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Article

A mathematical framework for understanding how lymph node architecture scales with host body size to produce an efficient immune response

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Abstract
The immune system can detect and respond against pathogens in time that does not vary with the size of the host animal. We suggest that this is due to the architecture of lymph nodes. Lymph nodes are anatomical structures that facilitate the otherwise serendipitous encounter of immune system cells with pathogens. We develop two complementary mathematical approaches to derive the optimal distribution of lymph nodes that enable a rapid immune response. Our work gives insights into the optimal design and architecture of the immune system and provides valuable inspiration for designing efficient computing systems.

Keywords immuno-computing;scale-invariant search and response; scaling in the immune system; lymph node scaling.

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1 Introduction
The immune system can detect and respond against pathogens in time that does not vary with the size of the host animal. Larger animals like elephants can detect and respond to pathogens in the same time as small animals like mice.

We suggest that this is due to the architecture of lymph nodes. Lymph nodes are anatomical structures that facilitate the otherwise serendipitous encounter of immune system cells with pathogens.

The area of tissue that drains into a lymph node is called the draining region. Immune system cells called dendritic cells sample the tissue in the draining region for pathogens. Upon encountering pathogens, dendritic cells migrate to the nearest lymph node and signal to other immune system cells called B cells to secrete chemicals called antibodies.

An animal 10,000 times larger than a mouse must generate 10,000 times more absolute quantities of antibody to achieve the same concentration of antibody in the blood (where blood volume is $\propto M$ (host body mass); Peters, 1983). A fixed antibody concentration is required to fight infections.

If organisms of all body sizes activated the same number of B cells, the time for a fixed number of B cells to produce antibody Ab is $\propto \log M$ (since immune system cells reproduce exponentially through clonal

amplification). For example, since it takes 4 days of exponential growth of activated B cells to produce sufficient neutralizing antibody in mice against West Nile virus (Diamond et al., 2003), then the corresponding time for a horse would be more than 2 months. This conflicts with empirical data on horses (Banerjee and Moses, 2010). We assume that the immune system of larger organisms must activate several antigen-specific B cells $\propto M$, to build up the critical density of antibodies in a fixed period.

Since only a very small number of pathogen-specific B cells reside inside the lymph node (1 in 10^6 immune system cells) (Banerjee and Moses, 2010), this implies that as the organism size increases, the infected site lymph node must recruit increasing numbers of B cells from other lymph nodes. However, having a larger lymph node means that the volume of the draining region it services will be very large (since the total amount of lymphoid tissue is proportional to body mass), which will increase the average time taken by immune system cells to reach the lymph node.

There is a tradeoff between having a larger lymph node (reduces global communication time involved in recruiting additional immune system cells to ensure a global antibody response) and a smaller lymph node (reduces local communication time involved in trafficking antigen-loaded dendritic cells to the draining lymph node). The optimal architecture that balances these two opposing goals is one where lymph nodes become larger as the host body size increases as well as more numerous (Banerjee and Moses, 2010; Moses and Banerjee, 2011; Banerjee, 2013; Banerjee et al., 2013).

In this work, I describe two different approaches for deriving how the number of lymph nodes should scale with host body mass, *M*. We then compare it against available empirical data.

2 Analysis and Results

I use the following model of antigen detection and dendritic cell trafficking. Each lymph node has a tissue draining region which it frequently samples for foreign pathogens. The general model of immune system dynamics in the lymph node and its draining region are shown in Fig. 1 and summarized as follows:

a) Stage 1: Dendritic cells randomly search for antigen in a local draining region. The time taken to detect antigen is denoted by t_{detect}^{DC}

b) Stage 2: Dendritic cells migrate to a local lymph node along a chemotactic gradient. The time taken to migrate is $t_{migrate}^{DC}$

c) Stage 3: Antigen-specific T cell in a lymph node detects antigen on a dendritic cell and the time taken to detect is $t_{detect}^{DC,cTcell}$

d) Stage 4: T cells then activate cognate B cells which undergo clonal amplification, an exponential growth process which produces some number of B plasma cells that then secrete antibody. The process of recruiting B cells (and hence cognate antigen-specific B cells) to the lymph node takes time $t_{recruit}$

