Methodological Benefits of Discrete Event Simulation models in Depicting Major Depressive Disorders Dynamics: A comparison with Markov Models

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Abstract

Background: Depression is among the major contributors to worldwide disease burden and adequate modelling requires a framework designed to depict real world disease progression as well as its economic implications as closely as possible.

Objectives: In light of the specific characteristics associated with depression (multiple episodes at varying intervals, impact of disease history on course of illness, sociodemographic factors), our aim was to clarify to what extent "Discrete Event Simulation" (DES) models provide methodological benefits in depicting disease dynamics.

Methods: We conducted a comprehensive review of published Markov models in depression and identified inherent limits to their methodology. A new model based on DES principles was developed to investigate the benefits and drawbacks compared with Markov modelling techniques.

Results The major drawback to Markov models is that they may not be suitable to tracking patients' disease history properly, unless the analyst defines multiple health states, which may lead to intractable situations. They are also too rigid to take into consideration multiple patient-specific sociodemographic characteristics in a single model. To do so would also require defining multiple health states which would render the analysis entirely too complex. We demonstrated that DES resolved these weaknesses and that it's flexibility permitted patients with differing attributes to move from one event to another in sequential order while simultaneously taking into account important risk factors such as age, gender, disease history and patients' attitude towards treatment, together with any disease-related events (adverse events, suicide attempt etc.).

Conclusion: DES modelling appears to be a more accurate, flexible and comprehensive means of depicting disease progression compared with conventional simulation methodologies. Its use in analysing recurrent and chronic diseases appears particularly useful compared with Markov processes.

Keywords: Discrete event simulation, Markov models, economic modelling, major depressive disorder, recurrence.

I. Introduction

Depression is a widespread medical condition, associated with significant functional and social deterioration as well as extensive direct and indirect health care costs. A recent review of epidemiological studies estimates the annual prevalence rate of major depression at approximately 5% in Europe (1). Within the next 20 years, depression is predicted to become one of the leading causes of disability worldwide (2).

In 2001, the National Institute of Mental Health proposed to strengthen new research on preventing relapse in major depression, as a part of a larger effort to find treatments capable of producing durable long-term recovery from major depression (3). Depression is a recurrent, potentially chronic and disabling condition. Acute treatments for depression, although effective, are often not sufficient enough to prevent neither later subsequent functional impairment due to residual symptoms, nor recurrent episodes, for a large percentage of persons experiencing a depressive episode. The primary objective of relapse prevention interventions for depression is to reach a full and sustained reduction of depressive symptoms. However, it is increasingly accepted that economic considerations need to be taken into account. The apparent rising cost of interventions, newly licensed antidepressants tend to be more highly priced than existing drug treatments, raising questions about the cost-effectiveness of prophylactic strategies. Economic evaluation can help out decision-makers by delivering information to support judgments on the allocation of available resources (4).

Quantifying the economic implications of a healthcare intervention requires precisely defining the target population, the characteristics of the disease and the therapeutic intervention. It also requires structuring the possible trajectory of patients in a logical, realistic order over time, considering the events that may occur, together with their health and economic implications. Therefore it necessitates providing a computational framework to picture disease progression over time as accurately as possible. Decision trees have been very successfully applied despite recognition of severe limitations when applied to medical problems (5). Markov models represented an alternative that allowed analysts to picture the course of a disease in terms of mutually exclusive health states and the transitions among them. While this technique considers time more explicitly, and can be analyzed very efficiently, it seems however that Markov models retain some structural rigidity (mainly due to the memory-less property of the stochastic process). Discrete Event Simulation (DES) models may appear as a natural way to adequately depict patients' course across the health system (6), making it possible to take into important prognostic factors.

In this case study, we intend to identify what may be the strengths and limits of discrete event simulation models in portraying depression dynamics compared with Markov models. In that regard, a first section is dedicated to the description of important clinical features specific to

unipolar major depression. Second, we propose a practical implementation of both methodologies with the intention to underline their ability to address disease-specific issues relevant for the context. Last, we will discuss both methodologies in terms of their computational implementation and in terms of their ability to adequately reflect disease progression across time.

II. Key clinical features of unipolar depression

MB. Keller and colleagues recently proposed a review on important factors predisposing patients to experience a recurrence of their depressive symptoms (7). The following section aims at highliting those risk factors that are necessary to take into consideration when modelling disease evolution.

