PET mapping of receptor occupancy using joint direct parametric reconstruction: in-vivo studies

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Background

- Receptor occupancy (RO) studies using PET play a critical role in the development of drugs targeting the central nervous system to quantify target engagement, assess drug performance [1]
- Conventional approaches perform frame by frame PET reconstruction, then kinetic mapping and estimate RO from binding potential (BP) estimates at baseline (B) and post-drug (D) injection:

$$RO = 1 - \frac{BP^{(D)}}{BP^{(B)}}$$

- Proposed method: Joint-direct estimation of RO from PET sinogram data (**Figure 1**)
  - Use simplified reference tissue model (SRTM) [2,3] for kinetic mapping
  - Estimate BP, k_2, R_1 at baseline and post-drug and RO simultaneously

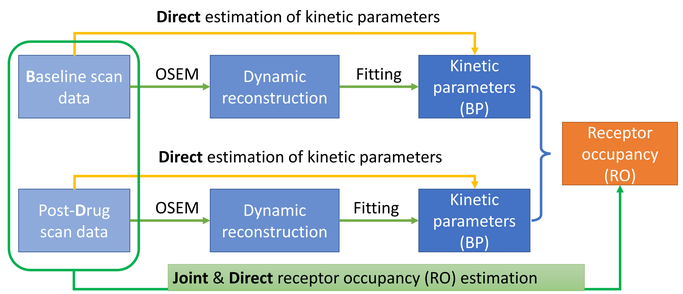


Figure 1. Proposed joint-direct reconstruction framework compared to conventional approaches

Objectives

- Develop joint-direct estimation of RO from baseline and post-drug scans
- Exploit assumption of uniform RO map
- Evaluate method on in-vivo data
- Compare to conventional (indirect) methods

Methods

Kinetic parameters $\theta = \left\{BP^{(B)}, k_2^{(B)}, R_1^{(B)}, RO, k_2^{(D)}, R_1^{(D)}\right\}$ are estimated from PET sinograms $y = \left[y^{(B)}, y^{(D)}\right]$ using a penalized log-likelihood objective function

$$\theta^* = \underset{\theta}{\operatorname{argmin}} -\mathcal{L}(y \mid \theta) + R(\theta)$$

- $R(\theta)$ penalizes (1) the variance of the RO map and (2) MRI weighted finite differences [4] on other kinetic parameters
- Solve optimization problem using nested alternating direction method of multipliers (ADMM) [5]

$$\theta^* = \underset{\theta}{\operatorname{argmin}} -\mathcal{L}(y \mid x) + R(\theta)$$
$$\text{s.t. } C(\theta) = \Gamma^{-1} x$$

- Subproblems result in (1) penalized image reconstruction, solved by BSREM [6], (2) SRTM fitting [3] and (3) image denoising solved using conjugate gradient

Results

- In-vivo non-human primate scans with ^{11}C-MK6884 and CVL-231 drug
- Reconstructed BP and RO maps using conventional and proposed joint direct method are shown in **Figure 2**.

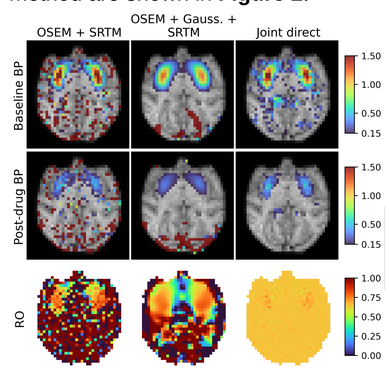


Figure 2. BP and RO estimation using conventional and proposed (joint direct) method. The proposed method reduces noise and allows RO estimation in the whole brain.

- BP images using the proposed joint direct method reduce noise compared to OSEM+SRTM and reduce bias compared to OSEM+Gauss+SRTM
- RO maps from the joint-direct method yield reasonable estimates in the whole brain (conventional methods are only reliable in the striatum (see regions in **Figure 4**)
- Regional RO values reported in **Figure 3** show robust estimation in the whole brain, with reduced variance compared to conventional methods

Figure 3. Estimated RO values averaged in different brain regions (± standard deviation). The proposed joint direct method results in uniform RO (with low variance), even in low binding regions.

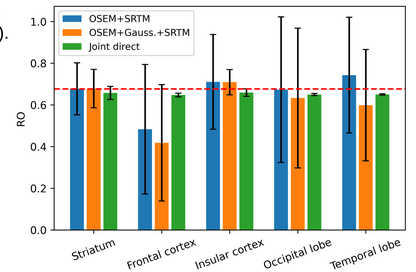
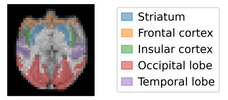


Figure 4. Brain regions used for regional analysis.



Conclusions

This work demonstrates a novel joint and direct reconstruction framework to estimate kinetic parameters and receptor occupancy from a pair of PET scans (baseline and post-drug injection). The proposed method solves an end-to-end objective function linking PET measurements to receptor occupancy. Reconstruction is carried out using ADMM, exploiting the uniformity of the RO map.

In-vivo results show that the proposed matches conventional methods in high binding regions (striatum) and significantly reduces both bias and variance in low binding regions, enabling robust estimation of RO in the whole brain.

References

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Acknowledgments

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