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Polish Journal of Medical Physics and Engineering
The Journal of Polish Society of Medical Physics
ISSN 1898-0309, doi: 10.2478/pjmpe-2023-0015

September 2023
Vol 29, Issue 3

Scientific Paper

Complexity analysis of VMAT prostate plans: insights from dimensionality reduction and information theory techniques

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(received 22 March 2023; revised 25 May 2023; accepted 21 June 2023)

Abstract

Introduction: Volumetric Modulated Arc Therapy (VMAT) is a state-of-the-art prostate cancer treatment, defined by high dose gradients around targets. Its unique dose shaping incurs hidden complexity, impacting treatment deliverability, carcinogenesis, and machine strain. This study compares various aperture-based VMAT complexity indices in prostate cases using principal component and mutual information analyses. It suggests essential properties for an ideal complexity index from an information-theoretic viewpoint.

Material and methods: The following ten complexity indices were calculated in 217 VMAT prostate plans: circumference over area (CoA), edge metric (EM), equivalent square field (ESF), leaf travel (LT), leaf travel modulation complexity score for VMAT (LTMCSV), mean-field area (MFA), modulation complexity score (standard MCS and VMAT variant MCSV), plan irregularity (PI), and small aperture score (SAS_{5mm}). Principal component analysis (PCA) was applied to explore the correlations between the metrics. The differential entropy of all metrics was also calculated, along with the mutual information for all 45 metric pairs.

Results: Whole-pelvis plans had greater complexity across all indices. The first three principal components explained 96.2% of the total variance. The complexity metrics formed three groups with similar conceptual characteristics, particularly ESF, LT, MFA, PI, and EM, SAS_{5mm}. The differential entropy varied across the complexity metrics (PI having the smallest vs. EM the largest). Mutual information analysis (MIA) confirmed some metrics' interdependence, although other pairs, such as LTMCSV/SAS_{5mm}, LT/MCSV, and EM/SAS_{5mm}, were found to share minimal MI.

Conclusions: There are many complexity indices for VMAT described in the literature. PCA and MIA analyses can uncover significant overlap among them. However, this is not entirely reducible through dimensionality reduction techniques, suggesting that there also exists some reciprocity. When designing predictive models of quality assurance metrics, PCA and MIA may prove useful for feature engineering.

Keywords: prostate cancer; VMAT; plan complexity.

Introduction

The prostate is the second most common organ, after skin, affected by cancer in men.[1] Surgery and radiation therapy (RT) remain the cornerstones of prostate cancer management.[2] During the past years, technological advances, such as Intensity Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy, allowed dose intensification without excess bladder and rectum toxicity.[3] Volumetric Modulated Arc Therapy (VMAT) constitutes the evolution of IMRT and is, arguably, the state-of-the-art treatment technique nowadays.[4] During VMAT, the linear accelerator revolves around the patient's body, continually irradiating with beamlets of alternating aperture shape and intensity.[5] Gantry speed and dose rate may also be varied if needed. This modulation results in a

Authors' contribution: A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

highly conformal dose gradient around the target volume and a sharp dose fall inside the neighboring normal tissues.

However, the favorable therapeutic ratio of VMAT comes at a price. The plans are intrinsically challenging for the linear accelerator to deliver, as the totality of engineering parameters (e.g., multileaf collimator leaves' position and speed, dose rate, and gantry speed) must vary harmonically within very tight mechanical constraints. Increased plan complexity has many repercussions on treatment deliverability, radiation safety, and strain on the linear accelerator.[6] Therefore, patient-specific quality assurance (QA) and verification processes have been integrated into RT departments' workflow.

During recent years there has been growing interest in quantifying plan complexity.[7,8] The main motive was to reduce quality assurance workload by predicting patient-specific QA outcomes based on complexity calculations[8]. Such metrics fall into two coarse groups, fluence map-based and aperture-based. The former track the variations of fluence's intensity and have been initially described for IMRT plans with multiple static gantry angles. On the other hand, aperture-based examine multileaf collimator (MLC) openings' size and shape and can be applied to both IMRT and VMAT plans.

