}_w$$

(i) Fluid-generated stress giving upstream migration

(ii) Diffusive migration

(iii) Chemotaxis of cells toward higher concentration of chemokine

Novelties of the paper

- Represent the unknown stochastic intratumoral vasculature as well as the collecting peritumoral lymphatic network in an appropriate form
- Show that the two competing fluid-sensitive migration mechanisms, when exposed to a realistic fluid velocity field, have the ability to create aggressive behavior
- Verify that this aggressive behavior, in terms of number of isolated islands that are formed, in fact are correlated to higher IFP

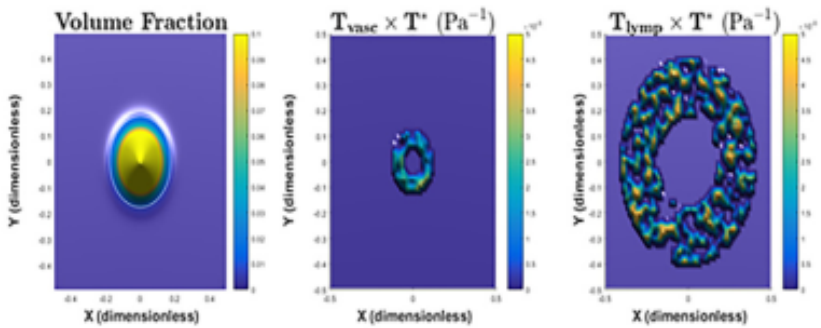
Unknown parameters
Ensemble of models

- Three spatial varying fields
  - Constant: k_w
    (description of fluid-ECM resistance (ECM density))
  - Gaussian variogram: T_v
    (describing density and position of microvascular vessels)
  - Gaussian variogram: T_l
    (describing density and position of peritumoral lymphatics)
- The fields are stochastically independent

