Inferring Treatment Resistance Actively: Modifying Partially Observable Markov Decision Processes for Adaptive Therapy

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Abstract

Contents

Introduction

A Primer on Adaptive Therapy

Worldwide, cancer is the cause of 1 out of 6 deaths. An estimated 90% of these cancer deaths are due to the development of drug resistance (Bukowski, Kciuk, and Kontek 2020). While initial cancer treatment usually shows a positive response in tumor burden, drug resistance develops over time. To highlight the inefficiency of traditional approaches, (Staňková et al. 2019) models cancer treatment as a game-theoretic contest between a physician and a tumor. In this model, the physician's move in each round is to apply a certain treatment to which the cancer adapts. While the game is asymmetrical—one player is the leader (the physician) and another player is a follower (the tumor)—the asymmetry is rarely exploited in oncology wards. Instead of using the advantage to steer the evolutionary pressures placed on tumors, tumors can adapt not only to the current round of the game but also to future rounds under standard care. Thus, the advantage of leading the game is lost. The authors analogize the current practice to a game of rock-paper-scissors:

> *" in which almost all cells within the cancer play, for example, "paper." It is clearly advantageous for the treating physician to play "scissors." Yet, if the physician only plays "scissors," the cancer cells can evolve to the unbeatable resistance strategy of "rock."*" (Staňková et al. 2019).

To exploit this asymmetry *Adaptive Therapy* (AT) controls intra-tumoral evolutionary dynamics by leveraging that cancer cells likely incur fitness costs when evolving mechanisms of drug resistance (Gatenby et al. 2009). If resistant and non-resistant cells are competing for space and resources, drug-sensitive cells should, over time, out-compete resistant cells. AT thereby utilizes Darwinian competition to make cancer suppress itself, a strategy that potentially could reduce cancer to a chronic but controllable disease.

Initial results from an ongoing pilot clinical trial applying AT in a group of *metastatic castrate-resistant prostate cancer* (mCRPC) patients are promising, showing both lower cumulative dosages and longer survival times compared to a similar group of patients receiving standard care. The trial utilizes a range-bounded heuristic to make treatment decisions: if the blood marker *Prostate-specific Antigen* (PSA), a proxy for tumor burden increases back to pre-trial levels, Abiraterone treatment is applied until PSA drops to 50% of pre-trial levels (Zhang et al. 2017).

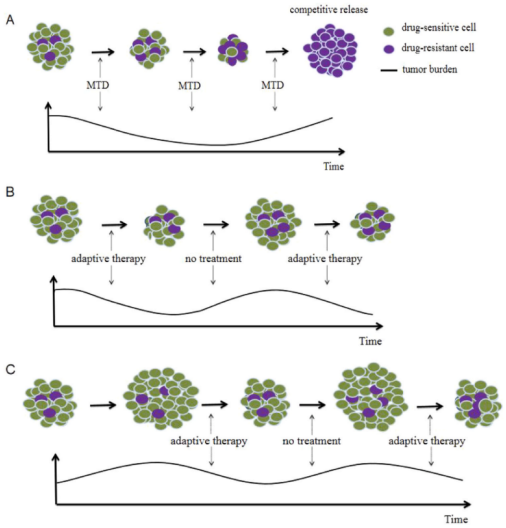


Figure 1: From Zhang et al. 2023. Panel A shows a typical "Maximal Tolerable Dose" treatment protocol. While the initial response in tumor burden is promising, a competitive release of resistant cells ensures. Panel B shows an AT approach with a small tumor burden. Panel C shows AT with a high tumor burden, which has been theorized to further increase the suppression of resistant cells.

POMPDs

Partially Observable Markov Decision Processes (POMDPs) is a class of controller models that model a Markov process —an environment that moves through discrete time steps and states, each step of the system only depends on the configuration of states in the prior time step. Partial observability refers to the fact that these models don't directly observe the actual environment but instead observe signals emitted by the environment (Åström 1969). This allows POMPDs to differentiate an observed signal from what it "believes" about the actual configuration of states and additionally to use a single reward function to trade off uncertainty to reach a certain goal state (Kaelbling, Littman, and Cassandra 1998).

Solving POMPDs with Active Inference

While POMDPs are typically difficult to solve analytically, various approximations exist. One approximation scheme is born out of the neuroscience paradigm *Active Inference* (AI) where POMPDs are typically used to model an agent's decision-making. AI POMPDs have been used to model psychopathology (Da Costa et al. 2020) but also applied to control scenarios such as the mountain car problem (Friston, Daunizeau, and Kiebel 2009) and, albeit augmented with deep learning, robotics control (Çatal et al. 2020). The approximation finds a solution by minimizing two objective functions:

- *Variational Free Energy* (VFE). A measure of fit between a generative model and sensory input.
- *Expected Free Energy* (EFE). A score of how well a course of action is expected to bring about a set of preferences penalized for expected uncertainty.

