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Cardiovascular toxicity prediction using sequential neural network with normalized thoracic radiation dose coordinate system

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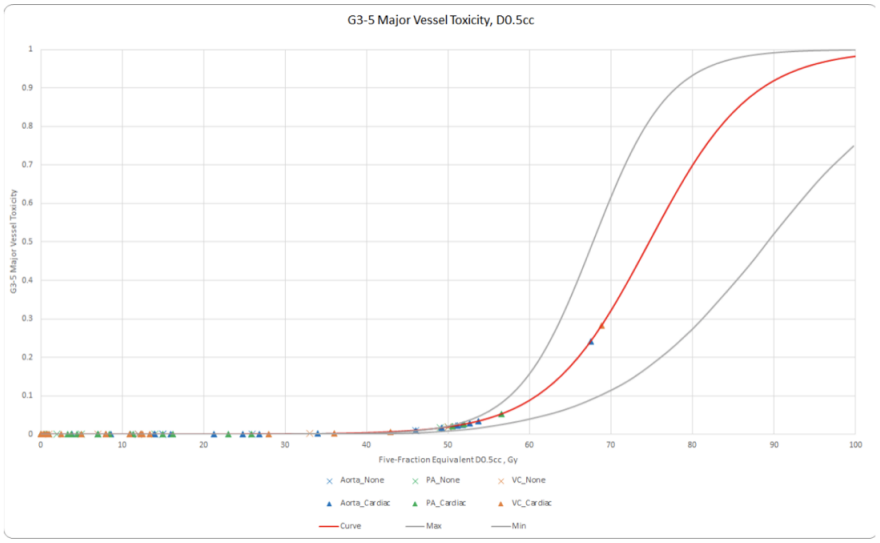
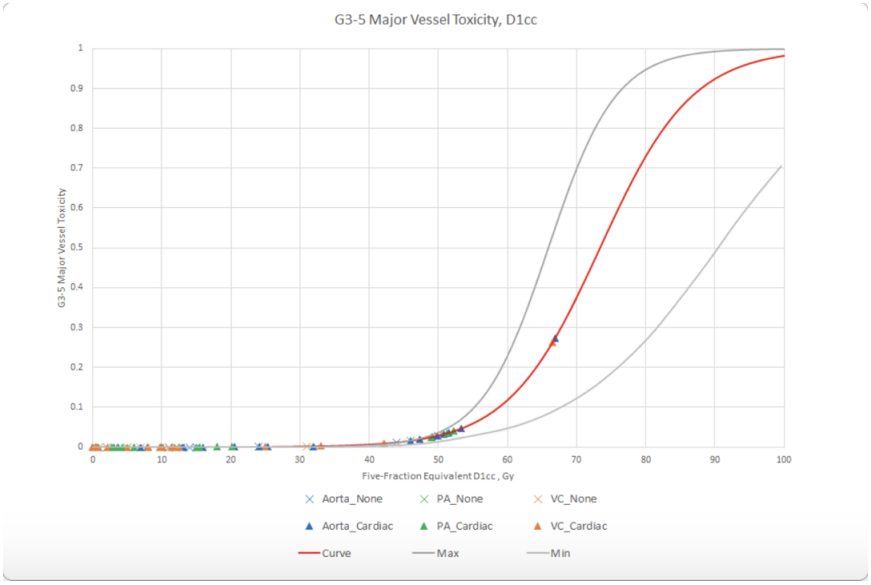
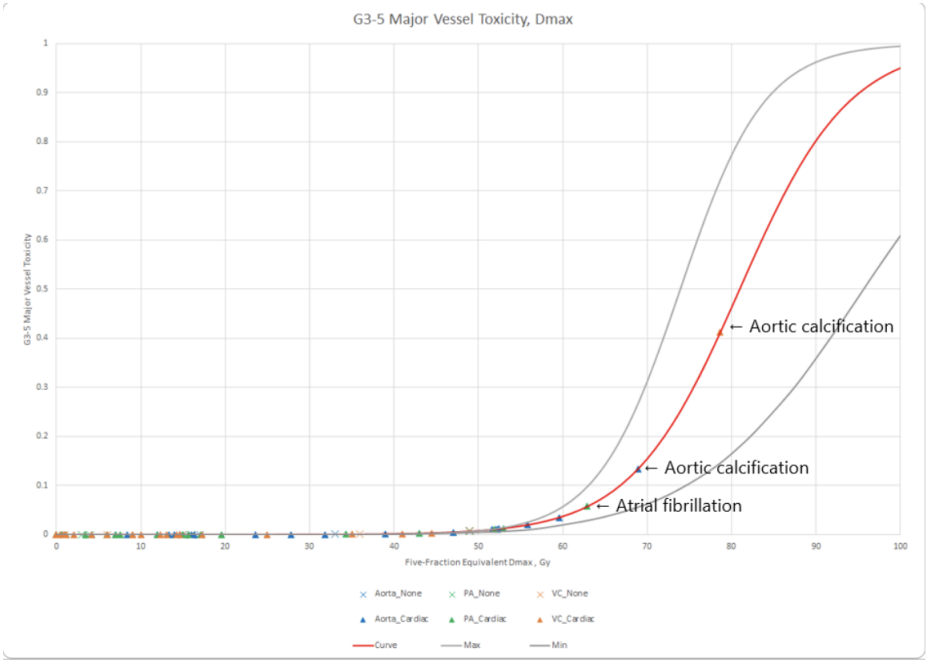
1 Introduction

