Numerical Deconvolution by a Monte Carlo Approach with Application to Dynamic Cardiac Perfusion Tc-99m SPECT

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Abstract

Accurate determination of the input function is essential for absolute quantification of physiological parameters in PET and SPECT imaging but it requires an invasive and tedious procedure of blood sampling that is impractical in clinical studies. We previously proposed a technique that simultaneously estimates kinetic parameters and the input function from the tissue impulse response functions and which, requires only two blood samples. A nonlinear least squares method was used to estimate all the parameters in the impulse response functions and the input function but it fails occasionally due to high noise levels in the data causing an ill-conditioned cost function. This study investigates the feasibility of applying a Monte Carlo method called simulated annealing to estimate kinetic parameters in the impulse response functions and the input function. Time-activity curves of teboroxime, which is very sensitive to changes in the input function, were simulated based on published data obtained from a canine model. The equations describing the tracer kinetics in different regions were minimised simultaneously by simulated annealing and nonlinear least squares. We found that the physiological parameters obtained with simulated annealing are more accurate and the estimated input function more closely resembled the simulated curve. We conclude that simulated annealing reduces bias in the estimation of physiological parameters and determination of the input function.

Keywords: Monte Carlo method, simulated annealing, input function, impulse response function, teboroxime, dynamic cardiac perfusion SPECT.

1 Introduction

Quantification of dynamic SPECT data requires an invasive procedure where a series of blood samples are taken to form an input function for kinetic modelling (Huang & Phelps 1986). The input function is generally obtained by sampling blood at the radial artery or from an arterialised vein in a hand. Although arterialised-venous (a-v) blood sampling has been accepted as an alternative to arterial blood sampling, which is regarded as the gold standard, the procedure is invasive and there is a potential risk of irreversible tissue ischaemia or arterial thrombosis. A number of methods for the estimation (or elimination) of input function have been proposed (Weinberg et al. 1988, Nelson et al. 1993, Onishi et al. 1996, Eberl et al. 1997, Feng et al. 1997, Chen et al. 1998, Wong et al. 2001). The population-based input function approach (Onishi et al. 1996, Eberl et al. 1997) that is used routinely at our institution, calibrates a standardised input function obtained from a large population by one or two arterial or a-v blood samples for an individual by assuming that the area under an individual input function can be closely approximated by the scaled population input function even if the shape of the individual input function differs from the scaled population input function. This method has been validated in tracers with slow kinetics such as [^{18}F]fluorodeoxyglucose (FDG) in PET and [^{123}I]iomazenil in SPECT (Onishi et al. 1996, Eberl et al. 1997). For tracers with fast kinetics (e.g. ^{15}O-water in PET and ^{99m}Tc-teboroxime in SPECT), however, the population-based input function approach is unlikely to be applicable as the approximation to the actual input function by the calibrated input function is no longer valid. The shape discrepancies and time-delay can cause erroneous estimation of physiological parameters. Moreover, repeated measurements in a group of patients or volunteers are required for constructing a new input function template whenever a new tracer or different infusion rate is used. Deriving input function by putting region-of-interest (ROI) over a vascular structure in the images has also been investigated (Weinberg et al. 1988, Chen et al. 1998). Frequent blood sampling can be completely obviated but the noise levels in the derived input function are very high and cannot be assumed to be negligible for kinetic modelling. In addition, the spillover from extravascular activity needs to be carefully considered. Further, the input function may not be available in some cases if the vascular structure is not covered by the field of view of the gantry.

The simultaneous estimation (SIME) method estimates parameters in the tissue's impulse response functions (IRFs) and the input function simultaneously and requires one or two blood samples for scaling (Feng et al. 1997, Wong et al. 2001). The nonlinear least squares method that has usually been regarded as the standard for kinetic modelling, has been used in SIME to estimate all the parameters in

the IRFs and recover the input function. However, the nonlinear least squares method fails occasionally due to ill-conditioning of the cost function caused by the high noise levels in the measurements and highly nonlinear parameter space (Wong et al. 2001). Thus it will be easily trapped into local minima and the physiological parameters may be biased due to poor estimation of the input function.

