Wound Healing

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The healing process

Healing in mammals is a complex process where a series of biomechanical and biochemical responses occur to close a wound by cell migration and contraction.

A greater comprehension of the biological mechanics behind the healing could represent a benefit for the clinical management of normal and abnormal wounds.

For our present work we will use the equations presented by Oster, Murray et al, and we will expand the work done by Maini et al for the two dimensional case with a finite difference approach.

Some definitions

- Collagen

  Main protein of connective tissue in animals

- Extracellular matrix

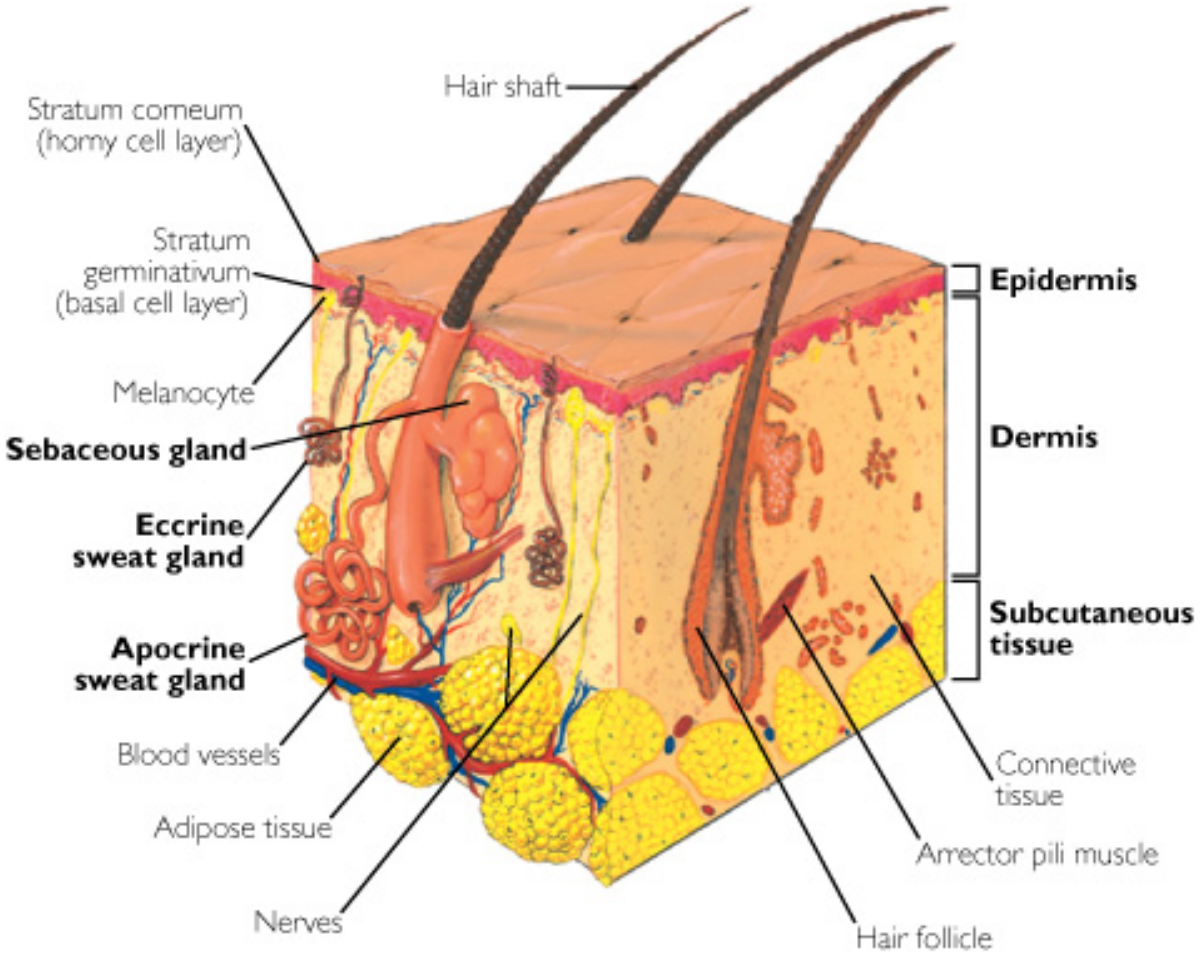
  Part of animal tissue that provides structural support

- Fibroblast

  Cell that synthesizes ECM matrix and collagen

- Growth Factor

  Substance capable of stimulating cellular growth, proliferation and differentiation.


Hair shaft
Stratum corneum (horny cell layer)
Stratum germinativum (basal cell layer)
Melanocyte
Sebaceous gland
Eccrine sweat gland
Apocrine sweat gland
Blood vessels
Adipose tissue
Nerves
Epidermis
Dermis
Subcutaneous tissue
Connective tissue
Arrector pili muscle
Hair follicle

Healing process

- Inflammation
- Proliferation
- Remodeling

Inflammation

A cloth is formed to stop the bleeding and growth factors are released to attract inflammatory cells to eliminate debris, bacteria and damaged tissue.

It usually last 2-3 days after the injury, if its last too long it can cause tissue damage leading to a chronic wound.

Proliferation

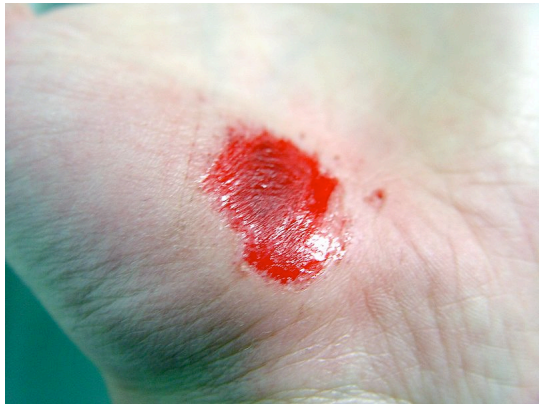
Fibroblasts start entering the wound site, endothelial cells from non injured blood vessels go through the ECM matrix into the wound site

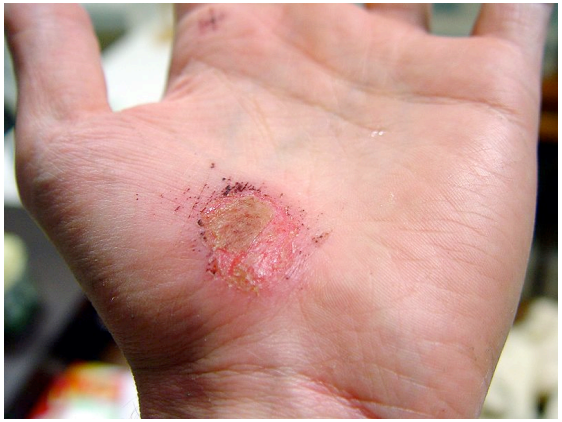
Before they start to migrate they must destroy the desmosomes, the attachments to other cells and the ECM matrix.

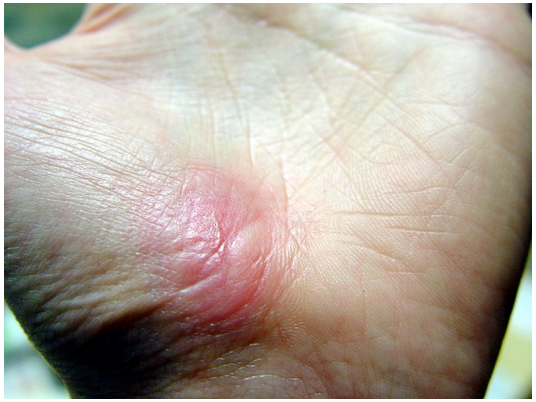
As the cell front advance new cells are produced at the wound edge, until the cells meet at the center of the wound and then stop their movement

Remodeling

This stage can take up to a year or more, its purpose is to convert the provisional ECM matrix into something more like the original ECM matrix, rearranging collagen fibers.







The equations

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}\left[n\frac{\partial u}{\partial t} + \chi(\rho)n\frac{\partial \rho}{\partial x} - D(\rho)\frac{\partial n}{\partial x}\right] = P(n,\rho),$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(\rho\frac{\partial u}{\partial t}) = B(n,\rho),$$

$$\frac{\partial}{\partial x}\left[n\frac{\partial^2 u}{\partial x \partial t} + E\frac{\partial u}{\partial x} + \tau(n,\rho)\right] = F(n,\rho)$$

Where,

- ρ(x,t) is the ECM density
- *n* is the cell density
- *u* is the displacement

- Body forces

  F measures the strength of the ECM matrix to the underlying tissues. Generally the ECM matrix is attached elastically to the epithelial layer

- Traction forces

  Depends on the adhesion between cell surface and collagen fibers.

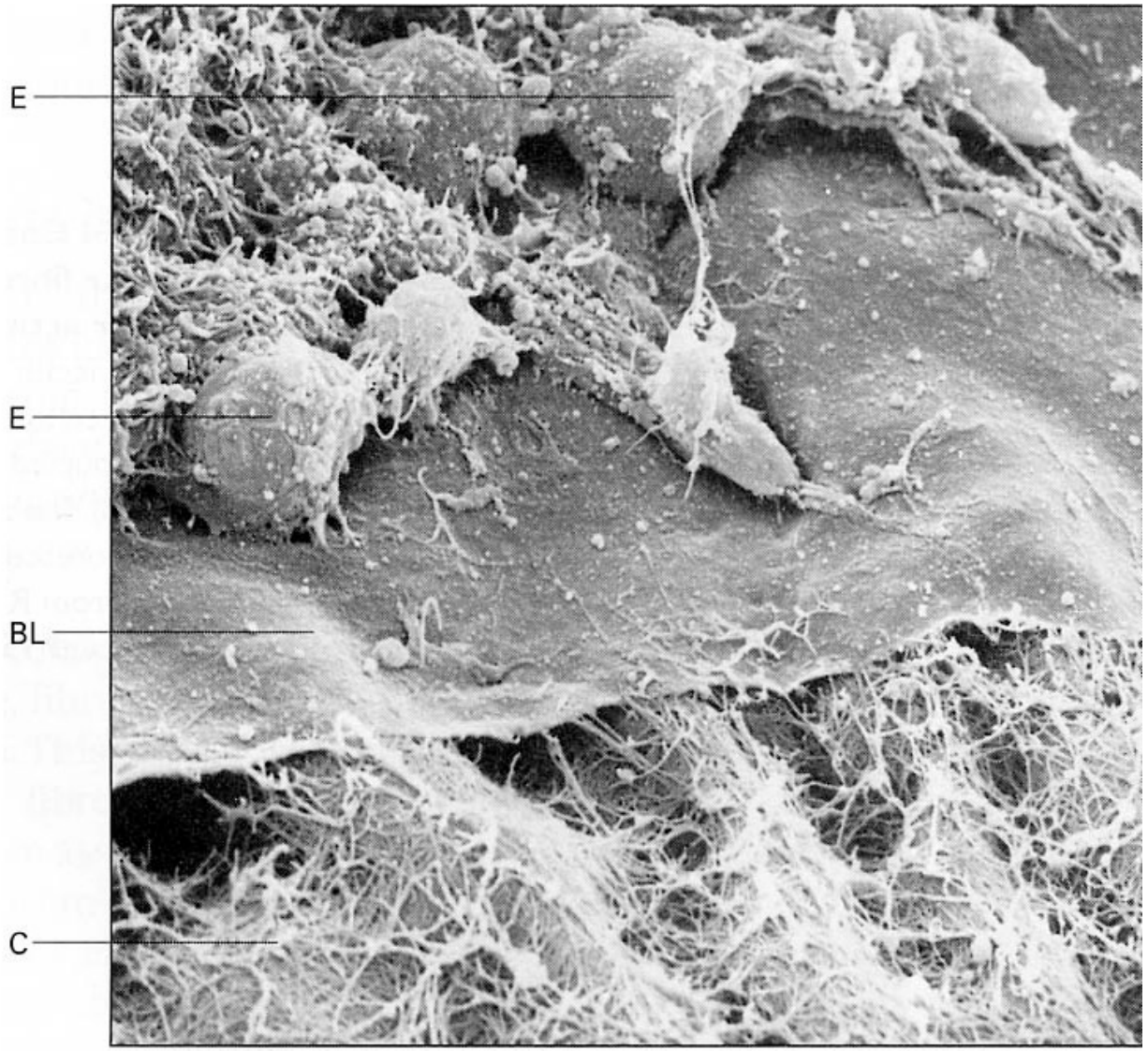
$$\tau(n,\rho) = \frac{T_0 n \rho}{R^2 + \rho^2}$$

Basal Lamina

- thin mat of extracellular matrix that separates all epithelial cell sheets and glands, and many other cell types (muscle, fat, Schwann cells), from the connective tissue.

