TMA4275 Life time analysis

Håkon Tjelmeland
Department of Mathematical Sciences
Norwegian University of Science and Technology

Illness/death model

(Reference: Section 3.4.2 in Aalen, Borgan and Gjessing, 2008)

$$\widehat{P}(s,t) = \prod_{(s,t]} \left(\mathbb{I} + d\widehat{A}(u)\right)$$
$$= \prod_{j: s < T_j \le t} \left(\mathbb{I} + \Delta \widehat{A}(T_j)\right)$$

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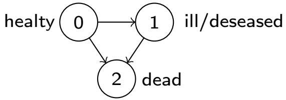

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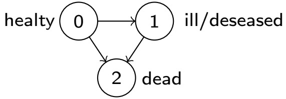

⋆ $P(s,t)$ has the following structure

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

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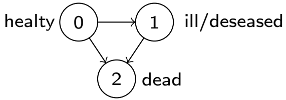

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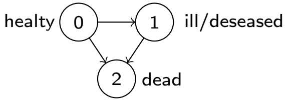

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- Want to find formulas for $\widehat{P}_{00}(s,t)$, $\widehat{P}_{01}(s,t)$ and $\widehat{P}_{11}(s,t)$

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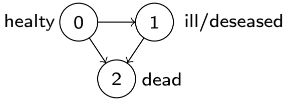

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  - $P_{00}(s,t) + P_{01}(s,t) + P_{02}(s,t) = 1$
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- Want to find formulas for $\widehat{P}_{00}(s,t)$, $\widehat{P}_{01}(s,t)$ and $\widehat{P}_{11}(s,t)$
- Strategy:
  - the factor $\left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$
  - product of two $\left(\mathbb{I} + \Delta\widehat{A})(T_j)\right)$ factors
  - product of three $\left(\mathbb{I} + \Delta\widehat{A})(T_j)\right)$ factors
  - "guess" on general formula
  - general formula can be proved by induction

The factor $\left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$

$$\widehat{P}(s,t) = \prod_{(s,t]} \left(\mathbb{I} + d\widehat{A}(u)\right) = \prod_{j: s < T_j \le t} \left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$$

$$\widehat{A}_{gh}(t) = \int_0^t \frac{J_g(s)}{Y_g(s)} dN_{gh}(s) = \sum_{j: T_j^{gh} \le t} \frac{1}{Y_g(T_j^{gh})}$$

$$\widehat{A}_{gg}(t) = -\sum_{h \neq g} \widehat{A}_{gh}(t)$$

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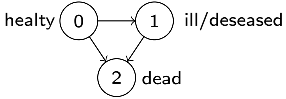

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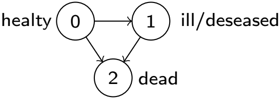

- ⋆ Recall: Observe n individuals following the illness-death model

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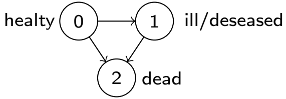

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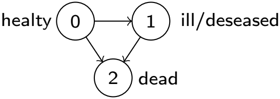

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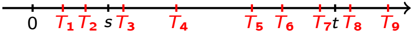
- ⋆ Notation: $0 < T_1 < T_2 < \ldots$



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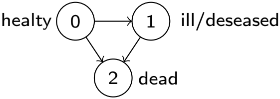

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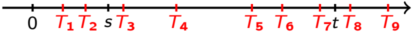

- ⋆ If we at time T_j observe a transition from state 0 to state 1 we have

$$\Delta\widehat{A}(T_j) = \begin{bmatrix} -\frac{1}{Y_0(T_j)} & \frac{1}{Y_0(T_j)} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

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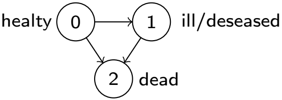

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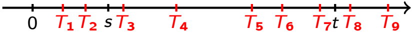

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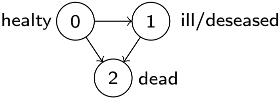

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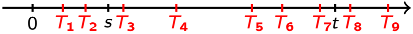

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- ⋆ Alternative formulation

$$\mathbb{I} + \Delta\widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{0\bullet}(T_j)}{Y_0(T_j)} & \frac{\Delta N_{01}(T_j)}{Y_0(T_j)} & \frac{\Delta N_{02}(T_j)}{Y_0(T_j)} \\ 0 & 1 - \frac{\Delta N_{12}(T_j)}{Y_1(T_j)} & \frac{\Delta N_{12}(T_j)}{Y_1(T_j)} \\ 0 & 0 & 1 \end{bmatrix}$$

