Generalized Adjoint Sensitivities of the Coupled Frequency Domain Fluorescence Diffusion Equations

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Abstract: The adjoint sensitivity method is applied to the coupled partial differential equations approximating complex fluence in fluorescing system. General equations are derived for Jacobian sensitivity matrices of complex fluence, at both excitation and emission wavelengths, with respect to arbitrary optical parameters. Finite element implementations of these equations are found to be computationally efficient and accurate.

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1. Introduction

Fluorescence image reconstruction techniques may require computation of a Jacobian sensitivity matrix [1], relating changes in observable quantities (such as phase and/or amplitude at excitation and/or emission wavelengths, possibly referenced or otherwise transformed) to changes in underlying optical properties (such as absorption, scattering, and/or fluorescence lifetime or some transformation of these parameters). These Jacobian matrices can be easily approximated using first [1] (or second [2]) order finite differences, but when the number of parameters is large these methods are computationally expensive, as the forward solution must be achieved once (or twice) for each unknown parameter. Lee and Sevick-Muraca [3] describe a computationally efficient method for computing the Jacobian of the (log of referenced) emission measurements relative to absorption due to fluorophore, using a Green's function approach and assuming no discontinuity in diffusion at the emission wavelength. The equations we derive here using the adjoint method [4,5] follow a similar approach, but are more general in that they can be used for any combination of measurement type and parameter type and they impose no assumptions on the continuity of the diffusion field.

2. Governing equations

The propagation of excitation (subscript x) and fluorescently generated emission (subscript m) light through highly scattering tissues can be modeled by the diffusion approximation to the radiative transport equations. In the frequency domain, the coupled elliptic equations describing complex excitation photon fluence (Φ_x) and emission photon fluence (Φ_m) throughout a 3-D domain (Ω) with Robin boundary conditions at the surface ($\partial\Omega$) can be represented compactly in matrix notation as:

$$\begin{cases} -\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\underline{\mathbf{\Phi}}}\right)+\underline{\underline{\mathbf{k}}}\,\underline{\underline{\mathbf{\Phi}}}=\underline{\underline{\mathbf{S}}} \quad \text{on} \quad \Omega \\ \\ \underline{\underline{\mathbf{D}}}\,\dfrac{\partial\underline{\underline{\mathbf{\Phi}}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\underline{\mathbf{\Phi}}}=\underline{\underline{0}} \quad \text{on} \quad \partial\Omega \end{cases} \tag{1}$$

where

$$\underline{\underline{\nabla}}\equiv\begin{bmatrix}\nabla & \underline{\underline{0}}\\ \underline{\underline{0}} & \nabla\end{bmatrix};\quad \underline{\underline{\mathbf{d}}}\equiv\begin{bmatrix}D_x\underline{\underline{\mathbf{I}}} & \underline{\underline{\mathbf{0}}}\\ \underline{\underline{\mathbf{0}}} & D_m\underline{\underline{\mathbf{I}}}\end{bmatrix};\ \underline{\underline{\mathbf{D}}}\equiv\begin{bmatrix}D_x & 0\\ 0 & D_m\end{bmatrix};\ \underline{\underline{\mathbf{\Phi}}}\equiv\begin{bmatrix}\Phi_x\\ \Phi_m\end{bmatrix};\quad \underline{\underline{\mathbf{k}}}\equiv\begin{bmatrix}k_x & 0\\ -\beta & k_m\end{bmatrix};\quad \underline{\underline{\mathbf{r}}}\equiv\begin{bmatrix}r_x & 0\\ 0 & r_m\end{bmatrix};\quad \underline{\underline{\mathbf{S}}}\equiv\begin{bmatrix}S_x\\ 0\end{bmatrix}. \tag{2}$$

and t is the transpose operator, $\nabla=[\partial/\partial x\ \ \partial/\partial y\ \ \partial/\partial z]^t$, $\underline{\underline{\mathbf{I}}}$ is the 3x3 identity matrix, $D_{x,m} = 1/(3[\mu_{a[x,m]i} +\mu_{a[x,m]f}+\mu'_{s[x,m]}])$, $k_{x,m}=i\omega/c+\mu_{a[x,m]i} +\mu_{a[x,m]f}$, $\beta = \phi\mu_{axf}\ (1\text{-}i\omega\tau)/(1+(\omega\tau)^2)$, $\mu_{a[x,m]i}$ is the absorption due to non-fluorescing chromophore (cm^{-1}), $\mu_{a[x,m]f}$ is the absorption due to fluorophore (cm^{-1}), $\mu'_{s[x,m]}$ is the isotropic scattering coefficient (cm^{-1}), ω is the modulation frequency (radians/s), c is the speed of light in the medium (cm/s), τ is the

