Markov Model for the Lausanne University Cost-effectiveness Analyses on Smoking Cessation Interventions

This analysis was based on a cohort simulation. At the starting point of the analysis, the simulated population consisted entirely of smokers. At each time interval, the smoking related status of the cohort was reassessed according to the probabilities (defined below) of remaining in or moving to one of three possible states, smoker, ex-smoker, and dead. The evolution of the movement between different states among the cohort was modeled according to the Markov process.

A model is said to have the Markov property if current probabilities depend only on immediately preceding probabilities, that is if the current state is determined by nothing other than the transition probabilities associated with immediate past state. This signifies that the present situation is sufficient for determining the future situation, independent of the initial position and all other positions leading up to the present position.

Consider a set of discrete time random variables X_n with $n \in N = \{0,\ 1,\ 2,\ 3,\ \ldots\}$ that are to be assigned to discrete and mutually exclusive states S (in our case, for example, "smoker", "ex-smoker", and "dead"). Suppose now that one knows, for each pair of states $(i, j) \in S$ and for each time $n \in N$, the probability p_{ij} of being in state j at time $n + 1$, given that one is in state i at time n :

$$p_{ij} = P(X_{n+1} = j \mid X_n = i) \tag{1}$$

This is the conditional probability of making a transition from state i to state j over the course of time $[n,\ n + 1]$, also called transition probability between stages.

A Markov model is generally presented under the form :

$$\underbrace{\begin{bmatrix} i \\ j \end{bmatrix}_{t+1}}_{[\mathit{Vector\ of\ distribution}\ \mathbf{V}_{n+1}]} = \underbrace{\begin{bmatrix} p_{ii} & p_{ji} \\ p_{ij} & p_{jj} \end{bmatrix}}_{[\mathit{Matrix\ of\ transition}\ \mathbf{P}]} \underbrace{\begin{bmatrix} i \\ j \end{bmatrix}_{n}}_{[\mathit{Vector\ of\ distribution}\ \mathbf{V}_{n}]} \tag{2}$$

The vector $\mathbf{V}_n$ represents the distribution of the population across the states i and j at time n. Each line of the transition probability matrix $\mathbf{P}$ represents the probabilities of moving to the corresponding states. The sum of the values of each column is equal to 1, as the total population remains constant.

The distribution of $\mathbf{V}$ according to time n can be written : $\mathbf{V}_n = \mathbf{P}^n \mathbf{V}_0$. The steady state of the distribution is reached when : $\mathbf{V}_n = \mathbf{V}_{n+1} = \mathbf{P}\mathbf{V}_n \Rightarrow (\mathbf{I} - \mathbf{P})\mathbf{V}_n = 0$

In the case of a cohort simulation, the steady state of the model is known from the start, as all individuals in the cohort will ultimately move to the "dead" state. The "dead" state is called an "absorbing state", since the probability of moving from this state to another is null. In the case of our analysis, the interest is not in the steady state of the model, but in the progression toward that state.

With this in mind, we used the following state probabilities :

$$p_j(n) = p(X_n = j) \qquad (n \in N \ and \ j \in S) \tag{3}$$

The distribution of X_n may then be written as $\mathbf{p}(n) = [\cdots,\ p_i(n),\ p_j(n),\ \cdots]^T$, for which the sum of terms equals 1. One can then write :

$$\mathbf{p}(n) = \mathbf{P}^n \mathbf{p}(0) \tag{4}$$

A Markov chain can therefore be completely defined if the matrix of probabilities of transition between states, as well as the distribution of X_0, is known. In the case of our model, the initial distribution was known, as we considered a homogeneous population of smokers of a given age.

If the analysis is limited to two states – f (smoker) and e (ex-smoker) – the modeling is rather simple and takes the following form :

$$\begin{bmatrix} f \\ e \end{bmatrix}_{n+1} = \begin{bmatrix} p^*_{ff} & p^*_{ef} \\ p^*_{fe} & p^*_{ee} \end{bmatrix} \begin{bmatrix} f \\ e \end{bmatrix}_{n} \tag{5}$$

given that $p_{fe} = P(ex - smoker\ at\ n+1 \mid smoker\ at\ n)$

The complexity lies in integrating the third state – d (dead) – into the model, as this introduces mortality rates into the transition probability matrix. For an ex-smoker, the mortality risk depends largely on the number of years of abstinence. Therefore, it is necessary to integrate the states e_i where $i = 1,\ 2,\ \cdots,\ 24$ representing the number of years of abstinence, and the state n (non-smoker). An individual achieves state n after 25 years of continuous abstinence, at which time they are considered to have the same smoking-related mortality risk as never smokers.

The new vector becomes $V = \begin{bmatrix} f & e_1 & e_2 & e_3 & \cdots & e_{24} & n & d \end{bmatrix}^T$ and the transition probability matrix $\mathbf{P}$ expands to $(27X27)$.

