A Differential Equation Based Model of Cell and Cytokine Activation Influenced by Glucose Dynamics and Elevated Cortisol Levels Due to Aging

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Abstract. *Immunosenescence refers to the alterations in the immune system that occur due to the aging process, which increases susceptibility to diseases and reduces vaccine efficacy. Consequently, understanding the impact of aging on the immune system is crucial for simulating the different ways in which it can be challenged, thereby increasing life expectancy and quality of life. This study combines two mathematical models to understand how cortisol affects and is affected by the glucose uptake and the pro- and anti-inflammatory cytokines under infection. Cortisol concentration follows a diurnal rhythm and increases with glucose intake. The model simulates the influence of cortisol on the immune response, specifically through cytokine regulation.*

1. Introduction

According to the World Health Organization, the parcel of the population over 60 years will increase from 1 billion in 2020 to 1.4 billion in 2030 and up to 2.1 billion in 2050 [WHO 2020]. People are living longer but that does not necessarily mean that longer lives are healthy lives until the end. Thus, understanding the aging process and its consequences is necessary, as we would all profit from increased longevity maintaining the best quality of life possible. Aging can be defined as the natural process of gradually reducing the functionality of the organism; the term senescence encompass that impact [Agondi et al. 2012].

The human body is extremely complex and is comprised of a set of systems that must act together like a symphony to guarantee proper behavior. Among those systems,

the most important against invaders is the Immune System. With aging a progressive decline in the functions of this system and, consequently, increased susceptibility to chronic diseases, infections and reduced response to vaccines is observed. This phenomenon is called immunosenescence and is a major concern for the future of the world population [Bosch et al. 2013].

Mathematical modeling is highlighted as a resourceful research tool in the area of computational biology. It provides great possibilities to explore and improve understanding of complex systems such as the immune system as it allows more simulations and experiments are performed without the need for *in vitro* studies, for example [Marchuk and Romanyukha 2010]. It is possible to test several hypotheses, represent the systems of the human body and interesting phenomena such as Immunosenescence that will be addressed in this work [Romanyukha et al. 2018].

Several mathematical models have been proposed to study the immune system in response to bacteria [Quintela et al. 2014] and other pathogens [Perelson 2002] and also there are several models that have been proposed to represent the endocrine system [Zavala, E et. al. 2019]. The first to our knowledge to represent both was a thesis [Pritchard-Bell 2016]. Based on their idea of coupling the immune system and the endocrine system models, we are proposing here a distinct coupled model to represent the effect of cortisol on the immune response over the decades. In the remainder of this work, we will present the models that we chose and the coupling strategy as well as the orchestration of the simulations as the models have distinct time scales. The preliminary results are also presented with gained insights and future directions.

2. Methods

The mathematical model proposed in this work to represent the influence of aging on the immune response was obtained by coupling two mathematical models from the literature [Pritchard-Bell 2016]. The main differences between the work proposed herein to the reference is the use of distinct and more complex models to represent the immune response and the insulin-glucose dynamics considering fluctuations over the course of each day with cortisol peaking after meals. Moreover, as the models of choice were simulated in different time scales we needed to orchestrate the simulations. The strategies that were used are also described in this section.

A model of the immune response to a bacteria proposed by [Talaei et al. 2021] was chosen as it represents the main cells and cytokines involved in the innate immune response. We considered 7 equations to represent the Activated Macrophages (AM), Resting Macrophages (RM), the pro- and anti-inflammatory interleukin (IL-6, IL-8, IL-10), Tumor Necrosis Factor (TNF-α) and *S. aureus* bacteria (A). That model was modified, so the cytokines are influenced by the presence of cortisol which was added as a new equation.