II.1 Conceptual definitions

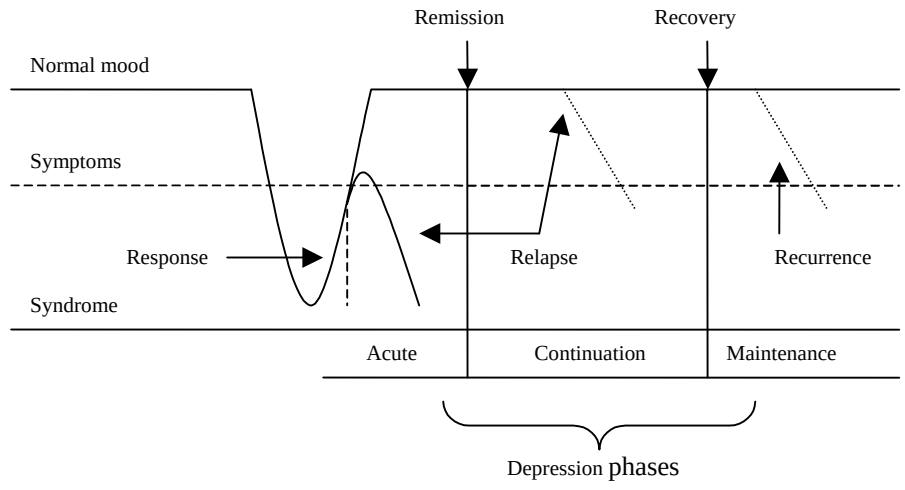
First of all, concentrating on prophylactic strategies for depression raises the question of consensus definitions for specific concepts such as *relapse* and *recurrences* of depressive symptoms. To address this issue, in 1988, the MacArthur Foundation Research Network on the Psychobiology of Depression (gathering psychiatrists from the department of psychiatry at the University of Pittsburgh) provided some conceptual scheme for these terms (8), related to illness phases. This consensus group agreed on the terms required to designate the relevant change points along the course of the illness. These definitions have entailed to provide a definitional scheme of what constitutes an "*episode*": two types of variations are fundamental to the definitions: severity and duration.

A conceptualization for remission can be stated as follows:

- Remission is "a relatively brief period during which an improvement of sufficient magnitude is observed so that the individual is asymptomatic, i.e. the patient no longer meets syndromal criteria for the disorder and has no more than minimal symptoms".
- Recovery could be defined as an asymptomatic period that lasts longer than the remission period. This term is used to designate recovery from the episode, not from the depressive symptoms *per se*, and implies a sustained remission of symptoms.
- Relapse is defined as the early return of depressive symptoms following an apparent remission.
- Recurrence is the appearance of a *new* episode of major depressive disorder and thus can only occur during a period of recovery.

Figure 1 below provides a visual understanding of how distinct phases of depression will impose to differenciate relapses from recurrences, and remission from full recovery.

Figure 1 Diagram of the five possible outcomes across the three phases of treatment of depression (figure extracted from Thase M.E., 2000. (7))



Acute phase: usually 2 to 3 months; Continuation phase: usually 4 to 6 months; Maintenance phase: can last up to 5 years *

* Kupfer et al. study, 1992 (9)

In this paper, a "depressive event" is defined as the occurrence of depressive symptoms. A depressive episode may include several depressive events.

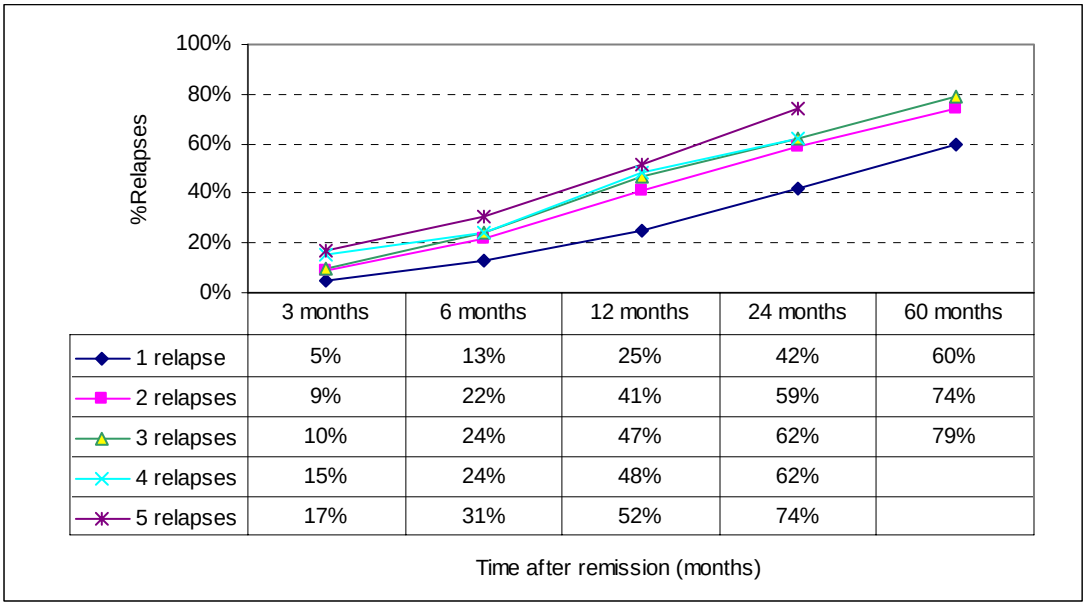
II.2 Important risk factors

The following section aims at highlighting key features in terms of risk factors for unipolar major depression. The illustrative data presented thereafter were extracted from published literature (7;10-12). Long-term prospective studies of patients with depression are somewhat scarce, therefore this work was mainly based on the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression study (7;11;12). This study was a prospective, naturalistic long-term follow-up that aimed at describing the episodic course of illness in major depressive disorder. Recruited individuals could receive either outpatient or inpatient care[1].

