Parallel Numerical Solution of Intracellular Calcium Dynamics

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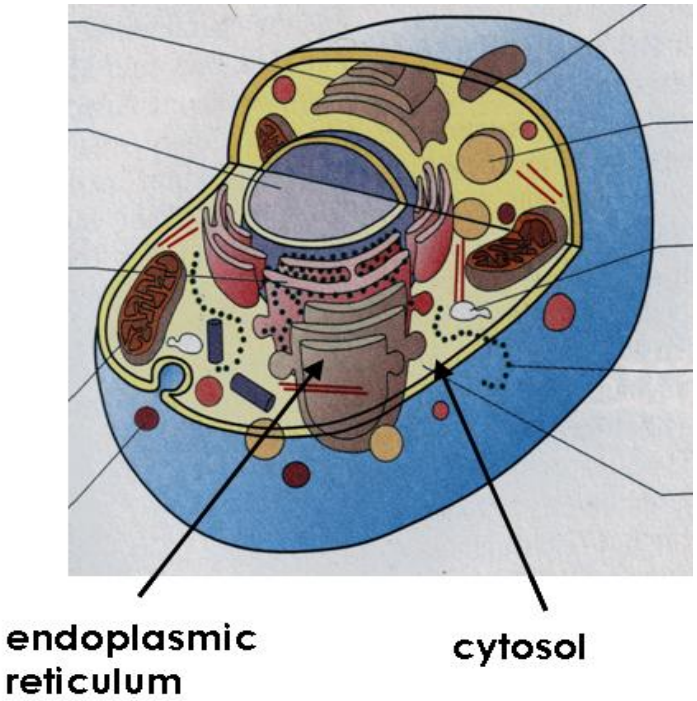
Outline

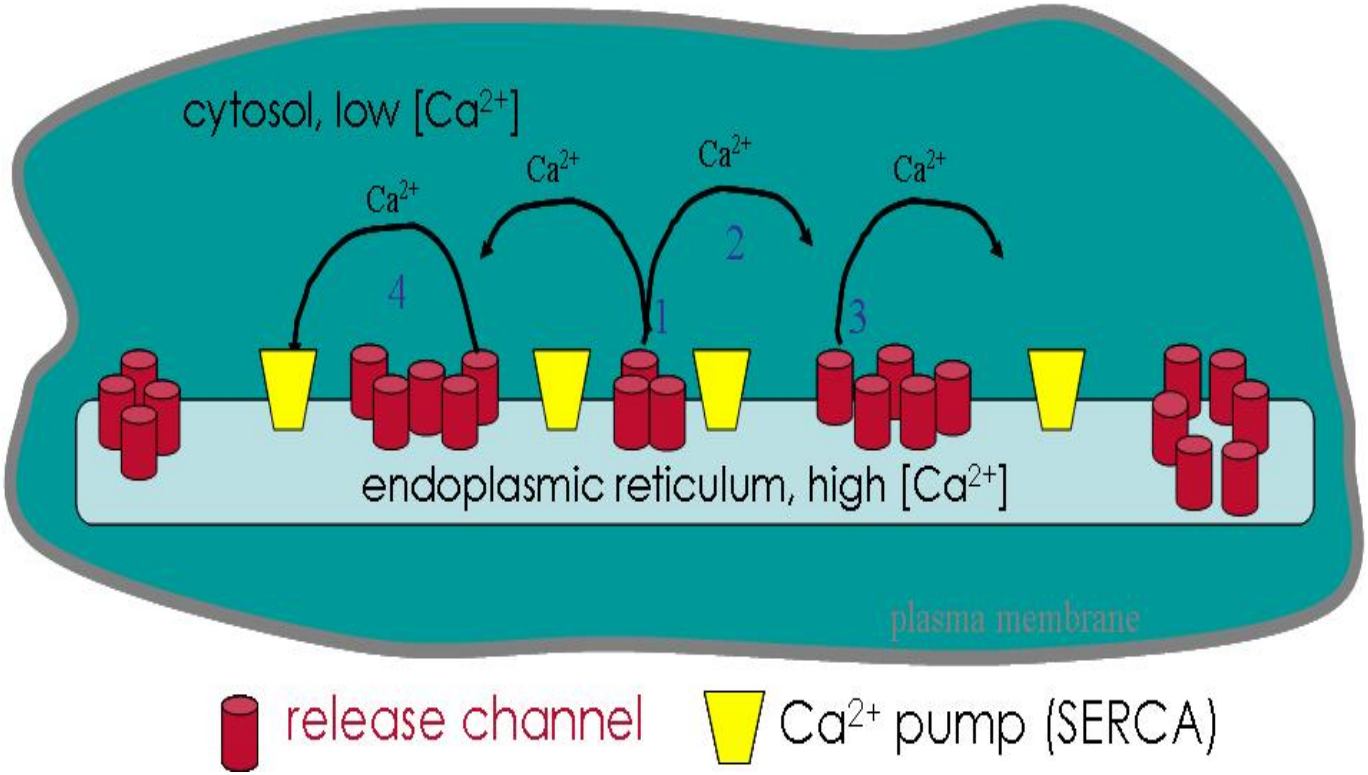
Introduction

- The endoplasmic reticulum (ER) has a high calcium concentration
- Channels: ER→cytosol, pumps: cytosol→ER
- Ca^{2+} is released by transient openings of channels

