The versatility of multistate models for the analysis of longitudinal health services data

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Event history data

Event history data

What is event history data?

Data on the number, timing, and nature of events occurring over the course of observation of an individual

Event history data

Main types of event history data
Time-to-event data
Competing risks data
Recurrent event data
Multiple event type data
Multistate data

Event history data

Time-to-event data

Individual experiences one occurrence of a single type of event over time.

Example. In a cohort study among patients with HIV, the event of interest may be the onset of AIDS.

T is a non-negative continuous random variable known as the event time/ failure time/survival time; it represents time from a well-defined origin to the occurrence of some event

Event history data

Competing risks data

- Several types of events are possible, however an individual experiences only one of these events.
- Usually, one type of event can be singled out as the event of interest.
- The remaining types of events prevent the event of interest from occurring, and are thus considered competing risks.

Example. In a cohort study on individuals with hydrocephalus who have received a shunt

event of interest - time to failure of an initial shunt due to infection

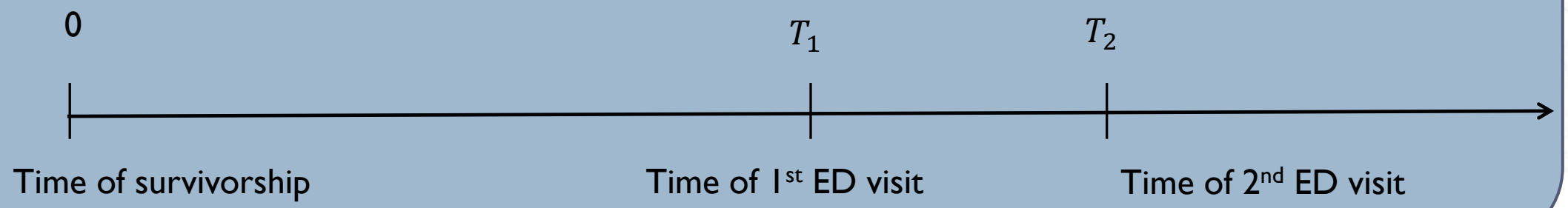
competing events - obstruction, death, and other causes for failure (as any of these may occur before infection)

Event history data

Recurrent event data

Individual experiences a repeated occurrence of a single type of non-fatal event over time.

Example. In a cohort study among cancer survivors, the repeated events may be the visits to a emergency department.

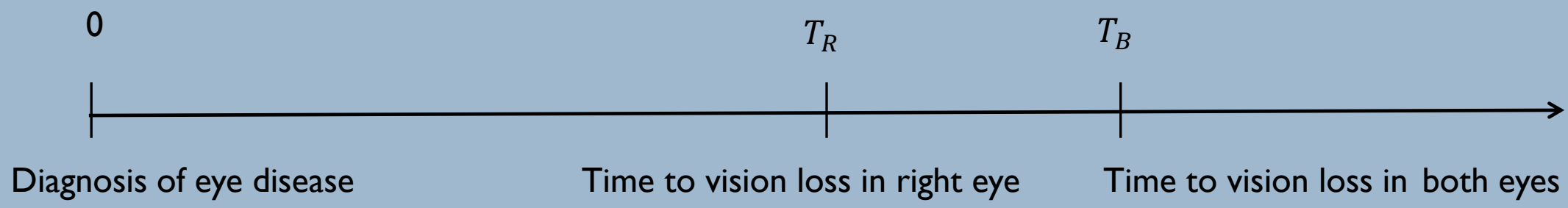


Event history data

Multiple event type data

Individual experiences multiple types of non-fatal events over time.

Example. In a cohort study on patients diagnosed with eye disease, two different types of complications are vision problems in the right eye and vision problems in the left eye.

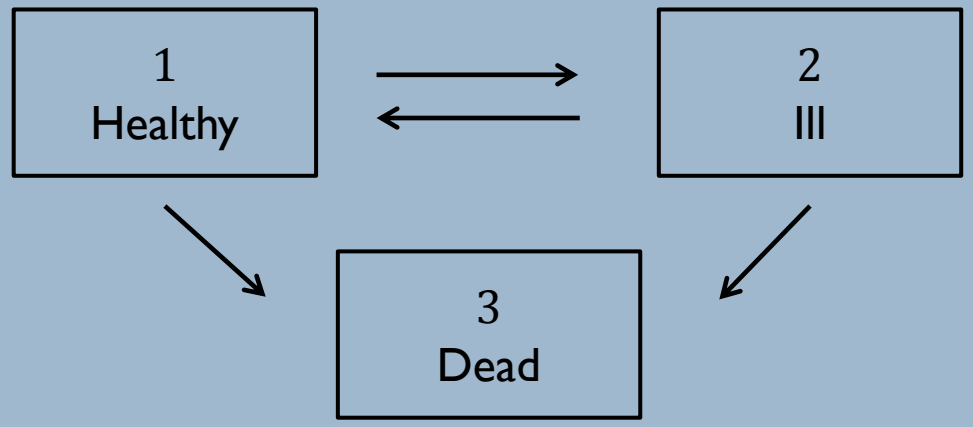


Event history data

Multistate data

Individual is observed to exist in one of a finite number of states at any given time during their observation period.

Example 1. In a simple healthy-illness-death model, an individual, at any given time, is classified to be in one of 3 states – healthy, ill, or dead.

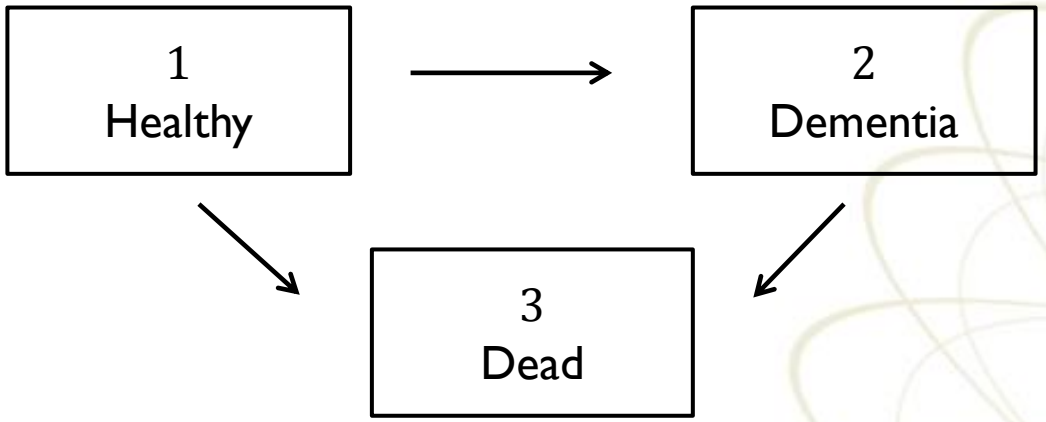


- This healthy-illness-death model allows for reversible transitions between the healthy and ill states.
- Death is known as an absorbing state, since obviously no transitions can be made after this point.

Event history data

Multistate data

Example 2. In this healthy-illness-death model, reversible transitions are not possible. This model is very useful in epidemiology to study both incidence of a disease and mortality rate.



We can estimate the incidence of dementia, the mortality rate among healthy patients, and the mortality rate among patients with dementia.

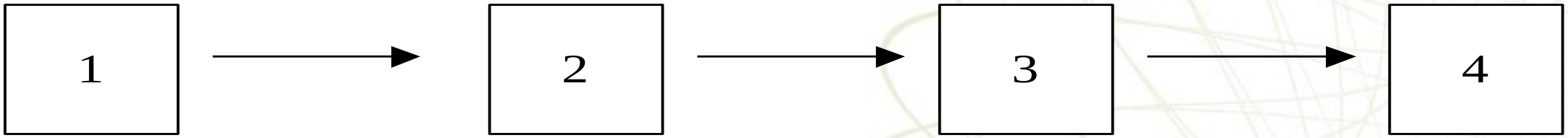
Event history data

Multistate data

(*Sutradhar R, Cook RJ. Analysis of interval-censored data from clustered multistate processes: application to joint damage in psoriatic arthritis. Applied Statistics 2008.*)

Example 3. Consider a cohort study on patients with Psoriatic Arthritis. The progression of damage for a joint can be described using a 4-State Progressive Model.

1- Normal 2- Surface Erosions 3- Joint Space Narrowing 4- Surgery

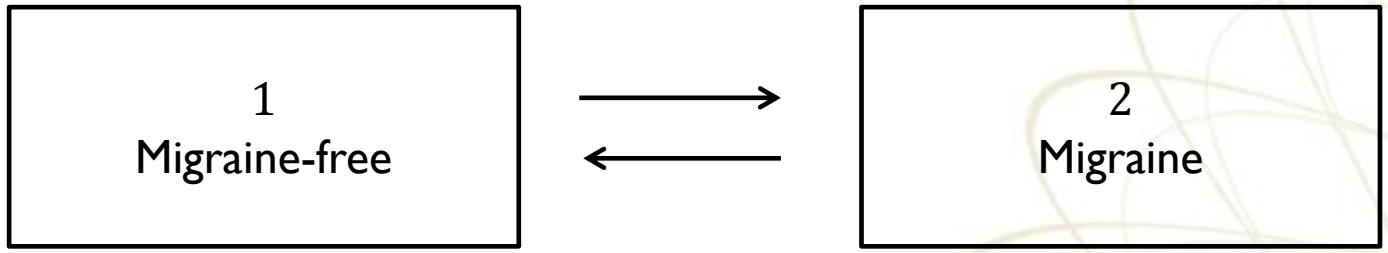


This is known as a progressive multistate model, as transitions are only possible in a forward direction.

Event history data

Multistate data

Example 4. Consider a study examining periods of migraine among pregnant women.



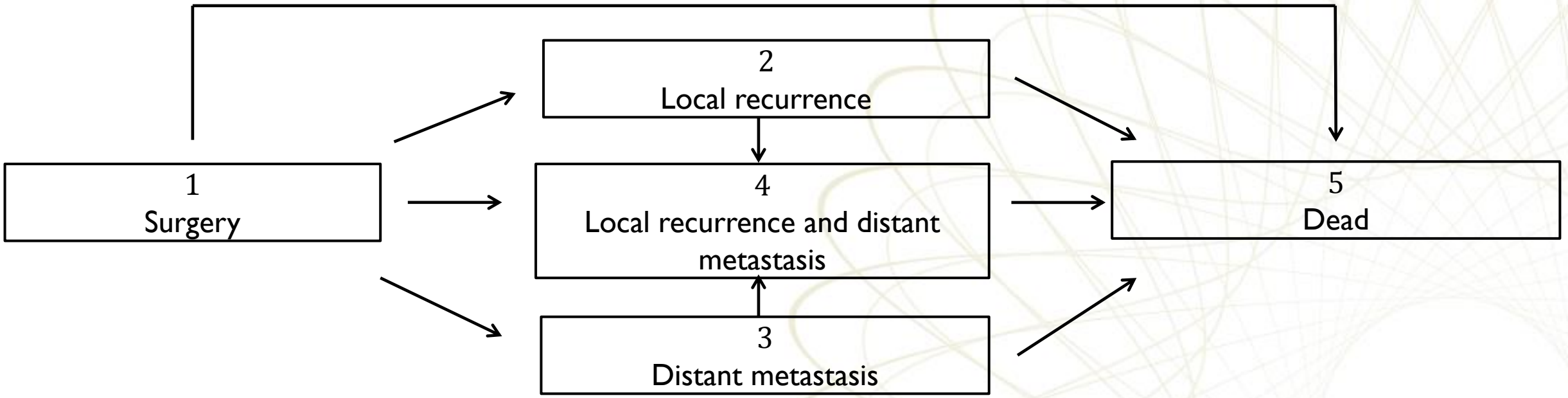
Although the number of changes (number of events) may be infinite, the number of states describing the conditions is typically finite.

Event history data

Multistate data

(*Putter H et al. Estimation and prediction in a multistate model for breast cancer. Biometrical Journal 2006.*)

Example 5. Consider a study of disease progression among women with breast cancer post-surgery.



Event history data

Examples of event history data analysis exist in a wide variety of fields:

Actuarial Science – Interest lies in characterizing individuals with repeat insurance claims in order to help set premiums

Sociology and Economics – Interest lies in factors affecting employment/unemployment patters

Banking and Finance – Interest lies in predicting credit card usage and payment patterns over time given demographic information and past financial records

Medical Research

- Describing the survival distribution from time of disease onset to death
- Examining factors affecting health services utilization
- Predicting time to various health conditions based on a patient's profile

Event history data

Typical aims when analyzing event history data:

Describing distributions
- rates of events
- distributions of "sojourns" or times between events
- proportion of individuals in a particular "state"
- transition probabilities between states

Covariate effects
- fixed
- time-varying

Associations between certain types of events

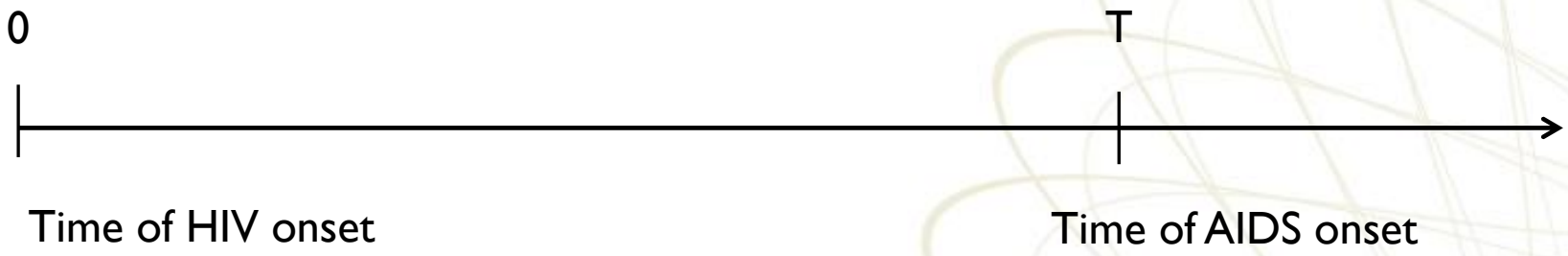
Prediction

Relationship between multistate models and …

Relationship between multistate models and …

… Time-to-event models

A time-to-event model is simply a unidirectional 2-state model.



