THE BIOLOGICAL SUBSYSTEM INTERACTIONS UNDERLYING THE STRESS RESPONSE OF THE HUMAN BODY: A DYNAMIC MODELING APPROACH

by

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ABSTRACT

THE BIOLOGICAL SUBSYSTEM INTERACTIONS UNDERLYING THE STRESS RESPONSE OF THE HUMAN BODY: A DYNAMIC MODELING APPROACH

The dynamic stress response of the human body to stressors is produced by nonlinear interactions among its physiological subsystems. The evolutionary function of the response is to enable the body to cope with stress. However, depending on the level, duration, and frequency of the stressors, the mechanism may lose its function and the body can go into a pathological state. Three subsystems of the body play the most essential role in the stress response: endocrine, immune and neural systems. In this study, we construct a simulation model of these three subsystems to imitate the stress response dynamics under different types of external stimuli. Cortisol, glucocorticoid receptors, proinflammatory cytokines, serotonin, and serotonin receptors are the main variables of the model. Using both qualitative and quantitative physiological data, the model is structurally and behaviorally well-validated. Model's capability of capturing the role of internal interactions in the system is authenticated with sensitivity analysis revealing bifurcations with respect to stress stimulus level and duration parameters. In subsequent scenario runs, we have successfully replicated the development of stress related abnormalities in the body. Depression-like dynamics, response sensitivity change as a result of earlier stress experience, and cytokine-induced sickness behavior are the real-life cases we simulate in this study. The model provides a quantitative representation of very well acknowledged qualitative hypotheses about the stress response of the body. This is a novel quantitative step towards the comprehension of stress response in relation with other disorders, and it provides us with a tool to design and test treatment methods.

ÖZET

İNSAN VÜCUDUNUN STRESE TEPKİSİNİ OLUŞTURAN BİYOLOJİK ALTSİSTEMLERİN ETKİLEŞİMLERİ: BİR DİNAMİK MODELLEME YAKLAŞIMI

İnsan vücudunun stres uyaranlarına verdiği dinamik stres tepkisi, vücudun fizyolojik altsistemleri arasındaki doğrusal olmayan etkileşimler sonucunda ortaya çıkar. Bu tepkinin evrimsel fonksiyonu vücudun stresle mücadelesini mümkün kılmaktır. Fakat bu mekanizma, stres uyaranının seviyesi, süresi ve sıklığına bağlı olarak fonksiyonunu yitirebilir ve vücut patolojik bir duruma girebilir. Vücudun üç altsistemi, stres tepkisinde en esas rolleri oynarlar: endokrin, bağışıklık ve sinir sistemleri. Bu çalışmada, farklı dışsal uyaranlar altındaki stres tepkisinin dinamiklerini üretmek üzere bu üç altsistemin benzetim modeli kurulmuştur. Kortizol, glukokortikoid reseptörleri, proinflamatuar sitokinler, serotonin ve serotonin reseptörleri modelin ana değişkenlerini oluşturmaktadır. Nitel ve nicel veriler kullanılarak modelin yapısal ve davranışsal geçerliliği test edilmiştir. Stres uyaranı seviyesi ve süresine yönelik yapılan duyarlılık analizlerinin ortaya çıkardığı bifurkasyonlar ile, modelin sistemin iç etkileşimlerini yakalayabildiği ortaya konmuştur. Bunu takiben yapılan senaryo koşumlarında, vücutta stresle alakalı olarak ortaya çıkan anormallikler model ile türetilebilmiştir. Depresyon benzeri dinamikler, önceden yaşanmış streslere bağlı olarak ortaya çıkan stres duyarlılığı değişimi ve sitokinler sebebiyle ortaya çıkan hastalık davranışı bu çalışmada türettiğimiz gerçek hayat vakalarıdır. Model, vücudun stres tepkisiyle ilgili literatürde saygın yeri olan nitel hipotezlerin nicel temsilini sunabilmektedir. Bu, stres tepkisinin diğer hastalıklarla ilişki içerisinde kavranmasına yönelik atılmış yeni bir nicel adımdır ve tedavi yöntemleri tasarlamak ve onları test etmek için bize bir araç sağlamaktadır.

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LIST OF ACRONYMS/ABBREVIATIONS

1S1D	One Stress Input Every Day
1S3D	One Stress Input Every Three Days
5-HT	5-hydroxytryptamine (Serotonin)
ACTH	Adrenocorticotropin
Adj	Adjustment
Avg	Average
CRH	Corticotropin-Releasing Hormone
CSF	Cerebrospinal Fluid
Cort	Cortisol
Deg	Degeneration
Del	Delay
DR	Dose-Response
Eff	Effect
GR	Glucocorticoid Receptor
HPA	Hypothalamus-Pituitary-Adrenal
IL-6	Interleukin-6
Max	Maximum
Min	Minimum
MR	Mineralocorticoid Receptor
PostR	Postreceptor
PreR	Prereceptor
ProCyt	Proinflammatory Cytokine
Ref	Reference
RelTime	Relieving Time
Ser	Serotonin
TRP	Tryptophan
TSST	Trier Social Stress Test
VAS	Visual Analogue Scale

Vol	Volume

1. INTRODUCTION

The nature of the human body is composed not only of its constituent molecules, cells, tissues, organs but also of their interactions. All take a role in the mechanisms that furnish the body with living being properties. Such mechanisms require a certain state of the body to function the way they are supposed to. This desired steady state of the body is termed as *homeostasis* by Walter Cannon [9].

Naturally, the human body is in active relationship with its external environment and it works against stimuli coming from outside to preserve homeostasis. Stimuli threatening the homeostasis is conceptualized as stress by Cannon. Hans Selye, known as the father of the stress concept, later described stress as "the nonspecific response of the body to any demand upon it" [10]. A complex set of physiological mechanisms is activated as a stress response to a stressor perturbing the balanced system. The main function of this acute reaction of the body is to prepare it against threats by providing the essential substrates for coping. The active state is called *allostasis*, which is a short-term, dynamic state to protect the healthy state in the long-term. Although stress response aims to maintain health, its prolonged activation is severely detrimental to the body. Contributing to this notion of Selye, Bruce S. McEwen has introduced allostatic load concept to the modern understanding of stress [11, 12]. Persistent stimulation keeps body in a long allostasis state, which accumulates stress response products as a physiological load on the body. Under such an allostatic load, there emerge biological disturbances and the system seeks a new level of steady state, which we diagnose as disease. As widely accepted and experimentally proven, exposure to physical or psychological stressors drives the body into a variety of disorders; psychiatric disorders, cardiovascular diseases, diabetes, obesity, and gastrointestinal problems being a few of them. Thus, understanding the mechanism behind the stress response of the human body is one common pathway into understanding its disorders.

Homeostasis of the human body is a product of cooperation among the different functional subsystems of it. Such a finely tuned cooperation is managed by feedback

loops. In case of a bodily system perturbed by stress, positive and negative feedback loops work simultaneously to operate the stress response. However, complexity brought by feedback loops into the structure of this system makes it hard to understand the stress response and assess its consequences. The complexity of stress response mechanism of the human body emerges not only from feedback loops, but also from nonlinearities and delays in its nature. High prevalence of stress related disorders and inefficient treatment cases point out the difficulty in understanding the real structure.

As Goldstein and Kopin delineated intelligibly in their paper [13], complex stress response of the human body requires to be approached with systemic perspective. In this respect, we attempt to model the physiological mechanisms underlying the stress response of the human body using dynamical systems theory approach. System dynamics methodology is applied since it is found to be the most appropriate modeling and simulation tool, as explained in Chapter 4.

In the following chapters, we first present a brief review of the theories about the stress response disorders and the modeling research with dynamical systems theory approach. Following the detailed description of our methodology and then the model, we discuss how the model is tested and validated. Finally, the results of some scenario and treatment analysis conducted with the valid model are provided.

2. MATHEMATICAL MODELING OF PHYSIOLOGICAL SYSTEMS

How the body of living beings composed of different units, such as organs, tissues, and cells, is capable of maintaining its functioning as a whole under different circumstances has been one of the most captivating topics in human history. Physiology field tries to answer this curiosity for the functioning of the bodily systems.

The feedback control mechanisms embedded in the structure of the body is the language of the body for its internal relations to operate in harmony. Physiology needs to understand the language to be able to properly comprehend the consequent functioning. While studying the emergent outcomes, *internality* is a critical feature of the body to take into account since it beclouds predictability. Thus, a systems approach to physiology must be adopted to be consistent with the nature of the body and to understand it objectively.

Physiology describes the body not only in a qualitative manner, but also quantitatively. Throughout their history, physiologists have been engaged with mathematics to express how the whole body works. Differential equations provide appropriate expressions for dynamic and continuous functions of the body. However, solving a complex set of differential equations is not easy, even impossible in many cases.

In more recent years, tremendous development in computational methods has brought a great convenience to modeling the body of living beings. Mathematical models that are not possible to be solved analytically then became possible to be solved numerically. Thus, mathematical modeling and computer simulations of physiological systems provide the field with huge opportunities for the analysis of complex bodily systems. They enable us to make health predictions and test treatment policies, which is an invaluable opportunity considering the limitations of experimental research on living beings.

3. PROBLEM DEFINITION AND RESEARCH OBJECTIVES

Stress response of the body is an emergent consequence of the body, and there has been considerable interest in its physiology. Particularly the endocrine system, immune system and nervous system, and their interactions constitute of the main internal mechanisms involved in the stress response of a person [14, 15]. It is even suggested that these three systems must be perceived as an integrated single system instead of three individual ones [16]. A new field with this approach to all three systems has emerged and it is called *psychoneuroimmunology*.

There is significant research elucidating interactions among these three systems in various scales from micro to macro. Especially in studies with major depression disorder, a number of theories has been proposed about the essential relations playing a role in the stress response and the following pathological state. The most acknowledged theories specifically about depression that integrate those systems include the monoamine hypothesis of depression [17], the HPA axis dysfunction theory [17, 18], the cytokine hypothesis of depression [19, 20], and the neurodegenerative hypothesis of depression [19].

Even though the integrity of the three systems in explaining stress response dynamics of the body has been qualitatively and quantitatively proven by physiologists, system biologists, and neuroscientists, there is a gap of mathematical modeling of the system as a whole in literature. Some dynamical systems theory techniques have been applied to model biological mechanisms related with stress response of the human body. However, they cover the system partially. Of the three, the relevant mechanism of the endocrine system, HPA axis, has been studied the most. Recently, Hosseinichimeh *et al.* [21] have reviewed and extended the existing HPA axis models with new parameter estimations using real-life data. Gupta *et al.* [22] have analyzed the stability of HPA axis dynamics with a mathematical model including glucocorticoid receptors as

well. Another interesting HPA axis modeling study is of Sriram *et al.* [23], relating the model with two different stress related disorders, major depression and PTSD. As a study with wider scope, there is a conceptual model of depression disorder constructed by Wittenborn *et al.* [24] with a macro perspective including socio-economic variables, but together with a biological portion that we are interested in.

Overall, although the field is ready with biological knowledge and calls for it, we could not find an appropriate mathematical model of endocrine, immune, and neural systems in combination to study the dynamics of stress response. There is an exciting potential of this system to be explored with modeling and simulation approaches.

We designed our study to answer the need for an integrative and quantitative approach to the stress system. We model the biological mechanisms of the human body that drive its stress response. By keeping in mind that the human body is a closed box of very complex subsystems, we attempt to model a few of those internal mechanisms that we and literature found crucial in explaining the stress response dynamics of a healthy body.

We first aim to model a healthy body that can handle reasonable stress. It will be a description of essential mechanisms of the stress response. Then, we use it under different stressful conditions, which will allow us to understand dynamic cooperation and coordination among the loops. After analyzing the model's sensitivity to different parameters, we finally aim to employ our validated model in imitating possible scenarios of psychoneuroimmunological disturbances. As a further work, our model can be extended to represent wider range of stress related disorders, and to allow treatment design.

4. RESEARCH METHODOLOGY

A system is a set of interrelated substituent units behaving like a single entity. The units determine the system; however, the system is more than the sum of them. Thus, understanding its compartments in isolation does not mean we can understand the system as a whole. When we are interested in the emergent behavior, as it is mostly the case in studies on nature, it is inevitable to engage with a systems theoretical framework. The human body for example, as a subsystem of the nature, necessitates systems approach without any doubt.

We, as humans with limited cognitive capacity, cannot easily foresee the emergent behaviors most of the time. We depend on mathematical and computational modeling and simulation tools to go beyond our capabilities. There are various tools to model and/or simulate systems, and the appropriate one must be chosen specifically for the system of interest. System dynamics methodology comes into play when we consider the system of our interest, human body.

System dynamics is a modeling and simulation methodology suitable for large-scale systems with feedback loops, nonlinearities, accumulations, and delays. The method allows us to model feedback loops in interaction and observe their clash under different system perturbations via simulation. Therefore, it aids us to get a better insight about the structure of systems, make experiments on them, and design better policies. Overall, if we want to go beyond qualitative analysis of systems with such distinguishing features, system dynamics method is an excellent choice to proceed with.

Generally the human body, more specifically the stress response subsystem of it, is a dynamic, closed system internally driven by feedback loops, and with delays and nonlinearities by its nature. In order to preserve its nature while modeling, we need a tool allowing us to construct such a structure, and system dynamics perfectly fulfills our need. Furthermore, using a properly constructed model of the stress response system, we can experiment with different external and internal conditions, which is not feasible

or ethical to conduct on a real human body.

Causal loop diagrams and stock-flow diagrams are among the main tools of system dynamics methodology which we have utilized in this study. The former style of diagrams qualitatively draws the causal relationships among the variables. It is an exceedingly helpful tool in the construction phase of the models since it aids to schematize our mental models and makes qualitative discussions possible (see Figures 5.1-5.9 below). Technical details of this tool and its application in our study are provided in Chapter 5.

Stock-flow diagrams, on the other hand, stand for quantitative relations within the system. These diagrams are made of three types of constructs: stocks, flows, and converters. Stocks are the accumulating entities of a system. System's inertia is represented by them; therefore, they are responsible for the endogenous dynamism of the system. Their rate of change is determined by the flow (rate) variables. Thus, they are the amounts of increase or decrease in stocks per time. If time is stopped, flows would have no meaning, but stocks would persist. The rest of the variables and parameters of a model are categorized as converters.

Stocks are represented as rectangular boxes while flows are the pipes flowing into or out of them. Converters are shown by circles (see Figure 4.1). The causal relations among these constructs are depicted with connecting arrows. The variable/parameter on the tail of an arrow has a causal effect on the variable/parameter on the head of the same arrow (see Figures 5.1-5.9 below). An example stock-flow diagram of a very simple model is presented in Figure 4.1.

$$\frac{dPopulation}{dt} = Birth\ Rate - Death\ Rate \tag{4.1}$$

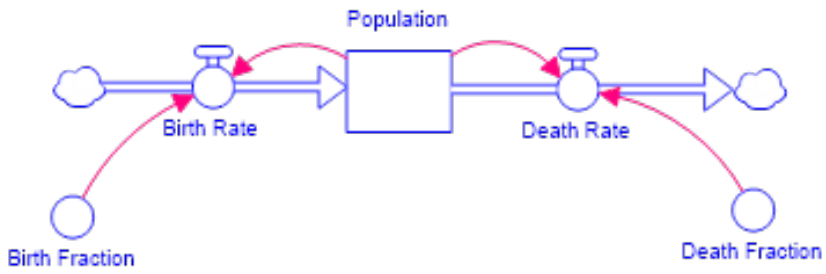


Figure 4.1. An example stock-flow diagram of a simple population model.

where

$$Birth\ Rate = Birth\ Fraction \times Population \tag{4.2}$$

and

$$Death\ Rate = Death\ Fraction \times Population \tag{4.3}$$

We have applied this modeling tool in our study to formulate our dynamic physiological system, and described its details in Chapter 6.

5. OVERVIEW OF THE MODEL

The body is coordinated with feedback control loops by means of efficient communication systems. There are several chemical systems in the human body that serve as communicators: (1) neurotransmitters, (2) endocrine hormones, (3) neuroendocrine hormones, (4) paracrines, (5) autocrines and (6) cytokines [2]. They are categorized as such according to where they are secreted and to where they carry the message. If one of those systems fail to maintain the desired level of communication, and cooperation, then homeostasis is lost. We have modeled the interrelations among some of these communicators to observe their cooperation in stress response dynamics.

Considering the purpose of our problem, we have modeled the key units and relations of the endocrine, immune, and neural systems, that have been consistently in the center of stress related studies. Cortisol and glucocorticoid receptors (GR), proinflammatory cytokines, and serotonin (5-HT) and its receptors are the representative variables of these three systems respectively. The most relevant causal relations among them form the causal loop diagram provided in Figure 5.1 which we based our model on. The references for every causal relation are provided next to the arrows.

The diagram depicts the main variables of the system and real-life causal relations among them. Links connecting two variables represent a causal effect of the variable located in the tail of the arrow, on the variable located in the head of the arrow. The sign next to the head of an arrow indicates the direction of the causality. If it is a "+", the direction of the change in the effect variable is the same as the change in the cause variable. On the other hand, the cause and effect variables move in opposite directions if it is a "-" causality.

There are five major negative feedback loops actively regulating the stress response of the body. The first loop is driven by the two different actions of cortisol: (i) it regulates the metabolism and energy resources of the body to be used in relieving stress, and (ii) it downregulates serotonin prereceptors that control the free serotonin

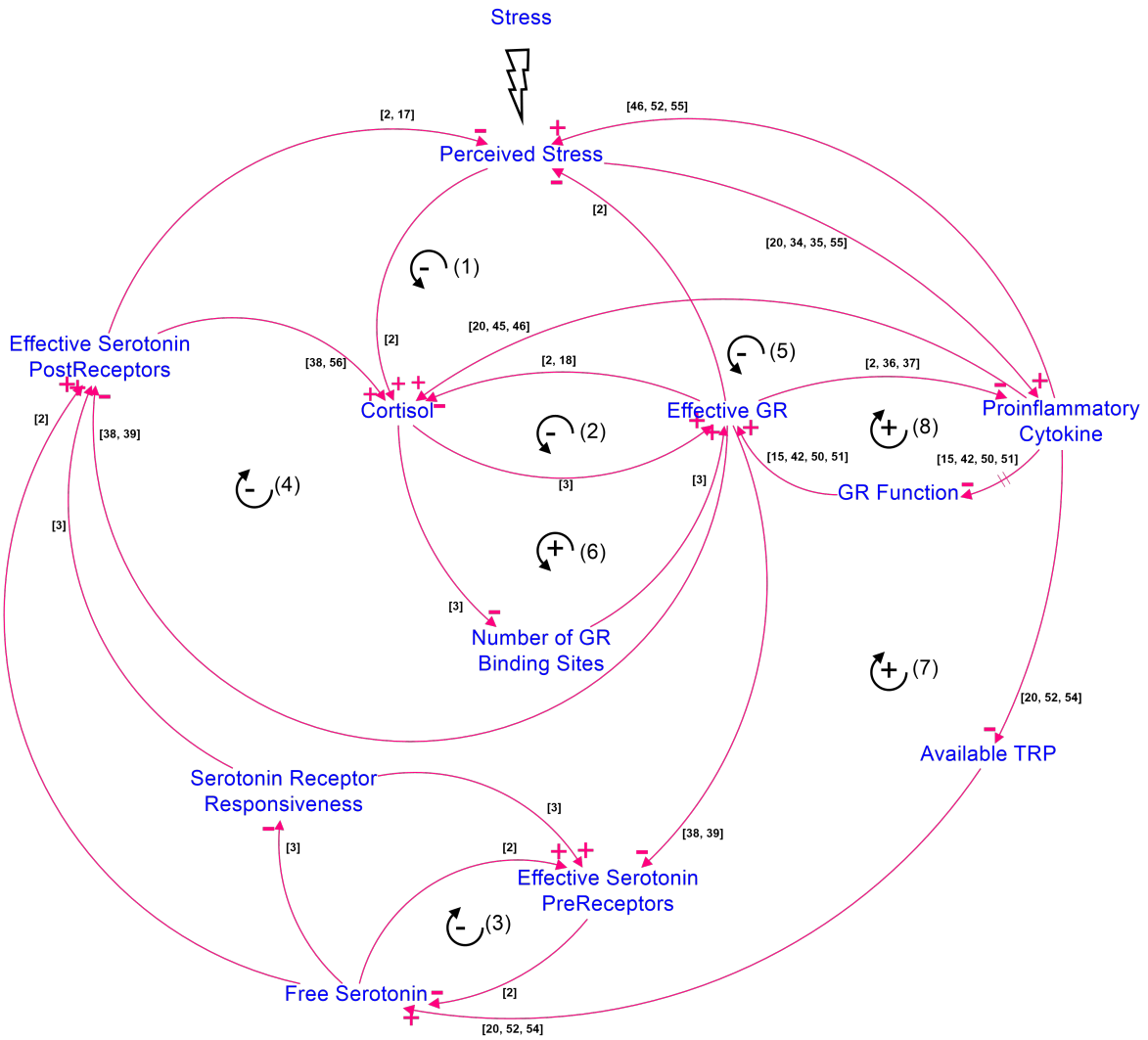


Figure 5.1. Causal loop diagram of the model.

level in the synaptic clefts. As a result of the latter action of cortisol, serotonin accumulates in the clefts, which is free to be carried to the relevant parts of the brain to bind with its postreceptors and act there. One very well-known function of the serotonin is to enhance the stress relief. Therefore, stress is relieved via this two-way control mechanism, as represented in the Stress Control Loop (1).

The Cortisol Control Loop (2) is the most fundamental control mechanism of the HPA axis on itself. When cortisol is released from adrenal glands, it binds with glucocorticoid receptors located on the HPA axis. The binding, in turn, inhibits the

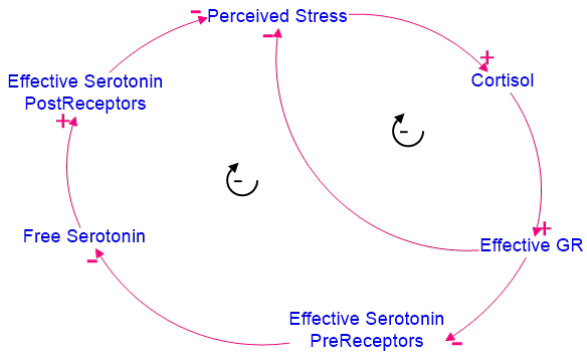


Figure 5.2. Stress Control Loop (1).

secretory functions of the axis. Thus, cortisol level in the blood is kept as desired.

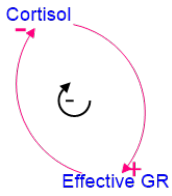


Figure 5.3. Cortisol Control Loop (2).

Free serotonin level in the synaptic clefts is controlled by its own prereceptors. Prereceptors are also known as autoreceptors, and their role is to release serotonin molecules into or reuptake them from synaptic clefts according to the currently desired free serotonin level. This is the mechanism of the Serotonin Control Loop (3).

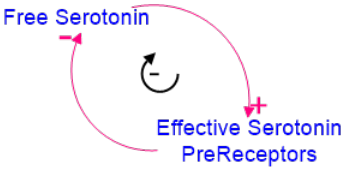


Figure 5.4. Serotonin Control Loop (3).

Another important control mechanism is on serotonin effectiveness. When there is intensive stress, cortisol is known to desensitize the postreceptors of serotonin. In

return, the stimulating effect on cortisol exerted by serotonin diminishes. The relationship is depicted in the Serotonin Effect Control Loop (4).

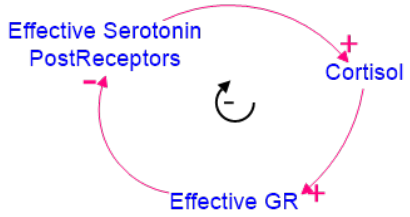


Figure 5.5. Serotonin Effect Control Loop (4).

Stress initiates immune reactions in the body, which is the preparation of the body against external threats. Proinflammatory cytokines are secreted from immune cells to fight the potential intruders. One function of these cytokines is to trigger the HPA axis for cortisol secretion. On the other hand, cortisol is known with its anti-inflammatory effects. Cortisol molecules bound with glucocorticoid receptors (GRs) located in the relevant immune cells inhibit the production of proinflammatory cytokines. Therefore, stress-initiated proinflammatory cytokines stimulates cortisol secretion, which in turn inhibits the production of proinflammatory cytokines, which is represented in the Proinflammatory Cytokine Control Loop (5).

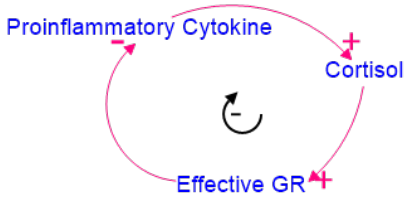


Figure 5.6. Proinflammatory Cytokine Control Loop (5).

Besides above and some other less significant balancing loops, three major positive feedback loops function in the stress response of the body. The first one is the Cortisol Effect Reinforcing Loop (6). As in the nature of hormone-receptor relations, when a hormone increases significantly, it shuts down its receptors to protect the target tissues from extreme stimulations. In our case, cortisol decreases the number of binding sites

of glucocorticoid receptors. Less binding sites means lower responsiveness of the target tissues, which in turn means more cortisol levels in the blood. Thus, cortisol effect over all its target tissues is reinforced with this loop.

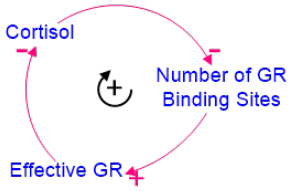


Figure 5.7. Cortisol Effect Reinforcing Loop (6).

Proinflammatory cytokines induce some chemical reactions that convert tryptophan (TRP) into other molecules. Since TRP is a precursor of serotonin, TRP depletion caused by elevated proinflammatory cytokines results in serotonin decrease. Lower serotonin means less stress relief as explained above, causing more proinflammatory cytokine production. This is the Stress Reinforcing Loop (or Serotonin Depletion Loop) (7).

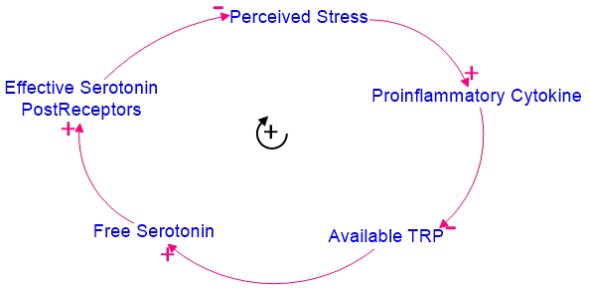


Figure 5.8. Stress Reinforcing Loop (7).

GR Resistance Reinforcing Loop (or GR Function Depletion Loop) (8) is constructed by another interesting impact of proinflammatory cytokines: they damage the functioning of glucocorticoid receptors. Lowered GR functioning cannot exert cortisol's anti-inflammatory effects, meaning higher proinflammatory cytokines.

The body is able to handle stress thanks to the above described regulatory mechanisms. Stress perturbs the system, and after a short while, the body comes back to

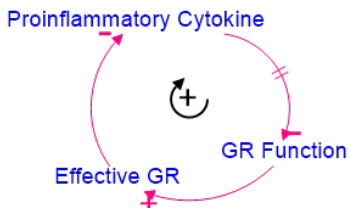


Figure 5.9. GR Resistance Reinforcing Loop (8).

its homeostatic levels unless the harmony among the loops is disturbed by an excessive perturbation. The model is constructed to explore how this harmony is altered according to the level and frequency of stress stimuli, and its structure is explained in the next chapter.

