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# Identification of a chemotactic sensitivity in a coupled system

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Chemotaxis is the process by which cells behave in a way that follows the chemical gradient. Applications to bacteria growth, tissue inflammation and vascular tumours provide a focus on optimization strategies. Experiments can characterize the form of possible chemotactic sensitivities. This paper addresses the recovery of the chemotactic sensitivity from these experiments while allowing for non-linear dependence of the parameter on the state variables. The existence of solutions to the forward problem is analysed. The identification of a chemotactic parameter is determined by inverse problem techniques. Tikhonov regularization is investigated and appropriate convergence results are obtained. Numerical results of concentration-dependent chemotactic terms are explored.

*Keywords*: inverse problem; chemotaxis; Tikhonov regularization.



## 1. Introduction

Biological and ecological research has investigated cell migration. To model cell migration, studies have been composed to include migration, diffusion, haptotaxis and chemotaxis (Keller & Segel, 1970, 1971a,b; Keller, 2006; Oster & Murray, 1989; Anderson *et al.*, 2000; Anderson & Chaplain, 1998; Dung, 2002). In this paper, the focus is chemotaxis. Chemotaxis describes the movement of an organism and/or groups of cells that either move towards or away from a chemical or sensory stimulus. In the early work by Keller & Segel (1970), chemotactic responses of amoebae to bacteria are studied in a cellular slime mould. Bacterial chemotaxis, which describes the ability of bacteria to move towards increased or decreased concentrations of attractants, is analysed at the macroscopic level through a microscopic model of individual cells (Erban & Othmer, 2004; Segel, 1977). It was first observed by Engelmann (1881). For example, if *Salmonella typhimurium*, a strain of salmonella associated with meat and poultry products, is introduced to a petri dish filled with a nutrient, the bacteria will migrate outwards, consuming the nutrient. As they consume the nutrient, they secrete a chemoattractant. After several days, the bacteria will have clustered in the areas of high chemical concentration. A structure of concentric rings is usually observed experimentally. The work by Chet & Mitchell (1976) describes patterns formed from *Escherichia coli* movement towards amino acids. Allweiss *et al.* (1977) investigate *Vibrio cholerae* which are inhibited by a pepsin digest that reduces the possibility of the vibrios attaching to the intestinal wall. Other authors (Fisher & Lauffenburger, 1990; Alt & Lauffenburger, 1985) have addressed chemotaxis in immune cell motility which when combined with tumour morphology is hoped to provide new avenues of treatment strategies. In addition, authors have analysed chemotactic responses in ecology (Lapidus, 1980) and investigated mathematical issues for the existence of global solutions in multiple dimensions (Kowalczyk, 2005; Herrero & Velázquez, 1996; Hillen & Levine, 2003; Childress &

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Percus, 1981; Chalub & Kang, 2006; Aida & Yagi, 2003; Jabbarzadeh & Abrams, 2005; Senba & Suzuki, 2002a,b; Horstmann, 2002; Gajewski & Skrypnik, 2003).

Chemotaxis also arises in a variety of medical applications. In particular, it has been studied in connection with myxobacteria (Sliusarenko *et al.*, 2006; Tosin *et al.*, 2006), leukocyte mobility in tissue inflammation (Alt & Lauffenburger, 1985), the migration of tumour cells towards bone (Orr *et al.*, 1979) and other issues in morphogenesis (Maini & Othmer, 2001). Another interesting problem involves the study of vascular tumours through angiogenesis. Angiogenesis involves the formation of capillary networks of blood vessels that are vital for the growth of tumours. Mathematical modelling of angiogenesis (Anderson *et al.*, 2000; Anderson & Chaplain, 1998; Bellomo & Preziosi, 2000; Corrias *et al.*, 2003; Hillen & Painter, 2001; Levine *et al.*, 2001; Orr *et al.*, 1979; Painter & Hillen, 2002; Sleeman & Levine, 2001; Velazquez, 2004a,b) has given new insight into tumour structure. Normal tissue, lymphocytes and other types of cells grow at the tumour site or are recruited through chemotaxis. The need to identify the nature of this recruitment is at the heart of this paper. The identification of a chemotactic term falls under the umbrella of an inverse problem. In principle, we can measure certain characteristics of the tumour concentration and use mathematical techniques to recover the chemotactic term, in particular the chemotactic sensitivity, that is driving the tumour growth Gatenby *et al.* (2002). To our knowledge, this 'inverse problem' approach has only been used in the analysis of chemotaxis models by Dolak-Struß & Kügler (preprint) under the assumption that the chemical concentration is explicitly known.

Since there are many applications in which chemotaxis arises, there are also different models of the chemotactic effect. There have been many different expressions proposed that model chemotactic velocity, see Keller & Segel (1971b), Lapidus & Schiller (1976), Ford & Lauffenburger (1991) and Tyson *et al.* (1999). This velocity is used in a bacterial conservation equation in the formulation of a system of partial differential equations that govern the particular application. The chemotactic sensitivity determines the velocity. Our goal is to develop a technique whereby the appropriate chemotactic sensitivity model, and hence chemotactic velocity, can be determined from available data. In particular, we consider a system of partial differential equations that was developed by Oster & Murray (1989) to model the pattern formation of cartilage condensation in a vertebrate limb bud. A similar system was studied by Myerscough *et al.* (1998). The numerical solution of similar systems was recently studied by Tyson *et al.* (2000) and Nakaguchi & Yagi (2001). Work by Fister & McCarthy (2003) has shown that the system of partial differential equations can in fact be controlled theoretically through the introduction of a mechanism controlling the number of cells being generated. Simulations provide optimal drug treatment programs for patients to facilitate the rebuilding of cartilage or the reduction of cancerous tumours. The chemotactic sensitivity in Fister & McCarthy (2003) was known and the control parameter was a harvesting term. Our goal in this work is to 'identify' the chemotactic sensitivity.

The paper is organized into six sections. In Section 2, the existence of the forward problem is proven. In Section 3, identifiability of the chemotactic sensitivity is established using the weak formulation of the state problem. In Section 4, Tikhonov regularization is used to approximate the solution through the use of minimization arguments. The rate of convergence of the approximate minimizer of the chemotactic sensitivity to the true parameter follows next. In Section 5, numerical experiments provide graphical depictions of the accuracy of the recovery of the parameter. In Section 6, concluding remarks are made.

## 2. Forward problem

In this model, $u(x,t)$ and $c(x,t)$ represent the concentration of the cells and the chemoattractant, respectively. The cells and the chemoattractant are governed by a convection–diffusion equation and

a reaction–diffusion equation as

$$u_t = M\Delta u - \nabla\cdot(\chi(u,c)u\nabla c) \quad \text{in } \Omega\times(0,T),$$

$$c_t = D\Delta c + \frac{bu}{u+h} - \mu c,$$

$$u(x,0) = u_0(x), \quad c(x,0) = c_0(x), \quad \text{for } x\in\Omega,$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial c}{\partial \nu} = 0 \quad \text{on } \partial\Omega\times(0,T), \tag{1}$$

where $\nu$ is the outward unit normal. $M$ and $D$ represent the diffusion coefficients of the cells and the chemoattractant. The Michaelis–Menten term, $\frac{bu}{u+h}$, represents a response of the chemoattractant to a maximum carrying capacity or saturation rate, assuming $b, h > 0$. We incorporate a decay term where $\mu$ denotes the degradation rate. We assume that there is no flux of the concentrations across the boundary and that the initial concentrations for the cells and chemoattractant are $u_0(x)$ and $c_0(x)$, respectively.