Although simulated annealing (Kirkpatrick et al. 1983) is not an efficient optimisation technique in computational terms, it is usually more reliable than other minimisation methods, because it is able to find the global optimum or a point very close to the global optimum in cases where others fail. To our knowledge, there are few reports that apply simulated annealing to emission tomography and most are devoted to image processing rather than to kinetic parameter estimation (Smith et al. 1985, Webb 1989, Girodias et al. 1991). The goal of this study was to investigate the feasibility of applying simulated annealing in SIME to deconvolve the input function and the IRFs. The combined method was evaluated with simulated cardiac dynamic SPECT ^{99m}Tc-teboroxime data.

2 Materials and Methods

2.1 Dynamic SPECT with ^{99m}Tc-teboroxime

Recent advances in attenuation and scatter correction methodologies in SPECT offer the possibility of quantifying the physiological functions *in vivo* by performing SPECT imaging dynamically, similar to what can be achieved with PET. One of the major applications of dynamic SPECT is to quantify myocardial perfusion, which is important for diagnosis and clinical management of coronary artery disease as the presence of perfusion defects after therapeutic intervention may indicate incomplete reperfusion or persistent coronary occlusion. Similar to dynamic PET, compartmental modelling is used in dynamic SPECT to quantify physiological parameters of interest. It has been demonstrated that myocardial perfusion can be studied by dynamic SPECT imaging of ^{99m}Tc-teboroxime using multi-headed SPECT systems (Smith et al. 1994). ^{99m}Tc-teboroxime is a neutral lipophilic compound with high myocardial extraction (80–90%) in the first pass and rapid clearance. Its kinetics can be modelled by a two-compartment model as shown in Figure 1, where $B(t)$ is the measured activity in the blood compartment at time t, $C(t)$ is the activity in the extravascular compartment at time t, k_{21} (in min^{-1}) and k_{12} (in min^{-1}) are the wash-in and wash-out rate constants of teboroxime, respectively. The kinetics of teboroxime in the extravascular compartment is given by

$$C(t) = B(t) \otimes k_{21}\, e^{-k_{12}t} \tag{1}$$

where $\otimes$ denotes the convolution integral operator. The myocardial tissue activity, however, cannot be solely modelled by equation (1) because a fraction of the measured activity is contributed by the blood activity owing to the presence of capillaries within or nearby the tissue and the partial volume effect due to the finite resolution of SPECT. Therefore, the myocardial tissue TAC, $M(t)$, acquired between the time $t - \Delta t$ and t is modelled by

$$M(t) = (1 - f_v) \int_{t-\Delta t}^{t} C(\tau)\, d\tau + f_v \int_{t-\Delta t}^{t} B(\tau)\, d\tau \tag{2}$$

where f_v represents the fraction of blood in the myocardial tissue. The parameters k_{21}, k_{12} and f_v can be estimated by nonlinear least squares fitting the measured tissue TAC to equation (2).

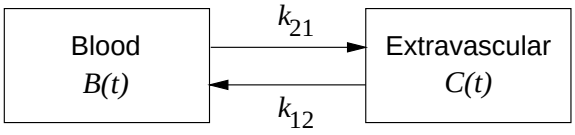

Figure 1: Two-compartment model for ^{99m}Tc-teboroxime.

2.2 Simultaneous Estimation

Different from other methods (Nelson et al. 1993, Onishi et al. 1996, Eberl et al. 1997) that estimated or eliminated the input function based on certain properties or assumptions of the radiotracer under consideration, SIME makes use of multiple tissue TACs that can be obtained by defining ROIs on the dynamic images to recover the input function embedded in the tissue TACs (Feng et al. 1997, Wong et al. 2001). SIME can be applied to different radiotracers or ligands, provided that the radiolabelled metabolites in blood and tissue are appropriately corrected. Since the tissue TAC is the convolution integration of the input function with the IRF of the corresponding region, the IRF parameters in multiple regions and the input function can be estimated by minimising the residual sum of square errors between the model predicted tissue response and the measurements in the corresponding ROIs simultaneously (Feng et al. 1997, Wong et al. 2001). Mathematically, the following cost function is to be minimised:

$$\begin{aligned} \Phi(\boldsymbol{p}) &= \sum_{i=1}^{n}\sum_{j=1}^{m}\left[\tilde{M}_i(t_j) - M_i(t_j)\right]^2 \\ &\quad + \sum_{k=1}^{c} w_k \left[\hat{B}(t_k) - \tilde{B}(t_k)\right]^2 \end{aligned} \tag{3}$$

