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ANALYZING HEPATITIS C SCREENING AND TREATMENT STRATEGIES USING PROBABILISTIC BRANCH AND BOUND

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ABSTRACT

Decisions must be made regarding screening and treatment strategies under budget constraints for chronic hepatitis C birth-cohorts in the U.S. A Markov model of disease progression is able to evaluate health utility gain using quality-adjusted life years (QALYs) for each strategy. Through conducting a simulation optimization algorithm, Probabilistic Branch and Bound (PBnB), we not only provide an optimal strategy over ten years, but also perform sensitivity analysis by approximating a set of good enough strategies. Specifically, we first identify time periods with obvious dominant strategies (allocate total budget to treatment in early years) through grid search, and then we perform PBnB to identify top 10 percent strategies for two major decision periods. Approximating a set of the top 10 percent strategies with PBnB provides decision makers the ability to explore combinations of good strategies. Also, a set of strategies indicates which decision time periods strongly impact the health utility gain.

1 INTRODUCTION

Chronic hepatitis C Virus (HCV) is an important public health problem in the U.S. (CDC 2013, Liu et al. 2013). Li (2015), Li et al. (2015), and Li et al. (2016) modeled the disease progression as a Markov model to evaluate health utility gain using quality-adjusted life years (QALYs) for different screening and treatment budget allocation by birth-cohort. Li (2015) performed a grid search over ten years and found a near optimal strategy for each target cohort and total budget scenario. However, the results are empirically searched without statistical understanding on the quality of the solution. More importantly, it does not provide further understanding on the impact of each decision period on the system performance.

Various simulation optimization algorithms provide statistical analyses and convergence to the global optimum. However, considering the complexity of the problem or computational budget, some algorithms search for "good enough" solutions instead of the best solution, also called goal softening (Ho et al. 2000, Ho et al. 2007). For instance, some of the ranking and selection algorithms analyze the quality of selecting one of the top k solutions instead of the best solution (Chen et al. 2008). For mixed continuous/discrete problem, the nested-partitioning method (Shi and Ólafsson 2000, Ólafsson 2004, Shi and Olafsson 2009) and empirical stochastic branch and bound (Xu and Nelson 2013) provide an approximation of the optimum, where we approximate a level set. In order to have a further understanding of the system, the approach we use is Probabilistic Branch and Bound (PBnB), which approximates a level set, e.g., top 10 percent solutions (Huang and Zabinsky 2013). PBnB is a partition based algorithm which creates subregions of the solution space that approximate a level set. A level set contains a set of good solutions rather than a single solution. Furthermore, it provides an understanding of the decision variables by providing ranges

of values. For this HCV application, our approach allows an understanding of how the screening and treatment decisions by time period impact the health utility gain.

In Section 2, we describe the details of the HCV Markov model. Section 3 discusses the optimization approach. In Section 4, we perform the numerical analysis on the strategies by grid search and PBnB and conclude in Section 5.

2 HEPATITIS C MARKOV MODEL

Li et al. (2016) developed a compartmental simulation model using a Markov decision process to mimic the HCV transmission, progression, screening, treatment, and death in the healthcare system. The model considers allocating a certain amount of budget across a ten year period, with a two-year budget planning cycle. The decision is the percentage of the budget to be used for screening and treatment in each of five two-year time periods, by HCV birth-cohort (born 1945-1975), to maximize health outcomes from a U.S. societal perspective.

An implementation strategy from Li (2015), Li et al. (2016) is considered in this paper: Allocate a percentage of the budget to screening, then treat patients with the rest of budget giving priority to the sickest patients. After the planning horizon, the model continues to simulate the progression of the people in the cohort until end-of-life (additional 60 years) with no further screening and treatment.

The population in each cohort is categorized into three major groups: (A) HCV status is unknown, which is the target screening population, (B) HCV+, identified treatment candidates who are waiting for treatment, and (C) HCV-, individuals who are not HCV infected, determined through screening or cleared infections by successful treatments or spontaneous viral clearance.

The large boxes in Figure 1 represent the three population groups and illustrate how people transition between groups. Screening could identify the individuals in group (A), and move them to group (B) or group (C) depending on whether they are tested HCV positive or negative. Also, HCV+ individuals could be successfully treated and become HCV-. However, individuals in group (C), HCV-, could be reinfected and rejoin group (A). Figure 1 also describes the natural history model within the boxes, which is a Markov model representing the health state and lifelong disease progression of chronic HCV patients with possible transitions occurring every three months. Combining the transitions between groups and the disease progression, a full Markov model (one for each age-cohort and gender) is developed, including transitions impacted by screening and treatment. The details of the model and parameters can be found in Li et al. (2016).

