An adjoint-enabled simulation framework for cardiac electrophysiology

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Outline

1. Inverting the heart
2. Point integrals
3. Multistage schemes and their adjoints

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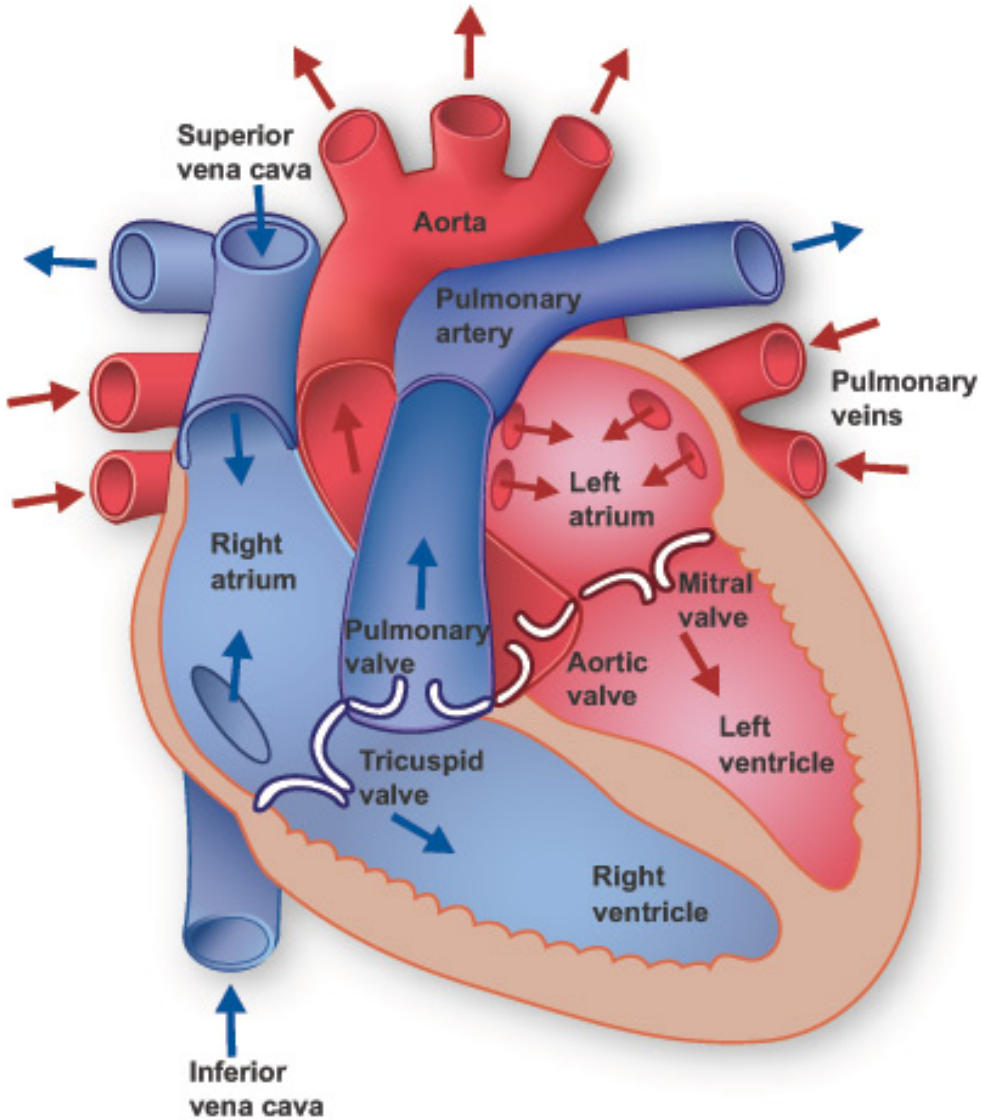
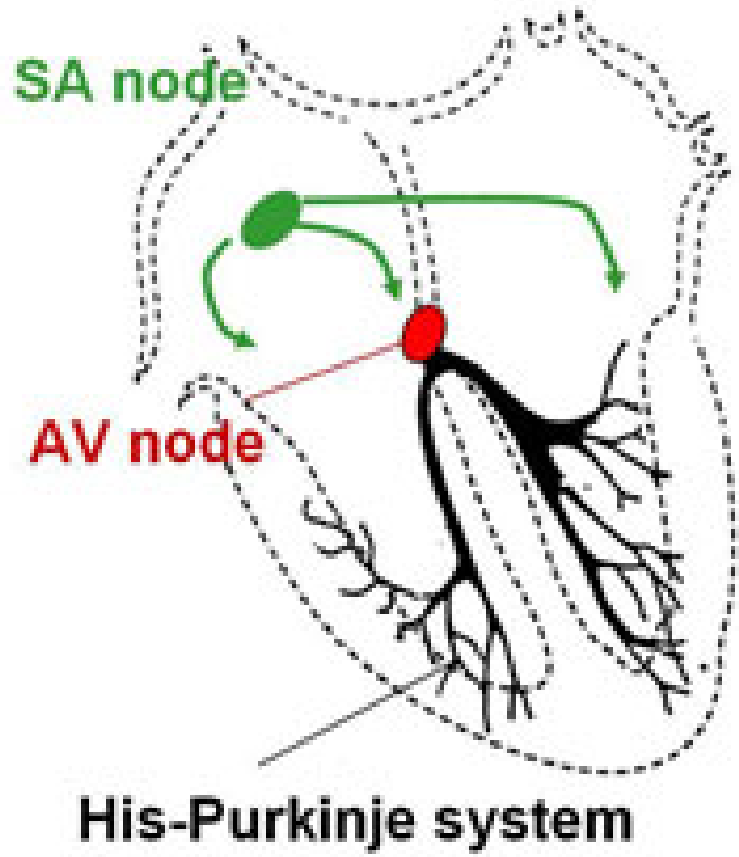
[simula . research laboratory]