where $\boldsymbol{p}$ denotes the vector of parameters to be estimated, including the wash-in and wash-out parameters in multiple tissue TACs and the parameters in the input function; n is the total number of ROIs incorporated into the model fitting procedure; m is the number of frames for each tissue TAC; $\tilde{M}_i(t_j)$ and $M_i(t_j)$ represent the measured and model predicted tissue activity concentrations at the jth frame in the ith ROI; $\hat{B}(t)$ is the estimated input function; c is the number of arterial blood samples taken late in the course of the study for calibration; $\tilde{B}(t_k)$ is the activity concentration in blood measured at time t_k $(k = 1, 2, \ldots, c)$; and w_k is chosen to be 100 (or any other reasonably large value) so that the blood samples are given more weight to discourage any discrepancy between the measured blood samples and their predictions.

2.3 Nonlinear Least Squares

Nonlinear least squares method has been a widely adopted standard for kinetic modelling. The principle of the nonlinear least squares method is to iteratively minimise a cost function based on a least squares criterion. Rapid convergence can be achieved if the shape of the isocontours of the cost function is approximately a concentric circle and can be well approximated by a quadratic around the minimum.

Table 1: Model parameters used to simulate ^{99m}Tc-teboroxime kinetics. Nominal initial values which were randomised during simulations and the physiological constraints imposed on the parameters are also shown.

Parameter	Region						Initial value	Bound	
	1	2	3	4	5	6		lower	upper
k_{21} (min^{-1})	0.590	1.109	0.482	0.760	0.856	0.652	0.5	0	10
k_{12} (min^{-1})	0.229	0.295	0.236	0.255	0.272	0.236	0.5	0	10
f_v (unitless)	0.166	0.606	0.184	0.276	0.441	0.207	0.2	0	1

In this study, the Marquardt algorithm (Marquardt 1963) was used as it usually performs well in locating the minimum and is reasonably insensitive to an initial estimate. However, there is no guarantee that the located minimum corresponds to the global minimum unless it is unique. Furthermore, in optimisation problems with a large number of parameters or with noisy data, the cost function is usually ill-conditioned because it has multiple minima, causing the algorithm to get stuck in the local minimum nearest to the initial estimate, or in the worst case, the algorithm does not converge if the cost function is nonsmooth or discontinuous in its domain.

2.4 Simulated Annealing

Simulated annealing is a generalisation of a Monte Carlo method based on the theory of statistical mechanics (Kirkpatrick et al. 1983). In condensed matter physics, annealing is a physical process of heating up a solid material by increasing the temperature to a maximum at which all molecules arrange themselves randomly in the liquid phase followed by a slow cooling process that results in the formation of a perfect crystal. Application of simulated annealing to optimisation problems is based on the analogy between the state of each molecule and the state of each parameter that affects the energy function (analogous to the cost function in the optimisation problem) to be minimised. The parameter values are randomly perturbed and if the perturbation reduces the cost function then it is accepted; otherwise it is accepted with probability $e^{-\frac{\Delta\Phi}{K_B T}}$ where $\Delta\Phi$ is the change in the cost function, K_B is the Boltzmann constant and T is the current system temperature which is a control parameter (Kirkpatrick et al. 1983). This is referred to as the Metropolis criterion (Kirkpatrick et al. 1983) and the scheme for reducing the temperature is called the cooling schedule. Providing that the starting maximum temperature is sufficiently high and the temperature T is lowered slowly, the algorithm is guaranteed to reach the global minimum or a point close to the global minimum of the cost function (Kirkpatrick et al. 1983).

2.5 Computer Simulations

To simulate ^{99m}Tc-teboroxime kinetics, a sum of two exponential decaying functions was used to generate an input function:

$$B(t) = 2500e^{-6(t-0.3)} + 350e^{-0.06(t-0.3)} \qquad (4)$$

where t represents the time abscissa in minutes. From two to six tissue TACs of teboroxime were simulated with a two-compartment model and the parameter values were based on a baseline study obtained from a canine model (Smith et al. 1994), and a 70 $\times$ 10 sec scanning protocol was assumed. Table 1 lists the values of the rate constants that were used for the simulations. Possion noise typical of the observed TAC was added to the generated TACs and 100 different noise realisations were generated. Initial estimates were randomised above a set of nominal initial values (see Table 1) and were used by both nonlinear least squares and simulated annealing for the same realisation. Note that simulated annealing is independent of the initial values, which influence the optimality of the parameter estimates and the convergence for iterative gradient-based optimisation techniques.