Using the Markov model, Li et al. (2016) calculated the number of people in each health state of each group. Li et al. (2016) evaluate each strategy by the total discounted health utility gain (QALYs),

$$\sum_t \sum_g \sum_i utility^i (A^i_{t,g} + B^i_{t,g} + C^i_{t,g}) \cdot (1-\delta_q)^{-t} \tag{1}$$

where t is the discrete time period in quarters (3 month period), g is gender, and i represents health state. The population groups $A^i_{t,g}$, $B^i_{t,g}$ and $C^i_{t,g}$ are the states of the Markov chain, and represent the number of individuals in the birth-cohort in gender g and health state i at time t. The $utility^i$ function maps the states at time t to a health utility gain, and δ_q is the discount factor for each quarter time period.

The decision variables include $S_{t,g}$ and $T^i_{t,g}$; where $S_{t,g}$ is the fraction of candidates in group A and gender g during time period t who are offered HCV screening tests, and $T^i_{t,g}$ is the fraction of patients in group B and gender g and health state i during time period t who are treated. The fraction of candidates is based on the budget allocation for each intervention and the implementation policy.

The progression of the disease in the Markov model, and how $A^i_{t,g}$, $B^i_{t,g}$ and $C^i_{t,g}$ are updated is based on Li et al. (2016). For group A, the number of individuals for each health state i on the next time period is based on the unscreened individuals from the last period and reinfected candidates from the last period.

