Application of Statecharts and Agent Based Modelling in Representing Clinically Relevant Aspects of Dementia and Depression in Alzheimer’s Disease

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ABSTRACT

The aim of the project was to translate the clinical case scenarios that are routinely used in medical practice into hierarchical statecharts that can be used in computer models. We tested the coherency and the underlying logic of the clinical scenarios by implementing the statecharts into a computer model of Alzheimer's disease. Clinicians often use clinical scenarios to describe typical signs and symptoms of the disease and its progression over time. Alzheimer's disease symptoms such as memory loss, cognitive impairment and behavioural changes vary by time, severity of disease, individual patient characteristics, setting – i.e. home or residential care, family support and state of general health. Behavioural and psychological symptoms of dementia (BPSD) such as depression, anxiety, aggression and agitation are common. As persons with dementia are mainly elderly, rates of physical co-morbidity are high and patients may be simultaneously treated for more than one disease condition.

Our results show that it is possible to describe the disease states and the progression of dementia and depression in Alzheimer's disease using the hierarchical statecharts. The visual formalism of statecharts as originally described by Harel was adequate to capture all essential aspects of the clinical knowledge regarding Alzheimer's disease, without losing any important medical assumptions. Furthermore, the logical consistency of the clinical scenarios was positively tested by making the representations of the statecharts computable using AnyLogic modelling software. This preliminary work offers a novel approach in dementia research and allows translation of clinical information into computable models where retention of the original factual information and the relationships between clinical findings is essential.

Keywords: Statecharts, Agent-Based Simulation Modelling, Clinical Scenario, Alzheimer’s Disease

INTRODUCTION

Clinicians use scenarios and case histories to describe disease conditions. The standard means of communication between medical personnel in regards to disease conditions is the use of disease names and/or signs and symptoms. This is the basic language of medicine. Clinicians may also use clinical scenarios to illustrate the most typical presentations of disease or may use case histories of individual patients to illustrate the real pathways through which Alzheimer’s patients may travel [14]. Additional information such as age, family situation, social-economical level or chronic health status (CHS) may also be included [16]. Therefore some scenarios may be rather simple when medical conditions are uncomplicated, but others can be very elaborate when medical conditions are complex. Such is the case with Alzheimer's disease: a debilitating progressive disease for which there is no cure. Patients decline progressively over a period of years [4]. Depression is one of the common co-morbidities of dementia and about 20-50 % of Alzheimer's patients will suffer from it at some stage of their illness [15] [18].

Computer models use statecharts to describe conditions of the complex systems. Computer models when applied to health care can be very useful tools in assisting clinicians and policy makers in finding answers to "what-if" type of questions and in foreseeing "what's-possible" given the current limitations of knowledge and material resources [9]. However, by contrast to clinicians' narrative descriptions of disease conditions, computer models can't use "descriptive" clinical scenarios in their original text-format as they appear in the medical guidelines or clinical notes. In order to explain the behaviour of complex living systems computer models require that the knowledge be translated into a form that is computable and logically consistent [6]. Harel first described the hierarchical statecharts in 1984 as "visual formalism for complex systems" [10]. Statecharts represent extension for traditional state-transition diagrams that are popular in all aspects of science and technology (so called "boxes and arrows" diagrams).
Three very essential components are included in that extension which is hierarchy, concurrency and communication [10]. These characteristics make statecharts expressive and compact which means that even very complex behaviour of the system, technical, biological or social, can be expressed with very few elements such as states, transitions and triggers. The statecharts are ideal tools for scientists and clinicians who are developing models of complex behaviours. They offer formal and logical representation of states and transitions that may occur during the dynamic performance of the system under consideration.

Translation of knowledge from clinical findings to computer models. Statecharts can be considered an intermediary between clinicians or researchers and the computer model. Thanks to the visual formalism of the statecharts they can be designed on paper or on the drawing board by a person without computer programming skills but who is an expert in the medical field and is thus best equipped to understand the behaviour of the system. In the case of this project the behaviour of the system is defined as the dynamics of depression in Alzheimer's patient, and the person with clinical knowledge is a specialist psychiatrist. Hierarchical statecharts can be designed and reviewed by other researchers as they are directly readable by humans - the visual representation that uses boxes and arrows can be easily understood. At the same time statecharts can be implemented into computer models because their visual formalism is compliant with the computational logic [7]. Therefore our assumption in this project is that application of the statecharts may become an efficient tool for translation of clinical knowledge about Alzheimer's disease into computable logic and then implemented into virtual model of disease.

**AIMS**

Aims of this project were focused on testing the following assumptions: (a) Essential aspects of clinical scenarios can be translated into hierarchical statecharts. (b) Logical consistency of clinical scenarios can be tested by making statecharts computable. (c) Group behaviour of virtual patients governed by identical but randomly initialised statecharts can be considered an emergent behaviour of the group and monitored during the virtual experiment.

