IEEE Access
Multidisciplinary | Rapid Review | Open Access Journal

Received March 26, 2019, accepted April 16, 2019, date of publication May 2, 2019, date of current version May 17, 2019.

Digital Object Identifier 10.1109/ACCESS.2019.2914473

Can C-Reactive Protein (CRP) Time Series Forecasting be Achieved via Deep Learning?

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This work was supported in part by the Cancer Council SA, in part by the Government of South Australia, and in part by The University of Adelaide.

ABSTRACT C-reactive protein (CRP) is a biomarker of inflammation and is widely considered as an indicator of cancer prognosis, risk, and recurrence in clinical experiments. Investigating the properties and behaviors of CRP time series has recently emerged as an area of significant interest in informing clinical decision making. The area of cancer immunotherapy is a key application where CRP forecasting is critically needed. Therefore, predicting the future values of a CRP time series can provide useful information for clinical purposes. In this paper, we focus on CRP time series forecasting, comparing autoregressive integrated moving average (ARIMA) modeling with deep learning. The CRP data are obtained from 24 patients with melanoma. This paper using CRP data indicates that deep learning provides significantly reduced prediction error compared to ARIMA modeling.

INDEX TERMS Biomedical engineering, forecasting, autoregressive modeling, ARIMA, machine learning, deep learning, recurrent neural networks, time series analysis, C-reactive protein, CRP, cancer, immunotherapy.

I. INTRODUCTION

In recent decades, C-reactive protein (CRP), a widely used acute-phase protein, has been considered as a sensitive indicator of inflammation, infection and tissue damage arising from stimulation of the immune system [1]. Notably, CRP is now viewed as a marker in forecasting cancer survival. There is a substantial body of literature describing the association between prognosis and C-reactive protein (CRP) in patients with cancer [2]–[21]. Recent research shows that elevated CRP levels are associated with increased risk of cancer and reduced survival [22], [23].

Moreover, CRP can be used as a reliable tool for making vital decisions in treatment or assessing the outcomes of patients with cancer [24], [25]. In order to develop a guideline, the ''Cancer Immunogram'' as a framework for describing the different interactions between cancer and the immune system has been proposed. The framework uses seven defined parameters containing CRP that characterize aspects of cancer-immune interactions for clinical decision making [26]. A study on immunotherapy in lung cancer illustrated that patients treated with nivolumab with CRP levels below the median had significantly longer median time to treatment failure than when CRP was above the median. Therefore, elevated CRP may indicate a reduced likelihood of response to immunotherapy [27]. In addition, the role of pre-treatment CRP and its variation after therapy in the anti-tumor effect of targeted agents in patients with metastatic renal cancer has been investigated [28]. The findings in a prostate cancer study also showed that elevated CRP levels were correlated with shorter biochemical failure-free survival for patients who received radiation therapy after undergoing radical prostatectomy [29].

Note that CRP is an emerging biomarker for predicting outcomes in immunotherapy. It is suggested that the CRP variation can improve stratification of patients with metastatic renal cancer [30]. Immunotherapy is of significant interest because traditional cytotoxic chemotherapy for advanced cancers, for example, shows only a *complete response*[1] median 7% (range 1–10%) [31]. In addition, a prescription

The associate editor coordinating the review of this manuscript and approving it for publication was Zehong Cao.

[1]Complete response is medical term that that signifies a therapy has resulted in disappearance of all detectable tumors, and is the criterion of successful treatment. Complete response rate is the percentage of patients that have a complete response to the treatment.

is provided for the minimum data sample rate required in frequency analyses experiments for improved testing of a periodic CRP signal hypothesis [32].

In previous research, patient CRP values were considered in two different groups, defined by a suitable cut-off value with concentrations above and below that value. Therefore, a study on the time domain behavior of CRP may potentially provide useful information for clinicians. More precisely, since CRP is correlated with inflammation, an approach for CRP prediction is significant for forecasting inflammation and cancer survival. In addition, CRP forecasting approaches may potentially guide decisions in cancer treatments, such as in immunotherapy [24].

