Modelling the interplay between Chronic Stress and Type 2 Diabetes on-set

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Abstract. Stress has become part of the day-to-day life in the modern world. A major pathological repercussion of chronic stress(CS) is Type 2 Diabetes (T2D). Modelling T2D as a complex biological system involves combining under-the-skin and outside-the-skin parameters to properly define the dynamics involved. In this study, a compartmental model is built based on the various inter-players that constitute the hallmarks involved in the progression of this disease. Various compartments that constitute this model are tested in a glucose-disease progression setting with the help of an adjacent minimal model.Temporal dynamics of the glucose-disease progression was simulated to explore the contribution of different model parameters to T2D onset. The model simulations reveal CS as a critical modulator of T2D disease progression.

Keywords: Diabetes · Computational modelling · Chronic stress · Allostatic Load · Disease progress · *in-silico* tool

1 Introduction

Type 2 Diabetes(T2D) is a slowly progressing metabolic disease characterized by elevated blood glucose [22]. Hyperglycemia(HG) in individuals can lead to devastating long-term and even irreversible complications. Metabolic disorders such as T2D are growing more common across the world, where 6.28% of the world population have developed T2D symptoms or disease on-set by 2017 [9]. No detailed data was released since, but global forecasts already predict numbers to reach around 8000±1500 cases of T2D cases per million population by 2040 [9]. With no apparent cure in sight, clinicians can only intervene at early stages of the disease, through behavioural changes. However, this "chance" at disease reversal is not fully explored and exploited in the healthcare system due to the complexity of all the inter-players in T2D pathogenesis [22].

CS is linked to the pathogenesis of T2D through a multitude of metabolic ways including the Central Nervous System(CNS) and partially the Peripheral Nervous System(PNS). In the pathogenesis of T2D, insulin production

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and sensitivity, Glucocorticoids(GC), cortisol and the Hypothalamic–Pituitary –Adrenal(HPA)-Axis play major roles. An in-silico modelling approach to filter the most significant inter-players and the feasible actions that can be taken towards minimizing T2D disease progress(DP) is imperative. Such methodology would be useful in a clinical decision making process after being carefully explored[17]. In this study, a new mechanistic computational model capable of relating each inter-player to its contribution towards T2D on-set and DP is proposed.

The hallmarks of T2D related to Chronic stress

β-cells are responsible for synthesizing, storing and releasing insulin [11]. Glucose[11], Free Fatty Acids(FFAs)[7] and Glucagon-1[21] play key roles in the process. β-cells can be generated by replication of the existing β-cells depending non-linearly on glucose concentration *in-medium*[20]. Human β-cell proliferative capacity is small and decreases with age, but when metabolic demand is high such as in obesity or during pregnancy, replication may increase [2]. β-cell mass can decrease by undergoing apoptosis(regulated cell death) or necrosis(unregulated cell death), which may be dependent on glucose concentration [20].

In a healthy person, the levels of circulating glucose are well regulated. When plasma glucose increases above 90 $mgdL^{-1}$, β-cells sense this and produce and secrete insulin, a hormone that triggers glucose absorption by the adipose, liver and muscle tissue, decreasing glucose in circulation. In normal circumstances this is easily kept in balance with a healthy diet [15], if no other disturbances affect the system. During T2D progression, insufficient insulin secretion and insulin resistance give rise to hyperglycemia [1].

