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Automated prediction of sepsis using temporal convolutional network

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ABSTRACT

Multiple organ failure is the trademark of sepsis. Sepsis occurs when the body's reaction to infection causes injury to its tissues and organs. As a consequence, fluid builds up in the tissues causing organ failure and leading to septic shock eventually. Some symptoms of sepsis include fever, arrhythmias, blood vessel leaks, impaired clotting, and generalised inflammation. In order to address the limitations in current diagnosis, we have proposed a cost-effective automated diagnostic tool in this study. A deep temporal convolution network has been developed for the prediction of sepsis. Septic data was fed to the model and a high accuracy and area under ROC curve (AUROC) of 98.8% and 98.0% were achieved respectively, for per time-step metrics. A relatively high accuracy and AUROC of 95.5% and 91.0% were also achieved respectively, for per-patient metrics. This is a novel study in that it has investigated per time-step metrics, compared to other studies which investigated per-patient metrics. Our model has also been evaluated by three validation methods. Thus, the recommended model is robust with high accuracy and precision and has the potential to be used as a tool for the prediction of sepsis in hospitals.

1. Introduction

The body's immune system is a highly developed response to infections that can be caused by bacteria, viruses, or fungi. However, when the immune system is unable to mount a tailored defence against infection, it releases an avalanche of inflammatory chemicals in order to create a mass effect, which leads to a state of sepsis within the body [1].

Sepsis is described as an extremely complex and deadly syndrome with divergent clinical indications, which altogether create a challenging environment for detection and treatment [2]. Presently, as per the international consensus, sepsis is defined as lethal organ malfunction, stemming from a disordered host response to an infection [2]. The keystone of organ damage results from a disparity between the tissue's metabolic needs, and the subsequent hypoperfusion state that arises from the body's inflammatory state. While inflammation-induced cardiac malfunction and systemic blood volume redistribution play a key role in this, it is exacerbated by oxygen use from the damaged tissue [3].

Angiopoietins are a subset of a family of vascular growth factors. The imbalance of angiopoietin-tyrosine kinase alongside immunoglobulin-like ligand-receptor system (Ang-tie), which is responsible for cardiovascular and lymphatic development, is of particular interest in sepsis research [2]. The improved expression of Ang-2 and the impediment of Ang-1 obstructs the Tie-2 receptor and proliferates vascular permeability, causing tissue edema [4]. A high serum Ang-2/Ang-1 ratio in turn results in heightened severity in organ malfunction and increased mortality, even in early sepsis [5]. The organs often damaged due to sepsis include the kidneys, lungs, liver, heart, central nervous

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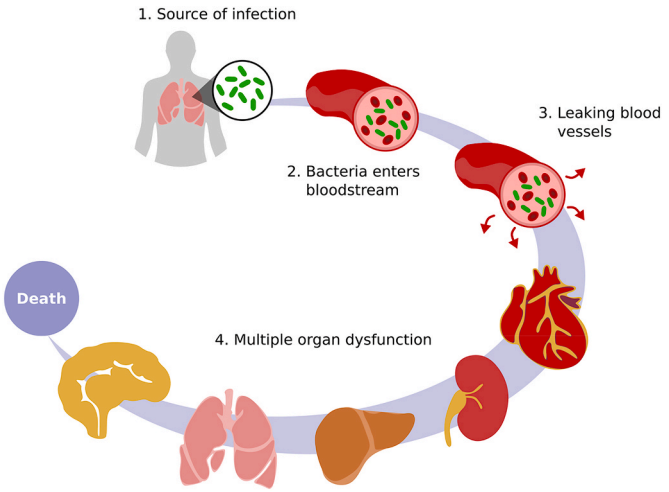

Fig. 1. Causes and consequences of sepsis.

hematologic systems [2].

The infections that contribute to sepsis are resistant to antibiotics, leading to quick deterioration of health conditions [6]. The symptoms of sepsis include fever, irregular heart rate, blood vessel leaks, inflammation and clotting difficulties [7]. Sepsis can be classified as sepsis 1, 2 or 3. Sepsis 1 is known to occur as a consequence of the systemic inflammatory response to known or suspected infections. Sepsis 2 is diagnosed based on inflammatory, hemodynamic, organ maladies and tissue perfusion parameters, while sepsis 3 is diagnosed based on life-threatening malady of the organ due to the imbalanced host response to infection [8]. Fig. 1 encapsulates causes and consequences of sepsis. Sepsis afflicts more than 30 million people globally, causing about 6 million deaths yearly [9].

Early detection and timely management of sepsis are crucial to lower the mortality and morbidity rates. Presently, blood cultures are examined and biomarkers such as procalcitonin(PCT), C-reactive protein (CRP), cell-free DNA(cfDNA) are used as the gold standard for early sepsis diagnosis [10,11]. However, using blood cultures as a diagnostic tool exhibit several shortcomings. Besides being invasive, biomarkers for sepsis have been reported to be lacking sensitivity or specificity for the diagnosis or even prediction of sepsis, owing to the overlap that exists between infectious and inflammatory conditions [12]. Multi-marker systems that were developed to address these were found to be costly and integration into clinical algorithms is an arduous task. Hence, a cost-effective automated diagnostic tool for the early identification of sepsis is important beyond measure, as this decreases the time for advanced diagnostics and paves the way for timely treatment [13].