The CRP data are unevenly sampled, sparse and noisy by nature, and an important open question that has never been answered before is, 'can the CRP time series be forecasted?' We are now able to answer this in the affirmative. Our analysis of CRP time series shows that autocorrelation is not localized and thus correlations in the data are not washed out by noise. This then supports the hypothesis that some level of forecasting is possible in principle, and we show that deep learning works remarkably well in this regard. This is an important step in field of biomedical signal analysis of CRP data, because previous work made little progress in this regard due to a large focus on searching for periodic patterns in CRP series that was fraught with difficulties in such sparse data. Time series forecasting can be defined as the estimation of future values of temporal measurements that are built based on mathematical and statistical models with specific assumptions about the underlying system [33].

Although several research studies on time series forecasting have been proposed with various solution techniques over the years, the prominent techniques fall into two broad categories, namely, statistical and soft computing techniques. Note that ARIMA is widely regarded as the most efficient statistical forecasting technique. The model significantly relies on past values of the time series and previous error terms for prediction. In contrast to many forecasting statistical techniques, which assume that the time series are generated from linear processes, soft computing approaches such as neural networks (NNs) are appropriate for most real-world problems that are nonlinear. The application, evaluation and comparison of both ARIMA and NNs for forecasting CRP time series are critical as they do not assume knowledge of any underlying pattern or relationship.

Note that the ARIMA model is widely utilized in biomedical signal processing [34]–[37]. The ARIMA model uses observations from previous time steps as input to a regression equation and predicts the value at the next time step.

Artificial intelligence techniques have been employed widely to cope with real-life applications in previous studies, e.g. [38]–[41]. Specifically, artificial neural networks (ANNs) are found to be very efficient in solving medical problems over the last two decades. Several studies have employed Recurrent Neural Networks (RNNs) to bio-signals including glucose measurements [42] and electrocardiograms [43]. The combination of deep neural networks and conditional random fields (CRFs) is used for biomedical named entity recognition (BNER) [44], [45]. Moreover, recurrent neural networks with long short-term memory (LSTM) have been widely employed for biomedical time series [46]–[51]. Deep learning with LSTM is also widely used for forecasting. It is shown that the application of LSTM provides solutions to a range of problems based on biomedical data [52]–[56].

This paper first presents a CRP forecasting approach using an ARIMA model, for comparison with forecasting based on deep learning. The deep learning approach uses Recurrent Neural Networks (RNNs), in particular networks with Long Short-Term Memory (LSTM) blocks—this is a powerful and increasingly deployed method for dealing with time series [57].

II. MATERIALS AND METHODS

Twenty-four melanoma patients were enrolled in the study and CRP levels were obtained. The CRP measurements were carried out on weekdays, with some exceptions where daily measurements were made.

Using a centrifuge, plasma was isolated from the whole blood collected, after removing cellular and protein debris; aliquoted and stored at –80Âř C for later use. The CRP levels were determined by laboratory enzyme-linked immunosorbent assay (ELISA). The test is a plate-based assay technique designed for detecting and quantifying peptides, proteins, antibodies and hormones. Note that ELISA is frequently performed in most clinical laboratories due to precision, low cost, and simplicity. It is deemed to be the best and most convenient method for long term clinical experiments such as in our study. For enhanced experimental precision, all samples are analyzed twice. For more recent datasets, finger-prick point-of-care testing was utilized for CRP measurements using comparable methodology, which allowed more convenient daily patient testing.

Before training, a series of preprocessing operations are performed, including data standardization to obtain zero mean and unit variance, and signal denoising using empirical mode decomposition (EMD). After the analyses, the predictions are unstandardized using the parameters calculated earlier.