The primary goal of this study is to conduct a comprehensive analysis of various existing aperture-based VMAT complexity indices in a prostate cohort by employing dimensionality reduction and information theoretic methodologies. We underscore the necessity of gaining a deep understanding of the relationships and distinctions between these indices prior to introducing new metrics, as is commonly done. Furthermore, this research identifies a set of fundamental mathematical attributes that an optimal complexity index should embody from an information-theoretic perspective. These key attributes endow a complexity index with efficacy in capturing the complexity of VMAT plans, including high informational content, minimal redundancy to other indices, and a robust association with quality assurance (QA) outcomes. However, it should be noted that this study's scope does not encompass the correlation between complexity metrics and QA outcomes such as gamma passing rates.

Methods

Dataset curation

Two hundred and seventeen VMAT prostate plans were exported from the Varian ARIA oncology information system (Varian Medical Systems, Palo Alto, CA) of the radiation oncology department at the institute. All patients were treated during the period 2017-2020, with a moderately hypofractionated external beam radiotherapy with a radical intent.[9,10] During this period, the Varian Eclipse treatment planning software was updated from version 11.0.47 to version 15.1.52. Approximately 32% of the plans were created with the older version. Depending on a patient's risk, the irradiation field encompassed prostate only (PO), prostate plus seminal vesicles (PSV), or the whole-pelvis (WPRT). All treatments were delivered by a 6MV energy Varian DHX linear accelerator (Varian Medical Systems, Palo Alto, CA) equipped with a 120-leaf MLC (field size 40 × 40 cm, central 20 cm of field – 5 mm leaf width, outer 20 cm of field – 10 mm leaf width), and an on-board imaging kV cone-beam CT system.

The extraction of raw data from RT-DICOM files and the calculation of complexity metrics were performed with in-house software written in Python.[†] All sensitive data were fully anonymized, and the research protocol was approved by the Institutional Review Board of the institute (Ref number: 336/12-11-2020/5.2ο).

For each plan, the following complexity indices were calculated: circumference over area (CoA),[11] edge metric (EM),[12] equivalent square field (ESF),[11] leaf travel (LT), leaf travel modulation complexity score for VMAT (LTMCSV),[13] mean-field area (MFA),[14,15] modulation complexity score (MCS),[16] and its VMAT variant (MCSV), plan irregularity (PI),[17] and small aperture score at 5mm threshold (SAS_{5mm}).[14] Regarding ESF, a conversion function, $f(x) = 1 - e^{-x}$ has been used to assign non-linearity in distances contributing to a field's complexity. In this study, distances contributed equally to the ESF score. For plans with *N* arcs, an MU-weighted average complexity, C_{plan}, was calculated using the formula:

$$C_{\text{plan}} = \sum_{i=1}^{N} C_{\text{arc},i} \frac{MU_{arc,i}}{MU_{plan}} \quad \text{Eq.1}$$

where $C_{arc,i}$ is the complexity of the *i*-th arc, $MU_{arc,i}$ the monitor units of the *i*-th arch, and MU_{plan} the plan's total monitor units.

The statistical analysis was done in R language version 3.6.3. The principal component analysis results were independently verified with IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. The mutual information analysis was carried out in Wolfram Mathematica version 12.1.

Summary statistics

Each variable was analyzed with the Shapiro-Wilk normality test and Q-Q plots before generating a summary of the data. All variables deviated from normality; therefore, their values are reported in median and interquartile ranges. The *p*-values were computed with the Kruskal-Wallis rank-sum test. The level of statistical significance was chosen as $a=0.05$.

Principal Component Analysis (PCA)

PCA is a dimensionality reduction technique that operates under the assumption of linear relationships, while Mutual Information Analysis (MIA) is a method to measure the dependence between variables, effective for both linear and non-linear relationships.

[†] http://test.ogkologia.gr/rteval

This makes MIA more versatile for a broader range of datasets. PCA is specifically designed for dimensionality reduction, transforming the original high-dimensional data into a lower-dimensional space while preserving the maximum amount of variance. MIA, on the other hand, does not directly reduce dimensions but can be used for feature selection. Also, PCA generates new, uncorrelated features (principal components) that are orthogonal to each other, which can be beneficial in various applications, such as reducing multicollinearity in regression problems.