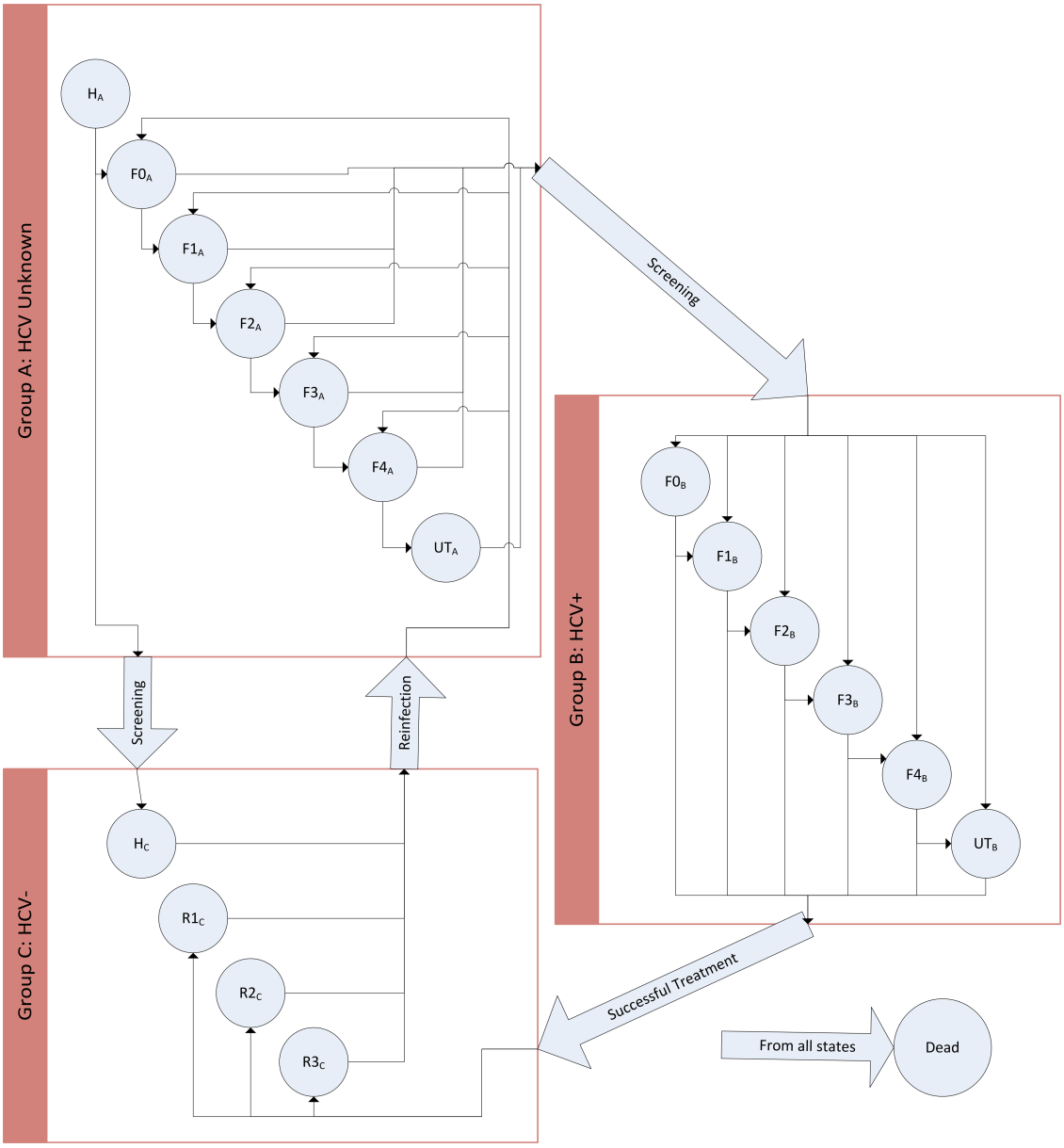

Figure 1: Hepatitis C Markov Model, combining three groups, (A) HCV status unknown, (B) HCV+ and (C) HCV-, and the natural history model. The natural history model has the following states: (H) Healthy, (F0) no fibrosis, (F1) portal fibrosis with no septa, (F2) portal fibrosis with few septa, (F3) numerous septa without cirrhosis, (F4) compensated cirrhosis, (UT) untreatable, (R1) recovered with history of mild fibrosis, (R2) recovered with history of moderate fibrosis, (R3) recovered with history of advanced fibrosis, and Dead state. (F0) and (F1) are considered mild fibrosis, (F2) and (F3) are moderate fibrosis, and (F4) is advanced fibrosis.

Specifically,

$$A^i_{t+1,g} = \sum_j \theta^{ji}_{g,waiting}(1-\alpha S_{t,g}\beta)A^j_{t,g} + C^i_{t,g}\gamma, \tag{2}$$

where $\theta^{ji}_{g,waiting}$ is the health states transition probability from health state i to j for untreated individuals. The coefficients, α and β, represents the proportion of cohort that goes to a healthcare provider and accept screening. The coefficient γ represents the proportion of cohort that may become reinfected. Similarly, the number of individuals in group B for the next time period is formed with new patients identified through screening, patients waiting for treatment, and patients with unsuccessful treatment. The function is described as follows,

$$B^i_{t+1,g} = \sum_j \theta^{ji}_{g,waiting}\alpha S_{t,g}\beta A^j_{t,g} + \sum_j \theta^{ji}_{g,waiting}(1-T_{t,g})B^j_{t,g} + \sum_j \theta^{ji}_{g,ongoing}T_{t,g}B^j_{t,g} \tag{3}$$

and $\theta^{ji}_{g,ongoing}$ is the transition probability from health state i to j for individuals undergoing treatment. The number of individuals in group C for the next time period is related to four sources: individuals screened with negative result, spontaneous viral clearance patients, successfully treated patients, and original C group individuals without reinfection. The equation is

$$C^i_{t+1,g} = \sum_j \theta^{ji}_{g,waiting}\alpha S_{t,g}\beta A^j_{t,g} + \sum_j \theta^{ji}_{g,waiting}(1-T_{t,g})B^j_{t,g} + \sum_j \theta^{ji}_{g,ongoing}T_{t,g}B^j_{t,g} + C^i_{t,g}(1-\gamma). \tag{4}$$

The model also includes a budget constraint with discounting, where $budget(\tau)$ represents the budget function for $\tau = 1,\ldots,10$, and each τ represents a one-year period. Specifically, the constraint is

$$\sum_{i,t\in Q_\tau,g} CS^i S_{t,g}A^i_{t,g}(1-\delta_q)^{-t} + \sum_{i,t\in Q_\tau,g} CT^i T^i_{t,g}B^i_{t,g}(1-\delta_q)^{-t} \le budget(\tau)(1-\delta)^{-\tau}, \tag{5}$$

where Q_τ is the quarter time periods in decision period τ and CS^i and CT^i are the costs for screening and treating individuals with health state i.

