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Cancer is a major cause of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012. The number of new cases is also expected to rise by around 70% over the next two decades. Although the death rate of cancer has dropped since the late twentieth century due to improvements in early detection and treatment, cancer remains to be a leading cause of death in the world and the second most common cause of death in the United States, only second to heart disease.

Cancer, also described as malignant tumor or neoplasm, is characterized by uncontrollable growth and spread of abnormal cells that invade the surrounding tissue. The transformation of a normal cell into a cancerous cell results from genetic and epigenetic alterations, which eventually spread through a population of cells. As the mutations accumulate, some cells acquire the ability to break off and form new tumors in other parts of the body far from the original tumor, a process known as metastasis. Cancer often becomes detectable clinically when distant metastases interfere with normal functions of organs and cause severe symptoms. Because of its systemic nature and the resistance of disseminated tumor cells to existing therapeutic agents, the emergence of metastasis greatly reduces the chance of successful treatment by chemotherapy or surgery. Moreover, metastasis can...
recur months or even years after successful treatment of the primary tumor. More than 90% of mortality from cancer is attributable to metastasis [5]. Therefore, it is crucial to gain a complete understanding of metastasis formation and progression in order to discover effective therapy for affected patients.

Despite its importance, the multistage process of metastasis remains not clearly understood. Mathematical models have proved useful for deriving a detailed understanding of cancer progression, identifying parameters the system is most sensitive to and making predictions about the overall dynamics. This paper aims to provide new insight into cancer metastasis using mathematical and computational tools as well as suggest optimal treatment methods for patients diagnosed with this formidable disease.

1.1 Biological Mechanism of Cancer Metastasis

Metastasis progression can be viewed as a complex succession of biological events, which are mediated by different types of metastasis related genes. The process, often termed as the invasion-metastasis cascade, involves the following basic steps – local invasion, intravasation, survival in the circulation, extravasation and colonization [5, 6].

Initially, the primary tumor is surrounded by an intact basement membrane, a specialized extracellular matrix that separates the epithelium from the underlying connective tissue. The basement membrane serves as an intrinsic barrier that prevents the spreading of cancerous cells. A change in adhesion, the initiation of cell motility and proteolysis of the extracellular matrix are required for the local invasion to occur, which typically arises from mutation [7]. The genes that determine these activities can be defined as metastasis initiation genes [6]. Transcription factors like TWIST and SLUG have been shown to mediate epithelial-mesenchymal transition (EMT), a process by which cells gain invasive properties.

These genetic changes result in the entry of cancer cells into the circulation, either directly or via the lymphatic system, which is called intravasation [5]. Tumor cells initiate the formation of new blood vessels within their microenvironment to supply nutrients to the cells and support their growth. Therefore, the mechanism is highly affected by the structural properties of tumor-associated blood vessels [5]. Some molecular changes can facilitate this process by enhancing the ability of tumor cells to penetrate epithelial walls.

Once having intravasated into the blood vessels, the circulating tumor cells (CTCs) must
overcome a variety of conditions in order to successfully survive in the circulation. Without the adhesion to the extracellular matrix, epithelial cells normally undergo a form of apoptosis called anoikis [8]. Moreover, hydrodynamic shear forces and attack from the immune system can also prevent CTCs from reaching distant organ sites [5]. Studies have suggested that many CTCs only spend very short periods of time in the circulation to escape from the bloodstream before anoikis is triggered [5, 9, 10]. In addition, a majority of CTCs are expected to become trapped in the capillaries soon after they enter the circulation, because their diameter (20-30 μm) is three to four times as large as that of the capillaries [5]. Therefore, the spatial distributions of CTCs within the bloodstream vary among different tumor types [10].

CTCs will eventually be arrested in a distant organ and rupture the vessel walls to make direct contact with parenchyma, the functional tissue of an organ [5]. This extravasation process should not be viewed as a mere reverse of intravasation, because the microenvironment and vascular permeability at metastatic sites are distinct from the primary tumor site [5]. Health tissues of the distant organs are likely to present more physical barriers to tumor cells. The characteristics of microenvironments also vary across different metastatic sites, contributing to organ-specific metastasis, an important concept that will be visited later.

In the event that the migratory cancer cells survive in the foreign tissue, they will first form a microcolony and try to adapt to the new environment. If successful, tumor cells persistently proliferate to form a metastatic tumor. It is worth noting that the colonization stage occurs inefficiently and is thus the rate-limiting step in metastatic dissemination [7].

