Abstract

In this paper, we delve into the dynamics of ovarian metastasis: in particular, we delve into a model first described by Scott, et. al. However, we make several modifications, with a focus on introducing persistence in blood borne tumor cells. This persistence is designed to allow testing of experimental conditions, as experiments with ovarian cancer in rats start not with tumors, but rather with tumor cells injected into the bloodstream. We first test the model with initial conditions that match natural ovarian cancer development, and obtain tumor self acceleration similar to that of Scott, et. al. Furthermore, when we run the simulation under experimental conditions, we not only see tumor self acceleration (albeit muted), we also see a distinct delay in the development of tumors in nonovarian sites compared to ovarian ones. When ovarian sites are removed from the system under experimental conditions, we observe a minor delay in tumor growth, but we observe a far more noticeable stunt in final tumor burden, more than can be accounted for by simple loss of carrying capacity from a decrease in site number. This indicates that, under experimental conditions, the ovaries are critical waypoints in enabling cancer metastasis.

Background

The importance of understanding the metastatic pathways of ovarian cancer is difficult to overstate: 47.5% percent of staged ovarian cancers are at stages III and IV, and the five year survival rate of such cancers is only 28.4%. (http://www.ovariancancer.org/about/statistics/). However, metastasis is a taxing and difficult process on the cancer, and in fact cancer metastasis seems to reduce the cancer's ability to survive. The organ of origin for a cancer can better sustain cancer cells than tissues far away from the cancer. Furthermore, metastasis requires substantial energy input from cancer cells, energy that would seem better spent on simply dividing more. However, work by Scott, et. al. suggests that metastasis is not simply a biological curiosity but rather a necessity for continuing the reproductive success of the original tumor.

Scott, et. al. builds a model in an effort to elucidate a phenomenon first theorized by Norton and Massangué: cancer metastasis is an effort by cancer tumors to self seed, creating tumors elsewhere in the body so that they can shed cells of their own and return them to the original tumor. This hypothesis was supported by work done Kim, et. al., in which breast cancer tumors in the same body were tagged with different fluorescent dyes to track them, after which cells from one tumor were found in the other. Scott et. al. extends this hypothesis and attempts to understand the phenomenon in greater detail by devising a mathematical model to clarify some of the mechanisms tumor self seeding.

However, testing metastatic pathways in vivo and in silico requires a slightly different approach from that presented by Scott, et. al. In vivo experiments involving tumor propagation usually begins with cancerous cells injected into the bloodstream of animal subjects. However, the Scott model begins with initial conditions that involve starting with the original tumor site already populated. To further complicate matters, at each time step in the Scott model, bloodstream cells die off entirely, making testing the experimental initial conditions difficult to impossible under their model. We are interested in the construction of model based on that of Scott, et. al, with the specific objective of applying it to ovarian cancer metastasis, especially under experimental conditions. Furthermore, we are interested in the pathways metastasis takes, which can be difficult to discern in the Scott et. al. model as all potential sites are treated mathematically equally. We approach the problem by compartmentalizing sites with different growth parameters in each compartment and giving bloodstream cells persistence so that they have a chance to implant into sites and grow, even under experimental conditions.

Methods

We make several assumptions in constructing our model. First, we assume that, at each tumor site, we will have logistic growth with identical carrying capacities for all sites, and we assume that the number of sites in each compartment has a finite upper limit. In addition, we assume that only surface cells can shed off of a tumor: however, all surface cells of all tumors have an identical probability of shedding. We take both shedding and implantation to be random events, proportional to the number of cells on the surfaces of tumors and in the bloodstream, respectively. Finally, we assume that cells in the bloodstream neither reproduce nor die: they can only increase by tumor shedding. In light of these assumptions, we derive the following difference equations:

$$N_i(t+1) = \frac{K(N_i(t)-r_i(t))e^\rho}{K+(N_i(t)-r_i(t))e^\rho-1} \qquad (1)$$

Where $N_i(t)$ is the amount of tumor cells in the ith site at the tth time step, K is the carrying of the tumor, ϱ is the growth rate of the tumor, and $r_i(t)$ is the amount of cells shed by the ith tumor at the tth time step. Note that equation 1 is the solution of the logistic growth differential equation, adjusted to account for tumor shedding.

Equation 2 describes the number of cells in the bloodstream as follows:

$$B(t+1) = B(t) + \sum_{i=1}^{n}(r_i(t+1)) - m(t+1) \quad (2)$$

The number of bloodstream cells at time t is denoted B(t), and m(t) is the number of tumors that have implanted at timestep t. The equation is constructed so that bloodstream cells persist through each time step, save for introduction via shedding and removal by implantation. The constant n denotes the total number of potential tumor sites currently in the body. For every time step t, we derive the following expression for $r_i(t)$:

$$r_i(t) = Binom([N_i^{2/3}], \lambda) \quad (3)$$

We raise N_i to the ⅔ power to reflect that only surface cells can be shed from the tumor. The parameter λ is constant for all tumors, and reflects how easily cells can break away from tumors: a higher lambda indicates that shedding is more likely.

