An Agent Model of Temporal Dynamics in Relapse and Recurrence in Depression

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Abstract. This paper presents a dynamic agent model of recurrences of a depression for an individual. Based on several personal characteristics and a representation of events (i.e. life events or daily hassles) the agent model can simulate whether a human agent that recovered from a depression will fall into a relapse or recurrence. A number of well-known relations between events and the course of depression are summarized from the literature and it is shown that the model exhibits those patterns. In addition, the agent model has been mathematically analyzed to find out which stable situations exist. Finally, it is pointed out how this model can be used in depression therapy, supported by a software agent.

Keywords: Agent Based Modeling, Temporal Dynamics, Relapse and Recurrent in Depression

1 Introduction

Unipolar depression is a mental disorder distinguished by a persistent low mood, and loss of awareness or contentment in usual activities [2]. Despite the modern era of pharmaceutical and holistic intervention, one of the primary problems with unipolar depression (i.e. a depression not related to other mental disorders) is that it has a very high rate of recurrent and relapse cases [14]. At least 60 percent of individuals who have had one depressive episode will have another, 70 percent of individuals who have had two depressive episodes will have a third, and 90 percent of individuals with three episodes will have a fourth episode [1]. Although the risk of relapse may decline with time, even for those who remain well for 5 years after an index episode, the rate of recurrence/relapse is 58 percent [3]. Despite the magnitude of the problem of recurrence and relapse, little attention has been focused on the symptom pattern in recurrent episodes of major depression [1][14]. In practice, there is a need to have a mechanism to monitor the condition of individuals who have had a previous encounter with unipolar depression, eventually improving their quality of life. In order to achieve this objective, the aim of the embedding research project is to develop an agent-based application that is able to support humans in the long term. The software agent is expected to have capabilities to understand its environment and

the individual, providing a better monitoring and assessment of the situation. To implement this capability in any software agent, it is required to incorporate a human agent model that shows how humans might fall into relapse / recurrence or stay healthy. In case a relapse or recurrence is predicted, the agent can provide to support by providing adequate remedies.

This paper focuses exclusively on the formal model for dynamics in relapse/recurrence, as it is one of the essential components in the development of a software agent that is able to monitor individuals' conditions. In the next section, the underlying principles in relapse and recurrence in unipolar depression are discussed (Section 2). From this perspective, a formal model is designed and formulated (Section 3). Later, in Section 4, simulation traces are presented to illustrate how this model satisfies the expected outcomes in recurrent / relapse. In Section 5, a detailed mathematical analysis is performed, to identify equilibria in the model. Finally, Section 6 concludes the paper.

2. Underlying Principles of Relapse and Recurrence in Depression

Before presenting the model, the main characteristics of recurrence and relapse of depression as known from the literature are described. First, the effect of repeated stressful events is explained. Then, the knowledge about the causes of relapse and recurrence are discussed.

Frequent stressful events (stressors) are correlated with a positive contribution to the development of recurrence and relapse [3]. Contrary to popular belief, repeated strikes, even when they are low, can have almost the same effect as a similar single instantaneous stressful event [1][7]. This can be explained by an analogy of striking a bell. Imagine when a bell is struck once, it emits a sound that is loud at first, and then decays in intensity. However, if each subsequent strike is applied before the sound of the preceding strike has diminished: the loudness will increase each time. Applying this to the real world, a single and low stressor event may initially be so miniscule that it is considered to cause no effect. However, lots of repeated and small stressor events will eventually lead to a higher level of potential stress than a single major stress producing event [3][12]. Therefore, the intensity of a single stressor event faced by an individual is not the only important factor, because if negative events are persistently present, they can have a stronger effect than an initial event with a higher intensity.

A key step in the development of a model to represent potential onset of relapse and recurrence is to understand how this condition may recur [12]. Stressors from the environment are the dominant components that will lead to recurrence or relapse of depression [9]. This primary mechanism however is regulated by two main apparent predisposing factors, which influence the process as moderators that can neutralize each other. These two components are simplified as *immunity* and *neuroticism* (vulnerabilities in the personality) [3][5][6]. These factors are induced by the observed evidences that there are personal differences and conditions that will increase or decrease the onset of recurrence or relapse in any individual [9][11]. In addition, in many works, these two components are assumed to influence not only the possibility of onset of a depression, but also affect the duration of it [11][12]. On the

