A Appendix: A comparison of classical methods

In recent years we have witnessed an interesting debate: HCC vs. the life-table method (LT). Even though the controversy seems to be closed after the insightful analyses of Elbasha and Chhatwal [1, 2], we hope that this appendix can still shed some light on the issue. Here "classical methods" are those not based on numerical integration.

A.1 Absence of within-cycle transitions

The usual way of presenting discrete-time Markov models states that transition can only occur at the boundaries between cycles, i.e., at $t = 0, \tau, 2\tau, 3\tau \ldots$ It implies that the state of the system does not change within a cycle. When transitions are not allowed at $t = 0$, most authors say that "transitions occur at the beginning of each cycle". In this case the probability in the interval $[i\tau, (i+1)\tau)$ is $P_i(s)$. With these assumptions and approximations, the total cost is

$$C_E = \tau \sum_{i=0}^{h-1} \sum_{s} P_i(s) \cdot c_i(s) \cdot \gamma(i\tau) \ , \tag{A.1}$$

where the subindex E stands for "end". When the instantaneous cost function (cf. Eq. 1) decreases monotonically, this assumption leads to an overestimation of the total cost, i.e.,C_E is higher than the true cost, C, given by Equation 2.

When transitions at $t = 0$ are allowed, it is said that "transitions occur at the beginning of the cycle". Therefore the probability in the interval $(i\tau, (i + 1)\tau]$ is $P_{i+1}(s)$ and the total cost is

$$C_B = \tau \sum_{i=0}^{h-1} \sum_{s} P_{i+1}(s) \cdot c_i(s) \cdot \gamma(i\tau) \ , \tag{A.2}$$

where the subindex B stands for "beginning". When the cost function decreases monotonically, this assumption leads to an underestimation of the total cost, so that we have $C_B < C < C_E$.

A.2 The half-cycle correction

In an attempt to obtain a better approximation, [3] introduced the half-cycle correction, which consists in including a cycle of length $\tau/2$ at the beginning of the process, in which no transition has yet occurred, and another cycle of the same length at the end, so that the total duration of the process is $h\tau$. This is equivalent to assuming that the transitions occur at the time points $\{0.5\tau, 1.5\tau, 2.5\tau, \ldots\}$, i.e., halfway through each cycle [3, 4]. The approach is justified in the literature as a method for approximating the *state-occupancy probabilities*—the vertical axis in Figure 10 in [3], reproduced as Figure 3 in [4], clearly shows it. Those figures also show that the HCC still assumes that transitions only occur at certain points in time, which makes the occupancy probability constant between consecutive points.

The approximate state-occupancy probabilities are multiplied by the cost of each state to compute the cost accrued in each interval. This calculation makes sense when the cost is constant, but encounters a problem when there is an abrupt discontinuity at the boundary between two intervals. In the HIV example there is a discontinuity at $t = 2\tau$, so it is not clear which costs this method should use for the second interval, which extends from 1.5τ to 2.5τ .

In practice, HCC is implemented using (the equivalent of) Equation 5, whose first term on the right-hand side can be interpreted as the cost accrued in a cycle of length $\tau/2$ in which no transition has yet occurred. However, that equation stems from applying the trapezoidal rule the *instantaneous costs*, not to the occupancy probabilities. This inconsistency was severely criticized by [5, 6], who proposed the life-table method as a better alternative.

A.3 The life-table method

This method, being consistent with the arguments put forward by the advocates of HCC, first estimates the average state-occupancy probabilities inside each cycle by averaging the

probabilities at its boundaries and then calculates the costs:

$$\int_{i\tau}^{(i+1)\tau} c(t) \cdot dt \approx \sum_{s} \frac{P_i(s) + P_{i+1}(s)}{2} \cdot c_i(s) \cdot \gamma(i\tau) \cdot \tau \ , \tag{A.3}$$

where $c_i(s)$ is the cost inside the i-th interval, again assumed to be constant. This implies that

$$C_{LT} = \sum_{i=0}^{h-1} \sum_{s} \frac{P_i(s) + P_{i+1}(s)}{2} \cdot c_i(s) \cdot \gamma(i\tau) \cdot \tau \ , \tag{A.4}$$

This is called the *life-table method* because it is based on the procedure that demographers use it to estimate life expectancy [5].