For each region, the kinetic parameters were estimated by SIME in combination with nonlinear least squares or simulated annealing, in addition to the estimation of the input function scaled with two 'blood' samples (8 and 11 min) by minimising equation (3) and were constrained to within their physiological ranges by the SUMT techniques (McCormick 1983). The mean absolute difference (MAD) between an estimated parameter $\hat{p}^i$ and its true value p^i in each of the n tissue TACs was used as a measure of bias (Welch et al. 1995):

$$\frac{1}{n}\sum_{i=1}^{n} |\, \hat{p}^i - p^i \,| \qquad (5)$$

and was computed over 100 realisations with different number of regions and initial estimates.

3 Results and Discussion

Figure 2 shows a typical plot of the cost function value over the course of minimisation using simulated annealing. A large variation of cost function value was observed initially due to energy changes caused by random perturbation on the parameters. There were some increases in the cost function during minimisation because uphill moves were also accepted according to the Metropolis criterion (Kirkpatrick et al. 1983). This is in contrast to iterative gradient-based techniques where only downhill moves are accepted. However, as $K_B T$ decreases, positive changes in the cost function (i.e. $\Delta\Phi > 0$) become less probable. After a large number of iterations, the minimum of the cost function was located and was almost freezing. This can be considered analogous to the perfect crystal formation where all molecules arrange themselves into a minimum energy state in which no further energy change takes place.

Figure 3 plots the MADs and their standard deviations over 100 noise realisations for k_{21}, k_{12} and f_v parameters as a function of number of regions. Very large fluctuation in parameter estimates obtained with nonlinear least squares is clearly evident. On the other hand, the estimation of physiological parameters using simulated annealing is very insensitive to noise as the bias was much less than those obtained with the nonlinear least squares method starting with the same initial estimate and was almost the same with different number of regions.

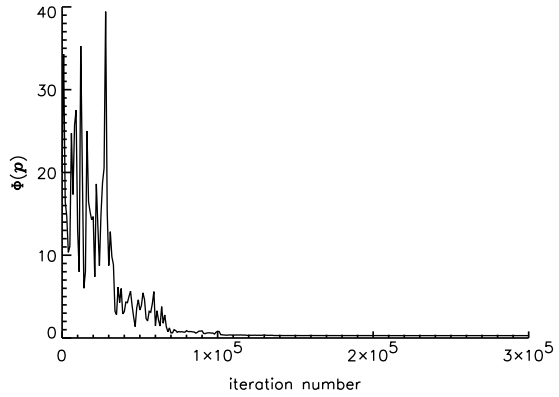

Figure 2: Variation of cost function over the course of minimisation.

Figure 4 shows the simulated blood curve and the estimated input functions over 100 noise realisations with four regions (Regions 1∼4) obtained by simulated annealing and nonlinear least squares. The estimated input function obtained with simulated annealing closely resembled the simulated blood curve while there was a biased estimation of input function in some of the noise realisations when nonlinear least squares was used. This was due to the nonlinear least squares algorithm being trapped in local minima because of its 'greedy' properties in only taking the best possible downhill moves by following the gradient of descent locally. Therefore, other optimal points with lower cost function values than the current point may not be reachable. On the contrary, simulated annealing occasionally accepts uphill moves, thus making it possible to escape local minima.

Choosing an appropriate set of initial estimates is very important for kinetic modelling when an iterative gradient-based technique is used. Any effort spent in obtaining good initial estimates of the parameters is well rewarded by rapid convergence of the minimisation algorithm and reduced chance of straying into an incorrect, local minimum. Incorporation of *a priori* information about the parameter estimates from theory or previous experimental results and shrinking the parameter space by constraining the parameter estimates to within certain limits are usually helpful. However, clinical data are always compounded by noise which perturb the smoothness of the cost function surface and create a number of minima. The minimum found by any iterative gradient-based approach may not be the global even with the use of constraints and *a priori* information since it is still likely that the algorithm will be trapped to a local minimum at which all the constraints are satisfied and those data do not guarantee the global optimality of the parameter estimates.

One of the major problems associated with simulated annealing is the large number of parameters to be adjusted in order to give optimal performance. Of particular importance is the cooling schedule which governs how the temperature is decreased. It has a major impact on the speed of convergence of the algorithm and the optimality of the parameter estimates. If the temperature is quickly reduced, the algorithm may be trapped at a sub-optimal point. On the other hand, long computation times are required for the algorithm to converge to a minimum if the temperature decreases too slowly.

Application of simulated annealing in parameter estimation has been limited because of the intensive computational burden as a huge number of function evaluations is required. Nonetheless, in the case of very ill-conditioned cost functions with many local minima (e.g. problems with many parameters), the expense on computation may be rewarded by obtaining better results than the nonlinear least squares method restarting at different points as many times as the

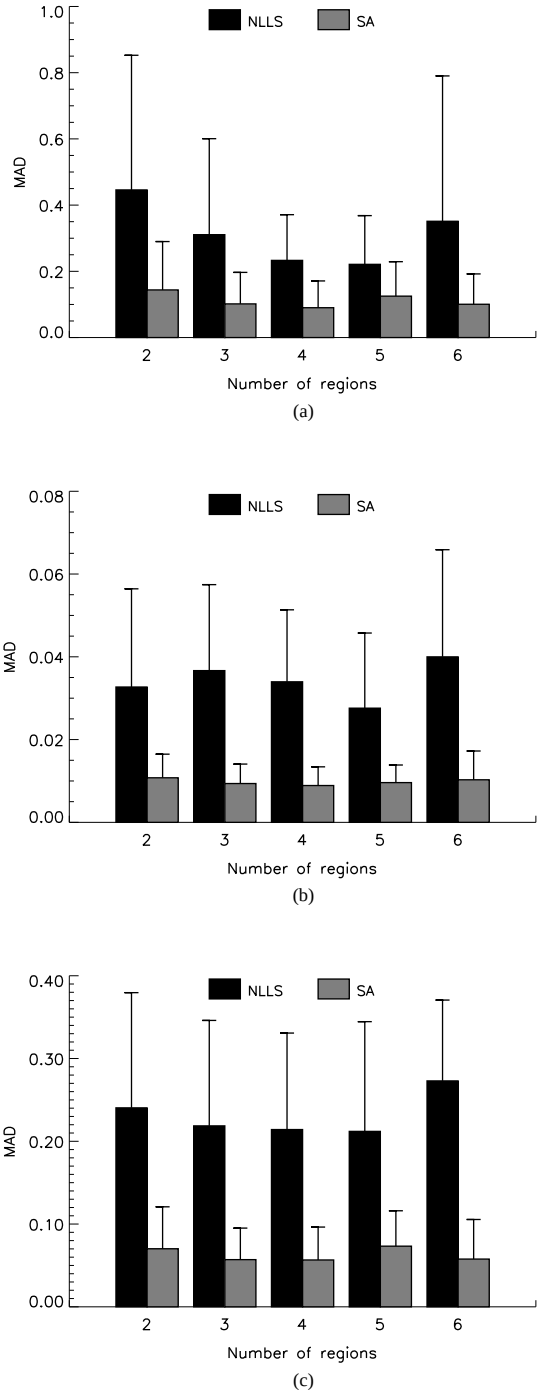

Figure 3: MAD of (a) k_{21}, (b) k_{12}, and (c) f_v as a function of number of regions. The standard deviation is represented by the error bar. (NLLS = nonlinear least squares; SA = simulated annealing).

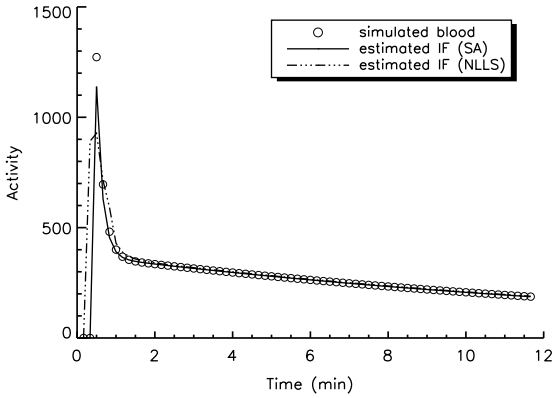

Figure 4: Simulated blood curve and estimated input functions using simulated annealing (SA) and nonlinear least squares (NLLS).

number of function evaluations required by simulated annealing. In addition, simulated annealing can still be applicable to problems where the cost function cannot be approximated by a quadratic function near the minimum or is nonsmooth or discontinuous in its domain. Searching for minima with gradient-based methods may not be feasible. Further, with recent advances in computer technology and speed, the problem of computational burden is disappearing or has virtually disappeared by running the algorithm on parallel computers.

