

# **A Reversible-Jump Markov Chain Monte Carlo Method for Deconvolution Problems**

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**Summary.** We consider applying Reversible-Jump Metropolis-Hastings (RJMH) to the nonparametric (regression and) deconvolution problem in order to automatically solve the corresponding model selection problem (determination of the location of the breakpoints). The algorithm was implemented and tested with several test functions for regression and deconvolution, and applied to the real data example of veralipride.

## INTRODUCTION

For a linear system, the system input-output relationship can be described by the convolution integral

$$y(t) = \int_0^t I(s)K(t-s)ds, \quad (1)$$

where  $y(t)$  is the output,  $I(t)$  is the input function and  $K(t)$  is the system disposition function (i.e., impulse response). To estimate the disposition function or the input function given measurements of the output (given estimates of the input and disposition function, respectively), we can use deconvolution. A typical case is found in pharmacokinetics (PK), where one estimates the system disposition function from the intravenous (IV) administration, and then estimates the input function from an oral administration using the estimated disposition function. Typically one can use a parametric model for  $K(t)$ , which describes the decay and distribution of drug: for example a multiexponential function. To represent the input function,  $I(t)$ , one can use a nonparametric representation: for example a spline.

However, in order to use the splines, the number and location of breakpoints has to be determined. Previous approaches to solve this model selection problem involved positioning the breakpoints at equispaced or quantile locations, combined with a model selection criterion, or the use of a smoothing spline. These methods rely on ad hoc positioning of the breakpoints, which might have no relationship with the shape of the underlying input function (Verotta, 1996). Employing Reversible-Jump Metropolis-Hastings (RJMH) algorithm (Green, 1995), one of the Markov Chain Monte Carlo (MCMC) algorithms, solves the problem of choosing the location of the breakpoints and has the potential to be particularly useful for the recovery of irregular input functions.

In this work, we consider applying the RJMH method to deconvolution problems in pharmacokinetics. The contents of this paper are as follows. In Methods section, we concisely explain the RJMH algorithm. In Results section, we first present the simulation study results (regression and deconvolution) using test functions, then deconvolution of the real data example of veralipride. We conclude with a few concluding remarks.

## METHODS

The curve to be fit or the unknown input function is represented by truncated power basis polynomial spline:

$$y(t) = \mathbf{a}_1 + \mathbf{a}_2 t + \mathbf{a}_3 (t - \mathbf{x}_1)_+ + \mathbf{a}_4 (t - \mathbf{x}_2)_+ + \dots + \mathbf{a}_{m+2} (t - \mathbf{x}_m)_+, \quad (2)$$

where  $\alpha$ 's are the coefficients,  $\xi$ 's are a sequence of nondecreasing points called breakpoints, and  $(x)_+ = x$  if the argument is strictly greater than zero,  $x > 0$ , and  $(x)_+ = 0$  otherwise (DeBoor, 1978).

In a deconvolution problem, one approach is to first estimate the system disposition function, second conditional on the parameter estimates to estimate the input function. Estimation of the disposition function can be done, if the disposition function is a parametric model such as multiexponential function, using available nonlinear regression software (or MCMC methods). To estimate the input function using the spline representation equation (2), the locations and number of the breakpoints have to be determined. RJMH can be used for this model selection problem: Figure 1 schematically shows how the RJMH algorithm iterates to search for the location and number of breakpoints.

Since there can be many models of differing dimension (that is, different number of terms in equation (2)), the prior probabilities of models were modeled using a Poisson distribution:

$$p(k | I) = I^k \exp(-I) / k! \quad (3)$$

The parameter  $\lambda$  of Poisson distribution gives highest prior probability to the model with as many as  $\lambda$  parameters, then gives decreasing probabilities to models that deviate from the mean. At each iteration, the RJMH performs one of birth, death, or move steps. The probabilities of going to a particular step are computed as follows:

$$\begin{aligned} b_k &= c \min\{1, p(k+1) / p(k)\}, \\ d_k &= c \min\{1, p(k) / p(k+1)\}, \\ m_k &= 1 - b_k - d_k, \end{aligned} \quad (4)$$

where  $c$  is an arbitrarily small constant that makes sum of the probabilities to one. Then the acceptance probabilities for birth, death, or move step can be defined as follows:

$$\begin{aligned} a_b &= \min\left\{1, \frac{l(k+1)}{l(k)} \frac{N - Z(k)}{N}\right\}, \\ a_d &= \min\left\{1, \frac{l(k)}{l(k+1)} \frac{N}{N - Z(k)}\right\}, \\ a_m &= \min\left\{1, \frac{l(k')}{l(k)}\right\}, \end{aligned} \quad (5)$$

