3. Relations between Incidence, Mortality, Prevalence and Time with Disease

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Relations Between Incidence, Mortality Prevalence and Time with Disease

3.1. Definitions and Notation

Incidence Rate. Proportion of new cases arising in a given interval of time; e.g. cancer incidence = 332/100,000 per year.

$I(t)dt$ = Probability of new case arising during $(t, t + dt)$

$I(t)$ = Point Incidence Function

t = chronological time or age

$$I(t, t+1) = \int_t^{t+1} I(x)dx$$

If t = chronological Time $\Rightarrow I(t, t+1)$ is incidence rate for year t.
If t = age $\Rightarrow I(t, t+1)$ is age specific incidence rate for age t.

Often age specific incidence rates are reported in 5-year intervals; e.g.

$$I(t, t+5) = \int_t^{t+5} I(x)dx.$$

<u>Point Prevalence Rate</u>: Proportion of people with disease at a given point in time $P(t)$ = Probability of having disease at time t (t may be chronological time or age).

Mortality Rate: Proportion of Deaths per unit time.

$M(t)dt$ = Probability of death during $(t, t+dt)$; t may refer to age or chronological time. Generally $M(t)$ is defined by a specific disease and for a fixed period of time (one year, 5 years, etc.); e.g. 166deaths/100,000 per year

$$M(t, t+1) = \int_t^{t+1} M(x)dx, \quad M(t, t+5) = \int_t^{t+5} M(x)dx.$$

In general $M(t, t+1)$ is proportion of deaths in year t where numerator is no. of deaths due to disease and denominator is total population.

$I(t)dt =$ Prob. of being incident with disease in age (or time) interval $(t, t+dt)$.

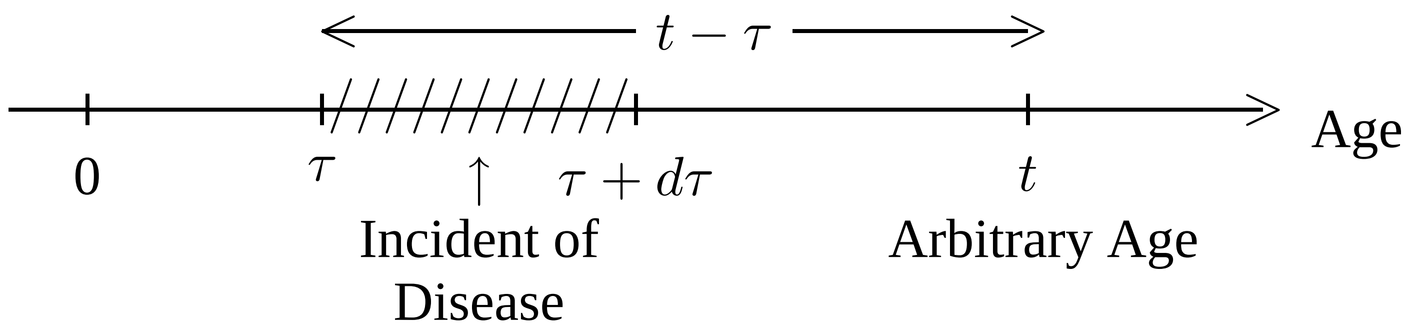
3.2. Relationships: t = age

What are relationships between $I(t)$, $P(t)$ and $M(t)$?

Assume $I(0) = P(0) = 0$.

Define $q(t)$: pdf of disease survival

$$Q(t) = \int_t^\infty q(x)dx = P\{T > t\}$$



We shall show

$$\boxed{\begin{aligned} &(1) \quad P(t) = \int_0^t I(\tau)Q(t-\tau)d\tau \\ &(2) \quad M(t)dt = \int_0^t I(\tau)q(t-\tau)d\tau dt \end{aligned}}$$

The probability of being prevalent at age t, requires being incident at an earlier age (τ) and having survival $> (t-\tau)$. The probability of being incident in the age interval $(\tau, \tau + d\tau)$ is $I(\tau)d\tau$. Hence the probability of the two events is $I(\tau)Q(t-\tau)d\tau$. Intergrating over all possible ages of incidence $(0, t)$ results in $P(t)$.

Similarly the probability of dying in the age interval $(t, t+dt)$ requires being incident in the interval $(\tau, \tau + d\tau)$ and having survival in the interval $(t-\tau, t-\tau+dt)$. the probability of these events is $I(\tau)q(t-\tau)d\tau dt$. Intergrating τ over $(0, t)$ gives value for $M(t)dt$.

$$P(t) = \int_0^t I(\tau)Q(t-\tau)d\tau$$

$$M(t) = \int_0^t I(\tau)q(t-\tau)d\tau$$

Taking Laplace Transforms

$$\boxed{\begin{array}{lll} (3) & P^*(s) & = I^*(s)Q^*(s) \\ & & \\ (4) & M^*(s) & = I^*(s)q^*(s) \end{array}}$$

Recall $Q^*(s) = [1 - q^*(s)]/s$

$$\therefore\ P^*(s) = I^*(s)\left\{\frac{1-q^*(s)}{s}\right\}$$

$$\boxed{(5) \quad sP^*(s) = I^*(s)\left\{1 - \frac{M^*(s)}{I^*(s)}\right\} = I^*(s) - M^*(s)}$$

Recall $\mathcal{L}\,\{\phi'(t)\} = s\phi^*(s) - \phi(0)$

$\therefore\ \mathcal{L}^{\,-1}\{s\phi^*(s)\} = \phi'(t) + \phi(0)\delta(t)$ as $\mathcal{L}\,\{1\} = \delta(t)$

$\mathcal{L}^{\,-1}\{sP^*(s)\} = P'(t) + \delta(t)P(0) = P'(t)$

$$\therefore \quad \boxed{(6) \quad \frac{dP(t)}{dt} = I(t) - M(t)}$$

In general $\mathcal{L}\,\{P'(t)\} = sP^*(s) - P(0)$ since $\mathcal{L}\,\{1\} = \delta(t)$,

$\mathcal{L}^{\,-1}\{sP^*(s)\} = P'(t) + \delta(t)P(0)$ and

$$\boxed{P'(t) + P(0)\delta(t) = I(t) - M(t)}$$

a. Stable Disease Model

Definition: Stable Disease Model

$$\frac{dP(t)}{dt} = 0 \quad \Rightarrow \quad I(t) = M(t)$$

$$\text{Prevalence} \quad = \quad P(t) = P = \text{Constant}$$

Some people refer to stable disease model as $I(t) = I$ in which case $M(t) = M$.

$$\boxed{(6) \quad \frac{dP(t)}{dt} = I(t) - M(t)}$$

$$\boxed{(7) \quad P(t) = P(0) + \int_0^t [I(x) - M(x)]dx}$$

If t refers to age, $P(0) = 0$

$$\boxed{(8) \quad P(t) = \int_0^t [I(x) - M(x)]dx}$$

$$P^*(s) = I^*(s)Q^*(s) \quad \text{and} \quad M^*(s) = I^*(s)q^*(s)$$

$$\boxed{(9) \quad \frac{P^*(s)}{M^*(s)} = \frac{Q^*(s)}{q^*(s)}}$$

Assume $q(t) = \lambda e^{-\lambda t},\ q^*(s) = \dfrac{\lambda}{\lambda + s} = (1+ms)^{-1},\ \ m = 1/\lambda$

$$\frac{Q^*(s)}{q^*(s)} = \frac{1 - q^*(s)}{sq^*(s)} = \frac{1-(1+ms)^{-1}}{s(1+ms)^{-1}} = \frac{(1+ms)-1}{s} = m$$

$$\therefore \qquad \boxed{P^*(s) = mM^*(s)}$$

$$\boxed{(10) \ \ P(t) = mM(t)}$$

<u>Stable Disease Model</u>: $P(t) = P \Rightarrow M(t) = M$

Hence if survival is exponential, $P(t) = mM(t)$ and if stable disease model holds, $M(t) = M$ and since $I(t) = M(t),\ I(t) = I$.

