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Comparing Markov and non-Markov Alternatives for Cost-effectiveness Analysis: Insights from a Cervical Cancer Case

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Abstract

Markov models allows medical prognosis to be modeled with health state transitions over time and is particularly useful for decisions regarding diseases where uncertain events and outcomes may occur. To provide sufficient detail for operations researchers to carry out a Markov analysis, we present a detailed example of a Markov model with five health states with monthly transitions with stationary transition probabilities between states to model the cost and effectiveness of two treatments for advanced cervical cancer. A different approach uses survival curves to directly model the fraction of patients in each state at each time period without the Markov property. We use this alternative method to analyze the cervical cancer case and compare the Markov and non-Markov approaches. These models provide useful insights about both the effectiveness of treatments and the associated costs for healthcare decision makers.

Keywords: Cost-effectiveness analysis, Markov process, Survival analysis, Stationary probabilities, Time-dependent probabilities

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1. Introduction

The progress of medicine, both in the prevention and in the diagnosis and treatment of diseases, has significantly increased life expectancy by curing or at least alleviating many ailments that had no remedy in the past. The downside of this progress is that health spending has increased dramatically in all countries. Thus, identifying whether the benefit a new treatment brings compensates for its cost remains a fundamental challenge faced by those involved in health policy decision making. Furthermore, the acknowledgement that resources are limited has further intensified pressure to identify health interventions that provide the greatest benefit at a reasonable cost (i.e. those that are cost-effective).

Since in many cases there is not enough information to estimate the cost and effectiveness of an intervention directly, it is necessary to use mathematical models to project the data from clinical and epidemiological studies across a patient's life span and compute summary measures for the entire patient population.

Disease status can often be characterized as a set of recurrent discrete states assessed over time. This natural history of the disease transitions is frequently modeled using Markovian transition models, as they provide a reasonably flexible class of models which can be fitted to the data. Such models are based on the Markov property, meaning that the conditional probabilities of transitioning from one state to another are independent of the past visited states and independent of the time spent in those states. Some recent examples in healthcare include progressions over time in psychiatric disorders, multiple sclerosis, hepatitis C, Alzheimer's disease, and psoriatic arthritis ([1], [2], [3], [4], [5]). A different approach uses survival curves to directly model the fraction of patients in each state at each time period without the Markov property.

Cost-effectiveness analysis (CEA) of medical treatments provides patients and doctors with better understanding of the performance of treatments. The aim of this paper is to demonstrate Markov and non-Markov alternatives for CEA and discuss the advantages and disadvantages of the alternative analyses using the cost-effectiveness evaluation of chemotherapy combined with bevacizumab in advanced cervical cancer patients as a case example. This provides a suitable example to demonstrate the issues most researchers might encounter when modeling disease evolution. Since there is always a gap between a model and the real world, narrowing this gap with more accurate and insightful models can help provide valid suggestions on treatment selection and thus improve life quality of patients.

The patients' length of survival is calculated using the transition probabilities of a Markovian process or via the direct estimation of percentages of patients surviving at different time periods. Besides examining the effectiveness of treatment in terms of survival times, we examine medical costs and the assignment of health utilities like, for example, Minion et al. [6] does for results on quality adjusted life months living with cervical cancer and Hazen [7] for multiple attribute quality adjusted life years.

Our paper differs from the literature as we consider the case when individual patient data (IPD) are not available.

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The structure of this paper is as follows. In section two we briefly review the past literature on Markov models for medical decision making. Section three presents the specific cervical cancer case that will be used as an example throughout this paper. Section four specifies the Markov states, their transition probabilities from one discrete time period to the next and the expected outcomes. A way to deal with uncertainty using probabilistic analysis is considered in section five, while section six contains some other issues to consider when using a Markov model. In section seven, we study how to deal with non-stationarity in probabilities with a different modeling approach without Markov state transition modeling. Section eight covers the advantages and disadvantages of both approaches. Appendices cover added details for those less familiar with these methods.

Unless otherwise noted, all the calculations and graphs were done using R v.3.5.2, packages "markovchain" (Spedicato et al. [8]) and "survival" (Thernaeu [9]). Also, calculations for costs and months were done with up to eight decimal places and then rounded to four to facilitate readability.

2. Background

In this study, we present a detailed example of a Markov model with five health states with monthly transitions with stationary transition probabilities between states to model the cost and effectiveness of two treatments for advanced cervical cancer.

When limited to available published data, that does not usually include individual patient data, it is challenging to directly derive time-dependent (non-stationary) transition probabilities. Therefore, the time-dependent Markov model, where the transitions probabilities vary with time, is not considered in the following. Instead, an alternative approach based on the published Kaplan-Meier curves will be presented.

We provide more modeling detail than is typical in a medical journal, for operations research modelers.

2.1. Markov Models

Markov models are recursive (repetitive) representations of randomly changing processes that have events (health states, in the case of a disease evolution) that may occur repeatedly over time and for whose chance of occurrence depends only on the most recently occurring event and not on the entire history of the process (exhibiting the memory-less Markov property).

Since the 1983 Beck and Pauker paper [10], where the use of Markov models for determining prognosis in medical applications was first described, there is a stream of literature aiming at building bridges between healthcare specific models and reality. A Markov model is able to represent a given process when a list of the possible states of that process, the possible transition paths between those states (often of fixed duration, e.g., weeks, months or years), and the rate/probabilities of those transitions (representing transition likelihoods) can be given.

For further background, there have been several reviews of Markovian process methodology (e.g. see Naimark et al. [11] or Sonnenberg and Beck [12]) that provide an introduction to basic concepts and problems. A much more detailed description of methods related to Markov cost-effectiveness analysis and the rationale behind them,

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with proposed exercises at the end of each chapter, can be found in Briggs et al. [13] and Gray et al. [14]. Furthermore, O'Mahony et al. [15] discuss several time-related methodological aspects of health economic evaluation models, like intervention duration, implementation period, analytic horizon, cycle length and changing the cycle length, as well as other issues like cohort selection or discounting future costs.

Finally, recently, a tutorial on how to carry out cost-effectiveness analysis using R (with all the code provided) for multi-state models (models of a continuous time stochastic process with a finite number of states) usable when IPD are available is in Williams et al. [16]. However, that is not usually the case for most researchers, where their problems are time discrete (patients are observed every cycle) and IPD are not available. R has many advantages over packages like TreeAge or spreadsheets, like Microsoft Excel, not the least of which is its versatility and free availability under the GNU General Public License. For Markov chain analysis using the statistical package R, see for example Bai et al. [17].

2.2. Non-Markov Models

Sometimes reporting of survival outcomes from clinical trials is limited to information on median survival times, hazard ratios, Kaplan-Meier curves and numbers at risk, making it challenging to conduct a cost-effectiveness analysis based on a Markov model. In that case, a possible procedure is to estimate the state probabilities, which can be time dependent, through the fitting of a non-linear model to the given Kaplan Meier curve.

Hoyle and Henley [18] and Guyot et al. [19] have developed methods to estimate individual patient data from published Kaplan Meier curves, data that can be used to directly estimate non-linear survival curves. This approach does not model Markov transitions from period to period, it just directly computes the fraction of patients in each state in each period. Because it is not constrained to depict period-by-period transitions, the non-Markov approach is more flexible, but it loses the clinical insight gainable from period-by-period transition patterns. We use this alternative method to analyze the cervical cancer case and compare the Markov and non-Markov approaches.

3. Base Case: Bevacizumab in Advanced Cervical Cancer Patients

Our analysis builds upon a published clinical trial GOG240 study in Tewari et al. [20] whose objective was to evaluate the effectiveness of combining the angiogenesis inhibitor[1] bevacizumab, whose brand name is Avastin, with non-platinum based chemotherapy versus using chemotherapy alone in patients with recurrent, persistent, or metastatic cervical cancer being treated in several medical centers worldwide between April 2009 and January 2012. In the clinical trial, 452 patients were randomly assigned to the two treatment groups (225 in the chemotherapy-alone group and 227 in the chemotherapy-plus-bevacizumab group). The results of the study indicate that after a median follow up of 20.8 months in both arms of the trial, there was a significant median overall survival gain of 3.7 months (17 months vs. 13.3 months) as well as a progression-free survival gain (8.2 vs. 5.9 months) when using bevacizumab with chemotherapy rather than just chemotherapy .

[1] An angiogenesis inhibitor is a drug that slows the growth of new blood vessels.

