Anticipating Diabetic Kidney Disease Through Measurements of Albumin in Diabetes Patients

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***Abstract*—We have proposed a system based in the continuous measurement of albumin in type-2 diabetes patients whose diagnosis was done 5 years ago or more. The main idea of this investigation consists in a plan of visits by the nurse to the localizations of the patients, in order to collect samples of urine and blood. From the results of lab, endocrinologist or nephrologist can provide an accurate prescription in order to anticipate the apparition of the diabetic kidney disease, particularly in those patients with a diagnosis of more than 10 years. We focus in those patients from Peri-urban areas of big cities, where most of them are not motivated to attend a public hospital due to the logistic involved and others aspects against the well-being of patient. When this system is used, the simulations has shown that 4 of 17 patients might surpass any type of kidney complications in the middle term.**

***Index Terms*—Diabetes, Kidney Disease, Albumin.**

I. Introduction

A. Motivation of the Paper

The disease of type-2 diabetes is nowadays one of the main causes of worldwide mortality and it seems to be that is showing a sustained increasing in the next decades [1][2][3]. For instance, in Latin American countries like Peru, new cases have been reported in young population around the thirties or even below, fact which might be perceived as the future deterioration of the quality of life of this population for the next 10 or 20 years [4]. When diabetes is not under control, it triggers irreversible and unexpected complications. One of them is the so-called diabetic kidney disease (DKD) which might be the most strong a complication of diabetes [5][6][7][8][9][10]. In most cases it has as consequence the permanent damage of kidney, so that the patients would pass to the phase of dialysis, fact which would deteriorate their quality of life imminently [11][12][13]. Due to the lack of resources, Peruvian public hospitals might not be well prepared to face future arrival of patients, concretely might exist the necessity of installing additional dialysis rooms. It would demand not only adequate infrastructure, supplies and full equipment labs of dialysis, but also the requirement that these labs are working continuously. Concretely, our interest focuses on the human groups belonging to the Peri-urban areas of Lima city showing a remarkable progress of type-2 diabetes. In praxis, these patients are potential candidates to acquire DKD in the middle term and it is expected that their quality of life is reduced drastically. Clearly, the worsening state of patient has an impact on their families deteriorating the social aspects as well.

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B. Main Contribution of this Paper

We have designed an E-Health system whose objective is the probabilistic prediction of the future concentrations of albumin from the samples of urine which are collected periodically. For this end, we have proposed the methodology called "the hospital goes where patient is". It consists in visits made by nurses to the diabetes patients, after of having identified their localization and corroborated their state of health. Nurse performs glucose measurements as well as takes blood and urine samples. These samples are expected to be sent to labs in order to obtain a full analysis of the presence of albumin in urine. In addition, blood test would corroborate some aspects which might be useful for doctor in order to take actions and carry out precise interventions. When results of prediction are indicating the possible degradation of the glomerulus's layers for a possible lapse of time, it might serve to the nephrologist to reconfigure a new pharmacological strategy and suggest new alimentary diets in order to decrease the probability of acquiring DKD in the middle term [14]. The scenario where "the hospital goes where the patient is", is featured by the acquisition of patient's data in short periods. This is clearly advantageous in the sense that the patient has a certain comfortability as to receive medic control at home. One actually expects that the outcomes after of applying this methodology would decrease the probability for passing to the phase of dialysis. Actually, this is contrary to the common case or "standard case" where patients attend hospitals, normally. The case of those diabetes patients which are characterized by having a social and economic vulnerability, the "standard case" might be considered a reason by which the patients abandon the visits to hospital due to the confluence of undesired bureaucracy and excess of logistic as commonly one finds in public hospitals of some Latin American cities. In second section all concerning to the E-Health system is presented. In third section, is formulated a simple model which is based on the behavior of glucose and albumin. The conjunction of these variables plays a crucial role in the dynamics of the system. With this, we propose the algorithm of prediction which is sustained in the method of Monte Carlo. It is expected that the algorithm would play a crucial role as software in a modern health system, working continuously. The algorithm

