Universität Konstanz

Modeling of delayed phenomena in PKPD by delay differential equations of lifespan type

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Content:

- General mathematical structure of PKPD models
- Transit compartments and lifespan models
- Main theoretical result
- Application to well-known tumor growth model
- Application of delay differential equation to develop an arthritis model
- Opinions to model delayed phenomena and comments to PKPD software

Mathematical structure of a PKPD model

Ordinary Differential Equation (ODE) – Traditional PKPD model

$$x'(t) = f\big(t, x(t)\big) \qquad\qquad x(0) = x^0$$

Delay Differential Equation (DDE)

$$x'(t) = f\big(t, x(t), x(t-T)\big) \qquad\qquad x(s) = \psi(s) \quad -T \le s \le 0$$

Delayed information

Modeling of the past necessary

- Delayed state $x(t-T)$
- Explicit delay parameter T
- Description of the past

Delay differential equations are **not new** in PKPD → Steimer et al 1982

Transit compartments – Traditional approach to describe delays or the lifespan in populations

Schematic representation of a transit compartment model (TCM)

$$\xrightarrow{k_{in}(t)} \boxed{x_1} \xrightarrow{k} \boxed{x_2} \xrightarrow{k} \cdots\cdots \xrightarrow{k} \boxed{x_n} \xrightarrow{k}$$

TCM with arbitrary initial values:

$$\begin{aligned} x_1'(t) &= k_{in}(t) - k \cdot x_1(t) \qquad & x_1(0) &= x_1^0 \\ x_2'(t) &= k \cdot x_1(t) - k \cdot x_2(t) \qquad & x_2(0) &= x_2^0 \\ &\vdots & &\vdots \\ x_n'(t) &= k \cdot x_{n-1}(t) - k \cdot x_n(t) \qquad & x_n(0) &= x_n^0 \end{aligned}$$

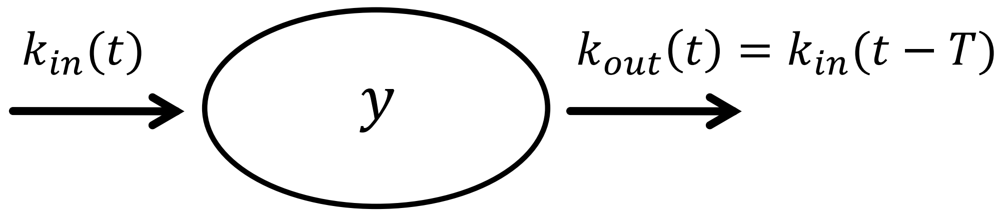
Mean residence time $T = {}^{n}/_{k}$

- $x_2, \dots, x_n$ are delayed versions of x_1 → Could be applied to describe delays
- $y_n = x_1 + \cdots + x_n$ describes a population (e.g. of cells) with a lifespan T

A general question: How to choose the number n of compartments?

Lifespan models (LSM) with constant lifespan T

Schematic representation:



What flows in flows out after T time units!

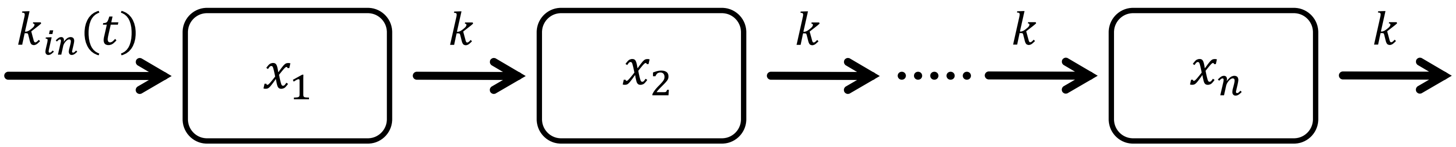
Lifespan model with constant lifespan T:

