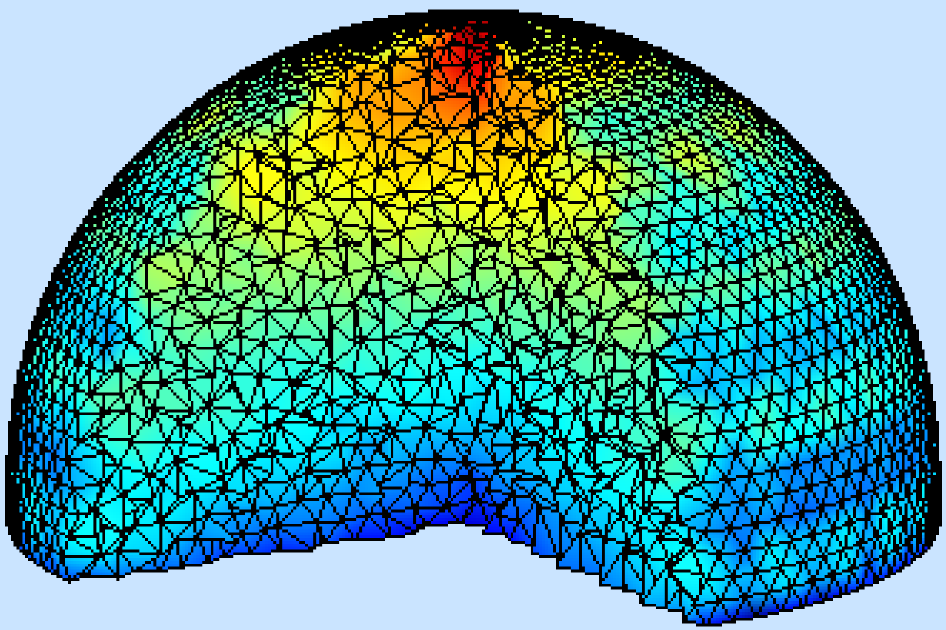
Generalized Adjoint Sensitivities of the Coupled Frequency Domain Fluorescence Diffusion Equations



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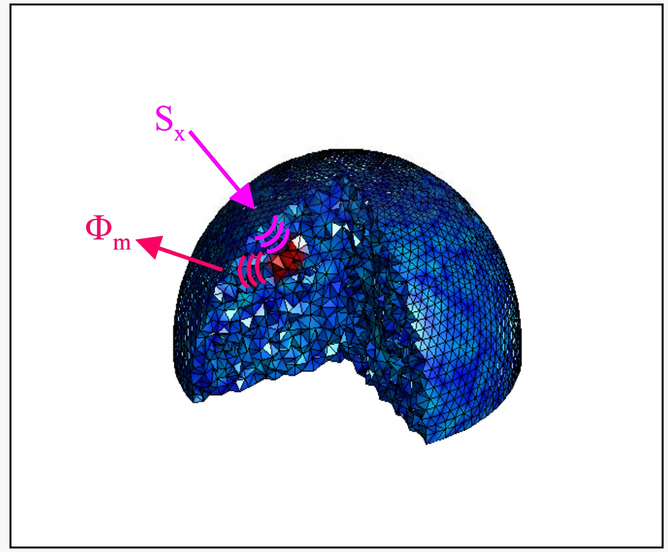
GOVERNING EQUATIONS

matrix formulation of coupled complex equations

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



$$\underline{\underline{\nabla}}\equiv\begin{bmatrix}\nabla & \underline{0}\\ \underline{0} & \nabla\end{bmatrix};\quad \underline{\underline{\mathbf{d}}}\equiv\begin{bmatrix}D_x\underline{\underline{\mathbf{I}}} & \underline{\underline{\mathbf{0}}}\\ \underline{\underline{\mathbf{0}}} & D_m\underline{\underline{\mathbf{I}}}\end{bmatrix};\ \underline{\underline{\mathbf{D}}}\equiv\begin{bmatrix}D_x & 0\\ 0 & D_m\end{bmatrix};\quad \underline{\underline{\mathbf{k}}}\equiv\begin{bmatrix}k_x & 0\\ -\beta & k_m\end{bmatrix};\quad \underline{\underline{\mathbf{r}}}\equiv\begin{bmatrix}r_x & 0\\ 0 & r_m\end{bmatrix};$$

