

Theoretical and numerical analysis on multispectral bioluminescence tomography

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[Received on 23 March 2006; accepted on 26 October 2006]

Recently, molecular imaging has been rapidly developed to study physiological and pathological processes *in vivo* at the cellular and molecular levels. Among molecular imaging modalities, optical imaging has attracted a major attention for its unique advantages. In this paper, we establish a mathematical framework for multispectral bioluminescence tomography (BLT) that allows simultaneous studies of multiple optical reporters. We show solution existence, uniqueness and continuous dependence on data as well as the limiting behaviours when the regularization parameter approaches zero or when the penalty parameter approaches infinity. Then, we propose two numerical schemes for multispectral BLT and derive error estimates for the corresponding solutions.

Keywords: multispectral bioluminescence tomography; optical molecular imaging; multiple optical reporters; well-posedness; numerical solution; convergence; error estimates.

1. Introduction

The contemporary thinking on biomedical imaging is significantly influenced by the development of systems biology and molecular medicine (Zerhouni, 2003). Currently, investigations of organisms are increasingly more focused on underlying systems, their connections and integration, instead of separate systems and individual parts. In this context, a system can be a gene regulatory mechanism, a protein structure and dynamics, a cell-based network, a metabolic pathway, a physiological system, a specific organ or an entire living body. Because this system's approach deals with numerous interacting components, it is highly desirable to develop spatially, temporally and spectrally resolving quantitative technologies. Aided by such imaging and sensing tools, the genes that govern various phenotypes and behaviours will be identified (Bassingthwaighe, 2000; Crampin *et al.*, 2004). Eventually, biology and medicine will be revolutionized from a science of largely descriptive nature to be quantitative and predictive, leading to individualized preventive medicine.

With the above grand background, over a past few years molecular imaging has been rapidly developed to study physiological and pathological processes *in vivo* at the cellular and molecular levels (Weissleder & Mahmood, 2001; Wang *et al.*, 2005). While some classic microscopic and spectroscopic

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techniques do reveal information on microstructures of the tissues, only recently have molecular probes been utilized along with imaging technologies to detect and image molecular targets sensitively, specifically, and *in vivo*. A molecular probe has a high affinity for attaching itself to a target molecule and a tagging ability with a marker molecule that can be tracked outside a living body.

Among molecular imaging modalities, optical imaging has attracted a major attention for its unique advantages, especially performance and cost-effectiveness (Contag & Ross, 2002; Weissleder & Ntziachristos, 2003; Ntziachristos *et al.*, 2005). Fluorescent and bioluminescent probes are commonly used for optical molecular imaging. Today, fluorescent and bioluminescent imaging modes are most widely applied in mouse studies, and to a limited extent in clinical research as well. Among various optical molecular imaging techniques, fluorescence molecular tomography (Ntziachristos *et al.*, 2002) and bioluminescence tomography (BLT) (Wang *et al.*, 2003, 2004; Cong *et al.*, 2005) are two emerging and complementary modes. In contrast to fluorescent imaging, bioluminescent imaging has unique capabilities in probing molecular and cellular processes. Furthermore, there is no or little background auto-fluorescence with bioluminescent imaging. With BLT, quantitative and localized analyses on a bioluminescent source distribution become feasible in a mouse, which reveal information important for numerous biomedical studies.

However, optical imaging of multiple molecular and cellular targets has not been popular because this type of studies is traditionally performed using a single reporter, instead of multiple reporters of different spectra. With simultaneous use of multiple optical reporters (Cong & Wang, 2006), it becomes now feasible to capture and decompose composite molecular and cellular signatures under *in vivo* conditions. That is, multispectral data can be measured in spectral bands on the body surface of a mouse, and the distributions of multiple biomarkers can be reconstructed in an integrated fashion using a sophisticated algorithm. This is the biomedical motivation and overall concept behind our development of multispectral BLT. Some theoretical studies, including results from numerical simulations, can be found in Han *et al.* (to appear) for a particular formulation of multispectral BLT.

In this paper, we provide a theoretical and numerical analysis on multispectral BLT. We consider the most general situation of using multiple bioluminescent reporters whose spectral characteristics may be affected by their *in vivo* environment. The rest of the paper is organized as follows: In Section 2, we present some preliminary materials and introduce notations. In Section 3, we introduce a mathematical framework for multispectral BLT through Tikhonov regularization and penalization, and establish the solution existence, uniqueness and continuous dependence on the data. We also study the limiting behaviours of the solution as the penalty parameter $M \rightarrow \infty$ in Section 4 and as the regularization parameter $\varepsilon \rightarrow 0+$ in Section 5. We then propose two numerical methods for solving the multispectral BLT problem. In the first method, there is no need to discretize the admissible sets for the source functions, as detailed in Section 6. In the second method, we discretize the admissible sets for the source functions, as discussed in Section 7. For both methods, the numerical solution exists uniquely and depends continuously on the data. Error estimates are derived for the numerical solutions. A concluding remark is given in Section 8.

2. Preliminaries

Experimental evidence shows that the range of light emission peaks is 460–630 nm for characterized luciferase enzymes (Zhao *et al.*, 2005). For this spectral range, scattering dominates for the photons in the tissue, and it is appropriate to use the diffusion approximation to describe the photon propagation (Arridge *et al.*, 1993). Let $\Omega \subset \mathbb{R}^d$ be the biological medium with the boundary Γ . Here, the dimension $d = 3$ for applications; however, we develop the theory without this restriction. In multispectral BLT,

the spectrum is divided into certain numbers of bands, say i_0 bands A_1, \dots, A_{i_0} , with

$$A_i = [\lambda_{i-1}, \lambda_i), \quad 1 \leq i \leq i_0 - 1, \quad A_{i_0} = [\lambda_{i_0-1}, \lambda_{i_0}].$$

Here, $\lambda_0 < \lambda_1 < \dots < \lambda_{i_0}$ is a partition of the spectrum range. Let there be j_0 biomarkers with bioluminescent source distributions $p_j \chi_{\Omega_j}$, $1 \leq j \leq j_0$. Here, Ω_j is a measurable subset of Ω and χ_{Ω_j} is the characteristic function of Ω_j . The set Ω_j is the permissible region for the source p_j . For each biomarker, its bioluminescent source distribution within the band A_j is $\omega_{ij} p_j \chi_{\Omega_j}$, $1 \leq i \leq i_0$, with the weights $\omega_{ij} > 0$ satisfying $\sum_{i=1}^{i_0} \omega_{ij} = 1$, for any $1 \leq j \leq j_0$. As an example, consider target cells tagged with reporters encoded with four kinds of luciferase enzymes hRLuc, CNGr68, Fluc+ and CBRed. Based on the experimental results of Zhao *et al.* (2005), it is proposed in Cong & Wang (2006) to split the photon emission spectral range [400 nm, 750 nm] into three regions: $A_1 = [400 \text{ nm}, 530 \text{ nm})$, $A_2 = [530 \text{ nm}, 630 \text{ nm})$ and $A_3 = [630 \text{ nm}, 750 \text{ nm}]$, with corresponding weights $\omega_1 = 0.29$, $\omega_2 = 0.48$ and $\omega_3 = 0.23$.

We now turn to a description of the relevant mathematical relations. We denote $p_{ij} = \omega_{ij} p_j$, the portion of the source function p_j in the band A_i . We allow variation of the source spectrum caused by the environment. Thus, we will reconstruct sources p_{ij} such that $p_{ij} \approx \omega_{ij} p_j$, with $p_j = \sum_{i=1}^{i_0} p_{ij}$. For each spectral band A_i , $1 \leq i \leq i_0$, we use the following diffusion equations to describe the photon density u_i in A_i :

$$-\text{div}(D_i \nabla u_{ij}) + \mu_{a,i} u_{ij} = p_{ij} \chi_{\Omega_j} \quad \text{in } \Omega. \quad (2.1)$$

Here, $D_i(\mathbf{x}) = 1/[3(\mu_{a,i}(\mathbf{x}) + \mu'_{s,i}(\mathbf{x}))]$, where $\mu_{a,i}(\mathbf{x})$ and $\mu'_{s,i}(\mathbf{x})$ are the absorption coefficient and the reduced scattering coefficient within the band A_i , respectively. The bioluminescent imaging experiments are usually performed in a dark environment so that the natural boundary condition takes the form (Schweiger *et al.*, 1995)

$$u_{ij} + 2AD_i \frac{\partial u_{ij}}{\partial \nu} = 0 \quad \text{on } \Gamma. \quad (2.2)$$

Here, $\partial/\partial \nu$ stands for the outward normal derivative,

$$A(\mathbf{x}) = \frac{1 + R(\mathbf{x})}{1 - R(\mathbf{x})}, \quad R(\mathbf{x}) \approx -1.4399\gamma^{-2} + 0.7099\gamma^{-1} + 0.6681 + 0.0636\gamma,$$

with γ being the refractive index of the medium. With the emission filters of bandpasses A_i , the measured quantities are the outgoing flux densities (Schweiger *et al.*, 1995)

$$\tilde{f}_i = -D_i \frac{\partial}{\partial \nu} \sum_{j=1}^{j_0} u_{ij}(q_{ij}) = \frac{1}{2A} \sum_{j=1}^{j_0} u_{ij}(q_{ij}) \quad \text{on } \Gamma_i, \quad 1 \leq i \leq i_0. \quad (2.3)$$

We assume that Γ_i is a nontrivial part of the boundary, i.e. $\text{meas}(\Gamma_i) > 0$. Thus, we allow the situation where the measurement of the outgoing flux densities is available only on parts of the boundary Γ . In most current applications, all the Γ_i are taken to be equal to Γ .

As noted in Han *et al.* (2006) in the case of a single type of bioluminescent reporters, the point-wise formulation (2.1)–(2.3), $1 \leq i \leq i_0$, is ill-posed. In general, there are infinitely many solutions. When the form of the source function is specified, there is no solution if data are inconsistent. Also, the source function does not depend continuously on the data. The purpose of the paper is to formulate the problem in a well-posed fashion that leads to a stable and convergent numerical solution.

Let us introduce some notations to simplify the exposition. In the rest of the paper, we always let the range of the index i to be $\{1, \dots, i_0\}$ and that of j to be $\{1, \dots, j_0\}$; in particular, \sum_i stands for $\sum_{i=1}^{i_0}$ and \sum_j stands for $\sum_{j=1}^{j_0}$. Matrix ($\mathbb{R}^{i_0 \times j_0}$)-valued variables, as well as their row or column vectors, will be indicated by Euler Fraktur alphabets, e.g. $\mathbf{p} = (p_{ij})$, $\mathbf{q} = (q_{ij})$, $\mathbf{u} = (u_{ij})$ and

$$\mathbf{q}_{*j} = (q_{1j}, \dots, q_{i_0j})^\top, \quad \mathbf{q}_{i*} = (q_{i1}, \dots, q_{ij_0}).$$

Vector-valued variables are indicated by boldface math fonts. We denote

$$\begin{aligned} S(\mathbf{q}_{*j}) &= \sum_i q_{ij}, \quad \ell_i(\mathbf{q}_{*j}) = q_{ij} - \omega_{ij} S(\mathbf{q}_{*j}), \quad \boldsymbol{\ell}(\mathbf{q}) = (\ell_i(\mathbf{q}_{*j})), \\ U_i(\mathbf{q}_{i*}) &= \sum_j u_{ij}(q_{ij}), \quad \mathbf{U}(\mathbf{q}) = (U_i(\mathbf{q}_{i*})). \end{aligned}$$

Then, the boundary measurement equation (2.3) can be written as

$$\tilde{f}_i = -D_i \frac{\partial U_i(\mathbf{q}_{i*})}{\partial \mathbf{v}} = \frac{1}{2A} U_i(\mathbf{q}_{i*}) \quad \text{on } \Gamma_i.$$

For a vector-valued variable with a subscript, we use ‘ \cdot_j ’ to indicate its j th component, e.g. $\mathbf{p}_\varepsilon = (p_{\varepsilon,j})$. Similarly, for a matrix-valued variable with a subscript, we use ‘ \cdot_{ij} ’ for its (i, j) th component, e.g. $\mathbf{p}_{\varepsilon M} = (p_{\varepsilon M, ij})$.

Then, we introduce some function spaces and sets. Let $\mathcal{Q}_j = L^2(\Omega_j)$, $V = H^1(\Omega)$ and $G_i = L^2(\Gamma_i)$; these are Hilbert spaces with their canonical inner products and norms. We denote by $\mathcal{Q}_{\text{ad},j}$ the admissible set for p_{ij} . We assume $\mathcal{Q}_{\text{ad},j}$ is a closed convex subset of the space \mathcal{Q}_j . Examples include $\mathcal{Q}_{\text{ad},j} = \mathcal{Q}_j$, or the subset of \mathcal{Q}_j of nonnegatively valued functions, or a finite-dimensional subspace or subset of linear combinations of specified functions such as the character functions of certain subsets of Ω_j . Let

$$\boldsymbol{\Omega} = \{\mathbf{q} = (q_{ij}): q_{ij} \in \mathcal{Q}_j\}$$

with the inner product and norm

$$(\mathbf{p}, \mathbf{q})_{\boldsymbol{\Omega}} = \sum_{i,j} w_{ij} (p_{ij}, q_{ij})_{\mathcal{Q}_j}, \quad \|\mathbf{q}\|_{\boldsymbol{\Omega}} = (\mathbf{q}, \mathbf{q})_{\boldsymbol{\Omega}}^{1/2},$$

for some positive weighting constants w_{ij} . Then, $\boldsymbol{\Omega}$ becomes a Hilbert space. We seek the unknown source field $\mathbf{p} = (p_{ij})$ of the multispectral BLT problem in

$$\boldsymbol{\Omega}_{\text{ad}} = \{\mathbf{q} \in \boldsymbol{\Omega}: q_{ij} \in \mathcal{Q}_{\text{ad},j}\}.$$

With possibly different positive weighting constants $w_{\ell,ij}$, we let

$$(\boldsymbol{\ell}(\mathbf{p}), \boldsymbol{\ell}(\mathbf{q}))_{\boldsymbol{\Omega}_\ell} = \sum_{i,j} w_{\ell,ij} (\ell_i(\mathbf{p}_{*j}), \ell_i(\mathbf{q}_{*j}))_{\mathcal{Q}_j}, \quad |\boldsymbol{\ell}(\mathbf{q})|_{\boldsymbol{\Omega}_\ell} = (\boldsymbol{\ell}(\mathbf{q}), \boldsymbol{\ell}(\mathbf{q}))_{\boldsymbol{\Omega}_\ell}^{1/2}.$$

We also need the Hilbert space $\mathbf{G} = G_1 \times G_2 \times \dots \times G_{i_0}$, endowed with the inner product and norm

$$(\mathbf{f}, \mathbf{g})_{\mathbf{G}} = \sum_i w_i (f_i, g_i)_{G_i}, \quad \|\mathbf{g}\|_{\mathbf{G}} = (\mathbf{g}, \mathbf{g})_{\mathbf{G}}^{1/2},$$

with positive constants w_i .

3. The multispectral BLT problem, well-posedness

We assume $\Omega \subset \mathbb{R}^d$ ($d \leq 3$) is a nonempty, open, bounded set with a Lipschitz boundary Γ ; $A(\mathbf{x}) \in [A_l, A_u]$ for some constants $0 < A_l \leq A_u < \infty$; $D_i \in L^\infty(\Omega)$, $D_i \geq D_0$ a.e. in Ω for some constant $D_0 > 0$; $\mu_{a,i} \in L^\infty(\Omega)$, $\mu_{a,i} \geq 0$ a.e. in Ω and $\tilde{f}_i \in L^2(\Gamma_i)$. For any $q \in Q_j$, define $u_{ij}(q) \in V$ to be the solution of the problem

$$\int_{\Omega} [D_i \nabla u_{ij}(q) \cdot \nabla v + \mu_{a,i} u_{ij}(q) v] dx + \int_{\Gamma} \frac{1}{2A} u_{ij}(q) v ds = \int_{\Omega_j} q v dx, \quad \forall v \in V. \quad (3.1)$$

From the assumptions on the data, we can apply the well-known Lax–Milgram lemma (Atkinson & Han, 2005; Evans, 1998) to conclude that the solution $u_{ij}(q)$ exists and is unique. Obviously, $u_{ij}(q)$ depends on q linearly, and for some constant $c > 0$,

$$\|u_{ij}(q)\|_V \leq c \|q\|_{Q_j}, \quad \forall q \in Q_j. \quad (3.2)$$

We write $f_i = 2A\tilde{f}_i$ and $\mathbf{f} = (f_i)$. Let $\varepsilon \geq 0$ and $M > 0$, and define a penalized Tikhonov regularization functional (Tikhonov, 1963; Engl *et al.*, 1996)

$$J_{\varepsilon M}(\mathbf{q}) = \frac{1}{2} \left[\|U(\mathbf{q}) - \mathbf{f}\|_G^2 + \varepsilon \|\mathbf{q}\|_{\Omega}^2 + M |\ell(\mathbf{q})|_{\Omega_l}^2 \right]. \quad (3.3)$$

This functional is smooth and for its first two derivatives, we have

$$J'_{\varepsilon M}(\mathbf{p})\mathbf{q} = (U(\mathbf{p}) - \mathbf{f}, U(\mathbf{q}))_G + \varepsilon (\mathbf{p}, \mathbf{q})_{\Omega} + M(\ell(\mathbf{p}), \ell(\mathbf{q}))_{\Omega_l},$$

$$J''_{\varepsilon M}(\mathbf{p})(\mathbf{q}, \mathbf{q}) = \|U(\mathbf{q})\|_G^2 + \varepsilon \|\mathbf{q}\|_{\Omega}^2 + M |\ell(\mathbf{q})|_{\Omega_l}^2,$$

for $\mathbf{p}, \mathbf{q} \in \Omega$. In particular, we note that $J_{\varepsilon M}$ is strictly convex for $\varepsilon > 0$. We then introduce the following multispectral BLT problem.

PROBLEM 3.1 Find $\mathbf{p}_{\varepsilon M} \in \Omega_{\text{ad}}$ such that $J_{\varepsilon M}(\mathbf{p}_{\varepsilon M}) = \inf\{J_{\varepsilon M}(\mathbf{q}) : \mathbf{q} \in \Omega_{\text{ad}}\}$.

We comment that other norms can be used in defining (3.3) and indeed, mathematically, it is more natural to choose $G_j = H^{1/2}(\Gamma_j)$. However, for actual simulation, it is more convenient to use the L^2 -norms in the objective function.

We now consider the existence and uniqueness issue.

THEOREM 3.2 Problem 3.1 with $\varepsilon > 0$ has a unique solution $\mathbf{p}_{\varepsilon M} \in \Omega_{\text{ad}}$, and the solution $\mathbf{p}_{\varepsilon M} \in \Omega_{\text{ad}}$ is characterized by a variational inequality

$$(U(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, U(\mathbf{q} - \mathbf{p}_{\varepsilon M}))_G + \varepsilon (\mathbf{p}_{\varepsilon M}, \mathbf{q} - \mathbf{p}_{\varepsilon M})_{\Omega} + M(\ell(\mathbf{p}_{\varepsilon M}), \ell(\mathbf{q} - \mathbf{p}_{\varepsilon M}))_{\Omega_l} \geq 0, \quad \forall \mathbf{q} \in \Omega_{\text{ad}}. \quad (3.4)$$

When $Q_{\text{ad},j} \subset Q_j$ are subspaces, the inequality is reduced to a variational equation

$$(U(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, U(\mathbf{q}))_G + \varepsilon (\mathbf{p}_{\varepsilon M}, \mathbf{q})_{\Omega} + M(\ell(\mathbf{p}_{\varepsilon M}), \ell(\mathbf{q}))_{\Omega_l} = 0, \quad \forall \mathbf{q} \in \Omega_{\text{ad}}. \quad (3.5)$$

Proof. The existence and uniqueness are deduced from a standard result on convex minimization (see, e.g. Atkinson & Han, 2005, Theorem 3.3.12). The space Ω is a Hilbert space and $\Omega_{\text{ad}} \subset \Omega$ is convex and closed. The functional $J_{\varepsilon M}: \Omega_{\text{ad}} \rightarrow \mathbb{R}$ is continuous, strictly convex and coercive, i.e.

$$J_{\varepsilon M}(\mathbf{q}) \rightarrow \infty \quad \text{as } \|\mathbf{q}\|_{\Omega} \rightarrow \infty.$$

So there is a unique solution $\mathbf{p}_{\varepsilon M} \in \mathfrak{Q}_{\text{ad}}$ to Problem 3.1. Moreover, $\mathbf{p}_{\varepsilon M} \in \mathfrak{Q}_{\text{ad}}$ is the solution if and only if it satisfies (see Atkinson & Han, 2005, Theorem 5.3.19)

$$J'_{\varepsilon M}(\mathbf{p}_{\varepsilon M})(\mathbf{q} - \mathbf{p}_{\varepsilon M}) \geq 0, \quad \forall \mathbf{q} \in \mathfrak{Q}_{\text{ad}},$$

that is precisely (3.4).

Now, assume $Q_{\text{ad},j} \subset Q_j$ are subspaces. We can take $\mathbf{q} = \mathbf{o}$ and $2\mathbf{p}_{\varepsilon M}$ in (3.4) to get

$$(U(\mathbf{p}_{\varepsilon M}) - f, -U(\mathbf{p}_{\varepsilon M}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}, -\mathbf{p}_{\varepsilon M})_{\mathfrak{Q}} + M(\ell(\mathbf{p}_{\varepsilon M}), -\ell(\mathbf{p}_{\varepsilon M}))_{\mathfrak{Q}_I} = 0.$$

So the inequality (3.4) is equivalent to

$$(U(\mathbf{p}_{\varepsilon M}) - f, U(\mathbf{q}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}, \mathbf{q})_{\mathfrak{Q}} + M(\ell(\mathbf{p}_{\varepsilon M}), \ell(\mathbf{q}))_{\mathfrak{Q}_I} \geq 0, \quad \forall \mathbf{q} \in \mathfrak{Q}_{\text{ad}}.$$

Since \mathfrak{Q}_{ad} is a subspace, this inequality is equivalent to the equality (3.5). \square

We then consider the continuous dependence of the solution on the data.

THEOREM 3.3 The solution $\mathbf{p}_{\varepsilon M}$ of Problem 3.1 depends continuously on the data.

Proof. The solution $\mathbf{p}_{\varepsilon M}$ depends continuously on all the data, including the weighting constants w_i , w_{ij} and $w_{\ell,ij}$. In order to maintain the length of the proof, in the following we only show the continuous dependence of $\mathbf{p}_{\varepsilon M}$ on ε , M , A , D_i , $\mu_{a,i}$ and f_i .

We write $\bar{\mathbf{p}}_{\varepsilon M} \in \mathfrak{Q}_{\text{ad}}$ for the solution of Problem 3.1 corresponding to the data $\varepsilon + \delta_\varepsilon$ with $|\delta_\varepsilon| \leq \varepsilon/2$, $M + \delta_M$ with $|\delta_M| \leq M/2$, $A + \delta_A$ with $\|\delta_A\|_{L^\infty(\Gamma)} \leq A/2$, $D_i + \delta_{D_i} \in L^\infty(\Omega)$ with $\|\delta_{D_i}\|_{L^\infty(\Omega)} \leq D_0/2$, $\mu_{a,i} + \delta_{\mu_{a,i}} \in L^\infty(\Omega)$ with $\mu_{a,i} + \delta_{\mu_{a,i}} \geq 0$ a.e. in Ω and $f_i + \delta_{f_i} \in G_i$ with $\|\delta_{f_i}\|_{G_i} \leq \|f_i\|_{G_i}/2$. In the proof, c represents a constant that may depend on ε , M , A , D_i , $\mu_{a,i}$ and f_i , but is independent of δ_ε , δ_M , δ_A , δ_{D_i} , $\delta_{\mu_{a,i}}$ and δ_{f_i} .

Similar to (3.1), for any $q \in Q_j$, we denote by $\bar{u}_{ij}(q) \in V$ the solution of the problem

$$\begin{aligned} & \int_{\Omega} [(D_i + \delta_{D_i}) \nabla \bar{u}_{ij}(q) \cdot \nabla v + (\mu_{a,i} + \delta_{\mu_{a,i}}) \bar{u}_{ij}(q)v] dx + \int_{\Gamma} \frac{1}{2(A + \delta_A)} \bar{u}_{ij}(q)v ds \\ & = \int_{\Omega_j} qv dx, \quad \forall v \in V. \end{aligned} \quad (3.6)$$

From $\bar{u}_{ij}(q)$, we similarly define $\bar{U}(\mathbf{q})$. The counterpart of (3.4) is

$$\begin{aligned} & (\bar{U}(\bar{\mathbf{p}}_{\varepsilon M}) - (f + \delta_f), \bar{U}(\mathbf{q}) - \bar{U}(\bar{\mathbf{p}}_{\varepsilon M}))_G + (\varepsilon + \delta_\varepsilon)(\bar{\mathbf{p}}_{\varepsilon M}, \mathbf{q} - \bar{\mathbf{p}}_{\varepsilon M})_{\mathfrak{Q}} \\ & + (M + \delta_M)(\ell(\bar{\mathbf{p}}_{\varepsilon M}), \ell(\mathbf{q} - \bar{\mathbf{p}}_{\varepsilon M}))_{\mathfrak{Q}_I} \geq 0, \quad \forall \mathbf{q} \in \mathfrak{Q}_{\text{ad}}. \end{aligned} \quad (3.7)$$

We denote $e_{ij}(q) = \bar{u}_{ij}(q) - u_{ij}(q)$ for the error. Subtracting (3.1) from (3.6), we obtain

$$\begin{aligned} & \int_{\Omega} [(D_i + \delta_{D_i}) \nabla e_{ij}(q) \cdot \nabla v + (\mu_{a,i} + \delta_{\mu_{a,i}}) e_{ij}(q)v] dx + \int_{\Gamma} \frac{1}{2(A + \delta_A)} e_{ij}(q)v ds \\ & = - \int_{\Omega} [\delta_{D_i} \nabla u_{ij}(q) \cdot \nabla v + \delta_{\mu_{a,i}} u_{ij}(q)v] dx + \int_{\Gamma} \frac{\delta_A}{2A(A + \delta_A)} u_{ij}(q)v ds, \quad \forall v \in V. \end{aligned}$$

Thus,

$$\|e_{ij}(q)\|_V \leq c \left[\|\delta_{D_i}\|_{L^\infty(\Omega)} + \|\delta_{\mu_{a,i}}\|_{L^\infty(\Omega)} + \|\delta_A\|_{L^\infty(\Gamma)} \right] \|u_{ij}(q)\|_V. \quad (3.8)$$

We take $\mathbf{q} = \bar{\mathbf{p}}_{\varepsilon M}$ in (3.4) to get

$$(\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, \mathbf{U}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}, \bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})_{\Omega} + M(\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}), \boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}))_{\Omega_I} \geq 0,$$

and take $\mathbf{q} = \mathbf{p}_{\varepsilon M}$ in (3.7) to get

$$\begin{aligned} & (\bar{\mathbf{U}}(\bar{\mathbf{p}}_{\varepsilon M}) - (\mathbf{f} + \delta_f), \bar{\mathbf{U}}(\mathbf{p}_{\varepsilon M} - \bar{\mathbf{p}}_{\varepsilon M}))_G + (\varepsilon + \delta_\varepsilon)(\bar{\mathbf{p}}_{\varepsilon M}, \mathbf{p}_{\varepsilon M} - \bar{\mathbf{p}}_{\varepsilon M})_{\Omega} \\ & + (M + \delta_M)(\boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M}), \boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \bar{\mathbf{p}}_{\varepsilon M}))_{\Omega_I} \geq 0. \end{aligned}$$

Using these two inequalities, we have

$$\begin{aligned} & \|\bar{\mathbf{U}}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})\|_G^2 + (\varepsilon + \delta_\varepsilon)\|\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}\|_{\Omega}^2 + (M + \delta_M)|\boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})|_{\Omega_I}^2 \\ & \leq (\bar{\mathbf{U}}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}(\mathbf{p}_{\varepsilon M}), \mathbf{U}(\mathbf{p}_{\varepsilon M} - \bar{\mathbf{p}}_{\varepsilon M}))_G + (\delta_f, \mathbf{U}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}))_G \\ & + (\bar{\mathbf{U}}(\mathbf{p}_{\varepsilon M}) - (\mathbf{f} + \delta_f), \mathbf{U}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}) - \bar{\mathbf{U}}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}))_G, \\ & - \delta_\varepsilon(\mathbf{p}_{\varepsilon M}, \bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})_{\Omega} - \delta_M(\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}), \boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}))_{\Omega_I}. \end{aligned}$$

Then,

$$\begin{aligned} & \|\bar{\mathbf{U}}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})\|_G^2 + (\varepsilon + \delta_\varepsilon)\|\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}\|_{\Omega}^2 + (M + \delta_M)|\boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})|_{\Omega_I}^2 \\ & \leq [\|\bar{\mathbf{U}}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}(\mathbf{p}_{\varepsilon M})\|_G + \|\delta_f\|_G] \|\mathbf{U}(\mathbf{p}_{\varepsilon M} - \bar{\mathbf{p}}_{\varepsilon M})\|_G \\ & + \|\bar{\mathbf{U}}(\mathbf{p}_{\varepsilon M}) - (\mathbf{f} + \delta_f)\|_G \|\mathbf{U}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}) - \bar{\mathbf{U}}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})\|_G, \\ & + |\delta_\varepsilon| \|\mathbf{p}_{\varepsilon M}\|_{\Omega} \|\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}\|_{\Omega} + |\delta_M| |\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M})|_{\Omega_I} |\boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})|_{\Omega_I}. \end{aligned}$$

With the use of (3.2), (3.8) and the inequality $ab \leq \delta a^2 + b^2/(4\delta)$ for any $\delta > 0$, we then have

$$\begin{aligned} & \|\bar{\mathbf{U}}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})\|_G^2 + \|\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}\|_{\Omega}^2 + |\boldsymbol{\ell}(\bar{\mathbf{p}}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})|_{\Omega_I}^2 \\ & \leq c \left\{ |\delta_\varepsilon| + |\delta_M| + \|\delta_A\|_{L^\infty(\Gamma)} + \max_i \left[\|\delta_{D_i}\|_{L^\infty(\Omega)} + \|\delta_{\mu_{a,i}}\|_{L^\infty(\Omega)} + \|\delta_{f_i}\|_{G_i}^2 \right] \right\}. \end{aligned}$$

Hence, the solution depends continuously on the data. \square

4. Limiting behaviour with respect to penalty parameter

Here, we consider the limiting behaviour of the solution $\mathbf{p}_{\varepsilon M}$ as the penalty parameter $M \rightarrow \infty$, for some fixed $\varepsilon > 0$. For this purpose, we introduce some more notations. Let

$$\mathcal{Q} = \{\mathbf{q} = (q_j): q_j \in \mathcal{Q}_j\}, \quad \mathcal{Q}_{\text{ad}} = \{\mathbf{q} \in \mathcal{Q}: q_j \in \mathcal{Q}_{\text{ad},j}\}.$$

In the space \mathcal{Q} , we use the inner product and norm

$$(\mathbf{p}, \mathbf{q})_{\mathcal{Q}} = \sum_j \left(\sum_i w_{ij} \omega_{ij}^2 \right) (p_j, q_j)_{\mathcal{Q}_j}, \quad \|\mathbf{q}\|_{\mathcal{Q}} = (\mathbf{q}, \mathbf{q})_{\mathcal{Q}}^{1/2}.$$

We adopt the convention that $\mathbf{q} = (q_j) \in \mathcal{Q}$ corresponds to $\mathbf{q} = (\omega_{ij} q_j) \in \Omega$.

As $M \rightarrow \infty$, if $\{\mathbf{p}_{\varepsilon M}\}_M$ has a limit \mathbf{p}_ε , then we expect $\ell_i(\mathbf{p}_{\varepsilon,*j}) = 0$, i.e. $p_{\varepsilon,ij} = \omega_{ij}S(\mathbf{p}_{\varepsilon,*j})$. We denote $\mathbf{p}_\varepsilon = (p_{\varepsilon,j})$ with $p_{\varepsilon,j} = S(\mathbf{p}_{\varepsilon,*j})$. Then, $p_{\varepsilon,ij} = \omega_{ij}p_{\varepsilon,j}$ and $u_{ij}(p_{\varepsilon,ij}) = \omega_{ij}u_{ij}(p_{\varepsilon,j})$. For $\mathbf{q} \in \mathcal{Q}$, let

$$\mathbf{W}(\mathbf{q}) = (W_i(\mathbf{q})), \quad W_i(\mathbf{q}) = \sum_j \omega_{ij}u_{ij}(q_j).$$

Then, $\mathbf{W}(\mathbf{q}) = \mathbf{U}(\mathbf{q})$. For any $\mathbf{q} \in \mathcal{Q}$, we define

$$J_\varepsilon(\mathbf{q}) = \frac{1}{2}[\|\mathbf{W}(\mathbf{q}) - \mathbf{f}\|_G^2 + \varepsilon\|\mathbf{q}\|_Q^2]$$

and introduce the following limiting problem.

PROBLEM 4.1 Find $\mathbf{p}_\varepsilon \in \mathcal{Q}_{\text{ad}}$ such that $J_\varepsilon(\mathbf{p}_\varepsilon) = \inf\{J_\varepsilon(\mathbf{q}): \mathbf{q} \in \mathcal{Q}_{\text{ad}}\}$.

Results similar to those presented in Section 3 hold for Problem 4.1.

THEOREM 4.2 Problem 4.1 with $\varepsilon > 0$ has a unique solution $\mathbf{p}_\varepsilon \in \mathcal{Q}_{\text{ad}}$ that is characterized by a variational inequality

$$(\mathbf{W}(\mathbf{p}_\varepsilon) - \mathbf{f}, \mathbf{W}(\mathbf{q} - \mathbf{p}_\varepsilon))_G + \varepsilon(\mathbf{p}_\varepsilon, \mathbf{q} - \mathbf{p}_\varepsilon)_Q \geq 0, \quad \forall \mathbf{q} \in \mathcal{Q}_{\text{ad}}. \quad (4.1)$$

When $\mathcal{Q}_{\text{ad},j} \subset \mathcal{Q}_j$ are subspaces, the inequality is reduced to a variational equation

$$(\mathbf{W}(\mathbf{p}_\varepsilon) - \mathbf{f}, \mathbf{W}(\mathbf{q}))_G + \varepsilon(\mathbf{p}_\varepsilon, \mathbf{q})_Q = 0, \quad \forall \mathbf{q} \in \mathcal{Q}_{\text{ad}}. \quad (4.2)$$

Moreover, the solution \mathbf{p}_ε depends continuously on the data.

The main theoretical result of the section is the following.

THEOREM 4.3 Suppose $0 \in \mathcal{Q}_{\text{ad},j}$. Then as $M \rightarrow \infty$, $\mathbf{p}_{\varepsilon M} \rightarrow \mathbf{p}_\varepsilon = (\omega_{ij}p_{\varepsilon,j})$ in \mathfrak{Q} .

Proof. Since $0 \in \mathcal{Q}_{\text{ad},j}$ and $\mathcal{Q}_{\text{ad},j}$ is convex, for any $\mathbf{q} \in \mathcal{Q}_{\text{ad}}$, $\mathbf{q} = (\omega_{ij}q_j) \in \mathfrak{Q}_{\text{ad}}$. In particular, $\mathbf{p}_\varepsilon \in \mathfrak{Q}_{\text{ad}}$. Note that $J_{\varepsilon M}(\mathbf{p}_\varepsilon) = J_\varepsilon(\mathbf{p}_\varepsilon)$. Then,

$$\frac{1}{2} \left[\varepsilon \|\mathbf{p}_{\varepsilon M}\|_{\mathfrak{Q}}^2 + M |\ell(\mathbf{p}_{\varepsilon M})|_{\mathfrak{Q}_l}^2 \right] \leq J_{\varepsilon M}(\mathbf{p}_{\varepsilon M}) \leq J_\varepsilon(\mathbf{p}_\varepsilon).$$

So as $M \rightarrow \infty$, $|\ell(\mathbf{p}_{\varepsilon M})|_{\mathfrak{Q}_l} \rightarrow 0$ and $\{\|\mathbf{p}_{\varepsilon M}\|_{\mathfrak{Q}}\}_M$ is uniformly bounded. Then, $\{\mathbf{p}_{\varepsilon M}\}_M$ contains a subsequence $\{\mathbf{p}_{\varepsilon M'}\}_{M'}$ converging weakly to $\tilde{\mathbf{p}}_\varepsilon \in \mathfrak{Q} : \mathbf{p}_{\varepsilon M'} \rightharpoonup \tilde{\mathbf{p}}_\varepsilon$ in \mathfrak{Q} . From

$$|\ell(\tilde{\mathbf{p}}_\varepsilon)|_{\mathfrak{Q}_l} \leq \liminf_{M' \rightarrow \infty} |\ell(\mathbf{p}_{\varepsilon M'})|_{\mathfrak{Q}_l} \rightarrow 0,$$

we obtain $\tilde{p}_{\varepsilon,ij} = \omega_{ij}\tilde{p}_{\varepsilon,j}$, with $\tilde{p}_{\varepsilon,j} = S(\tilde{\mathbf{p}}_{\varepsilon,*j})$.

We denote $\tilde{\mathbf{p}}_\varepsilon = (\tilde{p}_{\varepsilon,j})$. Let us show that $\tilde{\mathbf{p}}_\varepsilon$ is a minimizer of $J_\varepsilon(\cdot)$ over \mathcal{Q}_{ad} . For any $\mathbf{q} \in \mathcal{Q}_{\text{ad}}$, take $\mathbf{q} = (\omega_{ij}q_j) \in \mathfrak{Q}_{\text{ad}}$ in (3.4) to obtain

$$(\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, \mathbf{U}(\mathbf{q} - \mathbf{p}_{\varepsilon M}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}, \mathbf{q} - \mathbf{p}_{\varepsilon M})_{\mathfrak{Q}} \geq M |\ell(\mathbf{p}_{\varepsilon M})|_{\mathfrak{Q}_l}^2 \geq 0.$$

Let $M = M' \rightarrow \infty$, then

$$(\mathbf{U}(\tilde{\mathbf{p}}_\varepsilon) - \mathbf{f}, \mathbf{U}(\mathbf{q} - \tilde{\mathbf{p}}_\varepsilon))_G + \varepsilon(\tilde{\mathbf{p}}_\varepsilon, \mathbf{q} - \tilde{\mathbf{p}}_\varepsilon)_{\mathfrak{Q}} \geq 0,$$

i.e.

$$(\mathbf{W}(\tilde{\mathbf{p}}_\varepsilon) - \mathbf{f}, \mathbf{W}(\mathbf{q} - \tilde{\mathbf{p}}_\varepsilon))_G + \varepsilon(\tilde{\mathbf{p}}_\varepsilon, \mathbf{q} - \tilde{\mathbf{p}}_\varepsilon)_Q \geq 0, \quad \forall \mathbf{q} \in \mathcal{Q}_{\text{ad}}.$$

By the characterization (4.1), $\tilde{\mathbf{p}}_\varepsilon$ is a minimizer of $J_\varepsilon(\cdot)$ over \mathcal{Q}_{ad} . Since the minimizer is unique, $\tilde{\mathbf{p}}_\varepsilon = \mathbf{p}_\varepsilon$.

To show the strong convergence $\mathbf{p}_{\varepsilon M'} \rightarrow \mathbf{p}_\varepsilon$ in \mathcal{Q} , we write

$$\|\mathbf{U}(\mathbf{p}_{\varepsilon M'} - \mathbf{p}_\varepsilon)\|_G^2 + \varepsilon \|\mathbf{p}_{\varepsilon M'} - \mathbf{p}_\varepsilon\|_\Omega^2 = I + II + III,$$

where

$$\begin{aligned} I &= \|\mathbf{U}(\mathbf{p}_{\varepsilon M'}) - \mathbf{f}\|_G^2 + \varepsilon \|\mathbf{p}_{\varepsilon M'}\|_\Omega^2, \\ II &= -2(\mathbf{U}(\mathbf{p}_{\varepsilon M'}) - \mathbf{f}, \mathbf{U}(\mathbf{p}_\varepsilon) - \mathbf{f})_G - 2\varepsilon(\mathbf{p}_{\varepsilon M'}, \mathbf{p}_\varepsilon)_\Omega, \\ III &= \|\mathbf{U}(\mathbf{p}_\varepsilon) - \mathbf{f}\|_G^2 + \varepsilon \|\mathbf{p}_\varepsilon\|_\Omega^2 = 2J_\varepsilon(\mathbf{p}_\varepsilon). \end{aligned}$$

We have

$$\begin{aligned} I &\leq 2J_{\varepsilon M'}(\mathbf{p}_{\varepsilon M'}) \leq 2J_{\varepsilon M}(\mathbf{p}_\varepsilon) = 2J_\varepsilon(\mathbf{p}_\varepsilon), \\ \lim_{M' \rightarrow \infty} II &= -2\|\mathbf{U}(\mathbf{p}_\varepsilon) - \mathbf{f}\|_G^2 - 2\varepsilon \|\mathbf{p}_\varepsilon\|_\Omega^2 = -4J_\varepsilon(\mathbf{p}_\varepsilon). \end{aligned}$$

Thus,

$$\limsup_{M' \rightarrow \infty} [\|\mathbf{U}(\mathbf{p}_{\varepsilon M'} - \mathbf{p}_\varepsilon)\|_G^2 + \varepsilon \|\mathbf{p}_{\varepsilon M'} - \mathbf{p}_\varepsilon\|_\Omega^2] \leq 0.$$

Consequently,

$$\|\mathbf{p}_{\varepsilon M'} - \mathbf{p}_\varepsilon\|_\Omega \rightarrow 0 \quad \text{as } M' \rightarrow \infty.$$

Since the limit \mathbf{p}_ε is unique and is independent of the subsequence $\{M'\}$ we choose, the entire family converges: $\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_\varepsilon\|_\Omega \rightarrow 0$ as $M \rightarrow \infty$. \square

5. Limiting behaviour with respect to regularization parameter

In this section, we explore the solution behaviour when the regularization parameter $\varepsilon \rightarrow 0+$.

Similar to the characterization (3.4), we can show that a solution $\mathbf{p} = (p_{ij}) \in \mathcal{Q}_{\text{ad}}$ of Problem 3.1 with $\varepsilon = 0$ is characterized by the inequality

$$(\mathbf{U}(\mathbf{p}) - \mathbf{f}, \mathbf{U}(\mathbf{q} - \mathbf{p}))_G + M(\boldsymbol{\ell}(\mathbf{p}), \boldsymbol{\ell}(\mathbf{q} - \mathbf{p}))_{\Omega_l} \geq 0, \quad \forall \mathbf{q} \in \mathcal{Q}_{\text{ad}}. \quad (5.1)$$

We denote by $\mathfrak{S}_{0M} \subset \mathcal{Q}_{\text{ad}}$, the solution set of Problem 3.1 with $\varepsilon = 0$. As in Lions (1971), the following results hold.

PROPOSITION 5.1 Assume \mathfrak{S}_{0M} is nonempty. Then, \mathfrak{S}_{0M} is closed and convex.

Proof. Assume $\{\mathbf{p}_n\} \subset \mathfrak{S}_{0M}$ with $\mathbf{p}_n \rightarrow \mathbf{p}$ in \mathcal{Q} . From (3.1),

$$\int_{\Omega} [D_i \nabla u_{ij}(p_{n,ij}) \cdot \nabla v + \mu_{a,i} u_{ij}(p_{n,ij}) v] dx + \int_{\Gamma} \frac{1}{2A} u_{ij}(p_{n,ij}) v ds = \int_{\Omega_j} p_{n,ij} v dx, \quad \forall v \in V. \quad (5.2)$$

By (3.2), $\|u_{ij}(p_{n,ij}) - u_{ij}(p_{m,ij})\|_V \leq c\|p_{n,ij} - p_{m,ij}\|_{Q_j}$. So $\{u_{ij}(p_{n,ij})\}_n$ is a Cauchy sequence in V , and hence has a limit u_{ij} in V . Let $n \rightarrow \infty$ in (5.2) to see that $u_{ij} = u_{ij}(p_{ij})$. By the characterization (5.1), there holds

$$(U(\mathbf{p}_n) - f, U(\mathbf{q} - \mathbf{p}_n))_G + M(\boldsymbol{\ell}(\mathbf{p}_n), \boldsymbol{\ell}(\mathbf{q} - \mathbf{p}_n))_{\Omega_l} \geq 0, \quad \forall \mathbf{q} \in \Omega_{\text{ad}}.$$

Let $n \rightarrow \infty$ to obtain

$$(U(\mathbf{p} - f), U(\mathbf{q} - \mathbf{p}))_G + M(\boldsymbol{\ell}(\mathbf{p}), \boldsymbol{\ell}(\mathbf{q} - \mathbf{p}))_{\Omega_l} \geq 0, \quad \forall \mathbf{q} \in \Omega_{\text{ad}}.$$

Therefore, $\mathbf{p} \in \mathfrak{S}_{0M}$ and \mathfrak{S}_{0M} is closed.

Now, let $\mathbf{p}_1, \mathbf{p}_2 \in \mathfrak{S}_{0M}$ and $\theta \in (0, 1)$. Then, $u_{ij}(\theta p_{1,ij} + (1 - \theta)p_{2,ij}) = \theta u_{ij}(p_{1,ij}) + (1 - \theta)u_{ij}(p_{2,ij})$ and

$$J_{0M}(\theta \mathbf{p}_1 + (1 - \theta)\mathbf{p}_2) \leq \theta J_{0M}(\mathbf{p}_1) + (1 - \theta)J_{0M}(\mathbf{p}_2).$$

Thus, $\theta \mathbf{p}_1 + (1 - \theta)\mathbf{p}_2 \in \mathfrak{S}_{0M}$ and \mathfrak{S}_{0M} is convex. \square

Based on Proposition 5.1, we conclude that \mathfrak{S}_{0M} , if it is nonempty, contains a unique minimal Ω -norm solution $\mathbf{p}_{0M} \in \mathfrak{S}_{0M}$:

$$\|\mathbf{p}_{0M}\|_{\Omega} = \inf\{\|\mathbf{q}\|_{\Omega} : \mathbf{q} \in \mathfrak{S}_{0M}\}.$$

This solution is characterized by the variational inequality

$$(\mathbf{p}_{0M}, \mathbf{q} - \mathbf{p}_{0M})_{\Omega} \geq 0, \quad \forall \mathbf{q} \in \mathfrak{S}_{0M}.$$

THEOREM 5.2 Assume \mathfrak{S}_{0M} is nonempty. Then, \mathfrak{S}_{0M} is closed and convex. Moreover,

$$\mathbf{p}_{\varepsilon M} \rightarrow \mathbf{p}_{0M} \text{ in } \Omega, \quad \text{as } \varepsilon \rightarrow 0. \quad (5.3)$$

Proof. We take $\mathbf{q} = \mathbf{p}_{0M}$ in (3.4) to get

$$(U(\mathbf{p}_{\varepsilon M}) - f, U(\mathbf{p}_{0M} - \mathbf{p}_{\varepsilon M}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}, \mathbf{p}_{0M} - \mathbf{p}_{\varepsilon M})_{\Omega} + M(\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}), \boldsymbol{\ell}(\mathbf{p}_{0M} - \mathbf{p}_{\varepsilon M}))_{\Omega_l} \geq 0,$$

and take $\mathbf{q} = \mathbf{p}_{\varepsilon M}$ in (5.1) for $\mathbf{p} = \mathbf{p}_{0M}$ to get

$$(U(\mathbf{p}_{0M}) - f, U(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M}))_G + M(\boldsymbol{\ell}(\mathbf{p}_{0M}), \boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M}))_{\Omega_l} \geq 0.$$

Adding these two inequalities, we obtain

$$\varepsilon(\mathbf{p}_{\varepsilon M}, \mathbf{p}_{0M} - \mathbf{p}_{\varepsilon M})_{\Omega} \geq \|U(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M})\|_G^2 + M|\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M})|_{\Omega_l}^2.$$

Thus, $(\mathbf{p}_{\varepsilon M}, \mathbf{p}_{0M} - \mathbf{p}_{\varepsilon M})_{\Omega} \geq 0$ and

$$\|\mathbf{p}_{\varepsilon M}\|_{\Omega} \leq \|\mathbf{p}_{0M}\|_{\Omega}. \quad (5.4)$$

So $\{\mathbf{p}_{\varepsilon M}\}_{\varepsilon}$ is uniformly bounded in Ω . Let $\{\mathbf{p}_{\varepsilon' M}\}_{\varepsilon'}$ be a subsequence of $\{\mathbf{p}_{\varepsilon M}\}_{\varepsilon}$ converging weakly to some $\mathbf{p} \in \Omega$. We take the limit $\varepsilon' \rightarrow 0$ in (3.4) to see that the limit \mathbf{p} satisfies (5.1), i.e. $\mathbf{p} \in \mathfrak{S}_{0M}$. Let $\varepsilon = \varepsilon' \rightarrow 0$ in (5.4), then

$$\|\mathbf{p}\|_{\Omega} \leq \liminf_{\varepsilon' \rightarrow 0} \|\mathbf{p}_{\varepsilon' M}\|_{\Omega} \leq \|\mathbf{p}_{0M}\|_{\Omega}.$$

By the uniqueness of the minimizer \mathbf{p}_{0M} , $\mathbf{p} = \mathbf{p}_{0M}$. Since the limit $\mathbf{p} = \mathbf{p}_{0M}$ does not depend on the subsequence selected, $\{\mathbf{p}_{\varepsilon M}\}_{\varepsilon}$ converges weakly to \mathbf{p}_{0M} in Ω as $\varepsilon \rightarrow 0$. Strong convergence $\mathbf{p}_{\varepsilon M} \rightarrow \mathbf{p}_{0M}$ in Ω as $\varepsilon \rightarrow 0$ follows from the weak convergence and the boundedness of the family $\{\mathbf{p}_{\varepsilon M}\}_{\varepsilon}$. \square

As a simple consequence of the theorem, we have the next result.

COROLLARY 5.3 Suppose that the solution set $\mathfrak{S}_{0M} = \{\mathbf{p}_M\}$ is a singleton. Then,

$$\mathbf{p}_{\varepsilon M} \rightarrow \mathbf{p}_M \quad \text{in } \mathfrak{Q}, \quad \text{as } \varepsilon \rightarrow 0.$$

The set \mathfrak{S}_{0M} is nonempty when \mathfrak{Q}_{ad} is bounded. This is shown by applying a standard result on convex minimization, e.g. Atkinson & Han, 2005, Theorem 3.3.12. Another sufficient condition that ensures $\mathfrak{S}_{0M} \neq \emptyset$ is the following compatible assumption on the data:

$$\exists \mathbf{p}_1 \in \mathfrak{Q}_{\text{ad}} \text{ such that } U_i(\mathbf{p}_1) = f_i \text{ on } \Gamma_i, \quad 1 \leq i \leq i_0. \quad (5.5)$$

6. Numerical method without discretizing admissible set

In this and Section 7, we discuss numerical approximations of Problem 3.1 with $\varepsilon > 0$. The admissible source function space \mathfrak{Q}_{ad} may or may not need to be discretized. In this section, we consider the case without a discretization of \mathfrak{Q}_{ad} . This is natural where \mathfrak{Q}_{ad} is a finite-dimensional subspace or subset of linear combinations of specified functions such as the characteristic functions of certain subsets of Ω .

We introduce the linear finite-element spaces of V for discretization of the constraint (3.1). Let $\{\mathcal{T}_h\}$ (h : mesh size) be a regular family of finite-element partitions of $\overline{\Omega}$ such that each element at the boundary Γ has at most one nonstraight face (for a 3D domain) or side (for a 2D domain). For each triangulation $\mathcal{T}_h = \{K\}$, let $V^h \subset V$ be the linear element space. For any $q \in \mathcal{Q}_j$, we define $u_{ij}^h(q) \in V^h$ by

$$\int_{\Omega} [D_i \nabla u_{ij}^h(q) \cdot \nabla v^h + \mu_{a,i} u_{ij}^h(q) v^h] dx + \int_{\Gamma} \frac{1}{2A} u_{ij}^h(q) v^h ds = \int_{\Omega_j} q v^h dx, \quad \forall v^h \in V^h. \quad (6.1)$$

Like (3.1), (6.1) has a unique solution $u_{ij}^h(q)$. For $\mathbf{q} \in \mathfrak{Q}$, denote $U_i^h(\mathbf{q}_{i*}) = \sum_j u_{ij}^h(q_{ij})$ and $\mathbf{U}^h(\mathbf{q}) = (U_i(\mathbf{q}_{i*}))$, and define the approximation functional

$$J_{\varepsilon M}^h(\mathbf{q}) = \frac{1}{2} \left[\|\mathbf{U}^h(\mathbf{q}) - \mathbf{f}\|_G^2 + \varepsilon \|\mathbf{q}\|_{\mathfrak{Q}}^2 + M \|\boldsymbol{\ell}(\mathbf{q})\|_{\mathfrak{Q}_I}^2 \right]. \quad (6.2)$$

We then introduce the following discretization of Problem 3.1.

PROBLEM 6.1 Find $\mathbf{p}_{\varepsilon M}^h \in \mathfrak{Q}_{\text{ad}}$ such that $J_{\varepsilon M}^h(\mathbf{p}_{\varepsilon M}^h) = \inf\{J_{\varepsilon M}^h(\mathbf{q}) : \mathbf{q} \in \mathfrak{Q}_{\text{ad}}\}$.

Similar to Problem 3.1, we can show the following results for the discrete problem.

PROPOSITION 6.2 Problem 6.1 with $\varepsilon > 0$ has a unique solution $\mathbf{p}_{\varepsilon M}^h \in \mathfrak{Q}_{\text{ad}}$, and it is characterized by a discrete variational inequality

$$\begin{aligned} & (\mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h) - \mathbf{f}, \mathbf{U}^h(\mathbf{q} - \mathbf{p}_{\varepsilon M}^h))_G \\ & + \varepsilon (\mathbf{p}_{\varepsilon M}^h, \mathbf{q} - \mathbf{p}_{\varepsilon M}^h)_{\mathfrak{Q}} + M (\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}^h), \boldsymbol{\ell}(\mathbf{q} - \mathbf{p}_{\varepsilon M}^h))_{\mathfrak{Q}_I} \geq 0, \quad \forall \mathbf{q} \in \mathfrak{Q}_{\text{ad}}. \end{aligned} \quad (6.3)$$

When $\mathcal{Q}_{\text{ad},j} \subset \mathcal{Q}_j$ are subspaces, (6.3) reduces to a variational equation

$$(\mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h) - \mathbf{f}, \mathbf{U}^h(\mathbf{q}))_G + \varepsilon (\mathbf{p}_{\varepsilon M}^h, \mathbf{q})_{\mathfrak{Q}} + M (\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}^h), \boldsymbol{\ell}(\mathbf{q}))_{\mathfrak{Q}_I} = 0, \quad \forall \mathbf{q} \in \mathfrak{Q}_{\text{ad}}.$$

The solution $\mathbf{p}_{\varepsilon M}^h$ depends continuously on the data.

We denote $\mathbf{W}^h(\mathbf{q}) = \mathbf{U}^h(\mathbf{q})$ for $\mathbf{q} \in \mathcal{Q}$. If $0 \in \mathcal{Q}_{\text{ad},j}$, then $\mathbf{p}_{\varepsilon M}^h \rightarrow \mathbf{p}_\varepsilon^h = (\omega_{ij} p_{\varepsilon,j}^h)$ in \mathfrak{Q} as $M \rightarrow \infty$, where $\mathbf{p}_\varepsilon^h = (p_{\varepsilon,j}^h) \in \mathcal{Q}_{\text{ad}}$ is the unique minimizer of the functional

$$J_\varepsilon^h(\mathbf{q}) = \frac{1}{2} [\|\mathbf{W}^h(\mathbf{q}) - f\|_G^2 + \varepsilon \|\mathbf{q}\|_{\mathcal{Q}}^2] \quad (6.4)$$

over \mathcal{Q}_{ad} .

Suppose Problem 6.1 with $\varepsilon = 0$ has a solution, and we denote by \mathfrak{S}_{0M}^h the solution set. Then, $\mathfrak{S}_{0M}^h \subset \mathfrak{Q}_{\text{ad}}$ is closed and convex, and $\mathbf{p}_{\varepsilon M}^h \rightarrow \mathbf{p}_{0M}^h$ in \mathfrak{Q} as $\varepsilon \rightarrow 0$, where $\mathbf{p}_{0M}^h \in \mathfrak{S}_{0M}^h$ is the minimal norm solution:

$$\|\mathbf{p}_{0M}^h\|_{\mathfrak{Q}} = \inf\{\|\mathbf{q}\|_{\mathfrak{Q}} : \mathbf{q} \in \mathfrak{S}_{0M}^h\}.$$

For error estimation, we further assume

$$\Gamma \in C^{1,1}, \quad A \in C^{0,1}(\Gamma), \quad D_i \in C^{0,1}(\Omega), \quad \mu_{a,i} \in L^\infty(\Omega). \quad (6.5)$$

Then, $u_{ij}(q) \in H^2(\Omega)$ and

$$\|u_{ij}(q)\|_{H^2(\Omega)} \leq c \|q\|_{\mathcal{Q}_j}, \quad q \in \mathcal{Q}_j \quad (6.6)$$

(Grisvard, 1985, Theorems 2.3.3.6 and 2.4.2.6). The assumptions (6.5) are made to ensure the validity of the solution regularity (6.6) used below in error estimation. Without the solution regularity property, error estimates with lower convergence orders can still be derived.

Let us now recall the finite-element interpolation error estimate

$$\|v - \Pi_{V^h} v\|_{L^2(\Omega)} + h \|v - \Pi_{V^h} v\|_{H^1(\Omega)} \leq ch^2 \|v\|_{H^2(\Omega)}, \quad \forall v \in H^2(\Omega), \quad (6.7)$$

where $\Pi_{V^h} v \in V^h$ is the piece-wise linear interpolant of v . This error estimate is usually proved when Ω is a polyhedral/polygonal domain so that each element K in a finite-element partition \mathcal{T}_h has straight faces/sides on its boundary (e.g. Brenner & Scott, 2002; Ciarlet, 1978). For applications in BLT, Ω is a smooth domain and is not polyhedral. In such an application, the error estimate (6.7) still holds (Han *et al.*, 2006). Using an argument similar to that in Han *et al.* (2006), we can show that there is a constant $c > 0$ independent of h , ε and M such that

$$\|u_{ij}(q) - u_{ij}^h(q)\|_{G_i} \leq ch^{3/2} \|q\|_{\mathcal{Q}_j}, \quad \forall q \in \mathcal{Q}_j.$$

Then,

$$\|\mathbf{U}(\mathbf{q}) - \mathbf{U}^h(\mathbf{q})\|_G \leq ch^{3/2} \|\mathbf{q}\|_{\mathfrak{Q}}, \quad \forall \mathbf{q} \in \mathfrak{Q}. \quad (6.8)$$

A starting point for deriving error bounds is the following result.

THEOREM 6.3 There is a constant $c > 0$ independent of h , ε and M such that

$$\begin{aligned} & \| \mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h) \|_G + \varepsilon^{1/2} \| \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h \|_{\mathfrak{Q}} + M^{1/2} | \ell(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h) |_{\mathfrak{Q}_I} \\ & \leq c h^{3/4} \| \mathbf{U}(\mathbf{p}_{\varepsilon M}) - f \|_G^{1/2} \| \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h \|_{\mathfrak{Q}}^{1/2} + c h^{3/2} \| \mathbf{p}_{\varepsilon M} \|_{\mathfrak{Q}}. \end{aligned} \quad (6.9)$$

Proof. We take $\mathbf{q} = \mathbf{p}_{\varepsilon M}$ in (6.3) to get

$$(\mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h) - \mathbf{f}, \mathbf{U}^h(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h))_G + \varepsilon(\mathbf{p}_{\varepsilon M}^h, \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h)_\Omega + M(\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}^h), \boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h))_{\Omega_I} \geq 0,$$

and take $\mathbf{q} = \mathbf{p}_{\varepsilon M}^h$ in (3.4) to get

$$(\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, \mathbf{U}(\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}, \mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M})_\Omega + M(\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}), \boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M}))_{\Omega_I} \geq 0.$$

Adding the two inequalities, we can derive the following:

$$\begin{aligned} & \|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h)\|_G^2 + \varepsilon\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega^2 + M|\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h)|_{\Omega_I}^2 \\ & \leq (\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h), \mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h))_G \\ & \quad + (\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, \mathbf{U}(\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M}))_G. \end{aligned}$$

We bound the right-hand side by

$$\begin{aligned} & c\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h)\|_G^2 + \frac{1}{2}\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h)\|_G^2 \\ & \quad + c\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}\|_G\|\mathbf{U}(\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{\varepsilon M})\|_G, \end{aligned}$$

and then apply (6.8) to get (6.9). \square

Further error bounds require more information on the data. We present two sample results as consequences of Theorem 6.3.

First assume $Q_{\text{ad},j} \subset Q_j$ are bounded, an assumption valid in applications. Then, there is a constant $c > 0$ independent of h , ε and M such that

$$\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h)\|_G + \varepsilon^{1/2}\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega + M^{1/2}|\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h)|_{\Omega_I} \leq ch^{3/4}. \quad (6.10)$$

Next, assume the compatibility condition (5.5). Then, there is a constant $c > 0$ independent of h , ε and M such that

$$\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h)\|_G + \varepsilon^{1/2}\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega + M^{1/2}|\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h)|_{\Omega_I} \leq ch^{3/2}. \quad (6.11)$$

This is proved as follows: From

$$\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}\|_G^2 + \varepsilon\|\mathbf{p}_{\varepsilon M}\|_\Omega^2 + M|\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h)|_{\Omega_I}^2 \leq 2J_\varepsilon(\mathbf{p}_1) = \varepsilon\|\mathbf{p}_1\|_\Omega^2,$$

we know that for all ε , $M > 0$, $\|\mathbf{p}_{\varepsilon M}\|_\Omega \leq \|\mathbf{p}_1\|_\Omega$ and $\|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}\|_G \leq \varepsilon^{1/2}\|\mathbf{p}_1\|_\Omega$. Then, from (6.9), we obtain

$$\begin{aligned} & \|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^h)\|_G + \varepsilon^{1/2}\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega + M^{1/2}|\boldsymbol{\ell}_i(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h)|_{\Omega_I} \\ & \leq ch^{3/4}\varepsilon^{1/4}\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega^{1/2} + ch^{3/2}. \end{aligned}$$

Bound the first term on the right-hand side as follows:

$$ch^{3/4}\varepsilon^{1/4}\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega^{1/2} \leq \frac{1}{2}\varepsilon^{1/2}\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_\Omega + ch^{3/2}.$$

Thus, (6.11) holds.

When the regularization parameter ε is chosen related to the discretization parameter, we may bound the error $\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_{\Omega}$ in terms of the discretization parameter only. For example, in the context of (6.11), let $\varepsilon = ch^\beta$, $0 < \beta < 3$. Then,

$$\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_{\Omega} \leq ch^{(3-\beta)/2}.$$

Finally, we comment that when the solution set \mathfrak{S}_{0M} is nonempty, convergence of the numerical solution $\mathbf{p}_{\varepsilon M}^h$ to the solution $\mathbf{p}_{0M} \in \mathfrak{S}_{0M}$ follows from the triangle inequality

$$\|\mathbf{p}_{\varepsilon M}^h - \mathbf{p}_{0M}\|_{\Omega} \leq \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M}\|_{\Omega} + \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^h\|_{\Omega}$$

together with (5.3) and the convergence of $\mathbf{p}_{\varepsilon M}^h$ to $\mathbf{p}_{\varepsilon M}$ in Ω .

7. Numerical method with discretized admissible set

In this section, we study a numerical method where Ω_{ad} is also discretized. This is necessary where Ω_{ad} is a general subset of Ω . In addition to the regular family of finite-element partitions $\{\mathcal{T}_h\}$ of $\overline{\Omega}$, let $\{\mathcal{T}_{j,H}\}$ be a regular family of finite-element partitions of $\overline{\Omega}_j$ such that each element at the boundary $\partial\Omega_j$ has at most one nonstraight face (for a 3D domain) or side (for a 2D domain). The partitions \mathcal{T}_h and $\mathcal{T}_{j,H}$ do not need to be related; however, \mathcal{T}_h can be constructed based on $\mathcal{T}_{j,H}$. We may allow the mesh size of the partition on Ω_j to depend on j . However, to simplify the notation, we limit our discussion to the situation where mesh sizes of the partitions on all the subdomains are comparable.

Let $Q_j^H \subset Q_j$ be the piece-wise constant function space corresponding to the partition $\mathcal{T}_{j,H}$, $\Omega^H = \{\mathbf{q}^H \in \Omega: q_{ij}^H \in Q_j^H\}$ and $\Omega_{\text{ad}}^H = \Omega^H \cap \Omega_{\text{ad}}$. Using the functional $J_{\varepsilon M}^h$ of (6.2), we define the following discretization of Problem 3.1.

PROBLEM 7.1 Find $\mathbf{p}_{\varepsilon M}^{hH} \in \Omega_{\text{ad}}^H$ such that $J_{\varepsilon M}^h(\mathbf{p}_{\varepsilon M}^{hH}) = \inf\{J_{\varepsilon M}^h(\mathbf{q}^H): \mathbf{q}^H \in \Omega_{\text{ad}}^H\}$.

Similar to Problem 6.1, we have the following result for Problem 7.1.

PROPOSITION 7.2 Problem 7.1 with $\varepsilon > 0$ has a unique solution $\mathbf{p}_{\varepsilon M}^{hH} \in \Omega_{\text{ad}}^H$, and it is characterized by a discrete variational inequality

$$\begin{aligned} & (U^h(\mathbf{p}_{\varepsilon M}^{hH}) - f, U^h(\mathbf{q}^H - \mathbf{p}_{\varepsilon M}^{hH}))_G + \varepsilon(\mathbf{p}_{\varepsilon M}^{hH}, \mathbf{q}^H - \mathbf{p}_{\varepsilon M}^{hH})_{\Omega} \\ & + M(\ell(\mathbf{p}_{\varepsilon M}^{hH}), \ell(\mathbf{q}^H - \mathbf{p}_{\varepsilon M}^{hH}))_{\Omega_l} \geq 0, \quad \forall \mathbf{q}^H \in \Omega_{\text{ad}}^H. \end{aligned} \quad (7.1)$$

When $Q_{\text{ad},j} \subset Q_j$ are subspaces, (7.1) reduces to a variational equation

$$(U^h(\mathbf{p}_{\varepsilon M}^{hH}) - f, U^h(\mathbf{q}^H))_G + \varepsilon(\mathbf{p}_{\varepsilon M}^{hH}, \mathbf{q}^H)_{\Omega} + M(\ell(\mathbf{p}_{\varepsilon M}^{hH}), \ell(\mathbf{q}^H))_{\Omega_l} = 0, \quad \forall \mathbf{q}^H \in \Omega_{\text{ad}}^H.$$

The solution $\mathbf{p}_{\varepsilon M}^{hH}$ depends continuously on the data.

We denote $Q_{\text{ad}}^H = \{\mathbf{q}^H \in Q_{\text{ad}}: q_j^H \in Q_j^H\}$. If $0 \in Q_{\text{ad},j}$, then $\mathbf{p}_{\varepsilon M}^{hH} \rightarrow \mathbf{p}_{\varepsilon}^{hH} = (\omega_{ij} p_{\varepsilon,j}^{hH})$ in Ω as $M \rightarrow \infty$, where $\mathbf{p}_{\varepsilon}^{hH} = (p_{\varepsilon,j}^{hH}) \in Q_{\text{ad}}^H$ is the unique minimizer of the functional $J_{\varepsilon}^h(\mathbf{q}^H)$, defined in (6.4), over Q_{ad}^H .

Suppose Problem 7.1 with $\varepsilon = 0$ has a solution, and we denote by \mathfrak{S}_{0M}^{hH} the solution set. Then, $\mathfrak{S}_{0M}^{hH} \subset \Omega_{\text{ad}}^H$ is closed and convex, and $\mathbf{p}_{\varepsilon M}^{hH} \rightarrow \mathbf{p}_{0M}^{hH}$ in Ω as $\varepsilon \rightarrow 0$, where $\mathbf{p}_{0M}^{hH} \in \mathfrak{S}_{0M}^{hH}$ is the minimal norm solution:

$$\|\mathbf{p}_{0M}^{hH}\|_{\Omega} = \inf\{\|\mathbf{q}^H\|_{\Omega}: \mathbf{q}^H \in \mathfrak{S}_{0M}^{hH}\}.$$

For error estimation, we again assume (6.5). Then, we have the regularity bound (6.6). Introducing the orthogonal projection operator Π_j^H from \mathcal{Q}_j onto \mathcal{Q}_j^H , we obtain

$$\Pi_j^H q \in \mathcal{Q}_j^H, \quad (\Pi_j^H q, q^H)_{\mathcal{Q}_j} = (q, q^H)_{\mathcal{Q}_j}, \quad \forall q^H \in \mathcal{Q}_j^H, \quad q \in \mathcal{Q}_j. \quad (7.2)$$

We denote Π^H for the orthogonal projection operator from \mathfrak{Q} to \mathfrak{Q}^H . Easily,

$$\Pi^H(\mathbf{q}) = (\Pi_j^H q_{ij}), \quad \forall \mathbf{q} \in \mathfrak{Q}.$$

The following properties will be needed:

$$\|\Pi^H \mathbf{q}\|_{\mathfrak{Q}} \leq \|\mathbf{q}\|_{\mathfrak{Q}}, \quad \forall \mathbf{q} \in \mathfrak{Q}, \quad (7.3)$$

$$\|\mathbf{q} - \Pi^H \mathbf{q}\|_{\mathfrak{Q}} \leq cH \sum_{i,j} |q_{ij}|_{H^1(\Omega_j)}, \quad \forall \mathbf{q} \text{ with } q_{ij} \in H^1(\Omega_j). \quad (7.4)$$

Since $\mathfrak{Q}_{\text{ad}} \subset \mathfrak{Q}$ is convex, the element-wise formula

$$\Pi_j^H q|_K = \frac{1}{|K|} \int_K q \, dx, \quad \forall K \in \mathcal{T}_{j,H}, \quad q \in \mathcal{Q}_j,$$

guarantees that $\Pi^H: \mathfrak{Q}_{\text{ad}} \rightarrow \mathfrak{Q}_{\text{ad}}^H$, i.e. for $\mathbf{q} \in \mathfrak{Q}_{\text{ad}}$, its piece-wise constant orthogonal projection $\Pi^H \mathbf{q} \in \mathfrak{Q}_{\text{ad}}^H$.

We also have

$$\int_{\Omega_j} (q - \Pi_j^H q)v \, dx \leq cH \|q - \Pi_j^H q\|_{\mathcal{Q}_j} \|v\|_{H^1(\Omega_j)}, \quad \forall v \in H^1(\Omega_j), \quad q \in \mathcal{Q}_j. \quad (7.5)$$

Recalling the definition (6.1), we obtain

$$\|\mathbf{U}^h(\mathbf{q} - \Pi^H \mathbf{q})\|_{\mathcal{G}} \leq cH \|\mathbf{q} - \Pi^H \mathbf{q}\|_{\mathfrak{Q}}, \quad \forall \mathbf{q} \in \mathfrak{Q}. \quad (7.6)$$

We now introduce a preparatory result.

LEMMA 7.3 There is a constant $c > 0$ independent of h and H such that

$$\|\mathbf{U}(\mathbf{q}) - \mathbf{U}^h(\Pi^H \mathbf{q})\|_{\mathcal{G}} \leq cH \|\mathbf{q} - \Pi^H \mathbf{q}\|_{\mathfrak{Q}} + ch \|\mathbf{q}\|_{\mathfrak{Q}}, \quad \forall \mathbf{q} \in \mathfrak{Q}. \quad (7.7)$$

Proof. We denote $e_{ij}(q) = u_{ij}(q) - u_{ij}^h(\Pi_j^H q)$. Using the definition (3.1) for $u_{ij}(q) \in V$ and (6.1) for $u_{ij}^h(q)$, we have

$$\begin{aligned} & \int_{\Omega} [D_i \nabla e_{ij}(q) \cdot \nabla v^h + \mu_{a,i} e_{ij}(q) v^h] dx + \int_{\Gamma} \frac{1}{2A} e_{ij}(q) v^h \, ds \\ &= \int_{\Omega_j} (q - \Pi_j^H q) v^h \, dx, \quad \forall v^h \in V^h. \end{aligned}$$

Then, for any $v^h \in V^h$,

$$\begin{aligned} & \int_{\Omega} [D_i |\nabla e_{ij}(q)|^2 + \mu_{a,i} |e_{ij}(q)|^2] dx + \int_{\Gamma} \frac{1}{2A} |e_{ij}(q)|^2 ds \\ &= \int_{\Omega} [D_i \nabla e_{ij}(q) \cdot \nabla (u_{ij}(q) - v^h) + \mu_{a,i} e_{ij}(q) (u_{ij}(q) - v^h)] dx \\ & \quad + \int_{\Gamma} \frac{1}{2A} e_{ij}(q) (u_{ij}(q) - v^h) ds + \int_{\Omega_j} (q - \Pi_j^H q) (v^h - u_{ij}^h(\Pi_j^H q)) dx. \end{aligned}$$

We bound $\|v^h - u_{ij}^h(\Pi_j^H q)\|_V$ by $\|v^h - u_{ij}(q)\|_V + \|e_{ij}(q)\|_V$. After some manipulations with the use of (7.5), we obtain

$$\|e_{ij}(q)\|_V \leq c \left[\inf_{v^h \in V^h} \|u_{ij}(q) - v^h\|_V + H \|q - \Pi_j^H q\|_{\mathcal{Q}_j} \right]. \quad (7.8)$$

Then, using the error bound

$$\inf_{v^h \in V^h} \|u_{ij}(q) - v^h\|_V \leq ch |u_{ij}(q)|_{H^2(\Omega)}$$

and the regularity bound (6.6) in (7.8), we obtain

$$\|u_{ij}(q) - u_{ij}^h(\Pi_j^H q)\|_V \leq cH \|q - \Pi_j^H q\|_{\mathcal{Q}_j} + ch \|q\|_{\mathcal{Q}_j}, \quad \forall q \in \mathcal{Q}_j.$$

So (7.7) holds. \square

The main result on error estimate is the following.

THEOREM 7.4 There is a constant $c > 0$ independent of h , H , ε and M such that

$$\begin{aligned} & \|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^{hH})\|_G + \varepsilon^{1/2} \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}\|_{\Omega} + M^{1/2} |\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH})|_{\Omega_I} \\ & \leq c \|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}\|_G^{1/2} (H^{1/2} \|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega}^{1/2} + h^{3/4} \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}\|_{\Omega}^{1/2}) \\ & \quad + c(H \|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega} + h \|\mathbf{p}_{\varepsilon M}\|_{\Omega}). \end{aligned} \quad (7.9)$$

Proof. We take $\mathbf{q}^H = \Pi^H \mathbf{p}_{\varepsilon M}$ in (7.1) to get

$$\begin{aligned} & (\mathbf{U}^h(\mathbf{p}_{\varepsilon M}^{hH}) - \mathbf{f}, \mathbf{U}^h(\Pi^H \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}))_G \\ & \quad + \varepsilon (\mathbf{p}_{\varepsilon M}^{hH}, \Pi^H \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH})_{\Omega} + M (\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}^{hH}), \boldsymbol{\ell}(\Pi^H \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}))_{\Omega_I} \geq 0. \end{aligned}$$

and take $\mathbf{q} = \mathbf{p}_{\varepsilon M}^{hH}$ in (3.4) to get

$$(\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, \mathbf{U}(\mathbf{p}_{\varepsilon M}^{hH} - \mathbf{p}_{\varepsilon M}))_G + \varepsilon (\mathbf{p}_{\varepsilon M}, \mathbf{p}_{\varepsilon M}^{hH} - \mathbf{p}_{\varepsilon M})_{\Omega} + M (\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}), \boldsymbol{\ell}(\mathbf{p}_{\varepsilon M}^{hH} - \mathbf{p}_{\varepsilon M}))_{\Omega_I} \geq 0.$$

Using these inequalities, we have

$$\begin{aligned} & \|\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^{hH})\|_G^2 + \varepsilon \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}\|_{\Omega}^2 + M |\boldsymbol{\ell}(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH})|_{\Omega_I}^2 \\ & \leq (\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{f}, \mathbf{U}(\mathbf{p}_{\varepsilon M}^{hH} - \mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^{hH} - \Pi^H \mathbf{p}_{\varepsilon M}))_G \\ & \quad + (\mathbf{U}(\mathbf{p}_{\varepsilon M}) - \mathbf{U}^h(\mathbf{p}_{\varepsilon M}^{hH}), \mathbf{U}^h(\Pi^H \mathbf{p}_{\varepsilon M}) - \mathbf{U}(\mathbf{p}_{\varepsilon M}))_G. \end{aligned}$$

Hence,

$$\begin{aligned} & \|U(\mathbf{p}_{\varepsilon M}) - U^h(\mathbf{p}_{\varepsilon M}^{hH})\|_G^2 + \varepsilon \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}\|_{\Omega}^2 + M |\ell(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH})|_{\Omega_l}^2 \\ & \leq c \|U(\mathbf{p}_{\varepsilon M}) - f\|_G [\|U(\mathbf{p}_{\varepsilon M}^{hH} - \mathbf{p}_{\varepsilon M}) - U^h(\mathbf{p}_{\varepsilon M}^{hH} - \mathbf{p}_{\varepsilon M})\|_G + \|U^h(\Pi^h \mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M})\|_G] \\ & \quad + c \|U^h(\Pi^H \mathbf{p}_{\varepsilon M}) - U(\mathbf{p}_{\varepsilon M})\|_G^2. \end{aligned}$$

Applying the error bound (6.8), (7.6) and (7.7), we can then deduce (7.9). \square

Similar to (6.10) and (6.11), we have the next two sample results as consequences of Theorem 7.4.

If $Q_{\text{ad},j} \subset Q_j$ are bounded, then there is a constant $c > 0$ independent of h, H, ε and M such that

$$\begin{aligned} & \|U(\mathbf{p}_{\varepsilon M}) - U^h(\mathbf{p}_{\varepsilon M}^{hH})\|_G + \varepsilon^{1/2} \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}\|_{\Omega} + M^{1/2} |\ell(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH})|_{\Omega_l} \\ & \leq c(H^{1/2} \|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega}^{1/2} + h^{3/4}). \end{aligned} \quad (7.10)$$

If the compatibility condition (5.5) holds, then there is a constant $c > 0$ independent of h, H, ε and M such that

$$\begin{aligned} & \|U(\mathbf{p}_{\varepsilon M}) - U^h(\mathbf{p}_{\varepsilon M}^{hH})\|_G + \varepsilon^{1/2} \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH}\|_{\Omega} + M^{1/2} |\ell(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{\varepsilon M}^{hH})|_{\Omega_l} \\ & \leq c(h + H^{1/2} \varepsilon^{1/4} \|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega}^{1/2} + H \|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega}). \end{aligned} \quad (7.11)$$

These error bounds involve the projection error $\|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega}$. This is usually a small quantity, as the next result shows.

PROPOSITION 7.5 If $\mathfrak{S}_{0M} \neq \emptyset$, then $\|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega} \rightarrow 0$ as $H, \varepsilon \rightarrow 0$. If $p_{\varepsilon M,ij} \in H^1(\Omega_j)$, then

$$\|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega} \leq cH \sum_{i,j} |p_{\varepsilon M,ij}|_{H^1(\Omega_j)}.$$

Proof. We write

$$\begin{aligned} \|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega} & \leq \|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M}\|_{\Omega} + \|\Pi^H(\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M})\|_{\Omega} + \|\mathbf{p}_{0M} - \Pi^H \mathbf{p}_{0M}\|_{\Omega} \\ & \leq 2\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M}\|_{\Omega} + \|\mathbf{p}_{0M} - \Pi^H \mathbf{p}_{0M}\|_{\Omega}. \end{aligned}$$

Since $\|\mathbf{p}_{\varepsilon M} - \mathbf{p}_{0M}\|_{\Omega} \rightarrow 0$ as $\varepsilon \rightarrow 0$, $\|\mathbf{p}_{\varepsilon M} - \Pi^H \mathbf{p}_{\varepsilon M}\|_{\Omega} \rightarrow 0$ as $H, \varepsilon \rightarrow 0$. The error bound follows from (7.4). \square

Remarks similar to those at the end of Section 6 are valid concerning error bounds and convergence when ε is related to h and H .

8. Concluding remark

Multispectral BLT represents a new development in optical imaging with profound potential in biomedical applications. This paper introduces a general mathematical framework for multispectral BLT and provides a thorough analysis for its properties. The formulation is based on Tikhonov regularization and penalization. Theoretical results are rigorously established for solution existence, uniqueness, continuous dependence on the data as well as limiting behaviours of the solution as the penalty parameter

goes to infinity and as the regularization parameter approaches zero. The multispectral BLT problem can be solved only numerically, and numerical methods are introduced and studied distinguishing two cases. In the first case, there is no need to discretize the admissible sets for the source functions. In the second case, the admissible sets need to be discretized for the source functions. For both cases, the numerical solution exists uniquely and depends continuously on the data. Error estimates are derived for the numerical solutions. All these results provide a solid foundation for further research on the multispectral BLT, such as efficient numerical simulations and comparison of the numerical results with experimental results.

Acknowledgements

This work is supported by a National Institutes of Health grant EB001685. The authors are grateful for discussions with Drs Yue Wang, Michael Henry, Jeffrey McKinney, Edward Meighen and Sanjiv Gambhir. The authors thank the two anonymous referees whose comments led to an improvement of the presentation of the paper.

REFERENCES

- ARRIDGE, S. R., SCHWEIGER, M., HIRAOKA, M. & DELPY, D. T. (1993) A finite element approach for modeling photon transport in tissue. *Med. Phys.*, **20**, 299–309.
- ATKINSON, K. & HAN, W. (2005) *Theoretical Numerical Analysis: A Functional Analysis Framework*, 2nd edn. Texts in Applied Mathematics, vol. 39. New York: Springer.
- BASSINGTHWAIGHTE, J. B. (2000) Strategies for the physiome project. *Ann. Biomed. Eng.*, **28**, 1043–1058.
- BRENNER, S. C. & SCOTT, L. R. (2002) *The Mathematical Theory of Finite Element Methods*, 2nd edn. New York: Springer.
- CIARLET, P. G. (1978) *The Finite Element Method for Elliptic Problems*. Amsterdam: North Holland.
- CONG, A. X. & WANG, G. (2006) Multispectral bioluminescence tomography: methodology and simulation. *Int. J. Biomed. Imaging*, **2006**, 1–7.
- CONG, W. X., WANG, G., KUMAR, D., LIU, Y., JIANG, M., WANG, L. H., HOFFMAN, E. A., MCLENNAN, G., MCCRAY, P. B., ZABNER, J. & CONG, A. (2005) A practical reconstruction method for bioluminescence tomography. *Opt. Express*, **13**, 6756–6771.
- CONTAG, C. H. & ROSS, B. D. (2002) It's not just about anatomy: *in vivo* bioluminescence imaging as an eyepiece into biology. *J. Magn. Reson. Imaging*, **16**, 378–387.
- CRAMPIN, E. J., HALSTEAD, M., HUNTER, P., NIELSON, P., NOBLE, D., SMITH, N. & TAWHAI, M. (2004) Computational physiology and the physiome project. *Exp. Physiol.*, **89**, 1–26.
- ENGL, H. W., HANKE, M. & NEUBAUER, A. (1996) *Regularization of Inverse Problems*. Dordrecht: Kluwer Academic Publishers.
- EVANS, L. C. (1998) *Partial Differential Equations*. Providence, RI: American Mathematical Society.
- GRISVARD, P. (1985) *Elliptic Problems in Nonsmooth Domains*. Boston, MA: Pitman.
- HAN, W., CONG, W. X. & WANG, G. (2006) Mathematical theory and numerical analysis of bioluminescence tomography. *Inverse Probl.*, **22**, 1659–1675.
- HAN, W., CONG, W. X. & WANG, G. Mathematical study and numerical simulation of multispectral bioluminescence tomography. *Int. J. Biomed. Imaging* (to appear).
- LIONS, J. L. (1971) *Optimal Control of Systems Governed by Partial Differential Equations*. Berlin: Springer.
- NIZIACHRISTOS, V., TUNG, C. H., BREMER, C. & WEISSELEDER, R. (2002) Fluorescence molecular tomography resolves protease activity *in vivo*. *Nat. Med.*, **8**, 757–761.
- NTZIACHRISTOS, V., RIPOLL, J., WANG, L. V. & WEISSELEDER, R. (2005) Looking and listening to light: the evolution of whole-body photonic imaging. *Nat. Biotechnol.*, **23**, 313–320.

- SCHWEIGER, M., ARRIDGE, S. R., HIRAOKA, M. & DELPY, D. T. (1995) The finite element method for the propagation of light in scattering media: boundary and source conditions. *Med. Phys.*, **22**, 1779–1792.
- WANG, G., HOFFMAN, E. A., MCLENNAN, G., WANG, L. V., SUTER, M. & MEINEL, J. F. (2003) Development of the first bioluminescent CT scanner. *Radiology*, **229**, 566.
- WANG, G., JASZCZAK, R. & BASILION, J. (2005) Towards molecular imaging. *IEEE Trans. Med. Imaging*, **24**, 829–831.
- WANG, G., LI, Y. & JIANG, M. (2004) Uniqueness theorems in bioluminescence tomography. *Med. Phys.*, **31**, 2289–2299.
- WEISSLEDER, R. & MAHMOOD, U. (2001) Molecular imaging. *Radiology*, **219**, 316–333.
- WEISSLEDER, R. & NTZIACHRISTOS, V. (2003) Shedding light onto live molecular targets. *Nat. Med.*, **9**, 123–128.
- TIKHONOV, A. N. (1963) Regularization of incorrectly posed problems. *Sov. Dokl.*, **4**, 1624–1627.
- ZERHOUNI, E. (2003) Medicine, the NIH roadmap. *Science*, **302**, 63–72.
- ZHAO, H., DOYLE, T. C., COQUOZ, O., KALISH, F., RICE, B. W. & CONTAG, C. H. (2005) Emission spectra of bioluminescent reporters and interaction with mammalian tissue determine the sensitivity of detection *in vivo*. *J. Biomed. Opt.*, **10**, 041210/1–041210/9.