

Table of Contents

Deep Learning Based Determination of the Blood Input Function for Dynamic PET	1
<i>Dóra Varnyú, László Szirmay-Kalos</i>	

Deep Learning Based Determination of the Blood Input Function for Dynamic PET

Dóra Varnyú and László Szirmay-Kalos

Budapest University of Technology and Economics
{varnyu,szirmay}@iit.bme.hu

Abstract. The aim of dynamic positron emission tomography (PET) is to reconstruct the radiotracer density in every voxel of the measured volume. The Time-Activity Curves (TACs) of the voxels are searched in a fixed algebraic form according to a predefined kinetic model. A common input of kinetic models is the blood input function, which describes the amount of radiotracer in the blood that can diffuse into tissues at a certain point of time after tracer injection. The blood input function can be measured by taking blood samples, or a safer and less invasive solution is to estimate it in parallel with the kinetic parameters during the iterative reconstruction process. However, since kinetic parameter calculation requires the blood input function even at the start of the reconstruction, a good initial approximation of the input function is needed. In this paper, a deep CNN-LSTM-DNN network is proposed to provide a good initial value for the non-linear blood input parameters from which the iterative reconstruction process can start.

1 Introduction

With dynamic positron emission tomography (PET), we can determine the dynamics of radiotracer spreading and accumulation in tissues. The determined TAC function is expected to be consistent with biology, therefore it is searched in a pre-defined algebraic form that reflects the biological model.

The most popular approach is the *compartmental analysis* [9, 17, 18, 16], in which the algebraic form is based on the solution of differential equations expressing the tracer exchange between n compartments [7]. The solution has an algebraic form that is a non-negative linear combination of convolutions of the *blood input function* $C_p(t)$ and the *impulse response* $w(t)$ of the tissue. The impulse response is the non-negatively weighted sum of exponentials of unknown, non-negative *rate constants* α_i and constrained only for positive time values t by the Heaviside step function $\epsilon(t)$:

$$w(t) = \epsilon(t) \sum_{i=1}^n c_i e^{-\alpha_i t},$$

where c_i are the non-negative weights. Taking into account that a voxel is a mixture of tissue and blood, we obtain

$$\mathcal{K}(\mathbf{p}, t) = f_V C_W(t) + (1 - f_V) w(t) * C_p(t), \quad (1)$$

where $f_V \in [0, 1]$ is the unknown *fraction of blood* and C_W is the *total blood concentration function* taking into account also the portion of the radiotracer that cannot diffuse into the tissues. The blood input function for tissues, $C_p(t)$, may be different from the radioactivity of the whole blood, $C_W(t)$, because metabolism is limited. The two functions may be fitted separately, or we can assume that one of them can be obtained from the other with a tracer-dependent metabolic correction. In this paper, we assume that a known tracer-dependent factor γ can be used to express total blood concentration $C_W(t)$ from the blood input $C_p(t)$ as $C_W(t) = \gamma C_p(t)$.

In PET, we use radiotracer isotopes decaying with positron emission. The positron emitted at the decay of an isotope wanders a few millimeters in the tissues and then collides with an electron. As a result, both particles annihilate, and two oppositely directed gamma-photons are born, which might be detected by the tomograph. A PET/CT system collects the *events* of simultaneous photon incidents in detector pairs. An event is a composition of the identification of the detector pair, also called *Line Of Response* or *LOR*, and its time of occurrence. The raw input data of the reconstruction is the list of events, which is processed directly in list mode, or binned in *frames* (t_F, t_{F+1}) .

Using the concentration function $\mathcal{K}(\mathbf{p}_V, t)$ of voxel V , the expected number of radioactive decays, i.e. number of positrons generated in voxel V in frame $[t_F, t_{F+1}]$ is

$$\tilde{x}_F(\mathbf{p}_V) = \int_{t_F}^{t_{F+1}} \mathcal{K}(\mathbf{p}_V, t) \exp(-\lambda t) dt, \quad (2)$$

where λ is the decay rate of the radiotracer.

The correspondence between positron generation and gamma-photon detection is established by *system matrix* $\mathbf{A}$ that expresses the probability of generating an event in LOR L given that a positron is emitted in voxel V . The expected number of events $\tilde{y}_{L,F}$ in LOR L during frame F , i.e. in time interval (t_F, t_{F+1}) , is the sum of the contributions of all voxels in the volume during this time:

$$\tilde{y}_{L,F} = \sum_{V=1}^{N_V} \mathbf{A}_{L,V} \tilde{x}_F(\mathbf{p}_V). \quad (3)$$

As a result, the measured values in LOR L and frame F is of Poisson distribution with mean $\tilde{y}_{L,F}$. Note that the blood input function is scaled, convolved and integrated until it conforms to the expected value of the measured data, which is just a realization of a random variable, or from another point of view, it is also contaminated by noise. From the values of LORs and frames, we need to determine the global blood input parameters as well as the compartment model parameters of every voxel.