In practice today, current radiation oncologists treat thoracic cancers using a technique known as Stereotactic Body Radiation Therapy (SBRT). These types of cancers include tumors in the thoracic region of the body. SBRT works by delivering a massive dose of radiation, often in excess of 50Gy, to the Planning Target Volume (PTV) and thus eradicating the tumor. This type of radiation therapy is very effective at treating thoracic cancers and has been used extensively by oncologists for over 20 years. However, because of the lack of long-term data, it was only recently that the theory emerged that SBRT could pose harmful side effects. By definition, thoracic cancers occur in the central region of the human body. While a high dose to the PTV may kill the tumor, a given treatment plan may deliver an unnecessarily high dose to surrounding tissue. When this occurs for a thoracic tumor, surrounding tissue includes most of the vital organs of the body. These doses of radiation to the heart, great vessels, thoracic spine, etc. can dangerously increase cardiovascular toxicity. As exemplified in the Xue et al. paper (2), there is a statistically significant correlation between these doses to vital structures under SBRT and further health complications. This must be considered when planning a safe and effective treatment.


G3-5 Major Vessel Toxicity, D0.5cc
G3-5 Major Vessel Toxicity
Five-Fraction Equivalent D0.5cc , Gy
Aorta_None
PA_None
VC_None
Aorta_Cardiac
PA_Cardiac
VC_Cardiac
Curve
Max
Min


G3-5 Major Vessel Toxicity, D1cc
G3-5 Major Vessel Toxicity
Five-Fraction Equivalent D1cc , Gy
Aorta_None
PA_None
VC_None
Aorta_Cardiac
PA_Cardiac
VC_Cardiac
Curve
Max
Min



The images pictured above illustrate major vessel toxicity as it relates to increasing dose constraints D0.5cc, D1cc, and Dmax. D0.5cc and D1cc represent the dose value in Gy to 0.5cc and 1cc of the major blood vessels in the body. Dmax is the maximum point dose received by a voxel (3D pixel) of the great vessels during the treatment plan. The red line indicates the assumed exponential logistic model correlating Vessel Toxicity with dose. In the case of cardiovascular toxicity with SBRT treatments researchers have looked at 5 dosimetric parameters alone, which are: V25Gy, D0.5cc, D1cc, D4cc, and Dmax for the organ of interest (Xue et al. (2)). A log logistic curve can be readily described by a two parameter function as shown in

the equation below, with one parameter describing the dose at which 50 of patients exhibit complications, D50, and the second parameter, g, the normalized dose-response gradient (Bentzen et al. (4)). These curves of normal tissue complication probability can be generated as functions of any of the five dose parameters described above (i.e. Dv).