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The trial showed that chemotherapy combined with bevacizumab led to improved survival, but costs still had to be included in the analysis. Therefore, a trial-based economic evaluation was undertaken by Minion et al. [6], through a discrete-time Markovian model using the TreeAge Pro Healthcare software, to estimate the cost-effectiveness of chemotherapy plus bevacizumab versus chemotherapy alone based on the previously mentioned trial results [20] plus some updated data provided by the physician co-authors in [6]. A standard decision tree to decide between the two treatment arms was converted to a Markov decision tree by adding Markov nodes, which can be revisited as time passes. See the online supplementary material in [6] for the Markov decision tree.

The CEA base case reported a significant mean survival gain for chemotherapy plus bevacizumab compared to chemotherapy alone (the expected life months until death were calculated to be 18.5 months for chemotherapy plus bevacizumab and 15 months for chemotherapy alone), and found that chemotherapy plus bevacizumab was also more costly compared to chemotherapy alone (for each patient, the estimated total life-time cost of chemotherapy plus bevacizumab is $79,844 and of chemotherapy alone is $6,053).

As in many cases, the individual-level data are not available. The data we obtained from the clinical trial report includes the number of adverse events, response rate and progression rate every six months, Kaplan-Meier curves for progression-free survival, overall survival, and costs of treatments.

4. Markov Modeling

4.1. State Modeling

The first step when constructing a health related Markov model is to determine a set of health states that patients might reasonably experience and that are mutually exclusive, because each patient must be in one and only one state at all times in the model.

The specific characteristics of the disease natural history and the treatment under consideration guide the determination of the number of states, from the most commonly used three-state healthy-sick-dead model to the process with an infinite number of states. Also, it is very common that models include a Dead state, which is called an “absorbing” state, because from that state there is no possible transition to any other state. In clinical trials involving deadly diseases, the survival time from the start of the trial until death is often the key measure of treatment effectiveness.

In the Markov model used in [6], five possible health states were identified: respond (to treatment), progress (to be sicker), limited complications (hypertension), severe complications (fistula or thromboembolism, but not both), and dead, denoted by R, P, LC, SC and D respectively. The states and characteristics are similar to those used in Refaat et al. [21] for breast cancer treatment, with the only difference that their health state of complications was now divided into limited complications and severe complications. That division was necessary as patients in each of those two states behave very differently: those with the limited complication of hypertension are treated for those complications while still receiving the chemotherapy treatment before going back to the

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respond state in the next cycle, whereas those with severe complications stop receiving chemotherapy and transition to progress or stay in severe complications.

A patient was modelled as being in one state during a month, and she could transition to a different state with some probability in the following month. The cycle length was estimated to be a month since each round of chemotherapy treatment begins roughly a month apart.

--- Insert Figure 1 around here ---

A finite-state Markov chain is usually described by a square matrix P of transition probabilities, whose dimension is determined by the number of states. Such a finite-state stationary Markov process is also often described by a directed graph as in Figure 1 for the cervical cancer case. In this graphical representation, there is one node for each state and a directed arc for each non-zero one-month transition probability, otherwise the arc is omitted. Calculating those probabilities is the aim of the next subsection.

4.2. Determining Stationary Probabilities

We use a discrete-time stationary Markov process as it is common in most health-related Markov analyses. Estimating the transition probabilities for a stationary Markov process, i.e. where the individual probabilities of going from state i to state j in one cycle do not change with time ($p_{ij}(t) = p_{ij}$), is a relatively straightforward process, if data on counts of patients in each state at different points in time are available. Observing the illness state of a group of patients at the beginning and at the end of the cycle, the probability of moving from one state i to another j can be estimated by calculating the simple ratio of the number of patients that began the cycle in state i and ended up in state j divided by the total number of patients that began in state i. That estimator is a maximum-likelihood estimator of p_{ij} (see Anderson and Goodman[22]).

Published clinical trial data provide some information for a Markov model, upon which other calculations can be done to complete the model, with some further assumptions or judgments possibly being needed. The cervical cancer data in [20] were reported at 6-month intervals, and they were used to derive one-month transition probabilities. Please refer to Appendix A for more information on how to obtain the 6-month transition probabilities for the chemotherapy plus bevacizumab treatment, and to Appendix B on information on how to transform that 6-month matrix to the one-month transition probabilities matrix needed for our model. The resulting one-month transition probabilities for the chemotherapy plus bevacizumab arm of treatment are in Table 1. Note that the probabilities in a row sum to 1 since all patients who begin a month in that state will either stay there or move to a different state.

--- Insert Table 1 around here ---

A similar procedure can be followed to obtain the stationary probabilities for the chemotherapy-only arm of treatment (Table 2). Note that bevacizumab treatment has a slightly higher probability to stay in the respond state, along with higher probabilities of complications. See the concluding section for some possible biases in calculating these stationary probabilities.

--- Insert Table 2 around here ---

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For patients starting a month in the respond state (getting treatment for cervical cancer), 80.22% of those treated with chemotherapy alone would still be in the respond state at the beginning of the next month, since $P_{RR} = 0.8022$. In contrast, 82.56% of the chemotherapy plus bevacizumab patients would still be in the respond state.

A half-cycle correction is very often used to compensate for the fact that state membership is only known at the beginning and at the end of each cycle, but not in between, making state membership systematically overestimated or underestimated [14]. However, this is not a significant problem in our case as the chosen one-month cycle length is very short. Thus, no half-cycle correction has been used.

4.3. Calculate the Expected Outcome Values

Assuming all patients start in the respond state, 60 monthly cycles of each treatment can be calculated with month-by-month Markov transitions, keeping track of the cost of being in each health state for a month and how long patients live. The two therapies (using chemotherapy alone or replacing it with chemotherapy plus bevacizumab) can be compared by the incremental cost-effectiveness ratio (ICER), representing the cost per incremental unit of effectiveness (the extra cost per month gained with chemotherapy plus bevacizumab replacing chemotherapy alone).

$$ICER = \Delta C / \Delta E = [C(Beva) - C(Chemo)] / [E(Beva) - E(Chemo)]$$

where C(Beva) and C(Chemo) are the mean costs in the chemotherapy plus bevacizumab and chemotherapy alone arms of the trial, respectively, and E(Beva) and E(Chemo) are their respective mean health effects in expected months of life. These can be calculated with the Markov decision tree in the TreeAge software or in R.

Cost values, for both chemotherapy plus bevacizumab and chemotherapy alone, are presented in Table 3. Note that bevacizumab treatment costs about $7,000/month more than chemotherapy alone when the patient is getting the clinical trial cancer treatment (in the Respond or Limited Complications states).

--- Insert Table 3 around here ---

Utilities can be assigned representing the effectiveness of the treatment or the life quality during a month, so that if a patient moves to a worse health state the life quality is adjusted downward for that month. They are assumed to be the same for both arms of the study trial with values of 1 for response, 0.75 for limited complications, 0.5 for progress and severe complications and 0 for dead [21]. Note that for these advanced cervical cancer patients, getting a utility of 1 in one month means living with and responding to advanced cervical cancer treatment. Unlike traditional quality adjusted life years (QALYs), where a 1 means living in perfect health for one year, the choice to scale the measure in months (QALMccs) of cervical cancer life allows a focus on the relatively few remaining months of life for these patients, and the reality that the best health level possible is responding to the treatment (not a cure). For a more extended explanation of how the utilities were obtained see [6] or for a general approach for multiattribute quality adjusted life years see [7].

The long-term behavior of a Markov chain is depicted in each cycle by a probability distribution or probability vector over the set of states (a row vector whose entries are

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non-negative and sum to 1). The i^{th} component of that probability vector represents the probability that the chain starts in state i at the beginning of the cycle. At the beginning of the cervical cancer clinical trial case, since all patients are in the respond state, the initial probability vector is (1,0,0,0,0).

For each Markov cycle, the expected cost per month of care for a patient is found by multiplying the probability of each Markov state (obtained from the Markov model) by the appropriate cost and summing across the four living Markov states with no cost assigned to the death state. By summing these costs per cycle over 60 cycles, the total expected cost of care for a patient was derived.

