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SOME CONCLUSIONS OF STATISTICAL ANALYSIS OF THE SPECTROSCOPIC EVALUATION OF CERVICAL CANCER

by

Hailun Wang

Under direction of Yu-sheng Hsu

ABSTRACT

To significantly improve the early detection of cervical precancers and cancers, *LightTouch*[™] is under development by SpectRx Inc.. *LightTouch*[™] identifies cancers and precancers quickly by using a spectrometer to analyze light reflected from the cervix. Data from the spectrometer is then used to create an image of the cervix that highlights the location and severity of disease.

Our research is conducted to find the appropriate models that can be used to generate map-like image showing disease tissue from normal and further diagnose the cervical cancerous conditions. Through large work of explanatory variable search and reduction, logistic regression and Partial Least Square Regression successfully applied to our modeling process. These models were validated by 60/40 cross validation and 10 folder cross validation. Further examination of model performance, such as AUC, sensitivity and specificity, threshold had been conducted.

INDEX WORDS: Cervical cancer, Logistic Regression, Partial Least Square Regression, AUC, Sensitivity, Specificity, Threshold

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SPECTROSCOPIC EVALUATION OF CERVICAL CANCER**

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Hailun Wang

A Thesis Submitted in Partial Fulfillment of Requirements for the Degree of

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Georgia State University

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List of Abbreviations

ASC-US	Atypical Squamous Cells of Undetermined Significance
AGUS	Atypical glandular cells of undetermined significance
CIN	Cervical Intraepithelial Lesion
CN	Columnar Normal
FDA	Food and Drug Administration
LSIL	Low Grade Squamous Intraepithelial Lesion
Pap	Papanicolaou test
PLS	Partial Least Square
SN	Squamous Normal
TZ	Transformation Zone

Chapter One: Introduction

According to published reports, cervical cancer is the second most common cancer among women worldwide. Globally, there are approximately 371,000 cases of cervical cancer diagnosed annually and approximately 190,000 deaths per year^[1]. The incidence of cervical cancer is on the decline in more developed countries, largely due to implementation of the Pap test.

The most common findings on a Pap test are ASC-US and LSIL which provoke millions of follow-up Pap tests, colposcopies and biopsies. However, only about 5% of ASC-US and 10% of LSIL Paps actually reflect an immediate cancer precursor. Even with colposcopy, diagnosis is imperfect, with 50% - 80% sensitivity and around 50% specificity^{[3], [4]}. All of these mean that a significant number of women were misclassified through diagnosis of colposcopies and biopsies.

LightTouch[™], under development by SpectRx Inc., is being designed as a new non-invasive test. *LightTouch*[™] identifies cancers and precancers quickly by using a spectrometer to analyze light reflected from the cervix. Data from the spectrometer is then used to create an image of the cervix that highlights the location and severity of disease.

Florescence and reflectance spectroscopy have been shown to be valuable in cancer diagnosis by some investigators^[4]. A number of studies show the performance of either spectroscopy in discriminating between normal tissue and different epithelial

cancer grades use point measurements of area that are either suspect or normal. As an example, studies from the Richard Kortum's Lab indicate that variability between normal tissues in different patients is higher than variability between tissues with disease grades [5], [6]. In addition, reflectance spectra of cervical pre-cancer show consistent differences from that of normal tissue at multiple distances between the light source and detector. Spectral patterns in diffuse reflectance spectra can be used for the discrimination of normal cervical tissue from low grade and high grade intraepithelial lesions.

From 1999 to 2000, SpectRx's Fiber Optical System and Camera System were introduced into a feasibility studies. In 2001, a hybrid System of these was developed. Data collected from this device were used for algorithm development and a validation study. As equivalence to hybrid system, Alpha and Beta prototype systems were developed during 2002-2006. The pivotal trial data from this device were also used for algorithm validation.

Spectrx, Inc collected 648 patients' data in multicenter clinical trial. The device collected data from 56 spatial points on the surface of the cervix for each patient. For each point, reflectance spectrum wavelength ranging from 410nm-700nm and florescence spectrum wavelength ranging from 400nm-700nm was gathered. The point level algorithms were developed based on approximately 30,000 observations and 10,000 initial variables. The whole cervix models were built from 648 observations and 10,000 initial variables. It should be noticed that we only use many fewer inputs to the

algorithm. With the process of SpectRx pilot study, another 100 patients' data are available for model prediction examination.

At Georgia State University, three graduate students in statistics department have previously worked on the statistical analysis of the spectroscopic evaluation of cervical cancer. Wei Xu was first to compare the logistic regression models and CART models. In 2004, Kai Qu use cluster analysis to divide data into two parts then use partial least squares to classify both parts ^[7]. These results were compared with the one without using cluster analysis. Two years later, Chenghong Shen reconsidered variables which were not used before, and adding more newly created variables to built models ^[8].

This thesis is organized in the following order. In chapter two, the data manipulation and variable selection procedure for point level analysis are first introduced, followed by logistic regression, cross-validation. Then the results from different approaches are compared and a conclusion is presented. Chapter three is organized in the same way as previous chapter. The future studies are discussed in chapter four.

Chapter Two: Point Level Diagnosis

One objective of the medical device is to create an image of the cervix that highlights the location and severity of disease. Since the device collects data from 56 spatial points on the surface of cervix, point level analysis of disease would help us to find the location of the disease and the patient diagnosis could be also conducted by combining all of the spatial information. Furthermore, we would like to using point level diagnosis to render a cervix map that uses colors to represent the model output for each point. Then a “weather map”- like image can be generated for each patient with the brighter areas corresponding to increased likelihood of disease.

2.1 Data Manipulation and Variable Selection

1. Observations

The training dataset contains 510 evaluable subjects. For each subject, there are 56 records corresponding to 56 spatial points’ data. Since some of the data points are excluded from the training dataset for various reasons, the total number of observations is around 20000. However, these observations are not independent. The approaches we used to create independent observations are discussed in the methodology section. (Table 2.1 provides the lookup table for excluding points)

Table 2.1 Lookup table for excluding points

Artifact code	Description
0	No artifact
1	Specular Reflection
1.1	Possible Specular Reflection
2	Mucus
2.1	Possible Mucus
3	Blood
3.1	Possible Blood
4	Non-Cervical Tissue
4.1	Possibly Non-Cervical Tissue
5	White Marking Dot
5.1	Possibly White Marking Dot
6	Bad Interrogation Point
6.1	Possibly Bad Interrogation Point
999	Other artifact

2. Explanatory Variables

The spectra data which contains all important explanatory variables are stored in an ASCII file for each patient. It was composed of four spectrums: Reflectance spectrum; 340nm Fluorescence spectrum; 400nm Fluorescence spectrum; 460nm Fluorescence spectrum. The spectrum data format is described as following table:

Table 2.2 Spectrum data structure in database

Columns	Description	No. of wavelength elements
1	Point Number	NA
2-63	Reflectance Spectrum	62
69-126	340nm Fluorescence Spectrum	58
132-184	400nm Fluorescence Spectrum	53
189-228	460nm Fluorescence Spectrum	40

The initial number of explanatory variables is the sum of number of all wavelengths. These 213 initial variables was selected and reduced to 80 variables by

applying following rules which was established by Previous research from Spectrx:

- 1) Eliminate 400nm Fluorescence variables due to its little discriminating capability.
- 2) Average 2 neighboring spectra variables. (also called 10nm binning)
- 3) Divide the spectral variable by group mean. (also called self-normalization)

3. Response Variable

Biopsy conducted by pathologist and its result, histo-pathology, is considered as the gold standard. SpectRx uses the pathology as the response variable for all models.

Table 2.3 Pathology variable index

0	Squamous Normal
0.5	Transformation Zone
1	Columnar Normal
2	CIN 1
2.5	CIN 1/2
3	CIN 2
3.2	CIN 2/3
3.5	CIN 3+
9	Os
-1	Unknown Classification
999	Other Classification

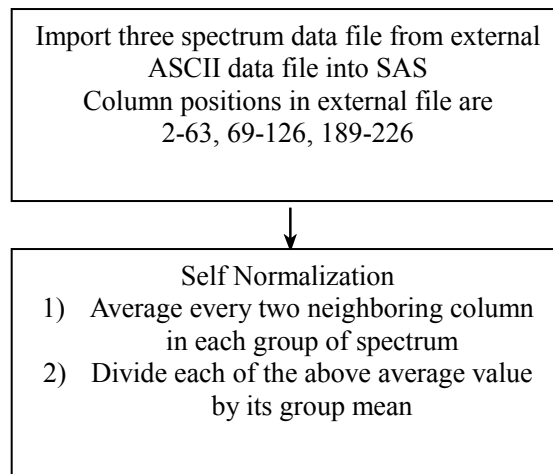
The points with pathology values equal to -1, 9, and 999 are not useful for our point diagnosis, so they need to be excluded first. FDA stated that patient with pathology diagnosis as CIN1 or CIN1/2 can be classified as either disease or non-disease. So, in our model building process, CIN1 and CIN 1/2 are also excluded. In order to create two distinct classes of disease, the cases were as positive for disease if the cases had pathology values greater than or equal to 3, while the non-disease were defined as a

pathology value less than 3.

4. Data manipulation process

The data manipulation process of importing external file and variable creation are illustrated by the table below:

Graph 2.1 Data manipulation process



2.2 Methodology

1. Observation independence

As described in 2.1, since each patient has multiple spectral records which are correlated, treating each spectrum record as single observation is not practical. Independent observation could be created by reducing the variability between patients. Several approaches have been applied to reduce the correlation among the records within patient.

It has been shown that the spectral intensity of a disease point is lower than non-

disease point at a low wavelengths. For each patient, if we can subtract non-disease part from each record, then the newly-created record will not involve disease (or non-disease) variability between patients. This problem therefore becomes to how to find the non-disease part for each patient.

From a biological perspective, squamous normal (SN), transformation zone (TZ) and columnar normal (CN) tissues can be treated as non-disease tissue. We tried several combinations of normalization by looking at difference between SN, TZ and CN. However, this approach needs pre-knowledge of the position of these three types of normal tissues.

As an alternative, using the assumption of normal tissues' position is more practical. It has been proved that cancer usually does not start on the peripheral region of the cervix. Thus, each patient's normal tissue can be found in the peripheral region.

2. Model building

Because our response variable is binary, which is either 1(disease) or 0(non-disease), the multiple linear regression model is not appropriate for our data. Partial Least Squares and Logistic Regression^{[9], [10]} can be used to accommodate binary data.

Logistic regression analyzes binomially distributed data of the form $Y_i \sim \mathbf{B}(p_i, n_i)$, for $i=1, \dots, m$, where the numbers of Bernoulli trials n_i are known and the probabilities of success p_i are unknown. For each i , there is a k -vector X_i of known explanatory variables (independent variables or covariates). Thus

$$p_i = E\left(\frac{Y_i}{n_i} \mid X_i\right)$$

The logits of the unknown binomial probabilities (*i.e.*, the logarithms of the odds) are modelled as a linear function of the X_i .

$$\log it(p_i) = \ln\left(\frac{p_i}{1-p_i}\right) = \beta_1 x_{1,i} + \dots + \beta_k x_{k,i}$$

Note that a particular element of X_i can be set to 1 for all i to yield an intercept in the model. The unknown parameters β_j are usually estimated by maximum likelihood. The interpretation of the β_j parameter estimates is the additive effect on the log odds ratio for a unit change in the j th explanatory variable. In the case of a dichotomous explanatory variable, for instance gender, e^{β} is the estimate of the odds ratio of having the outcome for, say, males compared with females. The model has an equivalent formulation of:

$$p_i = \frac{1}{1 + e^{-(\beta_1 x_{1,i} + \dots + \beta_k x_{k,i})}}$$

Extensions of the model exist to cope with multi-category dependent variables and ordinal dependent variables, such as polytomous regression. Multi-class classification by logistic regression is also known as multinomial logit modeling. An extension of the logistic model to sets of interdependent variables is the conditional random field.

We use Proc Logistic and Proc PLS procedures in SAS package (Cary, NC) to build logistic and PLS models respectively and discovered the logistic models performed better than the PLS model for most criterion in our point level analysis. The PLS approach is introduced in next chapter.

3. Assessing the fit of model

An intuitively appealing way to summarize the results of a fitted logistic regression model is via a classification table. This table is the result of cross-classifying the outcome variable, y , with a dichotomous variable whose values are derived from the estimated logistic probabilities.

To obtain the derived dichotomous variable we must define a threshold (or cutpoint), c , and compare each estimated probability to c . If the estimated probability exceeds c then we let the derived variable be equal to 1; otherwise it is equal to 0. The appeal of this type of approach to model assessment comes from the close relationship of logistic regression to discriminate analysis when the distribution of the covariates is multivariate normal within the two outcome groups.

The 2x2 classification table based on the logistics regression models in our study can be illustrate as below:

Table 2.4 2x2 classification table

Classified	Observed		Total
	Y=1	Y=0	
Y=1	a	b	a+b
Y=0	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$sensitivity = \frac{a}{a+c} \quad specificity = \frac{d}{b+d}$$

Sensitivity and specificity rely on a single cutpoint to classify a test result as positive. A more complete description of classification accuracy is given by the area under the ROC (Receiver Operating Characteristic) curve. This curve plots the probability of detecting true positive (sensitivity) and false negative (1-specificity) for an entire range of possible cutpoints.

The area under the ROC curve, which ranges from zero to one, provides a measure of the model's ability to discriminate between those subjects who experience the outcome of interest versus those who do not.

As a general rule, If ROC=0.5, a test shows no discrimination; If 0.7<ROC<0.8: this is considered acceptable discrimination; If 0.8<ROC<0.9: this is considered excellent discrimination; If ROC>0.9: this is considered outstanding discrimination.

