Mathematical modeling reveals hierarchy of lymphocyte recirculation kinetics in the whole organism

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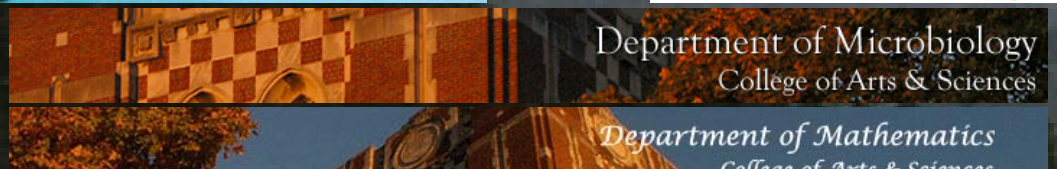


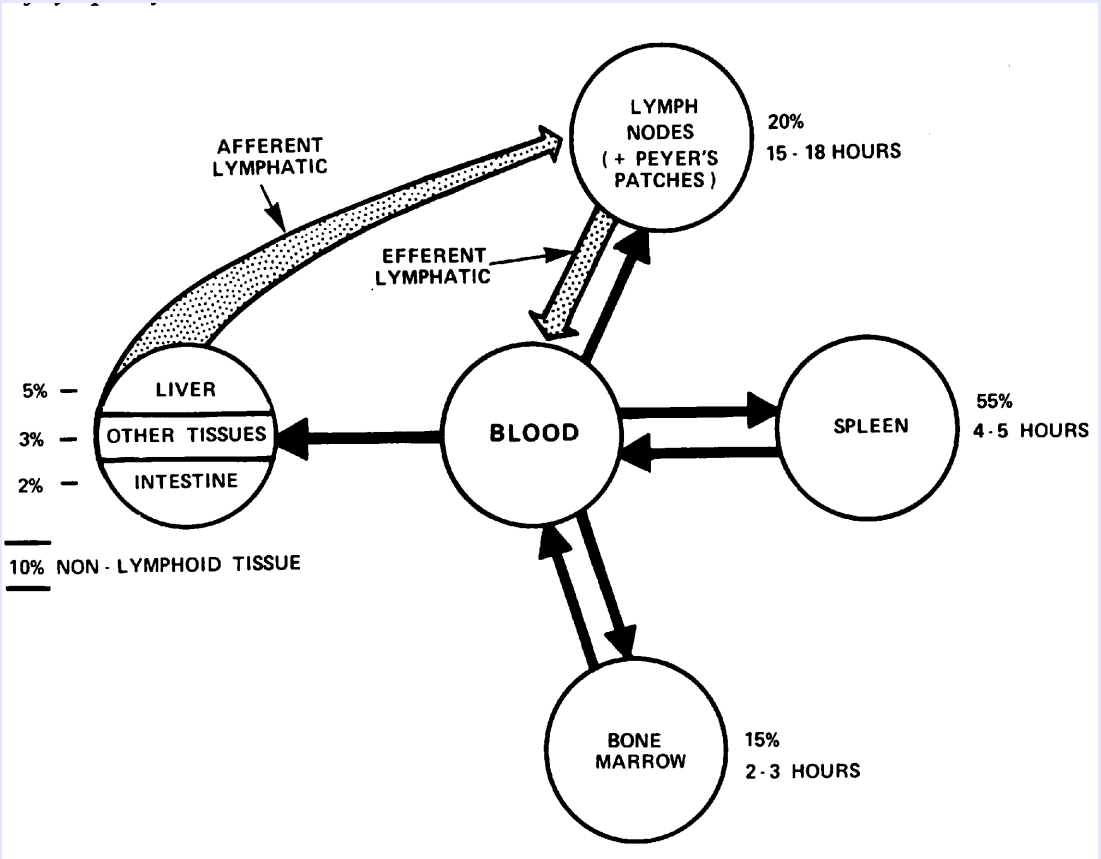
Outline

Lymphocyte migration

- Lymphocytes enter tissues via the blood and and most lymphocytes exit those tissues into the blood. When entering nonlymphoid tissues (e.g., skin), lymphocytes must migrate into a lymph node draining this site, and then migrate from the LN to the blood.
- Basic details of lymphocyte recirculation in mammals (e.g., rats) have been understood in 1960-80th. Molecules mediating entrance of lymphocytes into and exit from lymphoid tissues have been well characterized.
- The **kinetics** of lymphocyte recirculation between multiple organs (how quickly lymphocytes move from one organ to another) is incompletely understood.

Husband Migration and homing of lymphoid cells 1988; Kuby Immunology 2007; Girard et al. NRI 2012

Lymphocyte recirculation kinetics (rats)



Ford J Clin Path 1979

Lymphocyte recirculation kinetics (rats)

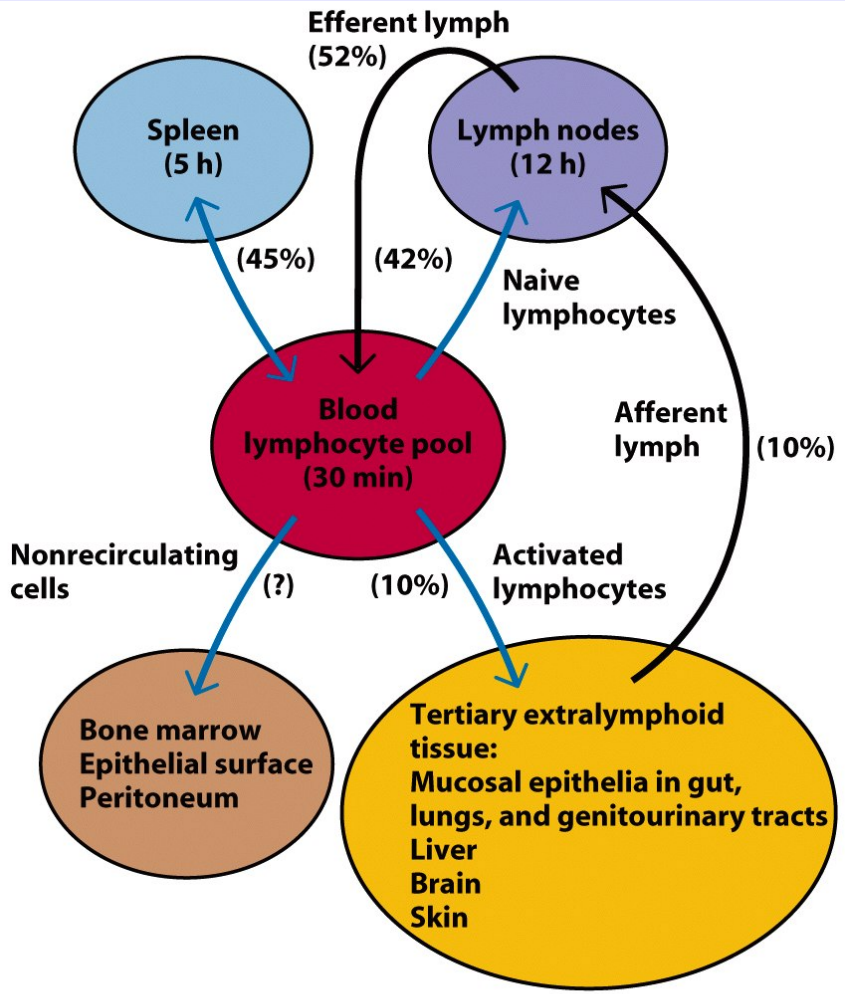


Figure 13-6
Kuby IMMUNOLOGY, Sixth Edition

Estimates of lymphocyte migration parameters

For thoracic duct lymphocytes (TDLs) or blood-derived lymphocytes

- Residence time in the **blood**: 20 to 40 min (rats, sheep, pigs, humans)
- Residence in the **spleen**: 5 hours (rats)
- Residence in **lymph nodes**: varies depending on the species from 15-18 hours (rats) to > 40 hours (sheep)

Smith and Ford Immunology 1983; Pabst and Trepel 1976; Ford Cell Tissue Kinet 1975; Pabst in Husband 1988

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Problem:

- Estimates of lymphocyte recirculation kinetics have been obtained using semi-quantitative approaches.

