RISK-FACTOR BASED DIAGNOSIS FOR CHRONIC PERIODONTITIS USING MACHINE LEARNING MODELS

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Abstract

Chronic periodontitis is one of the most common oral disease in world. The prevalence is 11.2% globally, 15-20% in Asians and 26% in Thai adults. Symptoms are negligible until it is too late and results in loss of tooth and quality of life. To diagnose chronic periodontitis, a chair side examination by a dentist or an oral hygienist is required to measure at six sites of the gingival sulcus for every available tooth. This process is time and resource consuming, so a predictive model to identify the risk of having chronic periodontitis in a person can be of assistance.

Currently, several literatures have applied logistic regression, using relevant demographic or risk behaviors as predictors. While logistic regression models are simple to interpret or to apply, their performance can be less optimal depending on features selection and engineering. Machine learning models recently has been increasingly applied in medical and health related fields for their more complex yet powerful performances.

With our study, we apply machine learning models such as mixed effects logistic regression, recurrent neural networks, and mixed effects support vector machine for diagnosis of chronic periodontitis. Using Electric Generation Authority of Thailand (EGAT) cohort 2nd survey, the models are trained upon longitudinal data. We observe that mixed effects logistic regression model (90.5% accuracy) performs better than conventional logistic regression models as well as other machine learning models (70.0% accuracy for RNN and 72.7% for MESVM) even after hyperparameter optimizations. Trained models can be applicable in situations such as screening in community and public health missions as well as electronic health records (EHRs).

KEY WORDS: SEVERE CHRONIC PERIODONTITS / MIXED EFFECTS LOGISTIC REGRESSION / RECURRENT NEURAL NETWORKS / MIXED EFFECTS SUPPORT VECTOR MACHINE

82 pages

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CHAPTER I
BACKGROUND & RATIONALE

1.1. Background and Rationale

Periodontitis is one of the most common oral diseases and causes of tooth loss in adults.[1] It is the world's 6th most prevalent oral disease, affected around 743 million people worldwide. The prevalence was at 11.2% globally, and 15.0-20.0% of Asians.[2] According to 8th Thailand national oral health survey (2017), the prevalence of periodontitis in Thai adults is 26%, and for the elderly, it is 36%. Periodontitis is a complex inflammatory disease that leads to the destruction of the supporting structures around the tooth, resulting in the loosening of the teeth and eventual tooth loss.[3] This leads to decreased occlusal ability, digestive ability and effectively the patient's quality of life.

In addition to oral manifestations, previous studies found an association of chronic periodontitis with systemic diseases and conditions.[4] The association between atherosclerotic vascular diseases (ASVD) and periodontitis has been established.[5] Joint of European Federation of Periodontology and American Academy of Periodontology (EFP/AAP) Workshop on Periodontitis and Systemic Diseases reported that there is consistent and strong epidemiologic evidence that periodontitis increased risk for future CVD.[6] Chronic periodontitis and diabetes mellitus have bidirectional relationships and it has also been reported that periodontitis and diabetes had significant direct and indirect effects mediated via each other on chronic kidney disease (CKD) incidence.[7] Relationships between periodontitis and other systemic disease, i.e., chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), Alzheimer's disease and erectile dysfunction, also have been reported.[8]

Severe chronic periodontitis is characterized by loss in alveolar bone height. To be diagnosed, radiographs are required. Diagnosis of less severe periodontitis requires a dentist or dental hygienist to manually measure the distance between the cementoenamel junction and the base of the periodontal pocket for all present teeth.

Such measure is gold-standard, but time and resource-consuming in multiple numbers of cases, for instance screening a community. Such a scenario can be more efficiently addressed by the presence of a risk prediction system, removing the need for oral examinations.

Risk scoring systems such as periodontal risk calculator (PRC)[9, 10] and periodontal risk assessment (PRA)[11] has been proposed by Page *et al.* and Lang *et al.* respectively. PRC scores the patient with a risk score between 1-5 (1 being low risk and 5 being high) as well as a disease state score between 1-100. It uses 9 features to score, including the radiographic bone height. As seen in Figure 1.1., PRA categorizes the patient into three distinct classes, namely low risk individual, moderate risk individual and high-risk individual. While it uses 6 parameters to score, its parameters include clinical measurements such as presence of bleeding on probing and residual pockets. While the measures enable the process to be more objective, inclusion of clinical parameters restricts the applicability of the system without the presence of dental professionals.

By excluding oral examinations, other parameters such as demographics and risk behaviors are used to assess the risk. Risk prediction models are typically developed by statistical modelling and commonly applied are multivariate logistic regression models. While logistic regression models are simple and efficient, they rely on proper selection of the features, which means feature engineering is vital for the model. A typical approach is to use a limited number of known risk factors and domain expert selected features. Supervised nature of the approach misses the opportunity to discover novel patterns, and limited model's performance leads to be suboptimal.

In recent years, machine learning emerges as an alternative for risk prediction. Machine learning algorithms can have features needed for prediction learned from the available dataset.[12] Machine learning models can learn with specified outcomes (supervised) or without specified outcomes (unsupervised) as well. While unsupervised models can be applied to detect the patterns in the data, supervised machine learning can be applied for both classification and regression tasks. A branch of machine learning called deep learning models are feature learning models, consisting of multiple layers of features, obtained by composing simple but nonlinear modules that each transform the feature at one layer (beginning from input layer) into a feature at a higher, slightly more abstract layer, resulting in improved prediction from data.[13, 14]

Over traditional statistical modeling, machine learning models can also improve the performance by applying hyperparameter optimization. Different data patterns require different sets of parameters, to minimize the loss of the classification model. For example, support vector machines can perform on non-linear relationships by applying soft margins, by allowing misclassifications or using kernels to make the classes linearly separable. Hyperparameters of deep learning models, such as activation functions, can be tuned to work with either linear or non-linear relationship between independent and dependent variables.

On the other hand, traditional statistical models have a descriptive model approach such as the relationship between the independent (age) and dependent (incidence of periodontitis) variables, hazard ratio of Cox regression and odd ratio of logistic regression. While this interpretability is preferable for clinical applications, machine learning models tend to have an algorithmic approach model, which performs better for prediction. High performance machine learning models such as deep learning and ensemble learning models are claimed to have "black box", due to their lack of interpretability. Artificial neural networks have complex network with interconnected nodes or neurons, either passing information to another neuron or not due to being deactivated. Both algorithms, feed forward and backward propagations are going back and forth for all training samples to optimize the model for minimal loss. While these intricate connections and processes lead the model towards higher performance, the relationship between the input (age) and the output (incidence of periodontitis) of the model can no longer be interpreted. For a pure diagnostical purposes, such a model might be less acceptable in a clinical environment. But by applying it in such a way that it can help screen the patients so that they can be informed to emphasize their effort on oral hygiene and dental visits, it can be more of a practical purpose. Our challenge here is to see if the predictive performance of machine learning models can be superior or desirable enough for the exchange with the interpretability of the model.

1.2. Research Question

Do machine learning models have better predictive performance than statistical models in diagnosis of chronic periodontitis?

1.3. Research Objectives

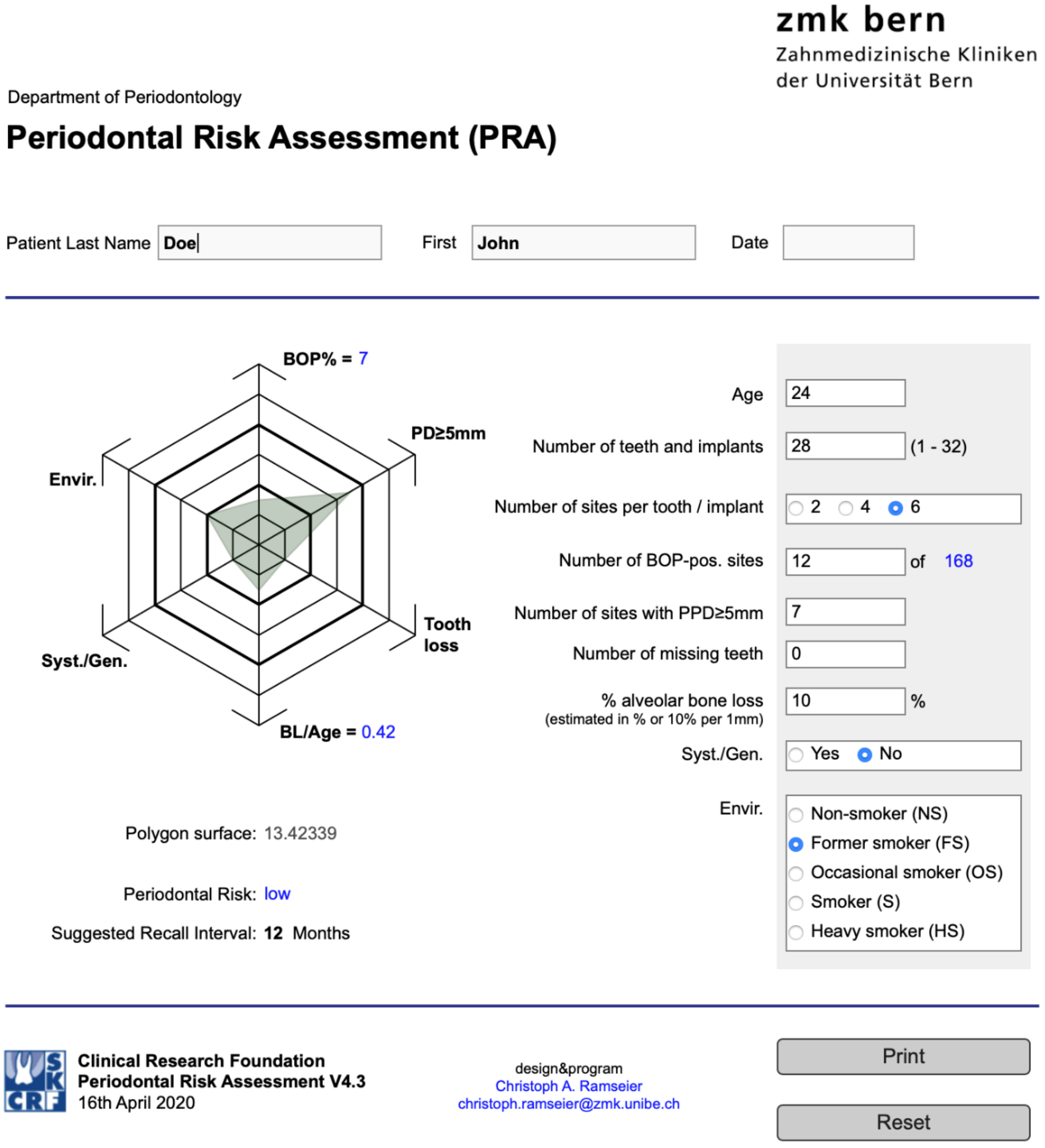
The objectives of the study are -

1. Develop statistical and machine learning predictive models on longitudinal data to diagnose severe chronic periodontitis.
2. Compare the performance of the predictive models between statistical model and machine learning models on longitudinal data for diagnosis of severe chronic periodontitis.

1.4 Expected Benefits

By deploying a diagnostic model, the process of periodontitis screening in community, should be less time consuming. Longitudinal modelling allows the prediction of periodontitis incidence using large longitudinal datasets, such as electronic health records and surveys.

Figure 1.1. Periodontal Risk Assessment by Lang and Tonetti (2003)[15]



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Department of Periodontology

Periodontal Risk Assessment (PRA)

Patient Last Name	Doe	First	John	Date	

Age	24	
Number of teeth and implants	28	(1 - 32)
Number of sites per tooth / implant	○ 2 ○ 4 ● 6	
Number of BOP-pos. sites	12	of 168
Number of sites with PPD≥5mm	7	
Number of missing teeth	0	
% alveolar bone loss (estimated in % or 10% per 1mm)	10	%
Syst./Gen.	○ Yes ● No	
Envir.	○ Non-smoker (NS) ● Former smoker (FS) ○ Occasional smoker (OS) ○ Smoker (S) ○ Heavy smoker (HS)	

Polygon surface: 13.42339

Periodontal Risk: low

Suggested Recall Interval: **12** Months

Clinical Research Foundation
Periodontal Risk Assessment V4.3
16th April 2020

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CHAPTER II
LITERATURE REVIEW

2.1. Epidemiology of Periodontitis

Periodontitis is the inflammation of periodontium, a disease involving the structure surrounding the tooth and it is considered one of the most common disease in humanity. From the 2009 and 2010 National Health and Nutrition Examination Survey (NHANES), over 47% of the U.S. adults who aged 30 years and older (64.7 million people), representing, had some form of periodontitis. And for adults 65 years and older, 70.1% have periodontal disease.[16]

While the bacterial plaque is considered to be the initiator of the condition, it always is present in the oral cavity as the dental plaque, in both healthy and compromised patients. It forms from the acquired pellicle, which is a layer of saliva mainly consisting of glycoprotein, and it forms shortly after tooth brushing or oral hygiene methods. It helps with the adhesion of the bacteria to the tooth and the mass of bacteria proliferates in the dental plaque, forming bacterial or microbial plaque. With insufficient or improper oral hygiene practices, the plaque builds up to become the tartar or calculus, which furthers help the adhesion of the bacterial plaque.

Fortunately, with effective immune system, the periodontal diseases will not develop as long as the balance between the microbial and host response is maintained. This balance is broken either by the hyper-responsiveness or the high virulence of the bacteria, or by the decrease in host immune by systemic factors. Then the periodontium becomes inflamed and subsequent destruction of alveolar bone happens. But during the initial stages of the inflammation, the symptoms are less noticeable, so the process is encouraged by the patient’s negligence of oral hygiene. The disease progresses and the patient may suffer from gingival bleeding with little provocation, gum swelling, dull pain, gingival abscess, and tooth mobility. This leads to tooth loss, decreasing the occlusal ability, digestive ability and, effectively, the patient’s quality of life.[17]

2.2. Classification of Periodontitis

Periodontitis is characterized by loss in alveolar bone height, so it is inferred the loss in attachment of junctional epithelium, which is the clinical attachment level. The severity of periodontitis is considered by the increasing measurement of clinical attachment level. Clinical attachment level is measured from the cementoenamel junction to the junction epithelium (base of the periodontal pocket). American Academy of Periodontology (1994) classifies chronic periodontitis as slight (1-2 mm), moderate (3-4 mm), or severe (≥ 5 mm).[18] Although the AAP 1999 definition was widely accepted in clinical circumstances, it was not uniformly adopted by periodontal researches.

According to a systematic review of a common definition for periodontitis[7], while most of the studies relies on clinical examination, selected periodontal parameters are quite different. It was found that several parameters, such as clinical attachment level, periodontal pocket depth and bleeding on probing, are used separately or jointly to define periodontitis. Also, other measures, such as the cut-off points for the measurements and, the distribution of periodontally compromised teeth, are lacking in uniformity.

During the literature review, it is observed that Centers for Disease Control and Prevention - American Academy of Periodontology (CDC-AAP) classification for periodontitis is mostly applied, as seen in Figure 2.1. However, it is also observed that self-determined criteria to classify periodontitis are applied nearly as much, signifying the lack of uniformity in defining the condition. While World Health Organization's CPI-TN (Community Periodontal Index for Treatment Needs) is applied as well, it should be noticed that the index tries to identify the level of treatment needed for the patient explicitly instead of diagnosing the condition. Consensus report of 5th European Workshop in Periodontology proposes a new criterion for identifying periodontitis by staging. The staging procedure takes three criteria in consideration: greatest decrease in clinical attachment level, radiographic bone loss and tooth loss due to periodontitis.

Due to lack of uniformity, the Centre for Disease Control and Prevention and American Academy of Periodontology proposed a new standard case definitions for surveillance of periodontitis and the criteria are stated in Table 2.1.[16, 19] Several literatures have used CDC-AAP definitions.[20-25]

2.3. Risk Factors of Periodontitis

Periodontitis is of complex etiological causes. While bacterial plaque is considered to be the initiator of the condition, by acting as the biofilm, there are other local factors such as mal-occlusion, dental restorations and oral prostheses, that encourage the formation of dental plaque. Also other systematic factors, such as mal-nutrition and poorly controlled diabetes mellitus increase one's susceptibility to periodontal disease. Oral habits such as smoking and betel quid chewing habits can increase one's risk while oral hygiene habits such as frequency of tooth brushing[22, 24-28] and flossing[24, 29] removes the dental plaque so reducing the risk of microbial plaque maturing. Smoking is a well-established risk factor[22-36] and it is also reported that severity of radiographical bone loss is enhanced by betel/pan chewing.[27, 29, 32, 37, 38] The number of teeth[24, 25] and sometimes decayed, missing, and filled teeth index (DMFT)[22, 25] are also included as oral risk factors for chronic periodontitis. As shown in Figure. 2.2, other factors such as tooth mobility, number of teeth with bleeding, and number of teeth which are mostly applied oral risk factors. Demographic risk factors such as smoking, age and sex appear in Figure. 2.3.

Demographically, it is reported that the prevalence of periodontitis increases as one grows older.[21-24, 26-28, 32, 33, 35, 36, 39] Also, periodontitis has a higher prevalence in men (~57%) compared to women (~39%).[21-27, 32, 33, 35, 36, 40] However the paper also advices that different socioeconomic and behavioral factors between genders might have influenced, rather than the gender bias.[40] Income[22, 24-26] and education levels[21-25, 33, 35-37] are common features in predictive models. Also, family size[25, 27], body mass index[25, 26, 41], drinking habit[21, 27, 34], diabetes mellitus[24, 31, 32, 34-36] and hypertension[25, 32, 42] are also suggested.

Several literatures study association between a limited number of potential biomarkers and chronic periodontitis, as shown in Figure 2.4. As stated before, periodontitis is initiated by the microbial dental plaque and the host susceptibility for it. The presence of sub-gingival pathogens induces local inflammatory response and large number of leukocytes are exuded and migrated as the first line of defense. It is observed that the number of white blood cells (WBC) increases in patients with chronic periodontitis and the increased number of neutrophils and lymphocytes are statistically significant.[43] Immunoglobulin G, part of humoral immunity, is also observed to be increased. Immunoglobulin G3 serum levels discriminate well between chronic periodontitis and healthy patients.[44] While there is local inflammation at site of periodontitis, it is also studied that patients with chronic periodontitis have low grade systemic inflammation. Interleukin-6 is produced at site of inflammation and considered to be dumped into systemic circulation, increasing interleukin-6 levels. Interleukin-6 also induces hepatic synthesis of C-reactive protein. It is observed that there is association of chronic periodontitis with high Interleukin-6 levels and high C-reactive protein, measured by high sensitivity C-reactive protein test[45]. Inflammation also adversely affects the lipoprotein levels, being observed the lower high-density lipoproteins levels (HDL) and higher low-density lipoproteins levels (LDL) in patients with chronic periodontitis.[43]

2.4. Predictive modelling of periodontitis

As seen in Figure. 2.5 and Figure. 2.6, it is observed that logistic regression is mostly applied for predictive modelling. However, application of different criteria for labelling samples result in different performance of the same model[23, 25]. Also, different performance metrics applied by each study reduce comparability, as shown in Table 2.2.

Studies on prediction models try to compare between the performance between including different combination of features (demographical features, risk behavior data, oral features). For self-reportable models, questionnaires are used to collect the oral features instead of clinical examination. Eke et al. observes that including both demographic and oral features in the model performs better than only including demographic features. In addition to other features, Verhulst et al. also applies biomarker data of the saliva, resulting in higher and more balanced performance of the model among the reviewed models. However, while it performs better, identifying biomarkers from saliva such as protease and chitinase also consume resources. We need to balance our models between predictive power and required resource.

Nevertheless, the common goal of the majority of the studies is to diagnose periodontitis without clinical examination. By applying only self-reportable features such as demographics and risk behaviors, the resulted model can be applied with a rapid non-invasive screening tool. With our study, we aim to improve model performance with machine learning models and hyperparameter optimizations.

2.5. Predictive model development

2.5.1. Feature Selection

Feature selection, also known as variable selection, is a procedure of nominating a subset of relevant independent variables to apply as predictors in model construction. While several deep learning procedures are representative learning, where the irrelevant features are weighted less or none at all, the process reduces the dimension of the training dataset, subsequently computational resource and the training time requirements. It also reduces the risk of the model overfitting on the training dataset, allowing the models to have relatively low bias and high variance. Feature selection methods can be grouped into three categories:

1. Filter methods
2. Wrapper methods and
3. Embedded methods.

Filter methods select the variables regardless of the model, by testing for difference in variance or correlation/association between independent (age) and dependent (chronic periodontitis) variables. The selected variables are used as the predictors for the classification or regression model. These methods are considered to be robust against overfitting and have less computational time. However, since they consider one-to-one relationships, such methods tend to select redundant variables (weight and body mass index) by not accounting for interaction between variables. Chi-square tests and analysis of variance (ANOVA) tests are considered as filter methods.

Unlike filter methods, wrapper methods evaluate subsets of variables, allowing to detect the possible interactions. It has greedy approach, evaluating all possible combination of variables. Applying to a specific model, candidate variables are added one by one, or applied as a whole and removed one by one. On a chosen model fit criterion such as Akaike information criterion (AIC), the variables are chosen if their presence as predictor improves the fit of the model. However, the computational cost is high on datasets with many features. Also, this procedure requires a model to be tested on the fit for the dataset, therefore it is considered to have high chance of overfitting. Wrapper methods include stepwise regression methods such as forward selection and backward elimination.

Embedded methods are proposed to combine the advantages of two prior methods. These methods are included as part of a model training procedure. They calculate the importance of a feature in making prediction. Tree-based methods report the contributions of each feature while regularization methods such as LASSO and Ridge decreases the coefficients of the less relevant variables to reduce its contribution towards final prediction. Like filter methods, these methods are considered to be robust against overfitting, while they also consider the interaction between the features like wrapper methods.

Stepwise selection

Part of filter methods of feature selection, stepwise selection can be applied in different ways, such as forward selection or backward elimination. In forward selection, the initial model is built with one variable, adding one by one. Using a model fit criterion, the variable is selected if its inclusion gives the most statistically significant improvement of the fit. After selection of second variable, all the remaining variables are tested again as the candidate for the third variable. This procedure is repeated until including more variables do not improve the model.

In backward elimination, the initial model is built with all available variables, removing one after another. Here, the variable is eliminated if the absence of it gives the most statistically insignificant deterioration of the fit. This procedure repeated until removing more variables results in statistically significant deterioration. Combination of both prior methods, called bidirectional elimination, tests for both including and excluding the variable at each step.

Other than testing for fit of the model, p-value is the common statistical entry and exit criteria of the variables. Multivariate regression models are applied as the model and the threshold is set for including or excluding the variable. Unlike conventional statistically significant value of 0.05, 0.15 is the typical value used and the variables with less p-value are included in the model for current step. Similarly, variables with p-value more than 0.15 are excluded.

2.5.2. Feature Engineering

For majority of machine learning models, both the inputs and outputs of the model are required to be numerical variables. While discrete and continuous variables can be included as it is, data manipulation is necessary for categorical data as in Table 2.3 and 2.4. Binary classes, such as gender, are encoded into 0 and 1.