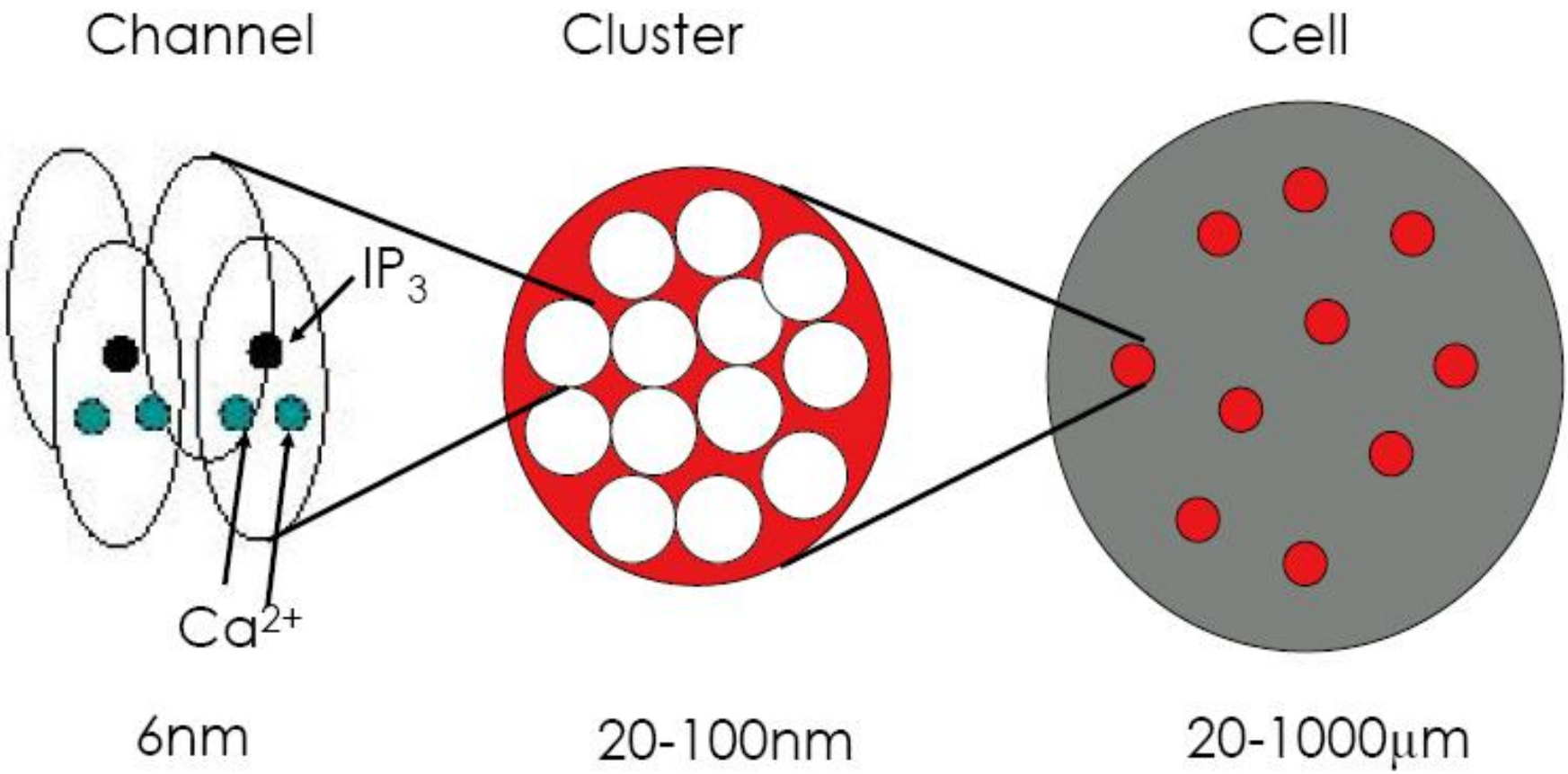


Introduction

- channel opens, releases Ca^{2+} from the ER into the cytosol
- Ca^{2+} diffuses to neighboring channels
- increase of Ca^{2+} favors opening: amplification
  very high Ca^{2+} decreases opening probability: inhibition
- Ca^{2+} is pumped back from the cytosol into the ER



Structure of Cluster and Channels



20,000-1000,000 nm

Experimental Result

$<$ *experimentmovie.avi* $>$
Puffs and waves in the stochastic regime (I. Parker, UC Irvine)

Deterministic Equations in 2D

$$
\begin{aligned}
\frac{\partial c}{\partial t} &= D_c \Delta c + (P_l + P_c(r))(E - c) - P_p \frac{c^2}{K_d^2 + c^2} - \sum_i H_i(c, b_i) \\
\frac{\partial E}{\partial t} &= D_E \Delta E - \gamma \left[(P_l + P_c(r))(E - c) - P_p \frac{c^2}{K_d^2 + c^2} \right] - \sum_j K_j(c, b_{E,j}) \\
\frac{\partial b_i}{\partial t} &= D_{b,i} \Delta b_i + H_i(c, b_i), \quad i = 0, n-1 \\
\frac{\partial b_{E,j}}{\partial t} &= D_{E,j} \Delta b_{E,j} + K_j(E, b_{E,j}), \quad j = 0, m-1.
\end{aligned}
$$

where

$$H_i = k_{b,i}^+ (B_i - b_i)c - k_{b,i}^- b_i$$

$$K_j = k_{E,j}^+ (G_i - b_{E,j})E - k_{E,j}^- b_{E,j}$$

B.C's: no flux at the boundaries [Thul 04; Falcke 03,04].

Determination of $P_c(r)$

Each cluster is given by a fixed position $\vec{X}_i$ and its radius

$$R_i = R_S\sqrt{N_{\text{open},i}}$$

$N_{\text{open},i}$ is the number of open channels in cluster i. This number is determined by channel dynamics.

$$P_c(\vec{r}_i) = \begin{cases} P_{ch} & \text{if } \left\|\vec{r}_i - \vec{X}_i\right\| < R_i \text{ for a cluster i} \\ 0 & \text{otherwise} \end{cases}$$

Zienkiewicz-Zhu Error Indicator

Let $Gu_h \in V_h$ be the $\langle ., . \rangle_h$-projection of ∇u_h onto V_h, calculated by

$$Gu_h(x_i) = \sum_{T \subset w_x} \frac{|T|}{|w_x|} \nabla u_{h|T}(x_i)$$

Error estimator

$$\eta_{Z,T} := \|Gu_h - \nabla u_h\|_{L^2(T)}$$

and

$$\eta_Z := \left\{ \sum_{T \in \mathcal{T}_h} \eta_{Z,T}^2 \right\}^{1/2}$$

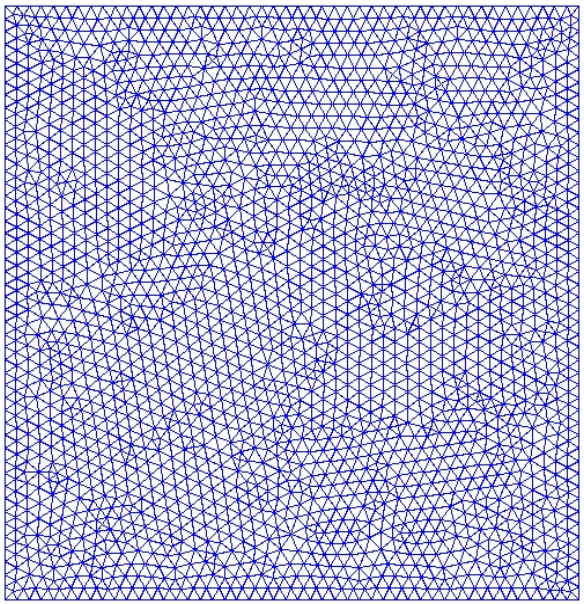
O. C. Zienkiewicz, J. Z. Zhu. A simple error estimator and adaptive procedure for practical engineering analysis. *Int. J. Num. Meth. Eng.* 24 (1987) 337-357

