Changing Cycle Lengths in State-Transition Models: Doing it the Right Way

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KEY POINTS

- The commonly used approach to convert between probabilities of different cycle lengths is not applicable to models with more than two states.
- The incorrect conversions can lead to bias in model outcomes such as total QALYs and costs.
- The correct approach for changing cycle length requires taking the root of the transition probability matrix.

INTRODUCTION

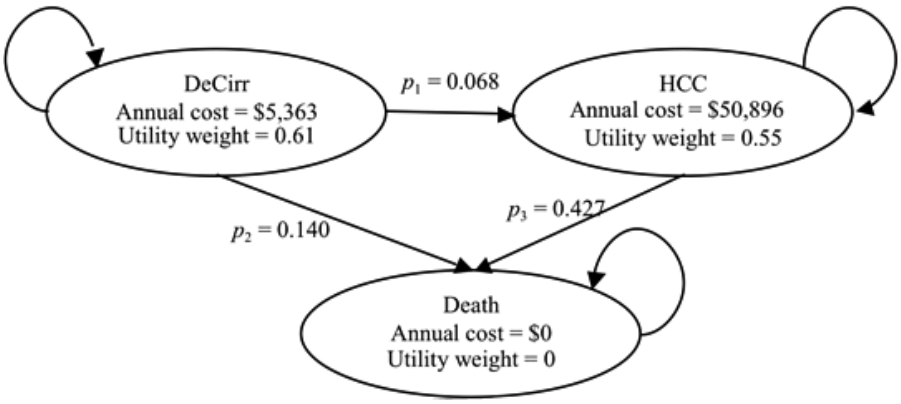
State-transition models (STMs) are commonly used in health care to inform funding and reimbursement decisions of new technologies, to optimize the use of limited resources, or to guide public health policies. These models typically simulate progression of events (e.g. disease stage, death) that evolve over time under some uncertainty. The common applications of STMs stipulate that time advances in fixed discrete steps known as cycles (e.g. month or year), and state transitions occur only at the beginning or end of a cycle.

A critical step in building STMs is the choice of cycle length. This is determined by a number of factors, including availability of data and frequency of clinical follow-up. For example, an annual cycle length may be appropriate for a model evaluating the cost-effectiveness of mammography screening; whereas, a weekly cycle length may be desired in modeling the cost-effectiveness of HIV treatment. The ISPOR-SMDM Modeling Good Research Practices Task Force report recommends that the cycle length should be short enough to represent the frequency of clinical events and interventions [1].

There is a tradeoff between shorter and longer cycle lengths. Because time runs continuously in real life, discretization of time in steps introduces bias in model outcomes. The bias arises mainly because discrete-tome STMs assume that state transitions occur only at fixed times, whereas in most biological and health care systems, as time runs continuously, state transitions can occur at any time. Use of half-cycle correction can reduce bias by making appropriate adjustments to outcomes in the first and last cycle. The bias, however, cannot be completely eliminated. The longer the cycle, the higher is the bias and vice versa [2]. Therefore, shorter cycles in STMs can reduce the bias by simulating events closer to the real life.

While shorter cycles reduce bias, they increase the computational burden. This sometimes can impose challenges in conducting probabilistic sensitivity analysis (PSA) or value of information (VOI) analysis in individual-level STMs such as Markov microsimulation or discrete-event simulation models. Increasing the cycle length can improve efficiency by substantially reducing the computational time needed for PSA or VOI analysis.

Figure 1: Markov model showing annual transition probabilities, costs and utilities associated.



Depending upon the situation, modelers may need to either increase or decrease the cycle length. Changing cycle lengths require changes in the following model parameters: costs, discount rates, and transition probabilities. In this article, we present an approach of shortening the cycle length of a given model from annual to t cycles in one year. The same approach is also applicable when cycle lengths needs to be increased to a longer time frequency.

The annual cost, c_i of state i can be converted to t-th cycle cost as $\tilde{c}_i = c_i/t$. There is no need to change health state utilities because they do not have time dimension. The adjusted discount rate, $\tilde{r} = (1+r)^{1/t}-1$; where r is the annual discount rate.

The commonly used approach of converting transition probabilities to a different cycle length in STMs is to first convert transition probabilities into rates, divide rates according to the new cycle length, and convert rates back into new probabilities [2]. For example, an annual probability p can be converted into a probability $\tilde{p}$ of $1/t$ per year according to: $\tilde{p} = 1-(1-p)^{1/t}$. This approach, however, is not applicable to models with more than two states [3,4] because it ignores competing risk among states. Next, we show that the above approach leads to bias in model outcomes using a simple Markov model (Fig. 1).

