Tumor Segmentation in PET and in Multimodality Images for Radiation Therapy

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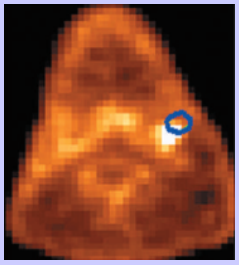
Outline

1. Tumor segmentation in PET
2. PET target segmentation methods developed at WU
3. Tumor segmentation in multi-modality images: a brief review
4. Summary

1. Tumor segmentation in PET

PET in Radiation Therapy

- Higher sensitivity and specificity
- Demonstrated useful in staging and detecting cancer, monitoring response
- Delineating tumor volume requires further investigation
  - Poor spatial resolution, blurred boundary
  - FDG uptake is a non-specific biological process
  - Inaccurate PET-CT registration
  - Typically large observer variation



Frank, S J, et al. 2005. Nat Clin Pract Oncol. 2: 526-33

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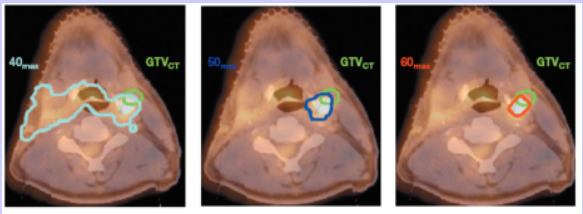
Threshold of Maximum Intensity



Altering threshold level can drastically influence the "tumor" volume

Frank, S J, et al. 2005. Nat Clin Pract Oncol. 2: 526-33

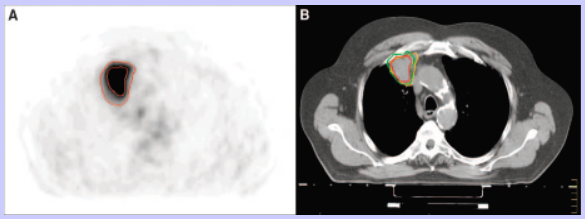
Is A Single Threshold Appropriate?

TABLE 1
Comparison of PET_{GTV} and CT_{GTV}

Tumors (*n*)	Mean ± SD			
	SUV_{max}	CT_{GTV} (cm^3)	PET_{GTV} at 40% threshold (cm^3)*	Optimal threshold (%)†
All (20)	12 ± 8	198 ± 277	44 ± 30	24 ± 13
<3 cm (4)	3.0 ± 0.4	13 ± 7	14 ± 14	42 ± 2
3–5 cm (10)	13 ± 9	90 ± 69	38 ± 22	24 ± 9
>5 cm (6)	16 ± 5	502 ± 348	69 ± 28	15 ± 6

Biehl, K J, Bradley, J D, et al. 2006. J Nucl Med. 47: 1808-12

Different Thresholding Methods



Narrow: 40% max
Wide: 2.5 SUV

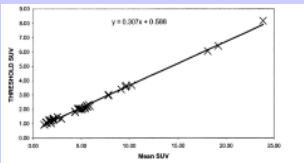
Red: 40% max
Green: 0.15 ×mean + background
Yellow: CT

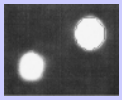
Nestle, U, et al. 2005. J Nucl Med. 46: 1342-8

Issues with Fixed Thresholding

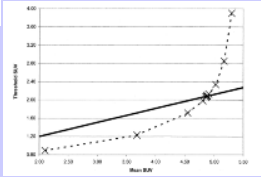
- A wide range of threshold values are used
- Tumor volume are sensitive to the threshold value
- Large differences between different threshold selection methods
- Fixed thresholding methods have inherent limitations for tumor delineation in PET
- New methods: adaptive thresholding, iterative thresholding, gradient-based, …

Iterative Threshold Selection as a Function of Mean SUV





Iteratively determined



- Background SUV or tumor volume is not an independent factor when mean SUV is applied
- 1% error in phantoms

Black, Q C, et al. 2004, Grills, I S, et al. 2007. Int. J. Radiat. Oncol. Biol. Phys.

