Physiol. Res. 48: 525-528, 1999

RAPID COMMUNICATION

Model of Lymphocyte Migration in Merino Ewes Under Physiological Conditions

L. DEDÍK, M. ĎURIŠOVÁ[1], W. SRIKUSALANUKUL[2], P. MCCULLAGH[2]

Faculty of Mechanical Engineering, Slovak University of Technology, Bratislava, [1]Institute of Experimental Pharmacology, Slovak Academy of Sciences, Bratislava, Slovak Republic and [2]Division of Molecular Medicine, John Curtin School of Medical Research, Australian National University, Canberra, Australia

Received April 26, 1999
Accepted May 25, 1999

Summary

The paper presents an example of a new type of a structured model containing time delays in parallel branches. This model was selected as optimal to describe mathematically the lymphocyte migration between the venous blood and prescapular lymph in Merino ewes under physiological conditions. The model allowed to identify and quantify several lymphocyte fractions exhibiting different migration dynamics.

Key words

Lymphocyte migration • Structured model • Biomarker • Surrogate • Physiological modeling

The study of the migration of lymphocytes between blood, the lymphatic system and non-lymphoid tissue has been of increasing concern, e.g. Dimitrov and Martin (1995), Ho *et al.* (1995), Stekel (1997), Stekel *et al.* (1997). The goal of this paper is to present an example of a new type of a structured model containing time delays in parallel branches, selected as optimal to describe mathematically the lymphocyte migration between venous blood and prescapular lymph in Merino ewes under physiological conditions.

Six healthy Merino ewes (3-5 years old, 25-35 kg of body weight) were randomly selected and kept in metabolic cages for a few days prior to the experiments. Lymph was collected from the cannulated efferent lymphatic vessel of the prescapular lymph node (Glover and Hall 1976). Lymphocytes were isolated (Hersey 1971) and labeled with 3-5 μM 5-(and 6)-carboxy-fluorescein diacetate succinimidyl ester. The viability of the lymphocytes was tested by propidium iodide staining and analyzed by a florescence-activated cell analyzer (FACScan, Becton Dickinson, CA). The labeled lymphocytes were injected back into the animal *via* an indwelling venous cannula. The concentration-time profiles of the labeled lymphocytes were determined in the venous blood and prescapular lymph using the FACScan. To represent mathematically the lymphocyte migration between the venous blood and prescapular lymph, a dynamic system describing this process was

© 1999 Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic
Fax +420 2 293 894
E-mail physres@biomed.cas.cz http://www.lf2.cuni.cz/physiolres/physiolres.htm

defined in such a way that the concentration-time profile of the labeled lymphocytes in the venous blood was considered the input of this system, while the concentration-time profile of the labeled lymphocytes in the prescapular lymph was considered the output of this system (Dedík and Ďurišová 1995). The procedure published in our earlier study (Ďurišová *et al.* 1995) was used to obtain a structured mathematical model of this system, taking the physiology of the lymphocyte migration process into account (Picker and Siegelman 1993).

The general structure of the mathematical models selected as optimal for the systems describing lymphocyte migration between the venous blood and the prescapular lymph in healthy Merino ewes is described by Eqs.1-3