In direct dynamic tomography, kinetic parameter calculation and reconstruction happen simultaneously, thus these functions or their approximations are needed from the start of the process. Possible methods to obtain the blood input function include the measurement of the real data, the application of the

average of similar measurements, and reconstructing the blood input function also from the PET data.

This paper investigates the problem of determining the blood input function, aiming at making estimations more reliable without taking blood samples. Our approach is in between image-derived and model-derived approaches. Similarly to image-derived methods, we do not require physically measured samples, but unlike image-derived techniques, our method works robustly without precise segmentation of the blood cells.

Reconstruction means identifying parameters $\mathbf{p} = (f_V, c_1, \alpha_1, c_2, \alpha_2, \dots)$ for every voxel. However, the algebraic form of Eq. (1) is not optimal for fitting since the TAC depends on these parameters non-linearly. Thus, we use an equivalent algebraic form, where $f_V^*, a_1, a_2, \dots$ are linear parameters if the rate constants are fixed [13]:

$$\mathcal{K}(\mathbf{p}, t) = f_V^* C_p(t) + \left(\epsilon(t) \sum_{i=1}^n a_i e^{-\alpha_i t} \right) * C_p(t), \quad (4)$$

where the correspondence between the new and the original parameters is $a_i = (1 - f_V) c_i$ and $f_V^* = \gamma f_V$.

The blood input function determination from the reconstructed data is an inverse problem related to this equation. We have $\mathcal{K}(t)$ or its integrals in various intervals, and from these function $C_p(t)$ needs to be recovered. However, this inverse problem is ill-posed and ambiguous, since the same function can be delivered with many different parameters and blood input functions. For example, the contribution of the fraction of blood parameter f_V^* can also be provided with making $\alpha_i \rightarrow \infty$ and $a_i e^{-\alpha_i t} \rightarrow f_V^* \delta(t)$. Thus, we need more a priori information, e.g. that the dynamics of the blood input function is much faster than the tissue response, or we can use a simplifying assumption, such as $f_V^* = 0$.

Note also that the automatic determination of the blood input function is a “chicken and egg” type problem. In order to find the TAC of voxels from which the blood input function can be extracted, we need a tomographic reconstruction. During direct tomographic reconstruction, we fit the TAC in every iteration, which requires the blood input function. We can break this evil loop by indirect reconstruction, which reconstructs frames independently, thus requiring no parameter fitting. However, with this we lose the advantages of direct reconstruction, namely that for the reconstruction of a frame, complete information of all frames can be exploited.

2 Previous work

There are different possibilities for the determination of blood parameters [20, 19, 5]. We can take blood samples from the artery. Artery samples represent the total blood function, from which the blood input function is calculated with tracer-dependent metabolic correction. Alternatively, venous samples can be taken during transient equilibrium.

Blood sampling is a difficult and error-prone process, especially in pre-clinical testing where small animals are investigated. Thus, there is a significant interest in methods requiring no, or just minimal number of such samples.

2.1 Population-Based Input Function

This approach takes the average of previously taken blood input functions and scales it based on just a few current samples. Therefore, this method does not eliminate the need of sampling, only drastically reduces the number of required samples. On the other hand, the shape of the blood input function is fixed, which may not prove to be flexible enough to describe the current case.

2.2 Image-Derived Input Function (IDIF)

The *Image Derived Input Function* (IDIF) method uses the reconstructed time-activity values of blood voxels, thus it requires the segmentation of the artery or the needle region. This method can determine the total blood function from which the blood input is calculated with metabolic correction. If the segmented region is thin or small, partial volume effect and spill-in may compromise the estimation, which is described by the following model [1]:

$$C_m(t) = C_W(t)R + C_t(t)S, \quad (5)$$

where $C_m(t)$ is the activity in the artery that results from the reconstruction, $C_W(t)$ is the real total blood concentration, $C_t(t)$ is the obtained activity in surrounding tissues, R is the recovery coefficient, and S is the spill-in coefficient.

The task is to obtain $C_W(t)$ from $C_m(t)$ and $C_t(t)$ when the recovery coefficient and the spill-in factor are also unknown. This problem is ill-posed in this form. For example, Eq. 5 contains the product of the recovery coefficient and the total blood activity, which is invariant to the simultaneous upscaling of the recovery coefficient and downscaling of the blood activity. To eliminate these ambiguities, additional information is needed.