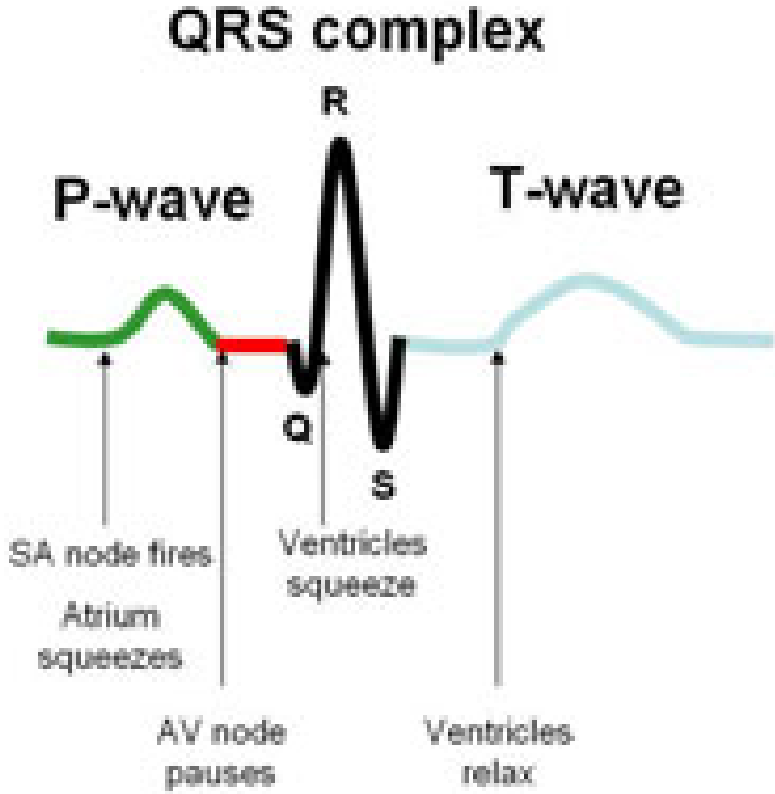
Heart disease is the leading cause of death in the world



[http://health-advisors.org]

The beating of the heart is driven by the electrical signalling of heart cells



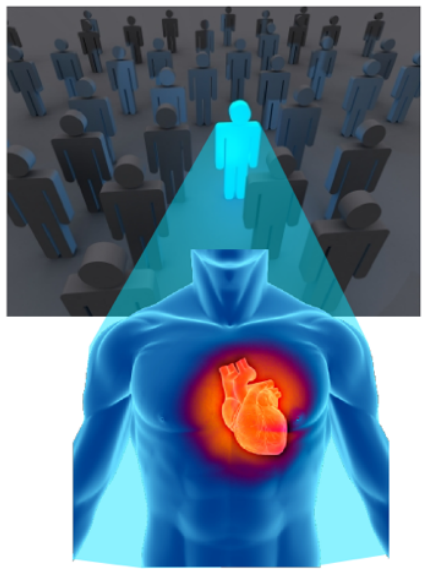


[http://www.bostonscientific.com]

