Pharmacodynamic Age Structured Population Model for Cell Trafficking

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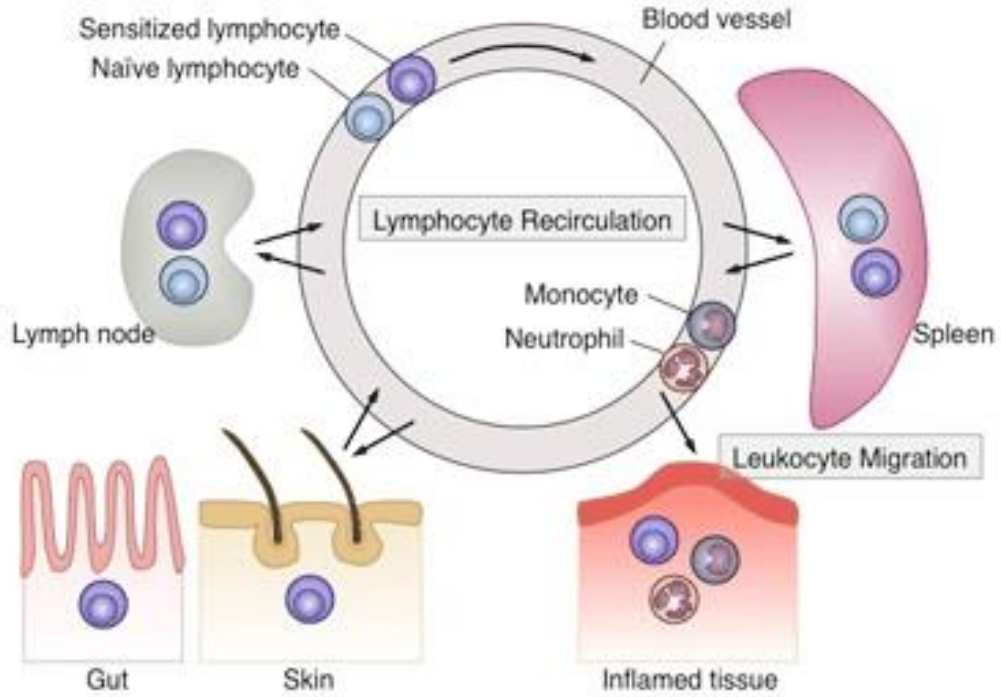
Immune Cell Trafficking



Immune cells traffic in the body, and their migratory patterns are different depending on the cell types. Lymphocytes **migrate** to peripheral tissues such as lymph nodes, spleen, skin, gut, and inflamed tissue. They **recirculate** to the blood from the peripheral tissues via the lymph, and back to blood.

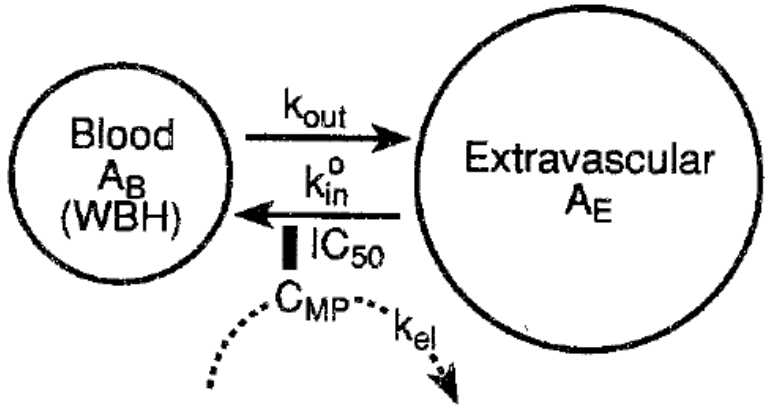
Figure obtained from www.shiga-med.ac.jp/~hqbio/research-e.html

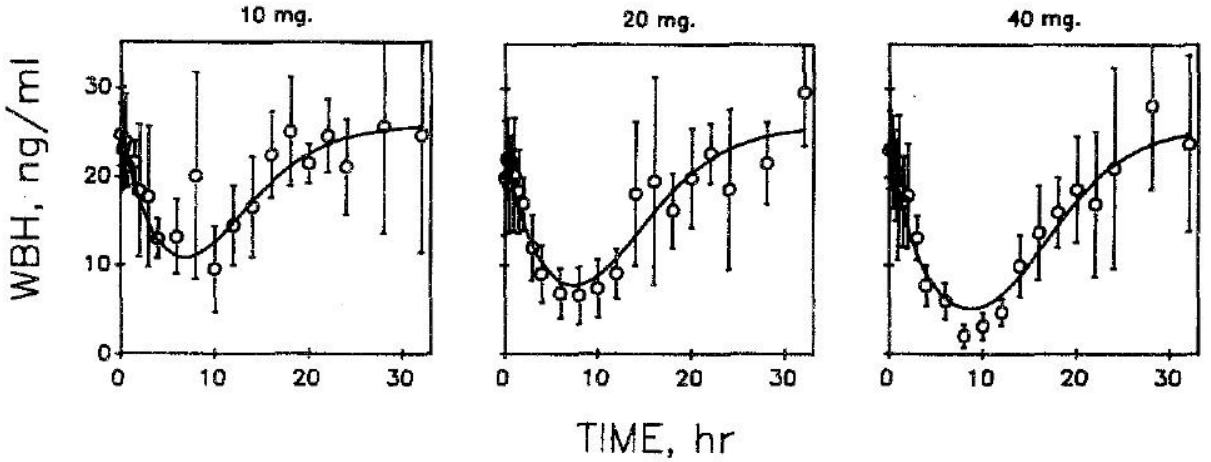
Basophil Pharmacodynamics

- Basophils are the least abundant granulocytes as they account for approximately 0.5% of circulating leukocytes and approximately 0.3% of nucleated marrow cells
- They differentiate and mature in the bone marrow and then they circulate in the blood
- Basophil lifespans under homeostatic conditions are about 1-2 days
- Basophils are effector cells responsible for inflammatory reactions during immune responses. In response to inflammatory signals, they rapidly expand in the bone marrow, are mobilized to the blood, and are recruited into peripheral tissues at sites requiring immunogenic responses
- Glucocorticoids inhibit movement of lymphocytes from the extravascular pool to the blood pool
- Basophils are used as markers of glucocorticoids suppression of inflammatory responses

Min et al. Understanding the roles of basophils: breaking down. Immunology 135:192–197 (2011) doi:10.1111/j.1365-2567.2011.03530.x
Milad et al. Pharmacodynamic model for joint exogenous and endogenous corticosteroid suppression of lymphocyte trafficking, J Pharmacokin Biopharm 22: 469-480 (1994) doi:10.1007/BF02353790

Two-Compartment Basophil Cell Trafficking Model





The basophil cell trafficking model in which A_B is the number of basophils in the blood measured as whole blood histamine (WBH); k_{out} is a first-order rate constant for the movement of basophils from blood to extravascular sites; A_E is the number of circulating basophils in the extravascular pool; k_{in} is the apparent zero-order return rate constant.

Mean whole blood histamine (WBH) for three dose levels of methylprednisolone administered IV into 5 male subjects. Symbols are the observed data and lines are the model fitted curves.