$$NTCP = \frac{e^{(4g_{50_V} * (\frac{D_V}{TD_{50_V}} - 1))}}{1 + e^{(4g_{50_V} (\frac{D_V}{TD_{50_V}} - 1))}} \tag{1}$$

The depicted data points show specific cardiovascular events in patients after treatment with corresponding dose constraints and cardiovascular toxicity value in the great vessels. Even though tumors may be killed, if unnecessarily high doses are delivered to vital structures, long term health complications can ensue. The model above considers only dose constraints as a factor in cardiovascular toxicity. However, other patient risk factors can contribute to cardiovascular toxicity. Our proposed model will consider relative dose location and attempt to account for potential genetic variation.

As described in the Darby paper (3) on cardiovascular toxicity after breast radiation, patient specific risk factors heavily influenced the likelihood of cardiac events. Patients with a history of ischemic heart disease had a 6.67 relative rate increase in cardiac events after radiation. A smaller, but significant

elevation in risk was also seen in patients with circulatory diseases, diabetes, and chronic obstructive pulmonary disease as well as smokers and patients with high body mass index. In addition to these patient specific risk factors, there appears to be a possible genetic component to toxicity risk. The demographics of our patient population allow us to test whether racial differences leading to genetic makeup affects the radiation induced cardiovascular toxicity. In addition to demographic and medical history collections of our patients, we plan on assessing any genetic testing performed and accessing the ORIEN system for relevant mutation information.

2 Methodology

The aim of this project is to apply machine learning to specific SBRT plans and create a model representative of cardiovascular toxicity for the purpose of evaluating the risk of a treatment plan. We plan to generate a 6D model for organ-specific cardiovascular toxicity from Lung SBRT based on: 1) dosimetric characteristics of the treatment plan, 2) 3D hot-spot locations within individual organs, 3) elapsed time between RT treatment and event of interest and 4) patient specific risk factors. A machine learning

model will therefore be trained to predict radiation induced toxicity in each cardiovascular structure (aorta, pulmonary artery, inferior vena cava, heart, heart chambers, and LAD) using the following inputs: Organ-specific V25Gy, D0.5cc, D1cc, D4cc, and Dmax from the SBRT plan; normalized 3D coordinates of the maximum dose point in the organ (determined using the NTCS system); the presence or absence of cardiovascular risk factors such as smoking, obesity, prior cardiac events, etc.; and patient specific criteria such as age, gender, race, and genetic mutations/variations.

We will utilize two techniques to help develop this model: a) a machine learning model (ML) model which will incorporate a neural network with two hidden layers with rectified linear unit (reLu) activation functions followed by a softmax function to perform classification in the output layer. The model output will be a prediction of whether or not a radiation induced toxicity will occur in the given organ. b) a multi-parametric model which will separately model independent risk factors by optimizing for equation 2 with physical characteristics: A_i, $F_{timelag}$ (expected latency of the cardiovascular event), $F_{position}$, $F_{genetics}$ (patient specific risk factors), and F_{age} as output.

Due to the relatively small sample size in our cohort, training and testing will be performed using ten-fold cross validation. In both processes, the

patients will be divided into training and testing groups (which will be used to perform model fitting and evaluation, respectively) over ten distinct iterations where different groupings are used in each loop. Repeating this process with each patient subset taking a turn as the test set allows for robust evaluation of the model accuracy while avoiding over-fitting. For each patient, the data points calculated above were input to the network along with other relevant patient information including patient age at treatment, time lag between treatment and cardiovascular event, and patient specific risk factors. In equation 2, each value of i represents each of the five dosimetric parameters given above, and $NTCP_i$ will be calculated per each of the five parameters using the $D50$, and g obtained from the reference Xue et al data (2). The location of Dmax point in 3D $\sqrt{x^2 + y^2 + z^2}$ per each organ will be used to obtain the positional information.

$$RISK_{OVERALL} = (\sum_{i=1}^{5} A_i * NTCP_i) * F_{timelag} * F_{position} * F_{genetics} * F_{age} \quad (2)$$