In general, when the HPA-axis is activated, it responds by producing and releasing GC, such as cortisol. While this is a healthy and natural reaction to short-term stress, it becomes dysfunctional when the stress signal is prolonged [8], like in the case of CS. Studies show that CS causes HPA-axis dysfunction and increases GC levels[4] and suggest that there is a link between increased GCs and T2D progression, demonstrating how GC excess leads to metabolic dysfunction [3]. Exposure to stressful conditions, an imbalance in effort, psychological traumatic experiences, low socio-economic status or even higher incidence of discrimination can be such examples of stress paradigms that could trigger CS on-set [14]. Continuous recursive activation of the SNS and HPA-axis occurs during CS and can cause physiological long term consequences that may result in accumulated small disturbances signified by "allostatic load" [10]. This concept is now put in use to help operationalize CS into measurable physiological units that allow identification of the relationships between different stressor types and the pathophysiology stages of T2D[6]. There are many hallmarks that can be associated with T2D progression. In this study we suggest 5 hallmarks that empirically were included in many other papers as pro-T2D progression based on Allostatic load [5,6]. These are Insulin Resistance(IR), HG, Low Grade Inflammation(LGI), Hypercortisolism(HC) and Hyperglucagonemia(HGC). These hall-

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marks, are connected through complex interactions and create feedback loops, which potentiate their impact when CS comes into play.

2 Methods

2.1 Model definitions

A summary of the model parameters and interconnected compartments is presented in SM-Figure 2(Supplementary Material[4](SM)-Section 1.2). Computational modelling can help identify the underlying mechanisms of any phenomenon[16], like CS, which can lead to the development of new therapies[18] and interventions[18,17]. As the study CS is complex and extensive, a short review on the computational models that relate it to T2D can be found in SM-Section 1.1. To simulate the healthy and diseased state dynamics we opted to use a simpler and well established minimal model firstly developed by Topp *et al., 2000*, for which the concept of added stress was then implemented by Mohammed *et al., 2019*. This model can emulate some of the connections in our conceptual model, for which we could apply our DP calculations on. The coupled SM-Equations 2, 3 and 4 and the parameters listed in SM-Table 6(SM-Section 1.3) were used to carry out the simulations in this study.

By simulating the dynamics of Glucose, Insulin and β-cell mass we were able to replicate a healthy a individual dynamics for the first 15 days, only to introduce forced disturbances of the system of ODEs later on with 'simulated stress', and to some extent by inclusion of periodic behaviour. We used k_0 from the Compartmental model(Figure 2) to represent food intake in the form of periodic glucose spikes, that varies within normal range in a non-CS situation and increases above 140 $mgdL^{-1}$ for a chronically stressed individual. This is also the variable that varies between individuals being simulated, as different people have different meals and different peaks of glucose. At each meal time(5 meals per day), the individual receives a glucose peak between $100mgdL^{-1}$ and $170mgdL^{-1}$ for non-stress situation(larger sample). A mix of the latter with glucose peaks between $225mgdL^{-1}$ and $350mgdL^{-1}$ for the stress situation(smaller sample). In both cases, glucose pick values a uniformly distributed. There is no simple minimal model that can include all the hallmarks we aim to use for DP calculation, however by using the model developed by Mohammed *et al., 2019*[13] we are able to replicate at least 2 hallmarks.

2.2 Algorithm definitions

Based on the works of Benthem *et al., 2022*[5], a methodology was built that would make use of threshold values for each of the following hallmarks which allow the calculation of Allostatic load within SM-Algorithm 2(SM-Section 1.3). These are: Hyperglycemia, where the high Glucose levels at certain time points are monitored; Insulin resistance, by using the Homeostasis model assessment

[4] Supplementary Material(SM) available at Github link

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insulin resistance index(HOMA-IR) applying SM-Equation 1 [12]; Low grade inflammation, by using the measure of the output from C_{CRP}(from SM-Figure 2); Hypercortisolism, based on the output of high cortisol level from the Cortisol compartment(C_C) and Hyperglucaconemia, based on outputs from high glucagon level from Glucagon compartment(C_E). The threshold values are the values for which the max peaks for different compartments are "surpassed" at time t, considering a broken elasticity phase where some "wear and tear" is inflicted. By using SM-Algorithm 2 the calculations were ran for Hyperglycemia and Insulin Resistance. This application would correspond to links regarding the $C_G, \beta_{MD}, C_I, C_X$ compartments disregarding constants $k_9, k_{10}, k_{17}, k_{41}, k_{42}, k_{43}$, k_{51}, k_{52}, k_{53}, k_{55}, k_{58} in the compartmental diagram in SM-Figure 2. A coupled Euler integration method(SM-Algorithm 1) was applied to solve the model SM-Equations 2, 3 and 4. By using the simulated values of Glucose and Insulin, the calculation of HOMA-IR is possible by using SM-Equation 1(SM-Section 1.3).

Going forward, we hypothesized that each hallmark would be present in this conceptual model. To develop SM-Algorithm 2, we assume that there is a need to quantify damage to the system modelled [5]. At the healthy state, the system remains in stable steady state. Therefore, in order for a change in state to occur, successive damage(W_S) under some weight(w). Moreover, there is always some resistance and resilience to this damage [19], under repair or healing(C_S). When the damage inflicted is higher than the recovery, some threshold T is surpassed and there is some damage to the system in the form of strain(e). To represent that a certain strain value(e) in case some threshold T would be reached or surpassed, a strain event (E_s) is evaluated at time t for each a strain calculation($S_t(t)$) for each hallmark. Where e_l is low strain, e_i is intermediate strain and e_h represents the high strain of that hallmark towards DP. To calculate the DP for T2D we used SM-Algorithm 2, where $w(e_x)$ is the weight of a certain strain towards DP and x is the equivalent to intensity of the strain(low, intermediate or high) and DP is the T2D progress estimation in % based on a cumulative sum of all counts for all hallmarks.

3 Results

The system was simulated for 100 different cases(Figures 1, 2 and 3) where only active components were taken into consideration. We resorted to this simple but effective model to extract and test the Event-Driven approach that calculates the DP over 45 days, while the model has a fixed minimal time of one day.
To this experiment were added event-driven meal-like instances of increase in Glucose, firstly in a non-stress setup for 15 days. In Figure 1 we see the dynamics means corresponding to SM-Equations 2(A - The dynamics of Glucose over time), 3(B - The dynamics of Insulin over time) and 4(C - The dynamics of β-cell mass over time). After 15 days, a CS on-set is induced by adding only disease-like values reached after meals(a direct consequence of CS). In Figure 2 we see the result of direct application of SM-Algorithm 2 to extract DP based on Allostatic load. On the x-axis(left) labeled as % is the % of DP and on the

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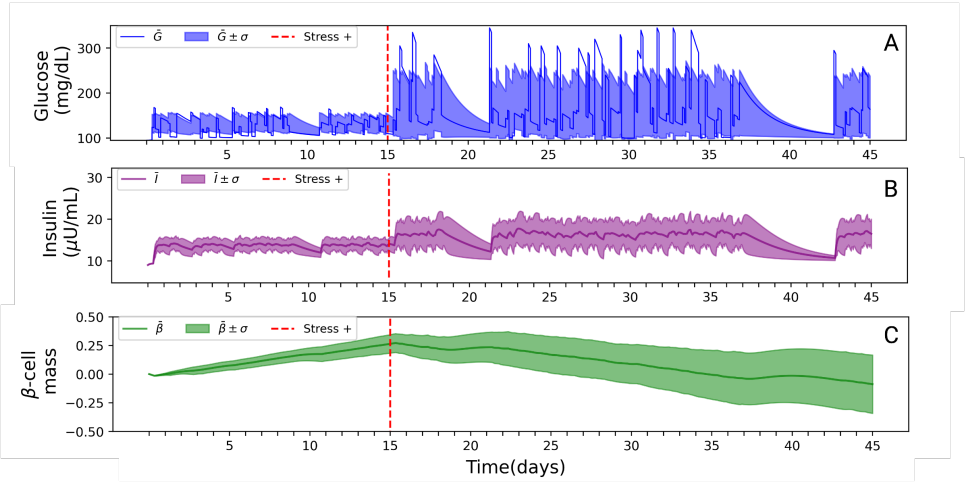