Smith and Ford Immunology 1983; Pabst and Trepel 1976; Ford Cell Tissue Kinet 1975; Pabst in Husband 1988

Migration via spleen

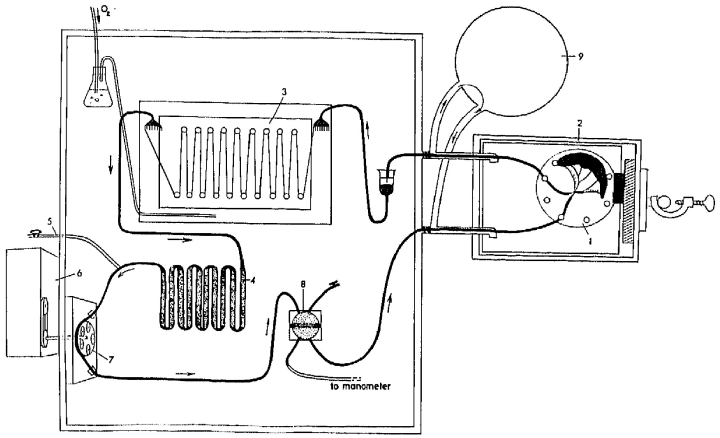


FIG. 1. Diagram of perfusion apparatus. The organ chamber, on the right, is represented as seen from above. In the pump-oxygenator, on the left, most of the components are drawn in elevation. 1, Perspex disk supporting spleen; 2, Perspex frame of the organ chamber; 3, oxygenator consisting of eight parallel channels of fine tubing (only one channel drawn); 4, reservoir; 5, sampling tube; 6, variable speed motor; 7, roller pump; 8, filter chamber; 9, water at 37°C circulated from bath by pump.

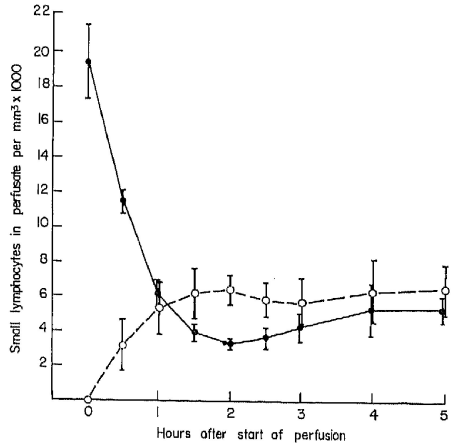


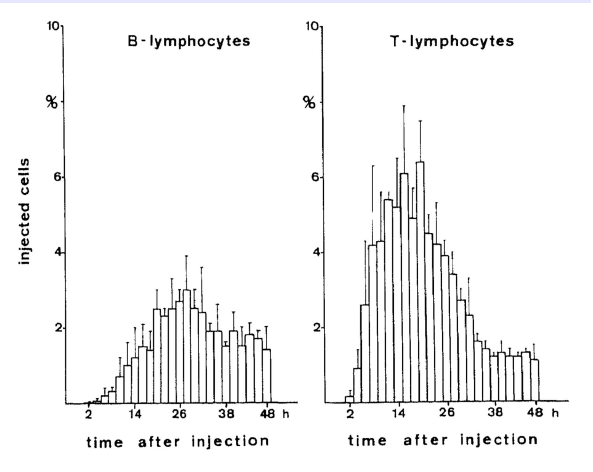
FIG. 2. Normal spleens perfused with blood containing labelled thoracic duct lymphocytes ('original' small lymphocytes). Mean concentrations ± SE of three perfusions of subgroup A_1. ●, Concentration of 'original' small lymphocytes; o, concentration of 'splenic' small lymphocytes. The concentration of 'original' small lymphocytes fell rapidly to a nadir after 2 hr and then rose again. The concentration of 'splenic' small lymphocytes rose to a plateau after 1–2 hr of perfusion.

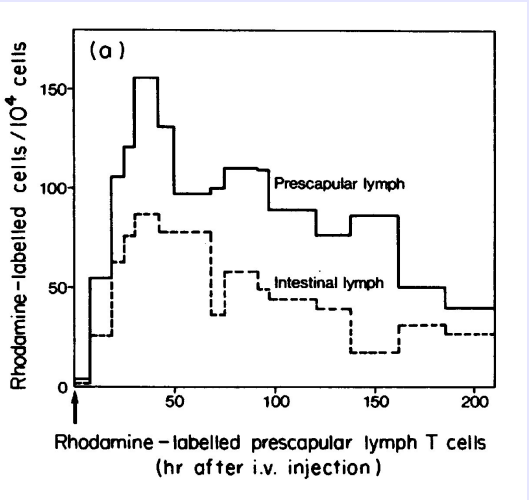
Ballpark estimates provided

- Residence time in the spleen of about 4-5 hours

Ford Cell Tissue Kinetic 1969

Migration via lymph nodes





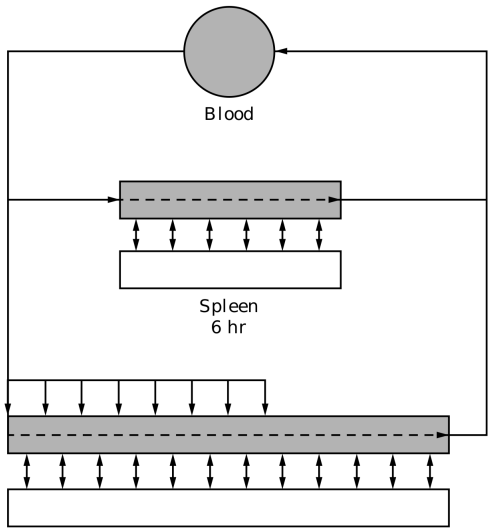
rat sheep

Residence times:

- 15-20 hours (rats, thoracic duct output)
- > 24 hours (sheep, single lymph nodes)
- Caveats: 1) only $\sim 75\%$ lymphocytes enter the blood from lymph nodes via the thoracic (left lymphatic) duct; 2) exit from a single node is influenced by lymphocytes entering the LN from the blood;

Westermann et al. SJI 1988; Reynolds et al. I 1982; Thomas et al. PLoS One 2012

Migration via lymph nodes: Stekel



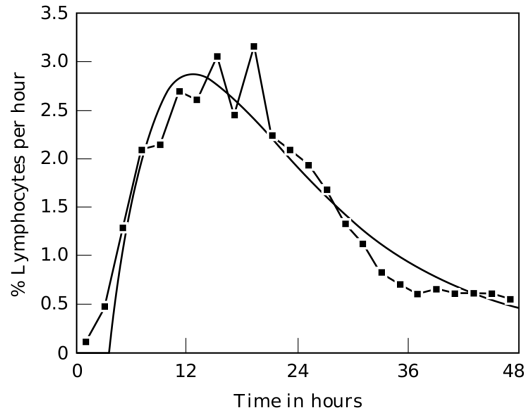


FIG. 3. Simulation of a recirculation experiment using the new model (thick line), alongside data from the same experiment performed by Westermann *et al*. (1988). There is close agreement between the model and the experimental data. The parameter values used are: $b = 2.2$, $d = 0.8$, $\hat{w}_0 = 1.6$, $v_l = 0.097$, $v_s = 0.335$, $x_H = 0.65$, $\alpha_s = 0.83$, $\alpha_l = 1.95$ and $e = 0.85$. v_s, α_s and α_l are set so that the mean transit time through the spleen is 6 hours, and so that at steady state, 3% of T cells are in the blood and 15% are in the spleen (see Appendix). It is assumed that 80% of the injected cells are recirculating.

- Stekel developed a mathematical model for lymphocyte migration via lymph nodes using transport equation. The average residence time of lymphocytes in lymph nodes (20 hours) was calculated by using the steady state distribution of labeled TDLs after transfer into syngenic hosts (Smith and Ford 1983) and assuming that lymphocytes spend 6 hours in the spleen.