A total average cost of $44,444 was obtained for the chemotherapy plus bevacizumab treatment arm while a $2,903 average cost was obtained for chemotherapy only. The expected remaining durations of life from the beginning of the study onward were E(Beva) = 9.5965 months versus E(Chemo) = 7.8193 months. The quality adjusted life months living with cervical cancer were $QALM_{cc}$(Beva) = 7.1409 months versus $QALM_{cc}$(Chemo) = 5.4161 months. The incremental cost-effectiveness ratio (ICER) was calculated to be ($44,444 – 2,903) / (9.5965 – 7.8193) = $23,374.4092/month of life or $24,084.5315 /QALMcc. Thus, the added cost for an added month of survival or an added quality adjusted month when treated with bevacizumab added to the baseline chemotherapy is around $23,000-24,000. Even though the addition of bevacizumab only costs $7,016 per month, the patient has to be on the treatment and incur the excess cost each month for the rest of her life to get the increase in survival.

Note that the different modelling assumptions in [6] led to higher transition probabilities from respond to respond, for both chemotherapy plus bevacizumab and chemotherapy alone treatment arms, thus higher months of remaining life and thus higher costs, but a similar ICER to what is found with the current analysis.

5. Probabilistic Modeling of Parameters in Markov Model

Due to the inherent imperfect information, even of a randomized trial sample of an intervention, there is a possibility that decisions based on the cost and effectiveness of the available information of the intervention under evaluation will be incorrect. That problem might be overcome by using probabilistic techniques (e.g., Monte Carlo simulation) to generate the sampling distribution of the joint mean cost and efficacy so that a quantification of the uncertainty surrounding those estimates can be obtained.

In this section we present a technique that fits functional forms to model parameters to conduct a Monte Carlo simulation. Monte Carlo (see for example Robert and Casella [24]) is a computational technique whose core idea is to generate other possible samples of the system under study (in the present case patients receiving chemotherapy combined with bevacizumab vs. patients receiving only chemotherapy) to learn about its behavior.

Another standard simulation approach (Bootstrap), like the one TreeAge software uses, takes the specified Markov decision tree's probabilities as fixed parameters and randomly samples patients from the pre-set discrete probability distributions. In contrast, in this approach a cloud of averages is calculated after sampling from possible parameter values to set a Markov decision tree's probability distribution, calculating the result, and then repeating to conduct another sample and set a different Markov decision tree's

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probability distribution, etc. Therefore, for each treatment arm, other possible evolutions are studied by generating different sets of probable transition frequencies for our Markov model.

In order to do so, the parameters of interest (data counts, in the present case) are ascribed a probability distribution reflecting the uncertainty concerning their true value. In most cases the form of the data, the type of parameter and the estimation process would only point to one or two different distributions that, for mathematical convenience (Rice [23]), is conjugate to the likelihood function based on the observed data.

In our case, only the first row and second row frequencies of the transition frequency matrices need to be sampled (see Table A.3 in Appendix A). Following Briggs et al. [13] (pp. 116-118) on how to characterize the uncertainty of input parameters using probability distributions, we have a dichotomous transition in the second row (progress to progress, or progress to death) that can, therefore, be characterized by a binomial distribution. However, in the first row we have a three transitions case (response to response, response to progress, or response to death) that it is naturally characterized by a multinomial distribution. Hence, the multinomial transition probabilities from response (R) to response, progress and dead are represented by a Dirichlet distribution (the conjugate of the Multinomial distribution), while the choice for the transition probabilities from progress (P) to progress and dead are represented by a Beta distribution (the conjugate of the Binomial probability distribution). Thus, the considered distributions for the data obtained from Tosari et al. [20] as explained in Appendix A, are:

- For chemotherapy plus bevacizumab: Dirichlet distribution Dir(233,169,55) for transitions from R to R, P and D, and Beta distribution β(12, 162) for transitions from P to P and D, where the respective parameters are the total counts that appear in first and second row, respectively, of Table A.3, Appendix A.
- For chemotherapy alone: Dirichlet distribution Dir(166,155,67) for transitions from R, and Beta distribution β(10, 150) for transitions from P, where the parameters for the first and second row of the frequency transition matrix are the corresponding counts in Appendix A.

Next, Monte Carlo simulation values were sampled at random from the previously deduced probability distributions and 3x3 6-month transition matrices were obtained for each of the generated values. For each of these matrices, the process detailed in Appendix A for calculating the stationary transition probabilities was carried out, to include the complications states, allowing the repeated calculation of the incremental cost and effectiveness for all of the "what-if" chemotherapy plus bevacizumab and chemotherapy-only generated scenarios.

Each set of samples is called an iteration, and the resulting outcome from that sample is recorded and plotted on the cost-effectiveness plane [25], where the incremental effects (in months) are measured on the horizontal axis and incremental costs are measured on the vertical axis. The axis selection is not arbitrary, having the advantage that the slope of the line joining any point of the plane with the origin is precisely the ICER [13]. Points along a given ray from the origin correspond to the same ICER. See in Figure 2 the range

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of possible outcomes that results from 1,000 Monte Carlo simulations as well as the base case model value (in pink in Figure 2).

--- Insert Figure 2 around here ---

As it can be seen from Figure 2 only a few points do not fall in the northeast quadrant of the plane, where both added costs and added health effects are positive, meaning a bevacizumab patient lives months longer at a higher cost, compared to having chemotherapy only. So there is a tradeoff in this situation where chemotherapy plus bevacizumab may be cost-effective compared with chemotherapy-only treatment, depending upon whether the ICER is above or below a given value the payer is able or willing to pay, taking into account that all ICER values are over $11,300 (see the line in Figure 2). The "cloud" of possible outcomes in the figure visually demonstrates that the ICER would differ for each clinical trial's sample of patients.

The advantage of this approach is that functional forms for distributions are specified prior to running simulations, reflecting the inherent uncertainties.

6. Additional Challenges in Markov Modeling

In the Markov analysis in the previous sections, by estimating the transition probability matrix from the patient counts, problems can be encountered when the number of transitions is small, usually caused by small population size. Discreteness effects will lead to noise in the transition probabilities. At times, this does not matter. Since some transitions are less important than others, they will have little impact on final average results. However, it is a factor to be aware of.

It has to be noted that the numbers in Table A.2 (Appendix A) are underestimated since 6-month data were used and also because the value for progression-free survival was used when calculating the number of patients in the respond state. And this value actually includes the number of complications. Similarly, the transition probabilities from respond to limited complications were calculated in a conservative way by computing total observations divided by total possible transitions.

Usually individual-level data are hard to get, especially for some disease states like complications. In many studies, like the present one, the only data available for complications is the aggregate number of patients who developed a complication any time during the treatment. Because of this, a further assumption is made that complications are independent and mutually exclusive to each other and have stationary transition probabilities.

However, as a matter of fact, some complications may be very likely to occur together. For example, nausea and vomiting often occur together. The independence assumption will result in a positive bias in the overestimation of the one-cycle transition probability from one state to another one, and may further induce underestimation in transition probabilities to other states.

Another feature of cancer treatment is that usually the total treatment time lasts many months and patients may switch from the initial treatment to another one, maybe just because they develop complications from the drugs they are taking. Failing to consider the patients switching treatment may lead to underestimating the difference in the

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outcomes. One way to deal with that is to not include these patients at the beginning of the study, but this may increase bias in the estimators. Another way is to consider the patients who switched as if they progressed, which may overestimate the progression rate. A third way is to model the process as multiple therapy lines (or at least a two-stage decision problem).

Some cancers, like ovarian cancer, have high relapse rates. For these kinds of cancer, patients may have multiple therapy lines, which means that the patient may respond to an initial treatment at first, but relapse after several months. Then that initial treatment is not effective anymore and the patient needs to change to another treatment, which is called a second line therapy. The process may continue until the patient recovers or dies. Usually, clinical researchers compare the treatments independently, regardless of the line and of what the previous lines of therapy were. However, the effect of different lines on the response rate is significant, Hanker et al. [26]. And the treatment effect may correlate with previous treatments. The combination of treatments should be compared as a whole rather than simply comparing each treatment independently in different therapy lines. A multi-stage decision model is needed in this scenario.

7. Non-Markovian Method: Direct Calculation of State Probabilities

The discrete time Markov chain model used in the previous sections to model the evolution of a disease is based on the assumption that the transition probabilities remain constant over time. But this assumption might be a little too restrictive and nonstationary (time dependent) behavior might be more appropriate to represent the transitions between states in each cycle. In our case, the difference of the outcomes for survival and progression free survival (PFS), for chemotherapy plus bevacizumab treatment arm patients, estimated from the Markov state modeling with stationary transition probabilities in Table 1 with 30 cycles and the real data, obtained from [20], is relatively large (see Table 4). That fact suggests the stationary process assumption is not completely adequate.