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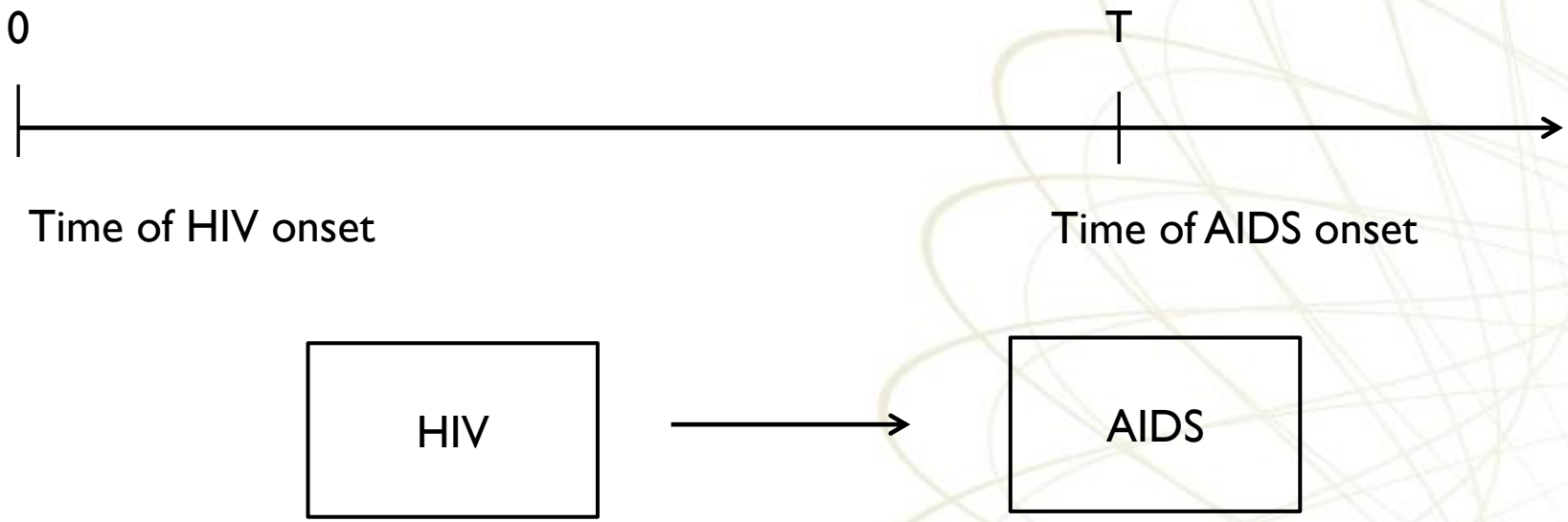

Relationship between multistate models and …

… Competing risks models

A competing risks model can be viewed as a multistate model with one initial state and several mutually exclusive absorbing states.

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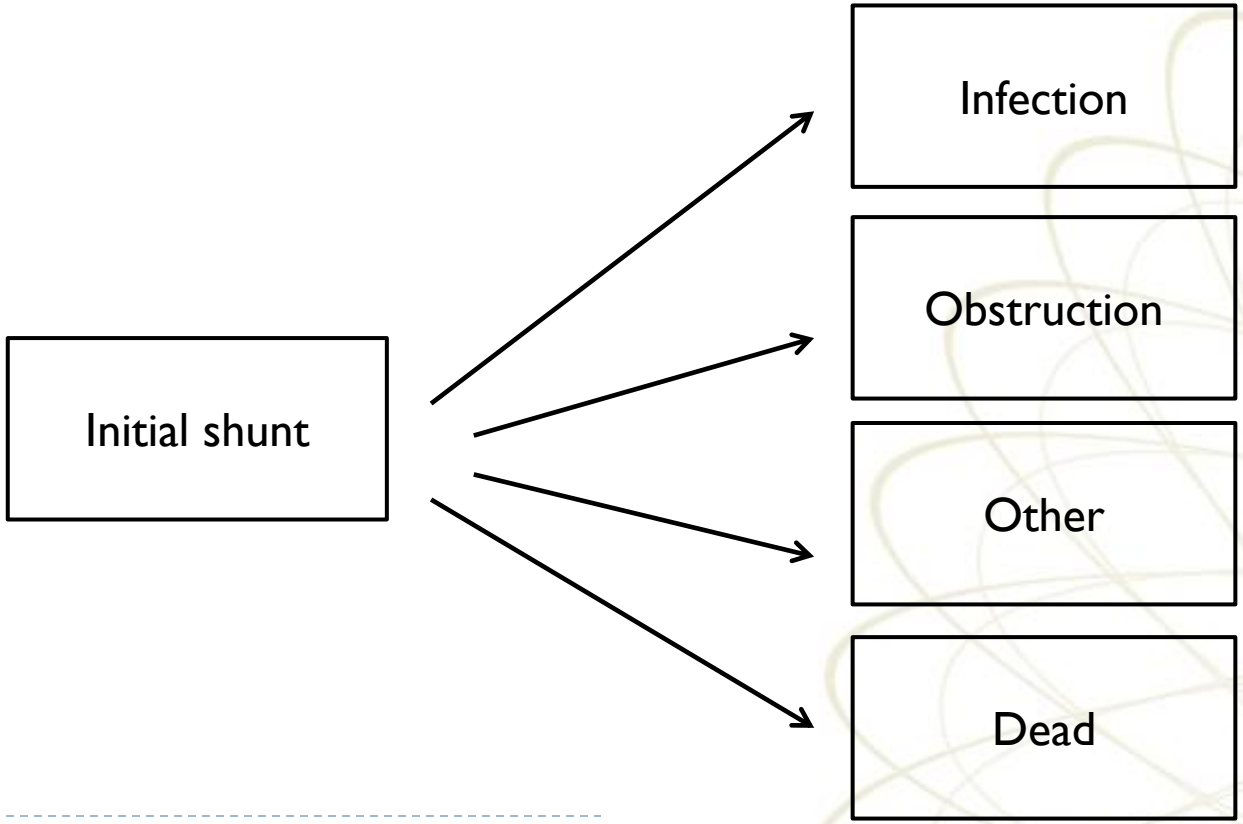
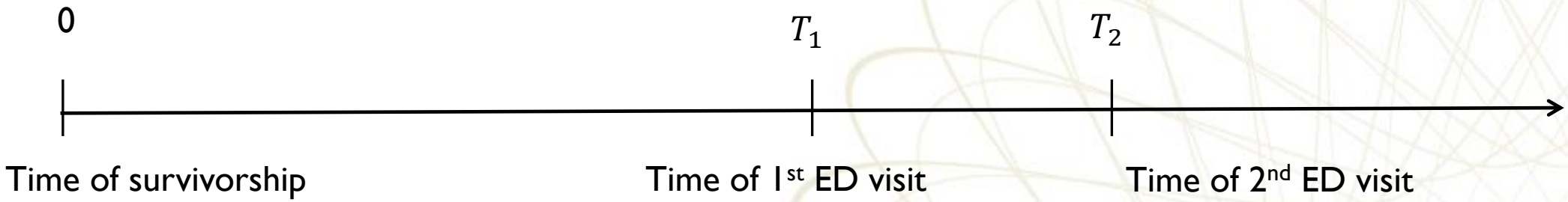


Relationship between multistate models and …

… Recurrent event models

Event occurrences may be viewed as transitions from one state to another; recurrent event times correspond to state transition times.



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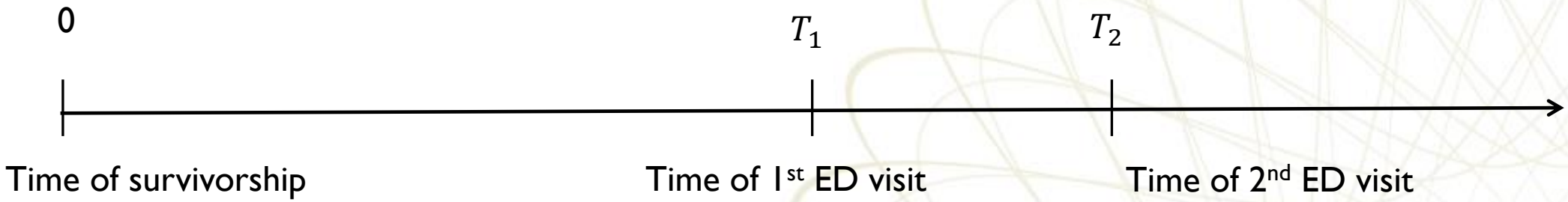
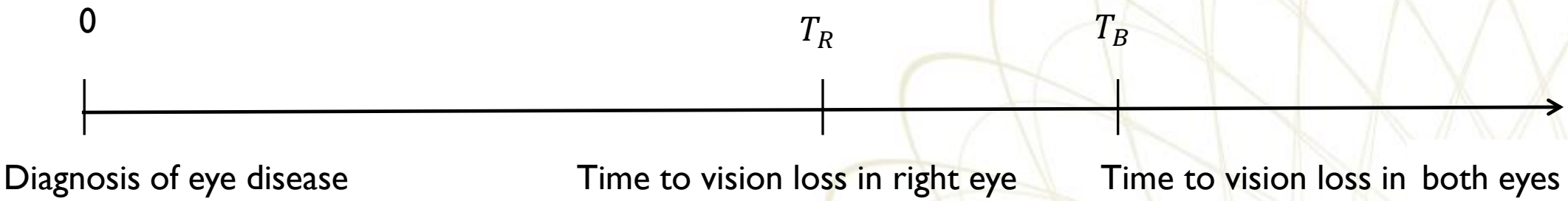


Relationship between multistate models and …

… Multiple event type models

Event types may be viewed as different states: event times correspond to state transition times.



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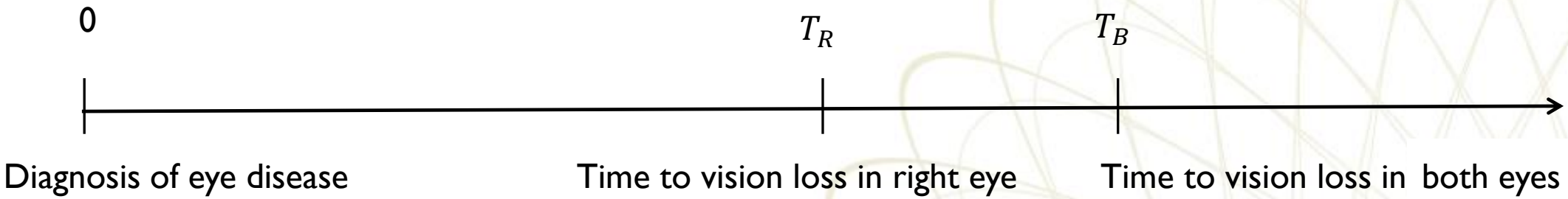
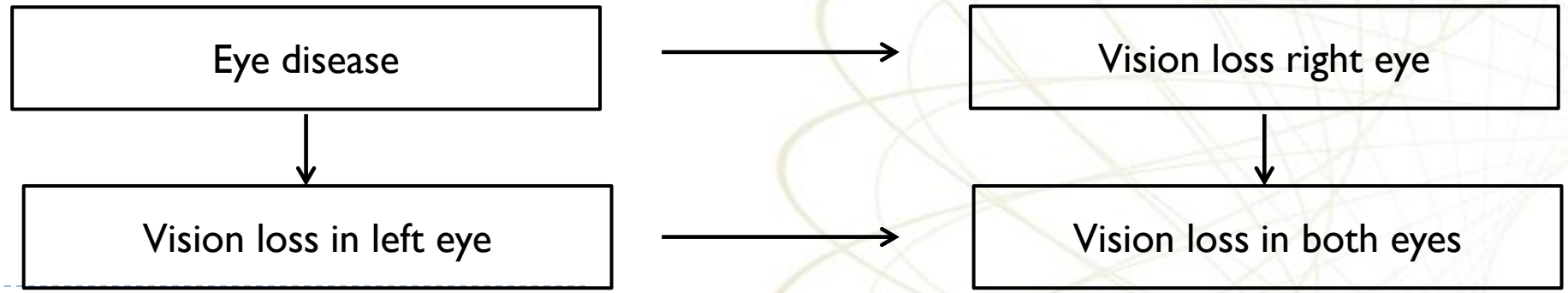


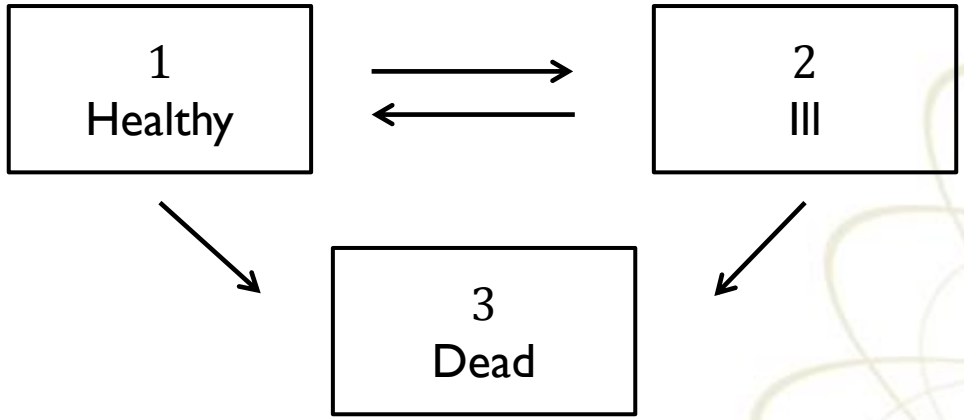


Introduction to multistate models, definitions, and notation

Introduction to multistate models, definitions, and notation

Q. When should we use a multistate model?

Multistate models are appropriate when the process involves transitions between several well-defined distinct states.