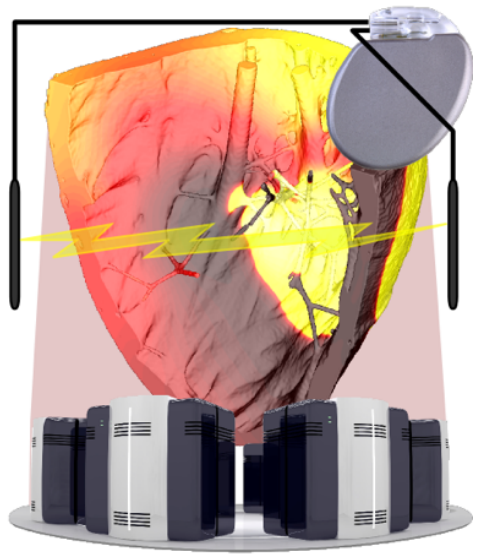
Research aims at commercially and clinically driven advances in cardiac diagnostics and treatments

Combine data from Ultrasound and ECG

Build patient-specific, electromechanical models of the heart



Use models to prescribe and optimize patient treatments



[Edvardsen, Maleckar, Wall et al]

Adjoints are ubiquitous

Constrained optimal control

$$\max_m J(u,m) \quad \text{while} \quad F(u,m) = 0$$

Gradient-based optimization algorithms require the gradient of J with respect to m.

$$\frac{\mathrm{d}J}{\mathrm{d}m} = J_u \frac{\partial u}{\partial m} + J_m$$

Define the adjoint solution z

$$F_u^* z = J_u$$

Then, the derivative computation only involves one forward solve for u and one backward solve for z independent of $\#m$:

$$\frac{\mathrm{d}J}{\mathrm{d}m} = -F_m z + J_m$$

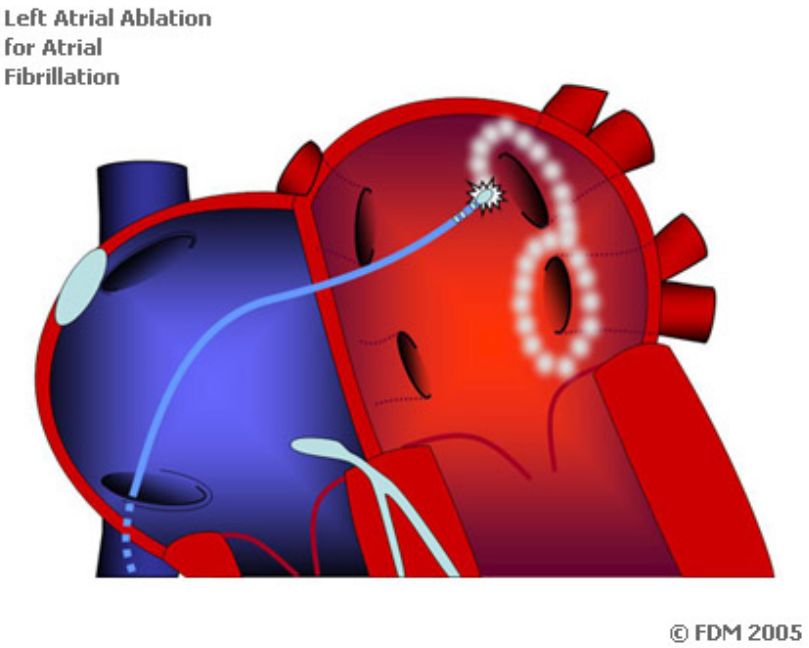
Other applications

Sensitivity analysis, data assimilation, error control, generalized stability theory, ...

Treating abnormal cardiac acitivity: How to find the optimal region to treat atrial fibrillation by ablation?

