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1. Introduction

1.1. Why we should POMDPs with FEP for Adaptive cancer therapy

1.1.1. What is the adapative cancer therapy

1.1.2. desired qualities of models

1.1.3. How do POMDPs meet these requirements

2. Methods

2.1. Simulation details

2.1.1. Enviroment

The simulated enviroment features discretized of planning cancer treatments. At each timestep a "cancer state" has a certain risk of increasing. If the tumor ever reaches the state 5, the simulation ends. To avoid this, a model has decide when to apply treatment. Applying treatment can reduce the tumor level - whether the treatment succesfully reduces the "cancer state" depends on a underlying *resistance state*. When the resistance is low, the chance of treatment succeeding is high, but probability declines as the resistance state increase. The resistance state has fixed probability of increasing when treatment is applied, and it can decrease when treatment is withdrawn. Whether the resistance state decreases depends on the tumor level. At high tumor levels, the resistance state is more likely to decrease, but thiscarries the risk of tumor growing out of control and "killing the patient". In order to succesfully manage the disease, a model will therefore also have to manage the resistance state. However, the resistance state is directly orbserable in the given simulation. It must therefore be inferred from how the tumor state responds to treatment.

2.1.2. Sim Runs:

Both the resistance state, and tumor states start at state 0 out of 5, meaning that a total is six states are possible in each. In both simulations, POMDPs transition matricies perfectly reflect the transition probabilties of the enviorment. Two slightly different simulations are used:

- Performance simulation, where a range-bounded approach to managing the tumor is used, where the treatment is begun each time the tumor state increases above level 3, and is withdrawn when the tumor state drops below 2. 100 runs at 4 different probabilities of increasing the tumor state is run for maximally 200 timesteps. For each run, vectors of outcomes are pregenerated, meaning that vector of whether the tumor increases of length 200 is predetermined where each entry has the probability specified for the entire simulation. Likewise vectors are generated for treatment outcomes at each resistance level, and outcomes for resistance drops. This is done to ensure comparibility between the range-bounded approach and POMDP models that consider different future outcomes at different lengths. In these runs the tumor state is perfectly observable, meaning a tumor state always generates tumor observation that corresponds to hidden factor. The POMPD can only observe the tumor level, and its prior preferences are uniform over all tumor states except for the highest. These POMPDS only consider a combination of policies at each timestep. They can only consider treating or not treating for three timesteps in a row. The shortest horizon model only considers one of these blocks, while the medium considers two blocks of treating or not treating, for total horizon of 6 steps into the future. The longest horizon model considers three blocks for a total of 9 steps into the future. This is done to ease the computational burden, since it greatly reduces the total number of policies to be evaluated.
- In the capacities simulation, a single run of a POMDP with a slightly different model structure is used. This model can observes a perfect signal of whether the patients is alive, whether the model is testing, treating and a noised signal of the tumor state if the model has decided to test the patient on the given run. Its prior preferences are heavily skewed against observing a dead patient, somewhat against treating and

little against treating. This means that it will have to balance the "cost" of all these actions". It is also handicapped further by the fact that the tumor signal is noised, and the resistance state, which must be inferred through the tumor signal is therefore doubly obfuscated. The likelihood mapping between however perfectly captures the maps the expected noise.