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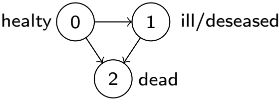

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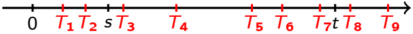

- ⋆ If we at time T_j observe a transition from state 0 to state 2 we have

$$\mathbb{I} + \Delta\widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{1}{Y_0(T_j)} & 0 & \frac{1}{Y_0(T_j)} \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

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$$\mathbb{I} + \Delta\widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{0\bullet}(T_j)}{Y_0(T_j)} & \frac{\Delta N_{01}(T_j)}{Y_0(T_j)} & \frac{\Delta N_{02}(T_j)}{Y_0(T_j)} \\ 0 & 1 - \frac{\Delta N_{12}(T_j)}{Y_1(T_j)} & \frac{\Delta N_{12}(T_j)}{Y_1(T_j)} \\ 0 & 0 & 1 \end{bmatrix}$$

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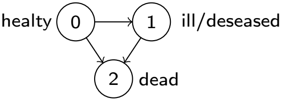

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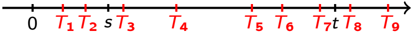

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Product of two $\left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$ factors

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- ⋆ Recall: we want $\widehat{P}_{\mathbf{00}}(s,t)$, $\widehat{P}_{\mathbf{01}}(s,t)$ and $\widehat{P}_{\mathbf{11}}(s,t)$
- ⋆ We write

$$\mathbb{I} + \widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \star \\ 0 & 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} & \star \\ 0 & 0 & \star \end{bmatrix} = \begin{bmatrix} a(T_j) & b(T_j) & \star \\ 0 & c(T_j) & \star \\ 0 & 0 & \star \end{bmatrix}$$

Product of two $\left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$ factors

$$\widehat{P}(s,t) = \prod_{(s,t]} \left(\mathbb{I} + d\widehat{A}(u)\right) = \prod_{j: s < T_j \le t} \left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$$

- ⋆ Recall: we found

$$\mathbb{I} + \Delta\widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{\mathbf{0\bullet}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{02}}(T_j)}{Y_{\mathbf{0}}(T_j)} \\ 0 & 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} & \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} \\ 0 & 0 & 1 \end{bmatrix}$$

- ⋆ Recall: we want $\widehat{P}_{\mathbf{00}}(s,t)$, $\widehat{P}_{\mathbf{01}}(s,t)$ and $\widehat{P}_{\mathbf{11}}(s,t)$
- ⋆ We write

$$\mathbb{I} + \widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{\mathbf{0\bullet}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \star \\ 0 & 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} & \star \\ 0 & 0 & \star \end{bmatrix} = \begin{bmatrix} a(T_j) & b(T_j) & \star \\ 0 & c(T_j) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- ⋆ This gives

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) = \begin{bmatrix} a(T_j) & b(T_j) & \star \\ 0 & c(T_j) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_k) & b(T_k) & \star \\ 0 & c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix}$$

Product of two $\left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$ factors

$$\widehat{P}(s,t) = \prod_{(s,t]} \left(\mathbb{I} + d\widehat{A}(u)\right) = \prod_{j: s < T_j \le t} \left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$$

- ⋆ Recall: we found

$$\mathbb{I} + \Delta\widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{02}}(T_j)}{Y_{\mathbf{0}}(T_j)} \\ 0 & 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} & \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} \\ 0 & 0 & 1 \end{bmatrix}$$

- ⋆ Recall: we want $\widehat{P}_{\mathbf{00}}(s,t)$, $\widehat{P}_{\mathbf{01}}(s,t)$ and $\widehat{P}_{\mathbf{11}}(s,t)$
- ⋆ We write

$$\mathbb{I} + \widehat{A}(T_j) = \begin{bmatrix} 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)} & \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)} & \star \\ 0 & 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} & \star \\ 0 & 0 & \star \end{bmatrix} = \begin{bmatrix} a(T_j) & b(T_j) & \star \\ 0 & c(T_j) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- ⋆ This gives

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) = \begin{bmatrix} a(T_j) & b(T_j) & \star \\ 0 & c(T_j) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_k) & b(T_k) & \star \\ 0 & c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix}$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

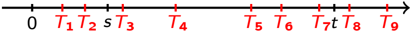
$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

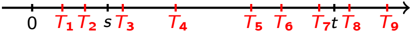
$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



$$\widehat{P}_{\mathbf{00}}(s,t) = \left[\prod_{j:s<T_j\leq t} \left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{\mathbf{11}} = \prod_{j:s<T_j\leq t} a(T_j)$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

