Abstract

Purpose: Radiation therapy treatment planning can be viewed as an iterative hyperparameter tuning process to balance conflicting clinical goals. In this work, we investigated the performance of modern Bayesian Optimization (BO) methods on automated treatment planning problems in high-dimensional settings.

Methods: 20 locally advanced rectal cancer patients treated with intensity-modulated radiation therapy (IMRT) were retrospectively selected as test cases. The adjustable planning parameters included both dose objectives and their corresponding weights. We implemented an automated treatment planning framework and tested the performance of two BO methods on the treatment planning task: one standard BO method (GPEI) and one BO method dedicated to high-dimensional problems (SAAS-BO). A random tuning method was also included as the baseline. The three automated methods' plan quality and planning efficiency were compared with the clinical plans regarding target coverage and organs at risk (OAR) sparing. The predictive models in both BO methods were compared to analyze the different search patterns of the two BO methods.

Results: For the target structures, the SAAS-BO plans achieved comparable hot spot control ($p = 0.43$) and homogeneity ($p = 0.96$) with the clinical plans, significantly better than the GPEI and random plans ($p<0.05$). Both SAAS-BO and GPEI plans significantly outperformed the clinical plans in conformity and dose spillage ($p<0.05$). Compared with clinical plans, the treatment plans generated by the three automated methods all made reductions in evaluated dosimetric indices for the femoral head and
the bladder. The analysis of the underlying predictive models has shown that both BO procedures have identified similar important planning parameters.

**Conclusions:** This work implemented a BO-based hyperparameter tuning framework for automated treatment planning. Both tested BO methods were able to produce high-quality treatment plans and reduce the workload of treatment planners. The model analysis also confirmed the intrinsic low dimensionality of the tested treatment planning problems.
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1. **Introduction**

The inverse planning in radiation therapy is achieved by minimizing a mathematical objective function with regard to the beam arrangements\(^3\). Traditionally, the treatment planner sets the planning parameters formulating the objective function, in order to satisfy multiple clinical goals. To find the optimal plan for an individual patient, the planner has to modify multiple planning parameters in a trial-and-error process to balance multiple conflicting clinical goals. When the number of adjustable parameters is large, performing the tuning process mentioned above is time-consuming. In addition, the planner’s experience and planning time constraints contribute to inconsistent plan qualities in the manual planning process. Previous studies have shown that automated treatment planning may mitigate the shortcomings of manual planning approaches\(^11\). In the literature, three major directions in automated treatment planning can be listed:

- **The knowledge-based planning** method leverages historical planning data to predict the dose-volume histograms (DVH), dose distributions, or optimization objectives. The predicted DVH/dose distributions of a new patient can serve as a warm start for the following optimization\(^4,5,49\). Another line of research aims to retrieve the planning parameters given the final treatment plan via the inverse optimization (IO) method\(^6,7,8\).

- **The multi-criteria optimization** (MCO) aims to handle conflicting objectives\(^2,9\) by searching for Pareto front for multiple objectives, instead of considering a composite scalar objective. The MCO algorithms can be separated based on the final plan decision strategy\(^42\) into *a posteriori* MCO\(^47\) and *a priori* MCO\(^48\). In either approach, sensitivity analysis of the objective weights or the constraint parameters is performed to quantify the parameter influence on the objective function\(^40,41\). However, this requires the knowledge of the specific form of the objective function for efficient derivative evaluation, which is not available in commercial treatment planning systems (TPS).

- **The automated iterative planning** formulates the automated planning as an iterative hyperparameter tuning process. A scoring function evaluating the current plan quality is defined, and the planning parameters for the next optimization cycle are adjusted\(^10\) according to previous optimization results. Numerous works have embraced this idea due to its simplicity and minimum interfacing requirement\(^12,13,14,39\).
Following the line of research in automated iterative planning, our work in this paper involves applying Bayesian Optimization (BO) in treatment planning. BO is a model-based hyperparameter optimization method used in a wide range of areas, including automatic machine learning\textsuperscript{17}, robotics\textsuperscript{18}, sensor networks\textsuperscript{16}, and engineering design\textsuperscript{19}. In radiation treatment planning, BO has been applied to solve beam angle optimization\textsuperscript{20} and hyperparameter tuning problems\textsuperscript{21,23}.

Although the performance of BO in these missions demonstrates some potential, the problem’s dimensionality in the aforementioned works has been kept relatively moderate ($\leq 20$). In clinical practice, the number of planning parameters can mount up to 50, posing issues for the iterative planning methods. Lu et al. detected sensitive parameters according to the correlation measures between each planning parameter and the composite plan quality\textsuperscript{25}. However, they identified the sensitive parameters based on a pre-calculated optimization dataset, limiting the application scope of the methods.

The work most similar to ours is Maass et al.\textsuperscript{23}, where the authors performed BO on the planning parameters for lung cancer SBRT planning. In this work, we further investigated the BO applications on automated treatment planning in high-dimensional settings. We implemented a hyperparameter optimization framework integrated with an Eclipse TPS (Varian Medical Systems, Inc., Palo Alto, CA). Based on this framework, we compared the performance of a recently proposed BO method for high-dimensional problems\textsuperscript{30} with a standard BO method in the context of rectal cancer intensity-modulated radiation therapy (IMRT) planning. Little expert knowledge was incorporated in the planning problem design, to fully demonstrate the potential of the BO applications in automated treatment planning. We demonstrate that both BO methods achieved comparable or better plan quality in organs at risk (OAR) sparing and target coverage than manual planning. In addition, an analysis was performed on both BO method’s predictive models. The analysis demonstrated that both BO methods identified similar sensitive planning parameters on-the-fly, without knowledge of prior optimized plans. Based on the the prediction model analysis, an explanation was provided on the different search behaviors of the two BO approaches.
II. Methods

The general scheme of the automated treatment planning framework performed in this work is presented in figure 1. For clarity, we omitted the processes prior to the planning parameter setup in the presented scheme (image registration, contouring, beam angle optimization, etc.). The main loop of this framework can be separated into two parts:

1. The first part involves emulating the manual planning process and the plan quality evaluation. A set of dose objectives and weights $\theta = \{w_i, i = 1, \ldots, s\}$ is sent to the TPS optimizer interface, specifying the fluence map optimization (FMO) problem to be solved. From the perspective of the FMO problem, $\theta$ is viewed as the hyperparameter set. Given the specific problem, the TPS optimizer outputs the optimal fluence map and the corresponding dose distribution. The plan quality was quantified by a predefined score function based on the corresponding dose distribution. The whole process is viewed as a black-box function $g(\theta)$, where the input is the planning parameters and the output is the corresponding plan quality score. At last, the newly observed $(\theta, g(\theta))$ are sent into the BO procedure.