One of the major findings from this long-term follow-up study suggested that the number of previous depressive symptoms events significantly influenced the probability of relapse of major depression (Figure 2).

[1] Outpatients represented 25% of the total sample

Figure 2 Cumulative probability of relapse after remission from depressive symptoms given the number of prior depression events.

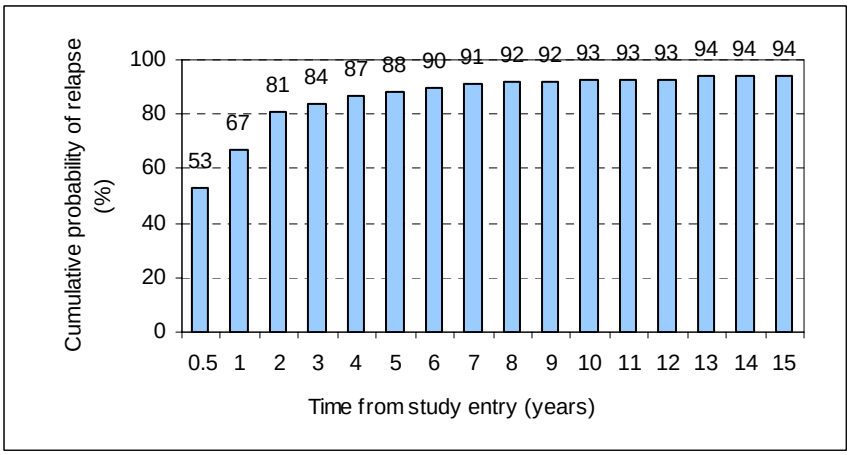


	3 months	6 months	12 months	24 months	60 months
1 relapse	5%	13%	25%	42%	60%
2 relapses	9%	22%	41%	59%	74%
3 relapses	10%	24%	47%	62%	79%
4 relapses	15%	24%	48%	62%	
5 relapses	17%	31%	52%	74%	

Source: Solomon et al. 2000 (12)

Furthermore, as the duration of the depressive symptoms increased, patients' further chances of remission declined (Figure 3), hence substantiating the chronic nature of the illness. However such a disease evolution was shown to occur in approximately 20% of cases (13).

Figure 3 Cumulative probability of remission from index episode of depression



Source : Keller et al. (7)

Moreover, the presence of residual depressive symoptoms has also been proven to be associated with an increased risk of short-term relapse as well as with a long-term chronic course. Patients' attitude towards treatment has also been widely discussed as a key factor predictive of the long-

term course of the disease. Olfson and colleagues (14) recently showed that approximately 4 of 10 patients (42.4%) who initiated antidepressant treatment for depression discontinued the antidepressant medication during the first 30 days of treatment, and among those who continued antidepressant therapy beyond 30 days, one-half (52.1%) discontinued the medication during the subsequent 60-day period. A 2-year naturalistic study showed superior long-term recovery in patients who were adherent to antidepressant medication compared with non-adherent patients (10;15).

Last, sociodemographic characteristics such as age and gender have also been proven to be significant factors to be taken into consideration (16).

Table 1 below summarizes the key factors for recurrent depression.

Table 1 Key risk factors for recurrent depression

Risk factors for recurrent depression
✓ History of multiple episodes
✓ Premature antidepressant withdrawal
✓ Long duration of individual episodes
✓ Poor symptoms control during continuation therapy
✓ Sociodemographic factors such as age and gender

Source: Keller et al (11)

The epidemiological key-aspects of the disease presented make evidence of the need to discriminate patients' clinical management with regards to their sociodemographic characteristics together with their disease history, both in terms of the number of prior episodes and in terms of compliance towards antidepressant therapy. Such traits deserve to be taken into account further when modelling disease progression over time. The following section intends to see to what extent Markov models and discrete event simulation appropriately handle these issues.

III. Application

Keeping in memory the important factors described previously, the objective of this study was to compare two computational frameworks for modelling real-life disease evolution in patients with major unipolar depression, seeking care both in the inpatient and outpatient setting, over a period of 10 years.

