A Predicative Patient Specific Model for Human Albumin Based on Deep Neural Networks

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Research

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RESEARCH

A Predicative Patient Specific Model for Human Albumin Based on Deep Neural Networks

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Abstract

Background: For a critically ill patient, an accurate predictive tool for biochemical markers based on the patient prior clinical data can aide physicians to design better patient-specific treatment plans. In this study, we develop a since dynamical system model based on neural networks capable of predicting concentrations of biochemical markers, including albumin, of a critically ill patient, in real-time.

Methods: The metabolic process of a patient follows a patient-specific dynamical system which can be uncovered with certain accuracy from sufficient prior data taken from the patient. For a given set of patient's biochemical markers, the dynamical system represented by deep neural networks is discovered from the prior data via deep learning methods.

Results: One critically ill, poly-trauma patient (injury severity score = 34 points) was enrolled in the study. Six biochemical markers (albumin (ALB), creatinine (Cr), osmotic pressure (OSM), alanine aminotransferase (ALT), total bilirubin (TB), direct bilirubin (DB)) were collected and exogenous albumin injection was administered to the patient for the total of 27 consecutive days during the study. A sliding window of data in 10 consecutive days was used as the training set and the 11th day's data as the test set to train and test the parameters in the neural network. The obtained dynamical system model is then used to forecast the chemical markers in the next 24 hours. The results are compared with the true clinical data with a relative error consistently less than 2%.

Conclusions: This study demonstrates that a dynamic system model can be established to monitor and predict concentrations of biochemical markers, including albumin, via neural networks and deep learning methods. This data-driven patient-specific modeling approach is applicable to any patient.

Trial registration: Metabolomics Dynamics Study for Severe Patient, Registered:17June,2014, <https://www.clinicaltrials.gov/ct2/show/NCT02164786?term=NCT02164786&draw=2&rank=1>

Keywords: Critical illness; Albumin; Deep learning; Dynamical systems; Neural networks

Background

We conduct a pilot study that aims to address following clinical challenges: how to predict blood albumin level accurately and quantify albumin dosage to maintain its blood level for critically ill patients. There have been ample evidence demonstrating that hypoalbuminemia is a strongly correlated precursor associated with the increase of mortality and many morbidities[1, 2]. Clinical practitioners have administered intravenous albumin to correct hypoalbuminemia in critically ill patients since decades ago. But controversies have remained on the use of albumin. These include the following. 1) The dosage and target of albumin administration has not been established rigorously, namely, what level of blood plasma albumin should be set as the optimal treatment level is not clear [3]. 2) The type of albumin: isotonic or hypertonic has not been settled. Albumin solutions that used for intravenous administration have a variety of concentrations. They are classified by hypertonic (20-25%) or isotonic (4-5%) solutions. It is still under debate about which concentration is better. Recent evidence and experts' consensus seem to favor the use of hypertonic albumin considering its effect on organ protection and edema correction [4]. 3) How to maintain the plasma albumin level at an optimal range by intravenous administration of albumin in selected time intervals [5]. So far, there have been a few clinical trials reported in the literature, targeting at the questions directly. It remains difficult to find any consistencies among these published studies [6, 7, 8, 9]. Despite of the controversies, the albumin has been widely used in intensive care unit and surgical settings as the top colloid products for critically ill patients [10].

There exists an urgent and practical need for clinic physicians to have a clear guideline to follow on how to optimize the use of albumin when an albumin regimen shall be prescribed. Given that the plasma albumin level and its metabolic process can be affected by a host of factors, for instance the fluid resuscitation, liver function, renal function, transfusion etc. and it evolves in time and varies from patient to patient, a traditional, routinely randomized control trial is not sufficient to manage such a number of parameters as well as the dynamical nature of human physiological processes. It then brings about the current pilot study to focus on quantifying albumin administration and its maintenance in 35g per liter over time on a critically ill patient.