2. The second part consists of employing BO to find the most promising $\theta$ for the next round of TPS optimization. Specifically, the BO procedure appends the newly observed data $(\theta, g(\theta))$ to the observed dataset, updates the surrogate model with the new data set, and proposes the next hyperparameter set for trial.

Aside from the main loop in the framework, an exit control has been included conditioned on the iteration numbers. The final treatment plan was generated with the currently best observed $\theta$, when the iteration number exceeds the predefined threshold. In the remainder of this section, we first detail the BO application in the automated treatment planning context and explain the methodology we adopted for high-dimensional BO in subsection II.A. and II.B.. The specific form of the plan quality score function is defined in subsection II.C. and the following subsections describe the implementation and the experimental setup.
Figure 1: The framework of BO approach applied to automatic treatment planning.

II.A. Bayesian Optimization

As shown in figure 1, the proposed framework employs BO to select the planning parameters for treatment planning. Because evaluating \( g(\theta) \) is expensive, we want to rely on a sample-efficient meta optimization method, as is the BO. As a model-based optimization algorithm, BO tunes the planning parameters in two main steps:

1. **Modelling**: A surrogate model \( \hat{g}(\theta) \) is used to approximate \( g(\theta) \), given an observed dataset \( \mathcal{D} = \{ \theta_i, g(\theta_i) \}_{i=1} \). The arguably most popular surrogate model in BO is the Gaussian Process (GP)\(^{27} \). GP can be thought of as a Gaussian distribution of functions, characterized by a mean function \( \mu \), and a covariance function \( k(\theta, \theta') \). Without loss of generality, \( \mu \) is set to 0, and the covariance function serves to describe the similarity between the function values (\( \hat{g}(\theta) \) and \( \hat{g}(\theta') \)) as a function of the distance measure between two hyperparameter sets \( r(\theta, \theta') \). In this work, a GP regression model equipped with a Matérn-5/2 covariance/kernel function was used to approximate the

II. METHODS

II.A. Bayesian Optimization
score function \( g(\theta) \), expressed as

\[
\text{distance} : \quad r(\theta, \theta')^2 = \sum_{i=1}^{s} ((w_i - w'_i)/l_i)^2,
\]

\[
\text{covariance} : \quad k(\theta, \theta') = \sigma_{\text{k}}^2 (1 + \sqrt{5}r + \frac{5}{3}r^2) \exp(-\sqrt{5}r),
\]

\[
\text{function value} : \quad \hat{g}(\theta) \sim \mathcal{GP}(0, k(\theta, \theta')),
\]

\[
\text{observation} : \quad g(\theta) \sim \mathcal{N}(\hat{g}(\theta), \sigma^2),
\]

where \( \sigma^2 \) denotes the observational noise, \( \sigma_{\text{k}}^2 \) the kernel variance. We considered the optimization environment noiseless, so \( \sigma^2 \) was set to \( 1 \times 10^{-6} \) for regularization purposes.

In the distance measure, the length scale \( l_i \) was introduced to control the relevance of the corresponding planning parameter \( w_i \). Generally, larger \( l_i \) indicates less relevance of \( w_i \) because identical variation with larger length scales corresponds to smaller changes in the distance measure. The GP model’s hyperparameter set \( \psi = \{\sigma_{\text{k}}, l_1, \ldots, l_s\} \) was determined by maximizing the model’s probability with regard to the observed dataset. Since \( l_i \) depends on the range of \( w_i \), we normalized \( \theta \) to the \([0, 1]^s\) domain before learning the GP model to ensure robust model performance. Note that at the initial stage of BO, the observed dataset was populated by pseudo-random hyperparameter sets \( \theta_{1:m} \) and their corresponding plan quality scores.

2. **Acquisition function**: When the GP regression model was learned, an acquisition function was used to find the next hyperparameter set for trial. While various acquisition functions have been proposed, we used in this work the expected improvement (EI) due to its computational efficiency and good empirical performance\(^{28}\). The EI is defined as

\[
\text{EI}(\theta) = \mathbb{E}[\max(0, g(\theta) - g(\theta^+))],
\]

where \( \mathbb{E} \) denotes the expected value, and \( g(\theta^+) \) denotes the currently best observed value. Note that the \( g(\theta) \) prediction incorporates both the mean and the variance, due to the probabilistic nature of the GP regression model. Therefore the EI inherently balance between exploration and exploitation. The hyperparameter set with the highest EI is then selected for the next trial. A summary of the described BO procedure is given in Algorithm 1.
### Algorithm 1 BO procedure for treatment planning

**Input:** score function $g(\cdot)$; initial evaluation budget $m$; total evaluation budget $T$.

**Output:** final maximizer and maximum $(\theta_{\text{max}}, g(\theta_{\text{max}}))$

1. Sample initial hyperparameter set $\theta_{1:m}$.
2. Query $g(\theta_i), i = 1, \ldots, m$ by passing $\theta_i$ to TPS for optimization.
3. Let $\mathcal{D} = \{(\theta_i, g(\theta_i)) \mid i = 1, \ldots, m\}$.
4. for $t = m + 1, \ldots, T$ do
   5. Fit GP with $\mathcal{D}$ to determine $\psi_t$.
   6. Optimize EI to obtain $\theta_t = \arg\max_{\theta} \text{EI}(\theta | \psi_t)$.
   7. Query $g(\theta_t)$.
   8. Append $(\theta_t, g(\theta_t))$ to $\mathcal{D}$.
   9. $\theta_{\text{max}} = \arg\max \{g(\theta_i) \mid i = 1, \ldots, t\}$.
10. return $(\theta_{\text{max}}, g(\theta_{\text{max}}))$