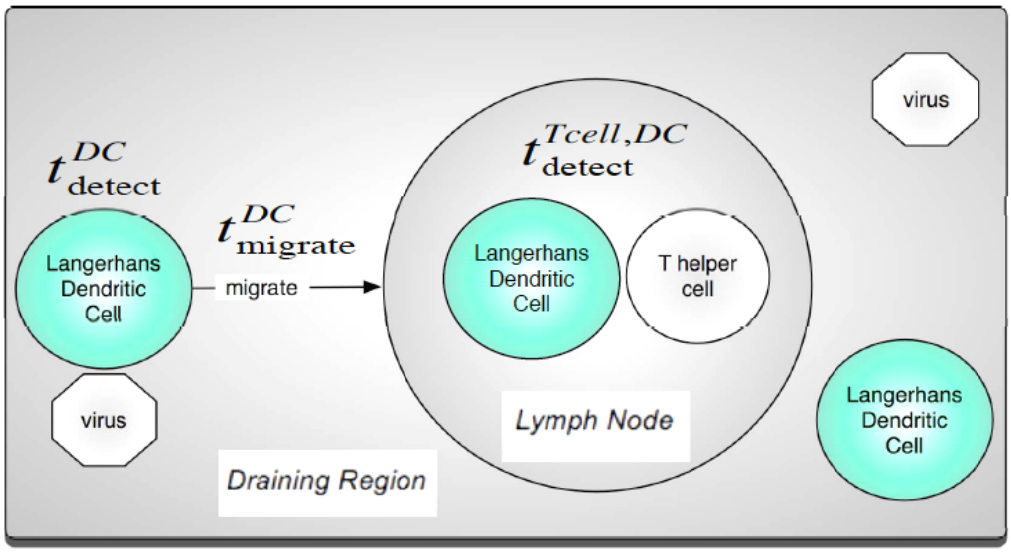

Fig. 1 Immune system dynamics within a lymph node and its draining region. Dendritic cells search for antigen in the draining region and upon detection migrate to the lymph node. T cells try to detect antigen on dendritic cells inside the lymph node. Figure adapted from Banerjee and Moses, 2010.

2.1 Assuming lymph node size remains constant over the duration of infection

In this approach, we only consider the total time taken by the immune system to detect antigen and secrete enough antibody to neutralize the pathogen (*T*). We also assume that lymph node size (for the same species) does not change over time. This can be represented as follows

$$T = t^{DC}_{detect} + t^{DC}_{migrate} + t^{DC,cTcell}_{detect} + t_{recruit} \qquad (1)$$

The absolute quantity of antibody (*Ab*) needed to be generated to neutralize a pathogen scales as $Ab \propto$ Volume of blood $\propto M$. The number of B cells (and cognate B cells) that the infected site lymph node must recruit ($N_{recruit}$) is proportional to the absolute amount of antibody that needs to be secreted and is inversely proportional to the number of cognate B cells already present (and hence inversely proportional to the lymph node volume V_{LN}):

$$N_{comm} \propto \frac{Ab}{V_{LN}} \qquad (2)$$

This analysis assumes that the number of cognate B cells that need to be activated scales linearly with host mass. This is justified by the following argument: let us assume a mouse (10 gm) needs 4 days to generate Ab_{mouse} amount of antibody multiplied by the number of cognate B cells. Then an elephant (10^7 gm) needs 4 * $log(10^6)$ = 24 days to generate $Ab_{elephant}$ = 10^6 * Ab_{mouse} amount of antibody with the same number of cognate B cells. The time to secrete the critical amount of antibody (*Ab*) grows as log *M*, which is clearly untenable.

The rate at which new B cells from other lymph nodes enter initially activated lymph nodes through the blood or lymphatic vessels ($rate_{comm}$) is proportional to the volume of the lymph node, assuming that a larger

lymph node will have proportionally more high endothelial venules

$rate_{comm.} \propto V_{LN}$ (3)

Combining (2) and (3), and noting that $Ab \propto M$ we get

$$t_{recruit} \propto \frac{M}{{V_{LN}}^2} \quad (4)$$

From simulations with an agent-based model (Banerjee and Moses, 2010), it was established that t_{detect}^{DC} and $t_{detect}^{DC,cTcell}$ do not scale with lymph node or draining region dimensions. Furthermore $t_{migrate}^{DC}$ scales as r_{DR} - r_{LN} which in turn scales as $V_{LN}^{1/3}$

$$T = a + b{V_{LN}}^{1/3} + c + d\ \frac{M}{{V_{LN}}^2}$$

Differentiating with respect to V_{LN} we get

$$V_{LN} \propto M^{3/7}$$

which in turn the gives the desired relation between number of lymph nodes (N) and host mass (M)

$$N \propto M^{4/7}$$

Hence, our method suggests that lymph node numbers should increase sub-linearly (slope < 1) with host body size.