Solving this optimization problem is not trivial due to the large number of variables and their interactions in the dynamic equations. Therefore, we redefined the decision variables to be the percentages of annual budget used for screening in five decision periods, denoted as $x_1,\ldots,x_5 \in [0,1]$, where each decision period is two years. Given a two year budget, x_k, the associated screening and treatment strategies $S_{t,g}$ and $T^i_{t,g}$ are determined in the optimization model. The budget constraint in (5) is revised to allow disaggregation of the two-year budget into screening and treatment decisions quarterly, as follows

$$\sum_{i,t\in Q_\tau,g} CS^i S_{t,g}A^i_{t,g}(1-\delta_q)^{-t} \le x_k budget(\tau)(1-\delta)^{-\tau}, \tag{6}$$

$$\sum_{i,t\in Q_\tau,g} CT^i T^i_{t,g}B^i_{t,g}(1-\delta_q)^{-t} \le (1-x_k)budget(\tau)(1-\delta)^{-\tau}. \tag{7}$$

The formulation determines the number of individuals screened and treated based on the implementation policy, and uses all of the available budgets in each two-year decision period.

3 OPTIMIZATION OF THE HEPATITIS C MARKOV MODEL

We analyze strategy decisions for three age groups: 40 to 49, 50 to 59, and 60 to 69. Also, two budget scenarios are considered in this paper: a high budget scenario with 50 billion dollars for the ten-year period (Hb), and a low budget scenario with 10 billion dollars (Lb). The combination of age groups and budget scenarios makes six scenarios. The initial population of each age cohort is: 40 to 49, 43,599,555; 50 to 59, 41,962,930; 60 to 49, 29,253,187.

Table 1: Summarized Grid Search Results from Li et al. (2016).

Abbreviation	Cohort Age Group	Total Budget	Grid Search Budget Screening Ratio $[x_1, x_2, x_3, x_4, x_5]$	Total QALYs (discounted)
40-Hb	40-49	50 billion	[**0.6**, **0**, 0, 0, 0]	3,842,081,631
50-Hb	50-59	50 billion	[0, **0.2**, **0.2**, 0, 0]	3,186,339,442
60-Hb	60-69	50 billion	[0, **0.2**, 0, **0.2**, 0]	1,802,296,572
40-Lb	40-49	10 billion	[**0**, **0**, 0, 0, 0]	3,839,336,212
50-Lb	50-59	10 billion	[**0**, **0**, 0, 0, 0]	3,182,871,728
60-Lb	60-69	10 billion	[**0**, **0**, 0, 0, 0]	1,800,940,994

We first used grid search on each scenario to understand the major decision period impacts on the performance, measured by health utility gain in QALYs, and summarized in Table 1. The decisions $(x_1, \ldots, x_5)$ in Table 1 represent the percentage of budget allocated for screening in the five decision periods.

When the budget is low (10 billion), the entire budget is allocated to treatment and there is no screening. When the budget is high (50 billion), we observe that at most only two decision periods are suggested to have budget allocated for screening. In order to understand the sensitivity of total health utility gain to the proportion of budget allocated to screening, we apply the Probabilistic Branch and Bound (PBnB) algorithm (Huang and Zabinsky 2013, Huang and Zabinsky 2016) to approximate the set of the top 10% solutions, called the level set. The shape of the level set indicates the sensitivity of each decision period, similar to performing a sensitivity analysis. Also, the decision makers are able to understand the trade-offs for selecting a non-optimal but good enough solution because some considerations are not easily quantifiable to be included into the model.

PBnB (Huang and Zabinsky 2013, Huang and Zabinsky 2016) is a partition based algorithm that uses branched subregions to approximate a target level set, where a level set is a set of solutions associated with a quantile, e.g., 10% quantile performs better than 90% of the solutions in the domain. PBnB is defined with three input parameters, δ, ε and α, where δ (e.g., 10%) represents the desired δ-quantile and associated level set, ε is the tolerance on the volume of incorrectly approximated solutions, and α is used for defining the probability bounds for the quality of approximated level set in terms of $1-\alpha$.

Two types of results are provided by PBnB. The first result is an approximation of the δ level set formed by maintained subregions $\widetilde{\Sigma}^M$ that are statistically confident in the level set, and bounded by $\widetilde{\Sigma}^C$, undecided subregions. The pruned region, $\widetilde{\Sigma}^P$, are outside the level set with $(1-\alpha)$ statistical confidence. Second, an interval estimate of the quantile (upper and lower bounds) is provided for decision makers on the performance of the level set. For analyzing the HCV screening and treatment strategies, we use $\delta = 0.1$, $\varepsilon = 0.025$, and $\alpha = 0.25$.