2. PET target segmentation methods developed at WU

Method 1: Two-Stage Segmentation Method

- Adaptive region growing

$$I(x,y,z) \geq T \times mean(R_0),\ I(x,y,z) \in R^3$$

Adaptively updated with the region

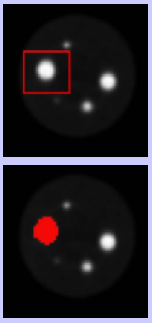
- Dual Front Active Contour (DFAC) Model

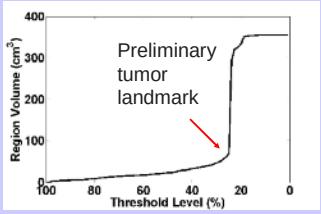
$$E(C) = \alpha \int_1^0 |C'(s)|^2 ds + \lambda \int_1^0 P(C(s)) ds$$

- Results do not depend on initial rough ROI

Li, H, and Lu, W et al. 2008. Med. Phys. 35: 3711-3721

A Phantom Case





There is a sharp volume increase at *T* = 25%

Li, H, and Lu, W et al. 2008. Med. Phys. 35: 3711-3721

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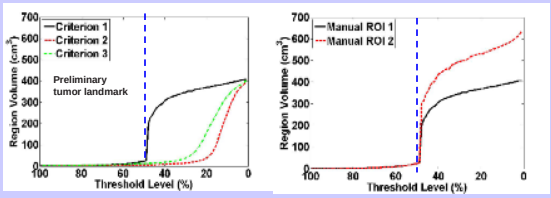
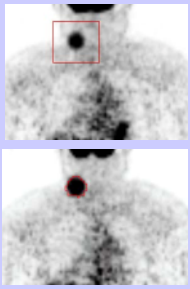
Grown Volume vs. *T*

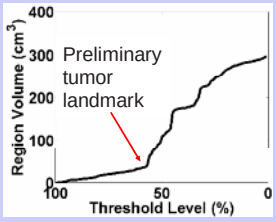


Define a preliminary tumor boundary at the sharp volume change. It's independent of the rough ROI.

Li, H, and Lu, W et al. 2008. Med. Phys. 35: 3711-3721

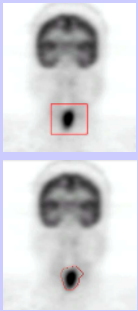
A Monte Carlo Simulated Tumor in Patient Image

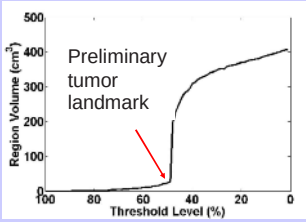




There is a sharp volume increase at *T* = 57%

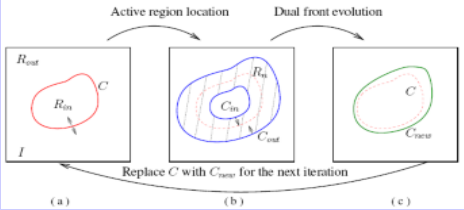
H/N Patient





There is a sharp volume increase at *T* = 49%

The Dual-front Active Contour Model



$$E(C) = \alpha \int_1^0 |C'(s)|^2 ds + \lambda \int_1^0 P(C(s)) ds$$

Evolve two fronts towards each other

Li and Yezzi, IEEE Trans Pattern Anal Mach Intell 29 (1)

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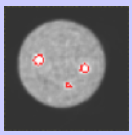
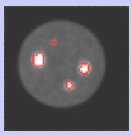
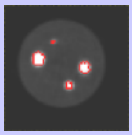
Effects of Source-to-Background Ratio and Tumor Size



