A New PET Reconstruction Formulation that Enforces Non-negativity in Projection Space for Bias Reduction in Y-90 Imaging

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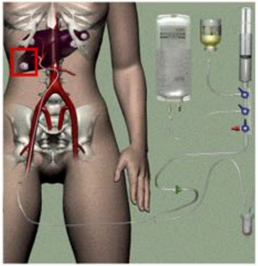
IEEE NSS/MIC 2017

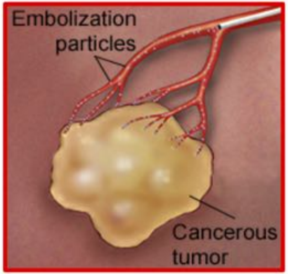
Radioembolization

- A therapy that irradiates unresectable liver tumors with Y-90 (radioactive isotope) microspheres

Figure: Illustration of Radioembolization



(a) Zoomed out

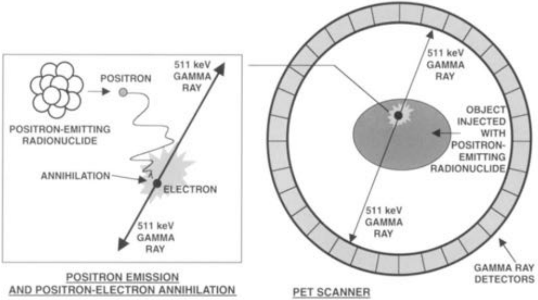


(b) Zoomed in

Quantitative Imaging

- Importance of quantitative imaging after radioembolization
  - Establish absorbed dose versus outcome relationship for future treatment planning
  - Find unexpected extra-hepatic deposition

Figure: Illustration[1] of Positron Emission Tomography (PET) as quantitative imaging modality



[1] Cherry, Simon R., and Sanjiv S. Gambhir. "Use of positron emission tomography in animal research." ILAR journal 42.3 (2001): 219-232.

Particulars about Y-90 imaging

- Y-90: Radioisotope for radioembolization
  - Almost pure beta emitter
  - Very low probability of positron emission : 3.2×10^{-5}
  - ^{176}Lu and Bremsstrahlung photons contribute to random coincidences
    $\rightarrow$ Low true coincidence counts & very high random fraction

Figure: Random coincidences in Y90 imaging

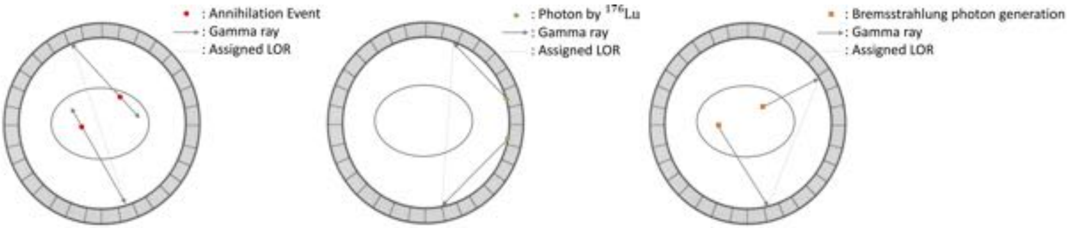


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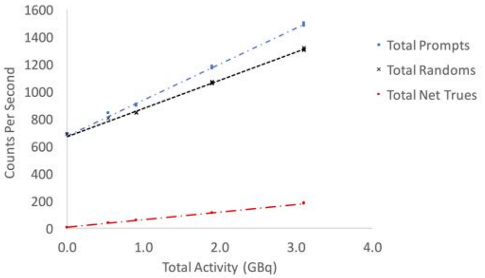
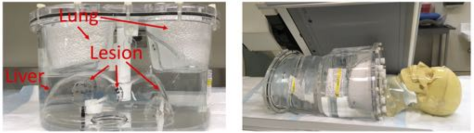
Figure: True/Random counts in measurement of our Y90 phantom study



Reported Problems

- Several Y-90 PET papers[2] reported bias in quantification
- Our in-house phantom study agreed with the results of those papers