4. Model Validation

Model validation is used to evaluate how well a model can be applied to any new data. We employed conventional cross-validation as well as K-folder cross-validation in the research. The conventional cross-validation is to randomly split the data into two parts. We use 60/40, the larger part for training and the smaller for validation. K-folder cross-validation is a technique to train and validate data on the same dataset. In our study, we divided the training dataset into 10 approximately equal sized subsets. Moreover, we ensure that patients with a certain Pap value are evenly allocated to each subset,

Therefore the 10 subsets are equivalent in size and content. The cross-validation process is then repeated 10 times, with each of the 10 sub samples used exactly once as the validation data. The 10 results from the folds then can be averaged (or otherwise combined) to produce a single estimation.

2.3 Results and Conclusions

In our study, we go through data manipulation and a variable reduction process. The classification methodologies were then employed to find appropriate models. In the point level analysis, we focused on Logistic regression and Partial Least Squares Regression. The earlier study results for PLS and Logistic models are listed below.

Table 2.5 earlier study results of point level diagnosis

Model	No. of var	AUC Train	AUC Validation (10 folder)
Logistic full model	80	0.84416	0.79609
Logistic stepwise model	NA	0.835577	0.80703
PLS full model	80	0.83493	0.80009
PLS reduced model	77	0.83378	0.79479

We should notice that these models are ignoring the dependency of the observations.

To get rid of variability between subjects, for each subject, we find the spectral value of mean of SN, TZ and CN points. (Denote by $\mu_{SN}, \mu_{TZ}, \mu_{CN}$). Every subject has a μ_{SN} , some subjects have μ_{TZ} , and some have μ_{CN} . Then we take the difference μ_{SN} with μ_{CN} . (Denote by $\mu_{SN} - \mu_{CN}$) If the subjects do not have CN points, take the

difference of μ_{SN} with. μ_{TZ} . (Denote by $\mu_{SN} - \mu_{TZ}$). Then, we subtract spectra values of each point from its $\mu_{SN} - \mu_{CN}$ or $\mu_{SN} - \mu_{TZ}$.

Table 2.5 illustrates the one patient's spectral data structure after the normalization process.

Table 2.6 Normalized data structure (e.g. Patient 1001)

Point	Before Normalization			Tissues type	Normal part for patient 1001			After Normalization	
	Var1	...	Var80		Var1	...	Var80	Var1	Var80
1	$X_{1,1}$...	$X_{1,80}$	SN	$N_1 = (X_{1,1} + X_{2,1} + X_{3,1})/3 - (X_{3,1} + X_{56,1})/2$...	$N_{80} = (X_{1,80} + X_{2,80} + X_{4,80})/3 - (X_{3,80} + X_{56,80})/2$	$X_{1,1} - N_1$	$X_{1,80} - N_{80}$
2	$X_{2,1}$...	$X_{2,80}$	SN				$X_{2,1} - N_1$	$X_{2,80} - N_{80}$
3	$X_{3,1}$...	$X_{3,80}$	TZ				$X_{3,1} - N_1$	$X_{3,80} - N_{80}$
4	$X_{4,1}$...	$X_{4,80}$	SN				$X_{4,1} - N_1$	$X_{4,80} - N_{80}$
5	$X_{5,1}$...	$X_{5,80}$	CN2				$X_{5,1} - N_1$	$X_{5,80} - N_{80}$
.....
56	$X_{56,1}$...	$X_{56,80}$	TZ				$X_{56,1} - N_1$	$X_{56,80} - N_{80}$

We later discovered that patients trend to have much more SN tissue than TZ or CN tissue. When the mean of SN, TZ and CN were taken respectively and followed by taking the difference of (CN-SN) or (TZ-SN), the weight of CN and TZ increase. Therefore, we treat CN, TZ as normal part is a solution.

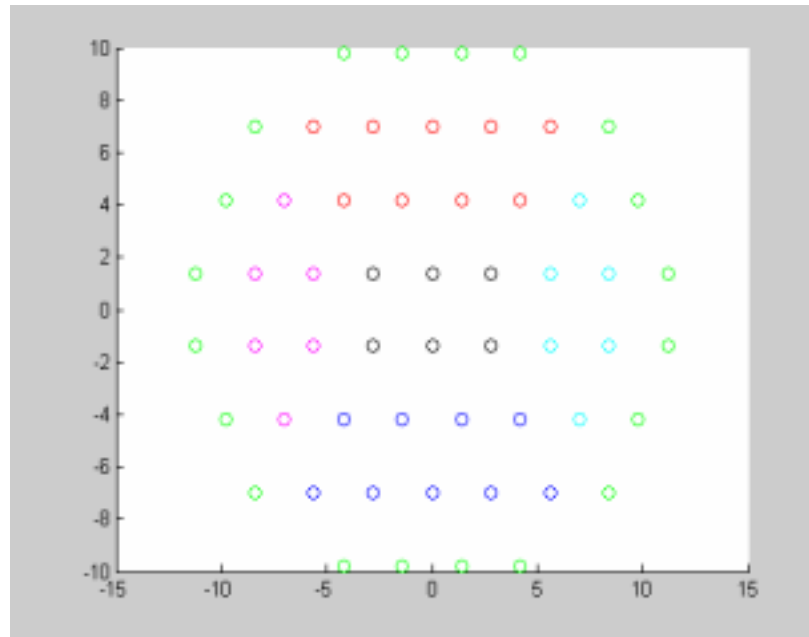
Table 2.7 Effectiveness of Normalization process --- Tissue Type

Model	Normalization	AUC Train	AUC Validation
Logistic full model	(CN-SN) or (TZ-SN)	0.90288	0.82423
PLS full model	(CN-SN) or (TZ-SN)	0.88376	0.85027
PLS reduced model	(CN-SN) or (TZ-SN)	0.88377	0.85041
Logistic full model	TZ or CN	0.90683	0.85522

Comparing table 2.6 with 2.4, both training and validation AUC are improved. This provides evidence that normalization process is useful for our point level diagnosis.

The major drawback of this approach is it has limit application for a new population, because it requires pre-knowledge of tissue type and the information about where these zones begin and end for new population, which is impracticable.

Graph 2.2 Cervix surface divided by peripheral vs central



As mentioned previously, cancer almost never starts on the peripheral region of the cervix and its spectral value are usually small, we tried to find the normal part by taking the low percentiles combination (e.g. 5th, 10th, 25th, 50th) of the 20 peripheral locations' spectral data. Then we subtract these percentiles with spectrum data to get rid of the variability between subjects.

Table 2.8 Effectiveness of Normalization process --- Percentile

Percentile	AUC Train	AUC Validation
P5	0.83281	0.72989
P10	0.81333	0.72322
P25	0.82765	0.75890
p50	0.80079	0.73381
p75-p5	0.87156	0.76555
p75-p10	0.87171	0.77955
p75-p25	0.86258	0.77270
p90-p5	0.87534	0.76521
p90-p10	0.87891	0.78125
p90-p25	0.85947	0.75531
p95-p5	0.86837	0.74421
p95-p10	0.87099	0.75372
p95-p25	0.86444	0.75104

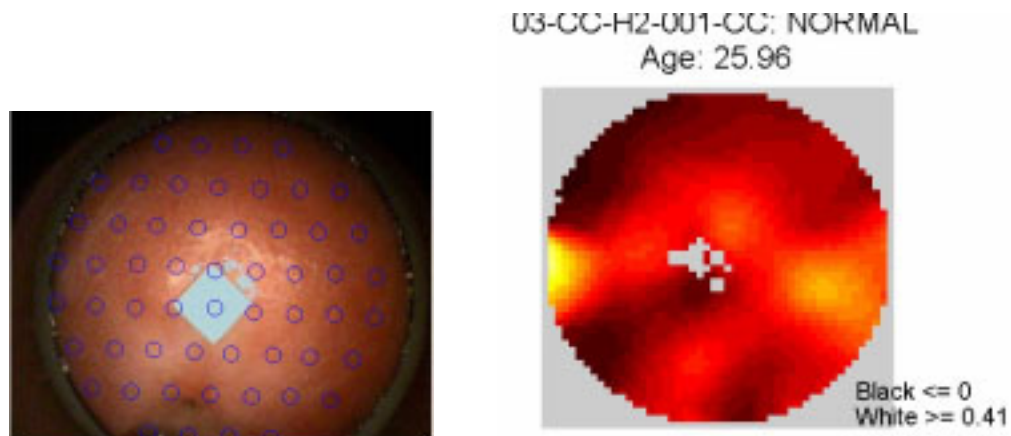
Finding the “real” normal part can further improve above models. The fixed twenty positions may not reflect the real peripheral locations, which depend on how the cervix images are taken.

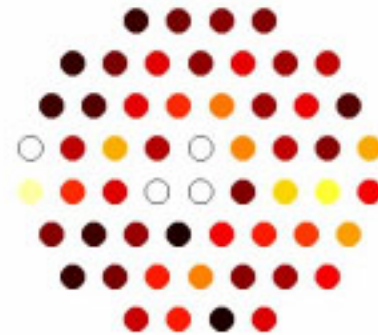
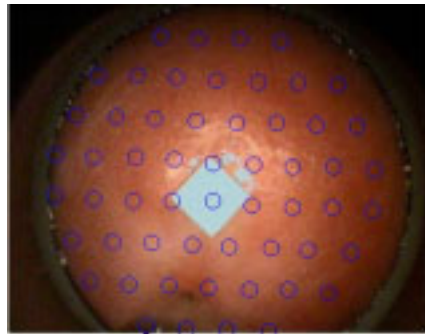
It was known that by identifying os location in cervix, the “true” central and peripheral group can be found. It is also known that areas close to the os have a higher likelihood of disease than those that are distant. Using the RGB image to identify those points that are peripheral vs. those that are central may help. This because contrition in not always assured. As a first step toward this approach we will use Os locations already identified in the point level data set to see if this helps. Use points neighboring the one marked 'Os' in the database as the central points and the remaining as peripheral.

Table 2.9 Model performance comparison --- RGB image information

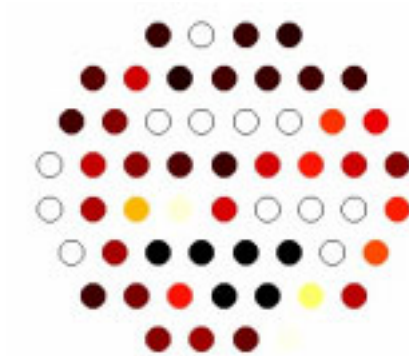
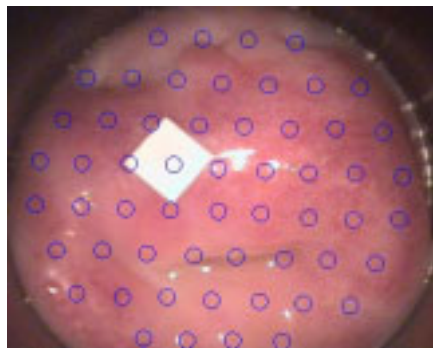
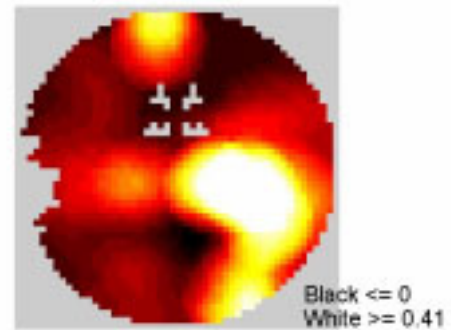
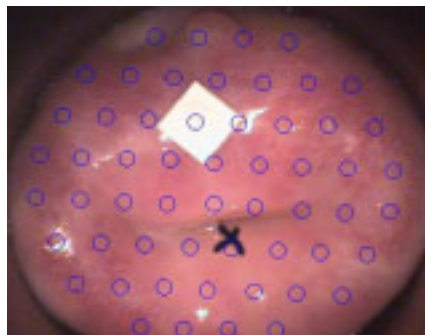
Percentile	AUC Train	AUC Validation
P5	0.85410	0.74893
P10	0.83922	0.71755
P25	0.86288	0.76410
p50	0.84781	0.76926
p75-p5	0.87086	0.76861
p75-p10	0.87857	0.77113
p75-p25	0.87725	0.77385
p90-p5	0.87787	0.77522
p90-p10	0.88121	0.76224
p90-p25	0.88210	0.77600
p95-p5	0.87983	0.78031
p95-p10	0.88276	0.76594
p95-p25	0.88447	0.76647

Based on output indices from model (p90-p10), SpectRx engineers developed color maps. The indices from logistic models range from 0 to 1, which represents probability of having cervical cancer or precancer. Given a disease threshold, for model (p90-p10), 0.41, any index below 0.41 will be colored as dark, as number getting close to threshold, the color appears to be light. Above the threshold point are colored as white.

Graph 2.3 Cervix surface color map



03-CC-H2-132-DA: CIN 1
Age: 40.63



The problem has to do with the approach of considering all points put together from all the subjects and then determining performance by the number of false negatives, false positives and so on. This compared to whole cervix performance where a true

positive occurs when, for example, only one point on the cervix of a person with disease needs to show up as positive. In other words, there can be many false negative points on the cervix but as long as we have one true positive we will be correct with this subject. This puts a very high performance demand on any point level algorithm.

To illustrate this problem using Model (90-10), we have been able to get a performance of 95/60 sensitivity/specificity. The algorithm result was about 8,000 False Positives and 12,000 True Negatives. Thus specificity is 60% ($TN/(TN+FP)$). However those 8,000 False Positives are distributed over almost all the subjects making it seem as if every subject has disease. Thus our whole cervix specificity is 0% and sensitivity 100%. It is clear that we must raise the threshold. This will make the performance on the "all points put together" population abysmal and obviate any "mapping for disease location" strategy.

Chapter Three: Diagnostic Methods

The color map is one approach for cervical cancer diagnosis. However, it requires the model having extremely high discrimination of disease point from non-disease point for all 56 locations. From subject level diagnosis perspective, it is not necessary to have all point level results. Past researchers^[8] have shown that the 25th percentile of the 56 locations' spectral data can best discriminate patients with CIN2 or higher. In this chapter, we further examine the 25th percentile model and other previous models by applying to our current clinical trial data. Since all pervious models^[8] might use too many variables, which can cause overfit of the model and low prediction powers. We conducted a thorough variable reduction process and the useful variable searching process is detailed in following sections.

