

Predicting Disease Progress with Imprecise Lab Test Results

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ABSTRACT

In existing deep learning methods, almost all loss functions assume that sample data values used to be predicted are the only correct ones. This assumption does not hold for laboratory test data. Test results are often within tolerable or imprecision ranges, with all values in the ranges acceptable. By considering imprecision samples, we propose an imprecision range loss (IR loss) method and incorporate it into Long Short Term Memory (LSTM) model for disease progress prediction. In this method, each sample in imprecision range space has a certain probability to be the real value, participating in the loss calculation. The loss is defined as the integral of the error of each point in the impression range space. A sampling method for imprecision space is formulated. The continuous imprecision space is discretized, and a sequence of imprecise data sets are obtained, which is convenient for gradient descent learning. A heuristic learning algorithm is developed to learn the model parameters based on the imprecise data sets. Experimental results on real data show that the prediction method based on IR loss can provide more stable and consistent prediction result when test samples are generated from imprecision range.

CCS CONCEPTS

• **Computing methodologies** → **Neural networks**; • **Applied computing** → **Health informatics**.

KEYWORDS

Prediction, neural networks, imprecise data, health care

1 INTRODUCTION

In healthcare, it is highly desirable to evaluate the current situation of a patient and predict his/her disease development. This evaluation and prediction provide a basis for treatments including the medication strategy, non-routine checkup, early active interventions, etc. Deep neural networks (DNNs) have been increasingly applied to the prediction, prevention, diagnosis and prognosis of diseases, leading to a promising capability for better decision-making [4][3]. Although DNNs have proven their merits in various tasks, the performance in noise, disturbance and imprecise data remains a challenge. Obtaining more stable and robust medical deep learning models is at the forefront of machine learning in healthcare.

Clinical lab tests play an important role in healthcare. From early detection of diseases to diagnosis to personalized treatment programs, lab tests guide more than 70% of medical decisions and personalized medication [2]. However, due to limitations of equipment, instruments, materials, test methods, etc., data inaccuracy always occurs [1][14] and has to be dealt with. Typically, test results are within respective tolerable ranges (or imprecision ranges,

values in this range are acceptable though imprecise). In our previous work [12], we studied the impact of imprecision on prediction results where a pre-trained model is used to predict future state of hyperthyroidism for patients. It was demonstrated that small ranges of imprecisions can cause large ranges of predicted results, which might cause mis-labeling and inappropriate actions (treatments or no treatments) for individual patients. In this paper, we study the issue of building robust models while taking imprecision into account with better generalization.

In image classification, it has long been found that if one image is visually imperceptibly perturbed, a prediction label may be different. To overcome this problem, a popular solution is noise injection [6]. The main focus was on methods to generate useful noisy or adversarial examples. By including noise-injected examples in training, resulting classification models are more sensitive to discriminate these images. In healthcare, adversarial patients have also been studied in different kinds of classification task [9][8]. Obviously, samples in imprecision range are not noise, since imprecise samples are also accepted values. The above approaches need to be extended to address imprecision range problem readily.

In existing deep learning methods, loss functions play a central role in model learning. By calculating the local gradient of a loss function, the gradient descent (GD) algorithm updates the model parameters in each iteration. Virtually all loss functions assume that the values in a learning dataset are the only correct values. A predicted value based on these is then used to calculate the loss for gradient descent. However, in lab tests for patients, the values in imprecision range usually have some probability of true values. By assuming the lab test results have the only correct values, the learned model will likely deviate from the real model, leading to incorrect, inconsistent predictions when predicting new samples.

In this paper, “IR loss” is proposed and incorporated into LSTM model for disease progress prediction. In our method, each data in imprecision range space has a certain probability to be the real value, participating in the loss calculation. So the loss is defined as the integral of the error of each point in the impression range space. Then the sampling method for imprecision space is designed. The continuous imprecision space is discretized, and a sequence of imprecise data sets are obtained. Then a heuristic learning algorithm is proposed to learn the model parameters based on the imprecise data sets sequentially. Experimental results on a real dataset show that the prediction method based on IR loss is more robust, which can provide more stable and consistent prediction result when test samples are generated from imprecision range.

The paper is organized as follows. Section 2 discusses related work. Section 3 introduces the proposed loss function and the corresponding model learning method. Section 4 presents experimental results. Section 5 concludes the paper.

*A part of work is done while visiting UCSB.

2 RELATED WORK

One area of work studied the influence of variety forms of input perturbations through experimental or theoretical analysis. In [13], an iterative algorithm was developed for approximately compute the sensitivity from neuron to layer, and finally to the entire CNN network. Impact of data precision on learning was first observed in our earlier paper [12], which also discussed related work. This paper continues the study by developing an effective learning method.

