A Stochastic Model for Cancer Metastasis: Branching Stochastic Process with Settlement

CHRISTOPH FREI
Department of Mathematical and Statistical Sciences
University of Alberta, Edmonton, Alberta, T6G2G1, Canada
cfrei@ualberta.ca

THOMAS HILLEN
Department of Mathematical and Statistical Sciences
University of Alberta, Edmonton, Alberta, T6G2G1, Canada
thillen@ualberta.ca

ADAM RHODES
Department of Mathematical and Statistical Sciences
University of Alberta, Edmonton, Alberta, T6G2G1, Canada
arhodes@ualberta.ca

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We introduce a new stochastic model for metastatic growth, which takes the form of a *branching stochastic process with settlement*. The moving particles are interpreted as clusters of cancer cells while stationary particles correspond to micro-tumors and metastases. The analysis of expected particle location, their locational variance, the furthest particle distribution, and the extinction probability leads to a common type of differential equation, namely, a non-local integro-differential equation with distributed delay. We prove global existence and uniqueness results for this type of equation. The solutions' asymptotic behavior for long time is characterized by an explicit index, a *metastatic reproduction number* R_0, and we prove that metastases spread for $R_0 > 1$ and become extinct for $R_0 < 1$. Using metastatic data from mouse experiments, we show the suitability of our framework to model metastatic cancer.

Keywords: branching processes, birth-jump processes, cancer metastasis, integro-differential equations, reproduction number.

1. Introduction

Metastasis is the leading cause of cancer related deaths. It is the process by which cancer spreads from a primary site to distant secondary sites. Because of its implication in over 90% of all cancer-related deaths (Gupta and Massague, 2006; Valastyan and Weinberg, 2011), it is recognized as one of the *hallmarks* of cancer (Hanahan and Weinberg, 2011). The *metastatic cascade* (Gupta and Massague, 2006; Valastyan and Weinberg, 2011; Riggi et al., 2018) provides a mechanistic description of the process, viewing it as an ordered sequence of biological events. Growth of the primary tumor leads to local invasion of surrounding normal tissue. Such local invasion eventually encounters a vessel of the lymphatic or circulatory system. Individual cancer cells — or small clusters of cells — can enter these vessels (intravasate), thereby gaining access to rapid transport throughout the body. If these circulating cells survive their journey and exit the vessel at some distant site (extravasate), they may be able to establish a micrometastasis. Evasion of local defenses and adjustment to the hostile foreign environment can see

the *micro*metastasis grow into a *macro*metastasis. Further growth may eventually lead to a secondary tumor.

The stochastic nature of metastasis makes experimental studies difficult, meaning that a thorough understanding of the process is lacking. While some of the steps in the metastatic cascade are well understood — for example, growth and invasion of primary tumors are well studied both experimentally and theoretically (see the reviews in Riggi et al. (2018); Scott et al. (2013)) — understanding of others remains elusive. Travel *to*, and establishment *at* secondary sites are particularly poorly understood, with many theoretical investigations ignoring these aspects altogether. Though recent results (Kaplan et al., 2005) have led to novel theories that metastasis may be more intricately orchestrated than previously thought (Shahriyari, 2016), the process is still believed to be largely stochastic.

Based on these observations, we introduce a new stochastic framework for metastatic spread in the form of a *branching stochastic process with settlement*. This model captures simultaneously temporal and locational dynamics. Stationary tumors emit, or shed, small clusters of cells into the vasculature at random times. These shed cells can then move randomly through the body, modeled by a spatial stochastic process. The moving clusters — also known as circulating tumor cells/clusters (CTCs) — can settle randomly according to a given rate. If the CTCs successfully settle, they may establish a secondary tumor, which itself may shed new CTCs into the blood stream. Both moving and stationary groups of cancer cells die, each at their own rate.

In contrast to existing stochastic metastasis models, our framework accounts for both travel between primary and secondary sites and establishment at the secondary sites. Hartung and Gomez (2014) propose a stochastic model with secondary metastatic emission as a cascade of Poisson point processes and link it to the deterministic model introduced by Iwata et al. (2000). Differently from us, Hartung and Gomez (2014) model only the size development over time and not the location.

From a probabilistic viewpoint, our model generalizes branching Brownian motion to arbitrary dynamics and the inclusion of settlement and death of particles. Branching Brownian motion has been analyzed for more than fifty years, starting with seminal work (Ikeda et al., 1968; McKean, 1975) on the fundamental link between branching Brownian motion and the Fisher-Kolmogorov-Petrovsky-Piscounov equation. Since then branching Brownian motion has been intensively studied in its own right. In statistical mechanics, branching Brownian motion is used for models of spin glasses (Bovier, 2016). Recently, branching processes have been found useful in simulating semi-linear partial differential equations (Henry-Labordere et al., 2017, 2014). To the best of our knowledge, this paper is the first to introduce branching processes with settlement and study their applications in the context of cancer metastasis.

For the branching stochastic process with settlement, we prove two sets of main results. The first set deals with the characterization of the following key quantities in our stochastic model: the expected location F of metastases, their locational variance V, the distribution H of the furthest invading metastasis, the metastatic extinction probability Q, and the ratio of moving versus stationary cancer cell groups. We show that each of the first four quantities — F, V, H, and Q — satisfies a non-local integro-differential equation with distributed delay. These non-local differential equations are of the same type for all cases and are non-linear in some cases. We present a detailed analysis of these non-local differential equations, including positivity, and local and global existence of solutions.

The second set of main results provides a simple classification of the asymptotic behavior. Despite the model complexity and stochasticity, we are able to find a *metastatic reproduction number* R_0, which is explicitly given in terms of the rates of metastatic shedding, settlement, and death. We prove a global stability result of extinction of metastases for $R_0 < 1$ and growth for $R_0 > 1$. By parametrizing the model on experimental mouse metastatic data, we numerically explore the resulting metastatic pattern

and confirm the suitability of our framework to model metastatic cancer.

The remainder of this paper is organized as follows. Section 2 introduces the model, presents the main results and relates the stochastic model to integro-differential equations. In Section 3, we analyze these integro-differential equations in more detail and characterize their asymptotic behavior using the metastatic reproduction number. Section 4 shows how our framework can be applied in the context metastatic cancer while Section 5 concludes and discusses possible extensions.

2. Branching stochastic processes with settlement

We define the *branching stochastic process with settlement* as follows: We start with one tumor that is located at locational position 0. We assume that the tumor sheds individual cells and small groups of cells into the circulatory system. It is believed that such CTCs are most responsible for metastasis formation (Friedl and Mayor, 2017). Hence, in this model, we focus on the shedding of cell clusters. At a random time ν, the primary tumor emits a cell cluster, which starts moving randomly. We model the movement of this cell cluster by a d-dimensional stochastic process $(B(t))_{t\geqslant 0}$ with cumulative distribution function $G(t,x) = P[B(t) \leqslant x]$ for $x \in \mathbb{R}^d$ and $t \geqslant 0$. Here and in the following, inequalities between vectors are understood element-wise: $y \leqslant x$ for $x, y \in \mathbb{R}^d$ if $y^i \leqslant x^i$ for all $i = 1, \dots, d$. We assume that for every fixed t, $G(t,.)$ is absolutely continuous so that there is a density function $g(t,.)$ with $G(t,x) = \int_{(-\infty,x^1]\times\cdots\times(-\infty,x^d]} g(t,y)\,\mathrm{d}y$ for all $x \in \mathbb{R}^d$. An example for $(B(t))_{t\geqslant 0}$ is a d-dimensional Brownian motion, in which case g is the multivariate normal density function $g(t,y) = \frac{1}{\sqrt{(2\pi)^d t \det \Sigma}} \mathrm{e}^{-\frac{1}{2t} y^\top \Sigma^{-1} y}$ for a positive-definite covariance matrix Σ, but our general framework allows for more realistic spatial processes $(B(t))_{t\geqslant 0}$. The primary tumor stays at the same location until it dies. We assume that the shedding time ν is exponentially distributed, $\nu \sim \mathrm{Exp}(\mu)$ for some parameter $\mu \geqslant 0$, using the convention that $\nu = \infty$ if $\nu \sim \mathrm{Exp}(0)$.

After an additional random time τ (namely, at time $\nu + \tau$), the cell cluster settles down and forms a metastasis. We assume that τ is exponentially distributed, $\tau \sim \mathrm{Exp}(\lambda)$ for some parameter $\lambda \geqslant 0$. When the cell cluster has settled down, it requires time to grow into a metastasis until it is able to shed cell clusters on its own. We model this time again with an exponential distribution with parameter $\mu \geqslant 0$. Established metastasis and the primary tumor will continue to emit further cell clusters after a time which is exponentially distributed with the same parameter $\mu \geqslant 0$, independently of the other random variables and processes. Cell clusters that are moving are destroyed at a rate $\delta_1 \geqslant 0$ while stationary tumors die at a rate $\delta_2 \geqslant 0$, again independently of the other particles, the movement and the growth. The process is repeated ad infinitum. Figure 1 illustrates our model.

We now extend the notion from cell clusters and metastases to particles since the branching stochastic process with settlement is also relevant to other applications such as seed dispersal, epidemic spread, and forest fire spread. In those cases, particles would refer to plant seeds, infectious agents, and burning branches, respectively. Hence "particle" can have very different meaning. In this paper, our focus is on CTCs for moving particles and metastases for stationary particles.

We denote by $N(t)$ the number of particles born before time t. Their positions at time t are $X_i(t)$ for $1 \leqslant i \leqslant N(t)$ where we enumerate the particles by their birthdates. For fixed t and i, $N(t)$ and $X_i(t)$ are random variables with values in $\mathbb{N}$ and $\mathbb{R}^d$, respectively. We denote by $M(t)$ the number of particles alive at time t. We are interested in the following quantities:

- expected location $F(t,x) = E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right]$: the expected number of particles located in the set $(-\infty,x^1] \times \cdots \times (-\infty,x^d]$ at time t,

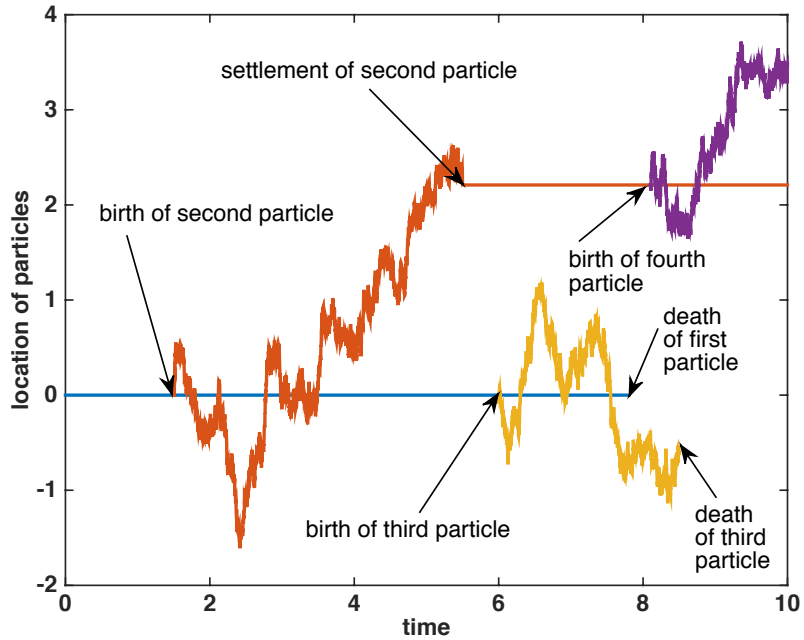

FIG. 1. Illustration of a branching stochastic process with settlement. Color figure online.