6. DESCRIPTION OF THE MODEL

The model consists of three sectors representing major subsystems of the body: endocrine sector, immune sector, neural sector; and one other sector as an interface of the body with its external environment, where stress is processed: stress sector. The stress sector consists of two stock variables: *Perceived Stress* and *Relieving Time*. The former stands for the perceived level of stress by the brain, and the latter for the adjusted time to relieve that perceived stress. The endocrine sector involves three stock variables: *Cortisol*, *GR Function*, and *GR Number*. They respectively denote the total cortisol concentration in blood plasma, effectiveness of the glucocorticoid receptor (GR) functioning, and the average number of GR binding sites per cell. The immune sector has *Proinflammatory Cytokine* stock representing the relevant cytokine (chosen as interleukin-6) concentration in blood plasma. *Serotonin* is the stock variable of the neural sector, and it tracks the level of free serotonin concentration in the cerebrospinal fluid (CSF).

Table 6.1. Units of the stock variables.

Stock Variable	**Unit**
Perceived Stress	unitless
Relieving Time	hour
Cortisol	nmol/liter
GR Function	unitless
GR Number	sites/cell
Proinflammatory Cytokine	picogram/ml
Serotonin	picogram/ml

Considering the purpose of this study, time unit of the model is chosen as hour. Some real-life parameters and relations change so rapidly or so slowly that their dynamics lose their meaning at hour level. The secretion of hormones and cytokines, and their clearance from the blood, for instance, occur within minutes. Therefore, to have

a special model structure that serves our hour-level purpose, our average hormone and cytokine levels are adjusted with adjustment flows, instead of real-life secretion and clearance flows. It also means that the hormones and cytokines in the model stand for the hourly average levels, not the instantaneous levels. Accordingly, the diurnal variation in hormone and cytokine levels is neglected in the model, due to the relatively fast rhythm of the circadian effect.

As widely studied and accepted, there are neurodegenerative aspects of the stress response of the human body [19, 25]. However, these structural alterations happen in years, which go beyond the scope of this study and are ignored in the model. Nevertheless, there is one structural change included in the model, that is the glucocorticoid receptor (GR) degeneration. As described before, proinflammatory cytokines harm GRs, that decreases the effectiveness of receptor functioning. This relatively long-term impact on GRs is modeled with a third order delay structure.

Reference values for all the variables are set as average healthy levels in a human body, and determined according to a set of medical sources as listed in Table 6.2.

Table 6.2. Reference values of the main variables used in the model.

Variable Name	**Reference Value**	**Source**
Cortisol	250 nmol/l	[5]
Proinflammatory Cytokine	1.5 pg/ml	[6]
Serotonin	3500 pg/ml	[26]
GR Number	6000 sites/cell	[27]
Tryptophan	79 micromole/l	[28]

6.1. General Model Structure

Of the seven main stock variables in the model, five are controlled with adjustment flows. Their formulation is in the general form:

$$\frac{dStock}{dt} = \frac{Implied\ Stock\ Level - Stock\ Level}{Adjustment\ Time} \tag{6.1}$$

Other two stock variables are controlled with distinct in- and outflows since they do not have symmetric control mechanisms. Their general form is:

$$\frac{dStock}{dt} = Inflow - Outflow \tag{6.2}$$

Formulations for all stock variables are specifically described in their own subsections.

Interactions within our model are built on the hormonal effects, therefore, the mechanism behind how hormones exert their effect on target tissues is very much our concern. While formulating these effect functions, we benefitted from a number of medical books [1–3, 29, 30]. Hormones are only effective when bound with their receptors. How much they will influence the target tissue is dependent on three variables: hormone level in blood, receptor level, and receptor efficiency. Dependent on all these three, dose-response curves are used to illustrate the amount of hormonal effect. They are s-shaped, indicating the fact that hormonal effects have thresholds and saturations. A general dose-response curve is presented in Figure 6.1.

As it is the case in this general figure as well, logarithm of the hormone amounts is used to draw the curves. Since a dose-response curve is specific to the target tissue, we have used similar but slightly different graphs for each hormonal effect created by cortisol and serotonin hormones in the model. If the hormone has an inhibitory effect, then the calculated effect of the hormone is subtracted from the maximum

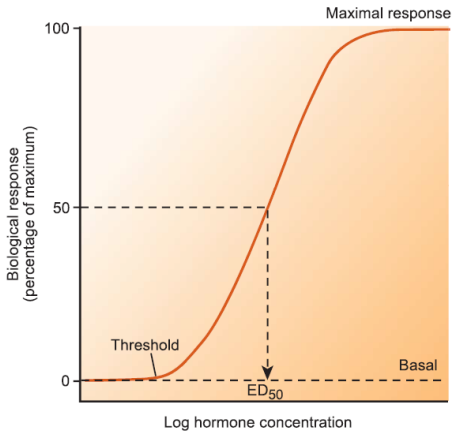


Figure 6.1. General dose-response curve [1].

responsiveness of the target to obtain a decreasing effect graph. Because cytokine is a different messenger category than hormone, the effect functions of *Proinflammatory Cytokine* is not modeled with a logarithm transformation.

One interesting part of our model is the degeneration and downregulation of the hormone receptors. As mentioned above, dose-response curves are dependent on the receptor number and efficiency which are both variables in the model: *GR Number* and *GR Function* are manipulated by *Cortisol* and *Proinflammatory Cytokine* respectively. Besides GR, the functioning of serotonin prereceptors and postreceptors are also variables in the model, controlled by *Cortisol*. The average amount of these receptors of *Serotonin* is dependent on *Serotonin* amount itself, as well.

Such alterations in receptors are modeled based on the following medical knowledge: the number of receptors changes the responsiveness of the target cells, which corresponds to a shrinkage or expansion of the y-axis of the dose-response curves. Moreover, the receptor function alters the sensitivity of the target cells to a certain amount of hormone, which is reflected by a shift in in the x-axis of dose response curves. These two phenomena are described very clearly in [3], [1] and [31], and shown in Figure 6.2.

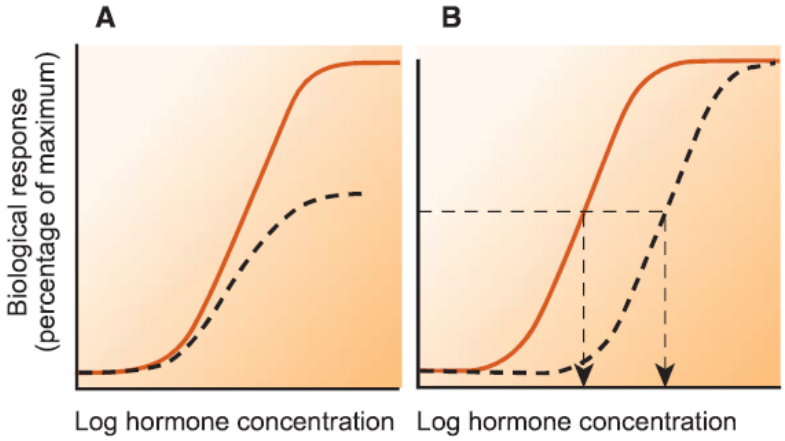


Figure 6.2. Altered target tissue responses reflected by dose-response curves [1]. A: Decreased target tissue responsiveness. B: Decreased target tissue sensitivity.

In the model, in order to reflect GR responsiveness change as a function of *GR Number*, the dose-response curves of *Cortisol* are multiplied with variable responsivenesses of the targets. The number of serotonin receptors, on the other hand, is not an explicit variable of our model due to their more sophisticated regulation and distribution over the body. Instead, *Serotonin* has a direct influence on the target tissue responsiveness as described more detailed in the Neural Sector section.

The general formulation of how responsiveness changes are reflected in the hormonal effect functions is as the following:

$$Effect\ of\ the\ Hormone = Dose\ Response\ Curve \times Responsiveness \tag{6.3}$$

$$Responsiveness = Reference\ Responsiveness \times Receptor\ Number\ Effect \tag{6.4}$$

Not only the responsiveness but also the sensitivities of the receptors are variables in our model. The sensitivity of the glucocorticoid receptors, first of all, is a function of *GR Function* which is a variable in the model. Secondly, the sensitivity of the

serotonin pre- and postreceptors are variables under the regulation of *Cortisol*. When the sensitivity of the receptors is altered, in order to shift the dose-response curve in horizontal direction, we have used varying reference values for the corresponding hormone levels, named *Shifted Reference Hormone* in the model. Then, as the input of the dose-response curves, $\frac{LOG(Hormone)}{LOG(Shifted\,Reference\,Hormone)}$ is used.

$$Shifted\,Reference\,Cortisol = Reference\,Cortisol \times GR\,Function\,Effect \tag{6.5}$$

$$Shifted\,Reference\,Serotonin = Reference\,Serotonin \times Cortisol\,Effect \tag{6.6}$$

6.1.1. Stress Sector

The structure of this sector is designed to reflect the interface of the body with its external environment. Externally created stress stimuli enter the body from here. It is first processed by the brain and the processed stress initiates a cascade of reactions in the rest of the body.

6.1.1.1. Background Information. The brief evolution and description of the stress concept was shared in Chapter 1. Things happen outside of the body and the body perceives them after processing the stimuli collected by the brain. How these stimuli are filtered and processed by the brain is a fascinating topic of cognitive science, and out of our scope and capability to involve in this study. We assume that the external stress stimulus is directly perceived as it is, and its level and duration are the only dimensions of the stimulus.

Perceived stress is relieved in time, but this relieving time is a highly complex variable since it is determined via some cognitive processes under the effect of physiological conditions. Some hormones and neurotransmitters affect the amount of time to relieve the stress, cortisol and serotonin being the mostly studied ones [2, 17]. They

enable the brain to function in a way that fastens the relieving process.

How to quantify a stress stimulus depends on its type. If it is a physiological stress, like electric shocks, then stimulus strength can be easily measured with appropriate tools. However, there is no global measure of real-life psychological stress due to its subjectivity. A given psychological stress can be unique in intensity for every individual.

Besides that, whatever the type of the stress is, it is difficult to quantify its processed version by the brain, the perceived stress. For that purpose, Visual Analogue Scales (VAS) are widely used in the literature [4,32,33]. It is a measurement instrument used in questionnaires to quantify subjective, continuous variables. The scale is kind of a ruler of 100mm, 100mm indicating the highest perceived stress level.

After being perceived, any type of stimuli has stimulatory effects on cortisol and proinflammatory cytokine secretions [2, 20, 34, 35]. This is the healthy reaction of the body due to the protective functions of these two physiological units in relation. Stimulated amounts of them, in return, have direct and indirect control over the relieving time of the perceived stress. There lays the most fundamental negative feedback control mechanism in the stress response system: perceived stress initiates reactions that will help to relieve itself in turn.

6.1.1.2. Sector Structure. The stock-flow diagram of the sector is shown in Figure 6.3. *Perceived Stress* and *Relieving Time* are the two main stock variables of the stress sector.

Perceived Stress stands for the instantaneous amount of stress felt by the brain. As mentioned before, its measurement is done by subjective techniques in literature, e.g. VAS. Inspired from this, we have defined *Perceived Stress* as a unitless variable

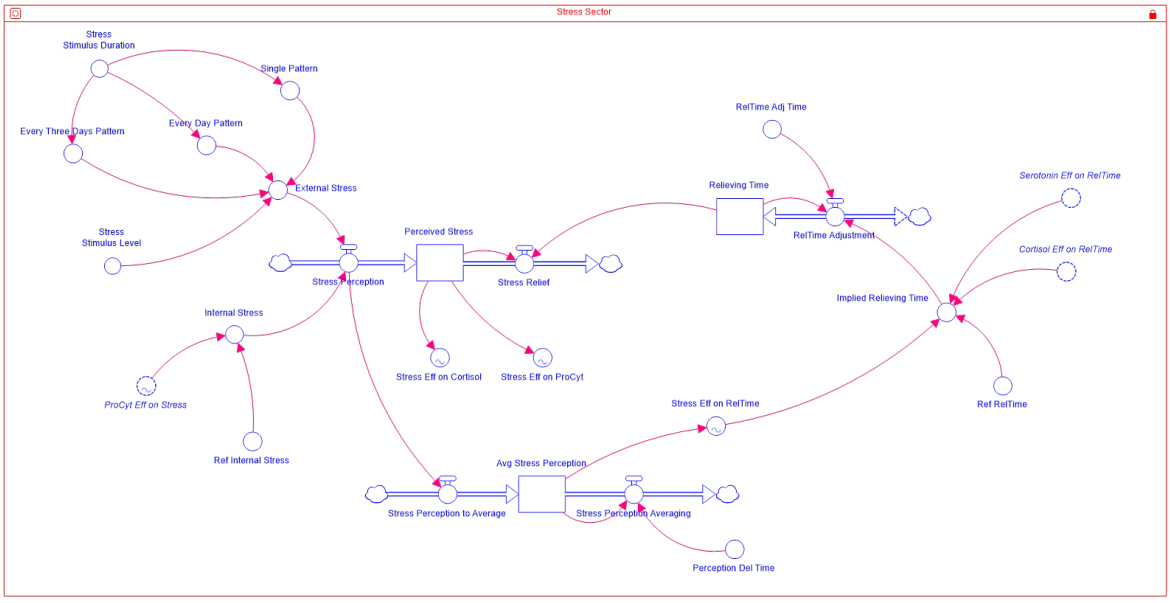


Figure 6.3. Stock-flow diagram of the stress sector.

ranging from 0 to 10 and formulated it as the following:

$$\frac{dPerceived\ Stress}{dt} = \underbrace{External\ Stress + Internal\ Stress}_{Stress\ Perception} - \underbrace{\frac{Perceived\ Stress}{Relieving\ Time}}_{Stress\ Relief} \quad (6.7)$$

Stress is fed by both externally and internally created stress stimuli. The former is given to the model with a graphical input function of time, to reflect the desired stress test. The latter (internal) form of stress is generated by *Proinflammatory Cytokine*.

$$Internal\ Stress = ProCyt\ Eff\ on\ Stress + Ref\ Internal\ Stress \quad (6.8)$$

where *ProCyt Eff on Stress* is a graphical function of $\frac{Proinflammatory\ Cytokine}{Ref\ ProCyt}$ as shown in Figure 6.15a.

Perceived Stress degrades over *Relieving Time* which keeps track of the average relieving time of the current perceived stress. *Relieving Time* is changed with an

adjustment flow as in the following equation:

$$\frac{dRelieving\,Time}{dt} = \frac{Implied\,Relieving\,Time - Relieving\,Time}{RelTime\,Adj\,Time} \tag{6.9}$$

where *Implied Relieving Time* is determined by *Cortisol*, *Serotonin*, and *Perceived Stress*:

$$Implied\,Relieving\,Time = Ref\ RelTime \times$$
$$(\underbrace{Cort\ Eff\ on\ RelTime}_{\text{Equation 6.23}} + \underbrace{Ser\ Eff\ on\ RelTime}_{\text{Equation 6.48}} + \underbrace{Stress\ Eff\ on\ RelTime}_{\text{Figure 6.4}}) \tag{6.10}$$

The graphical effect functions of *Cortisol* and *Serotonin* are going to be discussed in their own subsections, but *Stress Eff on RelTime* must be described here in detailed.

The model does not involve cognitive processes of the brain; there is no memory and no retrieval effect. Nor do we cover sociological and cultural aspects which are actually essential variables determining the effect of a certain type of stress stimulus on the stress felt by the human. Therefore, our *Perceived Stress* variable does not represent the long-lasting stress feelings of human, it is rather the accumulated perception at first encounter with the stress. In order to partially capture the long-lasting effects of stress type/source, we have taken an asymmetric average of *Stress Perception* input (see Equations 6.11 and 6.12) to use as the input of *Stress Eff on RelTime* (Figure 6.4).

$$\frac{dAvg\ Stress\ Perception}{dt} =$$
$$Stress\ Perception\ to\ Average - Stress\ Perception\ Averaging \tag{6.11}$$

where *Stress Perception to Average* is a co-flow of *Stress Perception*, and *Stress Perception Averaging* is a typical material delay output:

$$Stress\ Perception\ Averaging = \frac{Avg\ Stress\ Perception}{Perception\ Del\ Time} \tag{6.12}$$

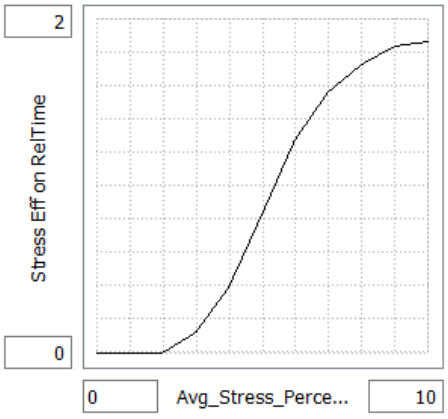
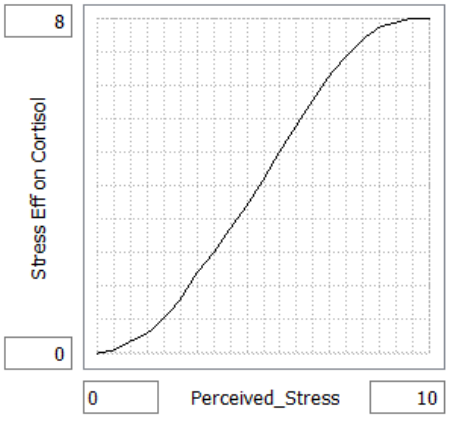
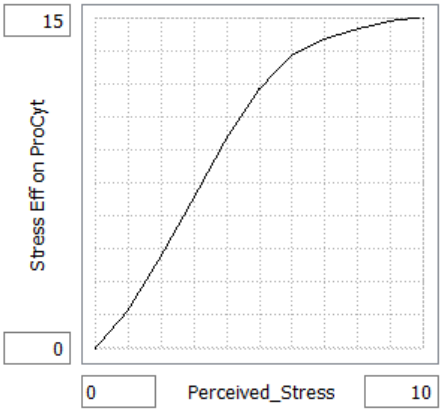


Figure 6.4. Effect of *Avg Stress Perception* on *Relieving Time*.

Perceived Stress, which is determined with the above described formulations, has influence on *Cortisol* and *Proinflammatory Cytokine* secretions. Its effects are provided to the model with the graphical functions of *Perceived Stress* as in Figures 6.5a and 6.5b.



(a) *Stress Eff on Cortisol*.



(b) *Stress Eff on ProCyt*.

Figure 6.5. Effects of *Perceived Stress* on its targets.

6.1.2. Endocrine Sector

The endocrine sector of the model is designed to represent the most fundamental strhspaceucture of the human endocrine system that has a big responsibility in stress response dynamics, the HPA axis in relation with immune and neural systems.

6.1.2.1. Background Information. The mechanism occupying the longest history of stress literature is the endocrine system, particularly the HPA (Hypothalamic-Pituitary-Adrenal) axis. The role of the endocrine system for the human body is extremely crucial since it is responsible for the regulation and coordination of multiple vital functions of the body. The tool of the endocrine system is hormones. Hormones are the messengers carrying regulatory signals of the endocrine system to the target cells. They are secreted either by glands or specialized cells (endocrine hormones), or by neurons (neuroendocrine hormones) into the blood circulation to be carried all over the body [2]. An interesting function of hormones is that they control their own secretion to keep the hormone amount in the blood in a healthy range. Thus, negative feedback control mechanisms are in the nature of hormonal systems.

There is a lock-and-key kind of mechanism between hormones and their receptors so that only specific hormones can activate specific target cells to process desired reactions [2]. The amount of hormones and receptors, and thereby the amount of activation, are sensitive variables that need to be controlled. The complex feedback nature of hormonal systems ensures a finely tuned control of the activation level. Indeed, the endocrine system constitutes of main regulatory feedback loops of all the human body. Reproduction, metabolism, development, water and electrolyte balance, and behavior are just some of the extremely vital functions of the human body that are finely regulated by the feedback loops of the hormonal mechanisms under the influence of their interactions with other chemical messenger systems [2].

The HPA axis is a three-layered substructure of the endocrine system involving a set of interactions among the hypothalamus, the pituitary gland, and the adrenal

glands. The first layer, the hypothalamus, is the signal center of the brain. It functions as a bridge between the brain and the endocrine system. According to the signals it gathers from all around the brain, it stimulates the pituitary gland via the relevant releasing factors (e.g. thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), growth-hormone-releasing hormone (GHRH)) [2].

The pituitary gland is an endocrine gland at the bottom of the brain. Its function is controlled by the hypothalamus located just above it. According to the type of the releasing factor it receives from the hypothalamus, it secretes hormones (e.g. thyroid-stimulating hormone (TSH), adrenocorticotropin (ACTH), human growth hormone (hGH)) targeting different tissues and cells [2]. One of its targets is the adrenal glands being the third layer of the HPA axis.

The adrenal glands are located over the kidneys and responsible for the secretion of epinephrine, norepinephrine, mineralocorticoid, glucocorticoid, and androgen hormones [2]. ACTH hormone secreted by the pituitary signals the adrenal glands to produce glucocorticoids, specifically cortisol hormone. The physiological functions of cortisol cause it to be called *stress hormone*.

The most fundamental role of cortisol is on metabolism regulation. Conducting the transportations of and transformations among proteins, carbohydrates and lipids, cortisol enables the body with required substrates. This feature of cortisol is the main asset of the body against stress, and it explains the relevance of the HPA axis to our context. Any type of stress stimuli triggers the HPA axis to secrete cortisol at the end [2]. Cortisol, in return, provides the body with essential energy resources to cope with stress threatening its homeostasis. Moreover, cortisol has strong anti-inflammatory effects via several pathways [2]. This role of cortisol, on the other hand, helps the body to maintain its homeostasis in case of inflammatory intruders, stress being one of them.

As expected from a hormone, cortisol controls its own secretion by inhibiting the secretion of CRH and ACTH after binding with its receptors located in the hypotha-

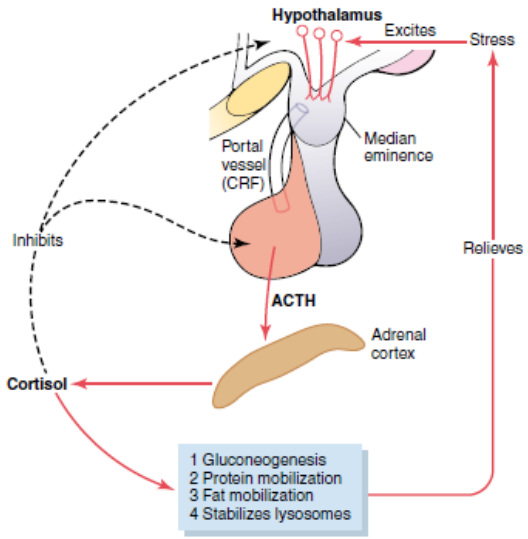


Figure 6.6. Structure of the HPA axis and its relation with stress (reproduced from [2]).

lamus and the pituitary gland, respectively. A representation of these mechanisms of the three-layered HPA axis is provided in Figure 6.6.

Cortisol flows with the blood in three forms: free, bound with proteins, and as cortisol metabolites. The free cortisol (unbound) is the active form that can directly bind with its target receptors, which is normally around 10 percent of the total plasma cortisol. This fraction is nonlinearly dependent on the total plasma cortisol amount.

In order to exert its effect, cortisol binds with its receptors located in its target cells. There are two types of receptors in the body that cortisol can bind: glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). The functions and relations that GRs are involved in the stress response are the relevant ones to our study [2], therefore, as a cortisol receptor, only GRs are involved in the model.

The number of hormone receptors are regulated by their agonists. When hormone level increases, the relevant receptor is downregulated in order to prevent the target tissues from excessive stimulation. Sensitivity of the receptors, on the other hand, is

also a variable in hormone-receptor relations. It is influenced by a number of different factors in the body. One very well acknowledged factor specifically on GR sensitivity is proinflammatory cytokines. They degenerate the structure of GRs decreasing their effectiveness to bind with their agonist, cortisol.

GRs are spread all around the body, thus, cortisol has influences on a big range of target cells. Besides its effect on stress relief, its inhibitory effect on proinflammatory cytokine secretion [2,36,37] and its regulatory effects on serotonin receptors [38,39] are the most relevant ones to our context. These causal relations are described in Chapter 5.

In summary, both physical and mental stress stimulate the HPA axis and the HPA axis, in return, triggers a cascade of reactions as a defense mechanism to cope with stress. Cortisol hormone, the product of the axis, generates the required state of the body by preparing the needed level of compounds in blood to be used as energy or to be used by other tissues. In other words, cortisol helps the body to physiologically recover from its stressful state. Thus, this mechanism includes an interesting negative feedback loop of the human body to keep its homeostasis, which should be interpreted as a product of evolution. Together with cortisol's bidirectional relations with the immune and neural systems, the HPA axis is an irrefutable part of the structure responsible for the stress response dynamics.

6.1.2.2. Sector Structure. *Cortisol*, *GR Function*, and *GR Number* are the stock variables of this sector as can be seen in Figure 6.7. They respectively stand for the average concentration of cortisol hormone in the blood plasma, average effectiveness of GR functioning, and the average number of GR binding sites per cell. Since cortisol can cross brain-blood barrier and we are interested in its actions all around the body, we have taken into account the total blood plasma concentration of cortisol. The function and number of GRs of the model are the average values for the GRs all around the body. We do not differentiate them according to their location since it does not have significance in our model boundary.

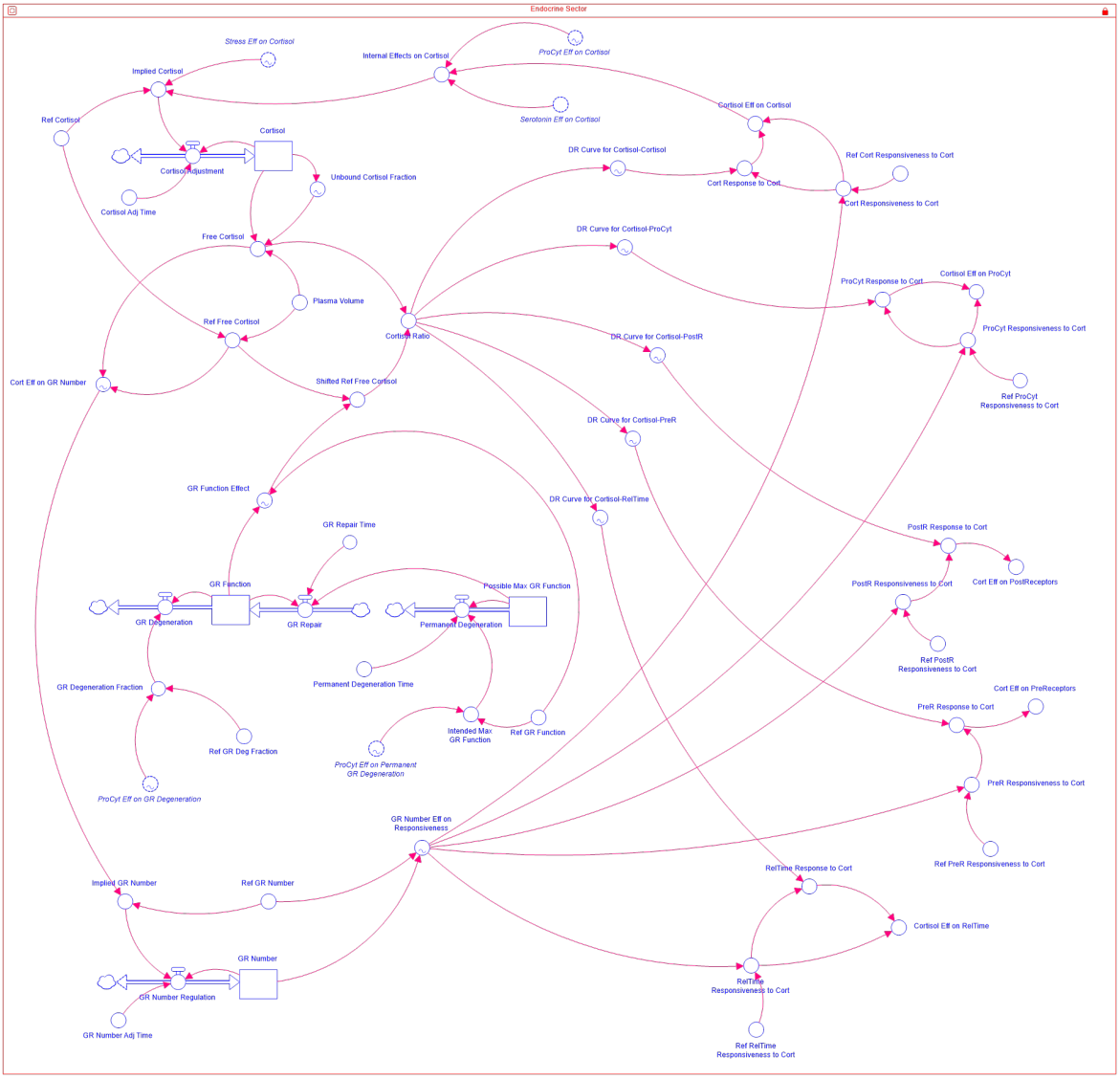


Figure 6.7. Stock-flow diagram of the endocrine sector.

