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Generalized Nets for the Diagnosis and Management of Diabetic Nephropathy

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Abstract: *This paper develops Generalized Nets for the diagnosis and management of diabetic nephropathy. The first net accounts for the development of nephropathy from an initial increase in glomerular filtration rates through mciroalbuminuria to end stage renal disease. The second net referes to the management of diabetes mellitus to increase the probability of preventing diabetic nephropathyor minimising its effects.*

Keywords: *Generalized Net, Proteinuria, Microalbuminuria, Glomerular filtration rate, Hypoglycaemia, Glycosuria.*

Introduction

This paper deals with the application of generalized nets (GNs) [4] to the problem of diagnosis of permanent proteinuria and the management of diabetes mellitus. Both GNs involve modifications to GNs described in [25] in that the former focuses exclusively on the diabetic aspects and the latter now also accounts for the release of glycogen from the liver during a hypoglycaemic episode ("insulin shock"). Recent research has renewed efforts to reduce all forms of renal disease in patients with diabetes.

The encoding of statistical analysis in a mathematical model and computer program is highly controversial – which is not to say that it should not be attempted. Streitberg [28] used arguments based on complexity classes to claim that it could not be done. "The subsequent discussion (which is well worth reading) showed that the developers did not accept the general arguments, while being very aware of the difficulties raised. The primary problem is that it presupposes that we can write down the rules of inference in a computer form" [20]. The use of informatics in the search for more adequate insights is increasing [23]. Moreover, a major advance in the development of GNs by Atanassov and others has been that they can utilise the flexibility of Atanassov's intuitionistic fuzzy logic [5]: this effectively counterbalances Nelder's caution.

The topic demands consideration because diabetic nephropathy is still the most common single cause of end-stage renal failure [15]. There has been increasing evidence that during the past 20 years the development of diabetic nephropathy is the most fateful event in the life of diabetic individual. It is associated with a very high mortality, and also with a significant increased risk of developing retinopathy, atherosclerosis, strokes and myocardial infarction. As far as renal disease in diabetes is concerned, the kidneys of people with diabetes may

suffer from a variety of diseases. Its high morbidity and mortality make nephropathy one of the most serious of the complications that characterize the evolution of diabetes mellitus. From the standpoint of prognosis, it is unquestionably the most serious. Despite intensive research the reasons why a substantial percentage of patients with diabetes develop nephropathy are still unclear. In view of the seriousness of this complication, the early detection of nephropathy might provide an opportunity to intervene therapeutically in an attempt to prevent end-stage renal failure and cardiovascular morbidity /mortality. It is now possible to diagnose diabetic nephropathy at an early stage in its natural history by the detection of microalbuminuria. Therefore screening for microalbuminuria is commonly performed among diabetes patients in order to diagnose the early stage of diabetic nephropathy [19]. The management of T1D through insulin injections is still problematic and targeting of CD3 (a protein complex expressed by all T cells) with immune-modulatory monoclonal antibodies can cause serious side effects [11].

Proteinuria

Proteinuria is usually the first manifestation of diabetic nephropathy and may be intermittent for many years before becoming persistent. Once persistent proteinuria has developed, renal function declines gradually but progressively, reaching end-stage renal failure on average with 7 years [3, 13]. Some elevation of blood pressure is usually present from the early, microalbuminuric stage of diabetic nephropathy [18, 2], and almost all patients with persistent proteinuria have hypertension which continues to worsen as the glomerular filtration rate (GFR) falls [21].

When the proteinuria is constant or persistent, quantitative measures of proteinuria excretion are useful for diagnosis and for following the patient's clinical progress. These are accomplished by measuring the total protein voided in a timed interval, usually 24 hours. Heavy proteinuria is generally found in patients with glomerulo nephropathy producing nephrotic syndrome. In primary diseases involving the tubulointerstitial area (e.g., pyelonephritis) the proteinuria as a rule is minimal, intermittent or absent. Research suggests that measurement of proteinuria is the most accurate way for the screening and diagnosis of overt diabetic nephropathy. Moreover, protein measurement in spot urine is a reliable and simple method for the screening and diagnosis of overt diabetic nephropathy [34].