Results of simulations

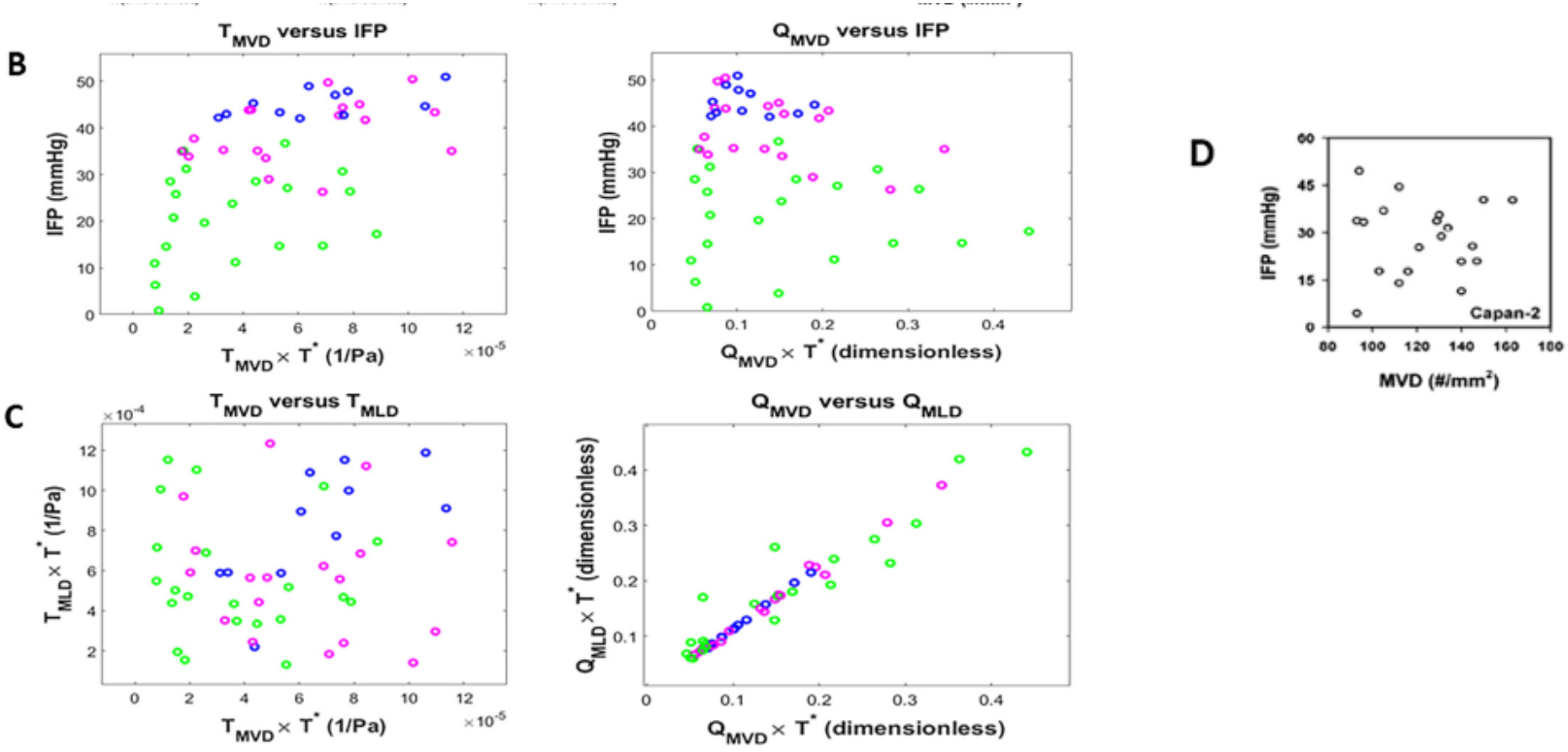
Measures

- Number of isolated islands of cancer cells
  $n \approx \overline{N} = \int_0^T N(s)\, ds$
- Interstitial fluid pressure ($IFP = \max_\Omega P_w(\mathbf{x})$
- Fluid produced from intratumoral vascular system
  $Q_{MVD} = \int_{\Omega_{\text{vasc}}} T_v(\mathbf{x})(\tilde{P}_v^* - P_w)\, d\mathbf{x}$
- "Density" of vascular network $T_{MVD} = \int_{\Omega_{\text{vasc}}} T_v(\mathbf{x})\, d\mathbf{x}$
- Fluid produced through peritumoral lymphatic system
  $Q_{MLD} = \int_{\Omega_{\text{vasc}}} T_l(\mathbf{x})(P_w - \tilde{P}_l^*)\, d\mathbf{x}$
- "Density" of lymphatic network $T_{MLD} = \int_{\Omega_{\text{lymp}}} T_l(\mathbf{x})\, d\mathbf{x}$