- **basement membrane** refers to the light microscopic appearance of the BL / reticular lamina beneath epithelia or the 2 fused BL in glomeruli / alveoli.

E = Epithelial cells
BL = Basal lamina
C = Collagen fibrils



(from Molecular Biology of the Cell)

Assumptions

- For normal tissue we set the cell and the ECM density to one.
- Fibroelastic cells prolifarate according to a logistic growth law,

$$P = rn(1 - n)$$

where r is the linear growth rate and r>0

- Set D>0 a constant.

- The rate of collagen biosynthesis and degradation are assumed to be proportional to n and -np.

$$B = \epsilon n(1-p)$$

- Where ε is very small in order to introduce the fact that the ECM remodeling takes more time than the proliferation of cells.

- The positive parameters μ and E quantify the viscous and elastic contributions.

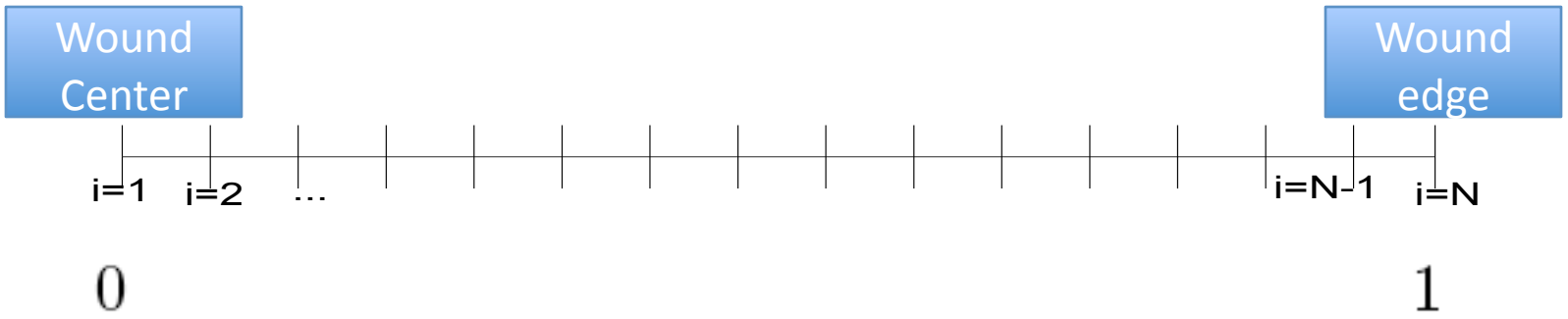
- We neglect haptotactic contributions

First step

To prove that we have understood the problem and its details the first thing to do is to reproduce the results obtained by Maini et al.

We will take the same values of the parameters used in the article, and recall their assumptions.

Our Domain



Boundary conditions

$$\frac{\partial n}{\partial x}(0,t) = \frac{\partial \rho}{\partial x}(0,t) = u(0,t) = 0$$

$$n(\infty,t) = \rho(\infty,t) = 1.$$

$$u(\infty,t) = 0.$$

Initial conditions

$$n(x,0) = H(x-1),$$
$$\rho(x,0) = \rho_i + (1-\rho_i)H(x-1),$$
$$u(x,0) = 0.$$

Where H is the Heaviside functions

To solve the partial differential equations that describe our problem we will use a finite difference approximation.

We discretize the system using Euler explicit in time and central difference for the second derivative.

We use forward or backward Euler depending on the direction of the flow.

If $\frac{\partial u}{\partial t} < 0$ we have;

$$C = \frac{n_{i+1}^N (u_{i+1}^{N+1} - u_{i+1}^N) - n_i^N (u_i^{N+1} - u_i^N)}{dx},$$

$$A = \frac{\rho_{i+1}^N (u_{i+1}^{N+1} - u_{i+1}^N) - \rho_i^N (u_i^{N+1} - u_i^N)}{dx}.$$

If $\dfrac{\partial u}{\partial t} > 0$ we have;

$$C = \frac{n_i^N(u_i^{N+1} - u_i^N) - n_{i-1}^N(u_{i-1}^{N+1} - u_{i-1}^N)}{dx},$$

$$A = \frac{\rho_i^N(u_i^{N+1} - u_i^N) - \rho_{i-1}^N(u_{i-1}^{N+1} - u_{i-1}^N)}{dx}.$$

Discretized Equations

$$n_i^{N+1} = n_i^N - C - \frac{\chi_i n_i dt(\rho_{i+1}^N - \rho_i^N) - \chi_{i-1} n_{i-1} dt(\rho_i^N - \rho_{i-1}^N)}{dx^2} + \frac{D_i dt(n_{i+1}^N - n_i^N) - D_{i-1} dt(n_i^N - n_{i-1}^N)}{dx^2}$$

$$+ dt P(n, \rho)_i,$$

$$\rho_i^{N+1} = \rho_i^N - A + B(n, \rho)_i,$$

$$(\frac{\mu}{dt} + E)(\frac{-u_{i+1}^{N+1} + 2u_i^{N+1} - u_{i-1}^{N+1}}{dx^2}) + F_i = \frac{\mu}{dt}(\frac{-u_{i+1}^N + 2u_i^N - u_{i-1}^N}{dx^2}) + \frac{\tau_{i+1}^N - \tau_i^N}{dx}$$

where

$$F_i = s\rho_i^N u_i^{N+1}.$$

From the last equation we get the following system

$$(\frac{\mu}{dt} + E)Bu^{N+1} = \frac{\mu}{dt}B_1 u^N + \tau^N$$

Implementation

For getting the results we will use tha aid of the Scilab software, and make a program that succesfully solves the problem.

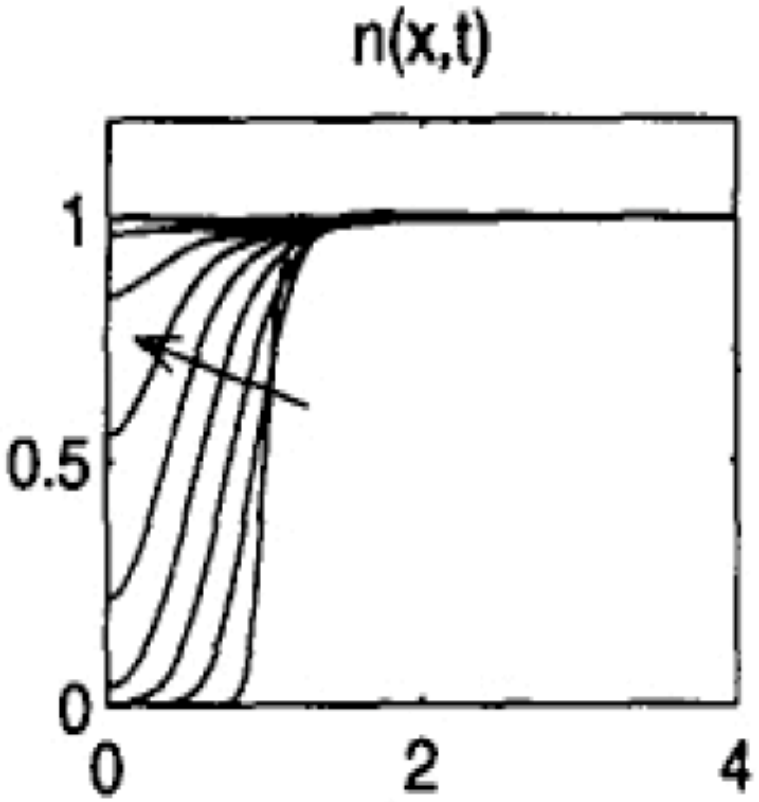
In this part we first need to construct the matrix for our linear system, that in this case has the shape of a tridiagonal matrix. Also we note that we are dealing with a definite positive matrix.

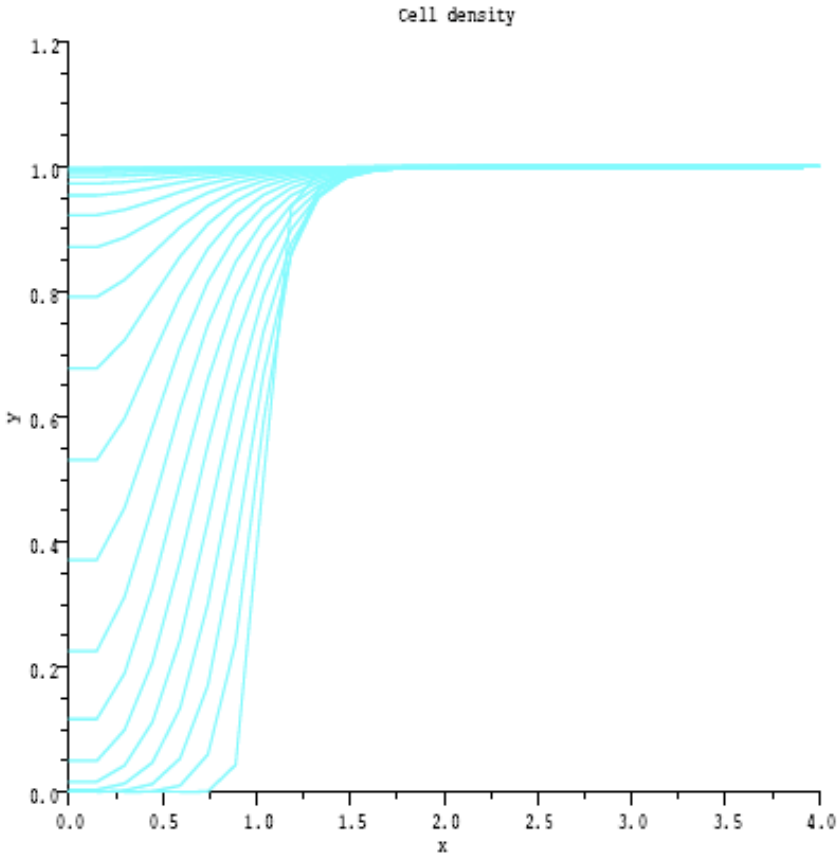
Our Matrix

$$\frac{1}{dx^2}\begin{pmatrix} 2 & -1 & 0 & \cdots & 0 \\ -1 & 2 & -1 & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & -1 & 2 & -1 \\ 0 & \cdots & 0 & -1 & 2 \end{pmatrix}$$

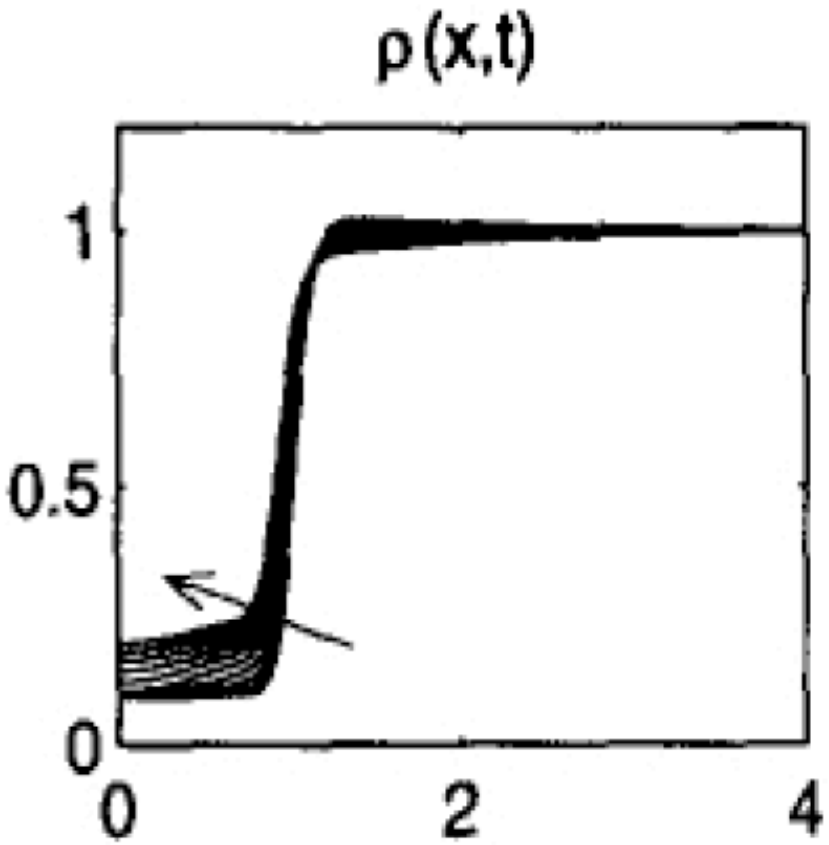
Once we have the values of the displacement for the next time step we proceed with the cell and ECM matrix values.