3.1 Data Manipulation and Variable Selection

1. Observations

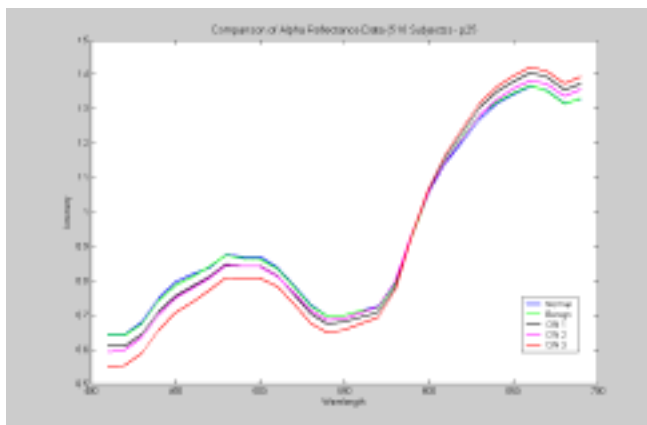
As we described in the previous chapter, for each subject, there are 56 records corresponding to 56 spatial points' data. In our subject level diagnosis, only one of the 56 observations could be chosen to represent a patient's disease status. The early study showed that the 25th percentile is most useful data for discrimination. Besides the 510 subject's data in SpectRx early clinical trial, we add more clinical trial data (e.g. dallas dataset, pilot alpha dataset, pilot beta dataset) to test model prediction.

2. Explanatory Variables

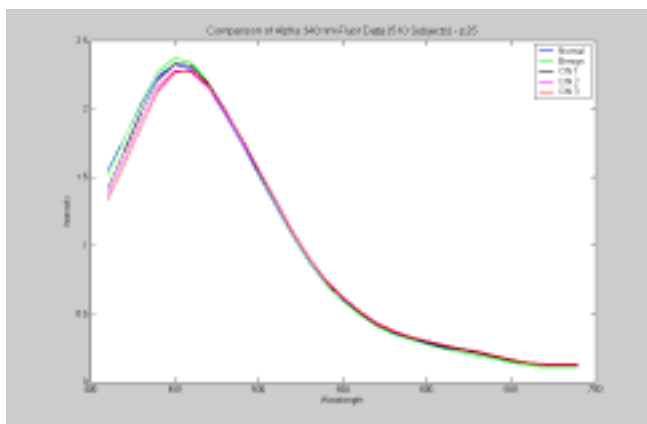
In SpectRx's early study, for all 78 spectral wavelengths, the 25th percentile was chosen to create 78 explanatory variables. Our recent research indicates that lower percentiles, such as 10th, 25th, are useful for discrimination for lower wavelengths of spectrum data; while the higher percentiles, such as 75th, 90th, contains discrimination information in the higher wavelengths of spectral data. Thus we extend 78 explanatory variables to 312 variables. This trend can be illustrated by the graphs which were produced by a SpectRx engineer.

Graph 3.1 Mean of P25 spectra for 522 Training subjects

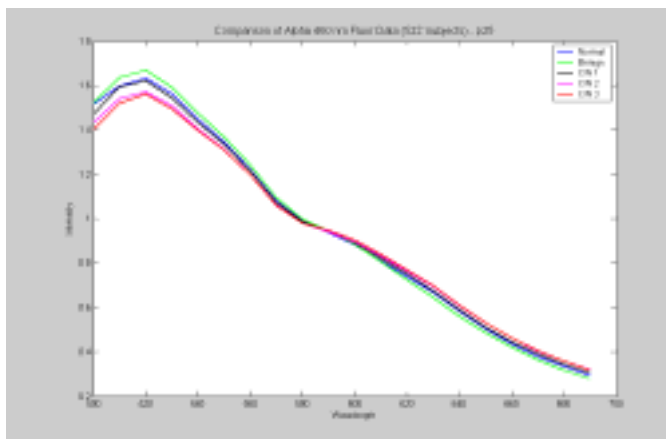
Reflectance Spectrum



340 nm Fluorescence Spectrum

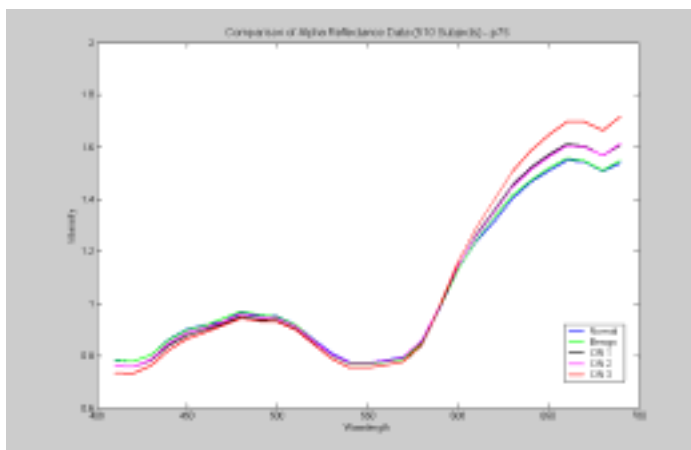


460nm Fluorescence Spectrum

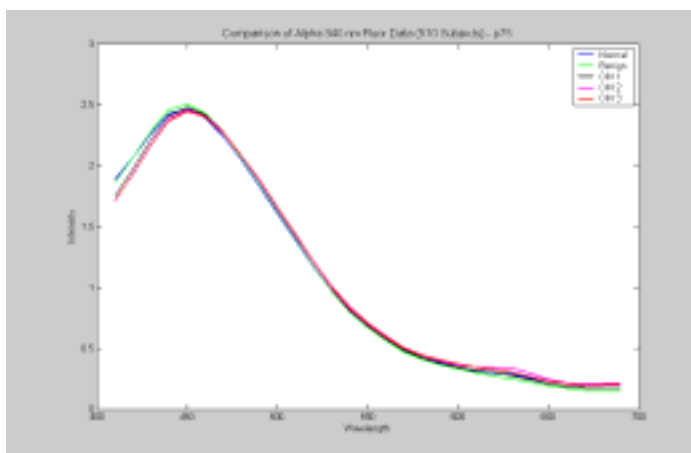


Graph 3.2 Mean of P75 spectra for 522 Training subjects

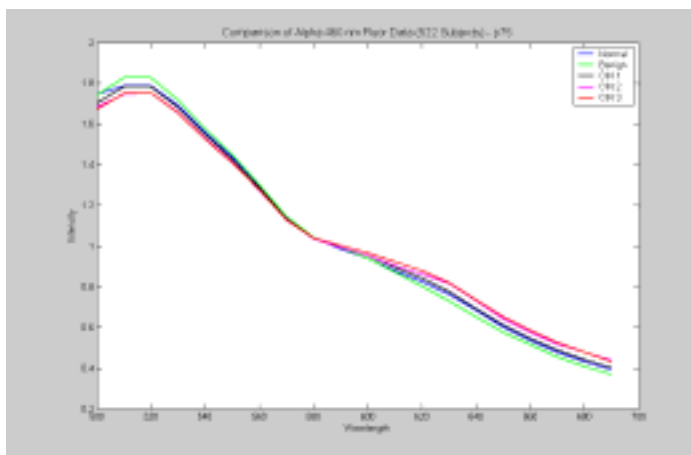
Reflectance Spectrum



340 nm Fluorescence Spectrum



460nm Fluorescence Spectrum



Following observations and conclusions may be made:

- We notice that at wavelengths below 590 nm spectra (blue wavelengths) diseased tissue has a lower intensity than normal tissue
- On the other hand, for wavelengths above 590 nm spectra (red wavelengths) diseased tissue has higher intensity than normal tissue
- At a lower percentile, 25th percentile for example, we would select spectra from diseased tissue (when present)
- The higher percentiles are better discriminator for red wavelengths.
- The higher percentiles are not as good as lower percentiles for selecting disease tissue

Table 3.1 summarizes these trends.

Table 3.1 Variable flip index

	Blue	Flip	Red
Reflectance (wavelength in nm)	410	590	690
Reflectance (wavelength variable)	1	19	29
Fluorescence 340 ex (wavelength in nm)	410	490	690
Fluorescence 340 ex (wavelength variable)	30	38	58
Fluorescence 460 ex (wavelength in nm)	500	590	690
Fluorescence 460 ex (wavelength variable)	59	68	78

To verify these findings in quantitative way, we conducted several mean comparison tests, including Wilcoxon test and t test. These tests were conducted as

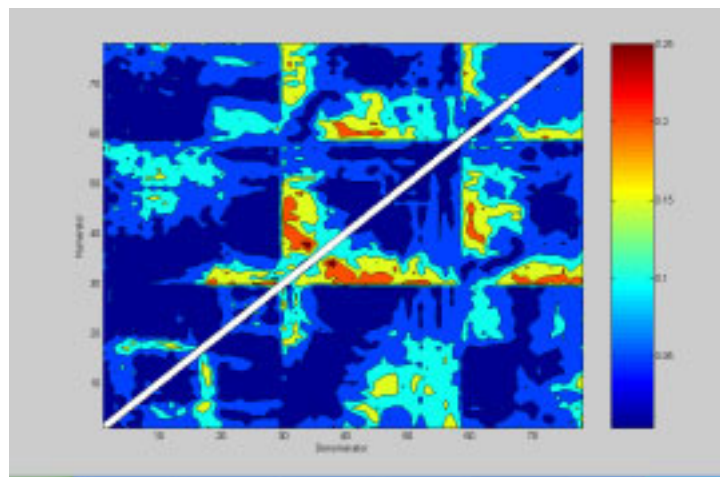
follows: within certain variables, observations are grouped by their pathology test results. Two groups are formed: cancer vs non-cancer. Calculate a score (t-statistic / wilcoxon rank statistic) for each variable. We ranked the 312 scores to find 312 variables' discrimination power. We finally reduced the simple explanatory variable number to 15 in the variable pre-selection.

We also discovered that taking the ratio between two simple variables increases discrimination. For the 510 subject training data set, using the 78 spectral variables, we created $78 \times 78 = 6084$ variables where each variable was divided by itself and the remaining 77 variables and so on. Then we generated ROC curves and from these pick the highest specificity obtained at 95% sensitivity or above.

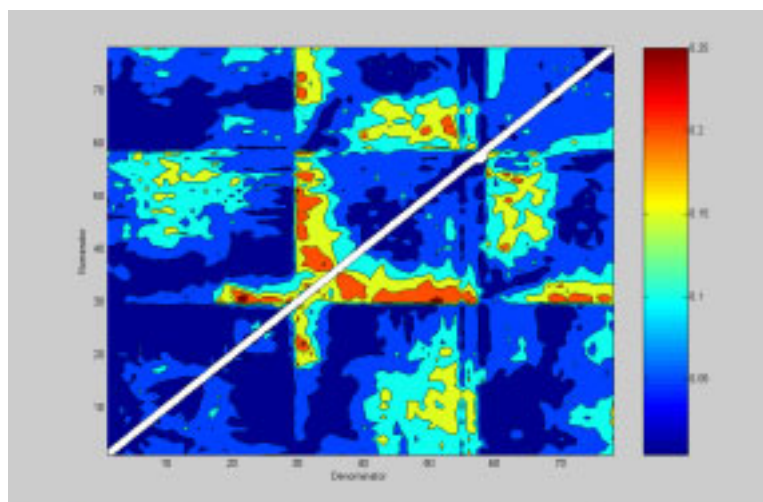
Graph 3.3 showed color plots where the color coded specificities are shown for each of p10, p25, p50 and p75 aggregate vectors.

Graph 3.3 ratio variable specificity performances under 95% sensitivity

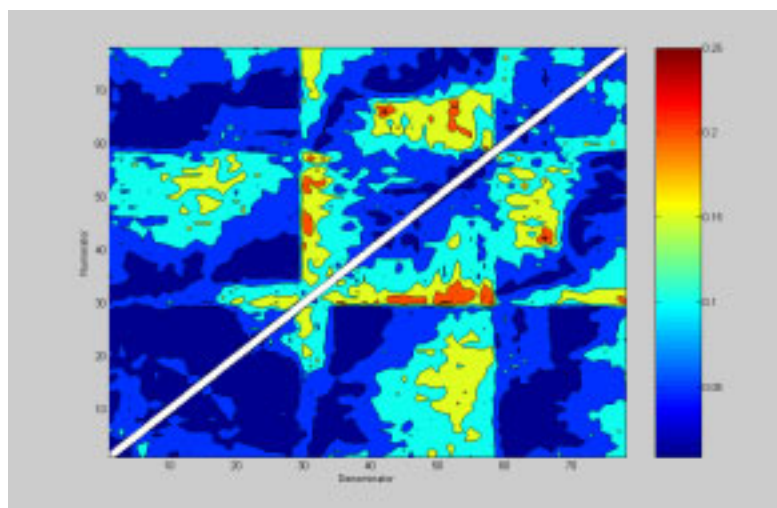
1. P10



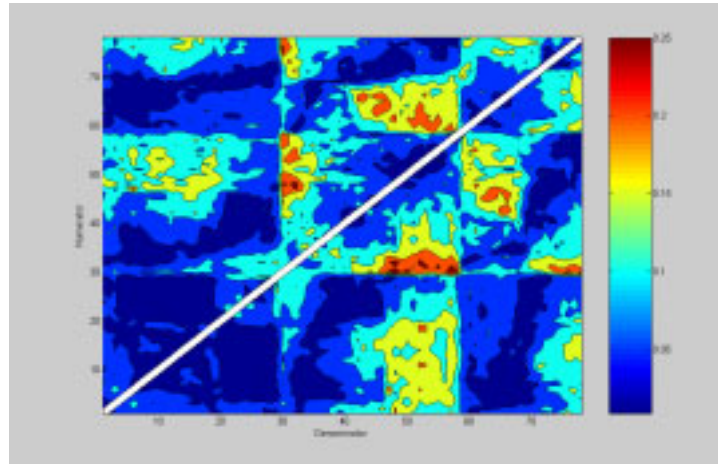
2. P25



3. P50



4. P75



In addition to spectral data, other test results, such as the Pap smear result (cytology), are collected. The pap test is microscopic examination of cells from the cervix. It is primarily designed to detect changes that may be cancerous or may lead to cancer. It may also detect infections and abnormalities. Because this information is available and may add information independent from the spectral variables, we can include it in the model.