PCA's assumptions were checked before applying the method. The correlation matrix of the ten complexity metrics was calculated with the Pearson method. For a variable to be included in PCA, it needed to have a correlation coefficient $|r| \geq 0.3$ with at least one of the other variables. Sampling adequacy was checked with the Kaiser-Meyer-Olkin (KMO) measure for the overall dataset and with the Measure of Sampling Adequacy (MSA) for each metric,[18] along with Bartlett's test of sphericity. For KMO and MSA calculations, the R package REdaS version 0.9.3 was used.[19] All data were centered and scaled before applying PCA. The analysis was conducted on the whole dataset and then reproduced to plans generated by the older vs. more recent TPS version.

Mutual information analysis (MIA)

Mutual Information Analysis (MIA) is a statistical method used to quantify the dependency between two or more variables. In this study, MIA is employed to examine the relationship among the chosen complexity metrics in order to gain insights into the degree of redundancy or uniqueness among them. The methodology for MIA involves calculating the mutual information (MI) between pairs of complexity metrics. MI quantifies the amount of information one variable (e.g., a complexity metric) provides about another variable. Higher MI values indicate a stronger association between the variables, while lower values suggest less dependency or redundancy.

Upon analyzing the results of MIA, researchers can identify which complexity metrics are more unique, providing distinct information from the others, and which metrics have high redundancy, indicating that they share a significant amount of information with other metrics. The goal is to identify an optimal set of complexity metrics that maximizes the information obtained while minimizing redundancy. By understanding these relationships, we can improve the overall efficiency and effectiveness of complexity evaluation in VMAT planning.

For every metric, its differential entropy was calculated with:

$$h(\mathrm{X}) = -\int_{S_X} p_X(x)\, log\, p_X\,(x)\mathrm{d}x = -\mathbb{E}[log\, p_X\,(x)\mathrm{d}x] \quad \text{Eq.2}$$

For every pair *X;Y* of complexity metrics, the mutual information (MI), *I(X;Y)*, was calculated via the following formula:

$$I(X;Y) = \int_{S_Y}\int_{S_X} p_{XY}(x,y)\log\left(\frac{p_{XY}(x,y)}{p_X(x)\,p_Y(y)}\right)\mathrm{d}x\,\mathrm{d}y \quad \text{Eq.3}$$

The probability density functions $p_X(x), p_Y(y), p_{XY}(x,y)$ were approximated with a smooth kernel distribution, given by a linearly interpolated version of a Gaussian kernel.[20] The bandwidth of the kernel was estimated with Silverman's rule.[21] Unlike the correlation coefficient, mutual information is more general and expresses how much the joint distribution of the pair $p_{XY}(x,y)$ differs to the product of the marginal distributions of $p_X(x)$ and $p_Y(y)$.[22] In the limit where *X* and *Y* are entirely independent, mutual information is zero, since $p_{XY}(x,y) = p_X(x)p_Y(y)$, and $log 1 = 0$.

Results

Summary statistics

Table 1 summarizes all complexity metrics' values broken down by field size. There was a statistically significant difference between small fields (PO, PSV) and large fields (WPRT) across all indices. **Figure 1** shows estimated probability density functions after centering the data by subtracting their mean and dividing by their standard deviation. Some distributions, like ESF, MFA, and PI, or MCS and MCSV, share evident similarities. The principal component analysis identifies any linear correlations to yield a substantial dimensionality reduction.

Table 1. Complexity metrics of prostate VMAT plans - summary table. PO: Prostate Only, PSV: Prostate plus Seminal Vesicles, WPRT: Whole Pelvis Radiation Therapy. Values are reported in median (IQR). P-values were computed with the Kruskal-Wallis rank-sum test.

