Group behaviour of virtual patients in response to therapeutic intervention in an agent-based model of dementia management.

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Abstract

This project created virtual patients who can respond to hypothetical therapeutic interventions in an agent-based model of dementia management. We evaluated the overall response of patients by collecting statistics and observing their group behaviour. In this model virtual patients were actively seeking treatment for symptoms of depression associated with dementia. Responses to hypothetical therapeutic interventions consisted of both generic (common to all patients) and individual (modified for each patient) components. The preliminary results show that even simple sets of rules governing behaviour of virtual patients can lead to quite complex responses at the group level. Furthermore, the lessons learned from monitoring the group behaviour provided valuable feedback which is now being used to modify the creation of individual virtual patients e.g. implementation of histories of previous successful and unsuccessful treatments.

Keywords: Virtual Patients, Dementia Management, Decision Support.

Introduction

Computer models are now frequently applied in medicine and public health policy. For example forecasting of prevalence and incidence of specific diseases is performed routinely with the aid of computer tools. The application of agent-based modelling is not yet as popular but potential benefits of such approaches have already been recognised in such areas as computational biology, computerised clinical guidelines and modelling of specific symptoms in disease conditions (Kitano, 2002). .

Virtual patients as intelligent reactive agents

Implementation of software-generated agents as virtual patients in computer simulations is now well established (Huang, Reynolds & Candler, 2007). There is still an ongoing debate about what constitutes intelligent behaviour but it is reasonably well accepted that autonomous agents which are able to respond to changing environment can be classified as 'intelligent'. However, more precise definitions are needed in particular with the onset of modelling of social behaviours (Decety & Grezes, 2006). It has been demonstrated experimentally that important physiological characteristics of real patients can be mapped and modelled accurately (Grinberg, Anor, Madsen, Yakhot & Karniadakis, 2008). Various attempts have been made in the past two decades to also include more complex social behaviours. In such models an expected range of behaviours may include perception of emotional and cognitive states of other agents (Meyer, 2006). In real life, decisions made by individual patients in response to a changing environment and severity of symptoms can be complex and interdependent. In clinical settings for example the onset of depression symptoms in dementia patients may trigger a sequence of events leading to hospitalisation which in turn may trigger further changes to a patient's life. Such a chain of events may be reversible in some individuals but in others may lead to severe limitation of future life choices. It would be advantageous to have similar complexities reflected by a set of rules describing behaviour of virtual patients in computer modelling projects.

Group behaviour in an agent-based model

The definition of group behaviour is not clear and different researchers put emphasis of different aspects of behaviour that are not predicted beforehand (Wu, Hu, Zhang & Fang, 2008). In its simplest form it is just the 'average' behaviour of the group, no more than sum total of the entire population. However if virtual patients become more autonomous e.g. their trajectory reflects their past history of symptoms, then their behaviour may become much less predictable. Health policy makers are predominantly interested in the overall response of larger populations to treatment options. They want to estimate the potential health and economic benefits of future health initiatives (Edge, 2008). It is generally accepted by health policy makers that the group is a collection of "typical" individuals; therefore what is therapeutically beneficial to the group will also be beneficial to the average individual.

Predicting outcomes of therapeutic interventions

Treatment of symptoms of depression in dementia patients is complex and factors causing symptoms are often unknown. Therapeutic interventions fall broadly into two groups: pharmacological, e.g. antidepressant medication, and non-pharmacological, e.g. cognitive-behavioural therapy, environmental improvement or increased

