# Estimation of the Glucose Metabolism from Dynamic PET-scans using Neural Networks.

Claus Svarer, Ian Law, Søren Holm, Niels Mørch, Olaf Paulson
Dept. of Neurology,
The National University Hospital
DK-2100 Copenhagen Ø, Denmark
email: csvarer@ei.dtu.dk

Lars Kai Hansen, Torben Fog
CONNECT, Electronics Institute, B349
Technical University of Denmark,
DK-2800 Lyngby, Denmark

***Abstract*** **– A method for fast pixel by pixel estimation of the Glucose Metabolism in the brain using the tracer [$^{18}$F]flourodeoxyglucose in dynamic PET-scan data is described. A neural network is trained to estimate the glucose metabolism on data generated by direct fitting of the rate constants in Sokoloff's model. The generalization ability of the neural network is tested on data from subjects not included in the training set. This method can be used to estimate changes of the metabolism in different brain regions for subjects with serious brain disorders. By using the neural estimation procedure the processing time for a brain scan volume is reduced from 48 hours to 4 minutes!**

## INTRODUCTION

The Positron Emission Tomography (PET) technique is an important tool for mapping the brain metabolism and functionality [3]. The primary aim of PET is reconstruction of concentrations of certain radioactive tracers in the brain. Useful tracers emit positrons that are locally annihilated to produce two 511 keV gamma rays propagating in opposite directions. The 3D distribution of the tracer can be reconstructed from the geometric constraints of coincident counts, using standard techniques (filtered backprojection). An important class of tracers are chemically equivalent to substrates of the basic brain metabolism. By reconstructing such tracer distributions important aspects of brain metabolism have been revealed. Furthermore, by investigating the *transient response* to a tracer injection, it is possible to identify fundamental kinetic rate constants on a set of dynamic PET images. The estimation of

the glucose metabolism in the present study has been applied on the Sokoloff model [6]. To gain maximal spatial resolution of the rate constant distribution we will compute the estimate on a pixel by pixel basis as originally described in the work of Kanno et al. [5].

We demonstrate the ability of a neural network to substitute for tedious parameter fitting procedures. The neural network system is trained to produce a smooth map relating a given transient pixel activity to a key parameter of metabolism, viz. the glucose utilization rate $R$. By identification of the inverse kinetics the estimate of the spatial distribution of $R$ may be obtained three orders of magnitude faster than by direct fitting of the kinetic model.

The work described in this article is a continuation of our work presented in the proceedings of NNSP'94 [1]. In particular we show that the neural net scheme can *generalize*, i.e., that the inverse kinetics map trained on data from one set of subjects may be used for interpretation of data from other test subjects.

## SOKOLOFF's KINETIC MODEL

In the present work we are considering the kinetics of the compound [$^{18}$F]flourodeoxyglucose (FDG). The kinetics of this tracer are similar to glucose in the initial phases of metabolism. It passes through the blood-brain barrier (BBB), and is phosphorylized intracellularly in a process analogous to glucose. The phosphorylized [$^{18}$F]flourodeoxyglucose compound does not enter into the Krebs cycle of glucose metabolism therefore it is effectively trapped. The kinetics can be modeled by a compartemental model involving one compartment representing the tracer density in the arterial blood outside the BBB, $C_{\mathrm{P}}^{*}$; one compartment representing the so-called *precursor pool*, $C_{\mathrm{E}}^{*}$; and finally a compartment representing the intracellular phosphorylized fraction behind the BBB, $C_{\mathrm{M}}^{*}$; see figure 1. In current experiments the arterial concentrations are measured continuously with the scans.

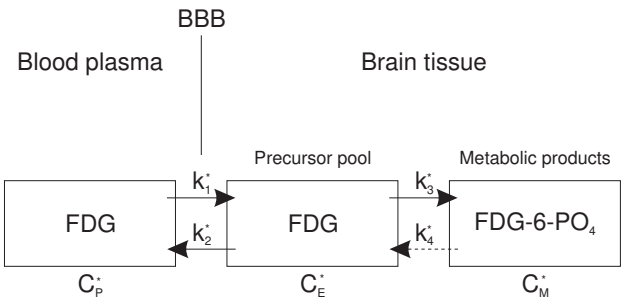


Figure 1: Sokoloff's three compartment model applied to phosphorylization of [$^{18}$F]flourodeoxyglucose (FDG). The star on the concentrations signifies that we consider tracer amounts and constants.

