VALIDATION OF A POROELASTIC MODEL

Tobias Ansaldi

21/06/2012

Abstract

This studies aim, is to verify from a mathematical point of view the validity of a model for the infusion of a drug inside a cancer tissue. Avery important parameter has been optimised in the description of the phiscal fenomenon the hydraulic conductivity K.

The optimal value has been determined with Lagrange's approach. The function K was considered as the optimal value that better represent sperimental data. The results show how the optimised function has a reasonable tendency from a phisycal point of view and furthermore has a singular tendency to the one obtained in the model.

The model

In this reasearch we hypothize the solid tumor to have a spherical form.The changes (deformations) that the tumor undergoes are to be considered infinitesimal, for that reason the deformations are governed by Hooke's law (elastic field).

We study the transfer of the therapeudic agent inside the tumor considering a porelastic medium carachterized by hydraulic conductivity k of the tissue (given the relationship between dinamic viscosity and permeability of the medium) and by Lame's coefficient G and λ.

The relationship between the therapeutical agent and blood vessels is governed by starling's law:

$$\Omega = L_p \frac{S}{V}(p_e - p) \tag{1}$$

where:

L_p = conduttività vascolare $[\frac{cm}{mmHg \cdot s}]$
$\frac{S}{V}$ = sup erci e vasc olare p er unità di volume$[\frac{cm^2}{cm^3}]$
p_e = pressione vascolare eettiva[mmHg].
p= pressione interstiz iale[mmHg].

Ωcan act both as a well or as a source based on the difference of pressure inside or outside the blood vessel. the tumor is by nature strongly heterogeneous, we only consider it in its radial direction, which is expressed by the hydraulic conductivity of the tumor K.

another study has observed that conductivity k is strongly influenced by the deformation of the tumor.

The farmaceutical agent is introduced in the center of the tumor, creating a small radius (a) cavity, which its dimensions can be compared to the tip of the needle.

The general strength acting on the tumor would be:

$$\underline{\underline{T}} = \underline{\underline{\sigma}} - p\underline{\underline{I}} \tag{2}$$

$\underline{\underline{T}}$ =tensor of effective stress
$\underline{\underline{\sigma}}$= tensor of contact stress
p= interstizial fluid pressure (IFP)

considering that the tension deformation of the tumor is governed by hooke's law, throught the equation of the bond we get:

$$\underline{\underline{T}} = -p\underline{\underline{I}} + \lambda(\nabla \cdot \overline{u})\underline{\underline{I}} + 2G[\frac{1}{2}((\nabla \cdot \overline{u}) + (\nabla \cdot \overline{u})^T)] \tag{3}$$

where
u=deformation of solid
$\lambda = \frac{2\nu}{1-2\nu}G$

dove

$\nu=$ is the Poisson's coefficient

assuming we found ourselves in stationary conditions, transforming the equation in cilindrical coordinates, and and remembering that all variables are hypotetically only expressed in accordance of the radial r coordinate, we obtain:

$$(2G+\lambda)\frac{d}{dr}(\frac{du}{dr}+\frac{2u}{r})=\frac{dp}{dr} \quad (4)$$

To be able to find the distribution of the pressure and deformation we need another equation. We have to consider the conservation of the mass:

$$\bar{\nabla}\cdot\bar{q}=\Omega \quad (5)$$

Please note that q has the direction and dimention of the velocity, But truthfully is not the actual velocity inside the pores, but it refers to the volumetric carrying for unit area.

The second meaning of55 represent, as already said, the relationship between the vascular net and the pharmaceutical agent during the evolution of this last one.

A fluid that evolves inside a pore is described by Darcy's law:

$$\bar{q}=-K\cdot\bar{\nabla}p \quad (6)$$

Taking into consideration the 1 and 5 becomes:

$$\bar{\nabla}\cdot(-K\cdot\bar{\nabla}p)=L_pS(p_e-p) \quad (7)$$

Taking into consideration the

$$-\frac{1}{r^2}\frac{d}{dr}(r^2K\frac{dp}{dr})=L_p\frac{S}{V}(p_e-p) \quad (8)$$

Regarding the hydraulic conductivity of the tumor it has been chosen to consider it as depending from the deformation with a semi-empiric exponential law:

$$K=K_0e^{M[\alpha\frac{du}{dr}+(1-\alpha)\frac{u}{r}]} \quad (9)$$

The equations are closed by the boundary conditions.

$$\begin{cases} p=0 & r=R' \\ p=p_{inf} & r=a' \\ \frac{du}{dr}+\frac{2\nu}{1-\nu}\frac{u}{r}=0 & r=R' \\ \frac{du}{dr}+\frac{2\nu}{1-\nu}\frac{u}{r}=0 & r=a' \end{cases}$$

where a' and R' are respectivly the inside and outside radiuous after the deformation.

