

Personalized Prognostic Models for Oncology: A Machine Learning Approach

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Abstract

We have applied a little-known data transformation to subsets of the Surveillance, Epidemiology, and End Results (SEER) publically available data of the National Cancer Institute (NCI) to make it suitable input to standard machine learning classifiers. This transformation properly treats the right-censored data in the SEER data and the resulting Random Forest and Multi-Layer Perceptron models predict full survival curves. Treating the 6, 12, and 60 months points of the resulting survival curves as 3 binary classifiers, the 18 resulting classifiers have AUC values ranging from .765 to .885. Further evidence that the models have generalized well from the training data is provided by the extremely high levels of agreement between the random forest and neural network models predictions on the 6, 12, and 60 month binary classifiers.

Author Summary

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Introduction

Opportunities are emerging in many industries today to develop and deploy services that cater to individual needs and preferences. Music aficionados can create their own radio stations from Pandora¹, bibliophiles can receive book recommendations from goodreads.com², and Google will provide directions between any two points, giving options such as mode of transportation and warnings of delays in realtime.³ These

¹Pandora Internet Radio - Listen to Free Music You'll Love, <http://www.pandora.com/> (accessed 27 Jan 2016)

²Share Book Recommendations With Your Friends, Join Book Clubs, Answer Trivia, <https://www.goodreads.com/> (accessed 27 Jan 2016)

³Google Maps, <https://goo.gl/1D7Jwf> (accessed 27 Jan 2016)

individualized services share many common features. In particular, they leverage large databases to learn and extract information relevant to individuals. A class of techniques that transforms data into actionable information goes by the name of Machine Learning [1]. Machine Learning has recently become a popular method to answer questions and solve problems that are too complex to solve via traditional methods.

The primary objective of this study is to show how machine learning methods can be trained to produce personalized survival prognosis curves. The methods presented below can be applied to any type of survival data. Traditionally, cancer survival curves have been estimated using Kaplan-Meier methods [2]. Kaplan-Meier methodology also uses large datasets to make predictions, but the resulting curves are summaries for a population and not necessarily relevant or particularly accurate for any given individual. This property of Kaplan-Meier methods is exacerbated when dealing with heterogeneous populations. The methods presented in this report generate personalized survival curves relevant to individual patients. This objective is aligned with Predictive, Preventive and Personalized Medicine (PPPM), which aims to leverage increasing amounts of health data to maximize quality of care and to eliminate inefficient use of resources [3]. This capability to provide individualized survival curve prognosis is a direct result of the recent advances in computing power and machine learning algorithms, and similar methodology is becoming commonplace in many industries. These techniques are now infiltrating the healthcare industry.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) has been collecting data since 1973. Intuitively researchers feel confident that this data will allow researchers to detect information crucial to patients and providers, including the relationships between the collected data (demographics, staging, treatment and disease characteristics) and survival outcomes. Though these relationships evade capture by traditional methods, it is possible to surface them with two machine learning techniques known as *Random Forests* and *Neural Networks*.

The SEER program is the most recognized authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28 percent of the US population.

One challenge of the SEER data that is shared by many survival datasets is the inclusion of censored data. Observations are labeled censored when the survival information is incomplete. The SEER data contains the number of months each patient survived, as well as the vital status. Traditional methods to deal effectively with this kind of "right-censored data" include Kaplan-Meier curves and Cox Proportional Hazard models [2].

Previous work applying machine learning methods to subsets of the SEER data include creative attempts to deal with the problems presented by right-censored data. Shin et al. [5] use semi-supervised learning techniques to predict 5 year survival, essentially imputing values for SEER records where the survival information is censored at a value less than 5 years. Zolbanin et al. [6] remove all records corresponding to patients who were living but censored within the 60 month study window. This treatment biases the predictions and leads to overly pessimistic predictions.

Previous work applying machine learning methods based on decision trees to survival data in general have a long history, starting with Gordon et al. [7]. A summary of more recent developments concerning *survival trees* is provided by Bou-Hamad et al. [8]. These methods focus on altering the splitting criteria used in decision tree growth to account for the censoring, and use 1958 Kaplan-Meier methods at the resulting nodes for prediction purposes. These methods do not generalize to non-tree-based machine learning algorithms, though Ishwaran et al. have extended the methodology to *random survival forests*, ensembles of *survival trees* [9].

Instead of modifying existing learning algorithms, we focus attention on the input data. This approach allows us to take advantage of powerful and rapidly improving machine learning derived discrete classifiers without modification. The essential idea is to recast the problem as a discrete classification problem (predicting the likelihood that a patient is alive in any given month) instead of a regression problem (predicting survival months). Treating months after diagnosis as just another discrete feature, the SEER data (or any other right-censored data) can be transformed to make predictions for the hazard function (probability of dying in the next month, given that the patient has not yet died). The survival function can then be derived from the hazard function.

Materials and Methods

For this study we use the publically available 1973-2012 SEER incidence data files corresponding to colon, breast and lung cancer contained in the list below. SEER requires that researchers submit a request for the data, which includes an agreement form. Detailed documentation explaining the contents of both the incidence data files used in this study as well as a data dictionary for the 1973-2012 SEER incidence data files are available without the need to register or submit a data request [10]. The raw data files in this study and the subsets defined by the appropriate filters are given in detail in subsection Raw SEER datafiles, in the appendix Supporting Information.

Data preparation and preprocessing

A great deal of data munging is necessary before using these SEER incidence files as input into machine learning algorithms. A preprocessing step common to each of the three cancer types studied involves the SEER STATE-COUNTY RECODE variable. The STATE-COUNTY RECODE field is a state-county combination where the first two characters represent the state FIPS code and the last three digits represent the FIPS county code. The FIPS code is a five-digit Federal Information Processing Standard (FIPS) code which uniquely identifies counties and county equivalents in the United States, certain U.S. possessions, and certain freely associated states. This particular field illustrates an important characteristic of machine learning, that is, the difference between *categorical features* and *numeric features*. All input into a machine learning algorithm must be numeric, but real numbers carry with them the usually extremely useful property known as the well-ordering property. Machine learning algorithms use the well-ordering property of the real numbers to learn. But if one is tasked with encoding a categorical feature into suitable numeric format for machine learning, it is necessary to do so in a way that removes the well-ordering property. Categorical variables are commonly encoded using one-hot encoding, in which the explanatory variable is encoded using one binary feature for each of the variable's possible values [11].

One-hot encoding needs to be applied to all of the nominal categorical variables in the SEER data that we wish to include in our predictive models. In particular, in order to include the geophgraphical information contained in the SEER categorical variable STATE-COUNTY RECODE, it becomes necessary to create a new feature variable for each of the distinct (state,county) pairs in the data. In the United States, there are approximately 3,000 counties. Clearly, transforming the STATE-COUNTY RECODE data representation into distinct (state_county) columns will explode the dataset to become wider than is optimal for machine learning. Adding extra columns to your dataset, making it wider, requires more data rows (making it taller) in order for machine learning algorithms to effectively learn [11]. Because one-hot coding STATE-COUNTY RECODE would cause such drastic shape changes in our data, we wish

to avoid doing so. Fortunately, this variable, though given as a categorical variable, is actually a recode for three ordinal variables. There is an ordering among the (state_county) columns, namely longitude, latitude, and elevation. We can transform the data in STATE-COUNTY RECODE into three new numerical columns: lat, lng, and elevation.

For example, Table (1) shows how five entries of STATE-COUNTY RECODE corresponding to counties within New Mexico can be represented by the elevation, lat, and lng features.

Table 1. Example of the transformation of STATE-COUNTY RECODE to elevation, lat, and lng.

STATE-COUNTY RECODE	address	elevation	lat	lng
35001	Bernalillo+county+NM	5207.579772	35.017785	-106.629130
35003	Catron+county+NM	8089.242628	34.151517	-108.427605
35005	Chaves+county+NM	3559.931671	33.475739	-104.472330
35006	Cibola+county+NM	6443.415570	35.094756	-107.858387
35007	Colfax+county+NM	6147.749089	36.579976	-104.472330

It is a simple exercise to construct the full lookup table from the SEER STATE-COUNTY RECODE variable to the corresponding three values elevation, lat, and lng. We use the publically available datafile from the United States Census Bureau [13] to map the state FIPS and county FIPS codes to query strings like those in the address field in Table (1). It is then possible to programmatically query the Google Maps Geocoding API for the latitude and longitude [14], and the Google Maps Elevation API for the corresponding elevation [15]. An added benefit of this shift from the single categorical variable STATE-COUNTY RECODE to the three continuous numerical variables lat, lng, and elevation is that input into the web applications described later are not restricted to the states and counties covered in the SEER registries; in fact, the input to the models can be any address you would enter into Google Maps and calls to the Google Maps Geocoding API and the Google Maps Elevation API provide the conversion from the address string to the input variables lat, lng, and elevation. The full lookup table analogous to Table (1) is available from a GitHub repository containing supplemental information for this study [16].