Find the optimal ablation region m to achieve defibrillation

$$\min_m J(u,m) \quad s.t. \quad F(u,m) = 0$$



[http://www.londonarrhythmiacentre.co.uk/]

For defibrillation, one may consider:

$$J(u,m) = \|u - u_{ideal}\|^2_{L^2(0,T;L^2(\Omega_{obs}))} + \alpha\mathcal{R}(m)$$

[Nagaiah et al, 2011]

The significant gap in maturity between forward and reverse cardiac modelling motivates a new adjoint-enabled simulation framework

Obtaining

```
$ hg clone ssh://hg@bitbucket.org/meg/adjoint-beat
$ cd adjoint-beat
$ python setup.py install --prefix=/home/meg/local
```

Usage

```
from beatadjoint import *
```

The governing equations: the bidomain model

Find the transmembrane potential $v = v(x,t)$, the extracellular potential $u_e(x,t)$ and the ionic current(s) $s = s(x,t)$ such that for almost all $t \in (0,T]$:

$$\begin{aligned} v_t - \operatorname{div}(M_i \nabla v + M_i \nabla u_e) &= -I_{\text{ion}}(v,s) + I_s, \\ \operatorname{div}\left(M_i \nabla v + (M_i + M_e) \nabla u_e\right) &= g, \\ s_t &= F(v,s), \end{aligned}$$

with boundary conditions

$$(M_i \nabla v + M_i \nabla u_e) \cdot n = 0, \quad (M_i \nabla v + (M_i + M_e) \nabla u_e) \cdot n = 0$$

and

$$\int_\Omega u_e = 0.$$

[Tung, 1978]

The typical discretization approach is based on operator splitting and iterations between an ODE and a PDE solve

1. With v^n and s^n as initial conditions at t_n, find v^* and s^* solving

$$v_t^* = -I_{\text{ion}}(v^*, s^*),$$
$$s_t^* = F(v^*, s^*)$$

   on $(t_n, t_n + \theta\kappa]$.
2. With v^* as initial condition, find $v^\dagger$ and u_e^{n+1} such that

$$v^\dagger{}_t - \operatorname{div}(M_i \nabla v^\dagger + M_i \nabla u_e^{n+1}) = I_s,$$
$$\operatorname{div}\left(M_i \nabla v^\dagger + (M_i + M_e) \nabla u_e^{n+1}\right) = g,$$

   on $I_n = (t_n, t_{n+1}]$.
3. If $\theta < 1$: with $v^\dagger$ and s^* as initial conditions at $t_{n+\theta\kappa}$, find v^{n+1} and s^{n+1} solving

$$v_t^{n+1} = -I_{\text{ion}}(v^{n+1}, s^{n+1}),$$
$$s_t^{n+1} = F(v^{n+1}, s^{n+1})$$

   on $(t_n + \theta\kappa, t_{n+1}]$.

[Sundnes et al, 2006]

The specific forms of the ODEs are known as cell models, and greatly vary in complexity

[Fitzhugh, 1961; Rodgers & McCulloch, 1994]

$$v_t = \frac{c_1}{v_a^2}(v - v_r)(v - v_{th})(v_p - v) - \frac{c_2}{v_a}(v - v_r)s$$

$$s_t = b(v - v_{\text{rest}} - c\,s)$$

[ten Tusscher & Panfilov, 2006, www.cellml.org]

```
</units>
<component name="environment">
   <variable name="time" units="millisecond" public_interface="out"/>
</component>
<component name="membrane">
   <variable name="V" units="millivolt" initial_value="-85.23" public_interface="out"/>
   <variable name="R" units="joule_per_mole_kelvin" initial_value="8314.472" public_interface=
   <variable name="T" units="kelvin" initial_value="310" public_interface="out"/>
   <variable name="F" units="coulomb_per_millimole" initial_value="96485.3415" public_interfac
   <variable name="Cm" units="microF" initial_value="0.185" public_interface="out"/>
   <variable name="V_c" units="micrometre3" initial_value="0.016404" public_interface="out"/>
   <variable name="time" units="millisecond" public_interface="in"/>
   <variable name="i_K1" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_to" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_Kr" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_Ks" units="picoA_per_picoF" public_interface="in"/>
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   <variable name="i_NaK" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_Na" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_b_Na" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_NaCa" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_b_Ca" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_p_K" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_p_Ca" units="picoA_per_picoF" public_interface="in"/>
   <variable name="i_Stim" units="picoA_per_picoF" public_interface="out"/>
```
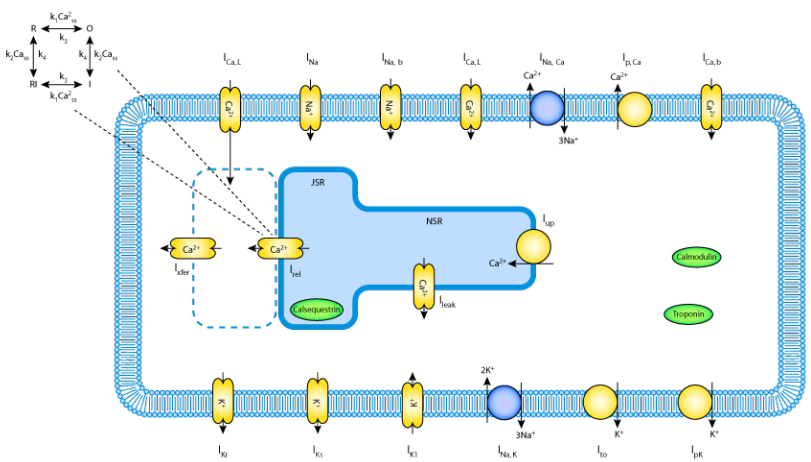



