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RESEARCH ARTICLE

NON PARAMETRIC ESTIMATION OF AN ILLNESS DEATH STOCHASTIC MODEL WITH RECOVERY STATE

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ABSTRACT

An illness death model is a Multi-state model where subjects progress though three different states. An illness death model is a discrete space continuous time stochastic process, for a random process $(X(t), t \in T)$ with a finite state space S = {1, 2 ... N}. Here, T = [0, τ], $\tau < \infty$ is a time interval and the value of the process at time t the state occupied at that time. The states are either transient or absorbing. An absorbing state is a state from which further transitions cannot occur while a transient state allows transition to other states. This paper deals with the Non parametric estimation of an illness death model with a recovery state, in which the patients move among disease free → diseased, diseased → disease free, diseased → death and diseased free → death. A longitudinal failure time data is being employed to describe the Non parametric estimators, Nelson Aalen (1972), Aalen Johansen (1978), and Kaplan Meier (1958) to estimate cumulative intensities, transition probabilities, and survival probabilities respectively and to study their statistical properties. The evolution of multi state model, an illness death model with recovery state has achieved by the method of episode spiting.

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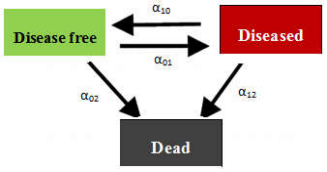
INTRODUCTION

The event history analysis set-up considered in classical survival models may be generalized in sequential of occurrence of event an individual. More than one type of events may be considered for each individual under study and or the event in question may happen more than once for each individual.More generally, any Markov process may be considered with a finite number of states which may be used to model the life-history of an individual.This paper deals with an illness death model with recovery state, represents four transitions and three states namely disease free (0) diseased (1) and dead (2) and the transitions 0→1, 1→0, 0→2, 1→2. The following diagram represents the illness death model with a recovery state also the transition probability matrix. Assume that there are samples of n individuals from the population. The observation of the survival times for these individuals will typically be subject to right censoring, meaning that for some individuals it is only known, that their true survival times exceed certain censoring times. The censoring is assumed to be independent in the sense that the additional knowledge of censorings before any time t does not alter the risk of failure at t.Right censoring is not the only kind of data incompleteness in survival analysis. Often, in epidemiological applications, individuals are not followed from time zero (in the relevant time scale, typically age), but only from a later entry time (conditional on survival until this entry time). Thus, in addition to right censoring, the survival data are subject to left truncation. The number at risk r_j, now is the number of individuals who have entered the study before time t_j and are still in the study just prior to t_j. For left truncated data the numbers at risk r_j, may be low for small values of t_j.



$$P(t) = \begin{bmatrix} P_{00} & p_{01} & p_{02} \\ p_{10} & p_{11} & P_{12} \\ 0 & 0 & 1 \end{bmatrix}$$

Figure 1. An illness death model with recovery and its transition probability matrix

Quite often the survival distribution function $S(t) = e^{-A(t)}$ needs to be estimated, representing the probability that an individual will be alive at time t. This may be done from right-censored and/or left-truncated survival data by the Kaplan-Meier estimator. The relation $A(t) = -\ln S(t)$ suggests that the