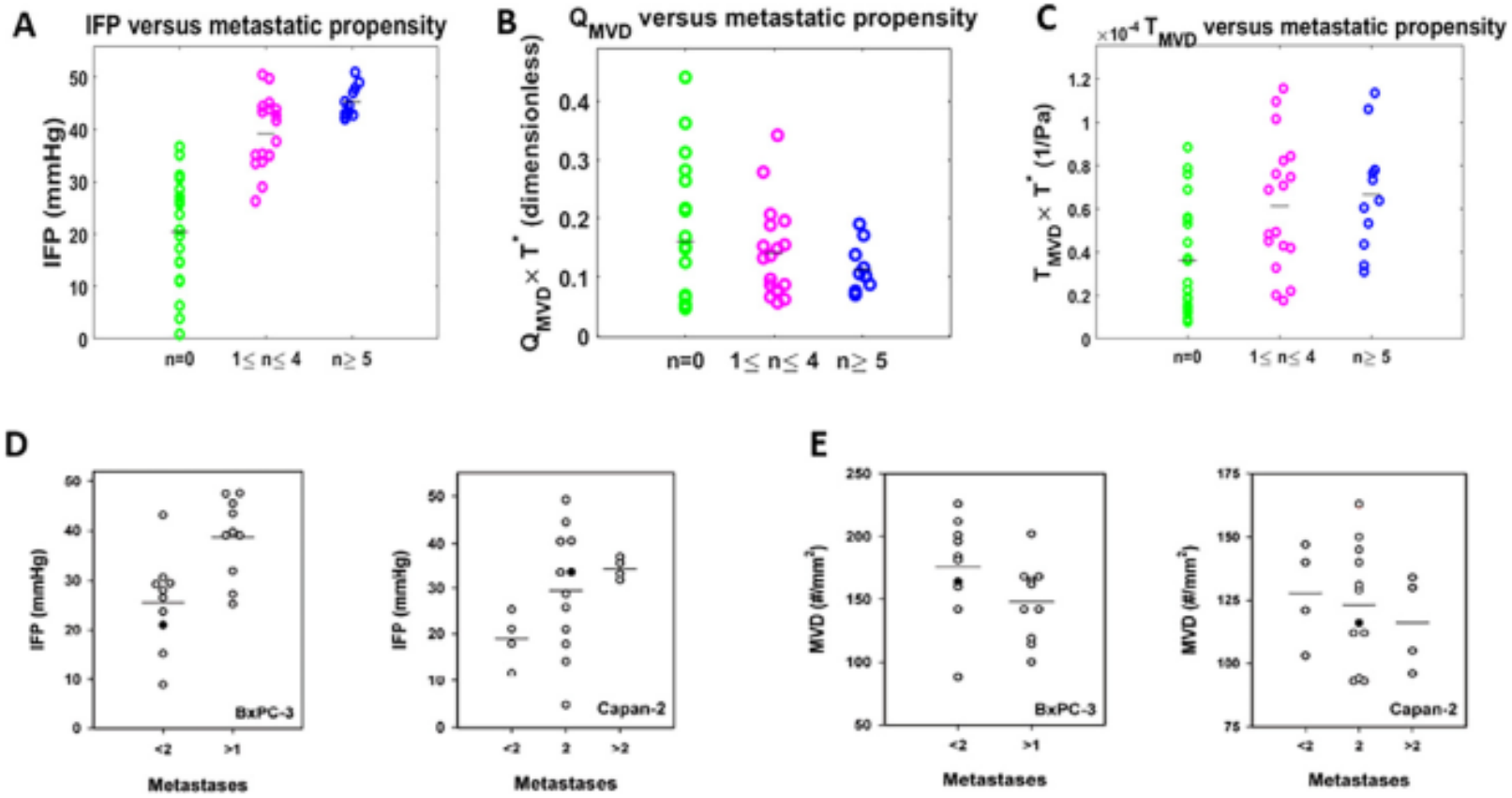
Results

IFP, T_{MVD}, Q_{MVD}, T_{MLD}, Q_{MLD}



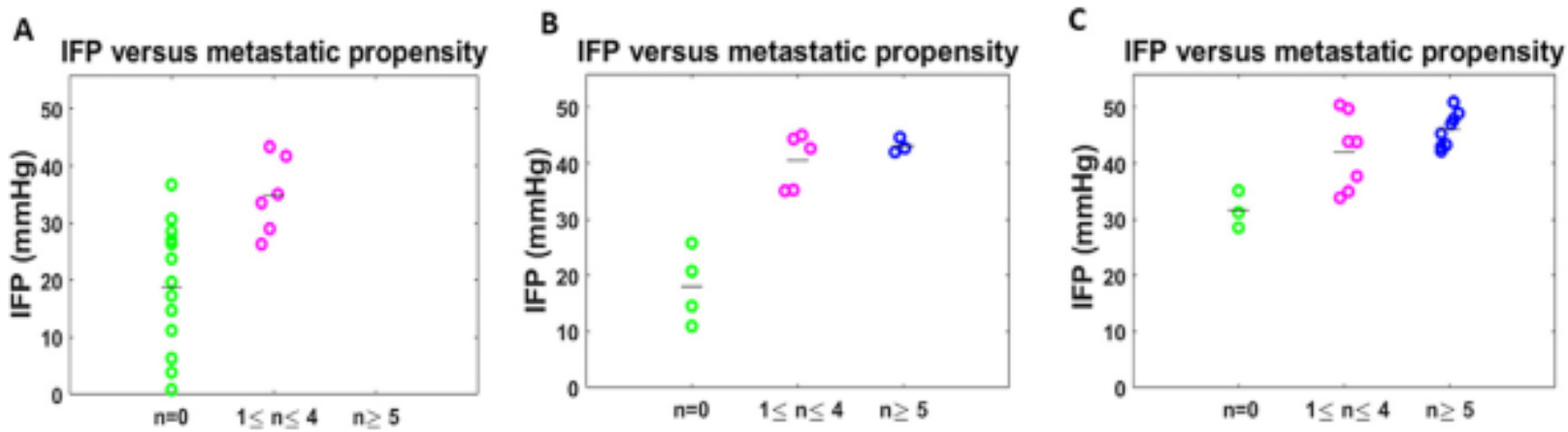
Green: Non-metastatic ($n = 0$). Pink: Medium metastatic propensity ($1 \leq n \leq 4$). Blue: High metastatic propensity ($n \geq 5$)