The shape of a five dimensional level set produced from PBnB is difficult to visualize. So we identified two dominant decision periods for each scenario, indicated in bold in Table 1. For the 40-Hb scenario, the first two decision periods x_1, x_2 are considered to have dominant impact and are selected as the major decision periods and x_3, x_4 and x_5 are set to zero. For the 50-Hb scenario, x_2 and x_3 are considered dominant, and for the 60-Hb scenario, x_2 and x_4 are dominant and the rest of the decision periods are set to zero. Similarly, 40-Lb, 50-Lb and 60-Lb scenarios also use x_1, x_2 as the major decision periods and set x_3, x_4 and x_5 to zero. We perform a PBnB search on all five decision periods to confirm the time periods with screening budget allocation. For instance, the PBnB five dimensional search result is $[0.4632, 0.5242, 0.0041, 0.0002, 0.0005]$ for the scenario 40-Hb representing the 40-49 age group with a high budget of 50 billion dollars. The search result shows that the algorithm finds low values on time periods 3, 4, and 5, but is not able to reach zero since the algorithm samples uniformly between 0 to 1.

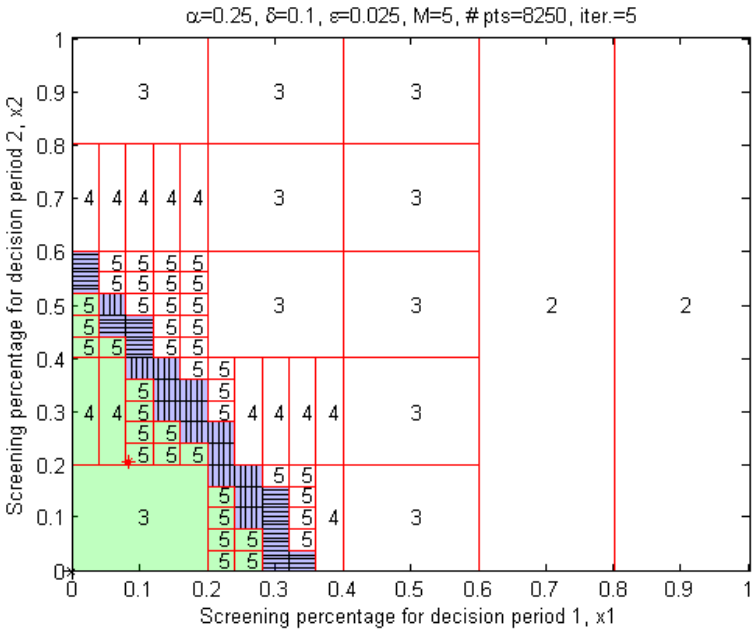

Figure 2: Approximated 0.1 Level Set for Scenario 40-Lb with $x_3, x_4, x_5 = 0$. The grid search solution (black star) is (0, 0), and the PBnB approximated best strategy (red star) is (0.08, 0.21).

4 RESULTS

The PBnB numerical results for the six scenarios are presented in Figures 2-7. The light gray (green) boxes are the maintained subregions and the dark gray (blue) boxes represent the undecided subregions. The white boxes are the pruned subregions. The numbers in the boxes indicate the iteration of the algorithm running when the subregion is pruned or maintained. The black star is the grid search solution and the red star is the PBnB approximated best strategy. We optimized all six scenarios with a PBnB level set analysis and observed four several patterns of level set within these six scenarios.

The shape of the level sets for the low budget scenarios, 40-Lb, 50-Lb, and 60-Lb in Figures 2, 3, and 4, is triangular, indicating that it is possible to allocate some budget screening in early years (x_1, x_2) without degrading the health utility gain too much. The shape of the level set in Figure 2 shows that x_1 is more sensitive than x_2, ranging up to 0.3 inside the level set, whereas x_2 ranges up to 0.5. The interval estimation of the 10% quantile is [3,839,318,552, 3,839,320,071]. The theory analysis of PBnB ensures that points in the level set have a health utility gain better than 3,839,318,552 QALYs with $1 - \alpha$ confidence. Hence, the solutions in the approximated 10% level set of scenario 40-10b perform at least 3,839,318,552 QALYs, and the difference between the best grid search performance, 3,839,336,212, and the lower bound is 17,660 QALYs, which is 0.00045% of the optimal strategy performance.

