Assessing best cost-effectiveness policy for urologic treatments by using Markov decision models

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Abstract.
Introduction and objectives: New medical treatments implementation can be associated with improving outcomes but at a cost. With the rising prices of healthcare, implementation of a fixed budget for different specific diseases would place pressure on doctors to choose the treatment option which is most cost effective for an individual patient. This study aims to provide a user-friendly tool to identify the most cost-effective treatment option for different severities of benign prostatic hyperplasia (BPH).
Methods: A set of health states were identified for BPH and utilities of each state were obtained from the published literature. These states were used to build a Markov chain with random transitions between states. The transition probabilities between states for a given intervention (surgery, pharmacotherapy or no intervention) were determined using mean changes in IPSS scores from the available literature as well as expert opinion. For each state, a utility value was associated and from these, disutility values were calculated (disutility = 1 - utility). A cost was associated to each intervention in a particular state. Linear programming was used to compute the average cost at a given disutility threshold in the Markov decision model. Base-case analyses and simulation testing were performed. Cost analysis was performed using outcomes and adverse event data from the literature for each of the interventions and hospital costs from hospital administration.
Results: A cost-effectiveness curve was created by varying the maximum allowed disutility values and determining the average cost (Fig. 2). In this way, a decision for each health state at a fixed disutility can be determined (see Table 4 for one particular disutility value).
Conclusions: Our model provides a useful tool for doctors to determine the most cost-effective treatment option for patients with different severities of BPH. This model can be applied to other disease states within medicine. Further studies are needed to validate the model for real-life application.

A. Introduction

A cost-effectiveness analysis (CEA) helps identify neglected management strategies by highlighting interventions that are relatively inexpensive, yet have the potential to reduce the disease burden substantially compared with the standard of care (1). According with the 2016 guidelines for cost effectiveness analyses (2), a CEA is an analytic tool in which the costs and outcomes of a program/intervention and at least one alternative is calculated and presented in a ratio of incremental cost to incremental effect. This definition implies the use of statistical and mathematical methods to compare multiple treatments in order to give meaningful recommendations to healthcare stakeholders. Currently, there are no models for clinicians to use

to differentiate the best cost-effective treatments by different initial patient health states. Most of the CEAs available in the literature compare only two treatments and do not allow the physician to tailor the treatment plan based on the severity of the patient's disease state. Additionally, there is a shift towards value based payment plans, with quality and the trade-off with cost becoming major factors in payment plans (3). This study proposes a Markov model to determine the most cost-effective algorithms for treating urologic conditions using benign prostatic hyperplasia (BPH) as an example, by comparing multiple treatment options and differentiating between different patient health states.

B. Material and Methods

1 Markov model for urologic treatments

The natural history of benign prostatic hyperplasia (BPH) of a generic patient was reproduced via a Markov chain model. The patient travels in the model, switching state every three months, until he ends up in an "absorbing" state and exits the model. As in Markov models, each state is memoryless: the condition of the patient depends only on the state, irrespective of the previous medical history. At the end of each three-month interval, the patient can transition either to the same state or to other states for the next three months, and so on. Each transition is a random event decided according with a pre-assessed "transition" probability. The transition probabilities are based on the outcomes of the chosen medical intervention. Eventually the patient leaves the system through one of the absorbing states. To simplify and show the potential of this model we picked Benign Prostatic Hypertrophy (BPH) as an example, being characterized by multiple possible treatments ranging from observation to medical therapy to surgery, with variable outcomes and costs.

2 States for Benign Prostatic Hyperplasia

Listed below are health states used in the model to trace the medical history of a patient with BPH.

– initial state H (for 'health'). Each patient starts from this healthy state and transitions to one of the other illness states. These transitions correspond to the first time a patient enters the medical system for intended treatment and therefore originate outside of the model. Therefore, there is no specific interval of time associated with these transitions;

– states L_{01}, L_{02} , L_{03}: refer to a patient who presents with Lower Urinary Tract Symptoms (LUTS) due to BPH classified as mild, moderate and severe based on the International Prostate Symptoms Score (IPSS) classification. The patient in this state either just entered the model and didn't receive any treatment or he already has received observation as a treatment;

– state A_0: corresponds to Acute Urinary Retention without prior medical intervention. Similar to states L_{01}, L_{02} , L_{03}, the patient in this state just entered the system with no prior medical treatment.

– states L_{11}, L_{12} , L_{13}: these refer to a patient that already received a treatment, either surgical or pharmacological, with possible outcomes of this treatment being mild, moderate or severe LUTS. The patient

can visit any one of these states multiple times, indicating that observation or medical treatments have to be repeated;

– state A_1: corresponds to Acute Urinary Retention after a medical intervention, with possible repeated visits.

Absorbing States: states in which no further medical therapy is needed or a different kind of therapy is needed, thus the patient is discharged and exits the system.

– state C (for 'cancer') corresponds to the diagnosis of prostate cancer after a surgical treatment for BPH.

– state B (for 'bad') corresponds to a patient discharged with severe LUTS according with the IPSS score after a treatment, for whom no medical treatment is considered to be effective.

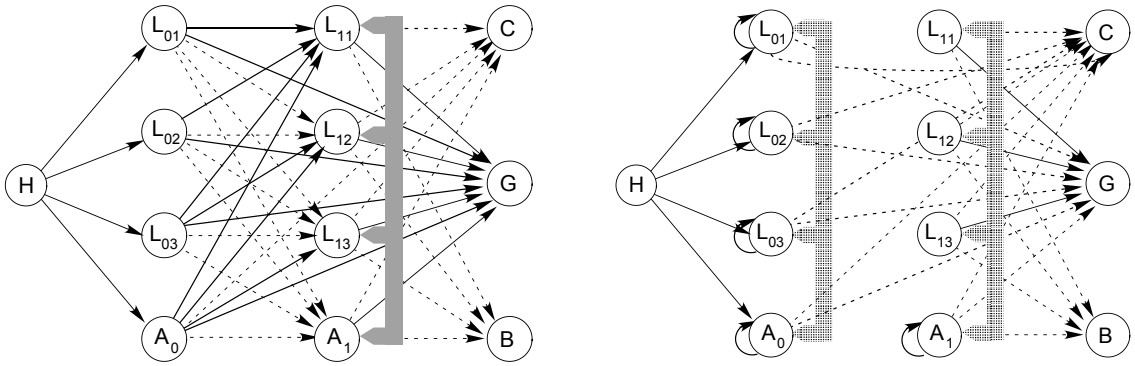
– state G (for 'good') corresponds to a state where the patient is asymptomatic according with their IPSS score.

3 Actions and Transitions

As previously mentioned, the transitions between states depend on the intervention selected. More specifically, for a patient in a given state, a set of possible actions is defined (including observation labeled as O) and the transition probability within the three month time interval into another state depends on the selected intervention. The possible interventions include four types of different laser surgeries for BPH treatment, including potassium-titanyl-phosphate-(GL) laser photovaporization, Bipolar Trans Urethral Resection of Prostate (TURP), Holmium laser enucleation (HL), and Thullium laser enucleation (TL), labeled as S_1, S_2, S_3 and S_4 , and pharmacologic treatment (dual treatment with alpha blocker and inhibitor of Type II 5α-reductase), labeled as P. The Markov chain is shown in graphical form in Fig. 1 . Transition probability values are detailed in Table 6. For this specific model, transition probabilities have been inferred by a combination of expert opinion and the available literature (see appendix 11,12 and 13 for full details). Literature selection was based on the systematic review PRISMA criteria (4-23). The solid lines represent the transitions with a 'high' (more than 20%) probability and the dotted lines with low or negligible values. The large grey bar indicates the set of all possible transitions between the indicated states (including returning to the same state). In Fig. 1(b) we show the transitions for observation as the intervention. Each chosen action has an associated cost, which will be described further in our cost analysis.

The goal of our model is to define for each state which action must be chosen such that the average global cost is minimized and stay within a specified average life quality parameter threshold.

We consider the following actions and transitions: State H is out of control of the medical system and therefore only one action can be envisioned for this state, that we may denote as observation. From H there is a transition to each of the states L_{01}, L_{02}, L_{03}, A_0. These transitions correspond to the first appearance of a patient seeking medical care. As such they do not involve costs. The transition probabilities are proportional to the number of patients that arrive with the corresponding illness degree. In the states L_{01}, L_{02}, L_{03}, and A_0 the actions S_1, S_2, S_3, S_4 and P induce transitions to each of the states L_{11}, L_{12}, L_{13}, A_1, C, B and G. The remaining action O induces transitions to each of the states L_{01}, L_{02}, L_{03}, A_0, C, and G. Indeed,



(a) with medical actions b) without medical actions

Fig. 1.

even if there is no medical intervention there may be a transition to a state with no symptoms, i.e., state G. The transition probabilities and the costs of all these transitions depend on the type of action. In the states L_{11}, L_{12}, L_{13}, and A_1 the same actions of the corresponding states L_{01}, L_{02}, L_{03}, A_0 and C are possible. However, these actions induce transitions back to the same states or to the states C, B or G. The states C, B and G are absorbing. The patient goes out of the system and therefore only self- transitions are possible for these two states. The presence of absorbing states makes all other states transient and therefore the average number of visits to the other states is finite. Since the costs depend on the transition undergone by each patient from the transient states we have to be able to count the number of transitions in order to assess the average cost for each patient. Hence we have to convert the machinery of Markov decision processes, that is usually tailored to irreducible chains and takes into account the stationary probability, to the presence of absorbing states. This is detailed in Section 9. We just recall that if there are absorbing states the stationary probability is null on the transient states, or, equivalently, is positive only on the absorbing states, and this would prevent assessing the cost by using the stationary probability.