This study focused on three different cancer types, namely colorectal cancer, lung cancer, and breast cancer. In the SEER data, there is a record for each primary tumor. If multiple records exist for a given patient, only the first chronologically was included. The full set of conditions defining the subsets of the SEER data used in this study follows below is included in section Supporting Information.

The four COLRECT.txt files were imported into a pandas DataFrame object. This data was then filtered according to the conditions in Table (2). The RESPIR.txt and BREAST.txt files were imported into separate dataframes in similar fashion and filtered according to the conditions in Table (3) and Table (4), respectively. The SEER variable CS TUMOR SIZE records the tumor size in millimeters if known. But if not known, CS TUMOR SIZE is given as '999', to indicate that the tumor size is "Unknown; size not stated; not stated in patient record." In this study, we discard those records, as indicated in Tables (4, 2, 3).

The following categorical features were one-hot encoded for each of the three datasets:

- SEX,
- MARITAL STATUS AT DX,

Table 2. Filters applied to the Colon Cancer data.

Column	Filter
SEQUENCE NUMBER-CENTRAL	≠ "Unspecified"
AGE AT DIAGNOSIS	≠ "Unknown age"
BIRTHDATE-YEAR	≠ "Unknown year of birth"
YEAR OF DIAGNOSIS	≥ 2004
SURVIVAL MONTHS FLAG	= "1"
CS TUMOR SIZE EXT/EVAL	≠ ""
CS TUMOR SIZE	≠ 999
SEER RECORD NUMBER	= 1
PRIMARY SITE	= "LARGE INTESTINE, (EXCL. APPENDIX)"
SEQUENCE NUMBER-CENTRAL	= 0

Table 3. Filters applied to the Lung Cancer data.

Column	Filter
SEQUENCE NUMBER-CENTRAL	≠ "Unspecified"
AGE AT DIAGNOSIS	≠ "Unknown age"
BIRTHDATE-YEAR	≠ "Unknown year of birth"
YEAR OF DIAGNOSIS	≥ 2004
SURVIVAL MONTHS FLAG	= "1"
CS TUMOR SIZE EXT/EVAL	≠ ""
CS TUMOR SIZE	≠ 999
SEER RECORD NUMBER	= 1
PRIMARY SITE	= "LUNG & BRONCHUS"
SEQUENCE NUMBER-CENTRAL	= 0

Table 4. Filters applied to the Breast Cancer data.

Column	Filter
SEQUENCE NUMBER-CENTRAL	≠ "Unspecified"
AGE AT DIAGNOSIS	≠ "Unknown age"
BIRTHDATE-YEAR	≠ "Unknown year of birth"
YEAR OF DIAGNOSIS	≥ 2004
SURVIVAL MONTHS FLAG	= "1"
CS TUMOR SIZE EXT/EVAL	≠ " "
CS TUMOR SIZE	≠ 999
SEER RECORD NUMBER	= 1
SEQUENCE NUMBER-CENTRAL	= 0

- RACE/ETHNICITY ,
- SPANISH/HISPANIC ORIGIN ,
- GRADE ,
- PRIMARY SITE ,

147
148
149
150

- LATERALITY , 151
- SEER HISTORIC STAGE A , 152
- HISTOLOGY RECODE--BROAD GROUPINGS , 153
- MONTH OF DIAGNOSIS , 154
- VITAL STATUS RECODE , 155

and the STATE-COUNTY RECODE variable was dropped and replaced with the elevation , lat , and lng variables for all three datasets as illustrated in Table (1). 156

Before applying machine learning models trained with these datasets, we review below the salient features of survival analysis and censored data. We then describe in detail a method that takes full advantage of all the data, including the right-censored data, and which involves a simple and intuitive transformation, culminating in the full set of features and target variable listed in the back of this report. 158

Transformation of Censored Data for Machine Learning 163

In this section we describe an intuitive way to transform right-censored data appropriately so that it may be used as input to machine learning algorithms that learn the hazard function. The full details of this transformation, and a large inspiration for this study, can be found in this blog post [18]. 164

The key observation is to note that the hazard function can be directly learned via standard machine learning methods. It can be rewritten as 165

$$\lambda(\mathbf{X}, t_i) = P(Y = t_i | Y \geq t_i, \mathbf{X}), \quad (1)$$

the probability that, if someone has survived up until month t_i , they will die in that month. where \mathbf{X} represents all of the data for that particular record, and in our case Y represents the true, uncensored number of survival months of the patient. What is actually provided in the SEER data is the related variable SURVIVAL MONTHS T (how long each subject was in the study), and whether they exited by dying or being censored (D), VITAL STATUS RECODE . D is a Boolean variable, so $D = 1$ if $T = Y$, and $D = 0$ if $T < Y$. 170

It follows directly from equation 1 that 171

$$P(Y = t_j | \mathbf{X}) = \lambda(\mathbf{X}, t_j) \prod_{i=1}^{j-1} (1 - \lambda(\mathbf{X}, t_i)) \quad (2)$$

Knowing $P(Y = t_j | \mathbf{X})$ for all t_j gives the full probability distribution of dying at time Y [18]. The survival function is then readily derived from this distribution as 172

$$S(\mathbf{X}, t_k) = 1 - CDF(\mathbf{X}, t_k) \quad (3)$$

where $CDF(\mathbf{X}, t_k) = \sum_{i=1}^k P(Y = t_i | \mathbf{X})$ is the cumulative density function corresponding to the probability mass function in equation 2 [12]. 180

Treating T as just another covariate is the key to the transformation. Each datapoint in the hidden classification problem is the combination of an \mathbf{X}_i in the original dataset plus some month t_j , and the classification problem is "did point \mathbf{X}_i die in month t_j ." We will call this new variable D_{ij} (newtarget). We can transform our original data set into a new one, with one row for each month that each \mathbf{X}_i is in the sample; train a standard classifier on this new dataset with D_{ij} as the target, and derive a survival model from the original dataset. Pseudocode for this transformation is found in section Pseudocode for the Data Transformation. 182

Explicit examples will help make this transformation clear. The untransformed datapoint represented Table (5) is transformed to the multiple records shown in Table (7). All uncensored data is transformed in this way. All censored data is similarly transformed. The untransformed datapoint represented Table (6) is transformed to the multiple records shown in Table (8).

Table 5. Example of four columns in an uncensored record in the untransformed dataset.

	cs_tumor_size	year_of_birth	survival_months	vital_status_recode_Death
newindex				
205	60	1951	3	1

Table 6. Example of four columns in a censored record in the untransformed dataset.

	cs_tumor_size	year_of_birth	survival_months	vital_status_recode_Death
newindex				
205	40	1950	3	0

Table 7. Example of four columns in an uncensored record in the transformed dataset.

	cs_tumor_size	year_of_birth	month	newtarget
newindex				
205	60	1951	0	0
205	60	1951	1	0
205	60	1951	2	0
205	60	1951	3	1

One obvious side effect of this transformation is that it explodes the length of the dataset. For this study, the original, untransformed colon cancer DataFrame has shape (113072, 103), and the total transformed colon cancer DataFrame has shape (4165251, 103). Similarly, the original, untransformed lung cancer DataFrame has shape (177089, 115), and the total transformed lung cancer DataFrame has shape (3079931, 115). The biggest explosion in dataset size occurred with the breast cancer data, which is a consequence of the relatively high survival rates in breast cancer. A subject who is censored with a recorded survival months of 48 will contribute an extra 48 rows to the transformed dataset. The original, untransformed breast cancer DataFrame has shape (329949, 67), and the total transformed breast cancer DataFrame has shape (15085711, 67). Training machine learning algorithms on such large datasets, even after splitting into training and testing sets described below, require large RAM. All computations for this study were performed on a Dell XPS 8700 Desktop with 32GB of RAM.

