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ANALYSIS OF A MODEL FOR TRANSFER PHENOMENA IN BIOLOGICAL POPULATIONS*

PETER HINOW†, FRANK LE FOLL‡, PIERRE MAGAL§, AND GLENN F. WEBB¶

Abstract. We study the problem of transfer in a population structured by a continuum variable corresponding to the quantity being transferred. The transfer of the quantity occurs between individuals according to specified rules. The model is of Boltzmann type with kernels corresponding to the transfer process. We prove that the transfer process preserves total mass of the transferred quantity and the solutions of the simple model converge weakly to Radon measures. We generalize the model by introducing proliferation of individuals and production and diffusion of the transferable quantity. It is shown that the generalized model admits a globally asymptotically stable steady state, provided that transfer is sufficiently small. We discuss an application of our model to cancer cell populations, in which individual cells exchange the surface protein P-glycoprotein, an important factor in acquired multidrug resistance against cancer chemotherapy.

Key words. transfer processes, population dynamics, multidrug resistance

AMS subject classifications. 34G20, 35K15, 92D25

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1. Introduction.

Transfer phenomena arise in a multitude of natural processes, and their mathematical formulations have a long history. A fundamental mathematical modeling approach of transfer phenomena has been integro-partial differential equations of Boltzmann type, in which interacting particles are viewed as members of a continuum population density. In these models transfer of physical quantities from one particle to another is modulated by a kernel function that specifies the transfer process. Many examples have been explored, and a recent review is found in Villani [24].

Our objective in this paper is to analyze Boltzmann-type transfer models applicable to biological cell population dynamics. A well-studied example of such a transfer is horizontal plasmid transfer of bacterial and mammalian cells [22]. Another example is the recent discovery that the protein P-glycoprotein (P-gp) is transferred between cells [13, 2]. This transfer process may confer resistance against cytotoxic drugs to cancer cells, as P-gp is well known to act as a drug-efflux pump [2]. The direct physical transfer of a protein that retains intrinsic chemotherapeutic resistance is, therefore, of major significance in designing optimal cancer treatment. In a companion paper [19] we will present experimental work about P-gp transfer in breast cancer cell lines and use the model developed here to assist in its understanding.

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†Corresponding author. Institute for Mathematics and its Applications, University of Minnesota, 114 Lind Hall, Minneapolis, MN 55455 (hinow@ima.umn.edu). The work of this author was supported by an IMA postdoctoral fellowship and the Vanderbilt Integrative Cancer Biology Center (VICBC) during a visit to Vanderbilt University.

‡Laboratory of Ecotoxicology UPRES-EA 3222, IFRMP 23, University of Le Havre, 25 rue Philippe Lebon, 76058 Le Havre cedex, France (frank.lefoll@univ-lehavre.fr).

§Department of Mathematics, University of Le Havre, 25 rue Philippe Lebon, 76058 Le Havre cedex, France (pierre.magal@gmail.com).

¶Department of Mathematics, Vanderbilt University, 1326 Stevenson Center, Nashville, TN 37240 (glenn.f.webb@vanderbilt.edu). The work of this author was supported by the NCI Integrative Cancer Biology Program (U54-CA113007) and the Vanderbilt Integrative Cancer Biology Center (VICBC).

Boltzmann-type models have been employed in the context of complex multiscale biological populations by many authors, and recent summaries are found in the book by Bellouquid and Delitala [5] and the review papers by Bellomo, Li, and Maini [4] and Bellomo and Delitala [3]. Transfer processes in proliferating cell populations present many challenging levels of modeling complexity, because of the unique character of cell growth, division, and function. Interacting populations of cells have far greater complexity than interacting populations of physical particles, because cells themselves are complex heterogeneous living organisms. We investigate here a model of cell population dynamics incorporating the transfer of a material constituent. We analyze the mathematical properties of this model, including existence and uniqueness of solutions, the conservation of cell count, the conservation of transfer quantity mass, and the convergence of the solutions over time. We investigate various formulations of the transfer processes and illustrate them with numerical examples. Our work is motivated by biological examples, but our results are applicable generally to systems in which transfer of quantities occurs within a population.

2. The transfer process. We assume a population of individuals structured by a continuous scalar variable $p \in [p_{min}, p_{max}]$, where p is the quantity of transferable material possessed by individuals in the population. We assume that after appropriate scaling $p_{min} = 0$ and $p_{max} = 1$. Let $u(p,t)$ denote the population density of individuals having quantity p at time t. Thus, assuming integrability,

$$\int_{p_1}^{p_2} u(t,p)dp$$

is the total number of individuals possessing a quantity of p between p_1 and p_2 at time t. We work in the space $L^1[0,1]$ with positive cone $L^1_+[0,1]$ and norm $||\cdot|| = ||\cdot||_{L^1[0,1]}$. Given $\phi \in L^1_+[0,1]$ and $n = 0,1,2,\dots$, we write

$$E_n(\phi) = \int_0^1 p^n \phi(p)\, \mathrm{d}p$$

for the nth moment. Clearly $E_0(u(t,.)) = ||u(t,.)||$ is the total number of individuals in the population at time t, and the first moment $E_1(u(t,.))$ is the total amount of p possessed by all individuals in the population at time t.

We first illustrate the transfer process in a simplified version with the following assumptions:

(A1) The probability that a pair of individuals is involved in a transfer event is independent of their p values, and the pairing is chosen randomly from all individuals.

(A2) The time between two transfer events follows an exponential law with mean $\tau^{-1} > 0$ (alternatively, τ is the rate of transfer per unit time).

(A3) Let $0 < f < 1$ (we call f the *transfer efficiency*). A transfer between two individuals, one with value p_1 and the other with value p_2, results in a transfer of the fraction f of their difference $f|p_1 - p_2|$ gained by the smaller and lost by the larger of the two.

To obtain a transfer operator from assumption (A3) we consider a transfer event with one partner in the pair having value $\hat{p}$ before the event and one partner having value p after the event. The four possibilities are illustrated in Figure 2.1. The transfer

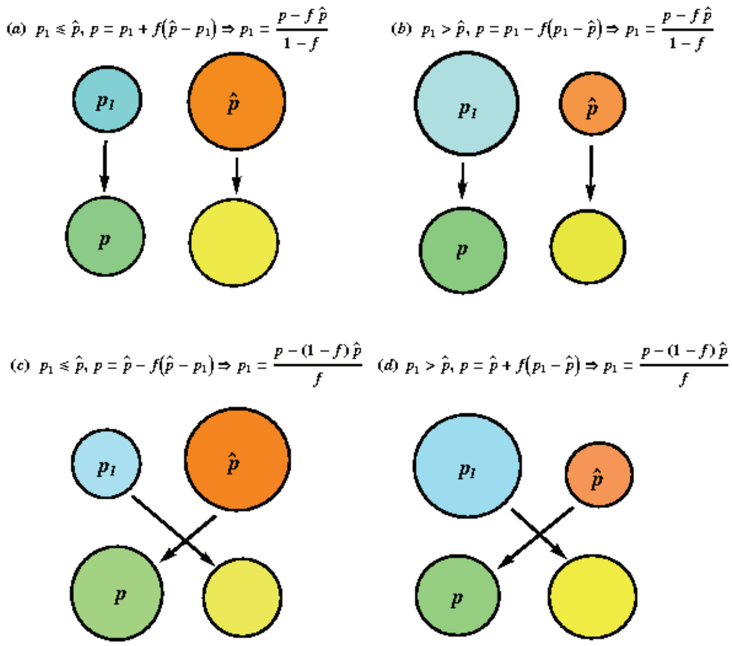

FIG. 2.1. *The four possibilities of transfer to a cell with value p after a transfer event with one predecessor cell having value $\hat{p}$ and the other predecessor cell having value $\frac{p-f\hat{p}}{1-f}$ ((a) and (b)) or $\frac{p-(1-f)\hat{p}}{f}$ ((c) and (d)).*

model under assumptions (A1)–(A3) is

(2.1)
$$\frac{\partial u}{\partial t}(t,p) = 2\tau \left(T_{f,0}(u(t,\cdot))(p) - u(t,p)\right), \text{ for } t \geq 0, \text{ and } u(0,p) = u_0(p) \in L^1_+ [0,1],$$

where $T_{f,0}(0) = 0$ and for $\phi \in L^1_+ [0,1]$, $\phi \neq 0$,

$$T_{f,0}(\phi)(p) = \frac{1}{\|\phi\|} \left[\int_0^1 K_{f,0}(p,\hat{p}) \phi \left(\frac{p - f\hat{p}}{1-f} \right) \phi(\hat{p}) \, \mathrm{d}\hat{p} + \int_0^1 K_{1-f,0}(p,\hat{p}) \phi \left(\frac{p-(1-f)\hat{p}}{f} \right) \phi(\hat{p}) \, \mathrm{d}\hat{p} \right]$$

with

$$K_f(p,\hat{p}) = \begin{cases} 1 \text{ if } 0 \leq \dfrac{p - f\hat{p}}{1-f} \leq 1, \\ 0 \text{ elsewhere.} \end{cases}$$

The kernels $K_{f,0}(p,\hat{p})$ and $K_{1-f,0}(p,\hat{p})$ constrain the values p and $\hat{p}$ to the allowable values of transfer pairs as delimited by assumption (A3). An illustration of the

