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

1 Supplementary Material(SM)

1.1 Computational models combining T2D and CS

In Figure 1, a timeline that situates the modelling approaches in retrospective to the direct association between CS and glucose metabolism and T2D modelling approaches. Many studies in this map studied glucose metabolism/T2D but never showed a direct association to CS or vice-versa. Moreover, CS was usually recognized as an "underlying" factor.

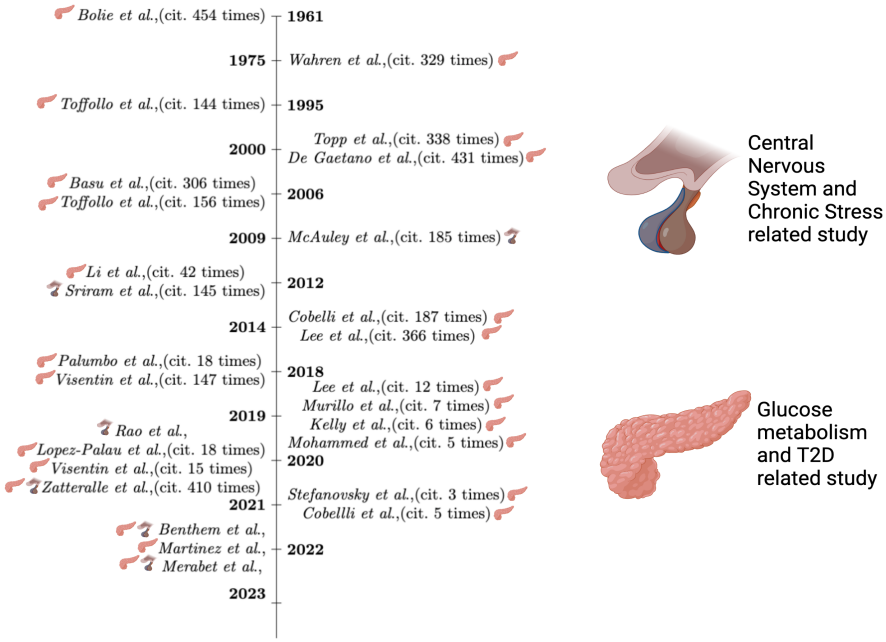

Fig. 1. Timeline of Glucose and T2D model related studies with citation number. Note that some papers are too recent and don't have a minimum of 3 citations.(Created by using BioRender.com)

Computational modelling can help identify the underlying mechanisms of any phenomenon[70], like CS, which can lead to the development of new therapies[72] and interventions[72, 71]. Minimal models are simplified versions of computational models of a phenomenon, without disregarding its main attributes.

The use of minimal models was imperative to reproduce glucose dynamics in a more simplistic way without disregarding the most important features of the phenomenon[16]. Such models started to be developed as early as 1961, when the first IVGTT was developed[7]. Later, models that allowed the estimation of insulin sensitivity and resistance[16], β-cell function[16][76][49], hepatic insulin extraction[75][16], 1^{st} and 2^{nd} phase β-cell responsivity[75] to oral glucose tests proposed. More precise dynamics were achieved by introducing more details into the system by adding new compartments, like FFA[50, 74, 42, 25], Glucagon [2, 44, 37], β-cell mass[49, 76] and delays or changes in the interaction between compartments[50, 17]. Triple tracer meal studies enhanced the minimal model methodology when more data became available and hence validation was possible[4]. Topp *et al., 2000* [76] suggested that chronic hyperglycemia might contribute to a second negative feedback loop, increasing β-cell mass through the change of β-cell replication and death rates, contributing to defects in system components in short-term and constituting chronic negative feedback loops.

Based on the existing T2D models on β-cell dynamics, in this work, we develop a novel T2D - CS coupled model to explore the influence of psychosocial parameters on the dynamics of T2D DP parameters. In this approach we attempt at facing some of the challenges other models have encountered by modelling CS[73, 18, 77].