The final health outcomes of interest were time spent without depressive symptoms (i.e. time in remission and full recovery) and the number of relapses and recurrences occurring over the study period. The simulation models described thereafter illustrate disease progression across time regardless of the therapeutic strategy, taking into consideration patients' realistic

behavioural patterns as well as important prognostic factors. We provide in the following further technical details on both Markov and Discrete Event Simulation models, together with a practical example of both modelling methods. The implementation of both models was perfomed using Treeage Pro 2006 Healthcare, release 0.1.

III.1 Markov models

Markov modelling is a decision-analytic technique that characterizes the prognosis of a cohort of patients by assigning them to a fixed number of health states and models transitions among those states (17). Markov models assume these transition probabilities to be constant over time; however it remains possible to bypass this strict assumption by modelling non-homogeneous (i.e. time-dependent) Markovian stochastic processes. Markov models are particularly suited to modelling programs in which the events occur repeatedly over a long time period (5;17). However an important limitation of Markov models is that they lack a memory. This is termed the Markovian assumption, that is, the probability of moving from one state to another is independent of the history of the patient before arriving in that state.

In our illustrative case (picture in Figure 4), health states were divided into three levels of risk (low, moderate, high), each being divided into multiple temporary states associated with varying probabilities of remission according to the time elapsed in the disease state (in order to handle illness persistence issues). Therefore for each level of risk, on the basis of a 1-week cycle, we defined 24 temporary depressed states, i.e. 24 weekly remission probabilities adjusted for the duration of the disease. If the patient was still depressed at week 24, a constant probability of remission was applied. The number of temporary states was chosen as per the accepted management of an episode (i.e. a continuation period of 6 months)(18;19).

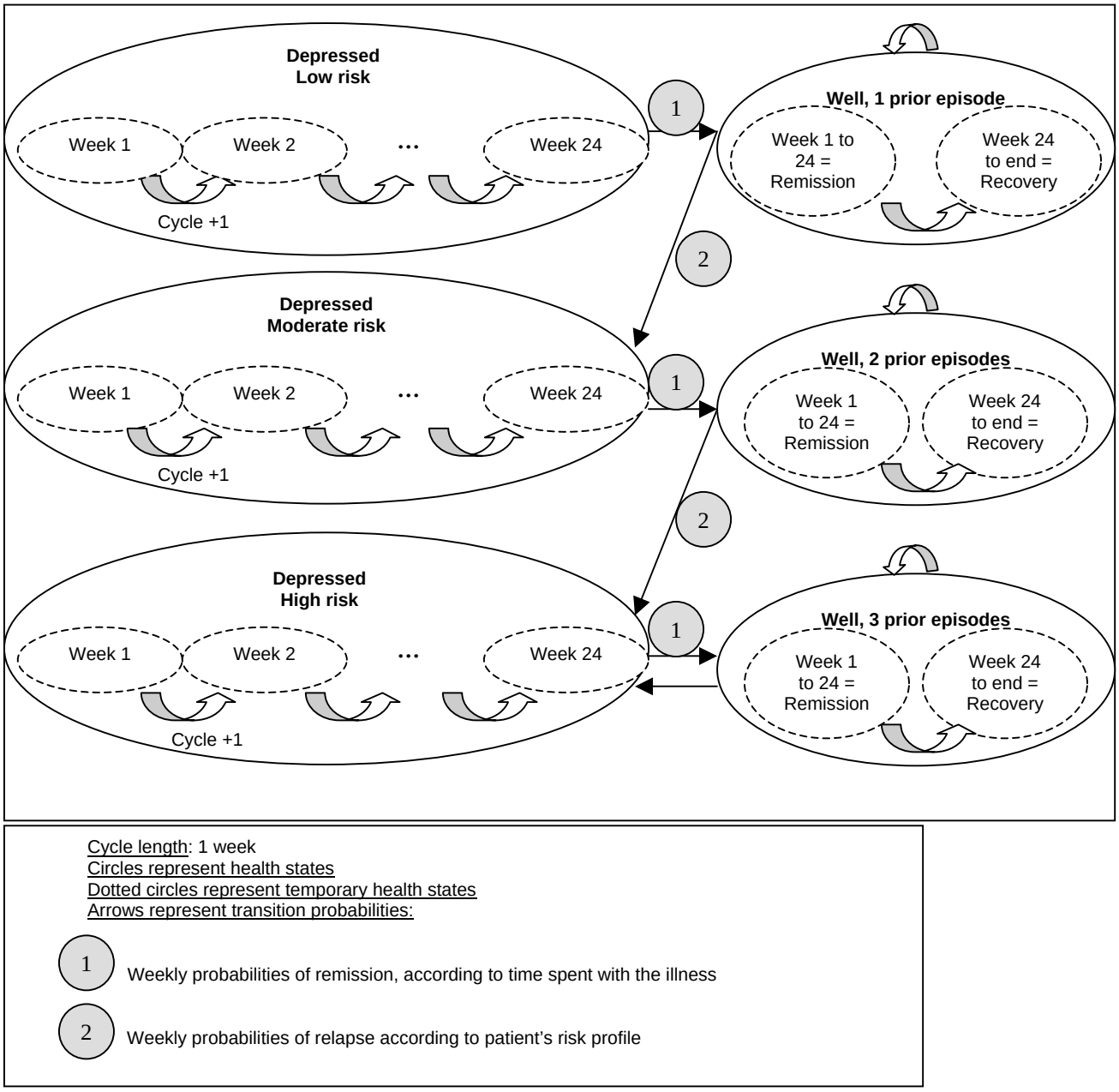
This entailed to define 24*3=72 (temporary) health states to account for risk levels and duration of the illness.