In this study, we develop a data-driven dynamical system model based on deep neural networks to predict the plasma albumin on the daily base, which calculates the exogenous dosage to elevate hypoalbuminemia patients' plasma albumin to 35g/L and to maintain it over time. The model is built on prior clinical data collected from a specific hypoalbuminemia patient and is meant to be patient specific. Once the model is calibrated/trained for a specific patient via deep learning methods, its methodology can readily be applied to any other patient. In this pilot study, we report results from one severe poly-trauma patient treated at Sichuan Provincial People's Hospital recently. The study protocol was approved by Medical Ethics Committee of Sichuan Provincial People's Hospital and Sichuan Academy of Medical Sciences (registration number: NCT02164786). The written informed consent was obtained from the patient.

Table 1 Biochemistry at admission

Items	Value	Items	Value
Age(years)	62	ALT(U/L)	42
Height(CM)	160	TBIL(umol/L)	13.1
Weight(Kg)	55	DBIL(umol/L)	5.4
BMI	21.48	WBC(10 ⁹ /L)	2.54
Cr(umol/L)	109.3	HGB(g/L)	101
OSM(mOsm/L)	295	PLT(10 ⁹ /L)	122
ALB(g/L)	19	HsCRP(mg/L)	87.26

Methods

Brief description of the patient

A woman in her 60s was struck by rocks and admitted into Sichuan Provincial People's Hospital because of poly-trauma and hemorrhagic shock. The vital signs when she was admitted into the emergency department were: body temperature 36.9 °C, pulse 135 beats/min, respiratory rate 28 beats/min, Blood Pressure 105/69mmHg, SPO2 100%(with oxygen inhalation by nasal catheter 5L/min). The patient was drowsy, and the Glasgow Coma Score (GCS) was 14 points(E3+V4+M5). Her APACHE II score was 23 points and the SOFA score was 10 points [8].

When the patient arrived, she received an emergency CT scan, which indicated that she had intra-abdominal organ rupture, hemorrhage and multiple fractures. The summary of admitting diagnosis: poly-trauma, including 1) abdominal closed injury (free intraperitoneal air), spleen laceration, seroperitoneum, 2) the left frontal bone and left ossa orbitale fracture, 3) closed trauma of chest, rib fracture, lung injury, bilateral pleural effusion, pericardial effusion, 4) left shaft of humerus open fracture, left shaft of femur comminuted fracture, S1-S2 fracture, right pubic fracture, L2-3 right transverse process fracture. Table 1 showed the major biochemical parameters of the patient at admission.

Physicians conducted an emergency operation to control the damage from her intra-abdominal injuries. During the operation, physicians found the rupture of transversum colon, and a large amount leakage of intestinal contents (faeces) and spleen laceration. The Hartmann procedure (consisted of a colectomy without colorectal anastomosis (CRA), closure of the transversum stump end the colostomy at left higher quarter two) was conducted. To repair spleen laceration, the splenorrhaphy procedure was conducted. After the emergency operation, the patient was transferred to the intensive care unit (ICU) for further resuscitation. When the patient's physiological and metabolic status were significantly stabilized, she received orthopedic operations at day 7 and day 12 after admission, to repair fractures of left forearm and pelvic, respectively. At day 18 after admission, physicians found an incision infection in the patient. The bacteria culture results indicated that the infection pathogens were fungus and *baumannii*. Physicians used Meropenem, tigecycline and carprofen acetate to treat the infection. At day 25, the patient was transferred from ICU to acute care surgery ward because the major infection had been controlled and the physiological/metabolic status was substantially improved. At day 40, the patient was finally discharged from the hospital and transferred to a local rehabilitation center. During the entire period of treatment, physicians monitored the patient and provided nutritional support while keeping the water and electrolyte balance. Table 2 shows the nutritional support regimen administered to the patient.

