

# Machine Learning for Survival Analysis: A New 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 afficianados can create their own radio stations tailored to their individual tastes from Pandora<sup>1</sup>, bibliophiles can receive highly trustworthy book recommendations from goodreads.com<sup>2</sup>, and Google will provide directions between any two points, giving options such as mode of transportation and as well as warnings of delays in realtime.<sup>3</sup> These individualized services share many

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

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

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

common features. In particular, they leverage large databases of aggregated information to learn and extract information relevant to individuals. Extracting actionable information from data is changing the fabric of modern business. 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 with data in cancer registries to produce personalized survival prognosis curves, but 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 information is not personal; 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 described below also take full advantage of all relevant aggregate information, but are able to provide personalized survival curves relevant to individual subjects. This objective is in keeping with the recent movement in medicine known as Predictive, Preventive and Personalized Medicine (PPPM), which aims to leverage increasing amounts of health related data to maximize quality of care and to intelligently eliminate inefficient and unnecessary use of resources [3]. This capability of providing 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, in spite of some of the data aggregation challenges posed by the Health Insurance Portability and Accountability Act (HIPPA) of 1996. This study makes use of a freely available data source that circumvents the restrictions imposed by HIPPA.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) has been collecting data because intuitively researchers feel confident that this data will eventually allow researchers to detect information crucial to patients and providers including the relationships between the types of data collected (demographic as well as staging information, treatment and disease characteristics) and the 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*. As will be demonstrated in section , these two methods produce very similar results when applied to the SEER dataset, and are based on almost diametrically opposed learning philosophies, which lends confidence in the validity of the results.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) 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.

Quoting directly from the SEER website [4]:

The SEER program registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. This program is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data. The mortality data reported by SEER are provided by the National Center for Health Statistics. The population data used in calculating cancer rates is obtained periodically from the Census Bureau.

Updated annually and provided as a public service in print and electronic formats, SEER data are used by thousands of researchers, clinicians, public health officials, legislators, policymakers, community groups, and the public.

One characteristic of the SEER data that is shared by many datasets in the medical field goes by the name of "censored data." Observations are labeled censored when the survival time information is incomplete. The SEER data contains the number of months each patient survived, as well as an indicator variable showing whether or not the patient is still alive at the end of the data collection period. Methods to deal effectively with this kind of "right-censored data" include Kaplan-Meier curves and Cox Proportional Hazard models [2]. The Kaplan-Meier techniques only give estimates for cohorts of patients and are not applicable for predicting the survival curve for a single patient, and the Cox Proportional Hazard models require a fairly restrictive set of assumptions to be satisfied in order to yield reliable results.

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 months information is censored at a value less than 5 years. Zolbanin et al. [6] investigate the effects of comorbidities; i.e., patients with two different cancer diagnoses, but their treatment of the censored data underestimates the survival probabilities. All records representing patients who survived at least 60 months as well as all those who died earlier than 60 months were considered, but patients alive prior to 60 months but censored out of the study before 60 months were not included. This treatment biases the data and the predictions, leading to overly pessimistic survival probabilities predicted by the models.

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].

IOBS has applied a little-known technique to transform the SEER data to make it amenable to more powerful machine learning methods. Instead of modifying existing learning algorithms in drastic ways, we focus attention on the input data. This approach allows for different machine learning algorithms to use the same data with no modification. The essential idea is to recast the problem to an appropriate discrete classification problem 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 full survival function can then be derived from the hazard function.

This paper is organized as follows. We introduce the subsets of the SEER data used for this study, and present survival curves computed from traditional methods based on this data for the three cancer types *lung*, *breast*, and *colon*. We then present the essential methodology of this work, the data transformation that allows censored survival data to be used as input to existing machine learning classifiers. Then we present the details of the trained models, including some subtleties arising from the data transformation pertaining to the partition into training and test datasets. The method of deriving binary classifiers from the models' predictions for the survival curves is presented. In this paper, we have constructed binary classifiers corresponding to 6, 12, and 60 months, as these are standard metrics in cancer survival prognosis. Then follows

a discussion of the evaluation of the trained models. The performance metrics are the 18 AUC curves associated with the 6, 12, and 60 month survival binary classifiers for the two models associated with each cancer type. We also present additional evidence supporting validity of the predictions by computing the levels of agreement between the random forest and neural network models for each of the 18 binary classifiers and find striking agreement. Next we provide urls for 6 web applications that use the trained models to predict individual cancer survival prognosis curves. These apps are hosted on the popular Heroku website, and allow for exploration of the nonlinear relationships between the input features and resulting survival prognosis. It is exactly these kinds of tools that are the goal of Predictive, Preventive and Personalized Medicine. Finally, we present avenues for future research.

