

# Estimation of Pharmacokinetic Parameters in Dynamic Contrast Enhanced MRI Via Random Forest Regression

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**Abstract.** We propose a novel alternative approach to estimate pharmacokinetic (PK) parameters of dynamic contrast enhanced (DCE)-MRI. Our approach leverages machine learning field and mainly targets to automatically learn temporal patterns of the voxel-wise concentration-time curves (CTCs) from a large amount of training samples in order to make accurate parameter estimations. We consider the estimation of parameters as a regression problem and specifically use Random Forest (RF) regression. We demonstrate its potential and utility to improve the conventional model-fitting based quantitative analysis of DCE-MRI especially in various noise conditions, and validate our method on clinical brain stroke datasets.

## 1 Purpose

The  $T_1$ -weighted dynamic contrast enhanced (DCE)-MRI is an imaging technique that provides a quantitative measure of pharmacokinetic (PK) parameters, such as vascular permeability ( $K^{\text{trans}}$ ) and fractional plasma volume ( $v_p$ ) [4]. Tracer kinetic (TK) modeling [10,8,9] is usually applied on the dynamic image series to estimate these physiological parameters which can be primarily used for diagnostic purpose in tumor and stroke studies. One of the key limitation of TK modeling methods is that they are simply based on the fitting of the voxel-wise PK parameters to contrast agent concentration-time curves (CTCs). However, the acquired voxel-wise CTCs are generally very noisy, hence the model fitting may likely produce substantial errors in PK parameter mapping [5]. In this work, we demonstrate a machine learning based approach to identify and learn the important features in temporal CTCs to directly output more robust estimates of PK parameters in DCE-MRI.

## 2 Methods

**Dataset.** We perform experiments on fully-sampled DCE-MRI datasets acquired from three patients with first clinically evident mild ischaemic stroke. DCE-MRI was acquired using a 1.5T clinical scanner with a 3D T1W spoiled gradient echo sequence (TR/TE = 8.24/3.1 ms, flip angle = 12°, FOV = 24 × 24 cm, matrix = 256 × 192, slice thickness = 4 mm, 42 slices, 73 sec temporal resolution). The total acquisition time for DCE-MRI was approximately 24 minutes. Two pre-contrast acquisitions were carried out at flip angles of 2° and 12° to calculated pre-contrast longitudinal relaxation times ( $T_{10}$ ).

**Preprocessing.** To generate noisy data, the noise-free (reference) data was corrupted by (1) undersampling the k-space, or (2) adding zero-mean Gaussian noise to the image space. Undersampling was retrospectively done in the  $k_x - k_y$  plane using a randomized golden-angle sampling pattern [11]. Dynamic image intensities  $S(r, t)$  were converted to contrast agent concentration  $C(r, t)$  by the steady-state spoiled gradient echo (SGPR) signal equation [3]. The Parker’s population-based arterial input function (AIF) [7] was generated to obtain PK parameters using Patlak model [8].

**Random Forest Regression.** The parameter estimation task is formulated as a regression problem which takes the voxel-wise  $C(r, t)$  as input and generates the PK parameters ( $K^{\text{trans}}, v_p$ ) as output. In this work, we adopt the random forest (RF) regression that has been shown to be effective in a wide range of classification and regression problems [1,2]. We train a separate RF model to estimate each PK parameter. The overall regression task is defined as,