Stekel JTB 1997

Migration via lymph nodes: Stekel

$$\frac{\partial u(x,t)}{\partial t} = -v\frac{\partial u(x,t)}{\partial x} - bu(x,t)\left(1 - \frac{w(x,t)}{w_0(x)}\right) + dw(x,t) + I(x)T(t) \quad (2)$$

$$\frac{\partial w(x,t)}{\partial t} = bu(x,t)\left(1 - \frac{w(x,t)}{w_0(x)}\right) - dw(x,t) \quad (3)$$

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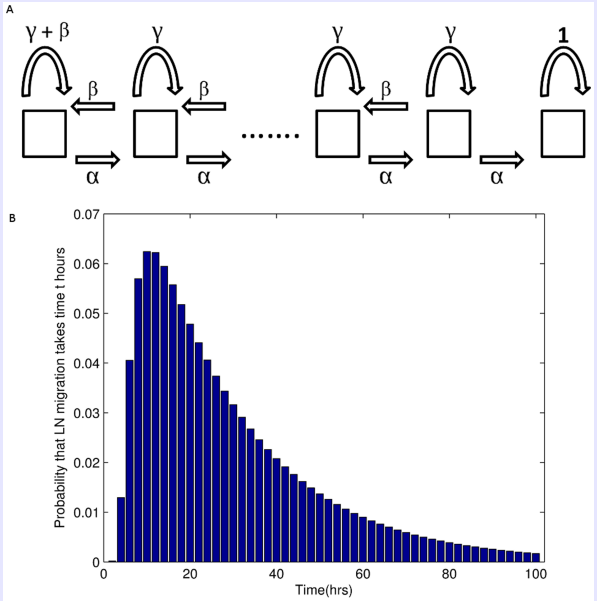
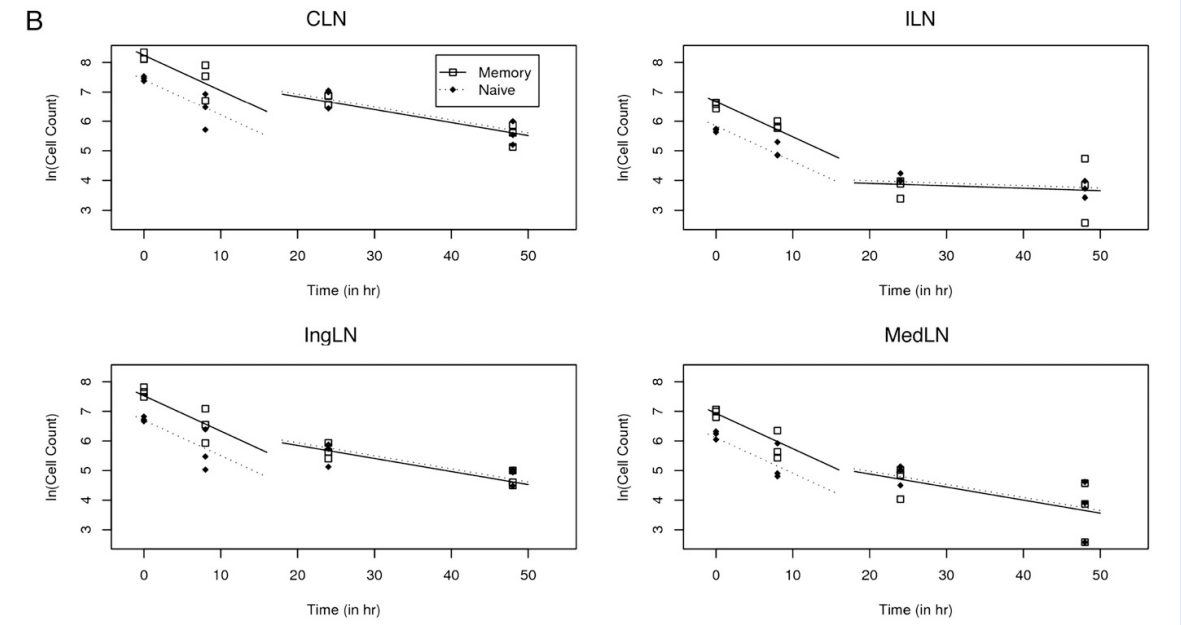
Migration via lymph nodes: Thomas et al.



- Thomas et al. using one dimensional random walk model to estimate residence times of lymphocytes in LNs using data on single LN cannulation. The provided estimates of residence times (> 30 hours) are likely overestimates because input of new cells from the blood into LNs was not taken into account.

Thomas et al. PLoS One 2012

Migration via lymph nodes: blocking entrance



Residence times:

- 8-20 hours (depending on lymphocyte type and study)
- Caveat: efficiency of treatment blocking lymphocyte entrance into LNs strongly influences the rate of lymphocyte decline.

Tomura et al. PNAS 2008; Harp et al. JI 2010; Mandl et al. PNAS 2012

Migration via nonlymphoid organs

- Blood delivers lymphocytes to nonlymphoid tissues, and even naive lymphocytes may enter parenchyma of nonlymphoid tissues (brain and gut LP).

Sprent Cell Immunol 1976; Pabst et al. Am Rev Respir Dis 1987; Bolton et al. JI 2010; Teijaro et al. JI 2011; Anderson et al JI 2012

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- To pass through some nonlymphoid tissues such as lung and liver, lymphocytes need travel via thin blood vessels (capillaries and sinusoids, respectively).

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  - Capillaries in the lung are thinner than lymphocytes ($d = 5 - 10\ \mu m$).

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  - Perfusion does not remove most lymphocytes in capillaries.

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  - Perfusion does not remove most lymphocytes in capillaries.
  - Leukocytes exit slowly from perfused lung ex vivo (Pabst).
  - In vitro activated lymphocytes reside in the lung for hours (Sprent and Bolton et al.).

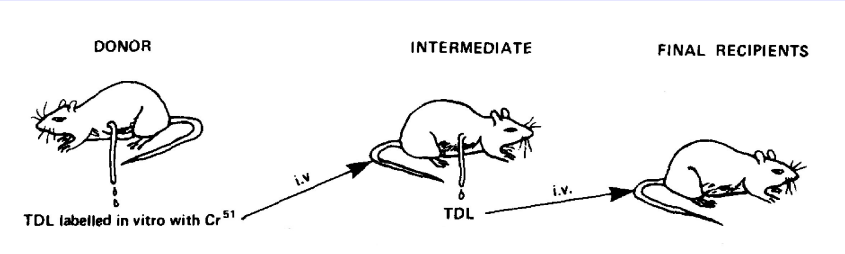
Sprent Cell Immunol 1976; Pabst et al. Am Rev Respir Dis 1987; Bolton et al. JI 2010; Teijaro et al. JI 2011; Anderson et al JI 2012

Challenge

Problem:

- While residence times of lymphocytes in lymphoid tissues are believed to be (relatively) well known, all these estimates are from different studies, for different species, for different subsets of lymphocytes, for different tissues/organs.
- Whether kinetics of migration via different LNs and Peyer's patches is the same is not well understood.
- Kinetics of migration of lymphocytes via nonlymphoid organs is not well understood.
- Can the rates of lymphocyte recirculation in the whole organism be estimated?