Cortisol is controlled with an adjustment rate with respect to the cortisol level implied by factors effective on it (Equation 6.13). Since *Cortisol* secretion is controlled with *Perceived Stress, Cortisol, Proinflammatory Cytokine* and *Serotonin*, *Implied Cortisol* is a function of these four components (Equation 6.14).

$$\frac{dCortisol}{dt} = \frac{Implied\,Cortisol - Cortisol}{Cortisol\ Adj\ Time} \tag{6.13}$$

$$Implied\,Cort = Ref\ Cort \times (\underbrace{Stress\ Eff\ on\ Cort}_{\text{Figure 6.5a}} + Internal\ Eff\ on\ Cort) \quad (6.14)$$

where

$$Internal\ Eff\ on\ Cort = \underbrace{Cort\ Eff\ on\ Cort}_{\text{Equation 6.24}} + \underbrace{ProCyt\ Eff\ on\ Cort}_{\text{Figure 6.15b}} + \underbrace{Ser\ Eff\ on\ Cort}_{\text{Equation 6.49}} \quad (6.15)$$

While formulating the effect functions of *Cortisol* on its target variables, we have considered *Free Cortisol* variable representing the average unbound volume of the cortisol in blood plasma. It is because of the fact that only the unbound (free) cortisol can bind with its receptors. This portion of cortisol in real life is nonlinearly dependent on the total plasma cortisol amount, which is represented with a graphical function in the model (Figure 6.8).

$$Free\,Cortisol = Cortisol \times Unbound\,Cortisol\ Fraction \times Plasma\,Volume \quad (6.16)$$

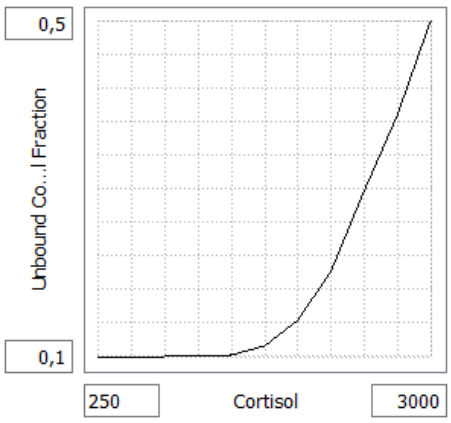


Figure 6.8. *Unbound Cortisol Fraction* function.

Furthermore, in the effect formulations of *Cortisol*, we have followed the general theories about hormone-receptor relations as described in the beginning of this section. Specifically, we have drawn s-shaped dose-response curves as a function of *Cortisol Ratio* being $\frac{LOG(Free\,Cortisol)}{LOG(Shifted\,Ref\,Free\,Cortisol)}$, where

$$Shifted\,Ref\,Free\,Cortisol = Ref\,Free\,Cort \times \underbrace{GR\,Function\,Eff}_{\text{Figure 6.13}} \tag{6.17}$$

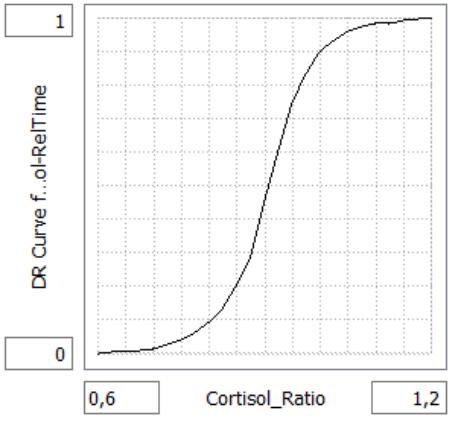
Cortisol has different influences on *Relieving Time, Cortisol, Proinflammatory Cytokine, Serotonin PreReceptors,* and *Serotonin PostReceptors.* The corresponding dose-response curves are provided in Figure 6.9.

Since the number of GRs is also a variable in the model, we have multiplied the output of dose-response curves with the variable responsiveness of the target tissues in order to find the response of the target tissue to *Cortisol.*

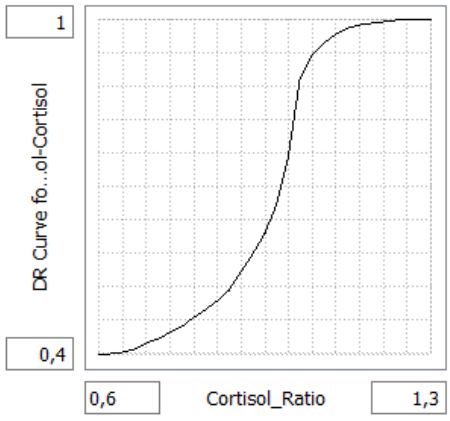
$$RelTime\,Response\,to\,Cort = DR\,Curve\,for\,CortRelTime \times RelTime\,Responsiveness\,to\,Cort \tag{6.18}$$

$$Cort\,Response\,to\,Cort = DR\,Curve\,for\,CortCort \times Cort\,Responsiveness\,to\,Cort \tag{6.19}$$

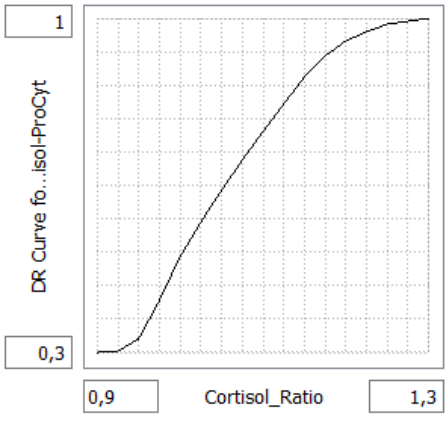
$$ProCyt\,Response\,to\,Cort = DR\,Curve\,for\,CortProCyt \times ProCyt\,Responsiveness\,to\,Cort \tag{6.20}$$



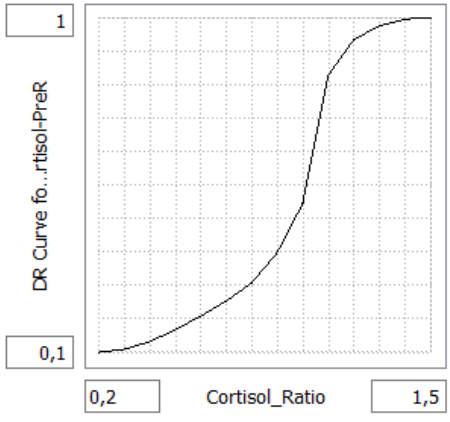
(a) *Cortisol-Relieving Time.*



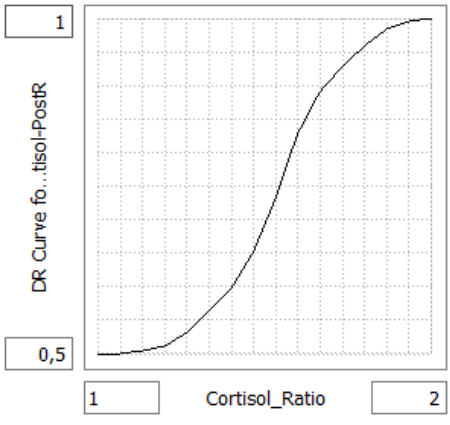
(b) *Cortisol-Cortisol.*



(c) *Cortisol-Proinflammatory Cytokine.*



(d) *Cortisol-Serotonin Prereceptors.*



(e) *Cortisol-Serotonin Postreceptors.*

Figure 6.9. Dose-response curves of *Cortisol*'s effects on its targets.

$$PreR\ Response\ to\ Cort =$$
$$DR\ Curve\ for\ CortPreR \times PreR\ Responsiveness\ to\ Cort \quad (6.21)$$

$$PostR\ Response\ to\ Cort =$$
$$DR\ Curve\ for\ CortPostR \times PostR\ Responsiveness\ to\ Cort \quad (6.22)$$

Responsiveness of the target tissues is calculated by multiplying their reference responsiveness with *GR Number Eff on Responsiveness* shown in Figure 6.10. This graphical function is drawn based on the general receptor knowledge gained from Goodman [3] as shown in Figure 6.11.

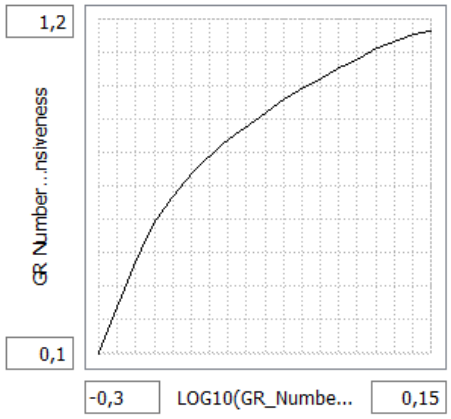


Figure 6.10. Effect of *GR Number* on responsiveness of the target tissues.

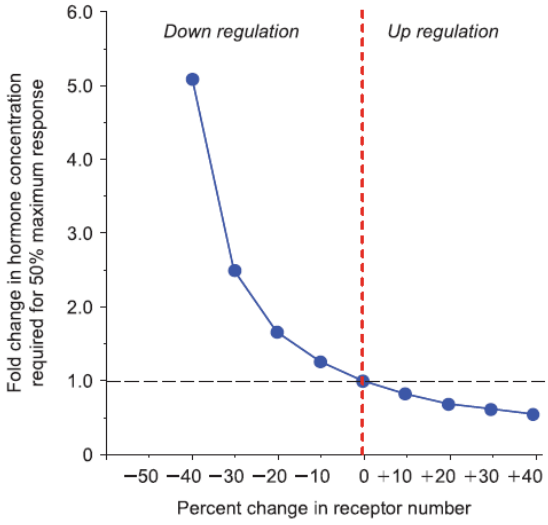


Figure 6.11. Receptor number vs. responsiveness graph provided in [3] in which abscissa is plotted on a logarithmic scale.

Although the responses of the target tissues always have positive slopes with respect to hormone amounts, *Cortisol* has inhibitory effects on some of them, specifically on *Relieving Time*, *Cortisol* itself, and *Proinflammatory Cytokine*. Considering this fact, we have formulated the ultimate effect functions of *Cortisol* on its targets with the following set of equations:

$$Cort\ Eff\ on\ RelTime = RelTime\ Responsiveness\ to\ Cort - RelTime\ Response\ to\ Cort \quad (6.23)$$

$$Cort\ Eff\ on\ Cort = Cort\ Responsiveness\ to\ Cort - Cort\ Response\ to\ Cort \quad (6.24)$$

$$Cort\ Eff\ on\ ProCyt =$$
$$ProCyt\ Responsiveness\ to\ Cort - ProCyt\ Response\ to\ Cort \quad (6.25)$$

$$Cort\ Eff\ on\ PreR = PreR\ Response\ to\ Cort \quad (6.26)$$

$$Cort\ Eff\ on\ PostR = PostR\ Response\ to\ Cort \quad (6.27)$$

The source of variability in the responsiveness of target tissues is the variable *GR Number* which is regulated by *Cortisol* via an adjustment flow.

$$\frac{dGR\ Number}{dt} = \frac{Implied\ GR\ Number - GR\ Number}{GR\ Number\ Adj\ Time} \quad (6.28)$$

where

$$Implied\ GR\ Number = \underbrace{Cort\ Eff\ on\ GR\ Number}_{\text{Figure 6.12}} \times Ref\ GR\ Number \quad (6.29)$$

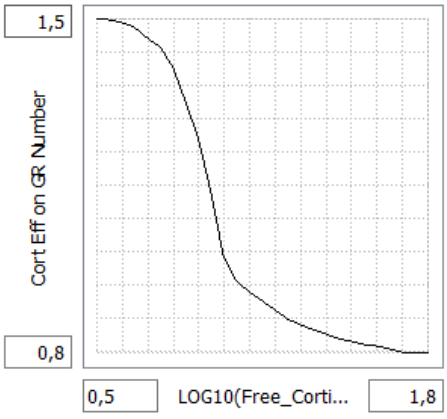


Figure 6.12. Effect of *Cortisol* on *GR Number*.

The source of variability in the effectivity of *Cortisol* on its target, on the other hand, is the sensitivity/efficiency of GRs which is measured by *GR Function*. It is subject to degenerative effects of *Proinflammatory Cytokine* and this is reflected in the outflow of *GR Function*. As in the nature of human body, GRs are repaired in time unless they are harmed permanently under the extreme amounts of *Proinflammatory Cytokine*. The inflow of *GR Function* is designed as a repair flow under the limiting effect of *Proinflammatory Cytokine*.

$$\frac{dGR\,Function}{dt} = GR\,Repair - GR\,Degeneration \tag{6.30}$$

$$GR\,Degeneration = GR\,Function \times GR\,Degeneration\,Fraction \tag{6.31}$$

where

$$GR\,Degeneration\,Fraction = \underbrace{ProCyt\,Eff\,on\,GR\,Degeneration}_{\text{Figure 6.15c}} + Ref\,GR\,Deg\,Fraction \tag{6.32}$$

and

$$GR\,Repair = \frac{Possible\,Max\,GR\,Function - GR\,Function}{GR\,Repair\,Time} \tag{6.33}$$

where *Possible Max GR Function* is controlled with an adjustment outflow:

$$\frac{dPossible\,Max\,GR\,Function}{dt} = -\frac{(Possible\,Max\,GR\,Function - Intended\,Max\,GR\,Function)}{Permanent\,Degeneration\,Time} \tag{6.34}$$

$$Intended\ Max\ GR\ Function = \underbrace{ProCyt\ Eff\ on\ \ Permanent\ GR\ Deg}_{\text{Figure 6.15e}} \times Ref\ GR\ Function \quad (6.35)$$

Consequently, *GR Function* exerts its influence on the *Shifted Ref Free Cortisol* variable with the graphical function in Figure 6.13 to shift dose-response curves through x-axis.

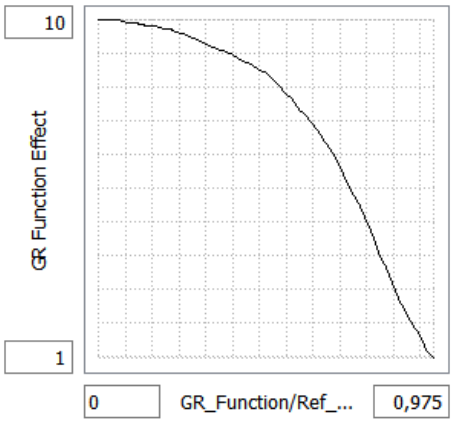


Figure 6.13. Effect of *GR Function* on *Shifted Ref Free Cortisol*.

6.1.3. Immune Sector

Immune sector of the model is a very brief picture of the most relevant parts of the immune system to stress response dynamics.

<u>6.1.3.1. Background Information.</u> The role of the immune system in stress response is played by cytokines. Cytokines are the messenger units of the immune system to coordinate the immune reactions. They are various types of small protein structures, very similar to but different than hormones, acting in a short distance from their target within a short while. They have various and varying functions depending on the target and setting in which they are activated [30, 40, 41]. Although their classification is

difficult because of this, one general category is about their role in inflammation.

Inflammation is mediated through counter regulative pro- and anti-inflammatory cytokines. Proinflammatory cytokines enhance inflammatory actions while anti-inflammatory cytokines suppress [42]. Cytokines are released when the immune system is activated due to a physical damage, an intruder, or an inflammation with any other reason. However, one of the interesting discoveries of the field is that mental stress also activates the immune system [20, 43, 44]. When stress is experienced, the autonomous nervous system is activated to prepare the body for a fight-or-flight response. Such a body state also includes increased immune system activity to fight with possible threats.

What is interesting in our context is the tight relationship of immune system with endocrine and neural systems. While stress stimulates the immune system, cortisol tries to calm it down. On the contrary, proinflammatory cytokines possess stimulating effect on the HPA axis to secrete cortisol [20, 43, 45, 46]. Thus, there is an essential negative feedback mechanism between the endocrine and immune systems in stress reactions of the body.

In the recent decades, proinflammatory cytokines are proven to be leading actors in mood disorders [20, 34, 42, 44, 47–49]. There are two fundamental reasons of the literature for claiming it. First of all, proinflammatory cytokines are found to be degenerative on glucocorticoid receptors [50, 51]. Excessive cytokine amounts harm the structure of GRs causing them to be less effective. This statement explains why both cortisol and proinflammatory cytokine levels in the blood samples of depression patients are found simultaneously high considering the above mentioned negative control mechanism between them. Secondly, proinflammatory cytokines are known to be mediators of tryptophan (TRP) conversion into some neurodegenerative factors [20, 52–54]. Since TRP is a precursor of serotonin, this creates a limiting effect on serotonin metabolism, which is strongly related with mood disorders considering the role of serotonin in mood, as explained in the following neural sector subsection.

One more thing to mention about proinflammatory cytokines is their direct effect on mood. People with infectious diseases, e.g. influenza, exhibit depressive-like symptoms like fatigue, lowered mood, loss of appetite, called *sickness behavior* [52,55]. Although such behavioral state does not mean to be a mood disorder, sickness behavior carries a risk factor for depression especially in vulnerable bodies.

6.1.3.2. Sector Structure. There are several subtypes of proinflammatory cytokines. Since it is the most studied type in the context of stress response in relation with cortisol and serotonin, we have chosen interleukin-6 (IL-6) as our actor while formulating proinflammatory cytokines in the model.

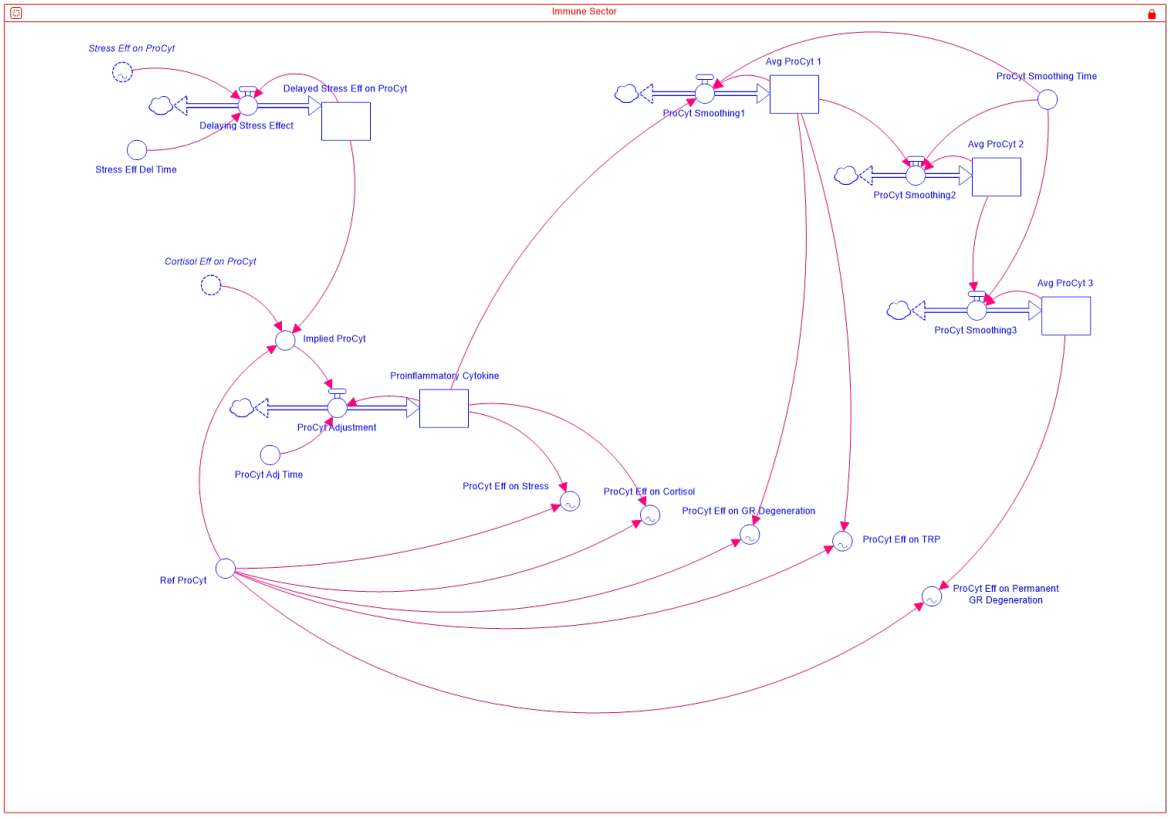


Figure 6.14. Stock-flow diagram of the immune sector.

Proinflammatory Cytokine is the main stock variable of the immune sector standing for the average interleukin-6 concentration in the blood. Since cytokines can cross

brain-blood barrier, we trace its concentration in the blood. This stock is controlled with an adjustment flow to keep it in its desired level determined by *Perceived Stress* and *Cortisol*. The stock-flow diagram of this sector is given in Figure 6.14.

$$\frac{dProCyt}{dt} = \frac{Implied\ ProCyt - ProCyt}{ProCyt\ Adj\ Time} \tag{6.36}$$

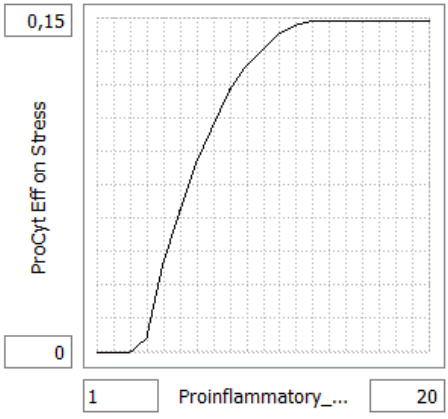
$$Implied\ ProCyt = \\ Ref\ ProCyt \times (\underbrace{Cort\ Eff\ on\ ProCyt}_{\text{Equation 6.25}} + Delayed\ Stress\ Eff\ on\ ProCyt) \tag{6.37}$$

where *Delayed Stress Eff on ProCyt* is the value of *Stress Eff on ProCyt* (Figure 6.5b) after a time delay. In order to capture the real-life dynamics of proinflammatory cytokines, we have modeled the effect of *Perceived Stress* on *Proinflammatory Cytokine* secretion with a first order delay structure as can be seen in Figure 6.14.

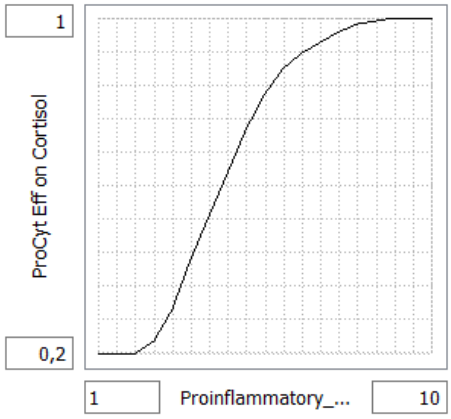
Proinflammatory Cytokine calculated under the effects of other variables exerts its influence on its target tissues with varying time scales. While its effects on *Perceived Stress* and *Cortisol* are observed within a short time period, its effects on *GR Degeneration* and *TRP* are exerted relatively slower. That is why we have modeled the latter effects with a first order delay structure unlike the former ones.

The faster effects are modeled by the graphical functions of $\frac{Proinflammatory\ Cytokine}{Ref\ ProCyt}$ as shown in Figure 6.15a and 6.15b, and the slower effects are modeled by the graphical functions of $\frac{Avg\ ProCyt\ 1}{Ref\ ProCyt}$ as shown in Figure 6.15c and 6.15d.

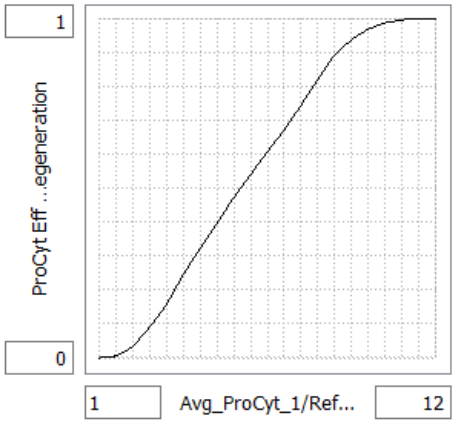
Permanent degeneration of GRs is also modeled as a cause of *Proinflammatory Cytokine* as discussed in the section for endocrine sector. However, such a structural change occurs only under intensive amount of proinflammatory cytokines. Therefore, we have modeled this long-term effect with a third order delay structure in order to utilize the smoothed (averaged) amount of *Proinflammatory Cytokine* in this formulation. The graphical effect function is drawn as in 6.15e and its input is $\frac{Avg\ ProCyt\ 3}{Ref\ ProCyt}$.



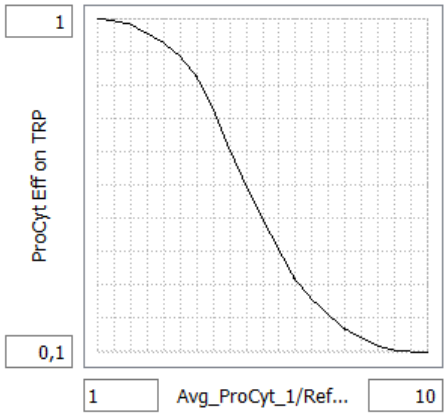
(a) *ProCyt Eff on Stress.*



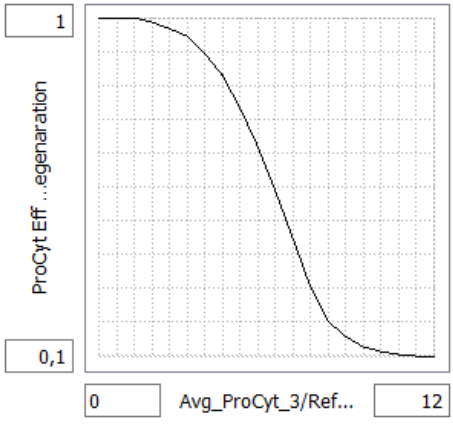
(b) *ProCyt Eff on Cortisol.*



(c) *ProCyt Eff on GR Degeneration.*



(d) *ProCyt Eff on TRP.*



(e) *ProCyt Eff on Permanent GR Degeneration.*

Figure 6.15. Effects of *Proinflammatory Cytokine* on its targets.

