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PHYSICS

MALIGNANT INVASION MODEL WITH A SMALL AMOUNT OF DIFFUSION IN THE FRAMEWORK OF THE NON-STANDARD SCALE RELATIVITY THEORY. ANALYTICAL SOLUTIONS (II)

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Abstract. Exact solutions for malignant invasion model with a small amount of diffusion in the framework of the Non-Standard Scale Relativity Theory using the factorization and the tanh methods are obtained. For small diffusion coefficients, we may conclude that there is a gap between the invasive cells front and the degraded connective tissue, the extracellular matrix is not continuously degraded by the concentration of proteases and the later one shows amplified followed by amortized oscillations and jumps between distinct levels.

Key words: malignant invasion model, Non-Standard Scale Relativity Theory, fractality, factorization method, tanh method.

1. INTRODUCTION

In a recent paper [1], a particular model of tumor progression was analyzed. Considering an action-reaction type law acting on the complex system formed by the extracellular matrix and the non-differential medium is results: artificial cancer cell proliferation satisfies a logistic law accounting for the competition for space with the non-differential medium, the connective tissues concentration increases proportionally to the real fractal velocity, squared and over small distances, even in avascular stages malignant tumors might propagate and invade healthy tissues.

In the present paper analytical solutions of Perumpanani's malignant invasion model extended are given.

2. ANALYTICAL SOLUTIONS

Since in equations (18 a,b) from [1] the first equation is decoupled, we start by solving this one first. Note, it is the Kolmogorov-Petrovskii-Piskunov (KPP) equation [2]. We solve it by using the factorization method as outlined in [3]. The equation is repeated below for convenience, as we use slightly different notation than in eq. (18 a):

$$\frac{\partial n}{\partial t}-\delta\frac{\partial^2 n}{\partial x^2}-n+n^2=0, \delta\equiv\overline{D}_n \cdot \tag{1 a,b}$$

If we assume a traveling wave solution of the form $n(x, t) = N(\xi)$, $\xi = k(x - \lambda t)$, with λ the velocity, and k the wavenumber, eq. (1) reduces to the traveling wave ODE (ordinary differential equation)

$$\frac{d^2N}{d\xi^2}+\gamma\frac{dN}{d\xi}+F(N)=0, \tag{2}$$

where $\gamma=\lambda/k\delta$ and $F(N)=(1/k^2\delta)(N-N^2)$. We factor the polynomial function of eq. (2) (the third-hand term) as

$$\frac{F(N)}{N}=f_1f_2=\frac{1}{\delta k^2}\left(1-N^{\frac{1}{2}}\right)\left(1+N^{\frac{1}{2}}\right) \tag{3}$$

and choose

$$f_1=\frac{1}{\sqrt{\delta}}\left(1-N^{\frac{1}{2}}\right)\frac{\alpha}{k},\qquad f_2=\frac{1}{\sqrt{\delta}}\left(1+N^{\frac{1}{2}}\right)\frac{1}{\alpha k},\qquad \alpha\neq 0, \tag{4 a-c}$$

where we have also introduced the constant α.

From [2,3] and (4 a-c), we obtain the following ODE

$$\frac{df_1}{dN}N+f_1+f_2=-\frac{1}{2\sqrt{\delta}}N^{\frac{1}{2}}\frac{\alpha}{k}+\frac{1}{\sqrt{\delta}}\left(1-N^{\frac{1}{2}}\right)\frac{\alpha}{k}+\frac{1}{\sqrt{\delta}}\left(1+N^{\frac{1}{2}}\right)\frac{1}{\alpha k}=-\gamma=-\frac{\lambda}{k\delta}. \tag{5}$$

Collecting terms and equating the coefficients of $N^{1/2}$ to zero (as the left-hand side of eq. (5) is equal to a constant) gives $\alpha=\pm\sqrt{2/3}$ and $\lambda=-5\sqrt{\delta/6}$. Also, as γ is a constant and is independent of the value of N, on setting $N = 0$, we find that $\gamma=-(k\sqrt{\delta})^{-1}(\alpha+\alpha^{-1})$. Therefore, adopting the grouping of Cornejo-Perez [4], it follows that

$$\frac{d^2N}{d\xi^2}\mp\frac{1}{k\sqrt{\delta}}(\alpha+\alpha^{-1})\frac{dN}{d\xi}+f_1f_2N=0. \tag{6}$$

Thus, the corresponding factorization $[D-f_2(N)][D-f_1(N)]N=0$, becomes

$$\left[D\pm\frac{1}{\alpha k\sqrt{\delta}}\left(1+N^{\frac{1}{2}}\right)\right]\left[D\mp\frac{\alpha}{k\sqrt{\delta}}\left(1-N^{\frac{1}{2}}\right)\right]N=0, \tag{7}$$

where $D = d/d\xi$. Therefore, it follows that eq. (6) is compatible with the first-order ODE

$$\frac{dN}{d\xi}\mp\frac{\alpha}{k\sqrt{\delta}}\left(1-N^{\frac{1}{2}}\right)N=0. \tag{8}$$

Integrating eq. (8 a,b) either manually or using Matlab or Mathematica yields

$$N=\left[1+K\exp\left(-\frac{\alpha\xi}{2k\sqrt{\delta}}\right)\right]^{-2}, \tag{9}$$

where K is an arbitrary constant of integration. Substituting back values for ξ, λ, and α, we find for $k=(1/\sqrt{6\delta})$ the final solution

$$n=\left\{1+K\exp\left[k\left(x-\lambda t\right)\right]\right\}^{-2}, \tag{10}$$

where k and λ are as defined above.

If we let $K=\pm\exp[kx_0]$, we arrive at the standard form of traveling wave solution

$$n^{\pm}=\left\{1\pm\exp\left[k\left(x-x_0-\lambda t\right)\right]\right\}^{-2}. \tag{11}$$

Let us solve now the second equation in (18 a,b) from [1]. If we assume a traveling wave solution of the form $c(x, t) = C(\xi)$, $\xi = k(x - \lambda t)$, with λ the velocity and k the wavenumber, the second eq. (18 a,b) reduces to the traveling wave ODE

$$\frac{dC}{d\xi} - \frac{1}{k\lambda} NC^2 = 0. \tag{12}$$

Integrating eq. (12) with the solution $N(\xi)$ from (9), either manually or using Mathematica, or Matlab yields

$$C = -\frac{k\lambda}{\xi - \ln\left(1 + K\exp(\xi)\right) + \left(1 + K\exp(\xi)\right)^{-1} + k\lambda K_1}, \tag{13}$$

with K_1 a new integration constant. Substituting back values for ξ we get the final solution for the system (18 a,b)

$$\begin{gathered} n = \left\{1 + K\exp\left[k\left(x - \lambda t\right)\right]\right\}^{-2} \\ c = -k\lambda / \left[k\left(x-\lambda t\right) - \ln\left(1 + K\exp\left(k(x-\lambda t)\right)\right) + \left(1 + K\exp\left(k(x-\lambda t)\right)\right)^{-1} + k\lambda K_1\right] \end{gathered} \quad \text{(14 a,b)}$$

Finally, the exact solution of our model, deduced in terms of NSRT, using the **factorization method** [5] reads

$$\begin{gathered} n = \left\{1 + K\exp\left[k\left(x - \lambda t\right)\right]\right\}^{-2} \\ c = -k\lambda / \left[k\left(x-\lambda t\right) - \ln\left(1 + K\exp[k(x-\lambda t)]\right) + \left(1 + K\exp[k(x-\lambda t)]\right)^{-1} + k\lambda K_1\right] \\ p = -\left[(k\lambda)\left(1 + K\exp[k(x-\lambda t)]\right)^{-2}\right] / \left[k\left(x-\lambda t\right) - \ln\left(1 + K\exp[k(x-\lambda t)]\right) + \left(1 + K\exp[k(x-\lambda t)]\right)^{-1} + k\lambda K_1\right]. \end{gathered} \quad \text{(15 a–c)}$$

If we take $x_0 = 0$ (replacing $K = \pm\exp[kx_0]$ in (15 a-c)) and $K_1 = t_0 = 0$ we get

$$\begin{gathered} n = \left\{1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right\}^{-2} \\ c = \frac{5}{6}\left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right) / \left[\left(\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right)\left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right) - \left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right)\ln\left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right) + 1\right] \\ p = \frac{5}{6}\left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right)^{-1} / \left[\left(\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right)\left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right) - \left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right)\ln\left(1 + \exp\left[\frac{5t}{6} + \frac{x}{\sqrt{6\delta}}\right]\right) + 1\right]. \end{gathered} \quad \text{(16a–c)}$$

Now, let us apply another method, i.e. the **tanh method** to solve eq. (18 a) written in the form (1), following the method from [6–8].

We substitute $N=F(Y)$ into eq. (2) (the traveling wave ODE of eq. (1)), and using [6-8], we obtain

$$\beta F(Y) - \beta F(Y)^2 + \gamma(1-Y^2)\frac{dF(Y)}{dY} + (1-Y^2)\left[-2Y\frac{dF(Y)}{dY} + (1-Y^2)\frac{d^2F(Y)}{dY^2}\right] = 0, \tag{17}$$

where $\gamma = \lambda/k\delta$ and $\beta = 1/k^2\delta$. We can now substitute into eq. (17) the summation from [6-8] to give

$$\begin{gathered} \beta\left(\sum_{i=0}^{M} a_i Y^i\right) - \beta\left(\sum_{i=0}^{M} a_i Y^i\right)^2 + \gamma(1-Y^2)\left(a_1 + 2a_2Y + 3a_3Y^2 + \ldots + Ma_MY^{M-1}\right) + \\ +(1-Y^2)\left[-2Y\times\left(a_1 + 2a_2Y + 3a_3Y^2 + \ldots + Ma_MY^{M-1}\right) + (1-Y^2)\times\left(2a_2 + 6a_3Y + \ldots + M\left(M-1\right)a_MY^{M-2}\right)\right] = 0. \end{gathered} \tag{18}$$

For eq. (18), we have to balance the largest exponent of Y in the highest order nonlinear term with the largest exponent of Y in the highest order linear term. The largest exponent of Y in the highest order nonlinear term occurs in the second term and is equal to $2M$. The largest exponent of Y in the highest order linear term occurs in the highest derivative term, the fourth term, and is equal to $4 + (M - 2)$. Therefore on balancing these exponents, we have

$$2M = 4 + (M-2) \rightarrow M = 2. \tag{19}$$

On rearranging, eq. (18) results in the following polynomial in *Y*:

$$\begin{aligned}&\left(6a_2 - \beta a_2^2\right)Y^4 + 2\left(a_1 - \beta a_1 a_2 - \gamma a_2\right)Y^3 + \left(-8a_2 - \beta a_1^2 + \beta a_2 - 2\beta a_0 a_2 - \gamma a_1\right)Y^2 + \\ &+\left(-2a_1 + \beta a_1 - 2\beta a_0 a_1 + 2\gamma a_2\right)Y + 2a_2 + \beta a_0 - \beta a_0^2 + \gamma a_1 = 0.\end{aligned} \tag{20}$$

We now have a fourth degree polynomial in *Y*, which is identically equal to zero, and for this to be true, it follows that the coefficients for each power of *Y* must also be identically equal to zero. Equating the coefficients to zero results in five simultaneous equations, *i.e.*,

$$\begin{gathered}6a_2 - \beta a_2^2 = 0\\ a_1 - \beta a_1 a_2 - \gamma a_2 = 0\\ (\beta - 8)a_2 - \beta a_1^2 - 2\beta a_0 a_2 - \gamma a_1 = 0\\ (\beta - 2)a_1 - 2\beta a_0 a_1 + 2\gamma a_2 = 0\\ 2a_2 + \beta a_0 - \beta a_0^2 + \gamma a_1 = 0,\end{gathered} \tag{21 a–e}$$

which we solve using Maple or Mathematica. The following five parameter solution sets are produced by Mathematica:

$$\begin{aligned}&a_0 = 0,\ a_1 = 0,\ a_2 = 0,\ \gamma = \gamma,\ \beta = \beta \ \text{:trivial solution}\\ &a_0 = 1,\ a_1 = 0,\ a_2 = 0,\ \gamma = \gamma,\ \beta = \beta \ \text{:trivial solution}\\ &\beta = 0,\ a_1 = 0,\ a_2 = 0,\ \gamma = \gamma,\ a_0 = a_0 \ \text{:trivial solution}\\ &\gamma = -10,\ \beta = -24,\ a_0 = 3/4,\ a_1 = -1/2,\ a_2 = -1/4 \ \text{:real solution}\\ &\gamma = 10,\ \beta = -24,\ a_0 = 3/4,\ a_1 = 1/2,\ a_2 = -1/4 \ \text{:real solution}\\ &\gamma = 0,\ \beta = -4,\ a_0 = 3/2,\ a_1 = 0,\ a_2 = -3/2 \ \text{:real solution}\\ &\gamma = 0,\ \beta = 4,\ a_0 = -1/2,\ a_1 = 0,\ a_2 = 3/2 \ \text{:real solution}\\ &\gamma = 10,\ \beta = 24,\ a_0 = 1/4,\ a_1 = -1/2,\ a_2 = 1/4 \ \text{:real solution}\\ &\gamma = -10,\ \beta = 24,\ a_0 = 1/4,\ a_1 = 1/2,\ a_2 = 1/4 \ \text{:real solution.}\end{aligned} \tag{22 a–i}$$

The final results are therefore found by substituting the parameter solution sets (22 a–i) into eq. (21 a–e) and then setting *Y* = tanh [*k*(*x*–*λt*)] in eq. (20), which yields the following twelve solutions (tested both numerically and symbolically) to eq. (1):

$$\begin{gathered}n(x,t) = \frac{1}{4}\left(1 - \tanh\left(-\frac{5t}{12} \pm \frac{ix}{2\sqrt{6\delta}}\right)\right)\left(3 + \tanh\left(-\frac{5t}{12} \pm \frac{ix}{2\sqrt{6\delta}}\right)\right)\\ n(x,t) = \frac{1}{4}\left(1 + \tanh\left(\frac{5t}{12} \pm \frac{ix}{2\sqrt{6\delta}}\right)\right)\left(3 - \tanh\left(\frac{5t}{12} \pm \frac{ix}{2\sqrt{6\delta}}\right)\right)\\ n(x,t) = \frac{3}{2} - \frac{3}{2}\tanh\left(\pm\frac{ix}{2\sqrt{\delta}}\right)^2\\ n(x,t) = -\frac{1}{2} + \frac{3}{2}\tanh\left(\pm\frac{x}{2\sqrt{\delta}}\right)^2\\ n(x,t) = \frac{1}{4}\left(1 - \tanh\left(-\frac{5t}{12} \pm \frac{x}{2\sqrt{6\delta}}\right)\right)^2\\ n(x,t) = \frac{1}{4}\left(1 + \tanh\left(\frac{5t}{12} \pm \frac{x}{2\sqrt{6\delta}}\right)\right)^2\end{gathered} \tag{23 a-f}$$

up to an arbitrary phase in the arguments of the "tanh" functions, which may be taken zero.

We integrate now eq. (12) with the solutions $N(\xi) = n(x,t)$ from (23 a–f) (we choose only the last one, since it is real and varies on both position *x* and time *t*), either manually or using Mathematica, or Matlab. Here, ξ is the argument of the *tanh* function and $k\lambda = \gamma/\beta$, hence we get first

$$C(\xi)=\frac{5}{6\xi-5K_2+6\ln(\cosh\xi)-3\tanh\xi}, \tag{24}$$

where K_2 is a new integration constant. Accordingly, the two real solutions for the connective tissue concentration read

$$c(x,t)=5/\left[6\left(\frac{5t}{12}\pm\frac{x}{2\sqrt{6\delta}}\right)-5K_2+6\ln\left(\cosh\left(\frac{5t}{12}\pm\frac{x}{2\sqrt{6\delta}}\right)\right)-3\tanh\left(\frac{5t}{12}\pm\frac{x}{2\sqrt{6\delta}}\right)\right]. \tag{25}$$

Finally, a new exact solution of Perumpanani's malignant invasion model extended, using the **tanh method** may be written (K_2 is set to zero following the same reasoning used when we deduced eq. (16 a–c))

$$\begin{aligned}
n&=\frac{1}{4}\left(1+\tanh\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)\right)^2\\
c&=\frac{5}{6}/\left[\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)+\ln\left(\cosh\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)\right)-\frac{1}{2}\tanh\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)\right]\\
p&=\frac{5}{24}\left(1+\tanh\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)\right)^2/\left[\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)+\ln\left(\cosh\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)\right)-\frac{1}{2}\tanh\left(\frac{5t}{12}+\frac{x}{2\sqrt{6\delta}}\right)\right]
\end{aligned} \tag{26 a–c}$$

(we choose the plus sign solution only, since the one with minus represents just a reflection along the *Ox* axis).

Note that one can find even more solutions to $N(\xi)$ (the KPP equation) using other methods, like *exp-* and *Riccati-* [3]. They also can be substituted in (6) to get new, different solutions for $C(\xi)$, $P(\xi)$ and consequently for the Perumpanani's malignant invasion model extended.

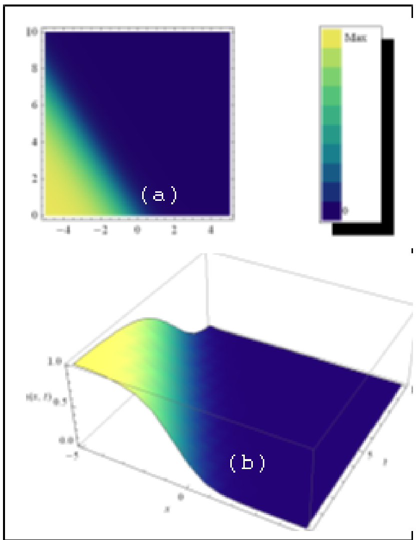

Fig. 1 – Dependences $n = n(x, t)$ from (16 a) in 2D (a) and 3D (b) for $\delta = 0.1$.

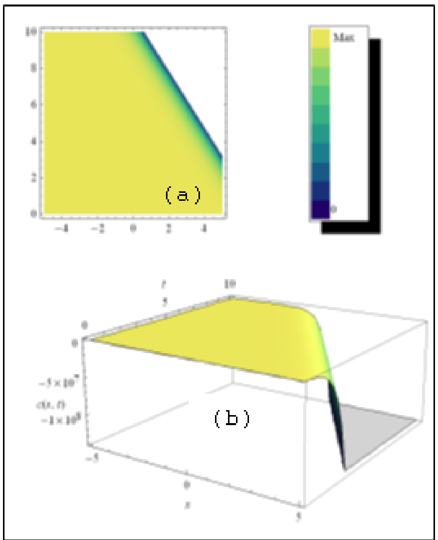

Fig. 2 – Dependences $c = c(x, t)$ from (16 b) in 2D (a) and 3D (b) for $\delta = 0.1$.

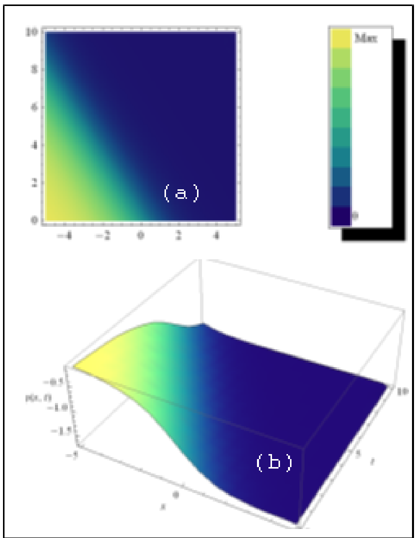

Fig. 3 – Dependences $p = p(x, t)$ from (16 c) in 2D (a) and 3D (b) for $\delta = 0.1$.

We depict graphically in Figs. 1–3 the solutions (16 a–c) taking $\delta = D_n = 0.1$. The invasive cells profile looks like the one of a classical traveling wave front. The proteases move the same way the invasive front does and the extracellular matrix is degraded alongside the travelling wave front, at a certain distance from it.

Furthermore, if we plot the solutions (16a–c) for small $\delta = D_n = 0.01$, we find in the proteases and extracellular matrix concentration, a line of irregularities at some particular distance from the front and oriented parallel to it (meaning it has the same velocity as the traveling wave), resembling the "blunt interface" solutions as described by Marchant et al in [9] (Figs. 4–6). After this line, chaos occurs – there are no regularities (Figs. 4–6). Note the invasive cells still move here like a traveling wave.

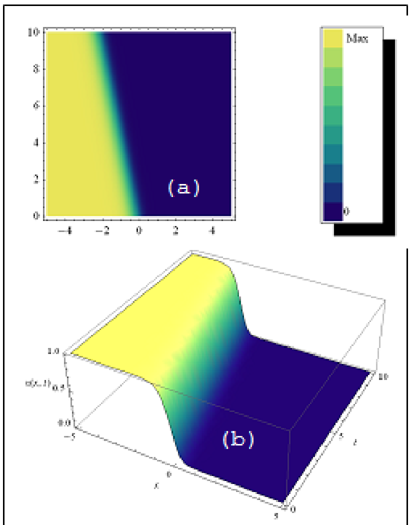

Fig. 4 – Dependences $n = n(x, t)$ from (16 a) in 2D (a) and 3D (b) for $\delta = 0.01$ (factorization method).

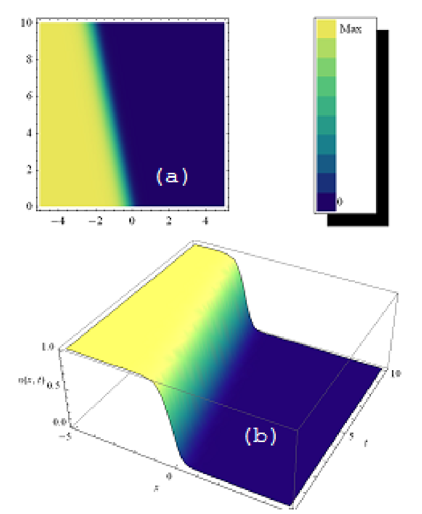

Fig. 5 – Dependences $c = c(x, t)$ from (16 a) in 2D (a) and 3D (b) for $\delta = 0.01$ (factorization method).

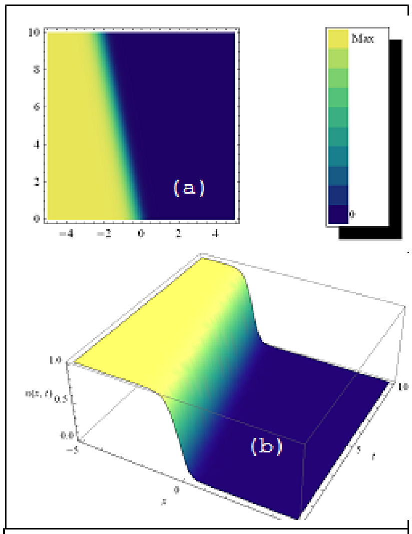

Fig. 6 – Dependences $p = p(x, t)$ from (16 a) in 2D (a) and 3D (b) for $\delta = 0.01$ (factorization method).

3. DISCUSSIONS AND CONCLUSIONS

We find exact solutions for the system (18 a, b) from [1], Perumpanani's malignant invasion model extended, using the **factorization method** and the **tanh method**.

We discuss in what follows only the solution obtained using the factorization method, eqs. (16a–c).

For a large diffusion coefficient, δ, the tumor cells profile looks like the one of a classical traveling wave front, the proteases motion looks like the invasive front's motion, but in the negative concentration zone and the extracellular matrix is degraded alongside the travelling wave front, and at a certain distance from it.

For small diffusion coefficients a line of irregularities occurs in the proteases and extracellular matrix concentration, at some particular distance ahead the front, having the same velocity as the traveling wave, and resembling the "blunt interface" solutions as described by Marchant *et al.* [9]. Then chaos occurs. Note also that the tumor cells still move like a traveling wave.

In Fig. 7 and 8 we plot the concentration of invasive cells, connective tissue and proteases dependence on time t, for different values of position x, and dependence on position x for different values of time t, respectively. The **factorization method** was used in both these representations to get the solutions. One can notice chaos intermittencies in the concentration of connective tissue and in the proteases concentration amplified, followed by amortized oscillations and jumps from one negative level to the zero level (two level intermittencies). The effect of an increased δ on these parameters, is that chaos, oscillations and jumps can be found closer to the origins of the x and t axis.

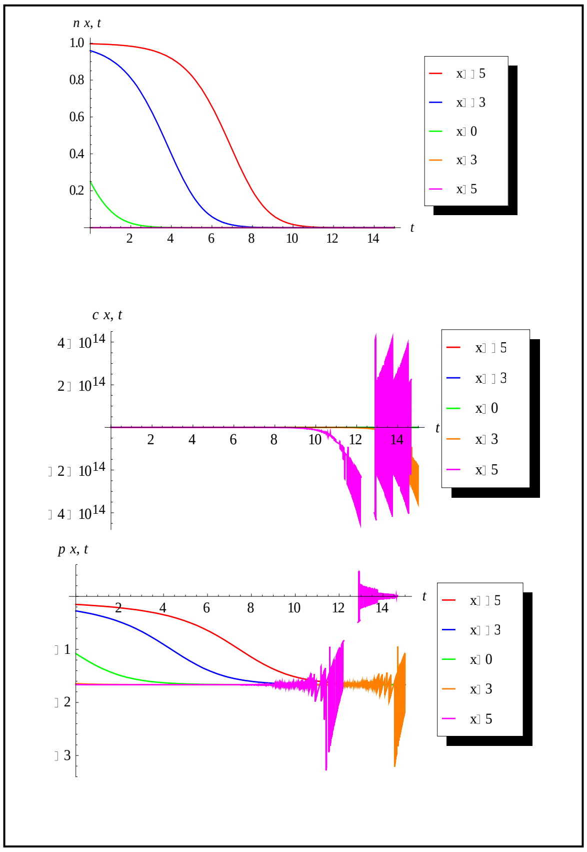

Fig. 7a – *n*(*x*, *t*), *c*(*x, t*) and *p*(*x, t*) dependences on time *t* and position *x* = –5, –3, 0, 3, 5 for *δ* = 0.1 (factorization method).

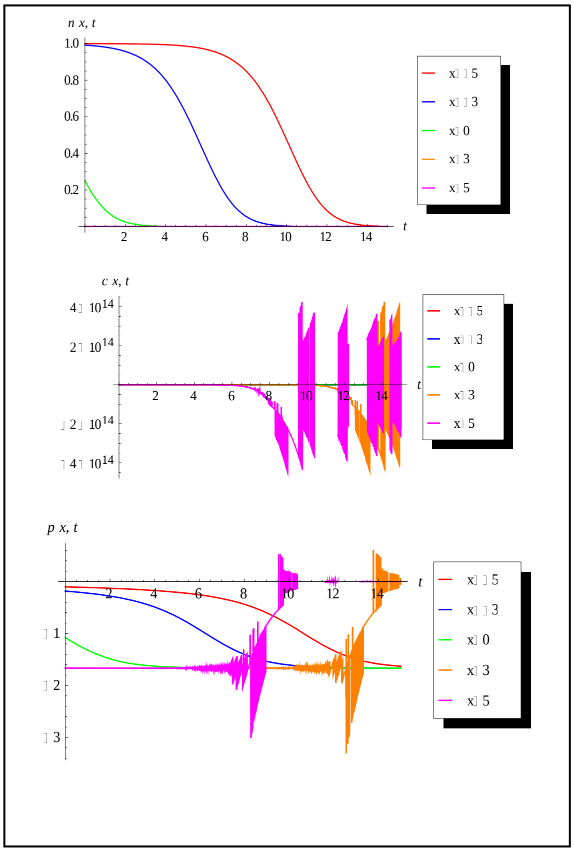

Fig. 7b – *n*(*x*, *t*), *c*(*x, t*) and *p*(*x, t*) dependences on time *t* and position *x* = –5, –3, 0, 3, 5 for *δ* = 0.05 (factorization method).

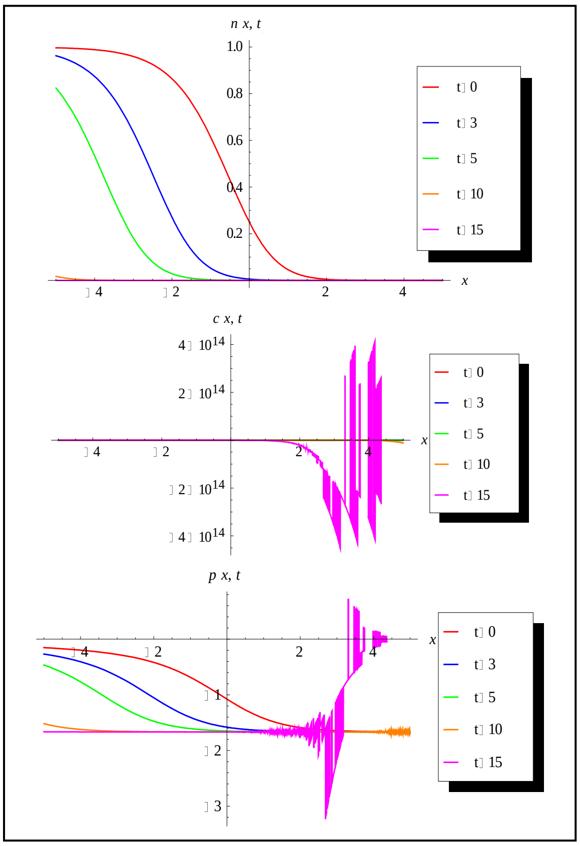

Fig. 8a – $n(x, t)$, $c(x, t)$ and $p(x, t)$ dependences on position x and time t = 0, 3, 5, 10, 15 for δ = 0.1 (factorization method).

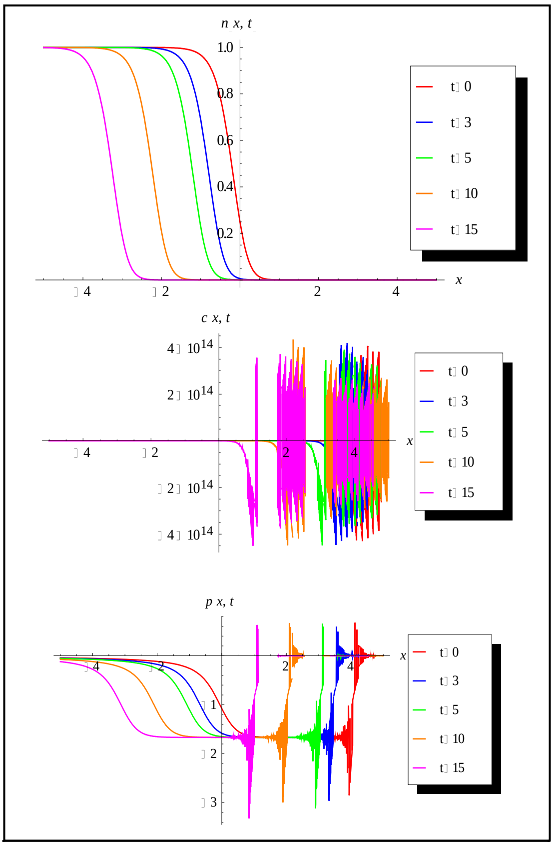

Fig. 8b – $n(x, t)$, $c(x, t)$ and $p(x, t)$ dependences on position x and time t = 0, 3, 5, 10, 15 for δ = 0.01 (factorization method).

Also, we may conclude that, there is a gap between the invasive cells front and the degraded connective tissue, the extracellular matrix is not continuously degraded by the concentration of proteases and the later ones show amplified followed by amortized oscillations and jumps between two distinct levels. We obviously have here a controlled proteolysis, since an uncontrolled one would contribute to abnormal development and to the generation of many pathological conditions characterized by either excessive degradation or a lack of degradation of ECM components.

Finally, it should be evidenced that our model clearly posits that the metastatic process would be better understood as a collective property of a "society of cells" (and not a specific feature of a "single" cell expressing the "metastatic potential") [10].

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