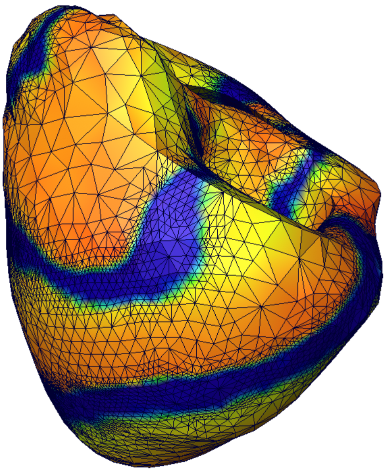
Multiscale Modelling in Computational Medicine

Peter Deuflhard



Zuse Institute Berlin

Free University of Berlin

DFG Research Center
MATHEON

Science Campus Dahlem

ZIB and FU Mathematics, Computer Science, Physics, Chemistry, Biology

Contents

- **Regional Hyperthermia**
- Thermoregulation model
- Temperature optimization
- Medical results
- **Electrocardiology**
- Heart models
- Adaptive Multiscale algorithms Numerical results

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Project Group Hyperthermia

ZIB Scientific Computing:

Computational Medicine

Peter Deuflhard, Martin Weiser
Anton Schiela, Tobias Gänzler, Susanne Gerber, Andre Massing

Medical Planning

Stefan Zachow, Hans Lamecker

Cooperation:

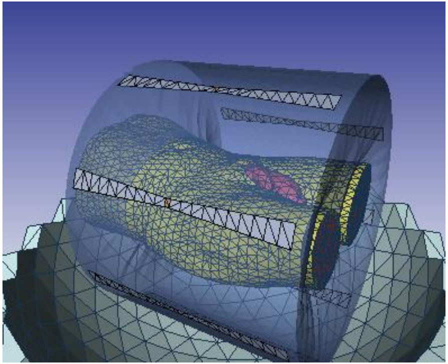
Fredi Tröltzsch, Prüfer (MATHEON)

Clinical Cooperation:

P. Wust, J. Gellermann (Charite Berlin)

Paradigm of Computational Medicine

Real Patient



Virtual Patient

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Bio-Heat Transfer Equation (Pennes, 1948)

linear PDE

$$\rho(x)\, c(x)\, \frac{\partial T(t,x)}{\partial t} = \mathrm{div}(\kappa(x)\ \mathrm{grad}\, T(t,x)) - \rho_b\, c_b\, \rho(x)\ \omega(x)\, (\, T(t,x) - T_a\,) + \frac{1}{2}\,\sigma(x)\, |E(t,x)|^2$$

for $t \in [0, T_{\mathrm{fin}}]\,,\ x \in \Omega$

boundary condition

$$-\kappa(x)\, \frac{\partial T(t,x)}{\partial n}\bigg|_{x\in\partial\Omega} = h\,(\,T(t,x) - T_{\mathrm{bolus}})\bigg|_{x\in\partial\Omega}$$

initial condition

$$T(0,x) = T_a$$

Time Harmonic Maxwell's Equations

$$\text{rot}\,\boldsymbol{H} = i\omega\epsilon\,\boldsymbol{E} \qquad \text{rot}\,\boldsymbol{E} = -i\omega\mu\,\boldsymbol{H}$$

$$\text{div}\,(\epsilon\,\boldsymbol{E}) = 0 \qquad \text{div}\,(\mu\,\boldsymbol{H}) = 0$$

$$F = \int \left\{ \frac{1}{\mu} |\text{rot}\,\boldsymbol{E}|^2 - \omega^2 \epsilon\, |\boldsymbol{E}|^2 \right\} \quad , \quad \delta F = 0 \quad \text{saddle point}$$

Inherent difficulties

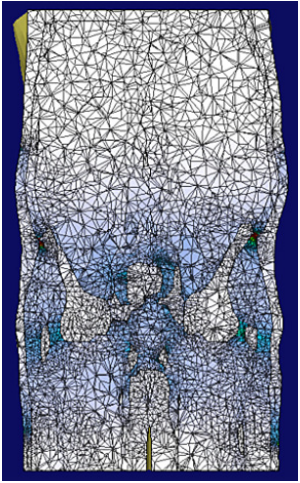
high frequency ($\sim$ 100 MHz)
heterogeneous material (ϵ-ratio $\sim$ 1:80)
body geometry comparable to wavelength in water

