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Distributed transit compartments for arbitrary lifespan distributions in aging populations

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HIGHLIGHTS

- We extend the transit compartment concept to approximately describe any lifespan distribution in aging populations.
- The developed distributed transit compartments are applied to solve the convolution integral in distributed lifespan models.
- The distributed transit compartments could be similarly implemented as traditional transit compartments.
- Applications to typical pharmacokinetics/pharmacodynamics questions are provided.

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ABSTRACT

Transit compartment models (TCM) are often used to describe aging populations where every individual has its own lifespan. However, in the TCM approach these lifespans are gamma-distributed which is a serious limitation because often the Weibull or more complex distributions are realistic. Therefore, we extend the TCM concept to approximately describe any lifespan distribution and call this generalized concept distributed transit compartment models (DTCMs). The validity of DTCMs is obtained by convergence investigations. From the mechanistic perspective the transit rates are directly controlled by the lifespan distribution. Further, DTCMs could be used to approximate the convolution of a signal with a probability density function. As example a stimulatory effect of a drug in an aging population with a Weibull-distributed lifespan is presented where distribution and model parameters are estimated based on simulated data.

1. Introduction

In a population every individual has its own and unique lifespan, typically described by a realization of a random variable with a probability distribution. For example, general human life expectancy or cell maturation processes could be well described by the Weibull distribution (Slob and Janse, 1988). In more specific mortality or survival analyses also more complex distributions are used, e.g. mixtures of Weibull distributions for human mortality with additional causes (Bebbington et al., 2007) or for red blood cell survival with early mortality (Korell et al., 2011a, 2011b). Also distributions like Gompertz–Makeham (Gavrilov and Gavrilova, 1991) or Heligman–Pollard (Heligman and Pollard, 1980) are common. Moreover, specialized distributions exist e.g. to account for growing late-life mortality (Bebbington et al., 2014).

In aging populations often an external stimulation or inhibition on the production (birth) or loss (death) controls the amount of individuals. In pharmacokinetic/pharmacodynamic (PKPD) modeling (Mager et al., 2003; Danhof et al., 2008) this is the effect of a drug on a clinical endpoint or biomarker (e.g. cell counts). In many PKPD models a transit compartment model (TCM) (Sun and Jusko, 1998; Koch et al., 2014), which are linked compartments described by ordinary differential equations (ODE), is used to describe aging populations. For example, with TCMs in Harker et al. (2000) and Krzyzanski et al. (2013) the thrombopoietic stimulation on megakaryocytes and platelets was described, in Pérez-Ruixo et al. (2008) the effect of erythropoitin on reticulocytes was modeled and in Simeoni et al. (2004) a TCM to describe the apoptotic tumor cell population caused by an anti-cancer agent attacking proliferating cells was applied. However, the TCM approach always provides a gamma-distributed lifespan which is a severe limitation of this tool. Therefore, the objective of this work is to extend the

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TCM concept to approximately describe any arbitrary lifespan distributions. We call this approach distributed TCMs (DTCMs).

We will demonstrate that the DTCM approximates any lifespan distribution. Furthermore, we present an equivalent mechanistic reformulation of the DTCM to visualize the effect of the lifespan distribution on the mortality of the individuals with various ages. Additionally, we demonstrate that in the limit the solution of the DTCM converges to the solution of a distributed lifespan model (DLSM) introduced in Krzyzanski et al. (2006). Therefore, DTCMs could also be used to handle these numerically difficult to solve DLSMs. More precisely, the presented DTCM is a method to solve general DLSMs without computationally expensive calculation of the convolution integral. Moreover, the DTCM is still based on the ODE system from the classical TCM and therefore could be similarly implemented. As application we simulate data in MATLAB (MATLAB, 2014) where the pharmacokinetics of a drug is described by a one-compartment model with non-linear elimination and stimulates an aging population with a Weibull-distributed lifespan. This data will be fitted and distribution as well as model parameters will be estimated with the ADAPT-5 software (D'Argenio et al., 2009) which is a state of the art program in PKPD modeling.

2. Theoretical

The classical TCM reads

$$\frac{d}{dt}x_1(t) = k_{in}(t) - kx_1(t), \quad x_1(0) = x_1^0 \tag{1}$$

$$\frac{d}{dt}x_i(t) = k(x_{i-1}(t) - x_i(t)), \quad x_i(0) = x_i^0 \quad \text{for } i = 2, \ldots, n \tag{2}$$

where k_{in} denotes the production/inflow into the first transit compartment x_1, the transit rate between the compartments is $k > 0$ and n denotes the integer number of compartments which is usually fixed a priori. The time necessary for an individual starting in compartment x_1 to subsequently pass through the compartments x_i, $i = 2, \ldots, n-1$, and finally to leave from the last compartment x_n is called the transit time τ. Assuming that the individuals move independent, the transit time can be described by a random variable $\mathcal{T}$. It can be shown that $\mathcal{T}$ is gamma-distributed with the probability density function (PDF)

$$l(\tau) = g_k^n(\tau) = \frac{k^n \tau^{n-1}}{(n-1)!}\exp(-k\tau) \tag{3}$$

(see Appendix A for details). The mean transit time (*MTT*) is

$$MTT = E(\mathcal{T}) = \int_0^\infty s l(s)\, ds = \frac{n}{k} \tag{4}$$

and the variance of the transit times (*VTT*) reads

$$VTT = Var(\mathcal{T}) = \int_0^\infty s^2 l(s)\, ds - MTT^2 = \frac{n}{k^2}. \tag{5}$$

Note that the TCM related parameters n and k in (1)–(2) are also the gamma distribution parameters in (3)–(5).

