

Papillary Thyroid Cancer, PTC: Identifying the Values of the Risk Factors that Will Minimize the Malignant Tumor Size Through Desirability Function Approach

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ABSTRACT

Thyroid cancer is one of the major cancers in today's society, and it is the fastest growing cancer diagnoses in the United States. One of the most important aspects of Thyroid Cancer, TC, is to identify the risk factors that contribute to TC growth. TC is separated into four main types, Papillary, Follicular, Medullary and Anaplastic. Papillary Thyroid Cancer, (PTC) is the most common thyroid cancer type; eight out of ten TC patients are classified with PTC. We have developed a real data driven analytical model to predict the malignant tumor size of PTC patients with high degree of accuracy using four of the nine individual risk factors that significantly contribute to PTC and most importantly the identified eleven bivariate interaction terms which are highly significant in contributing to the growth of the malignant tumor size of PTC patients, []. In the present study we utilized the Desirability Function Process to optimize (minimize) the malignant tumor size of PTC patients. That is, we identify the values of the risk factors that will minimize the malignant tumor size of PTC patients with at least 95% accuracy. To achieve our objective, we utilized the desirability function process and validated the necessary conditions required for the optimization process of the analytical model which includes individual risk factors as well as interaction terms with high desirability function of 1, implying that the risk factors are effective and robust in minimizing the malignant tumor size of PTC patients. This information is very important to the medical professionals in identifying and implementing appropriate treatment strategies for PTC patients.

Keywords: Papillary Thyroid cancer, Tumor Size, Risk Factors, Desirability Function Approach, Surface Response Analysis.

INTRODUCTION

One of the major leading causes of death in today's world is cancer disease that account one out of six deaths. This increasing trend of cancer patients should be a considerable factor and

many research studies were done based on identifying the risk factors and their contribution to the spread of the cancer, [1] [2]. Thyroid Cancer is one of the cancers increasing fast around the globe and is the seventh most common malignancy in women, [2]. The most recent estimates of American Cancer Society for Thyroid Cancer are about 44,020 new cases of Thyroid Cancer of which 12,500 are men and 31,520 are women and about 2,170 deaths due to Thyroid Cancer of which 990 are men and 1,180 are women for the year 2024 in the United States. From 2009 to 2018 the death rates have increased 0.6% per year, [3]. There are four main Thyroid Cancer types, Papillary, Follicular, Medullary and Anaplastic. But Papillary Thyroid Cancer, PTC is the most common Thyroid Cancer type which grows slowly and usually develops in only one lobe of the thyroid gland, [4]. Thus, in the present study we will concentrate on PTC patients to develop an optimization process that will minimize the malignant tumor size of a PTC patient.

Thyroid Cancer starts when a cell begins to grow out of control in the thyroid gland which produces hormones that help to regulate the metabolism, the heart rate, the blood pressure and the body temperature. In the front of the neck the thyroid cartilage which is called Adam's apple contains a thyroid gland, and it cannot be seen or felt for most patients. The thyroid gland has a butterfly shape with two lobes called left and right which have been joined by a narrow piece of gland called isthmus. Thyroid Cancer may spread or metastasize to other parts of the body, including lungs, bones, and occasionally the brain, [4]. A lump (nodule), change of voice (including hoarseness), difficulty swallowing, swollen lymph nodes in the neck and pain in the neck and throat are the most common symptoms of Thyroid Cancer, [5], [6].