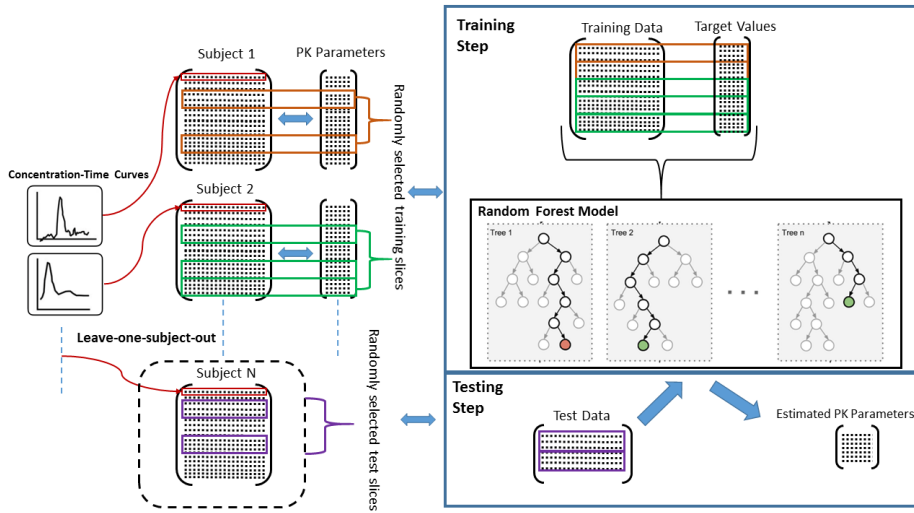
$$\mathcal{M}(C(r_i, t)) = y_i; \quad i \in [1, N], \quad (1)$$

where  $y_i$  is the target parameter value for voxel  $i$ ,  $N$  is the total number of training samples (voxels), and  $\mathcal{M}$  is the trained RF model. The target (reference) PK parameter values were estimated on noise-free data using Patlak model.

**Training-Testing.** Training and testing were carried out based on leave-one-patient-out cross-validation. The RF model  $\mathcal{M}$  was trained with almost 340K voxels to learn important features from the input data to attain better parameter estimation. The pipeline of training-testing of RF model is shown in Figure 1.

**Evaluation.** The parameter estimates of our RF based method was compared with the estimations obtained from Patlak model in both noise-free and various noise conditions. The root-mean-square-error (RMSE) was used for quantitative evaluations of parameter estimation based on the following formula,

