“Mathematical models and numerical methods in biomathematics - VIII "
Moscow, 31.10-03.11 2016

Systems approach to immunology

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Systems Immunology

- A field of **study of the interactions** between the components of the immune system, and **how these interactions give rise to the function and behavior** of that system

- The **application of systems theory** to the complexity of the immune interactions at all levels

964 PROCEEDINGS OF THE IEEE, VOL. 68, NO. 8, AUGUST 1980

A Systems Approach to Immunology

RONALD R. MOHLER, MEMBER, IEEE, CARLO BRUNI, AND ALBERTO GANDOLFI

Invited Paper

What to look for in Immunology for a Systems-level understanding?

Kitano, Science, 2002, 1662-1664; Csete & Doyle, Science, 2002, 1664-1669

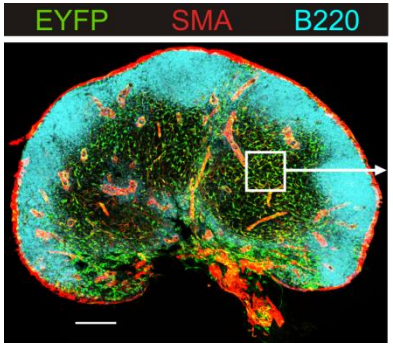
Immune system (response, Infection, disease)

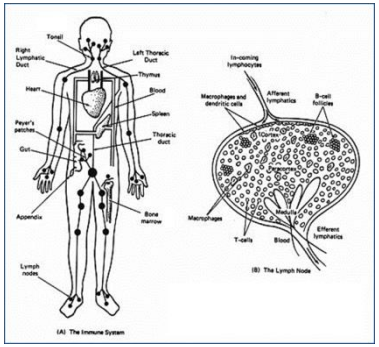
Structure

Design principles

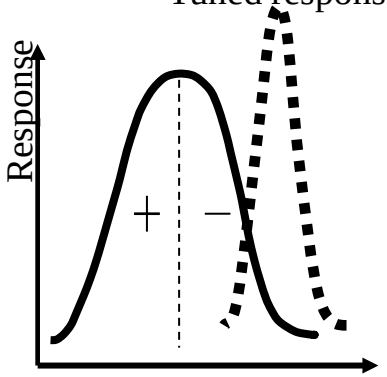
Control, regulation: *feedback feedforward*

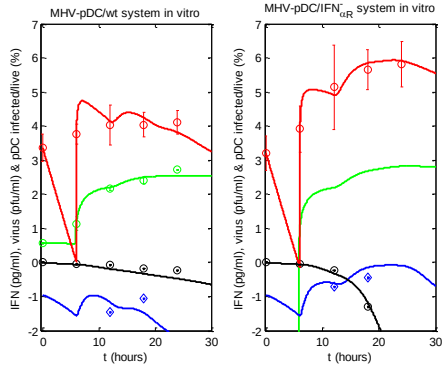
Dynamics





Tuned response





Topics

"…understanding cellular physiology and molecular details usually summarized by the term **'system biology'** or **'systematically, completely measured biology'** are eventually necessary to understand the strengths and weaknesses of immune defences."

R. M. Zinkernagel. Immunity Against Infections & Vaccines: Credo 2004. Scand J Immunol. 2004, 60: 9–13

1. **Identification of feedback mechanism for '*balance of growth and differentiation*' hypothesis**
2. **Modelling the structure of lymph node**

Systems Immunology approach to specific questions

- **Experiments + Measurements**
- **Big Data analyses + Mathematical Modeling +**
- **Theoretical concepts and Hypotheses**

Theoretical Immunology

The main body of immunology is constituted by **non-mathematical theories** (empirically derived):

1. *Clonal Selection Theory* (Nobel Laureate, F.M. Burnet)
2. ***Network-type (e.g. idiotypic) Theory of Immune Regulation*** (Nobel Laureate, N. Jerne)
3. *Spatiotemporal view of rules for immune responses regulation* (Nobel Laureate R.M. Zinkernagel)
4. *Balance of growth and differentiation; activation threshold tuning: conceptual framework of IR regulation*
   Immune system *responds to a rapid perturbation* in its homeostasis); Individual lymphocytes *respond to a rapid change in the level* of stimulation, rather than a stimulation *per se* (Z. Grossman, W.E. Paul)

…

- **Successful theories in immunology are still in the stage of growth & revision**

Regulation of clonal lymphocyte dynamics

- Antigen dose, time period during which it is available and its "geographical" distribution within this host influences immune responses

  (R.M. Zinkernagel: "Immunology and immunity against infection: general rules" JCAM 2005, 184:4-9)

- A program of antigen-independent clonal expansion and functional maturation: once triggered by a stimulatory APC, $CD8^+$ T lymphocytes primed in vivo or in vitro can proliferate through multiple rounds of division and differentiate in the absence of further stimulation

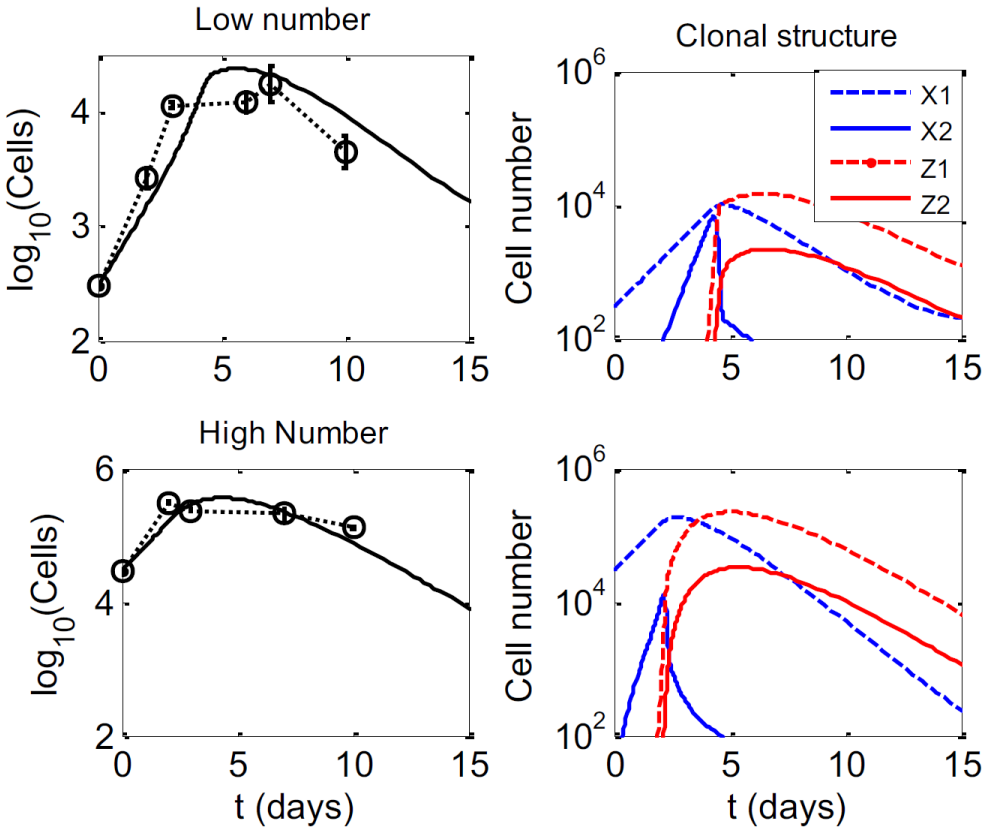
  (M.J.B. van Stipdonk et al., Nature Immunology 2001 2: 423-428;

  S.M. Kaech & Rafi Ahmed Nature Immunology 2001 2: 415-418)

Clonal expansion and contraction

Immune response ≡ Antigen-driven clonal dynamics

Results from proliferation-differentiation-death of heterogeneous cell populations

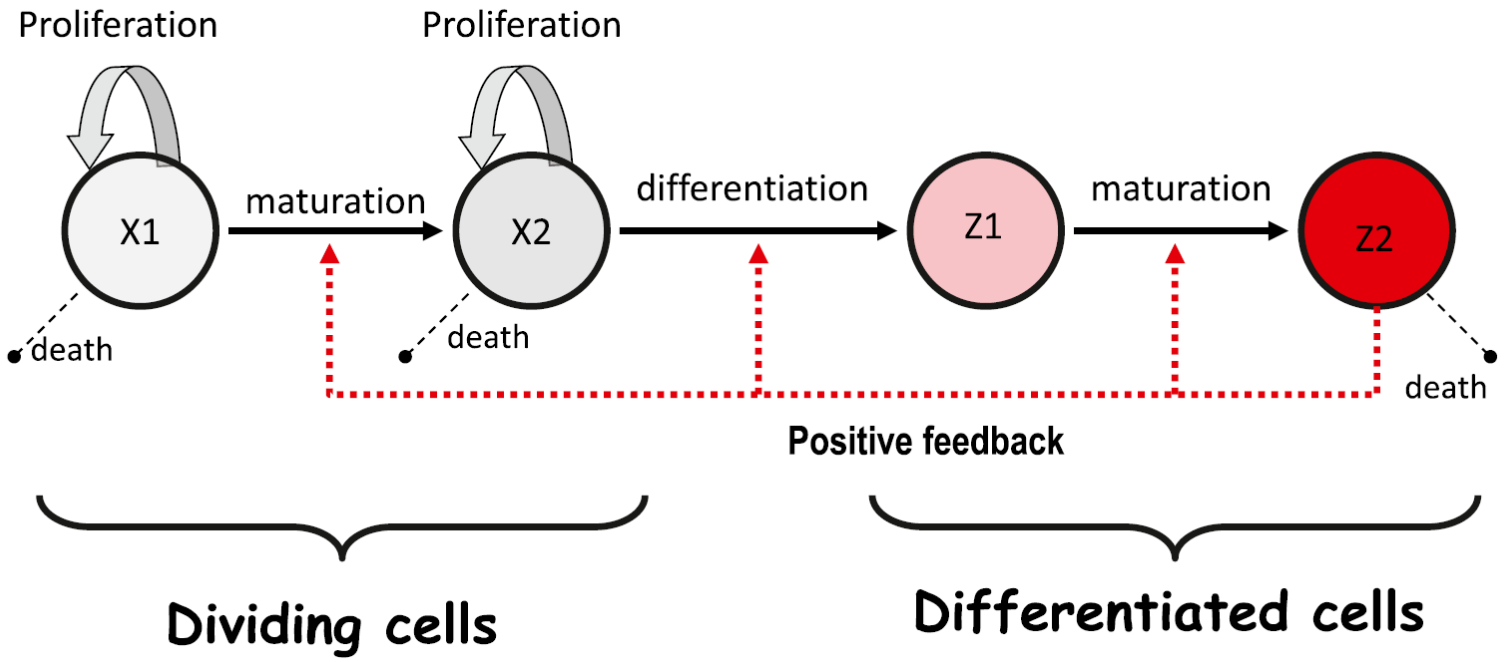


From Bocharov et al., *PNAS USA* 2011, 108:3318-3323

The concept of "feedback-regulated balance of growth & differentiation" *(Z. Grossman & W. Paul)*

1. Proliferation & differentiation

2. Feedback regulation



Precursor number profoundly affects "Factor of Expansion" (FE): *Low Precursor Frequency Shows More Proliferation*

The response of a single precursor in all the LNs could be detected

Antigen-stimulated CD4 T-cell expansion is inversely and log-linearly related to precursor number

Juan Quiel[a], Stephane Caucheteux[a], Arian Laurence[b], Nevil J. Singh[c], Gennady Bocharov[d], Shlomo Z. Ben-Sasson[a], Zvi Grossman[a], and William E. Paul[a,1]

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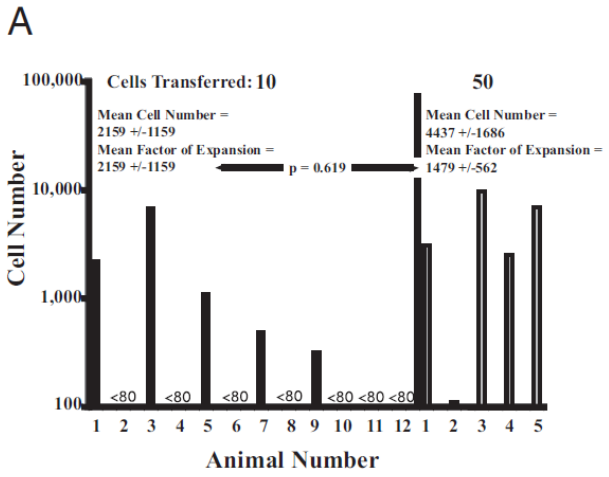