The root-mean-square error (RMSE) is calculated from the unstandardized predictions in order to compare the forecast results with actual CRP observations,

$$\mathrm{RMSE} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \hat{x}_i)^2}, \tag{1}$$

where x_i is predicted value, $\hat{x}_i$ represents observed value, and N indicates number of samples. The RMSE is widely employed in a number of regression studies. The fact that RMSE penalizes a higher deviation from the mean leads us to employ this metric in the study.

III. CRP TIME SERIES

The discovery of C-reactive protein (CRP) by Tillett and Francis [58] provides us with a relatively sensitive biomarker that indicates inflammation, infection and tissue damage. Although CRP is a broad indicator of inflammation, it is utilized in active clinical practice especially in surgery and oncology, where CRP has assumed a valuable role for monitoring immune system function in terms of the inflammatory response. In addition, CRP is widely utilized in oncology as a marker for prognosis [59], an indicator of cancer risk [66], marker for survival [16], as a biomarker for tumor recurrence [61], and as a reliable tool for making critical decisions in treatment [27].

These advantageous applications led to studies investigating the properties of CRP time series. The analysis of frequent serial CRP concentrations with overall low values obtained from healthy subjects shows that baseline CRP is not subject to time-of-day variation [62]. Moreover, it is reported that the CRP level in the serum of sickle cell trait subjects significantly fluctuates with higher than average levels within 24 hours [63].

The distribution of CRP measurements is also investigated in the literature. Using a particle-enhanced nephelometric assay for CRP, it is found that the distribution of CRP concentrations is non-Gaussian when evaluated for skewness and kurtosis [64], consistent with findings in other studies [65], [66]. The distribution of CRP is highly skewed, and a $\log(\cdot)$ representation that is more symmetric and less skewed is suggested for CRP [67]. The skewness of CRP's distribution can be observed in Fig. 1 that shows patient No. 1's CRP time series concentration levels and its corresponding distribution plotted as a histogram.

The oscillation of CRP levels about a mean with a periodicity of approximately six-to-seven days is reported [24]. The authors hypothesized that the CRP oscillations are part of a homeostatic immune response to advanced malignancy and preliminary data linking the timing of therapy to treatment success. In another study, the periodic behavior of CRP is questioned using a frequency domain analysis that is employed on a small number of CRP samples obtained at seven time-points over an interval of twelve days from a cohort of patients with gynaecological cancers [68]. However, it is shown that the data used in [68] contains insufficient numbers of data points to conclude whether the CRP data is periodic or not, particularly for a hypothesized period of seven days [32]. Moreover, the study [32] provides a prescription for the minimum data sample rate required in future experiments for improved testing of a periodic CRP signal hypothesis, showing that with current technology an impractically large number of data points is required.

Therefore, rather than trying to exploit periodicity to forecast CRP levels we turn to ARIMA modeling and deep learning as generalized methods that exploit any correlation in the data. This then circumvents the need to consider periodicity at all, as it has not yet been rigorously established. Considering Fig. 1(c), where we plot the autocorrelation of a CRP time series, clearly showing it is non-localized and hence rich in correlations.

IV. FORECASTING USING ARIMA MODEL

The autoregressive integrated moving average (ARIMA) model is a generalization of autoregressive moving average (ARMA). An ARMA model is a combination of autoregressive (AR) and moving average (MA) models. These models are briefly summarized in the following.

Note that AR is a time series model that uses observations from previous time steps as input to a regression equation to predict the value at the next time step, and mathematically is expressed as [69],

$$\begin{aligned} y_t &= c + \sum_{i=1}^{p} \varphi_i y_{t-i} + \varepsilon_t, \\ &= c + \varphi_1 y_{t-1} + \varphi_2 y_{t-2} + \ldots + \varphi_p y_{t-p} + \varepsilon_t, \end{aligned} \tag{2}$$

where y_t denotes actual value, and ε_t represents random error at time period t, the parameter c is a constant, and the coefficients φ_i are model parameters for $i = 1, 2, \ldots, p$. The number of lags, p, is commonly referred to as the order of model. Various methods are proposed to estimate the coefficients, such as the ordinary least squares procedure or method of moments through the Yule-Walker equations [70], [71].

