Modelling and analysis of inflammatory phase dynamics in diabetic wound healing

Work in progress

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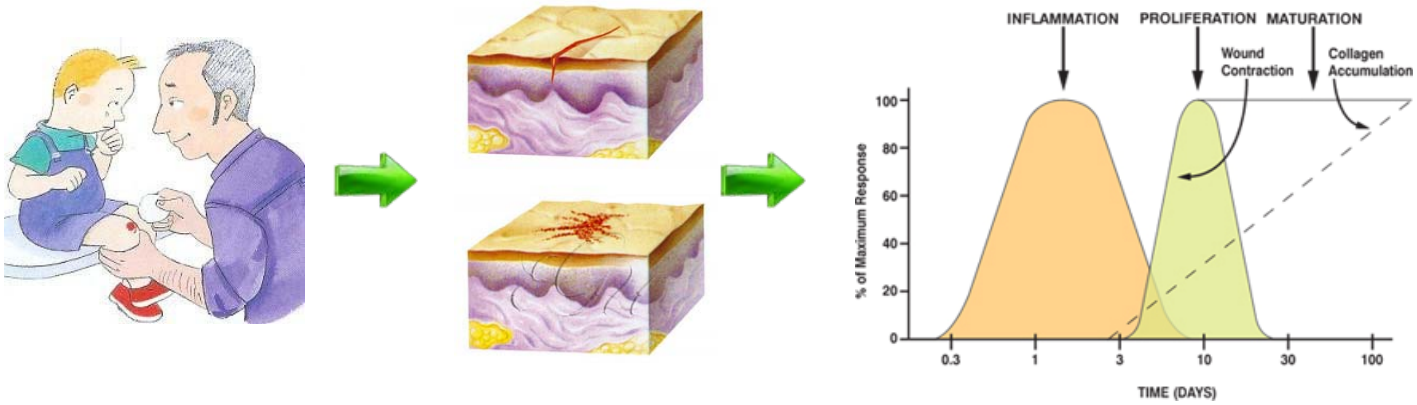
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Barcelona, June 2010

Outline

1. Introduction
2. Our model: a PDE approach
3. Analytical results
4. Numerical simulations
5. Future work

The problem

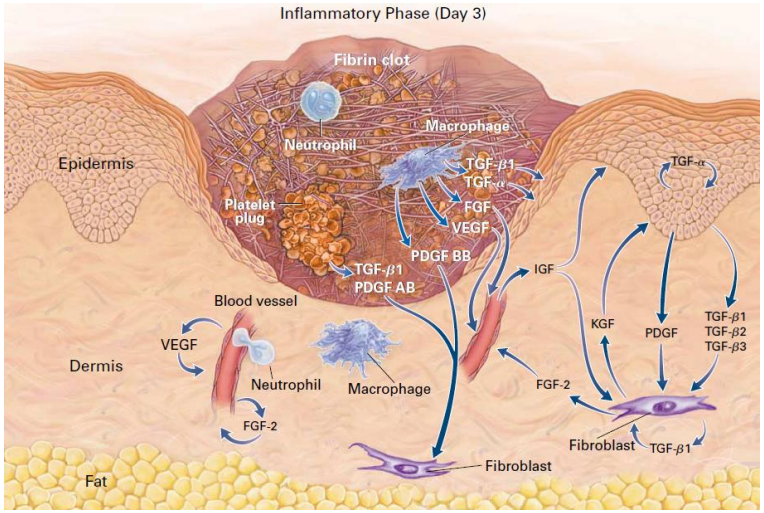
When an injure occurs:



We are interested in the **inflammatory phase** dynamics (activation of the whole process) in **diabetic** patients.

Why? Impaired healing: the inflammatory phase takes longer than normal (causes not very well understood)

Inflammatory phase:

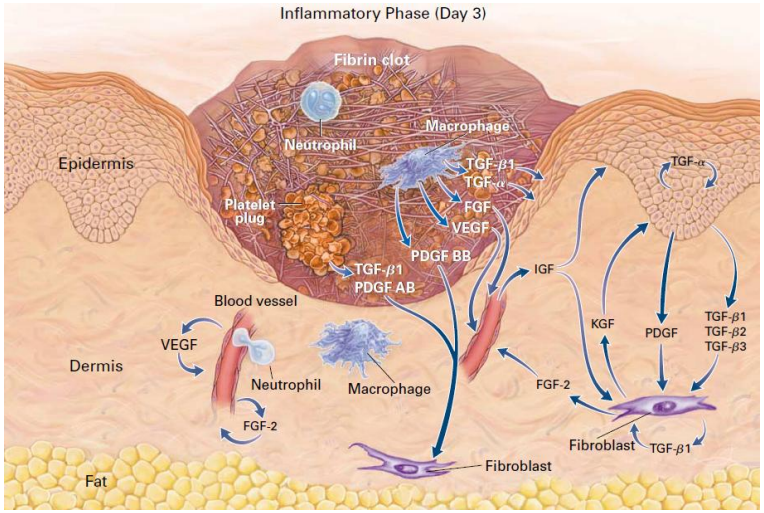


from Clark et al. (1999)

An injure activates the platelets to:

- stop blood loss
- release chemicals to clean the wound and to activate the healing process