Conventional machine learning techniques have been explored by some authors for the prediction of sepsis. Henry et al. [14], Umscheid

Table 1
Summarized studies for the prediction of sepsis using deep learning methods.

Authors	Techniques	Database/participants	Results
Kam et al. [36], 2017	• Insight model • Feedforward model • 20 features • LSTM model	MIMIC-II(version 3) database: 350 patients	**LSTM model:** **AUROC:** 92.9% **Insight model:** **AUROC:** 88.7% **Sensitivity**: 91%
Futoma et al. [37], 2017	• Multitask Gaussian process recurrent neural network(MGP-RNN) • RNN classifier	University health system, HER database: 49 312 patients	MGP-RNN outperforms GP-RNN baselines in the classification of sepsis.
Kamaleswaran et al. [38], 2018	• Logistic regression classifier • Random forest classifier • Deep CNN model	Le Bonheur Children's Hospital: Sepsis: 18 patients Normal: 473 subjects	**Logistic regression: (2–8 h before sepsis)** **ACCURACY**: 82.8% **SPECIFICITY**: 82.7% **SENSITIVITY**:85%
Fagerstrom et al. [39], 2019	• LiSep LSTM model • 6-fold validation	MIMIC-II database: About 59 000 septic shock patients	**AUROC:** 83.06%
Li et al. [40], 2019	• Convolutional neural network • Recurrent neural network • Ensemble bagging(combination of both models)	Physionet Challenge 2019 database: 40 336 data(2932 septic records)	**ACCURACY:** 92.7% **AUROC:** 96.4% **AUPRC:** 38.3%
Scherpf et al. [41], 2019	• Recurrent neural network • 4 fold-validation • Gated recurrent unit • 10 parameters	MIMIC-III database: Patients: 46520	**AUROC:** 81% **Sensitivity**: 85% **Specificity**: 67%
Moor et al. [42], 2019	• Multitask Gaussian Process Temporal Convolutional Network (MGP-TCN) • Dynamic time-warping k-nearest neighbour classifier • 3 iterations of random splitting	MIMIC-III database: Sepsis patients: 570 Normal : 5618 subjects	**AUPRC:** 40% **AUROC**: 86% **(7 hours before onset)**
Lauritsen et al. [43], 2020	• Convolutional + long short-term memory networks • 5-fold cross validation	Electronic health records from multiple Danish hospitals Full dataset: 52 229 patients Vital signs: 3129	**AUROC:** 85.6%(3 h before sepsis onset)
Bedoya et al. [44], 2020	• Multi-output gaussian processes recurrent neural network • Internal validation • Temporal validation	Electronic health records from quaternary academic hospital: Training and internal validation: 42979 encounters Temporal validation: 39 786 encounters	**AUROC:** 88.0%
This study	• **Gaussian Process Regression** • **Temporal convolutional network** • **40 features per record** • **10-fold cross validation**	**Beth Israel Deaconess Medical Center:** **1790 septic records** **Emory University Hospital:** **1142 septic records**	**Per-patient metrics:** **ACCURACY: 95.5%** **AUROC: 91.0%** **AUPRC: 68.0%** **Per-timestep metrics** **ACCURACY: 98.8%** **AUROC: 98.0%** **AUPRC: 65.0%** **UTILITY: 43.0%**

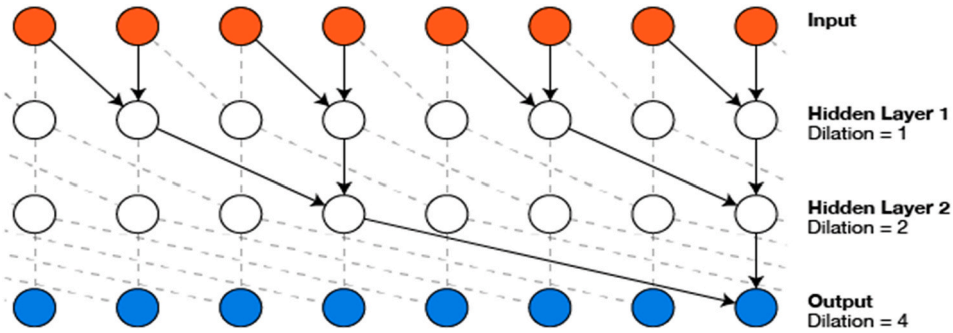

Fig. 2. Dilated convolution layers.

Table 2
Tuning of hyperparameters with grid search.

	Min	Max	Interval	Final value
Maximum learning rate	1e-5	1e0	e0.005	3e-4
Weight decay	0, 1e-5	3e-2	e0.5	1e-3
Minimum momentum	0.80	1.00	0.05	0.85
Maximum momentum	0.80	1.00	0.05	0.95

et al. [15], Delahanty et al. [16] and Lake et al. [17] investigated early warning scoring systems by building models using machine learning techniques. Calvert et al. [18], Mao et al. [19] and Desautels et al. [20], explored the insight algorithm to develop the prediction models. Mani et al. [21], Horng et al. [22] and Gultepe et al. [23] explored the support vector machine classifier amongst other models. Nemati et al. [24] and Shashikumar et al. [25,26] studied electronic medical record features. Other models such as random forest classifier, composite mixture and Rusboost classifiers were developed by Taylor et al. [27], Mayhew et al. [28] and Patidar et al. [29] respectively. Conventional machine learning techniques require the manual extraction and selection of features, and this has been proven to be cumbersome and tedious. The significant features are also selected by iterative trial and error, hence the process is time-consuming. Additionally, some of the studies discussed above have only generated qualitative results.