Table 3.2 Pap variable index

0	Normal
1	Benign Changes
2	ASCUS, not favoring neoplasia
2.8	ASCUS, favor neoplasia
3	LSIL
3.2	AGUS

2. Response Variable

The biopsy conducted by pathologist and its result, pathology, is considered as the

gold standard. SpectRx uses the pathology as the response variable for all models.

Table 3.3 Pathology variable index

0	Normal
1	Non-dysplastic change
2	CIN 1
2.5	CIN 1/2
3	CIN 2
3.2	CIN 2/3
3.5	CIN 3+

Patients with a pathology diagnosis as CIN1 or CIN1/2 can be regarded as either disease or non-disease. So, in our model building process, CIN1 and CIN 1/2 are excluded. The disease cases are defined as pathology value greater than or equal to 3, while the non-disease are pathology value less or equal to 1.

3.2 Methodology

Partial Least Squares (PLS) is a method for constructing predictive models when factors are many and highly collinear^{[11], [12]}. PLS balances objectives of explaining response variation and explaining predictor variation. A PLS model can be shown as

$$Y = t_1q_1 + t_2q_2 + t_3q_3 + \dots + t_nq_n + E_n,$$

Where t are the latent variables or scores; q are the loading vectors.

Note that the scores are chosen so that the relationship between successive pairs of scores is as strong as possible. In general, PLS is finding a linear combination of variables^[13]. It can be shown that PLS seeks directions that have high variance and high

correlation with the response in contrast to principal components. In particular, the m th principal component direction v_m solves:

$$\max_{\substack{\|\alpha\|=1 \\ v_l^T s\alpha=0, l=1, \dots, m-1}} \text{var}(X\alpha),$$

Where S is the sample covariance matrix of x_j . The conditions $v_l^T s\alpha = 0$ ensures that $z_m = X\alpha$ is uncorrelated with all the previous linear combinations $z_l = Xv_l$. The m th PLS direction \hat{g}_m solves:

$$\max_{\substack{\|\alpha\|=1 \\ \hat{g}_l^T s\alpha=0, l=1, \dots, m-1}} \text{Corr}^2(y, X\alpha) \text{Var}(X\alpha)$$

We calculated Area Under Curve (AUC), sensitivity and specificity to evaluate model performance. It is observed that model performance in terms of AUC is closely related to the number of variables and the variables chosen. Model can be built based on AUC criterion ^[14], but it was found to be asymptotically equivalent to stepwise regression. Therefore, we have to adopt both statistical methods and non-statistical (manual) methods in variable selection.

We evaluate our models by following criteria described as below:

- a Best specificity at 99/95/90 sensitivity levels will be evaluated.
- b Models should give sensitivity that does not vary more than +/- 5 percentage points when the same threshold is applied to all data sets.
- c The same PAP test scaling must be used in conjunction with criterion (b) above

when determining performance with PAP.

- d The model should meet a minimum performance benchmark for each Pap category across all data sets.
- e The candidate model will have the least shrinkage upon 10 folder cross validation

3.3 Results and Conclusion

With mean comparison test and trends we found in graph 3.1 and 3.2, we are able to select the most useful covariates. In this process, we tried to reduce the number of original 80 variables as much as possible.

Table 3.4 Variable Reduction Performance

Variables	Training AUC	Validation AUC
p10: 1-4 30-33 p25: 30-33 mean: 30-33 p75: 27-33	0.72619	0.70668
p10: 30-33 p25: 30-33 mean: 30-33 p75: 30-33	0.72107	0.68435
p25: 1-5 30-33	0.72599	0.71246
p25: 30-33 p75: 71-78	0.74480	0.70668
p75: 25-31	0.70245	0.76849
p25: 30-33	0.72599	0.70349
p25: 1-5 30-33 59-63	0.75633	0.71466
Model 2.0: p25: 1-5 30-32 p75: 25-31	0.74549	0.73141
Fan's Model 1: p25 1-80	0.84832	0.74696
Model 2.0 + pap	0.83346	0.82667
Fan's Model 1 + pap	0.90558	0.81373

Compared with SpectRx former model (model1.0), the number of variables in Model 2.0 reduced from 80 to 15, while it has only 1 percent AUC shrinkage. These 15 variables' performances are consistent in adding pap covariate.

In addition to simple percentile variables, we investigated the effectiveness of ratio variables which are defined in explanatory variables, section 3.1. We examine

individual ratio variables performance which provided in graph 3.3. In the graph, variables falls in the lightest color area are most potentially useful. Their discriminative ability is ranked by Wilcoxon statistics.

Table 3.5 Wilcoxon Rank for Ratio Variables

variable	Wilcoxon Statistics
fl25r30v45	6.91
fl25r30v48	6.84
fl25r30v46	6.79
fl25r30v49	6.77
fl25r31v45	6.76
fl25r30v50	6.75
fl25r30v47	6.75
fl75r30v50	6.75
fl10r30v45	6.70
fl75r30v49	6.69
fl25r30v51	6.67
fl50r30v48	6.66
fl75r31v50	6.65
fl50r30v45	6.63
fl50r30v50	6.63
fl75r31v49	6.62
fl10r30v46	6.61
fl50r30v49	6.61
fl10r31v45	6.60
fl75r30v48	6.60
fl10r30v47	6.59
fl10r30v48	6.58
fl25r31v48	6.58
fl75r31v48	6.58

Note: fl25r30v45 ratio variable represents variable 30 at 25th percentile (of 56 locations) divided by variable 45 at 25th percentile.

By combining simple variables with ratio variables, we were able to form several variable combinations to place into PLS regression. These models, with SpectRx previous models (model 1.0, 2, Mixed 1.5, Mixed 1.9) were evaluated for their specificities under 99/95/90 present sensitivity levels. Dallas dataset and pilot datasets

are used to validate model prediction on new populations.

Table 3.6 Model performance comparison chart I

Specificity at 90% Sensitivity							
	510 trainin g	62 case s	Dallas	Dallas 2	Pilot Beta1/Beta2		Equiv Alpha
Model 1.0	50	4	22	55	24	13	8
Model 1.1	50	42	28	61	27	17	12
Hailun 15 Coeff Model	47	0	13	23	28	25	16
Chenghong Mixed Model 1.5	58	50	20	29	12	9	12
Chenghong Mixed Model 1.9	58	42	15	52	16	9	8
Model 2.3: 15 simple+11 ratio	47	13	23	23	24	29	40
Mixed percentile (p25+p75)	58	25	28	52	20	4	4
Mixed percentile (p25+p90)	55	67	33	52	20	25	12
New ratio 1+15 coeff model	52			36			28
New ratio 2+15 coeff model	52			23			28
New ratio 3+15 coeff model	48			36			44
New ratio 4+15 coeff model	48			29			40
Mark F+ 15 + mix model	61		22		36	9	56
Mark F+ 15 + reduce mix model	40		30		32	26	48
New1 MarkF(p25/p75)+15	52		12		40	13	28
New2 Mark F (p25/p90)+ 15	55		15		36	17	36

Specificity at 95% Sensitivity							
	510 trainin g	62 case s	Dallas	Dallas 2	Pilot Beta1/Beta2		Equiv Alpha
Model 1.0	37	N/A	21	N/A	N/A	N/A	N/A
Model 1.1	41	N/A	28	N/A	N/A	N/A	N/A
Hailun 15 Coeff Model	36	N/A	11	N/A	N/A	N/A	N/A
Chenghong Mixed Model 1.5	38	N/A	17	N/A	N/A	N/A	N/A
Chenghong Mixed Model 1.9	38	N/A	13	N/A	N/A	N/A	N/A
Model 2.3: 15 simple+11	41	N/A	17	N/A	N/A	N/A	N/A

ratio							
Mixed percentile (p25+p75)	44	N/A	27	N/A	N/A	N/A	N/A
Mixed percentile (p25+p90)	45	N/A	23	N/A	N/A	N/A	N/A
New ratio 1+15 coeff model	32			N/A			N/A
New ratio 2+15 coeff model	34			N/A			N/A
New ratio 3+15 coeff model	29			N/A			N/A
New ratio 4+15 coeff model	27			N/A			N/A
Mark F+ 15 + mix model	45		22		N/A	N/A	N/A
Mark F+ 15 + reduce mix model	29		18		N/A	N/A	N/A
New Mark F (p25/p75) + 15	40		10		N/A	N/A	N/A
New2 Mark F (p25/p90) + 15	46		10		N/A	N/A	N/A

Specificity at 99% Sensitivity							
	510 trainings	62 cases	Dallas	Dallas 2	Pilot Beta1/Beta2		Equiv Alpha
Model 1.0	20	4	20	32	4	13	8
Model 1.1	15	42	28	29	12	13	8
Hailun 15 Coeff Model	16	0	2	3	28	0	8
Chenghong Mixed Model 1.5	17	21	15	26	0	9	4
Chenghong Mixed Model 1.9	27	25	12	19	8	9	8
Model 2.3: 15 simple+11 ratio	24	8	5	10	23	8	32
Mixed percentile (p25+p75)	18	8	17	32	4	0	4
Mixed percentile (p25+p90)	9	4	8	16	4	0	12
New ratio 1+15 coeff model	16			13			20
New ratio 2+15 coeff model	20			13			28
New ratio 3+15 coeff model	16			6			16
New ratio 4+15 coeff model	17			19			32
Mark F+ 15 + mix model	20		12		0	4	0
Mark F+ 15 + reduce mix model	22		5		28	9	4
New Mark F (p25/p75) + 15	7		2		20	0	16
New2 Mark F (p25/p90) + 15	17		5		32	0	24

From this performance chart, we find model 2.3 is the best candidate model, not only because of its reasonable performance on our training dataset, but also its high specificity for new datasets, especially for pilot data.

To complete the classification analysis, we include CIN1, CIN1/2 cases to our study. Model 2.31 has same covariates as 2.3, but with CIN1 and CIN1/2 cased in. The Model has little shrinkage under 10 folder cross validation.

Table 3.7 Model performance comparison chart II

Specificity at 90% Sensitivity							
	510 training	62 cases	Dallas	Dallas 2	Pilot Beta1/Beta2		Equiv Alpha
Model 2.3	38/48	11/8	23/23	20/23	24/24	29/29	36/40
Model 2.31	37/48	21/21	27/27	32/39	31/28	27/33	33/44
Model 2.31 (validation)	37/48	21/21	27/27	38/39	31/28	27/33	33/44

Specificity at 95% Sensitivity							
	510 training	62 cases	Dallas	Dallas 2	Pilot Beta1/Beta2		Equiv Alpha
Model 2.3	16/21	9/8	3/5	8/10	20/23	6/8	30/32
Model 2.31	22/31	9/4	4/10	5/0	19/24	6/8	28/36
Model 2.31 (validation)	22/31	9/4	4/10	5/0	19/24	6/8	28/36

Adding pap categories to model 2.3 using a decision tree method, we obtained a common threshold at -0.05 across all data sets. For model 2.3 itself, the common threshold for all datasets is also obtained at 0.08.

Table 3.8 Model performance comparison chart III

Model 2.3

Data Set	Sensitivity	Specificity
510	99%	18%
Dallas all	94%	26%
Equivalence alpha	100%	32%
Equivalence beta1	100%	24%
Equivalence beta2	92%	21%

Model 2.3 + pap

Data Set	Sensitivity	Specificity
510	132/133 (99%)	64/226 (29%)
Dallas2	9/10 (90%)	16/31 (52%)
Dallas all	16/17 (94%)	20/60 (33%)
Equivalence alpha	12/12 (100%)	8/25 (32%)
Equivalence beta1	12/12 (100%)	6/25 (24%)
Equivalence beta2	11/12 (92%)	5/23 (22%)
Total	192/195 (98.5%)	119/392 (30%)

In order to further reduce the variables in model 2.3, we did variable selection based on significance and correlation tests. The results are listed in table 3.9.

Table 3.9 Model performance comparison chart IV

	90%			95%			99%		
	510	Alpha	Beta	510	Alpha	Beta	510	Alpha	Beta
Model 2.3 (26 var)	47	46	28	41	46	NA	21	4	24
Model 2.37 (20 var)	50	48	28	37	41	NA	23	2	24
Model 2.38 (20var)	49	46	32	40	43	NA	25	2	28
Model 2.39 (20 var)	48	32	28	29	30	NA	20	2	28
Model 2.40(21 var)	50	39	24	45	29	NA	24	NA	24
Model 2.41(13 var)	42	11	16	35	7	NA	23	7	0
Model 2.42(18 var)	45	11	16	37	7	NA	23	7	0
Model 2.43(25 var)	42	11	20	29	7	NA	16	0	12

Note that Model 2.37 has 6 less variables than 2.3, but its performance is quite competitive. We compared them at common thresholds across all datasets.

Table 3.10 Model performance comparison chart V

	Model 2.3 at threshold 0.105	Model 2.37 at threshold 0.115
510	98.5 / 19	98.5 / 21
Alpha pick	95.5 / 46.4	95.5 / 41
Beta pick	100 / 24	91.7 / 28

Inspired by the color graph 3.3, we explored the ratio variable by this rule: the numerators (minimum) were always chosen from blue wavelengths and denominators

(maximum) from red (see table 3.1). To be consistent with biological theory, when mixed ratios are used the numerators are from the lower percentile and denominator from the higher percentile. The threshold for choosing variables was a minimum of 25% specificity at 95% sensitivity. When this threshold was raised to 30% the ratio groups highlighted in yellow survived although not all individual variables in that group. The ratios highlighted in red are unstable because they are too close to the flip point (from red to blue) wavelengths.