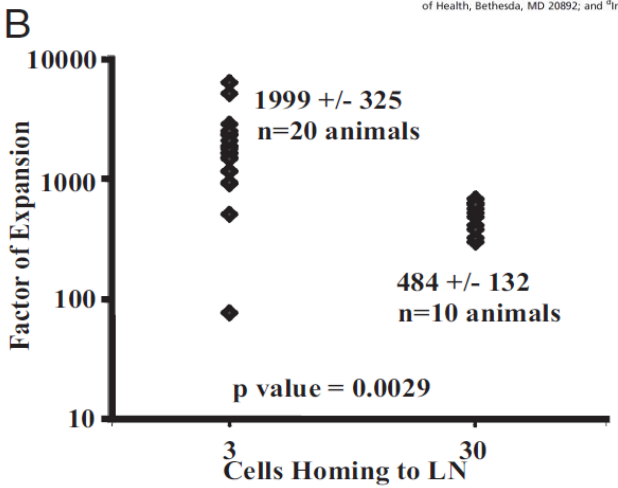

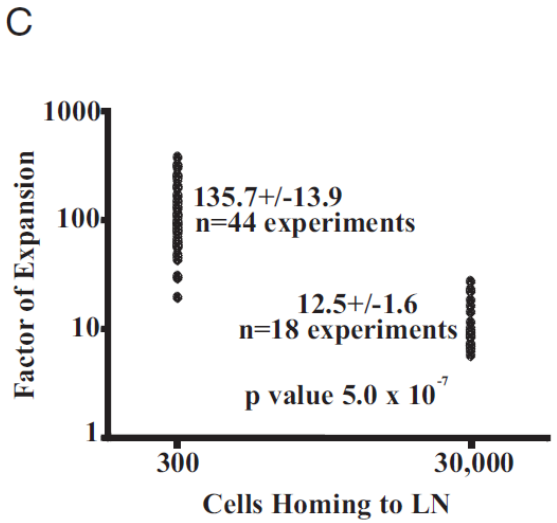

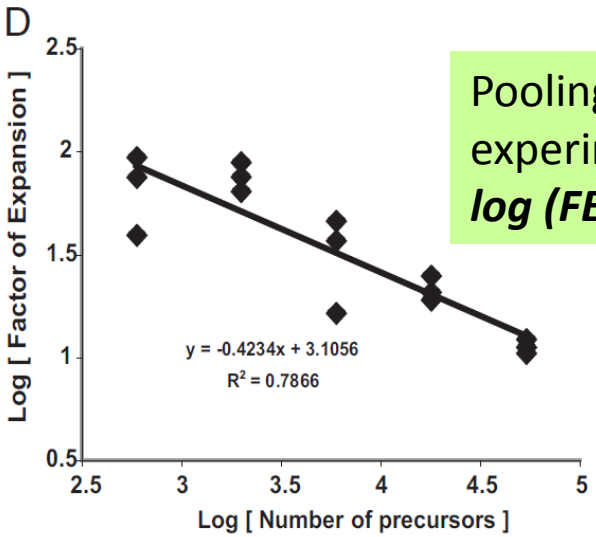

Pooling results from individual experiments reveals that ***log (FE) ~ -0.5 log (PN)***

Materials & Methods

Antigen-stimulated CD4 T-cell expansion is inversely and log-linearly related to precursor number

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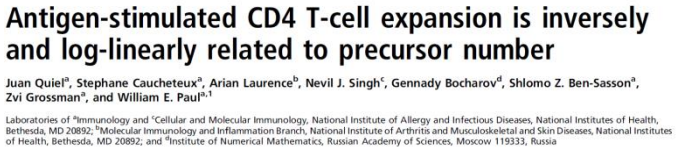
- **Mice**: 5C.C7 TCR transgenic, 5C.C7 *lpr/lpr*, 5C.C7 TNF-αR KO, 5C.C7 CTLA-4 KO, 5C.C7 IL-2 KO, 5C.C7 IFN-γ KO, B10.A, C57BL/6, OT-II TCR transgenic C57BL/6, DO11.10 TCR tg BALB/c, BALB/c
- **Adoptive Cell Transfer and immunization**:

1. 5C.C7 or 5C.C7 CD45.1+ lymph node cells were mixed with polyclonal B10.A lymph node cells to give a total of 10^6 transferred cells. Cells were allowed to home for 24 hrs. Animals were immunized s.c. by a single dose of 100 μg of cytochrome C protein or 10 μg of pigeon cytochrome peptide in PBS. (LPS 25 μg/animal was used as an adjuvant when indicated).
2. Similarly, DO11.10 tg, OT-II tg, Marylin tg, and A1(M) tg cells were transferred and recipients were immunized with 500 μg of OVA, 10 μg of HY peptide using 25 μg of LPS as an adjuvant.
3. Cytokines (10 μg) were delivered via an s.c. miniosmotic pump

- **In vivo proliferation and division rate:** Recipients were pulsed with 1 mg of BrdU for a period of 6 hr. Lymph nodes were processed using the APC BrdU Flow Kit
- **Enumeration of Cells Using Real-time PCR**: uses the primers and probe sets directed against a short segment of the CDR3 region of the 5C.C7 β chain. ***Resolution***: ***1 TCR tg T cell in 100,000 non-tg T cells***

Experimental observations



Antigen-stimulated CD4 T-cell expansion is inversely and log-linearly related to precursor number

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- No evidence for competition for antigen or Dendritic Cell (DC) increased lymphocyte killing or shortage of cytokines
- Factor of Expansion (FE) dependence on PN is not significantly affected by antigen amount, DC number, the exogenous IL-2, IL-7, IL-15, Fas, TNF-α receptor, CTLA-4
- No evidence of differential Foxp3$^+$ T reg involvement
- FE of small numbers of transgenic precursors is not significantly affected by concomitant responses of large numbers of cells specific for different antigens
- Some type of local feedback control could explain results.

Objectives

- To check the validity of 'feedback-regulated balance of growth and differentiation' concept

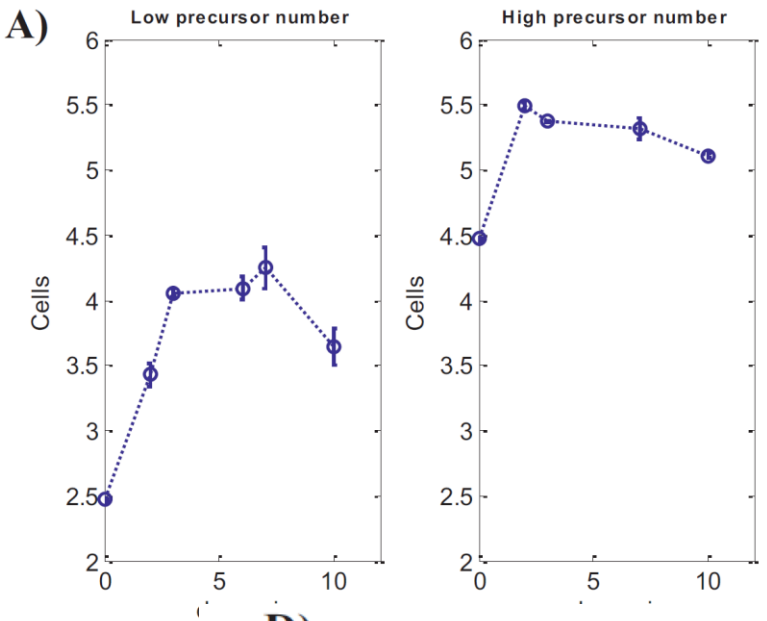
- To identify a parsimonious model of the kinetics of *physiological* regulation of antigen-driven $CD4^+$ T-cell expansion

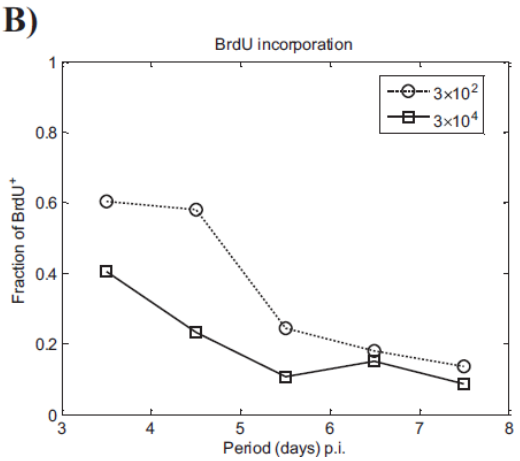
(*precursor number from 3 to 30,000 in the LNs;*

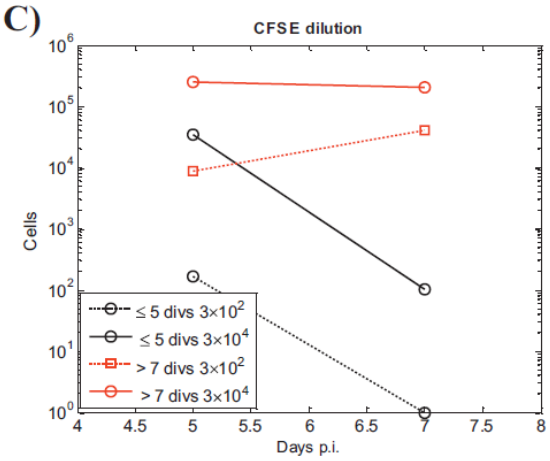
estimates of physiological frequencies range from

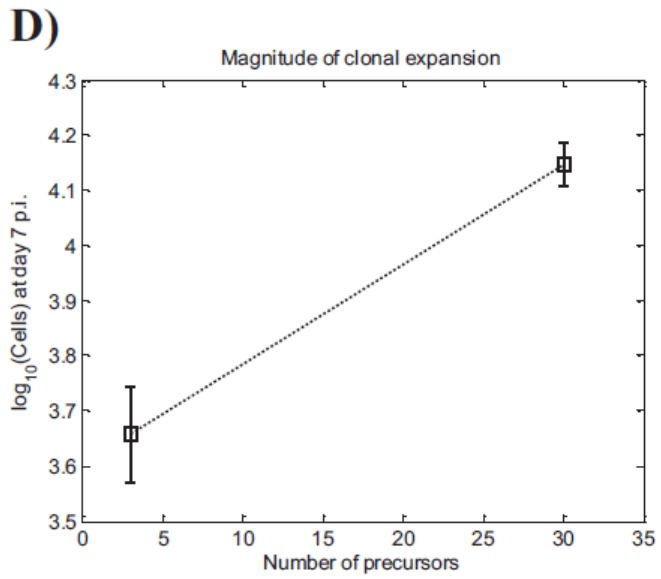
20 to 3,000 *per animal*)

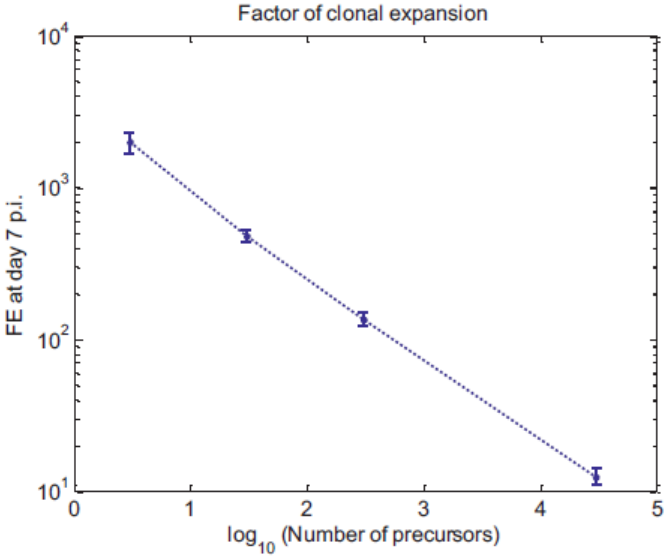
‘Global’ data set to available for the identifying the regulation scheme using mathematical model











