Modelling the structure and functioning of the reticular network in lymph node

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Our team

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- Dmitry Grebennikov (MIPT), Ruffina Tretyakova (MSU),
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- Dmitry Grebennikov, Raoul van Loon, Mario Novkovich, Lucas Onder, Rostislav Savinkov, Igor Sazonov, Rufina Tretyakova, Daniel J. Watson, Gennady Bocharov. **Critical issues in modelling lymph node physiology** // Computation, 2016 (Submitted)
- V.A. Chereshnev, D.S. Grebennikov, and G.A. Bocharov, '**Mechanisms of fibrosis progression during chronic virus infections**', Clinical Physiopathology, 2016.

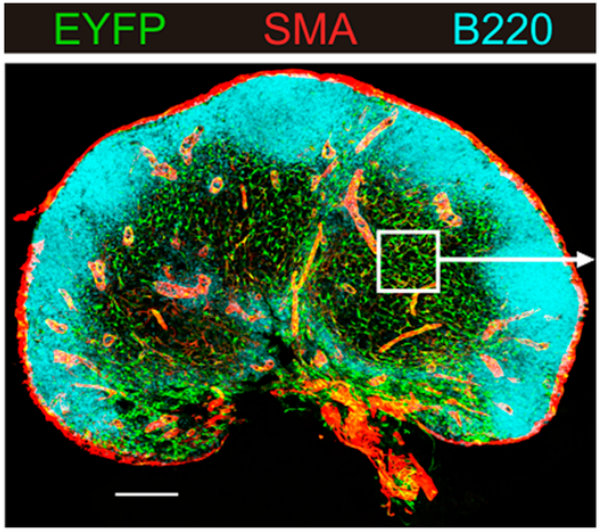
2 parts of the talk

Distinct prospects on reticular network of LN:

- The structure (geometrical voxel model)
- The functioning (ODE model of stromal homeostasis and immunopathology of lymphoid tissue *in chronic HIV infection*)

What the reticular network stands for

- Reticular network = Network of FRCs (fibroblastic reticular cells)
- FRCs enwrap the conduit system



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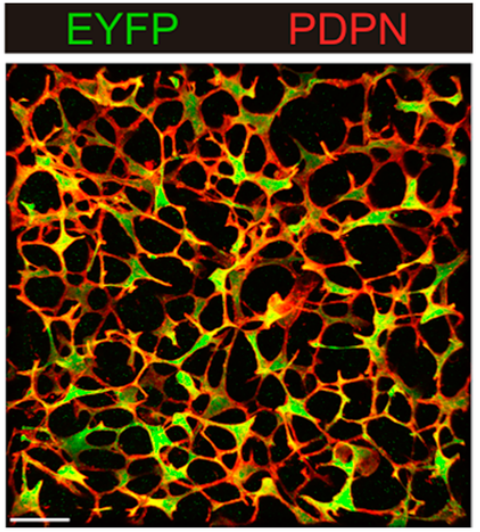

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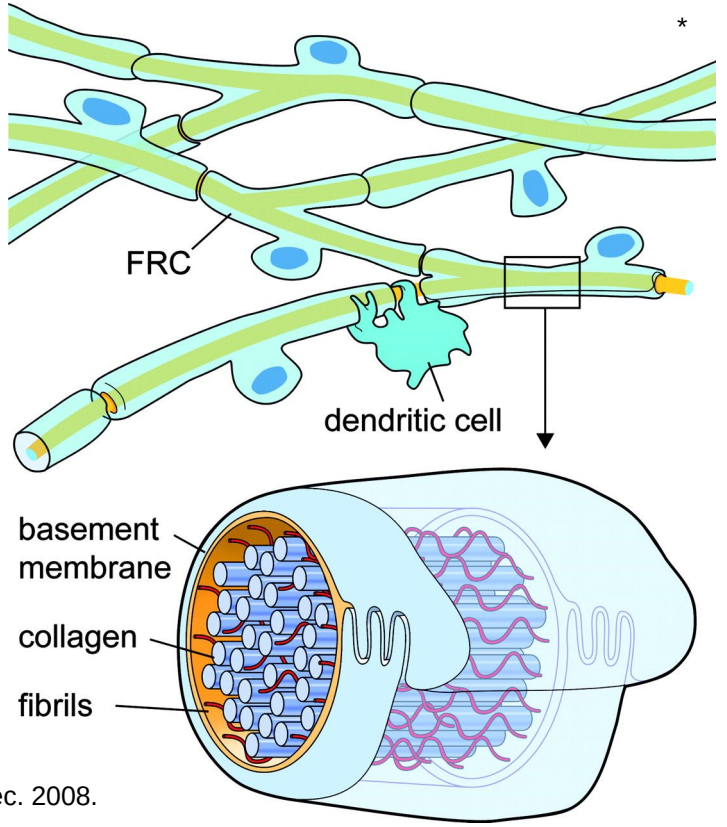


