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Grischott, Thomas ; Valeri, Fabio ; Falcato, Luis

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Sample Size Calculation using Markov Chains for a One-Arm Study of Heroin Administration Routes

(Short Title: Sample Size Calculation using Markov Chains)

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Abstract

Sample size calculations for trials with time-to-event outcomes are usually based on the assumption that an event - prototypically death in survival analysis - occurs only once per sample unit. However, events like changes in disease status or switches between treatment modalities may repeat over time. In trials with such outcomes, standard sample size formulae derived from the classical survival time models are not applicable. Instead, modeling the repeating transition events must precede the actual sample size calculation.

Markov chains are an obvious choice to model transitions. Accordingly, in order to determine the sample size for a one-arm feasibility and acceptability study of a new drug intake route, we model switches of administration routes by a homogeneous finite-state, higher order Markov chain. Assumptions about its transition matrix translate into multinomial distributions of the preferred administration routes at given points in time. From these distributions, the required sample size can then be calculated according to the study's specific question.

In this manuscript, we first introduce the method for the case of drug intake preferences, before we briefly discuss how the proposed method can also be used for power-based sample size calculation in multi-arm trials.

Keywords: Sample size, Markov chain, survival analysis, recurrent event model, study design

1. Introduction

1.1 Background

Survival analysis can be understood as the analysis of time-to-event data where events are transitions from one initial state (alive) to another absorbing state (dead). Since such transitions are irreversible, the same event can only happen once per sample unit. Popular models for this kind of data are the exponential model and Cox's proportional hazards model, and formulae for sample size calculations have been developed for two-arm problems under both models (Chow et al. 2017; Lachin 1981; Schoenfeld 1983). Obviously, these formulae are not applicable in situations when transitions are reversible and therefore the same transition event can occur repeatedly for the same unit.

Sample size formulae for studies with recurrent transition events must necessarily rest on a model of these transition events. Several recurrent event models have been proposed (Wei et al. 1989; Andersen et al. 1982; Prentice et al. 1981) and sample size formulae derived (Rebora et al. 2012; Tang et al. 2019). However, these models focus on rates or numbers of events rather than event times or states between the transition events, and their model assumptions can be too restrictive.

Markov processes are an obvious and more flexible class of models for situations with several states and possibly reversible transitions (Tan 1981; Barbu et al. 2004). For example, a Markov process could model disease progression and retrogression (i.e. healing) through states that correspond to levels or combinations of medical impairments. Markov models have also been used to describe transitions among different treatment modalities (e.g. chemo-, radio-, and hormonal therapy for breast cancer patients) (Pérez-Ocón 2001).

In the present paper, we describe how modelling recurrent events with a (higher order) Markov chain (MC) can be employed in the context of sample size calculation for a one-arm feasibility and acceptability study of a new drug administration route.

1.2 Study Description and Sample Size Rationale

Heroin-assisted treatment (HAT) has become an established and effective treatment option for opioid-dependent persons who do not respond to conventional opioid agonist treatment (OAT) with oral

