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Verification of an Agent Model for Chronic Fatigue Syndrome

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Abstract

Chronic fatigue syndrome (CFS) is a disorder that is caused by multiple factors. Much work has been conducted to understand CFS mechanisms but little attention has been paid to model the behaviour of a person who experienced chronic fatigue syndrome. The article aims to present verification results made on an agent model that was developed to simulate the dynamics of CFS under the influence of stressful events and related personal profiles. The model developed earlier combines ideas from research in affective disorder, prevention medicine, artificial intelligence, and dynamic modeling. These ideas are encapsulated to simulate how a person is fragile towards stressors, and further develops a CFS condition. The model contains eight main components that interacts each other to simulate temporal dynamics in CFS. These are predisposed factors, stressors, viral infection, demand, stress, exhaustion, fatigue and immune function. In order to verify the model, two approaches namely; mathematical verification and logical verification were used to check whether the model indeed generates results that adherence to psychological literatures.

Keywords: *Agent Based Modeling, Human Aware System, Cognitive Modeling, Chronic Fatigue Syndrome.*

1. Introduction

Chronic fatigue syndrome (CFS) is a disorder that is caused by multiple factors. CFS causes extreme fatigue and has been reported to decrease productivity of about 9.1 billion dollar per year in the United States [1,16]. CFS occur when a person experience fatigue for a duration of six months or more and experience problems such as muscle pain, memory problems, headaches, pain in multiple joints, sleep problems, sore throat and tender lymph nodes [7, 17]. CFS and fatigue is not similar. Fatigue is a common symptom in many illnesses, while CFS is quite rare. Works from [20, 21, 22] suggest various approaches to evaluate a person's psychological health. In this study, CFS conditions were not taken from evaluations of persons with CFS; however, the conditions were extracted from existing literatures. In general, post-conditions of CFS are overwhelming fatigue and weakness that make it extremely difficult for a person to perform routine and daily tasks [11,13]. Extreme fatigue may become worst with increased physical or mental activity. In CFS, fatigue that is not controlled will increase psychosocial burden. Bed rest cannot improve the situation [4, 10]. Although much work has been dedicated to understand the CFS mechanism, little attention has been paid to model the behaviour of a person who experienced chronic fatigue. As a result, an agent model was developed for the purpose and details of the model were discussed in [3]. (The agent model was verified using extensive simulations and results are presented in this article. The following presents descriptions of the remaining sections; Section 2 briefly describes the formal model for CFS. The verification process is described in Section 3. Later in Section 4, a number of simulation traces are presented to illustrate how the proposed model satisfies the expected outcomes. In Section 5, a mathematical analysis is performed in order to identify possible equilibrium in the model, followed by verification of the model against formally specified expected overall patterns, using an automated verification tool (Section 6). Finally, Section 7 concludes the article.

2. Formal Model of Chronic Fatigue Syndrome

This section presents the dynamic model. The characteristics of the proposed model are heavily inspired by the research discussed in the previous work on CFS [3]. In particular, this model combines ideas from research in affective disorder, prevention medicine, artificial intelligence, and dynamic modeling. Those ideas are encapsulated to simulate how a person is fragile towards stressors, and possibly further develops a CFS condition. All of these concepts (and their interactions) are discussed in the following paragraphs in this section. In this model, eight main components are interacting to each other to simulate temporal dynamics in CFS. These components are grouped as predisposed factors, stressors, viral infection, demand, stress, exhaustion, fatigue and immune function (refer to Figure 1).