The recovery coefficient and the spill-in factor may be estimated from the point spread function and the precise segmentation of the arteries, but this approach is complicated and not very accurate. Another option is to first extrapolate $C_W(t)$ from late venous samples or by selecting the maximum intensity voxels, then obtain the recovery coefficient and the spill-in factor with least squares estimation. Having them, the total blood input function is expressed from Eq. 5.

The method of Image-Derived Input Function requires the segmentation of blood cells and possibly the compensation of partial volume effects. Note that in case of small animals, the number of voxels that can be clearly identified as full blood is limited.

A sophisticated approach to separate real blood input and the contribution from the neighboring tissues is the application of *Independent Component*

Analysis [11]. This is done by assuming that two non-Gaussian, statistically independent components are added. Recalling the Central Limit Theorem, when two non-Gaussian, independent signals are added, the result will be closer to the Gaussian distribution than either of the two signals. Additionally, the components are expected to be of lower complexity than their sum.

Independent Component Analysis also suffers from the indeterminacy of the scaling factors, thus real blood samples are needed to scale the reconstructed functions.

2.3 Model-Based Input Function (MBIF)

The *Model-Based Input Function* method does not require anatomic information or the segmentation of the arteries. Instead, it estimates the blood input function and the kinetic parameters simultaneously. The MBIF method searches not only the impulse response, but also the blood input function in a pre-defined algebraic form. A proven choice for the algebraic form of $C_p(t)$ is the *Feng model* [6]:

$$C_p(t) = A_1(t - \tau)e^{-\beta_1(t-\tau)} + \sum_{j=2}^3 A_j \left(e^{-\beta_j(t-\tau)} - e^{-\beta_1(t-\tau)} \right) \quad (6)$$

if $t > \tau$, the time of injection, and zero otherwise.

Note that model-based methods also have ambiguity. The same Time Activity Curve can be obtained by scaling down the tissue model parameters a_i and f_V^* , and simultaneously scaling up the linear blood parameters A_1, A_2, A_3 . This can be resolved by taking a few blood samples.

3 Proposed method

Our proposed algorithm belongs to the category of both Image-Derived Input Functions, as it needs the identification of “blood voxels” that at least partially contain artery regions, and Model-Based Input Functions, since we find the parameters of the Feng model. Neither full nor total segmentation is needed, but the accuracy of the method increase if the selection includes more blood voxels. Selected blood voxels are assumed to have similar activity functions.

To address the “chicken and egg” problem, the TAC and the blood input function are estimated in parallel during the iterative reconstruction. The reconstruction should simultaneously determine the parameters of the Feng model and the per-voxel kinetic parameters. In order to guarantee fast and certain convergence, a crucial factor is the initialization of these unknown parameters. The measured data is a weighted sum of the TAC of different voxels, which are in turn a weighted sum of the convolution of the impulse responses and the blood input function. It means that the blood input function is involved in every voxel TAC and therefore in every LOR after convolutions with voxel-dependent impulse response functions. Our goal is to exploit this information and to obtain the non-linear $\beta_1, \beta_2, \beta_3$ parameters directly, which can be used to initialize the iterative reconstruction process.

4 Analysis of the dependence of the TAC and the sinograms on the blood input parameters

Calculating voxel activity requires the integration of the convolutions of exponential functions.

According to Eq. 2, the activity of a voxel in a time frame is expressed by a time integral. The antiderivative of the integrand is

$$I(t) = \int \left(\left(\epsilon(t) \sum_{i=1}^n a_i e^{-\alpha_i t} \right) * C_p(t) \right) e^{-\lambda t} dt = \sum_{i=1}^n a_i \left(A_1 H_i(t) + \sum_{j=2}^3 A_j (G_{ij}(t) - G_{i1}(t)) \right), \quad (7)$$

in which there are two types of convolutions from the blood input function and the impulse response. Using the $\alpha_i^* = \alpha_i + \lambda$ and the $\beta_j^* = \beta_j + \lambda$ notations, the first type is

$$G_{ij}(t) = \int (\epsilon(t) e^{-\alpha_i t} * \epsilon(t) e^{-\beta_j t}) e^{-\lambda t} dt = \frac{e^{-\alpha_i^* t} / \alpha_i^* - e^{-\beta_j^* t} / \beta_j^*}{(\alpha_i^* - \beta_j^*)}, \quad (8)$$

while the second one is

$$H_i(t) = \int (\epsilon(t) e^{-\alpha_i t} * \epsilon(t) t e^{-\beta_1 t}) e^{-\lambda t} dt = \frac{e^{-\beta_1^* t} / \beta_1^* - e^{-\alpha_i^* t} / \alpha_i^* - (\alpha_i^* - \beta_1^*)(t + 1/\beta_1^*) e^{-\beta_1^* t} / \beta_1^*}{(\alpha_i^* - \beta_1^*)^2}. \quad (9)$$

