GLOBAL EXISTENCE RESULTS FOR COMPLEX HYPERBOLIC MODELS OF BACTERIAL CHEMOTAXIS

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Abstract

Bacteria are able to respond to environmental signals by changing their rules of movement. When we take into account chemical signals in the environment, this behaviour is often called chemotaxis. At the individual-level, chemotaxis consists of several steps. First, the cell detects the extracellular signal using receptors on its membrane. Then, the cell processes the signal information through the intracellular signal transduction network, and finally it responds by altering its motile behaviour accordingly. At the population level, chemotaxis can lead to aggregation of bacteria, travelling waves or pattern formation, and the important task is to explain the population-level behaviour in terms of individual-based models. It has been previously shown that the transport equation framework [12, 13] is suitable for connecting different levels of modelling of bacterial chemotaxis. In this paper, we couple the transport equation for bacteria with the (parabolic/elliptic) equation for the extracellular signals. We prove global existence of solutions for the general hyperbolic chemotaxis models of cells which process the information about the extracellular signal through the intracellular biochemical network and interact by altering the extracellular signal as well. The conditions for global existence in terms of the properties of the signal transduction model are given.

1 Introduction

The flagellated bacteria (e.g. Escherichia coli, Salmonella typhimurium, Bacillus subtilis) are single-celled organisms. They are usually too small to be visible by the naked eye; typically, they have the size of microns (see [25, 18] for review). The behaviour of a bacterium is primarily influenced by concentrations of various chemicals inside the cell. Since bacteria are small, we can assume that the concentrations of the chemicals inside the cytoplasm are uniform. Therefore, we can suppose that the cells are points. Moreover, to create a mathematical description of a bacterium, we introduce the vector of internal state variables [12, 13, 10]

\[ \mathbf{y} = (y_1, y_2, \ldots, y_m)^T \in \mathbb{R}^m, \]

where \( y_i, i = 1, \ldots, m, \) are concentrations of various chemicals (proteins, receptor states etc.) inside the cell involved in the processes of interest. The individual behaviour of a cell primarily depends on the vector \( \mathbf{y} \) which is a function of time. Consequently, the state of bacterium is uniquely determined by the vector \( (t, \mathbf{x}, \mathbf{v}, \mathbf{y}) \) where \( \mathbf{x} \in \mathbb{R}^N \) is the position of a cell, \( \mathbf{v} \in \mathbb{R}^N \) is
its velocity, \( y \in \mathbb{R}^m \) is its internal state, \( t \) is time and \( N = 1, 2, \) or \( 3 \), is the dimension of the physical space.

During its life, a cell must communicate with its environment in order to find nutrients, to avoid repellents, to find mates etc. For this purpose, there are receptors in the cellular membrane which can detect various chemicals in the environment. We describe the chemicals outside the bacterium by the signaling vector (which depends on the position of the cell \( x \) and time \( t \))

\[
S(x, t) = (S_1, S_2, \ldots, S_M)^T \in \mathbb{R}^M.
\]

Then the evolution of the internal state vector \( y \) depends also on the signaling vector \( S \). Since we describe chemical processes, we can assume that \( y \) evolves according to system of ordinary differential equations

\[
\frac{dy}{dt} = F(S(x), y).
\]

This system formally captures all biochemistry inside the cell and therefore, the concrete form of the vector function \( F : \mathbb{R}^M \times \mathbb{R}^m \to \mathbb{R}^m \) can be very complicated depending on the number of details which are included in the model.

Bacterial movement and the signal transduction network \( F \) will be discussed in more details in Section 3. From the mathematical point of view, the movement of the flagellated bacteria can be viewed as a biased random walk. The properties of this random walk depend on the internal state \( y \) and bacterial velocity \( v \). The classical description of the bacterial movement is the so called velocity jump process \([20, 12, 13]\). It means that the bacterium runs with some velocity and at random instants of time it changes its velocity according to the Poisson process with the intensity \( \lambda(y) \).

Let \( f(x, v, y, t) \) be the density function of bacteria in a \((2N + m)\)-dimensional phase space with coordinates \((x, v, y)\) where \( x \in \mathbb{R}^N \) is the position of a cell, \( v \in V \subset \mathbb{R}^N \) is its velocity and \( y \in \mathbb{R}^m \) is its internal state, which evolves according to (3). Thus \( f(x, v, y, t)dx dv dy \) is the number of cells with position between \( x \) and \( x + dx \), velocity between \( v \) and \( v + dv \), and internal state between \( y \) and \( y + dy \). Then evolution of \( f \) is governed by the following transport equation \([12, 13]\)

\[
\frac{\partial f}{\partial t} + \nabla_x \cdot vf + \nabla_y \cdot F(S(x), y)f = -\lambda(y)f + \int_V \lambda(y)K(v, v', y)f(x, v', y, t)dv'
\]

where the kernel \( K(v, v', y) \) gives the probability of a change in velocity from \( v' \) to \( v \), given that a reorientation occurs. We assume that the random velocity changes are the result of a Poisson process of intensity \( \lambda(y) \) \([5]\). The kernel \( K \) is non-negative and satisfies the normalization condition

\[
\int_V K(v, v', y)dv = 1
\]

where

\[
V \text{ is a symmetric compact set in } \mathbb{R}^N.
\]

Realistic examples of the kernel \( K(v, v', y) \), set \( V \), signal transduction network \( F \) and the turning frequency \( \lambda(y) \) are given in Section 3. They all satisfy the above basic assumptions.

To write equation (4) in more compact form, we introduce the kernel \( T \) defined as a product of the turning frequency \( \lambda \) and the kernel \( K \), i.e.

\[
T(v, v', y) = \lambda(y)K(v, v', y).
\]
Moreover, our goal is to couple equation (4) with the realistic system of partial differential equations for the extracellular signal vector $S$. We assume that the external signal diffuses. It can be also produced or degraded by bacteria, degraded on its own or the components of $S$ can react with each other in the extracellular space. Hence, the general hyperbolic system of interest can be written in the following form:

$$\frac{\partial f}{\partial t} + \nabla_x \cdot v f + \nabla_y \cdot F(S(x), y)f = \int_V T(v, v', y)\left[f(v') - f(v)\right]dv'$$

(8)

$$\frac{\partial S}{\partial t} = D\Delta S + R(S, n)$$

(9)

where $n \equiv n(x, t)$ is the macroscopic density of individuals at point $x \in \mathbb{R}^N$ and time $t$ given as

$$n(x, t) = \int_{\mathbb{R}^m} \int_V f(x, v, y, t)dvdy,$$

(10)

$D$ is a diagonal $M \times M$ matrix which diagonal elements are diffusion constants of different chemicals in the extracellular signal vector $S$ and the term $R : \mathbb{R}^M \times \mathbb{R} \to \mathbb{R}^M$ describes the creation, reaction and degradation of the signals.

The goal of this paper is to prove global existence results for the system (8) – (9). We will focus on one-dimensional case in what follows. In Section 2, we will start with a simple model of the signal transduction (11) which was used previously [12, 13]. The simple model (11) has the essential properties of the realistic models of the signal transduction, but it is more tractable from the mathematical point of view than more complex models of bacterial chemotaxis. We prove the global existence of solutions of the one-dimensional version of (8) – (9) with the simplified model of the signal transduction.

In order to study the general case, we first review the relevant biology in Section 3. This will help us to specify the realistic conditions on signal transduction model (3), turning frequency $\lambda(y)$, turning kernel $K(v, v', y)$, set $V$, diffusion matrix $D$ and the reaction term $R(S, n)$ in equations (8) – (9). In Section 4, we study the global existence for the system (8) – (9) for general models of bacterial signal transduction which are introduced in Section 3. We also consider that equation (9) is at quasi-equilibrium, i.e. we consider the elliptic equation for the signal in Section 4.