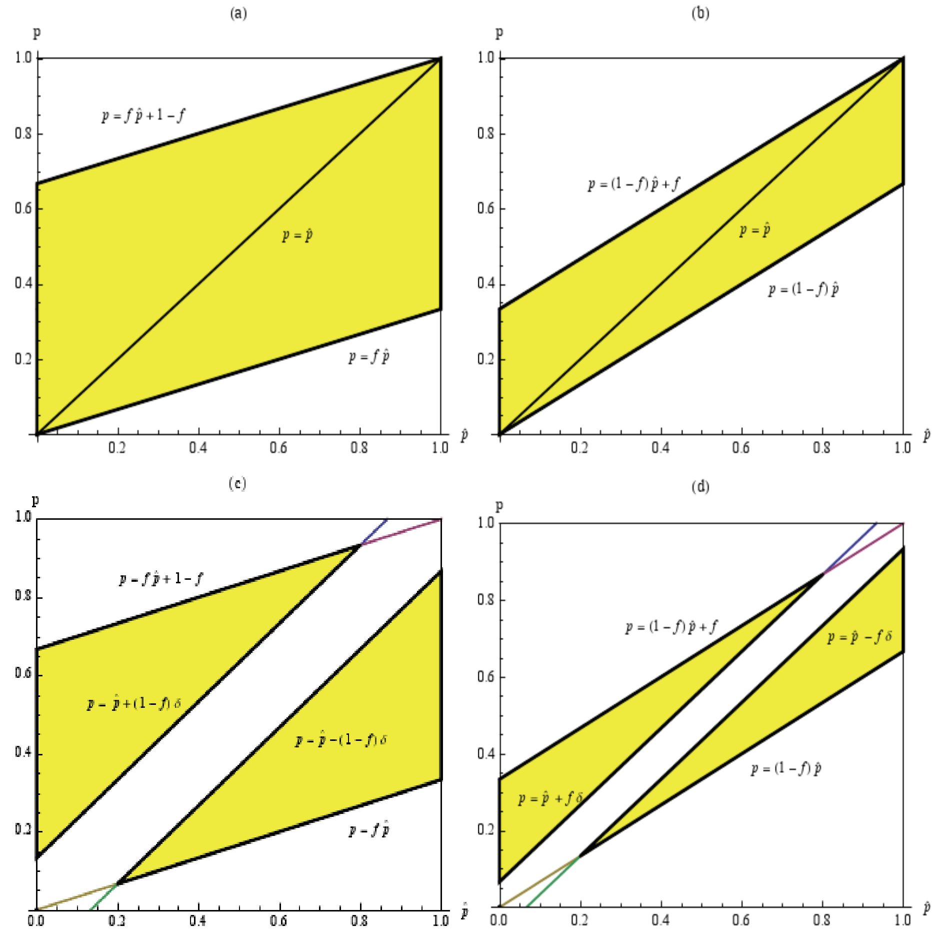

FIG. 2.2. *The domains of the transfer kernels.* (a) $K_{f,\delta}(p,\hat{p})$*,* $f = 1/3$*,* $\delta = 0$*;* (b) $K_{1-f,\delta}(p,\hat{p})$*,* $f = 1/3$*,* $\delta = 0$*;* (c) $K_{f,\delta}(p,\hat{p})$*,* $f = 1/3$*,* $\delta = 1/5$*;* (d) $K_{1-f,\delta}(p,\hat{p})$*,* $f = 1/3$*,* $\delta = 1/5$*. The kernels have the value* 1 *inside the outlined regions and* 0 *outside.*

domains of the kernels is given in Figures 2.2(a) and 2.2(b). An illustration of a solution to (2.1) is given in Figure 2.3, where it is seen that the transfer process results in concentration in a Dirac mass as $t \to \infty$. We will return to this in Theorem 4.3.

A generalization of the transfer process is obtained by requiring the following assumption:

(A4) An exchange takes place only if the difference of the transfer pair p_1 and p_2 in assumption (A3) is $> \delta$ (we call $\delta \in (0,1)$ the *transfer threshold*).

The transfer model under assumptions (A1)–(A4) is

(2.2)
$$\frac{\partial u}{\partial t} = 2\tau \left(T_{f,\delta}(u(t,\cdot))(p) - M_\delta(u(t,\cdot))(p)\right), \text{ for } t \geq 0, \text{ and } u(0,p) = u_0(p) \in L^1_+[0,1],$$

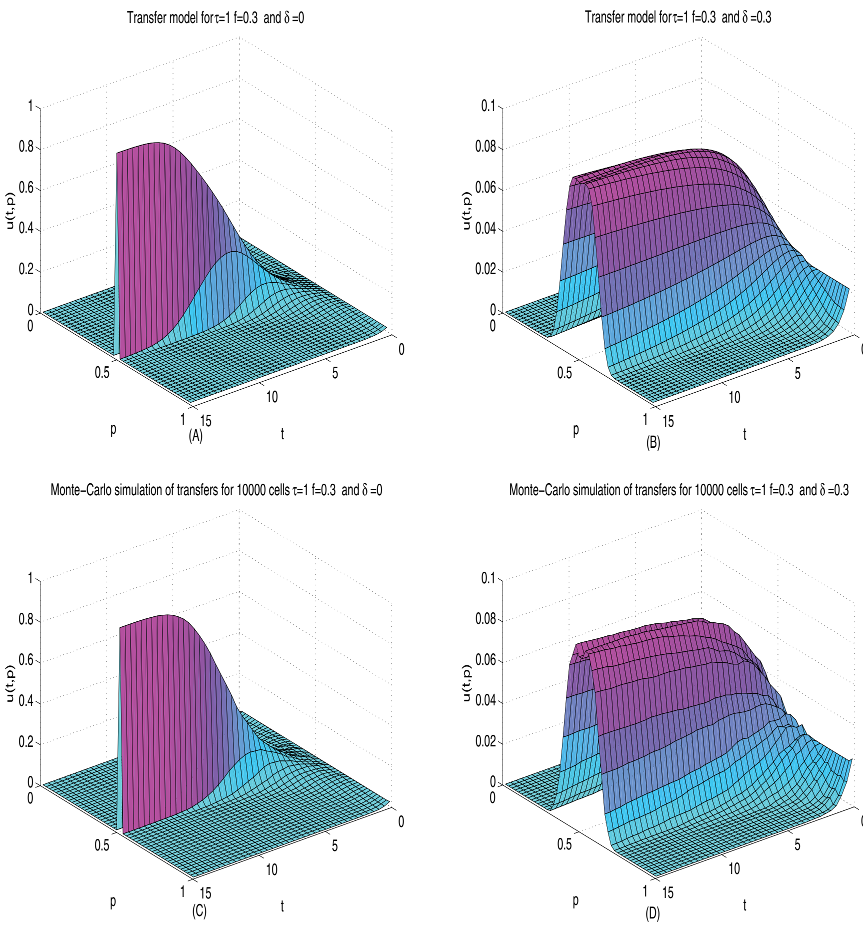

FIG. 2.3. *Simulation of the transfer model* (2.2) *with initial data* $u_0(p) = 1.0$ *using rule* (A3) *and rule* (A4). $f = 0.3$ *and* $\delta = 0$ *in* (A) *and* (C) *and* $f = 0.3$ *and* $\delta = 0.3$ *in* (B) *and* (D). *In* (A) *and* (C) *(*$\delta = 0$*) the solution approaches a Dirac* δ*-function centered at* $p = \frac{1}{2}$. *In* (B) *and* (D) *(*$\delta = 0.3$*) the solution approaches a bounded distribution with mean* $p = \frac{1}{2}$. (A) *and* (B) *are numerical simulations of the transfer model* (2.2). (C) *and* (D) *are Monte Carlo simulations of the model with* 10000 *individuals.*

where $T_{f,\delta}(0) = 0$ and for $\phi \in L^1_+[0,1]$, $\phi \neq 0$,

$$
\begin{aligned}
T_{f,\delta}(\phi)(p) = \frac{1}{\|\phi\|} \Bigg[& \int_0^1 K_{f,\delta}(p,\hat{p})\phi\left(\frac{p - f\hat{p}}{1-f}\right)\phi(\hat{p})\,\mathrm{d}\hat{p} \\
& + \int_0^1 K_{1-f,\delta}(p,\hat{p})\phi\left(\frac{p-(1-f)\hat{p}}{f}\right)\phi(\hat{p})\,\mathrm{d}\hat{p}\Bigg]
\end{aligned}
$$

with

$$
K_{f,\delta}(p,\hat{p}) = \begin{cases} 1 \text{ if } 0 \leq \dfrac{p - f\hat{p}}{1-f} \leq \hat{p} - \delta \text{ or } \hat{p} + \delta \leq \dfrac{p - f\hat{p}}{1-f} \leq 1, \\ 0 \text{ elsewhere} \end{cases}
$$