Adaptive versus Uniform Grids

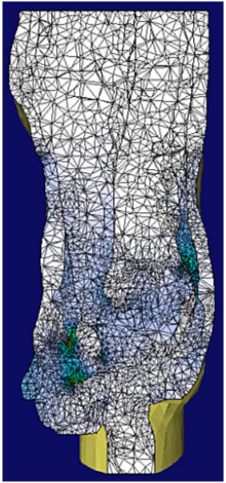
120.000 adaptive nodes
16.000.000 uniform nodes
(estimated)

Numerical simulation

- adaptive multilevel finite element method
- computing time proportional to number of nodes



frontal section



sagittal section

New: Multiscale Model of Thermoregulation

Project A1, DFG Research Center MATHEON

(Deuflhard, Tröltzsch, Weiser)

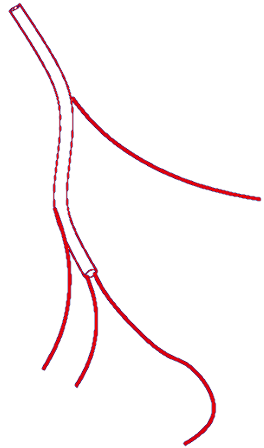
strong blood vessels 3D treatment

Multiscale Model of Thermoregulation

Project A1, DFG Research Center Matheon

(Deuflhard, Tröltzsch, Weiser)

strong blood vessels	3D treatment
medium size blood vessels	1D treatment Quarteroni, Tuveri, Veneziani 2000, Quarteroni, Formaggia 2004

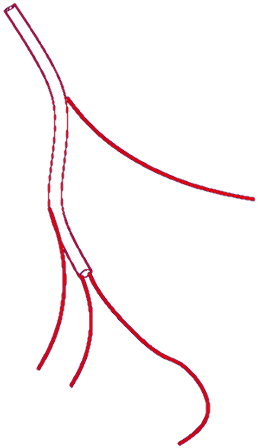


Multiscale Model of Thermoregulation

Project A1, DFG Research Center MATHEON

(Deuflhard, Tröltzsch, Weiser)

strong blood vessels	3D treatment	
medium size blood vessels	1D treatment Quarteroni, Tuveri, Veneziani 2000, Quarteroni, Formaggia 2004	
all blood vessels	ODE treatment Quarteroni et al. 2003, Kappel et al. 1997/2004	

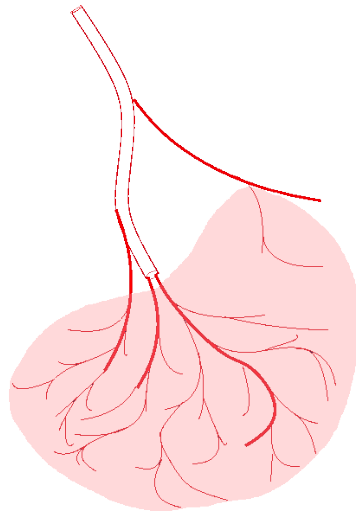


Multiscale Model of Thermoregulation

Project A1, DFG Research Center MATHEON

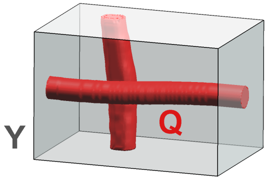
(Deuflhard, Tröltzsch, Weiser)

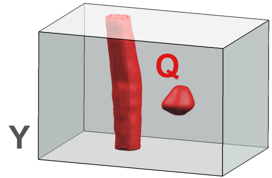
strong blood vessels	3D treatment	
medium size blood vessels	1D treatment Quarteroni, Tuveri, Veneziani 2000, Quarteroni, Formaggia 2004	
all blood vessels	ODE treatment Quarteroni et al. 2003, Kappel et al. 1997/2004	
capillaries	homogenization Deuflhard, Hochmuth 2003, Hochmuth, Deuflhard 2004	



Microvascular Model I

Deuflhard, Hochmuth 2003; Hochmuth, Deuflhard 2004





Scaling and periodic repetition $\longrightarrow \quad \varepsilon Y,\ \varepsilon Q$

$-\Delta T_\varepsilon$	$=$	S_ε	in Ω_ε	source term $S_\varepsilon(x) = \frac{1}{2}\sigma(x)\,\lvert E(x)\rvert^2$
T_ε	$=$	T_{bas}	on $\partial\Omega_\varepsilon$	exterior boundary conditions
$\frac{\partial T_\varepsilon}{\partial n}$	$=$	$\varepsilon\alpha(T^\varepsilon_{\mathrm{blood}} - T_\varepsilon)$	on $\partial(\varepsilon Q)$	interior boundary conditions