Finally, voxel activity in a time frame is

$$\tilde{x}_F(\mathbf{p}) = f_V \int_{t_F}^{t_{F+1}} C_W(t) dt + I(t_{F+1}) - I(t_F). \quad (10)$$

We can observe that every TAC is the weighted sum of functions $t e^{-\beta_1^* t}$, $e^{-\beta_1^* t}$, $e^{-\beta_2^* t}$, $e^{-\beta_3^* t}$, and also contains exponentials $e^{-\alpha_i^* t}$. The LOR data, which are the primary measured data, are the weighted sums of the TACs of the voxels. Thus, each data element is also a weighted sum of functions $t e^{-\beta_1^* t}$, $e^{-\beta_1^* t}$, $e^{-\beta_2^* t}$, $e^{-\beta_3^* t}$, and also contains a large mixture of exponentials $e^{-\alpha_i^* t}$, which is different in every LOR. In addition, we can assume that the dynamics of the blood input is quicker than the diffusion into the tissues, i.e. $\beta_j \gg \alpha_i$. The task is then to retrieve the exponential functions that are present in every measured data element and initialize the exponents of the blood input function accordingly.

If we had sine functions instead of exponentials, the solution would be quite straightforward. We would compute the Fourier transform of the signal and

identify the largest dominant frequencies as parameters $\beta_1, \beta_2, \beta_3$. Unfortunately, this concept is not directly applicable for exponentials since these functions are not orthogonal. Fitting with exponentials have been investigated [10, 3], but these are complicated and cannot handle the $te^{-\beta_1^* t}$ type terms. Consequently, we should attack this problem with more general approach, which is the application of a neural network.

Note that we do not aim at precise identification of the exponents, only at a reasonable guess that can be used to initialize the iterative reconstruction.

5 Using a neural network to predict initial values for optimization

In our work, we have constructed and trained a CNN-LSTM-DNN network to predict the exponents of the blood input function from series of time-activity data. The network was implemented using the Keras deep learning API [2] and hyperparameter optimization was performed with the Ray Tune library [12].

5.1 Dataset

The model was trained with series of simulated time-activity data obtained by evaluating Eq. 4 with randomized parameters, assuming $n = 2$ compartments. Parameters of the blood input function were selected from normal distributions proposed by Feng et al. [6] (Table 1). The α_1, α_2 exponents of the impulse response were sampled from interval $[\frac{1}{10}, \frac{\beta_1}{4}]$, while the linear parameters were chosen with standard uniform distribution. The fraction of blood parameter was set between 0.8 and 1.0 to simulate only voxels consisting primarily of blood, i.e. blood voxels. The total simulation time for each sample was 120 seconds, during which the TAC was evaluated in 100 points, resulting in 100 positive real activity values in order of magnitude 10^{-2} . As a preprocessing step, activity values were normalized to fill the interval $[0, 1]$ to promote the learning of the network. Our dataset consisted of 1 000 000 samples, of which we used 70% of for training, 15% for validating and the remaining 15% for evaluating our model.

	A_1	A_2	A_3	β_1	β_2	β_3
Mean	767.3	27.42	29.13	4.195	0.232	0.0165
Standard deviation	360.0	7.48	5.22	1.380	0.112	0.0076

Table 1. Mean and standard deviation of the normal distributions from which the blood input function parameters were drawn during data generation. The proposed values are based on the paper of Feng et al. [6].

5.2 Network Architecture

Our model had a CNN-LSTM-DNN architecture, using Convolutional Neural Network (CNN) layers for feature extraction, a Long Short-Term Memory (LSTM) layer for interpreting the features through time, and Dense Neural Network (DNN) layers to transform the features into a latent space that makes the output easier to predict.

Two 1D convolutional layers were stacked on top of the input, both followed by a spatial dropout layer with a dropout rate of 0.1 to introduce a degree of sparsity into the model. The convolutional layers learned 16 filters using kernels of size 8 and 4, respectively. Their output was passed to an LSTM layers with 50 units and a recurrent dropout rate of 0.1. At the end, two fully connected (FC) layers with 50 units transformed features into the latent space from which a final fully connected layer with 3 neurons predicted the three exponents. Dropout layers with rates of 0.3 were inserted after the two FC layers to prevent overfitting. All layers used ReLU activation, He uniform weight initialization [8], and a combination of L1 and L2 weight regularization.