### II. METHODS

#### II.B. High dimensional considerations

The dimension of the planning parameters in a realistic treatment planning problem varies from 20 to 50, depending on the tumor sites and prescription complexities. The high dimensionality poses a problem for many meta optimization approaches. In the context of BO, we have applied a recently proposed BO algorithm named “Sparse Axis Aligned Subspace BO” (SAAS-BO) to solve the high-dimensional treatment planning problems. The core idea of SAAS-BO is to introduce a sparsity-inducing prior on the GP length scales $\{l_i\}_{i=1}^s$, assuming that only a few parameters are important for the composite plan quality. This assumption is in accordance with previous findings that the effective dimension in treatment planning problems can be much smaller than the number of adjustable parameters. We chose this algorithm due to its great empirical performance and the model’s explicability since the dimension reduction was performed on the original axis of the planning parameters. The interested reader is referred to the cited reference for a detailed description of this method. To evaluate the SAAS-BO’s effectiveness in automated treatment planning, we have included both a standard BO (GPEI) and a random-sampling method (random) as baseline methods. In the GPEI approach, a uniform gamma prior was placed on all the length scales of the GP regression model. The EI was used as the acquisition function, identical to SAAS-BO. In the random sampling method, a Sobol sequence was used to generate the random planning parameters. The full GP regression model specifications in the SAAS-BO and GPEI methods were listed in the supplementary material for reference.
II.C. Score Function

To evaluate the agreement with the clinical goals, the score function was defined as a weighted sum of multiple plan quality metrics (PQM):

$$g(\theta) = \left( \frac{\sum_{i=1}^{n} \alpha_i F_i(m_i; \bar{m}_i) \right) / \sum_{i=1}^{n} \alpha_i,$$

(3)

$$F_i(m_i; \bar{m}_i) = \min_{j=1,2} \left( a_j (m_i - \bar{m}_i) / \bar{m}_i \right) \text{ and } \alpha_i = 2^{-p_i},$$

where $F_i(m_i; \bar{m}_i)$ denotes the $i$th scoring term, $m_i$ the corresponding PQM derived from the dose distribution generated by the planning parameter set $\theta$, and $\bar{m}_i$ the clinical goal to achieve. Specifically, we used 2-segment piecewise linear functions to characterize $F_i(m; \bar{m}_i)$, which serves to penalize the score severely when the clinical goal is not reached, and to reward slightly for the further improvement once the clinical goal is achieved. $a_j$ defines the slope of each segment in the piecewise linear function. Similar to Huang et al.\textsuperscript{12}, we grouped the clinical goals into several tiers indexed by $p_i$, and set the weight $\alpha_i$ associated with the $i$th goal as an inverse exponential function of $p_i$. We set the scoring terms related to the target structures to the top tier, to emphasize their importance in the plan evaluation. The terms related to dose sparing for OAR and healthy tissues were set to lower tiers, respectively. The specific formats of PQM terms used in this study included min/max dose, mean dose, dose-volume parameters (e.g., $D_{2\%}$ for hot spot control), and dose spillage ($R_{50\%}, R_{90\%}$).\textsuperscript{24} For the rectal cancer test cases, The clinical goals related to these terms were set according to the institutional requirements\textsuperscript{26}, as listed in table 1.

II.D. Implementation

The proposed auto planning framework was coupled with an Eclipse TPS v16.1, where the Python Eclipse Scripting Application Programming Interface (PyESAPI) was used for message passing between the BO procedure and the TPS. Within the Eclipse TPS, the Photon Optimizer (PO) was used for inverse planning, while the intermediate and final doses were calculated with the Acuros XB algorithm (AXB).\textsuperscript{33} The voxel sizes for PO and AXB were set at 2.5 mm, identical to the clinical configuration. All three automated treatment planning procedures (random, GPEI, SAAS-BO) have been implemented based on the open-source libraries ax/Botorch.\textsuperscript{32,45} We set the iteration budgets $m = 20$ and $T = 120$, respectively, to control the optimization time clinically relevant. To compare with the clinical plans, the
intermediate dose was calculated at the end of the hyperparameter tuning process, and the final optimization was performed based on the accurately calculated dose without changing any planning parameters. The treatment plans were normalized to satisfy the institutional prescription on target volumes. When the prescription contains multiple requirements, the smallest normalizing factor was chosen to fulfill all target volume prescriptions. To ensure this study as reproducible as possible, we have made the implementation publicly available\(^b\).

### II. METHODS

#### II.E. Clinical Experiment

The implemented iterative planning approach was tested on rectal cancer treatment plans. We obtained 20 preoperative IMRT treatment plans for locally-advanced rectal cancer patients in our institution. All treatment plans were manually optimized and previously treated. The plans were all designed with the Eclipse TPS to deliver equispaced 7-field IMRT plans with 10MV photon beam. The target prescription implements a concomitant boost technique with 22 fractions for the clinical target volume (CTV) and the gross tumor volume (GTV), respectively\(^26\). Additional target regions of interest (ROI) were created by expanding the aforementioned structures with a 5 mm margin, identified as the PTV and the PGTV. An auxiliary structure named “IrradVolume” was created by subtracting the PGTV from the PTV for additional dose distribution control. The institutional prescription requires 95% and 99.9% coverage of the PTV and the CTV with 41.8 Gy, and similarly 95%

\(^b\)https://github.com/inamoto85/BOPlanner
and 99.9% coverage of the PGTV and the GTV with 50.6 Gy\textsuperscript{26}. The OARs included the bladder, femoral head, external body, and avoidance, which is a support structure to spare both the anterior and posterior abdomen, covering mainly the small intestine and the bone marrow. The optimization objectives for the ROIs included max/min dose, mean dose, and dose-volume parameters. Both the dose objective and the corresponding weight were considered as adjustable parameters, formulating a 34-D problem. The adjustment range of the weights was defined uniformly as [100, 1000]. However, the target dose objective ranges were defined as [100\%, 105\%] of the respective dose prescriptions. The upper dose limits for the OARs were defined according to RTOG-0822\textsuperscript{37} and institutional experiences, while the lower dose limits for the OARs were set uniformly at 1 Gy. In addition, constraints on the dose objectives were introduced to avoid logically contradictory objectives, e.g., \( D_{\text{GTV}}^{\text{min}} < D_{\text{Body}}^{\text{max}} \).