For multiclass variables, it is dependent on the type of categorical variable. For ordinal categorical variables, such as education level, socioeconomic level and income level, the variables are encoded by ordinal encoding, which transforms non-numerical labels into numerical labels while retaining the ordinal nature of the variable. For example, the raw data in Table 2.2. has "Education level" as a feature. So, during data preparation in Table 2.3., the categories are encoded as Primary School" as 0, "Middle School" as 1, "High School" as 2 and "bachelor's degree" as 3.

But nominal variables do not have ordinal nature to it so, variables, such as occupation, need to be encoded using one-hot-encoding. For instance, the variable "occupation" has classes "programmer", "doctor" and "engineer". When the variable "occupation" is one hot encoded, three new variables are created for each separate class. For a "doctor", the value for the variable "doctor" is 1 while the values for "programmer" and "engineer" are zeros. For target variables, it is necessary to encode depending on the type of models. For example, support vector machine requires the target values to be -1 and 1, while neural networks require 0 and 1. However, in our study, we apply support vector regressor within the mixed effects machine learning model instead of support vector classifier, therefore all targets are transformed as 0 and 1, and logistic transformation is applied afterwards.

2.5.3. Logistic Regression

Data Transformation

Logistic Regression requires both the inputs and outputs of the model to be numerical. So, for categorical data, feature transformation is required. For target variables, it is necessary to label the target variables' classes as [1] for positive class and [0] for negative class.

Methodology

Logistic regression is a statistical model, which applies logistic function (sigmoid function) to determine the binary outcome of the sample in its basic form, although there are other complex adaptations of logistic regression for other purposes. In contrast to linear regression where dependent variable is linearly related to independent variable, the log-odds (logarithm of odds) of event is a linear combination of independent variables in logistic regression. It can be univariate (single predictor) or multivariate (multiple predictors). Depending on the number of outputs, it can be binomial (binary outcome), multinomial (more than two possible outcomes) or ordinal (dependent variables have ordinal nature). Logistic regression is usually the model of choice for stepwise feature selection.

2.5.4. Mixed effects Logistic Regression

For training of a classification model, i.i.d assumption (independent, identically distributed) for the training dataset is made. Therefore, vanilla logistic regression cannot be applied for longitudinal datasets, where correlation between repeated measurements violates i.i.d. Mixed effect models are applied in such settings by considering as levels or hierarchy.

Mixed effect models, also called multilevel models, are statistical models considering both fixed and random effects. In biostatistical sense, fixed effects are population-average and random effects are subject-specific effects (also called latent variables, which are assumed to be unknown). Mixed effects models extend the capability of the regression model, by recognizing that individuals in population are heterogenous. In mixed effects models, each subject is allowed to have their own subject-specific intercept and/or slope. Mixed effects logistic regression, like vanilla models, can also be applied for classification tasks.

$$y_{ij} = X_{ij}b + Z_{ij}u$$

- where

y = target variable (logit)

X = fixed effects feature

b = coefficient of feature X

Zu = random effects variable describing latent variables

i = cluster

j = observation of i^{th} cluster

2.5.5. Support Vector Machine

Data Transformation

Support vector machines requires both the inputs and outputs of the model to be numerical. So, for categorical data, feature transformation is required. For target variables, it is necessary to label the target variables' classes as [1] for positive class and [-1] for negative class.

Methodology

Support vector machine is a type of supervised machine learning algorithm. Support vector machines work exclusively on binary classifications. While the two classes are separated with a decision boundary, such boundary can be drawn in thousands of ways as a few shown in Figure. 2.11. The function of support vector machine is to search the best separating line, called the hyperplane, which leaves the maximum margin width from both classes. Support vector machine accomplishes this by considering only the support vectors, which are on the margin of the hyperplane, instead of considering all the data points, as shown in Figure 2.12. Support vectors are the data points that are closest to the other class in hard margins. For the output of the model, the hyperplane is considered zero and the support vectors are considered [1] and [-1]. Theoretically, a data point can be on the zero plane, which makes it neither in the positive nor the negative class. Practically, only negative values are considered negative [-1] class and other values such as zero and the positive values are considered positive [1] class. Support vector machine performs optimally in linearly separable data.

However, real-life data are rarely linearly separable, due to outliers or noise data. As seen in Figure 2.13., soft margins are applied by considering other data points as support vectors allowing some data points to be on the other side of the hyperplane (misclassified) instead of using a hard margin which has low variance and high bias by overfitting to the training data. Alternatively, using kernel functions increases the dimension of the dataset. For example, in Figure. 2.14., the two-dimensional dataset becomes three dimensions, which allows better separability by linear decision plane.

And, since support vector machine separates using a linear plane, they are limited for binary classifications. However, several workarounds such as one-vs-all approach enables it to be applicable for multiclass classifications as well.

2.5.6. Support Vector Regression

Methodology

Support vector regression is an adaptation of support vector machine applying the concept of linear regressions. In ordinary least squared regression, best fitted regression line is created from the data by minimizing the summation of squared error as shown in Figure. 2.15.

$$y'_i = wx_i + b$$

- where

y'_i = regressed value for data point i

x_i = feature of data point i

w = weight or coefficient of feature x

b = bias of the regression line

$$error_i = y_i - y'_i$$

$$min \sum_{i=1}^{n} ||error_i||^2$$

- where

y_i = actual value of data point i

$error_i$ = error of the regressor for data point i

In real life, the presence of noise data or outliers affect the regression line and by extension the error rate. In support vector regression[46], support vectors are determined to set the margin as in conventional support vector machine. Error is calculated only from the data points inside the margin therefore ignoring the outliers. The width of the margin must be controlled since a margin too wide will consider all data points with the model becoming influenced by noise and overfitted. On the other hand, small margin would not be able to learn from the data with the regression line becoming underfitted.

Therefore, for the support vector regression model, we would like to consider as much data points as we can while not becoming overfitted. As in Figure

2.16., the regression line (the hyperplane) and the margins are parallel, so the perpendicular distance between two parallel lines is widened as much as possible.

$$d = \frac{|y' - y|}{\sqrt{w^2 + 1}}$$

- where

d = perpendicular distance between the hyperplane and the margins

y = actual value of the support vector on the margin

y' = regressed value for the support vector

Since the perpendicular distance (d) is inversely proportional to weight (w), w is reduced instead of error as in linear regression. However, as d increases, more data points will be considered so risking overfitting. Therefore, the error for each data point is constrained under the amount of error we are willing to accept called epsilon (ϵ) and it is a hyperparameter.

$$min \sum ||w||^2$$

$$||error_i|| \leq \epsilon$$

Applying the concept of margins from conventional support vector machines, soft margins are applied in regression by considering some more data points outside of the acceptable error (ϵ) as shown in Figure 2.17. By increasing the constraint, we let the model consider more data points called slacks. But since we do not want the model to consider too much data points, we penalize the model based on how much slacks we are giving ourselves.

$$min \sum ||w||^2 + C\frac{1}{n}\sum_{i=1}^{n} ||\xi_i||$$

$$||error_i|| \leq \epsilon + ||\xi_i||$$

- where

ξ = the amount of slack allowed for the model

And C is also a hyperparameter how much we want to penalize for allowing slacks. Because we penalize only on the data points outside the epsilon zone, it is also known as epsilon insensitive loss. We cannot control how much slacks (may be too few or too many) but the amount of error we are willing to accept is set. This type of support vector regression is called Epsilon regression and it is shown in Figure. 2.16. In another type of support vector regression called nu-regression[47], epsilon (ϵ) is not a hyperparameter but part of the penalty term. Here, ν (nu) is a hyperparameter which determines control the amount of slacks left outside the margin and the value lies between 0 and 1. Since increasing ϵ reduce ξ and the penalty on ϵ is reduced by ν value, ϵ is increased rather than ξ resulting in less slacks.

$$min \sum ||w||^2 + C(\nu\epsilon + \frac{1}{n}\sum_{i=1}^{n} ||\xi_i||)$$

2.5.7. Mixed Effects Machine Learning

As stated before, linear mixed models consider random effects different between each cluster.

$$y = Xb + Zu$$

Xb is the population average value and it accounts for within-cluster variation. Zu is the subject-specific value and it accounts for between-cluster variation. On the other hand, non-linear mixed models estimate the relationship between features and the target variable as non-linear, and machine learning models can be applied for such relationship.

$$y_{ij} = f(X_{ij}) + Z_{ij}u$$

- where

$f(.)$ = non-linear function

Classical machine learning classification and regression algorithms do not generate high quality models on correlated data so mixed effects machine learning models[48, 49] are developed as an extension of traditional machine learning methods. They are longitudinal/clustered supervised machine learning, as that of learning the two components of a non-linear mixed model separately through an iterative expectation maximization-like algorithm, in which the fixed-effect component is estimated using machine learning methods and the random-effect component is estimated using linear mixed model. By including random effects within the model, Mixed effects machine learning is resistant to variabilities introduced by correlated data. Mixed effects machine learning can take advantage of dependencies between the observations to generate more robust and accurate models. It is to be noted that machine learning model applied here should be a regression model.

Expectation-Maximization Algorithm

It is an iterative algorithm as shown I Figure 2.18.

Step 1. Given a set of incomplete data, consider a set of starting parameters.

Step 2. Expectation step (E — step): Using the observed available data of the dataset, estimate (guess) the values of the missing data.

Step 3. Maximization step (M — step): Complete data generated after the expectation (E) step is used in order to update the parameters.

Step 4. Repeat step 2 and step 3 until convergence.

Regression

Initial random effects are set as zero. Since we consider the target value to be the summation of fixed and random effects, fixed effects are calculated by subtracting random effects from the target and they are trained as the modified target value for the machine learning regressor. After training the machine learning model, the model is used to predict the value for each observation. The predicted values are subtracted from the target and the residuals are estimated to be the random effects used to train the linear mixed model. By the trained linear mixed model, new random effects are re-estimated. The stopping criterion is set and until it is met, the fixed effects are calculated again by redacting random effects. Machine learning model is retrained, and the loop is continued as shown in Figure 2.19.

Stopping criteria is set in terms of maximum iterations and absolute change in likelihood of the mixed model. Recommended setting for maximum iterations value is not stated in the literature. Convergence in term of likelihood is set similar to statistical models as well where the iterations are proceeded until the change of the estimated parameter vector is negligible with respect to the accuracy of the estimates.[50] In STATA, tolerance for change is 1e-6 and maximum iteration is 300. In R(lme4), tolerance for change is 1e-6 and maximum iteration is 50.

When the model is applied, both the trained machine learning regressor and mixed model are used to predict the values and they are summed. For samples not in the training data, the random effects are unknown therefore zero is used, which means they are predicted in terms of fixed effects only as shown in Figure 2.20.

Classification

For classification, the target value must be transformed into numerical or logit value manually since we are applying two regressor models. All initial processes are similar with regression framework, until the convergence criteria are met. This is considered as the inner loop or micro iteration. After the inner loop, fixed effects are predicted by machine learning regressor and random effects are estimated by linear mixed model. Both effects are summed to create the logit value for each observation. The logit value is transformed into probability and the probabilities are dichotomized using a decision threshold. The resultant classes are considered as the new target class.

The new targets are transformed into logit values again, and previously estimated random effects are removed from this to create new fixed effects. Machine learning regressor is trained again with updated fixed effects and the inner loop is restarted. This step is called the outer loop or macro iteration. The inner loop is repeated until convergence criteria, and it leads to the outer loop again. The outer loop will have its own convergence criteria, and both will be repeated until both loops converge .

Convergence criteria for inner loop are the same as the regression framework. For the outer loop, there is no recommendation for maximum number of iterations as well so it must be set based on the computation resource and time resource availability. As shown in Figure 2.21. and 2.22., maximum of the absolute change in logit value is also monitored and the loop is continued as long as the value is more than the tolerance. During the application, the output of the model is calculated the same as before, but it is the logit value, so it is transformed into probability and dichotomized.

2.5.8. Artificial Neural Networks

Data Transformation

Artificial neural network requires both the inputs and outputs of the model to be numerical. So, for categorical data, feature transformation is necessary. For target variables, it is necessary to label the target variables' classes as [1] for positive class and [0] for negative class.

However, labeling of the target variable is also different based on the function of the model and the activation functions applied. For binary classification with sigmoid function, the samples are labeled 0 or 1. But SoftMax function requires separate target variables for each class, so the samples are labeled as [0,1] or [1,0]. In multi-class classifications where classes are mutually exclusive, it is necessary for the target to be one-hot-encoded such as [1,0,0], [0,1,0] and [0,0,1]. However, multi-label classifications where one sample can have multiple labels, targets are labeled as [1,1,1], [0,1,1], [1,0,1], [1,1,0], [0,0,1], [0,1,0], [1,0,0] and [0,0,0].

Methodology

Neural networks are loosely modeled after human brain, consisting of interconnected simple processing units, which learns from experience by modifying the connections. Neural networks are called deep learning as well, because of the presence of multiple hidden layers. While a neural network consists of multiple layers, the architecture can be categorized into three groups, input layer, hidden layers, and output layer.

The number of nodes(neurons) in the input layer are equal to all the features of the dataset or the features we selected for the prediction of the target variable. Neural networks require numerical values as input, so encoding for categorical variables is necessary. For ordinal variables, ordinal encoding is used, and one-hot-encoding is used for nominal variables.

Hidden layer can be single or multiple, and these layers are where major computations of the neural network happens. As in Figure 2.23., a neuron in hidden layer uses the concept of perceptron, which is assigning weights to each input of the node. However, the weights of the inputs are not known at the beginning of the model, so random weights to the inputs and bias to the layers are assigned. The combination of weights, inputs and bias creates the linear relationship between the inputs and output of the node, an activation function is used to introduce non-linearity. For example, as shown in Figure 2.24., sigmoid function compresses the output value [-∞, ∞] (x-axis) to [0, 1] (y-axis), and the output value is passed to the next layer, which can be either another hidden layer or the output layer.

The number of neurons in the output layer differs based on the function of the model and the activation functions applied. For regression, there is single neuron, and no activation function is required. For classification, it can also be single neuron (single output) if the classification is binary, and the activation function is sigmoid. However, for multiclass or multilabel classifications and other activation functions such as SoftMax, multiple nodes (multiple output) in output layer are necessary. This process of passing from input layer to hidden layers to output layer is called "feed-forward" as seen in Figure 2.25. (Left).

However, since our initial weights are assigned at random, chances are the output value of the model is different to real value as it is in Figure 2.25. (Right). So, another process called "backward propagation" is used to correct this, by comparing the predicted value with the real value. The loss of this prediction is calculated, and the weights of the nodes are updated based on the nodes' responsibility for the loss. The weights are increased or decreased to have the prediction closer to the ground value. This process of feed-forward, back-propagation is repeated for all samples in the dataset.

During the weight adjustment, some nodes get their weights changed into zero, which means the node will no longer contribute to the output. This is called "deactivated nodes", and this allows the neural network to be applied without feature selection. Also, one of the biggest advantages of artificial neural networks is ability to model non-linear and complex relationship. However, neural networks are extremely complex and uninterpretable, so they are said to have a "Black box" as well.

2.5.9. Recurrent Neural Networks

Data Transformation

Recurrent neural networks, similar to artificial neural networks, requires both the inputs and outputs of the model to be numerical. For target variables, it is necessary to label the target variables' classes as [1] for positive class and [0] for negative class, similar to artificial neural networks.

Also, unique for recurrent neural networks, the number of outputs can be as much as the number of time steps (observations) depending on the architecture. For multivariate models, the architecture can be many-to-one as well as many-to-many, as seen in Figure. 2.28.

Methodology

Recurrent neural networks are considered part of the representative learning algorithms, specializing in temporal sequence. Recurrent networks remember the past and its decisions are influenced by what it learnt from the past. Therefore, the outputs of the model are not only influenced by the weights applied to the input like traditional neural networks, but also the hidden state vector, representing the context of prior input and/or output. The major application of recurrent neural networks is natural language processing and voice recognition, where the previous context is necessary.

As in Figure. 2.29., the hidden state vector is initialized randomly and passed it into the activation function with the input. The activation is typically tanh function, which compress the output value [-∞, ∞] (x-axis) to [-1, 1] (y-axis). The output of the function is passed to another activation function, sigmoid or SoftMax depending on the model, for the output of the observation. However, the same output of the tanh function also passes to the next tanh function together with the next observation of the input and it is repeated for all the observations. Therefore, the context of the previous observations is stored and passed along the time steps. Recurrent neural networks are unique in a way that the same weight is applied to all the inputs of the same parameter, but the different outcomes at different observations are resulted by the different hidden state vectors resulting from previous outcomes. Recurrent neural networks are trained with one sample at a time. Of the same sample, RNN cells train from one time-step to another. The output of the model is compared with the ground value, and the loss is calculated using loss function. The weights of the model are readjusted using backward propagation and gradient descent.

Usually, the loss value is decreased by using gradient descent. Backward propagation finds the derivatives of the networks by moving layer by layer from final layer. However, since activation functions such as sigmoid and tanh compress the output value, the gradient decreases exponentially as we propagate backwards towards the initial layers. Small gradient means the weights will not be updated as effectively by each training sessions. But the initial layers are important to recognize the core elements of the input data, and this ultimately leads to inaccuracy of the model. Such problem is susceptible by deeper neural networks (more layers), and in recurrent neural networks solve this by applying more complex architecture, such as long short-term memory units.

2.6. Performance Metrics

Performance metrics of the classification models are based on true positive, false positive, true negative and false negative, such as AUC (Area under the ROC (receiver operating characteristic) Curve) of the classifier. Accuracy is a measure of how well a binary classifier correctly identifies or excludes a condition. The value is the ratio of correctly identified patients (true positive and true negative) to all patients examined by the model.

For medical applications, sensitivity and specificity are also the major metrics. Sensitivity is the proportion of actual positive patients (severe chronic periodontitis) to all positive patients while specificity is the proportion of actual negative patients (none or non-severe chronic periodontitis) to all negative patients. Some applies a specified threshold to be considered a good model such as addition of sensitivity and specificity more than 120 or 130. However, since sensitivity and specificity measure separate proportions of the results, such addition might under- or over-estimate the performance of the model.

Likelihood ratio is used to assess the value of performing a diagnostic test. It is the ratio of the probability of a person who has the disease testing positive to the probability of a person who does not have the disease testing positive. Positive predictive value (PPV) is the proportion of actual positive patients (severe chronic periodontitis) to predicted-as-positive patients while negative predictive value (NPV) is the proportion of actual negative patients (none or non-severe chronic periodontitis) to predicted-as-negative patients. PPV is also known as precision. For medical application such as screening, it is preferable to have the model to predict more false positives rather than more false negatives. Since these metrics are trade-offs between corresponding metric with variable thresholds, less specificity is more acceptable than less sensitivity and less PPV is more acceptable than less NPV.

Receiver operating characteristic (ROC) curve is a graphical plot, illustrating the diagnostic ability of a binary classifier. It is created by plotting true positive rate against false positive rate at various threshold settings. ROC curves are used to compare and evaluate different binary classifiers or classification models. Area under ROC curve (AUC), and concordance statistics (C-statistics) measures the discrimination ability of the model, and it is a measure of goodness of fit for binary classification models. A value of 0.5 means that the model is no better than predicting an outcome than random chance so, model with C-statistic value under 0.5 is considered to be a very poor model.

2.7. Conceptual Framework

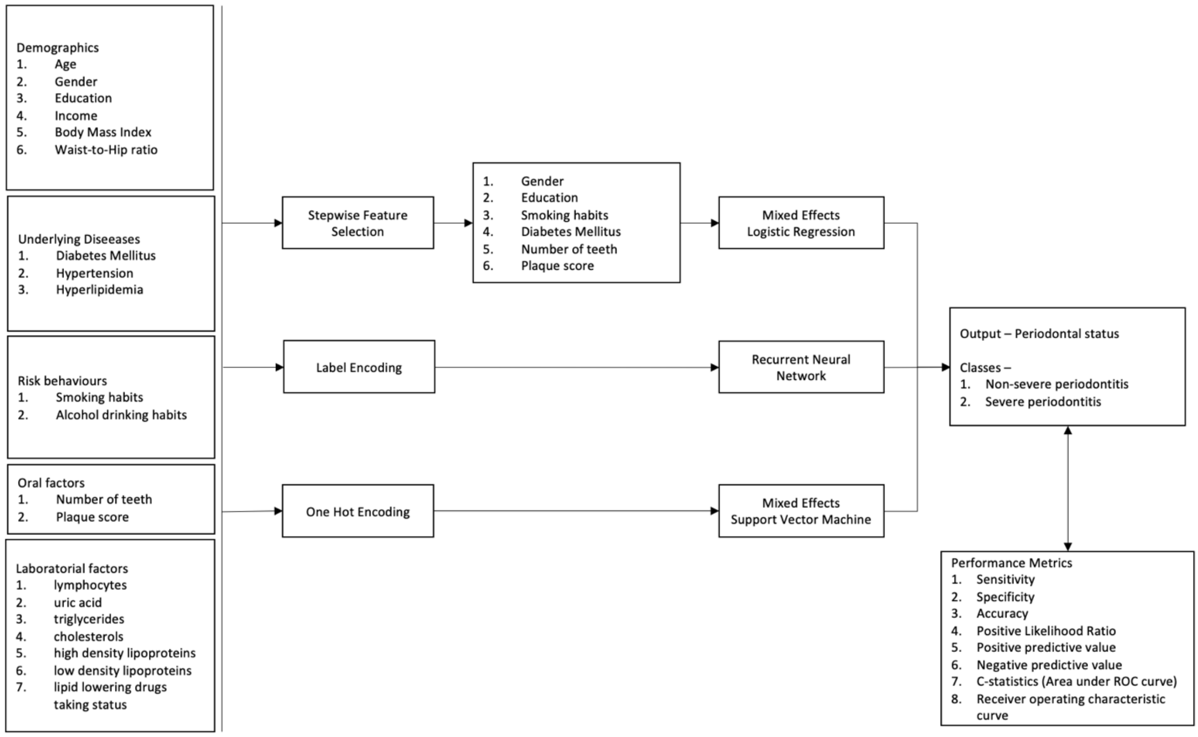


Table 2.1. Centre for Disease Control and Prevention - American Academy of Periodontology (CDC-AAP) classification

Case	Definition
No periodontitis	No evidence of mild, moderate, or severe periodontitis
Mild periodontitis	≥2 interproximal sites with clinical attachment level ≥3 mm, and ≥2 interproximal sites with periodontal pocket depth ≥4 mm (not on same tooth) or one site with periodontal pocket depth ≥5 mm
Moderate periodontitis	≥2 interproximal sites with clinical attachment level ≥4 mm (not on same tooth), or ≥2 interproximal sites with periodontal pocket depth ≥5 mm (not on same tooth)
Severe periodontitis	≥2 interproximal sites with clinical attachment level ≥6 mm (not on same tooth) and ≥1 interproximal site with periodontal pocket depth ≥5 mm

