Discrete Bayesian Drug Development Model with Phase-Dependent Salvage, Opportunity Cost, and Patient Numbers

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1 Introduction

In our model, the development process is divided into:

- **Phase 0 (Discovery):** Preclinical research provides an initial belief μ_0 regarding the drug's efficacy.
- **Phase 1 (Phase I Trials)**
- **Phase 2 (Phase II Trials)**
- **Phase 3 (Phase III Trials)**
- **Phase 4 (Regulatory Approval & Marketing):** Upon successful completion of Phase III, the drug is submitted for regulatory approval. Approval is obtained with probability P_{approve}; then, the firm chooses the best strategy: market in-house, license, or terminate.

At the end of each phase, the firm updates its belief about the drug's success via Bayes' rule and decides whether to continue to the next phase. Our objective is to determine the optimal threshold μ_τ^* and optimal patient numbers n_τ^* for each phase using backward induction.

2 Model Setup

2.1 State Variables and Parameters

State Variables:

- μ_τ: The firm's belief (posterior probability) that the drug will ultimately succeed (e.g., gain regulatory approval and yield profit) at phase τ.
- τ: The current phase, where $\tau \in \{0, 1, 2, 3, 4\}$ representing Discovery, Phase I, Phase II, Phase III, and Regulatory Approval/Marketing.
- n_τ: The number of patients enrolled in clinical trials at phase τ.

Parameters:

- $c_\tau(n_\tau)$: Cost incurred at phase τ with n_τ patients (with c_τ increasing with τ and n_τ). For example, c_0 is the Discovery cost, $c_1(n_1)$ for Phase I, $c_2(n_2)$ for Phase II, $c_3(n_3)$ for Phase III, and c_{RA} for regulatory approval.
- P: The market potential (expected profit) if the drug is marketed in-house.
- L: A baseline licensing payoff (to be used as a reference in the salvage function).
- O: A baseline outside option if the firm redeploys resources elsewhere.

- C_{term}: A direct termination cost (e.g., contract cancellation fees).
- ρ: The discount factor.
- $p_\tau(1, n_\tau)$: If the drug is truly effective, the probability of a positive outcome in phase τ with n_τ patients.
- $p_\tau(0, n_\tau)$: If the drug is not effective, the (lower) probability of a positive outcome in phase τ with n_τ patients.
- P_{approve}: The probability that the drug is approved by regulators after Phase III.

2.2 Patient-Dependent Cost and Information Structure

We model the cost of conducting trials as a function of patient numbers:

$$c_\tau(n_\tau) = c_{\tau,\text{fixed}} + c_{\tau,\text{variable}} \times n_\tau \tag{1}$$

where $c_{\tau,\text{fixed}} represents the fixed costs in phase \tau$ and $c_{\tau,\text{variable}} represents the per-patient cost.$

The probability of observing a positive outcome depends on both the true efficacy of the drug and the number of patients enrolled:

$$p_\tau(1, n_\tau) = p_{\tau,\text{base}}(1) + \alpha_\tau(1 - e^{-\lambda_\tau n_\tau}) \tag{2}$$

$$p_\tau(0, n_\tau) = p_{\tau,\text{base}}(0) - \beta_\tau(1 - e^{-\delta_\tau n_\tau}) \tag{3}$$

This formulation captures how increasing patient numbers improves the probability of correctly identifying effective drugs ($p_\tau(1, n_\tau)$ increases with n_τ) and reduces the probability of false positives for ineffective drugs ($p_\tau(0, n_\tau)$ decreases with n_τ).

2.3 Phase-Dependent Salvage and Opportunity Cost

Rather than a fixed termination cost (or salvage) for stopping, we allow both the licensing payoff and the opportunity cost (outside option) to depend on the phase and the current belief. That is, if the firm stops at phase τ with belief μ_τ, it obtains:

$$V_{\text{stop}}(\mu_\tau, \tau) = \max\{L_\tau(\mu_\tau), O_\tau(\mu_\tau)\} - C_{\text{term}}, \tag{4}$$

where the phase-dependent licensing payoff is defined by:

$$L_\tau(\mu_\tau) = L_{\tau,0} + \alpha_\tau^{(L)}\mu_\tau, \tag{5}$$

and the phase-dependent outside option is:

$$O_\tau(\mu_\tau) = O_{\tau,0} + \gamma_\tau\mu_\tau. \tag{6}$$

For example, if a drug is in an advanced phase (e.g., Phase III), you might have a higher baseline salvage value $L_{\tau,0}$ and a larger slope $\alpha_\tau^{(L)}$ compared to an early phase, reflecting that licensing an approved (or nearly approved) drug is more lucrative. Similarly, the outside option $O_\tau(\mu_\tau)$ may vary with phase if resources can be more effectively redeployed at earlier stages.

3 Value Function and Optimal Policy

Define the value function $V(\mu_\tau, \tau, n_\tau)$ as the maximum expected net payoff from state (μ_τ, τ) with n_τ patients. At each phase, the firm chooses between stopping and continuing:

$$V(\mu_\tau, \tau) = \max_{n_\tau}\{\max\{V_{\text{stop}}(\mu_\tau, \tau), V_{\text{continue}}(\mu_\tau, \tau, n_\tau)\}\}. \tag{7}$$

Stop:

$$V_{\text{stop}}(\mu_\tau, \tau) = \max\{L_\tau(\mu_\tau), O_\tau(\mu_\tau)\} - C_{\text{term}}. \tag{8}$$

Continue (Phases 0 to 3):

$$V_{\text{continue}}(\mu_\tau, \tau, n_\tau) = -c_\tau(n_\tau) + \rho \left[p_\tau(\mu_\tau, n_\tau) V \left(\mu_{\tau+1}^{\text{success}}, \tau + 1 \right) + (1 - p_\tau(\mu_\tau, n_\tau)) V_{\text{fail}} \right], \tag{9}$$

where

$$p_\tau(\mu_\tau, n_\tau) = \mu_\tau p_\tau(1, n_\tau) + (1 - \mu_\tau) p_\tau(0, n_\tau), \tag{10}$$

and V_{fail} is the value upon a failed phase (typically set to 0, or to some partial salvage if desired).