Table 2 details all the parameters, adjustment ranges, and constraints used for the two BO approaches. Finally, the normal tissue objective (NTO) was set with a fixed weight of 500 to control dose fall-off.

Table 2: Optimization parameters, ranges and constraints of rectal cancer cases treatment planning. Abbreviations: IV - IrradVolume; FH - Femoral Head; UB: Urinary Bladder.

| Parameter          | Type       | Dose Objective (Gy) | Weight       | Constraints                                      |
|--------------------|------------|---------------------|--------------|--------------------------------------------------|
| \( D_{\text{Body}}^{\text{max}} \) | upper      | [50.6, 53.13]       |              |                                                  |
| \( D_{\text{CTV}}^{\text{min}} \) | lower      | [41.8, 43.89]       |              |                                                  |
| \( D_{\text{PTV}}^{\text{min}} \) | lower      | [41.8, 43.89]       |              |                                                  |
| \( D_{\text{GTV}}^{\text{min}} \) | lower      | [50.6, 53.13]       |              |                                                  |
| \( D_{\text{PGTV}}^{\text{min}} \) | lower      | [50.6, 53.13]       |              |                                                  |
| \( D_{\text{IV}}^{\text{max}} \)  | upper      | [44.65, 49.35]      |              |                                                  |
| \( D_{\text{IV}}^{\text{min}} \)  | lower      | [41.8, 43.89]       |              |                                                  |
| \( D_{\text{Avoidance}}^{\text{max}} \) | upper      | [1, 45]             |              |                                                  |
| \( D_{\text{Avoidance}}^{\text{mean}} \) | upper   | [1.20]              | [100,1000]   | \( D_{\text{Avoidance}}^{\text{mean}} < D_{\text{Avoidance}}^{\text{max}} \) |
| \( D_{\text{FH}}^{\text{max}} \)  | upper      | [1.50]              |              |                                                  |
| \( D_{\text{FH}}^{25\%} \)      | upper      | [1.20]              |              |                                                  |
| \( D_{\text{FH}}^{40\%} \)      | upper      | [1.20]              |              |                                                  |
| \( D_{\text{FH}}^{\text{mean}} \) | upper      | [1.15]              |              |                                                  |
| \( D_{\text{UB}}^{\text{max}} \)  | upper      | [1.50]              |              |                                                  |
| \( D_{\text{UB}}^{15\%} \)       | upper      | [1.40]              |              |                                                  |
| \( D_{\text{UB}}^{40\%} \)       | upper      | [1.25]              |              |                                                  |
| \( D_{\text{UB}}^{\text{mean}} \) | upper      | [1.20]              |              |                                                  |

To investigate the effectiveness of the SAAS prior, we first compared the prediction accuracy between standard GP and SAAS-GP on an identical data set. The data set was...
created by optimizing one rectal cancer plan with planning parameters, including 2000 entries of \((\theta, g(\theta))\) pair. The standard GP model and the SAAS-GP model were trained on a subset of 100 samples, and another subset of unseen 100 samples was used to evaluate the prediction accuracies of both trained GP models. This procedure was repeated 20 times for statistical evaluation.

With each patient, three automated treatment plans were obtained to compare with the original treatment plan (clinical): the plan obtained by the random method and two BO plans obtained by GPEI and SAAS-BO, respectively. The plan quality was evaluated based on target homogeneity index (HI)\(^{44}\), conformity index (CI)\(^{43}\), and clinical goals in Table 1. The aforementioned dosimetric indices of the four plans were compared and analyzed using Wilcoxon signed-rank test, where the differences were considered statistically significant for \(p < 0.05\). In addition, the optimization efficiency among the three automated methods was compared in terms of planning time and improvement per iteration.

To further compare the two BO methods, the length scales of the final fitted GP models (standard GP and SAAS-GP) for each patient were analyzed to identify the sensitive optimization parameters. Following the automatic relevance determination (ARD) principle\(^{27}\), the relative importance of each parameter was quantified as the inverse of its corresponding length scales. At last, the optimal planning parameters of three automated planning methods were compared.

### III. Results

#### III.A. Prediction accuracy

Figure 2 demonstrates the predicted PQM score accuracy comparison of the standard GP model and the SAAS-GP model, given identical training and test data. Table 3 illustrates the statistical diagnostics on the 20 repeated comparisons, including Pearson correlation coefficient, Spearman’s rank correlation coefficient, mean absolute percentage error (MAPE)\(^{38}\), and log likelihood on the test dataset. The SAAS-GP model outperformed the GP model significantly in all the statistical measures. The reasons for such differences in prediction accuracy were twofold: 1) The 100 random samples in the 34-D parameter space were sparsely distributed; 2) There was a difference in the length scale assumptions for two GP models -
the standard GP model assumed equal importance of each dimension and the learned length scales were relatively small, of the same magnitude. Since a random testing point is highly likely to be far from the training samples (i.e., no similarity between the test input and the training samples can be exploited), the corresponding prediction reverts to the mean over the training dataset. In contrast, the SAAS-GP model assumed that only a limited number of dimensions were important (the length scales of these dimensions are small), and the resulting predictions were more meaningful for further optimization.

Table 3: Statistical diagnostics on the validation results for the standard GP and SAAS-GP model respectively.

|            | corr. coef. | rank corr. | MAPE   | log likelihood |
|------------|-------------|------------|--------|----------------|
| SAAS-GP    | 0.79 ± 0.04 | 0.75 ± 0.07 | 0.66 ± 0.28 | −281.31 ± 39.56 |
| GP         | 0.49 ± 0.09 | 0.55 ± 0.08 | 1.43 ± 0.57  | −330.89 ± 45.96  |

Figure 2: Prediction accuracies for both GP models on unseen sub-dataset, with the error bars representing 1 SD.

