

Adding noise to Markov cohort models

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Background

- Decision models have been used in various applications from clinical decision making to health technology assessment
- A Markov state-transition cohort model (MSTCM) [Beck and Pauker 1983] is often used to simulate the prognosis of an individual which is structured as transitions across various health states over time in discrete (equal) time steps
- A MSTCM generates only the average of population counts across states (Markov trace) [Iskandar 2018]
- To estimate the variance of a Markov trace, a microsimulation approach is often utilized, however it may be computationally expensive

Objective

To introduce a stochastic differential equation (SDE) model as an alternative modeling framework to MSTCM which efficiently estimates variance and has a simple mathematical representation

Stochastic cohort model [Iskandar 2018]

- A stochastic MSTCM where each individual follows a Markov chain on a finite set of mutually exclusive and completely exhaustive health states: $\mathbb{S} = \{S_1, S_2, \dots, S_s\}$, is defined as a stochastic process, $\{\mathbf{N}(t)\}_{t \geq t_0}$ where s is the number of states and t is time greater than some initial time t_0

- $\mathbf{N}(t)$ represents a random Markov trace:

$$\mathbf{N}(t) = [N_1(t) \ N_2(t) \ \dots \ N_s(t)],$$

in which $\mathbf{N}(t) = \mathbf{n}$ belongs to the set of counting numbers

- An individual transitioning from S_k to S_l is denoted by the i -th transition R_i where $k, l \in \{1 \dots, s\}$ and $i \in \{1 \dots, r\}$ (r is the total number of transitions and s^2 is the maximum number of possible transitions or $r \leq s^2$).
- A transition R_i occurring with a probability $\nu_i(\mathbf{n}, t)\tau$ in a time step τ alters the current state $\mathbf{N}(t) = \mathbf{n}$ to:

$$\mathbf{N}(t + \tau) = \mathbf{n} + \delta_i$$

- $\delta_i = \mathbf{e}_l - \mathbf{e}_k$ is a vector representing the change in Markov trace; where $\mathbf{e}_j$ is the j -th column of an identity matrix of size s
- $\nu_i(\mathbf{n}, t) = c_i(t)h_i(\mathbf{n})$ is a propensity function representing the intensity of i -th-transition with a transition rate, $c_i(t)$

Stochastic differential equation [Iskandar 2019]

- An SDE representation of a random Markov trace is given by:

$$d\mathbf{N}(t) = \mathbf{A}(\mathbf{n}, t)dt + \mathbf{B}(\mathbf{n}, t)d\mathbf{W}(t)$$

or

Change in Markov trace = Average + Variance (Noise)

- $\mathbf{W}(t)$ is a s -dimensional Wiener process
- $\mathbf{A}(\mathbf{n}, t)$ is a drift vector:

$$E[\Delta\mathbf{N}(t)] = \mathbf{v}(\mathbf{n}, t)d\tau = \mathbf{A}(\mathbf{n}, t)dt$$

- $\mathbf{B}(\mathbf{n}, t)$ is a diffusion matrix:

$$\begin{aligned} \sum (\Delta\mathbf{N}(t)) &= E[\Delta\mathbf{N}(t)\Delta\mathbf{N}(t)'] - E[\Delta\mathbf{N}(t)]E[\Delta\mathbf{N}(t)'] \\ &\approx \begin{pmatrix} \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{i1}^2 & \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{i1}d_{i2} & \dots & \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{i1}d_{is} \\ \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{i2}^2 & \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{i2}^2 & \dots & \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{i2}d_{is} \\ \vdots & \vdots & \ddots & \vdots \\ \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{is}^2 & \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{is}d_{i2} & \dots & \sum_{i=1}^r \nu_i(\mathbf{n}, t)d_{is}d_{is} \end{pmatrix} \\ &= \mathbf{B}(\mathbf{n}, t)dt \end{aligned}$$