To learning against input perturbations, a popular method is noise injection [10][6]. By adding the noisy or adversarial samples into training process, the model is expected to have more distinguish ability in classification task. The studies focused more on to generating such samples. In healthcare field, adversarial patient are defined and examined in [8]. Different methods [7][5] were provided to generate adversarial examples in medical deep learning classifiers. Obviously, we cannot treat each samples in imprecision range as noise, since imprecise samples could be accepted values. So the current solution cannot be used into imprecision problem readily. How to use unseen imprecise samples to build a more robust model is addressed in this paper.

For discretize the continuous input space, interval valued data regression method provides a potential solution. In [11], each interval valued observation was viewed as a hypercube. By dividing each side of a p -dimensional hypercube into m equal parts to discretize the interval data. However, the data in this paper is essentially different from interval data. In the interval method, each data value is an interval (e.g., cluster data) represented as a minimal and a maximal value. In this paper, a test result is single-valued element, but its value can be possibly anyone in imprecision range.

3 METHOD

In this paper, a prediction model f is developed to predict the progress of hyperthyroidism two years in advance based on the blood test data in the first k months. That is $y=f(x)$, where x is the blood test result sequence in the first k months. y is the predicted values two years later. After we obtain the predicted test values, the disease progress is obtained by analyzing the “normal”, “abnormal” states of the test measures. Since x can be regarded as a time series, we exploit LSTM as our basic prediction model. In the traditional LSTM modeling and training process, SGD method are often used to learn the model parameters based on an loss function. The traditional loss for a training sample x is:

$$L(x) = |y - f(x)|^\alpha \quad (1)$$

where α is 1 or 2, corresponding to the commonly used absolute loss function and square loss function.

In Equation (1), x is the group of blood test results. Each test value has an imprecision range, any value from this range is also acceptable. Obviously, the loss defined in Equation (1) does not consider the samples in the imprecision range. It simply assumes the lab test value is the only correct one. The predicted result based on this value is used to calculate the loss and gradient. If it is not the correct value, the above calculation may cause the deviation in parameter learning and correspondingly the inaccurate, inconsistent prediction results for the test data.

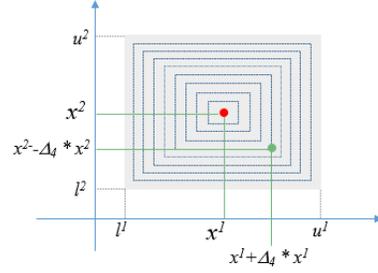


Figure 1: The discretization example in two dimensional space.

To deal with the above problem, we modify the imprecision range loss. Let $Ipr(x)$ denote the imprecision range for x . Assume data $x' \in Ipr(x)$ is the true value with a certain probability $p(x')$, then the loss at x could be defined as:

$$L_D(x) = \int_{Ipr(x)} P(x)L(x)dx \quad (2)$$

where $P(x)$ is the probability of x being the true value such that $\int_{Ipr(x)} P(x)dx = 1$. The probability $P(x)$ can also be regarded as the weight to control each samples in imprecision range contributed to the total loss of x . When $P(x) = 1$ and $P(x') = 0$ for each $x' \in Ipr(x)$ and $x' \neq x$, Equation (2) degenerates to the traditional loss function $L(x)$ in Equation (1). In this case, x is the only correct value.

The total loss for all training samples is given as:

$$Loss = \sum L_D(x) = \sum_{x \in D} \int_{Ipr(x)} P(x)L(x)dx, \quad (3)$$

The right side of the above equation is a continuous integral term, and is possibly hard to evaluate. We consider to simplify it by discretization. Since each x is a multivariate variable. Its imprecision ranges form an imprecision space with infinitely dense points. We use the points with fixed size steps to discretize this space.

Let x^k denote a single blood test result, r denote its maximum acceptable range as a percentage. The lower and the upper boundary are then $x^k \pm r * x^k$. We uniformly generate the imprecise sample x^k with fixed step s . The sample scale is defined as $\Delta_j = \Delta_0 + (j-1) * s$, where $\Delta_0 = 0$, $j = \{1, 2, \dots, N\}$, N is the total number of steps. Obviously, we have $N = r/s$. For example, if $r = 10\%$, $s = 0.01$, we have $N = 10$, and $\Delta = \{0.01, 0.02, \dots, 0.1\}$. This process can be easily extended to multidimensional input. Fig. 1 illustrates an example in a two-dimensional space. l^1, u^1, l^2, u^2 are the lower and upper boundaries of the imprecision space for the two dimensional input value $x = \{x^1, x^2\}$. The green dot is the generated imprecision sample when $\Delta = 0.04$. In this way, the discretized imprecision sample x_j is generated from its imprecision range as follows:

$$x_j = x \pm \Delta_j * x \quad (4)$$

For each sample x , we generate a set of imprecision samples $\{x_1, x_2, \dots, x_N\}$ from its imprecision space. Let x^0 be the lab returned value x . We further assume samples by using the same scale Δ share the same weight. We discretize the weight vectors $\{w_0, w_1, \dots, w_N\}$

from function $P(x)$. Then the loss could be updated as:

$$Loss = \sum_{x \in D} L_D(x) = \sum_{x \in D} \sum_{x_i \in I_{pr}(x)} P(x_i) L(x_i) \quad (5)$$

$$= \sum_{x \in D} \sum_{j=0}^N w_j L(x_j) \quad (6)$$

Equation (6) is also rewritten as $\sum_{x \in D} w_0 L(x) + \sum_{x \in D} \sum_{j=1}^N w_j L(x_j)$. The term $\sum_{j=1}^N w_j L(x_j)$ carries two meanings. The prediction based on each accepted samples in the imprecision range should be as centralized and close as possible. At the same time, all predictions should be as close as possible to the true value. It implies that the learning results should be accurate and stable, and consequently more trustable.

Further, the imprecision samples with the same sample scale Δ_j are grouped together to form the data set D_j . Then the loss could be rewritten as:

$$\begin{aligned} Loss &= \sum_{x_0 \in D_0} w_0 L(x_0) + \sum_{x_1 \in D_1} w_1 L(x_1) + \dots + \sum_{x_N \in D_N} w_N L(x_N), \\ &= \sum_{j=0}^N Loss_{D_j} \end{aligned} \quad (7)$$

where $Loss_{D_j} = \sum_{x_j \in D_j} w_j L(x_j)$.

The goal of model training is to find the optimal model parameters $\hat{\theta}$ to minimize the loss function defined in Equation (7):

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} Loss \quad (8)$$

To achieve this goal, we divide the global optimization problem into the combination of optimization problems on each individual imprecision set D_i . It is reasonable to assume that the closer to the center point x , the greater the weight should be. So we have $w_0 > w_1 > w_2 > \dots > w_N$. The model is trained sequentially from larger weights to smaller ones. Specifically, the model is trained on the first data set D_0 to obtain the initial parameters by minimizing $Loss_{D_0}$. Then, on the basis of the initial model, we use D_1 for the next training round to get model f_1 . The above process is carried out in turn. The final prediction model f_N is obtained after N iteration. The detailed learning process is illustrated in Algorithm 1.

Algorithm 1: Model learning

Input: training set

Output: model θ

0. SGD learning $\hat{\theta}_0$ by minimizing the loss $Loss_{D_0}$;
 1. for each $D_i \in \{D_1, D_2, \dots, D_N\}$;
 2. Initial model parameter using θ_{i-1} ;
 3. SGD training new θ to obtain f_i ;
 4. update model $f = f_i$;
 5. end for
 6. return final model f_N
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4 EXPERIMENTAL EVALUATIONS

4.1 Experimental Setup

There are 2,460 patients in the hyperthyroidism dataset used in our experiments, which is generated from Ruijin hospital, a reputable

hospital in Shanghai, China. The whole dataset is divided into a training set and a test set, with 1960 patients and 500 patients respectively. For hyperthyroidism disease, the blood test measures FT3, FT4, TSH, and TRAb are used for prediction.

In the LSTM network, there are 2 hidden layers, each layer containing 128 LSTM cell units. We employ dropout method to reduce over-fitting and apply the Adam-Optimizer in training. Each experiment runs for 10 times and each data given in the experimental results is the average of the 10 runs. For the parameter setting, r is set to be 10% and $s = 0.1$, then Δ is 0.01 ~ 0.1 with interval 0.01 to generate $D_1 \sim D_{10}$.

4.2 Evaluation Metrics

After predicting $f(x)$, the label $l(f(x))$ for “normal”, “abnormal” description can be obtained by comparing the value of $f(x)$ with the reference range. We use *Accuracy* to measure the label prediction accuracy of the prediction method. Given one label l , let TP model the positive samples in the test set and the predictions are correct. TN represents the negative samples and the predictions are correct. For each test patient x , we generate the imprecise sample x_j , $j = \{1, 2, \dots, N\}$ from its imprecision range. In order to measure the value prediction accuracy, we further define the *Distance* metric, which is the distance from the predicted value based on imprecision samples to the real value.

$$Accuracy = \frac{|TP| + |TN|}{|D_{\text{Test}}|}$$

$$Distance = \sum_{j=1}^N |f(x_j) - y|^\alpha$$

4.3 Findings

In experiments, we compare the performance of the new Imprecision Range Loss (IR Loss) with the one by adopting the traditional Least Square Error loss (LS Loss).