Fig. 1. Glucose(**A**), Insulin(**B**) and β-cell mean mass(**C**) dynamics simulation for 100 different cases during 45 days. The blue, purple and green bold line is the mean of the 100 different cases for Glucose, Insulin and β-cell mean mass, respectively. Each plot containing the bold line, also has an area around, representing the standard deviation between the 100 different cases relative to the mean. (A) Labeled on the y-axis, Glucose concentration in $mgdL^{-1}$ units on an interval between 100 and 310. (B) Labeled on the y-axis, Insulin concentration in μUmL^{-1} units on an interval between 5 and 30.(C) Labeled on the y-axis, β-cell mass ratio at an interval between -1 and 1, with 0 being the baseline β-cell mass. All plots are on the same labeled x-axis, the time-span simulated in days. The red intermittent line represents the day of CS induction. The time-step between calculation of one time-point to the other in all the plots is $24/60/60 \approx 0.0066$ days.

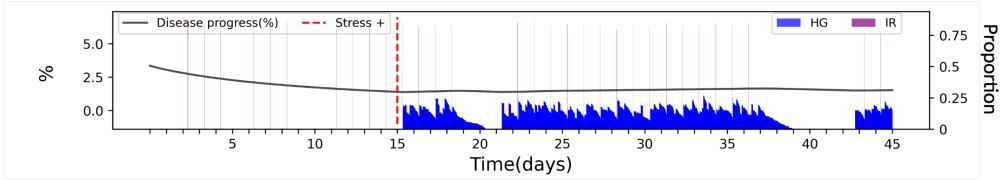

Fig. 2. DP mean simulation for 100 different cases during 45 days.

x-axis(right) labeled as proportion are proportions related to contribution of Hallmark at time t for DP calculation from each hallmark. On the x-axis the time-span simulated in days.

We tested whether SM-Algorithm 2 would be dependent on the time-span of simulation and if more accurate DP would be achieved if 100 different cases were simulated for 10 days(before CS-on set), $\frac{1}{2}$ year, 1 year and 1.5 years (Figure 3). Simulation of 100 different cases for different time-spans. Labeled as samples, on the y-axis the different time-span samples are shown, while on the x-axis the time-span simulated in days. Note that the length of each candle shows the

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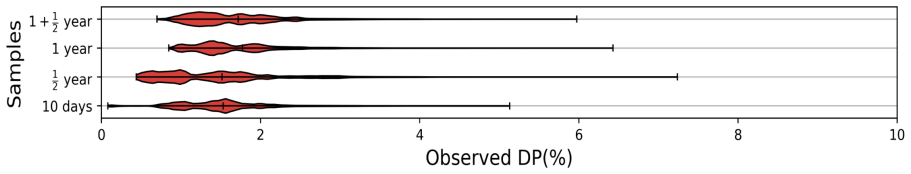

Fig. 3. Simulation of 100 different cases for different time-spans.

variation minimum and maximum peaks and, in red, the density distribution of each sample in terms of DP %. Notice that each candle has a mean DP value for each sample, shown by a vertical line inside the candle plot.

4 Discussions and Conclusions

The main research question was conceptualizing a model that could encompass the inter-players between T2D and CS and calculate the DP. The concept has been proven to work and disease progression calculation has been successfully achieved by using a simpler modelling approach. Biologically relevant results were obtained this way. In Figure 1A and 1B, we can observe normal behaviour of Glucose and Insulin dynamics, respectively. This is hinted by the peaks, which would show how individuals can sometimes have meals richer in carbohydrates that result in higher glucose and insulin peaks. To accompany this, enclosed by the normal individual dynamics, we see normal increase in mass of β-cells in Figure 1C. This dynamic ,in reality, has a *plateau* and in this setting in particular, represents that there is no stress to the β-cell mass(it increases). The same can be captured by our SM-Algorithm 2. Notice in Figure 2, that DP only decreased into a normalized value and no significant strain(under small stress events) can increase this value. Insulin(Figure 1B) also stays in the normal range of a healthy person and follows Glucose peaks.