Training and Test Partitions

After performing the data transformation adumbrated above, it is necessary to be mindful of how we partition the data into training and testing data. Each subject that was represented by a single row in the original untransformed dataset now potentially is represented by multiple rows in the transformed dataset, and care must be taken to ensure that all of the rows corresponding to a particular subject are either assigned exclusively to the training set or exclusive to the testing set. An additional

Table 8. Example of four columns in a censored record in the transformed dataset.

	cs_tumor_size	year_of_birth	month	newtarget
newindex				
205	40	1950	0	0
205	40	1950	1	0
205	40	1950	2	0
205	40	1950	3	0

characteristic of this transformed data that requires careful treatment involves balancing. The transformation results in many new records with the target variable `newtarget == 0`. The training and test sets must be chosen such that the ratio of the number of records with `newtarget == 0` to that of the number of records with `newtarget == 1` is the same in the training and test datasets. This ratio turns out to be ≈ 396 for the breast cancer data, ≈ 99 for the colon cancer data, and ≈ 22.75 for the lung cancer data. The shapes of the training and testing datasets for breast cancer used in this study are (14936862, 67) and (148849, 67), respectively. For lung cancer, the corresponding datasets have shapes (2988768, 115) and (91163, 115). Finally, for colon cancer the partition into training and test datasets of the transformed data have the shapes (3958008, 103) and (207243, 103). Multiple rows correspond to the same test patient in these datasets. The colon cancer test dataset represents 5654 distinct subjects; the breast cancer test dataset represents 3300 distinct subjects; and the lung test dataset contains data for 5313 distinct subjects.

The models described below are trained to learn the values of `newtarget`, which is a binary variable: a value of '0' indicating that the subject is still alive at the given month, while a value of '1' indicates that the patient died at that particular value of `months`. The random forests and neural networks described below are binary classifiers with the target `newtarget`. Fortunately, both the random forests and neural networks are capable of not only performing strict class prediction, i.e. predicting whether `newtarget` is '0' or '1', but are also able to predict the *probability* of `newtarget` being '0' or '1', and thus learning the hazard function.

Finally, we emphasize the crucial point that the features `survival_months` and `vital_status_recode_Dead` are dropped from both the training and testing data, and are replaced with the features `months` and `newtarget`, as illustrated in Tables (5, 6, 7, 8). The information of which subjects represent censored data (`vital_status_recode_Dead == 0`) and which died is retained and recoverable through the `newindex` variable and is needed for proper evaluation of the performance metrics; when evaluating AUC curves for the 6, 12, and 60 month binary classifiers, we need to limit the test data to those subjects that we know definitively whether or not they survived 6, 12 or 60 months respectively. This requirement will necessitate the elimination of some of the censored data when computing some of the performance metrics. We introduce the two machine learning algorithms used in this study below, chosen because of their high performance in machine learning competitions and their complementary methods, so that their mutual agreement shown below on the test datasets can be taken as indication that they are actually learning useful information.

Random Forests are made up of an ensemble of independent **Decision trees** that are purposefully exposed to only subsets of the data. The general philosophy is presented in the popular science book "The Wisdom of Crowds" [19]. The idea is that a large number of independent non-expert opinions converge on the correct answer when averaged. The success of this philosophy of prediction was startlingly shown by the

success of the political and world event predictions made by the prediction market site Intrade, before its forced closure by the Commodity Futures Trading Commission [20]. The other class of methods used by IOBS to develop predictive models are called neural networks, and are modelled on how the human brain learns high level concepts from lower level ones. As opposed to the crowd-based wisdom of a random forest, a neural network is analogous to a seasoned expert. A Neural network learns from repeated exposure to the training data and improves its predictions with each pass over the data. The general philosophy is similar to that represented by the well-known maxim that it takes 10,000 hours to become an expert in any given field [21].

Prediction Models

With the datasets transformed as described above, we are now able to use them to train and evaluate machine learning classifiers. The classifier models described in this section are learning the hazard function: given all of the data given in the Supporting Information section for each cancer type and includes the field `months` (the months after diagnosis), the models predict the target variable `newtarget`, which is a binary class label equal to 1 if the subject died in that month and 0 otherwise. Fortunately, both random forests and neural networks are capable of not only performing strict class prediction, i.e. predicting whether `newtarget` is 0 or 1, but are also able to predict the *probability* of `newtarget` being 0 or 1, and thus learning the hazard function. The models learn $\lambda(\mathbf{X}, \text{months})$. This prediction task should not be confused with the regression problem of trying to predict precisely in what month a patient will die.

The hazard functions thus learned and predicted are intermediary products; what we are really pursuing are the survival functions for each patient that are derived from the predicted hazard functions. From the resulting hazard functions for each unique patient, we can construct the resulting survival functions as presented in section () and Equation (??) and explicitly given in python code in the notebooks at the github repository containing supplemental material for this study [16]. For each subject i , all input data minus `months` and `newtarget` is represented by \mathbf{X}_i . After the classifier models have trained with target `newtarget` on the (very large) training set, each subject's survival function is computed in the corresponding (much smaller) test set. These functions are computed by using the model to predict $\lambda(\mathbf{X}_i, t_j)$ for j running from 0 to 107 months, and \mathbf{X}_i corresponds to the single row corresponding to subject i in the original untransformed dataset. 107 months was the maximum value of survival months in all three of the cancer datasets, and is a consequence of the data subsets chosen for this study.

Decision Trees and Random Forests *Decision tree* classifiers are attractive models because they can be interpreted easily. Like the name decision tree suggests, we can think of this model as breaking down our data by making decisions based on asking a series of questions. Based on the features in our training set, the decision tree model learns a series of questions to infer the class labels of the samples.

Random forests have gained huge popularity in applications of machine learning during the last decade due to their good classification performance, scalability, and ease of use. Intuitively, a random forest can be considered as an *ensemble of decision trees*. The idea behind ensemble learning is to combine *weak learners* to build a more robust model, a *strong learner*, that has a better generalization error and is less susceptible to overfitting.

The goal behind *ensemble methods* is to combine different classifiers into a meta-classifier that has a better generalization performance than each individual

classifier alone. For example, assuming that we collected predictions from 10 experts, ensemble methods would allow us to strategically combine these predictions by the 10 experts to come up with a prediction that is more accurate and robust than the predictions by each individual expert. The individual decision trees that make an ensemble are called base learners, and as long as the error rate of each base learner is less than .50, the combined random forest will benefit from the affects of combining predictions to achieve a far greater accuracy.

Figure (1) illustrates the power of ensemble methods; the Figure illustrates how the ensemble error rate is much lower than the Base learner error rate, as long as the Base learner error rate is less than 0.5. The Figure illustrates this effect for an ensemble of 500 base learners.

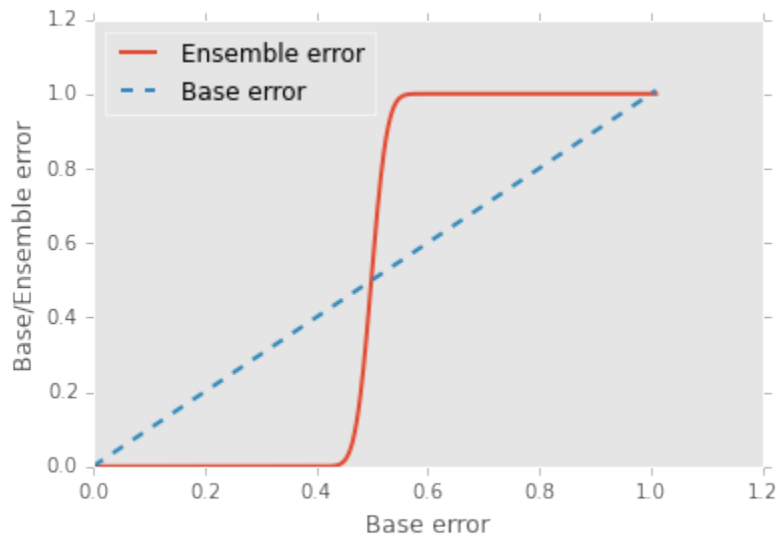


Figure 1. Illustration of ensemble methods showing how a collection of base learners with poor accuracy can combine to produce an accurate ensemble learner.

A big advantage of random forests is that honing in on suitable hyperparameter values (the number of trees in the forest, the depth of each decision tree, the specific measure of information gain used to choose the node splitting, etc) is not very difficult. The ensemble method is robust to noise from the individual decision trees, which helps to prevent overfitting (memorizing the training dataset targets instead of generalizing from learned rules to perform successfully on unseen data). The only parameter that has a clearly noticeable effect on performance is the number of trees to include in the forest; in general, the more trees the better the performance, but there is a price to pay in terms of computational cost. The number of trees for the forests trained in this study was relatively small, 20 trees for breast cancer and 25 for both the lung and colon cancer models.