$$\underline{\mathbf{\Phi}}\equiv\begin{bmatrix}\Phi_x\\ \Phi_m\end{bmatrix};\quad \underline{\mathbf{S}}\equiv\begin{bmatrix}S_x\\ 0\end{bmatrix}.$$

$$D_x=\frac{1}{3\left(\mu_{axi}+\mu_{axf}+\mu_{sx}\right)}\qquad D_m=\frac{1}{3\left(\mu_{ami}+\mu_{amf}+\mu_{sm}\right)}$$

$$k_x=\frac{i\omega}{c_x}+\mu_{axi}+\mu_{axf}\qquad k_m=\frac{i\omega}{c_m}+\mu_{ami}+\mu_{amf}\qquad \beta=\phi\frac{1-i\omega\tau}{1+(\omega\tau)^2}\mu_{axf}$$

THE FINITE DIFFERENCE APPROACH

$$\boxed{\frac{\delta \underline{\Phi}(\underline{x}_{\det})}{\delta p} \cong \frac{\underline{\Phi}(\underline{x}_{\det}, p+\delta p) - \underline{\Phi}(\underline{x}_{\det}, p)}{\delta p}}$$

$$\underline{\Phi}(\underline{x}, p+\delta p) \quad satisfy \begin{cases} -\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\Phi}\right) + \underline{\underline{\mathbf{k}}}\,\underline{\Phi} = \underline{\mathbf{S}} \;\; \textbf{on} \quad \Omega \\ \\ \underline{\underline{\mathbf{D}}}\dfrac{\partial \underline{\Phi}}{\partial n} + \underline{\underline{\mathbf{r}}}\,\underline{\Phi} = \underline{0} \quad \textbf{on} \quad \partial\Omega \end{cases} \qquad for \;\; p+\delta p$$

We need to solve the coupled PDEs for each node in the domain,

in order to evaluate $\dfrac{\delta \Phi}{\delta p}$ for all detectors at all nodes.

Computationally impractical for large domains !!!!

Others have applied a Green's function approach to the complex emission light fluence equation

- *Neglect effects on Φ_m of perturbing optical parameters in excitation equation*

$$-\nabla \bullet \left(D_x \nabla \Phi_x\right) + k_x \Phi_x = S_x$$

$$-\nabla \bullet \left(D_m \nabla \Phi_m\right) + k_m \Phi_m = \phi \frac{\mu_{axf}}{(1 - i\omega\tau)} \Phi_x = S_m$$

- *Assumption D_m smooth*

$$-\nabla^2 \Phi_m + \frac{k_m}{D_m}\Phi_m = \frac{S_m}{D_m} + \cancelto{0}{\frac{\nabla D_m \cdot \nabla \Phi_m}{D_m}}$$

- *Solve by Green's function*

$$\Phi_m \cong \int_\Omega G_m \frac{S_m}{D_m} d\Omega$$

$$-\nabla^2 G_m + \frac{k_m}{D_m} G_m = \delta(\underline{x}; \underline{x}_{\det})$$

- *Get Sensitivity*

$$\boxed{\delta\Phi_m = \int_\Omega G_m \frac{\partial}{\partial p}\left(\frac{S_m}{D_m}\right)\delta p \, d\Omega}$$

COMPLETE PERTURBATION EQUATIONS

Perturbation parameter

$$p \to p + \delta p \quad \Rightarrow \quad \underline{\mathbf{\Phi}} \to \underline{\mathbf{\Phi}} + \underline{\delta\mathbf{\Phi}}$$