1.2 Conceptual model

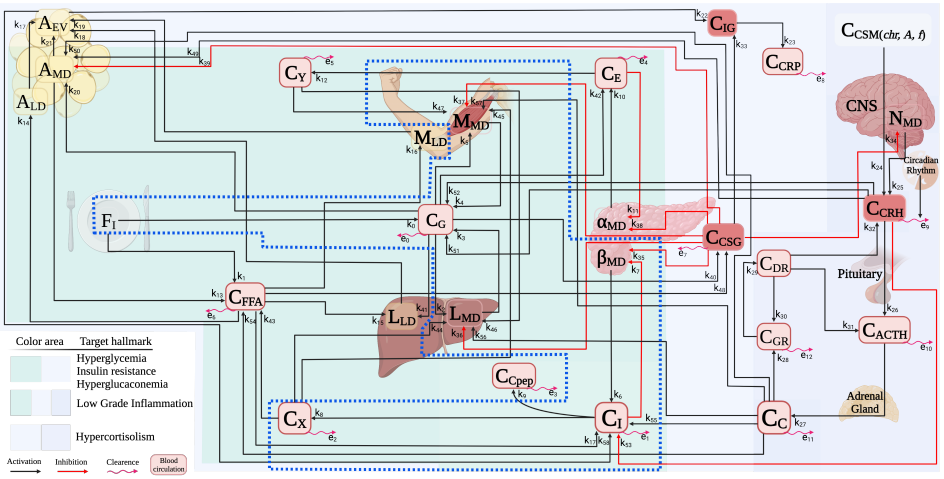

Fig. 2. Conceptual stock and flow modelling diagram of T2D progression related to CS(Created by using BioRender.com). Additional information regarding the parameters can be found in Tables 1, 2, 3, 4 and 5. Area delineated with intermittent blue delineates the analog compartments of the existing minimal model implemented by Mohammed *et al., 2019*.

Table 1. Compartment variables I for Figure 2

Symbol	Description	Relevant Citations
	Concentrations	
F_I	Food intake metabolized and added concentration to C_G or C_{FFA} by a function.	[81, 34, 28]
C_G	Concentration of plasma Glucose.	[37, 28]
C_I	Concentration of plasma Insulin.	[2, 37, 24, 7]
C_X	Concentration of Active Insulin.	[2, 37, 24, 76, 74]
C_E	Concentration of Glucagon.	[44, 37, 44, 15]
C_Y	Concentration of Active Glucagon.	[44, 22, 37, 44]
C_{FFA}	Concentration of plasma Free Fatty Acids.	[56, 74, 50]
C_{Cpep}	Concentration of plasma C-peptide.	[35, 16]
C_{CRH}	Concentration of Active CRH.	[47, 73, 60, 83]
C_{ACTH}	Concentration of active ACTH.	[47, 73, 60, 83]
C_C	Concentration of plasma Cortisol.	[32, 47, 60]
C_{GR}	Concentration of formed Glucocorticoid-Receptor complexes.	[58, 27, 47]
C_{DR}	Concentration of Nuclear activated GR complex.	[60, 47]
	Inflammation	
C_{CRP}	Concentration of plasma C-reactive Protein.	[61, 46]
C_{IG}	Concentration of General Inflammation.	[61, 43, 11, 13]
C_{GS}	Concentration of General Stress from cells.	[48, 68, 6, 10]
C_{CSM}	Concentration noise from the CSM(chronic stress derived).	[20, 82, 77, 73, 60, 83, 26, 47]
	Masses	
β_{MD}	β-Cell Mass Density.	[2, 64, 40, 76, 49]
α_{MD}	α-Cell Mass Density.	[31, 55, 28, 79]
M_{MD}	Muscle Mass Density.	[21]
L_{MD}	Liver Mass Density.	[21, 66]
A_{MD}	Adipose tissue Mass Density.	[80, 12, 41, 45, 56]
N_{MD}	Neurons Mass Density.	[51]
A_{EV}	Ectopic/Visceral Mass Density.	[43, 11]
	Clearence	
e_0	Disease state dependent Glucose Clearence	[9, 63, 24]
e_1	Insulin Clearence	[37]
e_2	Activated Insulin Clearence	[37]
e_3	C-peptide Clearence	[37]
e_4	Glucagon Clearence	[37]
e_5	Activated Glucagon clearence	[37]
e_6	FFA Clearence	[37]
e_7	General Cell Stress Clearence(protective behaviour)	[6, 10]
e_8	C-reactive protein Clearence	[61, 46]
e_9	CRH diurnal Clearence(circadian rhythm dependent)	[47, 50]
e_{10}	ACTH diurnal Clearence	[73]
e_{11}	Cortisol diurnal Clearence	[47]
e_{12}	Glucocorticoid-Receptor Clearence(uncoupling)	[47]

Table 2. Compartment variables II for Figure 2.

