AIMS Biophysics

AIMS Biophysics, 11(4): 403–426.
DOI: 10.3934/biophy.2024022
Received: 31 July 2024
Revised: 03 October 2024
Accepted: 14 October 2024
Published: 25 October 2024

http://www.aimspress.com/journal/biophysics

*Research article*

# Predicting the correlation between neurological abnormalities and thyroid dysfunction using artificial neural networks

**Dina Falah Noori Al-Sabak[1], Leila Sadeghi[1,2,*] and Gholamreza Dehghan[1,2]**

[1] Department of Animal Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran, P.O. Box 5166616471, Tabriz, Iran
[2] Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran

* **Correspondence:** Email: l.sadeghi66@yahoo.com, l.sadeghi@tabrizu.ac.ir; Tel: +984133392743; Fax: +984133356027.

**Abstract:** In this work, a deep learning model was developed to predict future neurological parameters for patients with hypothyroidism, enabling proactive health management. The model features a sequential architecture, comprising a long short-term memory (LSTM) layer, a bidirectional LSTM layer, and several fully connected layers. The study assessed the interplay between serum cortisol, dopamine, and GABA levels in hypothyroid individuals, aiming to illuminate how these hormonal fluctuations influence the condition's symptoms and progression, especially in relation to Parkinson's disease. Conducted at the Tabriz Sadra Institute of Medical Sciences in Iran, the observational study involved 80 hypothyroid patients and 80 age-matched healthy controls. The findings showed a correlation between cortisol levels and TSH and an inverse relationship with T3 and T4 levels among hypothyroid patients. Dopamine levels also correlated with TSH, T3, and T4, highlighting their potential impact on Parkinson's disease. Notably, hypothyroid patients aged 54–71 years old experiencing visual hallucinations had reduced occipital GABA levels correlating with hormone levels. The results indicated significant relationships among cortisol, dopamine, and GABA levels, providing insights into their roles in the pathophysiology of hypothyroidism and its association with neurological disorders. The BiLSTM model achieved the highest accuracy at 92.79% for predicting Parkinson's disease likelihood in adult hypothyroid patients, while the traditional LSTM model reached 84.48%. This research suggests promising avenues for future studies and has important implications for clinical management and treatment strategies.

**Keywords:** BiLSTM; deep learning network; neurological abnormalities; thyroid dysfunction; blood

samples; hypothyroidism; Parkinson

## 1. Introduction

Hashimoto's thyroiditis (HT) is a common autoimmune condition characterized by thyroid inflammation, lymphocytic infiltration, and increased autoimmune antibodies. Studies investigating the relationship between HT and cancer have yielded conflicting results, prompting a meta-analysis to clarify this connection [1]. Hypothyroidism, which predominantly affects women and the elderly, involves intricate interactions among thyroid function, the HPA axis, and cortisol, with T3 and T4 playing vital roles in metabolism and bodily functions [2]. Diagnosis typically involves evaluating TSH and T4 levels in the blood. Subclinical hypothyroidism, characterized by elevated TSH levels while T4 and T3 levels remain within normal range, has garnered attention. This study aimed to explore the potential links between thyroid hormones and neurological issues such as Parkinson's disease progression [3].

Factors such as stress and low blood sugar can trigger the release of cortisol. In Parkinson's disease, neurotransmitters like GABA [4], cortisol [5], and dopamine [6] play crucial roles in the progression and management of the condition. Research indicates that serum levels of autoimmune antibodies (AIAs) against α-synuclein (α-syn) could serve as a biomarker for Parkinson's disease, distinguishing PD patients from healthy individuals and those with other neurodegenerative diseases like Alzheimer's [7]. GABA regulates muscle tone, cortisol influences disease progression through stress-related mechanisms, and dopamine depletion contributes to both motor and emotional symptoms. Maintaining a balance in these neurotransmitter levels through medication, lifestyle modifications, and therapies is essential for effectively managing Parkinson's symptoms and improving patients' quality of life. Regular monitoring of these levels can provide valuable insights for optimizing treatment strategies, potentially aiding in the management of Parkinson's disease by enhancing our understanding of the connection with hypothyroidism. The main aim of this study is to investigate the relationship between neurological abnormalities, specifically Parkinson's disease, in individuals with thyroid dysfunction.

In primary hypothyroidism, heightened cortisol levels result in an increase in cortisol levels and a decrease in TSH levels. The complex interplay between the thyroid and adrenal systems involves cortisol influencing the secretion of hormones and feedback mechanisms. Autoimmune thyroiditis makes hypothyroidism more prevalent in elderly women. Disturbances in cortisol levels among hypothyroid patients can impact the presentation of the disease. Understanding the connection between cortisol and hypothyroidism is crucial for improving diagnosis and treatment. In Parkinson's disease (PD), dysfunction in the HPA axis related to cortisol levels is observed [8]. Research by Cramb et al. [9] has shown that deficits in dopamine release from nigrostriatal neurons are present in many models of Parkinson's disease before or without neurodegeneration. Exploring the relationship between cortisol and dopamine in hypothyroidism can provide insights into the progression and treatment of neurological abnormalities. Managing the body's condition during the emergence of hand tremors and lower levels of T3 and T4 are key aspects of PD. The primary focus of this study is to understand these scenarios. More than 50% of individuals experience hand tremors, prompting the investigation of the effects of dopamine, cortisol, and hypothyroidism. Elevated cortisol levels in Parkinson's disease play a significant role in cognitive decline and disease progression, as well as impacting the effectiveness

of vascular Parkinsonism treatment. PD also disrupts the cortisol cycle. While individuals with Parkinson's disease maintain a consistent circadian rhythm of cortisol, the amount of cortisol released increases in early Parkinson's disease [10].

## 2. Literature review

Gamma-aminobutyric acid (GABA) serves as the primary inhibitory neurotransmitter in the central nervous system (CNS), peripheral nervous system, and enteric nervous system. It is implicated in a wide range of physiological functions both within and outside the nervous system. Błaszczyk [11] proposed that the traditional understanding of Parkinson's disease (PD) as resulting from the specific loss of dopaminergic neurons in the midbrain should be revised to view it as a complex multisystem neurodegenerative disorder affecting the entire nervous system. The clinical manifestations of PD are believed to be closely linked to the localization and progression of GABA pathology. The connection between neurological disorders like PD, characterized by initial symptoms such as hand tremors, and thyroid dysfunction is undeniable [12]. Certain neurological parameters may play a crucial role in identifying individuals predisposed to Parkinson's disease and in determining the most effective treatment strategies. Understanding the intricate relationship between GABA, dopamine, cortisol, and thyroid function in the context of neurological disorders like PD is essential for advancing both diagnosis and treatment approaches. Further research into these interconnected systems could provide valuable insights into the pathophysiology of PD and potentially lead to more targeted therapeutic interventions.

The use of various artificial neural network techniques in medical sciences is increasing, particularly in forecasting disease progression. Numerous methods have been developed to predict blood levels. Shanthi [13] implemented an autoregressive integrated moving average (ARIMA) model for short-term predictions. Additionally, machine learning approaches [14] have been employed; for instance, Daskalaki et al. [15] created a real-time learning recurrent neural network (RNN) that combined glucose and insulin data, surpassing traditional models. Bunescu et al. [16] utilized support vector regression (SVR), considering daily elements such as insulin doses and meals, while Georga et al. [17] improved SVR by integrating models for meals, insulin, and exercise to provide personalized predictions. Recently, deep learning techniques have demonstrated enhanced performance due to their capacity for automatic feature extraction. Mhaskar et al. [18] introduced a deep convolutional neural network (DCNN) that exceeded the performance of shallower networks. Conventional RNNs often face challenges with long-term dependencies because of problems like vanishing or exploding gradients [19,20]. To address this, advanced architectures such as long short-term memory (LSTM) networks have been created, featuring memory cells and forget gates [21] that improve predictive accuracy by effectively combining historical and current data. LSTMs have been successful in various time series applications, including biopsy images detection [22], dynamics of virus spreading [23], and blood glucose behavior modeling [24,25]. Their rapid learning abilities and capacity to manage complex tasks have made them more favorable compared to older RNN algorithms [21]. Furthermore, deep bidirectional LSTM (Bi-LSTM) architectures facilitate the incorporation of information from both past and future contexts, as shown by Su et al.'s [26] study on blood pressure prediction.

Most studies have focused on a limited range of machine learning models, leading to restricted forecasting capabilities and less independence in predictions. Additionally, prior methods often relied on specific biomarkers, such as glucose and insulin levels, to make predictions. In contrast, the present

study examines the interplay between serum cortisol, dopamine, and GABA levels in individuals with hypothyroidism. This research seeks to shed light on how fluctuations in these hormones may affect symptoms and progression of the condition, particularly in relation to Parkinson's disease—an aspect that has been overlooked by other researchers. Moreover, a significant innovation in our approach lies in the use of correlation data to make predictions using BiLSTM neural networks, which we then compare to standard LSTM models. This application of correlated data prediction is a novel contribution, as previous studies have not addressed this aspect. In summary, our proposed model is designed to analyze and predict sequences of correlated data rather than solely handling individual data points.

This study focuses on using a deep neural network with bidirectional LSTM architectures to predict blood serum levels related to neurological conditions, particularly concerning disorders like Parkinson's disease. It investigates the levels of serum cortisol, dopamine, and GABA in individuals with hypothyroidism to better understand the complex interplay between these endocrine systems. The research explores how variations in these serum levels may influence the progression and management of hypothyroidism, especially in patients exhibiting hand tremors, which may indicate a predisposition to Parkinson's disease. The findings aim to enhance understanding of hormonal interactions and could lead to improved treatment strategies and personalized care for patients with hypothyroidism and neurological disorders. In a future chapter of this article, we will provide the material and methods containing clinical measurement, the structure of the ANN model to predict the correlations of data, and evaluation criteria. In another chapter, we will demonstrate the archived results and, finally, provide a conclusion to this work.