$$y'(t) = k_{in}(t) - k_{in}(t-T) \qquad y(0) = y^0$$

Need to supply $k_{in}(s)$ for $-T \leq s \leq 0$

Application / properties see the works of Krzyzanski , Jusko, Perez-Ruixo,…

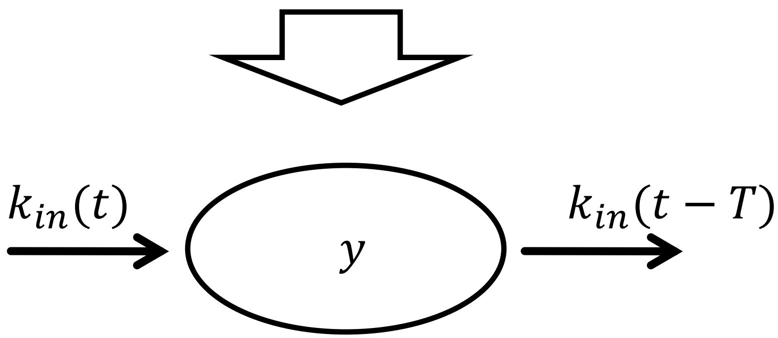
Main result - General relationship between transit compartments and lifespan models



Arbitrary initial values

Consider the total population: $y_n(t) = x_1(t) + \cdots + x_n(t)$

Let T be fixed. Then for $n \to \infty$

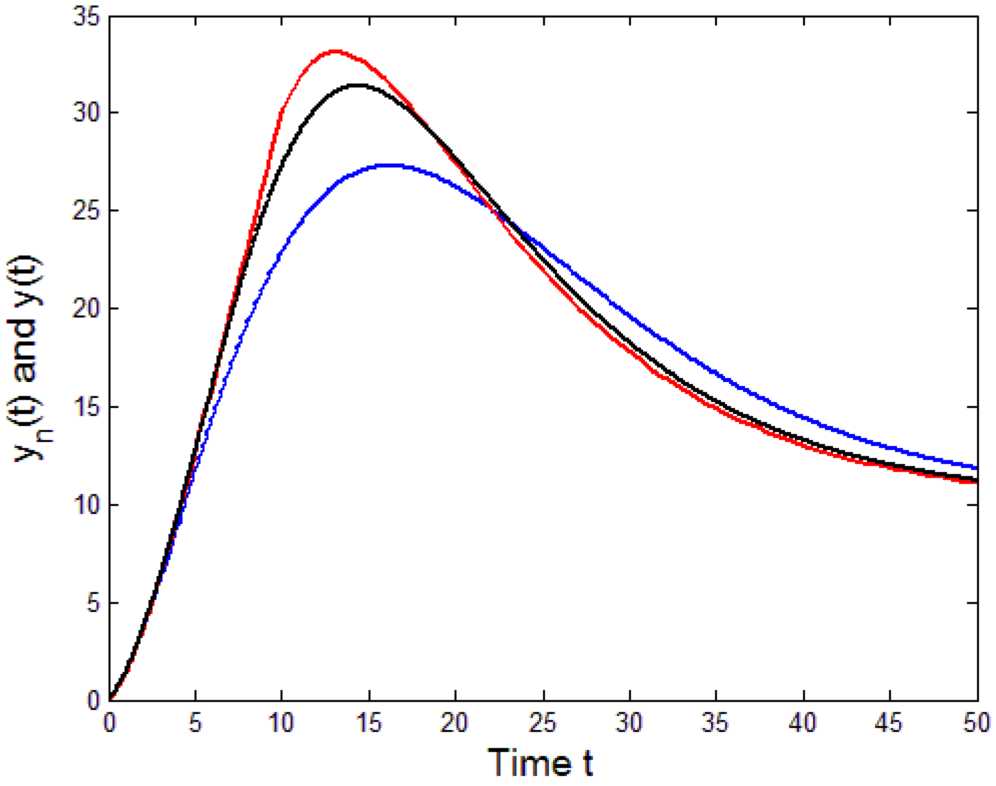


Corresponding past

- **The LSM appears as limiting system for the total population of a TCM !**
- **The TCM for a given n is an approximation of the LSM and vice versa !**

For mathematical proof see Koch and Schropp (appearing in the next weeks in JPKPD)