4 Cost Analysis

An itemized list of average variable costs for BPH treatment options was created, including KTP laser photovaporization (GL), Transurethral resection of the prostate (TURP), Holmium laser enucleation (HL), Thulium laser enucleation (TL) and Pharmacologic treatment (PH). Outcomes and adverse event rates, including transfusion rates, average inpatient hospital stay, continuous bladder irrigation necessity, outpatient follow-up, average operative times, laser times, etc., were extracted from meta-analyses, randomized clinical trials and large retrospective studies (4-23), and were used to determine the variable costs. Costs were determined from healthcare administration software and the literature (24-29), considering a 3-month time span and the actual procedure/medication cost. The only included fixed cost for surgical procedures was

Treatment	Cost (US$)	average post IPSS
Greenlight PVP	8,312	3.5
TURP	8,698	3.6
Holmium laser enucleation	10,298	2.6
Thulium laser enucleation	8,755	3.8
Pharmacological treatment	980	6.3
Observation	0	0

Table 1. Costs and average post IPSS for the considered medical actions

	GL	TURP	HL	TH
OR disposable material	202,45	202,45	202,45	202,45
FIBER/LOOP (and morc blade)	1,000.00	586.00	1,000.00	785.00
TRANSFUSION	2.52	18.48	5.04	7.14
POST OP CBI	0.23	38.94	38.94	38.94
INSTAYS	2,400.00	3,400.00	3,400.00	3,400.00
OR TIME	3,988.00	3,988.00	5,245.00	3,763.00
FOLLOW UP CLINIC VISIT	260.00	260.00	260.00	260.00
READMISSION AD	59.00	85.00	92.00	111.00
READMISSION INSTAYS	400.00	120.00	54.00	188.00
TOTAL	8,312.20	8,698.87	10,298.03	8,755.90

Table 2. Breakdown of costs (US$)

laser rental. Medication cost (Tamsulosin + Finasteride) was based on the average out of pocket price for 90 days (3 months). Table 1 shows the calculated average costs for each treatment and also the average post treatment IPSS according with the literature (Section 11 for further details). The costs reported on Table 1 are listed as itemized costs in Table 2.

5 Quality of Life Assessment

Each state is assigned a specific utility value between 0 and 1, with 1 being the optimal quality of life for a specific disease. In this case, the utility values for BPH states have been extracted from the available literature (30-31) (Table 3). Disutilities, defined as the complement to one of the utility (1-utility), were used in the model rather than utilities. We measured the quality of life of the patient by summing the disutilities incurred by the patient during the three months periods that the patient spent in the system, setting a maximum total disutility as a constraint for the model, so that patients go through the model for reasonable periods of time.

We opted to use disutility values instead of utility values as the quality of life measure, because of the following problem associated with utilities: since the wellness measured refers to each three months period,

	Pre-treatment	Post-treatment
Mild LUTS	0.993	0.99
Moderate LUTS	0.903	0.89
Severe LUTS	0.79	0.70
AUR	0.25	0.25
Prostate cancer	N/A	0.8

Table 3. Utility estimates used in the model

when all periods a patient is within the system are summed together, a paradoxical outcome results in that that the longer a patient is within the system, the higher the utility, and hence the better is his quality of life. Clearly, having a certain utility for one period is better than having it for a longer time period, especially if the utility value is less than 1. As shown in Section 10 (refer in particular to equation (6)) the total disutility is determined by the time in the system minus the total utility. Therefore, minimizing the total disutility we actually minimize a composite function that balances the time in the system versus the total utility. In particular, each additional time unit in the system (i.e., three months) has the same weight as a total loss of one utility. Section 7 discusses considerations about the choice of a total disutility versus an average disutility as a measure of the quality of life.

Considering an average value (either utility or disutility), we divide the total value by the time in system. Therefore, by the previous observation, the average utility and the average disutility complement to one, not surprisingly. By this observation minimizing the average disutility and maximizing the average utility are equivalent. Finally, the first time a patient enters the system because of mild, moderate or severe LUTS (or AUR) his disutility does not depend on his treatment in the past and, being out of the control of the provider, should not be taken into consideration into the model. However, this initial disutility is the same for each possible action the doctors can decide and therefore does not change the outcome of the model. It is just a bias that does not affect the best decision.

6 Objectives

A generic patient, from the time he enters the system (from state H) up to the time he exits the system (into one of the absorbing states), incurs a total cost, that is determined by the sum of the costs of each state visit determined by the treatment brought him to that specific state. A *policy* is defined as the specific medical treatment required in each state. Different policies have different costs. Moreover, different policies also involve different disutilities. Our aim in this model is to find an optimal policy, i.e., a policy that minimizes the total cost of a generic patient whilst keeping the total disutility below a certain threshold. In order to assess the trade-off between costs and quality of life, in this study we used the model to identify the policy which minimizes the total cost for varying values of disutility. This provides a Pareto frontier of efficient policies and will give the provider, the payer and/or the patient a meaningful tool to choose a particular policy among the efficient ones. In our model, it is also possible to fix a threshold on the percentage of

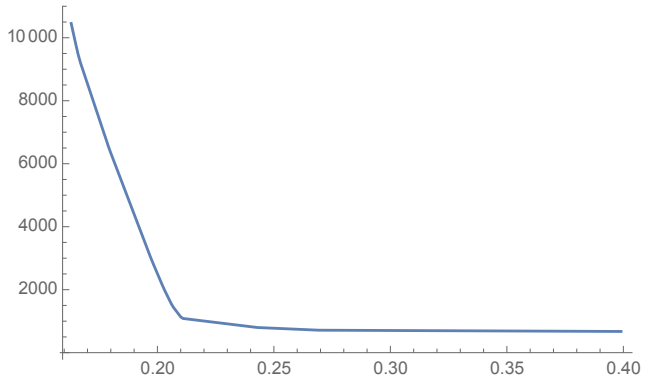


Fig. 2. Trade-off curve cost vs disutility (disutility range 0.1626–0.4)

patients exiting the system in the state G (cured). Increasing the percentage of cured patients is correlated with decreasing the disutility, and may be used as another tool within our model in future investigations. An optimal policy is determined by a standard Linear Programming Markov Decision Model, explained in detail in Sections 10 and 9. Assessment of the transition probabilities for the model is described in detail in Sections 11 and 12.

C. Results

7 The trade-off curve

We have run the Linear Programming model (8) described in Section 10 for various values of the disutility threshold K_t. We have totally relaxed the constraint on the fraction of patients ending in state G. To this purpose, referring to model (8), it is enough to fix $K_G = 0$. It turns out that with the data of Table 6 the minimum possible value of disutility is 0.18548 (=0.186 rounded to three decimal places). Hence we have solved (8) for all values K_t from 0.186 to 0.4 with a step of 0.001 (so we have solved 214 problems). The minimum cost in (8) as a function of K_t is shown in Fig. 2.

This trade-off curve exhibits a sharp bend around the disutility value 0.21 and a cost of 1,460 $. A further cost reduction can be done only at the expense of a large disutility increase, or worsening quality of life. Since the cost reduction is quite small, it is futile to base the policy decision above a disutility value of 0.21. Conversely, reducing the disutility from the 0.21 value leads to a sharp rise in cost. The critical decision-making range therefore in the disutility range 0.186-0.21. Fig. 3 shows the same trade-off curve in the restricted range 0.186-0.21, and indicates the intervals in which the curve has a constant slope. Although it is not clearly visible from the picture, the trade-off curve is a piecewise linear function. The figure explicitly shows the intervals where the function is linear. The disutility values where the slope has an abrupt change

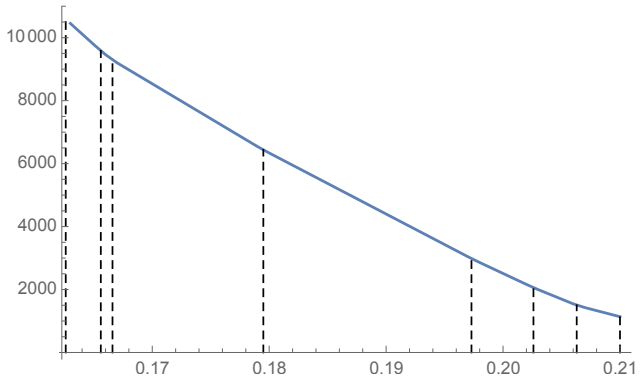


Fig. 3. Trade-off curve cost vs disutility (disutility range 0.1626–0.21)

are called *breakpoints*, indicated by the dotted lines in Fig. 3. Table 4 reports the optimal medical treatments at the breakpoints, together with the corresponding disutility values and the costs (Rows 1,2 and 10-17). Rows 3-6 show the total utility, the average utility and the time in the system, measured both as number of visits and number of actual months. We have already observed that the average disutility is just the complement to one of the average utility and therefore it has not been displayed. This table demonstrates the anomalous behavior of the total utility which increases/improves with diminishing costs. This supports our discussion on the choice of disutility versus utility. Rows 7 through 9 show the percentage of patients ending up in state G, B and C, respectively, for each optimal policy. Finally, rows 10 through 17 show the recommended action for the optimal solution to the model.