Perturbation equations

Matrix notation of coupled equations

$$-\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\delta\mathbf{\Phi}}\right) + \underline{\underline{\mathbf{k}}}\,\underline{\delta\mathbf{\Phi}} = \underline{\underline{\nabla}}^t\left(\frac{\partial \underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\mathbf{\Phi}}\right) - \frac{\partial \underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\underline{\mathbf{\Phi}}} \quad \text{on } \Omega$$

$$\underline{\underline{\mathbf{D}}}\frac{\partial \underline{\delta\mathbf{\Phi}}}{\partial n} + \underline{\underline{\mathbf{r}}}\,\underline{\delta\mathbf{\Phi}} = -\left(\frac{\partial \underline{\underline{\mathbf{D}}}}{\partial p}\delta p\frac{\partial \underline{\mathbf{\Phi}}}{\partial n} + \frac{\partial \underline{\underline{\mathbf{r}}}}{\partial p}\delta p\,\underline{\mathbf{\Phi}}\right) \quad \text{on } \partial\Omega$$

We are interested in $\underline{\delta\mathbf{\Phi}}$ At the detectors

ADJOINT EQUATIONS

Multiply by an arbitrary matrix $\underline{\underline{\Psi}}^{t}$

$$\int_{\Omega} \underline{\underline{\Psi}}^{t}\left(-\underline{\underline{\nabla}}^{t}\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\delta\boldsymbol{\Phi}}\right)+\underline{\underline{\mathbf{k}}}\,\underline{\delta\boldsymbol{\Phi}}\right)d\Omega=\int_{\Omega} \underline{\underline{\Psi}}^{t}\left(\underline{\underline{\nabla}}^{t}\left(\frac{\partial\underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\boldsymbol{\Phi}}\right)-\frac{\partial\underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\underline{\boldsymbol{\Phi}}}\right)d\Omega$$

Integration by parts twice & applying boundary conditions

$$\int_{\Omega}\left(-\underline{\underline{\nabla}}^{t}\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\underline{\Psi}}\right)+\underline{\underline{\mathbf{k}}}^{t}\,\underline{\underline{\Psi}}\right)^{t}\underline{\delta\boldsymbol{\Phi}}\,d\Omega=\int_{\Omega} \underline{\underline{\Psi}}^{t}\left(\underline{\underline{\nabla}}^{t}\left(\frac{\partial\underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\boldsymbol{\Phi}}\right)-\frac{\partial\underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}\right)d\Omega$$

$$+\int_{\partial\Omega} \underline{\underline{\Psi}}^{t}\left(-\frac{\partial\underline{\underline{\mathbf{D}}}}{\partial p}\delta p\,\frac{\partial\underline{\boldsymbol{\Phi}}}{\partial n}-\frac{\partial\underline{\underline{\mathbf{r}}}}{\partial p}\delta p\,\underline{\boldsymbol{\Phi}}\right)dS+\int_{\partial\Omega}\left(\underline{\underline{\mathbf{D}}}\,\frac{\partial\underline{\underline{\Psi}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\underline{\Psi}}\right)^{t}\underline{\delta\boldsymbol{\Phi}}\;dS$$

THE GREEN MATRIX

Choose $\underline{\underline{\Psi}}$ to be the ***"Green matrix"*** for the detector locations $\underline{\mathbf{x}}_{\det}$

$$\underline{\underline{\Psi}}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det})=\begin{bmatrix}\mathbf{\Psi}_{xx}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det}) & \mathbf{\Psi}_{xm}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det})\\ \cancelto{\mathbf{0}}{\mathbf{\Psi}_{mx}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det})} & \mathbf{\Psi}_{mm}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det})\end{bmatrix} \Rightarrow \begin{cases}-\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\underline{\Psi}}\right)+\underline{\underline{\mathbf{k}}}^t\,\underline{\underline{\Psi}}=\underline{\underline{\boldsymbol{\delta}}}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det})\ \text{ on }\ \Omega\\[2ex] \underline{\underline{\mathbf{D}}}\dfrac{\partial\underline{\underline{\Psi}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\underline{\Psi}}=0\ \text{ on }\ \partial\Omega.\end{cases}$$