$$RMSE = \sqrt{\frac{1}{N_i} \sum_{i=1}^{N_i} (y_i - f_i)^2}, \quad (2)$$

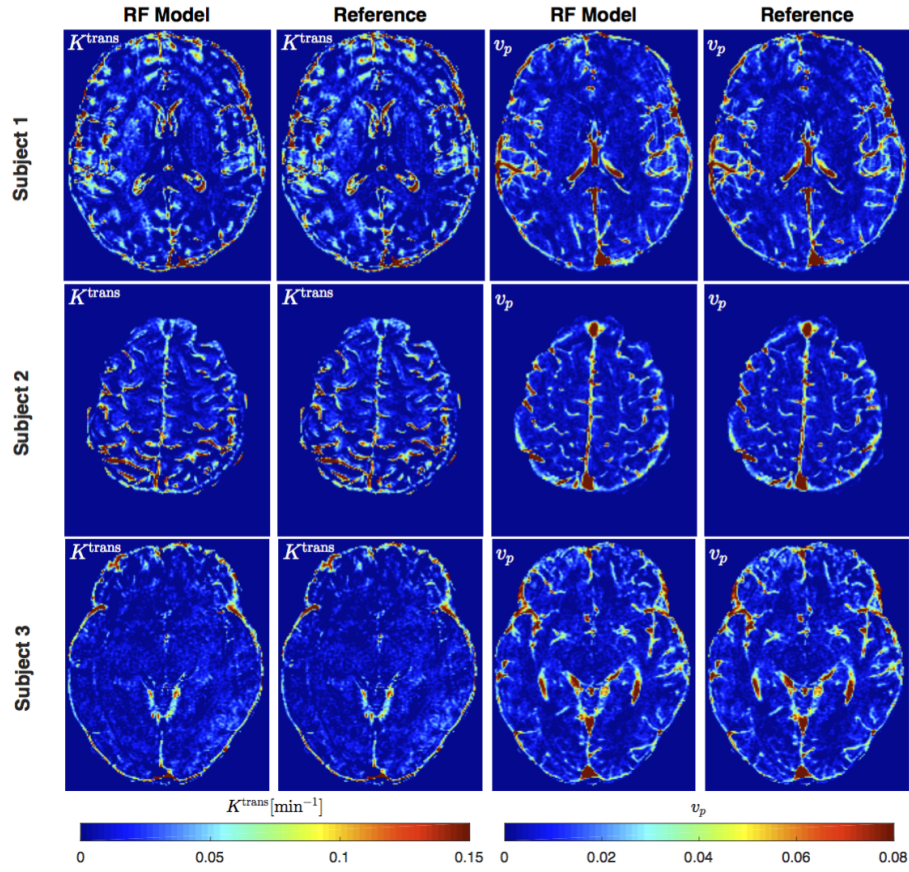


**Fig. 1.** A diagram illustrating the pipeline of the training and testing procedures of our method. Each subject’s data is represented with a matrix where each row involves a concentration-time curve (CTC) per voxel. Training data is created from randomly selected 12 slices of held-in subject’s data and test data is obtained from randomly selected 2 slices of held-out subject’s data. A RF model is trained from the training data and its corresponding target values. Testing is then performed by giving the test data as input to the RF model which outputs the estimated PK parameters. This process is repeated 50 times (trials) for each subject to obtain unbiased estimation.

where  $y_i$  is the target value,  $f_i$  is the estimated value, and  $N_i$  is the number of test samples.

### 3 Results

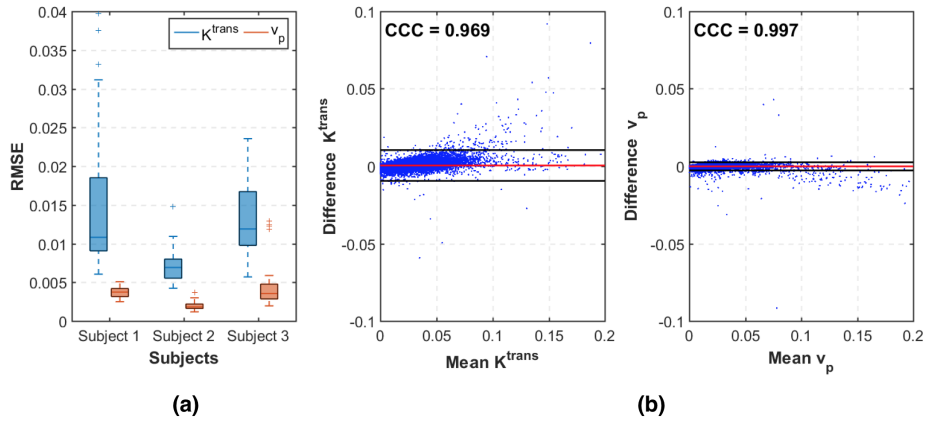
Figure 2 shows PK parameter maps estimated from noise-free data. The proposed RF model can yield parameter maps that are highly similar to reference. This is also evident in Bland-Altman plots shown in Figure 3. From the RMSE statistics in Figure 3, we can clearly observe that RF model provides more accurate estimation of  $v_p$  than  $K^{\text{trans}}$ . Figure 4 depicts estimated PK maps in various noise conditions. The proposed RF model is able to mitigate the over-estimation of parameters that is observable in Patlak model and caused by high level of noise introduced into the data. Figure 5 quantitatively reveals that RF regression model achieves lower RMSE of PK parameters with respect to increasing noise levels, therefore it appears more robust to noise than Patlak model.



**Fig. 2.** PK parameter maps estimated by RF model on noise-free data taken from each subject. The reference maps are also provided for comparison. In no-noise condition, the estimated maps by RF model are almost similar with reference maps. This asserts that it is possible to directly estimate accurate PK parameters of a subject using other subject’s data with the use of a RF based machine learning approach.