--- Insert Table 4 around here ---

In this section an alternative non-Markovian approach that allows time dependence is described as deriving the time dependent transition probabilities for a Markov model can be a challenging process (see Bai et al. [27], for a description of that method). This method does not require specification of month-to-month transition probabilities, instead it specifies the number of patients in each state in each month.

The percentage of patients in each health state at each successive cycle is now going to be determined by using the survival curve data. Therefore, using the so-called “area under the curve” method, there is no requirement to calculate the probabilities of monthly transitions between health states since the numbers in each state each month are directly derived from the overall and progression-free survival curves. (See Appendix D for a graphical interpretation of the area under the curve method.)

The overall and progression-free survival curves for chemotherapy plus bevacizumab and chemotherapy alone were estimated using the method proposed in [18]. The authors fit survival curves from the Kaplan-Meier curve and the data of the number of people at risk that usually comes alongside the graph in most published research. This new method

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takes into account an estimation of the censored data (patients dropped out of the trial) and improves the accuracy compared to traditional methods (e.g. regression or least squares).

GetData Graph Digitizer v. 2.24 was used to extract the original (x,y) Kaplan-Meier curve values from the scanned figure 3 in [20]. Those values were used as input to estimate the overall and progression-free survival curves for both arms of treatment, obtaining the best fit (lowest) Akaike information criterion (AIC) for the following models (Kalbfleisch and Prentice [28]), all of them with significant parameters:

- For chemotherapy plus bevacizumab overall survival to the every six month data points, the best fit is a Weibull model with parameters p = 1.3882 and λ = 0.0144. Therefore, the number of surviving patients at time t is $S_{beva}(t) = \exp[-0.0144 \cdot t^{1.3882}]$.
- For chemotherapy alone overall survival, the best fit is a Log-logistic model with parameters p = 1.6653 and λ = 0.0138. However a Weibull model with parameters p = 1.2673 and λ = 0.0245, whose AIC is very similar to the Log-logistic model, was chosen since it fits better in later months. Therefore, the number of patients $S_{chemo}(t) = \exp[-0.024526 \cdot t^{1.267266}]$. As can be seen in Figure 3, the fit is not totally adequate due to the misfit in the tail (since patients have a soon-to-be fatal disease), also caused because of lack of data towards the end.
- For chemotherapy plus bevacizumab progress-free survival, the best fit is a Lognormal model with parameters p = 1.1148 and λ = 0.0894. Therefore $PFS_{beva}(t) = 1 - \Phi(1.1148 \cdot \log(0.0894 \cdot t))$, with Φ being the normal N(0,1) density function.
- For chemotherapy only progress-free survival, the best fit is a Log-logistic model with parameters p = 1.6586 and λ = 0.0442. Therefore $PFS_{chemo}(t) = 1/(1+0.0442 \cdot t^{1.6653})$.

--- Insert Figure 3 around here ---

Thus, the probability of being in the respond state at each successive cycle and for both chemotherapy-only treatment and chemotherapy plus bevacizumab can be estimated by $\pi_R(t) = PFS(t)$, the probability for Progression by $\pi_P(t) = S(t) - PFS(t)$ and for Dead by $\pi_D(t) = 1 - S(t)$. Regarding the complications, both limited and severe, the only available information is the number of complications throughout the total period of the study trial. Therefore, it is going to be assumed that those events occur independently and their probability remains constant over the 30-month study period. For chemotherapy plus bevacizumab the number of limited complications and severe complications are, respectively, 54 and 31 (out of the total number of patients in respond through the study, obtained by summing over the expected number of patients in respond in each cycle, which yields 1,416), whereas for chemotherapy alone the number of limited and severe complications is 4 (out of the expected number of patients in respond in each cycle, which yields 1,148)

• For chemotherapy plus bevacizumab, $\pi_{LC}(t) = 0.0381$ and $\pi_{SC}(t) = 0.0219$

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• For chemotherapy alone, $\pi_{LC}(t) = \pi_{SC}(t) = 0.0035$

Therefore, the estimates of the average effects and costs for the chemotherapy plus bevacizumab treatment arm are, respectively, E(Beva) = 19.7164 months, Cost(Beva) = $112,680, QALMcc(Beva) = 15.8914 months living with cervical cancer. For the chemotherapy-only treatment arm, the results are E(Chemo) = 17.6994 months; Cost(Chemo) = $7,861; QALMcc(Chemo) = 13.3137 months living with cervical cancer. Hence an ICER of $52,017 per additional month is obtained as the summary of the chemotherapy plus bevacizumab intervention.

8. Advantages and Disadvantages of the Approaches

Two distinct methods for modeling the cost-effectiveness of cancer treatment were presented for a cervical cancer case. First, we provided details of how to build a Markov decision process with stationary transition probabilities between monthly health states. Second, an alternative non-Markov method to directly estimate the fraction of patients in each health state at different time periods was presented. Although both methods enable us to conjecture about future outcomes, there are, nevertheless, some observations and caveats that the users need to keep in mind (see also Woods et al. [38]).

A benefit of using Markov models compared to traditional survival curve methods used to report clinical trial outcomes is that they provide supplementary information in addition to expected survival time. Under a Markov model the transition probabilities are provided measuring how likely patients will stay at the same status, get better or get worse after one cycle and utilities and/or costs for staying in one state for one cycle can be incorporated.

Our Markov model chronicles monthly transitions between cervical cancer health states, so the path a patient takes over the months can be represented, helping analysts and health care providers understand the path a patient might take period-by-period. The disadvantage is that it has stationary transition probabilities. While Markov models can be specified with non-stationary probabilities, that can be challenging [27]. However, if the problem does not have cyclical patterns and uncertainties over time, we should not use a Markov model.

The method in section 5 of probabilistically modeling the parameters of the Markov model allows for the creation of a visual display (e.g., Figure 2) of the possible incremental cost effectiveness ratio amounts that would result, imagining different samples of clinical trial patients were drawn, following the existing data. This method helps emphasize that model results depend on the sample, and could easily vary for a different sample drawn for the same population.

While using a Markov model, one problem is that the number of transitions increases quadratically with the number of states. It is hard to estimate transition probabilities without detailed individual level data. Further, the Markov modeling analysis conducted in this study required a conversion of available data points from every six months to every month, to approximately match the cycle of a Chemotherapy treatment. Another problem is that a Markov model has some restrictive assumptions, such as constant transition probabilities and the "lack of memory" property. A relaxation of the constant

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transition probability assumption to allow for non-stationary transition probability requires more accurate individual level data, which are often not available. In addition, for the medical problems where the transition probabilities depend on the health experiences, tunnel states could be used to fix the problem (for more information see, for example, Sonnenberg and Beck [12]).

The alternative non-Markov approach, by directly using the Kaplan-Meier curves to compute the number of patients in each state at each time period has the benefit that, like other traditional statistical methods, it is easy to use and to present to the audience and it allows a wider range of models with multiple parameter implementation. Also, we do not need individual level data to fit the curve. Thus, there is no need to model the probabilistic transitions period-by-period as well as it is unaffected by possibly unrealistic Markov modeling assumptions. Furthermore, it does allow the analyst to determine the number of people in each state in a period, so the aggregated cost can be calculated. However, there are some drawbacks. First, we do not model the underlying process when fitting the survival curve, thus no monthly transitions are modeled, and the patient's path period-by-period is lost. Consequently, total cost for a single person cannot be obtained as only the costs for the aggregated group are available. Also, the Kaplan-Meier curves are derived from censored data, fitting such a curve may result in inaccuracies especially for the case when we do not have the original patient treatment records.

When choosing a modeling approach to represent the natural process of a disease, the issue is not whether that evolution is stationary or non-stationary (because they are always non-stationary) but, rather, whether the non-stationarity is substantial enough to require a complex characterization of the process, or whether a comparatively simple stationary stochastic model can accurately represent the process.