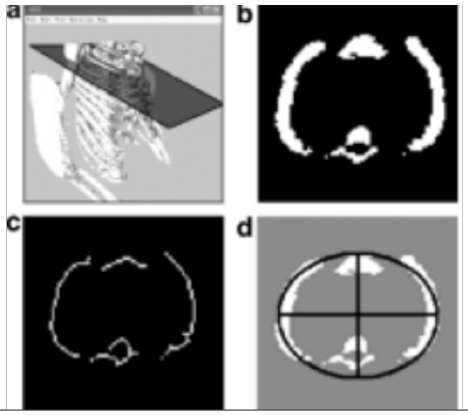
We will also establish uncertainties of the predictive model based on the uncertainties due to organ motion (5), organ delineation (6), cell survival curve, and scarcity of the input toxicity data as available outputs of the tox-

icity simulation for a given plan.

In future efforts, we can improve the precision of our model by collecting genome-wide genotype data on DNA specimens to be collected from the participants. These genotype data can be used (a) to compute principal components of genetic ancestry, (b) to compute the genetic risk of cardiovascular disease using an existing polygenic risk score as discussed in Khera et al. (7), and (c) to derive and compute the genetic risk score (GRS) of radiation induced toxicity. Each of these three measures drawn from genetic data can be used to improve the precision of our proposed predictive model in the future.

3 Data Normalization

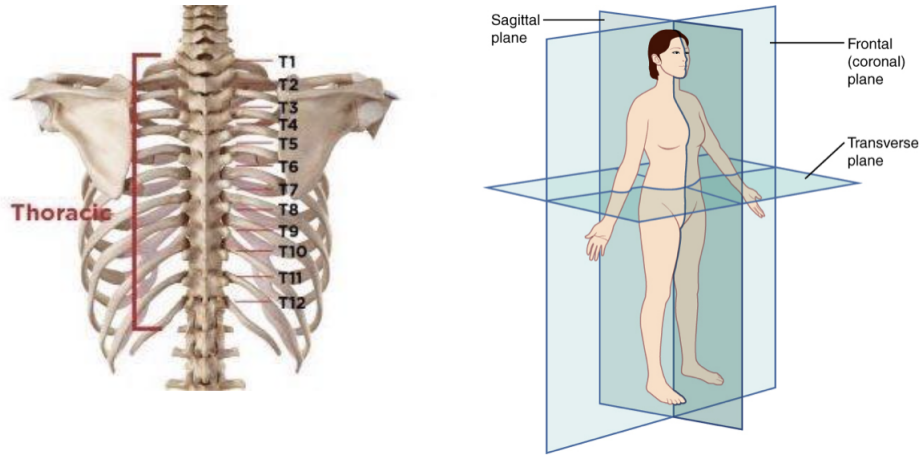
When working with different thoracic sizes among the population, one needs to define a normalized coordinate system to compare one patient to another. A normalized thoracic coordinate system (NTCS) will be used in this project as referenced by Wang et al. paper (1). In this coordinate system, the coordinate values are normalized by the individual thoracic size so that it is universal to the population as shown in the image below.



NTCS coordinate system. Right: Left –definition of the coordinate system and normalizing z dimension; Right-The calculation of x and y dimension for normalization. (a) The oblique plane which is manually selected to pass the second rib pair; (b) the cut image of the oblique plane in (a); (c) the centerlines of the cut-image in (b); (d) an ellipse is fitted to the centerlines in (c).

Treatment plans consist of numerous CT scans along with the dose plan, the dose files, and the organ structure contours in dicom format. When the dose dicom files for a specific patient's treatment are read in, the dose information is stored for each 3 dimensional voxel (Jonathan). For this project, we need to consider the coordinate location of each dose voxel within the body along with the magnitude of the dose. The initial voxel coordinates (x, y, z) are taken in with respect to the dose grid of the treatment plan. In this coordinate system, the x axis corresponds roughly to the sagittal axis of the body, the y axis corresponds to the coronal axis, and the z axis corresponds

to the vertical axis. This information varies between different treatments and different patients. For the coordinate system to have significant value in the predictive model, it must be consistent across all patients. In order to normalize these coordinates across different patient dose grids, we must change the coordinate system. This will be done in 2 parts.