by substitution

$$\int_\Omega \underbrace{\boxed{\left(-\underline{\underline{\nabla}}^t\left(\underline{\underline{\mathbf{d}}}\,\underline{\underline{\nabla}}\,\underline{\underline{\Psi}}\right)+\underline{\underline{\mathbf{k}}}^t\,\underline{\underline{\Psi}}\right)^t}}_{\boxed{\underline{\underline{\boldsymbol{\delta}}}(\underline{\mathbf{x}};\underline{\mathbf{x}}_{\det})}}\underline{\delta\mathbf{\Phi}}\,d\Omega=\int_\Omega\underline{\underline{\Psi}}^t\left(\underline{\underline{\nabla}}^t\left(\frac{\partial\underline{\underline{\mathbf{d}}}}{\partial p}\delta p\,\underline{\underline{\nabla}}\,\underline{\mathbf{\Phi}}\right)-\frac{\partial\underline{\underline{\mathbf{k}}}}{\partial p}\delta p\,\underline{\mathbf{\Phi}}\right)d\Omega$$

$$+\int_{\partial\Omega}\underline{\underline{\Psi}}^t\left(-\frac{\partial\underline{\underline{\mathbf{D}}}}{\partial p}\delta p\frac{\partial\underline{\mathbf{\Phi}}}{\partial n}-\frac{\partial\underline{\underline{\mathbf{r}}}}{\partial p}\delta p\,\underline{\mathbf{\Phi}}\right)dS+\int_{\partial\Omega}\overbrace{\boxed{\left(\underline{\underline{\mathbf{D}}}\frac{\partial\underline{\underline{\Psi}}}{\partial n}+\underline{\underline{\mathbf{r}}}\,\underline{\underline{\Psi}}\right)^t}}^{\boxed{\underline{\mathbf{0}}}}\underline{\delta\mathbf{\Phi}}\,dS$$

resulting in

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

FEM ADJOINT SENSITIVITY EQUATIONS
continuous formulation*

Solve for forward and adjoint field variables by three step processes

FE matrices

$$\underline{\varphi} = [\phi_1, \phi_2, \ldots, \phi_N]$$

$$\underline{\underline{\mathbf{K}}}(\rho) = \int_\Omega (\nabla \underline{\varphi})^t \rho \nabla \underline{\varphi} d\Omega$$

$$\underline{\underline{\mathbf{M}}}(\rho) = \int_\Omega \underline{\varphi}^t \rho \underline{\varphi} d\Omega$$

$$\underline{\underline{\mathbf{B}}}(\rho) = \int_{\partial\Omega} \underline{\varphi}^t \rho \underline{\varphi} dS$$

$$\left[\underline{\underline{\mathbf{K}}}(D_m) + \underline{\underline{\mathbf{M}}}(k_m) + \underline{\underline{\mathbf{B}}}(r_m)\right]\left[\underline{\mathbf{\Psi}}_{mm}\right] = \left[\underline{\boldsymbol{\delta}}_{\det}\right]$$

$$\left[\underline{\underline{\mathbf{K}}}(D_x) + \underline{\underline{\mathbf{M}}}(k_x) + \underline{\underline{\mathbf{B}}}(r_x)\right]\left[\underline{\mathbf{\Phi}}_x, \underline{\mathbf{\Psi}}_{xx}, \underline{\mathbf{\Psi}}_{xm}\right] = \left[\underline{S}_x, \underline{\boldsymbol{\delta}}_{\det}, \underline{\underline{\mathbf{M}}}(\beta)\underline{\mathbf{\Psi}}_{mm}\right]$$

$$\left[\underline{\underline{\mathbf{K}}}(D_m) + \underline{\underline{\mathbf{M}}}(k_m) + \underline{\underline{\mathbf{B}}}(r_m)\right]\left[\underline{\mathbf{\Phi}}_m\right] = \left[\underline{\underline{\mathbf{M}}}(\beta)\underline{\mathbf{\Phi}}_x\right]$$

Now compute all sensitivities of choice by simple integration:

$$\frac{\partial \mathbf{\Phi}_x}{\partial p} \approx -\underline{\mathbf{\Psi}}_{xx}^t \left[\underline{\underline{\mathbf{K}}}\left(\frac{\partial D_x}{\partial p}\right) + \underline{\underline{\mathbf{M}}}\left(\frac{\partial k_x}{\partial p}\right) + \underline{\underline{\mathbf{B}}}\left(\frac{\partial r_x}{\partial p}\right)\right]\underline{\mathbf{\Phi}}_x$$