Metric	Irradiation Field Size			p-value
	PO, N = 34	PSV, N = 78	WPRT, N = 105	
CoA (1/mm)	0.38 (0.05)	0.38 (0.10)	0.46 (0.06)	**<0.001**
EM (1/mm)	0.268 (0.011)	0.267 (0.010)	0.266 (0.009)	**0.038**
ESF (mm)	26 (6)	32 (10)	53 (8)	**<0.001**
LT	0.82 (0.06)	0.77 (0.08)	0.61 (0.10)	**<0.001**
LTMCSV	0.20 (0.05)	0.16 (0.04)	0.12 (0.03)	**<0.001**
MCS	0.234 (0.046)	0.218 (0.029)	0.206 (0.027)	**<0.001**
MCSV	0.234 (0.046)	0.217 (0.029)	0.205 (0.026)	**<0.001**
MFA (mm²)	2,278 (830)	2,766 (1,299)	5,962 (1,100)	**<0.001**
PI	23 (4)	26 (10)	49 (8)	**<0.001**
SAS_{5mm}	0.21 (0.10)	0.21 (0.08)	0.15 (0.06)	**<0.001**

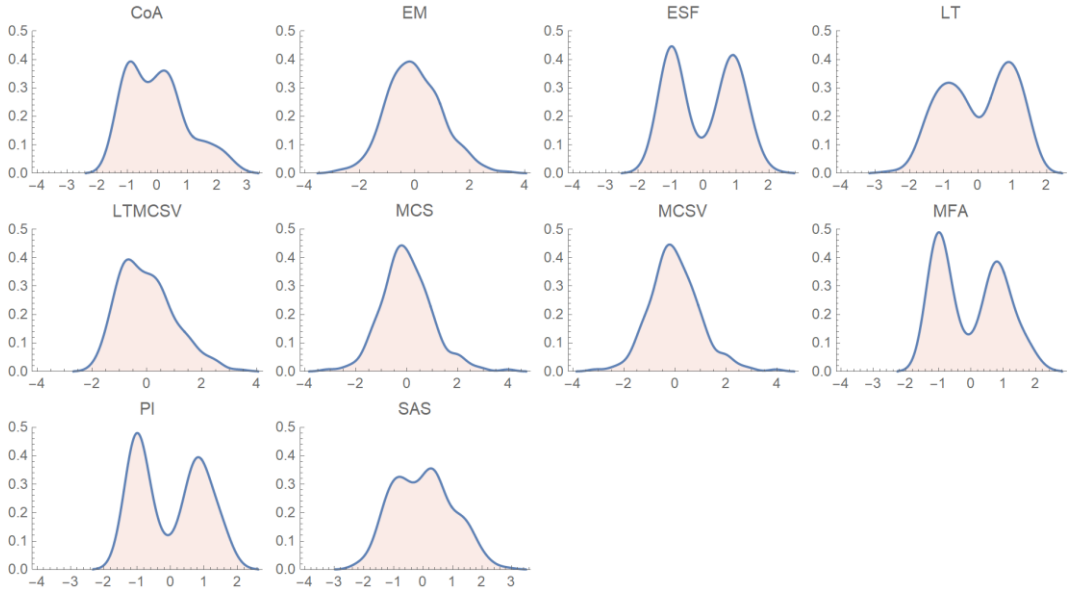

Figure 1. Probability density functions based on a smooth kernel density estimate for the various complexity metrics. The data have been centered by subtracting the mean and dividing by the standard deviation.

Principal component analysis

Table 2 shows the correlation matrix of the complexity indices. All indices, except for CoA, had at least one correlation that exceeded the threshold of $r \geq 0.3$. On this basis, CoA was excluded from the principal component analysis. Historically, Kaiser and Rice[18,23] proposed 0.5 as the minimum value for MSA. The MSA value of EM was remarkably low, and when removing it from the set, the overall KMO increased to 0.76. However, given the edge metric's importance, it was decided to include it in the analysis. The overall KMO value then was 0.66. Bartlett's test of sphericity, with edge metric included, produced strong evidence in favor of the existence of adequate correlations in our dataset ($p<0.0001$). Considering the correlation matrix findings, the overall KMO criterion, and Bartlett's test of sphericity, we concluded that principal component analysis was justified.