where  $l(k)$  is the likelihood of the model with the current  $k$  breakpoints,  $N$  is the total number of candidate breakpoint locations, and  $Z(k) = 2(l+1) + k(2l+1)$  is the number of candidate breakpoint locations where a new breakpoint can't be put so that a certain minimum distance (denoted by  $l$  in the equation) could be maintained between breakpoints, and  $k'$  is the new breakpoints after moving one of the existing  $k$  breakpoints. A detailed description of the algorithm can be found in Denison et al. (1998).

We introduced the following modifications to the original algorithm:

1. The first breakpoint can be located as early as the second measurement time. This is to ensure that there will be at least two measurements data between time zero and the first breakpoint.
2. The last breakpoint can be located as late as the 2nd to last measurement time, to ensure that there are at least 2 measurements after the last breakpoint.

3. The new breakpoint cannot be put closer to an existing breakpoint than the time difference between the existing breakpoint and the following observation measurement time. This is to ensure that there is at least one measurement data between the two adjacent breakpoints.

The algorithm iteration continues until the mean squared error (MSE) between the model prediction and data attains a specified precision. In the examples below we use 3 significant digits.

## SIMULATION RESULTS

We compare the performance of the RJMH algorithm with a standard method, see e.g. (Verotta, 1996), which, for any number of breakpoints, positions the breakpoints at the quantiles of the observations measurement times, fits the resulting model to the data using QPROG (QPROG), and chooses the number of breakpoints based on the Hannan-Quinn criterion (Hannan, 1987). We refer to this method as the QUANTILE method. To compare the RJMH and QUANTILE methods we compute the following quantities:

NMSE (Normalized Mean Squared Error)

$$NMSE = \frac{\sum_{i=1}^n (f(t_i) - \hat{y}(t_i))^2}{\sum_{i=1}^n (f(t_i) - \bar{f})^2} \quad (6)$$

NMAE (Normalized Mean Absolute Error)

$$NMAE = \frac{\sum_{i=1}^n |f(t_i) - \hat{y}(t_i)|}{\sum_{i=1}^n (f(t_i) - \bar{f})^2} \quad (7)$$

RMSB (Root Mean Squared Bias)

$$RMSB = \sqrt{\frac{1}{n} \sum_{i=1}^n (\bar{y}(t_i) - f(t_i))^2} \quad (8)$$

In the above formulae,  $f(t_i)$  is the true value,  $\hat{y}(t_i)$  is the model prediction,  $\bar{f}$  is the mean of the true values, and  $\bar{y}(t_i)$  is the mean model estimate over the total number of simulations.

## Regression

To test the RJMH algorithm we first applied it to the test functions used in Denison et al. (1998):

Case 1.

$$f(t) = t + 2 \exp(-16t^2) \quad t \in [-2,2]. \quad (9)$$

Case 2.

$$f(t) = \sin(2t) + 2 \exp(-16t^2) \quad t \in [-2,2]. \quad (10)$$

Sets of 200 data points were generated using  $t$  values from  $U(-2,2)$ . Then additive noise was added: a noise of  $N(0,0.4^2)$  to case 1 and  $N(0,0.3^2)$  to case 2 so that the signal-to-noise ratio is 3. Figure 1 shows the result of the one data set among 100 simulations. The upper panels were obtained using the QUANTILE method, trying 10 to 100 breakpoints. The lower panels were obtained using the RJMH algorithm. Table 1 summarizes the results. The NMSE's are smaller for the RJMH.

## Deconvolution

The second simulation study was deconvolution of a hypothetical input function which had positive input rate followed by negative input rate (see Figure 2). This corresponds to an experimental condition for which such substance as charcoal is given to extract the drug already distributed in the body. The system disposition function of the form  $K(t)=\exp(-0.144 \cdot t)/50$  was assumed. After the convolution of the input and the disposition function, an additive noise of  $N(0,0.01^2)$  was added to obtain the simulated measurement data. The numbers of breakpoints for the QUANTILE method goes from 3 to 10. Figure 2 shows the concentration and the retrieved input. Table 2 summarizes the results. All of the quantities in the table are smaller for RJMH.

