ICT4Depression

User-friendly ICT Tools to Enhance Self-Management and Effective Treatment of Depression in the EU

Grant Agreement Number: FP7 – 248778

Deliverable 3.2: Report with specification techniques as well as the actual specification of therapies

Due date of deliverable: 28-02-2011
Actual submission date: 28-02-2011

Start date of project: 01-01-2010 Duration: 36 months

Coordinator	VU University Amsterdam
Deliverable leading partner	VU University Amsterdam
Contributing partners (this deliverable only)	All partners involved in the project.
Revision	Version 2.0 (28-02-2011)

Project co-funded by the European Commission under the Seventh Framework Programme (FP7)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services).	
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Executive Summary

Within this document, a next step is made in the intelligent reasoning system to support depressed patients in a dedicated manner. This step encompasses the specification of a so-called virtual patient which allows the simulation of the internal states of a depressed patient. In order to come to such a model, theories from the domain of Clinical Psychology have been taken as a basis. In addition, the virtual patient is extended with the influences of the various therapies that are part of the ICT4Depression project, to enable the simulation of the response of the patient to the therapy. This fully specified virtual patient then allows running simulations to predict what will happen with the patient, given a certain therapy (or no therapy). These simulations enable a comparison between this prediction and the actual state of the patient (based upon the approach presented in D3.1), which can potentially be used to given dedicated feedback (which will be addressed in D3.4) and trigger the selection mechanism of the type of therapy (to be addressed in D3.3).

Contents

1. Introduction

Within the overall ICT4Depression system, one important aspect is to respond to the monitored behavior in an intelligent way. Such intelligent responses are generated by the reasoning part of the ICT4Depression system. In Deliverable 3.1 an approach has already been introduced which is able to derive the current trends in the behavior of the patient by aggregating information obtained from the sensors (i.e. the mobile phone, physiological sensors, MEMS, and the website). This aggregation leads to an overall picture of the patient which expresses the current state of the patient (i.e. how well is the patient doing) as well as the current therapeutic involvement of the patient. Interpreting this information in order to derive whether feedback should be generated, or whether another type of action should be undertaken is however far from trivial. The main problem in interpreting the information is that knowledge is needed on the expectations of the values of the patient in order to derive whether the patient lives up to the expectations, performs even better, or performs worse than the expectations. If for instance the patient state is not improving in the beginning of the therapy, and this was expected in advance, this would result in motivational feedback. In case a huge improvement was however expected in the beginning, more drastic measures could be undertaken (e.g. switch therapy). Hence, having a prediction on the development of the states of the patient and therapy is essential. In this deliverable, a model which can act as a virtual patient is introduced. The model consists of the most relevant states that play a role in people suffering from a depression and is able to predict the developments of these states over time. Also, therapies are part of the model, including their main principles of working, thereby showing the influence of the therapy upon the states of the patient.

This deliverable is organized as follows. First, in Section 2 the scientific background of the approach is presented. The general virtual patient is introduced in Section 3. Section 4 presents an extension of the virtual patient thereby also taking the influence of the various therapies into account. The connection with Deliverable 3.1 (patient state and therapeutic state trends) is made in Section 5, and finally, Section 6 is a discussion.

2. Scientific Background

Traditionally, emotions were often left out of consideration in the areas of cognitive modeling, and user modeling. Only few computational models of mood and depression have been developed (see [Davidson *et al.*, 2002] for an example). Avoiding negative moods may be a nontrivial challenge faced by a human organism. In the richer countries the number of persons struggling with longer periods of negative moods, like in a depression, is relatively high, and is expected to increase further. Major depression is currently the fourth disorder worldwide in terms of disease burden, and is expected to be the disorder with the highest disease burden in high-income countries by the year 2030 (cf. [Mathers, 2006]). To avoid or to recover from a negative mood requires mechanisms for mood regulation.

Within clinical psychology in the last decennia, several theories have been developed about the course and treatment of a depression. A classic behavioral model of uni-polar depression by **Lewinsohn** (1979) states that depression results from a stressful event that disrupts normal behavior patterns. According to Lewinsohn, a low rate of behavior (often caused by inadequate social skills) is the essence of the depression and the cause of all other symptoms. Part of his theory is the hypothesis that there is a causal relationship between lack of positive reinforcement from the environment and the depression.

According to many psychologists, the mood of a person is influenced by stressful events and the abilities a person has to cope with these events. In the stress, appraisal and coping theory by **Lazarus and Folkman** (1984) they emphasize that stress is not a direct response to a stressor, but a response to a situation that has been appraised as taxing or exceeding ones resources. When a situation has been identified as stressful, coping skills are applied. Coping is defined as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person". In the theory of Lazarus and Folkman, vulnerability is conceptualized in terms of coping resources. A vulnerable person is said to have "deficient coping resources". Commitments are also claimed to be important by Lazarus and Folkman. It is stated that "commitments are an expression of what is important to persons, and they underlie the choices persons make". Hence, commitments play a role in selecting the situation.

Aaron Beck developed a cognitive theory of depression (1972). He believes that depression is due to negative views towards the self, world, and future in particular. Depressed persons have thoughts like "nobody cares about me" or "I can't do this task". In his theory depressed persons also use faulty information processing, like selective attention, to maintain their negative views, even if the situation is actually more positive.

Gross (1998, 2001) developed a theory about emotion regulation. The core idea is that you can regulate emotions by choosing situations, subsituations, aspects and meanings with emotion levels that are near the preferred emotion level. By choosing and changing the emotional value of situations, the mood level can be regulated so that it is close to the prospected mood level. How well a person is able to do this depends on the sensitivity of a person.

The diathesis-stress model was first introduced by **Zubin and Spring** (1977) for schizophrenia. Now, there are many different stress-vulnerability models [Ingram and

Luxton, 2005], most of which involve predisposed factors (vulnerability or diathesis) and external influences (stress) that together determine whether a person develops a mental disorder or not. There is no typical definition, but most theories assume that vulnerability is a trait, is stable but can change, is endogenous to individuals and is usually latent [Ingram, Miranda, and Segal (1998)].

Besides theories that exist in clinical psychology also in recent neurological literature many contributions can be found about relations between mood regulation or depression and brain functioning; e.g., [Anand *et al.*, 2005; Beauregard, *et al.*, 2006; Davidson *et al.*, 2002; Drevets, 2003; Drevets, 2007; Harrison, 2002; Konarski, *et al.*, 2008; Levesque *et al.*, 2003; Mayberg, 2003]. Much neurological support has been found for the processes of emotion and mood regulation, and in particular for modulation (down-regulation) of a negative mood in order to avoid or recover from a depression; e.g., [Anand *et al.*; 2005; Beauregard, *et al.* 2006; Davidson *et al.*, 2002; Levesque *et al.*, 2003].

Next to the theories concerning the course of depression and general ideas of treatments, several specific treatments have been developed over the years including activity scheduling (cf. [Lewinsohn, 1979]), cognitive behavior therapy [Beck, 1972], problem solving (see e.g. [D'Zurilla and Nezu, 1982] and [D'Zurilla, 1986]), and exercise therapy (see e.g. [Cotman and Berchtold, 2002; Dunn *et al.*, 2005]).

3. General Model for Virtual Patient

In this section, a general model is presented for the virtual patient. Hereby, the most important states and relationship between these states are taken from the literature and formalized. Simulation results are shown, and verification is performed of the patterns that result from the model to see whether these results indeed comply with the theories.

3.1 Description of the Mood Regulation Model

The theories described in Section 2 have been used to develop the model of mood and depression. In the next subsection, the main concepts from the theories are identified. Then, the conceptual model is described. The last subsection provides the formalization of the conceptual model.

3.1.1 Concepts from theory

From the behavioral theory of Lewinsohn the idea is adopted that a lack of reinforcement from the environment (i.e., *situation*) influences the choice of a new situation via the mood. According to Beck the perception of the situation will be negatively influenced by the thoughts, this is referred to as the *appraisal*. This is also in line with the ideas of stress by Lazarus and Folkman: a part of the model represents the actual environmental situation experienced, whereas there is also a part that represents the interpretation of the situation specific for the person the model concerns. In addition, their idea of *vulnerability* (also called *diathesis)* is used, as having deficient coping resources and Zubin and Spring's idea of vulnerability as having a predisposition for developing a disorder. *Coping* is used in the model presented in this deliverable by means of continuously trying to adapt the situation in such a way that an improvement is achieved. This is done through a regulation system in the person, which is inspired by Gross's theory about emotion regulation by striving for a specific *prospected mood level*.

3.1.2 Conceptual model of mood dynamics

In the model, it is assumed that every situation has an emotional value, which represents the extent to which a situation is experienced as something positive. The *objective emotional value of situation* (OEVS) represents how an average person would perceive the situation. A situation can be an event or series of events one has no control over, or that are chosen or influenced by the person. The *appraisal* can differ from OEVS when the *thoughts* of the person are more positive or more negative than average. Negative thoughts will cause the appraisal to be lower than OEVS, which is often the case with a depression. How one perceives the situation (appraisal) influences the *mood* one is in and the *thoughts* one has. When the person is in a positive situation, mood level and thoughts will increase. For example, attending a birthday party, which is usually a positive experience, causes a better mood and more positive thoughts. In contrast, an argument with a close friend has a low emotional value and causes a bad mood and negative thoughts. By changing or choosing a situation, one can influence their own mood level (e.g. choosing to go to the birthday party when one feels down increases the mood level). The complex notion of mood is represented by the simplified concept *mood level*, ranging from low corresponding to a bad mood to high corresponding to a good mood. The mood level influences and is influenced by *thoughts*. Positive thinking has a positive effect on the mood and vice versa. The mood level someone strives for, whether conscious or unconscious is represented by *prospected mood level*. This notion is split into a *long term (LT) prospected mood level*, an evolutionary drive to be in a good mood, and a *short term (ST) prospected mood level*, representing a temporary prospect when mood level is far from the prospected mood level. The node *sensitivity* represents the ability to change or choose situations in order to bring mood level closer to prospected mood level. A high sensitivity means that someone's behavior is very much affected by thoughts and mood, while a low sensitivity means that someone is very unresponsive. The level of sensitivity itself is influenced by mood level and thoughts. A low mood level and negative thoughts can decrease the sensitivity and a high mood level and positive thoughts can increase the sensitivity. Mood level, prospected mood level and sensitivity together influence *OEVS* by choosing or changing a situation.

The new value of a node is determined by preceding nodes and the previous value of that node. Decay factors determine how fast the previous value of the node decays. For the entire model there are two decay factors: *vulnerability* for downward regulation and *coping* for upward regulation. The term *coping* represents the skills one has to deal with negative moods and situations. A person with very low vulnerability will probably never get a depression, because mood, thoughts and sensitivity will go down very slowly with a negative event. That person is therefore always capable of choosing situations that have a positive influence on his/her mood level and emotions. High vulnerability and low coping skills will cause a person to get a depression very easily when a negative event occurs, because mood, thoughts and sensitivity will decrease fast. It will be very difficult to climb out of a depression: the upward regulation of mood, thoughts and sensitivity will go very slow.

