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# Experimental versus numerical data for breast cancer progression

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ABSTRACT

This paper deals with a mouse model of breast cancer based on two mammary adenocarcinoma cell lines derived from a spontaneous tumor of the mammary gland in a female BALB/c mouse. We investigate both animal and mathematical models of tumor progression, and demonstrate a correspondence between the experimental and predicted data. The mathematical model is solved numerically and the laboratory data are utilized in order to find unknown parameters for the model equations. The results of the numerical experiments illustrate that the mathematical model has a potential to describe the growth of cancer cells *in vivo*.

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## 1. Introduction

Breast cancer is the most common type of malignant disease that occurs in women. In 2009, approximately 192,000 women were diagnosed with breast cancer in the United States [1]. Over 40,000 women diagnosed with the disease die yearly due to inadequate detection and treatment options, making breast cancer the second most common cause of cancer-related death for women in the US.

Cells progress from normal, to abnormal, to precancerous, and finally to invasive cancer as they accumulate mutations that inactivate their growth regulating mechanisms. Left undetected, cancer cells will spread from the primary tumor in the breast through the bloodstream or lymphatic system to secondary organs, in a process known as metastasis. Most breast cancer patients die due to the complications that arise from the growth of metastatic lesions in vital organs such as lung, liver, brain, and bone [2,3]. Developing effective therapeutics for breast cancer patients by studying the behavior and pathogenesis of cancer cells is a continuing area of research focus and funding. The use of various animal models allows cancer to be studied in a controlled environment to elucidate cellular mechanisms that could be targeted therapeutically. *Mus musculus* (mouse) is the primary animal model used by researchers to study the biology and progression of metastatic disease *in vivo*.

In addition to transgenic mice models of cancer, many researchers use a variety of methods to implant breast cancer cells into mice in order to study the different stages of tumor progression. Tail vein, subcutaneous, intracardiac, intraperitoneal, intratibial, or orthotopic injections are some of the techniques available for transplanting cancer cells into mice [4,5]. Each method allows the investigation of a different part of the metastatic cascade. The use of tail vein or intracardiac injections introduces cells directly into the circulation, thereby bypassing the primary tumor growth stage and allowing for maximum dispersal of the cancer cells and resultant metastases. On the other hand, an orthotopic injection refers to an injection of

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**Table 1**
Individual mice tumor average sizes ($mm^3$).

| Days | 4T1.2 cells | Days | 66c14 cells |
|---|---|---|---|
| – | – | 10 | 16.68 |
| 14 | 17.2 | 14 | 39.52 |
| 17 | 40.81 | 17 | 101.45 |
| 21 | 108.21 | 21 | 139.86 |
| 25 | 218.5 | 24 | 239.98 |
| – | – | 28 | 413.08 |
| 31 | 643.7 | 31 | 409.08 |
| – | – | 34 | 478.03 |

the cancer cells into their area of origin, in this case the mammary tissue. This method promotes primary tumor growth followed by potential, subsequent metastatic events [5]. Since metastasis is a multi-step process, cancer cell implantation techniques such as orthotopic injections accurately mimic human breast cancer progression.

## 2. The 66c14 and 4T1.2 orthotopic model of mouse mammary cancer

In this study, we utilized the 66c14 and 4T1.2 syngeneic mouse model of metastatic breast cancer. Our laboratory data are presented in Table 1. 66c14 and 4T1.2 cells were originally derived from a spontaneous tumor of the mammary gland in an inbred BALB/c mouse [6]. These cell lines were selected for their distinct metastatic profiles upon orthotopic reintroduction into BALB/c mice. 4T1.2 cells aggressively metastasize to lung, brain, liver, and bone mimicking the human situation, while 66c14 cells are mildly metastatic to lung and lymph node [6,7]. This difference in metastatic potential is thought to be due in part to the low caveolin-1 expression in 4T1.2 cells, which has previously been shown to be suppressed in metastatic human breast cancer [8].

In the work presented here, we were interested in studying the growth pattern of 66c14 and 4T1.2 primary tumors *in vivo*. 66c14 and 4T1.2 cells were maintained in minimum essential media alpha (MEM$\alpha$) containing 10% fetal bovine serum (FBS), 1 mM sodium pyruvate, and 100 units/ml of penicillin and streptomycin. The cells were incubated at 37 °C with 5% $CO_2$ and 95% humidity. 66c14 or 4T1.2 ($1 \times 10^5$) cells were orthotopically injected into the 4th mammary gland of 4-week old female BALB/c mice ($n = 5$). One hundred percent of mice injected with the cancer cells developed primary tumors, and tumor size was measured using calipers at set time-points ranging from 10 to 34 days. To calculate tumor volume in $mm^3$, the following equation was used: tumor volume ($mm^3$) = (length $\times$ width$^2$)/2. Our findings demonstrated that orthotopically injected 4T1.2 cells result in tumor growth at a faster rate than 66c14 cells (Table 1). Furthermore, the condition of the mice injected with 4T1.2 cells deteriorated faster, presumably due to a larger metastatic burden.

## 3. Mathematical model

In addition to *in vitro* and *in vivo* experiments, which are the major tools in cancer research, methods of mathematical modeling have been shown to be useful for better understanding of the processes of carcinogenesis. Mathematical and computational approaches possess the ability to describe in quantitative terms the complex and highly nonlinear interactions between non-cancerous and cancer cells [9–12]. In particular, over the last two decades, kinetic theory for active particles (KTAP) and partial differential equations have been successfully applied by Bellomo et al. to model the spread of tumors [11,13–15].

Within the framework of KTAP, the phenomena studied are described by integro-differential equations of Boltzmann type, which include a variable $u$ presenting the functional activity of interacting entities called active particles. This methodology has been successfully applied for modeling various processes and phenomena considered by applied and life sciences, for example, complex living systems [16,17], population dynamics [18], politics and social sciences [19,20], psychological relationships [21], investigation of traffic flow [22], etc. Recent development and applications of this theory can be found in the book by Bellomo [9].

Recently, it has been demonstrated in [23,24] that the KTAP has the potential to describe the growth of prostate and breast tumor cells. The theory has been used in [23] to predict prostate tumor progression and a correspondence has been obtained between the numerical [23] and laboratory [25] data. In [24], it has been demonstrated that it is possible to find such parameter values for the model partial differential equations so that their solutions correspond to clinical data, therefore showing the potential to extend the applications of the kinetic theory to breast cancer.

In this paper, we have applied the model equations to the 66c14 and 4T1.2 syngeneic mouse model. We have utilized the laboratory data to estimate the parameter values for the kinetic model and the results of our numerical experiments demonstrate that the dynamics of the model equations properly capture the development of the 66c14 and 4T1.2 primary tumors *in vivo*.

For the model equations, we consider the populations of cancer cells (the first population denoted with $i = 1$), helper T cells ($i = 2$), cytotoxic T lymphocytes ($i = 3$), antigen presenting cells ($i = 4$), antigen-loaded APCs ($i = 5$), and host environment cells ($i = 6$). The distribution density of the $i$th population with activation state $u \in [0, 1]$ at time $t \geq 0$ is