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Version post-print

Citation Liu, Y., Chan, T. C. Y., Lee, C.-G., Cho, Y.-B., & Islam, M. K. (2014). A
(published version) stochastic model for tumor geometry evolution during radiation therapy
in cervical cancer: A stochastic cervical tumor geometry evolution
model. Medical Physics, 41(2), 021705. 10.1118/1.4859355

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Publisher's Statement This is the peer reviewed version of the following article: Liu, Y.,
Chan, T. C. Y., Lee, C.-G., Cho, Y.-B., & Islam, M. K. (2014). A
stochastic model for tumor geometry evolution during radiation
therapy in cervical cancer: A stochastic cervical tumor geometry
evolution model. Medical Physics, 41(2), 021705.
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A stochastic model for tumor geometry evolution during radiation therapy in cervical cancer

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Abstract

Purpose: To develop mathematical models to predict the evolution of tumor geometry in cervical cancer undergoing radiation therapy.

Methods: We develop two mathematical models to estimate tumor geometry change: a Markov model and an isomorphic shrinkage model. The Markov model describes tumor evolution by investigating the change in state (either tumor or non-tumor) of voxels on the tumor surface. It assumes that the evolution follows a Markov process. Transition probabilities are obtained using maximum likelihood estimation and depend on the states of neighboring voxels. The isomorphic shrinkage model describes tumor shrinkage or growth in terms of layers of voxels on the tumor surface, instead of modeling individual voxels. The two proposed models were applied to data from 29 cervical cancer patients treated at Princess Margaret Cancer Centre and then compared to a constant volume approach. Model performance was measured using sensitivity and specificity.

Results: The Markov model outperforms both the isomorphic shrinkage and constant volume models in terms of the trade-off between sensitivity (target coverage) and specificity (normal tissue sparing). Generally, the Markov model achieves a few percentage points in improvement in either sensitivity or specificity compared to the other models. The isomorphic shrinkage model is comparable to the Markov approach under certain parameter settings. Convex tumor shapes were easier to predict.

Conclusions: By modeling tumor geometry change at the voxel level using a probabilistic model, improvements in target coverage and normal tissue sparing are possible. Our Markov model is flexible and has tunable parameters to adjust model performance to meet a range of criteria. Such a model may support the development of an adaptive paradigm for radiation therapy of cervical cancer.

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30 I. INTRODUCTION

The quality of an external beam radiation therapy treatment for cervical cancer is heavily influenced by the change in the volume, shape and location of the target over the course of treatment [1]. In the case of cervical cancer, the target volume can be reduced to a quarter of its original volume in five weeks of treatment [2]. Thus, the effectiveness of a treatment assuming a static target can be rapidly degraded, particularly from the perspective of sparing organs-at-risk (OARs). The concept of adaptive treatment planning in cervical cancer has shown substantial promise [3]. Adaptive radiation therapy (ART) is a feedback control strategy to manage patient specific variations during the course of radiation treatment. Key components of ART include dose assessment, variation evaluation, modification decisions and treatment modification [4]. Most clinical ART applications have been limited to target positional corrections and much effort is still required in 4D uncertainty modeling in order to “close the loop.” Our work in this paper aims to develop a mathematical model that can “predict” the evolution (primarily shrinkage) of the geometry of a cervical tumor undergoing radiation therapy. Such a model may support components of adaptive radiation therapy like *variation evaluation* by supplementing cheaper imaging modalities and reducing the need for expensive imaging activities and *modification decisions* by forecasting patient specific variations.

There are two primary classes of techniques used to model tumor shape change under radiation therapy: continuum models and discrete cell models. Continuum models describe the natural growth and shrinkage due to radiation using differential equations [5–8], thus modeling changes in continuous time. These models focus primarily on the volume of the tumor or the number of cells comprising the tumor. Discrete cell models describe the evolution of voxels between different discrete states in discrete time [9–12]. These models are more appropriate for studying changes in the actual geometry or shape of the tumor over time.

In this paper, our goal is to develop mathematical models to describe the change in a cervical tumor’s shape and size over time. Our approach falls within the class of discrete cell models, since we model the evolution of voxels in discrete time as a stochastic process. We classify static voxels as being in one of two states, cancerous or non-cancerous, at every epoch and we develop two models that describe how voxels change their state over time.

The first model is a Markov model, which uses probabilities to govern the process of state transitions of individual voxels. The second model takes a more coarse view of the tumor and models volume change by analyzing layers of voxels instead of individual voxels. We derive parameter values for our models from sequential MRI scans from Princess Margaret
65 Cancer Centre in Toronto, Canada. Our two models are then used to simulate the change in geometry of a cervical tumor over time. These simulations are tested against the real images. Lastly, we quantify the trade-off between tumor coverage and OAR sparing of our two models and a constant volume model.