6.1.4. Neural Sector

Neural sector of the model sketches the most relevant parts of the neural system for the stress response dynamics.

6.1.4.1. Background Information. Neurotransmitters are the third type of messengers that play a major role in the stress response besides, but in relation with, hormones and cytokines. They are released from the axon terminals of neurons into the synaptic clefts to bind with their receptors located on the target cells. Their function is to transmit signals from one neuron (presynaptic neuron) to another (postsynaptic neuron).

Neurotransmitters can be classified according to their structure mainly as amino acids, peptides, and monoamines. Due to their functions, monoamine transmitters have been central to the studies on mood disorders. Norepinephrine, epinephrine, dopamine, serotonin, and histamine are the main monoamines [2]. Their common task is to regulate mood, emotion and cognitive functioning, keeping in mind that all have other unique roles as well [17].

In terms of their location, neurotransmitter receptors are classified into two: prepreceptors and postreceptors. The former are located in the presynaptic neurons, and is activated when bound with its agonist, as usual. The corresponding biological response of a prereceptor is to inhibit the neuron's action to keep the neurotransmitter amount in the clefts around a desired level. This is being one of the natural negative feedback control mechanisms of the body. Postreceptors are located in the postsynapses of the target, to receive the message and act as wished.

Not only the location of the postreceptors, but also their type is decisive in the function of serotonin. There are 14 types of serotonin receptors. Considering the pertinent functions and relations of serotonin to the stress response dynamics, we have chosen the corresponding receptor type, $5HT_{1A}$, to model. Thus, wherever serotonin receptors are mentioned in our context, $5HT_{1A}$ type is meant.

Up- and downregulation of receptors with respect to the concentration of their agonists has been introduced in the earlier sections. The same phenomenon is also valid for serotonin receptors [3]. Besides that, sensitivity alterations of receptors is also a matter of serotonin receptors and cortisol is alleged to be responsible for that [38,39].

There are two underlying functions of serotonin in relation with the stress response. Maybe as the most popular knowledge about neurotransmitters, serotonin has a direct influence on mood [2,17]. Its stimulating effect on the HPA axis via its postreceptors located on the hypothalamus adds one more bidirectional relationship to our context [38,56].

6.1.4.2. Sector Structure. The stock-flow diagram of the sector is shown in Figure 6.16. *Serotonin* is the only stock variable of the sector which stands for the average serotonin concentration in the cerebrospinal fluid (CSF).

Although serotonin is spread all around the body, our serotonin variable in the model represents the serotonin concentration of the CSF, which is the fluid carried inside the brain and spinal cord. It is because the functions of serotonin in the brain are the relevant ones to the problem of interest, and serotonin cannot cross brain-blood barrier. In addition, what we mean by serotonin in the model is the free serotonin that is available to bind with its receptors. It is controlled with the following adjustment rate:

$$\frac{dSerotonin}{dt} = \frac{Possible\ Implied\ Serotonin - Serotonin}{Serotonin\ Adj\ Time} \tag{6.38}$$

Possible Implied Serotonin stands for the amount of serotonin that is desired in the synaptic clefts by its prereceptors but under the capacity effect of tryptophan (TRP). We have formulated such a capacity effect with a fuzzy minimum formulation

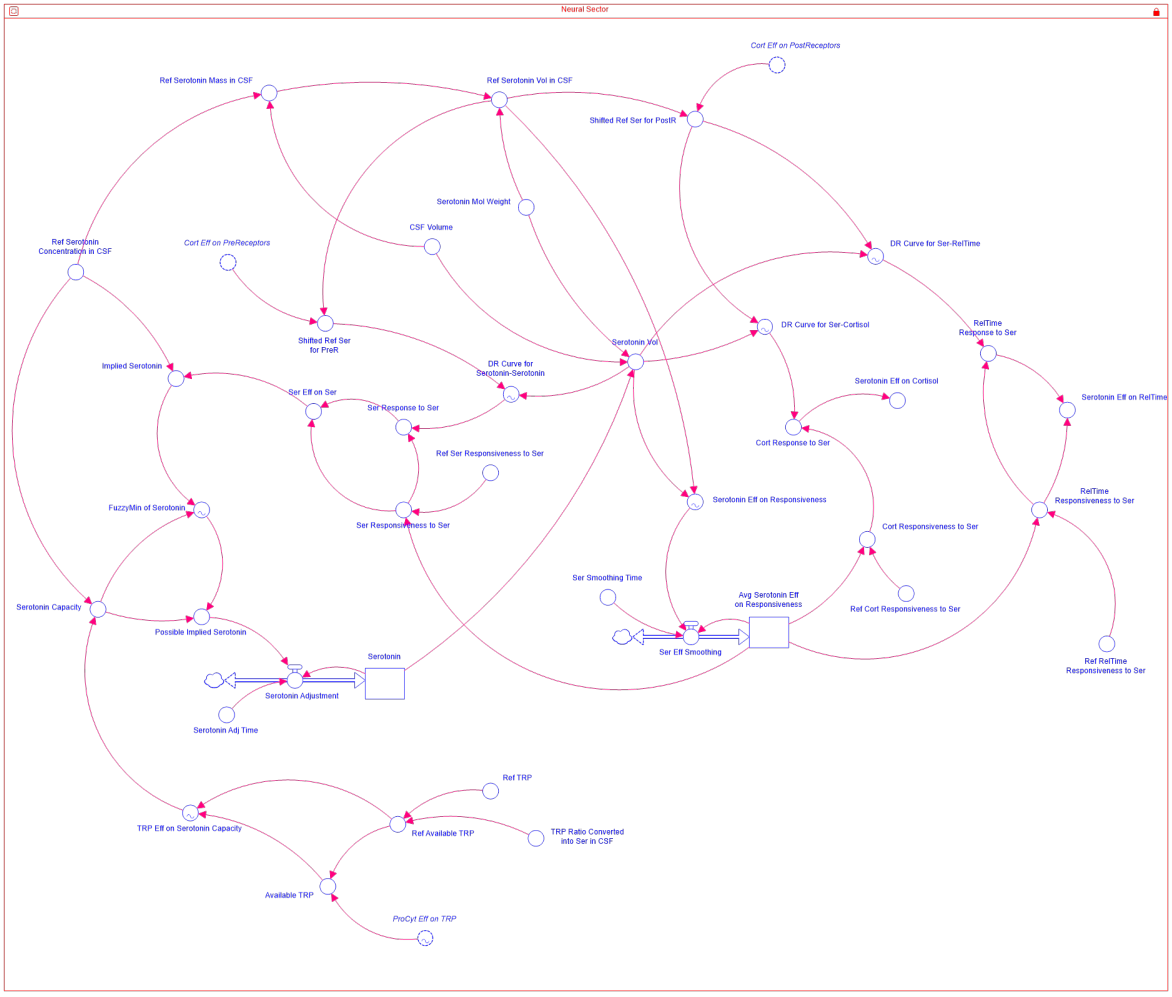


Figure 6.16. Stock-flow diagram of the neural sector.

for the sake of validity, as the following:

$$Possible\ Implied\ Serotonin = Fuzzy\ Min\ of\ Serotonin \times \underbrace{Serotonin\ Capacity}_{\text{Equation 6.40}} \tag{6.39}$$

where *Fuzzy Min of Serotonin* is a graphical function of $\frac{Implied\ Serotonin}{Serotonin\ Capacity}$ as in Figure 6.17.

As aforementioned, TRP is a precursor of serotonin meaning that serotonin is produced using available TRP. Thus, *Available TRP* has a positive effect on *Serotonin*

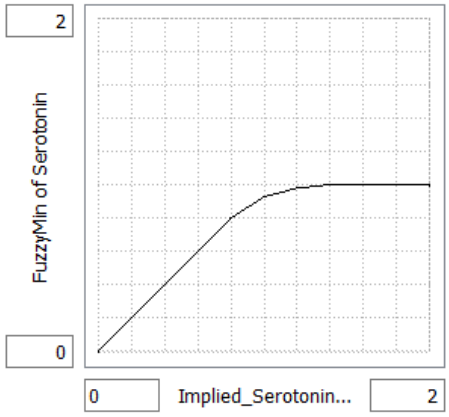


Figure 6.17. *Fuzzy Min of Serotonin* function.

Capacity via a nonlinear graphical function of $\frac{Available\,TRP}{Ref\ Available\,TRP}$ (Figure 6.18).

$$Serotonin\,Capacity = Ref\ Serotonin \times TRP\ Eff\ on\ Serotonin\,Capacity \quad (6.40)$$

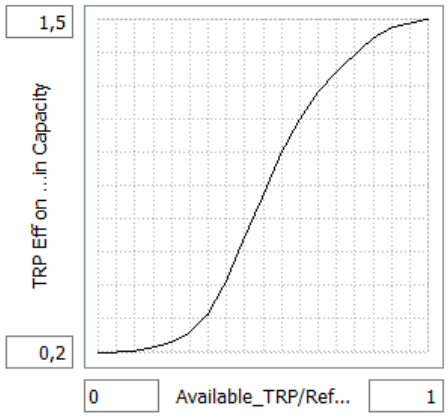


Figure 6.18. Effect of *TRP* on *Serotonin Capacity*.

Implied Serotonin, on the other hand, is independent from the capacity to produce *Serotonin*. As described earlier, serotonin level in synaptic clefts is controlled by its prereceptors with respect to the serotonin amount itself. *Implied Serotonin* keeps track of the amount implied by the current serotonin level via its prereceptors, as the

following:

$$Implied\ Serotonin = Ref\ Serotonin \times \underbrace{Ser\ Eff\ on\ Ser}_{\text{Equation 6.47}} \tag{6.41}$$

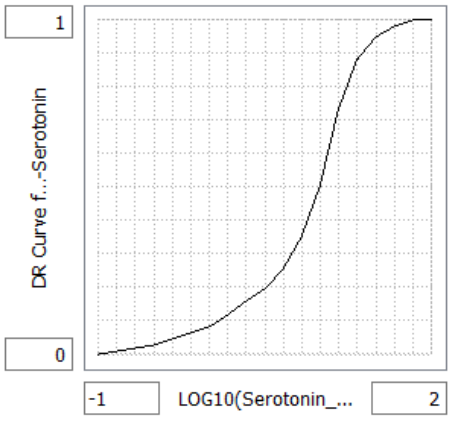
Serotonin exerts its effect on its target tissues via its postreceptors following aforementioned hormone-receptor relations. Both sensitivity and responsiveness of serotonin receptors are variables in the model and that is reflected in the dose-response curves of *Serotonin* with the same manner as of *Cortisol*.

Sensitivity of the receptors is affected by *Cortisol* via *Cortisol Effect on Prereceptors* (Equation 6.26), and *Cortisol Effect on PostReceptors* (Equation 6.27) respectively on *Shifted Reference Serotonin for PreReceptors*, and *Shifted Reference Serotonin for PostReceptors*. Thus, dose-response curves of *Serotonin* are drawn as a function of $\frac{LOG(Serotonin)}{LOG(Shifted\ Ref\ Ser\ for\ PreR)}$ and $\frac{LOG(Serotonin)}{LOG(Shifted\ Ref\ Ser\ for\ PostR)}$, for its actions exerted respectively via prereceptors and postreceptors.

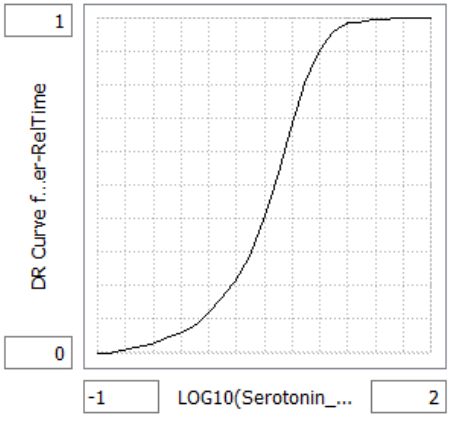
$$Shifted\ Ref\ Ser\ for\ PreR = Ref\ Ser \times \underbrace{Cort\ Eff\ on\ PreReceptors}_{\text{Equation 6.26}} \tag{6.42}$$

$$Shifted\ Ref\ Ser\ for\ PostR = Ref\ Ser \times \underbrace{Cort\ Eff\ on\ PostReceptors}_{\text{Equation 6.27}} \tag{6.43}$$

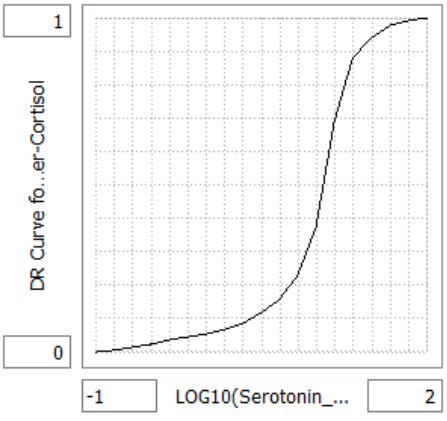
Serotonin bound with prereceptors controls its level with an inhibitive effect. If it is bound with postreceptors, it has a decreasing effect on *Perceived Stress* which is modeled as a decreasing effect on its *Relieving Time*. And, it has a stimulatory effect on *Cortisol* secretion. The effects *Serotonin* with its receptors follow the dose-response curves depicted in Figure 6.19.



(a) *Serotonin-Serotonin.*



(b) *Serotonin-Relieving Time.*



(c) *Serotonin-Cortisol.*

Figure 6.19. Dose-response curves of *Serotonin*'s effects on its targets.

Since responsiveness of both receptors are variables as well, we have multiplied the output of dose-response curves with the variable responsiveness of the corresponding target.

$$Ser\ Response\ to\ Ser = DR\ Curve\ for\ SerSer \times Ser\ Responsiveness\ to\ Ser \quad (6.44)$$

$$Cort\ Response\ to\ Ser = DR\ Curve\ for\ SerCort \times Cort\ Responsiveness\ to\ Ser \quad (6.45)$$

$$RelTime\ Response\ to\ Ser = DR\ Curve\ for\ SerRelTime \times RelTime\ Responsiveness\ to\ Ser \quad (6.46)$$

Responsiveness of the target tissues is calculated by multiplying their reference responsiveness with the *Avg Serotonin Eff on Responsiveness*, which is the average of *Serotonin Eff on Responsiveness* shared in Figure 6.20.

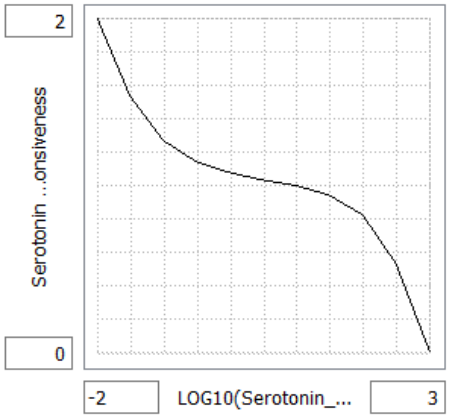


Figure 6.20. Effect of *Serotonin* on responsiveness of the target tissues.

Because of the inhibitory effect of *Serotonin* on *Serotonin* and *Relieving Time*, the outputs of the corresponding dose-response curves are subtracted from their own maximum values to reverse the effect direction. The ultimate effects of *Serotonin* are calculated as in the following formulas.

$$Ser\ Eff\ on\ Ser = Ser\ Responsiveness\ to\ Ser - Ser\ Response\ to\ Ser \quad (6.47)$$

$$Ser\ Eff\ on\ RelTime =$$
$$RelTime\ Responsiveness\ to\ Ser - RelTime\ Response\ to\ Ser \quad (6.48)$$

$$Ser\ Eff\ on\ Cort = Cort\ Response\ to\ Ser \quad (6.49)$$

As a summary of this chapter, a simplified stock-flow diagram of the model including the interactions between all sectors discussed in this chapter is presented below in Figure 6.21.

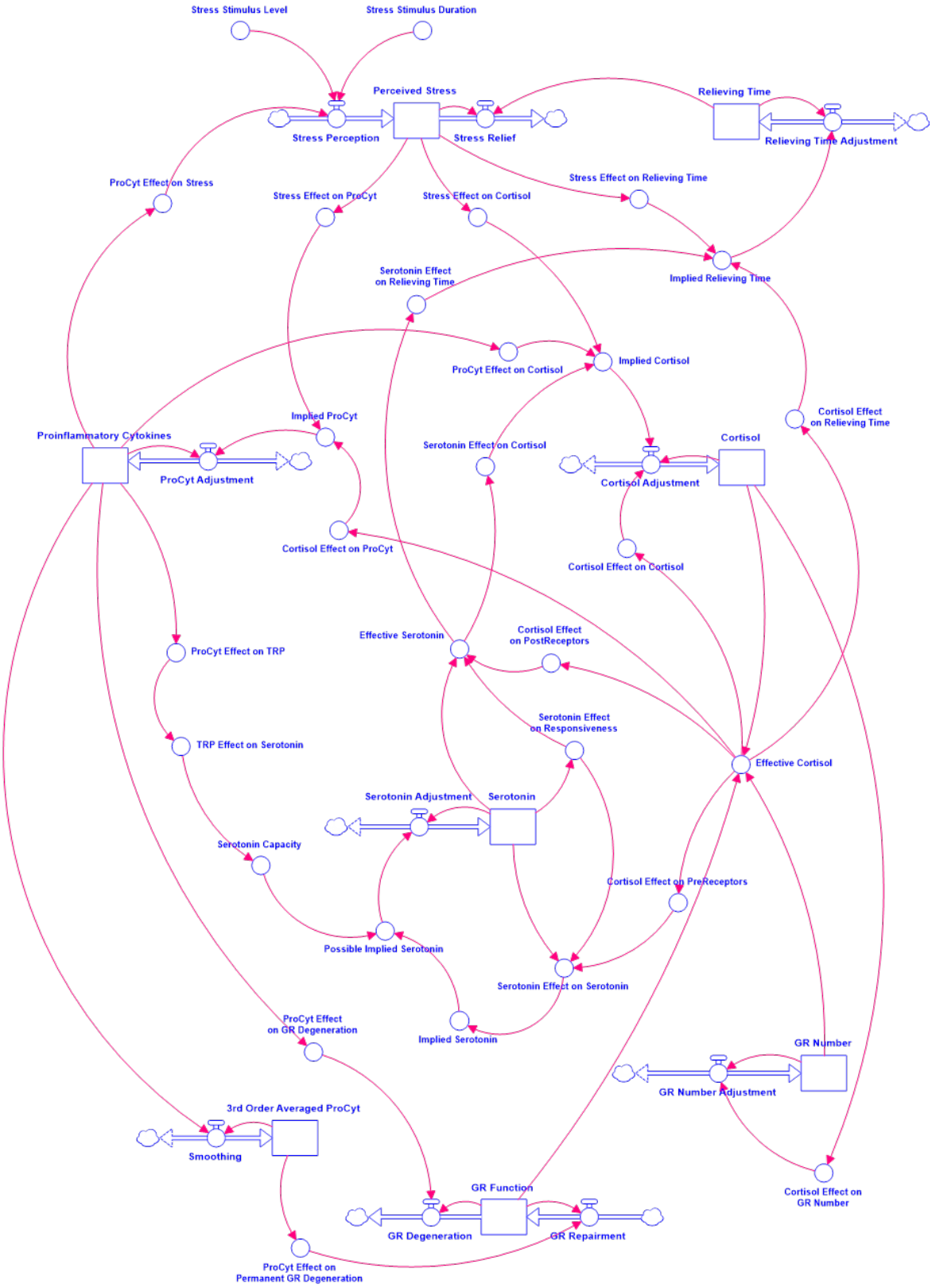


Figure 6.21. Simplified stock-flow diagram of the complete model.

7. MODEL BEHAVIOR AND VALIDATION

The model is simulated by Stella Architect software, version 1.5.1. The simulation time unit and time step are chosen as one hour and 1/128 hour, respectively.

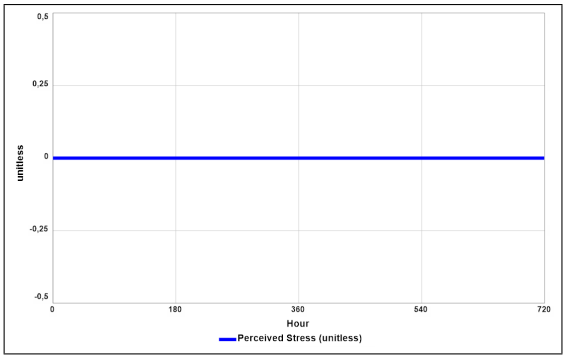
Throughout the modeling process, the parameter values and effect functions are set consistent with the medical literature. The units of the variables are chosen carefully, and the unit consistency holds as can be seen in the model equations shared in Appendix A. The ranges of the graphical functions are determined to be under control and tested at extremes. The model is structurally and behaviorally validated by testing under different conditions, as will be shared in this section.

Stress is the intruder of this system. We have run our model under five different settings of the stress input externally given to the model. All initial values are set to the reference values of the corresponding variable, which are the normal values found in a healthy body. Thus, the model is initialized as a healthy body.

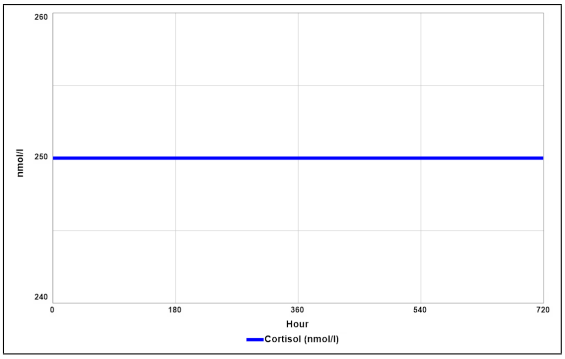
7.1. Equilibrium Run

Since we have modeled a healthy body, we expect it to stay in its equilibrium, homeostasis, if there is nothing perturbing the body. We tested this ideal/hypothetical condition by giving zero level of stress and observed the behaviors as in Figure 7.1.

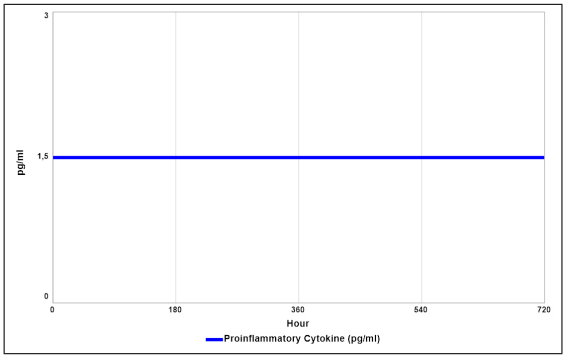
As expected, the variables stay constant, in their healthy equilibrium levels, when there is no stress input at all.



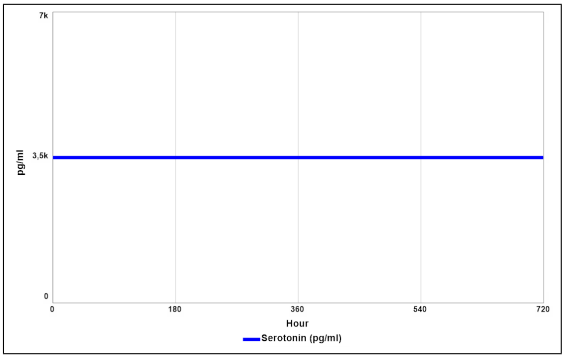
(a) *Perceived Stress.*



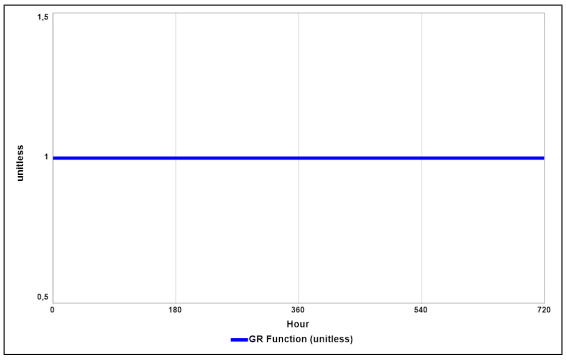
(b) *Cortisol.*



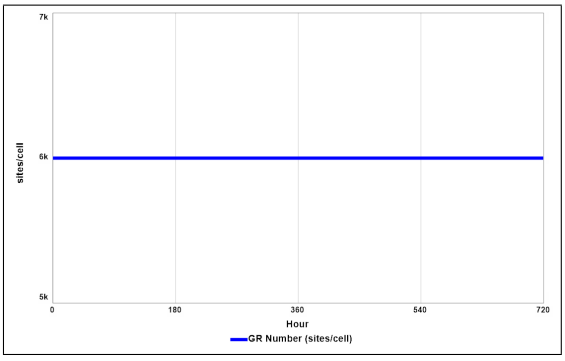
(c) *Proinflammatory Cytokine.*



(d) *Serotonin.*



(e) *GR Function.*



(f) *GR Number.*

Figure 7.1. Equilibrium behaviors of the major variables in reference conditions (no stress).

7.2. Trier Social Stress Test (TSST) Run (Base Run)

Trier Social Stress Test (TSST) is a protocol to induce a reasonable stress level in human participants in laboratory conditions. The procedure is introduced by Kirschbaum and colleagues [57] to be used as an instrument in psychobiological research. Following studies have also confirmed the reliability and validity of the procedure. Briefly, the procedure is composed of a prior 10-minute expectancy period and a 10- to 15-minute interview period in which participants perform free speech and mental arithmetic tasks in front of an audience.

In literature, TSST is usually utilized in experiments to compare the stress responses of people of different conditions. Examples include the studies comparing people from different ages [5], adults with childhood abuse [58], and so on.

Using the research, we have imitated the TSST settings in our model as our base run. Although we do not know the quantitative amount of stress exerted on the body by TSST, we have deduced it using the level of perceived stress it creates. Childs *et al.* [4], and Hellhammer *et al.* [33] have measured perceived stress levels of subjects before and just after the procedure, using Visual Analogue Scale (VAS) of 100 mm. There seems to be 20-30 mm perceived stress difference from the baseline just after the procedure, which is 2-3 over the range of 10 in our model. We have set the stress level of TSST procedure used in the model to 12 (per hour), the amount of stress that creates a 2.4 units increase in the *Perceived Stress* in 12 minutes.

In sum, we have given a 12-minute stress stimulus in the strength of 12 to the body to imitate the TSST procedure. The stress inflow is shown in Figure 7.2.

The behavior dynamics of *Perceived Stress*, *Cortisol*, and *Proinflammatory Cytokine* variables all fit well the real data gathered in TSST studies as shown in Figures 7.3, 7.4, and 7.5.