Zienkiewicz-Zhu Error Indicator

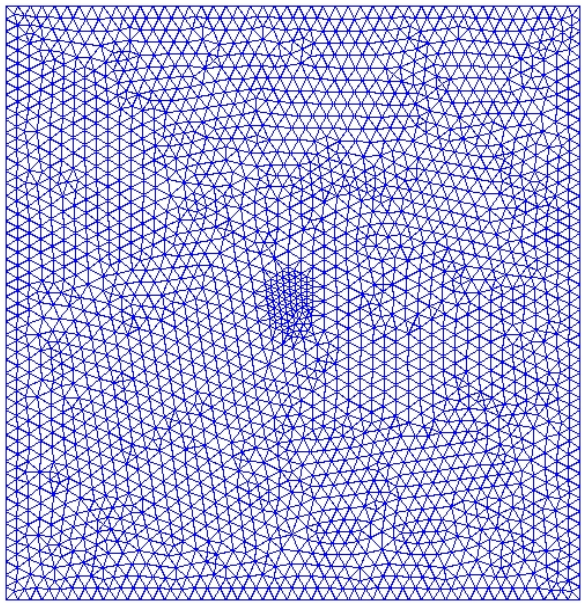
- Let $\lambda(T) \in \mathbb{N}_0$ be the refinement level of triangle $T \in \mathcal{T}_h$, $\lambda_{\max} \in \mathbb{N}_0$ be a given maximum refinement level
- $\varphi_1, \ldots, \varphi_{\lambda_{\max}}$ given real numbers satisfying $0 \leq \varphi_1 \leq \ldots \leq \varphi_{\lambda_{\max}}$.
- Triangle T is marked for refinement if $\eta_Z \in [\varphi_i, \varphi_{i+1}]$ and $\lambda(T) < i, \quad i = 0, \ldots, \lambda_{\max}$.
- Adaption parameters are $\lambda_{\max} = 6$ and $\varphi_1 = 0.0001, \varphi_2 = 0.0002, \varphi_3 = 0.0004, \varphi_4 = 0.0008, \varphi_5 = 0.0016, \varphi_6 = 0.0032$.
- Programm package UG (Unstructured Grid) developed by group of G. Wittum and P. Bastian at University of Heidelberg.

P. Bastian, K. Birken, S. Lang, K. Johannsen, N. Neuß, H. Rentz-Reichert and C. Wieners. UG: A flexible software toolbox for solving partial differential equations. *Computing and Visualization in Science, 1 (1997) 27–40*

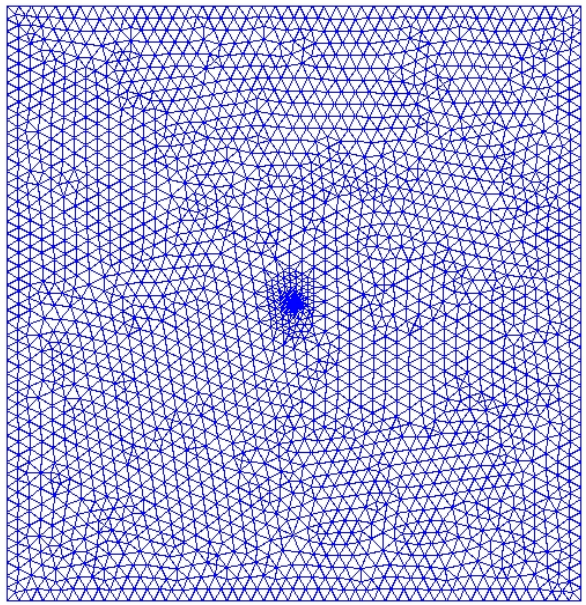
Adaptive Mesh for Single Cluster



level 0 (initial mesh)
nodes = 2378
elements = 4566

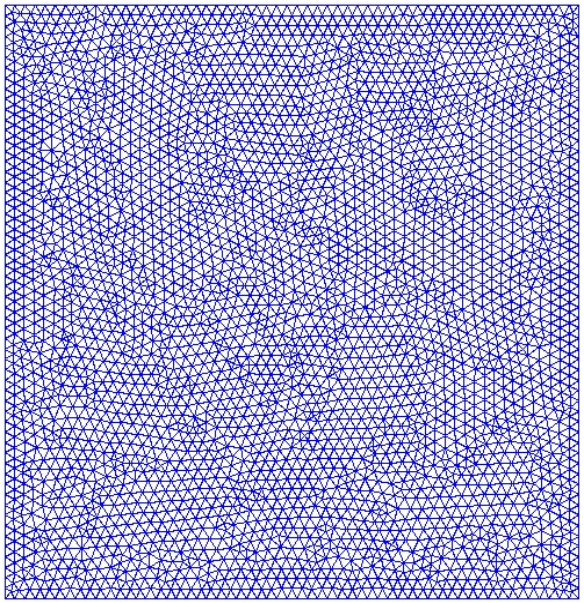


level 1
nodes = 2433
elements = 4676

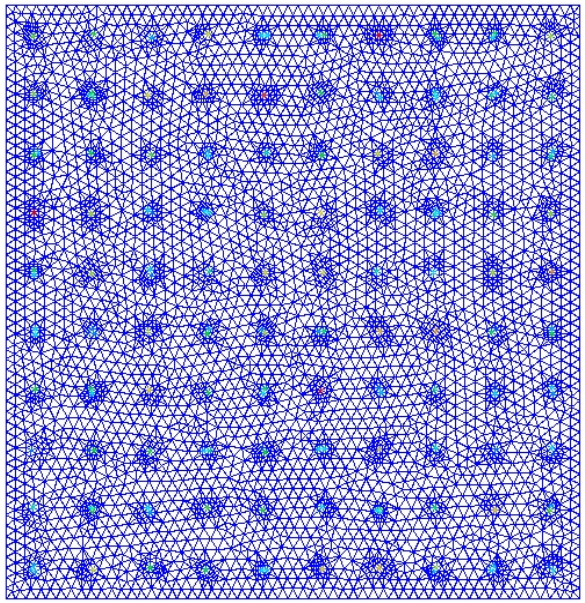


level 6
nodes = 2766
elements = 5342

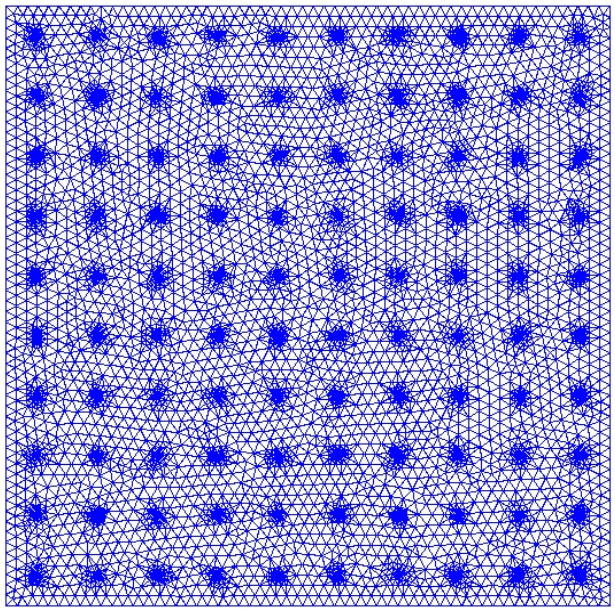
Adaptive Mesh for 100 Clusters



level 0 (initial mesh)
nodes = 3503
elements = 6776



level 1
nodes = 4964
elements = 9698



level 6
nodes = 19367
elements = 38204

Typical Problem

$$\frac{\partial u(\underline{x},t)}{\partial t} - \nabla \cdot (a(\underline{x})\nabla u(\underline{x},t)) + s(u(\underline{x},t)) = f(\underline{x},t) \quad \text{in } \Omega \times (0,T]$$

$$\frac{\partial u(\underline{x},t)}{\partial \eta} = 0 \quad \text{on} \quad \partial\Omega \times (0,T].$$

Spatial Discretization

Weak formulation

find $u \in V = H^1(\Omega)$ such that

$$\langle \frac{\partial u}{\partial t}, v \rangle + \langle a(\underline{x}) \nabla u, \nabla v \rangle + \langle s(u), v \rangle = \langle f, v \rangle \quad \text{for all} \quad v \in V$$

$$\langle \frac{\partial u_h}{\partial t}, v_h \rangle + \langle a(\underline{x}) \nabla u_h, \nabla v_h \rangle + \langle s(u_h), v_h \rangle = \langle f, v_h \rangle \quad \text{for all} \quad v_h \in V_h$$

Approximate the solution $u_h \in V_h$ using the basis functions

$u_h(t, x) = \sum_{i=1}^{N} u_i(t) \phi_i(x)$

Spatial Discretization

$$\mathbf{M}\dot{\mathbf{u}} + \mathbf{A}\mathbf{u} + \mathbf{S} = \mathbf{F} \tag{1}$$

where **M** - mass matrix, **A** - stiffness matrix. The matrices are defined as follows,

$$\mathbf{M} = \langle \phi_i, \phi_j \rangle, \qquad \mathbf{A} = \langle a(\underline{x}) \nabla \phi_i, \nabla \phi_j \rangle$$
$$\mathbf{S} = \langle s(\sum_{i=1}^{N} u_i(t)\phi_i(x)), \phi_j \rangle \qquad \mathbf{F} = \langle f, \phi_j \rangle.$$

Approximate the term **S** using quadrature rule

$$\mathbf{S} = \langle \phi_i, \phi_j \rangle s(u_i) = \mathbf{MR}.$$

Mass lumping, inverting the lumped mass matrix

$$\dot{\mathbf{u}} = -\mathbf{M}^{-1}\mathbf{A}\mathbf{u} - \mathbf{R} + \mathbf{M}^{-1}\mathbf{F} \tag{2}$$

Time Discretization

We considered the ODE problem

$$\frac{\partial \mathbf{u}}{\partial t} = F(t, \mathbf{u}), \qquad \mathbf{u}(t^0) = \mathbf{u^0}. \tag{3}$$

The i-th time step of a W-method of order p with embedding of order $\hat{p} \neq p$ has the form

$$(\mathbf{I} - \tau^i \gamma \mathbf{J})\mathbf{k}_j = F\left(t^i + \tau^i a_j, \mathbf{u}^i + \tau^i \sum_{l=1}^{j-1} b_{lj}\mathbf{k}_l\right) + \sum_{l=1}^{j-1} c_{lj}\mathbf{k}_l, \quad j = 1, \ldots, s, \tag{4}$$

$$\mathbf{u}^{i+1} = \mathbf{u}^i + \tau^i \sum_{l=1}^{s} d_l \mathbf{k}_l, \tag{5}$$

$$\hat{\mathbf{u}}^{i+1} = \mathbf{u}^i + \tau^i \sum_{l=1}^{s} \hat{d}_l \mathbf{k}_l. \tag{6}$$

B. A. Schmitt and R. Weiner. Matrix-free W-methods using a multiple Arnoldi iteration. *Appl. Num. Math. 18 (1995) 307-320*

Time Discretization

We use a W-method with $s = 3$ stages given by the coefficients

$$\gamma = 1 - \frac{1}{2}\sqrt{2}, \quad a_1 = 0, \quad a_2 = 1, \quad a_3 = 1, \quad b_{12} = 1, \quad b_{13} = 1, \quad b_{23} = 0,$$
$$c_{12} = -2 - \sqrt{2}, \quad c_{13} = -1, \quad c_{23} = -1 + \sqrt{2},$$
$$d_1 = 1, \quad d_2 = \frac{1}{2} - \frac{1}{2}\sqrt{2}, \quad d_3 = \frac{1}{2},$$
$$\hat{d}_1 = \frac{9}{10} - \frac{1}{20}\sqrt{2}, \quad \hat{d}_2 = \frac{9}{20} - \frac{11}{20}\sqrt{2}, \quad \hat{d}_3 = \frac{11}{20} + \frac{1}{20}\sqrt{2}. \tag{7}$$

This method was used by Schmitt and Weiner for the construction of a Krylov-W-method.