- $\mathbf{v}(\mathbf{n}, t)$ is a $1 \times r$ vector of propensities where the i -th column corresponds to the propensity function for the transition i
- $\mathbf{d}$ is an $r \times s$ matrix of δ s where the i -th row corresponds to the vector of changes associated with the transition i

Algorithm for developing an SDE

- S1** determine the state space ($\mathbb{S}$), all possible transitions (R_i) among the states in $\mathbb{S}$, and their corresponding propensities, ν_i
- S2** construct vector of propensities, $\mathbf{v}(\mathbf{n}, t)$, and the matrix of changes, $\mathbf{d}$;
- S3** calculate the drift vector and the diffusion matrix;
- S4** choose a numerical method for approximately solving the SDE by generating a Markov trace: $\hat{\mathbf{N}}(t)_{[t_0, T], k}^\tau$ where τ , $[t_0, T]$, and k , refer to the numerical method time step, the time interval of analysis, and the index of the samples, respectively;
- S5** and estimate a quantity of interest as a function of the Markov trace(s), i.e., $q = f(\hat{\mathbf{N}}(t)_{[t_0, T], k}^\tau)$, where: q is the quantity of interest and f is a mapping from the Markov trace to the quantity of interest.

Application of an SDE

- We developed an SDE model for a published Markov decision model [Alarid-Escudero 2017] which estimates the life expectancy associated with receiving chemotherapy among 55 year-old breast cancer patients
- Health states: healthy (S_H), healthy with treatment toxicity (S_T), metastasis (S_M), metastasis with treatment toxicity (S_{TM}), death due to treatment toxicity, death due to metastasis (S_{DM}), and death due to other causes (S_{DO})
- The 1×7 drift vector:

$$\mathbf{A}(\mathbf{n}, t) = \begin{pmatrix} -(c_T + c_M + c_{DO}(t))N_H(t) \\ c_T N_H(t) - (c_M + c_T + c_{DO}(t))N_T(t) \\ c_M(N_H(t) + N_T(t)) - (c_T + c_{DM} + c_{DO}(t))N_M(t) \\ c_M(N_T(t) + N_M(t)) - (c_{DT} + c_{DM} + c_{DO}(t))N_{TM}(t) \\ c_{DT}(N_T(t) + N_{TM}(t)) \\ c_{DM}(N_M(t) + N_{TM}(t)) \\ c_{DO}(t)(N_H(t) + N_T(t) + N_M(t) + N_{TM}(t)) \end{pmatrix}$$

- The 4-th column of 7×7 diffusion matrix:

$$\mathbf{B}_4(\mathbf{n}, t) = \begin{pmatrix} 0 \\ -c_M N_T(t) \\ -c_T N_M(t) \\ c_M N_T(t) + c_T N_M(t) + (c_{DT} + c_{DM} + c_{DO}(t))N_{TM}(t) \\ -c_{DT} N_{TM}(t) \\ -c_{DM} N_{TM}(t) \\ -c_{DO}(t)N_{TM}(t) \end{pmatrix},$$

- We applied the Euler-Maruyama method to generate 10000 sample paths of a cohort of 1000 55 year-old women, using a 1-year time step

Microsimulation vs. SDE

- As a comparison, we also developed a microsimulation model for the published cohort model [Alarid-Escudero 2017]
- The life expectancies for the chemotherapy arm were estimated to be 16.9 (standard deviation: 0.42) and 17.2 (standard deviation: 0.41) for the SDE and microsimulation methods, respectively
- The SDE model required a considerably less computational time than the microsimulation model to generate the 10000 Markov traces: **1.5 vs. 51.9 minutes**
- The codes for both models are available on: <https://github.com/rowaniskandar/SDE>

Conclusions

An SDE method expands the functionality of cohort models in practice by providing information on the variance of the process, decreasing computational time of Monte Carlo methods, and without necessitating additional data beyond what is usually required for developing cohort models

References

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