Sensitivity analysis for nonlinear maps and odes

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Outline

- I will talk about sensitivity analysis in the context of cardiac modelling. Familiar themes of
  - stochastic collocation (Gunzburger),
  - high dimensional integration using sparse grids (Sloan),
  - sensitivity measures (Saltelli).

  Different context with a new twist.
- I won't talk about other recent ideas for adaptive computation balancing numerical and stochastic (sampling) errors
  - Estep, D. Malqvist, A. and Tavener, S.J. 2009 Nonparametric density estimation for randomly perturbed elliptic problems I: Computational methods, *a posteriori* analysis, and adaptive error control *SIAM J. Sci. Comp.*, **31**, 2935–2959
  - Estep, D. Malqvist, A. and Tavener, S.J. 2009 Nonparametric density estimation for randomly perturbed elliptic problems II: Applications and adaptive modeling. *Int. J. Numer. Meth. Engr.*, **80**, 846–867.
- I hope that was the right choice!

Noble 1962 model

The Noble 1962 model for Perkinje fibre action and pace-maker potentials is

$$\left.\begin{aligned} \frac{dV}{dt} &= \frac{-(I_{Na} + I_K + I_{leak})}{C_m} \\ \frac{dm}{dt} &= a_m(1-m) \ - b_m \ m \\ \frac{dh}{dt} &= a_h(1-h) \ - b_h \ h \\ \frac{dn}{dt} &= a_n(1-n) \ - b_n \ n \end{aligned}\right\} . \tag{1}$$

$$E_{Na} = 40, \ g_{Na} = m^3 \ h \ g_{Na_{max}}, \qquad I_{Na} = (g_{Na} + 140)(V - E_{Na})$$

$$g_{K1} = g_{K_{max}} \exp((-V - 90)/50), \qquad g_{K2} = g_{K_{max}} \ n^4,$$

$$I_K = (g_{K1} + g_{K2})(V + 100), \qquad E_L = -60, \quad I_{leak} = g_L \ (V - E_L),$$

Parameters in red indicate those whose sensitivities are sought.

Parameters and initial conditions

The constants and expressions appearing in (1) are

$$a_m = 100\ (-V - 48)/(\exp((-V - 48)/15) - 1) \qquad a_h = 170\ \exp((-V - 90)/20)$$
$$a_n = 0.1\ (-V - 50)/(\exp((-V - 50)/10) - 1)$$

