Heterogenous Tumor Microenvironment in Non-Small Cell Lung Cancer derived from Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Data

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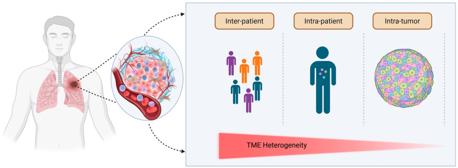
Motivation

- FDG-PET standardized uptake value (SUV) is a semiquantitative measure of how much glucose tracer (FDG) accumulates in tissue, reflecting its metabolic activity
- SUV is widely used in Non-Small Cell Lung Cancer (NSCLC) diagnosis
- Standard practice: average SUV → loss of spatial information
- Tumors are highly heterogeneous (cancer cells, vasculature, fluid)
- Goal: Extract **interpretable tumor microenvironment (TME) information** from static SUV



From Embaye et al., 2026, doi: 10.1111/imcb.70114

Key Question

Central question

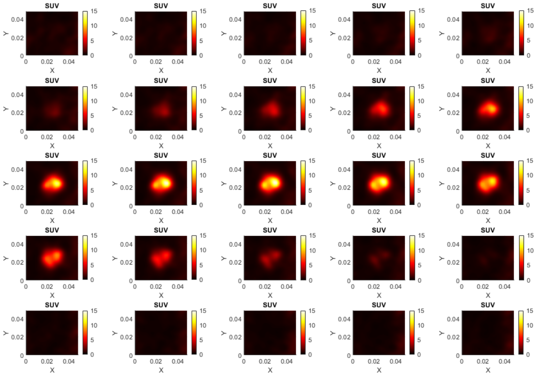
Can a single late-phase FDG-PET image reveal:

- Cancer cell distribution
- Vascular permeability
- Interstitial fluid velocity (IFV)

FDG get trapped in the cancer cells

- Images are acquired approximately 60 min post FDG-injection

SUV data from patient with NSCLC



Main Idea

- Constrain SUV with a **biophysical tumor model**
- Treat SUV as output of forward operator:

$$V \to G(V) = \text{SUV}$$

- Infer parameters, V, via Bayesian inversion
- Use **Ensemble Smoother with Multiple Data Assimilation (ES-MDA)**[1]

[1] Emerick & Reynolds, 2013

Tumor Microenvironment Model

Two-phase model:

- Cancer cells (α_c)
- Interstitial fluid (α_w)
- Extracellular matrix

Key processes:

- Darcy-type flow
- Leaky vasculature
- Interstitial pressure gradients
- Chemotaxis and transport

FDG Transport Model

- FDG concentration $d(x,t)$ in tissue:

$$d_t + \nabla \cdot (\mathbf{u}_w d) = \nabla \cdot (D_d \nabla d) + \varepsilon_{\mathrm{vasc}}^{c} Q_v d_v^* \\ + \varepsilon_{\mathrm{vasc}}^{d} P^* T_v (d_v^* - d) - \lambda_c (\alpha_c + \delta_d) d$$

- FDG concentration in cancer cells $d^c(x,t)$:

$$\frac{d}{dt} d^c(x,t) = \lambda_c (\alpha_c d - \delta_d^c d^c)$$

- Standardized uptake value – SUV:

$$\mathrm{SUV}(x) \sim d(x,t) + d^c(x,t)$$

Unknown Parameters

Parameter vector:

$$V = (\alpha_c^0(x), T_v(x), T_l(x), \varepsilon_{\mathrm{vasc}}^d, \varepsilon_{\mathrm{vasc}}^c, \delta_d)$$

Key targets:

- $\alpha_c^0(x)$: initial cancer cell distribution
- $T_v(x)$: leaky vasculature

Static SUV collapses transport and kinetics

- k_w: tissue resistance
- λ_c: FDG uptake rate

Will solve for 9 different cases:

	$k_w = 1$	$k_w = 4$	$k_w = 16$
$\lambda_c = 0.05$	DT_{11}	DT_{12}	DT_{13}
$\lambda_c = 0.15$	DT_{21}	DT_{22}	DT_{23}
$\lambda_c = 0.30$	DT_{31}	DT_{32}	DT_{33}