In literature researchers have identified some risk factors and their contribution to Thyroid cancer. Normally, Thyroid cancer can appear at any age, but priority goes with older people. When it comes to the tumor size of PTC patients, there is a significantly high increase in tumor size among young people at age 30 to 50, [7]. Usually, Thyroid Cancer occurs about 3 times more often in women than in men. The risk for Thyroid Cancer peaks earlier for women, often in their 40's and 50's. But for men peak usually in their 60's and 70's, [8], [9]. There are some risk factors that can be preventable such as exposure to radiation as a child or in their young ages due to medical treatments or radiation fallout from nuclear weapons or power plant accidents and the amount of iodine in the diet, [10], [11], [12], [13]. Also, one research found that there is an inverse relationship between the thyroid risk and the smoking of tobacco, [14]. Body Mass Index value and being overweight are other high-risk factors associated with Thyroid Cancer, [15]. The family history of Thyroid cancer patients is also an identified risk factor, [16]. Further literature on risk factors of Thyroid cancer can be read through the papers [17], [18], [19], [20], [21], [22].

In our previous study, [23], we have developed a real data driven analytical model that predicts the malignant tumor size of a PTC patient as a function of statistically significant four individual risk factors and eleven two-way interactions with a 90% high degree of accuracy. In this study, we develop a robust and efficient methodology to optimize the response (minimize the malignant tumor size) using the above identified contributing risk factors and the optimal values of those risk factors to achieve that minimal malignant tumor size. Thus,

the desirability function approach evaluates the relationship between the response variable and risk factors by achieving the optimal values of the most influential risk factors.

The Desirability Function Approach is a powerful response optimization strategy consisting of controllable independent variables and is widely applied in multi-response processes. It determines the operating conditions of controllable independent variables that provide the most desirable value of the dependent variable (response). In 1965 Harrington, [24] and in 1980 Derringer and Suich, [25], defined the desirability function for factor optimization which is based on all the responses from different scales and transforms an estimated response into one scale-free value between 0 and 1 where 1 represents the completely desirable value while 0 represents a completely undesirable value.

The Response Surface Methodology is used in classic experimental designs by exploring the relationship between the response variable and other factors and is more popular among researchers due to its simplicity and effectiveness. We utilize the combination of the Desirability function approach and the Response surface method to determine the optimal values of the responses which is known as the Desirability Optimization Methodology (DOM).

In this research, we apply the desirability function approach with a single response to achieve our main objective of finding the best optimal values of the risk factors that will optimize (minimize) the response (malignant tumor size of a PTC patient). To evaluate the accuracy of the results given by the desirability function method we used statistical measures such as R^2 , adjusted R^2 , desirability value, 95% confidence interval, and 95% prediction interval. In addition, in this study, we have developed a 2- and 3-dimension visualization of the developed optimization method. According to our findings the PTC patient's malignant tumor size will be minimized if the patient is at age 57 and has gallbladder and does not have high blood pressure and diabetes. Taking aspirin regularly will decrease the tumor size while taking ibuprofen has an inverse impact on the malignant tumor size.

THE REAL DATA

For developing the real data driven analytical model and optimization process, we used data obtained from Center of Disease Control (CDC), [26]. The original data consisted of 99 observations of patients with PTC including complete and incomplete observations. However, in the study [23] we used only complete observations to build our analytical predictive model. Thus, in the present investigation we utilize the same complete data set with only 62 observations. The complete data set consists of both numerical and categorical risk factors totaling 10 risk factors including the response. Table 1, given below, summarizes all the risk factors that were used in the process of developing the analytical predictive model and the desirability function approach.

Table 1: Risk Factors and the Response

Risk Factor	Recode
Age	X_1
BMI	X_2
Number of years smoke until diagnoses	X_3
Taking aspirin regularly, Yes = 1, No = 0	X_4

Taking ibuprofen regularly, Yes = 1, No = 0	X_5
High blood pressure, Yes = 1, No = 0	X_6
Diabetes, Yes = 1, No = 0	X_7
Gallbladder, Yes = 1, No = 0	X_8
Gender, Male =1, Female = 0	X_9
Malignant Tumor Size (centimeters)	Y

ANALYTICAL APPROACH FOR THE DEVELOPING PROCESS OF THE DESIRABILITY FUNCTION

Our objective is to identify the optimum values of the risk factors that minimize the malignant tumor size of an individual PTC patient by utilizing the desirability function method. The desirability function method is an analytical process of optimization that assigns values to a single or multiple response and selects the best choice of the risk factors that optimize the response values.