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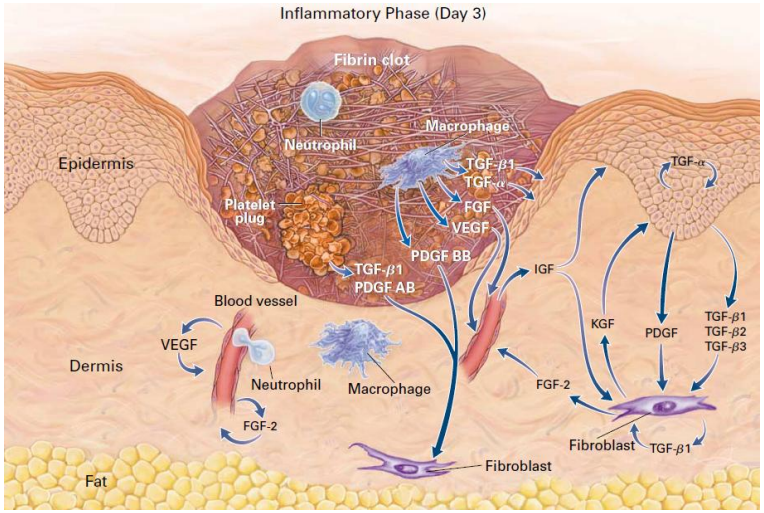
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One of these chemicals is the transforming growth factor β (**TGF-**β)

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An injure activates the platelets to:

- stop blood loss
- release chemicals to clean the wound and to activate the healing process

One of these chemicals is the transforming growth factor β (**TGF-β**)

TGF-β stimulates the influx of monocytes into the wound site and transforms them into:

- **inflammatory macrophages**: clean the wound and generate TGF-β.
- **repair macrophages**: clean the wound and generate new chemicals that allow to enter the next healing phase.

- Macrophages balance is **crucial** to go into the next phase.
- If not proper balance $\Rightarrow$ **chronic wounds** (the inflammatory phase lasts too much)
- This happens, for instance, when **diabetis** is present (persistence of inflammatory macrophages)

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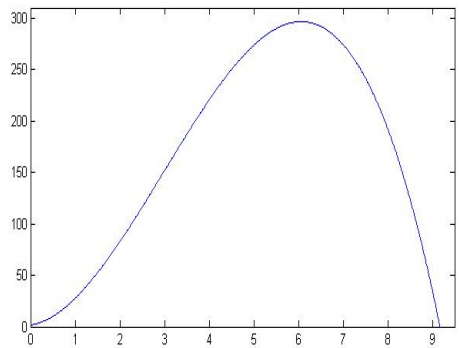
We want to model the dynamics of these macrophages and the growth factor at the inflammatory phase, some time after the injure has occurred and considering the effect of diabetis.

A first model: an ODE approach

J.Sherratt, H.Waugh (2006) (non-dimensional):

$$\begin{cases} u_t = \alpha K(T) - \delta_1 u + u(1-(u+v)) \\ v_t = (1-\alpha) K(T) - \delta_1 v + v(1-(u+v)) \\ T_t = u - \delta_2 T \end{cases}$$

$u(t) =$ inflammatory macrophages density
$v(t) =$ repair macrophages density
$T(t) =$ TGF-β density



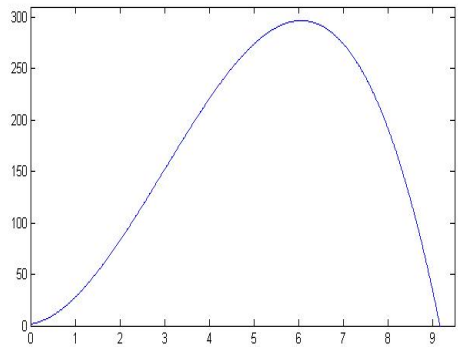
$K(T) > 0,\ T \in [0, T_Q)$
$K(T_Q) = 0$
maximum at T_{max}

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considers influx/migration+ natural loss + mitosis and crowding

Remarks:

- $\alpha \in (0, 1)$ and $\alpha_{\text{diabetic}} > \alpha_{\text{normal}}$
- Influx of monocytes governed by $K(T)$ and differentiation into macrophages by α and $1 - \alpha$
- The ODE model explains the persistence of inflammatory macrophages in diabetic patients
- Does not consider aspects as wound shape, non-homogeneous rate of healing, role of interior-boundary

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We propose a PDE model that generalizes the ODE approach

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$\Omega \subset \mathbb{R}^2$ (non-dimensional version)

$$
\begin{cases}
u_t = \Delta u + \xi\left[\alpha(x)K(T) - \delta_1 u\right] + u(1-(u+v)) \\
v_t = \Delta v + \xi\left[(1-\alpha(x))K(T) - \delta_1 v\right] + v(1-(u+v)) \\
T_t = D\Delta T + u - \delta_2 T \qquad \text{in } \Omega \\
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\dfrac{\partial v}{\partial n} = (1-\xi)\left[(1-\alpha(x))K(T) - \delta_1 v\right] \\
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\end{cases}
$$

$\alpha(x), \xi \in (0,1)$ (diabetic , interior-boundary); $D >> 1$, $\delta_2 >> \delta_1$

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Well-posedness

We write the PDE system as an evolution equation

$$\begin{cases} U_t + AU = F(U) \ \text{ in } \Omega \\ U_\nu = G(U) \ \text{ on } \partial\Omega \end{cases} \qquad \text{where } U = (u, v, T)$$

General hypotheses:

- K, α Lipschitz and regular enough
- K as in the ODE case.

It can be seen:

- existence, uniqueness and regularity of a local solution
- existence of a constant invariant set Q
  (*Proof. H.J. Kuiper (1980)*)
- boundedness of the semigroup in $Q \cap (H^1 \times H^1 \times H^1)$.

So, for any initial condition in Q,

- there exists a global solution in $Q \cap (H^1 \times H^1 \times H^1)$ that is, indeed, a classical solution

Proof. Using A.N. Carvalho, S.M. Oliva, A.L. Pereira, A. Rodriguez-Bernal (1997); or S.M. Oliva, A.L. Pereira (1995)

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  Remark: the problem is well-posed from a mathematical point of view but also from a biological point of view

Proof. Using A.N. Carvalho, S.M. Oliva, A.L. Pereira, A. Rodriguez-Bernal (1997); or S.M. Oliva, A.L. Pereira (1995)

Equilibria

It can be seen:

- Existence of equilibria in the invariant region Q.

- In Q, the ω-limit set is contained in the equilibria set.