However, the mortality rate also varies as a function of age. Therefore, it is necessary to introduce the age of the individuals into the model. In keeping with the standard Markov process, one should consider each possible age as a discrete category, subdivided between the 27 possible states. The transition probability matrix is then defined as the sum of the probability of moving to the next age category and the probability of dying, which is equal to 1, all the other cases in the matrix being nullified. The model can then be expressed with the aid of sub-matrices by age in the following way :

$$\begin{bmatrix} \vdots \\ \mathbf{V}_{45} \\ \mathbf{V}_{46} \\ \mathbf{V}_{47} \\ \mathbf{V}_{48} \\ \vdots \end{bmatrix}_{n+1} = \begin{bmatrix} \ddots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \cdots & 0 & 0 & 0 & 0 & \cdots \\ \cdots & \mathbf{P}_{45} & 0 & 0 & 0 & \cdots \\ \cdots & 0 & \mathbf{P}_{46} & 0 & 0 & \cdots \\ \cdots & 0 & 0 & \mathbf{P}_{47} & 0 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots \end{bmatrix} \begin{bmatrix} \vdots \\ \mathbf{V}_{45} \\ \mathbf{V}_{46} \\ \mathbf{V}_{47} \\ \mathbf{V}_{48} \\ \vdots \end{bmatrix}_{n} \qquad given \ \underbrace{P_a}_{27X27} \ and \ \underbrace{V_a}_{27X1} \tag{6}$$

If one considers that each iteration represents one year and that the simulation is carried out for a cohort of individuals aged 25-100, the transition probability matrix expands to $(2025X2025)$. This model is too cumbersome for efficient use, so given that the only non-nullified values are found on the diagonal of the sub-matrices $\mathbf{P}_a$, one can redefine the model as a series of transition sub-matrices. The model then takes the form :

$$\underbrace{\mathbf{V}_{a+1,\ n+1}}_{27X1} = \underbrace{\mathbf{P}_a}_{27X27} \underbrace{\mathbf{V}_{a,\ n}}_{27X1} \tag{7}$$

For the purpose of simplification, we assume that all ex-smokers who relapse do so after one year of abstinence, signified by :

$$p_{e_x e_z} = \begin{cases} 1 & if \ z = x + 1 \ and \ z > 2 \\ p_{e_x e_z} & if \ x = 1 \ and \ z = 2 \\ 0 & otherwise \end{cases}$$

$$p_{e_x f} = \begin{cases} p_{e_x f} & if \ x = 1 \\ 0 & otherwise \end{cases}$$

And as the state d is an absorbing state :

$$p_{di} = \begin{cases} 1 & if \ i = d \\ 0 & otherwise \end{cases}$$

The model is then written as :

$$\begin{bmatrix} f \\ e_1 \\ e_2 \\ e_3 \\ \vdots \\ e_{24} \\ n \\ d \end{bmatrix}_{n+1} =$$

$$\begin{bmatrix} p_{ff}(1-\omega_f) & p_{e_1f}(1-\omega_{e_1}) & 0 & 0 & \cdots & 0 & 0 & 0 \\ p_{fe_1}(1-\omega_f) & 0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & p_{e_1e_2}(1-\omega_{e_1}) & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & 1-\omega_{e_2} & 0 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 1-\omega_{e_{24}} & 1-\omega_n & 0 \\ \omega_f & \omega_{e_1} & \omega_{e_2} & \omega_{e_3} & \cdots & \omega_{e_{24}} & \omega_{e_n} & 1 \end{bmatrix} \begin{bmatrix} f \\ e_1 \\ e_2 \\ e_3 \\ \vdots \\ e_{24} \\ n \\ d \end{bmatrix}_n \tag{8}$$

given that :

$$\omega_i(age) = mortality\ rate \qquad with\ i \in S$$

$$\omega_{e_x} = (\omega_f^{(25-x)}\omega_n^x)^{\frac{1}{25}} \qquad with\ x \in [1,\ 2,\ \cdots,\ 24]$$

Equation (4) is now written as :

$$\mathbf{p}(n) = \left[\prod_{a=age\ at\ n=0}^{age\ at\ n} \mathbf{P}_a\right]\mathbf{p}(0) \tag{9}$$

This represents the probability of being in a given state at stage n for a cohort of smokers who have been followed since time 0.

To estimate the years of life saved by the pharmacological smoking cessation treatments, one must compare the evolution of two cohorts. The first cohort of smokers received only physician counseling, while the second cohort of smokers received counseling plus a pharmacological smoking cessation therapy. In each case, the intervention took place only once – at time 0 – and therefore influenced only the first transition probability matrix $\mathbf{P}_{age\ at\ n=0}$.

Equation (9) then becomes :

$$\mathbf{p}^{(c)}(n) = \mathbf{P}^{(c)}_{age\ at\ n=0}\left[\prod_{a=age\ at\ n=1}^{age\ at\ n} \mathbf{P}_a\right]\mathbf{p}(0) \tag{10}$$

for the cohort of smokers who received only cessation counseling (reference cohort), and :

$$\mathbf{p}^{(p)}(n) = \mathbf{P}^{(p)}_{age\ at\ n=0}\left[\prod_{a=age\ at\ n=1}^{age\ at\ n} \mathbf{P}_a\right]\mathbf{p}(0) \tag{11}$$

for the cohort of smokers who received cessation counseling plus a pharmacologic smoking cessation treatment (treatment cohort).

The sole difference between the evolution of these two cohorts rests in the first transition probability matrix $\mathbf{P}_{age\ at\ n=0}$, or more specifically, in the transition probabilities p_{fe_1} and p_{ff}, which also reflect the difference in probability of quitting smoking during the first year.

Finally, the expected number of life-years saved for a person to whom the treatment is proposed has been calculated as the difference between the probability of mortality for each cohort at each point in time, starting at time zero. This is formally signified by :

$$LYS = \sum_{n=0}^{n\ at\ age=100} (p_d^{(p)}(n) - p_d^{(c)})(1+r)^{-n} \tag{12}$$

In dividing the marginal cost of pharmacologic treatment by the result of Equation (12), which represents the marginal benefit of treatment, one obtains the cost per life year saved due to treatment.