interactions with others in daily activities (Zec & Burkett 2008). Depression is frequently associated with dementia and around 20-50 % of patients will suffer from depression at various levels of severity and duration during the course of their decline (Zubenko, Zubenko, McPherson, & Spoor, 2003). It is beneficial to diagnose depression early and treat symptoms effectively. The costs associated with treatment can be modest if a patient is just given an antidepressant. However, delayed or inappropriate treatment can interfere with recovery, which can be costly in personal and financial terms. Therefore only well proven treatments are accepted for implementation. However there is uncertainty about how effective different therapeutic strategies are for individual patients and if they have any cumulative effect or synergistic action when two different interventions are combined. Not all patients respond equally to even well proven pharmacological interventions (Bains, Birks & Dening, 2002). Similarly patient responses to less effective but long lasting treatments such as environmental changes and psychological interventions are even less predictable. Accurate projections of outcomes derived from such interventions are very difficult to make. Therefore clinicians and health policy makers could benefit from forecasts made with an aid of computer models.

Aims

The aim of this project was to test the following assumptions: (a) essential parameters of therapeutic interventions can be implemented into an agent-based model as a cluster of global variables and simultaneously available to all agents in the model, (b) the short and long term outcomes of hypothetical therapeutic interventions can be detected and estimated from the emergent behaviour of a large group of virtual patients. These assumptions were tested in the laboratory setting by using an existing model of dementia management and introducing an optional functionality of virtual treatment intervention. This paper presents interim results and hopes to contribute to the future design of virtual patients.

Methodology

The AnyLogic simulation software was used as a programming tool to build the model (http: //www.xjtek.com). Ten thousand virtual patients were initialised at the start of the experiment with characteristics such as age, gender, severity of dementia and severity of depression. Each patient was initialised with a different set of parameters according to probability distribution tables specific to the population of people with dementia in Australian context. The time-step of the model was 1 week and the model was allowed to run for maximum 1500 steps which is equivalent of around 30 years. The virtual patients behaved with relative autonomy and were able to respond to changes in their environment, most importantly to the introduction of new therapeutic interventions. The computer interface was developed as part of the BPSD management project at Dementia Collaborative Research Centre, Faculty of Medicine, UNSW Sydney (http://bpsd.dementia.unsw.edu.au/models).

Virtual Patient

The blueprint for the patient's behaviour was expressed by statecharts, variables and functions as shown on Figure 1. It covered such characteristics as age, gender, severity of

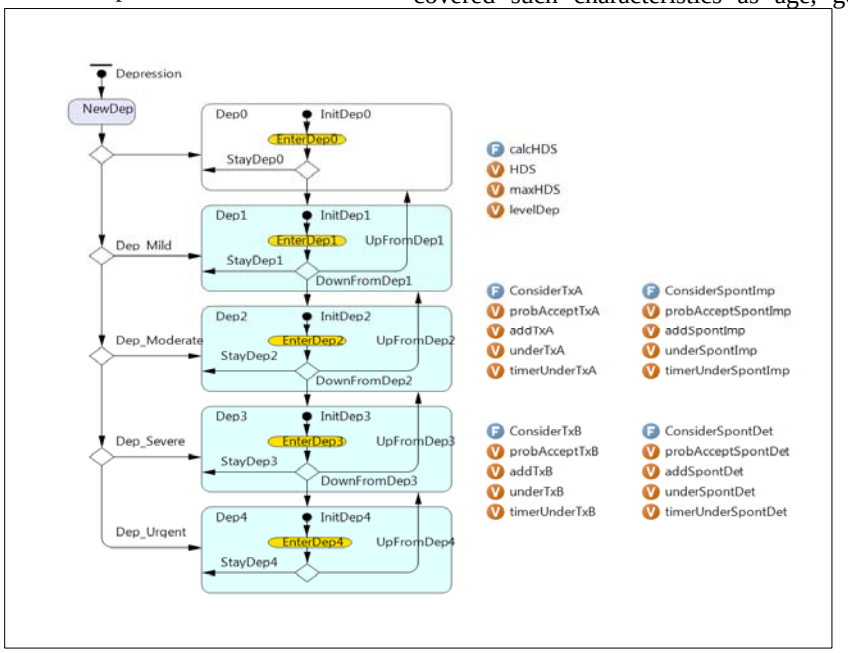

Figure 1. An example of the statechart with variables (V) and functions (F) which govern the behaviour of each individual patient.