The optimal medical treatment in a particular state for a disutility value between two adjacent breakpoints is the same as the one in the two breakpoints, if the same treatment is indicated in the two breakpoints. However, if the two treatments are different, the resulting optimal treatment is a combination of the two treatments. More specifically, it turns out that the optimal treatment is a random choice between the two treatments. The probability value for the random choice is given by linear interpolation.

For example, suppose that we choose a disutility value at 0.17. The two adjacent breakpoints are 0.1666 and 0.1794. The only treatment change concerns state L_{01} for which there is a change from Holmium Laser surgery to Pharmacological therapy. Hence, when the patient is in state L_{01} we will choose Pharmacological therapy with probability $(0.17 - 0.1666)/(0.1794 - 0.1666) = 0.266$.

It is unusual to have a policy which makes a random choice between two alternatives. In order to illustrate the reasoning behind this, we show in Fig. 4 the same trade-off curve of Fig. 3 with superimposed all points which can be obtained by the so called 'pure' policies, i.e., policies where exactly one alternative is chosen in each state. Actually, we show in the figure only the non-dominated points. Clearly, some pure strategies lie on the trade-off curve, corresponding to the breakpoints. All other pure strategies lie "above" the trade-off curve. In order to reach a value on the trade-off curve there is no option other than to combine together two different pure policies, as random events. Clinically, the model does not obligate adhering to a random choice. If the recommended combination is 30% of one policy and 70% of another, the clinician may decide which

tot disutility	0.1626	0.1656	0.1666	0.1794	0.1973	0.2026	0.2063	0.2100
cost US$	10,587	9,582	9,290	6,455	2,984	2,059	1,499	1,136
tot utility	1.493	1.523	1.529	1.579	1.645	1.651	1.649	2.642
av utility	0.902	0.902	0.902	0.898	0.893	0.891	0.889	0.926
time (# of visits)	1.655	1.689	1.695	1.759	1.842	1.854	1.855	2.852
time (months)	4.965	5.067	5.085	5.277	5.526	5.562	5.565	8.556
% G	92.1	91.8	91.7	91.0	90.0	89.9	90.1	90.8
% B	6.6	6.9	6.9	7.6	8.4	8.5	8.6	6.8
% C	1.3	1.3	1.4	1.4	1.6	1.6	1.3	2.4
L_{01}	HL	HL	HL	Ph	Ph	Ph	Ph	Obs
L_{02}	HL	GL	GL	GL	Ph	Ph	Ph	Ph
L_{03}	HL	HL	GL	GL	GL	Ph	Ph	Ph
A_0	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph
L_{11}	Obs	Obs	Obs	Obs	Obs	Obs	Obs	Obs
L_{12}	Obs	Obs	Obs	Obs	Obs	Obs	Obs	Obs
L_{13}	GL	GL	GL	GL	GL	GL	Obs	Obs
A_1	GL	GL	GL	GL	GL	GL	GL	GL

Table 4. Optimal medical treatments in the interesting disutility range

patients will be treated by a particular policy. This decision may be determined by physician preference, medical history, side effects, and other criteria not embedded in the model.

The cost of combining two pure policies is a linear interpolation of the individual costs of the pure strategies. Referring to the previous example, fixing a disutility value 0.17 corresponds to combining the strategies at breakpoints 0.1666 and 0.1794. Since these have costs $ 9,290 and $ 6,455 (Table 4), the cost for disutility 0.17 is $0.266 \cdot 6,455 + (1 - 0.266) \cdot 9,290 = 8,537$. The picture that results from 3 and Table 4 can be better understood if we compute the optimal cost for various disutility values by allowing only one surgery at a time to be selected by the model. Repeating this computation four times, four superimposed trade-off curves are created, graphically represented in Fig. 5. The lowest curve (blue line) is obtained by using only KTP surgery. It surpasses all the curves above the disutility value of 0.170. However, according with the data, KTP alone cannot decrease the disutility value below 0.170. In order to achieve a lower disutility, Holmium Laser is required, and is the only surgery to achieve the absolute minimum disutility at 0.16286.

Furthermore, Table 4 shows that to achieve the best disutility value, Holmium Laser enucleation is recommended for new patients, i.e., for patients that have not undergone any surgery yet. However, it turns out that for patients who have already undergone surgery, the same disutility can be reached by using KTP, a less expensive procedure. As we increase the disutility threshold, KTP continuously replaces Holmium Laser up to the breakpoint value 0.1794. From that value and onwards Holmium Laser guarantees the same quality of life as KTP, but at a larger expense, and therefore is not recommended.

One surprising result of the model is the non-monotonic behavior of the percentage of patients ending in state G. We expect that, as we relax the constraint on the disutility value, less effective therapies will

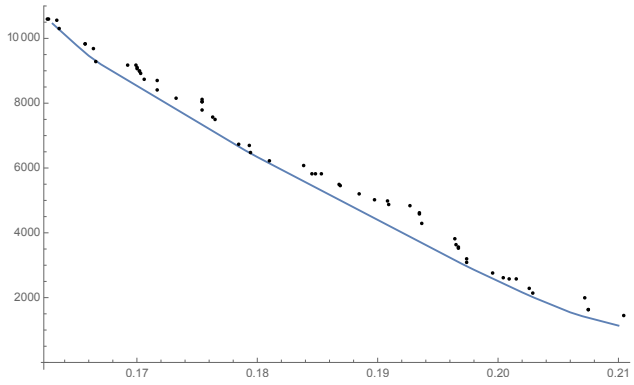


Fig. 4. Pure strategies vs Random strategies

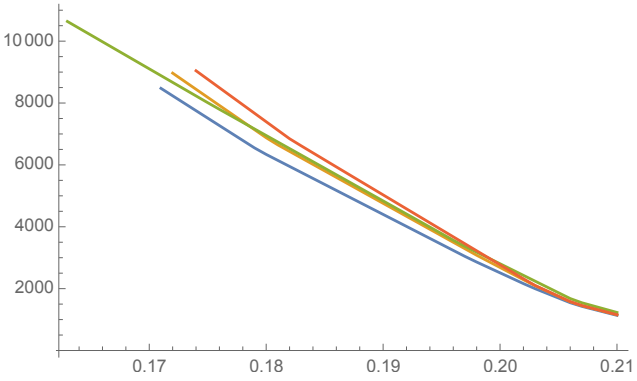
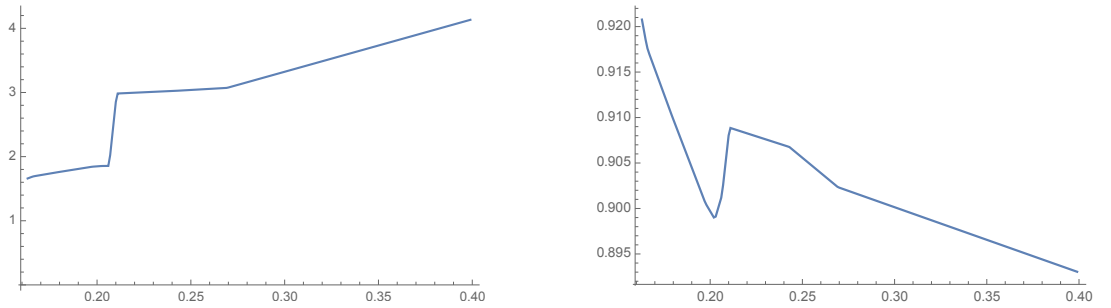


Fig. 5. Optimal trade-off curves for one surgery at a time:

become options in the model, and consequently, fewer patients will exit the system healthy. Fig. 6(b) plots the fraction of patients ending up in state G as a function of the disutility threshold. The sharp bend at the value 0.21 in Fig. 2 corresponds to the slope change of the graph in Fig. 6(b). The decreasing monotonic behavior is steadily resumed after value 0.23. The total disutility incurred by a patient also depends on the time in system. The longer the time in the system, the larger the disutility, and therefore the worse the quality of life of the patient. The relationship of the disutilities in single states and the time in system is complex. Fig. 6(a) plots the time in system as a function of the disutility. After value 0.21 there is a sharp increase of the time in system as observation of a patient becomes an option.

The cost computed by the model is based on the average cost incurred by the hospital during the three months period. Initially it seems, since this represents the cost of a patient during his time in the system, the cost should be divided by the time in the system in order to get the cost within the period. This would be correct if there were only one patient in the system. However, this is not the case. Hence the following needs to be considered: at each three month period a certain number of patients enters the system. Each



(a) time in system vs disutility

(b) percentage of patients in G state vs disutility

Fig. 6.

one of them incurs a cost (the same for all since we consider average costs) and this cost is divided over the time in the system of this patient. But in each three-month period, the system sees the patients that just arrived, plus the patients that entered in the previous period and that are still in the system plus patients of prior periods. Adding these costs, we get exactly the cost of one patient during his time in the system. So, for instance, choosing an average disutility of 0.17, which corresponds to a cost of $ 8,537, and 100 patients on average enter the system in each three-month period, this means that the total cost for each three-month period is $\$\ 8,537 \cdot 100 = \$\ 853,700$.