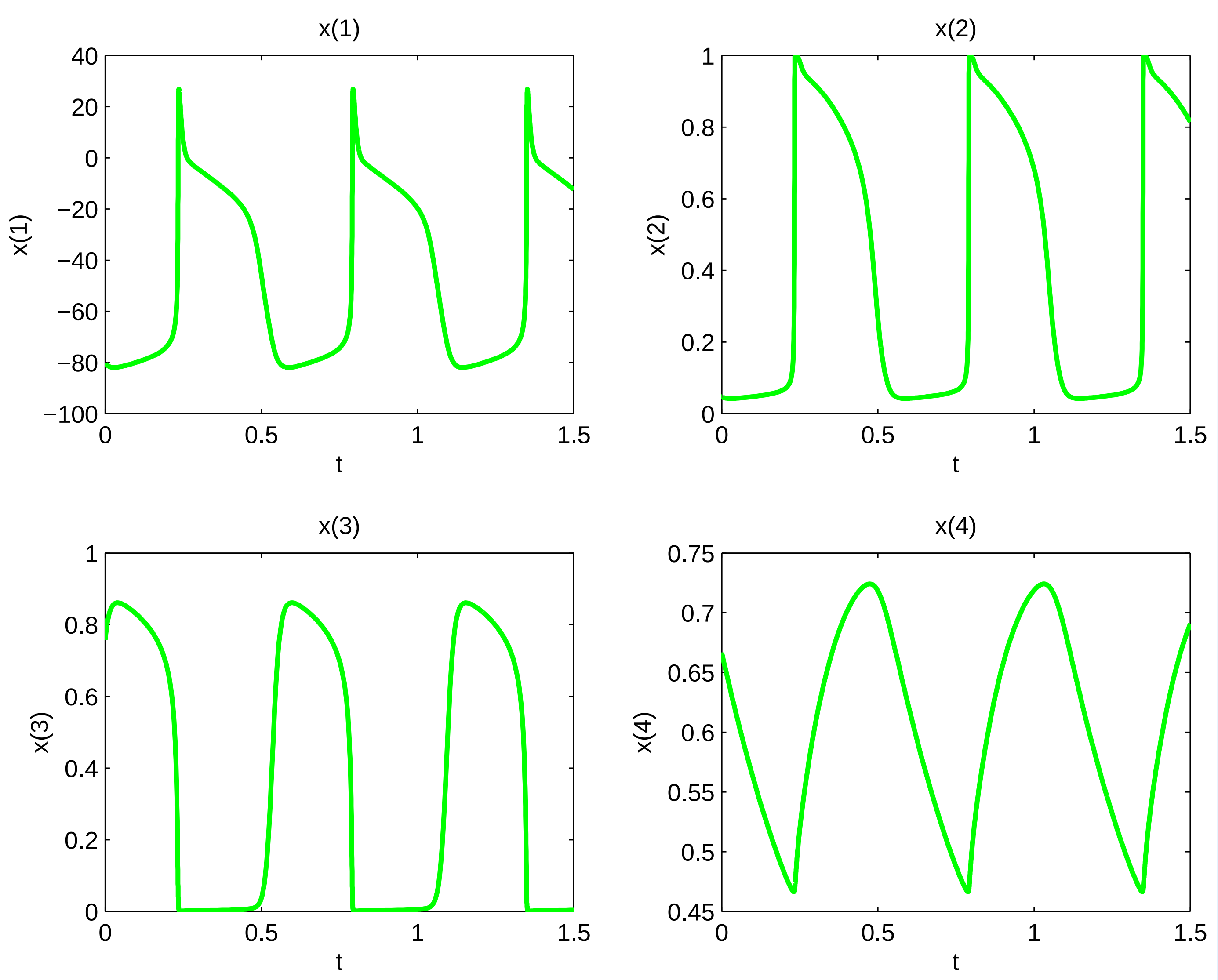
and

$$b_m = 20\ (V + 8)/(\exp((V + 8)/5) - 1) \qquad b_h = 1000/(1 + \exp((-V - 42)/10))$$
$$b_n = 2\ \exp((-V - 90)/80).$$

To minimize transience, choose the initial conditions and parameters as

$$V_0 = -80.01 \qquad g_{Na_{max}} = 400000$$
$$m_0 = 0.04638 \qquad g_{K_{max}} = 1200$$
$$h_0 = 0.7574 \qquad g_L = 75$$
$$n_0 = 0.6667 \qquad C_m = 12.$$

Noble 1962 solutions



Traditional sensitivity analysis for nonlinear o.d.e.s

Consider the following system of parametrized nonlinear first-order ordinary differential equations,

$$\left.\begin{aligned} \dot{\boldsymbol{x}}(t,\boldsymbol{p}) &= \boldsymbol{f}(\boldsymbol{x}(t,\boldsymbol{p}),\ \boldsymbol{p}) \\ \boldsymbol{x}(0) &= \boldsymbol{z} \end{aligned}\right\}$$

where $\boldsymbol{x} \in \mathbb{R}^{\mathrm{xdim}}, \boldsymbol{p} \in \mathbb{R}^{\mathrm{kdim}}$ and the initial conditions $\boldsymbol{z} \in \mathbb{R}^{\mathrm{xdim}}$.

Differentiating with respect to the kth parameter p_k (and reversing the order of differentiation w.r.t. t and w.r.t. p_k on the LHS) gives

$$\left.\begin{aligned} \frac{d}{dt}\left(\frac{\partial x_i}{\partial p_k}\right) &= \sum_{m=1}^{\mathrm{xdim}} \left(\frac{\partial f_i}{\partial x_m}\ \frac{\partial x_m}{\partial p_k}\right) + \frac{\partial f_i}{\partial p_k} \\ \frac{\partial x_i}{\partial p_k}(0) &= 0 \end{aligned}\right\}, \quad i = 1, \ldots \mathrm{xdim},\ k = 1, \ldots \mathrm{kdim}.$$