Here, $\chi(u,c)$ is the chemotactic sensitivity which monitors the chemical gradient attraction of the cells. It is this term that we seek to identify. In Oster & Murray (1989), Myerscough *et al.* (1998) and Fister & McCarthy (2003), the term $\chi(u,c)$ is simply a constant. More generally, $\chi(u,c)$ is a linear function of $u$ in Velazquez (2004a,b), Hillen & Painter (2001) and Painter & Hillen (2002), while in Keller & Segel (1970, 1971b), Lapidus & Schiller (1976), Ford & Lauffenburger (1991) and Tyson *et al.* (1999) it is a non-linear function of $c$. We assume henceforth that the chemotactic sensitivity has the form $\chi(u,c) = a(c)$ and is a bounded function. We restrict our analysis to the dimensionless system

$$u_t = M\Delta u - \nabla\cdot(a(c)u\nabla c) \quad \text{in } \Omega\times(0,T),$$

$$c_t = D\Delta c + \frac{u}{u+1} - c,$$

$$u(x,0) = u_0(x), \quad c(x,0) = c_0(x), \quad \text{for } x\in\Omega,$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial c}{\partial \nu} = 0 \quad \text{on } \partial\Omega\times(0,T). \tag{2}$$

We will establish a technique for the identification of $a(c)\in\mathcal{A}$, where

$$\mathcal{A} = \left\{ a\in H^1(I):\ \left\| \frac{\partial a}{\partial c}(c_1) - \frac{\partial a}{\partial c}(c_2)\right\|_{L^2(I)} \leqslant K\|c_1 - c_2\|_{L^2(I)} \right\}.$$

Observe that, with the available data, we can only expect to recover $a(c)$ on the interval $I = [c_{\min}, c_{\max}]$. The Lipschitz condition on the derivative of the chemotactic parameter is quite reasonable, since the chemotactic parameter has a rate of change that is bounded for bacteria growth (Ford & Lauffenburger, 1991).

In order to prove identifiability and to establish the rate of convergence to our method, we will need to establish existence of a solution of (2). Using the standard notation $H^k(\Omega)$ to represent the Sobolev space $W^{k,2}(\Omega)$, let $H^{k+\theta}(\Omega)$ denote the intermediate space between $H^k(\Omega)$ and $H^{k+1}(\Omega)$ for any $0<\theta<1$. Let $D$ be an interval in $[0,\infty)$. The space $L^p(D;X)$ is the $L^p$ space of measurable functions in $D$ with values in the Banach space $X$. The space $C^m(D;X)$, $m = 0, 1, 2, \ldots$, is the space of $m$-times

continuously differentiable functions in $D$ with values in $X$, while the space $C^{\theta}(D; X)$, $0 < \theta < 1$, is the space of Hölder-continuous functions in $D$ with values in $X$.

THEOREM 2.1 If $u_0, c_0 \in H^{1+\varepsilon}(\Omega)$ for $0 < \varepsilon \leqslant 1$ and $u_0(x) \geqslant 0$, $c_0(x) \geqslant \overline{c}_0 > 0$ on $\overline{\Omega}$, then a real unique local solution $u, c$ of (2) exists on an interval $[0, T]$ such that

$$u, c \in C^{\eta}([0, \infty); H^{1+\varepsilon_1}(\Omega)) \cap C([0, T); H^2(\Omega)) \cap C^1([0, T); L^2(\Omega))$$

with $0 < \varepsilon_1 < \min\left(\varepsilon, \frac{1}{2}\right)$ and $0 < \eta < \min\left(\frac{\varepsilon-\varepsilon_1}{2}, \frac{1-2\varepsilon_1}{4}\right)$. The solution satisfies the lower bounds

$$u(x, t) \geqslant 0, \quad c(x, t) \geqslant \overline{c}_0 \, \mathrm{e}^{-t} \quad \text{on } [0, T].$$

*Proof.* Let $X = L^2(\Omega) \times L^2(\Omega)$ and $Z = H^{1+\varepsilon}(\Omega) \times H^{1+\varepsilon}(\Omega)$. The system (2) can be formulated as an abstract quasilinear equation

$$\frac{\mathrm{d}v}{\mathrm{d}t} + A(v)v = f(v), \quad 0 < t < \infty,$$

$$v(0) = v_0$$

on the Banach space $X$.

Let

$$v = \begin{pmatrix} u \\ c \end{pmatrix}, \quad \hat{v} = \begin{pmatrix} \hat{u} \\ \hat{c} \end{pmatrix}, \quad v_0 = \begin{pmatrix} u_0 \\ c_0 \end{pmatrix}.$$

Clearly $v_0 \in Z$.

We define $A(v)$ to be the linear operator in $X$ such that

$$A(v)\hat{v} = \nabla \cdot \begin{pmatrix} -M\, a(c)u \\ 0 \quad -D \end{pmatrix} \begin{pmatrix} \nabla \hat{u} \\ \nabla \hat{c} \end{pmatrix} + \begin{pmatrix} M\ 0 \\ 0\ 1 \end{pmatrix} \begin{pmatrix} \hat{u} \\ \hat{c} \end{pmatrix}$$

with domain

$$D(A(v)) = \left\{ \hat{v} \in H^2(\Omega) \times H^2(\Omega); \frac{\partial \hat{u}}{\partial n} = \frac{\partial \hat{c}}{\partial n} = 0 \quad \text{on } \partial\Omega \right\}.$$

Let the vector $f(v)$ be the function

$$f(v) = \begin{pmatrix} Mu \\ \frac{u}{u+1} \end{pmatrix}.$$

Since $f(v)$ is Lipschitz, application of Yagi's work (Yagi, 1997, Theorems 2.1 and 3.4) yields our result. (See Appendix A for statements of Yagi's results.) □

We also note that Horstmann (2001) provides a related result for a constant $a$ and a Michaelis–Menton chemical production term via using Lyapunov functions to develop a global existence result.

## 3. Inverse problem statement and identifiability

In this section, we begin by establishing the identifiability of the parameter $a(c)$ from the available data $u(x, t)$ and $c(x, t)$ almost everywhere in $W = L^2((0, T), H^1(\Omega))$. Note that, in order for chemotaxis

to be observed biologically, cells must be present and a chemical gradient must exist. This means that $u(x,t)$ and $\nabla c(x,t)$ must be non-zero for a measurable subset of $\Omega \times (0,T)$.

We denote by $(u_a, c_a)$ and $(u_b, c_b)$ the solution pairs of (2) with chemotactic sensitivities $a(c)$ and $b(c)$, respectively.

THEOREM 3.1 Let $(u_a, c_a)$ and $(u_b, c_b)$ both be solutions in $W \times W$ of the direct problem (2) corresponding to $a(c_a)$ and $b(c_b)$. If $u_a = u_b$ and $c_a = c_b$ almost everywhere in $\Omega \times [0,T]$, then $a(c) = b(c)$.

*Proof.* We consider the weak form of the first equation of the direct problem (2) for $(u_a, c_a)$ and $(u_b, c_b)$ and subtract them:

$$\int_0^T \int_\Omega \frac{\partial}{\partial t}(u_a - u_b)\phi \,\mathrm{d}t \,\mathrm{d}x + M \int_0^T \int_\Omega (\nabla(u_a - u_b))\nabla\phi \,\mathrm{d}x \,\mathrm{d}t$$

$$= -\int_0^T \int_\Omega [a(c_a)u_a \nabla c_a - b(c_b)u_b \nabla c_b]\nabla\phi \,\mathrm{d}x \,\mathrm{d}t.$$

Since $u_a(x,t) = u_b(x,t)$ and $c_a(x,t) = c_b(x,t)$ almost everywhere, this reduces to

$$\int_0^T \int_\Omega [a(c_a) - b(c_a)]u_a \nabla c_a \nabla\phi \,\mathrm{d}x \,\mathrm{d}t = 0.$$

By definition, if $\phi$ is in $W = L^2((0,T); H^1(\Omega))$, then we can choose $\phi(x,t) = c_a(x,t)$. Hence,

$$\int_0^T \int_\Omega [a(c_a) - b(c_a)]u_a \,(\nabla c_a)^2 \,\mathrm{d}x \,\mathrm{d}t = 0.$$

Our existence result, Theorem 2.1, says that $u_a \geqslant 0$. We also employ our biological assumptions that $u_a \neq 0$ and $\nabla c_a \neq 0$ on a measurable subset of $\Omega \times (0,T)$. Thus,

$$a(c) = b(c)$$

almost everywhere. □

## 4. Output least squares and Tikhonov regularization

We wish to identify a function $a(c) \in \mathcal{A}$ from noisy measurements $(z_u, z_c)$ of $(u_a, c_a)$. Recall that

$$\mathcal{A} = \left\{ a \in H^1(I) : \left\| \frac{\partial a}{\partial c}(c_1) - \frac{\partial a}{\partial c}(c_2) \right\|_{L^2(I)} \leqslant K \|c_1 - c_2\|_{L^2(I)} \right\},$$

where $I = [c_{\min}, c_{\max}]$.