Furthermore, in order to differentiate remission periods from recovery periods (with the intention to be more precise when assessing the potential impact of a given strategy in its ability to delay further development of depressive symptoms), it was necessary to divide the “well” state into two separate temporary states: one applicable for the remission period, i.e. related to the first 24 weeks following symptoms disappearance (in accordance with clinical guidelines which define a minimum of 24 symptom-free weeks before concluding that the patient has achieved a full recovery), and another to define patients entering a full recovery period (i.e. remission period longer than 24 weeks).

The data required to specify this simulation model (in terms of clinical data exclusively) were survival distributions of remission and relapse at each cycle (i.e. weekly transition probabilities), conditional on the number of previous depression events. The time spent in the

"well" (respectively "depressed") state may be summed over the period (i.e. 10 years = 520 cycles) and eventually discounted (according to the rate applicable[2]).

Figure 4 Markov model synthetic representation



This somewhat "simple" model (i.e. in terms of the number of risk factors taken into account) demonstrates that Markov models seem to be quite suitable to addressing the key features of importance when modelling depression evolution across time. First, they handle the problem of patients' history of the disease by splitting health states according to different risk levels (low, moderate, high), which is computationally acceptable. Second, the chronic nature of the disease (for approximately 20% of patients, as mentioned previously) was managed at the expense of

[2] International Society for Pharmacoeconomics & Outcomes Research (ISPOR) comparative table: http://www.ispor.org/PEguidelines/COMP3.asp

defining multiple health states (i.e. 72 states encoded as “tunnel” variables), making it possible to assign varying transition probabilities according to the time elapsed in the “depressed” state. Last, Markov models proved to be able to distinguish remission periods from recovery periods by using temporary states (i.e. 6 more health states). Therefore a Markov representation of the problematic would necessitate the definition of at least 72+6=78 health states to properly take into consideration primary relevant risk factors (i.e. severity and duration of the disease). The efficiency of such a modeling method in more complicated scenarios may thus become questionable. Indeed, what if the analyst expects to take into consideration patients’ attitude towards treatment, which has been identified as a key factor of patients’ prognosis? In that regard, considering this factor would necessitate splitting each state in two separate states. This may become more and more difficult to handle properly when opting for a Markovian representation. Furthermore, what if the analyst wishes to include socio-demographic factors such as age or gender? And, adding further complexity, how would it be possible to efficiently take into consideration another event such as patient’s suicidal behaviour? The same reasoning as above applies: the integration of all relevant factors into a Markov model may entail to define much a too complex structure. Markov models have previously been used to model the cost-effectiveness of prophylactic interventions for recurrent depression (20-25) or as a tool to picture the epidemiology of depression (26), but failed to simultaneously take into consideration all relevant key factors beforehand exposed. Such constraints naturally lead to move towards a more flexible simulation method. Discrete event simulation models may be an opportunity to adequately address the limitations of Markov models, and our intention in the following is precisely to assess the benefits and drawbacks of DES compared with Markov models.

III.2 Discrete Event Simulation models

Discrete event simulation (DES) is one way of building up models in order to observe the time-dependent (or dynamic) behaviour of a system (27-29). DES models as a cost-effectiveness tool have been quite widely used in various disease areas, such as laparoscopic surgery (30), screening for gastric cancer (31;32), renal diseases (32), drug abuse (33), HIV transmission modelling (34), early breast cancer (35;36) or liver transplantation (37). To our knowledge, DES models have not been used yet within the field of major depression.

Recently, J.J Caro proposed to examine further DES models as a computational tool for cost-effectiveness analyses and reminded the key principles of the method (6):

- ✓ **Entities**

  Entities are the items that evolve through the simulation. In clinical simulation of a disease, most of entities are patients. In contrast to decision trees or Markov models,

which do not specify the patient but focus exclusively on outcomes or states, the patient is an explicit element of a discrete event simulation model. Patients have attributes (age, sex, duration of the disease) with each individual having a specific value for each characteristic. These values are defined at the start of the simulation and may be updated as events occur: age increases, disease severity decreases, the number of depressive events is incremented, etc. Other quantities that will govern the analysis, such as time horizon and discount rate, are encoded in variables. These values may change during the simulation.

