A multi-response model for rheumatoid arthritis based on delay differential equations in collagen induced arthritic mice treated with an anti-GM-CSF antibody

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Objectives

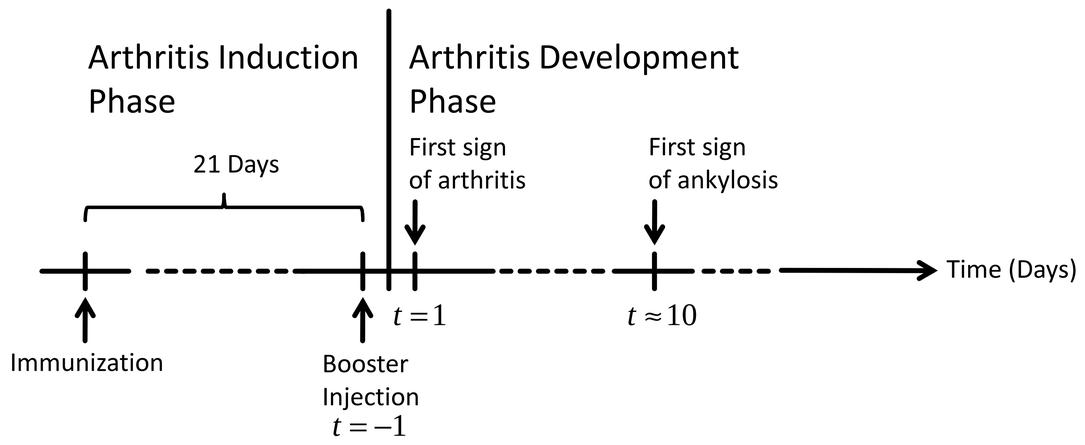
- Development of a **multi response model** to describe the time course of the total arthritic score and the strongly delayed ankylosis score measured in (collagen induced arthritic) CIA mice.
- **Three compartment delay differential equation model** to get a deeper understanding between cytokine level, inflammation and bone destruction.

CIA mouse model

Disease scoring

- A **total arthritic score (TAS)** (integers ranging from 0-4) was measured in each paw and summed up. TAS is an overall estimation of the disease.
- An **ankylosis score (AKS)** (integers ranging from 0-2) was measured in each paw and summed up. AKS describes the bone destruction.

Scheme of the CIA mouse model

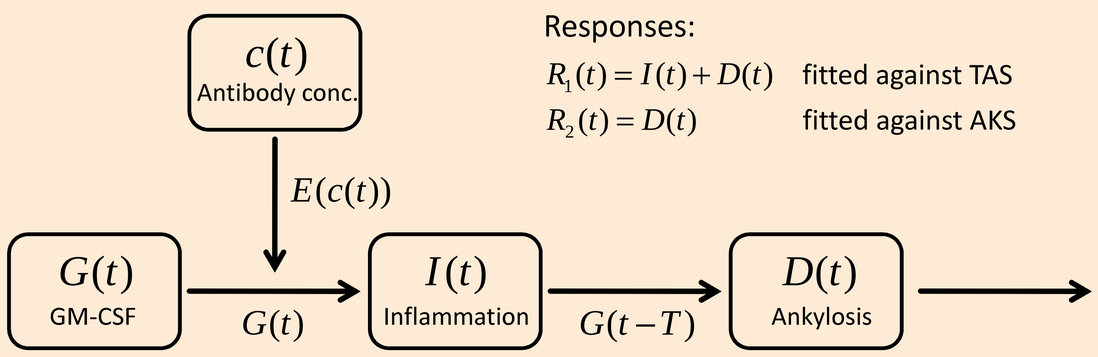


Basic assumptions

Basic assumptions of the arthritic disease development

1. The cytokine GM-CSF $G(t)$ drives the inflammation $I(t)$ and the bone destruction $D(t)$.
2. The arthritis starts with the inflammatory part which dominates the disease 1-2 weeks. Afterwards inflammation decreases but does not vanish completely and remains at a certain level.
3. The bone destructive part of the disease is **delayed by T time units** and appears when the inflammation subsides.

Scheme of the arthritic disease development



Remarks:

- Because we have three “players” in our experiment, more precisely GM-CSF, inflammation and ankylosis, the above scheme is the natural modeling approach for the assumptions 1.-3.