We define

$$F(a) \equiv (u_a(x,t), c_a(x,t)) \tag{3}$$

with

$$F: \mathcal{A} \to W \times W.$$

In the presence of perfect data $(z_u, z_c)$, we would solve the non-linear ill-posed problem

$$F(a^0) = (z_u, z_c), \tag{4}$$

where $(u_{a^0}, c_{a^0})$ is the solution of the direct problem with $a = a^0$. To do this, using Tikhonov regularization would involve approximating the solution by minimizing

$$\min_{a\in\mathcal{A}} \|F(a) - (z_u, z_c)\|^2_{W\times W} + \alpha\|a - a^*\|^2_{L^2(I)}, \tag{5}$$

where $\alpha > 0$ is a small parameter and $a^*$ is an *a priori* guess of the true solution $a^0$. In real applications, measurement errors mean that exact data are not available. Noisy data are assumed to have an error level $\delta$, which means that

$$\int_0^T \|u - z_u^\delta\|^2_{L^2(\Omega)}\mathrm{d}t \leqslant \delta^2, \quad \int_0^T \|c - z_c^\delta\|^2_{L^2(\Omega)}\mathrm{d}t \leqslant \delta^2, \tag{6}$$

where $u$ and $c$ are the true cell and the chemical concentrations associated with the chemotactic sensitivity $a^0$, and $z_u^\delta$ and $z_c^\delta$ are the noisy measurements of the cell and the chemical concentrations, respectively.

We assume attainability of a true solution, i.e. if $(z_u, z_c) \in W \times W$, there exists a $a^0 \in \mathcal{A}$ such that

$$F(a^0) = (z_u, z_c). \tag{7}$$

In the presence of noisy data $(z_u^\delta, z_c^\delta)$, the minimizer $a_\alpha^\delta \in \mathcal{A}$ of (5) minimizes

$$\begin{aligned} J_\alpha(a) &\equiv \|F(a) - (z_u^\delta, z_c^\delta)\|^2_{W\times W} + \alpha\|a - a^*\|^2_{L^2(I)} \\ &= \int_0^T \|u - z_u^\delta\|^2_{L^2(\Omega)}\,\mathrm{d}t + \int_0^T \|c - z_c^\delta\|^2_{L^2(\Omega)}\,\mathrm{d}t + \alpha\|a - a^*\|^2_{L^2(I)} \end{aligned} \tag{8}$$

for appropriate choices of $a \in \mathcal{A}$ and $\alpha$.

We begin by establishing the weak-closedness of the map $F(a)$.

THEOREM 4.1 If $a_n \rightharpoonup a_* \in \mathcal{A}$, then $u_{a_n} \rightharpoonup u_{a_*}$ and $c_{a_n} \rightharpoonup c_{a_*}$ in $W$.

*Proof.* Here, we give the outline of the proof and refer the reader to Fister *et al.* (2006) for details. Using that the solution to the state system (2) is unique, one can define $u_{a_n} = u(a_n)$ and $c_{a_n} = c(a_n)$. A transformation involving $\mathrm{e}^{-\lambda t}$ times each component of the solution pair is made with $\lambda$ to be chosen in order to obtain the boundedness of the solution in $W$. The weak definition of the solution associated with the transformed $u_{a_n}$ and $c_{a_n}$ in (3) is analysed via Cauchy's inequality and the boundedness of the coefficients. Using the boundedness (independent of $n$) of the solution pairs, subsequences are extracted that converge weakly to $u_*$ and $c_*$. Lastly, comparison results (Simon, 1987) are used so that one can pass to the limit in the weak formulation of the solution to show that $u_* = u_{a*}$ and $c_* = c_{a*}$. □

COROLLARY 4.1 For any data $(z_u^\delta, z_c^\delta) \in W \times W$, a minimizer $a_\alpha^\delta$ of (8) exists.

This is true because the existence of a minimizer $a_\alpha^\delta$ follows from the lower semicontinuity of $J_\alpha(a)$. In the following corollary, we give a result that highlights the continuous dependence on the data.

COROLLARY 4.2 For fixed $\alpha$, the minimizers depend continuously on the data $(z_u^\delta, z_c^\delta)$. If $\alpha(\delta)$ satisfies

$$\alpha(\delta) \to 0, \quad \delta^2/\alpha(\delta) \to 0 \quad \text{as } \delta \to 0,$$

then

$$\lim_{\delta \to 0} \|a_\alpha^\delta - a^0\|_{L^2(I)} = 0.$$

The result follows from standard results in Seidman & Vogel (1989) that prove the continuous dependence on the data $(z_u^\delta, z_c^\delta)$ for fixed $\alpha$, and the convergence of $a_\alpha^\delta$ towards the true parameter $a^0$ as the noise level $\delta$ and the regularization parameter $\alpha$ go to zero. As the noise levels converge to zero, we obtain the optimal result. Essentially, with this infinite set of data, the minimum is achieved and the corresponding sensitivities converge as the noise goes to zero.

### 4.1 *Convergence rate analysis*

Although we have noted (without proof) the convergence of the minimizer $a_\alpha^\delta$ to the true parameter $a^0$, the rate of convergence may be arbitrarily slow. We wish to determine a source condition that will guarantee a certain rate of convergence. Even when our regularization parameter $\alpha$ is comparable to our noise level $\delta$, such a source condition will require assumptions involving $u$ and $a^0 - a^*$.

Recall that we seek to solve the non-linear problem (4), $F(a) = (z_u, z_c)$, where $F(a) \equiv (u_a, c_a)$. The true solution is $a^0$, and $a^*$ is an *a priori* guess. In order to apply the theory of Engl *et al.* (1989, 2000), we must establish the following:

- $F$ is Frechet differentiable,
- $F'$ is Lipschitz with $\|F'(a) - F'(b)\| \leqslant \gamma \|a - b\|$,
- there exists $w \in L^2((0,T); H^1(\Omega))$ satisfying the source condition $a^0 - a^* = F'(a^0)^* w$,
- $\gamma \|w\| < 1$.

In practice, although computing $F'$ and $(F')^*$ is not difficult, it can be quite tricky to establish the Lipschitz condition on $F'$ with our system of coupled non-linear partial differential equations. Instead, our approach involves developing a 'source condition' without imposing differentiability constraints on $F$. Thus, we establish $\mathrm{O}(\sqrt{\delta})$ convergence. This technique is also found in the work of Engl & Kügler (2002).

THEOREM 4.2 Suppose that there exists a function $w \in L^2((0,T); H^1(\Omega))$ satisfying

$$w(x,0) = w(x,T) = 0, \quad \Delta w \in L^2((0,T); L^2(\Omega))$$

such that for any $\Psi \in \mathcal{A}$,

$$\langle a^0 - a^*, \Psi \rangle_{L^2(I)} = \int_0^T \int_\Omega \Psi(c_{a^0}) u_{a^0} \nabla c_{a^0} \cdot \nabla w \, \mathrm{d}x \, \mathrm{d}t.$$

If $\alpha \sim \delta$, then

$$\int_0^T \left\| u_{a_\alpha^\delta} - z_u^\delta \right\|_{L^2(\Omega)}^2 + \left\| c_{a_\alpha^\delta} - z_c^\delta \right\|_{L^2(\Omega)}^2 \mathrm{d}t = \mathrm{O}(\delta^2)$$

and

$$\|a^0 - a_\alpha^\delta\|_{L^2(I)} = \mathrm{O}(\sqrt{\delta}).$$

*Proof.* For clarity, we briefly describe the techniques used in this proof. Using that a minimizer to $J_\alpha(a)$ exists, we obtain an upper bound in terms of the error level $\delta$ and the norm of the difference in

the minimizer and optimal $a$ values. We then use our source condition with the weak formulation of the cell and the chemical differential equations to obtain a representation of the inner product of the appropriate differences of the approximating minimizers. This allows us to bound $J_\alpha(a)$. Specifically, we use triangle and Young's inequalities to bound the time and spatial derivatives of the differences in the state variables. Integration by parts and Hölder's inequality enable us to successfully bound the spatial derivatives of the states in terms of the states themselves. Using the assumptions from $\mathcal{A}$ and choosing $\epsilon$ sufficiently small, we can obtain the error of order $\sqrt{\delta}$ with $\alpha \sim \delta$.

