A GENERAL MODEL OF STRUCTURED CELL KINETICS

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Abstract. We present a modelling framework for the dynamics of cells structured by the concentration of a micromolecule they contain. We derive general equations for the evolution of the cell population and of the extra-cellular concentration of the molecule and apply this approach to models of silicosis, quorum sensing in Gram-negative bacteria and magnetic ion exchange.

Keywords: structured populations, transport equations, integro-differential equations, bistability

1. INTRODUCTION

Many physical systems involve the interaction of micro-scale objects and macro-scale objects within a region. For instance, in biology, the micro-scale objects could be molecules of a particular chemical with the macro-scale objects could be cells, and the region could be a Petri dish or an organ. This region, a domain \( \Omega \) of volume \( W \), may be of fixed size or change with time, but we assume that the micro-scale objects, of a species \( X \) (which from now we call molecules for brevity), have no volume while the macro-scale objects (which from now on we call cells) each have volume \( V_0 \). The \( X \) molecules may be present inside or outside the cells, with the concentration of \( X \) varying between the cells. We also assume that the molecules of \( X \) can participate in any subset of the following processes: they can be injected into or be removed from the domain, they can enter and exit cells and they can be produced, processed and destroyed by cells. Suppose also that the fate of a cell is dependent on the amount of \( X \) that it contains. The goal of the present paper is to introduce, using ideas of Metz and Diekmann [14] and of Brown [5], a modelling framework for such situations.

Below we describe in detail three specific examples of systems where our modelling approach is appropriate, the dynamics of silicosis, the biological background for which can be found in [18], quorum sensing in Gram-positive bacteria following Brown [5] and magnetic ion-exchange resin water treatment [2]. However, our framework is suitable for many other situations, some of which are briefly considered in Section 7. We are confident there are many other examples, in both biological and non-biological systems, where the proposed philosophy may be useful.

The structure of the paper is as follows. In Section 2 we introduce the biological background of silicosis and argue that the mathematical model of [18], which is couched in terms of coagulation-fragmentation equations, does not give a correct description of the dynamics; this is our original motivation for developing the present approach. In Section 3 we show how to derive the required equations in the general setting. In Section 4 we complete the specification of the silicosis model. In Section 5 we consider quorum sensing in Gram-positive bacteria. This is a useful setting for testing numerical approaches to the type of models we are interested in. Surprisingly, our model also allows a wealth of stationary solutions and an intriguing reinterpretation of the whole concept of bistability. In Section 6 we discuss a series of models for magnetic ion-exchange resin-based water treatment (MIEX). Finally, in Section 7 we suggest other areas of application of our framework, discuss general mathematical issues and draw conclusions.
Note that the present paper is purely methodological and that all results on existence, uniqueness, or asymptotic behaviour of solutions of the type of equations we derive here, are left to future work.

2. Silicosis: the Coagulation-Fragmentation Approach

Let us summarise the 1995 silicosis model of Tran et al. [18], which should be consulted for references. The biological background is as follows: quartz particles are ingested and arrive in the lung. There they may be picked up by macrophages, with the intent of being removed together with their quartz load via the muco-ciliary escalator. However, if a macrophage accumulates too large a quartz load, it becomes immobile and eventually dies by apoptosis in the lung, releasing its quartz load.

The variables in the model of Tran et al. are: free quartz dust in the lungs in concentration \( x(t) \) and concentrations of macrophages \( M_k(t) \) containing \( k \) particles of quartz. They write down an equation for the evolution of free quartz particle concentration and for \( M_k \), equations of the form

\[
\frac{dM_k}{dt} = \alpha_{k-1}xM_{k-1} - \alpha_kxM_k + \cdots,
\]

where \( \alpha_{k-1} \) and \( \alpha_k \) are the kinetic constants for the process of macrophages with \( k-1 \) and \( k \) particles of quartz, respectively, ingesting one additional quartz particle.

In eq. (1), the \( \cdots \) stand for the two different “death” processes: the disappearance of cells together with their quartz load via the the muco-ciliary elevator; or cell apoptosis accompanied by the release of the quartz load into the lungs. To make this model fully specified, it must be complemented by an equation for the production of naive macrophages, \( M_0(t) \); this rate in general depends on the quartz load in the lungs. See Section 4 below for a reasonable form of such an equation.

This model was later considered in [8]; mathematically it is interesting and falls in the framework of coagulation-fragmentation equations (see [1] for an up-to-date exposition of this area of infinite-dimensional dynamical systems). The global existence of its solutions has been proven in later work by da Costa and coauthors [9], and many mathematical questions connected with the model of Tran et al. are still open.

To understand our objections to the modelling of silicosis as a coagulation–fragmentation system, consider a typical coagulation–fragmentation reaction scheme,

\[
c_k + c_1 \rightleftharpoons c_{k+1}.
\]

Here \( c_k, c_1, c_{k+1} \) are concentrations of \( k \)-mers, monomers, and \((k+1)\)-mers of some chemical species, respectively. The equation for the evolution of \( c_{k+1} \) corresponding to this reaction scheme is

\[
\frac{dc_{k+1}}{dt} = \alpha_k c_k c_1 - \beta_{k+1} c_{k+1},
\]

where \( \alpha_k \) is the kinetic constant for the coagulation reaction between \( k \)-mers and monomers and \( \beta_{k+1} \) is the kinetic constant of the fragmentation of a molecule of \((k+1)\)-mer into a monomer and a \( k \)-mer. This equation is simply mass-action kinetics, and \( \alpha_k \) and \( \beta_{k+1} \) are assumed to be functions of \( k \) only.