Hence, this paper consists of two main mathematical results. First, we prove the global existence of solutions to the problem (8) – (9) for the simplified model of signal transduction (11) and for the system of parabolic equations (9) for the extracellular signal (see Section 2, Theorem 1). Then, we prove the global existence of solutions for the general model of signal transduction (3) coupled with the system of elliptic equations for the extracellular signal (see Section 4, Theorem 2). The necessary growth assumptions on turning frequency $T(v, v', y)$ are given in terms of the signal derivative along the cell trajectory. It means that the growth estimates on $T$ include the temporal derivative as well as the spatial derivative of the extracellular signal. Finally, we provide discussion and comparison with relevant results from the literature in Section 5.
2 Global existence for a simplified model of signal transduction

A simplified model of excitation-adaptation dynamics was studied in [12, 13, 22, 9] where \( y = (y_1, y_2)^T \in \mathbb{R}^2 \) and the right hand side of equation (8) was given as

\[
F = \begin{pmatrix} F_1 \\ F_2 \end{pmatrix} = \begin{pmatrix} \frac{g(S(x,t)) - (y_1 + y_2)}{t_e} \\ \frac{g(S(x,t)) - y_2}{t_a} \end{pmatrix}
\]

where \( t_e \) and \( t_a \) are positive constants and \( g : \mathbb{R}^M \to [0, \infty) \). We will see in Section 3 that the simplified model (11) has the essential properties of realistic signal transduction models. Hence, the model (11) is a natural starting point of this paper. For simplicity, we work in a one-dimensional physical space, i.e. \( N = 1 \), and the goal of this section is to prove Theorem 1 about the system (8) – (9). In what follows, we denote \( L^p(\Omega), 1 \leq p < \infty, \Omega \subset \mathbb{R}^d \), the Banach space of measurable functions with the finite norms

\[
\|h\|_{L^p} = \left( \int_{\Omega} |h(x)|^p \, dx \right)^{1/p}, \quad \text{for } 1 \leq p < \infty, \quad \text{and} \quad \|h\|_{L^\infty} = \operatorname{ess\, sup}_{\Omega} |h(x)|.
\]

We denote \( W^{k,p}(\Omega), 1 \leq p < \infty, \Omega \subset \mathbb{R}^d \), the usual Sobolev space

\[
W^{k,p}(\Omega) = \left\{ h \in L^p(\Omega) \mid \forall \alpha \in \mathbb{N}_0^d, |\alpha| \leq k \Rightarrow \frac{\partial^{|\alpha|} h}{\partial x_1^{\alpha_1} x_2^{\alpha_2} \cdots x_d^{\alpha_d}} \in L^p(\Omega) \right\}
\]

where \( \alpha = (\alpha_1, \alpha_2, \ldots, \alpha_d) \in \mathbb{N}_0^d \) is a vector of nonnegative integers and \( |\alpha| = \alpha_1 + \alpha_2 + \cdots + \alpha_d \). The norm in \( W^{k,p}(\Omega) \) is defined as

\[
\|h\|_{W^{k,p}} = \sum_{\alpha \in \mathbb{N}_0^d, |\alpha| \leq k} \left\| \frac{\partial^{|\alpha|} h}{\partial x_1^{\alpha_1} x_2^{\alpha_2} \cdots x_d^{\alpha_d}} \right\|_{L^p}
\]

To simplify mathematical formulas, we will make use of the following notation. For any function \( h : \mathbb{R}^d \to \mathbb{R} \), \( \nabla h \) denotes the gradient of \( h \) with respect to all variables and \( \nabla_{x_1 x_2} h \) is the 2-dimensional gradient vector with respect to the variables \( x_1 \) and \( x_2 \) only, i.e.

\[
\nabla h = \left( \frac{\partial h}{\partial x_1}, \frac{\partial h}{\partial x_2}, \ldots, \frac{\partial h}{\partial x_d} \right), \quad \text{and} \quad \nabla_{x_1 x_2} h = \left( \frac{\partial h}{\partial x_1}, \frac{\partial h}{\partial x_2} \right).
\]

We already made use of this notation in equation (8) where the gradients of the function \( f \) were taken only with respect to the selected parts of the state vector. In this section, we study the movement of cells in one dimension, i.e. \( N = 1 \). Moreover, we assume that the external signal diffuses and it is produced by bacteria and degraded on its own. Hence, the system of equations (8) – (9) reads as follows

\[
\frac{\partial f}{\partial t} + \nabla_x \cdot vf + \nabla_y \cdot F(S(x), y) f = \int_V T(v,v',y) \left[ f(v') - f(v) \right] dv'
\]

\[
\frac{\partial S_i}{\partial t} = d_i \frac{\partial^2 S_i}{\partial x^2} + k_i n - k_i^0 S_i, \quad i = 1, \ldots, M,
\]
where $d_i$, $k_i$ and $k_i^0$ are positive constants and $n \equiv n(x, t)$ is the macroscopic density of individuals at point $x \in \mathbb{R}$ and time $t$ given by (10). Position $x$ and velocity $v$ are scalars for $N = 1$, so we do not use bold letters for position and velocity in equation (13). Otherwise, equation (13) is the same as equation (8). Following notation (12), symbol $\nabla_x f$ denotes the partial derivative of distribution function $f$ with respect to $x$. Let us note that (depending on the form of function $g$ in (11)) some extracellular signals might be attractants and some extracellular signals might be repellents. If we have sufficient growth estimates on function $g$ and kernel $T$, we can guarantee the global existence of solutions of system (13)–(14) as it is shown in the following theorem.

**Theorem 1** Consider that the function $F$ is given by (11). Assume that there exist non-decreasing positive continuous functions $\Phi, \Psi \in C(\mathbb{R})$ satisfying

$$|g(z)| + |\nabla g(z)| \leq \Phi(|z|) \quad \text{and} \quad |T(v, v', y)| + |\nabla T(v, v', y)| \leq \Psi(|y|).$$

Assume that $f_0 \in W^{1,1}(\mathbb{R} \times V \times \mathbb{R}^2) \cap W^{1,\infty}(\mathbb{R} \times V \times \mathbb{R}^2)$ with compact support and $S_0 \in [W^{1,\infty}(\mathbb{R})]^M$ with compact support. Then there exist global solutions of the system (13)–(14) satisfying

$$f(\cdot, \cdot, t) \in W^{1,1}(\mathbb{R} \times V \times \mathbb{R}^2) \cap W^{1,\infty}(\mathbb{R} \times V \times \mathbb{R}^2),$$

and initial conditions $f(\cdot, \cdot, 0) = f_0(\cdot, \cdot)$ and $S(\cdot, 0) = S_0(\cdot)$.

First, the characteristics of the hyperbolic equation (13) are given for $N = 1$ as

$$\frac{dX}{ds} = V, \quad \frac{dV}{ds} = 0, \quad \frac{dY}{ds} = F(S(X(s), s), Y(s)).$$

Then along back-time characteristics starting at $(x, v, y, t)$, we have for $0 \leq s \leq t$,

$$X(s; x, v, y, t) = x - v(t - s),$$

$$Y(s; x, v, y, t) = y - \int_s^t F(S(X(\tau), \tau), Y(\tau)) d\tau.$$  

Next, we will prove several auxiliary lemmas.

**Lemma 1** Derivation of the characteristics (13) and (14) with respect to the initial conditions gives, for $0 \leq s \leq t$,

$$\frac{\partial X}{\partial x} = 1, \quad \frac{\partial Y}{\partial y} = \exp \left[ \frac{\partial F}{\partial y}(s-t) \right],$$

where

$$\frac{\partial F}{\partial y} = \begin{pmatrix} -1 & -1/t_e \\ -1/t_e & 0 \\ 0 & -1/t_a \end{pmatrix},$$

Moreover,

$$\det \frac{\partial Y}{\partial y} = \exp \left[ \left( \frac{1}{t_e} + \frac{1}{t_a} \right)(t-s) \right] \geq 1.$$
Proof. We differentiate (20) with respect to $y$ to get
\[
\frac{\partial Y}{\partial y} = I_2 + \int_t^s \frac{\partial F}{\partial y} \frac{\partial Y}{\partial y}(\tau) d\tau.
\] (23)
where $I_2$ is the $2 \times 2$ identity matrix. Let
\[
G(s) = \int_t^s \frac{\partial F}{\partial y} \frac{\partial Y}{\partial y}(\tau) d\tau,
\]
then we have
\[
G'(s) = \frac{\partial F}{\partial y} \frac{\partial Y}{\partial y}(s).
\]
Using (23), we obtain
\[
G'(s) - \frac{\partial F}{\partial y} G(s) = \frac{\partial F}{\partial y}.
\]
Integrating the last equation, we have
\[
G(s) = \exp \left[ \frac{\partial F}{\partial y}(s - t) \right] - I_2,
\]
which deduce (21). Computing the determinant of (21), we derive (22).

