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SELF-SIMILAR ASYMPTOTICS FOR LINEAR AND NONLINEAR MATHEMATICAL MODELS OF TUMOR ANGIOGENESIS: A REVIEW

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Abstract. We show that the long time asymptotic solutions of initial value problems for linear and nonlinear mathematical models of tumor angiogenesis are self-similar spreading solutions. The symmetries of the governing equations yield three-parameter families of these solutions given in terms of their mass, center of mass, and variance. Unlike the mass and center of mass, the variance, or "time-shift," of a solution is not a conserved quantity for the nonlinear problem.

1. Biological Background and the Derivation of the Model Equation

Angiogenesis, the formation of new capillaries (small blood vessels) from pre-existing vessels, is essential for tumor progression. It is critical for the growth of primary cancers. Solid tumors progress through essentially two distinct phases of growth, namely the avascular phase and the vascular phase. In the avascular phase, the tumor does not have its own blood supply. At this stage it is 2-3mm in diameter and grows by feeding on nutrients in the Extra Cellular Matrix (ECM), which are supplied to it via diffusion. In the vascular phase, the tumor has its own blood supply and rapidly grows. It is known that the tumor releases certain chemicals known as Tumor Angiogenesis Factor (TAF) which stimulates the Endothelial Cells (EC) in neighboring capillaries to migrate the tumor. Finally angiogenesis occurs.

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Figure 1: Formation of a new blood vessel.

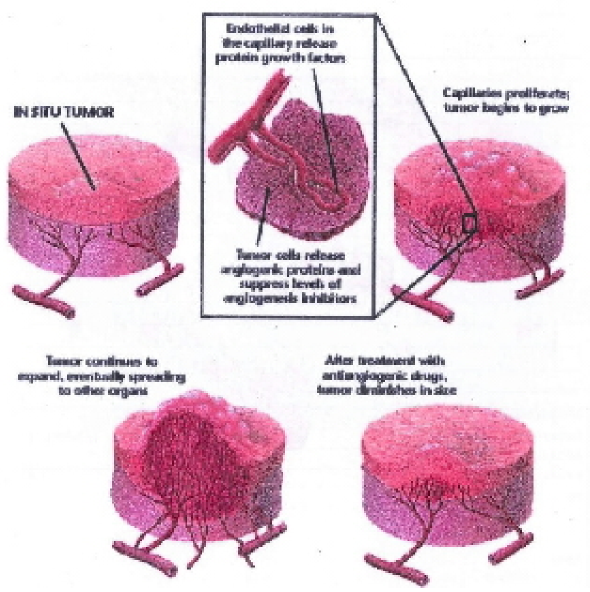

Figure 2: Formation of metastasis of a tumor.

As seen from the Figs.1 & 2, the real tissues can be treated as porous media. In [7] a code has been used to investigate the validity of the semi-infinite tumor assumption in an epithelial tissue model. The epithelial tissue model consists of three layers, which includes the top epithelium, the middle tumor and the bottom stroma. Usually each layer is assumed to be semi-infinite where the thickness is finite while the width and length are infinite. The tissue model in their program is layer structured in which each layer is assumed to be semi-infinite. Therefore, we will assume $-\infty < x < \infty$ for biological purposes. The porous medium equation is proposed in order to describe the distribution of the density of a substance that flows through a uniformly distributed porous medium. It often occurs in nonlinear problems of heat and mass transfer, cumbustion theory . For example it describes unsteady heat transfer in a quiescent medium with heat diffusivity being a power law function of temperature. It is usually derived as follows [2]. Let $\rho = \rho(x,t) \geq 0$ denote the density of the substance (TAF, EC, Epithelial Cell, for example). Moreover, $v = v(x,t) \in R^n$ denotes the velocity vector of the substance and $p = p(x,t) \in R$ denotes the pressure. By the conservation law we obtain

$$\partial_t \rho + div(\rho v) = 0. \tag{1.1}$$

By Darcy's law, which reflects the fact that the substance flows in a porous medium, we obtain

$$v = -\nabla p. \tag{1.2}$$

Assuming the constitutive law for pressure and densities one obtains

$$p(\rho) = \rho^\gamma, \quad \gamma \geq 1. \tag{1.3}$$

Substitution of (1.2) and (1.3) into (1.1) yields

$$\partial_t \rho - \frac{\gamma}{1+\gamma} \triangle \rho^{1+\gamma} = 0. \tag{1.4}$$

To simplify the last equation, we shall take a constant C such that $C^\gamma = \frac{\gamma}{1+\gamma}$, and set $u = C\rho$, and then (1.4) is equivalent to

$$\partial_t u - \triangle u^m = 0, \tag{1.5}$$

where $m = \gamma + 1$ [2]. The assumption $\gamma \geq 1$ corresponds to $m \geq 2$. For $m = 1$, (1.5) is the heat equation. While $m > 1$, it is called the porous medium equation. The equation is also important for m satisfying $0 < m < 1$, since it describes plasma phenomena, for example. We will only consider the case $m > 1$. Since u originally denotes a positive constant (multiple of the density), we consider only non-negative solutions.