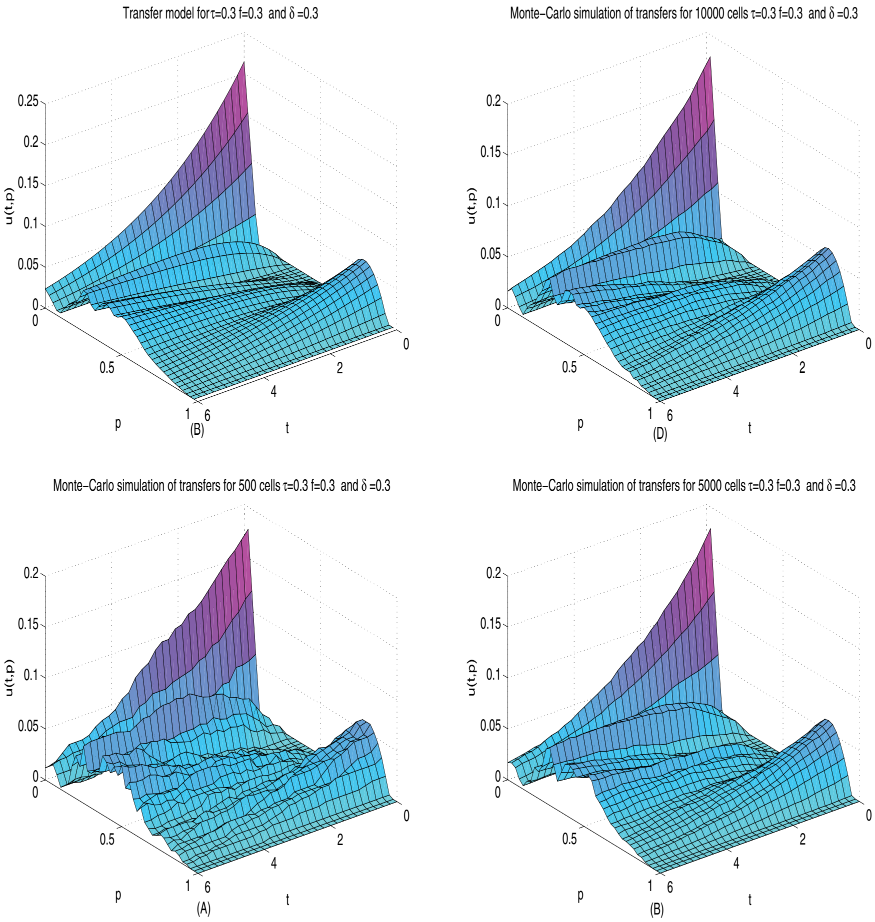

FIG. 2.4. (A) *simulates the experimental data in* [13] *for the transfer of P-gp in cocultured drug sensitive and drug resistant cancer cells with the transfer model* (2.2) *using the transfer rule* (A4) *with* $f = 0.3$ *and* $\delta = 0.3$. *The initial data* $u_0(p)$ *is chosen comparable to the initial distribution in* [13], *with sensitive cells expressing very low P-gp levels and resistant cells expressing high levels. The population shifts toward a stable population with two peaks at intermediate P-gp levels.* (B), (C), (D) *are Monte Carlo simulations of the model in* (A) *with the number of individual cells as* 10,000, 500, *and* 5,000, *respectively.*

and

$$M_\delta(\phi)(p) = \left[\frac{1}{||\phi||} \left(\int_0^{p-\delta} + \int_{p+\delta}^1 \right) \phi(\hat{p})\, \mathrm{d}\hat{p} \right] \phi(p).$$

An illustration of the domains of the kernels in the case $\delta > 0$ is given in Figures 2.2(c) and 2.2(d). An illustration of a solution to (2.2) is given in Figure 2.4, where it is seen that the transfer process with transfer threshold $\delta > 0$ results in stabilization to a bounded equilibrium, in contrast to the case $\delta = 0$.

The transfer processes in assumptions (A3) and (A4) can be extended to more general constraints on the cell pairs undergoing transfer. For the more general case we require in addition to assumptions (A1) and (A2) the following assumption:

(A5) Let $f \in L^\infty[0,1]$ with $0 \leq f \leq 1$. If two individuals whose difference in quantity is $\hat{p}$ are involved in a transfer, then the one with higher value loses $f(|\hat{p}|)$ times the difference of their p values and the one with lower p value gains exactly this amount.

In assumption (A5) a particle of size p can arise from a shorter particle that gains the portion $f(|\hat{p}|)\hat{p}$ of a certain size difference $\hat{p}$ or from a longer particle that loses the portion $f(|\hat{p}|)\hat{p}$ of the size difference $\hat{p}$. The two partners in such an exchange must have the complementary values $p + f(|\hat{p}|)\hat{p}$ and $p - (1 - f(|\hat{p}|))\hat{p}$. A particle of size p is lost when it is either the donor or the acceptor in a transfer. For any function ϕ defined on $[0,1]$ we denote by $\bar{\phi}$ its trivial extension by zero outside $[0, 1]$. The transfer operator $T : L^1_+[0,1] \to L^1_+[0,1]$ is given by $T(0) = 0$ and for $\phi \neq 0$ by

$$T(\phi)(p) = \frac{1}{||\phi||} \int_{-\infty}^{\infty} \bar{\phi}(p + \bar{f}(|\hat{p}|)\hat{p})\bar{\phi}(p - (1 - \bar{f}(|\hat{p}|))\hat{p})\,\mathrm{d}\hat{p}. \tag{2.3}$$

The reason for extending the integral to $\mathbb{R}$ is solely notational convenience (it allows us to freely shift the integration variable). The evolution equation for the transfer process is given by the *transfer equation*

$$\frac{\partial u}{\partial t} = 2\tau\left(T(u(t,\cdot))(p) - u(t,p)\right), \text{ for } t \geq 0, \text{ and } u(0,p) = u_0(p) \in L^1_+[0,1]. \tag{2.4}$$

Observe that the transfer rate τ must be multiplied by 2 as transfer involves two individuals. More precisely, a particle that emerges with quantity p may have been the smaller or larger partner in the transfer event.

Assumption (A5) generalizes assumption (A3) by taking the transfer efficiency $f \equiv \text{const}$, and it generalizes assumption (A4) by taking

$$f(|p|) = \begin{cases} f & \text{if } |p| \geq \delta, \\ 0 & \text{otherwise.} \end{cases} \tag{2.5}$$

With the choice as in (2.5), the transfer process becomes

$$T_1(\phi)(p) = \frac{1}{||\phi||}\left(\int_{s_1(p,f)}^{-\delta} + \int_{\delta}^{s_2(p,f)}\right)\phi(p + f\hat{p})\phi(p - (1-f)\hat{p})\,\mathrm{d}\hat{p}.$$

The boundaries of integration $s_1(p,f)$ and $s_2(p,f)$ must be chosen such that the inequalities

$$0 \leq p + f\hat{p} \leq 1, \quad 0 \leq p - (1-f)\hat{p} \leq 1$$

are satisfied. This is the case if we choose

$$s_1(p,f) = \max\left\{-\frac{p}{f}, -\frac{1-p}{1-f}\right\}, \quad s_2(p,f) = \min\left\{\frac{1-p}{f}, \frac{p}{1-f}\right\}.$$

In order to balance the gain at the level p we need to define the corresponding loss operator. Let

$$M(\phi)(p) = \frac{\phi(p)}{||\phi||}\left(\int_0^{\max\{p-\delta,0\}} + \int_{\min\{p+\delta,1\}}^1\right)\phi(\hat{p})\,\mathrm{d}\hat{p}.$$

The evolution equation for the transfer process with constant transfer efficiency but restricted to nonvanishing differences is given by

$$\frac{\partial u}{\partial t} = 2\tau\left(T_1(u(t,\cdot))(p) - M(u(t,\cdot))(p)\right) \quad \text{and} \quad u(0,p) = u_0(p) \in L^1_+[0,1]. \tag{2.6}$$

Indeed, with the special choice (2.5), T from (2.3) becomes

$$\begin{aligned} T(\phi)(p) &= \frac{1}{||\phi||}\left(\int_{s_1(p,f)}^{-\delta} + \int_{\delta}^{s_2(p,f)}\right)\phi(p+f\hat{p})\phi(p-(1-f)\hat{p})\,\mathrm{d}\hat{p} \\ &\quad + \frac{\phi(p)}{||\phi||}\int_{-\delta}^{\delta}\phi(p-\hat{p})\,\mathrm{d}\hat{p} \\ &= \frac{1}{||\phi||}\left(\int_{s_1(p,f)}^{-\delta} + \int_{\delta}^{s_2(p,f)}\right)\phi(p+f\hat{p})\phi(p-(1-f)\hat{p})\,\mathrm{d}\hat{p} \\ &\quad + \frac{\phi(p)}{||\phi||}\int_{\max\{p-\delta,0\}}^{\min\{p+\delta,1\}}\phi(\hat{p})\,\mathrm{d}\hat{p}. \end{aligned}$$

At the same time

$$\begin{aligned} \phi(p) &= \frac{\phi(p)}{||\phi||}\left(\int_0^{\max\{p-\delta,0\}} + \int_{\max\{p-\delta,0\}}^{\min\{p+\delta,1\}} + \int_{\min\{p+\delta,1\}}^{1}\right)\phi(\hat{p})\,\mathrm{d}\hat{p} \\ &= M(\phi)(p) + \frac{\phi(p)}{||\phi||}\int_{\max\{p-\delta,0\}}^{\min\{p+\delta,1\}}\phi(\hat{p})\,\mathrm{d}\hat{p}. \end{aligned}$$

In summary,

$$T(\phi)(p) - \phi(p) = T_1(\phi)(p) - M(\phi)(p);$$

that is, (2.4) with the transfer function from (2.5) is equivalent to (2.6).

The equivalence of the transfer models (2.1) and (2.6) can be shown using the change of variables $y = x - (1-f)s$ and $y = x + fs$. The reason for introducing the operators T_1 and M for this special case is that they are somewhat easier to implement numerically. The operators T_1 and M in (2.6) can be considered as the gain and loss operators, respectively, in an equation of Boltzmann type. The transfer operator in the special case that $f \equiv \frac{1}{2}$ was used in [18, 6] and also studied in [15].

An important aspect of this work is that we also perform Monte Carlo simulations of the transfer process (see section 6). When the number of individuals increases we observe that the normalized distribution obtained by Monte Carlo simulations approaches the normalized distribution obtained by solving the differential equation (2.6). In other words, the differential equation model conforms with the assumptions made for the stochastic process.