3.1 Regulatory Approval and Marketing (Phase 4)

After Phase III, the drug enters the Regulatory Approval stage. Let the value function at Phase 3 be:

$$V(\mu_3, 3) = \max \left\{ V_{\text{stop}}(\mu_3, 3), \max_{n_3} \{ -c_3(n_3) + \rho \mu_3 P_{\text{approve}} V_{\text{market}}(\mu_4, 4) \} \right\}. \tag{11}$$

At Phase 4 (Marketing), the firm selects the best option:

$$V_{\text{market}}(\mu_4, 4) = \max\{P, L_{\text{final}}, 0\}, \tag{12}$$

where $L_{\text{final}} is the licensing payoff if the fully approved drug is sold.$

4 Belief Updates with Patient Numbers

At the end of each phase, after a successful outcome, the firm's belief is updated by Bayes' rule, incorporating the impact of patient numbers:

$$\mu_{\tau+1}^{\text{success}} = \frac{\mu_\tau p_\tau(1, n_\tau)}{\mu_\tau p_\tau(1, n_\tau) + (1 - \mu_\tau) p_\tau(0, n_\tau)}. \tag{13}$$

The larger the patient sample size n_τ, the stronger the belief update (more pronounced separation between effective and ineffective drugs). If a phase results in failure, the project is terminated (and the firm receives $V_{\text{stop}}(\mu_\tau, \tau)$).

5 Backward Induction and Optimal Thresholds

We solve for $V(\mu_\tau, \tau)$ and the optimal patient numbers n_τ^* by backward induction. At each phase τ (for $\tau = 0, 1, 2, 3$), we have:

$$V(\mu_\tau, \tau) = \max_{n_\tau} \{ \max\{ V_{\text{stop}}(\mu_\tau, \tau), V_{\text{continue}}(\mu_\tau, \tau, n_\tau) \} \}. \tag{14}$$

Optimal Thresholds: At each phase, there exists a threshold μ_τ^* such that

$$V_{\text{continue}}(\mu_\tau^*, \tau, n_\tau^*) = V_{\text{stop}}(\mu_\tau^*, \tau). \tag{15}$$

If $\mu_\tau > \mu_\tau^*, continuing is optimal; if \mu_\tau \leq \mu_\tau^*, stopping is optimal. The optimal patient number \mathrm{n}_\tau^*$ is determined by:

$$n_\tau^* = \arg\max_{n_\tau} V_{\text{continue}}(\mu_\tau, \tau, n_\tau). \tag{16}$$

For example, in a simplified setting for Phase II one might have:

$$\mu_2^* = \frac{c_2(n_2^*)}{\alpha_2 R}, \tag{17}$$

but in our extended model, the threshold at each phase accounts for subsequent phases, the revised stop value, and the optimal patient numbers.

6 Discussion

In this model, the firm's decision at each phase is based on comparing the expected value of continuing development versus the stopping value, while also optimizing the number of patients to enroll in each trial phase. The stopping value is now given by

$$V_{\text{stop}}(\mu_\tau, \tau) = \max\{L_\tau(\mu_\tau), O_\tau(\mu_\tau)\} - C_{\text{term}}, \tag{18}$$

which reflects that if the firm terminates development it may either license the drug (obtaining a payoff $L_\tau(\mu_\tau)$) or redeploy resources to an alternative project (with outside option $O_\tau(\mu_\tau)$).

The optimal patient number n_τ^* reflects a trade-off between:

- Higher costs for larger trials: $c_\tau(n_\tau)$ increases with n_τ
- Better information quality: The gap between $p_\tau(1, n_\tau)$ and $p_\tau(0, n_\tau)$ widens with n_τ
- Stronger belief updates: The posterior belief $\mu_{\tau+1}^{\text{success}}$ is more sensitive to the true state with larger n_τ

Since drugs in later phases are more advanced and less risky, you can set the parameters in $L_\tau(\mu_\tau)$ and $O_\tau(\mu_\tau)$ so that they are higher for later phases. For instance:

$$L_\tau(\mu_\tau) = L_{\tau,0} + \alpha_\tau^{(L)}\mu_\tau, \tag{19}$$

$$O_\tau(\mu_\tau) = O_{\tau,0} + \gamma_\tau\mu_\tau. \tag{20}$$

This phase-dependent formulation ensures that licensing an approved (or nearly approved) drug is more valuable than licensing one at an early stage, and it also captures how firms optimize their patient enrollment strategies throughout the drug development process.

7 Simulation Results

7.1 Basic model visualization

Our analysis reveals distinct belief thresholds for each development phase:

Table 1: Drug Development Model Results

Optimal Belief Thresholds	
Phase 0	$\mu^* = 0.1450$
Phase 1	$\mu^* = 0.3050$
Phase 2	$\mu^* = 0.4650$
Phase 3	$\mu^* = 0.6050$
Simulation Results with Initial Belief $\mu = 0.6$	
Overall success rate	11.50%
Average patients enrolled	1374.0
Average development cost	\$136.5M
Phase Progression Rates	
Reached Phase 1	62.40%
Reached Phase 2	46.70%
Reached Phase 3	26.50%
Reached Phase 4	11.50%

We conducted 1,000 simulations of drug development paths starting with an initial belief $\mu = 0.6$. The results are summarized in Table 1.

Figure 1 presents the fundamental continue/stop and patient number optimizations in our model.