## 3. Materials and methods

Thyroid hormones (THs) are essential for the development and functioning of GABAergic neurons, where T3 enhances the activity of glutamic acid decarboxylase (GAD) necessary for converting glutamic acid into GABA. However, neonatal hypothyroidism decreases GAD activity, disrupting GABA metabolism, which may result in locomotor dysfunction and anxiety [27]. The effects of TH deficiency on GABA differ between neonates and adults—lowering GABA function in the former while potentially increasing GABA levels in the latter—while hyperthyroidism reduces GABA levels and elevates glutamate. T3 also facilitates GABA release by enhancing calcium uptake, and the regulation of the GABAergic system by THs varies with developmental stages, having significant implications for epilepsy [28−30]. Additionally, GABA inhibits thyroid function at the hypothalamic, pituitary, and thyroid levels, indicating a bidirectional relationship whereby THs may assist in seizure suppression during brain development (Figure 1). As an inhibitory neurotransmitter, GABA is implicated in various therapeutic effects for conditions like high blood pressure, diabetes, and insomnia, identifying GABA receptors as key drug development targets. However, inhibiting GABA neurons can raise dopamine levels, suggesting a link between GABA activation and dopamine suppression, particularly in the ventral tegmental area [28−30]. This study employs a deep neural network with BiLSTM architectures to predict blood serum levels related to neurological conditions, particularly Parkinson's disease. Cortisol, dopamine, and GABA levels are investigated in individuals with hypothyroidism to understand the complex interactions among these endocrine systems and how variations in serum levels may influence the progression and management of hypothyroidism, especially in patients with hand tremors indicative of Parkinson's risk. The findings will contribute to

a deeper understanding of hormonal interactions, potentially leading to improved treatment strategies and personalized care for patients with hypothyroidism and associated neurological disorders.

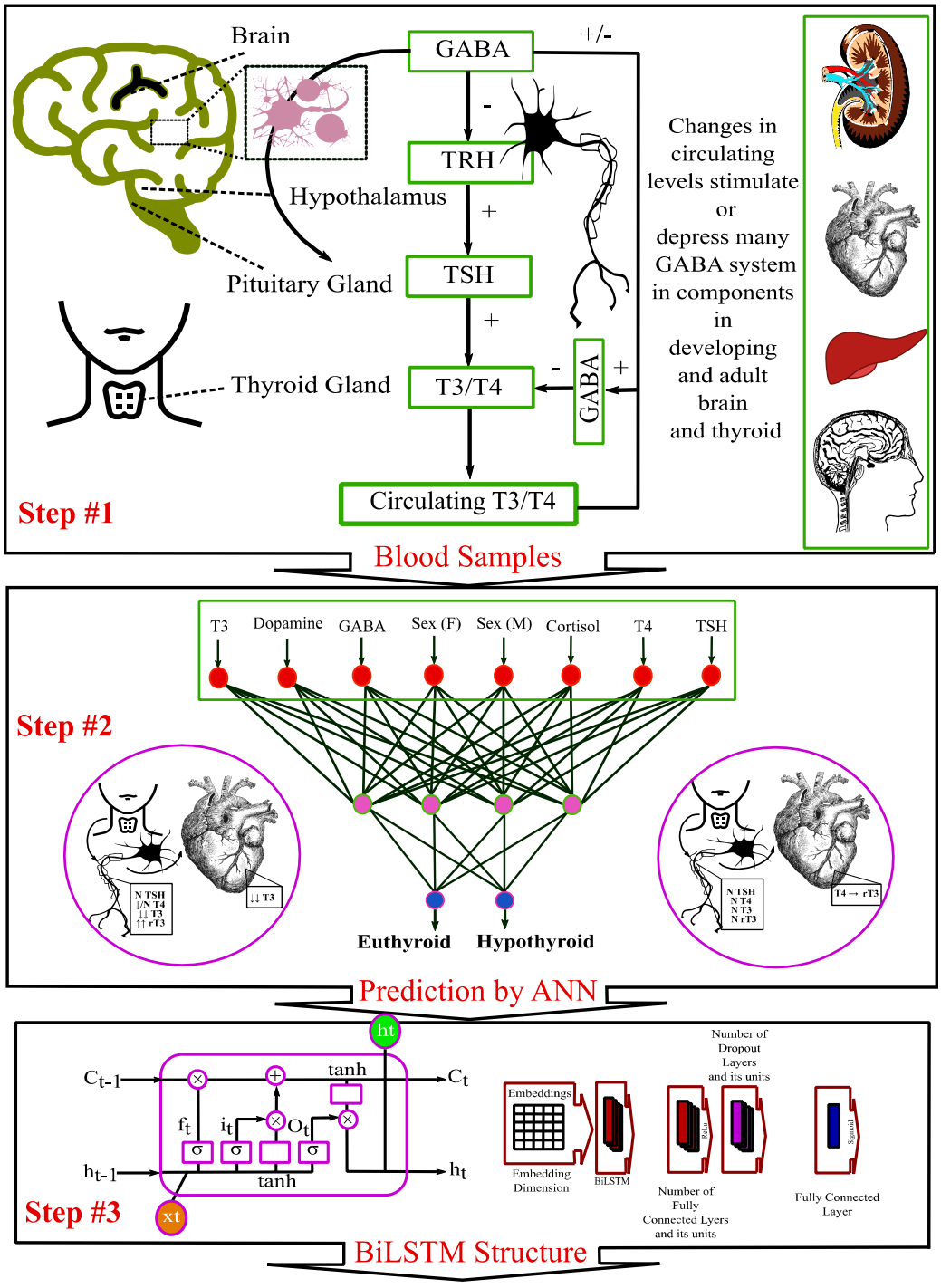


**Figure 1.** Structure of the present work.

### *3.1. Clinical measurements*

An observational exploration aiming to investigate serum cortisol, GABA, and dopamine levels

in individuals grappling with hypothyroidism [31] was undertaken at The Tabriz Sadra Institute of Medical Sciences in Tabriz, Iran, from July 2023 to November 2023. The investigation encompassed 80 hypothyroid patients and 80 healthy individuals of corresponding age, who were either outpatients or inpatients at the Department of Endocrinology and Department of General Surgery. Patients were chosen based on ATA criteria, and demographic information was obtained [32]. Exclusion criteria encompassed individuals undergoing thyroxin therapy, recent tobacco users, specific medical ailments, extensive medication usage, and recent administration of psychotropic medications or psychiatric hospitalization. Ethical endorsement for the inquiry was obtained from the Institutional Ethics Committee at the Tabriz Sadra Institute of Medical Sciences, and all participants provided informed consent. Stringent confidentiality and data safeguarding protocols were meticulously adhered to.

**Table 1.** P-values of gathered data.

| Parameter | Group | Age group | Significant difference (p-value) |
|---|---|---|---|
| TSH | Male | 18−35 | $P < 0.0001$ |
| | Male | 36−53 | $P = 0.0080$ |
| | Male | 54−71 | $P = 0.0022$ |
| | Female | 18−35 | $P < 0.0001$ |
| | Female | 36−53 | $P = 0.0061$ |
| | Female | 54−71 | $P = 0.0292$ |
| T4 | Male | 18−35 | $P = 0.0298$ |
| | Male | 36−53 | $P = 0.0278$ |
| | Male | 54−71 | $P = 0.0365$ |
| | Female | 18−35 | $P = 0.0050$ |
| | Female | 36−53 | $P = 0.0690$ |
| | Female | 54−71 | $P = 0.0750$ |
| T3 | Male | 18−35 | $P < 0.0001$ |
| | Male | 36−53 | $P = 0.3246$ |
| | Male | 54−71 | $P < 0.0001$ |
| | Female | 18−35 | $P < 0.1837$ |
| | Female | 36−53 | $P < 0.0001$ |
| | Female | 54−71 | $P < 0.0001$ |

Hematological samples were obtained early in the day following an 8–10 h fasting period to mitigate diurnal fluctuations in cortisol levels. The samples were handled by allowing coagulation, followed by centrifugation and preservation at −20 °C. Methodical labeling and documentation were upheld for precise monitoring and evaluation. Biochemical analysis included tests for TSH, T3, T4, serum cortisol, GABA, and dopamine using advanced technologies on the Abbott ARCHITECT system. Strict quality control procedures, such as equipment calibration and compliance with protocols, were implemented to ensure accurate results. Statistical analysis was performed using STATA software, applying descriptive statistics, t-tests, chi-square tests, and Pearson's correlation to compare and examine relationships between variables. A comprehensive logistic regression analysis was conducted to assess the impact of thyroid function parameters on serum cortisol levels, with a significance level set at $p < 0.05$. The results in Table 1 revealed that all p-values in the dataset were below 0.05, leading to the rejection of the null hypothesis. Additionally, the baseline values were significantly lower than the critical p-values.

Data was subjected to preprocessing to resolve issues such as missing values, outliers, duplicate entries, and inconsistent formatting. This step is crucial for ensuring data integrity and improving the overall quality of the dataset. During preprocessing, features may be scaled or normalized for more effective comparisons. Checking for missing values is essential, as they may indicate that an event did not happen, data was not available, or the data was irrelevant. The approach to dealing with missing data depends on the amount and pattern of the missing information, with potential strategies including removing affected rows or columns, imputing values using mean, median, or regression techniques, or utilizing more advanced methods like K-nearest neighbors (KNN) or multiple imputation. In this case, since the dataset contains no missing values, data cleaning is not required. The main focus of our preprocessing involved modifying or converting the units of the collected data to align with our proposed BiLSTM method.