ODE discretizations via multistage schemes

Let $w = (v, s)$ and $G = (-I_{\text{ion}}, F)$:

$$w_t(x,t) = G(x,t,w(x,t)),$$
$$w(0) = w_0.$$

c_1	a_{11}	a_{12}	$\dots$	a_{1s}
c_2	a_{21}	a_{22}	$\dots$	a_{2s}
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
c_s	a_{s1}	a_{s2}	$\dots$	a_{ss}
	b_1	b_2	$\dots$	b_s

For an s-stage scheme with time step κ_n and given w_n, solve

$$k_i(x) = \kappa_n G(x, t_n + c_i\kappa_n, w_n(x) + \sum_{j=1}^{s} a_{ij}k_j(x)), \quad i = 1, \dots, s$$

$$w(x)_{n+1} = w(x)_n + \sum_{i=1}^{s} b_i k_i(x).$$

The three types of solve have different requirements in the FEniCS context

Implicit non-linear solve ($a_{ij} \neq 0$ for all $j \geqslant i$)

$$k_i(x) - \kappa_n G(x, t_n + c_i\kappa_n, w_n(x) + \sum_{j=1}^{s} a_{ij}k_j(x)) = 0$$

Explicit via function evaluation ($a_{ij} = 0$ for all $j \geqslant i$)

$$k_i(x) = \kappa_n G(x, t_n + c_i\kappa_n, w_n(x) + \sum_{j=1}^{i-1} a_{ij}k_j(x))$$

Explicit via assignment

$$w(x)_{n+1} = w(x)_n + \sum_{i=1}^{s} b_i k_i(x).$$

[→ dolfin/multistage/*, site-packages/dolfin/multistage/*, demo/undocumented/multi-stage-solver/*]

Implementation of collocation methods motivated introducing the point measure

Definition

Let $\mathcal{X}$ be a collection of points associated with the domain Ω. We define the *point measure* $\mathrm{d}P$ relative to $\mathcal{X}$ by

$$\int_\Omega I \,\mathrm{d}P = \sum_{x \in \mathcal{X}} I(x) = \sum_{x \in \mathcal{X}} \int_\Omega I \delta_x \,\mathrm{d}x.$$

Example

```
V = FiniteElement("CG", tetrahedron, 1)
v = TestFunction(V)
f = Coefficient(V)
L = f*v*dP
```

[ufl/measure.py, ffc/quadrature/*]

FFC generated code for `f*v*dP`

```
// Array of quadrature weights.
static const double W1 = 1.0;
// Quadrature points on the UFC reference element: ()

// Values of basis functions at quadrature points.
// Reset values in the element tensor.
for (unsigned int r = 0; r < 3; r++)
{
  A[r] = 0.0;
} // end loop over 'r'
// Number of operations to compute geometry constants: 3.
double G[3];
G[0] = W1*w[0][0];
G[1] = W1*w[0][1];
G[2] = W1*w[0][2];

// Compute element tensor using UFL quadrature representation
// Optimisations: ('eliminate zeros', True), ('ignore ones', True), ('ignore zero tables'
switch (vertex)
{
case 0:
  {
    // Total number of operations to compute element tensor (from this point): 1

  // Loop quadrature points for integral.
  // Number of operations to compute element tensor for following IP loop = 1
  for (unsigned int ip = 0; ip < 1; ip++)
  {

    // Number of operations for primary indices: 1
    // Number of operations to compute entry: 1
    A[0] += G[0];
  } // end loop over 'ip'
```

For vector-valued Lagrange elements, the point measure allows for specifying and solving ODEs as variational forms.