Since $a_\alpha^\delta$ is a minimizer of $J_\alpha(a)$, we have $J_\alpha(a_\alpha^\delta) \leqslant J_\alpha(a^0)$. Using our definition of noise level (6), we find that

$$\begin{aligned}
&\int_0^T \left\| u_{a_\alpha^\delta} - z_u^\delta \right\|_{L^2(\Omega)}^2 + \left\| c_{a_\alpha^\delta} - z_c^\delta \right\|_{L^2(\Omega)}^2 \,\mathrm{d}t + \alpha \|a_\alpha^\delta - a^*\|_{L^2(I)}^2 \\
&\leqslant \int_0^T \|u_{a^0} - z_u^\delta\|_{L^2(\Omega)}^2 + \|c_{a^0} - z_c^\delta\|_{L^2(\Omega)}^2 \,\mathrm{d}t + \alpha \|a^0 - a^*\|_{L^2(I)}^2 \\
&\leqslant 2\delta^2 + \alpha \|a^0 - a^*\|_{L^2(I)}^2. \qquad (9)
\end{aligned}$$

Adding $\alpha \|a^0 - a_\alpha^\delta\|_{L^2(I)}^2$ to both sides of the inequality and using inner product properties yield

$$\begin{aligned}
&\int_0^T \left\| u_{a_\alpha^\delta} - z_u^\delta \right\|^2 + \left\| c_{a_\alpha^\delta} - z_c^\delta \right\|^2 \,\mathrm{d}t + \alpha \|a^0 - a_\alpha^\delta\|_{L^2(I)}^2 \\
&\leqslant 2\delta^2 + 2\alpha \langle a^0 - a^*, a^0 - a_\alpha^\delta \rangle_{L^2(I)}. \qquad (10)
\end{aligned}$$

Observe that our source condition

$$\langle a^0 - a^*, \Psi \rangle_{L^2(I)} = \int_0^T \int_\Omega \Psi(c_{a^0}) u_{a^0} \nabla c_{a^0} \cdot \nabla w \,\mathrm{d}x \,\mathrm{d}t$$

with $\Psi = a^0 - a_\alpha^\delta$, together with the weak forms of the cell equation in the forward problem (2) for $a^0$ and $a_\alpha^\delta$, is

$$\begin{aligned}
\langle a^0 - a^*, a^0 - a_\alpha^\delta \rangle_{L^2(I)} = &\int_0^T \int_\Omega \left( u_{a^0} - u_{a_\alpha^\delta} \right)_t w \,\mathrm{d}x \,\mathrm{d}t + \int_0^T \int_\Omega \nabla \left( u_{a^0} - u_{a_\alpha^\delta} \right) \cdot \nabla w \,\mathrm{d}x \,\mathrm{d}t \\
&+ \int_0^T \int_\Omega \left[ a_\alpha^\delta \left( c_{a_\alpha^\delta} \right) u_{a_\alpha^\delta} \nabla c_{a_\alpha^\delta} - a_\alpha^\delta (c_{a^0}) u_{a^0} \nabla c_{a^0} \right] \cdot \nabla w \,\mathrm{d}x \,\mathrm{d}t
\end{aligned}$$

and (10) becomes

$$\begin{aligned}
&\int_0^T \left\| u_{a_\alpha^\delta} - z_u^\delta \right\|_{L^2(\Omega)}^2 + \left\| c_{a_\alpha^\delta} - z_c^\delta \right\|_{L^2(\Omega)}^2 \,\mathrm{d}t + \alpha \|a^0 - a_\alpha^\delta\|_{L^2(I)}^2 \\
&\leqslant 2\delta^2 + 2\alpha \int_0^T \int_\Omega \left( u_{a^0} - u_{a_\alpha^\delta} \right)_t w \,\mathrm{d}x \,\mathrm{d}t + 2\alpha M \int_0^T \int_\Omega \nabla \left( u_{a^0} - u_{a_\alpha^\delta} \right) \cdot \nabla w \,\mathrm{d}x \,\mathrm{d}t \\
&+ 2\alpha \int_0^T \int_\Omega \left[ a_\alpha^\delta \left( c_{a_\alpha^\delta} \right) u_{a_\alpha^\delta} \nabla c_{a_\alpha^\delta} - a_\alpha^\delta (c_{a^0}) u_{a^0} \nabla c_{a^0} \right] \cdot \nabla w \,\mathrm{d}x \,\mathrm{d}t. \qquad (11)
\end{aligned}$$

We bound each integral in (11) separately using triangle and Young's inequalities. We find that

$$|I_1| = \left|\alpha \int_0^T \int_\Omega \left(u_{a^0} - u_{a_\alpha^\delta}\right)_t w \,\mathrm{d}x\,\mathrm{d}t\right|$$

$$\leqslant \varepsilon \int_0^T \left\|u_{a_\alpha^\delta} - z_u^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t + \frac{\alpha^2}{2\varepsilon}\int_0^T \|w_t\|_{L^2(\Omega)}^2 \mathrm{d}t + \varepsilon\delta^2$$

and

$$|I_2| = \left|\alpha M \int_0^T \int_\Omega \nabla\left(u_{a^0} - u_{a_\alpha^\delta}\right)\cdot\nabla w \,\mathrm{d}x\,\mathrm{d}t\right|$$

$$\leqslant \varepsilon M^2\delta^2 + \frac{\alpha^2}{2\varepsilon}\int_0^T \|\Delta w\|_{L^2(\Omega)}^2 \mathrm{d}t + \varepsilon M^2 \int_0^T \left\|u_{a_\alpha^\delta} - z_u^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t,$$

where $\varepsilon$ is an arbitrary parameter resulting from the use of Young's inequality. We utilize the assumptions

$$\eta_1 \leqslant \frac{\partial a}{\partial c} \leqslant \hat{\eta}_1, \quad \left\|\frac{\partial a}{\partial c}(c_1) - \frac{\partial a}{\partial c}(c_2)\right\|_{L^2(\Omega)} \leqslant K\|c_1 - c_2\|_{L^2(\Omega)},$$

Green's theorem, the boundary conditions and Hölder's inequality to obtain the estimate

$$|I_3| = \left|\alpha \int_0^T \int_\Omega \left[a_\alpha^\delta\left(c_{a_\alpha^\delta}\right) u_{a_\alpha^\delta}\nabla c_{a_\alpha^\delta} - a_\alpha^\delta(c_{a^0})u_{a^0}\nabla c_{a^0}\right]\cdot\nabla w \,\mathrm{d}x\,\mathrm{d}t\right|$$

$$\leqslant \varepsilon\left[\hat{\eta}_1^2\int_0^T \left\|u_{a_\alpha^\delta} - z_u^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t + \|u\|_{L^\infty(\Omega)}^2 K^2 \int_0^T \left\|c_{a_\alpha^\delta} - z_c^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t\right]$$

$$+ \frac{\alpha^2}{\varepsilon}\int_0^T \|\Delta w\|_{L^2(\Omega)}^2 \mathrm{d}t + \varepsilon\hat{\eta}_1^2\delta^2 + \varepsilon\|u\|_{L^\infty(\Omega)}^2 K^2\delta^2$$

$$+ \varepsilon\|\nabla u\|_{L^\infty(\Omega)}^2 K^2 \int_0^T \left\|c_{a_\alpha^\delta} - z_c^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t + \varepsilon\hat{\eta}_1^2\mu^2 \int_0^T \left\|u_{a_\alpha^\delta} - z_u^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t$$

$$+ \frac{\alpha^2}{\varepsilon}\int_0^T \|\nabla w\|_{L^2}^2 \mathrm{d}t + \varepsilon\|\nabla u\|_{L^\infty(\Omega)}^2 K^2\delta^2 + \varepsilon\hat{\eta}_1^2\mu^2\delta^2.$$

Grouping terms and relabelling constants, we have

$$\int_0^T \left\|u_{a_\alpha^\delta} - z_u^\delta\right\|_{L^2(\Omega)}^2 + \left\|c_{a_\alpha^\delta} - z_c^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t + \alpha\|a^0 - a_\alpha^\delta\|_{L^2(I)}^2$$

$$\leqslant 2\delta^2 + 2C_1\varepsilon\delta^2 + 2\varepsilon C_2 \int_0^T \left\|u_{a_\alpha^\delta} - z_u^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t$$

$$+ 2\varepsilon C_3 \int_0^T \left\|c_{a_\alpha^\delta} - z_c^\delta\right\|_{L^2(\Omega)}^2 \mathrm{d}t$$

$$+\frac{\alpha^2}{\varepsilon}\int_0^T (\|w_t\|^2_{L^2(\Omega)} + 3\|\Delta w\|^2_{L^2(\Omega)} + 2\|\nabla w\|^2_{L^2(\Omega)})\mathrm{d}t.$$

If $\varepsilon$ is chosen to be sufficiently small, then for the choices $\alpha \sim \delta$, we obtain

$$\int_0^T \left\| u_{a_\alpha^\delta} - z_u^\delta \right\|^2_{L^2(\Omega)} + \left\| c_{a_\alpha^\delta} - z_c^\delta \right\|^2_{L^2(\Omega)} \mathrm{d}t = \mathrm{O}(\delta^2)$$

and

$$\|a^0 - a_\alpha^\delta\|_{L^2(I)} = \mathrm{O}(\sqrt{\delta}). \qquad \square$$

We have now determined a condition on $a^0 - a^*$ that guarantees a practical rate of convergence for our regularization scheme. If we choose our regularization parameter $\alpha$ in such a way that it approaches zero at the same rate as the noise level $\delta$, then our recovered chemotactic sensitivity $a_\alpha^\delta$ will approach the true chemotactic sensitivity $a^0$ at a rate proportional to $\sqrt{\delta}$.