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cumulative hazard rate function alternatively may be estimated as minus the logarithm of the Kaplan-Meier estimator. Even though this estimator numerically will be close to the Nelson-Aalen estimator, the latter is the canonical one from a theoretical point of view. Further, the Nelson-Aalen estimator may be used in a number of different situations while the alternative estimator applies only to the survival data situation.In particular in a study involving treatment of cancer, state 0 could correspond to 'healthy' state 1 to 'acquired pneumonia' and state 2 to 'death'. The probability $p_{01}(s,t)$ is then the probability of being in response function suggested by Temkin (1978) and sometimes used as an outcome measure when studying the efficacy of therapy. Consider the state 0 could correspond to "diseased free", state 1 to "diseased" and state 2 to "dead". Thus the Aalen-Johansen and Nelsen-Aalen estimators are related in exactly the same way as are the transition probability matrix and the cumulative transition intensities themselves. This suggests that the Aalen-Johansen estimator is the canonical nonparametric estimator for the matrix of transition probabilities in a Markov process with a finite number of states. This statement is supported by the fact that it may also be given a nonparametric maximum likelihood interpretation (Johansen, 1978).This interpretation of the states is the one relevant for the following illustration of SIR3 in four sections.Section 1, introduction, section 2, non parametric estimators of an illness death model, section 3, analysis of SIR3 data and in section 4 interpretation of results.The specific data considered in this study is sir.cont is a subset of larger cohort denoted SIR3 (Spread of nosocomial Infections and Resistant pathogens). This data base is taken from the package mvna (2015) and estimated using R version 3.1.3 programme.

Back ground

An illness death model, Multi state models are systems of multivariate survival data where individuals transition through a series of distinct states following certain paths of possible transitions. Transitions between states may be reversible or irreversible while states can be either absorbing or transient. Multi state models have a wide range of application including epidemiology, dentistry, clinical trials, reliability studies in engineering and medicine, where individuals progress through the different states of diseases such as cancer and AIDS. Data in these applications are often subject to right censoring and possibly left truncation. Aalen (1978) and Nelson (1972) proposed an estimator for the integrated hazard under a broad class of counting process models. Aalen and Johansen (1978) obtained an estimator for the transition probability matrix and subsequently state occupation probabilities through product-limit integration of the Nelson-Aalen estimator. Datta and Satten,(2001) established that the resulting estimators of state occupation probabilities remained valid even when the process is non Markovian. Datta, and Satten, (2002) also proposed an estimator for state occupation probabilities that can handle state dependent censoring and other flexible models through a weighting function based on the censoring scheme. Estimation of state entry and exit distribution functions are also of interest, as discussed by Pepe (1991) and Datta and Ferguson (2011). This can be calculated through normalized sums of state occupation probabilities.

Non parametric estimation of an illness death model

Assume first that the transition intensities are the same for all individuals but that they are allowed to vary freely with time $\alpha_{hj}^{i}(t)=\alpha_{hj}(t)$. Statistical inference is then conveniently phrased in terms of the counting process approach pioneered by Aalen (Anderson *et al*., 1993). An important feature of the nonparametric approach is its elegant generalization, to estimating transition probabilities. The basic tool is the product integral. The Aalen-Johansen estimator of $P_{hj}(s,t)$ is obtained by plugging the matrix of Nelson-Aalen estimators $(\hat{A}_{hj}(t))$. The sufficient knowledge about $S(t)=e^{-A(t)}$ estimates the Kaplan Meier estimates of survival probabilities.

Nelson-aalen estimator

Consider a finite-state Markov process with transition intensities $\alpha_{gh}(t)$ for $g \neq h$ focusing on fixed g and h in the following, drop the subscripts and write just $\alpha(t)$ for the $g \rightarrow h$ transition intensity. Further denote by $t_1 < t_2 < \ldots$ the times when transitions from g to h are observed. Let d_j be the number of individuals who experience a $g \rightarrow h$ transition at t_j and write r_j for the number of individuals in state g i.e. at risk for a $g \rightarrow h$ transition just prior to time t_j. Then the cumulative $g \rightarrow h$ transition intensity $\hat{A}(t)=\int_0^t \alpha(s)ds$ may be estimated by $\hat{A}(t)=\sum_{t_j \le t}\frac{d_j}{r_j}$ and its variance by $\hat{\sigma}^2_{NA}(t)=\sum_{t_j \le t}\frac{(r_j-d_j)d_j}{(r_j-1)r_j^2}$. Similarly the integrated intensity of an non homogeneous Poisson process may be estimated with the t_j denoting the times of observed event, the $d_j$and r_j being the corresponding number of event and number at risk respectively.