PKPD model

Based on the assumptions 1. - 3. the complete PKPD model reads

$$G'(t) = k_3 - E(c(t))G(t) - \frac{k_1}{k_2}(1 - \exp(-k_2 t))G(t) \quad (1)$$

$$I'(t) = k_4 G(t) - k_4 G(t - T) \quad (2)$$

$$D'(t) = k_4 G(t - T) - k_5 D(t) \quad (3)$$

with the effect term $E(c(t)) = \sigma_1 \cdot \exp(-\sigma_2 \cdot c(t)) \cdot c(t) + \sigma_3 \cdot c(t)$ and with the responses

$$R_1(t) = I(t) + D(t), \qquad R_2(t) = D(t).$$

The initial properties for the delay differential equation (DDE) system (1)-(3) are

$$G(s) = a \exp(bs) \quad \text{for } 0 \geq s \geq -T\,, \quad (4)$$

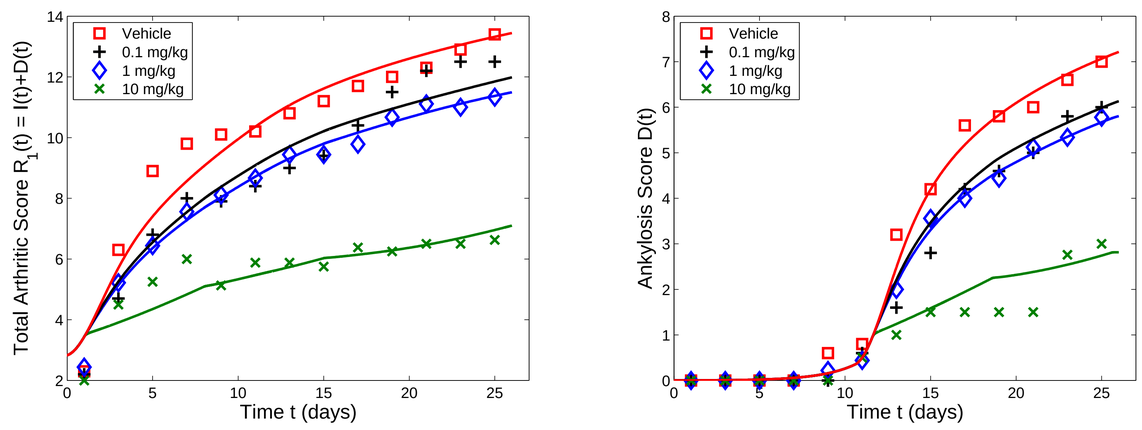
$I(0) = I_0 > 0$ and $D(0) = 0$. The model parameters are $\theta = (k_1, k_2, k_3, k_4, k_5, \sigma_1, \sigma_2, \sigma_3, a, b, T, I_0)$.

- Because DDEs use information from the past, see (2) and (3), one has to provide an initial function (4) which describes the GM-CSF concentration in the arthritic induction phase.

Results

We fitted simultaneously the responses TAS and AKS over all dosing levels (vehicle, 0.1 mg/kg (day 1,8,15), 1 mg/kg (day 1,8,15) and 10 mg/kg (day 1,8,15)).

Total arthritic score and ankylosis score data



Additional model output: Inflammation and qualitative GM-CSF behavior

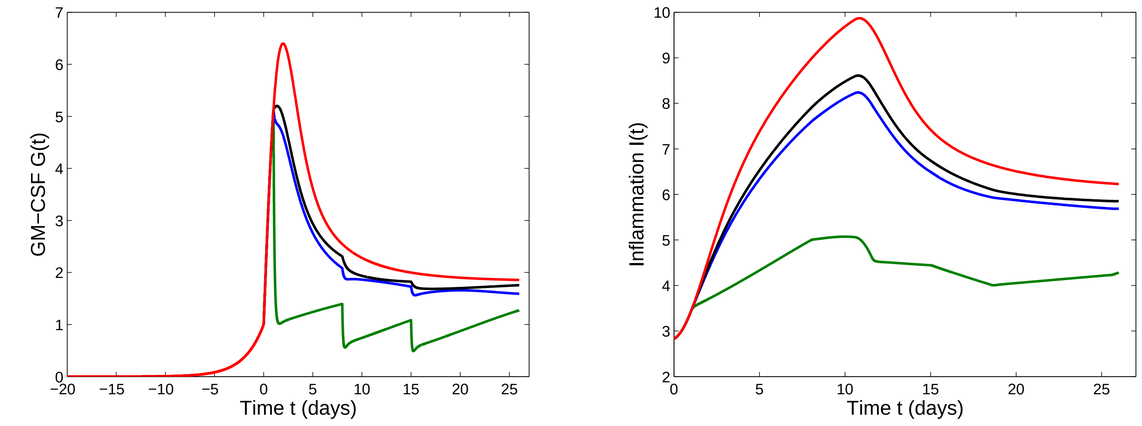


Figure: In every pattern the curves are top down vehicle, 0.1, 1 and 10 mg/kg.

In the fitting process the parameters k_3, a and b were fixed.

Conclusions

- We presented an PKPD model for CIA mice with three compartments and only three differential equations to describe the interaction of the cytokine GM-CSF, the inflammation and the bone destruction.
- The presented PKPD model could easily be reformulated as ordinary differential equation to grant the use of standard software (e.g. ADAPT).