Table 3.11 Ratio Variables List

P10	(31,32)/(41-43)	(33,34)/(37,38)			
P25	(30,31)/(21,22)	(30,31)/(50-56)			
P50	(30,31)/(50-56)				
P75	(30-32)/(47-58)	(30-32)/(75-78)			
P90	(30-32)/(47-58)				
P10_75	(30-32)/(49-57)	(30,31)/(75-78)	(33,34)/(37,38)	(61-66)/(41-43)	(62-64)/(46-48)
P10_90	(30-32)/(21-29)	(30,31)/(49-51)	(30-32)/(70-78)	(33,34)/(37,38)	
P25_75	(30-32)/(21-29)	(30,31)/(46-57)	(30,31)/(71-78)	(64-66)/(42,43)	(61-64)/(46-48)
P25_90	(30-32)/(21-29)	(30-32)/(49-57)	(30-32)/(69-78)		

There are a total of 22 cells, excluding 3 red cells. Each ratio variable can be created by applying a min/max rule which is effective in reducing the correlation among adjacent variables. For example, ratio var1 = min of (31, 32) / max of (41-43). Applying this rule, we built four new models with new ratio variables. Notice that Model 2.45: 22 min/max variables; Model 2.46: 15 single variables + 22 min/max; Model 2.47: reduced 2.45 to 11 vars; Model 2.48: 15 single var + 11 min/max. Table 3.10 shows that model 2.46 has best performance at 99% sensitivity levels for both 510 and pilot data.

Table 3.12 Model performance comparison chart VI

	90%			95%			99%		
	510	Alpha	Beta	510	Alpha	Beta	510	Alpha	Beta
Model 2.45	51	30	20	37	21	NA	20	21	4
Model 2.46	50	23	24	38	23	NA	25	20	20
Model 2.47	44	25	16	24	16	NA	18	13	16
Model 2.48	53	23	32	27	18	NA	18	11	32

Chapter Four: Future Study

One purpose of our point level analysis was to combine all diagnostic results of all 56 cervical surface locations to provide index for each subject. Thus, we have more information for patient level diagnosis. For each individual, once we have the 56 point indices which represent probabilities of having disease, the combination of these points may provide information for patient level diagnosis. Logistic algorithm and PLS algorithm could be adopted to find out relationship between point diagnosis and patient level diagnosis. Some work has been done by using point level models (p90-p10).

1. Point output indices from the point level model (AUC: 0.88(T) 0.78(V)) with Os location, totally are 273 subjects (no CIN1) and 56 variables(points), apply PLS algorithm:

10-folder AUC performance:

	Train	Validation
56 variables	0.725	0.714
56 variables + pap	0.888	0.834

2. Point output indices from the point level model (AUC: 0.88(T) 0.78(V)) with fixed 20 peripheral location, totally are 347 subjects (no CIN1) and 56 variables(points), apply PLS algorithm:

10-folder AUC performance:

	Train	Validation
56 variables	0.633	0.624
56 variables + pap	0.865	0.801

Compared with the models in chapter three, this approach did not improve AUC. One of the reasons might be that 28% points are missing which results in insufficient information for running PLS regression. To improve this, a simulation might be involved to solve the missing data problem. Since we have the point position information, once we have some point indices, their adjacent point having missing values might be simulated by some approximation methods.

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APPENDIX I: SAS CODE FOR INITIAL DATA MANIPULATION, VARIABLE REDUCTION IN POINT ANALYSIS

/* This is a program to manipulate data for point analysis

file: point_analysis_mani.sas
created by: Chenghong Shen
modified by: Hailun Wang
last update: 06/22/2006

*/

%include 'K:\intern\spectrx\fan\missing_mac.sas';
libname After 'K:\intern\spectrx\PointAnalysis\';

options nonotes;
options nonumber nodate;

data After.R;
 set _null_;
run;

%macro getpointdata(path1 = , path2 = , path3 = , path4 = , path5 = ,
 file = , spacing = 10, dataout = ,
 subselect = 1, pointselect = 0, disq = no, extype = manual, spectype =
orig,
 /*sub_id=, point_start=, point_end=, reflec=, fluore1=, fluore2=,
fluore3=*/);

data demo;
 infile "&path1&file" expandtabs lrecl = 10000 missover;
 input sub_id\$ available unclean datec\$ whole1 sitepath qa1 PriorPap PriorPatype
 DayofPap DayofPatype PreferredPap PreferredPatype scjvisible
colpoadequacy Age Race
 menstrual Menopause Gravida Para Abort Birthcontrol Priorsurgery1
DaysPriorsurgery1
 Priorsurgery2 DaysPriorsurgery2 Priorsurgery3 DaysPriorsurgery3
 Priorsurgery4 DaysPriorsurgery4 Priorsurgery5 DaysPriorsurgery5 height
weight
 smoking Cigarettesperday;
 d_id = substr(sub_id, 1, 1);

```

        year = substr(datec, 1, 4); month = substr(datec, 5, 2); day = substr(datec, 7, 2);
        date = mdy(month, day, year);
        %nmissing(varlist = available unclean whole1 sitepath qa1 PriorPap
PriorPaptype
        DayofPap DayofPaptype PreferredPap PreferredPaptype scjvisible
colpoadequacy Age Race
        menstrual Menopause Gravida Para Abort Birthcontrol Priorsurgery1
DaysPriorsurgery1
        Priorsurgery2 DaysPriorsurgery2 Priorsurgery3 DaysPriorsurgery3
        Priorsurgery4 DaysPriorsurgery4 Priorsurgery5 DaysPriorsurgery5 height
weight
        smoking Cigarettesperday, missing = -1 -2);
        if available and &subselect;
run;

proc sort data = demo; by sub_id; run;

data _null_; set demo end = last;
        call symput('sub'||left(_n_), trim(left(sub_id)));
        if last then call symput('nsub', _n_);
run;

proc sort data = demo; by sub_id; run;

data coordinates;
        infile
'k:\intern\spectrx\fan\nci\hybrid\data3\HybridInterrogationPointCoordsmm.txt'
expandtabs;
        input point x y;
run;

%do i = 1 %to &nsub;
%put Read Data File For Subject #&i out of %left(&nsub) &&sub&i;

/* Read the point analysis data */

%if %sysfunc(fileexist("&path4.&&sub&i._pointgold.txt")) %then %do;
data pointgold;

        infile "&path4.&&sub&i._pointgold.txt" expandtabs lrecl = 100000;
        input point pathology1 pathology2;

```

```

if pathology1>pathology2 then pathology=pathology1;
else pathology=pathology2;

if pathology=0.5 then pathology=0;

drop pathology1 pathology2;

run;

data pointcat;
  infile "&path3.&&sub&i.._excl_&extype..txt" expandtabs;
  input point reject;
run;

Data org;

  INFILE "&path2.&&sub&i.._spectra_autopeakrowdetect_notiszero2.txt"
expandtabs lrecl = 100000;

  input point rf_1-rf_63 b1-b4 f1_1-f1_59 b5-b8 f2_1-f2_53 b9-b12 f3_1-f3_41;
  array rf rf_1-rf_63; array f1 f1_1-f1_59; array f2 f2_1-f2_53; array f3 f3_1-f3_41;

  %spacingselfnorm;
  sub_id = "&&sub&i";

run;

data org_merge;
  merge org pointgold pointcat;
  *if reject in (&pointselect);
  by point;
run;

data After.R;
  set After.R org_merge;

run;
%end;

```

```
%end;
```

```
%mend;
```

```
%macro spacingselfnorm;
```

```
    %let t1 = 31; %let t2 = 29; %let t3 = 26; %let t4 = 20;
```

```
    array nrf nrf_1-nrf_&t1; array nfl nfl_1-nfl_&t2; array nf2 nf2_1-nf2_&t3; array nf3  
nf3_1-nf3_&t4;
```

```
    array rnrf rnrf_1-rnrf_&t1; array rnf1 rnf1_1-rnf1_&t2; array rnf2 rnf2_1-  
rnf2_&t3; array rnf3 rnf3_1-rnf3_&t4;
```

```
    %if &spacing = 5 %then %do;
```

```
        do i = 1 to &t1; nrf(i) = rf(i); end;
```

```
        do i = 1 to &t2; nfl(i) = fl(i); end;
```

```
        do i = 1 to &t3; nf2(i) = f2(i); end;
```

```
        do i = 1 to &t4; nf3(i) = f3(i); end;
```

```
    %end;
```

```
    %else %if &spacing = 10 %then %do;
```

```
        do i = 1 to &t1; nrf(i) = (rf(2 * i - 1) + rf(2 * i)) / 2; end;
```

```
        do i = 1 to &t2; nfl(i) = (fl(2 * i - 1) + fl(2 * i)) / 2; end;
```

```
        do i = 1 to &t3; nf2(i) = (f2(2 * i - 1) + f2(2 * i)) / 2; end;
```

```
        do i = 1 to &t4; nf3(i) = (f3(2 * i - 1) + f3(2 * i)) / 2; end;
```

```
    %end;
```

```
    %else %do;
```

```
        do i = 1 to &t1; nrf(i) = (rf(4 * i - 3) + rf(4 * i - 2) + rf(4 * i - 1) + rf(4 * i))  
/ 4; end;
```

```
        do i = 1 to &t2; nfl(i) = (fl(4 * i - 3) + fl(4 * i - 2) + fl(4 * i - 1) + fl(4 *  
i)) / 4; end;
```

```
        do i = 1 to &t3; nf2(i) = (f2(4 * i - 3) + f2(4 * i - 2) + f2(4 * i - 1) + f2(4 *  
i)) / 4; end;
```

```
        do i = 1 to &t4; nf3(i) = (f3(4 * i - 3) + f3(4 * i - 2) + f3(4 * i - 1) + f3(4 *  
i)) / 4; end;
```

```
    %end;
```

```
    avgnrf = mean(of nrf_1-nrf_&t1); stdnrf = std(of nrf_1-nrf_&t1);
```

```
    avgnfl = mean(of nfl_1-nfl_&t2); stdnfl = std(of nfl_1-nfl_&t2);
```

```
    avgnf2 = mean(of nf2_1-nf2_&t3); stdnf2 = std(of nf2_1-nf2_&t3);
```

```
    avgnf3 = mean(of nf3_1-nf3_&t4); stdnf3 = std(of nf3_1-nf3_&t4);
```



```

do i = 1 to &t1; mrf(i) = (nrf(i) / avgnrf); end;
do i = 1 to &t2; mrf1(i) = (nf1(i) / avgnf1); end;
do i = 1 to &t3; mrf2(i) = (nf2(i) / avgnf2); end;
do i = 1 to &t4; mrf3(i) = (nf3(i) / avgnf3); end;

```

```
%mend;
```

```
%getpointdata(path1 = k:\intern\spectrx\fan\Aftertrain\,
```

```
/* Data for training */
```

```
path2 = k:\intern\spectrx\workdir\DATA\,
```

```
path3 = k:\intern\spectrx\workdir>manual\,
```

```
path4 = k:\intern\spectrx\workdir\point_analysis\,
```

```
path5 = k:\intern\spectrx\workdir\graph\,
```

```
/*sub_id=4124,
```

```
point_start=29,
```

```
point_end=33,
```

```
reflec=1,
```

```
fluore1=1,
```

```
fluore2=1,
```

```
fluore3=1, */
```

```
file = HybridFINAL ClinicalData dm 2.txt, spacing = 10, dataout = All, disq = yes,
subselect = (unclean = 0 and whole1~= .));
```

APPENDIX II: SAS CODE FOR CREATING NEW VARIABLES IN POINT ANALYSIS USING TISSUE TYPE

/* This is the point data manipulation, treating the range of values between normal types of tissue in each subject as index to get rid of variability between subjects

file: test_point_model2.1_new_man1

Created by: Hailun Wang

Last update: 06/22/06*/

libname After 'k:\intern\spectrx\pointAnalysis';

option nodate nonotes;

data SN;

set After.M;

if pathology in (0);

run;

data CN;

set After.M;

if pathology in (1);

run;

data TZ;

set After.M;

if pathology in (0.5);

run;

proc means data=SN noprint;

var nrf_1-nrf_31 nfl_1-nfl_29 nf3_1-nf3_20;

by sub_id;

output out=SN_mean

mean=x1-x31 y1-y29 z1-z20;

run;

proc means data=CN noprint;

var nrf_1-nrf_31 nfl_1-nfl_29 nf3_1-nf3_20;

by sub_id;

output out=CN_mean

mean=m1-m31 n1-n29 k1-k20;

run;

proc means data=TZ noprint;

```

var nrf_1-nrf_31 nf1_1-nf1_29 nf3_1-nf3_20;
by sub_id;
output out=TZ_mean
mean=a1-a31 b1-b29 c1-c20;
run;

```

```

data SNandCN;
merge SN_mean CN_mean;
by sub_id;
if m1=. or x1=. then delete;
run;

```

```

data SNremain;
merge SN_mean CN_mean;
by sub_id;
if m1 not in(.) then delete;
drop m1-m31 n1-n29 k1-k20;
run;

```

```

data SNandTZ;
merge SNremain TZ_mean;
by sub_id;
if x1=. or a1=. then delete;
run;

```

```

data normalization1;
set SNandCN;
%macro norm;
%do i=1 %to 31;
norm1_&i=m&i-x&i;
%end;
%do j=1 %to 29;
norm2_&j=n&j-y&j;
%end;
%do h=1 %to 20;
norm3_&h=k&h-z&h;
%end;
%mend;
%norm;
run;

```

```

data normalization2;
  set SNandTZ;
  %macro norm;
    %do i=1 %to 31;
      norm1_&i=a&i-x&i;
    %end;
    %do j=1 %to 29;
      norm2_&j=b&j-y&j;
    %end;
    %do h=1 %to 20;
      norm3_&h=c&h-z&h;
    %end;
  %mend;
%norm;
run;

data normalization;
  set normalization1 normalization2;
run;

proc sort data=After.M;
  by sub_id point;
run;
proc sort data=normalization;
  by sub_id;
run;
data mix;
  merge After.M normalization;
  by sub_id;
  if x1=. then delete;
run;

data point_train;
  set mix;
  %macro group;
    %do i=1 %to 31;
      diff1_&i=nrf_&i-norm1_&i;
    %end;
    %do j=1 %to 29;
      diff2_&j=nfl_&j-norm1_&j;
    %end;
    %do k=1 %to 20;

```

```

    diff3_&k=nf3_&k-norm1_&k;
    %end;
    %mend;
    %group;
run;

```

```

data After.point_diff4;
    set point_train (keep=sub_id point pathology reject diff1_1-diff1_31 diff2_1-diff2_29
diff3_1-diff3_20);
run;

```

APPENDIX III: SAS CODE FOR CREATING NEW VARIABLES IN POINT ANALYSIS USING PERCENTILES IN PERIPHERAL GROUP

/* this is the point data manipulation, treating the difference between different percentiles in peripheral area in each subject as index to get rid of variability between subjects

file: test_point_model1.3(2)_new_man

Created by: Hailun Wang

Last update: 06/25/06*/

libname After 'k:\intern\spectrx\pointAnalysis';

data Peripheral;

set After.M;

where point in (1 2 3 4 5 11 12 19 20 28 29 37 38 45 46 52 53 54 55 56);

run;

proc means data=Peripheral **noprint**;

var rnrfl_1-rnrfl_31 rnf1_1-rnf1_29 rnf3_1-rnf3_20;

by sub_id;

output out=peripheral_mean

p10=a1-a31 b1-b29 c1-c20

p90=d1-d31 e1-e29 f1-f20;

run;

data peripheral_mean;

set peripheral_mean;

%macro normal;

%do i=1 %to 31;

x&i=d&i-a&i;

%end;

%do j=1 %to 29;

y&j=e&j-b&j;

%end;

%do k=1 %to 20;

z&k=f&k-c&k;

%end;

%mend;

```

%normal;
run;

proc sort data=After.M;
  by sub_id point;
run;

proc sort data=peripheral_mean;
  by sub_id;
run;

data mix;
  merge After.M peripheral_mean;
  by sub_id;
run;

data point_train;
  set mix;
  %macro group;
    %do i=1 %to 31;
      diff1_&i=rnrf_&i-x&i;
    %end;
    %do j=1 %to 29;
      diff2_&j=rnf1_&j-y&j;
    %end;
    %do k=1 %to 20;
      diff3_&k=rnf3_&k-z&k;
    %end;
  %mend;
%group;
run;

```

APPENDIX IV: SAS CODE FOR CALCULATING AUC ON TRAINING AND 10-FOLDER CROSS-VALIDATION DATASETS

/* This is a macro to carry out the n-folder cross validation.

It is modified from nfolder_mac.sas. It takes 3 sets of variables.

file name: nfolder_mac.sas

last updated: May 22, 2002

by: Fan Xu

Modified by: Hailun Wang

*/

%include 'k:\intern\spectrx\fan\macros\rocest_mac.sas';

%macro nfolder(datain = model, folder = n, response = whole, var1 = , var2 = , var3 = ,
n = , select = stepwise,
print = no, sig = **0.01**, pap = no);
option nonotes;

%foldermark(datain = &datain, folder = &folder);

/*proc princomp data = mark noprint out = prin prefix;
var &var1;
run;*/

%do i = **1** **%to** &folder;

%put &i out of &folder running...;
data oneout; set mark;
if group = &i then &response = .;
run;

proc logistic data = oneout descending noprint;
%if **%upcase**(&pap) = YES **%then** **%do**;
model &response = &var1 /*pm1-pm&n ps1-ps&n pt1-pt&n*/

preferredPap


```

%end;
%if %upcase(&pap) = NO %then %do;
model &response = &var1 /*pm1-pm&n ps1-ps&n pt1-pt&n*/
%end;
%if %upcase(&select) = STEPWISE %then %do;
/ fast selection = stepwise sle = &sig sls = &sig;
%end;
%else %do;

;
%end;
output out = lout pred = pred;
run;

data pred1; set lout; if group = &i ; keep pred; run;
data pred2; set mark; if group = &i ; keep &response; run;
data pred; merge pred1 pred2; run;

%if &i = 1 %then %do;
data valid; set _null_; run;
%end;

data valid; set valid pred; run;
%end;

proc logistic data = mark noprint descending ;
%if %upcase(&pap) = YES %then %do;
model &response = &var1 /* pm1-pm&n ps1-ps&n pt1-pt&n */
preferredPap
%end;
%if %upcase(&pap) = NO %then %do;
model &response = &var1 /*pm1-pm&n ps1-ps&n pt1-pt&n */
%end;
%if %upcase(&select) = STEPWISE %then %do;
/ selection = stepwise sle = &sig sls = &sig;
%end;
%else %do;

;
%end;
output out = lout pred = pred;
run;

```

```

%if %upcase(&print) = YES %then %do;
    %rocest(datain = lout, tests = pred, gold = &response);
    title 'Training Performance';
    proc print data = roc; run;
    %rocest(datain = valid, tests = pred, gold = &response);
    title 'Cross-Validation Performance';
    proc print data = roc; run;
%end;
%mend;

%macro foldermark(datain = , folder = );

    proc sort data = &datain; by whole1; run;

    data mark; set &datain;
        by whole1;
        if first.whole1 then obs = 0;
        else obs + 1;
        if last.whole1 then do;

            if whole1=3.2 then do;
                call symput('groupobs3_2', round(obs / &folder));
            end;

            if whole1=3.5 then do;
                call symput('groupobs3_5', round(obs / &folder));
            end;

            if whole1=3 then do;
                call symput('groupobs3', round(obs / &folder));
            end;

            if whole1=2.5 then do;
                call symput('groupobs2_5', round(obs / &folder));
            end;

            if whole1=2 then do;
                call symput('groupobs2', round(obs / &folder));
            end;

            if whole1=1 then do;

```

```

                                call symput('groupobs1', round(obs / &folder));
                                end;

                                if whole1=0 then do;
                                    call symput('groupobs0', round(obs / &folder));
                                end;

                                end;
run;

data mark; set mark;
    if whole1 = 0 then group = int(obs / &groupobs0) + 1;
    if whole1 = 1 then group = int(obs / &groupobs1) + 1;
    if whole1 = 3 then group = int(obs / &groupobs3) + 1;
    if whole1 = 3.2 then group = int(obs / &groupobs3_2) + 1;
    if whole1 = 3.5 then group = int(obs / &groupobs3_5) + 1;
    if group > &folder then group = &folder;
run;

%mend;

%include 'K:\intern\spectrx\workdir\programs\folder3_mac.sas';

data train;
    set Point_diff;
    whole1=pathology;
    if whole1 not in (2 2.5);
    if pathology not in (-1 -2 9 999);
    whole = (whole1 > 2);
    high = (whole1 >= 3);
    highlow = (whole1 >= 2);
    low = whole1 in (2 2.5);
run;

proc logistic data=train descending noprint;
    model whole= diff1_1-diff1_31 diff2_1-diff2_29 diff3_1-diff3_20/ scale=none
        clparm=wald
        clodds=pl
        rsquare
        outroc=roc1;
    output out=lout pred=pred p=prob XBETA=beta;
run;

```

```

data indice1;
  set lout(keep=sub_id point pred);
  if _n_ < 16000;
run;

data indice2;
  set lout(keep=sub_id point pred);
  if _n_ >= 16000;
run;
/*logistic 1.1(full)*/
%nfolder(datain = Train, folder = 10, response = whole, var1 = diff1_1-diff1_31
diff2_1-diff2_29 diff3_1-diff3_20, var2 = , var3 = , n = 3 , select = forward,
    print = yes, sig = 0.01, pap = no);

```

APPENDIX V: SAS CODE FOR DATA MANIPULATION AND PERCENTILE

VARIABLE CREATION IN WHOLE CERVIX DIAGNOSIS

```

/*
This is data manipulation to read 522 subjects with spectrum 410+
into sas data set .

Hailun Wang
last update: 02/28/2007
*/

%include 'G:\intern\spectrx\fan\missing_mac.sas';
libname After 'G:\intern\whole cervix model\sas data';

option nonotes;
options nonumber nodate;
%macro readdata(path1 = , path2 = , path3 = , file = , spacing = 10, dataout = ,
               subselect = 1, pointselect = 0, disq = yes, extype = manual);

data demo;
    infile "&path1&file" expandtabs lrecl = 10000 missover;
    input sub_id$ available unclean datec$ whole1 sitepath qa1 PriorPap PriorPaptype
          DayofPap DayofPaptype PreferredPap PreferredPaptype scjvisible
colpoadequacy Age Race
          menstrual Menopause Gravida Para Abort Birthcontrol Priorsurgery1
DaysPriorsurgery1
          Priorsurgery2 DaysPriorsurgery2 Priorsurgery3 DaysPriorsurgery3
          Priorsurgery4 DaysPriorsurgery4 Priorsurgery5 DaysPriorsurgery5 height
weight
          smoking Cigarettesperday;
    d_id = substr(sub_id, 1, 1);
    year = substr(datec, 1, 4); month = substr(datec, 5, 2); day = substr(datec, 7, 2);
    date = mdy(month, day, year);
    %nmissing(varlist = available unclean whole1 sitepath qa1 PriorPap
PriorPaptype
          DayofPap DayofPaptype PreferredPap PreferredPaptype scjvisible
colpoadequacy Age Race
          menstrual Menopause Gravida Para Abort Birthcontrol Priorsurgery1
DaysPriorsurgery1

```

```

Priorsurgery2 DaysPriorsurgery2 Priorsurgery3 DaysPriorsurgery3
Priorsurgery4 DaysPriorsurgery4 Priorsurgery5 DaysPriorsurgery5 height
weight
    smoking Cigarettesperday, missing = -1 -2);
    if available and &subselect;
run;

proc sort data = demo; by sub_id; run;

data _null_; set demo end = last;
    call symput('sub'||left(_n_), trim(left(sub_id)));
    if last then call symput('nsub', _n_);
run;

proc sort data = demo; by sub_id; run;

data coordinates;
    infile
'G:\intern\spectrx\fan\nci\hybrid\data3\HybridInterrogationPointCoordsmm.txt'
expandtabs;
    input point x y;
run;

%do i = 1 %to &nsub;
    %put Read Data File For Subject #&i out of %left(&nsub) &&sub&i;

Data org;
    /*infile "&path2.&&sub&i._spectra_&spectype..txt" expandtabs lrecl =
100000;*/
    INFILE "&path2.&&sub&i.. spectra_ autopeakrowdetect_notiszero2.txt"
        EXPANDTABS LRECL=100000;
    %if %upcase(&disq) = NO %then %do;
        input point rf_1-rf_63 f1_1-f1_63 f2_1-f2_57 f3_1-f3_45;
        array rf rf_1-rf_63; array f1 f1_1-f1_63; array f2 f2_1-f2_57; array f3
f3_1-f3_45;
        %if &spacing = 5 %then %do;
            %let t1 = 63; %let t2 = 63; %let t3 = 57; %let t4 = 45;
        %end;
    %else %if &spacing = 10 %then %do;
        %let t1 = 31; %let t2 = 31; %let t3 = 28; %let t4 = 22;
    %end;

```

```

        %else %if &spacing = 20 %then %do;
            %let t1 = 15; %let t2 = 15; %let t3 = 14; %let t4 = 11;
        %end;
    %end;

    %else %do;
        input point b1-b4 rf_1-rf_59 b5-b8 fl_1-fl_59 b9-b12 f2_1-f2_53 b13-b16
        f3_1-f3_41;
        array rf rf_1-rf_59; array fl fl_1-fl_59; array f2 f2_1-f2_53; array f3
        f3_1-f3_41;
        %if &spacing = 5 %then %do;
            %let t1 = 59; %let t2 = 59; %let t3 = 53; %let t4 = 41;
        %end;
        %else %if &spacing = 10 %then %do;
            %let t1 = 29; %let t2 = 29; %let t3 = 26; %let t4 = 20;
        %end;
        %else %if &spacing = 20 %then %do;
            %let t1 = 15; %let t2 = 14; %let t3 = 13; %let t4 = 10;
        %end;
    %end;
    %let t = %eval(&t1 + &t2 + &t3 + &t4);

    %spacingselfnorm;
    sub_id = "&&sub&i";
run;

data pointcat;
    infile "&path3.&&sub&i._excl_&extype.txt" expandtabs;
    input point reject;
run;

data org; merge org pointcat coordinates; by point; run;

%meanpro(datain = org, dataout = m&i);

%end;

data model; merge demo %mf;
    by sub_id;
run;

```

```

data &dataout; set model;
    CIN31 = (whole1 = 3.5);
    CIN32 = (whole1 >= 3.2);
    high = (whole1 >= 3);
    highlow = (whole1 >= 2);
    low = whole1 in (2 2.5);
    nandb = whole1 in (0 1);
    nc = whole1 = 1;
    normal = whole1 = 0;
run;

%mend;

%macro mf;
    %do j = 1 %to &nsb;
        m&j
    %end;
%mend;

%macro spacingselfnorm;

    array nrf nrf_1-nrf_&t1; array nfl nfl_1-nfl_&t2; array nf2 nf2_1-nf2_&t3;
    array nf3 nf3_1-nf3_&t4;
    array rnrf rnrf_1-rnrf_&t1; array rnfl rnfl_1-rnfl_&t2; array rn2 rn2_1-
    rn2_&t3; array rn3 rn3_1-rn3_&t4;

    %if &spacing = 5 %then %do;
        do i = 1 to &t1; nrf(i) = rf(i); end;
        do i = 1 to &t2; nfl(i) = fl(i); end;
        do i = 1 to &t3; nf2(i) = f2(i); end;
        do i = 1 to &t4; nf3(i) = f3(i); end;
    %end;
    %else %if &spacing = 10 %then %do;
        do i = 1 to &t1; nrf(i) = (rf(2 * i - 1) + rf(2 * i)) / 2; end;
        do i = 1 to &t2; nfl(i) = (fl(2 * i - 1) + fl(2 * i)) / 2; end;
        do i = 1 to &t3; nf2(i) = (f2(2 * i - 1) + f2(2 * i)) / 2; end;
        do i = 1 to &t4; nf3(i) = (f3(2 * i - 1) + f3(2 * i)) / 2; end;
    %end;
    %else %do;
        do i = 1 to &t1; nrf(i) = (rf(4 * i - 3) + rf(4 * i - 2) + rf(4 * i - 1) + rf(4 * i))
/ 4; end;
        do i = 1 to &t2; nfl(i) = (fl(4 * i - 3) + fl(4 * i - 2) + fl(4 * i - 1) + fl(4 *