3. Basic properties of the transfer operator.

THEOREM 3.1. *The operator T from* (2.3) *maps $L^1_+[0,1]$ into itself and has the following properties:*

(a) *T is positive homogeneous, and $T(cu) = cT(u)$ for all $c > 0$.*

(b) *T is globally Lipschitz continuous.*

(c) $\operatorname{supp} T(u) \subset conv\,(\operatorname{supp} u)$, *where conv denotes the convex hull.*

(d) *We have for* $u \in L^1_+[0,1]$ *and* $n = 0, 1$

$$E_n(T(u)) = E_n(u). \tag{3.1}$$

Proof. These properties stated in Theorem 3.1 are similar to those of the recombination operator used in the papers [18] and [15]; see in particular [18, Theorem 2.1]. Notice that in property (c), the convex hull of the closed set $\operatorname{supp} u$ is itself closed. For $u, v \in L^1_+[0,1]$ define the bilinear map

$$(u *_f v)(p) = \int_{-\infty}^{\infty} \bar{u}(p + \bar{f}(|\hat{p}|)\hat{p})\bar{v}(p - (1 - \bar{f}(|\hat{p}|))\hat{p})\,\mathrm{d}\hat{p}.$$

Notice that if $p \notin [0,1]$, then one of the two arguments $p + \bar{f}(|\hat{p}|)\hat{p}$ and $p - (1 - \bar{f}(|\hat{p}|))\hat{p}$ is also outside this interval and hence $(u *_f v)(p) = 0$. With this notation the transfer operator has the short form

$$T(u) = ||u||^{-1}\,(\,u *_f u\,)\,. \tag{3.2}$$

The following holds by Fubini's theorem:

$$\begin{aligned}\int_{\mathbb{R}} (u *_f v)(p)\,\mathrm{d}p &= \int_{\mathbb{R}^2} \bar{u}(p - (1 - \bar{f}(|\hat{p}|))\hat{p})\bar{v}(p + \bar{f}(|\hat{p}|)\hat{p})\,\mathrm{d}p\,\mathrm{d}\hat{p}\\ &= \int_{\mathbb{R}^2} \bar{u}(r - \hat{p})\bar{v}(r)\,\mathrm{d}r\,\mathrm{d}\hat{p} = \int_{\mathbb{R}^2} \bar{u}(s)\bar{v}(r)\,\mathrm{d}s\,\mathrm{d}r\\ &= \int_{\mathbb{R}} \bar{u}(s)\,\mathrm{d}s \int_{\mathbb{R}} \bar{v}(r)\,\mathrm{d}r.\end{aligned}$$

Applying this to $u = v$ and using (3.2) gives (3.1) for $n = 0$. The Lipschitz continuity of the transfer operator is proved as follows. It is clear that

$$||T(u) - T(0)|| = ||T(u)|| = ||u||.$$

If both $u, v \neq 0$, we have

$$\begin{aligned}&||T(u) - T(v)||\\ &= \left\| ||u||^{-1}\,(u *_f (u - v)) + (||u||^{-1} - ||v||^{-1})\,(u *_f v) + ||v||^{-1}\,((u - v) *_f v) \right\|\\ &\leq 2||u - v|| + \left(||u||^{-1} - ||v||^{-1}\right)||u||||v|| = 2||u - v|| + |||u|| - ||v|||\\ &\leq 3||u - v||.\end{aligned}$$

To see that the operator T preserves the first moment we calculate, again using Fubini's theorem along the way,

$$\begin{aligned}&\int_{\mathbb{R}} (u *_f u)(p) p\,\mathrm{d}p = \int_{\mathbb{R}^2} p\bar{u}(p - (1 - \bar{f}(|\hat{p}|))\hat{p})\bar{u}(p + \bar{f}(|\hat{p}|)\hat{p})\,\mathrm{d}p\,\mathrm{d}\hat{p}\\ &= \int_{\mathbb{R}^2} (r - \bar{f}(|\hat{p}|)\hat{p})\bar{u}(r - \hat{p})\bar{u}(r)\,\mathrm{d}r\,\mathrm{d}\hat{p}\\ &= \int_{\mathbb{R}^2} (r - \bar{f}(|\hat{p}|)\hat{p})\bar{u}(r - \hat{p})\,\mathrm{d}\hat{p}\,\bar{u}(r)\,\mathrm{d}r\\ &= \int_{\mathbb{R}^2} \bar{u}(r - \hat{p})\,\mathrm{d}\hat{p}\, r\bar{u}(r)\,\mathrm{d}r - \int_{\mathbb{R}^2} \bar{f}(|\hat{p}|)\hat{p}\,\bar{u}(r - \hat{p})\,\mathrm{d}\hat{p}\,\bar{u}(r)\,\mathrm{d}r\\ &= \int_{\mathbb{R}} \bar{u}(s)\,\mathrm{d}s \int_{\mathbb{R}} \bar{u}(s)s\,\mathrm{d}s - \int_{\mathbb{R}^2} \bar{f}(|\hat{p}|)\hat{p}\,\bar{u}(r - \hat{p})\,\mathrm{d}\hat{p}\,\bar{u}(r)\,\mathrm{d}r.\end{aligned}$$

By setting $\hat{p} = r - s$,

$$\begin{aligned}
&\int_{\mathbb{R}^2} \bar{f}(|\hat{p}|)\hat{p}\,\bar{u}(r-\hat{p})\,\mathrm{d}\hat{p}\,\bar{u}(r)\,\mathrm{d}r = \int_{\mathbb{R}^2} \bar{f}(|r-s|)(r-s)\bar{u}(s)\bar{u}(r)\,\mathrm{d}s\ \mathrm{d}r \\
&= \int_{\mathbb{R}^2} \bar{f}(|r-s|)r\bar{u}(s)\bar{u}(r)\,\mathrm{d}s\ \mathrm{d}r - \int_{\mathbb{R}^2} \bar{f}(|r-s|)s\bar{u}(s)\bar{u}(r)\,\mathrm{d}s\ \mathrm{d}r \\
&= \int_{\mathbb{R}^2} \bar{f}(|r-s|)r\bar{u}(s)\bar{u}(r)\,\mathrm{d}s\ \mathrm{d}r - \int_{\mathbb{R}^2} \bar{f}(|s-r|)s\bar{u}(s)\bar{u}(r)\,\mathrm{d}s\ \mathrm{d}r \\
&= 0.
\end{aligned}$$

In summary,

$$\int_{\mathbb{R}} \overline{T\,(u)}(p)(p)p\,\mathrm{d}p = \int_{\mathbb{R}} \bar{u}(p)p\,\mathrm{d}p. \qquad \square$$

4. Basic properties of the transfer model. As an immediate corollary of Theorem 3.1 we obtain that the transfer model (2.4) conserves the zeroth and the first moment.

THEOREM 4.1. *For each initial datum* $u_0 \in L^1_+[0,1]$, (2.4) *has a global positive solution. Moreover, for all* $t > 0$ *and* $n = 0, 1$,

$$E_n(u(t)) = E_n(u_0).$$

Proof. Equation (2.4) is an ordinary differential equation in a Banach space whose right-hand side is globally Lipschitz continuous. The solution has the representation

$$u(t) = e^{-2\tau t}u_0 + 2\tau \int_0^t e^{-2\tau(t-s)}T(u(s))\,\mathrm{d}s,$$

and the positivity of u follows. $\square$

We show the convergence of all moments and therefore the convergence of the solution to a Radon measure in the weak* topology.

THEOREM 4.2. *For each initial distribution* $u_0 \in L^1_+(0,1)$, *there exists a Radon measure* w *on* $[0,1]$ *such that*

$$\lim_{t\to\infty} \langle u(t), \phi \rangle = \langle w, \phi \rangle \tag{4.1}$$

for every $\phi \in C[0,1]$.

Proof. We show first that the moments E_n are nonnegative and decreasing along a trajectory and hence their limits as $t \to \infty$ exist. Then we use these limits to construct the desired Radon measure. Assume without loss of generality that $E_0(u(t)) \equiv 1$. A calculation gives

$$\begin{aligned}
&\int_{\mathbb{R}} (u *_f u)(p) p^n \,\mathrm{d}p \\
&= \int_{\mathbb{R}^2} p^n \bar{u}(p - (1 - \bar{f}(|\hat{p}|))\hat{p}) \bar{u}(p + \bar{f}(|\hat{p}|)\hat{p}) \,\mathrm{d}p \,\mathrm{d}\hat{p} \\
&= \int_{\mathbb{R}^2} (r - \bar{f}(|\hat{p}|)\hat{p})^n \bar{u}(r - \hat{p}) \bar{u}(r) \,\mathrm{d}r \,\mathrm{d}\hat{p} \\
&= \int_{\mathbb{R}^2} ((1 - \bar{f}(|\hat{p}|))r + \bar{f}(|\hat{p}|)(r - \hat{p}))^n \bar{u}(r - \hat{p}) \bar{u}(r) \,\mathrm{d}r \,\mathrm{d}\hat{p} \\
&= \sum_{k=0}^{n} \binom{n}{k} \int_{\mathbb{R}^2} ((1 - \bar{f}(|\hat{p}|))r)^k (\bar{f}(|\hat{p}|)(r - \hat{p}))^{n-k} \bar{u}(r - \hat{p}) \bar{u}(r) \,\mathrm{d}r \,\mathrm{d}\hat{p} \\
&= \sum_{k=0}^{n} \binom{n}{k} \int_{\mathbb{R}^2} ((1 - \bar{f}(|r - s|))r)^k (\bar{f}(|r - s|)s)^{n-k} \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r.
\end{aligned} \tag{4.2}$$

The terms of the last sum are estimated as follows. Observe first that if $z = \frac{r}{s} \in [0,1]$,

$$z^k(1 - z^{n-k}) \leq 1 - z^{n-k}$$

and therefore

$$z^k + z^{n-k} \leq 1 + z^n.$$

It follows for the last integral in (4.2) that

$$\begin{aligned}
&\int_{\mathbb{R}^2} ((1 - \bar{f}(|r - s|))r)^k (\bar{f}(|r - s|)s)^{n-k} \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \frac{1}{2} \int_{\mathbb{R}^2} \big[((1 - \bar{f}(|r - s|))r)^k (\bar{f}(|r - s|)s)^{n-k} \\
&\qquad + ((1 - \bar{f}(|s - r|))s)^k (\bar{f}(|s - r|)r)^{n-k} \big] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \int_{0 \leq r \leq s} \big[((1 - \bar{f}(|r - s|))r)^k (\bar{f}(|r - s|)s)^{n-k} \\
&\qquad + ((1 - \bar{f}(|s - r|))s)^k (\bar{f}(|s - r|)r)^{n-k} \big] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \int_{0 \leq r \leq s} \left[(1 - \bar{f}(|r - s|))^k \bar{f}(|s - r|)^{n-k} s^n \left(\left(\frac{r}{s}\right)^k + \left(\frac{r}{s}\right)^{n-k} \right) \right] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&\leq \int_{0 \leq r \leq s} \left[(1 - \bar{f}(|r - s|))^k \bar{f}(|s - r|)^{n-k} s^n \left(1 + \left(\frac{r}{s}\right)^n \right) \right] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \int_{0 \leq r \leq s} \left[(1 - \bar{f}(|r - s|))^k \bar{f}(|s - r|)^{n-k} (s^n + r^n) \right] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \frac{1}{2} \int_{\mathbb{R}^2} \left[(1 - \bar{f}(|r - s|))^k \bar{f}(|s - r|)^{n-k} (s^n + r^n) \right] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \int_{\mathbb{R}^2} \left[(1 - \bar{f}(|r - s|))^k \bar{f}(|s - r|)^{n-k} s^n \right] \bar{u}(s) \bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r.
\end{aligned}$$

We continue from the last line of (4.2):

$$\begin{aligned}
&\int_{\mathbb{R}} (u *_f u)(p) p^n \,\mathrm{d}p \\
&\leq \sum_{k=0}^{n} \binom{n}{k} \int_{\mathbb{R}^2} (1 - \bar{f}(|r-s|))^k \bar{f}(|r-s|)^{n-k} s^n \bar{u}(s)\bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \int_{\mathbb{R}^2} (1 - \bar{f}(|r-s|) + \bar{f}(|r-s|))^n s^n \bar{u}(s)\bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r \\
&= \int_{\mathbb{R}^2} s^n \bar{u}(s)\bar{u}(r) \,\mathrm{d}s \,\mathrm{d}r.
\end{aligned}$$

It follows that

$$\frac{dE_n(u(t))}{dt} = 2\tau(E_n(T(u)) - E_n(u)) \leq 0;$$

i.e., the moments are nonincreasing along a trajectory. Since all moments are nonnegative, the sequence of limits

$$E_n^{\infty} = \lim_{t\to\infty} E_n(u(t)), \quad n = 0, 1, 2, \ldots,$$

exists. Let $\varrho \in \mathcal{P}[0,1]$ be a polynomial

$$\varrho(x) = \sum_{k=0}^{m} a_k x^k.$$

We define a linear functional w by

$$\langle w,\, \varrho\rangle = \sum_{k=0}^{m} a_k E_k^{\infty}.$$

By construction,

$$\langle w,\, \varrho\rangle = \lim_{t\to\infty} \sum_{k=0}^{m} a_k E_k(u(t)) = \lim_{t\to\infty} \langle u(t),\, \varrho\rangle, \tag{4.3}$$

and since $\|u(t)\|_{L^1[0,1]} = \|u_0\|_{L^1[0,1]} = 1$,

$$|\langle w,\, \varrho\rangle| = \lim_{t\to\infty} |\langle u(t),\, \varrho\rangle| \leq \|u(t)\|_{L^1[0,1]} \, ||\varrho||_\infty \leq ||\varrho||_\infty,$$

the boundedness of w follows:

$$|\langle w,\, \varrho\rangle| \leq ||\varrho||_\infty.$$

By the Weierstrass approximation theorem, $\mathcal{P}[0,1]$ is dense in the space of continuous functions $C[0,1]$ and so w extends uniquely to an element of the dual space $C[0,1]'$, which we again denote by w. By the Riesz representation theorem the linear functional w can be identified with a Radon measure supported on $[0,1]$. To complete the proof, let $\phi \in C[0,1]$ and let $\varrho \in \mathcal{P}[0,1]$ be a polynomial with $||\phi - \varrho||_\infty \leq \varepsilon/2$. Then

$$\begin{aligned}
|\langle u(t),\, \phi\rangle| &\leq |\langle u(t),\, \phi - \varrho\rangle| + |\langle u(t),\, \varrho\rangle - \langle w,\, \varrho\rangle| + |\langle w,\, \phi - \varrho\rangle| \\
&\leq 2||\phi - \varrho||_\infty + |\langle u(t),\, \varrho\rangle - \langle w,\, \varrho\rangle|.
\end{aligned}$$

Using the limit property for polynomials (4.3) we obtain the result (4.1). ∎

The next theorem shows that in some cases the solution converges indeed only to a measure, not an integrable function. We consider the asymptotic behavior in the special case that $f(|p|) \equiv f$ for all p; i.e., a constant fraction is transferred at all times.

THEOREM 4.3. *If the transfer fraction f is constant, then for each $u_0 \in L^1_+[0,1] \setminus \{0\}$, the solution of the transfer model* (2.4) *converges to a Dirac measure in the weak* topology. More precisely let $m = \frac{E_1(u_0)}{E_0(u_0)}$ be the mean of the initial datum; then*

$$u(t) \overset{*}{\rightharpoonup} E_0(u_0)\delta_m$$

as $t \to \infty$.

Proof. A similar result was obtained in Theorem 3.2 in [15]. Assume without loss of generality that $2\tau = 1$. At first we consider solutions with $E_0(u(t)) \equiv 1$. For $n \geq 1$ let $x_n(t) = E_n(u(t))$ and $X_n(t) = (x_1(t), \ldots, x_n(t))$. We have the following system of ordinary differential equations for the moments:

$$\frac{dx_n(t)}{dt} = \sum_{k=0}^{n} \binom{n}{k} f^k (1-f)^{n-k} x_k(t) x_{n-k}(t) - x_n(t) \quad \text{and} \quad x_n(0) = E_n(u_0). \tag{4.4}$$

An easy recursive calculation shows that the sequence $(x_1(0)^n)_{n=1}^{\infty}$ is a steady state of the system (4.4) with the property $x_1(t) = x_1(0)$ for all $t \geq 0$. We want to show that $x_n(t) \to x_1(0)^n$ as $t \to \infty$ for all $n \geq 1$. Assume as the induction hypothesis that this is true for all $k = 1, \ldots, n-1$. Because of the inequalities

$$0 \leq x_n(t) \leq x_{n-1}(t) \leq \cdots \leq x_2(t) \leq x_1(t) = x_1(0),$$

the ω-limit set of $X_n(0)$ is nonempty and by the induction hypothesis

$$\omega(X_n(0)) \subset \{(x_1(0),\, x_1(0)^2, \ldots, x_1(0)^{n-1})\} \times [0, x_1(0)^{n-1}].$$

This set is invariant under the flow induced by (4.4) (see [9]), and we obtain the following ordinary differential equation for the last component $x_n(t)$ on the set $\omega(X_n(0))$:

$$\frac{d\xi(t)}{dt} = (f^n + (1-f)^n - 1)(\xi(t) - x_1(0)^n), \qquad \xi(0) \in [0, x_1(0)^{n-1}].$$

Because the last equation is linear in ξ and the invariance of $\omega(X_n(0))$, we must have $\xi(t) = x_1(0)^n$ and hence

$$\omega(X_n(0)) = \{(x_1(0),\, x_1(0)^2, \ldots, x_1(0)^{n-1}, x_1(0)^n)\}.$$

It follows that

$$\lim_{t\to\infty} x_n(t) = x_1(0)^n.$$

This implies that for every polynomial $\varrho \in \mathcal{P}[0,1]$

$$\lim_{t\to\infty} \langle u(t), \varrho\rangle = \delta_{E_1(u_0)}(\varrho).$$

Again this result extends to every $\phi \in C[0,1]$ by the Weierstrass approximation theorem. It remains to consider the general case where $E_0(u_0) \neq 0$ is arbitrary. Then for $v(t) = \frac{u(t)}{E_0(u(t))}$ we have that $E_n(v(t)) \to E_1(v_0)^n$ as $t \to \infty$ and

$$E_0(u(t))E_n(u(t)) \to E_0(u_0)\left(\frac{E_1(u_0)}{E_0(u_0)}\right)^n. \qquad ∎$$

5. The model with transport and diffusion. We add to our model the production and loss of the quantity transferred by individuals. In the case of the cell surface protein P-gp, production occurs during drug therapy [10] and loss occurs when no drug is present [20]. In addition, we include a diffusion term to account for stochastic effects and a nonlinear term to account for constrained population growth. For the sake of simplicity we choose a linear diffusion term (based on Fick's law) and a linear convection term. The full model is given by

$$\begin{aligned} &\frac{\partial u}{\partial t} = \varepsilon^2 \frac{\partial^2 u}{\partial p^2} - \frac{\partial}{\partial p}(h(p)u) + (c(p) - \mathcal{L}(u))u + 2\tau(T(u) - u), \\ &\varepsilon^2 \frac{\partial u}{\partial p} - h(p)u(t,p) = 0 \quad \text{for } p = 0 \text{ or } p = 1, \\ &u(0,\cdot) = u_0 \in L^1_+[0,1]. \end{aligned} \tag{5.1}$$

The function $h \in C^1([0,1], \mathbb{R})$ denotes a convection field and corresponds to production. The function $c \in L^\infty[0,1]$ is the combined proliferation and death rate in case of unlimited space and supply of nutrients (it can be of either sign). The effect of crowding is modeled through the positive linear functional $\mathcal{L} : L^1[0,1] \to \mathbb{R}$, and we assume that $\mathcal{L}(\varphi) > 0$ for all $\varphi \in L^1_+(0,1) \setminus \{0\}$. A common choice is $\mathcal{L}(u) = \gamma \int_0^1 u(p)dp$, where $\gamma > 0$ is a constant. Equation (5.1) without the transport term and with $f \equiv \frac{1}{2}$ has been treated in detail in [18].