Figure: Phantom study: Known activity deposition in each ROI



- Bias direction in calculation of the absorbed dose
  - Underestimation in hot (lesion) and warm (liver) region
    $\rightarrow$ Inaccurate absorbed dose-effect relationship
  - Overestimation in cold (no activity) region and total dose
    $\rightarrow$ False alarm due to high extra-hepatic (i.e., lung) deposition

[2] Carlier, Thomas, et al. "Y90 PET imaging: Exploring limitations and accuracy under conditions of low counts and high random fraction." Medical physics 42.7 (2015): 4295-4309.

Formulation of emission tomography

- Measurement follows Poisson statistical model:

$$Y_i \sim \mathrm{Poisson}(\bar{y}_i(x_{\mathrm{true}})), \quad i = 1, \ldots, n_d$$

$$\text{where, } \bar{y}_i(x_{\mathrm{true}})) = \mathrm{E}[Y_i] = [Ax_{\mathrm{true}}]_i + \bar{r}_i = \sum_{j=1}^{n_p} a_{ij} x_{\mathrm{true},j} + \bar{r}_i$$

- (Negative) Poisson log likelihood function $f(x)$:

$$f(x) \stackrel{c}{=} \sum_{i=1}^{n_d} \mathrm{h}_i([Ax]_i) = \sum_{i=1}^{n_d} \bar{y}_i(x) - y_i \log(\bar{y}_i(x))$$

- Goal of conventional emission tomography:

$$\hat{x} = \operatorname*{argmin}_x f(x)$$
$$\text{subject to } x \geq 0$$

Limitation of conventional constraint

- Cases in negative Poisson log-likelihood function

$$f(x) \stackrel{c}{=} \sum_{i=1}^{n_d} \mathrm{h}_i([Ax]_i) = \begin{cases} [Ax]_i + \bar{r}_i - y_i \log([Ax]_i + \bar{r}_i), & y_i > 0, \quad [Ax]_i + \bar{r}_i > 0 \\ [Ax]_i + \bar{r}_i, & y_i = 0 \\ \infty, & y_i > 0, \quad [Ax]_i + \bar{r}_i \leq 0 \end{cases}$$

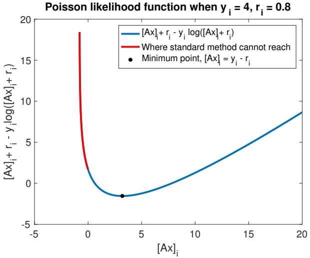


Figure: $y_i > 0$ case

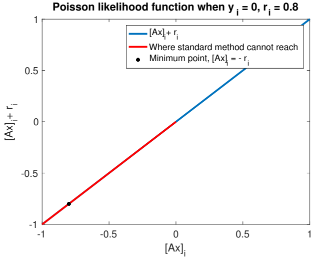
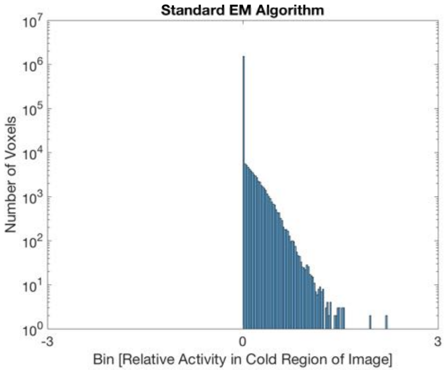


Figure: $y_i = 0$ case

Bias introduced in cold region

- Histogram in cold region (where there is no activity)



Proposed method

- Enforce non-negativity on projection space:

$$\hat{x} = \underset{x}{\operatorname{argmin}} f(x)$$
$$\text{subject to } Ax + \bar{r} \geq 0$$