### *3.2. Proposed structure for prediction by BiLSTM*

A key feature of long short-term memory (LSTM) networks is their memory cell (C) combined with a gate structure that enables the network to determine which information to retain or discard. Each LSTM cell contains four gates: the input gate (i), forget gate (f), control gate (c), and output gate (o). The output gate plays a vital role in producing the output and updating the hidden vector $h_{t-1}$. The mathematical formulation of these processes incorporates the sigmoid activation function sigma and the hyperbolic tangent function tanh, allowing LSTMs to effectively manage information over long sequences, making them well-suited for tasks involving temporal data. By dividing the state neurons of a standard RNN into forward and backward directions, BRNNs can separate outputs from these states and be trained in both directions. This bidirectional architecture can be applied to various RNN variants. In this study, we employed bidirectional LSTM (BiLSTM) [33,34]. The BiLSTM model, illustrated in Figure 1, is a specific type of RNN that addresses the vanishing gradient problem commonly faced by RNNs. Following the embedding layer, a bidirectional LSTM layer is implemented, accompanied by fully connected layers and dropout layers for regularization. The output layer of the BiLSTM consists of a fully connected layer with sigmoid activation units. The ReLU activation function is used in all hidden layers, and the model employs binary cross-entropy as its loss function. Additionally, gated recurrent units (GRU) consist of two gates: the update gate (z) and the reset gate (r). At timestep t, these gates generate output vectors labeled as $z_t$ and $r_t$, with the hidden layer's output at timestep t denoted as $h_t$. The calculations for these output vectors are described in detail as follows [35]:

$$z_t = \sigma\left(W_z x_t + U_z h_{t-1} + b_z\right) \tag{1}$$

$$r_t = \sigma\left(W_r x_t + U_r h_{t-1} + b_r\right) \tag{2}$$

$$h_t = \left(1 - z_t\right) \circ h_{t-1} + z_t \circ tanh\left(W_h x_t + U_h\left(r_t \circ h_{t-1}\right) + b_h\right) \tag{3}$$

Where t represents the time step index, the symbol ◦ denotes the Hadamard product operation, tanh indicates the hyperbolic tangent function, σ symbolizes the sigmoid function, and Wα, Uα, and bα stand for the weight matrix and bias elements of gate α, which are shared by hidden units within the

same layer. This configuration results in 3L sets of weight matrices and biases for a GRU-RNN with L layers. The output vector ht from the hidden unit is transmitted to the hidden unit at time step t + 1 in the same layer, or to the hidden unit at time step t in the next layer. Following the functions of the gates as described in equation (3), an increase in rt diminishes the impact of $h_{t-1}$ on updating ht, while an increase in $z_t$ lessens the influence of ht on resetting $h_t$ to $h_{t-1}$. The prediction model was built using Keras 2.0.8 in a Python 3.4.3 environment, featuring one LSTM layer and one BiLSTM layer, each with four units, along with three fully connected layers of 8, 64, and 8 units. The output layer was a single dense unit for predicting blood neurological values. Cross-validation (80% training, 20% validation) was used to prevent overfitting.

**Table 2.** A comparison of our proposed framework with baseline approaches utilized in previous studies.

| Authors | Approaches | Parameters | Precision |
|---|---|---|---|
| Krishnamoorthy et al. [36] | ARIMA–LSTM | Glucose and cholesterol | RMSE of 31.24 for ARIMA and 109.43 for LSTM |
| Zhang et al. [37] | ARIMA–LSTM–GRU | Dynamic blood glucose | * |
| Yang et al. [38] | ARIMA model with adaptive orders | Blood glucose concentrations and hypoglycemia | * |
| Ali et al. [39] | ANN | Blood glucose level in type 1 diabetes | Mean absolute percentage error of 3.87% |
| Robertson et al. [40] | Elman recurrent artificial neural networks | Blood glucose in AIDA diabetes | RMSE of 0.15 |
| Mamandipoor et al. [41] | LSTM | Blood lactate | AUC of 0.77 |
| Hu et al. [42] | Six machine learning algorithms—bagging, AdaBoost, GaussianNB, logistic regression, MLP, and SVC | Type 2 diabetes | MLP and AdaBoost models with AUC of 0.8487 and accuracy rates of 0.9249 |
| Song et al. [43] | LSTM–CNN | Hypertension | 0.90 = 0.95 |
| Yu et al. [44] | LSTM | Stroke neurologists | RMSE of 89.4 |
| Hong et al. [45] | LSTM | Alzheimer's disease by image preprocessing | AUC of 0.777 |
| Miri-Moghaddam et al. [46] | LSTM | Blood cells (LR-RBC), and platelets (PLT), PLT-apheresis, and fresh frozen plasma (FFP) | * |
| Benyamin et al. [47] | LSTM | Arrhythmias or abnormal blood pressure fluctuations | Accuracy of 83% |
| Present work | BiLSTM | Neurological | Mean accuracy was 92.79% for training |

Table 2 provides an in-depth overview of various methodologies employed by different researchers to forecast health-related parameters, highlighting a range of techniques and performance metrics. Several models have been tailored to address specific health conditions: the ARIMA–LSTM model for predicting glucose and cholesterol levels, the ARIMA–LSSVM–GRU method for dynamic blood glucose monitoring, and an adaptive ARIMA model for tracking blood glucose concentrations and hypoglycemia. Additional methodologies include leveraging artificial neural networks (ANN) for managing Type 1 diabetes, employing Elman recurrent neural networks for blood glucose regulation in the AIDA diabetes framework, utilizing LSTM networks for blood lactate analysis, and integrating LSTM–CNN for hypertension and various blood components. Furthermore, LSTM models have been utilized to forecast arrhythmias and abnormal fluctuations in blood pressure, underscoring the efficacy of artificial neural networks in predicting diverse health conditions.

Nevertheless, there is a notable scarcity of research exploring the use of BiLSTM networks in predicting abnormalities related to neurological parameters. This study seeks to fill that gap by introducing an innovative BiLSTM model. GABA (gamma-aminobutyric acid) plays a crucial role in understanding these neurological concerns. One emerging treatment modality is deep brain stimulation (DBS), which involves implanting a device in the brain to enhance neurological activity across various disorders [48]. Although research on the benefits of DBS for conditions like Parkinson's disease (PD) is still in its early stages, initial findings indicate it may exert diverse neurochemical effects at the network level, likely activating both inhibitory and excitatory pathways [49]. Studies show that GABA levels in the basal ganglia are significantly higher in PD patients compared to control groups, while glutamate and glutamine (Glx) levels are markedly lower. While GABA levels did not correlate significantly with post-surgery outcomes, basal ganglia glutamate levels emerged as a critical predictor, suggesting that glutamatergic neurotransmission may be pivotal in the success of DBS treatment for PD [49]. From a neurochemical perspective, cortisol levels—which are stress-sensitive—may influence certain PD symptoms. This is supported by various studies examining the impact of cortisol levels on motor symptoms, based on the Unified Parkinson's Disease Rating Scale. Elevated serum cortisol levels seem to correlate with anxiety, risk-taking behavior, sleep disturbances, and depressive symptoms, which are common and often troubling in PD patients suffering from neuroleptic malignant syndrome [50]. The exact mechanism by which dopaminergic medication affects cortisol levels remains unclear; however, it can be hypothesized that dopamine exerts a regulatory effect on thyroid dysfunction mechanisms responsible for cortisol release. The relationships among serum levels of dopamine, GABA, cortisol, and thyroid hormones are not well understood. We aim to illustrate these relationships by modeling BiLSTM, which represents a novel approach within the field of biophysics research.

## 4. Ablation study

An ablation study is a method utilized in the analysis of neural network research to assess the impact of various components or features within a model on its overall performance. The primary objective of this approach is to discern the significance of different elements by systematically removing or altering them and observing the resulting effects on model performance. Ablation studies play a crucial role in enhancing model interpretability, debugging, and refinement by providing insights into which model components are most advantageous for its learning process. In our study, we analyzed the relationship between loss and epochs to explore ablation behavior. As the number of epochs increases, the output from the LSTM becomes progressively more accurate. Figure 2 illustrates

the plot of epochs versus loss for the LSTM model. For the BiLSTM modeling, we set the number of epochs to 200. In this figure, we present the losses of the BiLSTM for (a) cortisol, (b) dopamine, and (c) GABA. Notably, the figure indicates that after reaching 200 epochs, the average losses stabilize and remain relatively unchanged.