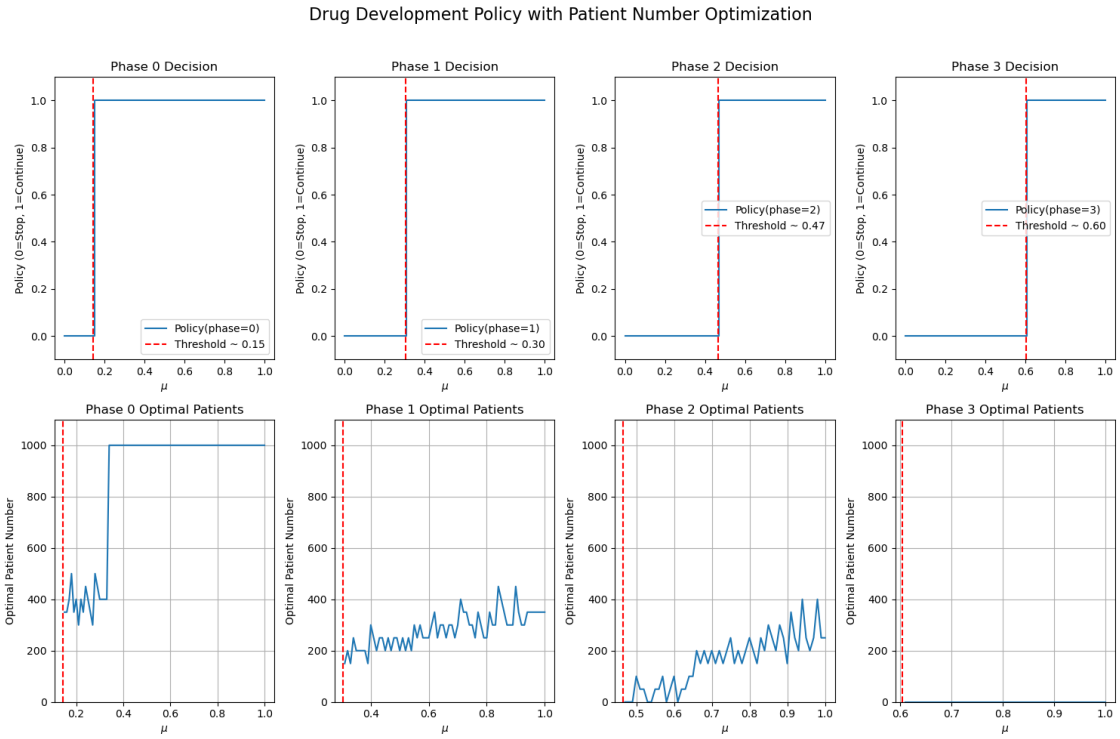

Figure 1: Drug development with belief and patient number optimization

The top row displays the binary stop/continue policy across the full range of belief states (μ) for each development phase. We observe clear threshold policies where development should be abandoned (policy = 0) when belief falls below the threshold, and continued (policy = 1) when belief exceeds it. The vertical red lines mark these thresholds: $\mu^* = 0.15$ for Phase 0, $\mu^* = 0.30$ for Phase 1, $\mu^* = 0.47$ for Phase 2, and $\mu^* = 0.60$ for Phase 3. This monotonically increasing pattern reflects the escalating costs and risks in later development stages, requiring progressively higher confidence in drug efficacy to justify continued investment.

The bottom row reveals a more nuanced aspect of our model: the optimal patient enrollment numbers conditional on continuing development. Several patterns are noteworthy: First, Phase 0 exhibits considerable volatility in patient numbers near the threshold, suggesting high sensitivity to small changes in belief at this early stage. Second, all phases show a general upward trend in patient numbers as belief increases, reflecting greater willingness to invest in larger trials for drugs with stronger efficacy signals. Third, the enrollment pattern differs across phases—Phase 2 shows a more consistent upward trend in patient numbers compared to the fluctuating patterns in Phases 0 and 1, likely due to the more decisive role of Phase 2 in determining ultimate success. Since Phase 3 is the FDA approval stage, it is not related to the number of patients the firm hires. Finally, comparing across phases, we observe that optimal patient numbers depend not just on absolute belief but on the phase-specific context, with each phase showing distinctive enrollment patterns.

The histograms in Figure 2 reveal:

- A trimodal distribution of patient numbers with peaks at approximately 1000, 1300, and 1700 patients, corresponding to termination after different trial phases
- A multimodal distribution of development costs with a high concentration at low costs (early termination) and secondary peaks around \$200M, \$250M, and \$300M (later-stage termination)

These distributions highlight the value of the sequential approach to drug development—most projects are terminated early, preserving resources, while promising candidates receive continued investment through later, more expensive phases.

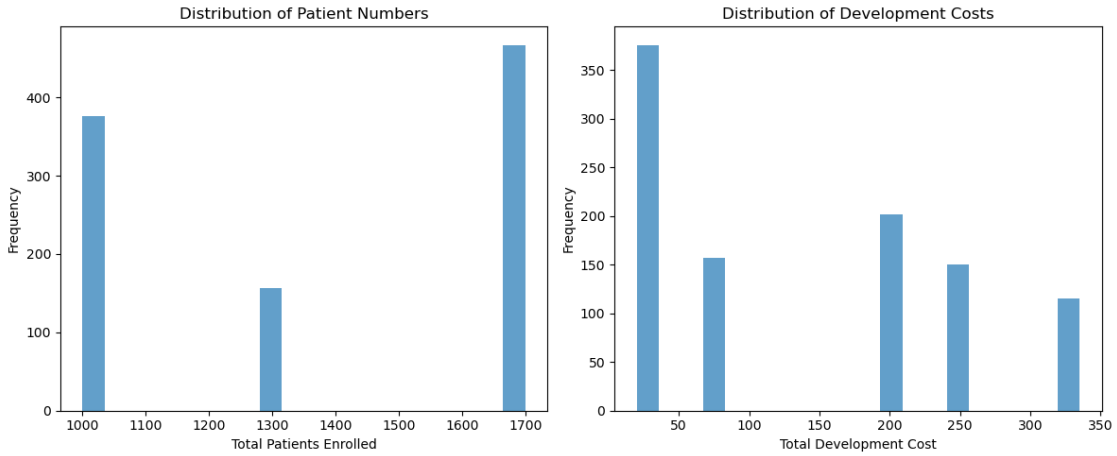

Figure 2: Distribution of patient numbers (left) and development costs (right)

7.2 Parameter sensitivity analysis

We analyzed how key economic and operational parameters affect the optimal development policy.