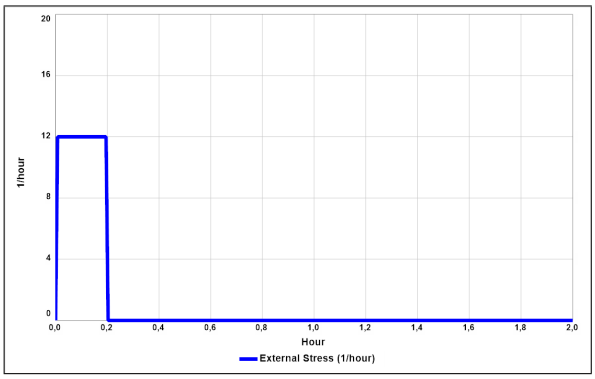
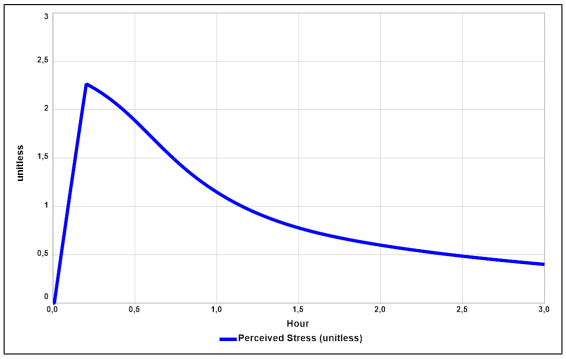
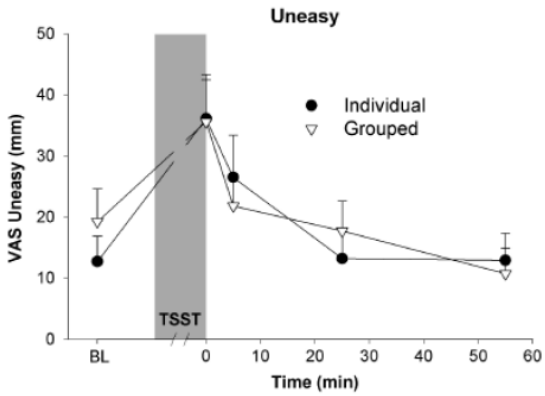


Figure 7.2. External stress input given to the model in TSST run.



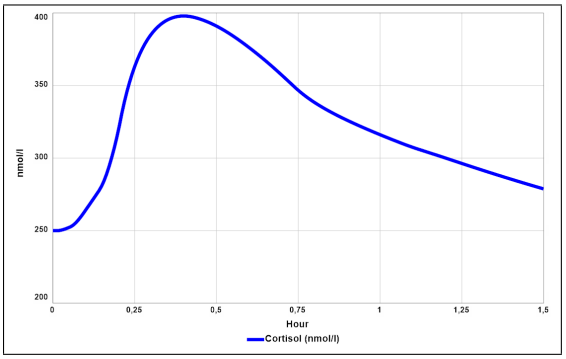
(a) *Perceived Stress* behavior in TSST run.



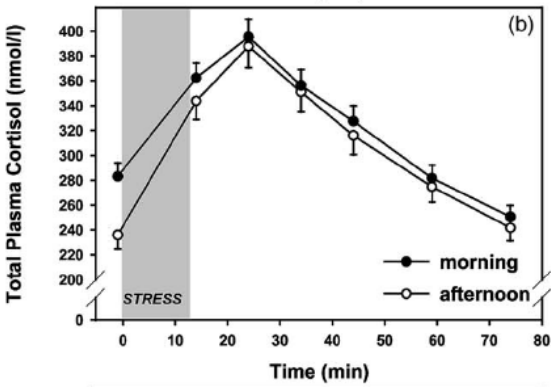
(b) Experimental uneasiness data of [4].

Figure 7.3. (*a*) *Perceived Stress* behavior in TSST run vs. (*b*) relevant experimental data retrieved from [4].

The dynamics of the other major variables of the model, *Serotonin, GR Function* and *GR Number*, are shown in Figures 7.6, 7.7 and 7.8. Although they could not be validated with time-series data because of its unavailability, they show reasonable behavior patterns according to literature. They all come back to their healthy steady-state levels after varying time horizons. Slower speed of the *GR Function* is an expected part of the stress response of the body as emphasized in the long-lasting sensitivity hypothesis studied by Koolhaas *et al.* [59], and Tilders *et al.* [7]. They emphasize that the time course of the consequences of stressors may vary in range from hours to weeks.

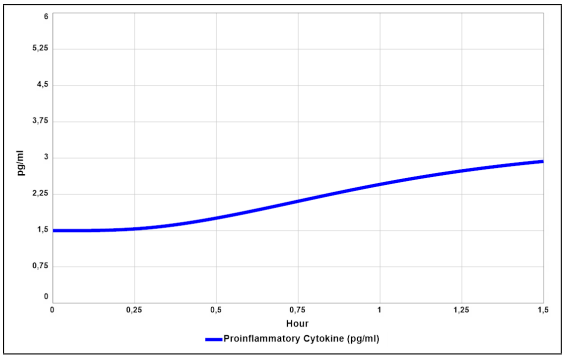


(a) *Cortisol* behavior in TSST run.

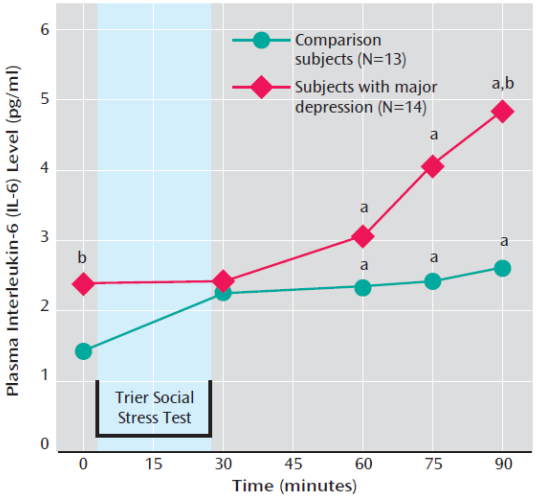


(b) Experimental cortisol data of [5].

Figure 7.4. (*a*) *Cortisol* behavior in TSST run vs. (*b*) relevant experimental data retrieved from [5].



(a) *Proinflammatory Cytokine* behavior in TSST run.



(b) Experimental interleukin-6 data of [6].

Figure 7.5. (*a*) *Proinflammatory Cytokine* behavior in TSST run vs. (*b*) relevant experimental data retrieved from [6].

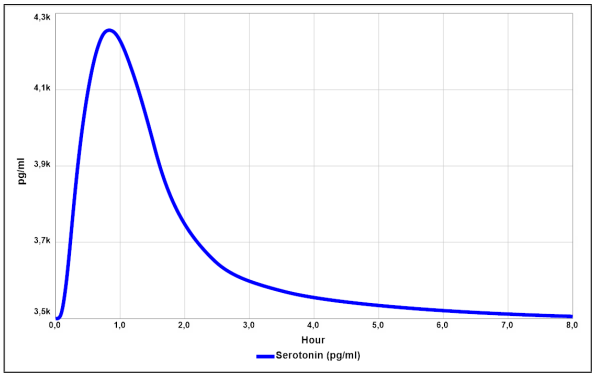


Figure 7.6. *Serotonin* behavior in TSST run.

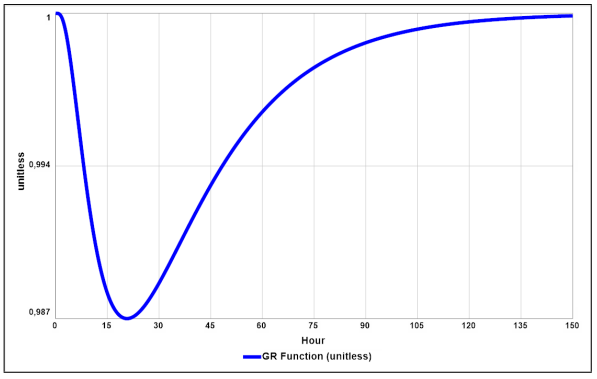


Figure 7.7. *GR Function* behavior in TSST run.

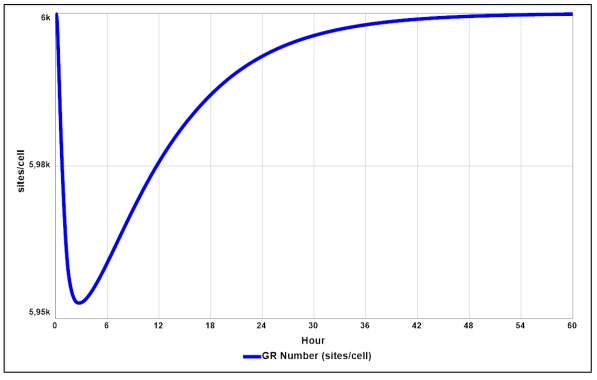


Figure 7.8. *GR Number* behavior in TSST run.

7.3. Repetitive Stress Runs

In order to validate our model with some acknowledged hypotheses about the effects of repetitive stress on the body, we have tested our model applying repetitive stress of different frequencies on the system. We used a stress stimulus of the same strength as in TSST run, 12 (per hour) that is given once in three days for 30 days, and once in a day for 10 days in two different scenarios. Thus, both scenarios include the same number of stress inputs, but with different frequencies.

7.3.1. One Stress Input Every Three Days

The external stress input used in this run is shown in Figure 7.9, and the corresponding behaviors of the representative variables are depicted in Figures 7.10-7.13. The y-axes of output graphs are scaled wider than required to make their comparison with One Stress Input Every Day (1S1D) run results convenient.

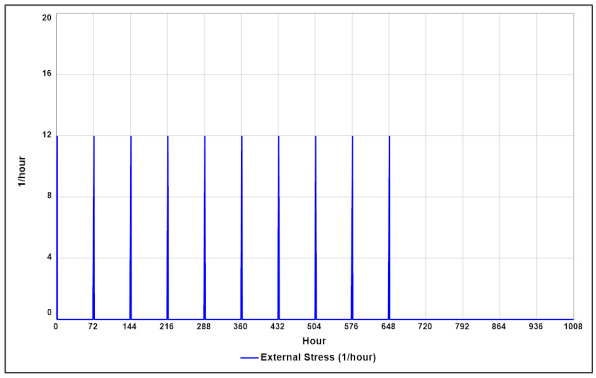


Figure 7.9. External stress input given to the model in One Stress Input Every Three Days (1S3D) run.

Chronic mild stress stimulating a body every three days does not create a different reaction than single mild stress situation (TSST run). The body consistently gives the same reaction to every single stimulus, which does not create an observable allostatic load on the body. Hormonal measures seem to come back to their healthy steady-state

values as in the initial condition.

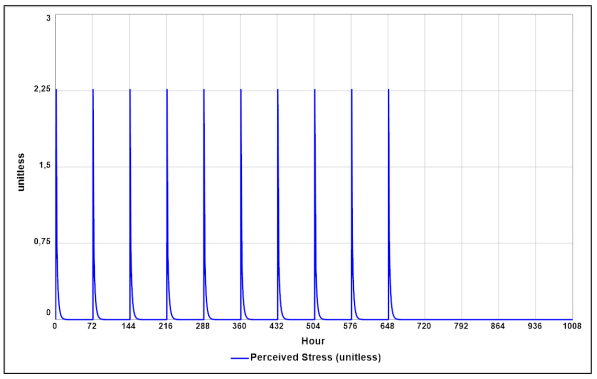


Figure 7.10. *Perceived Stress* behavior in 1S3D run.

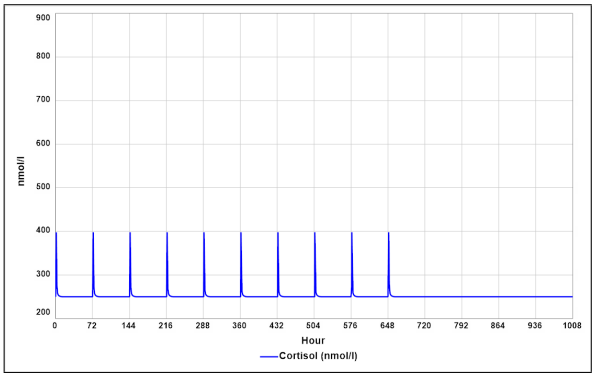


Figure 7.11. *Cortisol* behavior in 1S3D run.

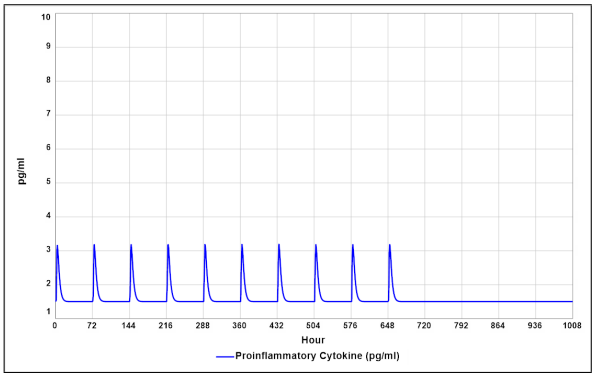


Figure 7.12. *Proinflammatory Cytokine* behavior in 1S3D run.

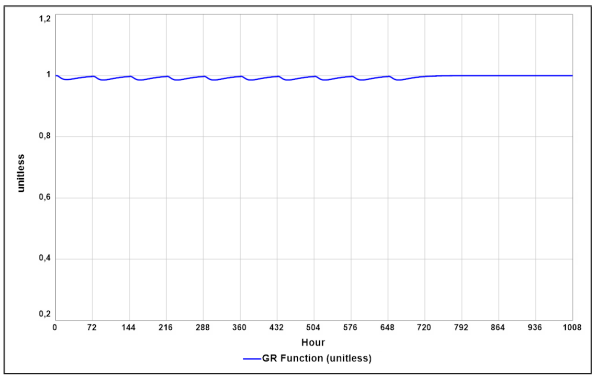


Figure 7.13. *GR Function* behavior in 1S3D run.

7.3.2. One Stress Input Every Day

The external stress input used in this run is shown in Figure 7.14, and the corresponding behavior of the representative variables are depicted in Figures 7.15-7.18.

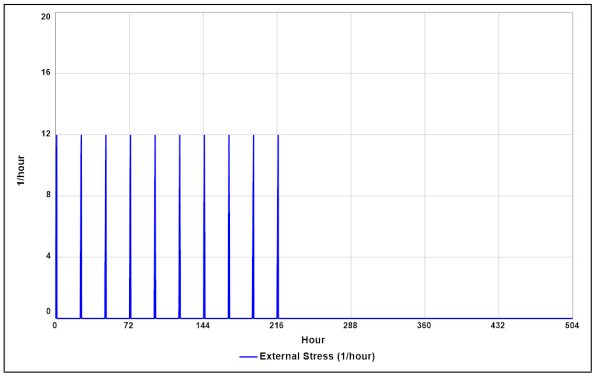


Figure 7.14. External stress input given to the model in One Stress Input Every Day (1S1D) run.

The model exhibits a clear threshold behavior for frequent stressors. All the model variables first show an allostasis behavior that is successfully calmed down until the next stressor. However, after a point, they all show growing reactions to a single stressor, and it takes exponentially longer to calm down the reactions. Moreover, hormonal

measures do not come back to their healthy levels but find a different steady-state than healthy homeostasis. We cannot claim that the body will stay in this new state forever, but the scope and time horizon of our model do not allow us to foresee longer-term dynamics. There might be other physiological processes repairing the disturbed body in a longer time, with more structural mechanisms involved.

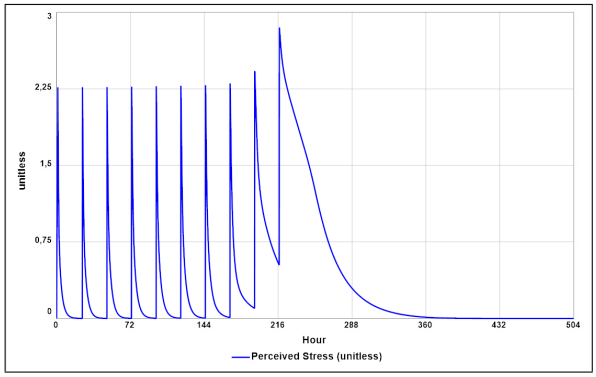


Figure 7.15. *Perceived Stress* behavior in 1S1D run.

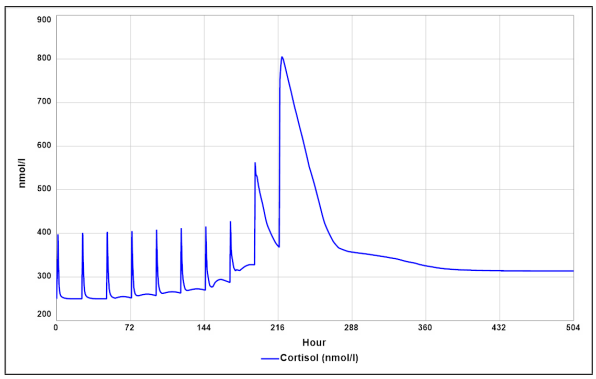


Figure 7.16. *Cortisol* behavior in 1S1D run.

As can be clearly seen in the comparable run results with different stress frequencies, when the frequency of the same stress stimulus is higher, the body loses its capability to handle stress in a nonlinear fashion. This phenomenon is conceptualized and introduced to the field as allostatic load by Bruce S. McEwen [11,12], as mentioned in Chapter 1. Our model results serve as a concrete demonstration of the concept. In our case, the accumulating load on the glucocorticoid receptors leading to a permanent degeneration seems to be main responsible actor of such dynamics.

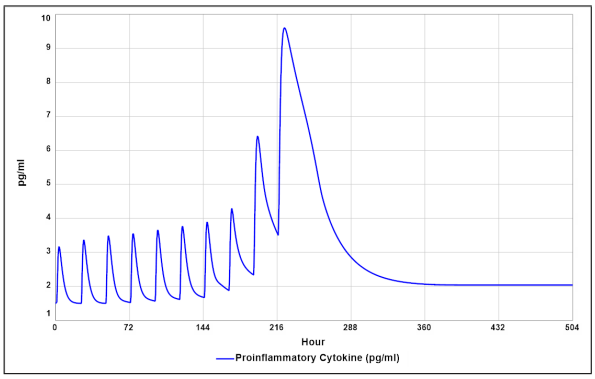


Figure 7.17. *Proinflammatory Cytokine* behavior in 1S1D run.

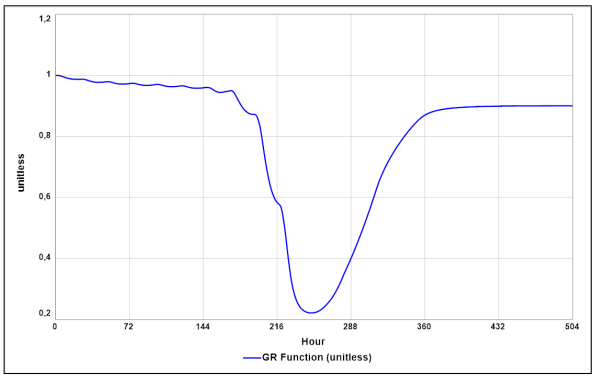


Figure 7.18. *GR Function* behavior in 1S1D run.

Another important hypothetical discussion of the phenomenon is presented to literature by Tilders and colleagues [7]. They hypothesize that HPA axis hyperactivity results in sensitivity to stressors, that, in turn, elevates HPA axis activity even more. Thus, the vulnerable period to stress is in a reinforcing feedback loop with the HPA axis activity due to a retarded feedback mechanism. Their hypothetical stress response dynamics under repetitive stress stimuli is presented in Figure 7.19. Such conceptual dynamics is illustrated in our model behavior. And in our case, negative feedback mechanisms seem to be retarded because of deficient glucocorticoid receptors.

From this point, we can conclude that our model is capable of reproducing expected stress response dynamics under mild-single and mild-repetitive stressful conditions. The model includes the threshold structure that is embedded in the nature

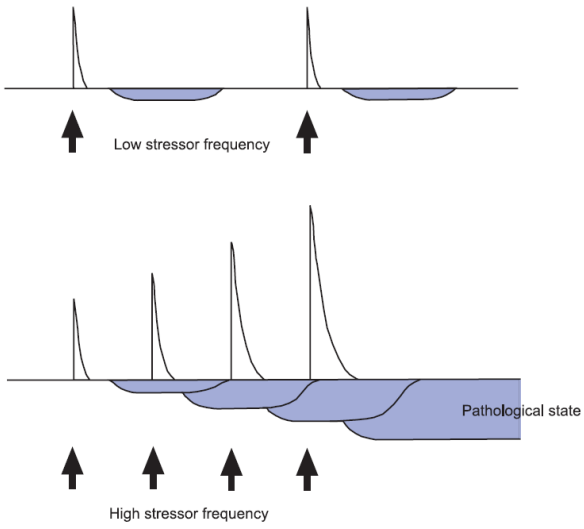


Figure 7.19. Conceptual dynamics of the stress response under different stressor frequencies presented in Tilders *et al.* [7].

of stress response system. Since it is not realistic to experiment with human under intensive stress stimulus, there are no real time-series data that can validate our model under such a condition. Nevertheless, we are confident about the model's validity since it could stand the essential structural and behavioral tests described above.

8. SENSITIVITY ANALYSIS

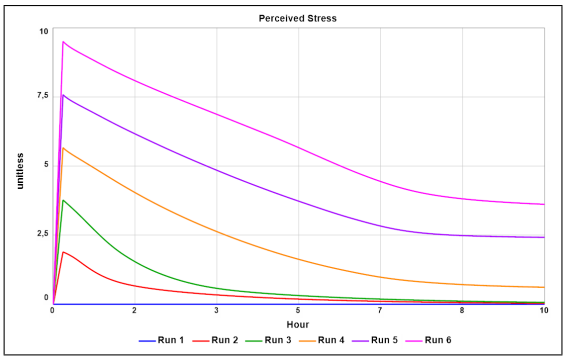
In order to examine the robustness of our model and to gain a deeper insight about the system, we have conducted some sensitivity analysis. Firstly, we have tested the model's sensitivity to stress stimulus conditions. These are expected to clarify how much of the variance in hormonal dynamics is explained by the variance in stress input. Stress stimulus is defined by two dimensions in the model: level and duration. We analyzed the model under possible combinations of the corresponding parameters *Stress Stimulus Level* and *Stress Stimulus Duration*, which are designed to range between 0 to 50 (unitless) and 0 to 1 (hour), respectively.

Besides the stress stimulus conditions, we have also analyzed the model sensitivity to Stress Control Loop to examine the significance of the loop in explaining the dynamics. We also wanted to provide an example of such a loop analysis in physiological systems.

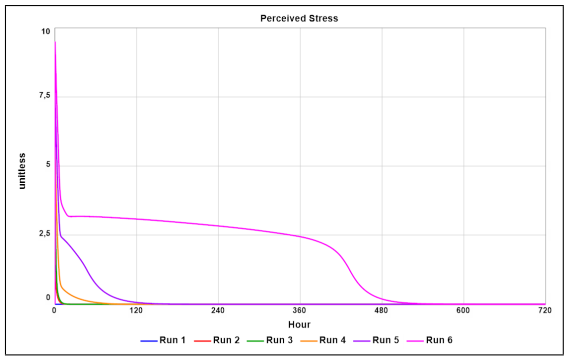
8.1. Sensitivity to Stress Stimulus Level

The model's sensitivity to external stress stimulus level has been tested by incrementally increasing *Stress Stimulus Level* by 10, from 0 to 50. Meanwhile, stress stimulus duration is kept constant at 0.2h. Some of the model outputs are provided as an example in Figures 8.1, 8.2 and 8.3. The other variables behave in the similar fashion.

Inferring from the outputs, higher *Stress Stimulus Level* means stronger allostasis reaction from the body, in the short-term. In the long-term, it takes exponentially longer time to relieve the stress, to repair the GRs, and to normalize the hormones. Furthermore, although *Perceived Stress* is completely relieved some time in the future, *Cortisol* and *GR Function* find abnormal steady-states. Hence, high level of external stress stimulus harms the body even though its duration is very short.

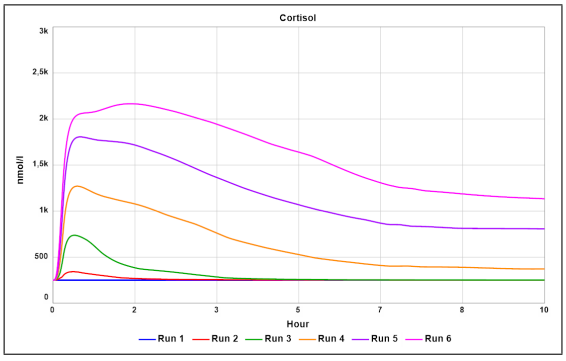


(a) *Perceived Stress* behavior in short-term.

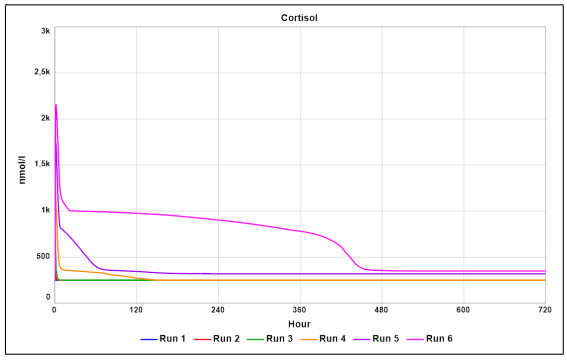


(b) *Perceived Stress* behavior in long-term.

Figure 8.1. *Perceived Stress* responses to incrementally increasing *Stress Stimulus Level* by 10, from 0 to 50 respectively in Run 1 to Run 6: (*a*) short-term, and (*b*) long-term dynamics.

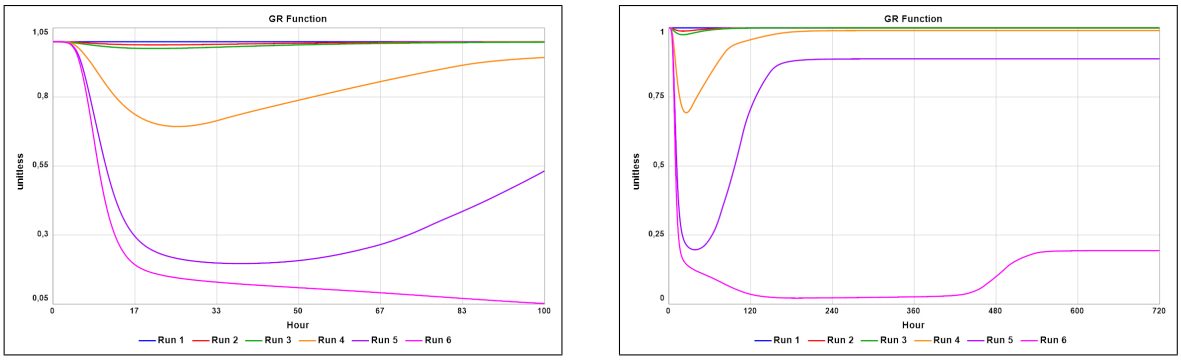


(a) *Cortisol* behavior in short-term.



(b) *Cortisol* behavior in long-term.

Figure 8.2. *Cortisol* responses to incrementally increasing *Stress Stimulus Level* by 10, from 0 to 50 respectively in Run 1 to Run 6: (*a*) short-term, and (*b*) long-term dynamics.



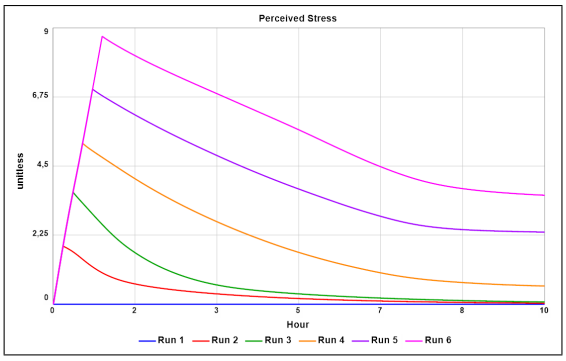
(a) *GR Function* behavior in short-term. (b) *GR Function* behavior in long-term.

Figure 8.3. *GR Function* responses to incrementally increasing *Stress Stimulus Level* by 10, from 0 to 50 respectively in Run 1 to Run 6: (*a*) short-term, and (*b*) long-term dynamics.