The model can be manipulated using the lag operator notation which is defined as $\mathrm{L}y_t = y_{t-1}$. Therefore, Eq. 2 is expressed as $\varepsilon_t = \varphi(\mathrm{L})y_t$, where $\varphi(\mathrm{L}) = 1 - \sum_{i=1}^{p} \varphi_i \mathrm{L}^i$.

Instead of past observation, the MA model uses past errors as the key variables. The MA(q) model is given by [72]

$$\begin{aligned} y_t &= \mu + \sum_{j=1}^{q} \theta_j \varepsilon_{t-j} + \varepsilon_t, \\ &= \mu + \theta_1 \varepsilon_{t-1} + \theta_2 \varepsilon_{t-2} + \ldots + \theta_q \varepsilon_{t-q} + \varepsilon_t, \end{aligned} \tag{3}$$

where q is considered model order, μ is the mean of the series, and θ_j are the model parameters for $j = 1, 2, \ldots, q$. The MA model can also be defined using the lag notation, $y_t = \theta(\mathrm{L})\varepsilon_t$, where $\theta(\mathrm{L}) = 1 + \sum_{j=1}^{q} \theta_j \mathrm{L}_j$.

The ARMA model may be generated from the combination of the last two models, represented as $\varphi(\mathrm{L})y_t = \theta(\mathrm{L})\varepsilon_t$ or

$$y_t = c + \varepsilon_t + \sum_{i=1}^{p} \varphi_i y_{t-i} + \sum_{j=1}^{q} \theta_j \varepsilon_{t-j}. \tag{4}$$

The ARMA model described here is used for stationary time series. To create a model fitting the data as well as possible, the ARIMA model is introduced that is able to deal with non-stationarity signals as well [72], [73]. The model is expressed in lag notation as

$$\begin{aligned} &\varphi(\mathrm{L})(1-\mathrm{L})^d y_t = \theta(\mathrm{L})\varepsilon_t, \text{ i.e.} \\ &\left(1 - \sum_{i=1}^{p} \varphi_i \mathrm{L}^i\right)(1-\mathrm{L})^d y_i = \left(1 - \sum_{j=1}^{q} \theta_j \mathrm{L}^j\right), \end{aligned} \tag{5}$$