Figure 3 demonstrates the best observed PQM scores per iteration for random, GPEI, and SAAS-BO methods. Additionally, the average PQM score of the clinical plans is also plotted for comparison. At the end of the tuning phase, the average scores achieved by SAAS-BO and GPEI surpassed that of the clinical plans with similar margins. Meanwhile, the SAAS-BO spent fewer iterations to achieve convergence compared to GPEI. Further, SAAS-BO achieved the smallest variance on the PQM score over most of the iterations, indicating a more robust improvement than the GPEI and random methods. The optimization time of
random, GPEI, and SAAS-BO are, respectively, 0.66 h (±0.06 h), 3.16 h (±0.81 h), and 6.91 h (±0.43 h).

Figure 3: PQM score progress as a function of the iterations, along with the average PQM score of clinical treatment plans, where the color bands represent 1 SD.

III.B. Dosimetric comparison

Figure 4 shows the mean DVH of the clinical, random, GPEI, and SAAS-BO plans with corresponding standard deviations. Compared with the clinical plans, all plans generated by three automated methods have shown some improvement in OAR sparing, especially in the high dose region. For the GTV/PGTV regions, the SAAS-BO plans have achieved comparable hot spot control with the clinical plans, while the random and GPEI plans exhibited excessive high dose tails. Compared with the random and GPEI plans, the SAAS-BO plans have shown disadvantages in the low-dose regions for the femoral head. Further dosimetric comparisons between clinical, random, GPEI, and SAAS-BO plans are summarized in table
4. All plans have satisfied the prescribed requirements on the dose coverages for the target ROIs. The SAAS-BO plans demonstrated comparable hot spot control ($D_{2\%}$ in the PGTV) with the clinical plans, significantly better than the GPEI and random plans ($p < 0.05$). Regarding the HI in the PGTV and the CI in the PTV, SAAS-BO plans achieved the best performances among the four plans with significance ($p < 0.05$). Related to the CI, both BO plans achieved better performances in the dose spillage indicators ($p < 0.05$), indicating quicker dose fall-off outside the PTV.

For the femoral head, significant reductions in $V_{20Gy}$, $V_{30Gy}$ and $D_{\text{max}}$ for three automatic plans have been observed versus the clinical plans. The GPEI and random plans achieved significant reductions in mean dose of the femoral head over the clinical plans. For the bladder, major reductions in $V_{25Gy}$ and mean dose have been observed in SAAS-BO and GPEI plans, compared with the clinical plans. However, the maximum dose in SAAS-BO plans was higher than that of the clinical plans ($p < 0.05$).

![Figure 4: DVH comparison on the rectal cancer treatment plan cohort. The solid lines represent the means and the color bands represent 1 SD, and dose prescriptions were represented by gray dashed lines.](image)

Last edited February 15, 2023 III.B. Dosimetric comparison
Table 4: Dosimetric statistics among clinical plans, SAAS-BO plans, and GPEI plans. The Wilcoxon signed-rank test is used to compare plans, with significant values marked in bold (p < 0.05).

| Structure | Parameter | Clinical | SAAS-BO | GPEI | Random | Clinical vs. SAAS-BO | Clinical vs. GPEI | Clinical vs. Random | SAAS-BO vs. GPEI | SAAS-BO vs. Random | GPEI vs. Random |
|-----------|-----------|----------|---------|------|--------|----------------------|------------------|---------------------|-----------------|-------------------|------------------|
| GTV       | $D_{50\%}$ | 50.40 (0.54) | 50.78 (0.38) | 50.92 (0.37) | 51.34 (0.98) | 0.009 | 0.001 | <0.001 | 0.036 | 0.013 | 0.056 |
|           | $D_{95\%}$ | 51.29 (0.83) | 52.09 (0.37) | 51.84 (0.46) | 51.60 (0.94) | 0.037 | 0.023 | <0.001 | 0.036 | 0.013 | 0.078 |
|           | HI        | 0.06 (0.01) | 0.06 (0.02) | 0.07 (0.02) | 0.09 (0.04) | 0.056 | 0.001 | 0.001 | 0.001 | 0.017 | 0.001 |
| CTV       | $D_{50\%}$ | 41.89 (0.46) | 42.20 (0.44) | 42.08 (0.35) | 42.10 (0.42) | 0.058 | 0.083 | 0.048 | 0.518 | 0.453 | 1.000 |
|           | $D_{95\%}$ | 42.10 (0.42) | 42.11 (0.46) | 42.09 (0.38) | 42.11 (0.43) | 0.063 | 0.052 | 0.048 | 0.518 | 0.453 | 1.000 |
|           | HI        | 0.06 (0.01) | 0.06 (0.02) | 0.07 (0.02) | 0.09 (0.04) | 0.056 | 0.001 | 0.001 | 0.001 | 0.017 | 0.001 |
| PGTV      | $D_{98\%}$ | 50.72 (0.47) | 50.86 (0.14) | 50.97 (0.38) | 51.19 (1.64) | 0.048 | 0.015 | 0.036 | 0.475 | 0.349 | 0.546 |
|           | $D_{95\%}$ | 50.99 (0.48) | 51.11 (0.35) | 51.26 (0.35) | 51.60 (0.94) | 0.133 | 0.005 | 0.007 | 0.651 | 0.119 | 0.189 |
|           | HI        | 0.06 (0.01) | 0.06 (0.02) | 0.07 (0.02) | 0.09 (0.04) | 0.056 | 0.001 | 0.001 | 0.001 | 0.017 | 0.001 |
| PTV       | $D_{50\%}$ | 41.46 (0.90) | 41.55 (0.55) | 41.61 (0.41) | 41.76 (0.89) | 0.153 | 0.011 | 0.004 | 0.123 | 0.058 | 0.114 |
|           | $D_{95\%}$ | 41.76 (0.89) | 41.85 (0.57) | 41.92 (0.42) | 42.02 (0.91) | 0.223 | 0.020 | 0.003 | 0.123 | 0.058 | 0.114 |
|           | HI        | 0.06 (0.01) | 0.06 (0.02) | 0.07 (0.02) | 0.09 (0.04) | 0.056 | 0.001 | 0.001 | 0.001 | 0.017 | 0.001 |
| Femoral Head | $V_{20\%}$ | 22.00 (1.81) | 21.70 (1.4) | 21.50 (1.3) | 21.30 (1.2) | <0.001 | <0.001 | <0.001 | 0.261 | 0.177 | 0.245 |
|           | $V_{30\%}$ | 2.88 (1.44) | 2.71 (1.15) | 2.58 (1.06) | 2.48 (1.04) | <0.001 | <0.001 | <0.001 | 0.784 | 0.044 | 0.076 |
| Bladder   | $V_{25\%}$ | 25.52 (4.99) | 24.60 (3.93) | 24.06 (3.64) | 23.92 (3.70) | <0.001 | <0.001 | <0.001 | 0.571 | 0.430 | 0.784 |
|           | $V_{45\%}$ | 3.63 (3.21) | 3.00 (2.65) | 2.92 (2.49) | 2.89 (2.39) | 0.058 | 0.006 | 0.003 | 0.571 | 0.430 | 0.784 |
|           | HI        | 0.06 (0.01) | 0.06 (0.02) | 0.07 (0.02) | 0.09 (0.04) | 0.056 | 0.001 | 0.001 | 0.001 | 0.017 | 0.001 |

