

Summer 2023 Internship

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In [1], Macrophage density is reported to be 192.8 cells/mm² in breast lobules without lobulitis, and 210.1 cells/mm² 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.

[2] suggested collagen density in human connective tissues, which is supposed to higher than in normal tissues. [3] 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 [4] which cited [5].

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 [6]. It is also stated in [6] that collagen density linearly associates with CAF and myofibroblast densities.

Myofibroblasts that are differentiated from fibroblasts are less motile compared to fibroblasts [7]. Figure 4 in [7] shows that myofibroblasts moves slower than fibroblasts, at $26\mu\text{m}/12h$. This estimates to at maximum $9e-8\mu\text{m}^2/s$ 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.

[8] measured a myofibroblast traction force of $\approx 300\text{ Pa/cell}$. [9] reported contractile forces from myofibroblasts ranging from $100\text{ pN}/\mu\text{m}^2$ to $2\text{ nN}/\mu\text{m}^2$.

A few collected parameter values are given in Table 1. In [10], the random motility and chemotaxis parameters for macrophages are obtained from previously published (Boyden chamber) experimental data, giving values in the range of $5 \times 10^{-15}\text{m}^2/s$. (See their Table 1.) Those values were used for modeling macrophage-tumor interactions in [10]. Those values are cited for a model of glioma in [11]. They are converted to more convenient units below.

In [11], we also find a typical proliferation rate of macrophages $\approx 0.3307/h$, and a carrying capacity (typical density) of 10^6 cells (domain size unspecified). Typical macrophage density: According to [12] 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 $/\mu\text{m}^2/s$. 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 $/\mu\text{m}/s$. Macrophages can survive in tissue “macrophages survive in tissue for weeks or months” according to [10], whereas other cells have a turnover time of days.

The paper by [13] provides some information about myofibroblast “recruitment” (transdifferentiation from fibroblasts), stating that (rabbit corneal) fibroblasts at a density of 5 or 500 cells/mm² produced 80% or 10% myofibroblasts after 5-7 days (in vitro experiment). According to [14] cancer associated fibroblasts (CAFs) can occupy about 80% of a tumor. Taking a typical cell diameter ($\approx 10\mu\text{m}$), and 50% of cells as fibroblasts in the tissue, we have a typical tissue fibroblast density of 0.05 cells $/\mu\text{m}$ (in 1D). Suppose half of these transdifferentiate into myofibroblasts in 7 days. Then we have a “basal myofibroblast recruitment rate” of $0.025/(7\text{ days})$ which is $\approx 4 \times 10^{-8}$ cells/s. [Note: myofibroblasts can be much larger than fibroblasts, about $50\mu\text{m}$ long and $25\mu\text{m}$ wide, [13].] They persist in cultures for about 3-7 days, so we can estimate their decay rate as $\delta_m \approx 1/7(\text{day})$, 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 [15] 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 $600\mu\text{m}$ at migration speeds of $0.5\text{-}1.4\mu\text{m}/\text{min}$. Taking a mean speed of $1\mu\text{m}/\text{min}$ 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 [15].

Parameter	Meaning	value	units	Source
D_ϕ	Macrophage random motility	0.005	$\mu\text{m}^2/\text{s}$	in cancer [10, 11]
D_m	Myofibroblast random motility		$\mu\text{m}^2/\text{s}$	[7]
a_0	Basal macrophage recruitment rate	10^{-5}	cells $\mu\text{m}^{-1}/\text{s}$	estimated from [12]
b_0	Basal myofibroblast recruitment rate	4×10^{-8}	cells/s	estimated from [13, 14]
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 [13]
δ_ϕ	Macrophage turnover rate	10^{-7}	1/s	order of magn slower [10]
ϕ	Normal macrophage density	1.54×10^7	cells/ μm^3	[1]
ϕ_0	Inflammed macrophage density	$5-10 \phi$	cells/ μm^3	rough guess
C	Typical collagen density	105	Amt/ μm^3	in mammals [2]
d_C	Typical collagen turnover rate	≈ 1	%/year	[4, 5]
M	Typical myofib density		cells/ μm^3	[6]
τ	Typical myofib traction force	≈ 300	Pa/cell	[8]

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

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