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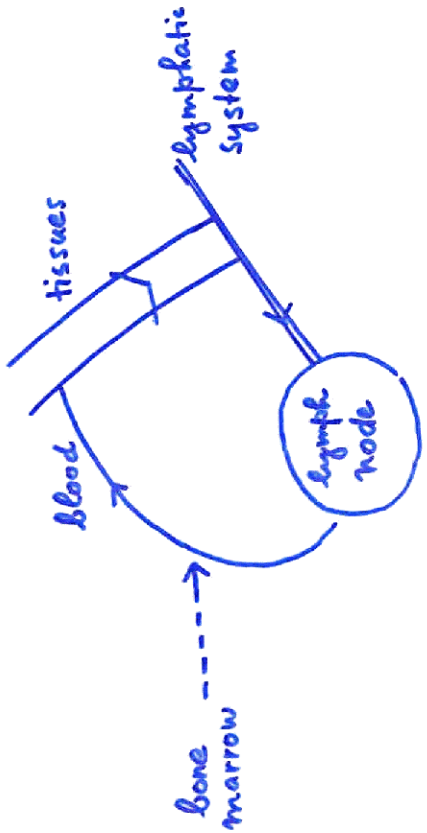
Scaling Laws in Immunology

or

WBE model + Immunology → What?



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Metabolic rate of Bone Marrow =

~ (Volume of Bones) · (Metabolic Rate per unit volume)

↓ $\sim M^{3/4}/M = M^{-1/4}$

(cross section) · (length) · (number of bones)

↓ $\sim M$ ↓ $\sim M^{1/3}$ ↓ $\sim M^0$ $= M^{4/3}$

Metabolic Rate of Bone Marrow $\sim M^{13/12}$

Rate of stem cell production $\sim M^{13/12}$

Rate of long-lived lymphocyte replacement $\sim \frac{M \ln(cM)}{M^{1/4}} = M^{3/4} \ln(cM)$

Conclusion: Over supply of stem cells in large animals

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Number of lymphocytes inside a service unit: N(t) belong to a single clone.

$$\frac{dN}{dt} = +\nu_0 - \nu_e N$$

ν_0: WBE: universal inflow with the blood

ν_e: escape probability, per sec, per cell, into lymphatic capillary

$$N^{eq} = \nu_0/\nu_e$$

Assume that B-cells performs random walk: jump ℓ each time ε

(nr. of different sites in service unit) $\cong$ $\frac{\text{volume service unit}}{\ell^3}$

One of them is the exit!

$$\nu_e \cdot \varepsilon \cong \frac{1}{(\text{nr})} \cong \frac{\ell^3}{\text{volume service unit}}$$

$D \sim \ell^2/\varepsilon$ and (volume service unit) $\sim M^{1/4}$ (WBE)

Conclusion: $\nu_e \sim D.\ell.M^{-1/4}$

$N^{eq} \sim \frac{1}{D\ell} \cdot M^{+1/4}$

Time inside serv.unit $\sim \frac{1}{\nu_e} \sim \frac{1}{D\ell} M^{+1/4}$

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This is the case where B-cells diffuse autonomously.

$\sim M^{1/4}$ copies in volume $\sim M^{1/4}$

antigen is caught in time independent of M!

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Scaling of B-cell clone size

(clone size) $\sim$ (nr. per service unit) $\cdot$ (nr. service units)

$\sim M^{1/4}$ $\sim M^{3/4}$

$\sim M$

Note: B-cell transport in blood: follows global metabolism (time $\sim M^{1/4}$)

B-cell time spent in tissue: autonomous, "priviliged" metabolism (time $\sim M^{1/4}$)

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Lymphocyte repertoire

WBE give: metabolic rate $\sim M^{3/4}$
life time $\sim M^{1/4}$
} total metabolic activity $\sim M$

We conjecture: total nr. of infections $= cM$

Hence reperloire should be large enough to overcome cM infections with probability near to 1.