## 5. Numerical results

In order to demonstrate the effectiveness of Tikhonov regularization for this application, we consider several examples.

All computations were carried out in MATLAB. The Tikhonov functional

$$J_\alpha(a) = \int_0^T \int_\Omega (|u - z_u^\delta|^2 + |c - z_c^\delta|^2)\mathrm{d}x\,\mathrm{d}t + \alpha\|a - a^*\|^2_{L^2(I)} \tag{12}$$

was minimized using lsqnonlin, a MATLAB implementation of the Levenberg–Marquardt method with line search (Levenberg, 1944; Marquardt, 1963). Although it was not tractable to do so in the convergence analysis, a gradient-based algorithm is appropriate here because computing the gradient and its adjoint is straightforward.

We restrict our discussion to $\Omega = [0, 1]$. Recall that $z_u^\delta$ and $z_c^\delta$ represent noisy data and $a^*$ represents an *a priori* guess of the chemotactic sensitivity $a$. Cell and chemoattractant concentration data on $\Omega = [0, 1]$ were generated using pdepe with high accuracy. During the computation of $J_\alpha(a)$, cell and chemoattractant concentrations $u(x, t)$ and $c(x, t)$ associated with a particular $a$ were computed using pdepe with moderate accuracy over coarser space and time meshes than those used to simulate data.

Since lsqnonlin requires objective functions of the form

$$\frac{1}{2}\|F\|_2^2 = \frac{1}{2}\sum_k f_k^2(x),$$

we approximated the first two terms of $J_\alpha(a)$ by

$$\sum_{j=1}^{M}\left\{\sum_{i=1}^{N}[u(x_i, t_j) - z_u(x_i, t_j)]^2 + \sum_{i=1}^{N}[c(x_i, t_j) - z_c(x_i, t_j)]^2\right\}(\Delta x)(\Delta t),$$

where $x_i = i(\Delta x)$ for $i = 0, \ldots, N$ with $\Delta x = 1/N$ and $t_j = j(\Delta t)$ for $j = 0, \ldots, M$ with $\Delta t = \sigma/M$.

We approximate $a(c)$ by

$$a(c) = \sum_{k=1}^{L} a_k \phi_k(c), \tag{13}$$

where $\phi_k$ are the usual piecewise linear hat functions defined over a partition of $[c_{\min}, c_{\max}]$. Note that any function $a(c)$ can be represented by its corresponding vector $\mathbf{a}$. Since the values of $c_{\min}$ and $c_{\max}$ may vary considerably for each $a$ used during the optimization, we choose instead an interval that is sufficiently large to include the range of $c$ for each $a$ considered by the algorithm. In practice, this means making a guess and expanding the interval when $c$ leaves our chosen interval.

The penalty term $\alpha \|a - a^*\|_{\mathcal{A}}^2$ can be replaced by

$$\left\| \sum_{i=1}^{L} (a_i - a_i^*)\phi_i \right\|_{\mathcal{A}} = (\mathbf{a} - \mathbf{a}^*)^\top B(\mathbf{a} - \mathbf{a}^*),$$

where the components of the matrix $B$ are given by $B_{ij} = (\phi_i, \phi_j)_{\mathcal{A}}$.

Various strategies for the choice of regularization parameters are discussed in Vogel (2002). In each of the following examples, we used an L-curve method to choose an optimal regularization parameter $\alpha$.

Recall that our chemotaxis system is

$$\begin{aligned} u_t &= M\Delta u - \nabla \cdot (a(c)u\nabla c) \quad \text{in } \Omega \times (0, T), \\ c_t &= D\Delta c + \frac{bu}{u+h} - \mu c, \\ u(x,0) &= u_0(x), \quad c(x,0) = c_0(x), \quad \text{for } x \in \Omega, \\ \frac{\partial u}{\partial \nu} &= \frac{\partial c}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, T). \end{aligned} \tag{14}$$

A similar system was used by Myerscough *et al.* (1998) in their numerical simulations of chemotaxis in limb bud development with parameters

$$M = 0.25, \quad D = 1, \quad a(c) = 2, \quad h = 1, \quad b = \mu, \quad u_0 = 1 + \varepsilon(x), \quad c_0 = 0.5, \quad \Omega = [0, 1],$$

where $\mu \in [0, 3000]$ and $\varepsilon(x)$ was a bounded perturbation function. In Examples 1–3, we used the Myerscough parameters with

$$\varepsilon(x) = \mathrm{e}^{-55(x-0.5)^2}, \quad T = 0.25, \quad b = \mu = 50.$$

EXAMPLE 1 Consider the chemotactic coefficient used by Myerscough *et al.* (1998)

$$a(c, u, x, t) = 2.$$

The cell and the chemoattractant concentrations associated with this $a$ are shown over the time interval $[0, 0.25]$ in Fig. 1. An initial guess of $a = 1$ was used. The *a priori* guess was also chosen to be $a^* = 1$. The parameter $a$ was recovered to within $1.461 \times 10^{-6}$ of the true value at $T = 0.25$.

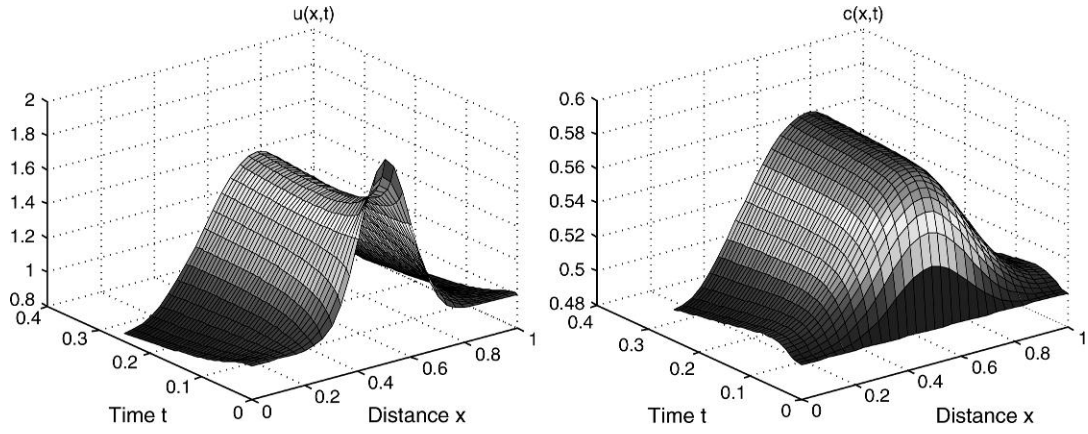


FIG. 1. Cell and chemical concentrations over time interval [0, 0.25] with $a(c, u, x, t) = 2$.

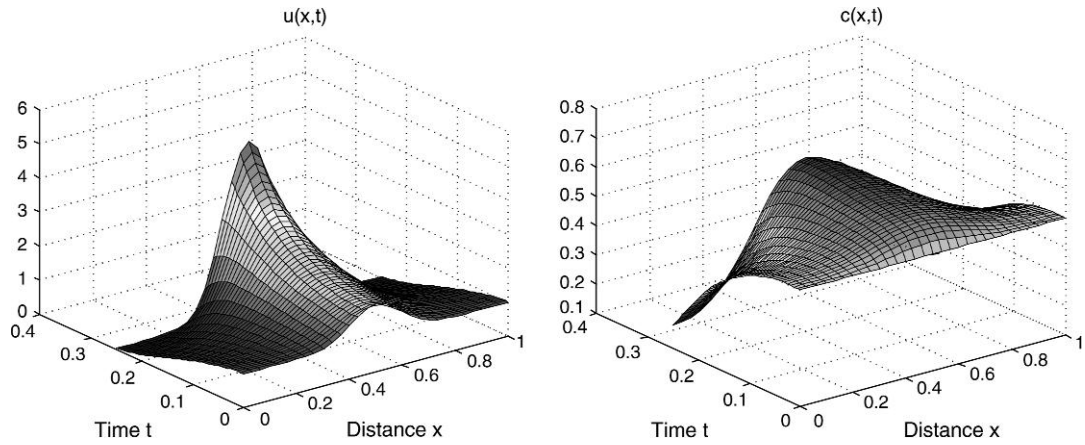


FIG. 2. Cell and chemical concentrations over time interval [0, 0.25] with $a(c, u, x, t) = 2/c$.