Table 2.2. Performance of current predictive models

Paper	Best performing model	Performance Metrics								
		Sens.	Spec.	Acc.	Prec.	AUC	PPV	NPV	Corr. Coef.	MSE
Leite et al. [25]	LR	67.57	67.50	--	--	0.670	--	--	--	--
Cyrino et al. [24]	LR	54.4	94.3	--	--	0.833	--	--	--	--
Thakur et al. [31]	ANN	--	--	--	--	--	--	--	0.82072	0.079978
Shankarapillai et al. [32]	ANN	--	--	--	--	--	--	--	0.97809	0.13281
Zhan et al. [23]	LR	80.0	72.7	--	--	0.830	74.6	78.5	--	--
Özden et al. [33]	SVM	--	--	--	0.98	--	--	--	--	--
Özden et al. [33]	ANN	--	--	--	--	--	--	--	0.4061	--
Özden et al. [33]	DT	--	--	--	0.98	--	--	--	--	--
Lai et al. [26]	LR	63.5	68.6	65.8	--	0.712	61.6	70.3	--	--
Javali et al. [27]	LR	--	--	61	--	0.7509	--	--	--	--
Eke et al. [22]	LR	93.5	29.2	--	--	0.79	--	--	--	--
Wu et al. [21]	LR	--	--	--	--	0.93	--	--	--	--
Verhulst et al. [36]	LR	80	88	--	--	0.91	93	69	--	--

Abbreviations –
Acc. = Accuracy
AUC = Area under receiver operating characteristic (ROC) curve
ANN = Artificial neural networks
Corr. Coef. = Correlation coefficient
DT = Decision tree
LR = Logistic regression
MSE = Mean squared error
NPV = Negative predictive value
PPV = Positive predictive value
Prec. = Precision
Sens. = Sensitivity
Sens. + Spec. = Sensitivity + Specificity
Spec. = Specificity
SVM = Support vector machine

Table 2.3 Example of raw data with 2 features and 2 Classes

Age	**Education Level**	**Occupation**	**Label**
35	Primary School	Programmer	Severe Chronic Periodontitis
25	Bachelor's degree	Doctor	None or non-severe C.P
21	Middle School	Doctor	None or non-severe C.P
30	Middle School	Programmer	Severe Chronic Periodontitis
29	High School	Doctor	Severe Chronic Periodontitis
22	High School	Engineer	None or non-severe C.P
22	High School	Doctor	None or non-severe C.P
29	Bachelor's degree	Engineer	None or non-severe C.P
33	High School	Engineer	Severe Chronic Periodontitis
29	High School	Programmer	Severe Chronic Periodontitis

Table 2.4. Example of transformed data with 2 features and 2 Classes

Age	Education Level (Ordinal)	Education	Occupation	Occupation_ doctor	Occupation_ engineer	Occupation_ programmer	Label	Class
	Ordinal Categorical variable	**Ordinal Encoding**	**Nominal Categorical variable**	**One Hot Encoding**			**Binary Categorical Variable**	**Binary Encoding**
35	Primary School	0	Programmer	0	0	1	Periodontitis	1
25	Bachelor's degree	3	Doctor	1	0	0	Healthy	0
21	Middle School	1	Doctor	1	0	0	Healthy	0
30	Middle School	1	Programmer	0	0	1	Periodontitis	1
29	High School	2	Doctor	1	0	0	Periodontitis	1
22	High School	2	Engineer	0	1	0	Healthy	0
22	High School	2	Doctor	1	0	0	Healthy	0
29	Bachelor's degree	3	Engineer	0	1	0	Healthy	0
33	High School	2	Engineer	0	1	0	Periodontitis	1
29	High School	2	Programmer	0	0	1	Periodontitis	1

Figure 2.1, Distribution of labeling criteria in literature review (Some papers apply multiple criteria and all criteria are counted)

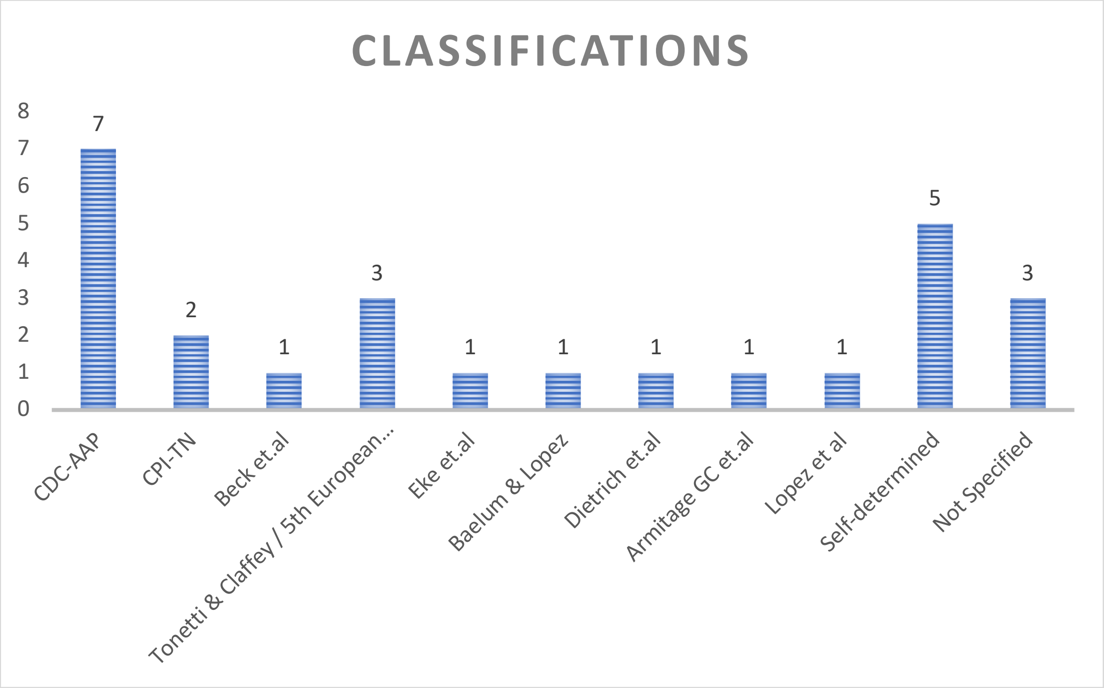


Figure 2.2. Oral Risk Factors applied in previous literatures and predictive models

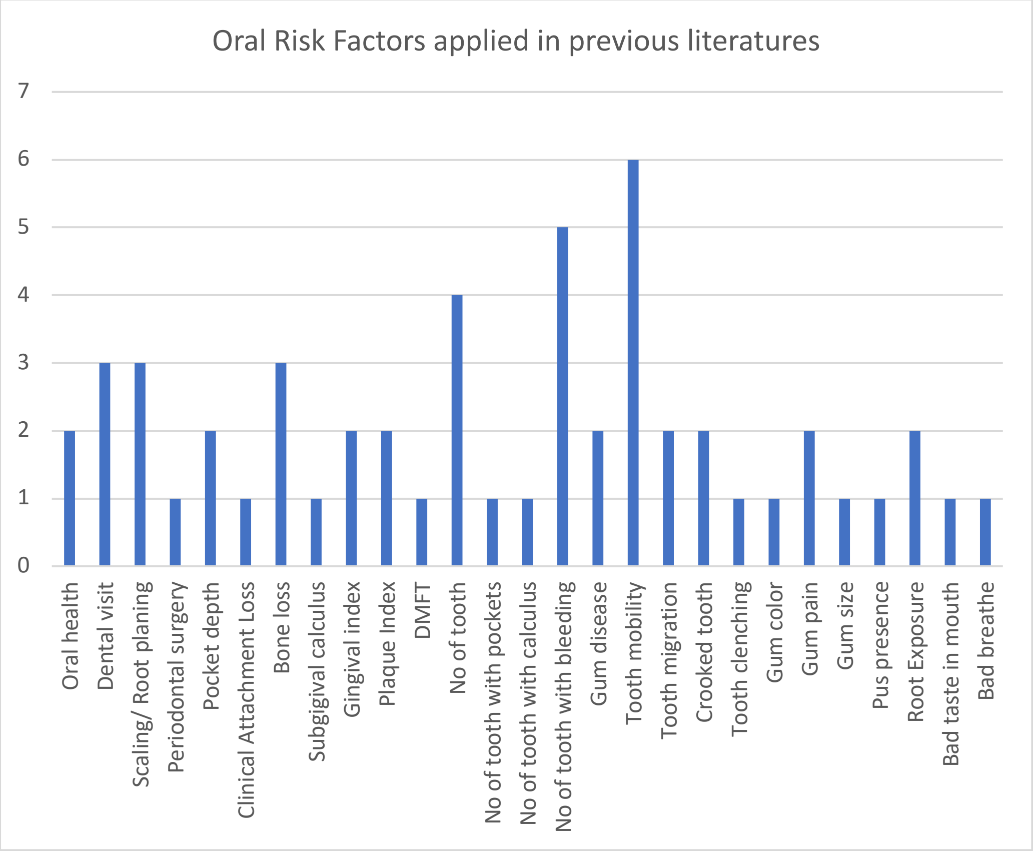


Figure 2.3. Demographic and Behavioral risk Factors applied in previous literatures and predictive models

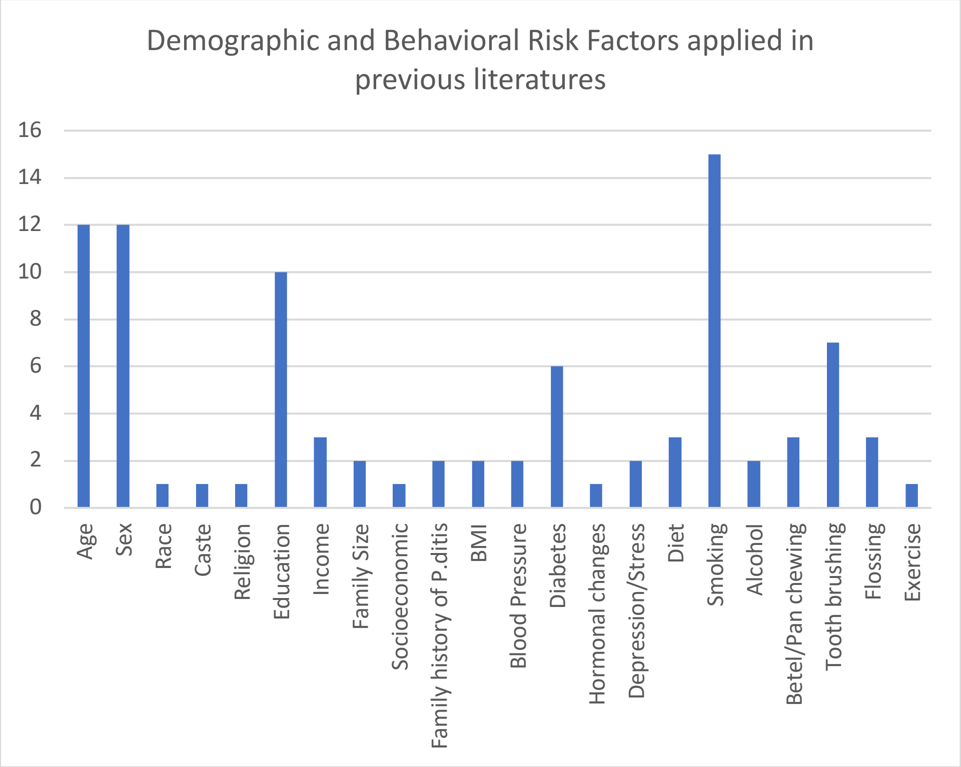


Figure 2.4. Laboratorial features and biomarkers applied in previous literatures and predictive models

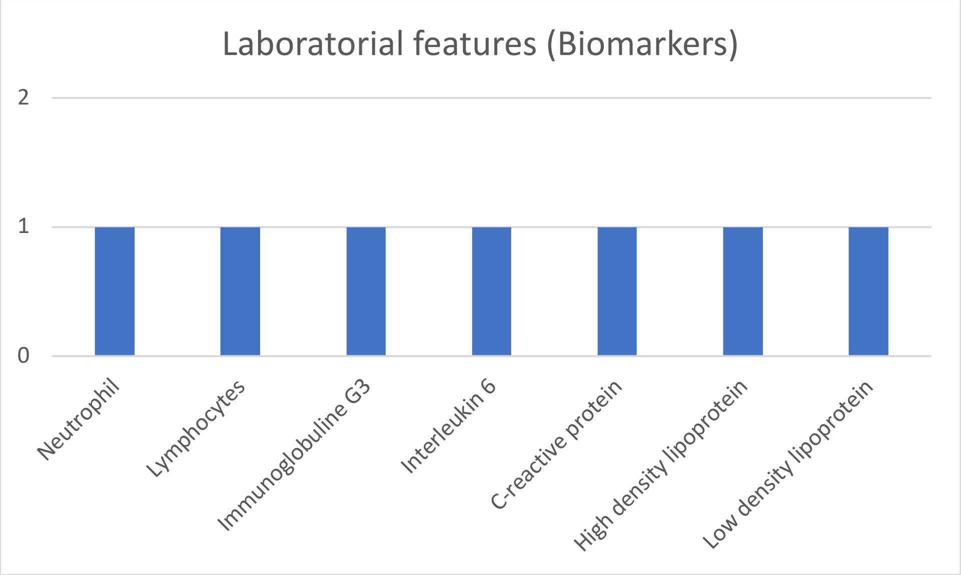


Figure 2.5. Number of papers in literature review, applying a particular model (Some papers apply multiple models, and each type is only counted once)

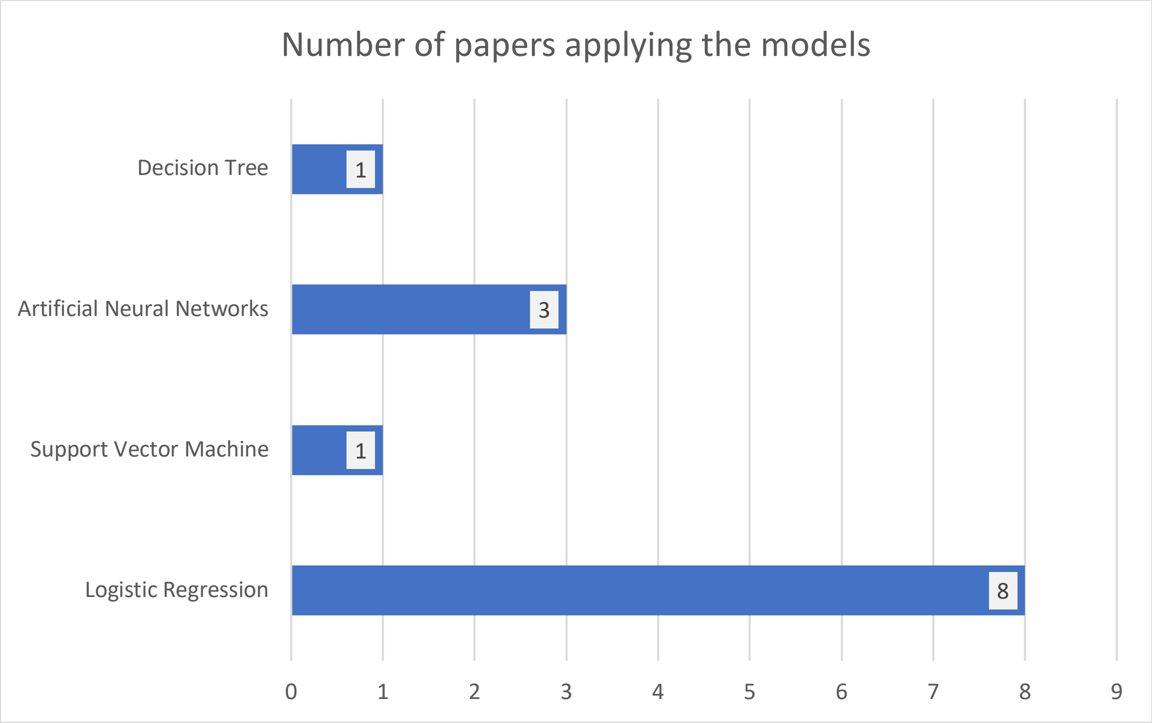


Figure 2.6. Distribution of models in literature review (Some papers apply multiple models, and all models are counted)

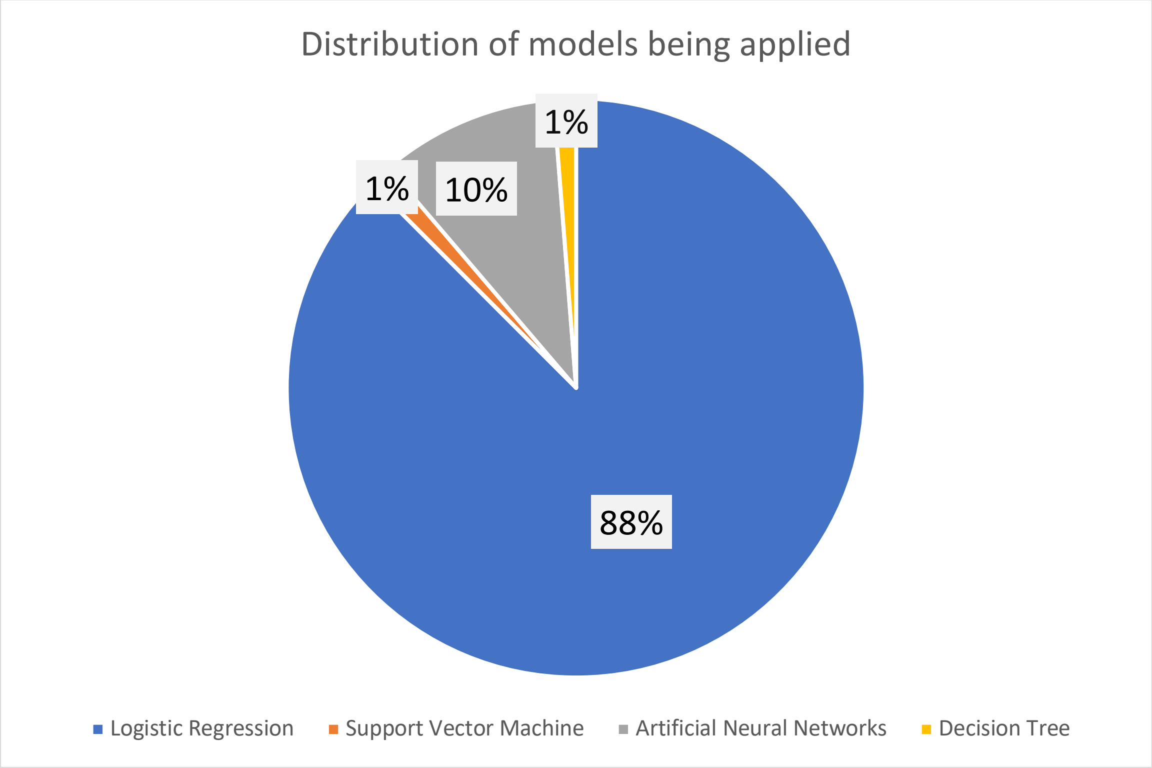


Figure 2.7. Flow chart for Mixed Effects Logistic Regression – Training Model Generation

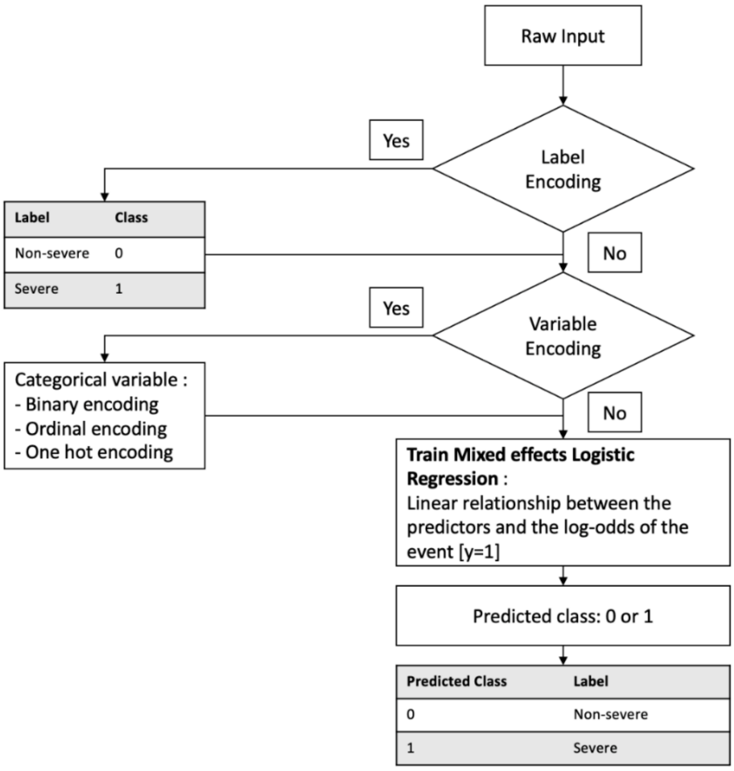
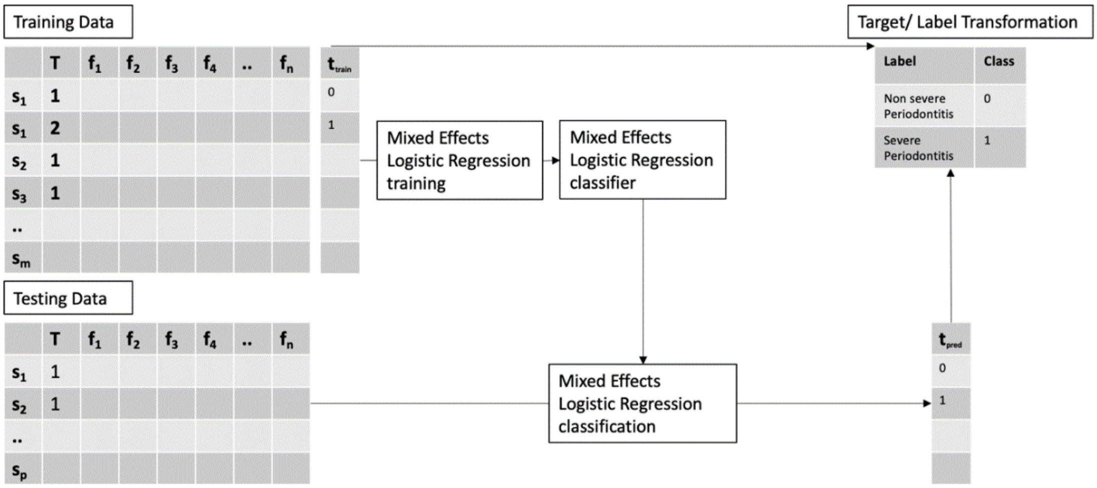
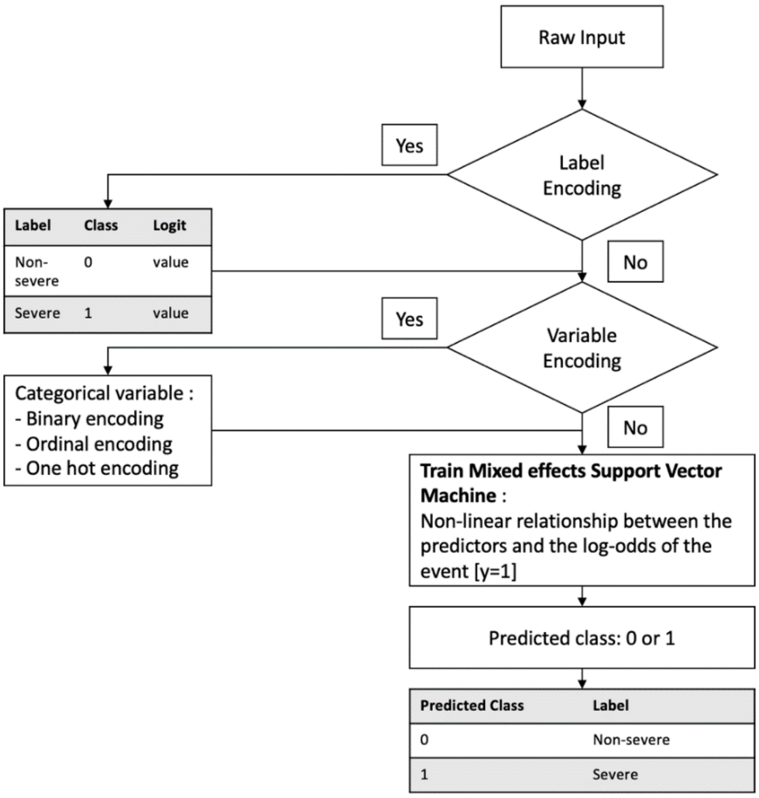


Figure 2.8. Block Diagram for Mixed Effects Logistic Regression – Testing and Target Transformation


Training Data
T f1 f2 f3 f4 .. fn
s1 1
s1 2
s2 1
s3 1
..
sm
t_train
0
1
Mixed Effects Logistic Regression training
Mixed Effects Logistic Regression classifier
Target/ Label Transformation
Label Class
Non severe Periodontitis 0
Severe Periodontitis 1
Testing Data
T f1 f2 f3 f4 .. fn
s1 1
s2 1
..
sp
Mixed Effects Logistic Regression classification
t_pred
0
1

$f_1, f_2, f_3, f_4, .., f_n$ are the features selected for the model.
$s_1, s_2, s_3, s_4, .., s_m$ are the patients included in the training dataset.
$s_1, s_2, .., s_p$ are the patients included in the testing dataset.
T is the time step (survey).
t_{train} is the periodontal status of the patients in the training dataset, classified by clinical measurements.
t_{pred} is the periodontal status of the patients in the training dataset, classified by mixed effects logistic regression.