In [3] it is described how this model has been used to represent "population pressure" in biological systems. It is called a degenerate parabolic differential equation because the diffusion coefficient $D(u) = u^m$ does not satisfy the conditions for classical diffusion equations, $D(u) > 0$. For the motion of thin viscous films, this equation with $m = 3$ can be derived from Navier-Stokes Equation.

Let us now calculate self similar solutions of the porous medium equation (1.5). If u satisfies (1.5) in $R^n \times (0, \infty)$ (and u and u^m are smooth), then

$$u_{\mu,\lambda} = \mu u(\lambda x, \lambda^2 \mu^{m-1} t), \quad \lambda > 0, \mu > 0 \tag{1.6}$$

also satisfies (1.5) in $R^n \times (0, \infty)$.

Moreover, it can be shown that its total mass $\int_{R^n} u(x,t)dx$ is conserved for evolution of time in the same way as for the heat equation. Since the total mass is conserved under the scaling transformation $u_{\mu,\lambda}$ with $\mu = \lambda^n$ above, we define the scaling transformation by

$$u_k(x,t) = \lambda^n u(kx, k^{2+(m-1)n} t), \;\; k > 0. \tag{1.7}$$

This preserves the total mass and is a generalization of the scaling transformation for the heat equation. Below we shall consider only the case $m > 1$. Let u be a function invariant under the scaling transformation (1.7), and which preserves the total mass. Then, it is clear that

$$u_k(x,t) = u(x,t), \;\; x \in R^n, t > 0, k > 0, \tag{1.8}$$

is satisfied.

Also u can be expressed as

$$u(x,t) = t^{-\ell} w(t^{-\ell/n} x), \tag{1.9}$$

with

$$w(y) = u(y,t), y \in R^n, k = t^{-\ell/n}, \ell = \frac{n}{2 + (m-1)n}. \tag{1.10}$$

A direct calculation shows that [2] a function u which is invariant under the scaling transformation (1.7) is a solution of (1.5) if and only if w satisfies

$$\triangle w^m(y) + \ell/n < y, \nabla w(y) > + \ell w(y) = 0, y \in R^n. \tag{1.11}$$

(This is a formal argument under the assumption that u and u^m are sufficiently smooth). Now we shall choose the pressure $v = w^{m-1}$ as a dependent variable instead of density. If $v > 0$, then we obtain an equation for $v = v(y)$ from equation (1.11):

$$v^{\frac{1}{m-1}} \frac{m}{m-1} \{\triangle v + \frac{1}{m-1} |\nabla v|^2 v^{-1} \frac{\ell}{mn} v^{-1} < y, \nabla v > + \frac{\ell(m-1)}{m}\} = 0, \tag{1.12}$$

for $y \in R^n$.

Let us find a non-negative solution radially symmetric with respect to the origin and quadratic in $|y|$ near the origin. We in particular consider a solution of the form

$$\bar{v}(y) = (\beta^2 - c^2 |y|^2)_+, \quad y \in R^n, \tag{1.13}$$

where $(a)_+ = max(a, 0)$. Here β and c are constants.

Since $\triangle\bar{v} = -2nc^2$ at $y \in R^n$ with $\bar{v}(y) > 0$, setting

$$c^2 = \frac{\ell(m-1)}{2nm}, \tag{1.14}$$

we have $\triangle\bar{v} + \frac{\ell(m-1)}{m} = 0$. By a direct calculation we obtain

$$\begin{aligned} \frac{1}{m-1}|\nabla\bar{v}|^2 + \frac{\ell}{mn} < y, \nabla\bar{v} > &= \frac{4c^4|y|^2}{m-1} - \frac{2\ell c^2|y|^2}{mn} \\ &= 2c^2|y|^2(\frac{2c^2}{m-1} - \frac{\ell}{mn}) \\ &= 0. \end{aligned} \tag{1.15}$$

The final equality is due to the choice of c in (1.14). This shows that $\bar{v}$ with (1.14) formally satisfies (1.12).