Wald et al.(1991) Two-compartment basophil cell trafficking model for methylprednisolone pharmacodynamics. J Pharmacokinet Biopharm 19:521-236 (1991) doi:10.1007/BF01062961

McKendrick-Von Foerster Model of Age-Structured Population

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(t,a)n$$

$$n(t,0) = \int_0^\infty \lambda(t,a)n(t,a)da$$

$$n(0,a) = n_0(a)$$

$n(t,a)$= age density at time t: $\int_{a_1}^{a_2} n(t,a)da$ =number of subjects of age $a_1 < a < a_2$

$\mu(t,a)$= death hazard at time t (per capita mortality rate)

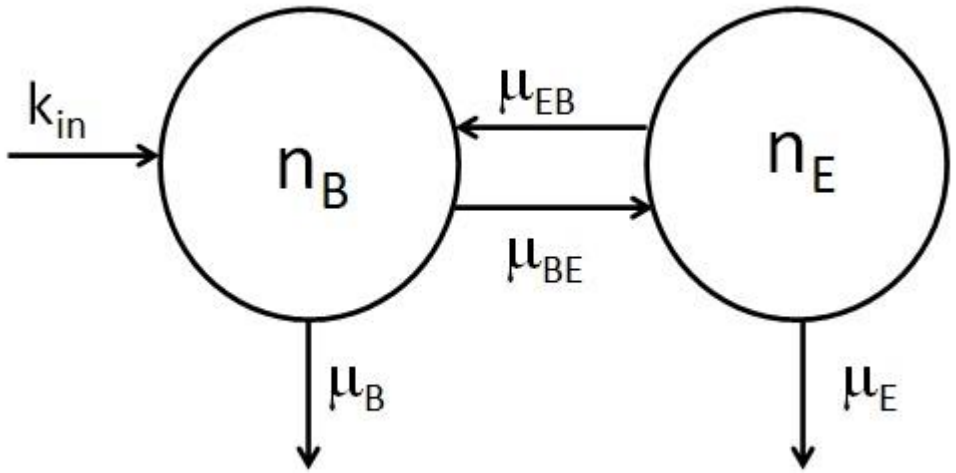
$\lambda(t,a)$= fertility rate at time t (renewal rate)

$n_0(a)$= initial age density

The McKendrick-Von Foerster model of age-structured population describes the evolution in time t the density of age a distribution among individuals in a given population $n(t,a)$. The age distribution is controlled by the mortality rate $\mu(t,a)$ and the birth rate $n(t,0)$ that is defined by the reproduction rate $\lambda(t,a)$.

Brauer F, Castillo-Chavez C, Mathematical Models in Population Biology and Epidemiology. Springer-Verlag, New York, 2001
McKendrick AG (1926) Applications of mathematics to medical problems. Proc Edinburgh Math Soc 40:98-130

Age-Structured Population Model for Cell Trafficking



$$\frac{\partial n_B}{\partial t} + \frac{\partial n_B}{\partial a_B} = -(\mu_B(t, a_B) + \mu_{BE}(t, a_B))n_B$$

$$\frac{\partial n_E}{\partial t} + \frac{\partial n_E}{\partial a_E} = -(\mu_E(t, a_E) + \mu_{EB}(t, a_E))n_E$$

$$n_B(t, 0) = k_{in}(t) + \int_0^\infty \mu_{EB}(t, a_E)\, n_E(t, a_E) da_E$$

$$n_E(t, 0) = \int_0^\infty \mu_{BE}(t, a_B) n_B(t, a_B) da_B$$

$$n_B(0, a_B) = n_{B0}(a_B) \quad n_E(0, a_E) = n_{E0}(a_E)$$

$n_B(t, a_B)$, $n_E(t, a_E)$: age densities in two cell populations: cells that contribute to the circulating blood (e.g., red blood cells, lymphocytes, granulocytes, platelets) and cells in the extravascular space that recirculate to the blood.

a_B, a_E: cell ages interpreted as the times that elapsed since a cell enter the blood or extravascular space (either by birth, recirculation, or trafficking from another tissue)

$\mu_{BE}(t, a_B)$, $\mu_{EB}(t, a_E)$: time dependent hazards of extravasation and recirculation, respectively

$\mu_B(t, a_B)$, $\mu_E(t, a_E)$: hazards of cell death understood as senescence or irreversible removal from the blood or the extravascular space

$k_{in}(t)$: cell production rate that accounts for the efflux of cells to the blood other than the recirculation (e.g., birth or release from other tissues such as the bone marrow)

$n_{B0}(a_B)$, $n_{E0}(a_E)$: age densities at time 0 (e.g., steady-state solutions)

Steady Sate Solutions

$$\frac{\partial n_{Bss}}{\partial a_B} = -\left(\mu_{Bss}(a_B) + \mu_{BEss}(a_B)\right) n_{Bss}$$

$$\frac{\partial n_{Ess}}{\partial a_E} = -\left(\mu_{Ess}(a_E) + \mu_{EBss}(a_E)\right) n_{Ess}$$

$$n_{Bss}(0) = k_{inss} + \int_0^\infty \mu_{EBss}(a_E) n_{Ess}(a_E) da_E$$

$$n_{Ess}(0) = \int_0^\infty \mu_{BEss}(a_B) n_{Bss}(a_B) da_B$$

Steady state solutions are the initial conditions for the cell trafficking model

$$n_{B0}(a_B) = n_{Bss}(a_B) \quad \text{and} \quad n_{E0}(a_E) = n_{Ess}(a_E)$$

Integral Formulation of Model

We assume that prior to the pharmacological intervention at time 0, the system is at steady state, then for nonnegative times $t \leq 0$:

$$k_{in}(t) = k_{inss}$$

$$\mu_B(t, a_B) = \mu_{Bss}(a_B) \text{ and } \mu_E(t, a_E) = \mu_{Ess}(a_E)$$

$$\mu_{BE}(t, a_B) = \mu_{BEss}(a_B) \text{ and } \mu_{EB}(t, a_E) = \mu_{EBss}(a_E)$$

Then the model can be formulated in the form of a system of integral equations:

$$n_B(t, a_B) = \left(k_{in}(t - a_B) + \int_0^\infty \mu_{EB}(t - a_B, a_E)\ n_E(t - a_B, a_E) da_E\right) S_B(\mathrm{t} - a_B, a_B)$$

$$n_E(t, a_E) = \int_0^\infty \mu_{BE}(t - a_E, a_B)\ n_B(t - a_E, a_B) da_B S_E(\mathrm{t} - a_E, a_E)$$

where

$$S_B(\mathrm{t}, a_B) = \exp\left(-\int_0^{a_B} \left(\mu_B(z + t, z) + \mu_{BE}(z + t, z)\right) dz\right)$$

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

$S_B(t, a_B) =$ probability of cell survival in the blood from time t to time $t + a_B$.

$S_E(t, a_E) =$ probability of cell survival in the extravascular tissue from time t to time $t + a_E$.