The above assumptions were tested using the computer model of the management of behavioural and psychological symptoms of Alzheimer's disease, specifically depression. This report describes use of statecharts for an extension of a model developed by us [3] focusing on the management of depression.

**METHODOLOGY**

In order to build the Agent Based computational model of Alzheimer's disease we converted the information from typical clinical scenarios into hierarchical statecharts and then used the statecharts as a blueprint for the behaviour of the virtual patients. The knowledge and experience of senior clinicians in regards to typical presentations of Alzheimer's disease were translated into a series of hierarchical statecharts. Each state represented one symptom or characteristic of various degrees of intensity. Movement between disease states was controlled by transitions for which specific conditions could be defined. The responses to the external and internal events were represented by conditional triggers. We elected to focus on one BPSD in order to develop our model. As a result of such translation all essential signs and symptoms of dementia and depression in Alzheimer's disease were represented exclusively by hierarchical statecharts.

The computer model is based on the clinical services model for management of BPSD [3]. The red and blue icons represent female and male patients moving across X (age) and Y (BPSD severity) space. Vertical bands mark the sectors of age groups (60-64 to 95-100) across which the virtual patient move when their age is increasing. Six horizontal bands mark the levels of intensity of BPSD: L1 indicates patients with dementia but free from BPSD and L6 indicates patient with dementia and very extreme presentation of BPSD.

The AnyLogic multi-method simulation modelling software [2][19] was used as a platform for the development of an agent-based model of management of biological and psychological symptoms of dementia in Alzheimer's patients. The model was based on 10 000 virtual patients. Individual characteristics such as gender, age, severity of dementia and severity of depression were assigned to each of the virtual patient during the initialisation of the model according to the predefined rules and probability distributions. An agent-based approach has been chosen to allow relative autonomy of the virtual patients and non-deterministic behaviour of the model. The behaviour of each virtual patient was governed by the statecharts that were developed in cooperation with a senior psychiatrist. The emergent behaviour of the virtual patients was monitored by acquisition of statistics from groups of agents selected by
criteria such as age group, gender and level of depression. The time step of the model was set to 1 week and the model was run over 1500 steps which is equivalent of 30 years.

Figure 2. The main statechart of the model.

The statechart represents general behaviour of each individual patient. Patient can be diagnosed as having behavioural and psychological symptoms of dementia at any time and to any level of severity. This is expressed by the arrows at the left side of the statechart pointing to the states BPSD1 ... BPSD6 representing different levels of BPSD severity. Active state can move up or down depending on the recovery from symptoms or on the progression of symptoms. As this model is specifically focused on symptoms of depression, state BPSD2 to BPSD5 are marked by different colours. Depression is not present in states BPSD1 and BPSD6 because in the first case patient is free from symptoms and in the second case other behavioural and psychological symptoms may be so severe that depression can't be reliably diagnosed. Therefore in our computer model symptoms of depression are only associated with states BPSD2 ... BPSD5.

The process of translating typical clinical scenarios of Alzheimer's disease into statecharts was considered completed when the senior clinician was satisfied with comprehensiveness and details with which clinical information was represented by specific states and transitions. The statecharts were then embedded into the computer model using the AnyLogic software development platform. The computer model of BPSD management in Alzheimer's disease used the statecharts as a blueprint to drive the behaviour of individual virtual patients. The probabilities of transitions between states were initially assigned according to the results of the research conducted and reported by others. That included demographic data, incidence and prevalence of dementia and depression in Australian population and age-specific and gender-specific mortality rates. However, as the model had been gradually developed it incorporated statecharts that represented other characteristics such as the level of dementia and/or level of depression and the relationships between these two clinical symptoms.

Also in order to induce dynamic behaviour of the virtual patient we introduced into the model two hypothetical interventions that represented the treatment for depression: intervention A with small effect size of 0.3 (e.g. training of nursing staff) was applied over longer period of time and represented one of non-pharmacological treatment of depression [1], and intervention B with large effect size of 0.51 (e.g. use of antidepressants such as Sertaline [12] was applied only for short period of 12 weeks and represented one of possible pharmacological treatment reported in literature [17]. Virtual patient could respond to these interventions depending on their intermittent characteristics and conditional triggers. For example responses to therapeutic interventions were influence by age and the level of depression. Outcomes of virtual intervention were monitored continuously during the progression of the virtual experiments.

Before the model could be used in virtual experiment, the AnyLogic framework did the initial check of the underlying logic of the assumptions upon which the statecharts were based. Logical errors were reported and they had to be rectified before the model could run successfully. This process of testing the logical assumption of the statecharts formed essential feedback that was later used to optimise the statecharts and to remove inconsistencies.

RESULTS

The results of the project are presented in Figure 3 and 4.

Figure 3. The statecharts for age, accommodation and chronic health status.

These characteristics are not strictly speaking "clinical" but they represent information that is frequently included in the clinical scenarios. Information regarding accommodation and overall state of health is used by clinicians to describe not only current situation of the patient but also to draw conclusion regarding possible therapeutic interventions. For example some interventions may require involvement of carers, and
other interventions may be rejected because of risk of side effects.

All three main features of statecharts are utilised here, that is hierarchy, concurrency and communication. Hierarchy is represented by inclusion of three statechart such as HowOld, CHS and Accommodation within statechart “Person”. Concurrency is demonstrated by simultaneous initialisation of all three statecharts and parallel execution that is being synchronised with the main timer of the model. As a result the sets of rules that govern the transitions between states in each of the individual statecharts can be implemented independently of each other if necessary. However the inter-dependency between statecharts can also be controlled by inclusion of conditional triggers (not visually represented on the diagram). Conditional triggers and send-receive messages provided communication links between the behaviour of separate statecharts. For example the likelihood of transition A12 that belongs to “Accommodation” statechart and represents change of residence from family home to a nursing home increases with increasing value of the “AgeCounter” which belongs to “HowOld” statechart. The same transition A12 is also dependent on a chronic health status when the likelihood of transition to nursing home is increased when “CHS” is in “Chronic” state. By the same token when “CHS” is in “Unstable” state likelihood of transitions A23 and A13 are increased, but the likelihood of transition A12 is decreased.

![Figure 4. The statecharts for dementia and depression.](image)

In case of patients who are already diagnosed with Alzheimer's disease one of the state Dem1 or Dem2 or Dem3 is always active. A transition between states that represent the severity of dementia can occur only between states Dem1 -> Dem2 or between states Dem2 -> Dem3 because in Alzheimer's disease symptoms of dementia are irreversible. On the other hand symptoms of depression are reversible by either spontaneous recovery or more typically in response to therapeutic intervention. Thus the statechart on the right represents four level of depression and includes transitions that can go up, stay at the same level or go down, which is equivalent to patients getting better, remaining the same or getting worst.

DISCUSSION

There is a growing need for new approaches in knowledge integration and transfer of that knowledge into clinical practice [11]. The prevalence of Alzheimer’s disease is increasing [8] and clinicians raise concerns regarding measurement of treatment benefits of various therapeutic interventions that are implemented in practice [5]. This includes treatment benefits for neuropsychiatric symptoms which complicate the management of Alzheimer’s disease [13] and lead to increased costs of care and carer burnout. While the electronic decision support systems (EDSS) has the potential to enhance the management of Alzheimer’s disease, translation of medical knowledge into computable algorithms remains a challenge for clinicians and researchers. The EDSS can only make limited use of clinical scenarios or patient medical records if they are available only in a text-based format.

Preliminary results obtained in this project indicate that it is possible to utilise statecharts and agent based modelling in representing clinical aspect of dementia and depression in Alzheimer's disease. Our current model of management of BPSD is based on six statecharts and represents both general and clinical characteristics of the patients. The most typical error that occurred in the process of developing the statecharts was "too many default exits" in conditional branches. Generally, the conditional "branches" are implemented in statechart to represent points of decision making and require that for each of the possible decision outcomes (transitions) there is a clear definition of the condition under which this transition can take place. Only one single output can be left as "default" in any one branch, meaning that if other conditions are not met, the default transition will always take place.

The behaviour of the groups of virtual patients was monitored by continuous acquisition of agent's statistics. Most interesting was the ability to see the collective response of the virtual patients to therapeutic interventions that targeted BPSD. This response was monitored over time and indicated that intervention with small effect size may give better long term outcomes when applied over extended period of time as compared with more effective intervention applied only for short period. These statecharts do not represent all possible clinical details. On the contrary, statecharts were designed specifically to capture only the fundamental characteristics without which the descriptive nature of the clinical scenarios would be incomplete. We are planning to make further development and refinement of the model which will include (1) introduction of more sophisticated rules for conditional transitions between disease states that have been reported in randomised clinical trials and (2) development of new testing protocols for the statecharts. In the first case we would like to link the model to the database of proven therapeutic interventions that had been evaluated in clinical trials. In the second case we would like to develop testing protocols for the
logical consistency of the statecharts. At present we only test the logical consistency of the statecharts using AnyLogic framework, and this is a test for ‘computable’ logic. We believe however that the more comprehensive testing should include also ‘clinical’ logic that represents the way in which clinicians think about their patients and therapeutic interventions. The new testing sequence will include the following stages: (a) translation of clinical scenarios to statecharts using consensus of the expert panel of clinicians, (b) evaluation of the computable logic using AnyLogic framework, (c) evaluation of the clinical logic by playing back the clinical scenarios through computer-based interface (animation) and asking clinicians to read back the clinical scenarios. In other words one group of clinicians would translate scenarios into statecharts as we have done so far, and another group of clinicians will be asked to "reverse engineer" the statecharts back to the clinical scenarios. They will do this by observing the playback of the computer animation and writing the clinical scenario that best describe the story which they see through the computer interface. Such two-stage experimental testing will be challenging but we believe that comprehensive testing of computer models needs to include input from clinicians in both phases that is during the development and during the evaluation stage.

REFERENCES

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