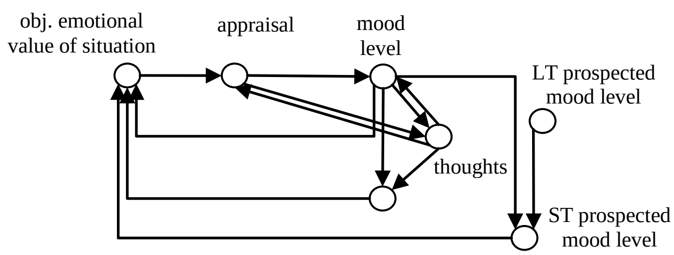

Figure 1. Model of mood dynamics

3.1.3 Formalization

The model described above is formed into a quantitative model in this section. The basic principle used to make this translation is to find equations that incorporate the qualitative trends observed in the literature described before. All nodes in the model have values between 0 and 1. The first formula (equation 1) describes the calculation of the new value for *OEVS* using *sensitivity*, *mood*, *LT prospected mood* and *beta*. If the mood level is below the *ST prospected mood* level (beta times LT prospected mood level), the new situation will be higher than the previous one. The amount of change is mediated by sensitivity (the higher the sensitivity, the faster the optimal situation is reached) and by the previous situation (the closer to the optimal situation, the smaller the steps).

$$
\begin{aligned}
& oevs(t+\Delta t) = oevs(t) - sensitivity(t) \cdot \varphi \cdot \Delta t \\
& \varphi = \begin{array}{c|l} oevs(t) \cdot \delta_{mood} & \delta_{mood} >= 0 \\ (1 - oevs(t)) \cdot \delta_{mood} & \delta_{mood} < 0 \end{array} \\
& \delta_{mood} = mood(t) - \beta \cdot lt\_prosp\_mood
\end{aligned}
\qquad (1)
$$

The *appraisal* (equation 2) depends on the *OEVS*, *thoughts* and *coping* and *vulnerability*. The value for thoughts has a negative influence on appraisal by projecting thoughts (within range [0,1]) onto the part of the scale below the old appraisal value (range [0, appraisal]). Thoughts have a positive influence by projection of thoughts onto the upper part of appraisal (range [appraisal, 1]). The factors coping and vulnerability determine the degree of positive and negative influence respectively.

Persons with high vulnerability for depression will use thoughts mostly to downregulate their appraisal, whereas balanced persons will consider their appraisal as similar to the OEVS and their thoughts.

$$\begin{aligned} & appraisal(t+\Delta t) = appraisal(t) + (\gamma - appraisal(t)) \cdot \Delta t \\ & \gamma = vulnerability \cdot oevs(t) \cdot thoughts(t) + \\ & \quad coping \cdot (1-(1-oevs(t)) \cdot (1-thoughts(t))) \end{aligned} \tag{2}$$

The new *mood level* (equation 3) is influenced by the *appraisal* (with weight $w_{appraisal\_mood}$) and *thoughts* (with weight $w_{thoughts\_mood}$). If the new mood level is to be increased, the decay factor of the previous mood is *coping*. If the new mood level is to be decreased, *vulnerability* is used to determine the speed of the fall.

Good coping skills result in a faster increase of mood when the situation and thoughts are increasing. Bad coping skills result in a faster decrease of mood when *SEVS* and thoughts are low.

$$\begin{aligned} & mood(t+\Delta t) = \begin{cases} mood(t) + coping \cdot (\phi - mood(t)) \cdot \Delta t & \phi >= mood(t) \\ mood(t) + vulnerability \cdot (\phi - mood(t)) \cdot \Delta t & \phi < mood(t) \end{cases} \\ & \phi = appraisal(t) \cdot w_{appraisal\_mood} + thoughts(t) \cdot w_{thoughts\_mood} \end{aligned} \tag{3}$$

The formula for the new *thoughts* value (equation 4) is similar to the formula for mood: thoughts is influenced by *appraisal* (with weight $w_{appraisal\_thoughts}$) and *mood* (with weight $w_{mood\_thoughts}$) The decay factors are *coping* and *vulnerability* for upwards and downwards regulation respectively.

$$\begin{aligned} & thoughts(t+\Delta t) = \\ & \begin{cases} thoughts(t) + coping \cdot (\phi - thoughts(t)) \cdot \Delta t & \phi >= thoughts(t) \\ thoughts(t) + volnurability \cdot (\phi - thoughts(t)) \cdot \Delta t & \phi < thoughts(t) \end{cases} \\ & \phi = appraisal(t) \cdot w_{appraisal\_thoughts} + mood(t) \cdot w_{mood\_thoughts} \end{aligned} \tag{4}$$

Again, equation 5 is similar: *sensitivity* is calculated using the values for *mood* and *thoughts* with the corresponding weights and is mediated by coping for upwards regulation and vulnerability for downwards regulation.

$$sens(t+\Delta t) = \begin{cases} sens(t) + coping \cdot (\phi - sens(t)) \cdot \Delta t & \phi >= sens(t) \\ sens(t) + vulnerability \cdot (\phi - sens(t)) \cdot \Delta t & \phi < sens(t) \end{cases} \quad (5)$$
$$\phi = mood(t) \cdot w_{mood\_sens} + thoughts(t) \cdot w_{thoughts\_sens}$$

The *ST prospected mood level* (equation 6) is a percentage (β) of the *LT prospected mood level*. The percentage is adjusted towards *mood level* with a factor (*vulnerability*) and towards *LT* prospected mood level with factor *coping*.

Persons with bad coping skills will let their *ST* prospected mood level be heavily influenced by mood and not by *LT* prospected mood. Healthy persons use a balanced influence to determine their new *ST* prospected mood level.

$$\begin{aligned} & st\_prosp\_mood(t+\Delta t) = \beta(t+\Delta t) \cdot lt\_prosp\_mood \\ & \beta(t+\Delta t) = \beta(t) + \Delta t \cdot ((vulnerability \cdot (mood(t) - \beta(t) \cdot lt\_prosp\_mood) + \\ & \quad coping \cdot (lt\_prosp\_mood - \beta(t) \cdot lt\_prosp\_mood) + \\ & \quad \beta(t) \cdot lt\_prosp\_mood) / lt\_prosp\_mood - \beta(t)) \\ & = \beta(t) + (vulnerability \cdot (mood(t) / lt\_prosp\_mood - \beta(t)) + coping \cdot (1 - \beta(t))) \cdot \Delta t \end{aligned} \quad (6)$$

3.2 Verification

This section describes three different verification methods. First, the formalization of the mood model is used to simulate several situations. Next, by way of a mathematical analysis it is shown that indeed two equilibria can be found in the model: one in which a depression occurs, and one in which a good mood is maintained as desired. In addition, the adherence of the model to the theories is validated by automatic verification of a number of properties that should hold for the model according to the theories.

3.2.1 Simulations

The model for depression was used to simulate three types of people in different situations. The different types are accomplished by setting the parameters coping, vulnerability and LT prospected mood level. The six weights between mood, thoughts and appraisal can also be varied to simulate different personal characteristics. However, in these simulations they have been set at the following values: $w_{appraisal\_mood}$ 0.7, $w_{thoughts\_mood}$ 0.3 (mood is influenced by SEVS for 70% and by thoughts for 30%), $w_{appraisal\_thoughts}$ 0.6, $w_{mood\_thoughts}$ 0.4 (thoughts is influenced by SEVS for 60% and by mood for 40%), $w_{mood\_appraisal}$ 0.5, $w_{thoughts\_appraisal}$ 0.5 (appraisal is influenced by mood and thoughts for both 50%). The first type, an emotionally stable person, is defined by having good coping skills that balance out any vulnerability, and by having the desire to have a good mood: coping value is 0.5, vulnerability 0.5 and LT prospected mood level 0.8. An emotionally slightly unstable person is defined by having some vulnerability and bad coping skills and the desire to have a medium mood: settings 0.1, 0.9 and 0.6 respectively. The third type, an emotionally very unstable person, is characterized by settings 0.01, 0.99 and 0.6. The start value for OEVS needs to be calculated for each type so that when no events occur, the person stays balanced with al variables equal to LT prospected mood level. For type the OEVS is 0.8, for type 2 it is 0.94 and for type 3 the stable OEVS is 0.999.

Each type of person has been simulated in different scenarios during 1000 time steps (representing 1000 hours, 1.5 months), resulting in a total of five simulations. In the first scenario (traces 1 and 5) one or two minor negative events with an emotional value 0.5 occur. In the second scenario (traces 2 and 4) a negative event with value 0.2 or 0.3 occurs and in the third scenario (trace 3) six major negative events occur. Table 1 describes the simulation settings (type of person and scenario) and results (min and max mood levels, occurrence and duration of depression and recovery within 1.5 months). A depression is defined as a mood level below 0.5 during at least 336 time steps (two weeks, 0).

Table 1. Settings and results of the simulations

* There is no recovery within the simulation time, but mood level is increasing and the person will recover after approximately 22 weeks.

#	Person	Scenario	Mood levels	Depression	Recovery
1	1	2 events 0.5	[0.63; 0.81]	no (0)	-
2	1	1 event 0.2	[0.52; 0.81]	no (0)	-
3	1	6 events 0.1	[0.36; 0.81]	yes (572)	yes
4	2	1 event 0.3	[0.09; 0.61]	yes (888)	no*
5	3	1 event 0.5	[0.01; 0.60]	yes (887)	no

The results show that an emotionally stable person is unlikely to develop a depression. Figure 2 shows the values of OEVS, appraisal, mood and the events for simulation trace 1. Note that the x-axis indicates time and the y-axis the respective values. Persons with very high vulnerability develop a depression already after one minor event (simulation trace 5, Figure 3).

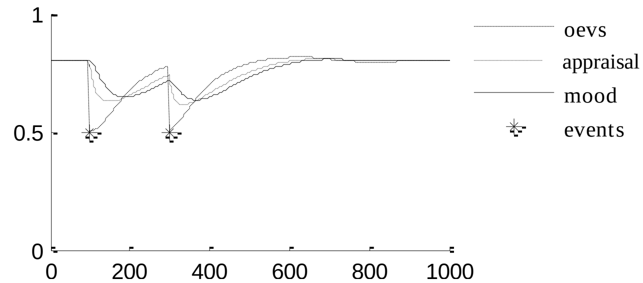

Figure 2. Simulation 1: emotionally stable person, 2 negative events

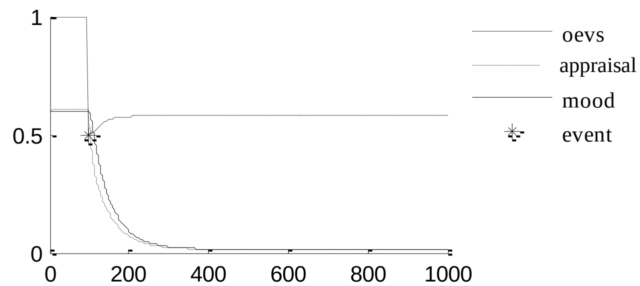

Figure 3. Simulation 5: emotionally unstable person, 1 negative event

3.2.2 Mathematical Analysis

It is also possible to show mathematically that two different situations can be distinguished in the model: one in which stressful events lead to a depression, and one in which this will not lead to a depression. To do so, the model is rewritten in a continuous form of the system of (nonlinear) differential equations shown below. Here O denotes *oevs*, M *mood*, T *thoughts*, S *appraisal*, σ *sensitivity*, and α *coping*. Note that these abbreviations are only used in this specific subsection, in the remainder of the deliverable these names are reused for parameters of the model. Moreover, $Pos(x) = x$ when $x \geq 0$, and 0 otherwise; alternatively $Pos(x) = (x + |x|)/2$.

$$\frac{dO(t)}{dt} = \sigma(t)\,(-\,O(t)\,Pos(M(t) - \beta(t)\lambda) + (1 - O(t))Pos(\beta(t)\lambda - M(t)))$$

$$\frac{dS(t)}{dt} = \alpha\,(1 - (1 - O(t))(1 - T(t))) + (1 - \alpha)\,O(t)\,T(t) - S(t)$$

$$\frac{dM(t)}{dt} = \alpha\,Pos(w_{sm}S(t) + (1-w_{sm})T(t) - M(t)) - (1 - \alpha)\,Pos(M(t) - w_{sm}S(t) - (1-w_{sm})T(t))$$

$$\frac{dT(t)}{dt} = \alpha\,Pos(w_{st}S(t) + (1-w_{st})M(t) - T(t)) - (1 - \alpha)\,Pos(T(t) - w_{st}S(t) - (1-w_{st})M(t))$$

$$\frac{d\sigma(t)}{dt} = \alpha\,Pos(w_{m\sigma}M(t) + (1-w_{m\sigma})T(t) - \sigma(t)) \;-$$

$$(1 - \alpha)\, Pos(\sigma(t) - w_{m\sigma}M(t) - (1-w_{m\sigma})T(t))$$

$$\frac{d\,\beta(t)}{dt} = \alpha\,(1 - \beta(t)) + (1 - \alpha)\,(M(t)/\lambda - \beta(t))$$