5.3 Network Training

The presented model was trained for 200 epochs using the NAdam optimizer [4] with $\alpha = 0.0001$ learning rate and the log hyperbolic cosine (log-cosh) loss function. The batch size was 128. Fig. 1 displays the training and Fig. 2 the validation loss during the process. The final training loss was 0.0169 and the validation loss was 0.0163.

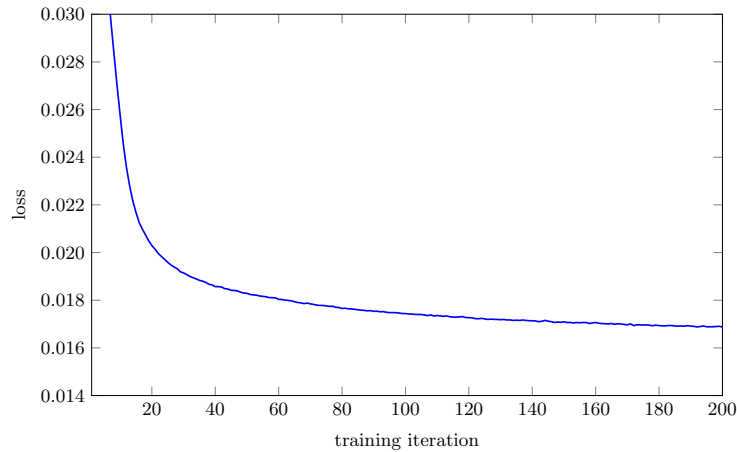


Fig. 1. Training loss

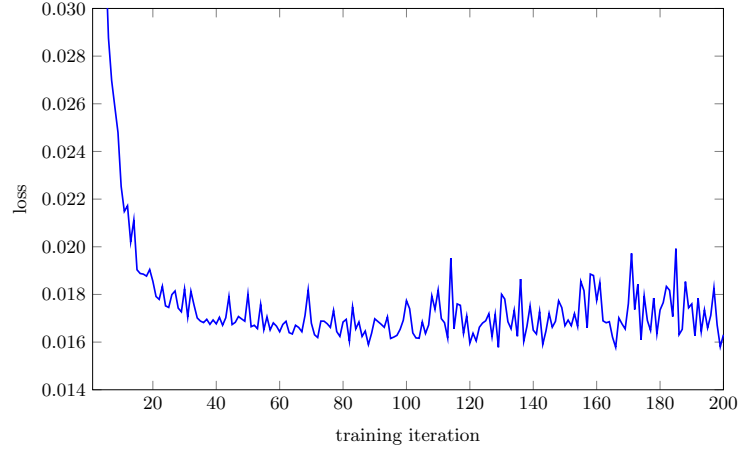


Fig. 2. Validation loss

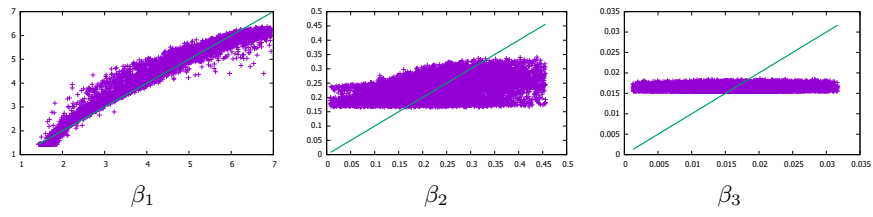


Fig. 3. Reconstruction of non-linear parameters $\beta_1, \beta_2, \beta_3$. The horizontal coordinate is the ground truth, the vertical is the reconstructed value. Perfect reconstructions would be on the diagonal line.

6 Results in reconstruction

The proposed methods are tested with a 2D brain phantom where the number of LORs is $N_L = 10k$ and the number of voxels is $N_V = 1024$ (Figure 4). The phantom has four anatomical parts, namely air, gray matter, white matter, and blood. Parameters of the two-tissue compartment model $[f_V, a_1, a_2, \alpha_1, \alpha_2]$ used in the test are listed in Table 2.

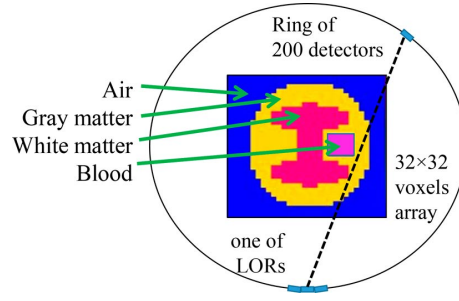


Fig. 4. 2D phantom and tomograph model

Region	a_1	a_2	α_1	α_2	f_V
Background	0	0	0	0	0
Gray matter	0.14	0.86	1.46	0.34	0
White matter	0.05	0.45	1.79	0.01	0
Blood	0	0	0	0	1

Table 2. Tissue parameters of the 2D brain phantom

Figure 5 demonstrates the difficulties of the blood input parameter estimation. This figure is the statistical analysis of the sinogram, in which the dynamics of the blood input function is embedded. However, due to the convolutions and averaging, the result has no resemblance to the blood input function, which is also shown by this figure. So, a simple extraction of the exponents from the sinogram would significantly underestimate the blood exponent parameters.