The desirability function with a single or multiple responses, $\hat{y}_j$ and input risk factors, x_i is the optimum $[\hat{y}_1(x), \hat{y}_2(x), \dots, \hat{y}_k(x)]$, subject to x_i risk factors where $j = 1, 2, \dots, k$ are the estimated response of the variables. The desirability function is a response surface optimization strategy including controllable input risk factors and transforms the fitted response into a free-scale value which is known as the desirability. The combination of controllable risk factors that optimize the response variable(s) can be identified using desirability function approach. However, the objective of the response employs three different desirability functions: minimize, maximize and obtain a target value. This process uses the constraints of the controllable risk factors to obtain the optimum values of each risk factor, x_i which provides the best desired value for the response(s), $\hat{y}_j$. The desirability function, $d_j(Y_j)$ assigns a score between 0 and 1 for each $\hat{y}_j$. Thus, the completely desirable value means $d_j(Y_j) = 1$ and $d_j(Y_j) = 0$ is the completely undesirable value of Y_j .

To obtain the overall desirability function, D , we utilize the Geometric mean of the combined individual desirability's, $d_j(\hat{Y}_j)$ which is given by,

$$D = (d_1(\hat{Y}_1)d_2(\hat{Y}_2) \dots d_k(\hat{Y}_k))^{1/k} = (\prod_{j=1}^k d_j(\hat{Y}_j))^{1/k} \quad (1)$$

where k denotes the number of responses.

The desirability functions for three objectives to minimize, maximize, and obtaining a target value for the response can be written as follows. Let L_j , U_j and T_j be the lower, upper and target values, respectively, with $L_j \leq T_j \leq U_j$.

If the objective is to obtain the target value of the response variable, the desirability function can be expressed as follows,

$$d_j(\hat{Y}_j) = \begin{cases} 0 & ; \text{ if } \hat{Y}_j(x) < L_j \\ \left(\frac{\hat{Y}_j(x) - L_j}{T_j - L_j}\right)^s & ; \text{ if } L_j \leq \hat{Y}_j(x) \leq T_j \\ \left(\frac{\hat{Y}_j(x) - U_j}{T_j - U_j}\right)^t & ; \text{ if } T_j \leq \hat{Y}_j(x) \leq U_j \\ 0 & ; \text{ if } \hat{Y}_j(x) > U_j, \end{cases} \quad (2)$$

where the exponents s and t determine how important it is to hit the target value.

When

- $s = t = 1$, the desirability function increases linearly towards T_j ,
- $s < 1$ and $t < 1$, the function is convex, and $s > 1$ and $t > 1$, the function is concave.

If our objective is to minimize the response (i.e., the best response with smaller value), the desirability function can be defined as,

$$d_j(\hat{Y}_j) = \begin{cases} 1 & ; \text{ if } \hat{Y}_j(x) < T_j \\ \left(\frac{\hat{Y}_j(x) - U_j}{T_j - U_j}\right)^t & ; \text{ if } T_j \leq \hat{Y}_j(x) \leq U_j \\ 0 & ; \text{ if } \hat{Y}_j(x) > U_j, \end{cases} \quad (3)$$

where T_j is a small enough value for the $\hat{Y}_j$.

Finally, if the objective is to maximize the response (i.e., the best response with larger value), the desirability function can be defined as,

$$d_j(\hat{Y}_j) = \begin{cases} 0 & ; \text{ if } \hat{Y}_j(x) < L_j \\ \left(\frac{\hat{Y}_j(x) - L_j}{T_j - L_j}\right)^s & ; \text{ if } L_j \leq \hat{Y}_j(x) \leq T_j \\ 1 & ; \text{ if } \hat{Y}_j(x) > T_j \end{cases} \quad (4)$$

where T_j is a large enough value for the $\hat{Y}_j$.