AI implementations of the POMDP scheme have been implemented in MATLAB and recently in Python with the Python package *pymdp* Heins et al. (2022a). AI POMDPs are technically a joint probability:

$$p(o, s, u; \phi)$$

where o are observations, s are hidden states to be inferred, u are actions that an agent can take to influence the environment, and ϕ are the hyperparameters of the mode. By conditioning on certain observations, the POMDP is solvable for Bayes-optimal posterior beliefs at a given time point given a specified generative model – the model an agent uses to generate predictions about future observations, states and actions. This yields a set of posterior beliefs about the current state of each *state factor* - the types of possible states in the environment -* a posterior probability distributions over what *policies*, possible courses of actions are most likely to achieve specified preferences while keeping expected uncertainty as low as possible. As an example, a POMDP could model the joint probability of observing a noisy signal of a particular tumor burden in a patient, an actual underlying tumor burden, and the course of action that is most likely to bring the tumor burden down. By modeling, actions, states, and observations as discrete events, the joint probability can be factorized into multiple categorical probability distributions. These distributions describe likelihood mappings between signals and specific states of the environment, transition probabilities of each state factor, and a desired probability of making certain observations

(Smith, Friston, and Whyte 2022). [1]

Aim of this Paper

The treatment decisions used in the pilot trial reported by Zhang et al. (2017) were based on a well-informed heuristic about how resistance dynamics would develop as a consequence of careful timing of applying and

[1]The Python package pymdp (Heins et al. 2022b) has numerous tutorial notebooks for implementing POMPDs in Python. Smith, Friston, and Whyte (2022) describes the process of constructing POMPDs for different scenarios in detail, albeit in MATLAB, and Da Costa et al. (2020) provides an in-depth mathematical account of POMPDs in Active inference.

withdrawing Abiraterone treatment. However, the actual resistance dynamics of each patient weren't explicitly modeled in real-time, and thus not used in treatment decisions. This paper primarily investigates whether the AI implementation of POMDPs can model and control the degree of treatment resistance of individual cancer patients in real-time — hoping that this strategy can eventually be applied in a clinical setting.

Analysis

Simulated environment

To investigate the appropriateness of the AI implementation of the POMDP scheme, multiple simulations of a clinical setting inspired by the pilot clinical trial were run. To comply with the canonical AI POMPD scheme discrete states and and time steps were used. Each simulation run simulated maximally of 200 time-steps. At each time-step, an agent had to keep a virtual cancer patient alive by deciding whether to apply a treatment based on a signal of the tumor burden. The signal could be observed at each time point, and treatment decisions were made by solving a slightly modified AI POMPD. The features of the environment were inspired by the use of PSA testing and Abiraterone treatment in the pilot trial (Zhang et al. 2017). In the simulations, the patient's *tumor state factor* determined whether they survived to the next time-step. If the tumor state factor reached the maximal state of six possible states, the virtual patient "died" and the simulation ended. The tumor state factor was always set to the lowest at the beginning of each simulation run and could increase at a fixed risk at each time step.

Whether a round of treatment successfully reduced the tumor state depended on an underlying *resistance state factor*. This also began at state 0 out of 5. For each round of treatment application, the resistance state had a fixed risk of increasing. The only remedy to the increasing resistance states, beyond favorable bouts of stochasticity, was to withdraw treatment which would allow the resistance state factor to lower. Inspired by the work of (Hansen and Read 2020), if the patient is in higher tumor states the chance of lowering resistance states was increased. ## Modifications to the POMDP Scheme

Typically when constructing AI POMDPs, different state factors (i.e i.e.es of states) such as the resistance factor and tumor factors are not modeled to affect each other directly. Instead, the interactions resulting

from particular configurations of states across state types are modeled as leading to different observations. This means that interactions between types of states would be coded in the likelihood distribution.

This setup was deemed incompatible with the environment that the agents had to model since it wouldn't let agents infer how changes in resistance state factor should influence the expected transition probabilities of the tumor state factor. Therefore, custom changes were made to pymdp to allow POMPDs to infer "occluded" state factors - state factors that don't produce signals themselves (e.g. the resistance state). The state of the occluded state factor instead needed to be inferred, through its effects on downstream state factors that generate signals (e.g. the tumor state).