$$X_0(t) = \sum_{i=1}^{n} G_i Y(t-\tau_i) \quad (1)$$

$$T_1 \frac{dX_1(t)}{dt} = X_0(t) - X_1(t) \quad (2)$$

$$T_2 \frac{dX_2(t)}{dt} = X_1(t) - X_2(t) \quad (3)$$

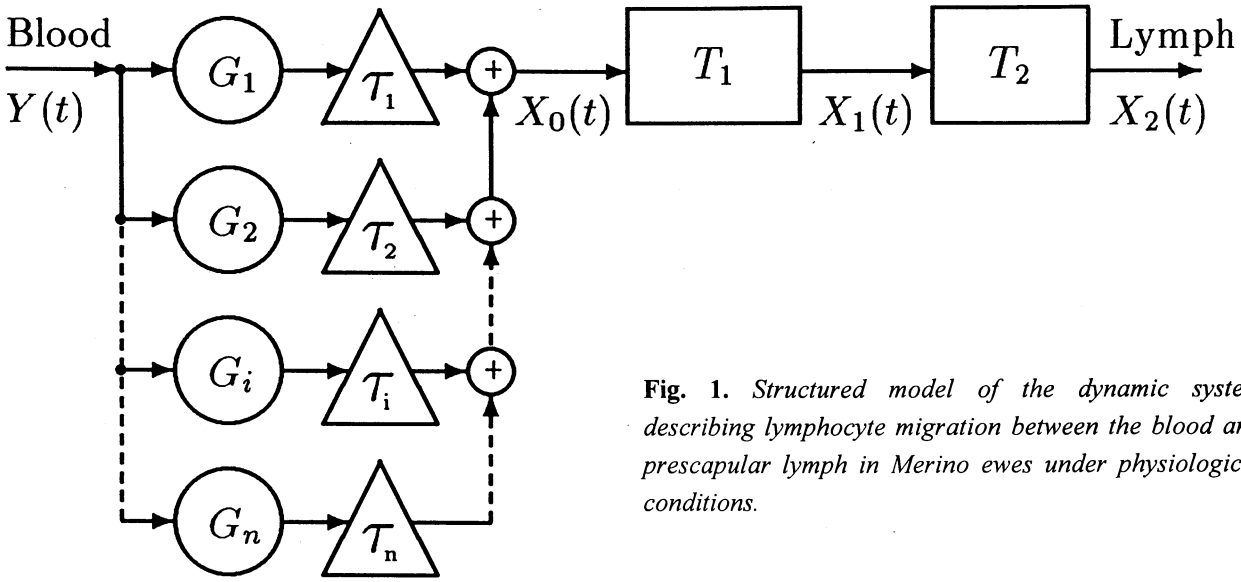

Fig. 1. *Structured model of the dynamic system describing lymphocyte migration between the blood and prescapular lymph in Merino ewes under physiological conditions.*

and is shown in Figure 1. This model structure consists of the two first-order submodels with the time constants T_1 and T_2 and the submodels of several parallel branches with the time delays τ_i and the gains G_i (Dedík and Ďurišová 1995), where n is the total number of the branches, t is time, Y is the concentration of the labeled lymphocytes in the venous blood, and X_0, X_1, and X_2 are the concentrations of the labeled lymphocytes through the transit pathways and in the prescapular lymph. This model structure and the procedure introduced in the study of Ďurišová *et al.* (1995) allowed to estimate:

- the fraction F_i of the total amount of the labeled lymphocytes traveling through the individual branch i, according to Eq. 4

$$F_i = \frac{G_i}{\sum_{i=1}^{n} G_i} 100(\%) \quad (4)$$

- the mean lymphocyte transit time MTT_i corresponding to the individual branch i, according to Eq. 5

$$MTT_i = T_1 + T_2 + \tau_i \quad (5)$$

- the mean lymphocyte transit time MTT corresponding to the whole dynamic system describing the lymphocyte migration between the venous blood and prescapular lymph, according to Eq. 6

$$MTT = \frac{1}{\sum_{i=1}^{n} G_i} \sum_{i=1}^{n} (T_1 + T_2 + \tau_i) G_i \qquad (6)$$

The concentration-time profiles of the labeled lymphocytes in the venous blood and prescapular lymph, respectively, in a representative animal are shown in Figures 2a and 2b. The optimal model of the dynamic system describing the migration of the labeled lymphocytes in this animal contained four parallel branches. The interval estimates of the parameters (estimate ± SD) of this model were: $T_1 = 9.82 \pm 2.34$ h, $T_2 = 4.88 \pm 2.09$ h, $G_1 = 1.19 \pm 0.02$, $\tau_1 = 4.29 \pm 0.55$ h, $G_2 = 0.15 \pm 0.05$, $\tau_2 = 60.71 \pm 3.97$ h, $G_3 = 0.10 \pm 0.04$, $\tau_3 = 84.70 \pm 5.91$ h, $G_4 = 0.08 \pm 0.02$, $\tau_4 = 122.90 \pm 7.73$ h. The response of this model to the measured input (Fig. 2a) of the dynamic system describing the lymphocyte migration between the venous blood and prescapular lymph is shown as the full line in Fig. 2b. The fractions F_i of labeled lymphocytes corresponding to the individual branches were: $F_1 = 78.2$ %, $F_2 = 9.9$ %, $F_3 = 6.6$ %, and $F_4 = 5.3$ % of the total amount of the labeled lymphocytes. The mean transit times of the lymphocytes corresponding to the individual branches were: $MTT_1 = 18.9$ h, $MTT_2 = 75.4$ h, $MTT_3 = 99.4$ h, and $MTT_4 = 137.6$ h. The mean transit time of the lymphocytes MTT corresponding to the whole dynamic system describing the lymphocyte migration between the venous blood and prescapular lymph was 36.1 h.