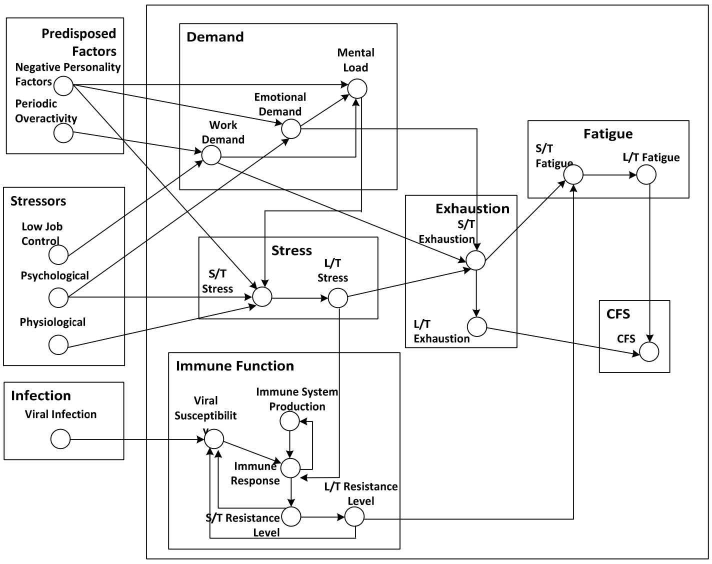

Figure 1. Global Relationships of Variables Involved in the Formation of CFS

Once the structural relationships in the model have been determined, the model can be formalized. In the formalization, all nodes are designed in a way to have values ranging from 0 (low) to 1 (high). This model involves a number of instantaneous and temporal relations, which have been discussed in greater detailed in [3].

3. Model Verification

Model verification is the process of ensuring that the conceptual description and the solution of the model are implemented correctly. Moreover, this process is performed to improve important understanding of system behaviour, improve computational models, estimate values of parameters, and evaluate system performance The first step is to make sure that the model reflects the real world. For instance, if the behaviours of the system of interest are linear, then those linear behaviours must be reflected in the formal specification underlying the model. To address this question, properties of the models and evaluate these properties with important characteristics reported in literature. Figure 2 summarizes the verification process that was involved in this model.

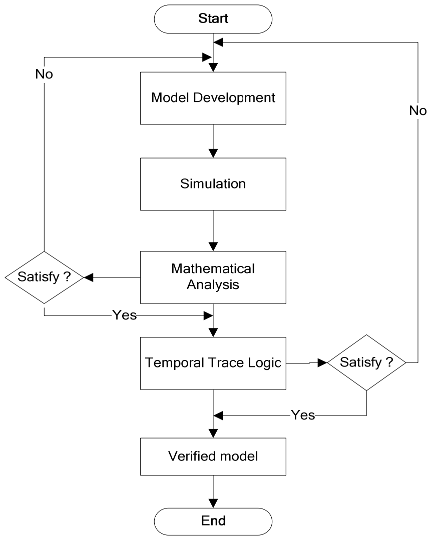

Figure 2. Verification Process

The first step is to generate simulated results (simulation) from the developed model. These simulated results provide essential traces and patterns to represent the behaviour of the model. It is assumed that these results are an abstract version of the real behaviour of CFS in humans. In this article, two methods were used for the verification process. These are mathematical analysis and logical verification. Mathematical analysis was conducted to verify the structural and theoretical correctness of the model. For this article, equillbria analysis was performed. The equilibria describe situations in which a stable situation has been reached. It means, if the dynamics of a system is described by a differential equation, then equilibria can be estimated by setting a derivative (or all derivatives) to zero. One important note that an equillibria condition(s) is considered stable if the system always returns to it after small disturbances. For example, using this autonomous equation,

$$dy/dx = f(y)$$

the equilibria or constant solutions of this differential equation are the roots of the equation

$$f(y) = 0$$

These equillibria conditions are interesting to be explored, as it is possible to explain them using the knowledge from the theory or problem that is modelled. As such, the existence of reasonable equilibria is also an indication for the correctness of the model.