Mean Transit Time

The probability density function for the distribution of the transit times among the cell in the tissue at time t can be inferred from the survival function:

$$\ell_B(t,\tau_B) = \big(\mu_{BE}(t+\tau_B,\tau_B) + \mu_B(t+\tau_B,\tau_B)\big)S_B(t,\tau_B)$$

$$\ell_E(t,\tau_E) = (\mu_{EB}(t+\tau_E,\tau_E) + \mu_E(t+\tau_E,\tau_E)S_E(t,\tau_E)$$

Then the mean transit times of cells in the blood and extravascular tissues at time t are:

$$MTT_B(t) = \int_0^\infty \tau_B \ell_B(t,\tau_B) d\tau_B$$

$$MTT_E(t) = \int_0^\infty \tau_E \ell_E(t,\tau_E) d\tau_E$$

Age-Structured Population Model for Basophil Trafficking

- As the basophils transit time in the circulation is of order of few hours, the hazard of their extravasation to the peripheral tissues is assumed to be age and time independent

$$\mu_{BE}(t, a_B) = \mu_{BE}$$

- Most of basophils die extravascularly, therefore the hazard of basophil death in the blood is much less than the hazard of extravasation:

$$\mu_B(t, a_B) \ll \mu_{BE}$$

- We assume that the hazard of recirculation of basophils to the blood is much higher than their senescence in the extravascular space:

$$\mu_E(t, a_B) \ll \mu_{EB}(t, a_B)$$

- We assume that the efflux of newly produced basophils from the bone marrow to the blood is much less then the efflux of basophils entering the blood from the extravascular space:

$$k_{in}(t) \ll \int_0^\infty \mu_{EB}(t, a_E)\, n_E(t, a_E) da_E$$

- The glucocorticoid inhibitory effect on basophil recirculation is described by the Emax model multiplying the baseline hazard $\mu_{EBss}(a_E)$:

$$\mu_{EB}(t, a_E) = \left(1 - \frac{I_{max} C(t)}{IC_{50} + C(t)}\right) \mu_{EBss}(a_E) \equiv E(C(t)) \mu_{EB}(a_E)$$

Age-Structured Population Model for Basophil Trafficking

$$\frac{\partial n_B}{\partial t} + \frac{\partial n_B}{\partial a_B} = -\mu_{BE} n_B$$

$$\frac{\partial n_E}{\partial t} + \frac{\partial n_E}{\partial a_E} = -E(C(t))\mu_{EB}(a_E) n_E$$

$$n_B(t, 0\ ) = E(C(t)) \int_0^\infty \mu_{EB}(a_E)\ n_E(t, a_E) da_E$$

$$n_E(t, 0\ ) = \mu_{BE} N_B(t)$$

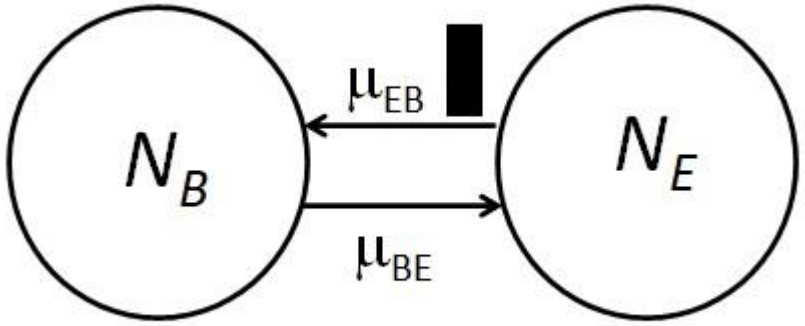
$$n_B(0, a_B) = n_{B0ss}(a_B) \text{ and } \ n_E(0, a_E) = n_{E0ss}(a_E)$$

Cell Count Model for Basophil Trafficking

$N_B(t) = \int_0^\infty n_B(t, a_B) da_B$ and $N_E(t) = \int_0^\infty n_E(t, a_E) da_E$

$N_B(t)$ = basophil count in the blood

$N_E(t)$ = basophil count in the extravascular tissues



Integration of the age-structured model differential equations with respect to a_B or a_B results in:

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

with the past condition

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

N_{B0} = baseline (steady-state) basophil count in the blood

In the absence of $k_{in}(t)$, $\mu_B(t, a_B)$, and $\mu_E(t, a_E)$, the cell count model becomes a closed system:

$$\frac{dN_B}{dt} + \frac{dN_E}{dt} = 0$$

$$N_E(t) = N_{B0} + N_{E0} - N_B(t)$$

N_{E0} = baseline count of basophils in the extravascular space:

$$N_{E0} = N_{B0} \mu_{BE} \int_0^\infty \exp\left(-\int_0^{a_E} \mu_{EB}(\ z)\ dz\right) a_E$$

Mean Residence Time of Basophils in Extravascular Space

The survival function $S_E(\mathrm{t}, a_E)$ for basophils in the extravascular space is

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

The probability density for the distribution of transit times is

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

The mean transit time for basophils in the extravascular tissues at time t defined is

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

Basophil Count Model with Constant Hazard of Recirculation to Blood

$$\mu_{EB}(a_E) \equiv \mu_{EB}$$

$$\frac{dN_B}{dt} = -\mu_{BE}N_B + \mu_{EB}E\big(C(t)\big)N_E$$

$$\frac{dN_E}{dt} = \mu_{BE}N_B - \mu_{EB}E\big(C(t)\big)N_E$$

Initial conditions:

$$N_B(0) = N_{B0} \text{ and } N_{E0} = N_{B0}\mu_{BE}/\mu_{EB}$$

The basophil count model reduces to the two-compartment basophil cell trafficking model.

One can show that

$$N_B(t) < N_{B0} \quad \text{for } t > 0$$

This implies that the two-compartment model does not allow $N_B(t)$ to rebound

Basophil Count Model with Weibull Hazard of Recirculation to Blood

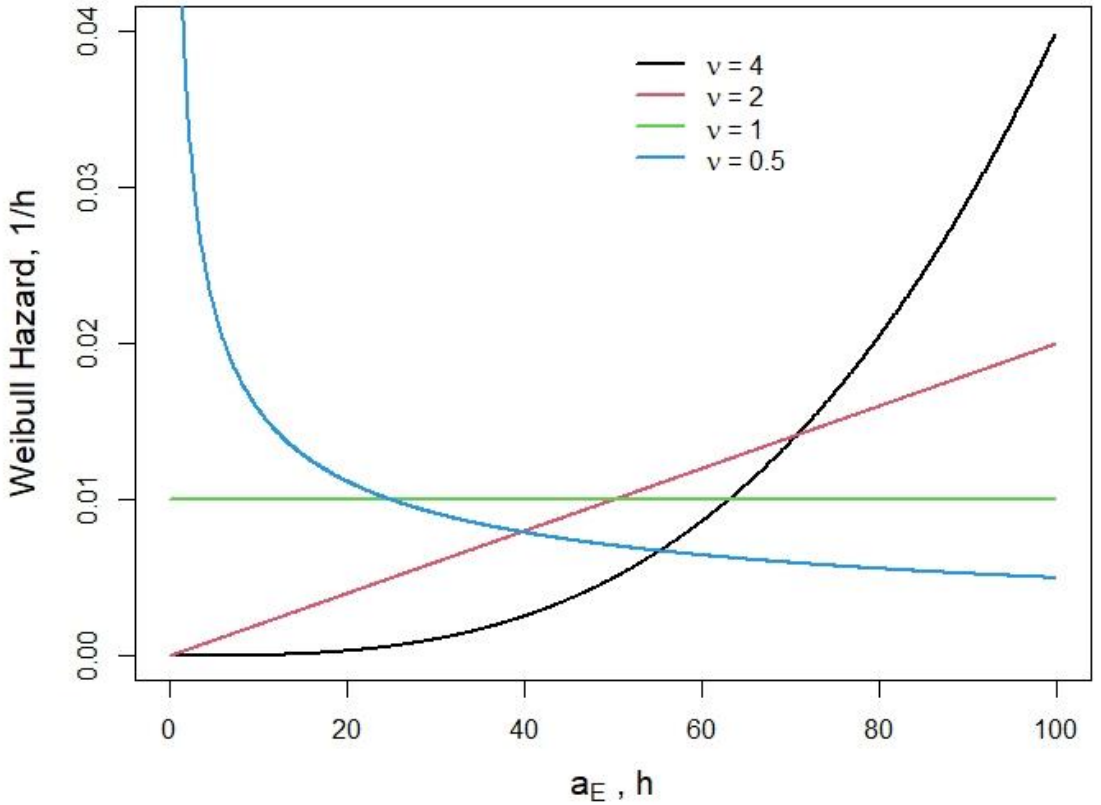
$$\mu_{EB}(a_E) = \nu\beta(\beta a_E)^{\nu-1}$$

β = scale parameter
ν = shape parameters

The baseline ($C(t) = 0$) mean transit time for the basophils in the extravascular tissues:

$$MTT_E = \frac{\Gamma(1+1/\nu)}{\beta}$$

$\Gamma(x)$ = gamma function.