Equilibria satisfy the following equations in $O, S, M, T, \sigma, \beta$:

(i) $\sigma(- O\,Pos(M - \beta\lambda) + (1 - O)Pos(\beta\lambda - M)) = 0$
(ii) $\alpha\,(1 - (1 - O)(1 - T)) + (1 - \alpha)\,O\,T - S = 0$
(iii) $\alpha\,Pos(w_{sm}S + (1-w_{sm})T - M) - (1 - \alpha)\,Pos(M - w_{sm}S - (1-w_{sm})T) = 0$
(iv) $\alpha\,Pos(w_{st}S + (1-w_{st})M - T) - (1 - \alpha)\,Pos(T - w_{st}S - (1-w_{st})M) = 0$
(v) $\alpha\,Pos(w_{m\sigma}M + (1-w_{m\sigma})T - \sigma) - (1 - \alpha)\,Pos(\sigma - w_{m\sigma}M - (1-w_{m\sigma})T) = 0$
(vi) $\alpha\,(1 - \beta) + (1 - \alpha)\,(M/\lambda - \beta) = 0$

Note that $Pos(x) \neq 0 \Rightarrow Pos(-x) = 0$. From (vi) it follows that either $M = \lambda\,\beta$ (if $\alpha = 0$) or $M = \lambda\,(\beta - \alpha)/(1 - \alpha)$ (if $0<\alpha<1$) or $\beta = 1$ (if $\alpha =1$). Using this, (i) provides for $0<\alpha<1$:

$$\sigma\;\lambda\,(\alpha/(1-\alpha))\,(- O\,Pos(\beta - 1) + (1 - O)Pos(1 - \beta)) = 0$$

This implies $\sigma = 0$ or $(- O\,Pos(\beta - 1) + (1 - O)Pos(1 - \beta)) = 0$, which implies either $\beta =1$ or $\beta>1$ and $O = 0$, or $\beta<1$ and $O = 1$. Two specific cases are as follows.

The case with $M = \lambda$ In this case $\beta = 1$ (by (vi)), and by (iii) and (iv) it follows:

$$\lambda = w_{sm}S + (1-w_{sm})T$$
$$T = w_{st}S + (1-w_{st})\lambda$$

Hence

$$\lambda = w_{sm}S + (1-w_{sm})(w_{st}S + (1-w_{st})\lambda)$$
$$= (w_{sm} + (1-w_{sm})\,w_{st})S + (1-w_{sm})(1-w_{st})\lambda$$

or

$$(1-(1-w_{sm})(1-w_{st}))\lambda = (w_{sm} + (1-w_{sm})\,w_{st})S$$
$$= (1 - (1 - w_{sm}) + (1-w_{sm})\,w_{st})S$$
$$= (1 - (1 - w_{sm})\,(1-w_{st})\,S$$

So, assuming the weights < 1, it follows $S = \lambda$, and from (iv) also $T = \lambda$. From (v) it follows $\sigma = \lambda$, and by (ii) O can be determined. This is an equilibrium which would be considered a good situation.

The case with $M = 0$ Another special case of an equilibrium is when the mood M is 0. From (iii) and (iv) it follows that also $S = 0$, and from (iii) that $T = 0$ (assuming the weights

<1). By (ii) $o = 0$, and by (v) $\sigma = 0$. Finally, from (vi) it follows $\beta = \alpha$. This is an equilibrium that would be classified as a depression.

3.2.3 Adherence to Theories

In order to verify whether the model indeed produces results that follow psychological observations, a number of properties have been identified in the psychological literature, which have been verified against representative traces (the ones described in Section 3.2.1 and additional traces). In order to conduct such a verification, the properties have been specified in a language called TTL (for Temporal Trace Language, cf. [Bosse *et al*,, 2009]) that features an automated checker. This predicate logical temporal language has been explained extensively in D3.1 and supports formal specification and analysis of dynamic properties, covering both qualitative and quantitative aspects. TTL is built on atoms referring to *states* of the world, *time points* and *traces*, i.e. trajectories of states over time. In addition, *dynamic properties* are temporal statements that can be formulated with respect to traces based on the state ontology Ont in the following manner. Given a trace γ over state ontology Ont, the state in γ at time point t is denoted by state(γ, t). These states can be related to state properties via the formally defined satisfaction relation denoted by the infix predicate |=, comparable to the Holds-predicate in the Situation Calculus: state(γ, t) |= p denotes that state property p holds in trace γ at time t. Based on these statements, dynamic properties can be formulated in a formal manner in a sorted first-order predicate logic, using quantifiers over time and traces and the usual first-order logical connectives such as ¬, ∧, ∨, ⇒, ∀, ∃. Below, the properties and the results of the verification upon the representative traces are shown.

The first property (P1) expresses that a person with bad coping and vulnerability values will get depressed after having encountered at least one negative situation. This property is supported by the theory of Lazarus and Folkman (1984).

P1: Bad coping person gets depressed after negative situation

∀γ:TRACE, t:TIME, R1, R2, R3:REAL
  [[∀t':TIME [state(γ, t') |= has_value(coping_factor, R1) & R1 < AVERAGE_COPING &
  state(γ, t') |= has_value(vulnerability_factor, R2) & R2 > AVERAGE_VULNERABILITY] &
  state(γ, t) |= has_value(objective_situation, R3) & R3 < AVERAGE_SITUATION]
    ⇒ ∃t2:TIME > t [depression(γ , t, MIN_DUR, MAX_LEVEL)]]

A depression is defined as having a mood value below a certain maximum for a certain time period.

depression(γ:TRACE, t:TIME, MIN_DUR:INTEGER, MAX_LEVEL:REAL) ≡

∀t2:TIME > t & t2 < t + MIN_DUR
[∃R:REAL state(γ, t2) |= has_value(mood, R) & R < MAX_LEVEL]

The property has been verified against the set of traces generated by the model. Hereby MIN_DUR has been set to 336 and MAX_LEVEL is set to 0.5 (see Section 2.3.1). Furthermore, the AVERAGE_COPING has been set to 0.4, AVERAGE_VULNERABILITY to 0.6 and AVERAGE_SITUATION to 0.5. Given these settings, this property indeed holds for the set of traces.

Property P2 expresses a similar property for persons with a healthy coping and vulnerability factor, stating that an emotionally stable person will not get depressed from one negative experience. This property is supported by the theories of Zubin and Spring (1977) and Lazarus and Folkman (1984).

P2: Good coping person does not get depressed after one negative situation

∀γ:TRACE, t:TIME, R1, R2, R3, R4:REAL
 [[∀t':TIME [state(γ, t') |= has_value(coping_factor, R1) & R1 ≥ AVERAGE_COPING &
 state(γ, t') |= has_value(vulnerability_factor, R2) & R2 ≥ AVERAGE_VULNERABILITY] &
 state(γ, t) |= has_value(objective_situation, R3) & R3 < AVERAGE_SITUATION &
 ¬∃t'':TIME > t + MAX_DUR, R4:REAL
 [state(γ, t'') |= has_value(objective_situation, R4) & R4 < AVERAGE_SITUATION]]
 ⇒ ¬∃t2:TIME > t [depression(γ , t, MIN_DUR, MAX_LEVEL)]]

Using the same parameters as stated before, this property was shown to be satisfied for all traces. Hereby, the MAX_DUR has been set to 75 hours.

Besides the influence of a situation upon the internal states of the person, the internal levels also influence the choice of situation. In case the thoughts are more negative for the same objective situation, then the judgment of the situation (i.e. appraisal) will be lower. This phenomenon is expressed in property P3. The theory of Beck (1972) supports this property.

P3: Negative thoughts result in lower appraisal

∀γ:TRACE, t1, t2:TIME, R1, R2, R3:REAL
[[state(γ, t1) |= has_value(objective_situation, R1) &
 state(γ, t2) |= has_value(objective_situation, R1) &
 state(γ, t1) |= has_value(thoughts, R2) & state(γ, t2) |= has_value(thoughts, R3) & R2 < R3]
 ⇒ ∃R4, R5 :REAL, D:integer < MAX_DELAY
 [state(γ, t1+D) |= has_value(appraisal, R4) &
 state(γ, t2+D) |= has_value(appraisal, R5) & R4 < R5]]

Again, this property is satisfied for the given traces with parameter MAX_DELAY set to 5.

A key element in avoiding a depression is to choose increasingly better situations. Property P4 draws inspiration from this observation. In case a person can constantly choose better situations during a certain period, this avoids a depression. The behavioral theory of Lewinsohn et al (1979) supports property P4.

P4: Increasingly more positive situations avoid depression
∀γ:TRACE, t:TIME, R:REAL
[[state(γ, t) |= has_value(objective_situation, R) & R < AVERAGE_SITUATION &
increasingly_better_situations(γ, t, EPSILON, MIN_DURATION)
⇒ ¬∃t2:TIME > t & t2 < t + MIN_DURATION
depression(γ , t, MIN_DUR, MAX_LEVEL)

Hereby, the increasingly better situations are defined by means of an epsilon that determines the minimum increase.

increasingly_better_situations(γ:TRACE, t:TIME, EPSILON:REAL, MIN_DUR:INTEGER) ≡
∀t2:TIME > t & t2 < t + MIN_DUR
[∀R1:REAL state(γ, t2) |= has_value(appraisal, R1)
⇒ ∃R2:REAL state(γ, t2 + 1) |= has_value(appraisal, R2) & R2 > R1 * EPSILON]

This property is satisfied for all traces with an epsilon value of 1.005 and a MIN_DUR of 336. These are chosen such that a person would be above a mood value considered too low from a mood level of 0.1 within 336 hours (i.e. before officially being in state of depression).

Property P5 specifies that in case thoughts are negative for a certain period, the person will become depressed. This property, together with property P3, is supported by the ideas of Beck (1972).

P5: Negative thoughts result in depression
∀γ:TRACE, t:TIME, R:REAL
[state(γ, t) |= has_value(thoughts, R) & R ≥ AVG_THOUGHTS &
negative_thoughts(γ, t + 1, MIN_DURATION, AVERAGE_THOUGHTS)
⇒ ∃t2:TIME > t [depression(γ , t2, MIN_DUR, MAX_LEVEL)]]

Hereby, negative thoughts means that the thoughts are below a certain threshold during the specified period.

negative_thoughts(γ:TRACE, t:TIME, MIN_DUR:INTEGER, AVG_THOUGHTS:REAL) ≡
∀t2:TIME > t & t2 < t + MIN_DUR, R :REAL
[state(γ, t2) |= has_value(thoughts, R) ⇒ R < AVG_THOUGHTS]

It was shown that this property is satisfied using the values as identified before, and in addition, a value of 0.5 for AVERAGE_THOUGHTS, and a MIN_DUR of 336, i.e. following the parameters used for the depression.

The final property to be satisfied is the monotonic increase of the mood level of an emotionally stable person in case no negative external situations are encountered. Gross' theory (1998, 2001) about emotion regulation supports this property.

P6: Monotonic increase of mood level for healthy person

```
∀γ:TRACE, t:TIME, R1, R2:REAL
[ [ [∀t':TIME  [state(γ, t') |= has_value(coping_factor, R1) & R1 ≥ AVERAGE_COPING &
     state(γ, t') |= has_value(vulnerability_factor, R2) &   R2 ≥ AVERAGE_VULNERABILITY ]
   state(γ, t-1) |= has_value(mood, R3) & R3 ≥ AVG_MOOD &
   state(γ, t) |= has_value(mood, R4) & R4 < AVG_MOOD ] &
   ¬∃t'':TIME > t + MAX_DUR, R5:REAL
     [state(γ, t'') |= has_value(objective_situation, R5) &  R5 < AVERAGE_SITUATION ] ]
  ⇒ ∃t2:TIME < t + MAX_DIP [monotonic_increase_mood(γ , t2, MIN_DUR) ] ]
```

Hereby, the monotonic increase is defined as follows.

```
monotonic_increase_mood(γ:TRACE, t:TIME, MIN_DUR:INTEGER) ≡
    ∀t2:TIME > t & t2 < t + MIN_DUR, R1 :REAL
    [ state(γ, t2) |= has_value(mood, R1) ⇒
      ∃R2:REAL state(γ, t2) |= has_value(mood, R2) & R1 ≥ R2]
```

This final property is also satisfied for the given traces with the parameters used throughout this section, and AVG_MOOD set to 0.5, MAX_DIP to 100 and MAX_DUR to 30.

4. Virtual Patient extended with Therapies

In Section 3 a model has been introduced which describes the relationship between the most prominent states of a human with respect to a depression. In order to be able to use this model of the virtual patient to make predictions of the future states of the patient following a certain therapy, this model is extended with therapeutic concepts in this section. First, a general extension of the model presented in Section 3 which allows for the addition of specific therapies is expressed. Hereby, some equations underlying the general model have been modified to allow for this extension. In Section 4.2 – 4.5 models for specific therapies are expressed (activity scheduling, cognitive behavior therapy, problem solving, and exercise therapy). Note that only the therapies that are not medicine related and are not mandatory have been modeled. This results in the fact that the motivation module has not been modeled, nor have the medicine adherence module and the relapse prevention. This choice has been made due to the nature of the other modules: it is hard to make predictions and a limited number of measurements is available. Furthermore, the task of selecting a module (which will be part of the next deliverable, but the virtual patient will be used for this purpose as well) is not applicable. Simulations of the aforementioned models are presented in Section 4.6, and a verification of the resulting patterns is presented in Section 4.7.

4.1 Virtual patient extended with general therapeutic concepts

States. In the model, a number of states are defined, whereby each state is represented by a number on the interval [*0,1*]. First, the states of the previous model will be explained. Hereby, the state *objective emotional value of situation* is present, which represents the value of the situation a human is in (without any influence of the current state of mind of the human). The state *appraisal* represents the current judgment of the situation given the current state of mind (e.g. when you are feeling down, a pleasant situation might no longer be considered pleasant). The *mood level* represents the current mood of the human, whereas *thoughts level* the current level of thoughts (i.e. the positivism of the thoughts).

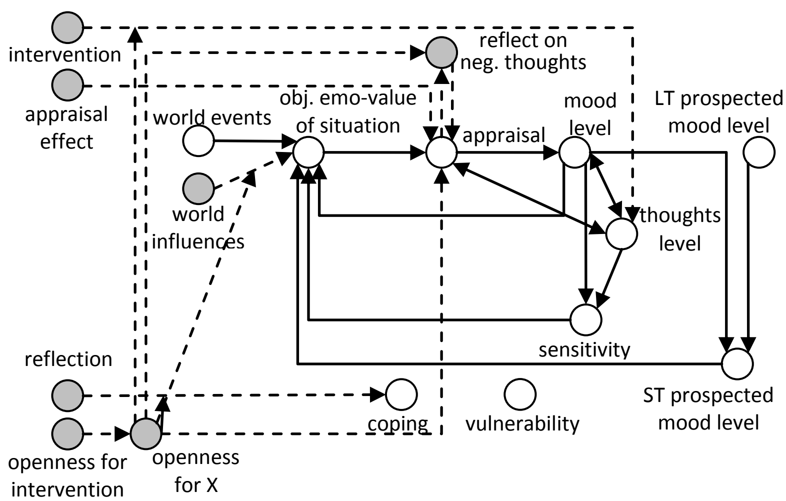

Figure 4. Model for mood and depression
(dashed lines and gray states indicate the extensions compared to Section 3)

The *long term prospected mood level* expresses what mood level the human is striving for in the long term, whereas the *short term prospected mood level* represents the goal for mood on the shorter term (in case you are feeling very bad, your short term goal will not be to feel excellent immediately, but to feel somewhat better). The *sensitivity* indicates the ability to select situations in order to bring the *mood level* to the *short term prospected mood level*. *Coping* expresses the ability of a human to deal with negative moods and situations, whereas *vulnerability* expresses how vulnerable the human is for getting depressed. Finally, *world event* indicates an external situation which is imposed on the human (e.g., losing your job). In addition to the states mentioned above, a number of states have been added to the model. First, a state representing the intervention (i.e., *intervention*) expressing that an intervention is taking place. The state *reflection on negative thoughts* expresses the therapeutic effect that the human is made aware of negative thinking about situations whereas the *appraisal effect* models the immediate effect on the appraisal of the situation. The *world influences* state is used to represent the impact of a therapy aiming to improve the *objective emotional value of situation*. The *openness for intervention* is a state indicating how open the human is for therapy in general, which is made more specific for each specific influence of the therapy in the state *openness for X*. Finally, *reflection* represents the ability to reflect on the relationships between various states, and as a result learn something for the future.

Dynamics. The states as explained above are causally related, as indicated by the arrows in Figure 1. These influences have been mathematically modeled. The first state to be discussed is the *objective emotional value of situation (oevs)*. This represents the situation selection mechanism of the human. First, the change in situation as would be selected by the human is determined (referred to as *action* in this case) as an intermediate step:

$$action(t) = oevs(t) + sensitivity(t)\ (Neg(oevs(t) \cdot (st\_prosp\_mood(t) - mood(t)) + Pos((1 - oevs(t)) \cdot (st\_prosp\_mood(t) - mood(t))))$$

In the equation, the *Neg(X)* evaluates to *0* in case *X* is positive, and *X* in case *X* is negative, and *Pos(X)* evaluates to *X* in case *X* is positive, and *0* in case *X* is negative. The formula expresses that the selected situation is more negative compared to the previous *oevs* in case the *short term prospected mood* is lower than the current mood and more positive in the opposite case. Note that the whole result is multiplied with the *sensitivity*. The *action* in combination with the external influences now determines the new value for *oevs*:

$$oevs(t+\Delta t) = oevs(t) + (world\_event(t) \cdot (action(t) + openness(t) \cdot world\_influence(t) \cdot (1 - action(t))) - oevs(t)) \cdot \Delta t$$

The above equations basically take the value of actions as derived before in combination with the external influences (i.e. *world influence* and *world event*). The second step is that the human starts to judge the situation (i.e. *appraisal*) based upon his/her own state of mind:

$$appraisal(t+\Delta t) = appraisal(t) + \alpha\ (\gamma + openness\_intervention(t) \cdot reflect\_neg\_th(t) - appraisal(t))\ \Delta t$$

where

$$\gamma = (vulnerability \cdot oevs(t) \cdot thoughts(t) + coping \cdot (1 - (1 - oevs(t)) \cdot (1 - thoughts(t))))$$

The value of *appraisal* is determined by the *thoughts* of the human in combination with the *coping* skills and *vulnerability*. In addition, the intervention related state *reflection on negative thoughts* plays a role (i.e. being aware that you are judging the situation as more negative than a person without a depression) in combination with the openness to this type of intervention. The state *reflection on negative thoughts* is calculated as follows:

$reflect\_neg\_th(t) = (basic\_reflection(t) + appraisal\_effect(t) \cdot openness\_X(t)) \cdot (1 - appraisal(t))$

Hence, the value increases based upon the *appraisal effect* of the intervention in combination with the *openness* to this specific part of the intervention. Furthermore, a *basic reflection* is expressed, which is the reflection already present in the beginning. Therapy can also dynamically change this *basic reflection* which can be seen as one of the permanent effects of therapy:

$$basic\_reflection(t+\Delta t) = basic\_reflection(t) + \alpha\ intervention(t) \cdot learning\_factor \cdot (1 - asic\_reflection(t))\Delta t$$

The value for *mood* depends on a combination of the current *appraisal* with the *thoughts*, whereby a positive influence (i.e. *thoughts* and *appraisal* are higher than *mood*) is determined by the *coping* and the negative influence by the *vulnerability*.

$$mood(t+\Delta t) = mood(t) + \alpha\ (Pos(coping \cdot (\varepsilon - mood(t))) - Neg(vulnerability \cdot (\varepsilon - mood(t))))\ \Delta t$$

where

$$\varepsilon = appraisal(t) \cdot w_{appraisal\_mood} + thoughts(t) \cdot w_{thoughts\_mood}$$

Thoughts is a bit more complex, and is expressed as follows:

$$thoughts(t+\Delta t) = thoughts(t) + \alpha\ (\zeta + (1 - (thoughts(t) + \zeta)) \cdot intervention(t) \cdot w_{intervention}(t))\Delta t$$

where:

$$\zeta = Pos(coping \cdot (appraisal(t) \cdot w_{appraisal\_thoughts} + mood(t) \cdot w_{mood\_thoughts} - thoughts(t))) - Neg(vulnerability \cdot (appraisal(t) \cdot w_{appraisal\_thoughts} + mood(t) \cdot w_{mood\_thoughts} - thoughts(t)))$$

$$w_{intervention}(t+\Delta t) = w_{intervention}(t) + \alpha\ (openness\_X(t) - w_{intervention}(t))\Delta t$$

This indicates that *thoughts* are positively influenced by the fact that you participate in an intervention (you start thinking a bit more positive about the situation, you are in therapy). The weight of this contribution depends on the *openness* for the intervention at that time point. In addition, the *thoughts* can either be positively influenced due to the higher combination of the levels of *mood* and *appraisal* (again multiplied with the *coping*), or negatively influenced by the same state (whereby the *vulnerability* plays a role). The *sensitivity* is calculated in a similar manner (without the influence of therapy of course):

$$sensitivity(t+\Delta t) = sensitivity(t) + \alpha\ (Pos(coping \cdot (\eta - sensitivity(t))) - Neg(vulnerability \cdot (\eta - sensitivity(t))))\Delta t$$

where

$$\eta = mood(t) \cdot w_{mood\_sens} + thoughts(t) \cdot w_{thoughts\_sens}$$

Finally, the *short term prospected mood* is calculated as follows:

$$st\_prospmood(t+\Delta t) = st\_prospmood(t) + \alpha\ (vulnerability \cdot (mood(t) - lt\_prospmood) + coping \cdot (lt\_prospmood - st\_prospmood(t)))\Delta t$$

4.2 Activity Scheduling (AS)

Activity scheduling (cf. [Lewinsohn, 1979]), also called behavioral activation therapy, works according to two principles: the patient learns the relationship between the selection of a relatively positive activity and the level of mood (i.e., when you do fun things, you will start to feel better). In order to learn this relationship again, the therapy imposes the selection of positive situations. In Figure 5 the main influences of this therapy are shown by means of the black arrows. Note that most of the influences have already been explained in the general overview in Section 4.1.

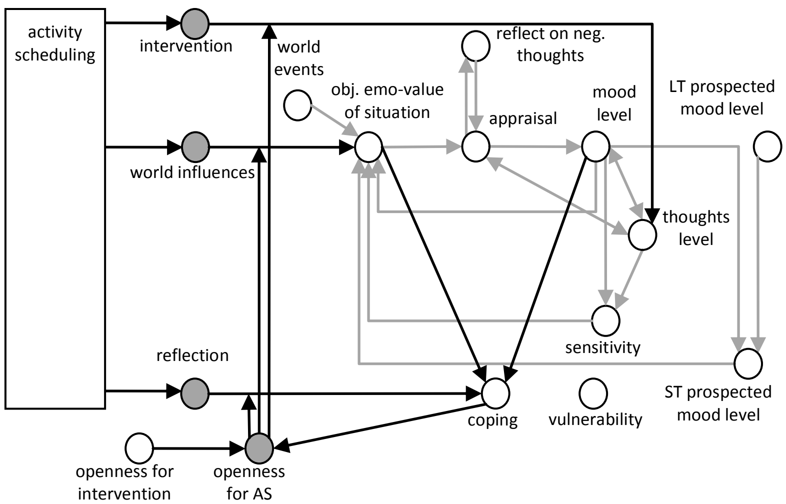

Figure 5. Computational model for activity scheduling therapy

One element part of the therapy states that learning the relationship between *mood* and *objective emotional value of situation* results in better *coping* (as the human can now better cope with a lower mood since he/she knows that an option is to select better situations). This is expressed as follows:

$$coping(t+\Delta t) = coping(t) + \alpha\ reflection(t) \cdot w_{reflection}(t) \cdot (1 - |oevs(t) - mood(t)|) \cdot (1 - coping(t))\ \Delta t$$

where

$$w_{reflection}(t+\Delta t) = w_{reflection}(t) + \alpha\ (openness\_as(t) - w_{reflection}(t))\ \Delta t$$

This states that the *coping* will increase as the difference between the *mood* and *oevs* is perceived small (which makes it easy to see the relationship and improve *coping*). Furthermore, an effect is that the openness for the specific therapy increases as the coping skills go up (since the human notices that the therapy works):

$$openness\_as(t+\Delta t) = openness\_as(t) + \vartheta\ \alpha \cdot ((coping(t) - coping(t-\Delta t))/dt)\ \Delta t$$

4.3 Cognitive Behavioral Therapy (CBT)

Most negative situations occur without being able to control them. It is impossible to avoid all bad situations, it is therefore wise to be able to deal with bad circumstances.

The theory behind Cognitive Behavioral Therapy (CBT, cf. [Beck, 1972]) assumes that emotions are determined by thoughts about a situation and not by the situation itself. In the mood regulation model, it is not the concept 'thoughts level' but the concept 'appraisal' that corresponds to thoughts in the CBT theory, because the thoughts in CBT are about a specific situation, as the state 'appraisal' in the mood regulation model, and do not represent thoughts in general. The intervention CBT consists of understanding (reflection) that thoughts about a situation determine your mood and by detecting and transforming negative thoughts into positive thinking. The fact that you are doing something about your depression improves the *thoughts* level, which is a shared effect of CBT with the other therapies. Figure 6 shows the relevant part of the model for CBT by means of the black arrows. In this case, the reflection is modeled by learning the relationship between *appraisal* and *mood*:

$$coping(t+\Delta t) = coping(t) + \alpha\, reflection(t) \cdot w_{reflection}(t) \cdot (1 - |appraisal(t) - mood(t)|\,) \cdot (1 - coping(t))\, \Delta t$$

In addition, the openness for CBT is increased by reflection in the same manner as the openness for AS.

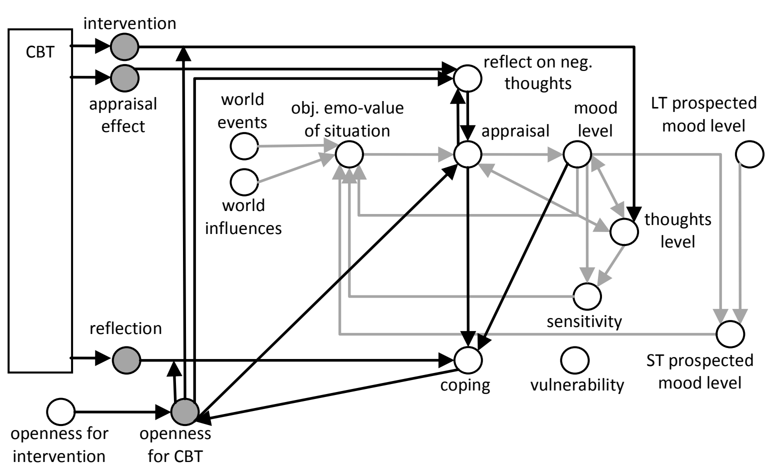

Figure 6. Computational Model for Cognitive Behavior Therapy

4.4 Problem Solving Therapy (PST)

Within problem solving therapy (see e.g. [D'Zurilla and Nezu, 1982] and [D'Zurilla, 1986]), patients are asked to identify the problems that influence their mood and to come up with solutions. This is done in a in a structured way. Patients will learn new skills to cope with their problems, so that the negative influence on their mood is reduced.

In the therapy, patients have to distinguish between three different categories of problems: (a) unimportant problems, (b) important and solvable problems, and (c) important and unsolvable problems. For each of these categories of problems, specific coping strategies are learned. The coping strategies for unimportant problems try to influence the appraisal of the problem. The problem can be seen as a specific aspect of the situation in the model. This influence is thus comparable with the influence on appraisal in CBT. For important and solvable problems, the therapy focuses on learning strategies to solve the problems. In this way, there is a direct influence on the situation. Finally, for the unsolvable problems, patients learn to strategies to accept the problems, which again is an influence on the appraisal of the situation.
Similar to the previously described therapies, PST also improves the understanding (reflection) that worrying about problems determine your mood and by detecting and transforming negative thoughts into positive thinking. Also, the fact that you are doing something about your depression improves the *thoughts* level. In Figure 7 the relevant part of the model for PST are shown (the black arrows). The reflection and openness is modeled in the same way as for CBT.

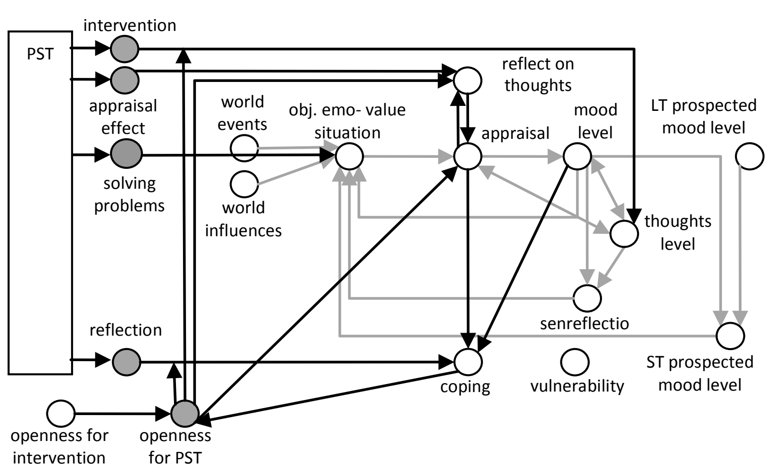

Figure 7. Computational Model for Problem Solving Therapy

4.5 Exercise Therapy

A specific area that receives more attention recently is the way in which brain functioning interacts with the amount of physical activity of a person; for example, it has been shown that a substantial level of physical activity has a positive effect on mood and brain plasticity; e.g., [Cotman and Berchtold, 2002; Dishman *et al.*, 2006; Duclos *et al.*, 2003]. Indeed, it is known that physical exercise may be an effective way for humans to improve mood (cf. [Biddle, 2000; Cotman and Berchtold, 2002]). In particular, this has been studied for the case of mood regulation mechanisms in depressions, among others by using an animal model for human learned helplessness; e.g., [Greenwood *et al.*, 2003 2005 2008 2009; Salmon, 2001]. It turns out that the extent of learned helplessness can substantially decrease when more physical activity is undertaken. It has been shown that persons who perform a substantial amount of physical exercise suffer from depression less frequently (cf. [Goodwin *et al.*, 2003]); therapies based upon physical exercise are reported, for example in ([Cotman and Berchtold, 2002; Dunn *et al.*, 2005]) and are found to be probably effective (for meta-analyses e.g. [Lawlor and Hopker, 2001; Daley, 2008]).

Physical activity and its effect on mood and depression have not been addressed in the basic model as described in Section 3 nor in the general therapeutic model addressed in Section 4.1. In this Section, inspired by the literature on the relevant biological mechanisms, a computational model is presented which models the role of physical exercise in mood regulation; the presented model subsumes the model described in Section 2 as well. This extension is described in Section 4.5.1. Furthermore, in Section 4.5.2 the main effects of interventions by Exercise Therapy upon mood and depression are described. Later, this will be used to simulate and analyze effects of Physical Exercise therapy.

4.5.1 A computational model incorporating the role of physical exercising

Figure 8 shows an overview of the relevant states within the model and the relations between the states. In the figure, the states and lines that are depicted in grey represent states from the original model presented in Section 3. States and dashed lines in black are the extensions as presented in Section 4.1. The thick black states and solid black lines represent the additional physical states.

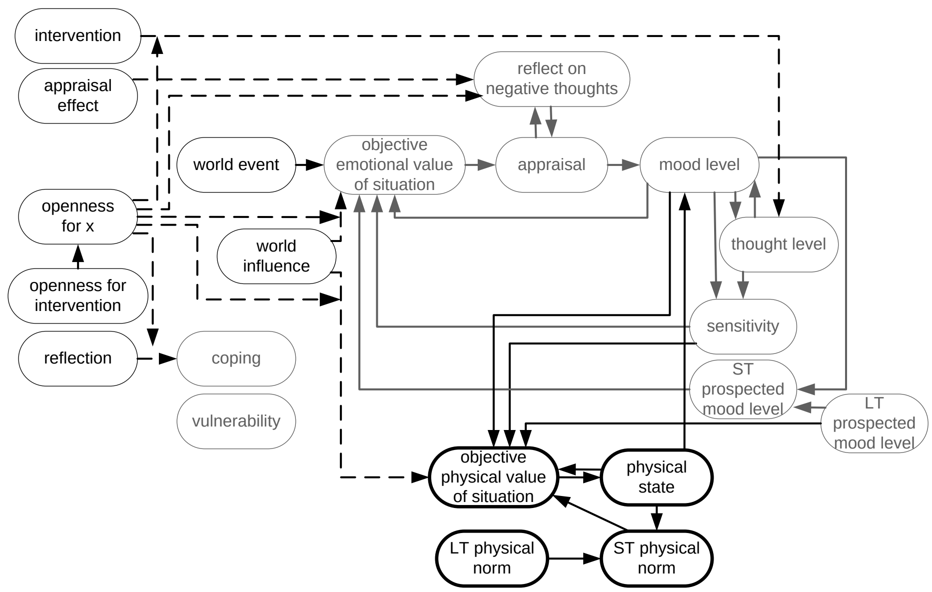

Figure 8. Model for mood and depression combined with physical exercising, the thick black states represent the additional physical characteristics

States directly related to physical action. In order to model the role of physical activity of a person, four states are introduced. First, the *physical state* of a human is used, which expresses a combination of physical properties that are influenced by exercise: endorphin, monoamine and cortisol levels [Duclos *et al.*, 2003]. Exercise itself is represented in *objective physical value of situation*, the value of the current physical situation the human is in. The *long term physical norm* (or *LT physical norm*) expresses what physical state the human is striving for in the long term, whereas the *short term physical norm (or ST physical norm*) represents the goal for physical state on the shorter term. Each state is represented by a number in the interval [*0,1*].