## 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].

- incidence\yr1973\_2012.seer9\COLRECT.txt
- incidence\yr1973\_2012.seer9\BREAST.txt
- incidence\yr1973\_2012.seer9\RESPIR.txt
- incidence\yr1992\_2012.sj\_la\_rg\_ak\COLRECT.txt
- incidence\yr1992\_2012.sj\_la\_rg\_ak\BREAST.txt
- incidence\yr1992\_2012.sj\_la\_rg\_ak\RESPIR.txt
- incidence\yr2000\_2012.ca\_ky\_lo\_nj\_ga\COLRECT.txt
- incidence\yr2000\_2012.ca\_ky\_lo\_nj\_ga\BREAST.txt
- incidence\yr2000\_2012.ca\_ky\_lo\_nj\_ga\RESPIR.txt
- incidence\yr2005\_lo\_2nd\_half\COLRECT.txt
- incidence\yr2005\_lo\_2nd\_half\BREAST.txt
- incidence\yr2005\_lo\_2nd\_half\RESPIR.txt

## 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 [11].

As a simple example of how to correctly treat categorical variables in a machine learning context, consider the SEER variable **SEX**. This variable is encoded in the

Code	Description
1	Male
2	Female

**Table 1.** Encoding of gender in the SEER incidence files. These types of categorical variables need to be transformed via one-hot-encoding.

SEER raw data files with a numeric 1 for males and a numeric 2 for females as shown in Table (1). Values such as "Male" and "Female" encoded as numbers are dangerous because if not handled properly, they can generate bogus results [12]. Leaving the information for **SEX** as in Table (1) implies that Female is somehow greater than Male. This implied ordering affects the machine learning algorithms' convergence on a model. Simply encoding Male by 2 and Female by 1 would result in a completely different model, because of the now completely reversed ordering implied in the **SEX** variable. The proper way to transform the SEER **SEX** variable is to create two additional variables: **sex\_Male** and **sex\_Female**, and then to eliminate the variables **SEX** and **sex\_Male** (keeping both of the variables **sex\_Male** and **sex\_Female** is a redundant representation). For example,

$$\begin{array}{|c|} \hline \text{Sex} \\ \hline 1 \\ \hline \end{array} \rightarrow \begin{array}{|c|c|} \hline \text{sex\_Male} & \text{sex\_Female} \\ \hline 1 & 0 \\ \hline \end{array} \rightarrow \begin{array}{|c|} \hline \text{sex\_Female} \\ \hline 0 \\ \hline \end{array} \quad (1)$$

and

$$\begin{array}{|c|} \hline \text{Sex} \\ \hline 2 \\ \hline \end{array} \rightarrow \begin{array}{|c|c|} \hline \text{sex\_Male} & \text{sex\_Female} \\ \hline 0 & 1 \\ \hline \end{array} \rightarrow \begin{array}{|c|} \hline \text{sex\_Female} \\ \hline 1 \\ \hline \end{array} \quad (2)$$

The procedure outlined in Equations (1, 2) is known as one-hot encoding and 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 geographical 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 (2) shows how five entries of **STATE-COUNTY RECODE** corresponding to counties within New Mexico can be represented by the **elevation**, **lat**, and **lng** features.

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 (2). It is then possible to programmatically query the

**Table 2.** 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

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 (2) 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 are instances of subjects with multiple rows; whenever a subject, or patient, is diagnosed with a new tumor, an additional record is added. In this study, we restrict attention to the data corresponding to the first record of each subject; i.e., we wish to make models that predict survival prognosis based on the data available right after diagnosis. The full set of conditions defining the subsets of the SEER data used in this study follows below.

The four COLRECT.txt files were imported into a pandas DataFrame object. This data was then filtered according to the conditions in Table (3). The RESPIR.txt and BREAST.txt files were imported into separate dataframes in similar fashion and filtered according to the conditions in Table (4) and Table (5), 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 pateint record." In this study, we discard those records, as indicated in Tables (5, 3, 4).