Aalen-johansen estimator

Consider that exact times for transitions between the states are recorded and are denoted by $t_1 < t_2 < \ldots$ the times when transitions between any two states are observed. Further for $g,h \in I, g \neq h$, let d_{ghj} be the number of individuals who experience a transition from state g to state h at t_j and introduce $d_{gj}=\sum_{g \neq h} g_{ghj}$ for the number of transitions out of state g at that time. Finally let r_{gj} be the number of individuals in state g just prior to time t_j. Then the Aalen-Johansen estimator takes the form $\hat{P}(s,t)=\prod_{s<t_j\le t}(I+\hat{a}_j)$ where I is the $(k+1)\times(k+1)$ identity matrix, $\hat{a}_j$ is the $(k+1)\times(k+1)$ matrix with entry (g,h) equal to $\hat{a}_{ghj}=\frac{d_{ghj}}{r_{gj}}$ *for* $g \neq h$ and entry (g, g) equal to $\hat{a}_{ggj}=-\frac{d_{gj}}{r_{gj}}$ and the matrix product is taken in the order of increasing t_j and their variances are

$$\widehat{cov}(\hat{P}_{gh}(s,t),\hat{P}_{mr}(s,t)=\sum_{i=0}^{k}\sum_{l=i}\sum_{s<t_j\le t}\hat{P}_{gi}(s,t_{j-1})\hat{P}_{ml}(s,t_{j-1})[\hat{P}_{lh}(t_j,t)-\hat{P}_{lh}(t_j,t)]*[\hat{P}_{ir}(t_j,t)-\hat{P}_{ir}(t_j,t)](r_{ij}-1)r_{ij}^{-3}d_{ilj}$$

Statistical properties of Non Parametric estimators are studied by the representation of Aalen-johansen and Nelson Aalen estimators as the Kaplan Meier estimator.

Application to real time data

The data base is in the form of a two dimensional array with 747 patients and six variables. The variables include ('id', representing the unique patient identification Number, 'from' representing the entry state, 'to' representing the exit state, 'time' representing the number of days spent in a particular state, 'age' representing the age of the patient measured in years and 'sex' representing the gender of the patients. In sir.cont data, all the variables except 'sex' are represented using numeric values and the 'sex' are with character representation ('M'-Male and 'F'- Female). The state consider in this analysis include'0' '1' and '2'. The state '0' denotes disease free nature of the patient, '1' denotes the diseased state (under ventilation) and '2' denotes death of the patient. Here state '2' is treated as an absorbing state. With the three states'0', '1' and '2' the transitions form 0 to 1, 0 to 2, 1 to 0, 1 to 2 and 0 to 2 are allowed. The other parts are restricted for this analysis. So model the disease-histories of the patients by the Markov illness-death model with the state 0 and 1 corresponding to "alive without pneumonia" and "alive with pneumonia", respectively and with pneumonia duration as time scale. The specific data considered in this section of the study is sir.cont is a subset of larger cohort denoted SIR3 (Spread of nosocomial Infections and Resistant pathogens). This data base is taken from the package mvna (2015). The data base is in the form of a two dimensional array with 747 patients and six variables.

The variables include ('id', representing the unique patient identification Number, 'from' representing the entry state, 'to' representing the exit state, 'time' representing the number of days spent in a particular state, 'age' representing the age of the patient measured in years and 'sex' representing the gender of the patients. In this data base all the variables except 'sex' are represented using numeric values and the 'sex' are with character representation ('M'-Male and 'F'- Female). The state consider in this analysis include'0' '1' and '2'. The state '0' denotes disease free nature of the patient, '1' denotes the diseased state (under ventilation) and '2' denotes death of the patient. Here state '2' is treated as an absorbing state. With the three states'0', '1' and '2' the transitions form 0 to 1, 0 to 2, 1 to 0, 1 to 2 and 0 to 2 are allowed. The other parts are restricted for this analysis.