Further details about this subject area can be found through the literature, [24], [25], [27], [28], [29], [30].

The desirability function process consists of five steps, Step 1: initialization step, Step 2 and 3: calculation phase and Step 4 and 5: decision making phases. The network of this step process is illustrated by Figure 1, below:

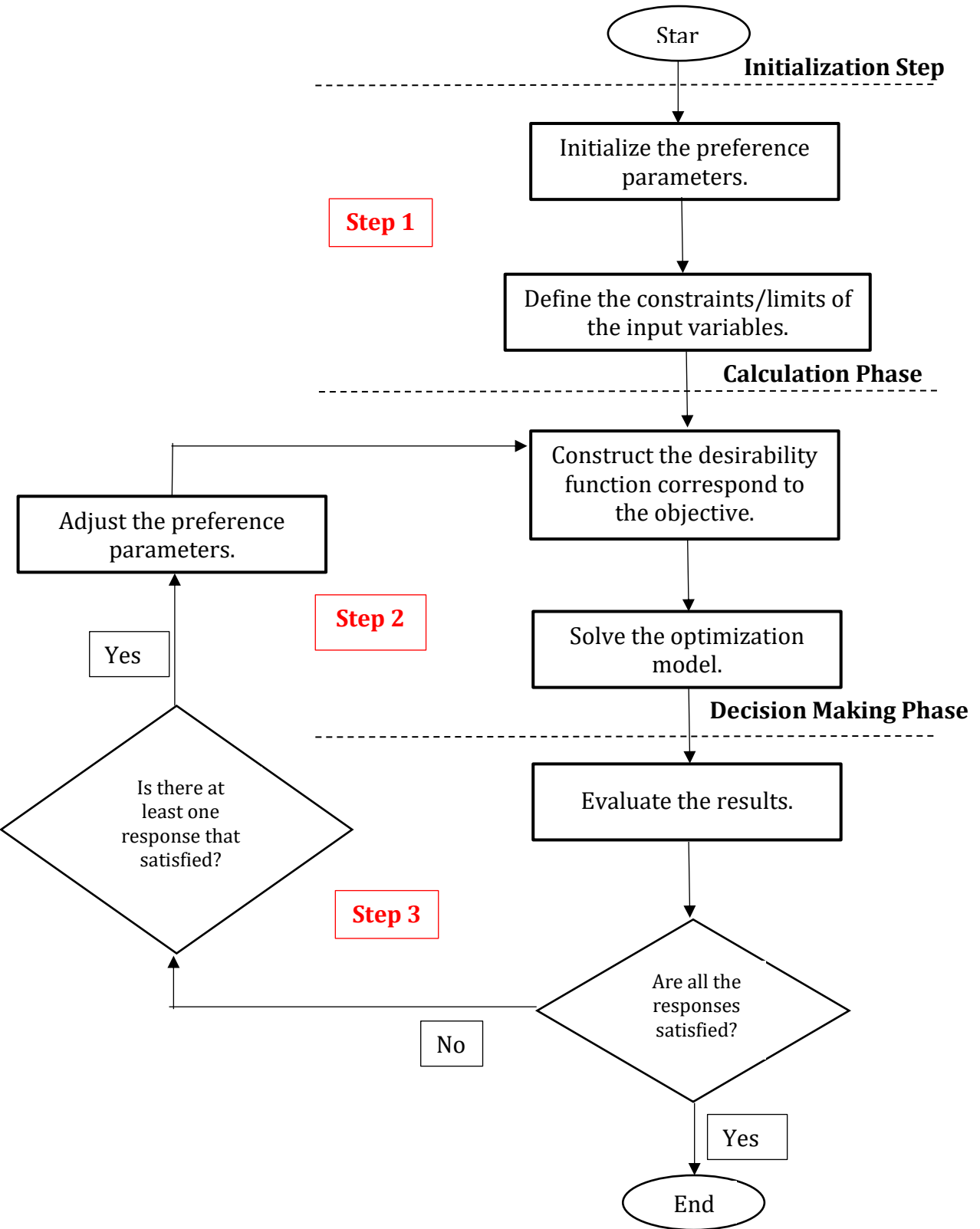


Figure 1: Flow Chart of the Desirability Process

THE PROCESS OF IDENTIFYING THE VALUES OF RISK FACTORS THAT MINIMIZE THE MALIGNANT TUMOR SIZE OF PTC PATIENTS

Our objective involves a single response variable, the malignant tumor size of PTC patients that is caused by several risk factors and want to identify their values that minimize the malignant tumor size. We utilize the desirability process defined by Equation (3) to minimize the response variable (malignant tumor size) subject to several risk factors.

To achieve our goal, we have developed a five-step process.

1. Build the analytical model that predicts the response variable with high accuracy.
2. Define the constraints / limits of the risk factors and the response.
3. Identify the desirability function that optimizes the response based on our objective (minimize, maximize, or target value).
4. Obtain the minimum value of response and the values of the risk factors by executing the desirability function approach.
5. Validate the results of the optimization process.

Step 1

We have built an analytical predictive model that is driven by four individual risk factors and eleven interactions terms and is given below, [23]. This model predicts the malignant tumor size of PTC patients with 90% accuracy.