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3 opioids (Strang et al. 2015). HAT includes the provision of pharmaceutical heroin (diamorphine, DAM)
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5 which is orally ingested (PO) or intravenously injected (IV) under clinical supervision.
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7 Reflecting the increasing intranasal (NAS) use of street heroin (EMCDDA 2017), and also in
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9 response to a growing proportion of the ageing opioid-dependent cohort being unable to inject DAM
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11 into peripheral veins (Vogel et al. 2015), HAT services in Switzerland are currently evaluating in an
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13 exploratory observational study (BASEC no 2020-00354) whether NAS administration may be a
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15 feasible and acceptable alternative or supplementary form of DAM maintenance in HAT with the
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17 potential to lastingly retain patients in this application form. Accordingly, the primary outcome of the
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19 study is holding time in treatment with NAS administration. Additional outcomes capture participants’
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21 experiences with and views on the new administration route.
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24 In order to prevent withdrawal, the study participants may use the PO route in addition to NAS
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26 application, but IV in parallel to NAS administration is not provided. Thus, study participants may
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28 choose among four mutually exclusive application schemes: nasal only (NAS), oral only (PO), nasal *and*
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30 oral (NAS + PO), and intravenous (IV). All participants initially start with the NAS scheme and may
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32 later change their preferred application scheme anytime and – with few exceptions – at will, and changes
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34 will be recorded at the study center in (ideally) regular intervals.
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37 Since all participants enter the study using the same administration scheme and are not subjected
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39 to different “arm-defining” treatments, the four administration schemes are not considered as different
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41 study arms. Instead, the four schemes are viewed as belonging to *one* study arm, and changes among
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43 them are modelled by *one* MC.
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45 Given its exploratory nature and one-arm design, the study does *not* aim at testing the primary
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47 outcome. Therefore, instead of being based on some power requirement, the sample size is to be
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49 determined based on the somewhat *unusual* requirement that, at a specified point in time (i.e. after
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51 $t = 12$ weeks), a defined minimal proportion of the study sample (60%) still sticks to the NAS scheme
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53 with sufficiently high probability (at least 80%). Even though the study is considered one-armed, this
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55 requirement loosely mirrors the situation of a two-arm study with 3:2 allocation to intervention and
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57 control groups, in which the intervention group would hold 60% of all participants. The rationale is to
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59 avoid premature termination of the study due to the majority of participants having abandoned the NAS
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administration route, and thus to ensure an acceptable cost-knowledge gain rate from the participants of primary interest.

1.3 Organization of the Article

First, we model switches among administration schemes by a somewhat simplistic first order MC whose states represent the four different schemes (subsection 2.1). In order to allow the transition probabilities to depend on the time already spent in the current states, we subsequently refine the model to higher order MCs (subsections 2.2 & 2.3). From these, we calculate and plot the (expected) proportion of participants using the NAS route over time together with quantile curves for different sample sizes. This allows to determine the required number of study participants both by calculation and visually (section 3).

Finally, we discuss possible extensions of the proposed MC approach beyond the somewhat limited context of the DAM administration study, and in particular to power-based sample size calculation for two- or multi-arm trials (section 4).

2. Materials and Methods

2.1 First Order Markov Chain

Assume that the sequence of administration schemes $(X_t^i)_{t \in \{0, 1, \dots, T\}}$ of participant $i \in \{1, 2, \dots, n\}$ forms a homogeneous first order MC with finite state space $S = \{1, 2, 3, 4\}$ where the states represent different DAM administration schemes: 1 = nasal only (NAS), 2 = oral only (PO), 3 = nasal and oral (NAS + PO), and 4 = intravenous (IV). Let the row vector $\mathbf{v}_t^i = (v_{t,1}^i, v_{t,2}^i, v_{t,3}^i, v_{t,4}^i)$ be the distribution of X_t^i , i.e. $v_{t,k}^i = P(X_t^i = k)$ for $k \in S$. Henceforth, we will further assume independent participants with identical state distributions for given times t (i.e. X_t^i iid with respect to i), and therefore omit the index i in order to simplify notation. Consequently, $\mathbf{v}_t = (v_{t,k})_{k \in S}$ can be understood as the (vector of) expected proportions of individuals in states $k \in S$ at time t . Specifically, $\mathbf{v}_0$ denotes the initial proportions of study participants in the different states.

The study protocol allows participants to switch their preferred administration schemes almost at will but with a few exceptions, and some other transitions are unpopular. The following figure 1 shows all states together with all non-zero transition probabilities $p_{kl} = p_{k \rightarrow l} = P(X_{t+1} = l | X_t = k)$:

Figure 1 here

Initially, all individuals are found in the NAS state, so $\mathbf{v}_0 = (1, 0, 0, 0)$. The transition probabilities p_{kl} (for a time span of one week) are given by the transition matrix

$$\mathbf{M} = [p_{kl}]_{k, l \in S} = \begin{bmatrix} 0.92 & 0.02 & 0.01 & 0.05 \\ 0.05 & 0.95 & 0 & 0 \\ 0.02 & 0.01 & 0.96 & 0.01 \\ 0.05 & 0 & 0 & 0.95 \end{bmatrix}$$

which is based on the following considerations and rules:

- The somewhat lower retention probability of the NAS state ($p_{11} = 0.92$) compared to the other administration schemes ($p_{22} = p_{44} = 0.95$, $p_{33} = 0.96$) is a conservative guess due to the novelty of this route. Only a small proportion of participants transitions from NAS to NAS + PO ($p_{13} = 0.01$), and those who leave NAS altogether usually change back to their administration route before the study (40% PO, 60% IV; $p_{12} \approx 0.4 \cdot 0.07$ and $p_{14} \approx 0.6 \cdot 0.07$, rounded towards IV).
- Retrying NAS after switching back to one's original administration route is unlikely ($p_{21} = p_{41} = 0.05$) and even more unlikely after NAS + PO ($p_{31} = 0.02$).
- Participants do not switch between PO and IV ($p_{24} = p_{42} = 0$).
- Transitioning to NAS + PO is only allowed for those already in state NAS ($p_{23} = p_{43} = 0$).

Obviously, the distribution $\mathbf{v}_1$ of an individual's state X_1 after the first time step is given by the first row of $\mathbf{M}$, so $\mathbf{v}_1 = (p_{11}, p_{12}, p_{13}, p_{14}) = \mathbf{v}_0 \cdot \mathbf{M}$.

Two-step transitions are achieved through intermediate states. Since transitions via different intermediate states are mutually exclusive, and if the two steps are independent, the law of total probability yields for the two-step transition probabilities $p_{k \cdot m} = p_{k \rightarrow \cdot \rightarrow m} = P(X_{t+2} = m | X_t = k)$:

$$p_{k \cdot m} = p_{k1} \cdot p_{1m} + p_{k2} \cdot p_{2m} + p_{k3} \cdot p_{3m} + p_{k4} \cdot p_{4m} = \sum_{l=1}^4 p_{kl} \cdot p_{lm} = \mathbf{M}^2|_{k, m}$$

In other words, $\mathbf{M}^2$ contains the two-step transition probabilities $p_{k \cdot m}$, and $\mathbf{v}_2 =$

$(p_{1 \cdot 1}, p_{1 \cdot 2}, p_{1 \cdot 3}, p_{1 \cdot 4}) = \mathbf{v}_0 \cdot \mathbf{M}^2$. A similar argument shows that $\mathbf{v}_t = \mathbf{v}_0 \cdot \mathbf{M}^t$ holds for all t .

Thus, for the distribution of the preferred administration schemes after 12 weeks, we find $\mathbf{v}_{12} = \mathbf{v}_0 \cdot \mathbf{M}^{12} \approx (49.2\%, 12.8\%, 6.6\%, 31.4\%)$. Not surprisingly, $v_{12,1} \approx 49.2\%$ is considerably higher than $0.92^{12} \approx 36.8\%$, the proportion to be expected if switching back after leaving state NAS were not possible.

2.2 Second Order Markov Chain

Modelling subsequent transitions as independent (as in the previous subsection) does not reflect the natural assumption that sticking to one's current administration scheme gets more likely the longer that same scheme has been uphold. We therefore refine our model, first for two consecutive steps.

Let $p_{jkl} = p_{jk \rightarrow l} = P(X_{t+1} = l | X_t = k, X_{t-1} = j)$. Note that this probability no longer depends on the current state at time t only but now also on the previous state at time $t - 1$. The probability of either adhering to or leaving one's current administration scheme k depending on the previously used scheme j can, by way of example and with one additional parameter $0 < c < 1$, be modelled as follows:

$$p_{jkl} = \begin{cases} p_{kl} + c \cdot (1 - p_{kl}) & \text{if } j = k = l \\ (1 - c) \cdot p_{kl} & \text{if } j = k \neq l \\ p_{kl} & \text{if } j \neq k \end{cases} \quad \text{for } j, k, l \in S$$

Throughout, we will use $c = 0.5$. Of course, arbitrarily more sophisticated formalizations are conceivable.