Time Discretization

A new time step τ_{new} is computed by

$$\bar{\tau} := \beta \tau^i \left(\frac{TOL_t}{\epsilon} \right)^{\frac{1}{\hat{p}+1}}, \quad \tau_{\text{new}} := \begin{cases} \beta_{\max} \tau^i, & \bar{\tau} > \beta_{\max} \tau^i, \\ \beta_{\min} \tau^i, & \bar{\tau} < \beta_{\min} \tau^i, \\ \bar{\tau}, & \text{otherwise.} \end{cases}$$

where $\beta > 0$ is safety factor.

Linear Solver

- Solve s linear systems of the general form

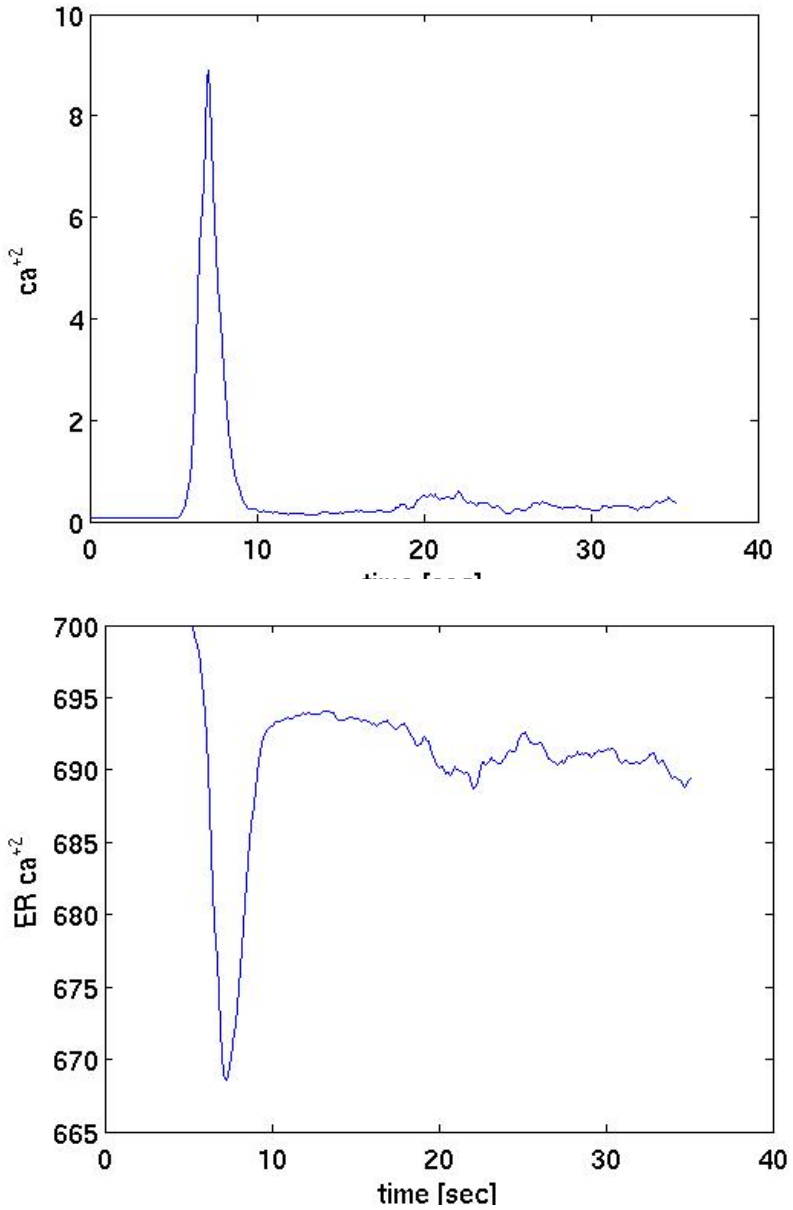
$$(\mathbf{I} - \tau^i \gamma \mathbf{J})\mathbf{k}_j = b_j, \quad j = 1, \ldots, s.$$

  where k_j are the unknown vectors and $A := \mathbf{I} - \tau^i \gamma \mathbf{J}$ is the same for all stages.
- Iterative solvers are appropriate
- BiCGSTAB method with ILU preconditioning.
- Tolerance for the linear solver is $TOL_{LS} = \alpha_{LS} TOL_t / \tau_i$

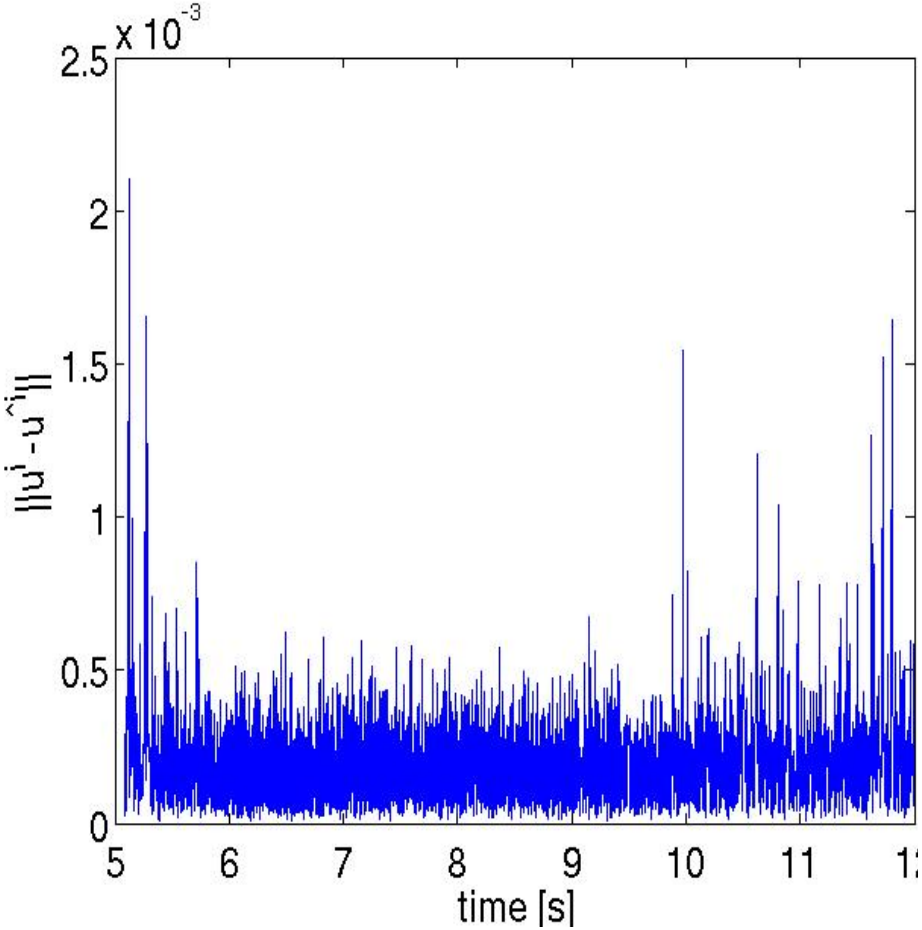
H.A. van der Vorst. Bi-CGSTAB: A fast and smoothly converging variant of Bi-CG for the solution of nonsymmetric linear systems. *SIAM J. Sci. Stat. Comput. 13 (1994) 631-644*