- locational variance $V(t,x) = \mathrm{Var}\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right]$: the variation in the number of particles located in $(-\infty,x^1]\times\cdots\times(-\infty,x^d]$ at time t due to randomness,

- furthest particle distribution $H(t,x) = P[\max_{i=1,\ldots,N(t)} X_i(t) \leqslant x]$: the probability that all particles are located in $(-\infty,x^1]\times\cdots\times(-\infty,x^d]$ at time t,

- survival probability $Q(t) = P[M(t) > 0]$: the probability that there is at least one particle alive at time t,

where we use the convention that $\mathbb{1}_{X_i(t)\leqslant x}$ is zero for all x and times t after the death time of particle i. We set $H(t,x) = 0$ for all x if no more particle exists at time t.

2.1 *Characterization via integro-differential equations*

We use the above branching stochastic process with settlement to find a common type of equation for the expected location F, the variance V, the distribution of the furthest particle H and the survival probability Q.

THEOREM 2.1 Consider the branching stochastic process with settlement defined above. The quantities

F, V, H, Q satisfy

$$\begin{aligned} F_t(t,x) &= -\delta_2 F(t,x) + \mu \mathrm{e}^{-(\lambda+\delta_1)t} G(t,x) \\ &\quad + \lambda\mu \int_0^t \int_{\mathbb{R}^d} F(t-u,x-z) g(u,z) \mathrm{e}^{-(\lambda+\delta_1)u} \,\mathrm{d}z\mathrm{d}u, \end{aligned} \tag{2.1}$$

$$\begin{aligned} V_t(t,x) &= -\delta_2 V(t,x) + \mu \mathrm{e}^{-(\lambda+\delta_1)t} h(t,x) \\ &\quad + \lambda\mu \int_0^t \int_{\mathbb{R}^d} V(t-u,x-z) g(u,z) \mathrm{e}^{-(\lambda+\delta_1)u} \,\mathrm{d}z\mathrm{d}u, \end{aligned} \tag{2.2}$$

with

$$\begin{aligned} h(t,x) &= G(t,x) + \mathrm{e}^{(\lambda+\delta_1)t} \frac{\delta_2}{\mu} F^2(t,x) \\ &\quad + \lambda \int_0^t \int_{\mathbb{R}^d} F^2(t-u,x-z) g(u,z) \mathrm{e}^{(\lambda+\delta_1)(t-u)} \,\mathrm{d}z\mathrm{d}u, \end{aligned}$$

$$\begin{aligned} H_t(t,x) &= \left[\mu \mathrm{e}^{-\lambda t}(1-\mathrm{e}^{-\delta_1 t}(1-G(t,x))) - (\mu+\delta_1)\right] H(t,x) \\ &\quad + \lambda\mu H(t,x) \int_0^t \int_{\mathbb{R}^d} H(t-u,x-z) g(u,z) \mathrm{e}^{-\lambda u} \,\mathrm{d}z\mathrm{d}u, \end{aligned} \tag{2.3}$$

$$\begin{aligned} Q'(t) &= -\left(\delta_2 + \mu \mathrm{e}^{-(\lambda+\delta_1)t}\right) Q(t) + \mu \mathrm{e}^{-(\lambda+\delta_1)t} \\ &\quad + \lambda\mu(1-Q(t)) \int_0^t Q(t-s) \mathrm{e}^{-(\lambda+\delta_1)s} \,\mathrm{d}s. \end{aligned} \tag{2.4}$$

Before we present the proof of Theorem 2.1 in Section 2.3, we bring the above four equations (2.1)–(2.4) into a common form using a convolution notation. We encounter integral kernels that depend on one variable and on two variables. We use the same convolution symbol for both cases; given two kernels $k_1(t,x)$ and $k_2(t)$ and two test functions $f(t,x)$ and $g(t)$, we denote

$$\begin{aligned} k_1 * f(t,x) &:= \int_0^t \int_{\mathbb{R}^d} f(t-u,x-z) k(u,z) \,\mathrm{d}z\mathrm{d}u \\ k_2 * g(t) &:= \int_0^t g(t-u) k(u) \,\mathrm{d}u. \end{aligned}$$

Then we combine equations (2.1)–(2.4) in the compact form

$$f_t = -qf + p + (r_1 + r_2 f)\, k * f, \tag{2.5}$$

where we identify parameters and functions as shown in Table 1.

In Section 3, we will analyze the general non-local integro-differential equation with distributed delay (2.5) and show positivity as well as local and global existence of solutions using a fixed-point argument. For the qualitative analysis, we encounter an index R_0, which can be understood as the *metastatic reproduction number*:

$$R_0 = \frac{\lambda}{\delta_1 + \lambda} \frac{\mu}{\delta_2}. \tag{2.6}$$

The fist factor $\lambda/(\delta_1+\lambda)$ denotes the settlement rate divided by the sum of the settlement rate and the death rate during movement. It describes the odds of being still alive while settling. The second factor in

(2.6), $\frac{\mu}{\delta_2}$, which refers to stationary particles, can be explained similarly, but here the effect of births of new particles needs to be considered. Indeed, when the ratio between shedding rate μ and total change rate $\delta_2+\mu$ (stationary deaths and shedding) is summed over all potential offsprings of the particles, we obtain

$$\sum_{j=1}^{\infty}\Big(\frac{\mu}{\delta_2+\mu}\Big)^j=\sum_{j=0}^{\infty}\Big(\frac{\mu}{\delta_2+\mu}\Big)^j-1=\frac{1}{1-\mu/(\delta_2+\mu)}-1=\frac{\mu}{\delta_2},$$

regaining the second term in (2.6).

Before we go into the details, we paraphrase the main results, assuming $\mu>0$ and $\lambda>0$:

- **Main result 1:** *Under suitable assumptions (A1), defined later, the solutions to the above integro-differential equations (2.1)–(2.4) exist as mild solutions globally in time, whereby the two probabilities H and Q are bounded by 1. See Theorem 3.1 for global existence and uniqueness.*

- **Main result 2:** *The asymptotic behavior is characterized by R_0:*

  - $R_0<1$*: The expected number of particles shrinks exponentially and the particles die out asymptotically with certainty.*

  - $R_0>1$*: The expected number of particles grows exponentially and the asymptotic survival probability is given by $1-1/R_0\in(0,1)$.*

  - $R_0=1$*: The particles die out asymptotically with certainty while their number explodes on a set with vanishing probability so that their expected number converges to a finite limit $\frac{1+\lambda/\delta_2}{\delta_2/\mu+\lambda/\delta_2}$.*

  See Lemma 3.3 for a threshold result of the survival probability Q and Corollary 3.1 for the asymptotic behavior of the expected particle number $E[M(t)]$.

Note that the survival probability in case $R_0>1$ equals $1-1/R_0$, which corresponds to the critical immunization threshold in common models for infectious diseases (Hethcote, 2000). As we will explain in Section 3.2, our second main result can be seen as a compact characterization in terms of R_0 for the extinction-survival dichotomy of two-type branching processes.

TABLE 1 *Parameter values for the different cases of expected location F, locational variance V, distribution of the furthest particle H and survival probability Q, using the abbreviation $q_H(t,x)=\mu+\delta_1-\mu e^{-\lambda t}(1-e^{-\delta_1 t}(1-G(t,x)))$.*

Case	r_1	r_2	$q(t,x)$	$p(t,x)$	$k(u,z)$
F	1	0	δ_2	$\mu e^{-(\lambda+\delta_1)t}G(t,x)$	$\lambda\mu e^{-(\lambda+\delta_1)u}g(u,z)$
V	1	0	δ_2	$\mu e^{-(\lambda+\delta_1)t}h(t,x)$	$\lambda\mu e^{-(\lambda+\delta_1)u}g(u,z)$
H	0	1	$q_H(t,x)$	0	$\lambda\mu e^{-\lambda u}g(u,z)$
Q	1	-1	$\delta_2+\mu e^{-(\lambda+\delta_1)t}$	$\mu e^{-(\lambda+\delta_1)t}$	$\lambda e^{-(\lambda+\delta_1)u}$

2.2 *Instantaneous relocation*

In many biological situations, the time scale of movement is very different from the time scale of reproduction or death. Most mammals, for example, explore their environment on a daily basis, while they reproduce once per year or less. And even cells in tissues can travel relative large distances in minutes, while typical cell cycles are about 8–12 h or longer. Hence on the macroscopic time scale of birth and death, relocation appears to be instantaneous. To model this situation, we consider the limit $\lambda \to \infty$ in (2.5). When individuals are moving, they will jump immediately to a new location with density function of the distances travelled given by $g(0,x)$. We will then ignore the time in $g(0,x)$ and simply use a spatial relocation density $g(x)$.

For fixed t, we consider a common term in (2.5)

$$\lim_{\lambda\to\infty}\int_0^t\int_{\mathbb{R}^d} f(t-u,x-z)g(u,z)\lambda\mathrm{e}^{-(\lambda+k_1)u}\,\mathrm{d}z\,\mathrm{d}u = \int_{\mathbb{R}^d} f(t,x-z)g(0,z)\,\mathrm{d}z.$$

Using integration by parts yields

$$\begin{aligned}
&\int_0^t\int_{\mathbb{R}^d} f(t-u,x-z)g(u,z)\lambda\mathrm{e}^{-(\lambda+k_1)u}\,\mathrm{d}z\,\mathrm{d}u\\
&= \underbrace{-\frac{\lambda}{\lambda+k_1}\mathrm{e}^{-(k_1+\lambda)t}\int_{\mathbb{R}^d} h_0(x-z)g(t,z)\,\mathrm{d}z}_{\to 0 \text{ for } \lambda\to\infty} + \int_{\mathbb{R}^d} f(t,x-z)g(0,z)\,\mathrm{d}z\\
&\quad \underbrace{-\int_0^t\int_{\mathbb{R}^d} f_t(t-u,x-z)g(u,z)\frac{\lambda}{\lambda+k_1}\mathrm{e}^{-(\lambda+k_1)u}\,\mathrm{d}z\,\mathrm{d}u}_{\to 0 \text{ for } \lambda\to\infty \text{ by monotone convergence}}.
\end{aligned}$$

Applying this scaling to the four equations (2.1)–(2.4) from Theorem 2.1 and using $g(x)$ instead of $g(0,x)$, we find

$$F_t(t,x) = -\delta_2 F(t,x) + \mu\int_{\mathbb{R}^d} F(t,x-z)g(z)\,\mathrm{d}z, \tag{2.7}$$

$$V_t(t,x) = -\delta_2 V(t,x) + \mu\int_{\mathbb{R}^d} V(t,x-z)g(z)\,\mathrm{d}z, \tag{2.8}$$

$$H_t(t,x) = -(\mu+\delta_1)H(t,x) + \mu H(t,x)\int_{\mathbb{R}^d} H(t,x-z)g(z)\,\mathrm{d}z, \tag{2.9}$$

$$Q'(t) = (\mu-\delta_2)Q(t)\left(1-\frac{\mu Q(t)}{\mu-\delta_2}\right). \tag{2.10}$$

The equations for the instantaneous relocation case (2.7)–(2.9) are linear integral equations as they have been studied in the classical literature (Krasnoselskii, 1964). They are also of the form of *birth-jump processes* as introduced by Hillen et al. (2015). Hence the branching stochastic process with settlement appears as a generalization of birth-jump processes.