If we now compare this coagulation–fragmentation process with eq. (1), we would suppose that the underlying reaction scheme is

\[
M_k + x \rightleftharpoons M_{k+1}.
\]

This situation is subtly different in that the reaction here is between the molecules of quartz outside the cells and the content of the cells. Though \( M_k, x, M_{k+1} \) have units of concentration,
the reaction encoded in this scheme in general involves the concentration of quartz, and not the number of quartz particles, inside the cells. As an example, consider the case of exchange of quartz between the outside and the inside of a cell driven by passive (Fickian) diffusion. Then the rate of exchange of molecules is proportional to \( (x - q_I) \), where \( q_I \) is the internal concentration of quartz.

However, the \( k \) in \( M_k \) denotes the number of quartz molecules in a cell, not their concentration. To define internal concentration of quartz, we cannot assume that a cell is a point object, and have to endow it with a volume, say \( V_0 \). But if cells now have finite volumes, it becomes clear that the concentration of free quartz is also a function of the number of cells which is not the case in the coagulation–fragmentation setup. This is precisely the kind of confusion of units that is avoided in the type of model proposed below.

### 3. Derivation of General Equations

![Figure 1](image.png)

**Figure 1.** The situation being modelled: the domain \( \Omega \) contains species \( X \) (red dots) and cells (black circles). The possible processes involved are: (a) naïve cells enter the domain; (b) species \( X \) enters the domain; species \( X \) (c) enters or (d) exits cells; (e) \( X \)-laden cells exit the domain and (f) cells release molecules of \( X \) in \( \Omega \); also present, but not indicated in this figure, are synthesis and degradation of \( X \).

We are modelling the situation sketched in Figure 1 and described as follows. The system consists of a domain \( \Omega \) of volume \( W \) that contains molecules of \( X \) (denoted by red dots in Fig. 1) with extracellular concentration \( x \), and a population of cells (the black circles in Fig. 1). We assume that the volume of each cell is \( V_0 \) and treat the molecules as having no volume.

The cells differ in their \( X \) content, and we define the time-dependent density of the cells with internal concentration of \( X \) being \( y \) to be \( M(y, t) \). That is, the number of cells with internal concentrations of \( X \) between \( y_1 \) and \( y_2 \), with \( y_1 < y_2 \), is

\[
\int_{y_1}^{y_2} M(y, t) \, dy.
\]

Then

\[
V(t) = V_0 \int_{0}^{\infty} M(y, t) \, dy
\]

is the total volume occupied by the cells and we assume that for all time \( t \), \( V(t) < W \). By this we mean that if \( V(0) < W \), the dynamics of the system ensures that \( V(t) < W \).
Furthermore, inside each cell we have a process that involves the substance $X$, which can be described by an ordinary differential equation such as

\[ \frac{dy}{dt} = f(x, y) = J(x, y) + g(y), \]

where we have separated the transport term $J(x, y)$, that may depend on both the internal and external concentration of $X$, and the intracellular synthesis and degradation term $g(y)$. This type of equation is called an $i$-equation (for individual) by Metz and Diekmann [14].

Metz and Diekmann [14] also show (in many different ways) how to derive the equation governing the evolution of $M(y, t)$, what they call the $p$-equation (for population),

\[ M_t(y,t) + (f(x,y) M(y,t))_y = P(M(y,t),y) + Q(M(y,t),y), \]

where in the right-hand side the terms $P$ and $Q$ encode all the population level processes (such as birth and death). Specifically, we denote by $Q(M(y,t),y)$, the population level processes that feed back into the $x$ dynamics (e.g. when cells die in $\Omega$ releasing their contents). The model is then closed by specifying the $x$ dynamics, adding suitable initial conditions $x(0)$ and $M(y,0)$, and a boundary condition for na"ïve cells entering $\Omega$, usually of the form

\[ f(x(t),0) M(0,t) = s(\cdot), \]

where the function $s$ can depend on a variety of variables. Thus the unknown dependent variables are $x(t)$ and $M(y,t)$.

Deriving the equation governing the evolution of $x(t)$ is algorithmic, by keeping account of the total number of molecules of $X$ in the extracellular space. In general, the result is an integro-differential equation. The derivation of the equation for $x(t)$ crucially uses the thinking of Brown [5], which we now discuss.

Brown [5] considers the system described above but with the simplification that every cell contains the same number of molecules, so that the concentration of $X$ in all cells is $y$, a constant. If $K(t)$ is the number of cells at time $t$, then the total volume occupied by cells is $V(t) = K(t)V_0$, the cell-free volume is $W - V(t)$ and the total number of molecules outside of cells is $N_E = (W - V(t)) x(t)$.

We will work in two stages. First we write equations for the transport of $X$ molecules between the interior and exterior of the cells, assuming that the flux is given by $J(x,y)$ and that it is positive when molecules enter the cells. We have

\[ \frac{dN_E}{dt} = -V J(x,y). \]

An obvious example of a flux would be $J(x,y) = D(x - y)$, with $D$ a diffusion constant, but in examples of interest, mechanisms involving facilitated transport or phagocytosis should be considered.

The proportionality to $V$ in eq. (4) comes from the consideration that the rate of change should be proportional to the available surface area of the cells, which, given we assume a fixed individual cell volume and surface area, is proportional to the number of cells and thus proportional to the total volume of cells.

Now let us rewrite these equations in terms of concentrations only. Since $N_E = x(W - V)$, we have

\[ \frac{dx}{dt} = -\frac{V}{W - V} J(x,y) + \frac{x}{W - V} \frac{dV}{dt}. \]
Now we add to this molecular transport equation terms involving synthesis and degradation terms which we collect in one term, $H(x, y)$; we have

$$\frac{dx}{dt} = -\frac{V}{W + V} J(x, y) + \frac{x}{W + V} \frac{dV}{dt} + H(x, y).$$

Here $H(x, y)$ incorporates all extracellular production and degradation of $X$ and all the population level processes that feed back into the extracellular concentration $x(t)$.

