European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

PROGNOSTICATING CLINICAL INCIDENTS VIA RECURRENT NEURAL NETWORKS BY USING CLINICAL DOCTOR AI

S.Kausalya[1], S.Kalaiselvi[2], D. Thamarai Selvi[3], Dr.V.Gomathi[4]
Department of Computer Science and Engineering, National Engineering College, India
1951002@nec.edu.in[1] , sks@nec.edu.in[2] , dts-cse@nec.edu.in[3] , vgcse@nec.edu.in[4]

Abstract: Doctor AI imitates human doctor's forecasting potential and gives diagnostic results that are clinically significant. Prognosticating Clinical Incidents is a timeseries based RNN model. It is implemented and employed to longitudinal time stamped electronic health record data from a twenty thousand patients over a decade. Encounter medical logs of patients data such as diagnosis codes, medication codes and procedure codes are input data to RNN to predict the diagnosis and medication types for a future visit of patients in a hospital. Doctor AI evaluates the history of patient's to prepare one label for each diagnosis predictions and medication types i.e.,multi-label forecasting/prediction. Leveraging huge historical patient details in electronic health records (EHR), a collective generic and comprehensive predictive model that covers perceived health state and medication uses for EHR, is new approach in disease progress identification.
Keywords- Electronic Health Records (EHR), Recurrent Neural Networks (RNN), Mimic, Neural Networks, ICD9.

1. INTRODUCTION

Healthcare is one of the most sensitive domain that is directly connected to us in emotionally, physically, mentally and financially. So, the impact of the new economy and technology in healthcare requires immediate attention to address the challenge they bring to the society. Insightful clinical conclusions aids foretell the information at the time of care particular to the victim and giver needs. The mores of connected medical devices and AI-integrated software application can give a huge amount of details to the healthcare peoples which they can utilize to produce benefical information.This data can be of diverse sorts such as administrative statements, patient health digital logs, connected device information, transliteration & clinical notes, and patient assessments. But, most care providers, even top healthcare companies, need advanced architecture and data management systems to regulate data collected from multiple origin. Electronic health records (EHR)/ Electronic Medical Records represent patients' and doctors' longitudinal experience in hospitals and clinics. The EHR data are being used with expanding prevalence to forecasting upcoming events. Previous research works has focused specialized forecasting analysis models that predicted a limited group of results. Although, everyday clinical practice contains an unplanned and diversified mix of incidents and requires several forecasting models for thousands of patients' information. It is unfeasible to create and assemble specialized models for each and every situation. Depending upon the enormous chronicled patient details in EHR, the planned research project is based on a predictive model for generic diseases covering perceived health conditions and preventive medication drug uses of disease and their procedures. It is a temporal dimensions model using RNN and was createed and implemented with documented time-stamped EHR data. The major theme of this work is whether or not chronicled data of EHR may forecast doctor upcoming clinical diagnoses and patient's medication order.

This article major goal was to utilize patient longitudinal visit information to forecast the upcoming visit's doctor diagnosis and medication order. As a secondary goal, the prediction of the next visit time for the patient is forecasted. Forecasting the next visit time smooth the direction of whether a patient may be or not in detain in seeking health care.

The Doctor AI model, carry out prediction for multi-label scenario. It means one for each and every disease or medication types over time whereas the sequence labeling tasks prognosticates unique label at every process. The main problem was to find out a adaptable and desirable model competent of executing the multi-label forecasting questions.

2. RELATED WORK

In handling with time based sequences, there are 2 most significant classes of approach had proposed.One is continuous-time Markov chain based models [1], and second significant one is intensity-based point process modeling techniques such as Hawkes processes [2]. The above mentioned models are costly to calculate, particularly for nonlinear problems. It frequently do strong suppositions about the information production process, which might not be genuine for EHR information. A modeling tactics is to create a non-specific approach to constitute the patient timebased medical care and health experience to forecast all the diagnoses, medication categories, and visit time. Recurrent neural networks (RNN) have been hugely used for sequential data in representation learning.

Most of the current scholars aiming to model the temporal progression of a specific disease based on either intensive use of domain-specific knowledge [3] or taking advantage of advanced statistical methods [4]. Research has been conducted on Alzheimer's disease [5] and [6], glaucoma [7], chronic kidney disease [8] and [9], diabetes mellitus [10], and abdominal aortic aneurysm [11].