IOBS has chosen to use the Python scikit-learn implemenation of the Random Forest machine learning classifier [22]. Random Forests are frequent winners of the Kaggle machine learning competitions [23]. The model parameters for each cancer type are given in sections (Lung Random Forest Model Hyperparameters, Colon Random Forest Model Hyperparameters, Breast Random Forest Model Hyperparameters).

Multi-Layer Perceptron Neural Networks Neural networks are a biologically-inspired programming paradigm that enable computers to learn from observational data [24]. Deep learning can be understood as a set of algorithms that

were developed to train artificial neural networks with many layers most efficiently. Neural networks are a hot topic not only in academic research, but also in big technology companies such as Facebook, Microsoft, and Google who invest heavily in artificial neural networks and deep learning research. As of today, complex neural networks powered by deep learning algorithms are considered as state-of-the-art when it comes to complex problem solving such as image and voice recognition. In addition, the pharmaceutical industry recently started to use deep learning techniques for drug discovery and toxicity prediction, and research has shown that these novel techniques substantially exceed the performance of traditional methods for virtual screening [?].

IOBS has chosen to use the Multi-Layer Perceptron Neural Network (MLP neural network) implementation Keras developed at MIT. Keras was initially developed as part of the research effort of project ONEIROS (Open-ended Neuro-Electronic Intelligent Robot Operating System) [25]. Keras is a minimalist, highly modular neural networks library, written in Python and capable of running on top of either TensorFlow or Theano. The model architecture for each cancer type are given in sections (Breast Neural Network Model Architecture, Colon Cancer Neural Network Model Architecture, Lung Cancer Neural Network Model Architecture). Training a neural network and choosing an appropriate architecture is as much art as science [24], and the search for a good neural network architecture for the lung cancer case was more demanding than for the breast and colon cases. The presence of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) in the SEER data may be the source of this need for more iterations and trials of different architectures when training the lung cancer neural network models.

Results

In order to evaluate the performance of the models, we first construct three binary classifiers corresponding to whether or not a subject survived 6, 12, or 60 months after diagnosis. This is done by iterating over all distinct patient indices in the test set, predicting the full survival function, and capturing the values corresponding to 6, 12, and 60 months. If the survival function evaluated at 6 months is greater than or equal to .5 for a given subject, then the 6 months binary classifier predicts that that subject will be alive 6 months after diagnosis. Similarly, if the survival function evaluated at 60 months is less than .5, then the 12 months binary classifier predicts that that subject will be dead 12 months after diagnosis. Figure (2) illustrates the method; in this case the 6-month and 12-month classifiers predict survival, while the 60-month classifier predicts expiry.

Because of censoring it is necessary to apply some Boolean filters to the data in order to correctly assess the resulting classifiers. To construct AUC curves for the 6 month classifier, we restrict ourselves to considering subjects in the test data where either of the following mutually exclusive conditions holds:

- `survival_months >= 6 AND vital_status_recode == 0`
- `vital_status_recode == 1`

That is, we restrict ourselves to subsets of the data where we know for certain whether or not the subject survived at least 6 months. Similarly for the 12 and 60 months survival classifiers.

Survival Curve Error Estimates The standard calculation of confidence intervals used in the Kaplan-Meier estimates of survival curves does not apply for these personal predictions. The following bootstrap method was used to calculate the upper and lower

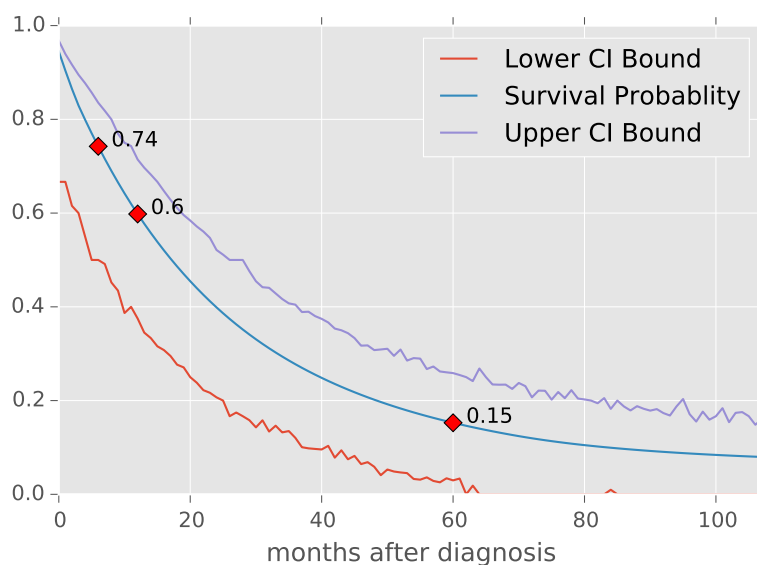


Figure 2. Example of the construction of the binary classifiers for 6, 12, and 60 months survival. A subject's hazard curve $\lambda(\mathbf{X}, t)$ is predicted by the model for times out to 107 months. The survival curve is then readily computed as in Equation (3). For this example, the 6-month and 12-month classifiers predict survival, while the 60-month classifier predicts expiry.

bounds corresponding to 95% confidence intervals. From equation 3, we can obtain the cumulative distribution function (CDF) associated with each individual survival curve. We then sample from this CDF in a way that reflects the underlying data used to produce the model. The training data used to create the model has an underlying distribution of survival months. In the transformed training dataset, each subject contributes as many rows as the number of survival months plus one (patients with zero survival months still represent one row of the training data). A subject that survived 50 months contributes 51 "points" to the training of the model. If all patients lived out to 107 months, the model would contain less uncertainty. This observation leads to the following algorithm for determining the error estimates to the predicted survival curves:

- compute the CDF associated with the survival curve
- use the underlying training data CDF of survival months to choose the number of points to draw from the survival curve CDF, and compute a new survival curve
- Repeat the previous step 10,000 times and collect the curves into a list. Changing the number of curves affects how smooth the upper and lower bounds are, but does not affect the interval size between for each month.
- extract for each month from the list of curves the .975 and .025 percentiles to record the values for the upper and lower curves

The process is somewhat analogous to the following hypothetical situation. Imagine a patient going to an expert, and the expert after collecting data on the patient and keeping records predicts the central, single survival curve. The patient then seeks multiple "second opinions." These second opinions are generated not from independent examinations of the patient, but by outside experts sampling from the data already collected by the expert initially consulted. Then the predictions of 95% of these 10,000 experts all fall within the band determined by the upper and lower curves.

Performance Metrics

The AUC scores for each of the 18 different binary classifiers are listed in Table (9). We emphasize the above-mentioned discussion concerning the correct treatment of the censored test data when evaluating performance metrics. Namely, when computing the AUC for the 12 month survival curve classifiers, we restrict the test data subjects to those that in the untransformed data set that satisfy either of the following mutually exclusive conditions:

- `survival_months >= 12 AND vital_status_recode == 0`
- `vital_status_recode == 1`

We limit evaluation data to subsets of the data where we know for certain whether or not the subject survived at least 12 months. Similar considerations apply to the 12 and 60 months AUC calculations. The lowest AUC in Table 9 is .765, corresponding to the lung neural network model predictions for 6 months survival, while the highest AUC in Table 9 is .885, corresponding to the breast random forest model predictions for 12 months survival.

Table 9. AUC values for the Random Forest and Neural Networks model binary classifiers derived from the full survival curve predictions; see text for details. The number of subjects that were used in the calculation of a given AUC score are given in parenthesis after the score.