other hand there are many factors that eventually help people to sustain their well-being. These factors are closely related to: (a) *coping skills*, (b) *being assertive*, and (c) *knowing when to seek help* [4][6][8]. The first is the ability to cope with the adversities. *Coping skill* is a behavioral and biologically wired tool which may be used by individuals to offset stressor events without correcting or eliminating the underlying condition. On the basis of many theories in depression, coping responses and strategies have been most frequently divided into problem focused coping and avoidant coping responses [9][10]. *Problem focus coping* responses allow an individual to increase the perceived control over their problem; it is proven in many studies that they are able to reduce the risk of onset of a depression [4]. They involve attempts to do something constructive about the stressful conditions that are harming an individual, rather than to make it worsen. In contrast, *avoidance coping* is detrimental in nature. When feelings of discomfort appear through stressor events, people find ways of not experiencing them. Such a strategy may work in a very short term, but it is mostly considered as an inadequate approach of coping [8]. The second component is being *assertive*. Individuals who are assertive tend to be aware of their emotions and communicate these in clear-cut manner and are able to make and meet goals and challenges through respect and perseverance [5]. In many cases, people with a high assertive level are more likely to be more proactive and problem focused rather than unassertive individuals [1][9].

The last component is the ability to seek *social support*, ("having positive interaction of helpful behavior provided to a person in need of support") [4]. As a multidimensional concept in nature, social support also includes many other facets that may finally determine if social support is constructed such as having the ability to create a support network [8][13]. There are many characteristics of individuals that influence their potential abilities of seeking support or vice versa. For example, an individual who is highly neurotic, using more avoidant coping and having a lack of self esteem may not be able to request support, and later it may disengage him/herself from potential social support.

In short, the following relations can be identified from the literature: *(1)* a series of smaller stressor events can lead to the recurrence or relapse; *(2)* stressor events directly affect the potential onset of relapse /recurrence; *(3)* neuroticism aggravates the effect of stressor events on the potential onset of a depression;*(4)* assertiveness and immunity will diminish the potential of onset, and *(5)* a combination of good social support and coping skills will reduce the risk of having future relapse/recurrence.

2 Model for Relapse and Recurrence

The characteristics of the proposed model are heavily inspired by the research discussed in the previous section on recurrence and relapse, especially in depression. In particular, this model combines ideas from research in affective disorder, prevention medicine, artificial intelligence, and dynamic modeling. Those ideas are encapsulated in a way that allows to simulate how an individual is fragile towards stressors, and possibly further develops a depression. All of these concepts (and their interactions) are discussed in the following paragraphs in this section.

3.1 Formalizing the Model Relationships

In this model, there are three major components that will represent dynamic interactions of human agent abilities involved in recurrence/relapse namely; *environment*, *personality*, *social support*, and *coping strategies*. By combining these characteristics together, it will allow a hypothesis or expected behavior for the human agent to be monitored.

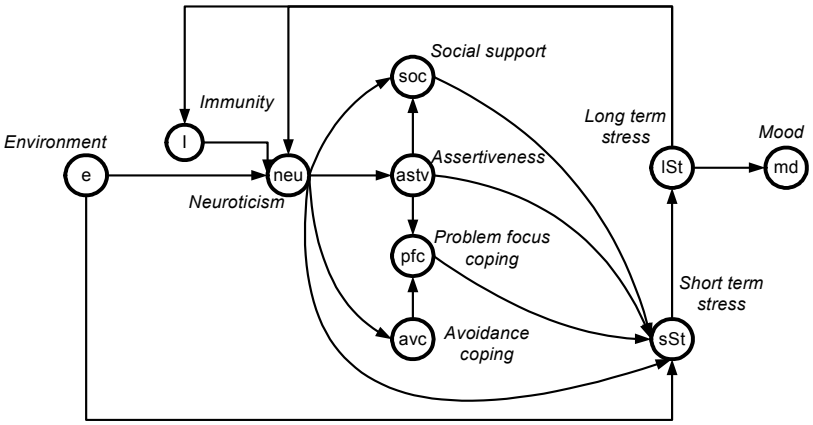

Fig. 1. Global Relationships of Variables Involved in the Onset of Relapse and Recurrence Depression

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). The interaction will determine the new value of it, either by a series of accumulations or an instantaneous interaction for each node.

Stressor Events: In the model, the stressor events *(e)* are generated by simulating potential effects throughout *t* time using weighted sum of three types of events; life (*le*), chronic (*ce*), and daily (*de*) events.

$$e(t) = w_1.le(t) + w_2.ce(t) + w_3.de(t), \quad \textbf{(1)}$$

The role of these factors in the model is to represent a series of events. Stressors are seen as very intense when $e(t) \rightarrow 1$, and no stressors are represented by $e(t) \rightarrow 0$.