```



```

i)) / 4; end;
do i = 1 to &t3; nf2(i) = (f2(4 * i - 3) + f2(4 * i - 2) + f2(4 * i - 1) + f2(4 *
i)) / 4; end;
do i = 1 to &t4; nf3(i) = (f3(4 * i - 3) + f3(4 * i - 2) + f3(4 * i - 1) + f3(4 *
i)) / 4; end;
%end;

avgnrf = mean(of nrf_1-nrf_&t1); stdnrf = std(of nrf_1-nrf_&t1);
avgnf1 = mean(of nf1_1-nf1_&t2); stdnf1 = std(of nf1_1-nf1_&t2);
avgnf2 = mean(of nf2_1-nf2_&t3); stdnf2 = std(of nf2_1-nf2_&t3);
avgnf3 = mean(of nf3_1-nf3_&t4); stdnf3 = std(of nf3_1-nf3_&t4);

do i = 1 to &t1; rnr(i) = nrf(i) / avgnrf; end;
do i = 1 to &t2; rnf1(i) = nf1(i) / avgnf1; end;
do i = 1 to &t3; rnf2(i) = nf2(i) / avgnf2; end;
do i = 1 to &t4; rnf3(i) = nf3(i) / avgnf3; end;

%mend;

%macro meanpro(datain = , dataout = );

proc means data = &datain noprint;
var rnr_1-rnr_&t1 rnf1_1-rnf1_&t2 rnf2_1-rnf2_&t3 rnf3_1-rnf3_&t4 ;
output out = &dataout

p10 = p10ra1-p10ra&t
p25 = p25ra1-p25ra&t
p50 = p50ra1-p50ra&t
p75 = p75ra1-p75ra&t
p90 = p90ra1-p90ra&t;
where reject in (&pointselect);
by sub_id;

run;

%mend;

%readdata(path1 =
\\SPRXDEV1\Can1\CCDataAnalysis\PreProcessedData\export\HybridFINAL\ClinicalD

```

```

ata\,
  path2 =
\\SPRXDEV1\Can1\CCDataAnalysis\PreProcessedData\export\HybridFINAL\Spectra\autopeakrowdetect_notiszero2\,
  path3 =
\\SPRXDEV1\Can1\CCDataAnalysis\PreProcessedData\export\HybridFINAL\ExcludedPoints>manual\,

```

```

      file = HybridFINAL_ClinicalData_dm_2.txt, spacing = 10, dataout =
After.clean522, disq = yes,
      subselect = (unclean = 0 and whole1~= .));

```

APPENDIX VI: SAS CODE FOR READ PILOT DATA INTO ALPHA PICK AND BETA PICK SETS

```

/*****
This is a program to read alpha polit data and generate
p10-p90 var and ratio var
*****/

libname After 'G:\intern\whole cervix model\sas data';

option nonotes;
options nonumber nodate;

%macro readdata (pointselect=, exctype = , dataout=);

proc import datafile="G:\intern\whole cervix model\pilot\clinicaldata_epa.xls"
out=demo dbms=excel;

data demo;
  set demo;
  if whole1=. then delete;
  sub_id=substr(subject,6,4);
run;

proc sort data = demo; by sub_id; run;

data _null_; set demo end = last;
  call symput('sub'||left(_n_), trim(left(sub_id)));
  if last then call symput('nsub', _n_);
run;
%do i = 1 %to &nsub;
  %put Read Data File For Subject #&i out of %left(&nsub) &&sub&i;

%macro spacingselfnorm;

      array nrf nrf_1-nrf_&t1; array nfl nfl_1-nfl_&t2; array nf3 nf3_1-nf3_&t4;
      array rnrf rnrf_1-rnrf_&t1; array rnfl rnfl_1-rnfl_&t2; array rnf3 rnf3_1-
rnf3_&t4;

```

```

do i = 1 to &t1; nrf(i) = (rf(2 * i - 1) + rf(2 * i)) / 2; end;
do i = 1 to &t2; nfl(i) = (f1(2 * i - 1) + f1(2 * i)) / 2; end;
do i = 1 to &t4; nf3(i) = (f3(2 * i - 1) + f3(2 * i)) / 2; end;

avgnrf = mean(of nrf_1-nrf_&t1);
avgnf1 = mean(of nfl_1-nfl_&t2);
avgnf3 = mean(of nf3_1-nf3_&t4);

do i = 1 to &t1; rnrf(i) = nrf(i) / avgnrf; end;
do i = 1 to &t2; rnfl(i) = nfl(i) / avgnf1; end;
do i = 1 to &t4; rnf3(i) = nf3(i) / avgnf3; end;

%mend;

Data org;
  infile "G:\intern\whole cervix
model\pilot\Spectra_alpha\11EPA&&sub&i..spectra.txt" expandtabs lrecl = 100000;
  input point b1-b4 rf_1-rf_58 b5-b9 fl_1-fl_58 b10-b14 f3_1-f3_41;

  array rf rf_1-rf_59; array fl fl_1-fl_59; array f3 f3_1-f3_40;
  %let t1 = 29; %let t2 = 29; %let t4 = 20;
  %let t = %eval(&t1 + &t2 + &t4);

  %spacingselfnorm;
  sub_id = "&&sub&i";
run;

data pointcat;
  infile "G:\intern\whole cervix
model\pilot\2filtercombo_alpha\11EPA&&sub&i.._excl_&extype..txt" expandtabs;
  input point reject;
run;

data org; merge org pointcat; by point; run;

%meanpro(datain = org, dataout = m&i);

%end;

```

```

data model; merge demo %mf;
    by sub_id;
run;

data &dataout; set model;
    CIN31 = (whole1 = 3.5);
    CIN32 = (whole1 >= 3.2);
    high = (whole1 >= 3);
    highlow = (whole1 >= 2);
    low = whole1 in (2 2.5);
    nandb = whole1 in (0 1);
    nc = whole1 = 1;
    normal = whole1 = 0;
run;

%mend;

%macro mf;
    %do j = 1 %to &nsub;
        m&j
    %end;
%mend;

%macro meanpro(datain = , dataout = );

proc means data = &datain noprint;
    var rnrf_1-rnrf_&t1 rnf1_1-rnf1_&t2 rnf3_1-rnf3_&t4 ;
    output out = &dataout

    p10 = p10ra1-p10ra&t
    p25 = p25ra1-p25ra&t
    p50 = p50ra1-p50ra&t
    p75 = p75ra1-p75ra&t
    p90 = p90ra1-p90ra&t;
    where reject in (&pointselect);
    by sub_id;

run;

%mend;

```

```
%readdata( pointselect = 0, exctype = 2filtercombo, dataout = polit_alpha);
```

```

/*****
This is a program to read beta1 polit data and generate
p10-p90 var and ratio var
*****/

```

```
libname After 'G:\intern\whole cervix model\sas data';
```

```
option nonotes;
options nonumber nodate;
```

```
%macro readdata (pointselect=, exctype = , dataout=);
```

```
proc import datafile="G:\intern\whole cervix model\pilot\clinicaldata_epb.xls"
out=demo dbms=excel;
```

```
data demo;
  set demo;
  if whole1=. then delete;
  sub_id=substr(subject,6,4);
run;
```

```
proc sort data = demo; by sub_id; run;
```

```
data _null_; set demo end = last;
  call symput('sub'||left(_n_), trim(left(sub_id)));
  if last then call symput('nsub', _n_);
run;
%do i = 1 %to &nsub;
  %put Read Data File For Subject #&i out of %left(&nsub) &&sub&i;
```

```
%macro spacingselfnorm;
```

```

  array nrf nrf_1-nrf_&t1; array nf1 nf1_1-nf1_&t2; array nf3 nf3_1-nf3_&t4;
  array rnrf rnrf_1-rnrf_&t1; array rnf1 rnf1_1-rnf1_&t2; array rnf3 rnf3_1-
rnf3_&t4;
```

```
  do i = 1 to &t1; nrf(i) = (rf(2 * i - 1) + rf(2 * i)) / 2; end;
```

```

do i = 1 to &t2; nf1(i) = (f1(2 * i - 1) + f1(2 * i)) / 2; end;
do i = 1 to &t4; nf3(i) = (f3(2 * i - 1) + f3(2 * i)) / 2; end;

avgnrf = mean(of nrf_1-nrf_&t1);
avgnf1 = mean(of nf1_1-nf1_&t2);
avgnf3 = mean(of nf3_1-nf3_&t4);

do i = 1 to &t1; nrf(i) = nrf(i) / avgnrf; end;
do i = 1 to &t2; nf1(i) = nf1(i) / avgnf1; end;
do i = 1 to &t4; nf3(i) = nf3(i) / avgnf3; end;

%mend;

Data org;
  infile "G:\intern\whole cervix
model\pilot\Spectra_beta\11EPB&&sub&i.._spectra_orig_iscorr_Sequence_1.txt"
expandtabs lrecl = 100000;
  input point b1-b4 rf_1-rf_58 b5-b72 f1_1-f1_58 b73-b77 f3_1-f3_40;

  array rf rf_1-rf_58; array f1 f1_1-f1_58; array f3 f3_1-f3_40;
  %let t1 = 29; %let t2 = 29; %let t4 = 20;
  %let t = %eval(&t1 + &t2 + &t4);

  %spacingselfnorm;
  sub_id = "&&sub&i";
run;

data pointcat;
  infile "G:\intern\whole cervix
model\pilot\2filtercombo_beta\11EPB&&sub&i.._excl_&extype._sequence_1.txt"
expandtabs;
  input point reject;
run;

data org; merge org pointcat; by point; run;

%meanpro(datain = org, dataout = m&i);

%end;

```

```

data model; merge demo %mf;
    by sub_id;
run;

data &dataout; set model;
    CIN31 = (whole1 = 3.5);
    CIN32 = (whole1 >= 3.2);
    high = (whole1 >= 3);
    highlow = (whole1 >= 2);
    low = whole1 in (2 2.5);
    nandb = whole1 in (0 1);
    nc = whole1 = 1;
    normal = whole1 = 0;
run;

%mend;

%macro mf;
    %do j = 1 %to &nsub;
        m&j
    %end;
%mend;

%macro meanpro(datain = , dataout = );

proc means data = &datain noprint;
    var rnrf_1-rnrf_&t1 rnf1_1-rnf1_&t2 rnf3_1-rnf3_&t4 ;
    output out = &dataout

    p10 = p10ra1-p10ra&t
    p25 = p25ra1-p25ra&t
    p50 = p50ra1-p50ra&t
    p75 = p75ra1-p75ra&t
    p90 = p90ra1-p90ra&t;
    where reject in (&pointselect);
    by sub_id;

run;

%mend;

```



```
%readdata( pointselect = 0, exctype = 2filtercombo, dataout = polit_beta1);
```

```
libname After 'G:\intern\whole cervix model\sas data';
```

```
libname Dallas 'G:\intern\whole cervix model\sas data\dallas';
```

```
libname comb 'G:\intern\whole cervix model\sas data\comb';
```

```
option nonotes;
```

```
options nonumber nodate;
```

```
data pilotalpha;
```

```
  set after.politalpha_mixratio;
```

```
  keep subject preferredpap whole1 p10ra1-p10ra78 p25ra1-p25ra78 p50ra1-p50ra78  
p75ra1-p75ra78 p90ra1-p90ra78 r1-r11 m1-m78;
```

```
run;
```

```
data pilotbeta1;
```

```
  set after.politbeta1_mixratio;
```

```
  length sub_id $10;
```

```
  machine='B1';
```

```
  sub_id=machine||subject;
```

```
  keep sub_id preferredpap whole1 p10ra1-p10ra78 p25ra1-p25ra78 p50ra1-p50ra78  
p75ra1-p75ra78 p90ra1-p90ra78 r1-r11 m1-m78;
```

```
run;
```

```
data dallas2;
```

```
  set dallas.dallas2_10remove_mixratio;
```

```
  keep sub_id subject priorpap whole1 p10ra1-p10ra78 p25ra1-p25ra78 p50ra1-p50ra78  
p75ra1-p75ra78 p90ra1-p90ra78 m1-m78 r1-r11;
```

```
  rename priorpap=preferredpap sub_id=subject;
```

```
run ;
```

```
data comb.comb1;
```

```
  length subject $10.;
```

```
  merge dallas2 pilotalpha;
```

```
  by subject;
```

```
run;
```

```
data comb.comb2;
```

```
  merge pilotbeta1;
```

```
  by sub_id;
```

```
run;
```

APPENDIX VII: SAS CODE FOR T-TEST, WILCOXON TEST

```
/*****This is program to conduct ttest for 15 single variables and 78 mixed
varialbes****/
```

```
libname After 'G:\intern\whole cervix model\sas data';
```

```
data ttest;
set after.diffpt;
if whole1 not in (2 2.5);
if whole1 >= 3 then group=1; else group=2;
run;
```

```
%macro ttest1;
```

```
%do i=1 %to 78;
ods listing close;
ods trace on;
ods output Stat.TTest.TTests=m&i;
```

```
proc ttest data=ttest;
class group;
var m&i;
run;
%end;
```

```
%mend;
```

```
%ttest1;
```

```
data result;
set %mj1;
if method='Satterthwaite';
run;
```

```
%macro mj1;
%do j=1 %to 78;
m&j
%end;
```

```

%mend;

data result;
  length variable $6.0;
  set %mj1;
  if method='Satterthwaite';
run;

proc sort data=result;
  by probt;
run;

/*****This is program to conduct ttest for model2.3 and 78 mixed variables*****/

data ttest;
  set after.clean510_ratio;
  if whole1 not in (2 2.5);
  if whole1 >= 3 then group=1; else group=2;
run;

ods listing close;
ods trace on;
ods output Stat.TTest.TTests=allvar;

proc ttest data=ttest;
  class group;
  var p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-p75ra58 r1-r11;
run;

data result2;
  length variable $8.0;
  set allvar result;
  if method='Satterthwaite';
run;

proc sort data=result2;
  by probt;
run;

/*****wilcoxon test*****/