dementia, severity of depression, chronic health status and place of residence. At the time of initialisation of the model each patient was allocated with randomly selected characteristics. During the run time of the model patients acted autonomously and they were constantly re-evaluating their own status e.g. rules and all functions were called to recalculate variables and send messages. The AnyLogic simulation engine which underpinned the computer simulation took care of synchronisation and parallel execution of all agents and their interaction with the environment. Figure 1 illustrates some of the components of the virtual patients that relate to the symptoms of depression and acceptance of treatment interventions. The overall design of virtual patients included five other statecharts with numerous functions and variables used to determine agent behaviour and graphical display during animation.

The transitions between states were driven by a set of rules which were identical for each patients therefore leading to a generic response. As time progresses each patient modifies his or her own characteristics according to choices made in previous steps resulting in individualised responses. Therefore the overall response of the patient is a mixture of both generic and individual components with increasingly variable behaviour.

Therapeutic intervention

Dynamic changes in virtual patients' behaviours were triggered by access to therapeutic interventions. The goal of each patient was to reduce the severity of depression if treatment was available. Two hypothetical interventions were available in the model: intervention TxA being equivalent to non-pharmacological treatment of depression e.g. training of nursing staff on how to increase social participation of patients, and intervention TxB representing pharmacological treatment e.g. prescription of an antidepressant such as sertraline (Bains, Birks & Dening, 2002). Intervention TxA had a weaker therapeutic effect (0.3) but was applied for much a longer period of time than intervention TxB, which had larger effect size (0.5) but was available only for a maximum of 12 weeks within a period of 3 years (Bains, Birks & Dening, 2002). The virtual patient had a choice of accepting the treatment and benefiting from it at the rate specified by an initial setting through the user interface as illustrated on Figure 2. The accuracy of modelling therapeutic interventions strongly depended on the accuracy of the parameters that were used to characterise different aspects of these interventions. For example it is known from the literature that depressed patients respond differently to treatment when their symptoms are at different severity levels. The speed of recovery may be initially very fast and then may slow down with the patient remaining mildly depressed for a longer period of time or may even stop responding to treatment (Bains, Birks & Dening, 2002). The user interface also included options to enable spontaneous improvement and/or spontaneous deterioration. Each patient was assigned with a randomly selected probability of responding to such improvement or deterioration.

Interaction between virtual patients and therapeutic interventions

10,000 virtual patients were initialised at the beginning of the experiment and each patient acquired general characteristics common to all. The required characteristics were either taken from look-up tables or were randomly allocated if appropriate. For example the initial severity of depression was randomised but mortality rates were taken from a table according to patient's age group. Once initialised, all agents behaved autonomously. In the current version of the model virtual patients do not communicate with each other but they communicate with the environment. They actively seek treatment if the severity of their symptoms is above a certain threshold. Each virtual patient can accept therapy if the required therapy is available during the patient's lifetime. Figure 3 illustrates