Alternative approach to sensitivity analysis

Consider a system of parametrized nonlinear first-order ordinary differential equations of the form

$$\left.\begin{aligned} \dot{\boldsymbol{x}}(t,\boldsymbol{\theta}) &= \boldsymbol{f}\big(\boldsymbol{x}(t,\boldsymbol{\theta}),\ \boldsymbol{\theta}\big) \\ \boldsymbol{x}(0) &= \boldsymbol{z} \end{aligned}\right\}, \qquad (2)$$

where $\boldsymbol{x} \in \mathbb{R}^{\mathrm{xdim}}$, $\boldsymbol{\theta} \in \mathbb{R}^{\mathrm{kdim}}$ and the initial conditions $\boldsymbol{z} \in \mathbb{R}^{\mathrm{xdim}}$.

Let $\boldsymbol{\theta}$ be a vector of *stochastic* parameters, i.e., let $\theta_1, \ldots, \theta_{\mathrm{kdim}}$ be random variables with pdfs $\rho(\theta_1), \ldots, \rho(\theta_{\mathrm{kdim}})$.

For simplicity, first consider kdim=1. Define

$$L_\rho(\theta) = \left\{ \boldsymbol{v}(\theta) : \int_\Omega \rho(\theta)\ ||\boldsymbol{v}(\theta)||_2^2\ \mathrm{d}\theta < \infty \right\},$$

where $\rho(\theta)$ is the probability density function for random variable θ.

Polynomial approximation of stochastic space

Idea: Construct a polynomial basis for $L_\rho(\theta)$ and let $\boldsymbol{x}(t,\theta)$ be a polynomial function of θ such that $\boldsymbol{x}(t,\theta) \in L_\rho(\theta)\ \forall\ t > 0$.

$(\star)$ Construct polynomials (of degree n) in $L_\rho(\theta)$ as linear combinations of Lagrange interpolating polynomials based at $(n+1)$ “basis” points θ_j, i.e.,

$$\boldsymbol{x}(t,\theta) = \sum_{j=1}^{n} \boldsymbol{x}_j(t) L_j(\theta) \quad \text{where} \quad L_j(\theta) = \prod_{k=0,k\neq j}^{n} \frac{\theta - \theta_k}{\theta_j - \theta_k}.$$

A weak solution of the i.v.p. (2) satisfies

$$\int_{-1}^{1} \rho(\theta)\ \dot{\boldsymbol{x}}(t,\theta) \cdot \boldsymbol{v}(\theta)\ \mathrm{d}\theta = \int_{-1}^{1} \rho(\theta)\ \boldsymbol{f}(\boldsymbol{x}(t,\theta),\theta) \cdot \boldsymbol{v}(\theta)\ \mathrm{d}\theta \qquad (3)$$

for all test functions $\boldsymbol{v}(\theta) = \sum_{j=0}^{n} \boldsymbol{v}_j L_j(\theta) \in L^2_\rho(\Omega)$.

Substitution and quadrature

Substituting the polynomial approximation for $\boldsymbol{x}(t,\theta)$ and $\boldsymbol{v}(\theta)$,

$$\int_\Omega \rho(\theta)\left(\sum_{j=0}^{n}\dot{\boldsymbol{x}}_j(t)L_j(\theta)\right)\cdot\left(\sum_{k=0}^{n}\boldsymbol{v}_k L_k(\theta)\right)\,\mathrm{d}\theta$$

$$=\int_\Omega \rho(\theta)\boldsymbol{f}\left(\sum_{j=0}^{n}\boldsymbol{x}_j(t)L_j(\theta),\theta\right)\cdot\left(\sum_{k=0}^{n}\boldsymbol{v}_k L_k(\theta)\right)\,\mathrm{d}\theta.$$

$(\star)$ Use numerical quadrature at the "basis" points, $\theta_m,\ m=0,\ldots,n$

$$\sum_{m=0}^{n} w_m\,\rho(\theta_m)\,\left(\sum_{j=0}^{n}\dot{\boldsymbol{x}}_j(t)L_j(\theta_m)\right)\cdot\left(\sum_{k=0}^{n}\boldsymbol{v}_k(t)L_k(\theta_m)\right)$$

$$=\sum_{m=0}^{n} w_m\,\rho(\theta_m)\,\boldsymbol{f}\left(\sum_{j=0}^{n}\boldsymbol{x}_j(t)L_j(\theta_m),\theta_m\right)\cdot\left(\sum_{k=0}^{n}\boldsymbol{v}_k(t)L_k(\theta_m)\right)$$