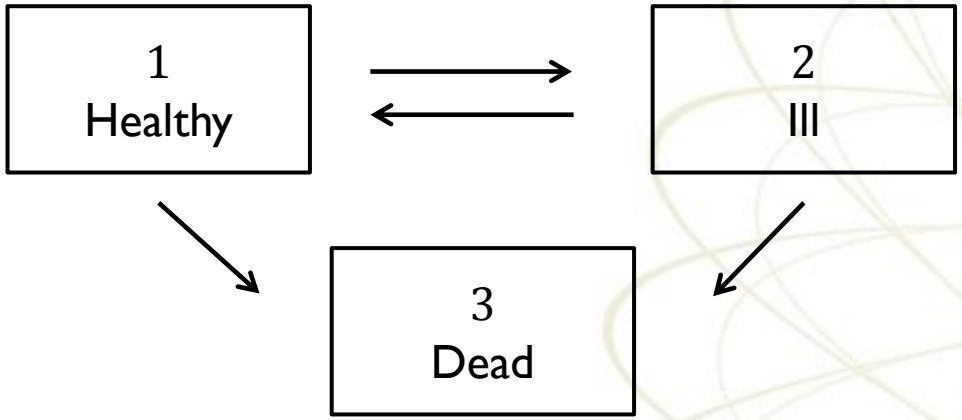
If further transitions are permitted out of a state, then the state is known as a non-absorbing state.

If further transitions are not permitted out of a state, then the state is known as an absorbing state.

Introduction to multistate models, definitions, and notation

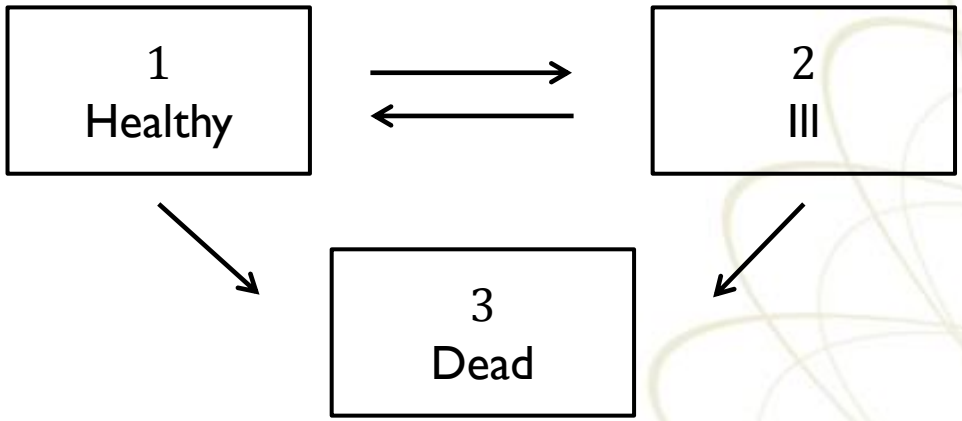
Q. How should a multi-state model be constructed?

- The states should represent the condition of an individual.
- Transitions from one state to another are referred to as "events". They should reflect distinct changes in the individual's condition. The times of transitions are referred to as the "event times".
- The direction of the arrows should be determined by the underlying nature of the event process. The arrows indicate which **instantaneous** state-to-state transitions are possible.



Introduction to multistate models, definitions, and notation

Q. In the analysis of time-to-event data, we know that a hazard function is used to model the event times. In the analysis of multistate data, what function do we use to model the state-to-state transition times?



Use a **transition intensity function**!

Introduction to multistate models, definitions, and notation

Transition intensity function:

$\lambda_{jk}(t \mid H(t))$ = instantaneous rate of transitioning from state j to state k within the interval t and $(t + dt)$, conditional on the history of the process at time t.

$$= \lim_{dt \to 0} \frac{P(\text{ state occupied at time } t+dt = k \mid \text{state occupied at time } t = j, H(t))}{dt}, \quad \text{for } j \neq k$$

$$= \lim_{dt \to 0} \frac{P(dN_{jk}(t) = 1 \mid H(t))}{dt}, \quad \text{for } j \neq k$$

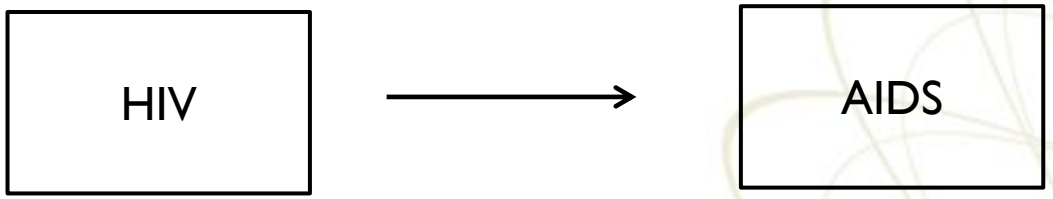
where $dN_{jk}(t)$ is the number of $j \rightarrow k$ transitions within the interval $[t, t + dt)$, and $H(t)$ is the history of the multistate process at time t (which provides information on all state-to-state transitions occurring just prior to time t).

Introduction to multistate models, definitions, and notation

$\lambda_{jk}\,(t \mid H(t))$ = rate of j to k transition (at time t | history up to time t)

Introduction to multistate models, definitions, and notation

If there were only 2 states in the multistate model, and if the transition was unidirectional, then the multistate model collapses to a time-to-event model. Subsequently, the transition intensity function simply becomes a hazard function.



$$\lambda_{HIV\ ,\ AIDS}\left(t \mid H(t)\right) \;=\; h(t)$$

Introduction to multistate models, definitions, and notation

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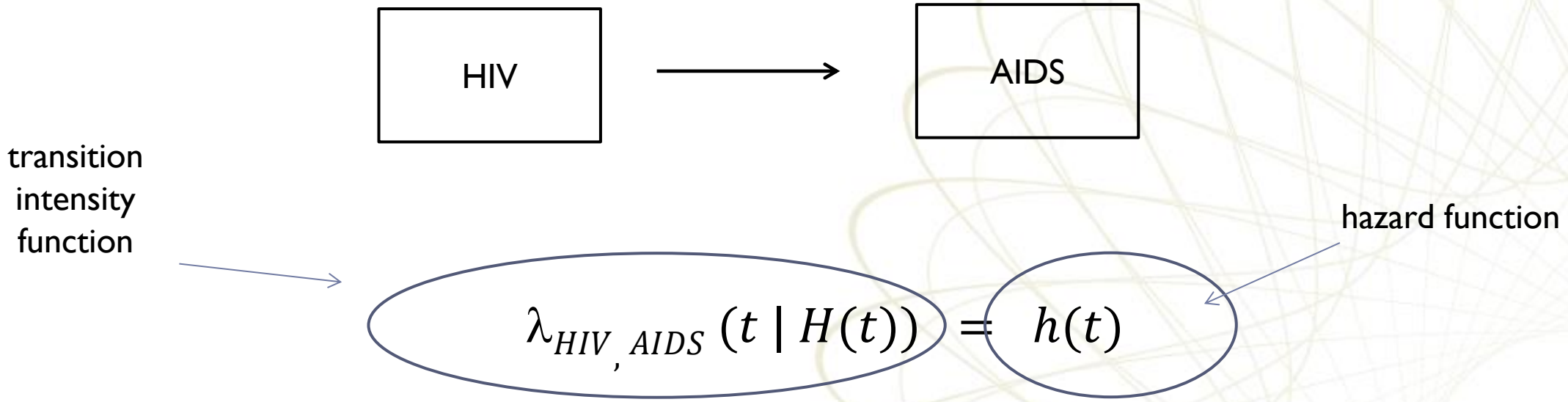
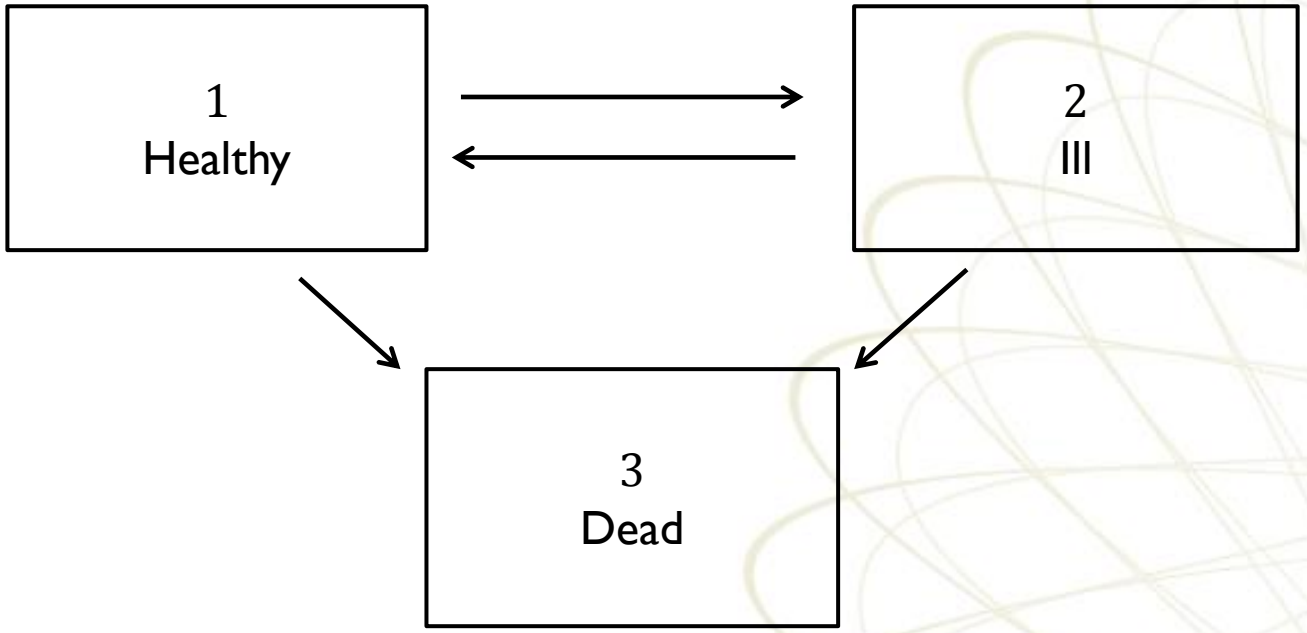


Introduction to multistate models, definitions, and notation

Going back to the healthy-illness-death illustration, which transition intensity functions describe this model?



Introduction to multistate models, definitions, and notation

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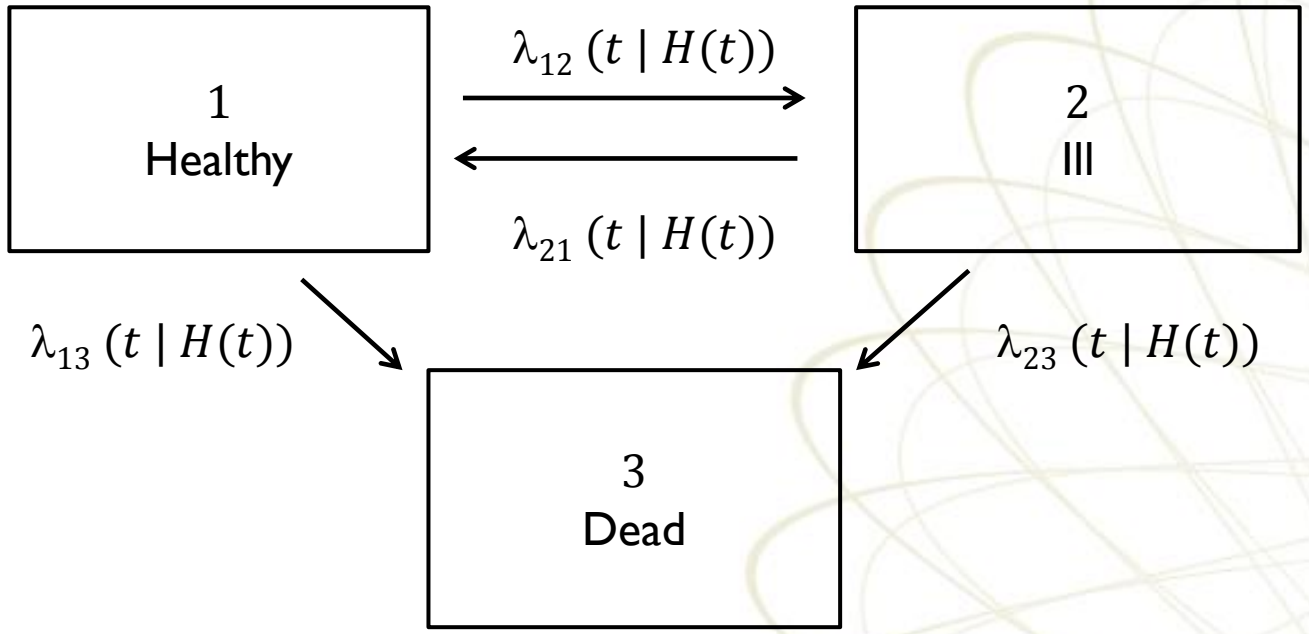


Introduction to multistate models, definitions, and notation

Our current aim is to estimate all of the transition intensity functions of the multistate model.

Transition intensity functions are modeling **instantaneous** state-to-state transitions which describe the underlying nature of the event process. Again the key word is **INSTANTANEOUS**!

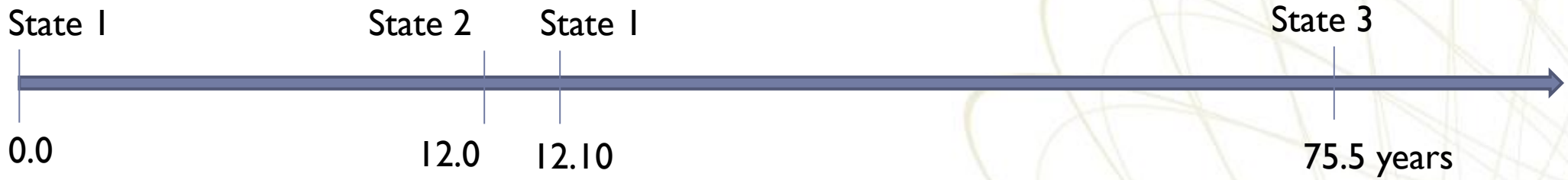
Q. But what does this really mean???

