

# Pharmacodynamic age structured population model for cell trafficking

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## Introduction

Cell trafficking encompasses movement of the immune system cells (e.g., granulocytes, lymphocytes) between the blood and the extravascular tissues (e.g., lymph nodes). Basophils are effector cells responsible for inflammatory reactions during the immune challenge. Basophils are used as biomarkers of inflammatory responses. Corticosteroids are known to suppress cell trafficking [1]. Existing models of cell trafficking employ the methodology of compartmental systems where the cells transfer between two compartments at first-order rates. Such an approach limits the model ability to account for prolonged times most of the immune cells spend outside the vasculature before recirculating to the blood. The age-structured population models introduce the transit time as a structure that allows to quantify the distribution of times the immune cells spend in the blood and the extravascular tissues. The key tools are the hazards of transfer between the tissues and hazards of cell death. The hazard can depend on the cell age (e.g., the time it spends in the tissue) and the time (e.g., through the time-dependent drug effect). The numerical challenge is that the age-structured population models are first-order partial differential equations with two independent variables (time and age) that require integration over the age domain to obtain the observable cell counts.

## Objectives

- To develop an age-structured population model capable of describing drug effects on cell trafficking
- To implement the model in pharmacometric software to enable parameter estimation and simulations
- To validate our model using published data on corticosteroid inhibition of the basophil counts in healthy volunteers

## Methods

We adopted the well-known McKendrick age-structured population model [2] to describe the age distributions  $n_B(t, a_B)$  and  $n_E(t, a_E)$  in two cell populations: blood cells and cells in the extravascular space. We neglected cell death since our focus was on the cell trafficking rather than cell elimination. The hazard of cell extravasation  $\mu_{BE}$  was assumed to be constant. The hazard of cell recirculation from the extravascular tissues was age dependent and described by the Weibull function parameters shape  $\nu$  and scale  $\beta$ . The drug effect on the cell trafficking was modeled as the product of the  $E_{\max}$  function of the drug plasma concentration and the Weibull hazard. The blood cell count  $N_B(t)$  was obtained by the integration of  $n_B(t, a_B)$  with respect to  $a_B$ . The integration reduced our model to a distributed delay differential equation (DDDE) with a constant past [3]. The model was implemented in NONMEM 7.5.1 (ICON LLC) where the DDDE was solved by a new approximation of the convolution integral based on the transit compartment models. The model was applied to the basophil data in 34 healthy subjects who received a single intramuscular (IM) or oral (PO) dose of 6 mg dexamethasone (DEX) [4]. A recently published pharmacokinetic model was applied to describe DEX plasma concentration [5]. Typical values of parameter estimates were further used to simulate the DEX effect of the basophil mean transit time in the extravascular tissues ( $MTT_E$ ).