Definition: Let $\bar{v}$ be a function on R^n of the form $\bar{v}(y) = (\beta^2 - c^2|y|^2)_+$ with $c^2 = \frac{\ell(m-1)}{2nm}$, $\ell = \frac{n}{2+(m-1)n}$. Take β^2 such that $\int_{R^n} \bar{v}(y)dy = 1$. For $L > 0$ we call

$$V_L(x,t) = L^{\frac{1}{m-1}} \frac{1}{(Lt)^\ell} \bar{v}(\frac{|x|}{(Lt)^{\ell/n}}), x \in R^n, t > 0, \tag{1.16}$$

a Barenblatt Self Similar Solution. From the expression of V_L we see that V_L is invariant under the scaling transformation (1.7). Also, V_L satisfies (1.5) at (x,t) where $V_L(x,t) > 0$. By the choice of β, we obtain

$$\int_{R^n} V_L(x,t)dx = L^{\frac{1}{m-1}}, \tag{1.17}$$

hence the total mass is conserved for $t > 0$. A similarity solution of (1.5) is [5]

$$u = u(z), z = \frac{x}{\sqrt{t}}, (0 \leq x < \infty), \tag{1.18}$$

where the function $u(z)$ is determined by the ODE

$$2(u^m u')' + zu' = 0. \tag{1.19}$$

To the particular solution of this equation with $u(z) = k_2 z^{2/m}$ there corresponds the solution

$$u(x,t) = \left[\frac{m(x-A)^2}{2(m+2)(B-t)}\right]^{1/m}. \tag{1.20}$$

With the boundary conditions $u = 1$ at $z = 0$, $u = 0$ at $z = \infty$, the solution of this differential equation is localized and has the structure [5]

$$u = \begin{cases} (1-Z)^{1/m} \frac{P(1-Z,m)}{P(1,m)}, & \text{for } 0 \leq Z \leq 1 \\ 0, & \text{for } 1 \leq Z < \infty, \end{cases} \tag{1.21}$$

where

$$Z = \frac{z}{z_0}, \quad z_0^2 = \frac{2}{mP(1,m)}, \quad P(\xi,m) = \sum_{k=0}^{\infty} b_k \xi^k. \tag{1.22}$$

Another self-similar solution of (1.5) is [5]:

$$u = t^{\frac{-1}{m+2}} F(\xi), \quad \xi = xt^{\frac{-1}{m+2}}, \quad (0 \leq x < \infty). \tag{1.23}$$

Here, the function $F = F(\xi)$ is determined by the first-order differential equation

$$(m+2)F^m F' + \xi F = C, \tag{1.24}$$

where C is an arbitrary constant. To $C = 0$ there corresponds the solution

$$u(x,t) = \left[A|t+B|^{\frac{-m}{m+2}} - \frac{m}{2(m+2)} \frac{(x+C)^2}{t+B} \right]^{1/m}. \tag{1.25}$$

Self-similar solution of a more general form can be obtained by setting [5]:

$$u = t^{\beta} g(\zeta), \quad \zeta = xt^{\frac{-(m\beta+1)}{2}}, \tag{1.26}$$

where β is any constant.

Here, the function $g = g(\zeta)$ is determined by the differential equation

$$G'' = A_1 \zeta G^{\frac{-m}{m+1}} G' + A_2 G^{\frac{1}{m+1}}, \quad G = g^{m+1}, \tag{1.27}$$

where $A_1 = \frac{-(m\beta+1)}{2}$ and $A_2 = \beta(m+1)$.

One obtains a generalized self-similar solution by setting:

$$u = e^{-2\lambda t} \varphi(\zeta), \quad \zeta = xe^{\lambda m t}, \tag{1.28}$$

where λ is any constant, and the function $\varphi = \varphi(\zeta)$ is determined by the differential equation

$$(\varphi^m \varphi')' = \lambda m u \varphi' - 2\lambda\varphi. \tag{1.29}$$

An unsteady point source solution may be given as follows [5]:

$$u(x,t) = \begin{cases} At^{-1/(m+2)} \left(\eta_0^2 - \frac{x^2}{t^{2/(m+2)}} \right) & \text{for } |x| \leq \eta_0 t^{1/(m+2)}, \\ 0 & \text{for } |x| > \eta_0 t^{1/(m+2)}, \end{cases} \tag{1.30}$$

where $A = \left[\frac{m}{2(m+2)} \right]^{1/m}$, $\eta_0 = \left[\frac{\Gamma(1/m+3/2)}{A\sqrt{\pi}\Gamma(1/m+1)} E_0 \right]^{m/(m+2)}$, with $\Gamma(z)$ being the gamma function. The above solution satisfies the initial condition $u(x,0) = E_0\delta(x)$, where $\delta(x)$ is the Dirac delta function, and the condition of conservation of energy is

$$\int_{-\infty}^{\infty} u(x,t)dx = E_0 > 0. \tag{1.31}$$

2. Self Similar Solutions of the Model

Throughout this paper the variable $u = u(x,t)$ will stand for the TAF concentration. The linear TAF equation is of the form

$$u_t = u_{xx}, \quad u(x,0) = u_0(x), \quad -\infty < x < \infty \tag{2.1}$$

and its nonlinear generalization, the porous medium equation, is of the form

$$u_t = (u^{n+1})_{xx}, n > 0, \quad u(x,0) = u_0(x), \quad -\infty < x < \infty, \tag{2.2}$$

for non-negative, integrable, compactly-supported initial data $u_0(x)$.