This model can also be utilized to determine the costs by state (see formula (1) in Section 9). Table 5 displays how the total cost of $8,537, as in our example, can be traced back either to the three absorbing states of the patients or, alternatively, to the single medical treatments performed in the entire system. For instance, almost 10% ($ 140 in C + $ 632 in B = $ 772) of the costs are in some sense "wasted" because they do not lead to health improvement. On the other hand, KTP laser absorbs almost all costs in the model. A possible repetition of KTP PVP (in states L_{13} and A_1, refer to Table 4) has a small incidence on the total cost ($ 163 + $ 446 = $ 509 out of $ 8,537).

8 Model reliability

It is important to recognize that all reported values in the various tables are averages. This means that in an actual realization of the Markov chain, the data may differ from the ones in the tables. Testing the limitations of the model is essential to determine the allowed range in differences of the data and how reliable the model is in the real world.

If there were just one patient we can compute the probability of each possible history in the system of the patient. For instance, taking again the disutility value 0.17, we may compute that the sequence of transitions $H \to L_{02} \to L_{11} \to G$ occurs with probability 0.238, the sequence $H \to L_{02} \to G$ with probability 0.173, the sequence $H \to L_{01} \to G$ with probability 0.133, the sequence $H \to L_{01} \to L_{11} \to G$ with probability 0.123, the sequence $H \to L_{03} \to L_{12} \to G$ with probability 0.056, and so on with diminishing probability values.

states	C	B	G	totals
L_{01}	34	155	2,306	2,495
L_{02}	55	295	3,889	4,239
L_{03}	15	106	1,043	1,164
A_0	1	3	26	30
L_{11}	0	0	0	0
L_{12}	0	0	0	0
L_{13}	9	18	136	163
A_1	26	55	365	446
Totals	140	632	7,765	8,537

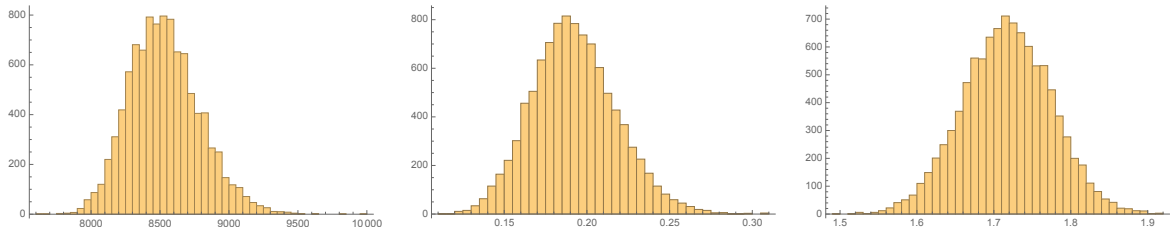
Table 5. Breakdown of costs

The first and second sequences share the same cost because in state L_{11} only observation is recommended which we assume has no costs. Since in state L_{02} KTP PVP is recommended for this disutility value, $ 8,312 is spent each time L_{02} occurs in a sequence of transitions. Hence the probability of passing through the state L_{02} is the sum of all sequence probabilities which include state L_{02}, resulting in a probability value of 0.5099. Multiplying this by $ 8,312 accounts for the value $ 4,239 that appears in Table 5 for state L_{02}.

In general, all these sequences may have quite different costs if they involve different treatments and the outcome of an actual realization can yield largely different results. However, by the law of large numbers if there are enough patients their different outcomes balance each other and decrease the dispersion around the mean. With a large number of patients, the actual global cost approximates a Gaussian distribution. This was determined by simulating a cohort of 100 patients, 10,000 times, at many values of the trade-off curve. Displayed in Figure 7 are the results for the disutility value of 0.17. The cost histogram of the 10,000 runs is shown in 7(a), whereas in Fig. 7(b) and (c) we see the histograms for the disutility and the time in system respectively. The standard deviations are $ 352.058 for cost, 0.0255458 for the disutility and 0.0569729 for the time in system and the correlation matrix for the three random variables cost, disutility and time is:

$$\begin{pmatrix} 1. & 0.533 & 0.250 \\ 0.533 & 1. & 0.359 \\ 0.250 & 0.359 & 1. \end{pmatrix}$$

There is a surprising positive correlation between cost and disutility. As shown by the trade-off curve, if the desired quality of life is lowered by increasing the disutility threshold, the cost is lower. Here the situation is somewhat different. We have already decided the health level we want to offer to the patients and our treatment is consistent with this decision. What happens is that sometimes a patient improves rapidly is health and there is no need of further treatments. As a consequence, both the cost and the disutility are less than the average. On the opposite side, it may happen that a patient does not improve his health as expected. We have to keep him longer in the system with more treatments. In this case costs and disutility increase both. Finally, almost all cost values of the simulation fall in the interval $ 8000-$ 9000 with an average of $ 8,532, consistent with the theoretical value $ 8,537.



(a) Cost (b) Disutility (c) Time in system

Fig. 7.

D. Mathematical issues

In the next sections we describe in detail the mathematical analysis on which our model is based. In particular we introduce in Section 10 the Linear Programming model that has to be solved to get the results outlined in the previous sections. In Section 9 we explain how we can count the average number of visits of the various states and hence get an estimate of the costs. This analysis gives the necessary mathematical background for the model (8). In Section 11 we describe the mathematical problem we have to solve in order to infer the transition probabilities, and in Section 12 we show how to solve this mathematical programming problem. Finally in Section 13 we explicitly provide all data we have used in the Markov Decision model.

9 Counting the visits of the transient states of a Markov chain

Let the states S of a Markov chain be partitioned into a transient set S_0 and a set S_1 of absorbing states. In more detail, each state in S_1 has a transition only to itself and is meant as a different 'exit' from the system. Let P be the transition matrix, whose generic entry is denoted as p_{ij}. Let us partition P as

$$P = \begin{pmatrix} Q & R \\ \mathbf{0} & I_1 \end{pmatrix}$$

where Q is over $S_0 \times S_0$, R over $S_0 \times S_1$ and I_1 is the identity matrix over S_1.

Let V be a matrix over $S_0 \times S_0$ where the element v_{ij} denotes the average number of visits of state j starting from state i. The element v_{ii} includes also the initial visit of state i. The following recursion holds

$$\begin{aligned} v_{ii} &= \sum_{k \in S_0} p_{ik}\, v_{ik} + 1 \qquad && i \in S_0 \\ v_{ij} &= \sum_{k \in S_0} p_{ik}\, v_{kj} \qquad && i \in S_0, j \in S_0 \setminus i \end{aligned}$$

that can be written in matrix form as

$$V = Q\,V + I_0 \quad \Longrightarrow \quad V = (I_0 - Q)^{-1}$$

where I_0 is the identity matrix over S_0. Consider a particular source state $s \in S_0$ and assume that there is a chain of transitions from state s to every other state. Let the state s be associated to the first row and column of P. We are interested in the average number v_{si} of visits from state s to a state $i \in S_0$.

If there is a cost c_i associated to each visit of state $i \in S_0$, the average cost $\bar{c}$ incurred by the Markov chain is

$$\bar{c} = \sum_{i \in S_0} v_{si}\, c_i$$

We may also compute the average number of visits of the transient states conditioned to end into a specific absorbing state $j \in S_1$. To this purpose we have to compute the limit probability $\lim_{k\to\infty} P^k = P^*$ that is given by

$$P^* = \begin{pmatrix} \mathbf{0} & F \\ \mathbf{0} & I_1 \end{pmatrix}$$

The first row of F represents the probability of ending in one of the absorbing states starting from s. Since, by definition of limiting probability,

$$P\,P^* = P^* \quad \Longrightarrow \quad \begin{pmatrix} Q & R \\ \mathbf{0} & I_1 \end{pmatrix} \begin{pmatrix} \mathbf{0} & F \\ \mathbf{0} & I_1 \end{pmatrix} = \begin{pmatrix} \mathbf{0} & F \\ \mathbf{0} & I_1 \end{pmatrix}$$

we have

$$Q\,F + R = F \quad \Longleftrightarrow \quad F = (I_0 - Q)^{-1}\,R = V\,R$$

Since $j \in S_1$ is absorbing, the entry P^k_{sj} is the probability that the chain is in the absorbing state j within the first k transitions. Hence the probability that the transition to the state $j \in S_1$ from some other state happens at the k-th transition is $P^k_{sj} - P^{k-1}_{sj}$. In order to compute this difference we have to compute the first row of

$$P^k = \begin{pmatrix} Q^k & \sum_{h=0}^{k-1} Q^h\,R \\ \mathbf{0} & I_1 \end{pmatrix}$$

and in particular we are interested in the difference

$$\sum_{h=0}^{k-1} Q^h\,R - \sum_{h=0}^{k-2} Q^h\,R = Q^{k-1}\,R$$

The average number of visits before ending in a specific absorbing state starting from s is given by the first row of

$$W = \sum_{k\geq 1} k\,Q^{k-1}\,R$$

So we have

$$W = R + \sum_{k\geq 2} k\,Q^{k-1}\,R = R + Q \sum_{k\geq 1} (k+1)\,Q^{k-1}\,R =$$

$$R + Q \sum_{k\geq 1} k\,Q^{k-1}\,R + Q \sum_{k\geq 1} Q^{k-1}\,R = R + Q\,W + Q\,F = R + Q\,W + F - R = Q\,W + F$$

so that

$$W = (I_0 - Q)^{-1} F = V\, F$$

Note that (where $\mathbf{1}$ is a column vector of ones)

$$W\,\mathbf{1} = V\, F\,\mathbf{1} = V\,\mathbf{1}$$

As expected the total number of visits to the transient states, partitioned according to the transient states, is equal to the total number of visits, partitioned according to the absorbing states (first rows of both matrices). We can actually tell more. The entries in the matrix

$$H_{ij} = v_{si}\, F_{ij}, \qquad i \in S_0,\ j \in S_1$$

represent the average number of visits of state i starting from s conditioned to end in state j. If we sum along the columns this matrix we obtain the first row of W and if we sum along the rows we obtain the first row of V. We can break down the total average cost $\bar{c}$ according to the absorbing states and to the transient states, as

$$\bar{c}_{ij} = H_{ij}\, c_i \tag{1}$$

This quantity is the total cost of visiting the transient state i (counting possible multiple visits) conditioned to end into the absorbing state j. Then $\sum_{i \in S_0} H_{ij}\, c_i$ is the total average cost conditioned to end into the absorbing state j and $\sum_{j \in S_1} H_{ij}\, c_i = v_{si}\, c_i$ is the total average cost in state $i \in S_0$. Table 5 reports the values $\bar{c}_{ij}$ for a specific set of transition probabilities and costs.