Persistent proteinuria is defined as a protein excretion > 0.5 g/24 h in at least four consecutive urine samples with an interval of at least 1 month in patients without renal infection. Persistent proteinuria is strongly associated with increased mortality in T1D, and risk of this condition can be predicted many years in advance by subclinical increases in albumin excretion rate (microalbuminuria) [7]. They also found that the reduction in albumin excretion rate was accompanied by a significant fall in median GFR and a fractional renal clearance of albumin. Kidney volume remained unchanged.

These results were in accord with the conclusions of [6] who showed that relative mortality was extremely high among patients with persistent proteinuria. Moreover, they found that in patients who developed proteinuria, relative mortality was higher in women than men at all ages. In patients who did not develop proteinuria, uraemia was the main cause of death in patients with persistent proteinuria, although cardiovascular deaths were more frequent than in patients without proteinuria. Hence they concluded that proteinuria is associated not only with death from uraemia but also from cardiovascular disease.

Microalbuminuria

Microalbuminuria, the early phase of diabetic nephropathy, is associated with increased cardiovascular morbidity and mortality, but the reason for this is not clear [10]. Others have assessed the prevalence of microalbuminuria, and found that its relative mortality in men and women was similar after the age of 35 [22]. Also they noticed that associations with other clinical features. The study showed that persistent microalbuminuria was found in a significant number of T2D patients at the time of diagnosis.

Similarly, the impact of microalbuminuria on mortality among a large cohort of T2D and other risk factors was investigated in [24]. They found that age, urine albumin concentration (UAC), known duration, and serum creatinine were the only significant risk factors. Similar findings have also shown that in T1D the increased cardiovascular risk (raised blood pressure and total cholesterol) associated with microalbuminuria in patients for more than 5 years was also apparent in those with diabetes for 1-5 years [27]. Increased urinary protein excretion is an important finding. In people with T1D, it is both the hallmark of diabetic nephropathy and a marker of more generalized vascular disease. However, they asserted that albumin excretion can be reduced by antihypertensive drugs and microalbuminuria can be lowered by improved glycaemic control.

More specifically, Turtle [29] explained that patients with microalbuminuria have an increased risk of developing diabetic nephropathy, hypertension, large vessel disease and retinopathy. Hence epidemiological studies have focused on the identification of risk factors for the development of microalbuminuria. In the same way, the United Kingdom Prospective Diabetes Study Group [30] concluded that urinary albumin excretion was associated with hyperglycaemia and hypertension, whereas urinary N-acetyglycaeminidase was primary associated with hyperglycaemia. Furthermore, Winocour *et al.*, [32] showed that the aggregation of risk factors for diabetes mellitus complicated by proteinuria helps to explain the increased prevalence of ischaemic heart disease and peripheral vascular disease reported in these patients. Moreover they concluded that early renal disease in T1D may have an important role in hypertension and alters lipoprotein metabolism.

The study of Klein *et al.*, [12] aimed at finding the risk factors associated with gross proteinuria (≥ 0.3 $g \cdot l^{-1}$). They discovered that gross proteinuria, a sign of diabetic nephropathy, is associated with increased risk of renal failure. The risk factors obtained from the data are hypertension, smoking and glycaemic control, and all are significant for the development of gross proteinuria. Mogensen and colleagues [16, 17] considered microalbuminuria in patients of either T1D or T2D. They found that it is predictive of clinical proteinuria and increased mortality, and it was also agreed that elevated blood pressure, in the presence of abnormal albuminuria, constitutes a risk factor of diabetic nephropathy. While normotensive Type 1 diabetic patients with microalbuminuria have a stable glomerular filtration rate (GFR), "efforts should be made to prevent the progression from microalbuminuria to diabetic nephropathy in every diabetic patient. Progression from microalbuminuria to diabetic nephropathy (urinary albumin excretion (UAE) > 300 mg/24h) is a bad sign, indicative of loss of kidney function" [15]. While there is evidence that strict glycaemic control in Type 1 diabetic patients may limit the progression from incipient to overt diabetic nephropathy, there have not been similar data for Type 2 diabetes. Gall *et al.*, (1997) have however shown that "several potentially modifiable risk factors, such as urinary albumin excretion rate, long term poor glycaemic control, and hypocholesterolaemia predict the development of incipient and overt diabetic nephropathy in normoalbuminuric patients with non-insulin dependent diabetes".