Table 2 Energy and Protein administered(daily)

Days after admission	Energy(Kcal/Kg·day)	Protein(g/Kg·d)
0-4	0	0
5	7.5	0.29
6-10	15	0.57
11	22.5	0.86
12-13	30	1.14
14-25	22.5	0.86

Table 3 Albumin administered(daily)

Days after admission	Blood ALB level (g/L)	Albumin Administered(g/d)
1	19,13.4,13.4	20+20
2	29.4,28.8,28.9,24.7,32.1,29.4	20+20
3	30.5,31.7	20+20
4	34.7,36.3	20
5	36.9,35.4,39.3	20
6	34.3,33.8,34.9	20
7	32.4	20
8	32.2	20
9	30.7	10
10	32.7	20
11	34.4	20
12	34	20
13	34.7,28.5	20
14	31.1	20
15	28.1	20
16	30.9	20
17	31.6	20
18	31.8	20
19	35.7	20
20	36.2	20
21	34.3	20
22	34.2	20
23	34.7	20
24	33.5	20
25	34.2	20
26	34.3	20
27	31	10

The intensive monitoring of the blood albumin and biochemical markers began at day 1 and ended at day 7 of admission. During this period, physicians tested blood albumin and biochemical markers 2-5 times per day. After day 7, monitoring of the blood albumin and biochemical markers was conducted daily. The patient received 20% albumin by intravenous infusion at a designated time daily except that two dosages were administered daily in the first three days. Table 3 shows the blood albumin level of the patient in the first 27 days.

Data source and preprocessing

We first collected data on blood routine, liver and kidney function, and additional albumin injection from the critically ill patient in an period of 10 days from day 7 to day 16. Based on the clinical experience, we selected six indicators/markers as variables for the model, including albumin (ALB), creatinine (Cr), osmotic pressure (OSM), alanine aminotransferase (ALT), total bilirubin (TB), direct bilirubin (DB), to characterize changes in albumin. We take the data collected for more than 16 days into account in hours, and use mathematical methods (spline interpolations) to restore its continuity. At the same time, the sampling point and injection point of each time are marked clearly.

(a) ALB

(b) Cr

(c) OSM

(d) ALT

(e) TB

(f) DB

Figure 1 The data are interpolated using splines and plotted

Figure 2 ALB-intake as a function of time. (b) is a blowup of a time period in (a).

Figure 1 depicts the selected data set and their spline interpolations:

We divide the above consecutive data into two parts, the training set which covers the first 10 days' data (6-246 in the table) and the testing set which covers the last day's data (246-270 in the table). We use the first set to train neural networks through which we get the slope field of the dynamical system model and then we test it using data taken from the test set.

Basic assumption of the model

For an effective treatment of critically ill patients, additional albumin needs to be injected at some point during the treatment. For the additional albumin injection, we assume that the duration of each injection is fixed at half an hour, which is basically in line with the clinical practice. To simplify the model, we also assume that the function of albumin injection is a piecewise linear function $g(t)$ given in Figure 2, and $g(t)$ is the rate of albumin intake. From the above assumption, we estimate that the patient takes in 10g of albumin in half an hour at each injection. So $g(t)$ as a function of time is either 20 or 0 at any given time t .

Formulation of the dynamical system model

In order to establish an effective mathematical model to monitor and predict the biochemical markers, we assume the change of the markers including albumin (ALB) is described by a transient dynamical system coupled to the other 5 selected blood

markers (Cr,OSM,ALT,TB,DB). Here, we denote the six related variables as $\vec{Y} = (y_{ALB}, y_{Cr}, y_{OSM}, y_{ALT}, y_{TB}, y_{DB})$ and propose the dynamical system as follows

$$\frac{d\vec{Y}}{dt} = F(\vec{Y}, \theta(w, b)) + \alpha \vec{G}(t), \quad (1)$$

where F is a part of the slope field of the dynamical system proposed in the form of a neural network with parameters $\theta(w, b)$, $\vec{G}(t) = (g(t), 0, \dots, 0)^T$ is the function of albumin injection. and α is a model parameter for characterizing albumin absorption, which we call it the absorption coefficient and will discuss it in more details later.

We apply machine learning method to train the slope field. Specifically, we give the initial value of $\vec{Y}(t_0)$ and the sequence of $\vec{G}(t_i)(i = 0, 1, 2 \dots n)$, then we use a Runge-Kutta method to solve the dynamical system to obtain $\vec{Y}(t_i)(i = 1, 2 \dots n)$. These will be used to define the loss function for training the neural network.