b. General Case

$$\frac{P^*(s)}{M^*(s)} = \frac{Q^*(s)}{q^*(s)} = \frac{1 - q^*(s)}{sq^*(s)}$$

$$q^*(s) = 1 - sm + \frac{s^2}{2}m_2 + O(s^3)$$

$$\frac{Q^*(s)}{q^*(s)} = \frac{1 - [1 - sm + \frac{s^2}{2}m_2 + O(s^3)]}{s[1 - sm + O(s^2)]}$$

$$= \frac{m - \frac{s}{2}m_2 + O(s^2)}{1 - sm + O(s^2)}$$

$$m + s[m^2 - \frac{m_2}{2}]$$

$$1 - sm + O(s^2) \quad \sqrt{m - \tfrac{s}{2} m_2 + O(s^2)}$$

$$\frac{m - sm^2 + O(s^2)}{}$$

$$s[m^2 - \frac{m_2}{2}] + O(s^2)$$

$$\frac{s[m^2 - \frac{m_2}{2}] + O(s^2)}{}$$

$$O(s^2)$$

$$\frac{Q^*(s)}{q^*(s)} = m + (m^2 - \frac{m_2}{2})s + O(s^2)$$

$$m_2 = \sigma^2 + m^2$$

$$\boxed{\frac{Q^*(s)}{q^*(s)} = m + (\frac{m^2 - \sigma^2}{2})s + O(s^2)}$$

$$\frac{Q^*(s)}{q^*(s)} = m + (\frac{m^2-\sigma^2}{2})s + O(s^2)$$
$$= m + \frac{m^2}{2}(1-C^2)s + O(s^2), \quad C = \sigma/m$$

C = coefficient of variaton ($C = 1$ for exponential)

Since $\frac{P^*(s)}{M^*(s)} = \frac{Q^*(s)}{q^*(s)}, \quad P^*(s) = M^*(s)[m + \frac{m^2}{2}(1-C^2)s + O(s^2)]$

Taking inverse Laplace Transforms

$$P(t) = mM(t) + \frac{m^2}{2}(1-C^2)\mathcal{L}^{-1}\{sM^*(s)\} + ...$$

Recall $\mathcal{L}^{-1}\{s\phi^*(s)\} = \phi'(t) + \phi(0)\delta(t)$

$\therefore \; P(t) = mM(t) + \frac{m^2}{2}(1-C^2)[M'(t) + M(0)\delta(t) + ...]$

$$\Rightarrow \boxed{\text{(11)} \; P(t) \cong mM(t)\left\{1 + \frac{m}{2}(1-C^2)\frac{d}{dt}\log M(t)\right\}}$$

Returning to

$$\frac{P^*(s)}{M^*(s)} = \frac{Q^*(s)}{q^*(s)}$$

Recall $\quad \lim_{s \to 0} s\phi^*(s) = \lim_{t \to \infty} \phi(t) = \phi(\infty)$

We have

$$\frac{sP^*(s)}{sM^*(s)} = \frac{Q^*(s)}{q^*(s)}$$

and taking the limit as $s \to 0$

$$\boxed{\frac{P(\infty)}{M(\infty)} = m}$$

as $Q^*(s) = m - \dfrac{s}{2}m_2 + \ldots$ and $q^*(s) = 1 - sm + \dfrac{s^2 m_2}{2} + \ldots$

Therefore for t large (older age) the ratio of $P(\infty)$ to $M(\infty)$ is mean time with disease.

3.3. Relationships: t chronological Time

Suppose a cohort group is being observed starting at chronological time 0.

Example: In San Francisco a group of homosexual men was being followed to study Kaposi's sarcoma. When the HIV was discovered as the virus causing AIDS, the cohort group was studied to determine the incidence of HIV and AIDS. At beginning of study (time = 0) it was discovered that some of the men already had the virus.

Model:
- S_0: disease free state
- S_d: disease state
- D : death (or absoring state)

Natural History: $S_0 \rightarrow S_d \rightarrow D$

Notation:

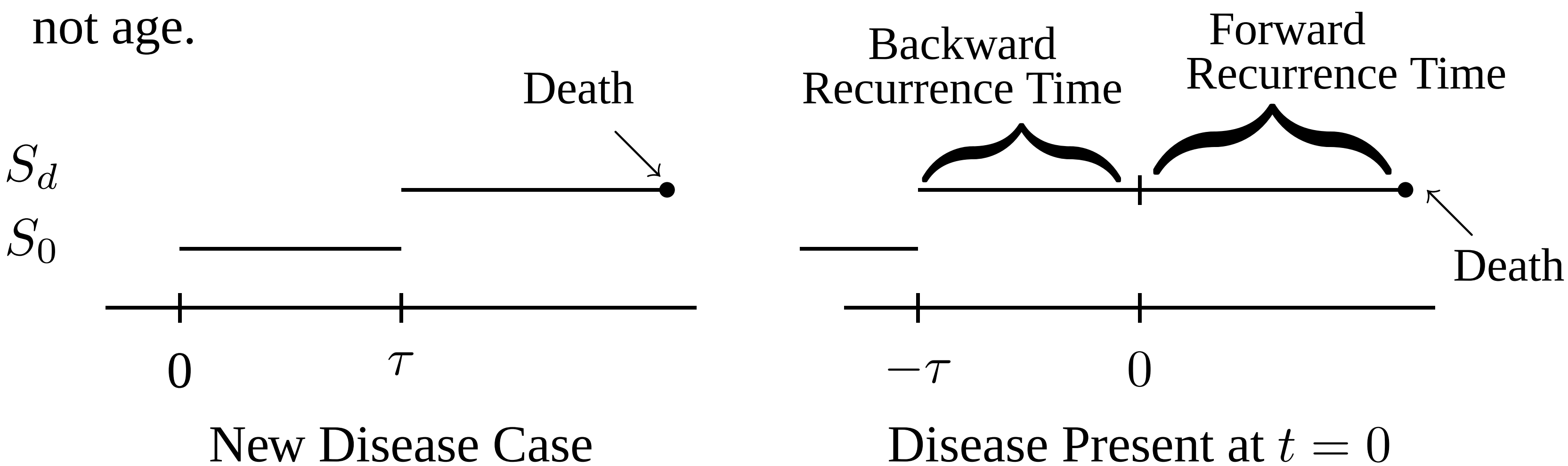
$P(t)$: Prevalence Probability

$q(t)$: pdf of survival with disease

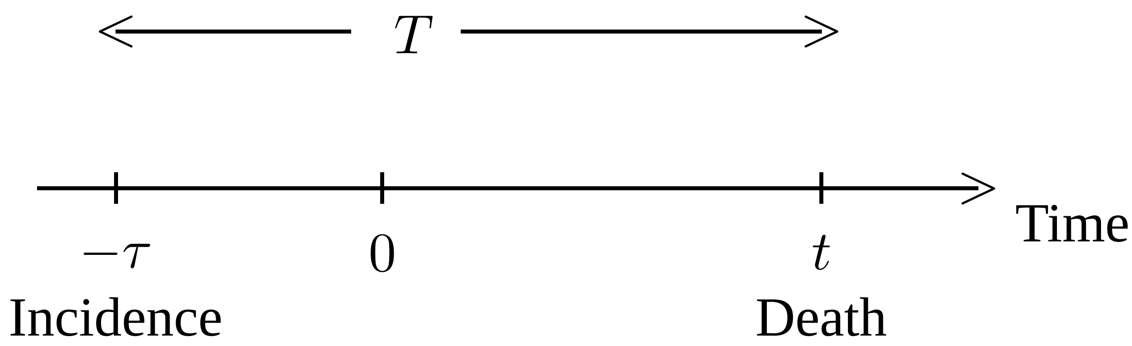
$M(t)$: Mortality rate

$I(t)$: Incidence rate of disease

Note: Time Parameter in $P(t), M(t), I(t)$ refers to chronological time — not age.