Consider the system: find $u \in V$ such that

$$\int_\Omega I_a(u, v)\,\mathrm{d}P = \int_\Omega I_L(v)\,\mathrm{d}P$$

for all $v \in V$.

Let $\mathcal{X}$ be the collection of vertices. Let $V = \mathcal{M}_1^N$.

For each $x_k \in \mathcal{X}$, find $\{u_j\}_{J_k}$ such that

$$\sum_{j \in J_k} I_a(\phi_j, \phi_i)(x_k) u_j = I_L(\phi_i)(x_k)$$

for $i \in J_k$ where J_k is the index set of basis functions that are non-zero at x_k, $|J_k| = N$.

The point measures can be used to define multi-stage schemes for solving collections of ODEs

Example case: Explicit via function evaluation

For each vertex x_k, evaluate

$$k_i(x_k) = \kappa_n G(x_k, t_n + c_i\kappa_n, w_n(x_k) + \sum_{j=1}^{i-1} a_{ij}k_j(x_k))$$

Equivalent FEniCS code

```
# Assume that G is an UFL Expr.
V = VectorElement("CG", T, 1, N)
v = TestFunction(V)
kappa = Constant(T)
rhs = kappa*inner(G, v)*dP
```

Outline of the PointIntegralSolver algorithm

```
def step(G, k_i):

  for x_k in vertices(mesh):
      # Identify one cell and local vertex number
      (cell, i) = cell_and_local_vertex(x_k)

      # Restrict any coefficients in G to this cell
      G.coefficients.restrict(w, cell)

      # Evaluate right hand side
      G.integrals[0].tabulate_tensor(b, w, cell, i)

      # Extract subset of active local dofs
      J_k = find_active_dofs(i)

      # Reduce size of b
      b = b[J_k]

      # Compute the corresponding global dofs
      dofs = ki.tabulate_dofs(cell)[J_k]

      # Update ki
      ki.vector().add(b, dofs)
```

The block structure of a forward multistage solution step

For simplicity of presentation, consider the case where

$$G(\cdot, \cdot, w) = Cw$$

Forward structure (s = 2)

$$\begin{pmatrix} I & 0 & 0 & 0 \\ -\kappa_n C(\cdot) & I - \kappa_n a_{11} C(\cdot) & -\kappa_n a_{12} C(\cdot) & 0 \\ -\kappa_n C(\cdot) & -\kappa_n a_{21} C(\cdot) & I - \kappa_n a_{22} C(\cdot) & 0 \\ -I & -b_1 & -b_2 & I \end{pmatrix} \begin{pmatrix} w_n \\ k_1 \\ k_2 \\ w_{n+1} \end{pmatrix} = \begin{pmatrix} w_0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

The block structure of an adjoint multistage solution step

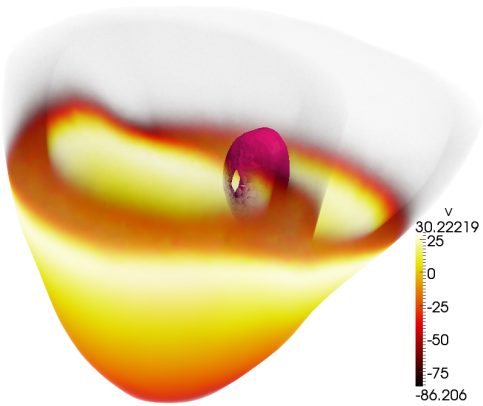
Adjoint structure

$$\begin{pmatrix} I & -\kappa_n C^*(\cdot) & -\kappa_n C^*(\cdot) & -I \\ 0 & (I - \kappa_n a_{11} C(\cdot))^* & -\kappa_n a_{21} C^*(\cdot) & -b_1 \\ 0 & -\kappa_n a_{12} C^*(\cdot) & (I - \kappa_n a_{22} C(\cdot))^* & -b_2 \\ 0 & 0 & 0 & I \end{pmatrix} \begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} = \frac{\partial J}{\partial w}$$