Introduction to multistate models, definitions, and notation

Exercise 1.

Suppose we can model hospital admissions over the lifetime of an individual using 3 states (state 1- admission-free, state 2- admission to hospital, state 3- dead).

For each individual, the exact times of hospital admission and discharge are available. Example:



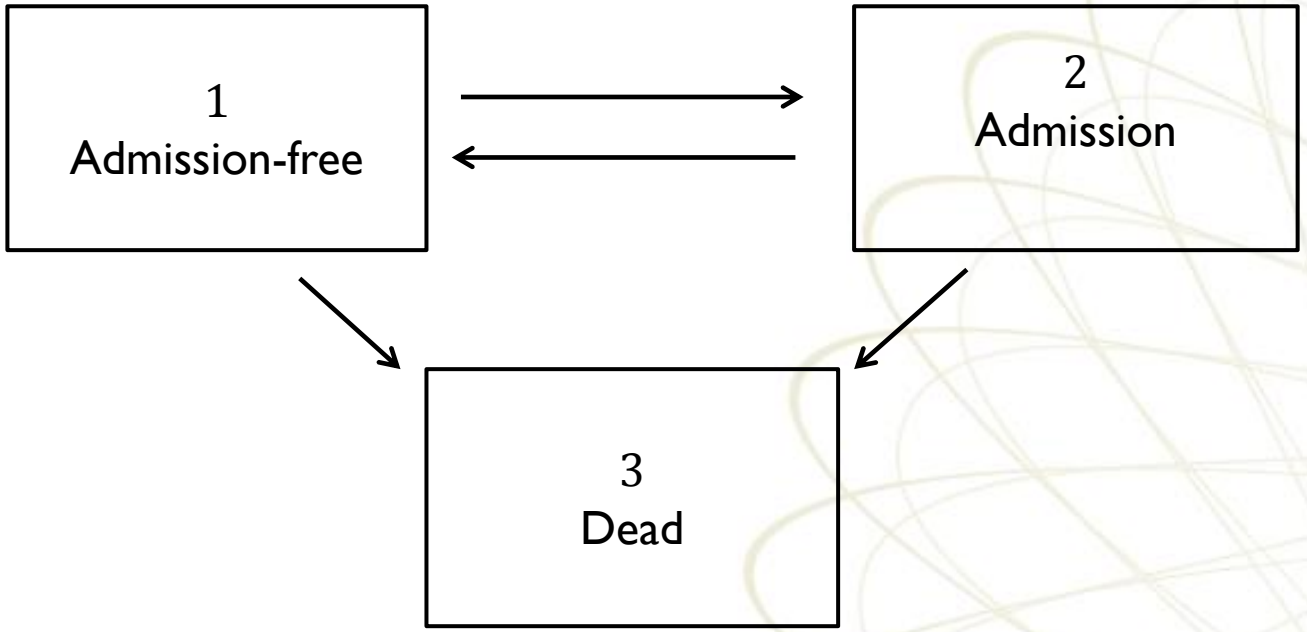
How do we construct the multi-state model?

Do we know which direction the arrows should go in?

Introduction to multistate models, definitions, and notation

Exercise 1.

Here is the appropriate multi-state model for describing hospital admissions over the lifetime of an individual:



Introduction to multistate models, definitions, and notation

Exercise 2.

Suppose we can model the progression of functional status in cancer patients using 4 states (state 1- stable state, state 2- transitional state, state 3- end of life state, state 4- death).

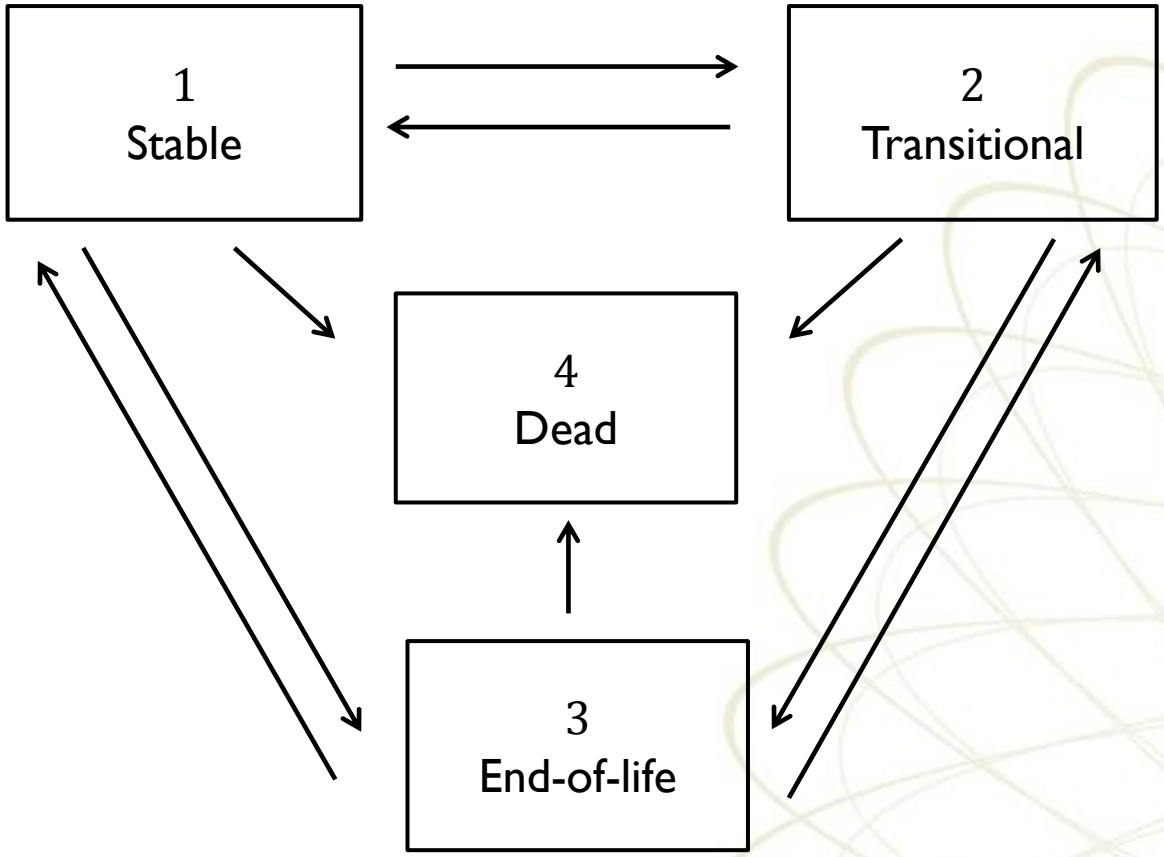
Each patient visits a cancer clinic periodically to have their functional status assessed. Example:

How do we construct the multi-state model?

Do we know which direction the arrows should go in?

Introduction to multistate models, definitions, and notation

Exercise 2. Does the following multistate model appropriately describe the progression of functional status?



Introduction to multistate models, definitions, and notation

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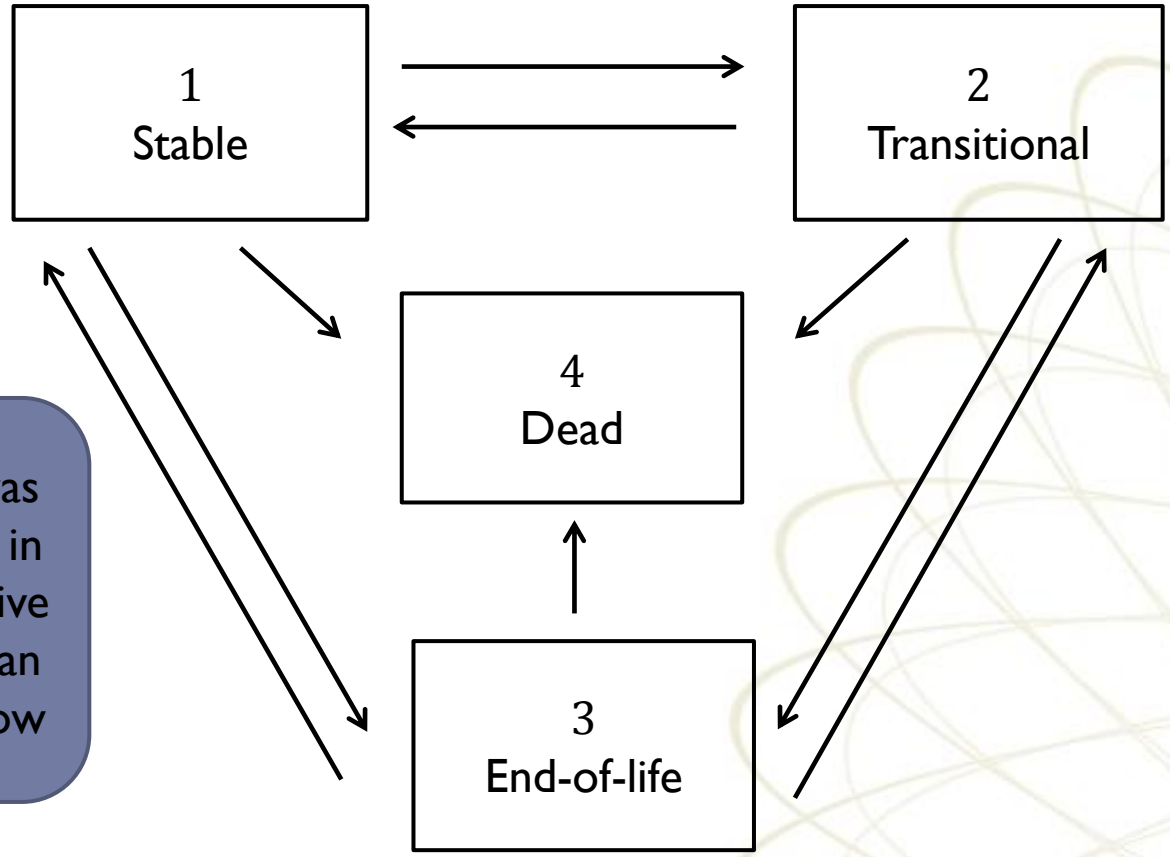


Although data indicates patient was in state 3 and then in state 1 at consecutive visits, does this mean that the 3 -> 1 arrow is permitted ?

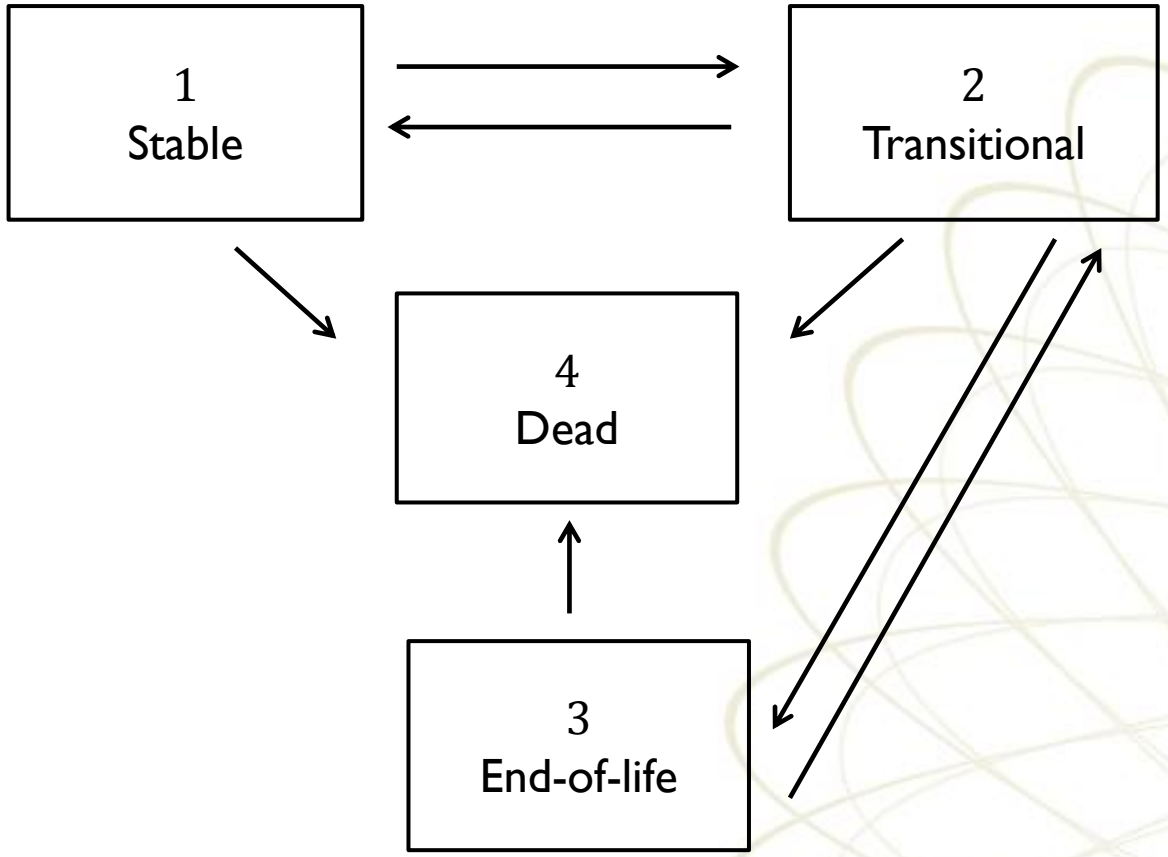
Introduction to multistate models, definitions, and notation

Exercise 2.