We now consider the more general case in which the cells may have different internal concentrations of $X$. This necessitates a number of changes. First of all, the total number of molecules being released per unit time by cellular processes, i.e $Q$ in eq. (3), is

$$V_0 \int_0^\infty y Q(M(y, t), y) \, dy$$

and hence we can write

$$H(x, y) = h(x) + \frac{V_0}{W + V} \int_0^\infty y Q(M(y, t), y) \, dy,$$

where $h(x)$ is the rate of extracellular production and degradation of $X$, which depends on the particular modelling context.

Secondly, the term $V(t) J(x, y) = V_0 K(t) J(x, y)$ is replaced by the integral $V_0 \int_0^\infty M(y, t) J(x, y) \, dy$. With these changes, the equation for the evolution of $x(t)$ becomes

$$\frac{dx}{dt} = h(x) + \frac{1}{W + V} \left[ -V_0 \int_0^\infty J(x, y) M(y, t) \, dy + V_0 \int_0^\infty y Q(M(y, t), y) \, dy + x \frac{dV}{dt} \right].$$

Therefore our modelling framework consists of the equation governing the cell population, the $p$-equation, eq. (3); the equation governing the concentration of $X$ external to the cells, the $x$-equation, eq. (6); and the data for any particular model set through the biologically determined terms $J(x, y), g(x), P(M(y, t), y), Q(M(y, t), y), h(x)$ and the boundary condition function $s(\cdot)$.

### 4. A New Model for Silicosis

In this section we formulate a model of silicosis based on the principles of Section 3. As in Tran et al. [18], we assume that quartz is being ingested at a constant rate. We set $M(y, t)$ to be the density of macrophages having internal quartz concentration $y$ at time $t$. As in [18], we assume that new macrophages are produced at rate $s$ determined by the quartz load, $L(t) := \int_0^\infty y M(y, t) \, dy$, such that

$$s(L(t)) = s_0 + u(L(t)),$$

where $s_0$ is a background level of recruitment of naïve cells into the domain when quartz is not present in any cells and $u(\cdot)$ is a bounded function, with $u(0) = 0$.

Cells with internal concentration of quartz $y$ are removed by the muco-ciliary escalator at a rate $p(y)$, where $p(y)$ is a decreasing function of $y$ since, as their quartz content increases, cells are increasingly immobile. Cells are also more liable to die by apoptosis as their quartz content increases, and so the rate of them releasing their contents inside the lungs, $q(y)$, is an increasing function of $y$.

As there is no intracellular processing of quartz, so that $g(y) = 0$ in eq. (2), we only need to specify the transport mechanism. Phagocytosis of quartz particles cannot be described by simple diffusion, so we set

$$\frac{dy}{dt} = J(x, y),$$
where the function $J$ is non-negative, bounded, increasing in $x$ and decreasing in $y$, as is also assumed in [18]. An example would be

$$J(x, y) = \frac{\gamma x}{x + y + x_{1/2}},$$

where $\gamma$ is the flux when $x \to \infty$ and $x_{1/2}$ at which the value of $x$ when the flux for naïve cells (i.e., $y = 0$) is half the maximum value, both positive constants.

So far we have all the information needed to specify the $p$-equation for $M$, which is therefore

$$M_t(y, t) + (J(x, y)M(y, t))_y = -(p(y) + q(y))M(y, t).$$

Now we need to formulate the equation for $x(t)$. From (6) it follows that all we need to do is to specify the function $h(x)$, the rate of change of concentration of quartz particles in the extracellular region due to introduction from outside the domain. If we assume that $A$ particles of quartz are ingested per unit time, we have

$$h(x) = \frac{A}{W - V},$$

and hence

$$\frac{dx}{dt} = \frac{1}{W - V} \left[ A - V_0 \int_0^\infty J(x, y)M(y, t) \, dy + V_0 \int_0^\infty yq(y)M(y, t) \, dy + x \frac{dV}{dt} \right].$$

We can derive an expression for $dV/dt$ in terms of the variables $M(y, t)$ to substitute in (10). Since $dV/dt$ is given by

$$\frac{dV}{dt} = V_0 \int_0^\infty M_t(y, t) \, dy,$$

integrating the $p$-equation by parts and assuming that that for all times $t > 0$ we have that

$$\lim_{y \to \infty} J(x, y)M(y, t) = 0,$$

we obtain

$$\frac{dV}{dt} = V_0 \left( s(L(t)) - \int_0^\infty (p(y) + r(y))M(y, t) \, dy \right).$$

In addition, we must specify suitable initial conditions $x(0)$ and $M(y, 0)$ as well as the boundary condition at $y = 0$, which, using eq. (7), is

$$J(x, 0)M(0, t) = s_0 + u(L(t)).$$

We note that the resulting system is a linear transport equation (for the population variable $M$) coupled to a nonlinear integro-differential differential equation for the extracellular quartz concentration $x$.

Having assumed that the load

$$L(t) = \int_0^\infty yM(y, t) \, dy$$

is finite for all time, the correct setting for the theory is a space of positive Radon measures with a finite first moment. Particular choices of the functions $p(y)$ and $r(y)$ and the input function $s(\cdot)$ must ensure that if $V(0) < W$, then $V(t) < W$. For example, this can be shown to be the case if we assume that $p(y) + r(y)$ is bounded below and that $s(\cdot)$ is bounded above by constants.
5. Quorum sensing in Gram-negative bacteria

5.1. Derivation of equations. A number of models for quorum-sensing in Gram-positive and Gram-negative bacteria that assume that the internal concentration of the signal molecule $X$, i.e., $y$, is the same in all cells, see [5]; we will review the model for Gram-negative bacteria below. The case of Gram-negative bacteria is an interesting test case of our approach, as, like the case of magnetic ion-exchange resin-based water treatment discussed in section [6] it involves a significant simplification: we can assume that the number of cells is constant, so $V \equiv \text{const}$ is now a parameter and $dV/dt = 0$. Below, as is done by Brown, we will find convenient to use the parameter $\phi = V/W$. Fickian diffusion of $X$ between the cells and the extracellular region is assumed, so that the $i$-equation is

$$
\frac{dy}{dt} = F(x, y) := D(x-y) + g_s(y) + g_d(y),
$$

where $D$ is a diffusion constant, and following [5], we include terms modelling intracellular synthesis $g_s(y)$, which we take to be a constant term $a_0$ plus a Hill-type term, and a linear intracellular degradation term $g_d(y)$. If we choose the Hill exponent to be 2, we have

$$
F(x, y) = D(x-y) + a_0 + \frac{a_1 y^2}{K^2 + y^2} - m_I y,
$$

for some values of the constants $a_1$ and $K$. The $p$-equation is

$$
M_t(y, t) + (F(x, y)M(y, t))_y = 0.
$$

The boundary condition is $M(0, t) = 0$ and the $x$ equation becomes

$$
\frac{dx}{dt} = \frac{V_0 D}{W - V} \int_0^\infty (y - x)M(y, t) dy - m_E x,
$$

where $m_E$ is the extracellular degradation rate.

5.2. Analysis of equilibria. The set of equilibria of the model given by (13)–(16) is quite rich. Analysis of this set changes our view of bistability, and so is definitely worth the effort. There are many cases to consider, and instead of an exhaustive analysis left to the reader, we present a classification of possible cases and analyse in detail a representative one.

First, assuming that all the cells have the same concentration $y$ of the signal molecule, we have the model of Brown as in [5]. Equations (3) and (in non-dimensional form) (4). The relevant results of numerically solving the steady state equations, are in [5] Fig. 1(B)]. The blue curve there corresponding to Hill exponent 2, which shows the dependence of the internal concentration of the signal on $\phi$ clearly shows bistability as it is commonly understood: for small enough $\phi$ there is a unique equilibrium with low concentration of $y$; call this branch of equilibria $y_L(\phi)$. Then there is a saddle-node bifurcation at $\phi_1$ in which two more branches of equilibria are born, call them $y_I(\phi)$ and $y_H(\phi)$ (for Intermediate and High, respectively); finally, $y_I(\phi)$ and $y_L(\phi)$ collide in yet another saddle-node bifurcation at $\phi_2 > \phi_1$ and only the $y_H(\phi)$ branch remains. In the (bistability) parameter regime $\phi_1 < \phi < \phi_2$, the system of 2 ODEs [5] Eq. (4) has three equilibria, which in our notation can be written as $(x_L(\phi), y_L(\phi))$, $(x_I(\phi), y_I(\phi))$, $(x_H(\phi), y_H(\phi))$, the first and the third of which are locally asymptotically stable, the second being a saddle point. Therefore, depending on the initial condition in the bistability regime, with probability 1 the solution of the system of ODES will converge either to $(x_L(\phi), y_L(\phi))$ or to $(x_H(\phi), y_H(\phi))$.

The situation is much more complex in the case of model [13]–[16] and requires a reassessment of what bistability means.
5.2.1. Notation and preliminaries. The analysis is absolutely elementary, but it requires careful notation. Consider the equation \( F(x, y) = 0 \). As it is linear in \( x \), from this equation, we can express \( x \) as a function of \( y \); thus we obtain one relation between \( x \) and \( y \) that must be satisfied at equilibrium. We record this as

\[
x = g(y) := y - \frac{1}{D} \left[ a_0 + \frac{a_1 y^2}{K^2 + y^2} - m_I y \right].
\]

Note that \( g(y) \sim (1 + m_I)y > y \) for large enough \( y \). This means that for any \( 0 < A < 1 \) the straight line \( x = Ay \) will intersect the graph of \( g \). Clearly, we can choose parameters \( D, a_0, a_1, K, m_I \) such that there is an interval of values of \( x \) which we denote by \( J := [x_{\text{min}}, x_{\text{max}}] \) such that if \( x_0 \in J \), the equation \( x_0 = g(y) \) has exactly 3 positive solutions (and never more). For such a choice, see [5, Table 1]. We denote these solutions by \( y_l(x_0) < y_m(x_0) < y_r(x_0) \), for obvious reasons.

Clearly, we also have \( y_m(x_{\text{min}}) = y_r(x_{\text{max}}) \) and \( y_l(x_{\text{max}}) = y_m(x_{\text{max}}) \).

We distinguish two fundamental configurations:

I: \( \frac{x_{\text{min}}}{y_l(x_{\text{min}})} > \frac{x_{\text{max}}}{y_r(x_{\text{max}})} \), and

II: \( \frac{x_{\text{min}}}{y_l(x_{\text{min}})} < \frac{x_{\text{max}}}{y_r(x_{\text{max}})} \).

Below we only deal with a particular case of configuration I; all the other cases are left to the reader. In fact, in configuration I there are five cases to consider, depending on the intersections of the lines \( x = Ay \) with \( x = g(y) \) as we vary \( A \). These are indicated in Figure 2:

\[\text{Figure 2. The 5 cases of configuration I.}\]
Note that in regions (1) and (5) there is no bistability; we concentrate on region (3), the analysis in regions (2) and (4) is similar, though the “bifurcation diagrams” in a sense to be defined below are different.

To start constructing stationary solutions of (13)–(16), pick a slope $A$ in region (3) of configuration I. Call the $y$-coordinates of intersections of the line $x = Ay$ and $x = g(y)$, $y_L(A) < y_I(A) < y_H(A)$. Let $x^* = Ay_I(A)$. For any $x_0 \in J$, as before, denote the $y$-coordinates of the intersections of the line $x = x_0$ with the graph of $g$ by $y_l(x_0) < y_m(x_0) < y_r(x_0)$. Finally, denote the $y$-coordinate of the intersection of the line $x = x_0$ the line $y = Ax$ by $y(A, x_0)$ to emphasise its dependence both on $A$ and $x_0$. See Figure 3.