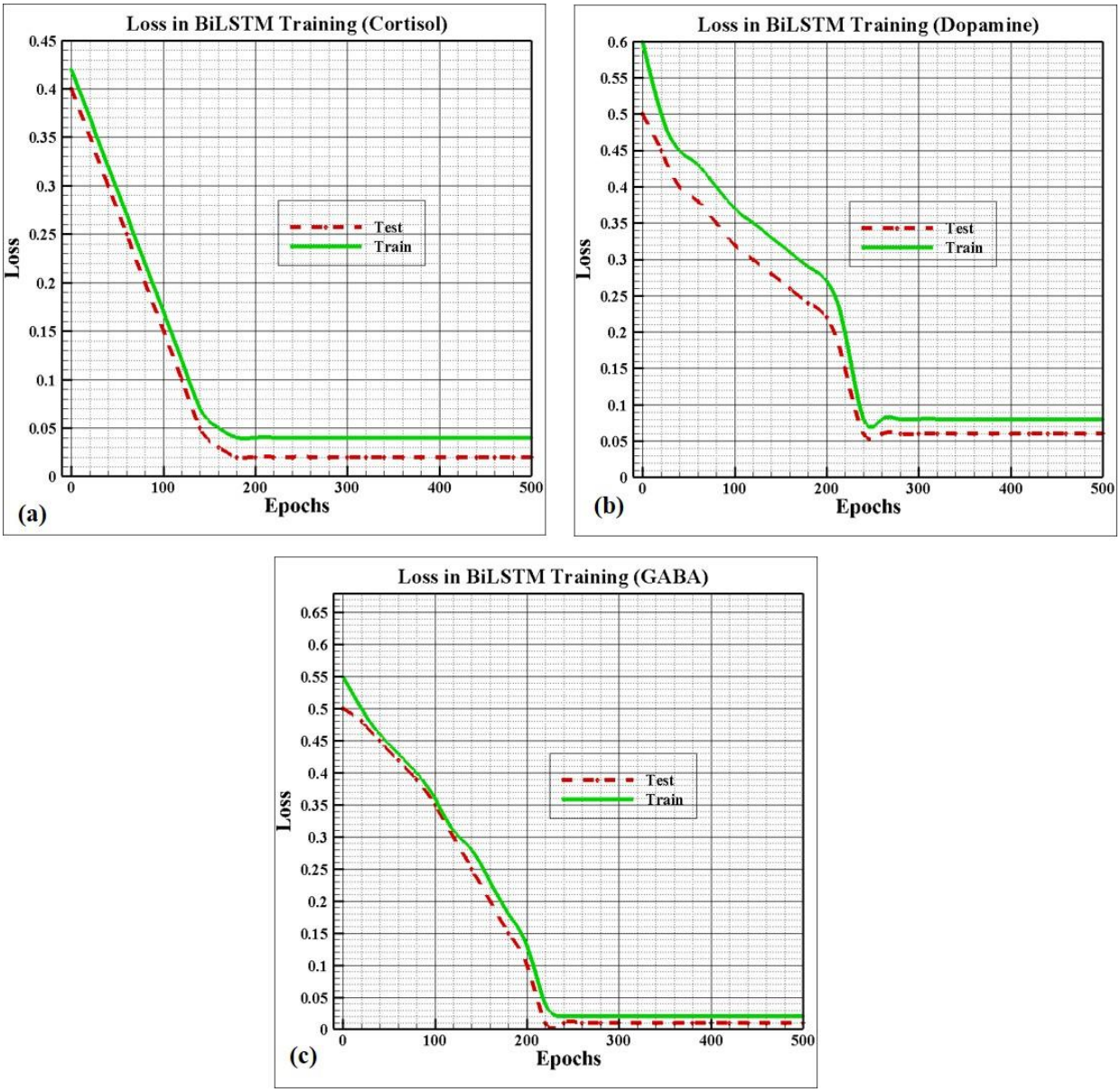


**Figure 2.** Epochs vs. loss for BiLSTM across different prediction levels.

## 5. Performance evaluation measures

In model evaluation, the main focus is on accuracy to assess the correctness of predictions. Accuracy is determined by dividing the total of true positives (TP) and true negatives (TN) by the overall population (TOTAL). The confusion matrix is used to analyze classification errors, allowing for the assessment of precision and true positive rate (TPR), also known as sensitivity or recall. Precision is computed by dividing TP by the number of positive predictions (POS PRED), while TPR is calculated by dividing TP by the total actual positive instances. The formulas for these metrics are

outlined in Table 3 for reference.

**Table 3.** Performance evaluation measures.

| Criteria | Equation |
|---|---|
| Precision | $\frac{\text{TP}}{\text{POS PRED}}$ |
| Sensitivity | $\frac{\text{TP}}{\text{ACTUAL POS}}$ |
| *Accuracy* | $\frac{\text{TP} + \text{TN}}{\text{TOTAL}}$ |

To comprehensively evaluate model performance, k-fold cross-validation is applied for reliable assessments. These evaluation metrics provide an in-depth analysis of the model's predictive ability by contrasting the actual test datasets with the predicted outcomes. The model's performance was evaluated using four primary metrics: root mean square error (RMSE), correlation coefficient (CC), time lag (TL), and fit. RMSE (mg/dL) measures the variance between the actual and predicted neurological parameters levels. It is calculated by taking the square root of the average of the squared differences, where lower RMSE values signify enhanced prediction accuracy [51]:

$$RSME = \sqrt{E((G-\hat{G})^2)} = \sqrt{\frac{1}{N}\sum(G-\hat{G})^2} \tag{4}$$

G and Ĝ represent the actual and predicted values of the neurological parameters, respectively. The CC assesses the linear relationship between the actual and predicted datasets and is calculated as follows [51]:

$$CC_{xy} = \frac{\sigma_{xy}}{\sigma_x \sigma_y} \tag{5}$$

where $\sigma_x$ and $\sigma_y$ denote the standard deviations, and $\sigma_{xy}$ represents the covariance. This formula can also be written as [51,52]:

$$CC = \frac{\sum(G-G_{mean})(\hat{G}-\hat{G}_{mean})}{\sqrt{\sum(G-G_{mean})^2 \sum\sqrt{(\hat{G}-\hat{G}_{mean})^2}}} \tag{6}$$

where $G_{mean}$ and $\hat{G}_{mean}$ are the average values of the actual and predicted neurological parameters, respectively. The TL indicates the smallest time shift necessary for the actual and predicted signals to reach the maximum correlation coefficient. The fit metric is determined by the ratio of RMSE to the root mean square difference between the target values and their average. A higher fit value indicates superior prediction performance [51,52]:

$$Fit = (1 - \frac{\sqrt{\frac{1}{N}\sum (G - \hat{G})^2}}{\sqrt{\frac{1}{N}\sum (G - G_{mean})^2}}) \times 100\% \quad (7)$$

## 6. Results and discussion

Out of 80 cases, 38 were males and 42 were females. The study also included 80 healthy controls matched for age and sex. Table 4 presents the biochemical and socio-demographic characteristics of the participants, along with the normal function test range according to ATA guidelines. The average age in the case and control groups was 40.2 ± 12.3 and 35.25 ± 11.20 years, respectively. There were no significant differences in age and sex between the case and control groups. A linear regression analysis was performed to identify the independent factors influencing the most significant changes in TSH, T3, T4, and cortisol levels. The average serum cortisol level in the case group was 60.01 ± 10.78 μg/dL.

**Table 4.** Lists of the biochemical and socio-demographic characteristics of the study participants. BMI: body mass index; TSH: thyroid stimulating hormone; T3: triiodothyronine; T4: thyroxine.

| | Normal range | Case (n = 80) | Control (n = 80) | p-value |
|---|---|---|---|---|
| Age (years) | NA | 40.2 ± 12.3 | 35.25 ± 11.20 | > 0.05 |
| BMI (kg/m$^2$) | 18.5–24.9 | 24.18 ± 3.1 | 24.45 ± 4.45 | > 0.05 |
| TSH (uIU/L) | 0.4–5.5 | 25.44 ± 9.42 | 6.62 ± 1.11 | < 0.05 |
| T3 (ng/mL) | 0.8–2 | 0.65 ± 0.10 | 1.32 ± 0.32 | < 0.05 |
| T4 (μg/dL) | 5.0–12.0 | 5.54 ± 1.21 | 9.1 ± 1.96 | < 0.05 |
| Cortisol (μg/dL) | 5–25 | 60.01 ± 10.78 | 14.25 ± 5.12 | < 0.05 |

The model was trained over 100 epochs, a time frame chosen to ensure adequate learning while minimizing the risk of overfitting. The learning rate was established at 0.0015, a pivotal hyperparameter that affects the speed at which the model updates its weights using gradient descent. Utilizing a categorical cross-entropy cost function, the model was adept at managing multi-class classification tasks, making it ideal for scenarios where the target variable includes multiple categories. To enhance performance, the Adam optimizer was applied. This adaptive learning rate optimization technique merges the advantages of two popular methods, AdaGrad and RMSProp, by keeping a moving average of both the gradients and their squares. This method facilitates efficient calculations and aids the model in converging more quickly and effectively to a minimum in complicated loss terrains. Throughout the training phase, the model's performance was meticulously monitored by evaluating both training and validation accuracies. Table 5 displays the accuracies achieved by the inception of BiLSTM and LSTM across all folds. The top fold for LSTM showed impressive outcomes, with a training accuracy of 87.23% and a validation accuracy of 77.36%, as illustrated in Table 4. According to the table, the mean accuracy for BiLSTM was 92.79%, 88.75%, and 89.58% for training, validation, and testing, respectively, while LSTM recorded values of 84.48%, 74.58%, and 74.62%. The results indicate a progression over the epochs, demonstrating the model's

improvement over time and the optimization point at which it reached its highest performance. Alongside tracking training and validation accuracies, a thorough evaluation of a distinct test set was conducted, resulting in overall accuracies of 96.4% and 87.3% for LSTM and 97.1% and 98.2% for BiLSTM, as shown in Figure 3, corresponding to fold 1. This metric is essential for assessing the model's generalization to new data, confirming that it is not simply memorizing the training data but is capable of making accurate predictions in real-world contexts. Additional performance insights across various folds are provided in Table 5, including (a) the confusion matrix for training data fold 1 (LSTM), (b) the confusion matrix for test data fold 1 (LSTM), (c) the confusion matrix for training data fold 1 (BiLSTM), and (d) the confusion matrix for test data fold 1 (BiLSTM), all presented in Figure 3. These tables offer a detailed breakdown of accuracy metrics for the training, validation, and test sets, reinforcing the model's reliability and robustness. Each fold represents a unique subset of data, and evaluating performance across these multiple folds enhances our understanding of the model's dependability and its capability to manage data variability. Analyzing these statistics can also highlight areas for improvement, such as refining hyperparameters, modifying the model architecture, or investigating additional data augmentation strategies to further boost performance. Overall, these findings lay a strong groundwork for further experimentation and development within the model's application context. In another section of the results, we compare the correlation of various neurological parameters to BiLSTM, which demonstrates superior prediction accuracy.