- Remember the arrows in a multi-state model must represent which **INSTANTANEOUS** state-to-state transitions can occur.
- We must take the underlying nature of the process into account, not what we observed from intermittent assessments.
- Ask ourselves: Which state-to-state transitions would occur if we could observe the patient all the time (that is, if the patient was **under complete observation**)?

Introduction to multistate models, definitions, and notation

Exercise 2. Here is the appropriate multistate model for describing the progression of functional status:



Transition intensity matrix and transition probability matrix

Transition intensity matrix and transition probability matrix

All of the transition intensity functions that arise in a multistate model are used to build a Transition Intensity Matrix (TIM):

- TIM is denoted by $\Lambda(t \mid H(t))$
- The $[j,k]$ entry of the TIM is $\lambda_{jk}\ (t \mid H(t))$

Transition intensity matrix and transition probability matrix

Recall in a survival model, once the hazard function is estimated its value can be used to compute other important functions.

Similarly, once the TIM is estimated, its values can be used to compute meaningful probabilities, such as the probability of making a transition from state j to state k over a certain interval of time.

Transition intensity matrix and transition probability matrix

Once we estimate the Transition Intensity Matrix (TIM), we can use its values to estimate the Transition Probability Matrix (TPM):

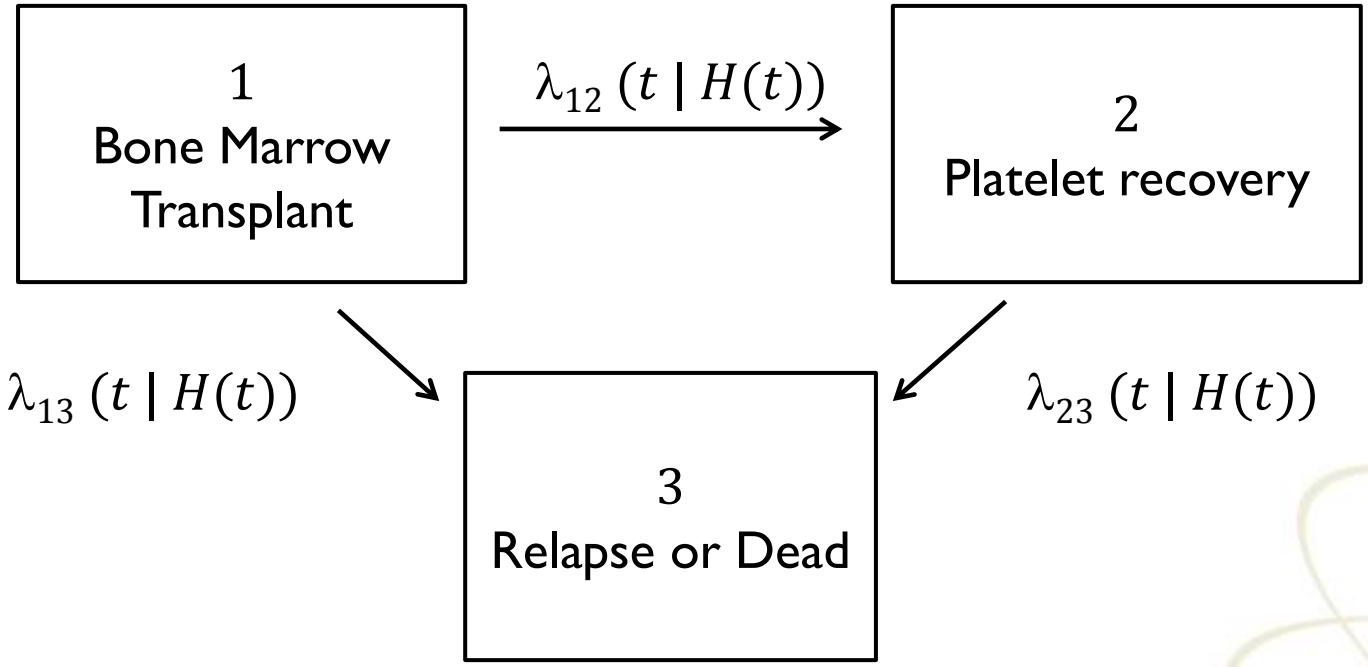
- TPM is denoted by $P(s,t \mid H(s))$
- The $[j,k]$ entry of the TPM is $p_{jk}\,(s,t \mid H(s))$ defined as

$$p_{jk}\,(s,t \mid H(s)) = P(state\ occupied\ at\ time\ t = k \mid state\ occupied\ at\ time\ s = j, H(s))$$

This is the probability of going from state j to state k over the time interval $(s,t]$, conditional of the history of the process at time s.

Transition intensity matrix and transition probability matrix

Exercise 1. Translate the following 3-state model into a TIM and TPM.



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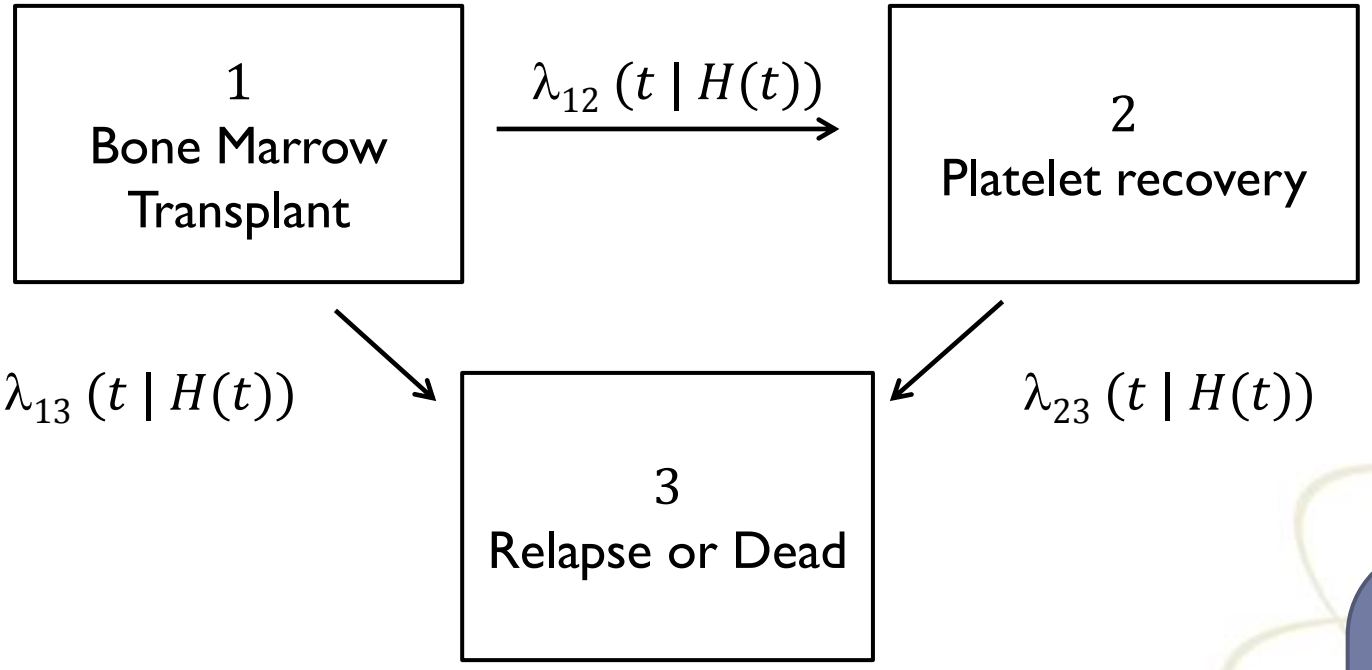


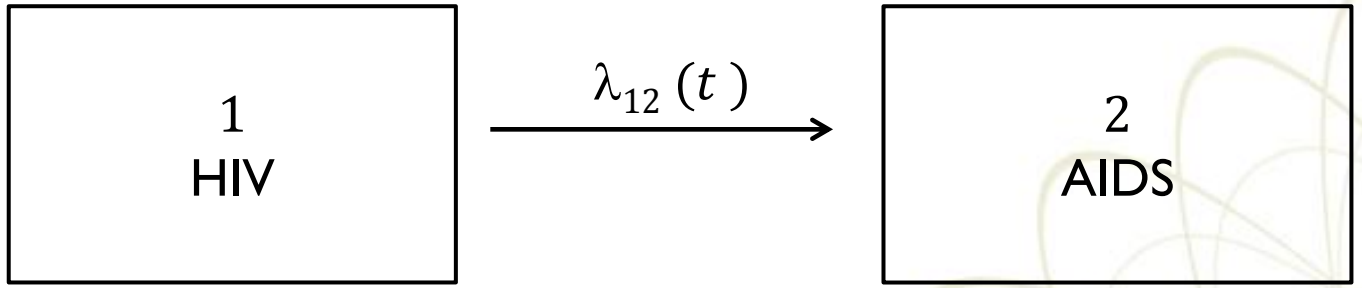
$$\text{TIM} = \Lambda(t \mid H(t)) = \begin{bmatrix} \lambda_{11} & \lambda_{12} & \lambda_{13} \\ 0 & \lambda_{22} & \lambda_{23} \\ 0 & 0 & 0 \end{bmatrix}$$

$$\text{TPM} = \mathrm{P}(s,\ t \mid H(s)) = \begin{bmatrix} p_{11} & p_{12} & p_{13} \\ 0 & p_{22} & p_{23} \\ 0 & 0 & 1 \end{bmatrix}$$

Given a bone marrow transplantation patient whose platelets have recovered after 60 days and who has had no further events at one year post-transplant, what is then the probability of surviving relapse-free for 2 more years?

Transition intensity matrix and transition probability matrix

Exercise 3. Translate the following 2-state model into a TIM and TPM.



Transition intensity matrix and transition probability matrix

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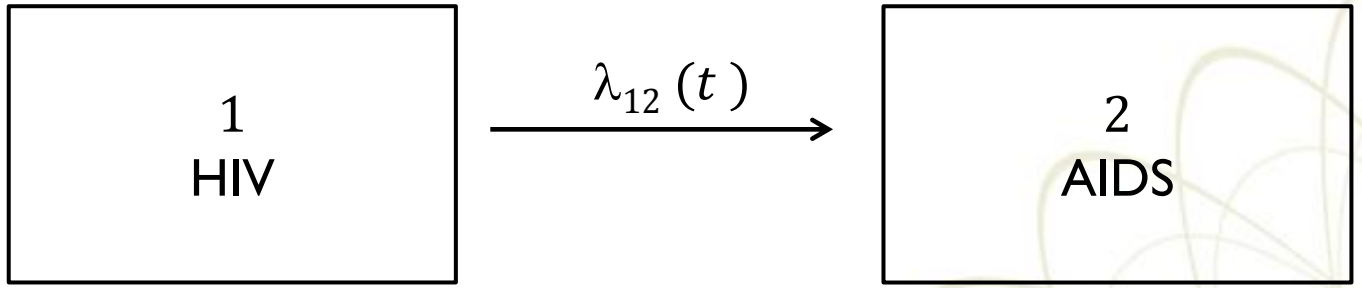

$$\text{TIM} = \Lambda(t) = \begin{bmatrix} \lambda_{11} & \lambda_{12} \\ 0 & 0 \end{bmatrix}$$

Transition intensity matrix and transition probability matrix

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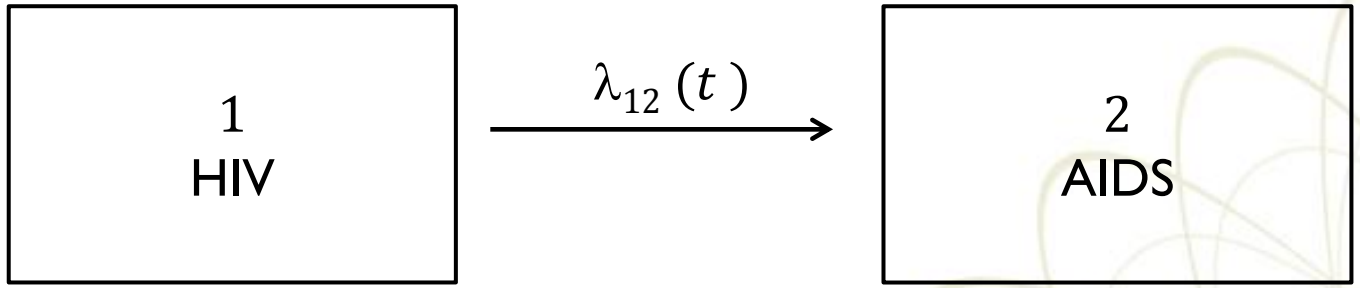

$$\text{TIM} = \Lambda(t) = \begin{bmatrix} \lambda_{11} & \lambda_{12} \\ 0 & 0 \end{bmatrix}$$

$$\text{TPM} = P(0,t) = \begin{bmatrix} p_{11} & p_{12} \\ 0 & 1 \end{bmatrix}$$

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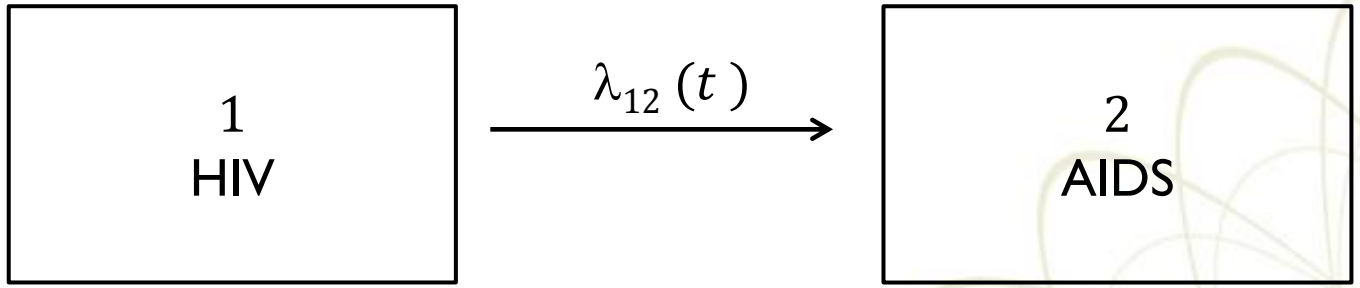


$$\text{TIM} = \Lambda(t) = \begin{bmatrix} \lambda_{11} & \lambda_{12} \\ 0 & 0 \end{bmatrix}$$

$$\text{TPM} = P(0,t) = \begin{bmatrix} p_{11} & p_{12} \\ 0 & 1 \end{bmatrix}$$

Survivor function $S(t)$

Cumulative distribution function $F(t)$

Assumptions about the history - Markov assumption

Assumptions about the history - Markov assumption

Markov assumption

- By specifying a Markov multistate model, we assume that the future evolution of the event process only depends on the current state.
- This means that the future evolution of the event process is independent of the history of the process ('memoryless' property).
- In other words, given that state j is occupied at time t, the transition intensity function for a $j \rightarrow k$ transition within the interval t and $(t + dt)$ is independent of the history $H(t)$:

$$\lambda_{jk}\,(t \mid H(t)) = \lambda_{jk}\,(t)$$

Assumptions about the history - Markov assumption

Q. In which scenarios is the Markov assumption appropriate?

- Processes where "aging effects" are present
  - Degenerative diseases such as arthritis
  - Wear out of equipment
- Diseases where time since onset is the dominant time variable
  - HIV infection
  - Cancer
- Scenarios where calendar time is the driving factor ('clock forward' approach)

Incorporating covariates

Incorporating covariates

Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002.