Following the injection of the tracer, hence, the rise of the arterial blood concentration $C_{\mathrm{P}}^*$, the flow through the BBB starts. The measured PET tracer activity is the sum of the activities of the two compartments to the right of the BBB in figure 1 and a certain fraction, $V_P^*$, of the arterial blood concentration. This can be calculated as

$$C_i^* = C_E^* + C_M^* + V_P^* C_P^*. \tag{1}$$

The dynamics of the three compartment model is given by:

$$\frac{dC_i^*}{dt} = \frac{dC_E^*}{dt} + \frac{dC_M^*}{dt} + V_P^* \frac{dC_P^*}{dt} \tag{2}$$

with

$$\frac{dC_M^*}{dt} = k_3^* C_E^*, \tag{3}$$

and

$$\frac{dC_E^*}{dt} = k_1^* C_P^* - k_2^* C_E^* - k_3^* C_E^*. \tag{4}$$

The reverse reaction rate constant $k_4^*$ corresponding to $k_3^*$ is neglected; it is not identifiable within the measurement time of the present experimental setup.

These linear differential equations describing the response of the activity of the arterial blood ($C_P^*(t')$) are straightforward to integrate yielding the two time dependent concentrations,

$$C_E^*(t) = k_1^* e^{-(k_2^*+k_3^*)t} \int_0^t e^{(k_2^*+k_3^*)t'} C_P^*(t') \; dt', \tag{5}$$

and

$$C_M^*(t) = k_1^* k_3^* \int_0^t \left[ e^{-(k_2^*+k_3^*)t'} \int_0^t e^{(k_2^*+k_3^*)t''} C_P^*(t'') \; dt'' \right] dt'. \tag{6}$$

Following injection these solutions describe the transient activity in terms of the measured $C_{\mathrm{P}}^*(t)$, the three rate constants $(k_1^*, k_2^*, k_3^*)$ and the plasma volume fraction $V_{\mathrm{P}}^*$. Conversely, for a given transient $C_{\mathrm{P}}^*(t)$ and for given measured sum of concentrations $C_{\mathrm{i}}^*(t)$ we may fit the three rate constants and the plasma volume fraction. We use a simple least squares cost function for the fit, hence implicitly assuming Gaussian residuals. Optimization over the four parameters ($k_1^*, k_2^*, k_3^*$ and $V_{\mathrm{P}}^*$) is carried out using a second order Newton scheme[1]

From these parameters we compute the important glucose utilization parameter $R$

[1] Based on the solution to the kinetic model it is straightforward to compute the second order derivatives.

$$R = \frac{c_{gl}}{LC} \frac{k_1^* k_2^*}{k_2^* + k_3^*} \tag{7}$$

where $c_{gl}$ is the glucose concentration measured in the blood for each subject and $LC$ the so-called *lumped constant* for the model. We use the value ($LC = 0.55$) [4].

Two different approaches have been used when estimating the kinetic constants. In [6, 3] it is assumed that the parameters are homogeneous in regions and therefore can be fitted using the region averaged activity. Alternatively the rate constants can be fitted at a pixel by pixel basis as proposed in [5]. However, this approach has not found widespread use since it is rather tedious to fit the kinetic model in all pixels.

The database used for these experiments are PET data collected at the PET center at Rigshospitalet, Copenhagen, and stems from 10 normal subjects. Data are acquired on a GE4096 plus (General Electric Medical Systems), sampling 15 slices simultaneously. The dynamic scans after injection of 200 MBq F-18 labeled FDG are performed over 60 minutes, providing 34 contiguous time frames of increasing duration in order to provide a reasonable sampling of the $C_i^*$ curve (10@6 sec; 3@20 sec; 8@60 sec; 5@120 sec; 8@300 sec). Two examples of input blood curves are shown in figure 2.