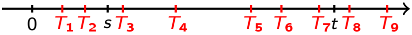
$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



$$\widehat{P}_{\mathbf{00}}(s,t) = \left[\prod_{j:s<T_j\le t} \left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{\mathbf{11}} = \prod_{j:s<T_j\le t} a(T_j) = \prod_{j:s<T_j\le t} \left(1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}\right)$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{0\bullet}(T_j)}{Y_0(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{01}(T_j)}{Y_0(T_j)}$$

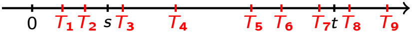
$$c(T_j) = 1 - \frac{\Delta N_{12}(T_j)}{Y_1(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



$$\widehat{P}_{00}(s,t) = \left[\prod_{j:s<T_j\le t} \left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{11} = \prod_{j:s<T_j\le t} a(T_j) = \prod_{j:s<T_j\le t} \left(1 - \frac{\Delta N_{0\bullet}(T_j)}{Y_0(T_j)}\right)$$

$$\widehat{P}_{11}(s,t) = \left[\prod_{j:s<T_j\le t} \left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{22} = \prod_{j:s<T_j\le t} c(T_j)$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

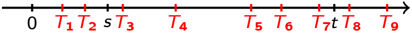
$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



$$\widehat{P}_{\mathbf{00}}(s,t) = \left[\prod_{j: s < T_j \le t} \left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{\mathbf{11}} = \prod_{j: s < T_j \le t} a(T_j) = \prod_{j: s < T_j \le t} \left(1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}\right)$$

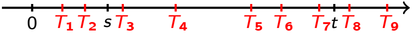
$$\widehat{P}_{\mathbf{11}}(s,t) = \left[\prod_{j: s < T_j \le t} \left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{\mathbf{22}} = \prod_{j: s < T_j \le t} c(T_j) = \prod_{j: s < T_j \le t} \left(1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}\right)$$

Product of three $\left(\mathbb{I} + \widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{0\bullet}(T_j)}{Y_0(T_j)}$$
$$b_h(T_j) = \frac{\Delta N_{01}(T_j)}{Y_0(T_j)}$$
$$c(T_j) = 1 - \frac{\Delta N_{12}(T_j)}{Y_1(T_j)}$$

$$\left(\mathbb{I} + \widehat{A}(T_j)\right) \times \left(\mathbb{I} + \widehat{A}(T_k)\right) \times \left(\mathbb{I} + \widehat{A}(T_l)\right)$$
$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k) + b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$
$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l) + a(T_j)b(T_k)c(T_l) + b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



$$\widehat{P}_{00}(s,t) = \left[\prod_{j:s<T_j\le t}\left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{11} = \prod_{j:s<T_j\le t} a(T_j) = \prod_{j:s<T_j\le t}\left(1 - \frac{\Delta N_{0\bullet}(T_j)}{Y_0(T_j)}\right)$$

$$\widehat{P}_{11}(s,t) = \left[\prod_{j:s<T_j\le t}\left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{22} = \prod_{j:s<T_j\le t} c(T_j) = \prod_{j:s<T_j\le t}\left(1 - \frac{\Delta N_{12}(T_j)}{Y_1(T_j)}\right)$$

$$\widehat{P}_{01}(s,t) = \left[\prod_{j:s<T_j\le t}\left(\mathbb{I} + \widehat{A}(T_j)\right)\right]_{12} = \sum_{j:s<T_j\le t}\left[\left(\prod_{k:s<T_k<T_j} a(T_k)\right) b(T_j) \left(\prod_{k:T_j<T_k\le t} c(T_k)\right)\right]$$

Product of three $\left(\mathbb{I}+\widehat{A}(T_j)\right)$ factors

$$a(T_j) = 1 - \frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

$$b_h(T_j) = \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)}$$

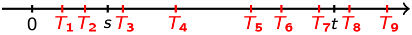
$$c(T_j) = 1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}$$

$$\left(\mathbb{I}+\widehat{A}(T_j)\right) \times \left(\mathbb{I}+\widehat{A}(T_k)\right) \times \left(\mathbb{I}+\widehat{A}(T_l)\right)$$

$$= \begin{bmatrix} a(T_j)a(T_k) & a(T_j)b(T_k)+b(T_j)c(T_k) & \star \\ 0 & c(T_j)c(T_k) & \star \\ 0 & 0 & \star \end{bmatrix} \times \begin{bmatrix} a(T_l) & b(T_l) & \star \\ 0 & c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

$$= \begin{bmatrix} a(T_j)a(T_k)a(T_l) & a(T_j)a(T_k)b(T_l)+a(T_j)b(T_k)c(T_l)+b(T_j)c(T_k)c(T_l) & \star \\ 0 & c(T_j)c(T_k)c(T_l) & \star \\ 0 & 0 & \star \end{bmatrix}$$