The so defined p_{jkl} describe transitions from pairs of states $(j, k) \in S \times S$ at times $(t - 1, t)$ to states $l \in S$ at time $t + 1$ and so do not form a quadratic matrix anymore. In order to get a quadratic transition matrix which can be raised to the t^{th} power, we need to combine state l at time $t + 1$ with its preceding state to get a pair of states similar to and of the same dimension as where the transition originates. We then define new transition probabilities $p_{jkk'l} = p_{jk \rightarrow k'l} = P(X_{t+1} = l, X_t = k' | X_t = k, X_{t-1} = j)$ between states of the *new* state space $S \times S$:

$$p_{jkk'l} = \begin{cases} p_{jkl} & \text{if } k' = k \\ 0 & \text{if } k' \neq k \end{cases} \quad \text{for } (j, k), (k', l) \in S \times S$$

Note that k and k' both denote the chain's state at the same current time t , but once as part of the origin of the transition, and then again as part of its destination. This implies that transitions with $k' \neq k$ are impossible, which is represented by zero probabilities in the equation above.

Coming from the first order transition matrix M as in subsection 2.1, we hence get the second order transition matrix – again called M for simplicity – with dots replacing zeros to improve readability:

$$M = \begin{bmatrix} 0.96 & 0.01 & 0.005 & 0.025 & 0.05 & 0.95 & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.02 & 0.01 & 0.96 & 0.01 & \cdot & \cdot & \cdot & \cdot \\ 0.92 & 0.02 & 0.01 & 0.05 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.05 & 0 & 0 & 0.95 \\ \cdot & \cdot & \cdot & \cdot & 0.025 & 0.975 & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.02 & 0.01 & 0.96 & 0.01 & \cdot & \cdot & \cdot & \cdot \\ 0.92 & 0.02 & 0.01 & 0.05 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.05 & 0 & 0 & 0.95 \\ \cdot & \cdot & \cdot & \cdot & 0.05 & 0.95 & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.01 & 0.005 & 0.98 & 0.005 & \cdot & \cdot & \cdot & \cdot \\ 0.92 & 0.02 & 0.01 & 0.05 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.05 & 0 & 0 & 0.95 \\ \cdot & \cdot & \cdot & \cdot & 0.05 & 0.95 & 0 & 0 & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.02 & 0.01 & 0.96 & 0.01 & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0.025 & 0 & 0 & 0.975 \end{bmatrix}$$

As we see, the new state space $S \times S$ is of dimension $|S| \cdot |S| = |S|^2 = 4^2$, so the new initial state distribution – also called v_0 again – is a vector of length 16. If 40% of all individuals used the PO and 60% the IV route before the study, and all participants start into the study with the NAS scheme then we have $v_{0,(2,1)} = 0.4$, $v_{0,(4,1)} = 0.6$, and $v_{0,(j,k)} = 0$ for all other states (j,k) . Thus we get the initial distribution $v_0 = (0, 0, 0, 0, 0.4, 0, 0, 0, 0, 0, 0, 0, 0.6, 0, 0, 0)$ over the states in the new state space $S \times S$. By summing $v_{12} = v_0 \cdot M^{12}$ over states (k', l) with identical l we expect to find 64.1%, 9.0%, 4.6% and 22.3% of all individuals in the original states (NAS, PO, NAS + PO, and IV) after 12 steps.

2.3 Higher Order Markov Chains

By analogous transformations to those presented in the previous subsection 2.2, the R code provided as additional file turns the $4^n \times 4^n$ transition matrix of the n^{th} order MC into the $4^{n+1} \times 4^{n+1}$ transition matrix of the corresponding $(n + 1)^{th}$ order chain.

For example, if at the start of the third order chain, 40% of all individuals are found in state (2, 2, 1) and 60% in state (4, 4, 1) – corresponding to PO and IV use before the study, respectively, and

NAS application at its onset – then 75.0% of all study participants can be expected to prefer the NAS administration route at $t = 12$.

3. Results

Since our primary interest lies in the new NAS administration route, we reduce the multinomial state distribution $\mathbf{v}_t$ over all states to a binomial distribution of the number of study participants preferring the NAS route. Let p_t be the *expected* proportion of study participants preferring NAS administration at time t . (For the first order MC, $p_t = v_{t,1}$, and in the case of higher order chains, p_t is the sum of appropriate elements of $\mathbf{v}_t$.) Be further $N_t \sim \text{Bin}(n, p_t)$ the *observed* number of individuals with preference for NAS at time t .