The images were reconstructed in $128x128$ matrices ($2mm^2$ pixels) by standard Filtered backprojection (Ramp filter with Hann window). Correction for attenuation was based on a separate transmission scan with a rotating Germanium pin source. For further introduction to PET scan techniques see e.g., [3]

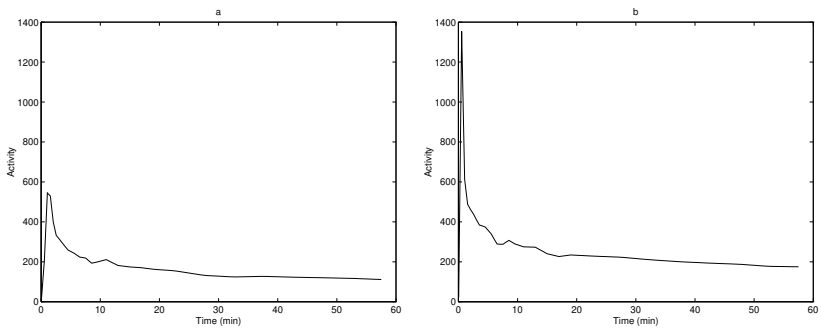


Figure 2: Input blood curve as a function of time for two different subjects. Note the large variation in the shape (value and time for maximum) of the blood curves for different subjects.

In figure 3 a fit of the three rate-constants and the calculated glucose utilization $R$ on a pixel by pixel basis in one slice is shown. We note that these rate constant pictures are rather noisy, reflecting the noise level of the

original pixel activity curves also shown in figure 4. To provide less noisy data for the neural net training procedure we have averaged and subsampled so that a "superpixel" in the new image is the average of $4 \times 4$ pixels of the original image. Another reason for subsampling is that it takes approximately 48 hours (on HP9000/735 workstation) to fit the parameters in Sokoloff's model on 1 slice, $128 \times 128$, image, using a Newton based method. A full brain volume consist of 15 slices.

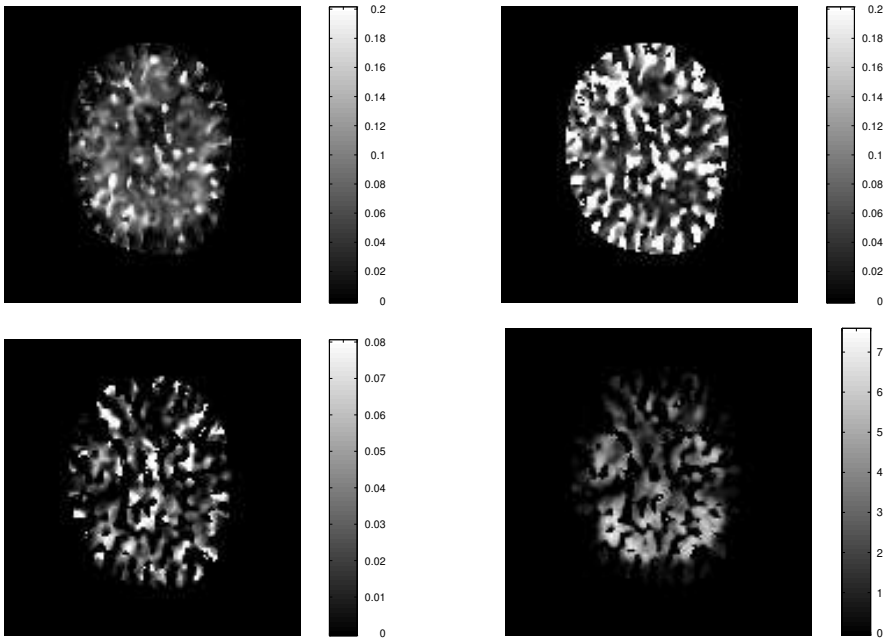


Figure 3: Parameters in Sokoloff's model fitted on a pixel by pixel basis, Upper-left: $K_1^*$, Upper-right: $K_2^*$, Lower-left: $K_3^*$, and Lower-right: $R^*$. R is calculated based on equation (7). Especially, the rateconstants $K_2^*$ and $K_3^*$ are very noisy.