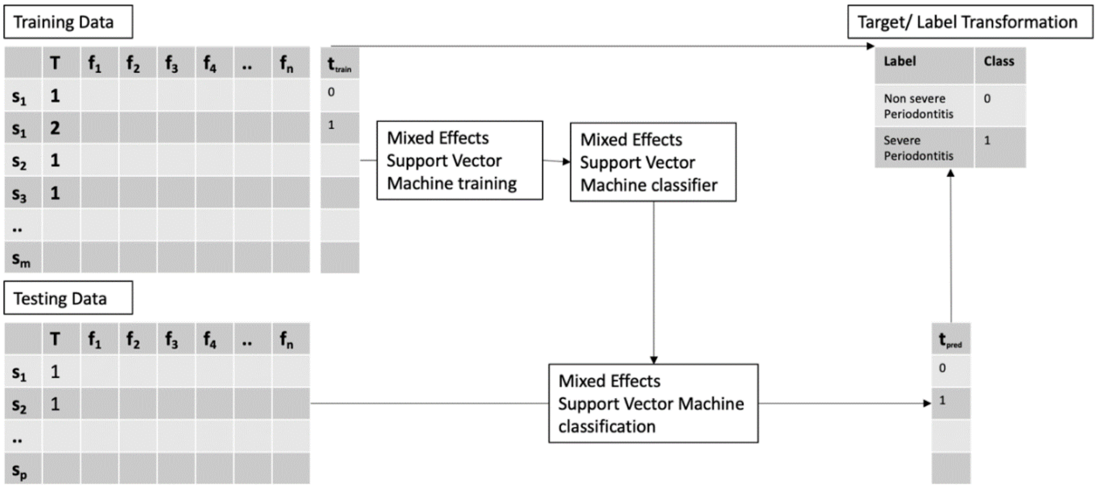
Figure 2.9. Flow chart for Mixed Effects Support Vector Machine – Training Model Generation



Label	Class	Logit
Non-severe	0	value
Severe	1	value

Predicted Class	Label
0	Non-severe
1	Severe

Figure 2.10. Block Diagram for Mixed Effects Support Vector Machine – Testing and Target Transformation


Training Data
T
f_1
f_2
f_3
f_4
..
f_n
t_{train}
s_1 1
s_1 2
s_2 1
s_3 1
..
s_m
0
1
Mixed Effects Support Vector Machine training
Mixed Effects Support Vector Machine classifier
Target/ Label Transformation
Testing Data
s_1 1
s_2 1
s_p
Mixed Effects Support Vector Machine classification
t_{pred}
0
1

Label	Class
Non severe Periodontitis	0
Severe Periodontitis	1

f_1, f_2, f_3, f_4, .., f_n are the features selected for the model.
s_1, s_2, s_3, s_4, .., s_m are the patients included in the training dataset.
s_1, s_2, .., s_p are the patients included in the testing dataset.
T is the time step (survey).
t_{train} is the periodontal status of the patients in the training dataset, classified by clinical measurements.
t_{pred} is the periodontal status of the patients in the training dataset, classified by mixed effects support vector machine.

Figure 2.11. A few possible decision boundary (hyperplanes) for the dataset

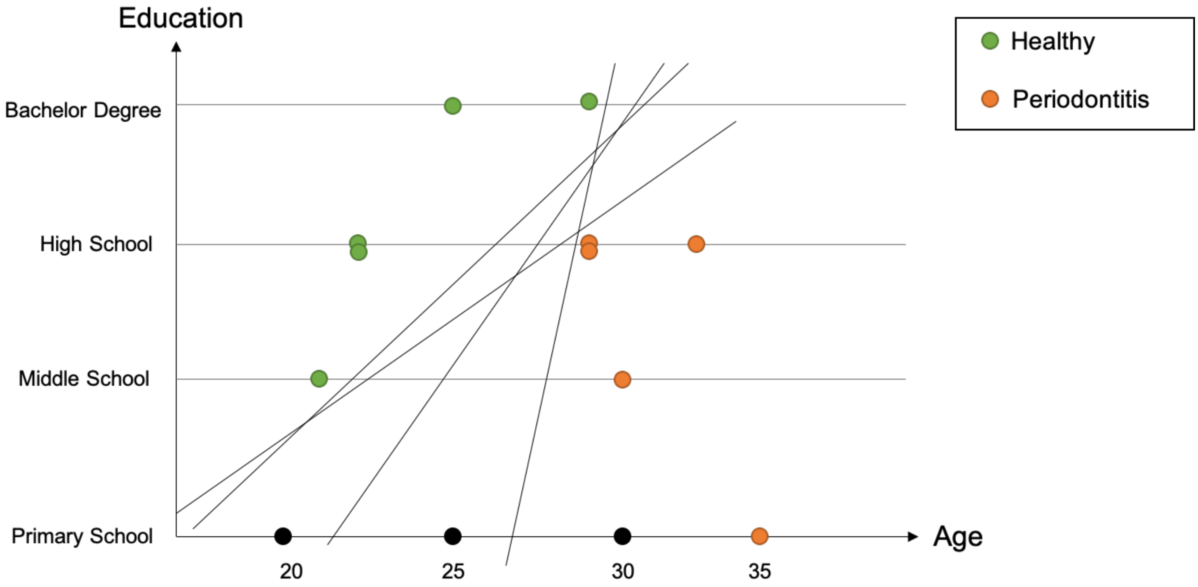


Figure 2.12. Optimal decision boundary (hyperplane) with maximum margin

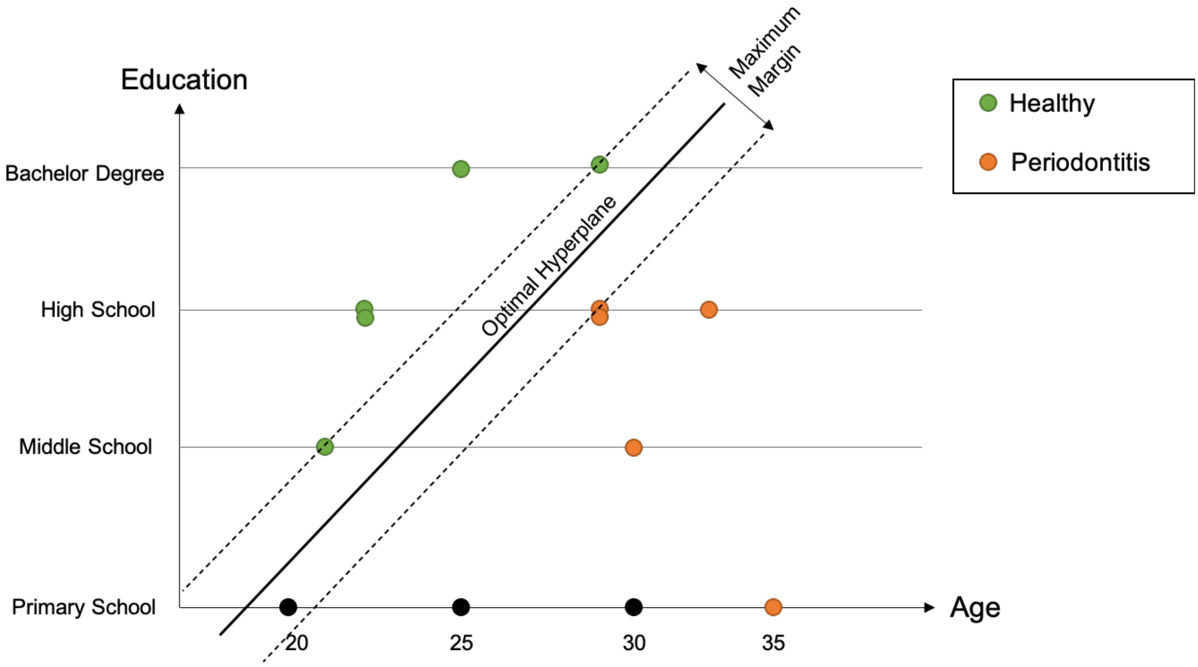


Figure 2.13. Soft margins allow misclassified data points. (The hyperplane is not optimal)

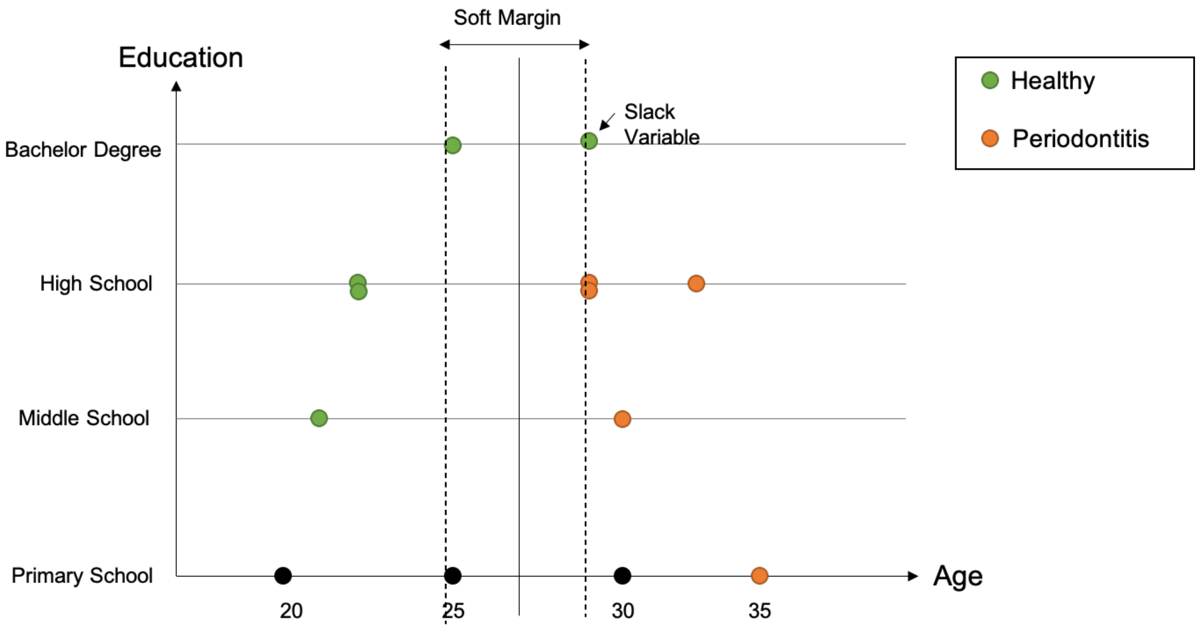


Figure 2.14. Kernel functions increase the dimension of the dataset, making it linearly separable.[51]

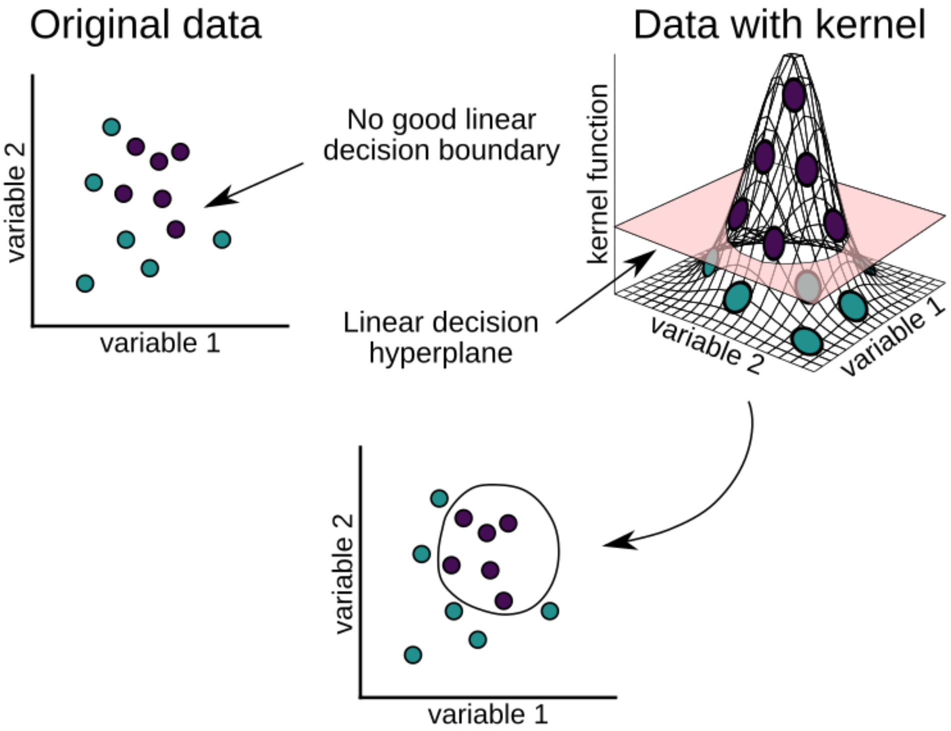


Figure 2.15. Ordinary Least Squared Regression

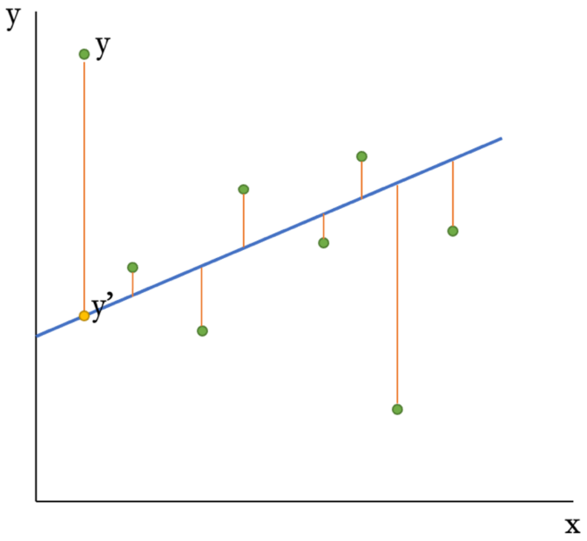


Figure 2.16. Support Vector Regression

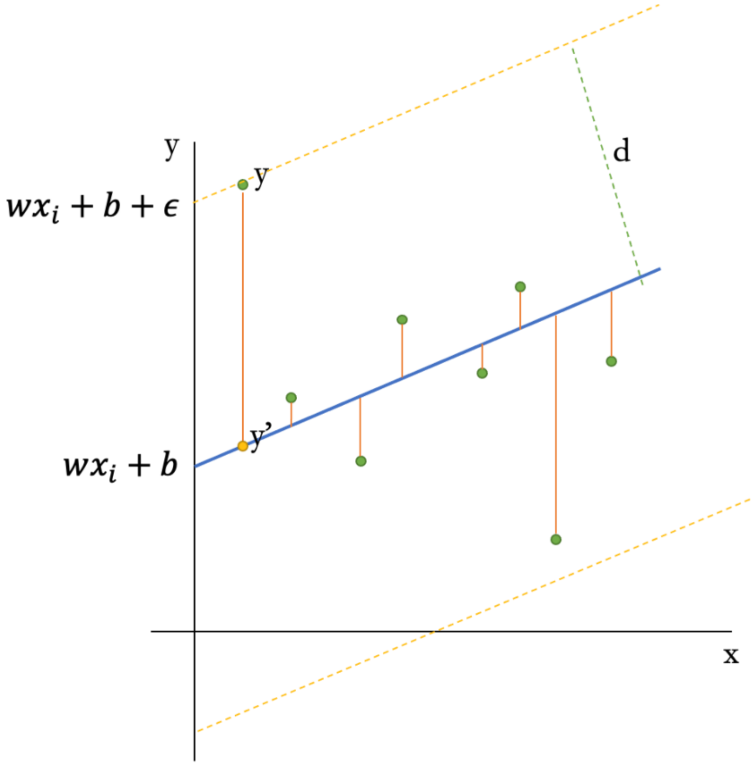


Figure 2.17. Soft Margin with Slacks

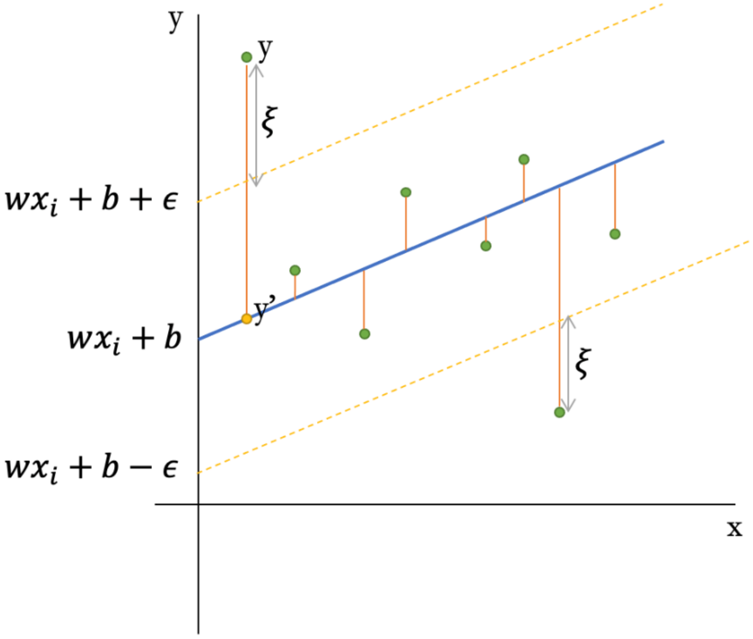


Figure 2.18. Expectation-Maximization Algorithm

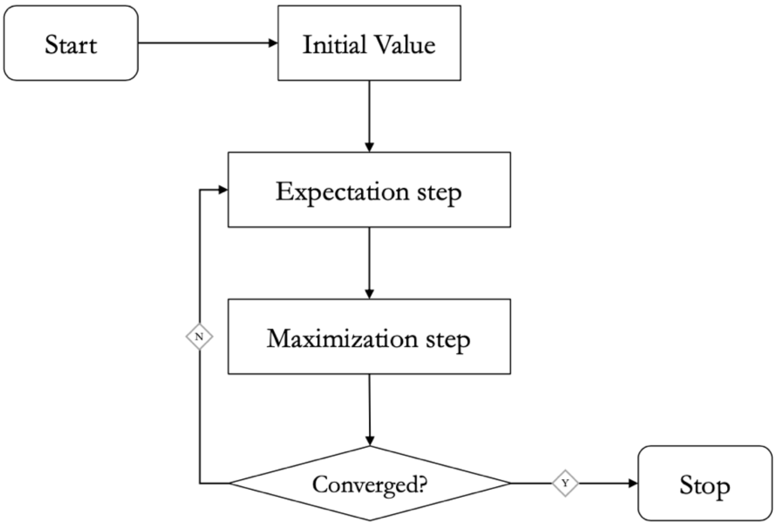


Figure 2.19. Training Mixed Effects Machine Learning Regression

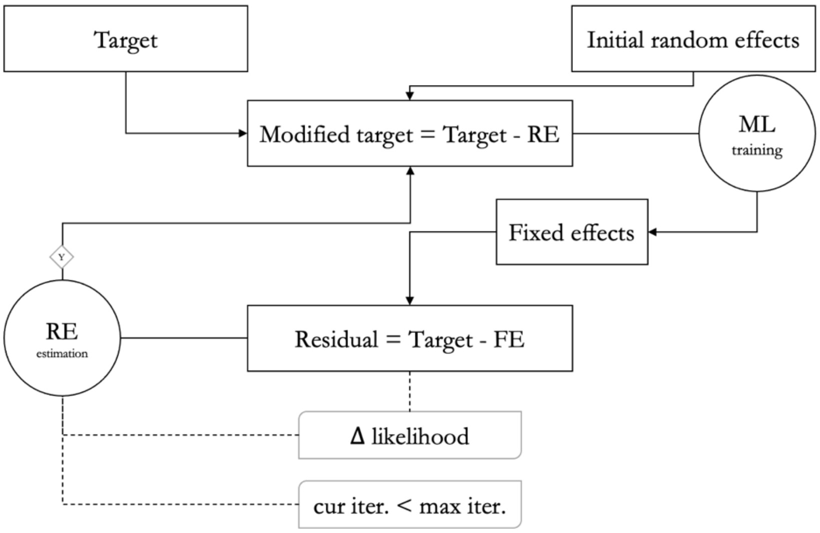


Figure 2.20. Mixed Effects Machine Learning Regression Framework

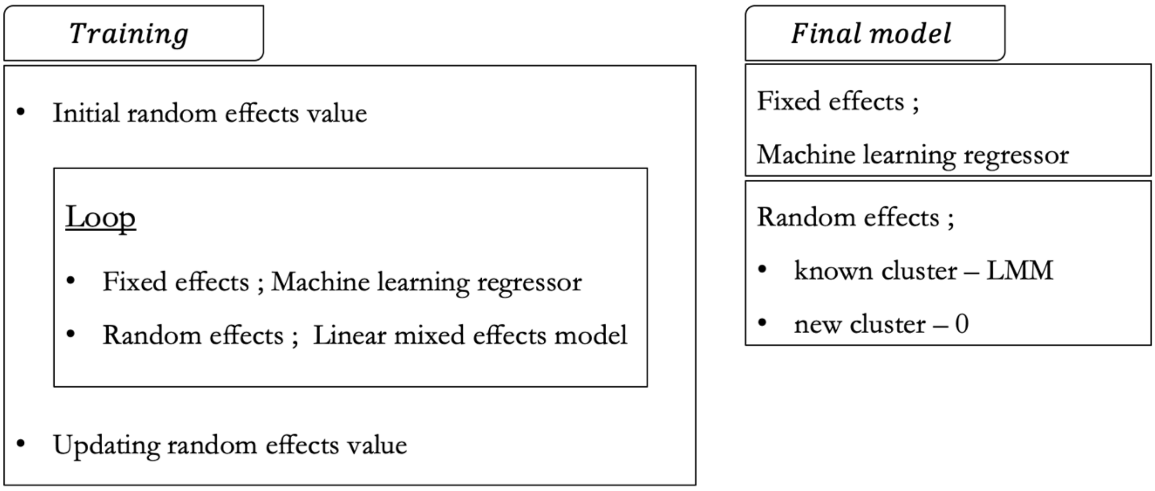

Training
Initial random effects value
Loop
Fixed effects ; Machine learning regressor
Random effects ; Linear mixed effects model
Updating random effects value
Final model
Fixed effects ;
Machine learning regressor
Random effects ;
known cluster – LMM
new cluster – 0