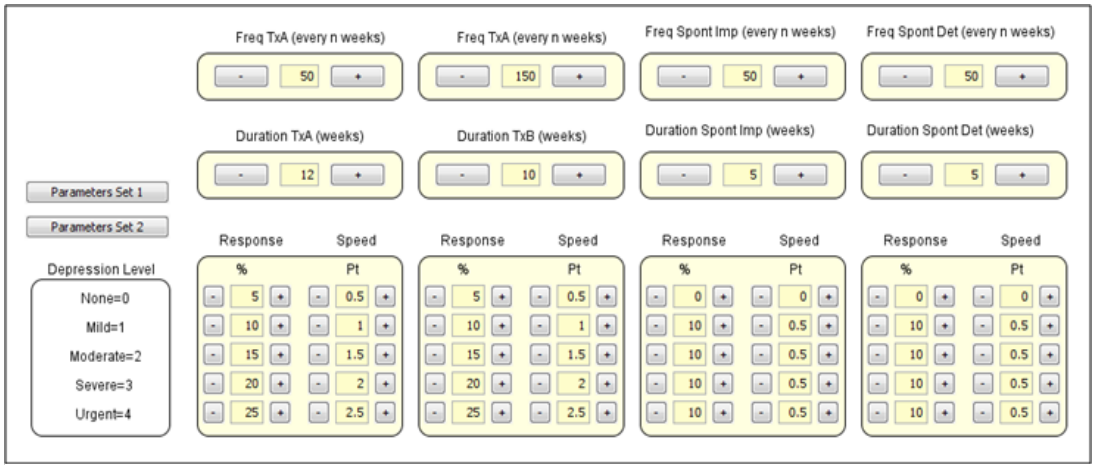

Figure 2. The user interface for setting up attributes of two therapeutic interventions.

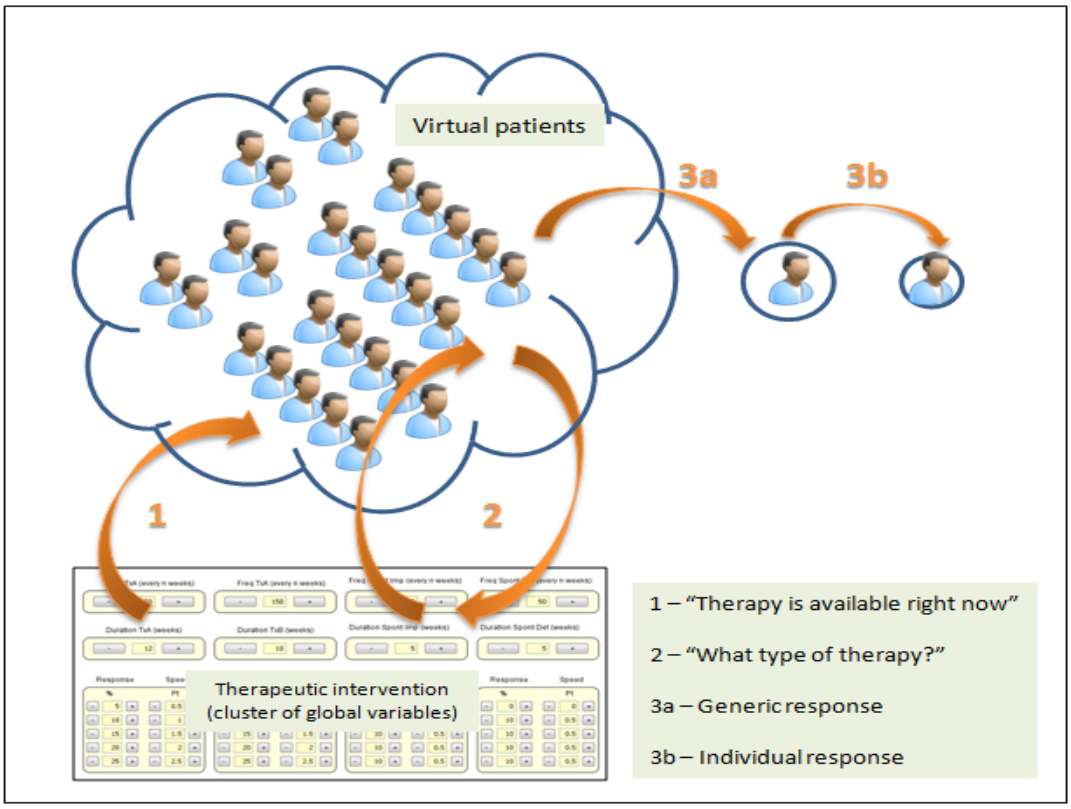

Figure 3. Sequence of steps in communication leading to therapeutic response.

this process of periodic checks of the availability of treatment. The group behaviour of patients was monitored continuously during the experiment by acquiring relevant statistics from each patient, for example, the overall number of patients was monitored at each level of symptom severity. Results were plotted simultaneously and analysed for differences. The availability of TxA and TxB was switched on and off via a button on the user screen but it could also be triggered by a timer at specific time intervals. The characteristics of therapeutic interventions were expressed as a cluster of global variables which the experimenter could modify before running the model.