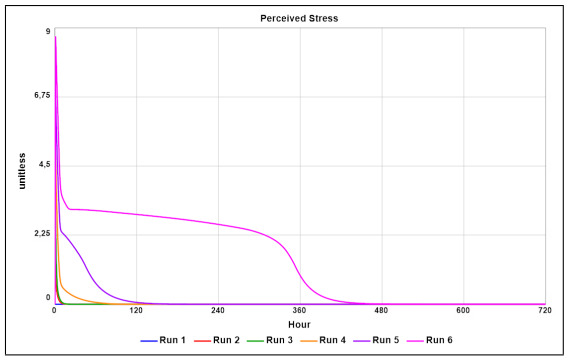
8.2. Sensitivity to Stress Stimulus Duration

The model's sensitivity to stress stimulus duration has been tested by incrementally increasing stress stimulus duration by 0.2h, from 0 to 1h. Meanwhile, stress stimulus level is kept constant at 10 (unitless). Some of the model outputs are provided as an example in Figures 8.4, 8.5 and 8.6. The other variables behave in the similar fashion.

As does the higher stress stimulus level, longer stress stimulus durations also exponentially increase the time it takes to relieve the stress, to repair the GRs, and to normalize the hormones. Even with a mild stress, it creates abnormal steady-state levels if the stress input lasts longer and longer.

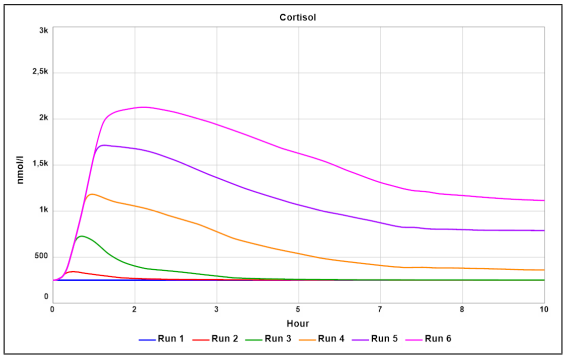


(a) *Perceived Stress* behavior in short-term.

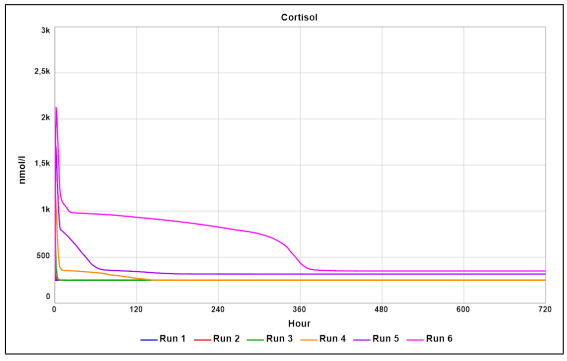


(b) *Perceived Stress* behavior in long-term.

Figure 8.4. *Perceived Stress* responses to incrementally increasing *Stress Stimulus Duration* by 0.2h, from 0 to 1h respectively in Run 1 to Run 6: (*a*) short-term, and (*b*) long-term dynamics.

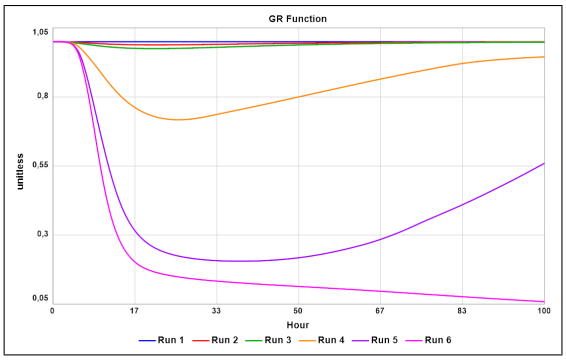


(a) *Cortisol* behavior in short-term.

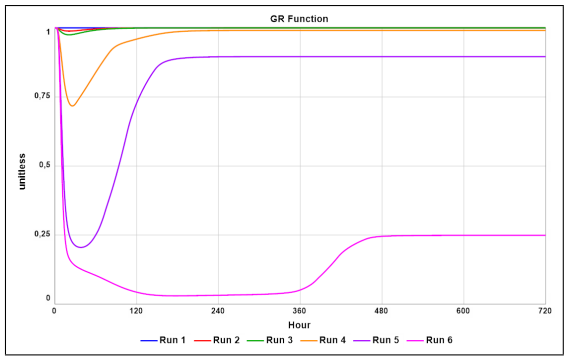


(b) *Cortisol* behavior in long-term.

Figure 8.5. *Cortisol* responses to incrementally increasing *Stress Stimulus Duration* by 0.2h, from 0 to 1h respectively in Run 1 to Run 6: (*a*) short-term, and (*b*) long-term dynamics.



(a) *GR Function* behavior in short-term.



(b) *GR Function* behavior in long-term.

Figure 8.6. *GR Function* responses to incrementally increasing *Stress Stimulus Duration* by 0.2h, from 0 to 1h respectively in Run 1 to Run 6: (a) short-term, and (b) long-term dynamics.

8.3. Sensitivity to Stress Stimulus Level-Duration Interaction

We have checked the reaction of the model for all the combinations of external stress stimulus level and duration in interaction. *Stress Stimulus Level* varies between 10 and 50 by 10, and *Stress Stimulus Duration* varies between 0.2h and 1h by 0.2h. Thus, 25 comparable simulation outputs are shown in each of Figures 8.7, 8.8 and 8.9. The y-axes of the first two graphs are shown partially in order to focus on the interesting parts of the group behaviors.

What is interesting to observe in these crowded graphs is the *bifurcations*: Sudden behavior changes occur between some certain parameter values, leading to alternative groupings in behavior mode. There are distinct attractor points especially for *GR Function*. We can infer from such an observation that the model's general behavior pattern and its steady-state are dependent on the stress stimulus level and duration, but not dictated by them. In other words, the high output variance is explained not by the input variance, but by the model structure, which is highly supportive for our model's capability to present an endogenous hypothesis of stress response dynamics.

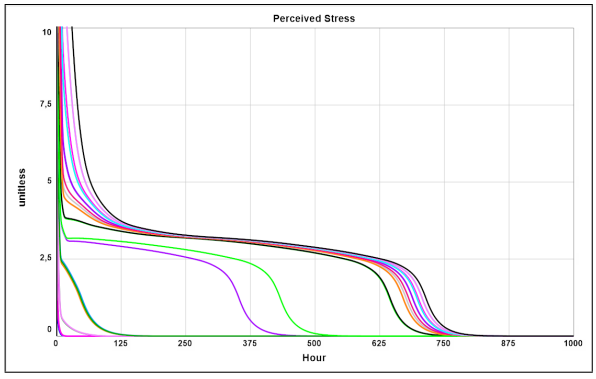


Figure 8.7. *Perceived Stress* responses to varying *Stress Stimulus Level* and *Stress Stimulus Duration* in interaction.

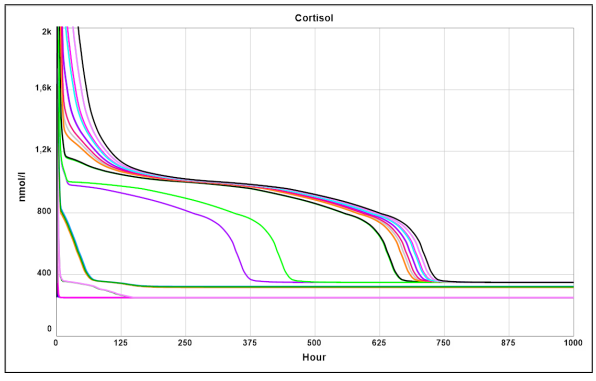


Figure 8.8. *Cortisol* responses to varying *Stress Stimulus Level* and *Stress Stimulus Duration* in interaction.

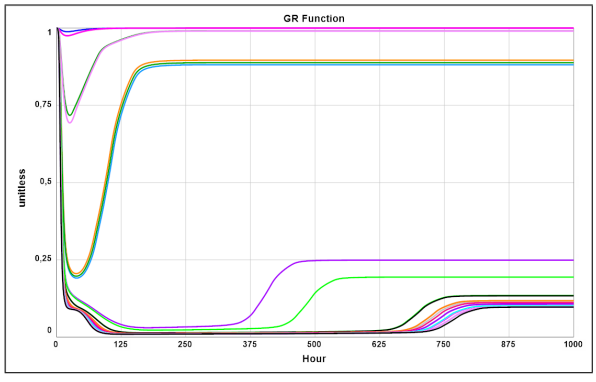


Figure 8.9. *GR Function* responses to varying *Stress Stimulus Level* and *Stress Stimulus Duration* in interaction.

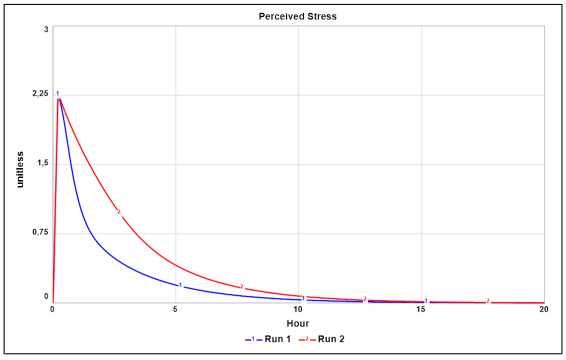
8.4. Sensitivity to Stress Control Loop

We have used the model to simulate what would happen if humans did not secrete cortisol as the primary reaction to stress. It can be a hypothetical case or a real medical problem, but in any case, it can provide further confidence about the model and also an insight about the evolution of such a mechanism in the human body. We deactivated Stress Control Loop by removing the causal link from stress to cortisol secretion and compared its results with the base case (Figure 8.10).

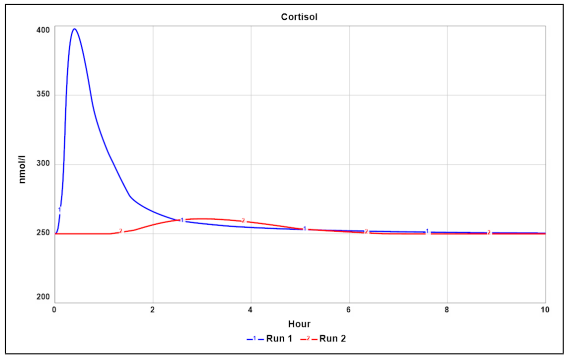
When stress stimuli do not activate the HPA-axis (Run 2), perceived stress by the body relieves at a lower rate due to lower allostasic levels of cortisol and serotonin. Stress keeps stimulating the immune system and there is not enough cortisol to inhibit proinflammatory cytokine secretion. Thus, there appears a higher amount of allostatic proinflammatory cytokine and more degeneration in GRs consequently. A mild increase in cortisol and serotonin are due to the triggering effect of proinflammatory cytokines on cortisol, and of cortisol on serotonin, respectively.

We have repeated the comparison with an intense but short-duration stress stimulus. We applied a 50 stress stimulus level for 0.2h and obtained the results depicted in Figure 8.11.

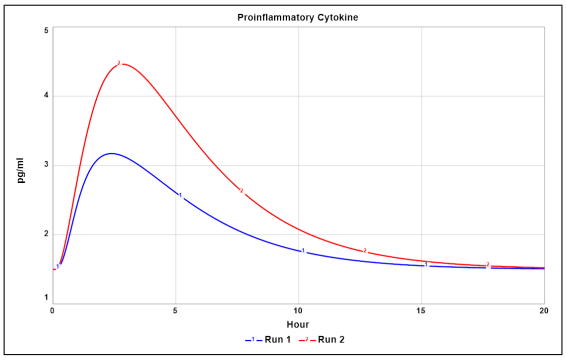
Under intensive stress, there seems to be a more striking difference if Stress Control Loop does not work. Perceived stress, first of all, does not relieve and the person feels consistent stress. In real life, such a constant stress would not be the case but as discussed earlier, our model does not cover the mechanisms that would possibly relieve the stress if the body is left alone for a longer while. On the other hand, even such out-of-scope mechanisms may not be enough to reverse this undesirable state and medication treatment would be needed. Although our model does not have the boundary to experiment on this hypothesis, we are able to judge the significance of the stress-cortisol causal relation, and the relevant, medium-term consequences of its absence.



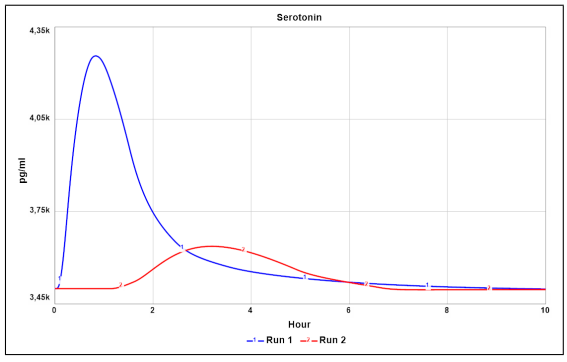
(a) *Perceived Stress.*



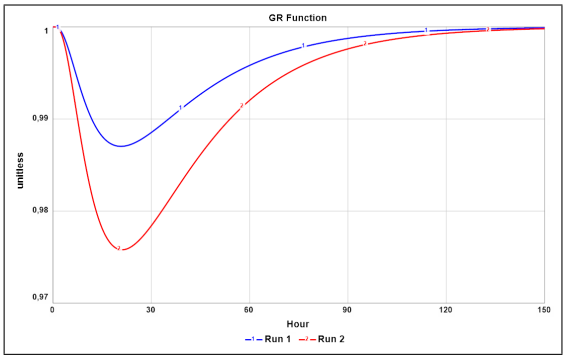
(b) *Cortisol.*



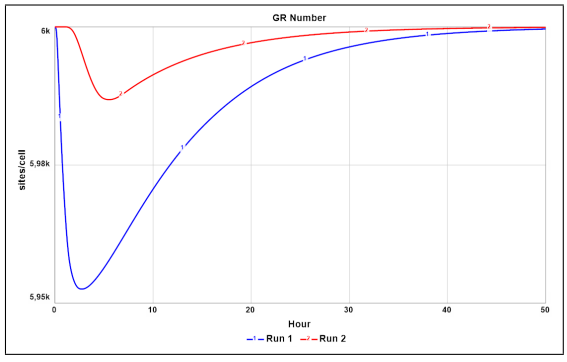
(c) *Proinflammatory Cytokine.*



(d) *Serotonin.*

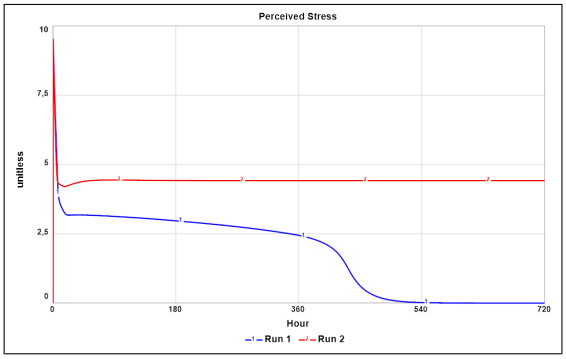


(e) *GR Function.*

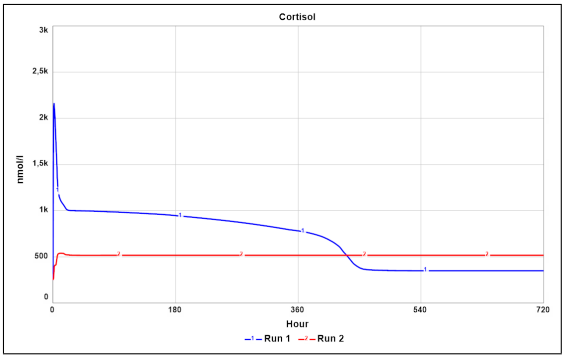


(f) *GR Number.*

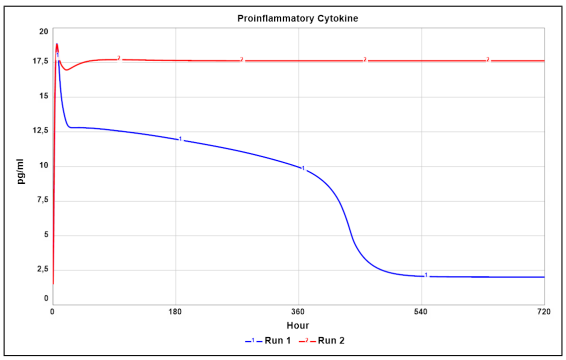
Figure 8.10. Behaviors of the major variables when the Stress Control Loop is activated (Run 1) and deactivated (Run 2), under a mild (base) stress.



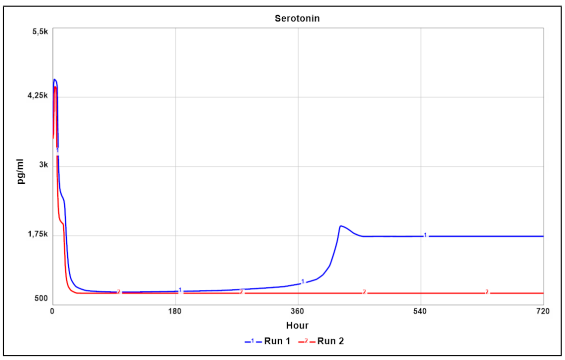
(a) *Perceived Stress.*



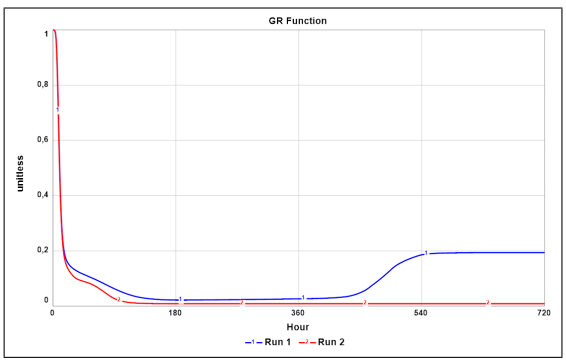
(b) *Cortisol.*



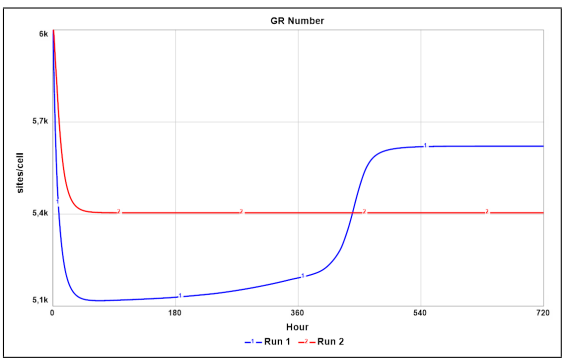
(c) *Proinflammatory Cytokine.*



(d) *Serotonin.*



(e) *GR Function.*



(f) *GR Number.*

Figure 8.11. Behaviors of the major variables when the Stress Control Loop is activated (Run 1) and deactivated (Run 2), under an intense stress.

9. SCENARIO ANALYSIS

9.1. Probable Depression Scenario

Major depression is one of the most common stress-related psychiatric disorders. According to the 2016 statistics of the National Institute of Mental Health, of all US adults, 6.7% have experienced major depression episode at least once in their life [60]. Globally, 216 million people have been diagnosed with major depression in 2015, and it is found to be the third leading disorder causing disability worldwide, while lower back and neck pain are the first [61]. There are no biological tests to diagnose major depression, but subjective tests based on person's history, and rating/scaling of the mood. The criteria of major depression diagnosis are listed in Diagnostic and Statistical Manual of Mental Disorders (DSM-V) by American Psychiatric Association (APA) [62], that is the most commonly used guidance worldwide.

First and foremost thing we know about depression disorders is that patients exhibit higher levels of cortisol and proinflammatory cytokines, and lower level of serotonin [17, 45]. The literature has consistently explained this fact by damaged feedback control mechanisms in depression, especially due to glucocorticoid receptor degeneracy [15, 45]. The second important relevant knowledge about depression is about how it begins. Some important research has focused on discovering the relation between the stressful life events and depression onset [63]. Accordingly, the possibility of a depression onset is causally dependent on the number and severity of the stressful life events experienced in the past. The third component of our depression comprehension is that a single major stressful event may lead people into a depression-like disorder within a month [64].

Being confident with the structural and behavioral validity of the model, we have used our instrument to simulate the evolution of depression-like dynamics. Combining qualitative and quantitative knowledge of literature about depression disorders, we have experimented in our model with a single major stress and observed the dynamics

for a month. The input stress used in the experiment, and the corresponding dynamics of the major variables are shown in Figures 9.1 and 9.2, respectively.

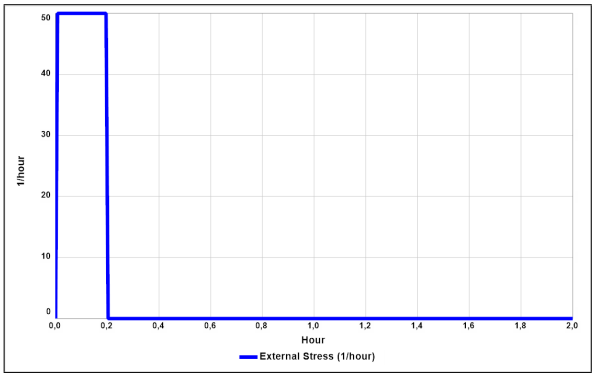
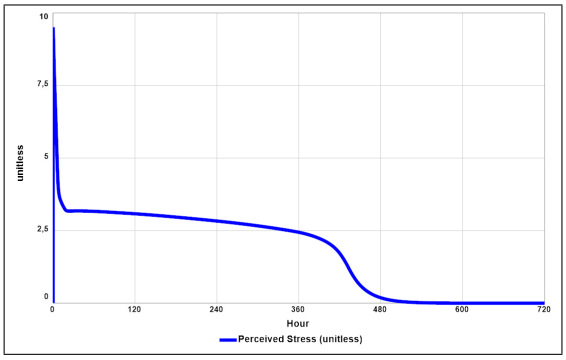


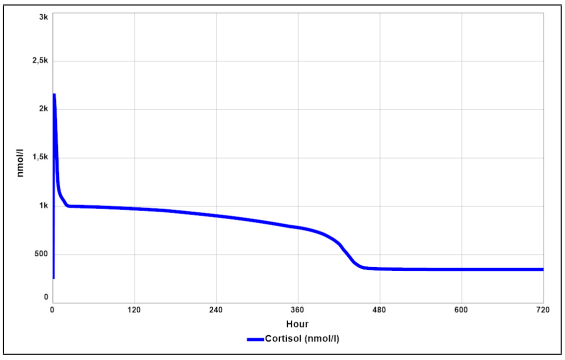
Figure 9.1. External stress input to the model in Probable Depression Scenario.

In the model behavior, we see a quite different picture in the acute and prolonged reactions of the body to the stimuli. Acute phase dynamics (see Figure 9.3), as in the TSST run results, involves rapid elevation in secretory activities of the three systems. The following chronic phase, on the other hand, has a very slow dynamic seeking its normal, healthy homeostatic level (see Figure 9.5). However, the concomitant changes in the structure of the body do not allow it to reach back its healthy equilibrium. Consequently, the equilibrium level of the body is altered, which is a pathological state. Depending on the amount, timing, and direction of the change, symptoms differ, and we diagnose the body with a corresponding disorder.

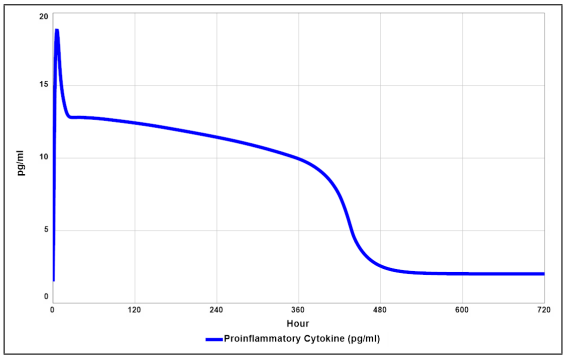
The values of the stock variables at time 720h and the corresponding data are listed in Table 9.1. The similarity of the results suggests us to diagnose the pathological state of the model as a depression-like disorder.



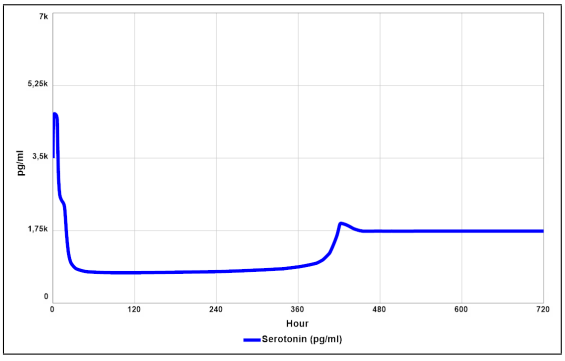
(a) *Perceived Stress.*



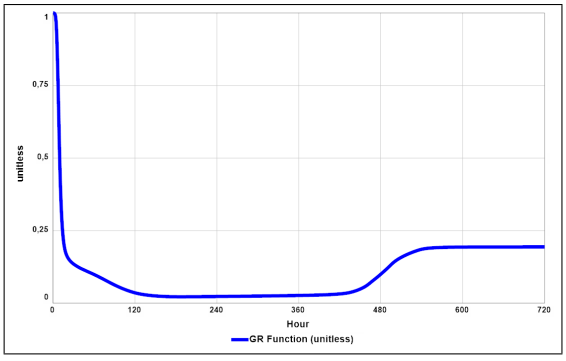
(b) *Cortisol.*



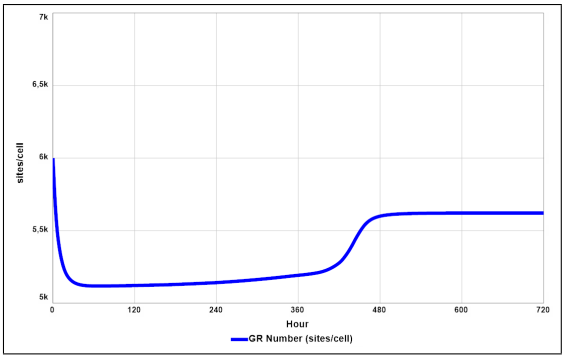
(c) *Proinflammatory Cytokine.*



(d) *Serotonin.*



(e) *GR Function.*



(f) *GR Number.*

Figure 9.2. Long-term behaviors of the major variables in Probable Depression Scenario.