Feature extraction and selection processes are naturally automated in deep learning techniques, easing classifications, hence deep learning models are increasingly being employed in the detection of various diseases [30–35]. In this study, we have employed the temporal convolutional network for the prediction of sepsis. Our proposed method not only predicts sepsis rapidly, but also with high accuracy. More details about our work are discussed in the subsequent sections; section 2 discusses the methodology, sections 3 and 4 discuss the results and comparisons with other works respectively, while section 5 concludes the paper with recommendations for future work. Table 1 details the summarized studies for sepsis prediction using deep learning methods.

2. Methodology

2.1. Data acquired and pre-processing method

The data used is the open source dataset released for the PhysioNet Computing in Cardiology 2019 Challenge [45]. This contains data from 2 hospitals: Beth Israel Deaconess Medical Center (hospital system A) and Emory University Hospital (hospital system B) which contain 1790 and 1142 septic records respectively. The data obtained were based on sepsis-3 criteria and each patient's record comprised 40 features: 8 vital signs, 26 laboratory measurements, and 6 demographic variables, recorded hourly. The Gaussian Process Regression (GPR) [46] was used to predict the distribution of possible values for each feature that contained entries, to ease the problem of missing values. As GPR generates a distribution of values as compared to filling in the missing values like other interpolation methods, this comes with the added advantage of being able to sample this distribution during training time, as it yields varied values according to the distribution. The Radial Basis Function (RBF) kernel combined with a White Noise kernel [47] was then used to produce the covariance matrix which describes the distribution of values. Besides filling in missing data, this step also creates noisy data, which helps to improve generalisation of the model used [47]. Any NaN(not a number) values left after this process were subsequently set to 0.

2.2. Temporal convolutional neural network

Deep learning models are neural networks that consist of a large number of layers and parameters that aid in classification tasks [48]. Deep models ranging from the convolutional neural networks(CNN) [49] to the long short-term memory(LSTM) [50] and autoencoders [51] are frequently used for the detection of arrhythmia [30,31,52] schizophrenia [32], congestive heart failure [33] among other maladies. In this study, a temporal convolutional network(TCN) [53] was employed. TCN is a convolutional network which convolves over the time domain. In TCN, calculations are conducted in such a way that each time-step is updated concurrently [54]. A temporal convolutional network is a convolutional network which convolves over the time domain. As the filters in these convolutions do not have access to timesteps in the future, dilated convolutions were implemented wherein a convolution filter is applied over a larger receptive field than its defined input size by skipping inputs from a given step size. These dilated convolutional layers are then stacked on top of each other with increasing dilation to increase the size of the receptive field exponentially [55]. Fig. 2 represents the dilated convolution layers used in our model.

In this study, the TCN was specifically chosen as a replacement/alternative of existing recurrent neural networks(RNN)/gated recurrent unit(GRU) architectures to improve training hardware requirements. TCNs retain benefits from RNNs such as variable length inputs via sliding of the 1-dimensional convolutional kernel windows and are less memory intensive than GRU/LSTM networks especially when the data length gets larger. The hyperparameters(as shown in Table 2) were tuned with a grid search. The grid can be described with 3 values: A minimum, maximum and interval. For maximum learning rate and weight decay, the grid values are incremented exponentially (eg. 1e-5, 1e-4.5, 1e-4, etc). Residual blocks are known to benefit deep learning models, as such, nine residual block were stacked, summing the output together with the output of the skip connections, followed by a linear transform on the sum. This output was then fed to a sigmoid activation function. Batch normalisation was done and dropout layers were added to prevent overfitting of the model. Fig. 3a and b present a typical residual block and the TCN architecture used in our study, respectively.