Figure 2 shows the loading plots of the principal component analysis. In the left plot, PCA in the original dataset was applied. In the right plot, the dataset was transformed so that LT, MCS, and MCSV increased in the same direction as the rest of the complexity indices, meaning that a higher complexity value would correspond to higher plan complexity.‡ The first group consists of ESF, LT, MFA, and PI (after reversing the sign of LT). The second group consists of EM and SAS_{5mm}. The last group loosely consists of MCS and MCSV, along with LTMCSV (depending on the sign of LT).

Table 2. Correlation matrix of the complexity indices, calculated with the Pearson method. All indices, except CoA, had at least one correlation that exceeded the threshold of $|r| \geq 0.3$.

	COA	EM	ESF	LT	LT MCSV	MCS	MCSV	MFA	PI	SAS_{5mm}
COA	1.00									
EM	0.12	1.00								
ESF	0.11	-0.46	1.00							
LT	0.03	0.28	-0.94	1.00						
LT MCSV	0.01	0.03	-0.74	0.85	1.00					
MCS	-0.01	-0.32	-0.19	0.31	0.76	1.00				
MCSV	-0.01	-0.32	-0.19	0.31	0.76	1.00	1.00			
MFA	0.10	-0.52	0.98	-0.89	-0.64	-0.04	-0.04	1.00		
PI	0.12	-0.41	0.99	-0.94	-0.73	-0.16	-0.16	0.99	1.00	
SAS_{5mm}	-0.17	0.37	-0.58	0.52	0.13	-0.41	-0.41	-0.64	-0.61	1.00

Table 3. Component matrix of principal component analysis. PCs are the eigenvectors of the covariance matrix scaled by the square roots of the respective eigenvalues.

Metric	Principal Component								
	1	2	3	4	5	6	7	8	9
EM	.404	-.562	.703	.159	.034	.000	.001	.002	.000
ESF	-.984	.117	-.024	.092	.074	.064	.017	.011	.000
LT	.968	.051	-.107	-.067	.209	-.019	.022	-.002	.000
LTMCSV	.834	.540	-.012	.030	.099	.039	-.033	.003	.000
MCS	.307	.936	.088	.138	-.057	-.007	.011	-.002	.007
MCSV	.307	.936	.086	.137	-.055	-.006	.009	.000	-.007
MFA	-.951	.259	-.018	.119	.097	-.063	-.012	.011	.000
PI	-.978	.136	.054	.116	.089	.008	-.005	-.022	.000
SAS_{5mm}	.555	-.635	-.384	.375	-.021	.000	.000	.000	.000

‡ LT is defined as $LT = \frac{1000(mm) - LT_{\text{mean}}(mm)}{1000(mm)}$. Therefore, as the mean leaf travel increases, i.e. as the complexity increases, the LT decreases. That is why the PCA was repeated after reversing the sign of LT.

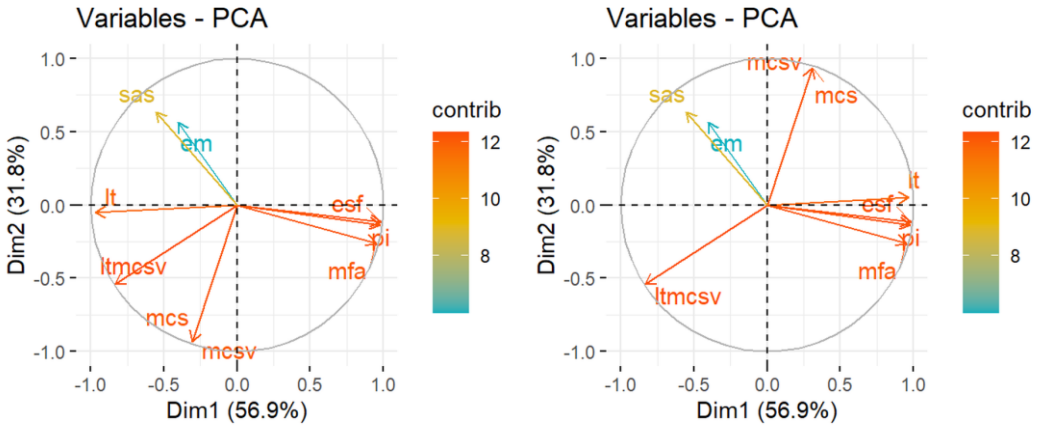

Figure 2. Loading plots of the principal component analysis. Left: PCA in the original dataset. Right: Transformed dataset so that LT increases with increasing complexity.