Visualization of the main result



LSM:

$$y'(t) = k_{in}(t) - k_{in}(t-T) \qquad y^0 = 0$$

$$k_{in}(s) = 0\,, -T \leq s \leq 0$$

TCM: $n = 2$

$$x_1'(t) = k_{in}(t) - kx_1(t) \qquad x_1(0) = 0$$

$$x_2'(t) = kx_1(t) - kx_2(t) \qquad x_2(0) = 0$$

$$y_2(t) = x_1(t) + x_2(t)$$

TCM: $n = 10$

$$x_1'(t) = k_{in}(t) - kx_1(t) \qquad x_1(0) = 0$$

$$\vdots$$

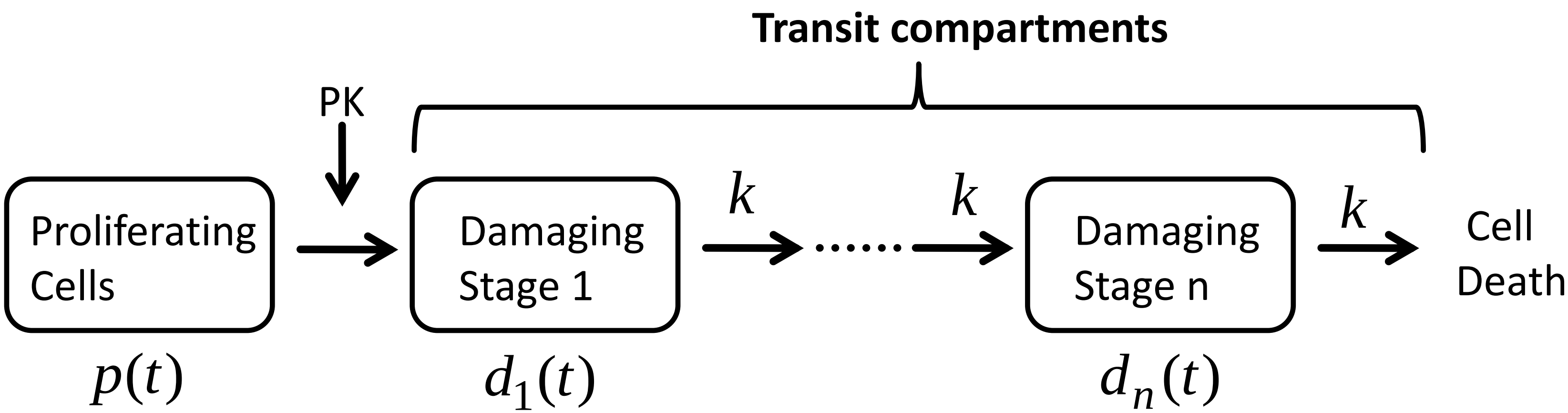
$$x_{10}'(t) = kx_9(t) - kx_{10}(t) \qquad x_{10}(0) = 0$$

$$y_{10}(t) = x_1(t) + \ldots + x_{10}(t)$$

Application to tumor growth model – From TCM to LSM

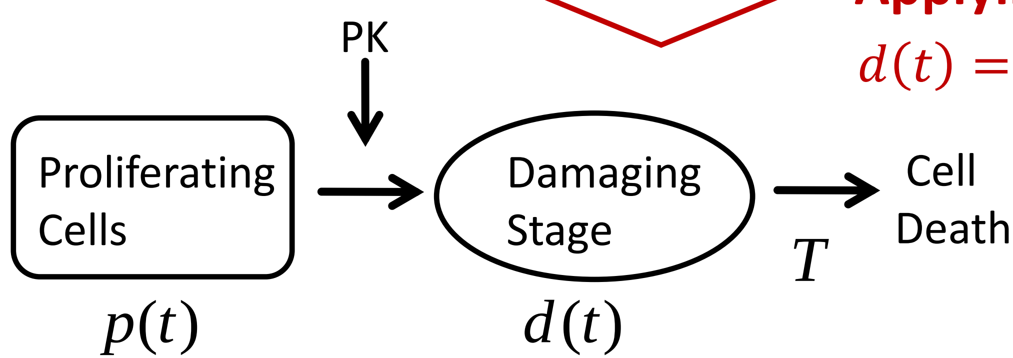
Situation: The population of attacked tumor cells by a drug has a lifespan. After this lifespan the cells irrevocably die!