Shape space (dimension 5-10) volume V

one clone of B-cells

all new antigens inside v_0 are eliminated

ϕ = probability N_0 clones fail to recognize new antigen $= \left(1 - \frac{v_0}{V}\right)^{N_0} \cong \exp\left(-N_0 \frac{v_0}{V}\right)$

→ Probability immune success in 1 infection: $(1-\phi)$

→ Idem in cM infections: $(1-\phi)^{cM} \cong \exp(-cM\phi)$

Near 1 iff $cM\phi \ll 1$ → $N_0 \gg \frac{V}{v_0} \ln(cM)$

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Conclusions: B-cell clonal diversity $= k \ln(cM)$

Clone size $\sim M$

Nr. of B-cells $\sim M \ln(cM)$

Experiments by Casrouge et.al. on mice clonal diversity
Arstila et. al. on humans " "

give: $k \cong 2.6 \times 10^6$

$c \cong 0.22\ g^{-1}$

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Lymphatic System

lymphocyte → lymph capillary → lymphatic vessels → lymph duct → lymph node

Humans transport ≅ 3 l/day lymph

One-way gaps in walls of lymph. capillaries
One-way valves in lymph. vessels
→ "passive" transport driven by surrounding tissues

Four mechanisms: Action of lungs
Action of heart
Peristaltic Movement intestines
Locomotion

1-3: Fraction of adjacent tissue (volume $\sim \xi' M$) is squeezed out during cycle with period $\sim M^{1/4}$.

Flux of lymph: $a' M^{3/4}$

4: Land animal (size $L \sim M^{1/3}$) has period of walking $\sim \sqrt{\frac{L}{g}} \sim M^{1/6}$

Flux of lymph = $a'' \xi M^{5/6}$
↑
fraction of time animal walks

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Total flux of lymph: $a' M^{3/4} + a'' \xi M^{5/6}$

Total flux of lymphocytes
in blood: $\sim M \ln(cM)/M^{1/4} = M^{3/4} \ln(cM)$

in tissues: $\sim M^{3/4} \ln(cM)\, M^{1/4}/M^{1/4} = M^{3/4} \ln(cM)$

Conclusion: larger animals have (slightly) larger concentration of lymphocytes in blood and tissues

and (slightly) lower in lymph

Experiments on rat: # recirculating lymphocytes $\cong 1.6 \times 10^9$
idem passing thoracic duct $(hr)^{-1} \cong 10.9 \times 10^6\ hr^{-1}$

→ Circulation time:

2.9	d	(mouse)
6.2	d	(rat)
27	d	(human)
58	d	(elephant)

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The Lymphnodes

Have "priviliged" metabolism: amount of blood delivered per gram, per min: $\cong 0.48$ ml $(\text{min})^{-1}$ g^{-1}.

Each node should contain the full repertoire at least once.

Two "design" requirements: I: Contact in the node between complementary B- and T- cells as fast as possible! Hence

(# of representatives of a clone in a single node) ..... maximal

II: Drainage area of a node as small as possible:

(# nodes) ..... maximal

Optimal choice is to choose

(# representatives/node) = (# nodes)

Solution: (# lymphnodes) = $\sqrt{(\text{clone size})}$.

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This yields 5 scaling laws:

(# nodes) $\sim M^{1/2}$

(# lymphocytes of a clone, inside a node) $\sim M^{1/2}$

(total # lymphocytes inside a node) $\sim M^{1/2} \ln(cM)$

(mass of lymphnode) $\sim M^{1/2} \ln(cM)$

(total mass of all nodes) $\sim M \ln(cM)$

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The flux of repaired lymphocytes through a single node =

$$= \frac{\text{total flux in blood}}{\text{nr. of nodes}} \sim \frac{M^{3/4} \ln(cM)}{M^{1/2}} \sim M^{1/4} \ln(cM)$$

assuming a lymphocyte passes through 1 node for repairs.