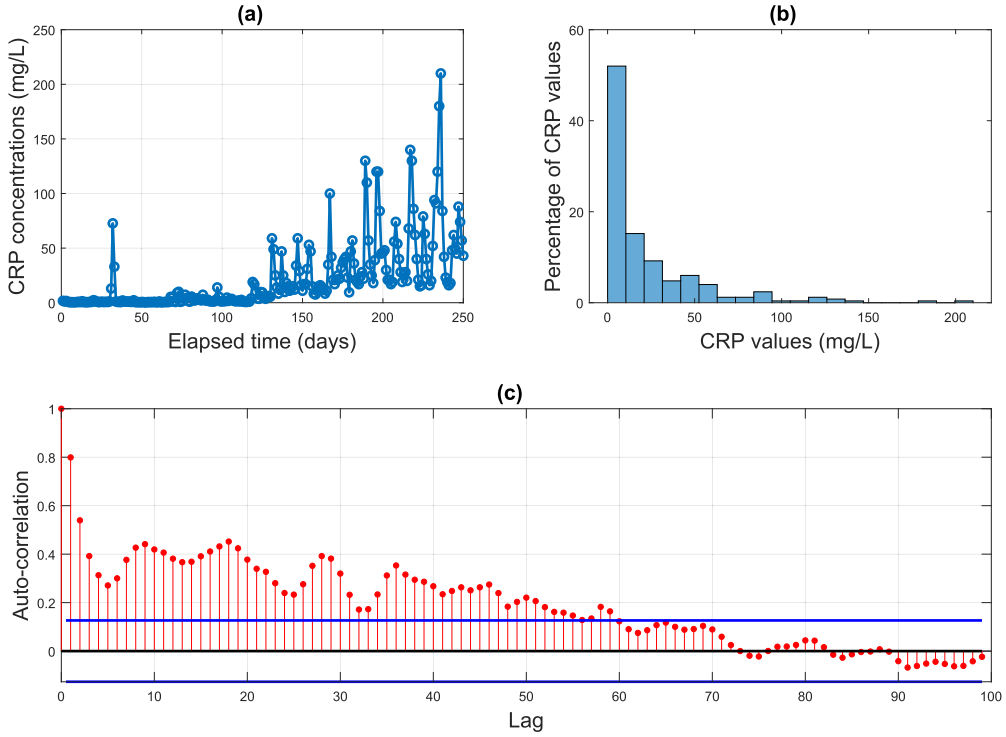

FIGURE 1. (a) CRP concentrations related to patient No. 1, (b) corresponding histogram, and (c) corresponding sample autocorrelation function (ACF) is shown. Note that ACF is plotted for 99 lags and displays 95% confidence bounds consisting of two standard errors in blue.

here, p refers to the order of the autoregressive term that indicates the evolving variable of interest is regressed on its own lagged values. The parameter q represents the order of moving average part that indicates the regression error is actually a linear combination of error terms whose values occurred contemporaneously and at various times in the past. Finally, d is the order of integrated part and indicates that the data values have been replaced with the difference between their values and the previous values.

For the implementation of the ARIMA model, we employ a multiple model parameters setting using the `estimate (Mdl; y)` MATLAB function that uses maximum likelihood to estimate the parameters of the `ARIMA(p;D;q)` model `Mdl` given the observed univariate time series y. First, we separate the data into training and test sets with 90% and 10% of observations. Then we develop an ARIMA model that can be used to predict the last 10 percent of the CRP data.

Fig. 2(a) demonstrates CRP concentrations related to patient No. 1 and the forecasted signal. The zoomed portion of the figure containing test and forecast data is shown in Fig. 2(b), and the corresponding error is shown in Fig. 2(c). The analysis shows that the root-mean-square error (RMSE) using ARIMA model is 43.05.

It may be seen that the trend and fluctuation form of test and forecast signal are almost similar; however, there is a degree of dissimilarity between them. The forecasted part obtained by ARIMA is dependent on the time series history. Therefore, it is challenging for ARIMA to accurately predict patterns that have not previously occurred. Although, this may not be the optimal model, it is generally a convenient benchmark for comparison.

V. FORECASTING USING LSTM RECURRENT NEURAL NETWORKS

The long short-term memory (LSTM) was introduced in 1997 [74] and improved significantly in 2000 [75]. Categorized under RNNs, the use of LSTM is particularly designed for sequential data such as time series data. In practice, it is difficult to train classic RNNs due to the resulting long-term dependencies, while a RNN with LSTM blocks is capable of solving the problem. Therefore, LSTM may potentially be an efficient approach to cope with long term dependencies observed in CRP time series. A common LSTM architecture is composed of a memory block, an input gate, an output gate and a forget gate. The input gate and the output gate control the flow of input activations into the memory block, and the output flow of cell activations into the rest of network respectively. The forget gate scales the internal state of the cell before adding it as input to the cell through the self-recurrent connection of the cell, therefore adaptively forgetting or resetting the cell's memory [76].