## 4 Conclusion

We have demonstrated a new machine learning based approach to directly estimate PK parameters in DCE-MRI. This approach leverages large cohort of training data to learn significant characteristics and features of CTCs. Extensive experiments validated its efficacy in parameter estimation and robustness to various noise levels. The proposed method is considerably faster than conventional model fitting. Training more than 300K samples takes around 5 minutes whereas testing takes only 1 second per slice. Future studies will involve improving the estimation performance of RF model for high subsampling rates to potentially enable accelerated acquisitions of DCE-MRI, and testing it on different tracer ki-



**Fig. 3.** (a) Boxplot displaying the RMSE statistics of PK parameters for each subject estimated from RF method on noise-free data. (b) Bland-Altman plots and 95% confidence intervals within two black lines for  $K^{\text{trans}}$  (left) and  $v_p$  (right) parameters of Subject 1. The RF model yields significantly lower median RMSE and less variance for  $v_p$  compared to  $K^{\text{trans}}$ . The difference (bias) between estimated and target values for both PK parameters are very close to 0. This indicates that estimated parameters by RF model significantly overlap with target values as quantitatively evaluated with concordance correlation coefficients (CCCs) displayed at the top-left corner of Bland-Altman plots.

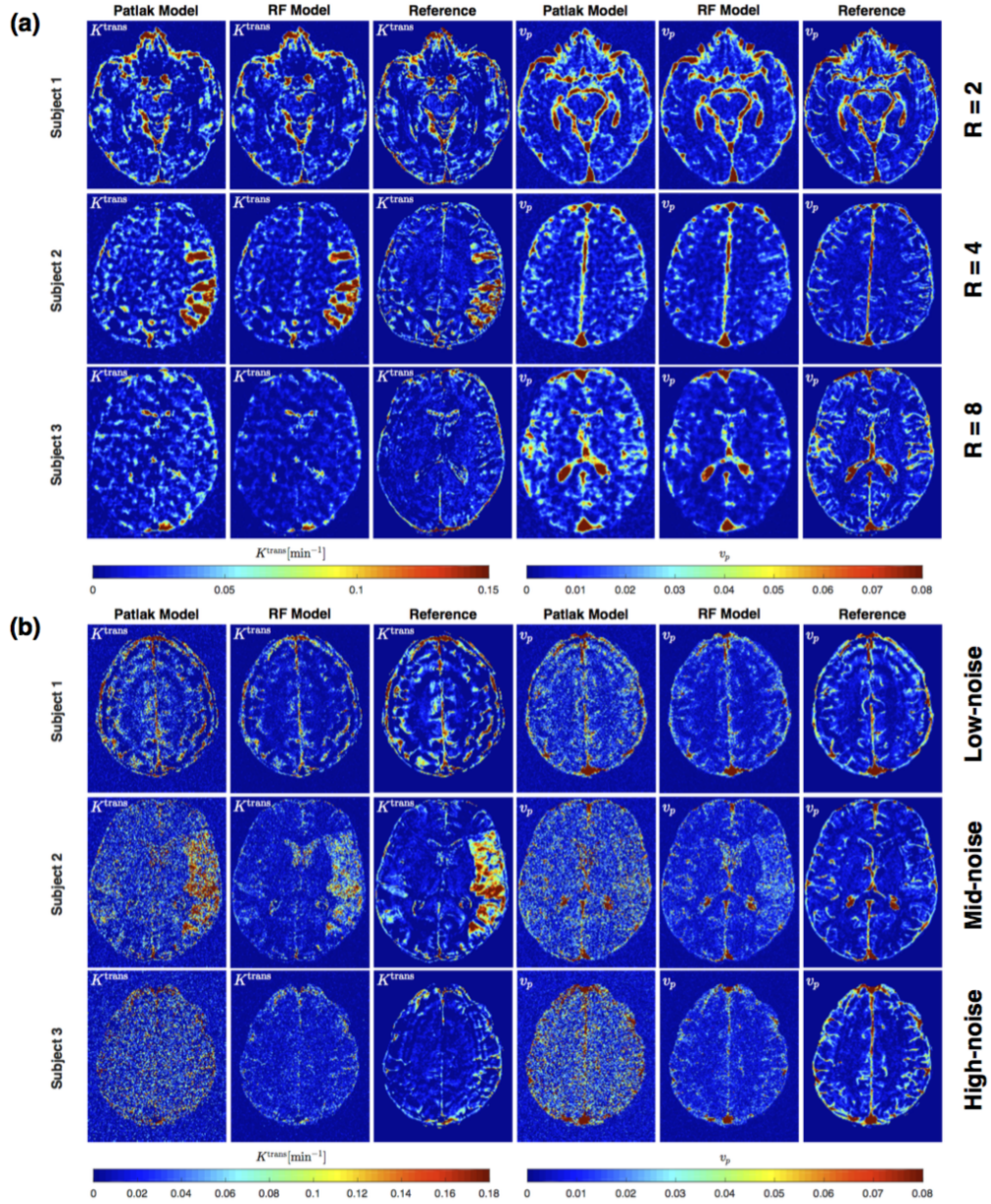
netic models such as extended Tofts model [10] and two-compartment exchange model [6].