Now we add actions in each state in S_0. Each action determines the transition probabilities and, in general, determines also the cost of the action in a given state. The addition of possible actions leads to Markov Decision models where the goal is to find a set of actions that minimizes the total cost. This is called an *optimal policy*. Formally for each state $i \in S_0$, let A_i be the set of actions that can be taken in state i. Let c_{ia} be the cost associated to the action a taken in state i and p_{ija} be the probability associated to the transition from state i to j when the action a is taken.

In order to apply the machinery of Markov Decision models, we want to convert the non irreducible Markov chain (there are absorbing states) into an irreducible one by replacing the self-transitions of the absorbing states to transitions (with probability 1) to the source state. Since we have assumed that, no matter the policy taken, there are transitions from s to every other state, the new chain is irreducible and admits a positive stationary probability. Therefore let P' be a new matrix obtained from P by replacing I_1 with a zero matrix and putting the value 1 on the entries of the first column corresponding to states in S_1. This operation can be written in matrix form as

$$P' = \begin{pmatrix} I_0 & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{pmatrix} \begin{pmatrix} Q & R \\ \mathbf{0} & I_1 \end{pmatrix} + \begin{pmatrix} \mathbf{0} \\ \mathbf{1} \end{pmatrix} \begin{pmatrix} e_s & \mathbf{0} \end{pmatrix}$$

where e_s is a row vector with all zeros except a 1 for state s. The positive stationary probability of P' (we recall that the new chain is irreducible) is

$$\pi\, P' = \pi \tag{2}$$

If we partition π as (π^0, π^1) we may rewrite (2) as

$$(\,\pi^0 \quad \pi^1\,)\begin{pmatrix} I_0 & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{pmatrix}\begin{pmatrix} Q & R \\ \mathbf{0} & I_1 \end{pmatrix} + (\,\pi^0 \quad \pi^1\,)\begin{pmatrix} \mathbf{0} \\ \mathbf{1} \end{pmatrix}(\,e_s \quad \mathbf{0}\,) = (\,\pi^0 \quad \pi^1\,)$$

from which

$$\pi^0\, Q + \pi^1 \mathbf{1}\, e_s = \pi^0, \qquad \pi^0\, R = \pi^1$$

so that

$$\pi^0 = (\pi^1\mathbf{1})\, e_s\, (I_0 - Q)^{-1} = (\pi^1\mathbf{1})\, e_s\, V, \qquad \pi^1 = (\pi^1\mathbf{1})\, e_s\, V\, R = (\pi^1\mathbf{1})\, e_s\, F \tag{3}$$

Hence the number of visits $e_s\, V$ (first row of V) is given by π^0 divided by $(\pi^1\mathbf{1})$. If, in particular, there are no transitions to state s (in the original chain) then the first column of P is null and we have

$$\pi_s = \pi^1\mathbf{1}$$

Hence the average number of visits of the transient states is simply given in this case by π^0/π_s. The vector $\pi^1/(\pi^1\mathbf{1})$ tells the fraction of times the chain ends in one of the absorbing states. From now on we consider only the case of no transitions to s. Note that the first row of F is π^1/π_s as apparent from (3).

10 A Linear Programming Markov Decision model

We are now in the position of building a Linear Programming model that computes the optimal policy. A standard Linear Programming model that minimizes the average cost for an infinite time horizon is the following

$$\begin{aligned} \min \quad & \sum_{i\in S}\sum_{a\in A_i} c_{ia}\, x_{ia} & & \\ & \sum_{i\in S}\sum_{a\in A_i} x_{ia} & = 1 & \\ & \sum_{i\in S}\sum_{a\in A_i} p_{ija}\, x_{ia} = \sum_{a\in A_j} x_{ja} & & j \in S \\ & x_{ia} \geq 0 & & a \in A_i, i \in S. \end{aligned} \tag{4}$$

where x_{ia} is the probability of being in state i and taking the action a. The first constraint imposes unity sum over all probability values and the second set of constraint is a balance constraint: the probability of being in state j must be equal to the probability of arriving in state j from all other states under all actions taken in the other states.

However, in our model we compute the cost by summing a finite set of costs and not by averaging an infinite set of costs. As we have shown in Section 9 only a simple modification of (4) is needed. It is just matter of normalizing the x values by putting $\sum_{a\in A_s} x_{sa} = 1$ instead of $\sum_{i\in S}\sum_{a\in A_i} x_{ia} = 1$. Actually,

since only one action is available in the source state H_0 we have:

$$\begin{aligned} \min \quad & \sum_{i\in S}\sum_{a\in A_i} c_{ia}\, x_{ia} \\ & \sum_{i\in S}\sum_{a\in A_i} p_{ija}\, x_{ia} = \sum_{a\in A_j} x_{ja} \qquad j \in S \\ & x_s = 1 \\ & x_{ia} \geq 0 \qquad\qquad\qquad\qquad a \in A_i, i \in S. \end{aligned} \tag{5}$$

In (5) the values x_{ia} are *not* probabilities. They correspond to the average number of visits of state i and taking action a for a transient state i. They do represent probabilities for the absorbing states. In particular they represent the fraction of patients ending in one of the absorbing states. Consequently the sum $\sum_{i\in S}\sum_{a\in A_i} x_{ia}$ is the average number of transitions before exiting the system, which, multiplied by the three month time step, gives the average time in the system for a generic patient.

Furthermore, if we associate to each state i a *disutility* $0 \leq d_i \leq 1$ we can measure the average total disutility incurred by a generic patient by the expression

$$\sum_i d_i \sum_{a\in A_i} x_{ia}$$

We comment again on the choice of a disutility expression versus an utility expression, which is perhaps more common. If we try to maximize a total utility we have to sum each utility for each three month step. The longer the medical treatments are the higher the utility is, so that we would have the paradoxical result that a patient is better off if he stays in the system for a long time. Indeed if we consider the utility u_i of patient i just the complement to one of the disutility, i.e., $u_i = 1 - d_i$ we see that

$$\sum_i d_i \sum_{a\in A_i} x_{ia} = \sum_i (1-u_i) \sum_{a\in A_i} x_{ia} = \sum_i \sum_{a\in A_i} x_{ia} - \sum_i u_i \sum_{a\in A_i} x_{ia} \tag{6}$$

i.e., the total disutility is given by the difference of the time in the system minus the total utility. Hence the total disutility takes also care of the time spent in the system. We may decide that the global disutility has to be not larger than a chosen parameter K_t and therefore we impose the constraint

$$\sum_i d_i \sum_{a\in A_i} x_{ia} \leq K_t \tag{7}$$

Since the values x_{ia} for the absorbing states are the probability of ending in the state i, we may also have control on the fraction of people that end into the state G and we may establish a minimum threshold K_G for this state. Therefore we may extend the model (5) by adding this inequality and the inequality (7):

$$
\begin{aligned}
\min \quad & \sum_i \sum_{a \in A_i} c_{ia}\, x_{ia} \\
& \sum_i \sum_{a \in A_i} p_{ija}\, x_{ia} = \sum_{a \in A_j} x_{ja} \qquad j \in S \\
& \sum_i \sum_{a \in A_i} d_i\, x_{ia} \quad \leq K_t \\
& x_G \geq K_G \\
& x_s = 1 \\
& x_{ia} \geq 0
\end{aligned}
\tag{8}
$$

Introducing these two inequalities has a disrupting effect on the mathematical structure of the Linear Programming model. While in (5) we are guaranteed that for each state i only one variable x_{ia} is positive and this indicates without ambiguity which action has to be taken in state i, this property is lost in (8). The fact that there may be two or more variables x_{ia} associated to the possible actions in state i means that we have to make a random choice choose among a set of actions. The probabilities for this random choice are clearly

$$
\frac{x_{ia}}{\sum_{b \in A_i} x_{ib}} \qquad a \in A_i \; i \in S
$$

11 Assessing the transition probabilities from aggregate IPSS score

In order to assess the transition probabilities it would be helpful to have available historical data reporting the percentage of patients that, after a definite medical treatment, end up with a specific healthy status. Unfortunately these data are not available and very likely they do not exist. It has to be said that usually data are tailored to specific needs. Since Markov models are quite new, no data explicitly fit to Markov models have been gathered yet.