The key property: $L_j(\theta_m) = \delta_{jm}$

$$\sum_{m=0}^{n} w_m \; \rho(\theta_m) \; \left(\sum_{j=0}^{n} \dot{\boldsymbol{x}}_j(t) \delta_{jm} \right) \cdot \left(\sum_{k=0}^{n} \boldsymbol{v}_k \delta_{km} \right)$$

$$= \sum_{m=0}^{n} w_m \; \rho(\theta_m) \; \boldsymbol{f} \left(t, \sum_{j=0}^{n} \boldsymbol{x}_j(t) \delta_{jm}, \theta_m \right) \cdot \left(\sum_{k=0}^{n} \boldsymbol{v}_k \delta_{km} \right)$$

or

$$\sum_{m=0}^{n} w_m \; \rho(\theta_m) \; \dot{\boldsymbol{x}}_m(t) \cdot \boldsymbol{v}_m = \sum_{m=0}^{n} w_m \; \rho(\theta_m) \; \boldsymbol{f} \left(\boldsymbol{x}_m(t), \theta_m \right) \cdot \boldsymbol{v}_m \quad \forall \boldsymbol{v}_m.$$

Hence

$$\dot{\boldsymbol{x}}_m(t) = \boldsymbol{f} \left(\boldsymbol{x}_m(t), \theta_m \right) \quad \forall m = 0, 1, \ldots, n. \tag{4}$$

Multiple dimensions

Multiple stochastic parameters raises several issues.

1. A tensor-product grid will contain

$$N_{\mathrm{tp}} = \prod_{k=1}^{\mathrm{kdim}} (n_k + 1)$$

   collocation points and therefore require N_{tp} solutions of the initial value problem. Decision: employ a sparse grid implementation
   (a) $\Omega = [-1,1] \otimes [-1,1] \otimes \cdots \otimes [-1,1]$
   (b) Collocate at Chebychev points, $\theta_j = \cos\left(\frac{j\pi}{n}\right), \; j = 0, 1, \ldots, n.$
   (c) Clenshaw-Curtis quadrature
   (d) Barycentric Legendre polynomial evaluation
2. Presentation (and interpretation) of results is complicated.

Expectations

Let ϑ be a *distinguished* stochastic parameter and compute the expectation with respect to all the other stochastic parameters.

Let $\underline{\boldsymbol{\theta}} \in \hat{\Omega}$ where $\underline{\Omega} = \Omega \backslash \mathrm{domain}\{\vartheta\}$. For $\tilde{\vartheta}$, a particular fixed value of ϑ we compute

$$E[Q(\tilde{\vartheta})] = \int_{\underline{\Omega}} \rho(\underline{\boldsymbol{\theta}}) Q(\tilde{\vartheta}, \underline{\boldsymbol{\theta}})\ \mathrm{d}\underline{\boldsymbol{\theta}} \quad \text{and} \quad E[Q^2(\tilde{\vartheta})] = \int_{\underline{\Omega}} \rho(\underline{\boldsymbol{\theta}}) Q^2(\tilde{\vartheta}, \underline{\boldsymbol{\theta}})\ \mathrm{d}\underline{\boldsymbol{\theta}}$$

and so given $\rho(\vartheta)$ we can calculate

$$\mathrm{Var}(Q(\vartheta)) \ = \ E[Q^2(\vartheta)] \ - \ (E[Q(\vartheta)])^2.$$

This enables us to define variance-based global sensitivity measures such as the *main effect* due to ϑ

$$S_\vartheta = \frac{\mathrm{Var}(Q(\vartheta))}{\mathrm{Var}(Q)}. \qquad (5)$$

(Buzzard & Xiu)

Noble 1962 solutions

We report two *phase invariant* quantities of interest,

(a) Δt_{10_90} (length of the action potential)

(b) Area_{10_90} (area under the action potential)

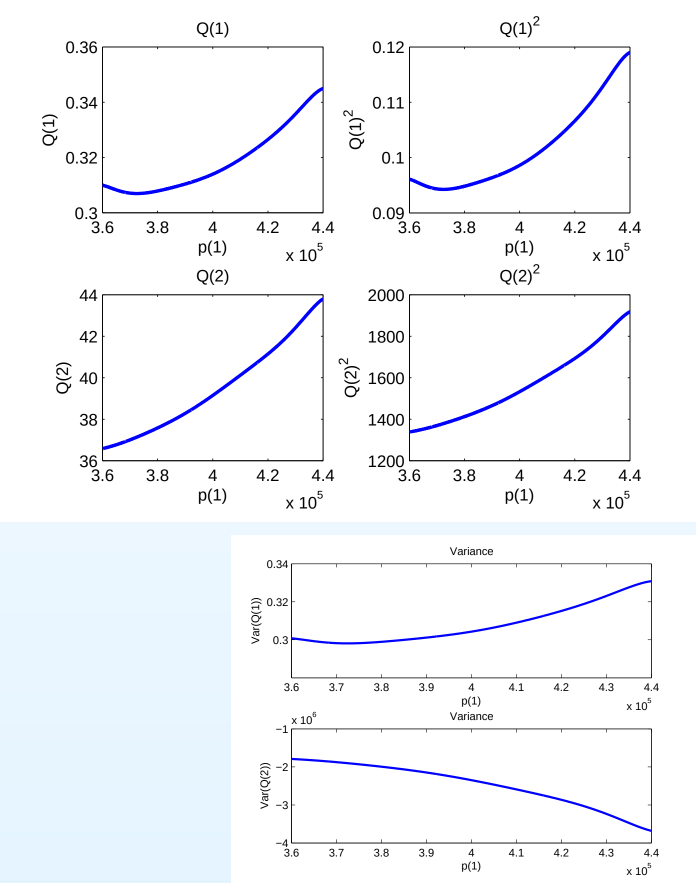
for the Noble 1962 model with 10% variation in the four parameters $g_{Na_{max}}$, $g_{K_{max}}$, g_L and C_m, i.e.,

$$\begin{aligned} g_{Na_{max}} &\sim \mathbb{U}[380000, 420000] & g_{K_{max}} &\sim \mathbb{U}[1140, 1260] \\ g_L &\sim \mathbb{U}[71.25, 78.75] & C_m &\sim \mathbb{U}[11.4, 12.6]. \end{aligned}$$

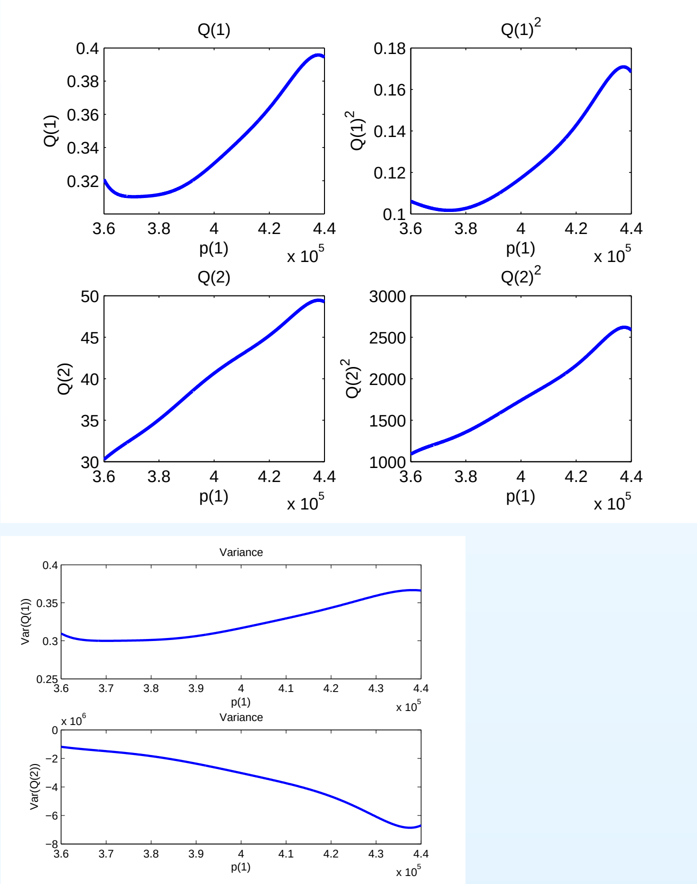
The *distinguished* parameter is $g_{Na_{max}} \sim \mathbb{U}[380000, 420000]$.

Distinguished parameter $g_{Na_{max}}$

Ranges of all stochastic parameters are $\pm 10\%$ of their “nominal” values.



Varying $g_{Na_{max}}$ only (OATS)



Varying all four parameters

Parameter estimation

1. M experimental observations $\boldsymbol{Q}(\boldsymbol{x}^{(i)})$ at locations $\boldsymbol{x}^{(i)}, i = 1, \ldots, M$
2. a “goodness-of-fit" function $\gamma(\cdot)$, e.g., $\gamma(\boldsymbol{u}) = ||\boldsymbol{u}||_2^2$
3. a parametrized model which provides solutions $\boldsymbol{q}(\boldsymbol{x}^{(i)}, \boldsymbol{p})$

Find the values of the parameters $\boldsymbol{p}$ so as to minimize

$$f(\boldsymbol{p}) = \sum_{i=1}^{M} \gamma\left(\boldsymbol{Q}(\boldsymbol{x}^{(i)}) - \boldsymbol{q}(\boldsymbol{x}^{(i)}, \boldsymbol{p})\right).$$

1. Assume the parameters $\boldsymbol{p}$ are independent uniformly distributed random variables $\boldsymbol{\theta}$
2. Construct polynomial approximation $P(\boldsymbol{\theta}) \sim f(\boldsymbol{\theta})$ by evaluating $f(\boldsymbol{\theta})$ at the nodes of an appropriate sparse grid for $\boldsymbol{\theta}$
3. Find $\boldsymbol{\theta}$ so as to minimize $P(\boldsymbol{\theta})$.

(Donahue, Buzzard & Rundell)

Inverse sensitivity analysis

1. MN observations $(\boldsymbol{Q}(\boldsymbol{x}^{(i)}))_j,\ j=1,\ldots,N$ locations $\boldsymbol{x}^{(i)},\ i=1,\ldots,M$
2. a “goodness-of-fit" function $\gamma(\cdot)$, e.g., $\gamma(\boldsymbol{u}) = ||\boldsymbol{u}||_2^2$
3. a parametrized model which provides solutions $\boldsymbol{q}(\boldsymbol{x}^{(i)},\boldsymbol{\theta})$ at locations $\boldsymbol{x}^{(i)}$ for given values of the parameters $\boldsymbol{\theta}$.

Assume parameters $\boldsymbol{\theta}$ to be independent random variables with unknown cumulative density functions $\mathbb{P}(\boldsymbol{\theta})$.

Find cumulative density functions $\mathbb{P}(\boldsymbol{\theta})$ so as to minimize

$$f(\boldsymbol{\theta}) = \sum_{i=1}^{M} \gamma\left(\mathbb{P}[\boldsymbol{Q}(\boldsymbol{x}^{(i)})] - \mathbb{P}[\boldsymbol{q}(\boldsymbol{x}^{(i)},\boldsymbol{\theta})]\right).$$

(Zabaras & Ganapathysubramanian, J. Comp. Phys. 2008)