## Results

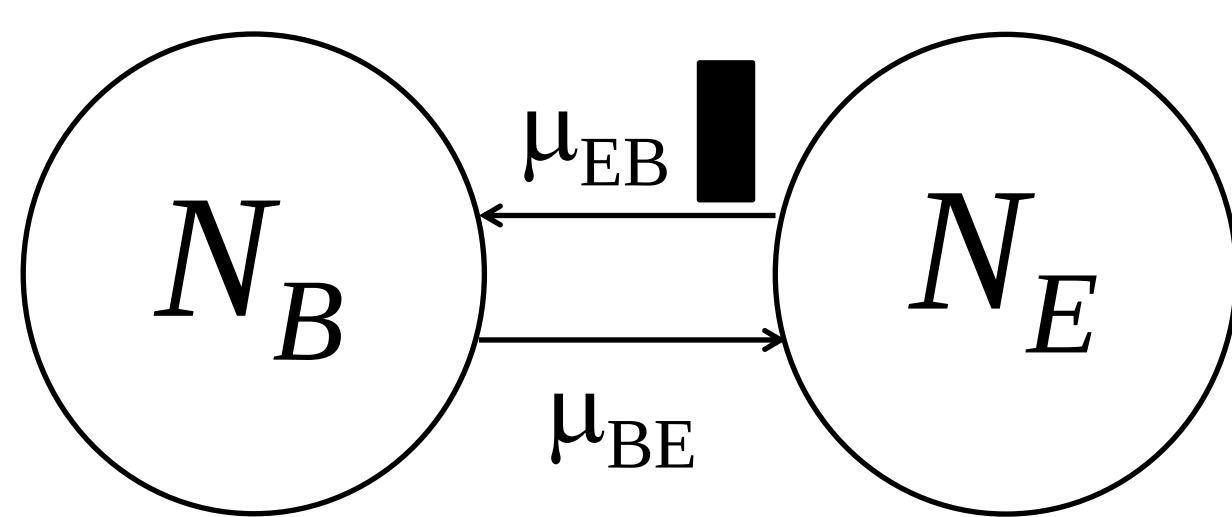


**Fig. 1.** Schematic diagram of an age structured cell population model for basophil trafficking. Blood basophils  $N_B$  are transferred to the extravascular space at the constant hazard  $\mu_{BE}$ . The basophils in the extravascular tissues  $N_E$  recirculate into the blood at the age dependent hazard  $\mu_{EB}(a_E)$  that is inhibited by corticosteroid plasma concentration  $C(t)$  with the inhibitory function  $E(C)$  described by the Emax model.

$$\frac{dN_B}{dt} = -\mu_{BE}N_B + \mu_{BE}E(C(t)) \int_0^\infty N_B(t - a_E)\mu_{EB}(a_E)S_E(t, a_E)da_E$$

$$N_B(t) = N_{B0}, \text{ for } t \leq 0$$

$$\mu_{EB}(a_E) = \beta\nu(\beta a_E)^{\nu-1}$$

$$E(C(t)) = 1 - \frac{I_{\max}C(t)}{IC_{50} + C(t)}$$

$$S_E(t, a_E) = \exp\left(-\int_0^{a_E} E(C(z+t-a_E))\mu_{EB}(z)dz\right)$$

$$MTT_E(t) = \int_t^\infty \exp\left(-\int_t^{\tau_E} E(C(z))\mu_{EB}(z-t)dz\right)d\tau_E$$

