An Adaptive Temporal-Causal Network Model for Stress Extinction Using Fluoxetine

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Abstract. In this paper, an adaptive temporal causal network model based on drug therapy named fluoxetine to decrease the stress level of post-traumatic stress disorder is presented. The stress extinction is activated by a cognitive drug therapy (here fluoxetine) that uses continuous usage of medicine. The aim of this therapy is to reduce the connectivity between some components inside the brain which are responsible for causing stress. This computational model aspires to realistically demonstrate the activation of different portions of brain when the therapy is applied. The cognitive model starts with a situation of strong and continuous stress in an individual and after using fluoxetine the stress level begins to decrease over time. As a result, the patient will have a reduced stress level compared to not using drug.

Keywords: temporal-causal network model, cognitive, extreme emotion, drug-therapy, fluoxetine.

1 Introduction

Stress is a vital response to physical and emotional threats with strong roots in human evolution. Stress is important to protect humans from dangerous conditions, where in early history it could have life-or-death consequences. A particular situation might trigger a fight or flight reaction, which could result in unnecessarily avoiding certain (social) circumstances. As it has been described in [1] depression is one of the most grueling psychiatric sicknesses and may decrease life-time expectancy with up to 20%.
Recent literature [8] shows that fluoxetine suppresses or decreases synaptic changes associated with stress. It has been also mentioned that fluoxetine relatively suppresses the impact of stress on the infusion of synaptic plasticity in the medial prefrontal cortex which is responsible for receiving direct fibers from the hippocampus.
There are some previous temporal causal network-oriented modeling literatures for decreasing stress have been proposed [20-30].

The paper is organized as follows. In Section 2 the underlying neurological principles concerning the parts of the brain involved in stress and in the suppression of stress are addressed. In Section 3 the integrative temporal-causal network model is introduced. In Section 4 the results of the simulation model are discussed, in section 5 the

mathematical analysis of the model is presented and eventually in the last section a conclusion is presented.

2 Underlying Neurological Principles

In many recent research literature [12, 13] it has been proven that fluoxetine decreases or suppresses changes in synapses caused by stress. In many researches [55-57] it has been proven that repeated stressful conditions and experiences bring a remarkable effect on neural plasticity in many brain components, especially in limbic structures like hippocampal changes, prefrontal cortex (PFC), and Amygdala. As it has been clearly mentioned in [13]:

'Acute stress inhibits long-term potentiation (LTP) at synapses from the hippocampus to prefrontal cortex in the rat, a model of the dysfunction in the anterior cingulate/orbitofrontal cortices which has been observed in human depression.
In major depressive disorder, decreased blood flow and metabolism have been regularly described in multiple areas of the prefrontal cortex (PFC) with occasional changes in the hippocampal region. Conversely, a beneficial response to antidepressants has been associated with reduced blood flow in the hippocampus and a return to baseline metabolism level or increase in blood flow in the anterior cingulate cortex.
Plasticity at hippocampal to PFC synapses can be regulated up and down, as assessed by long-term potentiation (LTP) and long-term depression (LTD), depending on specific patterns of afferent activation and this circuit contributes to working memory processes.
Antidepressant effects may be obtained by several mechanisms, such as inhibition of serotonin uptake, for fluoxetine.' [13]

Also, previous studies [15-16] revealed that chronic stress changes dendritic morphology not just in the hippocampus, but also in the mPFC (medial Prefrontal Cortex).

'Depression is said to be caused by chronically low levels of serotonergic transmission. SSRIs interfere with the activity of the serotonin transporter (5-HTT), a reuptake molecule that removes serotonin from the synapses. The putative low levels of synaptic serotonin in the depressed patient are elevated, and depression is relieved.
These manipulations of serotonin levels have little effect on mood except in individuals who are depressed or recently recovered from depression.' [11, pp.1]
'Studies of neurotransmitter release with microdialysis have demonstrated that acute olanzapine significantly increases both dopamine and norepinephrine levels in rat prefrontal cortex, nucleus accumbens, and striatum, and the combination of olanzapine plus fluoxetine produces a greater increase in levels of dopamine and norepinephrine in the rat prefrontal cortex than fluoxetine alone.' [2], pp.776.