Dynamics directly related to physical activity. The states as explained above are causally related, as indicated by the arrows in Figure 7. These influences have been mathematically modeled. The *physical state* is regulated towards the *long-term physical norm* by choosing physical situations (*opvs*) that help increase or decrease the physical state towards the *short-term physical norm*. The long-term physical norm *lt_physnorm* is considered a personal characteristic. The *ST physical norm* is determined as follows: *physical state* can have an increasing or a decreasing influence, the *LT physical norm* has a regulating function.

$$st\_physnorm(t+\Delta t) = st\_physnorm(t) + (vulnerability \cdot (phys\_state(t) - lt\_physnorm) + coping \cdot (lt\_physnorm - st\_physnorm(t))) \cdot \Delta t$$

The *objective physical value of situation* (*opvs*) is calculated in two steps. First, the change in *opvs* is *calculated based* on a physical regulation part using *physical state* and *ST physical norm* (*action_p1*) and a *mood* influence part (*action_p2*). When *mood level* is lower than *LT prospected mood level*, the action will have a lower value and therefore the human is less capable of choosing appropriate situations to increase the *physical state*. This models the idea that persons with a depression tend to be less physically active [Goodwin, 2003].

$$action\_p1 = opvs(t) + sens(t)\cdot(Neg(opvs(t)\cdot(st\_phys\_norm(t)-phys\_state(t))) + Pos((1-opvs(t))\cdot(st\_phys\_norm(t)-phys\_state(t))))$$

$$action\_p2 = opvs(t) + (1-sens(t))\cdot(Neg(opvs(t)\cdot(mood(t)-prospmood)) + Pos((1-opvs(t))\cdot(mood(t)-prospmood)))$$

$$action\_p(t) = w_{phys\_reg}\cdot action\_p1 + w_{mood}\cdot action\_p2$$

Second, the new *opvs* is determined using the action from above and influence from the world to do physical activities (*world influence*).

$$opvs(t+\Delta t) = opvs(t) + ((action\_p(t) + openness(t)\cdot world\_influence\_p(t)\cdot(1- action\_p(t))) - opvs(t))\cdot\Delta t$$

Physical state is affected by *opvs*. The adaptation factor *adapt_phys* determines the speed with which the *physical state* changes.

$$phys\_state(t+\Delta t) = phys\_state(t) + adapt\_phys\cdot(opvs(t)-phys\_state(t))\cdot\Delta t$$

4.5.2 Incorporating physical exercise therapy

After the introduction of physical exercising in the model, now the specific interventions in exercise *therapy* will be presented. Exercise Therapy consists of a structured form of exercise, often prescribed together with another intervention and/or anti-depressant medications.

Figure 9 shows the mood regulation and depression model with the influences of Exercise Therapy. *Appraisal effect* is shown in light grey, because Exercise Therapy does not influence this concept. Furthermore, arrows from *mood level* and *physical state* to *coping* are added, to represent the learning of coping skills by doing more physical activities.

The intervention influences the human via four states: *thought level*, *objective physical value of situation (opvs)*, *coping* and *openness for ET*. The *thought level* is increased by the fact that the human is participating in an intervention, the formula is explained in Section 2. Second, the choice for a situation with a certain value for physical activeness (*opvs*) is influenced by *world influence*. Again, this effect is described in Section 2. The third effect of the intervention is on *coping skills*: learning the relationship between *mood* and *objective physical value of situation* results in better *coping* (as the human can now better cope with a lower mood since he/she knows that an option is to select more situations with a higher value for physical activeness). This is expressed as follows:

$$coping(t+\Delta t) = coping(t) + \alpha\, reflection(t) \cdot w_{reflection}(t) \cdot (1 - |opvs(t) - mood(t)|) \cdot (1 - coping(t))\, \Delta t$$

where

$$w_{reflection}(t+\Delta t) = w_{reflection}(t) + \alpha\, (openness\_et(t) - w_{reflection}(t))\, \Delta t$$

When there is a moment of reflection in the therapy, the value for *coping* will increase as the difference between the *mood* and *opvs* is perceived small (which makes it easy to see the relationship and improve *coping*). The last effect is that the openness for the specific therapy increases as the coping skills go up (since the human notices that the therapy works). Theta (θ) is an adaptation factor determining the speed with which openness changes.

$$openness\_et(t+\Delta t) = openness\_et(t) + \theta \cdot ((coping(t) - coping(t-\Delta t))/\Delta t) \cdot \Delta t$$

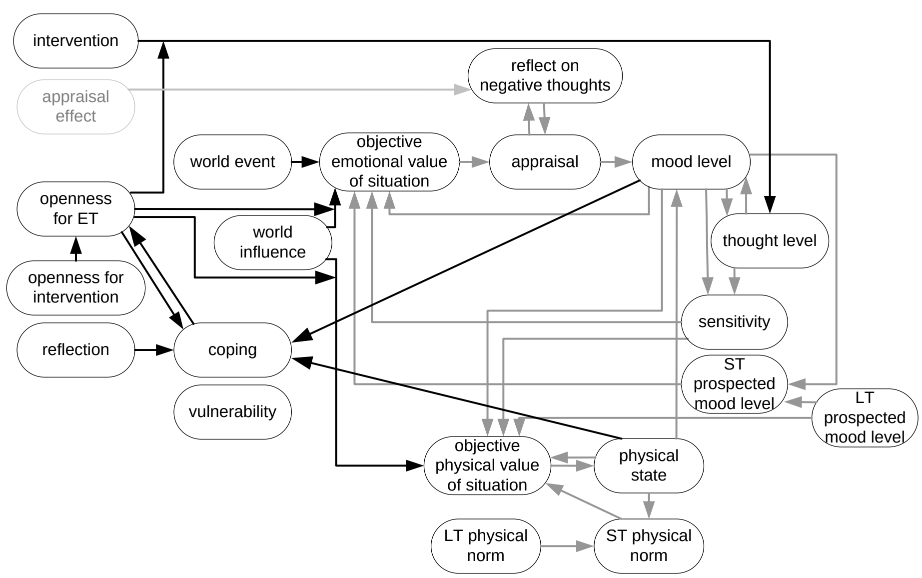

Figure 9. Computational model for Exercise Therapy.

4.6 Simulation results

Simulation experiments have been conducted for different types of patients and the four different types of therapy. In the following sections, a subset of the obtained simulation results are presented for the various therapies (not all have been shown for the sake of brevity). First, in Section 4.6.1 the simulation results based on the three models from

Sections 4.2, 4.3, and 4.4 are shown. In Section 4.6.2, the results are described of the simulations run with the model extended with physical concepts.

4.6.1 Activity Scheduling, Cognitive Behavior Therapy and Problem Solving Therapy

Three different fictional persons are studied with divergent values for coping and vulnerability. Furthermore, the value for openness is varied for each of these persons as well (*0.2* and *0.3* for less and more openness respectively). These values are chosen to show the different influences of the therapies on different types of people and are in accordance with real persons who will follow the therapies in the future. Table 1 shows the initial values for the most important variables of the model for each person:

Table 2. Initial values for the simulation experiments

	person 1	person 2	person 3
coping	*0.1*	*0.15*	*0.3*
vulnerability	*0.9*	*0.85*	*0.7*
oevs	*0.925*	*0.907*	*0.84*
appraisal, mood, thoughts, sensitivity, short term prospected mood, long term prospected mood	*0.6*	*0.65*	*0.7*

For the sake of brevity, this section will only discuss the results for person 1. First, the simulation without any form of therapy is shown in Figure 10. The person experiences very negative events during a substantial period (with value 0.1 during 80 hours). Since the person is highly vulnerable, a depression follows. Note that time is represented in hours.

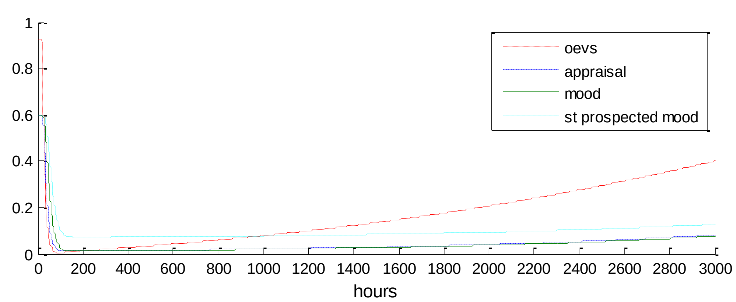

Figure 10. Person type 1 without therapy

The figure shows that a negative event of *0.1* is imposed on the person; this has a dramatic effect on all of the internal states of the patient: *mood* drops to a very low level and so do *appraisal* and the *short term prospected mood*. Eventually all states do start to increase again due to relatively good situations selected, but this goes very slowly.

Figure 11 shows an example whereby the patient is receiving cognitive behavioral therapy. The patient does however have a relatively low openness of *0.2* for this type of therapy.

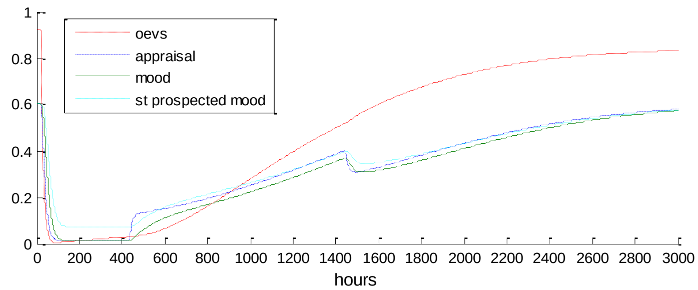

Figure 11. Person type 1 following CBT with a lower openness

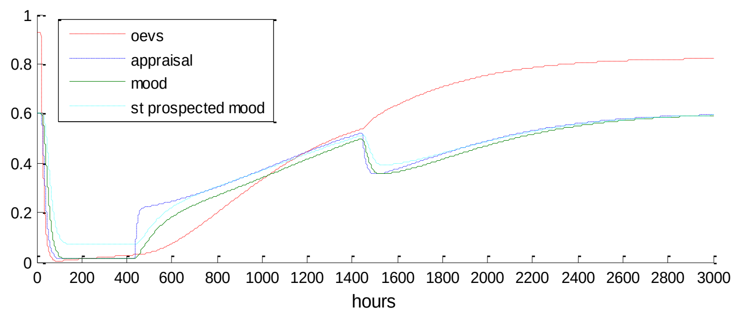

Figure 12. Person type 1 following CBT with a higher openness

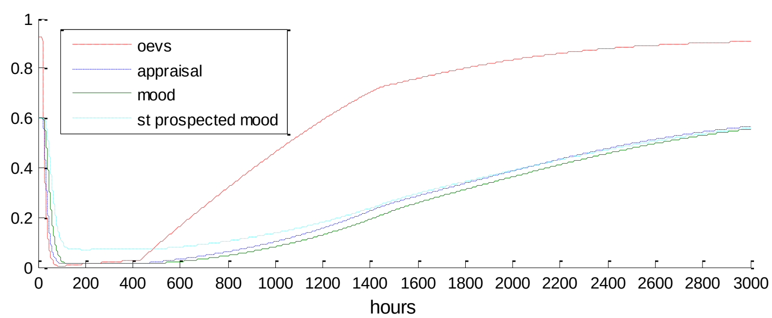

Figure 13. Person type 1 following AS with a lower openness

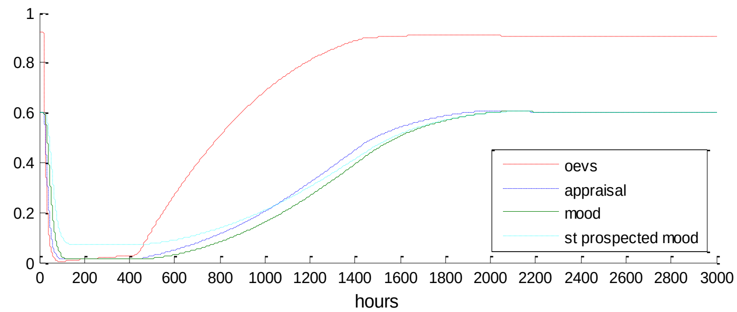

Figure 14. Person type 1 following AS with a higher openness

For this case, it can be seen that the *appraisal* is increased via reflection on negative thoughts, pulling the other states up as well. It does however still take quite some time to get the mood level sufficiently up. The dip after the intervention stops (after 6 weeks) is the result of the fact that the person is no longer reminded about the correctness/importance of appraisal, resulting in a slight search for a new equilibrium. If the openness is increased, the person recovers more quickly, because *reflection on negative thoughts* increases faster (see Figure 12). As the model for problem solving therapy is similar as the model for cognitive restructuring therapy (with the addition that the situation is also influenced directly), no specific simulations for PST have been performed.