Now-a-days, scholars are started to construct neural network-based methods to Electronic health record to employ its capacity to study tedious patterns from data. From the previous research works, such as phenotype learning [12] or representation learning [13], have not fully addressed the sequential nature of EHR. [14] It is specifically correlated to this project in that both system utilize RNN for sequence forecasting. Although, whereas [14] applies regular times series of real-valued variables collected from ICU patients to forecast upcoming diagnosis codes, we applied discrete medical codes (e.g., diagnosis, medication, procedure) extracted from longitudinal patient visit records. In every visit, the proposed model is forecasting the output of

European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

diagnosis, medication order in the next visit, and the time to the next visit of admitted patients in the particular hospital.

3. METHODS

The primary goal of this proposed system is to use the episodic patient visit proceedings to predict the doctor's diagnosis, medication and prescriptions order of the following visit time. The workflow of the proposed system is displayed in fig.1

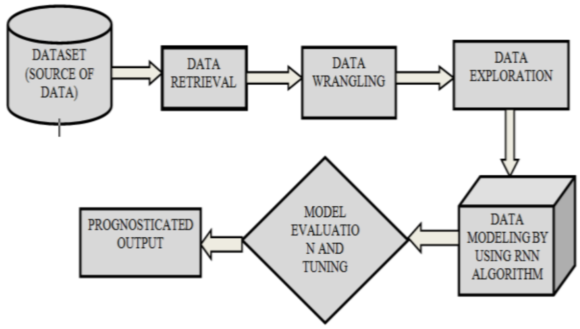

Fig.1. Flowchart of the proposed model

3.1 Problem setup

To forecast the doctor diagnosis and medication order of the upcoming visit .

3.2 Data

MIMIC-III (1.4V) integrates de-identified, broad-ranging; in-depth health data of patients' information admitted to the BIDMC in Boston, Massachusetts makes it broadly accessible to scholars and scientists internationally under an user data accordance. The general summary of MIMIC-III critical care database is shown in fig.2

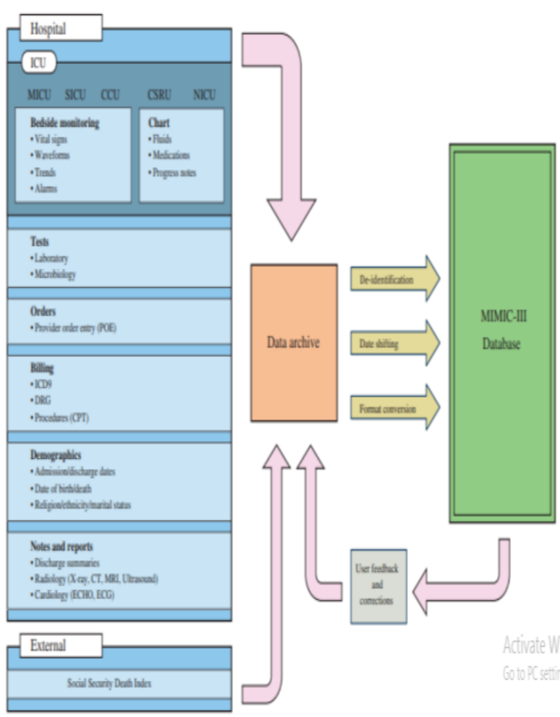

Fig.2.An Epitome of MIMIC-III critical care db

This database was the origin of medical information records such as time-stamped nurse and care taker-verified physiological measurements such as hourly taken documentation of various heartbeat rate, respiratory rate and arterial blood pressure . Then documented progress notes of care providers, continual intravenous drip medications and fluid balances of patients are noted in this database.

Table-1:Summary of the data tables constitute the critical care database of MIMIC-III (v1.3)

