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Detection of Measurement Outliers in Tracer Kinetics

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Abstract: In tracer kinetic studies for extracting biological information, measurement noise and error in the kinetics could affect the reliability of the estimated biological parameters. While the effect of statistical noise has been studied extensively before, the effect of outliers has not been addressed as much. In this study, we described an algorithm for detecting and removing outliers. Computer simulation was used to generate kinetic data sets corresponding to those of the FDG tracer used in PET studies to evaluate the effect of outliers and the performance of the outlier detection algorithm. Results show that outlier could increase drastically the variability of the estimated rate constants of FDG transport and phosphorylation. The outlier detection algorithm imbedded in a regular model fitting procedure was found to have a low probability of missing outliers in the kinetics. The probability of falsely identifying non-outliers as outliers was high, but these false positive detections did not affect the reliability of the biological estimates. With the outlier detection, the variability of the parameter estimates in the simulated FDG kinetics with outliers could be reduced by a factor of more than 5. The present study demonstrated the importance of outlier detection in interpreting tracer kinetics. Some areas for future studies are also discussed.

1. INTRODUCTION

In extracting biological information from tracer kinetics, measurement noise and error in tracer kinetics could be propagated to the biological parameters estimated from the kinetics and affect the accuracy of the resulted biological estimates. In positron emission tomography (PET), for example, tracer kinetics in local tissue regions can be measured simultaneously over tens of thousands of voxels of cubic milli-meters in size. However, the kinetics for each pixel have high noise levels. Furthermore, due to subject movement during the kinetic measurement or artifacts from tomography reconstruction, occasional large errors unaccountable by statistical noise are seen. Another example is in the in vivo measurement of transport rate constants of FDG across the red blood cells (RBC) in mice (Huang et al, 2007). The measurements are derived from tiny blood samples (<30 micro-liters), and go through multiple processing steps. Some measurements appear clearly out of line with the others. They could drastically affect the model fitting results if not properly dealt with. A common approach is to examine the tracer kinetics visually by an experienced expert and throw out what he considers as the outliers before applying the model fitting to the kinetics. However, this approach is labor-intensive and could also be criticized as being subjective.

An alternative approach is to use a regression algorithm that is not sensitive to outliers. While there are many possible algorithm candidates, we have explored the use of a two-step approach. It involves in first finding the outliers automatically and then removing the outliers before the regular model fitting procedure (the second step). Outlier detection is not a new topic. Many outlier finding or detection algorithms/methods have been proposed and developed for various applications, including statistics, business, sociology, signal processing, and real-time automatic control. They have different properties to suit different types of outliers in different applications. In this paper, we described an outlier detection method that we have adopted from a real-time automatic control application (Menold et al, 1999), and we have tested its performance with computer simulated kinetic data. The results of the evaluation are reported and the implications of automatic outlier detection on biological estimates and parametric images are discussed. The effect of outliers in tracer kinetics on the extracted biological information is also examined. Additional investigations or developments to address further the outlier problem in tracer kinetics are also discussed.

2. AN OUTLIER DETECTION ALGORITHM

The algorithm that we have used in this study for detecting outliers in tracer kinetics is adopted from one originally employed for a real-time automatic control problem (Menold et al, 1999). Modifications however have been made to adapt to the special characteristics of tracer kinetics.

2.1 Assumptions

A measurement in the tracer kinetics is considered to be an outlier, if it deviates from its expected value by more than 2 standard deviations of the noise level of other measurements in that kinetics. A tracer kinetic time activity curve (TAC) can have more than one outlier, but outliers are assumed not adjacent to each other in the measurement sequence. The noise level of the measurements in a TAC is assumed to be describable by a zero mean Gaussian random variable. The noise variance is constant over time or varies in a known way.

2.2 Detection algorithm

The outlier detection algorithm is imbedded in a least-square model fitting procedure. At the end of an iteration of the model fitting procedure, the noise variance (and standard deviation) of the data is estimated and the deviation of each measurement is compared to the estimated noise standard deviation. If the deviation is larger than a threshold based on the estimated standard deviation, the corresponding measurement is considered to be an outlier candidate. The deviation of each measurement is estimated as the difference of the measurement from the model fitted value at the end of that model fitting iteration. The model fitting procedure is based on the least-square Marquardt algorithm and is identical to what is used in the KIS modelling software package (Huang et al, 2005).