For scenarios 50-Lb and 60-Lb, the lower bounds on the 10% quantile are 3,182,760,942 and 1,800,895,621. The triangular patterns are similar to scenario 40-Lb, as shown in Figures 3 and 4, however the range of x_1 goes up to 0.4 as opposed to 0.3 for 40-Lb. Also, their differences between the grid search optimal strategy, 3,182,871,728 and 1,800,940,994, and the 10% quantile lower bounds, are 110,786 and 45,373 respectively, that are 0.0034% and 0.0025% of their optimal strategy performance.

Figure 5 shows the PBnB results for scenario 40-Hb, where the two decision variables are x_1 and x_2, while setting $x_3, x_4, x_5 = 0$. The maintained region in Figure 5 indicates that x_1 can ranges between 0.4 to 0.85, which means x_1 is not very sensitive if we set x_2 close to zero. Also, $0 < x_2 < 0.12$ is also a viable choice when x_1 is close to 0.45. Some part of the approximated level set appears as a vertical undecided region when x_1 is close to 0.5. This may be due to the difficulty that PBnB has in correctly determining the

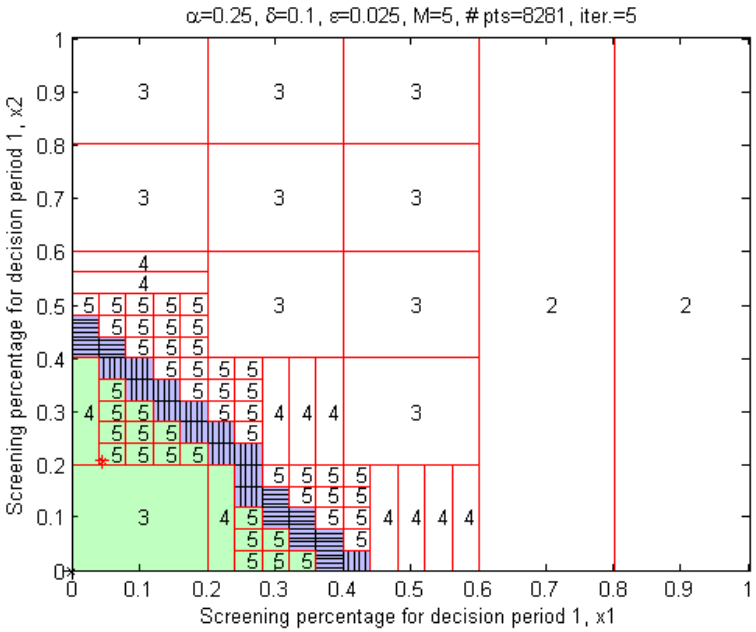

Figure 3: Approximated 0.1 Level Set for Scenario 50-Lb with $x_3, x_4, x_5 = 0$ The grid search solution (black star) is (0, 0), and the PBnB approximated best strategy (red star) is (0.04, 0.21).

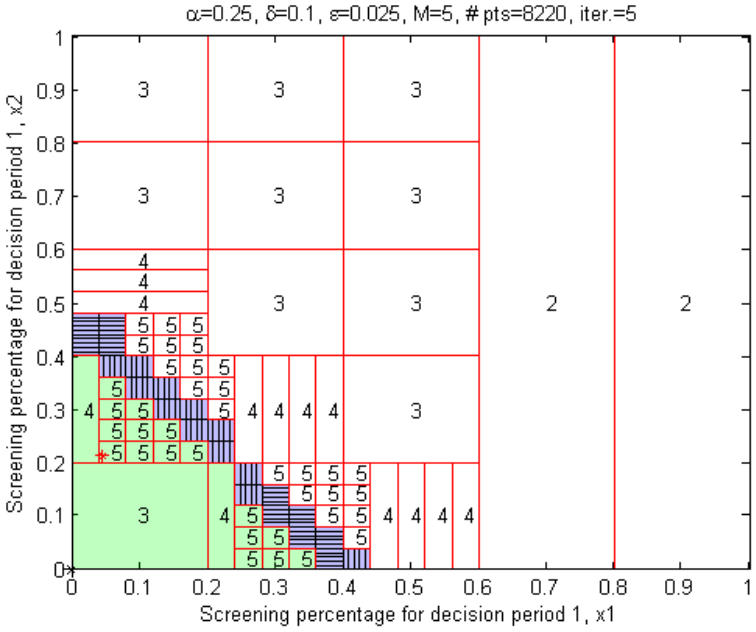

Figure 4: Approximated 0.1 Level Set for Scenario 60-Lb with $x_3, x_4, x_5 = 0$ The grid search solution (black star) is (0, 0), and the PBnB approximated best strategy (red star) is (0.04, 0.21).