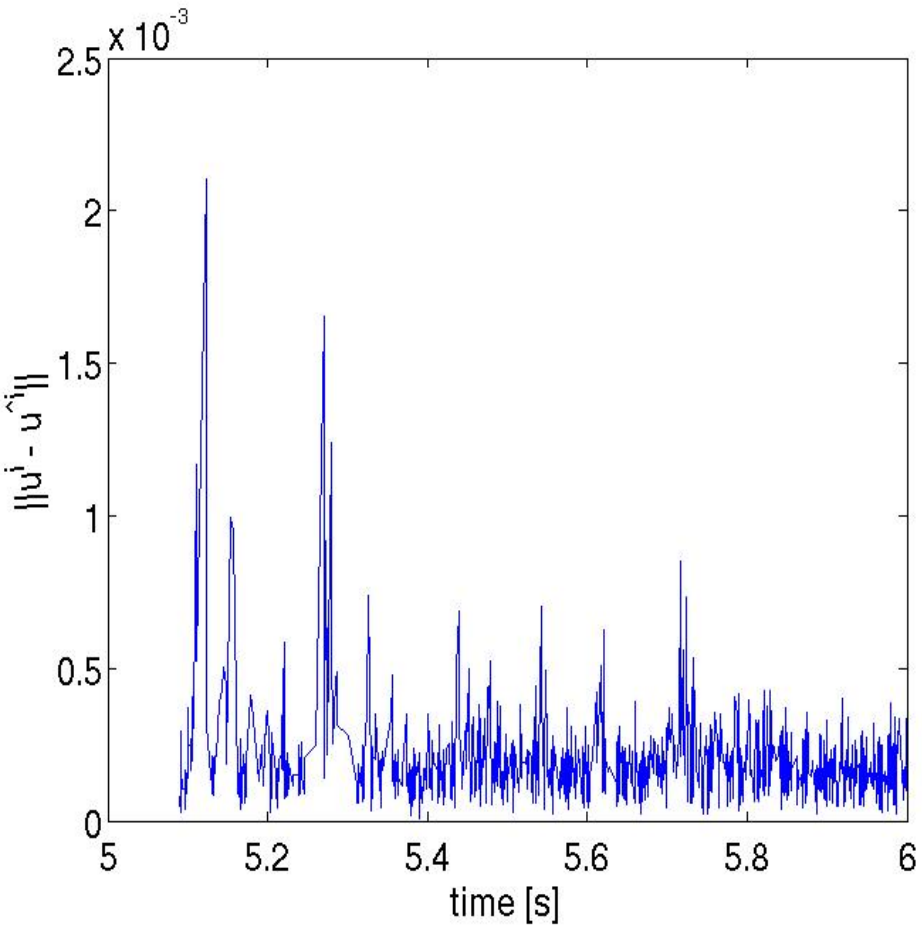
Numerical Results

< *Calcium*100*clustersStoc.avi* >

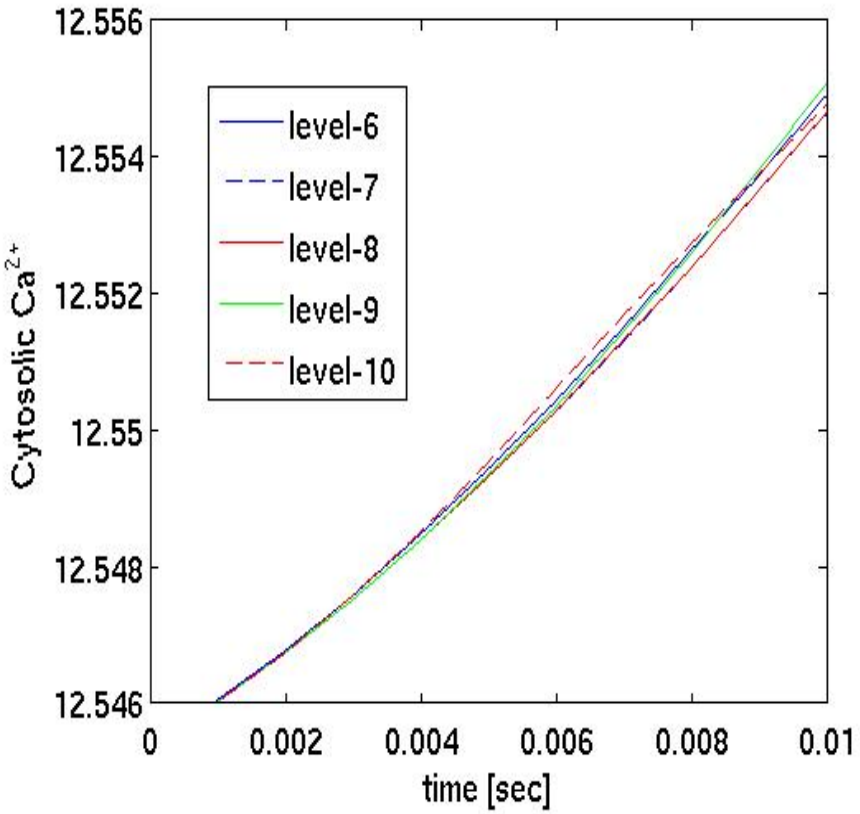


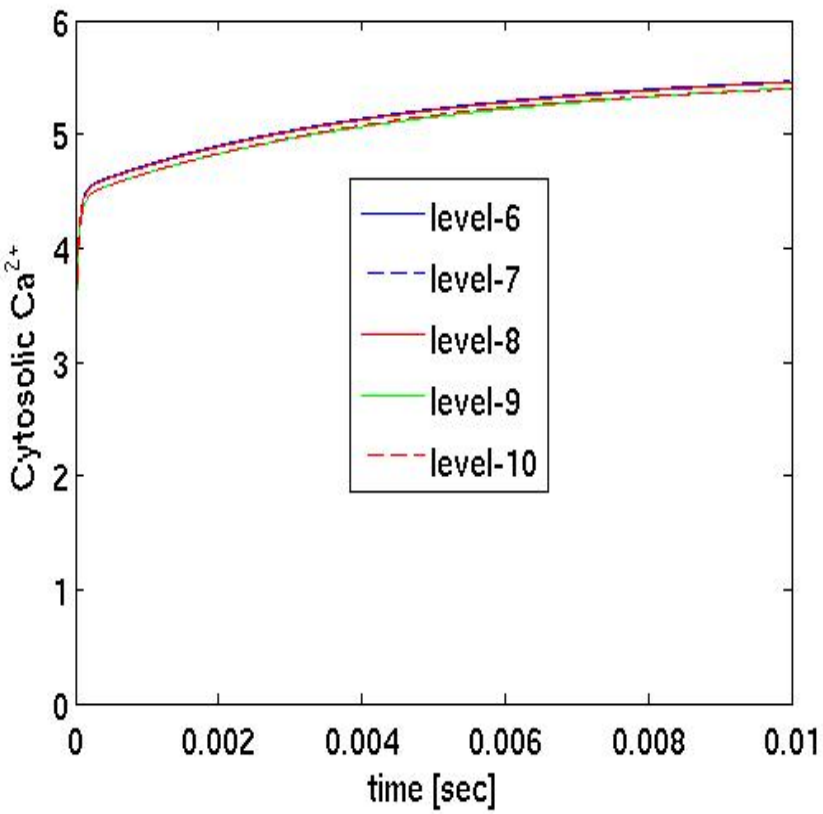
