#### **Supplementary Information for the Paper:**

# **Predictive Modeling the Progression of Alzheimer's Disease with Recurrent Neural Networks**

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#### **Detailed data information**

Supplementary Table S1 shows the feature categories and their corresponding variables used in this study. Some variables were derived from the original dataset by the authors. Note that the descriptions of most variables are directly extracted from the National Alzheimer's Coordinating Center (NACC) Researcher's Data Dictionary — Uniform Data Set (RDD-UDS). The types of variables were assigned by the authors.

<b>NACC</b> <b>Categories</b>	<b>Variable</b> <b>Name</b>	Variable <b>Type</b>	Descriptions <sup>1</sup>			
AD stage	<b>CDRGLOB</b>	Ordinal	Global CDR score, which is used to define the AD progression stages in this study,			
Time interval TI		Continuous	Derived by authors; Time interval between two consecutive visits			
<b>Subject</b> A1 <b>Demographics</b>	AGE	Continuous	Derived by authors			
	<b>SEX</b>	Nominal	Subject's sex			
	<b>RACE</b>	Nominal	Subject's race			
	<b>PRIMLANG</b>	Nominal	Primary language			
	<b>EDUC</b>	Ordinal	Years of education			
	<b>NACCLIVS</b>	Nominal	Living situation			
	<b>INDEPEND</b>	Ordinal	Level of independence			
	<b>RESIDENC</b>	Nominal	Type of residence			
	<b>MARISTAT</b>	Nominal	Marital status			
	<b>HANDED</b>	Nominal	Is the subject left- or right-handed?			

Supplementary Table S1. Feature categories and variable descriptions

<span id="page-0-0"></span> <sup>1</sup> National Alzheimer's Coordinating Center (Walter A. Kukull, PhD, Director), Researcher's Data Dictionary — Uniform Data Set (RDD-UDS), version 3.0, March 2015.







#### **Implementation tools**

Logistic Regression (LR), Support Vector Machine (SVM), Decision Tree (DT) and Random Forest (RF) models were implemented in the Scikit-learn v0.19.1 with sklearn.linear\_model.LogisticRegression, sklearn.svm.LinearSVC, sklearn.tree.DecisionTreeClassifier, and sklearn.ensemble.RandomForestClassifier, respectively. The proposed RNN models were implemented with the Tensorflow.

## **Implementation information for the proposed RNN model**

### Input padding

After the data imputation and encoding was completed, the input had 234 dimensions (the dimensions would be 233 for the model without time intervals). The output stayed the same with 5 dimensions. For a patient, the number of his/her visits defines his/her time step dimension. Because the input of each patient to the model requires the same length of sequences in the time step dimension, zero sequences were padded to the input matrix to get the same length with respect to ones who had the maximum visits. In addition, since the proposed model has a time window shift between the input and the output, a pad with zero vectors for the  $(T + 1)$ <sup>th</sup> visit was performed on the input.

#### Network parameters initialization

In the constructed network in this study, each hidden unit was an LSTM cell and the Softmax function was used as the activation function of the output layer. The initialization value of each weight of the network was generated from a truncated normal distribution so that a large variance can be avoided. Technically, the initialization value of each weight was first generated from a predefined normal distribution, i.e.,  $N(\mu, \sigma^2)$ . If the generated value was within the range of  $[\mu - 2\sigma, \mu + 2\sigma]$ , then the value would be taken as the weight initialization value, otherwise the value would be discarded; the initialization process repeated until an appropriate initialization value was obtained. Note that  $\mu$  and  $\sigma$  were the mean and the standard deviation of the normal distribution, which were set to 0 and 0.001, respectively. The initialization values of biases were constant, which were set to 0.001 in this study.

#### Hyper parameters for the training process

In this study, learning rate decay and moving average decay mechanisms were used to train the proposed model to achieve the best performance effectively.

When an RNN model is trained, learning rates play a key role in its converging process. Large learning rates will lead to large fluctuation in the values of learned parameters, resulting in that the model has a difficulty in getting converged. While small learning rates will usually result in a slow converging process. Hence, a chosen learning rate should be neither too large nor too small. To tackle the challenge in setting a right learning rate, a flexible learning rate scheme was used in this study. Technically, the training process starts with a base learning rate, and then in each epoch the learning rate decreased exponentially with a given decay rate. Note that an epoch means that the training process performs completely on the whole training dataset. The training process will keep going until the model gets converged or the training computation reaches the designated maximum of iterations. According to the learning rate decay mechanism that was described above, the base-learning rate was set to 0.01. The learning rate decreased exponentially in the training process with a decay rate 0.96.

Exponential moving average decay mechanism was applied to make the model more robust. In detail, an exponential moving average class was defined for all the training variables, i.e., weights and bias. Moving average decay was applied and accordingly the moving average for the variables got repeatedly updated throughout the training iterations. Note that the decay rate of the moving average mechanism will be responsible for model updating rate. For the initialization, the decay rate of the moving average mechanism is set to 0.99 and it will be adjusted dynamically in the train process. To avoid overfitting, we used L2 regularization by assigning the regularization rate to 0.0001.