Figure 3 shows the explained variance vs. the number of principal components (PCs). The inflection point of the scree plot is realized at *N=3*. The cumulative explained variance of the data, with 3 PCs, is 96.2%. There were no essential differences in PCA outcomes between the two TPS versions' plans, even though there were differences across individual metrics.

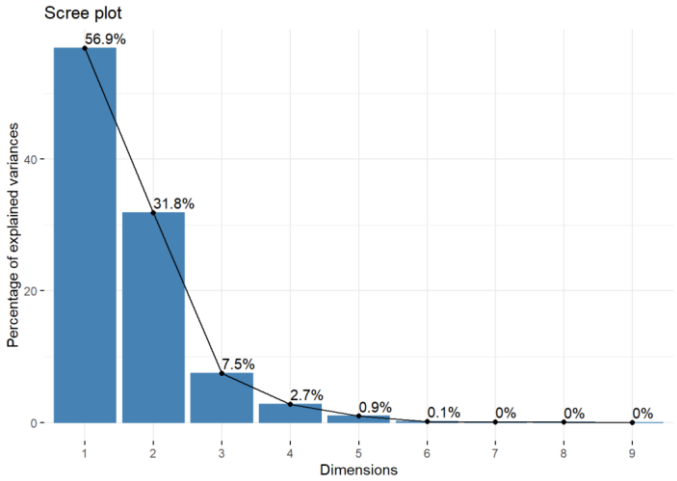

Figure 3. Scree plot of principal components. The inflection point is located at N=3. The cumulative explained variance of the data, with 3 PCs, is 96.2%.

Mutual information analysis

Figure 4 shows the differential entropy (in nats) of the complexity metrics. Differential entropy, in the context of information theory, is a concept that extends the idea of entropy to continuous random variables. Entropy, introduced by Claude Shannon, quantifies the average amount of information required to describe the outcome of a random process. For a continuous distribution with a known mean, μ, and known variance, σ, it can be proven that the maximum entropy distribution is the normal distribution.[22] The value of the maximum entropy is then equal to $\frac{1}{2}(1+\ln(2\pi\sigma^2))$. In our case, it was $\sigma=1$, since the data have been standardized; therefore, the theoretical upper limit is $h_{max}(X) = 1.42$. However, in **Figure 4**, there are variables exceeding this upper bound. We hypothesize that this is an issue of the approximate nature of numerical integration and kernel density estimation. Having said that, the important thing to note is the relative informational content between different complexity metrics. For example, ESF, MFA, and PI are characterized by low differential entropy relative to EM, LTMCSV, or SAS_{5mm}. Consequently, if one were required to select a single complexity index to correlate with QA outcomes, EM would, e.g., likely be a more suitable candidate than ESF, assuming all other factors are equal.

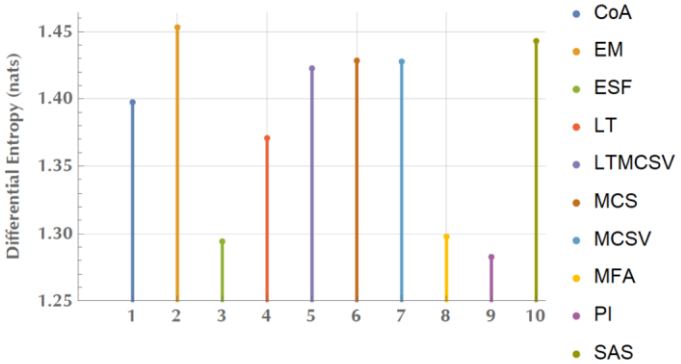

Figure 4. Differential entropy of complexity metrics (in nats). The higher the entropy the larger the information content contained in the respective metric.