Microvascular Model II: Homogenization

Theorem

Let $\theta_2 := \frac{|\partial(\varepsilon Q)|}{|\Omega \backslash \varepsilon Q|}, \quad \theta_3 := \frac{|\Omega \backslash \varepsilon Q|}{|\Omega|} < 1, \quad |\cdot|$ Lebesgue measure

Assume $S_\varepsilon \rightharpoonup \theta_3 S, \quad T^\varepsilon_{\text{blood}} \rightharpoonup \theta_3 T_{\text{blood}}$

Then $T_\varepsilon \rightharpoonup \theta_3 T_0$

$$-\nabla(\mathcal{A}\nabla T_0) + \alpha\theta_2(T_0 - T_{\text{blood}}) = S \quad \text{in } \Omega$$

$$T_0 = T_{\text{bas}} \quad \text{on } \partial\Omega$$

$$\mathcal{A} = (a_{ij}), \quad a_{ij} = \delta_{ij} - \frac{1}{|Y \backslash \varepsilon Q|} \int_{Y \backslash Q} \frac{\partial \chi^j}{\partial y_i}\, dy$$

where

$$-\Delta\chi^j = 0 \quad \text{in } Y \setminus Q$$

$$\frac{\partial(\chi^j - y_j)}{\partial n} = 0 \quad \text{on } \partial Q$$

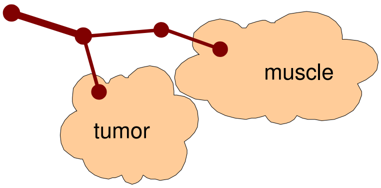
$$\chi^j \quad Y - \text{periodic}$$

Perfusion Model and Steal Effect

Weiser 2006

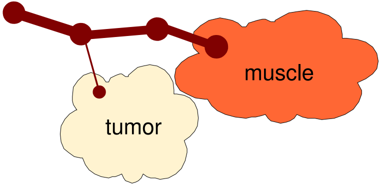
regional perfusion model

- peripheral resistance depends on temperature
- tissue regions compete for blood supply
- regional coupling



steal effect

- heating of healthy tissue decreases tumor perfusion
- observed in clinical practice
- new possibilities for optimizers



Contents

Old: L_2-Optimization with Penalty Functional

minimize the objective function

$$f(p) \quad = \int\limits_{\substack{x \in V_{tm} \\ T(x,p) < T_{th}}} (T_{th} - T(x,p))^2 \, dx \quad + \quad W_h \int\limits_{\substack{x \notin V_{tm} \\ T(x,p) > T_h}} (T(x,p) - T_h)^2 \, dx$$

"no cold spots"

"no hot spots":
penalty for bound violation

V_{tm}	tumor region
W_h	weighting factor
T_{th}	therapeutic temperature (43°C)
T_h	threshold for "hot spots" (42°C)

New: L_∞-Optimization

minimize the objective function

$$f(p) \quad = \int\limits_{\substack{x \in V_{tm} \\ T(x,p) < T_{th}}} (T_{th} - T(x,p))^2 dx$$

"no cold spots"

subject to the box constraints

$$T(x,p) \leq T_h \quad \text{in} \quad \Omega \setminus V_{tm}$$

"no hot spots":

no violation of bound

Function Space Oriented Optimization

Project A1, DFG Research Center MATHEON

(Deuflhard, Tröltzsch, Weiser)

Interior point adaptive multilevel algorithm
complementarity function approach

1D novel approach to optimal control (ZIB)

Weiser, Deuflhard 2001 algorithmic realization

Weiser 2003 linear convergence, mesh independence

3D extensions (ZIB + TU Berlin)

Weiser, Schiela 2004 elliptic problems

Prüfert, Tröltzsch, Weiser 2004 mixed constraints

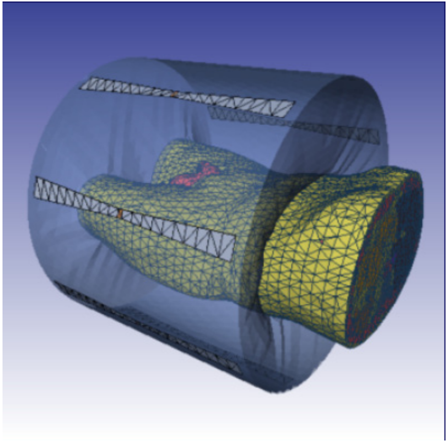
Weiser, Gänzler, Schiela 2004 control reduction, coarse grids