Q.E.D.

Lemma 2 Let us assume (11) and (15). Then the solution of (18) satisfies
\[
|Y(\tau)| \leq C \left\{ 1 + \Phi \left( \sup_{0 \leq s \leq \tau} |S(X(s), s)| \right) \right\}
\] (24)
where $C$ depends on the $y$-support of $f_0$ and $S_0$, $t_a$, and $t_e$.

Proof. Using the assumption (15) and applying the Gronwall inequality to the ordinary differential equation (18) yields
\[
Y_2(\tau) = Y_2(0) \exp(-\tau/t_a) + \frac{1}{t_a} \int_0^\tau g(S(X(s), s)) \exp[(s - \tau)/t_a] ds
\]
\[
\leq |Y_2(0)| + \frac{1}{t_a} \Phi \left( \sup_{0 \leq s \leq \tau} |S(X(s), s)| \right).
\]
In a similar way, we get
\[
Y_1(\tau) = Y_1(0) \exp(-\tau/t_e) + \frac{1}{t_e} \int_0^\tau \{g(S(X(s), s)) - Y_2(s)\} \exp[(s - \tau)/t_e] ds
\]
\[
\leq |Y_1(0)| + \frac{1}{t_e} \sup_{0 \leq s \leq \tau} |Y_2(s)| + \frac{1}{t_e} \Phi \left( \sup_{0 \leq s \leq \tau} |S(X(s), s)| \right).
\]
Thus we deduce (21).

Q.E.D.
Lemma 3 If \( n \in L^\infty([0, \infty) : L^1(\mathbb{R}) \cap L^2(\mathbb{R})) \), then the solution \( S \) of the system of equations \( (14) \) satisfies
\[
\|S(t)\|_{L^\infty} \leq C \sup_{0 \leq \tau \leq t} \|n(t)\|_{L^1} = C \|n(0)\|_{L^1},
\]
\[
\left\| \frac{\partial S}{\partial x}(t) \right\|_{L^\infty} \leq C \left[ 1 + \|n(0)\|_{L^1} \left( 1 + (\ln t)_+ + \left| \ln \left( \sup_{0 \leq \tau \leq t} \|n(\tau)\|_{L^2} \right) \right| \right) \right]
\]
where \((\cdot)_+\) means the positive part and the constant \( C \) depends only on \( k_i, k_0^0 \) and \( d_i \).

Proof. See [16, Lemma 4]. \( \quad \) Q.E.D.

Proof of Theorem 1 Integrating \((13)\) along the characteristic \((19) - (20)\) from 0 to \( t \) and using \((15)\), we get
\[
f(x, v, y, t) \leq f_0(X(0), v, Y(0)) +
(C \int_0^t \Psi(|Y(\tau)|) \times \left[ f(X(\tau), v, Y(\tau), \tau) + \int_{V'} f(X(\tau), v', Y(\tau), \tau) \, dv' \right] \, d\tau +
\int_0^t |\nabla_y \cdot F(S(X(\tau)), Y(\tau))| f(X(\tau), v, Y(\tau), \tau) \, d\tau.
\]
Since \( \nabla_y \cdot F = -\frac{1}{t_c} - \frac{1}{t_a} \), we get (using Lemma 2)
\[
f(x, v, y, t) \leq f_0(X(0), v, Y(0)) + C \int_0^t f(X(\tau), v, Y(\tau), \tau) \, d\tau +
(C \int_0^t \Psi \left( C \left[ 1 + \Phi \left( \sup_{0 \leq s \leq \tau} |S(X(s), s)| \right) \right] \right) \times
\left[ |V| f(X(\tau), v, Y(\tau), \tau) + \int_{V'} f(X(\tau), v', Y(\tau), \tau) \, dv' \right] \, d\tau
\]
where \( C \) is a constant depending only on support of \( f_0, S_0, t_c \) and \( t_a \). Using Lemma 1 we have
\[
\left( \det \frac{\partial Y}{\partial y} \right)^{-1} \leq 1, \quad \left( \det \frac{\partial X}{\partial x} \right)^{-1} = 1
\]
and so
\[
\int_{\mathbb{R} \times V} \int_{\mathbb{R}^M} f^p(X(\tau), v', Y(\tau), \tau) \, dv' \, dx \, dy =
|V| \int f^p(X(\tau), v', Y(\tau), \tau) \left( \det \frac{\partial Y}{\partial y} \right)^{-1} \left( \det \frac{\partial X}{\partial x} \right)^{-1} \, dv' \, dx \, dY \leq
\leq |V| \int f^p(X(\tau), v', Y(\tau), \tau) \, dv' \, dX \, dY.
\]
Taking the \( p \)-th power of \((25)\) and integrating over \( x, v, \) and \( y \) yields
\[
\|f(t)\|_{L^p} \leq
\]
\[
(27)\]
Lemma 3 implies
\[ \sup_{0 \leq \tau \leq t} \| S(\cdot, \tau) \|_{L^\infty} \leq C \sup_{0 \leq \tau \leq t} \| n(t) \|_{L^1} = C \| n(0) \|_{L^1} \leq C \| f_0 \|_{L^1}. \]  
(28)

Consequently, using (27) and (28), we obtain
\[ \| f(t) \|_{L^p} \leq C \{ 1 + \Psi (1 + \Phi (C \| f_0 \|_{L^1})) \} \times \int_0^t \| f(\tau) \|_{L^p} d\tau. \]  
(29)

Applying the Gronwall inequality, we obtain, for all \( 1 \leq p \leq \infty \),
\[ \| f(t) \|_{L^p} \leq C \left( k_i, k_i^0, d_i, t_e, t_a, \| f_0 \|_{L^p}, \text{supp} \ f_0, \Psi, \Phi, |V| \right) < \infty. \]  
(30)

We now compute a priori estimates on derivatives of \( f \). We differentiate (13) with respect of \( x \), integrate along the characteristic (19) - (20) from 0 to \( t \) and use (15) to get
\[
\left| \frac{\partial f}{\partial x} (x, v, y, t) \right| \leq \left| \frac{\partial f_0}{\partial x} (X(0), v, Y(0)) \right| + C \int_0^t \Psi (|Y(\tau)|) \times \\
\times \left[ |V| \left| \frac{\partial f}{\partial x} (X(\tau), v, Y(\tau), \tau) \right| + \int_V \left| \frac{\partial f}{\partial x} (X(\tau), v', Y(\tau), \tau) \right| dv' \right] d\tau + \\
+ \int_0^t \left| \nabla_y \cdot F( S(X(\tau)), Y(\tau)) \right| \left| \frac{\partial f}{\partial x} (X(\tau), v, Y(\tau), \tau) \right| d\tau + \\
+ \int_0^t \left| \frac{\partial g}{\partial z}( S(X(\tau))) \right| \left| \frac{\partial S}{\partial x} (X(\tau), \tau) \right| \left| \nabla_y f(X(\tau), v, Y(\tau), \tau) \right| d\tau.
\]