Nelson-Aalen estimates of cumulative intensities

The Nelson-Aalen estimates of cumulative intensities of an illness death model as prescribed in section 2 is illustrated in the following table.

The cumulative intensities tabulated above for different transitions are represented in the following Figures.

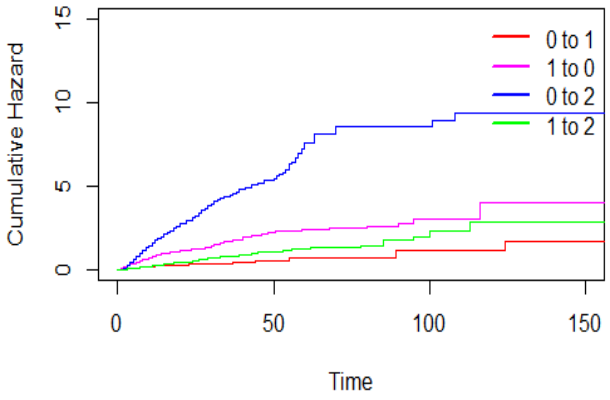
The transition specific cumulative intensities estimated and graphed provide a clue, through their slopes. By comparing the slopes of the four possible transitions, it is seen that the cumulative hazard changes rapidly when transition takes place from 'disease free' state to 'death' state. The slope is least for the transition from 'disease free' state to 'diseased' state. This indicates the varying nature of the transitions and its impact on the cumulative intensities.

Table 1. The Nelson-Aalen estimates of cumulative intensities and their variances for different transitions Transition

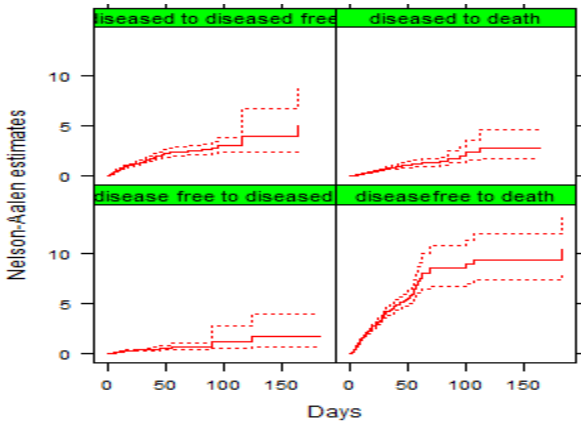
Time	Nelson-Aalen Estimates	Variance Aalen	Variance Greenwood	Lower Limit	Upper limit	No of Risk	No. of Event
The Nelson-Aalen estimates of cumulative intensities and their variances for Transition 0 → 1							
0	0.00	0.00	0.00	0.00	0.00	367	0
15	0.26	0.00	0.00	0.20	0.34	106	2
34	0.38	0.00	0.00	0.27	0.54	26	0
55	0.67	0.02	0.02	0.43	1.04	10	1
89	1.17	0.27	0.15	0.49	2.81	2	1
130	1.67	0.52	0.27	0.71	3.90	1	0
The Nelson-Aalen estimates of cumulative intensities and their variances for Transition 0 → 2							
0	0.00	0.00	0.00	0.00	0.00	367	0
15	2.10	0.01	0.01	1.90	2.33	106	15
34	4.33	0.07	0.06	3.85	4.86	26	2
55	6.29	0.19	0.16	5.50	7.21	10	3
89	8.58	1.04	0.66	6.79	10.83	2	0
130	9.41	1.40	0.86	7.35	12.04	1	0
The Nelson-Aalen estimates of cumulative intensities and their variances for Transition 1 → 0							
Time	Nelson-Aalen Estimates	Variance Aalen	Variance Greenwood	Lower limit	Upper Limit	No of Risk	No. of Event
0	0.00	0.00	0.00	0.00	0.00	380	0
14	0.95	0.00	0.00	0.83	1.09	137	6
33	1.57	0.01	0.01	1.36	1.80	49	5
54	2.34	0.04	0.04	1.97	2.78	14	0
85	2.61	0.07	0.06	2.15	3.18	8	0
130	3.98	1.14	0.12	2.36	6.73	1	0
The Nelson-Aalen estimates of cumulative intensities and their variances for Transition 1 → 2							
0	0.00	0.00	0.00	0.00	0.00	380	0
14	0.29	0.00	0.00	0.23	0.38	137	2
33	0.77	0.01	0.01	0.62	0.96	49	2
54	1.16	0.02	0.02	0.89	1.50	14	0
85	1.79	0.09	0.07	1.28	2.50	8	3
130	2.82	0.49	0.30	1.73	4.60	1	0