$$\hat{Y}^T = \begin{cases} 3.498 - 0.7497 \ln(X_2) - 1.360 X_4 - 2.318 X_8 - 8.637 X_9 \\ - 0.0002962 X_1 : \ln(X_3) + 0.3913 \ln(X_2) : X_4 \\ + 0.7145 \ln(X_2) : X_8 + 2.582 \ln(X_2) : X_9 \\ + 0.03733 \ln(X_3) : X_4 - 0.02509 \ln(X_3) : X_6 \\ + 0.02698 \ln(X_3) : X_8 + 0.1844 X_5 : X_4 - 0.3055 X_5 : X_6 \\ + 0.3555 X_5 : X_8 + 0.2361 X_4 : X_7 \end{cases} \quad (3.5)$$

where,

$$\hat{Y}^T = (\hat{Y})^{0.217}.$$

We need to retransform the $\hat{Y}^T$ value to get the original malignant tumor size as follows,

$$\hat{Y} = (\hat{Y}^T)^{\frac{1}{0.217}}.$$

In this predictive model all the risk factors are not individually significant, but their contribution with the interactions is statistically significant. That is, in developing the model only four of the nine risk factors contribute individually, however all the nine risk factors contribute significantly by interacting among themselves. Thus, all the nine individual variables were included for the response optimization.

Step 2

The constraints / limits of the nine risk factors and the response variable, malignant tumor size is given in Table 2, below.

Table 2: Constraints/Limits of the Response and Risk Factors

Variable		Minimum	Maximum
$\hat{Y}^T$	(Malignant Tumor Size) ^{0.217}	0.60673633	1.099526649
X_1	Age	57	78
$\ln(X_2)$	Ln (BMI)	3.0349	3.9389
$\ln(X_3)$	Ln (Number of years smoke until diagnoses)	-9.21034	3.66356
X_4	Taking aspirin regularly	0	1
X_5	Taking ibuprofen regularly	0	1
X_6	High blood pressure	0	1
X_7	Diabetes	0	1
X_8	Gallbladder	0	1
X_9	Gender	0	1

Step 3

Our response variable is the malignant tumor size of PTC patients. The growth of the tumor is normally proportional to the level of the cancer. Therefore, we need to minimize the response malignant tumor size and the objective of the optimization process is minimization. Thus, the desirability function defined by Equation (3) was used to minimize the malignant tumor size.