Weibull hazard functions for various shape parameters for β = 0.01 1/h

Transit Compartments Approximation of Basophil Count

The differential equation for N_B requires evaluation of the integral $\int_0^\infty \mu_{EB}(a_E)\ n_E(t,a_E)da_E$:

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

$$\int_0^\infty \mu_{EB}(a_E)\ n_E(t,a_E)da_E \approx \int_0^{T_{END}} \mu_{EB}(a_E)n_E(t,a_E)da_E = \sum_{i=1}^{m}\int_{(i-1)T_{END}/m}^{iT_{END}/m} \mu_{EB}(a_E)n_E(t,a_E)da_E$$

If m is sufficiently large, then

$$\int_{a_{i-1}}^{a_i} \mu_{EB}(a_E)n_E(t,a_E)da_E \approx \mu_{EB}(a_i)n_E(t,a_i)\Delta a = \mu_{EB}(a_i)N_{Ei}(t)$$

where $\Delta a = T_{END}/m$, $a_i = i\Delta a$, and $N_{Ei}(t) = n_E(t,a_i)\Delta a$

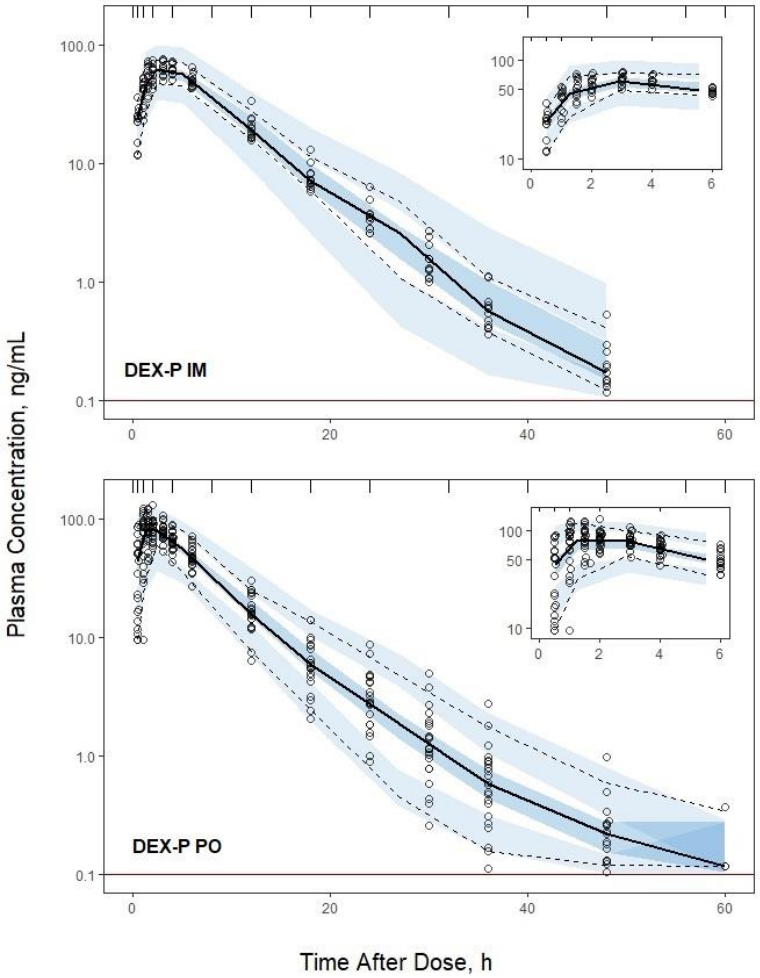
$$\frac{\partial}{\partial t}\int_{a_{i-1}}^{a_i} n_E(t,a_E)da_E + n_E(t,a_i) - n_E(t,a_{i-1}) = -E\big(C(t)\big)\int_{a_{i-1}}^{a_i} \mu_{EB}(a_E)n_E(t,a_E)da_E$$

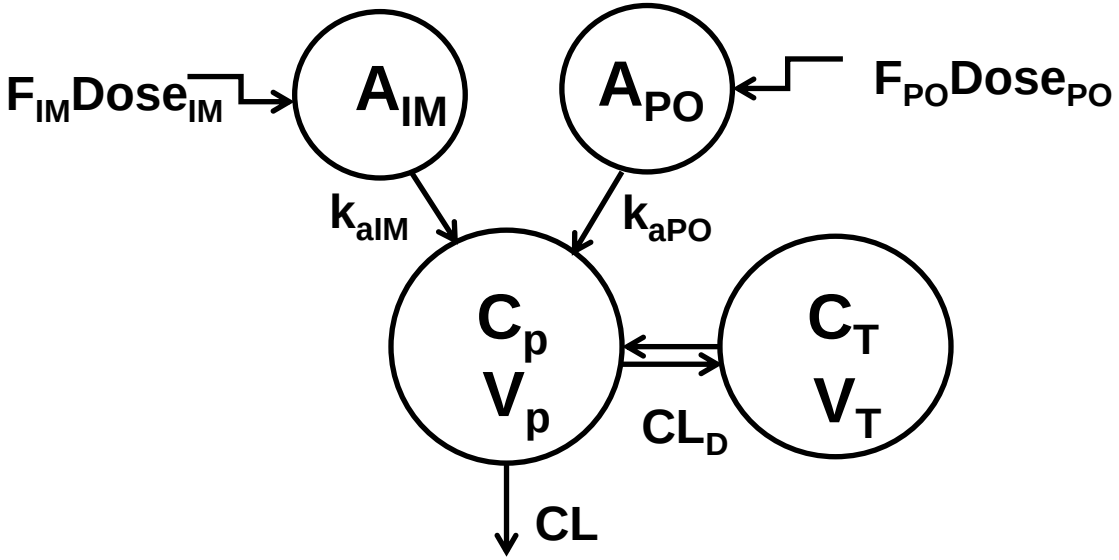
$$\boldsymbol{\frac{dN_{Ei}}{dt} = \frac{m}{T_{END}}(N_{Ei-1} - N_{Ei}) - E\big(C(t)\big)\mu_{EB}(a_i)N_{Ei}(t)} \qquad i = 1,\dots,m$$

$$\boldsymbol{N_{E0}(t) = \frac{\mu_{BE}T_{END}}{m}N_B(t)}$$

Koch et al. Distributed transit compartments for arbitrary lifespan distributions in aging populations. J Theor Biol 380:550-558 (2015)