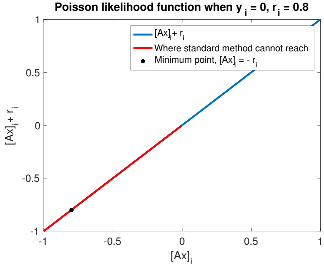


Figure: $y_i = 0$ case with conventional constraint

$\longrightarrow$

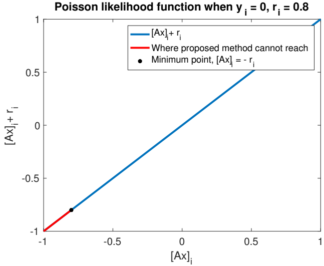
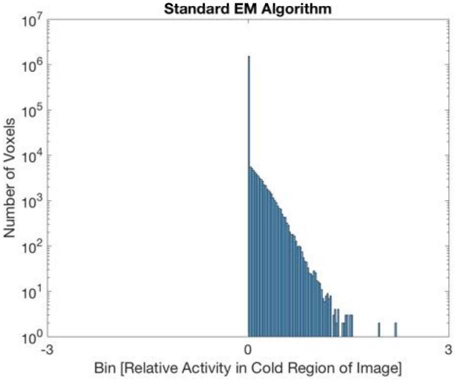
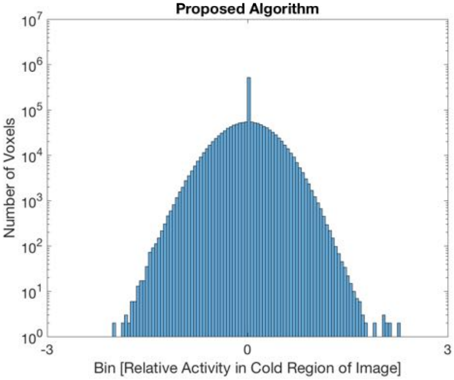


Figure: $y_i = 0$ case with proposed constraint

Overview of our proposed method

- Histogram in cold region (where there is no activity)





Changing the formulation to solvable form

- To solve the new formulation, we introduce a function and a variable:

$$\hat{x} = \underset{x}{\operatorname{argmin}} f(x) \text{ subject to } Ax + \bar{r} \geq 0$$

$$\hat{x} = \arg\min_{x \in \mathbb{R}^{n_p}} f(x) + g(Ax + \bar{r}), \text{ where } g(v) = \begin{cases} \infty, & \text{any } v_i < 0 \\ 0, & \text{all } v_i \geq 0 \end{cases}$$

$$\hat{x} = \arg\min_{x \in \mathbb{R}^{n_p}} \min_{z \in \mathbb{R}^{n_d}} f(x) + g(z) \text{ subject to } Ax + \bar{r} - z = 0$$

- We form augmented Lagrangian based on above minimization problem:

$$\begin{aligned} \Psi(x, z, \lambda) =& f(x) + g(z) + \lambda^T(Ax + \bar{r} - z) + \frac{\rho}{2}||Ax + \bar{r} - z||_2^2 \\ \overset{u=\lambda/\rho}{=}& f(x) + g(z) + \frac{\rho}{2}||Ax + \bar{r} - z + u||_2^2 - \frac{\rho}{2}||u||_2^2 \end{aligned}$$

How to solve?

- Solve minimization problem using ADMM[3]:

$$x^{(n+1)} = \underset{x}{\operatorname{argmin}} \left(f(x) + \frac{\rho}{2} ||Ax + \bar{r} - z^{(n)} + u^{(n)}||_2^2 \right)$$
$$z^{(n+1)} = \underset{z}{\operatorname{argmin}} \left(g(z) + \frac{\rho}{2} ||Ax^{(n+1)} + \bar{r} - z + u^{(n)}||_2^2 \right)$$
$$u^{(n+1)} = u^{(n)} + (Ax^{(n+1)} + \bar{r} - z^{(n+1)})$$

- z-update: $z^{(n+1)} = [Ax^{(n+1)} + \bar{r} + u^{(n)}]_+$
- x-update: No analytical solution $\rightarrow$ Iteratively update
- Adaptively tune the parameter ρ to achieve faster convergence[4]

[3]Boyd, Stephen, et al. "Distributed optimization and statistical learning via the alternating direction method of multipliers." Foundations and Trends in Machine Learning 3.1 (2011): 1-122.