Linearization of equations

The linearization of the equation is made through a perturbative analysis of the model which functions in accordance to a characteristic parameter of the problem.

$p^*=\frac{p}{p_{inf}-pe}$; $\underline{\underline{T}}^*=\frac{\underline{\underline{T}}}{2G+\lambda}$; $r^*=\frac{r}{R}$; $u^*=\frac{u}{r}$; $K^*=\frac{K}{K_0}$;

and the equations become:

$$\frac{d}{dr^*}(\frac{du^*}{dr^*}+\frac{2u^*}{r^*})=\delta\frac{dp^*}{dr^*} \quad (10)$$

$$\frac{d}{dr^*}(r^{*2}K^*\frac{dp^*}{dr^*})=r^{*2}\gamma^2(p^*-p_e^*) \quad (11)$$

$$K^*=e^{M[\alpha\frac{du^*}{dr^*}+(1-\alpha)\frac{u^*}{r^*}]} \quad (12)$$

having $\gamma^2=\frac{L_p}{K_0}\frac{S}{V}R^2$ e $\delta=\frac{p_{inf}-p_e}{2G+\lambda}$

Its around the adimensional value of δ that the linearization is executed and stopping at the first order we have:

$$u^*=u_0^*+u_1^*\delta$$

$$K^*=K_0^*+K_1^*\delta$$

$$p^*=p_0^*+p_1^*\delta$$

Please note that we are taking into account the hypothesis of small movements and therefore we can express the exponential as the development in series of mclaurin stopping at the first order

$$K^* = 1 + M[\alpha\frac{du^*}{dr^*} + (1-\alpha)\frac{u^*}{r^*}]$$

Now lets move on to express the conditions on the boundaries of points $\frac{a}{R}$ and $\frac{R}{R}$assuming we are moving linearly from point $\frac{a}{R}$ until $\frac{a'}{R}$ and from 1 to $\frac{R'}{R}$.

For example $p(a') = p_{inf} \backsimeq p(a) + \frac{dp(a)}{dr}(a'-a)$ with $a'-a = u(a)$.

We can now write our equations in orderδ^0:

$$\begin{cases} \frac{d}{dr^*}(\frac{du_0^*}{dr^*} + \frac{2u_0^*}{r^*}) = 0 \\ \frac{d}{dr^*}(r^{*2}K_0^*\frac{dp_0^*}{dr^*}) = r^{*2}\gamma^2(p_0^* - p_e^*) \\ K_0^* = 1 + M[\alpha\frac{du_0^*}{dr^*} + (1-\alpha)\frac{u_0^*}{r^*}] \end{cases}$$

c.c.

$$\begin{cases} p_0^* = 0 & r^* = 1 \\ p_0^* = 0 & r^* = \frac{a}{R} \\ \frac{du_0^*}{dr^*} + \frac{2\nu}{1-\nu}\frac{u_0^*}{r^*} = 0 & r^* = 1 \\ \frac{du_0^*}{dr^*} + \frac{2\nu}{1-\nu}\frac{u_0^*}{r^*} = 0 & r^* = \frac{a}{R} \end{cases}$$

It can also be demonstrated that$u_0^* = 0 \Longrightarrow K_0^* = 1$. Even $p_0$has an analytical answer such as:

$$p_0^* = p_e^* + \frac{A}{r^*}e^{\gamma r^*} + \frac{B}{r^*}e^{-\gamma r^*}$$

with A and B known from boundary conditions At the order δ^1 the equations are:

$$\begin{cases} \frac{d}{dr^*}(\frac{du_1^*}{dr^*} + \frac{2u_1^*}{r^*}) = \frac{dp_0^*}{dr^*} \\ \frac{d}{dr^*}(r^{*2}K_0^*\frac{dp_0^*}{dr^*}) = r^{*2}\gamma^2 p_1^* \\ K_1^* = 1 + M[\alpha\frac{du_1^*}{dr^*} + (1-\alpha)\frac{u_1^*}{r^*}] \end{cases}$$

c.c.

