Statistical Aspects of Imaging Cancer with PET

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Positron Emission Tomography (PET) BASICS



Imaging Model

Data ~ Poisson(S+AR λ) λ is the target isotope emission distribution (where the tracer ends up)

R (Radon Transform); **A** (Attenuation); **S** (Scatter)

Dose Limited Resolution -> Statistical Aspects are Important (Vardi et al,...Nychka, Wahba...Leahy..)

CLINICAL PET IMAGING

Scanner (PET/CT)









Metabolic State of Cancer?

Normal Glucose (FDG) Pattern

Source: Radiological Society of North America

PET Scans used in Cancer Medicine

Diagnosis/Staging

Treatment Response

Recurrence Assessment

Increasing Emphasis on Clinical Validation: PET measurements - Patient Outcomes [Survival, Disease Progression, Morbibity]

18 year PET-FDG study at UW ~ 900 Sarcoma patients (scans and outcome data)

Human Sarcoma

- Class of malignant tumors affecting soft conjonctive tissue, cartilage and bone
- Can arise anywhere in the body, frequently hidden deep in the limbs
- Represents ~1% of adult cancers, more prevalent with children (~15-20%), ~10% of all cancers overall
- 5-year mean survival rate:
 ~90% (stage 1), ~75% (stage 2), ~54% (Stage 3) [statistics for the USA]
- Soft tissue sarcomas usually appear as a lump or mass, rarely cause pain, swelling, or other symptoms. Often misdiagnosed. Sometimes thought to be sports injuries.
- "Late detection" is not unusual \rightarrow potentially advanced stage of development

PET-FDG Sarcoma Studies





Soft Tissue

High Grade

Heterogeneity Measurement

Evaluate Conformity to a Pattern in the Spatial Distribution of the Metabolically Active Elements.



Homogeneous



Heterogeneous

CV Spatially Insensitive





Spatially Coherent

Spatially Incoherent



CV is 0.71 for Both!

Ellipsoidal Model for Homogeneous Tumor



 $\lambda(x|\theta,g) \approx g((x-\mu)'\Sigma^{-1}(x-\mu))$

g (monotone); $\theta = (\mu, \Sigma)$

Heterogeneity

$$H = 1 - R^2$$

O'Sullivan, Roy, Eary et al (2003,2005,2009)

H=0.06

Heterogeneity Measurements













Predictor Variable (X)	Scale	%Change in Risk(unit change in X)	95% C.I.	P-value
AGE (years)	16.8	34	(-12,101)	0.150
SUV(max) (ml/gm)	6.14	-38	(-60,-29)	0.037
Heterogeneity	7.4%	87	(35,160)	0.0002

Necrosis



TIME

BLOOD VESSEL INSIDE THE TUMOR



Roose, Chapman and Maini, SIAM Review, 2008.

Cristini, Gatenby, Sutherland, Casciari, Rasey, Krohn 1986...2010





Tumor Synthesis (Growth Pattern)



PROLIFERATIVE QUIESCENT NECROTIC

PHEROID RADIU

Co-ordinate Transformations Principal Axes : $(x_1, x_2, x_3) \rightarrow (z_1, z_2, z_3)$ Flexible Cyclinder: $(z_1, z_2, z_3) \rightarrow (h, \theta, r)$

Uptake Model

radial distance



Chemotherapy Response





MODEL:PRE : quasi-Poisson(μ)POST : quasi-Poisson($e^{\beta}\mu$)

GLM-Test: $RESPONSE = \frac{\hat{\beta}}{\hat{\sigma}_{\beta}}$ — Correlation Adjusted!

Dynamic PET Studies: Scans after Tracer Input



Blood

Tissue

Quantitative Data Analysis: Separate Delivery and Retention

 $C_T(t) = V_B C_P(t - \Delta) + \int_0^t \frac{R(t - s) \cdot C_P(s - \Delta)}{ds}$

Residue

Directly Sampled

•Image Extracted_(Statistically Guided) O'Sullivan et al. IEEE-TMI (2010)

<u>Data</u>

AIF

• Parametric (compartmental)

•Non-Parametric (non-compartmental)

O'Sullivan et al. JASA (2009)

Quantitative Analysis of Dynamic PET Data



Nonparametric Residue Analysis

0



$$C_T(t) = V_B C_P(t - \Delta) + \int_0^t R(t - s) \cdot C_P(s - \Delta) ds$$

$$R(t) = 1 - \gamma \int_0^t h(\tau) d\tau \quad \longleftarrow \quad \text{(Survival Function)}$$

h is the residence density for tracer label *K* is flow, V_B is blood volume and γ extraction

Meier and Zierler (1954), Bassingthwaighte (1971), Ostergaard et al. (1996)

Estimation based a cross-validated regularization procedure involving Positivity/Monotonicity and Smoothness Constraints.

