Solution and implementation of distributed lifespan models

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Introduction and Objective

A population of individuals (e.g. cells) where every individual has its own and unique lifespan could be described by a **distributed lifespan model**. Such models were introduced by Krzyzanski, Woo and Jusko [1] to PKPD modeling in the indirect response context.

Distributed lifespan model (DLSM)
The lifespan τ of the individuals is described by a distribution (e.g. Weibull or gamma) with the corresponding probability density function $l(\tau)$ for $\tau \geq 0$ and $l(\tau) = 0$ for $\tau < 0$. The cumulative distribution function is denoted by $L(\tau)$, the expectation is T and the distribution parameters are a and b. The **distributed lifespan model** in the **rate of change formulation** for the population $N(t)$ with the production term $k_{in}(t)$ reads

$$\frac{d}{dt}N(t) = k_{in}(t) - (k_{in} * l)(t) \tag{1}$$

where " $*$ " is the convolution operator defined by the integral

$$(k_{in} * l)(t) = \int_0^\infty k_{in}(t-s)l(s)\,ds\,. \tag{2}$$

The initial condition is given by $N(0) = \int_0^\infty l(x) \int_{-x}^0 k_{in}(s)\,ds\,dx$ and reduces to $N(0) = k_{in}^0 T$ in case of a constant past $k_{in}(t) = k_{in}^0$ for $t < 0$.

Difficulties:

- For any time point t, an integral (2) (the convolution) has to be calculated.
- In standard PKPD software the convolution can not be directly implemented.
- The convolution needs to be approximated by the user (Possible but difficult to implement / Computationally slow.)

An equivalent formulation of the DLSM for implementation is necessary!

Method

The **solution representation** of (1) reads

$$N(t) = \int_0^\infty (1 - L(s))\, k_{in}(t-s)\,ds\,. \tag{3}$$

Advantage: Formulation (3) could be simply approximated by standard integration methods like the Riemann sum or the trapezoidal rule.

For illustration purpose, the simplest approximation (**Riemann sum formulation**) of (3) for implementation reads

$$N(t) \approx h \sum_{i=1}^{n} (1 - L(ih))\, k_{in}(t-ih) \tag{4}$$

where n is the number of partitions of the lifespan interval $[0, \tau_{end}]$ and $h = \frac{\tau_{end}}{n}$.

Results

Summary

Model: $\frac{d}{dt}N(t) = k_{in}(t) - (k_{in} * l)(t)$ with $N(0) = k_{in}^0 T$

Solution: $N(t) = \int_0^\infty (1 - L(s))\, k_{in}(t-s)\,ds$

Implementation: $N(t) \approx h \sum_{i=1}^{n} (1 - L(ih))\, k_{in}(t-ih)$

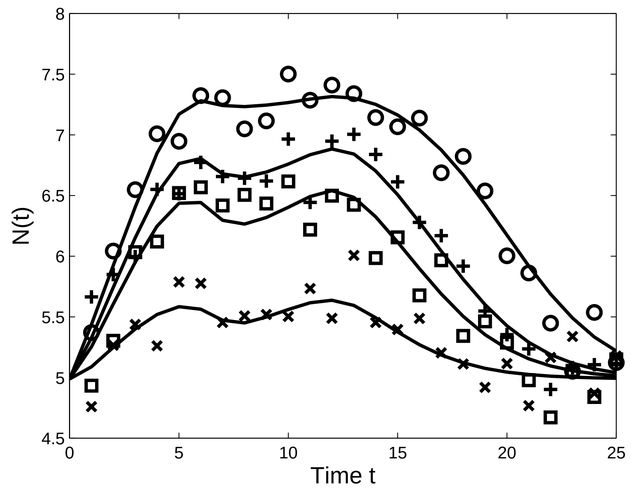
- With the presented method, DLSMs could be implemented in every PKPD software like e.g. ADAPT or NONMEM.
- The presented technique is also applicable for models with precursors.