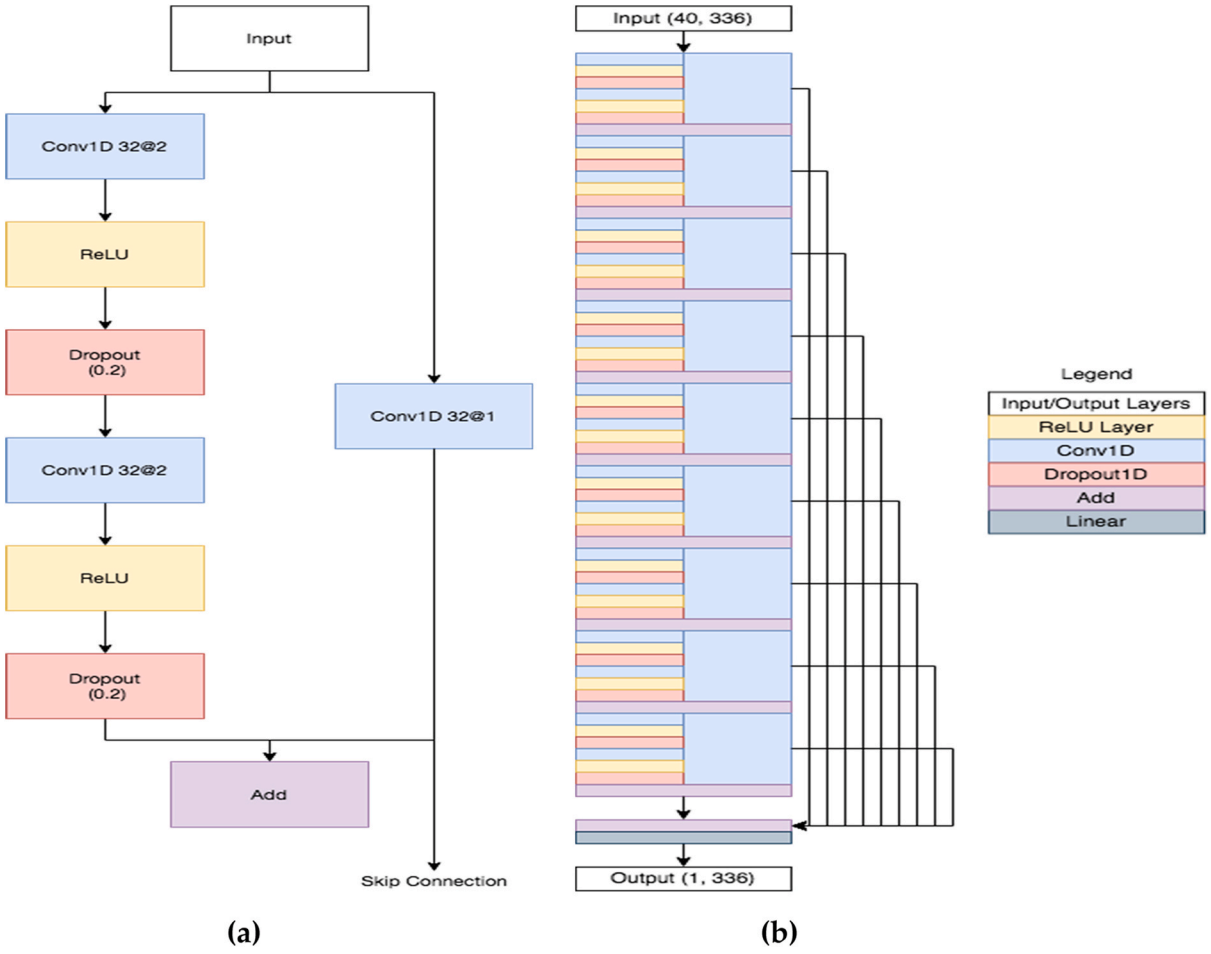

Fig. 3. (a) Temporal Residual Block and (b) Temporal Convolutional Network architecture.

Table 2a
Classification results based on per-patient metrics.

Accuracy(%)	Sensitivity(%)	Specificity(%)	AUROC	AUPRC
95.5	57.1	98.5	91.0	68.0
80.0	85.0	79.6	91.0	68.0

Table 2b
Classification results based on per time-step metrics.

Accuracy(%)	Utility(%)	AUROC	AUPRC
98.8	43.0	98.0	65.0

2.3. Training, testing and validation of model

The predicted values for each patient are labels that signify the onset of sepsis at each timestep. These labels are 1, starting from the onset of sepsis and throughout the sepsis episode and are 0 otherwise. The data was shifted 6 h into the past to train the proposed model to predict the onset of sepsis by 6 h. The model was trained over 20 epochs using the Python module fastai's implementation of the one cycle policy in Refs. [56], which is a variant of the cyclical learning rates introduced in Ref. [57]. The optimal maximum learning rate and weight decay is found using the learning rate finder in Smith et al.'s work in Ref. [46] and a grid search over a range of values for weight decay. 10-fold stratified cross validation [58] was used to evaluate the model wherein 90% of the data was used for training and 10% for validation at each fold. Area under the receiver operating characteristics (AUROC) and area under the precision-recall curve (AURPC) values were also computed to validate the model. The metrics calculated for each fold over the validation set were split into 2 categories: per-patient metrics, which are calculated once per patient in the validation set, which gives rise to a binary classification; and per-timestep metrics, which are calculated at each timestep and include a utility function as defined in Ref. [45] which penalises a model based on its sensitivity, as well as how early or late its prediction of sepsis onset is.

3. Results

Tables 2a and 2b present the results of the classification based on per-patient and per time-step metrices respectively. It is apparent that the highest accuracy and AUROC of 98.8% and 98.0% were achieved respectively, for the per time-step metrics. A relatively high accuracy and AUROC of 95.5% and 91.0% were achieved respectively, for the per-patient metrics. When the sensitivity of the proposed model was set to 85%, to compare with work done by other authors who set their sensitivity values between 80 and 90%, our model achieved accuracy and AUROC values of 80% and 91% respectively.