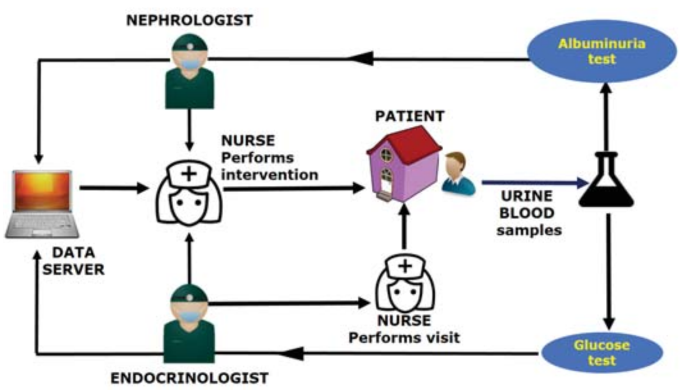

Fig. 1. Sketch of the E-Health system proposed in this paper. Nurse makes visit to the patient. Based on evidences, nurse makes the decision to extract blood and urine samples to be sent to the lab. If glucose values are above the allowed ones, the endocrinologist would work on a new strategy to put down glucose values. If albumin test are above of the allowed ones, the nephrologist adjust the treatment to the kidney. All test results go to the server where prediction is performed. If future values of albumin are increasing then both doctors suggest to nurse to take soon intervention.

TABLE I
DATA FOR 5 VARIABLES OF 17 TYPE-2 DIABETES PATIENTS.

Age/Weight/SBP (y.o./kg/mmHg)	Glucose Average (mg/dL)	Nephro Risk Level	Years with Diabetes
1/38/88/168	190	high	> 5
2/41/100/142	177	middle	> 10
3/42/90/122	130	low	≈ 4
4/45/80/118	196	low	≈ 1
5/45/86/130	230	middle	>4
6/53/71/130	102	low	≈ 5
7/53/73/136	122	low	>10
8/53/79 /129	139	low	≈ 5
9/54/82/130	164	middle	>10
10/57/90/150	310	middle	≈ 2
11/62/93/180	275	high	>10
12/67/90/170	225	high	≈ 5
13/67/82/166	207	high	>8
14/69/70/155	249	high	>5
15/70/68/167	211	middle	≈ 8
16/71/71/148	290	high	>5
17/75/72/156	145	middle	> 10

has analyzed the data of 17 type-2 diabetes patients. In fourth section, results of this paper are presented. Mainly 3D histograms were plotted [15]. Finally, the conclusion of paper is drawn.

II. Proposal of the System

A. The E-Health Functionality

The main idea of the proposal of E-Health system is sketched in Fig. 1. Firstly, nurse has identified the address of the patient in order to make visits. According his perception and point of view, nurse collects both urine and blood samples to be sent to labs. Actually it is done same day of the visit. Results of test are expected on next day. Lab informs about the results to the doctors: nephrologist and endocrinologist. Once the doctors have received the results of the tests, they fill E-forms in order to be sent to a data server through text message. The data server makes estimates by using a predictive algorithm (see next section). According to the results of the predictions, the server sends a text message to nurse [1][3][7]. In this manner, nurse performs intervention consisting in a plan of visits continuously. Also nurse receives suggestions from doctors previous to the visits. Actually, doctors can also do recommendations to the nurse such as to program an interview in the hospital in those cases where the situation of patient is abnormal. For instance, in the case that the server gives as result a rapid increase of the values of albumin for the next six months, the nephrologist can recommend to the nurse which more attention should be paid on the control of the intake of Sodium. Thus nurse explains to the patient the disadvantages of including salt in the foods, and the future consequences in their kidneys [8]. Together to the recommendations of the nephrologist there is also the ones of the endocronologist which can suggest a dedicate control of the glucose values. In effect, if patient is showing a change or fluctuations in the glucose values and there is evidence of trend in the short or middle term, then nurse should apply a firm strategy which would guarantee that the patient is capable of lowering and maintain the glucose values for the next days and weeks. It is also highly recommended that the nurse starts a program of surveillance whose aims is the continue monitoring of the glucose values from measurements ranging between 2 to 3 times per week [16]. One critic point of this system is that of the connectivity between the server and the mobile phone of nurse which should be running in a unstoppable manner.