Model	6 Months AUC	12 Months AUC	60 Months AUC
Breast RF	.846 (3035)	.885 (2797)	.844 (1392)
Breast NN	.855 (3035)	.867 (2797)	.836 (1392)
Colon RF	.804 (5281)	.806 (5003)	.828 (3232)
Colon NN	.797 (5281)	.804 (5003)	.841 (3232)
Lung RF	.772 (5019)	.796 (4860)	.874 (4143)
Lung NN	.765 (5019)	.796 (4860)	.875 (4143)

Model Agreement

An additional means of validating the predictions of these models is by comparing their predictions to each other for the same set of input data. Table 10 shows the strong agreement between the random forest and neural network classifiers for each cancer type. Python code showing how the values in Table 10 are computed is available in the files `NewPatientBreastCF.html`, `NewPatientColonCF.html`, and `NewPatientLung.html` in the GitHub repository containing supplemental material for this study [16]. Table 10 is computed as follows. For each cancer type (breast, colon, and lung), do the following:

- use the corresponding Random Forest and Neural Network models to compute the survival curves for all of the test subjects
- extract the values of the survival curve evaluated for 6, 12, and 60 months for both models
- if both models predict less than .5 or both models predict greater than or equal to .5, that counts as agreement
- otherwise, the models disagree

The high level of agreement between two models lends confidence to the notion that they have both learned from the training data and are generalizing well. Figures (4, 3, 5) show box plots of the value of the random forest prediction subtracted

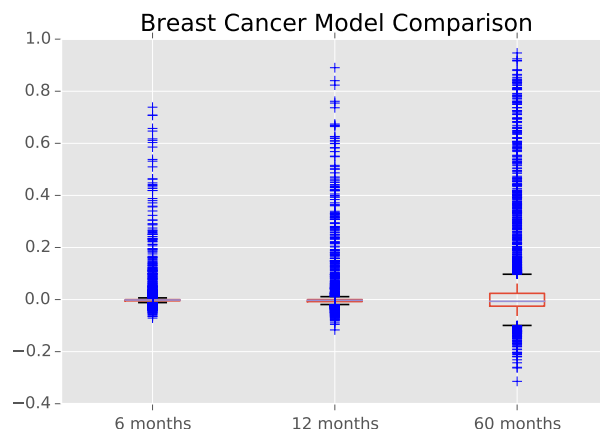


Figure 3. Box plots showing the distributions of the signed difference between the MLP model's prediction for the probability of surviving 6 months and the Random Forest model's prediction of the same quantity for breast cancer. The plot shows the same quantity for the 12 and 60 months classifiers. It is apparent from the figures that the outliers are due to the neural network models predicting higher survival probabilities than the random forest for some few cases. These differences were evaluated for the 3300 test patients in the breast cancer data.

from the neural network prediction. We emphasize that when evaluating the model agreement, we put no restrictions on the distinct subjects in the respective test datasets; we are confronting the models against each other, not some known ground truth as in the AUC performance metric calculations. The number of distinct subjects in all three of the colon cancer survival binary classifiers (6, 12, and 60 month survival) was 5654; for lung cancer the number of subjects entering into the calculation of Table (10) was 5313; and for breast cancer it was 3300.

Table 10. Percentage agreement for the Random Forest and Neural Network classifiers for 6, 12, and 60 month survival predictions on the test data for each cancer type.

Cancer Type	% agreement 6 months	% agreement 12 months	% agreement 60 months
Colon	.981	.971	.915
Breast	.994	.984	.938
Lung	.861	.883	.900

Survival Curve Prediction Apps

The six models described in section Prediction Models, namely the random forest and MLP neural network models for each of the three cancer types considered in this study, have their full hyperparameter and architecture presented in section Supporting Information. Python code for all six model training and evaluation is available at the github repository containing supplemental material for this study [16].

Using the popular Flask microframework for web applications [26], we have made web applications corresponding to the six models. The list of web applications below will allow readers to freely experiment with the models.

1. breast cancer

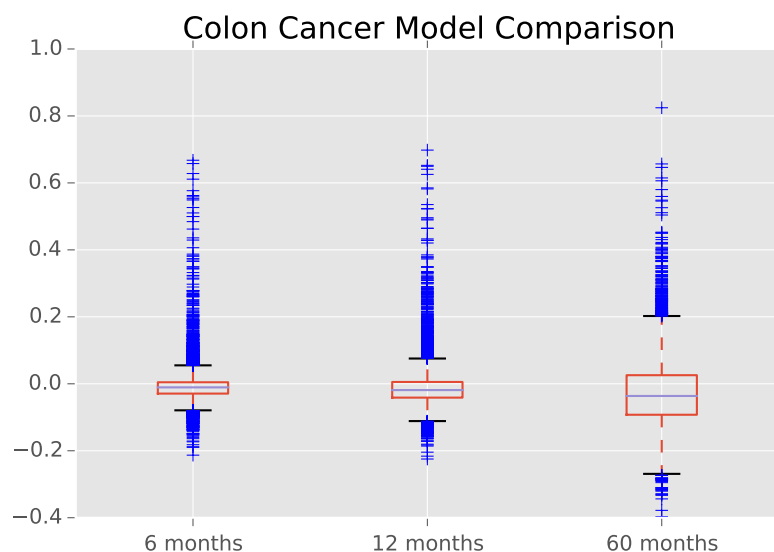


Figure 4. Box plots showing the distributions of the signed difference between the MLP model's prediction for the probability of surviving 6 months and the Random Forest model's prediction of the same quantity for colon cancer. The plot shows the same quantity for the 12 and 60 months classifiers. It is apparent from the figures that the outliers are due to the neural network models predicting higher survival probabilities than the random forest for some few cases. These differences were evaluated for the 5654 test patients in the colon cancer data.

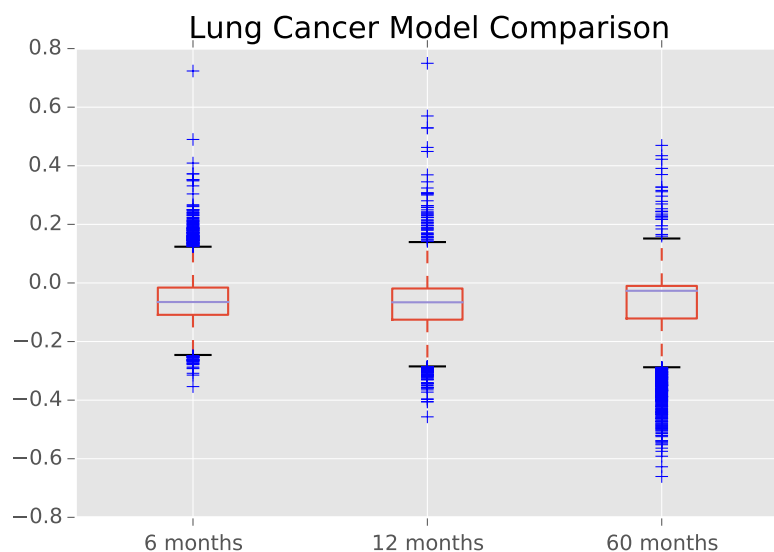


Figure 5. Box plots showing the distributions of the signed difference between the MLP model's prediction for the probability of surviving 6 months and the Random Forest model's prediction of the same quantity for lung cancer. The plot shows the same quantity for the 12 and 60 months classifiers. These differences were evaluated for the 5313 test patients in the lung cancer data. The Interquartile Ranges for lung cancer are visibly larger than those for breast cancer and colon cancer shown in fig 3 and fig 4.

- (a) random forest: 458
<https://github.com/doolingdavid/breast-cancer-rf-errors.git> 459
- (b) neural network: 460
<https://github.com/doolingdavid/breast-cancer-nn-errors.git> 461
2. lung cancer 462
- (a) random forest: 463
<https://github.com/doolingdavid/lung-cancer-rf-errors.git> 464
- (b) neural network: 465
<https://github.com/doolingdavid/lung-cancer-nn-errors.git> 466
3. colon cancer 467
- (a) random forest: 468
<https://github.com/doolingdavid/colon-cancer-rf-errors.git> 469
- (b) neural network: 470
<https://github.com/doolingdavid/colon-cancer-nn-errors.git> 471

After downloading the .zip file associate with one of the above web applications, and assuming python is installed on your system, you can launch the application by running 472 473

```
>python hello.py 474
```

and pointing the browser to the local server: <http://127.0.0.1:5000> . 475

These machine learning models are used to predict survival curves for a given set of 476 input data. The resulting survival curves predict the probability that a patient with the 477 given input data will survive at least up to month x . 478

For example, using the Colon Cancer neural network app, and inputting the values listed in Table (11) results in the survival curve depicted in Figure (6); the predicted probabilities of living at least 6, 12, and 60 months are .89, .83, and .50, respectively.

Table 11. Example input data to the Colon Cancer neural network app
<https://github.com/doolingdavid/colon-cancer-nn-errors.git>.

Variable	Value
What is the tumor size (mm)	300
What is the patient's address?	boston massachusetts
Grade	moderately differentiated
Histology	adenomas and adenocarcinomas
Laterality	not a paired site
Marital Status at Dx	Single, never married
Month of Diagnosis	Jan
How many primaries	1
Race_ethnicity	White
seer_historic_stage_a	Regional
Gender	Male
spanish_hispanic_origin	Non-spanish/Non-hispanic
Year of Birth	1940
Year of Diagnosis	2010

Changing the data in Table 11 so that the address field is changed from Boston, Massachusetts to Denver, Colorado but keeping all other variables are unchanged results in the predicted probabilities of living at least 6, 12, and 60 months: .945, .902, .665. Behind the scenes, the apps use the input to the address field to make a call to the Google Maps API to convert the address into a latitude, longitude and elevation. These probabilities are noticeably higher and reflect the documented effects of both longitude and elevation on cancer treatment and prognosis in the United States [27].

A similar example of how changing the inputs to the models affects the predicted survival curves in interesting ways can be seen with the random forest model for lung cancer. Changing the data in Table 12 by toggling between the male/female, and married/single four possible permutations results in the following prediction probabilities for 6, 12, and 60 month survival:

- male/married: .53, .27, .01
- male/single: .35, .18, .009
- female/married: .55, .31, .01
- female/single: .50, .27, .01

Inputting the same combinations of data into the lung cancer neural network app <https://github.com/doolingdavid/lung-cancer-nn-errors.git> yields the following probabilities:

- male/married: .42, .24, .04
- male/single: .40, .22, .03
- female/married: .44, .26, .04
- female/single: .42, .24, .04

It is interesting to note that both the random forest and neural network lung cancer models predict greater 6 month survival rates for married people, with a slightly greater benefit for males than females. The effect is greater in the random forest model, but is also visible in the neural network model.

Colon Cancer Survival Curve Prediction

Prediction:

1. Probability of Surviving 6 months is **0.897**
2. Probability of Surviving 12 months is **0.831**
3. Probability of Surviving 60 months is **0.504**

Predicted Survival Curve from Model

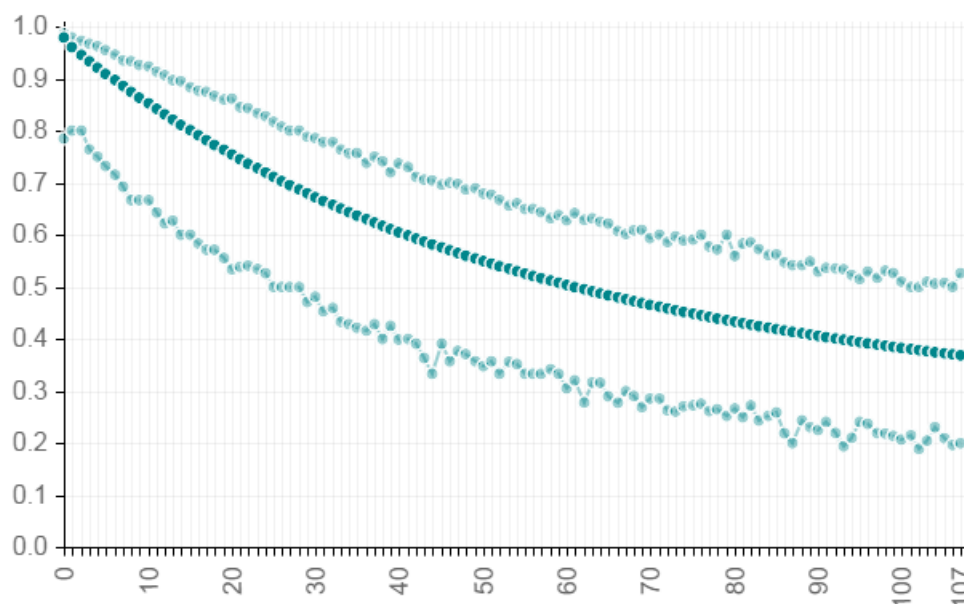


Figure 6. Colon Cancer Survival Curve predicted from the data in Table (11) using the neural network web app
<https://github.com/doolingdavid/colon-cancer-nn-errors.git>.

Discussion

The purpose of this study has been twofold; to develop a general methodology of data transformation to survival data with censored observations so that machine learning algorithms can be applied and to help further the cause of PPPM medicine by developing models of personalized survival curve prognosis. To help further refine the methodology, we would like to apply it to different survival datasets [28], not necessarily within the healthcare domain. In particular, the methods presented in this paper do not take into account time varying features. For example, the `cs.tumor_size` variable that has been a part of this study is kept fixed at the value measured at diagnosis for all records corresponding to a given subject. Clearly, the actual tumor size varies along with time and a sophisticated model can be developed to take this into account, given available datasets. Unfortunately, the SEER datasets considered in this study do not provide this kind of granularity over time.

The SEER database has been linked with claims data in the SEER-Medicare Linked Database [29]. This linkage allows for the identification of additional clinical data for

Table 12. Example input data to the Lung Cancer random forest app
<https://github.com/doolingdavid/lung-cancer-rf-errors.git>.

Variable	Value
What is the tumor size (mm)	500
What is the patient's address?	newark new jersey
Grade	well differentiated
Histology	acinar cell neoplasms
Laterality	bilateral involvement, lateral origin unknown; stated to be single primary
Marital Status at Dx	Married including common law
Month of Diagnosis	Jan
How many primaries	1
Race_ethnicity	White
seer_historic_stage_a	Distant
Gender	Female
spanish_hispanic_origin	Non-spanish/Non-hispanic
Year of Birth	1970
Year of Diagnosis	2011

each record in the SEER database and allows for an enrichment of the models presented in this study, and is an avenue for further investigation.

An additional avenue of research concerns the broad concept of causality. As demonstrated in section Survival Curve Prediction Apps, there appears to be a correlation between marital status and survival prognosis. Does this mean that if a single person in Boston, Massachusetts is diagnosed with cancer, that they should immediately get married and move to Denver? Of course not. But personal discussions with providers has confirmed for one of the authors (D.D.) that married males tend to be much more diligent in following instructions than their single counterparts. What appears to be in effect is that some of the SEER data is providing an identifiable signature of underlying causes not directly represented by the data. Latent variables not directly seen in the data are still providing echos of patterns in the data and the sheer volume allows us to see glimpses of these patterns. Marital status is in some instances a surrogate for the presence of a strong social structure and support group surrounding a patient, which presence presumably leads to more desirable survival prognosis. The daunting and exciting task of teasing out actual causality relationships within machine learning contexts has been pioneered by Judea Pearl of the University of California, Los Angeles ⁴ and seems particularly relevant and applicable to censored survival data. Combining the methodology presented in this study for the marriage of machine learning and censored survival data with that of the pioneering work of Judea Pearl on causality will be a fruitful avenue for future research.

Supporting Information

Raw SEER datafiles

- incidence\yr1973_2012.seer9\COLRECT.txt
- incidence\yr1973_2012.seer9\BREAST.txt
- incidence\yr1973_2012.seer9\RESPIR.txt

⁴Judea Pearl homepage at the University of California, Los Angeles, http://bayes.cs.ucla.edu/jp_home.html, accessed 11 Jan 2016.

- incidence\yr1992_2012.sj_la_rg_ak\COLRECT.txt 550
- incidence\yr1992_2012.sj_la_rg_ak\BREAST.txt 551
- incidence\yr1992_2012.sj_la_rg_ak\RESPIR.txt 552
- incidence\yr2000_2012.ca_ky_lo_nj_ga\COLRECT.txt 553
- incidence\yr2000_2012.ca_ky_lo_nj_ga\BREAST.txt 554
- incidence\yr2000_2012.ca_ky_lo_nj_ga\RESPIR.txt 555
- incidence\yr2005.lo_2nd_half\COLRECT.txt 556
- incidence\yr2005.lo_2nd_half\BREAST.txt 557
- incidence\yr2005.lo_2nd_half\RESPIR.txt 558

Colon Cancer Feature Selection 559

The feature set used as input into both the Random Forest and Neural Network models, after the transformation described in section Transformation of Censored Data for Machine Learning is given below and also available in full detail in the file NewPatientColonML.html . 560
561
562
563