- From this we see that



$$\widehat{P}_{\mathbf{00}}(s,t) = \left[\prod_{j:s<T_j\le t}\left(\mathbb{I}+\widehat{A}(T_j)\right)\right]_{\mathbf{11}} = \prod_{j:s<T_j\le t} a(T_j) = \prod_{j:s<T_j\le t}\left(1-\frac{\Delta N_{\mathbf{0}\bullet}(T_j)}{Y_{\mathbf{0}}(T_j)}\right)$$

$$\widehat{P}_{\mathbf{11}}(s,t) = \left[\prod_{j:s<T_j\le t}\left(\mathbb{I}+\widehat{A}(T_j)\right)\right]_{\mathbf{22}} = \prod_{j:s<T_j\le t} c(T_j) = \prod_{j:s<T_j\le t}\left(1-\frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}\right)$$

$$\widehat{P}_{\mathbf{01}}(s,t) = \left[\prod_{j:s<T_j\le t}\left(\mathbb{I}+\widehat{A}(T_j)\right)\right]_{\mathbf{12}} = \sum_{j:s<T_j\le t}\left[\left(\prod_{k:s<T_k<T_j} a(T_k)\right) b(T_j) \left(\prod_{k:T_j<T_k\le t} c(T_k)\right)\right]$$

$$= \sum_{j:s<T_j\le t}\left[\widehat{P}_{\mathbf{00}}(s,T_{j-\mathbf{1}}) \cdot \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{0}}(T_j)} \cdot \widehat{P}_{\mathbf{11}}(T_j,t)\right]$$

Proof for the formulas

- Want to proof the formulas

$$\widehat{P}_{\mathbf{00}}(s,t) = \prod_{j:s<T_j\le t}\left(1 - \frac{\Delta N_{\mathbf{0\bullet}}(T_j)}{Y_{\mathbf{0}}(T_j)}\right)$$

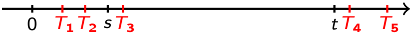
$$\widehat{P}_{\mathbf{11}}(s,t) = \prod_{j:s<T_j\le t}\left(1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)}\right)$$

$$\widehat{P}_{\mathbf{01}}(s,t) = \sum_{j:s<T_j\le t}\left[\widehat{P}_{\mathbf{00}}(s,T_{j-\mathbf{1}})\cdot\frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{1}}(T_j)}\cdot\widehat{P}_{\mathbf{11}}(T_j,t)\right]$$

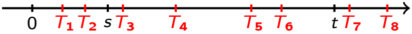
- Given

$$\widehat{P}(s,t) = \prod_{j:s<T_j\le t}\left(\mathbb{I} + \Delta\widehat{A}(T_j)\right)$$

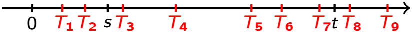
- Proof by induction
  - proof formulas when only one observed transition in $(s,t]$



  - assume formulas correct for k observed transition in $(s,t]$,

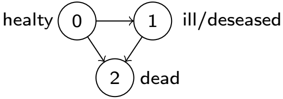


and show that then it is also correct with $k+1$ observed transitions in $(s,t]$



Summary

- Illness-death model:



- Used Kaplan–Meier estimator for general Markov chain

$$\widehat{P}(s,t) = \prod_{(s,t]} \left(\mathbb{I} + d\widehat{A}(u) \right) = \prod_{j: s < T_j \le t} \left(\mathbb{I} + \Delta \widehat{A}(T_j) \right)$$

- Showed that

$$\widehat{P}_{\mathbf{00}}(s,t) = \prod_{j: s < T_j \le t} \left(1 - \frac{\Delta N_{\mathbf{0\bullet}}(T_j)}{Y_{\mathbf{0}}(T_j)} \right)$$

$$\widehat{P}_{\mathbf{11}}(s,t) = \prod_{j: s < T_j \le t} \left(1 - \frac{\Delta N_{\mathbf{12}}(T_j)}{Y_{\mathbf{1}}(T_j)} \right)$$

$$\widehat{P}_{\mathbf{01}}(s,t) = \sum_{j: s < T_j \le t} \left[\widehat{P}_{\mathbf{00}}(s, T_{j-\mathbf{1}}) \cdot \frac{\Delta N_{\mathbf{01}}(T_j)}{Y_{\mathbf{1}}(T_j)} \cdot \widehat{P}_{\mathbf{11}}(T_j, t) \right]$$