We assume that all bloodstream cells will have the opportunity to bond with any unoccupied site, and so we derive the following expression for m(t)

$$m(t) = \sum_{i=1}^{n} C_i Binom(B(t), p_i) \quad (4)$$

Where C_i is an indicator variable that is equal to one only if the ith site is unoccupied, and zero otherwise. The variable p_i, or implantation probability, varies by site, and, to differentiate ovarian sites from nonovarian ones, we make p_i higher for the former. For convenience, we denote the ith term in this series to be $m_i(t)$. In addition, we call the initial time of implantation for the ith site k_i, and the number of cells that originally implanted around a site to be M_i. If M_i is greater than one, however, we consider a given site to have evolved multiple tumors. In order to account for multiple tumors in the same site, we derive the following expression for N(t), the total number of tumor cells in the body at time t:

$$N(t) = \sum_{i=1}^{n} M_i N_i(t) \quad (5)$$

Equation 5 uses the assumption that multiple tumors in the same site have sufficiently similar dynamics that they can be treated as mathematically identical. This assumption is used because such twin tumors would be in very similar locations and exposed to sufficiently similar conditions that we can neglect the negligible factors that would cause them to act slightly differently.

We use the following values for our parameters (all values derived from Scott unless noted):

Table 1: List of parameters used and their units

Parameter name	Units	Value
K	# cells	1e6
ϱ	day^{-1}	ln(2)
λ	n/a	10^{-3}
$p_{ovaries}$	n/a	.01
p_{other}	n/a	.001*

*We divided by 10 in order to introduce a difference of an order of magnitude between ovary metastasis and metastasis into other sites
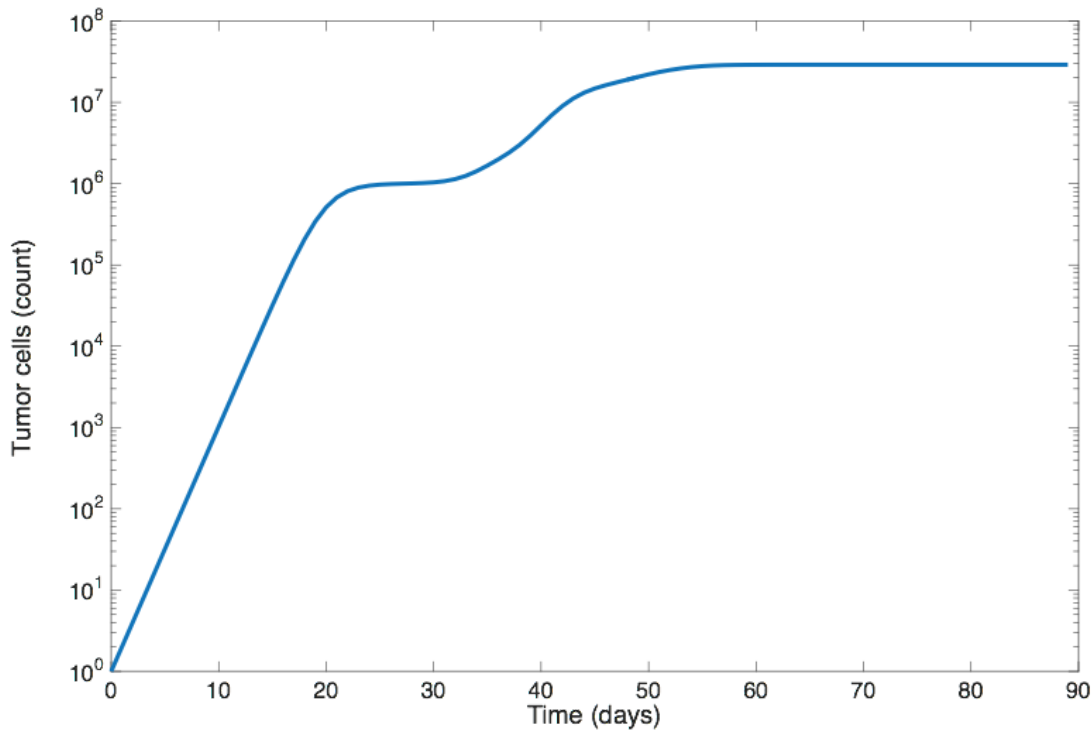
Results:

Figure 1: Cancer growth under natural tumor conditions ($N_1(1)=1$, $B(1)=0$, $n=90$). 45 sites were considered ovarian.