**Table 5.** Achieved accuracies of inception BiLSTM and LSTM across all folds.

| BiLSTM | Fold 1 | Fold 2 | Fold 3 | Fold 4 | Fold 5 | Average |
|---|---|---|---|---|---|---|
| Train | 89.31% | 89.99% | 92.52% | 95.36% | 96.78% | 92.79% |
| Validation | 85.63% | 86.96% | 89.36% | 90.30% | 91.65% | 88.75% |
| Test | 86.34% | 87.65% | 90.25% | 91.32% | 92.36% | 89.58% |
| LSTM | Fold 1 | Fold 2 | Fold 3 | Fold 4 | Fold 5 | Average |
| Train | 83.22% | 85.31% | 84.35% | 85.28% | 87.23% | 84.48% |
| Validation | 71.22% | 76.33% | 71.65% | 76.34% | 77.36% | 74.58% |
| Test | 74.34% | 75.36% | 71.23% | 77.63% | 74.36% | 74.61% |

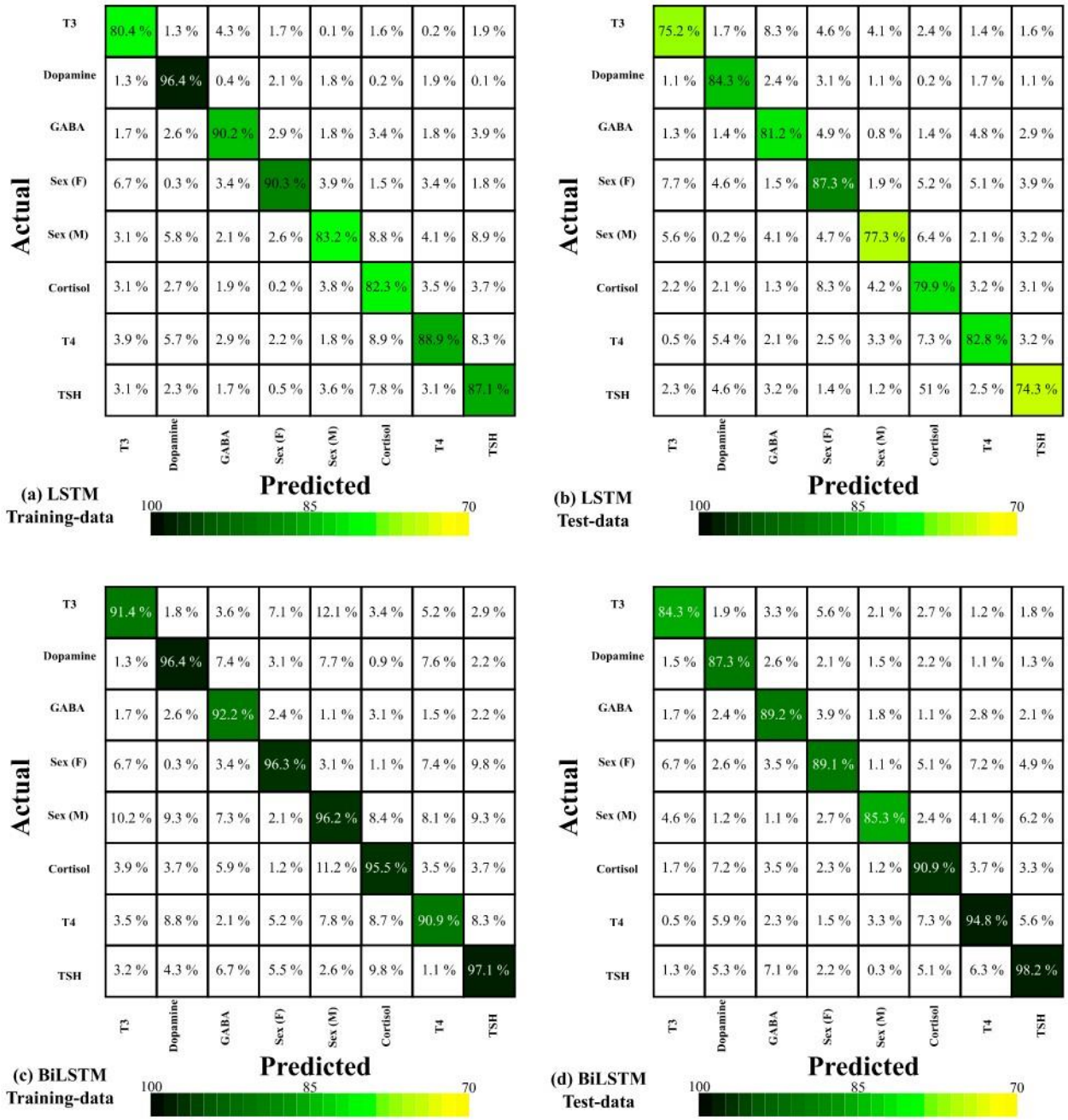


**Figure 3.** (a) Confusion matrix for training data fold 1 (LSTM); (b) confusion matrix for test data fold 1 (LSTM); (c) confusion matrix for training data fold 1 (BiLSTM); (d) confusion matrix for test data fold 1 (BiLSTM).

### *6.1. Correlation between T3, T4, TSH, and cortisol for BiLSTM*

Neurological abnormalities are linked to cortisol levels, as shown in Figure 4a–c, which reveals that women have higher cortisol levels than men. These cortisol levels are closely associated with depression, with depressed women exhibiting elevated evening cortisol and cortisol awakening response (CAR), alongside reduced stress reactivity compared to healthy women. Previous research has established a direct connection between neurological disorders and the progression of Parkinson's

disease [53−55]. The current study aims to elucidate this relationship by leveraging deep learning networks. Similarly, depressed men also show higher overall cortisol levels in both the morning and evening compared to their healthy counterparts. Gender differences play a crucial role in assessing cortisol levels within the context of depression. One possible therapeutic approach to address neurological abnormalities is to assist individuals in adopting new roles—such as becoming mothers to alleviate postpartum depression symptoms or engaging in volunteering after retirement, which can aid in their recovery. The results from the BiLSTM analysis are illustrated in Figure 4d–f. A comparison of this figure with Figures 4a–c reveals a strong relationship between clinical outcomes and predicted results. The correlation of serum cortisol levels with T3, T4, and TSH is presented in Table 6. Table 6 illustrates a strong positive correlation (r = 0.932) between serum cortisol and TSH, as well as strong negative correlations (r = −0.915 and −0.912) between serum cortisol and T3 and serum cortisol and T4, respectively.

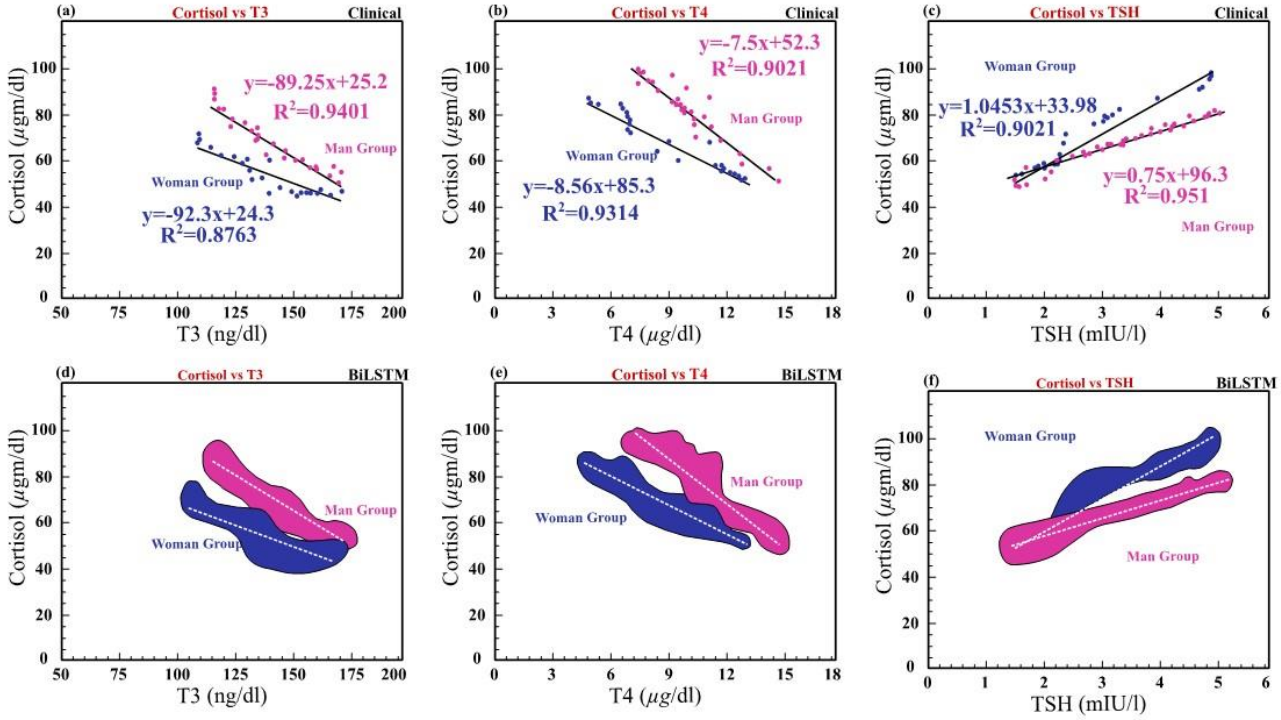


**Figure 4.** Correlation between T3, T4, TSH, and cortisol.

**Table 6.** Correlation of serum cortisol levels with T3, T4, and TSH.

| Serum cortisol (μg/dL) | Correlation |
|---|---|
| TSH (mIU/L) | 0.932 |
| T3 (ng/mL) | −0.915 |
| T4 (μg/dL) | −0.912 |

The study investigated the relationship between serum cortisol levels and hypothyroidism, revealing a strong positive correlation between TSH and cortisol, as depicted in Figure 4a–c. Negative linear correlations were observed between serum T4, T3, and cortisol levels in the hypothyroidism group. The research emphasized the intricate connection between cortisol dynamics and thyroid function, highlighting the significance of considering the HPA axis in hypothyroidism. Elevated

cortisol levels were detected in individuals with more severe hypothyroidism, indicating a compensatory mechanism initiated by the HPA axis in response to metabolic disturbances. The study emphasizes the importance of evaluating both thyroid function and cortisol dynamics in managing hypothyroid patients, suggesting that assessing blood cortisol levels alongside traditional thyroid function tests could provide valuable insights for treatment. The findings underscore the complex interplay between cortisol and hypothyroidism, underscoring the need for further research to explore potential therapeutic implications and enhance personalized treatment strategies for individuals with hypothyroidism.