fluorescence lifetime (s^{-1}), ϕ is the quantum efficiency, S_x is the excitation source term (W/cm^3), n is the direction normal to the surface, $r_{x,m}$ =(1-$R_{x,m}$)/(2+2$R_{x,m}$), and $R_{x,m}$ are the effective reflection coefficients. Absorption, scattering, lifetime, and quantum efficiency may all be position dependent.

3. Adjoint Sensitivities

Suppose we are interested in seeing how the fluence $\underline{\Phi}$ varies as some arbitrary parameter p varies (e.g., p may be a localized value of absorption, scattering, lifetime, reflection coefficient, etc.). If we perturb p by a small amount δp, it will introduce a variation $\underline{\delta\Phi}$ in the fluence. The perturbed equations, neglecting higher order terms and assuming that the excitation source term S_x is independent of the parameter p, are:

$$\begin{cases} -\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\delta\boldsymbol{\Phi}}\right)-\underline{\underline{\nabla}}^t\left(\dfrac{\partial\underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\boldsymbol{\Phi}}\right)+\underline{\underline{\mathbf{k}}}\,\underline{\delta\boldsymbol{\Phi}}+\dfrac{\partial\underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}=\underline{0} \quad \text{on } \Omega \\ \underline{\underline{\mathbf{D}}}\dfrac{\partial\underline{\delta\boldsymbol{\Phi}}}{\partial n}+\dfrac{\partial\underline{\underline{\mathbf{D}}}}{\partial p}\delta p\dfrac{\partial\underline{\boldsymbol{\Phi}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\delta\boldsymbol{\Phi}}+\dfrac{\partial\underline{\underline{\mathbf{r}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}=\underline{0} \quad \text{on } \partial\Omega \end{cases} \tag{3a,b}$$

We multiply equation (3.a) by the transpose of an arbitrary tensor $\underline{\underline{\boldsymbol{\Psi}}}$, integrate over the domain, rearrange terms, and apply Green's Theorem along with the boundary conditions (3.b) to yield:

$$\begin{aligned} \int_\Omega\left(-\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\underline{\boldsymbol{\Psi}}}\right)+\underline{\underline{\mathbf{k}}}^t\,\underline{\underline{\boldsymbol{\Psi}}}\right)^t\underline{\delta\boldsymbol{\Phi}}\,d\Omega &= \int_\Omega\underline{\underline{\boldsymbol{\Psi}}}^t\left(\underline{\underline{\nabla}}^t\left(\dfrac{\partial\underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\boldsymbol{\Phi}}\right)-\dfrac{\partial\underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}\right)d\Omega \\ &+\int_{\partial\Omega}\underline{\underline{\boldsymbol{\Psi}}}^t\left(-\dfrac{\partial\underline{\underline{\mathbf{D}}}}{\partial p}\delta p\dfrac{\partial\underline{\boldsymbol{\Phi}}}{\partial n}-\dfrac{\partial\underline{\underline{\mathbf{r}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}\right)dS+\int_{\partial\Omega}\left(\underline{\underline{\mathbf{D}}}\dfrac{\partial\underline{\underline{\boldsymbol{\Psi}}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\underline{\boldsymbol{\Psi}}}\right)^t\underline{\delta\boldsymbol{\Phi}}\;dS \end{aligned} \tag{4}$$