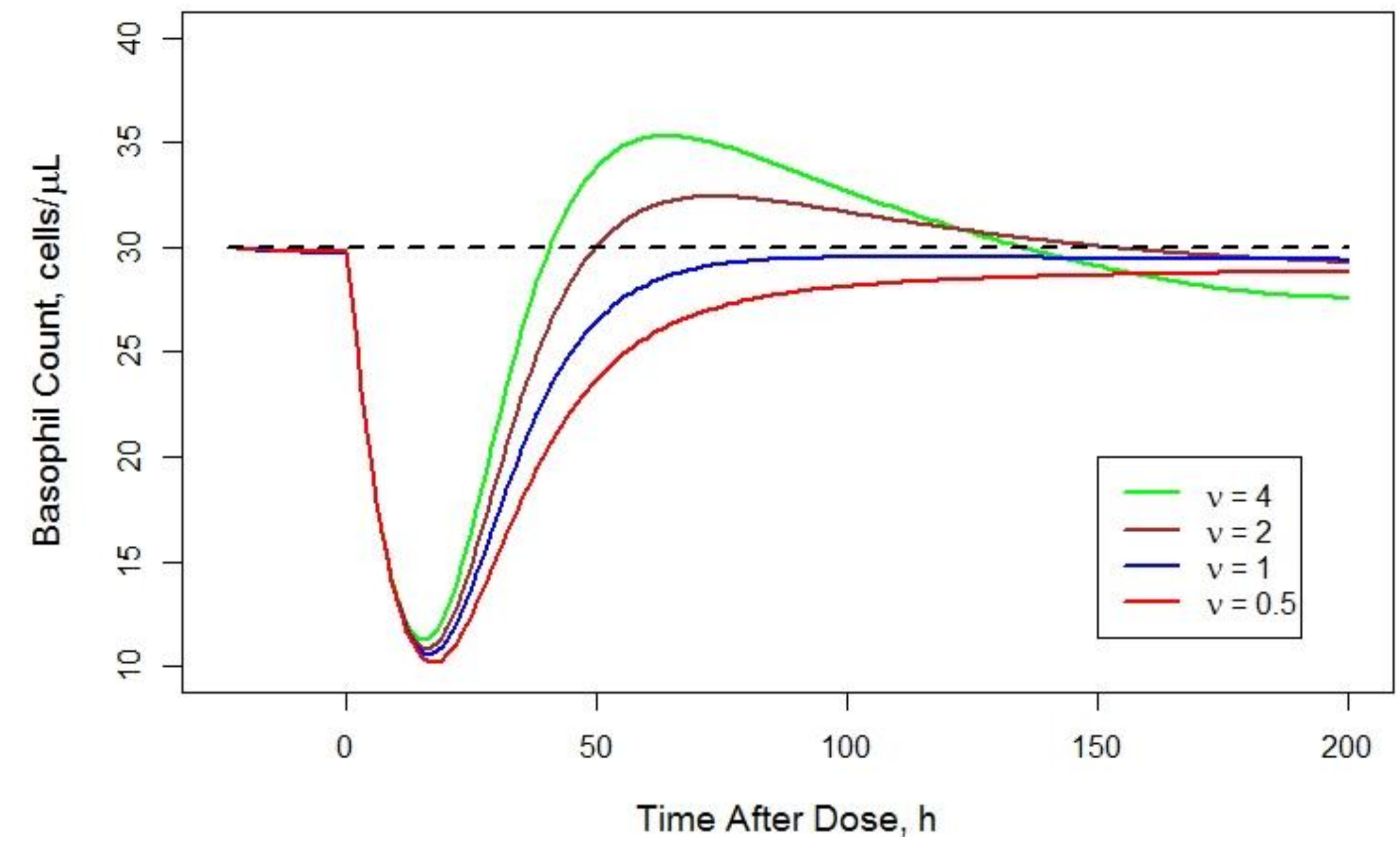


**Fig. 2.** Simulated time courses of basophil counts following IM injection of 6 mg of DEX in a typical subject for varying values of the shape parameter  $\nu$ . Only for  $\nu > 1$  the rebound in the response curve can be observed. The remaining PD parameters used for simulations were  $N_{B0} = 30$  cells/ $\mu\text{L}$ ,  $\mu_{BE} = 1$  h<sup>-1</sup>,  $\beta = 0.005$  h<sup>-1</sup>,  $IC_{50} = 5$  ng/mL, and  $I_{\max} = 1$ .

| Parameter                       | Definition                                                                               | Typical Value (%RSE) | IIV (%RSE) (%IIV)*  |
|---------------------------------|------------------------------------------------------------------------------------------|----------------------|---------------------|
| $N_{B0}$ , cells/ $\mu\text{L}$ | Baseline basophil count in blood                                                         | 29.1 (6.5)           | 0.137 (20.2) (38.3) |
| $\mu_{BE}$ , 1/h                | Hazard of cell transfer from blood to extravascular tissues                              | 0.131 (0.2)          | 0**                 |
| $\nu$                           | Shape factor for Weibull hazard of cell transfer from extravascular space to blood       | 6.76 (16.3)          | 0.0536 (172) (23.5) |
| $\beta$ , 1/h                   | Scale factor for Weibull hazard of cell transfer from extravascular space to blood       | 0.00489 (8.4)        | 0.0108 (101) (10.4) |
| $I_{\max}$                      | Maximal inhibition of basophil trafficking                                               | 1.0**                | NA                  |
| $IC_{50}$ , ng/mL               | DEX plasma concentration eliciting 50% of the maximum inhibition of basophil trafficking | 6.35 (20.9)          | 0.835 (23.5) (114)  |
| $\sigma^2$                      | Variance of residual error for basophil count                                            | 0.0907 (5.6)         | NA                  |

\* %IIV =  $\sqrt{\exp(IIV) - 1} \cdot 100\%$ ; \*\* Parameter was fixed.