Similarly, differentiating (13) with respect of \( y_1 \) or \( y_2 \), integrating along the characteristic (19) - (20) from 0 to \( t \) and using (15), we obtain
\[
\left| \nabla_y f(x, v, y, t) \right| \leq \left| \nabla_y f_0(X(0), v, Y(0)) \right| + C \int_0^t \Psi (|Y(X(\tau), \tau)|) \times \\
\times \left\{ |V| \left[ |f| + |\nabla_y f| \right] (X(\tau), v, Y(\tau), \tau) + \int_V \left[ |f| + |\nabla_y f| \right] (X(\tau), v', Y(\tau), \tau) dv' \right\} d\tau + \\
+ C \int_0^t \left| \nabla_y \cdot F( S(X(\tau)), Y(\tau)) \right| \left| \nabla_y f(X(\tau), v, Y(\tau), \tau) \right| d\tau.
\]

If the interior of set \( V \) is nonempty, we can also define the derivatives of \( f \) with respect of \( v \) for any point in the interior of set \( V \). Differentiating (13) with respect of \( v \) and integrating along the characteristic (19) - (20) from 0 to \( t \), it implies
\[
\left| \frac{\partial f}{\partial v} (x, v, y, t) \right| \leq \left| \frac{\partial f_0}{\partial v} (X(0), v, Y(0)) \right| + \int_0^t \left| \frac{\partial f}{\partial v} (X(\tau), v, Y(\tau), \tau) \right| d\tau + \\
+ C \int_0^t \Psi (|Y(\tau)|) \times \left\{ |V| \left| f(X(\tau), v, Y(\tau), \tau) \right| + \\
\right.
\]

\[ + |V| \left| \frac{\partial f}{\partial v} (X(\tau), v, Y(\tau), \tau) \right| + \int_V \left| f (X(\tau), v', Y(\tau), \tau) \right| dv' \right\} d\tau + \]
\[ + \int_0^t \left| \nabla_y \cdot F (S(X(\tau)), Y(\tau)) \right| \left| \frac{\partial f}{\partial v} (X(\tau), v, Y(\tau), \tau) \right| d\tau. \]

Using (30), (26), Lemma 3 and Gronwall inequality, we deduce
\[ \left\| \frac{\partial f}{\partial x} (t) \right\|_{L^p} + \left\| \frac{\partial f}{\partial v} (t) \right\|_{L^p} + \left\| \nabla_y f (t) \right\|_{L^p} \leq \]
\[ \leq C \left( k_i, k_1^0, d_i, \alpha, t, \| f_0 \|_{W^{1, p}}, \| S(0) \|_{W^{1, p}}, \text{supp} f_0, \text{supp} S_0, \Psi, \Phi, |V| \right) < \infty. \]

Combining (30) and (31), we obtain (16). Using Lemma 3 we get the estimate (17).

Q.E.D

Remark. Using Sobolev embedding theorems, we get global existence of classical solutions provided that initial data are smooth.

3 Biological background

In order to study the general system (8) – (9), we have to first specify realistic assumptions on the parameters of the model. To this end, we summarize the relevant biological processes in Section 3.1 and we extract the mathematical assumptions in Section 3.2. These assumptions will be later used to prove the global existence results in Section 4.

3.1 Bacterial chemotaxis

As discussed before, the bacterial movement can be viewed as a biased random walk. Bacterial motility is commonly provided by flagella, which are long, spiral-shaped protein rods that stick out from the surface of the cell [25]. The example of flagellated bacterium is the enteric bacterium *E.coli* which has 6-8 flagella. It has two modes of behaviour based on counterclockwise and clockwise flagellar rotation. When the flagella rotate counterclockwise (CCW), they all point in one direction and consequently the cell moves forward in a straight “run”. The speed of running is \( s = 10–20\mu m/sec \). Clockwise (CW) rotation of the flagella causes the flagella to point in different directions, and the cell tumbles in place. Tumbling reorients the cell, so that it can move in new direction when running starts again.

For *E.coli*, the duration of both runs and tumbles are exponentially distributed with means of 1 sec and \( 10^{-1} \) sec respectively if an extracellular chemical signal is not present [5]. Under the influence of an attractant, the cell increases its time in running in a favourable direction – see Figure 1. As the mean time for tumbling is ten times smaller than the mean time of running, we can often neglect the time spent tumbling and we can model the movement of the bacterium as a velocity jump process [20, 12, 13] as we already did in Section 1. It means that the bacterium runs in some direction and at random instants of time it changes its direction with mean turning rate \( \lambda(y) \).

Since the bacteria move with more or less constant speed, the set \( V \) of all available velocities might be considered equal to \( V = sS^{N-1} \) where \( S^{N-1} \) is a unit sphere in \( \mathbb{R}^N \) and \( s \) is the speed of the bacterium. Let us note that set \( V = sS^{N-1} \) satisfies the general condition (6) (the presented theory works for any set \( V \) which satisfy (6)).
The kernel $K(v, v', y)$ gives the probability of a change in velocity from $v'$ to $v$, given that a reorientation occurs. The simplest possibility is to assume that kernel is constant, i.e.

$$K(v, v', y) = \frac{1}{|V|}. \quad (32)$$

This formula satisfies the normalization condition.

The underlying assumption behind (32) is that (during the tumble) bacterium simply choose a new direction randomly which is relatively a good approximation for the bacterial chemotaxis, although there is also some bias in the direction of the preceding run. More realistically, one can assume that the turning kernel is a function of the angle between new and old velocity, i.e.

$$K(v, v', y) = k(\theta), \quad \text{where} \quad \cos(\theta) = \frac{v \cdot v'}{|v| |v'|}. \quad (33)$$

Whatever the choice of $K(v, v', y)$ is, we may assume that it is bounded from above by a constant, i.e.

$$K(v, v', y) \leq C \quad (34)$$

where $C$ is independent of $v$, $v'$ and $y$. Next, we have to specify the choice of $K$ and the properties of the turning frequency $\lambda(y)$.

Chemotaxis is the process by which a cell alters its movement in response to an extracellular chemical signal. From the microscopic (cell) point of view, bacterial chemotaxis consists of several steps. First, the cell detects the signal using its receptors. Then the signal information propagates through the signal transduction biochemical network described by (3). The output of this network is a phosphorylated form of the protein CheY (denoted CheY-P) which alters the motor behaviour of the flagellar motors and consequently, the movement of the cell. CCW is the default state in the absence of CheY-P, which binds to motor proteins and increases CW rotation. Attractant binding to a receptor reduces the phosphorylation rate of CheY and thereby increases the time spent in running state which constitutes the fast response to a signal called excitation of signal transduction network. Another important aspect of signal transduction network is adaptation which means that the response (probability per unit time of CCW/CW rotation of flagella) returns to baseline levels on a time scale that is slow compared to excitation, provided that there is no further change in attractant concentration around the cell.

A schematic of the signal transduction pathway is shown in Figure 2 and it can be described as follows. Aspartate, the attractant most commonly-used in experiments (denoted S in Figure 2), binds directly to the periplasmic domain of its receptor, Tar. The cytoplasmic domain of Tar forms a stable complex with the signaling proteins CheA and CheW (denoted A and W, respectively, in Figure 2), and the stability of this complex is not affected by ligand binding. The signaling currency is in the form of phosphoryl groups (-P), made available to the CheY...
slow methylation (slow) adaptation: attractant binding increases (fast) excitation: attractant binding reduces autophosphorylation rate of CheA and it decreases concentration of CheY−P

Figure 2: Excitation and adaptation in signal transduction pathway of E. coli (from [10], with permission).

(denoted Y in Figure 2) and CheB (not shown in Figure 2) through autophosphorylation of CheA. Receptor complexes have two alternative signaling states. In the attractant-bound form, the receptor inhibits CheA autokinase activity; in the unliganded form, the receptor stimulates CheA activity. Consequently, the response of the signal transduction network to a step increase of the attractant concentration is as follows. First, the attractant binding to a receptor reduces the autophosphorylation rate of CheA. The level of phosphorylated CheA is thus lowered, causing less phosphate to be transferred to CheY, yielding a lowered level of CheY−P. As a result, tumbling is suppressed, and the cell’s run length increases. This constitutes the excitation response of the system. Next slow methylation and demethylation reactions begin to influence the response. Ligand-bound receptors are more readily methylated than unliganded receptors, and the lowered level of CheA-P causes a decrease in the level of CheB-P, thereby reducing its demethylation activity. As a result, the equilibrium of the system shifts in the direction of the higher methylation states. The autophosphorylation rate of CheA is faster when the associated Tar-CheA-CheW complex is in a higher methylation state, and so there is finally a shift back toward the receptor states containing CheA-P. As a result, CheY-P returns to its prestimulus level, and thus so does the CW bias of the cell. This constitutes the adaptation response. These key steps, excitation via reduction in CheY-P, when a receptor is occupied, and adaptation via methylation of the receptors, have been already incorporated in the mathematical models of the bacterial signal transduction [27, 2, 19].