EXAMPLE 2 Keller–Segel model

We consider the non-linear chemotactic coefficient

$$a(c) = 2/c$$

proposed in the original Keller–Segel model for chemotaxis (Keller & Segel, 1970). The cell and the chemoattractant concentrations associated with this $a$ are shown in Fig. 2.

From the data, we find that $[c_{\min}, c_{\max}] = [0.1794, 0.6398]$ when $a(c) = 2/c$. Since the optimization algorithm will use approximations of other chemotactic functions, we attempt to reconstruct $a(c)$ over a larger interval. We found the interval $[0.1, 0.7]$ to be sufficiently large to include the range of $c$ for each $a$ considered by the algorithm.

An initial guess of $a = 15(1 - c)^2$ was used. The *a priori* guess was also chosen to be $a^* = 15(1 - c)^2$. Figure 3 shows the chemotactic function $a$ and its recovery of $a_{\text{noise}}$ with and without

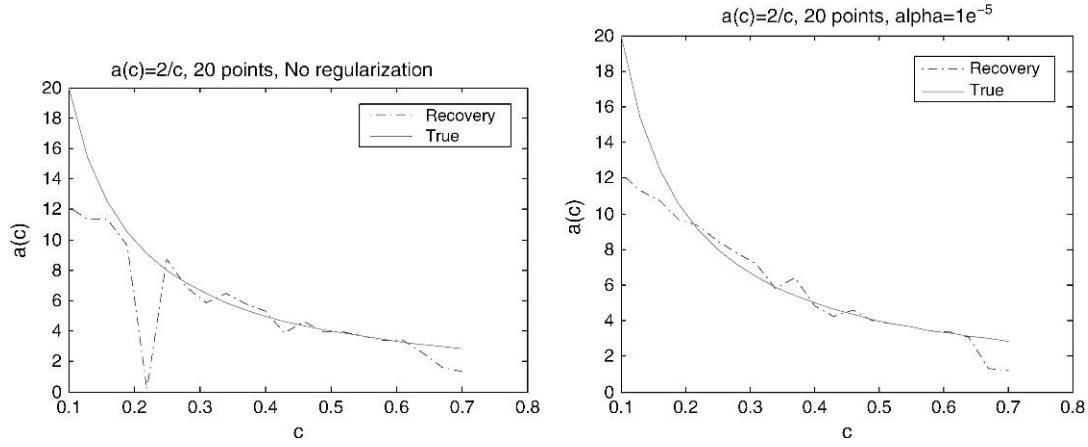


FIG. 3. True chemotactic coefficient $a(c) = 2/c$ and its recovery with no regularization (left) and a regularization parameter of $\alpha = 10^{-5}$.

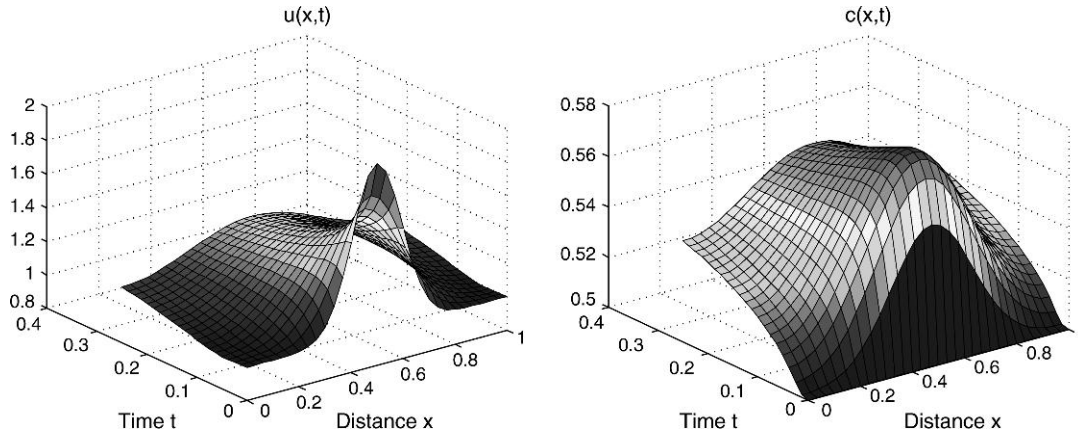


FIG. 4. Cell and chemical concentrations over time interval [0, 0.25] with $a(c, u, x, t) = 2/(1 + c)^2$.

regularization. A regularization parameter of $\alpha = 10^{-5}$ was chosen by an L-curve method. Note that the regularized recovery is quite reasonable over the interval $[c_{\min}, c_{\max}] = [0.1794, 0.6398]$ and that its quality degrades, as expected, outside this interval.

EXAMPLE 3 Reaction kinetics model

A non-linear chemotactic coefficient

$$a(c) = \frac{2}{(1+c)^2}$$

based on reaction kinetics was proposed by Segel (1977). The cell and the chemoattractant concentrations associated with this $a$ are shown in Fig. 4. From the data, we find that $[c_{\min}, c_{\max}] = [0.5, 0.5799]$

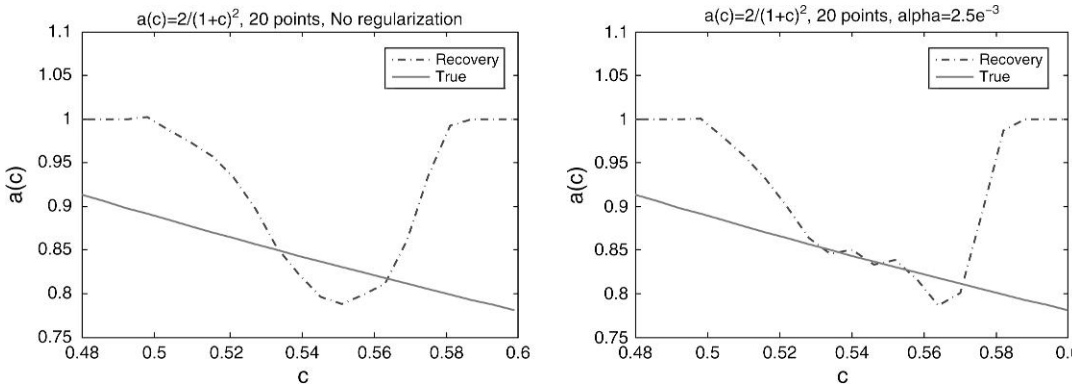


FIG. 5. True chemotactic coefficient $a(c) = 2/(1+c)^2$ and its recovery with no regularization (left) and a regularization parameter of $\alpha = 2.5 \times 10^{-3}$.

when $a(c) = 2/(1 + c)^2$. Once again, we attempt to reconstruct $a(c)$ over a larger interval. We found the interval $[0.48, 0.6]$ to be sufficiently large to include the range of $c$ for each $a$ considered by the algorithm.

An initial guess of $a = 1$ was used. The *a priori* guess was also chosen to be $a^* = 1$. Figure 5 shows the chemotactic function $a$ and its recovery of $a_{\text{noise}}$ with and without regularization. A regularization parameter of $\alpha = 2.5 \times 10^{-3}$ was chosen by an L-curve method. Note that the regularized recovery is quite reasonable over the interval $[0.52, 0.57]$ and that its quality degrades, as expected, outside this interval.

**Comments**. The number of iterations used by the algorithm is quite sensitive to the choice of initial function $a_0$ and the number of piecewise linear basis functions used in (13). For experimental data, we must acknowledge that the quality of the recovery degrades with increased noise in the data. In certain applications such as pattern formation in *E. coli* or *S. typhimurium*, see Tyson *et al.* (1999), the size of the interval $[c_{\min}, c_{\max}]$ is sometimes too small to give adequate information for the recovery of the chemotactic coefficient. This can be avoided by taking a larger time interval $[0, T]$. In numerical simulations, this requires a careful choice of numerical method for the solution of the chemotaxis system, see Tyson *et al.* (2000). An alternative approach is to restrict our measurements to a particular time, rather than an interval of time. The efficacy of this approach will be discussed in a future paper.