The functionality of chronic stress on brain parts particularly on the Hippocampus is mentioned in [3, 4].

‘The volume of the hippocampus is decreased in patients with depression or posttraumatic stress disorder.’ [3], pp. 975
‘The reduction in hippocampal volume is inversely proportional to the amount of time a patient is medicated with an antidepressant, and reduced hippocampal volume is partially reversed after antidepressant treatment.’ [4], pp.577
‘In the striatum, there was a tendency for an increase in the number of BrdU-positive cells that is similar in magnitude to that in hippocampus. This effect is consistent with highly significant and robust induction of cell proliferation reported in a recent study, and the greater increase could be due to the higher dose of olanzapine used (10mg/kg) relative to the current study (2 mg/kg).
In the current study, we found that the combination of olanzapine plus fluoxetine did not produce a greater increase in the number of BrdU-positive cells than either drug alone. This suggests that fluoxetine alone would be sufficient to produce a maximum response and therefore could not account for the augmentation that has been observed clinically; however, the clinical approach has been to add olanzapine after a patient has failed to respond to an SSRI like fluoxetine’ [4], pp.577.

Many researches illustrate that the hippocampus and other sections in the medial temporal lobe are interfered with detection of novelty [16, 17]. In other research [18] it has been proved that using of antidepressant drugs (Ads) will enhance the levels of extracellular epinephrine and serotonin.

‘The ability to detect unusual events occurring in the environment is essential for survival. Several studies have pointed to the hippocampus as a key brain structure in novelty detection, a claim substantial by its wide access to sensory information through the entorhinal cortex and also distinct aspects of its intrinsic circuity.’ [15], pp.18286

In [10] it has been shown that small amounts of fluoxetine might block stress-facilitated hippocampal LTD and eventually helps in memory retrieval impairment.

‘Chronic fluoxetine treatment reinstates ocular dominance plasticity in the primary visual cortex of adult rats, a form of developmentally regulated plasticity that is significantly reduced in the mature brain, and enhances long-term potentiation (LTP) in the dentate gyrus of adult mice. Results show that chronic fluoxetine treatment suppresses LTP in the primary auditory cortex and hippocampus of adult rats.
It has been well documented that exposure to acute stress impairs LTP and facilitate LTD in rats, as well as to produce learning and memory impairment in rats and monkeys. A single systematic injection of fluoxetine is able to reverse the impairment in LTP at synapses from the hippocampus to prefrontal cortex in the rats, caused by stress on elevated platform.’ [10], pp.1

In [10, pp.7] the influences of antidepressant agents such as fluoxetine is clearly mentioned:

'The chronic effects of antidepressant agents including fluoxetine, are involved in the regulation of intracellular transduction pathways, implicating changes in the cyclic adenosine monophosphate (cAMP) second messenger system, cAMP response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) in antidepressant action.'

In [14] explicitly the effect of chronic stress on medial Prefrontal Cortex and Amygdala has been mentioned:

'Chronic stress significantly suppressed cytogenesis in the mPFC and neurogenesis in the dentate gyrus, but had minor effect in nonlimbic structures. Fluoxetine treatment counteracted the inhibitory effect of stress. Hemispheric comparison revealed that the rate of cytogenesis was significantly higher in the left mPFC of control animals, whereas stress inverted this asymmetry, yielding a significantly higher incidence of newborn cells in the right mPFC. Fluoxetine treatment abolished hemispheric asymmetry in both control and stressed animals.
Structural alterations including suppressed dentate neurogenesis may contribute to the pathogenesis of depression.
Antidepressant treatment with fluoxetine or electroconvulsive seizure modulates cell proliferation not only in the dentate gyrus, but also in the medial PFC (mPFC) in adult rats. (pp.1490)'