Specifically, modifications were made to the structure of the agent's beliefs about the environment's transition probabilities Usually, three-dimensional *tensors* describe expected transition probabilities within a state factor. This means a tensor for a type of state typically holds one dimension for the current state, one dimension for the next state, and a third dimension for every allowed action. Each cell of the tensor then contains the probability of transitioning from one state to another state conditional on a certain action. Another dimension was added to relevant tensors. This dimension corresponded to another state factor. Concretely, this means that the tensor for tumor transition probabilities had a fourth dimension corresponding to the possible resistance states. The expected transition probabilities could then be estimated by matrix multiplying the tumor transition tensor with a vector containing expected probabilities of each resistance state at a given time point. One can imagine that instead of having only one tensor for the transition probabilities between tumor states, multiple tensors of tumor transition probabilities were specified, where each tensor corresponded to a specific resistance level. This modification to the generative model necessitated taking an average of across these tensors weighted by the posterior probabilities for each resistance state at a given time point. This amounts to calculating the expected transition probabilities between tumor states conditional on a set of beliefs about the resistance states. This modification strategy was repeated for the resistance level since decreases in the resistance state depended on the tumor state. It should be noted that this modification means that the order in which beliefs about states are evaluated must be specified. While these changes rendered much of the functionality of pymdp immediately unusable, the modification strategy should be able to model arbitrarily complex dependencies between states.

Exploratory Simulation

An exploratory simulation was conducted, where for each run an agent instantiated as a modified POMPD controlled whether to treat and test. It received the following signals:

- A noiseless signal of whether the patient was alive.
- A noiseless signal of whether it was applying tests.
- A noiseless signal of whether it was applying treatment.
- If testing was applied at the time step, the agent received a noised signal of the tumor state factor.

The agent's prior preferences were heavily skewed against observing a dead patient, somewhat against observing treating, and slightly against observing testing. This was done to simulate the cost of both treating and testing. This means that the agent had to balance the cost of its actions while considering the potential information gain from each choice. These costs were introduced to investigate whether the POMPD scheme could potentially be used to strike a balance between drug toxicity, and tumor burden while optimizing real-time data collection as desired by key researches in AT (West et al. 2020). The model was further handicapped by noising the tumor signal, meaning that the resistance state, which had to be inferred through the tumor signal, was doubly obfuscated.

However, the agent's generative model did perfectly map the expected noise in the tumor signal, and its initial expected transition probabilities were identical to the actual transition probabilities of the environment. Additionally, the agent was given uniform priors over initial states, meaning it had no information on the configuration of states at the beginning of each run. The same set of predetermined policies that considered the next 6 time-steps were evaluated at each step. This limited set of policies was done to ease computation by limiting the search space of possible actions. The set of policies consisted of two blocks of either testing or treating for three time-steps in a row for permuted each possible sequence of applying testing or not for the time horizon of the policies.

Inferring the Resistance State

In the following example of an exploratory simulation run, the agent managed to keep the patient alive for 68 time-steps and chose to test on 55 of these (see Fig. 2).

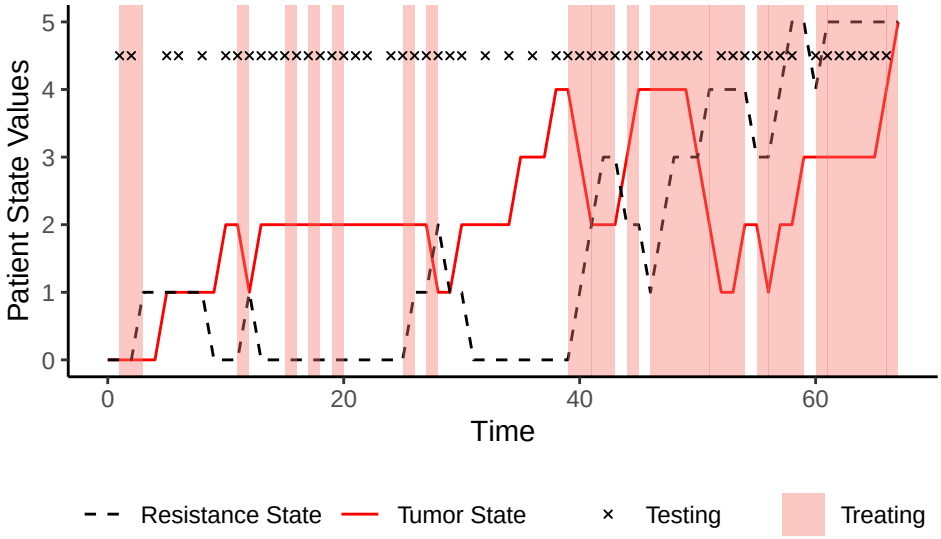


Figure 2: A simulation run for exploratory purposes. The simulation ended before time-step 200 since the simulated patient "died" when the tumor state factor reached the state 5.

The agent appears to be somewhat sensibly applying treatment, but it doesn't apply the treatment at a pivotal period approximately between steps 30 and 39. Interestingly, the agent decides to apply treatment at the first timestep, despite the tumor state and resistance state being at their lowest possible values. Considering that the generative model had uniform priors over both resistance state and tumor states, this behavior is appropriate from the perspective of the agent, since treating and testing would immediately provide information about both states. The model further seemed to prefer testing when treatment is being applied. This suggests that it found testing to be more worthwhile while also treating. Given that by combining treatment and testing, the agent can learn about both the resistance and tumor state factors, all else being equal, the expected information gain should therefore be increased by this behavior. A plot of the model's beliefs about the resistance state at each time-point (see Fig. 3) shows that its beliefs about the resistance state generally follow the development of the actual resistance state despite the lack of direct signal.

In summary, the modification to the POMPD structure appears to have allowed the agent to infer the occluded resistance states in real-time. While the results are initially promising, the particular agent did

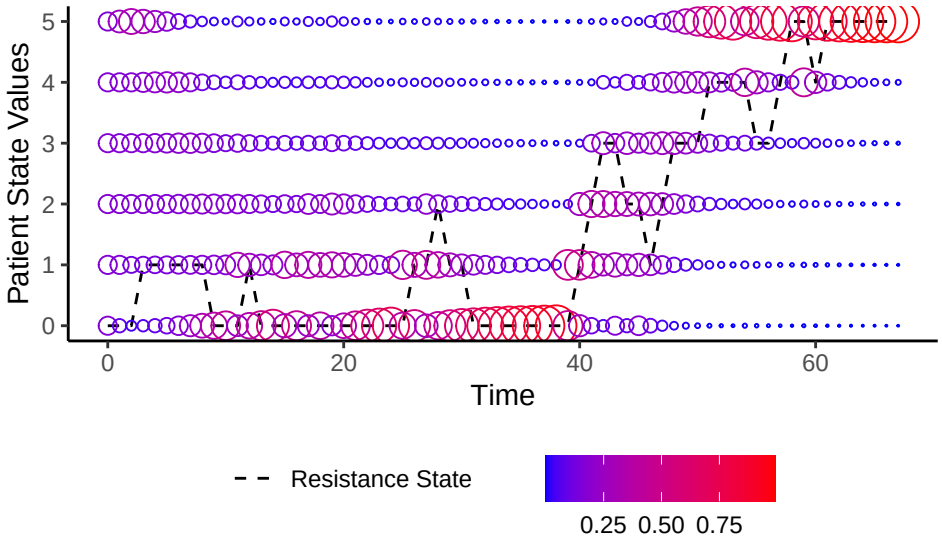


Figure 3: Agents beliefs about the patient's resistance state at every timepoint. Size and color of circles indicate the probability that the agent assigns to each value of the state at a given time-step.

make questionable choices regarding the timing of treatment. It's decision-making is dissected in-depth in Appendix C.

Performance of POMPDs against a Range-Bounded Strategy

Several agents instantiated as modified POMPDs were tested against a range-bounded strategy. This was done to benchmark the performance of POMPDs against a strategy inspired by the treatment protocol used in the pilot clinical trial (Zhang et al. 2017). The generative models used were simplified for ease of computation — they only observed a noiseless signal of the tumor state and whether treatment was being applied at every time-step. They were also only given prior preferences for observations of tumor states. The preferences were uniform over all survivable observations of survivable tumor burdens, and the probability of observing the maximal burden was set to 0. The following three agents were tested:

- A short policy horizon POMPD that could consider a block of treating or not treating for the next three steps.
- A medium policy horizon POMPD that could consider two blocks of treating or not treating for three steps, yielding a total horizon of 6 timesteps.
- A long policy horizon POMPD that could consider four blocks of treating or not treating for three steps, resulting in a total horizon of 12 steps.

The agents were benchmarked on four different tumor growth rates, to investigate how a cancer's aggressiveness would affect the agent's ability to keep a patient alive. The tested tumor growth rates were 0.1, 0.3, 0.5, and 0.7 probability of an increase in tumor state at each timestep. For each setting, 100 simulations were run. For each run, the environment was predetermined by generating 200 outcome variables for each combination of tumor state, resistance state, and treatment state to ensure comparability between the tested agents and the RB strategy at the level of each run.