What is distribution of forward recurrence times for cases prevalent at $t = 0$?



Define $a = 1$ if person has disease at time 0.

First problem: What is distribution of T conditional on $a = 1$.

$q(t)$: pdf of time with disease

Suppose $T = t$ is fixed.

$$P\{a = 1 | T = t\} \propto t$$

$$P\{a = 1, t < T \le t + dt\} \propto tq(t)dt$$

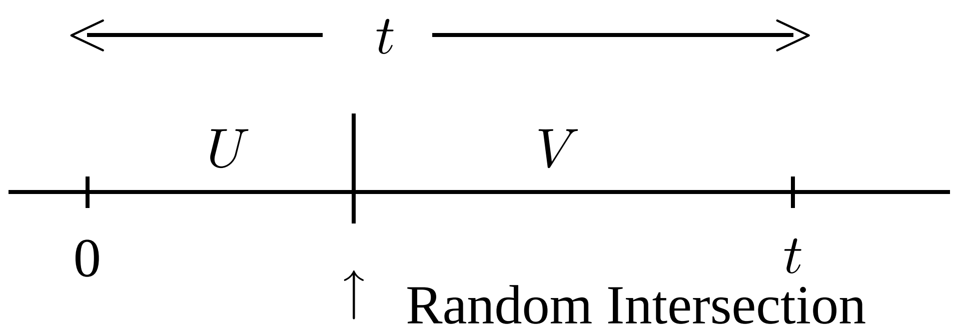
$$f(t|a = 1) = P\{t < T \le t + dt | a = 1\} \quad = \frac{tq(t)dt}{\int_0^\infty tq(t)dt}$$

$$\boxed{(12) \quad f(t|a = 1) = tq(t)/m}$$

Note: $E(T|a = 1) = \dfrac{E(T^2)}{m} = \dfrac{\sigma^2 + m^2}{m} = m(1 + \sigma^2/m^2)$

If T is exponential $E(T|a = 1) = 2m$ as $\sigma^2/m^2 = 1$

Consider a realization of $T \quad (T = t)$.



$$t = U + V$$

The forward recurrence time is V if t is interesected at U. The line is intersected at a random point. Hence the distribution of U is uniform over the interval t; i.e.

$$g(u|t, a = 1) = \frac{1}{t}, \quad 0 < u \leq t \quad \text{or} \quad g(v|t, a = 1) = \frac{1}{t}, \quad 0 < v \leq t$$

$$P\{v < V \leq v + dv, t < T \leq t + dt | a = 1\} = \frac{1}{t} \frac{tq(t)}{m} dv dt$$

for $0 < v \leq t$

$$* \quad q_f(v) = P\{v < V \leq v + dv | a = 1\} = \int_v^\infty \frac{q(t)}{m} dt$$

$$\boxed{q_f(v) = \frac{Q(v)}{m}}$$

$*$ subscript refers to forward recurrence time.

$$\boxed{(13) \quad q_f(t) = Q(t)/m}$$

$$
\begin{aligned}
q_f^*(s) &= \frac{Q^*(s)}{m} = \frac{1-q^*(s)}{sm} = \frac{1-[1-sm+\frac{s^2}{2}m_2+\frac{s^3}{3!}m_3]}{sm} \\
&= 1-\frac{s}{2}\;\frac{m_2}{m}+\frac{s^2}{2}\;\frac{m_3}{3m}\;+\ldots \\
E(T_f) &= \frac{m_2}{2m},\;\; E(T_f^2) = \frac{m_3}{3m} \\
E(T_f) &= \frac{1}{2}\;\frac{(\sigma^2+m^2)}{m} = \frac{m}{2}(1+C^2),\;\; C^2 = \sigma^2/m^2
\end{aligned}
$$

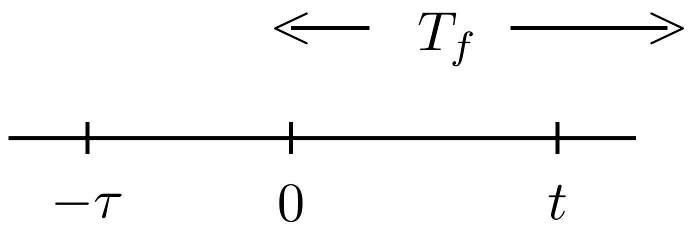
Note: If $q(t) = \lambda e^{-\lambda t}$, $m = 1/\lambda$, then $q_f(t) = \dfrac{Q(t)}{m} = \lambda e^{-\lambda t}$

<u>Conclusions:</u> Prevalent cases (cases prevalent at $t = 0$) have a different survival distribution then the population of cases).

The survival time from $t = 0$ of prevalent cases is $q_f(t) = Q(t)/m$.

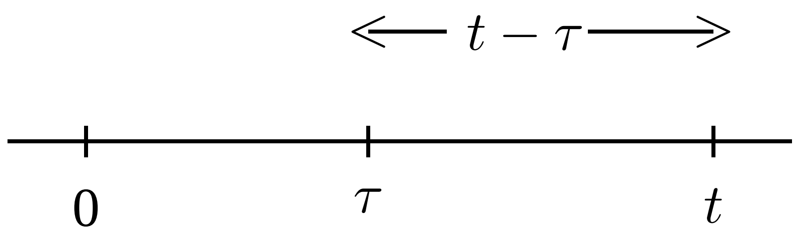
Cases Prevalent at t ($t > 0$)

(i) Prevalent at $t = 0$ and lived at least another t units of time



$$P\{T_f > t\} = Q_f(t)$$

(ii) New cases who were incident at τ and lived at least $T - \tau$ units of time



$$\boxed{(14) \quad P(t) = P(0)Q_f(t) + \int_0^t I(\tau)Q(t-\tau)d\tau}$$

$$\boxed{(14)\quad P(t) = P(0)Q_f(t) + \int_0^t I(\tau)Q(t-\tau)\,d\tau}$$

<u>Mortality at $t (t > 0)$</u>

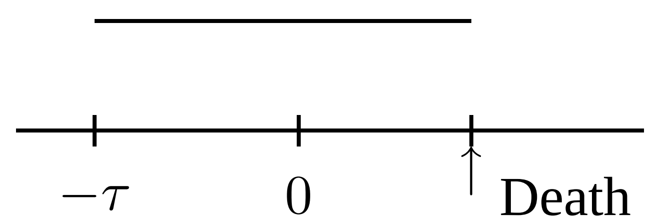
(i) Mortality from cases prevalent at $t = 0$