Models analogous to that presented above were identified for all the animals in this study. In all the animals, the greater was the time delay of a branch, the lesser was the corresponding fraction of the lymphocytes, while the reciprocal value of the lymphocyte fraction was linearly dependent on the time delay. The n parallel branches in the model shown in Figure 1 correspond to the various lymphocyte inputs into the lymphatic/interstitial pool assumed in the model presented by Stekel (1997) and Stekel *et al.* (1997). However, in contrast to the abstract model presented in these two papers, the model in the form of Eqs. 1-3 represents the real relationship between the measured concentration-time profiles in the venous blood and prescapular lymph, since it mathematically takes into account both these profiles. The procedure used in this work (Ďurišová *et al.* 1995) can be employed in building models of lymphocyte migration under physiological and/or pathological conditions, or models of relationships between drug levels and dynamics of lymphoid cells proposed as a biomarker or surrogate endpoint, *etc.*, as well as in testing changes in the parameters of these models.

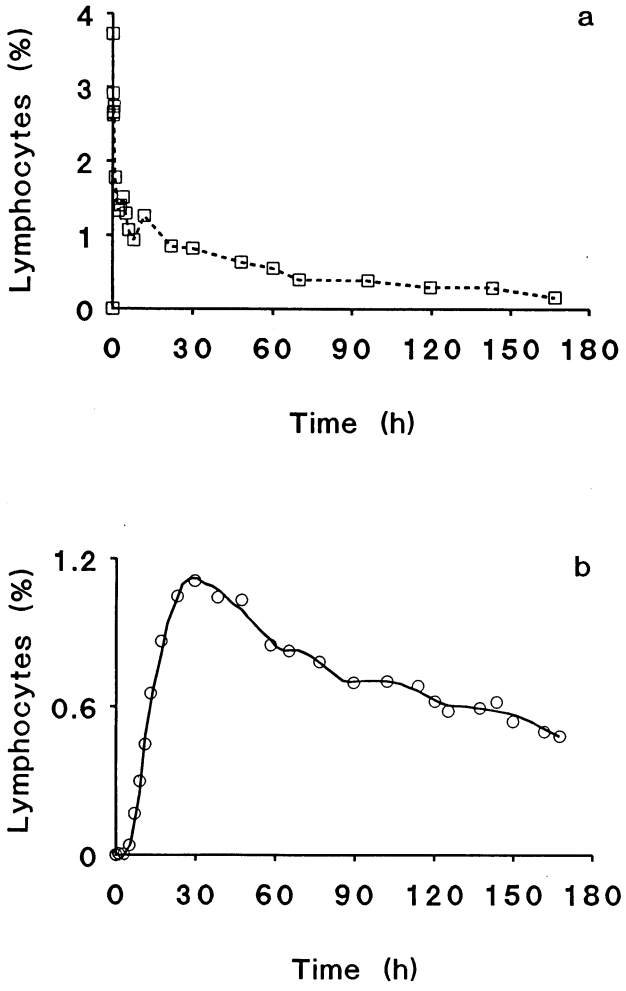

Fig. 2. *a) Time profile of the concentration of labeled lymphocytes in the venous blood in the representative animal (squares). b) Time profile of the concentration of labeled lymphocyte in the prescapular lymph in the representative animal (circles). Response of the structured model of the dynamic system describing lymphocyte migration between the blood and prescapular lymph in this animal (full line).*

Acknowledgments

This work was supported in part by Grant 1/4249/97 from the Slovak Grant Agency.

References

DEDÍK L, ĎURIŠOVÁ M: CXT - a programme for analysis of linear dynamic systems in the frequency domain. *Int J Bio-Med Comput* **39**: 231-241, 1995.

DIMITROV DS, MARTIN MA: HIV results in the frame CD4+ cell turnover. *Nature* **375:** 194-195, 1995.

ĎURIŠOVÁ M, DEDÍK L, BALAN M: Building a structured model of a complex pharmacokinetic system with time delays. *Bull Math Biol* **57**: 787-808, 1995.

GLOVER DJ, HALL JG: A method for the collection of lymph from the prescapular lymph node of unanaesthetized sheep. *Lab Anim* **10**: 403-408, 1976.

HERSEY P: The separation and ^{51}chromium labeling of human lymphocytes with in vivo studies of survival and migration. *Blood* **38**: 360-371, 1971.

HO DD, NEUMANN AU, PERELSON AS, CHEN W, LEONARD JM, MARKOWITZ M: Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* **373**: 123-126, 1995.

PICKER LJ, SIEGELMAN MH: Lymphoid tissues and organs. In: *Fundamental Immunology,* WE PAUL (ed), Raven Press, New York, 1993, pp 145-197.

STEKEL DJ: The role of inter-cellular adhesion in the recirculation of T lymphocytes. *J Theor Biol* **86**: 491-501, 1997.

STEKEL DJ, PARKER CE, NOWAK MA: A model of lymphocyte recirculation. *Immunol Today* **18**: 216-221, 1997.

Reprint requests

M. Ďurišová, Institute of Experimental Pharmacology, Slovak Academy of Sciences, Dúbravska cesta 9, 842 16 Bratislava, Slovak Republic.