Maximum likelihood parameter estimation

$$\frac{d}{dt}\mathbf{y}(t) = \mathbf{f}\left(\mathbf{y}(t), \mathbf{y}(t-\tau), \mathbf{p}\right), \quad t \in [t_0, T], \quad \tau > 0$$

$$\mathbf{y} \in R^{n_\mathbf{Y}}, \quad \mathbf{p} \in R^{n_\mathbf{p}}$$

$$\mathbf{y}(t) = \varphi(t),\ t \in [t_0 - \tau, t_0].$$

- Observation data $\left\{t_j, \mathbf{y}_j\right\}_{j=1}^{n_{obs}}$

- Likelihood function

$$\mathbf{y}_j \sim \mathcal{N}\left(\mathbf{y}(t_j), \Sigma_j\right)$$

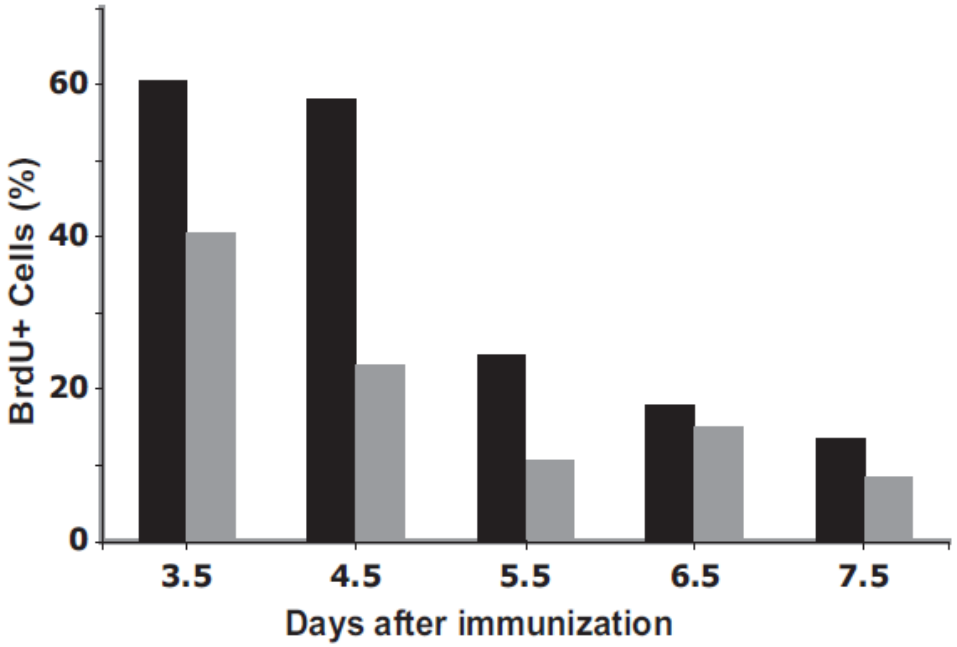
$$\mathcal{H}\left(\mathbf{y}_j; \mathbf{p}\right) = \frac{1}{\sqrt{(2\pi)^{n_y} \det \Sigma_j}} \exp\left\{-\frac{1}{2}\left[\mathbf{y}(t_j) - \mathbf{y}_j\right]^{\mathrm{T}} \Sigma_j^{-1} \left[\mathbf{y}(t_j) - \mathbf{y}_j\right]\right\}$$

$$\mathcal{L}(\mathbf{p}) = \prod_{j=1}^{n_{obs}} \mathcal{H}\left(\mathbf{y}_j; \mathbf{p}\right)$$

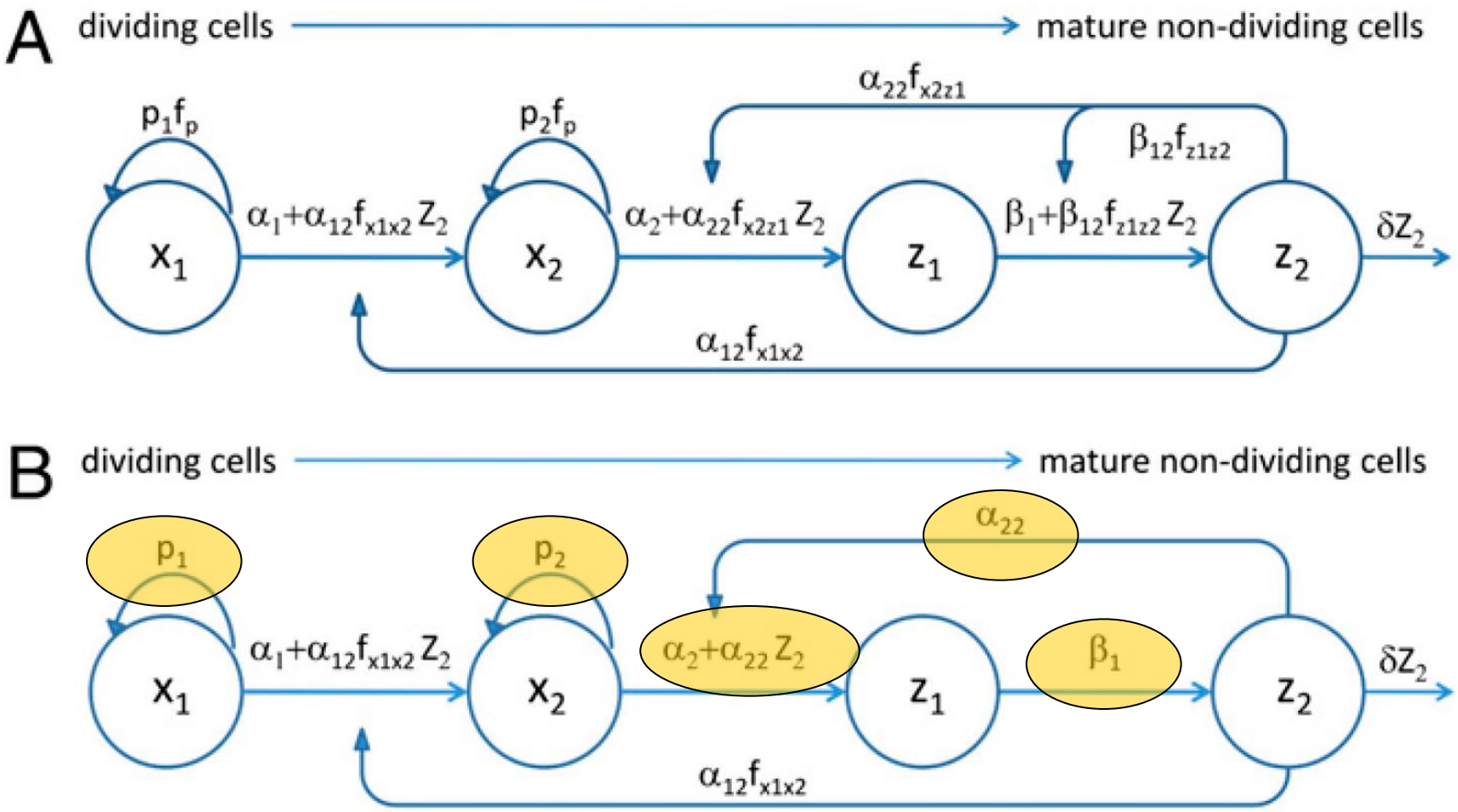
$$\mathbf{p}^* = \arg\max_{\mathbf{p} \in D} \mathcal{L}\left(\mathbf{p}\right)$$

Data on Changes in Proliferation Rates

- Immunization of recipients of 300 and 30,000 cells
- Treatment with BrdU and killing them 6 h later
- The proportion of BrdU+ and BrdU- cells among CD45.1 cells evaluated via FACS analysis



Nested mathematical models to describe the feedback regulation of T cell expansion and contraction



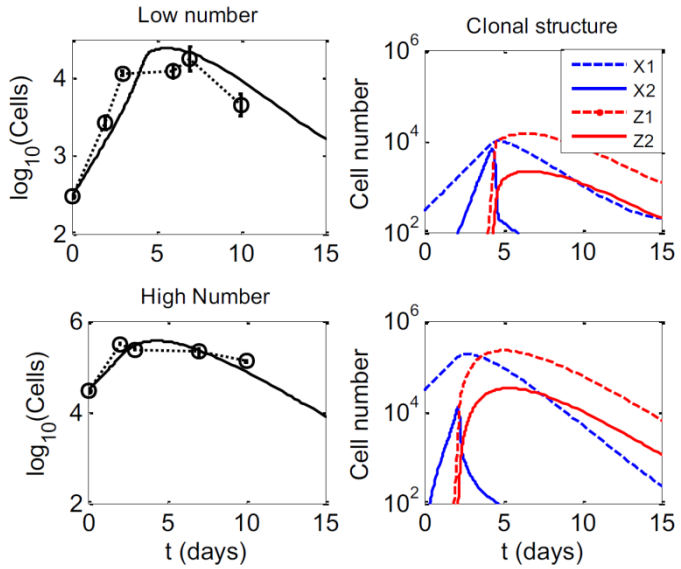
Basic Model of DC4 T cell dynamics

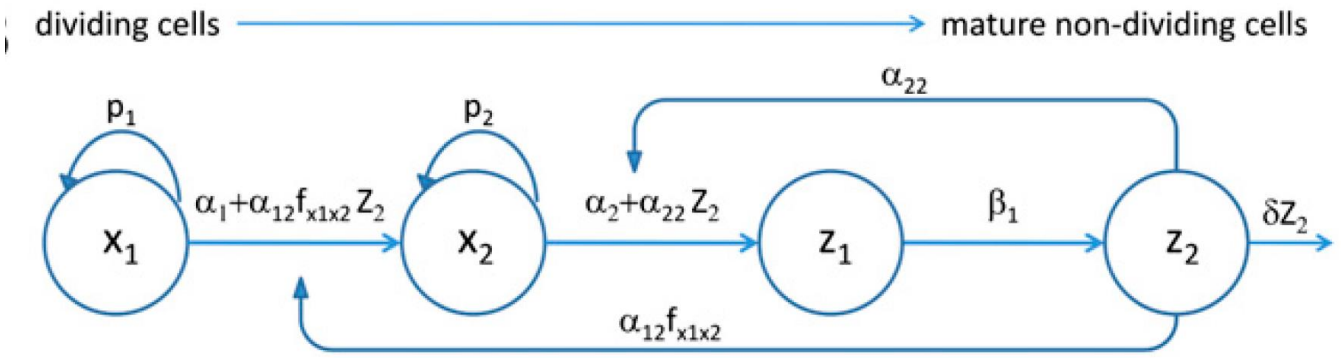
$$\frac{dX_1}{dt} = p_1 \cdot X_1 - (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot Z_2) \cdot X_1,$$

$$\frac{dX_2}{dt} = p_2 \cdot X_2 + (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot Z_2) \cdot X_1 - (\alpha_2 + \alpha_{22} \cdot Z_2) \cdot X_2,$$