```

```

options nonotes nodate;
libname after 'G:\intern\whole cervix model\sas data';

data cin1out; set after.clean510_dmratio; if whole1 not in (2 2.5); whole = (whole1 > 2);
run;

proc npar1way wilcoxon data=cin1out noprint;
  class whole;
  var p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57 p75ra58 r1-r11
  dmr1-dmr18 d1-d8;
  output out=all wilcoxon;
run;

```

APPENDIX VIII: SAS CODE FOR GENERATING COEFFICIENTS OF ALL WHOLE CERVIX MODEL

```
/*This is a program to generate coefficients for all models*/
```

```
libname after 'G:\intern\whole cervix model\sas data';
```

```
/*model 1.0*/
```

```
data cin1out; set after.p25_80var; if whole1 not in (2 2.5); whole = (whole1 >=3); run;
```

```
proc pls data = cin1out ;
    model high = p25ra1-p25ra80/solution;
run;
```

```
/*model1.01*/
```

```
data all; set After.p25_80var; whole=int(whole1); run;
```

```
proc pls data = all ;
    model whole = p25ra1-p25ra80/solution;
run;
```

```
/*model1.02 */
```

```
data cin1out; set After.clean510; if whole1 not in (2 2.5); whole = (whole1 >=3); run;
```

```
proc pls data = cin1out noprint;
    model high = p25ra1-p25ra58 p25ra85-p25ra104/solution;
run;
```

```
/*model1.03*/
```

```
data all; set After.clean522; whole=int(whole1); run;
```

```
proc pls data = all ;
    model whole = p25ra1-p25ra58 p25ra85-p25ra104/solution;
    output out = fan2 predicted=fan2;
run;
```

```
/*helen's 15 var model*/
```

```
data cin1out; set After.clean510; if whole1 not in (2 2.5); whole = (whole1 >=3); run;
```

```

proc pls data = cin1out noprint;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58/solution;
    output out = var15 predicted = var15;
run;

```

```

/*helen's 15+ratio var model*****Model 2.3*****/
data cin1out; set After.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;

```

```

proc pls data = cin1out noprint;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 r1-r11/solution;
run;

```

```

/*mixed percentile model*/
data cin1out; set After.clean510; if whole1 not in (2 2.5); whole = (whole1 >=3); run;

```

```

proc pls data = cin1out noprint;
    model high = p25ra1-p25ra19 p25ra30-p25ra38 p25ra85-p25ra94 p75ra20-
p75ra29 p75ra39-p75ra58 p75ra95-p75ra104/solution;
    output out=mix1 predicted = mix1;
run;

```

```

/*mixed percentile mode2*/

```

```

data cin1out; set After.clean510; if whole1 not in (2 2.5); whole = (whole1 >=3); run;

```

```

proc pls data = cin1out noprint;
    model high = p25ra1-p25ra19 p25ra30-p25ra38 p25ra85-p25ra94 p90ra20-
p90ra29 p90ra39-p90ra58 p90ra95-p90ra104/solution;
    output out=mix2 predicted = mix2;
run;

```

```

/*chenghong's 1.5*/

```

```

data cin1out; set after.diffpt; if whole1 not in (2 2.5); whole = (whole1 >=3); run;
proc pls data = cin1out noprint;
    model whole = p25ra1-p25ra17 p25ra22-p25ra35 p25ra39-p25ra58 p25ra85-
p25ra92 p25ra95-p25ra104/solution;
    output out = ch1_5 predicted = ch1_5;
run;

```

```
/*chenghong's 1.9*/
```

```
data cin1out; set after.diffpt; if whole1 not in (2 2.5); whole = (whole1 >=3); run;
proc pls data = cin1out;
    model whole = p25ra8-p25ra19 p25ra22-p25ra35 p25ra39-p25ra58 p25ra85-
p25ra104 m1-m12 m18-m28 m31 m32/solution;
    output out = ch1_9 predicted = ch1_9;
run;
```

```
/*510 no cin1 model output*/
```

```
data fan2;
    set fan2;
    if whole1 not in (2 2.5);
run;
```

```
data total;
    merge fan2 var15 ch1_5 ch1_9 mix1 mix2;
    by sub_id;
    keep sub_id preferredpap whole1 fan2 var15 ch1_5 ch1_9 mix1 mix2;
    if fan2=. then delete;
run;
```

```
/******Model 2.3 with CIN1 cases in******/
```

```
data all; set After.clean510_ratio; select (whole1);
    when (0) high=0;
    when (1) high=1;
    when (2) high=2;
    when (2.5) high=3;
    when (3,3.2,3.5) high=4;
end;
run;

proc pls data = all;
    model high = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 r1-r11/solution;
    output out = model2_3_all predicted = pred;
run;
```

```
data output;
    set model2_3_all;
```

```

keep sub_id whole1 preferredpap pred;
run;

/*****10 folder cv on Model 2.3*****/

data cin1out; set After.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;

proc pls data = cin1out cv=split(10) noprint;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 r1-r11/solution;
run;

/*****Model 2.3 + pap +Mars*****/

data cin1out;
set After.clean510_ratio;
if whole1 not in (2 2.5); whole = (whole1 >=3);
    if preferredpap eq 3 or preferredpap eq 4 then
        BF1 = 1;
    else
        BF1 = 0;

    if (preferredpap eq 0 or preferredpap eq 1 or preferredpap eq 3) then
        BF3 = 1;
    else
        BF3 = 0;
run;

proc pls data = cin1out;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 r1-r11 preferredpap BF1 BF3/solution;
run;

/*****model 2.43 new: model 2.3 train by 451 data (apply 15-exclude
rule to 510 data)*****/
data cin1out; set After.retrain510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;

proc pls data = cin1out noprint;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-

```



```
p75ra58 r1-r11/solution;
run;
```

```
/******model 2.44: 15 single var + david 18 ratio + 8 difference
var*****/
data cin1out; set after.clean510_dmratio; if whole1 not in (2 2.5); whole = (whole1
>=3); run;
```

```
proc pls data = cin1out;
    model whole =p25ra1-p25ra4 p25ra30-p25ra32 p75ra25-p75ra29 dmr1-dmr3
dmr5-dmr6 dmr9 dmr11 dmr14-dmr15 d1 d3 d4 d7 / solution;
run;
```

```
/******model 2.45: min/max ratio variables*****/
data cin1out; set after.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;
```

```
proc pls data = cin1out;
    model whole = p10m1 p25m1 p25m2 p50m1 p75m1 p75m2 p90m1 p10_75m1
p10_75m2 p10_75m3 p10_75m4 p10_90m1 p10_90m2 p10_90m3 p25_75m1
p25_75m2 p25_75m3 p25_75m4 p25_75m5 p25_90m1 p25_90m2 p25_90m3/solution;
run;
/******model 2.46: 15 single var + 22 min/max ratio variables*****/
data cin1out; set after.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;
```

```
proc pls data = cin1out;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 p10m1 p25m1 p25m2 p50m1 p75m1 p75m2 p90m1 p10_75m1 p10_75m2
p10_75m3 p10_75m4 p10_90m1 p10_90m2 p10_90m3 p25_75m1 p25_75m2
p25_75m3 p25_75m4 p25_75m5 p25_90m1 p25_90m2 p25_90m3/solution;
run;
```

```
/******model 2.47: reduce 2.45 to 11 vars*****/
data cin1out; set after.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;
```

```
proc pls data = cin1out;
    model whole = p10m1 p25m1 p25m2 p75m2 p90m1 p10_75m2 p10_90m1
p25_75m2 p25_75m4 p25_75m5 p25_90m3/solution;
run;
```

```

/*****model 2.48: 15 single var + 11 min/max*****/

```

```

data cin1out; set after.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;

```

```

proc pls data = cin1out;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 p10m1 p25m1 p25m2 p75m2 p90m1 p10_75m2 p10_90m1 p25_75m2
p25_75m4 p25_75m5 p25_90m3/solution;
run;

```

```

/*****model 2.46+pap: 15 single var + 22 min/max ratio+pap
variables*****/

```

```

data cin1out; set after.clean510_ratio; if whole1 not in (2 2.5); whole = (whole1 >=3);
run;

```

```

proc pls data = cin1out;
    model whole = p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-
p75ra58 p10m1 p25m1 p25m2 p50m1 p75m1 p75m2 p90m1 p10_75m1 p10_75m2
p10_75m3 p10_75m4 p10_90m1 p10_90m2 p10_90m3 p25_75m1 p25_75m2
p25_75m3 p25_75m4 p25_75m5 p25_90m1 p25_90m2 p25_90m3
preferredpap/solution;
run;

```

APPENDIX IX: SAS CODE FOR SENSITIVITY AND SPECIFICITY CALCULATION

libname After 'G:\intern\whole cervix model\sas data';

libname Dallas 'G:\intern\whole cervix model\sas data\dallas';

%macro sspec(datain=, applydata=, var1=, var2=, scale=);

data cin1out; set &datain; if whole1 not in (2 2.5); whole = (whole1 > 2); run;

data apply_cin1out; set &applydata; if whole1 not in (2 2.5); whole = (whole1 > 2); run;

ods listing close;

ods html close;

ods trace off;

ods output ParameterEstimates=solution;

proc pls data = cin1out;

 model high = &var1/solution;

run;

data solution(keep=high rename=(high=coeff));

 set solution;

run;

data response (KEEP= whole);

 set apply_cin1out;

run;

DATA INPUTS (KEEP= &var2);

 set apply_cin1out;

RUN;

option notes;

ods listing;

PROC IML;

START Sens_Spec;

USE INPUTS;

```

READ ALL VAR _ALL_ into X;
CLOSE INPUTS;

USE response;
READ ALL VAR _ALL_ into whole;
CLOSE response;

USE SOLUTION;
READ ALL VAR _ALL_ into coefficients;
CLOSE SOLUTION;

Z=NROW(coefficients);

M2= coefficients[2:Z,1:1];

/* Calculate all the response variables */

Y2= coefficients[1,1] + X* M2;
N = NROW(Y2);

O=J(1000,4,0);

DO J=1 TO 1000 by 1;

    CUTOFF= &scale + J * 0.001;
    R = J(N, 1, CUTOFF);

    Diff = Y2 - R;

    ALL = WHOLE[LOC(WHOLE=1),];
    COUNT_ALL = NROW(ALL);

    DIF = DIFF[LOC(WHOLE=1),];
    indices = LOC(DIF>0);

    if nrow(indices) > 0 then
        do;
            TEST_P = DIF[LOC(DIF>0),];

```

```

        COUNT_P = NROW(TEST_P);
        SENS = COUNT_P/COUNT_ALL;
    end;
else SENS = 0;

/* FIND SPECIFICITIES */

    ALL = WHOLE[LOC(WHOLE=0),];
    COUNT_ALL = NROW(ALL);

    DIF = DIFF[LOC(WHOLE=0),];

    indices = LOC(DIF<=0);

    if nrow(indices) > 0 then
        do;
            TEST_N = DIF[LOC(DIF<=0),];
            COUNT_N = NROW(TEST_N);
            SPEC = COUNT_N/COUNT_ALL;
        end;
    else SPEC = 0;

    /* PUT CUTOFF SENS SPEC INTO MATRIX O FOR OUTPUT */
    O[J,1]=CUTOFF;
    O[J,2]=SENS;
    O[J,3]=1-SPEC;
    O[J,4]=SPEC;

end;

CREATE SSPEC FROM O;
APPEND FROM O;

FINISH;
RUN Sens_Spec;
quit iml;
run;

data mark (drop=col3 rename=(col1=cutoff col2=sens col4=specs));

```

```
set SSPEC;
run;
```

```
%mend;
```

```
/*Fan's model1*/
```

```
%sspec(datain=After.clean522, applydata=After.clean522, var=p25ra1-p25ra58  
p25ra85-p25ra104, scale=0);
```

```
/*15var+ratio*/
```

```
%sspec(datain=After.clean522_ratio, applydata=After.clean522_ratio, var1=p25ra1-  
p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-p75ra58 r1-r11,  
var2=p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra31 r1-r11, scale=-0.5);
```

```
/*chenghong's 1.5*/
```

```
%sspec(datain=After.diffpt, applydata=After.diffpt, var= p25ra1-p25ra17 p25ra22-  
p25ra35 p25ra39-p25ra58 p25ra85-p25ra92 p25ra95-p25ra104  
m1-m13 m26-m29, scale=-0.5);
```

```
/*chenghong's 1.9*/
```

```
%sspec(datain=After.diffpt, applydata=After.diffpt, var=p25ra8-p25ra19 p25ra22-  
p25ra35 p25ra39-p25ra58 p25ra85-p25ra104  
m1-m12 m18-m28 m31 m32, scale=0.02);
```

```
/*helen's 15var on pilot alpha*/
```

```
%sspec(datain=After.clean510, applydata=After.politalpha, var1=p25ra1-p25ra5  
p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-p75ra58,  
var2=p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-p75ra58, scale=-0.5);
```

```
/*helen's 15var+ratio on pilot alpha*/
```

```
%sspec(datain=After.clean510_ratio, applydata=After.politalpha, var1=p25ra1-p25ra5  
p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-p75ra58 r1-r11,  
var2=p25ra1-p25ra5 p25ra30-p25ra32 p75ra25-p75ra29 p75ra57-p75ra58 r1-r11,  
scale=-0.5);
```