Since the turning rate of bacterium is altered by CheY [8], we can write \( \lambda(y) \equiv \lambda(y_1) \), where \( y_1 \) denotes the concentration of the phosphorylated form of CheY. Hence, the individual-based model for bacterial chemotaxis is fully specified by the equation (3) which is integrated along the trajectory of each cell, and by the \( y_1 \) component of the solution together with \( \lambda = \lambda(y_1) \). The essential aspects of the dynamics which must be captured by model (3) are (i) it must exhibit excitation, which here means a change in the turning frequency \( \lambda(y_1) \) in response to a stimulus, (ii) the bias must return to baseline levels (i.e., the response must adapt) on a time scale that is slow compared to excitation, and (iii) the signal transduction network should amplify signals appropriately [6, 26]. The mathematical assumptions on (3) and \( \lambda(y_1) \) are given in Section 3.2.

### 3.2 Mathematical assumptions on the signal transduction network

The mathematical model of the signal transduction network (3) can be rewritten in the following form

\[
\frac{dy}{dt} = F(C(t), y) \quad \text{where} \quad C(t) = S(x(t), t).
\] (35)
The vector function $C(t)$ gives signal values which are seen by a cell along its trajectory. Time evolution of $y$ in equation (35) is controlled by the input time dependent vector $C(t)$. Therefore, it is natural to describe the behaviour of $F$ in terms of the input function $C(t)$.

The mathematical formulation of the adaptation property of the signal transduction network (3) can be written in the following form. There exists a universal constant $\overline{y}_1$ such that for any constant signal along the trajectory $C_0$, i.e. $C(t) \equiv C_0 = \text{const}$ and for any initial condition $y(0) = y_0$, the solution of the system (3) satisfies

$$\lim_{t \to \infty} y_1(t) = \overline{y}_1.$$  \hspace{1cm} (36)

Formula (36) describes the perfect adaptation. From the application point of view, it is desirable that the signal transduction model satisfies (at least approximately) the adaptation property for a reasonably large set of signals. However, the existence theorems presented in Section 4 do not require perfect adaptation and we will prove the existence of solutions even for models which do not satisfy (36). It is worthwhile to note that the simplified model of excitation-adaptation dynamics (11) from Section 2 satisfied adaptation property (36). In fact, $y_1(t) \to 0$ as $t \to \infty$ for any constant signal, i.e. $y_1$ adapts perfectly to any constant stimulus. Moreover, model (11) describes the excitation-adaptation dynamics as discussed in Section 3.1 provided that we choose $t_e < t_a$. Here, the time constants $t_e$ and $t_a$ are labeled in anticipation of using $y_1$ for the internal response, and $y_2$ as the adaptation variable, and therefore we call $t_e$ and $t_a$ the excitation and adaptation time constant, respectively [12].

In order to model the random walk of the individual bacterium, we must have a good understanding of the dependence of the (output) turning rate $\lambda(y_1)$ on the (input) signal function $C(t)$. If the input signal function is constant then the behaviour of $\lambda(y_1)$ follows the adaptation property. On the other hand, time dependent input $C(t)$ can introduce large variations in $\lambda(y_1)$. The time derivative of $C(t)$, i.e. the time derivative of the signal seen by a cell, is equal to

$$\frac{dC}{dt} = v \cdot \frac{\partial S}{\partial x} + \frac{\partial S}{\partial t}.$$ \hspace{1cm} (37)

To see what type of conditions on the turning rate $\lambda$ are reasonable, let us consider the time independent signal (attractant) with a maximum at the point $x_m$ as it is schematically shown in one dimension in Figure 3 (panel in the middle). We consider that bacteria move with the fixed speed either to the right or left and we discuss the following two simple cases of dependence of output $\lambda(y_1)$ on input $C(t)$.

\begin{align*}
(a) \quad \lambda(y_1) &= \begin{cases} 
1 & \text{for } dC/dt \geq 0; \\
\infty & \text{for } dC/dt < 0;
\end{cases} \\
(b) \quad \lambda(y_1) &= \begin{cases} 
0 & \text{for } dC/dt \geq 0; \\
1 & \text{for } dC/dt < 0.
\end{cases}
\end{align*}

Figure 3: Schematic of behaviour of hypothetical cells which “perfectly avoid going in wrong directions” (panel on the left) and hypothetical cells which “perfectly follow good directions” (panel on the right). Details are explained in the text.
Let us note that cases (a) and (b) are considered as definitions of the input-output behaviour in two extreme cases (these definitions are not connected with any underlying differential equation in this example).

First, suppose that a bacterium is at the position \( x < x_m \). If we use input-output behaviour (a), then the cell goes to the right. It sometimes “turns” to the left but it instantly turns back. So, the cell spends all the time going to the right, and case (a) is an example of the individual-based model where cells perfectly avoid going in wrong directions. If we use input-output behaviour (b), then the right going cells never turn (for \( x < x_m \)). Hence, case (b) is an example of the individual-based model where cells perfectly follow good directions. Both cases (a) and (b) describe the simple transport of bacteria for \( x < x_m \). The difference of these models is when cells reach the maximum of the signal \( x_m \). In case (a), cells instantly turn back. It means that the final positions of all bacteria are equal to \( x_m \) and a Dirac-like distribution is created in finite time (see Figure 3, panel on the left). In case (b), cells continue movement to the region \( x > x_m \) and the final distribution profile is smooth, as shown schematically in Figure 3 (panel on the right).

The previous simple example shows that singularities might develop if the turning rate is too large (without a reasonable control by the signal change), as in case (a) where cells perfectly avoid going in wrong directions. This observation suggests for growth conditions on \( \lambda(y_1) \) from above which prevent formation of singularities. The necessary conditions on the turning frequency \( \lambda(y_1) \) is \( \lambda(y_1) \geq 0 \) and our heuristic conclusions can be incorporated to the following growth estimate

\[
\lambda(y_1) \leq C \left( 1 + \Lambda(|C|) + \left| \frac{dC}{dt} \right| \right),
\]

where \( \Lambda(\cdot) \in \mathcal{C}(\mathbb{R}) \) is a non-negative, nondecreasing continuous function. The verification of growth estimate (38) depends on the particular form of \( F(\cdot, \cdot) \) and \( \lambda(\cdot) \). For example, if (3) and \( \lambda(\cdot) \) satisfy

\[
|y_1| \leq C_1 \left( 1 + \left| \frac{dC}{dt} \right|^\omega \right), \quad \lambda(y_1) \leq C_2(1 + |y_1|^\sigma), \quad \omega\sigma \leq 1,
\]

then (38) follows. There are several other conditions on \( F(\cdot, \cdot) \) and \( \lambda(\cdot) \) which also guarantee growth estimate (38). Hence, we do not formulate our growth estimates in terms of \( F(\cdot, \cdot) \) and \( \lambda(\cdot) \), but we simply assume (38) directly in our existence theorems. Using formula (7), we can formulate the estimate (38) also in terms of the kernel \( T(v, v', y) \).