Numerical Approximations for Residence

0.





Approximations



 $h_B(\tau) \approx \phi_1 B_1(\tau) + \phi_2 B_2(\tau) + \dots + \phi_p B_p(\tau)$ • Compartmental

$$h_{C}(\tau) \approx \alpha_{1} e^{-\lambda_{1}\tau} + \alpha_{2} e^{-\lambda_{2}\tau} + \dots + \alpha_{p} e^{-\lambda_{p}\tau}$$

Mixtures

B - splines

$$h_{_{M}}(\tau) \approx \pi_{_{1}}h_{_{1}}(\tau) + \pi_{_{2}}h_{_{2}}(\tau) + \dots + \pi_{_{p}}h_{_{3}}(\tau)$$

Mendelsohn and Rice (1984); Cunningham and Jones(1993), O'Sullivan et al (2009)

Most Widely Used Compartmental Model for PET



Implies a Residence Density of the form:

$$h_{C}(\tau) \approx \alpha_{1} e^{-\lambda_{1}\tau} + \alpha_{2} e^{-\lambda_{2}\tau} + \dots + \alpha_{p} e^{-\lambda_{p}\tau}$$

May be reasonable in-vitro, but for in-vivo PET ROI data???

PET FDG Data from Normal Brain ROIs





Nonparametric and Compartmental Analysis

[A formal statistical test rejects the compartmental model, p-value=0.046]

Nonparametric Residue Analysis vs Parametric Compartment Model

120 TACs:10 Brain Regions and 12 Subjects



(analysis uses a reference distribution constructed by simulation – c.f. Cox. Wahba. Yandell. Wang. Li. Raz etc)

Adaptation for Parametric Mapping



Tissue Concentration Model (voxel x and time t)

$$C_T(t,x) \approx V_B(x)C_P(t-\Delta(x)) + K(x)\int_o^t R(t-s,x)C_P(s-\Delta(x))ds$$

Mixture Analysis of Residence Density

$$h(t,x) \approx \pi_1(x)h_1(t) + \pi_2(x)h_2(t)\cdots + \pi_J(x)h_J(t)$$

Residue Function

$$\mathbf{R}(t,x) \approx 1 - \zeta(x) \int_{o}^{t} [\pi_{1}(x)h_{1}(\tau) + \pi_{2}(x)h_{2}(\tau) \cdots + \pi_{J}(x)h_{J}(\tau)]d\tau$$

Residue Analysis of Segment Time Course Patterns





Diagnostic **Assessment:**

Voxel-Level Residuals



.

20

20

15

15

Separation Width (pixels)







0.0

0.025

mL/g/min

0.0 2.21

mL/g

0.0 0.13

mL/g

Variance of Residues

$$\hat{R}(t,x) = e^{-\Lambda(t,x|\hat{\theta}_x)}$$

(Greenwood's Formula)

$$Var(\hat{R}(t,x)) \simeq R(t,x)^2 \cdot Var(\Lambda(t,x|\hat{\theta}_x))$$

Approximation:

$$\begin{split} Var(\hat{R}(t,x)) &\approx \alpha^2 K(x)^{-1} \bar{R}(t)^2 c(t|C_p,\tau_{\frac{1}{2}})^2 \\ & \text{Flow} \qquad \text{Mean} \qquad \text{AIF} \end{split}$$

-> Variation in Functionals by the Delta-Method

 $Var(\hat{R}(t,x)) \approx \alpha^2 K(x)^{-1} \bar{R}(t)^2 c(t|C_p,\tau_{\frac{1}{2}})^2$



Regional Voxel-Level Residues and Flow Distribution







Standardized Voxel-Level Residues (Measured)

Some Analysis

z_{ib} Poisson with mean $\kappa f_b K(x_i) R_b \Delta_b$

$$R_b = e^{-\Lambda_b} = e^{-(\lambda_1 \Delta_1 + \lambda_2 \Delta_2 + \dots + \lambda_b \Delta_b)}$$

Asymptotic Variance of MLEs

$$Var(\hat{R}_b) \simeq (\Delta_1 \kappa)^{-1} K(x_i)^{-1} R_b^2 \cdot \left(1 + \frac{\Delta_1}{f_b R_b \Delta_b}\right)$$

Summary

- PET in Cancer Imaging Diagnosis/Staging Response Assessment Treatment Planning
- Spatial and Temporal Aspects of PET Data Important
- Detailed Measurement and Modeling of the Disease Process is key to adaptive treatment

Statistics (Wisconsin style) has much to offer. (*Please keep it going for another 50... at least!*)