![Figure 3. Notation used in the construction.](image)

The solutions we will be constructing for $M(y)$ are sums of Dirac deltas at some locations $y_1, y_2$, etc. In fact we will show that there can be only 3 terms in such a sum. If there is only one term in the sum, then we call such a solution a 1-$\delta$ solution, if there are 2, a 2-$\delta$ solution, and if 3, a 3-$\delta$ solution.

Note that to satisfy the volume constraint, we must have that such an $n$-$\delta$ solution has the form

$$ M(y) = \frac{V}{V_0} \sum_{k=1}^{n} \alpha_k \delta_{y_k}(y), \quad \alpha_k \geq 0, \quad \sum_{k=1}^{n} \alpha_k = 1. \quad (18) $$

Before we start, we prove a simple lemma.
Lemma 1. If for some \( x = x_0 \), \( M(y) \) has the representation (18), then \( x_0 = g(y_k) = 0 \) and hence \( n \leq 3 \).

Proof. Since in that as in the sense of distributions \( (F(x_0, y)M(y))_y = 0 \), multiplying by a test function \( u \) on \( \mathbb{R}_+ \) and integrating over \( y \) we have that

\[
\sum_{k=1}^{n} F(x_0, y_k)\alpha_k u(y_k) = 0,
\]

and this can only be true for all test functions \( u \) if \( F(x_0, y_k) = 0 \). The second claim follows as \( x_0 = g(y) \) has at most 3 solutions by our assumptions on \( F(x, y) \).

(a) 1-\( \delta \) solutions: Using Lemma 1 these are simply obtained by computing the \( y \)-coordinates of the intersection of the graph of \( g \) defined in (17) with the straight line \( x = Ay \), where from (16) we have that

\[
A = \frac{\phi D}{m_E(1 - \phi) + \phi D}.
\]

Thus \( 0 \leq A \leq 1 \) and \( A \) is a monotone increasing function of \( \phi \). Note that in region (3) of configuration I, we have that

\[
\frac{x_{\text{max}}}{y_l(x_{\text{max}})} \leq A \leq \frac{x_{\text{min}}}{y_l(x_{\text{min}})}.
\]

To summarise: for \( A \) in region (3) of configuration I there are three 1-\( \delta \) solutions with support in \( y_L(A) \), \( y_L(A) \) and \( y_H(A) \); the corresponding values of \( x \) are \( Ay_L(A) \), \( Ay_L(A) \) and \( Ay_H(A) \), respectively.

Thus the set of 1-\( \delta \) equilibrium solutions is exactly the same as the set of equilibria in the ODE model of Brown [5]. We also expect \( (V/V_0\delta_{y_L(A)}, Ay_L(A)) \), \( (V/V_0\delta_{y_H(A)}, Ay_H(A)) \) to be stable in some definable sense, while \( (V/V_0\delta_{y_L(A)}, Ay_L(A)) \) should not be stable, as in the ODE case. Of course if we are in regions (1) or (5) of Figure 2 there exists a unique 1-\( \delta \) solution and this exhausts the whole set of equilibria.

(b) 2-\( \delta \) solutions: Here we will show that for each value of \( x_0 \in J \) there are two 2-\( \delta \) solutions and globally in region (3) of configuration I they form a continuum. Note that the construction is made for a fixed \( A \), i.e. by (19), for a fixed value of \( \phi \), and we do not attempt to make a global bifurcation diagram using \( \phi \) (or \( A \)) as a bifurcation parameter.

Pick any value of \( x_0 \) in Figure 3 we chose \( x_0 < x^* \); the other case is similar. Then the only allowable supports of the Dirac deltas are at \( y_l(x_0) \), \( y_m(x_0) \) and \( y_r(x_0) \). At the same time, we have \( A\gamma(A, x_0) = x_0 \). As for \( x_0 < x^* \) and so \( \gamma(A, x_0) \in (y_l(x_0), y_m(x_0)) \), we can satisfy all the conditions for an equilibrium by choosing \( r_1 \in (0, 1) \) so that \( r_1y_l(x_0) + (1 - r_1)y_m(x_0) = \gamma(A, x_0) \), or \( r_2 \in (0, 1) \) so that \( r_2y_l(x_0) + (1 - r_2)y_r(x_0) = \gamma(A, x_0) \), which is clearly possible by the geometry of Figure 3.

But this means that for any fixed value of \( x_{\text{min}} < x_0 < x^* \) we have constructed two 2-\( \delta \) solutions,

\[
M_1(y) = V_0 \left[ r_1\delta_{y_l(x_0)}(y) + (1 - r_1)\delta_{y_m(x_0)}(y) \right] \quad \text{and} \quad M_2(y) = V_0 \left[ r_2\delta_{y_l(x_0)}(y) + (1 - r_2)\delta_{y_r(x_0)}(y) \right],
\]

and there can be no others. Note that the dependence of these solutions on \( A \) is via \( \gamma(A, x_0) \) and hence the constants \( r_1 \) and \( r_2 \). Clearly, as \( x_0 \to x_{\text{min}} \) from above, the two solutions approach each other and disappear in a “saddle-node” bifurcation at \( x_0 = x_{\text{min}} \).
For $x_0 > x^*$, the situation is similar, and we still have exactly two $2\delta$ solutions,

$$M_1(y) = \frac{V}{V_0} \left[ r_1 \delta_{y_l(x_0)}(y) + (1 - r_1) \delta_{y_r(x_0)}(y) \right]$$ and $$M_2(y) = \frac{V}{V_0} \left[ r_2 \delta_{y_m(x_0)}(A) + (1 - r_2) \delta_{y_r(x_0)}(y) \right],$$

and again these two solutions disappear in a “saddle-node” bifurcation as $x_0 \to x_{\text{max}}$ from below.