B. Patients Selection

Patients were selected under the following criteria: (i) evidence that the diabetes patients are abandoning their pharmacological treatment due to unknown reasons, (ii) evidence that the patient is showing a rapid increasing of their glucose values surpassing 250 mg/dL, (iii) evidence that the patient has not a firm policy about their foods and drinks, (iv) the patient is living in peripheral areas of Lima city, (v) the patient has not contact with health specialists since 6 months ago or more, (vi) evidence that the patient has a very low level of self-care. Once all this package of criteria is applied, were identified up to 17 diabetes patients. All of them are above 25 y.o, and signed the consent form as part of the ethics policy of this study. In Table I the sample containing up to 17 patients is listed. It is shown information per patient of up to 5 variables. Firstly, we can see that the ages are ranging between 38 and 75 y.o. Secondly, the weights between 71 and 100 kg. Clearly various cases of obesity can be identified. The third variable is given by the systole blood pressure (SBP) which is showing high values in conjunction with overweighted cases, anticipating that the sample is already containing cases of risk. The average of glucose measurements during the last three months are shown in fourth column. All cases are showing irregular control with values between 102 and 310 mg/dL. In fifth column is listed the level of nephropathy whose estimation comes from interviews, as well as the conjunction of glucose and

SBP. Indeed, patients were asked to describe their habits of nutrition, intake of sodium, salt, and fat. Finally, last column indicates the number of years by which the patient is living with the disease, counted from the moment where patient has received the diagnosis of type-2 diabetes.

III. Monte Carlo Simulation of System and Results

A. *Mathematical Model as Basis of System's Software*

In order to propose a mathematical model in according to the standard knowledge of the scales of concentration of albumin and well-known scenarios [11][12][13], we pass to define the levels of albumin as follows

$$\mathcal{A} = \begin{cases} \mathcal{A}_1 \equiv \text{normal} & 0 < \mathcal{W} \leq 30\text{mg/dL} \\ \mathcal{A}_2 \equiv \text{microalbumin} & 30 < \mathcal{W} \leq 300\text{mg/dL} \\ \mathcal{A}_3 \equiv \text{macroalbumin} & \mathcal{W} > 300\text{mg/dL} \end{cases}$$

Clearly, one can see up to three phases which would appear in the next years during the progress of the disease [14]. Starting from the fact that these phases are each other connected as sequences in time, then is possible to associate them a multi-step function which would be that of the Erf functions. However, it is crucial as behaves the amplitude of these functions because the progressive increasing of albumin might be strongly correlated to the temporal evolution of glucose as well. In this way, we can write below the proposal of albumin as function of time

$$\mathcal{A}(t) = \sum_{j=1}^{N} \mathcal{G}_j(t) \otimes \text{Erf}\left(\frac{t - \mu_j}{\zeta_j}\right) \tag{1}$$

where μ_j and ζ_j denote the parameters of the step functions which are associated to the morphology of the temporal evolution. We can see that the integer number j runs up to N curves, and $\mathcal{G}_j(t)$ denotes the changing amplitude of the albumin curve which might be governed by the glucose behavior. It is possible to extend the meaning of $\mathcal{G}_j(t)$ in the sense that it can depend upon others parameters which would have direct impact on the temporal behavior of the glucose [7][8]. We can express the glucose curve as follows

$$\mathcal{G}_j(t, \rho_j, \gamma_j, \beta_j) = \frac{\rho_j\left[1 + \mathcal{W}_j \text{Sin}^3(t^{\gamma_j})\right]}{1 + \text{Exp}(-\beta_j t)}, \tag{2}$$

where $\mathcal{W}_j, \rho_j, \gamma_j$ and β_j are related to the patient's behavior. As proposed in [7], the stability of the diabetes patient would depend on the full control of these parameters in order to avoid a rapid growth of glucose in short periods of time. For instance, all of them are well determined by the psychology of patient as well as by its aptitude to face the possible apparition of unexpected complications due to the progress of disease. In Table II, the meaning and range of values of these parameters are listed. Under this view we can formulate the proposal of model. Thus, with (1) and (2) we can write down the main equation which would denote the function of albumin in time, and expressed in gr/dL,

$$\mathcal{A}(t) = \sum_{j=1}^{N} \frac{\rho_j\left[1 + \mathcal{W}_j \text{Sin}^3(t^{\gamma_j})\right]}{1 + \text{Exp}(-\beta_j t)} \text{Erf}\left(\frac{t - \mu_j}{\zeta_j}\right), \tag{3}$$