- ✓ **Events**

  The second major element of the simulation is the events that may occur. An event is defined as anything that can happen during the simulation. Thus it can be either the occurrence of depressive symptoms, remission from depressive symptoms, patient stopping treatment, a suicide attempt, an adverse event etc. This concept extends well beyond the transitions in a Markov model, as the event need not imply a change in the patient' state. These events can happen in a logical sequence and even simultaneously. They can recur if that happens in reality and they can change the course of a given patient's experience by influencing that patient's attributes and the occurrence of future events. The rates at which events occur can take any functional distribution supported by the data. They can be dependent on any attributes or variables and these functions can change over time as appropriate.

- ✓ **Time**

  The third fundamental component of a DES is time itself. An explicit simulation clock keeps track of the passage of time. This makes it possible for the analysts to clearly signal the start and end of the simulation and to create secondary clocks that track interim periods such as depression episode duration or remission periods. By making time explicit, a DES enables handling of time that is much more flexible than in Markov models, as there is no need to declare cycle length.

Discrete event simulation models belong to the class of individual sampling modelling methods (38): rather than following a cohort through the model by assigning proportions to different states, discrete event simulation can model the pathway of an individual by sampling probabilities from an a priori distribution, allowing greater realism in the description of patient's evolution in the healthcare system, and more flexibility in the data requirements for the model. Indeed DES models provide an adequate tool to picture stochastic processes where multiple risk

factors and non-Markovian structures are present[3] (i.e. non memory-less stochastic processes).

Along with the simulation process, new information (depending on the triggered events) can be tracked and stored into a temporary variable, so that future events' probabilities could be updated with regards to the new patient's clinical and socio-demographic profile. Patients may then acquire attributes as certain events occur within the model (higher risk of relapse). The attributes of a particular patient influence his/her pathway through the simulation, as well as the economic outcomes associated with the events undergone.

Due to the strength of the assumptions the technique offers and by modelling individual patient pathways, DES provide flexibility which, given adequate data, may allow greater confidence in the results (41).

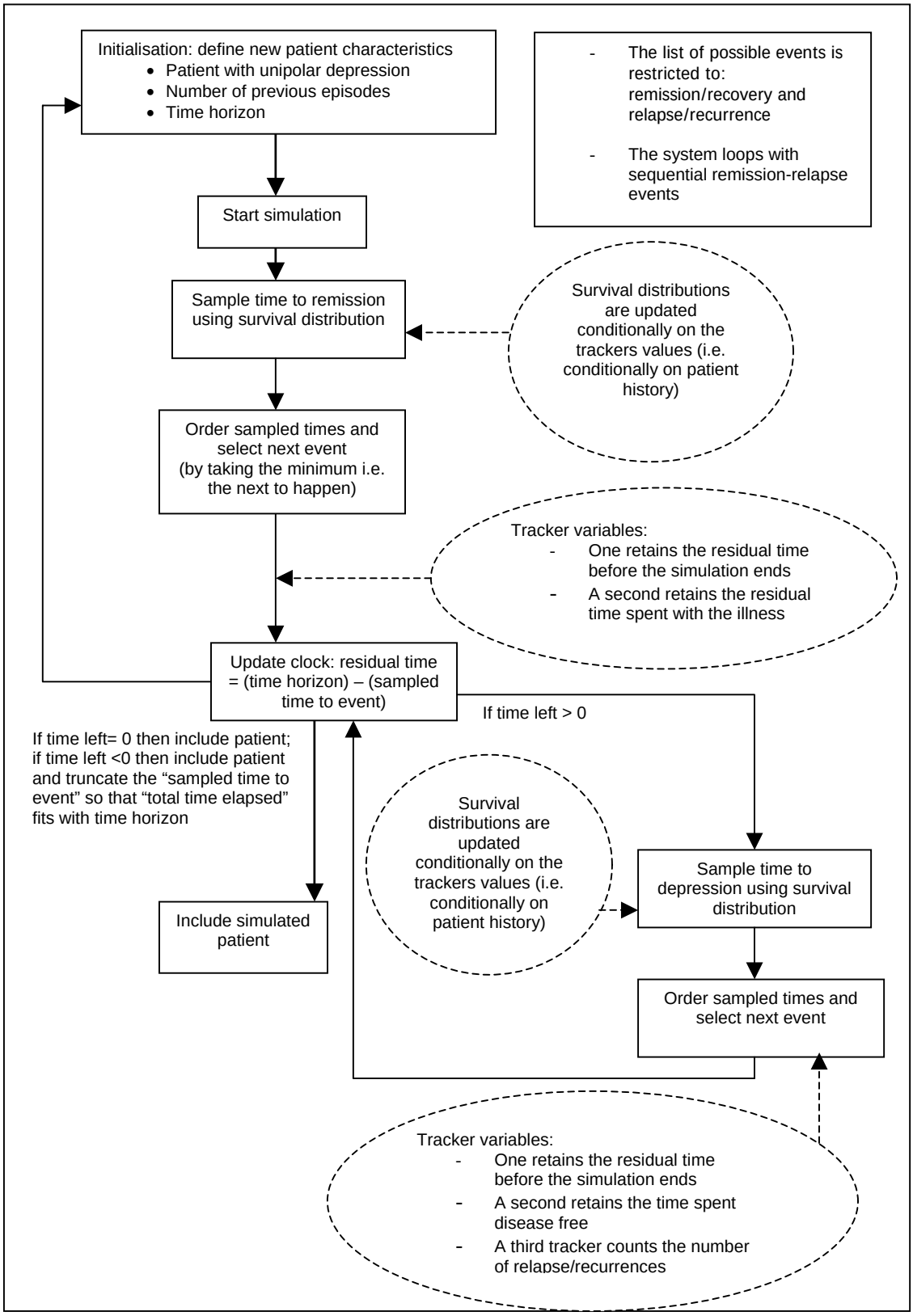
We decided to examine the properties of DES models when applied to the depiction of depression dynamics in order to value their use in practice. The algorithm associated to our problematic is depicted in Figure 5. There are no cycle length to declare and no health states. Disease evolution is pictured out using the events that will trigger a change of health state. A method to select the next occurring event was chosen following Barton et al. work (42): The underlying idea was "sample times for each possible event and take the minimum" (following the logic according to which the first event to happen is preferably chosen). Here, for each event were required survival distributions assuming that no other event was possible. Then a time is sampled for each event and the earliest time determines which event happens. This is implemented by taking other events as censored events and the other times are discarded.