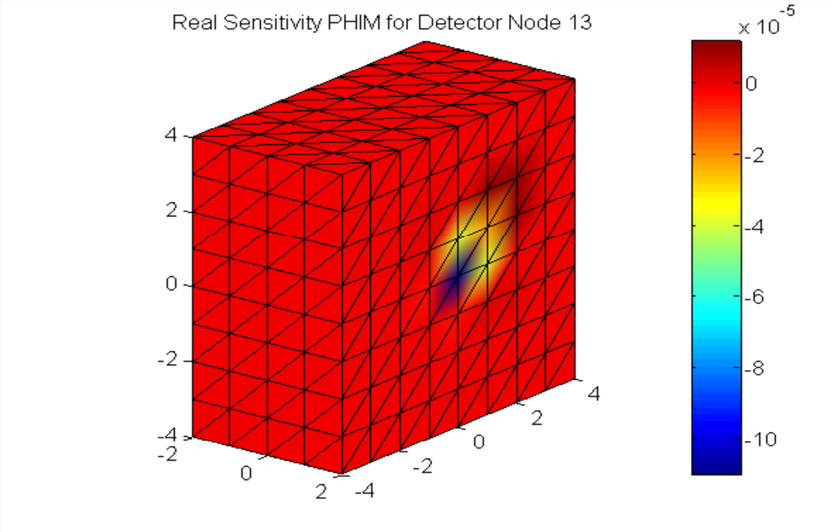
$$\frac{\partial \mathbf{\Phi}_m}{\partial p} \approx -\underline{\mathbf{\Psi}}_{xm}^t \left[\underline{\underline{\mathbf{K}}}\left(\frac{\partial D_x}{\partial p}\right) + \underline{\underline{\mathbf{M}}}\left(\frac{\partial k_x}{\partial p}\right) + \underline{\underline{\mathbf{B}}}\left(\frac{\partial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

$$p \in \left\{\mu_{axf}(i), \mu_{axi}(i), \mu_{amf}(i), \mu_{ami}(i), \mu_{sx}^{'}(i), \mu_{sm}^{'}(i), \tau(i), \phi(i), r_x(i), r_m(i)\right\}, \quad \forall i = 1..\#nodes$$

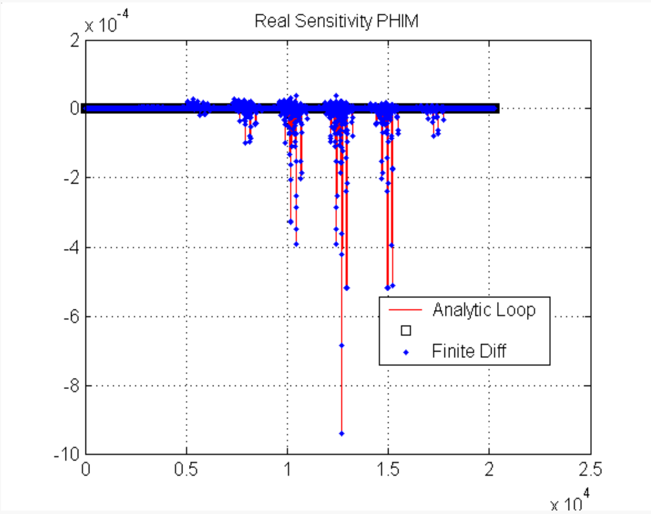
*Coincident with the direct adjoint formulation of the FEM discretized coupled equations