Smith and Ford study



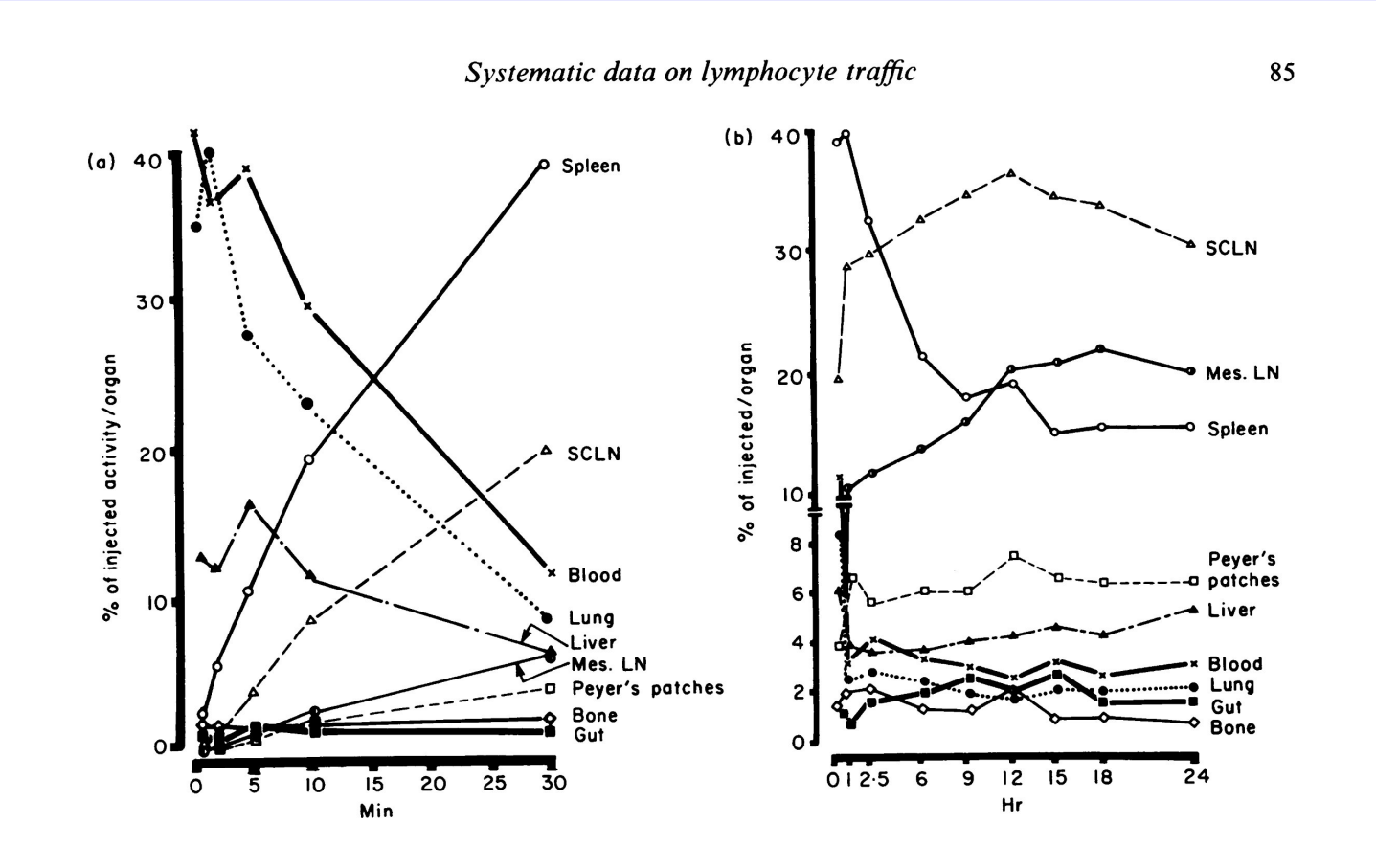
- Thoracic duct lymphocytes (TDLs) were collected overnight and labeled with ^{51}Cr (16 hours, 0^0 C).
- TDLs were passaged through an intermediate host.
- TDLs were collected from intermediate hosts and after minimal handling (1h, room temperature) injected into final hosts.
- Final hosts were sacrificed at different times after cell transfer and the percent of transfered TDLs in multiple murine organs was calculated.

Smith and Ford Immunol 1983

Out of 100 lymphocytes in the blood where will most lymphocyte migrate in the next 10 minutes?

- Lung
- Liver
- Spleen
- Lymph nodes
- Peyer's patches

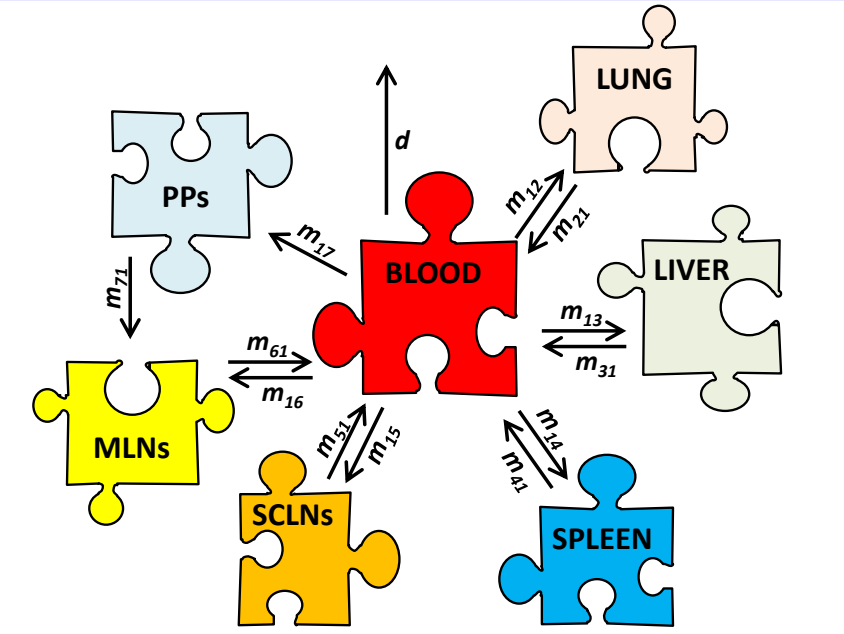
Smith and Ford study



Data were digitized using Engauge Digitizer (digitizer.sourceforge.net) software package.

Smith and Ford Immunol 1983

Model cartoon



Organs

- **SCLNs**: subcutaneous LNs which include six superficial cervical LNs, two to four deep cervical LNs, two to three coeliac LNs, the popliteal LNs
- **MLNs**: mesenteric LNs (excluding the ileocaecal LNs)
- **PPs**: Peyer's patches
- Note that in the model cells from Peyer's patches migrate to the mesenteric LNs, not the blood.

Mathematical model

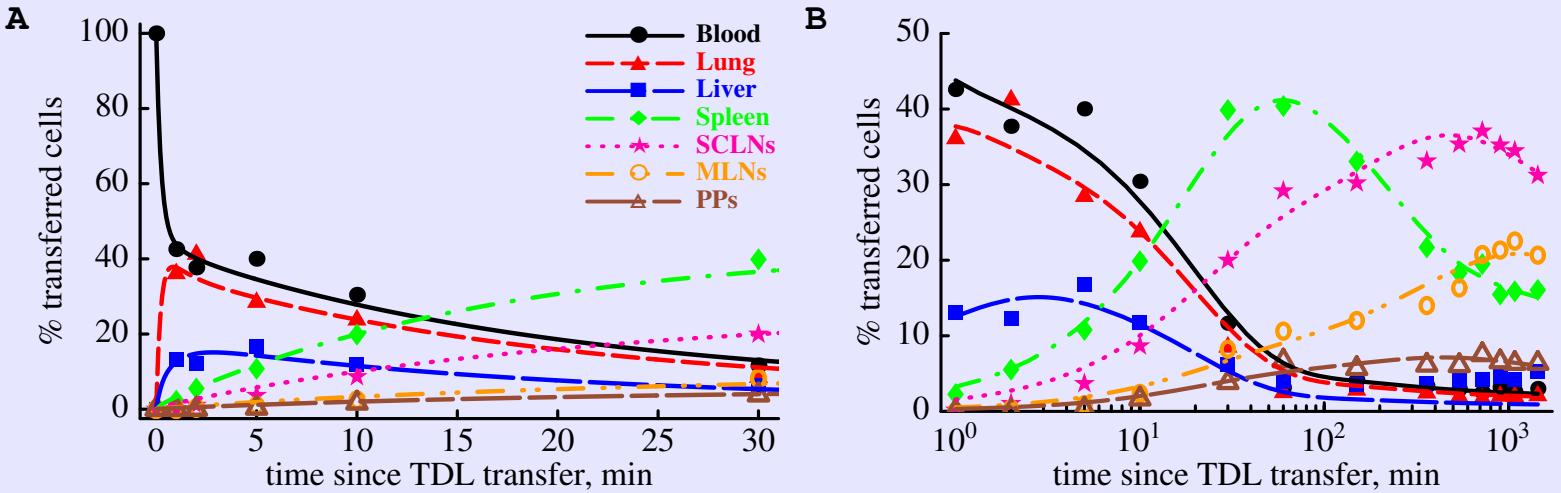
$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -x_1\left(d + \sum_{i=2}^{7} m_{1i}\right) + \sum_{i=2}^{6} m_{i1}x_i, \tag{1}$$

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = m_{1i}x_1 - m_{i1}x_i, \qquad i = 2,3,4,5,7, \tag{2}$$

$$\frac{\mathrm{d}x_6}{\mathrm{d}t} = m_{16}x_1 - m_{61}x_6 + m_{71}x_7, \tag{3}$$

where x_1 is the percent of labeled cells found in the blood, and x_i is the percent of labeled cells found in other organs of rats: lung ($i = 2$), spleen ($i = 3$), liver ($i = 4$), SCLNs ($i = 5$), Mesenteric LNs (($i = 6$), Peyer's Patches ($i = 7$). m_{1i} is the rate of migration of cells from the blood to the i^{th} organ, and m_{i1} is the rate of migration from the i^{th} organ to the blood (and m_{71} is the rate of migration of lymphocytes from Peyer's patches to MLNs), and d is the rate of removal of lymphocytes from circulation.

