A Bayesian Decision Framework for Optimizing Sequential Combination Antiretroviral Therapy in People with HIV

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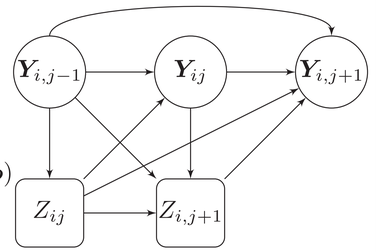
1. Abstract

Numerous adverse effects (e.g., depression) have been reported for combination antiretroviral therapy (cART) despite its remarkable success on viral suppression in people with HIV. To improve long-term health outcomes for people with HIV, there is an urgent need to design personalized optimal cART with the lowest risk of comorbidity in the emerging field of precision medicine for HIV. However, the large number of possible drug combinations for cART makes the estimation of cART effects a high-dimensional combinatorial problem, imposing challenges in both statistical inference and decision-making. We develop a two-step Bayesian decision framework for optimizing sequential cART assignments. Applying the proposed method to a dataset from the Women's Interagency HIV Study (WIHS), we demonstrate its clinical utility in assisting physicians to make effective treatment decisions, serving the purpose of both viral suppression and comorbidity risk reduction.

2. Two-Step Bayesian Decision Framework

Problem Formulation:

- Data: $\mathcal{D}_{ij} = \{\boldsymbol{X}_{i0}, \boldsymbol{t}_i, \overline{\boldsymbol{Y}_{ij}}, \overline{Z_{ij}}\}$
- Baseline covariates: $\boldsymbol{X}_{i0}$
- Longitudinal health state: $\boldsymbol{Y}_{ij}$
- cART regimen: Z_{ij}
- Dynamic: $\boldsymbol{Y}_{i,j+1} = f(\overline{\boldsymbol{Y}_{ij}}, \overline{Z_{i,j+1}}; \boldsymbol{\phi})$
- Policy: $Z_{i,j+1} = \pi(\overline{\boldsymbol{Y}_{ij}}, \overline{Z_{ij}}; \boldsymbol{\theta})$
- Reward: $r_i(\boldsymbol{Y}_i^{\text{new}})$



Goal: Find the optimal personalized cART assignment policy $\pi(\cdot, \cdot; \boldsymbol{\theta}_i^\star)$ that maximizes the expected reward $\boldsymbol{\theta}_i^\star = \arg\max_{\boldsymbol{\theta}} R_i(\boldsymbol{\theta})$, where

$$R_i(\boldsymbol{\theta}) = \int E_{(\boldsymbol{Y}_i^{\text{new}}, \boldsymbol{Z}_i^{\text{new}}) \sim p(\boldsymbol{Y}_i^{\text{new}}, \boldsymbol{Z}_i^{\text{new}} | \mathcal{D}, \boldsymbol{\phi}, \boldsymbol{\theta})}[r_i(\boldsymbol{Y}_i^{\text{new}})] p(\boldsymbol{\phi} \mid \mathcal{D}) d\boldsymbol{\phi}.$$

Method:

- First step: use the multivariate Gaussian process (MGP) to model the joint distribution of individual's longitudinal health states.
- Second step: conduct the uncertainty-penalized policy optimization [2] with respect to $\widetilde{r}_i(\boldsymbol{Y}_i^{\text{new}}) = r_i(\boldsymbol{Y}_i^{\text{new}}) - \lambda u(\boldsymbol{Y}_i^{\text{new}}, \boldsymbol{Z}_i^{\text{new}})$ in a pessimistic environment, to mitigate the distribution shift issue.