2.2 Lymph node size changes over time as the infection progresses

We also look at another approach that considers the fact that the infected site lymph node size is increasing with time (after infection) due to the following reasons:

1) upregulation of ligands near high endothelial venules
2) more high endothelial venules in infected site
3) expansion of blood vessel feeding lymph nodes, and
4) antigen specific immune system cells retained within lymph nodes ("lymphocyte shutdown")

We augment equation (4) with a time-varying lymph node size

$$t_{recruit} \propto \frac{M}{V(t)_{LN}^2} \quad (5)$$

Lymph node size increases linearly over time after infection (Soderberg et al., 2005), giving us the functional form: $V_{LN}(t) \propto V_{LN,B} * t$ where $V_{LN,B}$ is the initial or baseline volume of the lymph node. Substituting this in Eq. 4, we get

$$t_{recruit} \propto \frac{M}{V_{LN,B}^2} \frac{1}{t^2}$$

and assuming $t \sim T$ we have

$$t_{recruit} \propto \frac{M}{V_{LN,B}^2}\frac{1}{T^2}$$

Substituting in equation (1) we have

$$T = t_{detect}^{DC} + t_{migrate}^{DC} + t_{detect}^{DC,cTcell} + \frac{d\,M}{V_{LN,B}^2\,T^2}$$

With the usual substitutions, we have

$$T = a + b'\,V_{LN,B}^{1/3} + c + \frac{d\,M}{V_{LN,B}^2\,T^2}$$

Rearranging in terms of T

$$T^3 - \rho T^2 - \beta = 0$$

where $\rho = a + b'\,V_{LN,B}^{1/3}$ and $\beta = \frac{d\,M}{V_{LN,B}^2}$

The solution of the cubic equation (real root) is

$$T = \frac{\rho}{3} - \frac{1}{3}\sqrt[3]{\frac{\left(-2\rho^3 - 27\beta + \sqrt{(-2\rho^3 - 27\beta)^2 - 4\rho^6}\right)}{2}} - \frac{1}{3}\sqrt[3]{\frac{\left(-2\rho^3 - 27\beta + \sqrt{(-2\rho^3 - 27\beta)^2 - 4\rho^6}\right)}{2}}$$

Neglecting the term within the square root of the square root and differentiating with respect to $V_{DR,B}$ we have upon considerable simplification:

$$2a^3V_{LN,B}^3 + 2b'V_{LN,B}^{\frac{11}{3}} + 2ab'V_{LN,B}^{\frac{10}{3}} = 27dMV_{LN,B}^{\frac{2}{3}}$$

Using this to bound the exponent on M, we have for the largest exponent

$$O\left(V_{LN,B}^{\frac{11}{3}}\right) = 27dMV_{LN,B}^{\frac{2}{3}}$$

$\Rightarrow V_{LN,B} \propto M^{\frac{1}{3}}$

$\Rightarrow N \propto M^{\frac{2}{3}}$

and the smallest exponent

$$O\left(V_{LN,B}^{3}\right) = 27dMV_{LN,B}^{\frac{2}{3}}$$

$$\Rightarrow \quad V_{LN,B} \propto M^{\frac{3}{7}}$$

$$\Rightarrow \quad N \propto M^{\frac{4}{7}}$$

In summary, the scaling exponent for lymph node volume lies between 4/7 and 2/3. Both our models predict that the exponent for how lymph node volume and numbers scale with host body size is sub-linear (< 1).

Substituting the scaling relation for the number of lymph nodes into Equation (1) gives us a predicted scaling for the time to detect and respond (T) as between 1/7 and 1/3.