* R. Roozendaal et al. '**The conduit system of the lymph node**', Int. Immunol., vol. 20, no. 12, pp. 1483–1487, Dec. 2008.

Reasons why for modelling

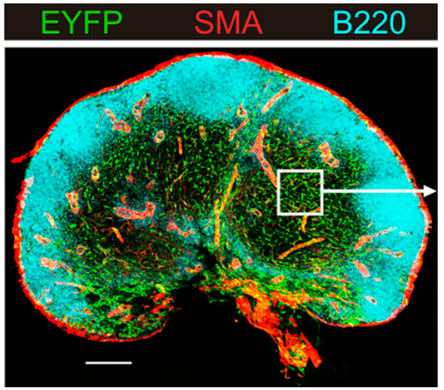
Geometrical structure:

- FRCn topology dictates lymphocytes locomotion → effectiveness of antigen-presentation
- Having the object to incorporate in multiscale agent-based models, models of lymph flow in conduits
- FRCn scaffold expands (up to x10) during inflammation, contracts after infection
- FRCn is a target of virus infections and becomes partially destroyed → analyze threshold and robustness

Immunological functioning:

- FRCs are essential for maintaining homeostasis of immunocompetent cells in LN
- Disruption of homeostasis during HIV infection leads to LT damage: fibrosis and $CD4^+$ TCs depletion (AIDS), even for some ART-treated patients
- Determine robustness of FRCn in regard to immune homeostasis: cytokines (survival & growth factors) signaling and collagenation thresholds

FRCn geometry modelling background



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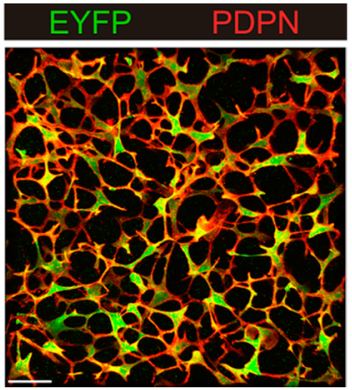

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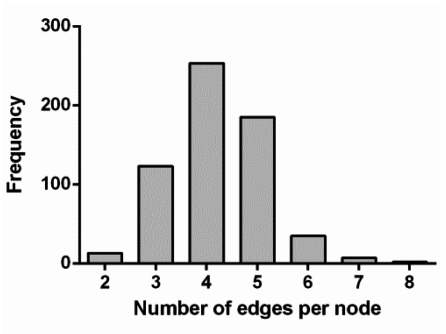

