

Distributed transit compartments for arbitrary lifespan distributions in aging populations

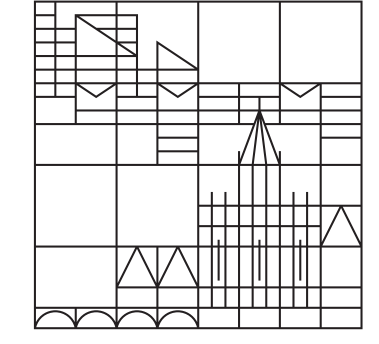
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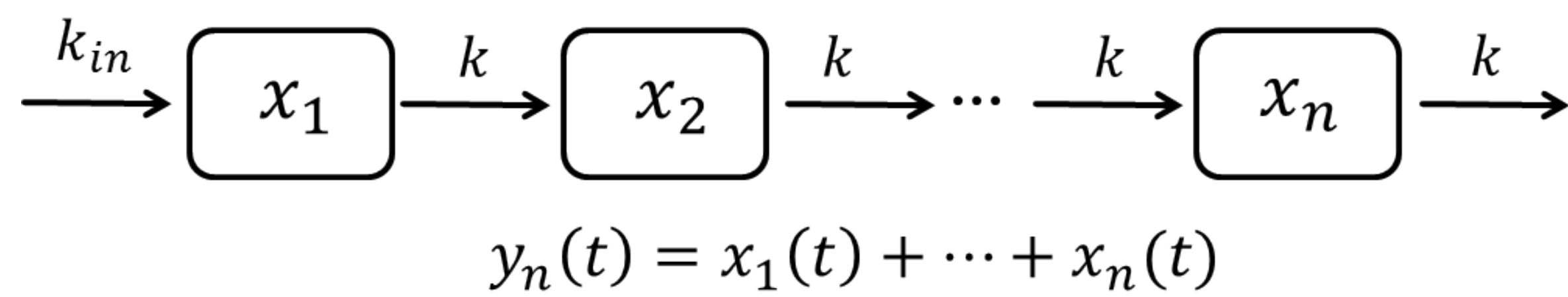


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Introduction and Objective

In an **aging population** every individual has its own and unique lifespan. Often such a population is describe by a **transit compartment model (TCM)**:



- The compartments x_i describe the amount of individuals with a certain age range.
- The total sum y_n is the total amount of individuals in the population

The TCM realizes a **gamma distributed lifespan**

Objective: Extension of the TCM concept to approximately describe **any lifespan distribution**, called distributed transit compartment models (DTCM).

Method

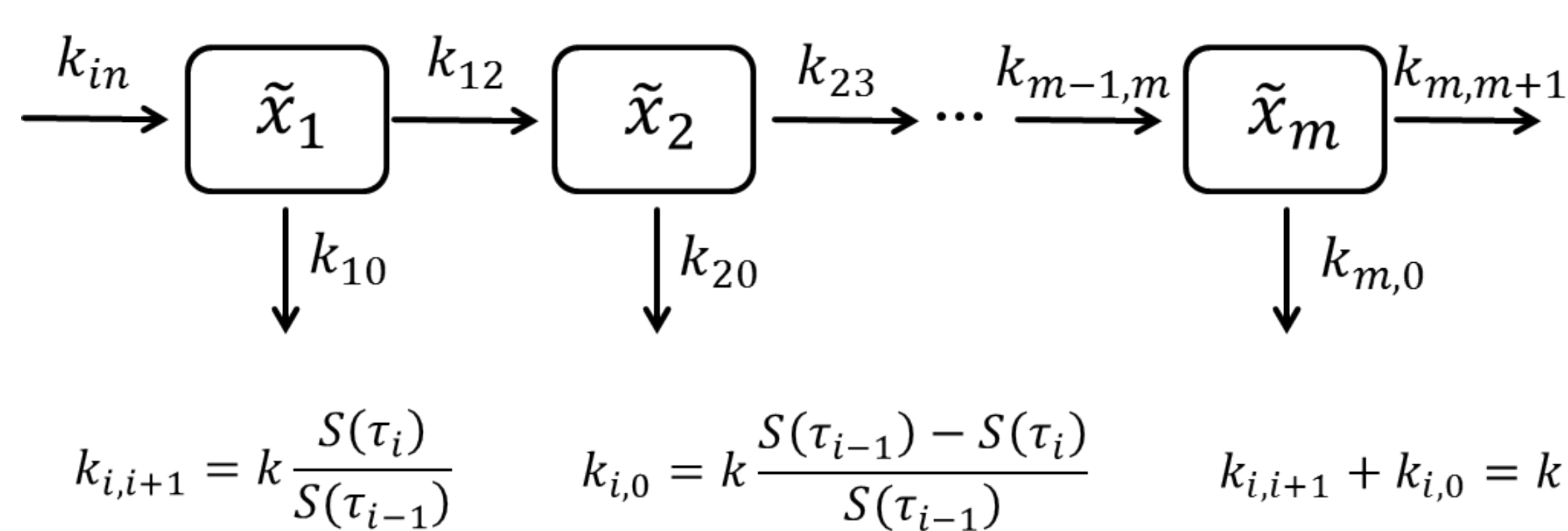
With l we denote the probability density function (PDF) of the desired lifespan distribution and assume that negative lifespans are not possible, i.e. $l(\tau) = 0$ for $\tau < 0$. The probability that an individual achieves a certain lifespan τ is given by the **survival function**

$$S(\tau) = 1 - \int_0^{\tau} l(s) ds = 1 - L(\tau)$$

where L is the cumulative distribution function.

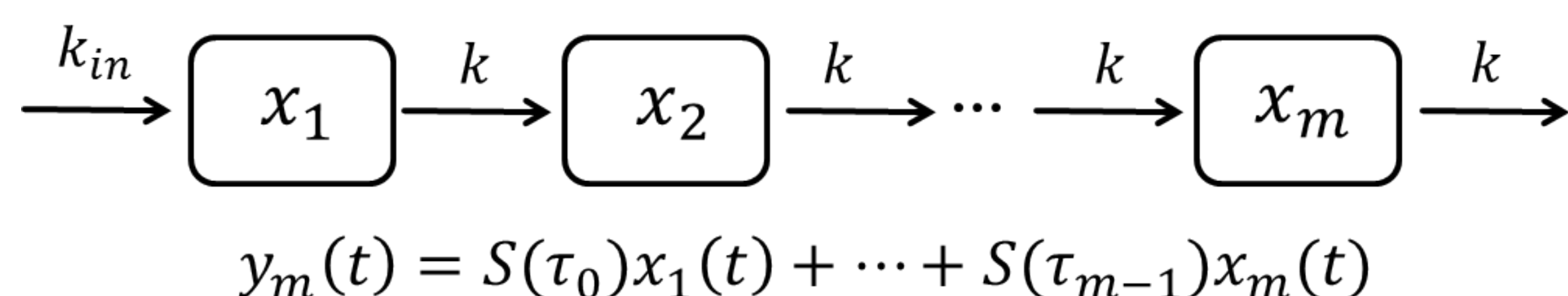
Distributed transit compartment model (DTCM) [1]:

Let $\tau_i = \frac{i}{k}$, $i = 0, \dots, m$, define the age classes $[\tau_{i-1}, \tau_i]$, $i = 1, \dots, m$, and let τ_m be a suitable bound for the lifespan. To include any desired lifespan distribution from every compartment a loss takes place:



Implementation as standard TCM:

DTCM can be similarly implemented as TCMs, and only summation of the compartments differs:



References:

- [1] Koch G, Schropp J (2015) Distributed transit compartments for arbitrary lifespan distributions in aging populations. J Theor Biol (accepted)
- [2] Krzyzanski W, Woo S, Jusko WJ (2006) Pharmacodynamic models for agents that alter production of natural cells with various distributions of lifespans. J Pharmacokinet Pharmacodyn 33(2):125-66