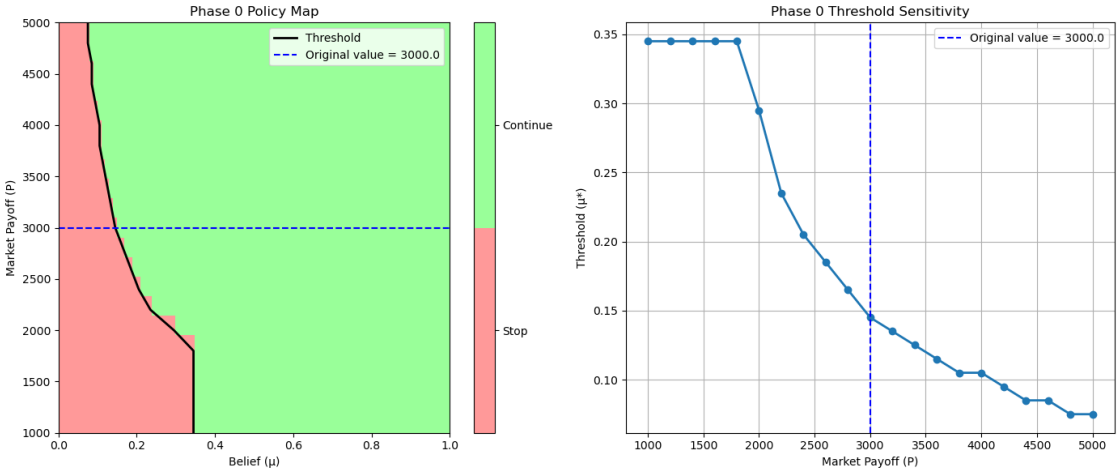

Figure 3: Sensitivity to market payoff (P). Policy map (left) showing regions where stopping (red) or continuing (green) is optimal, and threshold sensitivity curve (right).

Market payoff (Figure 3) has a substantial but non-linear effect on development thresholds. The policy map (left) shows a clear boundary between red (stop) and green (continue) regions that shifts leftward as market payoff increases The threshold curve (right) demonstrates that higher market potential substantially lowers the belief threshold needed to continue development. This relationship is non-linear - increasing payoff from 1000 to 3000 drops the threshold dramatically (0.33 to 0.16), but further increases have diminishing returns.

The heatmap (left) in Figure 4 reveals higher patient numbers (yellow) are optimal at higher belief values Patient numbers are nearly maximized once belief exceeds the threshold The slice view (right) shows that market payoff primarily affects the decision threshold, while having less impact on the optimal number of patients once development continues.

Phase 0 fixed costs affect both development decisions and patient enrollment strategies, see Figure 5 and 6. Figure 5 shows a clear boundary between optimal stopping (red) and continuing (green) regions as a function of belief state and fixed costs. At the baseline fixed cost of $20M (blue dashed line), the threshold is

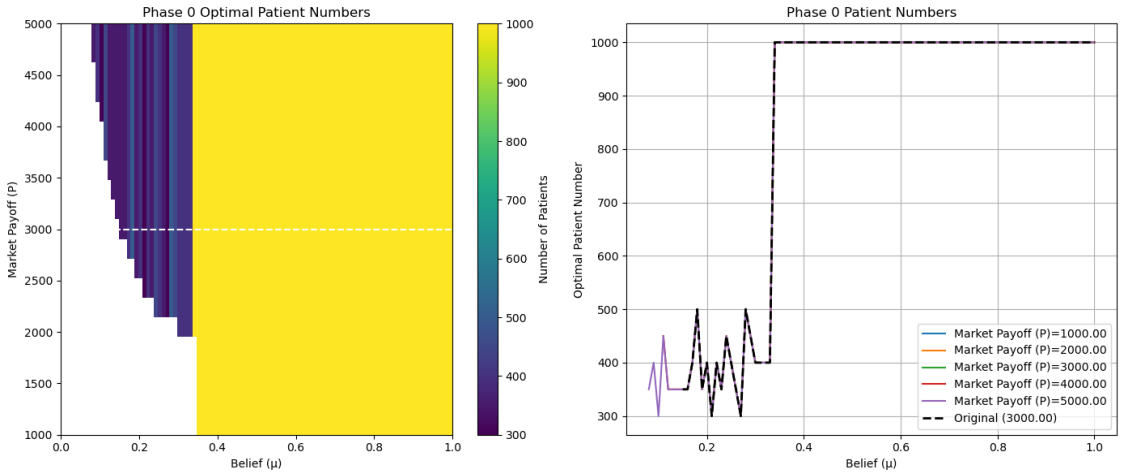

Figure 4: Optimal patient numbers heatmap (left) and slices at selected market payoff values (right).

approximately $\mu^* = 0.15$. As fixed costs increase, the threshold boundary shifts rightward, requiring higher confidence to justify development. For very low beliefs ($\mu < 0.1$), stopping is optimal regardless of fixed costs. For high beliefs ($\mu > 0.4$), continuing is optimal even with substantial fixed costs up to \$40M. The relationship is remarkably linear(right in Fig 5), each \$5M increase in fixed cost raises the threshold by approximately 0.03-0.04 points.