Recall the transition intensity function:

$$\lambda_{i\,jk}\,(t \mid H_i\,(t))$$

Now suppose we have a $(p \times 1)$ vector of covariates for a specific patient i. (some may be fixed covariates and some may be time-varying covariates): $\boldsymbol{X}_i(t)$

How do we incorporate these covariates into the transition intensity function?

Incorporating covariates

Transition intensity function with covariates under Markov assumption:

$$\lambda_{i\,jk}\,(\,t \mid H_i\,(t), \boldsymbol{X}_i(t)) \;=\; \lambda_{i\,jk}\,(\,t \mid \boldsymbol{X}_i(t)\,)$$

(under Markov assumption)

$$= \lambda_{0,jk}(t)\,\exp\{\boldsymbol{X}_i(t)^T\boldsymbol{\beta}_{jk}\}$$

association is specific to the transition

Baseline transition intensity function (under Markov assumption).

This is the value of the transition intensity function at time t if the covariates are set to 0.

$\boldsymbol{\beta}_{jk}$ is a vector of regression parameters, which is a measure of the association between the covariates and the transition intensity function.

$\boldsymbol{X}_i(t)^T\boldsymbol{\beta}_{jk}$ is simply a 1×1 number (it is known as the linear predictor)

$\exp\{\boldsymbol{X}_i(t)^T\boldsymbol{\beta}_{jk}\}$ modulates the baseline transition intensity function in a multiplicative manner.

Incorporating covariates

Comparing survival model with covariates against multistate model with covariates:

Hazard function with covariates for a survival model

$$h_i\,(t \mid \boldsymbol{X}_i(t)\,) = \; h_0\,(\,t\,)\,\exp\{\boldsymbol{X}_i(t)^T\boldsymbol{\beta}\}$$

Transition intensity function with covariates for a multistate model

$$\lambda_{i\,jk}\,(\,t \mid \boldsymbol{X}_i(t)\,) \;\; = \lambda_{0,jk}(t)\,\exp\{\boldsymbol{X}_i(t)^T\boldsymbol{\beta}_{jk}\}$$

Incorporating covariates

Comparing survival model with covariates against multistate model with covariates:

Hazard function with covariates for a survival model

$$h_i\,(t \mid \boldsymbol{X}_i(t)\,) = h_0\,(\,t\,)\exp\{\boldsymbol{X}_i(t)^T\boldsymbol{\beta}\}$$

Cox proportional hazards regression model

Provides hazard ratio (HR)

Transition intensity function with covariates for a multistate model

$$\lambda_{i\,jk}\,(\,t \mid \boldsymbol{X}_i(t)\,) = \lambda_{0,jk}(t)\exp\{\boldsymbol{X}_i(t)^T\boldsymbol{\beta}_{jk}\}$$

Relative rate regression model

Provides relative rate (RR)

Counting process data structure

Counting process data structure for multistate analysis with covariates

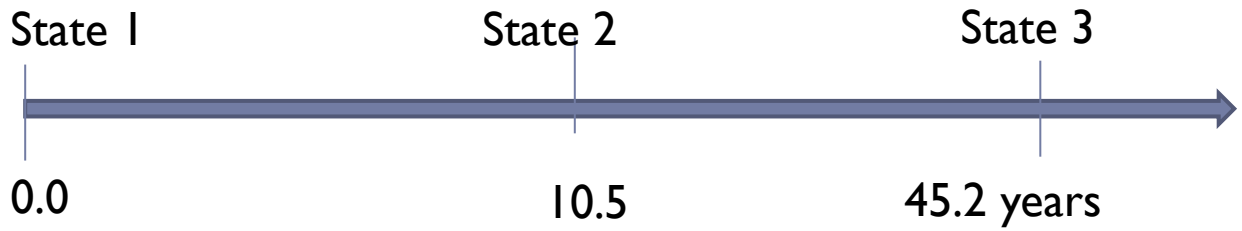
The counting process data structure (also known as the long format data structure) is often used to set-up the multistate data so that analysis can be conducted using statistical programs such as R and SAS.

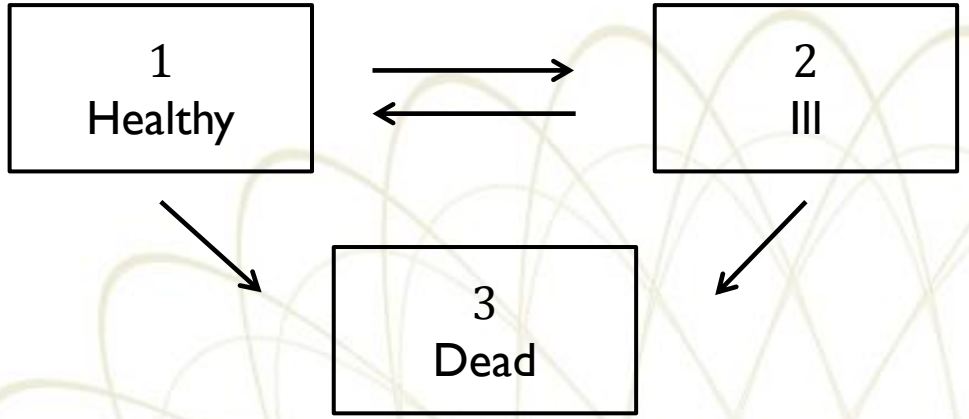
[Meira-Machado et al. Multi-state models for the analysis of time-to-event data. Stat Methods Med Res 2009.]

Counting process data structure for multistate analysis with covariates

Exercise 1. We have the following data on a particular patient:

- ID number 156
- Time 0.0 is time of wedding
- Covariate baseline age = 35.5
- Exact transition times are known





How do we structure this data?

Counting process data structure for multistate analysis with covariates

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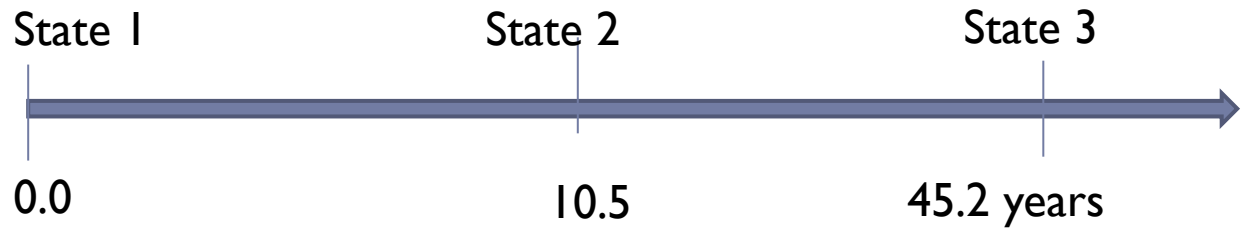

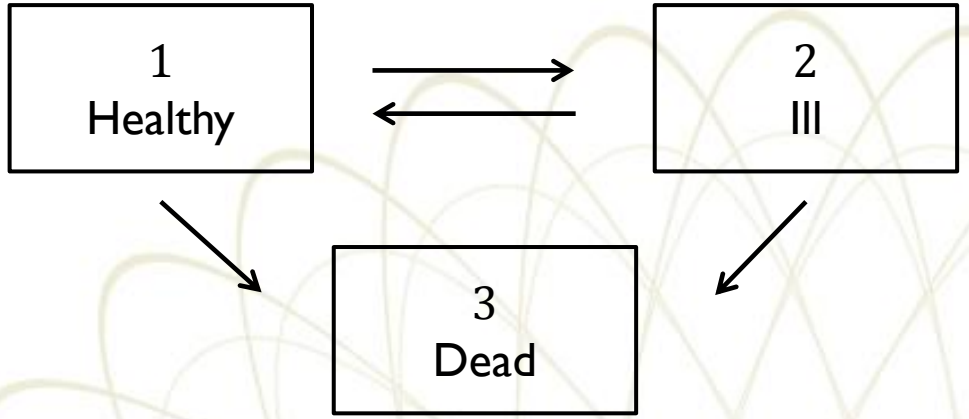

How do we structure this data?

id time1 time2 status type1 type2 age

Counting process data structure for multistate analysis with covariates

Exercise 1. We have the following data on a particular patient:

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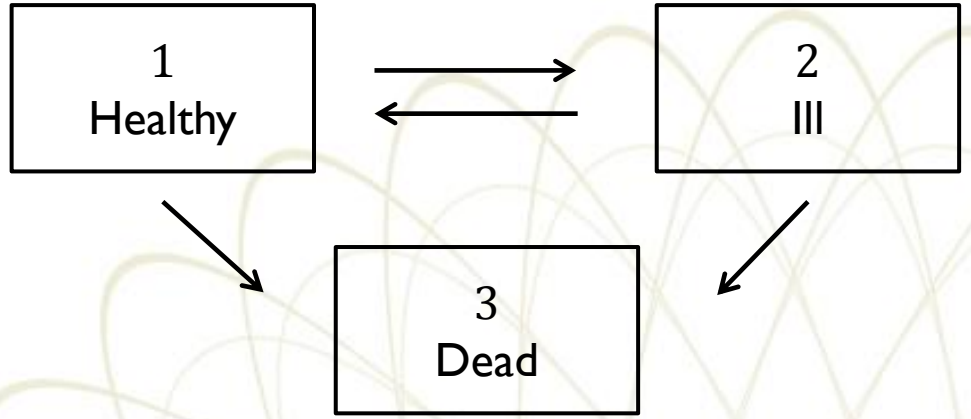
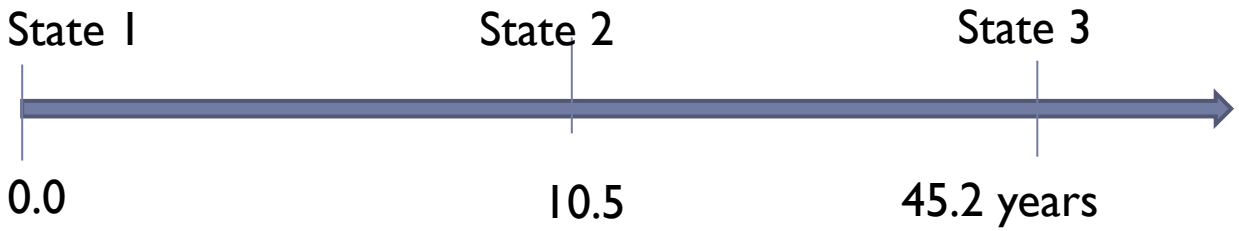
- Time 0.0 is time of wedding
- Covariate baseline age = 35.5
- Exact transition times are known





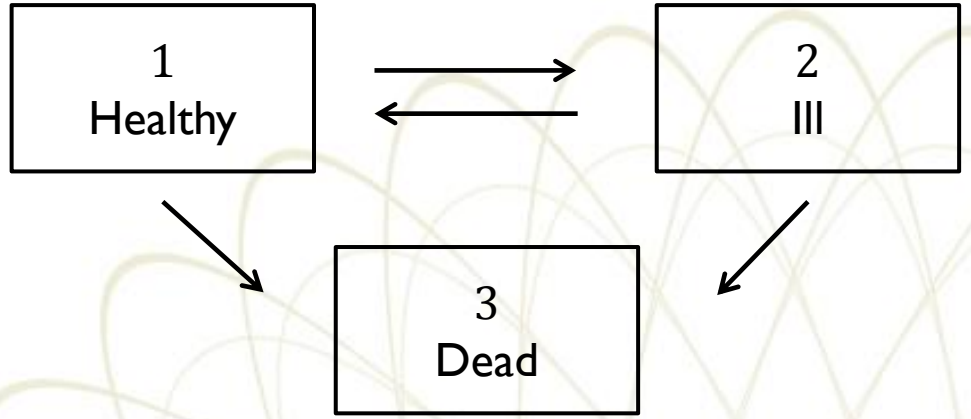
How do we structure this data?