For activity scheduling the same types of experiments have been conducted. Figure 13 shows an example of a person with a lower openness for this type of therapy. In this case, the world influence changes due to the therapy (since the therapy results in better situations being selected). This results in an increase of the *objective emotional value of situation*, pulling the rest of the states up as well. In case the person is more sensitive to the therapy, the *oevs* increases more quickly and therefore it takes less time for the person to recover (Figure 14).

4.6.2 Exercise Therapy

For the simulations using the physical concepts extension, again three fictional persons are studied which are all susceptible for depression (low coping skills and high vulnerability) and a high openness for intervention. These persons are referred to as person 1, 2, and 3 respectively. The *LT physical norm* is set to low, medium, and high for person 1, 2, and 3 respectively. The values are chosen to show the effect of different physical norms on the mood level and on the influences of the therapy. In all traces, a world event with a very low value occurs at the beginning of the simulation (value 0.1 during 80 hours). For half of the simulations the intervention starts after two weeks of low mood and lasts for ten weeks. In the other half, no intervention is simulated.

Figure 15 shows the simulation trace of person 1 (with a low *LT physical norm*) whereby no intervention is present. Panel a shows the values for *objective emotional value for situation*, *mood* and *ST prospected mood level*; the bottom graph (b) shows the values for *objective physical value for situation*, *physical state* and *ST physical norm*. It can be seen that the person recovers very slowly from the negative event.

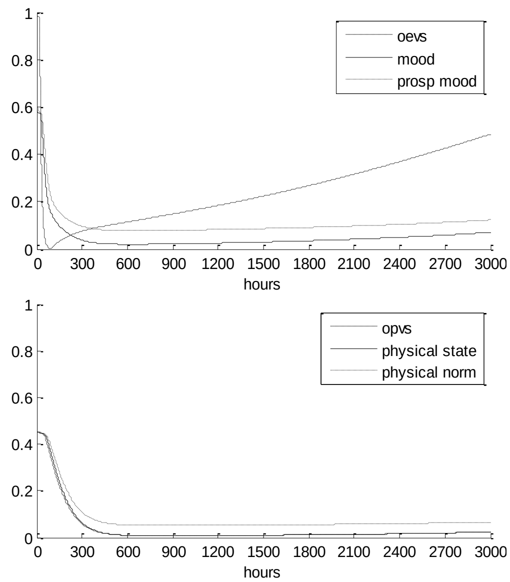

Figure 15a and b. Simulation trace of person 1 (low value for *LT physical norm*) with no intervention. The top panel (a) shows the mood related values; the bottom panel (b) shows the physical state values.

Figure 16 shows the simulation run where the same person does follow the exercise therapy intervention, this results in a more rapid recovery. In Figure 17 person 3 (with a high *LT physical norm*) is shown, following the same intervention is. This results in a faster recovery compared to the person with a low physical norm.

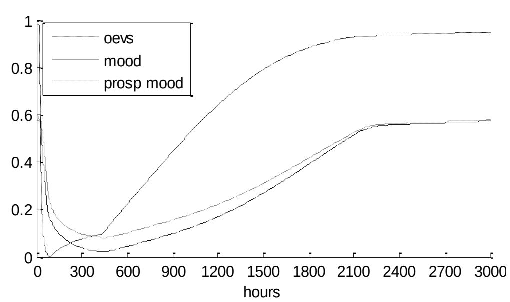

Figure 16a. Simulation trace of person 1 (low value for LT physical norm)

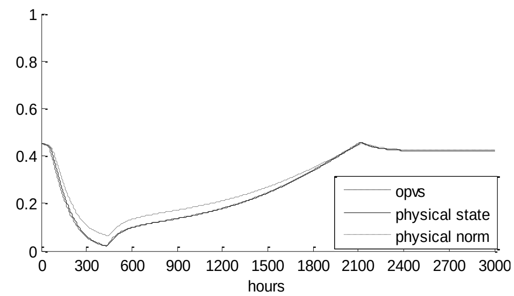

Figure 16b. Simulation trace of person 1 (low value for LT physical norm)

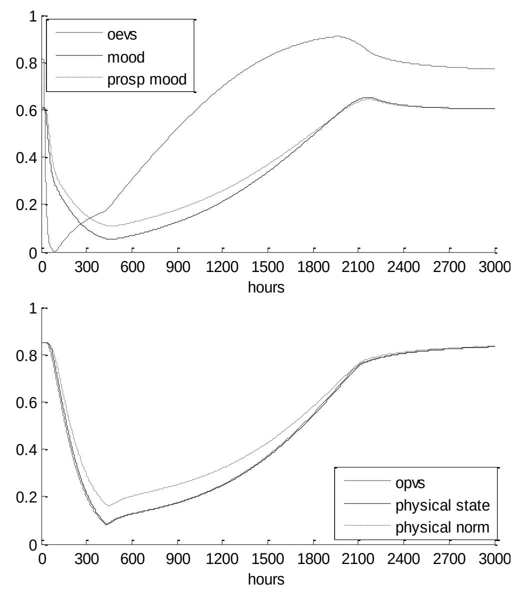

Figure 17a and b. Simulation trace of person 3 (high value for LT physical norm)

4.7 Computational Analysis of Therapeutic Models

In this section, an analysis of the model described above is presented. Two different types of analysis have been performed, with partly different purposes. First, in order to verify the patterns produced by the model, a number of temporal patterns have been specified that reflect a number of general characteristics of the process of depression and its treatment. For example, the characteristic that the length of a depression should be shorter for persons that follow a therapy than for people that did not follow a therapy. These properties have been automatically verified for different simulation traces of the model (of which several have been explained in Section 4.6). The verification of these properties is explained in Section 4.7.1.

Second, the effect of specific therapies on the change of the values for the different variables in the model has been analyzed. This analysis is also useful for verification of the intended effect of a therapy, but can be used for a different purpose as well. Based on the order in which different model variables start changing in reaction to a specific therapy, it is possible to derive which type of therapy is given. Thus, this analysis forms a basis for a diagnostic process that can detect that a person follows some specific type of therapy, based on observations of values of variables that are present in the model (e.g., reports about the mood or an analysis of the objective emotional value of the situation). This part of the analysis is described in Section 4.7.2.

4.7.1 Verification

The following temporal properties that reflect a number of general patterns and characteristics of the process of depression and the treatment have been formulated. The properties have again been specified in the TTL language [Bosse *et al.,* 2009]. A number of simulations (thereby considering all the different types of persons mentioned in Section 4.6 in combination with different openness to therapy) have been used as basis for the verification and were confirmed.

P1a: Effectiveness of Therapy

Persons that follow a therapy are depressed for a shorter period than persons who do not.
∀γ1, γ2:TRACE, ∀ t:TIME

[[[state(γ1, t) |= intervention_CBT | state(γ1, t) |= intervention_AS] &
state(γ2, t) |= not intervention_AS & state(γ2, t) |= not intervention_CBT]

⇒ ∃t2:TIME > t, R1,R2 :REAL [R1 < MIN_LEVEL & R2 > MIN_LEVEL &
state(γ2, t2) |= has_value(mood, R1) & state(γ1, t2) |= has_value(mood, R2)]

P1b: Effectiveness of Exercise Therapy

Persons that follow exercise therapy are depressed for a shorter period than persons who do not.
∀γ1, γ2:TRACE, ∀ t:TIME

[[state(γ1, t) |= intervention_ET & state(γ2, t) |= not intervention_ET]

⇒ ∃t2:TIME > t, R1,R2 :REAL [R1 < MIN_LEVEL & R2 > MIN_LEVEL &
state(γ2, t2) |= has_value(mood, R1) & state(γ1, t2) |= has_value(mood, R2)]

P2: Openness to therapy helps

Persons more open to therapy remain depressed for a shorter period than those less open.
∀γ1, ∀γ2:TRACE, ∀ R1,R2: REAL, t:TIME

[[state(γ1 t) |= has_value(openness,R1) & state(γ2 t) |= has_value(openness,R2) & R2 < R1)]

⇒ ∃t2:TIME, R3,R4 :REAL [R3 < MIN_LEVEL & R4 > MIN_LEVEL &
state(γ2, t2) |= has_value(mood, R3) & state(γ1, t2) |= has_value(mood, R4)]

P3a: Effect on coping skills
After a person has followed therapy for some time, the coping skills have improved.
∀γ:TRACE, t:TIME, R1:REAL

[[[state(γ, t) |= intervention_CBT | state(γ, t) |= intervention_AS)] & state(γ, t) |= has_value(coping, R1)]

⇒ ∃t2:TIME > t + MIN_DURATION, R2 :REAL
[R2 > R1 + MIN_INCREASE & state(γ, t2) |= has_value(coping, R2)]

P3b: Effect of exercise therapy on coping skills
After a person has followed exercise therapy for some time, the coping skills have improved.
∀γ:TRACE, t:TIME, R1:REAL

[[state(γ, t) |= intervention_ET & state(γ, t) |= has_value(coping, R1)]

⇒ ∃t2:TIME > t + MIN_DURATION, R2 :REAL [R2 > R1 + MIN_INCREASE & state(γ, t2) |= has_value(coping, R2)]

P4: CBT results in higher appraisal than AS
After a person has followed CBT, appraisal is higher than after following AS.
∀γ1, γ2:TRACE, ∀ R1,R2: REAL, t1, t2:TIME

[[state(γ1, t1) |= intervention_CBT & state(γ2, t1) |= intervention_AS &
state(γ1, t2) |= has_value(appraisal, A1) & state(γ2, t2) |= has_value(appraisal, A2) &
T2 > T1 + MIN_DUR] ⇒ A1 > A2]

This latter property was confirmed for persons with the same openness for therapy; those following AS with a high openness may end up with a higher appraisal than those following CBT with a low openness.

The following two properties were tested against the simulation traces of Section 4.6. Property P5 was shown to be satisfied, however, P6 did not satisfy. This can be explained by the fact that the physical norm has a large influence on the physical state in the long run. In other words, a person with a high physical norm can have a higher physical state without following exercise therapy, than a person that did follow exercise therapy but has a lower long term physical norm. For persons with the same level of physical norm, the property does hold.