Some partial analytical solutions of the problem (2.2) was obtained in [4].
In the porous medium case there can be no entrance of EC into the ECM for a finite time after the tumor begins to emit TAF. We will now discuss the issues involved in selecting the correct long-time asymptotic self-similar solution for these problems.

For sufficiently localized initial conditions, as $t \to \infty$ the solution of problem (2.1) approaches a self-similar spreading Gaussian pulse (see Fig.3(a)) [6]:

$$u(x,t) \sim \frac{1}{\sqrt{4\pi(t+t_*)}} exp\left(\frac{1}{4}\left(a_*^2 - \frac{(x-x_*)^2}{t+t_*}\right)\right) + O((t+t_*)^{-2}) \tag{2.3}$$

Similarly, as $t \to \infty$, the solution of problem (2.2) for the porous medium equation approaches a Barenblatt similarity solution
(see Fig.3(b))[1]:

$$\begin{aligned} u(x,t) \quad &\sim \quad \frac{1}{(t+t_*)^\alpha}\left(\frac{n\alpha}{2(n+1)}\left(a_*^2 - \left(\frac{x-x_*}{(t+t_*)^\alpha}\right)^2\right)_+\right)^{\frac{1}{n}} \\ &+ \quad O((t+t_*)^{-(3n+4)\alpha}) \end{aligned} \tag{2.4}$$

Here $w_+ \equiv max(w,0)$ and $\alpha = \frac{1}{n+2}$.

(2.3) and (2.4) are characterized by three parameters (a_*, x_*, t_*) that correspond to their mass, center of mass, and variance. Parameters x_* and t_* denote spatial and temporal coordinate translations, and a_* denotes a change of mass rescaling. We rewrite the diffusion equations in terms of their mass-preserving similarity variables. In these coordinates the similarity solution corresponds to a steady state. Linearizing about this state yields an eigenvalue problem that governs the rate of decay of deviations from the stable similarity solution. The rate of convergence can

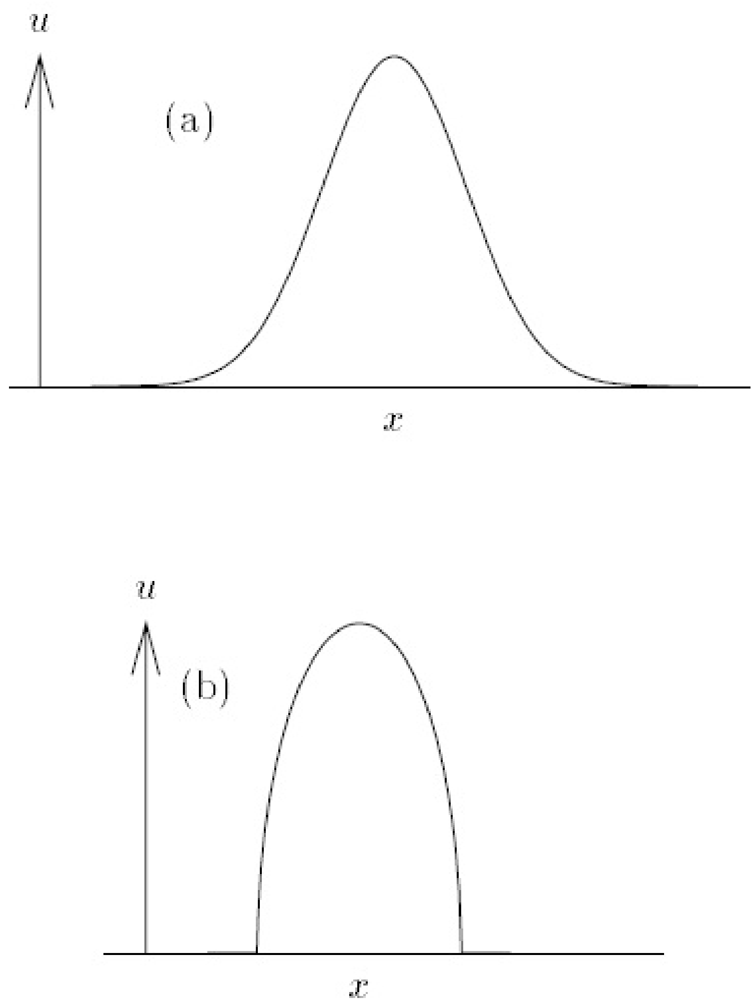

FIGURE 1. **Figure 3:** (a) Gauss solotion, (b) Barenblatt solotion

be maximized by selecting the values of (a_*, x_*, t_*) that eliminate the first three terms in the eigenfunction expansion. The similarity solution with these values for the parameters is called the optimal similarity solution.

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