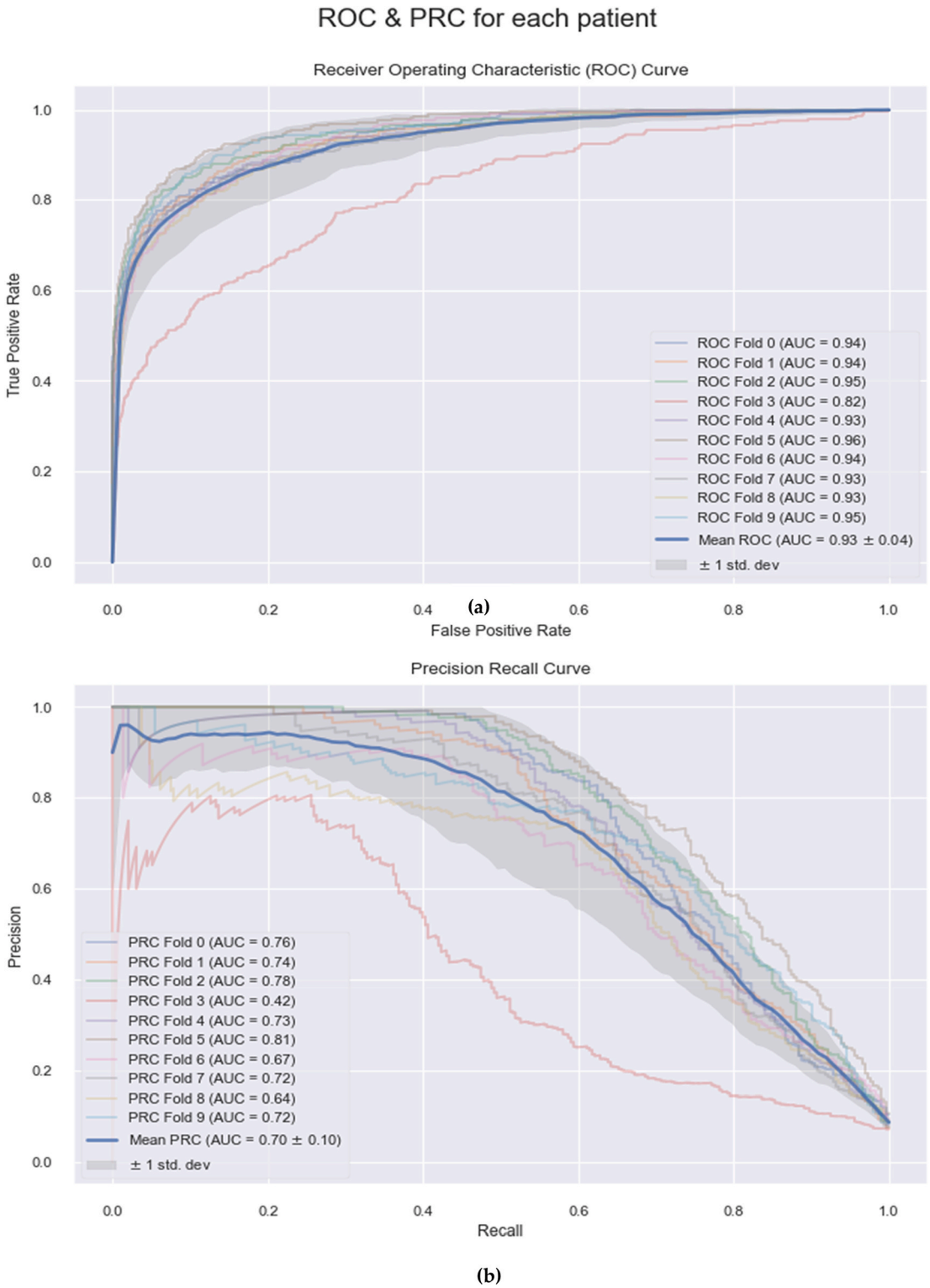

Fig. 4. (a) ROC curve and (b) Precision Recall curve for each patient.