The largely available medical data are the so called IPSS, which report the medical status of a patient from the answers given to a specific questionnaire. Mean post treatment IPSS score decrease value have been recorded from a systematic review of the literature. These values have been adjusted to be proportional to the pretreatment IPSS score of our population based on epidemiological studies and mean post treatment IPSS scores have been calculated accordingly. Finally, these values have been used to adjust expert opinion probabilities (previously equal for every treatment) via a Lagrangian approach (Section 12).

From a mathematical point of view we are faced with the following situation: we know the numbers $a_1, \ldots, a_m$ where a_i is the percentage of people belonging to state i prior to some medical treatment. There are n posterior states to which each person will end up after treatment at the end of the three month period. The yet unknown transition probabilities p_{ij} turn the percentages $a_1, \ldots, a_m$ into percentages $b_1, \ldots, b_n$ as $b_j = \sum_i p_{ij}\, a_i$, (clearly $\sum_i a_i = \sum_j b_j$). The percentages b_j are unknown. What is known is the IPSS score of the patients after treatment, but not for all n posterior states. Data have been gathered only for a subset $J \subset [1..n]$. For each posterior state $j \in J$ a score w_j, derived from the IPSS score, is defined and the overall

score is

$$K_1 = \sum_{j \in J} w_j \, b_j \tag{9}$$

The number K_1 is the available data and we want to estimate transition probabilities p_{ij}, $i \in [1..m]$, $j \in J$, such that they are consistent with the value K_1.

There are infinitely many transition probability matrices that satisfy this consistency requirement. Hence we must refine our choice. The way we have chosen is to first define some prior transition probabilities $\bar{p}_{ij}$ based on expert opinion and then to find the least square deviation from these prior probabilities that is also consistent with the value K_1. In the Appendix B we report the mathematical analysis and the algorithm we have to run in order to find the transition probabilities. Note that we cannot infer the transition probabilities for posterior states not in J, and therefore we directly fix these values as $p_{ij} = \bar{p}_{ij}$, for $j \notin J$.

12 A Lagrangian approach to estimate the transition probabilities

According to the notation already introduced in Section 11 we have to solve the following mathematical programming problem:

$$\begin{aligned}
\min \ & \sum_{i=1}^{m} \sum_{j \in J} (p_{ij} - \bar{p}_{ij})^2 \\
& \sum_{j \in J} p_{ij} = \sum_{j \in J} \bar{p}_{ij} && i = 1, \ldots, m \\
& \sum_{i=1}^{m} \sum_{j \in J} a_i \, p_{ij} \, w_j = K_1 \\
& p_{ij} \geq 0 && i = 1, \ldots, m, \ j \in J
\end{aligned} \tag{10}$$

where the objective function is the sum of the squares of the deviations from the prior values $\bar{p}_{ij}$, the constraints $\sum_{j \in J} p_{ij} = \sum_{j \in J} \bar{p}_{ij}$ and $p_{ij} \geq 0$ simply impose that the values p_{ij} have to be transition probabilities (note that the constraint $p_{ij} \leq 1$ is already implied by the other constraints and can be omitted) and the constraint $\sum_{ij} a_i \, p_{ij} \, w_j = K_1$ is the consistency requirement with respect to the global IPSS score K_1.

This is a quadratic programming problem with linear constraints that can be solved via a Lagrangian approach. The Lagrangian function is

$$L(\mu, \lambda) := \min_{p \geq 0} \frac{1}{2} \sum_{i=1}^{m} \sum_{j \in J} (p_{ij} - \bar{p}_{ij})^2 + \sum_{i=1}^{m} \mu_i \sum_{j \in J} (\bar{p}_{ij} - p_{ij}) + \lambda \, (K_1 - \sum_{i=1}^{m} \sum_{j \in J} a_i \, p_{ij} \, w_j)$$

The Karush-Kuhn-Tucker conditions for optimality say that p_{ij} is an optimal solution of (10) if and only if

$$\frac{\partial L(\mu, \lambda)}{\partial p_{ij}} \geq 0 \quad \text{if} \quad p_{ij} = 0, \qquad \frac{\partial L(\mu, \lambda)}{\partial p_{ij}} = 0 \quad \text{if} \quad 0 < p_{ij} \leq 1$$

Let $Z_i := \{j \in J : p_{ij} = 0\}$, i.e., the set of states for which a transition from the state i has zero probability at optimality. Let $\bar{Z}_i$ be its complement in J. Clearly, we do not know in advance the set Z_i. The way we approach the optimality conditions is by first guessing an empty set Z_i and then resetting this set if the formulas will give a negative answer.

From the condition

$$\frac{\partial L(\mu, \lambda)}{\partial p_{ij}} = 0 \quad \text{if} \quad j \in \bar{Z}_i$$

we get

$$p_{ij} = \bar{p}_{ij} + \mu_i + \lambda\, a_i\, w_j \qquad j \in \bar{Z}_i \tag{11}$$

By imposing the constraint $\sum_{j\in J} p_{ij} = \sum_{j\in J} \bar{p}_{ij}$ we have

$$\sum_{j\in \bar{Z}_i} (\bar{p}_{ij} + \mu_i + \lambda\, a_i\, w_j) = \sum_{j\in J} \bar{p}_{ij}$$

i.e.,

$$|\bar{Z}_i|\, \mu_i = \sum_{j\in Z_i} \bar{p}_{ij} - \lambda\, a_i \sum_{j\in \bar{Z}_i} w_j$$

from which we get the values for μ_i

$$\mu_i = \frac{\sum_{j\in Z_i} \bar{p}_{ij} - \lambda\, a_i \sum_{j\in \bar{Z}_i} w_j}{|\bar{Z}_i|}$$

For notational purposes it is convenient to define

$$\pi_i = \frac{\sum_{j\in Z_i} \bar{p}_{ij}}{|\bar{Z}_i|}, \qquad \bar{w}_i = \frac{\sum_{j\in \bar{Z}_i} w_j}{|\bar{Z}_i|}$$

so that

$$\mu_i = \pi_i - \lambda\, a_i\, \bar{w}_i$$

and (11) can be written as

$$p_{ij} = \bar{p}_{ij} + \pi_i + \lambda\, a_i\, (w_j - \bar{w}_i) \qquad j \in \bar{Z}_i, \qquad\qquad p_{ij} = 0 \qquad j \in Z_i$$

Now we have to impose the constraint $\sum_{i=1}^{m} \sum_{j\in J} a_i\, p_{ij}\, w_j = K_1$ which leads to

$$\sum_{i=1}^{m} \sum_{j\in \bar{Z}_i} a_i\, (\bar{p}_{ij} + \pi_i)\, w_j + \lambda\, a_i^2\, (w_j^2 - \bar{w}_i\, w_j) = K_1$$

from which we can get the value for λ. For notational purposes it is convenient to define

$$K_0 := \sum_{i=1}^{m} \sum_{j\in \bar{Z}_i} a_i\, (\bar{p}_{ij} + \pi_i)\, w_j$$

so that we have

$$\lambda = \frac{K_1 - K_0}{\sum_{i=1}^{m} a_i^2 \left(\sum_{j \in \bar{Z}_i} w_j^2 - |\bar{Z}_i|\, \bar{w}_i^2\right)}$$

Summing up, the computations we have to carry out are:

$$\pi_i = \frac{\sum_{j \in Z_i} \bar{p}_{ij}}{|\bar{Z}_i|}, \qquad \bar{w}_i = \frac{\sum_{j \in \bar{Z}_i} w_j}{|\bar{Z}_i|}$$

$$K_0 := \sum_i \sum_{j \in \bar{Z}_i} a_i \left(\bar{p}_{ij} + \pi_i\right) w_j, \qquad \lambda = \frac{K_1 - K_0}{\sum_i a_i^2 \left(\sum_{j \in \bar{Z}_i} w_j^2 - |\bar{Z}_i|\, \bar{w}_i^2\right)}$$

$$p_{ij} = \bar{p}_{ij} + \pi_i + \lambda\, a_i \left(w_j - \bar{w}_i\right) \qquad j \in \bar{Z}_i, \qquad\qquad p_{ij} = 0 \qquad j \in Z_i$$

Clearly the p_{ij} thus computed must be all nonnegative. Furthermore, we must also have $\frac{\partial L(\mu,\lambda)}{\partial p_{ij}} \geq 0$ for all $j \in Z_i$, i.e.,

$$p_{ij} \geq \bar{p}_{ij} + \mu_i + \lambda\, a_i\, w_j \quad \Longrightarrow \quad \bar{p}_{ij} + \mu_i + \lambda\, a_i\, w_j \leq 0 \tag{12}$$

If this last condition is verified and the p_{ij} are all nonnegative, the computation is over and we have found the optimal solution. Otherwise if $p_{ij} < 0$ from some pair (i, j) with $j \in \bar{Z}_i$, then we revise the set Z_i by adding this index j, and if (12) is violated we revise the set Z_i by dropping this index j. This is only a heuristic procedure, since we are not guaranteed that the procedure may be looping by repeatedly adding and dropping the same indices, but it does work well in our case and we get the solution in a few steps.