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- In Q, the ω-limit set is contained in the equilibria set.
  - *Proof.* $\exists\, s_0 > 0$ *such that*

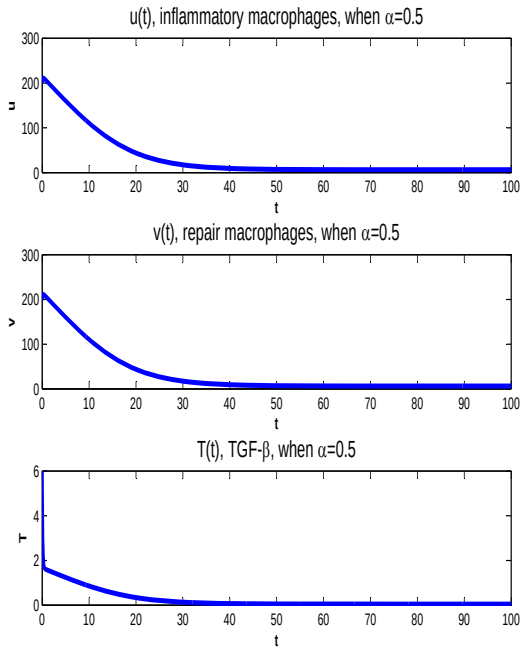
$$\left(\int_{s_0}^{\infty} \left\| \frac{dU(t)}{dt} \right\| dt \right)^{1/2} < \infty$$

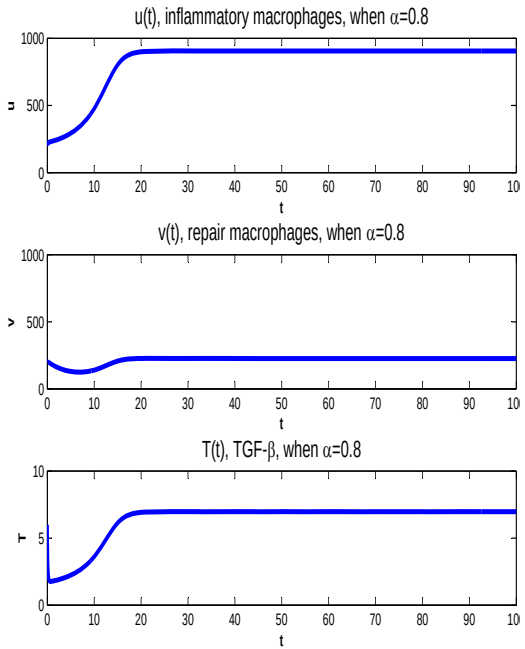
(as in S.M. Oliva (1999))

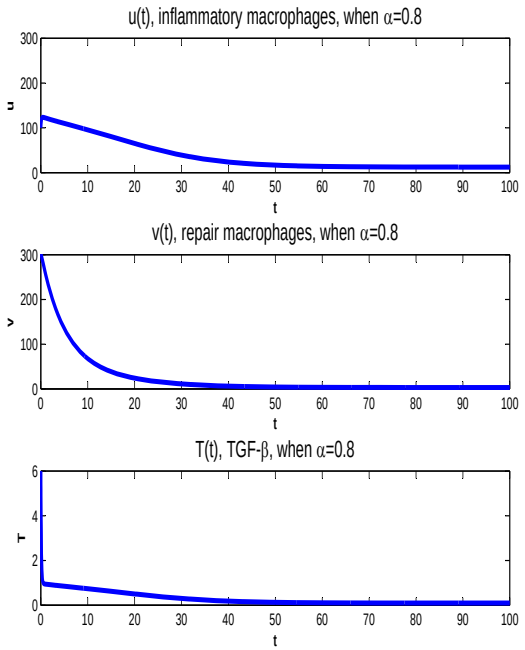
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ODE simulation







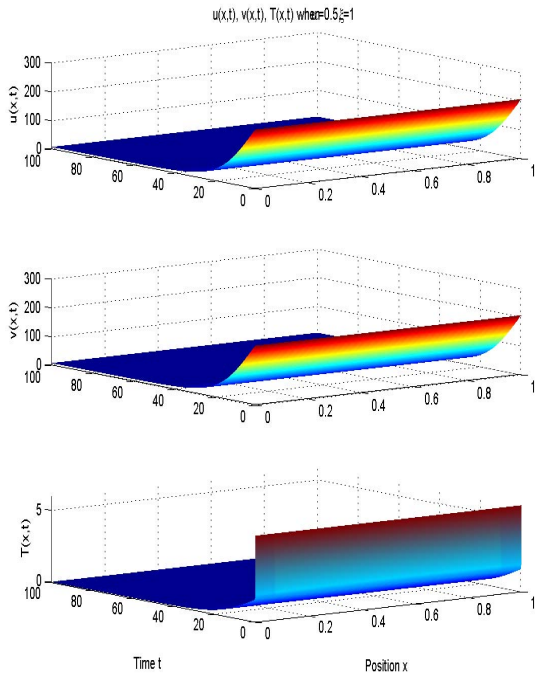
$\alpha = 0.5$ (**non-diabetic**)

$\alpha = 0.8$ (**diabetic**)