We choose the tensor $\underline{\underline{\boldsymbol{\Psi}}}$ such that

$$\underline{\underline{\boldsymbol{\Psi}}}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right)=\begin{bmatrix}\boldsymbol{\Psi}_{xx}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right) & \boldsymbol{\Psi}_{xm}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right)\\ \boldsymbol{\Psi}_{mx}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right) & \boldsymbol{\Psi}_{mm}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right)\end{bmatrix} \tag{5}$$

and

$$\begin{cases} -\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\underline{\boldsymbol{\Psi}}}\right)+\underline{\underline{\mathbf{k}}}^t\,\underline{\underline{\boldsymbol{\Psi}}}=\underline{\underline{\boldsymbol{\delta}}}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right) \text{ on } \Omega \\ \underline{\underline{\mathbf{D}}}\dfrac{\partial\underline{\underline{\boldsymbol{\Psi}}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\underline{\boldsymbol{\Psi}}}=0 \text{ on } \partial\Omega. \end{cases} \tag{6}$$

where

$$\underline{\underline{\boldsymbol{\delta}}}\left(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}}\right)=\begin{bmatrix}\boldsymbol{\delta}\left(\underline{\mathbf{x}}-\underline{\mathbf{x}}_{\text{det}}\right) & 0\\ 0 & \boldsymbol{\delta}\left(\underline{\mathbf{x}}-\underline{\mathbf{x}}_{\text{det}}\right)\end{bmatrix} \tag{7}$$

is the Dirac impulse tensor, $\underline{\mathbf{x}}=(x,y,z)$ is a generic point in the domain, and $\underline{\mathbf{x}}_{\text{det}}=(x_{\text{det}},y_{\text{det}},z_{\text{det}})$ is the location of a detector on the surface of the domain. Thus, $\underline{\underline{\boldsymbol{\Psi}}}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}})$ is a Green tensor representing the adjoint field variable at all locations in the domain in response to a Dirac impulse at the location of the detector. Substituting equation (6) into equation (4) yields the variation in the fluence in response to a change in the parameter p, as follows:

$$\underline{\delta\boldsymbol{\Phi}}(\underline{\mathbf{x}}_{\text{det}})=\int_\Omega\underline{\underline{\boldsymbol{\Psi}}}^t(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}})\left(\underline{\underline{\nabla}}^t\left(\dfrac{\partial\underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\boldsymbol{\Phi}}\right)-\dfrac{\partial\underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}\right)d\Omega+\int_{\partial\Omega}\underline{\underline{\boldsymbol{\Psi}}}^t(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}})\left(-\dfrac{\partial\underline{\underline{\mathbf{D}}}}{\partial p}\delta p\dfrac{\partial\underline{\boldsymbol{\Phi}}}{\partial n}-\dfrac{\partial\underline{\underline{\mathbf{r}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}\right)dS \tag{8}$$

By solving equations (6) once for the Green tensor $\underline{\underline{\boldsymbol{\Psi}}}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\text{det}})$ we are able to solve for the sensitivities of fluence at the detectors caused by a perturbation in the parameter p by evaluating the integral formula (8), regardless of which parameter p is being perturbed.

4. Finite Element Formulation

Suppose that we have discretized equations (1) over the domain into finite elements with linear basis functions $\underline{\boldsymbol{\varphi}} = [\phi_1, \phi_2, ..., \phi_N]$, where

$$\underline{\underline{\mathbf{K}}}(\rho) = \int_{\Omega} (\nabla \underline{\boldsymbol{\varphi}})^t \rho \nabla \underline{\boldsymbol{\varphi}} d\Omega, \quad \underline{\underline{\mathbf{M}}}(\rho) = \int_{\Omega} \underline{\boldsymbol{\varphi}}^t \rho \underline{\boldsymbol{\varphi}} d\Omega, \quad \underline{\underline{\mathbf{B}}}(\rho) = \int_{\partial\Omega} \underline{\boldsymbol{\varphi}}^t \rho \underline{\boldsymbol{\varphi}} dS \tag{9}$$

are functions that create the finite element stiffness, mass, and boundary matrices, respectively, given an arbitrary field parameter ρ. Then it can be shown that the finite element solution equations for the fluence and adjoint field variables are:

$$\begin{cases} \left[\underline{\underline{\mathbf{K}}}(D_m) + \underline{\underline{\mathbf{M}}}(k_m) + \underline{\underline{\mathbf{B}}}(r_m)\right]\left[\underline{\boldsymbol{\Psi}}_{mm}\right] = \left[\underline{\boldsymbol{\delta}}_{\det}\right] \\ \left[\underline{\underline{\mathbf{K}}}(D_x) + \underline{\underline{\mathbf{M}}}(k_x) + \underline{\underline{\mathbf{B}}}(r_x)\right]\left[\underline{\boldsymbol{\Phi}}_x, \underline{\boldsymbol{\Psi}}_{xx}, \underline{\boldsymbol{\Psi}}_{xm}\right] = \left[\underline{S}_x, \underline{\boldsymbol{\delta}}_{\det}, \underline{\underline{\mathbf{M}}}(\beta)\underline{\boldsymbol{\Psi}}_{mm}\right] \\ \left[\underline{\underline{\mathbf{K}}}(D_m) + \underline{\underline{\mathbf{M}}}(k_m) + \underline{\underline{\mathbf{B}}}(r_m)\right]\left[\underline{\boldsymbol{\Phi}}_m, \underline{\boldsymbol{\Psi}}_{mx}\right] = \left[\underline{\underline{\mathbf{M}}}(\beta)\underline{\boldsymbol{\Phi}}_x, \underline{0}\right] \end{cases} \tag{10}$$

Here, $\underline{\boldsymbol{\delta}}_{\det}$ is the discrete Dirac delta; i.e., it is a column vector of all zeros except for a 1 in position *det* where a detector is located (or a matrix of such columns for multiple detectors). Note that $\underline{\boldsymbol{\Psi}}_{mx}$ will be zero by this formulation, so that it may be omitted from the computations. The finite element implementation of the variational equation (8) can be used to compute the Jacobian as follows:

$$\begin{cases} \dfrac{\partial \boldsymbol{\Phi}_x}{\partial p} \approx -\underline{\boldsymbol{\Psi}}_{xx}^t \left[\underline{\underline{\mathbf{K}}}\left(\dfrac{\partial D_x}{\partial p}\right) + \underline{\underline{\mathbf{M}}}\left(\dfrac{\partial k_x}{\partial p}\right) + \underline{\underline{\mathbf{B}}}\left(\dfrac{\partial r_x}{\partial p}\right)\right]\underline{\boldsymbol{\Phi}}_x \\ \dfrac{\partial \boldsymbol{\Phi}_m}{\partial p} \approx -\underline{\boldsymbol{\Psi}}_{xm}^t \left[\underline{\underline{\mathbf{K}}}\left(\dfrac{\partial D_x}{\partial p}\right) + \underline{\underline{\mathbf{M}}}\left(\dfrac{\partial k_x}{\partial p}\right) + \underline{\underline{\mathbf{B}}}\left(\dfrac{\partial r_x}{\partial p}\right)\right]\underline{\boldsymbol{\Phi}}_x - \underline{\boldsymbol{\Psi}}_{mm}^t \left[\underline{\underline{\mathbf{K}}}\left(\dfrac{\partial D_m}{\partial p}\right) + \underline{\underline{\mathbf{M}}}\left(\dfrac{\partial k_m}{\partial p}\right) + \underline{\underline{\mathbf{B}}}\left(\dfrac{\partial r_m}{\partial p}\right)\right]\boldsymbol{\Phi}_m + \underline{\boldsymbol{\Psi}}_{mm}^t \underline{\underline{\mathbf{M}}}\left(\dfrac{\partial \beta}{\partial p}\right)\underline{\boldsymbol{\Phi}}_x \end{cases} \tag{11}$$

The computational results of equations (11) were computed for fully distributed $p \in \{\mu_{axi}, \mu_{axf}, \mu'_{sf}, \tau, \phi\}$; in all cases the results were identical to those produced by a second order finite difference approximation of the Jacobian.

5. Conclusions

We have derived the continuous adjoint sensitivity equations for the coupled frequency domain fluorescence diffusion equations and discretized them using a finite element approach. Although not shown here, the same results are obtained if one derives the discrete adjoint sensitivity equations directly from the finite element formulation of the governing equations. The adjoint variables can be solved for once, using the same system that is used to solve for the fluence itself, and then used to compute the Jacobian sensitivity matrix of the complex fluence with respect to any of a number of optical parameters fundamental to the governing equations. With careful implementation on the computer, the computations for computing the Jacobian can be vectorized such that the largest loop is the number of the detectors, regardless of whether parameters are discretized by nodes or elements. When the number of detectors is much less than the number of parameters, the adjoint method can be orders of magnitude faster than, although just as accurate as, a finite difference method for computing the Jacobian. This computationally efficient and accurate method for computing the Jacobian can be exploited in fluorescence tomography algorithms such as [1] that would otherwise not be feasible on large 3-D domains.

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