Applications

Example 1: PKPD test problem
The PK $c(t)$ is simulated with the Bateman function. Four dosing groups are created with dosing time points at day 0 and 7. The production term for the population $N(t)$ described by (1) reads

$$k_{in}(t) = k_{in}^0 \left(1 + \frac{S_{max}c(t)}{SC_{50} + c(t)}\right) \quad \text{for } t \geq 0$$

with $k_{in}(t) = k_{in}^0$ for $t < 0$. Artificial data is produced by (3) with a Weibull distributed lifespan $L(\tau) = 1 - \exp(-(\tau/b)^a)$ and perturbed with a normal distributed error. The solution (3) is approximated by the trapezoidal rule and implemented in ADAPT and NONMEM to fit the produced data.



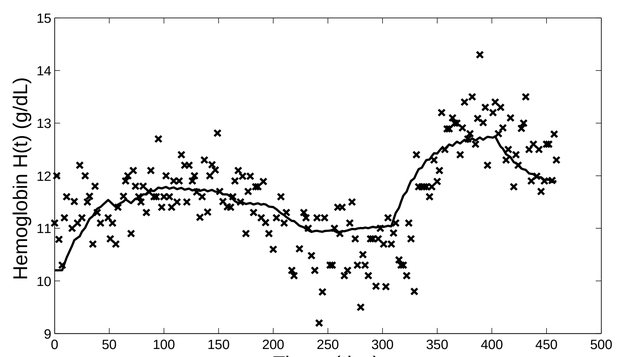
S_{max}	SC_{50}	k_{in}^0	a	b	T	σ^2
0.50 (3.16)	9.12 (11.4)	1.02 (4.21)	6.36 (3.09)	5.24 (7.51)	4.87 (7.65)	0.80 (10.9)

Estimates are calculated with ADAPT. Expectation T and variance σ^2 are secondary parameters. The values in the brackets denote the $CV\%$. The NONMEM estimates are comparable to those of ADAPT. The estimates are confirmed with the original model (1) in MATLAB.

Example 2: Stimulation of Hemoglobin (Hgb) by rHuEPO
In [2] hemoglobin measurements over 460 days in patients with a renal disease are presented. 186 measurements and doses are performed. The model for red blood cells (RBC) from [2] reads

$$\frac{d}{dt}M(t) = k_{in}(t-D) - (k_{in} * l)(t-D)\,, \quad k_{in}(t) = \frac{S_{max}E_P(t)}{SC_{50} + E_P(t)} \tag{5}$$

where a second order $(a = 2)$ gamma distribution describes the RBC lifespan. The time required for hematopoietic stem cells to become RBCs is D. The sum of endogenous EPO and rHuEPO is denoted by $E_P(t)$. Endogenous concentration of Hgb is H_{en} and the Hgb concentration is described by $H(t) = K_H M(t)$, where $K_H = 29.5$ (g/dL) is the average amount of Hgb per RBC. We applied the presented method and approximated the explicit solution $M(t)$ with the trapezoidal rule. Data was fitted with ADAPT.



H_{en} (g/dL)	SC_{50} (IU)	D (day)	b	T (day)	σ^2
10.26 (1.97)	86.71 (83.1)	6.98 (10.0)	0.605E-1 (10.0)	33.08 (10.0)	547 (20.0)

The PK (no measurements) is described by a non-linear approach and we fixed the parameter to $V_{max} = 6980$ (IU/day) and $K_m = 1042$ (IU). Additionally, one drug-effect related parameter, $S_{max} = 0.207$E-1 (cell/day), is also fixed. Values were taken from the original work [2]. Expectation T and variance σ^2 are secondary parameters. Values in brackets denote the $CV\%$. The estimates are confirmed with the original model (5) in MATLAB.

References

[1] Krzyzanski W, Woo S, Jusko WJ (2006) Pharmacodynamic models for agents that alter production of natural cells with various distributions of lifespans. JPKPD 33(2):125-66
[2] Nichols B, Shrestha RP, Horowitz J, Hollot CV, Germain MJ, Gaweda AE, Chait Y (2011) Simplification of an Erythropoiesis Model for Design of Anemia Management Protocols in End Stage Renal Disease. 33rd Annual International Conference of the IEEE EMBS Boston, Massachusetts, USA

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