To represent the dynamics of glucose and insulin, the model of choice was proposed by [Uluseker et al. 2018]. From that model we considered 16 equations to represent glucose intake and its dynamics throughout the body: Stomach Glucose (S), Intestinal Glucose (L), Blood Glucose (G), Insulin (I), Incretin (W), Glucagon concentration (E), Liver Glucose (C), Glucose in muscle tissue (M), in the adipose tissue (A), the concentration of Leptin (Y), of Ghrelin (Q), the ingestion of Glucose (H), Interstitial Insulin (II),

Interstitial Glucose (IG) and transporters (G4m and GLUT4).

Therefore, by adding an equation to represent cortisol and coupling the aforementioned models we have a mathematical model with 24 ODEs that represent the behavior of the innate immune system, when exposed by the bacterium *S. aureus* considering also the dynamics of the endocrine system. To improve understanding of the model, we refer to each part as as the Cell-Cytokine Model (CCM) and the Glucose-Insulin Model (GIM). The equations that were either added or modified are detailed below.

2.1. Modified Cell Cytokine Model (CCM)

The Cell Cytokine Model proposed by part of the authors in a previous publication [Talaei et al. 2021] was chosen to represent the immune system activation.

Bacterium *S. aureus*: A(t);
Activated macrophages: MA(t);
Resting macrophages: MR(t);
Interleukin-6 (pro-inflammatory): IL6(t);
Interleukin-8 (pro-inflammatory): IL8(t);
Interleukin-10 (anti-inflammatory):IL10(t).
Tumor Necrosis Factor-α : TNF(t);
Cortisol Hormone: COR(t).

We have added the following equation to represent cortisol dynamics as a simplification of the reference [Pritchard-Bell 2016]. The first term represents that cortisol concentration depends on the concentrations of glucose and TNF-α and is limited by $kmtc$ and C_{max} and the second term represents natural decay at a constant rate (kcd).

$$\frac{\mathrm{dCOR}}{\mathrm{dt}} = ktc(\frac{TNF(t)}{TNF + kmtc})(C_{max} - COR(t))gluc(t) - kcdCOR(t). \tag{1}$$

Therefore, the TNF-α dynamics also include the added cortisol variable:

$$\frac{dTNF}{dt} = k_{TNF}H^D_{TNF}(IL6)H^D_{TNF}(IL10)M_A - kltCOR(t)(1 - \frac{COR(t)}{COR(t) + kmct}) \\ -k_{TNF}(TNF(t) - q_{TNF}). \tag{2}$$

First and third terms represent, respectively, regulation from interactions with IL-6 and IL-10 and decay and were kept as described in [Talaei et al. 2021]. The second term was added to represent cortisol influence. For more information regarding the other equations please refer to [Talaei et al. 2021].

2.2. Modified Glucose-Insulin Model (GIM)

The following 16 Equations were chosen from the literature [Uluseker et al. 2018] to represent the Glucose-Insulin dynamics:

Stomach Glucose: S(t);
Intestinal Glucose: L(t);
Blood Glucose: G(t);

Insulin: I(t);
Incretin: W(t);
Glucagon concentration: E(t);
Liver Glucose: C(t);
Glucose in muscle tissue: M(t);
Glucose in the adipose tissue: A(t);
Leptin: Y(t);
Ghrelin: Q(t);
Glucose intake: H(t);
Interstitial Insulin: II(t);
Interstitial Glucose: IG(t);
Transporters: G4m(t) and GLUT4(t).

As cortisol also influences glucose intake we have also modified Eq. H(t) to include cortisol:

$$\frac{dH(t)}{dt} = \frac{b_{17}Q(t)}{b_{18}Y(t)+1}\exp^{-rI(t)} - b_{19}G(t)H(t) - b_9H(t) - kc2gCOR(t), \tag{3}$$

The other equations of the Glucose-Insulin model were kept the same. Thus, for more information please refer to [Uluseker et al. 2018].