## 6. Conclusions

In this work, we have explored a particular mathematical aspect of the chemotactic sensitivity within the gradient. The identification of a chemotactic sensitivity with functional dependence has been determined. The interesting aspect of this work is that, to our understanding, no one has been able to capture the chemotactic sensitivity information from limited data with dependence on the chemical in a system. We have proven the existence of the state solutions in specific Sobolev spaces and formulated an inverse problem. We have employed Tikhonov regularization to recover the chemotactic sensitivity from noisy measurements. In doing so, a minimization problem is formed and the necessary convergence results for an approximating minimizer to the true parameter are discussed.

Another significant result is that we have established a source condition that guarantees a particular rate of convergence by imposing a Lipschitz condition on the derivative of the chemotactic sensitivity. In practice, this is biologically reasonable, since the chemotactic sensitivity has a rate of change that is bounded for bacterial growth (Ford & Lauffenburger, 1991).

Numerically, we have utilized models from Myerscough *et al.* (1998), Keller & Segel (1970) and Segel (1977) for the studies of the comparison of our proposed work to the actual scenarios. With the use of Tikhonov regularization, we have been able to recover the chemotactic sensitivity with reasonable accuracy. We note that this method, which although gives us accurate results for the chosen recoveries, may not be able to distinguish between similar chemical sensitivity forms. This paper does provide an initial framework to address these studies and further investigations to discern the differences in relative chemical sensitivities will follow. A biological benefit of this knowledge is the ability for one to understand the growth associated with chemotaxis within tumour studies, leukocyte dynamics and bacterial patterns based on the specific gradient information that can be recovered from imperfect data.

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## References

AIDA, M. & YAGI, A. (2003) Global attractor for approximate system of chemotaxis and growth. *Dyn. Contin. Discrete Impuls. Syst. A*, **10**, 309–315.

ALLWEISS, B., DOSTAL, J., CAREY, K., EDWARDS, T. & FRETER, R. (1977) The role of chemotaxis in the ecology of bacterial pathogens of mucosal surfaces. *Nature*, **266**, 448–450.

ALT, W. & LAUFFENBURGER, D. (1985) Transient behavior of a chemotaxis system modelling certain types of tissue inflammation. *J. Math. Biol.*, **24**, 691–722.

ANDERSON, A. R. A. & CHAPLAIN, M. A. J. (1998) Continuous and discrete mathematical models of tumor-induced angiogenesis. *Bull. Math. Biol.*, **60**, 857–900.

ANDERSON, A. R. A., CHAPLAIN, M. A. J., NEWMAN, E. L., STEELE, R. J. C. & THOMPSON, A. M. (2000) Mathematical modelling of tumour invasion and metastasis. *J. Theor. Med.*, **2**, 129–154.

BELLOMO, N. & PREZIOSI, L. (2000) Modeling and mathematical problems related to tumor immune system interactions. *Math. Comput. Model.*, **31**, 413–452.

CHALUB, F. A. C. C. & KANG, K. (2006) Global convergence of a kinetic model of chemotaxis to a perturbed Keller-Segel model. *Nonlinear Anal.*, **64**, 686–695.

CHET, I. & MITCHELL, R. (1976) Ecological aspects of microbial chemotactic behavior. *Annu. Rev. Microbiol.*, **30**, 221–239.

CHILDRESS, S. & PERCUS, J. K. (1981) Nonlinear aspects of chemotaxis. *Math. Biosci.*, **56**, 217–237.

CORRIAS, L., PERTHAME, B. & ZAAG, H. (2003) A chemotaxis model motivated by angiogenesis. *C. R. Acad. Sci.*, **336**, 141–146.

DOLAK-STRUSS, Y. & KÜGLER, P. Identification of chemotaxis parameters based on Tikhonov regularisation. *Preprint*. Available at http://homepage.univie.ac.at/yasmin.dolak-struss/DolakKuegler.pdf.

DUNG, L. (2002) On a time-dependent bio-reactor model with chemotaxis. *Appl. Math. Comput.*, **131**, 531–558.

ENGELMANN, T. W. (1881) Neue Methode zur Untersuchung der Sauerstoffaussheidung pflanzlicher und tierischer organismen. *Pflugers Arch. Ges. Physiol. Menschen Tiere*, **25**, 285–292.

ENGL, H. W., HANKE, M. & NEUBAUER, A. (2000) *Regularization of Inverse Problems*. New York: Kluwer Academic Publishers.

ENGL, H. W. & KÜGLER, P. (2002) Identification of a temperature dependent heat conductivity by Tikhonov regularization. *J. Inverse Ill-posed Probl.*, **10**, 67–90.

ENGL, H. W., KUNISCH, K. & NEUBAUER, A. (1989) Convergence rates for Tikhonov regularisation of nonlinear ill-posed problems. *Inverse Probl.*, **5**, 523–540.

ERBAN, R. & OTHMER, H. (2004) From individual to collective behavior in bacterial chemotaxis. *SIAM J. Appl. Math.*, **65**, 361–391.

FISHER, E. S. & LAUFFENBURGER, D. (1990) Analysis of the effects of immune cell motility and chemotaxis on target elimination dynamics. *Math. Biosci.*, **98**, 73–102.

FISTER, K. R. & MCCARTHY, M. L. (2003) Optimal control of a chemotaxis system. *Q. Appl. Math.*, **61**, 193–211.

FISTER, K. R., MCCARTHY, M. L. & OPPENHEIMER, S. F. (2006) The identification of a time dependent sorption parameter from soil column experiments. *SIAM J. Appl. Math.*, **66**, 1407–1423.

FORD, R. & LAUFFENBURGER, D. (1991) Analysis of chemotactic bacterial distributions in population migration assays using a mathematical model applicable to steep or shallow attractant gradients. *J. Math. Biol.*, **53**, 721–729.

GAJEWSKI, H. & SKRYPNIK, I. V. (2003) To the uniqueness problem for nonlinear elliptic equations. *Nonlinear Anal.*, **52**, 291–304.

GATENBY, R. A., MAINI, P. K. & GAWLINSKI, E. T. (2002) Analysis of tumor as an inverse problem provides a novel theoretical framework for understanding tumor biology and therapy. *Appl. Math. Lett.*, **15**, 339–345.

HERRERO, M. & VELÁZQUEZ, J. J. L. (1996) Chemotactic collapse for the Keller-Segel model. *J. Math. Biol.*, **35**, 177–194.

HILLEN, T. & LEVINE, H. (2003) Blow-up and pattern formation in hyperbolic models for chemotaxis in 1-d. *Z. Angew. Math. Phys.*, **54**, 839–868.

HILLEN, T. & PAINTER, K. (2001) Global existence for a parabolic chemotaxis model with prevention of overcrowding. *Adv. Appl. Math.*, **26**, 280–301.

HORSTMANN, D. (2001) Lyapunov functions and $L^p$-estimates for a class of reaction-diffusion systems. *Coll. Math.*, **87**, 113–127.

HORSTMANN, D. (2002) On the existence of radially symmetric blow-up solutions for the Keller-Segel model. *J. Math. Biol.*, **44**, 463–478.

JABBARZADEH, E. & ABRAMS, C. F. (2005) Chemotaxis and random motility in unsteady chemoattract fields: a computational study. *J. Theor. Biol.*, **235**, 221–232.

KELLER, E. (2006) Science as a medium for friendship: how the Keller-Segel models came about. *Bull. Math. Biol.*, **68**, 1033–1037.

KELLER, E. & SEGEL, L. (1970) Initiation of slime mold aggregation viewed as an instability. *J. Theor. Biol.*, **26**, 399–415.

KELLER, E. & SEGEL, L. (1971a) Model for chemotaxis. *J. Theor. Biol.*, **30**, 225–234.

KELLER, E. & SEGEL, L. (1971b) Traveling bands of chemotactic bacteria: a theoretical analysis. *J. Theor. Biol.*, **30**, 235–248.

KOWALCZYK, R. (2005) Preventing blow-up in a chemotaxis model. *J. Math. Anal. Appl.*, **305**, 566–588.