3 The Temporal-Causal Network Model

First the Network-Oriented Modelling approach used to model the integrative overall process is briefly explained. As discussed in detail in [17, Ch 2, 18, 19] this approach is based on temporal-causal network models which can be represented at two levels: by a conceptual representation and by a numerical representation. A conceptual representation of a temporal-causal network model in the first place involves representing in a declarative manner states and connections between them that represent (causal) impacts of states on each other, as assumed to hold for the application domain addressed. The states are assumed to have (activation) levels that vary over time. In reality, not all causal relations are equally strong, so some notion of *strength of a connection* is used. Furthermore, when more than one causal relation affects a state, some way to *aggregate multiple causal impacts* on a state is used. Moreover, a notion of *speed of change* of a state is used for timing of the processes. These three notions form the defining part of a conceptual representation of a temporal-causal network model:

- **Strength of a connection $\omega_{X,Y}$** Each connection from a state X to a state Y has a *connection weight value* $\omega_{X,Y}$ representing the strength of the connection, often between 0 and 1, but sometimes also below 0 (negative effect) or above 1.
- **Combining multiple impacts on a state $\mathbf{c}_Y$(..)** For each state (a reference to) a *combination function* $\mathbf{c}_Y$**(..)** is chosen to combine the causal impacts of other states on state Y.
- **Speed of change of a state η_Y** For each state Y a *speed factor* η_Y is used to represent how fast a state is changing upon causal impact.

Combination functions can have different forms, as there are many different approaches possible to address the issue of combining multiple impacts. Therefore, the Network-Oriented Modelling approach based on temporal-causal networks incorporates for each state, as a kind of label or parameter, a way to specify how multiple causal impacts on this state are aggregated by some combination function. For this aggregation a number of standard combination functions are available as options and a number of desirable properties of such combination functions have been identified.

Fig. 1 represents the conceptual representation of the temporal-causal network mode. The components of the conceptual representation shown in Fig. 1 are explained here. The state ws_c shows the world state of the contextual stimulus c. The states ss_c and ss_{ee} are the sensor state for the context c and sensor state of the body state ee for the extreme emotion. The states srs_c and srs_{ee} are the sensory representation of the contextual stimulus c and the extreme emotion, respectively. The state srs_{ee} is a stimulus influencing the activation level of the preparation state. Furthermore, ps_{ee} is the preparation state of an extreme emotional response to the sensory representation srs_c of the context c, and fs_{ee} shows the feeling state associated to this extreme emotion. The state es_{ee} indicates the execution of the body state for the extreme emotion. All these relate to the affective processes. The (cognitive) goal state shows the goal for absorbing fluoxetine in the body. The (cognitive) state ps_{pil} is the preparation state of taking a pill (here fluoxetine). The state es_{pil} is the execution state of taking pill (fluoxetine). The other states relate to biological brain parts (Norepinephrine, Hippocampus, Thalamus, Serotonin, Prefrontal Cortex, Amygdala, Lateral Cerebellum, Striatum) which are involved in the stress condition, and in the influence of the fluoxetine applied.

Table 1 Explanation of the states in the model

X_1	ws_{ee}	World (body) state of extreme emotion *ee*
X_2	ss_{ee}	Sensor state of extreme emotion *ee*
X_3	ws_c	World state for context *c*
X_4	ss_c	Sensor state for context *c*
X_5	srs_{ee}	Sensory representation state of extreme emotion *ee*
X_6	srs_c	Sensory representation state of context *c*
X_7	fs_{ee}	Feeling state for extreme emotion *ee*
X_8	ps_{ee}	Preparation state for extreme emotion *ee*
X_9	es_{ee}	Execution state (bodily expression) of extreme emotion *ee*
X_{10}	goal	Goal of using fluoxetine
X_{11}	ps_{pil}	Preparation state of using pill
X_{12}	es_{pil}	Execution of using pill
X_{13}	Norepinephrine	Brain part
X_{14}	Hippocampus	Brain part
X_{15}	Thalamus	Brain part
X_{16}	Serotonin	Brain part
X_{17}	Prefrontal Cortex	Brain part
X_{18}	Amygdala	Brain part
X_{19}	Lateral Cerebellum	Brain part
X_{20}	Striatum	Brain part
X_{21}	ps_{act}	Preparation of action inside the brain