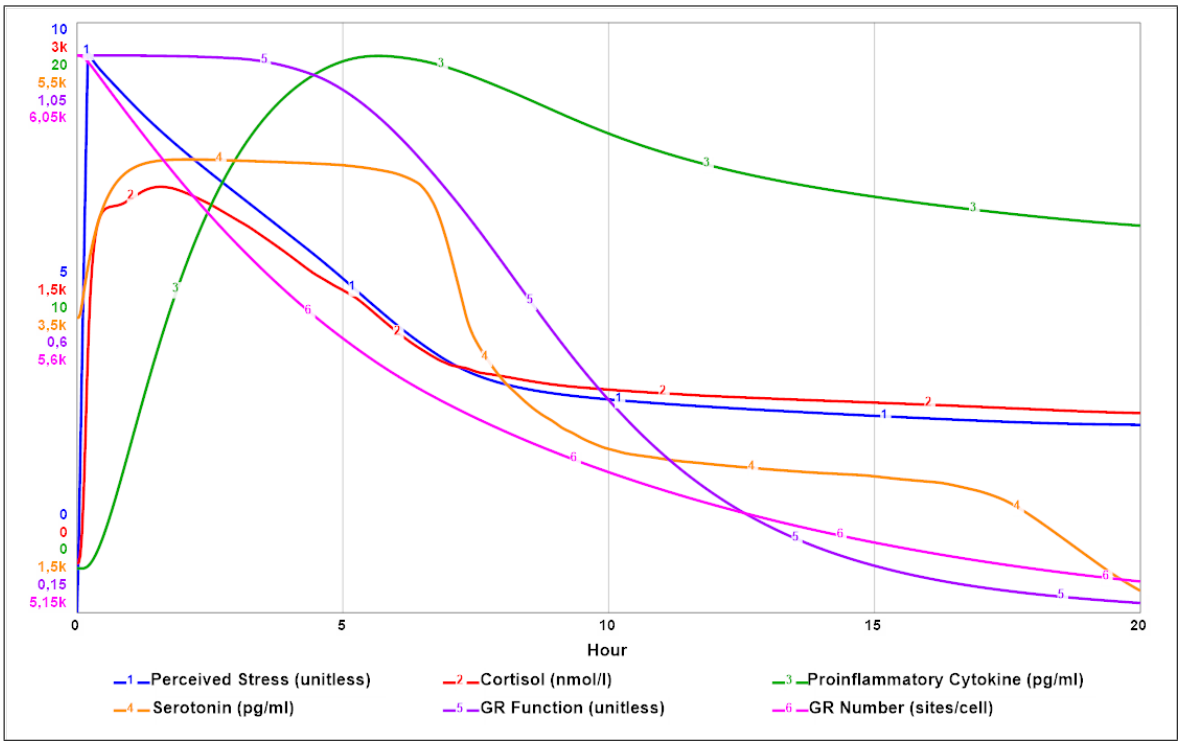


Figure 9.3. Behaviors of the major variables in the first 20 hours of Probable Depression Scenario.

Van den Berghe and colleagues [8] have emphasized the difference between the response of the body in acute and prolonged illnesses. They claim that neuroendocrine dynamics of an acute response of the body is different than its chronic response. They base this statement on the clinical data gathered from patients with protracted illnesses suggesting a different dynamical scenario for neuroendocrine alterations in two different phases. Their hypothesis is not specific for a disorder, but for general chronic illnesses, which renders our model results even more interesting.

The clinical data of Van den Berghe *et al.* [8] are qualitatively represented in their paper as reproduced below in Figure 9.4.

The general picture of our model dynamics shown in Figure 9.5, with three phases of the stress response, manifests a strong similarity with the suggested dynamics of the relevant hormone categories by Van den Berghe. In the acute phase of our model, *Cor-*

Table 9.1. Values of some stock variables at time 720h and the corresponding data.

Stock Variable	**Value at 720h**	**Simulated Output versus Baseline**	**Data of Depression Patients versus Healthy**	**Source**
Cortisol	349 nmol/l	1.4 fold higher	1.41 fold higher	[65]
Proinflammatory Cytokine	2.02 pg/ml	1.35 fold higher	1.46 fold higher	[66]
Serotonin	1740 pg/ml	0.5 fold lower	0.36 fold lower	[26]

tisol and *Proinflammatory Cytokine* rapidly increase as a protective reaction of the body, while *Serotonin, GR Function* and *GR Number* are strongly inhibited towards the end of the acute phase. In the chronic phase of our model, *Cortisol* and *Proinflammatory Cytokine* are slowly going down towards their normal values while *Serotonin*, one of the target hormones mentioned by Van den Berghe, and *GR Function* stay under their normal values. The recovery phase of our model can be observed after time 200h where all the variables seek their normal values with a faster speed. The anterior pituitary hormones are not included in our model, and proinflammatory cytokines are not shown in the graph of Van den Berghe *et al.* [8].

In summary, with our model, we have demonstrated the combination of three fundamental knowledge about depression disorders: (i) the difference of the variables from the baseline at the end of one-month run matches well the real-data, (ii) depression evolution can be triggered by a single major stress, and (iii) the pathology has emerged within a month period. Moreover, the behavioral similarity with the data of Van den Berghe implies that the model is able to capture not only the depression-like dynamics, but also the general long-term psychiatric dynamics of the body.

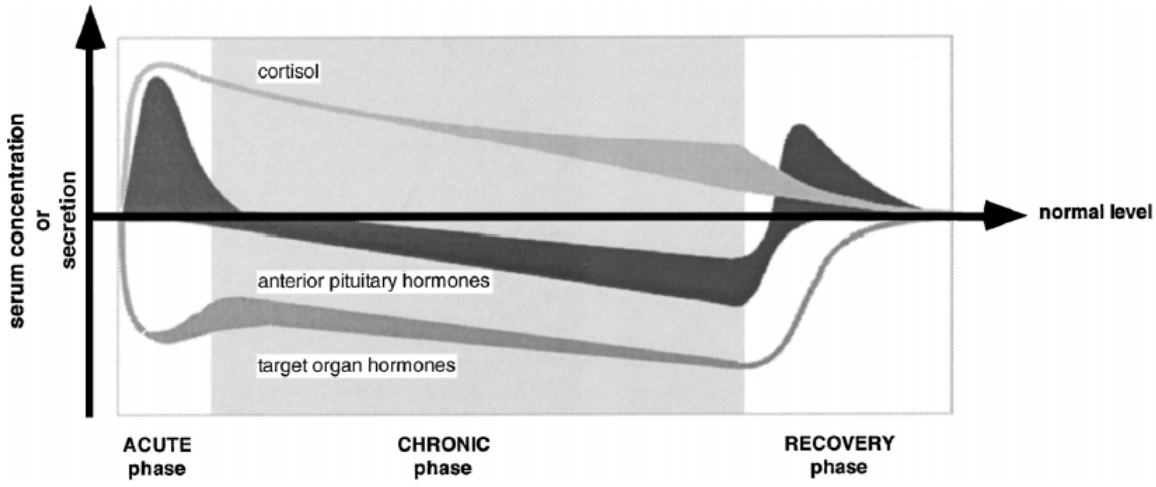


Figure 9.4. A general representation of the long-term neuroendocrine trend in prolonged illnesses based on the clinical data presented in Van den Berghe *et al.* [8].

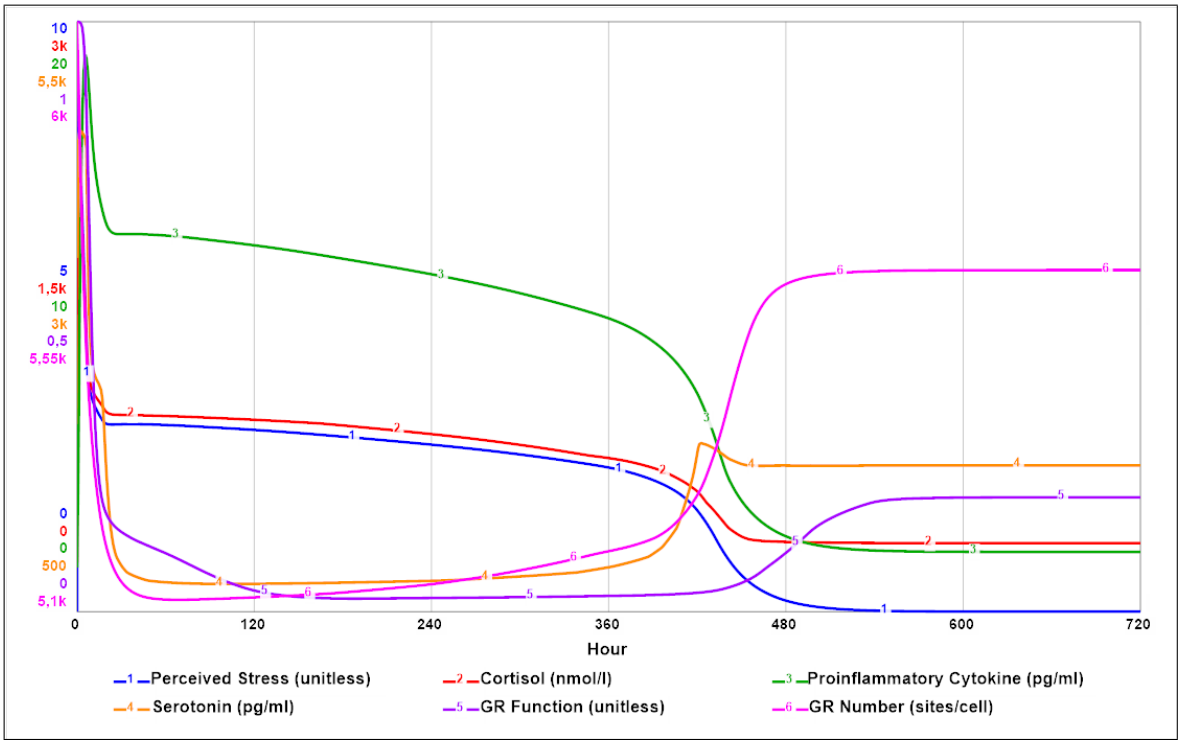


Figure 9.5. Overall model behavior in Probable Depression Scenario.

9.2. Earlier Stress Experience

Another aspect of the stress response of the body that caught attention in literature is its effects on future vulnerability to stress. A common theory is that traumatic events in people's history render them more vulnerable to stressful conditions in their adulthood. The studies of Heim *et al.* have a leading role in such theories [67–69].

As aforementioned, our model boundary does not cover long-term structural alterations as a part of the stress response dynamics. Thus, we cannot test and analyze the effects of childhood stress on adulthood, but we can draw a picture about what to expect from the bodies within a post-period of experiencing strong stress. For that purpose, we have compared two bodies: the first one, the control subject, receives only one mild stress (*Stress Stimulus Level*=12, *Stress Stimulus Duration*=12min) at time 800h, and the second one receives one intense stress (*Stress Stimulus Level*=50, *Stress Stimulus Duration*=12min) at time 0 together with the same mild stress as the first body at time 800h. We have run the model for 1000 hours and compared the behaviors after time 800h. Since we already know the first 720 hours dynamics of these two runs from TSST run and Probable Depression Scenario run respectively, only the model outputs after 720h are presented in Figures 9.6, 9.7, and 9.8.

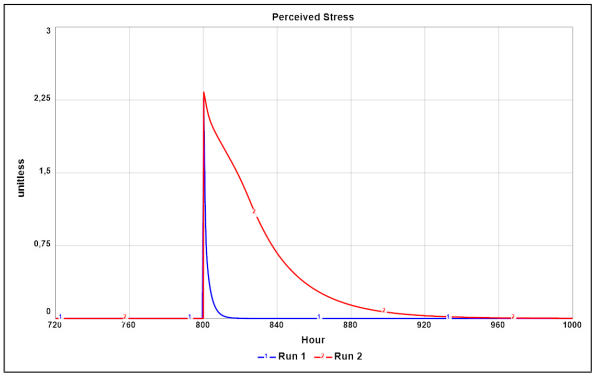


Figure 9.6. Comparison of long-term *Perceived Stress* dynamics of the body with (Run 2) and without (Run 1) earlier stress experience.

Perceived Stress increases approximately by the same amount from the baseline, but the body who experienced an intense stress a month ago relieves that stress in

significantly longer time. The same comparison applies for all the model outputs: they come back to their steady-state in much longer time in an earlier stress situation. *Cortisol* and *GR Function* are shown as representative dynamics in Figures 9.7 and 9.8.

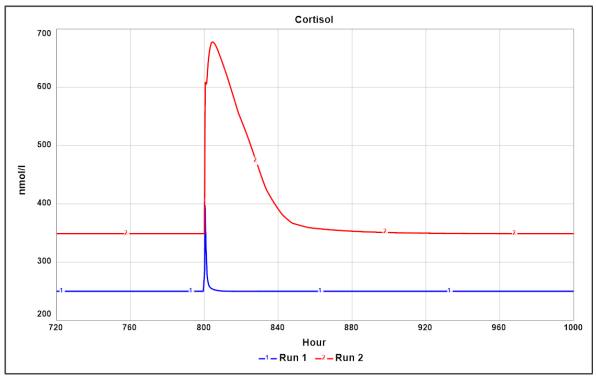


Figure 9.7. Comparison of long-term *Cortisol* dynamics of the body with (Run 2) and without (Run 1) earlier stress experience.

Another interesting part of the model behavior is that both *Cortisol* and *GR Function* exhibit stronger reactions to the same stress stimulus in the body that faced the earlier stress. The reactions of *Cortisol* to the same stimulus at time 800h are 1.59 fold (up to 398 nmol/l) and 1.94 fold (up to 678 nmol/l) higher than their baseline (250 nmol/l and 349 nmol/l), respectively for the cases without and with earlier stress experience. *GR Function* decreases by 1% (down to 0.99) and 64% (down to 0.07) from the baselines of 1 and 0.194, respectively.

The percentage differences between the two cases denote the sensitivity differences to stressors. What we can claim based on these outputs is that if the body experienced stress some reasonable amount of time ago, then the body gets more sensitive to the stressors so that it gives stronger stress response. The sensitivity change can be explained by the altered GR efficiency as a result of intense stress experienced in the past.

Staying within our model boundary, this scenario serves for the theories about the behavioral and physiological effects of early traumatic events on near future. The

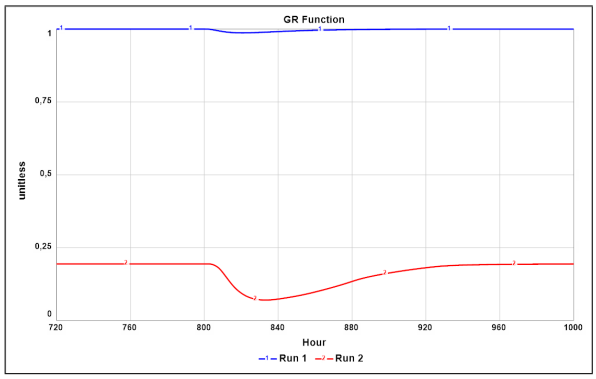


Figure 9.8. Comparison of long-term *GR Function* dynamics of the body with (Run 2) and without (Run 1) earlier stress experience.

stress response dynamics differ both in terms of time horizon and allostasic strength.

9.3. Cytokine-Induced Sickness Behavior

There has been a consensus in literature about the behavioral alterations caused by infectious diseases. We are all familiar with the sickness feeling during an illness period: a combination of fatigue, loss of appetite, reduced physical and social activity, cognitive deficiencies and so on. It is even found as a risk factor for depression disorders [43, 52, 70]. Such a behavioral state is called as sickness behavior in literature [71].

Proinflammatory cytokines are the actors of infectious diseases, and certain types are experimentally found to influence the brain to induce sickness behavior [52, 55, 72]. Especially in cancer and hepatitis patients receiving immunotherapy, major depression has been observed highly concomitant [43, 47].

Briefly, cytokines gained tremendous attention in psychoneuroimmunology field and stress related disorder research. We applied the above notion in our model to analyze the scenario. We have added a new input called *Cytokine Input* to the model, which administers proinflammatory cytokine (IL-6) once in a week (168h) in a pulsatile fashion starting at hour 1. Since our *Proinflammatory Cytokine* stock is an average value in the blood, we have taken first order average of *Cytokine Input* (Figure 9.9)

and plugged it into the model as in Equation 9.1.

$$\begin{aligned} Implied\ ProCyt &= (Ref\ ProCyt + Average\ Cytokine\ Input) \\ &\times (Cort\ Eff\ on\ ProCyt + Delayed\ Stress\ Eff\ on\ ProCyt) \end{aligned} \quad (9.1)$$

We have run the model for 1680 hours (10 weeks) and obtained the behaviors in Figures 9.10, 9.11 and 9.12.

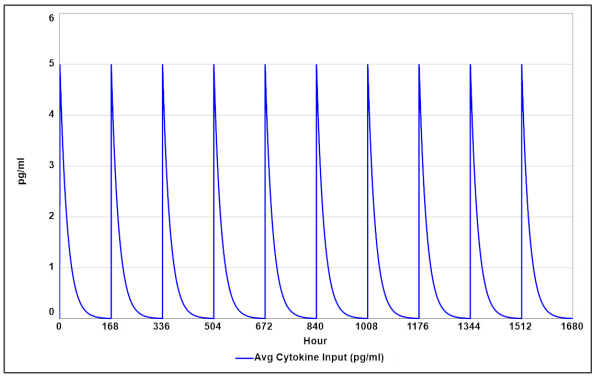


Figure 9.9. Externally given *Avg Cytokine Input* to the immune sector in a hypothetical immunotherapy scenario.

Depending on our outputs, we can claim that immune stimulation initiates the stress response of the body but from a different starting point. Although there is no external stressful situation, the body feels stress which is termed as sickness behavior. Interestingly, average *Perceived Stress* nonlinearly increases and finds a high steady state. We can interpret it as a depression-like abnormality evolution after a long-lasting sickness behavior.

This scenario should not be seen as an exact application example of immunotherapy in real life. It is rather a hypothetical scenario that gives an insight about the expectable stress reactions of the body. Regular immune stimulation brings allostatic load on the body as does repetitive stress. It reveals the threshold in the structure of this system, and the connections between infectious and stress-related disorders.

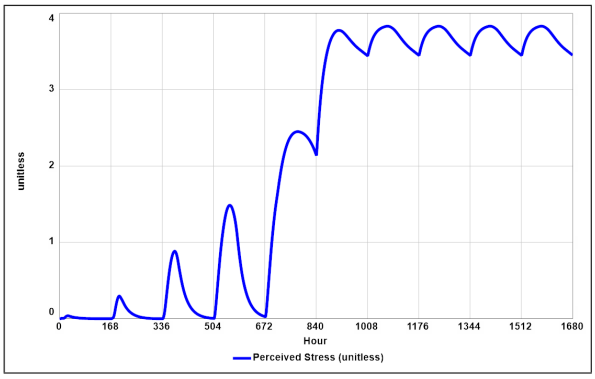


Figure 9.10. *Perceived Stress* dynamics in a hypothetical immunotherapy scenario.

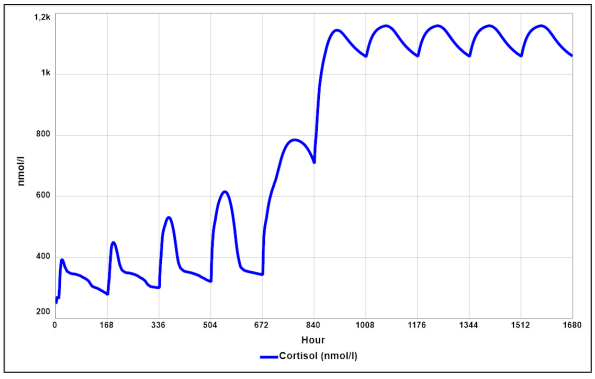


Figure 9.11. *Cortisol* dynamics in a hypothetical immunotherapy scenario.

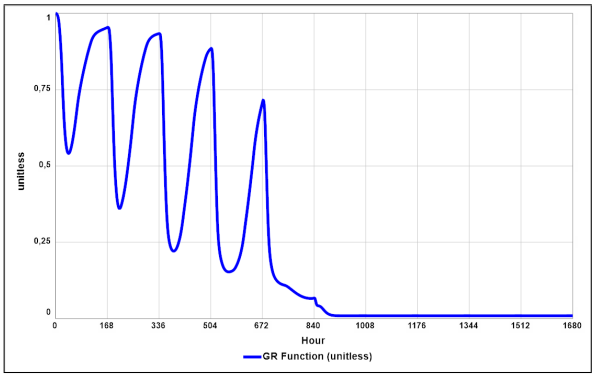


Figure 9.12. *GR Function* dynamics in a hypothetical immunotherapy scenario.

10. CONCLUSION

We constructed a system dynamics model of the biological mechanisms determining the stress response dynamics of the human body. The stress response involves whole of the body, but is primarily centered around three subsystems: endocrine, immune, and neural systems. The model represents a healthy body comprising the most relevant and fundamental functions of these three physiological systems. Among the countless feedback loops involved in this multi-scale system; five balancing and three reinforcing feedback loops are hypothesized to play the most crucial roles at hour-level maintenance of the homeostasis against stressors.

The stress response dynamics are naturally related with the intensity and frequency of stressors. We have designed our model in a way that would respond reasonably to stress inputs with different intensities and frequencies. The model is tested and validated under four different settings: no stressor, single-minor stressor, repetitive-minor stressor with low frequency, and repetitive-minor stressor with high frequency. The dynamic outputs of the model show a high resemblance with available qualitative and quantitative real-life data. Moreover, the model provides a quantitative representation of some highly acknowledged qualitative hypotheses about the stress response of the body, such as allostatic load construct of Bruce S. McEwen [11, 12].

To analyze how much of the output variance is explained by the input variance and the internal structure of the model, we have analyzed the sensitivity of the model behavior to stressor properties, such as level and duration. The analysis reveals bifurcations in output dynamics for which the model structure is responsible. Thus, the analysis has increased the confidence on the model's capability to provide an endogenous, systemic explanation of stress response dynamics. Further analysis on bifurcation points can yield great opportunity in predictions about stress-induced abnormalities. Additionally, we have examined the model's sensitivity to a very fundamental feedback control loop of the body by removing the causal link from stress to cortisol secretion. By doing so, we could judge the significance of the stress-cortisol causal interaction and

medium-term consequences of its absence. Such an analysis can yield valuable opportunities in targeting the right subsystems and structures to intervene in stress-related disorders.

Having established enough confidence in its validity, we have used the model to replicate stress-caused abnormalities. First, we have applied a single but major stress to imitate depression-like dynamics. The model can successfully generate one-month dynamics. Moreover, the model outputs exhibit high similarity with the data from patients with prolonged illnesses. Secondly, we have experimented with an additional mild stress to a body that experienced a single major stress approximately one month ago. In other words, we have tested the response of a patient with a depression-like disorder to a mild stress input. The model reveals an interesting fact: a body with past experience reacts more sensitive to a mild stress than a body without a stress history. The last scenario we have analyzed is the cytokine-induced sickness behavior. In this case, proinflammatory cytokine is externally applied to the model instead of a psychological stressor. The model demonstrates the abnormality dynamics of the stress measures of the body, following a sickness behavior period.

The above are not just expected results, but novel quantitative steps towards the comprehension of stress response in relation with other disorders. The significance of such an integrated understanding in disease analysis and treatment occupies a central part of systemic medical discussions. Thus, our model holds a highly promising potential to cover the essential dynamics of the body sinking into multiple types of psychological disorders. Overall, the model serves well our purposes in this study: it provides us with a theoretically grounded quantitative tool to observe, understand, and experiment with the stress response mechanisms. The ultimate aim of such a research would be to provide a comprehensive systemic approach to the body's relations with external environment and use this approach to design and test treatment strategies, with or without drugs.

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APPENDIX A: MODEL EQUATIONS

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Endocrine_Sector:

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Cort_Eff_on_GR_Number = GRAPH(LOG10(Free_Cortisol)/LOG10(Ref_Free _Cortisol))

(0,500, 1,5000), (0,550, 1,4968), (0,600, 1,4905), (0,650, 1,4810), (0,700, 1,4588), (0,750, 1,4398), (0,800, 1,3986), (0,850, 1,3258), (0,900, 1,2498), (0,950, 1,1357), (1,000, 1,0000), (1,050, 0,9489), (1,100, 0,9267), (1,150, 0,9077), (1,200, 0,8887), (1,250, 0,8697), (1,300, 0,8570), (1,350, 0,8475), (1,400, 0,8380), (1,450, 0,8285), (1,500, 0,8222), (1,550, 0,8158), (1,600, 0,8127), (1,650, 0,8063), (1,700, 0,8000), (1,750, 0,8000), (1,800, 0,8000)

UNITS: unitless

Cort_Eff_on_PostReceptors = PostR_Response_to_Cort

UNITS: Unitless

Cort_Eff_on_PreReceptors = PreR_Response_to_Cort

UNITS: Unitless

Cort_Response_to_Cort =

"DR_Curve_for_Cortisol-Cortisol"*Cort_Responsiveness_to_Cort

UNITS: Unitless

Cort_Responsiveness_to_Cort =

GR_Number_Eff_on_Responsiveness*Ref_Cort_Responsiveness_to_Cort

UNITS: Unitless

Cortisol(t) = Cortisol(t - dt) + (Cortisol_Adjustment) * dt

INIT Cortisol = Ref_Cortisol

UNITS: nmol/l

INFLOWS:

Cortisol_Adjustment = (Implied_Cortisol-Cortisol)/Cortisol_Adj_Time

UNITS: nmol/l/Hour

Cortisol_Adj_Time = 0,1

UNITS: hour

Cortisol_Eff_on_Cortisol = (Cort_Responsiveness_to_Cort-Cort_Response_to_Cort)

UNITS: Unitless

Cortisol_Eff_on_ProCyt =

(ProCyt_Responsiveness_to_Cort-ProCyt_Response_to_Cort)

UNITS: Unitless

Cortisol_Eff_on_RelTime =

RelTime_Responsiveness_to_Cort-RelTime_Response_to_Cort

UNITS: unitless

Cortisol_Ratio = LOG10(Free_Cortisol)/LOG10(Shifted_Ref_Free_Cortisol)

UNITS: unitless

"DR_Curve_for_Cortisol-Cortisol" = GRAPH(Cortisol_Ratio)

(0,6000, 0,4000), (0,6250, 0,4000), (0,6500, 0,4027), (0,6750, 0,4081), (0,7000, 0,4190), (0,7250, 0,4271), (0,7500, 0,4380), (0,7750, 0,4489), (0,8000, 0,4652), (0,8250, 0,4787), (0,8500, 0,4950), (0,8750, 0,5140), (0,9000, 0,5466), (0,9250, 0,5792), (0,9500, 0,6145), (0,9750, 0,6661), (1,0000, 0,7500), (1,0250, 0,8914), (1,0500, 0,9348), (1,0750, 0,9566), (1,1000, 0,9729), (1,1250, 0,9837), (1,1500, 0,9891), (1,1750, 0,9919), (1,2000, 0,9946), (1,2250, 0,9973), (1,2500, 1,0000), (1,2750, 1,0000), (1,3000, 1,0000)

UNITS: Unitless

"DR_Curve_for_Cortisol-PostR" = GRAPH(Cortisol_Ratio)

(1,000, 0,5000), (1,06666666667, 0,5000), (1,13333333333, 0,5045), (1,200, 0,5113), (1,26666666667, 0,5317), (1,33333333333, 0,5656), (1,400, 0,5973), (1,46666666667, 0,6516), (1,53333333333, 0,7308), (1,600, 0,8281), (1,66666666667, 0,8910), (1,73333333333, 0,9280), (1,800, 0,9590), (1,86666666667, 0,9842), (1,93333333333, 0,9955), (2,000, 1,0000)

UNITS: Unitless

"DR_Curve_for_Cortisol-PreR" = GRAPH(Cortisol_Ratio)

(0,200, 0,1000), (0,300, 0,1081), (0,400, 0,1285), (0,500, 0,1611), (0,600, 0,1977), (0,700, 0,2385), (0,800, 0,2873), (0,900, 0,3688), (1,000, 0,5000), (1,100, 0,8452), (1,200, 0,9410), (1,300, 0,9770), (1,400, 0,9950), (1,500, 1,0000)

UNITS: Unitless

"DR_Curve_for_Cortisol-ProCyt" = GRAPH(Cortisol_Ratio)

(0,9000, 0,3000), (0,9250, 0,3032), (0,9500, 0,3285), (0,9750, 0,4077), (1,0000, 0,5000), (1,0250, 0,5724), (1,0500, 0,6389), (1,0750, 0,7023), (1,1000, 0,7624), (1,1250, 0,8195), (1,1500, 0,8765), (1,1750, 0,9208), (1,2000, 0,9525), (1,2250, 0,9715), (1,2500, 0,9873), (1,2750, 0,9937), (1,3000, 1,0000)