A GN model for permanent proteinuria

The tokens (patients) enter place l_1 (see Fig. 1) with an initial characteristic "permanent proteinuria". A dipstick urine screen is performed . The dipstick, a firm plastic strip, contains a paper area impregnated with an indicator that is sensitive to protein concentration. Other types of test strips also have areas that are sensitive to blood, glucose, leucoytes, nitrite and other chemicals.

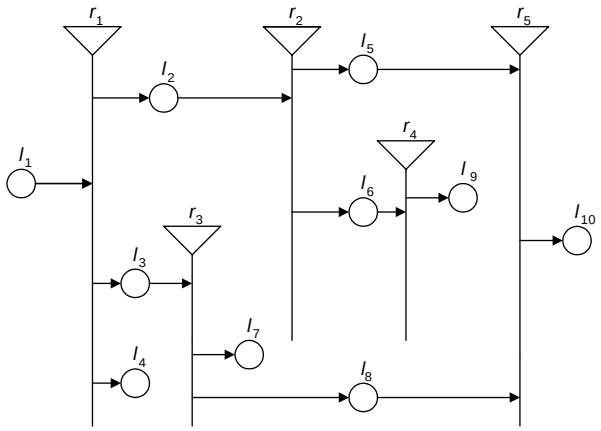

Fig. 1 GN model for permanent proteinuria

Adjacent to l_1 the token splits and proceeds to the sections with initial places l_2, l_3 and l_4 so that each one obtains an appropriate characteristic:

- the result of the complete urinalysis (in l_2),
- values of serum creatinine levels (or glomerular filtration rates) (in l_3), and
- radiological studies of the urinary tract are necessary (in l_4).

In the last case, the token leaves this GN. The transaction conditions r_1 and r_2 have the forms:

$r_1 =$

	l_2	l_3	l_4
l_1	true	true	true

$r_2 =$

	l_5	l_6
l_2	true	true

The token in place l_2 splits into two tokens which enter places l_5, and l_6 according to their characteristics:

- l_5 : quantity of 24-hour proteinuria;
- l_6 : presence of glycosuria ;

Now for the third transition we have the transition condition

$r_3 =$

	l_7	l_8
l_3	W_1	W_2

where: W_1 = "finds out renal insufficiency", W_2 = -W_1

The fourth transition is

$$r_4 = \begin{array}{|c|c|} \hline & l_9 \\ \hline l_6 & \text{true} \\ \hline \end{array}$$

In place l_9 the token obtains characteristic

"return for glucose tolerance test in 3 months".

The fifth transition is

$$r_5 = \begin{array}{|c|c|} \hline & l_{10} \\ \hline l_5 & \text{true} \\ \hline l_8 & \text{true} \\ \hline \end{array}$$

In place l_{10} the token obtains characteristic

"renal failure is imminent".

The token leaves this GN if there is glycosuria. Glycosuria occurs when glucose is detectable in the urine. Most glucose that is filtered through the glomeruli is usually re-absorbed by the proximal renal tubule and so glycosuria represents an abnormal state. It does not always indicate that this state is due to diabetes. In fact, false positives occur when a substance other than glucose gives a positive result.

The level of blood glucose at which it spills into the urine is called the renal threshold. Long-term, poorly controlled patients often have a low renal threshold. Under normal circumstances, this is around 10 mmol/L. In the days when Fehling's or Benedict's reagents were used to test for glucose, a false positive could be achieved from other reducing sugars or other reducing substances. Sucrose is not a reducing sugar. Tablets such as Clinitest™ detect reducing substances and have the same problem. Nowadays it is much more usual to use plastic strips carrying glucose oxidase and a colour indicator, usually o-toluidine. Trade names include Diastix™, Medi-test™ and Diabur-test 5000™. Hence they are much more specific and unlikely to give positive results for substances other than glucose. For most practical purposes, glucose oxidase strips have superseded reagents for reducing substances.