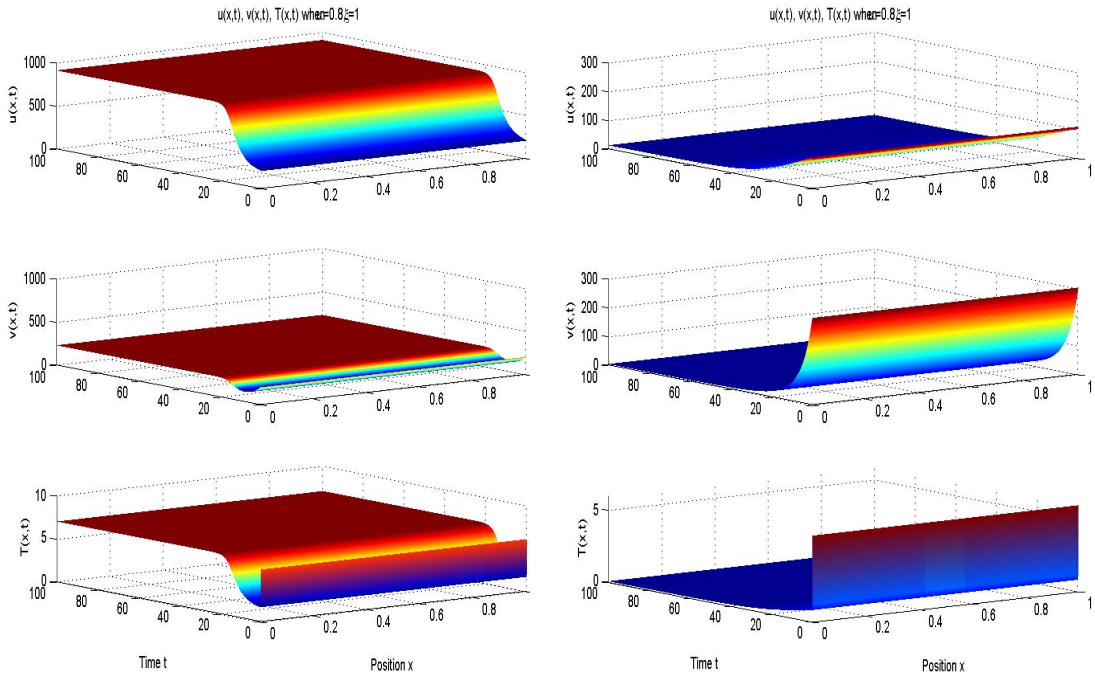
Remarks:

- $u = v$ when $\alpha = 0.5$; persistence of u when $\alpha = 0.8$;
- 2 stable equilibria when $\alpha = 0.8$ (another non-stable).

PDE 1D: evolution of solutions ($\xi = 1$)



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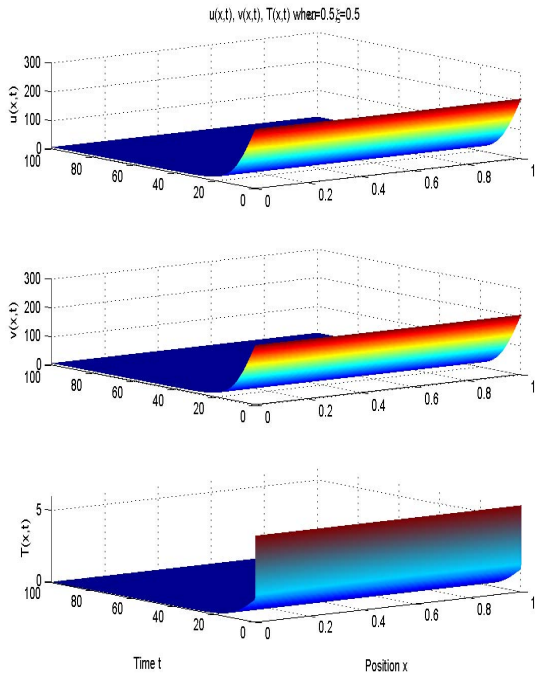


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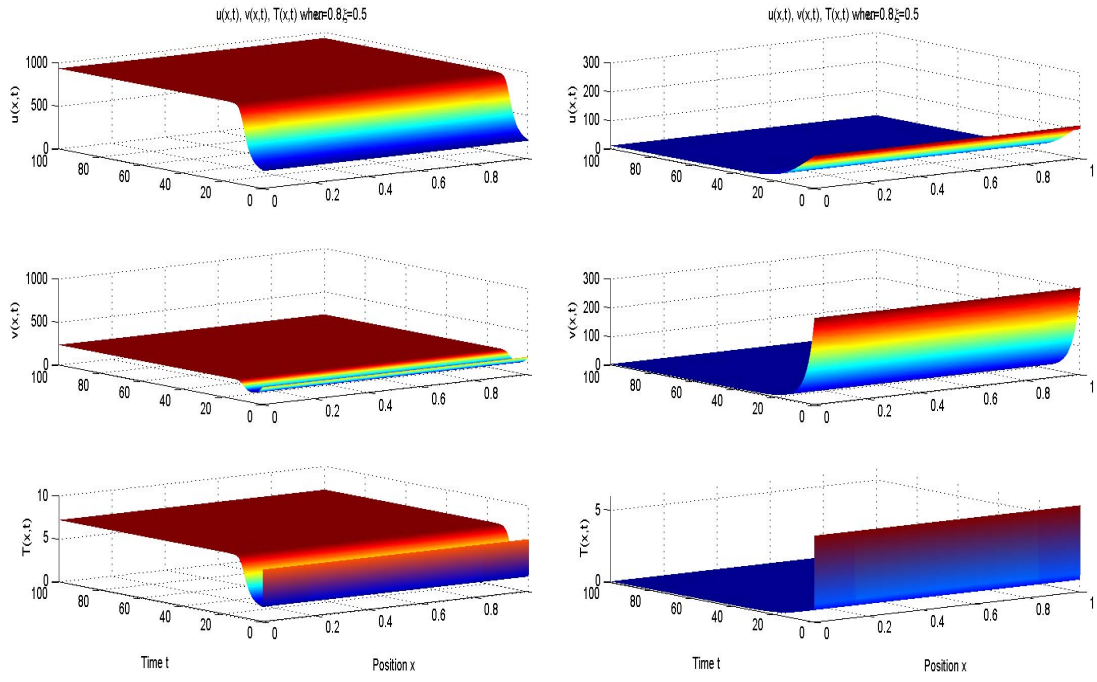
Remarks:

- $u = v$ when $\alpha = 0.5$; persistence of u when $\alpha = 0.8$;
- 2 stable constant equilibria when $\alpha = 0.8$ (the ODE ones).