2.1.3. Changes to POMDP specification.

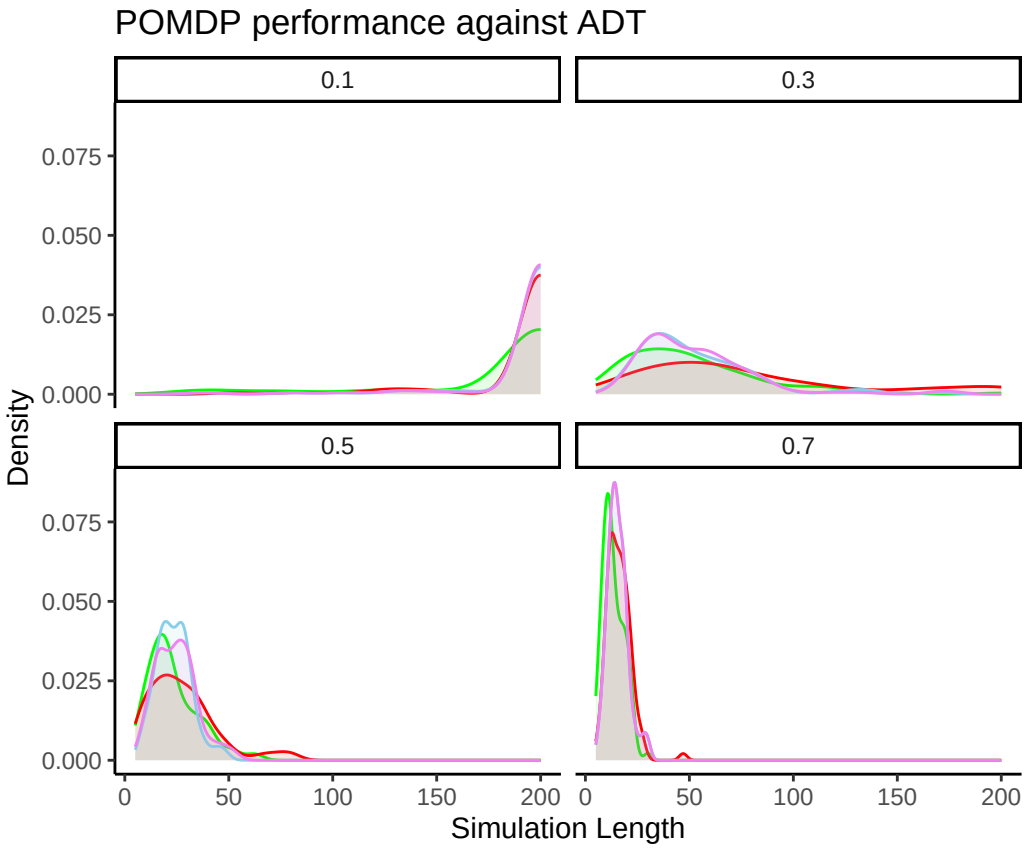
Hidden state factors do typically not affect each other at the state level. Instead their interactions are typically modelled as resulting from observations. This setup was deemed inadequate for the current experiment. It necessitated the that generative model could accurately model how the resistance state factor influences the probability of treatment succeeding. This was done in order to accurately portray issue of resistance levels generally being in accessible to current testing methodology and the evolutionary dynamics that are suspected to be at play in reducing resistance in real-world tumors.

Accurately modelling how higher tumor levels makes decreases in resistance more likely was also crucial. Typically, transition probabilties in the generative models are constructed using three dimensional "B-tensors", which describe expected transition probabilties within a state factor: one dimension the current state, one dimension for what ever action is chosen and third for the resulting state.

For the present project another dimension was added, this dimension corresponds to the state of another state factor. Concretely, this meant that the tumor state factor had fourth dimension. By matrix multiplication the expectation over this fourth dimension is factored in. One could choose to view it as there are now as many three dimensional b-tensors for the tumor state factor as there are states in the resistance factor. Effectively, matrix multiplying these result in a probability weighted average of expected tumor transition probabilities, i.e. the expectation. However, it should be noted that it is not trivial the order in which states are evaluated and that this must be specified. This also resulted in much pymdp functionality breaking, since it was presumably built only with three dimensional b-tensors in mind.