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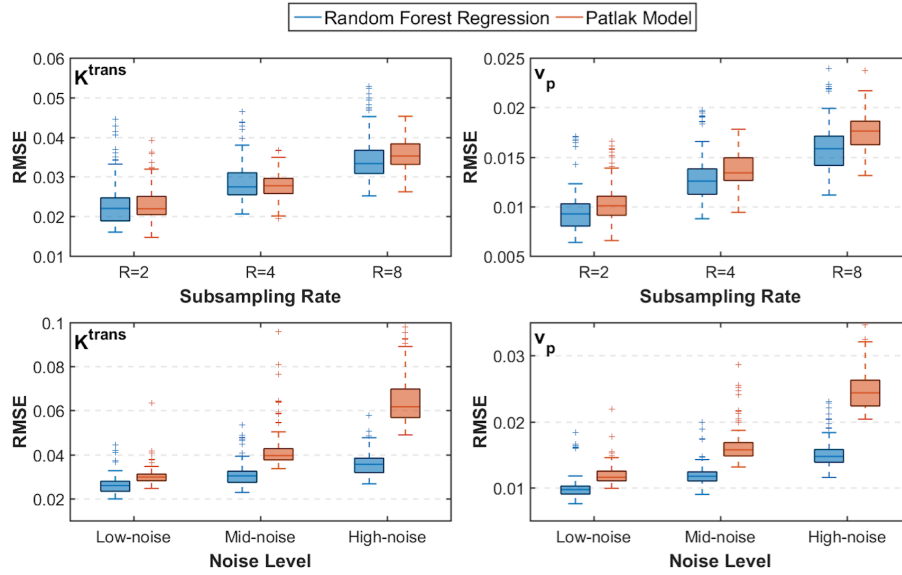
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**Fig. 4.** PK parameter maps estimated by RF regression model and Patlak Model in various noise conditions: (a) Increasing subsampling rates, (b) Increasing Gaussian noise levels. The reconstruction of undersampled data was performed via direct FFT. The reference maps are also provided for comparison. The Patlak model usually produces over-estimated PK parameter regions and corrupted or missing boundaries inside the brain when the level of the noise introduced into the data is increased. However, RF model can considerably eliminate these deficiencies and yield parameter maps which are closer to reference maps. The results demonstrate that RF model is more robust to noise than Patlak model.



**Fig. 5.** Boxplots displaying the RMSE statistics of PK parameters –  $K^{trans}$  (left),  $v_p$  (right) – obtained from our RF regression model and Patlak model on noisy data. The top plots depict results for increasing subsampling factors whereas the bottom plots show results for increasing additive Gaussian noise levels. The RMSE statistics are reported from in total 150 trials of three subjects. The results demonstrate that RF model mostly produces lower median RMSE compared to Patlak model for both PK parameters. Another main conclusion is that RF model is more robust to increasing noise levels rather than subsampling rates.