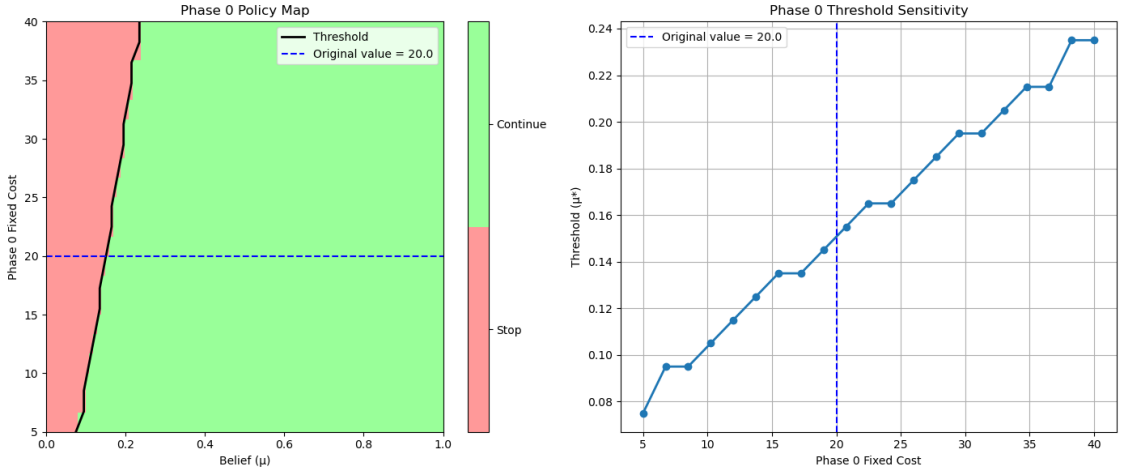

Figure 5: The relationship between μ and fixed cost

Figure 6 reveals how fixed costs and beliefs jointly determine optimal trial sizes (left) and how optimal enrollment varies with belief for different fixed cost values (right). For beliefs just above the threshold, relatively few patients (300-500, purple/blue) are optimal Once belief exceeds a certain level, maximum enrollment (1000 patients, yellow) becomes optimal (left). Despite different fixed costs, the pattern of enrollment remains similar once development continues, so fixed costs primarily affect whether to develop rather than how to develop (right).

Figure 7 and 8 show how per-patient costs fundamentally transform both development decisions and enrollment strategies. Figure 7 shows that variable costs have a threshold effect rather than a gradual impact on decision-making (left). It also implies there is a saturation effect where beyond a certain per-patient cost, further increases does not substantially change the stop/continue decision. The left part of Figure 8 shows unlike fixed costs, variable costs dramatically reduce optimal patient numbers even for high-belief projects. The right part shows at the original variable cost of 0.0, enrollment jumps from 400 to 1000 patients as

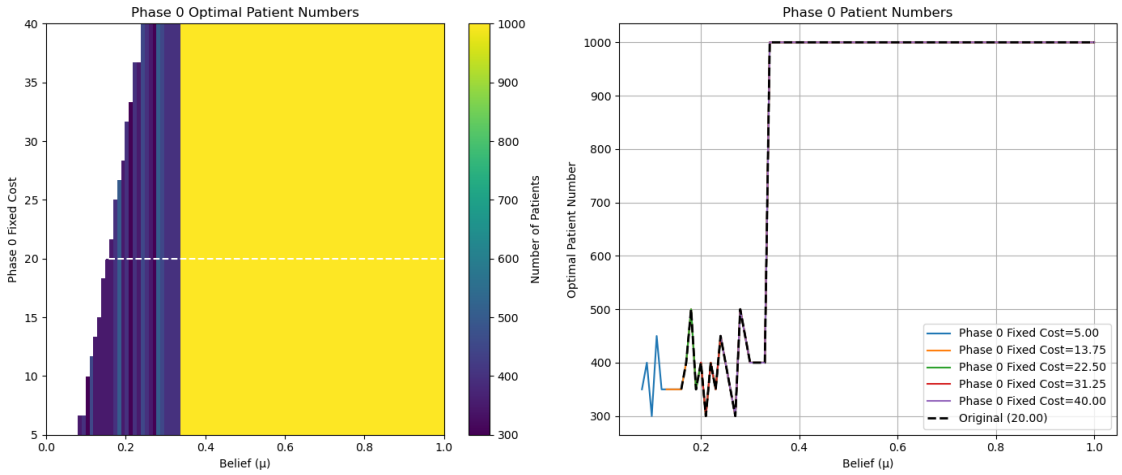

Figure 6: The relationship between optimal patient and fixed cost

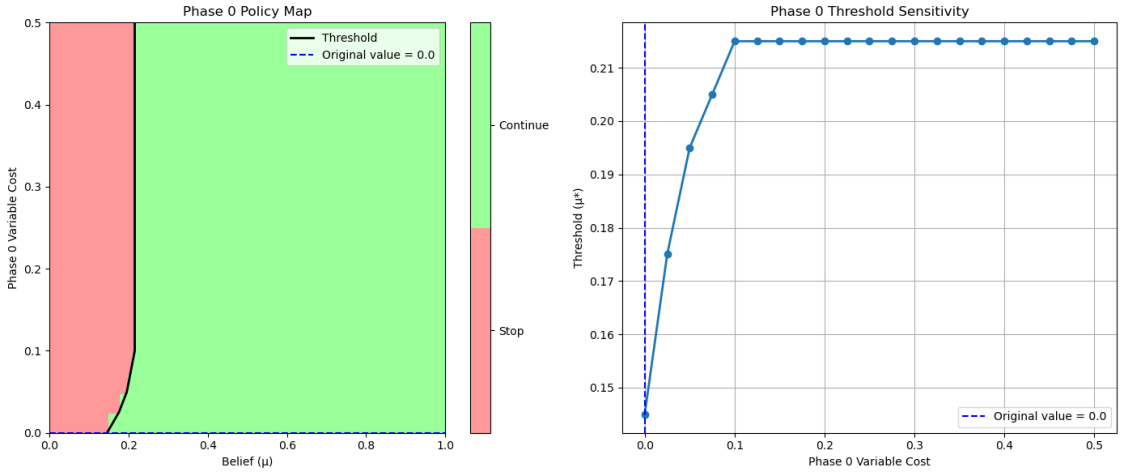

Figure 7: The relationship between μ and per-patient cost

belief increases. As variable cost increases, optimal enrollment collapses. At 0.12 (orange line), enrollment falls to 50-200 patients. At 0.25 (green line), enrollment is further reduced with many regions at zero. At 0.38 and 0.50 (red and purple lines), enrollment is essentially zero across most belief values. The staggered pattern shows how higher variable costs progressively eliminate larger trial sizes from consideration.