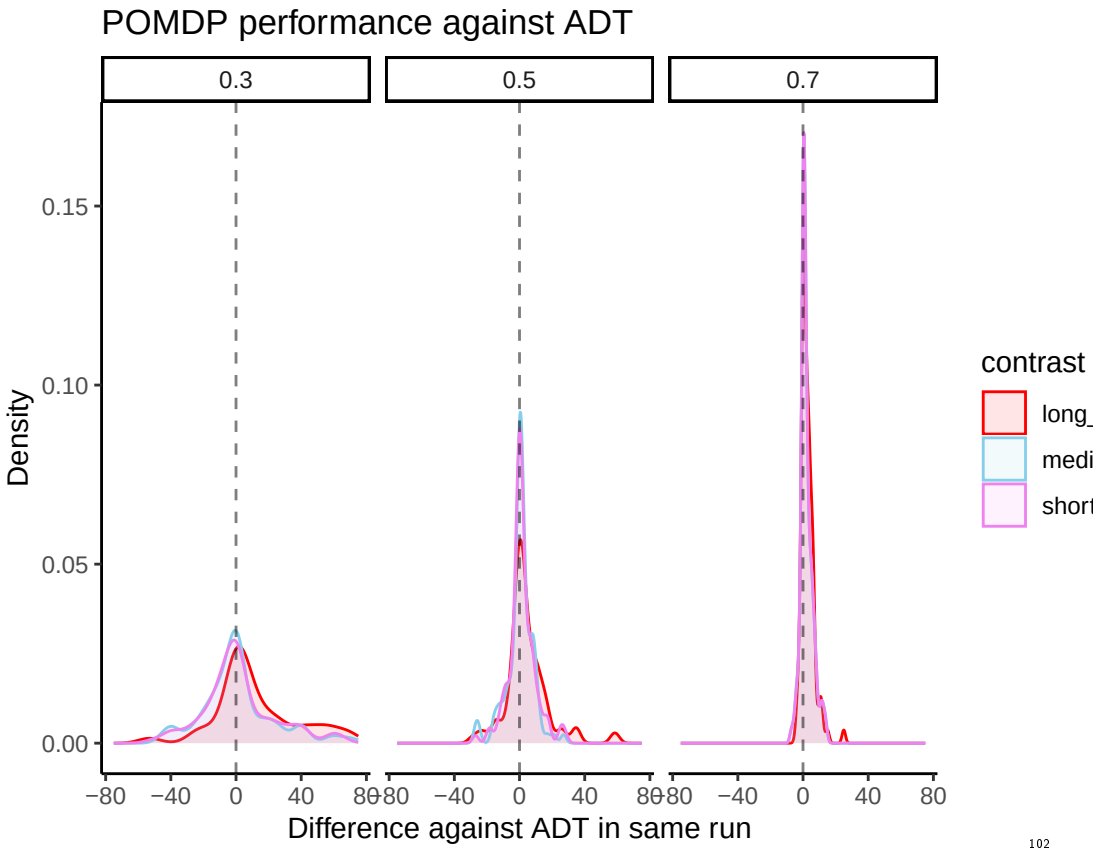
3. Results

3.1. Performance of POMDPs vs ADT heuristic

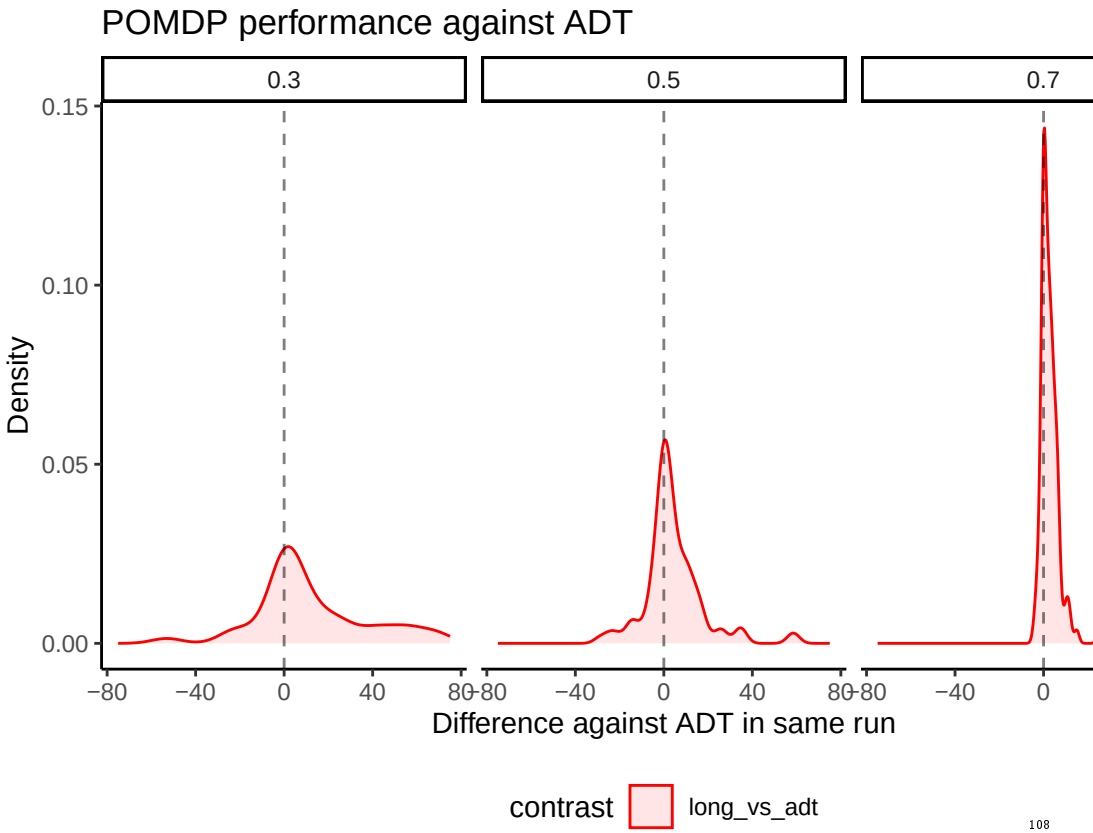


Four different simulation runs each consisting of 100 runs, of maximally 200 timesteps for different rates of tumor growth (respectively 1. .3, .5, and .7 probability of increasing the tumor state) . On each run the the outcomes on each of the potential 200 random variables are generated and each strategy is therefore tested on a the same enviroment. On the lowest tumor growth rate almost all the runs reach maximal length.

Contrasts against ADT-performance for growth rate .3, .5 and .7 are plotted. .1 is omitted since it appears that maximal perforamnce was achieved for each policy horizon of the POMPD strategies.