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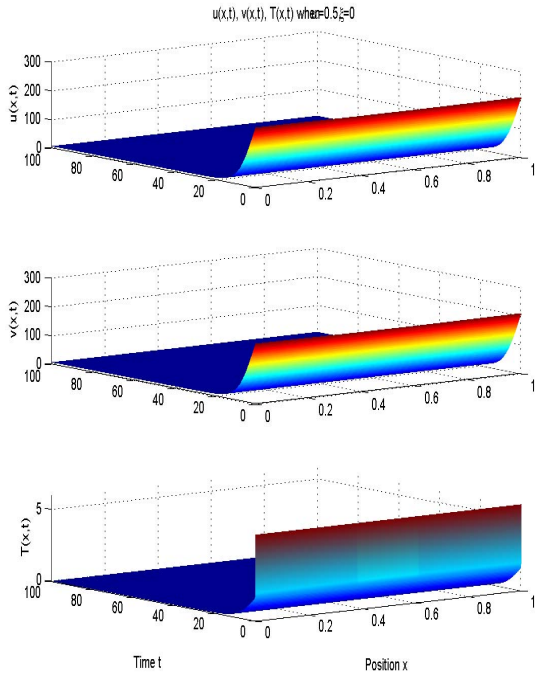


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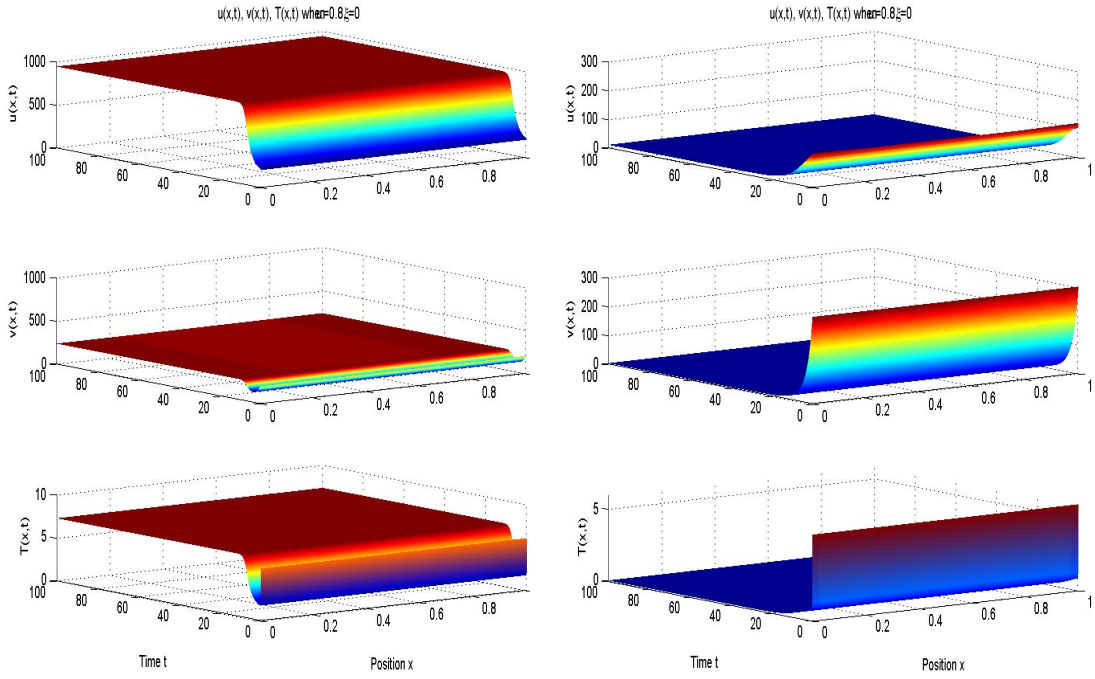
Remarks:

- $u = v$ when $\alpha = 0.5$; persistence of u when $\alpha = 0.8$;
- 2 stable constant equilibria when $\alpha = 0.8$ (the ODE ones).

PDE 1D: evolution of solutions ($\xi = 0$)



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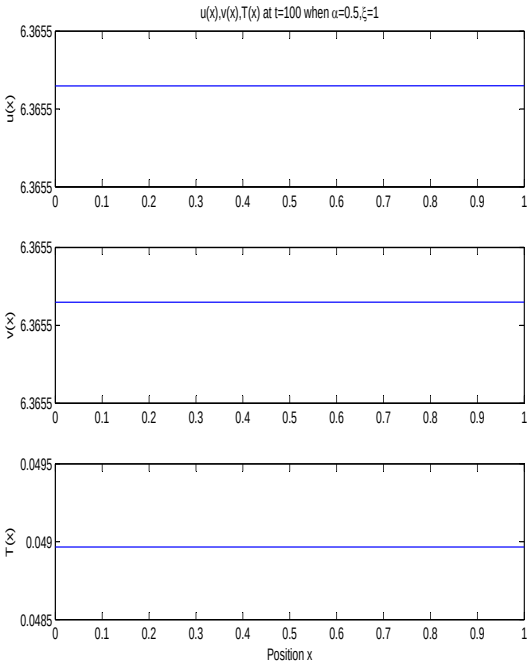