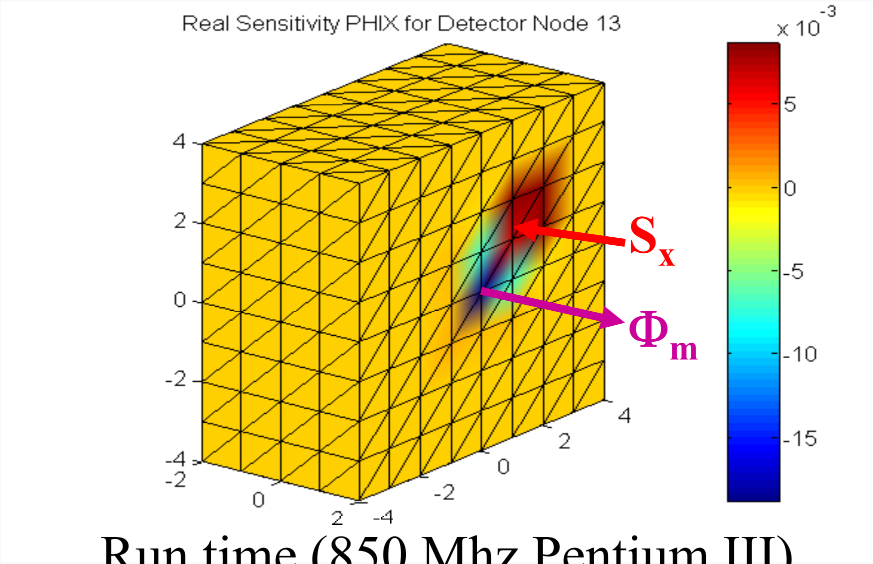
Sample Results: small homogeneous domain

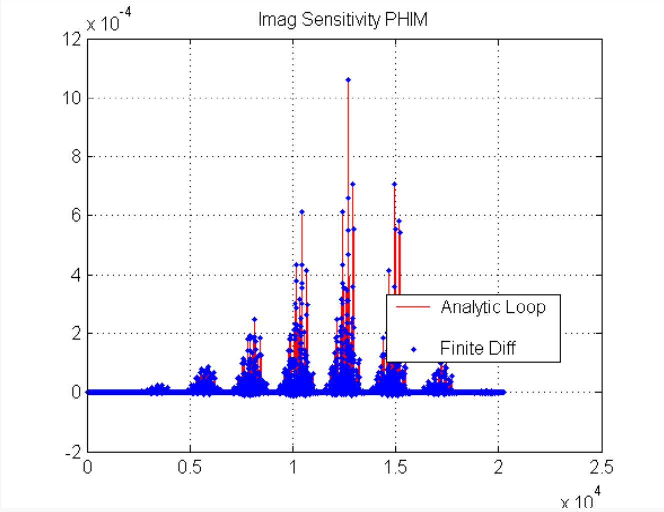
(405 nodes, 1536 elements, 1 source, 50 detectors)



$$\frac{\partial \Phi_m}{\partial \mu_{axf}}$$





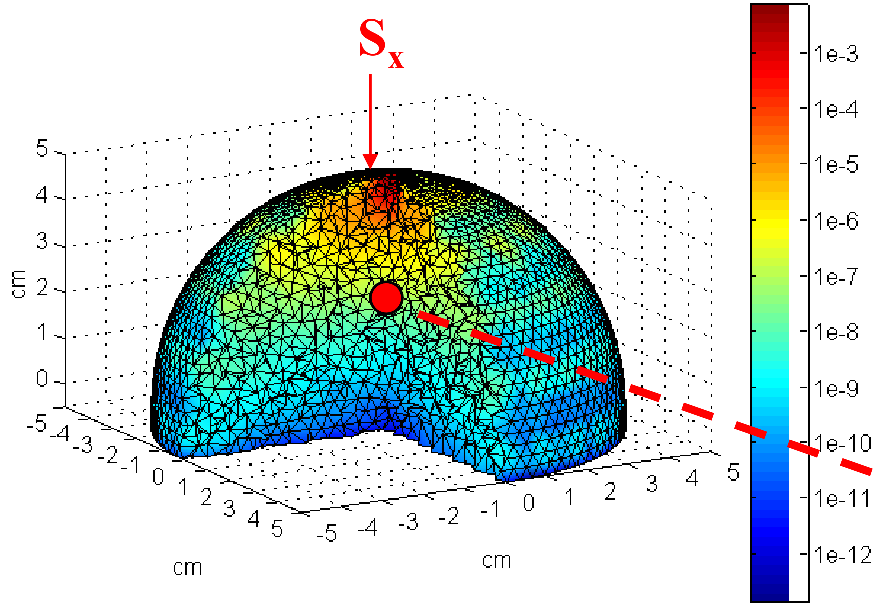


Run time (850 Mhz Pentium III)
Adjoint 0.23 min
FD 4.07 min

Adjoint and FD results were identical.