Model fits of the data



Symbols: data, lines: predictions of the model.

Parameter estimates (mean and 95% CIs)

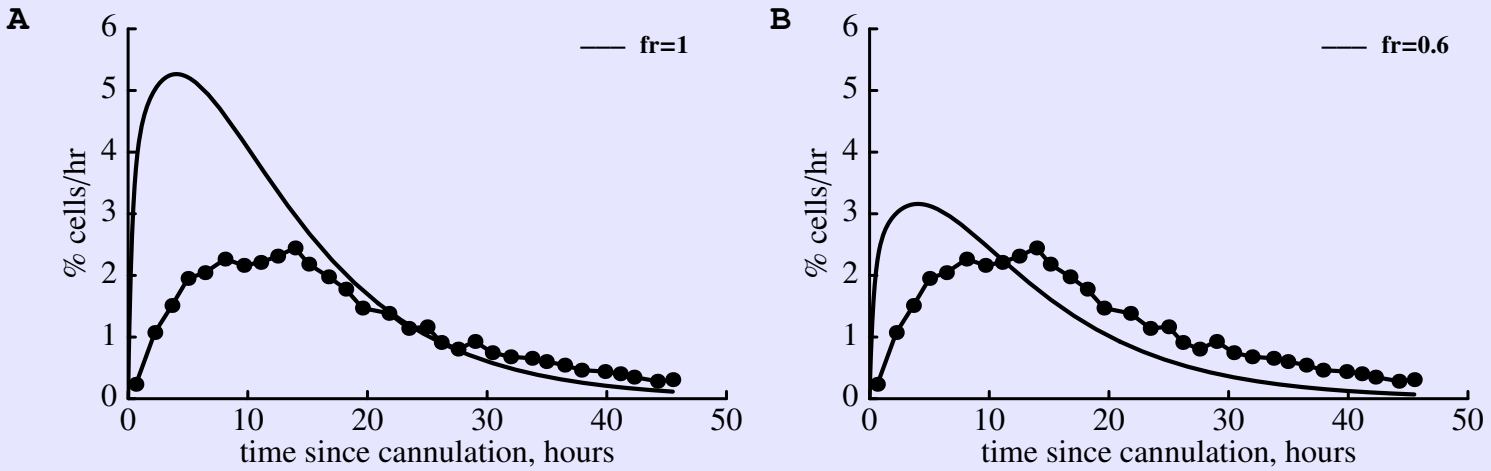
Organ	Rate of entrance from blood m_{1i}, 1/min	Percent cells going to organ from blood	Rate of exit from organ to blood m_{i1}, 1/min	Residence time in organ, mins
Lung	1.86 (1.32–2.21)	80.4 (68.8–85.3)	2.22 (1.59–2.69)	0.45 (0.37–0.63)
Liver	0.35 (0.24–0.61)	15.2 (10.2–25.2)	0.89 (0.56–1.67)	1.12 (0.59–1.79)
Spleen	0.057 (0.052–0.063)	2.5 (2.0–3.1)	0.009 (0.007–0.011)	111 (91–137)
SCLNs	0.028 (0.025–0.031)	1.2 (1.0–1.6)	0.002 (0.002–0.003)	454 (377–568)
MLNs	0.009 (0.007–0.011)	0.4 (0.3–0.5)	0.002 (0.001–0.002)	569 (423–780)
PPs	0.006 (0.004–0.008)	0.2 (0.2–0.4)	0.002^* (0.001–0.004)	432 (260–789)

*: m_{71} is the rate of migration of TDLs from PPs to MLNs. The rate of removal of cells from the blood to all organs, $d + \sum_i m_{1i}$, is 2.3 min^{-1} or the average residence time is 26 sec. The percent of cells leaving the blood into a particular organ is given by the ratio $m_{1i}/(d + \sum_i m_{1i})$. A residence time of cells in a particular organ is calculated as $1/m_{i1}$. Exit rates from subcutaneous LNs, mesenteric LNs, and Peyer's patches (and, thus, residence times in these lymphoid tissues) are statistically similar as judged by the F-test for nested models ($F_{2,85} = 1.78$, $p = 0.18$); the average estimated residence time is 7.8 hours.

Rapid migration of lymphocytes via lung and liver vasculature

- We predict that lymphocytes are rapidly removed from the blood (basic blood vessels).
- Most lymphocytes in the blood (80%) enter the lung capillary bed at any point of time.
- Lymphocytes travel via lung capillary bed within 30 sec.
- Little more time is taken by lymphocytes to travel via the liver (50 sec).
- Rapid recirculation of lymphocytes between blood, lung, and liver results in a relatively slow decline of the percent of transferred lymphocytes in the blood (as observed in many studies).

Cannulation



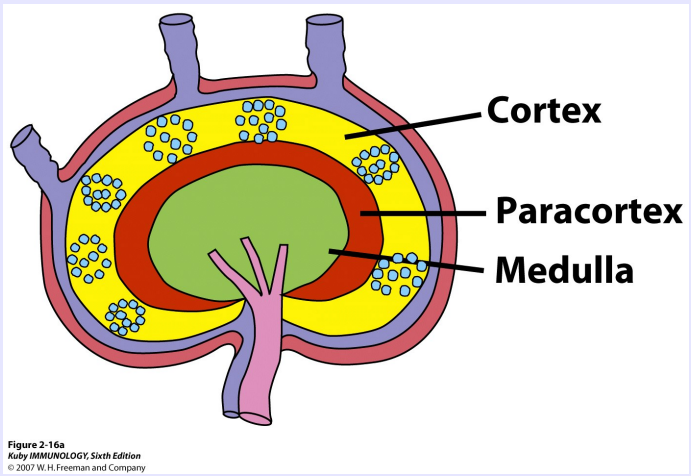
Cannulation after transfer of labeled TDLs

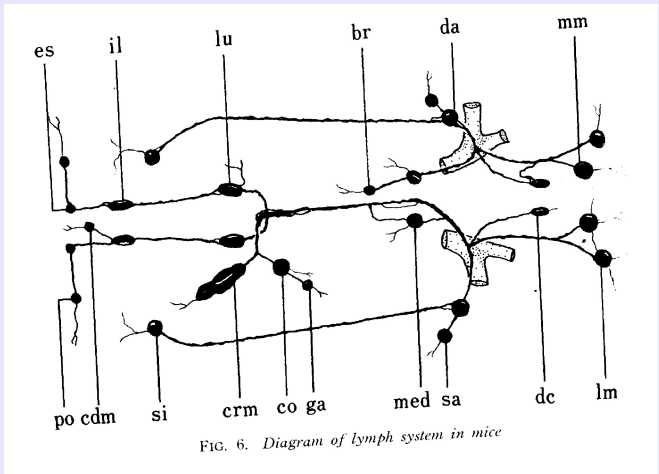
- In additional experiments, the percent of labeled lymphocytes exiting via the thoracic duct per hour was measured (dots).
- The model does not predict TDL output (panel A).
- Scaling of output does not resolve the problem of an earlier peak in the model (panel B).

Non-exponentially distributed residence time in LNs

LNs

- LNs and PPs have a complicated structure
- LNs in mammals are often organized in chains where exit from one LN is an entrance into another LN
- Migration via individual lymph nodes follows a tailed distribution (lognormal or gamma).