The genetic profile of metastatic cancer has been an important topic of investigation. Particularly, pro-metastatic genes that confer metastatic potential to tumor cells are gradually being revealed. As early as 1986, the activation of the RAS oncogene was shown to cause a large number of metastatic nodules in mice [11]. A tumor suppressor gene CDH1 has been linked to both tumorigenesis and metastasis formation. CDH1 produces the cell-adhesion receptor E-cadherin, whose loss of function is characteristic of epithelial-mesenchymal transition (EMT) in local invasion [12]. NM23, another tumor suppressor gene, decreases *in vivo* metastatic abilities of colon cancer cells [4, 12], whereas the genetic inactivation of SMAD4 is highly correlated with metastasis formation in pancreatic cancer [13]. These examples suggest that a major pro-metastatic gene is sufficient to endow tumor cells with metastatic function [4, 13].
In addition to elucidating the molecular mechanism of the metastatic process, there is the need to address the growth dynamics of cancer metastasis and its connection with clinical treatments. Metastasis formation has been traditionally viewed as a late stage in tumorigenesis, because the metastatic function of cancerous cells may be acquired only when the tumor has reached a large size with pro-metastatic mutations [3]. This theory is supported by recent research which suggests that metastasis is a late event in the evolution of pancreatic cancer [14]. However, a different concept proposes that the metastatic ability is determined by early mutations in tumor development, and many patients may already have micrometastases at diagnosis of cancer [15]. Because the probability and size of metastases greatly influence diagnosis, prognosis and treatment methods, a clear understanding of the dynamics of metastasis progression is crucial to clinical success [4].

1.2 Existing Mathematical Models

Many mathematical models have been proposed to enhance the understanding of cancer metastasis dynamics, including logistic regression models, competition models, and Moran process models.

Bosl et al. designed a multivariate logistic regression model to predict the prognoses of patients with metastatic testicular cancer [16]. A competition model between tumor and normal cells during chemotherapy was developed by Panetta to investigate relapse due to a small number of remaining metastatic cells [17]. To study the connection between the delayed surgery and the risk of metastasis, Thames et al. proposed a mathematical model that determines the frequency of metastatic events in breast cancer. He showed that the delay increases the risk of metastatic events [18]. Wodarz examined the growth dynamics of metastatic tumors under the assumption that metastasis is an early event in tumorigenesis [19].

Notably, Michor and colleagues used Moran process to calculate the expected number of metastases from a primary tumor of constant size when metastatic ability arises from one mutation [20] and two mutations [21] of tumor cells. Considering the fact that most primary tumors constantly grow instead of being fixed in size, Ding et al. subsequently developed a model that analyzed metastasis of expanding tumors using branching process [22]. Haeno et al. also used branching process to investigate the effect of drug administration.
and tumor resection on tumor metastasis evolution and predicted survival time of cancer patients [4]. He applied the computational framework to well-annotated data of pancreatic cancer patients and suggested that therapies that reduce the growth rate of cancer cells early in treatment are more beneficial than upfront tumor resection [13].

1.3 Organ Tropism: Site-Specific Metastasis

One of the most interesting aspects of metastasis is the pattern of metastatic dissemination, but organ tropism has not been explored in detail in existing mathematical models. Physicians have noted that specific primary tumor types form metastases in only a limited subset of distant organs [5]. For example, breast cancer disseminates primarily to bone and lung and less frequently to liver and brain [6, 12]. Prostate cancer metastasizes to bone almost exclusively, creating osteoblastic lesions and mineralized bone matrix [12]. On the other hand, pancreatic cancer and colon cancer favor dissemination to the liver and lung [6, 12].

Experimental studies have shown that site-specific metastasis results from cell-to-cell recognition and specific adhesive interactions [23]. In other words, different primary tumors tend to metastasize to different sites with various rates, and therefore have their own primary metastatic sites. Besides, Cunningham et al. found that different primary tumors evolving on identical metastatic sites exhibit similar adaptive strategies, indicating the importance of studying specific features of metastatic sites [24]. Valastyan and Weinberg also suggested that specific microenvironments at metastatic sites strongly influence the fate of migratory tumor cells [5]. Moreover, metastatic sites have prognostic power clinically. For example, liver metastasis may be used as a predictor for chemotherapy responses in colorectal cancer [25] and bone metastasis is a good prognostic factor on breast cancer patient survival rate [26].