Figure 2.21. Training Mixed Effects Machine Learning Classification

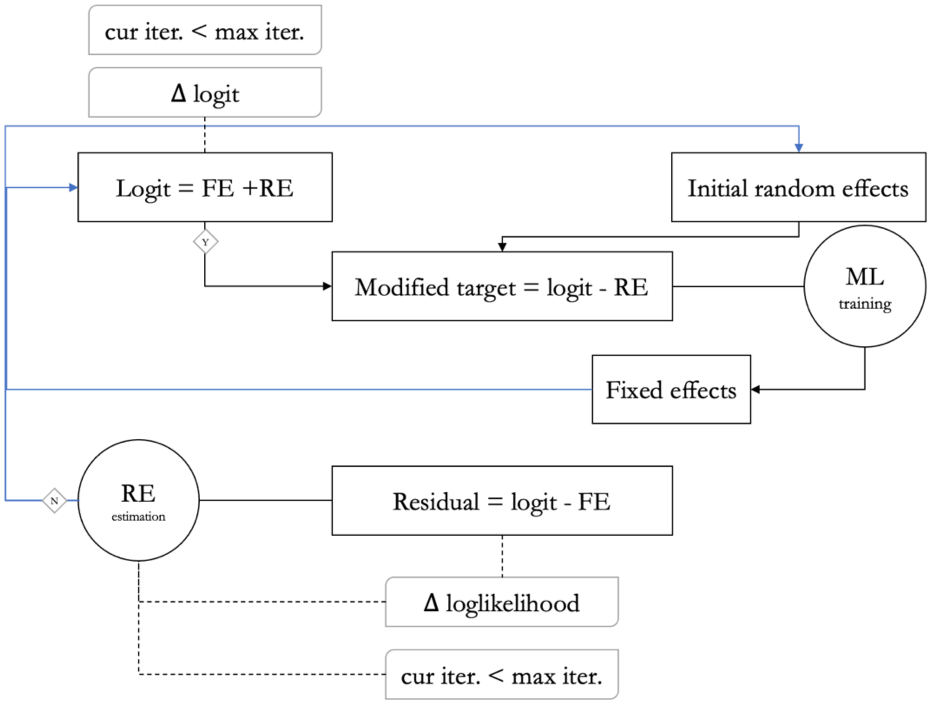


Figure 2.22. Maximum of the absolute change in logit value

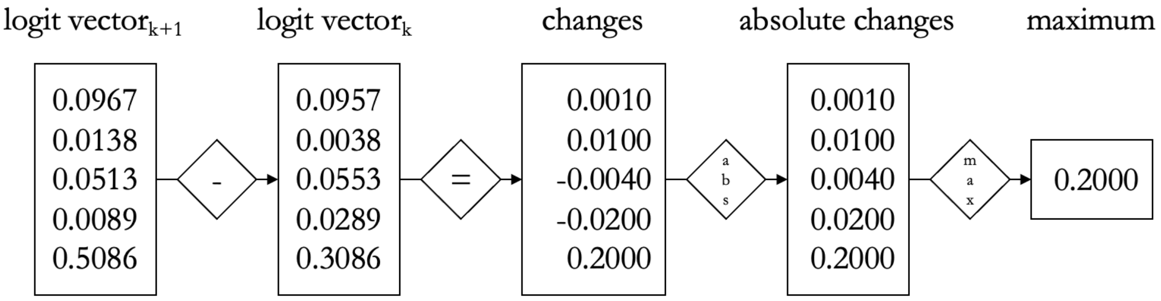


Figure 2.23. Perceptron of a neural network

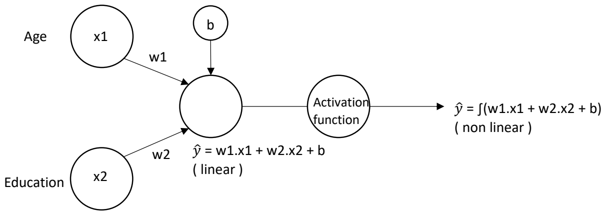


Figure 2.24. Sigmoid curve or logistic curve[52]

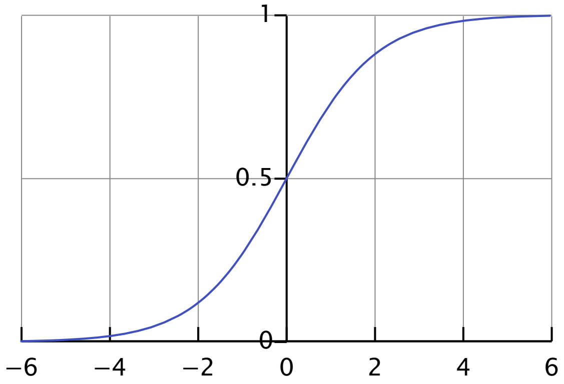


Figure 2.25. Architecture of a neural network (Left) and Training error in feed forward network (Right)

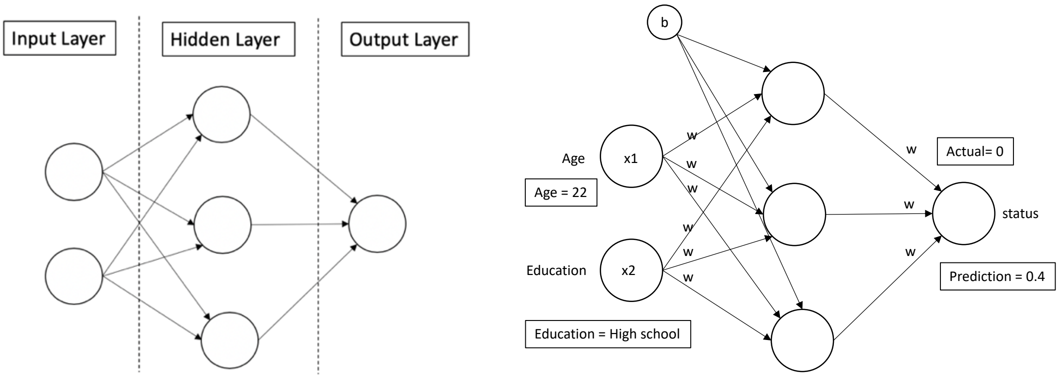


Figure 2.26. Flow chart for Recurrent Neural Networks – Training Model Generation

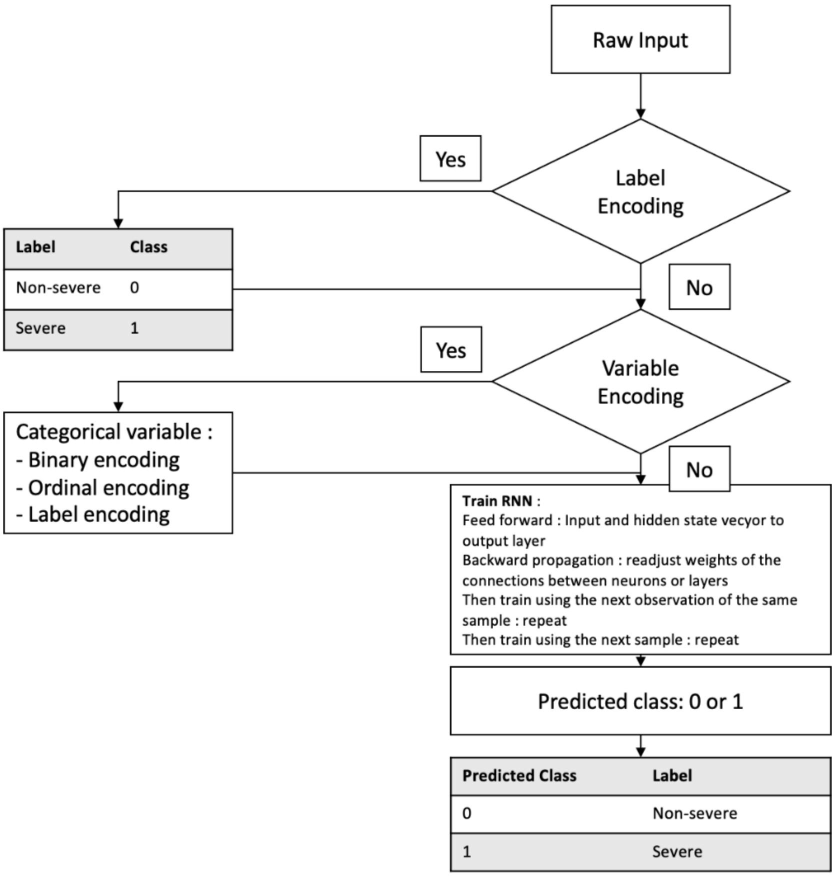
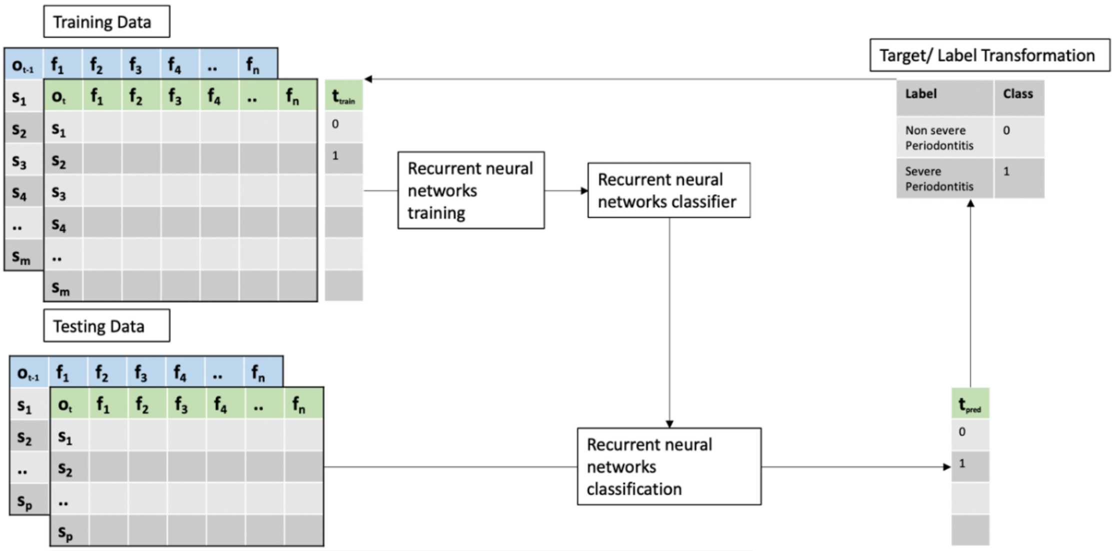
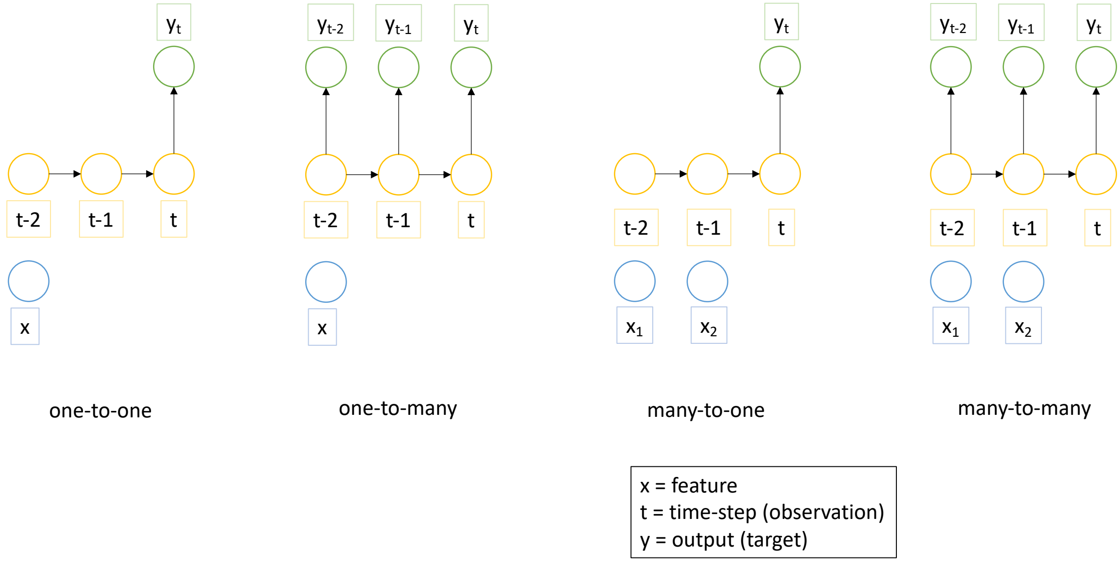

Raw Input
Label Encoding
Yes
No
Label | Class
Non-severe | 0
Severe | 1
Variable Encoding
Yes
No
Categorical variable :
- Binary encoding
- Ordinal encoding
- Label encoding
Train RNN :
Feed forward : Input and hidden state vecyor to output layer
Backward propagation : readjust weights of the connections between neurons or layers
Then train using the next observation of the same sample : repeat
Then train using the next sample : repeat
Predicted class: 0 or 1
Predicted Class | Label
0 | Non-severe
1 | Severe

Figure 2.27. Block diagram for Recurrent Neural Networks – Testing and Target Transformation


Training Data
o_{t-1} f_1 f_2 f_3 f_4 .. f_n
s_1 s_2 s_3 s_4 .. s_m
o_t f_1 f_2 f_3 f_4 .. f_n
s_1 s_2 s_3 s_4 .. s_m
t_{train}
0
1
Recurrent neural networks training
Recurrent neural networks classifier
Target/ Label Transformation
Label | Class
Non severe Periodontitis | 0
Severe Periodontitis | 1
Testing Data
o_{t-1} f_1 f_2 f_3 f_4 .. f_n
s_1 s_2 .. s_p
o_t f_1 f_2 f_3 f_4 .. f_n
s_1 s_2 .. s_p
Recurrent neural networks classification
t_{pred}
0
1

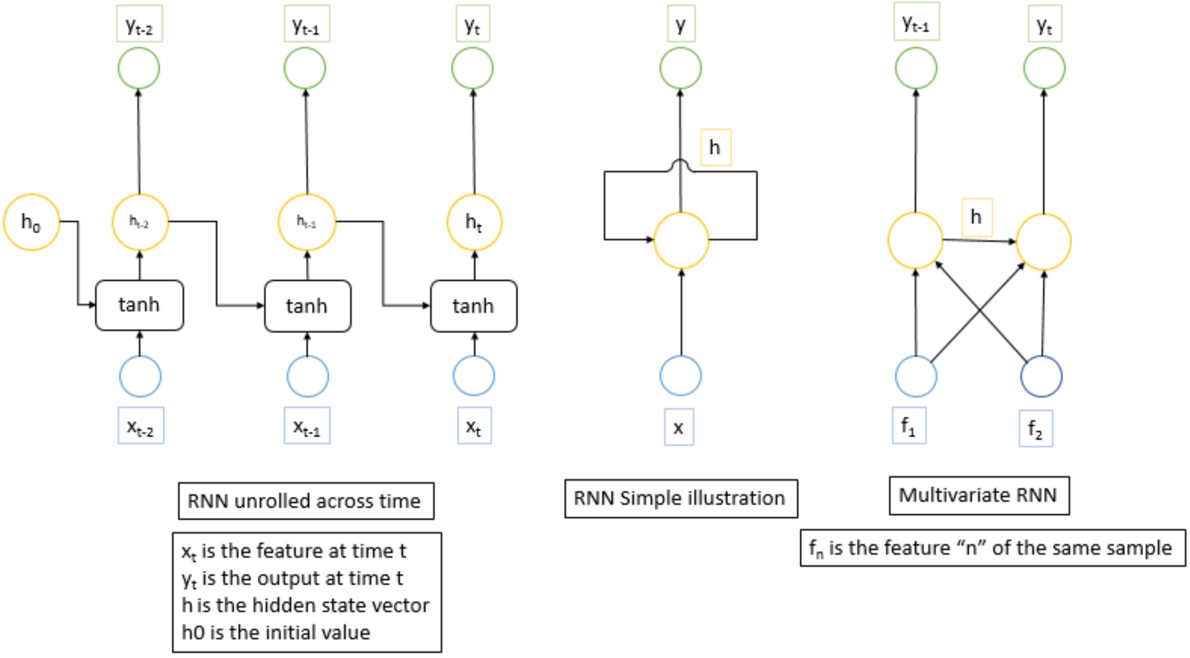
o_t is the observations of the features at time t (EGAT 2/4).
o_{t-1} is the observations of the features at time t-1 (EGAT 2/3).
f_1, f_2, f_3, f_4, .., f_n are the features selected for the model.
s_1, s_2, s_3, s_4, .., s_m are the patients included in the training dataset.
s_1, s_2, .., s_p are the patients included in the testing dataset.
t_{train} is the periodontal status of the patients in the training dataset, classified by clinical measurements.
t_{pred} is the periodontal status of the patients in the training dataset, classified by recurrent neural networks.

Figure 2.28. Architectures of a recurrent neural network



x = feature
t = time-step (observation)
y = output (target)

Figure 2.29. Illustration of a one-to-many recurrent neural network



x_t is the feature at time t
y_t is the output at time t
h is the hidden state vector
h0 is the initial value

f_n is the feature “n” of the same sample

Chapter III
Methodology

3.1. Study Setting and Design

This study is a sub-cohort of prospective cohort study, namely Electric Generating Authority of Thailand (EGAT) cohort, by retrieving 5-years follow up period. Details about EGAT cohort are referenced[53], but in short, EGAT project contains three parallel cohorts, also known as EGAT1, EGAT2 and EGAT3. Each cohort begin in 1985, 1998 and 2009 respectively. Each follow up is examined every 5 years, except for 12 years gap between 1st survey (1985) and 2nd survey (1997) of EGAT1. In the 3rd survey (2002) of EGAT1, periodontists collaborated with the cohort by including half-mouth examination in the study. In 2003, 2nd survey of EGAT2, also known as EGAT 2/2, started including full-mouth examination. EGAT 2/3 (2008) and 2/4 (2013) included more questionnaires about oral health and habits.

This study was conducted applying EGAT2 cohort. The EGAT 2/3 and 2/4 are used as the training and testing datasets. EGAT 2/3 and EGAT 2/4 are defined as the patient characteristics 5 years before and now respectively. All models predict the periodontal status of the samples into two classes (severe chronic periodontitis and none or non-severe chronic periodontitis). Rationale and setting details of the research objective are as follows.

3.1.1. Objective

Rationale

We aim to diagnose the periodontal status of a subject without comprehensive periodontal probing. From literature reviews and expert opinions, the features that are correlated with periodontitis are selected, such as demographics, underlying diseases, risk behaviors, oral and laboratorial features. Selected features are applied for the models as predictors. Periodontal status is the target variable for all models.

Setting

For longitudinal modelling, we will apply both EGAT 2/3 and EGAT 2/4 dataset. The models to be applied are mixed effects logistic regression, recurrent neural networks, and mixed effects support vector machines The model performances are measured by six performance metrics: sensitivity, specificity, area under receiver operating curve, positive likelihood ratio, positive predictive value, and negative predictive value. The models are compared against each other.

3.2 Study Subjects

All available subjects in EGAT 2/3 are included unless they meet the exclusion criteria. For EGAT 2/4, only subjects followed up from EGAT 2/3 are included unless they meet the exclusion criteria.

Some subjects were not present in ALL periodontal examinations due to (1) refusal to participate, (2) systemic conditions which required antibiotic prophylaxis before dental procedure including congenital heart disease or valvular heart disease, previous history of bacterial endocarditis or rheumatic fever, total joint replacement, and end-stage renal disease, and (3) fully edentulous subjects. Such subjects are excluded for all models.

3.3 Data Collection

In each survey, general demographic data (age, gender, educational level, income, marital status), behavioral data (smoking status, alcohol consumption, exercise/physical activity), family history of illness, underlying diseases (diabetes mellitus, hypertension) are collected by self-administered questionnaires. Physical examinations, i.e., blood pressure (BP), heart rate, blood glucose level, weight, height, and waist & hip circumference, were performed by clinicians and trained personnel from Ramathibodi Hospital. Laboratory tests under fasting state were carried out included glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), immunoglobulin G3, interleukin 6 and a complete blood count (CBC).

3.4. Study Factor and Measurements

3.4.1. Self-administered data

Demographics

Demographic data such as age, gender, education and income are reported by the individual themselves using case-report forms.

Risk behaviors

Subjects are categorized into (1) non-smoker (2) ex-smokers and (3) current-smokers, based on multiple questionnaires such as past/current smoking habits, quantity and duration of smoking, age at start or quit smoking.

Alcohol drinking habits are also classified as similar, based on history of alcohol consumption, along with frequency, duration, and type of alcohol.

Oral factors

Oral and dental examinations are carried out by experienced periodontists from the Department of Periodontology, Faculty of Dentistry, Chulalongkorn University in mobile dental units. Number of teeth and oral hygiene index (plaque score) are measured as part of oral parameters.

3.4.2. Physical Examinations

Body measurements

Height was measured in centimeters and weight was measured in kilograms, while being dressed in normal clothing with shoes taken off. Waist and hip circumferences are measured in centimeters with measuring tapes by trained personnel. Body mass index (BMI) is calculated from the recorded weight in kilograms divided by squared height in meters. Waist-to-hip ratio is calculated from the recorded waist circumference in centimeters divided by hip circumference in centimeters.

Underlying conditions

Underlying conditions are identified from physical and laboratorial examinations, along with prescribed medications. Diabetes mellitus was diagnosed if an individual had fasting blood sugar (FBS) $\geq$ 126 mg/dl or had been taking anti-diabetic drugs. Hypertension was diagnosed if the participant had systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg or had been taking prescribed anti-hypertensive drugs. Dyslipidemia is identified if the subject has high-density lipoprotein (HDL) < 40 mg/dl in male or HDL < 40 mg/dl in female OR low-density lipoprotein (LDL) ≥ 160 mg/dl OR triglyceride ≥150 mg/dl OR used any lipid-lowering medications.