With $n = 200$ and $p_{12} = 64.1\%$ (result from subsection 2.2) it follows that the probability of finding (e.g.) at least 60% of all individuals using the NAS administration route after 12 steps is $P(N_{12} \geq 0.6 \cdot n) \approx 90.1\%$. If, the other way round, a NAS preference rate of at least 60% is required with a probability of at least 80% then solving $P(N_{12} \geq 0.6 \cdot n) \geq 80\%$ for n yields a minimum sample size of $n = 108$ individuals. (To be precise, the inequality also holds for some smaller n because $P(N_{12} \geq 0.6 \cdot n)$ is not monotonic in n , but the condition is consistently fulfilled for all $n \geq 108$.) This number satisfies the original sample size requirement as described in the introduction.

Figure 2 shows the expected proportion $p_t = E[N_t]/n$ of individuals preferring the NAS route as a function of time t for different choices of n , together with 10% (solid) and 20% (dotted) quantile curves of the distribution of N_t/n , again using p_t calculated from the second order MC in subsection 2.2. The figure can be used as a nomogram to determine sample sizes visually.

Figure 2 here

Reading example:

After 24 steps, the expected proportion of individuals preferring NAS administration amounts to 49.3%. With probabilities $\geq 90\%$, proportions of at least 43% of $n = 100$ or at least 35% of $n = 20$ individuals use the NAS administration route.

4. Discussion

Markov chains provide an intuitive approach to sample size calculations which is not widely used. Chow et al.'s (2017) standard work on sample size calculation lists formulae for the exponential model, for Cox's proportional hazards model and for the weighted log-rank test, but MCs are not even mentioned in its keyword index.

The particular strength of Markov chains lies in their ability to model recurrent events, and we are not suggesting to use them outside this scope. However, the method is not limited to the quite narrow use-case presented above but is instead rather flexible. In some brevity, we would like to sketch how the method can be adapted to the more familiar situation of calculating the sample size needed for testing an outcome difference between two (or more) study arms with sufficient power (prestudy power analysis).

Typically, sample sizes are calculated so that a clinically meaningful alternative H_A to the null hypothesis H_0 is not overlooked, that is, the probability of the test statistic falling into the rejection region – which is determined based on H_0 and α – should be large enough, i.e. at least $1 - \beta$. Extending our approach to cover this common situation is straightforward: First, both null and alternative hypotheses are formulated in terms of MC transition matrices, as explained in section 2. (Note that we still assume that transitions in both study arms are reversible; otherwise we suggest to use standard methods.) Following both chains until time t then yields $p_t^{(0)} = E_0[N_t]/n$ and $p_t^{(A)} = E_A[N_t]/n$. Thus, the original test situation, where hypotheses are represented by matrices, translates into $N_t \sim \text{Bin}(n, p_t)$ with $H_0: p_t = p_t^{(0)}$ vs. $H_A: p_t = p_t^{(A)}$, and sample sizes can then be calculated using known formulae for comparing proportions (see e.g. Chow et al. 2017, p.77).

Complex study protocols with accrual periods $\neq 0$ or censoring can be allowed for by (dynamically) modifying (subsets of) $\mathbf{v}_t$ or via introduction of additional states, respectively. Modelling transitions by MCs can not only serve for sample size calculations but also to determine other quantities of interest (e.g. the median holding times $0.5/\log p_{kk}$ in states k). Another advantage worth mentioning is the particular ease of fitting a MC model once the data has been collected. For the specific case presented in this article, this implies that the outcome of interest can be determined in a natural way from the same model that was used for sample size calculation.

Limitations: We only considered a first order MC with 4 states (but generalization to $|S| \neq 4$ is straightforward). The specific procedure chosen to determine transition matrices of higher order MCs leads to higher overall probabilities of remaining in current states which might be an unwanted effect. However, starting with lower sojourn probabilities can address this limitation: If e.g. $p_{111 \rightarrow 1} = 95\%$ is required then the corresponding transition probabilities in the lower order MC should be chosen as $p_{11 \rightarrow 1} = 90\%$ and $p_{1 \rightarrow 1} = 80\%$.