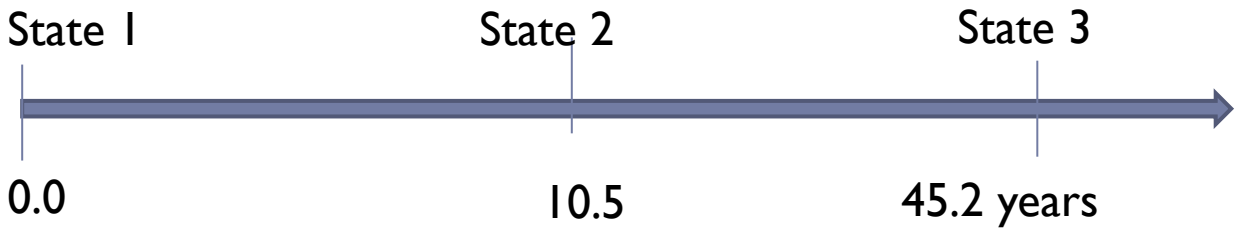
id	time1	time2	status	type1	type2	age
156	0.0	10.5	1	1	2	35.5
156	0.0	10.5	0	1	3	35.5

Counting process data structure for multistate analysis with covariates

Exercise 1. We have the following data on a particular patient:

- ID number 156
- Time 0.0 is time of wedding
- Covariate baseline age = 35.5
- Exact transition times are known





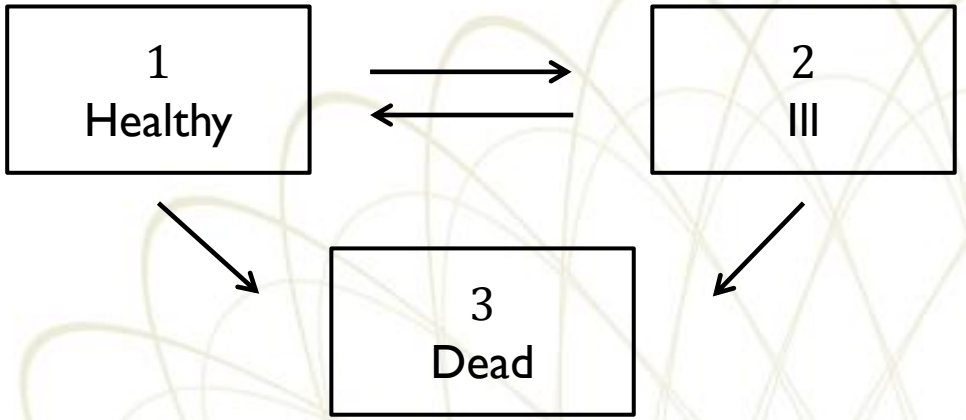
How do we structure this data?

id	time1	time2	status	type1	type2	age
156	0.0	10.5	1	1	2	35.5
156	0.0	10.5	0	1	3	35.5
156	10.5	45.2	1	2	3	35.5
156	10.5	45.2	0	2	1	35.5

Counting process data structure for multistate analysis with covariates

Exercise 2. We have the following data on another patient:

- ID number 235
- In state 2 at time 0.0 years
- Makes a state 2 $\rightarrow$ state 1 transition at time 3.8 years
- Censored at time 10.2 years
- Covariate baseline age = 40.0
- Number of children = 0 at time 0.0
  = 1 at time 4.5



How do we structure this data?

Counting process data structure for multistate analysis with covariates

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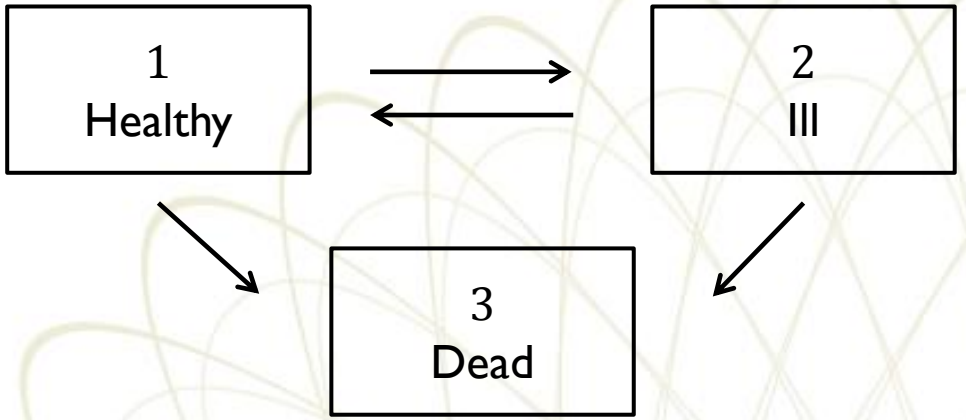

How do we structure this data?

id time1 time2 status type1 type2 age # children

Counting process data structure for multistate analysis with covariates

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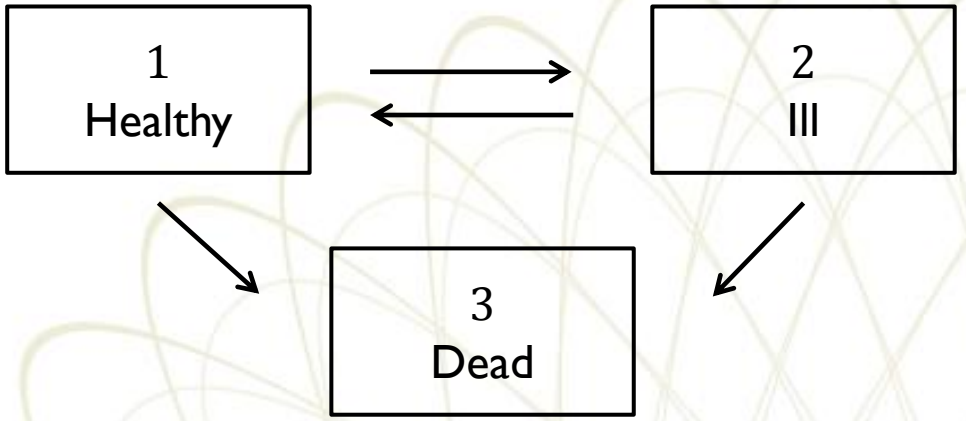

How do we structure this data?

id	time1	time2	status	type1	type2	age	# children
235	0.0	3.8	1	2	1	40.0	0
235	0.0	3.8	0	2	3	40.0	0

Counting process data structure for multistate analysis with covariates

Exercise 2. We have the following data on another patient:

- ID number 235
- In state 2 at time 0.0 years
- Makes a state 2 $\rightarrow$ state 1 transition at time 3.8 years
- Censored at time 10.2 years
- Covariate baseline age = 40.0
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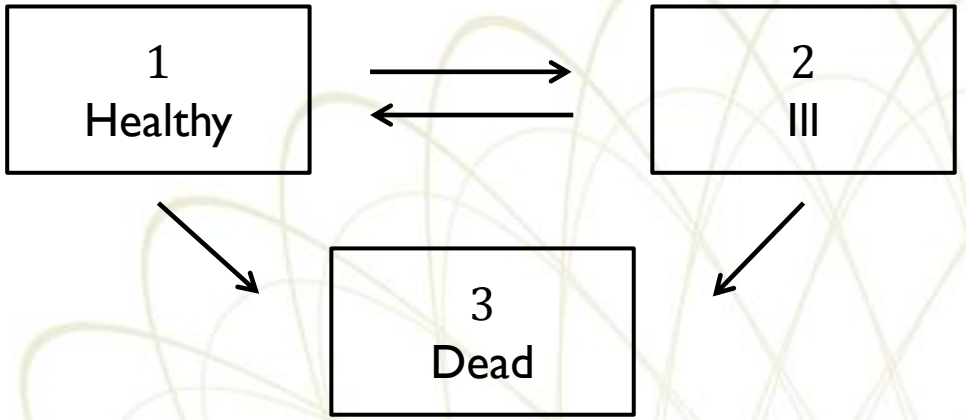
  = 1 at time 4.5



How do we structure this data?

id	time1	time2	status	type1	type2	age	# children
235	0.0	3.8	1	2	1	40.0	0
235	0.0	3.8	0	2	3	40.0	0
235	3.8	4.5	0	1	2	40.0	0
235	3.8	4.5	0	1	3	40.0	0

Counting process data structure for multistate analysis with covariates

Value of each covariate is CONSTANT within a row of data.

The value of the covariate MUST reflect its measure at "time1", NOT at "time2"!!!

Exercise 2. We have the following data on another patient:

- ID number 235
- In state 2 at time 0.0 years
- Makes a state 2 → state 1 transition at time 3.8 years
- Censored at time 10.2 years
- Covariate baseline age = 40.0
- Number of children = 0 at time 0.0
  = 1 at time 4.5

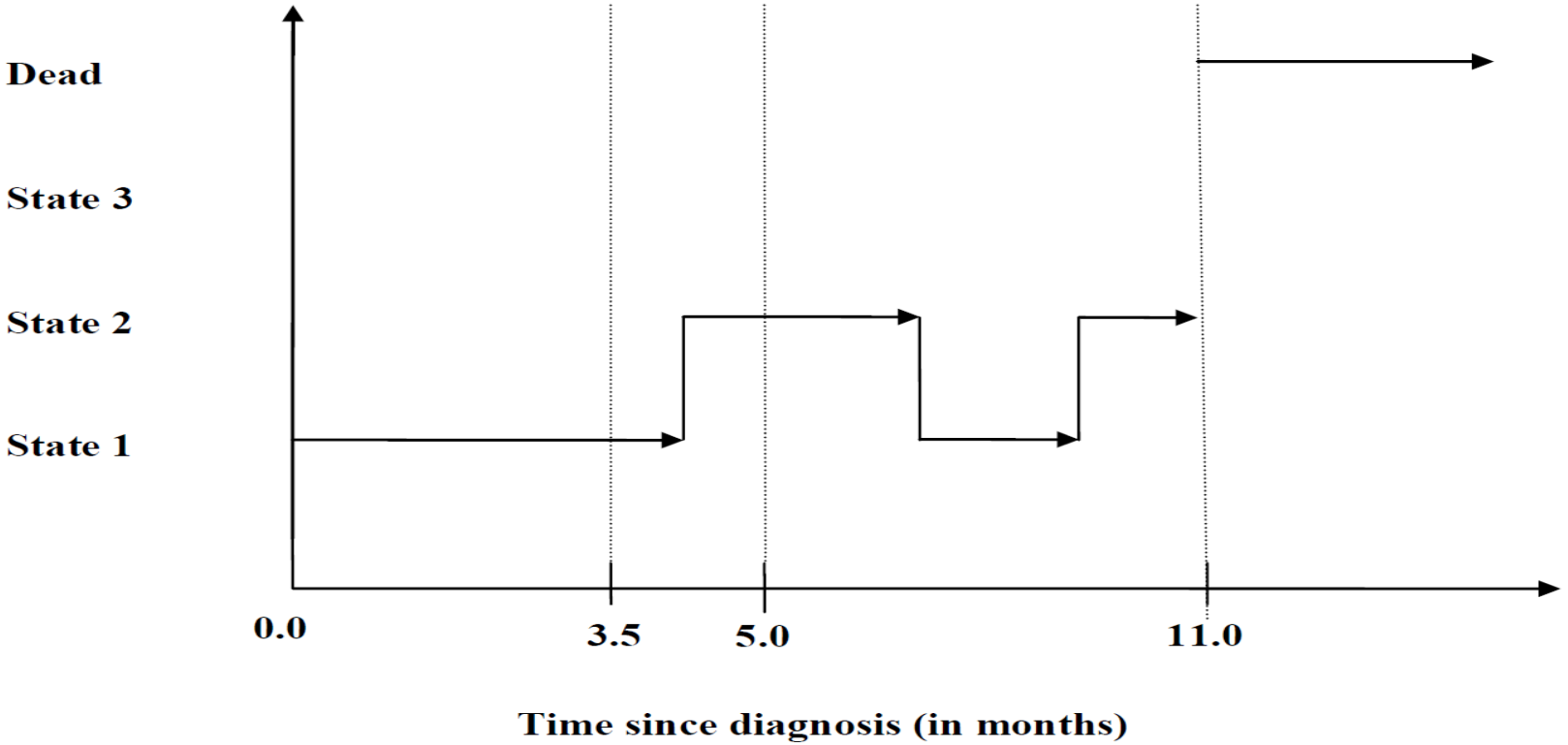
How do we structure this data?

id	time1	time2	status	type1	type2	age	# children
235	0.0	3.8	1	2	1	40.0	0
235	0.0	3.8	0	2	3	40.0	0
235	3.8	4.5	0	1	2	40.0	0
235	3.8	4.5	0	1	3	40.0	0
235	4.5	10.2	0	1	2	40.0	1
235	4.5	10.2	0	1	3	40.0	1

Dealing With Intermittent Observation

Dealing with intermittent observation

Plot of observed vs. underlying progression of disease status for a hypothetical patient based on a 4-state model (State 1 – Mild, State 2 - Moderate, State 3 - Severe, State 4- Dead):