3.4.3. Laboratorial Examinations

Blood samples were collected after 12-hour overnight fasting. Blood glucose was measured by plasma samples in mg/dl (Peridochrome, Boehringer Mannheim, Mannheim, Germany). High-density lipoproteins and low-density lipoproteins were measured in mg/dl using enzymatic-calorimetric assays (Boehringer Mannheim, Mannheim, Germany). immunoglobulin G3 in mg/dl, interleukin 6 in mg/dl and a complete blood count (CBC) is measured in count per micro liter.

3.5. Primary Outcome and Measurements

The outcome of interest is the periodontal status of the subject at the period of examination. The subjects are labelled as “severe” or “non-severe” periodontitis and severe periodontitis, according to the periodontitis definition of the Center for Disease Control and Prevention – American Academy of Periodontology (CDC-AAP), which defined “severe periodontitis” as harboring two or more interproximal sites with clinical attachment level ≥ 6 mm that are not on the same tooth AND one or more interproximal sites with periodontal pocket depth ≥ 5 mm.

3.5.1. Periodontal Examinations

Periodontal examinations included periodontal pocket depth, and gingival recession which were carried out on all fully erupted teeth, except third molars and retained roots. Periodontal pocket depth is the measurement from coronal margin of gingival margin to the tip of a periodontal probe, and gingival recession is the measurement from coronal margin of gingival margin to the cementoenamel junction. The parameters are measured applying a periodontal probe - University of North Carolina 15 (PCP-UNC15) on six sites, i.e., mesial, mesio-buccal, mesio-lingual, disto-buccal, disto-lingual, and lingual site of the gingival sulcus per tooth. These measurements were made in millimeters and were rounded to the nearest whole millimeter.

Calibration and standardization for periodontal measurements were implemented among six to eight examiners before the survey. The weighted kappa coefficients (±1 mm) were used to determine the agreement of inter-examiner and intra-examiner (Table 3.1). Between each pair of examiners, the kappa ranged from 0.72 to 1.00 for periodontal pocket depth and 0.67 to 1.00 for clinical attachment level/ gingival recession. The weighted kappa coefficients (±1 mm) within each examiner ranged from 0.85 to 1.00 for periodontal pocket depth and from 0.80 to 1.00 for clinical attachment level.

3.5.2. Periodontal classification

Due to the absence of homogenous classification for chronic, we label the samples of our dataset based on CDC-AAP classification. To classify a sample as chronic periodontitis, clinical attachment level is required, so it is calculated. The subtraction of gingival recession from pocket depth results in the measurement from the cementoenamel junction to the tip of the periodontal probe, hence clinical attachment level is resulted. Whereas CDC-AAP criteria has four classes of periodontitis (non, mild, moderate, and severe), we categorize our samples into two, severe periodontitis and non-severe periodontitis (non, mild, and moderate) as in Table 3.2.

3.6. Sample size estimation

There is no explicit guideline for sample size estimation for machine learning model. According to this literature review[54], the researchers recommend number of sample size for developing a clinical prediction model should be :

$$n = \left(\frac{1.96}{\delta}\right)^2 \hat{\phi}\,(1 - \hat{\phi})$$

- where

n = number of sample size

δ = absolute margin of error

$\hat{\phi}$ = anticipated outcome proportion

We aim for margin of error ≤ 0.05. The prevalence of severe periodontitis in Thai adult population is 26%. So, we anticipate the outcome proportion in our study population to be 0.3. At least 322.69 ~ 323 subjects including 97 subjects with severe periodontitis is required for our models.

Available sample size is explored. EGAT 2/3 (2008) has 2,271 subjects and 2,016 subjects are followed up in EGAT 2/4 (2013). We consider our study to have enough sample size to train and test our models

3.7 Data Management

3.7.1 Data Acquirement

Demographic and medical records

Demographic and medical data were retrieved from the EGAT databases. These were merged with the Excel worksheets of the civil registrations for additional data.

Periodontal databases

Periodontal databases were constructed, all periodontal parameters for EGAT 2/3 and 2/4 were computerized as follows:

Building the periodontal databases

Databases were constructed using Epidata version 3.1, separately by EGAT 2/3 and 2/4, because there were some variables were differently measured for each survey. Data entry systems were designed with "tooth by tooth" system. Users had to entry all parameters of one tooth including periodontal pocket depth, and gingival recession, before moving on to the next tooth. If a particular tooth is missing, the system would not allow users to entry any data for that tooth. In addition, databases were encoded with specified value or range for each variable to prevent error during data entry.

Data entry (Periodontal parameters)

Data from case record forms (CRF) were manually checked by a data manager before entering data. Legibility of handwriting, minor missing data and consistency of all parameters were revised. If handwriting was not clear, the query was done directly to the recorder. Then, data were independently entered twice by two persons. These two data sets were then validated, any inconsistence was checked and corrected. Finally, all records were manually checked and edited based on the original CRF, again.

3.7.2 Data Cleaning

Selected features and data were retrieved from the main databases. The variables were renamed systematically across both datasets in order to combine them all together. Then, data cleaning was performed by the data cleaning team, which consisted of Prof. Ammarin Thakkinstian, Dr. Anuchate Pattanateepapon, Dr. Attawood Lertpimonchai, and Dr. Htun Teza. Regular meeting at least twice a month was organized to solve any incorrectness or unclear data. Data were summarized and cross-checked using pandas library and python 3.8. Any inconsistency or outliners were verified and checked with the CRFs to check data validity. All variables, except gender and height, were assigned as the time-varying variables for necessary models.

Gender

Gender is considered to be consistent across all datasets. Inconsistent data value between observations is validated by original case-report form.

Date of examination

The time length between the date of examination and the date of birth is calculated for the age of the subject at time of examination. The date has to be during the survey period and the values that are not or missing are recoded as the middle time of the survey period.

Date of birth

Similar with gender, date of birth is also assumed to be consistent across all dataset. However, when discrepancies are observed, civil registration databases are also used as the source. Between the three datasets, the majority value for date of birth is selected.

Education

The level of education cannot be decreased. Illogical declinations are detected and decided by the team.

Risk behaviors

Smoking and alcohol drinking habits were classified within each period with multiple questions in questionnaire, then the datasets are merged. The values are checked to be logical, such as “current smoker” cannot become a “never smoker” in the next observation. If inconsistency was present, the decision is made by the team.

Body Measurements

Height, weight, waist and hip were summarized and checked for outliers (i.e., exceeds mean ± 4SD). If outliers presented, the original CRF is checked. The change of the value overtime would also be checked after merging the datasets. Substantial change of weight, waist and hip would be list, and then, its possibility would be validated by comparing with other relevant variables.

Blood pressure

To determine the data validity of blood pressure, guidelines such as : presence of data for both systolic and diastolic blood pressure, within proper range of the value, and SBP value being higher than DBP are used.

Laboratory results

All laboratory results, which were reported in continuous data, were checked for outliers (i.e., exceeds mean ± 4SD). If outliers existed, the likelihood of the value is discussed and decided by the team. Illogical values are recoded to be missing values.

3.7.3 Carried forward/backward methods

To replace missing data for some variables, the forward/backward carry over methods were used. For example, carried backward method means that never smokers in EGAT 2/4 are imputed in EGAT 2/3 as “never smoker” as well.

3.8 Data Preparation

3.8.1 Feature Transformation

Logistic regression, recurrent neural networks and mixed effects support vector machine require the input of the models to be numerical values. In Table 3.3, categorical variables are encoded based on the type of categorical variable. Binary variables are encoded as 0 and 1. Ordinal variables such as education level are encoded using ordinal encoding, and for nominal categories, label encoding is used for recurrent neural networks and one-hot-encoding for mixed effects support vector machine.

3.8.2 Target Labelling

CDC-AAP criteria uses both the measurement of clinical attachment level and periodontal pocket depth to classify as periodontitis as stated in Table 3.2. Subjects that are eligible for “Severe” criterion of the classification are labelled as “Severe”, and the rest are labelled as “Non-severe”. For support vector machine, “Non-severe” subjects are encoded as -1 and “Severe” subjects are encoded as 1. For other models, “Non-severe” subjects are encoded as 0 and “Severe” subjects are encoded as 1.

3.9 Model Architecture

3.9.1 Feature Selection

From EGAT datasets, the features are extracted as observed from literature reviews and as recommended by expert opinion in periodontology. For mixed effects logistic regression model, stepwise forward selection method is used and none for machine learning models.

3.9.2 Data Splitting

The total samples are split in 80% for model training and 20% for model performance testing as per Pareto principle.

3.9.3 Model Development

The extracted features are age, gender, education, income, body mass index, waist and hip circumferences, smoking, alcohol drinking, diabetes mellitus, hypertension, hyperlipidemia, number of tooth present, plaque score, lymphocytes, uric acid, triglycerides, cholesterols, high density lipoproteins, low density lipoproteins and lipid lowering drugs taking status.

For statistical model, logistic regression model is applied with Ridge penalization (L2 regularization). For machine learning models, recurrent neural networks and mixed effects support vector machine are applied and hyperparameters are tuned.

For support vector machine, hyperparameters are

1. kernel type,
2. C (regularization parameter) and
3. gamma (kernel coefficient) values.

For recurrent neural networks, hyperparameters are

1. number of hidden layers,
2. activation functions and
3. batch size.

3.9.4 Performance Evaluation

The performance of all models will be evaluated using accuracy, sensitivity, specificity, positive likelihood ratio, positive predictive value, negative predictive value, C-statistics (area under receiver operating characteristic curve), receiver operating characteristic curve.

3.10 Limitations

From literature reviews, it is observed that including oral features in the models predict better than not including them. Electric Generation Authority of Thailand (EGAT) dataset does not include much oral features, such as tooth mobility, bleeding on stimulation and more. While we would try to compensate the issue by deploying more complex and higher performing models, the good models should perform better with such features.

3.11 Budget

No.	Item	Units	No of units	Unit cost (THB)	Total cost (THB)
1	Manuscript Publication	Article	1	3,000	3,000
2	Data Management	Record	4,325	5	21,625
3	Data Analysis	Analysis	40,000	1	40,000
Total					64,625

3.12 Time Frame

No.	TOR	Time (months)															
		2020											2021				
		2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5
1	Proposal Development	*	*	*	*	*	*										
2	Finalized proposal						*	*									
3	Proposal defend						*	*									
4	Ethics Committee							*	*								
5	Data management								*	*							
6	Data preprocessing								*	*	*						
7	Model development and evaluation								*	*	*	*	*	*			
8	Proceeding manuscript											*	*				
9	Proceeding submission												*				
10	Thesis Manuscript													*	*	*	*
11	Thesis defense																*

Table 3.1. Calibration of periodontal examination (weight kappa ± 1mm)

	Periodontal pocket depth		Clinical attachment level/ Gingival Recession	
	Inter-examiner	Intra-examiner	Inter-examiner	Intra-examiner
EGAT 2/3	0.77 – 0.89	0.87 – 0.91	0.67 - 0.94	0.90 - 0.96
EGAT 2/4	0.74 - 1.00	0.87 - 1.00	0.78 - 1.00	0.87 - 1.00

Table 3.2. Labeling Criteria for the dataset

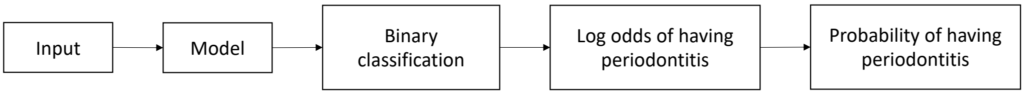
Label	**Case**	**Definition**
Non-severe periodontitis	No periodontitis	No evidence of mild, moderate, or severe periodontitis
	Mild periodontitis	≥2 interproximal sites with clinical attachment level ≥3 mm, and ≥2 interproximal sites with periodontal pocket depth ≥4 mm (not on same tooth) or one site with periodontal pocket depth ≥5 mm
	Moderate periodontitis	≥2 interproximal sites with clinical attachment level ≥4 mm (not on same tooth), or ≥2 interproximal sites with periodontal pocket depth ≥5 mm (not on same tooth)
Severe periodontitis	Severe periodontitis	≥2 interproximal sites with clinical attachment level ≥6 mm (not on same tooth) and ≥1 interproximal site with periodontal pocket depth ≥5 mm

Table 3.3. Feature transformation

Feature	**Original Form**		**Encoding**	**Model Required Form**
	Type	**Possible value**		**Encoded value**
Demographics				
Age	continuous	≥43	Similar to original form	
Gender	categorical	Male, Female	Binary Encoding	0, 1
Education	categorical	Less than secondary school, vocational or diploma, higher bachelor's degree, missing value	Ordinal Encoding	0, 1, 2
Income	categorical	< 20,000, 20,000 – 49,999, >50,000	Ordinal Encoding	0, 1, 2
Body Mass Index	continuous	~	Similar to original form	
Waist-to-hip ratio	continuous	~	Similar to original form	
Underlying diseases				
Diabetes Mellitus	categorical	negative, positive	Binary Encoding	0, 1

Hypertension	categorical	negative, positive	Binary Encoding	0, 1
Hyperlipidemia	categorical	negative, positive	Binary Encoding	0, 1
Risk behaviors				
Smoking habit	categorical	non-smoker, ex-smoking, current smoker	Ordinal Encoding	0, 1, 2
Alcohol drinking habit	categorical	Never drinker, ex-drinker, current drinker	Ordinal Encoding	0, 1, 2
Oral features				
Number of teeth	continuous	≥1 & ≤28	Similar to original form	
Plaque score	continuous	0~100	Similar to original form	
Laboratorial factors				
Lymphocytes	continuous	~	Similar to original form	
Uric acid	continuous	~	Similar to original form	
Triglycerides	continuous	~	Similar to original form	
Cholesterols	continuous	~	Similar to original form	
High density lipoproteins	continuous	~	Similar to original form	
Low density lipoproteins	continuous	~	Similar to original form	
Lipid lowering drugs taking status	categorical	negative, positive	Binary Encoding	0,1

Figure 3.1. Model Architecture


Input
Model
Binary classification
Log odds of having periodontitis
Probability of having periodontitis

CHAPTER IV
RESULTS

4.1. Data Preparation

As shown in Figure 4.1, 2271 subjects are included in the EGAT 2/3 survey, and 2016 subjects are examined in EGAT 2/4 survey. Interested features are initially selected by consultations with the advisor team. In five groups, the initial variables are –

1. Demographics – age, gender, education level, income, body mass index, and waist to hip ratio
2. Underlying diseases – diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease
3. Risk behaviors – smoking and alcohol drinking habits
4. Oral features – number of present/remaining teeth and plaque score
5. Laboratorial features – lymphocytes, uric acid, triglycerides, cholesterols, high density lipoproteins, low density lipoproteins, and lipid lowering drugs taking status.

The resulting data is split into 1817 distinct training subjects (80%) and 454 distinct testing subjects (20%) datasets using Pareto principle and the process is done cautiously to avoid situations where the same individual appears in both datasets.

4.2. Models

Seed of 1996 is set in all developing environments for reproducibility. All models are developed using 64bit 2.3 GHz Dual-Core Intel Core i5 processor.

4.2.1. Mixed effects logistic regression

The model is developed in STATA/SE (Special Edition) version 16.0 for 64-bit Intel processors. Built-in library of "melogit" — Multilevel mixed-effects logistic regression is used to fit models for binary and binomial responses which is appropriate for our objective. Mixed effects model with random intercept is applied with random effects for each subject.

Data Manipulation

Dataframe is managed in the long format where repeated measures of the same individual are recorded in separate row. Within 1817 distinct training subjects, 1817 subjects are observed in 2008 and 195 subjects in 2013.

Feature selection

Appropriate feature selection is required for statistical modelling, and stepwise forward selection is done. From the selected variables, univariate mixed effects models for each are developed, and they are ranked in increasing order based on their statistical significance which is p-value of Wald chi-squared test less than 0.1. It results in 15 significant variables out of initial 21. Afterwards, multivariate models are built by including one variable by one beginning from the most significance (least p-value). If the significant variable is no longer significant in multivariate regression, it will not be included in the subsequent regression with next significant variable.

Model Development

For the multivariate regression, final model includes six variables – gender, education level, diabetes mellitus, smoking habits, number of present/remaining teeth and plaque score. Fixed effects coefficients of the included variables are stated in Table 4.1. The output of the model is dichotomized using the prevalence of severe periodontitis in our dataset which is 35% and the final model is evaluated using the following metrics: sensitivity, specificity, accuracy, discrimination, positive likelihood ratio, positive and negative predictive value.

Performance

Application of the final model as the risk prediction model has great performances. Without considering the known random effects of the training samples, the model identifies 91.3% of positive cases and 90% of negative cases correctly with 90.5% overall accuracy. It has 82.9 and 95.2 positive and negative predictive value respectively. The positive likelihood ratio is 9.18 and the area under receiver operating curve is 0.98. It is good discrimination ability, allowing the model to have high sensitivity and specificity simultaneously. Figure 4.2. presents the receiver operating characteristic curves of the model on training and testing data.

When the same model is applied on the testing dataset, the model performs similarly with discriminative power of 0.98. Discriminative power is evaluated using area under receiver operating characteristic curve and values over 0.9 is considered outstanding. It is 91.5% accurate with 89.5 sensitivity and 92.5 specificity. Positive likelihood ratio of 11.9, positive predictive value of 86.2 and negative predictive value of 94.4 are observed. The performance of the model is shown in Table 4.2.

4.2.2. Recurrent Neural Network

The model is developed in Python 3.8.2 using Spyder integrated development environment 4.2.5 version. During the model development process, several libraries are applied along the data pipeline. For dataframe management and manipulation, NumPy version 1.19.2 and pandas version 1.2.3 are applied. Scalers and sample weights are created using Scikit-learn version 0.23.2 and recurrent neural networks are developed using Keras version 2.4.3 and TensorFlow version 2.31. For data visualizations, Matplotlib version 3.3.1 is used.

Data Manipulation

Data frame is managed in the cube format which is similar to the long format except the repeated measurements of each individual are stacked in the third dimension. Since all training individuals are required to have equal timesteps for recurrent neural networks, subjects with only one measurement are dropped and only 1345 distinct subjects are left.

For neural networks, numerical inputs are required so discrete or continuous variables are included as they are after applying MinMaxScaler to bound the values between 0 and 1. Label encoding is applied for categorical variables with more than binary class, as in Table 4.3.

Feature Selection

All 21 features are applied as the input of the model and dropout layers are applied between each hidden layer instead of manual feature selections.

Model development

Out of 2690 training data, only 858 records have chronic severe periodontitis, so class imbalance problem is anticipated. Therefore, class weights of 0.734 and 1.568 for negative and positive classes are calculated using Scikit-learn package. However, Keras consider the concept of class to be ambiguous in 3 and more dimensional data so the sample weights are applied using class weight values as a workaround.

For the hyperparameter tuning, basic specifications are set to find the best performing model on the data. For all feature sets, 20% of training data is used for validation. Simple RNN layer cells and Tanh activation functions are used for all nodes in the hidden layers. Dropout rate of 0.2 is put between every hidden and output layers so 20% of all connections between nodes are randomly deactivated, therefore it is not a fully connected model. One node in the output layer; sigmoid activation function is used for binary classification. Binary Cross Entropy is used for loss function and accuracy is the monitor metric. Stochastic Gradient Descent is used for optimizer. Batch size of 64 is applied for mini-batch optimization. 1000 epochs with early stopping are used for time and computation resource constraints. The outputs of the model are dichotomized using 0.35 according to the prevalence of severe chronic periodontitis in the dataset. Number of hidden layers, number of nodes in each hidden layer and learning rate of the optimizers are tuned for the optimal performance metrics. Models are trained with various combinations of only one hidden layer to six hidden layers, nodes in each layer ranging from 21 to 80 and the learning rate from 1 to 0.001,

Performance

Recurrent neural network with three hidden layers and 70 Simple RNN nodes in each layer is applied and learning rate of 1 is used to optimize model loss. The resulting model is 92.3% accurate overall with 87.4% sensitivity and 94.7% specificity. Along with 88.4% positive predictive value and 94.1% negative predictive value, the model has 16.3 positive likelihood ratio. AUC measures the probability that a model can correctly discriminate between randomly selected individuals with or without the event and 0.95 means the model is very proficient.

However, as shown in Table 4.4., when the same model is applied on the testing data, the performance diminishes overall with 65.2 accuracy, 42.7 sensitivity and 75.7 specificity. The discrimination becomes 0.65 which is very poor. Comparing the positive likelihood ratio of 1.7, positive predictive value of 45.3 and negative predictive value of 73.8 to respective performances on training dataset, the model can be considered overfit. Figure 4.3. presents the receiver operating characteristic curves of the overfit model on training and testing data.

Instead, a new set of hyperparameters is searched with the condition that we allow ±5% discrepancy in accuracy performance between two datasets. The final model has four hidden layers with 62, 72, 72 and 62 RNN nodes in feed forward order and learning rate of 0.01 for optimizer. As seen in Table 4.5., it is evident that the performance of the model is inferior compared to the preceding models. Area under receiver operating curve of 0.75 is considered only moderate but the model is no longer overfit to the training data. Receiver operating characteristic curves of the final model on training and testing data are compared in Figure 4.4.

4.2.3. Mixed effects – Support Vector Machine

The model is developed in R version 4.02 using R Studio 1.3.1056 version. Support vector machine is applied as machine learning regressor in mixed effects machine learning model. Several packages are applied for the data management and model development process. readstata version 0.9.2 is used for importing STATA datasets. For the mixed effects – support vector machine, e1071 version 1.7-4 is used to model SVM and lme4 version 1.1.-26 to estimate the random effects. pROC version 1.16.2 and epiR version 2.0.19 is used to evaluate the model performance.

Data Manipulation

Data frame is managed in the long format same as mixed effects logistic regression models. For support vector machines, numerical inputs are required so one hot encoding is applied for categorical variables. No additional data scaling is done other than default parameter in e1071 library.

Feature selection

No additional feature reduction is done after initial 21 features selected by literature reviews and expert opinion. On the contrary, one hot encoding the categorical variables with more than binary class result in additional input features totaling 26 variables.

Model development

Hyperparameters of the overall model are set to be 10 maximum macro iterations with 0.01 tolerance and 50 maximum micro iterations with 0.001 tolerance. Initial random effect of zero is set. Instead, the hyperparameters of support vector regressor are tuned. Kernels, C value and gamma value when applicable are also tuned. Nu regression is applied while optimizing multiple nu values. Various combinations of nu-value 0.1 to 0.6; linear, gaussian, polynomial kernels with C value 0.1 to 0.0001 are applied during the optimization process.

Performance

Support vector regressor with nu value of 0.4 is applied. Radial kernel with 0.2 gamma value and C value of 0.1 is set. Resulting model perform very good with overall accuracy of 98.4%. The metrics are 99.7% sensitivity (true positive rate) and 97.7% specificity (true negative rate). The model are 43.3 times more likely to correctly identified the true positive subjects as positive than incorrectly consider the negative patients as such. Discriminative power of 0.99 can be considered very proficient.