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Declaration of Interest Statement

The authors declare that there is no conflict of interest.

References

- Andersen, P. K., Gill, R. D. (1982), "Cox's Regression Model for Counting Processes: A Large Sample Study," *Annals of Statistics*, 10:4, 1100-1120, DOI: [10.1214/aos/1176345976](https://doi.org/10.1214/aos/1176345976).
- Barbu, V., Boussemart, M., Limnios, N. (2004), "Discrete Time Semi-Markov Model for Reliability and Survival Analysis," *Communications in Statistics - Theory and Methods*, 33:11, 2833-2868, DOI: [10.1081/STA-200037923](https://doi.org/10.1081/STA-200037923).
- BASEC (2020-00354), *Swiss Ethics Committees on research involving humans*, <https://swissethics.ch>.
- Chow, S. C., Shao, J., Wang, H., Lokhnygina, Y. (2017), *Sample Size Calculations in Clinical Research* (3rd ed.), Boca Raton, FL: Taylor & Francis, ISBN: 978-1-138-74098-3.
- EMCDDA (2017), *European Drug Report 2017*, Luxembourg: Publications Office of the European Union, DOI: [10.2810/46831](https://doi.org/10.2810/46831)
- Lachin, J. M. (1981), "Introduction to Sample Size Determination and Power Analysis for Clinical Trials," *Controlled Clinical Trials*, 2:2, 93-113, DOI: [10.1016/0197-2456\(81\)90001-5](https://doi.org/10.1016/0197-2456(81)90001-5).

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Pérez-Ocón, R., Ruiz-Castro, J. E., Gámiz-Pérez, M. L. (2001), “A piecewise Markov process for analysing survival from breast cancer in different risk groups,” *Statistics in Medicine*, 20:1, 109-122, DOI: [10.1002/1097-0258\(20010115\)20:1<109::aid-sim615>3.0.co;2-n](https://doi.org/10.1002/1097-0258(20010115)20:1<109::aid-sim615>3.0.co;2-n).

Prentice, R. L., Williams, B. J., Peterson, V. (1981), “On the regression analysis of multivariate failure time data,” *Biometrika*, 68:2, 373-379, DOI: [10.1093/biomet/68.2.373](https://doi.org/10.1093/biomet/68.2.373).

Rebora, P., Galimberti, S. (2012), “Sample size calculation for recurrent events data in one-arm studies,” *Pharmaceutical Statistics*, 11:6, 494-502, DOI: [10.1002/pst.1541](https://doi.org/10.1002/pst.1541).

Schoenfeld, D. A. (1983), “Sample-Size Formula for the Proportional-Hazards Regression Model,” *Biometrics*, 39:2, 499-503, DOI: [10.2307/2531021](https://doi.org/10.2307/2531021).

Strang, J., Groshkova, T., Uchtenhagen, A., Van den Brink, W., Haasen, C., Schechter, M., ..., Metrebian, N. (2015), “Heroin on trial: Systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction,” *British Journal of Psychiatry*, 207:1, 5-14, DOI: [10.1192/bjp.bp.114.149195](https://doi.org/10.1192/bjp.bp.114.149195).

Tan, W. Y. (1981), “The MARKOV Process Approach to Survival Analysis,” *Biometrical Journal*, 23:5, 467-475, DOI: [10.1002/bimj.4710230507](https://doi.org/10.1002/bimj.4710230507).

Tang, Y., Fitzpatrick, R. (2019), “Sample size calculation for the Andersen-Gill model comparing rates of recurrent events,” *Statistics in Medicine*, 38:24, 4819-4827, DOI: [10.1002/sim.8335](https://doi.org/10.1002/sim.8335).

Vogel, M., Dürsteler, K. M., Strasser, J., Schmid, O., Müller, E., Himmelheber, P., Lang, U., Walter, M., Krausz, M. (2015), “Injektionen in die Leistenvene – Prävalenz und Umgang in heroingestützter Behandlung,” *Suchtmedizin*, 17:2, 57-62.