II. METHODS AND MATERIALS

70 A. Patient data

We obtained MRI scans for 33 cervical cancer patients treated at Princess Margaret Cancer Centre who were enrolled in a research ethics board approved study [2]. All patients received one MRI and one computed tomography (CT) scan for planning purposes and either four or five additional weekly MRI scans during radiation therapy. The GTVs
75 were contoured by a radiologist and reviewed by a radiation oncologist. Standard treatment for cervical cancer patients is chemo-radiation therapy with an external radiation beam and a dose prescription of 1.8Gy or 2Gy per fraction for 25 fractions to the whole pelvis ($\pm$ node), followed by brachytherapy of 40Gy to the residual target or intensity-modulated radiation therapy if brachytherapy is not feasible.

80 B. Data processing

For our analysis, we excluded four patients who had small tumors (fewer than 280 voxels) in the planning image. We also excluded four of the weekly MRI scans from the remaining 29 patients where the tumor shrinkage was substantial, spanning at least two layers of voxels. In total, there were 53 pairs of consecutive weekly scans, which we refer
85 to as “transitions” (e.g., if we have scans from week 2, 4, and 5 for a patient, we have one transition: $4 \rightarrow 5$). The time interval between the planning image and the start of treatment (i.e., between the first and second MRI scan) varied across patients. Therefore

the planning scans were not included in our study.

Based on the voxel size of the available reconstructed image, a $0.4 \times 0.4 \times 0.4 \text{ cm}^3$ spatial voxel grid was used for each image. A spatial voxel was classified as “tumor” if the proportion of the voxel that is covered by the tumor was non-zero. Otherwise, it was classified as “non-tumor”. An illustrative figure for one slice of a tumor is shown in Figure 1. The dotted outline shows the tumor contour and the shaded cells represent tumor voxels in our spatial grid. Next, we rigidly aligned each MRI scan to the planning image by minimizing the distance between the centers of mass of the tumors on both images, while maintaining an aligned voxel grid. Note that we only consider translation in the alignment process since we found rotation to be negligible in almost all cases. The rotation analysis can be found in [13].

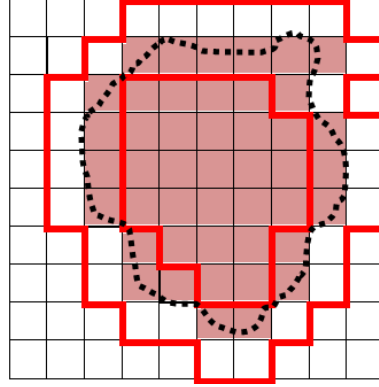


FIG. 1: An example slice from a 3D tumor. The dotted outline shows the tumor contour and the shaded cells represent tumor voxels in our spatial voxel grid. The voxels bounded by the solid lines comprise the bi-voxel layer on the tumor surface.

C. A Markov model: modeling individual voxels on the tumor surface

In the Markov model, we assume that the evolution of the tumor geometry follows a Markov process. A Markov process is a stochastic process where the future depends only on the current state of the process and not on any additional history [14]. In the present context, the Markov assumption implies that only the current geometry of the tumor (and not previous geometries) influences the evolution of the tumor shape in the future. To support this assumption, we assume that the dose delivered is uniform over the tumor

each week and affects all voxels in the same way. In the following subsections, we define the states of the Markov process, estimate the corresponding transition probabilities, and describe how to simulate the evolution of a tumor geometry.

1. Voxel states and geometries

Formally, we define the state of voxel i at time t to be $S_t(i)$, which can take either a value of 1 (tumor state) or 0 (non-tumor state). Rather than modeling the state change of each voxel in the tumor, we focus on state changes of voxels on the tumor surface. Such cells are killed more effectively with radiation [15, 16] and tumor shrinkage can be represented as surface voxels changing from a tumor to non-tumor state. To account for both shrinkage and growth on the tumor surface, we define a new quantity, the bi-voxel, which is composed of two adjacent voxels. For example, a bi-voxel overlapping the surface of the tumor will include one voxel on the surface of the tumor and one adjacent non-tumor voxel. An example bi-voxel layer on the tumor surface is shown in Figure 1 as the region between the two solid lines.

Formally, we define the state of bi-voxel (i, j) at time t to be $B_t(i, j) := S_t(i) + S_t(j)$. In particular,

$$B_t(i, j) = \begin{cases} 0, & \text{if } S_t(i) = 0, S_t(j) = 0, \\ 1, & \text{if } S_t(i) = 1, S_t(j) = 0 \text{ or } S_t(i) = 0, S_t(j) = 1, \\ 2, & \text{if } S_t(i) = 1, S_t(j) = 1. \end{cases} \quad (1)$$

On the tumor surface, all bi-voxels are in state 1. Modeling tumor shrinkage or growth can now be accomplished by modeling a change in the state of the appropriate bi-voxels from state 1 to either state 0 or 2, respectively. Unless otherwise stated, future references to “bi-voxel” refer to a bi-voxel on the tumor surface.