Moreover, we used the 10-fold cross-validation to evaluate the predictive model: randomly partition the data into 10 equal size subsets, and 9 subsets are used to train the model and the remaining one is used to test the model, and the process is then repeated 10 times/folds. Then we get the performance of the model by averaging the 10 test results from the folds.

For each fold of the cross validation, we used the mini-batch method for the model training. The batch size was set to 60. We performed 200 epochs on the whole training dataset. In addition, at the beginning of each training epoch, we shuffle training dataset. At the end of each epoch (i.e., a training process has been performed completely on the whole training dataset once and a trained model has been achieved), we use the test dataset to test the trained model to detect the trend of the model performance. The model performance of each fold was derived from the  $200<sup>th</sup>$  epoch. For example, Figure 1 and Figure 2 show the loss and the accuracy of training data and test data in one specific fold of the 10-fold cross validation for the proposed model *LSTM with TI*.



(A) Loss of training data



(B) Loss of testing data

Supplementary Figure S1: Loss of trianing data and testing data of the first fold (*LSTM with TI*)



(A) Accuracy of training data



(B) Accuracy of testing data

Supplementary Figure S2: Accuracy of trianing data and test data of the first fold (*LSTM with TI*)

## **Accuracy, PPIA, SPIA in each fold for Table 3 and Table 4 in the main text**

Accuracy, PPIA and SPIA in each fold of 10-fold cross validation for all models in this study are illustrated in the following tables (Supplementary Table S2 – Supplementary Table S14).



Supplementary Table S2. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (*LSTM with TI*)

Supplementary Table S3. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (*LSTM w/o TI*)



Supplementary Table S4. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (LR)



3rd-Fold	0.7793	0.7296	0.7808	0.6953	0.5867	0.6967	0.6777	0.5612	0.6791
4th-Fold	0.7891	0.7213	0.7891	0.6680	0.5082	0.6680	0.6699	0.4973	0.6699
5th-Fold	0.7676	0.6847	0.7736	0.6816	0.5271	0.6870	0.6855	0.5517	0.6909
6th-Fold	0.7949	0.7083	0.7965	0.6660	0.4896	0.6654	0.6855	0.5104	0.6849
7th-Fold	0.7891	0.7192	0.7984	0.6445	0.4975	0.6502	0.6602	0.4828	0.6660
8th-Fold	0.7656	0.6335	0.7671	0.6602	0.4293	0.6614	0.7090	0.5026	0.7104
9th-Fold	0.8047	0.7612	0.8107	0.6484	0.5373	0.6529	0.6387	0.5025	0.6430
10th-Fold	0.8145	0.7173	0.8193	0.6797	0.5026	0.6837	0.7266	0.5969	0.7308
<b>Mean</b>	0.7955	0.7126	0.7986	0.6652	0.5057	0.6674	0.6803	0.5209	0.6825
Std. Dev.	0.0216	0.0345	0.0211	0.0162	0.0409	0.0163	0.0243	0.0370	0.0243

Supplementary Table S5. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (SVM)



Supplementary Table S6. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (DT)



6th-Fold	0.7031	0.6146	0.7045	0.5957	0.4896	0.5969	0.5976	0.4531	0.5969
7th-Fold	0.6973	0.6749	0.7055	0.5625	0.4138	0.5672	0.5566	0.4680	0.5632
8th-Fold	0.6758	0.5916	0.6771	0.5918	0.4450	0.5930	0.5976	0.4031	0.5988
9th-Fold	0.6895	0.6070	0.6943	0.5723	0.5025	0.5759	0.6093	0.5224	0.6134
10th-Fold	0.7188	0.6073	0.7230	0.5898	0.4764	0.5914	0.5781	0.5079	0.5815
<b>Mean</b>	0.7035	0.6223	0.7058	0.5810	0.4463	0.5829	0.5916	0.4705	0.5934
Std. Dev.	0.0206	0.0267	0.0200	0.0199	0.0470	0.0196	0.0204	0.0458	0.0196

Supplementary Table S7. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (RF)



Supplementary Table S8. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without CDR)





Supplementary Table S9. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without GDS)



Supplementary Table S10. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without FAQ)



Supplementary Table S11. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without CDR, GDS)





Supplementary Table S12. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without CDR, FAQ)



Supplementary Table S13. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without GDS, FAQ)





Supplementary Table S14. Values of Accuracy, PPIA and SPIA of 10-fold cross validation (Model without CDR, GDS, FAQ)



Supplementary Table S15. Mean and standard deviation of 10-fold cross validation (full model, basic model, and basic model with incorporating one feature of CDR/FAQ category at a time)