The discount factor (Figure 9) strongly influences thresholds, with lower discount factors significantly increasing the required belief to continue development. This relationship is highly non-linear, with the effect becoming more pronounced at lower discount factors.

The effective base probability (Figure 10) has a substantial impact on thresholds. As the base probability increases, the threshold decreases dramatically, reflecting the reduced risk of continuing development when trials are more likely to detect efficacy correctly.

7.3 3D Visualizations

The value function surface in Figure 11 provides additional insights. The steep gradient around $\mu = 0.15$ marks the belief threshold where value increases rapidly. The surface slope along the patient axis shows diminishing returns to larger trial sizes. The yellow plateau region indicates that once belief exceeds approximately 0.4,the maximum value is achieved with maximum patient enrollment. The purple flat region shows

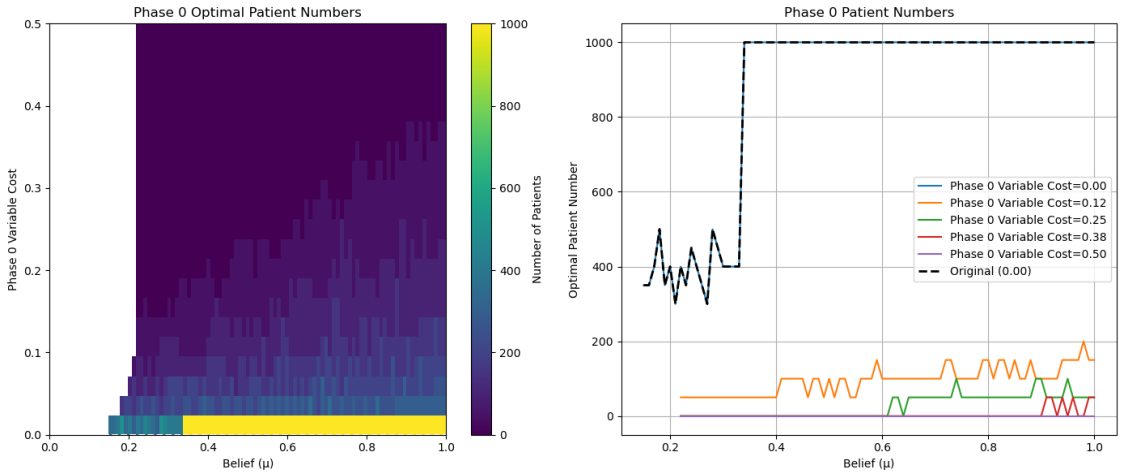

Figure 8: The relationship between optimal patient and per-patient cost

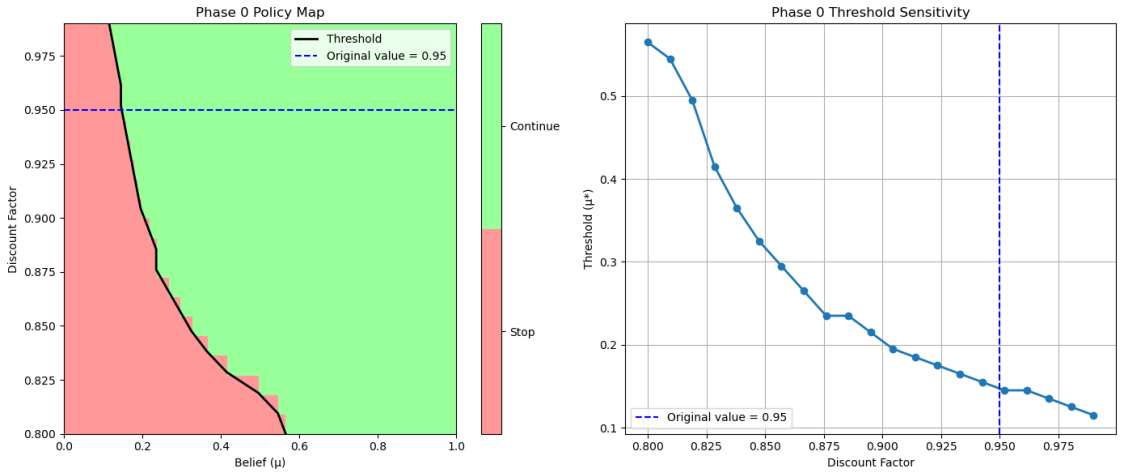

Figure 9: Sensitivity to discount factor.

that for very low beliefs, value is minimally affected by patient numbers.

Figure 12 reveals several critical insights about the decision structure. The decision boundary is not simply a vertical plane, indicating that optimal decisions depend on both belief and patient enrollment decisions. For low beliefs ($\mu < 0.15$), stopping is optimal regardless of patient numbers (red region). For moderate beliefs ($0.15 < \mu < 0.4$), the continuation decision becomes patient-dependent, with continuation becoming optimal as patient numbers increase. For high beliefs ($\mu > 0.4$), continuing development with maximum patient enrollment is optimal (green region).

7.4 Analytical threshold derivation

For Phase 3, we derive an analytical approximation for the optimal threshold by linearizing the value functions and finding their intersection point.