We compare four blood input acquisition strategies:

- *Ground truth*: In this case, we assume that the parameters of the Feng model are known a priori. In case of simulation, the same parameters are used to generate the measured data as the setting of the blood input function before reconstruction.

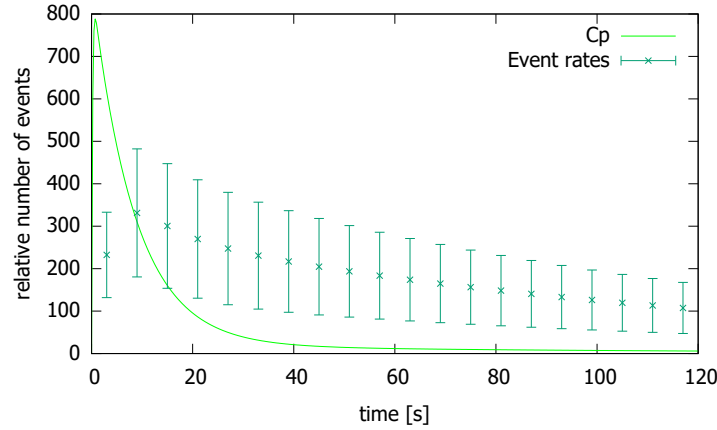


Fig. 5. Number of hits per LOR per unit time with error bars showing the standard deviation divided by four. The ground truth of the blood input function is also shown scaled. Note that the dynamics of the sinogram does not reveal the dynamics of the included blood input function.

- *Model-based*: This is the classical approach when the statistical analysis of the sinogram data provides an initial estimation, which is refined in parallel with the iterative ML-EM estimation of the tissue parameters.
- *Deep learning*: This approach uses the trained neural net to provide $\beta_1, \beta_2, \beta_3$ blood parameters in response of the sinogram data. These parameters are set and only the A_1, A_2, A_3 linear parameters are subject to iterative optimization together with the ML-EM iteration.
- *Deep learning + Model-based*: The initial estimation of the $\beta_1, \beta_2, \beta_3$ parameters are taken from the trained neural net, and these are kept fixed during the first 10 iterations. Then the algorithm becomes a model-based method and further refines the parameters.

Fig. 8 depicts the reference blood input function and the TAC in different tissues, as well as the TAC and the macroparameter reconstructions of the examined methods. The total number of coincidences during the 120-second measurement is 47 million. The measurement time is decomposed into 40 frames.

Fig. 6 and Fig. 7 show the convergence speed of the tissue and blood input reconstruction, respectively, for the compared methods. The deep learning solutions are quite close to the optimal case when the blood input function is known a priori. The same conclusions can be drawn from looking at the reconstructed TACs and macroparameter maps (Fig. 8).