LAPIDUS, I. R. (1980) Microbial chemotaxis in flowing water in the vicinity of a source of attractant or repellent. *J. Theor. Biol.*, **85**, 543–547.

LAPIDUS, I. R. & SCHILLER, R. (1976) A model for the chemotactic response of a bacterial population. *Biophys. J.*, **16**, 779–789.

LEVENBERG, K. (1944) A method for the solution of certain non-linear problems in least squares. *Q. Appl. Math.*, **2**, 164–168.

LEVINE, H., NILSEN-HAMILTON, M. & SLEEMAN, B. (2001) Mathematical modelling of the onset of capillary formation initiating angiogenesis. *J. Math. Biol.*, **42**, 195–238.

MAINI, P. & OTHMER, H. (2001) *Mathematical Models for Biological Pattern Formation*. New York: Springer.

MARQUARDT, D. (1963) An algorithm for least-squares estimation of nonlinear parameters. *SIAM J. Appl. Math.*, **11**, 431–441.

MYERSCOUGH, M. R., MAINI, P. K. & PAINTER, K. J. (1998) Pattern formation in a generalized chemotactic model. *Bull. Math. Biol.*, **60**, 1–26.

NAKAGUCHI, N. & YAGI, A. (2001) Full discrete approximation by Galerkin method for chemotaxis-growth model. *Nonlinear Anal.*, **47**, 6097–6107.

ORR, W., VARANI, J., GONDEK, M., WARD, P. & MUNDY, G. (1979) Chemotactic responses of tumor cells to products of resorbing bone. *Science*, **203**, 176–178.

OSTER, G. & MURRAY, J. D. (1989) Pattern formation models and developmental constraints. *J. Exp. Zool.*, **25**, 186–202.

PAINTER, K. & HILLEN, T. (2002) Volume-filling and quorum-sensing in models for chemosensitive movement. *Can. Appl. Math. Q.*, **10**, 501–543.

SEGEL, L. (1977) A theoretical study of receptor mechanisms in bacterial chemotaxis. *SIAM J. Appl. Math.*, **32**, 653–665.

SEIDMAN, T. I. & VOGEL, C. R. (1989) Well-posedness and convergence of some regularization methods for non-linear ill-posed problems. *Inverse Probl.*, **5**, 227–238.

SENBA, T. & SUZUKI, T. (2002a) Time global solutions to a parabolic-elliptic system modelling chemotaxis. *Asymptot. Anal.*, **32**, 63–89.

SENBA, T. & SUZUKI, T. (2002b) Weak solutions to a parabolic-elliptic system of chemotaxis. *J. Funct. Anal.*, **191**, 17–51.

SIMON, J. (1987) Compact sets in the space $L^p(0, T; B)$. *Ann. Mat. Pura Appl.*, **147**, 65–96.

SLEEMAN, B. & LEVINE, H. (2001) Partial differential equations of chemotaxis and angiogenesis. *Math. Methods Appl. Sci.*, **24**, 405–426.

SLIUSARENKO, O., CHEN, J. & OSTER, G. (2006) From biochemistry to morphogenesis in myxobacteria. *Bull. Math. Biol.*, **68**, 1039–1051.

TOSIN, A., AMBROSI, D. & PREZIOSI, L. (2006) Mechanics and chemotaxis in the morphogenesis of vascular networks. *Bull. Math. Biol.*, **68**, 1819–1836.

TYSON, R., LUBKIN, S. R. & MURRAY, J. D. (1999) A minimal mechanism for bacterial pattern formation. *Proc. R. Soc. Lond. B*, **266**, 299–304.

TYSON, R., STERN, L. G. & LEVEQUE, R. J. (2000) Fractional step methods applied to a chemotaxis model. *J. Math. Biol.*, **41**, 455–475.

VELAZQUEZ, J. J. L. (2004a) Point dynamics for a singular limit of the Keller-Segel model, I. Motion of the concentration regions. *SIAM J. Appl. Math.*, **64**, 1198–1223.

VELAZQUEZ, J. J. L. (2004b) Point dynamics for a singular limit of the Keller-Segel model, II. Formation of the concentration regions. *SIAM J. Appl. Math.*, **64**, 1224–1248.

VOGEL, C. (2002) *Computational Methods for Inverse Problems*. Philadelphia, PA: SIAM.

YAGI, A. (1997) Norm behavior of solutions to a parabolic system of chemotaxis. *Math. Japonica*, **45**, 241–265.

## Appendix A

For more thorough understanding of Theorem 2.1, we include the parabolic problem convention used in Yagi (1997):

$$\begin{aligned} u_t &= \nabla \cdot (a(u, p)\nabla u - ub(p)\nabla p) \quad \text{in } \Omega \times (0, \infty), \\ p_t &= d\Delta p + uf(p) - g(p)p \quad \text{in } \Omega \times (0, \infty), \\ u(x, 0) &= u_0(x), \quad p(x, 0) = p_0(x), \quad \text{for } x \in \Omega, \\ \frac{\partial u}{\partial \nu} &= \frac{\partial p}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, \infty). \end{aligned} \tag{A.1}$$

In Yagi (1997, Theorem 2.1), it states

THEOREM A1 Let $u_0, p_0 \in H^{1+\varepsilon_0}(\Omega)$ for $0 < \varepsilon_0 \leqslant 1$ and $u_0(x) \geqslant 0$, $p_0(x) \geqslant \delta_0 > 0$ on $\overline{\Omega}$. Assume that a real local solution $(u, p)$ to (A.1) exists on the interval $[0, S]$ such that

$$u, p \in C([0, S); H^{1+\varepsilon_1}(\Omega)) \cap C([0, S); H^2(\Omega)) \cap C^1([0, S); L^2(\Omega))$$

for some $\varepsilon_1 > 0$. In addition, assume that $p$ satisfies $p(x, t) > 0$ on $\overline{\Omega} \times [0, S]$ and an estimate

$$\|p(t)\|_{H^2} \leqslant At^{\frac{(\varepsilon_2 - 1)}{2}} \quad \text{on } 0 < t \leqslant S,$$

for some $\varepsilon_2 > 0$ and constant $A$. Then,

$$u(x, t) \geqslant 0, \quad p(x, t) \geqslant \underline{p}(t), \quad \text{for all } (x, t) \in \overline{\Omega} \times [0, S],$$

where $\underline{p}$ denotes a positive function defined as the global solution to an ordinary differential equation

$$\begin{aligned} \frac{\mathrm{d}\underline{p}}{\mathrm{d}t} &= -g(\underline{p})\underline{p}, \quad \text{on } 0 < t < \infty, \\ \underline{p}(0) &= \delta_0 > 0. \end{aligned} \tag{A.2}$$

For further connection to our work, we utilize the continuation to a unique solution that Yagi developed (Yagi, 1997, Theorem 3.4) with the following theorem.

THEOREM A2 Let $u_0, p_0 \in H^{1+\varepsilon_0}(\Omega)$ for $0 < \varepsilon_0 \leqslant 1$ and $u_0(x) \geqslant 0$, $p_0(x) \geqslant \delta_0 > 0$ on $\overline{\Omega}$ and $0 < \eta < \beta - \alpha$. Then, in the function space, $C^\eta([0, \infty); H^{1+\varepsilon_1}(\Omega))$, the problem (A.1) possess a unique local solution

$$u, p \in C([0, S); H^2(\Omega)) \cap C^1([0, S); L^2(\Omega))$$

with the lower bounds

$$u(t) \geqslant 0, \quad p(t) \geqslant \underline{p}(t), \quad \text{for } t \in [0, S],$$

where $\underline{p}(\cdot)$ is a positive function defined by equations in (A.2). The interval $[0, S]$ on which the solution exists at least is determined by the norms $\|u_0\|_{H^{1+\varepsilon_0}}$ and $\|p_0\|_{H^{1+\varepsilon_0}}$ and the initial lower bound $\delta_0$.

It is to be noted that by this theorem from Yagi's work a maximal solution to (A.1) can be uniquely defined in the space $C^\eta([0, S); H^{1+\varepsilon_1}(\Omega))$ for $0 < \eta < \beta - \alpha$ for each $u_0, p_0$ such that $u_0, p_0 \in H^{1+\varepsilon_0}(\Omega)$ for $0 < \varepsilon_0 \leqslant 1$ and $u_0(x) \geqslant 0$, $p_0(x) \geqslant \overline{c}_0 > \delta_0 > 0$ on $\overline{\Omega}$.