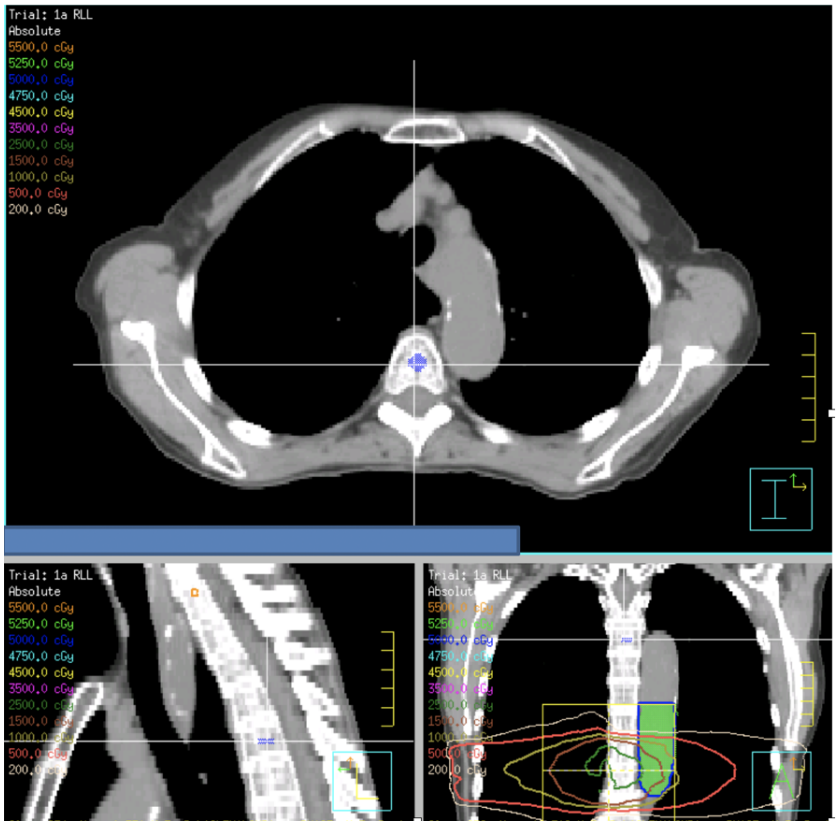


Numbered thoracic vertebrae and bodily axes pictured for reference

Part 1:

First, we must use a translation of axes such that the resulting origin of the translation lies on the 10th thoracic vertebrae (T10). Essentially, each dose coordinate must be shifted by the original coordinate point of T10 so that T10 will be the new origin, and the spatial relation between all other points will be preserved. If T10 has the original voxel coordinates (a, b, c), every voxel point

$p = (x, y, z)$ must be shifted to p' such that $p' = (x', y', z') = (x-a, y-b, z-c)$. Effectively, this will shift every coordinate point by the coordinates of T10, constructing a new coordinate system with T10 at its origin.



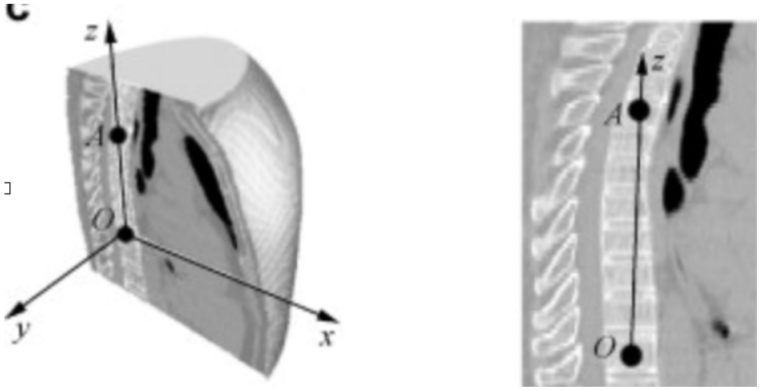
Contoured in orange is T5, and Blue is T10 for one of the training patients

Part 2:

Now, the coordinate systems across patients will have a common origin. However, the slope of the thorax with respect to the vertical can be vastly different

between patients. We believe if the slope of the spinal canal is aligned or taken as the z axis for all patients, all other main thoracic organs could be mapped. Furthermore, using the distance from T5 to T10, we will be able to normalize different thorax heights (Wang et al. (1)). To create a better approximation and account for this variation, we will transform the axes of the coordinate system. The line segment stretching from the 5th thoracic vertebrae (T5) to T10 is roughly parallel to the vertical axis of the body. The coordinate system will be transformed such that this line will lie on the new z axis. In order to accomplish this, we will perform a change of basis on the vector space represented by our current coordinate system. First, the line between T5 and T10 must be found. Let vector v be the vector from the origin (T10) to the coordinates of T5. This vector can be calculated by subtracting the original coordinates of T10 from the original coordinates of T5.

Once the vector $v = [v_1, v_2, v_3]$ from T10 to T5 is found, we must find the other vectors to form the basis. We will fix the y-axis to the coronal plane denoted as the coronal vector y' and then find a new orthogonal vector to define the new x-axis. Denote this vector x' such that x' is defined as the cross product of the other two basis vectors. $x' = [x'_1, x'_2, x'_3] = v \times y'$ Once



this new vector is calculated, the new orthogonal basis can be established and the change of basis matrix will be created. We will define an orthogonal basis B of the new coordinate system to be $\{[x'_1, x'_2, x'_3], [y'_1, y'_2, y'_3], [v_1, v_2, v_3]\}$ as we will keep the y axis constant but transform the x and z axes to reflect vectors x' and v.

Any point in the desired coordinate system with basis B can be represented by the coordinates (x_n, y_n, z_n). Therefore, by the definition of a change of basis, any coordinate point with respect to the standard basis $(x, y, z) = U * (x_n, y_n, z_n)$ where U is the matrix with columns as the vectors of basis B. Then, any point (x, y, z) in the original coordinate system can be transformed to its corresponding point with respect to the new basis using $(x_n, y_n, z_n) = U^{-1} * (x, y, z)$.

4 Implementation

The code pipeline was created to read in both the dose dicom files and the treatment plan of a given patient and compile the dose values to each voxel of the patients thoracic region specified by the dose grid of the treatment plan. Along with the dose values, the structure contours included in the treatment plan were read in. These structure contours were used to create boolean mask arrays for each organ (jonathan). Together with both the organ masks and the dose grid, the pipeline creates separate arrays that differentiate the dose voxels by organ. At that point, a data frame is created for each organ consisting of a mapping of dose to the corresponding coordinates with respect to the specific treatment dosegrid.

In the next step, these organ dataframes were used to calculated the desired dose constraints for each organ. As stated above, V25cc, D0.5cc, D1cc, D4cc, and Dmax were calculated for each thoracic organ. Dmax was simply found to be the highest point dose value of each organ and its specific coordinates were tracked. V5cc, V10cc, and V25cc are defined as the volume of the organ receiving a dose greater than the specified value. For V25cc, the doses to each organ that were greater than or equal to 25Gy were counted. Since each dose corresponds to a voxel, and the voxels have a volume $2.5mm^3$,

the volume V25cc can be calculated simply.

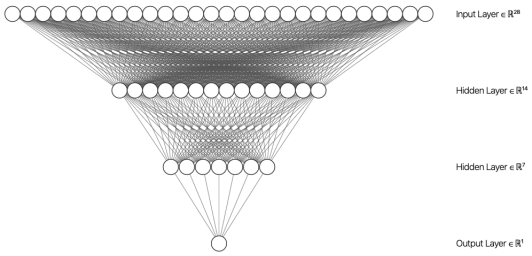
Next, we calculated D0.5cc, D1cc, and D4cc for each organ. D1cc of a given organ is defined as the dose to 1cc of that organ. In other words, D1cc is the highest dose received by the entirety of 1cc of the organ. D1cc is calculated by finding the minimum dose to the highest 1cc of voxels. Given that each voxel has a volume of $2.5mm^3$, it follows that 64 voxels make up 1cc of total volume. Therefore, D1cc of a given organ is equal to the 64th highest dose to a voxel in that organ. A similar methodology was used in the calculation of D0.5cc and D4cc.