Population PK Model of Dexamethasone In Healthy Subjects





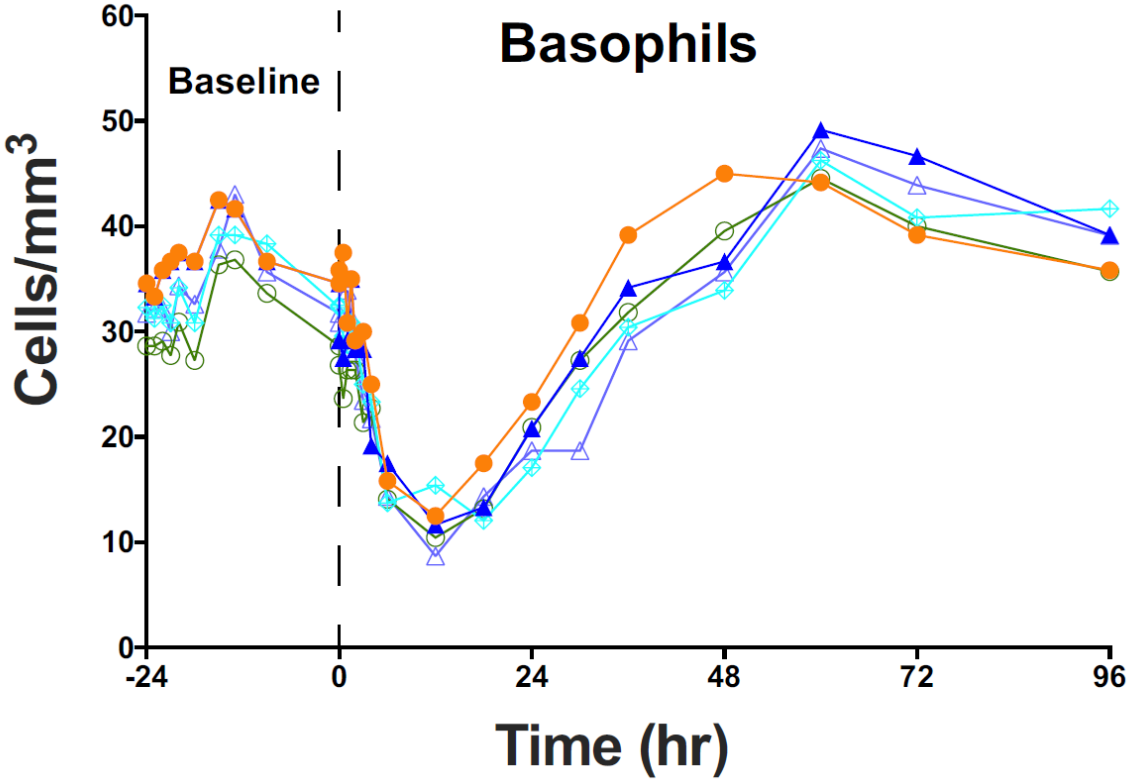
Parameter	Estimate (%RSE) of typical value	Estimate (%RSE) of variance
CL/F_{IM}, L/h	9.29 (4.4)	0.0265 (4.7) (16.4)*
V_p/F_{IM}, L	51.3 (4.4)	0**
k_{aIM}, 1/h	0.460 (8.8)	0.0633 (29.7) (25.6)*
k_{aPO}, 1/h	0.936 (15.2)	0.395 (23.6) (69.6)*
F_r	1.04 (5.3)	NA
CL_D/F_{IM}, L/h	0.538 (4.1)	NA
V_T/F_{IM}, L	5.06 (4.7)	NA
σ^2	0.0455	18.9

34 Indian women received a single 6mg dose of dexamethasone IM or PO. A two-compartment population model was used to describe individual DEX plasma concentrations

Krzyzanski et al., Population pharmacokinetic modeling of intramuscular and oral dexamethasone and betamethasone in Indian women. J Pharmacokinet Pharmacodyn 48:261-272 (2021) doi:10.1007/s10928-020-09730-z

Basophil Count Response to DEX in Healthy Subjects

- Moderate circadian rhythm
- Nadir at 15 h
- Return to baseline at 44 h
- Rebound peak at 65 h
- Decline to baseline at 72 h



Mean basophil counts in healthy Indian women following a single 6 mg dose of dexamethasone or betamethasone PO or IM.

Jobe et al. Pharmacokinetics and pharmacodynamics of intramuscular and oral betamethasone and dexamethasone in reproductive age women in India. Clin Transl Sci 13:391-399 (2020) doi: 10.1111/cts.12724

NONMEM Control Stream for Basophil Trafficking Model: $PK

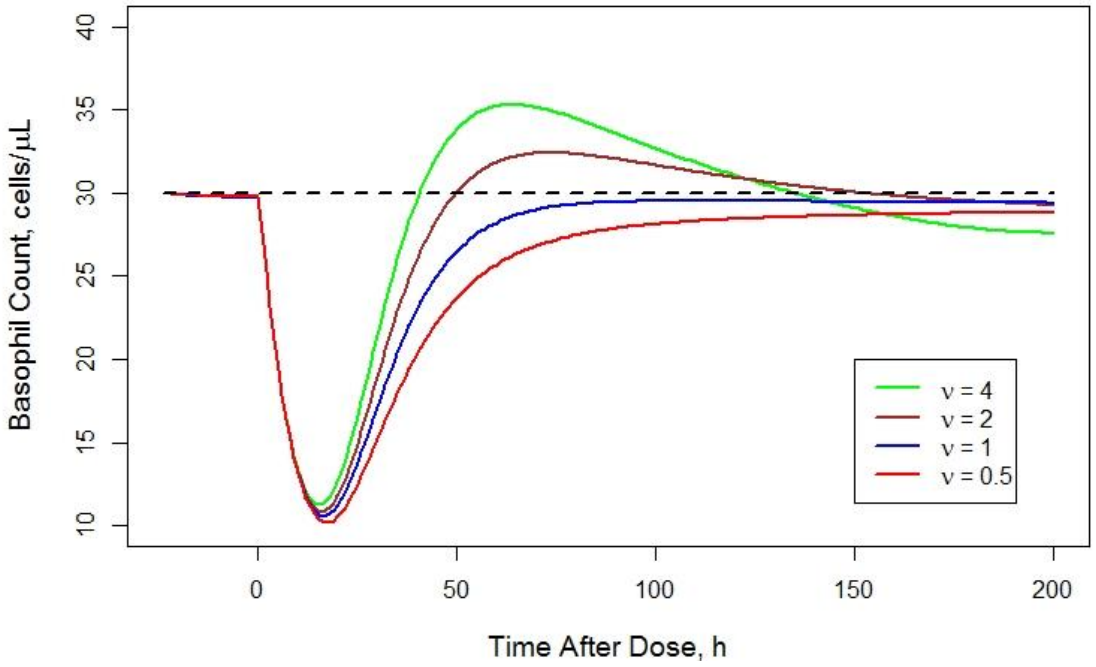
```
$PK
   CALLFL=-2
   MXSTEP=2000000000
   MU_1=LOG(THETA(1))
   MU_2=LOG(THETA(2))
   MU_3=LOG(THETA(3))
   MU_4=LOG(THETA(4))
   MU_5=LOG(THETA(5))

   CB0  =THETA(1)*EXP(ETA(1))
   KOUT =THETA(2)*EXP(ETA(2)) ;MU_BE
   NU   =THETA(3)*EXP(ETA(3))
   BETA =THETA(4)*EXP(ETA(4))
   IC50 =THETA(5)*EXP(ETA(5))
   IMAX =THETA(6)
   F4 = FR

;INITIAL CONDITIONS
   A_0(1)  = CB0
   A_0(2)  = 0
   A_0(3)  = 0
   A_0(4)  = 0
   A_0(5)  = 0

   NN=100
   TEND=1000
   KTR=NN/TEND
```