Table name	Description
ADMISSIONS	Every unique hospitalization for each patient in the database (defines HADM_ID).
CALLOUT	Information regarding when a patient was cleared for ICU discharge and when the patient was actually discharged.
CAREGIVERS	Every caregiver who has recorded data in the database (defines CGID).
CHARTEVENTS	All charted observations for patients.
CPTEVENTS	Procedures recorded as Current Procedural Terminology (CPT) codes.
D_CPT	High level dictionary of Current Procedural Terminology (CPT) codes.
D_ICD_DIAGNOSES	Dictionary of International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes relating to diagnoses.
D_ICD_PROCEDURES	Dictionary of International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes relating to procedures.
D_ITEMS	Dictionary of local codes ('ITEMIDs') appearing in the MIMIC database, except those that relate to laboratory tests.
D_LABITEMS	Dictionary of local codes ('ITEMIDs') appearing in the MIMIC database that relate to laboratory tests.
DATETIMEEVENTS	All recorded observations which are dates, for example time of dialysis or insertion of lines.
DIAGNOSES_ICD	Hospital assigned diagnoses, coded using the International Statistical Classification of Diseases and Related Health Problems (ICD) system.
DRGCODES	Diagnosis Related Groups (DRG), which are used by the hospital for billing purposes.
ICUSTAYS	Every unique ICU stay in the database (defines ICUSTAY_ID).
INPUTEVENTS_CV	Intake for patients monitored using the Philips CareVue system while in the ICU, e.g., intravenous medications, enteral feeding, etc.
INPUTEVENTS_MV	Intake for patients monitored using the iMDSoft MetaVision system while in the ICU, e.g., intravenous medications, enteral feeding, etc.
OUTPUTEVENTS	Output information for patients while in the ICU.
LABEVENTS	Laboratory measurements for patients both within the hospital and in outpatient clinics.
MICROBIOLOGYEVENTS	Microbiology culture results and antibiotic sensitivities from the hospital database.
NOTEEVENTS	Deidentified notes, including nursing and physician notes, ECG reports, radiology reports, and discharge summaries.
PATIENTS	Every unique patient in the database (defines SUBJECT_ID).
PRESCRIPTIONS	Medications ordered for a given patient.
PROCEDUREEVENTS_MV	Patient procedures for the subset of patients who were monitored in the ICU using the iMDSoft MetaVision system.
PROCEDURES_ICD	Patient procedures, coded using the International Statistical Classification of Diseases and Related Health Problems (ICD) system.
SERVICES	The clinical service under which a patient is registered.
TRANSFERS	Patient movement from bed to bed within the hospital, including ICU admission and discharge.

The input features are medication codes,procedure codes and ICD9 codes are utilized. The International Classification of Diseases Ninth Revision (ICD) is a globally used diagnostic tool for epidemiology, health management and clinical purposes.The ICD is originally developed as a health care classification system, providing a system of diagnostic codes for classifying diseases, including nuanced classifications of a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. This system is designed to map health conditions to corresponding generic categories together with specific variations, assigning for these a designated code, up to six characters long. Thus, major categories are designed to include a set of similar diseases. The International Code of Diseases version9 contains the codes from encounter visits of patients in medical condition of patient problem, medication, surgery procedure and diagnosis codes. Generic product identifier medication codes and current procedural terminology codes are excerpted from medication and procedure orders.

All codes are mapped with time-stamped with exact patient visiting time. If a patient get more codes in one visit, that codes are assigned with the same timestamp. So, in this research, we removed patients that made less than two visits. Table I shows the summary of the data tables comprising the MIMIC-III (v1.3) critical care database.

3.3 Proposed model

This step sketch the RNN-GRU model for multi-label point processes. It also describes how the doctorAI going to forecast diagnosis code, medication order, and patients visit time using this algorithm.

Every patient, the observations are reported from a multi-label point process in the form of (t_i, x_i) for i= 1. . . n. Each and every pair represents an incident/event, such as Outpatient care, ambulant services, patient visit, during which many medical codes such as ICD-9 diagnosis codes, procedure codes, or medication codes are recorded in the victim medical log. The artificial vector i.e.,multi hot-vector xi ∈ {0, 1} p represents the medical codes assigned at time ti, where p indicates the number of distinctive medical codes. At every timestamp, it may excerpt higher-level codes for prediction utilization and denote them by y_i. The number of visits and events vary for every patient.

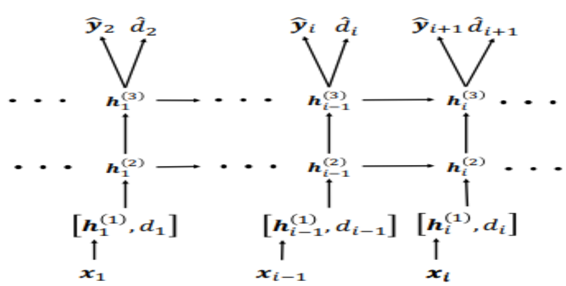

Fig.3. Representation of next visit time prediction

Fig.3. shows how RNN is applied to findout the forecasting of the next patients' visits time and the codes mapped during each visit. The first layer fitted with the top-dimensional put in vectors

in a low-dimensional scope. The succeeding layers are the recurrent layer units (hither two layers), which study the patient's status at each timestamp as a real-valued (original) vector. The status vector has been used. We apply two dense layers to produce the codnext timestamp's codesd the duration until the next visit.

Gated Recurrent Units Prefatory:

Specifically, in this project, RNN is implemented by using Gated recurrent units. GRU is related to LSTM (Long Short Term Memory) as both are utilizing different way if gating information to prevent vanishing gradient problem. The GRU controls the flow of information like the LSTM unit, but without having to use a memory unit. It just exposes the full hidden content without any control over the system.GRU is relatively new, the performance is on par with LSTM, but computationally more efficient and less complex structure. So the researchers and scientists are applying it more and more in the real time scenario. To accurately describe the structure of network applied in this project, we reiterate the mathematical equation (eq.1) of Gated recurrent unit as follows:

$$\begin{aligned} \boldsymbol{z}_i &= \sigma(\boldsymbol{W}_z\boldsymbol{x}_i + \boldsymbol{U}_z\boldsymbol{h}_{i-1} + \boldsymbol{b}_z) \\ \boldsymbol{r}_i &= \sigma(\boldsymbol{W}_r\boldsymbol{x}_i + \boldsymbol{U}_r\boldsymbol{h}_{i-1} + \boldsymbol{b}_r) \\ \tilde{\boldsymbol{h}}_i &= \tanh(\boldsymbol{W}_h\boldsymbol{x}_i + \boldsymbol{r}_i \circ \boldsymbol{U}_h\boldsymbol{h}_{i-1} + \boldsymbol{b}_h) \\ \boldsymbol{h}_i &= \boldsymbol{z}_i \circ \boldsymbol{h}_{i-1} + (1-\boldsymbol{z}_i) \circ \tilde{\boldsymbol{h}}_i \end{aligned} \tag{1}$$

Where z_i is the update gate and the r_i is the reset gate, $h^{\sim}_i$ the intermediate memory unit, and h_i the hidden layer, all at time step t_i.

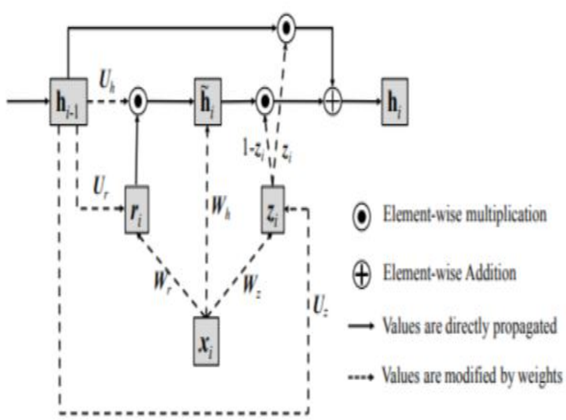

Fig.4. Architecture of GRU

Fig.4 depicts GRU Architecture, where x_i, z_i, and r_i respectively represent the input, update gate and the reset gate, $h^{\sim}_i$ the intermediate memory unit, hi the hidden layer, all at timestep t_i. W_h, W_z, W_r, U_h, U_z, U_r are the weight matrices to be studied.

The Elman Network (Recurrent Neural Network) and GRU's outstanding difference is that the previously hidden layer h_{i-1} and the present input x_i didn't alter the current hidden layer h_i.

In lieu of, they alter the values of both gates z_i, r_i, and the intermediate memory unit $\tilde{h}_i$. Now the present hidden layer hi is updated by $\tilde{h}_i$ and z_i. Due to the σ function, both gates z_i and r_i have values between in the ranges of 0 and 1. So, that the reset gate r_i is close to the value 0, the intermediate memory unit $\tilde{h}_i$ will ignore the previous values of the hidden layer h_{i-1}. If the update gate z_i is close to one, the current hidden layer hi will ignore that current input x_i and keep the value from the past time step h_{i-1}.

The reset gate permits the intermediate layer of hidden to release any details and information regarding the project that is unuseful in making a forecasting and the update gate manage how much data from the previously hidden layer could be communicated to the current hidden layer for future prediction in output. So, these Gated recurrent unit attributes are useful and it will be really difficult to find out the important information to forecasting the succeeding diagnosis, medication codes and the time duration of patient until the next visit.

4. RESULTS

4.1Dataset Collection

MIMIC-III is a medical relational digital database of
25 tables. The tables are connecnted by identifiers, which generally having the suffix 'ID.' In this db, SUBJECT_ID represents an individual patient; HADM_ID represents to a unique admission to the hospital. ICUSTAY_ID represents to an unique admission to an intensive care unit.

Charted measured events are doctor notes, laboratory tests, and fluid balance are collected in a series of 'events' tables. The OUTPUTEVENTS table contains all measurements related to output for a patient, whereas the LAB EVENTS table holds the laboratory test results for a patient.

The tables are prefixed with 'D_' are dictionary tables and provide definitions for identifiers.So, every row of CHARTEVENTS is combined with a single ITEMID, denoting the events measured, but it does not include the measurement's orginal name.

By merging of CHARTEVENTS and D_ITEMS on ITEMID, it is feasible to find out the method denoted by the given ITEMID.

The queried output of relational database attributes and features are in CSV sheets of the MIMIC3 dataset is used for this proposed system implementation is shown in fig.5.

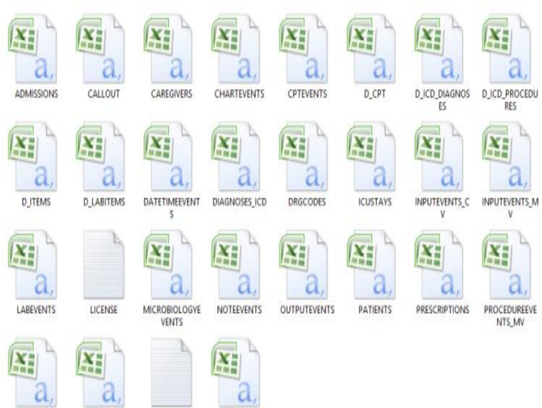

Fig.5. Clinical CSV of Mimic III (1.4) data

European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 08, Issue 03, 2021

4.2 Data Wrangling

The normal range of lab values was extracted from the given information.

Table-2 shows the patient lab measurement of minerals in their body with their lower limit and upper limit compared to their recorded standard measurement values.

Table-2: Normal range of lab values

Lab Value	Lower limit	Upper Limit	Units
Bicarbonate	22	32	mEq/L
BUN	6	20	mEq/L
Calcium	8.4	10.3	mg/dL
Chloride	96	108	mEq/L
Creatinine	0.4	1.1	mEq/L
Hemoglobin	11.2	15.7	g/dL
Lactate	0.5	2	mmol/L
Magnesium	1.6	2.6	mg/dL
Phosphate	2.7	4.5	mg/dL
Platelet count	150	400	K/uL
Potassium	3.3	5.1	mEq/L
Sodium	133	145	mEq/L

Duration of patient lab events from input events is used to predict their chart events for a further hour treatment.

Table-3 shows the chart events of lab measurements of a patient with KCL and Calcium in their body with timely measurement.

Table-3: Duration of patient lab events from input events

Durations from INPUTEVENTS for one patient with KCl...

	label	starttime	endtime	rate_min	rate_max	rateuom	statusdescription
0	KCl	Day 11, 21:30	Day 12, 02:30	4.000000	4.000000	mEq./hour	FinishedRunning
1	KCl	Day 11, 23:45	Day 12, 20:30	9.997713	10.285715	mEq./hour	Paused
2	Calcium	Day 11, 23:45	Day 12, 20:30	1.201625	2.002708	grams/hour	Paused
3	Calcium	Day 12, 21:30	Day 13, 15:54	1.206690	1.805171	grams/hour	FinishedRunning
4	KCl	Day 12, 21:30	Day 13, 16:29	6.005904	9.997634	mEq./hour	Stopped
5	KCl	Day 13, 18:15	Day 13, 23:15	6.000000	6.000000	mEq./hour	FinishedRunning
6	Calcium	Day 13, 18:15	Day 13, 23:15	1.602136	1.602136	grams/hour	Paused
7	KCl	Day 14, 15:28	Day 16, 16:04	4.007380	6.000000	mEq./hour	Stopped
8	Calcium	Day 14, 15:28	Day 16, 16:05	1.196013	1.990426	grams/hour	Stopped

Patient admission details in the Emergency ward are collected to know about their causes of admission and the particular hospital's treatment.

Table-4: displays the patient admission details in Beth Israel hospital in the ICU unit.

ISSN 2515-8260 Volume 08, Issue 03, 2021

Table-4: Patient admission details in the Emergency ward

	row_id	subject_id	gender	dob	dod	dod_hosp	dod_ssn	expire_flag
0	9467	10006	F	05-03-94 0:00	12-08-65 0:00	12-08-65 0:00	12-08-65 0:00	1
1	9472	10011	F	05-06-90 0:00	28-08-26 0:00	28-08-26 0:00	NaN	1
2	9474	10013	F	03-09-38 0:00	07-10-25 0:00	07-10-25 0:00	07-10-25 0:00	1
3	9478	10017	F	21-09-75 0:00	12-09-52 0:00	NaN	12-09-52 0:00	1
4	9479	10019	M	20-06-14 0:00	15-05-63 0:00	15-05-63 0:00	15-05-63 0:00	1
5	9486	10026	F	1895-05-17 00:00:00	24-11-95 0:00	NaN	24-11-95 0:00	1
6	9487	10027	F	15-01-08 0:00	14-09-90 0:00	NaN	14-09-90 0:00	1
7	9489	10029	M	10-04-61 0:00	21-09-40 0:00	NaN	21-09-40 0:00	1
8	9491	10032	M	29-03-50 0:00	21-05-38 0:00	21-05-38 0:00	21-05-38 0:00	1
9	9492	10033	F	21-04-51 0:00	09-09-33 0:00	NaN	09-09-33 0:00	1
10	9494	10035	M	13-04-53 0:00	30-03-33 0:00	NaN	30-03-33 0:00	1
11	9495	10036	F	1885-03-24 00:00:00	26-03-85 0:00	26-03-85 0:00	26-03-85 0:00	1
12	9497	10038	F	27-01-56 0:00	17-03-47 0:00	17-03-47 0:00	17-03-47 0:00	1
13	9499	10040	F	23-10-61 0:00	05-09-50 0:00	05-09-50 0:00	05-09-50 0:00	1