Weiser, Schiela 2005 superlinear convergence

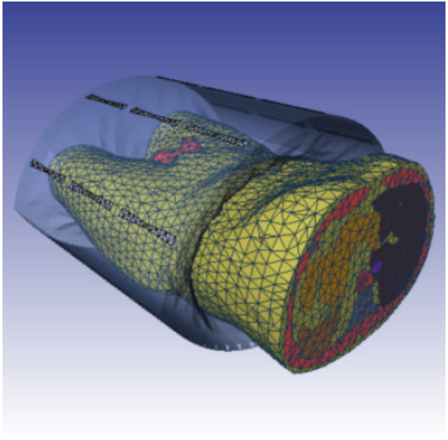
Griesse, Weiser 2005 parametric sensitivities

Contents

Old versus New Applicator

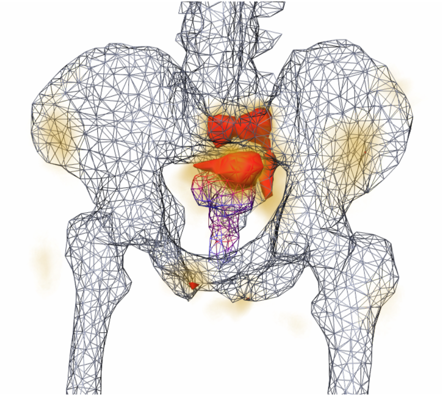


8 antennas, circular cross section

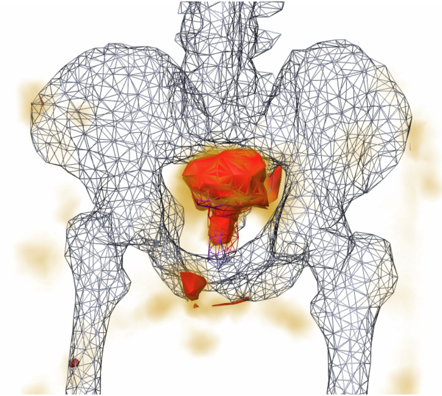


24 antennas, eye-shaped

Old versus New Applicator: Rectum Carcinoma

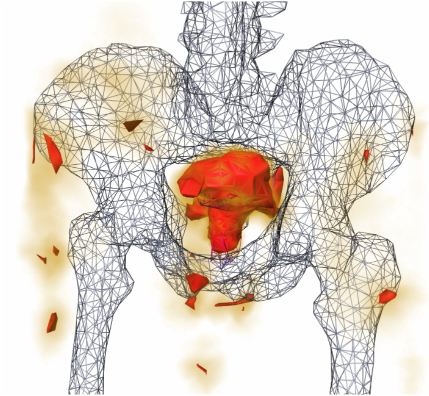


8 antennas

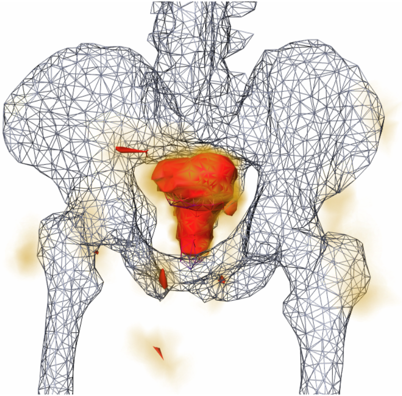


24 antennas

New Applicator: Rectum Carcinoma



150 MHz



200 MHz

Hybrid MRT-Hyperthermia System

- 3D temperature measurement with MRT: feedback loop for optimization

  Gänzler, Volkwein, Weiser 2004 perfusion identification,

  Gellermann, Weihrauch, Weiser et. al. 2006, identification of E fields

- improved patient model regarding treatment situation

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Project Group Electrocardiology

ZIB Scientific Computing:

Computational Medicine

Peter Deuflhard, Bodo Erdmann, Rainer Roitzsch

Cooperation:

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Piero Colli Franzone (Pavia)

Luca Pavarino (Milano)

Glenn Terje Lines, Aslak Tveito (Simula, Oslo)

Contents

Membrane Models and Ionic Currents (ODEs)

reaction $I_{ion}(v,w,c) = \sum_{k=1}^{N} G_k(v,c) \prod_{j=1}^{M} w_j^{p_{j_k}} (v - v_k(c)) + H(v,c)$

dynamics $\partial_t w_j = \alpha_j(v)(1-w_j) - \beta_j(v) w_j, \quad j = 1,\ldots,M$

gating variables	$w := (w_1, \ldots, w_M)$
ionic concentration variables	$c := (c_1, \ldots, c_Q)$
Nernst equilibrium potential	v_k
membrane conductance	G_k
pump and exchanger currents	H
integers	p_{j_k}
coefficients	$\alpha_j > 0$, $\beta_j > 0$