TRADITIONAL APPROACH

We present a simple 3-state STM of an advanced-stage liver disease that progress from decompensated cirrhosis (DeCirr) to hepatocellular carcinoma (HCC) or death. The annual transition probabilities, health-state utilities, and costs are shown in Figure 1. The transition from one state to another during a single year is given by the following transition probability matrix:

	DeCirr	HCC	Death
DeCirr	0.700	0.068	0.140
HCC	0.000	0.573	0.427
Death	0.000	0.000	1.000

This can be rewritten in matrix notation as:

$$P = \begin{pmatrix} 0.700 & 0.068 & 0.140 \\ 0.000 & 0.573 & 0.427 \\ 0.000 & 0.000 & 1.000 \end{pmatrix}.$$

The first row presents transitions from DeCirr state, i.e. from left to right, the probability of staying in DeCirr, moving to HCC, and moving to Death

state. Similarly, the second and third row present transitions from HCC and Death, respectively. Using the traditional approach, we convert the off diagonal elements of the annual transition probability matrix into monthly probabilities as follows: $\tilde{p} = 1-(1-0.068)^{1/12} = 0.0059$, $\tilde{p}_2 = 1-(1-0.140)^{1/12} = 0.0125$, and $\tilde{p}_3 = 1-(1-0.427)^{1/12} = 0.0453$.

We present the Markov trace of 1,000 people starting in DeCirr at time 0 (Table 1). Using monthly transition probabilities from above, the outcomes at *n*-th cycle represent the number of patients who transitioned to either HCC or Death in *n* months. At the 12th cycle (i.e. end of 1 year), we found that 49 patients developed HCC and 150 patients died; using the original probabilities with annual cycle length, however, 68 patients developed HCC (1000 * 0.068) and 140 patients transitioned to Death state (1000 * 0.140). Therefore, the traditional formula to convert transition probabilities to a different cycle did not provide the same results. In fact, the use of the traditional formula led to a different Markov chain (i.e. one with the same health states but different transition probability matrix).

EIGENDECOMPOSITION APPROACH

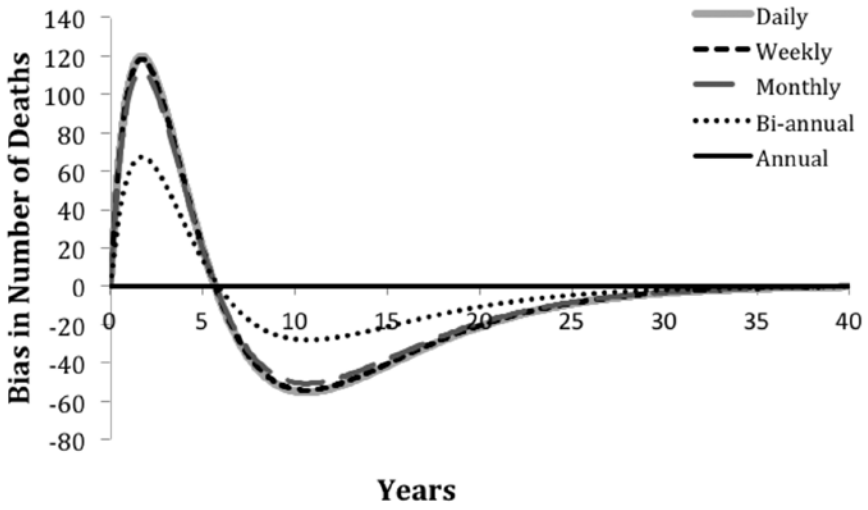
We first discuss some of the properties of the state transition probability matrix *P*. The state transition probability matrix must satisfy the following conditions: each element of the matrix must be non-negative (because transition probabilities cannot be negative); and the elements of each row should sum up to one (because the probability of staying or leaving any one state should equal to one). Any matrix that satisfies the above two properties is called a *stochastic matrix*.

Next, we present an approach for converting the annual transition probability matrix into a shorter cycle length. We find the monthly transition probabilities ***by taking the 12-th root of the annual transition probability matrix***, *P*. In general, converting an annual cycle length to a shorter, *n*-th cycle will require finding the *n*-th root of the annual transition probability matrix. Similarly, converting an annual cycle length to a longer, *m*-th cycle (e.g. 5-year cycle) would require taking *m*-th power the annual transition probability matrix. The root of the matrix is found by eigendecomposition approach. Decomposing *P* into $P = V * D * V^{-1}$ where *D* is a diagonal matrix consisting of eigenvalues of matrix P and V is the associated matrix of eigenvectors. This is called the eigendecomposition of the matrix P then $P^{1/t} = V * D^{1/t} * V^{-1}$ This yields:

$$\tilde{P} = \begin{pmatrix} 0.7 & 0.068 & 0.140 \\ 0 & 0.573 & 0.427 \\ 0 & 0 & 1 \end{pmatrix}^{1/12} = \begin{pmatrix} 0.909 & 0.08 & 0.011 \\ 0 & 0.955 & 0.045 \\ 0 & 0 & 1 \end{pmatrix}.$$

Performing eigun decomposition or taking the root of a matrix are complex matrix operations, but can be easily achieved using most modern mathematical computing packages such as R, MATLAB® and Mathematica®.