State changes of a bi-voxel (i, j) may be influenced by the states of the neighboring voxels. That is, these changes may be influenced by whether the voxels adjacent to either i or j in the sagittal, coronal, and transverse directions are tumor or non-tumor. Thus, we define distinct geometric configurations around a tumor surface bi-voxel, based on the states of the neighboring voxels. Each voxel has six neighbors so a bi-voxel has 10 neighboring voxels. Each of the 10 neighboring voxels can be in one of the two states

130 (tumor or non-tumor). Therefore, there are 2^{10} possible geometric configurations surrounding each bi-voxel, though some are highly unlikely to be realized in any realistic tumor. Each voxel has six face-connected neighbors, twelve edge-connected neighbors and eight vertex-connected neighbors. We focus on the six face-connected voxels because they are the closest to the central voxel and because this approach keeps the number of
135 geometric configurations manageable given the small dataset.

There were a total of 41,441 bi-voxels in the included MRI scans analyzed. After combining isomorphic configurations and eliminating any geometric configurations that have a frequency of occurrence of less than 1% (i.e., less than 414 bi-voxels with such a configuration), 14 geometric configurations (out of 2^{10}) remained. The frequency of occurrence
140 for each geometric configuration is shown in Table I along with a visual representation of the configuration. A solid dot represents a voxel in a tumor state and a clear dot represents a voxel in a non-tumor state. The first configuration was the most prevalent and is intuitively what we would expect to see – a complete separation between the tumor (six solid dots on the left) and the non-tumor voxels (six clear dots on the right). We found
145 that the relative frequencies were stable over the treatment course.

2. Transition Probability Estimation

State changes of the bi-voxels can be influenced by multiple factors including motion of the tumor and cell death due to radiation. We focus on changes induced by radiation and therefore we eliminate the effect of motion via the previously described image alignment process. We assume that the state of bi-voxel (i, j) at time t is dependent only on the state of bi-voxel (i, j) and the states of the neighboring voxels to i and j at time $t - 1$. In other words, we assume a Markov process for the state transitions according to the following equation:

$$P(B_t(i, j) = s_t \mid B_{t-1}(i, j) = s_{t-1}, G_{t-1} = g), \quad (2)$$

where s_t and s_{t-1} take values in $\{0, 1, 2\}$, G_{t-1} is the state of the geometric configuration of the neighboring voxels at time $t - 1$, and $g \in \{g_1, \dots, g_{14}\}$ (see Table I).

Since we focus on bi-voxels on the tumor surface, we are only interested in the transition probabilities in equation (2) where $s_{t-1} = 1$. We estimate these probabilities using

TABLE I: Frequency of occurrence of key geometric configurations

Index	Frequency	Geometry	Index	Frequency	Geometry
g_1	10,697		g_8	1,390	
g_2	5,918		g_9	1,142	
g_3	5,245		g_{10}	1,041	
g_4	4,486		g_{11}	1,041	
g_5	2,525		g_{12}	974	
g_6	2,368		g_{13}	902	
g_7	1,446		g_{14}	850	

maximum likelihood estimation (MLE): if there are n bi-voxels with geometry g on the tumor surface at time $t - 1$, and n_0 , n_1 and n_2 ($n_0 + n_1 + n_2 = n$) are in state 0, 1 and 2 respectively, at time t , then the transition probability conditional on geometry g is

$$P(B_t(i, j) = k \mid B_{t-1}(i, j) = 1, G_{t-1} = g) = \frac{n_k}{n}, \quad (3)$$

for $k = 0, 1, 2$.

We define a matrix Π_t of dimension 14×3 , which contains the transition probabilities for all 14 possible configurations and three possible state changes. The (l, k) -th element of the matrix is

$$P(B_t(i, j) = k \mid B_{t-1}(i, j) = 1, G_{t-1} = g_l), \quad (4)$$

150 for $k = 0, 1, 2$ and $l = 1, \dots, 14$.

We estimate Π_t for each week t and each patient. For those patients who have few (less than 20) or no bi-voxels of configuration g_t in week $t - 1$, we derive the transition probability from the entire population of patients who have configuration g_t in week $t - 1$. The value 20 was chosen as a lower limit to ensure granularity in the probability values
155 of at least 0.05 ($20 = 1/0.05$). Therefore more than 20 voxels associated with each of the 14 geometric configurations is required on the tumor surface in order for the tumor to be included in the study (recall the definition of “small” in our inclusion/exclusion criteria and note that $280 = 14 \times 20$).

3. *Simulation*

160 For each patient, we estimate Π_t from MRI scans at time $t - 1$ and t . Then, based on the MRI scan at time t , which tells us the states of the bi-voxels at time t , we predict the state of the bi-voxels at time $t + 1$. At time t , for each configuration g_t , we simulate the state change of the associated bi-voxels 500 times according to the estimated transition probabilities. Then we average the simulated images to generate a probability map, where
165 each voxel has a value corresponding to the probability it is in a tumor state at time $t + 1$. Finally, we convert the voxel-specific probability back to a binary “tumor”/“non-tumor” classification by using a probability threshold β , above which the voxel is classified as “tumor”. Lastly, we add a margin of size α around the predicted tumor shape where α ranges from 0 to 0.4 cm.