As shown in Figure 13, we approximate the threshold by fitting linear functions to the stop and continue values. The threshold occurs where these functions intersect, yielding the formula:

$$\mu^* \approx \frac{c_3 + 190.0}{300.0 - \rho \times 0.56 \times V_{RA}} \tag{21}$$

This analytical approximation captures how the threshold depends on phase costs, discount factor, and

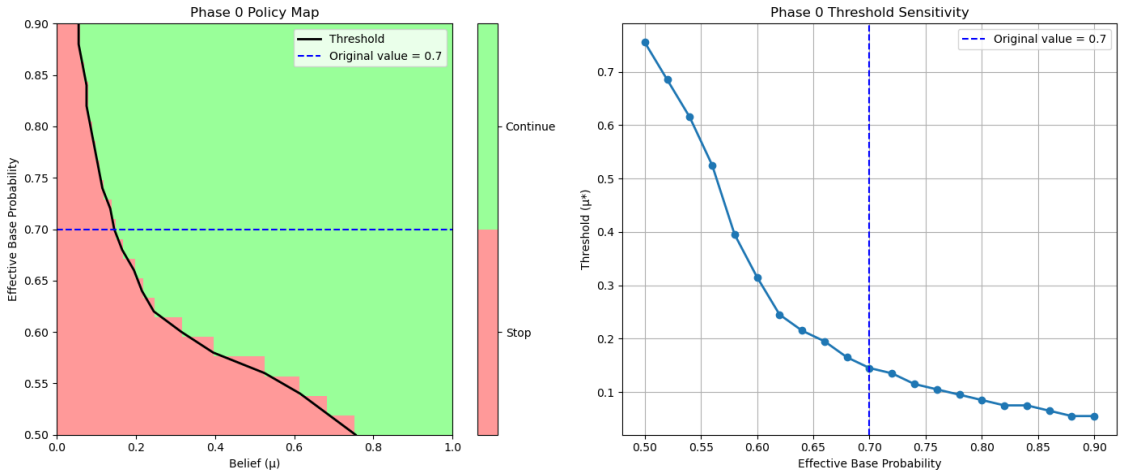

Figure 10: Sensitivity to effective base probability. Higher probabilities of success for effective drugs substantially reduce the threshold required to continue development.

expected regulatory approval value, providing a closed-form expression that enhances the interpretability of our numerical results.

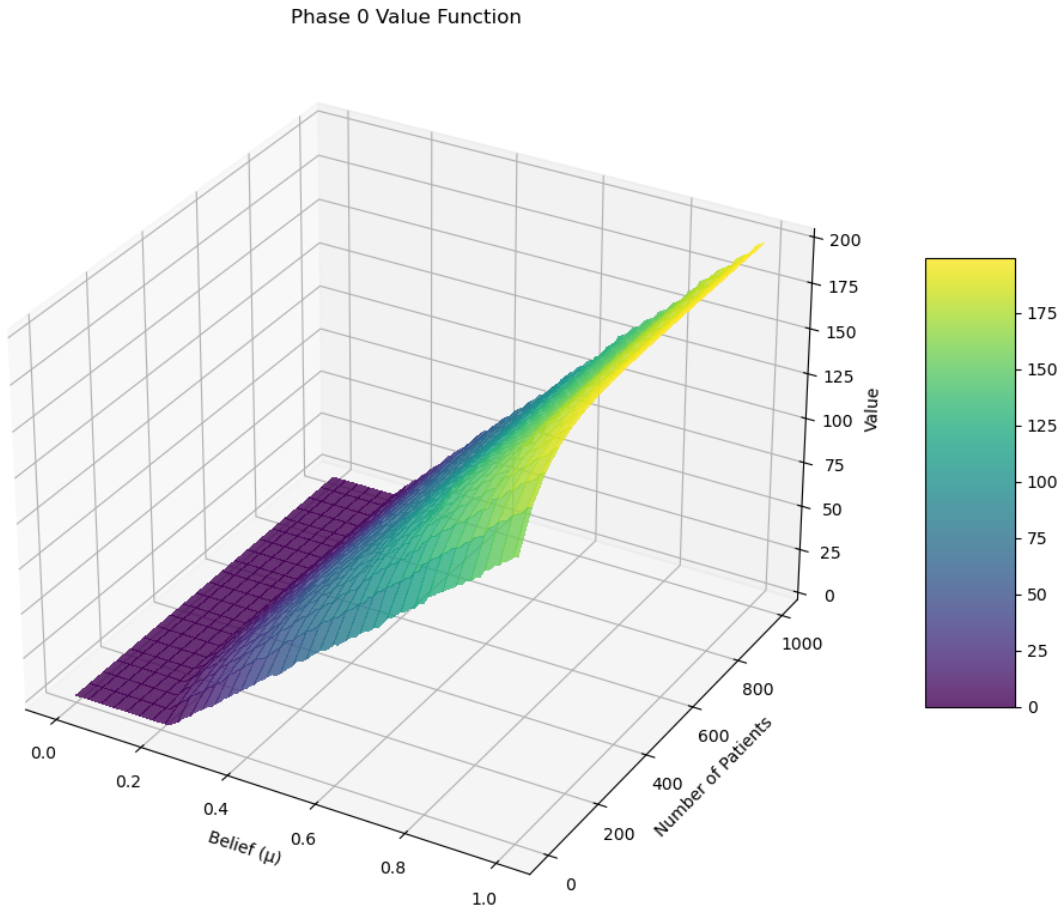

Figure 11: Phase 0 value function across belief states and patient numbers. The color gradient (purple to yellow) represents expected value, showing how value increases with both belief and patient numbers.