For the logical verification, the ability of the Temporal Trace Language (TTL) and its software environment as a specification language and verification tool was used. TTL allows researchers to verify both qualitative and quantitative of process under analysis and has the ability to reason about time [5]. The interval of such checks varied from one second to a couple of months, related to the complexity of the models. In order to verify whether the model indeed generates results that adherence to psychological literatures, a set of properties have been identified from related literatures. These properties have been specified in a language called Temporal Trace Language (TTL). TTL is built on atoms referring to states of the world, time points, and traces. This relationship can be presented as $holds(state(\gamma, t), p)$ or $state(\gamma, t)| = p$, which means that state property p is true in the state of trace γ at time point t [5]. It is also comparable to the *Holds*-predicate in the Situation Calculus. Based on that concept, dynamic properties can be formulated using a hybrid sorted predicate logic approach, by using quantifiers over time and traces and first-order logical connectives such as $\neg$, $\wedge$, $\vee$, $\Rightarrow$, $\forall$, and $\exists$. If the verification results do not meet expected outcomes, the model was then revised. Otherwise, the model can be regarded as a model that can simulate the respected domain. The implementation of this process will be covered in Section 5 and 6.

4. Simulation Results

In this section, the model was executed to simulate a large number of conditions of individuals. With variation of these conditions, some interesting patterns were obtained. In order to visualize related patterns, three fictional humans are shown: a healthy individual (*A*), an individual with a moderate potential risk of chronic fatigue *(B*), and an individual with a high risk of chronic fatigue (*C*). Table 1 shows the initial values for each respective individual.

Table 1. Initial Values for the Simulation Experiments

Individual	Negative Personality	Periodic Activity	Low Job Control	Viral Infection
A	0.1	0.2	0.1	0.2
B	0.3	0.4	0.5	0.4
C	0.7	0.8	0.7	0.6

For both psychological and physiological stressors, two conditions were introduced, one with a very high constant stressor, and with no stressor event. These events simulate the condition of where a person was facing a sudden change in his or her life. In addition to this, there are several parameters that can be varied to simulate different characteristics. However, in this simulation, the following settings were used: $t_{max} = 500$ (to represent a monitoring activity up to 200 days), change rate $\Delta t = 0.3$, regulatory rates = 0.5 and flexibility rates = 0.2. These settings were obtained from several experiments and used to determine the most suitable parameter values for the model. For the sake of brevity, this section will only discuss the results of individual A and C. First, the simulation of person with low risk in CFS is shown (Fig. 3).

Case #1: A Healthy Person (Low Risk in CFS):

For a healthy person (A), despite the high intensity of stressors (both psychological and physiological) in the first half of the simulation trace, he or she manages to reduce future development of long-term fatigue and exhaustion.

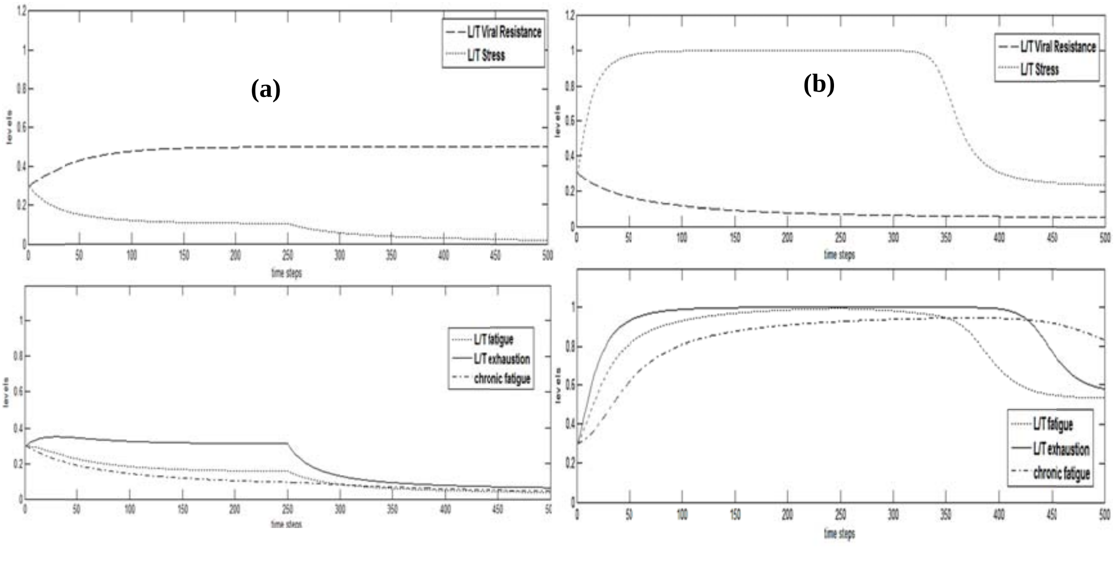

Figure 3. Simulation Results (a) Person with Low Risk in CFS and (b) Person with High Risk in CFS