Furthermore, once these dose parameters were calculated, the coordinates were normalized according to the above process. Both T5 and T10 were included in the contours of the dose plan and their relative coordinates were found. Using these coordinates and the dimensions of the dose voxels, the euclidian distance between T5 and T10 was calculated and vector v was found. Similarly, using the extreme coordinates of the second rib pair, the vector y' was calculated in the direction of the coronal plane. Following the process described above, the vector x' was calculated and then both were used to create the new orthogonal coordinate basis. At this point, the data was fully preprocessed and ready to be used in the model.

5 Toxicity Evaluation Procedure

Once the input parameters were preprocessed, we set out to create the model. To start, a sequential neural network will be created with two hidden layers. For each patient, each of the 5 dose constraints ($V25cc$, $D0.5cc$, $D1cc$, $D4cc$, and $Dmax$) will be used to calculate the Normal tissue Complication probability with respect to that specific constraint for each of the target organs (Heart, Aorta, Vena Cava, and Pulmonary Artery). This assumes that cardiac toxicity follows a log logistic curve relative to specific dose parameters as asserted in Xue et al (2). In addition to these 5 dose constraints and the normalized max coordinate for each organ, the following parameters are also used as inputs to the model: time between treatment and cardiovascular event, patient age, and patient genetic information. In the event that no cardiovascular event occurred, the time between treatment and present date is included.

With the dose constraint values and coordinates for each patient's heart, aorta, vena cava, and pulmonary artery in addition to the other specific patient parameters, the sequential network begins with an input layer of 28 parameters. The first layer reduction occurs to a 14 node hidden layer and



then the second layer reduction to the 7 node hidden layer. Finally, the neural network converges to a single node in the output layer indicating 1 for a cardiovascular event, and 0 for a non-event. Once created, this model can then be trained on the set of training patients and its accuracy will be tested on the remaining patients. After training, the model will be able to produce the probability that a given treatment plan will cause a cardiac event.

Using 10-fold cross validation the model will be trained and evaluated. Patients will be split into a training group and a testing group so that the model can be verified. Due to the relatively small number of patients that we have access to, the subset of training patients will be shuffled with the testing patient to train the model with different variations. Each time the model's results will be tested on the coo responding testing subset of patients. This aggregate accuracy will then be used to evaluate the model in a more comprehensive manner.

6 Preliminary Results

The coordinate normalization and dose constraint calculation processes were performed on 10 test patients. These patients were anonymized for the purpose of preserving the privacy of their respective medical information. Each of the 5 dose constraints including Dmax, V25cc, D0.5cc, D1cc, and D4cc were calculated for each of the 4 target thoracic organs. This was accomplished using the dose-voxel information included in each patient's specific treatment plan. The results for one specific patient denoted BE is shown below.

BE	heart_av	aorta_av	pa_av	vc_av
max_dose	12.39885119	66.51084845	1.690538059	8.234731602
max_coord	[53 82 67]	[58 86 71]	[53 83 63]	[46 68 75]
axis_scale_factors	[109 149 95]	[109 149 95]	[109 149 95]	[109 149 95]
v25cc	0	4.00003	0	0
D0.5cc	7.819624871	50.69093361	1.045227256	7.709189693
D1cc	5.476514203	42.04014973	0.911217542	7.30229655
D4cc	1.5225426	24.81150924	0.632208545	2.832789336

After calculation, a sample of 5 of these patients was taken and the dose constraint values were compared to those in the Pinnacle system which holds the true values from a given treatment. Additionally, included in the results are the normalized coordinate values for the max dose to each organ of the test patients.

Upon comparison to the calculated data, percent errors were calculated for each of the dose constraints of each organ for all 5 patients. The percent error for each constraint was then averaged across each organ and then accumulated for all 5 patients to determine an estimate of the calculation's accuracy. The table below details the results.

Dose Constraint	Average % error
Max Dose	5.014613856
V25cc	11.33928806
D0.5cc	6.431076421
D1cc	7.416983291
D4cc	17.12369398

References:

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