The data needed were survival data conditional on the number of prior depressive events. The time spent in the "well" (respectively depressed) state is obtained by summing the tracked sampled times leading to relapse (respectively remission). Other tracker variables make it possible to count the number of relapses or recurrences occurring along the study period accordingly. The simulated patient starts its progression through the model with a first depressive event (i.e. no prior depressive events). The only event extracting the patient from depression is to achieve a remission of his symptoms. Therefore a "time to remission" is sampled conditionally on patients' proper history. The clock advances of the simulated "time to remission" and a test is performed to check if there is time left to continue the simulation (according to the fixed time horizon) or not. Then once the patient is symptom-free, he is still subject to relapse. Therefore a "time to depression" is sampled and the clock is advanced of this sampled "time to depression". If the sampled time were inferior to 24 weeks then the patient was in "simple remission" so we speak of relapse; if the sampled time were superior to 24 weeks then the patient was in full recovery so we have to use the term "recurrence".

[3] Peter W. Glynn describes a mathematical formalism for the underlying stochastic process, named "Generalized Semi-Markov Process" (GSMP). A GSMP is an established formalism for modeling continuous-time stochastic discrete event systems (39;40).

Conditionally on these tests, tracker variables count the number of events occurring. Figure 5 below displays a graphical representation of the algorithm.

Figure 5 Discrete Event Simulation algorithm



This DES model reflects a simple pathway with a very limited list of possible events: there are no competing events, which renders the analysis simplistic. However this practical example makes it possible to visualize the flexibility with which DES models can cope with multiple competing events. This simple model shows that DES models appear as a powerful means to address both the problem of patient's history and the risk for illness persistence using survival distributions conditional on tracker values. In the same way, remission and recovery periods can be easily distinguished by tracking the sampled "time to depression" and see if this sampled time is inferior or superior to a threshold value (here it should be defined at 24 weeks as per the consensus definitions). If the sampled time to depression was less than 24 weeks, then the simulated patient could not be in full recovery, being therefore only in a "remission phase". By implementing various queries, it is possible to define new trackers that will memory if the simulated patient was either completely cured or if he was not.

Until there, DES models are proven to be as efficient as Markov models, with maybe a little more flexibility in the way they can be implemented. But what if the analyst wishes to handle the problem of patients' adherence to treatment, which was previously reported as a key factor to be modelled? DES models have the flexibility to manage this issue quite easily, just by adding an event to the list of the possible events a patient is likely to experience (together with its proper survival distribution) and let the model run: the sequence of events experienced by the patient will be randomly generated according to the event selection method exposed previously (i.e. sample "time to events", the first event to happen is selected). In the same way, events such as suicide attempt, adverse events or any event (for which we have adequate data) can be easily handled.

Therefore, DES models seem to be a promising simulation technique, very flexible and easy to follow for any analyst who may not be familiar either with the key aspects of the disease or with simulation tools in general. DES models are able to bypass Markov models limitations especially in their ability to take account of multiple events, which can be crucial when aiming to depict disease progression as close to reality as possible.