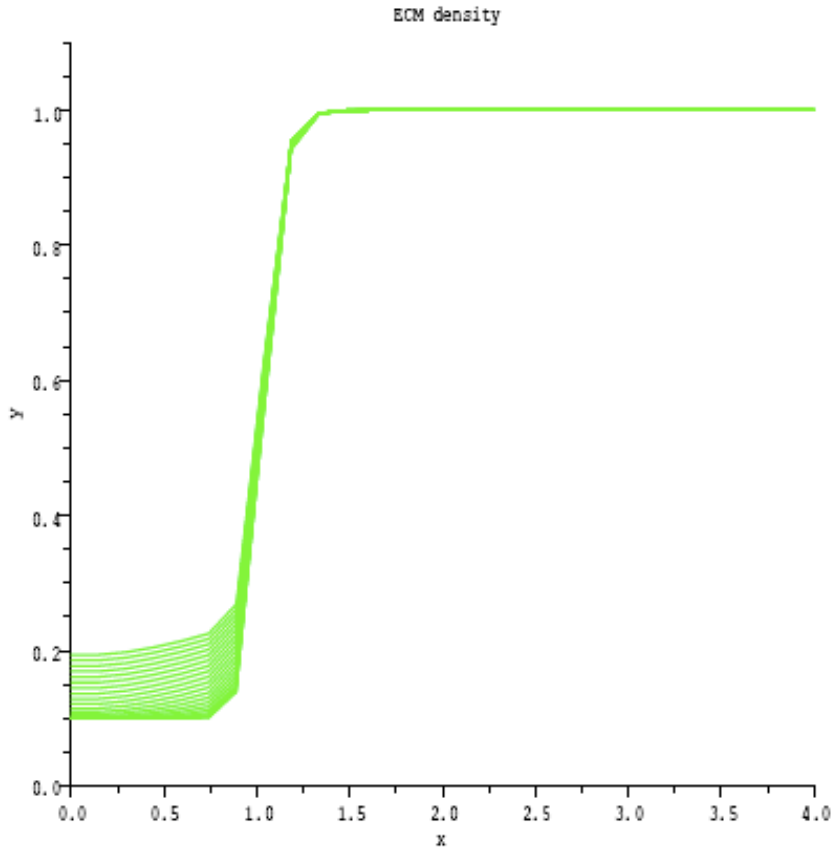
Results: cell density



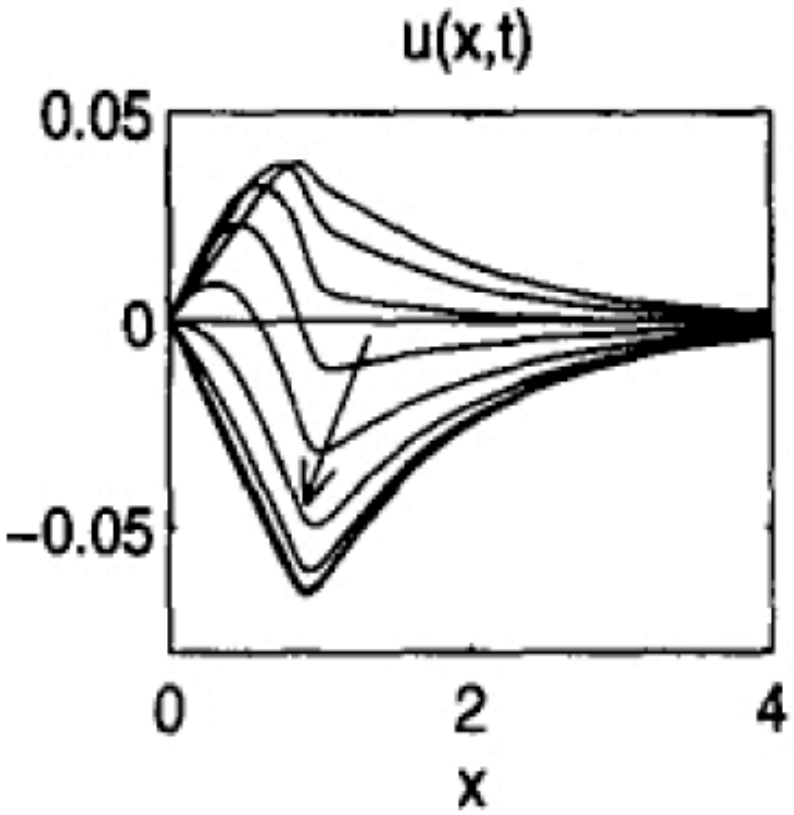


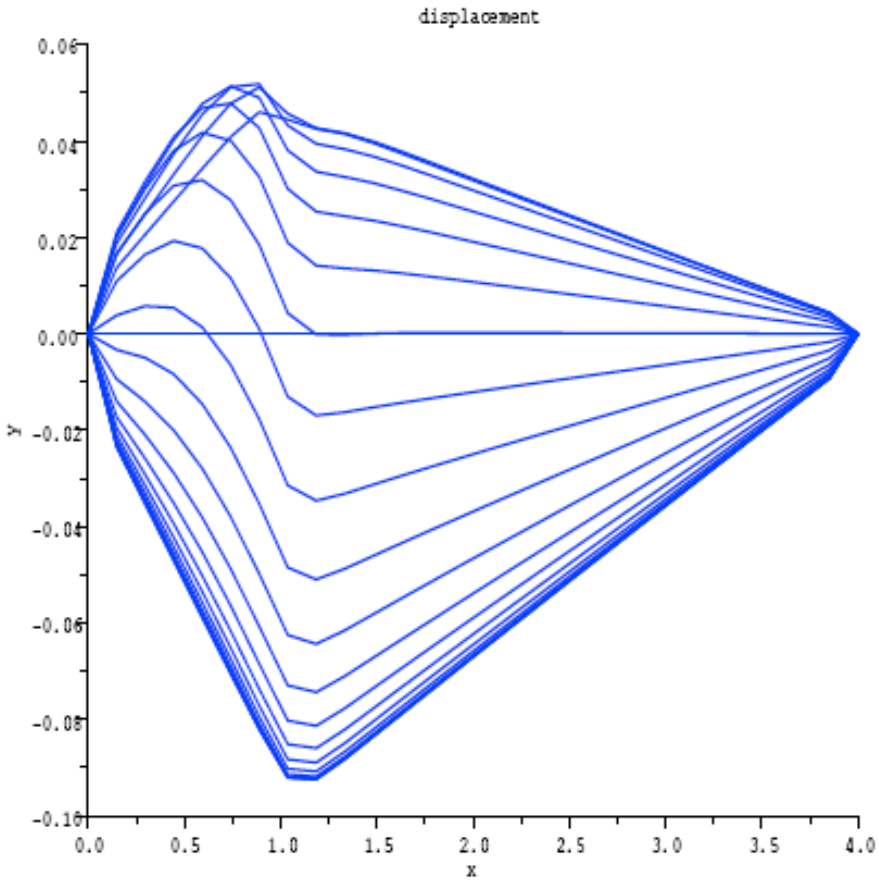
Results: ECM density





Results: Displacement





Internship conclusions

Luis:

- Scilab
- Programming
- Finite difference

Second step

Now that we have seen that our approach is good we can proceed to model the two dimensional case.

The first thing to do in these part is to transform the equations into 2d equations, thus getting.

2d equations

$$\frac{\partial n}{\partial t} + div\left[n\frac{\partial \mathbf{u}}{\partial t} + \chi(\rho)n\nabla\rho - D(\rho)\nabla n\right] = P(n,\rho)$$

$$\frac{\partial \rho}{\partial t} + div(\rho\frac{\partial \mathbf{u}}{\partial t}) = B(n,\rho)$$

$$-div\left[\mu\frac{\partial(\nabla\mathbf{u})}{\partial t} + E\nabla\mathbf{u} + \tau(n,\rho)I\right] + F(n,\rho) = 0$$

We divide the displacement in u_1 and u_2 for the movement in x and y direction respectively

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}\left[n\frac{\partial u_1}{\partial t} + \chi(\rho)n\frac{\partial \rho}{\partial x} - D(\rho)\frac{\partial n}{\partial x}\right] + \frac{\partial}{\partial y}\left[n\frac{\partial u_2}{\partial t} + \chi(\rho)n\frac{\partial \rho}{\partial y} - D(\rho)\frac{\partial n}{\partial y}\right]$$

$$= P(n,\rho)$$

,

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(\rho\frac{\partial u_1}{\partial t}) + \frac{\partial}{\partial y}(\rho\frac{\partial u_2}{\partial t}) \;=\; B(n,\rho)$$

$$-\left[\mu\begin{pmatrix}\frac{\partial(\Delta u_1)}{\partial t}\\ \frac{\partial(\Delta u_2)}{\partial t}\end{pmatrix} + E\begin{pmatrix}\Delta u_1\\ \Delta u_2\end{pmatrix} + \begin{pmatrix}\frac{\partial \tau}{\partial x}\\ \frac{\partial \tau}{\partial y}\end{pmatrix}\right] + F(n,\rho) \;=\; 0$$

Boundary conditions

$$n(x,0,t) = n(x,\infty,t) = \rho(x,0,t) = \rho(x,\infty,t) = 1$$

$$\frac{\partial n}{\partial x}(0,y,t) = \frac{\partial n}{\partial x}(\infty,y,t) = \frac{\partial \rho}{\partial x}(0,y,t) = \frac{\partial \rho}{\partial x}(\infty,y,t) = 0$$

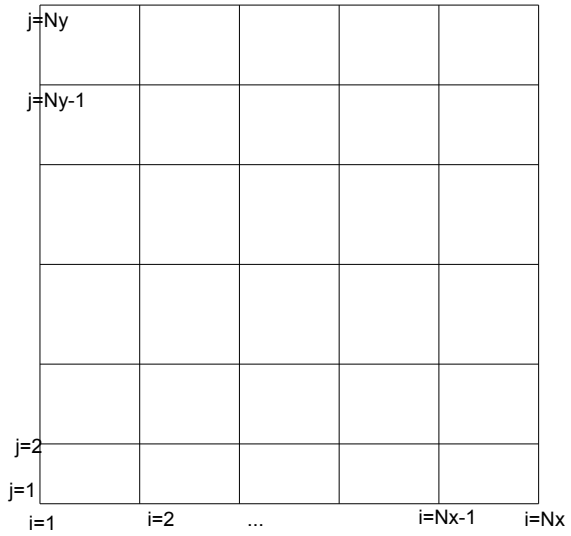
$$u(x,0,t) = u(x,\infty,t) = u(0,y,t) = u(\infty,y,t) = 0$$