Using estimate (41) and definition (7), we can write the growth assumption on \( T \) in the following form

\[
T(v, v', y) \leq C|\lambda(y_1)|.
\]

We also have to assume a growth assumption of \( \nabla_y F \). In Theorem 2 we assume that there exists a non-negative, nondecreasing continuous function \( \Pi(\cdot) \in \mathcal{C}(\mathbb{R}) \) satisfying

\[
|\nabla_y F(z, y)| \leq C \left( 1 + \Pi(|z|) \right).
\]

Notice that our simple model (11) satisfies (41). A different condition on \( \nabla_y F \) is studied also in Corollary 1.
3.3 Mathematical assumptions on the dynamics of the extracellular signals

Various forms of \( R(S, n) \) can be considered. The simplest case from the mathematical point of view is when the extracellular signals are nutrients which are consumed by cells, i.e.

\[
R(S, n) = -KSn
\]

where \( K \) is a diagonal nonnegative \( M \times M \) matrix (with rate constants on the diagonal). One can also assume that the cells produce signals which are degraded at some rate, i.e.

\[
R(S, n) = n[k_1, k_2, \ldots, k_M]^T - KS
\]

where \( k_1, \ldots, k_M \) are rates of production of the different components of the signal and \( K \) is a diagonal nonnegative \( M \times M \) matrix. If we allow the nondiagonal terms in matrix \( K \), then the extracellular coupling of the signals (e.g. reactions between signals) is added to the model. One can also consider that some signals can be produced by cells and some signals can be degraded by cells, i.e. effectively combining (42) and (43). Moreover, we can also assume that some signals can be attractants while other signals can be repellents etc.

Depending on the model system, there are many possibilities to specify the dynamics of the extracellular signal. In what follows, we use (43). However, it is possible to modify and prove the following existence theorems using different evolution equations for the extracellular signal too. The only requirement is that the evolution equation for the extracellular signal must satisfy suitable growth estimates similar to the estimates which are proven in Lemma 6 for (43).

4 Global existence for the general signal transduction models

In this section, we prove global existence results using the framework of Sections 3.2 and 3.3. We will work in one-dimensional physical space, i.e. \( N = 1 \) and we first assume the case of elliptic equations for the extracellular signals. Hence, system of equations (8) – (9) reads as follows

\[
\frac{\partial f}{\partial t} + \nabla_x \cdot v f + \nabla_y \cdot F(S(x), y)f = \int_V T(v, v', y)[f(v') - f(v)]dv',
\]

\[
d_i \frac{\partial^2 S_i}{\partial x^2} + k_i n - k_i^0 S_i = 0, \quad i = 1, \ldots, M,
\]

where \( d_i, k_i \) and \( k_i^0 \) are positive constants and \( n \equiv n(x, t) \) is the macroscopic density of individuals at point \( x \in \mathbb{R} \) and time \( t \) given by (10). Now, we can formulate the existence theorem.

**Theorem 2** Let us assume (38), (40), and (41). Assume that \( f_0 \in L^1 \cap L^\infty(\mathbb{R} \times V \times \mathbb{R}^m) \) and let initial condition \( S_0 = [W^{2,p}(\mathbb{R})]^M \) satisfies (43). Then there exists a global solution of system (44) – (45) satisfying, for all \( t \geq 0 \)

\[
f(\cdot, \cdot, t) \in L^1 \cap L^\infty(\mathbb{R} \times V \times \mathbb{R}^m),
\]

\[
S(\cdot, t) \in [W^{2,p}(\mathbb{R})]^M, \quad \text{for all } 1 \leq p < +\infty,
\]

and initial conditions \( f(\cdot, \cdot, 0) = f_0(\cdot, \cdot, \cdot) \) and \( S(\cdot, 0) = S_0(\cdot) \).
Remark. To avoid technicalities, we focus in Theorem 2 only on $L^p$ estimates of $f$. The results could be extended to $W^{k,p}$ estimates under suitable growth assumptions on derivatives of $T(v, v', y)$ and $F$.

In order to prove Theorem 2, we formulate some auxiliary lemmas. We start with the generalization of the Gronwall inequality.

**Lemma 4** Let $a(s)$ and $b(s)$ be positive integrable functions on $[0, t]$. Let $w(t)$ be positive and differentiable in $t$, and satisfy

$$w' \leq a(t) w \ln w + b(t) w.$$

Then

$$w(t) \leq \left[ w(0) \exp \left( \int_0^t b(s) e^{-\int_0^s a(\tau) d\tau} ds \right) \right] \exp \left( \int_0^t a(s) ds \right).$$

**Proof.** See [16, Lemma 4].

Q.E.D.

The characteristics of the hyperbolic equation (44) are given for $N = 1$ as the solution of (18). The back-in-time characteristics starting at $(x, v, y, t)$ are given as

$$X(s; x, v, y, t) = x - v(t - s), \quad (48)$$

$$Y(s; x, v, y, t) = y - \int_s^t F(S(X(\tau), \tau), Y(\tau)) d\tau. \quad (49)$$

The generalization of Lemma 1 is given as the following Lemma.

**Lemma 5** Derivation of the characteristics (48) and (49) with respect to the initial conditions gives

$$\frac{\partial X}{\partial x} = 1 \quad \text{and} \quad \frac{\partial Y}{\partial y} = \exp \left[ -\int_s^t \frac{\partial F}{\partial y}(S(X(\tau), \tau), Y(\tau)) d\tau \right]. \quad (50)$$

Moreover,

$$\det \frac{\partial Y}{\partial y} = \exp \left[ -\int_s^t \nabla_y \cdot F(S(X(\tau), \tau), Y(\tau)) d\tau \right]. \quad (51)$$

**Proof.** We differentiate (49) with respect to $y$ to get

$$\frac{\partial Y}{\partial y} = \mathbf{I}_m + \int_s^t \frac{\partial F}{\partial y}(S(X(\tau), \tau), Y(\tau)) \frac{\partial Y}{\partial y}(\tau) d\tau. \quad (52)$$

where $\mathbf{I}_m$ is the $m \times m$ identity matrix. Let

$$G(s) = \int_s^t \frac{\partial F}{\partial y}(S(X(\tau), \tau), Y(\tau)) \frac{\partial Y}{\partial y}(\tau) d\tau,$$

then we have

$$G'(s) - G(s) \frac{\partial F}{\partial y}(S(X(\tau), \tau), Y(\tau)) = \frac{\partial F}{\partial y}(S(X(\tau), \tau), Y(\tau)).$$
Integrating the last equation, we obtain \( \text{50} \). Since the determinant of the exponential of the matrix is the exponential of the trace of the matrix, we have
\[
\det \frac{\partial \mathbf{Y}}{\partial y} = \exp \left[ \text{trace} \left( - \int_s^t \frac{\partial \mathbf{F}}{\partial \mathbf{y}} (\mathbf{S}(X(\tau), \tau), \mathbf{Y}(\tau)) \, d\tau \right) \right] = \exp \left[ - \int_s^t \nabla_y \cdot \mathbf{F} (\mathbf{S}(X(\tau), \tau), \mathbf{Y}(\tau)) \, d\tau \right].
\]
Hence, we have proved \( \text{51} \).

Q.E.D.

Next, we present the growth estimates on the extracellular signal \( \mathbf{S} \) and on its derivatives. The time and space derivatives of the signal vector \( \mathbf{S} \) are controlled by logarithm of the \( L^2 \)-norm of the cell density. Note that the analogous result was also shown in \([16, \text{Lemma 4}]\) for the parabolic equation for the extracellular signal. The difference between \([16, \text{Lemma 4}] \) and Lemma \(6\) is that we prove also the estimate on the space derivative as well as the estimate on the time derivative.

**Lemma 6** If \( n \in L^\infty([0, \infty) : L^1(\mathbb{R}) \cap L^2(\mathbb{R})) \), then the solution \( \mathbf{S} \) in \( \text{45} \) satisfies
\[
\| \mathbf{S}(t) \|_{L^\infty} \leq C \| n(t) \|_{L^1} = C \| n(0) \|_{L^1},
\]
\[
\left\| \frac{\partial \mathbf{S}}{\partial x} (t) \right\|_{L^\infty} \leq C \left[ 1 + \| n(0) \|_{L^1} \{ 1 + \ln (\| n(t) \|_{L^2} + 1) \} \right], \tag{53}
\]
\[
\left\| \frac{\partial \mathbf{S}}{\partial t} (t) \right\|_{L^\infty} \leq C \left[ 1 + \| n(0) \|_{L^1} \{ 1 + \ln (\| n(t) \|_{L^2} + 1) \} \right]. \tag{54}
\]
where the constant \( C \) depends only on \( k_i, k_i^0, d_i \) and \( V \).