The metastatic reproduction number (2.6) becomes in this case

$$\lim_{\lambda\to\infty} R_0 = \frac{\mu}{\delta_2}$$

The survival probability Q satisfies a logistic differential equation (2.10), which can be analyzed quickly. If $R_0 < 1$, then the origin is asymptotically stable, and solutions converge to 0: metastasis dies out. If

$R_0 > 1$, then Q converges to a limit

$$\lim_{t\to\infty} Q(t) = 1 - \frac{1}{R_0}.$$

If $R_0 = 1$, then $Q(t) = Q(0)$ is constant.

This also corresponds to the classical result for the asymptotic extinction probability of a birth-death process; see, for example, Section 4.4 of Durrett (2012). Indeed, in the limit $\lambda \to \infty$, the number of particles evolves according to a Markov chain starting at 1 and with jump rates $q(i,i+1) = \mu i$ and $q(i,i-1) = \delta_2 i$ when there are i particles.

2.3 *Derivation of the integro-differential equations (proof of Theorem 2.1)*

The main idea to derive equations (2.1)–(2.4) from Theorem 2.1 is to use a renewal argument based on the recursive structure of branching stochastic processes with settlement. Since this goes similarly for the different functions, F, V, H, and Q, we give a detailed proof in the case of F and mention afterwards how to start the proofs for V, H and Q, with the subsequent analysis being done analogously to that of F. We start by conditioning on time ν of the birth of the second particle, which means writing

$$F(t,x) = E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right] = \int_0^\infty E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\middle|\nu = s\right]\mu \mathrm{e}^{-\mu s}\,\mathrm{d}s. \tag{2.11}$$

In the event $\{\nu > t\}$, the birth of the second particle happens only after time t so that at time t either only the first particle exists, which is located at zero, or no particle at all exists if the first particle has died before time t. We denote by $A_2(t)$ the event that the first particle has not died before time t, which has probability $P[A_2(t)] = \int_t^\infty \delta_2 \mathrm{e}^{-\delta_2 s}\,\mathrm{d}s = \mathrm{e}^{-\delta_2 t}$. For $s > t$, we have

$$E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\middle|\nu = s\right] = E\left[\mathbb{1}_{A_2(t)}\mathbb{1}_{X_1(t)\leqslant x}\middle|\nu = s\right] = \mathrm{e}^{-\delta_2 t}\mathbb{1}_{0\leqslant x}.$$

On the other hand, in the event $\{\nu \leqslant t\}$, the second particle was born before time t if the first particle was then alive. We need to distinguish two cases on $\{\nu \leqslant t\}$. The first case is when the second particle has not yet settled down at time t. This happens when $\nu + \tau > t$ and then the distribution of $\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}$ conditional on $\nu = s$ and the first particle being alive at time s is equal to the sum of $\mathbb{1}_{A_1(t-s)}\mathbb{1}_{B(t-s)\leqslant x}$ and $\sum_{i=1}^{N(t-s)} \mathbb{1}_{X_i(t-s)\leqslant x}$, where $B(t-s)$ is an independent stochastic process at time $t-s$ (movement of second particle) with $A_1(t-s)$ the event that the second particle born at time s is alive at time t. The term $\sum_{i=1}^{N(t-s)} \mathbb{1}_{X_i(t-s)\leqslant x}$ arises because we can start again at time $\nu = s$ in the same way as at time zero thanks to the recursive structure and the memoryless property. The probability of the first particle being alive at time s is $\mathrm{e}^{-\delta_2 s}$ while the survival probability of the second particle is

$$P[A_1(t-s)] = \int_{t-s}^\infty \delta_1 \mathrm{e}^{-\delta_1 u}\,\mathrm{d}u = \mathrm{e}^{-\delta_1(t-s)}.$$

Therefore, we have for $s \leqslant t$ and $u > t-s$ that

$$E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\middle|\nu = s, \tau = u\right]$$

$$
\begin{aligned}
&= \mathrm{e}^{-\delta_2 s-\delta_1(t-s)} E\left[\mathbb{1}_{B(t-s)\leqslant x}\right] + \mathrm{e}^{-\delta_2 s} E\left[\sum_{i=1}^{N(t-s)} \mathbb{1}_{X_i(t-s)\leqslant x}\right] \\
&= \mathrm{e}^{-\delta_2 s-\delta_1(t-s)} G(t-s,x) + \mathrm{e}^{-\delta_2 s} F(t-s,x).
\end{aligned}
$$

For the other case where $\nu+\tau \leqslant t$, the second particle has already settled down before time t and behaves in the same way at $\nu+\tau$ as the first particle did at time 0, but with starting point $B(\tau)$ and conditional on being then still alive. Therefore, the distribution of $\sum_{i=1}^{N(t)} X_i(t)$ conditional on $\nu = s$, $\tau = u$ and the first particle being alive at time s is then equal to the sum of independent copies of the random variables $\mathbb{1}_{A_1(u)} \sum_{i=1}^{N(t-s-u)} \mathbb{1}_{X_i(t-s-u)+B(u)\leqslant x}$ and $\sum_{i=1}^{N(t-s)} \mathbb{1}_{X_i(t-s)\leqslant x}$. This yields for $s+u \leqslant t$ that

$$
\begin{aligned}
&E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x} \middle| \nu = s, \tau = u\right] \\
&= \mathrm{e}^{-\delta_2 s-\delta_1 u} E\left[\sum_{i=1}^{N(t-s-u)} \mathbb{1}_{X_i(t-s-u)+B(u)\leqslant x}\right] + \mathrm{e}^{-\delta_2 s} E\left[\sum_{i=1}^{N(t-s)} \mathbb{1}_{X_i(t-s)\leqslant x}\right] \\
&= \mathrm{e}^{-\delta_2 s-\delta_1 u} E\left[F\big(t-s-u, x-B(u)\big)\right] + \mathrm{e}^{-\delta_2 s} F(t-s,x) \\
&= \mathrm{e}^{-\delta_2 s-\delta_1 u} \int_{\mathbb{R}^d} F\big(t-s-u, x-z\big) g(u,z)\,\mathrm{d}z + \mathrm{e}^{-\delta_2 s} F(t-s,x).
\end{aligned}
$$

Combining the terms, we obtain

$$
\begin{aligned}
F(t,x) &= \int_0^\infty E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x} \middle| \nu = s\right] \mu \mathrm{e}^{-\mu s}\,\mathrm{d}s \\
&= \mathrm{e}^{-\delta_2 t}\mathrm{e}^{-\mu t}\mathbb{1}_{0\leqslant x} + \int_0^t \big(\mathrm{e}^{-\delta_2 s-\delta_1(t-s)} G(t-s,x) \\
&\qquad\qquad + \mathrm{e}^{-\delta_2 s} F(t-s,x)\big)\mathrm{e}^{-\lambda(t-s)}\mu \mathrm{e}^{-\mu s}\,\mathrm{d}s \\
&\quad + \int_0^t \int_0^{t-s} \Bigg(\mathrm{e}^{-\delta_2 s-\delta_1 u} \int_{\mathbb{R}^d} F(t-s-u, x-z) g(u,z)\,\mathrm{d}z \\
&\qquad\qquad + \mathrm{e}^{-\delta_2 s} F(t-s,x)\Bigg) \lambda \mathrm{e}^{-\lambda u}\,\mathrm{d}u\, \mu \mathrm{e}^{-\mu s}\,\mathrm{d}s \\
&= \mathrm{e}^{-(\mu+\delta_2)t}\mathbb{1}_{0\leqslant x} + \int_0^t \big(\mathrm{e}^{-(\lambda+\delta_1)s} G(s,x) + F(s,x)\big)\mu \mathrm{e}^{-(\mu+\delta_2)(t-s)}\,\mathrm{d}s \\
&\quad + \int_0^t \int_0^s \int_{\mathbb{R}^d} F(s-u, x-z) g(u,z)\,\mathrm{d}z \lambda \mathrm{e}^{-(\lambda+\delta_1)u}\,\mathrm{d}u\, \mu \mathrm{e}^{-(\mu+\delta_2)(t-s)}\,\mathrm{d}s.
\end{aligned}
\tag{2.12}
$$

We deduce by differentiating with respect to t that

$$
\begin{aligned}
F_t(t,x) &= -(\mu+\delta_2)F(t,x) + G(t,x)\mathrm{e}^{-(\lambda+\delta_1)t}\mu + F(t,x)\mu \\
&\quad + \int_0^t \int_{\mathbb{R}^d} F(t-u, x-z) g(u,z) \lambda \mathrm{e}^{-(\lambda+\delta_1)u} \mu\,\mathrm{d}z\,\mathrm{d}u,
\end{aligned}
$$

which shows that F satisfies (2.5) for the choices mentioned in Table 1.

The proof for the integro-differential equations of V, H and Q go analogously. For V, we start by decomposing it as

$$V(t,x) = \mathrm{Var}\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right] = \underbrace{E\left[\left(\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right)^2\right]}_{=:\tilde{F}(t,x)} - \left(\underbrace{E\left[\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right]}_{=F(t,x)}\right)^2.$$

This implies $V_t(t,x) = \tilde{F}_t(t,x) - 2F(t,x)F_t(t,x)$ so that the integro-differential equation of V follows from such equations for F and $\tilde{F}$. Similarly to (2.11), we write

$$\begin{aligned}
\tilde{F}(t,x) &= E\left[\left(\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right)^2\right] = \int_0^\infty E\left[\left(\sum_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right)^2 \middle| \nu = s\right] \mu \mathrm{e}^{-\mu s}\,\mathrm{d}s,\\
H(t,x) &= P\Big[\max_{i=1,\dots,N(t)} X_i(t) \leqslant x\Big] = P\big[X_i(t) \leqslant x \text{ for all } i = 1,\dots,N(t)\big]\\
&= E\left[\prod_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x}\right] = \int_0^\infty E\left[\prod_{i=1}^{N(t)} \mathbb{1}_{X_i(t)\leqslant x} \middle| \nu = s\right] \mu \mathrm{e}^{-\mu s}\,\mathrm{d}s,\\
Q(t) &= P[M(t) > 0] = \int_0^\infty P[M(t) > 0 | \nu = s] \mu \mathrm{e}^{-\mu s}\,\mathrm{d}s.
\end{aligned}$$

The subsequent steps for $\tilde{F}$, H and Q go analogously to the analysis done for F by using decompositions similar to (2.12). □

3. Analysis of the integro-differential equations

In this section, we first prove existence and uniqueness results for the integro-differential equations (2.5). We then analyze the mean numbers of moving and stationary particles, where we already see that R_0 has a threshold of 1 that distinguishes between metastatic growth or decay. Finally, we prove the main stability theorem.