Two interpretations emerge from the contrasted simulation lengths. As the the growth rate increases, the POMDP seems to run for longer than the specific instance of the range bounded approach. It also seems that longer policy horizon seems beneficial. When the tumor state had .7 probability of increasing each timestep, the longest POMPD with the longest policy horizon performed as follows.

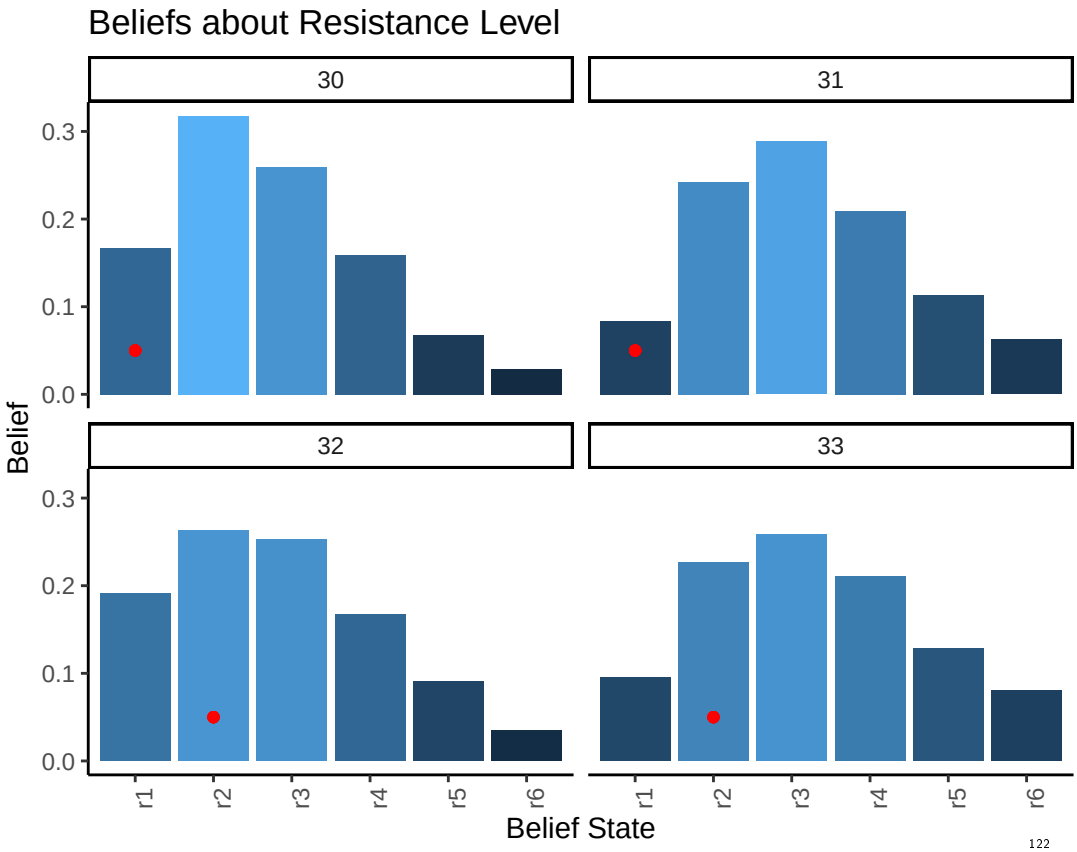


At more aggressive cancer rates, the simulation consistently to outperform the range bounded approach. The absoulute increase in timesteps decreases however.