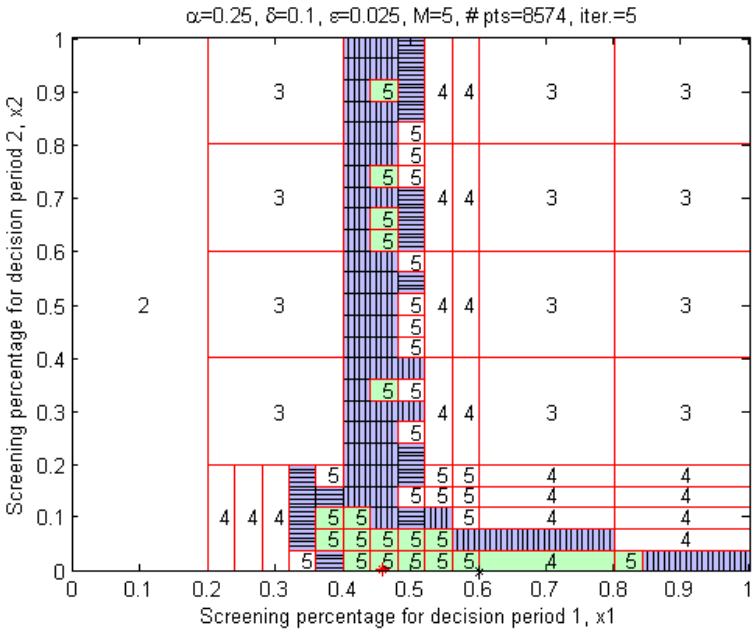

Figure 5: Approximated 0.1 Level Set for Scenario 40-Hb with $x_3, x_4, x_5 = 0$. The grid search solution (black star) is (0.6, 0), and the PBnB approximated best strategy (red star) is (0.45, 0.004).

level set in this scenario, because 40-Hb is a relatively young cohort where the health utility gain difference between different screening budget settings is small.

The algorithm also provides an interval estimation on the 10% quantile as [3,842,041,405, 3,842,041,540], indicating that the strategies in the maintained boxes statistically have at least 3,842,041,405 QALYs gain with $1-\alpha$ confidence. Comparing to the PBnB approximated best strategy with 3,842,081,631 QALYs gain, choosing one in the level set may have 40,226 less QALYs (about 0.0014% of the best strategy performance). However, it could still be a good enough strategy while considering some other preferences that are not easily quantified and modeled.

The 50-Hb scenario has different major decision periods, x_2 and x_3, and the pattern of the level set is shown in Figure 6. The pattern of the 50-Hb scenario is a heavily stretched shape with a more flexible combination of x_2 and x_3. Figure 6 shows that x_2 and x_3 have a strong correlation to sum up to about 0.4. The performance of the maintained strategies is bounded by the 10% quantile lower bound, 3,186,265,607, where the PBnB approximated optimal strategy is 3,186,349,671. The difference between 10% quantile lower bound and the PBnB approximated optimal is 84,064 QALYs, which is 0.0026% of the best strategy performance and slightly greater than scenario 40-Hb. It may indicate the 50-Hb scenario is more sensitive to the screening and treatment budget allocation since the older cohort may have more immediate treatment requirements.

Figure 7 shows the level set for scenario 60-Hb, with a similar pattern as that for the scenario 50-Hb but with different major decision periods x_2 and x_4 instead of x_2 and x_3 for 50-Hb. The relationship between x_2 and x_4 in scenario 60-Hb has a steeper slope compared to 50-Hb, which shows that x_2 has a stronger impact in the 60-69 cohort. The health utility gain of the 60-Hb maintained strategies is bounded by 1,802,259,934, where the PBnB approximated optimal is 1,802,298,104 and the difference is 0.0021% of the best strategy performance.