2.3. Coupling Strategy

Cortisol increases after each meal following the glucose intake dynamics and affects the immune response by regulating TNF-α. Thus, both models are connected by that variable (Figure 1). Cortisol variable is represented in the Cell-Cytokine Model interacting at each time step with TNF-α variable as shown in Eqs (1) and (2). The Glucose-Insulin model uses the outcome of cortisol over one day converted to minutes and that is represented in Eq. (3).

2.4. Orchestration of the Simulations

As the GIM considers the dynamics of the endocrine system by minute and the CCM considers the dynamics of the immune system by day, we have a multi-scale situation that need orchestration to guarantee both models work properly with their optimized parameters. We propose two approaches for the simulations including the conversion from days to minutes and vice-versa (Figure 2).

The first approach considers that the glucose dynamics are similar everyday, thus, we simulate the MGI model only once after running one day of MCC without glucose influence, so we can have the cortisol variable over the course of one day (Figure 2.A)). Then, we iterate only the MCC over the number of days of interest for the simulation. That is useful, for example, to see the dynamics of the innate response for the first few days. However, as the glucose dynamics are also affected by cortisol, it would be interesting to iterate both models over longer periods of time. Figure 2.B) shows how we propose the orchestration to represent that both models are being updated by the other model outcomes.

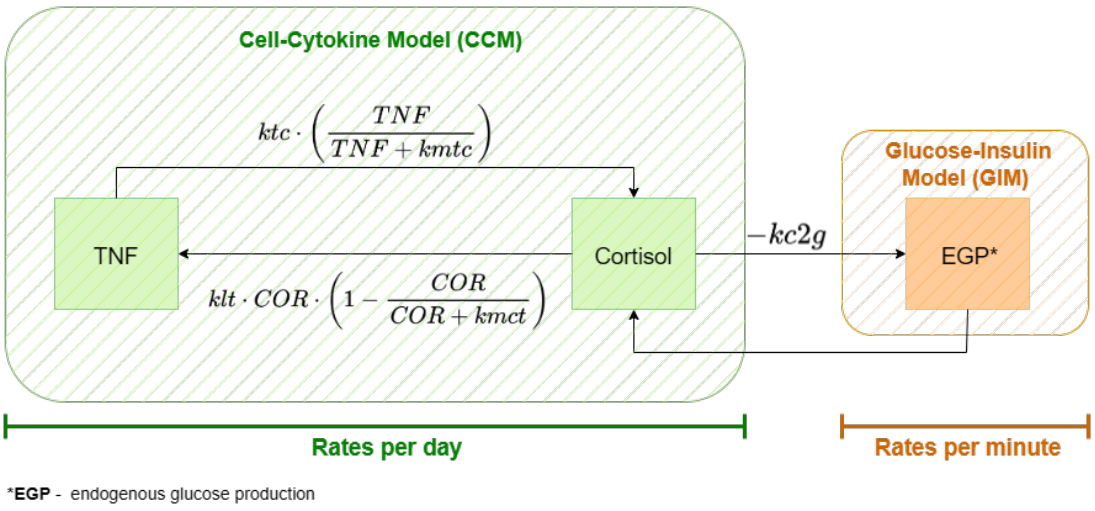


Figure 1. Cortisol increases after each meal considering glucose intake and affects TNF-α and glucose.