$$\begin{cases} p_1^* = -u_1^*\frac{dp_0^*}{dr^*} & r^* = 1 \\ p_1^* = -u_1^*\frac{dp_0^*}{dr^*} & r^* = \frac{a}{R} \\ \frac{du_1^*}{dr^*} + \frac{2\nu}{1-\nu}\frac{u_1^*}{r^*} = 0 & r^* = 1 \\ \frac{du_1^*}{dr^*} + \frac{2\nu}{1-\nu}\frac{u_1^*}{r^*} = 0 & r^* = \frac{a}{R} \end{cases}$$

The carrying that goes through the tumor in the non linear model has value (adimensional):

$$Q^* = 4\pi r^{*2}q^*$$

In the linear case it would be

$$Q^* = 4\pi r^{*2}(q_0^* + \delta q_1^*) \qquad (13)$$

where

$$q_0^* = -\frac{dp_0^*}{dr^*}$$

$$q_1^* = -K_1^*\frac{dp_0^*}{dr^*} - \frac{dp_1^*}{dr^*}$$

Optimal K_1 determination

why K_1?

It has been decided to optimize the conductivity of the hydraulic mean K for essentially two reasons:

- - The relationship between K and the deformation u is crucial for it's use in the poroelastic theory. It is as a matter of fact the mainly responsible for the interation between fluid and pharmaceutical

- - Both in literature and in our model it is still not clear how to combine K with the deformation u.

This study does not doubt the exponential relationship that goes on between deformation and conductivity, but wants to verify if the exponential curve that better approximates the experimental values (strictly determined by a mathematical method) is qualitatively similar to the one chosen in our model(determined with a physical-empiric method).

The experimental data reported in the 1were taken from the work of McGuire et al. and for each value of p_{inf} (37,52,69 $mmHg$) ... is calculated Q_{inf} media ($Q^I = 0.15$,$Q^{II} = 1.4$,$Q^{III} = 0.35$).

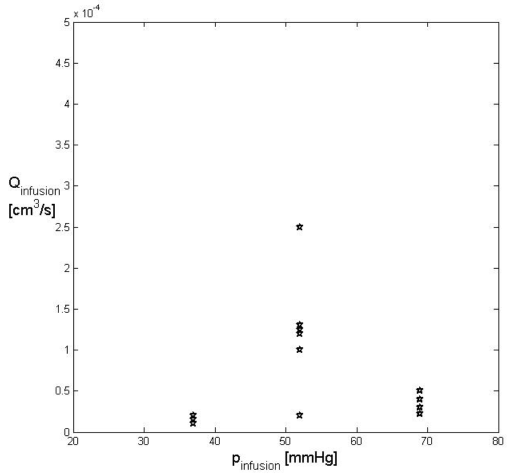

Figure 1: experimental values

Lagrangian approach

To make it easier from now on we will omit ∗remembering that all measurements are adimensional

From the optimization we have K_{ott} for every value of Q_{inf}.

For this reason the size that has to be minimized has been expressed as follows:

$$J = (Q(a') - Q^I)^2 + \frac{\xi}{2}\int_a^1 K_1^2 dr \quad (14)$$

The optimization has been done for the linear equations stopping at the 1 order, furthermore, for reasons tied to the method of functionality . . . is expressed as follows

$$Q(a') = \int_a^1 Q(r)\delta_D dr \quad (15)$$

where δ_D is a known function *delta di Dirac.*

Taking into account that 13 13 and remembering that 14 linearization has stopped on order 1 the 14 becomes :

$$J = \chi_0 + \int_a^1 (\chi_1 \frac{p_1}{dr} + \chi_2 K_1)\delta_D dr + \frac{\xi}{2}\int_a^1 K_1 dr \quad (16)$$

where:

- $\chi_0 = (Q^I)^2 + 16\pi^2 a'^4 (\frac{dp_0}{dr})^2 + 8Q\pi a'^2 \frac{dp_0}{dr}$
- $\chi_1 = 32\pi^2 \frac{dp_0}{dr}\epsilon r^4 + 8Q^I \pi r^2 \epsilon$
- $\chi_2 = 32\pi^2 \epsilon r^4 (\frac{dp_0}{dr})^2 + 8Q^I \pi r^2 \epsilon \frac{dp_0}{dr}$

We can now define the lagrangiana definition as follows:

$\mathcal{L}(p_1, K_1, \alpha, b, c) = J - \int_a^1 \alpha \cdot (\frac{d^2 p_1}{dr} + \frac{2}{r}\frac{dp_1}{dr} - \gamma^2 p_1 + (\frac{2}{r}\frac{dp_0}{dr} + \frac{d^2 p_0}{dr^2})K_1 + (\frac{dp_0}{dr})(\frac{dK_1}{dr}))dr - b\cdot(p_1(a) + u_1(a)\frac{dp_0(a)}{dr}) - c\cdot(p_1(1) + u_1(1)\frac{dp_0(1)}{dr})$

where α, b, c are moltiples of Lagrange.

imposing:

$$\nabla\mathcal{L} = 0 \quad (17)$$

We obtain the conditions necessary for the resolution of the problem. Therefore we have:

- $\frac{\partial\mathcal{L}}{\partial p_1} = 0$
  $\frac{d^2\alpha}{dr} - \frac{2}{r}\frac{d\alpha}{dr} - \gamma^2\alpha = -8\pi\epsilon\frac{d}{dr}((4\pi\frac{dp_0}{dr}r^4 + Q^I r^2)\delta_D)$
  $\alpha(a) = 0$
  $\alpha(1) = 0$
  $b = \frac{d\alpha}{dr}(a))$
  $c = -\frac{d\alpha}{dr}(1)$
- $\frac{\partial\mathcal{L}}{\partial K_1} = 0$
  $K = \frac{1}{\xi}[-8\pi\epsilon\frac{d}{dr}((4\pi\frac{d^2 p_0}{dr^2}r^4 + Q^I\frac{dp_0}{dr}r^2)\delta_D) + \alpha(\frac{2}{r}\frac{dp_0}{dr} + \frac{d^2 p_0}{dr^2}) - \frac{d}{dr}(\alpha\frac{dp_0}{dr})]$
- $\frac{\partial\mathcal{L}}{\partial\alpha} = 0$
  $\frac{d^2 p_1}{dr} + \frac{2}{r}\frac{dp_1}{dr} - \gamma^2 p_1 + (\frac{2}{r}\frac{dp_0}{dr} + \frac{d^2 p_0}{dr^2})K_1 + (\frac{dp_0}{dr})(\frac{dK_1}{dr}) = 0$
- $\frac{\partial\mathcal{L}}{\partial b} = 0$
  $p_1(a) = -u(a)\frac{dp_0(a)}{dr}$
- $\frac{\partial\mathcal{L}}{\partial c} = 0$
  $p_1(1) = -u_1(1)\frac{dp_0(1)}{dr}$

please note that:

- Deriving from $p_1$we are able to determine the three multiplicators of lagrange α, b, c
- - Deriving in respect to K_1 we obtain $K_{1,ott}$

- deriving in repect to α we obtain the direct

- deriving in respect to$b$ e c we obtain the initial conditions of the direct

Discretization of the method

The equation system generated from the 15 becomes discretized by an explicit method at the second order

Results

As stated before, we face the problem separately for each of the three values of the infusion range.

Given the obvious impossibility to impose a punctual condition on the function it has become necessary the introduction of a gaussiana function such as $f = C(\theta)e^{-\theta r^2}$(delta di Dirac approssimato) ....which would have the effect of blocking the information on all of r given different weights for every point. In this way, acting onθ We can choose the strength of our control. Obviously according to the choices made on δ_D the calculus grid must be modified. To make the calculations easier, the study will be executed with a $\delta_D$the most ample possible t.c. $\int_a^1 \delta_D dr$ which doesn't have to move from the unit for more than a variation of 1.5%.