III.C. Parameter importance

Figure 5 summarizes the relative importance statistics of the 34 planning parameters at the end of the BO (i.e., $T = 120$) for both GPEI and SAAS-BO methods. We first note that the most important parameters between the two GP models were quite consistent — 4 out of the top 5 most important parameters in the SAAS-BO model were in the top 5 in the GPEI model. Among the four common important parameters, three were related to the bladder, and one to the avoidance structure. The detected important parameters were consistent with the clinical experiences: both the contoured bladder and avoidance ROIs were large, close to the targets, and often overlapped with the targets, therefore affecting the PQM score significantly with small parameter changes. Some differences can be though observed between the parameter importance of the two methods: The magnitudes of the length scales from the GPEI methods were relatively uniform, where the minimum relative importance was 83% of the maximum relative importance. Meanwhile, the minimum relative importance was 19% of the maximum relative importance in the SAAS-BO methods. This observation was mainly due to the different priors between the SAAS-GP and GP models. For both methods, although the important parameters were distinguishable from the others, the distributions of their relative importance spanned large ranges, indicating that these
parameters were deemed not important in some cases. The large variance might be caused by the correlated optimization parameters, e.g., the mean dose objective and its weight for the bladder. On average, the target objectives were less important than their corresponding weights, because all parameter ranges were normalized to [0, 1], while the varying ranges of the dose objectives for the targets were much smaller than those of the objective weights.

Figure 5: Relative importance box plot of the GP models related to the SAAS-BO and GPEI methods, averaged over the 20 rectal cancer treatment plans, normalized to the corresponding maximum values. The parameters were sorted according to their importance in descending order. The top 5 planning parameters in the SAAS-GP model were marked in bold, the orange line representing the median value.
III.D. Optimal planning parameters

We demonstrate the optimal parameter distributions for three automated planning methods in figure 6. In general, the optimal dose objectives for the OAR in SAAS-BO were set higher on average compared to those in GPEI and random methods, indicating less focus on the OAR sparing. However, the SAAS-BO methods emphasized on the hot spot control in the target ROIs (i.e., $D_{\text{Body}}^\text{max}$ and its related weight) compared to the other two methods. We note that most of the optimal parameter distributions in SAAS-BO span larger ranges compared to those in GPEI, indicating that GPEI performed more localized searches in the parameter space.
Figure 6: Optimal planning parameter distribution for 3 automated planning methods
IV. Discussion

Our method to automate the planning process belongs to the automated iterative planning approach. The core idea is to incorporate an additional global optimization loop so that optimal planning parameters can be found during the outer iterations, which does not require prior plan data. The advantages of this hyperparameter optimization approach are in two main aspects:

- The clinical goals for the final plan quality evaluation do not need to be the same as the objectives used for inverse planning, and the clinical practice often falls into this scenario. The hyperparameter optimization enables some flexibility in this regard, since a lot of dosimetric indices used in the plan quality evaluation might not be readily available as objectives in the optimization algorithm. This flexibility enables easier adaptation to clinical goal changes if patient-specific concern appears.

- The hyperparameter optimization was built on top of the TPS, acting as a self-contained module in the optimization workflow. The modular design reduces coupling with the inverse planning algorithm. Any update or feature change in the optimization can be adopted and inherited via hyperparameter optimization with less effort.

Among numerous global optimization methods, BO utilizes the GP regression to model the underlying relation between the planning parameter space and PQM score. Compared with the work of Maass et al., we further studied the BO application in automated iterative planning with higher dimensionality. In addition, we included both the dose limit and the corresponding weight into the adjustable set, testing the automated planning approach in a more challenging scenario (with minimum expert knowledge). We evaluated the performance of the recently proposed SAAS-BO approach by comparing it with a GPEI method and a random search method. Both BO methods achieved similar PQM scores on the tested rectal cancer plans, significantly outperforming the clinical plans in terms of the PQM score and the dosimetric indices (heterogeneity, conformity, dose spillage, and DVH metrics).

Unlike other derivative-free optimization methods, the BO approaches provide a GP regression model which learned the latent function mapping the planning parameters to the PQM score. By analyzing the length scales of the learned GP model, we observed that on
average, both GP models identified similar important planning parameters. In addition, the identified parameters were consistent with clinical planning experiences. However, large variance for the planning parameters can be observed, even for the most important parameters, probably caused by the fact that the intrinsic problem dimension is small, and the over-parameterization introduced many correlated planning parameters. Although the over-parameterization seemed excessive in our problem setting, this reflected to some extent the common clinical practice. Our results demonstrated that the BO approaches were able to outperform the clinical treatment plans, even under severe over-parameterization conditions.