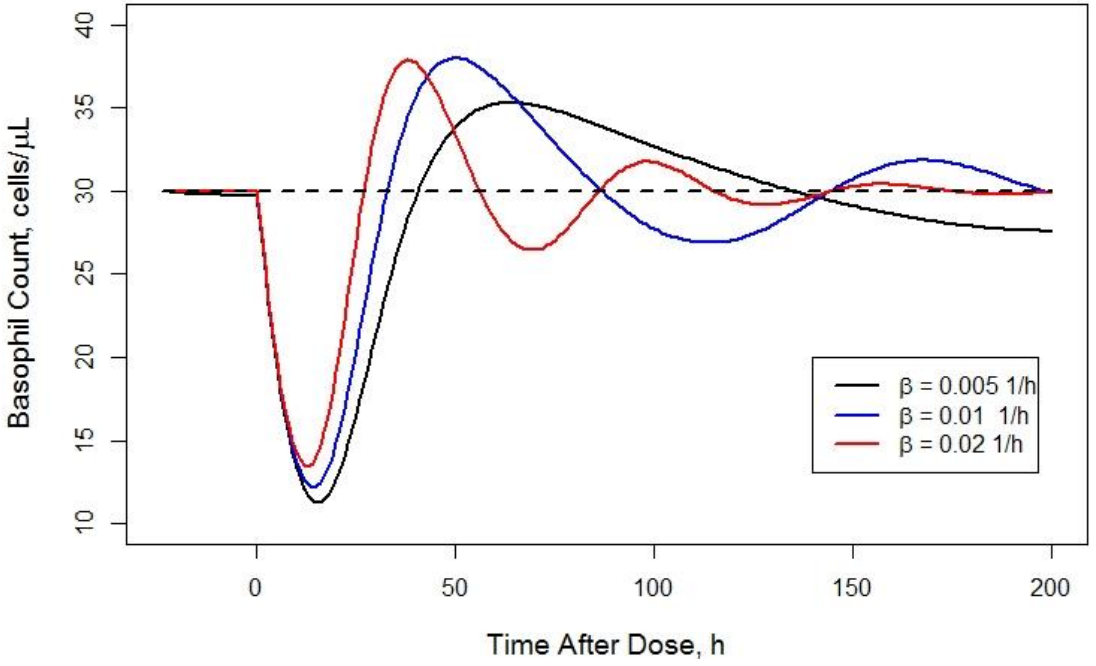
```
; Following is hazard density MU_EB as a function of AE=I/KTR

DOE (I=1,100)
    BB[I]=NU*BETA*(BETA*[I]/KTR)**(NU-1.0)
ENDDOE

   A_0(6)  = KOUT/(KTR+BB1)*CB0

; Initial steady state values of extracellular age
;  sub-compartments

DOE (I=7,104) (J=6,103) (K=2,99)
    A_0(I)=KTR/(KTR+BB[K])*A_0(J)
ENDDOE

    A_0(105)=KTR/BB100*A_0(104)
```

NONMEM Control Stream for Basophil Trafficking Model: $DES

```
$DES
  CP=A(2)/V
  EMAX=1.0-IMAX*CP/(IC50+CP)

; Blood compartments
; First term  is -MU_BE*NB (where A(1)=NB, KOUT=MU_BE), which is transfer from blood to E compartment
; Following this, are EMAX*BBx*Ai return components from E compartment of a specific age AE
; where BBx=MU(AE), A(I)=MU_BE*NB(t-AE)*SE(t,AE)

DADT(1)  = -KOUT*A(1) &
DOE (I=6,105) (J=1,100)
    +EMAX*BB[J]*A(I) &
ENDDOE

; Each extracellular age compartment has rate of exit to blood based on this same EMAX*BBx*Ai

DADT(6)=KOUT*A(1)-(KTR+EMAX*BB1)*A(6)
DOE (I=7,104) (J=6,103) (K=2,99)
   DADT(I)=KTR*A(J)-(KTR+EMAX*BB[K])*A(I)
ENDDOE
   DADT(105)=KTR*A(104)-EMAX*BB100*A(105)
; PK compartments
   DADT(2)  =   KAIM*A(5)+KAPO*A(4)-CL/V*A(2)-CLD/V*A(2)+CLD/VT*A(3)
   DADT(3)  =                                CLD/V*A(2)-CLD/VT*A(3)
   DADT(4)  = - KAPO*A(4)
   DADT(5)  = - KAIM*A(5)
```

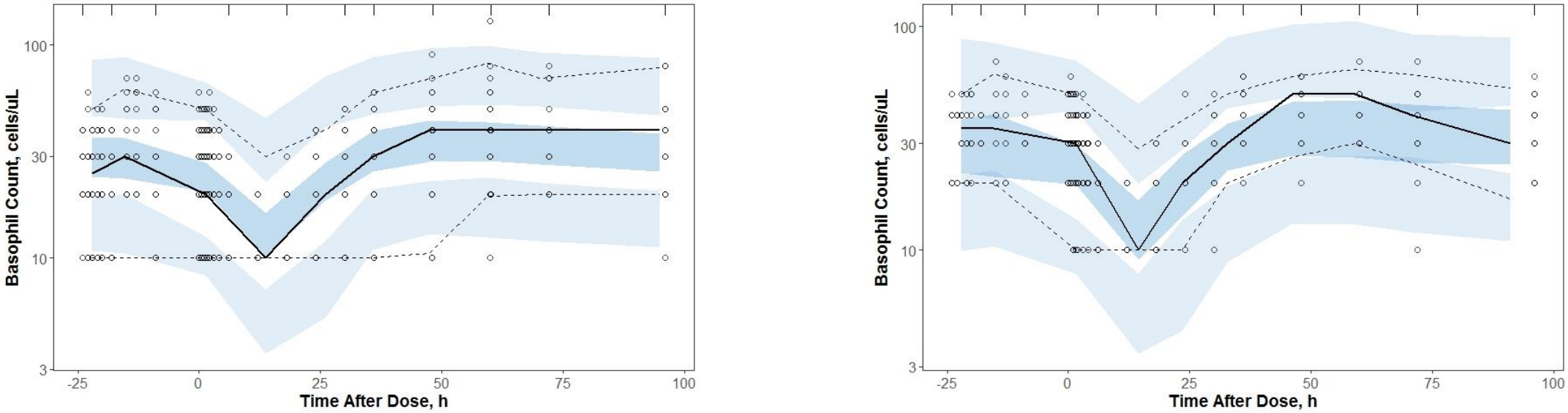
Simulations of Basophil Counts in Blood





Simulations of basophil counts using the cell trafficking model for various shape and scale Weibull parameters. Only for ν >1 can the rebound in the response curve be observed. The base values were ν = 4 and β= 0.005 1/h. The PK parameters were set at the typical values for DEX for IM administration of 6 mg. The remaining model parameters were C_{B0}= 30 cells/µL, $\mu_{BE} = 0.1$ 1/h, $\nu = 4$, $\beta = 0.005$ 1/h, $I_{max} = 1.0$, $IC_{50} = 5$ ng/mL.

Visual Predictive Check Plots



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

Population Parameter Estimates

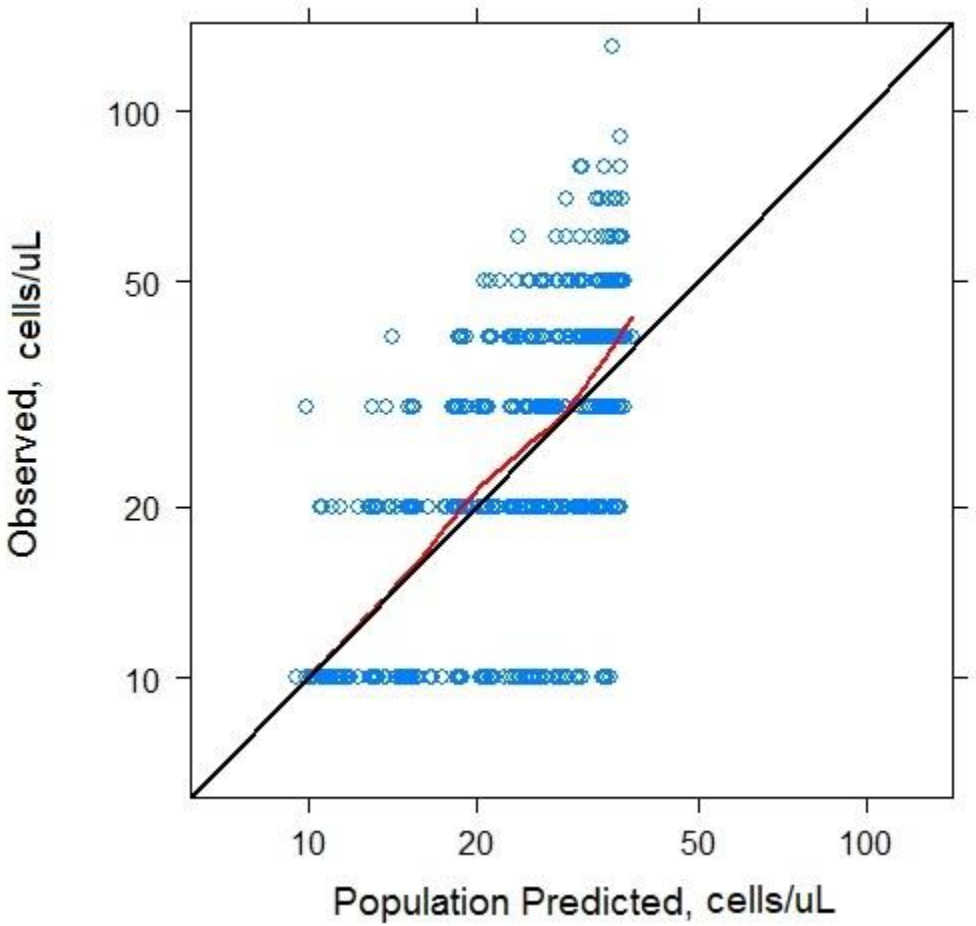
Parameter	Definition	Typical Value (%RSE)	IIV (%RSE) (%IIV)**
C_{B0}, cells/μL	Baseline basophil count in blood	29.1 (6.5)	0.137 (20.2) (38.3)
μ_{BE}, 1/h	Hazard of cell transfer from blood to extravascular tissues	0.13 (0.2)	0*
ν	Shape factor for Weibull hazard of cell transfer from extravascular space to blood	6.76 (16.3)	0.0536 (172) (23.5)
β, 1/h	Scale factor for Weibull hazard of cell transfer from extravascular space to blood	0.00489 (8.4)	0.108 (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)
σ^2	Variance of residual error for basophil count	0.0907 (5.6)	