In this work, we apply TCMs in the context of aging populations and call the *MTT* the mean lifespan, denoted with T, and the compartments x_i, $i = 1, \ldots, n$, in (1)–(2) are the aging stages describing the amount of individuals within a specific age range (also called a cohort). The sum of all aging stages

$$y_n(t) = x_1(t) + \cdots + x_n(t) \tag{6}$$

is the total amount of individuals in the aging population. In Fig. 1, the scheme of the TCM (1)–(2) with (6) is shown. Note that no outflow from the intermediate aging stages exist and all individuals leave the population from the last compartment.

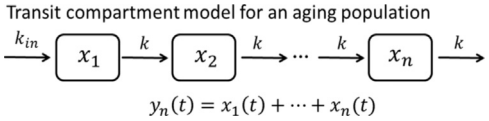

Fig. 1. The transit compartment model (1)–(2), (6) for an aging population with gamma-distributed lifespans.

To introduce our general framework let $\mathcal{T}$ be an arbitrary random variable describing the lifespan τ. With l we denote the probability density function (PDF), assume that negative lifespans are not possible, i.e. $l(\tau) = 0$ for $\tau < 0$, and that $l(\tau)$ for $\tau \geq 0$ is piecewise continuous. The probability that an individual achieves a certain lifespan τ is given by the survival function

$$S(\tau) = \mathbb{P}[\mathcal{T} > \tau] = 1 - \mathbb{P}[\mathcal{T} \leq \tau] = 1 - \int_0^\tau l(s)\, ds = 1 - L(\tau) \tag{7}$$

where L is the cumulative distribution function (CDF).

To construct a distributed transit compartment model (DTCM) which realizes the lifespan distribution $\mathcal{T}$, we create an equidistant discrete grid of the lifespan interval $I = [0, \tau_{end}]$ where τ_{end} is a natural given bound of the lifespan, i.e., τ_{end} is the minimal positive number which fulfills the condition

$$\tau_{end} = \min\{\tau | S(\tau) = 1 - L(\tau) \leq \alpha\} \tag{8}$$

for a given probability significance level α, compare Koch and Schropp (2013) and see Fig. 2. Then we set the grid

$$\tau_i = \frac{i}{k} \quad \text{for } i = 0, \ldots, m$$

with

$$\tau_{end} = \frac{m}{k}.$$

This defines the age classes

$$I_i = [\tau_{i-1}, \tau_i[, \quad i = 1, \ldots, m$$

with length

$$\tau_i - \tau_{i-1} = \frac{1}{k}, \quad i = 1, \ldots, m.$$

Note, for PDFs with compact support $[t_a, t_b]$ we set $\tau_{end} = t_b$ and obtain $S(\tau_{end}) = 0$, and a significance level α is needless.

The prescribed distribution of $\mathcal{T}$ is included into the TCM by weighting the amount of individuals in the aging stages x_i with the probability that an age τ_i will be achieved. With the survival function (7) we set the effective population in each aging stage as

$$\tilde{x}_i(t) = S(\tau_{i-1})x_i(t) \quad \text{for } i = 1, \ldots, m. \tag{9}$$

Summing up the stages $\tilde{x}_i$ then results in the effective population according to the CDF

$$y_m(t) = S(\tau_0)x_1(t) + \cdots + S(\tau_{m-1})x_m(t). \tag{10}$$

Summarizing, the resulting DTCM reads

$$\frac{d}{dt}x_1(t) = k_{in}(t) - kx_1(t), \quad x_1(0) = x_1^0 \tag{11}$$

$$\frac{d}{dt}x_i(t) = k(x_{i-1}(t) - x_i(t)), \quad x_i(0) = x_i^0 \quad \text{for } i = 2, \ldots, m \tag{12}$$

$$y_m(t) = S(\tau_0)x_1(t) + \cdots + S(\tau_{m-1})x_m(t) \tag{13}$$

see Fig. 3A for a schematic. The DTCM consists of the transit rate k, the integer number of compartments m and additionally of the distribution parameters in the CDF L. We emphasize that the differential equations in the DTCM (11)–(12) are the same as in the classical TCM. Only the summation of the stages differs in (13). The matrix notation of (11)–(12) is