S/B = 2

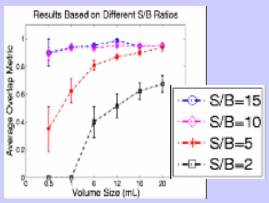


S/B = 5



S/B = 10

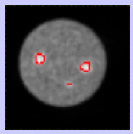
S/B = 15



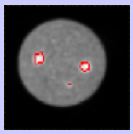
Higher S/B → better segmentation
Larger tumor → better segmentation

Li, H, and Lu, W et al. 2008. Med. Phys. 35: 3711-3721

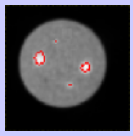
Effect of Scan Duration



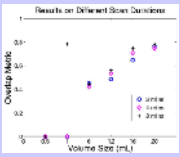
2 min



4 min

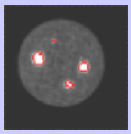


8 min



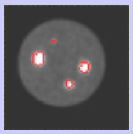
- S/B = 2, reduction in statistical noise
- The 1 mL tumor, imperceptible in 2 and 4 min scans, becomes detectable in 8 min
- Some improvement for middle-sized tumors (12, 16 mL)
- No change on the smallest (0.5 mL) or largest tumor (20 mL)

Effect of Reconstruction Algorithm and Smoothing Filter

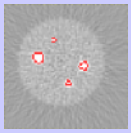


OSEM–unsmoothed

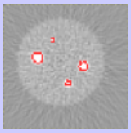
OSEM–2mm



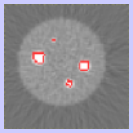
OSEM–5mm



FBP–unsmoothed

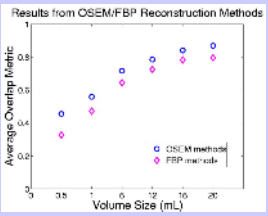


FBP–2mm

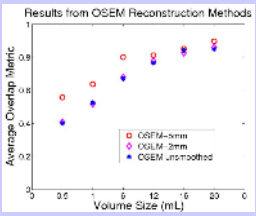


FBP–5mm

Effect of Reconstruction Algorithm

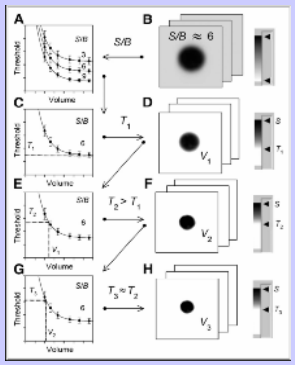


OSEM is better than FBP



5mm-FWHM post-reconstruction smoothing filter is better than 2mm-FWHM or unsmoothed

Iterative S/B Thresholding



- Calibrated threshold-S/B curves from phantom
- Depends on the initial tumor segmentation
- Phantoms:
  10% error for > 1 mL
  Large spheres → smaller errors
- Patients (lung, H/N):
  9% for 0.8 – 7.5 mL,
  15% for > 7.5 mL
  Larger tumors → larger errors ?

Jentzen, W, et al. 2007. J Nucl Med. 48: 108-14

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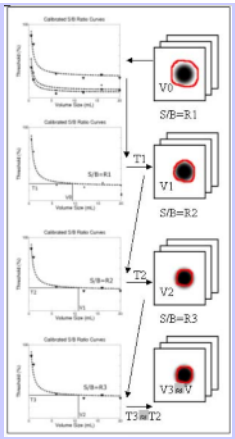
Method 2: Improved Iterative Thresholding

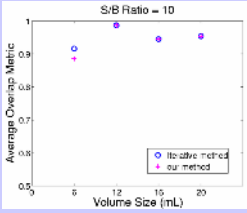
1. Source activity measured on the entire region vs. in a small region around max
   - Better estimate of source activity for a heterogeneous target
   - Including partial volume effect in calibrating S/B Threshold-Volume curves
2. Interpolate Threshold-Volume curves based on the S/B vs. choose a pre-defined one
3. Update S/B Threshold-Volume curves in addition to update volume and threshold
   - For 2 and 3, the curve for the exact S/B is used