P5: A higher physical norm results in a shorter depression
Persons that have a higher long term physical norm remain depressed for a shorter period than those with a lower norm.
∀γ1, ∀γ2:TRACE, ∀ R1,R2: REAL, t:TIME

[[state(γ1 t) |= has_value(phys_norm,R1) & state(γ2 t) |= has_value(phys_norm,R2) & R2 < R1)]

⇒ ∃t2:TIME, R3,R4 :REAL [R3 < MIN_LEVEL & R4 > MIN_LEVEL &
state(γ2, t2) |= has_value(mood, R3) & state(γ1, t2) |= has_value(mood, R4)]

P6: Effect of exercise therapy on physical state

After a person has followed exercise therapy for some time, his physical state is higher than the physical state of person that did not follow exercise therapy

∀γ1, γ2:TRACE, ∀ R1,R2: REAL, t1, t2:TIME

[[state(γ1, t1) |= intervention_ET & state(γ2, t1) |= not intervention_ET &
state(γ1, t2) |= has_value(physical_state, PS1) & state(γ2, t2) |= has_value(physical_state, PS2) &
T2 > T1 + MIN_DUR] ⇒ PS1 > PS2]

4.7.2 Effects of therapy types

In order to analyze the effect of the different types of therapies on the model variables, it is useful to see when a specific model variable starts changing as a result of the therapy, and in particular which variable changes first. The order in which the different concepts start being influenced by the treatment, is a characteristic of the therapy. For example, when following activity scheduling it is assumed that the *objective emotional value of the situation* will be affected before the mood itself will change. In contrast, cognitive behavioral therapy will first affect the *reflection on negative thoughts*. To detect the moment when an intervention affects a variable, we look at a sudden change in the increase or decrease of the value of a concept over time: a form of *acceleration*. Formally, this can be determined by looking at the relative second-order derivative of a variable over time: the second-order derivative divided by the first-order derivative. This can be calculated more easily by dividing the change of the value of a variable in the current time step ($t + \Delta t$) by the change of this value in the previous time step ($t - \Delta t$), as this is mathematically almost equivalent:

$$(y(t + \Delta t) - y(t)) / (y(t) - y(t - \Delta t)) - 1 \quad = \quad [\, (y(t+\Delta t) - y(t))/\Delta t \,] / [\, (y(t) - y(t-\Delta t))/\Delta t] - 1$$
$$= \; y'(t) / y'(t-\Delta t) - 1 \quad = \quad [y'(t) - y'(t-\Delta t)\,] / y'(t-\Delta t)$$
$$= [\, [[y'(t) - y'(t-\Delta t)\,]/\Delta t] / y'(t-\Delta t)\,] \;\; \Delta t \quad = \quad [\, y''(t-\Delta t)/y'(t-\Delta t)\,] \; \Delta t$$

So, to be precise, for mood this relative acceleration $y''(t-\Delta t)/y'(t-\Delta t)$ can be measured by:

$$mood\_acceleration(t) = [(mood(t + \Delta t) - mood(t)) / (mood(t) - mood(t - \Delta t)) - 1] / \Delta t$$

The acceleration values for the concepts *mood*, *objective emotional value of the situation* and *reflection on negative thoughts* can be calculated similarly.

All acceleration values have been determined from 5 time steps before the start of the intervention till 15 time steps after the start. Figures 18 and 19 illustrate the order of change of the different variables for the different types of therapy. It can be seen that all therapies start having an effect at time point $t = 0$. Moreover, Figure 18 shows that AS indeed first affects the *situation* before the *mood* is affected. Similarly, CBT first affects the *reflection on negative thoughts* (Figure 19), however, this is a bit more difficult to see. At $t = 0$, the acceleration of *reflection on negative thoughts* is very low (far below the bottom of the graph), because of the large increase of this concept at the start of the intervention. At $t = 1$ this value is almost zero (and therefore visible again in the graph), after which another dip follows at $t = 2$. This is because the concept stays at the high level for one time step and then starts dropping again, which can be seen in the left panel of Figure 19. However, the conclusion is that the reflection is influenced before the mood is affected.

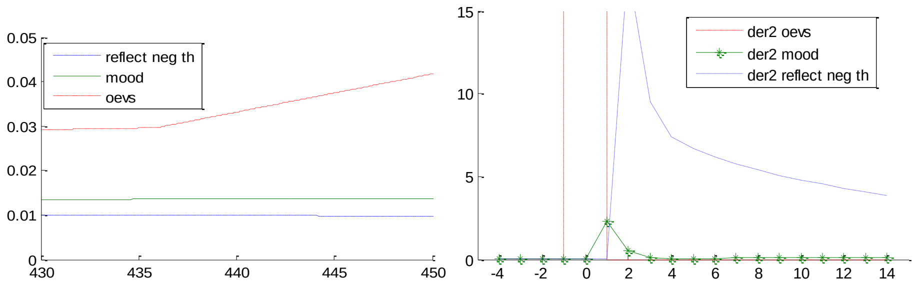

Figure 18. Original (left) and acceleration (right) of values for a patient following AS

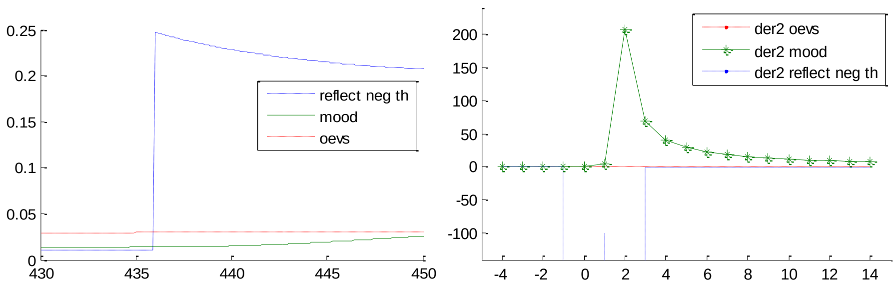

Figure 19. Original (left) and acceleration (right) of values for a patient following CBT.

5. Virtual Patient combined with Patient State and Therapeutic Involvement

Given the approach of the virtual patient presented above, the next step is to make a comparison between what has been predicted for the patient (given the model of the virtual patient), and what actually holds in the real world as seen by means of the trends of the measurements. Hereby, two mappings can be made, namely between the trends in therapeutic involvement and the prediction of the virtual patient, and the trend in patient state and the prediction of the virtual patient.

5.1 Patient State and Virtual Patient

The mapping between the overall trend in the patient state (which has been determined following the approach presented in D3.1) and the concepts in the virtual patient is not a trivial matter. In the virtual patient, there is no general concept of the overall patient state, but much more specific states are present. When it comes to the trend observed by the measurements, only one general value is derived about the state of the patient. This has been done intentionally to be able to combine all measurements, and also to make sure that missing measurements do not harm the system too much (e.g. in case the patient is very passive with providing information based upon questions posed, other elements can still be used to create a good idea of the current general state of the patient, such as the activity level). It is assumed that this overall patient state can be mapped to a combination of the most prominent internal states of the patient, namely the combination of appraisal (the feeling the patient has concerning the situations), mood level, and the thoughts level. This assumption is in our opinion valid because the idea of the patient state is to have an idea of the overall functioning of the patient, which is a composition of the "score" on the most prominent states associated with depression, namely the aforementioned mood level, thoughts, and appraisal. In this case, it is assumed that the average of the above states can be taken and compared to the overall patient state that has been observed for the patient. In the future it is prospected that the overall virtual patient model can be compared on a more fine-grained scale with the data obtained from the patient (also based upon the relationships in the data that show during the pilot study of the ICT4Depression system).

5.2 Therapeutic State and Virtual Patient

The therapeutic state is in this case not used to compare with the virtual patient, but is used as an input parameter for the model. Assuming that the virtual patient will be used to predict the development of the patient from time point t till $t + d$, the general therapeutic state between $t – d$ and t will be used whereby the value of this therapeutic state is mapped to the value of the openness for the therapy. In case the therapeutic state is *bad*, this is mapped to a low value for parameter *openness* in the virtual patient model associated with the therapy. In case the therapeutic state was good this is mapped to a high value for the parameter openness in the virtual patient associated with the therapy.

5.3 Comparison between trends

Of course, the most important usage of the virtual patient is to make a comparison between the predictions concerning the patient (based upon the model) and the actual observations. The above two mappings already give some indication how this can be done. In order to run the model, it is assumed that certain parameters are fixed in advance, whereas others depend on the patient and the development of the patient in the past. In principle, the following values are used as input for the model:

- Openness for therapy
- Initial level of mood
- The coping skills
- The vulnerability

The openness for therapy can be derived from the therapeutic state as has already been indicated in Section 5.2. The initial level of mood can be obtained by looking at the information provided by the patient (i.e. the mood that the patient has rated). In case this information is not available, the value for the patient states that has been derived from all sensory information will be used. The coping skills and vulnerability follow from the initial questionnaire that the patient has filled in (the psychologists within the project will provide us with information how this can be extracted from the answers provided by the patient). Given that these parameters are known, a simulation of the patient following the specific therapy can be performed, and trends can be predicted for the patient.

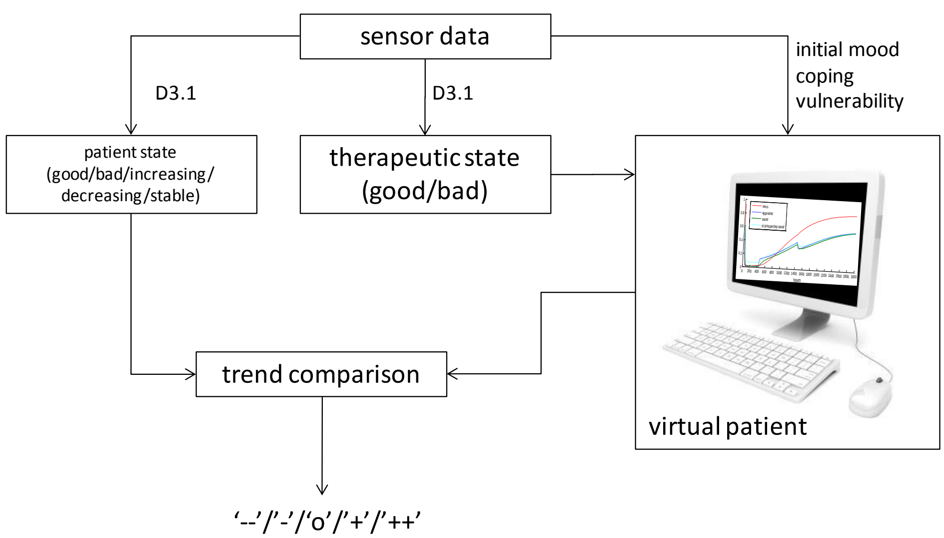

Figure 20. Usage of the virtual patient

A general overview of the interaction of the virtual patient with the general trends and sensor information is presented in Figure 20. The final step is to determine how the predicted trend using the virtual patient compares with the actual trend observed for the patient state. Essentially, five trends have been distinguished in Deliverable 3.1 with respect to the development of the patient state:

1. good
2. bad
3. increasing
4. stable
5. decreasing

Of course, from the virtual patient, the equivalent of the patient state can be derived by averaging the values appraisal, mood, and thoughts as explained in Section 5.1. Using these values, the trends can be defined according to the definitions as expressed previously in Deliverable 3.1. As a result, both the trends predicted by the virtual patient expressing a general good or bad state, and an increasing, stable or decreasing trend can be compared with the actual measurements. A comparison between the trends can be made according to Table 3.

Table 3. Comparison between trends

	Virtual patient state trend	good			bad		
Patient state trend		increasing	stable	decreasing	increasing	stable	decreasing
good	increasing	o	+	++	++	++	++
	stable	-	o	+	+	+	++
	decreasing	--	-	o	o	o	o
bad	increasing	o	o	o	o	+	++
	stable	--	-	-	-	o	+
	decreasing	--	--	--	--	-	o

‘o’ = approximately as predicted
‘-‘ = patient is performing slightly worse than predicted
‘--‘ = patient is performing significantly worse than predicted
‘+’ = patient is performing slightly better than predicted
‘++’ = patient is performing significantly better than predicted

Once this information has been obtained, it can be used as a trigger for providing feedback (which will be addressed in Deliverable 3.4) and it can also be used as a trigger to investigate the suitability of the therapy in case things are going worse than expected (Deliverable 3.3).

6. Discussion

In this deliverable, an approach has been presented that allows for the simulation of a patient following therapy to make predictions concerning the development of various relevant states of the patient. In order to do so, an initial model of a virtual patient has been developed based upon existing psychological theories and rigorously validated by means of simulations, mathematical analysis, and formal verification. This model of a virtual patient has been published as [Both *et al.*, 2008]. As an extension to this model, the mechanisms behind various therapies have been included in the model as well (published as [Both *et al.*, 2010a] and [Both *et al.*, 2010b]). Also these models have been thoroughly evaluated in a similar manner as the general virtual patient. Finally, an approach to combine the predictions of the virtual patient with the information obtained by means of abstracting the information coming in from sensors. This comparison allows the derivation of information whether the patient is functioning according to the expectations or not. This can then be used to provide appropriate feedback to the patient.

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