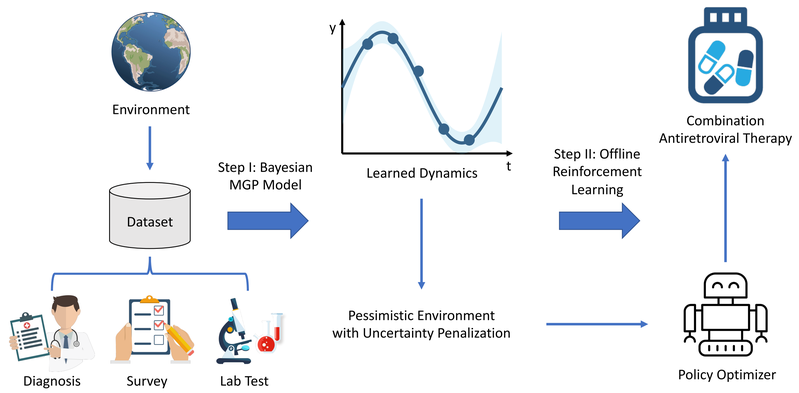


Figure 1: Illustration of the proposed two-step Bayesian decision framework for optimizing sequential cART assignments with proper uncertainty propagation.

3. First Step: Modeling Longitudinal States

Multivariate Gaussian process:

$$Y_{im}(t) = f_{im}(t) + \epsilon_{im},$$

$$\boldsymbol{f}_i(t) \sim \mathcal{MGP}(\boldsymbol{\mu}_i(t), \boldsymbol{\Omega}_i(t, t')), \quad \epsilon_{im} \overset{i.i.d}{\sim} \mathcal{N}(0, \sigma_m^2)$$

$$\mu_{im}(t) = \boldsymbol{X}_{i0}\boldsymbol{\beta}_m + \boldsymbol{V}_i(t)\boldsymbol{\alpha}_{im} + h_m(\overline{Z_i(t)}), \quad \boldsymbol{\Omega}_i(t, t') = C^M \bigotimes C^t(t, t').$$

Drug combination effects:

$$h_m(\overline{Z_i(t)}) = \underbrace{\frac{\sum_{d=1}^D \kappa(Z_i(t), z_d)\gamma_{md}}{\sum_{d=1}^D \kappa(Z_i(t), z_d)} + \sum_{s=1}^S \frac{\sum_{d=1}^D \kappa(Z_i(t), z_d) X_{i0s}\widetilde{\gamma}_{mds}}{\sum_{d=1}^D \kappa(Z_i(t), z_d)}}_{\text{Instantaneous drug effect}}$$

$$+ \underbrace{\sum_{n=1}^N \delta_{mn} \int_0^t \mathbb{I}(\mathcal{A}_n \in Z_i(t')) e^{-(t-t')} dt'}_{\text{Accumulated drug effect}}$$

Subset-tree kernel [1] $\kappa(\cdot, \cdot)$ to measure drug similarity:

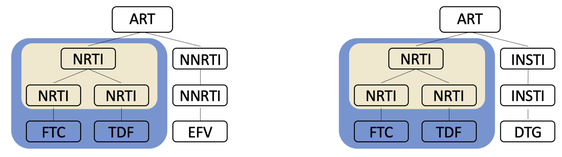


Figure 2: Tree representations of cART regimens. Common substructures that induce drug similarities are highlighted by the yellow and blue boxes.

4. Second Step: Optimizing cART Assignments

Decision process for assigning cART:

$$\pi(Z_{i,j+1} \mid \overline{\boldsymbol{Y}_{ij}}, \overline{Z_{ij}}; \boldsymbol{\theta}) =$$

$$\underbrace{p(Z_{i,j+1}^{(1)} \mid \overline{\boldsymbol{Y}_{ij}}, \overline{Z_{ij}}; \boldsymbol{\theta}^{(1)})}_{\text{First level: hard thresholding}} \underbrace{p(Z_{i,j+1}^{(2)} \mid Z_{i,j+1}^{(1)}, \overline{\boldsymbol{Y}_{ij}}, \overline{Z_{ij}}; \boldsymbol{\theta}^{(2)})}_{\text{Second level: multi-class logistic regression}}$$

$$\underbrace{p(Z_{i,j+1}^{(3)} \mid Z_{i,j+1}^{(1)}, Z_{i,j+1}^{(2)}, \overline{\boldsymbol{Y}_{ij}}, \overline{Z_{ij}}; \boldsymbol{\theta}^{(3)})}_{\text{Third level: Wallenius' noncentral hypergeometric distribution}}$$