However, when validated by the testing dataset as in Table 4.6, the model performance is reduced greatly to AUC value of 0.62 when is considered poor. Figure 4.5. presents the receiver operating characteristic curves of the overfit model on training and testing data. The overall accuracy is 62% with only 38.1% of positive predictions and 80.1% negative predictions are correctly predicted. The model is considered overfit to the training dataset so new hyperparameter sets are searched.

Nu-regression with nu value of 0.5 and radial kernel is applied. C-value of 0.1 and gamma value of 0.3 is set and the resulting model is considered as the optimized model with balanced performances. Area under receiver operating curve is 0.76 is only moderate but when compared to performances on the testing data, it is observed that the model is no longer overfit to the training data. Receiver operating characteristic curves of the final model on training and testing data are compared in Figure 4.6. The performances of the final mixed effects – support vector machine is shown in Table 4.7. Table 4.8. presents comparison of all final classification models (Mixed effects logistic regression, Recurrent neural networks, and Mixed effects support vector machine).

Table 4.1. Fixed Effects Coefficients and Odds Ratio Estimates for Significant Variables Retained in the Final Multivariate Mixed Effects Logistic Regression Model

Variables	*Covariates*	*Coefficient (SE)*	*Odd ratios (95% CI)*	*P-value*
Gender	Male	0.97 (0.23)	2.63 (1.68 to 4.10)	< 0.001
	Female	ref	ref	
Education	< High school	2.04 (0.38)	7.68 (3.62 to 16.30)	< 0.001
	Vocational School	1.35 (0.35)	3.86 (1.93 to 7.72)	< 0.001
	Bachelor's degree	0.29 (0.35)	1.34 (0.68 to 2.64)	< 0.001
	> Bachelor's degree	ref	ref	0.393
Smoking	Non-smoker	ref	ref	
	Ex-smoker	0.73 (0.21)	2.09 (1.38 to 3.17)	0.001
	Current smoker	1.68 (0.25)	5.38 (3.28 to 8.83)	< 0.001
Diabetes Mellitus	Positive	0.50 (0.22)	1.66 (1.07 to 2.57)	0.024
	Negative	ref	ref	
Number of teeth	-	-0.06 (0.02)	0.94 (0.91 to 0.97)	< 0.001
Plaque score	-	0.03 (0.004)	1.03 (1.02 to 1.03)	< 0.001

Abbreviation: CI: Confidence Interval; SE: Standard Error; ref: Reference covariate group.

Table 4.2. Performance of Mixed effects logistic regression

	On Training data *(95% CI)*	***On Testing data*** *(95% CI)*
%Sensitivity	91.3 (89.5 – 93.0)	89.5 (85.1 – 92.9)
%Specificity	90.0 (88.7 – 91.3)	92.5 (89.9 – 94.6)
%Accuracy	90.5 (89.4 – 91.5)	91.5 (89.3 – 93.3)
AUC	0.98 (0.98 – 0.98)	0.98 (0.98 – 0.99)
Positive Likelihood Ratio	9.18 (8.05 – 10.46)	11.93 (8.77 – 16.25)
%Positive Predictive Value	82.9 (80.7 – 85.0)	86.2 (81.6 – 90.1)
%Negative Predictive Value	95.2 (94.1 – 96.1)	94.4 (92.0 – 96.2)

Table 4.3. Label encoding for categorical variables

Categorical variable	*Covariate*	*Labels*
Education	< High school	0
	Vocational School	1
	Bachelor's degree	2
	> Bachelor's degree	3
Income	< 20,000	0
	20,000-49,999	1
	50,000 ++	2
Smoking	never smoker	0
	ex-smoker	1
	current smoke	2
Alcohol drinking	non-drinker	0
	occasional drinker	1
	frequent drinker	2

Table 4.4. Performance of overfit recurrent neural network

	On Training data *(95% CI)*	***On Testing data*** *(95% CI)*
%Sensitivity	87.4 (85.0 – 89.6)	42.7 (36.0 – 49.7)
%Specificity	94.7 (93.5 – 95.6)	75.7 (71.5 – 79.6)
%Accuracy	92.3 (91.3 – 93.3)	65.2 (61.4 – 68.8)
AUC	0.95 (0.94 – 0.96)	0.65 (0.61– 0.70)
Positive Likelihood Ratio	16.3 (13.5 – 19.8)	1.7 (1.4 – 2.2)
%Positive Predictive Value	88.4 (86.1 – 90.5)	45.3 (38.3 – 52.4)
%Negative Predictive Value	94.1 (93.0 – 95.2)	73.8 (69.5 – 77.7)

Table 4.5. Performance of final recurrent neural network

	On Training data *(95% CI)*	***On Testing data*** *(95% CI)*
%Sensitivity	63.1 (59.7 – 66.3)	58.2 (51.3 – 64.9)
%Specificity	73.3 (71.2 – 75.3)	73.5 (69.2 – 77.5)
%Accuracy	70.0 (68.3 – 71.8)	68.6 (64.9 – 72.1)
AUC	0.75 (0.73 – 0.77)	0.73 (0.68 – 0.77)
Positive Likelihood Ratio	2.36 (2.16 – 2.59)	2.20 (1.82 – 2.66)
%Positive Predictive Value	52.5 (49.4 – 55.6)	50.8 (44.4 – 57.3)
%Negative Predictive Value	80.9 (78.9 – 82.8)	78.9 (74.7 – 82.7)

Table 4.6. Performance of overfit Mixed Effects – Support Vector Machine

	***On Training data** (95% CI)*	***On Testing data** (95% CI)*
%Sensitivity	99.7 (99.1 – 99.9)	69.6 (62.8 – 75.8)
%Specificity	97.7 (96.9 – 98.3)	52.0 (47.4 – 56.5)
%Accuracy	98. 4 (97.8 – 98.9)	57.2 (53.4 – 61.0)
AUC	0.99 (0.99 – 1.0)	0.62 (0.58 – 0.66)
Positive Likelihood Ratio	43.3 (32.2 – 58.2)	1.45 (1.27 – 1.65)
%Positive Predictive Value	95.6 (94.1 – 96.8)	38.1 (33.1 – 43.2)
%Negative Predictive Value	99.8 (99.5 – 100)	80.1 (75.3 – 84.4)

Table 4.7. Performance of final Mixed Effects – Support Vector Machine

	***On Training data** (95% CI)*	***On Testing data** (95% CI)*
%Sensitivity	52.8 (49.5 – 56.0)	46.1 (39.1 – 53.2)
%Specificity	82.7 (80.9 – 84.4)	78.2 (74.2 – 81.8)
%Accuracy	72.7 (71.0 – 74.4)	68.6 (65.0 – 72.1)
AUC	0.76 (0.75 – 0.77)	0.70 (0.68 – 0.73)
Positive Likelihood Ratio	3.05 (2.72 – 3.43)	2.11 (1.69 – 2.64)
%Positive Predictive Value	60.5 (57.0 – 63.8)	47.2 (40.1 – 54.4)
%Negative Predictive Value	77.8 (75.9 – 79.6)	77.4 (73.4 – 81.0)

Table 4.8. Performance of all final models (Performance with 95% Confidence Interval)

Metrics\Models	*Mixed effects Logistic Regression*		*Recurrent Neural Network*		*Mixed effects Support Vector Machine*	
	Train	Test	Train	Test	Train	Test
%Sensitivity	91.3 (89.5 – 93.0)	89.5 (85.1 – 92.9)	63.1 (59.7 – 66.3)	58.2 (51.3 – 64.9)	52.8 (49.5 – 56.0)	46.1 (39.1 – 53.2)
%Specificity	90.0 (88.7 – 91.3)	92.5 (89.9 – 94.6)	73.3 (71.2 – 75.3)	73.5 (69.2 – 77.5)	82.7 (80.9 – 84.4)	78.2 (74.2 – 81.8)
%Accuracy	90.5 (89.4 – 91.5)	91.5 (89.3 – 93.3)	70.0 (68.3 – 71.8)	68.6 (64.9 – 72.1)	72.7 (71.0 – 74.4)	68.6 (65.0 – 72.1)
AUC	0.98 (0.98 – 0.98)	0.98 (0.98 – 0.99)	0.75 (0.73 – 0.77)	0.73 (0.68 – 0.77)	0.76 (0.75 – 0.77)	0.70 (0.68 – 0.73)
Positive Likelihood Ratio	9.18 (8.05 – 10.46)	11.93 (8.77 – 16.25)	2.36 (2.16 – 2.59)	2.20 (1.82 – 2.66)	3.05 (2.72 – 3.43)	2.11 (1.69 – 2.64)
%Positive Predictive Value	82.9 (80.7 – 85.0)	86.2 (81.6 – 90.1)	52.5 (49.4 – 55.6)	50.8 (44.4 – 57.3)	60.5 (57.0 – 63.8)	47.2 (40.1 – 54.4)
%Negative Predictive Value	95.2 (94.1 – 96.1)	94.4 (92.0 – 96.2)	80.9 (78.9 – 82.8)	78.9 (74.7 – 82.7)	77.8 (75.9 – 79.6)	77.4 (73.4 – 81.0)

Figure 4.1. Model Development Diagram

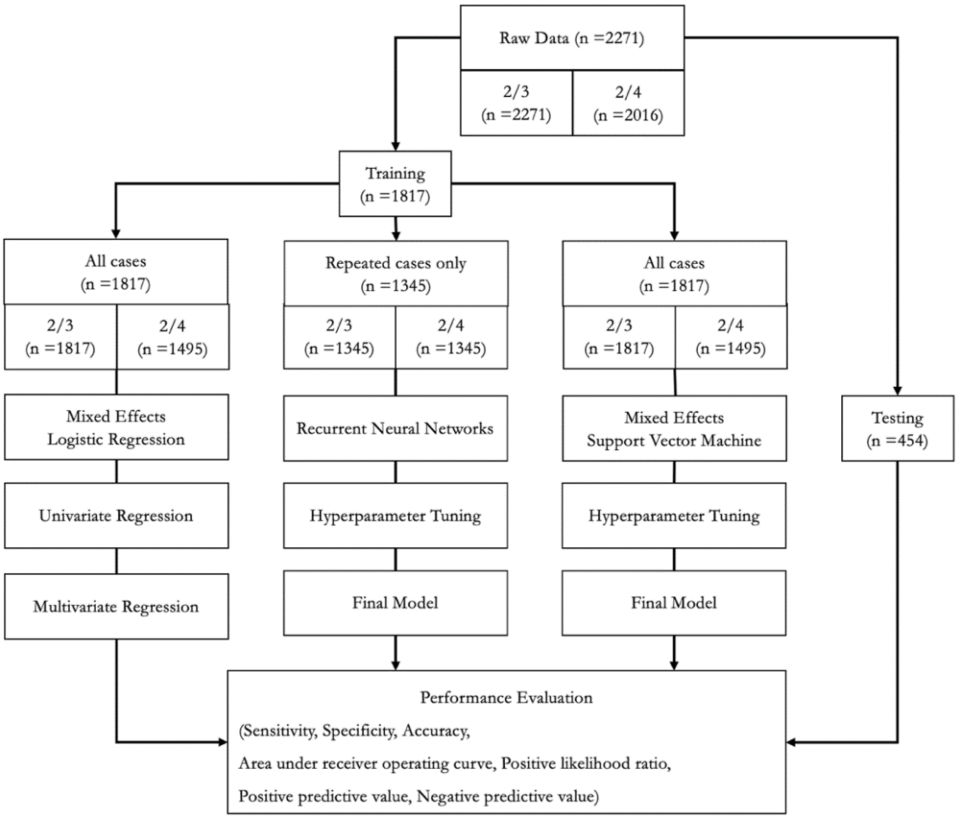


Figure 4.2. Receiver operating curve of mixed effects logistic regression (left – on training data and right – on the testing data)

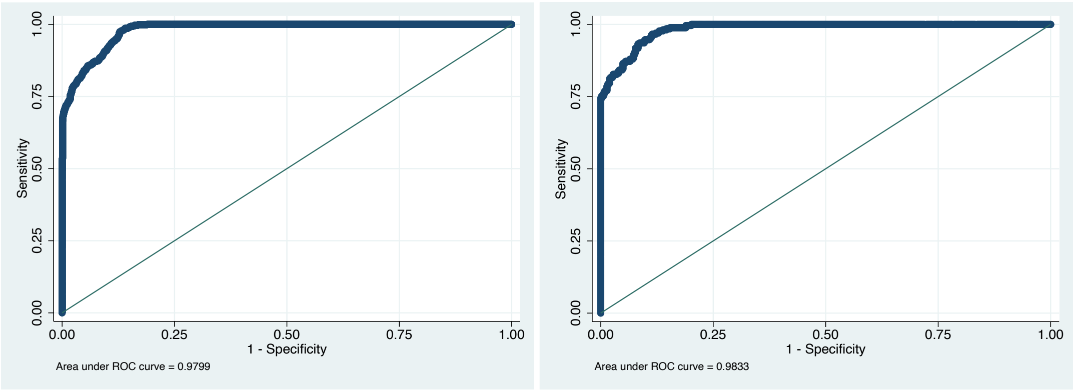


Figure 4.3. Receiver operating curve of overfit recurrent neural network

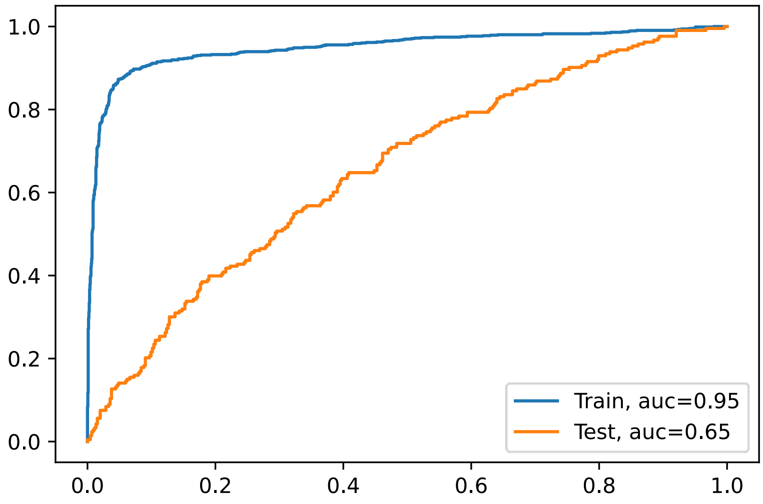


Figure 4.4. Receiver operating curve of final recurrent neural network

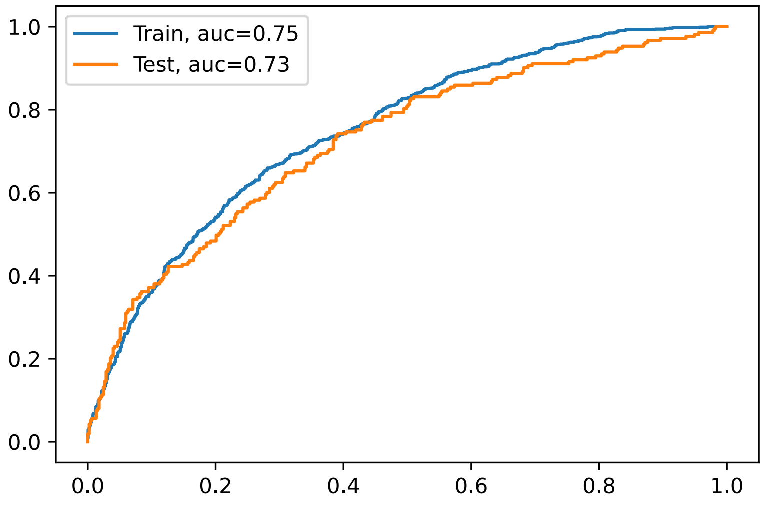


Figure 4.5. Receiver operating curve of overfit Mixed Effects – Support Vector Machine

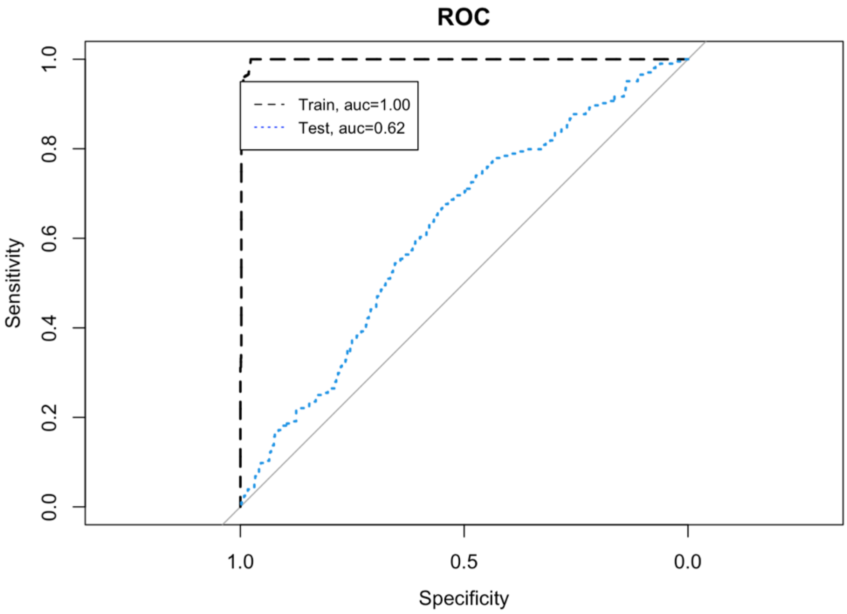
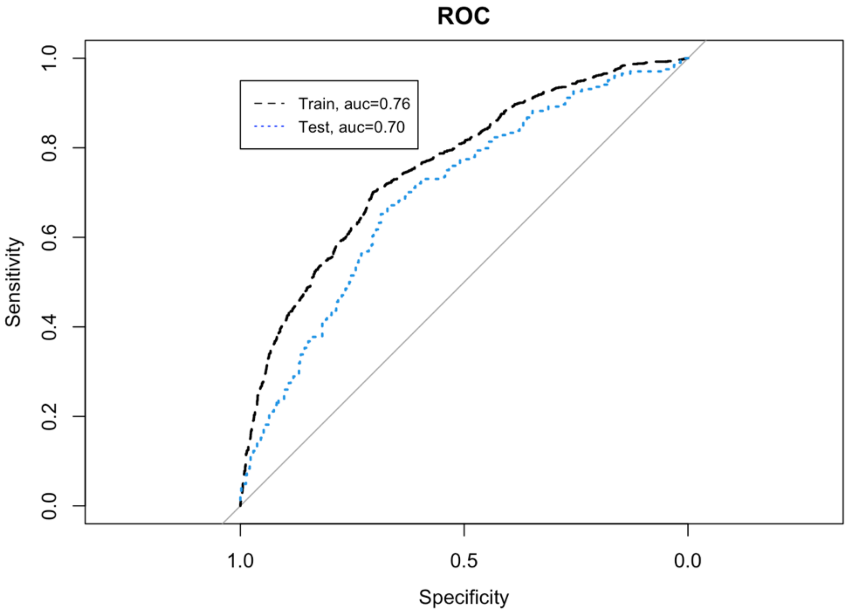


Figure 4.6. Receiver operating curve of final Mixed Effects – Support Vector Machine



CHAPTER V
DISCUSSIONS

5.1. Minority positive class

In many real-life problems, imbalanced datasets happen due to multiple reasons such as selection of survey population done correctly or not. The class imbalance problem can be better understood as three separate problems, which are –

1. assuming that a performance metric is appropriate when it is not
2. assuming that the test distribution matches the training distribution when it is not
3. assuming that there is enough minority class when it is not.

Provost F. (2000)[55] states that two fundamental assumptions are made in traditional classifiers. The first is that the goal of the classifiers is maximum accuracy (minimum error rate); the second is that the class distribution of the training and test datasets is the same. Under these two assumptions, predicting everything as the majority class for an imbalanced dataset is often the right thing to do.

Within 776 observations of our 454 testing subjects, 509 observations are negative. Considering if a classification model predicts all observations to be negative, 267 observations are incorrectly identified as negative (false negative), and 509 observations are correctly identified as negative thus true negative. While there are zero observations for both correctly identified positives (true positive) and incorrectly identified positives (false positive), we will have 65.6% accuracy rate regardless of the usability of such model.

Thus, we evaluate our models with six different metrics including sensitivity and specificity. Sensitivity is the ratio of true positive to all positive observations where specificity is the same but for negative cases. Positive predictive value is the ratio of true positive to all observations predicted as positive and the same goes for negative predictive value with negative cases. In the stated scenario, the sensitivity of this model is zero in contrast to 100% specificity, meaning the model is unusable. Similarly, negative predictive value will be 65.6% and positive predictive value is zero as well since the model cannot detect positive (non-disease) subjects.

Therefore, in machine learning algorithms, hyperparameter tuning is done during the training process to optimize the performance of the model. Depending on the chosen set of hyperparameters, the model can become overfit to the training dataset like several reported models in chapter 4. The model pays a lot of attention to random noises in the training data, so they fail to generalize on the data it has not seen before and they are considered as high variance. As a result, they perform very well on the training dataset but high error rate on the testing dataset. On the contrary, the model can become biased by paying very little attention to the training data, resulting in oversimplified models. They lead to high error rate on both training and testing data. Further, hyperparameter optimization process is done to balance between bias-variance tradeoff by comparing the model performance on both training and testing data.

Even with appropriate optimization, the training data distribution should reflect the true distribution or prevalence of the condition, so that the model can learn to generalize and perform similarly on new subjects as well. That also applies with the data splitting where the testing data distribution should reflect the training data. According to 8th Thailand national health survey (2017), 26% of Thai adults and 36% of Thai elderly people have severe chronic periodontitis. Our surveys include subjects who are current employees of Electricity Generating Authority of Thailand with the mean age of 54.4 (43.7 – 75.3) and our training dataset reflects to 1,094 (34.6%) from 3,158 observations having severe chronic periodontitis which can be considered consistent. The testing data includes 267 positive observations (34.4%) out of 776, which also matches appropriately.

Ling (2010)[56] states that the imbalanced class problem becomes meaningful only if one or both two assumptions above are false; that is, if the cost of different types of error (false positive and false negative in the binary classification) is not the same, or if the class distribution in the test data is different from that of the training data. The first problem is effectively dealt with cost-sensitive models. In recurrent neural networks, the amount of error in each subject is evaluated with a loss function such as binary cross entropy as shown in Figure 5.1, and the overall error of the model is considered the cost of the model. During the training process, for each set of weights and biases for the hidden layers, the cost value is calculated, and these sets are adjusted to decrease the cost value as much as possible. Thus, by adjusting the loss value for misclassification, we can guide the model into more balanced performance instead of preferring the majority class. In Figure 5.2, class weights are applied to make it more expensive to misclassify a minority class into majority class than a majority into minority, which would further encourage prediction of everything as the majority class. Since we have similar class distribution for all our datasets, we can disregard the second problem as well. Then the literature suggests inadequate number of samples in the minority class for the classifier to learn adequately, which means we have a problem of insufficient or small training class which is different from imbalanced class problem. It can only be addressed by collecting more minority class subjects.