3 Empirical Data

We conducted a literature search of available empirical data on the number and size scaling of lymph nodes. We found that mice weighing 20 gm have 24 lymph nodes averaging 0.004gm each (Halin et al., 2005). Humans are 3000 times bigger and have 20 times more lymph node, with each lymph node being 200 times bigger (Halin et al., 2005; Altman and Dittmer, 1974). Elephants have lymph nodes the size of an entire mouse and horses have approximately 8000 lymph nodes (Altman and Dittmer, 1974).

We show the available data in Figure 2. Our analysis suggests that the volume of individual lymph nodes increases sub-linearly with body size (slope = 0.72, p-value = 0.006) (Fig. 2, right panel).

It has also been reported that the time to peak viremia (after infection with West Nile virus) is invariant with host body size (Banerjee and Moses, 2010). The time to peak viremia correlates with time taken by the immune system to detect and respond against pathogens. Our analysis suggests that the time taken to detect and respond to pathogens is invariant with host body size (Banerjee and Moses, 2010). We summarize the available experimental data on time to peak viremia in Fig. 2 (left panel).

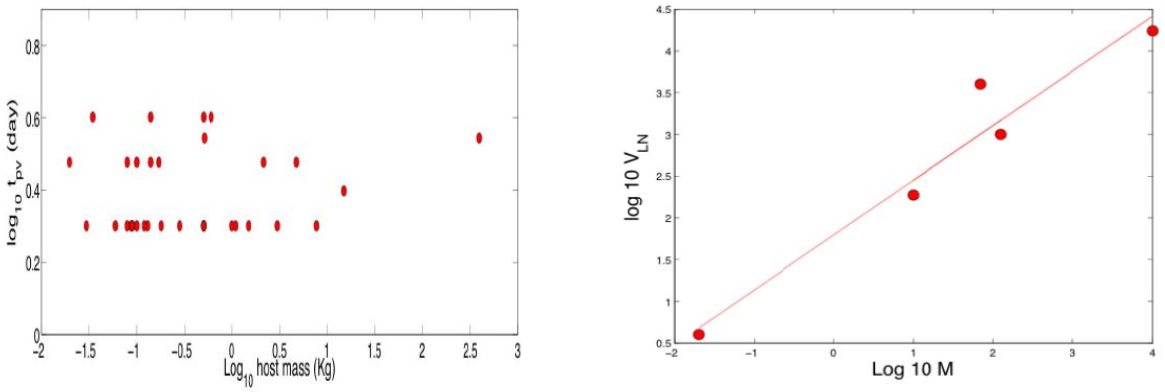

Fig. 2 (Left Panel) Empirically measured time between infection and peak viral concentration in blood vs. host body mass (M) on logged axes (there is no significant slope, p = 0.35, reproduced from Banerjee and Moses, 2010) for species ranging from sparrows to horses. (Right Panel) Volume of a lymph node vs. host body mass on logged axes (there is a significant slope with p = 0.006 showing a clear increase with mass as predicted by our calculations). Figure adapted from Moses and Banerjee, 2011.

4 Discussion

The immune system can detect and respond against pathogens in time that does not vary with the size of the host animal. We suggest that this is due to the architecture of lymph nodes. Lymph nodes are anatomical structures that facilitate the otherwise serendipitous encounter of immune system cells with pathogens. We develop two complementary mathematical approaches to derive the optimal distribution of lymph nodes that enable a rapid immune response.

Using two approaches, we analytically derive how the number and size of lymph nodes should scale with host body size to respond against pathogens in time that is invariant with body size. Our second approach explicitly accounts for the increase in lymph node size over time as the infection progresses. Both approaches suggest that the scaling exponent is sub-linear (< 1), suggesting that lymph node numbers and volumes both increase with host body size (although not as fast as linearly).

Our model predictions agree with available empirical data suggesting that the volume of lymph nodes increases sub-linearly with body size. We are not able to rule out a specific scaling exponent. As more data on lymph node numbers and sizes becomes available, it should be possible to make better estimates of the scaling exponent.

Our models give us mechanistic insight into how the immune system can efficiently remove pathogens in a timely manner. This can also lead to immune system inspired architectures and strategies that replicate these dynamics in human-engineered distributed systems like robots, intrusion detection systems and peer-to-peer networks (Banerjee and Moses, 2010; Moses and Banerjee, 2011; Banerjee, 2013; Banerjee et al., 2013; Banerjee, 2015; Banerjee, 2016; Banerjee, 2017a; Banerjee, 2017b).

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