## REAL DATA RESULTS

### Veralipride Deconvolution

Figure 4 shows the plasma concentration of veralipride after IV or oral (capsule and solution) dose (Plusquellec et al., 1987). This drug shows a double-peaked concentration profile, which is unusual and difficult to analyze using standard PK models. It was postulated by Plusquellec et al. that the double-peaked phenomenon was due to the differential absorption of the drug along the intestine. Using the IV data, estimates of system disposition function (of the form  $K(t)=A \cdot \exp(-K_1 \cdot t)+B \cdot \exp(-K_2 \cdot t)$ ) were obtained (Table 3). Then the system disposition function was fixed at these estimated values, and the input identification problem, deconvolution, was solved using the RJMH algorithm. Figure 5 shows the retrieved input profile after oral administration as a capsule using RJMH. A double-peaked input profile comparable to the results of Plusquellec et al. (1987) or Verotta (1996) was obtained, note the location of the breakpoints in the lower panel which group around the peak.

## CONCLUSION

A RJMH algorithm was successfully applied to the (regression and) deconvolution problem, and the performance was demonstrated with several examples including real veralipride data. This automatic determination of breakpoints is especially useful when the function to be retrieved is highly irregular (i.e., double-peaked, triple-peaked, etc.) because of the ability of adapting to the data by putting more breakpoints wherever they are necessary.

We are currently further investigating the benefit of RJMH method using simulated and real studies.

## REFERENCES

- DeBoor, C. (1978) *A Practical guide to splines*. New York: Springer-Verlag.
- Denison, D. G. T., Mallick, B. K. and Smith A. F. M. (1998) Automatic Bayesian curve fitting. *Journal of the Royal Statistical Society Series B*, **60**, 333-350.
- Green, P. J. (1995) Reversible jump Markov chain Monte Carlo computation and Bayesian model determination. *Biometrika*, **82**, 711-732.
- Hannan, E. J. (1987) Rational transfer function approximation. *Statist. Sci.*, **2**, 1029-1054.
- Plusquellec, Y., Campistron, G., Staveris, S., Barre, J., Jung, L., Tillement, J. P. and Houin, G. (1987) A double-peak phenomenon in the pharmacokinetics of veralipride after oral administration: A double-site model for drug absorption. *Journal of Pharmacokinetics and Biopharmaceutics*, **15**, 225-239
- Verotta D. (1996) Concepts, properties, and applications of linear systems to describe distribution, identify input, and control endogenous substances and drugs in biological systems. *Critical Reviews in Biomedical Engineering*, **24**, 73-139.
- IMSL. *QPROG*, City West Boulevard, Houston, TX.

FN1	NMSE	NMAE	Nxi.avg
QNT	0.00146	0.0176	20.8
RJMh	0.000681	0.0141	28.2

Case 1

FN2	NMSE	NMAE	Nxi.avg
QNT	0.000888	0.0220	33.7
RJMh	0.000842	0.0228	27.4

Case 2

Table 1. Comparison of quantile breakpoints and RJMH for curve fitting case 1 (upper table) and curve fitting case 2 (lower table). QNT, quantile breakpoints; RJMH, Reversible-Jump Metropolis-Hastings; NMSE, normalized mean squared error; NMAE, normalized mean absolute error; Nxi.avg, average number of breakpoints among 100 simulations.

	Output			Input			Nxi.avg
	NMSE	NMAE	RMSB	NMSE	NMAE	RMSB	
QNT	0.00695	0.509	0.00726	0.210	0.0498	2.22	12
RJMh	0.00491	0.433	0.00110	0.141	0.0426	1.70	10.5

Table 2. Comparison of quantile breakpoints and RJMH for deconvolution using the hypothetical input function. RMSB, root mean squared bias.

	A	$K_1$	B	$K_2$
SBJ1	6.59	0.303	40.8	7.49
SBJ2	6.11	0.216	50.3	8.34
SBJ3	4.82	0.200	34.6	6.05

Table 3. Estimates of system disposition functions (of the form  $K(t)=A \cdot \exp(-K_1 \cdot t)+B \cdot \exp(-K_2 \cdot t)$ ) for the three subjects of the veralipride example.