[4]Xu, Zheng, Mrio AT Figueiredo, and Tom Goldstein. "Adaptive ADMM with spectral penalty parameter selection." arXiv preprint arXiv:1605.07246 (2016).

Details on x-update

- x-update: No analytical solution $\rightarrow$ Iteratively update
  - Derived separable quadratic surrogate $Q_{h,j}(x_j; x^{(n)})$ for the Lagrangian penalty term $h(x) = \frac{\rho}{2}||Ax + \bar{r} - z^{(n)} + u^{(n)}||_2^2$
  - Update along with the surrogate function $Q_{f,j}$ for $f(x)$ using Newton's method
- Form of x-update:

$$x_j^{(n+1)} = x_j^{(n)} - \frac{\frac{\partial Q_{f,j}(x_j; x^{(n)})}{\partial x_j}\Big|_{x_j = x_j^{(n)}} + \frac{\partial Q_{h,j}(x_j; x^{(n)})}{\partial x_j}\Big|_{x_j = x_j^{(n)}}}{\frac{\partial^2 Q_{f,j}(x_j; x^{(n)})}{\partial x_j^2} + \frac{\partial^2 Q_{h,j}(x_j; x^{(n)})}{\partial x_j^2}}$$

$$= x_j^{(n)} - \frac{\sum_{i=1}^{n_d}(1 - \frac{y_i}{\bar{y}_i^{(n)}})a_{ij} + \rho \sum_{i=1}^{n_d} a_{ij}([Ax^{(n)}]_i + \bar{r}_i - z_i^{(n)} + u_i^{(n)})}{\sum_{i=1}^{n_d} \breve{c}_i^{(n)} a_{ij} a_i + \rho \sum_{i=1}^{n_d} a_{ij} a_i}.$$

  - $\breve{c}_i^{(n)}$ denotes optimal curvature[5]

[5] Fessler, Jeffrey A., and Hakan Erdogan. "A paraboloidal surrogates algorithm for convergent penalized-likelihood emission image reconstruction." Nuclear Science Symposium, 1998. Conference Record. 1998 IEEE. Vol. 2. IEEE, 1998.

Regularization

- Add regularization term to cost function:

$$\begin{aligned}
&\hat{x} = \arg\min_x f(x) + \beta \mathrm{R}(x) \\
&\text{subject to } Ax + \bar{r} \geq 0 \text{ (proposed)} \\
&\text{or } x \geq 0 \text{ (conventional)},
\end{aligned}$$

where $\mathrm{R}(x) = \sum_{k=1}^{K} \frac{([Cx]_k)^2}{2}$, C is a $K \times n_p$ finite differencing matrix.

- Benefit of adding regularization
  - To penalize the roughness and control the noise (varying β value)
  - Cost function becomes strictly convex $\rightarrow$ unique solution[6]

[6] Ahn, Sangtae, and Jeffrey A. Fessler. "Globally convergent image reconstruction for emission tomography using relaxed ordered subsets algorithms." IEEE Transactions on Medical Imaging 22.5 (2003): 613-626.

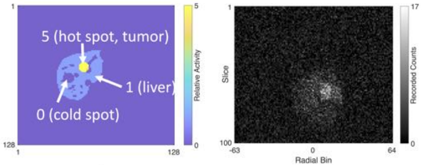
Experimental setting

- Simulation conditions

	Patient A	Patient B
Y-90 Injection (GBq)	3.9	0.9
True Prompts	675K	97K
Random Prompts	3.3M	1.7M
Total Prompts	3.9M	1.8M
Random Fraction (%)	83	95

* Random Fraction = (Random prompts / Total prompts) $\times$ 100

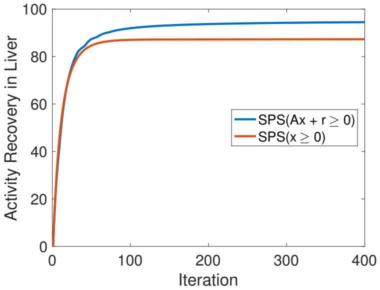
- Digital phantom and projection



True image   Projection

Underestimation in hot/warm region (lesion/liver) solved?