170 **D. An isomorphic shrinkage model: modeling voxel layers on the tumor surface**

For the second approach, we consider a simple alternative to the Markov model that focuses on the volume of the entire tumor rather than modeling individual voxels. The isomorphic shrinkage approach assumes that the proportional change in tumor volume from week $t - 1$ to t is the same for week t to $t + 1$. For each patient, the tumor volume
175 for week t in terms of the number of voxels in the tumor, $\text{Vol}(t)$, is calculated from the MRI scan. To generate the volume in week $t + 1$, we first calculate the number of layers of voxels, in increments of 0.1 cm, to eliminate from the volume at week $t - 1$ so that the new volume matches the volume at week t . Then, we remove a number of layers which

TABLE II: Statistics from the conceptual illustration in Figure 2.

	TP	TN	FP	FN	Sensitivity	Specificity
Markov model	170	190	12	8	0.96	0.94
Isomorphic shrinkage model	155	200	2	23	0.87	0.99

is proportional to the radius of an equivalent spherical volume, i.e., the nearest integer
to $\sqrt[3]{\text{Vol}(t+1)/\text{Vol}(t)}$, from the volume at week t to generate the volume at week $t+1$.
Like the Markov model, after the proportional shrinkage operation, we add a margin of
size α around the predicted tumor shape where α ranges from 0 to 0.4 cm.

E. A constant volume model

In this approach, we assume the GTV remains constant for the duration of the treat-
ment. This replicates the most common practice currently employed clinically and serves
as a point of comparison for the previous two models.

F. Performance metrics

In the computational results, we compare the predicted tumor geometries generated
by the three models against the actual geometries using sensitivity and specificity. In
the radiotherapy context, sensitivity and specificity represent the level of tumor coverage
and OAR sparing, respectively. Let TP (true positive) be the number of voxels that
we correctly predict to be tumor, TN (true negative) be the number of voxels that we
correctly predict to be non-tumor, FP (false positive) be the number of voxels that we
incorrectly predict to be tumor, and FN (false negative) be the number of voxels that we
incorrectly predict to be non-tumor. Formally, sensitivity and specificity are defined as

$$\text{sensitivity} = \frac{\text{TP}}{\text{TP}+\text{FN}}, \quad \text{specificity} = \frac{\text{TN}}{\text{TN}+\text{FP}}. \quad (5)$$

Figure 2 is a conceptual illustration of the two metrics discussed above, with the
associated statistics given in Table II. Note that even small absolute differences in the
positive and negative counts can substantially impact sensitivity and specificity.