Wei, L. J., Lin, D. Y., Weissfeld L. (1989), “Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions,” *Journal of the American Statistical Association*, 84:408, 1065-1073, DOI: [10.1080/01621459.1989.10478873](https://doi.org/10.1080/01621459.1989.10478873).

Appendix/Online Supplement

MCs4SSCalc_RCode.pdf

Figure 1:

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Figure 2:

Figure legends:

Figure 1: States and transition probabilities of the first order Markov chain. IV: intravenous; NAS: nasal; PO: oral.

Figure 2: Proportion N_t/n of individuals preferring nasal administration at time t for different sample sizes n (expected value with 10%- and 20%-quantile curves). The dotted lines illustrate the reading example in the text below.

For Peer Review Only

States and transition probabilities of the first order Markov chain. IV: intravenous; NAS: nasal; PO: oral.

Proportion N_t/n of individuals preferring nasal administration at time t for different sample sizes n (expected value with 10%- and 20%-quantile curves). The dotted lines illustrate the reading example in the text below.

```

#####
### Modelling transitions between preferred DAM administration routes      ###
### Thomas Grischott, 12 Nov 2019 - 20 Aug 2020                          R version 3.5.0 ###
#####

library(expm) # provides matrix exponentiation %^%

#####-----

### toolbox for calculating transition matrices
###          and distribution over original state space

tm_of_next_order_mc <- function(mat, s = 4, c = 0.5) {
  #' expand s^n      x s^n      transition matrix mat of n      -th order MC
  #' into s^(n+1) x s^(n+1) transition matrix      of (n+1)-th order MC
  #' increase all prob(kk...k -> k) by c * (1 - prob(kk...k -> k)),
  #' and decrease prob(kk...k -> l) for l != k accordingly
  #' s = size of state space of underlying 1st order MC

  # dimension of transition matrix and order of original (i.e. n-th order) MC
  d <- nrow(mat)
  n <- log(d) / log(s)

  # dimension compatibility check
  if (n %% 1 != 0)
    stop('incompatible transition matrix and state space dimensions')

  # assemble original transition matrices into square panel of appropriate size
  mat <- mat[rep(1:d, s), rep(1:d, s)]

  # adjust rows where needed
  for (i in 1:s) {
    i_row <- 1 + (d * s - 1) / (s - 1) * (i - 1) # rows needing to be modified
    for (i_col in 1:(d * s)) {
      if (i_col == i_row)
        mat[i_row, i_col] <- mat[i_row, i_col] + c * (1 - mat[i_row, i_col])
      else
        mat[i_row, i_col] <- (1 - c) * mat[i_row, i_col]
    }
  }

  # clear entries where needed
  for (i_row in 1:(d * s)) {
    i_block2keep <- (i_row - 1) %% d + 1
    block2keep <- ((i_block2keep - 1) * s + 1):(i_block2keep * s)
    for (i_col in 1:(d * s)) {
      if (!(i_col %in% block2keep))
        mat[i_row, i_col] <- 0
    }
  }

  # return transition matrix of new (n+1)-th order MC
  return(mat)
}

reduce_distr <- function(v, s = 4) {
  #' reduce distribution over states of (n+1)-th order chain
  #' to distribution over states of underlying 1st order MC
  #' v = distribution over states of (n+1)-th order chain
  #' s = size of state space of underlying 1st order MC

  p <- numeric(s)
  for (i in 1:s)
    p[i] <- sum(v[seq(i, length(v), by = s)])

  return(p)
}