To avoid the tedious fitting procedure we here investigate the possibility of identifying the *inverse model* of the kinetics: we search for a *map* that provides an estimate of the glucose utilization $R$ in each pixel [1]. Our basic vehicle will be a simple feed-forward network.

The input to the neural network is the measured activity of a given pixel. Futhermore, we saw in figure 2, that the input blood curve ($C_{\mathrm{P}}^*$) varies considerably between subjects due to variations in the way doses were injected and a individual blood circulation. Hence, we need to provide this information to the neural network model if we want it to be able to generalize from one subject to another. C.f. (7) the total blood glucose concentration is also provided as an input to the neural network. This concentration can be

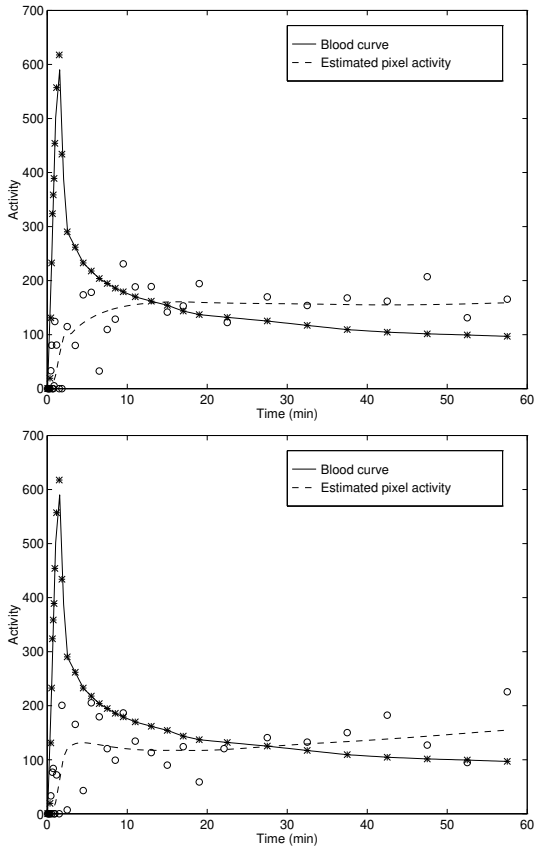


Figure 4: Result of simulating the Sokoloff model in two different pixels within the brain. The measured activity data for a single pixel, shown by 'o's, is very noisy, noise levels are highest for the first data points where the measuring time is only 5-10 seconds. The measured blood curve data is shown by '$*$'s. The dashed curve shows the result of a simulation using the estimated model.

considered constant during a scan. This gives us a total of 69 inputs to the neural network: 34 inputs describing the transient activity in the given pixel, another 34 measurements of the activity in the blood (the blood curve), and 1 measurement of the glucose concentration in the blood.

The fact that we have subsampled the data for the training set does not prevent us from using the network on the individual pixels in the test set.

## NETWORK DESIGN

The feed-forward neural network used comprises 6 hidden units using $tanh$ activation functions and a linear output unit. The network is trained using a pseudo-Gauss Newton method (a diagonal approximation to the Hessian matrix is used) as described in [7], and pruned using the Optimal Brain Damage method described in [2] to minimize computation and to improve generalization. The "optimal" network architecture is chosen by using a validation data set from a subject which has not been incorporated in the training or the test sets.

4000 examples from 8 subjects (500 from each) are used for training the neural network, and the generalization ability is then tested using 8000 examples from the same group of subjects (1000 from each). The examples which go into the training and test set are chosen so the estimated glucose utilization ($R$) is in the interval $[1.0, 12.0]$. Pixels with $R$-values outside this interval were typically found outside the brain or were discarded as severe noise outliers. Further, the generalization ability is tested on a data set consisting of 1500 examples from a subject not included in the training set. The "optimal" network is chosen using a validation data set consisting of 1500 examples from still another subject which has not been used for training or testing.