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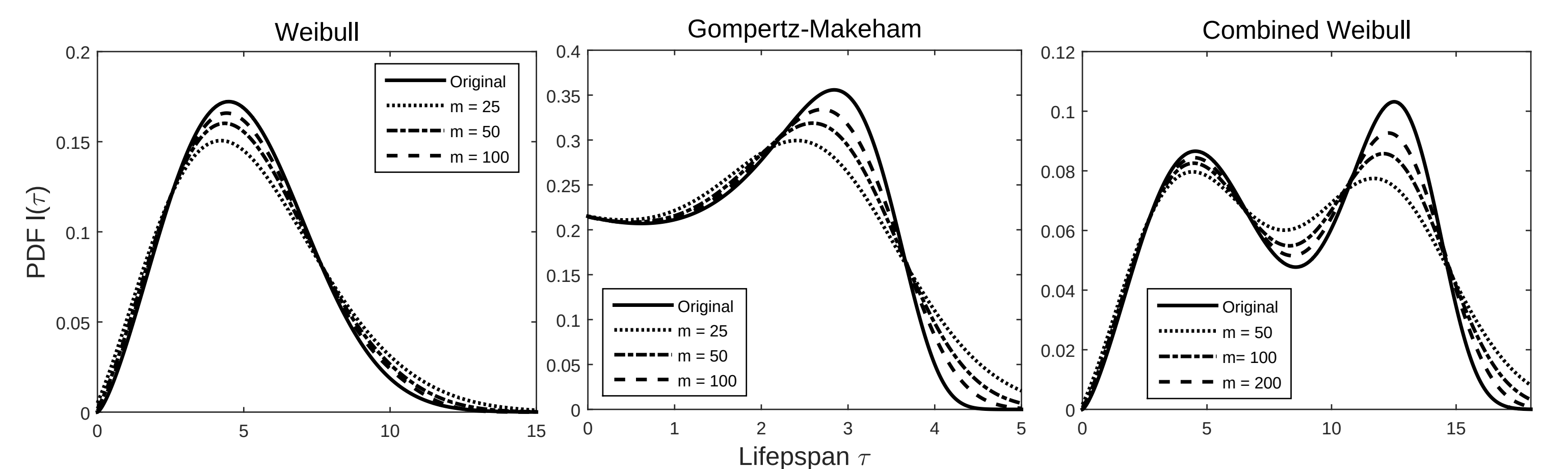
Application

Convergence property:

To investigate the approximation quality of the lifespan distribution from the DTCM, all individuals start at $t = 0$ with the same age (i.e. all individuals are at $t = 0$ in the same compartment) and the total out-flow $out(t)$ from the DTCM is investigated. The approximate lifespan distribution is then given by

$$l^{DTCM}(t) = \frac{out(t)}{\int_0^{\infty} out(s) ds} \quad \text{and} \quad l^{DTCM}(t) \rightarrow l(t), \quad t \geq 0.$$

Example for typical distributions:



Solving distributed lifespan models:

We consider a distributed lifespan model (DLSM) with Weibull-distributed lifespan. The drug is described by non-linear kinetics and stimulates the production of individuals. The lifespan is included via the convolution operator, compare [2]:

$$\frac{d}{dt}c(t) = -\frac{V_{max}c(t)}{V_{50} + c(t)}, \quad c(0) = \frac{dose}{V} \quad (1)$$

$$\frac{d}{dt}y(t) = k_{in}(t) - (k_{in} * l_{Wei})(t), \quad y(0) = k_0 T \quad (2)$$

$$k_{in}(t) = k_0 \left(1 + \frac{S_{max}c(t)}{SC_{50} + c(t)} \right) \quad (3)$$

$$l_{Wei}(t) = \frac{a}{b} \left(\frac{t}{b} \right)^{b-1} \exp \left(- \left(\frac{t}{b} \right)^a \right) \quad (4)$$