Anisotropic Bidomain Model (B)

$$\begin{aligned}
c_m \partial_t v - \operatorname{div}(D_i \nabla u_i) + I_{ion}(v,w,c) &= 0 && \text{in } \Omega \times (0,T) \\
-c_m \partial_t v - \operatorname{div}(D_e \nabla u_e) - I_{ion}(v,w,c) &= -I^e_{app} && \text{in } \Omega \times (0,T)
\end{aligned}$$

$$\begin{aligned}
&\partial_t w - R(v,w) = 0 && \text{in } \Omega \times (0,T) \\
&\partial_t c - S(v,w,c) = 0 && \text{in } \Omega \times (0,T)
\end{aligned}$$

$$\begin{aligned}
&\mathbf{n}^T D_{i,e} \nabla u_{i,e} = 0 && \text{in } \partial\Omega \times (0,T) \\
&v(\mathbf{x},0) = v_0(\mathbf{x}), \;\; w(\mathbf{x},0) = w_0(\mathbf{x}), \;\; c(\mathbf{x},0) = c_0(\mathbf{x}) && \text{in } \Omega,
\end{aligned}$$

intra-extra-cellular potentials	$u_i(\mathbf{x},t)$, $u_e(\mathbf{x},t)$
transmembrane potential	$v(\mathbf{x},t) = u_i(\mathbf{x},t) - u_e(\mathbf{x},t)$
gating variables	$w(\mathbf{x},t)$
ion concentrations	$c(\mathbf{x},t)$
conductivity tensors	D_i, D_e
capacitance	c_m
reaction terms	I_{ion}, $R(v,w)$, $S(v,w,c)$
applied extra-cellular current per unit volume	I^e_{app}
uniqueness of solution u_i, u_e by imposing	$\int_\Omega u_e dx = 0$

Anisotropic Monodomain Model (M)

$$
\begin{aligned}
&c_m \partial_t v - \mathrm{div}(D_m \nabla v) + I_{ion}(v,w,c) = I_{app}^m && \text{in } \Omega \times (0,T) \\
&\partial_t w - R(v,w) = 0 && \text{in } \Omega \times (0,T) \\
&\partial_t c - S(v,w,c) = 0 && \text{in } \Omega \times (0,T) \\
&\mathbf{n}^T D_m \nabla v = 0 && \text{in } \partial\Omega \times (0,T) \\
&v(\mathbf{x},0) = v_0(\mathbf{x}),\;\; w(\mathbf{x},0) = w_0(\mathbf{x}),\;\; c(\mathbf{x},0) = c_0(\mathbf{x}) && \text{in } \Omega.
\end{aligned}
$$

transmembrane potential	$v(\mathbf{x},t) = u_i(\mathbf{x},t) - u_e(\mathbf{x},t)$
gating variables	$w(\mathbf{x},t)$
ion concentrations	$c(\mathbf{x},t)$
conductivity tensors	D_m
capacitance	c_m
reaction terms	$I_{ion},\; R(v,w),\; S(v,w,c)$
applied extra-cellular current per unit volume	I_{app}^m

FitzHugh-Nagumo Model (FHN)

$M = 1$, $N = 1$

$$
\begin{aligned}
I_{ion}(v, w) &= Gv(1 - v/v_{th})(1 - v/v_p) + \eta_1 vw, \\
\partial_t w &= \eta_2 \, (v/v_p - \eta_3 w)
\end{aligned}
$$

threshold potential	v_{th}
peak potential	v_p
positive real coefficients	G, η_1, η_2, η_3

FHN variant due to Rogers and McCulloch (1994)

Luo-Rudy Phase-I Model (LR1)

$M = 6$, $N = 6$, $Q = 1$

$$
\begin{aligned}
I_{ion} &= I_{Na} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b \\
\partial_t w_j &= \alpha_j(v)(1 - w_j) - \beta_j(v) w_j, \quad j = 1, \dots, 6 \\
\partial_t c &= 0.07(10^{-4} - c) - 10^{-4} I_{si}
\end{aligned}
$$

two inward currents $I_{Na}(w,c)$, $I_{si}(w,c)$
four outward currents $I_K(w,c)$, I_{K1}, I_{Kp}, I_b