Prescriptions of drugs for the patients with their ICD9 code mapping are used to predict the timely guidance to take particular prescript medications for recorded patients. Table V displays the prescriptions of drugs and their generic name for particular patients admitted to the ICU ward.

Table-5: Prescriptions of drugs for the patients

	row_id	subject_id	hadm_id	icustay_id	startdate	enddate	drug_type	drug	drug_name_poe	drug_name_generic	formulary_drug_c
0	32600	42458	159647	NaN	2146-07-21 00:00:00	2146-07-22 00:00:00	MAIN	Pneumococcal Vac Polyvalent	Pneumococcal Vac Polyvalent	PNEUMOcoccal Vac Polyvalent	PNEU2
1	32601	42458	159647	NaN	2146-07-21 00:00:00	2146-07-22 00:00:00	MAIN	Bisacodyl	Bisacodyl	Bisacodyl	BISA
2	32602	42458	159647	NaN	2146-07-21 00:00:00	2146-07-22 00:00:00	MAIN	Bisacodyl	Bisacodyl	Bisacodyl (Rectal)	BISA10
3	32603	42458	159647	NaN	2146-07-21 00:00:00	2146-07-22 00:00:00	MAIN	Senna	Senna	Senna	SENN18
4	32604	42458	159647	NaN	2146-07-21 00:00:00	2146-07-21 00:00:00	MAIN	Docusate Sodium (Liquid)	Docusate Sodium (Liquid)	Docusate Sodium (Liquid)	DOCU100
5	32605	42458	159647	NaN	2146-07-21 00:00:00	2146-07-22 00:00:00	MAIN	Heparin	Heparin	Heparin Sodium	HEPA

4.3 Data Exploration

The time-stamped recording of patient lab measurements from an input, chart, and KCL procedure events is displayed in fig.6.

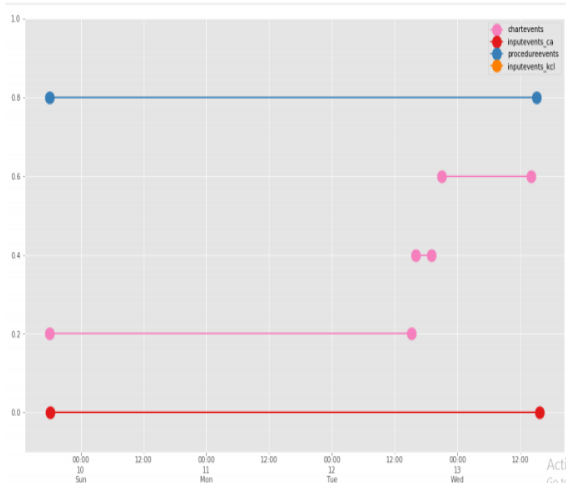

Fig.6. Inputs and procedures for longitudinal visits

The fig.7 displays Hours since admission the Value of Measurement of Arterial Blood Pressure Alarm- Low and High Value, Heart Rate Alarm– Low and High Value, O2 Saturation Pulseoxymetry Alarm – High and Low, Respiratory Alarm – High and Low.,