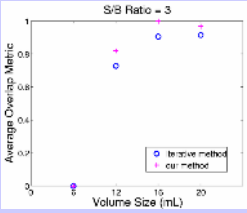
Improved Iterative Thresholding

1. Calibrated S/B threshold-volume curves from phantom, S defined using the entire sphere phantom
2. Start with an initial volume V0, such as 40% max
3. Calculate its S/B ratio = R1
4. Generate a threshold-volume curve for R1
5. Find T1 @ V0, using 4.
6. T1 ⇒ V1
7. Repeat 2-6 until converged

Phantoms with Increased Heterogeneity



Modified Iterative Thresholding

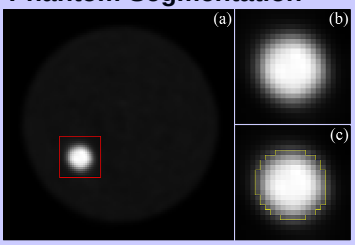


Iterative Thresholding

Some improvements in small tumors and low S/B ratios

Lu, W, Li, H, et al., TH-D-213A-2

Method 3: Spectral Clustering for PET Phantom Segmentation

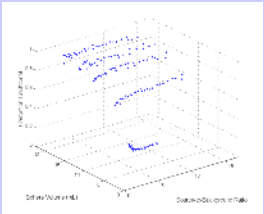


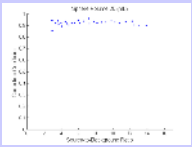
- Supervised clustering in a graphic representation of image
- Based on both spatial proximity and brightness similarity
- Extendable to multiple image features or multi-modality images

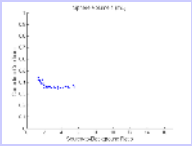
$$w_{ij} = \begin{cases} e^{\frac{-\|I(i)-I(j)\|^2}{\sigma_I^2}} \times e^{\frac{-\|X(i)-X(j)\|^2}{\sigma_X^2}}, & \text{if } \|X(i)-X(j)\|_2 < r \\ 0, & \text{otherwise} \end{cases}$$

Yang, F, Lu, W, et al., TH-D-213A-4

Correction for Partial Volume Effects: Recovery Coefficient vs. Volume and S/B

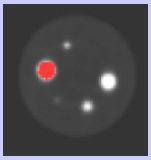






Large spheres:
independent on S/B
Small spheres:
decrease w/ S/B

How to Evaluate Segmentation Results in Patient?



- Volume overlap with known "tumor" =
  97% 86% ??
- There is no ground truth in patient data
- Manual contouring has large inter-observer variations
- Feasibility of constructing a pathology tumor volume, and and correlating with patient images

3. Tumor segmentation in multi-modality images: a brief review

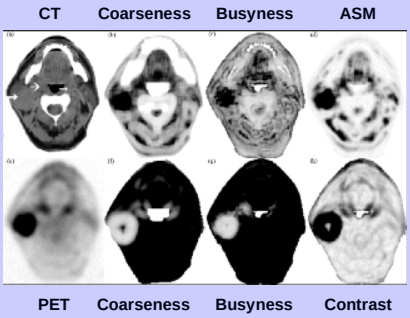
Objective and Key Issue

- Combine information from multi-modality images: anatomical and functional for tumor and normal tissue segmentation
- Key: how to combine them
  - Visual appreciation (PET, fused PET/CT, CT)
  - Weighting: equal weighting; empirical weighting; normalized to $\mu = 0$, $\sigma = 1$
  - Information combination operators

Methods

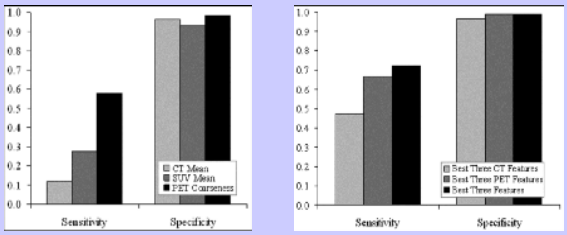
1. Classification or clustering in multi-dimensional data: KNN, fuzzy C-Mean, neural network
2. Active contour model or level set: weighting multi-modality images in the energy function
3. Potential methods: region growing, combined registration / segmentation, data fusion, rule-based
4. Feature extraction, dimensionality reduction by principal component analysis