Symbol	Description	Relationship vector	Relevant Citations
k_0	Glucose extraction from food intake caloric, based on normal, obese and diet variations	Food Intake $\rightarrow C_G$	[28]
k_1	FFA extraction from Food Intake, based on diet variations	Food intake $\rightarrow C_{FFA}$	[56]
k_2	Insulin Dependent Glucose Absorption rate by the Hepatic Cells	$C_G \rightarrow L_{MD}$	[21]
k_3	Net Rate of Glucose Production at Zero G Level(from hepatic cells)	$L_{MD} \rightarrow C_G$	[76, 49]
k_4	Net Rate of Glucose Production at Zero Activity level(from muscle cells)	$M_{MD} \rightarrow C_G$	[76, 49]
k_5	Net Rate of Glucose Absorption with Physical Activity	$C_G \rightarrow M_{MD}$	[52]
k_6	Rate of Insulin Production and Secretion	$\beta_{MD} \rightarrow C_I$	[76, 24, 49]
k_7	Rate of Cell Death due to Insulin Overproduction	$C_I \rightarrow \beta_{MD}$	[76, 49]
k_8	Rate of Conversion of Insulin to Active insulin	$C_I \rightarrow C_X$	[50, 37]
k_9	Rate of C-peptide byproduct from Insulin production	$C_I \rightarrow C_{Cpep}$	[37, 35]
k_{10}	Rate of Glucagon Production and Decretion	$\alpha_{MD} \rightarrow C_E$	[59, 44]
k_{11}	Rate of Cell Death due to Glucagon overproduction	$C_E \rightarrow \alpha_{MD}$	[31]
k_{12}	Rate of Conversion of Glucagon to Active Glucagon	$C_E \rightarrow C_Y$	[44, 31]
k_{13}	Lipolysis Rate	$A_{MD} \rightarrow C_{FFA}$	[19, 50]
k_{14}	Rate of Lipid Droplets Formation in the Adipose Tissue derived directly from FFA Concentration	$C_{FFA} \rightarrow A_{LD}$	[43, 19]
k_{15}	Rate of Lipid Droplets formation in the Liver Tissue derived directly from FFA Concentration	$C_{FFA} \rightarrow L_{LD}$	[43, 19]

Table 3. Compartment variables III for Figure 2.

Symbol	Description	Relationship vector	Relevant Citations
k_{16}	Rate of Lipid Droplets Formation in the Muscle Tissue derived directly from FFA Concentration	$C_{FFA} \rightarrow M_{LD}$	[43, 19]
k_{17}	Rate of Lipid Droplet accumulation from Adipose Tissue in the Adipose Tissue Actopic/Visceral area	$A_{LD} \rightarrow A_{EV}$	[43, 19]
k_{18}	Rate of Lipid Droplet accumulation from Liver Tissue in the Adipose Tissue Ectopic/Visceral area	$L_{LD} \rightarrow A_{EV}$	[43, 19]
k_{19}	Rate of Lipid Droplet accumulation from Muscle Tissue in the Adipose Tissue Ectopic/Visceral area	$M_{LD} \rightarrow A_{EV}$	[43, 19]
k_{20}	Rate of Glucose mediated Lipogenesis	$C_G \rightarrow A_{MD}$	[80, 74]
k_{21}	Rate of Conversion of Adipose Tissue Mass to Ectopic/Visceral Adipose Tissue	$A_{MD} \rightarrow A_{EV}$	[43, 83]
k_{22}	Rate of Pro-Inflammatory Response by Ectopic/Visceral Adipose Tissue Formation	$A_{EV} \rightarrow C_{IG}$	[43, 11]
k_{23}	Rate of Conversion of General Inflammatory response to C-reactive Protein Concentration	$C_{IG} \rightarrow C_I$	[61]
k_{24}	Rate of Change of CRH Concentration by the individuals Chronic Stress	$C_{CSM} \rightarrow C_{CRH}$	[60, 26, 38, 47, 73]
k_{25}	Rate of Diurnal CRH Production	$N_{MD} \rightarrow C_{CRH}$	[60, 26, 38, 47, 73]
k_{26}	Rate of Diurnal ACTH Production	$C_{CRH} \rightarrow C_{ACTH}$	[60, 26, 38, 47, 73]
k_{27}	Rate of Diurnal Cortisol production	$C_{ACTH} \rightarrow C_C$	[60, 26, 38, 47, 73]
k_{29}	Rate of DR Complex Activation	$C_{GR} \rightarrow C_{DR}$	[60, 47, 73]
k_{30}	Rate of DR Complex Inactivation	$C_{DR} \rightarrow C_{GR}$	[60, 47, 73]

Table 4. Compartment variables IV for Figure 2.