(ii) Mortality from new cases

$$\boxed{(15)\quad M(t) = P(0)q_f(t) + \int_0^t I(\tau)q(t-\tau)\,d\tau}$$

We can also calculate $P(0)$

$$\boxed{(16)\quad P(0) = \int_0^\infty I(-\tau)Q(\tau)\,d\tau}$$



(14) $\boxed{P(t) = P(0)Q_f(t) + \displaystyle\int_0^T I(\tau)Q(t-\tau)d\tau}$

(15) $\boxed{M(t) = P(0)q_f(t) + \int_0^t I(\tau)q(t-\tau)d\tau}$

Taking Laplace Transforms

$$(16) \quad P^*(s) = P(0)Q_f^*(s) + I^*(s)Q^*(s)$$

$$(17) \quad M^*(s) = P(0)q_f^*(s) + I^*(s)q^*(s)$$

Solving for $q^*(s) = \dfrac{M^*(s) - P(0)q_f^*(s)}{I^*(s)}$ in (17) and substituting in (16).

$$P^*(s) = P(0)Q_f^*(s) + I^*(s)\left[\frac{1-q^*(s)}{s}\right]$$

$$sP^*(s) = sP(0)\frac{[1-q_f^*(s)]}{s} + I^*(s) - [M^*(s) - P(0)q_f^*(s)]$$

$$sP^*(s) = P(0) + I^*(s) - M^*(s)$$

$$\mathcal{L}\{\tau'(t)\} = s\tau^*(s) - \tau(0)$$

$$\tau'(t) = \mathcal{L}^{-1}\{s\tau^*(s) - \tau(0)\delta(t)\}$$

$$\mathcal{L}^{-1}\{s\tau^*(s)\} = \tau'(t) + \tau(0)\delta(t)$$

Since $\mathcal{L}^{-1}\{sP^*(s)\} = P'(t) + P(0)\delta(t) = P(0)\delta(t) + I(t) - M(t)$

(18) $$\boxed{\frac{dP(t)}{dt} = I(t) - M(t)}$$

(18) $\boxed{\dfrac{dP(t)}{dt} = I(t) - M(t)}$ $\boxed{P(t) = P(0) + \int_0^t [I(x) - M(x)]dx}$

If $\dfrac{dP(t)}{dt} = 0 \Rightarrow P(t) = P(0)$ and $I(t) = M(t)$ and we have the Stable Disease Model.

(19) $P^*(s) = P(0)Q_f^*(s) + I^*(s)Q^*(s)$

(20) $M^*(s) = P(0)q_f^*(s) + I^*(s)q^*(s)$

Solve for $I^*(s) = \dfrac{P^*(s) - P(0)Q_f^*(s)}{Q^*(s)}$ in (19) and substitute in (20) gives

$$M^*(s) = P(0)q_f^*(s) + \frac{q^*(s)}{Q^*(s)}[P^*(s) - P(0)Q_f^*(s)]$$

$$M^*(s) = P(0)q_f^*(s) + \frac{q^*(s)}{Q^*(s)}[P^*(s) - P(0)Q_f^*(s)]$$

Since $\quad q_f(t) = Q(t)/m, \quad q_f^*(s) = Q^*(s)/m = \dfrac{1 - q^*(s)}{sm}$

$$M^*(s) = \frac{P(0)Q^*(s)}{m} + \frac{q^*(s)}{Q^*(s)} \left\{ P^*(s) - P(0)\left[\frac{1 - Q^*(s)/m}{s}\right]\right\}$$

which simplifies to

(21) $\quad M^*(s) = \dfrac{P(0)}{sm} + \dfrac{q^*(s)}{Q^*(s)} \left[P^*(s) - \dfrac{P(0)}{s}\right]$

(21) $$\boxed{M^*(s) = \frac{P(0)}{sm} + \frac{q^*(s)}{Q^*(s)}\left[P^*(s) - \frac{P(0)}{s}\right]}$$

a. Case 1: Stable Disease Model

$$P(t) = P \quad \text{for all } t$$

Then $P(0) = P$ and $P^*(s) = P/s$

$$\Rightarrow \qquad M^*(s) = P/sm$$

Taking inverse transforms $M(t) = P/m$ which implies $M(t) = M$ and we have

(22) $\boxed{P = mM}$

However in stable disease model $M(t) = I(t) = I$

(23) $\boxed{P = mI}$

(24) $$\boxed{M^*(s) = \frac{P(0)}{sm} + \frac{q^*(s)}{Q^*(s)}\left[P^*(s) - \frac{P(0)}{s}\right]}$$

b. <u>Case 2:</u> Suppose $q(t) = \lambda e^{-\lambda t}$

$$\begin{aligned}
q^*(s) &= \frac{\lambda}{\lambda + s} = (1 + sm)^{-1}, \quad m = 1/\lambda \\
Q^*(s) &= \frac{1 - q^*(s)}{s} = \frac{1 - \dfrac{1}{1 + sm}}{s} = m/(1 + sm) \\
M^*(s) &= \frac{P(0)}{sm} + \frac{1}{m}\left[P^*(s) - \frac{P(0)}{s}\right] = \frac{P^*(s)}{m} \\
M^*(s) &= P^*(s)/m
\end{aligned}$$

(25) $\Rightarrow$ $\boxed{M(t) = P(t)m}$

Conversely suppose $M(t) = P(t)/m,$ then $M^*(s) = P^*(s)/m$. Substituting in (24)

$$(26) \quad \frac{P^*(s)}{m} = \frac{P(0)}{sm} + \frac{q^*(s)}{Q^*(s)}\left[P^*(s) - \frac{P(0)}{s}\right]$$

The solution to (26) requires $\dfrac{q^*(s)}{Q^*(s)} = \dfrac{1}{m}$. Therefore

$$\frac{q^*(s)}{[1 - q^*(s)]/s} \;=\; \frac{1}{m}$$

$$\Rightarrow \;\; q^*(s) = (1 + sm)^{-1} \;\Rightarrow\; q(t) = \lambda e^{-t}, \;\; \lambda = 1/m$$

We have proved the necessary and sufficient condition for $P(t) = mM(t)$ is that the survival distribution be exponential with mean m.

c. <u>Case 3:</u> Relation for $t \to \infty$

$$M^*(s) = \frac{P(0)}{sm} + \frac{q^*(s)}{Q^*(s)}\left[P^*(s) - \frac{P(0)}{s}\right]$$

$$\lim_{s \to 0} sM^*(s) = M(\infty)$$

$$\lim_{s \to 0} sP^*(s) = P(\infty)$$

$$\lim_{s \to 0} sM^*(s) = M(\infty) = \frac{P(0)}{m} + \frac{1}{m}[\lim_{s \to 0} sP^*(s) - P(0)] = \frac{1}{m}P(\infty)$$

(27) $\boxed{M(\infty) = \frac{1}{m}P(\infty)}$ or $\boxed{\lim_{t \to \infty} P(t) = m \lim_{t \to \infty} M(t)}$

Case 3 (continued): $t \to \infty$

$$(a) \quad P^*(s) = P(0)Q_f^*(s) + I^*(s)Q^*(s)$$
$$(b) \quad M^*(s) = P(0)q_f^*(s) + I^*(s)q^*(s)$$

Multiplying (a) and (b) by s

$$(c) \quad sP^*(s) = P(0)(1 - q_f^*(s)) + sI^*(s)Q^*(s)$$
$$(d) \quad sM^*(s) = P(0)q_f^*(s)s + sI^*(s)q^*(s)$$

Since $\displaystyle\lim_{s \to 0} sP^*(s) = P(\infty)$

$$\lim_{s \to 0} sI^*(s) = I(\infty)$$
$$\lim_{s \to 0} sM^*(s) = M(\infty)$$

We have

$$P(\infty) = I(\infty)m \quad \text{as } Q^*(0) = m$$
$$M(\infty) = I(\infty) \quad \text{and } q^*(0) = 1$$

d. Case 4: General Case

$$M^*(s) = \frac{P(0)}{sm} + \frac{q^*(s)}{Q^*(s)}\left[P^*(s) - \frac{P(0)}{s}\right]$$