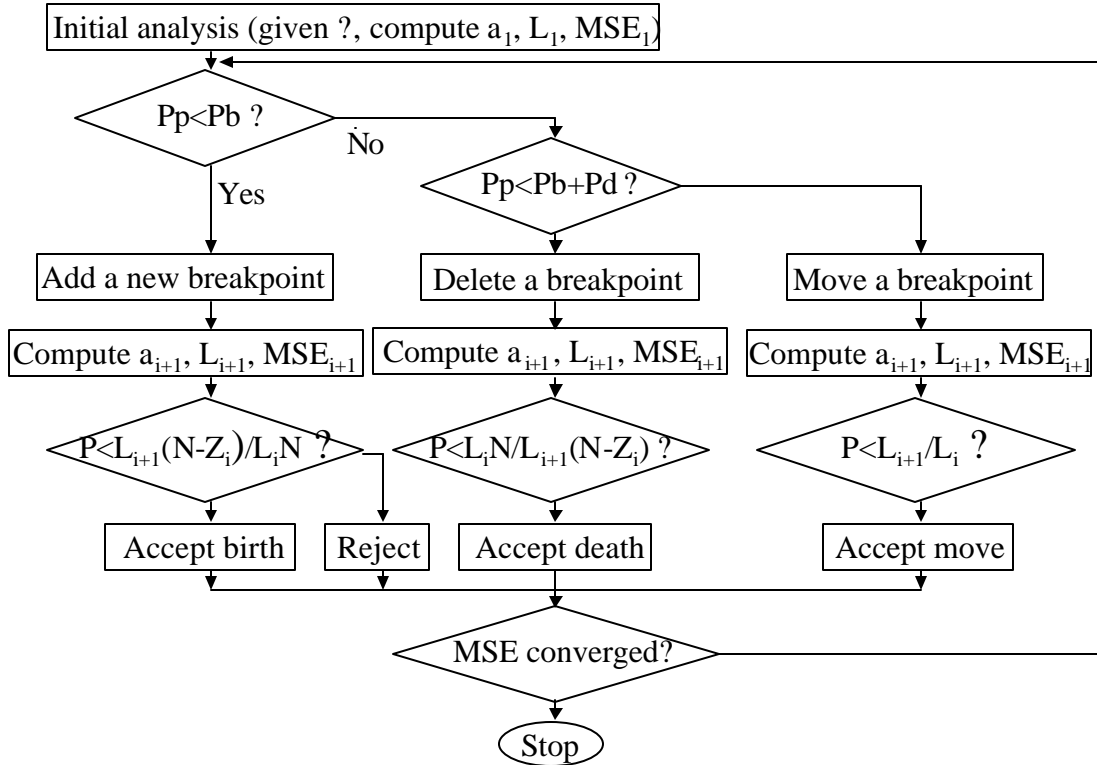


Fig. 1. Flow chart of the Reversible-Jump Metropolis-Hastings algorithm.  $\cdot$ , breakpoints;  $a_{i+1}$ , coefficients in spline representation (of equation (2)) at the  $i+1$ st iteration;  $L_{i+1}$ , likelihood at the  $i+1$ st iteration;  $MSE_{i+1}$ , mean squared error at the  $i+1$ st iteration;  $P_p$ , a random number generated from  $U(0,1)$ ;  $P_b$ , probability of going to birth step;  $P_d$ , probability of going to death step;  $N$ , number of candidate breakpoint locations;  $Z$ , number of candidate breakpoint locations where a new breakpoint cannot be put (see text).