The connection weights ω_i in Fig.1 are as follows. The sensor states ss_{ee}, ss_{cc} have two incoming connections from ws_{ee} and ws_c (weights ω_1, ω_2). The world state of extreme emotion ws_{ee} has one arriving connection from es_{ee}, ω_{11} as a body-loop with weight. The sensory representation state of an extreme emotion srs_{ee} has an incoming connection weights ω_8 from state preparation state of an extreme emotion ps_{ee}. The feeling state fs_{ee} has one outgoing connection weight ω_5 from srs_{ee}. The preparation state of an extreme emotion ps_{ee} has two incoming connection weights ω_{36}, ω_{37} from states Striatum and es_{act}, respectively. The preparation state of an extreme emotion ps_{ee} has three outgoing connection weights, es_{ee}, Thalamus, and the connection weight between states Hippocampus and Prefrontal Cortex, (ω_{10}, ω_{15}, ω_{20}) respectively.

The goal has one arriving connection weight from the sensory representation srs_{ee} (ω_{27}) and preparation state ps_{pil} an entering connection from the goal with weight ω_{28}. The execution of taking the drug (here fluoxetine) is named es_{pil}, and has an entering connection weight ω_{29} from preparation state of taking ps_{pil}. The state Thalamus has three entering connection weights ω_{12}, ω_{14} and ω_{22} from preparation state of extreme emotion ps_{ee}, Hippocampus and Amygdala, respectively. The Norepinephrine of brain has an arriving connection weight ω_{16} from es_{pil}. The Hippocampus in brain has four incoming connection weights, ω_{17}, ω_{24}, ω_{15} and ω_{13} from Serotonin, Prefrontal Cortex, Norepinephrine and Thalamus. Note that the connection weight between states Prefrontal Cortex and Hippocampus is adaptive and using Hebbian learning means through time will be changed. The state Serotonin has an arriving connection from es_{pil} (ω_{19}). Prefrontal Corte state has an incoming connection weight from amygdala with ω_{25} and three outgoing connection weights to Amygdala, Lateral Cerebellum and ps_{act}, ω_{26}, ω_{30}, and ω_{31}. The state Lateral Cerebellum has two incoming connection weights from Prefrontal Cortex and Amygdala ω_{30}, ω_{32}, respectively and it has an outgoing connection weight to Striatum ω_{34}. The state Striatum has two outgoing connection weights to ps_{act},

ps_{ee} named ω_{35}, ω_{36}. Finally, the state ps_{act} has an outgoing connection weight to ps_{ee} named ω_{37}.