Aalen-Johnsen Estimator

The output, including empirical transition matrix corresponding to Aalen-Johnsen estimator is provided below shows the uncorrelated structure among the transitions.



Transition wise Nelson-Aalen estimates of cumulative intensities



Transition wise Nelson-Aalen estimates of cumulative intensities with lower and upper limits

Figure 2. Transition wise Nelson-Aalen estimates of cumulative intensities with lower and upper limits

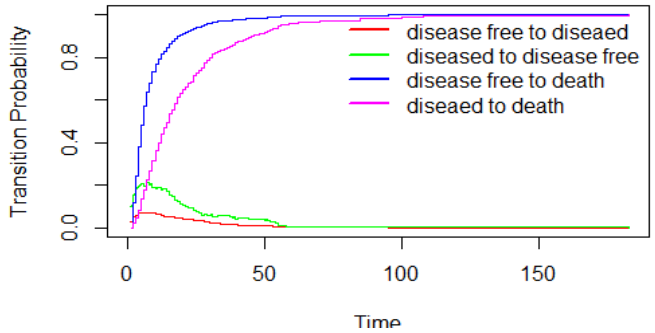
Table 2. Estimate of covariance matrix for P(1, 183) using Aalen-Johnsen estimator

	0→0	1→0	2→0	0→1	1→1	2→1	0→2	1→2	2→2
0→0	0	0	0	0	0	0	0	0	0
1→0	0	0	0	0	0	0	0	0	0
2→0	0	0	0	0	0	0	0	0	0
0→1	0	0	0	0	0	0	0	0	0
1→1	0	0	0	0	0	0	0	0	0
2→1	0	0	0	0	0	0	0	0	0
0→2	0	0	0	0	0	0	-2.864E-20	-1.126E-19	0
1→2	0	0	0	0	0	0	-4.785E-20	2.710E-19	0
2→2	0	0	0	0	0	0	0	0	0

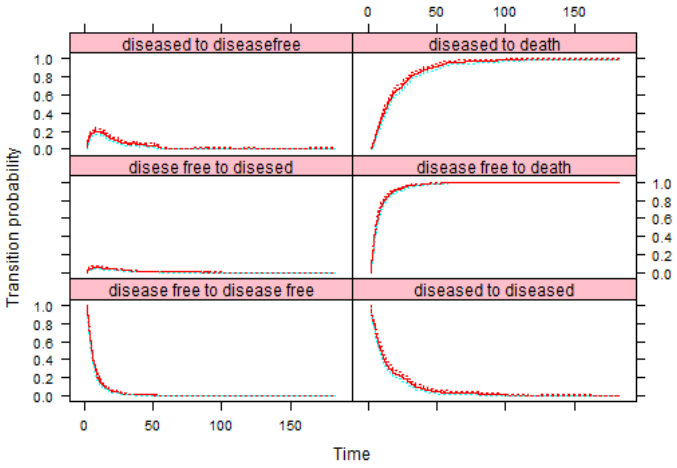
Table 3. Aalen-Johnsen Estimates of Transition Probability for different transitions