A GN model for the management of diabetes

Successful management of diabetes mellitus requires adequate control of blood glucose levels. Hypoglycaemia refers to the situation where there is less than the normal amount of glucose in the blood, usually caused by administration of too much insulin, excessive secretion of insulin by the islet cells of the pancreas or excessive exercise. Some "unexplained hypos" happen for no obvious reason and some occur without prior warning signals (asymptomatic). On the other hand, glucagon is a hormone produced in the alpha cells of pancreatic islets of Langerhans. It causes the breakdown of glycogen into glucose thus preventing blood sugar from falling too low in normal circumstance. Hence glucagon prevents hypoglycaemia by maintaining glucose production at a rate sufficient to meet the needs of the human body. A dangerous situation arises when a patient has a series of "hypos" without giving the liver a chance to replenish its supply of glycogen.

However, among diabetic patients when uncontrolled insulin release has been reported (insulin shock), and if the release of glycogen from the liver is not sufficient to counteract the effect of the consequence of the insulin excess, hypoglycaemia will occur. The effect may vary from mild episodes, to severe and intractable hypoglycaemia leading to convulsions and even death in some cases.

Let TIME be the current-time-moment and for a token p, we denote by x_0^p and x_{cu}^p the initial and the current characteristics of the token p.

- α – tokens enter places l_1 with initial characteristics "receiving of signals by the pancreas to begin functioning",
- β – tokens enter place l_4 with initial characteristics: x_0^b = manufactured insulin; its quantity; the current time-moment'; and
- γ – tokens enter place l_9 with initial characteristic: x_0^c = carbohydrate; its quantity; the food's type; its quantity; the current time-moment + the necessary time for digestion.

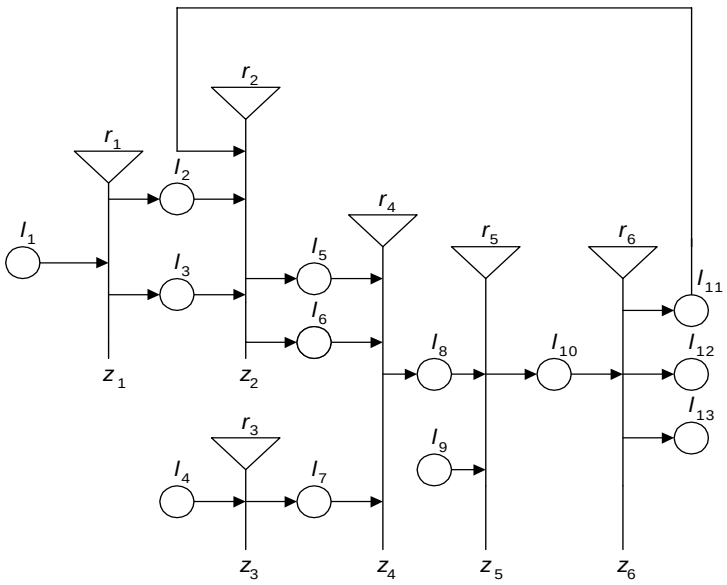

Fig. 2 GN model for diabetes mellitus

Fig. 2 represents a GN model for diabetes mellitus. The form of the GN-transitions are the following:

$$z_1 = \langle \{l_1\}, \{l_2, l_3\}, r_1, \wedge l_1 \rangle$$

where

$r_1 =$

	l_2	l_3
l_1	true	true

The tokens from place l_2 receive the characteristic "insulin; its quantity; the current time-moment"; the tokens from l_3 receive the characteristic "C-peptide ; its quantity; the current time-moment;

$$z_2 = \langle \{l_2, l_3, l_{11}\}, \{l_5, l_6\}, r_2, \vee(\wedge(l_2, l_3), l_{10}) \rangle,$$

where

$r_2 =$

	l_5	l_6
l_2	$W_{2,5}$	$W_{2,6}$
l_3	$W_{3,5}$	$W_{3,6}$
l_{11}	true	true

where: $W_{2,5}$ = "plasma glucose levels are too low", $W_{2,6}$ = "plasma glucose levels are too high", $W_{3,5}$ = "$TIME - pr_3 x_1^a \geq C_1$", and $W_{3,6}$ ="$TIME - pr_3 x_1^a \geq C_2$", in which C_1 and C_2 are

insulin time administration constants: $5 \leq C_1, C_2 \leq 15$ min (which vary between different patients and within the same patient from day to day).