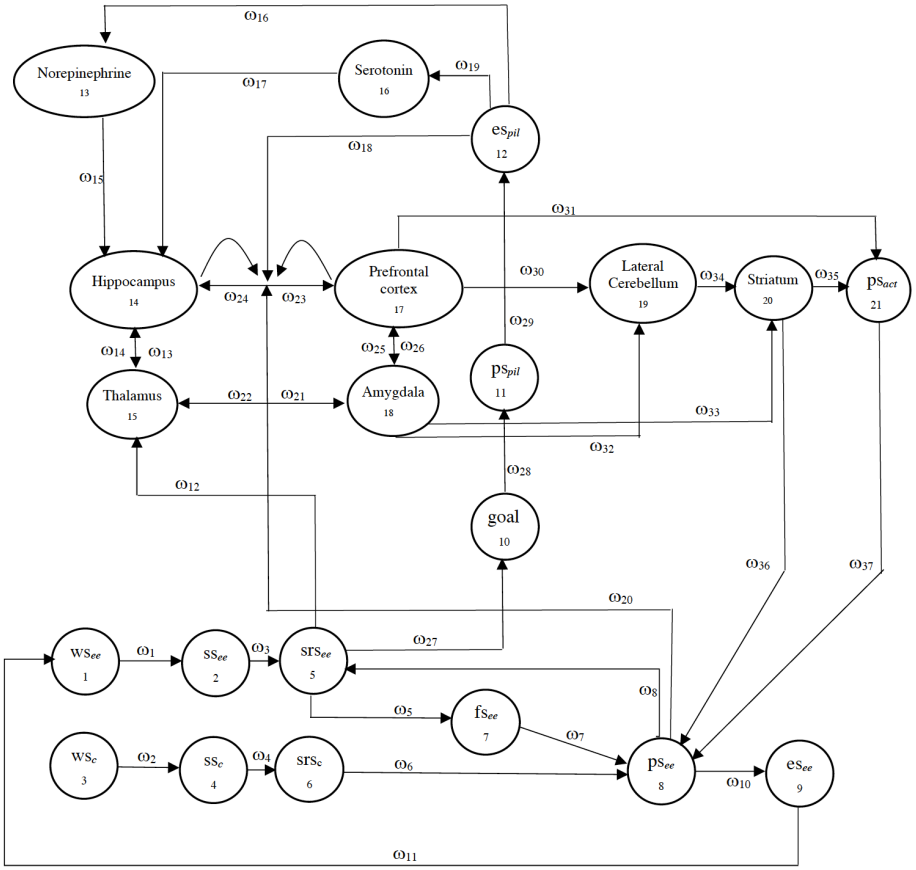

Figure 1. Conceptual representation of the temporal-causal network model

This conceptual representation was transformed into a numerical representation as follows [17, Ch 2, 18, 19]:

- at each time point *t* each state *Y* in the model has a real number value in the interval [0, 1], denoted by *Y(t)*
- at each time point t each state *X* connected to state *Y* has an impact on *Y* defined as $\mathbf{impact}_{X,Y}(t) = \omega_{X,Y} X(t)$ where $\omega_{X,Y}$ is the weight of the connection from *X* to *Y*
- The *aggregated impact* of multiple states X_i on *Y* at *t* is determined using a *combination function* $\mathbf{c}_Y(..)$:

  $\mathbf{aggimpact}_Y(t) = \mathbf{c}_Y(\mathbf{impact}_{X_1,Y}(t), \ldots, \mathbf{impact}_{X_k,Y}(t))$

  $= \mathbf{c}_Y(\omega_{X_1,Y} X_1(t), \ldots, \omega_{X_k,Y} X_k(t))$

  where X_i are the states with connections to state *Y*
- The effect of $\mathbf{aggimpact}_Y(t)$ on *Y* is exerted over time gradually, depending on speed factor η_Y:

$$Y(t+\Delta t) = Y(t) + \eta_Y\,[\mathbf{aggimpact}_Y(t) - Y(t)]\,\Delta t$$

or $$\mathbf{d}Y(t)/\mathbf{d}t = \eta_Y\,[\mathbf{aggimpactY(t)} - Y(t)]$$

- Thus, the following *difference* and *differential equation* for Y are obtained:

$$Y(t+\Delta t) = Y(t) + \eta_Y\,[\mathbf{c}_Y(\omega_{X_1,Y}X_1(t), \ldots, \omega_{X_k,Y}X_k(t)) - Y(t)]\,\Delta t$$

$$\mathbf{d}Y(t)/\mathbf{d}t = \eta_Y\,[\mathbf{c}_Y(\omega_{X_1,Y}X_1(t), \ldots, \omega_{X_k,Y}X_k(t)) - Y(t)]$$