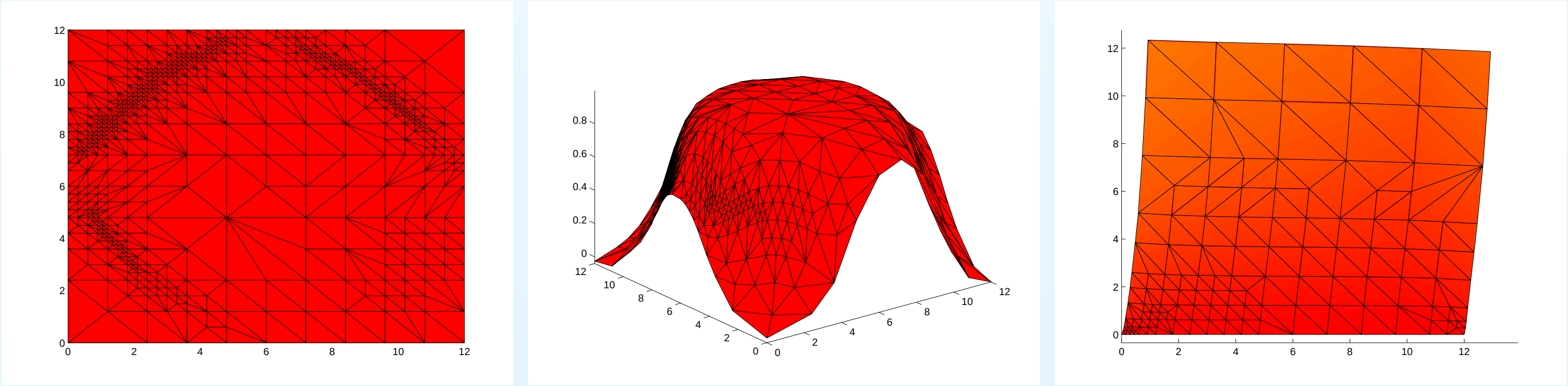
Coupled electro-mechanical cardiac models

(With Kathryn Gillow, Alex Walter and Jon Whiteley.)

Electro-physiological models $\longrightarrow$ active tension $\longrightarrow$ (non)linear elasticity (e.g. Noble 1962)

Goal: Develop a procedure to adapt the finite element meshes for the electrical and mechanical computations independently using adjoint-based *a posteriori* error estimation that takes account of the transfer error.

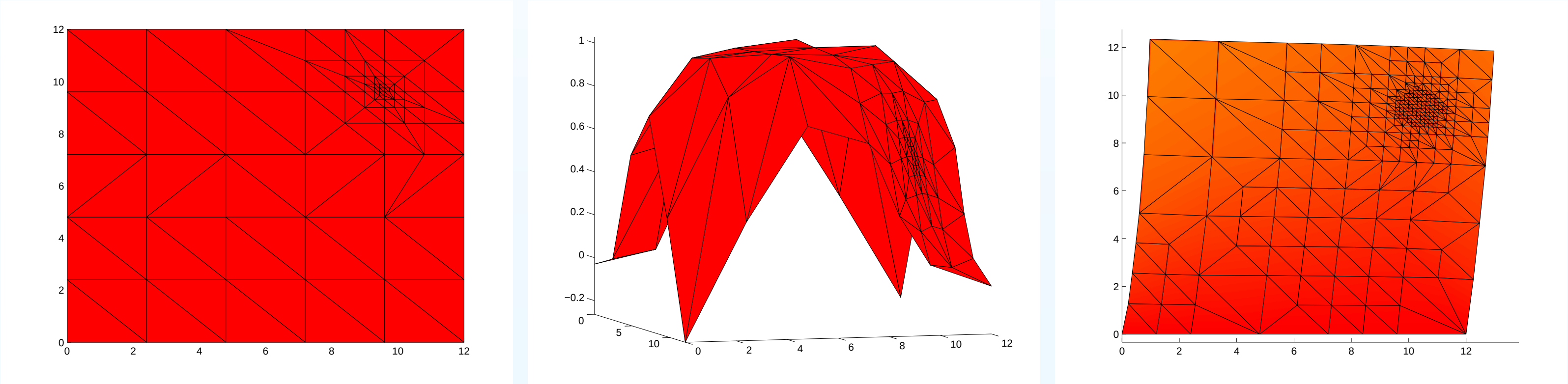
Quantity of interest equal to the average displacement



(a) electrical activity (b) active tension (c) elastic deformations

Coupled electro-mechanical cardiac models

Quantity of interest equal to a localized displacement



(a) electrical activity (b) active tension (c) elastic deformations

Future objectives

- Sensitivity analysis for coupled systems
  - Pretty immediate (in the bad old ways) using derivative information at a fixed point in parameter space
- Error estimation (including transfer errors) and adaptivity for coupled systems with stochastic parameters for a particular quantity of interest
  - (Mathelin & le Maître, CAMCS 2007)
- Inverse sensitivity analysis for coupled systems with stochastic parameters