Probability	Time	Variance	Lower limit	Upper limit	No. of risk	No. ofevent
Aalen-Johnsen Estimates of Transition Probability from 0→1						
0.000000	1.5	0.0000000	0.000000	0.000000	394	0
0.043086	16.0	0.0000410	0.030500	0.055672	93	1
0.015684	35.0	0.0000093	0.009719	0.021650	28	0
0.006327	56.0	0.0000032	0.002826	0.009828	6	0
0.002433	90.0	0.0000012	0.000284	0.004582	1	0
0.000000	183.0	0.0000000	0.000000	0.000000	1	0
Aalen-Johnsen Estimates of Transition Probability from 0→2						
0.000000	1.5	0.000000	0.000000	0.000000	394	0
0.872251	16.0	0.000152	0.848070	0.896432	93	9
0.969663	35.0	0.000023	0.960362	0.978963	28	2
0.991268	56.0	0.000005	0.987034	0.995502	6	1
0.996595	90.0	0.000002	0.994043	0.999147	1	0
1.000000	183.0	0.000000	NA	NA	1	1
Aalen-Johnsen Estimates of Transition Probability from 1→0						
0.005666	1.5	0.00002	0.000000	0.013496	353	2
0.152624	16.0	0.00024	0.121884	0.183363	122	3
0.061281	35.0	0.00013	0.038447	0.084114	38	0
0.012543	56.0	0.00003	0.001628	0.023459	14	0
0.005714	90.0	0.00002	0.000000	0.013559	6	1
0.000000	183.0	0.00000	0.000000	0.000000	0	0
Aalen-Johnsen Estimates of Transition Probability from 1→2						
Probability	Time	variance	LowerLimit	Upperlimit	No. ofrisk	No. ofevent
0.000000	1.5	0.000000	0.000000	0.000000	353	0
0.553994	16.0	0.000541	0.508419	0.599570	122	2
0.840423	35.0	0.000032	0.805174	0.875672	38	0
0.949825	56.0	0.000121	0.928248	0.971401	14	1
0.979865	90.0	0.000054	0.965494	0.994237	6	0
1.000000	183.0	0.000000	NA	NA	0	0

The Transition Probabilities tabulated above for different transitions are represented in the following Figures



Transition wise Aalen-Johnsen estimate of Transition probabilities



Transition wise Aalen-Johnsen estimate of Transition probabilities with upper and lower limits

Figure 3. Transition wise Aalen-Johnsen estimate of Transition probabilities with upper and lower limits

The transition specific transition probabilities, estimated and graphed provide a pattern, through their increasing or decreasing structures. By comparison it is seen that for the transitions 'disease free to death' and 'diseased to death', transition probability increases over the time. Also it is seen that for the transitions 'diseased to diseased' and 'disease free to disease free', transition probability decreases over the time. This again indicates differing patterns for different transitions that can be made use for proper identification and intervention programs.

Kaplan Meier estimates of survival probabilities

The Kaplan-Meier (product-limit) estimators for the censored observations are given by,

$$\hat{S}(t) = \begin{cases} \prod_{t_j \le t} \frac{(n_j - d_j)}{n_j} ; & t_j \le t \le t_{(j+1)},\ j = 1, 2, ..., r \\ 0 ; & t > t(r) \ \text{if} \ t(r) \ \text{is the last observation} \end{cases}$$

and the same represented in the table given below.

The transition specific Kaplan-Meier estimates derived are pictorially represented in Figure 3.3.1

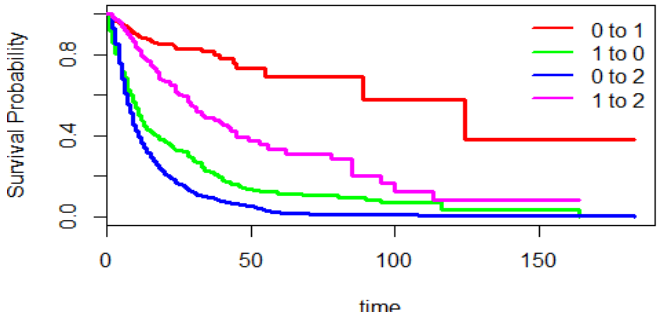


Figure 4. Transition wise Kaplan-Meier Estimate

Table 4. Transition wise Kaplan-Meier Estimate of Survival Probability with Confidence bounds (edited version)

