Quantitative Imaging in SPECT/CT

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Conflict of Interest Disclosure

Under a licensing agreement between the GE Healthcare and the Johns Hopkins University, I (Eric Frey) am entitled to a share of royalty received by the University on sales of iterative reconstruction software used to obtain some results in this presentation. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.
Outline

• Define quantitative SPECT
• Discuss measures of quantitative reliability
• Discuss how to obtain optimal quantitative SPECT images
• Show achievable levels of accuracy and precision for SPECT
Quantitative SPECT/CT

- Estimate activity (or average activity concentration) in an object of interest
Image Quality

- Quantitative versus Detection Tasks

Simulated 24 hr In-111 Zevalin Images

Better for Detection Task?

Better for Organ Activity Quantification

OS-EM
5 iterations
32 subsets

OS-EM
30 iterations
32 subsets
Measures of Quantitative Quality

• Accuracy:
  – How close measurement is on average to truth
  – Bias: estimate minus truth averaged over many trials

• Precision
  – Variability of estimate about its mean
  – Variance: \((\text{estimate} - \text{mean})^2\) averaged over many trials

• Reliability
  – Mean Square Error (MSE): square of truth minus estimate averaged over many trials
  – \(\text{Bias}^2 + \text{Variance}\)
Example

- \( \text{var}=0.1, \text{bias}=0.0 \)
- \( \text{var}=0, \text{bias}^2=0.1 \)
- \( \text{var}=\text{bias}^2=0.05 \)

Equal MSE

Estimated Value (arbitrary units)

Trial Number

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Effects of Accuracy and Precision on Diagnostic Reliability

- Measured, normal
- Measured, disease
- Truth, normal
- Truth, disease

Test Value

Diagnostic Threshold

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Requirements for Quantitative SPECT/CT

- Quality Control/Calibration
- Acquisition
- Reconstruction/Processing
Quality Control & Calibration

- Routine Camera and CT QC
- Registration of SPECT and CT
- Background Measurement
- Calibration Measurement
Background Measurement

- Importance depends on radiation environment
- Background count rate is angle-dependent
- Ideally done for each patient with fast SPECT acquisition before or after patient acquisition
- Alternative: check background count rate before acquisitions
Image Calibration Factor

• Units of voxels in SPECT depend on
  – Sensitivity of collimator-detector system
  – Acquisition time per view
  – Number of views
  – Reconstruction algorithm
  – Manufacturer implementation

• Calibration factor is needed to convert SPECT voxel values to activity concentration
Calibration Factor Measurement

• Use phantom study to determine factor
  – Acquire SPECT study of object with known activity
  – Reconstruct and compute counts
  – Scale factor is true phantom activity/image counts
  – Calibration factor should be theoretically predictable for “ideal” reconstruction algorithms

• Daily measurement of sensitivity
  – Static image of standard source in air at known distance from camera
  – Sensitivity = std. counts/(std. activity * acq. time)
  – Correct calibration factor by ratio sensitivity on day of patient scan to sensitivity at time of phantom study
Acquisition Parameters

- Collimator selection
- Injected activity/acquisition time
- Pixel size
- Number of views
- Energy windows
Collimator

• Resolution/sensitivity tradeoff
• Appropriate for energy of radionuclide

Images of Collimator Response for $^{131}$I source 10 cm from collimator face
Acquisition Time & Injected Activity

- Precision directly related to product of acquisition time and injected activity
- Longer acquisition times → more motion
- Injected activity limited by radiation dose
- Precision not a big issue for large objects
Pixel Size

- Pixel size determined by matrix size and zoom
- Entire patient in field of view
- Pixel size = 1/2-1/3 of collimator-detector full-width at half maximum resolution at distance of center of rotation
Number of Views

• Theoretically: #views equal to 3 times number of voxels across reconstructed field of view over 360°

• Practically: #views over 360 degrees equal to matrix size

• 360° versus 180° not well studied
  – Either is probably o.k. with appropriate quantitative reconstruction
  – 180° may be better for objects near surface
  – Non-circular orbits preferred for best resolution
Energy Windows

• Use all major photopeaks
• Wider windows (e.g. 20% Tc-99m) provide more stable sensitivity
• Choose appropriate scatter windows if using energy-based scatter compensation, e.g., triple energy window (TEW) method
Image Processing and Reconstruction

- Image reconstruction
- Compensation for image degrading factors
- VOI definition
Image Reconstruction Algorithms

- **Analytic Algorithms (e.g., FBP)**
  - Limited ability to compensate for image degrading factors
  - Require combinations of compensation methods
  - Sub-optimal noise properties
  - Fast and widely available