We conjecture that such mixture solutions are “stable” if their support does not include $y_m(x_0)$ and unstable if it does.

Finally, at $x_0 = x^*$, one of these two equilibria degenerates into a $1\delta$ solution supported at $y_m(x^*) = y_I(A)$.

Note that for a fixed $A$ we have constructed a closed curve of $2\delta$ equilibria in the space $\mathbb{R} \times \mathcal{M}^2_{V/V_0}$, where $\mathcal{M}_{V/V_0}$ is the space of positive measures of mass $V/V_0$. Visualising it in $\mathbb{R}^3$ is an interesting question.

(c) $3\delta$ solutions. Clearly, for each $x_0 \in J$ we can find $r, s \in [0, 1]$ such that

$$\mathcal{F}(A, x_0) = ry_l(x_0) + sy_m(x_0) + (1 - r - s)y_r(x_0),$$

which will correspond to a $3\delta$ solution. The geometry of the resulting surface in the $(x_0, r, s)$ space is an intriguing question. We expect that all these $3\delta$ solutions will be unstable.

5.2.2. A remark and a conjecture. We see that in the system (13)–(16) the meaning of bistability differs from that it usually has in lumped systems. Here it means the coexistence of an uncountable number of invariant sets with nonempty domains of attraction. These collapse to a unique set as $A(\phi)$ increases or decreases sufficiently. It is true that individually each of the $2\delta$ solutions has a vanishing domain of attraction, but the whole set of these solutions collectively has a domain of attraction comparable to that of the $1\delta$ solutions supported at $y_L(A)$ and $y_H(A)$.

We have the following conjecture:

**Conjecture 2.** Suppose the initial conditions $(x(0), M(y, 0))$ are such $M(y, 0) \in A$, where $A$ is the set of positive measures $P(y)$ of mass $V/V_0$, such that the support of $P(y)$ contains $y_m(x(0))$. Then the set of elements in $A$ such that the solution of (13)–(16) does not converge to a $2\delta$ stationary solution is null.

6. Magnetic Ion-Exchange Resin-based Water Treatment

This section has been written in collaboration with Geraldine Knops.

6.1. Background and a minimal model. The minimal scheme for MIEX technology is as in Figure 4. This figure is taken from [2]; other references are in the work of Boyer [3, 4].

The model is formulated under the following assumptions:

- Regeneration occurs all the time (and not as it really does, on breakout) and it is perfect;
- There is no loss of resin ever;
- All resin beads have the same size.

Set $x$ to be the DOM concentration in the contactor tank and $M(y, t)$ to be the number density of resin beads there. Then if the volume of a resin bead is $V_0$, the assumption is that the total volume
of resin,
\[ V(t) = V_0 \int_0^\infty M(y, t) \, dy \]
is constant. Which is good news as it makes equations much simpler, but what I do not like is that I have to use it to derive the boundary condition. We will assume that the absorption of DOM particles onto a bead has kinetics given by some \( f(x, y) \geq 0 \), where \( f(0, y) = 0 \), and \( f(x, y) \to 0 \) for all \( x \) as \( y \to \infty \). Following our machinery, if the inflow of DOM is at rate of \( A \) particles per unit time (can be \( A(t) \)), and the outflow of species \( X \) is at rate \( \alpha X \), the equations are

\[ M_t(y, t) + (f(x, y)M(y, t))_y = -\alpha M(y, t). \tag{20} \]

and

\[ x' = -\alpha x + \frac{1}{W - V} \left[ A - V_0 \int_0^\infty f(x, y)M(y, t) \, dy \right]. \tag{21} \]

Now take the \( M \)-equation \( \tag{20} \), multiply it by \( V_0 \) and integrate it wrt \( y \). Then we have

\[ V'(t) + V_0 \lim_{y \to \infty} f(x, y)M(y, t) - V_0 f(x, 0)M(0, t) = -\alpha V. \]

Since by assumption \( V'(t) = 0 \), and we can (can we? I guess the answer is yes if we are in a \( y \)-weighted \( L^1 \) space as we should be) assume that the limit is 0, we have that

\[ V_0 f(x, 0)M(0, t) = \alpha V \in \mathbb{R}, \]
as \( V \) is just a parameter; this time-dependent boundary condition can be written as

\[ M(0, t) = \frac{\alpha V}{V_0 f(x(t), 0)}, \tag{22} \]

and it makes sense that increasing \( x(t) \), the effluent concentration of DOM means we will have fewer immaculate beads \( M(0, t) \).
6.2. Stationary solutions in the minimal model. Let us assume we scale variables so that

\[ f(x, y) = \frac{x}{x + y + 1}, \]

Set \( \int_0^\infty M(y) \, dy = s. \)

Then solving the \( M(y) \) equation with the boundary condition

\[ M(0) = \frac{\alpha s}{f(x, 0)}, \]

with \( f \) as above, we have

\[ M(y) = \frac{\alpha s}{x} (x + y + 1) e^{-\frac{\alpha s (y + 2x + 2)}{2x}}. \]

Check: the boundary condition is satisfied and

\[ \int_0^\infty M(y) \, dy = s. \]

Let us introduce some additional notation. Let

\[ g(\alpha, x) = 1 - \text{erf} \left( \sqrt{\frac{\alpha}{2x}}(x + 1) \right), \]

Notice that

\[ \int_0^\infty yM(y) \, dy = \sqrt{\frac{x\pi}{2\alpha}} \exp \left( \frac{\alpha(x + 1)^2}{2x} \right) g(\alpha, x) < \infty \]

for any values of parameters, so that we stay in \( L^1((0, \infty), y) \). \( \int_0^\infty yM(y) \, dy \) is an increasing function of \( x \) with and we have

\[ \lim_{x \to \infty} \int_0^\infty yM(y) \, dy = \frac{s}{\alpha}, \]

which makes sense.

Now we need to say something about \( x \). So first we need \( \int_0^\infty f(x, y)M(y) \, dy \). This is computable. We have

\[ \int_0^\infty f(x, y)M(y) \, dy = s \sqrt{\frac{\alpha x}{2\alpha}} g(\alpha, x) \exp \left( \frac{\alpha(x + 1)^2}{2x} \right) := sH(x); \]

by inspection \( H(x) \) is a monotone increasing function,

\[ \lim_{x \to 0} H(x) = 0, \quad \lim_{x \to \infty} H(x) = 1. \]

Hence the \( x \) coordinate of the stationary solution solves the equation

\[ \frac{A}{W + V} - \alpha x = \frac{V}{W + V} H(x), \]

and from the monotonicity properties of \( H(x) \) we see that we have proved the following lemma:

**Lemma 3.** For every value of the parameters \( A > 0, \alpha > 0, V > 0 \) there exists a unique stationary solution of (21) and (20), with the boundary condition (22).

Furthermore this stationary solution is an increasing function of \( A \) as it should be.

Let us fix all the parameter apart from \( V \). The we can denote the unique equilibrium concentration of \( x \) by \( x(V) \). We have the following lemma.

**Lemma 4.** The total amount of DOM at equilibrium in the contactor tank, \( Y(V) = \alpha x(V)(W - V) \), is decreasing function of \( V \).
Proof. First of all, \( Y(V) = A - VH(x(V)) \). Hence
\[
\frac{dY}{dV}(V) = -H(x(V)) - VH'(x(V)) \frac{dx}{dV}(V).
\]
Therefore if it so happens that \( \frac{dx}{dV}(V) \geq 0 \), we necessarily have that \( \frac{dY}{dV}(V) < 0 \). On the other hand, since by definition
\[
\frac{dY}{dV}(V) = -\alpha x(V) + \alpha(W - V) \frac{dx}{dV}(V),
\]
if \( \frac{dx}{dV}(V) < 0 \), we also have that \( \frac{dY}{dV}(V) < 0 \). □

6.3. A non-local imperfect regeneration model. A different, more realistic model no longer assumes that regeneration is perfect.

For \( x \), we still have the same equation, (21). Now let us introduce a parameter \( \beta > 1 \), which is efficiency of cleaning of the beads from the DOM gunk. For now let us assume that the regeneration is instantaneous. So if a bead has concentration \( y \) of DOM, regeneration instantaneously creates (no losses) a bead with concentration \( y/\beta \). This seems to me the easiest. That means that now the \( M \) equation is
\[
(23) \quad M_t(y,t) + (f(x,y)M(y,t))_y = -\alpha M(y,t) + \alpha M(\beta y,t).
\]
This is consistent: perfect regeneration corresponds to \( \beta = \infty \) and for all \( y > 0 \),
\[
\lim_{\beta \to \infty} M(\beta y,t) = 0.
\]
Now take the \( M \)-equation (23), multiply it by \( V_0 \) and integrate it wrt \( y \). Then we have
\[
V'(t) + V_0 \lim_{y \to \infty} f(x,y)M(y,t) - V_0 f(x,0)M(0,t) = -\alpha V + V_0 \alpha \int_0^y M(\beta y,t) \, dy = -\alpha V \left( 1 - \frac{1}{\beta} \right).
\]
Since by assumption \( V'(t) = 0 \), and we can assume that the limit is 0, we have that
\[
V_0 f(x,0)M(0,t) = \alpha \left( 1 - \frac{1}{\beta} \right) V \in \mathbb{R},
\]
as our new time-dependent boundary condition. As before, it can be written as
\[
(24) \quad M(0,t) = \frac{\alpha V}{V_0 f(x(t),0)} \left( 1 - \frac{1}{\beta} \right).
\]
So the boundary condition transforms very nicely. However, the \( M \)-equation (23) though still linear is now intractable, and the analysis of stationary solutions no longer holds. Obviously, one could do a continuation argument in \( \epsilon = 1/\beta \) as \( \epsilon \to 0 \).

6.4. A two tank model. In this subsection we consider a completely new type of model, which we will call a two-tank model. This type of models seems to be very promising.

The \( x \) equation is still (21). What we do next is to consider two tanks: the contactor tank and the regeneration tank. Call the number densities of beads in the contactor tank \( M(y,t) \) as before and the number densities of the ones in the regeneration tank \( N(y,t) \). Let the cleaning \( i \)-equation be
\[
(25) \quad y' = -c(y),
\]
For example, let us take \( c(y) = \beta y \).
The $M$ equation now is
\begin{equation}
M_t(y, t) + (f(x, y)M(y, t))_y = -\alpha M(y, t) + \alpha N(y, t),
\end{equation}
and the $N$ equation is
\begin{equation}
N_t(y, t) - (c(y)N(y, t))_y = \alpha M(y, t) - \alpha N(y, t),
\end{equation}
We assume thus $c(y) \sim y$, so $c(0) = 0$ (nothing to clean). Therefore adding (26) and (27), multiplying by $V_0$ and integrating wrt $y$ between 0 and infinity, we have (since $V = V_0 \left( \int_0^\infty M(y, t) dy + \int_0^\infty N(y, t) dy \right)$ is constant) that
\[
V'(t) + V_0 \lim_{y \to \infty} f(x, y)M(y, t) - V_0 f(x, 0)M(0, t) - V_0 \lim_{y \to \infty} c(y)N(y, t) + V_0 \lim_{y \to 0} c(y)N(y, t) = 0.
\]
Since $V'(t) = 0$, and we can assume that both limits as $y \to \infty$ are 0, we have that
\begin{equation}
f(x, 0)M(0, t) - V_0 \lim_{y \to 0} c(y)N(y, t) = 0 \text{ for all } t > 0.
\end{equation}
Note that $f(x, 0) > 0$.