Solve for $P^*(s)$

$$\begin{aligned} P^*(s) &= \left[M^*(s) - \frac{P(0)}{sm}\right]\frac{Q^*(s)}{q^*(s)} + \frac{P(0)}{s} \\ P^*(s) &= \frac{P(0)}{s}\left[1 - \frac{Q^*(s)}{mq^*(s)}\right] + M^*(s)\frac{Q^*(s)}{q^*(s)} \end{aligned}$$

We had earlier shown

$$\frac{Q^*(s)}{q^*(s)} = m + \frac{m^2}{2}(1-C^2)s + O(s^2)$$

$$\left[1 - \frac{Q^*(s)}{mq^*(s)}\right] = 1 - \left[1 + \frac{m^2}{2}(1-C^2)s + O(s^2)\right]$$

$$= -\left[\frac{m^2}{2}(1-C^2)s + O(s^2)\right]$$

$$\begin{aligned} P^*(s) &= M^*(s)\left[m + \frac{m^2(1-C^2)}{2}s + O(s^2)\right] \\ &\quad - \frac{P(0)}{s}\left[\frac{m^2}{2}(1-C^2)s + O(s^2)\right] \end{aligned}$$

$$
\begin{aligned}
P^*(s) \quad &= M^*(s)\left[m + \frac{m^2(1-C^2)}{2}s + O(s^2)\right] \\
&\quad - \frac{P(0)}{s}\left[\frac{m}{2}(1-C^2)s + O(s^2)\right]
\end{aligned}
$$

Taking inverse transforms

$$P(t) = mM(t) + \frac{m^2(1-C^2)}{2}\left[M'(t) + \delta(t)M(0)\right] + \ldots$$

(28) $$\boxed{P(t) \cong mM(t)\left\{1 + \frac{m(1-C^2)}{2}\frac{d}{dt}\log M(t)\right\}}$$

Summary

1. If stable disease model holds $P = mI = mM$ and $M = I$.

2. A necessary and sufficient conditon for $P(t) = mM(t)$ is that the survival time be exponential with mean m.

3. For large values of t, $\lim_{t \to \infty} P(t) = m \lim_{t \to \infty} M(t)$.

4. A first order correction is
$$P(t) \simeq mM(t) \left[1 + \frac{(1 - C^2)}{2} \frac{d}{dt} \log M(t) \right].$$

5. The above expressions hold for annual incidence and mortality.

6. General Case

$$\begin{aligned}
P(t,t+1) &= \int_t^{t+1} P(x)dx = \text{ Average Prevalence during Year} \\
M(t,t+1) &= \int_t^{t+1} M(x)dx = \text{ Total Mortality during Year } t \\
\int_t^{t+1} M'(x)dx &= M(t+1) - M(t) = \text{Change in mortality}
\end{aligned}$$

i.e. Suppose $M(t) = a + bt$

$$M(t+1) - M(t) = b$$

$$\begin{aligned}
\therefore\ P(t,t+1) &\cong mM(t,t+1) + \frac{m(1-C^2)}{2}[M(t+1) - M(t)] \\
&\cong m\left[a + b\frac{(1+2t)}{2}\right] + \frac{m(1-C^2)}{2}b
\end{aligned}$$

3.4. Relationships: Age and Chronological Time

z = Age

t = Chronological Time

$P(t, z)dz$ = Probability of having disease at time t and having age within interval $(z, z + dz)$.

$I(t, z)dtdz$= Probability of being incident within time $(t, t + dt)$ and having age within interval $(z, z + dz)$.

$q(x)$: = pdf of survival (not dependent on chronological time or age).

Assume $0 < t \leq z$ (study time is smaller than age)

A person who is prevalent at time t and is z years of age either

(i) Was prevalent at $t = 0$ and was $z - t$ years of age and had a forward recurrence time $\geq t$; or

(ii) became incident at time τ and was $z - (t - \tau)$ years of age and survived at least $t - \tau$ years.

(29) $P(t,z)dz = [P(0,z-t)Q_f(t) + \int_0^t I(\tau, z+\tau-t)Q(t-\tau)d\tau]dz.$

Similarly

(30) $M(t,z)dtdz = [P(0,z-t)q_f(t)dtdz$

$$+ \int_0^t I(\tau, z+\tau-t)q(t-\tau)d\tau]dtdz$$

$P(z|t)dz$ $=$ Prob age is within interval $(z, z+dz)$ conditional on having disease at time t.

$$P(z|t) = P(t,z)/P(t), \quad P(t) = \int_t^\infty P(t,z)dz$$

$m_p(t)$ $=$ Mean age of people who are prevalent at time t

$$\boxed{m_p(t) = \int_t^\infty zP(z|t)dx} = \frac{1}{P(t)} \int_t^\infty zP(z,t)dz$$

$$m_p(t) = \frac{1}{P(t)} \left\{ Q_f(t) \int_t^\infty zP(0, z-t)dz \right.$$

$$\left. + \int_t^\infty z \int_0^t I(\tau, z+\tau-t)Q(t-\tau)d\tau dz \right\}$$

Consider $\int_t^\infty zP(0, z-t)dz$

let $y = z - t$

$$\int_t^\infty zP(0, z-t)dz = \int_0^\infty (y+t)P(0,y)dy$$

$$= \int_0^\infty yP(0,y)dy + t\int_0^\infty P(0,y)dy$$

$$\int_t^\infty zP(0, z-t)dz = \boxed{P(0)m_p(0) + tP(0)}$$

$$
\begin{aligned}
\text{Consider} \quad & \int_t^\infty z \int_0^t I(\tau, z+\tau-t) Q(t-\tau) d\tau dz \\
x \quad & = z + \tau - t \\
& = \int_0^t Q(t-\tau) \int_\tau^\infty (x+t-\tau) I(\tau, x) dx d\tau \\
& = \int_0^t Q(t-\tau) [\int_\tau^\infty x I(\tau, x) dx + (t-\tau) \int_\tau^\infty I(\tau, x) dx] d\tau \\
& = \int_0^t Q(t-\tau) [I(\tau) A(\tau) + (t-\tau) I(\tau)] d\tau
\end{aligned}
$$

$$
\boxed{m_p(t) = \frac{P(0) Q_f(t) [m_p(0) + t] + \int_0^t I(\tau) [A(\tau) + t - \tau] Q(t-\tau) d\tau}{P(t)}}
$$

where $A(\tau) = \int_\tau^\infty \frac{zI(\tau, z) dz}{I(\tau)}$ = Average Age for those incident at τ.

Define

$$M(z|t)dz = \frac{M(t,z)}{M(t)} = \text{ Conditional on dying at } t$$

the prob. age is within $(z, z+dz)$.

$$m_M(t) = \int_t^\infty zM(z|t)dx = \text{ Average Age of Death for}$$

those dying $t, t+dt$

$$m_M(t) = \frac{1}{M(t)}\{P(0)q_f(t)[m_p(0)+t] + \int_0^t I(\tau)[A(\tau)+t-\tau]q(t-\tau)dz\}$$

$$
\begin{aligned}
\Delta(t) &= m_M(t) - m_P(t) \\
&= P(0)[m_p(0) + t]\left[\frac{q_f(t)}{M(t)} - \frac{Q_f(t)}{P(t)}\right] \\
&\quad + \int_o^t I(\tau)[A(\tau) + t - \tau]\left[\frac{q(t-\tau)}{M(t)} - \frac{Q(t-\tau)}{P(t)}\right] d\tau
\end{aligned}
$$

$$
\Delta(t) = 0 \quad \text{if} \quad \frac{q_f(t)}{M(t)} = \frac{Q_f(t)}{P(t)}, \qquad \frac{q(t-\tau)}{M(t)} = \frac{Q(t-\tau)}{P(t)} \quad \text{for all } \tau
$$

Suppose $\quad q(t) = \lambda e^{-\lambda t}$

$$
\begin{aligned}
\Rightarrow \qquad & q_f(t) = q(t) \\
& P(t) = mM(t)
\end{aligned}
$$

and $\Delta(t) = 0$ as $\quad \dfrac{q_f(t)}{M(t)} = \dfrac{Q_f(t)}{P(t)}$ and $\dfrac{q(t-\tau)}{M(t)} = \dfrac{Q(t-\tau)}{P(t)}$.

We have proved that a necessary condition for $\Delta(t) = m_M(t) - m_P(t) = 0$ is that $q(t)$ be exponential.

We now will prove that the sufficient condition for $\Delta(t) = 0$ is that $q(t)$ be exponential. Suppose $\Delta(t) = m_M(t) - m_P(t) = 0$. Then the following relations must hold

$$\frac{q_f(t)}{M(t)} = \frac{Q_f(t)}{P(t)} \quad \text{and} \quad \frac{q(t-\tau)}{M(t)} = \frac{Q(t-\tau)}{P(t)}$$

or rewriting

$$\boxed{\frac{q_f(t)}{Q_f(t)} = \frac{q(t-\tau)}{Q(t-\tau)} = \frac{M(t)}{P(t)}}$$

$$h(t-\tau) \ = \ \text{hazard function} \ = \ \frac{M(t)}{P(t)} \quad \text{for all } t \text{ and } \tau < t$$

Only satisfied if $h(t-\tau) = $ constant ind. of $t-\tau$. Therefore $h(t) = q(t)/Q(t) = \lambda$ and $\dfrac{M(t)}{P(t)} = $ constant $= \dfrac{1}{m} = \lambda.$

$$\Delta(t) = m_M(t) - m_P(t)$$

We have proved that the necessary and sufficient condition that the mean age of death equals the mean age of prevalent cases is that the survival distribution be exponential.

We will now find another expression for $\Delta(t) = m_M(t) - m_P(t)$. We had earlier shown

$$
\begin{aligned}
m_M(t) - m_P(t) &= \Delta(t) \\
&= P(0)[m_p(0) + t]\left[\frac{q_f(t)}{M(t)} - \frac{Q_f(t)}{P(t)}\right] \\
&+ \int_o^t I(t-y)[A(t-y) + y]\left[\frac{q(y)}{M(t)} - \frac{Q(y)}{P(t)}\right] dy
\end{aligned}
$$

Suppose	$P(t,z)$	$= P\ (\cdot, z)$	Independent of
	$I(t,z)$	$= I\ \ (\cdot, z)$	chronological
	$M(t,z)$	$= M\ (\cdot, z)$	time

$$\Rightarrow \quad m_P(t) = m_p \quad \text{for all } t \;\; \left(m_P(t) = \int_t^\infty zP(z|t)dz\right)$$

$$A(t) = A \qquad \text{for all } t \;\; \left(A(t) = \int_t^\infty zI(t,z)dz/I(t)\right)$$

Also let $t \to \infty$

$$\begin{aligned}
\Delta = \lim_{t\to\infty} \Delta(t) &= P(0)m_P \lim_{t\to\infty}\left[\frac{q_f(t)}{M} - \frac{Q_f(t)}{P}\right] \\
&+ P(0)\lim_{t\to\infty}\left[\frac{tq_f(t)}{M} - \frac{tQ_f(t)}{P}\right] \\
&+ I\int_0^\infty (A+y)\left[\frac{q(y)}{M} - \frac{Q(y)}{P}\right]dy
\end{aligned}$$

The first two terms $\to 0$ and since $P = mI,\ M = I$.

$$\Delta = \lim_{t\to\infty}\Delta(t) = I\left\{A\left[\frac{1}{M} - \frac{m}{P}\right] + \left[\frac{m}{M} - \frac{m_2/2}{P}\right]\right\} = m - \frac{\sigma^2 + m^2}{2m}$$

$$= m/2 - \sigma^2/2m = \frac{m}{2}(1 - C^2),\ \ C^2 = \sigma^2/m^2$$

Note: Mean of forward recurrence time is

$$L = \int_0^\infty x q_f(x) dx = \int_0^\infty \frac{xQ(x)dx}{m} = \frac{m}{2}(1 + C^2), \quad C = \sigma/m.$$

Since $L = \frac{m}{2}(1 + C^2) = m - \frac{m}{2}(1 - C^2) = m - \Delta$
and $\Delta = m_M(t) - m_P(t)$, L may be estimated by $m - \Delta$.

For stable disease model $P = mI$ and hence $\boxed{L = \frac{P}{I} - \Delta}$

This estimate does not require observing the forward recurrence time distribution.

We can also solve for σ^2 from the above relationship; i.e.
$\Delta = \frac{m}{2}(1 - C^2)$ resulting in $\sigma^2 = m(m - 2\Delta)$.

Note that since $\sigma^2 \geq 0$, we must have $\Delta \leq m/2$ which is a strict upper bound on Δ.

Problem Set

1. Forward Recurrence Time of Cohort Group when Age is Important

Suppose a cohort group having different ages is assembled at some point in chronological time. Let t_0 refer to the age of an individual in the cohort group. Define $q(t)$ as the pdf with disease and

$$
\begin{aligned}
P(t_o) &= \text{Probability an individual with age } t_0 \\
&\quad \text{has disease at time cohort group is formed.} \\[1em]
Q_f(v|t_0) &= P\{T_f > v|t_0\} \\
&= \text{Forward Recurrence time of tail distribution for} \\
&\quad \text{someone having disease when cohort group is formed} \\
&\quad \text{being of age } t_0.
\end{aligned}
$$

Assume incidence function only depends on age.

i. Find $P(t_0)Q_f(v|t_0)$ and $P(t_0)$.

Hint: Incidence of disease must be in the interval $(0, t_0]$

ii. Define

$$Q_f(v) = \frac{\int_0^\infty P(t_0)Q(v|t_0)dt_0}{\int_0^\infty P(t_0)dt_0}$$

This is the weighted average of the forward recurrence time distribution. Show that

$$q_f(v) = Q(v)/m \quad \text{or} \quad Q_f(v) = \frac{\int_v^\infty Q(x)dx}{m}$$

Hint: Change order of integration in numerator; denominator is equal to numerator with $v = 0$; i.e. $Q_f(0|t_0) = P\{T_f > 0|t_0\} = 1$ for all t_0.

(Problem Set continued)

2. Backward Recurrence Time Distribution with Age.

Use same notation as Problem 1. Define T_0 as random variable of backward recurrence time and

$$Q_b(u|t_0) = P\{T_0 > u|t_0\}$$

i. Show that

$$P(t_0)Q_b(u|t_0) = \int_0^{t_0-u} I(\tau)Q(t_0-\tau)d\tau$$

and thus $0 < T_b \leq t_0$ (Backward recurrence time cannot be larger than age).

ii. Show that

$$\frac{\displaystyle\int_0^\infty P(t_0)Q_b(u|t_0)dt_0}{\displaystyle\int_0^\infty P(t_0)dt_0} = Q_b(u) = \int_u^\infty \frac{Q(x)dx}{m}$$

Hence the weighted backward recurrence time distribution is the same as the weighted forward recurrence time distribution.