- **Iterative Methods (e.g., ML-EM, OS-EM)**
  - Allow compensation for image degrading factors
  - Unified compensation for all effects is possible
  - Optimal noise properties in terms of quantitation
  - Computationally intensive and less-widely available
Compensation for Image Degrading Factors

- Attenuation
- Scatter
- Collimator-detector response (CDR)
- Partial volume effects
- Motion
Reconstruction-Based Compensation

Initial Estimate -> Project Each Angle -> Computed Projections

Computed Projections -> Compare Computed & Measured

Compare Computed & Measured -> Model

Model -> Update Estimate

Update Estimate -> New Estimate

New Estimate -> Measured Projections

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Components of Reconstruction-Based Compensation

• Cost Function
  – ML (unbiased)
  – MAP (trades bias for improved precision)
  – ...

• Iterative Algorithm
  – EM (or OS version)
  – Coordinate descent
  – ...

• Model of Imaging System
  – Analytic
  – Measurement-based
  – Monte Carlo Simulation
OS-EM w/Attenuation Compensation

- Reconstruction-based
- Allows accurate modeling of attenuation
- Very fast
- Not convergent
  - Selection of subsets critical
  - For high noise data use fewer subsets
Attenuation Map

- Map must be registered to SPECT image by better than 1 pixel
- Translation of CT values to SPECT attenuation coefficients is necessary
  - Contrast agents complicate translation
- Noise in attenuation map not very critical
- Resolution should be “matched” to resolution in SPECT image
Scatter Compensation

• Scatter estimation method
• Scatter compensation algorithm
Triple Energy Window (TEW)

- Acquire data in scatter windows above and below photopeak
- Estimate scatter using trapezoidal approximation
- Use care in selecting windows
- Use smoothing to reduce noise in scatter estimates
Model-Based Scatter Estimates

- Use current estimate of activity distribution to estimate scatter in projection data
- Accurate model must be spatially varying and model non-uniform attenuation in body
- E.g. Effective Source Scatter Estimation (ESSE)
- Limited commercial availability
Validation of ESSE:
Tc-99m Voxel Sources

Detector

Intensity (arbitrary units)

Projection Bin Number
Monte Carlo Scatter Estimation

- Use Monte Carlo simulation methods to propagate photons in body
- Use some approximations to speed up the simulation
- Estimates will have some noise
- Low-noise estimates can be done in < 10 seconds per iteration
Results: scatter in nonuniform object

Atten.  Source  EffSrc.
Scatter Compensation Algorithms

- Pre-reconstruction subtraction of scatter estimate
- Incorporate scatter estimate into iterative reconstruction
  - Add to estimated projections
  - Model in projector and/or backprojector
Collimator-Detector Response (CDR) Compensation

- Inverse Filtering
  - Spatially invariant
    - Metz Filter
    - Wiener Filter
  - Spatially variant: frequency-distance relationship-based methods
- Iterative Reconstruction-Based Methods
Metz Filter

- Assume CDR is spatially invariant
- Apodize to control high frequency noise
- Can apply pre- or post-reconstruction

\[ \text{Metz}(\tilde{\nu}) = \text{CDRF}^{-1}(\tilde{\nu}) \left[ 1 - \left( 1 - \text{CDRF}(\tilde{\nu})^2 \right)^n \right] \]

\( n = \text{filter order} \)
Reconstruction-Based

- Model CDR in projection and backprojection operations
  - Convolution in planes parallel to detector
  - Various methods for accelerating
- Allows modeling spatial variance
- Increasing commercial availability
Modeling the CDR

- Low energy photons: analytic expressions for geometric response function
- High-energy photons: measure or Monte Carlo simulated CDR as a function of distance from the collimator
Partial Volume Effects

Phantom Reconstruction

Spill In

Spill Out

Phantom

Reconstruction

Image Intensity (Arbitrary Units)

0 100 150 200 250

Pixel

0 0.02 0.04 0.06 0.08 0.1 0.12 0.14 0.16

Intensity
Partial Volume Compensation (PVC)

- Calibration-based methods (e.g., recovery coefficient)
- Post-reconstruction image processing methods
  - Voxel-based
  - Region-based
- Reconstruction-based methods
Calibration-Based Methods

• Concept
  – Use phantoms to measure size-dependent calibration factor
  – Apply to estimated VOI activities post-reconstruction

• Limitation: Calibration factor depends on location, size, shape, orbit, activity distribution, …
Geometric Transfer Matrix (GTM) PVC

\[
\hat{t} = W \cdot \hat{T}
\]

\{ 
\begin{align*}
T_i &: \text{True count in ROI } i, \quad (i=1, \ldots 4) \\
t_i &: \text{Measured count in ROIs,} \\
W &: \text{GTM} \\
\end{align*}
\}