Based on Fig. 3 (a), there is a gradual reduction in a long-term stress, fatigue, and exhaustion while improving resistance against viral infection. In addition, it can be seen all temporal effects are decreasing rapidly after the absent of negative events. This person tends to be stable and reduce the risk of having chronic fatigue [11].

Case #2: A Person with a High Risk in CFS:

Obviously, during this simulation, a highly vulnerable person (C) experiences CFS faster and higher as compared to person A and B (see Figure 3(b)). The result from this simulation trace is consistent with a number of findings in prior works related to the CFS [7, 8, 15, 19]. To wrap up these experimental results, the simulation traces described above satisfactorily explain the relations as summarized in Section 2. In all simulation traces, it is shown that persons with a positive personality (less neurotic), high job control and capable to manage the assigned tasks, develop CFS less often than those who are not. It is consistent with a number of findings as reported in [7, 10].The distillation of the above evidences and traces illustrates that the model reflects the basic relations that are known to influence CFS, given certain criteria of events and personality attributes.

5. Mathematical Verification

In this section, the equilibria that may occur under certain conditions are analyzed. One important assumption should be made; all exogenous variables are having a constant value. Assuming all parameters are non-zero, this leads to the following equations where an equilibrium state is characterized by:

Table 2. Nomenclature for Concepts in CFS

Concepts	Formalization
Long-term stress	*Ls*
Long-term viral resistance	*Lr*
Long-term exhaustion	*Le*
Long-term fatigue	*Lf*
Chronic fatigue	*Cf*
Short-term stress	*Ss*
Short-term exhaustion	*Se*
Short-term fatigue	*Sf*
Short-term resistant level	*Sr*
Long-term effect of exhaustion and fatigue	*Pc*
Viral susceptibility	*Vs*
Immune system production	*Ip*
Immune response	*Ir*
Emotional demand	*Ed*
Work demand	*Wd*
Viral infection	*Vi*

Where, λ_{ls}, β_{lr}, β_{le}, $\beta_{lf}\,\beta_{cf}$ are flexibility rates for respective temporal relations.

$$dLs(t)/dt = \lambda_{ls} . (Ss - Ls). Ls.(1-Ls) \quad (1)$$
$$dLr(t)/dt = \beta_{lr}.(Sr - Lr). Lr.(1-Lr) \quad (2)$$
$$dLe(t)/dt = \beta_{le} . (Se - Le) . Le . (1 - Ls) \quad (3)$$
$$dLf(t)/dt = \beta_{lf} . (Sf - Lf). Lf . (1 - Lf) \quad (4)$$
$$dCf(t)/dt = \beta_{cf} . (Pc - Cf) . Cf . (1 - Cf) \quad (5)$$

Next, the equations are identified

$$dLs(t)/dt = 0, dLr(t)/dt = 0, dLe(t)/dt=0, dLf(t)/dt =0, dCf(t)/dt = 0$$

Assuming both adaptation rates are equal to 1, therefore, these are equivalent to;

$$(Ss= Ls) \vee (Ls = 0) \vee (Ls=1) \quad (6)$$
$$(Sr= Lr) \vee (Lr=0) \vee (Lr=1) \quad (7)$$
$$(Se = Le) \vee (Le=0) \vee (Ls=1) \quad (8)$$
$$(Sf = Lf) \vee (Lf =0) \vee (Lf=1) \quad (9)$$
$$(Pc = Cf) \vee (Cf=0) \vee (Cf=1) \quad (10)$$