For states the following combination functions $\mathbf{c}_Y(\ldots)$ were used, the identity function $\mathbf{id}(.)$ for states with impact from only one other state, and for states with multiple impacts the scaled sum function $\mathbf{ssum}_\lambda(\ldots)$ with scaling factor λ, and the advanced logistic sum function $\mathbf{alogistic}_{\sigma,\tau}(\ldots)$ with steepness σ and threshold τ.

$$\mathbf{id}(V) = V$$

$$\mathbf{ssum}_\lambda(V_1, \ldots, V_k) = (V_1 + \ldots + V_k)/\lambda$$

$$\mathbf{alogistic}_{\sigma,\tau}(V_1, \ldots, V_k) = [(1/(1+e^{-\sigma(V_1+\ldots+V_k-\tau)})) - 1/(1+e^{\sigma\tau})]\,(1+e^{-\sigma\tau})$$

4 Example Simulation

The simulation results of the cognitive temporal causal network model, which was constructed based on the neurological science which contains qualitive empirical information (such as fMRI) both for the mechanism by which the brain components work and for emerging result of the processes, has been shown in Figure 2.
Therefore, one can imply that the best option for declining the stress level has been chosen, given the usage of fluoxetine. The model used the Matlab codes which have been implemented in [22]. Using appropriate connections weights make the model numerical and adapted to qualitative empirical information. Table 2 illustrates the connection weights that has been used, where the values for are initial values as these weights are adapted over time. The time step was $\Delta t = 1$. The scaling factors λ_i for the nodes with more than one arriving connection weights are mentioned in Table 2. At first, an external world state of an extreme emotion-stimuli context c (represented by ws_c) will influence the affective internal states of the individual by influencing the emotional response es_{ee} (via ss_c, srs_c, and ps_{ee}) conducted to manifest the extreme emotion by body state ws_{ee}. As a consequence, the stressed individual senses the extreme emotion (and at the same time all the biological brain components increased over time), so as a cognitive process, as a next step the goal becomes active to decrease this stress level by using fluoxetine at time around 300.

Table 2 Connection weights and scaling factors for the example simulation

Connection weight	ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	ω_8	ω_{10}	ω_{11}	ω_{12}	ω_{13}
Value	1	1	1	1	1	1	1	1	1	1	1	1
Connection Weight	ω_{14}	ω_{15}	ω_{16}	ω_{17}	ω_{18}	ω_{19}	ω_{20}	ω_{21}	ω_{22}	ω_{23}	ω_{24}	ω_{25}
Value	1	1	1	1	-0.7	1	0.7	1	1	0.4	0.4	1
Connection Weight	ω_{26}	ω_{27}	ω_{28}	ω_{29}	ω_{30}	ω_{31}	ω_{32}	ω_{33}	ω_{34}	ω_{35}	ω_{35}	ω_{35}
Value	1	1	1	1	1	1	1	1	1	1	1	-0.9
Connection Weight	ω_{37}											
Value	–0.9											

state	X_5	X_8	X_{14}	X_{15}	X_{17}	X_{18}	X_{19}	X_{20}	X_{21}
λ_i	2	3	3.4	3	1.4	2	2	2	2