The threshold for identifying a deviation as the outlier is selected as

Threshold=max(ck·MAD, Tm),

where

ck=2.96· $(1+2^{(3-i)})$ with i=the iteration number of the regression,

MAD is the median absolute deviation of the difference between the measurements and the model predictions (Menold et al, 1999),

and

Tm=2·sqrt(estimated noise variance).

The dependency of ck on the iteration number gives a larger threshold value at the beginning. It intends to decrease the sensitivity of the outlier detection to the initial condition used in the model fitting.

To avoid picking up too many false positive outliers due to possible poor model predictions at early stage of the model fitting procedure, the estimated deviation sequence is smoothed (with a filter [1/3 1/3 1/3]), and the amount of reduction in the deviation after smoothing was checked to see if it is larger than 30% of the original deviation. For an outlier candidate, if it passes the check, the measurement is then declared as an outlier.

After the detected outlier is removed (i.e., by assigning it a zero weighting), the iterative regression procedure is continued and the outlier checking steps are repeated. The procedure would continue till no more outlier is detected and the model fitting satisfies the convergence criterion.

For the case of non-constant noise variance, the deviations are weighted by the inverse of the square root of the variance before the thresholds for the deviations are checked.

3. COMPUTER SIMULATIONS

Computer simulation was used to generate tracer kinetics for evaluating the performance of the outlier detection algorithm described in Section 2 above. The FDG model (Huang et al, 1980; Phelps et al, 1979) was used to generate the underlying tissue TAC from 0 to 60 min, using a measured plasma FDG TAC in a mouse experiment as the input function. The measurements were assumed to follow a PET scanning protocol of 2x0.5, 1x1, 1x2, and 12x5 min. The values for the rate constants of the model were selected to be 0.1 ml/min/g, 0.2 /min, 0.04 /min and 0.01 /min for K1, k2, k3 and k4, respectively.

Measurement noise was simulated as a zero-mean Gaussian variable with a standard deviation equal to 0.3, which is ~2% of the tissue TAC value of 15 at 60 min. For the case of non-constant noise, the noise variances at early measurements were adjusted higher (with the resulted variance inversely proportional to the scan duration).

Outliers were added randomly. The probability of having an outlier for each measurement was 13.5%, so the number of outliers per TAC (of 16 measurements) was about 2. The magnitude of the outlier was also random (uniformly distributed between 4 and 10).

In two cases of simulations, no outlier was added. In one of them, the measurement noise was increased by 10 times.

After a simulated TAC was generated, the kinetics was model fitted using the outlier-detection-imbedded procedure described in Section 2 above. One hundred realizations were performed for each condition.

The initial condition of the parameter values for the model fitting was the true values. To evaluate the effect of the initial condition, the initial parameter values in one case were changed to [0.07, 0.3, 0.02, 0.004] that were significantly different from the true values.

The number of outliers detected and the number of false detection were recorded. The estimated values of the model rate constants with outlier detection and removal were compared to those without outlier detection. Other than the outlier detection part, the regression routines used were identical between the two cases.

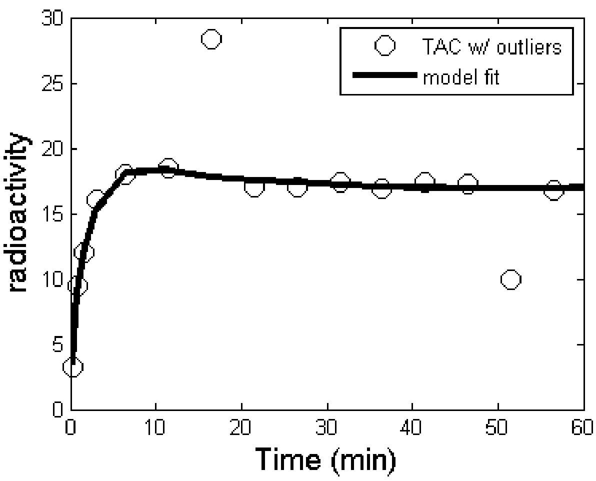

Fig. 1. a simulated FDG kinetics (circles) with outliers. The solid curve is a model fit after outliers have been detected and removed.