We now compare the different behavior between the SAAS-BO and the GPEI methods in detail. On random optimized datasets, the SAAS-GP exhibited significant advantages over the standard GP in prediction accuracy, as shown in figure 2. This is consistent with the observation that SAAS-BO made a quicker PQM score improvement in the early tuning process than GPEI, as shown in figure 3. However, the SAAS-BO progress quickly reached bottlenecks in the subsequent tuning process and underperformed the GPEI in the end. In addition, we note that SAAS-BO explored much larger search spaces than GPEI on the optimal planning parameter distributions. Combining these two observations, we concluded that the reason for this behavior is that the intrinsic important parameters were not as sparse as the SAAS-BO prior assumed. As a result, SAAS-BO tends to propose query input far to the current best input for most of the “unimportant” parameters (i.e., parameters with large length scales), and this search pattern reduces the optimization efficiency at the end of the tuning process. On the contrary, the explored region of the GPEI was very concentrated. This is because the standard GP model overfitted and returned the trivial mean of the training dataset for most of the search space (shown in figure 2). The acquisition function proposed query input very close to the current best input. In retrospect, a better optimization strategy might be a hybrid one, i.e., performing the SAAS-BO to identify first the important parameters and then switching to GPEI for more localized searches.

The optimization time using BO approaches was relatively long, especially for the SAAS-BO. In SAAS-BO, the GP model was learned in a fully Bayesian manner, i.e., the Markov Chain Monte Carlo (MCMC) sampler was used to infer the hyperparameter posterior density. The sampling approach increased the model fitting time drastically compared to the gradient-based maximum likelihood approach. In addition, we found that the numerous constraints in table 2 significantly increased the evaluation time in the acquisition function.
an ablation study, we removed all the constraints and performed hyperparameter optimization with the random, GPEI and SAAS-BO with identical settings (PQM score function, iteration budget, etc.). The average optimization time of random, GPEI, and SAAS-BO are $0.41 \pm 0.01$ h, $0.80 \pm 0.15$ h, and $2.86 \pm 0.39$ h, respectively. On average, the optimization time was reduced to $\sim 40\%$ of the time used in the constrained setting. Conversely, the average final PQM scores without constraints were reduced by $20\%$, $6\%$, and $5\%$ compared with the average scores with constraints for the random, GPEI, and SAAS-BO methods. Among three automated planning methods, SAAS-BO benefited the least from the constraints, indicating its intrinsic dimension reduction ability. The corresponding PQM score progress plots and the DVHs were attached to the supplementary material. To reduce further the hyperparameter optimization time, techniques such as early stopping and parallel BO are to be considered.

Nevertheless, this work is subject to some limitations. The current BO implementation considers the PQM score function as a black box, where the GP model seemed overly flexible for some input dimensions. One way to improve the optimization efficiency would be composite function BO\textsuperscript{35}, i.e., exposing the PQM score function structure to the BO algorithm and modeling various terms in the score function by multi-output GP. Another direction would be to investigate the performance of the projection-based BO\textsuperscript{34} method in automated treatment planning since many planning parameters appeared strongly correlated, as shown in this work. In terms of clinical application, we hope to extend the developed BO approach to other sites (e.g., H&N, lungs, etc.), investigating the dimensionality influences in more complex cases.

V. Conclusion

In this work, we compared the performances of two BO approaches (SAAS-BO and GPEI) applied in automated treatment planning in high dimensional settings. The clinical experiment was performed in the context of rectal cancer treatment planning. We demonstrated that both BO methods were able to produce comparable or superior plans compared with the clinical plans for all evaluated dosimetric indices. Both methods were able to identify similar sensitive sets of planning parameters with minimum expert knowledge. The developed approach can be integrated with any TPS including a scripting API, and is expected
to ameliorate plan quality and reduce the planning workload.

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This document contains the detailed model specifications and supplementary results to accompany the manuscript named: “High-dimensional Automated Radiation Treatment Planning via Bayesian Optimization”.

1 GP model specification

Here the full specifications for the SAAS-GP and GP regression models are listed, respectively.

GP (used in the GPEI):

- **kernel scale**: \( \sigma_k^2 \sim \text{Gamma}(2, 0.15) \),
- **length scale**: \( l_i \sim \text{Gamma}(3, 6) \) for \( i = 1, \ldots, s \),
- **distance**: \( r(\theta, \theta')^2 = \sum_{i=1}^{s} \left( (w_i - w_i')/l_i \right)^2 \),
- **covariance**: \( k(\theta, \theta') = \sigma_k^2 \left( 1 + \sqrt{5}r + \frac{5}{3}r^2 \right) \exp(-\sqrt{5}r) \),
- **function value**: \( \hat{g}(\theta) \sim \mathcal{GP}(0, k(\theta, \theta')) \),
- **observation**: \( g(\theta) \sim \mathcal{N}(\hat{g}(\theta), \sigma^2) \),
SAAS-GP (used in the SAAS-BO):

- **Kernel scale**: \( \sigma_k^2 \sim \text{Gamma}(2, 0.15) \),
- **Shrinkage scale**: \( \tau \sim \mathcal{HC}(0.1) \),
- **Inverse squared length scale**: \( \rho_i \sim \mathcal{HC}(\tau) \) for \( i = 1, \ldots, s \),
- **Length scale**: \( l_i = \sqrt{1/\rho_i} \),

where \( \mathcal{HC} \) denotes the half-Cauchy distribution. One can notice the major difference between the two model lies in the length scale priors. Such difference in the priors leads to different inference strategies to infer the posterior density of the GP hyper-parameters \( \psi = \{\sigma_k, l_1, \ldots, l_s\} \) given the data.

According to the Bayes’ theorem, the posterior distribution of the \( \psi \) for the standard GP model can be expressed as

\[
p(\psi|\Theta, g) \propto p(g|\Theta, \psi)p(\psi),
\]

where \( \Theta = \{\theta_i\}_{i=1}^N \) denotes the \( N \) set of planning parameters, \( g = \{g(\theta_i)\}_{i=1}^N \) the corresponding observed PQM scores, and \( p(g|\Theta, \psi) \) the marginal likelihood, which can be calculated in closed form

\[
p(g|\Theta, \psi) \sim \mathcal{N}(g, K_{\psi} + \sigma^2 I),
\]

where \( K_{\psi} \) denotes the \( N \times N \) covariance matrix governed by the hyperparameters \( \psi \). The rhs product in eq.1 can be computed in closed form, and maximizing \( p(\psi|\Theta, g) \) with regard to \( \psi \) yields the MAP estimate of \( \psi \). In the SAAS-GP, the length scale prior is hierarchical, where the shrinkage scale \( \tau \) is governed by another half-Cauchy prior distribution. The joint posterior of \( \tau \) and \( \psi \) is expressed as

\[
p(\tau, \psi|\Theta, g) \propto p(g)p(\psi|\tau)p(\tau),
\]

where \( \mathcal{GP} \) denotes the Gaussian process.
where $p(\tau)$ denotes the prior distribution for $\tau$, and $p(\psi|\tau)$ the prior for $\psi$ governed by $\tau$. A straightforward way to infer the joint posterior distribution with the hierarchical model in eq.3 is to perform MCMC sampling. In this work, the No-U-Turn Sampler was used to perform inference, and the resulting posterior distribution of the hyperparameters was represented by multiple samples $\{\psi_i\}_{i=1}^n$. As a result, the MCMC-based inference is much slower than the MAP-based inference.