UNITS: Unitless

"DR_Curve_for_Cortisol-RelTime" = GRAPH(Cortisol_Ratio)

(0,6000, 0,000), (0,6250, 0,005), (0,6500, 0,005), (0,6750, 0,009), (0,7000, 0,014), (0,7250, 0,027), (0,7500, 0,041), (0,7750, 0,063), (0,8000, 0,095), (0,8250, 0,136), (0,8500, 0,204), (0,8750, 0,285), (0,9000, 0,452), (0,9250, 0,602), (0,9500, 0,747), (0,9750, 0,833), (1,0000, 0,900), (1,0250, 0,932), (1,0500, 0,959), (1,0750, 0,973), (1,1000, 0,982), (1,1250, 0,982), (1,1500, 0,991), (1,1750, 0,995), (1,2000, 1,000)

UNITS: unitless

Free_Cortisol = Cortisol*Unbound_Cortisol_Fraction*Plasma_Volume

UNITS: nmol

GR_Degeneration_Fraction = ProCyt_Eff_on_GR_Degeneration+Ref_GR_Deg_Fraction

UNITS: 1/hour

GR_Function(t) = GR_Function(t - dt) + (GR_Repair - GR_Degeneration) * dt

INIT GR_Function = Ref_GR_Function

UNITS: unitless

INFLOWS:

GR_Repair = (Possible_Max_GR_Function-GR_Function)/GR_Repair_Time

UNITS: 1/hour

OUTFLOWS:

GR_Degeneration = GR_Function*GR_Degeneration_Fraction

UNITS: 1/hour

GR_Function_Effect = GRAPH(GR_Function/Ref_GR_Function)

(0,0000, 10,000), (0,0195, 10,000), (0,0390, 10,000), (0,0585, 10,000), (0,0780, 9,919), (0,0975, 9,878), (0,1170, 9,878), (0,1365, 9,837), (0,1560, 9,837), (0,1755, 9,796), (0,1950, 9,715), (0,2145, 9,715), (0,2340, 9,633), (0,2535, 9,593), (0,2730, 9,511), (0,2925, 9,430), (0,3120, 9,348), (0,3315, 9,267), (0,3510, 9,186), (0,3705, 9,145), (0,3900, 9,063), (0,4095, 8,941), (0,4290, 8,860), (0,4485, 8,778), (0,4680, 8,656), (0,4875, 8,575), (0,5070, 8,412),

(0,5265, 8,249), (0,5460, 8,005), (0,5655, 7,882), (0,5850, 7,597), (0,6045, 7,434), (0,6240, 7,231), (0,6435, 6,986), (0,6630, 6,701), (0,6825, 6,457), (0,7020, 6,131), (0,7215, 5,724), (0,7410, 5,357), (0,7605, 5,072), (0,7800, 4,665), (0,7995, 4,258), (0,8190, 3,729), (0,8385, 3,403), (0,8580, 2,955), (0,8775, 2,507), (0,8970, 2,181), (0,9165, 1,855), (0,9360, 1,600), (0,9555, 1,200), (0,9750, 1,000)

UNITS: Unitless

GR_Number(t) = GR_Number(t - dt) + (GR_Number_Regulation) * dt

INIT GR_Number = Ref_GR_Number

UNITS: sites/cell

INFLOWS:

GR_Number_Regulation = (Implied_GR_Number-GR_Number)/GR_Number_Adj_Time

UNITS: sites/cell/Hour

GR_Number_Adj_Time = 10

UNITS: hour

GR_Number_Eff_on_Responsiveness = GRAPH(LOG10(GR_Number/Ref_GR_Number))

(-0,3000, 0,100), (-0,2750, 0,249), (-0,2500, 0,399), (-0,2250, 0,528), (-0,2000, 0,613), (-0,1750, 0,687), (-0,1500, 0,747), (-0,1250, 0,802), (-0,1000, 0,843), (-0,0750, 0,888), (-0,0500, 0,933), (-0,0250, 0,969), (0,0000, 1,000), (0,0250, 1,037), (0,0500, 1,064), (0,0750, 1,100), (0,1000, 1,123), (0,1250, 1,146), (0,1500, 1,159)

UNITS: Unitless

GR_Repair_Time = 10

UNITS: hour

Implied_Cortisol = Ref_Cortisol*(Stress_Eff_on_Cortisol+Internal_Effects_on_Cortisol)

UNITS: nmol/l

Implied_GR_Number = Cort_Eff_on_GR_Number*Ref_GR_Number

UNITS: sites/cell

Intended_Max_GR_Function = ProCyt_Eff_on_Permanent_GR_Degeneration*Ref_GR_Function

UNITS: unitless

Internal_Effects_on_Cortisol =

(Cortisol_Eff_on_Cortisol+ProCyt_Eff_on_Cortisol+Serotonin_Eff_on_Cortisol)

UNITS: Unitless

Permanent_Degeneration_Time = 10

UNITS: hour

Plasma_Volume = 3

UNITS: l

Possible_Max_GR_Function(t) =

Possible_Max_GR_Function(t - dt) + (- Permanent_Degeneration) * dt

INIT Possible_Max_GR_Function = Ref_GR_Function

UNITS: unitless

OUTFLOWS:

Permanent_Degeneration =

(Possible_Max_GR_Function-Intended_Max_GR_Function)/Permanent_Degeneration

_Time

UNITS: 1/hour

PostR_Response_to_Cort =

"DR_Curve_for_Cortisol-PostR"*PostR_Responsiveness_to_Cort

UNITS: Unitless

PostR_Responsiveness_to_Cort =

GR_Number_Eff_on_Responsiveness*Ref_PostR_Responsiveness_to_Cort

UNITS: Unitless

PreR_Response_to_Cort =

"DR_Curve_for_Cortisol-PreR"*PreR_Responsiveness_to_Cort

UNITS: Unitless

PreR_Responsiveness_to_Cort =

GR_Number_Eff_on_Responsiveness*Ref_PreR_Responsiveness_to_Cort

UNITS: Unitless

ProCyt_Response_to_Cort =

"DR_Curve_for_Cortisol-ProCyt"*ProCyt_Responsiveness_to_Cort

UNITS: Unitless

ProCyt_Responsiveness_to_Cort =

GR_Number_Eff_on_Responsiveness*Ref_ProCyt_Responsiveness_to_Cort

UNITS: Unitless

Ref_Cort_Responsiveness_to_Cort = 2

UNITS: Unitless

Ref_Cortisol = 250

UNITS: nmol/l

Ref_Free_Cortisol = 0,1*Ref_Cortisol*Plasma_Volume

UNITS: nmol

Ref_GR_Deg_Fraction = 0

UNITS: 1/hour

Ref_GR_Function = 1

UNITS: Unitless

Ref_GR_Number = 6000

UNITS: sites/cell

Ref_PostR_Responsiveness_to_Cort = 2

UNITS: Unitless

Ref_PreR_Responsiveness_to_Cort = 2

UNITS: Unitless

Ref_ProCyt_Responsiveness_to_Cort = 2

UNITS: Unitless

Ref_RelTime_Responsiveness_to_Cort = 5

UNITS: unitless

RelTime_Response_to_Cort =

RelTime_Responsiveness_to_Cort*"DR_Curve_for_Cortisol-RelTime"

UNITS: unitless

RelTime_Responsiveness_to_Cort =

Ref_RelTime_Responsiveness_to_Cort*GR_Number_Eff_on_Responsiveness

UNITS: unitless

Shifted_Ref_Free_Cortisol = Ref_Free_Cortisol*GR_Function_Effect

UNITS: nmol

Unbound_Cortisol_Fraction = GRAPH(Cortisol)

(250, 0,1000), (525, 0,1000), (800, 0,1000), (1075, 0,1009), (1350, 0,10181), (1625, 0,1127), (1900, 0,1434), (2175, 0,2014), (2450, 0,2973), (2725, 0,3878), (3000, 0,5000)

UNITS: Unitless

****

Immune_Sector:

****

Avg_ProCyt_1(t) = Avg_ProCyt_1(t - dt) + (ProCyt_Smoothing1) * dt

INIT Avg_ProCyt_1 = Proinflammatory_Cytokine

UNITS: pg/ml

INFLOWS:

ProCyt_Smoothing1 =

(Proinflammatory_Cytokine-Avg_ProCyt_1)/ProCyt_Smoothing_Time

UNITS: pg/ml/Hour

Avg_ProCyt_2(t) = Avg_ProCyt_2(t - dt) + (ProCyt_Smoothing2) * dt

INIT Avg_ProCyt_2 = Proinflammatory_Cytokine

UNITS: pg/ml

INFLOWS:

ProCyt_Smoothing2 = (Avg_ProCyt_1-Avg_ProCyt_2)/ProCyt_Smoothing_Time

UNITS: pg/ml/Hour

Avg_ProCyt_3(t) = Avg_ProCyt_3(t - dt) + (ProCyt_Smoothing3) * dt

INIT Avg_ProCyt_3 = Proinflammatory_Cytokine

UNITS: pg/ml

INFLOWS:

ProCyt_Smoothing3 = (Avg_ProCyt_2-Avg_ProCyt_3)/ProCyt_Smoothing_Time

UNITS: pg/ml/Hour

Delayed_Stress_Eff_on_ProCyt(t) =

Delayed_Stress_Eff_on_ProCyt(t - dt) + (Delaying_Stress_Effect) * dt

INIT Delayed_Stress_Eff_on_ProCyt = Stress_Eff_on_ProCyt

UNITS: unitless

INFLOWS:

Delaying_Stress_Effect =

(Stress_Eff_on_ProCyt-Delayed_Stress_Eff_on_ProCyt)/Stress_Eff_Del_Time

UNITS: 1/hour

Implied_ProCyt =

Ref_ProCyt*(Delayed_Stress_Eff_on_ProCyt+Cortisol_Eff_on_ProCyt)

UNITS: pg/ml

ProCyt_Adj_Time = 2

UNITS: hour

ProCyt_Eff_on_Cortisol = GRAPH(Proinflammatory_Cytokine/Ref_ProCyt)

(1,000, 0,2000), (1,500, 0,2000), (2,000, 0,2000), (2,500, 0,2290), (3,000, 0,3050), (3,500, 0,4244), (4,000, 0,5294), (4,500, 0,6308), (5,000, 0,7357), (5,500, 0,8190), (6,000, 0,8805), (6,500, 0,9167), (7,000, 0,9421), (7,500, 0,9674), (8,000, 0,9855), (8,500, 0,9928), (9,000, 1,0000), (9,500, 1,0000), (10,000, 1,0000)

UNITS: Unitless

ProCyt_Eff_on_GR_Degeneration = GRAPH(Avg_ProCyt_1/Ref_ProCyt)

(1,00, 0,000), (1,55, 0,005), (2,10, 0,032), (2,65, 0,090), (3,20, 0,154), (3,75, 0,244), (4,30, 0,321), (4,85, 0,394), (5,40, 0,471), (5,95, 0,538), (6,50, 0,606), (7,05, 0,670), (7,60, 0,742), (8,15, 0,819), (8,70, 0,891), (9,25, 0,937), (9,80, 0,968), (10,35, 0,986), (10,90, 0,995), (11,45, 1,000), (12,00, 1,000)

UNITS: 1/hour

ProCyt_Eff_on_Permanent_GR_Degeneration = GRAPH(Avg_ProCyt_3/Ref_ProCyt)

(0,00, 1,0000), (0,631578947368, 1,0000), (1,26315789474, 1,0000), (1,89473684211, 0,9878), (2,52631578947, 0,9715), (3,15789473684, 0,9511), (3,78947368421, 0,9063), (4,42105263158, 0,8493), (5,05263157895, 0,7638), (5,68421052632, 0,6620), (6,31578947368, 0,5439), (6,94736842105, 0,4176), (7,57894736842, 0,2873), (8,21052631579, 0,1937), (8,84210526316, 0,1529), (9,47368421053, 0,1244), (10,1052631579, 0,1122), (10,7368421053, 0,1041), (11,3684210526, 0,1000), (12,00, 0,1000)

UNITS: Unitless

ProCyt_Eff_on_Stress = GRAPH(Proinflammatory_Cytokine/Ref_ProCyt)

(1,00, 0,0000), (1,95, 0,0000), (2,90, 0,0000), (3,85, 0,0063), (4,80, 0,0398), (5,75, 0,0633), (6,70, 0,0851), (7,65, 0,1014), (8,60, 0,1176), (9,55, 0,1285), (10,50, 0,1357), (11,45, 0,1430), (12,40, 0,1466), (13,35, 0,1484), (14,30, 0,1484), (15,25, 0,1484), (16,20, 0,1484), (17,15, 0,1484), (18,10, 0,1484), (19,05, 0,1484), (20,00, 0,1484)

UNITS: 1/hour

ProCyt_Eff_on_TRP = GRAPH(Avg_ProCyt_1/Ref_ProCyt)

(1,000, 1,0000), (1,450, 0,9923), (1,900, 0,9837), (2,350, 0,9593), (2,800, 0,9348), (3,250, 0,8982), (3,700, 0,8452), (4,150, 0,7597), (4,600, 0,6498), (5,050, 0,5520), (5,500, 0,4624), (5,950, 0,3769), (6,400, 0,2955), (6,850, 0,2425), (7,300, 0,2004), (7,750, 0,1618), (8,200, 0,1386), (8,650, 0,1155), (9,100, 0,1039), (9,550, 0,1000), (10,000, 0,1000)

UNITS: Unitless

ProCyt_Smoothing_Time = 24

UNITS: hour

Proinflammatory_Cytokine(t) =

Proinflammatory_Cytokine(t - dt) + (ProCyt_Adjustment) * dt

INIT Proinflammatory_Cytokine = Ref_ProCyt

UNITS: pg/ml

INFLOWS:

ProCyt_Adjustment =

(Implied_ProCyt-Proinflammatory_Cytokine)/ProCyt_Adj_Time

UNITS: pg/ml/Hour

Ref_ProCyt = 1,5

UNITS: pg/ml

Stress_Eff_Del_Time = 0,5

UNITS: hour

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Neural_Sector:

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Available_TRP = Ref_Available_TRP*ProCyt_Eff_on_TRP

UNITS: micromole/liter

Avg_Serotonin_Eff_on_Responsiveness(t) =
Avg_Serotonin_Eff_on_Responsiveness(t - dt) + (Ser_Eff_Smoothing) * dt
INIT Avg_Serotonin_Eff_on_Responsiveness = Serotonin_Eff_on_Responsiveness
UNITS: unitless
INFLOWS:
Ser_Eff_Smoothing =
(Serotonin_Eff_on_Responsiveness-Avg_Serotonin_Eff_on_Responsiveness)/Ser
_Smoothing_Time
UNITS: 1/hour
Cort_Response_to_Ser = Cort_Responsiveness_to_Ser*"DR_Curve_for_Ser-Cortisol"
UNITS: unitless
Cort_Responsiveness_to_Ser =
Ref_Cort_Responsiveness_to_Ser*Avg_Serotonin_Eff_on_Responsiveness
UNITS: unitless
CSF_Volume = 150
UNITS: ml
"DR_Curve_for_Ser-Cortisol" =
GRAPH(LOG10(Serotonin_Vol)/LOG10(Shifted_Ref_Ser_for_PostR))
(-1,000, 0,000), (-0,833333333333, 0,005), (-0,666666666667, 0,014), (-0,500, 0,023), (-0,333333333333, 0,036), (-0,166666666667, 0,045), (0,000, 0,054), (0,166666666667, 0,068), (0,333333333333, 0,086), (0,500, 0,118), (0,666666666667, 0,158), (0,833333333333, 0,231), (1,000, 0,375), (1,16666666667, 0,692), (1,33333333333, 0,882), (1,500, 0,941), (1,66666666667, 0,977), (1,83333333333, 0,991), (2,000, 1,000)
UNITS: Unitless
"DR_Curve_for_Ser-RelTime" =
GRAPH(LOG10(Serotonin_Vol)/LOG10(Shifted_Ref_Ser_for_PostR))
(-1,000, 0,000), (-0,875, 0,000), (-0,750, 0,009), (-0,625, 0,018), (-0,500, 0,027), (-0,375, 0,045), (-0,250, 0,059), (-0,125, 0,081), (0,000, 0,118), (0,125, 0,167), (0,250, 0,217), (0,375, 0,290), (0,500, 0,398), (0,625, 0,525), (0,750, 0,674), (0,875, 0,810), (1,000, 0,900), (1,125, 0,959), (1,250, 0,982), (1,375, 0,986), (1,500, 0,995), (1,625, 0,995), (1,750, 1,000), (1,875, 1,000), (2,000, 1,000)

UNITS: Unitless

"DR_Curve_for_Serotonin-Serotonin" =

GRAPH(LOG10(Serotonin_Vol)/LOG10(Shifted_Ref_Ser_for_PreR))

(-1,000, 0,000), (-0,833333333333, 0,009), (-0,666666666667, 0,018), (-0,500, 0,027), (-0,333333333333, 0,045), (-0,166666666667, 0,0635), (0,000, 0,0815), (0,166666666667, 0,1175), (0,333333333333, 0,1585), (0,500, 0,1945), (0,666666666667, 0,2535), (0,833333333333, 0,350), (1,000, 0,500), (1,16666666667, 0,7285), (1,33333333333, 0,878), (1,500, 0,9455), (1,66666666667, 0,9775), (1,83333333333, 0,9955), (2,000, 1,000)

UNITS: unitless

FuzzyMin_of_Serotonin = GRAPH(Implied_Serotonin/Serotonin_Capacity)

(0,000, 0,000), (0,200, 0,200), (0,400, 0,400), (0,600, 0,600), (0,800, 0,800), (1,000, 0,927), (1,200, 0,979), (1,400, 1,000), (1,600, 1,000), (1,800, 1,000), (2,000, 1,000)

UNITS: unitless

Implied_Serotonin = Ref_Serotonin_Concentration_in_CSF*Ser_Eff_on_Ser

UNITS: pg/ml

Possible_Implied_Serotonin = FuzzyMin_of_Serotonin*Serotonin_Capacity

UNITS: pg/ml

Ref_Available_TRP = Ref_TRP*TRP_Ratio_Converted_into_Ser_in_CSF

UNITS: micromole/liter

Ref_Cort_Responsiveness_to_Ser = 0,8

UNITS: unitless

Ref_RelTime_Responsiveness_to_Ser = 5

UNITS: unitless

Ref_Ser_Responsiveness_to_Ser = 2

UNITS: unitless

Ref_Serotonin_Concentration_in_CSF = 3500

UNITS: pg/ml

Ref_Serotonin_Mass_in_CSF = CSF_Volume*Ref_Serotonin_Concentration_in_CSF

UNITS: pg

Ref_Serotonin_Vol_in_CSF = Ref_Serotonin_Mass_in_CSF/Serotonin_Mol_Weight

UNITS: nmol

Ref_TRP = 79

UNITS: micromole/liter

RelTime_Response_to_Ser =

"DR_Curve_for_Ser-RelTime"*RelTime_Responsiveness_to_Ser

UNITS: unitless

RelTime_Responsiveness_to_Ser =

Avg_Serotonin_Eff_on_Responsiveness*Ref_RelTime_Responsiveness_to_Ser

UNITS: unitless

Ser_Eff_on_Ser = Ser_Responsiveness_to_Ser-Ser_Response_to_Ser

UNITS: unitless

Ser_Response_to_Ser =

"DR_Curve_for_Serotonin-Serotonin"*Ser_Responsiveness_to_Ser

UNITS: unitless

Ser_Responsiveness_to_Ser =

Ref_Ser_Responsiveness_to_Ser*Avg_Serotonin_Eff_on_Responsiveness

UNITS: unitless

Ser_Smoothing_Time = 12

UNITS: hour

Serotonin(t) = Serotonin(t - dt) + (Serotonin_Adjustment) * dt

INIT Serotonin = Ref_Serotonin_Concentration_in_CSF

UNITS: pg/ml

INFLOWS:

Serotonin_Adjustment =

(Possible_Implied_Serotonin-Serotonin)/Serotonin_Adj_Time

UNITS: pg/ml/Hour

Serotonin_Adj_Time = 0,5

UNITS: hour

Serotonin_Capacity =

Ref_Serotonin_Concentration_in_CSF*TRP_Eff_on_Serotonin_Capacity

UNITS: pg/ml

Serotonin_Eff_on_Cortisol = Cort_Response_to_Ser

UNITS: unitless

Serotonin_Eff_on_RelTime =

(RelTime_Responsiveness_to_Ser-RelTime_Response_to_Ser)

UNITS: unitless

Serotonin_Eff_on_Responsiveness =

GRAPH(LOG10(Serotonin_Vol)/LOG10(Ref_Serotonin_Vol_in_CSF))

(-2,000, 2,000), (-1,500, 1,529), (-1,000, 1,267), (-0,500, 1,140), (0,000, 1,077), (0,500, 1,032), (1,000, 1,000), (1,500, 0,941), (2,000, 0,824), (2,500, 0,534), (3,000, 0,018)

UNITS: unitless

Serotonin_Mol_Weight = 176,215*1000

UNITS: pg/nmol

Serotonin_Vol = CSF_Volume*Serotonin/Serotonin_Mol_Weight

UNITS: nmol

Shifted_Ref_Ser_for_PostR = Ref_Serotonin_Vol_in_CSF*Cort_Eff_on_PostReceptors

UNITS: nmol

Shifted_Ref_Ser_for_PreR = Ref_Serotonin_Vol_in_CSF*Cort_Eff_on_PreReceptors

UNITS: nmol

TRP_Eff_on_Serotonin_Capacity = GRAPH(Available_TRP/Ref_Available_TRP)

(0,000, 0,200), (0,0555555555556, 0,200), (0,111111111111, 0,205), (0,166666666667, 0,219), (0,222222222222, 0,238), (0,277777777778, 0,276), (0,333333333333, 0,347), (0,388888888889, 0,476), (0,444444444444, 0,647), (0,500, 0,806), (0,555555555556, 0,976), (0,611111111111, 1,106), (0,666666666667, 1,212), (0,722222222222, 1,294), (0,777777777778, 1,359), (0,833333333333, 1,424), (0,888888888889, 1,465), (0,944444444444, 1,482), (1,000, 1,500)

UNITS: Unitless

TRP_Ratio_Converted_into_Ser_in_CSF = 0,01

UNITS: Unitless

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Stress_Sector:

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Avg_Stress_Perception(t) =

Avg_Stress_Perception(t - dt) + (Stress_Perception_to_Average - Stress_Perception _Averaging) * dt

INIT Avg_Stress_Perception = Perceived_Stress

UNITS: unitless

INFLOWS:

Stress_Perception_to_Average = Stress_Perception

UNITS: 1/hour

OUTFLOWS:

Stress_Perception_Averaging = Avg_Stress_Perception/Perception_Del_Time

UNITS: 1/hour

Every_Day_Pattern = IF((TIME>1) AND (TIME<1+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>25) AND (TIME<25+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>49) AND (TIME<49+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>73) AND (TIME<73+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>97) AND (TIME<97+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>121) AND (TIME<121+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>145) AND (TIME<145+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>169) AND (TIME<169+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>193) AND (TIME<193+Stress_Stimulus_Duration)) THEN (1) ELSE(0) +IF((TIME>217) AND (TIME<217+Stress_Stimulus_Duration)) THEN (1) ELSE(0)

UNITS: unitless

Every_Three_Days_Pattern = IF((TIME>1) AND (TIME<1+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>73) AND (TIME<73+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>145) AND (TIME<145+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>217) AND (TIME<217+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>289) AND (TIME<289+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>361) AND (TIME<361+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>433) AND (TIME<433+Stress_Stimulus _Duration)) THEN (1) ELSE(0) +IF((TIME>505) AND (TIME<505+Stress_Stimulus

_Duration)) THEN (1) ELSE(0) +IF((TIME>577) AND (TIME<577+Stress_Stimulus
_Duration)) THEN (1) ELSE(0) +IF((TIME>649) AND (TIME<649+Stress_Stimulus
_Duration)) THEN (1) ELSE(0)

UNITS: unitless

External_Stress =
(0*Single_Pattern+0*Every_Day_Pattern +0*Every_Three_Days_Pattern)*Stress
_Stimulus_Level

UNITS: 1/hour

Implied_Relieving_Time =
Ref_RelTime*(Stress_Eff_on_RelTime+Serotonin_Eff_on_RelTime+Cortisol_Eff_on
_RelTime)

UNITS: hour

Internal_Stress = (ProCyt_Eff_on_Stress+Ref_Internal_Stress)

UNITS: 1/hour

Perceived_Stress(t) =
Perceived_Stress(t - dt) + (Stress_Perception - Stress_Relief) * dt

INIT Perceived_Stress = 0

UNITS: unitless

INFLOWS:

Stress_Perception = External_Stress+Internal_Stress

UNITS: 1/hour

OUTFLOWS:

Stress_Relief = (Perceived_Stress/Relieving_Time)

UNITS: 1/hour

Perception_Del_Time = 24

UNITS: hour

Ref_Internal_Stress = 0

UNITS: 1/hour

Ref_RelTime = 3

UNITS: hour

Relieving_Time(t) = Relieving_Time(t - dt) + (RelTime_Adjustment) * dt

INIT Relieving_Time = Ref_RelTime

UNITS: hour

INFLOWS:

RelTime_Adjustment =

(Implied_Relieving_Time-Relieving_Time)/RelTime_Adj_Time

UNITS: unitless

RelTime_Adj_Time = 0,1

UNITS: hour

Single_Pattern =

IF((TIME>0) AND (TIME<Stress_Stimulus_Duration)) THEN (1) ELSE(0)

UNITS: unitless

Stress_Eff_on_Cortisol = GRAPH(Perceived_Stress)

(0,00, 0,000), (0,50, 0,072), (1,00, 0,290), (1,50, 0,471), (2,00, 0,833), (2,50, 1,267), (3,00, 1,919), (3,50, 2,389), (4,00, 2,968), (4,50, 3,511), (5,00, 4,127), (5,50, 4,814), (6,00, 5,430), (6,50, 6,045), (7,00, 6,624), (7,50, 7,095), (8,00, 7,493), (8,50, 7,783), (9,00, 7,891), (9,50, 8,000), (10,00, 8,000)

UNITS: Unitless

Stress_Eff_on_ProCyt = GRAPH(Perceived_Stress)

(0,00, 0,00), (1,00, 1,72), (2,00, 4,16), (3,00, 6,79), (4,00, 9,50), (5,00, 11,76), (6,00, 13,30), (7,00, 14,03), (8,00, 14,48), (9,00, 14,84), (10,00, 15,02)

UNITS: unitless

Stress_Eff_on_RelTime = GRAPH(Avg_Stress_Perception)

(0,00, 0,000), (1,00, 0,000), (2,00, 0,000), (3,00, 0,122), (4,00, 0,394), (5,00, 0,828), (6,00, 1,276), (7,00, 1,561), (8,00, 1,724), (9,00, 1,833), (10,00, 1,860)

UNITS: unitless

Stress_Stimulus_Duration = 0

UNITS: hour

Stress_Stimulus_Level = 0

Stress_Stimulus_Level = 0

UNITS: 1/hour

{ The model has 138 (138) variables (array expansion in parens).

In root model and 0 additional modules with 4 sectors.

Stocks: 14 (14) Flows: 17 (17) Converters: 107 (107)

Constants: 35 (35) Equations: 89 (89) Graphicals: 23 (23)

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