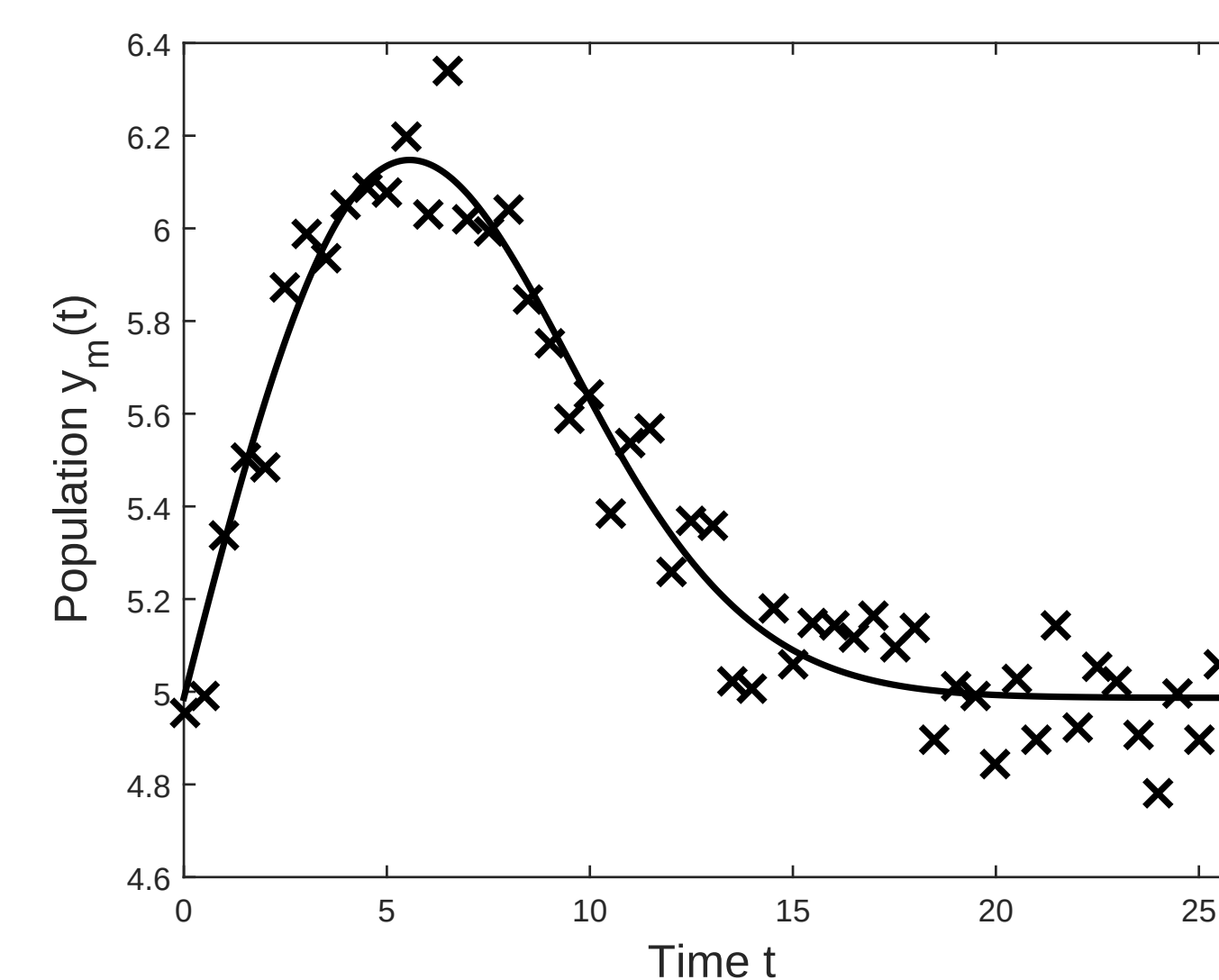
Substitution of Eq. (2) containing the convolution with the DTCM:

$$\frac{d}{dt}x_1(t) = k_{in}(t) - kx_1(t), \quad x_1(0) = \frac{k_0}{k} \quad (5)$$

$$\frac{d}{dt}x_i(t) = k(x_{i-1}(t) - x_i(t)), \quad x_i(0) = \frac{k_0}{k}, \quad i = 2, \dots, m \quad (6)$$

$$y_m(t) = S_{Wei}(\tau_0)x_1(t) + \dots + S_{Wei}(\tau_{m-1})x_m(t) \quad (7)$$

The DLSM with the DTCM is given by Eqs. (1),(3)-(7) and implemented in ADAPT-5 with $m = 100$.



	Original	Initial	Final Esti.
SC_{50}	5	10	4.42 (9.9)
k_0	1	0.8	1.04 (10.0)
a	2.38	7	2.17 (33.3)
b	5.64	6.5	5.38 (10.2)
T	5	6.08	4.76 (10.3)
σ^2	5	1.04	5.33 (41.9)

S_{max} was fixed. T and σ^2 was calculated from the distribution parameter a and b , and data was generated with the proportional residual error model $1 + \varepsilon$, $\varepsilon \sim \mathcal{N}(0, 0.02)$

Hence, DLSMs can be implemented without solving the numerically difficult and computationally costly convolution.

Results

- With a DTCM any lifespan distribution can be approximately described
- DTCMs are similarly implemented as TCMs
- The convolution in a DLSM can be substituted with a DTCM