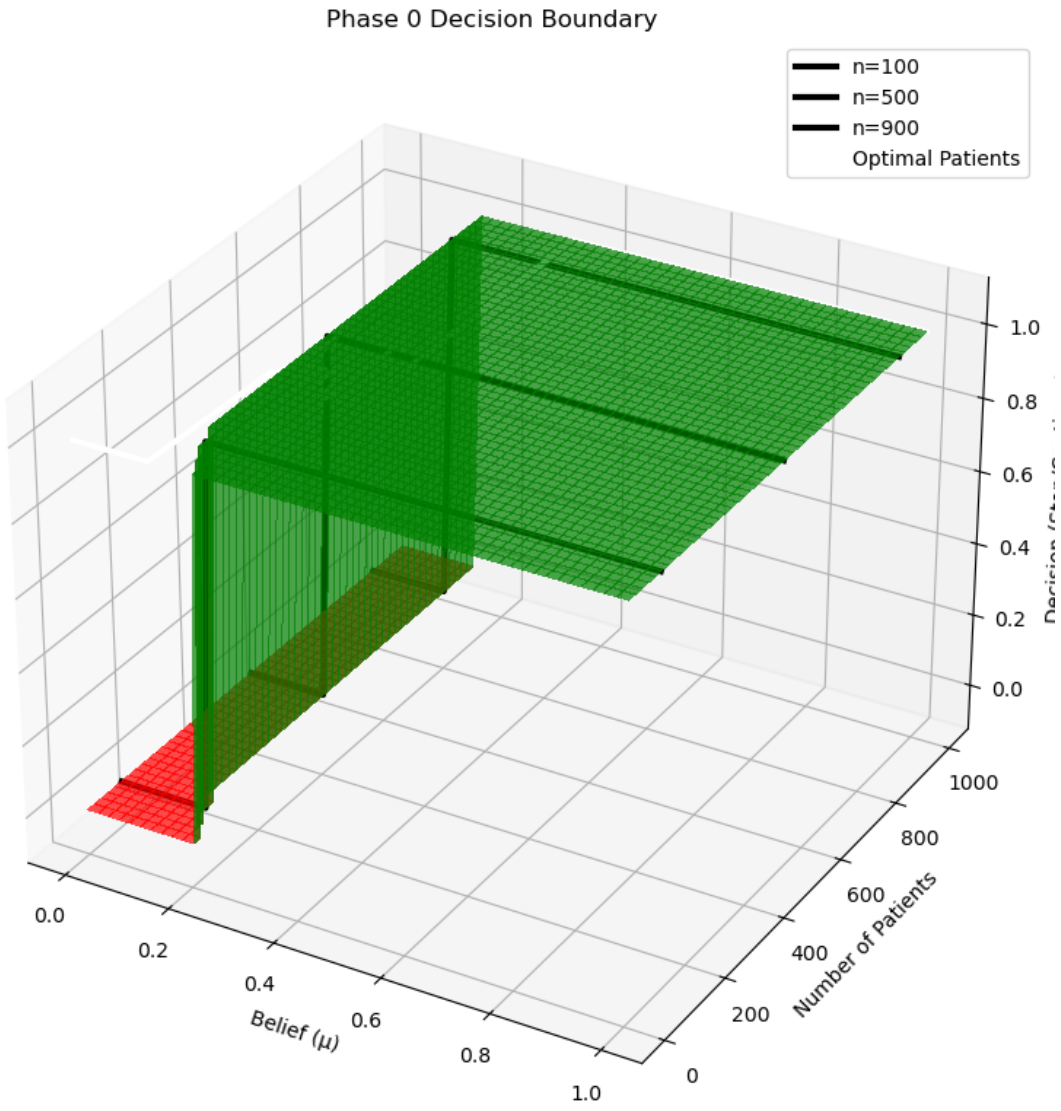

Figure 12: Phase 0 decision boundary in 3D space. The surface shows the optimal decision (red=stop, green=continue) as a function of belief state (μ) and patient numbers. Black lines indicate decision boundaries at specific patient numbers (n=100, n=500, n=900), while the white line shows the optimal patient enrollment path.

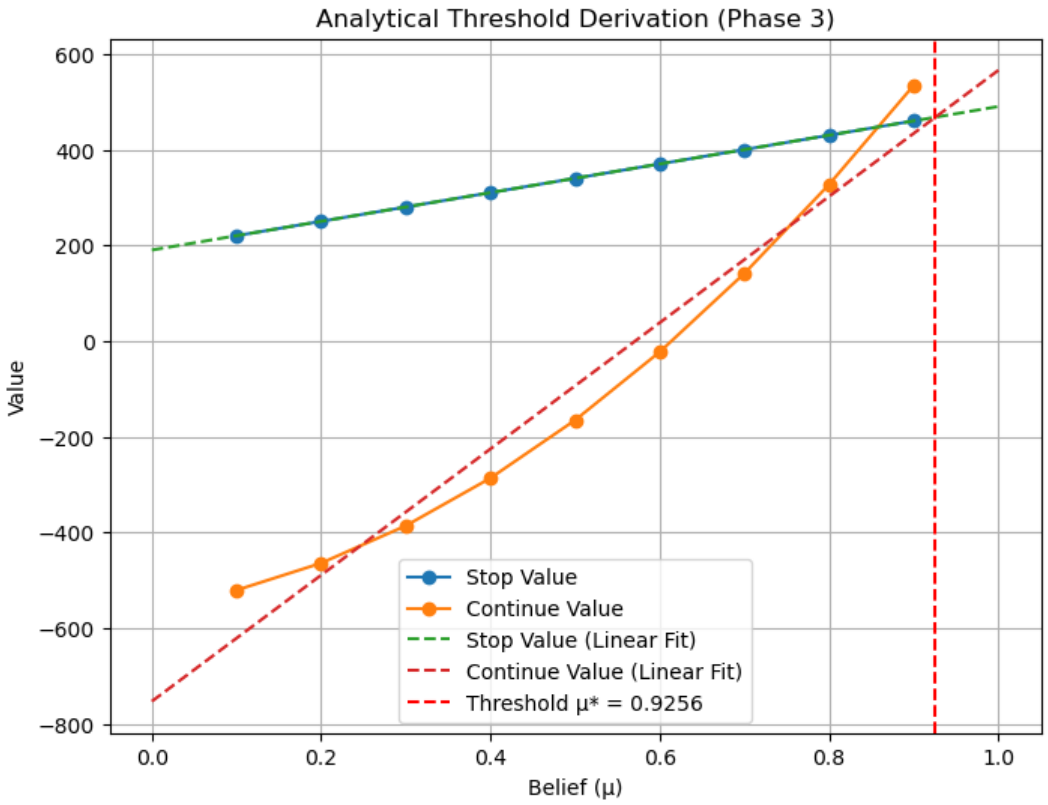

Figure 13: Analytical threshold derivation for Phase 3. The blue line represents stop values across beliefs, while the orange line shows continue values. Their intersection at $\mu^* = 0.9256$ defines the threshold. Dashed lines show the linear approximations used to derive the analytical formula.