Step 4

The optimization process was done by using Minitab 21 and the estimated optimum response value, malignant tumor size and the corresponding risk factor values that minimize the response variable are given below, in Table 3 and 4. Table 3 has the optimization values for the transformed variables and Table 4 includes the original values of the optimization.

Table 3: The Optimal Values for the Response and Risk Factors (With Transformation)

$\hat{Y}^T$	X_1	$\ln(X_2)$	$\ln(X_3)$	X_4	X_5	X_6	X_7	X_8	X_9
0.711728	57	3.0349	-9.21034	1	0	0	0	1	1

Table 4: The Optimal Values for the Response and Risk Factors (Without Transformation)

$\hat{Y}^T$	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9
0.2087	57	20.7988	0	1	0	0	0	1	1

Step 5

We proceed to optimize (minimize) the malignant tumor size with the maximum desirability function $d_j(\hat{Y}_j) = 1$. Table 5, given below, provides the R^2 (the variation in the response explained by the risk factors) and adjusted R^2 of the optimum model.

Table 5: Validation Values of the Optimization Process

R^2	Adjusted R^2	$d_i(\hat{Y}_i)$	SE Fit	95% CI	95% PI
89.61%	84.88%	1	0.0231	(0.1523, 0.2801)	(0.1412, 0.2991)

The 95% confidence interval, CI and 95% prediction interval, PI, values can be used to verify the hypothesis,

- H_0 : The optimal response value is statistically significant.
Vs.
- H_1 : The optimal response value is not statistically significant.

Since the optimum malignant tumor size (0.2087) is in the 95% CI and PI, we cannot reject our null hypothesis and conclude that the optimal malignant tumor size is statistically significant at 5% level of significance.

GRAPHICAL VISUALIZATION OF THE OPTIMIZATION RESULTS

The graphical visualization of a contour plot and a surface plot are important for medical professionals which allow them to visualize three-dimensional data in a two-dimensional plot and a three-dimensional plot by considering only two controllable risk factors at a time as they affect the response, respectively. They illustrate the optimum conditions for any two controllable continuous risk factors concerning the desired value of the response while all the other risk factors are fixed, [31], [32]. The proposed analytical model consists of two continuous controllable variables, Body Mass Index of the individuals and Number of years of smoking. Thus, the graphical visualization can be used to illustrate the behavior of the transformed malignant tumor size with transformed BMI and transformed years of smoking. Thus, the following contour plot, Figure 2, and surface plot, Figure 3, visually illustrate the behavior of the transformed malignant tumor size as a function of BMI and years of smoking. From Figure 2, we can clearly see that when BMI is approximately below 3.18 and transformed years of smoking approximately below -1 (provided that the other risk factors are fixed) then the transformed malignant tumor size has minimum values less than 0.8. The dark blue region in Figure 2, represents the region that minimizes the transformed malignant tumor size with respect to minimum values with transformed BMI and years of smoking which confirms the accuracy of the results of the optimization process that we have developed. The surface plot of the transformed malignant tumor size vs transformed BMI and years of smoking also illustrates the fact that when we maintain a minimum number of smoking years and a minimum BMI value then it may reduce the malignant tumor size as shown in Figure 2.