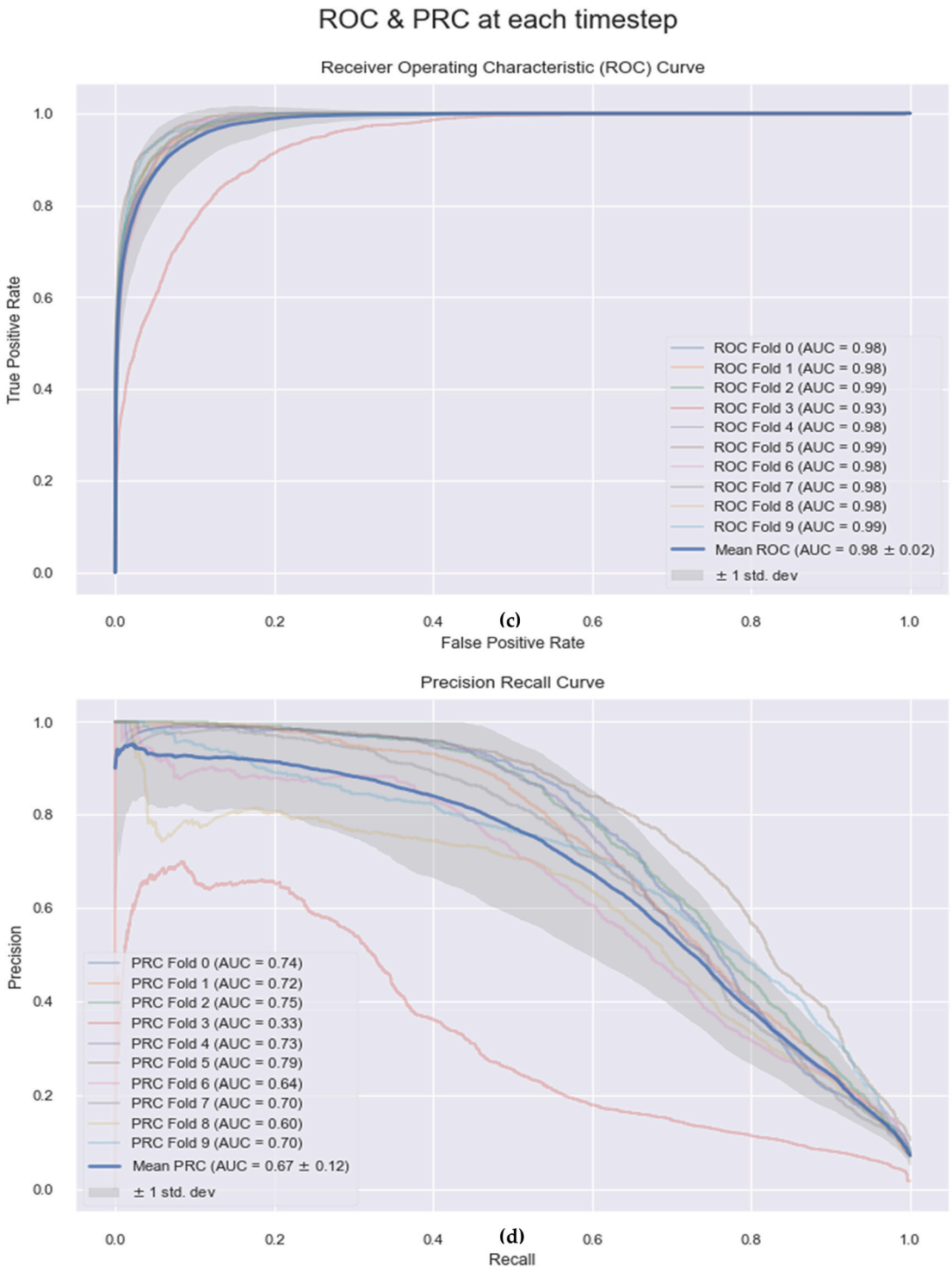

Fig. 4. (*continued*).

4. Discussion

From Table 1, it is worth noting that our proposed model has achieved the highest classification accuracy of 98.8% for the per time-step metrics, followed by 95.5% for the per-patient metrics. The study is novel because we have investigated and reported results on two metrices, while the other studies reported only on per-patient metrics. A higher utility score of 43.0% was also achieved, wherein the entry for the Physionet 2019 competition only received a normalised utility score of 23.7% for the entire dataset [40]. Since the competition entries were tested on a hidden dataset, wherein there has been no updates if these data is available for other researchers' testing, we have compared our results with those of the competition, based on k-fold validation techniques, used in both studies. Comparing the CNN model, logistic regression and random forest classifiers, Kamaleswaran et al. [38] reported the highest classification accuracy of 82.8% achieved with the logistic regression classifier, which is a lower accuracy than ours.

From Table 1 it is clear that Moor et al [42] were the first group to have employed the TCN model for the prediction of sepsis. While we have also explored the TCN model similar to Moor et al [42], the two works discuss different methods used. Moor et al [42] proposed the