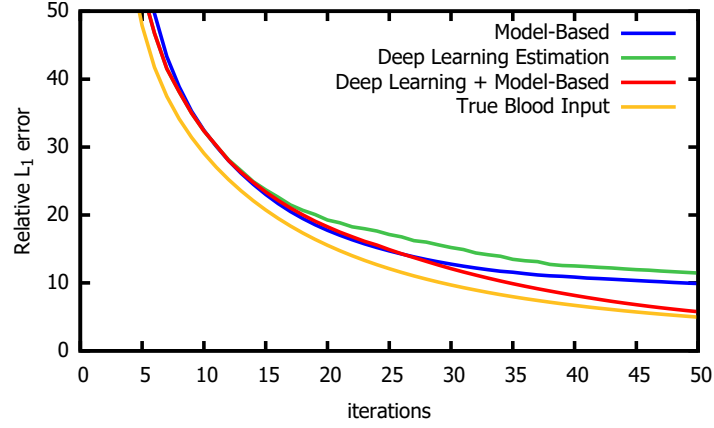


Fig. 6. Error of the TACs with different blood input function estimation methods

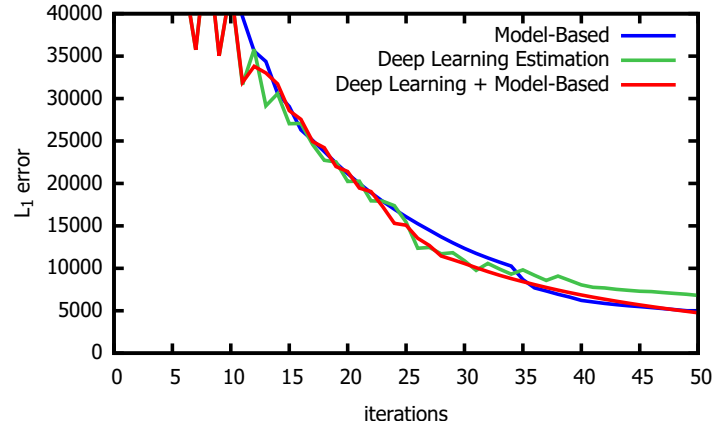


Fig. 7. Error of the $C_p(t)$ blood input function reconstruction

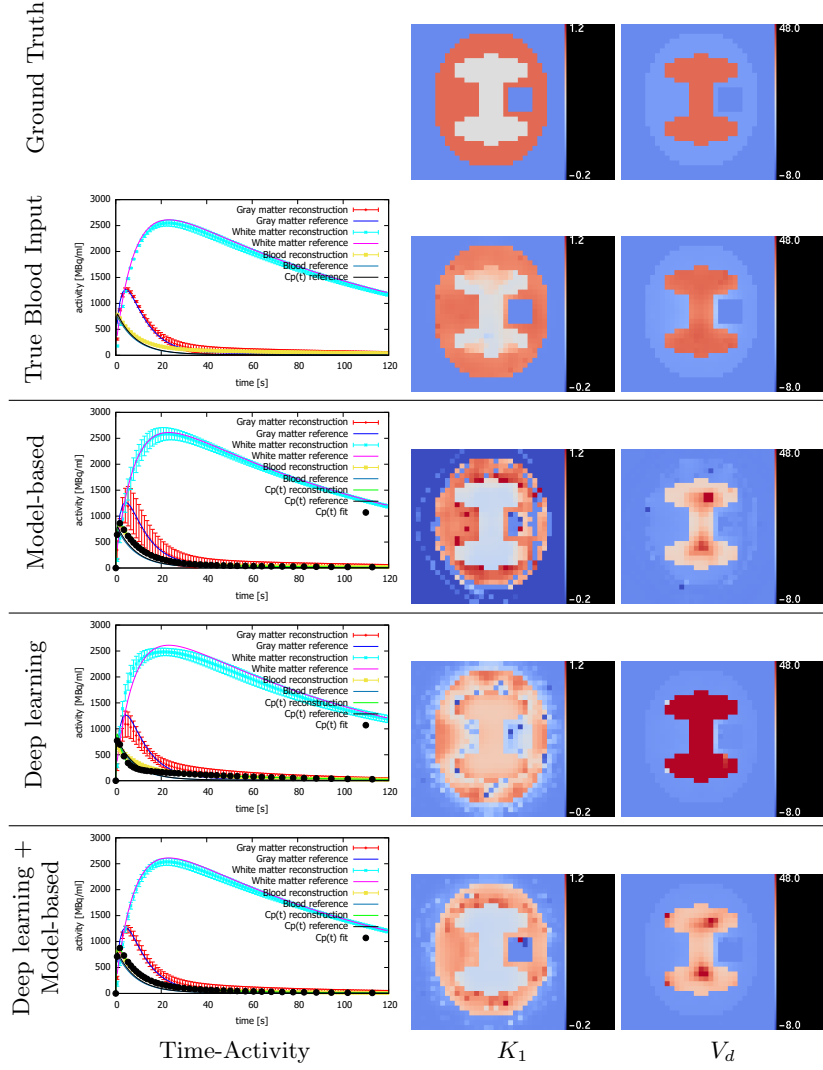


Fig. 8. The reconstructed TACs and kinetic macro parameters using the examined blood input estimation methods

7 Conclusions

This paper proposed a deep-learning-based method to estimate the exponents of the Feng-type blood input function from sinogram data. The estimated parameters are used to initialize an ML-EM reconstruction scheme that simultaneously determines both the blood input parameters and the tissue parameters.

Acknowledgements

This research has been supported by OTKA K-124124.