PET/CT Texture Features in Tumor Segmentation



Yu, H. et al. IEEE Trans. Med. Imaging (in press)

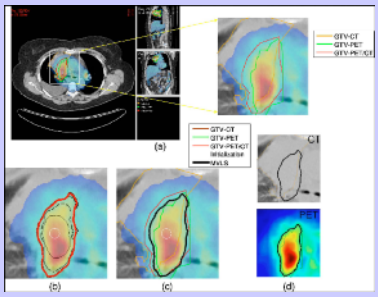
KNN Classification Results in 40 Patients:
Evaluated against manual segmentation



- Best feature: PET coarseness
- Best 3 features: CT coarseness, busyness, PET coarseness, sensitivity = 0.75, specificity = 0.95

Yu, H. et al. IEEE Trans. Med. Imaging (in press)

Multi-Valued Level Set



- Empirically weighting normalized PET/CT by 1:1.65
- Less uncertain results combining PET/CT

El Naqa, et al. 2007. Med Phys

Fuzzy C-Mean Clustering

- Fuzzy C-Mean with the degree of fusion, depending on the membership functions of both modalities to a tissue class and the degree of conflict between them (Banerjee, *et al.* 1999)

$$F = k * I_1 + (1 - k) * I_2,$$

$$k_i = (m_i^1 + m_i^2 + \text{conflict}(m_i^1, m_i^2)) + 0.5,$$

- Possibility fuzzy C-Mean (sum of membership $\neq 1$), typicality vs. probability (Masulli and Schenone 1999)
- Spatial fuzzy C-Mean (Zhu, et al. 2002)

Fuzzy C-Mean with Data Fusion

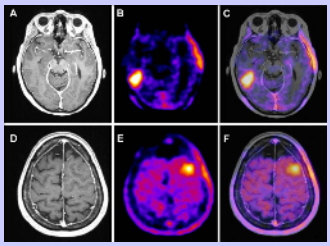
$$F = k * I_1 + (1 - k) * I_2,$$

$$k_i = (m_i^1 + m_i^2 + \text{conflict}(m_i^1, m_i^2)) + 0.5,$$

Tissue type	k (Fig. 1b)	k (Fig. 2b)
Air	0.46	0.40
V and CSF	0.38	0.30
Brain matter	0.38	0.30
Fat tissue	0	0
Skull	1.0	1.0

- K_i is the degree of fusion of CT and MRI, for the tissue class *i*

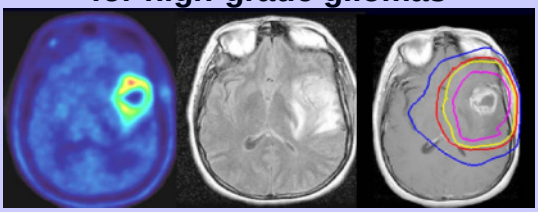
^{18}F-FET PET for high-grade gliomas



- Direct measure of the cellular proliferation rate
- Both tumors are only detectable in FET PET

Vees, H, et al. 2009. Eur J Nucl Med Mol Imaging. 36: 182-93

Carbon 11 (^{11}C) methionine PET for high-grade gliomas



- Reflect metabolic activity through increased transport mediated by type L amino acid carriers
- Highly expressed in malignant tumors compared with low uptake in the normal brain

Tsien, C I, et al. 2009. Seminars in radiation oncology. 19: 155-62

Summary

- Quite a few target segmentation methods in PET have been developed. Need comprehensive tests in more realistic phantom data and patient data
- Multimodality images provide important functional information. Will see multimodality image segmentation for more applications in RO
- Evaluation in patients remains a challenge

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