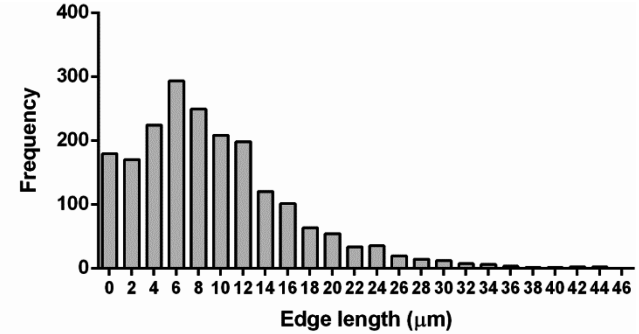

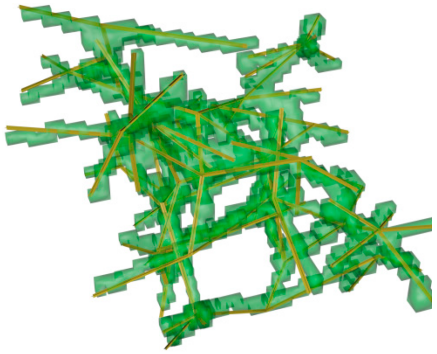

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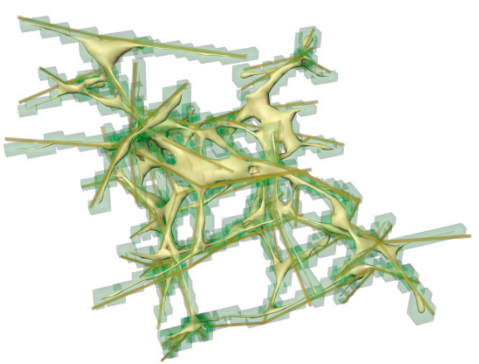

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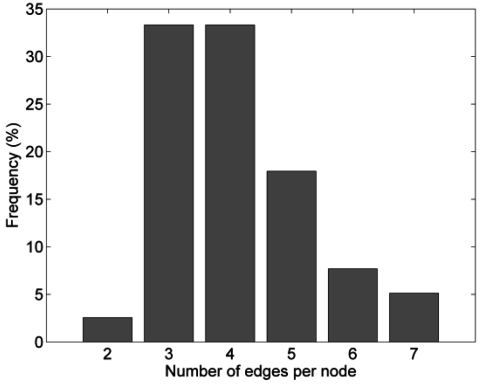

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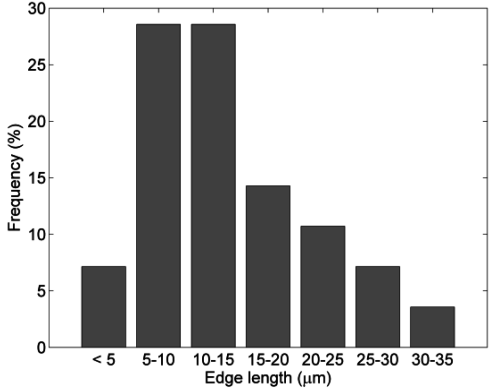
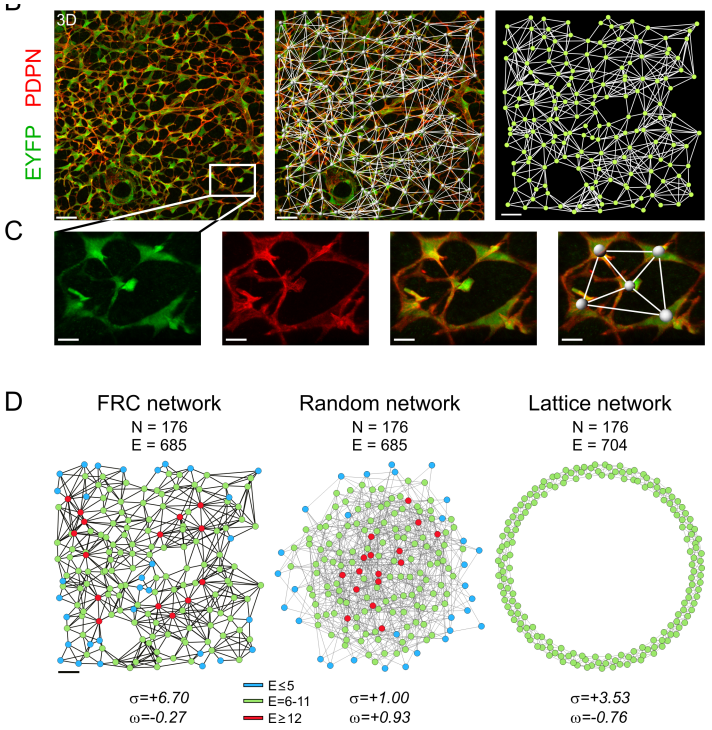


(b)

A. Kislitsyn, R. Savinkov, M. Novkovic, L. Onder, and G. Bocharov, '**Computational approach to 3D modeling of the lymph node geometry**', Computation, vol. 3, no. 2, pp. 222–234, 2015

What determines the FRCn topology?