3. <u>Forward and Backward Recurrence Times</u>

Assume $I(t) = I$ (independent of age)

Using your results from problems 1 and 2, find $Q_f(v|t_0)$ and $Q_b(u|t_0)$. What do you conclude?

3.5 Application to Screening for Disease

$m_P(t)$ = mean age of prevalence cases at chronological time t

$m_M(t)$ = mean age of cases who die at chronological time t

$$\Delta(t) \quad = \; m_P(t) - m_M(t)$$

Model: No Disease $\longrightarrow$ Disease $\longrightarrow$ Death

$$S_0 \quad \longrightarrow \quad S_1 \quad \longrightarrow \quad S_2$$

Application: Early Detection of disease

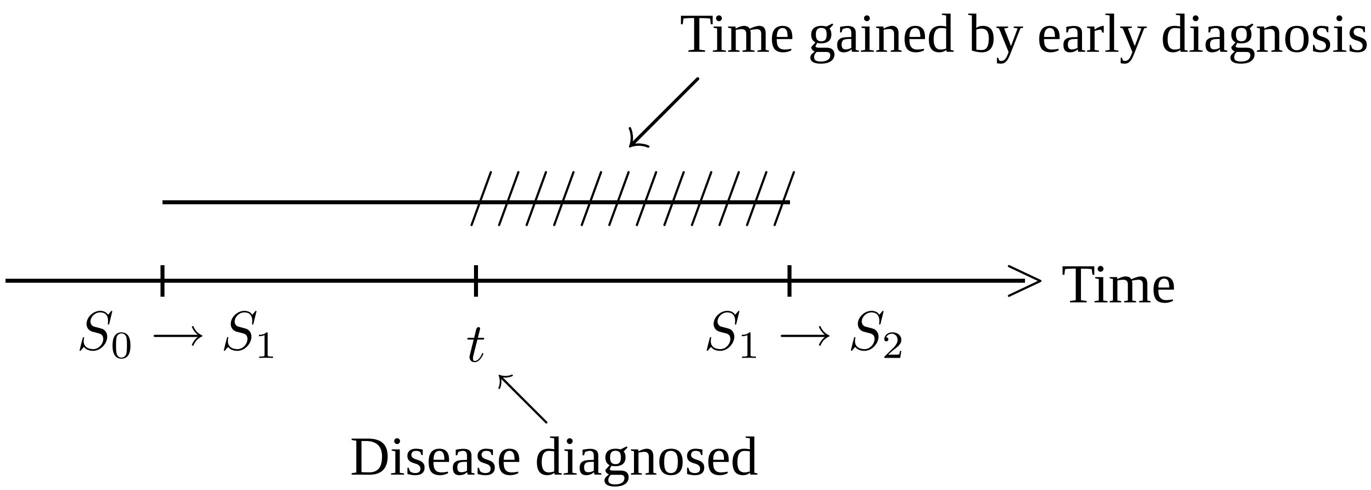
S_0 : No disease or disease which cannot be detected

S_1 : Pre-clinical state; i.e. has disease but is unaware of it.

S_2 : Clinical diagnosis

At time t, individuals are examined and prevalent cases are found.

$S_0 \to S_1 \to S_2$ (Progressive Disease)



$m_M(t) = m_2(t)$: mean age of cases which are clinically diagnosed at time t (normal medical care)

$m_P(t) = m_1(t)$: mean age of cases which are found by early detection exam at time t.

$$\Delta(t) = m_2(t) - m_1(t)$$

Example Early Detection of Breast Cancer Using Mammography and Clinical Exam (HIP Study)

$$
\begin{aligned}
1^{st}\text{ Year Results} &= \int_0^1 \Delta(t)dt \\
&= \text{average difference between ages of} \\
&\quad\ \text{prevalent (cases diagnosed by exam) and} \\
&\quad\ \text{cases diagnosed in control group.}
\end{aligned}
$$

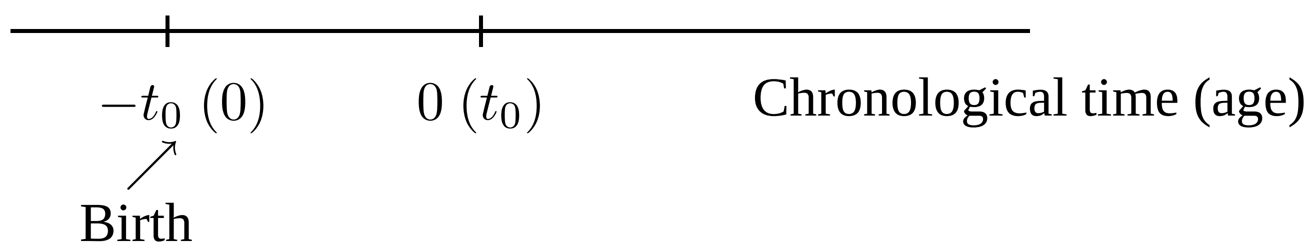
$$
\boxed{\begin{matrix}\text{R}\\\text{A}\\\text{N}\\\text{D}\end{matrix}}
\quad
\begin{matrix}\rightarrow \quad \text{screen} \\ \\ \rightarrow \quad \text{observe}\end{matrix}
$$

$m_1 = m_P = 53.8$ Years $\quad (n = 54)$

$m_2 =$ Average Age of Incidence $= 53.3$ Years $\quad (n = 45)$
(control group)

3.6. Recurrence Time Problems: Age Related

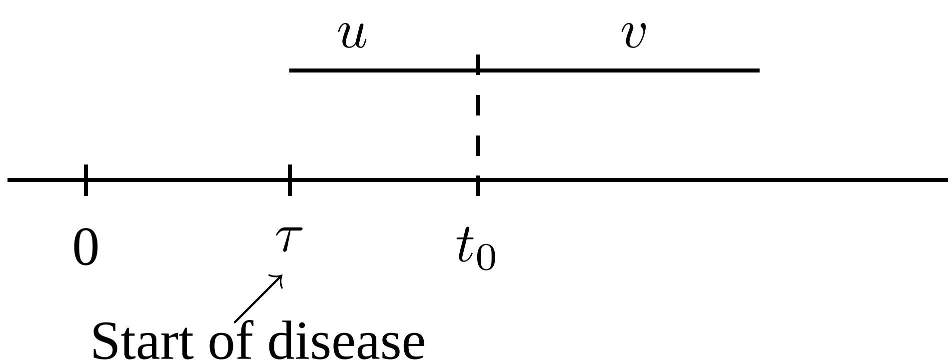
Assume incidence only depends on age. When a cohort group is assembled at chronological time $t = 0$, there will be a distribution of ages. Consider an individual having age t_0 at chronological time $t = 0$.