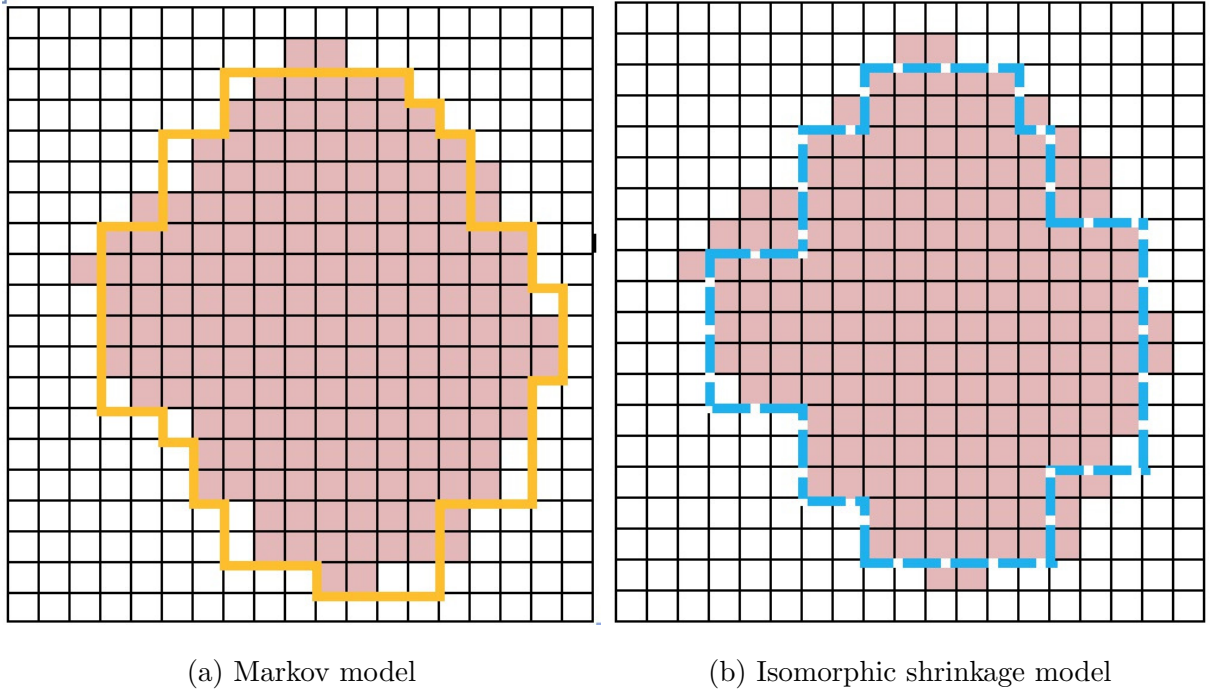


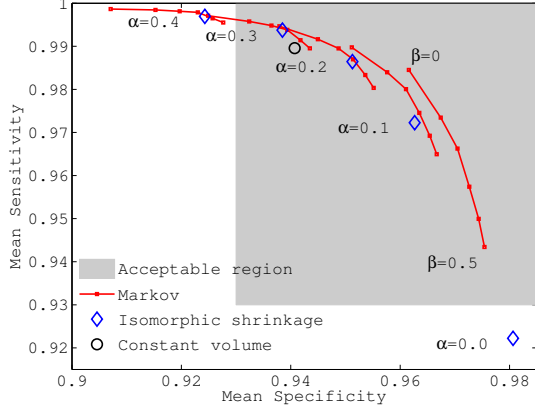
FIG. 2: Comparing one slice of tumor predicted by the developed model (area bounded by the line) and the actual tumor (the shaded area).

An “acceptability” threshold of 0.93 was chosen for both sensitivity and specificity. These metrics have a similar interpretation as the conformity index. Our choice of 0.93 is derived from the conformity index criteria from Hazard et al. [17]. Note that the exact value chosen is not critical, but the primary observations we make in the next section hold regardless of the specific numerical threshold.

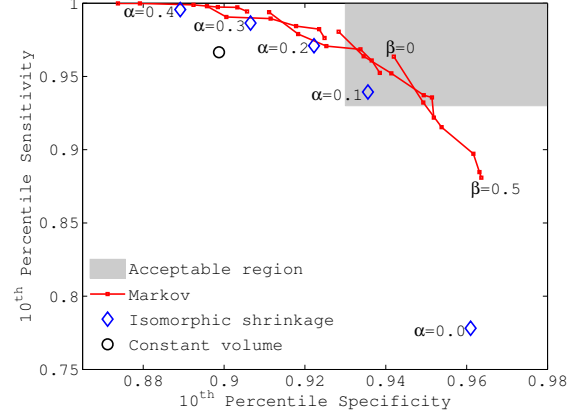
III. RESULTS

A. Comparing the three models

Figure 3 compares the sensitivity and specificity values achieved by the three models across a range of parameter settings. Each curve of solid dots is associated with a different α value: increasing α corresponds to curves towards the right. Within a curve, the dots correspond to different β values: points generally move down and to the right with increasing β . The diamonds represent the isomorphic shrinkage model, one per α moving to the right with increasing α . The circle represents the constant volume model.



(a) Mean performance



(b) Performance at 10th percentile

FIG. 3: Performance of the three models in terms of sensitivity and specificity, where α is the margin size and β is the probability threshold.

Figure 3a plots the mean sensitivity and specificity values, averaged over all transitions of all patients. Figure 3b plots the combination of 10th percentile of the sensitivity and specificity distributions, derived from all transitions of all patients.

First, a clear and expected trade-off is evident across all models: increasing sensitivity is generally accompanied by decreasing specificity and vice versa. For the Markov model, given a fixed α , sensitivity decreases and specificity increases as β increases, as expected. Figure 3a shows that the isomorphic shrinkage model is comparable with the Markov model when mean performance is considered. The Markov model slightly outperforms the constant volume model in terms of mean performance: for the same level of sensitivity, the Markov model can improve specificity by 1.1%. However, a more difference between the Markov model and the other two models is observed when the lower part of the sensitivity and specificity distributions are considered. Figure 3b shows that the Markov model dominates both the isomorphic shrinkage model and the constant volume model when evaluating the 10th percentile of the sensitivity and specificity distributions, and that the Markov model has the most “overlap” with the acceptable region. In other words, there are parameter settings for the Markov model in which the results demonstrate both sensitivity and specificity values above 0.93. On the other hand, the constant volume model does not enter the acceptable region. Furthermore, for the same level of sensitivity, the Markov model can improve specificity by 4.8% compared to the constant