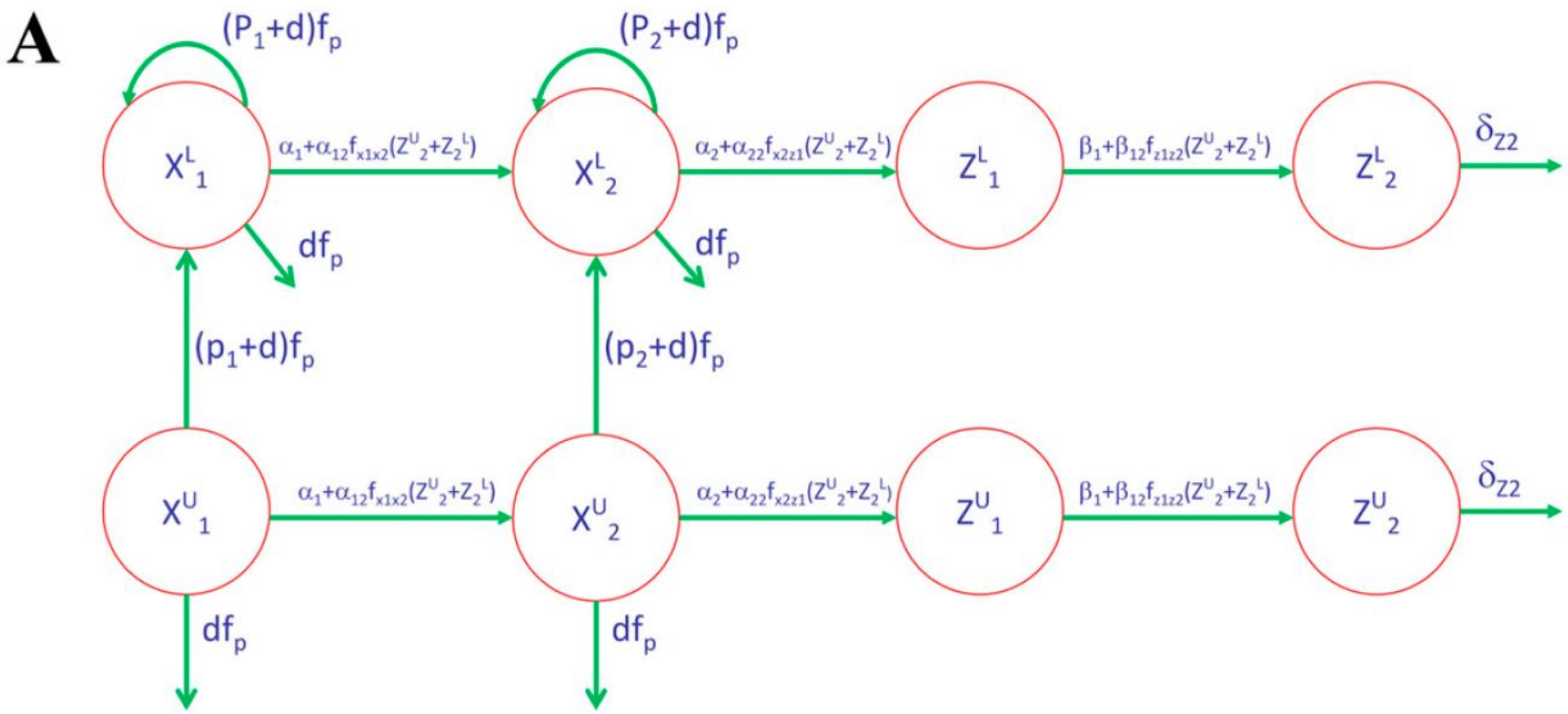
$$\frac{dZ_1}{dt} = (\alpha_2 + \alpha_{22} \cdot Z_2) \cdot X_2 - \beta_1 \cdot Z_1,$$

$$\frac{dZ_2}{dt} = \beta_1 \cdot Z_1 - \delta \cdot Z_2.$$

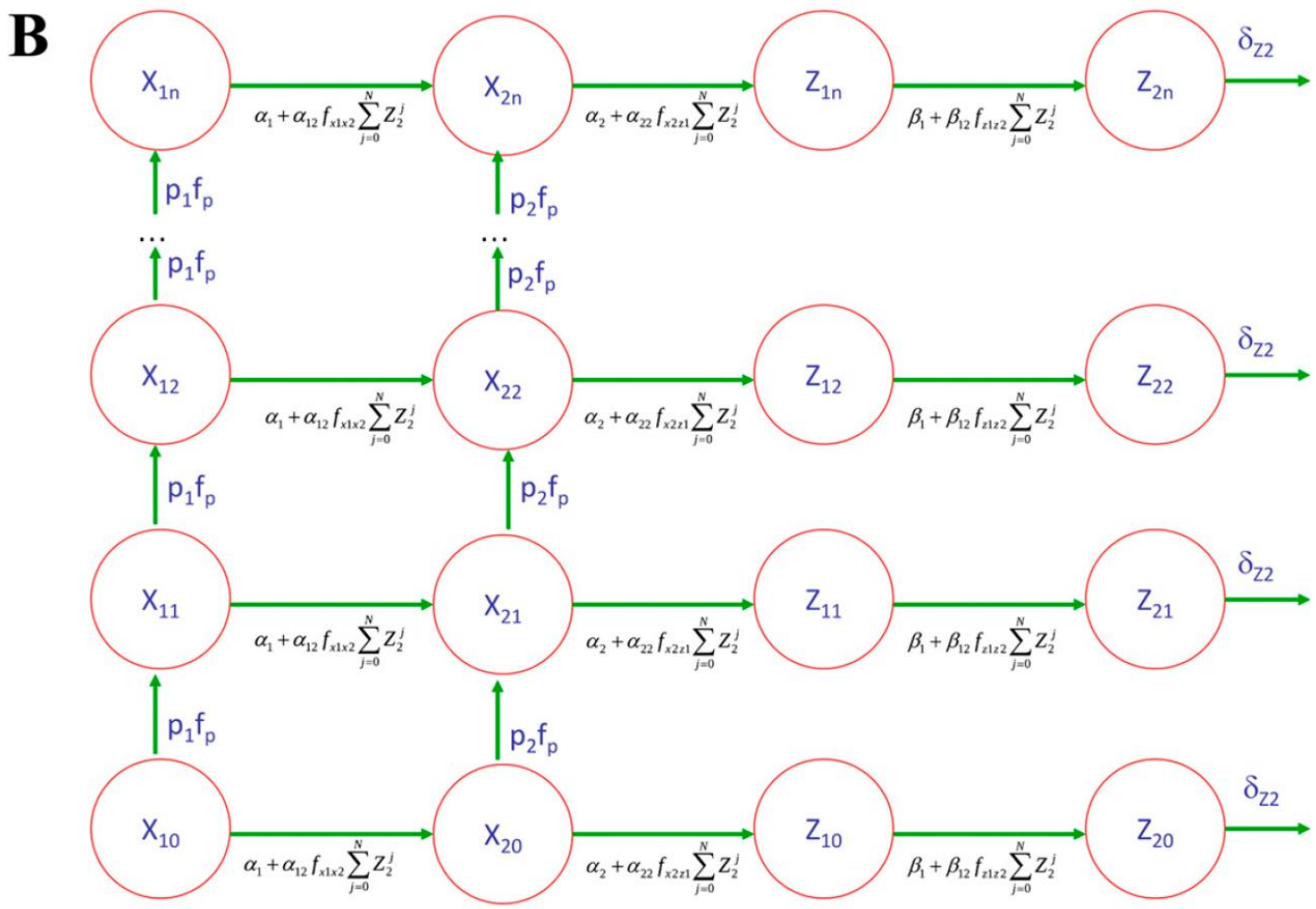




Extension of the model for assimilation of the BrdU data



Extension of the model for the analysis of CFSE labeling data



Inverse problem -> data assimilation

Regulation: Clonal dynamics

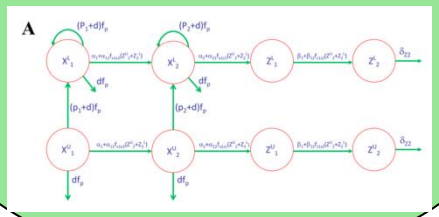
$$\frac{dX_1}{dt} = p_1 \cdot X_1 - (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot Z_2) \cdot X_1,$$

$$\frac{dX_2}{dt} = p_2 \cdot X_2 + (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot Z_2) \cdot X_1 - (\alpha_2 + \alpha_{22} \cdot Z_2) \cdot X_2,$$

$$\frac{dZ_1}{dt} = (\alpha_2 + \alpha_{22} \cdot Z_2) \cdot X_2 - \beta_1 \cdot Z_1,$$

$$\frac{dZ_2}{dt} = \beta_1 \cdot Z_1 - \delta \cdot Z_2.$$

BrdU label



$$\frac{dX_1^{\mathrm{U}}}{dt} = -(p_1 + d) \cdot f_p \cdot X_1^{\mathrm{U}} - (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_1^{\mathrm{U}} - d \cdot f_p \cdot X_1^{\mathrm{U}}$$

$$\frac{dX_2^{\mathrm{U}}}{dt} = -(p_2 + d) \cdot f_p \cdot X_2^{\mathrm{U}} + (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_1^{\mathrm{U}} - (\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_2^{\mathrm{U}} - d \cdot f_p \cdot X_2^{\mathrm{U}}$$

$$\frac{dX_1^{\mathrm{L}}}{dt} = 2 \cdot (p_1 + d) \cdot f_p \cdot X_1^{\mathrm{U}} + (p_1 + d) \cdot f_p \cdot X_1^{\mathrm{L}} - (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_1^{\mathrm{L}} - d \cdot f_p \cdot X_1^{\mathrm{L}}$$

$$\frac{dX_2^{\mathrm{L}}}{dt} = 2 \cdot (p_2 + d) \cdot f_p \cdot X_2^{\mathrm{U}} + (p_2 + d) \cdot f_p \cdot X_2^{\mathrm{L}} + (\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_1^{\mathrm{L}} - (\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_2^{\mathrm{L}} - d \cdot f_p \cdot X_2^{\mathrm{L}}$$

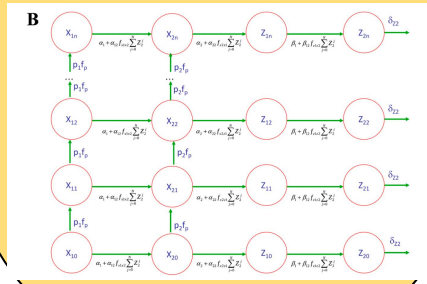
$$\frac{dZ_1^{\mathrm{U}}}{dt} = (\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_2^{\mathrm{U}} - (\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot Z_1^{\mathrm{U}}$$

$$\frac{dZ_2^{\mathrm{U}}}{dt} = (\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot Z_1^{\mathrm{U}} - \delta \cdot Z_2^{\mathrm{U}}$$

$$\frac{dZ_1^{\mathrm{L}}}{dt} = (\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot X_2^{\mathrm{L}} - (\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot Z_1^{\mathrm{L}}$$

$$\frac{dZ_2^{\mathrm{L}}}{dt} = (\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot (Z_2^{\mathrm{U}} + Z_2^{\mathrm{L}})) \cdot Z_1^{\mathrm{L}} - \delta \cdot Z_2^{\mathrm{L}}.$$

CFSE label



$$\frac{dX_1^0}{dt} = -p_1 \cdot f_p \cdot X_1^0 - \left(\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_1^0$$

$$\frac{dX_2^0}{dt} = -p_2 \cdot f_p \cdot X_2^0 + \left(\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_1^0 - \left(\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_2^0$$

$$\frac{dZ_1^0}{dt} = \left(\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_2^0 - \left(\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot Z_1^0$$

$$\frac{dZ_2^0}{dt} = \left(\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot Z_1^0 - \delta \cdot Z_2^0$$

and for cells that divided n times ($n = 1, \ldots, N$) the equations are

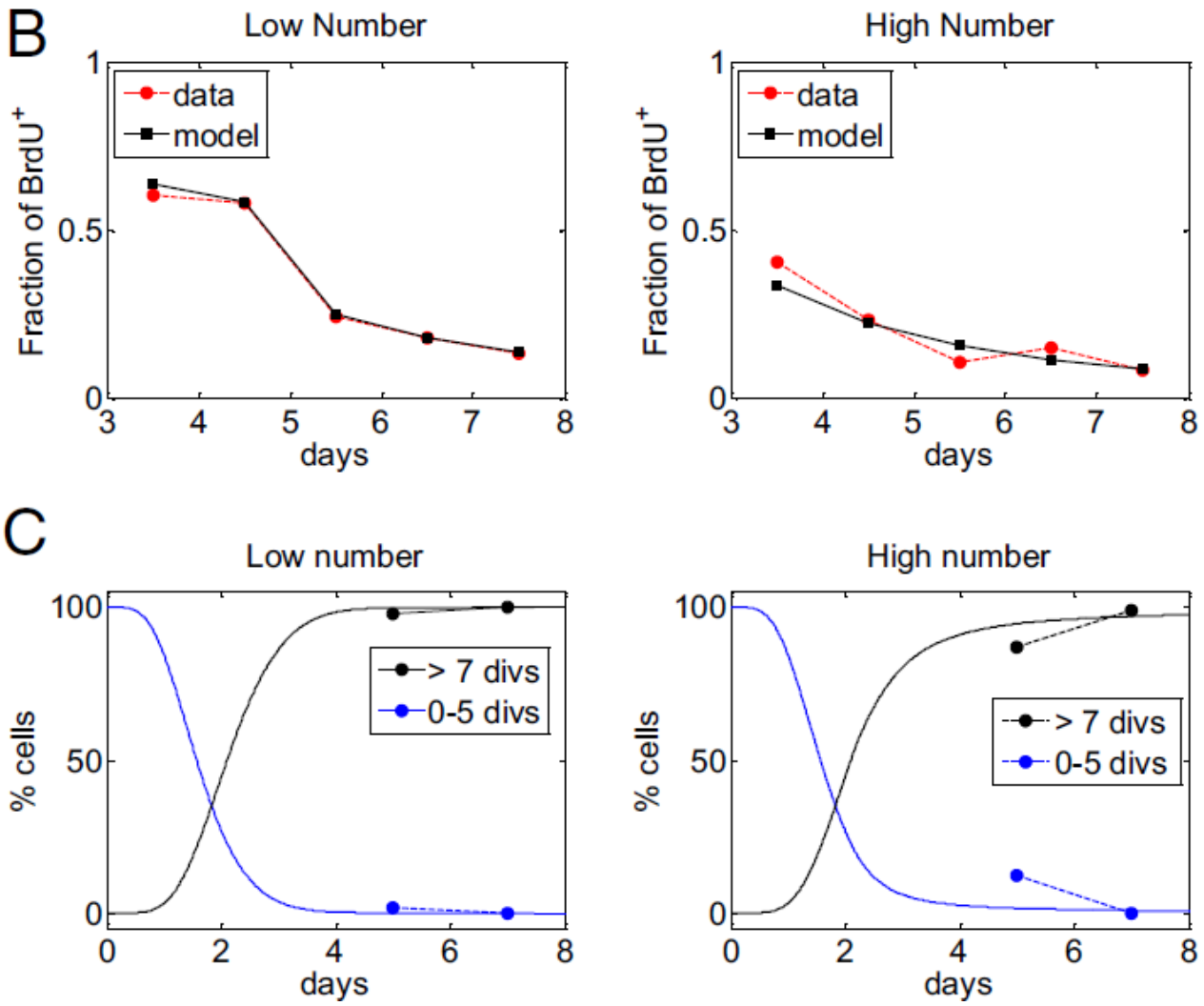
$$\frac{dX_1^n}{dt} = 2p_1 \cdot f_p \cdot X_1^{n-1} - p_1 \cdot f_p \cdot X_1^n - \left(\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_1^n$$

$$\frac{dX_2^n}{dt} = 2p_2 \cdot f_p \cdot X_2^{n-1} - p_2 \cdot f_p \cdot X_2^n + \left(\alpha_1 + \alpha_{12} \cdot f_{x1x2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_1^n - \left(\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_2^n$$

$$\frac{dZ_1^n}{dt} = \left(\alpha_2 + \alpha_{22} \cdot f_{x2z1} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot X_2^n - \left(\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot Z_1^n$$

$$\frac{dZ_2^n}{dt} = \left(\beta_1 + \beta_{12} \cdot f_{z1z2} \cdot \sum_{j=0}^{N} Z_2^j\right) \cdot Z_1^n - \delta \cdot Z_2^n.$$

Assimilation of the data on BrdU labeling & validation of the model by CFSE dilution data



The general parametric structure of the mathematical model of feedback regulation

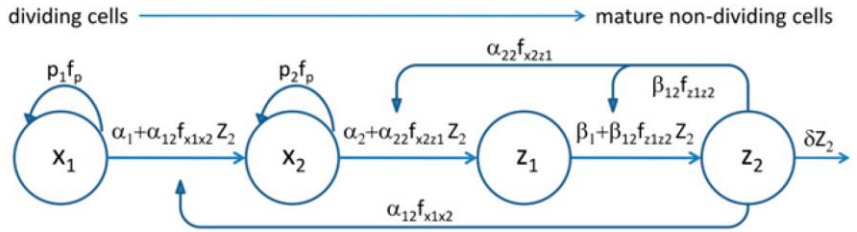


Table S1. Model parameters, their best-fit estimates, and 95% confidence intervals

Parameter	Notation (units)	Best-fit estimate	95% confidence interval
Net proliferation rate of CD4 T cells at initial stage X_1	p_1 (d^{-1})	0.81	[0.80*, 1.12]
Net proliferation rate of CD4 T cells at transit stage X_2	p_2 (d^{-1})	2.0*	[1.0, 2.0*]
Death rate of proliferating CD4 T cells	d (d^{-1})	0.95	[0.45, 1.0]
Maximal effect parameter of cell crowding on proliferation rate	γ	5.0×10^{-4}	$[0, \infty)$
Threshold cell number for the onset of the effect of cell crowding on proliferation rate	c (cell)	2.8×10^{5}	$(0, \infty)$
Constitutive maturation rate of proliferating cells	α_1 (d^{-1})	0.0038	[0, 0.23]
Rate constant of the feedback-regulated maturation of proliferating cells	α_{12} ($d^{-1}\cdot cell^{-1}$)	0.06	$[10^{-4}, >10^{10}]$
Constitutive differentiation rate of proliferating cells into nonproliferating stage	α_2 (d^{-1})	0.001*	$[10^{-3}, >1.0]$*
Rate constant of the feedback-regulated differentiation of proliferating cells into nonproliferating cells	α_{22} ($d^{-1}\cdot cell^{-1}$)	0.023	$[3 \times 10^{-4}, >10^{10}]$
Constitutive terminal differentiation rate of nonproliferating cells	β_1 (d^{-1})	0.5	$[10^{-3}, >1.0]$*
Rate constant of the feedback-regulated terminal differentiation of nonproliferating cells	β_{12} ($d^{-1}\cdot cell^{-1}$)	9.0×10^{1}	$[0, \infty)$
Threshold nonproliferating cell number for the onset of the saturation in the maturation rate of proliferating cells	θ_{x1} (cell)	2.4×10^{1}	$[<10^{-10}, \infty)$
Threshold nonproliferating cell number for the onset of the saturation in the differentiation rate of proliferating cells	θ_{x2} (cell)	3.5×10^{2}	$[<10^{-10}, \infty)$
Threshold nonproliferating cell number for the onset of the saturation in the maturation rate of nonproliferating cells	θ_z (cell)	8.9×10^{-2}	$(0, \infty)$
Death/migration rate of terminally differentiated cells	δ (d^{-1})	0.59	[0.21, 1.25]

*Lower or upper bound constrained estimation.

The parsimonious version of the general mathematical model:
its complexity is optimal with respect to the information content of the data set

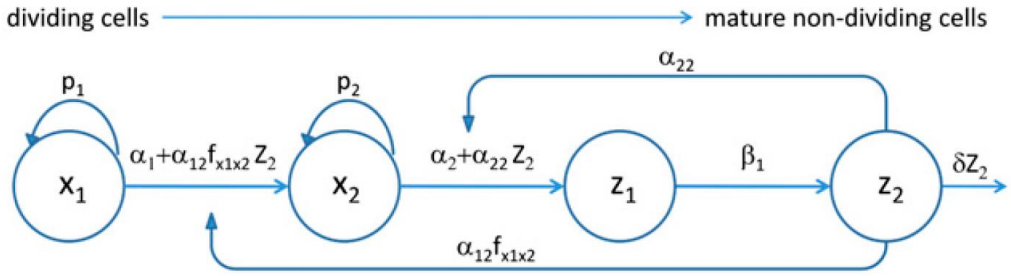


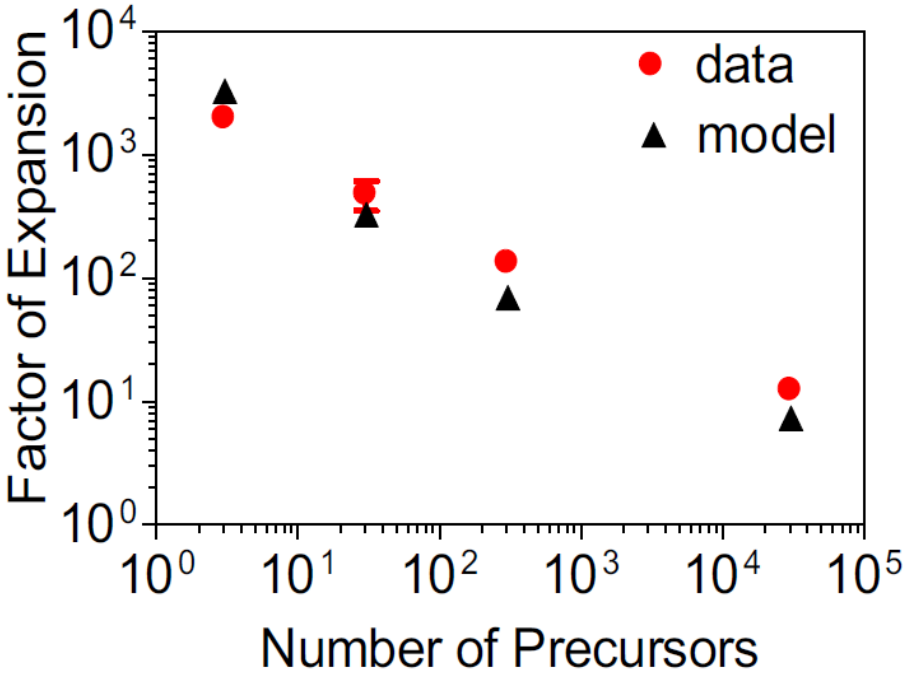
Table S2. Parameters of the parsimonious model with their best-fit estimates and 95% confidence intervals

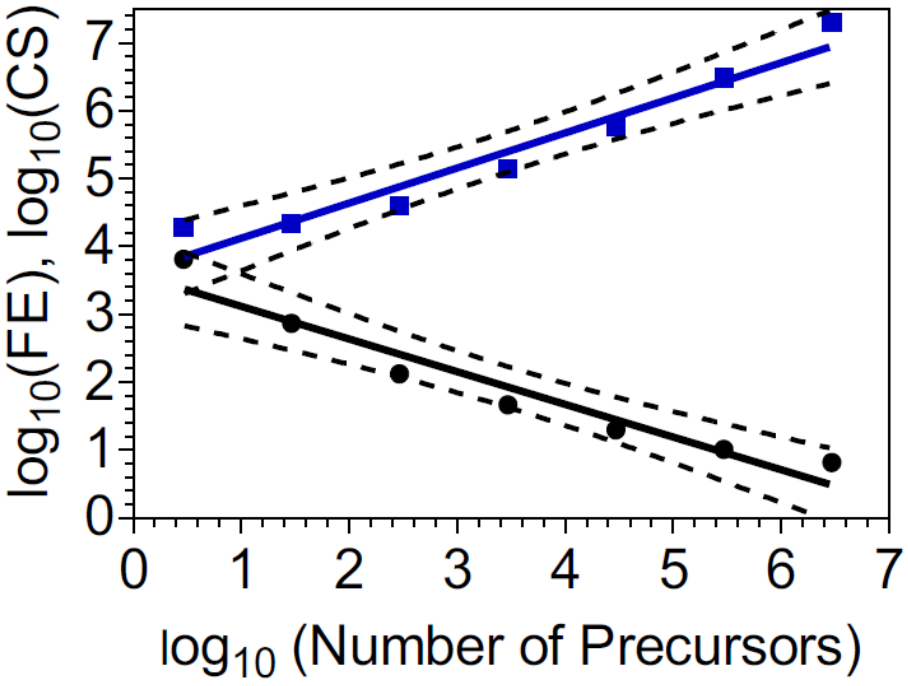
Parameter	Notation (units)	Best-fit estimate	95% confidence interval
Net proliferation rate of CD4 T cells at initial stage X_1	p_1 (d^{-1})	0.80*	[0.80*, 1.02]
Net proliferation rate of CD4 T cells at transit stage X_2	p_2 (d^{-1})	2.0*	[1.17, 2.0*]
Death rate of proliferating CD4 T cells	d (d^{-1})	0.99	[0.41, 1.0*]
Constitutive maturation rate of proliferating cells	α_1 (d^{-1})	0.0059	[0.0018, 0.104]
Rate constant of the feedback-regulated maturation of proliferating cells	α_{12} ($d^{-1}\cdot cell^{-1}$)	0.012	[9×10^{-4}, 90]
Constitutive differentiation rate of proliferating cells into nonproliferating stage	α_2 (d^{-1})	0.001*	[10^{-3}*, 0.35]
Rate constant of the feedback-regulated differentiation of proliferating cells into nonproliferating cells	α_{22} ($d^{-1}\cdot cell^{-1}$)	0.045	[4×10^{-3}, 0.25]
Constitutive terminal differentiation rate of nonproliferating cells	β_1 (d^{-1})	0.52	[0.15, 1.0*]
Threshold nonproliferating cell number for the onset of the saturation in the maturation rate of proliferating cells	θ_{x1} (cell)	842	[0.05, 5.2×10^3]
Death/immigration rate of terminally differentiated cells	δ (d^{-1})	3.45	[0.51, 17.2]

*Lower or upper bound constrained estimation.

Quantitative relationship between the *FE* & the *PN*

D $\log_{10}(\text{FactorExpansion}) = -0.54 \cdot \log_{10}(\text{PrecursorNumber}) + 3.4$





Day 7 $FE = (PN)^{-0.54} \times 2512$ and $CS = (PN)^{0.46} \times 2512$

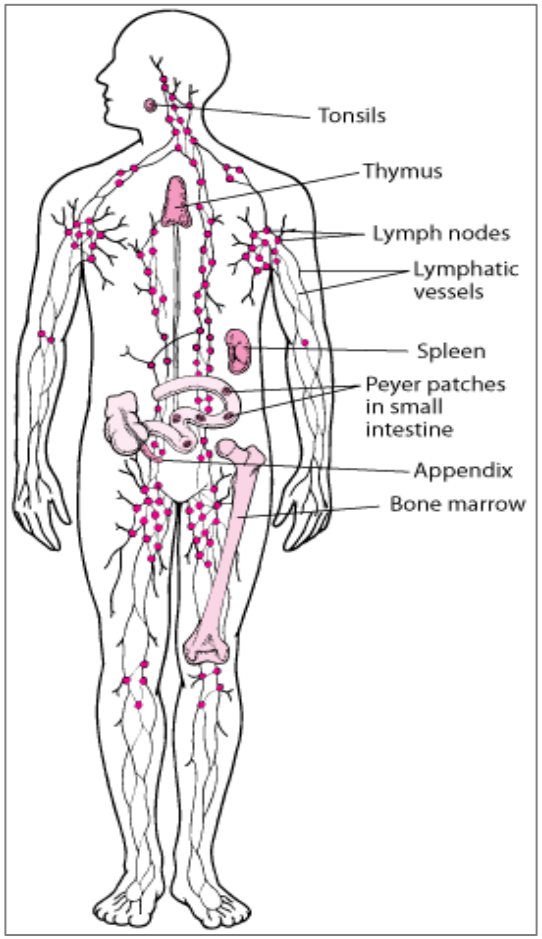
max $FE = (PN)^{-0.48} \times 3981$ $CS = (PN)^{0.52} \times 3981$

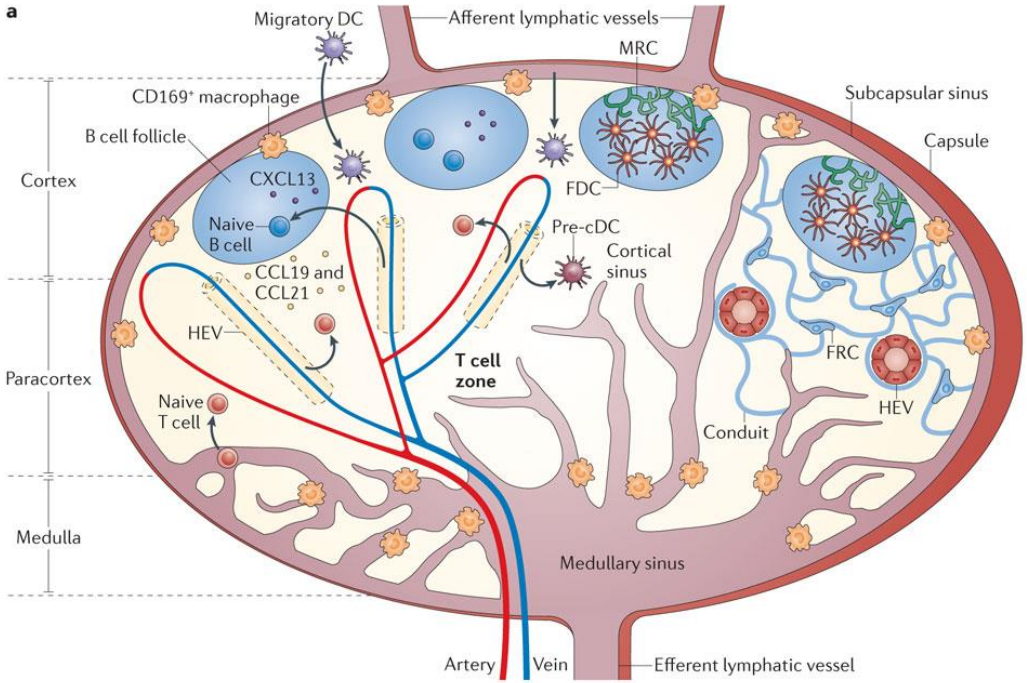
Conclusions

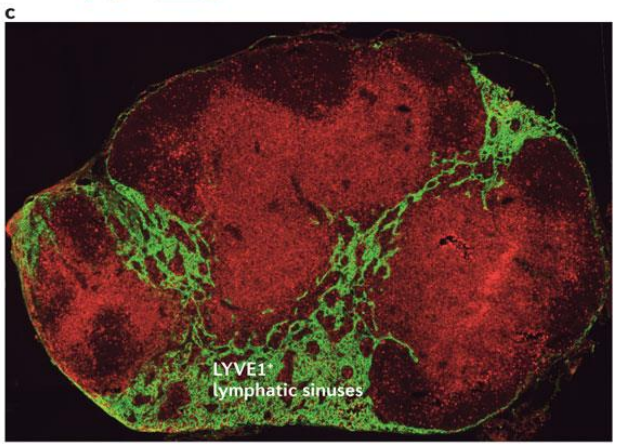
- There is a log-linear relation between $CD4^+$ T-cell precursor number (PN) and factor of expansion (FE), with a slope of ~ -0.5 over a physiological range of 3-30,000 precursors per mouse

- The '***feedback-regulated balance of growth and differentiation***' is a ***valid concept*** which can explain the kinetics of $CD4^+$ T-cell responses to antigenic stimulation

Lymph node center of immune responses



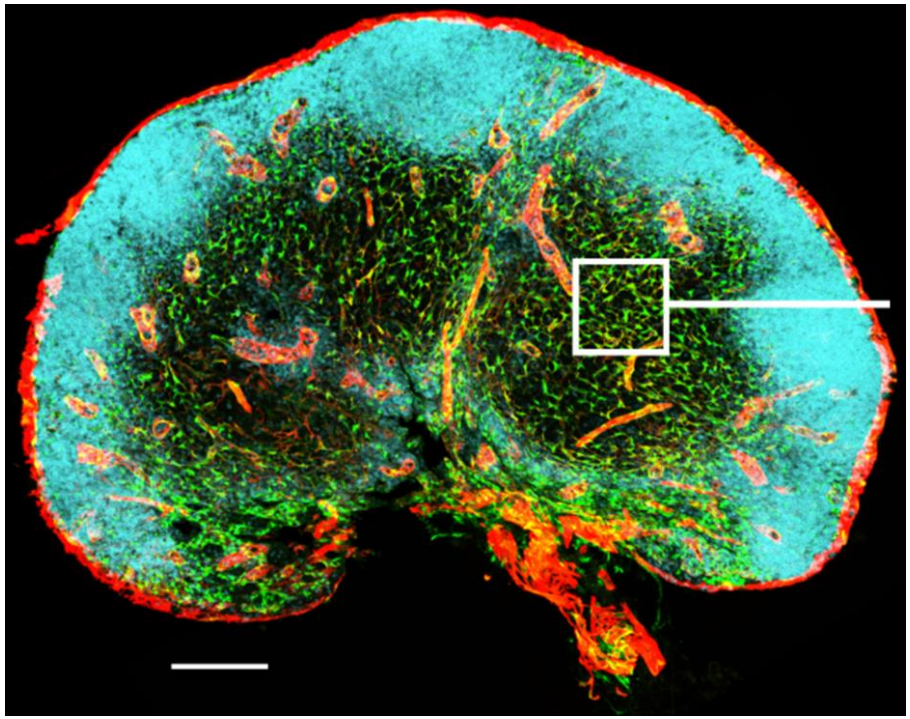




Nature Reviews | Immunology

Nat Rev Immunol. 2012 ;12(11):762-73.
HEVs, lymphatics and homeostatic immune cell trafficking in lymph nodes.
Girard JP[1], Moussion C, Förster R.

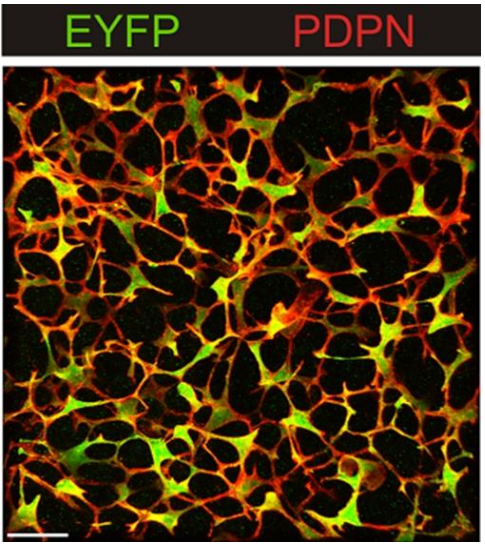
Imaging and visualization of LN structures

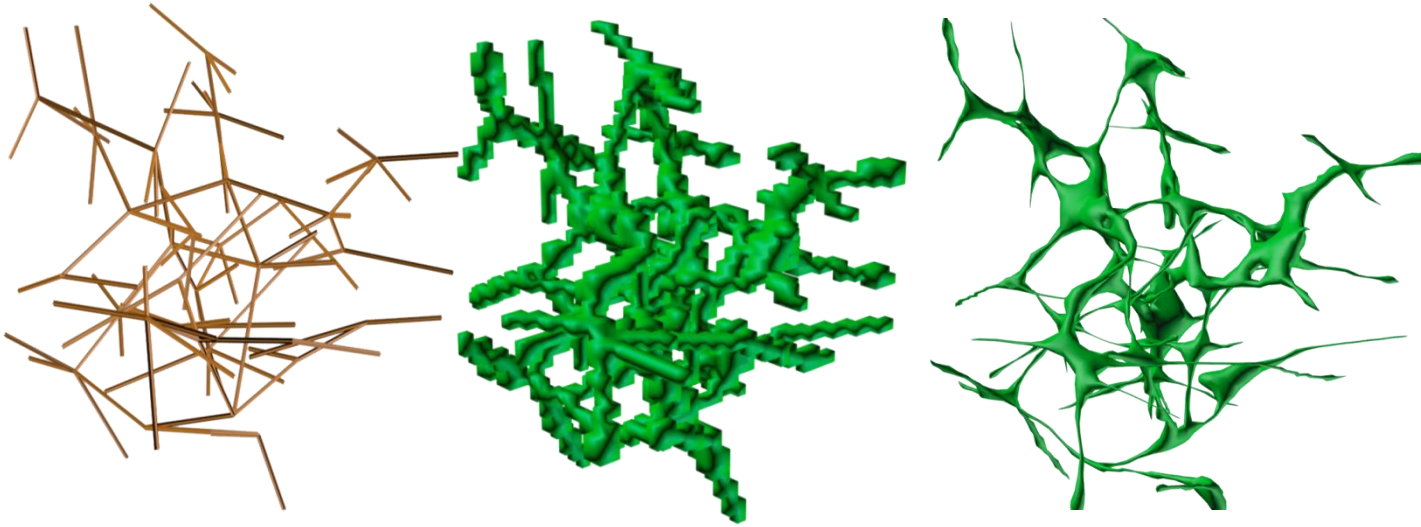


Lymph node (LN) architecture with major structural units: subcapsular sinus (red), efferent lymphatic vessel (red), B cell follicles (cyan) and the FRC network (green). White rectangle indicates representative T cell zone. Scale bar represents 200 µm

Data from: Burkhard Ludeiwg, Mario Novkovic, Lucas Onder
Institute of Immunobiology, Kantonsspital St. Gallen, St. Gallen

Topology - geometry - solid model





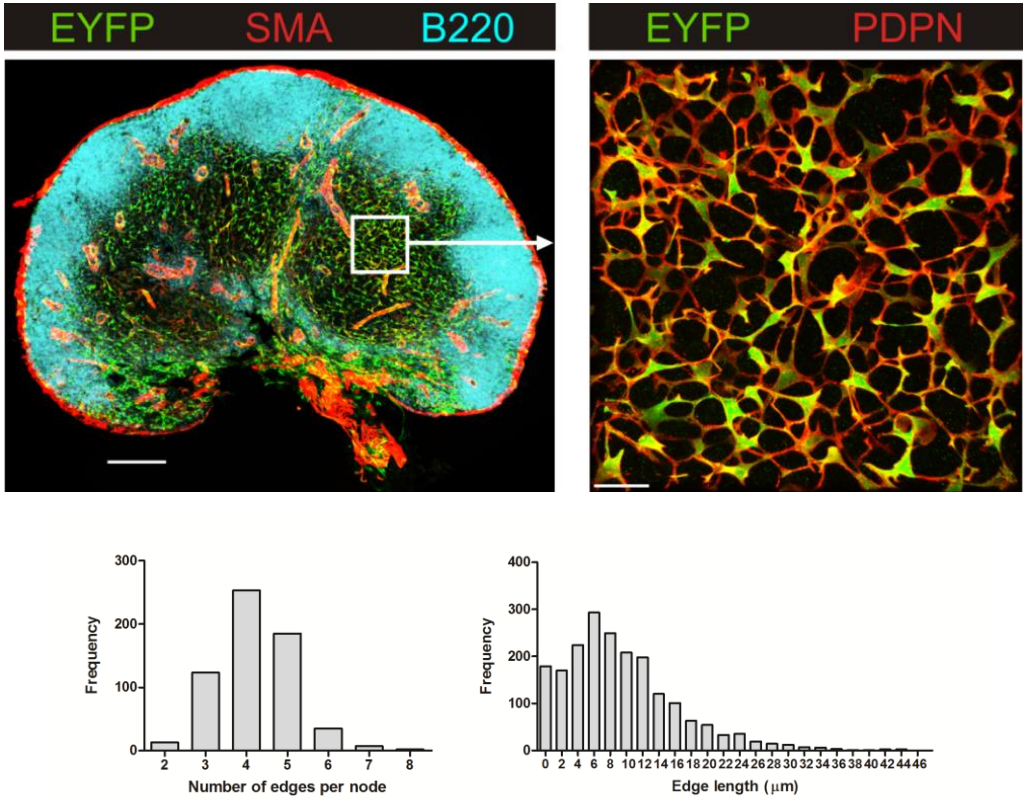
Real Object

Mathematical model

Voxel-based generation of the FRC network. The network graph model; initial local structure; smoothed solid model of the local structure.

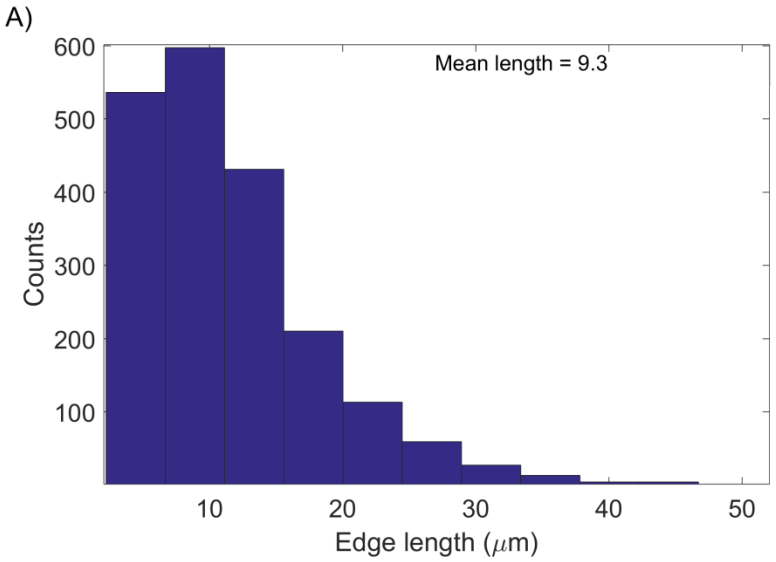
3D anatomically correct constructive solid geometry model of the lymph node

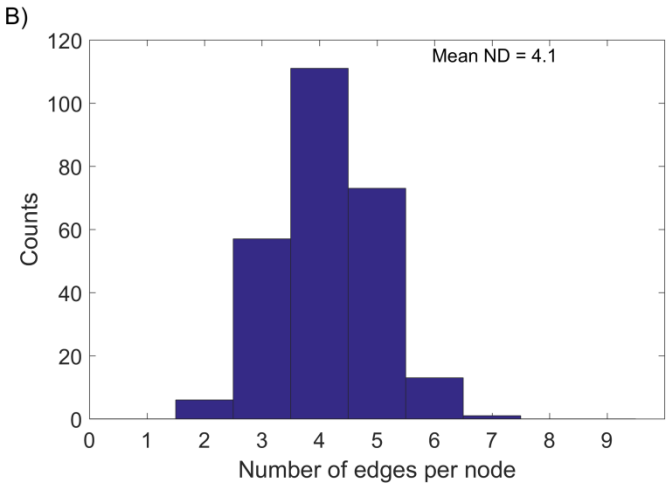
Experimental data1

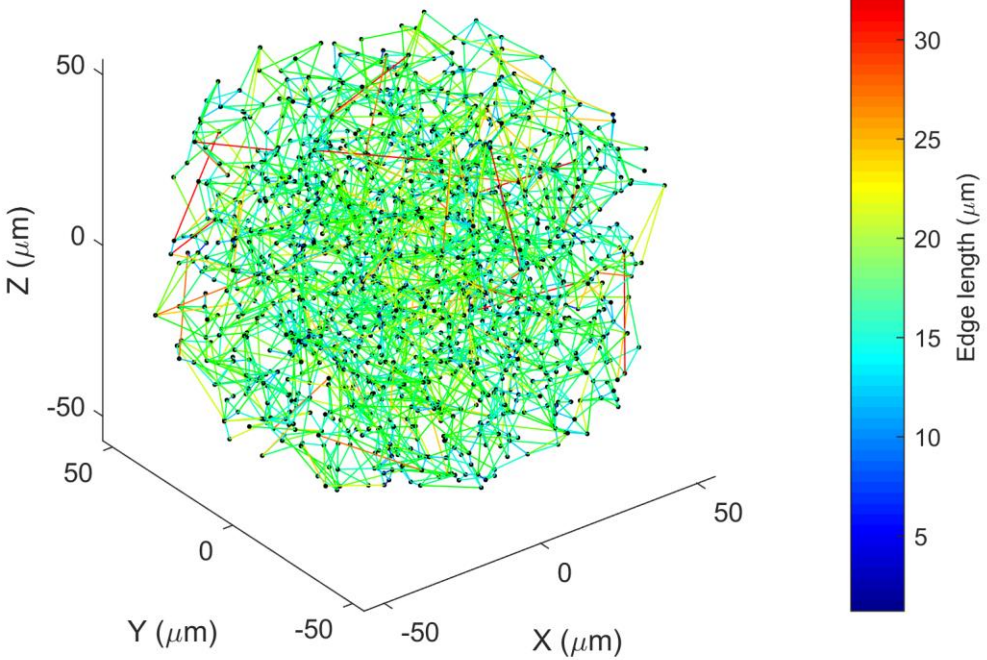


FRC network topology parameters: the edges per node- and the edge length for the T cell zone FRC network. Data obtained from *n* = 7 mice from two independent experiments