Dynamics of Neuroticism: In this model, the neurotic level *(neu*) describes the interactions between environment (*e*), personal immunity trait (*I*), and prior exposure to long-term stress (*lSt*), in a time interval between t and $t+\Delta t$. Here, α_{neu} is a parameter for a change rate, and β_{neu} is a parameter for the contribution effect of the previous neurotic rate in this equation.

$$neu(t+\Delta t)= neu(t)+\alpha_{neu}.(1-neu(t)).[(f(e(t),I(t)).lSt(t))-\beta_{neu}.neu(t))]. \Delta t \quad \textbf{(2)}$$

where, $f(e(t),I(t))$ is a logistic unit function, $1/(1+\eta e^{-\alpha(e(t)-I(t))})$

Social Support, Problem Focus Coping, Assertiveness, and Immunity: Social support (*soc)* is computed by multiplying the factor of being assertive by the ability of less or non- neurotic. Problem focus coping *(pfc)* is also computed with the same approach, but with a negative association in avoidant coping (*avc)*. The α_{avc} is a proportional rate for the effect of neurotic level in *avc*.

$$soc(t)=astv(t).(1-neu(t)) \quad \textbf{(3)}$$

$$pfc(t)=astv(t).(1-avc(t)) \quad \textbf{(4)}$$

$$avc(t)=\alpha_{avc}.neu(t) \quad \textbf{(5)}$$

Assertiveness *(astv)* depends on the interaction between the normal assertive value within an individual and the condition of being less or non-neurotic. The immunity *(I)* level interaction also having a similar behavior, but it is related to the interaction in a long term stress level.

$$astv(t) = \alpha_{astv}.astv_{norm}+(1-\alpha_{astv}).(1-neu(t)). astv_{norm} \quad \textbf{(6)}$$

$$I(t) = \alpha_I.I_{norm}+(1-\alpha_I).(1-lst(t)). I_{norm} \quad \textbf{(7)}$$

Dynamics of Short Term Stress, Long Term Stress, and Mood: Short term stress *(sSt)* is modeled by instantaneous relationships between the environment, neurotic level, and reducer components, ψ (a combination of social support, assertiveness, and problem focus coping). Long term stress *(lSt)* is primarily contributed the accumulation exposure towards short term stress and later will influence the level of mood *(md)* in a time interval between t and $t+\Delta t$.

$$sSt(t)=\beta_{sst}.e(t)+(1-\beta_{sst}).neu(t).(1-e(t)).(1-\psi) \quad \textbf{(8)}$$

$$lSt(t+\Delta t) = lSt(t)+ \alpha_{lst}. (1- lSt(t)).(sSt(t)- \beta_{lst} lSt(t)).\Delta t \quad \textbf{(9)}$$

$$md(t+\Delta t) =md(t)+ \eta_{md}. (1-md(t)).(lSt(t)- \beta_{md}.md(t)).\Delta t \quad \textbf{(10)}$$

where η_{md} ,β_{md} , α_{lSt} , β_{sSt} and β_{lSt} denote the proportion change rates for all respective equations.

4 Example Simulation Traces

In this section, the model was executed to simulate a large number of conditions of individuals. In this section, three examples are shown: a healthy individual **(A)**, an individual with a potential risk of relapse and recurrence **(B),** and an individual with severe conditions **(C).** The initial settings for the different individuals are the following (*neu (t=0), $astv_{norm}$, I_{norm}*); **A** (*0.1, 0.8, 0.8*), **B** (*0.5, 0.5, 0.4*), and **C** (*0.8, 0.2, 0.1*). In all cases, the initial long term stress and mood value is initialized as 0.3, 0.1 respectively. Corresponding to these settings, the level of severity (or potential onset) is measured, defining that any individuals scored more than 0.5 in their mood

level (within more than 336 time steps) will be considered as reaching the recurrent or relapse stage. These simulations used the following parameters settings: $t_{max}=1000$ (to represent a monitoring activity up to 42 days), $\Delta t=0.3$, $\alpha_{lst}=0.3$, $\eta_{md}=0.2$, $\beta_{sst}=0.3$, $\alpha_{I}=0.7$, $\alpha_{astv}=0.5$, $\alpha_{avc}=0.5$, $\alpha_{neu}=0.4$, and with all decay terms are assigned as 0.02.