Results
Metastatic propensity



Results

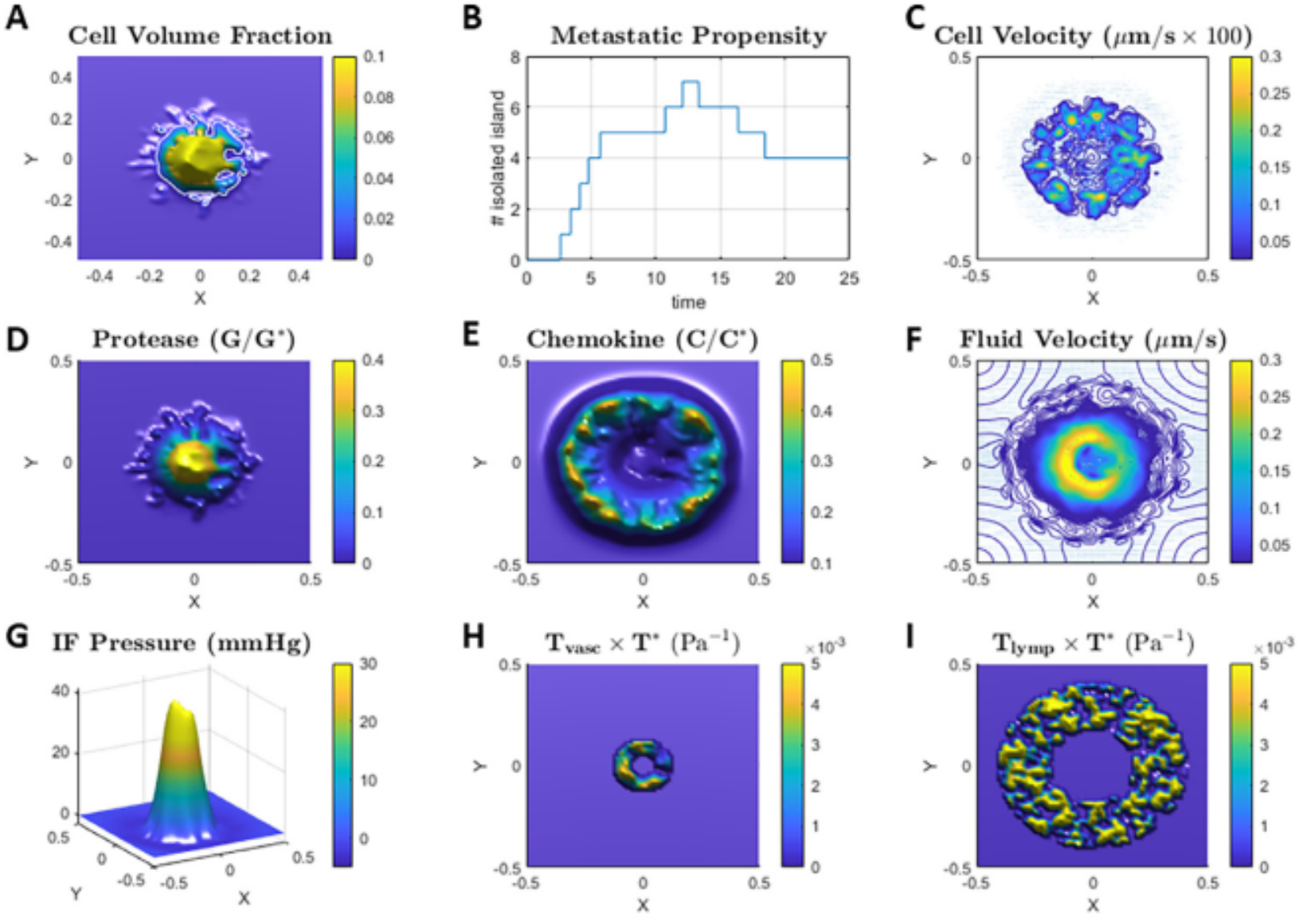
Metastatic propensity vs. varying ECM density