From equation (7) it can be seen that when $R$ is calculated the rateconstant factor is multiplied by a global factor $c_{gl}$ for each subject: the glucose concentration in the blood. To assist the training problem, the glucose utilization $R$ is divided by this global factor for each subject (it is difficult for a feed-forward net to learn a multiplication). The neural network is then trained to estimate $R/c_{gl}$.

The data sets used for training and testing the neural network are normalized to have unit variance. Further, intial experiments have shown that it is very difficult to train the neural network to estimate the global mean glucose utilization level. The problem is that only 8 different subject are represented in the training set. The global mean factor for each subject is therefore subtracted from the output of the network and the learning/test set outputs. The normalized squared errors shown in the following figures are calculated from the mean subtracted data.

In figure 5 the result of a pruning session of weights in the network is shown. We see that the network easily generalizes to the (interpolation) test data derived from the same 8 subjects that were used to collect the training set. The minimum of the validation error is seen to be for a network with 278 weights. This network architecture also generalizes well to the independent test set.

In figure 6 the left panel shows the direct estimate of the glucose utilization for a subject from the training set ($4 \times 4$ superpixels), while the right panel shows the output from the trained neural network. The neural network generalizes very well from the 500 examples taken from this subject to the

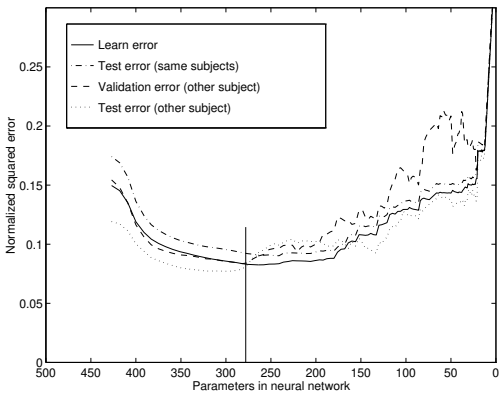


Figure 5: Normalized training and test errors (unit variance, mean subtracted for each subject) during a pruning session of the neural network. The parameters are pruned using the OBD method. For test data from the same subjects as used in the training set the test error closely follows the training error curve. The validation error is used for chosing "optimal" network architecture. It can be seen that this network also generalizes well for the independent test set.

rest of the pixels in the image.

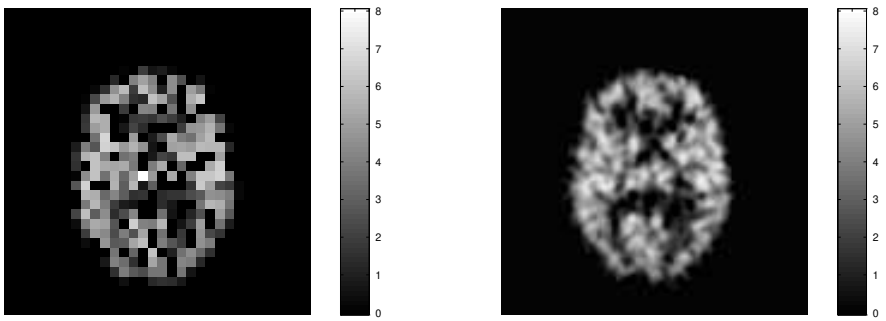


Figure 6: Images showing the glucose utilization as determined by fitting the kinetic model (subsampled $4 \times 4$ superpixels) using a second Newton scheme (left panel) and as determined by the neural net operating as inverse model for the kinetics (right panel). A total of 500 examples from the 15 slices for this subject is used as a training set, together with 500 examples from each of 7 other subjects. The right panel shows the result of evaluating the neural network on each pixel in the slice, the network generalizes very well for this subject.

Figure 7 shows the estimate of the glucose utilization for a subject, which was not used in the training set. Qualitatively the similarity is striking.

However, it can be seen that there is a problem in estimating the global level. Especially, the low level (the background) can be seen to have an offset.