Figure 2. Bias in total number of deaths using traditional method to convert transition probabilities to shorter cycle lengths.



Next, we present a trace of cohort simulation of 1000 patients for 12 months using the updated monthly transition probabilities (Table 2). The Markov trace at 12th cycle matches those obtained using 1-step annual probabilities. This confirms that we did not alter the underlying Markov process.

We also plotted the bias in the model outcomes when the traditional method was used to convert annual transition probabilities to monthly transition probabilities. Figure 1 shows the bias in number of deaths with cycle run time (in years). The bias was defined as the difference in the number of deaths between traditional versus eigendecomposition approach. The incorrect approach overestimated the number of deaths until year 6 and underestimated the number of deaths after year 6. We also presented bias with bi-annual, monthly, weekly and daily cycle length (Fig. 1). Interestingly, the bias increased as the cycle length decreased. In addition, we estimated bias in cumulative incidence of HCC, total costs and QALYs using traditional approach, which were estimated as –35%, –17% and 0.5%, respectively. The negative bias implies that the model with traditional approach underestimated the corresponding outcome.

CHALLENGES

While the eigendecomposition approach successfully finds a n-th root of a matrix, many previous studies have shown that it does not guarantee that the resulting matrix root is always stochastic (i.e. some of the elements of the matrix may be negative) [5,6]. The problem of finding stochastic roots of general Markov transition matrices is a fundamental limitation, and is connected to a deep problem in the literature known as the embeddability problem. If the matrix is non-stochastic, it can be converted to a stochastic matrix using one of the several numerical methods; one approach is to add the negative values back to all entries of the same row, proportional to their absolute value. Alternatively, one can use an iterative approach that approximates the non-stochastic matrix to the closest stochastic root of the matrix [7].

Table 1. Markov trace of 1,000 patients starting in decompensated cirrhosis state with traditional conversion approach

Annual

Cycle	DeCirr	HCC	Death
0	1,000	0	0
1	**792**	**68**	**140**

Monthly

Cycle	DeCirr	HCC	Death
0	1,000	0	0
1	982	6	12
2	964	11	25
3	946	16	38
4	929	21	50
5	912	26	63
6	895	30	75
7	878	34	88
8	862	37	100
9	847	41	113
10	831	44	125
11	816	47	138
12	**801**	**49**	**150**

The second issue with finding the root of a matrix is that the root may not always be unique. This implies that a Markov chain can be represented by two different stochastic matrices. Essentially, the limitation arises from trying to identify which Markov processes arise from shorter time-cycle processes. We note that even the theoretical literature on finding stochastic n-th roots and identifiability is relatively scarce. More theoretical advances are needed before such problems can be addressed in a systematic way.

DISCUSSION

In this article, we highlighted methods to change the cycle length of a state-transition model. We >>

Table 2. Markov trace of 1,000 patients starting in decompensated cirrhosis state with eigendecomposition approach

Annual Cycle	DeCirr	HCC	Death
0	1,000	0	0
1	**792**	**68**	**140**
Monthly Cycle	**DeCirr**	**HCC**	**Death**
0	1,000	0	0
1	981	8	11
2	962	16	22
3	943	23	34
4	925	29	45
5	907	36	57
6	890	41	69
7	873	47	81
8	856	52	92
9	840	56	104
10	823	60	116
11	808	64	128
12	**792**	**68**	**140**

showed that the traditional approach of converting transition probabilities to different cycle lengths is not correct. We further provided the correct method based on taking the root of a transition probability matrix to change cycle lengths. Using a simple example, we showed that incorrect conversions can lead to bias in model outcomes. In general, shorter cycle lengths provide better approximations of model outcomes; however, it may not be the case if incorrect transformations are used to convert transition probabilities into shorter cycle lengths.

For simplicity, we only focused on constant transition probabilities. In practice, however, almost all state-transition models use non-constant probabilities. Further research is needed on application of eigendecomposition of approach to time-varying probabilities.

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