FRCn organizes in ‘Small-World’ topology:

$$C_i = \frac{|N(i) \cap N(N(i))|}{k(i)(k(i)-1)}$$

$$\bar{L} = \frac{1}{n(n-1)} \sum_{i}^{n} \sum_{j \neq i}^{n} L(i,j)$$

$$\hat{C} = \bar{C}/\bar{C}_{rand}, \hat{C} = \bar{L}/\bar{L}_{rand}$$

$$\sigma = \bar{C}/\bar{L}, \quad \sigma_{exp} \approx 6.1$$

M. Novkovic et al., ‘**Topological Small-World Organization of the Fibroblastic Reticular Cell Network Determines Lymph Node Functionality**’, PLOS Biol, vol. 14, no. 7, p. e1002515, Jul. 2016.

Aim of my contribution (algorithm for FRCn generation from given conduit system topology)

- Limitations of previous network generation algorithms
- Propose algorithm based on modified Cellular Potts Model
- Pros: simplicity, explicit control of FRCn volume, FRC body diameter, direct incorporation in further developing CPM-based multiscale models

Modifications of Cellular Potts Model (coordinate-based intrinsic motility)

$$E = E_{adhesion} + E_{volume} = 0 + \sum_{\sigma} \lambda(\sigma)\left(V(\sigma) - V_{target}(\sigma)\right)^2$$

$$p(\sigma(v_{source}) \rightarrow \sigma(v_{target})) = \min\left\{1,\ \exp\left(-\frac{\Delta E}{T}\right)\right\}$$

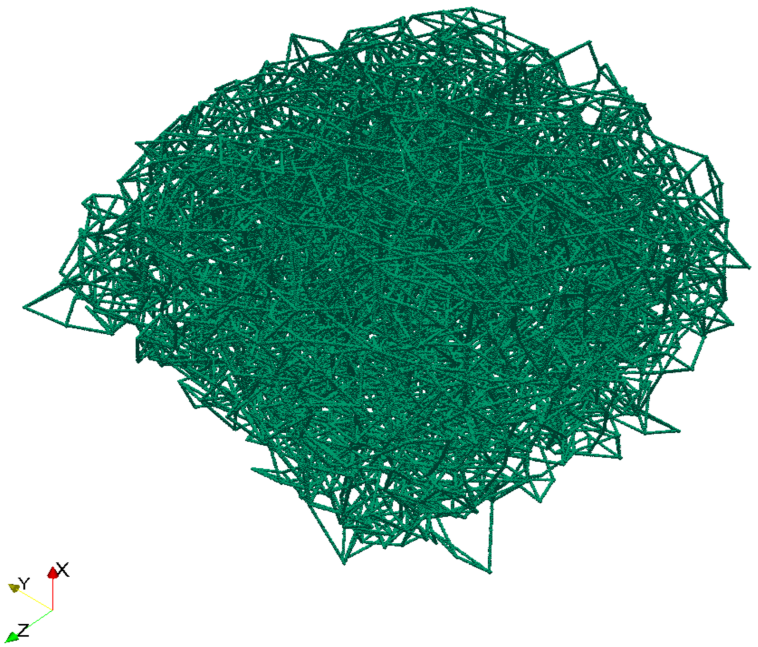
$$p(\sigma(v_{source}) \rightarrow \sigma(v_{target})) = \tanh(T_m)^{*} \cdot \min\left\{1,\ \exp\left(-\frac{\Delta E}{T_m}\right)\right\}$$

$$T(v(\sigma)) = T_{max} \cdot \exp\left(-\|v(\sigma) - v_c(\sigma)\|^2 / s^2\right)$$

Result: elastic cells bodies, ‘frozen’ protrusions (forming FRC-FRC junctions)

* M. Scianna and L. Preziosi, ‘**Multiscale developments of the cellular Potts model**’, Multiscale Modeling & Simulation, vol. 10, no. 2, pp. 342–382, 2012.