\hat{T} = W^{inv} \cdot \hat{t}

Diagonal elements are object-dependent recovery coefficients
Off-diagonalelements are object-dependent spill-in factors
Reconstruction-Based PVC

- Constrain activity to be uniform in VOIs
- Directly estimate activity in VOI

Reconstruction-Based PVC using Striatal VOIs and Voxel Object Model
Reconstruction-Based PVC

Distribution I: OS-EM, OS-VOI, OS-VOI+Vox
Distribution II: OS-EM, OS-EM+PVC, OS-VOI, OS-VOI+Vox
Distribution III: OS-ROI-STR, OS-ROI-ALL

Percent error of activity estimates (%):

- Distribution I
  - OS-EM: ~5%
  - OS-EM+PVC: ~0%
  - OS-VOI: ~-5%
  - OS-VOI+Vox: ~-10%

- Distribution II
  - OS-EM: ~-15%
  - OS-EM+PVC: ~-10%
  - OS-VOI: ~-20%
  - OS-VOI+Vox: ~-25%

The graph shows the percent error of activity estimates for different distributions and object models.
VOI Definition

- Accurate definition of VOIs important
- Well-registered CT image can improve VOI definition
- Resolution of CT image should be as good as or better than SPECT image
Examples of Quantitative Accuracy

- Striatal activity for I-123 agent
- In-111 radio-labeled antibody
  - Organ and tumor activity for single phantom
  - Organ residence time for phantom population
Accuracy of Activity Quantification:
I-123 Brain SPECT

- GE Millennium VG/Hawkeye (5/8” thick crystal)
- LEHR Collimator
- 128 views/360°, 128*128 projection w/ 0.24 cm pixels
- CT attenuation maps
- Manually defined VOIs using registered MR Images
- Activity concentrations:
  - Bkg: 110 kBp/ml
  - Left Caudate: 212 kBq/ml
  - Left Putamen: 154 kBq/ml
  - Right Caudate: 1770 kBp/ml
  - Left Putamen: 222 kBq/ml

Non-specific background uptake

RSD Striatal Phantom

Right caudate
Left caudate

Right putamen
Left putamen

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Accuracy of Activity Quantitation: I-123 Brain SPECT

OS-EM w/
Attenuation Scatter &
CDRF Compensation
Post-Reconstruction
pGTM PVC

% Error in Activity Estimate

Background Left Caudate Left Putamen Right Caudate Right Putamen
Quantitative Accuracy of SPECT: In-111 Imaging

- $^{111}$InCl solution placed in the heart, lungs, liver, and background with ratios of 19:5:20:1
- Two spherical lesions with diameters 25 mm and 35 mm were placed in the phantom (concentrations relative to background were 17:1 and 156:1).
- The total activity used was ~185 MBq (5 mCi)
- Imaged Using GE Discovery VH SPECT/CT system with 1” thick crystal
- MEGP collimator
- Manually defined VOIs using SPECT and CT images
Sample Reconstructed Images

NC = No Compensation
A = Attenuation Compensation
AS = Attenuation and Scatter Compensation
AD = Attenuation and CDR Comp
ADS = Attenuation, CDR and Scatter Comp

Atn Map

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### Accuracy of Activity Quantitation: RSD Phantom and In-111

% Error in total activity estimation: (true-estimate)/true x 100%

<table>
<thead>
<tr>
<th>Organ</th>
<th>No Comp</th>
<th>Attenuation Comp</th>
<th>Attenuation + Scatter Comp</th>
<th>Attenuation + Compton + Scatter Comp</th>
<th>Attenuation + Compton + Scatter + PVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>-77.60%</td>
<td>24.63%</td>
<td>-11.76%</td>
<td>-3.72%</td>
<td>-2.11%</td>
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<tr>
<td>Lungs</td>
<td>-62.78%</td>
<td>31.39%</td>
<td>-0.96%</td>
<td>4.23%</td>
<td>6.45%</td>
</tr>
<tr>
<td>Liver</td>
<td>-74.38%</td>
<td>29.22%</td>
<td>-7.47%</td>
<td>2.71%</td>
<td>4.14%</td>
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<tr>
<td>20.6 cc sphere</td>
<td>-78.88%</td>
<td>-14.85%</td>
<td>-29.81%</td>
<td>-3.36%</td>
<td>-1.97%</td>
</tr>
<tr>
<td>5.6 cc sphere</td>
<td>-88.24%</td>
<td>-51.53%</td>
<td>-56.75%</td>
<td>-21.55%</td>
<td>-11.95%</td>
</tr>
</tbody>
</table>

With appropriate reconstruction, quantitative SPECT is possible!
Accuracy and Precision of Activity Estimates: In-111 SPECT

- 3D NCAT phantom:
  - Organ activity concentrations based on 8 clinical studies using In-111 Zevalin
  - Non-uniform activity distribution in heart and lungs.