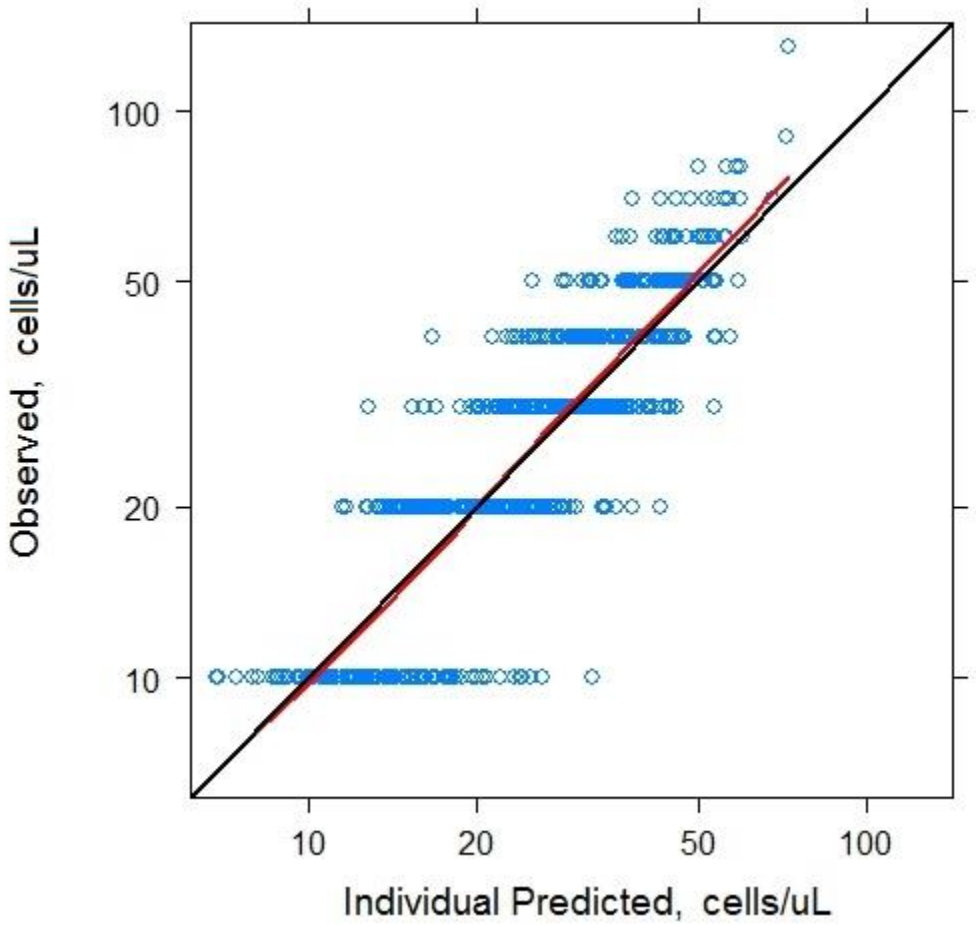
* Parameter was fixed

** $\%IIV = \sqrt{\exp(IIV) - 1} \cdot 100\%$

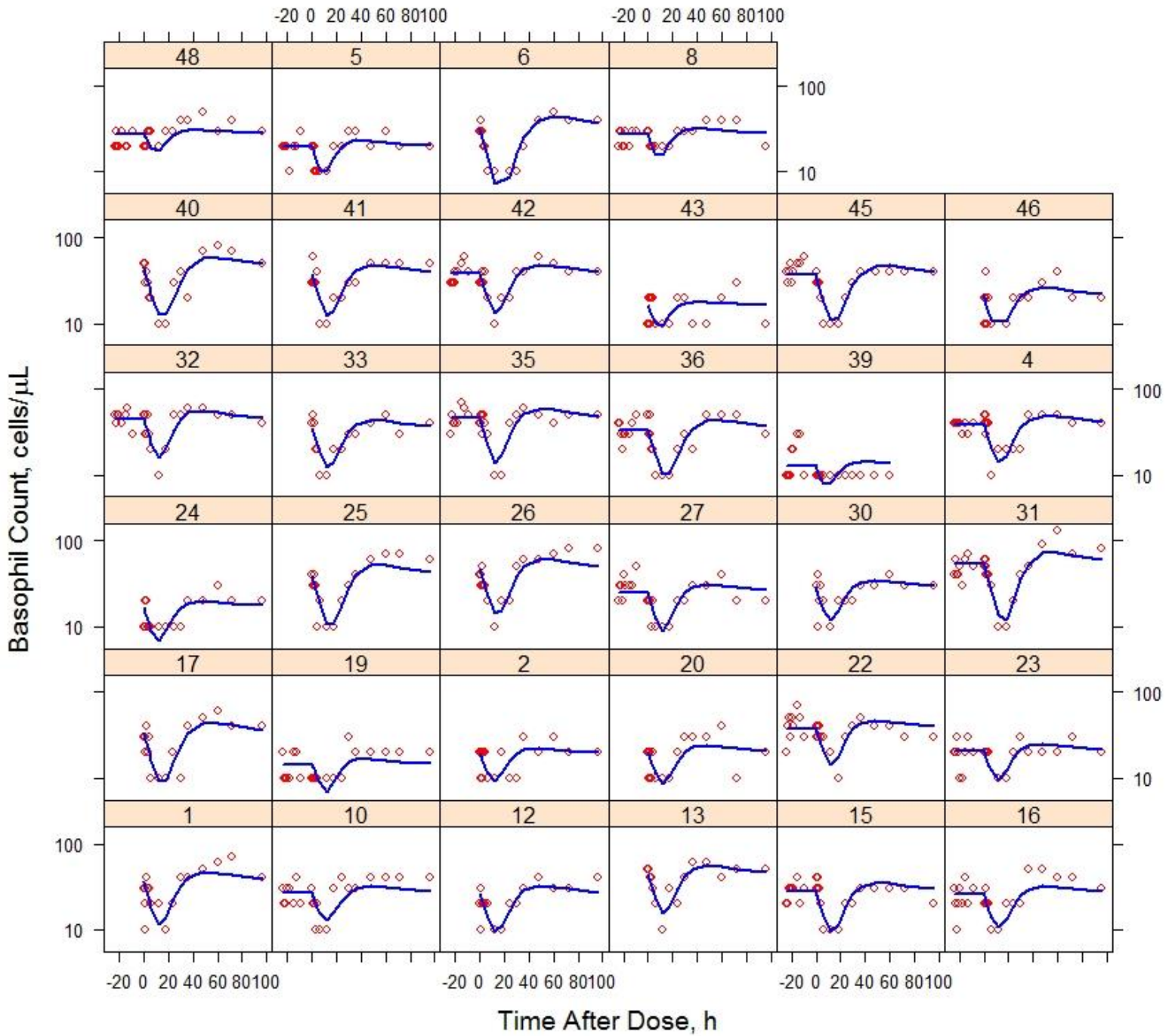
Estimates of PD parameters, their relative standard errors (RSE), and inter-subject variabilities (IIV) obtained by the importance sampling method of minimization of the log-likelihood.

Observed vs Predicted Diagnostic Plots



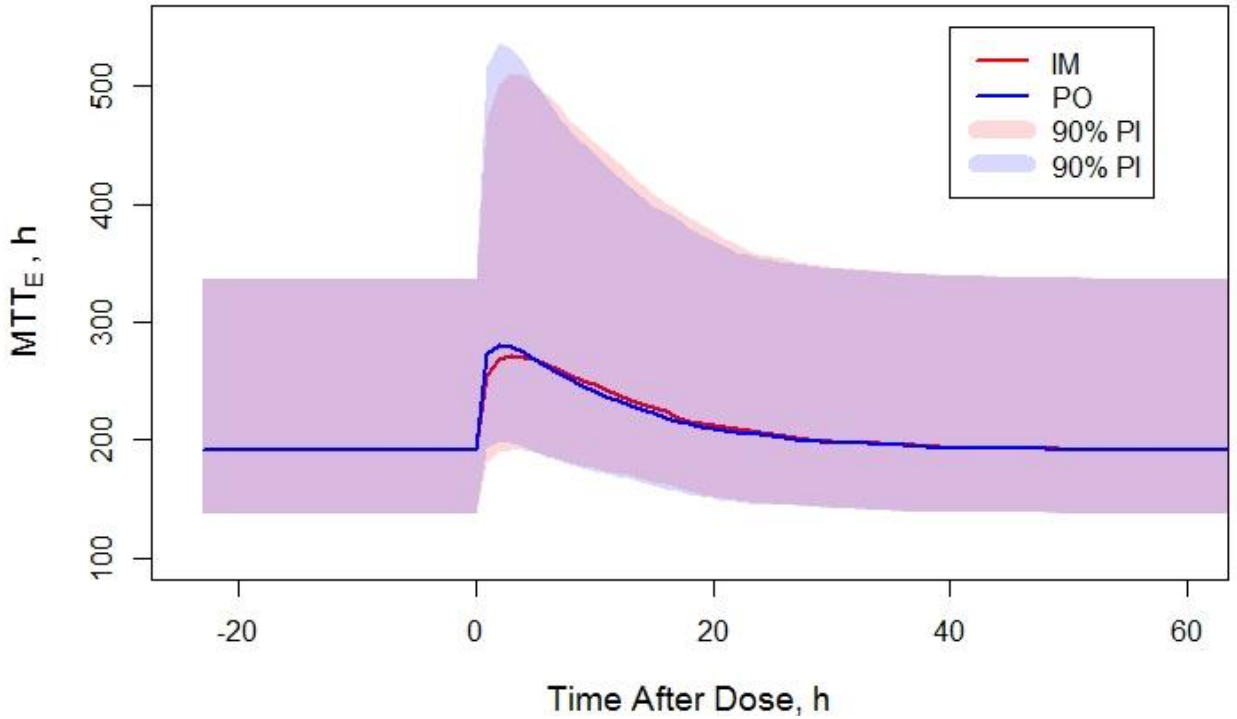


Predictions of Individual Basophil Counts



Basophil mean transit times in blood and extravascular space

- Population estimates of model parameters were used to evaluate the DEX effect on the mean transit time of basophils in the blood and extravascular space.
- The mean transit time of basophils in the circulation is $MTT_B = 1/\mu_{BE}$
- Our estimates of μ_{BE}implied that $MTT_B = 7.2$ h (IM) and $MTT_B = 8.0$ h (PO).



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 convolution integral in model equations was approximated by solutions to a system of transit compartments
- The model was implemented in NONMEM 7.5.1 with *doexpand* utility
- The model was validated using the basophil responses to dexamethasone treatment of healthy subjects
- Our estimates of baseline mean transit times of basophils in the blood and extravascular tissues were in the ranges reported in the hematology text books
- The estimate of dexamethasone plasma concentrations eliciting 50% of the maximal inhibition of the basophil recirculation agreed with the analogous values reported in the literature
- The future model extensions will include cell trafficking with time-varying blood count baselines

Resources

- NONMEM control stream and example dataset for the basophil trafficking population model are available at https://www.page-meeting.org/default.asp?abstract=9995

- Questions regarding the age-structure population model for cell trafficking can be e-mailed to Dr. Wojciech Krzyzanski at wk@buffalo.edu