Digital tumor candidates

Inverse Problem and ES-MDA

$$Y = G(V) + \eta$$

Minimize $J(V)$:

$$J(V) = \frac{1}{2}(Y - G(V))^T \Gamma^{-1} (Y - G(V))$$

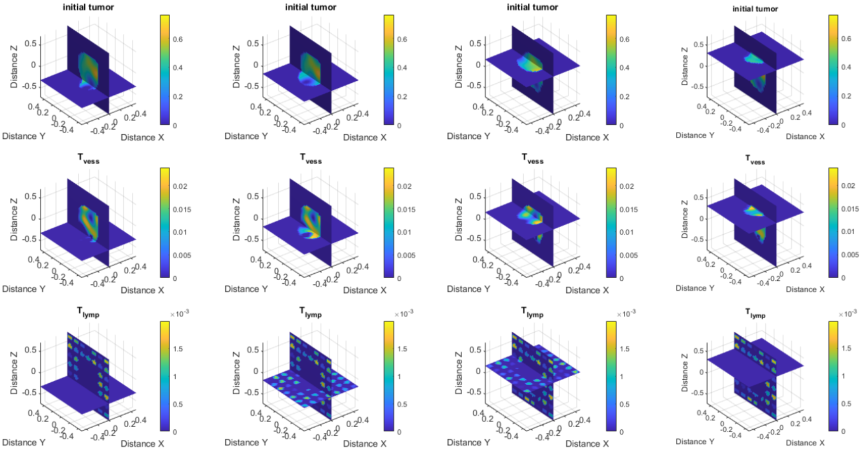
ES-MDA:

- Generate ensemble $\{V_i\}$ from prior distribution
- Iterative updates (using 4 iterations)
- Match simulated to measured SUV

Prior distribution:

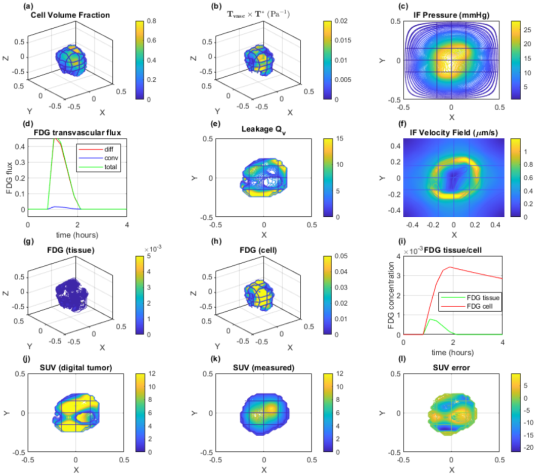
- $\alpha_c^0(x)$: Gaussian variogram
- $T_v(x)$: Gaussian variogram & multiplied by a random factor
- $T_l(x) = \sum_{l,k} T_{l,k} J_k(x)$
- $\varepsilon_{\mathrm{vasc}}^d$, $\varepsilon_{\mathrm{vasc}}^c$, δ_d, $T_{l,k}$: uniformly distributed

Spatial fields of initial ensemble member



Top: $\alpha_c(x, 0)$, middle: $T_v(x)$, bottom: $T_l(x)$

Simulation result – initial ensemble member

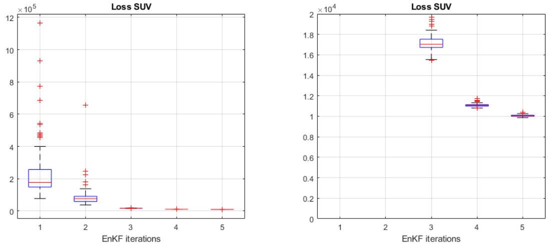


Strategy

- Fix weakly identifiable parameters:
  - $\lambda_c \in \{0.05, 0.15, 0.30\}$ (low/medium/high uptake of FDG)
  - $k_w \in \{1, 4, 16\}$ (sparse/dense tumor tissue)
- Estimate remaining parameters with ES-MDA

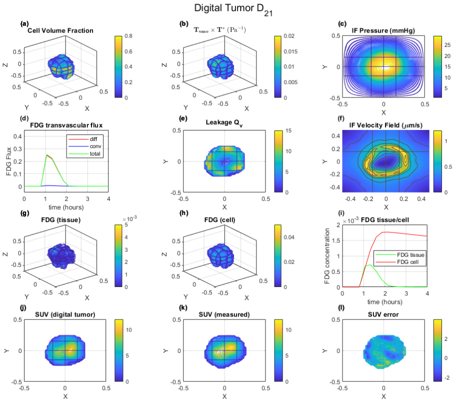
Results: Digital Tumors

- 3 $\times$ 3 matrix of candidate tumors
- All match observed SUV
- Each represents different physics:
  - Flow regimes
  - Metabolic activity