Fig. 2 illustrates the *Accuracy* comparisons. We can see that the average *Accuracy* and the *Accuracy* of all the four test measures based on the proposed method are higher than the traditional ones. Especially for the TRAb measure, there are 4% improvements.

From the definition, the metric *Distance* describes the degree of deviation between the predicted values and the true values when x are sampled from the imprecision range. According to Fig. 3, we can see that the *Distance* of the proposed method are all smaller than the traditional method. It demonstrates that the method based on the proposed IR loss could provide more consistent prediction in the small range.

Our previous work demonstrated that the performance declines when test samples are generated from its imprecision range [12]. To see how the proposed IR loss address this problem, in Fig. 4, we provide the results when the proposed method applied to imprecise test data when *Delta* is set to be different values. From the figure, we can see that the accuracy of the proposed IR loss is always higher than that of traditional loss. In addition, when Δ increases, the decrease rate of *Accuracy* of the proposed method is much lower than that of the traditional method. This trend is more obvious when Δ is large.

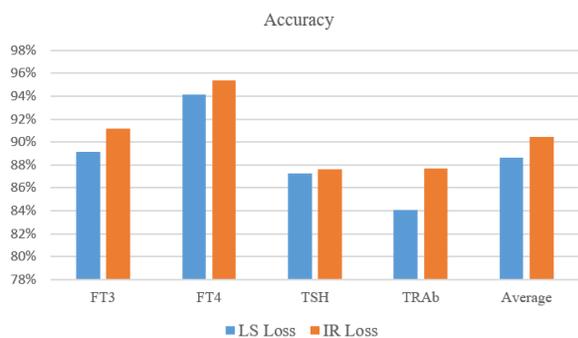


Figure 2: The Accuracy comparison of LS loss and IR Loss

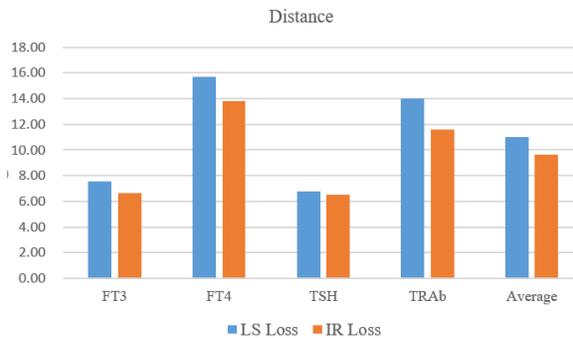


Figure 3: The Distance comparison of LS loss and IR Loss

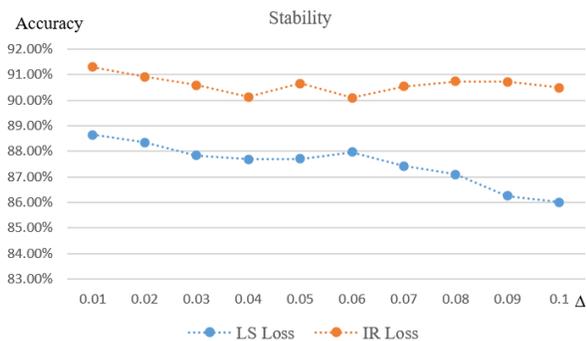


Figure 4: The prediction stability of the proposed IR Loss

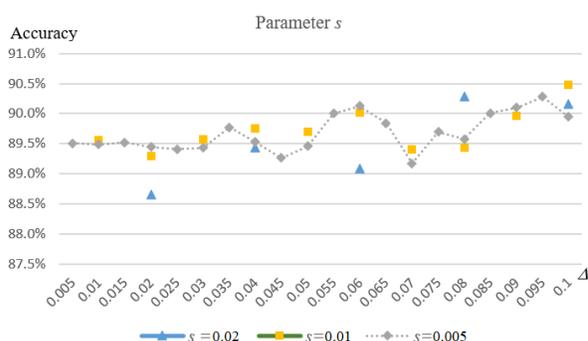


Figure 5: The performance with different parameter setting

Discretization is very important in the proposed method. In this experiment, Discretization parameter s is set to be 0.02, 0.01, 0.005 respectively. Then three different Δ sequences obtained. The prediction performance in different sampling sequences is illustrated in Fig. 5. The figure does not establish that finer the sampling granularity provides better results. When $s = 0.01$, the method achieve the best performance. Similarly, it is not clear that the more imprecise data sets are introduced, the better the performance will be. The increase of Δ means the number of imprecise data set increases, the performance does not steadily increase.

5 CONCLUSIONS

The learning method presented in this paper centers around a refined error function and input data imprecision range. This basically addressed the problems observed in our previous study [12] with a satisfactory solution. Further improvements may possibly take into consideration of output data imprecision range and probability distributions of the imprecise samples. Also, it remains to be seen if such methods are effective in other applications in, e.g., healthcare and engineering.

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