TABLE II
Meaning of Parameters Used in Eq. 2 [7].

Parameter	Meaning	Range
ρ	Pharmacology	1 - 300
β	Diet	0.01 - 10
$\mathcal{W}$	Alimentary disorder (without pharmacology)	0.01 - 1.0
γ	Alimentary disorder (with pharmacology)	1 - 5

Algorithm of System

DO p = 1, 17 (patients)
  DO j = 1, N (unit of time)
    Extract a random number r
    Defines $\mu_{p,j+1}, \zeta_{p,j+1}$
    Defines $\rho_{p,j+1}, \beta_{p,j+1}, \gamma_{p,j+1}, \mathcal{W}_{p,j+1}$
    Normalizes $\mathcal{A}(t_{p,j+1}), \mathcal{A}_1, \mathcal{A}_2, \mathcal{A}_3$
      IF $\mathcal{A}(t_{p,j+1}) > r$ **THEN**
        IF $\mathcal{A}_(t_{p,j+1}) \rightarrow \mathcal{A}_1$ **THEN**
        nurse makes a visit
        ELSEIF $\mathcal{A}_(t_{p,j+1}) \rightarrow \mathcal{A}_2$ **THEN**
        neprho and endocrino make suggestions
        ELSEIF $\mathcal{A}_(t_{p,j+1}) \rightarrow \mathcal{A}_3$ **THEN**
        neprho makes suggestions
        ENDIF
        $\mathcal{A}(t_{p,j+1}) \rightarrow \mathcal{A}(t_{p,j+2})$
        DO q = 1, Q (future values)
          DO r = 1, R (future of parameters)
          fills $\mu_{p,j+r}, \zeta_{p,j+r}$
          fills $\rho_{p,j+r}, \beta_{p,j+r}, \gamma_{p,j+r}, \mathcal{W}_{p,j+r}$
          ENDDO
          fills $\mathcal{A}(t_{p,j+q})$
        ENDDO
      ENDIF
  ENDDO
ENDDO
END

which would define a 6-parameters model, and depending on the time. Basically it is the multiplication of the glucose's behavior and the albumin. Clearly, we keep the basic idea that the albumin in urine might be proportional to the glucose concentration. In effect, we take for example the parameter ρ_j that in according to Table II, it would absorb the effects of the pharmacology against the progress of diabetes and other positive effects on the patients. Eq. (3) also exhibits the nonlinearity of the albumin behavior in time. In fact, the presence of the $\mathcal{W}_j$ which multiplies the term $\text{Sin}^3(t^{\gamma_j})$ is actually the responsible to increase or decrease the level of nonlinearity on $\mathcal{A}$. This is linked to the alimentary disorder of patient when no any pharmacology is taken.