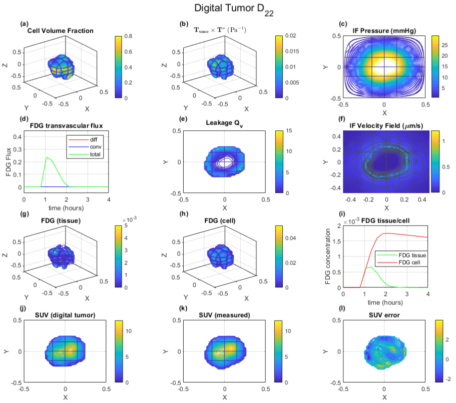


Loss function per iteration
Case DT_{31}
$\lambda_c = 0.30$ & $k_w = 1$

Results



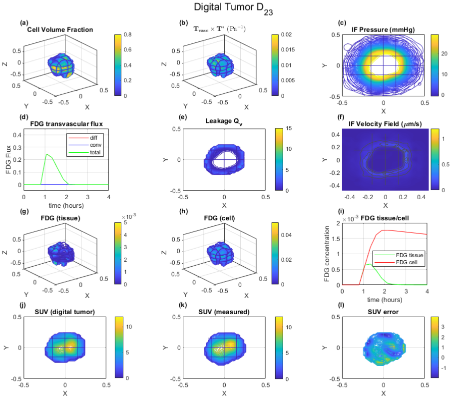
Digital Tumor D21
(a) Cell Volume Fraction
(b) $\mathbf{T}_{vasc} \times \mathbf{T}^{*}$ (Pa^{-1})
(c) IF Pressure (mmHg)
(d) FDG transvascular flux
diff
conv
total
FDG Flux
time (hours)
(e) Leakage Q$_v$
(f) IF Velocity Field (μm/s)
(g) FDG (tissue)
(h) FDG (cell)
(i) FDG tissue/cell
FDG concentration
FDG tissue
FDG cell
time (hours)
(j) SUV (digital tumor)
(k) SUV (measured)
(l) SUV error



Digital Tumor D22
(a) Cell Volume Fraction
(b) $\mathbf{T}_{vasc} \times \mathbf{T}^{*}$ (Pa^{-1})
(c) IF Pressure (mmHg)
(d) FDG transvascular flux
diff
conv
total
FDG Flux
time (hours)
(e) Leakage Q$_v$
(f) IF Velocity Field (μm/s)
(g) FDG (tissue)
(h) FDG (cell)
(i) FDG tissue/cell
FDG concentration
FDG tissue
FDG cell
time (hours)
(j) SUV (digital tumor)
(k) SUV (measured)
(l) SUV error

Key Findings

- Spatial SUV $\rightarrow$ strong information on:
  - Cell distribution
  - Vascular heterogeneity
- Interstitial fluid velocity (IFV) magnitude poorly identifiable
- Structure of IFV field is robust



Interpretation & Important Insight

- SUV is influenced by:
  - Delivery (vasculature + flow)
  - Uptake (cell metabolism)
- Model separates these contributions

Hidden information

SUV can hide viable tumor regions:

- No FDG delivery $\Rightarrow$ low SUV
- Cancer cells can still be present

Role of ensemble-based data assimilation

- Robust for high-dimensional parameter fields
- Naturally handles uncertainty
- Produces ensemble of plausible tumors

Implications

- Non-invasive TME characterization
- Patient-specific digital tumors
- Basis for treatment simulation

Limitations:

- Non-uniqueness remains
- Requires prior assumptions
- Static SUV lacks temporal information

Future Work

- Test on more data sets
- Do the results provide biomarkers predicting the outcome?
- Combine SUV with additional data (other images)
- Extend model to simulate therapy response
- Use for other cancer types

Take-home Message

Conclusion

Static PET (SUV) + physics-based model + data assimilation

$\Rightarrow$ Recover hidden tumor structure

Thank you!