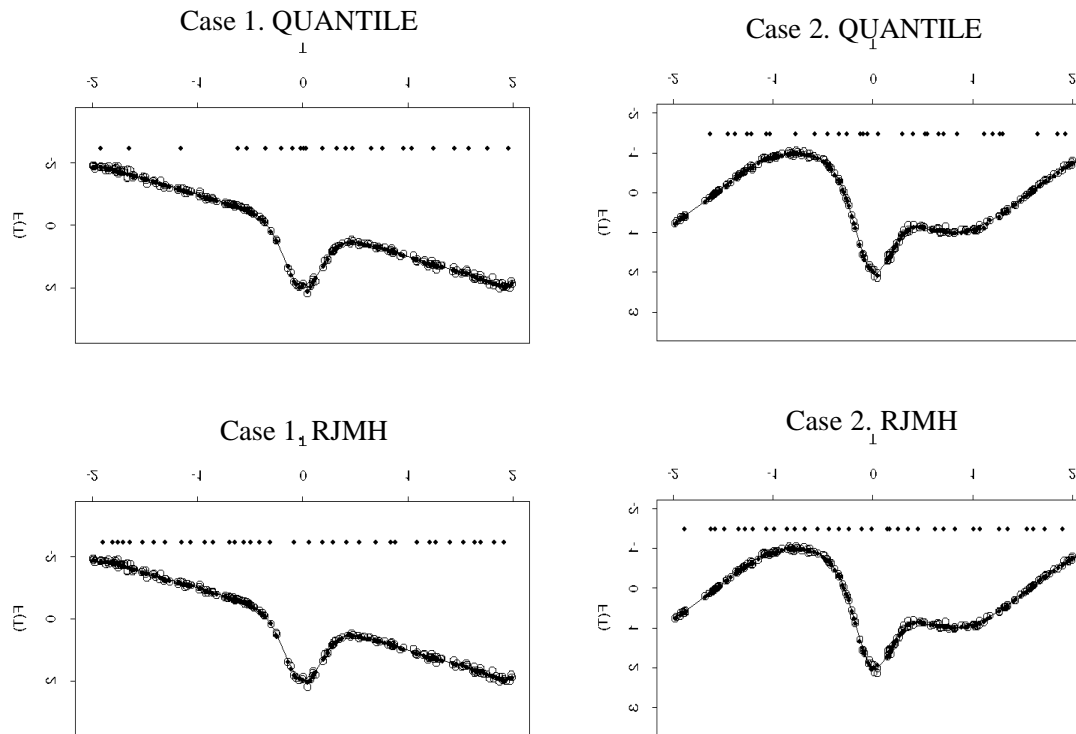


Fig. 2. Examples of the results of regression using the two test functions (case 1 (equation (9)) and case 2 (equation (10))). Upper panels are the results of using quantile breakpoints, and the lower panels are the results of using RJMH. In each figure, the solid line is the true curve ( $F(X)$ ), the open circles are 200 generated data points obtained by adding additive noise of  $N(0,0.4^2)$  for case 1 (left panels) and  $N(0,0.3^2)$  for case 2 (right panels), the filled circles are model predictions, and the dots in the bottom of the figure are the breakpoint locations.

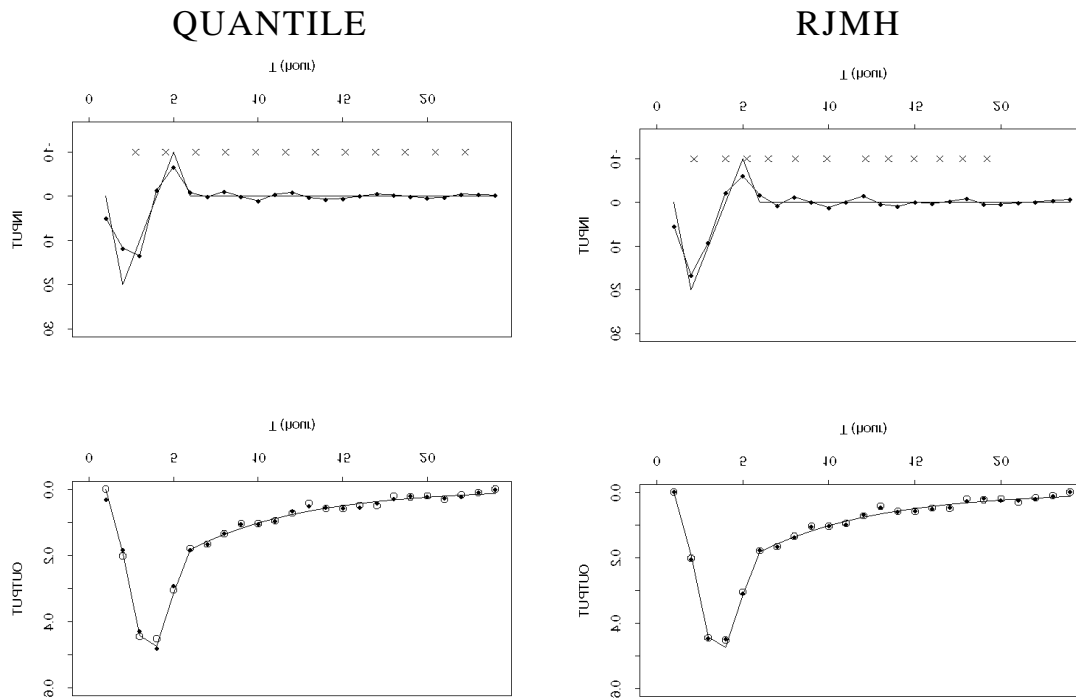
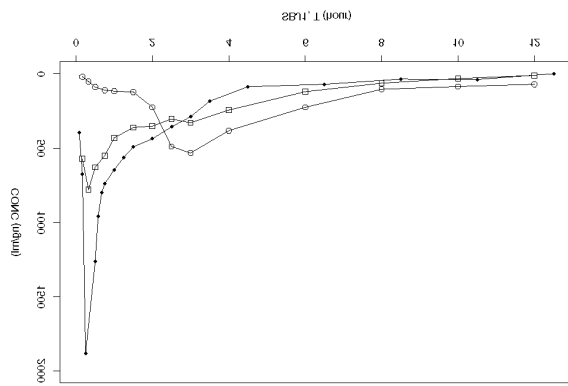