B. *Algorithm of Prediction and E-Health System*

The software which is expected to be running in the data server (Fig. 1) is based entirely in the Eq. (3). Furthermore, the simulation has contemplated the following requirements: (i) nurse visits patients at least twice per week. It means that the data server stores around 8 samples per months. We have considered that $N = 3$, which is in according to the expected levels namely normoalbumin, microalbumin, and macroalbumin [14]. The algorithm of system can be described as follows: in line-1 and line-2 the loops for the number of patients and times are initialized. Between lines 3 and 6 the parameters are defined, together with the initialization of the random number which is extracted from a generators machine (external subroutine). Doctors have received the test results from lab for both: glucose and albumin. The results go to data server continously. In line-7 the Monte Carlo step is applied. It consists in the question of that if the amount of normalized albumin (whose values are ranging between 0 and 1) for a subsequent time of the last measurement is greater than the random number. When it is satisfied then the next task is locate the value of albumin inside the expected ranges $\mathcal{A}_{1,2,3}$. Depending on it, the system would start communications with nurse and/or endocrinologist and/or nephrologist, in order to make intervention if any. Actually, this is in agree with scheme of Fig. 1 where data server stores and activates warnings in those cases where there is evidence of risk of high values of albumin. In line-15 is seen that the system opts for analyzing again for a subsequent time by passing from t_{j+1} to t_{j+2}. In lines 18 and 19 are filled the future values for the parameters of Eq. (3). Once the parameters were calculated for the future, we proceed to estimate the albumin value as given in line-21. Here is saved the values of glucose in order to count the number of patient with their respective predictions.

IV. Results of Simulation

A. Simulation for Glucose and Albumin for 3 Years

In Fig. 2, up to 4 3D histograms [15] for simulations contemplating 6, 12, 24 and 36 months are displayed. In top left histogram is denoted the case for 6 months, which turns out to be insufficient for any conclusion. It is seen that the patients has not any evidence of the possible future states of diabetic nephropathy. It is because the averages are around 100 mg/dL and 120 mg/dL of albumin and glucose, respectively. It is also perceived that the E-Health predictive system might be yielding linear outputs for short terms. In top right, is presented the simulation expected to be of 12 months. In this case, the Monte Carlo has demanded that the quantity $\mathcal{W}$ has nonlinear behavior. As consequence, the patients might be showing minor signs of diabetic nephropathy, in particular those with an old diagnosis of diabetes. We find that 6 patients are already developing the DKD. In bottom left histogram, is shown the case of a period of 24 months. We have identified up to 8 patients already developing DKD. And finally, in bottom right histogram, the simulation expected to be for a time of 36 months is presented. Here we have assumed that the patients were capable of putting down their concentrations of glucose. According to the algorithm, in line-13, when nephrologist make suggestions or schedule interviews with the patients, it has effect on the prediction of future values of the parameters of Eq. 3 in the sense that the future values might decrease under the compromise that the nurse would make

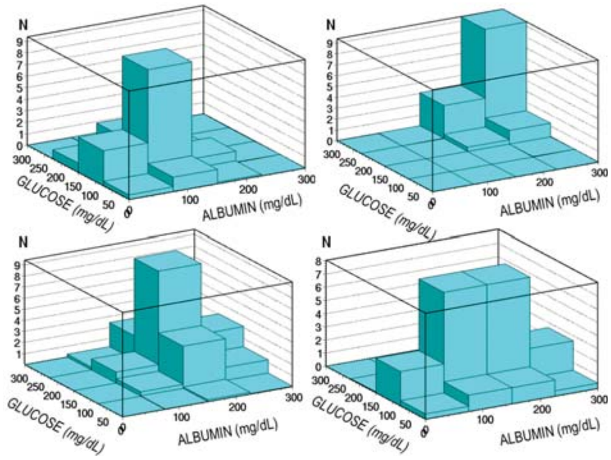

Fig. 2. Different 3D histograms derived from the simulation by following the indication of line-21 of algorithm. The number of patients is plotted against the predicted values of glucose and albumin. The histograms denote the simulations for a time of 6 (top left), 12 (top right), 24 (bottom left) and 36 (bottom right) months.

further visits, as well as the patient would receive suggestions and conversations with doctors (through cell phones). From all histograms and after a statistical analysis, we can arrive that at least 4$\pm$1 patients would represent the subsample which might be inhibited for acquiring DKD, in contrast with the case where all patients would be in potential risk for acquiring diabetic nephropathy and dialysis. According to our predictions, the patients labeled by **5**, **11**, **13** and **16** might not be affected with the DKD if only if the system is working continuously through visits, prediction and doctors communications. This result encompasses the goal of the E-Health system by which is expected to reduce the number of diabetic patients from Peri-urban areas of big cities which are in constant risk for kidney's complications.