4. PERFORMANCE OF OUTLIERS DETECTION

Figure 1 shows a simulated tissue kinetic curve with outlier measurements. The number of outliers missed and the number of false positive detection in 100 simulated kinetics are tabulated in Table 1.

Table 1. accuracy in identifying outliers

Simulations	total outliers	false positive	missed
Constant noise level	185	108 (109)*	5 (17)*
Non-constant noise	191	152	8
No outliers	0	15 (39)**	0

*for case with a second set of initial condition.
**for case when noise level was 10 times larger.

The mean and standard deviation of the estimated values of the rate constants with and without outlier detection (and removal) are shown in Table 2. Of the 100 realizations, the ones that had much larger residual sum of squares than the rest were not included in the calculation of the mean and standard deviation.

Table 2. estimated values of the rate constants in model

	K1w*	K1	k2w	k2	k3w	k3	k4w	k4
const. noise	0.104# 0.027	0.109 0.049	0.217 0.135	0.276 0.459	0.042 0.009	0.052 0.042	0.011 0.005	0.010 0.011
non-constant	0.105 0.018	0.116 0.047	0.222 0.098	0.301 0.440	0.043 0.014	0.055 0.048	0.010 0.003	0.011 0.012
no outlier	0.100 0.002	0.100 0.002	0.200 0.011	0.200 0.011	0.040 0.004	0.040 0.004	0.010 0.002	0.010 0.002
no outlier, high noise	0.118 0.041	0.113 0.039	0.37 0.52	0.35 0.53	0.074 0.098	0.070 0.096	0.013 0.014	0.013 0.014
diff. initial values	0.102 0.015	0.105 0.017	0.207 0.049	0.236 0.105	0.040 0.008	0.052 0.034	0.010 0.006	0.011 0.011

* w denotes the estimates with outlier detection and removal. # first number is mean and second number is standard deviation. The true values of K1, k2, k3, and k4 used in the simulation were 0.1, 0.2, 0.04, and 0.01, respectively.

5. DISCUSSIONS

Based on the results in Tables 1 and 2, the outlier detection algorithm described in this paper performed well in detecting (and removing) outliers in tracer kinetics. The outliers escaped detection were those adjacent to another outlier (not excluded in the simulation). Although there are a large number of false positive detections, the resulted estimates of the rate constants were still close to the true values and with small variations.

By comparing the standard deviations in row 1 with those in row 3 in Table 2, outliers are seen to have large effects on the variability of the estimated model parameters, especially when outliers were not detected/removed. For the case without outliers added but with enhanced measurement noise level (row 4), the use of outlier detection did not adversely affected the results, indicating that the use of outlier detection is not harmful even when there are no outliers in the tracer kinetics.

If each of the simulated kinetic corresponds to the kinetics from a single pixel location in an image (10x10 in size), the estimated rate constants can form parametric images of the estimated rate constants. The standard deviations of the rate constants shown in Table 2 thus reflect directly the noise levels on these parametric images.

One general concern for outlier detection/removal in nonlinear regression is the initial condition. Altering the initial condition of the model fitting is seen to have a large effect on the estimated parameter values. In practice, one can use the group average from regular model fitting as the initial condition. Another strategy is to perform multiple model fittings for each kinetic curve with various sets of initial conditions. The Akaike Information Criterion (AIC) (Akaike, 1974), for example, can be used to select the best among multiple results.

Optimization of the thresholds used in the outlier detection in this study has not been performed. It is possible that the thresholds can be adjusted to achieve better results. If the measurement noise level and the outlier occurrence probability are significantly different from those used in this study, the thresholds may need to be tuned to achieve satisfactory results.

The present study only examines the kinetics of one common model using a single input function and a single set of true parameter values. It is likely that the algorithm will need to be modified for other cases. However, the characteristics observed in this study are expected to be valid in more general cases. It warrants doing more studies in the future.

6. CONCLUSION

The outlier detection algorithm described and imbedded in a least-square model fitting routine gave good results in detecting and removing outliers in tracer kinetics and thus improved the reliability of the parameter estimates in model fitting. Addition work is needed to improve further its performance and its general applicability.

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