- Simulation:
  - Experimentally validated Monte Carlo simulation w/detailed collimator modeling
  - Parameters for a GE VH/Hawkeye camera (1” crystal, MEGP collimator)
  - Generated 50 realizations of Poisson noise corresponding to noise level of
    - 5 mCi In-111 injected activity
    - 30 seconds per view
    - 120 views over 360°

- Used true organ VOIs to estimate organ activities
SPECT Residence Time Estimation

- SPECT Proj.
- CT

0 hr
4 hr
24 hr
72 hr
144 hr

SPECT Activity Estimation

Curve Fitting

Residence Time

\[ \frac{A_{\text{organ}}(t)}{A_0} \]

Time (hours)
Accuracy and Precision
In-111 SPECT

Reconstructed using OS-EM w/attenuation, scatter, CDR and partial volume compensation

Error bars show standard deviations of activity estimates

Precision better than accuracy for most organs

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Phantom Variations

- Anatomic parameters obtained from 7 Zevalin patient studies
  - Gender: 3 males and 4 females
  - Body, rib, liver, stomach, spleen, kidneys, heart size
- Bio-kinetics parameters from 7 Zevalin patient studies
  - Organ activity at time 0
  - Effective half-life of organ activity
- Used all possible combinations of anatomic and biokinetic parameters (7x7=49 total phantoms)
Ensemble Bias and Variance

OS-EM Reconstruction w/Attenuation, CDR and Scatter Compensation
Quantification of Small Objects

- 2.2 cm diameter tumors
Quantification of Very Small Objects

- 0.9 cm diameter tumors

![Graph showing error in activity estimates over iterations for Tumor 4 and Tumor 2.](attachment:image.png)
Optimal Number of Iterations

- Tumors with diameter > 2.0 cm

RMSE / True * 100%

# of Iterations (24 subsets/iteration)
Optimal Number of Iterations

- “Small” tumors (diameter < 2.0 cm)
Effect of Acquisition Time

30 iterations OS-EM, 24 subsets

After Butterworth Filtering

- Simulated 24 hr $^{111}$In Zevalin Images
- Uptake and counts based on patient data w/5 mCi injection
- 49 phantom/activity distribution combinations
- Reconstructed using OS-EM w/atten, CDR and scatter compensation
- Quantified using true organ boundaries
Effect of VOI Definition

• For estimation of total activity in an object, the accuracy of the definition of the VOI is critical
• Use of registered anatomical image can improve accuracy of VOI definition
  – Mis-registration of anatomical image can lead to mis-registration of VOIs
  – Bias or imprecision in VOI definition leads to mis-definition
Effects of VOI Mis-Registration

![Graph showing the effects of VOI mis-registration on liver and kidneys. The graph plots the % Change in Organ Total Activity against Lateral Shift (voxels). The liver data points are represented by red circles, and the kidneys data points are represented by blue squares. The graph shows a trend where the activity decreases as the lateral shift increases.](image-url)
Mis-definition of VOI

Random

Erosion

Dilation

<table>
<thead>
<tr>
<th>1/16</th>
<th>2/16</th>
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Effects of VOI Mis-definition

- Mis-definition has larger effects for smaller organ than for bigger organ
- Bias due to drawing VOIs too large or too small are larger than

<table>
<thead>
<tr>
<th>Method \ Organs</th>
<th>Liver</th>
<th>Left Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random</td>
<td>-0.33 ± 0.05 %</td>
<td>-1.24 ± 0.38 %</td>
</tr>
<tr>
<td>Dilation</td>
<td>2.06 ± 0.05 %</td>
<td>5.27 ± 0.15 %</td>
</tr>
<tr>
<td>Erosion</td>
<td>-2.85 ± 0.06 %</td>
<td>-7.52 ± 0.19 %</td>
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Conclusions

• Optimal image is task-dependent
• Use of SPECT/CT enables attenuation compensation, improved VOI definition, and partial volume compensation
• Careful compensation for image degrading factors is essential
• Use of optimal methods and parameters can provide excellent quantification for organs and very good quantification for large tumors (> 2 cm diameter)
• Quantification of small objects requires careful partial volume compensation
Acknowledgements

• Funding: NIH Grants
  – R01 EB 000288
  – R01 CA109234
  – R01 EB 000168

• People
  – Benjamin M.W. Tsui
  – W. Paul Segars
  – Bin He
  – Yong Du