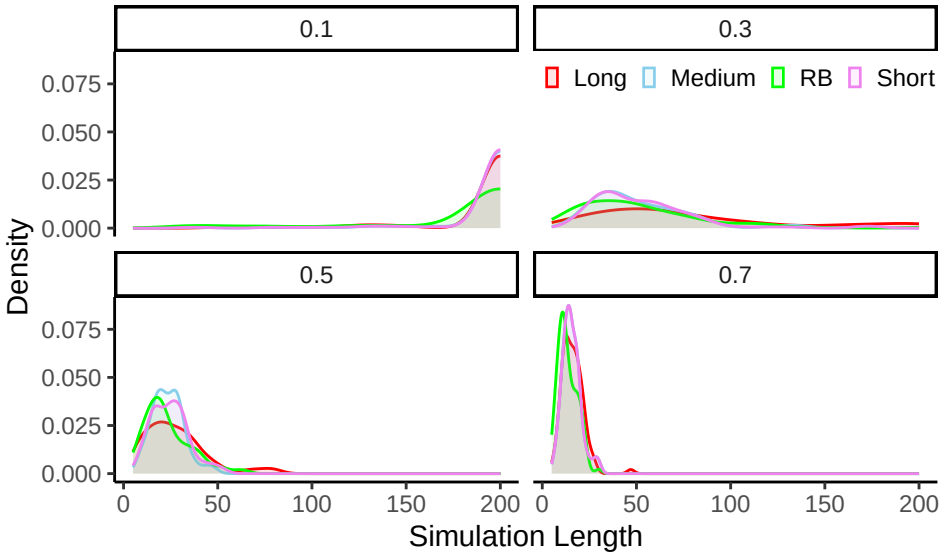
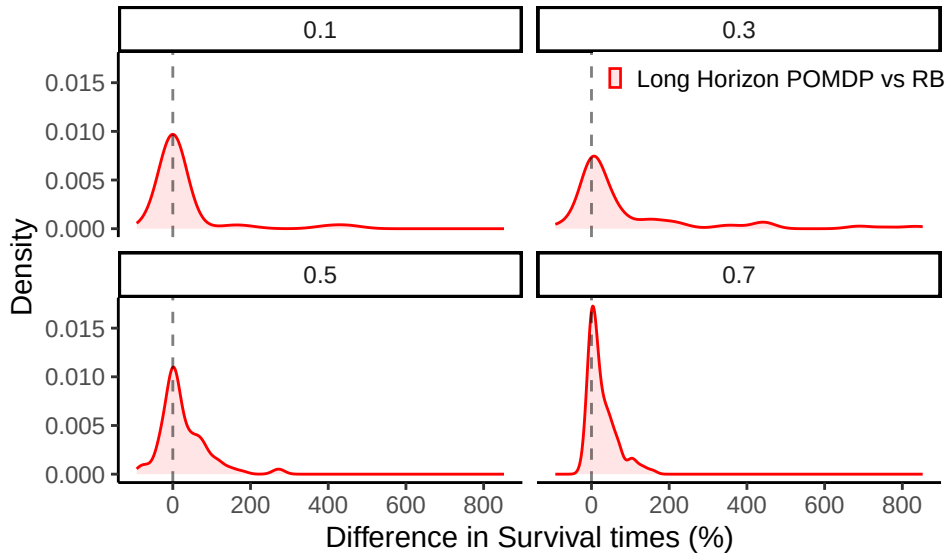


Figure 4: Simulated observed patient survival times for each POMPD agent and the range-bounded strategy.

At the lowest tumor growth rate, nearly all the runs reached the maximal length (see Fig. 4). On the other runs, the long horizon model also appears to be slightly outperforming the others. Contrasts as the percentage difference in survival from switching from the baseline RB-strategy to the long horizon POMPD are computed for each run (see Fig 5.).



In the 100 runs with a 0.1 risk of tumor growth, the long-horizon POMPD seems to perform similarly to the RB strategy. However, as the tumor growth risk increases, the POMPD agent increasingly shows large percentage improvements compared to the RB strategy. Potentially a consequence of a greater need for proactive action when tumor dynamics accelerate, which in turn could favor models that explicitly model how treatment will effect future resistance dynamics.

Discussion

Findings

This project tested a modification to how POMDPs are typically implemented in AI to investigate whether POMDPs could infer and control state factors that don't emit signals, but instead influence other state factors. This was accomplished. In a simulated environment designed to mimic the dynamics of AT, the modification allowed agents, instantiated as POMDPs, to inferan underlying resistance states that modulated the efficacy of cancer treatment, despite the underlying resistance states not producing observable signals themselves

Modified POMPDs were further tested against a range-bounded treatment strategy inspired by a pilot clinical trial using AT, and were found to outperform the range-bounded strategy substantially. The performance gap is largest in simulations of aggressive tumor growth rates and for agents with an ability to

consider longer future courses of action. These results in concert with a recent review of needed developments in AT models (West et al. 2023) underscore the potential of drawing inspiration from the AI paradigm for real-time planning of treatment and testing decisions. Perhaps the modified POMDP could be a useful model architecture that, with refinement, could come to improve real-time patient-specific therapy treatment decisions.