Looking at the representation in Figure 4 of the raw survival percentages extracted from the Kaplan-Meier curve and their approximation using the stationary Markov transition probabilities versus the non stationary survival fitted percentages in each state in each time period, it seems that the Markov model somewhat underestimates those percentages in the cervical cancer case, while the survival fitted percentages mimic more accurately the actual patients' evolution. Also, the Mean squared error between the model and the clinical trial data is smaller in the case of the non-Markov survival fitted model (see table 5) for both arms of treatment (0.0005 non-Markov vs. 0.0053 Markov for Chemotherapy plus bevacizumab, 0.0013 non-Markov vs. 0.0864 Markov for Chemotherapy alone).

--- Insert Figure 4 around here ---

Researchers need to decide whether using the stationary transition Markov probability model with its appealing insights for clinicians about prognosis period-by-period will suffice or if the greater flexibility from directly fitting survival percentages at each time point in a non-Markov model or deriving non-stationary probabilities for Markov model is warranted. We also recommend any researcher to do a comparison of better fit to the actual data, like for example the one presented here in Figure 4 and a calculation of the Mean Squared Error.

--- Insert Table 5 around here ---

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For this case study, there is a sizable difference between the results obtained from the non-Markov direct calculation of percentages method (section 7) and the results obtained by calculating the expected outcome values in the Markov model (section 5) supposing the probabilities are stationary (see Table 5 for a comparison of both).

Mean life expectancy in the Markov model is about half as long as with the non-Markov model. With shorter lives, there are lower costs. It can be deduced from Figure 4 that the non-Markovian approach mimics more accurately the actual behavior of the sample. So, it seems that in the cervical cancer treatment case, the non-Markov modeling approach gives a more accurate result compared to the clinical trial data, but that is not always true, as sometimes the results with both methods will be very similar. For example, while the means differ from the two baseline modeling approaches, Figure 2 visibly depicts how a range of incremental cost effectiveness ratio values would result when modeled with the Markov approach if different clinical trial samples are simulated (see section 5 for this approach).

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Tables

Table 1. Chemotherapy plus bevacizumab treatment's one-month transition probabilities p_{ij} of going from the health state in row i to the one in column j in the following month

	R	LC	P	SC	D
R	0.8256	0.0231	0.1444	0.0069	0
LC	1	0	0	0	0
P	0	0	0.6404	0	0.3596
SC	0	0	0.9	0.1	0
D	0	0	0	0	1

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Table 2. Chemotherapy alone treatment's one-month transition probabilities p_{ij}

	R	LC	P	SC	D
R	0.8022	0.0017	0.1944	0.0017	0
LC	1	0	0	0	0
P	0	0	0.63	0	0.37
SC	0	0	0.9	0.1	0
D	0	0	0	0	1

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Table 3. Monthly costs depending on treatment and health state

State	Chemotherapy + bevacizumab	Chemotherapy alone
Respond	$7,540	$524
Limited Complications	$7,825	$80[illegible]
Progress	$262	$2[illegible]
Severe Complications	$4,240	$ [illegible]76

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Table 4. Estimated and real number of patients for chemo+beva treatment arm

	Time t (months)	0	6	12	18	24	30
Real data	**Survival**	227	184	121	69	20	10
	Respond(PFS)	227	132	70	22	6	3
Outcomes from Markov state modeling	**Survival**	227	133	51	19	7	2
	Respond(PFS)	227	82	30	11	4	1

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Table 5. Comparison of results

		Markov model	Non Markov model
Chemotherapy plus bevacizumab	Total expected cost	$44,444	$112,780
	Expected remaining duration of life	9.5965 months	19.7164 months
	Quality adjusted life months	7.1409 months	15.8914 months
	Mean squared error (MSE) compared with clinical trial data	0.0053	0.0005
Chemotherapy alone	Total expected cost	$2,903	$7,861
	Expected remaining duration of life	7.8193 months	17.6994 months
	Quality adjusted life months	5.4161 months	13.3137 months
	Mean squared error (MSE) compared with clinical trial data	0.0864	0.0013
Incremental cost-effectiveness ratio (ICER)	Cost per extra month of life with bevacizumab treatment	$23,375	$52,017

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Figure Legends

Figure 1. 1-month state transition diagram

Figure 2. Cost-Effectiveness plane for chemotherapy + bevacizumab replacing chemotherapy alone

Figure 3. Overall survival fit for chemotherapy alone

Figure 4. Probability of survival for both arms of treatment

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Appendix A. Calculation of 6-month transition probabilities matrix

Enough detail is provided in these appendices so both decision analyst and health economist newcomers could conduct a similar study using only the usually available information with no individual data available for each patient separately.

Consider the data about survival and progress-free survival (PFS) that appear in the Kaplan-Meier survivor curves in Figures 3A and 3B in [20] p. 740, as well as the number of patients at risk, every 6 months, for both chemotherapy-only treatment and chemotherapy plus bevacizumab entered below the x-axis in those figures. That data for bevacizumab with chemotherapy is listed below in Table A.1 in the boxes for survival and respond (which is the same thing as progression-free survival). For the time being, disregard the complications states. At time 0 of the clinical trial, all 227 patients who receive bevacizumab treatment are in the respond state, so they are all surviving at time 0 and responding to treatment (in progression-free survival) at that time.

Table A.1 shows the steps for deriving patient counts, disregarding complications states. Clinical data are in a bold font, while derived data are in a regular font.

First, we can fill into Table A.1 the known clinical data S(t) for counts of patients Surviving at each time period and R(t) for those Responding to treatment at time t. Assume that those Responding at time t came from the Respond state at time t-6 months, denoted "R(t-6)toR(t)".

Beginning at time t = 6 months, we can fill in Table A.1 step by step.

a. Determine those in Dead categories.

Step a.1. Derive D(t), the number Dead at time t = N total patients – Patients Surviving S(t) at time t: D(6) = 227 – 184 = 43 patients.

Step a.2. Look up D(t-6), those already dead before time t. Those already dead patients remained in the (absorbing) Dead state moving from time t-6 to time t, denoted "D(t-6)toD(t)": D(t-6)toD(t) = D(t-6), so D(0)toD(6) = D(0) = 0 patients.

Step a.3. Assume the newly dead (D(t)-D(t-6)) come from those in Progress in the prior period as much as feasible, since those patients are worse off than those in the Respond state. If the newly dead exceed those in Progress in the prior period, step a.4 will draw from those in Respond in the prior period. Derive those newly dead who moved from Progress at time t-6 to dead at time t, denoted "P(t-6)toD(t)":

Min (P(0), newly dead D(t)-D(t-6)) = min (0, 43-0) = 0 patients.

Step a.4. Find those moving from Respond to Dead, denoted "R(t-6)toD(t)":

R(0)toD(6) = a.1 answer – (a.2 answer+a.3 answer) = 43-(0+0) = 43 patients.

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Table A.1. Bevacizumab with chemotherapy patient counts in different health states derived iteratively, beginning at time 6 months. Clinical data are in bold font, derived data are in regular font. (N = 227 total patients)

<table>
<tr><th colspan="2">0 months</th><th colspan="3">6 months</th><th colspan="3">12 months</th></tr>
<tr><td rowspan="2">Survival
S(0)
227</td><td>Respond
R(0)
227</td><td rowspan="2">Survival
S(6)
184</td><td colspan="2">Respond R(6)
R(0)toR(6)
132</td><td rowspan="2">Survival
S(12)
121</td><td colspan="2">Respond R(12)
R(6)toR(12)
70</td></tr>
<tr><td>Progress
P(0)
0</td><td>Step b.1
Progress
P(6)
52</td><td>Step b.2
P(0)toP(6)
0
Step b.3
R(0)toP(6)
52</td><td>Step b.1
Progress
P(12)
51</td><td>Step b.2
P(6)toP(12)
0
Step b.3
R(6)toP(12)
51</td></tr>
<tr><td rowspan="3">Dead
D(0)
0</td><td rowspan="3"></td><td rowspan="3">Step a.1
Dead
D(6)
43</td><td colspan="2">Step a.2
Already dead
D(0)toD(6)
0</td><td rowspan="3">Step a.1
Dead
D(12)
106</td><td colspan="2">Step a.2
Already dead
D(6)toD(12)
43</td></tr>
<tr><td colspan="2">Step a.3
P(0)toD(6)
0</td><td colspan="2">Step a.3
P(6)toD(12)
52</td></tr>
<tr><td colspan="2">Step a.4
R(0)toD(6)
43</td><td colspan="2">Step a.4
R(6)toD(12)
11</td></tr>
</table>

b. Determine those in Progress categories.