Transition 0→1							Transition 1→0					
t	r_j	d_j	Survival Probability	S.E	Lower CI	Upper CI	T	r_j	d_j	Survival Probability	S.E	Lower CI	Upper CI
1	686	11	0.98	0.00	0.98	0.99	1.0	455	38	0.92	0.01	0.89	0.94
2	675	11	0.97	0.01	0.96	0.98	1.5	417	2	0.91	0.01	0.89	0.94
3	617	4	0.96	0.01	0.95	0.98	2.0	415	26	0.85	0.02	0.82	0.89
4	559	7	0.95	0.01	0.93	0.97	2.5	381	1	0.85	0.02	0.82	0.89
.	.		.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.	.	.	.
45	32	1	0.73	0.05	0.65	0.83	90.0	7	1	0.08	0.02	0.05	0.14
55	17	1	0.69	0.06	0.58	0.82	95.0	6	1	0.07	0.02	0.04	0.13
89	6	1	0.58	0.12	0.39	0.86	116.0	2	1	0.03	0.03	0.01	0.16
124	3	1	0.38	0.17	0.16	0.94	164.0	1	1	0.00	NA	NA	NA
Transition 0→2							Transition 1→2						
t	r_j	d_j	Survival Probability	S.E	Lower CI	Upper CI	T	r_j	d_j	Survival Probability	S.E	Lower CI	Upper CI
2	675	47	0.93	0.01	0.91	0.95	2	415	8	0.98	0.01	0.97	0.99
3	617	54	0.85	0.01	0.82	0.88	3	380	5	0.97	0.01	0.95	0.99
4	559	62	0.75	0.02	0.72	0.79	4	351	3	0.96	0.01	0.94	0.98
.	.	.	.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.	.	.	.
70	7	1	0.01	0.01	0.01	0.03	85	10	3	0.20	0.06	0.11	0.34
101	5	1	0.01	0.00	0.00	0.03	95	6	1	0.17	0.06	0.09	0.32
108	4	1	0.01	0.00	0.00	0.02	100	4	1	0.12	0.05	0.05	0.30
183	1	1	0.00	NA	NA	NA	113	3	1	0.08	0.05	0.03	0.27

Conclusion

An illness death model is a multi state model generalizes the usual survival analysis, in which more than two states are involved in the time sequence. This necessitates transition wise estimate of survival probability and cumulative intensities. The behaviour in different transitions is captured through analysis of SIR3 data through illness death models that account for individual transition specific events. The nonparametric approach proposed by Nelson-Aalen, Kaplan Meier and Aalen-Johnsen are effectively employed to derive the cumulative intensities and transition probabilities for different transitions. Also their variance estimates and their corresponding 95% confidence bounds are estimated. Graphical representation of cumulative intensities indicate the slopes of four possible transitions vary considerably and that the cumulative hazard changes rapidly when transition takes place from 'disease free' state to 'death' state. The slope is least for the transition from 'disease free' state to 'diseased' state. This indicates the varying nature of the transitions and its impact on the cumulative intensities. The state specific transition probabilities, estimated and graphed provide a pattern, through their increasing or decreasing structures. It is seen that for the transitions 'disease free to death' and 'diseased to death', transition probability increases over the time. Also it is seen that for the transitions 'diseased to diseased' and 'disease free to disease free', transition probability decreases over the time. This again indicates differing patterns for different transitions that can be made use for proper identification and intervention programs. The decline in the survival curve of Kaplan meier estimates also evidences the transition nature of different states. Thus, the Illness death model with three state and four transition is effective in bringing out the differing structures, in terms of transition probabilities and cumulative intensities. This model provides a more general global view of the transitions that are ignored under usual two state survival models.

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