Finally, for a particular case we must demonstrate the convergence of the results at the varying of δ_D As long as the grid was chosen accurately. In this case study will be shown 3 different cases with a δ_D ever more forced.

$\int_a^1 \delta_{D_1} dr = 0.9831$; $\int_a^1 \delta_{D_2} dr = 0.9999$; $\int_a^1 \delta_{D_3} dr = 1$.

δ_{D_1}:

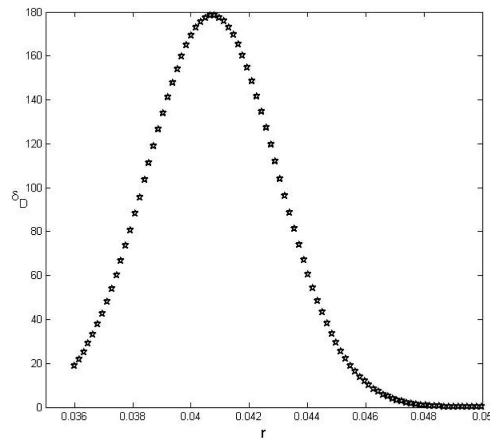

Figure 2: first case and 6000 points

If we know decided to keep on using a grid of 6000 points even forδ_{D_3}we would obtain something like this:

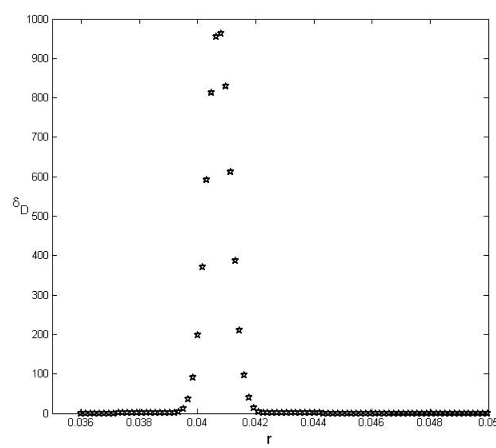

Figure 3: third case and 6000 points

It is clear that if we wish to keep on using this grid we would have to raise the number of points on the grid. The following will show a grid of 10000 points:

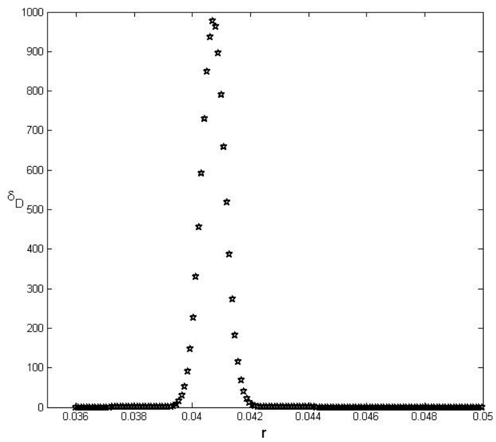

Figure 4: fourth case and 10000 points

Whileδ_{D_2}has the following form (grid of 8000)

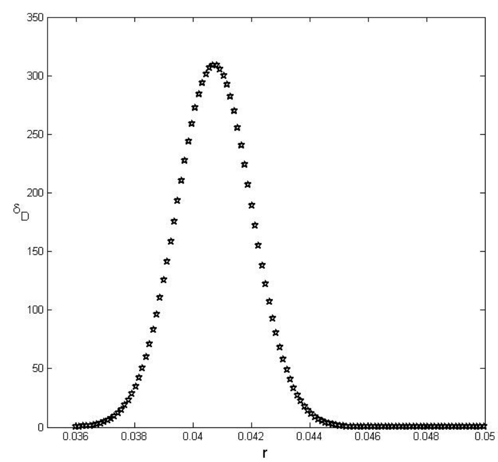

Figure 5: second case and 8000 points

The optimization is obviously strongly influenced by the freedom that is given to the control. The parameter responsible for such choice is ξ,the more it assumes small values the more the control is free to go its own way despite the energy spent to make all this possible.

