FUZZY STATISTICAL UNSUPERVISED LEARNING BASED TOTAL LESION METABOLIC ACTIVITY ESTIMATION IN PET IMAGES (SLAC)

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CONTRIBUTION: ACCURATE TLA ESTIMATION

Accurate total tumor lesion metabolic activity (**TLA**) estimation is critical for tumor staging and follow up studies. Positron emission tomography (PET) successfully images the lesion metabolic activity. Recently, PET images were modeled as a fuzzy Gaussian mixture to delineate tumor lesions accurately [1]. In this work, we propose a statistical lesion activity computation (**SLAC**) approach to robustly estimate **TLA** directly from the modeled Gaussian partial volume mixtures. **TLA** was estimated from 3 state-of-

the-art PET delineation schemes, namely a stochastic (**FLAB** [1]), a gradient based (**GDM** [2]) and an adaptive threshold based (**ATM** [3]) method, for comparison. A threshold based region growing method (**T40** - 40% threshold) was also evaluated. Synthetic lesions were simulated and reconstructed using maximum likelihood expectation maximization (**MLEM**) algorithm with 4 iterations over 16 subsets as in clinical routine (post-smoothed with 5mm Gaussian full width half maximum (FWHM)).

METHODS: STATISTICAL TLA

Let the observed PET image and the hidden segmentation map be realizations $\mathbf{y} = \{y_s\}_{s \in \mathcal{S}}$ and $\mathbf{x} = \{x_s\}_{s \in \mathcal{S}}$ of the random fields $\mathcal{Y} = \{\mathcal{Y}_s\}_{s \in \mathcal{S}}$ and $\mathcal{X} = \{\mathcal{X}_s\}_{s \in \mathcal{S}}$ respectively, where $\mathcal{S} = \{1, \dots, N\}$ is the set of voxels. Integrating the activity y_s over the whole $\mathcal{S}$, the total PET activity (TPA), constituting contributions from the lesion (**TLA**) and the background activities, can be mathematically defined as

$$\text{TPA} := \int y_s ds = \int \zeta h(\zeta) d\zeta \equiv N \int \xi f(\xi) d\xi = N \times E(\mathcal{Y}_s)$$

The observed histogram $h(\zeta)$ containing the frequency of occurrence for each ζ can be related to the density $f(\xi)$ defining the distribution of $\mathcal{Y}_s = \xi$. $E(\mathcal{Y}_s)$ is the associated expectation.

Let $\mathbf{c} = \{c_k\}_{k \in \mathcal{K}}$, where $\mathcal{K} = \{1, \dots, Q\}$, be the Q class labels associated with the segmentation map. Then $\mathcal{Y}_s$ can be modeled as a finite mixture of conditional densities such that $f(\xi) = \sum_k \gamma_k f(\xi | c_k)$, where γ_k stands for the mixing probabilities $P(\mathcal{X}_s = c_k)$ and $f(\xi | c_k)$ denotes the density defining the distribution of $\mathcal{Y}_s = \xi$ conditional to $\mathcal{X}_s = c_k$. If $E(\mathcal{Y}_s | c_k)$ represents the conditional expectation of $\mathcal{Y}_s$ given $\mathcal{X}_s = c_k$, then the TPA can be modified as

$$\text{TPA} := N \sum_k \gamma_k \left(\int \xi f(\xi | c_k) d\xi \right) = N \sum_k \gamma_k E(\mathcal{Y}_s | c_k)$$

To model $\mathcal{Y}_s$ with the PVE, let the noise associated with the tumor and the background be modeled by 2 Gaussian random variables $\mathcal{Y}_1$ and $\mathcal{Y}_0$ with the density $\mathcal{N}(\mu_1, \sigma_1^2)$ ($f(\xi | \mathcal{X}_s = 1)$) and $\mathcal{N}(\mu_0, \sigma_0^2)$ ($f(\xi | \mathcal{X}_s = 0)$) defining the distributions of $\mathcal{Y}_s$ conditional to $\mathcal{X}_s = 1$ and $\mathcal{X}_s = 0$ respectively. Then the partial volume activities can be modeled by linear combinations of these independent random variables as $\mathcal{Y}_s = (1 - \epsilon)\mathcal{Y}_0 + \epsilon\mathcal{Y}_1$, for $\mathcal{X}_s = \epsilon \in [0, 1]$. $\mathcal{Y}_s$ is again Gaussian distributed with density $\mathcal{N}(\mu_\epsilon, \sigma_\epsilon^2)$

($f(\xi | \mathcal{X}_s = \epsilon)$) conditional to $\mathcal{X}_s = \epsilon$, such that $\mu_\epsilon = (1 - \epsilon)\mu_0 + \epsilon\mu_1$ and $\sigma_\epsilon^2 = (1 - \epsilon)^2\sigma_0^2 + \epsilon^2\sigma_1^2$. Let M fuzzy classes be used to model the partial volume mixtures, then $\mu_{\epsilon_k} = (1 - \epsilon_k)\mu_0 + \epsilon_k\mu_1$ with $\epsilon_k = k/(M+1)$, $k = 1, \dots, M$. Therefore, for the tumor and the background, $\mu_{\epsilon_{M+1}} = \mu_1$ and $\mu_{\epsilon_0} = \mu_0$ respectively, with $\epsilon_0 = 0$ and $\epsilon_{M+1} = 1$. Here $\mathbf{c} = \{0, 1, \epsilon_k\}$, $Q = M+2$. In eq. 1, out of the total activity in a fuzzy mixture class F_{ϵ_k} in $E(\mathcal{Y}_s | \epsilon_k)$, only $\epsilon_k\mu_1$ originates from the tumor lesion. Adding up the contributions from 1 hard class and M fuzzy classes representing tumor and partial volume voxels respectively, we propose that, the statistical **TLA** can be estimated from TPA as