Result # 1: Simulation Trace for Prolonged-Fluctuating Stressor Events
During this simulation, each type of individual has been exposed to an extreme stream of stressor events, with a rapid alteration between each corresponding event. This kind of pattern is comparable to the repeated strike event, where stressor events always occur when the previous events were ended.

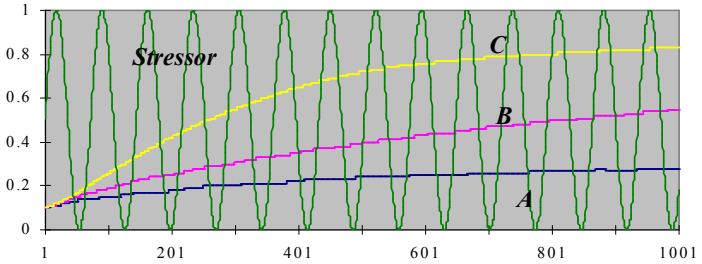

Fig.2. Relapse / Recurrent Onset for Each Individual in Prolonged Stressor Events

In this simulation trace, it shown that an individual C (*high neurotic, low in assertive* and *immunity*) tends to get into onset much faster compared to other individuals. Note that the individual B (*moderate neurotic, assertive,* and *immunity*) shows a gradual increasing level of potential onset and possibly will experience relapse / recurrent if that individual is having constant exposure towards stressors. Individual A however is less prone to develop a potential onset condition within a short period of time.

Result # 2: Simulation Trace for Decrease Stressor Events
This simulation trace shows two types of periods, one with a very high constant and with a very low constant stressor event. These events occurred in a constant behavior for a certain period of time (approximately within 20 days).

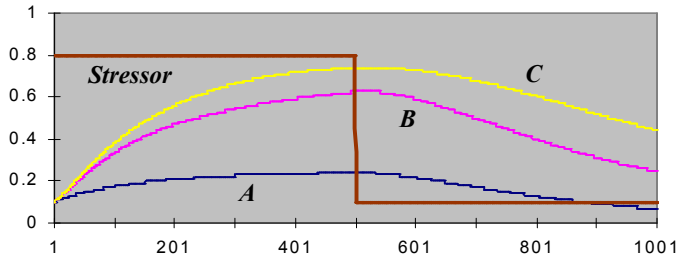

Fig.3. Relapse / Recurrent Onset for Each Individual in Fluctuated Stressor Events

Also here it can be seen that individual C gets into a bad mood much faster than the others. Moreover, even at the end of the simulation time, the mood of individual C is

worse than the mood of the other two individuals. Using a similar experimental setting, with t_{max}=10,000, the end of the experimental results show all individuals will have a normal mood level.

Result # 3: Simulation Trace with Social Support, and Problem Focus Coping Skills (Reducer)

As initially discussed in Section 2, a combination of social support, and problem focus coping skills is expected to help any individuals to reduce potentially risk in relapse / recurrence. The combination of these factors will be represented by R_A, R_B, and R_c for the respective human agents. To visualize the effect of these, frequently repeating low stressor events were simulated. Figure 4 illustrates how these combinations, mood levels and stressor events are influencing each other.

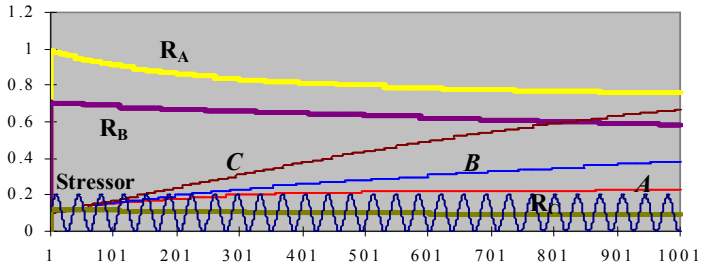

Fig.4. Relapse / Recurrent Onset for Each Individual with a Combination of Reducer

Figure 4 shows that a healthy individual (*A*) has much higher reducer factors than less healthy individuals. These reducing factors limit the effect of the incoming stressors. Also it can be seen that the reducer factors decrease over time, due to the relatively low but frequent stressors. The patterns for the different individuals are the same as in Figure 2, although the final mood level is lower in Figure 4 because of the less intense stressors fluctuation.