Step b.1. Derive P(t), the total number in Progress at time t = S(t) - R(t); so P(6) = S(6) - R(6) = 184 - 132 = 52 patients.

Step b.2. Find those going from Progress at time t-6 to Progress at time t, denoted "P(t-6)toP(t)". In step a.3 we filled the newly dead from those in Progress in the prior period as much as feasible. Anyone left over in the Progress group after step a.3 shows up here:

P(0)toP(6) = max (0, P(t-6) - [newly dead D(t) - D(t-6)]) = (0, 0 - [43-0]) = 0 patients.

Step b.3. Find those moving from Respond in the prior period to Progress in the current period, denoted "R(t-6)toP(t)": R(0)toP(6) = b.1 answer - b.2 answer = 52 – 0 = 52 patients.

Move to the next time period 6 months later and repeat steps a and b. The answers for the 12 months time period are shown in Table A.1. The results for the entire study are in Table A.2

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Table A.2. Number of patients in each 6 month transition group for chemotherapy + bevacizumab

Time t (months)	0	6	12	18	24	30
Survival	**227**	**184**	**121**	**69**	**30**	**10**
Respond(PFS)	**227**	**132**	**70**	**22**	**6**	**3**
	R(t-6)toR(t)	132	70	22	6	3
	R(t-6)toP(t)	52	51	47	16	3
	R(t-6)toD(t)	43	11	1	0	0
	P(t-6)toP(t)	0	0	0	8	4
	P(t-6)toD(t)	0	52	51	30	20
	D(t-6)toD(t)	0	43	126	198	197

Now from the data in Table A.2, the transition frequencies n_{ij} can be calculated and entered in a two-way 3x3 table (Table A.3). For example, the Respond to Respond transition frequency is 233 in Table A.3. This means that over the course of the study, there were 233 times a patient went from Respond to Respond over a single 6 month time span. This is calculated by just adding up the Respond to Respond transition patients from 6 months onward in Table A.2 (132+70+22+6+3). For example, at 6 months there were 132 patients in Respond, so those 132 patients transitioned from R at the beginning of the study to stay in R at 6 months.

Table A.3. Transition frequencies n_{ij} for chemotherapy plus bevacizumab

	R	P	D
R	233	169	55
P	0	12	152
D	0	0	504

Table A.4. Six-month stationary probabilities q_{ij} for chemotherapy plus bevacizumab

	R	P	D
R	0.5098	0.3698	0.1204
P	0	0.0690	0.9310
D	0	0	1

The stationary estimates of six month stationary probabilities q_{ij} (values in Table A.4) are the respective i,j^{th} entry of the table of n_{ij}'s (Table A.3) divided by the sum of the corresponding entries in the i^{th} row.

The same process can be followed for the chemotherapy alone arm of treatment, obtaining the following matrices.

Table A.5. Transition frequencies n_{ij} for chemotherapy alone

	R	P	D
R	166	155	67
P	0	10	150
D	0	0	577

Table A.6. Six-month stationary probabilities q_{ij} for chemotherapy alone

	R	P	D
	0.4278	0.3995	0.1727
	0	0.0625	0.9375
	0	0	1

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Appendix B. Change cycle in a transition probability matrix from six months to one month

Transition probabilities are usually derived from an intervention cohort observed at specific follow-up times. But those follow-up intervals are oftentimes different from the model cycle length, so a conversion is required. Traditionally transition probabilities were converted to different cycle lengths using the relationship between probabilities and rates but, as Chhatwal et al. prove [29][30], this is not the correct way to compute the model transition probabilities.

In most cases the correct calculation of those transition probabilities for the desired cycle length is quite straightforward from the spectral decomposition of the estimated follow-up transition matrix (the decomposition into its eigenvalues and eigenvectors). For more details on the spectral decomposition of a matrix see, for example, Strang [31]. However, the problem becomes more cumbersome in the not unlikely case of some of those eigenvalues being negative. Since their appropriate (even) nth root would be complex it is necessary to use another method. As this is not our case, we will not discuss it further in this appendix, but we provide references in Appendix C.

For the cervical cancer case, the transition cycles have been established as monthly, so the obtained 6-month transition probabilities have to be transformed accordingly. Therefore, to calculate the sixth root of the previous matrix (TableA.4), its spectral decomposition was calculated obtaining the following eigenvalues: 1, 0.5968, and 0.0690. As all the eigenvalues are positive, the sixth root of the 6-month transition matrix (S) is calculated using the formula $S^{1/6} = V \cdot T^{1/6} \cdot V^{-1}$, where T is the diagonal matrix consisting of the eigenvalues of matrix S, and V is the associated square matrix whose ith column is the corresponding eigenvector and V-1 is its inverse. The sixth root of the diagonal matrix, T, is found by simply taking the sixth root of the diagonal entries, i.e., the sixth root of the eigenvalues which yields: 1, 0.8938, 0.6404.

$$S^{1/6}=V\cdot T^{1/6}\cdot V^{-1}=\begin{pmatrix}0.5774 & 0 & -0.6426\\ 0.5774 & 0 & 0.7662\\ 0.5774 & 0 & 0\end{pmatrix}\begin{pmatrix}1 & 0 & 0\\ 0 & 0.5968 & 0\\ 0 & 0 & 0.6404\end{pmatrix}\begin{pmatrix}0 & 0 & 1.7321\\ 1 & 0.8388 & -1.8388\\ 0 & 1.3052 & -1.3052\end{pmatrix}$$
$$=\begin{pmatrix}0.8938 & 0.2126 & -0.1064\\ 0 & 0.6404 & 0.3596\\ 0 & 0 & 1\end{pmatrix}$$

But, since row 1 has a negative number, this matrix is not stochastic (i.e. a valid transition probability matrix where all entries are non-negative and all rows sum to 1), so using the Kreinin and Sidelnikova algorithm [32], the obtained one month stochastic transition matrix is

$$\begin{pmatrix}0.8406 & 0.1594 & 0\\ 0 & 0.6404 & 0.3596\\ 0 & 0 & 1\end{pmatrix}$$

We have therefore the transitions between respond, progression and dead in a one month unit, and now we have to incorporate the complications, both limited and severe.

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The counts for the complications were obtained from [20] p. 742, taking into account that 54 hypertension cases were considered as limited complications, while 31 cases of severe complications included thromboembolisms and fistulas, generally lasting one cycle, but with a chance of remaining in the severe complication state. The only path into both limited and severe complications comes from Respond, so the entry in Table B.1 from R to LC is 54 divided by the total number of patients in respond through the study (obtained by summing over the expected number of patients in respond in each cycle, what yields 1,416). Similarly, the number from R to SC is 31, representing the first cycle when a severe complication occurs. So, in Table B.1, the entry from R to SC is 31 divided by 1,416.

We also know, from the doctors' experience [20], that a patient having limited complications will be treated within one month and return to the response state in the following month, so the probability 1 is entered from LC to R in Table B.1. However, the aforementioned doctors' experience also states that for severe complications the patient remains in severe complications with a 0.1 probability or transitions to progression with a 0.9 probability.

Table B.1. Intermediate step in constructing one-month transition matrix for chemotherapy + bevacizumab

	R	LC	P	SC	D
R	0.8406	0.0381	0.1524	0.0219	0
LC	1	0	0	0	0
P	0	0	0.6404	0	0.3596
SC	0	0	0.9	0.1	0
D	0	0	0	0	1

But this Table B.1 matrix is not stochastic (since adding the complications pushes the sum of the entries in first row above 1.0), so using again the Kreinin and Sidelnikova algorithm [32], the obtained stochastic matrix is in Table B.2. (This is Table 1 in the main part of the paper.)

Table B.2. Final one-month chemotherapy + bevacizumab transition probabilities p_{ij}

	R	LC	P	SC	D
R	0.8256	0.0231	0.1444	0.0069	0
LC	1	0	0	0	0
P	0	0	0.6404	0	0.3596
SC	0	0	0.9	0.1	0
D	0	0	0	0	1

A similar process is followed to determine Table 2 in the main of the paper with one-month chemotherapy alone transition probabilities.

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Appendix C. Dealing with Negative Eigenvalues

There have been some recent papers which look at changing the cycle length when the spectral decomposition method fails, and although that is not our case we include a short review for those who have to deal with at least one negative eigenvalue in calculating an even nth root.

First, Kreinin and Sidelnikova [32] find the nearest stochastic matrix to the actual appropriate nth root complex matrix using regularization techniques. The method operates separately on each row of the invalid short-interval transition matrix such that the norm of the difference between its power and the original transition probability matrix is at a minimum.