Time Step Rejections



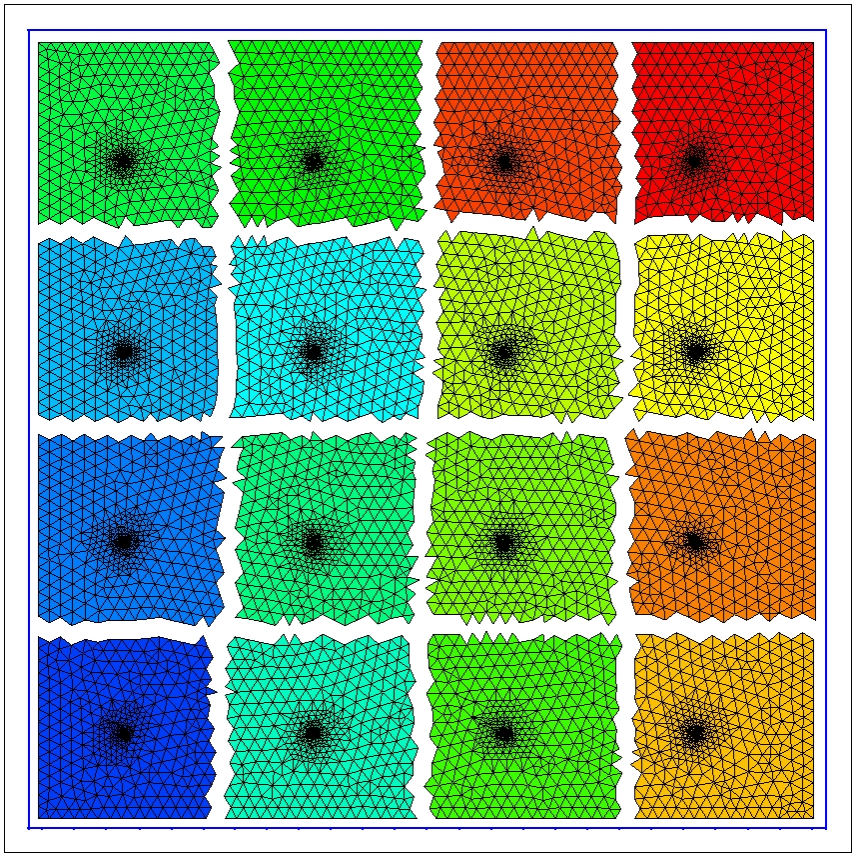


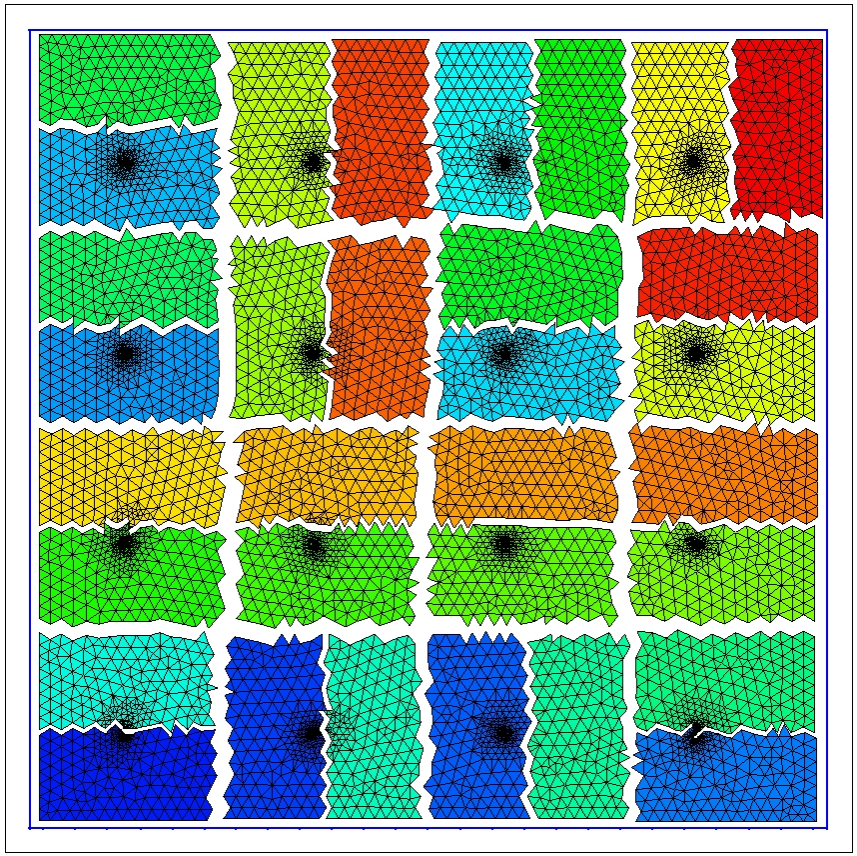
Numerical Result with One Opening Channel