- cs_tumor_size 564
- elevation 565
- grade_cell type not determined 566
- grade_moderately differentiated 567
- grade_poorly differentiated 568
- grade_undifferentiated; anaplastic 569
- grade_well differentiated 570
- histology_recode_broad_groupings_acinar cell neoplasms 571
- histology_recode_broad_groupings_adenomas and adenocarcinomas 572
- histology_recode_broad_groupings_blood vessel tumors 573
- histology_recode_broad_groupings_complex epithelial neoplasms 574
- histology_recode_broad_groupings_complex mixed and stromal neoplasms 575
- histology_recode_broad_groupings_cystic, mucinous and serous neoplasms 576
- histology_recode_broad_groupings_ductal and lobular neoplasms 577
- histology_recode_broad_groupings_epithelial neoplasms, NOS 578
- histology_recode_broad_groupings_fibromatous neoplasms 579
- histology_recode_broad_groupings_germ cell neoplasms 580
- histology_recode_broad_groupings_lipomatous neoplasms 581
- histology_recode_broad_groupings_miscellaneous bone tumors 582
- histology_recode_broad_groupings_myomatous neoplasms 583
- histology_recode_broad_groupings_neuroepitheliomatous neoplasms 584
- histology_recode_broad_groupings_nevi and melanomas 585
- histology_recode_broad_groupings_parangliomas and glumus tumors 586
- histology_recode_broad_groupings_soft tissue tumors and sarcomas, NOS 587
- histology_recode_broad_groupings_squamous cell neoplasms 588
- histology_recode_broad_groupings_synovial-like neoplasms 589
- histology_recode_broad_groupings_transistional cell papillomas and carcinomas 590
- histology_recode_broad_groupings_unspecified neoplasms 591
- lat 592
- laterality_Left: origin of primary 593
- laterality_Not a paired site 594
- laterality_Only one side involved, right or left origin unspecified 595
- laterality_Paired site, but no information concerning laterality; midline tumor 596
- laterality_Right: origin of primary 597
- lng 598
- marital_status_at_dx_Divorced 599

• marital_status_at_dx_Married (including common law)	600
• marital_status_at_dx_Separated	601
• marital_status_at_dx_Single (never married)	602
• marital_status_at_dx_Unknown	603
• marital_status_at_dx_Unmarried or domestic partner	604
• marital_status_at_dx_Widowed	605
• month_of_diagnosis_Apr	606
• month_of_diagnosis_Aug	607
• month_of_diagnosis_Dec	608
• month_of_diagnosis_Feb	609
• month_of_diagnosis_Jan	610
• month_of_diagnosis_Jul	611
• month_of_diagnosis_Jun	612
• month_of_diagnosis_Mar	613
• month_of_diagnosis_May	614
• month_of_diagnosis_Nov	615
• month_of_diagnosis_Oct	616
• month_of_diagnosis_Sep	617
• number_of primaries	618
• race_ethnicity_Amerian Indian, Aleutian, Alaskan Native or Eskimo	619
• race_ethnicity_Asian Indian	620
• race_ethnicity_Asian Indian or Pakistani	621
• race_ethnicity_Black	622
• race_ethnicity_Chinese	623
• race_ethnicity_Fiji Islander	624
• race_ethnicity_Filipino	625
• race_ethnicity_Guamanian	626
• race_ethnicity_Hawaiian	627
• race_ethnicity_Hmong	628
• race_ethnicity_Japanese	629
• race_ethnicity_Kampuchean	630
• race_ethnicity_Korean	631
• race_ethnicity_Laotian	632
• race_ethnicity_Melanesian	633
• race_ethnicity_Micronesian	634
• race_ethnicity_New Guinean	635
• race_ethnicity_Other	636
• race_ethnicity_Other Asian	637
• race_ethnicity_Pacific Islander	638
• race_ethnicity_Pakistani	639
• race_ethnicity_Polynesian	640
• race_ethnicity_Samoan	641
• race_ethnicity_Thai	642
• race_ethnicity_Tongan	643
• race_ethnicity_Unknown	644
• race_ethnicity_Vietnamese	645
• race_ethnicity_White	646
• seer_historic_stage_a_Distant	647
• seer_historic_stage_a_In situ	648
• seer_historic_stage_a_Localized	649
• seer_historic_stage_a_Regional	650
• seer_historic_stage_a_Unstaged	651

- sex_Female
- spanish_hispanic_origin_Cuban
- spanish_hispanic_origin_Dominican Republic
- spanish_hispanic_origin_Mexican
- spanish_hispanic_origin_Non-Spanish/Non-hispanic
- spanish_hispanic_origin_Other specified Spanish/Hispanic origin (excludes Dominican Repuclic)
- spanish_hispanic_origin_Puerto Rican
- spanish_hispanic_origin_South or Central American (except Brazil)
- spanish_hispanic_origin_Spanish surname only
- spanish_hispanic_origin_Spanish, NOS; Hispanic, NOS; Latino, NOS
- spanish_hispanic_origin_Uknown whether Spanish/Hispanic or not
- year_of_birth
- year_of_diagnosis
- month

and `newtarget` is the target variable, indicating whether or not the subject died in month given by the value of the `month` variable.

Lung Cancer Feature Selection

The feature set used as input into both the Random Forest and Neural Network models, after the transformation described in section Transformation of Censored Data for Machine Learning is given below and also available in full detail in the file `NewPatientLungML.html` .

- cs_tumor_size
- elevation
- grade_cell type not determined
- grade_moderately differentiated
- grade_poorly differentiated
- grade_undifferentiated; anaplastic
- grade_well differentiated
- histology_recode_broad_groupings_acinar cell neoplasms
- histology_recode_broad_groupings_adenomas and adenocarcinomas
- histology_recode_broad_groupings_blood vessel tumors
- histology_recode_broad_groupings_complex epithelial neoplasms
- histology_recode_broad_groupings_complex mixed and stromal neoplasms
- histology_recode_broad_groupings_cystic, mucinous and serous neoplasms
- histology_recode_broad_groupings_ductal and lobular neoplasms
- histology_recode_broad_groupings_epithelial neoplasms, NOS
- histology_recode_broad_groupings_fibroepithelial neoplasms
- histology_recode_broad_groupings_fibromatous neoplasms
- histology_recode_broad_groupings_germ cell neoplasms
- histology_recode_broad_groupings_gliomas
- histology_recode_broad_groupings_granular cell tumors & alveolar soft part sarcomas
- histology_recode_broad_groupings_lipomatous neplasms
- histology_recode_broad_groupings_miscellaneous bone tumors
- histology_recode_broad_groupings_miscellaneous tumors
- histology_recode_broad_groupings_mucoepidermoid neoplasms
- histology_recode_broad_groupings_myomatous neoplasms
- histology_recode_broad_groupings_myxomatous neoplasms

• histology_recode_broad_groupings_nerve sheath tumors	701
• histology_recode_broad_groupings_neuroepitheliomatous neoplasms	702
• histology_recode_broad_groupings_nevi and melanomas	703
• histology_recode_broad_groupings_osseous and chondromatous neoplasms	704
• histology_recode_broad_groupings_paragangliomas and glumus tumors	705
• histology_recode_broad_groupings_soft tissue tumors and sarcomas, NOS	706
• histology_recode_broad_groupings_squamous cell neoplasms	707
• histology_recode_broad_groupings_synovial-like neoplasms	708
• histology_recode_broad_groupings_thymic epithelial neoplasms	709
• histology_recode_broad_groupings_transistional cell papillomas and carcinomas	710
• histology_recode_broad_groupings_trophoblastic neoplasms	711
• histology_recode_broad_groupings_unspecified neoplasms	712
• lat	713
• laterality_Bilateral involvement, lateral origin unknown; stated to be single primary	714
• laterality_Left: origin of primary	715
• laterality_Not a paired site	716
• laterality_Only one side involved, right or left origin unspecified	717
• laterality_Paired site, but no information concerning laterality; midline tumor	718
• laterality_Right: origin of primary	719
• lng	720
• lng	721
• marital_status_at_dx_Divorced	722
• marital_status_at_dx_Married (including common law)	723
• marital_status_at_dx_Separated	724
• marital_status_at_dx_Single (never married)	725
• marital_status_at_dx_Unknown	726
• marital_status_at_dx_Unmarried or domestic partner	727
• marital_status_at_dx_Widowed	728
• month_of_diagnosis_Apr	729
• month_of_diagnosis_Aug	730
• month_of_diagnosis_Dec	731
• month_of_diagnosis_Feb	732
• month_of_diagnosis_Jan	733
• month_of_diagnosis_Jul	734
• month_of_diagnosis_Jun	735
• month_of_diagnosis_Mar	736
• month_of_diagnosis_May	737
• month_of_diagnosis_Nov	738
• month_of_diagnosis_Oct	739
• month_of_diagnosis_Sep	740
• number_of primaries	741
• race_ethnicity_Amerian Indian, Aleutian, Alaskan Native or Eskimo	742
• race_ethnicity_Asian Indian	743
• race_ethnicity_Asian Indian or Pakistani	744
• race_ethnicity_Black	745
• race_ethnicity_Chamorran	746
• race_ethnicity_Chinese	747
• race_ethnicity_Fiji Islander	748
• race_ethnicity_Filipino	749
• race_ethnicity_Guamanian	750
• race_ethnicity_Hawaiian	751
• race_ethnicity_Hmong	752