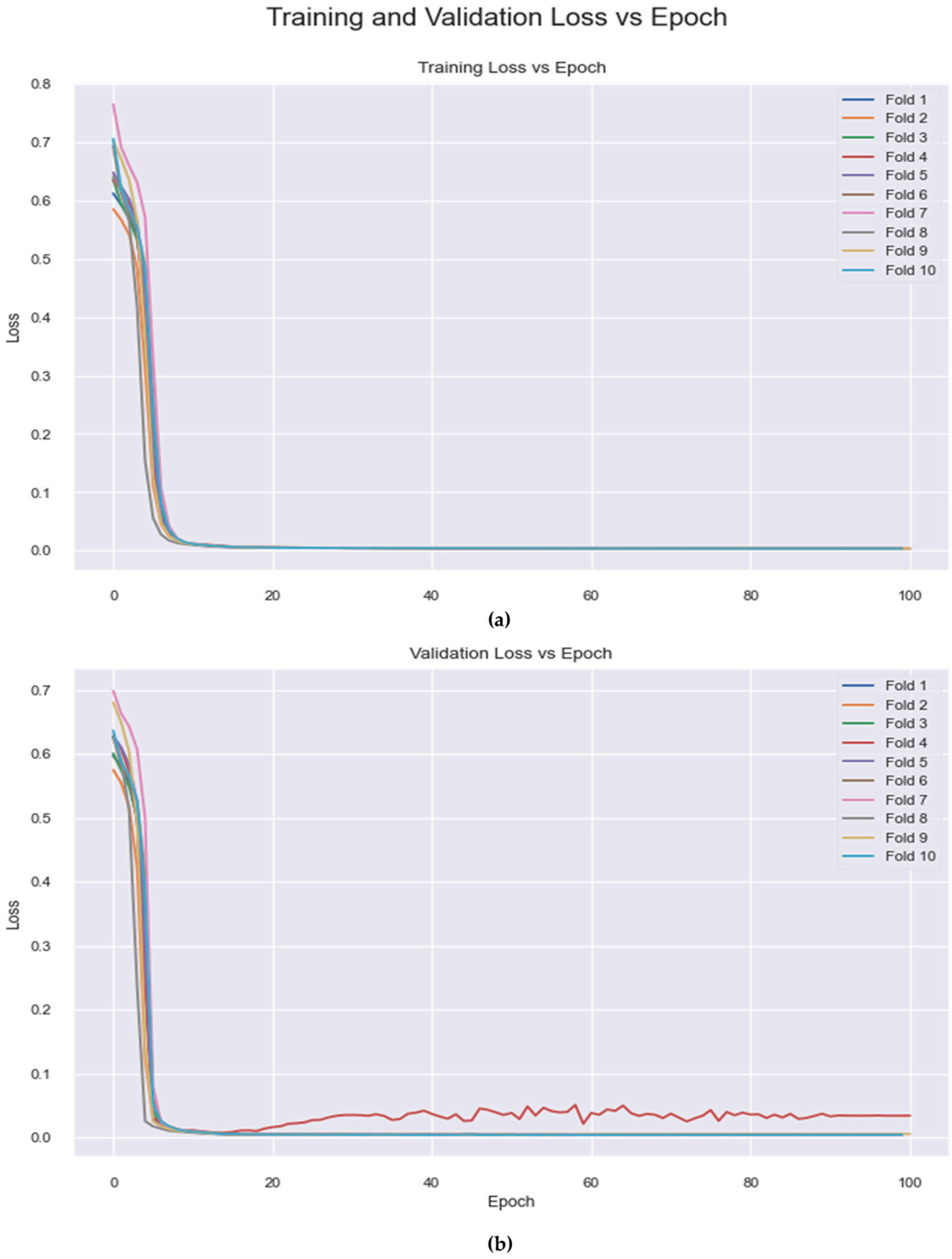

Fig. 5. (a) Training loss vs epoch graph and (b)Validation loss vs epoch graph.

Multitask Gaussian Process(MGP) TCN classifier and also employed the Dynamic Time Warping k-nearest neighbour classifier as an additional comparison partner while we only explored the GPR-TCN model. The datasets used are also different wherein Moor et al [42] had used the MIMIC III database alone, while we had used data from both the MIMIC III database and Emory University Hospital. Furthermore, we have employed 10-fold cross validation while they have employed three iterations of random splitting (Monte Carlo cross validation). It is evident that we had obtained higher AUPRC values of 68% and 65% for per--patient and per-timestep metrics respectively as compared to that achieved by Moor et al [42] for the classification task. Nevertheless, we observe that the two experimental scenarios are different: we follow the online (i.e. time-step wise) prediction task of the PhysioNet Computing in Cardiology 2019 Challenge [45], while Moor et al. performed an early prediction analysis to evaluate different prediction horizons in hours before sepsis onset. As the second type involved a temporal case-control alignment (where large parts of the controls data are discarded for making the task harder but more realistic), a direct comparison of the resulting performance measures is not applicable. Kam et al. [36] achieved a higher AUROC value of 92.9% as compared to 91% in our study. However, only a small dataset of 350 patients were used to train the model in this study, larger datasets are needed to train deep learning models. Li et al. [40] also used the same dataset as our study and achieved a higher AUROC value of 96.4%. Although the AUROC value was higher, a lower AURPC of 38.3% was reported, as compared to our study which achieved AUROC value of 68%. Similar to our study, the dataset used in this study was imbalanced. ROC plots do not reflect the true classification performance of a classifier wherein imbalanced datasets are used, as this would result in a misleading interpretation of the model's sensitivity [59]. PRC plots, in contrast, provide a more accurate prediction of future classification performance of the model, as a fraction of true positives amongst positive predictions is computed in these plots [59]. Hence, as an alternative to ROC plots, PRC is known to be robust even under imbalanced datasets [60,61]. Thus, AUPRC is more representative of the model's performance instead of AUROC. So, with the higher AUPRC obtained, our model still performed better than that of Li et al. [40]. Futoma et al. [37] reported on qualitative results while the remaining studies obtained lower AUROC values. Our model has also been validated by three techniques; 10-fold validation, AUROC and AUPRC, hence it is robust, besting the other models discussed in Table 1.

Fig. 4a and b show the AUROC and AUPRC plots derived from our study. From Fig. 4a, it is apparent that the mean ROC of our proposed model has a true positive rate of about 1.0 and a false positive rate of about 0.0. From Fig. 4b, it is noteworthy that the mean PRC of our model has a precision value of about 1.0 and recall value less than 1.0. Although our model is not the best(the best model has both precision and recall values close to 1.0), it can be considered as a better model as compared to those in Table 1. Fig. 4a and b clearly indicate that our model is highly accurate to be implemented for sepsis prediction in the hospitals. The ROC and PRC plots obtained by our model for per-patient metrics are depicted in Fig. 4c and d respectively(Please see the appendix section). Fig. 5a and b depict the training and validation loss versus epoch graphs respectively. It is observable from both graphs that the loss decreases across the epochs as the model learns the data, hence it can be seen that the model performs better, as the training continues. The closer the loss value is to 0, the better the model is performing. There are some benefits and limitations of our study to be discussed below.

4.1. Benefits

1. Sizeable data can be trained by the model.
2. The model has been validated by 3 techniques, hence it is very robust.
3. The dataset is not localized and contains data from 2 different clinical settings.
4. Feature extraction and selection processes can be done automatically by the model for any classification tasks.

4.2. Limitations

1. GPR process is time-consuming, hence pre-processing and training phases may take longer than traditional pre-processing.
2. GPR process produces output with high variance and noise when the number of samples in the feature are low.
3. GPR is also very computationally expensive, both during the regression process; where the distribution of points is estimated and the sampling process; where the estimated distribution is sampled before the data is fed into the model.
4. GPR sampling method, which results in a lot more data points being produced than is realistically possible in a hospital environment. This can lead to the model potentially performing sub-par when given unprocessed data although this is yet to be tested.