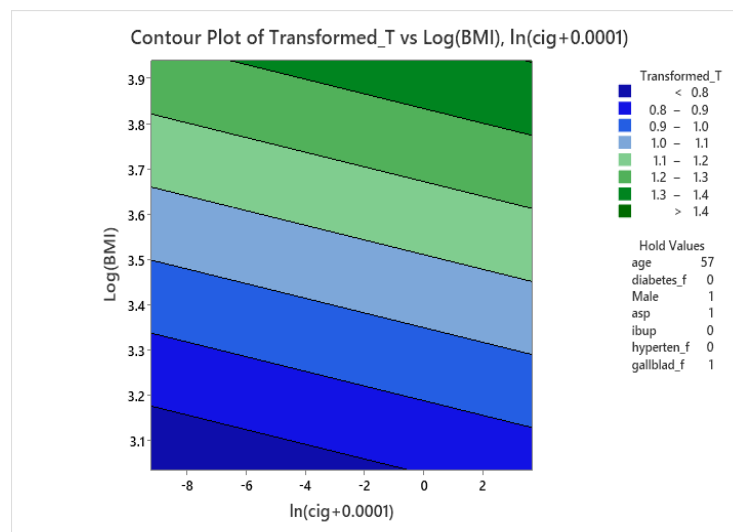


Figure 3: Contour Plot of Transformed Tumor Size VS Log (BMI) and Log (Years Smoke)

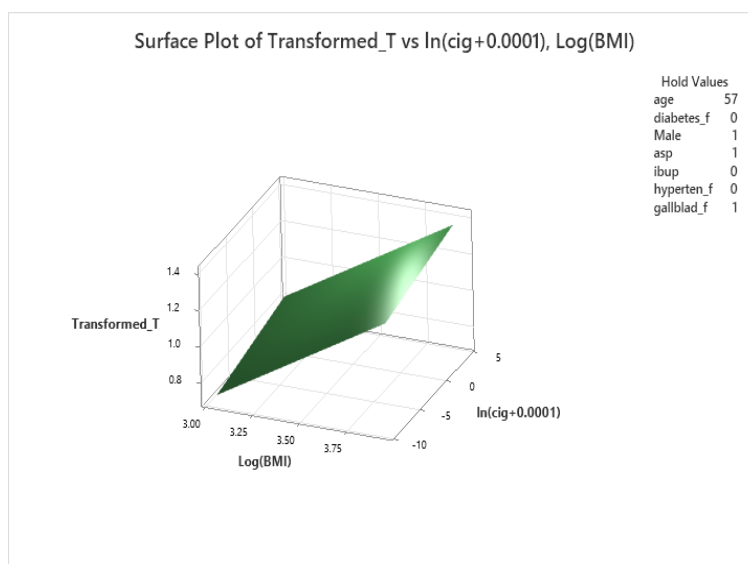


Figure 4: Surface Plot of Transformed Tumor Size VS Log (BMI) and Log (Years Smoke)

CONCLUSION

We utilized the desirability function approach in response surface optimization analysis to identify the risk factors that will minimize the malignant tumor size of a PTC patient. In achieving our objective, we utilized the real data driven analytical model that we have built to predict the malignant tumor size of an individual PTC patient with 90% accuracy, [23]. This model consists of four out of nine individual risk factors and eleven interaction terms. It is important to identify that only four individual predicting variables are statistically significant but the bivariate interaction terms are significant with all the nine predicting variables.

In developing the optimization process our model includes four individual risk factors and eleven interactions terms and obtained the constraints/ limits for the response and all the individual risk factors, that are given in Table 2. The used model has the exact R^2 and adjusted R^2 as our original model. Then we applied the optimization process to achieve the minimization objective and obtained the minimum malignant tumor size 0.2087 cm with the desirability function of 1 which is the highest desirability function value that describes the effectiveness of optimization process. The optimum values of the risk factors that minimize the response were given in Table 4. The male patients at age of 57 years have the minimum malignant tumor size. Taking aspirin regularly and having gallbladder may have a positive impact on minimizing the malignant tumor size. Inversely taking ibuprofen and not controlling diabetes and high blood pressure may negatively affect minimizing the malignant tumor size. Also, nonsmoking may affect positively to minimize the malignant tumor size.

In our optimization process we obtained an R^2 of 89.61% and an adjusted R^2 of 84.88% which are exactly the same results as the original model. The 95% confidence interval and predicted interval were calculated, and the intervals are (0.6647, 0.7587) and (0.6539, 0.7696), respectively. Since the minimum tumor size belongs to the above intervals, the optimum malignant tumor size is significant at 5% level of significance.

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