Under natural tumor conditions, we obtain a multilogistic curve, indicative of tumor self acceleration. Growth is initially exponential, but begins to level off before 20 days. However, at approximately 35 days, growth begins again at a still exponential but slower pace than before. Growth attempts to taper off around day 40, but the tumor self accelerates almost immediately, though at a much slower rate than before. The final tumor burden of approximately $3*10^7$ tumor cells is reached slightly after the 55 day mark (Figure 1).
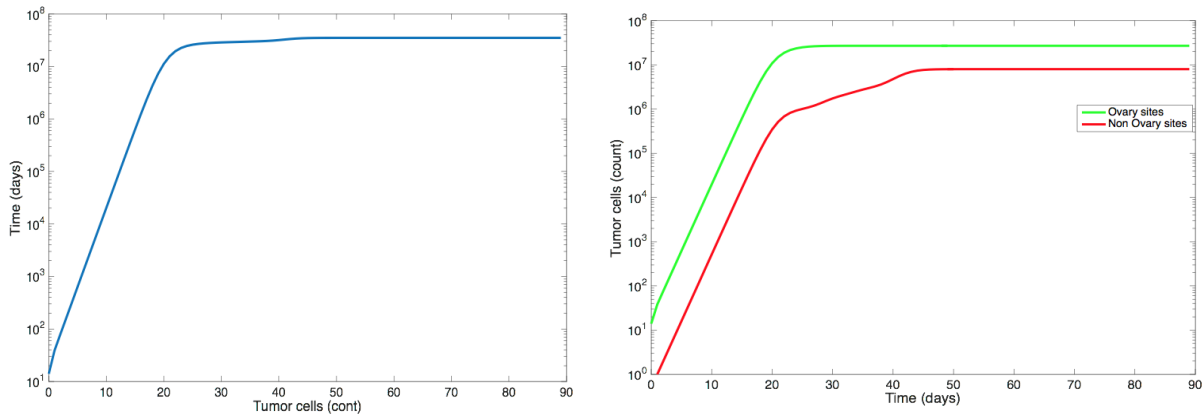

Figure 2: Cancer growth under experimental conditions ($N_1(1)=0$, $B(1)=100$, $n=89$). 44 sites were considered ovarian. **a)** Plot of all tumor cells in the body. **b)** Plots of tumor cells in the ovary and implanted elsewhere.

Under experimental conditions, tumor self acceleration still occurs, but less markedly. Growth occurs more quickly in the initial stages of metastasis as compared to natural tumor conditions (Figures 2a, 1). However, cancer growth overall still levels off close to the 20 day mark, and the secondary growth phase that starts at about 40 days is not easily noticeable in Figure 2a. However, Figure 2b reveals the inner mechanics of the system: while the tumors in the ovaries are do not seem to show self acceleration, the tumors in nonovarian sites display distinct multiphasic growth. Because the nonovarian sites are populated by cells an approximately an order of magnitude less than the ovarian sites, the growth is not as clearly displayed as it was under the natural tumor conditions.

Discussion

The results of the simulation under natural tumor evolution are more or less consistent with the results achieved by Scott, et. al. The system displays clearly marked secondary seeding events, accelerating the growth of the tumor (as shown in Figure 1). Furthermore, the steady state of the system is a tumor burden of $3*10^7$ cells, which is consistent with the Scott results. This phenomenon is also consistent with experiment; in particular, Kim, et. al. conclusively demonstrated that tumor secondary seeding is an important hallmark of metastasis.

However, in the exploration of the experimental condition of the model, we discover several new phenomena in the model. First, we realize that while the overall system clearly displays bilogistic behavior (Figure 2a), the ovarian cancer sites are merely logistic (Figure 2b). This appears counterintuitive, as ovarian cancer sites have a higher probability of seeding. Further analysis reveals that result comes about because seeding occurs early in the evolution of the ovarian site tumors: the higher p_i associated with seeding in an ovarian sites enables seeding to occur before the cancer has an opportunity to establish a period of stability. In contrast, the nonovarian sites have a much lower p_i, enabling them to show multilogistic behavior (Figure 2b). We also observe that Figure 2b displays a clear correlation between ovarian site saturation and nonovarian site secondary seeding. Secondary seeding in nonovarian sites does not begin until approximately 25 days, approximately 5 days after the ovarian sites achieve steady state.

Conclusion

A more thorough understanding of ovarian cancer metastasis is needed in order to help ameliorate disease progression more effectively. Secondary seeding and understanding the routes ovarian cancer metastasis takes throughout the body are essential in learning about the process of metastasis. Potential extensions of this model would incorporate more differences between potential metastatic sites, e.g. differentiating between liver and lung metastases. It is hoped that this model or a refinement thereof will be useful in understanding the problem of ovarian cancer metastasis.