This paper implemented a POMPD capable of combining multiple actions, i.e. treating and testing. Only computation and our ability to specify likelihood and transition probabilities prohibit constructing more complicated generative models. Potentially opening the door to combining multi-drug therapies with multiple types of testing embedded in increasingly detailed real-time models of tumor biology — all of which are desiderata reported by West et al. (2023).

But to avoid having to figure out how quarks and leptons might interact to produce a cancer cell, we will have to limit our desire for higher causal resolution at some point. While simulating finer-grained mechanisms of tumor biology likely will benefit clinical adaptions of AT, abstracting away physical mechanisms as random fluctuations inherent to the modeled environment will eventually be necessary. Models for real-time treatment decisions will therefore have to need the capacity to model the uncertainty of the environment and account for it in decision-making.

Another quality of the AI paradigm is its ability to quantitatively incorporate expected utility and uncertainty in decision-making. In doing so, these models blur the line between testing and treating. For example, a model could correctly believe that two patients have exactly the same tumor burden but suggest treatment for one patient and not the other. This is a feature, not a bug. If the model is certain in its beliefs about one patient's resistance dynamics, the expected gain in information from treating will be small. Yet if the model is uncertain about the resistance dynamics of the other patient, it might be worthwhile to apply treatment simply for the information gain. Curiously, this could result in two patients with exactly the same tumor burden, but only one of them should receive treatment. Factoring in measures of uncertainty drastically alter how to optimally collect real-time data patient data. It would allow for careful and quantitative reasoning of when to use treatment responses to investigate resistance dynamics. Treatment responses were implicitly used as an information gathering tool in the pilot trial, Zhang et al. (2017) report only including patients

who showed a substantial drop in PSA after an initial round of treating, but models inspired by AI could carefully and quantitatively balance information gathering against other objectives such as drug toxicity, patient well-being, delaying the emergence of resistance or financial costs.

Suggestions for Future Research

While the results are initially promising, the simple nature of the simulated clinical setting prohibits drawing any strong conclusions about the prospect of using AI POMPDs in a clinical setting.

To further investigate whether POMDPs could viably be applied in a clinical setting, multiple problems will need to be solved. For example, in the present study, the environment featured only discrete values. Since biomarkers and dosage intensities will likely take continuous values, some combination of binning continuous values to discrete values or adapting the model structure to work with continuous data is necessary. In the face of similar constraints, deep learning has been used to construct likelihood mappings and transition probabilities in POMDPs (Çatal et al. 2020). Finding better methods for searching the policy spaces will likely also be pivotal — Da Costa et al. (2020) suggest how the space of possible actions could be pruned to decrease search times.

Another key issue is determining how to inform likelihood and transition probabilities in a fashion that is compatible with a clinical setting. The present study used the actual transition probabilities of the simulated environment and, depending on the simulation run, noiseless likelihood mappings. Possibly, simulations of cancer dynamics, such as those by Zhang et al. (2017), could be used to inform transition probabilities, and a clinical model could potentially readjust to patient data. The AI implementation of POMDPs has developed literature on online learning of the categorical probability distributions needed to accurately represent the environment. Even potential information gains from learning transition and likelihood probabilities can be factored into decision-making Da Costa et al. (2020).

In the present paper, the ranges of the baseline range-bounded strategy were selected arbitrarily — the chosen range produced managed to control tumor states for a substantial amount of time. A systematic benchmarking framework in AT could ease the comparison of future models. The work of West et al. (2023) could potentially be translated to a set of simulation environments used for benchmarking. Wrapping existing

simulations into environments that can easily facilitate actions and observations with simulated agents could be done by using an API like the one used in Gymnasium (formerly OpenAI Gym) (Towers et al. 2024). This would hopefully minimize friction for non-oncology researchers wishing to contribute to the field by allowing them to prioritize improving model performance over spending excessive time deciphering how to construct useful metrics themselves.

POMPDs could also be "reverse-engineered" from more complex models, which could more easily be trained if a benchmarking suite existed. For example, if a black-box model, like a neural network, can be shown to successfully control treatments, fitting a POMPD to its behavior would probably be a fairly straightforward endeavor since AI POMPDs often have been used in computational psychiatry to model human decision-making. The same techniques could potentially allow us to translate otherwise non-transparent models into the structure of a POMPD, thus combining the performance of the black-box model with the transparency of the POMPD scheme.

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Appendix A: In-Depth Description of the AI POMPD Scheme

The canonical implementation of POMDPs in Active Inference requires specifying the following categorical probability distributions. These are fundamental to an agent's generative model, since they dictate what types of states an agent can infer, what actions it can take, and what type of observations it can make.