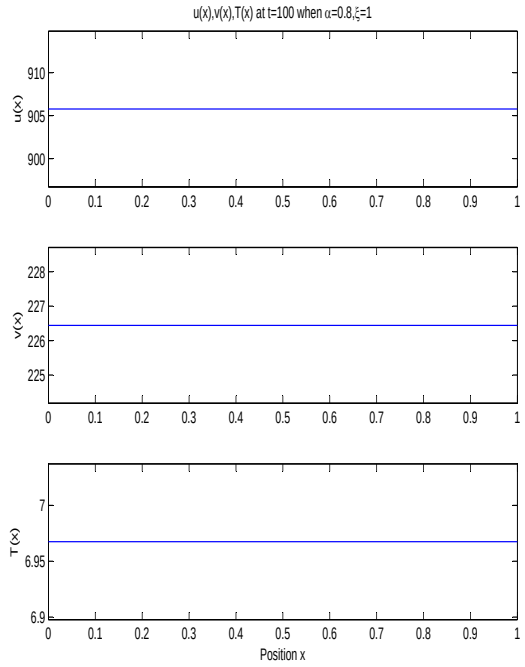
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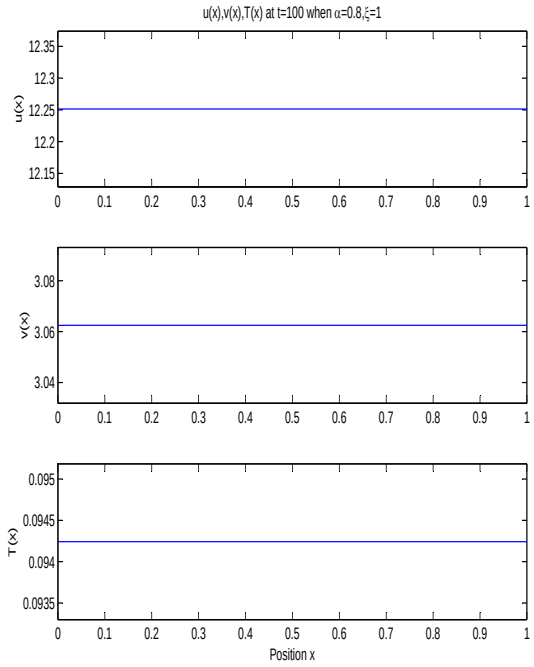
Remarks:

- $u = v$ when $\alpha = 0.5$; persistence of u when $\alpha = 0.8$;
- 2 stable constant equilibria when $\alpha = 0.8$.

PDE 1D: asymptotic behaviour ($\xi = 1$)







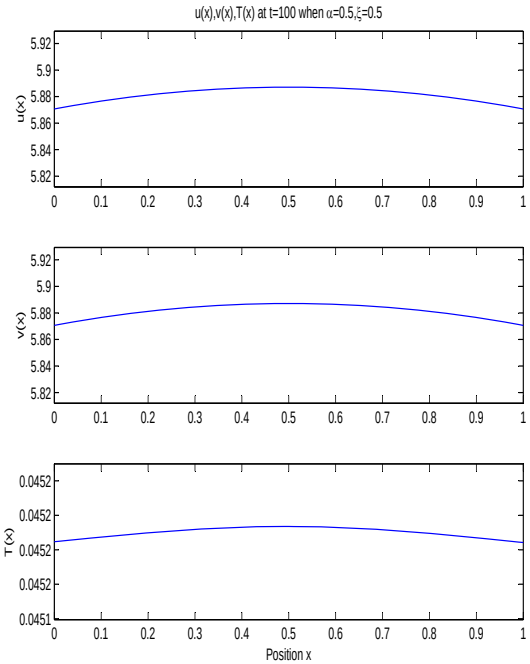
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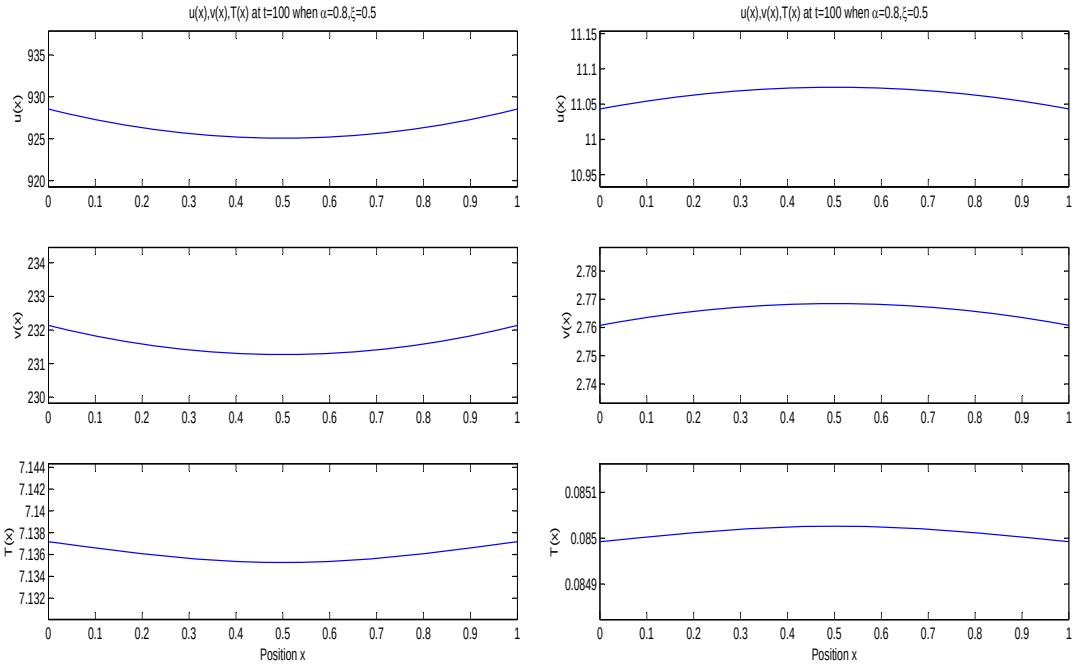
$\alpha = 0.8$ (**diabetic**)

Remarks:

- constant equilibria when $\xi = 1$;
- the equilibria are the ODE ones.