It is easy to check that

$$C_{LT} = \frac{C_E + C_B}{2} \ .$$

We have already seen that when the total-cost function decreases monotonically, C_E is an overestimation of the true cost and C_B is an underestimation, so their arithmetic mean, C_{LT}, is expected to be closer to the true value than if we assumed that all transitions occur either at the beginning or at the end of each cycle.

Please note that this method is insensitive to discontinuities that occur at the boundary between intervals, which explains the small error it returned for the HIV model—see Table 1.

A.4 A comparison of HCC and LT

The justification of HCC implicitly assumes that the instantaneous cost for each state is time independent; this allows us to write $c(s)$ instead of $c(s,t)$. Under this assumption, HCC computes exactly the same value as the trapezoidal rule, C_{TR}. Equation 5 stems from Equation 4, which can be rewritten as

$$\int_{i\tau}^{(i+1)\tau} c(t) \cdot dt \approx \sum_{s} \frac{P_i(s) \cdot \gamma(i\tau) + P_{i+1}(s) \cdot \gamma((i+1)\tau)}{2} \cdot c(s) \cdot \tau \ . \tag{A.5}$$

Comparing this expression with Equation A.3, we can see that they only differ in the way of applying the discounts.[1] When the cycle length τ is short or the discount function decreases slowly, then $\gamma(i\tau) \approx \gamma((i+1)\tau)$ and $C_{LT} \approx C_{TR}$. The main difference is that Equation A.5, implicitly used by the trapezoidal rule and HCC, applies the correct discount at each boundary of the cycle, while LT applies the same discount, $\gamma(i\tau)$, from the beginning to the end of the cycle.

Therefore we disagree with *some* of the arguments claiming the superiority of LT over HCC.[2] For example, Barendregt [5] argued that the standard HCC method is incompatible with discounting. Naimark et al. [8], who were initially strong advocates of the HCC, finally agreed with him. However, the computation of C_{TR} clearly uses the discounted costs (cf. Eqs. 1 and 5).

Barendregt [5] also said: "I know of very few relevant Markov models in medical decision making where QALY weights and unit costs are constant across all cycles". However, HCC does not require that the cost function $c(t)$, given by Equation 1, be constant. In our analysis, the derivation of Equation 5 only required that $c(s,t)$ be constant for every state s, as it is in many models—the HIV examined in this paper is rather an exception.

In turn, [8] said that "the standard approach to the HCC assumes that the state membership curve is declining and monotonic." However, when Equation 5 is justified as the application of the trapezoidal rule, it does not require that assumption.

In summary, we claim that there was nothing wrong in the application of the HCC in the absence of discontinuities. On the contrary, C_{TR}, given by Equation 5, is generally more accurate than C_{LT} , given by A.4. The problem was in the way of explaining and justifying the method.

[1] Therefore, the assertion of [2] that the trapezoidal rule gives the same result as LT is true only when there is no discount. In fact, Section 9.2.1 in [7] shows an example in which the two methods yield different numerical results.

[2] In these remarks we agree with [1, 2], except for minor details that do not deserve a discussion here.

References

[1] E. H. Elbasha and J. Chhatwal. Myths and misconceptions of within-cycle correction: a guide for modelers and decision makers. *Pharmacoeconomics*, 34:13–22, 2016.

[2] E. H. Elbasha and J. Chhatwal. Theoretical foundations and practical applications of within-cycle correction methods. *Medical Decision Making*, 36:115–131, 2016.

[3] F. A. Sonnenberg and J. R. Beck. Markov models in medical decision making: A practical guide. *Medical Decision Making*, 13:322–339, 1993.

[4] D. M. J. Naimark, M. Bott, and M. Krahn. The half-cycle correction explained: two alternative pedagogical approaches. *Medical Decision Making*, 28:706–712, 2008.

[5] J. J. Barendregt. The half-cycle correction: banish rather than explain it. *Medical Decision Making*, 33:961–970, 2009.

[6] J. J. Barendregt. The life table method of half-cycle correction: getting it right. *Medical Decision Making*, 29:500–502, 2014.

[7] A. M. Gray, P. M. Clarke, J. Wolstenholme, and S. Wordsworth. *Applied Methods of Cost-effectiveness Analysis in Healthcare*. Oxford University Press, New York, 2011.

[8] D. M. J. Naimark, N. N. Kabboul, and M. D. Krahn. The half-cycle correction revisited: redemption of a kludge. *Medical Decision Making*, 33:961–970, 2013.