• race_ethnicity_Japanese	753
• race_ethnicity_Kampuchean	754
• race_ethnicity_Korean	755
• race_ethnicity_Laotian	756
• race_ethnicity_Melanesian	757
• race_ethnicity_Micronesian	758
• race_ethnicity_New Guinean	759
• race_ethnicity_Other	760
• race_ethnicity_Other Asian	761
• race_ethnicity_Pacific Islander	762
• race_ethnicity_Pakistani	763
• race_ethnicity_Polynesian	764
• race_ethnicity_Samoan	765
• race_ethnicity_Thai	766
• race_ethnicity_Tongan	767
• race_ethnicity_Unknown	768
• race_ethnicity_Vietnamese	769
• race_ethnicity_White	770
• seer_historic_stage_a_Distant	771
• seer_historic_stage_a_In situ	772
• seer_historic_stage_a_Localized	773
• seer_historic_stage_a_Regional	774
• seer_historic_stage_a_Unstaged	775
• sex_Female	776
• spanish_hispanic_origin_Cuban	777
• spanish_hispanic_origin_Dominican Republic	778
• spanish_hispanic_origin_Mexican	779
• spanish_hispanic_origin_Non-Spanish/Non-hispanic	780
• spanish_hispanic_origin.Other specified Spanish/Hispanic origin (excludes Dominican Repuclic)	781
• spanish_hispanic_origin.Puerto Rican	783
• spanish_hispanic_origin.South or Central American (except Brazil)	784
• spanish_hispanic_origin.Spanish surname only	785
• spanish_hispanic_origin.Spanish, NOS; Hispanic, NOS; Latino, NOS	786
• spanish_hispanic_origin.Uknown whether Spanish/Hispanic or not	787
• year_of_birth	788
• year_of_diagnosis	789
• month	790

and `newtarget` is the target variable, indicating whether or not the subject died in month given by the value of the `month` variable.

Breast Cancer Feature Selection 793

The feature set used as input into both the Random Forest and Neural Network models, after the transformation described in section Transformation of Censored Data for Machine Learning is given below and also available in full detail in the file `NewPatientBreastML.html` . 794
795
796
797

- `cs_tumor_size` 798
- `elevation` 799
- `grade_moderately differentiated` 800
- `grade_poorly differentiated` 801

• grade_ndifferentiated; anaplastic	802
• grade_well differentiated	803
• histology_recode_broad_groupings_adenomas and adenocarcinomas	804
• histology_recode_broad_groupings_adnexal and skin appendage neoplasms	805
• histology_recode_broad_groupings_basal cell neoplasms	806
• histology_recode_broad_groupings_complex epithelial neoplasms	807
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• lat	813
• laterality_Bilateral involvement, lateral origin unknown; stated to be single primary	814
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• lng	817
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• marital_stats_at_dx_Divorced	819
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- seer_historic_stage_a.Unstaged
- sex_Female
- spanish_hispanic_origin.Cuban
- spanish_hispanic_origin.Mexican
- spanish_hispanic_origin.Non-Spanish/Non-hispanic
- spanish_hispanic_origin.Other specified Spanish/Hispanic origin (excludes Dominican Republic)
- spanish_hispanic_origin.Spanish surname only
- spanish_hispanic_origin.Spanish, NOS; Hispanic, NOS; Latino, NOS
- year_of_birth
- year_of_diagnosis
- month

and `newtarget` is the target variable, indicating whether or not the subject died in month given by the value of the `month` variable.

Pseudocode for the Data Transformation

```
def train(X, T, D)
    // X, T, D are the original dataset
    X' = []
    D' = []

    // the transformation
    for each index i in X:
        for t=1 to T[i]:
            new_D = (0 if t < T[i], else D[i])
            append new_D to D'
            new_X = (X[i], t)
            append new_X to X'

    return a decision tree trained on (X', D')
```

```
def pmf(h, X)
    // X is a single datapoint
    // returns an array A where A[i] = P(Y = i | X)
    A = []
    p_so_far = 1 // this is p(T >= t | X)
    for t = 1 to (the last month where h has any data):
        // h knows p(T = t | T >= t, X), we call this p_cur
        p_cur = h's prediction for (X, t)
        append (p_so_far * p_cur) to A
        p_so_far *= (1 - p_cur)
```

Breast Random Forest Model Hyperparameters

```
f = RandomForestClassifier(n_estimators=20,min_samples_split=3,
                           max_depth = 15,
                           max_features = .8,
                           n_jobs=5,verbose=2,random_state=33)
```

Colon Random Forest Model Hyperparameters

```
rf = RandomForestClassifier(n_estimators=25,min_samples_split=3,
                           max_depth = 10,
                           max_features = .5,
                           n_jobs=5,verbose=2,random_state=3)
```

Lung Random Forest Model Hyperparameters

```
rf = RandomForestClassifier(n_estimators=25,min_samples_split=3,
                           max_depth = 11,
                           max_features = .8,
                           n_jobs=5,verbose=2,random_state=3)
```

Breast Neural Network Model Architecture

The architecture of the Keras multilayer perceptron neural network model trained on the breast cancer data is given explicitly below:

```
modelbreast = Sequential()
modelbreast.add(Dense(114, input_shape=(66,) ,init='normal'))
modelbreast.add(Activation('relu'))
modelbreast.add(Dropout(0.05))
modelbreast.add(Dense(50, init='normal'))
modelbreast.add(Activation('relu'))
modelbreast.add(Dropout(0.05))

modelbreast.add(Dense(36, init='normal'))
modelbreast.add(Activation('relu'))
modelbreast.add(Dropout(0.05))

modelbreast.add(Dense(2, init='normal'))
modelbreast.add(Activation('softmax'))

rms = RMSprop(lr=0.001)

modelbreast.compile(loss='binary_crossentropy',
                    optimizer=rms, class_mode="binary")
```

and trained with a batch size of 1500 for 200 epochs.

Colon Cancer Neural Network Model Architecture

The architecture of the Keras multilayer perceptron neural network model trained on the colon cancer data is given explicitly below:

```
modelcolon = Sequential()
modelcolon.add(Dense(114, input_shape=(102,) ,init='normal'))
modelcolon.add(Activation('relu'))
modelcolon.add(Dropout(0.05))
modelcolon.add(Dense(50, init='normal'))
```

```
modelcolon.add(Activation('relu'))
modelcolon.add(Dropout(0.05))
```

```
modelcolon.add(Dense(35, init='normal'))
modelcolon.add(Activation('relu'))
modelcolon.add(Dropout(0.05))
```

```
modelcolon.add(Dense(2, init='normal'))
modelcolon.add(Activation('softmax'))
```

```
rms = RMSprop(lr=0.001)
```

```
modelcolon.compile(loss='binary_crossentropy',
                    optimizer=rms, class_mode="binary")
```

and trained with a batch size of 1500 for 200 epochs.

Lung Cancer Neural Network Model Architecture

The architecture of the Keras multilayer perceptron neural network model trained on the lung cancer data is given explicitly below:

```
modellung = Sequential()
modellung.add(Dense(114, input_shape=(114,) ,init='normal'))
modellung.add(Activation('relu'))
modellung.add(Dropout(0.1))
modellung.add(Dense(80, init='normal'))
modellung.add(Activation('relu'))
modellung.add(Dropout(0.1))
modellung.add(Dense(40, init='normal'))
modellung.add(Activation('relu'))
modellung.add(Dropout(0.1))
```

```
modellung.add(Dense(2, init='normal'))
modellung.add(Activation('softmax'))
```

```
rms = RMSprop(lr=0.001)
```

```
modellung.compile(loss='binary_crossentropy',
                  optimizer=rms, class_mode="binary")
```

and trained with a batch size of 2000 for 50 epochs.

S1 Video

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S1 Text 991

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S1 Fig 995

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S2 Fig 999

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S1 Table 1003

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Acknowledgments 1007

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