Summer 2023 Internship

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By uki

In [1], Macrophage density is reported to be 192.8 cells/mm^2 in breast lobules without lobulitis, and 210.1 cells/mm^2 in breast lobules with lobulitis. Lobulitis is a rare inflammatory state and this data can be used to estimate inflammed macrophage density. Note that in mastectomies breast lobules are usually removed so I'm not sure how well this applies to breast cancer patients. The paper also points out the immune cells in normal breast tissues are primarily confined to breast lobules. A scaling of $\times 0.1$ might be considered for density in extralobular tissues.

Notes: (1) We will usually take "ballpark estimates", so 192 and 210 will both be approximated as "200". However, we have to be very careful with interpreting densities. We should think of our 1D model as a block of tissue with length L, width w, and height h, where $0 \leq x \leq L$ is the spatial coordinate, and w, h are "small" fixed values (for example, 1 mm each). We need to express our estimates of density in terms of cells per unit volume, and multiply by our chosen values for wh to convert to density per unit length. This should be done consistently to avoid goofs. So, for example, in the above estimates for macrophages, we need to know what was the "thickness" of the microscopy slide, or estimate it somehow, to get cells/mm^3.

There are some review papers about wound healing with references that can be helpful, e.g. see Chap 3 in [2] and [3]. In papers such as [4], the macrophage density in normal tissue is compared to the density in keloid scars. There are 2.3 times more macrophages in those abnormal scars (several years after wounding).

uki: [5] suggested tissues for H&E staining should have thickness no more than 1mm. They used 7 μm thick slices. [6] used 2-10 μm slices for their study, looking at the nature of this study we can maybe assume that this is the common range used.

[7] suggested collagen density in human connective tissues, which is supposed to higher than in normal tissues. [8] reported 17.9-21.3% breast tissue composition for collagen, this was measured by volume by optical spectroscopy (OS). Collagen Type I turnover rate in human connective tissues is $\approx$1% per year according to [9] which cited [10].

In ductal carcinoma in situ (considered the earliest form of breast cancer), fibroblasts consists of 12.1% normal fibroblasts, 23.5% myofibroblasts, 47% resting fibroblasts and 17.4% CAF [11]. Excellent and useful information! And it is already "nondimensional", in %, which is also great. It is also stated in [11] that collagen density linearly associates with CAF and myofibroblast densities.

Myofibroblasts that are differentiated from fibroblasts are less motile compared to fibroblasts [12]. Figure 4 in [12] shows that myofibroblasts moves slower than fibroblasts, at $26\mu m/12h$. This estimates to at maximum 9e-8 $\mu m^2/s$ if travelling in a square with equal distance to perpendicular directions, this does not make sense compared to the macrophage random motility value given in the table. Yes, something fishy here.

[13] measured a myofibroblast traction force of $\approx$ 300 Pa/cell. [14] reported contractile forces from myofibroblasts ranging from 100 pN/μm^2 to 2 nN/μm^2. See also [15] for comparison of traction forces of various cell types.

Parameter	Meaning	value	units	Source
D_ϕ	Macrophage random motility	0.005	$\mu m^2/s$	in cancer [16, 17]
D_m	Myofibroblast random motility	9×10^{-8}	$\mu m^2/s$	[12]
a_0	Basal macrophage recruitment rate	10^{-5}	cells $\mu m^{-1}/s$	estimated from [18]
b_0	Basal myofibroblast recruitment rate	4×10^{-8}	cells/s	estimated from [19, 20]
b	macrophage-induced myof recruit rate	$\approx 2 - 10 \times b_0$	cells/s	very rough guess
δ_m	Myofibroblast turnover rate	10^{-6}	1/s	estimated from [19]
δ_ϕ	Macrophage turnover rate	10^{-7}	1/s	order of magn slower [16]
ϕ	Normal macrophage density	$\approx 1.9 \times 10^{-5}$	cells/μm^2	guessed from [1]
ϕ_0	Inflammed macrophage density	$\approx 2.1 \times 10^{-5}$	cells/μm^2	guessed from [1]
C	Typical collagen density	105	Amt/μm^3	in connective tissues [7]
δ_C	Typical collagen turnover rate	$\approx$1	%/year	[9, 10]
M	Typical myofib density		cells/μm^3	[11]
τ	Typical myofib traction force	≈ 300	Pa/cell	[13]

Table 1: Typical ball-park estimates for some parameters in the model.

By Leah

A few collected parameter values are given in Table 1. In [16], the random motility and chemotaxis parameters for macrophages are obtained from previously published (Boyden chamber) experimental data, giving values in the range of 5 $\times 10^{-15} m^2/s$. (See their Table 1.) Those values were used for modeling macrophage-tumor interactions in [16]. Those values are cited for a model of glioma in [17]. They are converted to more convenient units below.

In [17], we also find a typical proliferation rate of macrophages ≈ 0.3307/h, and a carrying capacity (typical density) of 10^6 cells (domain size unspecified). Typical macrophage density: According to [18] there are 0.1 (normal) to about 1.0-1.2 (in injured tissue) macrophages $\times 10^{-4}$ per μm^2. This buildup typically takes about 7 days. This leads to an estimate for recruitment rate of about $10^{-4}/(6 \times 10^5) \approx 10^{-10}$ cells $/\mu m^2/s$. But in our 1D model, we need the square-root of the above domain, so obtaining a basal recruitment rate of around $a_0 \approx 10^{-5}$ cells/μm/s. Macrophages can survive in tissue "macrophages survive in tissue for weeks or months" according to [16], whereas other cells have a turnover time of days.

The paper by [19] provides some information about myofibroblast "recruitment" (transdifferentiation from fibroblasts), stating that (rabit corneal) fibroblasts at a density of 5 or 500 cells/mm^2 produced 80% or 10% myofibroblasts after 5-7 days (in vitro experiment). According to [20] cancer associated fibroblasts (CAFs) can occupy about 80% of a tumor. Taking a typical cell diameter ($\approx 10\mu$m), and 50% of cells as fibroblasts in the tissue, we have a typical tissue fibroblast density of 0.05 cells/μm (in 1D). Suppose half of these transdifferntiate into myofibroblasts in 7 days. Then we have a "basal myofibroblast recruitment rate" of 0.025/(7 days) which is $\approx 4 \times 10^{-8}$ cells/s. [Note: myofibroblasts can be much larger than fibroblasts, about 50μm long and 25μm wide, [19].] They persist in cultures for about 3-7 days, so we can estimate their decay rate as $\delta_m \approx 1/7$(/day), which is roughly 10^{-6}/s.

What we also need to estimate is the macrophage-induced rate of myofibroblast recruitment b (likely dependent on cytokines secreted by macrophages etc.). However, we could ball-park estimate that $b \approx 2 - 10 \times b_0$.

We refer to [21] for parameters of stress-related macrophage recruitment rate. According to this paper, macrophages are attracted to a stress field of myofibroblasts within a radius of around 600 μm at migration speeds of 0.5-1.4 μm/min. Taking a mean speed of 1μm/min resulting in a recruitment rate constant of roughly $1/(600 \cdot 60) \approx 3 \times 10^{-5}$/s. This is still not what we need for the parameter a_1 (or a_2) in our model's function $a(\sigma)$ as we need information about number (or density) of cells recruited per unit stress per unit time. We may be able to get some information about the stress field induced by myofibroblasts (i.e. obtain $\alpha f(m)$ for our model) from the paper [21].

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