3.1 *Local and global existence*

For the general equation (2.5), we make the following assumptions:

Assumptions (A1):

- We assume $r_1 \geqslant 0$, $r_2 \in \mathbb{R}$,
- $q(t,x) \geqslant \delta > 0$ is uniformly bounded and Lipschitz continuous in t and x.
- For each $T > 0$ $p(t,x) \geqslant 0$ is uniformly bounded on $[0,T]$ by P, absolute continuous in x and continuous in t.
- For the cases F,H,V: $k(u,z) \geqslant 0$ is continuous in x and satisfies for some constant $K > 0$ that

$$\int_0^t \int_{\mathbb{R}^d} k(u,z)\,\mathrm{d}z\mathrm{d}u < K.$$

- For the case Q: $k(u) \geqslant 0$ satisfies for some constant $K > 0$ that

$$\int_0^t k(u)\,\mathrm{d}u < K.$$

- The initial condition $f_0(x) = f(0,x) \geqslant 0$ is bounded in $L^\infty\big(\mathbb{R}^d\big)$.

3.1.1 *Mild solutions* To prove local existence and uniqueness, we consider $T > 0$ and use as phase space

$$\mathscr{X} = L^\infty\big(0,T;\mathbb{R}^d\big)$$

with the essential supremum norm $||\cdot||_\infty$. To find a mild formulation of (2.5), we define an integrating factor

$$W(t,s,x) = \exp\left(-\int_s^t q(u,x)\,\mathrm{d}u\right) \tag{3.1}$$

where the x-dependence arises only in the case of $f = H$. Since q is Lipschitz continuous and $q > 0$ we have that $W(t,s,x)$ is a non-negative evolution family with $0 < W(t,s,x) \leqslant 1$ for all $0 \leqslant s \leqslant t \leqslant T$. We use the variation of constant formula to formally solve (2.5) as

$$f(t,x) = f_0(x)W(t,0,x) + \int_0^t W(t,s,x)\Big[p(s,x) + (r_1 + r_2 f)\; k * f(s,x)\Big]\mathrm{d}s, \tag{3.2}$$

with $f(0,x) = f_0(x)$, which is our mild formulation.

Based on the various interpretations of f as probability or variance, we are interested in non-negative solutions.

LEMMA 3.1 Assume (A1) and let $f \in \mathscr{X}$ be a mild solution of (2.5).

1. Then $f(t,x) \geqslant 0$ as long as the solution exists.
2. If $f(t_0,x_0) = 0$ for a point (t_0,x_0), then this implies that

$$f_0(x_0) = 0 \quad \text{and} \quad p(t,x_0) = 0 \qquad \text{for all} \quad 0 \leqslant t \leqslant t_0. \tag{3.3}$$

3. If in addition $p(t,x) > 0$ for all $(t,x) \in (0,T) \times \mathbb{R}^d$ then $f(t,x) > 0$ for all $(t,x) \in (0,T) \times \mathbb{R}^d$.

Proof.

1. Consider any time t_0 such that $f(t,x) \geqslant 0$ for all $0 \leqslant t \leqslant t_0$ and all $x \in \mathbb{R}^d$. Define

$$\Omega^0 := \{x \in \mathbb{R}^d : f(t_0,x) = 0\}.$$

Then at each of the points (t_0,x), $x \in \Omega^0$, we have the following signs of the terms in (2.5):

$$\begin{aligned} f(t_0,x) &= 0, \\ p(t_0,x) &\geqslant 0, \\ \int_0^{t_0}\int_{\mathbb{R}^d} k(u,z) f(t_0-u,x-z)\,\mathrm{d}z\mathrm{d}u &\geqslant 0, \\ r_1 + r_2 f(t_0,x) = r_1 &\geqslant 0, \end{aligned}$$

hence from (2.5), we find $\frac{\partial}{\partial t} f(t_0,x) \geqslant 0$ for all $x \in \Omega^0$, and the solution does not decay further.

2. Taking a point (t_0, x_0) with $f(t_0, x_0) = 0$, we find from the mild formulation (3.2) that

$$0 = f_0(x_0)W(t_0, 0, x_0) + \int_0^{t_0} W(t_0, s, x_0)(p(s, x_0) + r_1 k * f(s, x_0))\,\mathrm{d}s, \tag{3.4}$$

   where all terms are non-negative. Hence (3.3) follows.

3. If $p > 0$, we see that (3.4) is not possible, hence $f > 0$.

□

PROPOSITION 3.1 Assume (A1). Then there exists a time $T > 0$ and a unique mild solution $f \in \mathscr{X}$ which satisfies (3.2).

Proof. Given a function $\tilde{f} \in \mathscr{X}$, we define an iteration operator $A : \tilde{f} \to f$ where f is the unique solution of

$$f_t = -qf + p + (r_1 + r_2\tilde{f})\, k * \tilde{f}. \tag{3.5}$$

Using the integrating factor (3.1) we solve (3.5) as

$$f(t,x) = f_0(x)W(t,0,x) + \int_0^t W(t,s,x)\left[p(s,x) + (r_1 + r_2\tilde{f})\, k * \tilde{f}(s,x)\right]\mathrm{d}s. \tag{3.6}$$

Step 1: Given an initial condition $f_0 \in \mathscr{X}$ with norm $\|f_0\|_{\mathscr{X}} = M_0$. We show that for each constant $M > 0$ there exists a time $T_1 > 0$ such that $A : B_M(f_0) \to B_M(f_0)$ for all $T \leqslant T_1$, where $B_M(f_0) \subset \mathscr{X}$ denotes the closed ball of radius M in $\mathscr{X}$ with center f_0. Consider $\tilde{f} \in B_M$ then $\tilde{f}$ has norm

$$\|\tilde{f}\|_{\mathscr{X}} \leqslant M_0 + M.$$

From (3.6) we find

$$\begin{aligned} f(t,x) - f_0(x) = {} & (W(t,0,x) - 1)f_0(x) \\ & + \int_0^t W(t,s,x)\left[p(s,x) + (r_1 + r_2\tilde{f})\, k * \tilde{f}(s,x)\right]\mathrm{d}s. \end{aligned}$$

Since $W(t,0,x) < 1$ for all $t > 0$, we can ignore the first term and estimate

$$\|f(t,.) - f_0\|_\infty \leqslant tP + r_1 Kt\left\|\tilde{f}\right\|_{\mathscr{X}} + |r_2|Kt\left\|\tilde{f}\right\|_{\mathscr{X}}^2,$$

which implies that

$$\begin{aligned} \|f - f_0\|_{\mathscr{X}} &\leqslant T\left(P + r_1 K\|\tilde{f}\|_{\mathscr{X}} + |r_2|K\left\|\tilde{f}\right\|_{\mathscr{X}}^2\right) \\ &\leqslant T\left(P + r_1 K(M_0 + M) + |r_2|K(M_0 + M)^2\right). \end{aligned}$$

To ensure $\|f - f_0\|_{\mathscr{X}} \leqslant M$, we need

$$T\left(P + r_1 K(M_0 + M) + |r_2|K(M_0 + M)^2\right) \leqslant M,$$

which is true for all

$$T \leqslant T_1 := \frac{M}{P + r_1 K(M_0 + M) + |r_2|K(M_0 + M)^2}.$$

Hence, for $T \leqslant T_1$, we have $A : B_M(f_0) \to B_M(f_0)$.

Step 2: We show that A is a contraction for $T \leqslant T_2$ for some $T_2 > 0$.
Given $\tilde{f}, \tilde{g} \in B_M(f_0)$ with $\tilde{f}_0(x) = \tilde{g}_0(x) = f_0(x)$. Then from (3.6), we find

$$\begin{aligned}
\|f(t,.) - g(t,.)\|_\infty &\leqslant \left\| \int_0^t \left(\left(r_1 + r_2 \tilde{f}\right) k * \tilde{f} - (r_1 + r_2 \tilde{g})\, k * \tilde{g} \right) \mathrm{d}s \right\|_\infty \\
&\leqslant r_1 \left\| \int_0^t k * \left(\tilde{f} - \tilde{g}\right) \mathrm{d}s \right\|_\infty + |r_2| \left\| \int_0^t \left(\left(\tilde{f} - \tilde{g}\right) k * \tilde{f} + \tilde{g}\, \left(\tilde{f} - \tilde{g}\right) \right) \mathrm{d}s \right\|_\infty \\
&\leqslant r_1 K t \left\|\tilde{f} - \tilde{g}\right\|_{\mathscr{X}} + |r_2| K t \left\|\tilde{f}\right\|_{\mathscr{X}} \left\|\tilde{f} - \tilde{g}\right\|_{\mathscr{X}} + |r_2| K t \left\|\tilde{f} - \tilde{g}\right\|_{\mathscr{X}} \\
&= K t \left(r_1 + |r_2| \left\|\tilde{f}\right\|_{\mathscr{X}} + |r_2| \left\|\tilde{g}\right\|_{\mathscr{X}}\right) \|\tilde{f} - \tilde{g}\|_{\mathscr{X}}.
\end{aligned}$$

Hence

$$\begin{aligned}
\|f - g\|_{\mathscr{X}} &\leqslant K T \left(r_1 + |r_2| \left\|\tilde{f}\right\|_{\mathscr{X}} + |r_2| \|\tilde{g}\|_{\mathscr{X}}\right) \left\|\tilde{f} - \tilde{g}\right\|_{\mathscr{X}} \\
&\leqslant K T \left(r_1 + 2|r_2|(M_0 + M)\right) \left\|\tilde{f} - \tilde{g}\right\|_{\mathscr{X}}.
\end{aligned}$$

Then A is a contraction for all

$$T < T_2 := \frac{1}{K(r_1 + 2|r_2|(M_0 + M))}.$$

Step 3: For $T < \min\{T_1, T_2\}$ the Banach fixed point theorem applies, and A has a unique fixed point in $\mathscr{X}$, which satisfies the mild formulation (3.2). □

The local existence times T from the above proof depend on the norm of the initial condition, hence we cannot simply repeat the argument to obtain global existence. Nevertheless, we show next that solutions are global.

3.1.2 *Global existence*

THEOREM 3.1 The unique mild solutions from Proposition 3.1 exist for all times. The probabilities H and Q are globally bounded by 1 (as solutions of their corresponding integro-differential equation).

Proof.

- For the cases F and V we have $r_2 = 0$, hence (2.5) becomes a linear equation in f. We estimate

  $$\|f(t,.)\|_\infty \leqslant \|f_0\|_\infty + tP + r_1 K \int_0^t \|f(s,.)\|_\infty \mathrm{d}s$$

  and Gronwall's lemma implies that $\|f(t,.)\|_\infty$ grows at most exponentially, hence proving global existence.

- In the case Q the parameter $r_2 = -1$ is negative. Hence in the global estimate, we can remove the quadratic term. Again Gronwall's lemma applies and global existence follows. To show that the survival probability Q is bounded by 1, we assume that $Q(t_0) = 1$ and $Q(t) < 1$ for all $0 \leqslant t < t_0$, or $t_0 = 0$ and $Q(0) = 1$. Then at t_0 we find from (2.4) that

  $$\begin{aligned}
  Q_t(t_0) &= -\left(\delta_2 + \mu \mathrm{e}^{-(\lambda+\delta_1)t_0}\right) Q(t_0) + \mu \mathrm{e}^{-(\lambda+\delta_1)t_0} \\
  &\quad + \lambda \mu (1 - Q(t_0)) \int_0^t Q(t_0 - s) \mathrm{e}^{-(\lambda+\delta_1)s} \mathrm{d}s \\
  &= -\delta_2.
  \end{aligned}$$

  Hence Q decays near 1. In our specific application we have $Q(0) = 1$, hence Q decays initially

and as survival probability, $Q(t)$ is non-increasing.