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 individuals with higher assertiveness, immunity and less neurotic levels develop less often a relapse compared those who are not. In addition, a higher neurotic level eventually aggravates the potential risk of onset, as illustrated in all simulation traces. The effects of stressor events on relapse/ recurrence onset are also exemplified. In all simulation traces, it is apparent that frequent or high stressor events contribute to the potential risk of onset. Furthermore, the effect of the reducers is also examined, where in Figure 4, it depicts that when the reducer level is decreasing, the person is also prone to a relapse, or vice versa. This distillation of above evidences and traces illustrates that this model reflects the basic relations that are known to influence relapse and recurrence, given certain criteria of events and personality attributes.

5 Mathematical Analysis

In this section the equilibria are analyzed that may occur under certain conditions. The equilibria describe situations in which a stable situation has been reached. Those equilibria are interesting as it should be possible to explain them using the knowledge of the domain that is modeled. As such, the existence of reasonable equilibria is an indication for the correctness of the model. To analyze the equilibria, the available temporal and instantaneous equations are filled with values for the model variables such that the derivatives or differences between time point t and $t + \Delta t$ are all 0 (in particular for neuroticism, long term stress and mood). Moreover, for an equilibrium, the external input is also assumed to be constant. To start, for an equilibrium for neuroticism it holds as ; $(1\text{-}neu).(f(e,I).lSt - \beta_{neu}.neu) = 0$

This is equivalent to $neu = 1$ or $neu = f(e,I).lSt/\beta_{neu}$, where $f(e,I) = 1/(1+\eta e^{-\alpha(e-I)})$. Assuming high steepness of the threshold function provides the cases $e \leq I$ (where $f(e,I) = 0$) or $e > I$ (where $f(e,I) = 1$). Under this assumption the cases are $neu = 1$ or $neu = 0$ and $e \leq I$ or $neu = lSt/\beta_{neu}$ and $e > I$. For an equilibrium for assertiveness it holds;

$$astv = \alpha_{astv}.astv_{norm} + (1\text{-}\alpha_{astv}).(1\text{-}neu).astv_{norm}$$
$$= astv_{norm} - (1\text{-}\alpha_{astv}).\ neu.\ astv_{norm}$$

Meanwhile, for an equilibrium for immunity it holds:

$$I = \alpha_I.I_{norm} + (1\text{-}\alpha_I).(1\text{-}lst).\ I_{norm} = I_{norm} - (1\text{-}\alpha_I).lSt.I_{norm}$$

For an equilibrium for long term stress it holds $(1\text{-}\ lSt).(sSt - \beta_{lst}\ lSt) = 0$, which is equivalent to $lSt = 1$ or $sSt = \beta_{lst}\ lSt$. For an equilibrium for mood it holds $(1\text{-}md).(lSt - \beta_{md}.md) = 0$ which is equivalent to $md = 1$ or $md = lSt\ /\beta_{md}$. Table 1 provides a summarization of these equilibria.

Table 1. Equilibrium Equations for Respective Variables

Var.	Equilibrium equations
neu	$neu = 1$ or $e \leq I$ and $neu = 0$ or $e > I$ and $\beta_{neu}\ neu = lSt$
astv	$astv = astv_{norm} - (1\text{-}\alpha_{astv}).\ neu.\ astv_{norm}$
soc	$soc = astv.(1\text{-}neu) = (\ astv_{norm} - (1\text{-}\alpha_{astv}).\ neu.\ astv_{norm})(1\text{-}neu)$
avc	$avc = \alpha_{avc}.neu$
pfc	$pfc = astv.(1\text{-}avc) = (\ astv_{norm} - (1\text{-}\alpha_{astv}).\ neu.\ astv_{norm})\ (1\text{-}\alpha_{avc}.neu)$
I	$I = I_{norm} - (1\text{-}\alpha_I).lSt.\ I_{norm} = I_{norm} - (1\text{-}\alpha_I).lSt.\ I_{norm}$
sSt	$sSt = \beta_{sst}.e + (1\text{-}\beta_{sst}).neu.(1\text{-}e).(1\text{-}\psi),\ where\ \psi = w_1.soc + w_2.pfc + w_3.astv$ $= \beta_{sst}.e + (1\text{-}\beta_{sst}).neu.(1\text{-}e).(1\text{-}(w_1.(astv_{norm}\text{-}(1\text{-}\alpha_{astv}).neu.\ astv_{norm})(1\text{-}neu)) + w_2(astv_{norm}\text{-}(1\text{-}\alpha_{astv}).neu.astv_{norm})\ (1\text{-}\alpha_{avc}.neu)) + w_3.(\ astv_{norm} - (1\text{-}\alpha_{astv}).\ neu.\ astv_{norm})))$
lSt	$lSt = 1$ or $sSt = \beta_{lst}\ .lSt$
Md	$md = 1$ or $md = lSt\ /\ \beta_{md}$

