Step 1: Initialize Parameters for Each Heterogeneous ctDNA Sample

Parameter Optimization: Initializing Parameters to Build Surrogate Models

FP/FN Constraint : Initializing Parameters to Build Surrogate Models

Step 2: Decoupling Parameter Optimization and Constraint Condition by ADMM

ADMM Alternates optimization between **the parameter & constraint** surrogate model

$$\mathcal{L}_\rho(P_c, P_d, d, z_1, z_2, y_1, y_2, y_3) =$$
$$f(P_{cd}^c) + \frac{\rho}{2} \| P_d^c - d \|_2^2 + \sum_{i=1}^{2} \left[MI(c_i(z_i) > 0) + y_i^T (\{P_c P_d^c\} - z_i) + \frac{\rho}{2} \| \{P_c P_d^c\} - z_i \|_2^2 \right]$$

Step 3: Optimal Constraint Decision by AGENT

AGENT : Iteratively constraints for optimal decision-making, with the constraint valu passed to ADMM for optimization.

$$L(\theta) = E_{(s,a,r,s') \sim D} \left[\left(r + \gamma \max_{a'} Q(s', a'; \theta^-) - Q(s, a; \theta) \right)^2 \right]$$

Step 4:Repeat Step 3 and Step 2 iteratively.

For each **heterogeneous ctDNA sample**, the agent determines the constraint value, while ADMM optimizes the parameter configuration.

Step 5:Train the meta-model.

Link **heterogeneous ctDNA genomic** data meta-features with their corresponding optimal variant detection parameter configurations to construct a comprehensive meta-dataset.

$$y^* = \arg\min_y \mathcal{L}(y, g(X)) + \lambda \cdot \mathcal{C}(y, X)$$