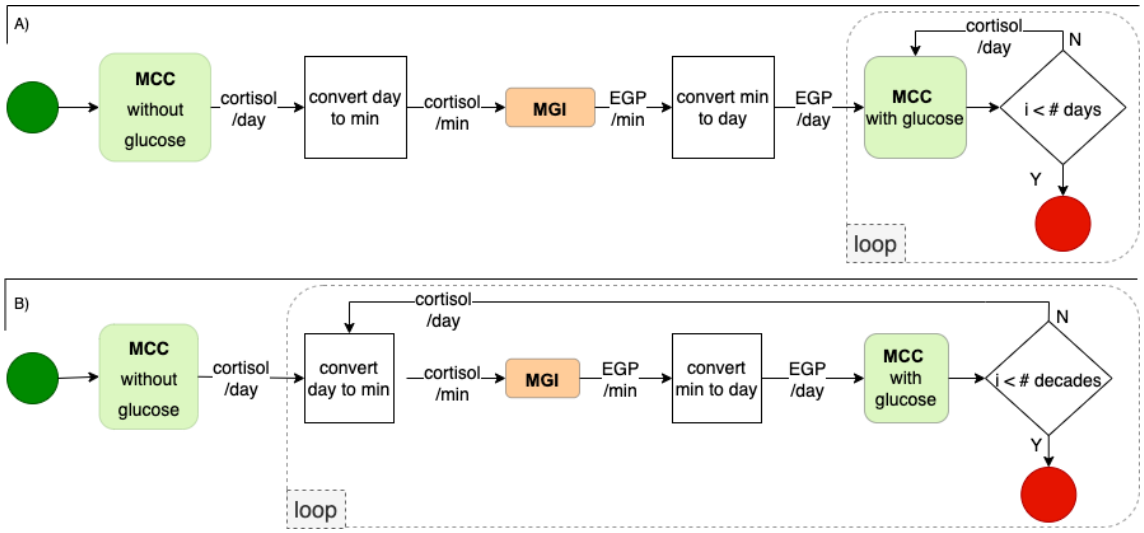


Figure 2. Proposed orchestrations for the simulations of the multiscale models. A) we keep the same fluctuation for glucose dynamics and run MGI only once. B) we consider that glucose also varies depending on cortisol levels and iterate both models over the decades.

In this later scenario, the simulations also start by running the MCC without glucose, then convert cortisol variable to minutes to run the MGI model. The MGI model outcomes the glucose values per minute, which are converted to days and then the MCC model is run a second time but now considering the glucose influence. The updated cortisol valued are then passed to MGI model again and this iteration occurs running one day for each decade.

2.5. Experimental Data

To represent the variation of cortisol with aging, we extracted the experimental data from [Miller et al. 2016] as initial condition for each decade simulated. We are considering the

last five decades from 40 to 90 years old (Figure 3).

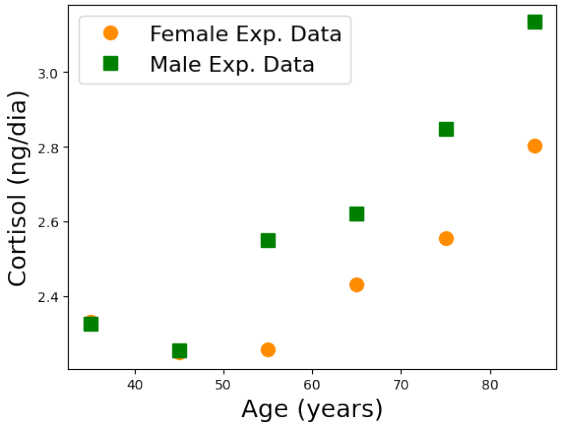
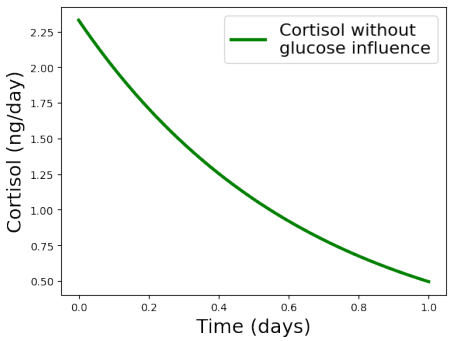


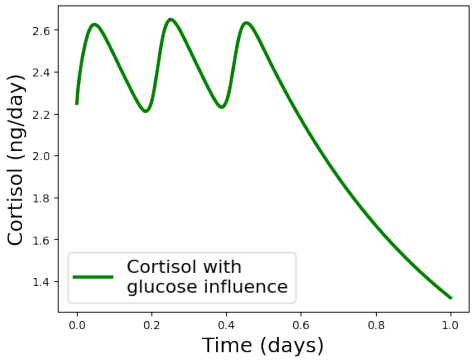
Figure 3. Cortisol experimental data used as initial condition for each decade.