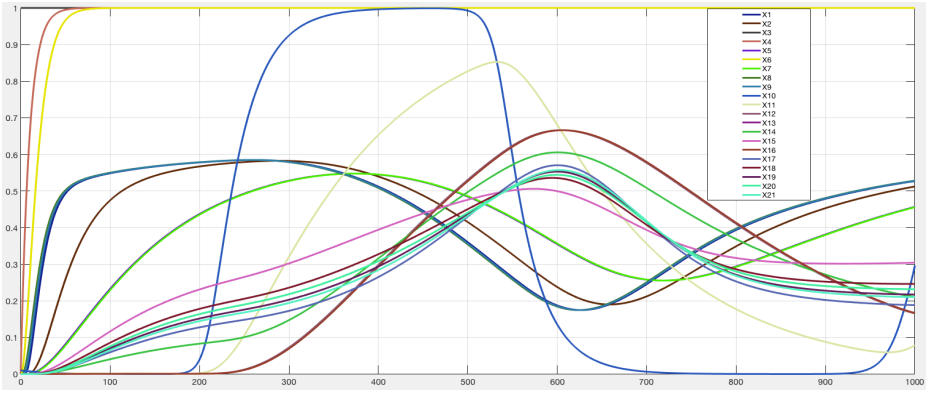

Figure 2. Simulation results for temporal-causal network modeling of the therapy by fluoxetine

As a biological process, the goal and in further steps, execution of taking drugs triggers the changes and suppression of execution of stress at the first state and this affects other brain components to be less active around time 300 and for stress level around 600. However, this effect is just temporary, and as the stressful context c still is present all the time, after a while the stress level goes up again, which in turn again leads to activation of the goal and performing another desire or prescription of eating fluoxetine, and so on and on repeatedly until the person or the doctor decides to stop taking drugs. The fluctuation in Figure 2 shows how in real life the repeated usage of medicine (here fluoxetine) decreases the stress level over each intake. It is worth to tell that all of this fluctuation is produced internally by the model; the environment is constant, external input for the model is only the constant world state ws_c. Therefore, based on the simulation results it is illustrated that the model for the drug therapy (fluoxetine) works as expected.

In Figure 3, the equilibrium situation where there is not any active goal (intake) has been shown. Based on this figure, when there is no intake (the goal is blocked in an artificial manner here), the stress level and activity of brain parts go up and stay high.

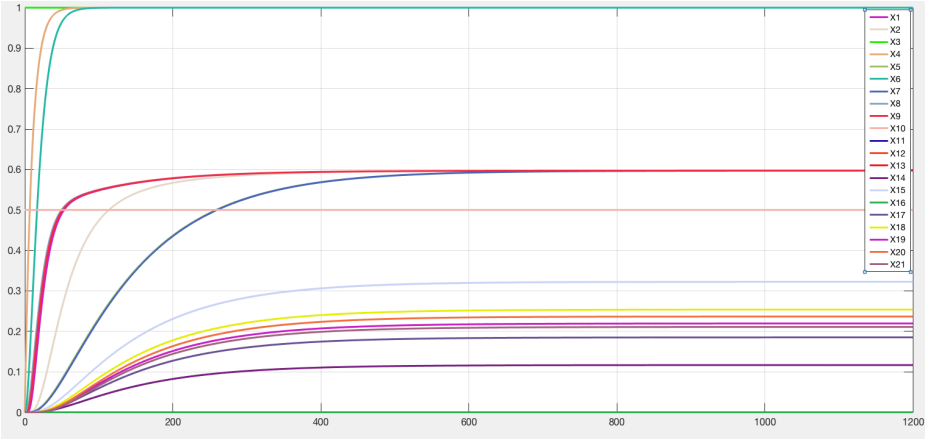

Figure 3. Simulation results for equilibrium state without eating drug

The adaptivity connection (Hebbian learning) and suppression of connection between two brain parts; Hippocampus and Prefrontal Cortex is shown in Figure 4. As it can be seen from Figure the adaptivity, learning to cope with stress and decreasing that over time starts at time around 100 and continues until time 600 to stay constant.