A LSTM network provides a mapping from an input sequence $x = (x_1, ..., x_T)$ to an output sequence $y = (y_1, ..., y_T)$ by calculating the network unit activation using the following equations iteratively from $t = 1$ to T [76],

$$i_t = \sigma(W_{ix}x_t + W_{im}m_{t-1} + W_{ic}c_{t-1} + b_i), \quad (6)$$
$$f_t = \sigma(W_{fx}x_t + W_{fm}m_{t-1} + W_{fc}c_{t-1} + b_f), \quad (7)$$

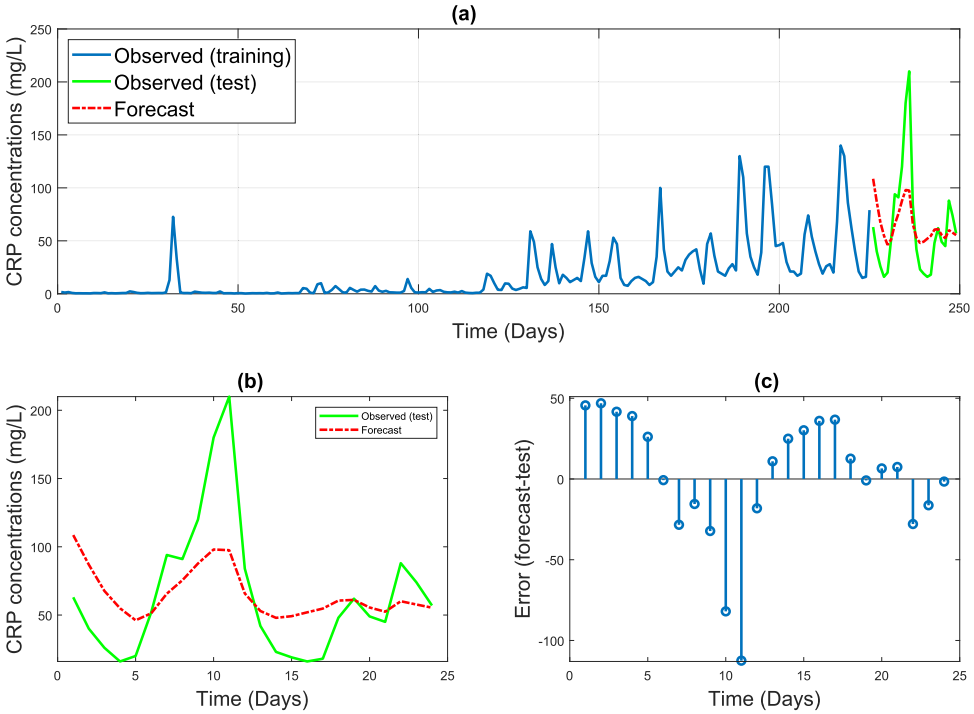

FIGURE 2. The result of CRP forecast using ARIMA approach for patient No. 1 is demonstrated. (a) The CRP data containing training and test segments, and forecast data are shown in blue, green, and red, respectively. (b) The zoomed portion of test and forecast data is shown. (c) The difference of test and forecast time series is used to plot errors in each individual day.