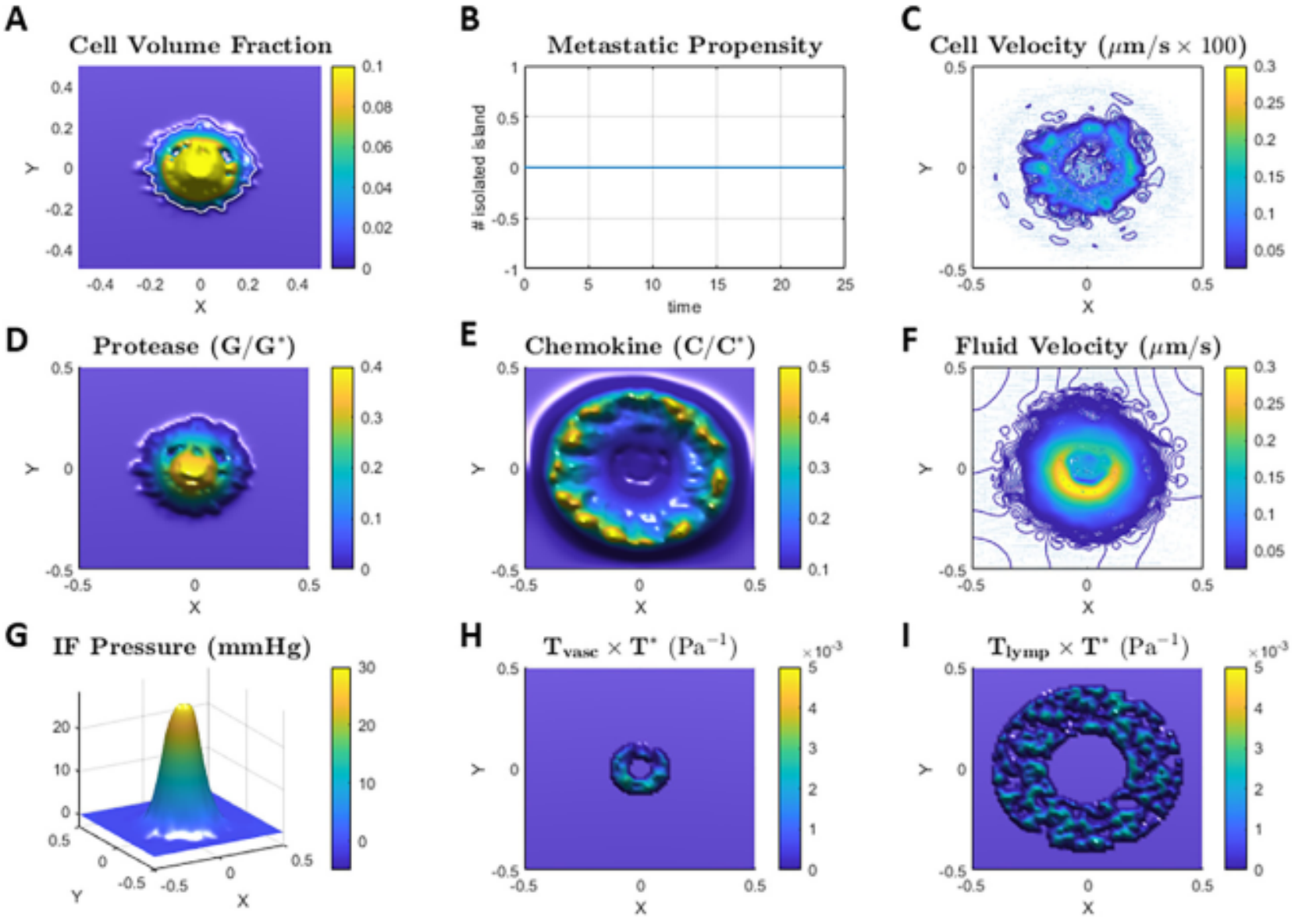
A: Sparse ECM ($1 \leq k_w \leq 11$).
B: Medium ECM ($11 < k_w < 19$)
C: Dense ECM: ($19 \leq k_w \leq 30$)