4 Conclusions

Our results demonstrate that it is feasible to apply simulated annealing to simultaneously estimate the physiological parameters and the input function as it is more insensitive to noise than the nonlinear least squares method. The physiological parameters obtained with simulated annealing are more accurate and the estimated input function more closely resembled the simulated curve. We conclude that simulated annealing reduces bias in the estimation of physiological parameters and determination of the input function.

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References

Chen, K., Bandy, D., Reiman, E., Huang, S. C., Lawson, M., Feng, D., Yun, L. S. & Palant, A. (1998), 'Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, ^{18}F-fluoro-2-deoxyglucose, the Patlak method, and an image-derived input function', *J. Cereb. Blood Flow Metab.* **18**, 716–723.

Eberl, S., Anayat, A. R., Fulton, R. R., Hooper, P. K. & Fulham, M. J. (1997), 'Evaluation of two population-based input functions for quantitative neurological FDG PET studies', *Eur. J. Nucl. Med.* **24**(3), 299–304.

Feng, D., Wong, K. P., Wu, C. M. & Siu, W. C. (1997), 'A technique for extracting physiological parameters and the required input function simultaneously from PET image measurements: Theory and simulation study', *IEEE Trans. Inform. Technol. Biomed.* **1**, 243–254.

Girodias, K. A., Barrett, H. H. & Shoemaker, R. L. (1991), 'Parallel simulated annealing for emission tomography', *Phys. Med. Biol.* **36**, 921–938.

Huang, S. C. & Phelps, M. E. (1986), Principles of tracer kinetic modeling in positron emission tomography and autoradiography, *in* M. E. Phelps, J. C. Mazziotta & H. R. Schelbert, eds, 'Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart', Raven Press, New York, USA, pp. 287–346.

Kirkpatrick, S., Gelatt, Jr., C. D. & Vecchi, M. P. (1983), 'Optimization by simulated annealing', *Science* **220**, 671–680.

Marquardt, D. W. (1963), 'An algorithm for least-squares estimation of nonlinear parameters', *J. Soc. Ind. Appl. Math.* **11**, 431–441.

McCormick, G. P. (1983), *Nonlinear Programming: Theory, Algorithms, and Applications*, Wiley, New York, USA.

Nelson, A. D., Miraldi, F., Muzic, Jr., R. F., Leisure, G. P. & Semple, W. E. (1993), 'Noninvasive arterial monitor for quantitative oxygen-15-water blood flow studies', *J. Nucl. Med.* **34**, 1000–1006.

Onishi, Y., Yonekura, Y., Nishizawa, S., Tanaka, F., Okazawa, H., Ishiza, K., Fujita, T., Konishi, J. & Mukai, T. (1996), 'Noninvasive quantification of iodine-123-iomazenil SPECT', *J. Nucl. Med.* **37**(2), 374–378.

Smith, A. M., Gullberg, G. T., Christian, P. E. & Datz, F. L. (1994), 'Kinetic modeling of teboroxime using dynamic SPECT imaging of a canine model', *J. Nucl. Med.* **35**, 484–495.

Smith, W. E., Paxman, R. G. & Barrett, H. H. (1985), 'Application of simulated annealing to coded-aperture design and tomographic reconstruction', *IEEE Trans. Nucl. Sci.* **32**, 758–761.

Webb, S. (1989), 'SPECT reconstruction by simulated annealing', *Phys. Med. Biol.* **34**, 259–281.

Weinberg, I. N., Huang, S. C., Hoffman, E. J., Araujo, L., Nienaber, C., GroverMcKay, M., Dahlbom, M. & Schelbert, H. R. (1988), 'Validation of PET-acquired input functions for cardiac studies', *J. Nucl. Med.* **29**, 241–247.

Welch, A., Smith, A. M. & Gullberg, G. T. (1995), 'An investigation of the effect of finite system resolution and photon noise on the bias and precision of dynamic cardiac SPECT parameters', *Med. Phys.* **22**, 1829–1836.

Wong, K. P., Feng, D., Meikle, S. R. & Fulham, M. J. (2001), 'Simultaneous estimation of physiological parameters and the input function–*in vivo* PET data', *IEEE Trans. Inform. Technol. Biomed.* **5**, 67–76.