We consider the linear operator $A : D(A) \subset L^1[0,1] \to L^1[0,1]$, defined by

$$A\varphi(x) = \varepsilon^2 \varphi''(x) - (h(x)\varphi(x))',$$

$$D(A) = \left\{ \varphi \in W^{2,1}[0,1] : \varepsilon^2 \varphi'(x) - h(x)\varphi(x) = 0 \text{ for } x = 0 \text{ or } x = 1 \right\}.$$

We assume that $\varepsilon > 0$, and $h \in C^1([0,1], \mathbb{R})$, with $h(0) \geq 0$ and $h(1) \leq 0$. We first consider the linear operator $\widehat{A} : D(\widehat{A}) \subset X \to X$ defined by $\widehat{A}\varphi(x) = \varepsilon^2 \varphi''(x)$ and $D(\widehat{A}) = D(A)$. It is well known that $\widehat{A}$ is the infinitesimal generator of an analytic semigroup [8, 14]. Consider the linear operators $\widehat{B} : D(\widehat{B}) \subset L^1[0,1] \to L^1[0,1]$, $\widehat{B}\varphi = -(h\varphi)'$, $D(\widehat{B}) = W^{1,1}[0,1]$, and $A = \widehat{A} + \widehat{B}$. From [23, Theorem 7.3.10], we deduce that A is sectorial and its resolvent is compact. We obtain the following lemma (see also Theorem 10.3 of Amann's paper [1]).

LEMMA 5.1. *The linear operator A is the infinitesimal generator of analytic semigroup $\{S_A(t)\}_{t \geq 0}$ of bounded linear operators in $L^1[0,1]$ with growth bound ω_A, and $S_A(t)$ is compact for each $t > 0$.*

LEMMA 5.2 (maximum principle). *The linear operator A is resolvent positive; that is, there exists $\omega_1 > \omega_A$ such that, for each $\lambda > \omega_1$,*

$$(\lambda I - A)^{-1} L^1_+[0,1] \subset L^1_+[0,1].$$

Proof. We consider the function $f(x) = x^- := \max(-x, 0)$. f is differentiable except at 0 and

$$f'(x) = \begin{cases} 0 \text{ if } x > 0, \\ -1 \text{ if } x < 0. \end{cases}$$

Let

$$F(x) := \int_0^x f(s)\, \mathrm{d}s = -\frac{(x^-)^2}{2}.$$

We set

$$\omega_1 = \max\left(- \sup_{x\in[0,1]} \frac{h'(x)}{2}, \omega_A \right).$$

Let $\psi \in L^1_+[0,1] \setminus \{0\}$, let $\lambda > \omega_1$, and let

$$\varphi = (\lambda I - A)^{-1} \psi \Leftrightarrow \begin{cases} \lambda\varphi - \varepsilon^2 \varphi'' + (h\varphi)' = \psi, \text{ and} \\ \varepsilon^2 \varphi'(x) - h(x)\varphi(x) = 0 \text{ for } x = 0 \text{ or } x = 1. \end{cases} \tag{5.2}$$

Then

$$\begin{aligned} 0 &\le \int_0^1 \varphi(x)^- \psi(x)\,\mathrm{d}x = \int_0^1 \varphi(x)^- \left[\lambda\varphi(x) - \varepsilon^2\varphi''(x) + (h(x)\varphi(x))'\right]\,\mathrm{d}x \\ &= -\int_0^1 \lambda \left(\varphi(x)^-\right)^2\,\mathrm{d}x + \int_0^1 \varphi(x)^- \left[-\varepsilon^2\varphi''(x) + (h(x)\varphi(x))'\right]\,\mathrm{d}x \\ &= -\lambda\int_0^1 \left(\varphi(x)^-\right)^2\,\mathrm{d}x + \left[\varphi(x)^- \left(-\varepsilon^2\varphi'(x) + h(x)\varphi(x)\right)\right]_0^1 \\ &\quad - \int_0^1 \varphi'(x) f'(\varphi(x)) \left[-\varepsilon^2\varphi'(x) + h(x)\varphi(x)\right]\,\mathrm{d}x \\ &= -\lambda\int_0^1 \left(\varphi(x)^-\right)^2\,\mathrm{d}x + \int_0^1 \varepsilon^2 \varphi'(x)^2 f'(\varphi(x))\,\mathrm{d}x - \int_0^1 \varphi'(x) f'(\varphi(x)) h(x)\varphi(x)\,\mathrm{d}x. \end{aligned}$$

Since

$$\begin{aligned} &-\int_0^1 \varphi'(x) f'(\varphi(x)) h(x)\varphi(x)\,\mathrm{d}x = -\int_0^1 h(x)\varphi'(x) f(\varphi(x))\,\mathrm{d}x \\ &= -\left[F(\varphi(x))h(x)\right]_0^1 + \int_0^1 F(\varphi(x))h'(x)\,\mathrm{d}x \\ &= -h(1)F(\varphi(1)) + h(0)F(\varphi(0)) - \int_0^1 \frac{(\varphi(x)^-)^2}{2} h'(x)\,\mathrm{d}x, \end{aligned}$$

we obtain the following inequality:

$$\begin{aligned} 0 \le \int_0^1 \varphi(x)^-\psi(x)\,\mathrm{d}x &= -\int_0^1 \left(\lambda + \frac{h'(x)}{2}\right)\left(\varphi(x)^-\right)^2\,\mathrm{d}x \\ &+ \int_0^1 \varepsilon^2\varphi'(x)^2 f'(\varphi(x))\,\mathrm{d}x + h(1)\frac{\left(\varphi(1)^-\right)^2}{2} - h(0)\frac{\left(\varphi(0)^-\right)^2}{2}. \end{aligned}$$

Since $h(1) \le 0$, $h(0) \ge 0$, and $f'(x) \le 0$ and $\left(-\lambda - \frac{h(x)'}{2}\right) < 0$ for all $x \in [0,1]$, we deduce that

$$\int_0^1 (\varphi(x)^-)^2\,\mathrm{d}x = 0,$$

which implies that $\varphi^- = 0$. □

LEMMA 5.3 (strong maximum principle). *There exists $\omega_2 \geq \omega_1$ such that, for each $\psi \in C_+([0,1],\mathbb{R}) \setminus \{0\}$ and for each $\lambda > \omega_2$,*

$$\inf_{x\in[0,1]} (\lambda I - A)^{-1}(\psi)(x) > 0.$$

Proof. Let $\psi \in C_+([0,1],\mathbb{R}) \setminus \{0\}$. Then $\varphi = (\lambda I - A)^{-1}\psi$ is equivalent to (5.2). Since $\psi \in C([0,1],\mathbb{R})$ we deduce that $\varphi \in C^2([0,1],\mathbb{R})$, and by using Lemma 5.2 we deduce that $\varphi \in C_+([0,1],\mathbb{R}) \setminus \{0\}$. By using the boundary condition in (5.2), and the fact that $\varphi \geq 0$, we deduce that

$$\varphi(x) = 0 \Rightarrow \varphi'(x) = 0 \quad \forall x \in [0,1]. \tag{5.3}$$

Moreover, from the first equation of (5.2) we deduce that

$$\psi(x) > 0 \Rightarrow \varphi(x) > 0 \quad \forall x \in [0,1]. \tag{5.4}$$

We fix $\omega_2 > \omega_1$ such that $\omega_2 > -\sup_{x\in[0,1]} h'(x)$. We set $u(x) = \varphi(x)$, and $v(x) = \varphi'(x)$, and the first equation of system (5.2) can be rewritten as

$$\begin{pmatrix} u'(x) \\ v'(x) \end{pmatrix} = M(x) \begin{pmatrix} u(x) \\ v(x) \end{pmatrix} - \begin{pmatrix} 0 \\ \frac{\psi(x)}{\epsilon^2} \end{pmatrix}, \tag{5.5}$$

where

$$M(x) = \begin{pmatrix} 0 & 1 \\ \frac{\lambda + h'(x)}{\epsilon^2} & \frac{h(x)}{\epsilon^2} \end{pmatrix}.$$

Then there exists a family $\{U(x,y)\}_{1\geq x\geq y\geq 0} \in M_2(\mathbb{R})$ such that, for each $X \in \mathbb{R}^2$, $x \to U(x,y)X$ is the unique solution of the nonautonomous Cauchy problem

$$\frac{dU(x,y)X}{dx} = M(x)\, U(x,y)X \quad \forall x \in [y,1], \text{ with } U(y,y)X = X \in \mathbb{R}^2.$$

Moreover, since $\lambda + h'(x) \geq 0$, we deduce that

$$U(x,y)X \geq \begin{pmatrix} 1 & 0 \\ 0 & \exp\left(\int_y^x \frac{h(l)}{\epsilon^2} dl\right) \end{pmatrix} X \quad \forall X \in \mathbb{R}^2_+.$$

The solution of (5.5) is then given by

$$\begin{pmatrix} u(x) \\ v(x) \end{pmatrix} = U(x,y) \begin{pmatrix} u(y) \\ v(y) \end{pmatrix} - \int_y^x U(x,l) \begin{pmatrix} 0 \\ \frac{\psi(l)}{\epsilon^2} \end{pmatrix} \mathrm{d}l \quad \forall\, 0 \leq y \leq x \leq 1. \tag{5.6}$$