Second, Charitos, de Waal and van der Gaag [33] also present a method based on regularization techniques and their algorithm's optimal solution satisfies the Kuhn–Tucker conditions for each row.

Third, Craig and Sendi [34] use the expectation–maximization EM algorithm (Dempster et al. [35]) to estimate the actual transition matrix. The drawback of this method is that convergence to the maximum likelihood estimator is not guaranteed so the method has to be repeated with several initial transition matrices.

Fourth, Higham and Lin [36] and Lin [37] propose several algorithms based on Gaussian elimination with partial pivoting and compare their performance.

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Appendix D.

In computing the area under the curve (roughly a triangular shape for the living patients), one can think of it as adding up the height of thin vertical slices corresponding to living patients (each monthly cycle's fraction of patients who are alive = the probability a patient is alive), see Figure D.1.

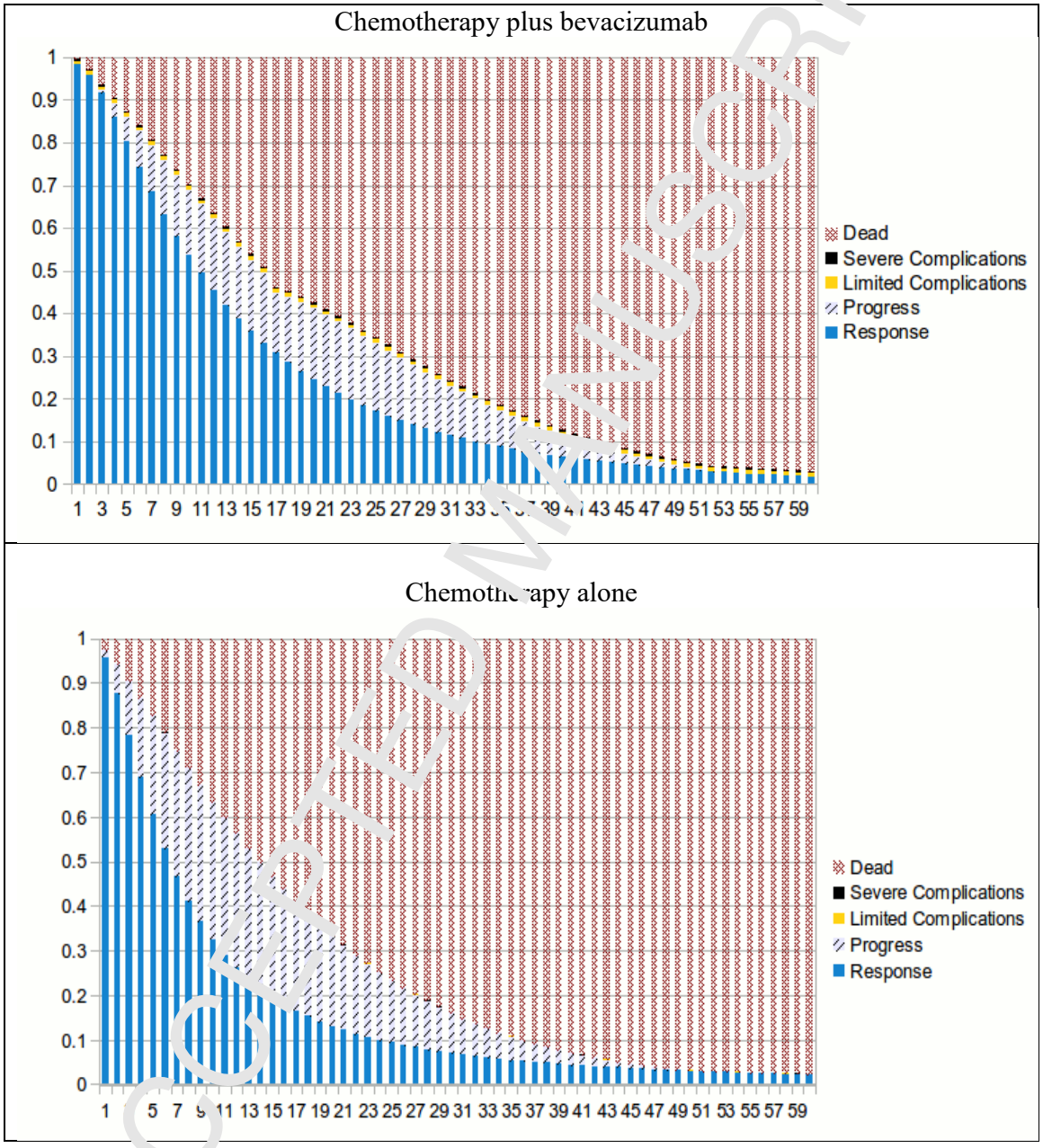

Figure D.1. Predicted probabilities stacked bar for each state at each time period

Another way to think of it is adding up thin horizontal slices, with some patients living a short time at the top of the triangle, and some living a long time at the bottom of the

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triangle (Figure D.2). To find the average length of time of survival, geometrically imagine taking the small light colored (yellow) triangle in the right tail of the longest living patients, and flip it over to fill in a rectangle above the blue quadrilateral polygon. The width of the resulting yellow blue rectangle is the average length of time a patient survives.

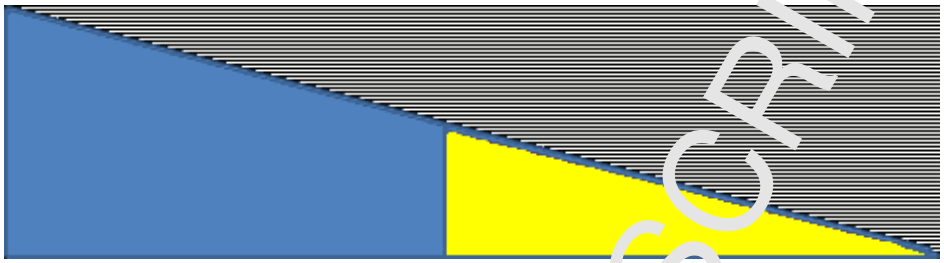

Figure D.2. Stylized graph of the fraction surviving at each time period (lower triangle, colored by blue on the left and yellow on the right), and the fraction who are dead (in black striped triangle)

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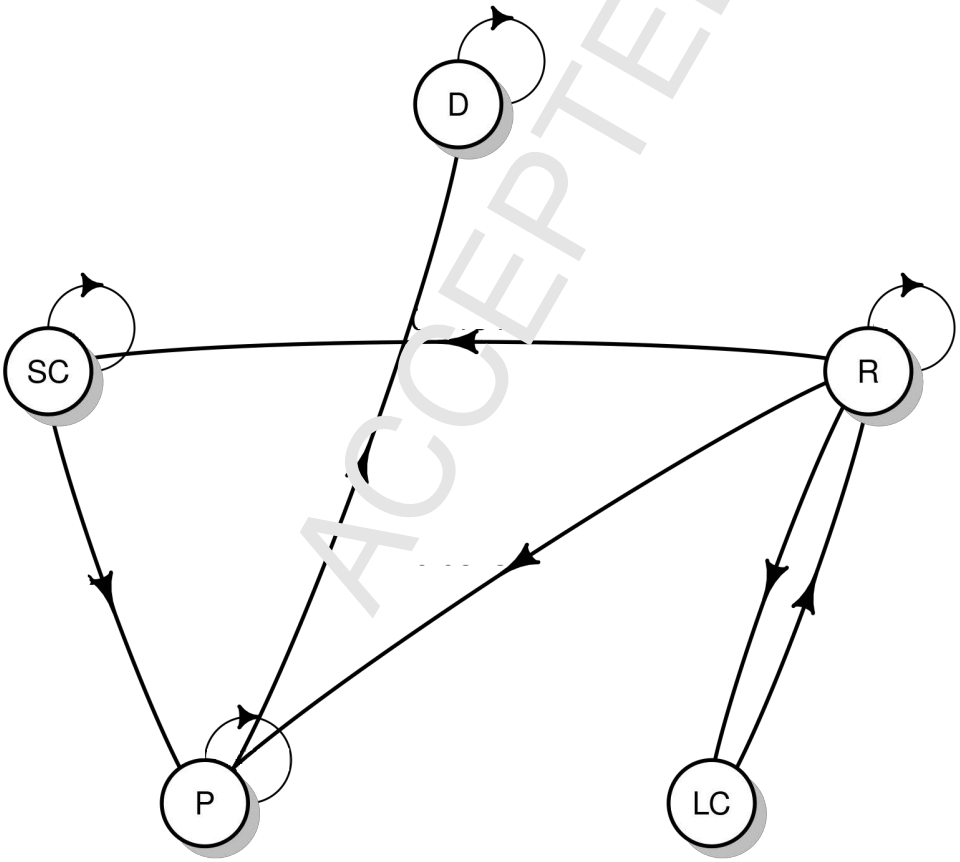