The likelihood model, A. A is typically a set of arrays where each array corresponds to a *modality* — a category of observations. Each cell of the array describes the likelihood of making a particular observation in the modality given some configuration of states. For example, PSA readings could be considered a modality, and different test results would be the observations within the modality. The likehoods within the modality could then be modeled as a perfect signal of tumor burden, i.e., the same tumor burden always gives the same test result, or as a noisy signal.

The transition model, B, describes the probability of each possible transition within a type of state between time steps. B also encodes how actions are expected to influence the transition probabilities between states. For example, it could describe how a tumor is likely to evolve from one time-step to the next depending on whether treatment is being applied. The transition model is usually coded as a collection of three-dimensional arrays, a first dimension for the next state, a dimension for the current state, and a third dimension with the length of each action that would influence the transition probabilities of the state.

A prior over preferred states C. A particularity of AI POMPDs is that utility is the probability of making certain observations. It can be considered the states that the system attempts to "self-organize" around. This method of modeling preferences can superficially seem odd, but its benefits will be clear later.

A prior over initial states D. These are vectors of probabilities specifying initial beliefs. In continuation with the example above, D could specify how probable a model believes different levels of tumor burden are before making any observations. When AI POMPDs are solved on multiple time steps, the posterior beliefs

of the preceding time step replace D.

Appendix B: Simulation parameters

The transition dynamics of the simulated environments were.

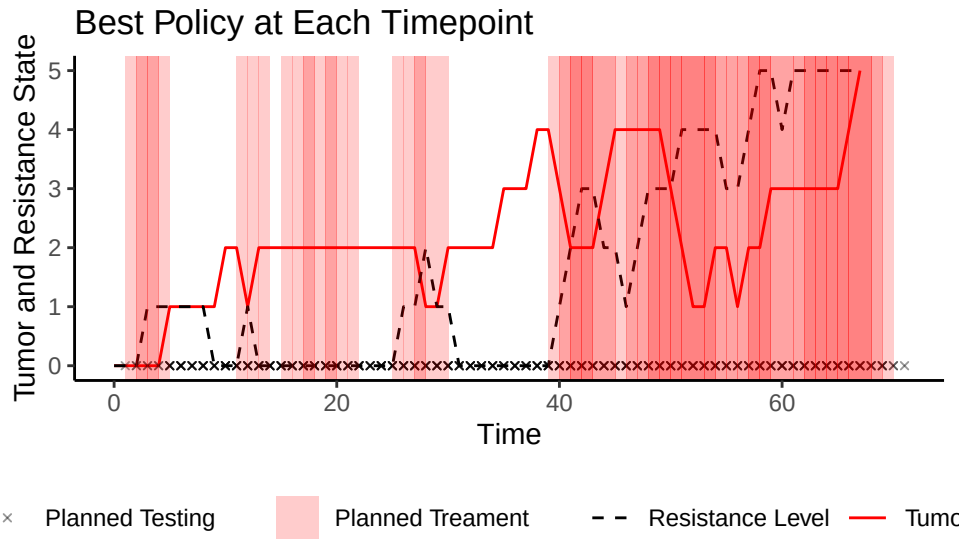
Exploratory simulation:

Outcome	Probability
Risk of Tumor Growth	0.3
Risk of Resistance Increase	0.5
R0 Chance of Treatment Success	1.0
R1 Chance of Treatment Success	0.8
R2 Chance of Treatment Success	0.6
R3 Chance of Treatment Success	0.5
R4 Chance of Treatment Success	0.4
R5 Chance of Treatment Success	0.2
T0 Chance of Resistance Decrease	0.0
T1 Chance of Resistance Decrease	0.2
T2 Chance of Resistance Decrease	0.4
T3 Chance of Resistance Decrease	0.7
T4 Chance of Resistance Decrease	0.8
T5 Chance of Resistance Decrease	0.9

Appendix C: A Dissection of Decision-making by POMPD

For each policy, the agent evaluates the expected trajectory of the hidden states. These evaluations provide insights into the model's uncertainty and what it expects to happen under the best policy at each time point. The amount of "flip-flopping" on decisions can also be investigated by examining what policy the model finds

the most promising at each time step (see Fig. 4).



Curiously, there is a long stretch, approximately from timesteps 30 to 39, where the model never considers treating to be the optimal course of action, even though the resistance level is low. The model also holds accurate beliefs about the resistance level at this time point (see Fig. x). However, this is likely due to a combination of multiple factors. First, there is a cost to treating, which means that the model generally prefers not to treat. It also underestimates the tumor burden at this time point (see Fig. x) and gets "caught off guard" by a sudden rise in the tumor level. Since there is a cost associated with testing, it is also hesitant to apply tests during this period. Because it only considers six timesteps into the future, it likely doesn't consider the long-term consequences of not reducing the tumor level.