**Table 3.** 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 4.** 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 5.** 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

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

- SEX ,
- MARITAL STATUS AT DX ,
- RACE/ETHNICITY ,
- SPANISH/HISPANIC ORIGIN ,
- GRADE ,
- PRIMARY SITE ,
- LATERALITY ,
- SEER HISTORIC STAGE A ,
- HISTOLOGY RECODE--BROAD GROUPINGS ,
- MONTH OF DIAGNOSIS ,
- VITAL STATUS RECODE ,

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 (2).

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.

## Traditional Survival Analysis

Survival analysis pertains to data containing survival times, which are *intervals* between certain kinds of events, e.g.; cancer diagnosis date and expiry date. These intervals are often affected by a kind of "partial missingness" called *censoring*. Censored data must be analyzed in a special way to avoid biased estimates and bogus conclusions. Special methods have been developed long ago to analyze censored data properly.

With survival data, including the SEER data considered in this study, you may not know the exact time of death for some subjects. Some of the SEER subjects are still alive at the the time of the latest SEER data release. When the **VITAL STATUS RECODE** variable indicates that the subject is still alive, the **SURVIVAL MONTHS** variable is only a lower bound on the true number of survival months; this is called the *date of last contact* mode of censoring. You know that each subject either died on a certain date or was definitely alive up to some last-seen date (and you don't know how far beyond that date he or she may ultimately have lived). The latter situation is called a *censored* observation.

Statisticians have developed some traditional techniques to utilize the partial information contained in censored observations: the life-table method and the Kaplan-Meier method. Both of these methods make use of the partial information to provide unbiased estimates of the two fundamental concepts: - *hazard* and *survival*, both of which are functions of time:

- **The hazard rate**  $\lambda(t)$  is the probability of dying in the next small interval of time, assuming that the subject is alive right now.
- **The survival rate**  $S(t)$  is the probability of living for a certain amount of time after some starting point.

Incorrect treatment of survival data still seen in practice, and leading to biased results, includes simply excluding all subjects with a censored survival time from any survival analysis, and *imputing* (replacing) the censored (last-seen) date with some reasonable value. Both of these techniques destroy the partial information contained in the censored observations and nullify the validity of the resulting estimates for the hazard rate and survival rate [2].

In 1958, Edward L. Kaplan and Paul Meier collaborated to publish the seminal paper on how to estimate the hazard and survival rates for data containing censored observations [?]. The method is straightforward and for small datasets can be performed by hand. As an example, consider the survival data shown in Table (6). In the Kaplan-Meier calculation of the survival curve, the first step is to sort the subjects in Table (6) labeled 0 through 9 by *Survival Time* in ascending order. This process results in the first two columns (*Censored Status*, and *Survival Times*) in Table (??). The *At Risk* column decreases by one for each row; in every row a subject has either been censored out of the study or has died. The hazard rate is then computed for each value of *Survival Time* (necessarily a discrete function because the number of subjects is countable), by dividing the value in *Censored Status* by the value in *At Risk*. The hazard function is shown in the *Hazard Function* column in Table (??). It is then straightforward to calculate the survival function; 1 - hazard function represents the probability of not dying in the next interval of time, assuming that the subject has survived up until now and is represented by column *Prob of Surv*. The cumulative survival probability can then be obtained by successively multiplying all these individual time-slice probabilities together. In order to survive 2.4 years, first the subject has to



survive .5 years, then survive .75 years, 2.3 years and 2.4 years. The probability of surviving 2.4 years is then the product of these 3 probabilities and is given as .666 in Table(??) in the *Survival Function* column. The Kaplan-Meier survival estimate corresponding to the data given in Table (6) is shown in Table (??).

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**Table 6.** Example data to illustate traditional Survival Analsysis.

Survival Time (Years)	Censored Status	
0	0.75	1
1	6.10	1
2	7.00	0
3	2.40	1
4	0.50	0
5	4.50	1
6	3.50	0
7	5.80	0
8	2.30	1
9	5.20	1

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## Results

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Discussion

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## Supporting Information

### S1 Video

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### S1 Text

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### S1 Fig

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### S2 Fig

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### S1 Table

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## Acknowledgments

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