13 Data of the model

We have first assessed the tables of prior transition probabilities. The transitions from state H to states L_{01}, L_{02}, L_{03} and A_0 have probabilities that correspond to the percentages of people that first arrive to the hospital with the corresponding disease. We have estimated these values as

$$p_{HL_{01}} = 0.32, \qquad p_{HL_{02}} = 0.51, \qquad p_{HL_{03}} = 0.14, \qquad p_{HA_0} = 0.03$$

In case a patient is in one of the states L_{01}, L_{02}, L_{03} or A_0 and a medical action is undertaken, by definition there are no transitions to the states L_{01}, L_{02}, L_{03} and A_0. The probabilities of the transitions from the states L_{01}, L_{02}, L_{03}, A_0 (rows) to the states L_{11}, L_{12}, L_{13}, A_1, C and G (columns) have been estimated by an expert as:

$$\bar{P}_{01} = \begin{pmatrix} 0.40 & 0.20 & 0.05 & 0.05 & 0.01 & 0.29 \\ 0.49 & 0.20 & 0.05 & 0.05 & 0.01 & 0.20 \\ 0.24 & 0.50 & 0.10 & 0.05 & 0.01 & 0.10 \\ 0.14 & 0.40 & 0.30 & 0.05 & 0.01 & 0.10 \end{pmatrix}$$

We note that these values are the same for each possible medical treatment. We have considered that it is difficult even for an expert to discriminate in detail between different medical actions. The transition probabilities will be later diversified by revised them according to the IPSS score.

In case of no medical action the transition probabilities from the states L_{01}, L_{02}, L_{03}, A_0 (rows) to the states L_{01}, L_{02}, L_{03}, A_0, C and G (columns) have been estimated as (no other transition is possible):

$$\bar{P}_{00} = \begin{pmatrix} 0.80 & 0.01 & 0.01 & 0.01 & 0.01 & 0.16 \\ 0.01 & 0.80 & 0.15 & 0.01 & 0.01 & 0.02 \\ 0.01 & 0.01 & 0.80 & 0.15 & 0.01 & 0.02 \\ 0.01 & 0.01 & 0.01 & 0.15 & 0.01 & 0.02 \end{pmatrix}$$

In case a patient is in one of the states L_{11}, L_{12}, L_{13} or A_1, no transition back to L_{01}, L_{02}, L_{03} or A_0 is possible. In case a surgical action is undertaken the probability transitions from L_{11}, L_{12}, L_{13} or A_1 (rows) to the states L_{11}, L_{12}, L_{13}, A_1, C, B or G have been estimated as:

$$\bar{P}_{11} = \begin{pmatrix} 0.10 & 0.05 & 0 & 0 & 0.05 & 0.10 & 0.70 \\ 0.10 & 0.05 & 0 & 0 & 0.05 & 0.10 & 0.70 \\ 0 & 0.10 & 0.05 & 0.05 & 0.05 & 0.10 & 0.65 \\ 0 & 0.05 & 0.10 & 0.05 & 0.05 & 0.10 & 0.65 \end{pmatrix}$$

and in case of a pharmacological action the transition probabilities have been estimated as:

$$\bar{P}_{12} = \begin{pmatrix} 0.20 & 0.05 & 0 & 0 & 0 & 0.10 & 0.65 \\ 0.05 & 0.20 & 0 & 0 & 0 & 0.10 & 0.65 \\ 0 & 0.30 & 0.30 & 0.05 & 0 & 0.10 & 0.25 \\ 0 & 0 & 0.10 & 0.50 & 0 & 0.10 & 0.30 \end{pmatrix}$$

Finally if no medical action is undertaken the transition probabilities from the states L_{11}, L_{12}, L_{13} or A_1 (rows) to the states L_{11}, L_{12}, L_{13}, A_1, C, G or B have been estimated as:

$$\bar{P}_{10} = \begin{pmatrix} 0.05 & 0 & 0 & 0 & 0 & 0.10 & 0.85 \\ 0.05 & 0.05 & 0 & 0 & 0 & 0.10 & 0.80 \\ 0 & 0 & 0.10 & 0.10 & 0 & 0.10 & 0.70 \\ 0.01 & 0.01 & 0.16 & 0.62 & 0 & 0.10 & 0.10 \end{pmatrix}$$

Now we have to refine these values by matching them against the IPSS scores. IPSS scores are applied only to LUTS patients. An IPSS score is a number between 0 and 35. The ranges 0-7, 8-19, 20-35 identify mild, moderate and severe LUTS respectively. Some patients may be discharged because they are found healthy. In this case we may assume that these patients have zero score. It is important to note that we do not have available data for single patients. What we know is an aggregate value for a group of patients that have undergone a particular medical treatment. Necessarily, we have to reason on average values and this implies replacing each range by its average value. Hence we have fixed the following IPSS scores for all patients as:

$$w(L_{11}) = 3.5, \qquad w(L_{12}) = 13.5, \qquad w(L_{13}) = 27.5, \qquad w(G) = 0$$

We note that scores take into account patients after a medical intervention. Hence they refer to states L_{11}, L_{12}, L_{13} or G either after a transition from the states L_{01}, L_{02}, L_{03} (the only states for which a patient is measured via an IPSS core) or after a transition from the states L_{11}, L_{12}, L_{013}. In the former case the patient is interviewed after the first medical treatment. In the latter case after a subsequent medical intervention.

Again the information we have is an aggregate one and we do not know whether the score refers to the first or to a subsequent intervention. Consequently we take the same IPSS score no matter whether patients have undergone a medical treatment or not. Mean post treatment IPSS score decrease value have been recorded from a systematic review of the literature. These values have been adjusted to be proportional to the pretreatment IPSS score of our population based on epidemiological studies and mean post treatment IPSS scores have been calculated accordingly obtaining the values reported in the second column of Table 1. They correspond to the numbers K_1 in (9). These numbers depend only on the medical actions.

By applying the method described in Appendix B we get the table of transition probabilities displayed in Table 6. In the table we list on rows the starting states and on column the arriving states. For each starting state we have a row for the corresponding medical action.

The remaining data are the costs for each possible medical action and the disutilities for each possible state. They have been reported in the first column of Table 1. Costs are invariant for each of the states L_{01}, L_{02}, L_{03}, A_0, L_{11}, L_{12}, L_{13}, A_1. For the starting state H and the absorbing states C, B and G the cost is zero, because no medical action is expected in these states.

Disutilities values have been borrowed from previous studies as

$$d_{L_{01}} = d_{L_{11}} = 0.01,\ d_{L_{02}} = d_{L_{12}} = 0.11,\ d_{L_{03}} = d_{L_{13}} = 0.3,\ d_{A_0} = d_{A_1} = 0.75,\ d_C = 0.2$$

E. Discussion

The problem that this paper is addressing is a need for a more comprehensive cost effectiveness model for health care decision making that can be used by any of the major stakeholders (patient, provider or payer). In our opinion, this need has been met changing the mathematical approach to the problem. Our model is in this regard very innovative in his concept in respect of the classic cost-effectiveness studies which typically compare only two treatments not giving any specific case by case treatment indication. This model instead predicts the average cost necessary to obtain a given effectiveness including every available treatment in the decision-making process. Specifically, our goal to find an optimal policy to minimize the cost whilst keeping the total disutility below a given threshold choosing among multiple treatments has been accomplished.

The general trade-off curve (Fig. 2) represents an invaluable, user friendly tool that can be utilized for different purposes. A hospital or a provider will find it useful for clinically guided budget planning. In example in a bundle payment system, given an acceptable clinical effectiveness threshold (through the disutility value) the curve will predict the average per patient cost. On the other hand, a payer, in a fee for value environment, given a certain cost can expect a specific clinical outcome. Finally, a patient given a certain clinical outcome can predict a fair charge. Despite a large amount of literature showing little or any association between overall spending and improved outcomes (32-35) our model is projecting a clear association between increasing expenditure (more surgery) and better outcomes (lower disutility).

The optimal policy for each clinical state (Table 4) is the most important output of the model because it gives specific indications to the user (whether a provider, a payer or a patient) on what treatment to pick according with the chosen disutility and the patient pretreatment state. Essentially, it is a roadmap to