Fig. 3. Examples of the results of deconvolution using hypothetical input function. Left panels are the results of quantile breakpoints, and the right panels are the results of RJMH. In the upper panel figures, the solid line is the true concentration, the open circles are measurements obtained by adding additive noise of  $N(0,0.01^2)$ , and the filled circles are the model predictions. In the lower panel figures, the solid line is the true input profile, the filled circles are estimated input, and the crosses in the bottom are the breakpoint locations.



●: IV  
 □: Solution  
 ○: Capsule

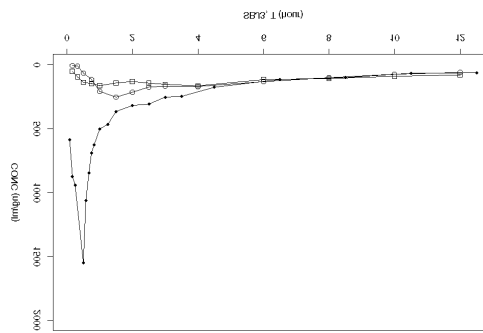
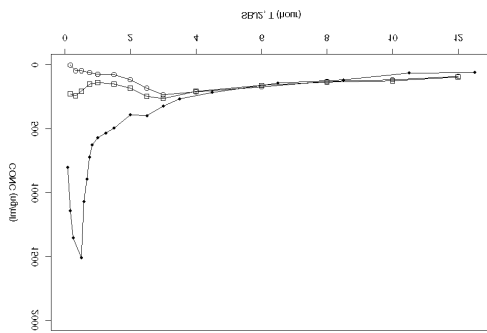


Fig. 4. Plasma concentration data of veralipride after IV or oral (capsule and solution) administration.

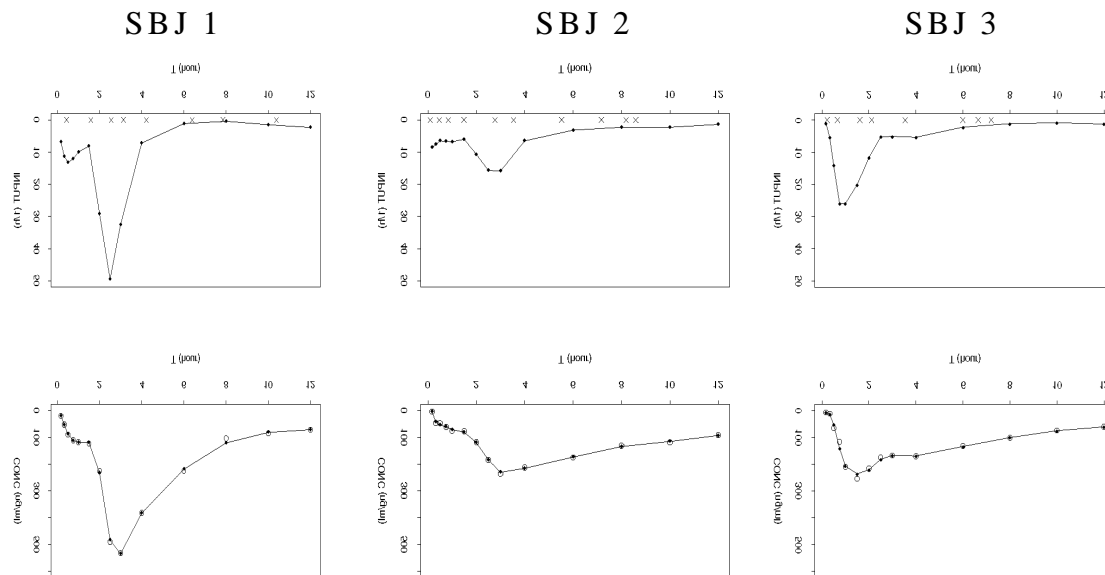


Fig. 5. Measurement data vs. model prediction and estimated input for the three subjects after oral administration of veralipride as a capsule. In the upper panels, the open circles are the measurement data, and the filled circles are the model predictions. In the lower panels, the solid line is the estimated input and the crosses are the breakpoint locations found by RJMH.