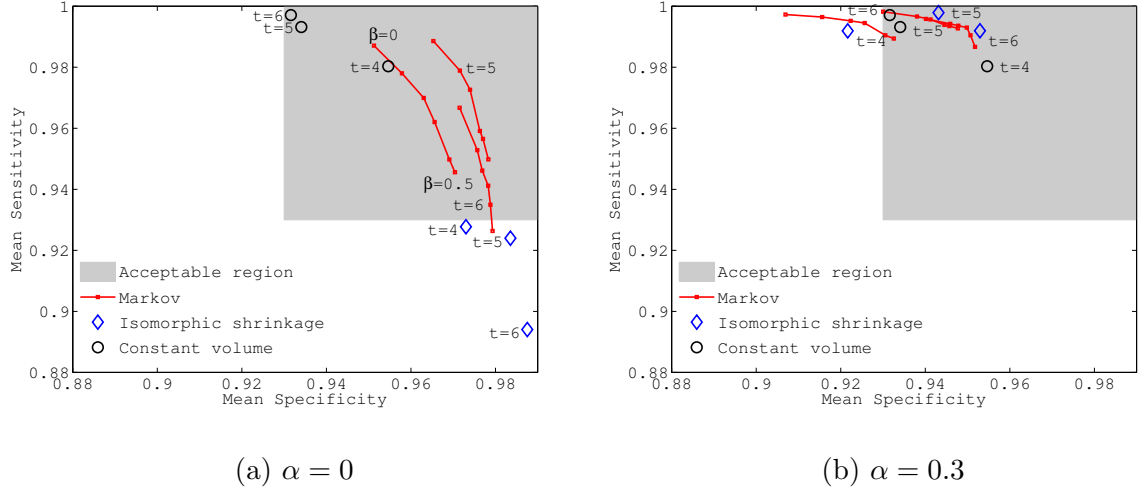


FIG. 4: Weekly performance of the three models with and without a margin, where t is the week at prediction and β is the probability threshold.

volume model. Both Figures 3a and 3b indicate that the best performance in sensitivity and specificity is attained by combinations of small margin parameter (α) with a small probability threshold (β) or a large margin parameter with a large probability threshold.

Figure 4 compares the weekly performance of the models. Generally, the performance of the Markov model improves over the course of treatment. On the other hand, the performance of the constant model, particularly specificity, degrades as t increases. Notice that performance of all three models becomes similar as α increases. Regardless of the value of the chosen margin parameter, the Markov model generates acceptable results by adjusting the parameter β accordingly (larger β for larger α and vice versa).

B. A statistical comparison between the Markov and isomorphic shrinkage models

We performed a Wilcoxon signed-rank test against the hypothesis that the Markov model is significantly different from the isomorphic shrinkage model in terms of sensitivity and specificity. The p-values are shown in Table III (sensitivity) and IV (specificity), for different combinations of α and β . Shaded cells indicate a p-value of less than 0.05 (i.e., significant at the 95% level). The two models perform differently when α or β are small. In those cases, the Markov model outperforms the isomorphic shrinkage model in both

240 sensitivity and specificity as can be seen in Figure 3. There are also cases when β is large and α is moderate to large where the Markov model also outperforms the isomorphic shrinkage model in sensitivity.

TABLE III: p-values of Wilcoxon signed-rank test on sensitivity. Null hypothesis: no difference between the Markov and isomorphic shrinkage models in sensitivity. Shaded cells correspond to cases where the null hypothesis is rejected ($p < 0.05$).

		β					
		0.0	0.1	0.2	0.3	0.4	0.5
α	0.0	0.000	0.000	0.001	0.007	0.062	0.245
	0.1	0.000	0.002	0.291	0.758	0.234	0.093
	0.2	0.000	0.040	0.666	0.421	0.086	0.018
	0.3	0.000	0.266	0.695	0.201	0.024	0.006
	0.4	0.010	0.027	0.200	0.797	0.201	0.069
	0.5	0.000	0.000	0.000	0.000	0.000	0.000

TABLE IV: p-values of Wilcoxon signed-rank test on specificity. Null hypothesis: no difference between the Markov and isomorphic shrinkage models in specificity. Shaded cells correspond to cases where the null hypothesis is rejected ($p < 0.05$).

		β					
		0.0	0.1	0.2	0.3	0.4	0.5
α	0.0	0.000	0.000	0.000	0.000	0.000	0.002
	0.1	0.000	0.003	0.131	0.579	0.757	0.461
	0.2	0.000	0.002	0.092	0.434	0.913	0.591
	0.3	0.000	0.003	0.143	0.591	0.709	0.363
	0.4	0.000	0.001	0.043	0.247	0.792	0.785
	0.5	0.000	0.000	0.000	0.000	0.000	0.000

IV. DISCUSSION

We believe the Markov model offers several advantages over the other models. The Markov model takes the most granular approach to modeling geometry, considering each voxel (or bi-voxel) separately. This, along with the additional adjustable parameter β , provides the Markov model with the capability to achieve generally better performance in terms of the sensitivity-specificity trade-off. We imagine that sensitivity outweighs specificity in clinical situations. However, given a particular acceptability threshold for sensitivity, it appears that it is possible for the Markov model to meet the same level of sensitivity but with increased specificity, compared to the other models. Note that if the definition of “acceptable” changes, the Markov model provides flexibility through the β parameter to try and meet the new acceptability criteria. The strength of the Markov model over the other two models is most evident in Figure 3b, which depicts performance at the 10th percentile (i.e., 90% of transitions), which is more clinically relevant than mean performance.