- Plot: Activity Recovery(%) in Liver vs Iteration (Initial x is 0)



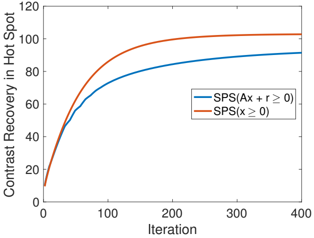
- Comparison between regularized methods

	$x \geq 0$	$Ax + \bar{r} \geq 0$
Activity Recovery in Liver	89.5%	94.8%

Table: Result averaged 4 different cases (varying β value, simulation condition: Patient A,B)

Underestimation in hot/warm region (lesion/liver) solved?

- Plot: Contrast Recovery(%) in Hot Spot vs Iteration (Initial x is 0)



- Comparison between regularized methods

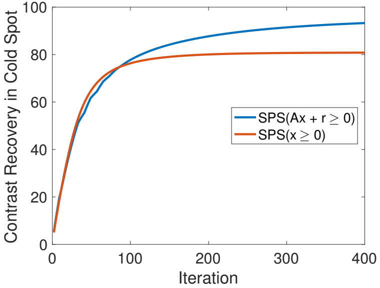
	$x \geq 0$	$Ax + \bar{r} \geq 0$
Contrast Recovery in Hot Spot	105.0%	98.9%

Table: Result averaged 4 different cases (varying β value, simulation condition: Patient A,B)

- Activity recovery is similar to each other

Overestimation in cold (no activity) region solved?

- Plot: Contrast Recovery(%) in Cold Spot vs Iteration (Initial x is 0)



- Comparison between regularized methods

	$x \geq 0$	$Ax + \bar{r} \geq 0$
Contrast Recovery in Cold Spot	81.5%	92.2%

Table: Result averaged 4 different cases (varying β value, simulation condition: Patient A,B)

Estimated measurement mean comparison

- Comparison between y (a realization of measurement) and $\bar{y}(x^{(n)})$ (estimated measurement mean)
  - Estimated measurement with constraint $x \geq 0$ is always above $\bar{r}$.

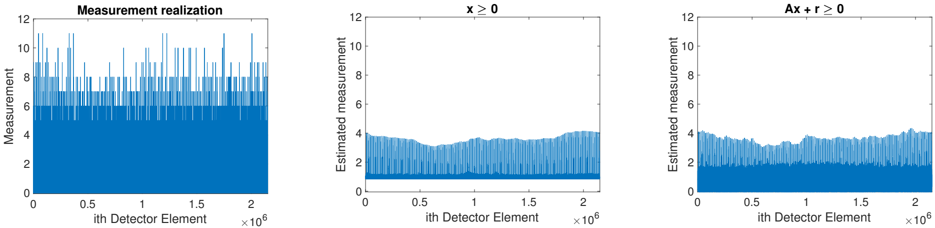


Figure: A realization of measurement

Figure: Estimated measurement with $x \geq 0$.

Figure: Estimated measurement with $Ax + \bar{r} \geq 0$.

Conclusion

- Applicable to other low true count rates and high random fractions imaging situations
  - Ion-beam therapy
- Comparison between related works[7] is shown in our recent paper submitted to Physics in Medicine & Biology (in review process)
  - Our proposed algorithm is distinct in avoiding modifying or approximating the Poisson log-likelihood used in the data term.
- Remained challenges and Future work
  - Computation time: Takes $\times 1.63$ time more than reconstruction with $x \geq 0$
    $\rightarrow$ Implement and test ordered subsets version
  - Apply to the real measurement data with time of flight information
- This work is supported by NIH grant R01EB022075

[7] Van Slambrouck, Katrien, et al. "Bias reduction for low-statistics PET: maximum likelihood reconstruction with a modified Poisson distribution." IEEE transactions on medical imaging 34.1 (2015): 126-136.

Thank You