Appendix

Principles of LMA algorithm.

LMA is an automated segmentation algorithm in which ROIs are defined on the basis of local differences in the kinetics of radiotracers and in the activity levels.

The segmentation is performed through five steps:

Step 1: *extraction of the anatomical contour from the background noise.*

Voxels outside the studied region (here the head) are excluded from the segmentation process since they contain only noise and reconstruction artifacts. This exclusion is performed using a threshold of the summed image extracted by cumulated histogram multi-scale analysis (1). The resulting mask is then regularized using standard morphological mathematics operators.

Step 2: *points inside each organ are extracted.*

The noise variance in the PET image is assumed equal to $\sigma^2_{n,t} = \alpha^2 \times S_{n,t} \times DC_t / \Delta_t$ for statistical iterative reconstruction (SI) methods and $\sigma^2_{n,t} = \alpha^2 \times DC_t / \Delta_t$ for filtered back projection reconstructions (FBP), where $\sigma^2_{n,t}$ and $S_{n,t}$ are respectively the noise variance and the signal at voxel n and time t and where Δ_t is the duration of time frame t and DC_t is the noise increase due to radioactive decay correction. The factor α^2 is assumed stationary over space and time. It is thus assumed equal to $\alpha^2 = \Delta_t \times \sigma^2_{n,t} / (S_{n,t} \times DC_t)$ (SI) and $\alpha^2 = \Delta_t \times \sigma^2_{n,t} / DC_t$ (FBP) and can be estimated in image regions non-affected with PVE by:

- SI: $\Gamma_n = \frac{1}{T} \times \sum_{1 \le t \le T} \left(\frac{\Delta_t}{\#(V_n) - 1} \times \sum_{j \in V_n} \frac{(Y_{j,t} - \mu_{n,t})^2}{\mu_{n,t}} \right)$
- FBP: $\Gamma_n = \frac{1}{T} \times \sum_{1 \le t \le T} \left(\frac{\Delta_t}{\#(V_n) - 1} \times \sum_{j \in V_n} (Y_{j,t} - \mu_{n,t})^2 \right)$

Where V_n is a neighborhood of voxel n of given shape and size (e.g. a ball of radius r centered on voxel n). $\mathbf{\mu_n}$ is the mean TAC over V_n and an estimate of the signal $\mathbf{S_n}$. Γ_n value partly reflects noise, partly PVE and/or physiological movements. It is minimum and is a good approximation of α^2 when V_n is affected neither with PVE nor with physiological movement, and it is locally minimum in the organ cores, least affected by PVE.

Γ_n assesses the amplitude of TAC local variations inside V_n, corrected for the noise dependency on signal and on Δ_t. Γ_n is expected to take low values if V_n is not or lightly affected with PVE, and low Γ_n values correspond to good estimations of α^2. Γ_n is computed for each voxel n inside the mask of head defined at step 1. The voxel belonging to $\Lambda = \{n \mid \forall j \in V_n, \Gamma_n < \Gamma_j\}$, i.e. the set of the locations of all local spatial minima of the Γ map, are extracted.

Step 3: *Estimation of the organ's pharmacokinetics*

The local mean TAC and global noise characteristics are computed in the neighbourhood of the voxels in the Λ set. The noise global parameter α^2 is estimated using the lowest Γ_m values of the set $\{\Gamma_m \mid m \in \Lambda\}$.

Step 4: *Image segmentation*

Following Cohen and Kimmel (2), we used a Sethian Fast Marching Approach (3) in order to extract simultaneously the minimal energy active contours that join m to any voxel n in its vicinity. Voxel n is aggregated to the voxel m in the set Λ that minimizes the energy of the minimal path (2) joining m and n. To avoid the unnecessary computation of as many energy maps as there are elements in the set Λ, the energy maps are computed concurrently on the

same map from all voxels in the set Λ. The animal or subject is then separated into as many regions as the extracted minima, each region being a connected component.

Step 5: *Fusion of extracted points using a hierarchical linkage algorithm*

Regions corresponding to similar TAC are merged using a hierarchical linkage algorithm. In the process of image segmentation, an organ can be split into several regions using the fusion cost between two aggregates ag_1 and ag_2: $Cost(ag_k, ag_l) = \frac{1}{T}\sum_{1\le t\le T}\left(\mu_{m_k,t} - \mu_{m_l,t}\right)^2$, where $m_k = \arg\min_{m\in ag_k}(\Gamma_m)$ and $m_l = \arg\min_{m\in ag_l}(\Gamma_m)$. Indeed, as in step 2 and step 3, we assume that the lowest Γ_m correspond to the V_m that are the least affected by spillover and physiological movements.

The fusion result is represented as a multilevel label image, containing r aggregates at level r, allowing the user to select the number of classes (i.e. regions) in the segmented image posterior to segmentation.

References

1. Mangin JF, Coulon O, Frouin V. Robust brain segmentation using histogram scale-space analysis and mathematical morphology. *Proceedings of the 1998 MICCAI conference,* Cambridge MA 1998; 1496:1230–1241.

2. Cohen LD, Kimmel R. Global minimum for active contour models: A minimal path approach. *Int. J. Comput. Vision* 1997;24:57-78.

3. Sethian J. A fast marching level set method monotonically advancing fronts. *Proc Natl Acad Sci U S A.* 1996;93:1591-5