**Proof.** Let \( 1 \leq i \leq M \). Taking the Fourier transform of \( \text{45} \) in the \( x \)-variable, we obtain
\[
\hat{\hat{S}}_i(\xi, t) = \frac{k_i}{d_i} \frac{\hat{\hat{n}}(\xi, t)}{\xi^2 + k_i^0/d_i}.
\]
Thus we have
\[
\| \hat{\hat{S}}_i(t) \|_{L^\infty} \leq \| \hat{\hat{n}}(t) \|_{L^1} \int_{-\infty}^{\infty} \frac{1}{\xi^2 + k_i^0/d_i} \, d\xi \\
\leq C \left( \frac{k_i}{d_i} \frac{k_i^0}{d_i} \right) \| n(t) \|_{L^1} = C \left( \frac{k_i}{d_i} \frac{k_i^0}{d_i} \right) \| n(0) \|_{L^1}.
\]
Next we estimate the \( x \)-derivative of the signal as follows.
\[
\| \frac{\partial \hat{\hat{S}}_i}{\partial x} (t) \|_{L^\infty} \leq \| \hat{\hat{x}} \hat{\hat{S}}_i(t) \|_{L^1} \leq \frac{k_i}{d_i} \int_{-\infty}^{\infty} \frac{|\xi| |\hat{\hat{n}}(\xi, t)|}{\xi^2 + k_i^0/d_i} \, d\xi = \frac{k_i}{d_i} \{ I_1 + I_2 \},
\]
where
\[
I_1 = \int_{|\xi| \leq \| n(t) \|_{L^2}} \frac{|\xi| |\hat{\hat{n}}(\xi, t)|}{\xi^2 + k_i^0/d_i} \, d\xi \quad \text{and} \quad I_2 = \int_{|\xi| \geq \| n(t) \|_{L^2}} \frac{|\xi| |\hat{\hat{n}}(\xi, t)|}{\xi^2 + k_i^0/d_i} \, d\xi.
\]
First, we estimate the integral $I_1$. We obtain
\[
I_1 \leq \| \hat{n}(t) \|_{L^\infty} \int_{|\xi| \leq \| n(t) \|_{L^2}^4} \frac{|\xi|}{\xi^2 + k_i^0/d_i} d\xi = 
\]
\[
\| \hat{n}(t) \|_{L^\infty} \ln \left( \frac{\| n(t) \|_{L^2}^4}{k_i^0/d_i} + 1 \right) \leq \| n(t) \|_{L^1} \ln \left( \frac{\| n(t) \|_{L^2}^4}{k_i^0/d_i} + 1 \right) 
\]
We use Hölder’s inequality with $p = q = 2$ to estimate $I_2$ as
\[
I_2 \leq \| \hat{n}(t) \|_{L^2} \left( \int_{|\xi| \geq \| n(t) \|_{L^2}^2} \frac{\xi}{(\xi^2 + k_i^0/d_i)^2} d\xi \right)^{1/2} \leq \| n(t) \|_{L^2} \left( \int_{|\xi| \geq \| n(t) \|_{L^2}^2} \xi^{-2} d\xi \right)^{1/2} \leq \sqrt{2}. 
\]
By combining the estimates for $I_1$ and $I_2$, we obtain (53). In order to estimate the time derivative of the extracellular signal, we take the time derivative of (45) and apply the Fourier transform in the $x$-variable to get
\[
\frac{\partial \hat{S}_i}{\partial t}(\xi, t) = \frac{k_i}{d_i} \frac{\partial \hat{n}}{\partial t}(\xi, t) \frac{1}{\xi^2 + k_i^0/d_i}. 
\]
By integrating (44) over $v$ and $y$, we get
\[
\frac{\partial n}{\partial t} = -\frac{\partial j}{\partial x} \quad \text{where} \quad j(x, t) = \int_{V \times \mathbb{R}^m} v f(x, v, y, t) dvdy. 
\]
Thus we have
\[
\frac{\partial \hat{S}_i}{\partial t}(\xi, t) = \frac{k_i}{d_i} \frac{-i\xi \hat{j}(\xi, t)}{\xi^2 + k_i^0/d_i}. 
\]
Then we have
\[
\left\| \frac{\partial \hat{S}_i}{\partial t}(t) \right\|_{L^\infty} \leq \left\| \frac{\partial \hat{S}_i}{\partial t}(t) \right\|_{L^1} \leq \frac{k_i}{d_i} \int_{-\infty}^{\infty} \frac{|\xi|}{\xi^2 + k_i^0/d_i} d\xi. 
\]
Notice that
\[
\| j(t) \|_{L^\infty} \leq \| j(t) \|_{L^1} \leq \int_{\mathbb{R} \times V \times \mathbb{R}^m} |v| f(x, v, y, t) dxdvdy \leq 
\]
\[
\leq C(V) \| n(t) \|_{L^1} = C(V) \| n(0) \|_{L^1}, 
\]
\[
\| j(t) \|_{L^2} = \| j(t) \|_{L^2} \leq \left( \int_{\mathbb{R}} \left( \int_{V \times \mathbb{R}^m} |v| f(x, v, y, t) dvdy \right)^2 dx \right)^{1/2} \leq 
\]
\[
\leq C(V) \| n(t) \|_{L^2} 
\]
where we have used that $V$ is compact. Using similar ideas as in the proof of estimate (53), we prove (54).

Q.E.D.
Lemma 7 Let \( F \) satisfy (44). Then the characteristics (48) – (49) satisfy for all \( 0 \leq s \leq t \),
\[
\left[ \det \frac{\partial Y}{\partial Y}(s) \right]^{-1} \leq \exp \left[ Ct \left\{ 1 + \Pi \left( C \|f_0\|_{L^1} \right) \right\} \right].
\]

Proof. Using Lemma 5 and (41), we obtain
\[
\text{Lemma 7}
\]
Let \( t \) Using Lemma 7, we obtain for all \( s \leq t \)
\[
\int_s^t \nabla_y \cdot F (S(X(\tau), \tau), Y(\tau)) \, d\tau 
\leq \exp \left[ C \int_s^t 1 + \Pi (|S(X(\tau), \tau)|) \, d\tau \right] \leq \exp \left[ Ct \left\{ 1 + \Pi \left( \sup_{0 \leq \tau \leq t} \|S(\tau)\|_{L^\infty} \right) \right\} \right].
\]

Using Lemma 6, we deduce (55). Q.E.D.

Proof of Theorem 2. Using (38) and (40), we obtain
\[
T(v, v', y) \leq C \left( 1 + \Lambda (|C|) + \left| \frac{dC}{dt} \right| \right).
\]

Integrating (44) along the characteristic (48) – (49) from 0 to \( t \) and using (55), we obtain
\[
f(x, v, y, t) \leq f_0(X(0), v, Y(0)) +
+ C(V) \int_0^t \left\{ \left( 1 + \left[ \Lambda (|S|) + \left| \frac{\partial S}{\partial t} \right| + \left| \frac{\partial S}{\partial x} \right| \right] (X(\tau), \tau) \right) \times \right.
\times \int_V f(X(\tau), v', Y(\tau), \tau) \, dv' \, d\tau +
\left. + \int_0^t \left| \nabla_y \cdot F (S(X(\tau)), Y(\tau)) \right| f(X(\tau), v, Y(\tau), \tau) \, d\tau \right.
\]
\[
\text{where we used that } V \text{ is compact. By virtue of assumption (11), } |\nabla_y \cdot F| \text{ is bounded by } C \left( 1 + \Pi (|S(\tau)|) \right). \text{ Thus we have}
\]
\[
f(x, v, y, t) \leq f_0(X(0), v, Y(0)) +
+ C(V) \int_0^t \left\{ \left( 1 + \left[ \Lambda (|S|) + \left| \frac{\partial S}{\partial t} \right| + \left| \frac{\partial S}{\partial x} \right| \right] (X(\tau), \tau) \right) \times \right.
\times \int_V f(X(\tau), v', Y(\tau), \tau) \, dv' \, d\tau +
\left. + C(V) \int_0^t (1 + \Pi (|S(\tau)|)) f(X(\tau), v, Y(\tau), \tau) \, d\tau \right. \]
\[
\text{Using Lemma 7 we obtain for } t \geq 0,
\]
\[
\int_{\mathbb{R} \times V \times \mathbb{R}^M} \int_V f^p(X(\tau), v', Y(\tau), \tau) \, dv' \, dx \, dy =
\]
\[
= |V| \int f^p(X(\tau), v', Y(\tau), \tau) \left( \det \frac{\partial Y}{\partial Y} \right)^{-1} \left( \det \frac{\partial X}{\partial x} \right)^{-1} \, dv' \, dx \, dY \leq
\]