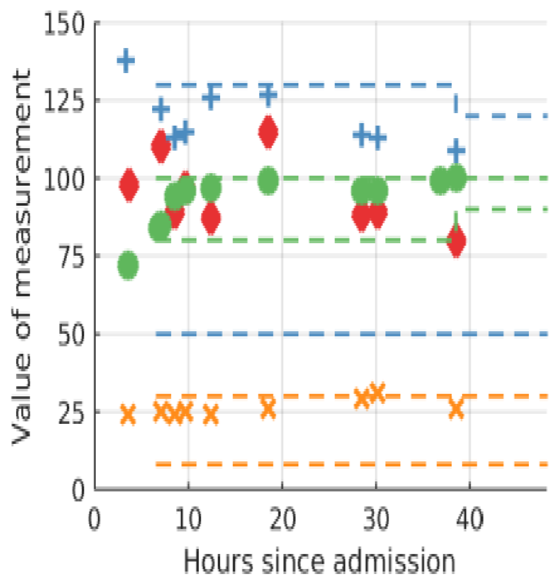

Fig.7 Hourly measurement of lab events

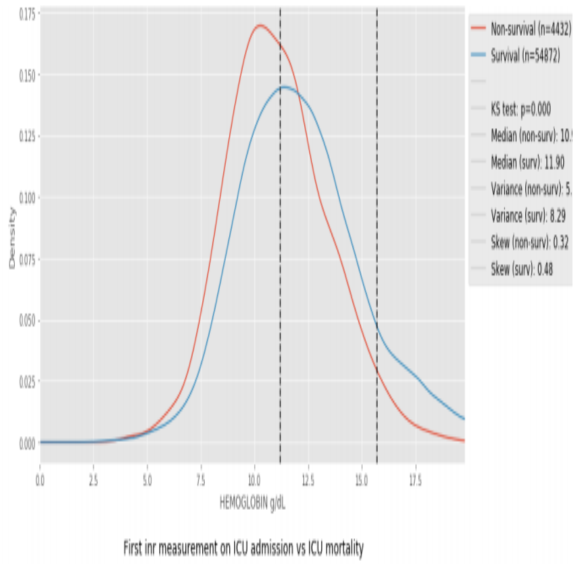

Fig. 8 displays the First lab measurement of Hemoglobin on the ICU admission patients with their survival and non-survival condition in ICU.

The below fig.9. displays the total number of patients having vancomycin disease positive on a particular day in the hospital.

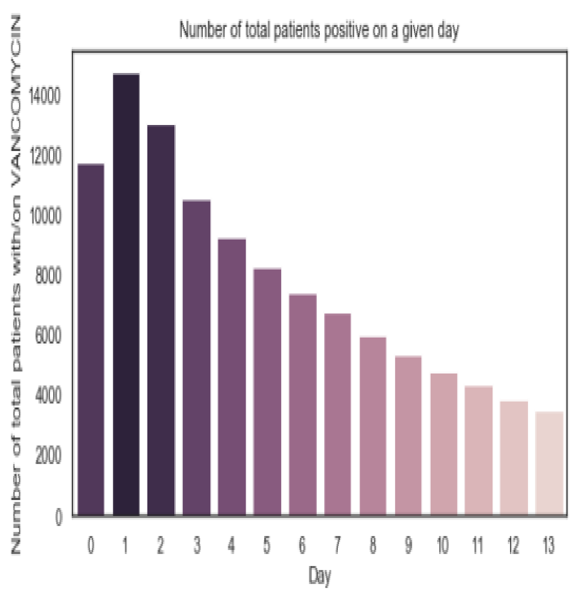

Fig.9 Total patients Vancomycin positive

4.4 Implementation of RNN Algorithm

Model is split into 80% of the patients as the training set and 20% as the test set. Over fitting was avoided by using dropout. Dropout is used between GRU layers, where GRU layers are used for code prediction and the prediction layer is used for time duration distribution and prediction.

Norm-2 regularization is used on both W_{code} and W_{time}. RNN can learn precise attribute representations of patients by collecting the exact information from the past and the present set of codes, which outstands the performance of random details of frequency baselines in implementation.

This results shows RNN model with many layers has the capacity to learn effective representations. But the results, indicate single layer have more strength to learn dynamic representation of medications. The output displays RNN can learn a good prediction of the patient condition as it sees huge and longer patient records. Patient visits are mapped with health is in danger (i.e., poor health). Patient with higher visit shows they are suffering from severe ill diseases and from this it is easy to predict the future scenario. Fig.10. shows training data of the RNN model.

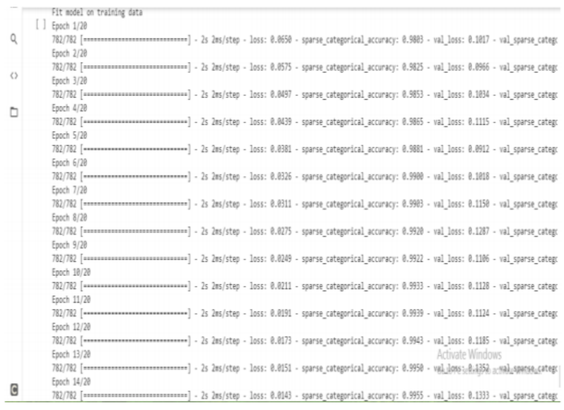

Fig.10. Training data

5. CONCLUSION

This project is proposed using RNN based model to learn efficient patient from many longitudinal patient records and predict patients' future events. Patient visiting numbers and the uniqueness of codes highly correlated with the performance. The logical analysis by a medical expert confirmed that Doctor AI mimics human doctors' predictive power and provides diagnostic results that are clinically meaningful.