**Table 1.** Estimates of PD parameters, their relative standard errors (RSE), and inter-subject variabilities (IIV).

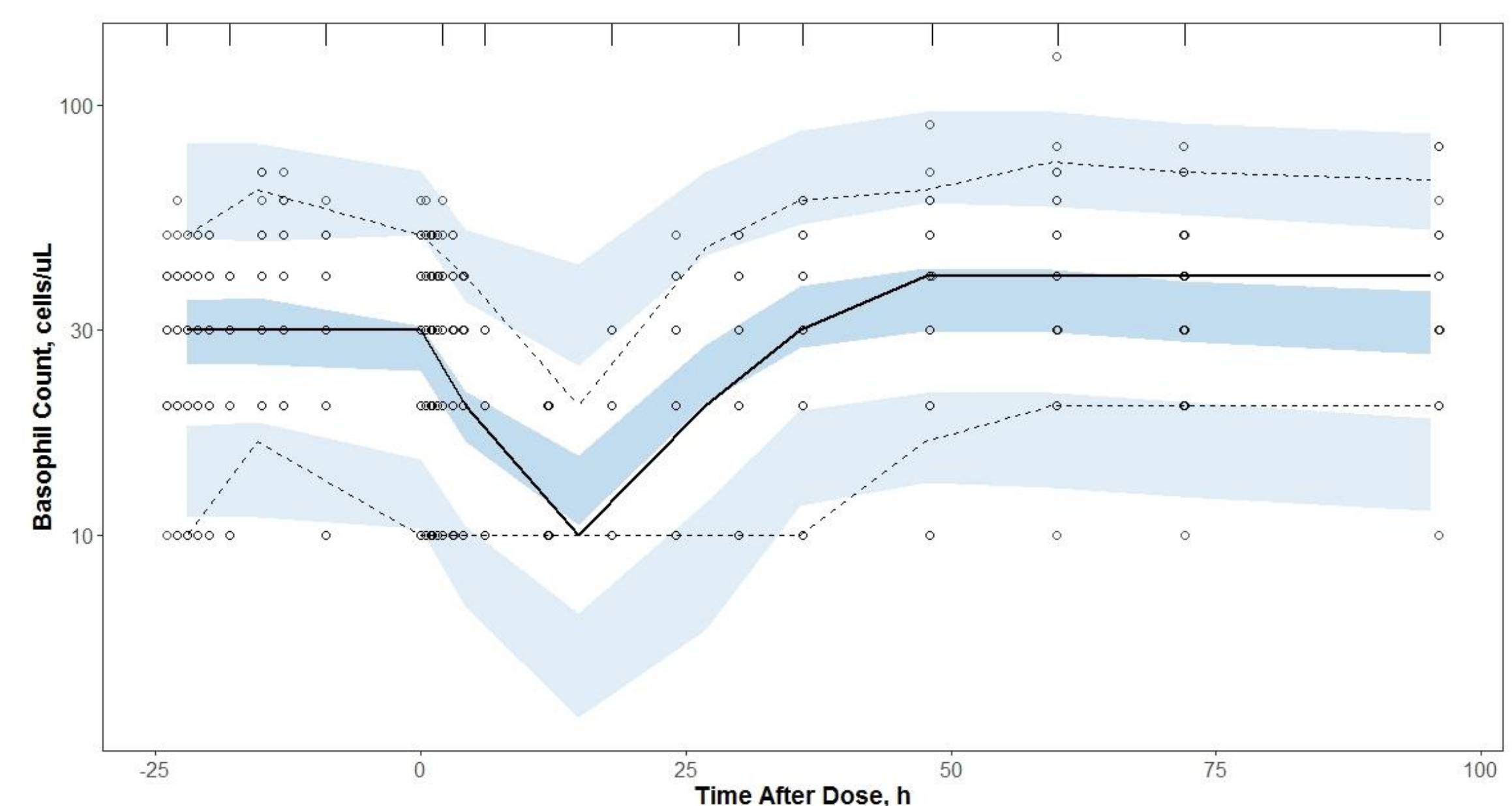


**Fig. 3.** Visual predictive check plots for basophil counts in healthy subjects following IM or PO administration of 6 mg of DEX. Symbols represent observed cell counts, continuous line is the median, and dashed lines are 5<sup>th</sup> and 95<sup>th</sup> percentiles of observed values. The shaded regions are model-predicted confidence intervals for these percentiles.