As shown in Figure 4, the performance of the Markov model generally improves as the treatment progresses. Though tumor cells may be killed right after the start of treatment, it may take a few weeks for complete cell clearance, only after which volume reduction is observed [2]. The degradation in the performance of the constant volume model as t increases is intuitive: specificity relates to OAR sparing and modeling a shrinking tumor using a constant volume will result in increased OAR dose.

A few items related to data should be noted. First, we excluded patients whose initial tumor size was less than 280 voxels – such small tumors would have fewer voxels on the tumor surface, making it difficult to estimate transition probabilities accurately. Second, we excluded 4 out of 57 transitions where the tumor shrunk more than 2 layers of voxels (0.8 cm) in one week. Modeling substantial shrinkage is possible with the sufficient data. But ultimately that is not what our model should focus on – substantial shrinkage should trigger full re-planning. For small tumors, the gains in using such a model to improve OAR sparing, for example, would also be limited, so while applicability may be more narrow, impact is not necessarily reduced by too much. Eliminating small and fast-shrinking tumors also biases the sensitivity upwards. However, the bias is less extreme with the Markov approach compared to the constant volume model. Third, delineation uncertainty

is an important consideration in our data. We believe this uncertainty is contained as much
275 as possible because a single radiologist did all the contouring. Delineation uncertainty
may be higher among certain similar geometries, but transition probabilities will also be
similar among similar geometries, so the overall effect is dampened.

While the Markov model seems to perform well against the isomorphic shrinkage and
constant volume models, there were instances when it did not predict tumor geometry
280 change well. Out of the 53 included transitions (i.e., a prediction of tumor geometry
change in consecutive weeks for a particular patient), there were 50 transitions where
some part of the sensitivity-specificity trade-off curve overlapped the acceptable region
for some value of α and β . In the remaining three cases, no value of α or β resulted in
performance within the acceptable region. For those three transitions, we attempted to
285 understand what may be a factor in the poor performance of the Markov model. We
found that the convexity of the tumor influences how well the Markov model predicted
geometry change: tumor shapes that are highly non-convex are harder to predict. Mayr
et al. [25] reported that most cervical tumors have irregular shapes. However, most
of the tumors with which our method performs well are also irregularly shaped according
290 to the definition in Mayr et al.

We computed a convexity measure [26] for the tumor at the start of each transition:
the higher the convexity measure the more convex the shape is (see Figure 5). Figure 6
shows that tumors with the smallest convexity measures are hard to predict from the
perspective of sensitivity. Specificity prediction does not seem to be affected by tumor
295 convexity, which is expected as specificity relates to OAR sparing. Note that there are
examples in Figure 6 where high convexity measures may still generate relatively low
sensitivity values (in the range of 0.94). Further study is needed to understand the
factors that challenge tumor geometry prediction using our Markov model.

In the case that high quality scans are not available to train the Markov model, the
300 isomorphic shrinkage model may be a viable alternative. While the isomorphic shrinkage
model is generally dominated by the Markov model, recall that performance was similar
for intermediate to larger α and β values (see Tables III and IV). Increasing β will result in
more voxels in the bi-voxel layer of interest being classified as non-tumor and increasing α
will put less emphasis on the voxel by voxel classification of the Markov model, eventually
305 eliminating the difference between the Markov and isomorphic shrinkage models.