5. Conclusion and future work

Sepsis is a condition that arises when one's immune response releases large amounts of inflammatory chemicals, to fight back an infection caused by pathogens. The release of large amounts of chemicals causes fluid to build up in one's tissues, leading to organ dysfunction, eventually leading to septic shock. Prediction is more imperative than detection, to prevent sepsis altogether and the lasting effects this can have on the body. Deep learning models are increasingly taking over conventional machine learning techniques. In this study, we have employed a deep temporal convolution network for the prediction of sepsis. Acquired data was fed to the model and a high accuracy and AUROC of 98.8% and 98.0% were achieved respectively, for the per time-step metrics. A relatively high accuracy and AUROC of 95.5% and 91.0% were achieved respectively, for the per-patient metrics. Our model has been evaluated by three validation methods; 10-fold, AUROC and AUPRC. Our experiments have shown that our proposed model is an effective automated diagnostic tool, of high accuracy and precision, that can be used to predict sepsis.

For our future work, we hope to improve the performance of our model by training it using a larger data set as compared to the present, with more varied data comprising sepsis 1,2 and 3 criteria. With more and varied data, the model is bound to learn better and hence classify with a higher accuracy. Also, in future, we intend to test our model using new unknown database and evaluate the performance of the model. Attention-based neural networks can be a solution to automatic feature extraction and selection. It would also be interesting to observe how our proposed model performs on more authentic, varied clinical settings.

Declaration of competing interest

There is no conflict of interest in this work.

Appendix

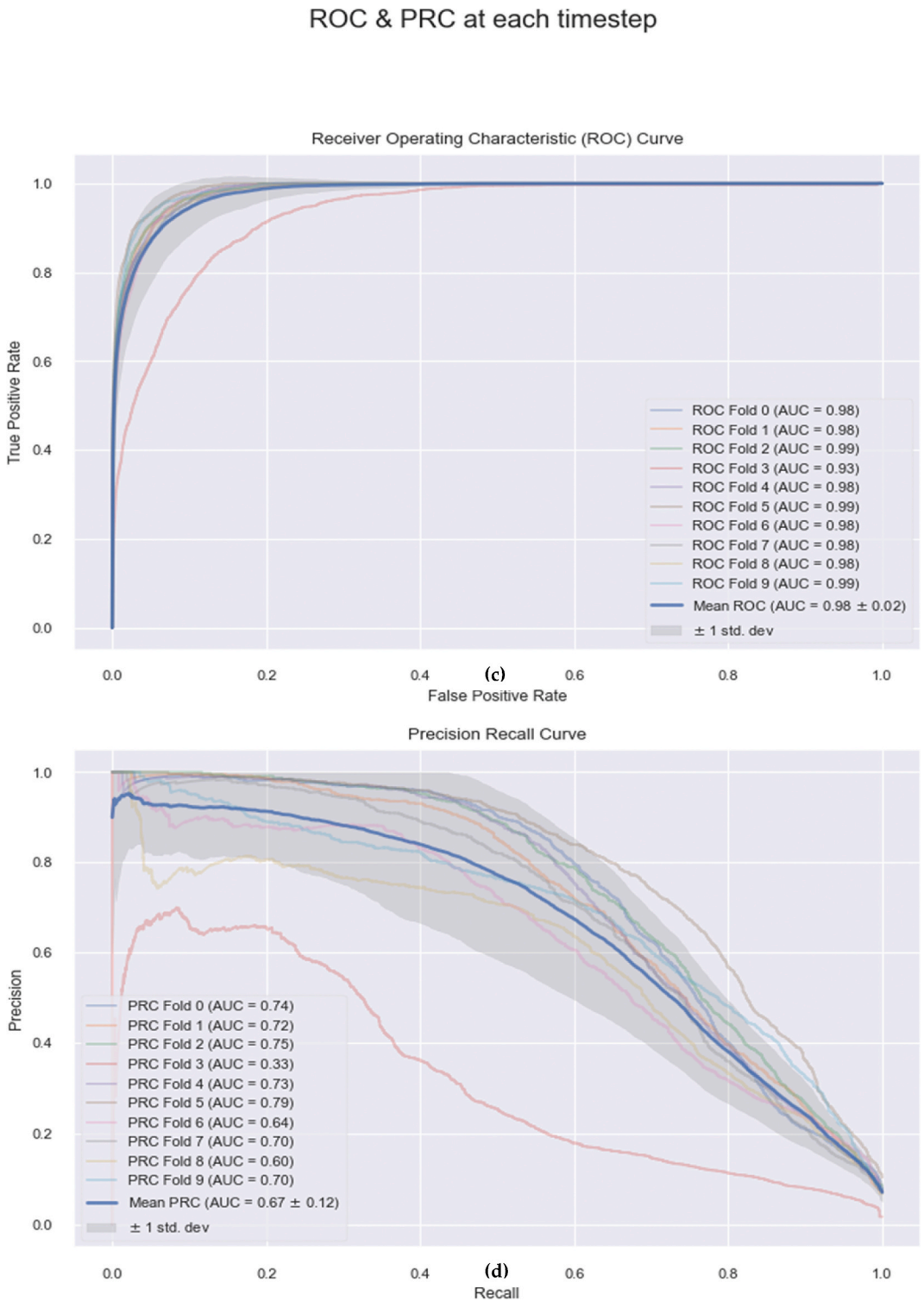

Fig. 4. (c) ROC curve and (d) Precision Recall curve for each time step.1.

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