IV. Discussion

The brief overview of the key prognostic factors of depression presented in section II aimed to help understanding to what extent this disease should be specifically modelled, accounting for various specific risk factors. This overview intended to provide a comprehensive picture of the key-points that should be addressed when modelling the course of depression.

Importantly, the timeframe of the model needed to be large enough to be able to capture all events occurring during the disease span and beyond (periods of remission). As such, distinction between relapses and recurrences (according to whether the patient is experiencing a new

episode of depression or not) were shown to be important issues to be taken into consideration in order to more precisely assess the capacity of a given strategy to delay further risk of developing depressive symptoms. The number of previous depressive events, their duration and severity together with patients' adherence to therapy were also proven to be key factors that should be taken into account in the computational framework.

Markov models were shown to be efficient to some extent. Despite their memory less property, Markov models managed to handle the problem of patient history by specifying various health states defined according to risk levels (low, moderate, high risk of relapse), and the issue of disease persistence was somewhat adequately addressed at the expense of defining multiple temporary health states. However a major drawback was pointed out (multiple events handling), especially when the analyst aimed to fit to reality as closely as possible by considering more complicated scenarios and take account of patients' attitude towards treatment (as well as gender and age effects). When such events or patients' attributes are necessary to be taken into consideration, analysts may be more likely to move towards more elaborate modelling methods such as discrete event simulation.

It should however be noticed that health service research in general and economic evaluation in particular is commonly associated with a lack of adequate data. Here the intention was to validate the use of a DES model in a conceptual way, i.e. in terms of its computational validity, which was proven to be reasonable. In order to be able to quantify (numerically) the benefits of DES over Markov models, one may have sought some kind of empirical validation. Future research would necessitate comparing simulated results with those obtained from observational data (i.e. perform an external validation). Further research would thus focus on both the internal and external validity of the conceptual model (43), by first collecting adequate data (after systematic review of the literature), choosing appropriate statistical distributions on parameters, and by calibrating the model with reference to results obtained from naturalistic studies. However, when reliable data is not available, DES may be a good information system that could be used to run a series of different « what if?» scenarios, allowing the user to understand the interaction of the model parameters, and their effects on the output of interest. For example in the context of exploratory analyses which purpose would be to identify what are the preferred health outcomes to be included alongside a clinical trial, this may help defining more precisely what are the requirements for a definitive economic analysis and determine a strategy for data collection, although ideally the pre-data collection would have been done before the launch of the trial (35).

Nevertheless, there are certain limits to the wholesale adoption of a DES that deserve to be

pointed out. Firstly, greater flexibility may only be reached at the expense of supplementary specialist analytic knowledge, which may reduce the evaluator's direct access to the model. Also it may take time to develop, implement and check the conceptual model. Moreover, individual sampling models like DES models can be really time-consuming, as multiple replications are needed to get good estimates of mean effects. However variance reduction methods are applicable to help reducing the number of replications and hence the time needed (28). Finally, DES may induce over-specification, whereby the possible pathways of a patient are made more complex than is necessary, thus implying an increase in data requirements.

We deliberately chose here to focus on the methodological aspects of the modelling methods, regardless of the therapeutic strategies and without any costing purpose. However costing would be equally feasible in both methods: DES models would use variables associated to each event undergone, while Markov models would associate a monetary value to health states.
In order to provide decision makers with a fully specified tool aiming at prioritizing prophylactic actions for depression, further work should incorporate, in the form of a DES model, both clinical and economic data in accordance with national and international clinical and pharmacoeconomic guidelines.

V. Conclusion

The practical examples described previously tend to show that discrete event simulation appears as a more appropriate technique compared with Markov modelling when applied to depression. Although discrete event simulation has a quite long history in operation research for industry-related issues (44;45), it is only newly employed to assess the value of healthcare interventions. DES seems to provide a comprehensive tool to picture the course of depression, thus allowing greater flexibility in depicting the cost-effectiveness of prophylactic interventions for recurrent depression. In general, the biggest advantage of DES is that it allows the analyst to model more complex and dynamic systems that other types of modelling, as well as allowing experimentations that might not be feasible otherwise (using "what if?" scenarios). The greater flexibility specific to the use of DES also enables the model to capture more detail about the uncertainty in the system being modelled.
However, the trade-off between the simplicity of use of a methodology and the necessary accuracy of the picture of reality is open to question, although it is expected to fit more to the true course of events. The choice of a decision model should be based on an assessment of the additional benefits, in terms of reliance in the model, which are yielded at the expense of the incremental costs (analysts input, complexity of data collection) of implementing a more complicated modelling methodology.

Future work should consist in assessing both the internal and external validity of DES a model and to depict the outcomes incurred by prophylactic strategies for depression. Further conclusions could be drawn with regards to the benefits/drawbacks induced by such a methodology.

Conflicts of interest: H. Lundbeck A/S provided funds for this study, as part of a PhD thesis within the Economics & Pricing Division.

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