Results

Sparse ECM with medium metastatic propensity

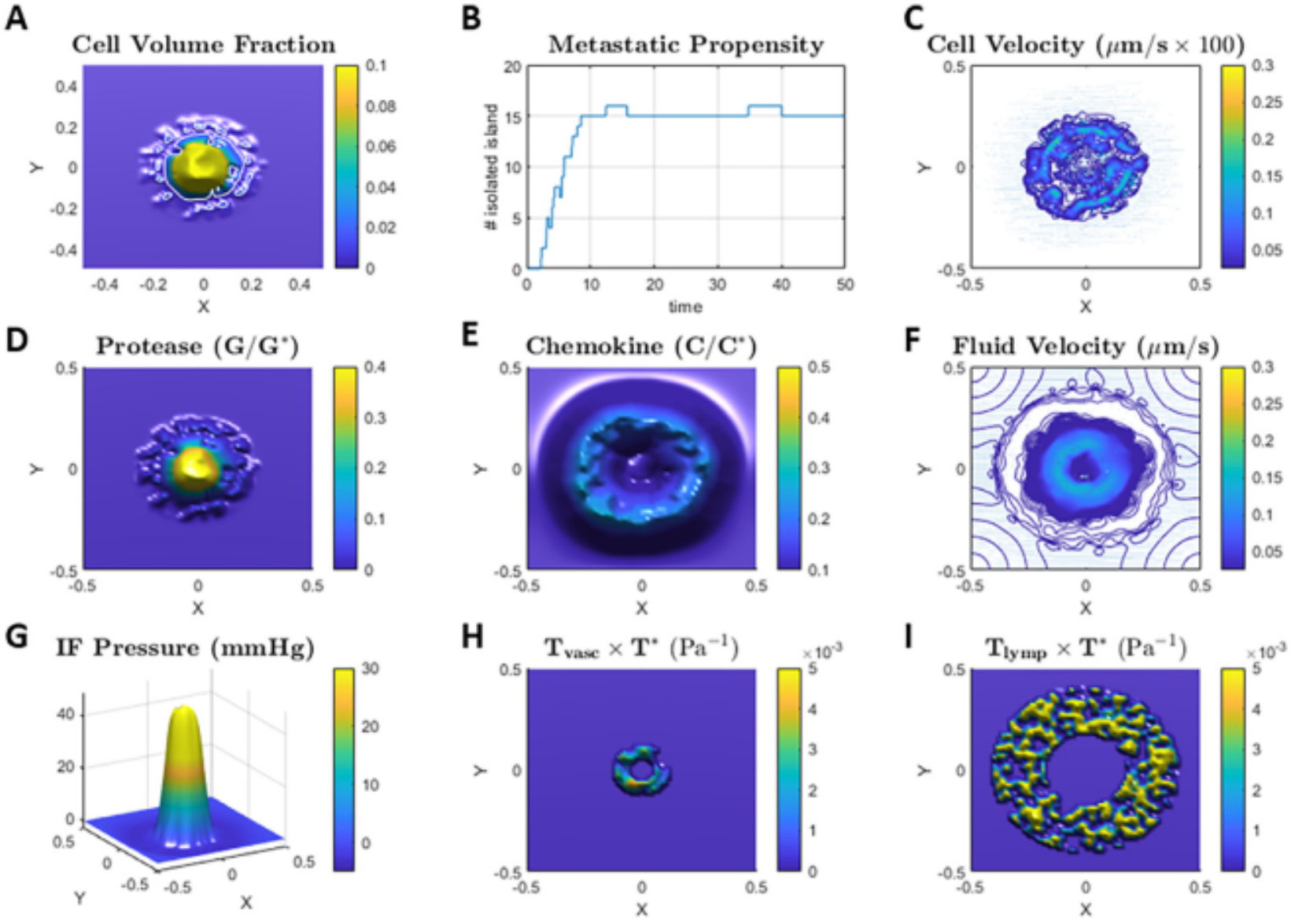


Results
Sparse ECM – non-metastatic



Results

Dense ECM with high metastatic propensity



Conclusions

- Similarities with preclinical study [2]
  - No correlation between IFP and amount of leaked fluid
  - No association between amount of leaked fluid and metastatic propensity
  - Clear association between high IFP and metastatic propensity
- High ECM density gave most aggressive tumors
- Other cancers with similar behavior: cervic cancer, breast cancer, melanoma, and brain cancer
- Potential further work: Combine with data assimilation for better characterization and potential simulation of drug delivery

References

[1] Geir Nævdal et al. “Fluid-sensitive migration mechanisms predict association between metastasis and high interstitial fluid pressure in pancreatic cancer”. In: *Journal of Biomechanics* 145 (Dec. 2022), p. 111362. DOI: 10.1016/j.jbiomech.2022.111362.

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[3] 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.