Symbol	Description	Relationship vector	Relevant Citations
k_{31}	Rate of ACTH production Inhibition by Complex Inactivation	$C_{DR} \rightarrow C_{ACTH}$	[60, 47]
k_{32}	Rate of CRH Production Inhibition by Complex Inactivation	$C_{DR} \rightarrow C_{CRH}$	[60, 47]
k_{33}	Rate of Low Grade Inflammation(from Cell Stress) Conversion to General Inflammation	$C_{CSG} \rightarrow C_{IG}$	[83, 3]
k_{34}	Rate of CRH Producing Neuron Cell Death due to General Cell Stress	$C_{CSG} \rightarrow N_{MD}$	[83, 3]
k_{35}	Rate of β-Cell Death due to General Cell Stress	$C_{CSG} \rightarrow \beta_{MD}$	[64, 76, 49, 53]
k_{36}	Rate of Liver Cell Death due to General Cell Stress	$C_{CSG} \rightarrow L_{MD}$	[39]
k_{37}	Rate of Muscle Cell Death due to General Cell Stress	$C_{CSG} \rightarrow M_{MD}$	[21, 39]
k_{38}	Rate of α-Cell Death due to General Cell Stress	$C_{CSG} \rightarrow \alpha_{MD}$	[31]
k_{39}	Rate of Adipose Tissue Cell Death due to General Cell Stress	$C_{CSG} \rightarrow A_{MD}$	[41, 83, 57]
k_{40}	Rate of Cell Stress generation due to Glucose Levels *in-serum*	$C_G \rightarrow C_{CSG}$	[8, 9, 39]
k_{41}	Rate of Lipid Droplet formation in the Liver caused by Glucose Level	$C_G \rightarrow L_{LD}$	[69, 19, 23, 56]
k_{42}	Rate of Glucose Level mediated Production of Glucagon	$C_G \rightarrow C_E$	[59]
k_{43}	Rate of Production of FFA from Insulin Activation in the Adipose Tissue	$C_X \rightarrow C_{FFA}$	[19, 54]
k_{44}	Rate of Glucose release mediated by Insulin Activation in the Liver	$C_X \rightarrow L_{MD}$	[62, 65]
k_{45}	Rate of Glucose release mediated by Insulin Activation in the Muscle	$C_X \rightarrow M_{MD}$	[21]
k_{46}	Rate of Glucose absorption mediated by Glucagon Activation in the Liver	$C_Y \rightarrow L_{MD}$	[78, 59, 37]

Table 5. Compartment variables V for Figure 2.

Symbol	Description	Relationship vector	Relevant Citations
k_{47}	Rate of Glucose absorption mediated by Glucagon Activation in the Muscle	$C_Y \rightarrow M_{MD}$	[39]
k_{48}	Rate of Cell Stress generation due to FFA accumulation	$C_{FFA} \rightarrow C_{CSG}$	[3, 33, 13, 5]
k_{49}	Rate of Adipose Tissue indirect change in mass due to CRH level	$C_{CRH} \rightarrow A_{MD}$	[41, 57, 54]
k_{50}	Rate of Adipose Tissue mass change by GC presence *in-serum*	$C_C \rightarrow A_{MD}$	[41, 57, 45]
k_{51}	Rate of Glucose level change by indirect GC release by stimulation of Hepatic Cells	$C_{CRH} \rightarrow C_G$	[66, 57]
k_{52}	Rate of Glucose level change by indirect GC release by stimulation of Muscle Cells	$C_{CRH} \rightarrow C_G$	[21, 39]
k_{53}	Rate of Insulin Level change by indirect CRH stimulation	$C_{CRH} \rightarrow C_I$	[14, 12, 41]
k_{54}	Rate of FFA level change by indirect Cortisol(GC) stimulation	$C_C \rightarrow C_{FFA}$	[29, 30]
k_{55}	Rate of Insulin level change by indirect Cortisol(GC) stimulation	$C_C \rightarrow C_I$	[67, 36]
k_{56}	Rate of Glucose level change by direct GC stimulation of Hepatic Cells	$C_C \rightarrow L_{MD}$	[80, 29]
k_{57}	Rate of Glucose level change by direct GC stimulation of Muscle Cells	$C_C \rightarrow M_{MD}$	[29, 1]
k_{58}	Rate of change of Insulin Concentration by the presence of Ectopic/Visceral Adipose Tissue	$A_{EV} \rightarrow C_I$	[43, 54]

1.3 Extended Methods

HOMA-IR model

$$H_{IR} = \frac{C_{I_0}(\mu U m L^{-1}) C_{G_0}(mg dL^{-1})}{405} \tag{1}$$

where C_{I_0} is the fasting insulin and C_{G_0} is the fasting glucose at the beginning of each day for each individual. Values of $H_{IR} \leq 3$ were ignored for this calculation.