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We take the $p$-th power of $f(t)$ and integrate over $x$, $v$, and $y$ to get for $t \geq 0$,
\[
\| f(t) \|_{L^p} \leq \| f_0 \|_{L^p} + C (V) e^{Ct} \int_0^t \left\{ (1 + \Lambda (\| S(\tau) \|_{L^\infty}) + \Pi (\| S(\tau) \|_{L^\infty}) + \int \left\{ (1 + \Pi (\| S(\tau) \|_{L^\infty}) + \right\} \right\} \times \| f(\tau) \|_{L^p} d\tau.
\]
Using Lemma 6, we get for all $0 \leq t \leq T$ and with $p = 2$
\[
\| f(t) \|_{L^2} \leq \| f_0 \|_{L^2} + C e^{Ct} \int_0^t \left[ 1 + \| n(0) \|_{L^1} \{ 1 + \ln (\| n(\tau) \|_{L^2} + 1) \} \right] \times \| f(\tau) \|_{L^2} d\tau \leq \| f_0 \|_{L^2} + C e^{Ct} \int_0^t \left[ 1 + \| f(0) \|_{L^1} \{ 1 + \ln (\| f(\tau) \|_{L^2} + 1) \} \right] \times \| f(\tau) \|_{L^2} d\tau.
\]
By applying the Gronwall Lemma 4 to (59), we obtain for $t \geq 0$,
\[
\| f(t) \|_{L^2} \leq C (k_i, k_i^0, d_i, \Lambda, \Pi, V, \| f_0 \|_{L^1}, \| f_0 \|_{L^2}) < \infty,
\]
where we used Lemma 5 to get estimate (60). We now apply (60) to (58) and we get (for $t \geq 0$ and for all $1 \leq p \leq \infty$)
\[
\| f(t) \|_{L^p} \leq C (k_i, k_i^0, d_i, \Lambda, \Pi, V, \| f_0 \|_{L^1}, \| f_0 \|_{L^2}, \| f_0 \|_{L^2}) < \infty,
\]
i.e. we have obtained (61). Using the elliptic equation (45), the second derivative of the extra-cellular signal can be expressed as
\[
\frac{\partial^2 S_i}{\partial x^2} = -\frac{k_i}{d_i} n + \frac{k_i^0}{d_i} S_i.
\]
Using (61) and the elliptic theory, we deduce (62). Thus we complete the proof of Theorem 2.
Q.E.D.

We conclude this section with two corollaries. They provide other conditions for the global existence of solutions. The proofs are omitted because they are similar to proofs of Theorem 1 and Theorem 2.

**Corollary 1** Assume (52) and (50). Suppose there exists a non-negative, nondecreasing continuous function $\Pi (\cdot) \in C (\mathbb{R})$ and $\gamma > 0$ with $\omega \gamma \leq 1$ satisfying
\[
\nabla_y F \leq 0 \quad \text{and} \quad \nabla_y F (z, y) \leq C (1 + \Pi (|z|) + |y|^\gamma)
\]
Assume that $f_0 \in L^1 \cap L^\infty (\mathbb{R} \times V \times \mathbb{R}^m)$ and let the initial condition $S_0 \in [W^{2,p}(\mathbb{R})]^M$ satisfy (44). Then there exists a global solution of the system (44)-(45) satisfying, for all $t \geq 0$
\[
f (\cdot, \cdot, \cdot, t) \in L^1 \cap L^\infty (\mathbb{R} \times V \times \mathbb{R}^m),
\] 
\[
S(\cdot, t) \in [W^{2,p}(\mathbb{R})]^M, \quad \text{for all } 1 \leq p < +\infty
\] and initial conditions $f(\cdot, \cdot, \cdot, 0) = f_0(\cdot, \cdot, \cdot)$ and $S(\cdot, 0) = S_0(\cdot)$. 

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Corollary 2 Assume
\[ \lambda(y_1) \leq C, \quad T(v, v', y) \leq C(1 + |\lambda(y_1)|). \] (64)

We further assume that \( F \) satisfies either (41) or (63). Assume that \( f_0 \in L^1 \cap L^\infty(\mathbb{R} \times V \times \mathbb{R}^m) \) and \( S_0 \in [W^{1,\infty}(\mathbb{R})]^M \) with compact support. Then there exists a global solution of system of equations (44) and (14) satisfying
\[ f(\cdot, \cdot, \cdot, t) \in L^1 \cap L^\infty(\mathbb{R} \times V \times \mathbb{R}^m), \]
\[ S(\cdot, t) \in [W^{1,\infty}(\mathbb{R})]^M \]
and initial conditions \( f(\cdot, \cdot, \cdot, 0) = f_0(\cdot, \cdot, \cdot) \) and \( S(\cdot, 0) = S_0(\cdot) \).

5 Discussion

The simplified model of the bacterial signal transduction was studied in \([12, 13]\) where equation (3) was given as (11). Using model (11) for the steady extracellular signal, one can derive the closed macroscopic (Keller-Segel, chemotaxis) equation for some parameter regimes. See \([12]\) in 1D and \([13]\) in 2D/3D. Hence, the transport equation framework can be used to study the macroscopic behaviour in terms of microscopic parameters for the steady extracellular signals and simplified models of the signal transduction.

Here, we focused on more complex models where we coupled the complex transport equation (8) with the parabolic or elliptic equation for the signal (9). The starting point of the analysis of such complex models is the existence theory. In this paper, we provided several sets of sufficient conditions for the global existence of solutions of system (8) – (9). There are many open questions remaining, e.g., the existence theory in \( N \)-dimensional physical space. It is also not clear whether one can derive the closed evolution equation for the density of cells \( n(x, t) \) as we did for the simple case of noninteracting particles \([12, 13]\). If we are not able to derive the macroscopic equations then suitable computational approaches have to be used to study the macroscopic behaviour of bacteria \([11]\).

There are several related results on kinetic models of the cellular movement. They often do not take the intracellular dynamics into account. Kinetic models were derived in \([11, 20]\) using stochastic models of the movement of cells like bacteria or leukocytes. Reference \([21]\) addresses the formal diffusion limit of kinetic models to the classical Keller-Segel model. The discussion on issues of aggregation, blow-up, and collapse for certain class of random walks can be found in \([23]\). A Boltzmann-type kinetic model for chemotaxis without the internal dynamics coupled with an elliptic equation for the extracellular signal is studied in \([7]\) where global existence and rigorous diffusion limit to the Keller-Segel model were proven. In \([15, 17]\), a more general kinetic model was treated in two and three dimensions. A one-dimensional hyperbolic model was studied in \([16]\). The papers \([15, 16, 17]\) took into account the effect of the gradient and the temporal derivative of the chemical signal and showed the global existence of smooth solutions with smooth initial data as well as the rigorous diffusive limit to the classical Keller-Segel model. However, all the rigorous global existence results so far have not included the temporal derivative of the signal in the growth condition of the turning frequency as we did in this paper. See also \([24]\) for more related works.
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