Kuby Immunology 2007; Kawashima et al. JJVR 1964; Reynolds et al. I 1982; Thomas et al. PLoS One 2012

Gamma distributed residence time in LNs and PPs

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -x_1\left(d + \sum_{i=2}^{n} m_{1i}\right) + \sum_{i=2}^{4} m_{i1}x_i + \sum_{i=5}^{6} m_{i1}x_{ik}, \quad (4)$$

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = m_{1i}x_1 - m_{i1}x_i, \qquad i = 2, 3, 4, \quad (5)$$

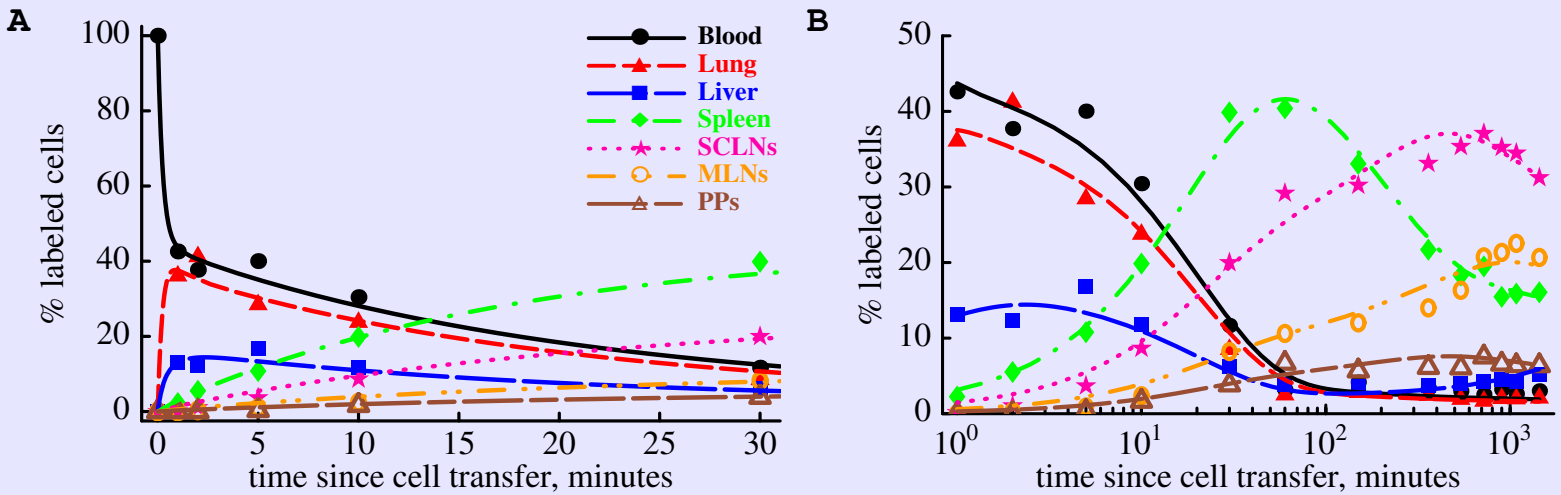
$$\frac{\mathrm{d}x_{i1}}{\mathrm{d}t} = m_{1i}x_1 - m_{i1}x_{i1}, \qquad i = 5, 7, \quad (6)$$

$$\frac{\mathrm{d}x_{61}}{\mathrm{d}t} = m_{16}x_1 - m_{61}x_{61} + m_{71}x_{7k}, \quad (7)$$

$$\frac{\mathrm{d}x_{ij}}{\mathrm{d}t} = m_{1i}x_{ij-1} - m_{i1}x_{ij} \qquad i = 5, \ldots n, j = 2, \ldots, k \quad (8)$$

there is in total k compartments per lymphoid tissue (LNs or PPs) and transition through a given compartment is m_{i1}.

Fits of the "gamma" model to kinetic data ($k = 2$)



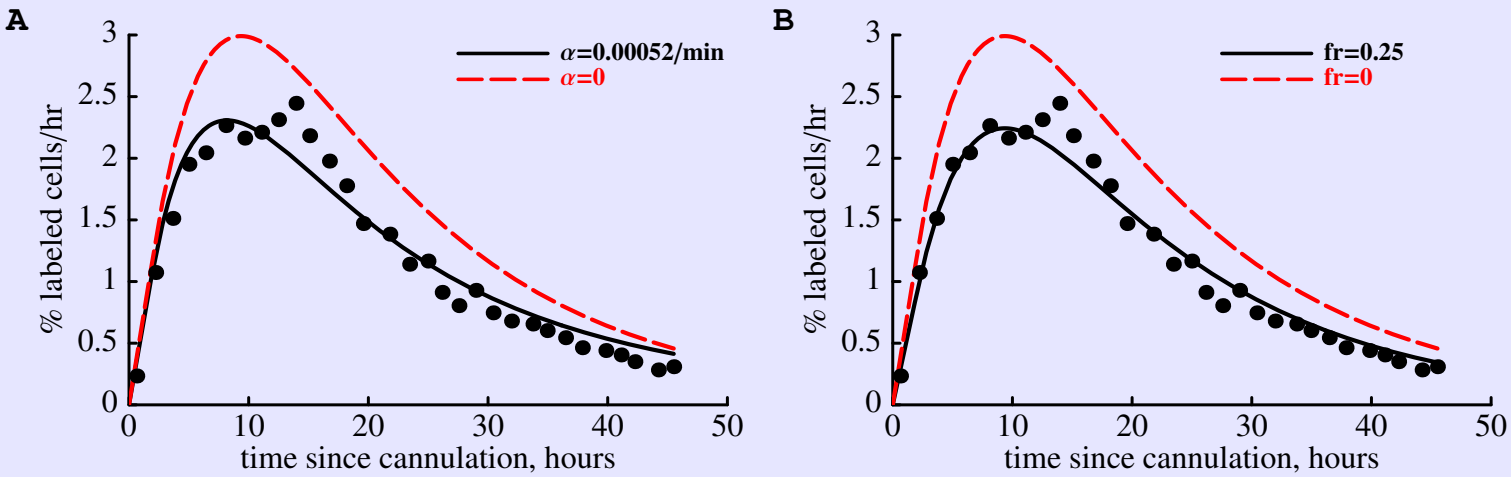
Note: we also assume that a fraction of cells in the blood with a "dying" phenotype migrate to the liver.

Parameters of the "gamma" model

Organ	Rate of entrance from blood m_{1i}, min^{-1}	Percent cells going to organ from blood	Rate of exit from organ to blood m_{i1}, min^{-1}	Residence time in organ, mins
Lung	1.83 (1.34–2.25)	78.2 (64.2–84.0)	2.17 (1.59–2.63)	0.46 (0.38–0.62)
Liver	0.41 (0.26–0.82)	17.4 (11.4–31.2)	1.14 (0.69–2.46)	0.88 (0.40–1.46)
Spleen	0.056 (0.051–0.061)	2.4 (1.8–3.0)	0.007 (0.0058–0.0087)	144 (115–173)
SCLNs	0.026 (0.024–0.028)	1.11 (0.85–1.36)	0.0034 (0.0029–0.004)	593 (498–693)
MLNs	0.011 (0.009–0.012)	0.46 (0.34–0.56)	0.0034 (0.0029–0.004)	593 (498–693)
PPs	0.005 (0.004–0.006)	0.23 (0.17–0.29)	0.0034 (0.0029–0.004)	593 (498–693)

Residence time of cells in a particular organ is calculated as $1/m_{i1}$ (for lung, liver, and spleen) or $2/m_{i1}$ (SCLNs, MLNs, PPs). We assume $k = 2$ subcompartments in LNs and PPs. Estimated fraction cells migrating to the liver and dying is $f_d = 0.23\ (0.16 - 0.32)$ and the rate of cell migration to other organs in the body $d = 0.0057\ (0.0042 - 0.0070)$ min^{-1}. Exit rates from subcutaneous LNs, mesenteric LNs, and Peyer's patches (and, thus, residence times in these lymphoid tissues) are statistically similar as judged by the F-test for nested models ($F_{2,84} = 1.37$, $p = 0.26$); the average estimated residence time in these tissues is 9.9 hours.