It turns out that all values can be expressed in terms of either *neu* or *lSt*: in the Table 1 the values *astv, soc, avc, pfc* have been expressed in *neu*, and the values *md, sSt, I* have been expressed in *lSt.* Then by the equation for short term stress the value *lSt* can be expressed in *neu*.

$$\beta_{lst}\, lSt = \beta_{sst}.e+(1-\beta_{sst}).neu.(1-e).(1-(w_1.(astv_{norm} - (1-\alpha_{astv}).neu.astv_{norm})(1-neu)) + w_2(astv_{norm} - (1-\alpha_{astv}).neu.astv_{norm})(1-\alpha_{avc}.neu)) + w_3.(astv_{norm} - (1-\alpha_{astv}).neu.astv_{norm})))$$

From the equation for neuroticism two cases occur; $e \leq I$ and $neu = 0$ or $e > I$ and $\beta_{neu}\, neu = lSt$. These cases will be addressed in some more detail.

Analysis of Case $e \leq I$ and $neu = 0$: In this case, the following values are found:

$neu = 0,\ astv = astv_{norm}$, $soc = astv_{norm}$, $avc = 0$, $pfc = astv_{norm}$

$sSt = \beta_{sst}.e$, $lSt = \beta_{sst}.e\ /\beta_{lst}$, $I = I_{norm} - (1-\alpha_I).\ \beta_{sst}.e\ /\beta_{lst}.\ I_{norm}$

$md = 1$ or $md = \beta_{sst}.e\ /\beta_{lst}\ \beta_{md}$

Here the condition $e \leq I$ is equivalent to: (1) $ie \leq I_{norm} - (1-\alpha_I).\ \beta_{sst}.e\ /\beta_{lst}.\ I_{norm}$, (2) $e\ (1+(1-\alpha_I).\ \beta_{sst}.\ /\beta_{lst}.\ I_{norm}) \leq I_{norm}$, and (3) $e \leq I_{norm}\ /(1+(1-\alpha_I).\ \beta_{sst}.\ /\beta_{lst}.\ I_{norm})$ These conditions illustrate the generic condition that an extremely healthy individual (not neurotic at all) that encounters only events that are less intense than its immunity level will never develop a relapse or recurrence.

Analysis of Case $e > I$ and $\beta_{neu}\, neu = lSt$: In this case the equation becomes:

$$\beta_{lst}\, \beta_{neu}\, neu = \beta_{sst}.e+(1-\beta_{sst}).neu.(1-e).(1-(w_1.(astv_{norm} - (1-\alpha_{astv}).neu.astv_{norm})(1-neu)) + w_2(astv_{norm} - (1-\alpha_{astv}).neu.astv_{norm})(1-\alpha_{avc}.neu)) + w_3.(astv_{norm} - (1-\alpha_{astv}).neu.astv_{norm})))$$

Rewriting this equation in general, provides an equation of third degree, which for given values of the parameters can be solved in an algebraic manner or numerically. For some special cases of parameter values the equation becomes simpler. For example, when $\alpha_{astv} = 1$, it becomes a quadratic equation:

$$\beta_{lst}\, \beta_{neu}\, neu = \beta_{sst}.e+(1-\beta_{sst}).neu.(1-e).(1-(w_1.astv_{norm}\,(1-neu) + w_2\, astv_{norm}\,(1-\alpha_{avc}.neu)) + w_3.\, astv_{norm}\, neu.\, astv_{norm})))$$

This situation describes how an individual that encounters events which are more intense than its immunity level will not change, if his long-term stress level is in balance with his level of neuroticism.

6 Conclusion

The grand challenge addressed in the research that is reported in this paper is to develop a software agent that is capable of monitoring individuals' condition in certain events. In this paper a first step has been taken. A model has been developed that is able to explain the onset of recurrence and relapse based on personal characteristics and stressor events. The proposed model is heavily inspired by

scientific findings about the relapse or recurrence onset. Having this foundation, a formal model has been developed and used to simulate different individuals' situations, which corresponded to their personality and characteristics. A mathematical analysis has been performed to demonstrate the occurrence of equilibrium conditions, fundamentally beneficial to describe convergence and stable state of the model. The proposed model provides a basic building block in designing a software agent that will support the human. Future work of this agent and model integration will be specifically focus 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.

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