Now we need to think. Since
\[
\int_0^\infty N(y, t) dy < \infty \text{ and } \int_0^\infty yN(y, t) dy < \infty, 0,
\]
for our choice of $c(y)$, we must have $N(y, t)$ go slower than $y^{-1}$ as $y \to 0$. This means that the limit in (28) must be zero. Therefore the boundary condition for $M(y, t)$ is
\begin{equation}
M(0, t) = 0.
\end{equation}
and for $N(y, t)$ we have
\begin{equation}
\lim_{y \to 0} c(y)N(y, t) = 0.
\end{equation}
We also have
\[
\int_0^\infty (M(y, t) + N(y, t)) dy = V/V_0.
\]
Let us now deal with the (unique) equilibrium. By adding the equations we have
\[
f(x, y)M(y) - c(y)N(y) = 0,
\]
which allows us to solve for $N(y)$ in terms of $M(y)$ (thus not having to divide by $y!$):
\begin{equation}
M(y) = \frac{c(y)N(y)}{f(x, y)}.
\end{equation}
So now we can substitute (31) into the equilibrium $N(y)$ equation, solve it generating a constant of integration, find $M(y)$ from (31), and then get the constant from the integral constraint. But that is what Nigel has already done. By construction, for every $x$ the solution is unique. Then need to substitute in the $x$ equation and find its value(s) (probably unique as well).

The equilibrium $N(y)$ equation is
\begin{equation}
(-c(y)N(y))_y - \alpha(M(y) - N(y)) = 0,
\end{equation}
\footnote{Actually we need to prove that the lhs here is continuous on $[0, \infty)$.}
integrating which we immediately have that at equilibrium
\[ \int_0^\infty M(y) \, dy = \int_0^\infty N(y) \, dy, \]
which is to be expected. Solving (32), we have
\[ N(y) = Cy^{\alpha/\beta} \frac{1}{\beta x} \exp\left(-\frac{\alpha y(2x+2+y)}{2x}\right), \]
which shows \( N(y) \) is in the right space and that so is \( M(y) \) as well by (31). Note that as Nigel said, if \( \alpha > \beta \), \( N(0) = 0 \). Here \( C \) is a constant of integration to be found later. Then \( M(y) \) is given by
\[ M(y) = C y^{\alpha/\beta} \frac{1}{\beta x} \exp\left(-\frac{\alpha y(2x+2+y)}{2x}\right). \]

If we set
\[ I(\alpha, \beta, x) = \int_0^\infty y^{\alpha/\beta} \, dy, \]
which can be computed in Maple in general in terms of Gamma and Laguerre functions\(^2\), we have finally that
\begin{equation}
C = \frac{V}{2V_0 I(\alpha, \beta, x)}.
\end{equation}

6.5. **Equilibria in the two-tank model.** From now on we simplify to \( \beta = \alpha = 1 \); everything can be done in full generality but the formulae are very unpleasant. Defining
\[ g(x) = \exp\left(\frac{(x+1)^2}{2x}\right) \quad \text{and} \quad h(x) = \text{erf}\left(\frac{x+1}{\sqrt{2x}}\right), \]
we have
\[ I(1,1,x) = \sqrt{\frac{x}{2}} g(x)(1-h(x)), \]
and hence using (33), we have the equation for \( x \) (\( \alpha = 1 \)),
\begin{equation}
\frac{A}{W-V} - x = VH(x),
\end{equation}
where
\[ H(x) = \frac{\sqrt{\frac{x}{2}}(1+x)g(x)(h(x)-1)+x}{2I(1,1,x)}. \]
This function \( H(x) \) is by inspection non-negative and monotone increasing,
\[ \lim_{x \to 0} H(x) = 0, \quad \lim_{x \to \infty} H(x) = 1/2, \]
so by (34), for every value of \( V \) we have a unique solution, which we can call \( x^* \), and hence our system has a unique equilibrium. The argument proving that \( x^*(W-V) \) is an increasing function of \( V \) is the same pretty argument as before.

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\(^2\)If \( \alpha = \beta \), the integral is in terms of the error function.
7. Remarks

We start by briefly mentioning other possible applications. The list is clearly incomplete.

- $X$ can be a drug that interacts with specific cells, so this is a suitable framework for chemotherapy modelling;
- $X$ may be bacteria that are ingested by neutrophiles, and can multiply inside the cell. This framework is therefore a possible model of bacterial infection and resistance [13];
- $X$ can be a mitogen, giving a model of stem cell number maintenance in which cells that ingest enough mitogen will multiply, and divide their mitogen label among the daughter cells, while cells that do not have enough mitogen, die [12].

Clearly the $i$-equation for $y$ could have been an stochastic differential equation; then the $x$-equation would have been an integro-stochastic differential equation, and the $M$ equation a stochastic partial differential equation. Furthermore, extensions to multidimensional $x$ and $y$ are straightforward although incorporating spatial structure seems to us much more challenging (as it is for coagulation–fragmentation equations).

To summarise, we have presented a modelling framework that seems to cover a vast number of possible modelling contexts beyond the reach of coagulation–fragmentation equations. Such a framework necessitates the analysis of complicated mathematical objects and so work on existence, structure of equilibria, convergence to equilibria and their regularity, etc., is required when specific examples are considered. The search will be for measure-valued solutions, and relevant work in this direction has been undertaken by Carrillo, Gwiazda and co-workers; see, for example, [6, 10]. In terms of possible numerical solutions to the governing equations, there are no off-the-shelf numerical methods that we know of, although it seems that escalator box train (EBT) methods could be adapted to the problem (see related work of Carrillo, Gwiazda and Ulikowska [7]).

Finally, we note that in many of the biological settings for which this framework could be used, deeper understanding of the active transport of molecules in and out of cells may be needed. Good models of transport across membranes (facilitated transport, phagocytosis, pumps etc.) are relatively sparse in the literature (though see, e.g., [15, 16]) and further work on such models would be of significant benefit.

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