From here, the first conclusion can be derived based on equilibrium $Ls=1$, $Ss=Ls$, or $Ls=0$ (refer to Equation 21). By combining these three conditions, it can be re-written into a set of relationship in $(A \vee B \vee C) \wedge (D \vee E \vee F)$ expression:

$$\begin{aligned}&(Ss= Ls \vee Ls = 0 \vee Ls=1) \wedge (Sr= Lr \vee Lr=0 \vee Lr=1) \wedge \\ &(Se = Le \vee Le=0 \vee Ls=1) \wedge (Sf = Lf \vee Lf =0 \vee Lf=1) \wedge \\ &(Pc = Cf \vee Cf=0 \vee Cf=1)\end{aligned} \tag{11}$$

This expression can be elaborated using the *law of distributivity* as $(A \wedge D) \vee (A \wedge E) \vee,..,\vee (C \wedge F)$.

$$\begin{aligned}&(Ss= Ls \wedge Sr= Lr \wedge Lr=0 \wedge Se = Le \wedge Sf=Lf \wedge Pc=Cf) \vee, \ldots,\vee \\ &(Ls=1 \wedge Lr = 1 \wedge Lf =1 \wedge Cf =1)\end{aligned} \tag{12}$$

This later provides possible combinations of equillibria points that can be further analyzed. However, due to the huge amount of possible combinations, (in this case, 3^5= 243 possibilities), it is hard to come up with a complete classification of equilibria. However, for some typical cases the analysis can be pursued further.

Case # 1: $Ls=1 \wedge Lr = 1 \wedge Lf =1 \wedge Cf =1$ For this case, from equation (5) it follows that, $Vs = Vi . (1 – [\kappa_v.Sr + (1- \kappa_v)])$ and hence by equation (7) $Ir = [\gamma_i . Vs + (1 - \gamma_i)]. Ip(t)$ Moreover, from (9) it follows that $Se= \lambda_{e1}. Ed + \lambda_{e2} . Wd + \lambda_{e3}$ Finally, from (10), it follows $Sf = 0$	**Case # 2: $Lr = 0$** From equation (5) it follows that this is equivalent to $Vs = Vi . (1 – \kappa_v.Sr)$ and from (10) it follows that $Sf = Se$
Case #3: $Ls = 0$ For this case, from equation (7) it follows that the case is equivalent to: $Ir = [\gamma_i . Vs)]. Ip$ Assuming $\lambda e1$ and $\lambda e2 > 0$, this is equivalent to: $Se= \lambda_{e1}. Ed + \lambda_{e2} . Wd$	**Case #4: $Sr = Lr$:** From equation (5) it follows that $Vs(t) = Vi(t) . (1 – [\kappa_v.Sr(t) + (1- \kappa_v).Sr(t)])$ Assuming $\kappa_v = 0$, this case is equivalent to $Vs(t) = Vi(t) . (1 – Sr(t))$

Where parameters κ_v , γ_i, λ_{e1}, λ_{e2} ,and λ_{e3} provide a proportional contribution in respective relations.

6. Logical Verification

A number of simulations including the ones described in Section 4, have been used as a basis for verification of the identified properties and were successfully confirmed. Note that *tb* and *te* are the initial and final time points of the simulation period. The verification processes are as follows:

VP1: Monotonic Increase of CFS

For all time points *t1* and *t2* between *tb* and *te* in trace *γl*
if at t1 the value of the CFS is R1 and at t2 the value of the CFS is R2 and t1 < t2, then R1 ≤ R2.

P1 ≡∀γ: TRACE, ∀R1, R2: REAL, t1,t2:TIME, ∀A1:AGENT
[state(γ,t1)|= chronic_fatigue_syndrome(A1, R1) &
state(γ,t2)|= chronic_fatigue_syndrome (A1, R2) &
tb ≤ t1 ≤ te & tb ≤ t2 ≤ te & t1< t2 ⇒ R1 ≤ R2]

By checking property VP1, one can verify whether a person's CFS increases monotonically over a certain time interval. For example, the person's long-term stress turned out to increase over the second half of the trace for person that have experienced intense conditions that causes prolonged fatigue and exhaustion.