PDE 1D: asymptotic behaviour ($\xi = 0.5$)





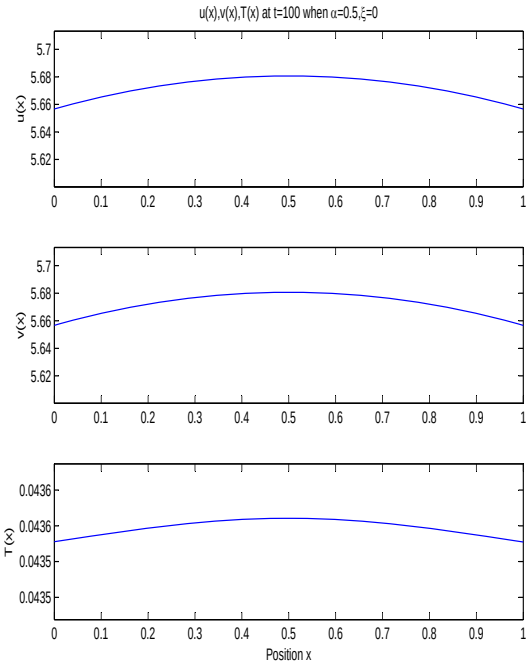
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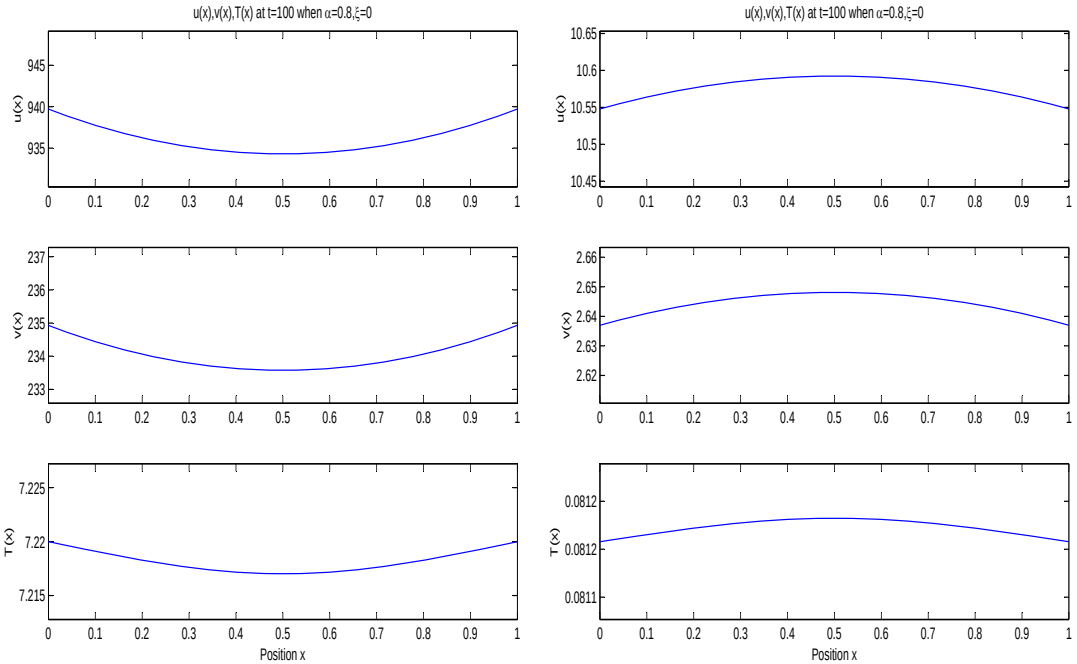
Remarks:

- non-constant equilibria when $\xi \neq 1$ (even for constant α);
- tend to the ODE ones as $\xi \longrightarrow 1$.

PDE 1D: asymptotic behaviour ($\xi = 0$)



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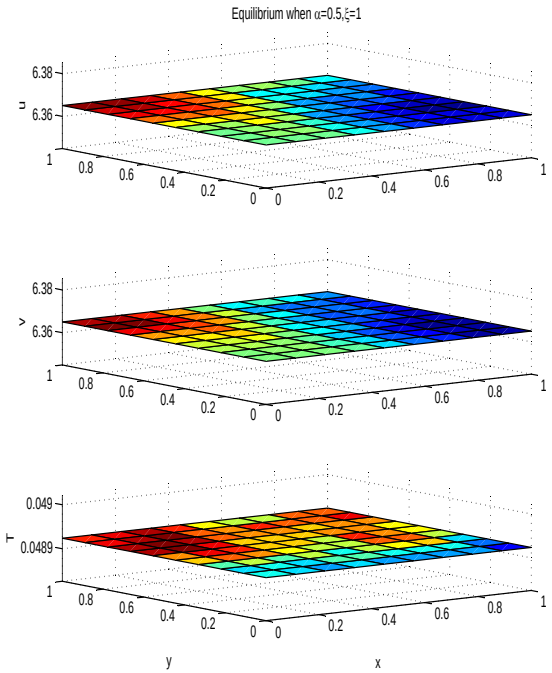


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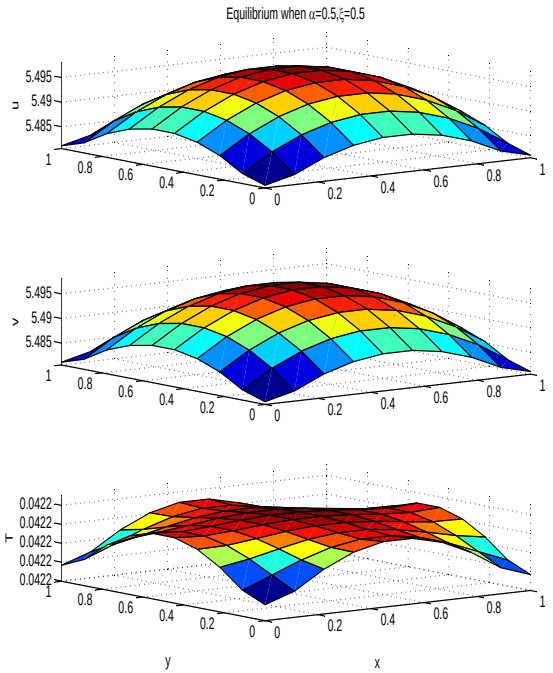
Remarks:

- more non-constant as $\xi \longrightarrow 0$;
- ODE model does not apply.