References

1. Kewei Chen, Daniel Bandy, Eric Reiman, Sung-Cheng Huang, Michael Lawson, Dagan Feng, Lang sheng Yun, and Anita Palant. Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, 18f-fluoro-2-deoxyglucose, the patlak method, and an image-derived input function. *Journal of Cerebral Blood Flow & Metabolism*, 18(7):716–723, 1998. PMID: 9663501.
2. François Chollet et al. Keras. <https://github.com/fchollet/keras>, 2015.
3. P. De Groen and B. De Moor. The fit of a sum of exponentials to noisy data. *Journal of Computational and Applied Mathematics*, 20:175 – 187, 1987.
4. Timothy Dozat. Incorporating nesterov momentum into adam. 2016.
5. D. D. Feng, K. Chen, and L. Wen. Non-invasive input function acquisition and simultaneous estimations with physiological parameters for pet quantification: A brief review. *IEEE Transactions on Radiation and Plasma Medical Sciences*, pages 1–1, 2020.
6. Dagan Feng, Sung-Cheng Huang, and Xinmin Wang. Models for computer simulation studies of input functions for tracer kinetic modeling with positron emission tomography. *International Journal of Bio-Medical Computing*, 32(2):95 – 110, 1993.
7. Roger N. Gunn, Steve R. Gunn, and Vincent J. Cunningham. Positron emission tomography compartmental models. *Journal of Cerebral Blood Flow & Metabolism*, 21(6):635–652, 2001. PMID: 11488533.
8. Kaiming He, Xiangyu Zhang, Shaoqing Ren, and Jian Sun. Delving Deep into Rectifiers: Surpassing Human-Level Performance on ImageNet Classification. In *Proceedings of the IEEE International Conference on Computer Vision (ICCV)*, pages 1026–1034, december 2015.
9. M.E. Kamasak, C.A. Bouman, E.D. Morris, and K. Sauer. Direct reconstruction of kinetic parameter images from dynamic pet data. *IEEE Trans Med Imaging*, 24(5):636–650, 2005.
10. Bernhard Kaufmann. Fitting a sum of exponentials to numerical data. 06 2003. [arXiv:physics/0305019](https://arxiv.org/abs/physics/0305019) [physics.data-an].
11. Jih-Shian Lee, Kuan-Hao Su, Wen-Yuan Chang, and Jyh-Cheng Chen. Extraction of an input function from dynamic micro-pet images using wavelet packet based sub-band decomposition independent component analysis. *NeuroImage*, 63(3):1273–1284, 2012.

12. Richard Liaw, Eric Liang, Robert Nishihara, Philipp Moritz, Joseph E Gonzalez, and Ion Stoica. Tune: A research platform for distributed model selection and training. *arXiv preprint arXiv:1807.05118*, 2018.
13. L. Szirmay-Kalos, Á. Kacsó, M. Magdics, and B. Tóth. Robust compartmental model fitting in direct emission tomography reconstruction. *The Visual Computer*, 2020.
14. L. Szirmay-Kalos, M. Magdics, and B. Tóth. Multiple importance sampling for PET. *IEEE Trans Med Imaging*, 33(4):970–978, 2014.
15. L. Szirmay-Kalos, M. Magdics, B. Tóth, and T. Bükki. Averaging and Metropolis iterations for positron emission tomography. *IEEE Trans Med Imaging*, 32(3):589–600, 2013.
16. Guobao Wang and Jinyi Qi. An optimization transfer algorithm for nonlinear parametric image reconstruction from dynamic pet data. *IEEE Trans Med Imaging*, 31(10):1977–1988, 2012.
17. Hiroshi Watabe, Yoko Ikoma, Yuichi Kimura, Mika Naganawa, and Miho Shidahara. Pet kinetic analysis—compartmental model. *Annals of Nuclear Medicine*, 20(9):583, Nov 2006.
18. Jianhua Yan, Beata Planeta-Wilson, and R.E. Carson. Direct 4d list mode parametric reconstruction for pet with a novel em algorithm. In *Nuclear Science Symposium Conference Record, 2008. NSS '08. IEEE*, pages 3625–3628, Oct 2008.
19. Paolo Zanotti-Fregonara, Kewei Chen, Jieih-San Liow, Masahiro Fujita, and Robert B Innis. Image-derived input function for brain pet studies: Many challenges and few opportunities. *Journal of Cerebral Blood Flow & Metabolism*, 31(10):1986–1998, 2011. PMID: 21811289.
20. Paolo Zanotti-Fregonara, El Mostafa Fadaili, Renaud Maroy, Claude Comtat, Antoine Souloumiac, Sebastien Jan, Maria-Joao Ribeiro, Véronique Gaura, Avner Bar-Hen, and Régine Trébossen. Comparison of eight methods for the estimation of the image-derived input function in dynamic [18f]-fdg pet human brain studies. *Journal of Cerebral Blood Flow & Metabolism*, 29(11):1825–1835, 2009. PMID: 19584890.