[dolfin/site-packages/multistage, dolfin-adjoint/dolfin_adjoint/pointintegralsolver.py]

Cardiac wave propagation with abnormal tissue conductivities as a basic example

```
# Set-up simulation scenario
cell = FitzhughNagumo()
heart = CardiacModel(mesh, time, M_i, M_e, cell, I_s)
solver = SplittingSolver(heart)

# Solve as you go along
solutions = solver.solve((0, T), k_n)
for (timestep, fields) in solutions:
    # Do something with solution fields
```



$$v_t - \operatorname{div}(M_i \nabla v + M_i \nabla u_e) - I_{\text{ion}}(v, s) = I_{\text{s}}$$

$$\operatorname{div}(M_i \nabla v + (M_i + M_e) \nabla u_e) = 0$$

$$s_t = b(v - v_{\text{rest}} - c\, s)$$

$$M_{\text{i|e}} = A G_{\text{i|e}} A^T, \quad G_{\text{i|e}} = \operatorname{diag}(g_{\text{i|el}}, g_{\text{i|et}}, g_{\text{i|et}})$$

[Thanks to Sjur Gjerald and Johan Hake for patient-specific mesh (generated from ultrasound), fibers and sheets]

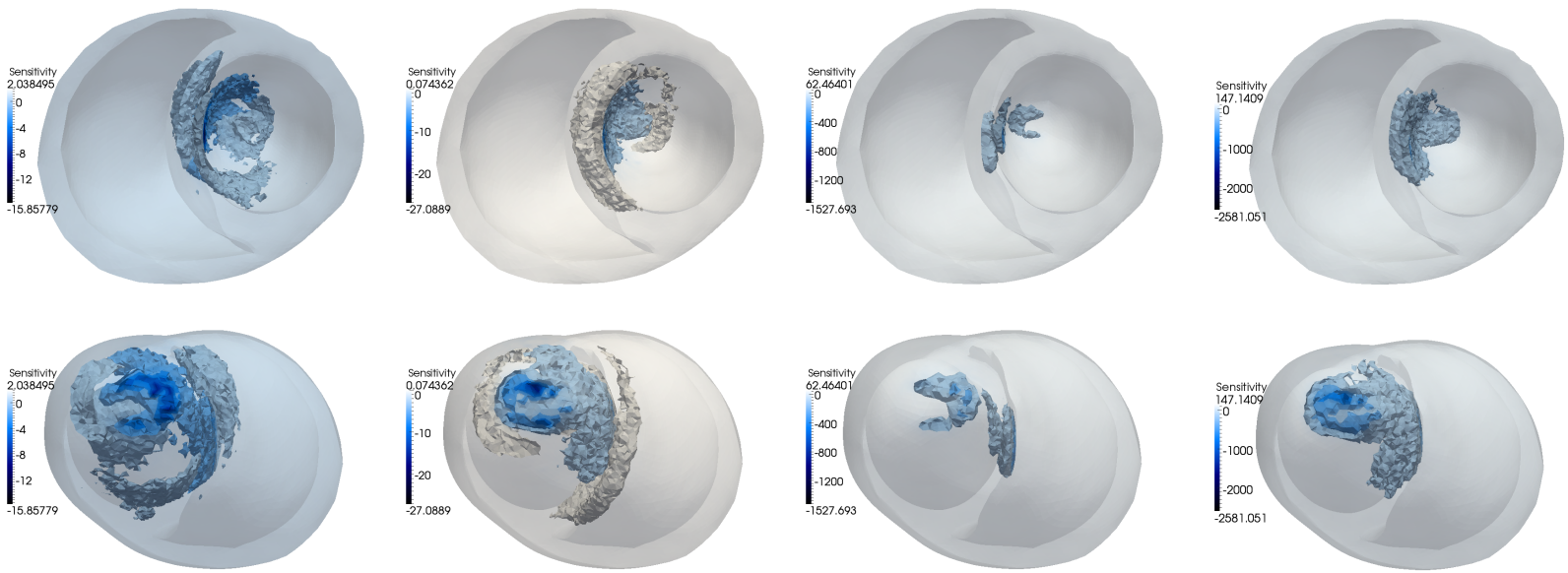
http://youtu.be/r6tLfMARKA0

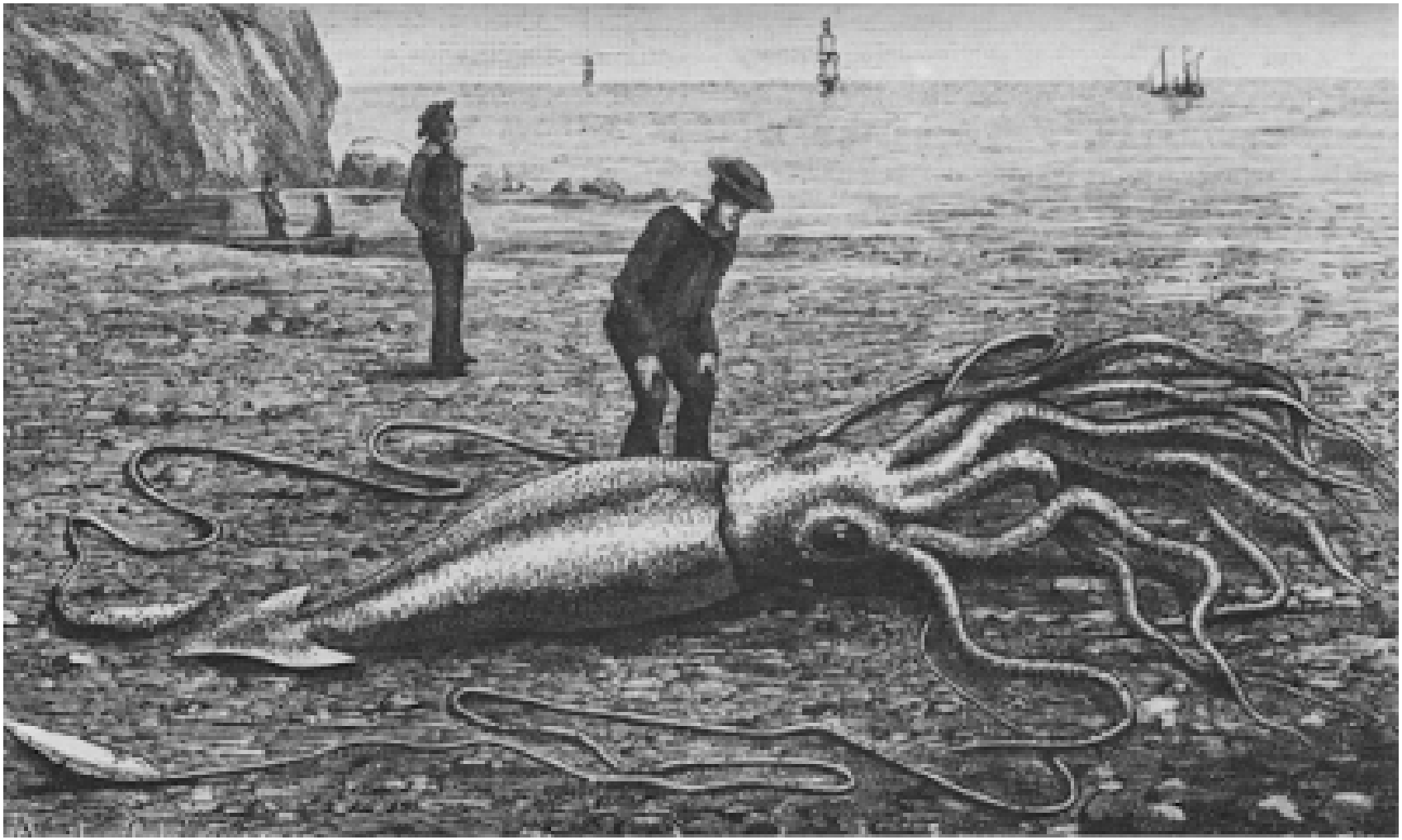
What is the sensitivity of the abnormal wave propagation to the local tissue conductivities?

The wave propagation abnormality at a given time T:

$$J(v, s, u) = \|v(T) - v_{\text{obs}}(T)\|^2, \qquad \frac{\partial J}{\partial g_{\text{e|i|l|t}}} = ?$$

```
v_obs = Function(V, "healthy_obs_200.xml.gz")
J = Functional(inner(v - v_obs, v - v_obs)*dx*dt[T])
dJdg_s = compute_gradient(J, gs)
```





[Wikimedia Commons]