Sample Results: large (breast-shaped) homogeneous domain

(12657 nodes, 65509 elements, 1 source, 129 detectors)

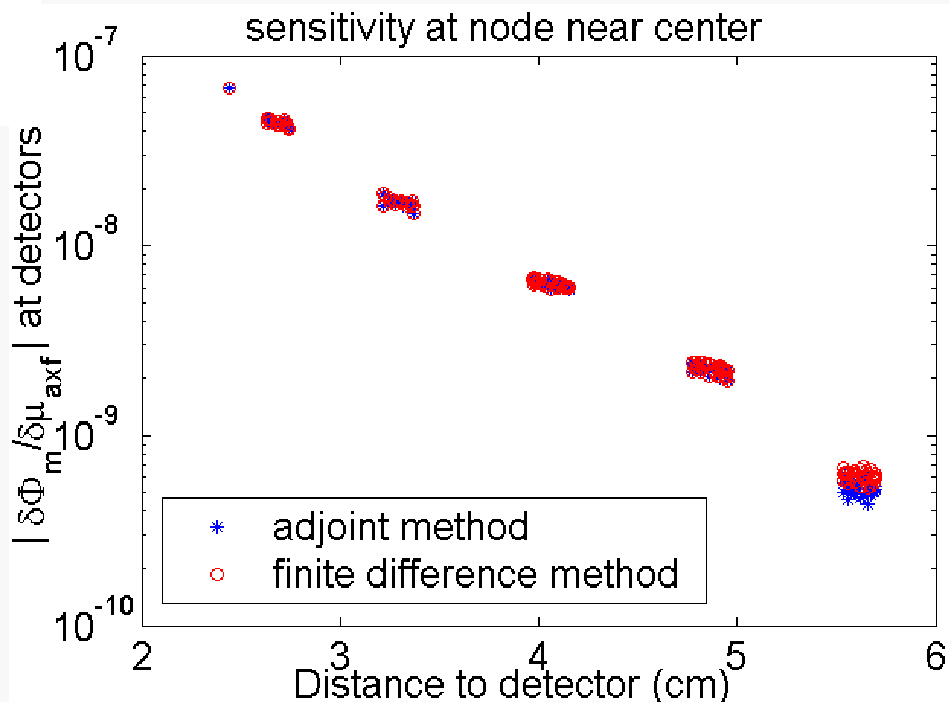


$$\frac{\partial \Phi_m}{\partial \mu_{axf}}$$ Adjoint: 19 min

FD: projected 9 days

Sensitivity drops off exponentially with distance to detector.

Adjoint and FD within 1e-9 of each other.



CONRIBUTION OF TERMS IN EMISSION SENSITIVITIES

$$\boxed{\frac{\partial \mathbf{\Phi}_m}{\partial \mu_{axf}} \approx} \quad \textit{sensitivity}$$

$$-\underline{\mathbf{\Psi}}^t_{xm}\left[\underline{\underline{\mathbf{K}}}\left(\frac{\partial D_x}{\partial \mu_{axf}}\right)+\underline{\underline{\mathbf{M}}}\left(\frac{\partial k_x}{\partial \mu_{axf}}\right)+\underline{\underline{\mathbf{B}}}\left(\frac{\partial r_x}{\partial \mu_{axf}}\right)\right]\underline{\mathbf{\Phi}}_x \qquad \text{Term 1}$$