Results

Only preliminary results of the experiments are presented in this paper. They consist of responses of five groups of patients selected by the increased level of severity of symptoms. At the time of initialisation of the model allocation of the patient to each of the severity levels was 39% with no symptoms of depression, 30 % with mild, 20 % with moderate, 10 % with severe and 1% with depression so severe that it required urgent intervention. Each virtual patient who responded to treatment contributed to the statistics for these levels as they either improved or deteriorated with their symptoms. Patient who did not respond to treatment remained at the same level unless they randomly responded to spontaneous improvement or deterioration.

Response without therapeutic intervention

A graph presented in Figure 4 shows the generic behaviour of virtual patients over time in the absence of any therapeutic intervention. The number of patients with a particular level of severity remains almost the same through 1500 steps (weeks) of the model's runtime. Some variability of the numbers is associated with the stochastic nature of the patient's behaviour. For example new patients were constantly initialised according to projected increases in population, while other patients were dying in accordance with age-dependent mortality rates. Spontaneous deterioration and spontaneous improvement in symptoms of depression were also contributing to small changes in baseline percentages. It is important to mention that all virtual patients had the capacity to make decisions e.g. accept the treatment and to decrease symptoms of depression over time. However such decisions could not be made until the therapeutic intervention was available. For example if the patients belief was indicating preference of TxA (non-pharmacological treatment) and no such intervention was made available or only TxB was available, the patient continued without treatment . The same situation would occur in the case of preference for TxB when only

TxA was provided. Therefore the results in Figure 4 would be the same when another therapeutic intervention was available but none of the patients accepted it.

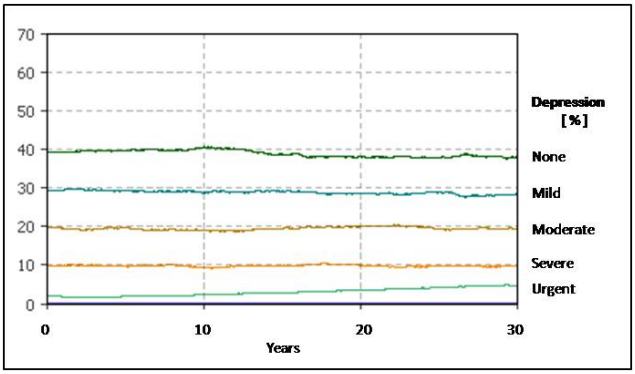

Figure 4. Percentage of virtual patients with different levels of symptom's severity.

Response to therapeutic intervention

The response of virtual patients to the introduction of therapeutic intervention was certainly not homogenous and at the group level changes are clearly visible. Figure 5 shows changes in five groups of patients according to their level of symptom's severity.

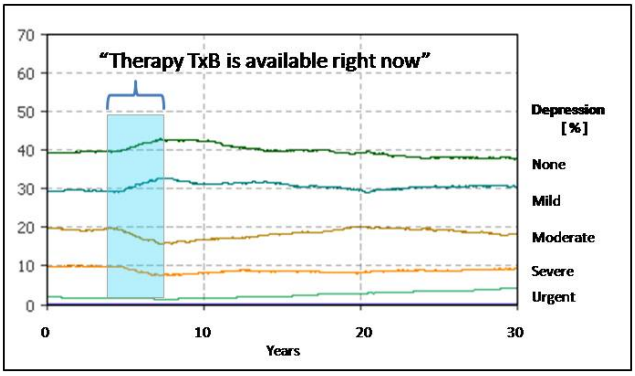

Figure 5. Response of virtual patients to therapeutic intervention TxB.