In this paper, I design and analyze a mathematical model that takes into account a variety of cell migration rates and cell growth rates for different metastatic sites. The model sheds light on optimal therapy design and the prediction of patient outcomes.
A stochastic mathematical model is developed to study the evolution of metastasis formation and secondary site selection. To account for the growing cancer cell population, the model is based on the branching process, a stochastic modeling approach with Markov properties and the assumption that each individual event occurs independently of the population size or composition [27–29].

2.1 Mathematical Framework

The cancer cells are considered to expand exponentially starting from a single cell that has not yet evolved the ability to metastasize in the primary tumor (state $0$). The exponential model is used here because it provides a better fit for the data of tumor cell growth [13]. In the model, the events follow a stochastic process: during each time step (measured as one cell division), a cell is chosen with a probability proportional to fitness for growth, death or dissemination to metastatic sites. The state-0 cells grow at rate $r_0$ and die at rate $d_0$. The metastatic ability is treated as the consequence of a single genetic or epigenetic change, for example the inactivation of NM23 [4, 12], based on biological evidence presented in the previous chapter. Such pro-metastatic event occurs with rate $u$ per cell division. Cells with the mutation become state-1 cells with growth rate $r_1$ and death rate $d_1$. They can then
migrate from the primary tumor to distant organ sites and establish metastatic colonies. The integrated probability of being exported from the primary tumor, surviving in the circulation and successfully founding a new colony at a metastatic site \(i\) is denoted by \(q_i\), to distinguish among different sites. The relative fitness of state-1 cells compared to state-0 cells can be expressed by 
\[
\omega_1 = \frac{(r_1 - d_1 - q_i)}{(r_0 - d_0)}
\]
because the export rate \(q_i\) leads to the loss of state-1 cells and thus its selective disadvantage. \(\omega_1 = 1\) suggests that pro-metastatic mutation does not endow primary tumor cells with a fitness advantage or disadvantage. The result is neutral. If \(\omega_1 > 1\), the mutation gives an advantage to primary tumor cells, possibly due to an increased growth rate or decreased death rate. If \(\omega_1 < 1\), the mutation gives a disadvantage to those cells through a decreased growth rate, increased death rate or an extremely large rate of export for state-1 cells. Once a state-1 cell is lodged in a distant organ, it resumes exponential growth with division and death rates specific to the new site, \(a_i, b_i\). The metastatic cells at site \(i\) are referred to as state-2-i cells. Similarly, we can derive the relative fitness of state-2-i cells as compared to state-1 cells: 
\[
\omega_2 = \frac{(a_i - b_i)}{(r_1 - d_1 - q_i)}
\]
If \(\omega_2 = 1\), the fitness of state-2-i cells is neutral. If \(\omega_2 > 1\), it is favorable and if \(\omega_2 < 1\), it is unfavorable. A schematic view of the mathematical framework is provided by Fig. 2.1.

Figure 2.1: Mathematical framework of the stochastic model.
Computer simulations of the stochastic model were performed. Let \( x, y, \) and \( z_i \) denote the total number of state-0, state-1 and state-2-\( i \) cells respectively, in which \( i \) specifies the \( i^{th} \) metastatic site. \( N_1 \) denotes the total number of all types of tumor cells at diagnosis, and \( N_2 \) denotes the total number of tumor cells at autopsy. Let \( I \) denote the total number of metastatic sites at autopsy. Here, diagnosis refers to the initial detection of tumor, and autopsy refers to the time of patient death when the tumor is assessed. The meaning of diagnosis and autopsy here is consistent with the available data for validation [13].

A change in \( x, y, \) and \( z_i \) can occur by cell division (possibly with mutation), cell death, or export from the primary site. Each time an export event occurs, a new metastatic colony at a different site is established. Based on the design of the math model, initially there is one state-0 cell and no state-1 or state-2 cells. Therefore, at \( t = 0, x = 1 \) and \( y = z_i = 0 \) for all \( i \in I \). The chance of each event occurring is proportional to its rate normalized by the sum of the rates of all possible events. The sum of rates is given by:

\[
\lambda = (r_0 + d_0)x + (r_1 + d_1 + \sum_i q_i)y + \sum_i (a_i + b_i)z_i
\]

The timing of the first event is given by a negative exponential distribution with mean \( 1/\lambda \). The stochastic process ends when all cells go extinct or the total cell number reaches a final size, \( N_1 \) at diagnosis or \( N_2 \) at autopsy.

We are thus able to derive the transition probabilities for all states. The probability that the number of state-0 cells, or unmutated primary tumor cells, increases by 1 is given by:

\[
Pr_{x \rightarrow x+1} = x r_0 (1 - u) / \lambda
\]

The number of state-1 cells increases by 1 either by cell division or mutation of the state-0 cells. Therefore, the probability that the number of state-1 cells increases by 1 is given by:

\[
Pr_{y \rightarrow y+1} = (x r_0 u + y r_1) / \lambda
\]

The number of state-2-\( i \) cells changes from 0 to 1 when a mutated cell with metastatic abil-
ity is exported to a metastatic site. Therefore, \( z_i \) increases by 1 when \( y \) decreases by 1. Besides, the number of total metastatic sites \( I \) increases by 1 because another new site is established. The probability is given by:

\[
Pr_{(y,z_i=0) \rightarrow (y-1,z_i=1)} = yq_i / \lambda 
\]

In addition, the probability that the number of state-2-i cells increases by 1 from a non-zero number is given by:

\[
Pr_{(y,z_i) \rightarrow (y,z_i+1)} = z_i a_i / \lambda 
\]

Similarly, we can derive the transition probabilities of \( x, y \) and \( z_i \) decreasing by 1:

\[
Pr_{x \rightarrow x-1} = xd_0 / \lambda \\
Pr_{(y,z_i) \rightarrow (y-1,z_i)} = yd_1 / \lambda \\
Pr_{z_i \rightarrow z_i-1} = z_i b_i / \lambda 
\]

The computer simulation of the mathematical model were performed using the exact stochastic simulation algorithm in C++. The parameter values for the model in this paper will be drawn from distributions of the estimated values by Haeno et al., who investigated pancreatic cancer progression using accurate autopsy data and estimated the model parameters including the growth rate, death rate, mutation rate and metastatic rate [13] (Table 1.). The estimations are highly valuable due to the scarcity of high-quality autopsy data. To account for variations in the dissemination rate of tumor cells to different metastatic sites, the export rate \( q_i \) is not treated as a constant as in the paper by Haeno et al.[13], but is assumed to be normally distributed. The growth and death rates at metastatic sites, \( a_i \) and \( b_i \), also have a normal distribution with mean and variance drawn from patient data presented by Haeno et al.[13].

A thousand independent runs of the stochastic process are executed to simulate random fluctuations. Results are recorded and analyzed to reveal the probability of metastasis at a given site, the expected number of metastatic sites and the expected total number of metastatic cells. The parameter dependence of each quantity is also investigated.
Table 1. Parameter values of the mathematical model to investigate cancer metastasis progression based on data from Haeno et al.[13].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter</th>
<th>Value (per cell division)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation rate</td>
<td>$u$</td>
<td>$6.31 \times 10^5$</td>
</tr>
<tr>
<td>Growth rate of primary tumor cells</td>
<td>$r_0$</td>
<td>0.16</td>
</tr>
<tr>
<td>Death rate of primary tumor cells</td>
<td>$d_0$</td>
<td>0.0016</td>
</tr>
<tr>
<td>Growth rate of cells with metastatic potential</td>
<td>$r_1$</td>
<td>0.16</td>
</tr>
<tr>
<td>Death rate of cells with metastatic potential</td>
<td>$d_1$</td>
<td>0.0016</td>
</tr>
<tr>
<td>Export rate of cells with metastatic potential</td>
<td>$q$</td>
<td>$N(6.31 \times 10^{-7}, \sigma^2)^*$</td>
</tr>
<tr>
<td>Growth rate of metastatic cells</td>
<td>$a$</td>
<td>$N(0.58, 2.72)$</td>
</tr>
<tr>
<td>Death rate of metastatic cells</td>
<td>$b$</td>
<td>$N(0.0058, 2.72 \times 10^{-4})$</td>
</tr>
<tr>
<td>Size of the tumor at diagnosis</td>
<td>$N_i$</td>
<td>$10^{N(70, 0.59)}$</td>
</tr>
</tbody>
</table>
Simulation Results and Analytical Approximations

Direct computer simulation and derived analytical approximations are used to investigate the relationship between the distribution of the export rate \( q \) of disseminating tumor cells and each of the three important quantities in the clinical context at diagnosis: the probability of metastasis regardless of treatment options, the expected number of metastatic sites and the expected total number of tumor cells.

3.1 Probability of Metastasis

Let \( P(x) \) denote the probability that the first successful branch of state-1 cells arises when there are \( x \) state-0 cells. It is the product of the probability that no successful branch arises when the number of state-0 cells is less than \( x, \) \( (1, 2, 3, \ldots, x - 1) \). Assuming that the number of state-1 cells created when there are \( x \) state-0 follows a Poisson distribution with mean \( \alpha_x \), Iwasa et al. showed that \( \alpha_x = u / (1 - d_0 / r_0) \), which is independent of \( x \) [30]. We have

\[
P(x) = \prod_{i=1}^{x-1} e^{-\omega t_i} (1 - e^{-\omega t_i})
\]
where $\omega = 1 - (d_1 + q)/r_1$ is the non-extinction probability, with $q$ being the normal random variable. We substitute $\beta$ for $\omega \alpha_x$ and have [31]:

$$P(x) = e^{-(x-1)/\beta} (1 - e^{-\beta})$$

We then consider the probability of having at least one surviving state-2 cell which arises from a lineage of state-1 cells. Let $k$ be the number of state-1 cells present when the total cell number reaches $N_1$ at diagnosis and $M$ be the mean of export events occurring when the number of state-1 cells increases from 1 to $k$. Because the unit rate of increase of state-1 cell is $r_1 - d_1 - q$ and the average unit rate of export is $\bar{q}$,

$$M = \frac{(k - 1)\bar{q}}{r_1 - d_1 - q} \approx \frac{k\bar{q}}{r_1 - d_1 - q}$$

with $k \gg 1$. Therefore the probability that at least one metastatic site is established is given by

$$Q(x) = 1 - \exp\left(\frac{-k\bar{q}(1 - \bar{b}/\bar{a})}{r_1 - d_1 - q}\right)$$

In the equation, $1 - \bar{b}/\bar{a}$ is the probability of non-extinction of a state-2 lineage, in which $\bar{a}, \bar{b}$ are the average growth and death rates at metastatic sites. $k = \exp[(r_1 - d_1 - q)t_x]$ in which $t_x$ is the time between the emergence of the first successful state-1 cell and when the total number of state-0 and state-1 cells reaches $N_1$. We can solve for $t_x$ numerically using $xe^{(r_0-d_0)t_x} + e^{(r_1-d_1-q)t_x} = N_1$ [4].

Finally, the probability of metastasis at diagnosis is given by

$$P_d = \sum_{x=1}^{N_1-1} P(x)Q(x)$$

$$= \sum_{x=1}^{N_1-1} e^{-(x-1)/\beta} (1 - e^{-\beta})(1 - \exp\left(\frac{-k\bar{q}(1 - \bar{b}/\bar{a})}{r_1 - d_1 - q}\right))$$

The probability of metastasis at diagnosis is shown in Fig. 3.1. The analytical approximation accurately predicts the results of the computed simulation. An increase in the variance of the export rate increases the probability of metastasis at diagnosis. It suggests that
a higher level of variation across different metastatic sites or a greater deviation from the mean makes it more likely that the patient harbors metastatic cancer at diagnosis.

![Figure 3.1: The probability of metastasis at diagnosis. The red curve is from the prediction of the analytical approximation derived above, while the dots are based on the results of the exact stochastic simulation.]

### 3.2 Expected Number of Metastatic Sites

Based on the derivation presented in 3.1, it is easy to obtain the expected number of metastatic sites when there are \( x \) state-0 cells:

\[
E_x = \frac{e^{(r_1-d_1-q)\beta}q(1 - \bar{b}/\bar{a})}{r_1 - d_1 - q}
\]

Therefore, the expected number of metastatic sites at diagnosis given that metastasis has occurred is:

\[
E_d = \frac{1}{P_d} \sum_{x=1}^{N_1-1} e^{-(x-1)/\beta} (1 - e^{-\beta}) E_x
d\]

\[
= \frac{1}{P_d} \sum_{x=1}^{N_1-1} e^{-(x-1)/\beta} (1 - e^{-\beta}) \frac{e^{(r_1-d_1-q)\beta}q(1 - \bar{b}/\bar{a})}{r_1 - d_1 - q}
\]
The distribution of the number of metastatic sites at diagnosis for different variance values is shown in Fig. 3.2. The histogram shows that the distribution peaks at around $Ed = 2 - 4$ for all three variance values. A larger variance of the export rate $q$ corresponds to a wider spread of the number of metastatic sites, as expected.

![Histogram of metastatic sites](image-url)

**Figure 3.2:** The distribution of the number of metastatic sites at diagnosis. The black bar is for $\sigma^2 = 10^{-7}$. The red bar is for $\sigma^2 = 10^{-6}$. The yellow bar is for $\sigma^2 = 10^{-5}$

### 3.3 Expected Total Number of Cells

We now derive the expected total number metastatic cells at all sites at diagnosis. Consider $L(\tau)$, the probability that a state-2 cell is generated at time $\tau$ from a state-1 lineage, which should be the product of the probability that no metastasis occurs before time $\tau$ ($P_A$) and the probability that one metastatic site is established at $\tau$ ($P_B$). Using results from 3.1, we
can see that:

\[
P_A = \exp\left(- \int_0^\tau \frac{qe^{(r_1-d_1-q)\tau}(1 - \bar{b}/\bar{a})}{r_1 - d_1 - q} dt\right)
= \exp\left(-\left(e^{(r_1-b_1-q)\tau} - 1\right)q(1 - \bar{b}/\bar{a})\right)
\]

\[
P_B = 1 - \exp\left(-qe^{(r_1-d_1-q)\tau}(1 - \bar{b}/\bar{a})\right)
\]

Therefore,

\[
L(\tau) = \exp\left(-\left(e^{(r_1-b_1-q)\tau} - 1\right)q(1 - \bar{b}/\bar{a})\right) \times \left(1 - \exp\left(-qe^{(r_1-d_1-q)\tau}(1 - \bar{b}/\bar{a})\right)\right)
\]

Let \( \gamma_{x,\tau} \) denote the amount of time between the emergence of the first successful state-2 lineage, which arises from state-1 cells produced when there were \( x \) state-0 cells, and diagnosis. \( \gamma_{x,\tau} \) is given by \( xe^{(r_0-d_0)(\tau+\gamma_{x,\tau})} + e^{(r_1-d_1-q)(\tau+\gamma_{x,\tau})} + e^{(\bar{a}-\bar{b})\gamma_{x,\tau}} = N_1 \) [4]. Because the state-2 cells at metastatic sites follow exponential growth until diagnosis, and \( t_x \) is the time period during which state-1 cells may migrate from the primary tumor, the expected number of state-2 cells at diagnosis is:

\[
R(x) = \int_0^{t_x} L(\tau)e^{(\bar{a}-\bar{b})\gamma_{x,\tau} d\tau}
\]

Hence, the expected total number of cells at all metastatic sites given that metastasis has occurred can be expressed as:

\[
T_d = \frac{1}{P_d} \sum_{x=1}^{N_1-1} P(x)R(x)
= \frac{1}{P_d} \sum_{x=1}^{N_1-1} e^{-(x-1)/\beta}(1 - e^{-\beta}) \int_0^{t_x} L(\tau)e^{(\bar{a}-\bar{b})\gamma_{x,\tau} d\tau}
\]

Because the expression \( P(x) \) decreases with \( x \), intuitively we can see that when the primary tumor size becomes very large, the length of time during which there are exactly \( x \) primary tumor cells becomes very short. The expected number of mutations when there are \( x \) state-0 cells becomes independent of \( x \) [4].
A stochastic mathematical model is developed to analyze metastatic progression and localization of metastasis using branching process for a growing tumor. With computer simulations and analytical approximations, the model is used to investigate the probability of metastasis at a given site, the expected number of metastatic sites and the expected number of metastatic cells at those sites. The parameters are validated by clinical data from pancreatic cancer patients. The model shows that a large variation in the dissemination rate of the tumor cells is correlated with higher probability of metastasis at diagnosis and a wider spread of the distribution of metastatic sites.

The model is helpful to predict the likelihood of cancer metastasis at diagnosis and develop optimal treatment strategies for them by showing the relationship between the distribution of metastasis export rate and clinically relevant measurements of tumor burden. In future studies, it will be important to obtain more clinical data on other types of cancer to further validate the model.
References