Domain

We assume that the walls of our domain are normal healthy tissue, so the density of the ECM matrix and the cells are equal to one. We neglect the flow coming from the boundary

x=1 to x=Nx,

y=1 to y=Ny



For the discretization we will use the same as for the 1d case. We also need to add one condition for the flow in the y direction

Flow: x direction

If $\frac{\partial u_1}{\partial t} < 0$ we have:

$$C_1 = \frac{n^N_{i+1,j}(u^{N+1}_{1(i+1,j)} - u^N_{1(i+1,j)}) - n^N_{i,j}(u^{N+1}_{1(i,j)} - u^N_{1(i,j)})}{dx},$$

$$G_1 = \frac{\rho^N_{i+1,j}(u^{N+1}_{1(i+1,j)} - u^N_{1(i+1,j)}) - \rho^N_{i,j}(u^{N+1}_{1(i,j)} - u^N_{1(i,j)})}{dx}.$$

If $\frac{\partial u_1}{\partial t} > 0$ we have:

$$C_1 = \frac{n^N_{i,j}(u^{N+1}_{1(i,j)} - u^N_{1(i,j)}) - n^N_{i-1,j}(u^{N+1}_{1(i-1,j)} - u^N_{1(i-1,j)})}{dx},$$

$$G_1 = \frac{\rho^N_{i,j}(u^{N+1}_{1(i,j)} - u^N_{1(i,j)}) - \rho^N_{i-1,j}(u^{N+1}_{1(i-1,j)} - u^N_{1(i-1,j)})}{dx}.$$

Flow: y direction

If $\frac{\partial u_2}{\partial t} < 0$ we have:

,

$$C_2 = \frac{n^N_{i,j+1}(u^{N+1}_{2(i,j+1)} - u^N_{2(i,j+1)}) - n^N_{i,j}(u^{N+1}_{2(i,j)} - u^N_{2(i,j)})}{dy}$$

$$G_2 = \frac{\rho^N_{i,j+1}(u^{N+1}_{2(i,j+1)} - u^N_{2(i,j+1)}) - \rho^N_{i,j}(u^{N+1}_{2(i,j)} - u^N_{2(i,j)})}{dy}.$$

If $\frac{\partial u_2}{\partial t} > 0$ we have:

$$\frac{n^N_{i,j}(u^{N+1}_{2(i,j)} - u^N_{2(i,j)}) - n^N_{i,j-1}(u^{N+1}_{2(i,j-1)} - u^N_{2(i,j-1)})}{dy},$$

$$G_2 = \frac{\rho^N_{i,j}(u^{N+1}_{2(i,j)} - u^N_{2(i,j)}) - \rho^N_{i,j-1}(u^{N+1}_{2(i,j-1)} - u^N_{2(i,j-1)}).}{dy}$$

Discretized Equations

$$n_{i,j}^{N+1} = n_{i,j}^{N} - C_1 - \frac{dt(\chi_{i,j}^{N} n_{i,j}(\rho_{i+1,j}^{N} - \rho_{i,j}^{N}) - \chi_{i-1,j}^{N} n_{i-1,j}(\rho_{i,j}^{N} - \rho_{i-1,j}^{N}))}{dx^2} +$$

$$\frac{dt(D_{i,j}^{N}(n_{i+1,j}^{N} - n_{i,j}^{N}) - D_{i-1,j}^{N}(n_{i,j}^{N} - n_{i-1,j}^{N}))}{dx^2}$$

$$-C_2 - \frac{dt(\chi_{i.j}^{N} n_{i,j}^{N}(\rho_{i,j+1}^{N} - \rho_{i,j}^{N}) - \chi_{i.j-1}^{N} n_{i,j-1}^{N}(\rho_{i,j}^{N} - \rho_{i,j-1}^{N}))}{dy^2} +$$

$$\frac{dt(D_{i,j}^{N}(n_{i,j+1}^{N} - n_{i,j}^{N}) - D_{i,j-1}^{N}(n_{i,j}^{N} - n_{i,j-1}^{N}))}{dy^2} + dtP_{i,j}^{N}$$

$$\rho_{i,j}^{N+1} = \rho_{i,j}^{N} - G_1 - G_2 + dtB_{i,j}^{N}$$

$$(\frac{\mu}{dt}+E)(\frac{u^{N+1}_{1i+1,j}-2u^{N+1}_{1i,j}+u^{N+1}_{1i-1,j}}{dx^2}+\frac{u^{N+1}_{1i,j+1}-2u^{N+1}_{1i,j}+u^{N+1}_{1i,j-1}}{dy^2})+F^{N+1}_{1i,j}=$$

$$\frac{-\mu}{dt}(\frac{u^{N}_{1i+1,j}-2u^{N}_{1i,j}+u^{N}_{1i-1,j}}{dx^2}+\frac{u^{N}_{1i,j+1}-2u^{N}_{1i,j}+u^{N}_{1i,j-1}}{dy^2})+\frac{\tau^{N}_{i+1,j}-\tau^{N}_{i,j}}{dx}$$

$$-(\frac{\mu}{dt}+E)(\frac{u^{N+1}_{2i+1,j}-2u^{N+1}_{2i,j}+u^{N+1}_{2i-1,j}}{dx^2}+\frac{u^{N+1}_{2i,j+1}-2u^{N+1}_{2i,j}+u^{N+1}_{2i,j-1}}{dy^2})+F^{N+1}_{2i,j}=$$

$$-\frac{\mu}{dt}(\frac{u^{N}_{2i+1,j}-2u^{N}_{2i,j}+u^{N}_{2i-1,j}}{dx^2}+\frac{u^{N}_{2i,j+1}-2u^{N}_{2i,j}+u^{N}_{2i,j-1}}{dy^2})+\frac{\tau^{N}_{i,j+1}-\tau^{N}_{i,j}}{dy}$$

From the last equation we get the following systems

$$(\frac{\mu}{dt} + E)A_1 u_1^{N+1} = \frac{\mu}{dt} A_2 u_1^N + \tau_1^N$$

$$(\frac{\mu}{dt} + E)A_1 u_2^{N+1} = \frac{\mu}{dt} A_2 u_2^N + \tau_2^N$$

Implementation

Again for these case we will use Scilab to get the results for our equation, we will only make some changes to the 1d code to adapt it to the new conditions.

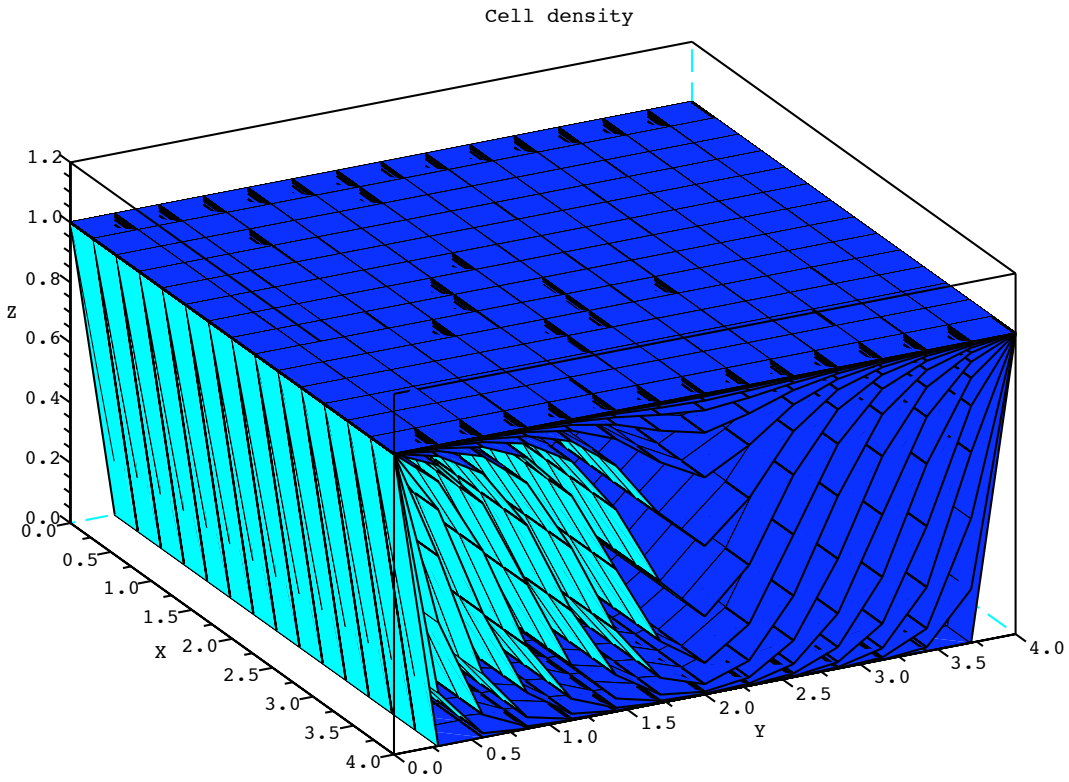
2d Matrix

$$
\begin{pmatrix}
\frac{2}{dx}+\frac{2}{dy} & \frac{-1}{dx} & 0 & \frac{-1}{dy} & 0 & \cdots & & & 0 \\
\frac{-1}{dx} & \frac{2}{dx}+\frac{2}{dy} & \frac{-1}{dx} & \ddots & & & & & \vdots \\
0 & \frac{-1}{dx} & \ddots & 0 & & & & & \\
\frac{-1}{dy} & \ddots & 0 & & \frac{-1}{dx} & & & & \\
0 & & & \frac{-1}{dx} & & \frac{-1}{dx} & & & 0 \\
\vdots & & & & \frac{-1}{dx} & & 0 & & \frac{-1}{dy} \\
 & & & & & 0 & & \frac{-1}{dx} & 0 \\
 & & & & & & \frac{-1}{dx} & & \frac{-1}{dx} \\
0 & \cdots & & & 0 & \frac{-1}{dy} & 0 & \frac{-1}{dx} & \frac{2}{dx}+\frac{2}{dy}
\end{pmatrix}
$$

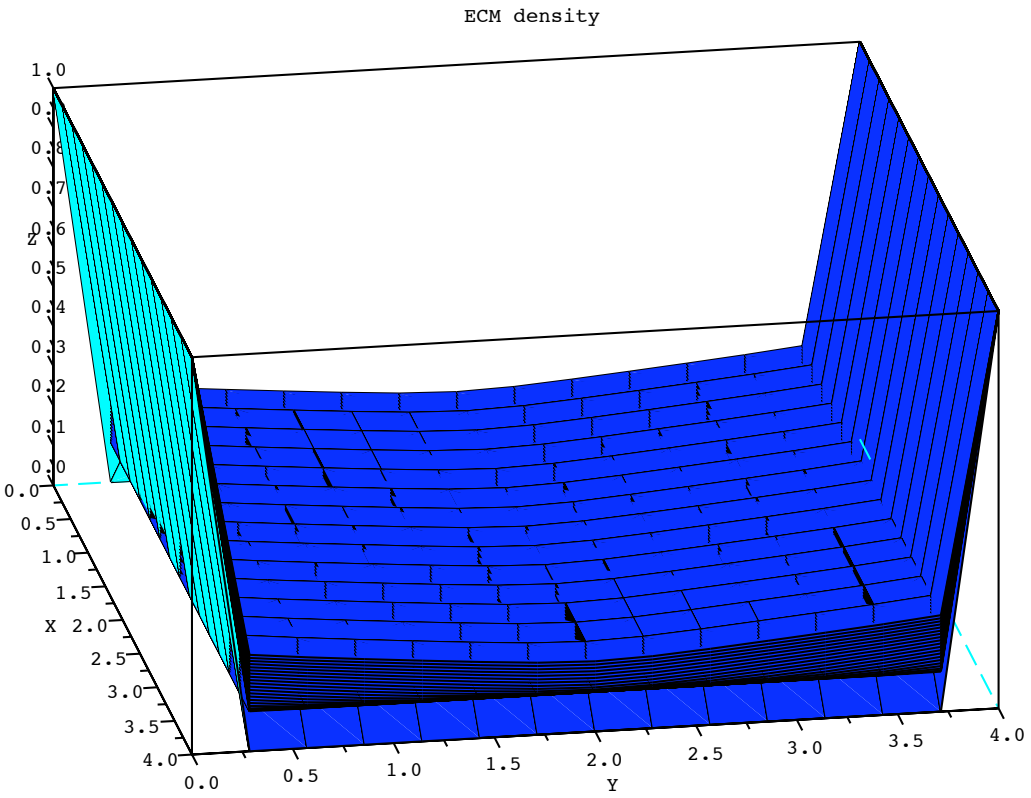
Results

- The parameters we use are:
- R=0.2
- s=1,
- ρ_i=0.1
- μ=1
- ε=0.01
- E=0.01
- τ=0.1

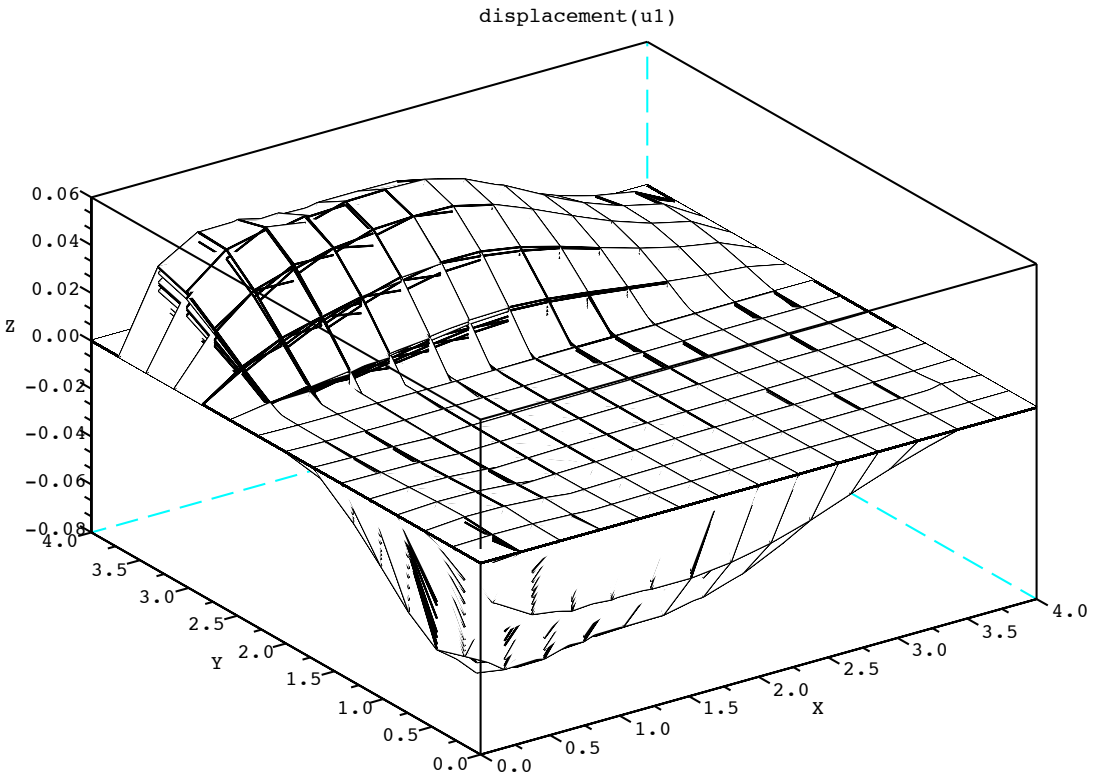
Cell density



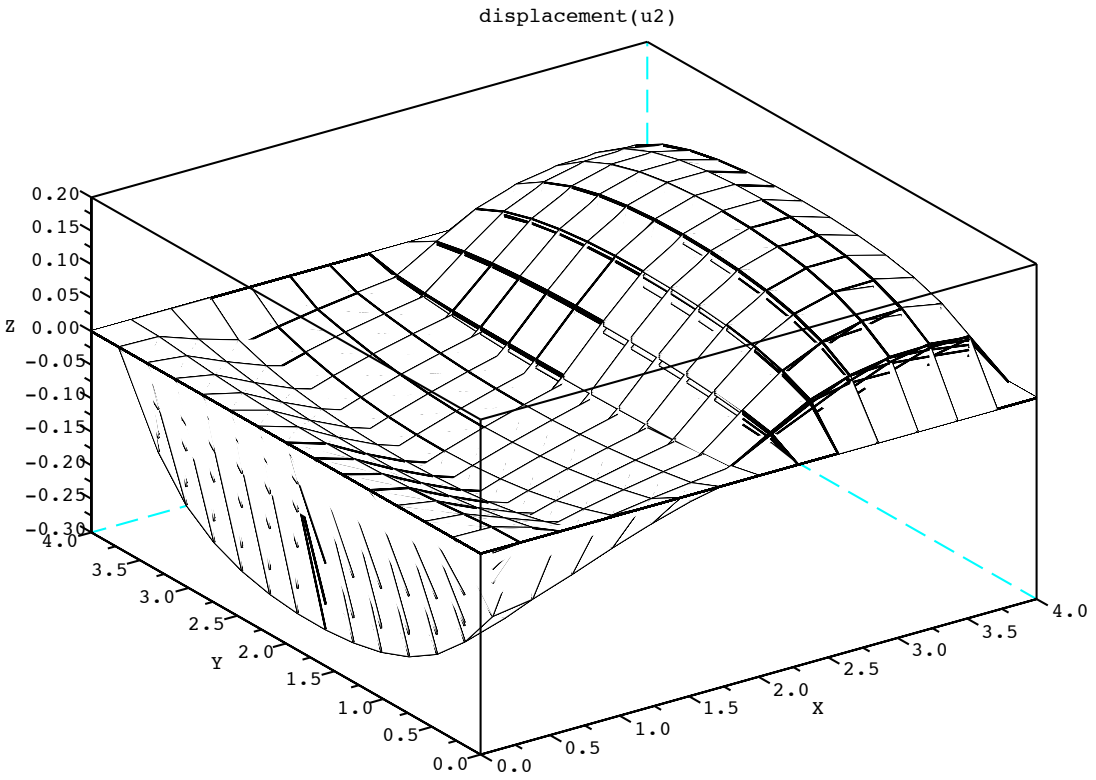
ECM matrix density



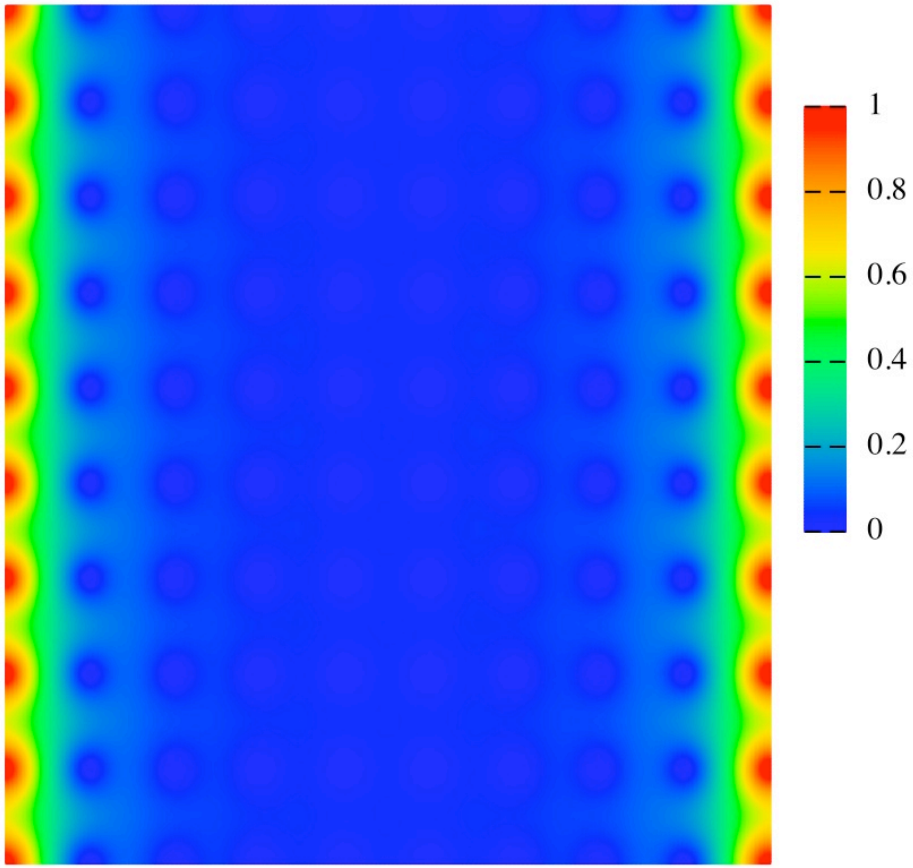
Displacement in x

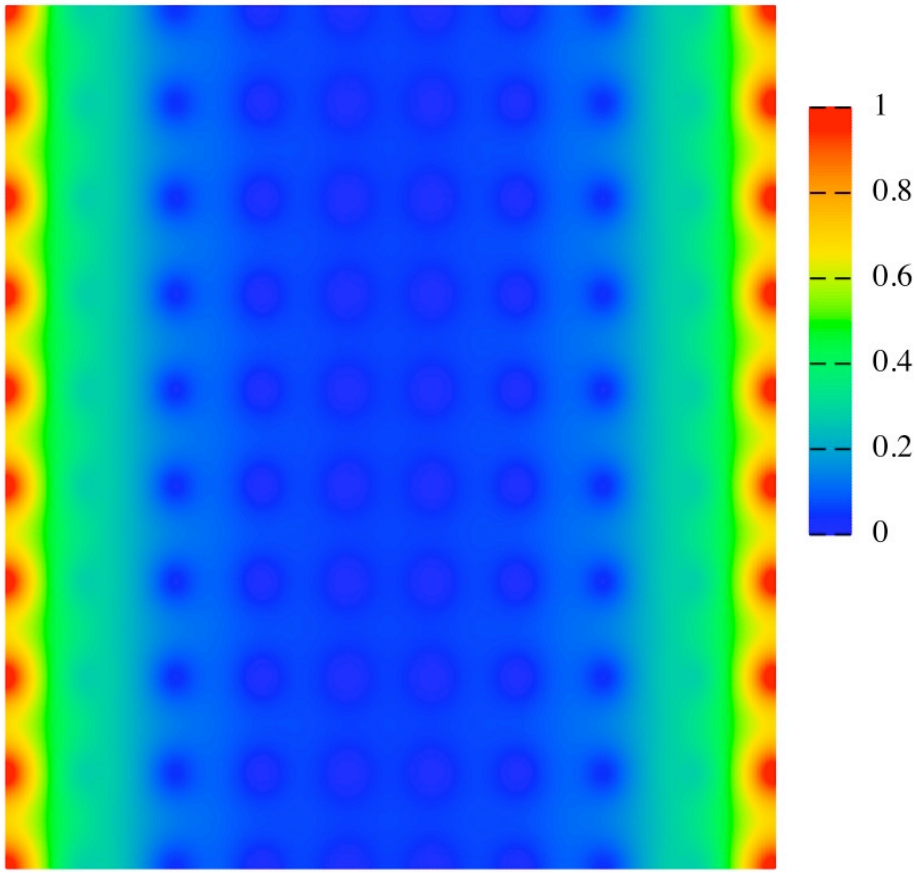


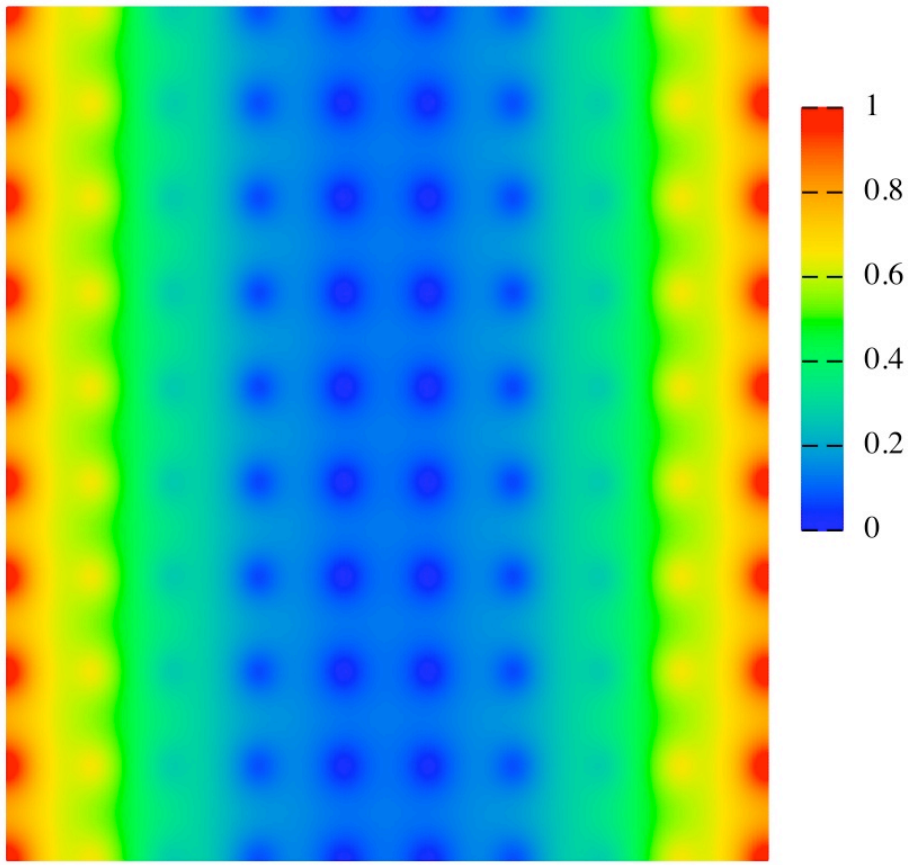
Displacement in y



Colormaps: Change of cell density in time




1
0.8
0.6
0.4
0.2
0


1
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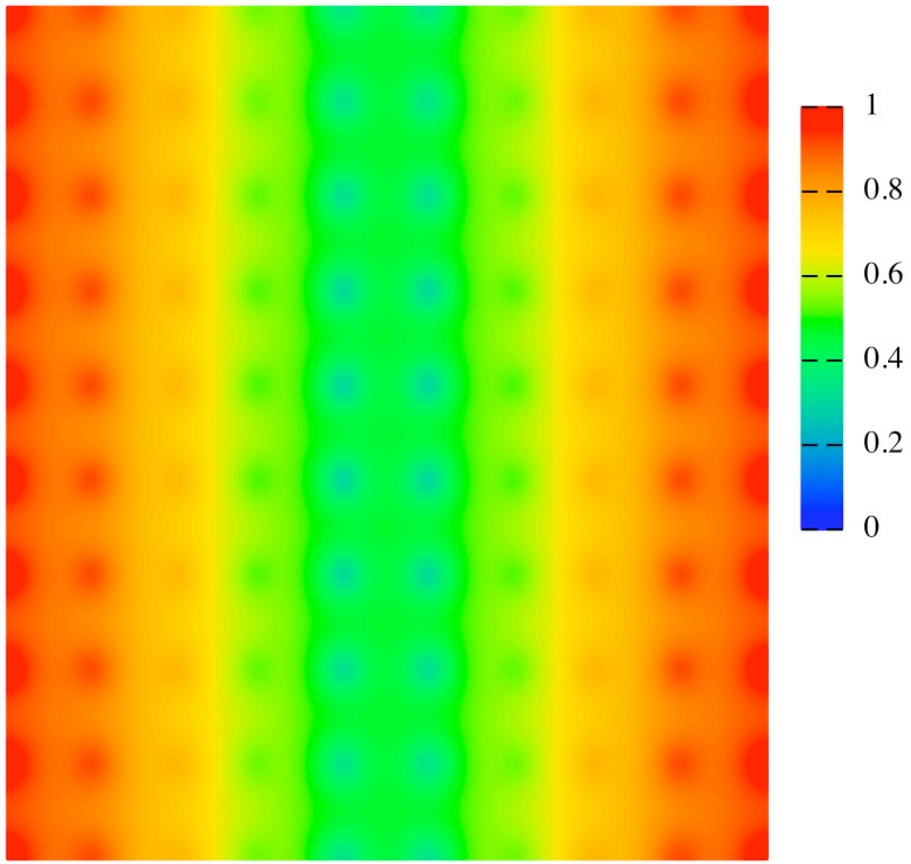
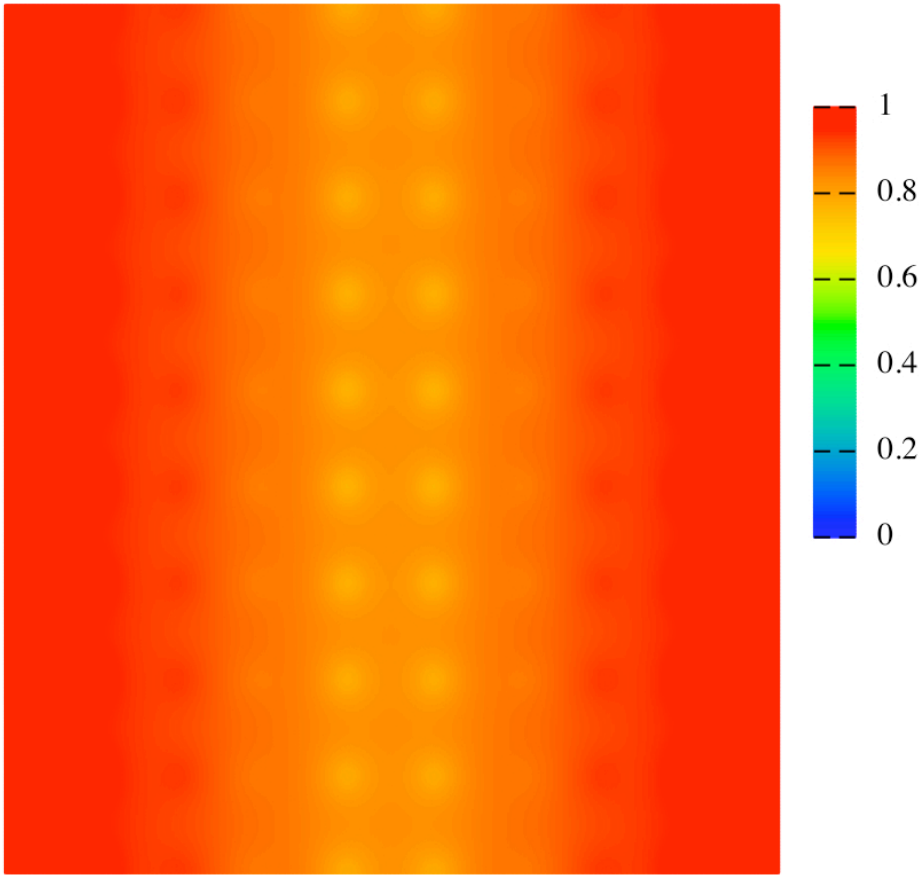
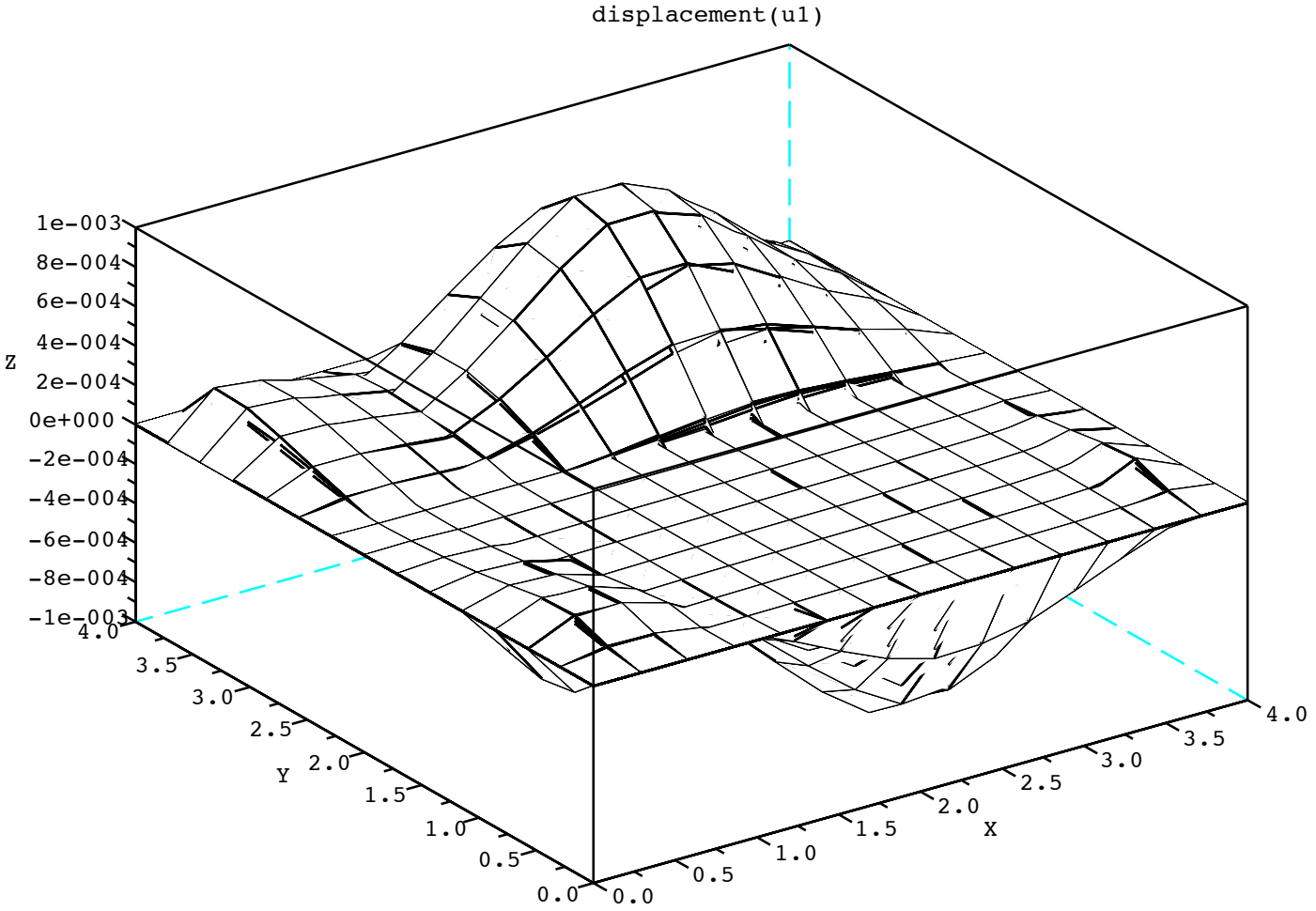
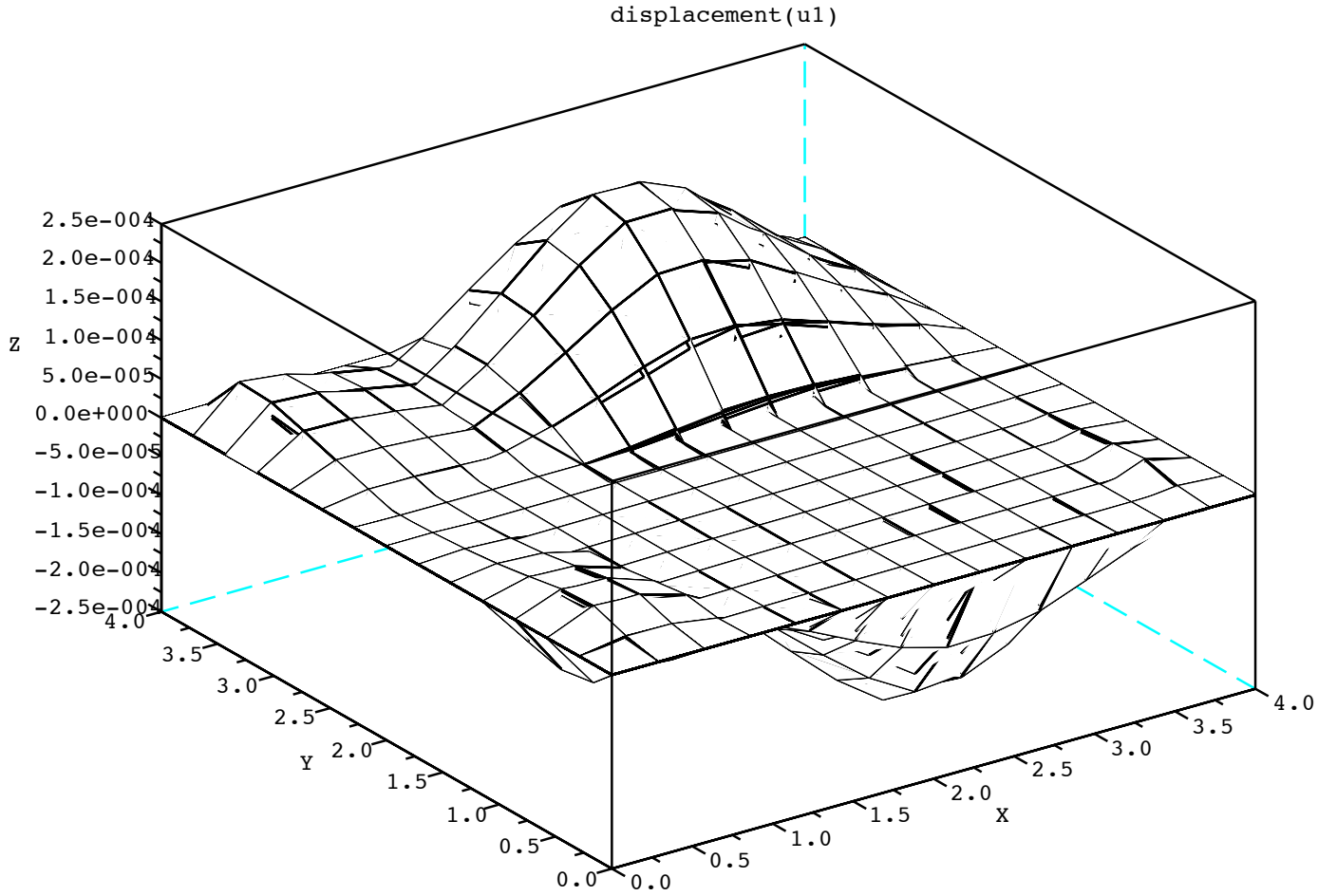

1
0.8
0.6
0.4
0.2
0


1
0.8
0.6
0.4
0.2
0

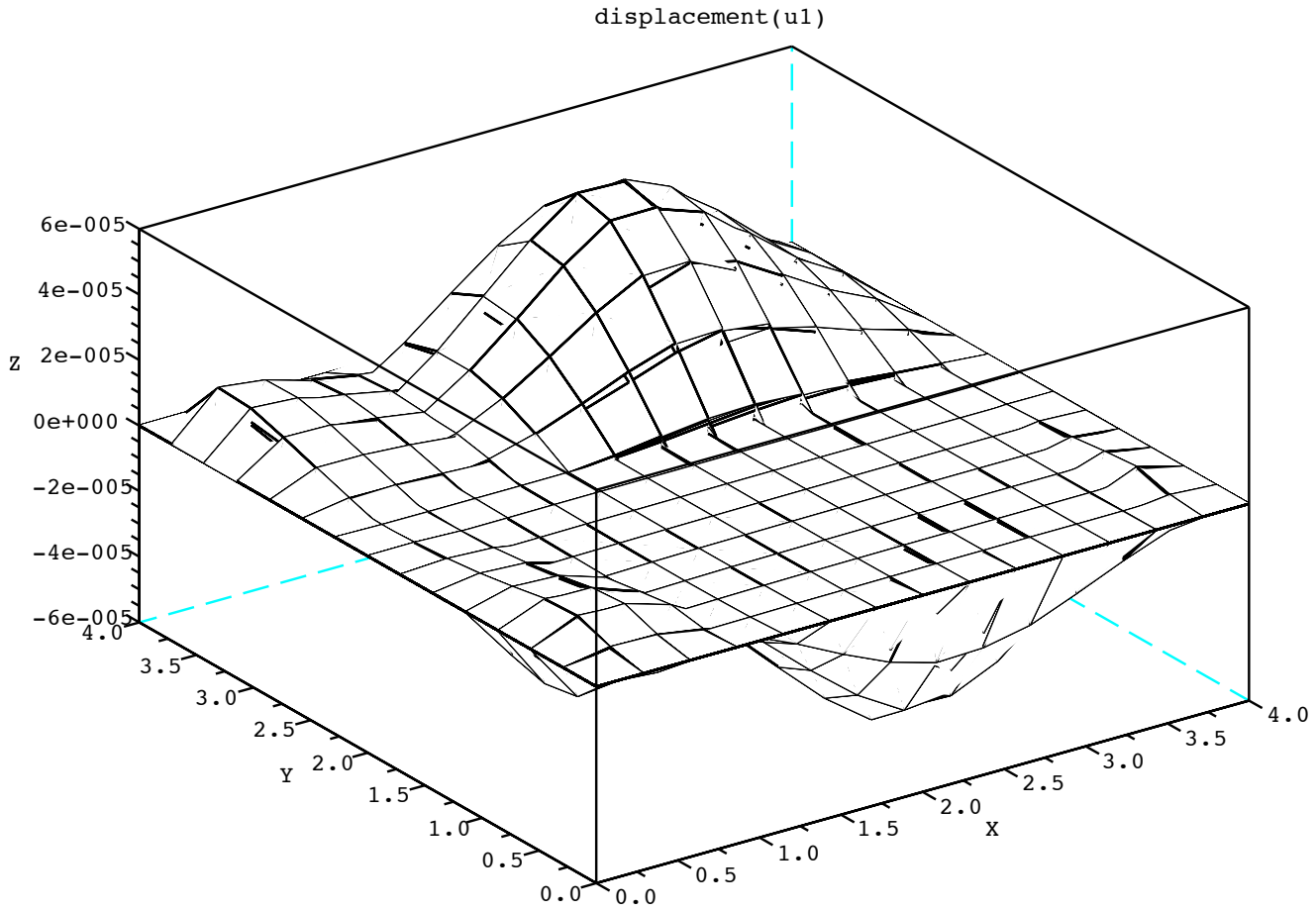
μ=10, Displacement in x



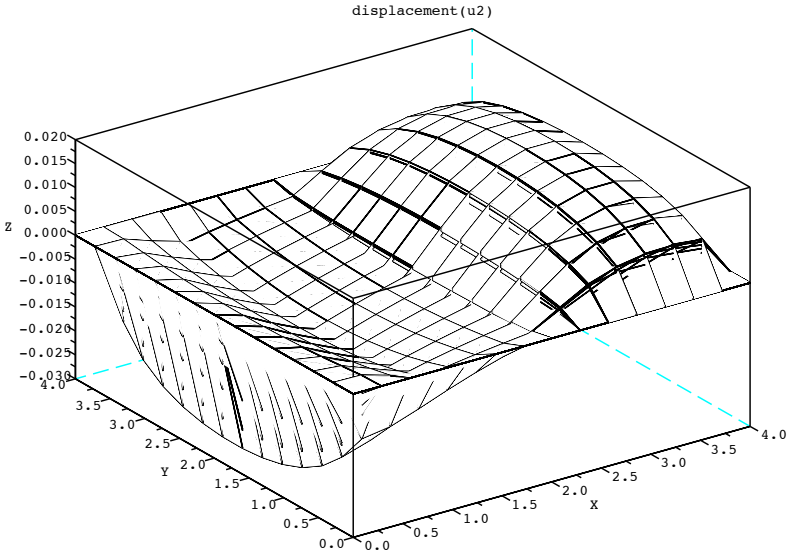
M=20, Displacement in x

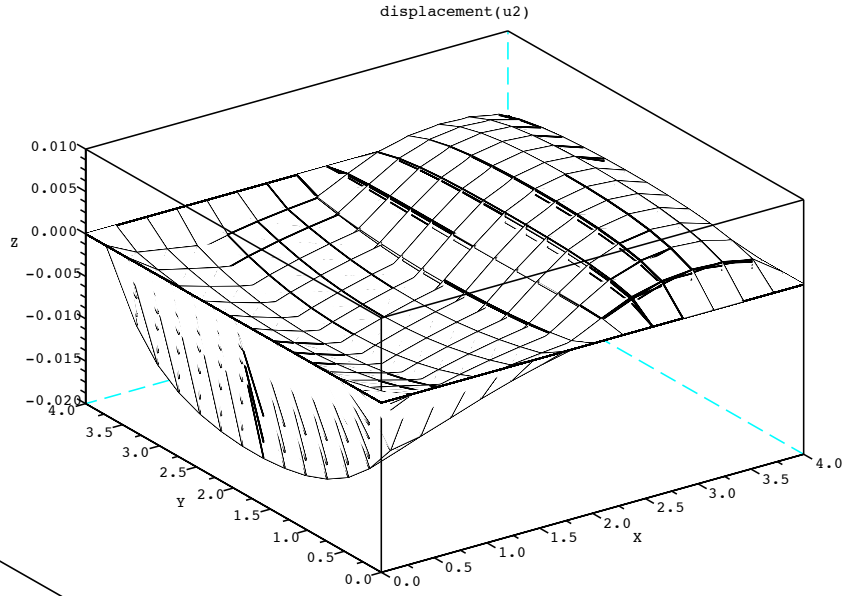


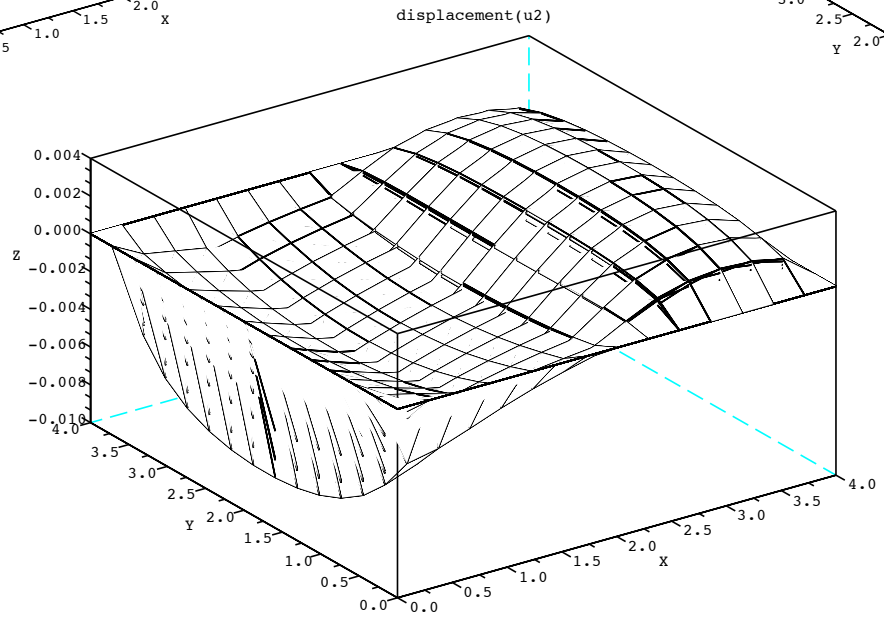
M=40, Displacement in x



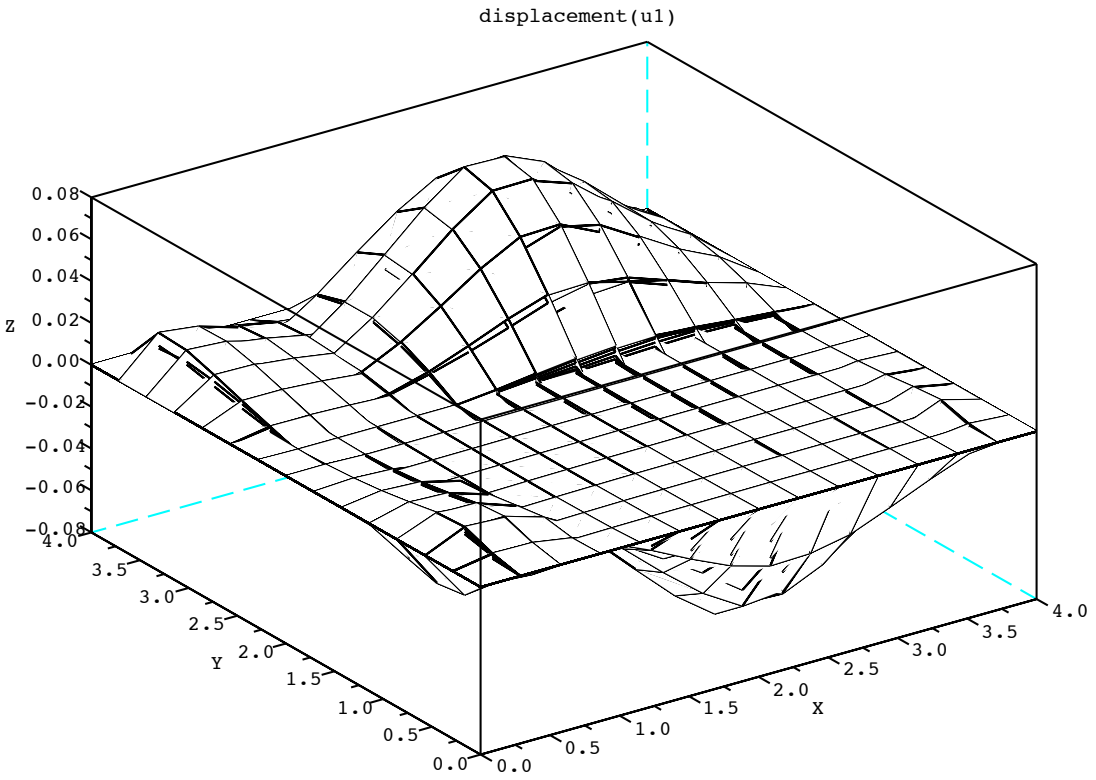
μ=10,20,40 Displacement in y



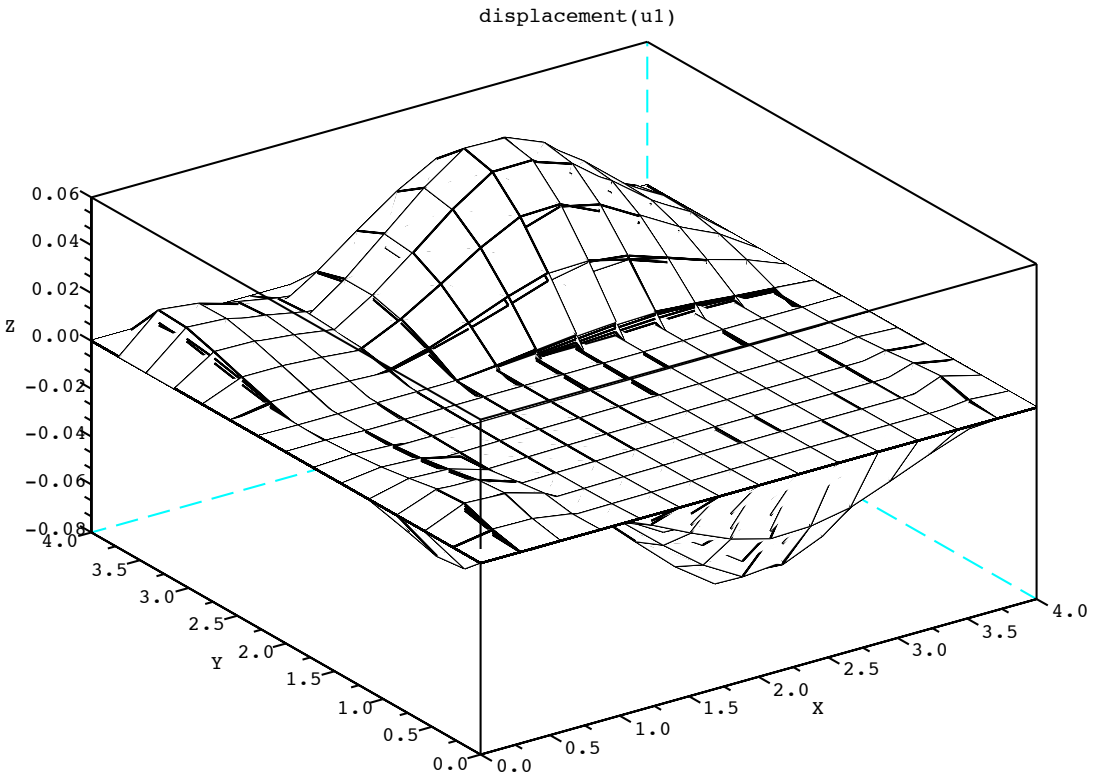




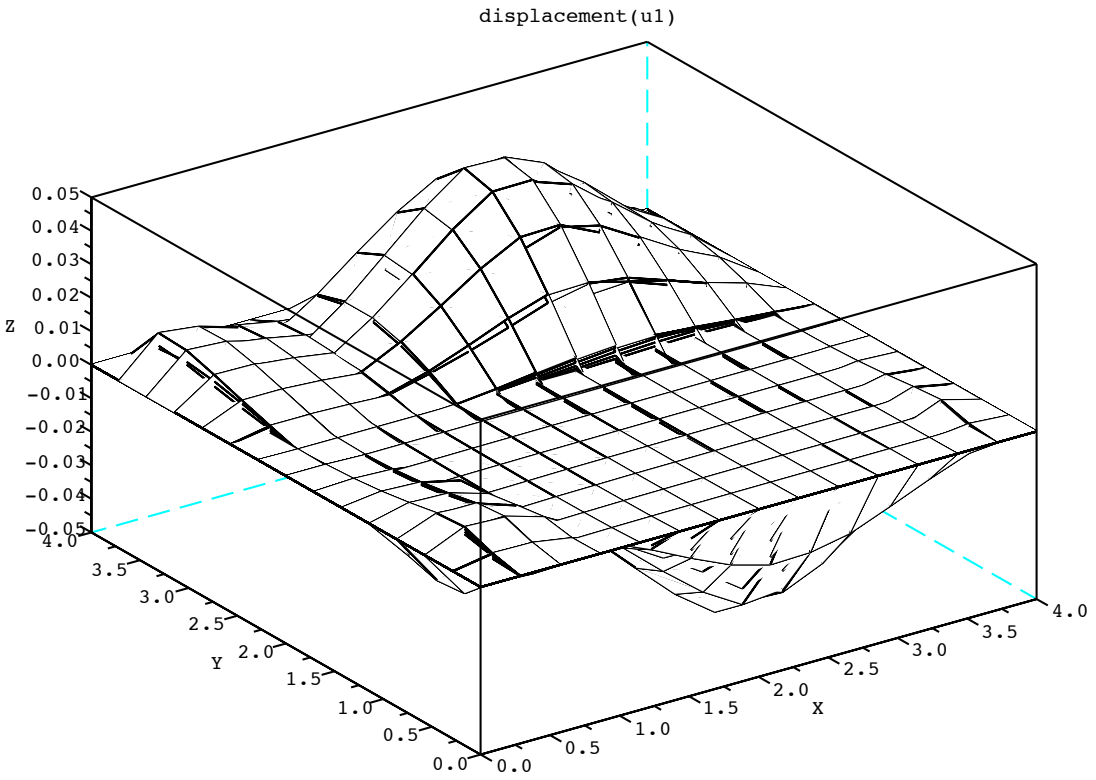
E=10, Displacement in x



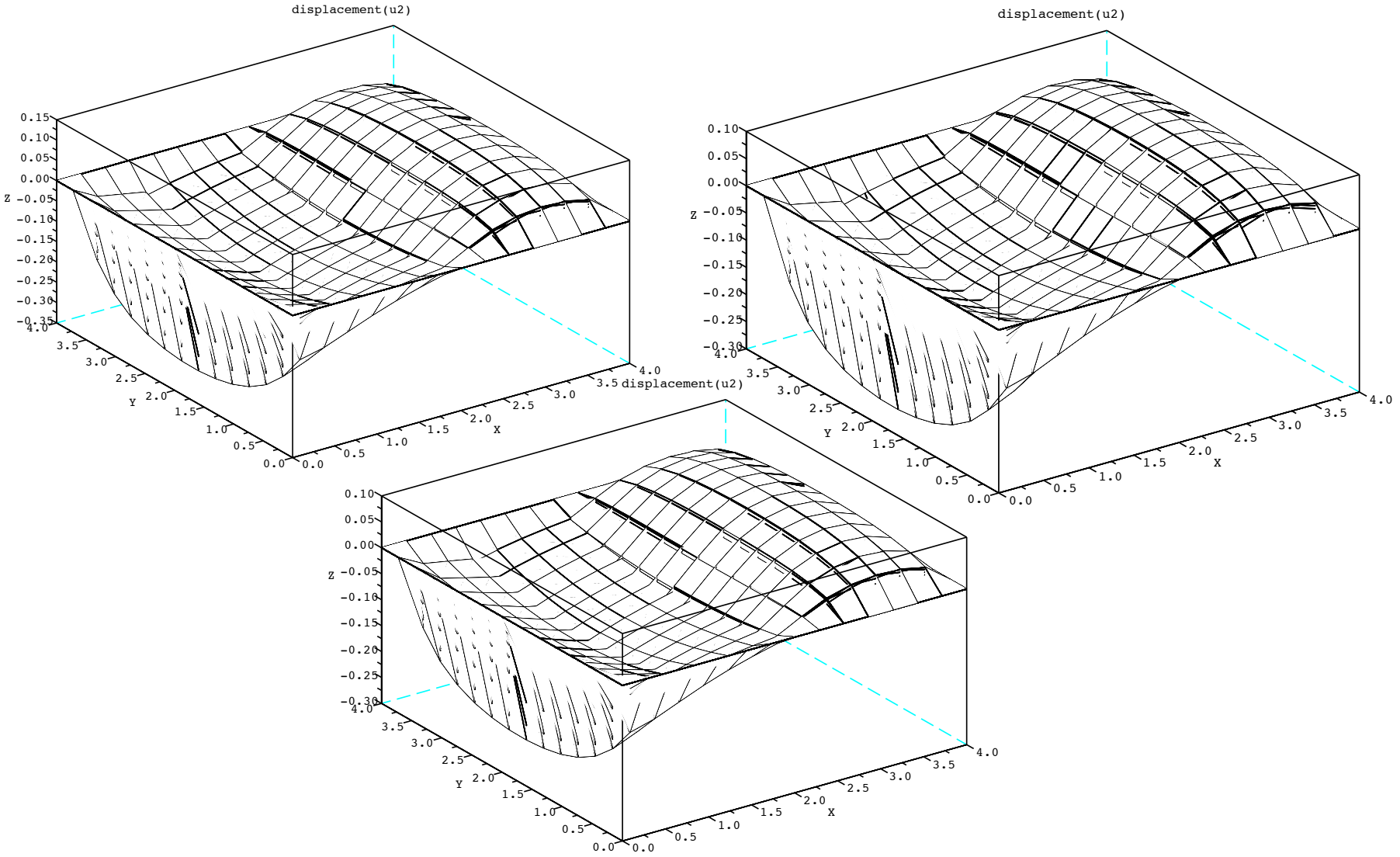
E=20, Displacement in x



E=40, Displacement in x



E=10,20,40 Displacement in y



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