Topp et al 2000 model

The glucose dynamics are modelled as a function of the net rate of glucose production at zero glucose level(R_0), total glucose effectiveness at zero insulin(E_{G0}), total insulin sensitivity(S_I), and blood Glucose concentration at time t ($G(t)$):

$$\frac{dG}{dt} = R_0 - (E_{GO} + S_I)G(t) \tag{2}$$

,the insulin dynamics are modelled as a function of β-cell mass at time $t(\beta(t))$, maximum rate of insulin secretion(σ), $G(t)$, insulin clearence rate for muscles, liver and kidney(K) and blood insulin concentration at time $t(I(t))$:

$$\frac{dI}{dt} = \frac{\beta(t)\sigma G(t)^2}{\alpha + G(t)^2} - KI(t) \tag{3}$$

and the β-cell mass dynamics are modelled as a function of beta cell natural death rate(d_0), constant beta cell glucose tolerance ranges(r_1 and r_2), $G(t)$ and β-cell mass at time $t(\beta(t))$:

$$\frac{d\beta}{dt} = (-d_0 + r_1 G(t) - r_2 G(t)^2)\beta(t) \tag{4}$$

Algorithms

First we define Algorithm 1, which is used to simulate the dynamics for all our results in Section 3.

Algorithm 1 Coupled Euler algorithm.

Require: t_{end}, Initial conditions, dt
  while $0 < t \leq t_{end}$ **do**
    $\frac{dx}{dt} = y_n$
    $t_{n+1} = t_n + dt$ ▷ Calculate the slope
    $y_{n+1} = y_n + \frac{dx}{dt} dt$ ▷ Calculate the new y value using slope and derivative
  end while

Algorithm 2 Calculation of DP based on Allostatic Load.

Require: $t_{end}, e_l, e_i, e_h, T_l, T_i, T_h$ ▷ The strain of each Threshold surpassed, $e_l + e_i + e_h = 1$
Require: $w(e_l), w(e_i), w(e_h)$ ▷ The weight of each strain towards DP, $w(e_l) + w(e_i) + w(e_h) = 1$
$W_S = C_{e_l} w(e_l) + C_{e_i} w(e_i) + C_{e_h} w(e_h)$ ▷ Calculation of weighted sum
$C_S = C_{e_0} + C_{e_l} + C_{e_i} + C_{e_h}$ ▷ Calculation of counted sum
while $t \leq t_{end}$ **do** ▷ Calculation of hallmark strain and their counts over time
  if $S_t < T_l$ **then**
    $E_s(t) = 0$
    $C_{e_0(t)} + 1$
  end if
  if $T_l \leq S_t < T_i$ **then**
    $E_s(t) = e_l$
    $C_{e_l(t)} = C_{e_l(t)} + 1$
  end if
  if $T_i \leq S_t < T_h$ **then**
    $E_s(t) = e_i$
    $C_{e_i(t)} = C_{e_i(t)} + 1$
  end if
  if $S_t \geq T_h$ **then**
    $E_s(t) = e_h + 0.25 \frac{T_h}{S_t(t)}$
    $C_{e_h(t)} = C_{e_h(t)} + 1$
  end if
end while
$DP = \frac{100}{W_S \cdot C_S}$ ▷ Calculation of Normalized total DP

Next, the algorithm that we propose, able to calculate allostatic load based on hallmarks, Algorithm 2. Note that we take $[e_l, e_i, e_h] = [0.25, 0.5, 0.75]$ in our calculations. For the simulations carried, the same parameters were used altogether(Table 6). The variation depends only on Glucose peaks.

Table 6. Parameter symbols, units and parameters for Equations 2, 3 and 4. Original parameters from Topp *et al., 2000*[76].

Parameters		
Symbol	Given units	Value
$G(0)$	$\frac{mg}{dL}$	95
$I(0)$	$\frac{\mu Um}{dL}$	9.0
$\beta(0)$	mg	300
R_0	$\frac{md}{dL}$	864
E_{GO}	$\frac{1}{day}$	1.44
SI	$\frac{ml}{\mu Uday}$	0.72
dt	days	0.006

Parameters		
Symbol	Given units	Value
σ	$\frac{\mu U}{mLday}$	43.2
α	$\frac{mg^2}{dL^2}$	20000
K	$\frac{1}{day}$	432
d_0	$\frac{1}{day}$	0.065(0.060 in [76])
r_1	$\frac{dL}{mgday}$	$0.84e^{-3}$
r_2	$\frac{dL^2}{mg^2day}$	$0.24e^{-5}$

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