## 7. Correlation between T3, T4, TSH, and dopamine for BiLSTM

Dopamine has long been recognized as a key contributor to Parkinson's disease, a progressive neurodegenerative condition that may begin with mild hand tremors and gradually impair movement coordination. Interestingly, levels of dopamine are positively correlated with thyroid hormones like TSH, T3, and T4. This connection highlights the complex relationship between dopamine dysregulation and thyroid function in the context of Parkinson's disease. Gaining insight into how these neurotransmitter and hormone systems interact can shed light on the underlying mechanisms of Parkinson's disease progression and symptoms. In Figure 5a–c, correlation coefficients illustrate a positive relationship between TSH, T3, T4, and dopamine, indicating a direct association between serum T4, T3, and dopamine levels in individuals facing hypothyroidism. Our research emphasizes the interaction between dopamine dynamics and thyroid function, pointing out the importance of considering the HPA axis in hypothyroid patients. Additionally, we observed a significant link between serum cortisol levels and indicators of thyroid dysfunction. Thyrotropin (TSH) governs the production of T3 and T4 by the thyroid gland, where increased TSH levels with low T3/T4 levels indicate hypothyroidism and low TSH with high T3/T4 levels suggest hyperthyroidism. It is critical to monitor TSH levels within the 0.4–4.0 mIU/L range for diagnosing thyroid disorders, with any deviations necessitating further investigation of T3, T4, and TSH levels for effective management.

Optimal T3 levels generally range from 100 to 200 ng/dL, T4 levels should be between 5.0 and 12.0 μg/dL, and free T4 levels ideally range from 0.8 to 1.8 ng/dL. Hormonal imbalances can indicate thyroid problems that may lead to symptoms such as weight loss, sleep issues, Graves' disease, and other severe consequences [56,57]. Although thyroid hormones are vital for dopamine neuron function, excessive levels can result in hyperthyroidism. Therefore, it is crucial to develop thyroid hormone derivatives that enhance dopamine function without causing hyperthyroidism in Parkinson's treatment. Studies highlight the significance of iodine in serotonin and dopamine synthesis, with low iodine levels potentially leading to neurotransmitter deficiencies [58,59]. The enzyme tyrosine hydroxylase (TH) is instrumental in the biosynthesis of DA and other catecholamines, suggesting that modulating TH could improve gene therapy strategies and other therapeutic approaches. Notably, Figure 5 shows that dopamine levels in males were higher than those in females, indicating that excessively elevated dopamine levels in the brain can result in various neurological and psychiatric disorders. Effective regulation of dopamine signaling is vital for optimal brain health, as imbalances can lead to a spectrum of neurological and psychiatric conditions. The slope of the interpolated line for both sexes was quite similar, with the most significant difference observed in serum T4 levels. In individuals with hypothyroidism, dopamine levels exhibited strong positive correlations with T3 ($r = 0.89$, $p = 0.021$), T4 ($r = 0.901$, $p = 0.026$), and TSH ($r = 0.81$, $p = 0.026$) serum levels in both groups. The

results from the BiLSTM analysis, which illustrate the correlation between T3, T4, TSH, and dopamine, are presented in Figure 5d–f. This figure, when compared to Figure 5a–c, highlights a robust relationship between clinical findings and predicted outcomes. Additionally, the correlation of dopamine levels with T3, T4, and TSH is detailed in Table 7.

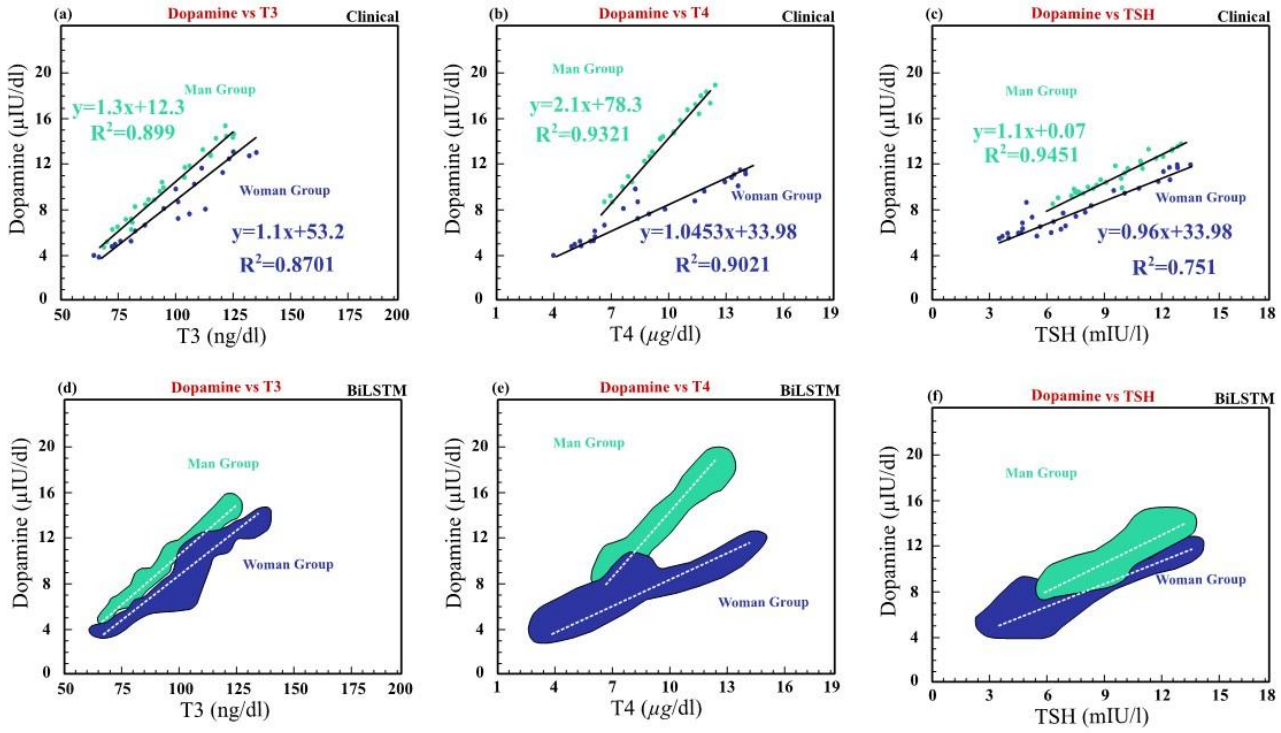


**Figure 5.** Correlation between T3, T4, TSH, and dopamine.

**Table 7.** Correlation between dopamine levels and T3, T4, and TSH.

| Dopamine (μIU/dL) | Correlation |
|---|---|
| TSH (mIU/L) | 0.810 |
| T3 (ng/mL) | 0.890 |
| T4 (μg/dL) | 0.901 |

## 8. Correlation between T3, T4, TSH, and GABA for BiLSTM

Figure 6a–c illustrates the correlations between GABA levels and T3, T4, and TSH levels in individuals suffering from hypothyroidism. In this group, GABA levels exhibited strong positive correlations with T3 ($r = 0.942$, $p = 0.016$), T4 ($r = 0.962$, $p = 0.026$), and TSH ($r = 0.917$, $p = 0.026$) serum levels. Thyroid hormones are essential for the production and breakdown of GABA, influencing its levels, release, reuptake, and receptor function in the brain. The effect of thyroid hormones on the GABA system differs between developing and adult brains, generally enhancing GABA function during development and inhibiting it in adulthood. Additionally, there is evidence that GABA can affect the thyroid system by inhibiting TRH release in the hypothalamus, thereby reducing TSH secretion from the pituitary and thyroid hormone release from the thyroid gland [60]. While some studies present conflicting results, the interaction between thyroid hormones and GABA is likely

significant, especially given the link between thyroid disorders and neurological issues related to GABA. In patients with Parkinson's disease experiencing visual hallucinations and aged 54−71, there is a notable association with decreased occipital GABA levels. GABA, known for its inhibitory role on neuronal activity, shows a fascinating positive correlation with thyroid hormones like TSH, T3, and T4. The correlation between T3, T4, TSH, and GABA for the BiLSTM is illustrated in Figure 6d–f. This relationship suggests a potential interaction between GABA neurotransmission and thyroid function in these patients. Since thyroid hormones are crucial in regulating various bodily functions, including brain activity, investigating the link between GABA levels and thyroid hormone concentrations in Parkinson's patients with visual hallucinations could provide important insights into the mechanisms behind these symptoms. Understanding these relationships might lead to novel therapeutic approaches to manage visual hallucinations and improve the overall quality of life for those living with Parkinson's disease.

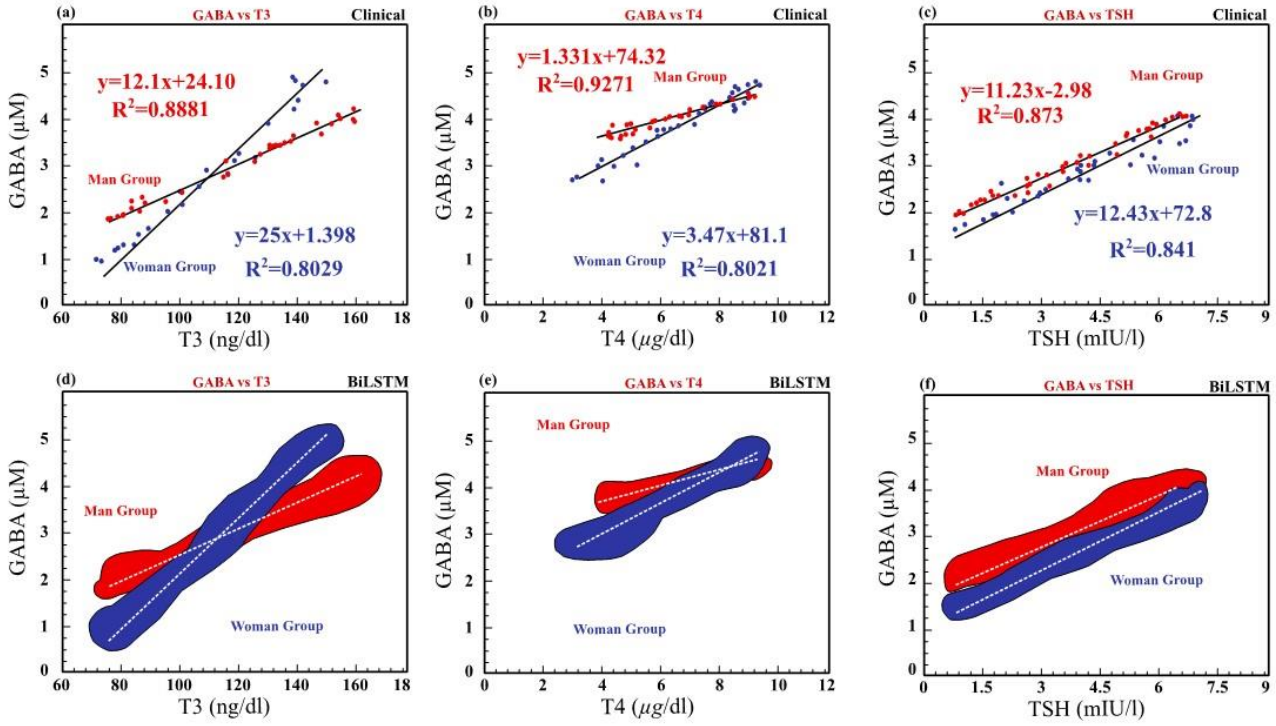


**Figure 6.** Correlation between T3, T4, TSH, and GABA.

**Table 8.** Correlation of GABA levels with T3, T4, and TSH.

| GABA (μM) | Correlation |
|---|---|
| TSH (mIU/L) | 0.917 |
| T3 (ng/mL) | 0.942 |
| T4 (μg/dL) | 0.962 |