Since $u(x) = \varphi(x)$, and $v(x) = \varphi'(x)$, from (5.3) and (5.6), we deduce that if $y \in [0,1]$ and $\varphi(y) = 0$, then $\varphi'(y) = 0$ and for $x \in [y,1]$

$$\begin{aligned} \begin{pmatrix} \varphi(x) \\ \varphi'(x) \end{pmatrix} &= \begin{pmatrix} 0 \\ 0 \end{pmatrix} - \int_y^x U(x,l) \begin{pmatrix} 0 \\ \frac{\psi(l)}{\epsilon^2} \end{pmatrix} \mathrm{d}l \\ &\leq \begin{pmatrix} 0 \\ 0 \end{pmatrix} - \int_y^x \begin{pmatrix} 1 & 0 \\ 0 & \exp\left(\int_l^x \frac{h(\hat{l})}{\epsilon^2} \mathrm{d}\hat{l}\right) \end{pmatrix} \begin{pmatrix} 0 \\ \frac{\psi(l)}{\epsilon^2} \end{pmatrix} \mathrm{d}l \quad \forall 0 \leq y \leq x \leq 1, \end{aligned}$$

which implies that $\varphi(x) = 0$. Interchange x and y to conclude that if $x \in [0,1]$ and $\varphi(x) = 0$, then $\varphi(y) = 0$ for $y \in [x,1]$. Observe that $\widehat{\varphi}(y) = \varphi(1-y)$, $\widehat{h}(y) = -h(1-y)$, $\widehat{\psi}(y) = \psi(1-y)$ satisfy system (5.2). By using the first part of the proof, we observe that if $x \in [0,1]$ and $\widehat{\varphi}(x) = 0$, then $\widehat{\varphi}(y) = 0$ for $y \in [x,1]$, which implies that if $x \in [0,1]$ and $\varphi(x) = 0$, then $\varphi(y) = 0$ for $y \in [0,x]$. Thus, if $\varphi(x) = 0$ for some $x \in [0,1]$, then $\varphi = \psi \equiv 0$ on $[0,1]$. ∎

PROPOSITION 5.4. *The semigroup $\{S_A(t)\}_{t\geq 0}$ is positive and irreducible, that is,*

$$S_A(t)L^1_+[0,1] \subset L^1_+[0,1] \quad \forall t \geq 0,$$

and for each $\varphi \in L^1_+[0,1] \setminus \{0\}$, and for each $\chi \in L^\infty_+[0,1] \setminus \{0\}$, there exists $t > 0$ such that

$$\int_0^1 \chi(x)\, S_A(t)(\varphi)(x)\, \mathrm{d}x > 0.$$

Proof. We first prove that for each $\lambda > 0$ large enough,

$$\int_0^1 \chi(x)\,(\lambda I - A)^{-1}(\varphi)(x)\, \mathrm{d}x > 0 \quad \forall \varphi \in L^1_+(0,1)\setminus\{0\},\ \forall \chi \in L^\infty_+[0,1]\setminus\{0\}. \tag{5.7}$$

Let $\varphi \in L^1_+[0,1] \setminus \{0\}$, let $\chi \in L^\infty_+[0,1] \setminus \{0\}$, and let $\lambda > \omega_2$. Since we have

$$(\lambda I - A)^{-1} = \sum_{n=0}^{+\infty} (\mu - \lambda)^n (\mu I - A)^{-(n+1)}$$

whenever $\lambda < \mu$ and $|\lambda - \mu| \left\| (\mu I - A)^{-1} \right\| < 1$, it is sufficient to prove that

$$\int_0^1 \chi(x)\,(\mu I - A)^{-2}(\varphi)(x)\,\mathrm{d}x > 0.$$

But

$$\int_0^1 \chi(x)\,(\mu I - A)^{-2}(\varphi)(x)\,\mathrm{d}x = \int_0^1 \chi(x)\,(\mu I - A)^{-1}\left((\mu I - A)^{-1}\varphi\right)(x)\,\mathrm{d}x$$

and

$$(\mu I - A)^{-1}\varphi \in C_+([0,1],\mathbb{R}) \setminus \{0\}.$$

So by using Lemma 5.3, we deduce that

$$\inf_{x\in[0,1]} (\mu I - A)^{-2}(\varphi)(x) > 0$$

and

$$\int_0^1 \chi(x)\,(\lambda I - A)^{-1}(\varphi)(x)\,\mathrm{d}x \geq (\mu - \lambda)\int_0^1 \chi(x)\,(\mu I - A)^{-2}(\varphi)(x)\,\mathrm{d}x > 0.$$

The positivity of the semigroup $\{S_A(t)\}_{t\geq 0}$ is an immediate consequence of Lemma 5.2 and follows from the fact that for each $t > 0$, and each $\varphi \in L^1[0,1]$,

$$S_A(t)\varphi = \lim_{n\to+\infty} \left(\frac{n}{t}\right)^n \left(\frac{n}{t}I - A\right)^{-n} \varphi.$$

To prove the last part of the proposition, it is sufficient to observe that for each $\lambda > 0$ large enough

$$(\lambda I - A)^{-1} \varphi = \int_0^{+\infty} e^{-\lambda t} S_A(t)\varphi \, \mathrm{d}t.$$

It follows that

$$\int_0^1 \chi(x) (\lambda I - A)^{-1} (\varphi)(x) \, \mathrm{d}x = \int_0^{+\infty} e^{-\lambda t} \int_0^1 \chi(x) S_A(t) (\varphi) (x) \, \mathrm{d}x \, \mathrm{d}t,$$

and if we assume by contradiction that $\int_0^1 \chi(x) S_A(t) (\varphi) (x) \, \mathrm{d}x = 0$, for each $t > 0$, we obtain a contradiction with assertion (5.7). ∎

Proposition 5.5. *We have the following properties:*

(a)

$$\int_0^1 S_A(t)(\varphi) \, \mathrm{d}x = \int_0^1 \varphi(x) \, \mathrm{d}x \quad \forall \varphi \in L^1[0,1], \forall t \geq 0.$$

(b)

$$\|S_A(t)\varphi\|_{L^1} \leq \|\varphi\|_{L^1} \quad \forall \varphi \in L^1[0,1], \forall t \geq 0.$$

(c) 0 *is a simple dominant eigenvalue of* A, *and the projection on this eigenspace is*

$$\Pi_A (\varphi) (x) = \int_0^1 \varphi(l) \, \mathrm{d}l \, \chi(x),$$

where

$$\chi(x) = \frac{\exp\left(\int_0^x h(y) \, \mathrm{d}y\right)}{\int_0^1 \exp\left(\int_0^l h(r) \, \mathrm{d}r\right) \, \mathrm{d}l}.$$

Proof. Let $\varphi \in D(A)$; then $S_A(t)(\varphi) \in D(A)$, for each $t \geq 0$, and we have

$$\begin{aligned} \frac{d}{dt} \int_0^1 S_A(t)(\varphi)(x) \, \mathrm{d}x &= \int_0^1 AS_A(t)(\varphi) (x) \, \mathrm{d}x \\ &= \varepsilon \frac{dS_A(t)(\varphi) (1)}{dx} - h(1) S_A(t)(\varphi) (1) \\ &\quad + \varepsilon \frac{dS_A(t)(\varphi) (0)}{dx} - h(1) S_A(t)(\varphi) (0) \\ &= 0. \end{aligned}$$

So

$$\int_0^1 S_A(t)(\varphi)(x) \mathrm{d}x = \int_0^1 \varphi(x) \, \mathrm{d}x \quad \forall t \geq 0.$$

Now by using the density of the domain $D(A)$ in $L^1[0,1]$, assertion (a) follows.

To prove (b) it is sufficient to observe that $S_A(t)$ is a positive operator and use the first part of the proof to conclude that

$$\|S_A(t)\varphi\|_{L^1} = \||S_A(t)\varphi|\|_{L^1} \leq \|S_A(t)\,|\varphi|\|_{L^1} = \||\varphi|\|_{L^1} = \|\varphi\|_{L^1}\,.$$

From the irreducibility and the compactness property of the semigroup $\{S_A(t)\}_{t\geq 0}$ it follows that A has a simple dominant eigenvalue $\lambda_0 \in \mathbb{R}$ associated with a positive eigenvector $\chi \in L^1_+[0,1]\setminus\{0\}$ [21]. By using (b) is it clear that this eigenvalue must be $\lambda_0 \leq 0$. By using (a) it follows that $\lambda_0 = 0$. Observe that χ satisfies

$$\varepsilon^2\chi''(x) - (h(x)\chi(x))' = 0 \quad \forall x \in [0,1]\,, \text{ and}$$
$$\varepsilon^2\chi'(x) - h\,(x)\,\chi(x) = 0 \quad \text{for } x = 0 \text{ or } x = 1,$$

which is equivalent to

$$\varepsilon^2\chi'(x) = h(x)\chi(x) \quad \forall x \in [0,1]\,,$$

and (c) follows. ▯

Next we consider $B : D(B) \subset L^1[0,1] \to L^1[0,1]$ the linear operator defined by

$$B\varphi = A\varphi + c\varphi \quad \forall \varphi \in D(B) := D(A),$$

where $c \in L^\infty[0,1]$ is the function defined in system (5.1). Since B is a bounded perturbation of A, we deduce that B is the infinitesimal generator of a compact analytic semigroup $\{S_B(t)\}_{t\geq 0}$ on $L^1[0,1]$ [23, Proposition 3.1.4 and Corollary 3.3.2]. By using the formula

$$S_B(t) = e^{-\lambda t}S_A(t) + \int_0^t e^{-\lambda(t-s)}S_A(t-s)\,(c+\lambda)\,S_B(s)\,\mathrm{d}s$$

for $\lambda > \|c\|_{L^\infty[0,1]}$, it follows that $\{S_B(t)\}_{t\geq 0}$ is a positive and irreducible semigroup. So by using the formula in [7] (see also Proposition 3.3 in [16]) we obtain the following result.