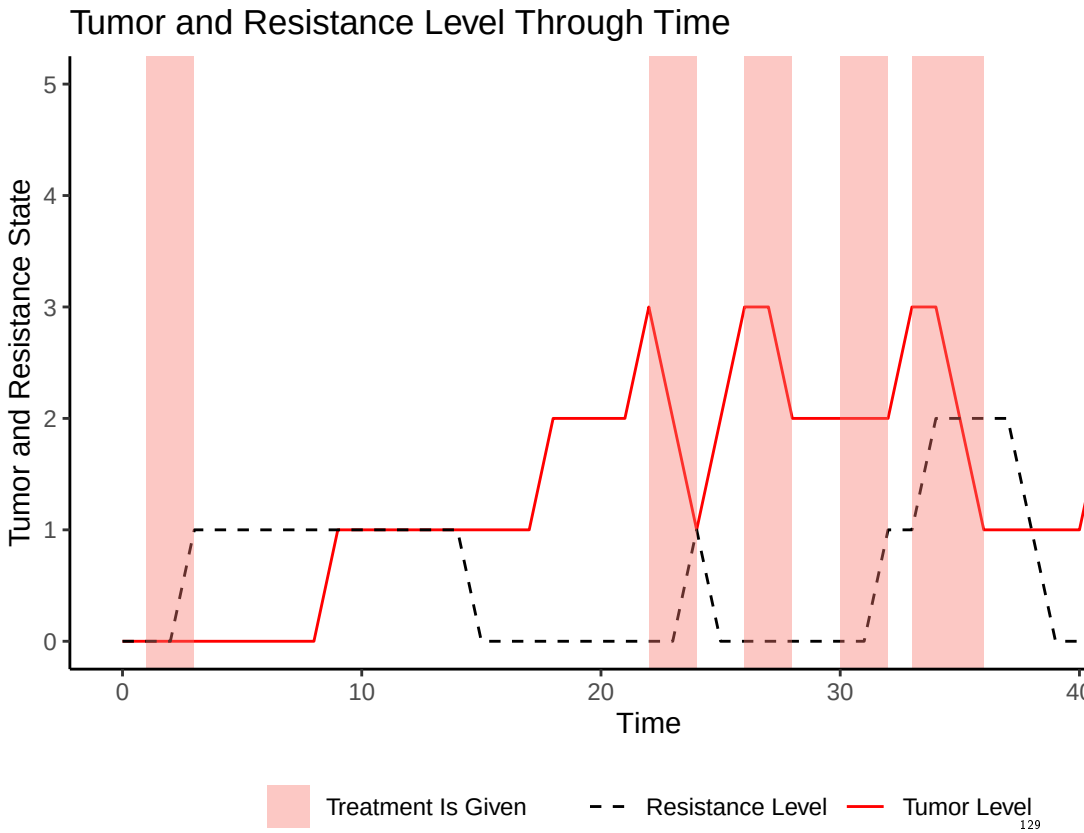
3.2. Capabilities

3.2.1. Learning underlying hidden state

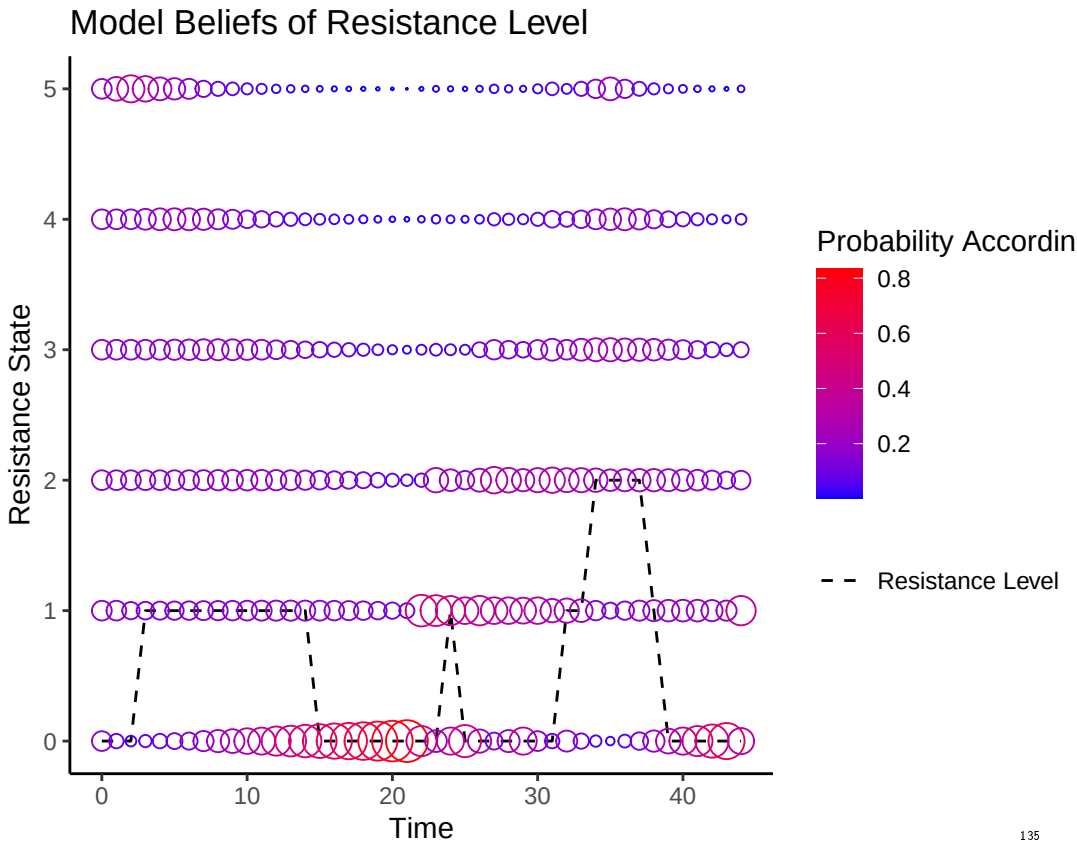
The POMDP structure is capable of inferring an underlying hidden state: the resistance state. Even though this not directly observable, this can be inferred to how the tumor state responds to treatment. Applying treatment for longer time without any beneficial effect would suggest that the resistance level is high, while immediately observing that the tumor level decreases would suggest that the resistance level is low. At each timestep the POMDPs perform infer the most likely state of every state factor, given their current observation and prior beliefs. Through custom changes to the 'get_expected_states' function in PYMDP that allowed the models to consider how one hidden state factor (resistance factor) would influence another (the tumor factor).



The above plot shows the strength of beliefs in t probabilities for a subset of timesteps [30 - 34], and the red dot show the actual the resistance levels. A time progresses the resistance level increases, and the model adjusts its beliefs. While the tumor level doesn't increase durings this time_period, this would also signal the model that the resistance level is low. This is the case since the enviroment always has change of increasing the tumor state, but such an increase would be negated by succesful round of treatment.