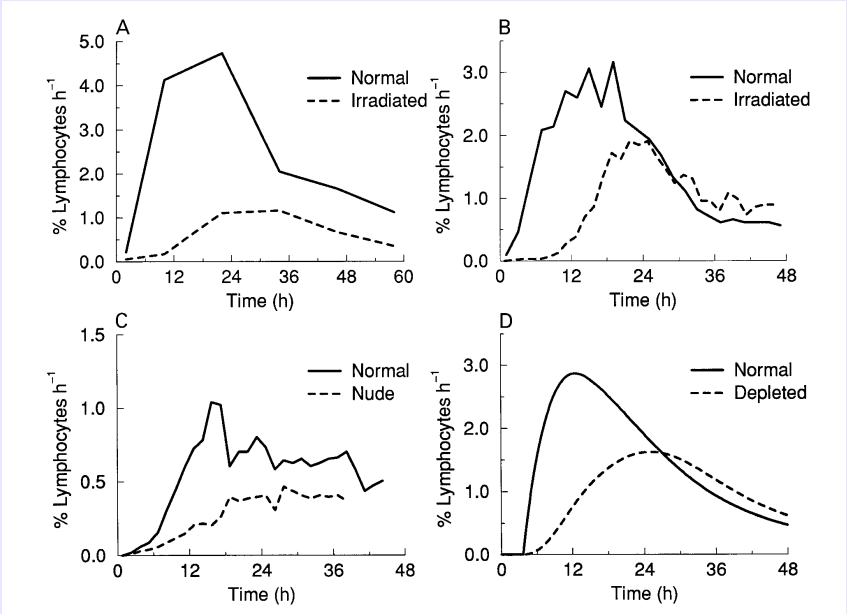
Predicting thoracic duct output in the "gamma" model

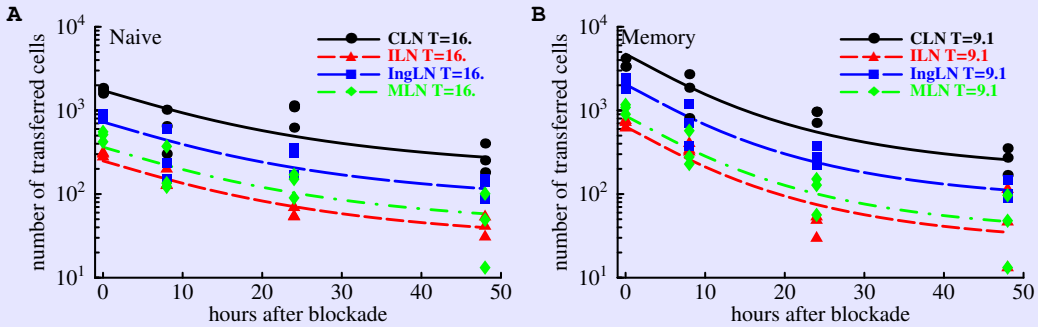


Additional biological info:

1. Only a fraction of lymphocytes ($f_t = 65 - 85\%$) exit lymph nodes into the blood via the thoracic duct; other lymphocytes enter the blood via the right lymphatic duct.
2. A fraction of lymphocytes (f_r) may become resident in lymph nodes during cannulation (i.e., will have infinite residence time).
3. The rate of lymphocyte migration via lymph nodes may decline over time due to loss of LN cellularity.

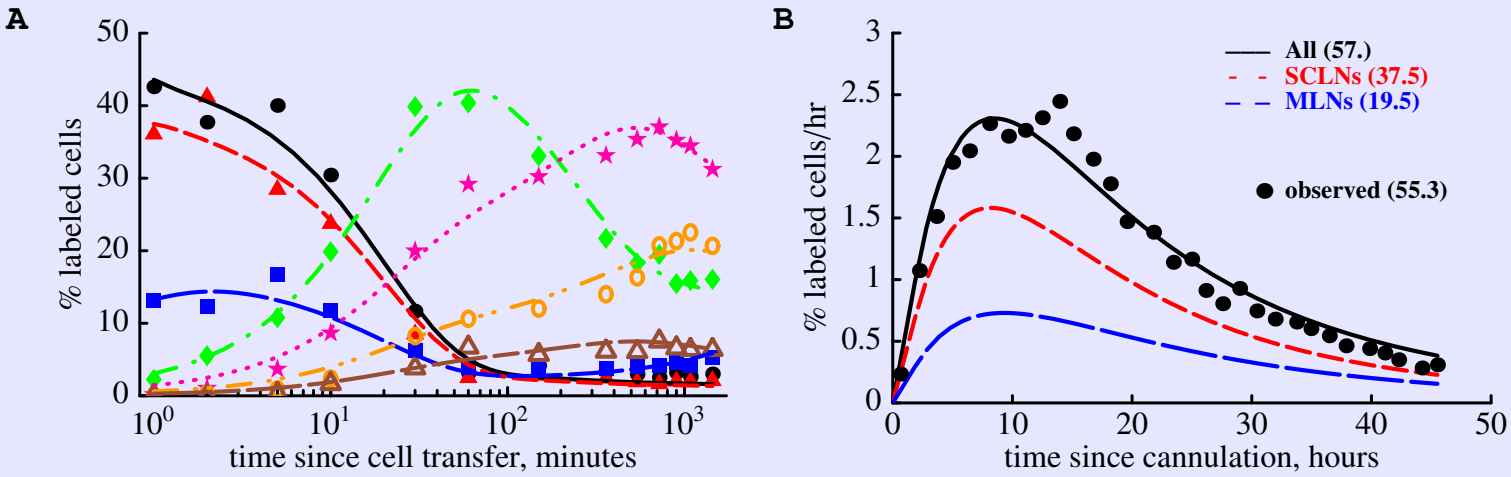
Change in lymphocyte exit rate in irradiated and nude rates and during long-term CD62L blockade





Stekel SJI 1998; Harp et al. JI 2010

Explaining cannulation data

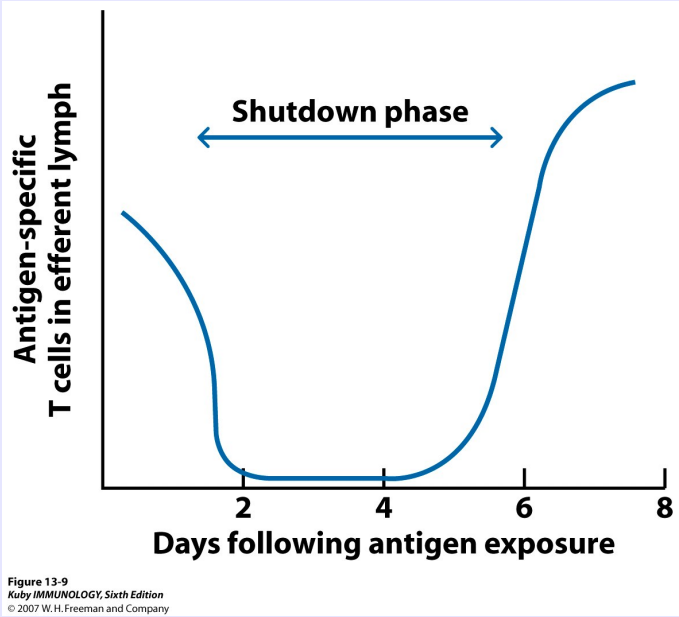


To describe the data

1. Only a fraction of lymphocytes ($f_t = 86\%$) exit lymph nodes into the blood via the thoracic duct.
2. The rate of lymphocyte migration via lymph nodes declines over time due to loss of lymphocytes ($\alpha = 6.4 \times 10^{-4}$ min^{-1}).
3. The latter is similar to the assumption that some lymphocytes become lymph node resident during cannulation (e.g., $f_r \approx 75\%$).

Why Ag-stimulated LNs enlarge?

1. increased input of lymphocytes into Ag-stimulated LNs
2. decreased output of lymphocytes from Ag-stimulated LNs
3. increased lymphocyte proliferation rate in Ag-stimulated LNs

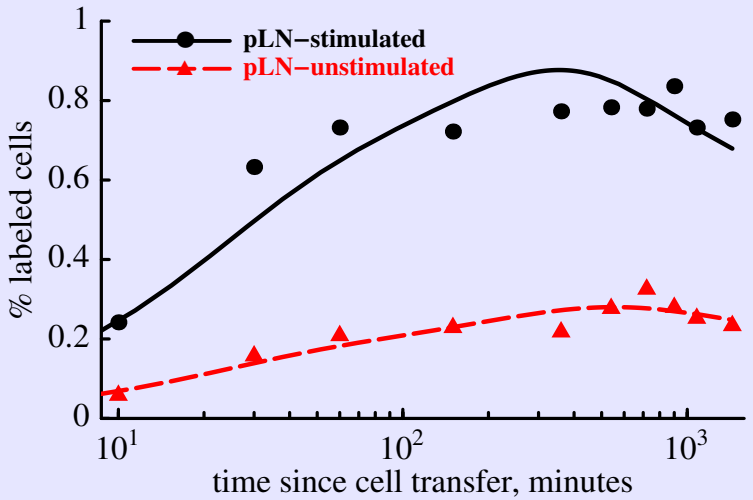


Kuby Immunology 2007; Hasbold et al. 1988; Kumamoto et al. PNAS 2011; Yates et al. Blood 2012

Ag-stimulated vs. unstimulated lymph nodes

- One popliteal LN (pLN) was stimulated with sheep erythrocytes 3 days prior to transfer of ^{51}Cr-labeled TDLs; another pLN was kept as a control.
- pLNs were includes in the SCLNs
- We let the dynamics of labeled lymphocytes in the pLNs to be described as for other lymph nodes but with different migration rates.
- Parameters for migration via other organs are kept constant.