2 Ablation study: BO without constraints

As mentioned in the discussion, we performed an ablation study based on identical settings (PQM score function, iteration budget, etc.) to the previous experiment, except for removing all constraints on the adjustable parameters. The results obtained by four auto-planning methods (random, GPEI, and SAAS-BO, Nelder-Mead) are shown in figure 1 and 2. Compared with the progress with constraints in the manuscript, one can observe that the early progress advantage for the SAAS-BO is more obvious in the no-constraint experiment.
Figure 1: automated planning PQM scores without parameter constraints as a function of the iterations, along with the average PQM score of clinical treatment plans, where the color bands represent 1 SD.
Figure 2: DVH comparison on the rectal cancer treatment plan cohort without constraints in the search space. The solid lines represent the means and the color bands represent 1 SD, and dose prescriptions were represented by gray dashed lines.

3 DVH data for the random method

As mentioned in the methods, DVH for the random method are shown in figure 3. The results of clinical, GPEI, and SAAS-BO methods are identical to the DVH results in the main text.

For the GTV and PGTV, the random plans exhibited excessive high dose tails and poor hot spot control. However, the random plans have shown good control in the low-dose region for the femoral head.
Figure 3: DVH comparison on the rectal cancer treatment plan cohort with constraints in the search space. The solid lines represent the means and the color bands represent 1 SD, and dose prescriptions were represented by gray dashed lines.

4 The impact of different clinical goal priorities

We designed score functions with three different sets of clinical goal priorities, as is shown in table 1, where the PQM_{target} is identical to the priority settings reported in the manuscript. In this set of priority settings, the target was given the most important priority and the OAR, dose spillage were considered with less importance. In PQM_{equal}, all scoring terms are set equally important, while PQM_{OAR} sets the terms of OAR and dose spillage to the top tier and the target was set less important.

The relative importance statistics of the 34 planning parameters for GPEI and SAAS-BO methods based on different score functions were shown in figure 4 and 5, respectively. We made the following qualitative observations. When the terms of targets are at the top priority, the relative importance
of the parameters corresponding to the target area (PTV and PGTV) and its surrounding structures (avoidance and bladder) are ranked higher. As the priority of OAR and dose spillage increased, the relative importance of parameters that are less relevant to the target increased in the ranking, such as the terms of femoral head.

The DVHs with the different sets of priorities were shown in figure 6. It is easy visible that the control in target hot spot and the maximum dose of the femoral head are susceptible to the influence of changes in the priorities.

Table 1: Three sets of clinical goal priorities $p_i$.

| Target OAR     | Dose Spillage |
|----------------|---------------|
| $PQM_{target}$ | 1 2 ($p_i$ for femoral head are 3) 2 |
| $PQM_{equal}$  | 1 1 1         |
| $PQM_{OAR}$    | 2 1 1         |
Figure 4: Relative importance box plot of GPEI methods based on different clinical priorities, normalized to the corresponding maximum of 34 median importance values over 20 cases. The parameters were sorted according to their importance in descending order. The top 10 planning parameters in the GPEI PQM_{target} model were marked in bold, the orange line representing the median value.
Figure 5: Relative importance box plot of SAAS-BO methods based on different clinical priority sets.
Figure 6: DVH comparison for GPEI and SAAS-BO methods based on different clinical priority sets. The solid lines represent the means and the color bands represent 1 SD, and dose prescriptions were represented by gray dashed lines.

5 Performance of the Nelder-Mead method given longer planning time

In the manuscript, the test methods were limited to 120 iterations, but the planning time of each method varied significantly. Although we explain two factors for the fast runtime of the Nelder-Mead method in the footnote of
page 13, we have set the iteration limit in the Nelder-Mead method to 1000 (noted as Nelder−Mead\textsubscript{1000}) and repeated the planning experiments on 20 patients to further explore the performance of the Nelder-Mead method. The average best PQM score progress of the Nelder-Mead method compared with previous results was shown in Figure 7 and the mean DVH comparison of the Nelder-Mead method was shown in Figure 8. Further, the progress of dose distribution generated by the Nelder-Mead plans also be investigated in the three typical cases (same as the cases in the manuscript) in Figure 9.

As Figure 7 shown, the Nelder−Mead\textsubscript{1000} plans achieved the same level of average plan quality as the BO plans when iterating to approximately 200 which is twice as many iterations as the BO plans. In subsequent iterations, the average PQM score surpassed that of the BO plans, and the progress was investigated by comparing mean DVH and dose distributions. Figure 8 clearly demonstrated that the femoral head had the most significant dose reduction and the hot spot control was improved by extending the planning time of the Nelder-Mead method, which were two main contributors to the score progress. However, the Nelder-Mead plans had the problems of hot spots outside the PTV, and more low-dose wash regardless of the number of iterations, which can be visible in patient B and C.
Figure 7: PQM score progress of 1000 iterations of the Nelder-Mead method and 120 iterations of the Nelder-Mead, GPEI and SAAS-BO method along with the average PQM score of clinical treatment plans, where the color bands represent 1 SD.
Figure 8: DVH comparison between 120 iterations of the Nelder-Mead method (right) and 1000 iterations of the Nelder-Mead method (left) on the rectal cancer treatment plan cohort. The solid lines represent the means and the color bands represent 1 SD, and dose prescriptions were represented by gray dashed lines.

Figure 9: Comparison of dose distributions (100% to 45% prescribed dose) for three typical cases with the structures of PGTV(yellow), PTV(red), bladder(blue) and femoral head (green)