$$\text{TPA} := N \sum_k \gamma_k \{(1 - \epsilon_k)E(\mathcal{Y}_0) + \epsilon_k E(\mathcal{Y}_1)\} \quad (1)$$

$$\text{TLA} := N \sum_k \gamma_k \epsilon_k E(\mathcal{Y}_1) = \sum_{s \in \mathcal{S}} \epsilon_s E(\mathcal{Y}_1) \quad (2)$$

A line profile through the PET image (37, 28, 22, 17, 13 and 10mm lesions) and the ground truth is shown in red and black lines respectively. Area in light gray shade denotes the **TLA** computed from the delineation profile, where as the area in dark gray shade represents the activity missed in that computation.

Slices of a simulated liver lesion (*left*) and the estimated hidden classifier labels (*middle*) obtained after the fuzzy SEM modeling. Actual histogram (*right*) as a finite mixture of tumor (red), background (blue) and partial volume voxels (in a combination of red and blue shades); **TLA** being contributed from tumor class ($\gamma_{M+1}\mu_1$) and M partial volume classes ($\gamma_1\epsilon_1\mu_1, \dots, \gamma_M\epsilon_M\mu_1$).

SIMULATED TUMOR LESIONS: IEC & NCAT PHANTOM

VALIDATIONS: QUANTIFICATION ACCURACY METRIC

Different segmentation methods were evaluated by comparing the **TLA** estimated from delineated PET volumes against a resampled fuzzy ground truth knowledge (8mm³ voxels). **TLA**_{SLAC} was estimated directly and compared. For quantify-

ing the error in **TLA**, δTLA was computed as $\left(\frac{\text{TLA}_{\text{Estimator}} - \text{TLA}_{\text{True}}}{\text{TLA}_{\text{True}}} \right) \times 100$ in %. $\text{TLA}_{\text{Estimator}}$ stands for **TLA** estimated from a delineation method or the proposed direct approach. TLA_{True} stands for the actual **TLA** in the ground truth.

ALGORITHM: SLAC PSEUDOCODE

Inputs: Image voxels $\mathbf{y} = \{y_s\}_{s \in \mathcal{S}}$, # Random starts RS, Cut off err_{cutoff} , # Iterations T

Outputs: TLA_{SLAC}

Initialization:

```

k ← 0, MML ← ∞
while k < RS do
  k ← k + 1, Θk ← FCMClustering(y)
  [Θk = {μC, σC2, γC}, C = {0, 1, F}]
  ML ← MessageLength(y, Θk) as in [5]
  if ML < MML then
    MML ← ML, Θinit ← Θk

```

Stochastic Expectation Maximization:

```

t ← 0, TLASLAC ← 0, Θ ← Θinit
while t < T do
  repeat
    t ← t + 1
    v(s) ← γ0(s) f(ys | 0) + γ1(s) f(ys | 1) +
      (1 - γ0(s) - γ1(s)) ∫01 f(ys | θ) dθ
    wC(s) ← γC(s) f(ys | C) / v(s) ∀ s ∈ S
    Zs ← arg maxC wC(s)
    if Zs = F then
      Zs ← arg maxεk f(ys | εk)
    γH(s) ← (∑r ∈ Ws δ(Zr, H)) / Card(Ws) [H ∈ {0, 1}]
    [Ws is a w × w × w local window]
    μH ← (∑s ys δ(Zs, H)) / (∑s δ(Zs, H))
    σH2 ← (∑s (ys - μC)2 δ(Zs, H)) / (∑s δ(Zs, H))
    μεk ← (1 - εk)μ0 + εkμ1
    σεk2 ← (1 - εk)2σ02 + εk2σ12
    γC ← (∑s δ(Zs, C)) / N
    TLA ← N ∑k γk εk μ1
    err ← |TLA - TLASLAC|
    TLASLAC ← TLA
  until err < errcutoff
return TLASLAC

```

PLOTS: δTLA

RESULTS:

Few methods developed taking into account the need to estimate actual metabolic activity.

Due to the limitation imposed by the PET acquisition system, any accurate delineation will potentially end up underestimating activity.

FLAB estimates **TLA** from delineation ignoring the estimated PVE information, thereby losing activity in the lower partial volumes.

SLAC outperforms **FLAB**, exploiting the PVE model to have a better **TLA** estimate.

SLAC is less dependent on support window size & number of fuzzy classes, relative to **FLAB**.

SLAC is computationally fast (takes only a few seconds to process 30³ voxels).

SLAC is robust to initialization due to the MML search and use of SEM instead of EM.

SLAC tends to give the best estimate with lesions of varying size (> 1cc), shape and contrast.

As a con, almost all methods including the **SLAC** showed increase in deviation (95% CI) with decrease in lesion size.

Selection of ROI is critical, however, **SLAC** can be easily extended to handle multi class images.

FUTURE WORK:

We are investigating how reliable **SLAC** is with other probability distributions, multi-class data, clinical PET images, heterogeneous tumors and varying reconstruction parameters.

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