General structure of a traditional transit compartment based tumor growth model (see e.g. Simeoni et al 2004)



Applying our result !

$$d(t) = d_1(t) + \cdots + d_n(t)$$



Application to tumor growth – From TCM to LSM - In formulae

Formulation with transit compartments:

$$p'(t) = g\big(\eta, p(t), d_1(t) + \cdots + d_n(t)\big) - k_{pot} \cdot c(t) \cdot p(t) \qquad p(0) = w_0$$

$$d_1'(t) = \underbrace{k_{pot} \cdot c(t) \cdot p(t)}_{= k_{in}(t)} - k \cdot d_1(t) \qquad d_1(0) = 0$$

$$d_2'(t) = k \cdot d_1(t) - k \cdot d_2(t) \qquad d_2(0) = 0$$

$$\vdots$$

$$d_n'(t) = k \cdot d_{n-1}(t) - k \cdot d_n(t) \qquad d_n(0) = 0$$

TCM

$$w(t) = p(t) + d_1(t) + \cdots + d_n(t)$$

Formulation as delay differential equation of lifespan type:

$$p'(t) = g\big(\eta, p(t), d(t)\big) - k_{pot} \cdot c(t) \cdot p(t) \qquad p(0) = w_0$$

$$d'(t) = \underbrace{k_{pot} \cdot c(t) \cdot p(t)}_{= k_{in}(t)} - \underbrace{k_{pot} \cdot c(t-T) \cdot p(t-T)}_{= k_{in}(t-T)} \qquad d(0) = 0$$

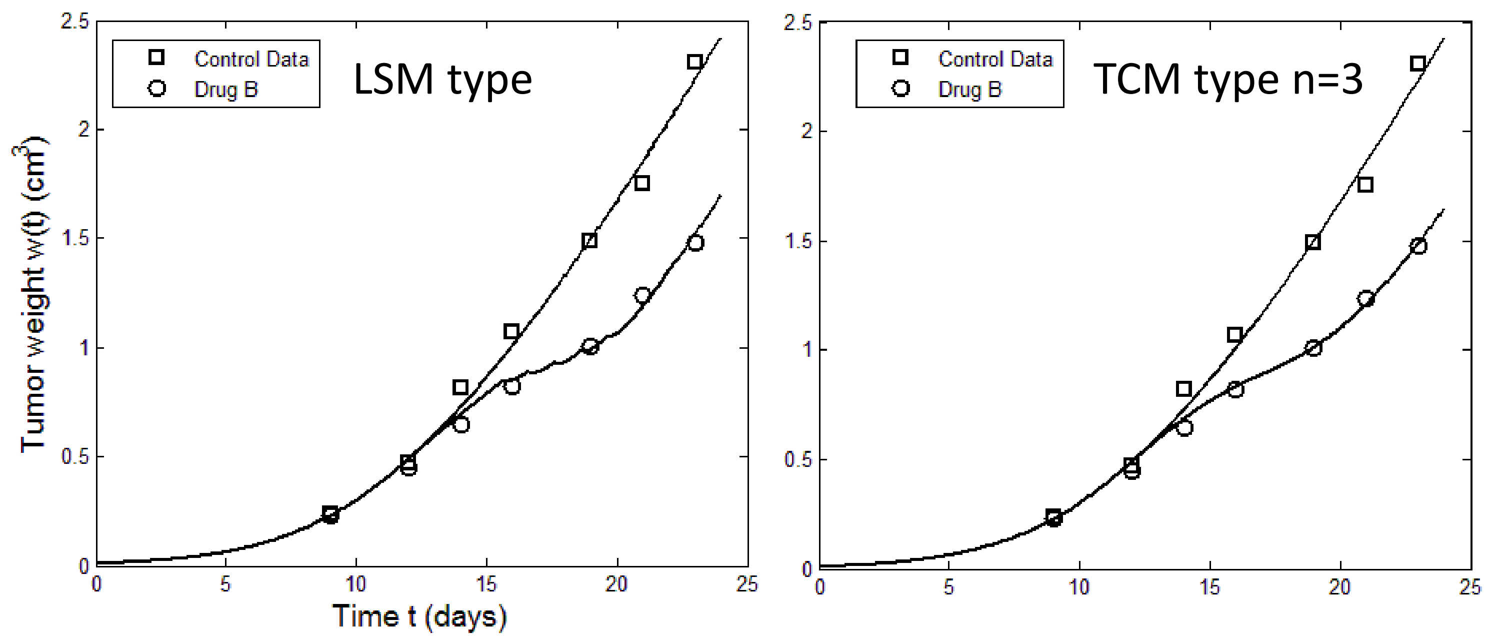
LSM

$$w(t) = p(t) + d(t)$$

Need to provide a past for the outflow in the LSM equation

$$k_{in}(s) = k_{pot} \cdot c(s) \cdot p(s) = 0 \text{ for } -T \leq s \leq 0$$

Results for the tumor growth model in TCM and LSM formulation



- Sum of squares of both models are similar for all our experiments (Xenograft mice)
- The amount of parameters is equal for both formulations
- But the lifespan type model has exactly two states instead of $n+1$ states
  - One for proliferating cells / One for damaging cells
- Lifespan is directly fitted from the data and not calculated as a secondary parameter