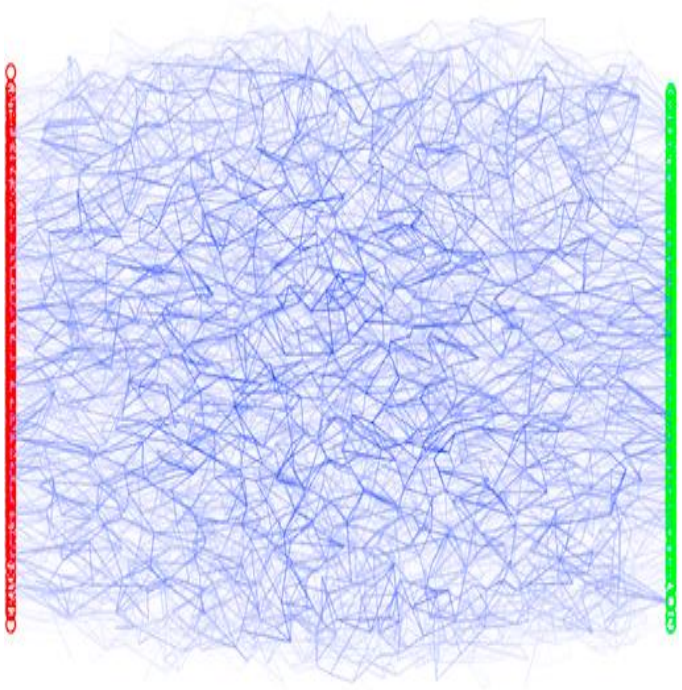
Modeling FRC network topology

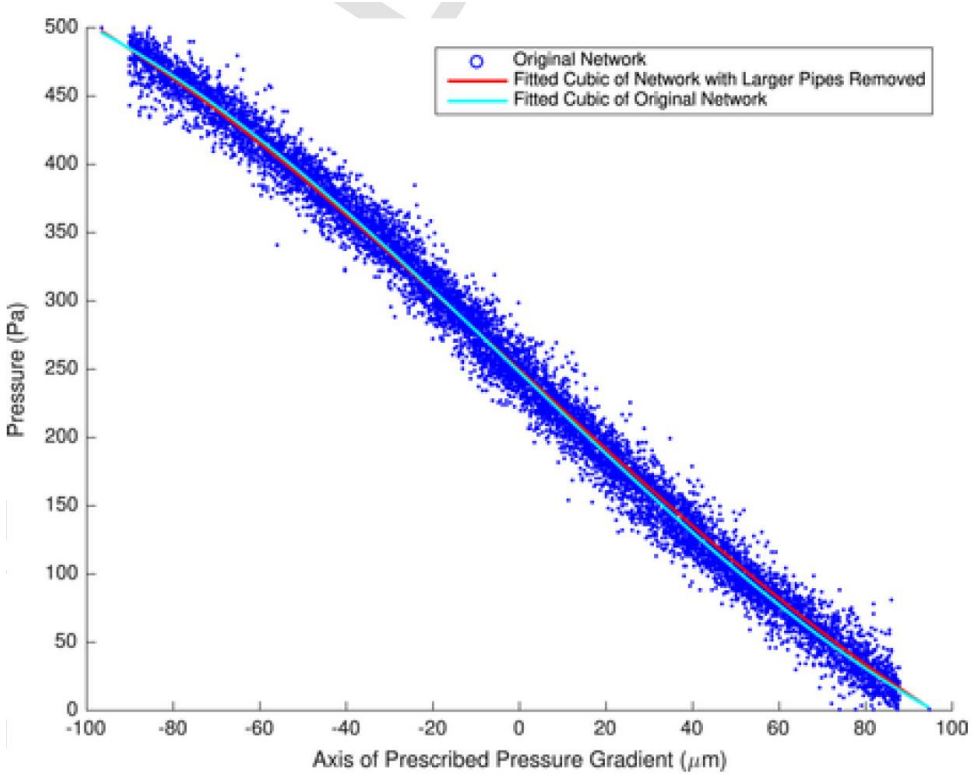




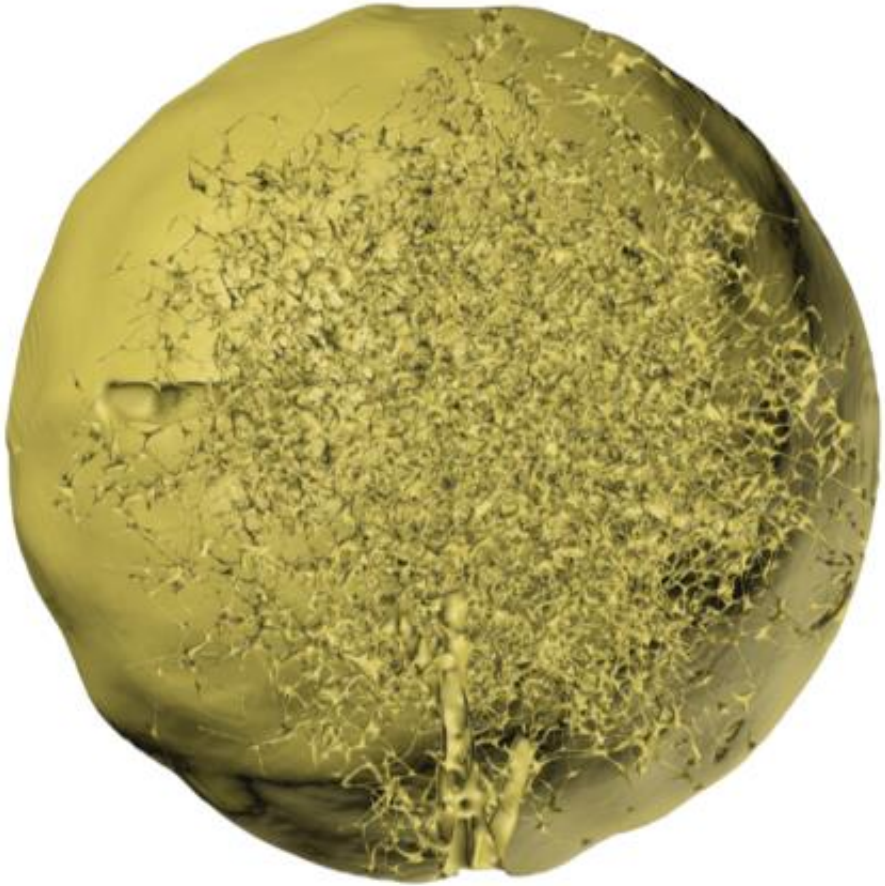


Computation of the effective permeability of the FRC network

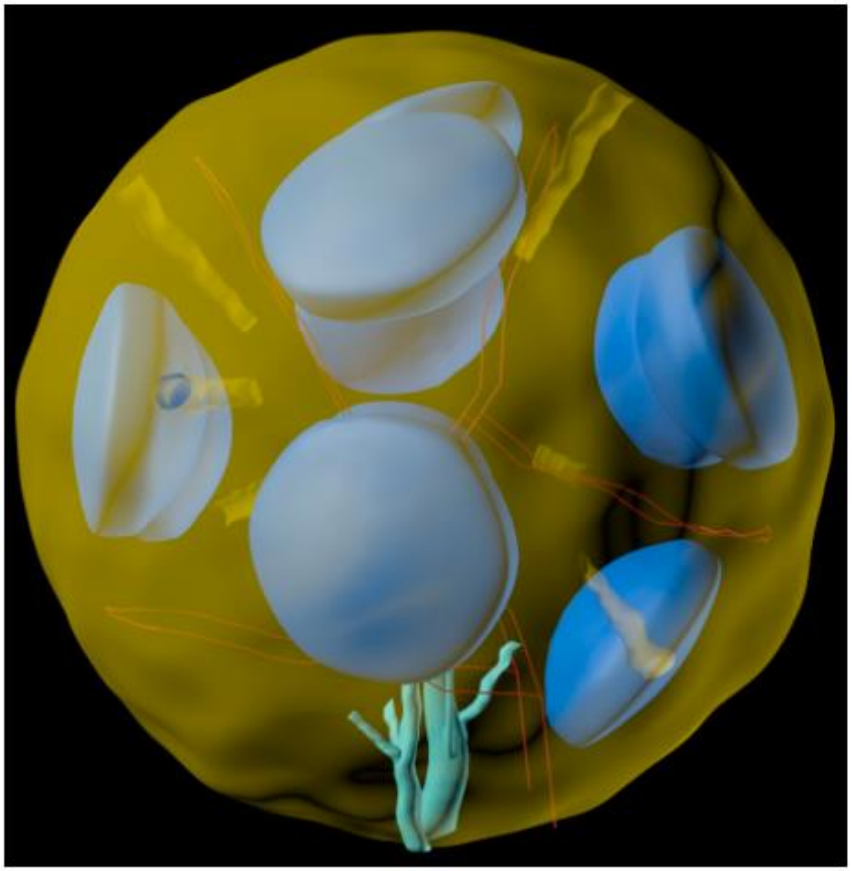




3D geometric model of the LN

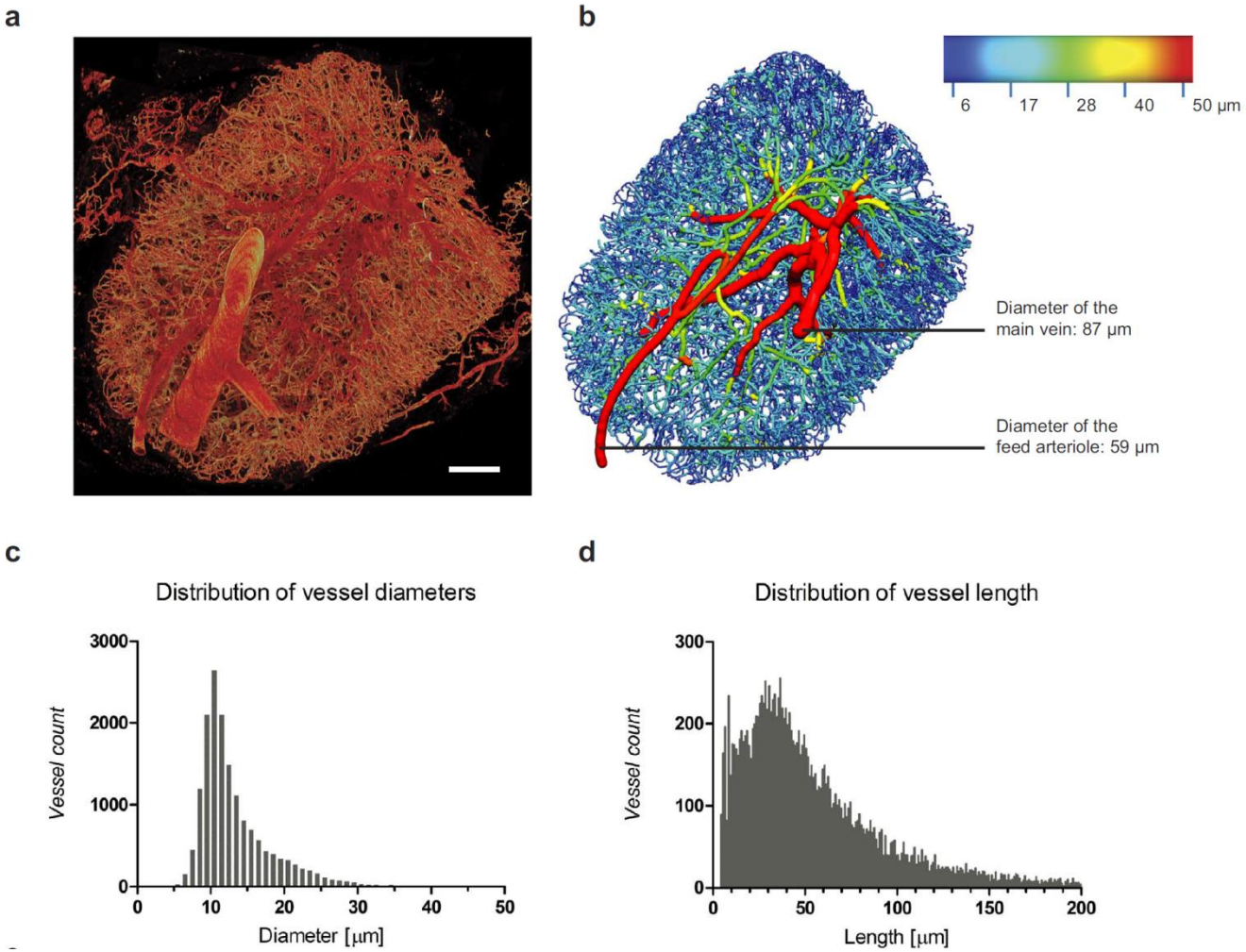


The FRC network inside



B cell follicles, trabecular sinuses medulla

Blood microvascular network of LN



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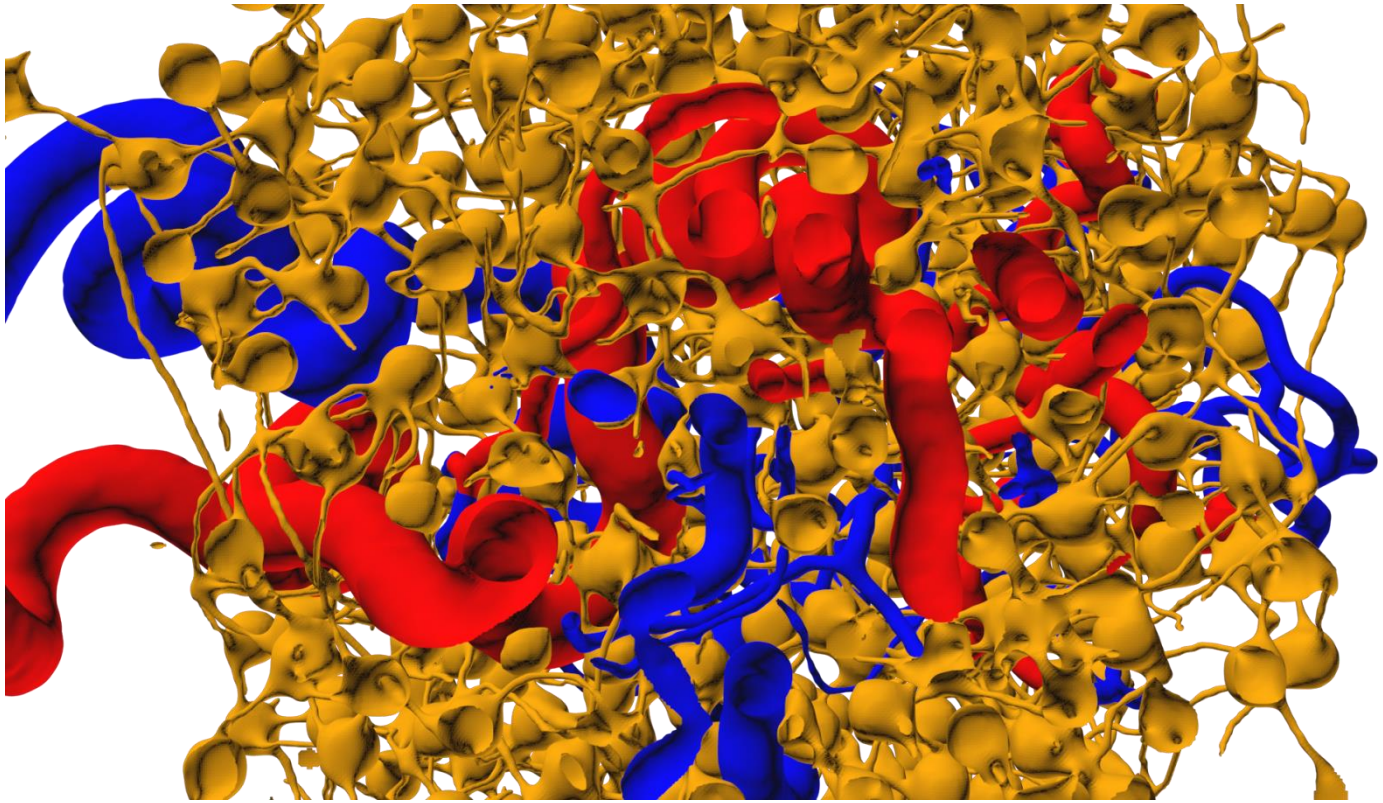
Organ-wide 3D-imaging and topological analysis of the continuous microvascular network in a murine lymph node

Inken D. Kelch[1,2], Gib Bogle[1,3], Gregory B. Sands[3], Anthony R. J. Phillips[1,2,4], Ian J. LeGrice[3,5] & P. Rod Dunbar[1,2]

40 μm section of the integrated vascular networks



Research directions

- Modelling the structure-function relationships for lymphoid organs
- Anatomically based mathematical models integrating the regulatory processes across multiple scales (multi-physics)
- Translational studies on data-driven application of models for predicting the immune function in virus infections (HIV, LCMV)

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CRDF U.S. Civilian Research & Development Foundation

RSF Russian Science Foundation

RFBR Russian Foundation for Basic Research

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