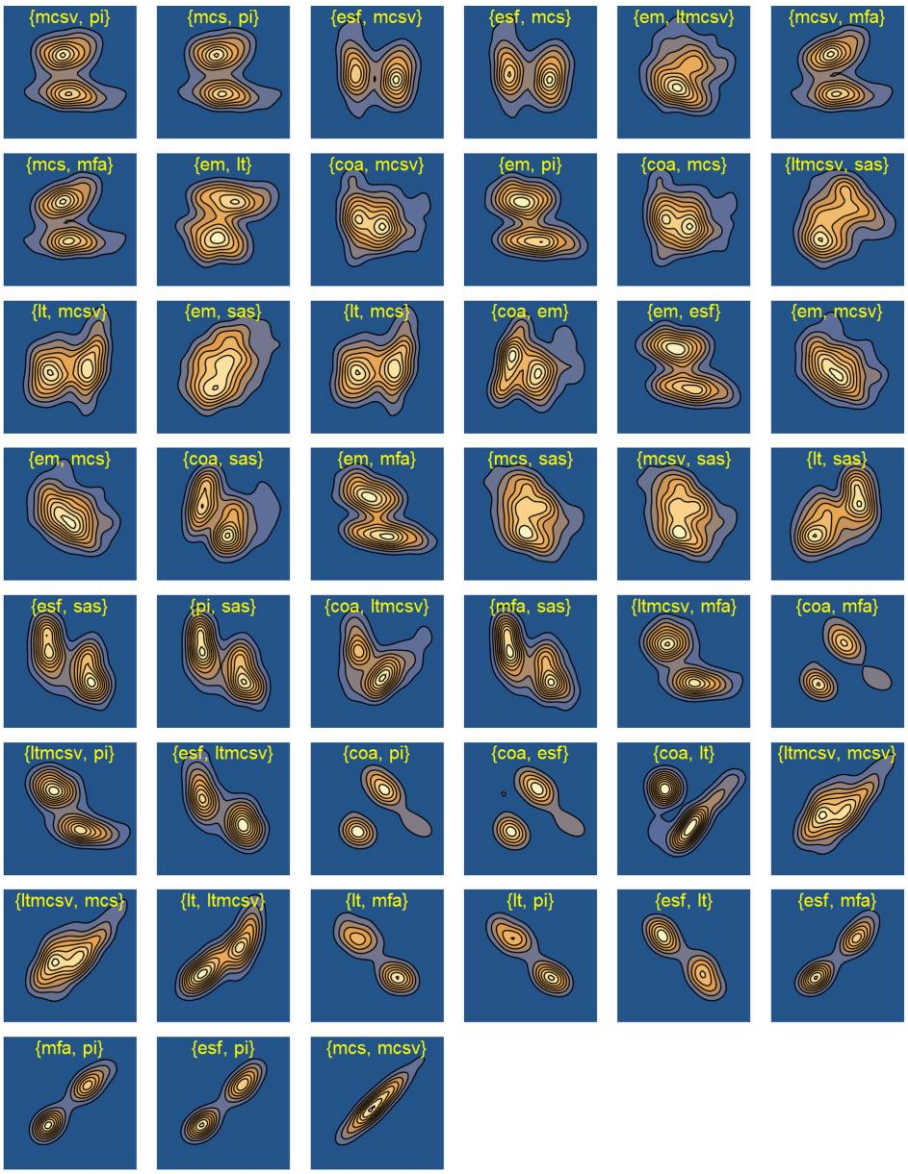

Figure 5. Joint probability distributions of complexity metric pairs sorted in ascending order of their mutual information.

Figure 5 shows all the probability density distributions sorted by their MI value in ascending order (from left to right and top to bottom). Pairs with particularly low mutual information represent good candidates for the construction of a multiplicative combination. Promising pairs with high differential entropy, low mutual information, and a strong effect on both first two principal components include LTMCSV/SAS_{5mm}, LT/MCSV, and EM/SAS_{5mm}, to name a few.