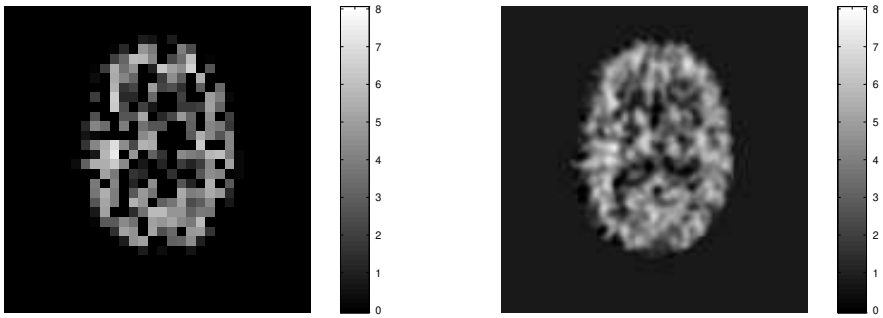


Figure 7: Images showing the glucose utilization as determined by fitting the kinetic model (pixel by pixel) using a second Newton scheme (left panel) and as determined by the neural net operating as inverse model for the kinetics (right panel). This subject has not been incorporated in the training set. A major part of the generalization error is caused by a global offset; the origin of this offset it is not clear at present.

It is important to note the difference in the computational burden of the two methods. The execution time for the neural network is orders of magnitude less than the time needed to fit the rate constants in Sokoloff's model by the Newton method. Using the neural network it is possible to estimate the glucose metabolism in 15 slices of $128 \times 128$ pixel images in less that 4 minutes on the HP9000/735 workstation, compared to about 48 hours required by the fitting procedure.

## CONCLUSION

In this article it has been shown how a neural network can be trained to learn the inverse model for the three compartment PET tracer kinetic model. The neural network way of estimating the glucose utilization is significantly faster than fitting the kinetic rate constants directly and the generalization ability of the neural network solution seems very good even to subjects which have not been incorporated in the training set. We are currently pursuing robust estimation of the global mean glucose utilization, also we expect that the neural network can be used to estimate the glucose utilization in pixels from a subject with serious diseases, e.g. Alzheimers disease.

## REFERENCES


[1] T. Fog, L.H. Nielsen, L.K.Hansen, S. Holm, I. Law, C. Svarer, and O. Paulson: "Neural Estimation of Kinetic Rate Constants from Dynamic PET-Scans" in *Neural Networks for Signal Processing*, Vols. IV, IEEE, Piscataway, NJ (1994).

[2] Y. Le Cun, J.S. Denker, and S.A. Solla: "Optimal Brain Damage" in *Advances in Neural Information Processing Systems*, Vols. II, Morgan Kaufmann, San Mateo (1990).

[3] M.E. Phelps: "Positron Emission Tomography (PET)". In: J.C. Maziotta and S. Gilman (Eds.):*Clinical Brain Imaging, Principles and Applications*, F.A. Davis Company, Philadelphia (1992).

[4] M. Reivich, A. Alavi, A. Wolf, J. Fowler, J. Russell, C. Arnett, R.R. MacGregor, C.Y Shiue, H. Atkins, A. Anand, R. Dann, and J.H Greenberg: "Glucose metabolic rate kinetic model parameter determination in humans: the lumped constants and rate constants for $[^{18}F]$fluorodeoxyglucose and $[^{11}C]$deoxyglucose." in Journal of Cerebral Blood Flow **5** 179-192 (1985).

[5] H. Sasaki, I. Kanno, M. Murakami, F. Shishido, and K. Uemuda: "Tomographic Mapping of Kinetic Rate Constants in the FDG model Using Dynamic PET". Journal of Cerebral Blood Flow **6** 447-454 (1986).

[6] L. Sokoloff, M. Reivich, C. Kennedy, M.H. Des Rosiers, C.S. Patlak, K.D. Pettigrew, O. Sakurada, and M. Shinohara: "The C-14-Deoxyglucose Method for the Measurement of local Cerebral Glucose Utilization: Theory, Procedures and Normal Values in the Conscious and Anesthetized Albino Rat" Journal of Neurochemistry **28** 897-916, (1977).

[7] C. Svarer, L.K.Hansen, and J. Larsen: "On design and evaluation of tapped-delay neural network architectures" in *IEEE International Conference on Neural Networks*, Vols. I, IEEE, Piscataway, NJ (1993).