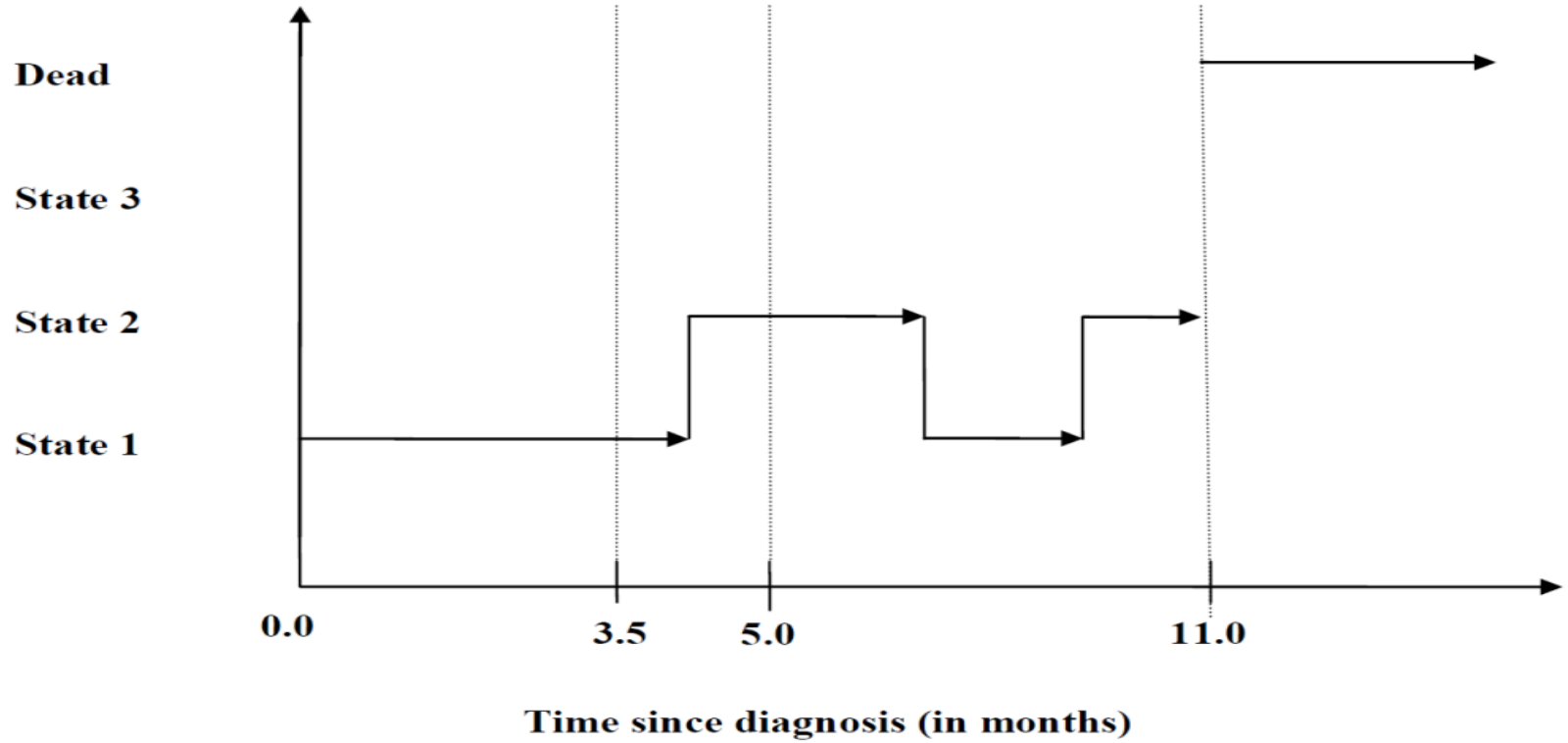
Such intermittent observation gives rise to panel data, where we simply know the visit times and the states occupied at each visit time.

Dealing with intermittent observation

How do intermittent observation schemes affect the multistate model?

1. Interval-censored transition times

- All we know is that the transition time is within a certain interval.

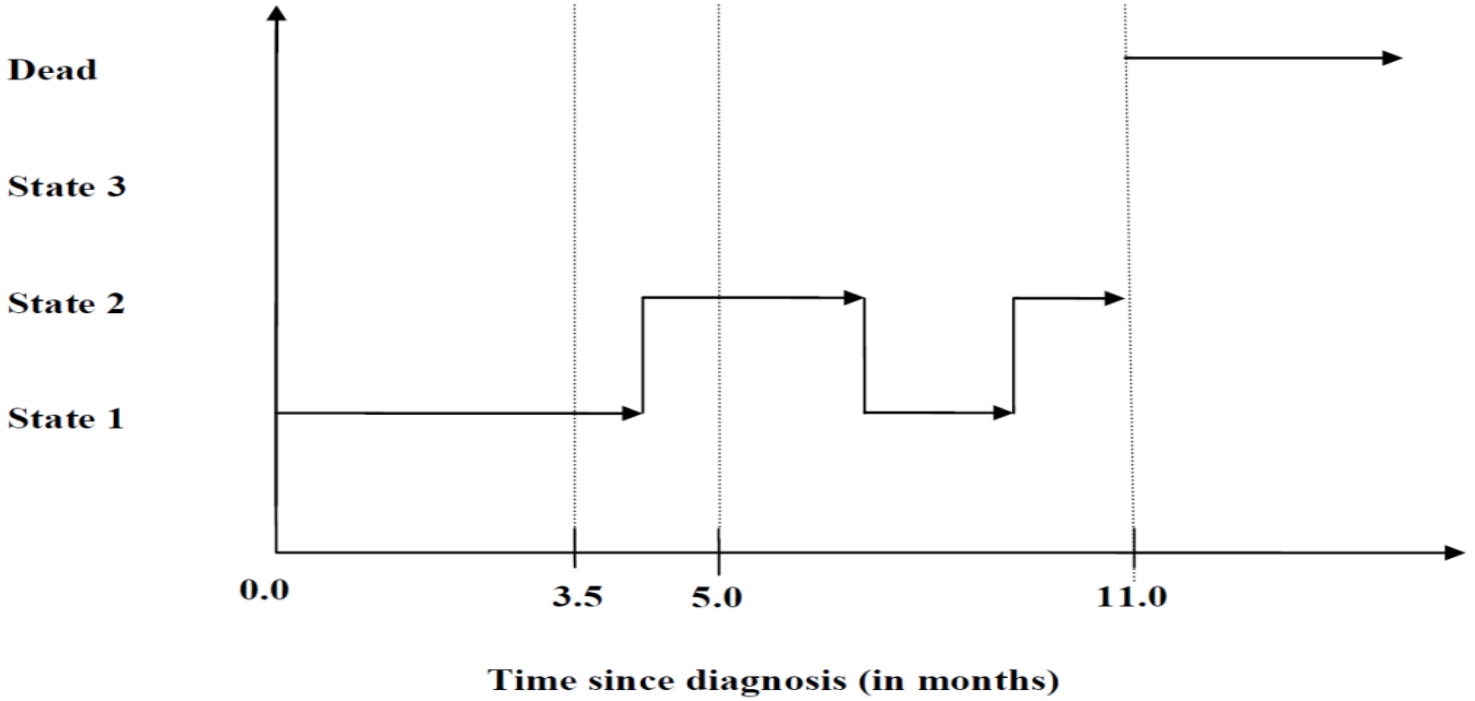


Dealing with intermittent observation

How do intermittent observation schemes affect the multistate model?

2. Unknown state prior to death

- In many studies, it is common for the time of death to be known, but the state occupied just prior to death is unknown.



Dealing with intermittent observation

How do intermittent observation schemes affect the multistate model?

3. Unknown state at end of follow-up date.

- A patient who is alive is considered censored at the time at which follow-up terminates.

- Under intermittent observation, if there is no assessment at the end of follow-up date, the state of the patient at this time is unknown.

Example: Analysis of multistate data under intermittent observation

Progression of performance status among cancer patients

Background

In 2007 cancer centres in Ontario began systematically collecting performance status scores in cancer outpatients

A validated tool, known as the Palliative Performance Scale (PPS), was used to assess performance status

PPS is an ordinal 10-point scale, where a score of 100 is the best and a score of 10 is the worst.

Progression of performance status among cancer patients

Aims

Examine the longitudinal transitions of performance status.

Determine the chances of improvement and deterioration in performance status over time.

Progression of performance status among cancer patients

Why these aims?

Understanding the probabilities of improvement and deterioration in performance status over time can assist provides in determining the appropriate time to initiate palliative care support.

Progression of performance status among cancer patients

What have others done?

- Prior research has shown that performance status is a predictor of survival, but this work simply used performance status at baseline to measure this association.

What have we done?

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American Journal of Epidemiology

DOI: 10.1093/aje/kwq384

Practice of Epidemiology

Multistate Analysis of Interval-Censored Longitudinal Data: Application to a Cohort Study on Performance Status Among Patients Diagnosed With Cancer

Rinku Sutradhar*, Lisa Barbera, Hsien Seow, Doris Howell, Amna Husain, and Deborah Dudgeon

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Initially submitted March 25, 2010; accepted for publication October 18, 2010.

Original Article

Modeling the Longitudinal Transitions of Performance Status in Cancer Outpatients: Time to Discuss Palliative Care

Rinku Sutradhar, PhD, Hsien Seow, PhD, Craig Earle, MD, Deborah Dudgeon, MD, Clare Atzema, MD, Amna Husain, MD, Doris Howell, PhD, Ying Liu, MSc, Jonathan Sussman, MD, and Lisa Barbera, MD

Original Article

PALLIATIVE MEDICINE

Palliative Medicine
2014, Vol 28(2) 184–190

DOI: 10.1177/0269216313499059
pmj.sagepub.com
SAGE

A Markov multistate analysis of the relationship between performance status and death among an ambulatory population of cancer patients

Rinku Sutradhar[1,2] and Lisa Barbera[1,3,4]

Progression of performance status among cancer patients

Study population, outcome, and covariates

Province-wide cohort: Patients diagnosed with cancer in Ontario from 2007-2010, and had at least one PPS assessment

Outcome: PPS score over time

Clinical categorizations of performance status:
PPS score 70-100 implies **Stable** performance status
PPS score 40-60 implies **Transitional** performance status
PPS score 10-30 implies **End-of-life** performance status

Progression of performance status among cancer patients

Study population, outcome, and covariates

Time was measured in months since cancer diagnosis

Patients were censored when the study ended on December 31st, 2010 or when they were lost to follow-up, whichever occurred first.

Covariates: Information on age at diagnosis, gender, neighborhood income quintile, type of cancer diagnosis, and co-morbidity

Progression of performance status among cancer patients

What specific questions can this model answer?

Question 1. How much higher is the rate of progression to death from the end of life state than from the transitional state?

Question 2. For a patient in the end-of-life state, what is the chance of experiencing an improvement in performance status at the end of 6 months.

Question 3. What is the average duration of time a patient spends in the end-of-life state?

Progression of performance status among cancer patients

Results

There were a total of 11,342 patients with over 70,000 assessments of performance status.

Majority of patients received 4 or more PPS assessments during their follow-up period.

Of the 4806 patients who died, nearly half were last measured to be in the transitional state before dying.

Progression of performance status among cancer patients

Maximum likelihood estimate of $\Lambda =$

State[a]	Stable		Transitional		End-of-life		Dead	
	MLE	95% CI	MLE	95% CI	MLE	95% CI	MLE	95% CI
Stable	−0.059	−0.061, −0.058	0.058	0.056, 0.059	0.0		$4.4e^{-04}$	$2.0e^{-04}$, $9.9e^{-04}$
Transitional	0.144	0.137, 0.151	−0.529	−0.545, −0.514	0.145	0.126, 0.166	0.239	0.221, 0.259
End-of-life	0.0		0.142	0.113, 0.178	−1.588	−1.757, −1.436	1.446	1.298, 1.611
Dead	0.0		0.0		0.0		0.0	

- Once a patient is in the end of life state, the rate of progression to death is 10 times higher than the rate of recovery to the transitional state (1.446/0.142).
- Answer 1. The rate of transition to death is 6 times higher from the end of life state than from the transitional state (1.446/0.239).

Progression of performance status among cancer patients

Maximum likelihood estimate of $P(1\ month) =$

Month and State[a]	Maximum Likelihood Estimate			
	Stable	Transitional	End-of-life	Dead
1 month				
Stable	0.945	0.044	0.003	0.008
Transitional	0.109	0.596	0.053	0.242
End-of-life	0.005	0.052	0.207	0.735
Dead	0.0	0.0	0.0	1.0

Interpretation:

- A patient in the transitional state has an 10.9% chance of being in the stable state, a 5.3% chance of being in the end of life state, and a 24% chance of being dead at the end of 1 month.
- The probability of being dead at the end of 1 month was 0.8% for a patient in the stable state and 73.5% for a patient in the end-of-life state.

Progression of performance status among cancer patients

Maximum likelihood estimate of $P(6\ months) =$

Month and State[a]	Maximum Likelihood Estimate			
	Stable	Transitional	End-of-life	Dead
6 months				
Stable	0.750	0.087	0.009	0.154
Transitional	0.216	0.068	0.008	0.708
End-of-life	0.019	0.008	0.001	0.972
Dead	0.0	0.0	0.0	1.0

Interpretation:

- A patient in the stable state has a 75% chance of being in this state at the of 6 months.
- Answer 2. A patient in the end-of-life state has a 2.7% (= 0.019 + 0.008) chance of experiencing an improvement in performance status at the end of 6 months.

Progression of performance status among cancer patients

Answer 3.

Estimated sojourn times in each non-absorbing state, overall and stratified for each type of cancer diagnosis:

	Estimated Mean Sojourn Time (Mo)					
	Stable[a]		Transitional[b]		End of Life[c]	
Cancer Type	Estimated Mean	95% CI	Estimated Mean	95% CI	Estimated Mean	95% CI
All	16.74	16.35–17.14	1.88	1.83–1.94	0.63	0.56–0.69
Lung	8.74	8.42–9.07	1.64	1.56–1.71	0.38	0.32–0.45
Breast	81.46	72.84–91.09	2.23	1.93–2.57	1.22	0.64–2.34
Gastrointestinal	15.53	14.84–16.25	1.65	1.56–1.75	0.38	0.31–0.46
Genitourinary	25.21	22.92–27.72	2.05	1.81–2.31	1.88	1.28–2.75

- These results illustrate how performance status can contribute to the physician's ability to determine a patient's future needs.
- Performance status may serve as one possible sign to guide the timing of palliative care referral.
- Waiting until a patient reaches the end-of-life state to initiate palliative care services means that many patients would not receive palliative care until days before death.
- The transitional state may be a more appropriate time to review options for hospice and end-of-life care.

Progression of performance status among cancer patients

Transition[a]	Maximum Likelihood Estimate	
	Intermittent Observation Scheme	Complete Observation Scheme
Stable to Dead	0.154	0.161
Transitional to Dead	0.708	0.566
End-of-life to Dead	0.972	0.851

- Conducting the multistate analysis by incorrectly assuming continual observation leads to misleading results.
- Upon entering the end-of-life state, the estimated chance of dying within the next 6 months is 85%, whereas by correctly assuming intermittent observation, the estimated chance of dying within the next 6 months is 97%.
- This emphasizes the importance of selecting a statistical model that best represents the nature of the data and the way in which the data were collected.

Take home messages

Multistate models can offer further insight into the nature of a disease process, beyond that offered by the traditional time-to-event model.

Multistate models can be implemented to account for intermittent observation, which is a common phenomenon in longitudinal studies.