B. Simulation of Albumin for 5 years

Finally, in Fig. 3, the curves corresponding to theoretical, the Monte Carlo simulation, and one which would only correspond to the transition of microalbumin to macroalbumin are plotted. The orange-line curve denotes the theoretical which is calculated with the best values for the parameters of the Eq. (3). This curve would be the template for the Monte Carlo simulation. In fact, the curve with dots (sky blue color) is the resulting after of simulating the functionality of the E-Health system with the method of Monte Carlo. We have used the orange line as the reference for the simulation. The prediction was obtained by assuming the continuous functionality of the E-Health system and focused on the patients **5**, **11**, **13** and **16**. The resulting curve represents the average the predicted values of albumin of these patients for 5 years. We can see that there is of up to two predictions per years. The dots are superimposed to a continuous curve. Indeed, one can see the apparition of stochastic fluctuations along the horizon of prediction which can be interpreted as a limited aspect of the computational simulation. Clearly, it would reduce the quality

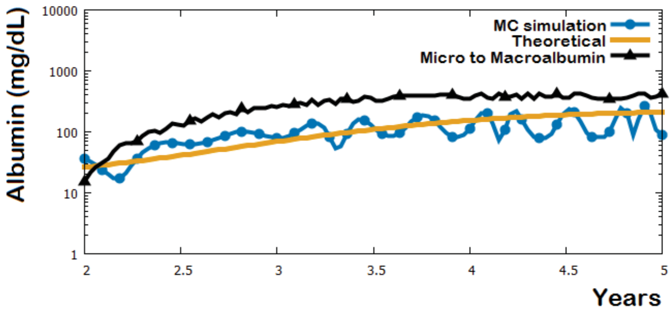

Fig. 3. Curves of temporal behavior of albumin for patients labeled by **5**, **11**, **13** and **16** for three cases: Monte Carlo simulation (black), theoretical (orange), and the transition from microalbumin to macroalbumin (blue sky).

of the prediction. The error attached to the simulations was of order of 18%. The fluctuations appear as result that the Monte Carlo has selected $\mathcal{W}_{1,2,3}$ (the parameters responsible for nonlinearities) ≈0.5 and ζ_1=2.4, ζ_1=3.8, and ζ_3=5.5. Finally, the black line is the simulated with the highest values of the parameter ρ, by which from 595 Monte Carlo steps, at least a 2% might surpass the trajectory of the orange line. This might be perceived as the origin for the transition of microalbumin to macroalbumin. This scenario might correspond to the cases where the patients are already with a diagnostic of DKD. The simulation has yielded that the patients labeled by **9**, **10**, **12** and **15** might be part of this scenario. In this way, the nurse can prepare an aggressive plan of visits and teleconsults aiming to maintain a constant surveillance of the albumin and glucose through successive tests. In addition, doctors can also improve the prescriptions and recommend interviews with patients in the short term [16][17][18].

V. Conclusion

In this paper, we have proposed and computationally tested a E-Health system that aims to be used in vulnerable and diabetic populations of Lima city. It might be a useful tool to reduce the number of patients which would be potentially users of the dialysis processes. We have formulated a mathematical methodology based on step-functions which can be interpreted as the phases of the evolution of glucose in patients. This formualtion mathematical depends on parameters which are related to the lifestyle of patients. This formalism is further used as part of a software system working in a data server. The system contains an algorithm with capabilities for making predictions in the middle term up to 5 years. These predictions depend on the method of Monte Carlo, since the evolution of diabetic patients acquires certain randomness fact which is entirely attributed to the semi stochastic behavior of patient. Clearly, the fluctuations of the evolution temporal of glucose is driven basically by a inadequated alimentation and the abandon of pharmacology. The worsening of the state of the diabetic patient is also triggered by the lack of interviews between the patient and the health specialists. From a sample of 17 patients, our results have indicated that at least 4 of 17 might not develop the DKD for the next 5 years. On the other hand, at least 4 patients were identified which might acquire DKD in the upcoming 3 years, fact which would be discussed and stressed by doctors in order to improve the quality of the pharmacological prescriptions in the short and middle term.

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