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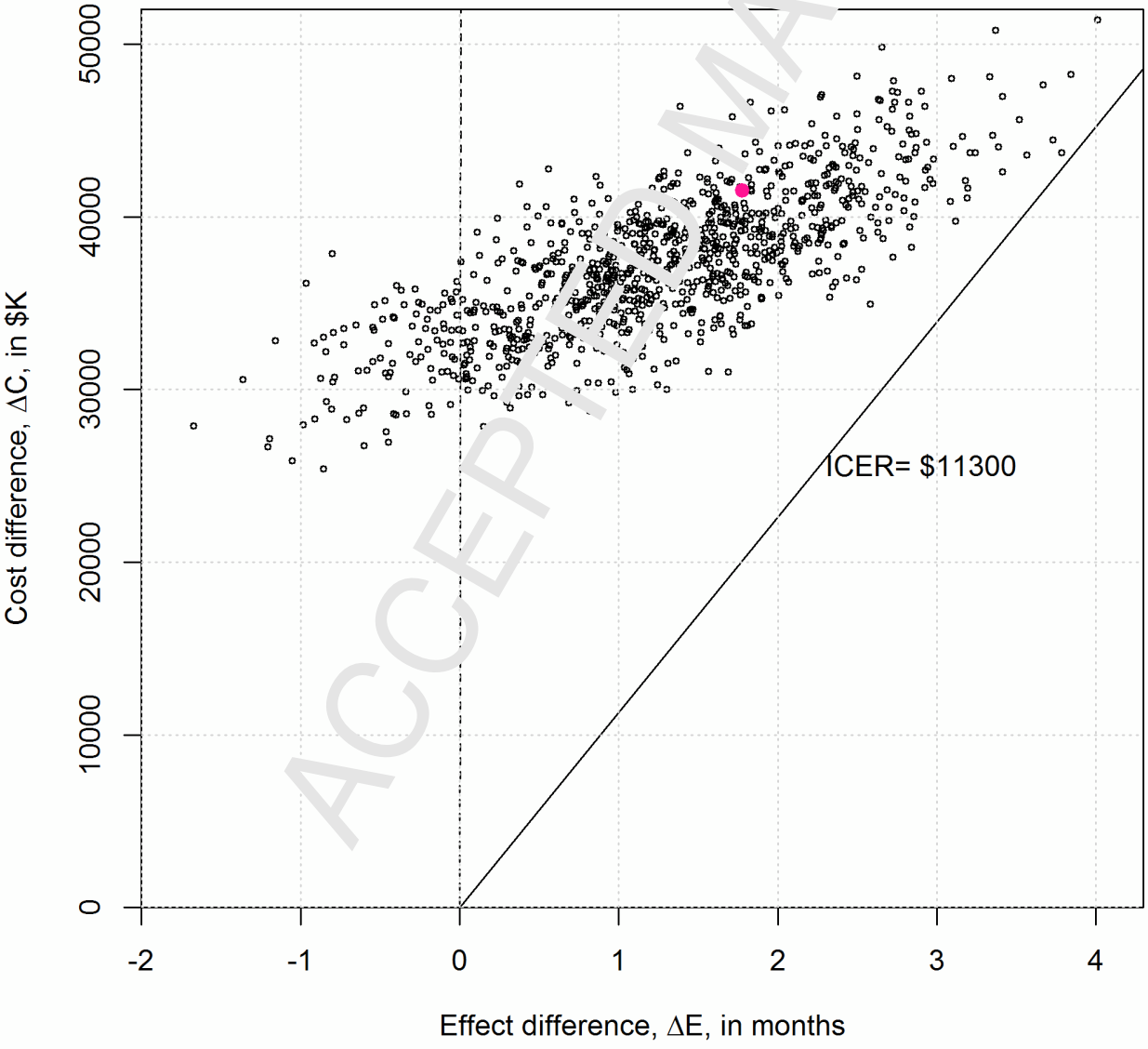

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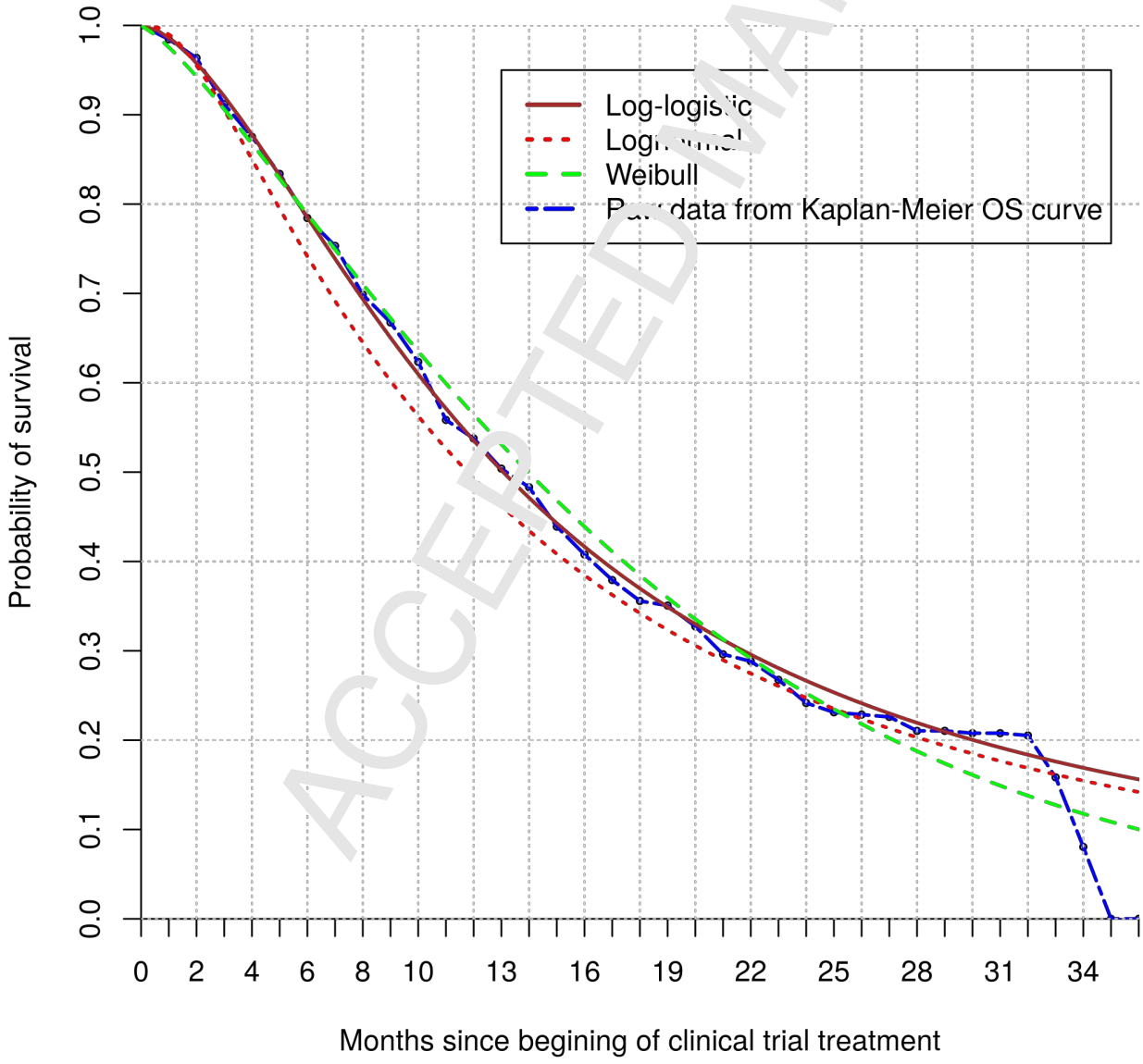

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