Results: generation of FRCn from conduit system



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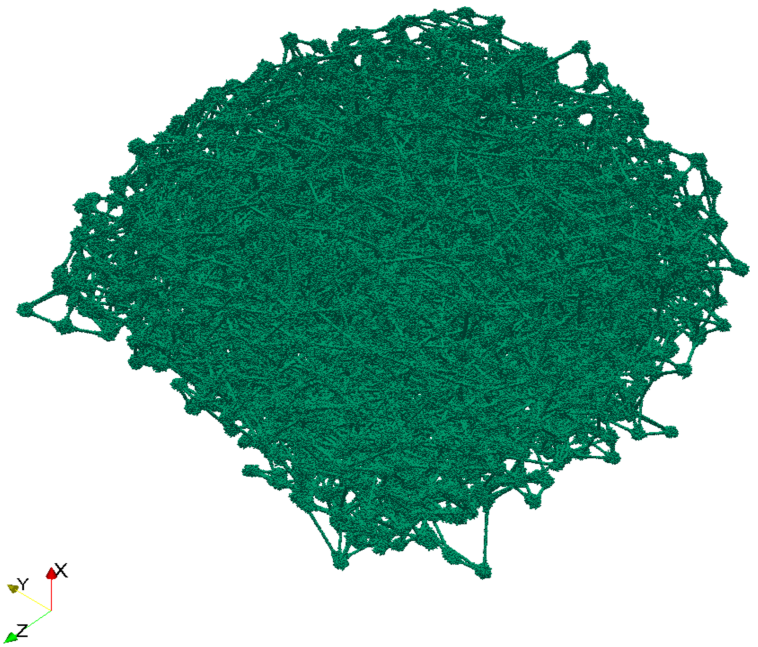


(b)

$$177.0\ \mu m \times 197.4\ \mu m \times 201.0\ \mu m$$

20 MCS burn-in (<10min), 3373 FRCs, s = 1.8 um, FRCn volume fraction = 4%, 0.3 um resolution

Background on FRCs immunocompetence research

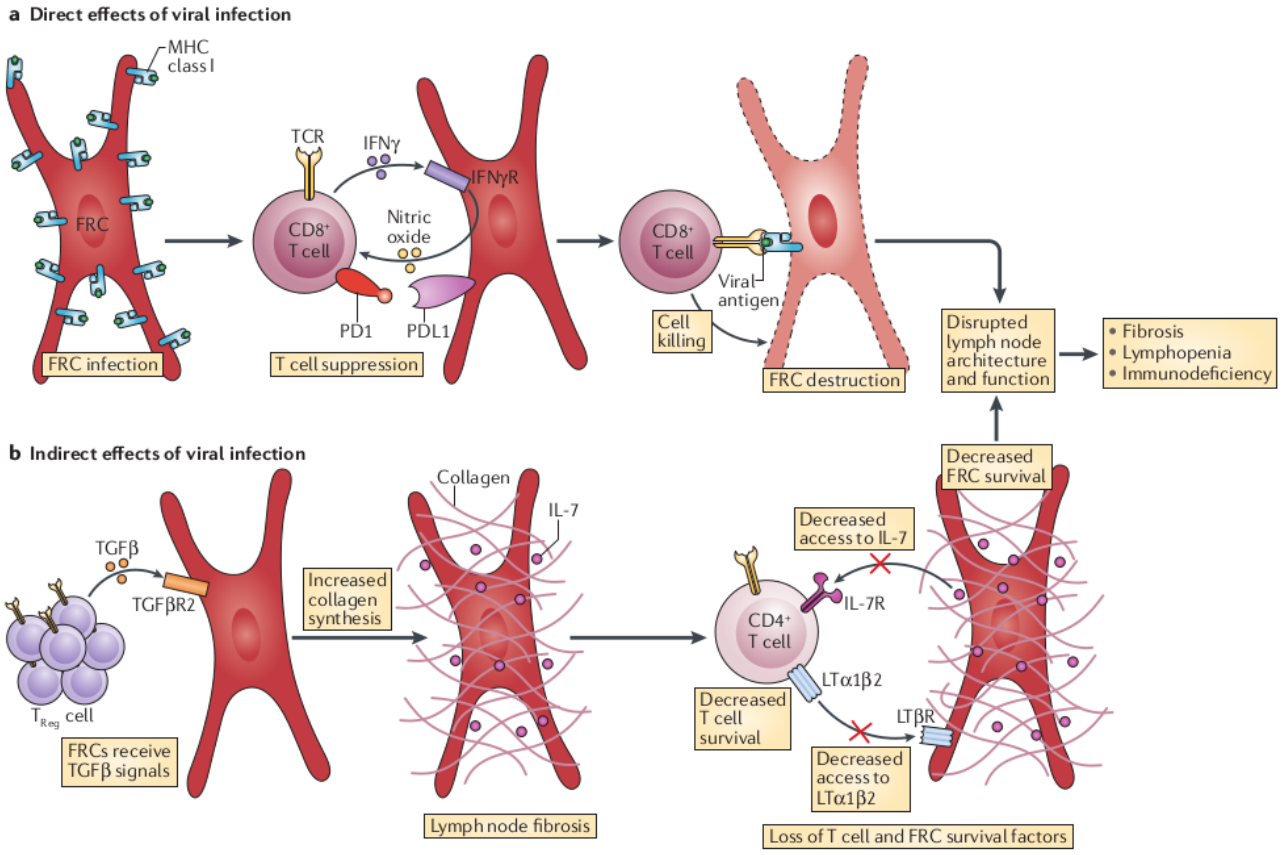
- Introduction of ‘vicious cycle’ concept, explaining LT damage (fibrosis and depletion) during HIV infection:

  M. Zeng, A. T. Haase, and T. W. Schacker, ‘**Lymphoid tissue structure and HIV-1 infection: life or death for T cells**’, Trends in immunology, vol. 33, no. 6, pp. 306–314, 2012.

- Developing the math model of stromal homeostasis (Master thesis)
- Another math model published:

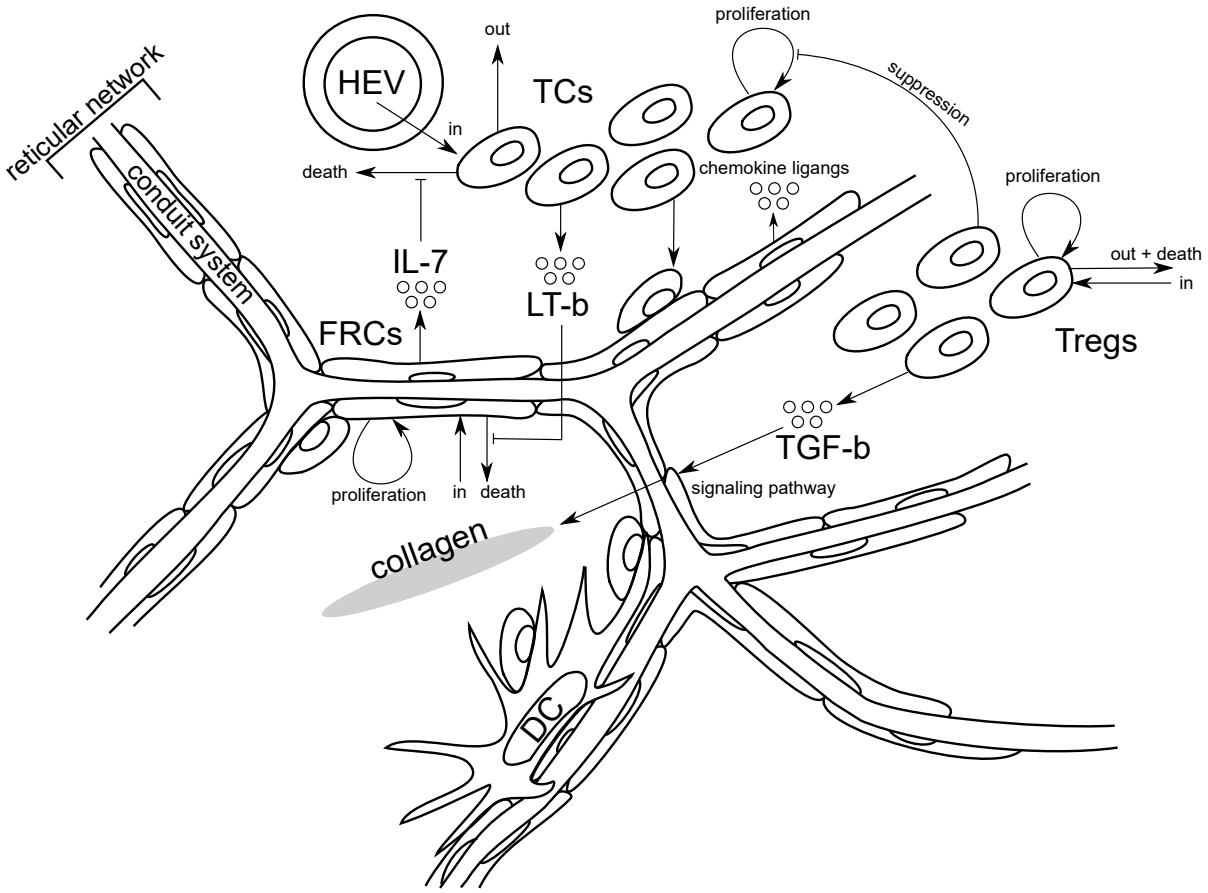
  G. M. Donovan and G. Lythe, ‘**T cell and reticular network co-dependence in HIV infection**’, Journal of theoretical biology, vol. 395, pp. 211–220, 2016.