The exact "decision-making" for each policy can be evaluated. Each policy is evaluated for its EFE, which is a combination of the expected utility penalized for expected uncertainty (see Fig. 6).

The free energy components reveal several interesting decision-making points. At first, the model, given its uniform priors, is very uncertain about outcomes, and decreasing uncertainty weighs heavily in its decision-making. This uncertainty also means that the model believes it is more likely to be in a risky situation, and reducing this risk is a priority. During the earlier identified pivotal period between timesteps 30-39, there is a concerning lack of increase in the weight of the utility component. This could mean that the model is too concerned with avoiding both treating and testing. It is only from timestep 40 onwards that the model realizes the severity of the situation, i.e., the rising tumor level (see Fig. 5). This analysis warrants strategies

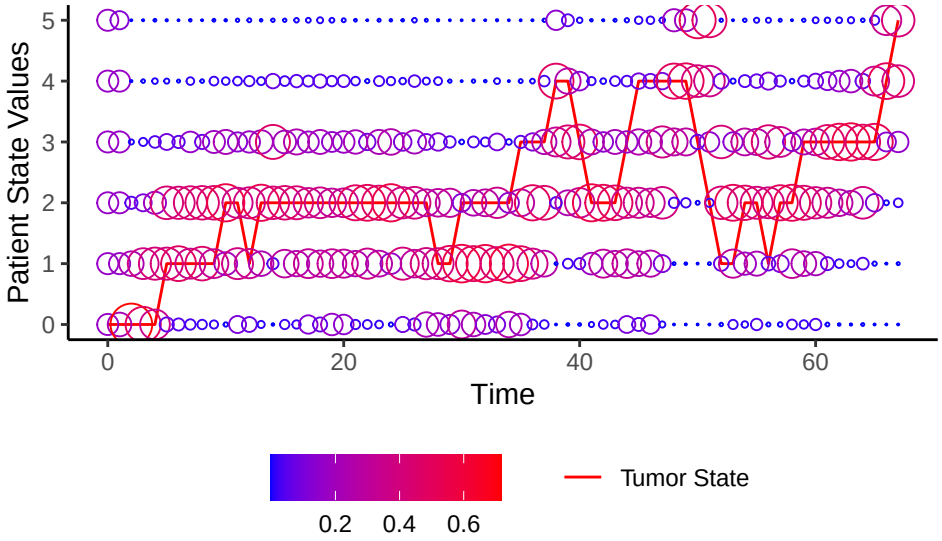


Figure 5: Plot of Agent's beliefs about patients tumor state.

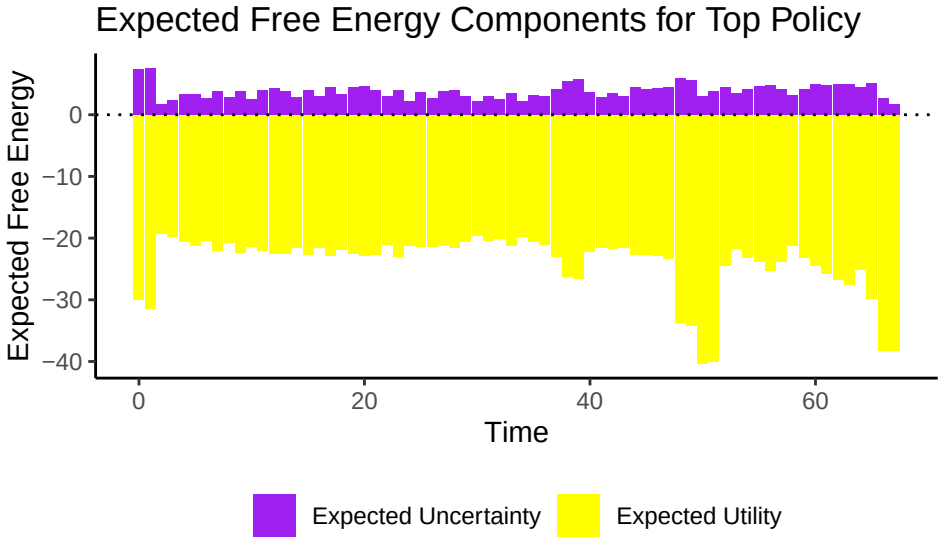


Figure 6: Plot of FEP Components for top policy at each timepoint.

to increase the model's ability. Changing the prior preferences to make testing and treatment "cheaper" in terms of utility might help. However, simply treating and testing more would translate to actual costs, both financial and to patient well-being. While it is important that the prior preferences are tuned to costs in a clinical setting, it would probably be more fruitful to give the model longer policies to consider. This would hopefully yield models that are better tuned to the risks of not detecting and controlling tumor levels at low values.