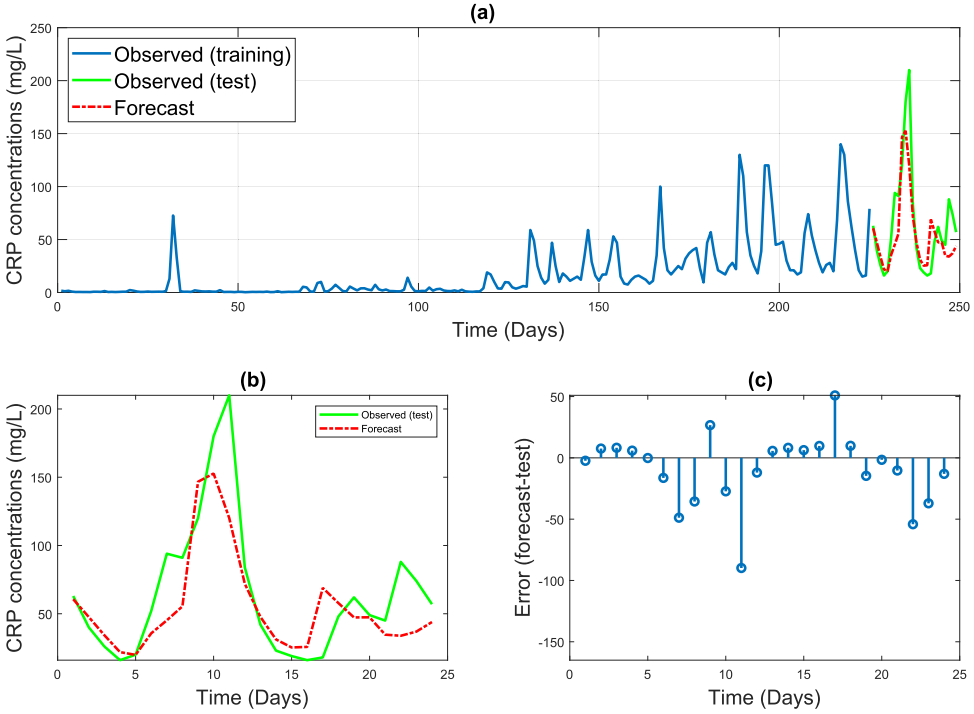

FIGURE 3. The result of CRP forecast using deep learning approach for patient No. 1 is demonstrated. (a) The CRP data containing training and test segments, and forecast data are shown in blue, green, and red, respectively. (b) The zoomed portion of test and forecast data is shown. (c) The difference of test and forecast time series is used to plot errors in each individual day.

$$c_t = f_t \odot c_{t-1} + i_t \odot g(W_{cx}x_t + W_{cm}m_{t-1} + b_c), \quad (8)$$

$$o_t = \sigma(W_{ox}x_t + W_{om}m_{t-1} + W_{oc}c_t + b_o), \quad (9)$$

$$m_t = o_t \odot h(c_t), \quad (10)$$

$$y_t = \phi(W_{ym}m_t + b_y), \quad (11)$$

where σ refers to the logistic sigmoid function. The W terms indicate weight, for example W_{ix} is the matrix of weights

TABLE 1. Calculated RMSE from ARIMA and deep learning approaches.

Patient No.	ARIMA RMSE *	Deep learning RMSE *
1	43.052	32.120
2	20.357	18.681
3	1.350	1.115
4	0.802	0.506
5	37.510	15.018
6	40.201	34.699
7	43.424	51.385
8	2.425	0.258
9	18.904	17.680
10	5.322	3.940
11	102.012	97.784
12	0.312	0.257
13	7.237	1.701
14	3.184	4.873
15	35.924	29.241
16	79.012	21.745
17	3.480	2.312
18	51.941	50.985
19	64.327	60.102
20	6.925	1.283
21	3.231	2.481
22	12.957	21.384
23	15.244	11.015
24	1.214	0.786

* Note that RMSE is a size and scale dependent metric of forecast accuracy. Therefore, variation of RMSEs among different patients have no useful meaning.

from the input gate. Moreover, b terms indicate bias vectors (b_i is the input gate bias vector), and i, o, f, and c are respectively the input gate, output gate, forget gate, and cell activation vectors. Here, m is output vector of the LSTM unit, g and h are the cell input and cell output activation functions, $\tanh(\cdot)$, ϕ is the network output activation function. And the operator $\odot$ denotes the Hadamard product (entry-wise product).

To forecast the values of future time steps of CRP concentrations, we train a sequence to sequence regression LSTM network, where the responses are the training sequences with values shifted by one time step. That is, at each time step of the input sequence, the LSTM network learns to predict the value of the next time step.