Application of delay differential equations to arthritis for strongly delayed bone destruction

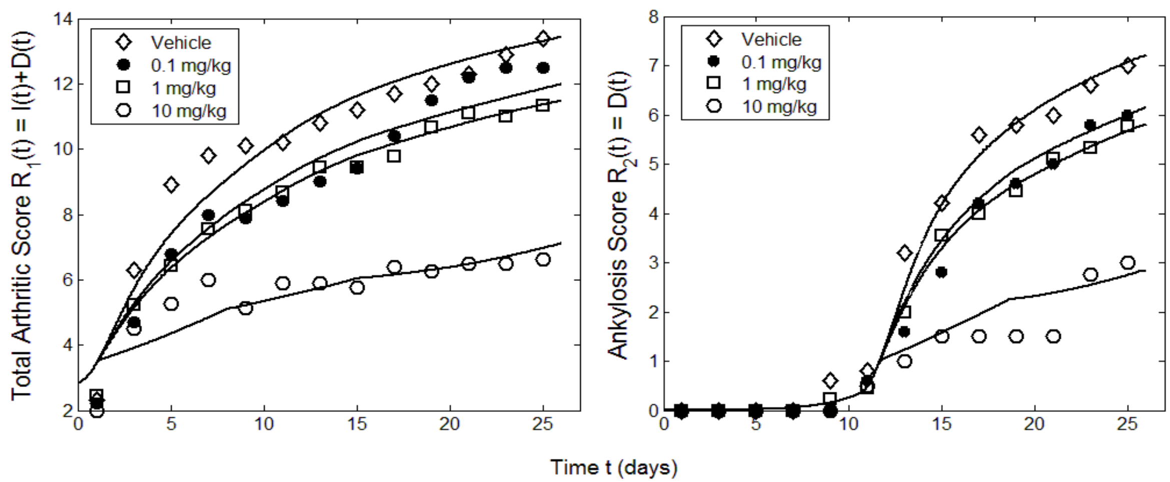
Assumption: The cytokines drive the inflammation and bone destruction in CIA mice

Cytokine: $G'(t) = k_3 - e(c(t), \sigma) \cdot G(t) - k(t) \cdot G(t)$ $\quad G(s) = \exp(bs)$, $-T \leq s \leq 0$

Inflammation: $I'(t) = k_4 \cdot G(t) - k_4 \cdot G(t-T)$ $\quad I(0) = I^0$

Bone destruction: $D'(t) = k_4 \cdot G(t-T) - k_5 \cdot D(t)$ $\quad D(0) = 0$

Delayed development of bone destruction driven by the cytokines!



Optinions to describe delayed phenomena in PKPD

- Delay between PK and PD: → Transit/effect compartment
- 2-3 physiological interpretable population stages: → 2-3 Transit compartments
- Unknown physiological population stages: → Lifespan type models (LSM)
- Large delayed phenomena: → Apply delay differential equations
    - Avoids the use of several unexplainable compartments
    - Direct application of an interpretable delayed state

PKPD Software and DDEs

MATLAB: Internal DDE Solver available - **No Problems**

ADAPT: Internal DDE Solver from Krzyzanski and Bauer will be soon available at BMSR website

NONMEM (Fortran based)**: In principle possible!** (see Perez-Ruixo et al 2005)

MONOLIX (MATLAB based)**: In principle possible!**

Wish and Call to NONMEM/MONOLIX developer:
Please include a numerical DDE solver in PKPD software !

Conclusion

- Main result: The sum of transit compartments is an approximation of the lifespan model
- In general delay differential equations could be used to describe lifespans of cell populations (e.g. dying tumor cells) and strongly delayed phenomena (see e.g. bone destruction in arthritis)
- DDEs avoid the use of unnecessary help differential equations whose states are not really interpretable

Thank you !

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