What are distributions of forward and backward recurrence times conditional on being age t_0 at chronological time $t = 0$?

a. <u>Forward Recurrence Time Distribution</u>

Let $T_f = r.v.$ for forward recurrence time and denote $Q_f(v|t_0) = P\{T_f > v|t_0\}$ where the condition t_0 refers to age at $t = 0$.



$$P(t_0)Q_f(v|t_0) = P\{\text{age } t_0 \text{ at } t = 0 \text{ and } T_f > v\}$$

$$P(t_0)Q_f(v|t_0) = \int_0^{t_0} I(\tau)Q(t_0 - \tau + v)d\tau.$$

Since $Q_f(0|t_0) = P\{T_f > 0|t_0\} = 1$

$$\boxed{P(t_0) = \int_0^{t_0} I(\tau) Q(t_0 - \tau) d\tau}$$

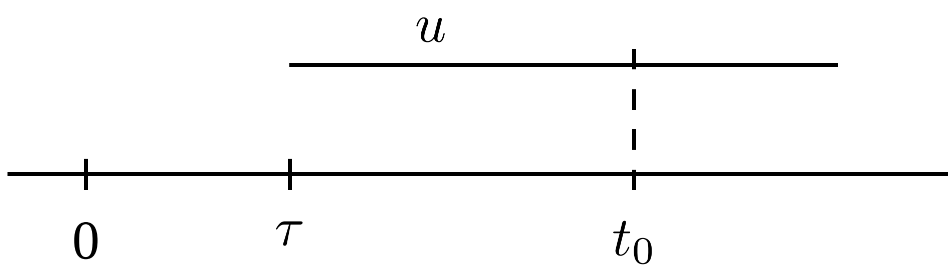
and

$$\boxed{Q_f(v|t_0) = \frac{\displaystyle\int_0^{t_0} I(\tau) Q(t_0 - \tau + v) d\tau}{\displaystyle\int_0^{t_0} I(\tau) Q(t_0 - \tau) d\tau}}$$

$\Rightarrow$ The forward recurrence time distribution depends on age.

b. Backward Recurrence Time Distribution

T_b: Backward Recurrence Time $\qquad Q_b(u|t_0) = P\{T_b > u|t_0\}$



If τ is time of transition $S_0 \to S_d$, then $T_b > u$ if

$t_0 - \tau > u \Rightarrow t_0 - u > \tau$.

$$\boxed{P(t_0)Q_b(u|t_0) = \int_0^{t_0-u} I(\tau)Q(t_0-\tau)d\tau, \quad 0 < u \le t_0}$$

$$\boxed{Q_b(u|t_0) = \frac{\displaystyle\int_0^{t_0-u} I(\tau)Q(t_0-\tau)d\tau}{\displaystyle\int_0^{t_0} I(\tau)Q(t_0-\tau)d\tau}}$$

Summary

$$Q_f(v|t_0) = \int_0^{t_0} I(\tau)Q(t_0 - \tau + v)d\tau / P(t_0)$$

$$Q_b(u|t_0) = \int_0^{t_0-u} I(\tau)Q(t_0 - \tau)d\tau \;/P(t_0) \qquad 0 < u \leq t_0$$

$$P(t_0) = \int_0^{t_0} I(\tau)Q(t_0 - \tau)d\tau$$

c. Special Cases:

Case 1: $Q(t) = e^{-\lambda t}$ (Exponential)

$$Q(t_0 - \tau + v) = e^{-\lambda(t_0 - \tau + v)} = e^{-\lambda(t_0 - \tau)} e^{-\lambda v} = Q(t_0 - \tau) Q(v)$$

$$Q_f(v|t_0) = Q(v) \frac{\int_0^{t_0} I(\tau) Q(t_0 - \tau) d\tau}{P(t_0)} = Q(v) = e^{-\lambda v}$$

But there are no simplifications for $Q_b(u|t_0)$.

Case 2: $I(t) = I$ (Constant Incidence)

$$Q_f(v|t_0) = I \int_v^{v+t_0} Q(y) dy \Big/ I \int_0^{t_0} Q(y) dy$$

$$\boxed{Q_f(v|t_0) = [Q_f(v) - Q_f(v + t_0)]/[1 - Q_f(t_0)]}$$

Case 2 (Cont'd) $I(t) = I$

$$\boxed{Q_f(v|t_0) = [Q_f(v) - Q_f(v + t_0)]/[1 - Q_f(t_0)]}$$

where
$$\begin{aligned} Q_f(v) &= \int_0^\infty Q(y)dy/m. \\ Q_b(u|t_0) &= \int_0^{t_0-u} I(\tau)Q(t_0-\tau)d\tau / P(t_0) \\ Q_b(u|t_0) &= I\int_0^{t_0-u} Q(t_0-\tau)d\tau \Big/ I\int_0^{t_0} Q(t_0-\tau)d\tau \\ &= \int_u^{t_0} Q(y)dy \Big/ \int_0^{t_0} Q(y)dy \end{aligned}$$

$$\boxed{Q_b(u|t_0) = [Q_f(u) - Q_f(t_0)]/[1 - Q_f(t_0)] \text{ for } 0 < u \le t_0}$$

$\Rightarrow$ If incidence is independent of age; i.e. $I(t) = I$ the backward and forward recurrence times are still dependent on age at t_0.

Case 3: Marginal Distribution of Forward and Backward Recurrence Time Distribution

$$P(t_0)Q_f(v|t_0) = \int_0^{t_0} I(\tau)Q(t_0-\tau+v)d\tau$$

Consider $\quad Q_f^*(v) = \dfrac{\displaystyle\int_0^\infty P(t_0)Q_f(v|t_0)dt_0}{\displaystyle\int_0^\infty P(t_0)dt_0}$

$$= \frac{\displaystyle\int_0^\infty \left[\int_0^{t_0} I(\tau)Q(t_0-\tau+v)d\tau\right] dt_0}{\displaystyle\int_0^\infty P(t_0)dt_0}$$

$$0 < \tau \leq t_0 < \infty$$

$(*)$ Reverse order of integration in numerator

$$
\begin{aligned}
Q_f^*(v) = &\quad \int_0^\infty I(\tau)\left[\int_\tau^\infty Q(t_0-\tau+v)dt_0\right]d\tau \Big/ \int_0^\infty P(t_0)dt_0 \\
= &\quad \int_0^\infty I(\tau)d\tau \cdot \int_v^\infty Q(y)dy \Big/ \int_0^\infty I(\tau)d\tau \cdot \int_0^\infty Q(y)dy \\
= &\quad \int_v^\infty Q(y)dy \Big/ m = Q_f(v)
\end{aligned}
$$

The weighted conditional forward recurrence time distribution is the same forward recurrence distribution when only choronological time is included.

Note: $$\int_0^\infty P(t_0)dt_0 = \int_0^\infty \int_0^{t_0} I(\tau)Q(t_0-\tau)d\tau dt_0$$

$$= \int_0^\infty I(\tau)\left[\int_\tau^\infty Q(t_0-\tau)dt_0\right]d\tau$$

$$= \int_0^\infty I(\tau)d\tau x \int_0^\infty Q(y)dy$$

Case 3: (continued)

$$P(t_0)Q_b(u|t_0) = \int_0^{t_0-u} I(\tau)Q(t_0-\tau)d\tau$$

Consider $Q_b^*(u) = \int_0^\infty P(t_0)Q_b(u|t_0)dt_0 \Big/ \int_0^\infty P(t_0)dt_0$

$$= \int_0^\infty \int_0^{t_0-u} I(\tau)Qt_0-\tau)d\tau dt_0 \Big/ \int_0^\infty P(t_0)dt_0$$

$$= \int_0^\infty \left[\int_u^{t_0} I(t_0-y)Q(y)dy\right] dt_0 \Big/ \int_0^\infty P(t_0)dt_0$$

$$0 < u \leq y \leq t_0 < \infty$$

Reversing order of integration

$$
\begin{aligned}
Q_b^* &= \int_\mu^\infty Q(y)\left[\int_y^\infty I(t_0 - y)dt_0\right]dy \Big/ \int_0^\infty P(t_0)dt_0 \\
&= \int_u^\infty Q(y)dy \cdot \int_0^\infty I(z)dz \Big/ \int_0^\infty Q(y)dy \cdot \int_0^\infty I(z)dz
\end{aligned}
$$

$$\boxed{Q_b^* = \int_u^\infty Q(y)dy/m = Q_f(u)}$$

$$\Rightarrow \quad Q_b^*(u) = Q_f(u) = Q_f^*(u)$$

Unconditional (weighted) Forward and Backward Recurrence times are the same.