		H	L_{01}	L_{02}	L_{03}	A_0	L_{11}	L_{12}	L_{13}	A_1	C	B	G
H		0	0.32	0.51	0.14	0.03	0	0	0	0	0	0	0
L_{01}	S_1	0	0	0	0	0	0.45	0.11	0.00	0.05	0.01	0.00	0.38
	S_2	0	0	0	0	0	0.44	0.12	0.00	0.05	0.01	0.00	0.38
	S_3	0	0	0	0	0	0.47	0.01	0.00	0.05	0.01	0.00	0.46
	S_4	0	0	0	0	0	0.44	0.13	0.00	0.05	0.01	0.00	0.37
	P	0	0	0	0	0	0.40	0.20	0.05	0.05	0.01	0.00	0.29
	O	0	0.80	0.01	0.01	0.01	0	0	0	0	0.01	0.00	0.16
L_{02}	S_1	0	0	0	0	0	0.55	0.05	0.00	0.05	0.01	0.00	0.34
	S_2	0	0	0	0	0	0.55	0.06	0.00	0.05	0.01	0.00	0.33
	S_3	0	0	0	0	0	0.54	0.00	0.00	0.05	0.01	0.00	0.40
	S_4	0	0	0	0	0	0.54	0.08	0.00	0.05	0.01	0.00	0.32
	P	0	0	0	0	0	0.49	0.20	0.05	0.05	0.01	0.00	0.20
	O	0	0.01	0.80	0.15	0.01	0	0	0	0	0.01	0.00	0.02
L_{03}	S_1	0	0	0	0	0	0.28	0.50	0.00	0.05	0.01	0.00	0.16
	S_2	0	0	0	0	0	0.28	0.49	0.01	0.05	0.01	0.00	0.16
	S_3	0	0	0	0	0	0.30	0.44	0.00	0.05	0.01	0.00	0.20
	S_4	0	0	0	0	0	0.28	0.49	0.02	0.05	0.01	0.00	0.15
	P	0	0	0	0	0	0.24	0.50	0.10	0.05	0.01	0.00	0.10
	O	0	0.01	0.01	0.80	0.15	0	0	0	0	0.01	0.00	0.02
A_0	S_1	0	0	0	0	0	0.14	0.40	0.30	0.05	0.01	0.00	0.10
	S_2	0	0	0	0	0	0.14	0.40	0.30	0.05	0.01	0.00	0.10
	S_3	0	0	0	0	0	0.14	0.40	0.30	0.05	0.01	0.00	0.10
	S_4	0	0	0	0	0	0.14	0.40	0.30	0.05	0.01	0.00	0.10
	P	0	0	0	0	0	0.14	0.40	0.30	0.05	0.01	0.00	0.10
	O	0	0.01	0.01	0.15	0.80	0	0	0	0	0.01	0.00	0.02
L_{11}	S_1	0	0	0	0	0	0.09	0.05	0.01	0.00	0.06	0.08	0.71
	S_2	0	0	0	0	0	0.09	0.05	0.02	0.00	0.07	0.08	0.69
	S_3	0	0	0	0	0	0.10	0.05	0.00	0.00	0.05	0.10	0.70
	S_4	0	0	0	0	0	0.08	0.05	0.02	0.00	0.07	0.08	0.70
	P	0	0	0	0	0	0.16	0.05	0.04	0.00	0.04	0.05	0.66
	O	0	0	0	0	0	0.05	0	0	0	0	0.10	0.85
L_{12}	S_1	0	0	0	0	0	0.08	0.05	0.02	0.00	0.07	0.08	0.70
	S_2	0	0	0	0	0	0.08	0.05	0.02	0.00	0.07	0.07	0.71
	S_3	0	0	0	0	0	0.10	0.05	0.00	0.00	0.05	0.10	0.70
	S_4	0	0	0	0	0	0.08	0.05	0.03	0.00	0.08	0.07	0.69
	P	0	0	0	0	0	0.00	0.19	0.07	0.00	0.07	0.02	0.65
	O	0	0	0	0	0	0.05	0.05	0	0	0	0.10	0.80
L_{13}	S_1	0	0	0	0	0	0.00	0.10	0.05	0.05	0.05	0.09	0.66
	S_2	0	0	0	0	0	0.00	0.10	0.06	0.05	0.06	0.09	0.64
	S_3	0	0	0	0	0	0.00	0.10	0.05	0.05	0.05	0.10	0.65
	S_4	0	0	0	0	0	0.00	0.10	0.06	0.05	0.05	0.10	0.64
	P	0	0	0	0	0	0.00	0.29	0.32	0.05	0.01	0.08	0.25
	O	0	0	0	0	0	0	0	0.10	0.10	0.00	0.10	0.70
A_1	S_1	0	0	0	0	0	0.00	0.05	0.10	0.05	0.05	0.10	0.65
	S_2	0	0	0	0	0	0.00	0.05	0.10	0.05	0.05	0.10	0.65
	S_3	0	0	0	0	0	0.00	0.05	0.10	0.05	0.05	0.10	0.65
	S_4	0	0	0	0	0	0.00	0.05	0.10	0.05	0.05	0.10	0.65
	P	0	0	0	0	0	0.00	0.00	0.10	0.50	0.00	0.10	0.30
	O	0	0	0	0	0	0.01	0.01	0.16	0.62	0.00	0.10	0.10
C		1	0	0	0	0	0	0	0	0	0	0	0
B		1	0	0	0	0	0	0	0	0	0	0	0
G		1	0	0	0	0	0	0	0	0	0	0	0

Table 6. Transition probabilities

mathematically guide the decision making toward a guaranteed average outcome for an average cost. It is interesting to notice that the model never chooses two of the four available surgical treatments. Looking at the single treatment trade-off curves (Fig 5) we better understand the reason. Some surgical treatment such as HL have a very effective but more expensive trade-off, some other such as GL have a good cost-effectiveness trade-off but they cannot guarantee the minimal possible disutility, the other two surgical treatments (TURP and TL) don't have the same effectiveness and they are not sensibly less costly than the other two. The pharmacologic treatment (PH) is the cheapest but is less effective than any other surgical treatment. The model will therefore tend to choose HL in the left part, GL in the central part and PH in the right part of the general trade-off curve. TURP and TL are not chosen simply because they don't offer a good effectiveness-cost trade in comparison with the other treatments. These results are obviously based and rather "biased" by the transition probabilities calculated from an average of the available literature and not from a real series of patients. The ideal use of the model would be through cost and outcomes from previous procedure of the same provider whose we are trying to guide in the decision making.

The percentage of G state for any given disutility (Table 4 and Fig. 6(b)) provides a precise tool to project what's percentage of patients will be considered cured and therefore will exit from the model for any given disutility. Clinically this is an information more valuable and more comprehensible that the sum of the disutility by any of the stakeholder. Using this information will allow for example the provider to choose an acceptable disutility threshold or the patient to better understand the amount of money that will be spent in order to give him that specific chance to be cured.

The time spent in the system for any given disutility (Table 4 and Fig. 6(a)) is a unique feature of this model. Time is not enough considered in classic cost effectiveness models but we think it has an enormous weight on the medical decision-making process. An important assumption underlying these studies is that costs and effects are constant but they don?t consider that variations in costs and effects are likely to occur over time (36).For this reason, we decided to fix our horizon and transition time at 3 months, which also coincides with the global period of insurance coverage after most procedures. The ideal treatment needs to have a good cost effectiveness trade-off in a reasonable time. In other words, if a specific treatment can offer a very high effectiveness for a very low cost but it requires the patient to stay in the system for a very long time, it has not to be considered the best treatment. Our model is able to give the average time spent in the system for every disutility chosen which will allow the user to consider the time factor in the decision making.

The breakdown of the costs gives the decision maker specific expenditure for each non-absorbing and absorbing states (Table 5)) for any given disutility. This information will provide a precise picture on how the resources will be allocated state by state. This tool essentially will let us know for any given disutility how much of the average cost is spent in order to exit from the model through the three absorbing states (C, B or G). This information needs to be paired with the percentage of patients exiting the model through the G state for any given disutility (e.g., for disutility of 0.2, the percentage of G is 91% and the cost for G is \$ 6,317 out of a total cost of \$ 6,990). The user can therefore compare these numbers with other disutilities choosing the disutility with highest G percentage for a lower specific G cost.

Finally, the simulation (Fig. 7) as an alternative to the sensitivity tests is extremely important for any user because it describes the range within our projection could actually fall. This range is determined through a computer simulation which calculate the possible extreme variability of patient populations in terms of different pretreatment states. Interestingly enough the simulation with 100 patients for 10,000 cycles didn't show a wide range of variance both for costs and disutility showing the model to be solid from a mathematical standpoint. Clinically speaking this is an invaluable tool to produce a solid budget and a reliable prediction of clinical outcomes.

The Authors were unable to find any similar model in the medical literature to compare and discuss, showing as this approach, maybe more popular in other fields is definitely innovative in health care.

The Authors acknowledge that this model has several limitations. The main one is probably coming from the transition probabilities calculation which are inferred with a Lagrangian method from a combination of expert opinion and data from the medical literature. Essentially the expert would give a plausible transition probability which will be equal for all the treatments and eventually these values will be diversified according with the average IPSS score decrease taken from the literature. This method has been necessary due to the impossibility of getting access to the entirety of data from the published papers and we think is an acceptable approximation of the real, average transition probabilities. Additionally, this model should really be used with specific transition probabilities of the provider whose performance we want to project. Analogue limitation and same comment on the ideal use of the model comes with the cost analysis based on hospital administration databases and complication rates from the literature.

Another limitation is the use of the IPSS score as the only clinical parameter on which the population is classified by different states. IPSS does not capture any information about complication which might influence the quality of life such as stress or urge incontinence. In light of this, some treatment might look very effective based on IPSS only but they might be doomed by high incontinence rate. This limitation can be overcome adding more states to the model. Finally, a general limitation of this kind of models involves the necessity of total collaboration by the clinical provider to make the projection realizes. The provider is supposed to totally embrace the concept of having his clinical decision making guided by a model. Noncompliance with the model indications will mean non-accuracy of the projection.

F. Conclusion

Markov model has been available for a long time but never really penetrated the medical decision-making process. Our model offers a user-friendly approach which gives specific indications about what procedure perform in specific patients. Additionally, it can be tailored to the specific provider using his own transition probabilities and costs. This model needs validation on real patient populations but it represents an innovative and more practical approach to apply cost effectiveness in day to day practice.

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