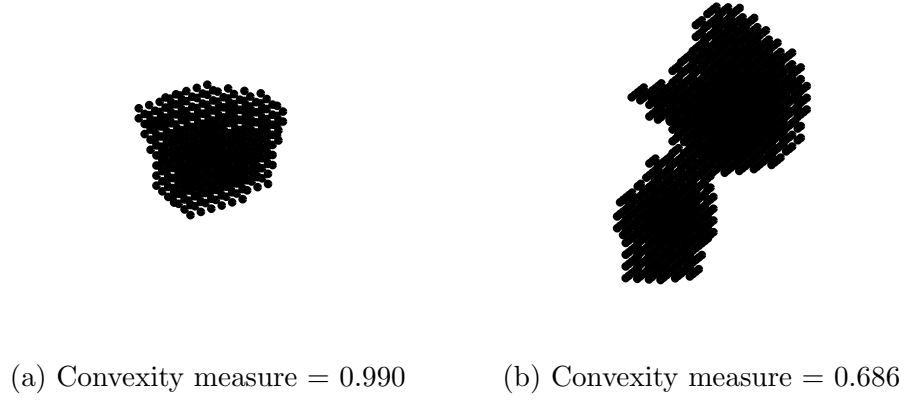


FIG. 5: Example of tumors with different convexity measure

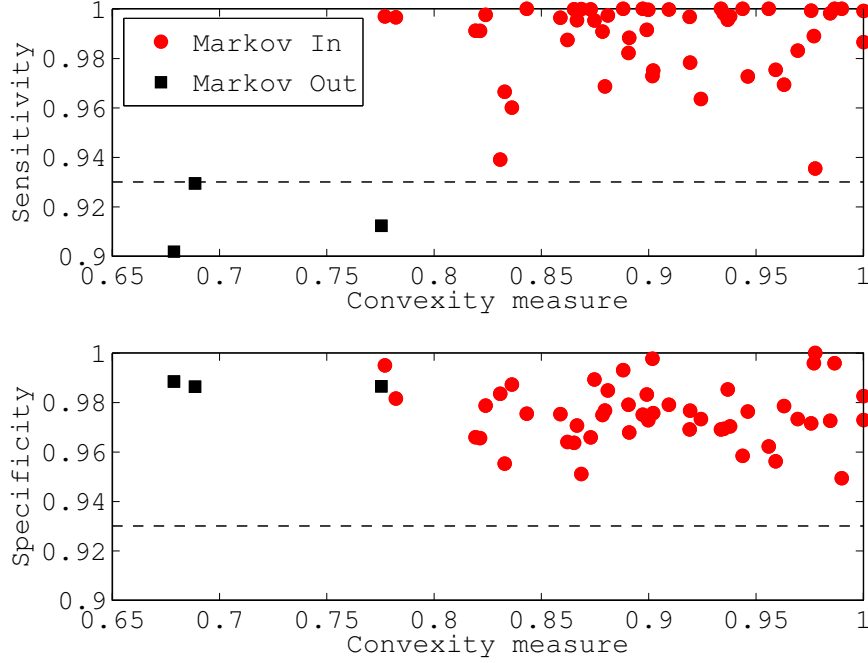


FIG. 6: Sensitivity and specificity plotted against the convexity measure. The higher the convexity measure the more convex the tumor shape is. “In” and “out” refers to the Markov curve overlapping or not overlapping the acceptable region, respectively.

There are several directions for future study. First, with the current dataset it is not possible to rigorously validate the assumption that the evolution of a cervical tumor follows a Markov process. An anatomical voxel grid that can capture motion rather than a static voxel grid is needed. Second, in most clinical situations, weekly high quality images (e.g.,

310 MRI) over the course of treatment are not available. In such cases, transition probability
 estimates could be derived from a group of patients with few images rather than from
 the individual undergoing the treatment. Multiple groups may be required to describe
 geometry changes of tumors with different levels of response to radiation. If these different
 “archetypes” exist, class solutions (i.e., transition probability matrices) may be applicable
 315 and generate results that are still individualized. An interesting byproduct of the Markov
 model is the probability map, which estimates the likelihood of a particular voxel being
 cancerous. This probability map might find application in optimization approaches where
 voxel-specific doses or weighting factors are used to plan and adapt treatments [18, 21,
 22, 24]. Deformation was not explicitly modeled, though we recognize that substantial
 320 deformation (which was not present in our dataset) would affect our models. Third, our
 model aims to predict a binary image that aligns with the actual tumor image. Future
 work should also consider dosimetry in addition to geometric prediction to increase clinical
 relevance. Lastly, the general approach we developed may find application beyond cervical
 cancer and for different types of target volumes (CTV, PTV, etc.).

325 V. CONCLUSION

In this paper, we compared three approaches to modeling the evolution of a cervical
 tumor’s geometry undergoing radiation therapy. Our Markov approach models individual
 voxel changes and is a novel way to model geometry changes under radiation treatment
 in a probabilistic manner. Tunable parameters give this model flexibility to meet a wide
 330 variety of criteria, which we measured using sensitivity and specificity, and the capability
 to generally outperform both the isomorphic shrinkage and constant volume models. In
 certain cases, the isomorphic shrinkage model is comparable to the Markov model and
 may be an acceptable alternative when sequential, high-quality imaging information is
 not available. We also found that convex tumor shapes are easier to predict. Overall,
 335 prediction of tumor geometry changes may help reduce normal tissue dose and enhance
 target coverage by triggering treatment plan changes ahead of time. For cervical cancer,
 such prediction may aid clinicians in evaluating whether sufficient tumor shrinkage has
 occurred in the initial chemo-radiation phase of treatment to move to the brachytherapy
 phase, or whether other patient specific interventions are needed beyond the standard

340 two-phase approach.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support of and helpful suggestions from Dr. Michael Milosevic in this research project and in particular for providing access to the patient data used in this paper. This research was supported in part by the Ontario
345 Consortium for Adaptive Interventions in Radiation Oncology (OCAIRO) funded by the Ontario Research Fund (ORF) and the MITACS Accelerate Internship Program.

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