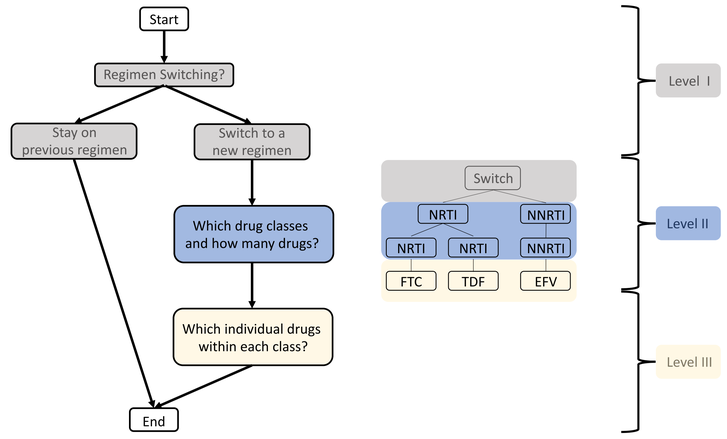


Figure 3: Illustration of the three-level decision process for selecting cART regimen conditional on individuals' preceding states and treatment histories.

5. Application: WIHS Data Analysis

We applied the proposed two-step Bayesian decision framework to the Women's Interagency HIV Study (WIHS) dataset, which is a large prospective, observational, multicenter study designed to investigate the impact of HIV infection on multimorbidity in women with HIV in the United States.

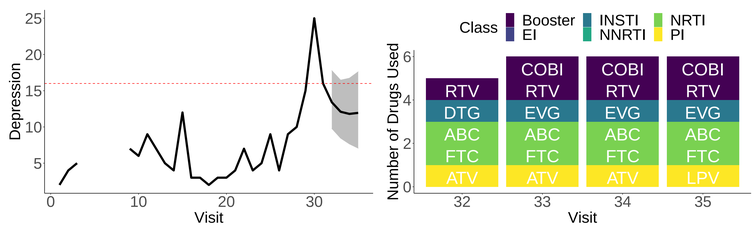


Figure 4: Left panel: observed (visit 1-31) and predicted (visit 32-35) depression scores for individual I_1 (randomly selected from the WIHS dataset). The shaded area represents the 95% predictive credible band and the dashed red line represents the depression threshold. Right panel: personalized optimal sequential cART assignments for individual I_1.

Interpretation of uncertainty penalization:

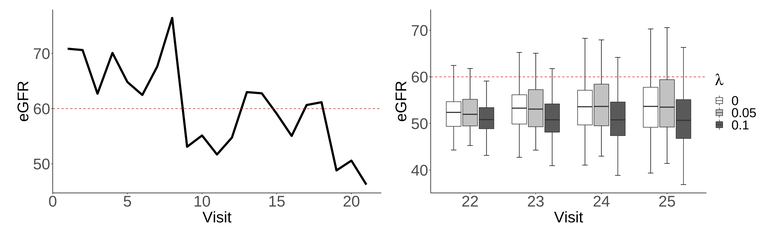


Figure 5: Left panel: observed eGFR (kidney function indicator) for individual I_2. Right panel: predicted eGFR under I_2's personalized optimal cARTs with respect to $\lambda = 0, 0.05, 0.1$. The dashed red lines represent the eGFR threshold.

The drug combination 3TC+ABC ($\lambda = 0.05, 0.1$) is sold as one pill (brand name *Epzicom*), making it more commonly prescribed than FTC+ABC ($\lambda = 0$) in clinical practice due to better adherence. Therefore, there is a **trade-off** between exploring regimens that are rarely or never used in the data with higher expected rewards and selecting commonly-prescribed regimens with lower risks.

6. Reference

[1] Wei Jin, Yang Ni, Leah H Rubin, Amanda B Spence, and Yanxun Xu. A Bayesian Nonparametric Approach for Inferring Drug Combination Effects on Mental Health in People with HIV. *Biometrics*, 2021.

[2] Tianhe Yu, Garrett Thomas, Lantao Yu, Stefano Ermon, James Y Zou, Sergey Levine, Chelsea Finn, and Tengyu Ma. MOPO: Model-based Offline Policy Optimization. *Advances in Neural Information Processing Systems*, 33:14129–14142, 2020.