Discussion

VMAT is one of the best delivery methods for treating prostate cancer. However, such plans end up being complex, consisting of beamlets with many degrees of freedom. If this complexity increases beyond a critical point, it may hurt plan deliverability and jeopardize patient safety. This is why VMAT plans must undergo thorough quality assurance and verification procedures before they are delivered to the patients. The prediction of QA metrics, such as gamma passing rates, via complexity has been an area of intense research during past years.[24,25]

Regarding complexity, it is a critical concept in assessing the fitness of a VMAT plan, although often overlooked. Two plans may have distinctive complexity footprints despite similar target coverage and organ sparing. Having said that, a high degree of complexity is not a priori a bad thing. E.g., a tricky target involving both convex and non-convex parts may necessitate an elaborate plan to meet all optimization objectives. In other cases, however, complexity may represent a byproduct of exhaustive optimization without any meaningful clinical impact.

Since plan complexity has been recognized as an essential factor in VMAT, many indices have been described in the literature.[7,8] This is partly because different treatment planning systems adopt different modulation strategies (e.g., modulation of leaves vs. gantry speed/dose rate).[7] In this study, we calculated ten widely used aperture-based complexity scores in

a cohort of 217 VMAT prostate plans. As the field's size increased, from PO/PSV to WPRT, so did the complexity, irrespective of the index (**Table 1**). This finding was expected since, in WPRT, larger volumes are treated, exposing the bladder and rectum to steep dose gradients that necessitate intricate leaf sequences for successful implementation.

Subsequently, we applied principal component analysis, a widely used dimensionality reduction technique. PCA exploits linear correlations between the variables in a dataset to find low-dimensional orthogonal projections that maximally preserve the data's variance. These projections are known as principal components. By using three such components, we accounted for 96.2% of our dataset's variance. We also generated a loading plot, which shows how strongly a variable affects the principal components (**Figure 2**). In this figure, ESF, LT, MFA, and PI cluster, same as EM and SAS_{5mm}, whereas the grouping of MCS, MCSV, and LTMCSV is less definite. These findings suggest that there exists a substantial overlap among the various metrics. E.g., ESF, MFA, and PI are strongly influenced by the field's open area, meaning that they likely measure the same aspect of a plan. Of particular note is the EM, with relative low loadings on the first two PCs, and a high loading on the third principal component, unlike any of the rest of the metrics (**Table 3**).

We also calculated the information entropy (**Figure 4**) of all metrics and the mutual information for every pair (**Figure 5**). The differential entropy varied across the complexity metrics, with PI having the smallest value vs. EM that assumed the largest. Ideally, an index should have high informational entropy to be useful. Regarding MI, given *N=10* metrics, there are *N(N-1)/2=45* pairs. MI quantifies the information one gains about a variable through the observation of its pair. This methodology could help us find our way in the complexity landscape by combining indices whose MI is minimal. This is the case of LT and MCSV, whose MI was very low compared to other pairs. The construction of the multiplicative combination, LTMCSV, already described in the literature[13], is sound from an information-theoretic perspective in retrospect.

The importance of PCA and MIA is twofold. First, they provide us with insights regarding how seemingly different complexity metrics are connected. In the literature, there are more than forty complexity metrics.[8] Second, it opens up new possibilities for devising an index that would have the best chance to correlate with QA metrics. As we have mentioned, the correlation between complexity and QA metrics has not been fruitful despite many efforts.[25] To overcome this barrier, a "PCA/MIA informed" linear combination of existing complexity metrics could conceivably be used to construct a new one. This new index would, arguably, incorporate the different informational content across many indices. There have been only a few published papers utilizing PCA to study VMAT plans' complexity, and none using MIA, to the best of our knowledge.[24,26,27] Concretely, Santos et al. introduced the Plan Complexity Score (PCS) as the weighted sum $PCS = \sum_{i=1}^{n}(v_k/v) \times PC_k$, where v_k is the variance explained by the PC_k, v is the variance explained by the retained principal components, and n is the minimum number of PCs needed to explain at least 80% of the total variance. Such approaches are promising when developing statistical or machine learning models for predicting QA outcomes based on complexity metrics.

Conclusion

The unparallel dose conformance and normal tissue sparing of VMAT have come at the hidden cost of increased complexity. The literature is full of aperture-based complexity metrics. Principal component and mutual information analyses suggest that there is both a common and unique informational content among many of them. Future studies trying to correlate complexity with QA metrics could benefit from PCA or MIA.

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