LEMMA 5.6. *For every $u_0 \in L^1_+[0,1]$, (5.1) has a unique global mild solution in $L^1_+[0,1]$, and*

$$U_\tau(t)u_0 = \frac{V_\tau(t)u_0}{1 + \int_0^t \mathcal{L}\left(V_\tau(s)u_0\right)\,\mathrm{d}s},$$

where $t \to V_\tau(t)u_0$ is the unique solution of

$$V_\tau(t)u_0 = S_B(t)u_0 + \int_0^t S_B(t-s)2\tau\left[T(V_\tau(s)u_0) - V_\tau(s)u_0\right]\,\mathrm{d}s.$$

Since $\{S_B(t)\}_{t\geq 0}$ is compact and irreducible, we can apply the results in [25] and [21, Proposition 3.5, p. 310], and we deduce that B has a simple eigenvalue $\lambda_0(B) \in \mathbb{R}$. Moreover, there exists $\widehat{\psi} \in L^\infty_+[0,1]\setminus\{0\}$ strictly positive (i.e., $\int_0^1 \widehat{\psi}\,(x)\,\varphi(x)\,\mathrm{d}x > 0$ for all $\varphi \in L^1_+[0,1]\setminus\{0\}$), and there exists $\widehat{\chi} \in L^1_+\,(0,1)\setminus\{0\}$ quasi-interior (i.e., $\int_0^1 \widehat{\chi}\,(x)\,\varphi(x)\,\mathrm{d}x > 0$ for all $\varphi \in L^\infty_+[0,1]\setminus\{0\}$) such that the projection on the eigenspace space associated with $\lambda_0(B)$ takes the form

$$\Pi_B\,(\varphi)\,(x) = \int_0^1 \widehat{\psi}\,(x)\,\varphi(l)\,\mathrm{d}l\widehat{\chi}(x) \quad \forall \varphi \in L^1\,(0,1)\,.$$

Furthermore, the projection Π_B satisfies the following properties:

$$S_B(t)\Pi_B = \Pi_B S_B(t) = e^{\lambda_0(B)t}\Pi_B \quad \forall t \geq 0,$$

and there exist $M \geq 1$ and $\delta > 0$ such that

$$\|(I - \Pi_B)\, S_B(t)\, (I - \Pi_B)\| \leq M e^{(\lambda_0(B)-\delta)t} \quad \forall t \geq 0.$$

Finally, by combining Proposition 3.2 and Theorem 4.1 in [16], we obtain the following result.

THEOREM 5.7. *We have the following alternative:*

(a) *If $\lambda_0(B) < 0$, there exists $\tau^* > 0$ such that*

$$\lim_{t \to +\infty} U_\tau(t)u_0 = 0 \quad \forall \tau \in [0, \tau^*]\,, \forall u_0 \in L^1_+[0,1].$$

(b) *If $\lambda_0(B) > 0$, there exists $\tau^* > 0$ such that, for all $\tau \in [0, \tau^*]$, there exists $v_\tau \in D(B) \cap L^1_+[0,1] \setminus \{0\}$, with $\|v_\tau\| = 1$, $\mu_\tau \in \mathbb{R}$, and*

$$(\mu_\tau + \lambda_0(B))\, v_\tau = Bv_\tau + 2\tau\, [T\,(v_\tau) - v_\tau]\,,$$

with

$$\mu_\tau + \lambda_0(B) > 0.$$

Moreover, $\overline{u}_\tau := (\lambda_0(B) + \mu_\tau)\, \frac{v_\tau}{\mathcal{L}(v_\tau)}$ is the unique positive equilibrium of the system in $L^1_+[0,1] \setminus \{0\}$ and

$$\lim_{t \to +\infty} U_\tau(t)u_0 = \overline{u}_\tau \quad \forall u_0 \in L^1_+[0,1] \diagdown \{0\}\,.$$

Furthermore, $\overline{u}_\tau$ is locally exponentially asymptotically stable.

6. Numerical results. We illustrate our continuum transfer model with numerical simulations. We also provide accompanying discrete Monte Carlo simulations of the transfer model to demonstrate the robustness of our continuum model. The simulations were implemented using MATLAB and Mathematica (the codes are available at http://awal.univ-lehavre.fr/∼magal/cancer/cancer.htm and from the corresponding author upon request). In all simulations we choose the transfer rate $\tau = 1$.

We first illustrate in Figure 2.3(A) the transfer model (2.2) with transfer rule (A3). When the transfer efficiency f is constant and the transfer threshold $\delta = 0$, the solution converges to a Dirac measure, as predicted by Theorem 4.3. In Figure 2.3(B) we illustrate the transfer model (2.2) with transfer rule (A4). When the transfer efficiency f is constant and the transfer threshold $\delta > 0$, we see that the solution stabilizes to a bounded distribution. In Figures 2.3(C) and 2.3(D) we provide comparable Monte Carlo simulations of the continuum model simulations in Figures 2.3(A) and 2.3(B), respectively.

In Figure 2.4 we show numerical simulations of our model motivated by the experimental data in [13, Figure 1a]. In these experiments P-gp negative and positive human neuroblastoma BE (2)-C cells were cocultured in vitro and their P-gp levels tracked over 8 days using a fluorescent marker. P-gp is a large molecular edifice which zigzags inside and outside the cell membrane with 12 membrane spanning segments [2]. The P-gp positive cell population, which possessed intrinsic resistance to the cancer drug colchicine, was initially equally mixed with the drug sensitive P-gp negative cell population. Before the experiment, the intrinsically resistant cell population exhibited stable P-gp expression levels in the absence of the drug. Within hours of coculture the sensitive cell population shifted toward higher P-gp levels, continued gradual shifting higher over a period of 2–3 days, and stabilized at a distribution with two intermediate peaks. Our model is directly applicable to this transfer process, since P-gp does not travel passively between cells, and its insertion into specific membrane microdomains can be described by a transfer rule such as (A.4). In Figure 2.4(A) we simulate the data in [13, Figure 1a] using model (2.2) and the transfer rule (A4). In Figures 2.4(B)–(D) we compare the continuum model simulation in Figure 2.4(A) with Monte Carlo simulations using different numbers of individual cells. We observe the convergence to the deterministic model simulation when the number of individuals is large enough.

7. Discussion. We have analyzed general models of dynamic transfer phenomena applicable to biological populations. In our model the population is viewed as a continuum density structured by the quantity of material transferred. The models (2.2), (2.4), (2.6), and (5.1) are integro-partial differential equations of Boltzmann type, for which we have developed results concerning existence, uniqueness, conservation properties, and asymptotic behavior of solutions. The transfer process is specified by rules dependent on the interaction of individuals involved in the transfer phenomenon. The rules governing transfer, such as (A3), (A4), and (A5), are natural descriptions that may be formulated as continuum or discrete based models. The Monte Carlo simulations we have presented in Figures 2.3 and 2.4 demonstrate that our continuum approach and an individual based probabilistic approach are complementary.

Our work is motivated by a particular application demonstrating the direct cell-cell transfer of the surface protein P-glycoprotein (P-gp) present in cancer cells [13]. The significance of direct cell-cell transfer of P-gp has potential importance in understanding the development of resistance to cancer drugs, since P-gp is a cellular efflux pump for many chemotherapeutic agents.

Mathematical models offer a means to quantify the biological elements of transfer phenomena such as direct cell-cell protein transfer. One element is the stabilization of such processes, and our results quantify this behavior in certain cases. Our numerical illustrations (Figures 2.3 and 2.4) demonstrate that different choices of transfer rules can yield very different stabilization outcomes. The transfer rule (A3), in which the transfer efficiency has no minimum threshold condition, yields destabilization in the sense that the density approaches a Dirac mass. Based on our numerical simulations, we conjecture that for the transfer rule (A4), in which the transfer efficiency has a positive minimum threshold, solutions converge to a bounded steady state. Recall that under the rule (A4) an exchange takes place only if the difference in the transferable quantity exceeds a threshold $\delta > 0$. Using the operators $T_{f,\delta}$ and M_δ from (2.2), it is easy to show that for a function $\phi \in L^1_+[0,1]$ with *diam* $\operatorname{supp} \phi \leq \delta$,

$$T_{f,\delta}(\phi) - M_\delta(\phi) = 0,$$

and hence such a function is a steady state of (2.2).

CONJECTURE 7.1. *Assume that* $f|_{[0,\delta]} = 0$ *for some* $\delta > 0$ *and let* $u(t)$ *be a solution of* (2.4) *with* $u(0) \in L^\infty_+[0,1]$. *Then there exists a function* $u_\infty \in L^\infty_+[0,1]$ *with* $E_0(u_\infty) = E_0(u_0)$, $E_1(u_\infty) = E_1(u_0)$, *and diam* $\operatorname{supp} u_\infty \leq \delta$ *such that (in* $L^1_+[0,1]$*)*

$$\lim_{t\to+\infty} u(t) = u_\infty.$$

Theorem 5.7 establishes for another case that solutions converge to a globally attracting steady state if diffusion effects are present and the transfer rate is sufficiently small. The biological distinction of different stabilization outcomes depends on the complexities of the biochemical and biomechanical elements of the transfer process. In future work we will investigate further the mathematical issues developed here, including extensions of these models incorporating spatial structure, cell-cycle behavior, and other features applicable to multiscale description of biological transfer phenomena.

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