VP2: Higher Resistant Level Against Long Term Fatigue

For all time points t1 and t2 in trace γ, If at t1 the level of long term resistance of agent A1 is m1, and m1 $\geq$ 0.8 (high) and at time point t2 the level of the long term fatigue of agent A1 is m2 and t2 $\geq$ t1+d, then m2 $\leq$ 0.4 (low).

P2 $\equiv$ $\forall\gamma$:TRACE, $\forall$t1, t2:TIME, $\forall$m1, m2, d:REAL , $\forall$A1:AGENT
state(γ, t1)|= long_term_resistance(A1, m1) &
state(γ, t2)|= long_term_fatigue(A1, m2) &
m1 $\geq$ 0.8 & t2= t1+d $\Rightarrow$ m2 $\leq$ 0.4

Property VP2 can be used to check whether higher resistance level against viral infection buffers the person's long term fatigue. It is checked whether if the long term resistance in agent A1 is high (a value higher or equal to 0.8), then the long term fatigue level of agent A1 will have a low value after some time (having a value below or equal to 0.4). The property succeeded on the traces, where the resistance level against viral infection was higher or equal to 0.8.

VP3: Stability of Variable v

For all time points t1 and t2 between tb and te in trace γ if at t1 the value of v is X1 then at t2 the value of v is between X-α and X+α, where α is a constant parameter.

VP3$\equiv\forall\gamma$:TRACE,t1,t2, tb, te:TIME, X1, X2: REAL, v:VAR
[state(γ, t1)|= has_value(v, X1) &
state(γ, t1)|= has_value(v,X2) &
tb $\leq$ t1 $\leq$ te & tb $\leq$ t2 $\leq$ te] $\Rightarrow$ X1-$\alpha \leq$ X2 $\leq$ X1 + α

Property VP3 can be used to verify in which situations a certain variable does not change much. It has been found, for example, that one of the traces for a healthy person remains stable between time point 250 and 500.

VP4: Monotonic Decrease of CFS for Any Individual When Low Job Control, Low Viral Infection, Negative Personality Factor and Psychological Stressors are Reduced

When a person manages to control job, reduce possible viral infection, think positively, and avoid potential psychological stressors throughout time, then the person will reduce the level of CFS in future.

VP4 $\equiv$ $\forall\gamma$:TRACE,t1,t2:TIME,D1,D2,E1,E2,F1,F2,G1,G2,H1,H2:REAL,X:AGENT
[state(γ, t1)|= low_job_control(X, D1) & state(γ, t2)|= low_job_control (X, D2) &
state(γ, t1)|= viral_infection(X,E1) & state(γ, t2)|= viral_infection (X,E2) &
state(γ, t1)|= negative_personality(X,F1) & state(γ, t2)|= negative_personality (X,F2) &
state(γ, t1)|= psychological_stressors(X,G1) & state(γ, t2)|= psychological_stressors (X,G2) &
state(γ, t1)|= chronic_fatigue_syndrome (X,H1) & state(γ, t2)|= chronic_fatigue_syndrome (X,H2)
& D2 $\geq$ D1 & E1 $\geq$ E2 & F1 $\geq$ F2 & G1 $\geq$ G2] $\Rightarrow$ H2 $\leq$ H1

Property VP4 can be used to verify person's condition when negative factors (e.g., low job control, viral infection, negative personality, and psychological stressors) that cause CFS are decreasing throughout time [9,15].

7. Conclusion

A model was developed earlier [3] to explain the development of CFS based on personal characteristics and stressor events. Next, based on the model, a mathematical analysis was performed to demonstrate the occurrence of equilibrium conditions, fundamentally beneficial to describe convergence and stable state of the model. To prove the relations, simulations were conducted and results were verified based on several properties using mathematical analysis and logical verification. It can be concluded that the proposed model provides a basic building block in designing a software agent that will support the human. Future works of this agent and model integration will be focusing on how interactions and sensing properties can be further developed and enriched, to promote a better way to fluidly embedded this into any monitoring and health informatics system [2].

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