In the figure below are reported the values of the solutions not optimized and not linearized for each of the three experiments (Q^I, Q^{II}, Q^{III}) confronted with the values of the optimization at the change of the parameter ξ:

Case 1 (Q^I)

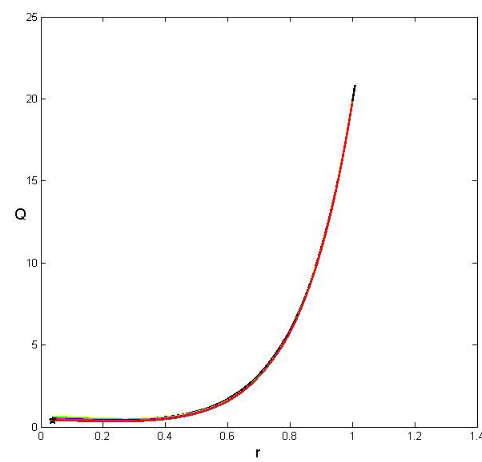

Figure 6: Q for different values of ξ

Which enlarged in the point of interest shows the validity of the optimization:

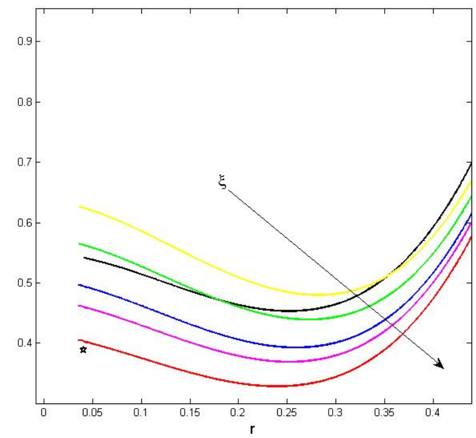

Figure 7: zoom

The black curve represents the non linear solution the others have a value of ξ respectively of $1, 0.1, 0.05, 0.04, 0.03$.

The figure beneath, is in reference to the different hydraulic conductivity of the mean K:

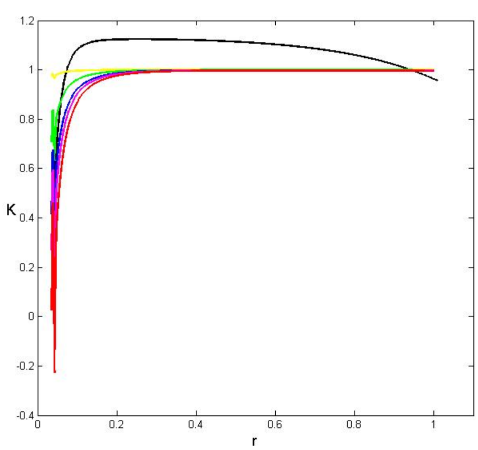

Figure 8: K for different values of ξ

Which enlarged in the point of interest:

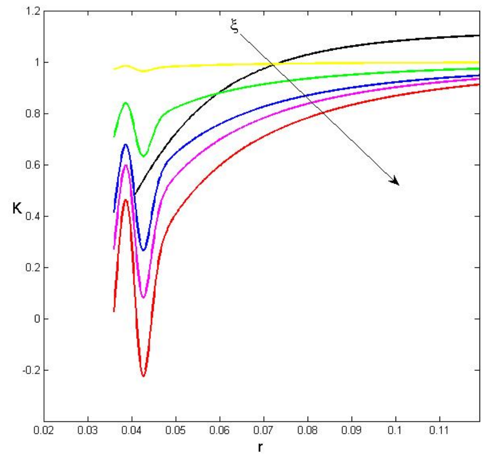

Figure 9: zoom

Beneath are reported the values taken by J at the varying of the control parameter ξ:

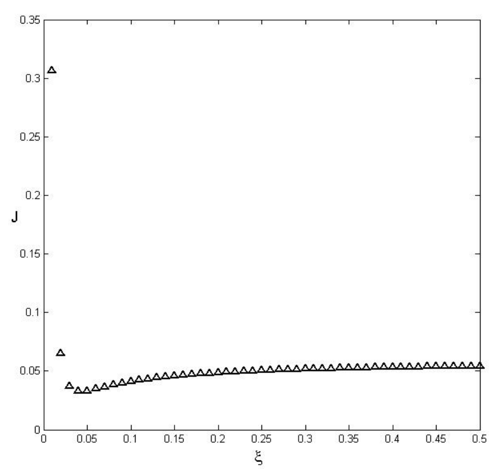

Figure 10: J for different values of ξ

In the end, to verify if the chosen grid is sufficient the values are reported for one of the cases calculated above before, with the 6000 point grid and then with a 1000 point grid