An improvement in moderate and severe groups (20% and 10% baseline) is indicated by a decrease in number of patients at these levels. However the numbers of patient with mild or no symptoms show strong increases. This can be easily explained when we consider that when patients with severe symptoms improve they "move' to the moderate group, and if improvement continues they move again to the group with mild depression. A similar situation occurs with patients at moderate and mild levels. However when the patient improves and reaches the mild severity level intervention TxB becomes less effective. Therefore many more patients remain mild instead of reaching the top level without any symptoms. When the intervention is no longer available then there is a slow reversal of improvement and after some considerable delay all levels return to their baseline values. This delay is in itself an interesting phenomenon driven primarily by mortality of the patients who previously improved but no longer contribute to the statistics after dying. Therefore initialisation of newly diagnosed patients with symptom severity assigned according the distribution of 39, 30, 20, 10 and 1 percent will gradually return the distribution to a baseline level.

Discussion

There is an increasing demand for new methods for evaluation of therapeutic interventions and in particular their effectiveness at the population level over time. The incidence of depression is on the increase therefore foreseeing outcomes of potential interventions could have beneficial effects on future policy making and costs. The preliminary results of our experiments indicate that such evaluations are plausible and that estimates could be made long before any real-life clinical trials are implemented. The value of virtual experiments will be in selecting the most probable clinical scenarios for therapeutic interventions e.g. single vs. combined interventions which are implemented over longer or shorter periods of time.

Computer models are effective tools for making forecasts and are routinely used in marketing and economics. However they are less popular in medicine mainly due to much greater complexity and unpredictable nature of human behaviour. We tested the possibility of conducting experiments on populations of virtual patients and foreseeing outcomes of hypothetical interventions. Most exciting was the possibility of monitoring a large population of virtual patients and their group or 'collective' response to the same event. We made the distinction between general response and individual response. The difference was in the amount of specific rules by which a virtual patient made the decision of accepting and responding to particular type of treatment. In real life that is indicated by personal beliefs which patients may have e.g. strong preference for one type of therapy.

The agent-based model was stable in performance and fast enough to accommodate a large number of virtual patients. This gives us the possibility of further development of much more complex rules governing patient behaviour and designing much more realistic environments where key players such as doctors, nurses and hospital services are also modelled. The next step in the development of the virtual patients will be introduction of history of responses to therapeutic interventions and linking them with decision making algorithms.

There are number of limitations in the design of this study and ways in which these experiments were conducted. First, there is a question regarding the 'autonomy' of patients in

this model. It is essential to emphasise that the set of rules governing behaviour was identical for each agent. Individual behaviour was shaped by the decisions made by each agent during the runtime of the model. Some of these decisions where based on randomly assigned values e.g. probability of spontaneous recovery and other decisions were expressions of patient's beliefs e.g. preference for pharmacological interventions when symptoms were moderate or severe. Second, the environmental trigger in a form of a message 'Therapy TxB is available right now' was continuously monitored by each agent but did not automatically invoke change in behaviour.

Third, validation of the model is an issue that can't be easily resolved. Our primary effort was in modelling individual response to the therapeutic interventions. We know quite a lot about individual responses from published medical literature. However there is little understanding of group treatment behaviour in this domain. In contrast validation of consumer behaviour in marketing models can be done by using sales figure and attributes of the purchased products. Unfortunately there is no data which will accurately describe what the group behaviour of real patient choices under a particular treatments should look like. In fact the whole purpose of building the model and conducting virtual experiments was to get better understanding of what this group behaviour might be. Perhaps our effort in this modelling project will be rewarded in future by the next generation of research projects which originated from the results of virtual experiments. By showing clinicians what the plausible future might be we could expect that real-life clinical trials will be strongly influenced and guided by the results of in-silico experiments.

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