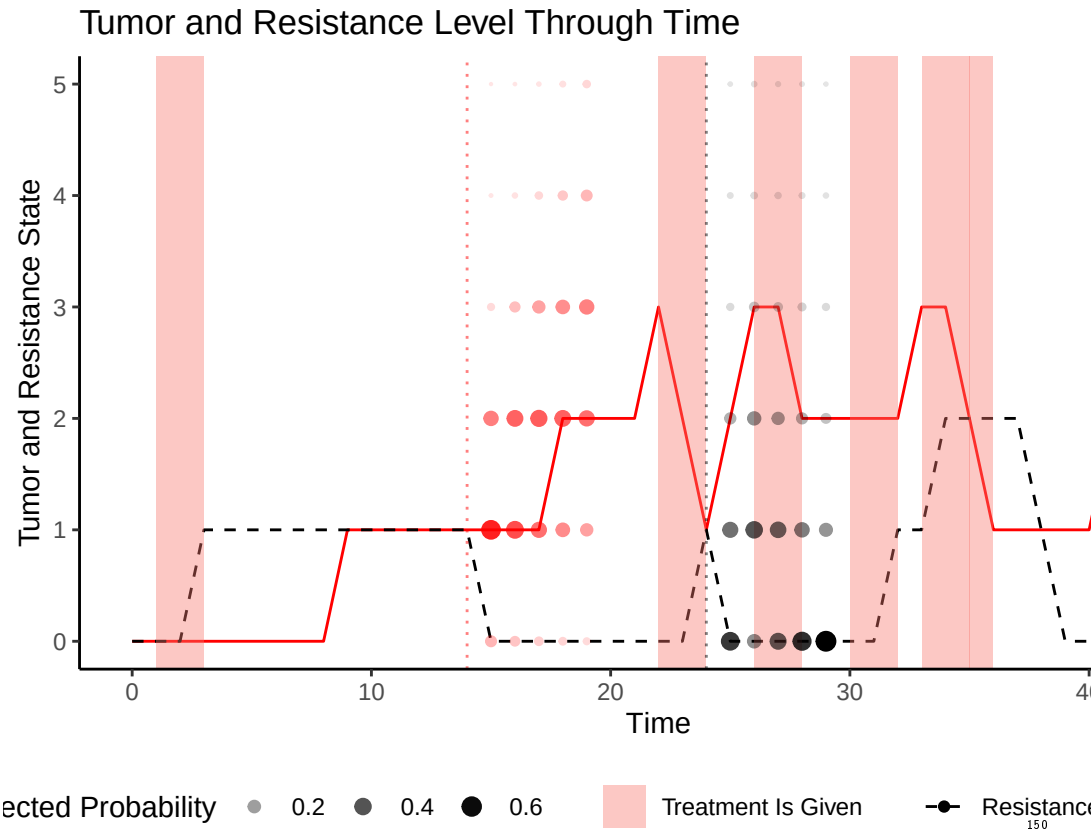
The entire run is plotted for the given. Only the tumor level is observable to the POMDP. It must combine its knowledge about how resistance level likely increases after applying treatment, and how the tumor level responds to treatment depenping on the the resistance level. While the model far from perfectly knows the resistance level. Model beliefs for the entire run is plotted.



The model begins fairly agnostic. Given that the model was initialized with a uniform prior over resistance states this makes sense. Thorought out the course of the simulation it then finds loweer values of resistance state more likely.

3.2.2. Beliefs, current/future and uncertainty is accessible

This current simulated model used a slightly different implementation than those compared to performance of rangebounded therapy planning. While the those models had longer policy horizons, they didn't consider the entire space possible actions. A model with a shorter policy horizon that would instead search every single possible action four steps is plotted to investigate the structure of decision-making by the POMDP model. The enviroment was also more unceartain. Instead of featuring a 1-to-1 mapping of the observations of the tumor to actual tumor state, it recieved a noised signal. It must therefore. The beliefs about how tumor state will evolve as a consequence of the most promising policy at time step 14 is plotted, and the expectation of resistance states at t=24 is plotted too.



Dotted vertical lines indicated the time-point for which the evaluation of expected states are extracted.

4. Discussion

4.1. Does it work for other sorts of medical planning

4.2. FEP components can besued to balance testing and treating

4.3. Would longer policy search be better

4.4. Only one range bound

4.5. Future Research

4.5.1. Continuous state space or binning illness

4.5.2. Learning the transition parameters

4.5.3. searching policy space better

4.5.4. other fep models

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/1010000/s1, Figure S1: title; Table S1: title; Video S1: title.

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Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals
TLA	Three letter acronym
LD	linear dichroism

Appendix E

Appendix E.1

The appendix is an optional section that can contain details and data supplemental to the main text. For example, explanations of experimental details that would disrupt the flow of the main text, but nonetheless remain crucial to understanding and reproducing the research shown; figures of replicates for experiments of which representative data is shown in the main text can be added here if brief, or as Supplementary data. Mathematical proofs of results not central to the paper can be added as an appendix.

Appendix F

All appendix sections must be cited in the main text. In the appendixes, Figures, Tables, etc. should be labeled starting with 'A', e.g., Figure A1, Figure A2, etc.