- A similar argument is applied for H. We assume that $H(t,x) \leqslant 1$ for all $t \leqslant t_0$ and that there exists a point x_0 with $H(t_0,x_0) = 1$. Then at (t_0,x_0) we observe

$$\begin{aligned} H_t(t_0,x_0) &= \left[\mu \mathrm{e}^{-\lambda t_0}(1-\mathrm{e}^{-\delta_1 t_0}(1-G(t_0,x_0))) - (\mu+\delta_1)\right] H(t_0,x_0) \\ &\quad +\lambda\mu H(t_0,x_0)\int_0^{t_0}\int_{\mathbb{R}^d} H(t_0-u,x_0-z)g(u,z)\mathrm{e}^{-\lambda u}\,\mathrm{d}z\mathrm{d}u \\ &\leqslant \mu\mathrm{e}^{-\lambda t_0} - (\mu+\delta_1) + \mu(1-\mathrm{e}^{-\lambda t_0}) = -\delta_1 \end{aligned}$$

and $H(t_0,x_0) = 1$ decays.

□

3.2 *Metastatic reproduction number R_0*

To introduce the metastatic reproduction number, we reduce the above model by looking at the expected numbers of moving and stationary particles. We denote by $a(t)$ and $b(t)$ the expected numbers of moving and stationary particles, respectively. Moving particles die at rate δ_1 and become stationary at rate λ while new moving particles are born at rate μ from the stationary particles. This reasoning leads to

$$a'(t) = -(\delta_1+\lambda)a(t) + \mu b(t). \tag{3.7}$$

Formally, we can prove (3.7) analogously to the first part of the proof of Theorem 3.2. Similarly, stationary particles die at rate δ_2 and moving particles become stationary at rate λ, leading to

$$b'(t) = -\delta_2 b(t) + \lambda a(t). \tag{3.8}$$

The differential equations for a and b form a linear system with coordinate matrix

$$A_1 = \begin{pmatrix} -(\delta_1+\lambda) & \mu \\ \lambda & -\delta_2 \end{pmatrix}. \tag{3.9}$$

The matrix A_1 has trace and determinant as

$$\mathrm{tr}A_1 = -(\delta_1+\delta_2+\lambda), \qquad \det A_1 = \delta_2(\delta_1+\lambda) - \lambda\mu.$$

The trace is negative, hence the origin is asymptotically stable for $\det A_1 > 0$ and unstable for $\det A_1 < 0$. Using

$$R_0 = \frac{\lambda}{\delta_1+\lambda}\frac{\mu}{\delta_2},$$

we find the following result:

LEMMA 3.2 Consider (3.7), (3.8).

- If $R_0 < 1$ then $(0,0)$ is globally asymptotically stable.
- If $R_0 > 1$ then $(0,0)$ is unstable (it is a saddle).
- If $R_0 = 1$ then $(0,0)$ is non-hyperbolic and we have a continuum of steady states in direction $(\delta_2,\lambda)^T$.

Proof. For the first two statements note that we can write

$$\det A_1 = \delta_2(\delta_1+\lambda)(1-R_0).$$

For the third statement we find that for $R_0 = 1$ the vector $(\delta_2, \lambda)^T$ is an eigenvector of A_1 with eigenvalue 0. □

It should be noted that $a(t)+b(t) = E[M(t)]$ with the formula for the expected total number $E[M(t)]$ of particles.

Using specific initial conditions $(a(0), b(0)) = (0,1)$ we can explicitly solve equations (3.7), (3.8) and we find the asymptotic ratio of moving versus stationary particles

$$\lim_{t\to\infty} \frac{a(t)}{b(t)} = \frac{\delta_2-\delta_1-\lambda+\sqrt{(\delta_2-\delta_1-\lambda)^2+4\lambda\mu}}{2\lambda}.$$

An alternative way to analyze the asymptotic number of particles is to relate our process to a two-type branching process in discrete time and to use results available for such processes. The two types are the moving and stationary particles. As explained in Section 2.3 of (Haccou et al., 2005), for multi-type branching processes, the asymptotic extinction-survival behavior is characterized by the Perron root ρ (maximal eigenvalue that corresponds to an eigenvector with positive entries) of the mean matrix M, which generalizes the mean reproduction in the one-type case. The process is called subcritical if $\rho < 1$, critical if $\rho = 1$, and supercritical if $\rho > 1$. For our model, the mean matrix is given by

$$\begin{aligned} M &= \begin{pmatrix} \frac{2\mu+\delta_2}{2\mu+\lambda+\delta_1+\delta_2} & \frac{\mu}{2\mu+\lambda+\delta_1+\delta_2} \\ \frac{\lambda}{2\mu+\lambda+\delta_1+\delta_2} & \frac{2\mu+\lambda+\delta_1}{2\mu+\lambda+\delta_1+\delta_2} \end{pmatrix} = \frac{1}{2\mu+\lambda+\delta_1+\delta_2}\begin{pmatrix} 2\mu+\delta_2 & \mu \\ \lambda & 2\mu+\lambda+\delta_1 \end{pmatrix} \\ &= \mathbb{1} + \frac{1}{2\mu+\lambda+\delta_1+\delta_2} A_1, \end{aligned}$$

where we recall A_1 from (3.9). If v is eigenvector of A_1 with eigenvalue α, then it is eigenvector of M with eigenvalue $1+\frac{\alpha}{2\mu+\lambda+\delta_1+\delta_2}$. Hence, M has an eigenvalue greater than 1 if and only if A_1 has a positive eigenvalue, which is the case if and only if $R_0 > 1$, as explained before Lemma 3.2. Also note that such an eigenvalue corresponds to an eigenvector

$$\begin{pmatrix} \mathrm{tr}A_1/2+\sqrt{(\mathrm{tr}A_1)^2/4-\det A_1}+\delta_2 \\ \lambda \end{pmatrix},$$

which has positive entries. Therefore, the Perron root ρ of the mean matrix M is greater than one (supercritical case) if and only if $R_0 > 1$. Similarly, the critical case $\rho = 1$ and the subcritical case $\rho < 1$ are equivalent to $R_0 = 1$ and $R_0 < 1$, respectively.

3.3 *Survival probability $Q(t)$*

The survival probability Q is a special case of (2.5), where there is no spatial variable. In this case, (2.5) becomes

$$Q'(t) = -\underbrace{\delta_2 Q(t)}_{A} + \underbrace{(1-Q(t))\mu \mathrm{e}^{-(\delta_1+\lambda)t}\left(1+\int_0^t Q(s)\lambda \mathrm{e}^{(\delta_1+\lambda)s}\,\mathrm{d}s\right)}_{B}. \tag{3.10}$$

where

A: death rate of original particle times the survival probability at time t. Note that this is the only term if $\mu = 0$ (no births), in which case, the survival probability equals $Q(t) = \exp(-\delta_2 t)$.

B: correction term because the birth of particles leads to a higher survival probability than in the case $\mu = 0$. If the original particle has offsprings, all of the original particle, the offsprings of the original particle and further offsprings must die to extinct all particles, which is reflected in the term B.

Based on (3.10), we can derive a second-order ODE for Q, namely,

$$\begin{aligned} Q''(t) &= \big((\delta_1+\lambda)\big(Q(t)-1\big) - Q'(t)\big)\mu \mathrm{e}^{-(\delta_1+\lambda)t}\left(1+\int_0^t Q(s)\lambda \mathrm{e}^{(\delta_1+\lambda)s}\,\mathrm{d}s\right) \\ &\quad - \delta_2 Q'(t) + \mu\lambda Q(t)\big(1-Q(t)\big) \\ &= \left(\frac{Q'(t)}{Q(t)-1} - \delta_1 - \lambda\right)\big(Q'(t)+\delta_2 Q(t)\big) - \delta_2 Q'(t) + \mu\lambda Q(t)\big(1-Q(t)\big) \end{aligned}$$

This equation can be transformed into a system of first-order ODEs as

$$\begin{aligned} Q' &= P, \\ P' &= \left(\frac{P}{Q-1} - \delta_1 - \lambda\right)\big(P+\delta_2 Q\big) - \delta_2 P + \mu\lambda Q\big(1-Q\big). \end{aligned} \tag{3.11}$$

We show the following result:

LEMMA 3.3 Consider system (3.11).

- If $R_0 < 1$ then $(0,0)$ is locally asymptotically stable.
- If $R_0 > 1$ then $(0,0)$ is locally unstable (it is a saddle).

Proof. The linearization of (3.11) at $(0,0)$ is

$$\begin{pmatrix} 0 & 1 \\ -\delta_2(\delta_1+\lambda)+\mu\lambda & -\delta_1-\delta_2-\lambda \end{pmatrix}.$$

This matrix has the same trace and determinant as the matrix A_1 that we encountered in Lemma 3.2. Hence for $R_0 < 1$, the origin is locally asymptotically stable, and for $R_0 > 1$, it is a saddle. □

3.4 *Asymptotic behavior as $t \to \infty$*

In this section, we study how the average number of particles and the survival probability behave in the limit $t \to \infty$. We first provide an explicit formula for the average number of particles at an arbitrary time t.

THEOREM 3.2 For $\mu \neq 0$, and $\lambda \neq 0$ or $\delta_1 \neq \delta_2$, the average number of particles alive at time t is given by

$$E[M(t)] = \frac{\mu-\delta_2-\alpha_-}{\alpha_+-\alpha_-}\mathrm{e}^{\alpha_+ t} + \frac{-\mu+\delta_2+\alpha_+}{\alpha_+-\alpha_-}\mathrm{e}^{\alpha_- t},$$

where

$$\alpha_\pm = \frac{-\delta_2-\delta_1-\lambda \pm \sqrt{(\delta_2+\delta_1+\lambda)^2 + 4(R_0-1)\delta_2(\lambda+\delta_1)}}{2}. \tag{3.12}$$

For $\mu = 0$ or both $\lambda = 0$ and $\delta_1 = \delta_2$, the average number of particles at time t equals $E[M(t)] = (1+\mu t)\mathrm{e}^{-\delta_1 t}$.