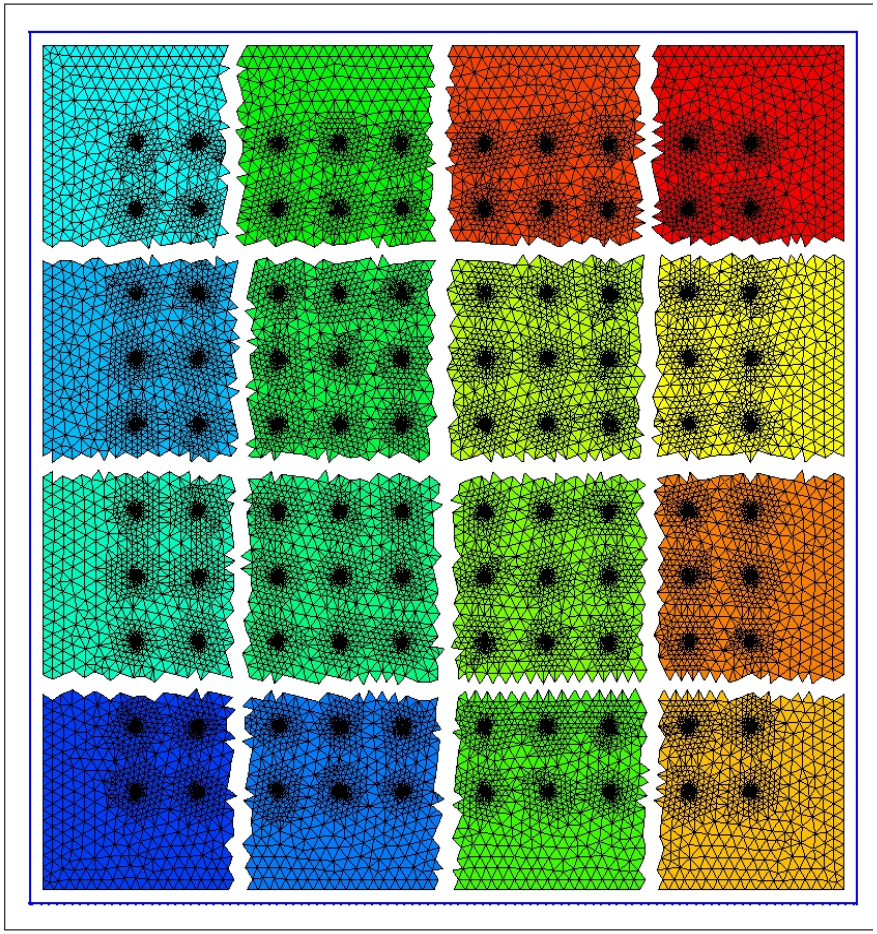
Domain Decomposition using RIB algorithm

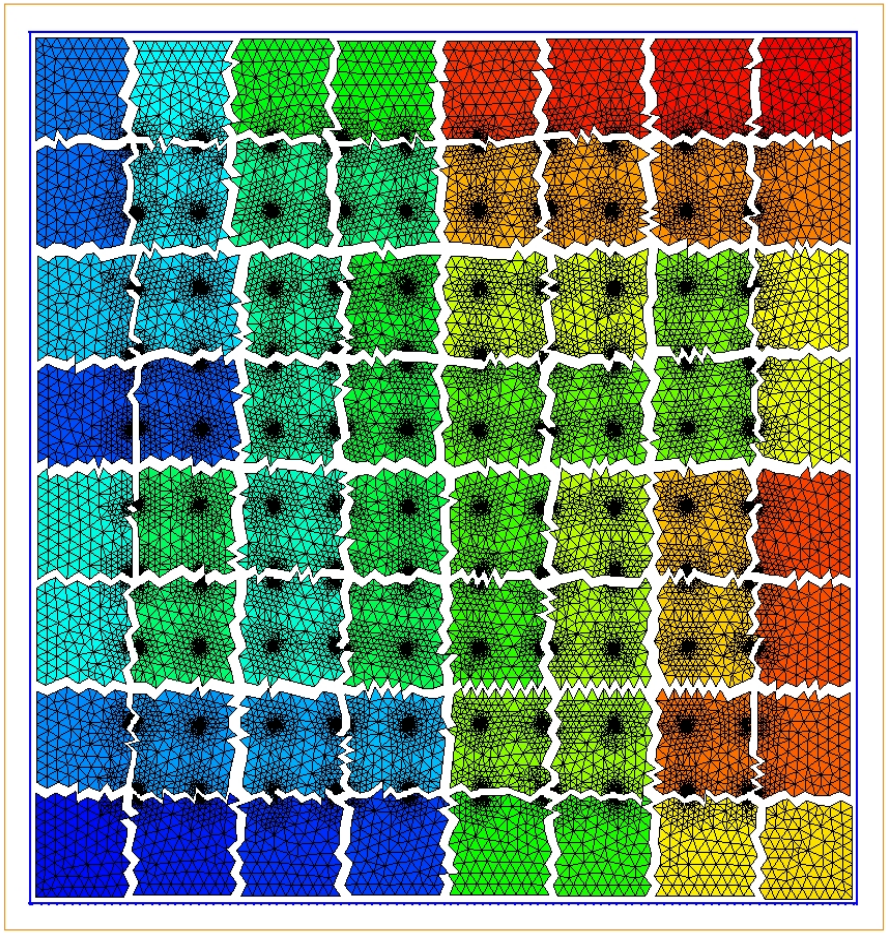




B. Hendrickson, R. Leland. The CHACO user's guide 1.0. Technical Report SAND93-1301, Sandia National Laboratory, 1993.

Domain Decomposition using RIB algorithm





nodes = 33,322 elements = 66,370 unknowns = 133,288
nodes = 32,417 elements = 64,560 unknowns = 129,668

Simulation Result

< *CytosolCalDD.avi* >

Conclusions and Future Work

- Obtained good results in 2D with many clusters and channels.
- Good results in 3D with one cluster and many channels.
- Obtained good results in 2D using domain decomposition methods with deterministic opening of channels.
- Increasing the efficiency with different time stepping methods.
- Numerical results for the 3D with many clusters effectively.
- Increasing the parallel efficiency.