```

```

72  ###-----
73
74  ### 1st order markov chain
1  75  ### states are DAM administration routes
2  76  ### 1 = nasal (NAS)
3  77  ### 2 = oral (PO)
4  78  ### 3 = both nasal and oral (NAS + PO)
5  79  ### 4 = intravenous (IV)
6  80
7  81  # initial distribution
8  82  v0 <- c(1, 0, 0, 0)
9  83
10 84  # transition matrix
11 85  mat1 <- matrix(c(
12 86      0.92, 0.02, 0.01, 0.05, # from NAS      to NAS, PO, NAS + PO, and IV
13 87      0.05, 0.95, 0.00, 0.00, # from PO      to NAS, PO, NAS + PO, and IV
14 88      0.02, 0.01, 0.96, 0.01, # from NAS + PO to NAS, PO, NAS + PO, and IV
15 89      0.05, 0.00, 0.00, 0.95  # from IV      to NAS, PO, NAS + PO, and IV
16 90  ), nrow = 4, byrow = T)
17 91
18 92  # state probabilities
19 93  v1 <- v0 %*% (mat1 %^% 1); reduce_distr(v1) # after 1 unit of time (e.g. week)
20 94  v2 <- v0 %*% (mat1 %^% 12); reduce_distr(v2) # after 12 units
21 95  v3 <- v0 %*% (mat1 %^% 24); reduce_distr(v3) # after 24 units
22 96  v4 <- v0 %*% (mat1 %^% 36); reduce_distr(v4) # after 36 units
23 97
24 98  ### 2nd order markov chain
25 99  ### states are pairs of states of the 1st order markov chain
26 100
27 101  # initial distribution
28 102  v0 <- c(0, 0, 0, 0, 0.4, 0, 0, 0, 0, 0, 0, 0, 0, 0.6, 0, 0, 0)
29 103
30 104  # transition matrix
31 105  mat2 <- tm_of_next_order_mc(mat1)
32 106
33 107  # state probabilities
34 108  v1 <- v0 %*% (mat2 %^% 1); reduce_distr(v1) # after 1 unit of time (e.g. week)
35 109  v2 <- v0 %*% (mat2 %^% 12); reduce_distr(v2) # after 12 units
36 110  v3 <- v0 %*% (mat2 %^% 24); reduce_distr(v3) # after 24 units
37 111  v4 <- v0 %*% (mat2 %^% 36); reduce_distr(v4) # after 36 units
38 112
39 113  ### 3rd order markov chain
40 114  ### states are triplets of states of the 1st order markov chain
41 115
42 116  # initial distribution
43 117  v0 <- c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
44 118      0, 0, 0, 0, 0.4, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
45 119      0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
46 120      0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0.6, 0, 0, 0, 0, 0)
47 121
48 122  # transition matrix
49 123  mat3 <- tm_of_next_order_mc(mat2)
50 124
51 125  # state probabilities
52 126  v1 <- v0 %*% (mat3 %^% 1); reduce_distr(v1) # after 1 unit of time (e.g. week)
53 127  v2 <- v0 %*% (mat3 %^% 12); reduce_distr(v2) # after 12 units
54 128  v3 <- v0 %*% (mat3 %^% 24); reduce_distr(v3) # after 24 units
55 129  v4 <- v0 %*% (mat3 %^% 36); reduce_distr(v4) # after 36 units
56 130
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```

```
143 ###-----
144
145 ### expected proportions in individual states and "upper tail probabilities"
1
146
2 147 ssize <- 500
3 148 #ssize <- 100
4 149 #ssize <- 20
5 150
6 151 # expected proportions preferring NAS administration
7 152 p1 <- reduce_distr(v1)[1] # after 1 unit of time (e.g. week)
8 153 p2 <- reduce_distr(v2)[1] # after 12 units
9 154 p3 <- reduce_distr(v3)[1] # after 24 units
10 155 p4 <- reduce_distr(v4)[1] # after 36 units
11 156
12 157 # "upper tail probabilities"
13 158 pbinom(ceiling(0.50 * ssize - 1), ssize, p1, lower.tail = F) # after 1 unit of time
14 159 pbinom(ceiling(0.25 * ssize - 1), ssize, p2, lower.tail = F) # after 12 units
15 160 pbinom(ceiling(0.15 * ssize - 1), ssize, p3, lower.tail = F) # after 24 units
16 161 pbinom(ceiling(0.10 * ssize - 1), ssize, p4, lower.tail = F) # after 36 units
17 162
18 163 # examples in manuscript
19 164 ssize <- 200
20 165 pbinom(ceiling(0.6 * ssize - 1), ssize, p2, lower.tail = F)
21 166 ssize <- 101:200
22 167 pbinom(ceiling(0.6 * ssize - 1), ssize, p2, lower.tail = F) >= 0.8
23 168
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```