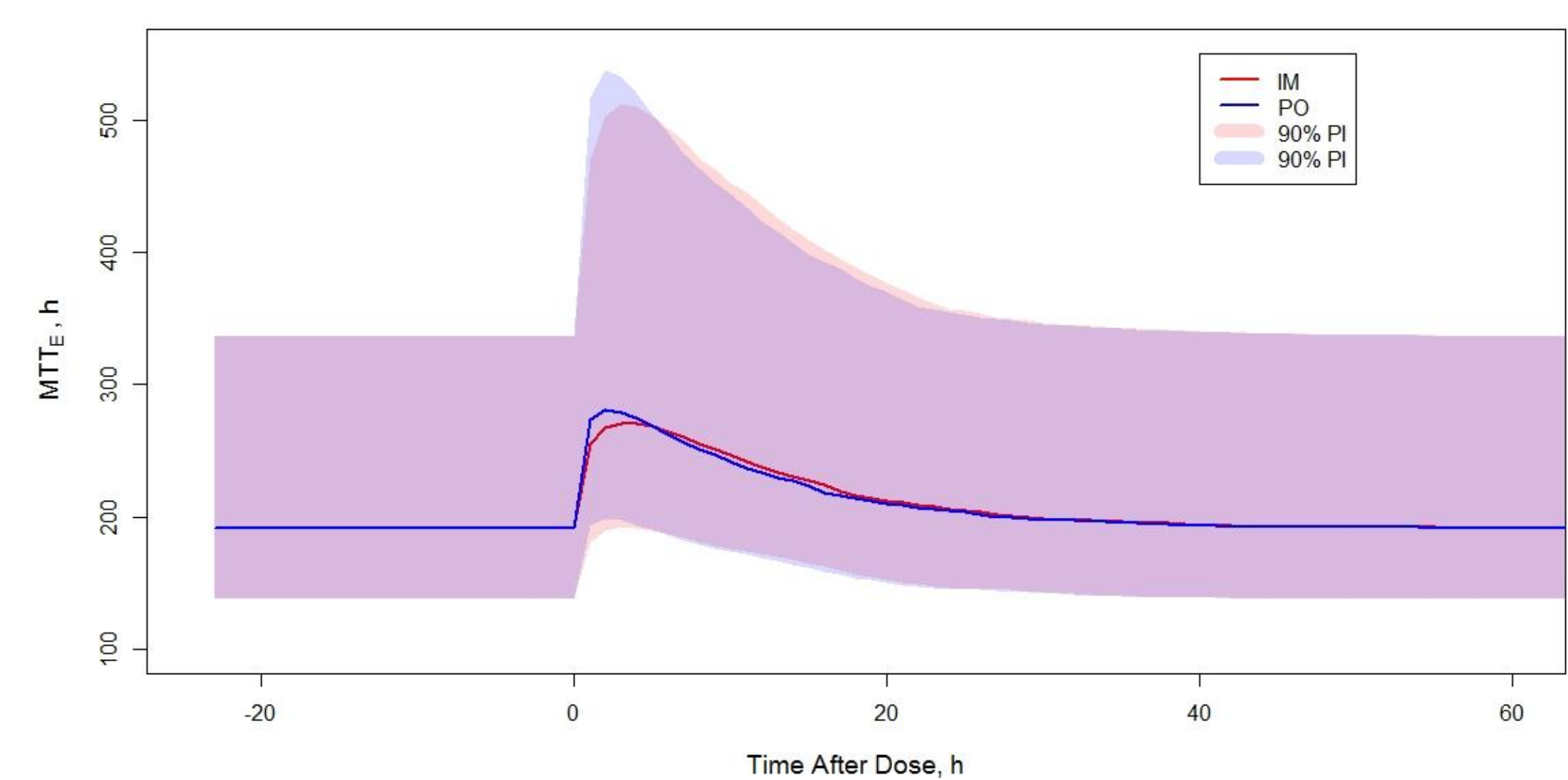


**Fig. 4.** Simulated time courses of the basophil mean transit time in the extravascular space following IM or PO administration of 6 mg of DEX. The continuous lines indicate the median  $MTT_E$ , and the shaded regions are 90% prediction intervals. A single dose of DEX increases  $MTT_E$  up to 271.0 h (IM) and 281.0 h (PO) from the baseline value of 191.4 h.

## Conclusions

We introduced an age-structured population model to describe cell trafficking between the blood and extravascular tissues. The model was adopted to account for the inhibitory drug effect on the cell recirculation. We showed that the age structure is essential to explain the rebound observed in the blood count response to a single dose drug administration. The model was validated using the basophil responses to DEX treatment in healthy subjects.

## References

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