In Parkinson's disease patients aged between 54 and 71 years old who experience visual hallucinations, there is a noticeable decrease in occipital GABA concentrations. Notably, GABA exhibits a positive correlation with thyroid hormones, including TSH, T3, and T4, within this specific group of individuals. This association underscores the possible interaction between GABA

neurotransmission and thyroid function in Parkinson's disease patients experiencing visual hallucinations within this age group. Table 8 illustrates the correlation between GABA levels and the hormones T3, T4, and TSH.

## 9. Conclusions

A new deep learning architecture, specifically the BiLSTM model, was developed to predict outcomes in patients with hypothyroidism, showing better performance than existing models. This model effectively captures multi-correlation features from various neurological parameters for assessing Parkinson's disease risk in hypothyroid patients. As incidences of thyroid cancer rise, research is focusing on the links between thyroid hormones and neurological disorders. Managing hypothyroidism typically involves synthetic hormone medications, while hyperthyroidism may require radioactive iodine, anti-thyroid drugs, or surgery, along with lifestyle changes like diet and exercise. Parkinson's disease, characterized by dopamine neuron loss, results in symptoms like tremors and cognitive issues. Its causes are not fully understood but may involve genetic and environmental factors. Treatment mainly focuses on symptom management through medication and support systems. Research indicates correlations between cortisol, TSH, T3, and T4 hormone levels, with BiLSTM achieving higher accuracy (92.79%) compared to LSTM at 84.48%. These findings highlight potential future research directions and implications for treatment strategies in managing these conditions.

The current study faces limitations in extracting additional neurotransmitter parameters that may be critical for understanding neurological changes associated with thyroid dysfunction. While this research has focused on key neurological parameters related to the disease, we recommend incorporating other relevant parameters. Key neurotransmitters, such as glutamate, acetylcholine, serotonin, norepinephrine, and melatonin, may all play a role in the abnormalities observed in individuals with thyroid dysfunction. To analyze these parameters, researchers may primarily utilize two methods: cerebrospinal fluid (CSF) analysis, which involves collection via lumbar puncture, and brain tissue analysis, which examines post-mortem samples for neurotransmitter levels and protein expression. However, brain tissue analysis presents challenges due to the need for surgical procedures and limitations to specific locations and laboratories. This research suggests including the effects of the aforementioned neurotransmitters and integrating them into the under-studied parameters. Additionally, we propose using alternative artificial neural network (ANN) models to predict neurological parameters related to thyroid dysfunction. Furthermore, future research should consider employing image segmentation techniques for analyzing MRI scans, potentially utilizing various ANN architectures, such as convolutional neural networks (CNN) and long short-term memory networks (LSTM), to better predict the progression of thyroid-related changes.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

## Acknowledgments

The authors express gratitude to the Head of the Natural Sciences Department, the Medical

Superintendent, the Director, and the Ethics Committee of Tabriz Sadra Institute of Medical Sciences, Tabriz, for granting permission to conduct the study at the institute.

## Conflict of interest

Participants in this study provided consent, or consent was waived. Approval (110/IEC/TSIM/2023) was obtained from the Institutional Ethics Committee at Tabriz Sadra Institute of Medical Sciences (TSIM), Tabriz. The study did not involve animal subjects or tissue. The authors disclosed no conflicts of interest, stating that no financial support was received for the submitted work. They also confirmed no financial relationships in the past three years with organizations that may have an interest in the work. Additionally, the authors declared no other relationships or activities that could be perceived as influencing the submitted work.

## Author contributions

Dina Falah Noori Al-Sabak and Leila Sadeghi conceptualized the study, designed the methodology, conducted data analysis, supervised the project, and contributed to writing and revising the manuscript. Gholamreza Dehghan assisted with the literature review, collected data, and contributed to writing and revising the manuscript.

## References

1. Erge E, Kiziltunc C, Balci SB, et al. (2023) A novel inflammatory marker for the diagnosis of Hashimoto's thyroiditis: platelet-count-to-lymphocyte-count ratio. *Diseases* 11: 15. https://doi.org/10.3390/diseases11010015
2. Abonowara A, Quraishi A, Sapp JL, et al. (2012) Prevalence of atrial fibrillation in patients taking TSH suppression therapy for management of thyroid cancer. *Clin Invest Med* 35: 152−156. https://doi.org/10.25011/cim.v35i3.16591
3. Gong Y, Qian S, Chen D, et al. (2023) Serum BLMH and CKM as potential biomarkers for predicting therapeutic effects of deep brain stimulation in Parkinson's disease: a proteomics study. *J Integr Neurosci* 22: 163. https://doi.org/10.31083/j.jin2206163
4. Katunina EA, Blokhin V, Nodel MR, et al. (2023) Searching for biomarkers in the blood of patients at risk of developing Parkinson's disease at the prodromal stage. *Int J Mol Sci* 24: 1842. https://doi.org/10.3390/ijms24031842
5. Knezevic E, Nenic K, Milanovic V, et al. (2023) The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. *Cells* 12: 2726. https://doi.org/10.3390/cells12232726
6. Pereira Jr JC, Pradella-Hallinan M, Pessoa HDL (2010) Imbalance between thyroid hormones and the dopaminergic system might be central to the pathophysiology of restless legs syndrome: a hypothesis. *Clinics* 65: 547−554. https://doi.org/10.1590%2FS1807-59322010000500013
7. Shalash A, Salama M, Makar M, et al. (2017) Elevated serum α-synuclein autoantibodies in patients with parkinson's disease relative to Alzheimer's disease and controls. *Front Neurol* 8: 720. https://doi.org/10.3389/fneur.2017.00720

8. Yu H, Farahani P (2015) Thyroid stimulating hormone suppression post-therapy in patients with Graves' disease: a systematic review of pathophysiology and clinical data. *Clin Invest Med* 38: E31−E44. https://doi.org/10.25011/cim.v38i1.22574
9. Cramb KM, Beccano-Kelly D, Cragg SJ, et al. (2023) Impaired dopamine release in Parkinson's disease. *Brain* 146: 3117−3132. https://doi.org/10.1093/brain/awad064
10. Souza-Talarico JND, Marin MF, Sindi S, et al. (2011) Effects of stress hormones on the brain and cognition: Evidence from normal to pathological aging. *Dem Neuropsychol* 5: 8−16. https://doi.org/10.1590/S1980-57642011DN05010003
11. Błaszczyk JW (2016) Parkinson's disease and neurodegeneration: GABA-collapse hypothesis. *Front Neurosci* 10: 198655. https://doi.org/10.3389/fnins.2016.00269
12. Charoenngam N, Rittiphairoj T, Ponvilawan B, et al. (2022) Thyroid dysfunction and risk of parkinson's disease: a systematic review and meta-analysis. *Front Endocrinol* 13: 863281. https://doi.org/10.3389/fendo.2022.863281
13. Shanthi S, Kumar (2011) A novel approach for the prediction of glucose concentration in type 1 diabetes ahead in time through ARIMA and differential evolution. *Adv Eng Inform* 38: 4182−4186.
14. Wang Z, Zhang W, Wu T, et al. (2024) Time series models in prediction of severe fever with thrombocytopenia syndrome cases in Shandong province, China. *Infect Dis Model* 9: 224−233. https://doi.org/10.1016/j.idm.2024.01.003
15. Daskalaki E, Prountzou A, Diem P, et al. (2012) Real-time adaptive models for the personalized prediction of glycemic profile in type 1 diabetes patients. *Diabetes Technol Ther* 14: 168−174. https://doi.org/10.1089/dia.2011.0093
16. Bunescu R, Struble N, Marling C, et al. (2013) Blood glucose level prediction using physiological models and support vector regression. *12th International Conference on Machine Learning and Applications, IEEE.* 1: 135−140. https://doi.org/10.1109/ICMLA.2013.30
17. Georga EI, Protopappas VC, Fotiadis DI (2011) Glucose prediction in type 1 and type 2 diabetic patients using data driven techniques, Knowledge-Oriented Applications in Data Mining, 277−296. https://doi.org/10.5772/13222
18. Mhaskar HN, Pereverzyev SV, Van der Walt MD (2017) A deep learning approach to diabetic blood glucose prediction. *Front Appl Math Stat* 3: 14. https://doi.org/10.3389/fams.2017.00014
19. Bengio Y, Simard P, Frasconi P (1994) Learning long-term dependencies with gradient descent is difficult. *IEEE Trans Neural Netw* 5: 157−166. https://doi.org/10.1109/72.279181
20. Kumar K, Ghosh R (2024) Parkinson's disease diagnosis using recurrent neural network based deep learning model by analyzing online handwriting. *Multimedia Tools Appl* 83: 11687−11715. https://doi.org/10.1007/s11042-023-15811-1
21. Hochreiter S, Schmidhuber J (1997) Long short-term memory. *Neural Comput* 9: 1735−1780. https://doi.org/10.1162/neco.1997.9.8.1735
22. Sankaran NK, Kesavadas T (2020) RNN-LSTM based tissue classification in robotic system for breast biopsy. 8th IEEE RAS/EMBS International Conference for Biomedical Robotics and Biomechatronics, 846−852. https://doi.org/10.1109/BioRob49111.2020.9224378
23. Nisar KS, Anjum MW, Raja MAZ, et al. (2024) Recurrent neural network for the dynamics of Zika virus spreading. *AIMS Public Health* 11: 432−458. https://doi.org/10.3934/publichealth.2024022