3. Results and Discussion

Assuming a baseline morning peak of cortisol and the presence of bacterial infection, we initially observed a slow cortisol decay throughout the day, as demonstrated in Figure 4a. By integrating the glucose intake factor into our coupled model, we incorporated that cortisol levels also peaked after each meal, as shown in Figure 4b. In our simulations, we assumed that individuals consumed three meals per day. This approach allowed us to capture a more comprehensive understanding of the complex interplay between cortisol and glucose intake.



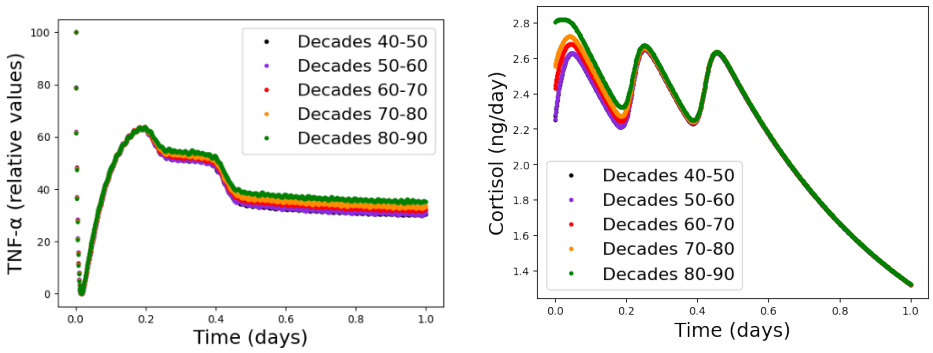
(a) Peaks in the morning and decays without glucose intake.



(b) Peaks after each meal.

Figure 4. Cortisol dynamics over one day.

Through the proposed coupled model, we have developed a framework to simulate the intricate dynamics of immune response to a pathogen, taking into account the day-to-day and year-to-year fluctuations in cortisol levels. In Figure 5, we illustrate the daily patterns of TNF-α (Figure 5a) and cortisol (Figure 5b), with the initial cortisol condition varied across each decade, as per the experimental data. This analysis was performed through the use of an orchestration approach, as described in Figure 2B, allowing us to investigate the impact of cortisol fluctuations on the immune response.



(a) TNF-α **(b) Cortisol.**

Figure 5. Daily dynamics for each decade based on female data.

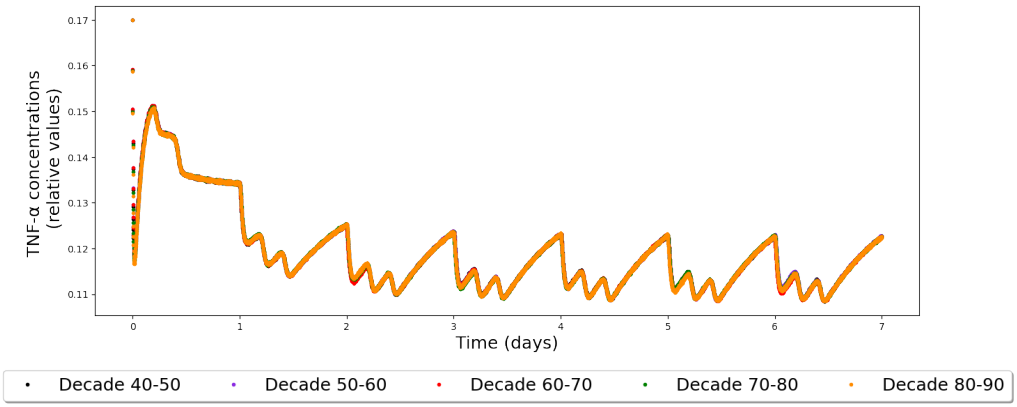
In addition, we have conducted simulations of one week following the onset of infection for each decade, as outlined in Figure 2.A). The parameters utilized in these simulations were consistent with those established in the literature [Talaei et al. 2021], and represent that the immune system is able to eliminate the bacteria in less than one day. Figure 6 shows the dynamics of TNF-α and cortisol over one week of simulation. Our results indicate that the concentrations of TNF-α are higher on the first day with the presence of bacteria (Figure 6a) and subsequently vary over time following cortisol levels (Figure 6b).