5.2. Limitations of current study

To adjust for the second assumption made above, class weights are planned to be applied for recurrent neural networks. Keras library is a python library with TensorFlow backend, a major utility for training neural networks and deep learning and our source of choice for the recurrent neural networks. This library considers the concept of class to be ambiguous in data with 3 or more dimensions, which is the input data dimension for recurrent neural networks. Thus, sample weights based on class weights are applied instead as shown in Figure 5.3. For mixed effects support vector machine, e1071 library being applied for support vector machine in the model does not have an option to adjust for class weights. However, observing that mixed effects logistic regression does not require adjusting class weights and recurrent neural networks having similar problems even with class weights applied, we consider the poor performances are the problem of insufficient positive class rather than imbalanced class problem.

Mixed effects logistic regression models are considered to be superior to simple logistic regression models because they consider random effects in addition to fixed effects estimated by conventional models by considering multiple observations of the same subject as well. Compared to the best performing model during the literature review, Verhulst et al.[20] had the most balanced performance for sensitivity and specificity with 80% and 88% respectively and AUC of 0.91. When compared, our model performed much better. During the training process, observations of different subjects are used by logistic regression to estimate the fixed effects or population average effects of the selected predictor variables (gender, education, number of teeth) on the target variable which is likelihood of having the condition. In mixed models, multiple records of the same subject are used to adjust for subjects specific or random effects as well. On the contrary, recurrent neural networks require all the training subjects to have exactly same number of timesteps. For other applications of recurrent neural networks such as natural language processing, padding and masking techniques are applied to adjust, but it is not done in our study. Therefore, we had to remove subjects with only one observation from the training and testing data, resulting in decreased number of subjects in comparison with other models. We consider this to be one of the major factors affecting the performance of our neural network.

Main advantage of recurrent neural networks is the ability to consider previous timesteps in terms of hidden vectors together with current features. However, since we have only two timesteps, the first timestep is basically a multilayer perceptron (simple artificial neural networks) mapping from features to diagnosis at the first timestep. The second timestep will include the context from the first timestep, however it is observed that the performance of the recurrent neural networks is inferior compared to mixed effects logistic regression model. Typically, the problem with similar models is that the model forgetting over long sequences but here we believe small number of timesteps as well as small training class result in poor performance of the model.

For our machine learning models, we did not do further dimensional reduction over expert opinions and decision with the advisor team. Mixed effects logistic regression, the statistical model requires feature reduction, since including too much can result in overfitting. However, we need to balance the appropriate number of features since not including all features correlated with the target will result in inferior performance of the model. While we do not have a set limit on numbers of included parameters within the model, several rules of thumb such as one predictor parameter for ten events (one in ten rule), one in twenty rule and one in fifty rules have been suggested.[57] Here we applied stepwise forward selection with statistical significance of 0.1 for univariate and 0.05 for multivariate regression. Of course, this approach is not without its drawbacks, since stepwise method is considered unstable[58] in a sense that addition or removal of a covariate can result in varying p-value of the parameter, including scenarios where they become insignificant in multivariate regressions. However, we would consider our mixed effects logistic regression to have appropriate performance without overfitting or inferior predictive ability.

For sigmoid-based classification models, the output of the models are probabilities of having the positive class. Therefore, we must select a threshold on which we would dichotomize the value. The default value would be 0.5, but currently the decision threshold is 0.35 to reflect the prevalence of the condition in our data (34.6%). However, we can adjust the threshold to overestimate or underestimate since the cost of having more false predictions is different based on the problem. By lowering the decision threshold, the model will overestimate by considering subjects with lower probability to be positive, which means that it will result in less false negatives and more false positives. We are willing to accept more false positive subjects since we do not want to miss the opportunity of early diagnosis by getting a false negative in the screening step. Although the follow up examination is what we are trying to circumvent, the screening system will reduce the overall workload necessary regardless as shown in Figure 5.4. We need to balance between demerits of following up and demerits of not following up.

5.3. Application on mock data

Four mock samples who were present at both surveys are selected and a subset of their features which were applied by mixed effects logistic regression model are shown in Table 5.1. Four subjects have different disease progression over different observations,

1. continuing healthy periodontium,
2. persisting severe chronic periodontitis,
3. developing over time and
4. recovering over time.

The selected mock population have 25% female and 3 subjects are 75% non-smokers. All subjects have at least a bachelor's degree, and none has diabetes mellitus. Average number of present teeth in the first survey is 23.5 and in the second, it is 22.25 teeth with two subjects losing dentition over time. The female subject has decreased oral hygiene over time from 22.7% to 31.8% of tooth surfaces with dental plaque adhesion in second survey but still has a better oral hygiene compared to the male subjects with average of 63.12 plaque score. Models with selected final sets of hyperparameters are performed on the mock samples to evaluate their performance. All models are logit based and the output of the model are transformed into probability which subsequently dichotomized into positive and negative. For subjects with higher or equal probability with 35%, they are considered to have severe chronic periodontitis.

The predicted diagnosis and the probabilities outputted by the model are reported in Table 5.2. Out of eight observations with 4 positive and 4 negative cases, mixed effects logistic regression model has 75% accuracy, 100% sensitivity and 50% specificity. Recurrent neural networks are also 75% accurate with 75% sensitivity and 75% specificity. Mixed effects support vector machine is 75% accurate, 50% sensitive and 100% specific. Considering positive subjects to have 100% probability and negative subjects as 0% probability, mixed effects logistic regression model has average 7.25% deviation in probability, recurrent neural networks have 13.63% deviation and mixed effects support vector machine performs the worst with 19.75% deviation.

Although it should be noted that mixed effects models tried to predict the same class for the same subject regardless of the timestep, recurrent neural network was able to identify correctly for both surveys of subject D. For subject C, the model predicts incorrectly for both timesteps but unlike the competitors, the model is not predicting the same class for the same subject. This might be due to the recurrent neural networks including more features than mixed effects logistic regression, but mixed effects support vector machines include as much features as the neural networks. Then, we should consider recurrent neural networks being aware of previous timestep in terms of hidden state vector unlike the mixed effects models not knowing the random effects of the new subjects that were not in the training dataset.

5.4. Application in real life scenarios

Logistic regression models have been traditionally applied as scoring systems. Since logistic regressions are linear relationship of predictor features to the log-odds, the intercept of the model with the coefficients of each features multiplied with the features of a subject can output the logit of the subject, which in turn can be converted to the probability of having the condition. To assess the risk score for developing severe periodontitis,

Risk score = -3.93 + (0.97 x male)
+ (2.04 x education < High school)
+ (1.35 x education Vocational School)
+ (0.29 x education Bachelor's degree)
+ (0.73 x Ex-smoker) + (1.68 x Current smoker)
+ (0.50 x diabetes mellitus)
+ (-0.06 x number of teeth) + (0.03 x plaque score)

– where the covariate should be replaced with 1 if applicable and 0 if else. From the risk score, the subject's risk of developing the condition can be calculated as $\frac{e^{Risk\ score}}{1+\ e^{Risk\ score}}$.

With machine learning models, the concepts of coefficients are ambiguous to calculate manually. Instead, the models are outputted as a file format such as flask, pickle, or hierarchy data format (.hdf5/ .h5py). The model can be imported in web services such as Amazon Web Service (AWS) or Heroku to be deployed. Advantage of this approach is that the web application can be built to be visually appealing and easily applicable by the intended user. The complex applications are done in the background and additional processes such as data scraping and preprocessing from electronic medical records can be automated as well.

With necessary internet connectivity, the model can be updated in the backend with new data that can also be collected with a web application. With new data, the effects of each predictor known as coefficients or weights can be readjusted or updated with new evidence. Similar systems can be built for logistic regression models as well, but unlike machine learning models, all the previous training data must be stored and trained together with the new data so that the coefficient can be updated. Of course, the validity of the user-inputted data would be a concern to be included as the training data as well as there will be privacy concern for valid data. Easy access of risk assessment programs can lead to overuse or apprehension of those who might not be the target population.

5.5. Future Research and Study

For both training and testing of our models, we apply data from the same source. For proper model evaluation, external validation using data from other centers or surveys is required. Data from other Thai populations as well as different countries or ethnicities should be used to evaluate the capability of the model to generalize. If necessary, the models should be updated applying new data, especially the recurrent neural networks which we consider to be suffering from insufficient training class and insufficient timesteps to make full use of its unique capability.

With appropriate or acceptable performance, the models should be able to deploy so that they can help screening the situations where large numbers of people are to be periodontally examined such as public health missions. Application programming interfaces (APIs) can be used to scan the health information systems to screen the patients ahead of time. Web or desktop applications can be deployed at the stations where history taking interviews are done. Mobile applications should help the staffs to apply while on the go, or even let the examinees apply by themselves. The models will be able to save time, material, and human resources necessary to manually measure 168 individual sites per every examinee.

Table 5.1. Subset of mock data samples

ID	*Survey*	*Sex*	*Education*	*Smoking*	*Diabetes Mellitus*	*Number of teeth*	*Plaque score*	*Diagnosis*
A	2/3	Female	> Bachelor's degree	Non-smoker	Negative	22	22.7	Negative
A	2/4	Female	> Bachelor's degree	Non-smoker	Negative	22	31.8	Negative
B	2/3	Male	Bachelor's degree	Non-smoker	Negative	21	85.7	Positive
B	2/4	Male	Bachelor's degree	Non-smoker	Negative	21	95.2	Positive
C	2/3	Male	Bachelor's degree	Non-smoker	Negative	26	100	Negative
C	2/4	Male	Bachelor's degree	Non-smoker	Negative	25	74	Positive
D	2/3	Male	Bachelor's degree	Ex-smoker	Negative	25	44	Positive
D	2/4	Male	Bachelor's degree	Ex-smoker	Negative	21	50	Negative

Table 5.2. Performance of different classification models on the mock data samples (0.35 as decision threshold)

ID	*Survey*	*True Diagnosis*	*MELR*	*RNN*	*MESVM*
A	2/3	Negative	N (0.01)	N (0.06)	N (0.24)
A	2/4	Negative	N (0.01)	N (0.03)	N (0.23)
B	2/3	Positive	P (0.85)	P (0.75)	P (0.36)
B	2/4	Positive	P (0.88)	P (0.53)	P (0.36)
C	2/3	Negative	P (0.50)	P (0.45)	N (0.31)
C	2/4	Positive	P (0.35)	N (0.23)	N (0.31)
D	2/3	Positive	P (0.36)	P (0.57)	N (0.30)
D	2/4	Negative	P (0.46)	N (0.29)	N (0.31)

Abbreviations-

MELR = Mixed Effects Logistic Regression

MESVM = Mixed Effects Support Vector Machine

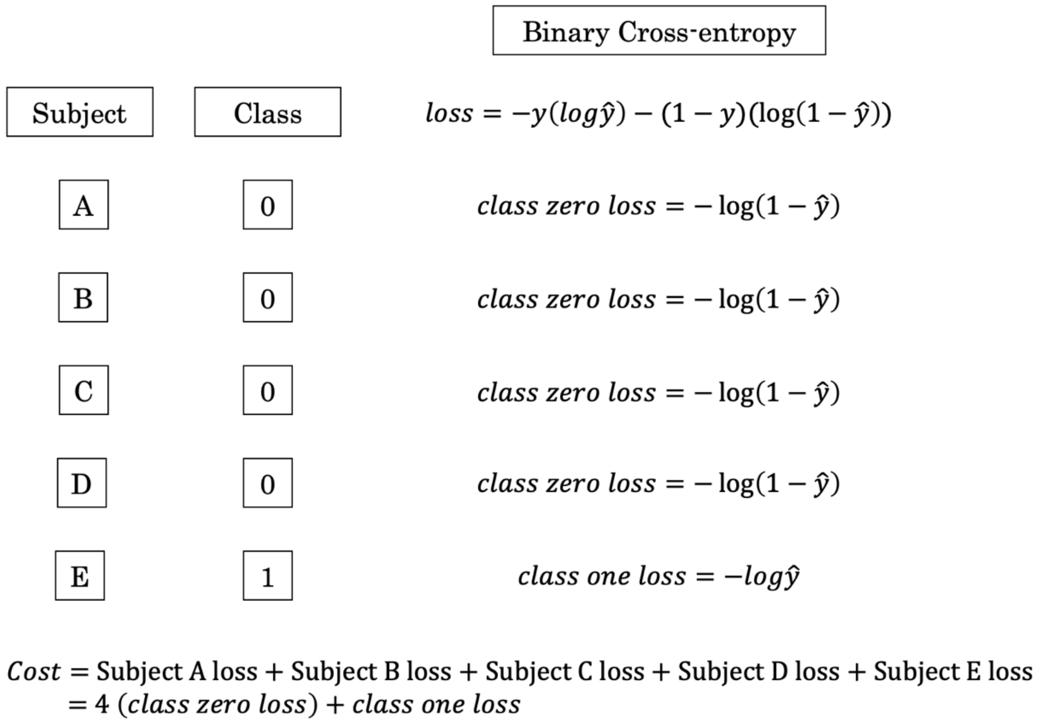
N = None or Non-severe chronic periodontitis

P = Severe chronic periodontitis

X (0.0) = Predicted diagnosis (probability of having severe chronic periodontitis)

RNN = Recurrent Neural Networks

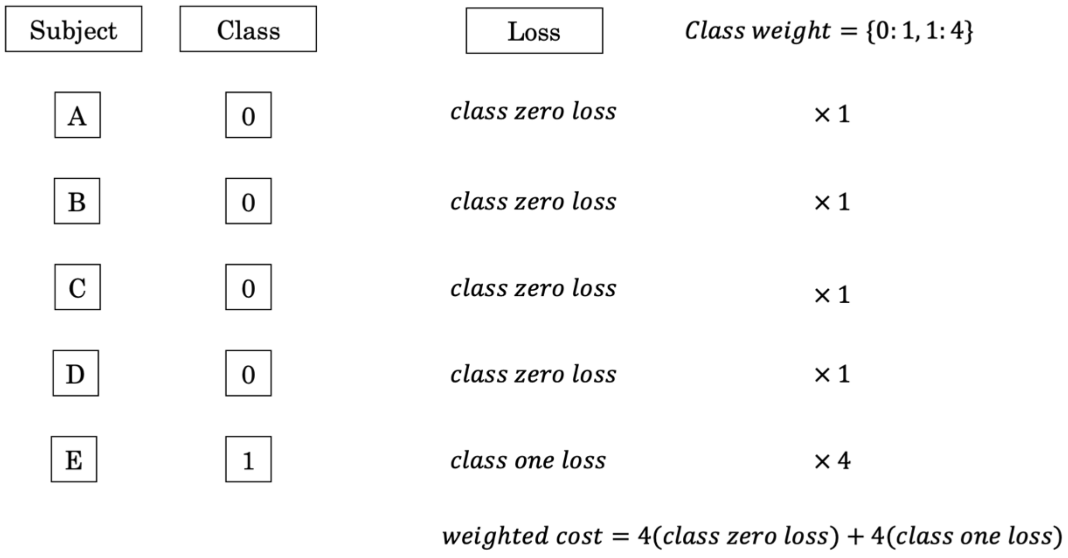
Figure 5.1. Cost function for imbalanced class



		Binary Cross-entropy
Subject	Class	$loss = -y(log\hat{y}) - (1-y)(\log(1-\hat{y}))$
A	0	$class\ zero\ loss = -\log(1-\hat{y})$
B	0	$class\ zero\ loss = -\log(1-\hat{y})$
C	0	$class\ zero\ loss = -\log(1-\hat{y})$
D	0	$class\ zero\ loss = -\log(1-\hat{y})$
E	1	$class\ one\ loss = -log\hat{y}$

$$\begin{aligned} Cost &= \text{Subject A loss} + \text{Subject B loss} + \text{Subject C loss} + \text{Subject D loss} + \text{Subject E loss} \\ &= 4\ (class\ zero\ loss) + class\ one\ loss \end{aligned}$$

Figure 5.2. Class weight-adjusted cost function



Subject	Class	Loss	$Class\ weight = \{0{:}\,1, 1{:}\,4\}$
A	0	$class\ zero\ loss$	$\times 1$
B	0	$class\ zero\ loss$	$\times 1$
C	0	$class\ zero\ loss$	$\times 1$
D	0	$class\ zero\ loss$	$\times 1$
E	1	$class\ one\ loss$	$\times 4$

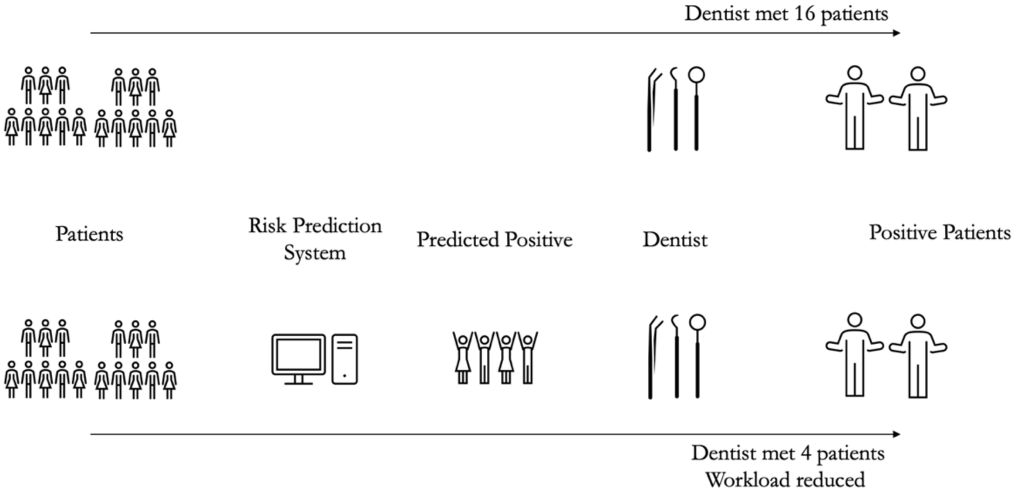
$$weighted\ cost = 4(class\ zero\ loss) + 4(class\ one\ loss)$$

Figure 5.3. Sample weight-adjusted cost function

Subject	Class	Loss	$Sample\ weight = \{A{:}\,1, B{:}\,1, C{:}\,1, D{:}\,1, E{:}\,4\}$
A	0	*class zero loss*	× 1
B	0	*class zero loss*	× 1
C	0	*class zero loss*	× 1
D	0	*class zero loss*	× 1
E	1	*class one loss*	× 4

$$weighted\ cost = 4(class\ zero\ loss) + 4(class\ one\ loss)$$

Figure 5.4. Screening system in action



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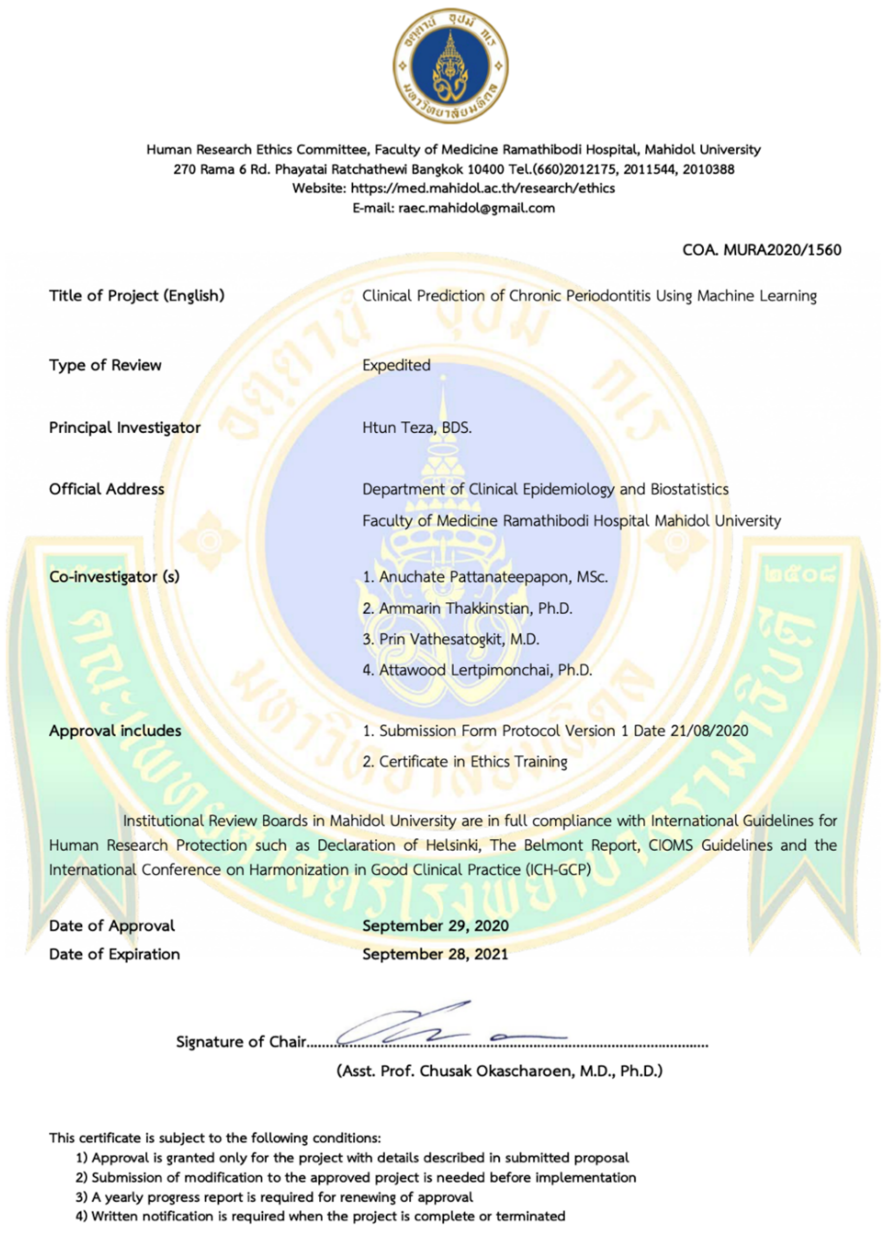
APPENDIX A
ETHICAL CLEARANCE



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COA. MURA2020/1560

Title of Project (English)	Clinical Prediction of Chronic Periodontitis Using Machine Learning
Type of Review	Expedited
Principal Investigator	Htun Teza, BDS.
Official Address	Department of Clinical Epidemiology and Biostatistics Faculty of Medicine Ramathibodi Hospital Mahidol University
Co-investigator (s)	1. Anuchate Pattanateepapon, MSc. 2. Ammarin Thakkinstian, Ph.D. 3. Prin Vathesatogkit, M.D. 4. Attawood Lertpimonchai, Ph.D.
Approval includes	1. Submission Form Protocol Version 1 Date 21/08/2020 2. Certificate in Ethics Training

Institutional Review Boards in Mahidol University are in full compliance with International Guidelines for Human Research Protection such as Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Date of Approval	**September 29, 2020**
Date of Expiration	**September 28, 2021**

Signature of Chair...

(Asst. Prof. Chusak Okascharoen, M.D., Ph.D.)

This certificate is subject to the following conditions:

1) Approval is granted only for the project with details described in submitted proposal
2) Submission of modification to the approved project is needed before implementation
3) A yearly progress report is required for renewing of approval
4) Written notification is required when the project is complete or terminated