24. Rubin-Falcone H, Lee JM, Wiens J (2024) Learning control-ready forecasters for blood glucose management. *Comput Biol Med* 180: 108995. https://doi.org/10.1016/j.compbiomed.2024.108995
25. Mirshekarian S, Bunescu R, Marling C, et al. (2017) Using LSTMs to learn physiological models of blood glucose behavior. 39th Annual international conference of the IEEE engineering in medicine and biology society, 2887−2891. https://doi.org/10.1109/embc.2017.8037460
26. Su P, Ding XR, Zhang YT, et al. (2018) Long-term blood pressure prediction with deep recurrent neural networks. IEEE EMBS International conference on biomedical and health informatics, 323−328. http://dx.doi.org/10.1109/BHI.2018.8333434
27. Honegger P, Lenoir D (1980) Triiodothyronine enhancement of neuronal differentiation in aggregating fetal rat brain cells cultured in a chemically defined medium. *Brain Res* 199: 425−434. https://doi.org/10.1016/0006-8993(80)90699-X
28. Bernal J, Guadaño-Ferraz A, Morte B (2003) Perspectives in the study of thyroid hormone action on brain development and function. *Thyroid* 13: 1005−1012. https://doi.org/10.1089/105072503770867174
29. Hashimoto H, Walker CH, Prange Jr AJ, et al. (1991) The effects of thyroid hormones on potassium-stimulated release of 3H-GABA by synaptosomes of rat cerebral cortex. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* 5:49−54. https://pubmed.ncbi.nlm.nih.gov/1930611/
30. Mason GA, Walker CH, Prange Jr AJ (1990) Depolarization-dependent 45Ca uptake by synaptosomes of rat cerebral cortex is enhanced by L-triiodothyronine. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* 3: 291−295. https://pubmed.ncbi.nlm.nih.gov/2400546/
31. Alamara DO, Sadeghi L, Dehghan G (2023) The relationship between thyroid deficiency and blood-based biomarkers of cognitive disorders. *Neuroendocrinol Lett* 44: 216−222.
32. Cooper DS, Doherty GM, Haugen BR, et al. (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. *Thyroid* 19: 1167−1214. https://doi.org/10.1089/thy.2009.0110
33. Lin H, Zhang S, Li Q, et al. (2023) A new method for heart rate prediction based on LSTM-BiLSTM-Att. *Measurement* 207: 112384. https://doi.org/10.1016/j.measurement.2022.112384
34. Huang M, Lai H, Yu Y, et al. (2021) Deep-gated recurrent unit and diet network-based genome-wide association analysis for detecting the biomarkers of Alzheimer's disease. *Med Image Anal* 73: 102189. https://doi.org/10.1016/j.media.2021.102189
35. Zhang L, Shi R, Youssefi N (2024) Oral cancer diagnosis based on gated recurrent unit networks optimized by an improved version of northern goshawk optimization algorithm. *Heliyon* 10: e32077. https://doi.org/10.1016/j.heliyon.2024.e32077
36. Krishnamoorthy U, Karthika V, Mathumitha MK, et al. (2024) Learned prediction of cholesterol and glucose using ARIMA and LSTM models–a comparison. *Results Control Optim* 14: 100362. https://doi.org/10.1016/j.rico.2023.100362
37. Zhang Y, Ning Y, Li B, et al. (2021) Short-term prediction for dynamic blood glucose trends based on ARIMA-LSSVM-GRU model., 2021 International Conference on Electrical Engineering and Computer Technology, 012057. https://doi.org/10.1088/1742-6596/2030/1/012057

38. Yang J, Li L, Shi Y, et al. (2018) An ARIMA model with adaptive orders for predicting blood glucose concentrations and hypoglycemia. *IEEE J Biomed Health Informat* 23: 1251−1260. https://doi.org/10.1109/JBHI.2018.2840690
39. Ali JB, Hamdi T, Fnaiech N, et al. (2018) Continuous blood glucose level prediction of type 1 diabetes based on artificial neural network. *Biocybern Biomed Eng* 38: 828−840. https://doi.org/10.1016/j.bbe.2018.06.005
40. Robertson G, Lehmann ED, Sandham W, et al. (2011) Blood glucose prediction using artificial neural networks trained with the AIDA diabetes simulator: a proof-of-concept pilot study. *J Electr Comput Eng* 2011: 681786. https://doi.org/10.1155/2011/681786
41. Mamandipoor B, Yeung W, Agha-Mir-Salim L, et al. (2022) Prediction of blood lactate values in critically ill patients: a retrospective multi-center cohort study. *J Clin Monit Comput* 36*:* 1087−1097. https://doi.org/10.1007/s10877-021-00739-4
42. Hu TL, Chao CM, Wu CC, et al. (2024) Machine learning-based predictions of mortality and readmission in type 2 diabetes patients in the ICU. *Appl Sci* 14: 8443. https://doi.org/10.3390/app14188443
43. Song X, Zhu L, Feng X, et al. (2021) Combined forecast model of lstm-cnn hypertension based on eemd. Proceedings of the 2021 4th International Conference on Signal Processing and Machine Learning, 117−122. https://doi.org/10.1145/3483207.3483227
44. Yu Y, Parsi B, Speier W, et al. (2019) LSTM network for prediction of hemorrhagic transformation in acute stroke. Medical Image Computing and Computer Assisted Intervention–MICCAI 2019: 22nd International Conference, 177−185. https://doi.org/10.1007/978-3-030-32251-9_20
45. Hong X, Lin R, Yang C, et al. (2019) Predicting Alzheimer's disease using LSTM. *IEEE Access* 7: 80893−80901. https://doi.org/10.1109/ACCESS.2019.2919385
46. Miri-Moghaddam E, Bizhaem SK, Moezzifar Z, et al. (2024) Long-term prediction of Iranian blood product supply using LSTM: a 5-year forecast. *BMC Med Inform Decis Mak* 24: 213. https://doi.org/10.1186/s12911-024-02614-z
47. Benyamin MPS, Sugiartawan P, Noviaty PS (2024) Identification of heart disease in patients using the long short-term memory (LSTM) method. First International Conference on Applied Mathematics, Statistics, and Computing, 149−159. https://doi.org/10.2991/978-94-6463-413-6_15
48. Al-Kasar BCM, Asl SK, Asgharzadeh H, et al. (2024) Denoising deep brain stimulation pacemaker signals with novel polymer-based nanocomposites: porous biomaterials for sound absorption. *AIMS Bioeng* 11: 241−265. https://doi.org/10.3934/bioeng.2024013
49. Tuura RLG, Baumann CR, Baumann-Vogel H (2018) Neurotransmitter activity is linked to outcome following subthalamic deep brain stimulation in Parkinson's disease. *Parkinsonism Relat Disord* 50: 54−60. https://doi.org/10.1016/j.parkreldis.2018.02.014
50. van Wamelen, DJ, Wan YM, Chaudhuri KR, et al. (2020) Stress and cortisol in Parkinson's disease. *Int Rev Neurobiol* 152: 131−156. https://doi.org/10.1016/bs.irn.2020.01.005
51. Sun Q, Jankovic MV, Bally L, et al. (2018) Predicting blood glucose with an lstm and bi-lstm based deep neural network. 2018 14th symposium on neural networks and applications, 1−5. https://doi.org/10.1109/NEUREL.2018.8586990
52. Butt FM, Hussain L, Mahmood A, et al. (2021) Artificial Intelligence based accurately load forecasting system to forecast short and medium-term load demands. *Math Biosci Eng* 18: 400−425. https://doi.org/10.3934/mbe.2021022

53. Wissel BD, Dwivedi AK, Merola A, et al. (2018) Functional neurological disorders in Parkinson disease. *J Neurol Neurosurg Psychiatry* 89: 566−571. https://doi.org/10.1136/jnnp-2017-317378
54. Onofrj M, Russo M, Carrarini C, et al. (2022) Functional neurological disorder and somatic symptom disorder in Parkinson's disease. *J Neurol Sci* 433: 120017. https://doi.org/10.1016/j.jns.2021.120017
55. Fu P, Gao M, Yung KKL (2019) Association of intestinal disorders with Parkinson's disease and Alzheimer's disease: a systematic review and meta-analysis. *ACS Chem Neurosci* 11: 395−405. https://doi.org/10.1021/acschemneuro.9b00607
56. Lamichhane TR, Lamichhane HP (2020) Structural changes in thyroid hormone receptor-beta by T3 binding and L330S mutational interactions. *AIMS Biophy* 7: 27−40. https://doi.org/10.3934/biophy.2020003
57. De Leo S, Lee SY, Braverman LE (2016) Hyperthyroidism. *Lancet* 388: 906–918. https://doi.org/10.1016/s0140-6736(16)00278-6
58. Sinha SR, Prakash P, Keshari JR, et al. (2023) Assessment of serum cortisol levels in hypothyroidism patients: a cross-sectional study. *Cureus* 15: e50199. https://doi.org/10.7759/cureus.50199
59. Zimmermann MB (2020) Iodine and the iodine deficiency disorders. *Present Knowl Nutr* 1: 429−441. https://doi.org/10.1016/B978-0-323-66162-1.00025-1
60. Chen C, Ma Q, Chen X, et al. (2015) Thyroid hormone-Otx2 signaling is required for embryonic ventral midbrain neural stem cells differentiated into dopamine neurons. *Stem Cells Dev* 24: 1751−1765. https://doi.org/10.1089%2Fscd.2014.0489



AIMS Press