The tokens from places l_2 and l_3 are united and then split again and enter the places l_5 and l_6 according to their characteristics:

- l_5: activation of liver's store of glycogen;
- l_6: insulin; its quantity; the current time-moment.

$$z_3 = \langle \{l_4\}, \{l_7\}, r_3, \wedge(l_4) \rangle,$$

where

r_3 =	l_7
l_4	$W_{4,7}$

and $W_{4,7}$ = "$TIME - pr_3 x_1^a \geq C_1$".

The tokens from place l_7 receive the characteristic: "insulin; its quantity; the current time-moment".

$$z_4 = \langle \{l_5, l_6, l_7\}, \{l_8\}, r_4, \vee(\wedge(l_5, l_6), l_7) \rangle,$$

where

r_4 =	l_8
l_5	$W_{5,8}$
l_6	$W_{6,8}$
l_7	$W_{7,8}$

where: $W_{5,8} = W_{6,8}$ = "$TIME - pr_3 x_{cu}^a \geq C_3$", $W_{7,8} = W_{7,8}$ = "$TIME - pr_3 x_1^b \geq C_3$", in which C_3 is a constant for which $10 \leq C_3 \leq 30$ min, with variations again between and within patients.

In place l_8 the α-tokens and β-tokens from place l_6 and l_7 respectively are united in one α-token with the characteristic: "insulin; its quantity; glucose; its quantity; there is/there is not hypoglycaemia; the current time-moment".

$$z_5 = \langle \{l_8, l_9\}, \{l_{10}\}, r_5, \vee(l_8, l_9) \} \rangle$$

where

r_5 =	l_{10}
l_8	true
l_9	$W_{9,10}$

and $W_{9,10}$ = "$TIME - pr_3 x_0^c \geq 0$".

In place l_{10} the α-tokens and the γ-tokens from l_8 and l_9 respectively, are united in one α-token with the previous token's characteristic (place l_8 "insulin; its quantity; the current time-moment".

$$z_6 = \langle \{l_{10}\}, \{l_{11}, l_{12,}, l_{13}\}, r_6, \wedge(l_{10}) \rangle,$$

in which

r_6 =	l_{11}	l_{12}	l_{13}
l_{10}	$W_{10,11}$	$W_{10,12}$	$W_{10,13}$

where: $W_{10,11}$ = " $pr_2 x_{cu}^a \geq C_4$ " & " $pr_4 x_{cu}^a \geq C_5$ ", $W_{10,12}$ = " $pr_2 x_{cu}^a \geq C_4$ ", $W_{10,13}$ = " $pr_4 x_{cu}^a \geq C_5$ ".

The α-tokens from place l_{10} go to one of the places l_{11}, l_{12} and l_{13} where they receive, respectively, the following characteristics:

- in place l_{11} : " $pr_1 x_{cu}^a ; pr_2 x_{cu}^a ; pr_5 x_{cu}^a$ ";
- in place l_{12} : "it is necessary to add insulin";
- in place l_{13} : "it is necessary to add glucose".

Conclusion

The GN-model outlined above is an initial attempt to track specific diabetic nephropathy which affects the glomerulus, which in turn gives rise to proteinuria, sometimes nephrotic syndrome and finally chronic renal failure. Patients with this type of disease nearly always have diabetic retinopathy in addition and may be blind. Renal failure is the common cause of death in Type 1 diabetes, who more frequently suffer from vascular disease. Nor can diet be neglected in the long-term care of patients with diabetes [26], whether from the dietetic [14] or the biochemical point of view [32].

Persons with diabetes are more than usually prone to hypertension and vascular disease, and these may also damage the kidney and accelerate renal failure (cf. Adeghate *et al.*, 2006). Further research will embed these aspects in a GN because they are often a precursor to retinopathy problems (George *et al*., 1999). Further research will also attempt to incorporate intuitionistic fuzzy logic into these GNs [5]. Finally, an aspect of the graphic role of GNs in modelling which has not yet been considered is their ability to align interesting data and clever display: "a window on data can be a window on discovery" (in another context) [32].

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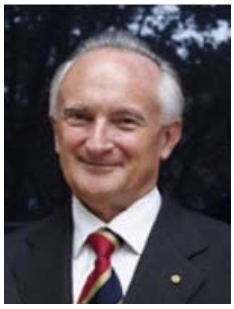

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