Proof. Similarly to the proof of Theorem 2.1, we find

$$\begin{aligned}
E[M(t)] &= \int_0^\infty E[M(t)|\nu = s]\mu \mathrm{e}^{-\mu s}\,\mathrm{d}s \\
&= \mathrm{e}^{-(\delta_2+\mu)t} + \int_0^t \big(\mathrm{e}^{-\delta_2 s - \delta_1(t-s)} + \mathrm{e}^{-\delta_2 s}E[M(t-s)]\big)\mathrm{e}^{-\lambda(t-s)}\mu\mathrm{e}^{-\mu s}\,\mathrm{d}s \\
&\quad + \int_0^t\int_0^{t-s} \big(\mathrm{e}^{-\delta_2 s-\delta_1 u}E[M(t-s-u)] + \mathrm{e}^{-\delta_2 s}E[M(t-s)]\big)\lambda\mathrm{e}^{-\lambda u}\,\mathrm{d}u\,\mu\mathrm{e}^{-\mu s}\,\mathrm{d}s \\
&= \mathrm{e}^{-(\delta_2+\mu)t} + \int_0^t \big(\mathrm{e}^{-(\delta_1+\lambda)s} + E[M(s)]\big)\mu\mathrm{e}^{-(\delta_2+\mu)(t-s)}\,\mathrm{d}s \\
&\quad + \int_0^t\int_0^s \mathrm{e}^{-(\delta_2+\mu)(t-s)-(\delta_1+\lambda)u}E[M(s-u)]\lambda\mu\,\mathrm{d}u\,\mathrm{d}s.
\end{aligned}$$

We deduce that

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}E[M(t)] &= -(\delta_2+\mu)E[M(t)] + \mu\mathrm{e}^{-(\delta_1+\lambda)t} + \mu E[M(t)] \\
&\qquad + \int_0^t \mathrm{e}^{-(\delta_1+\lambda)u}E[M(t-u)]\lambda\mu\,\mathrm{d}u \\
&= -\delta_2 E[M(t)] + \mu\mathrm{e}^{-(\delta_1+\lambda)t} + \int_0^t \mathrm{e}^{-(\delta_1+\lambda)(t-u)}E[M(u)]\lambda\mu\,\mathrm{d}u, \\
\frac{\mathrm{d}^2}{\mathrm{d}t^2}E[M(t)] &= -\delta_2\frac{\mathrm{d}}{\mathrm{d}t}E[M(t)] - (\delta_1+\lambda)\Big(\frac{\mathrm{d}}{\mathrm{d}t}E[M(t)] + \delta_2 E[M(t)]\Big) + E[M(t)]\lambda\mu \\
&= -(\delta_2+\delta_1+\lambda)\frac{\mathrm{d}}{\mathrm{d}t}E[M(t)] + \big(\lambda\mu - (\delta_1+\lambda)\delta_2\big)E[M(t)],
\end{aligned}$$

which shows that $E[M(t)]$ satisfies a linear ordinary differential equation, whose solution is of the form $E[M(t)] = c_+\mathrm{e}^{\alpha_+ t} + c_-\mathrm{e}^{\alpha_- t}$ with

$$\begin{aligned}
\alpha_\pm &= \frac{-\delta_2-\delta_1-\lambda \pm \sqrt{(\delta_2+\delta_1+\lambda)^2 + 4\lambda\mu - 4(\delta_1+\lambda)\delta_2}}{2} \\
&= \frac{-\delta_2-\delta_1-\lambda \pm \sqrt{(\delta_2+\delta_1+\lambda)^2 + 4(R_0-1)\delta_2(\lambda+\delta_1)}}{2}
\end{aligned}$$

if $\delta_2 \neq \delta_1+\lambda$ or $\lambda\mu \neq 0$. To find the constants c_- and c_+, we use the boundary conditions

$$E[M(0)] = M(0) = 1 \quad \text{and} \quad \frac{\mathrm{d}}{\mathrm{d}t}E[M(t)]\Big|_{t=0} = \mu - \delta_2,$$

where we applied that at time 0 there is one particle which will be either eliminated (at rate δ_2) or doubled (at rate μ). This yields

$$c_- + c_+ = 1 \quad \text{and} \quad \alpha_- c_- + \alpha_+ c_+ = \mu - \delta_2$$

which gives $c_- = \frac{\mu-\delta_2-\alpha_+}{\alpha_- - \alpha_+}$ and $c_+ = \frac{-\mu+\delta_2+\alpha_-}{\alpha_- - \alpha_+}$. In the case $\lambda = 0$ and $\delta_1 = \delta_2$, we have

$$\frac{\mathrm{d}}{\mathrm{d}t}E[M(t)] = -\delta_1 E[M(t)] + \mu\mathrm{e}^{-\delta_1 t},$$

which satisfies

$$\frac{\mathrm{d}}{\mathrm{d}t}\big(\mathrm{e}^{\delta_1 t}E[M(t)]\big) = \mu,$$

hence $E[M(t)] = (1+\mu t)\mathrm{e}^{-\delta_1 t}$. In the case $\mu = 0$, we have $\frac{\mathrm{d}}{\mathrm{d}t}E[M(t)] = -\delta_2 E[M(t)]$ so that $E[M(t)] = \mathrm{e}^{-\delta_1 t}$. □

For $\mu \neq 0$, and $\lambda \neq 0$ or $\delta_1 \neq \delta_2$, we obtain from Theorem 3.2 that

$$\begin{aligned}\frac{E[M(t)]}{\mathrm{e}^{\alpha_+ t}} &= \frac{\mu-\delta_2-\alpha_-}{\alpha_+-\alpha_-} + \frac{-\mu+\delta_2+\alpha_+}{\alpha_+-\alpha_-}\mathrm{e}^{-\sqrt{(\delta_2-\delta_1-\lambda)^2+4\lambda\mu}t} \\ &= \frac{2\mu-\delta_2+\delta_1+\lambda+\sqrt{(\delta_2-\delta_1-\lambda)^2+4\lambda\mu}}{2\sqrt{(\delta_2-\delta_1-\lambda)^2+4\lambda\mu}} + o(1)\end{aligned}$$

for $t \to \infty$ so that $E[M(t)]$ has exponential growth with rate α_+.

Note that $\alpha_+ > 0$ in (3.12) if and only if $R_0 > 1$ and $\alpha_+ < 0$ whenever $R_0 < 1$. Also note that α_+ is real for all $R_0 \in [0,1]$. From this reasoning, we deduce the following result.

COROLLARY 3.1 $E[M(t)]$ has the following asymptotic behavior: it ...

$$\begin{cases} \text{equals } (1+\mu t)\mathrm{e}^{-\delta_1 t} & \text{if } \mu = 0 \text{ or both } \lambda = 0 \text{ and } \delta_1 = \delta_2, \\ \text{grows exponentially at rate } \alpha_+ & \text{if } R_0 > 1 \text{ and not case 1}, \\ \text{converges to } \frac{1+\lambda/\delta_2}{\delta_2/\mu+\lambda/\delta_2} & \text{if } R_0 = 1 \text{ and not case 1}, \\ \text{shrinks exponentially to 0 at rate } \alpha_+ & \text{if } R_0 < 1 \text{ and not case 1}. \end{cases}$$

In Lemma 3.3 we have already shown the corresponding threshold phenomenon for the survival probability Q. In more detail, we can also compute the asymptotic value as $t \to \infty$.

LEMMA 3.4 The asymptotic survival probability is

$$\lim_{t\to\infty} Q(t) = \begin{cases} \max\big\{1-\frac{1}{R_0}, 0\big\} & \text{if } \mu > 0 \text{ and } \lambda > 0, \\ 1 & \text{if } \{\mu = 0 \text{ or } \lambda = 0\} \text{ and } \delta_2 = 0, \\ \frac{\mu}{\mu+\delta_2} & \text{if } \lambda = 0 \text{ and } \delta_1 = 0 \text{ and } \delta_2 > 0, \\ 0 & \text{otherwise.} \end{cases}$$

Proof. We first observe that if $\delta_2 = 0$, then $Q(t) = 1$ for all t and hence $\lim_{t\to\infty} Q(t) = 1$ because the first particle then lives forever. Now consider the case where $\delta_2 > 0$ and $\delta_1 = \lambda = 0$ so that (3.10) becomes

$$Q'(t) = -\delta_2 + \big(1-Q(t)\big)(\mu+\delta_2), \quad Q(0) = 1,$$

whose solution is $Q(t) = \frac{\mu+\delta_2\mathrm{e}^{-(\mu+\delta_2)t}}{\mu+\delta_2}$, which converges to $\lim_{t\to\infty} Q(t) = \frac{\mu}{\mu+\delta_2}$. Let us now consider $\delta_1+\lambda > 0$ and $\delta_2 > 0$. Because $M(t) = 0$ implies $M(s) = 0$ for all $s \geqslant t$ (after particles died out, there will always be zero particles), we obtain

$$Q(t) = P[M(t) > 0] = 1 - P[M(t) = 0] \geqslant 1 - P[M(s) = 0] = Q(s)$$

for all $s \geqslant t$, which shows that Q is a non-increasing function. Since Q is also bounded from below by 0, it converges to some limit $Q(\infty) := \lim_{t\to\infty} Q(t)$. Using $\lim_{t\to\infty} Q'(t) = 0$ and taking limits in (3.10) gives

$$0 = -Q(\infty)\delta_2 + \big(1-Q(\infty)\big)\lim_{t\to\infty}\int_0^t Q(t-u)\mu\lambda\mathrm{e}^{-(\delta_1+\lambda)u}\,\mathrm{d}u.$$

From L'Hôpital's rule, it follows that

$$\begin{aligned}\lim_{t\to\infty}\int_0^t Q(t-u)\mu\lambda \mathrm{e}^{-(\delta_1+\lambda)u}\,\mathrm{d}u &= \lim_{t\to\infty}\frac{\int_0^t Q(u)\mu\lambda \mathrm{e}^{(\delta_1+\lambda)u}\,\mathrm{d}u}{\mathrm{e}^{(\delta_1+\lambda)t}}\\ &= \lim_{t\to\infty}\frac{Q(t)\mu\lambda \mathrm{e}^{(\delta_1+\lambda)t}}{(\delta_1+\lambda)\mathrm{e}^{(\delta_1+\lambda)t}}\\ &= Q(\infty)\frac{\mu\lambda}{\delta_1+\lambda}.\end{aligned}$$

Therefore, $Q(\infty)$ satisfies the quadratic equation

$$0 = \Big(\frac{\mu\lambda}{\delta_1+\lambda}-\delta_2\Big)Q(\infty) - \frac{\mu\lambda}{\delta_1+\lambda}Q(\infty)^2.$$

If $\lambda = 0$ or $\mu = 0$, its solution is $Q(\infty) = 0$ while otherwise, the solutions are zero or

$$Q(\infty) = \frac{\mu\lambda - \delta_2(\delta_1+\lambda)}{\mu\lambda} = 1 - \frac{1}{R_0}.$$

Note that $Q(t)$ cannot cross the level $1-\frac{1}{R_0}$ so that it will converge at $1-\frac{1}{R_0}$ if this quantity is greater than 0. □

4. Murine Metastatic Cancer Data

In this section, we apply the modeling framework developed above in the context of metastatic cancer data for mice. We recall that moving particles correspond to CTCs while stationary particles correspond to metastases. This interpretation requires an appropriate identification of the model parameters from biologically reasonable estimates obtained from the literature. We then make a brief note on the numerical implementation, followed by a presentation of the results themselves.

4.1 *Murine data*

Because of the scarcity of quantitative data for metastatic cancer in humans, the majority of the values discussed below have come from experimental models of metastasis in mice. Many of the studies mentioned below follow a similar procedure (those in Cameron et al. (2000); Fidler (1970); Luzzi et al. (1998); Sindelar et al. (1975) for example), and we provide a brief outline of their methods. Tumor-free mice are injected with radio-labeled cancer cells (B16 melanoma (Fidler, 1970), M19 Fibrosarcoma (Sindelar et al., 1975), B16F1(0) melanoma (Cameron et al., 2000; Luzzi et al., 1998)), and observed and/or sacrificed at various time points ranging from 1 minute to 14 day post-injection. Organs of interest (multiple organs (Fidler, 1970), lungs (Cameron et al., 2000; Sindelar et al., 1975), and liver (Luzzi et al., 1998) are removed and analyzed for the number and location of cancer cells, cancer cell clusters, and metastases. In addition to the radio-labeled cancer cells, the Chambers group (Cameron et al., 2000; Luzzi et al., 1998) injected inert microspheres that become lodged within the microvasculature of the target organ in order to accurately determine the change in cell numbers over time. Details of specific experimental models can be found in the cited references.

4.2 *Modeling metastatic cancer*

In order to apply our model to the metastatic dissemination of cancer, we must first carefully define what is meant by 'stationary' and 'mobile' particles in this context. 'Stationary' particles will play the role of established tumors capable of shedding mobile particles without exhausting themselves. 'Mobile particles', therefore, will represent small clusters of individual cancer cells that are actively circulating through the vasculature. This interpretation necessitates different scales for the two classes of particles, with established tumors consisting of at least 10^8 cells — corresponding to a tumor volume of approximately 1cm^3 (Del Monte, 2009) — and CTCs consisting of anything between a single cell to several dozen (Friedl and Mayor, 2017). Such a distinction requires careful attention when parameterizing the model. Below we discuss our approach to address this concern.

First we consider the shedding rate, μ. Assuming that an established tumor consists of 10^8 cells (Del Monte, 2009) and that the number of CTCs shed per day range between $0.0001\% - 0.01\%$ of the cells available within the established tumor (Weiss, 1990), we may choose $\mu \in [100, 10000]$ particles per day. For the simulations presented herein, we chose $\mu = 346$ particles/day. This choice was made in order to have an average of 10 established tumors by the end of 14 days (Sindelar et al., 1975) (determined using the asymptotic expected ratio of moving to stationary particles from the comment after Lemma 3.2).

Second, we estimate the stationary particle death rate, δ_2. With the interpretation of a stationary particle as an established tumor, δ_2 corresponds to the rate of spontaneous tumor remission. We use Jessy's estimate of $p = 10^{-5}$ (Jessy, 2011) for the probability of spontaneous remission and assume that $p = \delta_2/\lambda$ to obtain the value of δ_2 reported in Table 2.

Third, we consider the rate of mobile particle settlement, λ. Experimental murine models of metastasis suggest that nearly 80% of the CTCs shed from the primary tumor into the vasculature will survive through the circulation and successfully extravasate at a secondary site (Cameron et al., 2000; Luzzi et al., 1998). For the purposes of our model however, successful extravasation alone does not represent 'settlement'. 'Settlement' in our model includes not only successful extravasation at a secondary site, but survival and growth to a palpable secondary tumor as well. For this reason, we use the more suggestive terminology 'establishment' instead of 'settlement'. Moreover, we assume that the establishment rate, λ, is related to the shedding rate, μ, via $\lambda = \mu q$ where q denotes the probability (per cell) of establishment. The probability q has been estimated by several investigators to range between 0.0001 and 0.00001 (Chambers et al., 2002; Fidler, 1970; Luzzi et al., 1998; Sindelar et al., 1975). In the results presented below, we have used the lower estimate of $q = 0.00001$ (Luzzi et al., 1998).

Fourth, we require an estimate for the mobile particle death rate, δ_1. While approximately 80% of cancer cells released into circulation will survive in the vasculature and successfully extravasate at a

TABLE 2 *Model Parameters and the values used in presented simulations. See text for further details.*

Parameter	Description	Value	Units	References
μ	Shedding rate	346	particles/day	Del Monte (2009); Weiss (1990)
λ	Establishment rate	0.0035	particles/day	Luzzi et al. (1998)
δ_1	Mobile death rate	7	particles/day	Chambers et al. (2002); Fidler (1970); Liotta and DeLisi (1977)
δ_2	Stationary death rate	3.46×10^{-8}	particles/day	Jessy (2011)

secondary location (Cameron et al., 2000; Luzzi et al., 1998), the fraction of these extravasated cells that will grow and form a metastasis is very small (Cameron et al., 2000). Consequently, our estimate for the mobile particle death rate must also include the death rate of successfully extravasated cells that do not become metastases, and will be much larger than if we included only deaths during transit. Additionally, the time that CTCs spend traveling through the circulation has been estimated to be between 1 and 3 hours (Luzzi et al., 1998; Sindelar et al., 1975). Therefore, assuming that 'mobile particle' means 'CTC', we expect these particles to be short-lived. Combining these observations, and based on previous results (Chambers et al., 2002; Fidler, 1970; Liotta and DeLisi, 1977), we chose to have 99.9% of all the CTCs that are shed over the course of a day perish that day. Under this assumption, the mobile death rate becomes $\delta_1 = 7$ particles/day.

Finally, we must choose a stochastic process, $(B(t))_{t\geqslant 0}$, to model the movement of mobile particles. In the simulations presented below, we have modeled the movement of mobile particles as a scaled one-dimensional Brownian motion of the form

$$B(t) = \sigma W(t),$$

where $(W_t)_{t\geqslant 0}$ is a standard Brownian motion, and $\sigma = \sqrt{2D}$ is the volatility, with $D > 0$ the *effective* diffusivity — that is to say, the diffusivity estimated assuming that movement between tumor sites is accomplished entirely by diffusion. In order to simulate the worst case scenario of full metastatic colonization of a 16cm mouse after 14 days we choose $D = 37\text{cm}^2/\text{day}$ (see Figure 4). Whereas we recognize that the transport of CTCs from a primary site to a distant secondary site through the vascular system does not occur exclusively through diffusion, we have, for the sake of simplicity, chosen to model vascular transport as a diffusive process. We leave as future work the development and inclusion of more realistic models of spatial spread based on blood circulation mechanisms (see Section 5 for further discussion).

4.3 *Numerical results*

Simulation of the model was done using a variant of the Gillespie algorithm (Erban et al., 2008; Gillespie, 1976). The key feature of this algorithm is its non-uniform time stepping which is ideally suited for our model, as our model can see (for example) the total rate of mobile particle creation double upon successful establishment of a secondary tumor because of the assumption of independence amongst the stationary particles. Our implementation of Brownian motion is equivalent to a discrete-time random walk with step sizes normally distributed with mean zero and variance $2D\Delta t$, where $\Delta t > 0$ is the time step. For details concerning the simulation of Brownian motion using the Gillespie approach, consult (Erban et al., 2008). The implemented algorithm assumes a finite spatial domain, whereas the theoretical work presented in the previous sections does not. In order to simulate an infinite domain, we have chosen the finite domain to be 'sufficiently large' so that there are no collisions between our mobile particles and the domain boundaries within the time of interest. The meaning of 'sufficiently large' depends on the movement of the mobile particles. With the modeling choices outlined above, the spatial domain $[-75\text{cm}, 75\text{cm}]$ divided into $K = 1500$ bins each of width 0.1cm was 'sufficiently large' for our purposes, as demonstrated by the fact that no individual realization had particle-boundary collisions.

In Figures 2–4, we present the average results of 1000 distinct realizations of the stochastic model simulated over a period of 14 days. Validation of our simulations is done in Figure 2 by comparing the simulated results to the exact analytic solution derived in Theorem 3.2. The average percent error over the 14 days simulated is 0.77%, with a maximum value of 2.43%. Further validation of the simulation framework was done using the extinction probability, $1 - Q(t)$, where $Q(t)$ is the survival probability

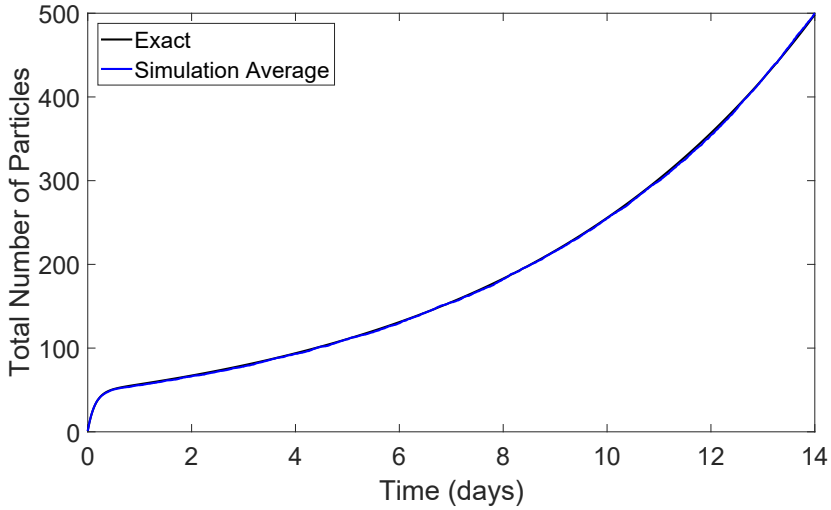

FIG. 2. Total number of particles (stationary and mobile) as a function of time. Comparison of the theoretical expected value from Theorem 3.2 (black) and the average of 1000 realizations of the stochastic model (blue). Parameters as in Table 2. Color figure online.

described by the ODE system (3.10), in which good agreement between the theoretical and empirical trajectories was obtained (results not shown). We note that we have not compared the spatio-temporal simulation results (Figures 3 and 4) to the integro-differential equation descriptions (2.1)–(2.3) due to the difficulty in accurately simulating such models, and the development of efficient numerical methods to accurately solve this type of equation is left as future work.

Figure 2 shows a comparison between the exact dynamics from Theorem 3.2 (black curve) and the average dynamics over 1000 individual realizations of the stochastic model (blue curve). While the simulations all begin with a single stationary particle, the expected number of particles increases to approximately 50 within the first day. This rapid increase is due to the relatively high shedding rate, resulting in the rapid creation of mobile particles. The slow-down upon reaching 50 particles reflects the expected asymptotic ratio of moving to stationary particles (comment after Lemma 3.2) which is approximately 48 with the parameters from Table 2. With the metastatic reproduction number $R_0 \approx 5 \times 10^6 \gg 1$, we expect the total particle number to grow exponentially at rate $\alpha_+ \approx 0.167$ (Corollary 3.1). After an initial period of transience, we do see exponential growth, both in the exact and simulated results.

Figure 3 illustrates the average spatio-temporal dynamics of the stochastic model. The left column presents the full spatio-temporal dynamics of the stationary (top) and mobile (bottom) particles, while the right column shows the spatial distribution of the stationary (top) and mobile (bottom) particles at time $t = 14$ days. In no individual simulation did we see the original established tumor perish. This result is not unexpected given the probability of a tumor perishing over the 14 days considered in our simulations is $1 - \exp(-14\delta_2) = 4.48 \times 10^{-7}$. Consequently, we always have at least one stationary particle located at position $x = 0$. This explains both the horizontal line in the top left plot (note the difference in scales), as well as the tall bar at the origin in the top right plot. The histograms on the right side of Figure 3 show relatively symmetric distributions of both stationary and mobile particles centered around the origin. While the individual location of each particle is given by a normal distribution as a result of the Brownian dynamics, the distribution of the aggregate particles (both stationary and mobile)

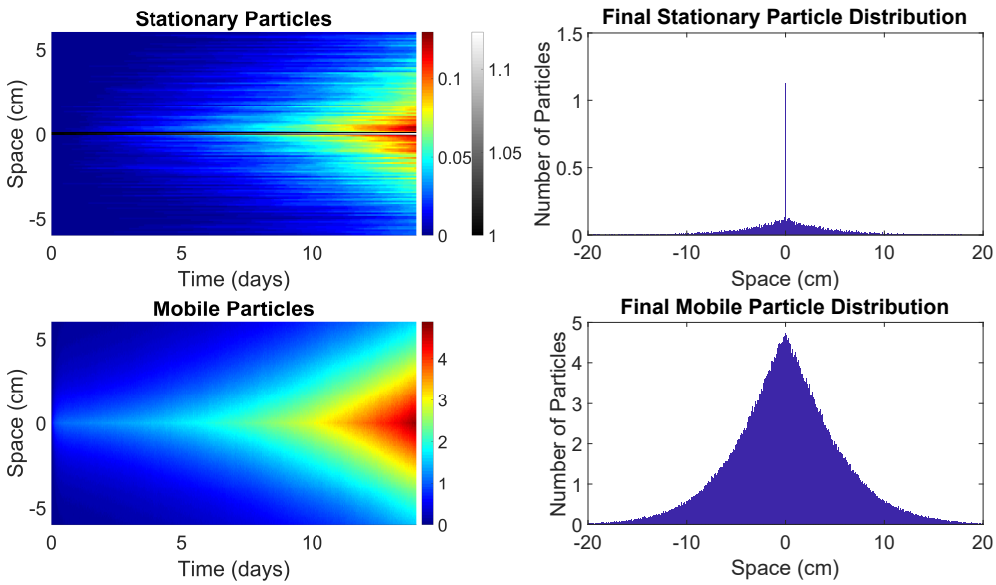

FIG. 3. Average results of 1000 individual realizations of the stochastic model. Left column: spatio-temporal dynamics of the stationary (top) and mobile (bottom) particles. The horizontal axis is time (in days) while the vertical axis denotes space (in m from location of primary tumor). Number of particles indicated by the coloring (color figure online). Note the different scales in the top plot. Right column: average spatial distribution of the stationary (top) and mobile (bottom) particles at the end of the 14 day simulations. Note the difference in scales from top to bottom. Parameters used as in Table 2.

is not normal. The reason is that shedding, settlement and death cause additional randomness. Even when $\lambda = 0$ (no settlement) and $\delta_1 = \delta_2 = 0$ (no deaths) so that only one stationary particle sheds moving particles, the distribution of the aggregate moving particles will not be normal. This can be seen from (2.1), which becomes $F_t = \mu G$, hence the density of the aggregate moving particles in this case is an integral of normal densities and not a normal density itself.

In order to more clearly see the interface between empty space and invading cancer cells, we have taken the data in the left column of Figure 3, and simplified them to be either 1 if there was, on average, at least 0.025 particles in that location across all 1000 simulations, or 0 otherwise. The results of this simplification are presented in Figure 4. We can see that for stationary particles, it takes close to four days before we see any significant establishment events. This result mirrors the observations made by Cameron et al. (2000) that no metastases established in the first four days post-injection.

Following a rapid initial jump, the mobile particle boundary appears to invade at a more or less constant speed. These mobile 'boundary' dynamics (Figure 4) are in stark contrast with the 'interior' dynamics (bottom left in Figure 3, in particular, the blue-teal interface) where the level sets form triangular regions with edges whose slopes are increasing as we advance through time.

5. Conclusion and Discussion

We introduced and analyzed a *branching stochastic process with settlement* and we applied it to metastatic cancer growth. The fact that the expected number F of particles, the variance V, the distribution H of the furthest particle and the extinction probability Q satisfy the same type of integro-differential equation with distributed delay (2.5) reveals the recursive structure of this process. Methods from differential

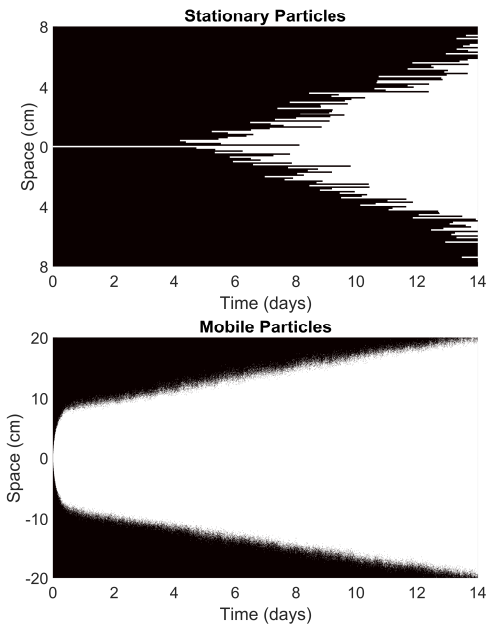

FIG. 4. Manipulation of the plots from the left column of Figure 3 showing the areas that may be significantly affected by the primary tumor and its metastatic spread. More specifically, areas that have, on average, at least 0.025 particles over all 1000 simulations are colored white. Areas in which this is not the case are colored black. The top shows results for stationary particles, and the bottom for mobile particles.

equations theory become available to analyze the qualitative behavior of this stochastic process. A recurring quantity was identified to play the role of a basic reproductive number, similar to epidemic models (Hethcote, 2000), which we call the *metastatic reproductive number*

$$R_0 = \frac{\lambda}{\delta_1 + \lambda} \frac{\mu}{\delta_2}.$$

For the mouse data that we analyzed as an example, we found $R_0 \sim 10^6$, which, of course, is huge. This is expected, as cell lines for metastasis studies are chosen specifically to generate metastases efficiently and reliably.

The value of R_0 for a typical human cancer will be quite different, and we leave a detailed estimate of R_0 for human cancers for further studies. Still, we can already see the impact of various possible treatment strategies. To shrink R_0, we like to reduce the shedding rate μ and the settlement rate λ while increasing the death rates δ_1 and δ_2 for moving and stationary particles, respectively. For example, the death rate δ_1 for CTCs could be increased through platelet inhibitors. Platelets are known to shield cancer cells from the immune surveillance, and less platelets can make cancer cells more exposed and more vulnerable (Coupland et al., 2012; Riggi et al., 2018; Shahriyari, 2016). The settlement rate λ might be reduced through decreasing the availability of metastatic niches (Riggi et al., 2018). This can be achieved through very simple means such as reduced pH-levels of tissue (Silva et al., 2009) to very advanced means such as novel immunotherapies designed to disrupt the preparation of the pre-metastatic niche (Kaplan et al., 2005). However, removing 90% of cancer sites would not change the final outcome since the reproductive number is unchanged. A partial removal would significantly delay

cancer spread, but metastasis would recur over time. Overall, the index R_0 has the potential to become a useful quantity in treatment planning.

We see various extensions and limitations of the model as we discuss now.

1. While we started with a stationary individual, we could have started with a particle that is moving randomly, but this would make the analysis more difficult. Furthermore, if we know the function F of our model, we can find the corresponding function $\tilde{F}$ in a model with randomly moving first particle by

$$\begin{aligned}\tilde{F}(t,x) &= E\left[\sum_{i=1}^{N(t-\min\{\tau,t\})} \mathbb{1}_{X_i(t-\min\{\tau,t\})+B(\min\{\tau,t\})\leqslant x}\right]\\ &= \int_0^t E\left[\sum_{i=1}^{N(t-s)} \mathbb{1}_{X_i(t-s)+B(s)\leqslant x}\right]\lambda \mathrm{e}^{-\lambda s}\mathrm{e}^{-\delta_1 s}\,\mathrm{d}s + \int_t^\infty P[B(t)\leqslant x]\lambda \mathrm{e}^{-\lambda s}\mathrm{e}^{-\delta_1 t}\,\mathrm{d}s\\ &= \int_0^t \int_{\mathbb{R}^d} F(t-s,x-y)g(s,y)\lambda \mathrm{e}^{-(\lambda+\delta_1)s}\,\mathrm{d}y\,\mathrm{d}s + G(t,x)\mathrm{e}^{-(\lambda+\delta_1)t},\end{aligned}$$

   where $B(\min\{\tau,.\})$ is a random process describing the movement of the first particle up to time τ, and the factor $\mathrm{e}^{-\delta_1 s}$ is the survival probability of the first particle at time s.

2. A classical related model is branching Brownian motion (Bovier, 2016), where all particles move according to Brownian motion and there are no deaths, no settlements and births occur independently at some exponentially distributed time $\nu \sim \mathrm{Exp}(\mu)$. Similarly to the proof of Theorem 2.1, it can be shown that the expected location function $\bar{F}$ satisfies

$$\bar{F}_t(t,x) = G_t(t,x) + \mu G(t,x).$$

   Note that this is different from our model even when assuming no deaths ($\delta_1 = \delta_2 = 0$) and no settlement ($\lambda = 0$). Indeed, for $\delta_1 = \delta_2 = \lambda = 0$, F in our model satisfies $F_t(t,x) = \mu G(t,x)$. The reason for this difference to the case of branching Brownian motion is that, in our model with $\delta_1 = \delta_2 = \lambda = 0$, there is always a particle located at zero, and only this particle emits further particles.

3. In the one-dimensional, linear case with $r_2 = 0$ and for constant decay rate $q(t) =$ const. we can use Fourier and Laplace transforms to find an explicit solution of the general non-local model (2.5). Let $\mathscr{F}, \mathscr{F}^{-1}$ denote the Fourier transform and its inverse and let $\mathscr{L}, \mathscr{L}^{-1}$ denote the Laplace transform and its inverse, respectively. We use the hat $\hat{f}$ to denote the Fourier transform of a function and the tilde $\tilde{g}$ for the Laplace transform, i.e.

$$\hat{f}(\omega) := \mathscr{F}(f(x))(\omega), \qquad \tilde{g}(s) := \mathscr{L}(g(t))(s).$$

   Transforming the general model (2.5) in the case of $r_2 = 0$ and $q(t) =$const. leads to

$$s\tilde{\hat{f}} - \hat{f}(0) = -q\tilde{\hat{f}} + \tilde{\hat{p}} + r_1\sqrt{2\pi}\tilde{\hat{k}}\tilde{\hat{f}}$$

   for an unknown function $\tilde{\hat{f}}(s,\omega)$ in Laplace-Fourier space. We can solve this algebraic equation and find

$$\tilde{\hat{f}}(s,\omega) = \frac{\tilde{\hat{p}}(s,\omega) + \hat{f}(0)}{s + q + \sqrt{2\pi}r_1\tilde{\hat{k}}(s,\omega)}$$

Hence the solution of (2.5) for $r_2 = 0$ and $q(t) = \text{const.}$ is:

$$f(t,x) = \mathscr{F}^{-1}\mathscr{L}^{-1}\left(\frac{\tilde{\hat{p}}(s,\omega) + \hat{f}(0)}{s + q + \sqrt{2\pi}r_1\tilde{\hat{k}}(s,\omega)}\right).$$

It has to be seen if this formula can shed valuable information about the branching stochastic process with settlement.

4. The spatial transport and settlement of a real cancer in a human body is much more complicated than assumed in our example. Here, as an example, we considered Brownian motion as spatial process and a homogeneous settlement rate, λ. However, our framework is based on a general spatial process, $(B(t))_{t\geqslant 0}$, whose distribution could reflect more realistic body-wide properties. Such a specification is a complex issue and left for future research.

5. It is well known that certain tumors tend to metastasize to certain organs, for example prostate cancer preferentially metastasizes to the bone, and breast tumors often spread to the brain, bone, liver, and lungs (Chambers et al., 2002). In this case, the settlement rate, λ, is no longer homogeneous, rather it depends on the location x. Moreover, this spatial dependency encodes the locations of pre-metastatic niches (Kaplan et al., 2005). However, the branching stochastic process with settlement would then lose its recursive nature, which was crucial in the proofs of our results. Consequently, additional work must be completed before this intricacy can be included into future iterations of the model.

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