REFERENCES

[1]. Uri Nodelman, Christian R Shelton, and Daphne Koller. "Continuous-time Bayesian networks." In UAI, pages 378–387. *Morgan Kaufmann Publishers* Inc., 2002.

[2]. Thomas Josef Liniger. “Multivariate hawkes processes”.*PhDthesis*, Diss.,Eidgen¨ossische Technische Hochschule ETH Z¨urich, Nr. 18403, 2009.

[3]. Willem De Winter, Joost DeJongh, Teun Post, Bart Ploeger, Richard Urquhart, Ian Moules, DavidEckland, and Meindert Danhof. “A mechanism-based disease progression model for comparing long-term effects of pioglitazone, metformin, and gliclazide on disease processes underlying type 2 diabetes mellitus”. *Journal of pharmacokinetics and pharmacodynamics*, (33(3):313–343), 2006.

[4]. Jiayu Zhou, Jun Liu, Vaibhav A Narayan, and Jieping Ye. “Modeling disease progression via a fused sparse group lasso." *In KDD*, pages (1095–1103), 2012

[5]. Kaori Ito, Sima Ahadieh, Brian Corrigan, Jonathan French, Terence Fullerton, Thomas Tensfeldt, Alzheimer 's Disease Working Group, et al. "Disease progression meta-analysis model in Alzheimer's disease." *Alzheimer's & Dementia*, 6(1):39–53, 2010.

[6]. Minh Nguyen, Tong He, "Alzheimer's Disease Neuroimaging Initiative Predicting Alzheimer'sdiseaseprogressionusingdeeprecurrentneuralnetworks"Availablefrom*https://doi.org/10.1016/j.neuroimage.2020.1172031053-8119/© 2020* The Author(s). *Published by Elsevier Inc*.

[7]. Yu-Ying Liu, Hiroshi Ishikawa, Mei Chen, Gadi Wollstein, Joel S Schuman, and James M Rehg. "Longitudinal modeling of glaucoma progression using 2-dimensional continuous-time hidden Markov model". *In Medical Image Computing and Computer-Assisted Intervention*–MICCAI 2013, pages (444–451). 2013.

[8]. Navdeep Tangri, Lesley A Stevens, John Griffith, Hocine Tighiouart, Ognjenka Djurdjev, David Naimark, Adira Levin, and Andrew S Levey."A predictive model for progression of chronic kidney disease to kidney failure". *Jama*, 305(15):1553–1559, 2011.

[9]. Anima Singh, Girish Nadkarni, Omri Gottesman, Stephen B. Ellis, Erwin P. Bottinger, John V. Guttag an "Incorporating temporal EHR data in predictive models for risk stratification of renal function deterioration," *Journal of Biomedical Informatics 53 (2015) 220–228@ 2014 Elsevier Inc*.

[10]. Edward Choi Mohammad Taha Bahadori Elizabeth Searles Catherine Coffey Jimeng Sun Multi-layer Representation Learning for Medical Concepts arXiv: 1602.05568v1 [cs.LG] 17 Feb 2016.

[11]. Willem de Winter, Joost DeJongh, Teun Post "Mechanism-based Disease Progression Model for Comparison of Long-term Effects of Pioglitazone, Metformin and Gliclazide on Disease Processes Underlying Type 2 Diabetes Mellitus",1567-567X/06/0600-0313/0 © 2006 *Springer Science+Business Media, Inc.*

[12]. Christopher H Jackson, Linda D Sharples, Simon G Thompson, Stephen W Duffy, and Elisabeth Couto."Multistate Markov models for disease progression with classification error". *JRSS-D, 2003*.

[13]. Zhengping Che, David Kale, Wenzhe Li, Mohammad Taha Bahadori, and Yan Liu. "Deep computational phenotyping". *Proceedings of the 21st ACM SIGKDD International Conference on Knowledge Discovery and Data Mining,* (pages 507–516). ACM, 2015.

[14]. Youngduk Choi, Chill I Chiu, and David Sontag. "Learning low-dimensional representations of medical concepts". *In AMIA CRI*, 2016b.

[15]. Zachary C Lipton, David C Kale, Charles Elkan, and Randall Wetzell. "Learning to diagnose with lstm recurrent neural networks", 2016.