We anticipated observing more significant differences in cytokine profiles in response to changes in cortisol levels across the lifespan. However, it is important to note that we maintained the models using parameters established in the literature and only manipulated the initial cortisol conditions. TNF-α exhibits peak expression in the presence of bacteria and subsequently decays as it is contained by the immune system [Talaei et al. 2021]. Our simulation results (as illustrated in Figure 5a) demonstrate that TNF-α expression profiles are influenced by diurnal cortisol peaks, while stabilizing at different levels across each simulated decade. Similarly, Figure 5b shows differences in initial cortisol values across age groups, though cortisol expression patterns remain consistent across decades.

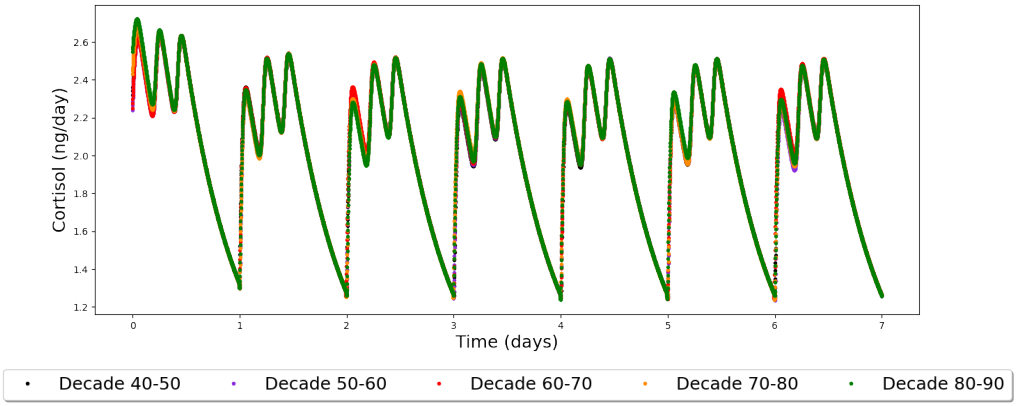
Further simulations are required to establish the optimal sets of parameters that accurately represent each decade, as our results indicate that initial conditions alone are insufficient to capture the full range of dynamic behaviors. Future studies should incorporate a broader range of experimental data, and employ other sophisticated modeling techniques as sensitivity analysis and uncertainty quantification to accurately capture the complex interplay between cortisol and immune response across various time scales and physiological contexts.

4. Conclusions

In this study, we have successfully achieved our main goal of developing a differential equation-based model that incorporates the effects of glucose dynamics and increasing cortisol levels with aging on cell and cytokine activation. By coupling two existing models, we were able to capture the complex interplay between these factors and simulate the dynamics of immune response to bacterial infection over time.



(a) TNF-α



(b) Cortisol.

Figure 6. Daily dynamics for each decade based on female data. Orchestration as shown in Figure 2A.

However, further simulations are needed to fully validate the proposed model. Our ultimate goal is to apply the model to simulate the dynamics of the immune response over the course of 40 years, while fitting the parameters of the coupled model to experimental data reported in the literature [Miller et al. 2016]. This will enable us to more accurately capture the long-term effects of cortisol on immune response and observe the same increase in cortisol levels observed in the literature.

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