Discovery of the model: deep learning

Given the success of neural networks in applications such as imaging, computer vision [11, 12, 13](e.g. self-driving cars and picture classification), language processing [14](e.g. Google Translate), reinforcement learning etc. [15](e.g. AlphaGo Zero), we expect a neural network, as a nonlinear approximant to a function, would do a better job than a traditional linear approximant at any given number of parameters [16, 17](Universal Approximation Theorem). Namely, for any given number of target values that an approximant has to hit, the neural network can perform much better [18, 19, 20, 21].

Firstly, we use an interpolation spline function to restore the continuity of the original data, and then obtain the time series of six markers including ALB at much finer time scales. We use 360 hours of data from the first 15 days as a training set and the data from the following 24 hours as a testing set. We select points at equal intervals of 0.01 hours to obtain training data consisting of 36,000 points. Here, we propose firstly the deep neural network $\mathcal{N}_1$ with 10 hidden layers and 50 nodes in each hidden layer to fit the data. Considering that this data set is a time series with six markers, we build $\mathcal{N}_1$ as follows

$$\mathcal{N}_1 : t \rightarrow \mathbb{R}^{6+}, \quad (2)$$

to fit the marker data. We rewrite it as $\vec{Y} = (y_{ALB}, y_{Cr}, y_{OSM}, y_{ALT}, y_{TB}, y_{DB})$. The loss function associated with the machine learning process is defined by

$$loss_u = \sum_{i=1}^n \frac{1}{n} \|\vec{Y}(t_i) - \mathcal{N}_1(t_i)\|_{L_2}. \quad (3)$$

After learning it with the training set and test set, we obtain a convergent network with a loss value at 5.54361810^{-5} .

Secondly, we build the second neural network based on the first network to describe the slope field in the dynamical system. Based on the result of the first neural

network, the slope field $\mathcal{F}$ is approximated by a second neural network, which has 4 hidden layers with 50 nodes in each hidden layer,

$$\mathcal{N}_2 : \mathbb{R}^{6+} \rightarrow \mathbb{R}^{6+}. \quad (4)$$

The loss function is defined as follows

$$loss_f = \sum_{i=1}^n \frac{1}{n} \left\| \frac{d\mathcal{N}_1(t_i)}{dt} - \left(\mathcal{N}_2(\mathcal{N}_1(t_i)) + \alpha \overrightarrow{G(t_i)} \right) \right\|_{L_2}, \quad (5)$$

where α is the albumin absorption coefficient, regarded as a trainable parameter directly to be determined in the process of machine learning. The range of α is estimated using the diffusion equation and given by $\alpha < 0.22$.

Finally, we build the third neural network which has the same structure as the previous two with a loss function defined as the combination of the former two. So, the structure of neural network $\mathcal{N}_3$ is consisted of two parts. The output of the first part is the input of the second part.

$$\mathcal{N}_{3_1} : t \rightarrow \mathbb{R}^{6+}, \quad (6)$$

$$\mathcal{N}_{3_2} : \mathbb{R}^{6+} \rightarrow \mathbb{R}^{6+}. \quad (7)$$

The loss function is given by

$$loss = loss_u + loss_f, \quad (8)$$

where

$$loss_u = \sum_{i=1}^n \frac{1}{n} \left\| \overrightarrow{Y(t_i)} - \mathcal{N}_{3_1}(t_i) \right\|_{L_2}, \quad (9)$$

$$loss_f = \sum_{i=1}^n \frac{1}{n} \left\| \frac{d\mathcal{N}_{3_1}(t_i)}{dt} - \left(\mathcal{N}_{3_2}(\mathcal{N}_{3_1}(t_i)) + \alpha \overrightarrow{G(t_i)} \right) \right\|_{L_2}. \quad (10)$$

These three neural networks will yield the dynamical system describing time-dependent changes in human albumin and other markers. After we obtain convergent neural networks $\mathcal{N}_{3_1}$ and $\mathcal{N}_{3_2}$ through machine learning. We use $\mathcal{N}_{3_2}$ to define the slope field of the dynamical system. We then make predictions by solving the dynamical system up to the time of the medical interest.

Results

Prediction of ALB

As mentioned above, we regard α as a trainable parameter and use the data of the first 10 days to train the neural network model in the selected dat set. By this

Table 4 Parameter and loss function values for network structure

α	$loss_u$	$loss_f$	$loss$
$\alpha = 0.13$	5.673057e-05	3.573956e-02	2.580269e-02

method, we get the convergent neural network. The loss values of the three neural networks are 5.673057e-05, 3.573956e-02, 2.580269e-02 respectively. At the same time, the value of α obtained by training is $\alpha = 0.13$. The results are summarized in table 4.

From a simple asymptotic analysis of the diffusion equation, we obtain $\alpha < 0.22$. We find its optimal value at 0.13 through machine learning. So, we adopt the machine learning result $\alpha = 0.13$ in the model and use the convergent neural network result obtained through the first 10 days' data to make predictions for the 11th day's ALB value and compare that with the clinical data. The result is shown in Figure 3.

In the figure, the fitted clinical or true ALB value change is given by the blue line, in which albumin was injected into the patient at the 248th hour in the clinical process. The red line shows the model predicted result, while the middle part of the jump (around 248th hour) actually corresponds to the injection time of albumin in the clinical process.

Based on our hypothesis (in part 2.3) and the numerical method, the jump here is reasonable. (The same is true for the red line at the 260th hour.) We can see that the result (red line) of our model can approach the clinical process in 10 and 24 hours with errors controlled within the order of 0.2 and 0.5, respectively. At the same time, we also predict a trend (black line) of ALB without any albumin intakes. Note that all errors predicted up to the 24 hours are less than 1.7% measured in the relative error. Clinically, this is very accurate! This demonstrates the approximate power of a nonlinear approximant such as a neural network.

Prediction of other five biochemical markers

Our neural network model is based on six biochemical markers (ALB, Cr, OSM, ALT, TBIL and DBI), and the data of these markers are processed the same way. We have used this model to predict the ALB value while the converging neural network

Table 5 Parameter and loss function values for network structure

α	$loss_u$	$loss_f$	$loss$
$\alpha = 0.09$	5.294857e-05	2.596312-02	2.301726e-02

model can predict other markers as well. Here we show the 10 hour predictions of the other five markers in Figure 4 (more results are shown in Appendix).

We repeat the modeling approach using training data from day 14 to day 23 and test data on day 24. The results are shown in table 6 and Figure 5, respectively.

The loss values of the neural network model are 5.294857e-05, 2.596312-02 and 2.301726e-02 respectively, similar to the previous model shown in Table 4. The predicted error of ALB is also well controlled and the accuracy is comparable to the previously trained model. Moreover, the value of α is still obtained by deep learning and is at 0.09 in this case.

Discussion

Since the last century, physicians have linked hypoalbuminemia to the increase of mortality and morbidities [22]. New evidence has continuously emerged to indicate the important role that hypoalbuminemia can play in making accurate diagnosis and implementing effective treatment for critically ill patients [23, 24, 25, 26]. Today, it seems to have reached a consensus among physicians that providing exogenous albumin to critically ill patients can lead to increased survival rate. But a Cochrane meta-analysis published in 1998 initiated a new debate on this issue, which has continued up to today [27].

In our opinion, the lack of a quantitative method that can accurately predict the dynamic of albumin and the metabolic process related to the biochemical markers is the main reason that impedes a satisfied answer for the debate. If it had existed, it would have provided a good metric for clinicians to monitor albumin dynamics and to adjust the administration of albumin regimen in a time-sensitive and patient specific fashion to benefit the treatment.

In an emergency department/intensive care unit setting, any accurate near term predictions would provide crucial clinical insights for attending physicians in cases of critically ill patients. Based on our clinical experience and knowledge as well as our mathematical modeling capability, we predicate the existence of a dynamical system for the absorption of human albumin and biochemical markers Cr, OSM, ALT, TBIL and DBIL. It turns out that such a dynamical model fully describes the absorption process of albumin within the clinically negligible error ($< 1.7\%$) up to at least 24 hours.

Given the fact that patient specific clinical data never belong to the large data category, we propose a new data-driven deep learning paradigm to develop the dynamical system model. Specifically, we use three deep neural networks to identify the dynamical system model. The first neural network serves as a priori estimate of the fine scale data in a time series, which can help us avoid the problem of poor conditioning and instability in optimization. Based on the results of the first neural network, a second neural network describing the slope field of the dynamical system is established. The convergence results of the former two network parameters are saved and initialized as the initial values for the third or the final neural network.

(a) Cr-prediction 10 hours

(b) OSM-prediction 10 hours

(c) ALT-prediction 10 hours

(d) TB-prediction 10 hours

(e) DB-prediction 10 hours

Figure 4 Comparison of the model predictions and the clinical data.

The final dynamical system model is determined by minimizing the loss function by penalizing the errors in the data and the residue of the dynamical system at the same time. From this, we eventually identify the neural network describing the dynamical system model, through which near future predictions can be made in albumin (ALB) as well as other markers fairly accurately. Once the initial conditions of the dynamical system are given, we use a Runge-Kutta method to solve it to make predictions.

We illustrate the modeling paradigm using a case where a critically ill patient was admitted into the emergency room. We use data within a window of 11 consecutive days to identify the model, in which we use the data acquired from the first 10 days to train the neural networks and the data of the last day to test it. The neural networks are obtained from a convergent optimization procedure. We then use the dynamical model to make predictions for the 10 hour and 24 hour period, respectively, and compare the predicted results with the true clinical data. The comparison looks very promising. In addition to ALB, the model can also predict Cr, OSM, ALT, TB and DB at the same time. Accuracy of the model predictions seem to be independent of the windows of data we used. This modeling methodology provides a viable way to develop patient-specific models to monitor and predict the patient-specific biochemical markers in a clinical setting. In principle, this modeling method can be applied to other situations where biochemical markers of a specific patient are available as well.

Conclusions

This study demonstrates that a dynamical system model can be established to monitor and predict concentrations of biochemical markers, including albumin, via neural networks and deep learning. This modeling approach is general enough so that it is applicable to any patient. We hope this predictive tool can be used in clinical settings to fully explore the beneficial role of Albumin in the treatment of critically ill patients and thereby put an end to the debate on the usefulness of Albumin to critically ill patients.

List of abbreviations

Table 6 Parameter and loss function values for network structure

ALB	Cr	OSM	ALT	TB	DB
albumin	creatinine	osmotic pressure	alanine aminotransferase	total bilirubin	direct bilirubin

Ethics approval and consent to participate

The study protocol was approved by Medical Ethics Committee of Sichuan Provincial People's Hospital and Sichuan Academy of Medical Sciences (registration number: NCT02164786). The written informed consent was obtained from the patient.

Consent for publication

Not applicable.

Availability of data and materials

Any inquiries regarding the dataset can be addressed to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Hua Jiang and Qi Wang designed the study and revised the manuscript critically for important intellectual content. Cheng Lei, Yu Wang took responsibility for the accuracy of the data analysis, prepared the figures and wrote the draft paper. Qi Wang, Cheng Lei and Jia Zhao developed the mathematical model. Kexun Li and Yu Wang had full access to all of the data in the study and take responsibility for the integrity of the data. All Authors contributed to the final version of the manuscript.

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Figures

(a) ALB

(b) Cr

(c) OSM

(d) ALT

(e) TB

(f) DB

Figure 1

The data are interpolated using splines and plotted

(a) ALB-intake: $g(t)$

(b) ALB-intake: Local magnification

Figure 2

ALB-intake as a function of time. (b) is a blowup of a time period in (a).

Figure 3

Comparison of predicted values and clinical data.

Figure 4

Comparison of the model predictions and the clinical data.

Figure 5

The projected ALB injections are predicted based on historical data.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [MLALBAppendix.pdf](#)