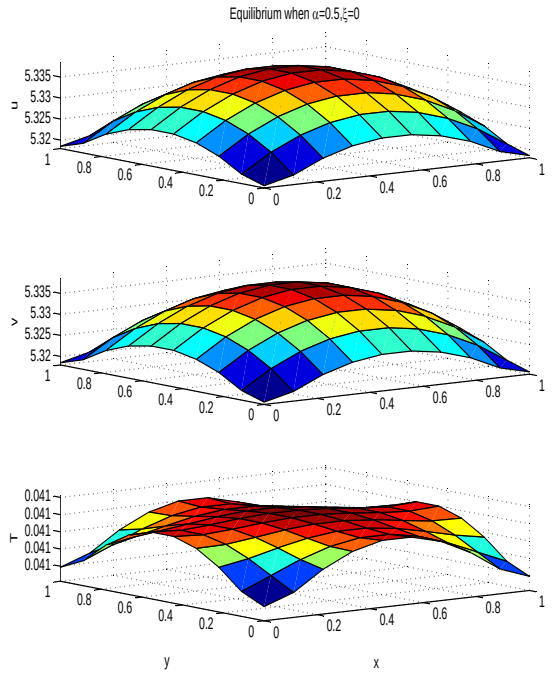
PDE 2D: equilibria in a square ($\alpha = 0.5$)



$\xi = 1$

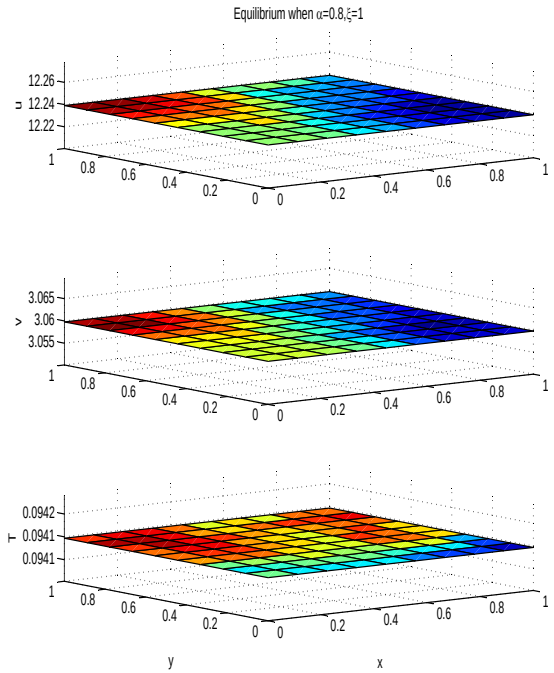


$\xi = 0.5$

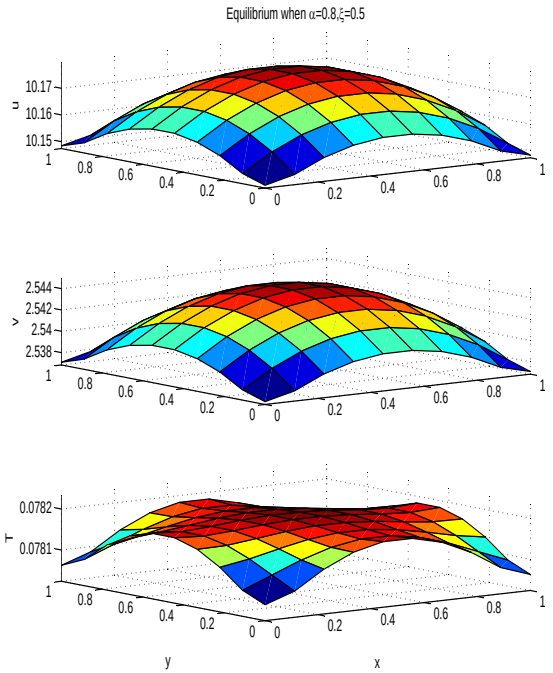


$\xi = 0$

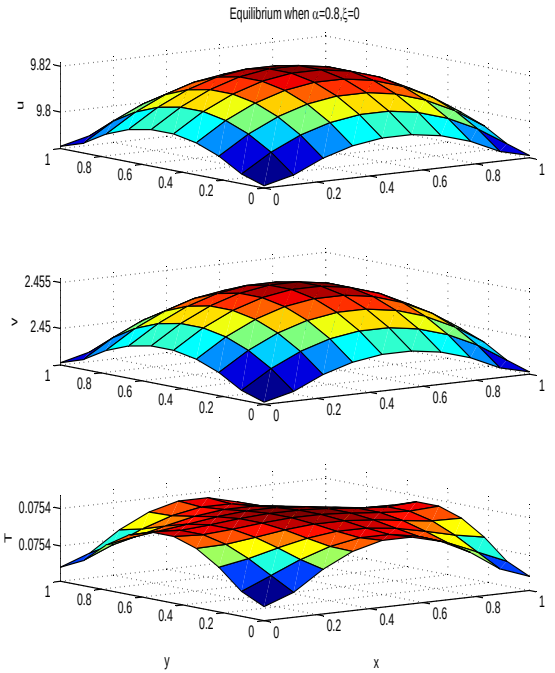
PDE 2D: equilibria in a square ($\alpha = 0.8$)



$\xi = 1$



$\xi = 0.5$



$\xi = 0$

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Some questions:

- stability of equilibria - comparison with ODE results
- influence of different geometries of the wound on the solutions
- $\alpha(x)$ non-constant
- behaviour of solutions in terms of ξ (interior-boundary reaction)
- convergence to the equilibria: once below a threshold is mantained there?
- speed of convergence/ healing rate
- simulation of healing treatments
  (as in J. Sherratt, H. Waugh (2007))
- ...

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