Finite difference scheme for transport-diffusion-reaction of antibodies in a tumor : Analysis of consistency and stability

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Abstract: According to the mathematical model presented in a scientificité modeling text in the French external agregation competition (public 2008), antibodies are transported between tumors and are reacted with antigens in a transport-diffusion reaction. As a result of the proposed model, an unstable system is produced. Under certain conditions, we propose modifications that result in a new system that is stable and consistent. In this paper, a detailed study of the stability and consistency of this new system is presented, with demonstrations and proofs that are validated numerically.

Key-Words: Finite difference scheme, antibodies, tumor, antigens, consistency, stability, simulation.

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1. Introduction

An analysis of antibody penetration into a prevascular tumor nodule embedded in normal tissue is presented in [1]. According to the mathematical model presented in a scoentific modeling text in the French external agregation competition (public 2008), a numerical method is proposed for calculating antibody and antigen concentrations when reaction speed is moderate. Although the proposed mathematical model describes well the transport-diffusion reaction of antibodies in a tumor and their interactions with antigens, it has a significant limitation. In fact, the system has been shown to be unstable and requires modification. An analysis of the stability and consistency is proposed, and the theoretical results are validated by numerical tests after increasing the reaction factor. The proposed work provides a detailed analysis of a modified scheme, the effects of the reaction factor, and the behavior of the new scheme at infinity. We seek solutions to the system in the form of progressive waves of the "front" type.

2. Mathematical Model of simultaneous of antibody-antigen reaction in a tumor

2.1 Notations

We suppose :

The liquid carrying the antibodies occupies all the inert spaces in the medium.

The antigens are fixed to the internal walls of the inertial cells.

The porosity ratio $w = \frac{volume\ liquid}{total\ volume} \in]0.1[$ is known.

The process takes place in a fairly thin tube, of section A and the flow occurs through section wA. (ie We can confuse the dimension of the tube with a one-dimensional medium in space.)

Notations :

The concentration of the antibody $c(x,t) = \frac{number\ of antibodies}{volume\ of\ fluid}$.

The concentration of the antigen $s(x,t) = \frac{number\ of antigen}{volume\ total}$.

The flow of antibodies $q(x,t) = \frac{number\ of antibodies\ passed\ in\ x}{time \times surface}$ which is a function of c and s.

The antibody-antigen reaction function $f[c(x,t),s(x,t)] = \frac{number\ of antibodies\ retained\ by\ antigens}{time \times volume}$.

2.2 Basic Equation

For a time Δt and in a volume $A.\Delta x$, as a result of the principle of mass conservation, we have:

$$\Delta c(x,t).\Delta x.Aw = -\Delta q(x,t).\Delta t.A - f[c(x,t),s(x,t)].\Delta t.\Delta x.A$$

Thus, dividing by $\Delta t.\Delta x.A$ and passing on to partial derivatives we obtain:

$$w\frac{\partial c(x,t)}{\partial t} + \frac{\partial q(x,t)}{\partial x} = -f[c(x,t),s(x,t)] \quad (1)$$

There are two components to the flow $q = q_a + q_d$:

A transport flow is defined as $q_a(x,t) = u.c(x,t)$ where u represents the transportation speed as assumed here to be constant.

The diffusion flux $q_d(x,t) = -v.\frac{\partial c(x,t)}{\partial x}$ where v is the diffusion factor assumed to be constant.

2.3 System setup

2.3.1 The mass conservation of antigens

As the antigens are fixed, only the time t, the antibody-antigen reaction function f and the valency p of the antibodies determine their number.

$$C + pS \rightarrow S_pC \quad (2)$$

A variation in the number of antigens equals $-p\times$ (the number of antibodies) retained by the antigens, we have:

$$\Delta s(x,t).\Delta x.A = -pf[c(x,t),s(x,t)].\Delta t.\Delta x.A$$

By dividing by $\Delta t.\Delta x.A$ and passing to partial derivatives, we obtain:

$$\frac{\partial s(x,t)}{\partial t} = -p.f[c(x,t),s(x,t)] \quad (3)$$

We obtain $\frac{\partial s(x,t)}{\partial t} = -p.k.c(x,t).s(x,t)$, with k as the factor of reaction assumed to be constant and f as the form: $f = k.c.s$ (4)

2.3.2 The system of partial differential Equations

Based on the framework previously defined, we search for c and s that are defined on the $[0,L]\times[0,T]$, $L,T \in \mathbb{R}^{*+}$. Then we give ourselves: $w \in]0,1[$, $u,v,k,s_0 \in \mathbb{R}^{*+}$, $p \in \mathbb{N}^*$ and a regular function c_d on $[0,T]$. Therefore, the problem is as follows:

$$\begin{cases} w\frac{\partial c}{\partial t} + u\frac{\partial c}{\partial x} - v\frac{\partial^2 c}{\partial x^2} + k.c.s & = 0 \quad (5) \\ \frac{\partial s}{\partial t} + p.k.c.s & = 0 \quad (6) \end{cases}$$

With initial and boundary conditions:

$$\begin{cases} c(0,t) = c_d(t) & c(L,t) = 0 & t \in [0,T] \\ c(x,0) = 0 & s(x,0) = s_0 & x \in [0,L] \end{cases} \quad (7)$$

3. Numerical resolution

An explicit scheme:
Let $M,N \in \mathbb{N}^*$ and the spatial and temporal discretization steps: $\Delta x = L/M$ and $\Delta t = T/N$. We consider the progressive scheme in time and centered in space :

$$\begin{cases} \frac{\partial c(x_j,t_n)}{\partial t} & \approx & \frac{c_j^{n+1}-c_j^n}{\Delta t} \\ \frac{\partial s(x_j,t_n)}{\partial t} & \approx & \frac{s_j^{n+1}-s_j^n}{\Delta t} \\ \frac{\partial c(x_j,t_n)}{\partial x} & \approx & \frac{c_j^n-c_{j-1}^n}{\Delta x} \\ \frac{\partial^2 c}{\partial x^2} & \approx & \frac{c_{j+1}^n-2c_j^n+c_{j-1}^n}{\Delta x^2} \end{cases}$$

Where $(x_j,t_n) = (j.\Delta x, n.\Delta t)$, $c_j^n = c(x_j,t_n)$ and $s_j^n = s(x_j,t_n)$. Which give:

$$\begin{cases} w\frac{c_j^{n+1}-c_j^n}{\Delta t} + u\frac{c_j^n-c_{j-1}^n}{\Delta x} - v\frac{c_{j+1}^n-2c_j^n+c_{j-1}^n}{\Delta x^2} + k.c_j^n.s_j^n & = 0 \quad (8) \\ \frac{s_j^{n+1}-s_j^n}{\Delta t} + p.k.c_j^n.s_j^n & = 0 \quad (9) \end{cases}$$

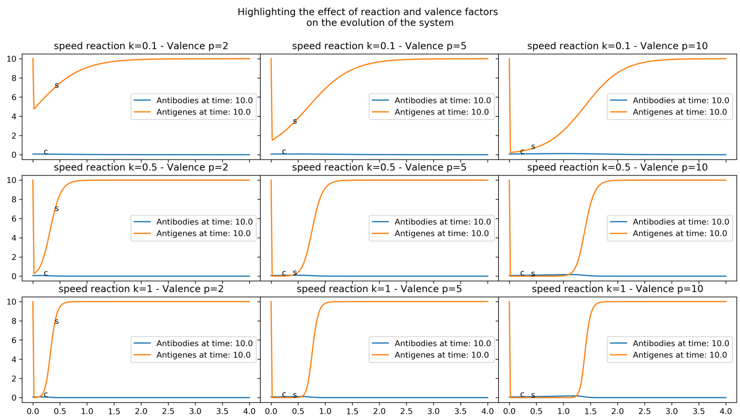
With initial and boundary conditions:

$$\begin{cases} c_j^0 = 0 & j \in |[0,M]| \quad (10) \\ c_0^n = c_d(t_n) & n \in |[1,N]| \quad (11) \\ s_j^0 = s_0 & j \in |[0,M]| \quad (12) \end{cases}$$

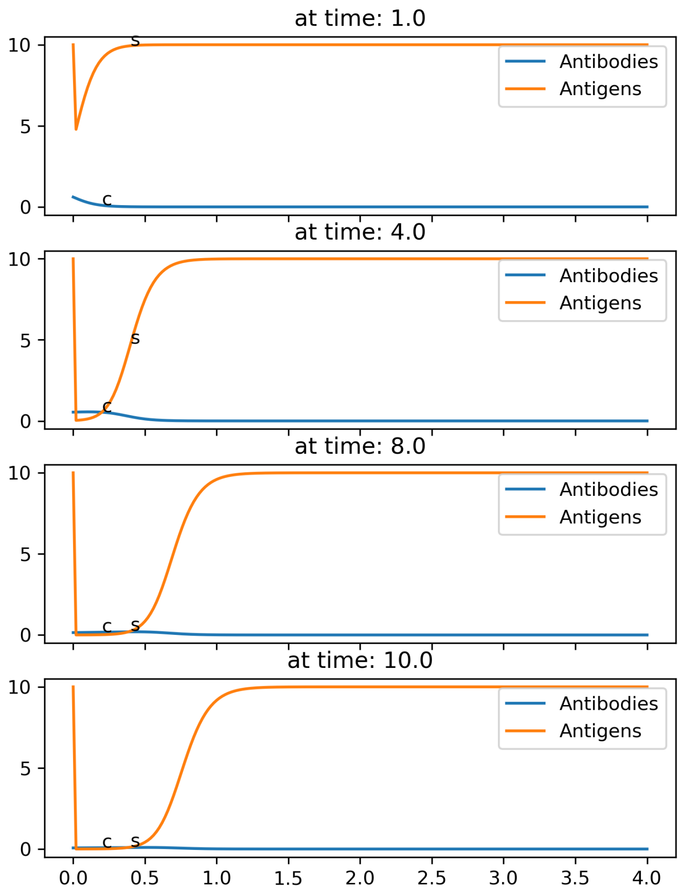
* Numerical simulation of the explicit scheme :

with function $c_d(t) = 1$ and values:

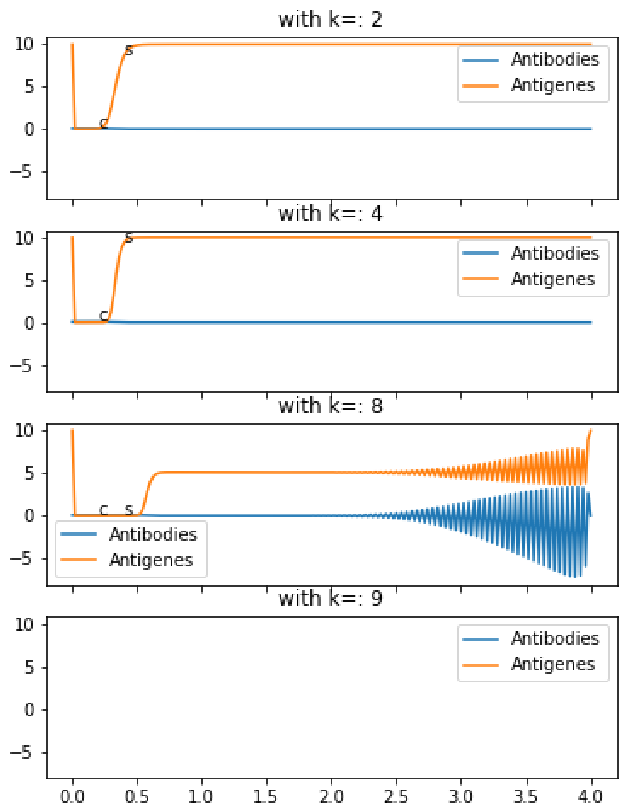
w	u	v	s0	M	dt	T	L	k	p
0.9	0.1	0.003	2	100	0.01	20	1	1e4	3



Concentrations with a reaction rate k=0.5 and a valence p=5



The effect of increasing the reaction factor k on the scheme.



3.1 Consistency analysis and stability

The scheme $(8-9)$ is consistent with the equation $(5-6)$ and it is order 1 accurate in time and space

According to Taylor's developments we have:

$$\begin{cases} c_j^{n+1}-c_j^n & =\Delta t\frac{\partial c(x_j,t_n)}{\partial t}+\mathscr{O}(\Delta t^2) \\ c_{j+1}^n-c_j^n & =\Delta x\frac{\partial c(x_j,t_n)}{\partial x}+\frac{\Delta x^2}{2}\frac{\partial^2 c(x_j,t_n)}{\partial x^2}+\mathscr{O}(\Delta x^3) \\ c_{j-1}^n-c_j^n & =-\Delta x\frac{\partial c(x_j,t_n)}{\partial x}+\frac{\Delta x^2}{2}\frac{\partial^2 c(x_j,t_n)}{\partial x^2}+\mathscr{O}(\Delta x^3) \\ c_{j+1}^n-2c_j^n+c_{j-1} & =\Delta x^2\frac{\partial^2 c(x_j,t_n)}{\partial x^2}+\mathscr{O}(\Delta x^4) \\ s_j^{n+1}-s_j^n & =\Delta t\frac{\partial s(x_j,t_n)}{\partial t}+\mathscr{O}(\Delta t^2) \end{cases}$$

And by replacing the obtained equations in the first members of $(8-9)$ we obtain the errors :

$$\begin{cases} E_c & = w\frac{\partial c(x_j,t_n)}{\partial t} + \mathscr{O}(\Delta t) + u\frac{\partial c(x_j,t_n)}{\partial x} \\ & + \frac{\Delta x}{2}\frac{\partial^2 c(x_j,t_n)}{\partial x^2} + \mathscr{O}(\Delta x^2) - v\frac{\partial^2 c(x_j,t_n)}{\partial x^2} \\ & + \mathscr{O}(\Delta x^2) + k.c_j^n.s_j^n \\ & = \mathscr{O}(\Delta x, \Delta t) \\ E_s & = \frac{\partial s(x_j,t_n)}{\partial t} \\ & + \mathscr{O}(\Delta t) + p.k.c_j^n.s_j^n \\ & = \mathscr{O}(\Delta x, \Delta t) \end{cases}$$

Scheme (8-9) is stable with equation (5-6) under the condition:

$$\Delta t \leq min\{\frac{w}{\frac{u}{\Delta x} + \frac{2v}{\Delta x^2} + ks_0}, \frac{1}{kpK}\} \ \ Where\, K = \max_{1\leq n\leq N} c_d(t_n)$$

by induction :

We have $0 \leq c_j^0 \leq K$ et $0 \leq s_j^0 \leq s_0$

Suppose $0 \leq c_j^n \leq K$ and $0 \leq s_j^n \leq s_0$ for a $n \in \mathbb{N}^*$.

From $(8-9)$ we have:

$$\begin{cases} c_j^{n+1} = & c_j^n + \frac{u\Delta t}{w\Delta x}(c_{j-1}^n - c_j^n) \\ + & \frac{v\Delta t}{w\Delta x^2}(c_{j+1}^n - 2c_j^n + c_{j-1}^n) - \frac{k\Delta t}{w}c_j^n s_j^n \\ = & (\frac{u}{w\Delta x} + \frac{v}{w\Delta x^2})\Delta t c_{j-1}^n + (1 - (\frac{u}{w\Delta x} \\ + & \frac{2v}{w\Delta x^2} + \frac{k}{w}s_j^n)\Delta t)c_j^n + \frac{v}{w\Delta x^2}\Delta t c_{j+1}^n \\ s_j^{n+1} = & s_j^n - \frac{pk\Delta t}{w}c_j^n s_j^n \end{cases}$$

Finaly we obtain : $\begin{cases} 0 & \leq c_j^{n+1} & \leq K \\ 0 & \leq s_j^{n+1} & \leq s_0 \end{cases}$

4. Behavior for large k

4.1 Modified scheme of the method

We consider the scheme $(15-16)$ by replacing the terms $c_j^n s_j^n$ by $c_j^{n+1}s_j^{n+1}$, which can be written again in the form:

$\begin{cases} X + A_1XY + B_1 & = 0 \quad (15') \\ Y + A_2XY + B_2 & = 0 \quad (16') \end{cases}$ where $A_1 = \frac{k\Delta t}{w}$, $A_2 = \frac{pk\Delta t}{w}$ and

$$\begin{cases} B_1 & = -c_j^n - \frac{u\Delta t}{w\Delta x}(c_{j-1}^n - c_j^n) - \frac{v\Delta t}{w\Delta x^2}(c_{j+1}^n - 2c_j^n + c_{j-1}^n) \\ & = (\frac{u\Delta t}{w\Delta x} + \frac{2v\Delta t}{w\Delta x^2} - 1)c_j^n - (\frac{u\Delta t}{w\Delta x} + \frac{v\Delta t}{w\Delta x^2})c_{j-1}^n - \frac{v\Delta t}{w\Delta x^2}c_{j+1}^n \end{cases}$$

$B_2 = -s_j^n$, $X = c_j^{n+1}$ and $Y = s_j^{n+1}$.

The system $(15' - 16')$ is equivalent to:

$$\begin{cases} A_2X^2 + (1 + A_2B_1 - A_1B_2)X + B_1 & = 0 \quad (15'') \\ Y + A_2XY + B_2 & = 0 \quad (16') \end{cases}$$

With equation $(5-6)$, the scheme $(15-16)$ is:

i) consisting and it's order 1 accurate in time and space .

ii) stable under the condition:

$$\Delta t \leq \frac{w}{\frac{u}{\Delta x} + \frac{2v}{\Delta x^2}}$$

and therefore in this case it's stable independently of k.

We proceed also by induction.
We should demonstrate that (c_j^{n+1}, s_j^{n+1}) exists and $0 \leq c_j^{n+1}, 0 \leq s_j^{n+1}$; (h).
The equation $(15'')$ is of 2nd degree, with discriminant $\Delta = (1 + A_2B_1 - A_1B_2)^2 - 4B_1A_2$ and admits a unique positive solution because: $\frac{u\Delta t}{w\Delta x} + \frac{2v\Delta t}{w\Delta x^2} - 1 \leq 0$ so $B_1 \leq 0$ and $\Delta \geq 0$. As $\sqrt{\Delta} \geq |1 + A_2B_1 - A_1B_2|$, the equation $(15'')$ admits 2 solutions $X_1 \geq 0$ and $X_2 \leq 0$ (not necessarily distinct. and the equation $(16')$ shows that $Y \geq 0$ as soon as $X \geq 0$ (because $-B_2 = s_j^n \geq 0$).
Let us now show that $c_j^{n+1} \leq K, s_j^{n+1} \leq s_0$:
From $(15\ and\ 16)$ we have:

$$\begin{cases} c_j^{n+1} & = (\frac{u}{w\Delta x} + \frac{v}{w\Delta x^2})\Delta t c_{j-1}^n + (1 - (\frac{u}{w\Delta x} + \frac{2v}{w\Delta x^2})\Delta t)c_j^n + \frac{v}{w\Delta x^2}\Delta t c \\ s_j^{n+1} & = s_j^n - \frac{pk\Delta t}{w}c_j^{n+1}s_j^{n+1} \end{cases}$$

And according to induction hypotheses we have:

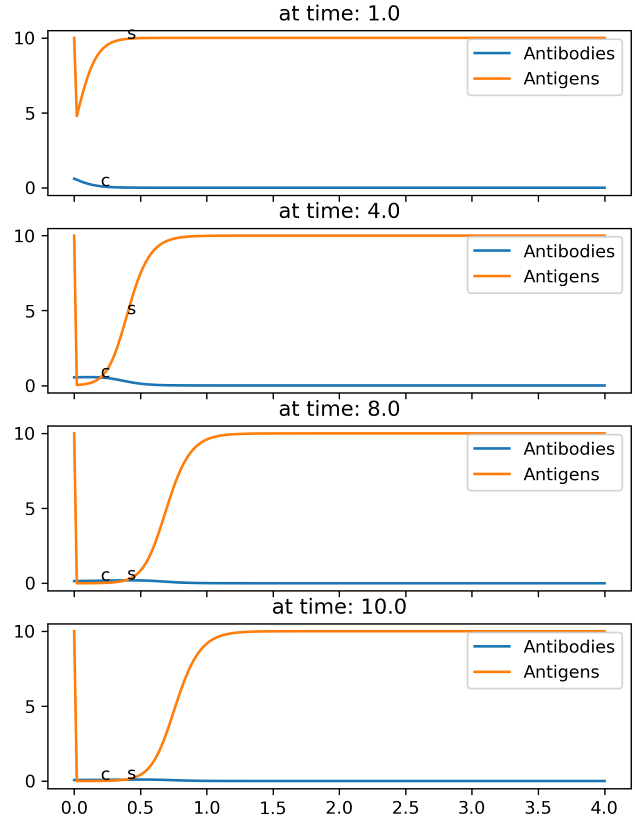
$$\begin{cases} c_j^{n+1} & \leq (\frac{u}{w\Delta x} + \frac{v}{w\Delta x^2})\Delta t K + (1 - (\frac{u}{w\Delta x} + \frac{2v}{w\Delta x^2})\Delta t)K + \frac{v}{w\Delta x^2}\Delta t K \\ s_j^{n+1} & \leq s_j^n \end{cases}$$

Numerical simulation of the modified scheme :

with function $c_d(t) = 1$ and values:

w	u	v	s0	M	dt	T	L	k	p
0.9	0.1	0.003	2	100	0.01	20	1	1e4	3

Concentrations with a reaction rate k=0.5 and a valence p=5



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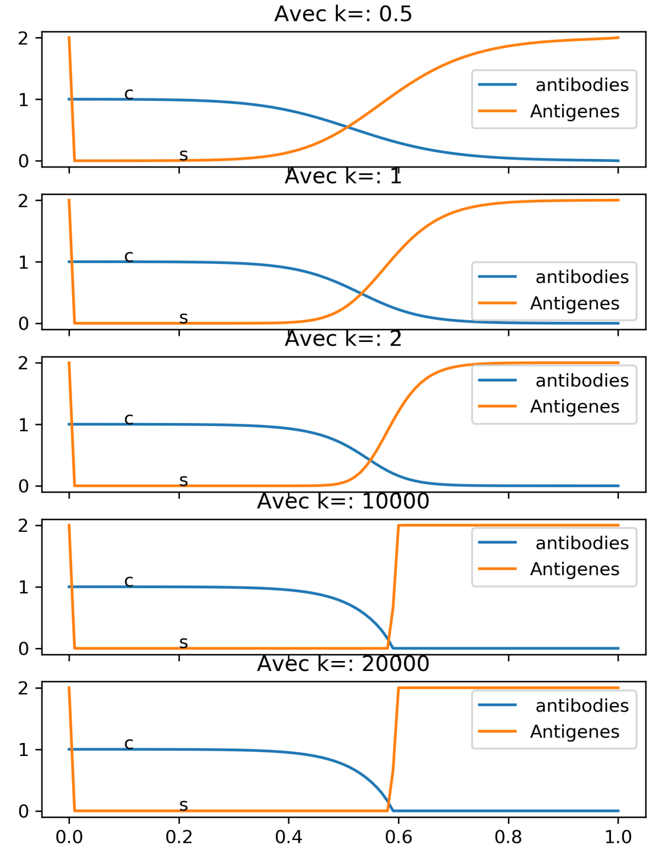


4.2 Behavior when $\mathbf{k} \to +\infty$

To get an idea of the appearance of c and s for large k, we consider the solution (c^k, s^k) of the system $(5-6)$ for a certain k and we make $k \to +\infty$:

$$\begin{cases} w\frac{\partial c^k}{\partial t} + u\frac{\partial c^k}{\partial x} - v\frac{\partial^2 c^k}{\partial x^2} + kc^k s^k & = 0 \quad (5) \\ \frac{1}{-pk}\frac{\partial s^k}{\partial t} & = c^k s^k \quad (6) \end{cases} \Leftrightarrow$$

$$\begin{cases} \frac{\partial (wc^k - s^k/p)}{\partial t} + u\frac{\partial c^k}{\partial x} - v\frac{\partial^2 c^k}{\partial x^2} & = 0 \\ \frac{1}{-pk}\frac{\partial s^k}{\partial t} & = c^k s^k \end{cases}$$

we make $k \to +\infty$ we obtain :

$$\frac{\partial (wc^\infty - s^\infty/p)}{\partial t} + u\frac{\partial c^\infty}{\partial x} - v\frac{\partial^2 c^\infty}{\partial x^2} = 0 \quad (13)$$

If we assume that $\frac{\partial s^k}{\partial t}$ is bounded with respect to the values of $k \in \mathbb{R}^{*+}$, then $c^\infty s^\infty = 0$.
We concluded that :

$$\begin{cases} c^\infty > 0 \quad and \quad s^\infty = 0 \\ Or \\ c^\infty = 0 \quad and \quad s^\infty = s_0 \end{cases} \quad (14)$$

4.2.1 Interpretation

With a large reaction factor, we have at a position x:

If there are antibodies ($c^\infty > 0$) then all antigens react ($s^\infty = 0$).

If there are no antibodies ($c^\infty = 0$) then there is no reaction ($s^\infty = s_0$)

5. Travelling waves

We shall now seek a solution of the following type: $c(x,t) = C(z) \quad s(x,t) = S(z)$, $z = x - \sigma t$ and C, S are functions that describe wave profiles propagating at constant speed σ. In order to achieve a progressive (non-stationary) framework, we may replace the domain of study with $\mathbb{R} \times \mathbb{R}^+$ and the boundary conditions with:

$$\begin{cases} \lim\limits_{z\to-\infty} C(z) = c_d > 0 & \lim\limits_{z\to+\infty} C(z) = 0 \\ \lim\limits_{z\to-\infty} S(z) = 0 & \lim\limits_{z\to+\infty} S(z) = s_0 > 0 \end{cases}$$

The C and S profiles verify the ODE:

$$vC'' + (w\sigma - u)C' - \frac{\sigma}{p}S' = 0 \quad (17)$$

where

$$\sigma = \frac{u}{w + \frac{s_0}{pc_d}} \quad (18)$$

We have:

$$\begin{cases} \frac{\partial c(x,t)}{\partial t} = \frac{\partial c(x,t)}{\partial z}\frac{\partial z}{\partial t} \\ = -\sigma C'(z) \end{cases} \quad \text{and}$$

$$\begin{cases} \frac{\partial c(x,t)}{\partial x} = \frac{\partial c(x,t)}{\partial z}\frac{\partial z}{\partial x} \\ = C'(z) \end{cases}$$

we obtain $\frac{\partial^2 c(x,t)}{\partial x^2} = C''(z)$ and $\frac{\partial s(x,t)}{\partial t} = -\sigma S'(z)$ Accordingly, we concluded:

$$\begin{cases} -w\sigma C' + uC' - vC'' & = -kCS \\ -\sigma S' & = -kpCS \end{cases} \text{ and then } \begin{cases} vC'' + (w\sigma - u)C' & -\frac{\sigma}{p}S' = 0 \\ \sigma S' & = kpCS \end{cases}$$

We integrate in an interval $[-z, z], z > 0$:

$$\int_{-z}^{z} [vC'' + (w\sigma - u)C' - \frac{\sigma}{p}S']dz = 0 \Rightarrow v[C']_{-z}^{z} + (w\sigma - u)[C]_{-z}^{z} - \frac{\sigma}{p}[S]_{-z}^{z} = 0$$

Taking into account the boundary conditions, C admits 2 horizontal asymptotes: $y = c_d$ in $-\infty$ and $y = 0$ in $+\infty$ we find by passing to the limit $z \to +\infty$:

$$-(w\sigma - u)c_d - \frac{\sigma}{p}s_0 = 0$$

In the case of large k and in the context of (14),

$$C_\infty(z) = c_d(1 - e^{\frac{u - w\sigma}{v}z}) \quad (19)$$

is solution of (17)

For large k and within the context of (14); the solution (C_∞, S_∞) verify: $\begin{cases} S_\infty = 0 & if \quad C_\infty > 0 \\ S_\infty = s_0 & if \quad C_\infty = 0 \end{cases}$

Such :

$$\begin{cases} S_\infty(x - \sigma t) = 0 & si \quad x < \sigma t & \text{the wave has exceeded } x \\ S_\infty(x - \sigma t) = s_0 & si \quad x \geq \sigma t & \text{the wave has not yet pass} \end{cases}$$

So we can consider S_∞ constant then $\begin{cases} vC''_\infty + (w\sigma - u)C'_\infty = 0 & \text{on }]-\infty, 0] \quad (17') \\ C_\infty = 0 & \text{on } [0, +\infty[\quad (17'') \end{cases}$.

And like $u - w\sigma = u - w\frac{u}{w + \frac{s_0}{pc_d}} = u(1 - \frac{1}{1 + \frac{s_0}{wpc_d}}) > 0$, the equation $(17')$ admits as solution: $z \to \alpha + \beta e^{\frac{u - w\sigma}{v}z}$. And applying the conditions:

$$\begin{cases} C_\infty(0) = 0 \\ \lim\limits_{z\to-\infty} C_\infty(z) = c_d \end{cases} \Rightarrow \begin{cases} \alpha + \beta = 0 \\ \alpha = c_d \end{cases} \Rightarrow \begin{cases} \beta = -c_d \\ \alpha = c_d \end{cases}$$

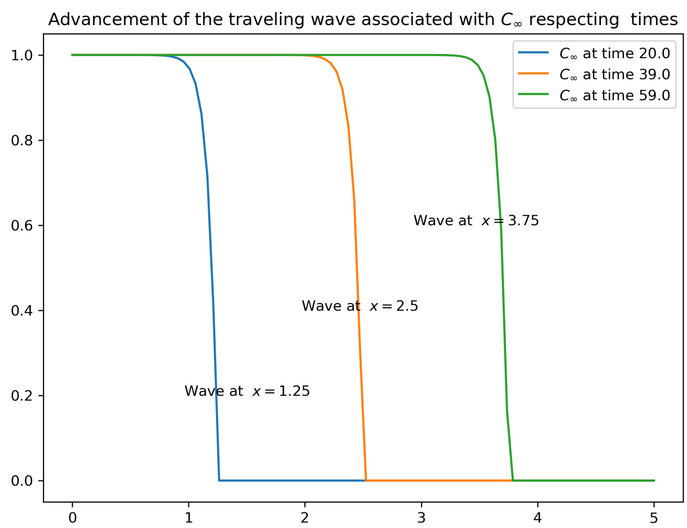
From where:

$$\begin{cases} C_\infty(z) = c_d(1 - e^{\frac{u - w\sigma}{v}z}) & z \in]-\infty, 0] \\ C_\infty(z) = 0 & z \in [0, +\infty[\end{cases}$$

5.1 Simulation

with function $c_d(t) = 1$ and values:

w	u	v	s0	cd	Nx	NT	p
0.9	0.1	0.003	2	1	100	5	3



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6. Conclusion

Initially, the analysis relied on a mathematical model proposed in a scientificité modeling text in the French external agregation competition (public 2008), that calculates antibody and antigen concentrations when reaction speed is moderate. Despite this, the inherent instability of the system presented a significant challenge that had to be carefully considered.

We proposed modifications in our study that transformed an unstable system into one that is stable and consistent under certain conditions. This paper provides detailed proofs of the stability and consistency of the newly devised system, supported by both theoretical and numerical analyses. As a robust method of evaluating the effectiveness and reliability of the modified scheme, numerical tests were included, particularly after augmenting the reaction factor.

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