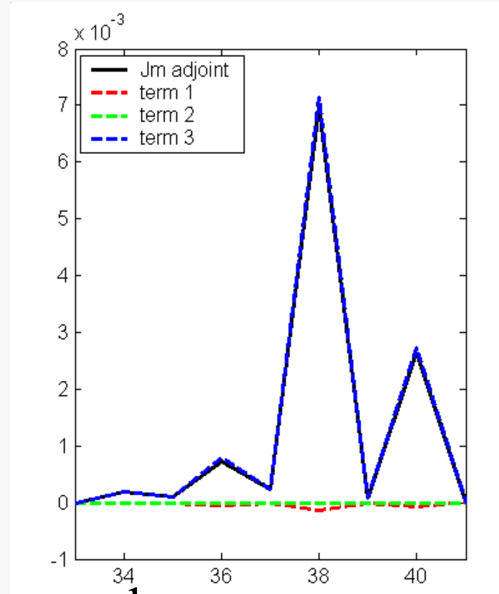
$$-\underline{\mathbf{\Psi}}^t_{mm}\left[\underline{\underline{\mathbf{K}}}\left(\frac{\partial D_m}{\partial \mu_{axf}}\right)+\underline{\underline{\mathbf{M}}}\left(\frac{\partial k_m}{\partial \mu_{axf}}\right)+\underline{\underline{\mathbf{B}}}\left(\frac{\partial r_m}{\partial \mu_{axf}}\right)\right]\underline{\mathbf{\Phi}}_m \qquad \text{Term 2}$$

$$+\underline{\mathbf{\Psi}}^t_{mm}\underline{\underline{\mathbf{M}}}\left(\frac{\partial \beta}{\partial \mu_{axf}}\right)\underline{\mathbf{\Phi}}_x \qquad \text{Term 3}$$

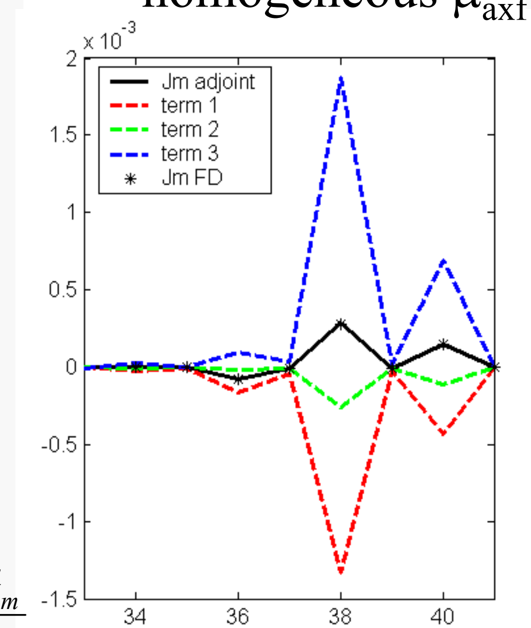
- If absorption is low & homogeneous, Term 3 is sufficient, but if there is an absorbing fluorescent heterogeneity, Terms 1 and 2 become important

- For smooth D_m , Green's function approach is equivalent to Term 3.

- If D_m is not smooth additional errors of order $\propto G_m \dfrac{\nabla D_m \cdot \nabla G_m}{D_m}$ are introduced in Green's function approach.



homogeneous μ_{axf}



heterogeneous μ_{axf}

CONCLUSIONS

- We have derived exact generalized adjoint sensitivity equations of the coupled frequency-domain fluorescence equations. No limiting assumptions are imposed on smoothness of optical properties.

- The equations can be used to solve for a variety of sensitivities:

$$\frac{\partial\{\Phi_x, \Phi_m\}}{\partial\{\mu_{axf}, \mu_{axi}, \mu_{amf}, \mu_{ami}, \mu'_{sx}, \mu'_{sm}, \tau, \phi, r_x, r_m\}}$$

- We have derived finite element discretizations of the sensitivity equations; continuous and discrete formulations are equivalent.

- An efficient vectorized implementation of the adjoint sensitivity of emission fluence w.r.t. absorption due to fluorophore is shown to be orders of magnitude faster than a finite difference implementation, but with the same accuracy.

- All terms in the full coupled adjoint solution are shown to be necessary for accurate sensitivities when fluorescent heterogeneities are present.