As in the previous section, we train on the first 90% of CRP time series and test on the last 10%. In order to reach optimal performance of the approach we prepared multiple algorithm's parameters setting. In summary, the experiment settings and parameters are mentioned as follows:

- Network layer number: 3, 4, 5
- Size of data: 90% training and 10% test
- Training method: Adam
- Hidden units: 5, 10, 20, 50, 100, 120, 150, 200, 250, 300
- Neuron cell unit: LSTM
- Loss function: RMSE
- Learning rate: We chose an initial learning rate of 0.005. We reduced the rate, after 125 epochs, by multiplying by 0.2, to give a final rate of 0.001.

Fig. 3(a) demonstrates CRP concentrations related to patient No. 1 and forecasted signal using deep learning approach. The zoomed portion of test and forecast data is demonstrated in Fig. 3(b), and the corresponding error is shown in Fig. 3(c). In this case, the root-mean-square error (RMSE) using deep learning approach is 32.12.

It can be seen that the predictions are more accurate when using the deep learning approach instead of the ARIMA model. Despite the modeling using ARIMA, in LSTM approach there is a sequence of dependence among the input variables, and the method is powerful in handling of the dependency.

VI. RESULTS

In this section, we illustrate the performance of both the ARIMA and the deep learning approaches on the CRP data obtained from the entire cohort of twenty-four patients. The root-mean-square error (RMSE) is calculated from the data for both approaches in Table 1. From Table 1, the deep learning method provides superior performance over the ARIMA model.

Neural networks have been found to be very efficient in solving nonlinear problems including many applications in the real world. This is in contrast to a number of traditional approaches for time series forecasting, such as ARIMA, that assume the series are generated from linear processes, and therefore might be inappropriate for nonlinear real-world problems. In particular, in ARIMA the output is related to past observations via a linear function, whereas deep learning algorithms such as RNNs containing LSTM blocks are capable of nonlinear modeling, and this may possibly explain why deep learning outperforms ARIMA in most cases.

VII. LIMITATIONS OF STUDY

The data containing twenty-four CRP time series may limit the scope of the analyses. Collecting daily blood samples from cancer patients for a long period is a challenging process in clinical trials. This CRP dataset consisting of CRP concentrations, date and time, is a first of its kind, and there are no other available CRP datasets for cancer patients measured at such high rate. As a pilot study, this work may open new avenues for future studies containing a significantly larger data set.

VIII. CONCLUSION

As a widely used biomarker of inflammation, CRP is known as an indicator of cancer prognosis, risk, and recurrence, and it is considered as a clinical decision-making tool. In order to provide a statistical and computational model for CRP, the present study has investigated the feasibility of CRP time series prediction. Initial autocorrelation analyses reveal that there are some dependencies or correlations between CRP observations. These hidden patterns lead the study to

take advantage of statistical and computational techniques for CRP time series forecasting. With the advent of machine learning-based approaches such as ARIMA and deep learning, these approaches are gaining significance for biomedical signal analysis. In this paper, we compare two learning methods, ARIMA model and LSTM deep learning, to predict future values of a CRP time series. Here, the root mean square error (RMSE) that is the standard deviation of the residuals (prediction errors) is used as an evaluation metric for both the ARIMA and LSTM approaches. The experiments on CRP time series show that the deep learning method achieves a lower prediction error compared to the forecasting approach based ARIMA in terms of RMSE. A possible explanation may be that the CRP time series possess nonlinear properties. Moreover, ANNs are found to be very efficient in solving nonlinear problems. However, traditional statistical methods such as ARIMA that assume the series under analysis are generated from linear processes and this is inappropriate for nonlinear problems. Having now established that CRP can be forecasted, this motivates future studies to examine the utility of other techniques, e.g. support vector machine, fuzzy systems etc.

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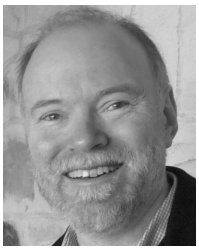

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