In the lower budget scenarios, we observe that grid search solution of (0, 0) is better than the PBnB approximated solution for two reasons. First, the box including (0, 0) is maintained in an early iteration of PBnB. Once a box is maintained, the algorithm does not continue to sample there refining the optimal

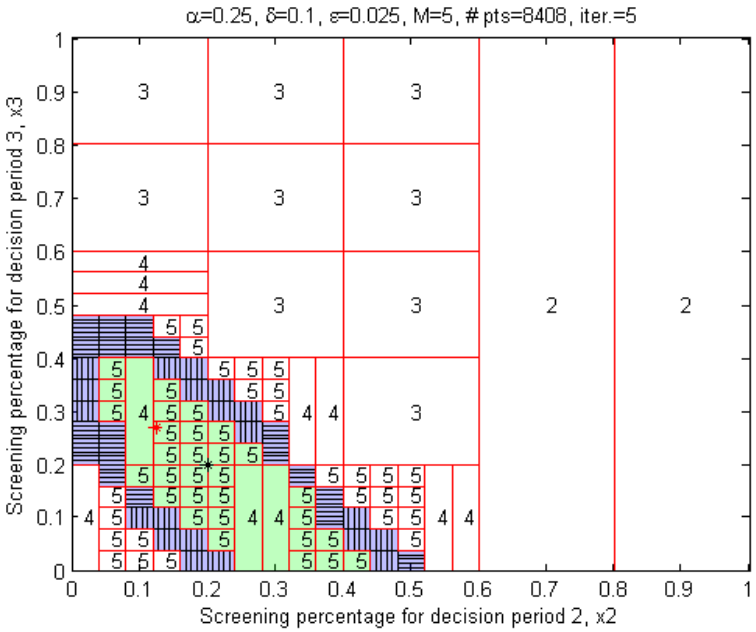

Figure 6: Approximated 0.1 Level Set for Scenario 50-Hb with $x_1, x_4, x_5 = 0$. The grid search solution (black star) is (0.2, 0.2), and the PBnB approximated best strategy (red star) is (0.12, 0.27).

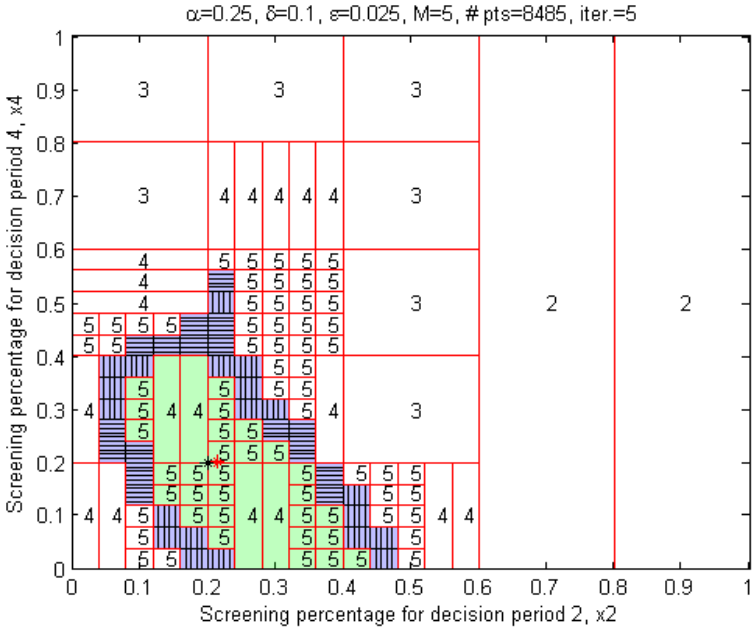

Figure 7: Approximated 0.1 Level Set for Scenario 60-Hb with $x_1, x_3, x_5 = 0$. The grid search solution (black star) is (0.2, 0.2), and the PBnB approximated best strategy (red star) is (0.22, 0.20).

solution. The second reason is that PBnB performs uniform sampling in the box, and there is practically impossible to hit (0, 0). For the high budget scenarios, the grid search optimum is not at (0, 0), and hence, PBnB is able to find a better solution than the grid search.

5 CONCLUSION

This study incorporates a simulation optimization algorithm, PBnB that approximates a target level set, to analyze the screening and treatment budget allocation strategies for chronic hepatitis C. With PBnB, we are able to perform further analysis by approximating a level set. We first identify two major decision periods for each scenario through a grid search on five decision periods. By focusing on two major decision periods, a visualization of the approximated level set for each scenario is provided. Using the level set, we analyze the relationship between the two major decision periods and provide information for decision makers on the sensitivity of the decisions. We also provide the impact of the implementation policy on population health outcomes and the trade-offs between screening and treatment efforts to eliminate a major disease in the U.S. healthcare systems.

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