Ag-stimulated vs. unstimulated lymph nodes



LN	entrance rate, 10^{-4} min^{-1}	exit rate, 10^{-3} min^{-1}
stimulated	6.65	3.95
unstimulated	1.86	3.07

- Entrance into stimulated LN is increased 3.5 fold, and exit rate is the same ($F_{1,24} = 1.51$, $p = 0.23$).
- Conclusion is the same if residence times in LNs are exponentially distributed.

Summary

- Very rapid recirculation of TDLs between blood, lung, and liver (residence time < 1 min).
- Short-residence time of lymphocytes in the spleen (average 2.5 h)
- Gamma distributed residence time of TDLs in lymph nodes and Peyer's patches (average 10 hours).
- Accumulation of TDLs in Ag-stimulated lymph nodes is due to increased entrance rate (3.5 fold).

Blood recirculation kinetics (rats)

- Total blood volume is about 20 mL
- Volume of the heart is about 1-2mL
- 30% is pumped per beat (humans)
- Heart beat is about 300 per min

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Algebra

- Per 1 min, rat heart will pump (at most)

$$0.3 \times 1m\text{L} \times 300 = 90m\text{L}$$

  of blood which is about 4-5 times the blood volume.
- Average blood turnover time is about 10-15 seconds. Lymphocytes are able travel via lung capillaries and liver sinusoids nearly as fast as the blood.

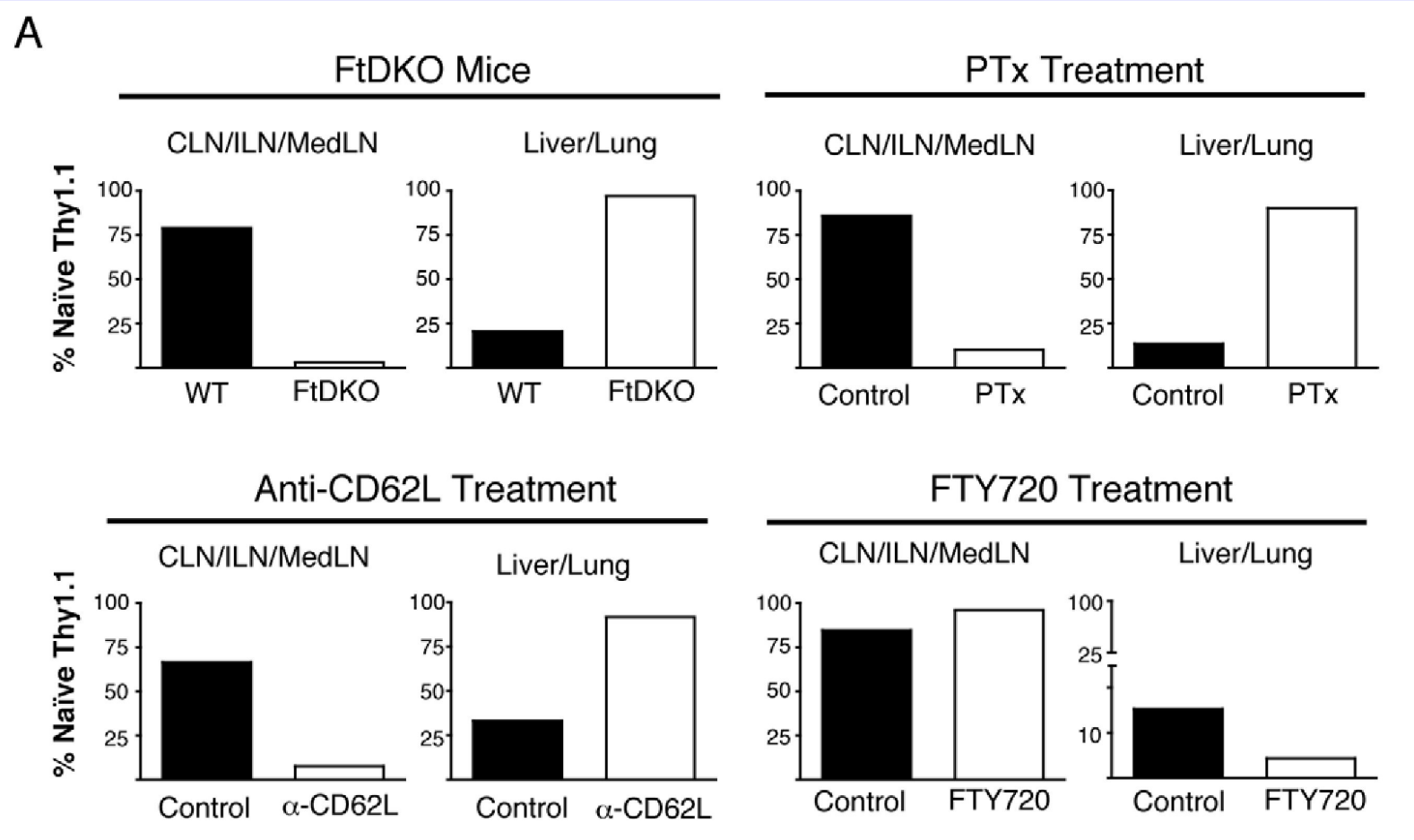
Influencing lymphocyte migration

Organ	Control	Increased residence in lung (inflammation)	Blocked LN entrance (anti CD62L Ab)	Blocked LN exit (FTY720)
Blood	2.6 (2.2–3.2)	1.8 (1.6–2.1)	8.6 (7.6–9.9)	0.2 (0.1–0.2)
Lung	2.2 (1.9–2.7)	**31.1 (27.6–35.5)**	7.3 (6.4–8.4)	0.1 (0.1–0.2)
Liver	0.9 (0.8–1.2)	0.7 (0.5–0.8)	3.1 (2.6–3.8)	0.1 (0.–0.1)
Spleen	20.9 (19.5–22.1)	14.7 (13.6–15.6)	**68.9 (66.3–70.8)**	1.4 (1.3–1.5)
SCLNs	**40.3 (38.8–41.4)**	28.4 (26.1–30.1)	6.6 (6.1–7.2)	**54. (52.1–55.7)**
MLNs	24.8 (23.5–26.1)	17.5 (15.8–19.1)	4.1 (3.7–4.6)	33.2 (31.9–34.5)
PPs	8.3 (7.2–9.3)	5.8 (5.–6.7)	1.4 (1.2–1.6)	11.1 (9.8–12.4)

Predicting lymphocyte distribution in the model

1. control animal
2. following increased average residence time in the lung (20 fold, from 27 seconds to 9 minutes) due to, for example, inflammation in the lung;
3. following a decreased entrance rate of TDLs into lymph nodes and Peyer's patches (20 fold, e.g., by using anti CD62L antibody);
4. following a decreased exit rate of TDLs from lymph nodes and Peyer's patches (20 fold, e.g., using FTY720).

Influencing lymphocyte migration: data



Harp and Onami PLoS One 2010

Questions for future research

- If lymphocytes travel rapidly via lung and liver, why can't lymphocytes be perfused from these tissues?
- Simple migration data (as in this work or other studies) do not allow to estimate the distribution of residence times since different distributions will be consistent with the data. Additional data on migration via individual organs may need to be utilized.
- Why does it take longer for lymphocytes to travel via LNs than via spleen?
- Is there any biological reason for gamma distributed residence times (with $k = 2$: S1P$_1$ - exponential, and exit - exponential)?

Acknowledgments and Contributions

- **Research**
  - Ann Wells (Engineering), Angela Dautartas (Antropology), and Jeremy Auerbach (Math) started first analysis of the data as a part of their assignment during 600-level course
- **Funding**
  - University of Tennessee

NIMBioS: National Institute for Mathematical and Biological Synthesis

Funding support for:

- Investigative Workshops (up to 40 people) or Working Groups (3-10 individuals)
- Post-doc positions ($51k per year for 2 years, need to write a short proposal)
- Short-term visitors (few days to several months)
- Overall goal is to use mathematics to address important (unsolved?) problems in biology (all areas)

We are currently looking for a new Director of the Institute(!)