Negative feedback loop of LN tissue disruption



A. L. Fletcher, S. E. Acton, and K. Knoblich, '**Lymph node fibroblastic reticular cells in health and disease**', Nature Reviews Immunology, vol. 15, no. 6, pp. 350–361, 2015.

Illustration of biological processes



Cellular dynamics

FRCs:
$$\frac{dF}{dt} = \alpha_F F - \gamma_F V F - \delta_F \left(1 + \frac{1}{c_{LF} + L\left(1 - \frac{C}{C_M}\right)}\right) F$$

Tregs:
$$\frac{dR}{dt} = (R_S + R_{Cin} - R_{Cout} R)\left(1 - \frac{C}{C_M}\right) + \alpha_R R -$$
$$- \gamma_R V R - \delta_R \left(1 + \frac{1}{c_{IR} + I\left(1 - \frac{C}{C_M}\right)}\right) R$$

T Cells:
$$\frac{dT}{dt} = (T_S + T_{Cin} - T_{Cout} T)\left(1 - \frac{C}{C_M}\right) + \alpha_T T \left(1 - \frac{R}{R_M}\right) -$$
$$- \gamma_T V T - \delta_T \left(1 + \frac{1}{c_{IT} + I\left(1 - \frac{C}{C_M}\right)}\right) T$$

Cytokines dynamics

TGFβ: $$\frac{dG}{dt} = \beta_G R - \delta_G G - \gamma_G F G \left(1 - \frac{C}{C_M}\right)$$

IL-7: $$\frac{dI}{dt} = \beta_I F - \delta_I I - \gamma_I (T + R) I \left(1 - \frac{C}{C_M}\right)$$

LTβ: $$\frac{dL}{dt} = \beta_L \varepsilon T - \delta_L L - \gamma_L F L \left(1 - \frac{C}{C_M}\right)$$

Dynamics of collagen

Collagen: $$\frac{dC}{dt} = \beta_C F(t) G(t-\tau) - \delta_C C$$

Current developments

- Improving functional forms (IL-7 signaling, IL7R downregulation)
- Parametrizing Tregs as fraction of TCs
- Adding blood TCs to fit model to clinical data of ART-naive patients treatment
- Performing sensitivity analysis
- Identifying reasons for different disease outcome with/without ART treatment (LTNP vs pregressors, responders vs nonresponders)

Thank you for your attention!

Conclusions:

- The new algorithm of generating FRCn voxel approximation from given topology is proposed (based on CPM modification)
- The ODE-based model of FRC functioning in HIV infection is developing which is targeted to reproduce the LT fibrosis progression and CD4+ T cells depletion