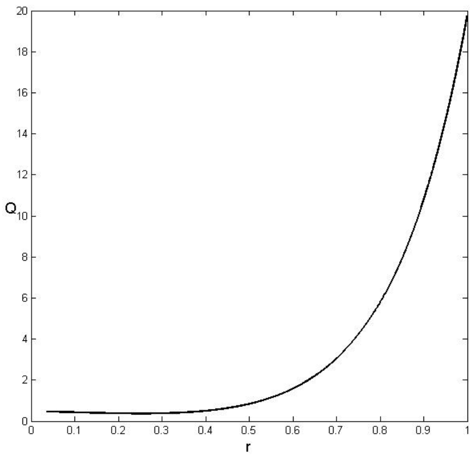

Figure 11: conversetion

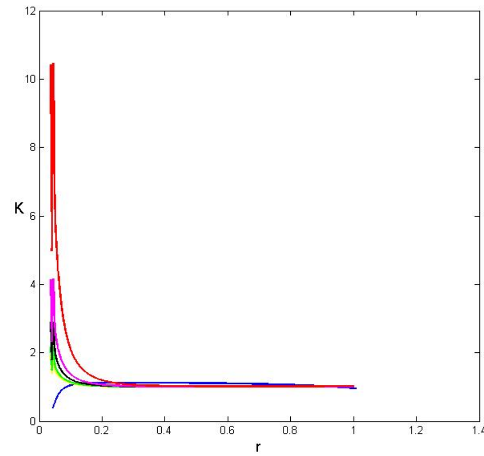

Figure 13:

The problem has now reached perfect conversion.

Case 2 Q^{II}

We report in the same order of the first case the results obtained.

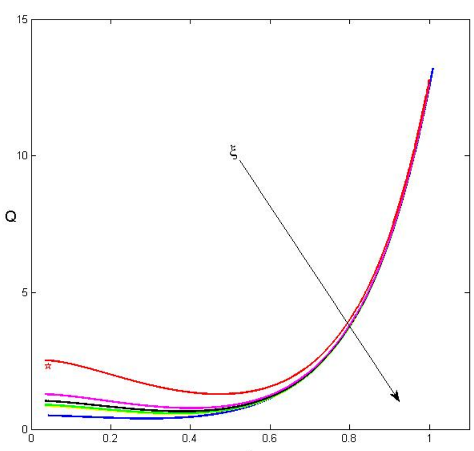

Figure 12:

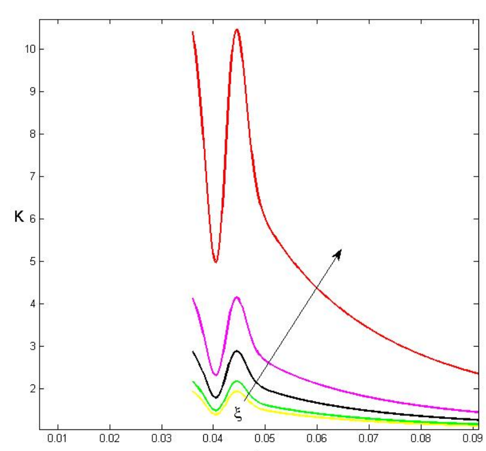

Figure 14:

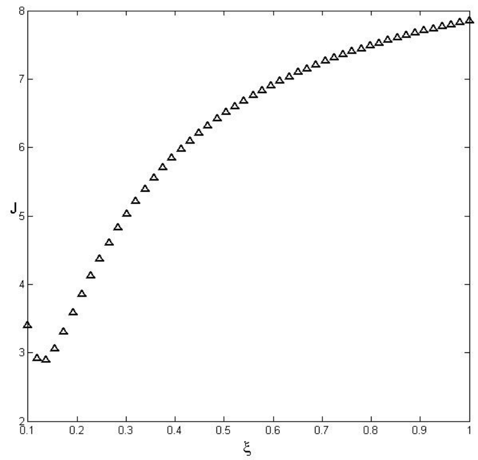

Figure 15:

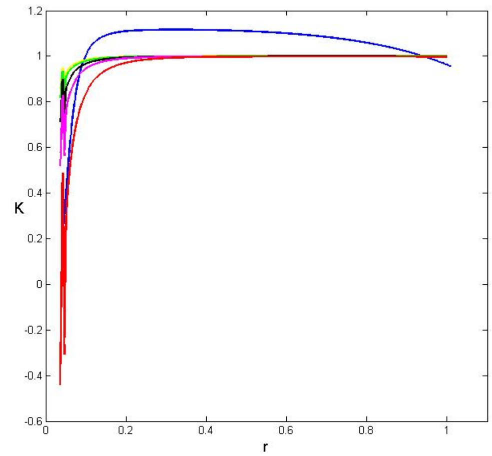

Figure 17:

case 3 (Q^{III})

The optimization in the third case has taken the following values:

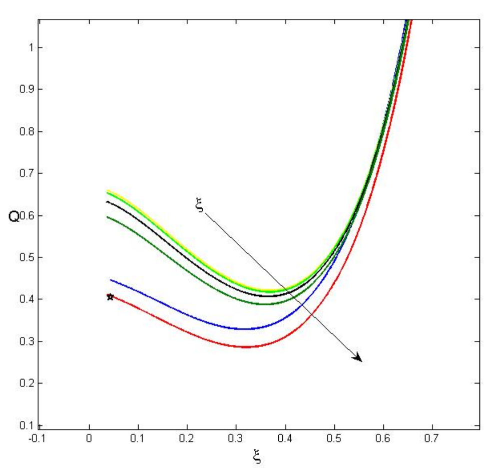

Figure 16:

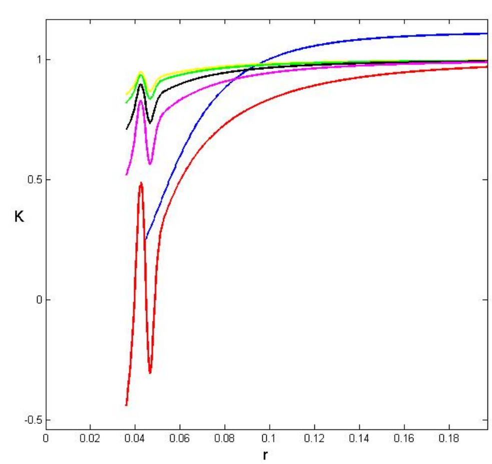

Figure 18:

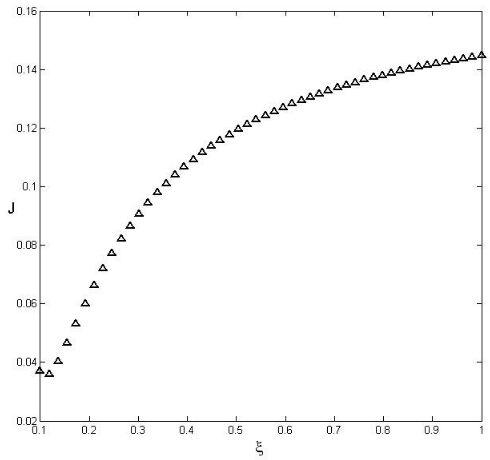

Figure 19:

Convergence

The graphic shows the convergence of the compute when you increase the dots on the grid:

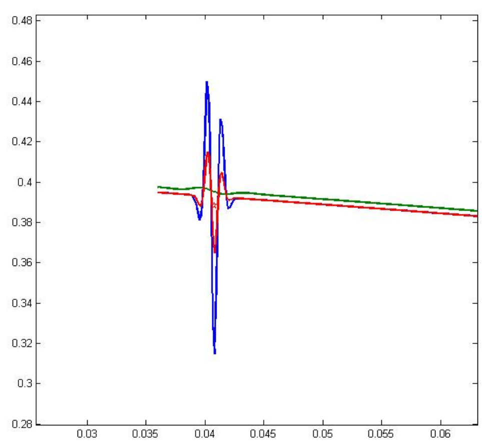

Figure 20: