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Jump neural network for online short-time prediction of blood glucose from continuous monitoring sensors and meal information

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ABSTRACT

Several real-time short-term prediction methods, based on time-series modeling of past continuous glucose monitoring (CGM) sensor data have been proposed with the aim of allowing the patient, on the basis of predicted glucose concentration, to anticipate therapeutic decisions and improve therapy of type 1 diabetes. In this field, neural network (NN) approaches could improve prediction performance handling in their inputs additional information. In this contribution we propose a jump NN prediction algorithm (horizon 30 min) that exploits not only past CGM data but also ingested carbohydrates information. The NN is tuned on data of 10 type 1 diabetics and then assessed on 10 different subjects. Results show that predictions of glucose concentration are accurate and comparable to those obtained by a recently proposed NN approach (Zecchin et al. (2012) [26]) having higher structural and algorithmical complexity and requiring the patient to announce the meals. This strengthen the potential practical usefulness of the new jump NN approach.

1. Background

Prediction is of central importance in a large variety of scientific disciplines and in particular, in medicine, prediction methods are largely used for tuning therapies and for forecasting risks of development and progression of diseases, see e.g. [1] for a review on advances in genetics for predicting the occurrence of some diseases. In subjects affected by chronic pathologies, highly risky events could be forecasted by exploiting short-time prediction methods, with 20–30 min of anticipation, see [2] for an application in epilepsy for impending seizure detection. The present contribution is devoted to short-time prediction (30 min) of glucose levels, a practice proposed at the beginning of XXI century to facilitate and improve diabetes therapy, see e.g. [3].

Diabetes mellitus is characterized by dysfunctions in insulin secretion and action: in type 1 diabetes the pancreas is unable to produce insulin, while in type 2 diabetes derangements in insulin secretion and action occur. Therefore glucose concentration can exceed the normal range (70–180 mg/dl), with short- and long-term complications: hypoglycemia (glycemia below 70 mg/dl) can progress from measurable cognition impairment to aberrant behaviour, seizure and coma [4]; hyperglycemia (glycemia above 180 mg/dl) predisposes to invalidating pathologies, such as neuropathy, nephropathy, retinopathy and diabetic foot ulcers [5]. Conventional type 1 diabetes therapy aims at maintaining glycemia in the normal range by tuning diet, insulin infusion and physical activity on the basis of 3–4 daily fingerstick self-monitoring blood glucose (SMBG) measurements, obtained by the patient through portable devices [6]. The recent development of

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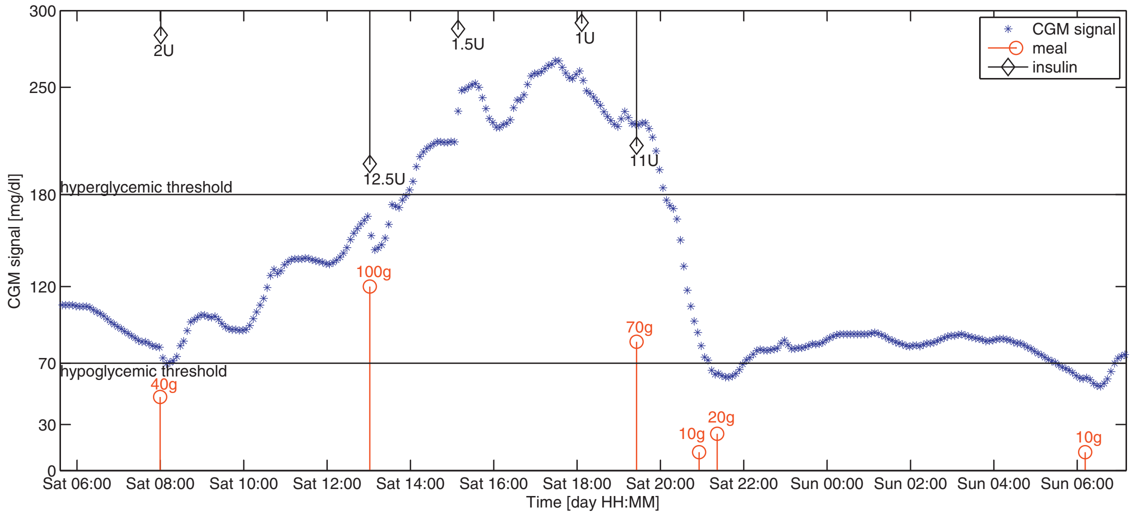