Luo and Rudy (1991)

Aliev-Panfilov Model (AP)

$M = 1,\, N = 1$

$$
\begin{aligned}
I_{ion}(v,w) &= (v_p - v_r)(G_a v(v-a)(v-1) + vw) \\
\partial_t w &= 0.25 \left(\varepsilon + \frac{\mu_1 w}{v + \mu_2}\right)(-w - G_s v(v-a-1))
\end{aligned}
$$

rest potential	v_r
peak potential	v_p
positive real coefficients	$G_a,\, G_s,\, \mu_1,\, \mu_2,\, \varepsilon$

FitzHugh-Nagumo variant due to Aliev and Panfilov (1996)

Complexity of Bidomain Model (Lines, Tveito et al 2003)

heart volume (250 cm^3)

heart beat cycle time (500 ms)

Space (uniform mesh):	50 nodes / cm / dimension 125,000 / cm^3 31,000,000 nodes for full heart memory: 2 KB/node total memory consumption: 50 GB
Time (constant time steps):	minimum time step 0.01 ms 50,000 time steps per heart beat cycle CPU: 1ms / node / time step total CPU time of 50 years per heart beat fibrillation: full series of heart beats!

Multiscale Spreading

Space

cardiac tissue	$\approx$	10 cm
steep excitation front	$\approx$	0.1 mm

spread factor 10^3

Time

heartbeat	$\approx$	1 s
rapid kinetics	$\approx$	0.1-500 ms
timesteps	$\approx$	0.001 ms or less

spread factor 10^6

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Rothe Method: first Time, then Space Discretization

Time Discretization

Rosenbrock scheme

with timestep control

System of Linear Elliptic Problems

adaptive multilevel FEM

Bornemann (1990), Lang, Walter (1993),

Deuflhard, Lang, Nowak (1996), Lang (2000)

Rothe Method II: Code KARDIO

Time

Rosenbrock scheme ROS3PL (Lang, 2006)

- linearly implicit
- L-stable
- order 3
- no order reduction in parabolic PDEs

Space

Finite elements 3D (Deuflhard, Leinen, Yserentant 1989, Bornemann, Erdmann, Kornhuber, 1993)

- linear elements
- adaptive refinement
- multilevel code family KASKADE (ZIB or TU Darmstadt)

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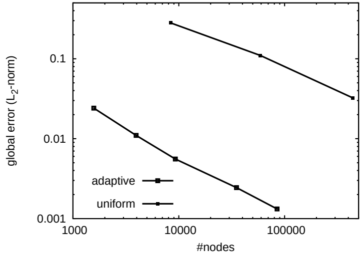
Adaptivity Gain (M-FHN)

Observed time scale spreading (stepsize control):

spread factor $\sim 10^3$

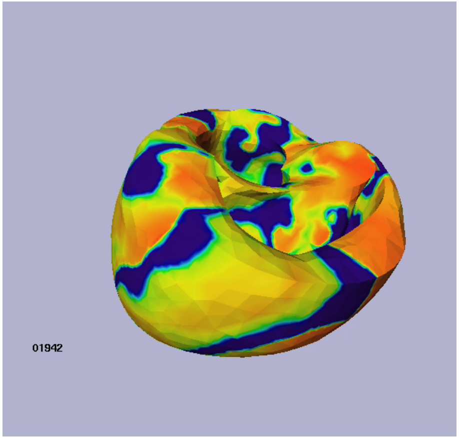
Observed spatial scale spreading (adaptive multilevel FEM):

spread factor $\sim 10^2$



Colli Franzone, Deuflhard, Erdmann, Lang, Pavarino, 2006

Fibrillation Cooperation: Tveito, Lines (2006)



Second stimulus $\sim$ 221 ms out of phase, simulation over ~ 600 ms

CPU time: $\sim$ 10 s per 1 ms for $TOL_t = 0.001, TOL_x = 0.01$

Electrocardiological Models: complexity comparison

Depolarization / repolarization of action potential

	domain	membrane model	PDEs	ODEs	KARDIO
B-LR1	bi	Luo-Rudy	2	7	200
B-FHN	bi	FitzHugh-Nagumo	2	1	3
M-LR1	mono	Luo-Rudy	1	7	60
M-FHN	mono	FitzHugh-Nagumo	1	1	1

Reentrant cardiac arrhythmias

	domain	membrane model	PDEs	ODEs	KARDIO
M-AP	mono	Aliev-Panfilov	1	1	1