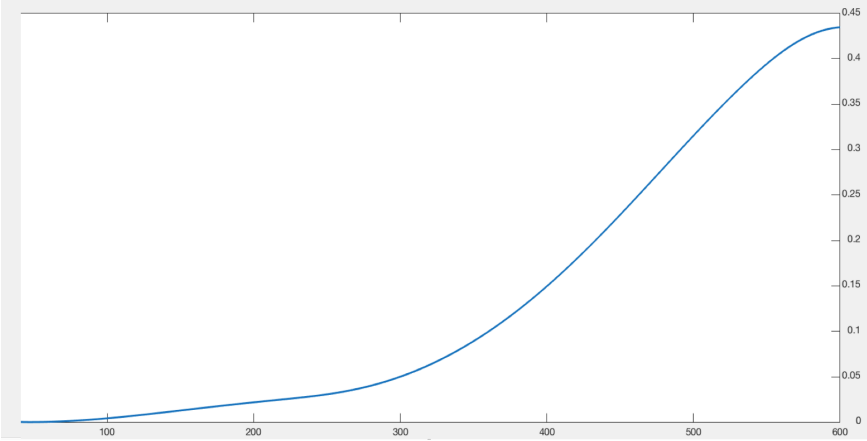

Figure 4. Simulation results for adaptivity connection weight between Prefrontal Cortex and Hippocampus

5 Mathematical Analysis

Emerging dynamic properties of dynamical models can be analyzed by simulation experiments, but some types of properties can be found by calculations in a mathematical

manner using the WIMS Linear Solver[1]. For verification of the proposed temporal-causal network model, stationary points are investigated.

To analyze the model mathematically, the solutions of linear equations of each state of the model are achieved and by comparing the outcome with the simulation results of the model using Matlab [22] one can verify the model.

$$
\begin{aligned}
&x1=x9\\
&x2=x1\\
&x3=1\\
&x4=x3\\
&2*x5=x2+x8\\
&x6=x4\\
&x7=x5\\
&2*x8=x6+x7-0.9*x20-0.9*x21\\
&x10=0.5\\
&x12=x11\\
&x11=x10\\
&x13=x12\\
&4*x14=x13 + x15+ x16+ 0.47*x17\\
&3*x15=x14+x12+x19\\
&x16 = x12\\
&2*x17=x18+0.47*x14\\
&2*x18=x17+x15\\
&2*x19=x17+x18\\
&2*x20=x18+x19\\
&2*x21=x17+20
\end{aligned}
$$

To compare mathematical results with simulation results, in particular the ones illustrated in Fig. 1 and 2, the parameter values for X3 =1 and the value of the X10 (goal) = 0.5 were used, due to the fact that the other states that are goal dependent are not able to go up and would not reach equilibrium. Some of the comparisons among simulation and mathematical analysis of states is depicted in Table 3.

Table 3. Comparing Analysis and Simulation

State	ws_c X_3	ss_c X_4	srs_c X_6	goal X_{10}	ps_{pil} X_{11}	es_{pil} X_{12}	Norepine X_{13}
Simulation	1,0000	1.0000	1.0000	0.5000	0.5000	0.5000	0.5000
Analysis	0.9999	0.9999	0.9999	0.4900	0.4900	0.4900	0.4900
Deviation	0.0001	0.0001	0.0001	0.0100	0.0100	0.0100	0.0100

[1] https://wims.unice.fr/wims/wims.cgi?session=K06C12840B.2&+lang=nl&+module=tool%2Flinear%2Flinsolver.en

State	Thal X_{15}	PFC X_{17}	Amyg X_{18}	Late.Cer X_{19}	Striatum X_{20}
Simulation	0.3158	0.2460	0.2482	0.2144	0.2312
Analysis	0.3225	0.1891	0.2538	0.2195	0.2367
Deviation	0.0067	0.0569	0.0056	0.0051	0.0055

6 Conclusion

In this paper a cognitive temporal causal network-oriented model of therapy by using drug (fluoxetine) for individuals under stress is introduced in which usage of medicine is used. The proposed model can be used to test different hypothesis and neurological principles about the impacts of the brain and the effects that different brain areas have the extinction of stress, but also on other processes.
Some simulations have been implemented, one of which was presented in the paper. This model can be used as the basis of a chatbot, a virtual agent model and to get insight in such processes and to bring up a certain cure or treatment of individuals to perform the therapies of extreme emotions for post-traumatic disorder individuals.

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