After day 15, we emulate CS, where after each meal, the peak values of Glucose and Insulin become aberrant and switch to diseased state values, surpassing disease thresholds and creating strain on the system. This can be clearly seen in Figures 1A and 1B, where mean Glucose can rise up to 350 $mgdL^{-1}$ or even beyond and Insulin level reach 20 μUmL^{-1}. As per randomization of Glucose values, we see that the mean deviates from the standard deviation in some cases, this is a sign of the difference between individual cases simulated, which is crucial to have when HG states are reached for different reasons. Within this implementation, we see a direct consequence of CS applied to β-cell mass production that fails to keep β-cell mass stable, as shown in Figure 1C. This would imply that in a case of decrease in β-cell mass, we would also observe a decrease in Insulin secretion. However this is not the case. Induced CS not only damages the β-cell mass, but also indirectly makes the remaining β-cell mass compensate for the loss in mass, keeping the Insulin/Glucose dynamics unchanged(Figure 3). This finding has the capability to represent one more of the Hallmarks discussed in

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Section 2, under the name of LGI which in most cases is usually ignored as it takes part in the cellular stress. This hallmark was not possible to introduce into our calculation as there are no suggested LGI measures other than C-Reactive Protein(CRP) in a clinical setup. In the future, we intend to fix this by applying separate compartments for Cell Stress(C_{CSG}), LGI(C_{CRP} as an input from data and C_{IG} as a stand-in that holds general body inflammation events) shown in SM-Figure 2. As the CS induced dynamics unfold, in Figure 2 we can already observe the counts being introduced as proportions for the calculation of DP. Hallmark HG is more evident since Insulin dynamics are able to closely follow HG in order to not count as IR markers. To this effect, we can observe a slowly increasing mean DP depending solely on two hallmarks. Moreover, we questioned whether the mean of DP would eventually find a steady-state if the time-span of simulation would be increased or decreased as well. This is shown in Figure 3, as we took different time-spans and sampled 100 different cases. Results show that for a sample of 10 days(before CS induction), DP mean is lower than in the case of 1 year and 1.5 years samples. This suggests that the initial 15 days can be used as calibration for the algorithm following introduction of real data. The 0.5 year sample mean is very close to the one for 10 day, but a very big variation between cases is observed which is most probably the main cause for this mean value. Beyond that, the 1 year and 1.5 years samples are the best time-span samples to give closer results of DP to the mean for 45 days in Figure 2. This suggests that 45 days is not enough as time-span. Variation for 1.5 years in Figure 3 is also lower, additional testing is needed to verify whether this value is just a minimum value needed for subject following or larger time-span is needed. The experimental setup points towards a successful application and evaluation of SM-Algorithm 2. This indicates that SM-Algorithm 2 has adaptive plasticity to drastic changes in dynamics(favored by nature), producing limiters to DP inherently. This hints at the need of very critical behaviour to change and overcome disease on-set and disease un-set which is suggested in other CS studies. Empirically, the need of real life data is evident for subjects at different CS stages, with or without T2D on-set or even in other disease cases in order to observe differences as well as different hallmarks and fixed clinically observed threshold values to use as indicators for our SM-Algorithm 2. At this stage, *in-silico* simulated data can only provide limited information. However, a methodology is already being developed to account for this need as the conceptual model in SM-Figure 2 now exists. The randomness in the simulations clearly affects the variation of our calculation, nevertheless it is clear that this effect decreases with increased period of simulation and this is essential when searching for most favorable inter-players in disease progression later on. The next steps are being taken towards acquisition of data that can be used to further develop the conceptual model(SM-Figure 2) into a better T2D simulation tool which can be used to further ameliorate Algorithm 2, culminating into an ultimate tool for T2D appraisal and search of key inter-players to which the DP can decrease.

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