Fig. 1 – Representative CGM signal (blue stars) measured by the Seven Plus device and information on meals (red stems) and insulin doses (black stems) of a patient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

portable continuous glucose monitoring (CGM) sensors, able to measure glycemia every 5–10 min for up to 7–10 days, allows tracking glucose dynamics much more effectively than SMBG. As reviewed in [7–9] most of the current CGM sensors exploit a needle electrode and are thus invasive, although minimally, but non-invasive prototypes, e.g. [10], have been also proposed and recent results are promising, see e.g. [11]. It is today largely accepted in clinical research that CGM sensors can permit the improvement of glycemic control [12–14], both by suggesting the refinement of the patient individual therapy on the basis of the retrospective (Holter-like) assessment of glycemic recordings and in real-time, by alerting the patient when hypo- and hyper-glycemic thresholds are exceeded. Moreover, a research community of applied mathematicians and biomedical engineers is active to improve CGM sensor outcomes and strengthen the impact of applications by developing real-time algorithms for denoising, signal enhancement, prediction and alert generation, see e.g. [15,16] for reviews and [17] for the recently proposed "algorithmically smart sensor" concept. In addition, the CGM sensor is the key input of the so-called artificial pancreas, a device able to command commercial minimally invasive continuous subcutaneous insulin infusion pumps by means of closed-loop control algorithms, see [18] for a recent perspective.

Of particular interest in the present paper is the possibility of predicting glucose concentration, allowing the patient to take therapeutic decisions on the basis of future instead of current glycemia, possibly mitigating/ avoiding imminent critical events, see [19,20] for a quantification of reduction of number and duration of hypoglycemic events performed in an *in-silico* environment and [21,22] for preliminary applications in clinical research centers. However, given the presence of many (often not measurable/quantifiable) factors influencing glycaemia (meal intake, physical activity, administration of drugs including insulin, stress, emotions) and inter- and intra-individual variability, prediction of future glucose levels is a challenging topic.

To better grasp the ingredients of the glucose prediction problem, in Fig. 1 we show the time-course of glucose concentration (blue stars) measured during the day of a type 1 diabetic subject by the Seven Plus CGM sensor (Dexcom Inc., San Diego, CA), together with information on meals (red stems) and insulin injections (black stems). Hypo- and hyperglycemic thresholds are also reported (thin horizontal lines).

As we can note, at time 08:00, 13:00, and 19:25 the subject eats and takes an insulin bolus to counterbalance the effects of carbohydrates. During the afternoon, glycemia reaches hyperglycemic levels, thus the subject mitigates this event by resorting to a first correction bolus of insulin, at time 15:10, and to a second one at time 18:05. After dinner (time 21:00 approximately), blood glucose concentration unexpectedly falls in the hypoglycemic range. To correct the hypoglycemic event the subject ingests fast-acting carbohydrates (sugar) at time 20:55 and, again, at time 21:20. During the night glycemia is initially stable in the euglycemic range, but, at 5:30 it drops below the hypoglycemic threshold. The patient is alerted and, as indicated by the red stem, ingests a small amount of sugar at 06:10 in order to re-enter the safe range. This example shows that, ideally, forecasting glucose concentration in a certain prediction horizon (PH) should use several inputs (Fig. 2): CGM is the most important and easily usable, while the other sources of information are difficult to formalize in mathematical terms (e.g. meal, insulin) or hard to define quantitatively (e.g. stress).

For these reasons, as documented in the reviews [3,15,16], the majority of published glucose prediction methods solely use the CGM signal as input. The ability of neural networks (NNs) of learning the behaviour of empirical nonlinear models, by utilizing among their inputs heterogeneous signals, suggests to investigate their use for forecasting glycemia using collateral information, in addition to CGM signal. A short review of the few NN based glucose predictors proposed so far in the literature [23–26] will be reported in Section 2 of the present paper.