Scaling Laws in Cancer: The Dynamic Behaviour of the Power Exponent $p$

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**Abstract**

We have previously reported that a ‘universal’ growth law with *fixed* scaling exponent $p$, as proposed by West and collaborators for all living organisms, appears to be able to describe also the growth of tumors *in vivo*. Here, we investigate in more detail the *dynamic* behaviour of $p$ using data from the literature. We show that $p$ initially *decreases* before it again *increases* up to or even beyond $3/4$. These results support the notion that $p$ can vary over time and yet its dynamics are *independent* from the cancer type. We argue that this behaviour reflects the underlying evolving tumorigenesis in that the *minimum* of $p$ signals the emergence of a fractal-like distribution network corresponding to the ‘angiogenetic switch’ towards a *perfusion*-dominated nutrient supply mechanism.
Introduction

In a previous paper we reported that West et al.’s model of ‘universal growth’ (West et al., 2001) can also describe the growth dynamics of experimental in vivo tumors and, furthermore, that it can also be applied to selected data from experimental tumors as well as clinical cancer data (Guiot et al., 2003). In that study, the scaling exponent \( p \) is assumed to be fixed over time. Here, we introduce a modification to our tumor growth model allowing the exponent \( p \) to vary dynamically and continuously over time to reflect changes in the nutrient-supply mechanisms during tumorigenesis. Using our dynamic framework, we investigate biomedical data reported in the literature to test the validity of the proposed mechanisms.

According to West et al. (2001), the actual mass \( m \) and its rate of growth, \( dm/dt \), are non-linearly related:

\[
\frac{dm}{dt} = a m^p \left(1 - \left(\frac{m}{M}\right)^{1-p}\right),
\]

where \( M \) is the asymptotic value of \( m(t) \) and \( a \) is a parameter related to the metabolic rate of the particular tumor cell line. It can be shown using Eq. (1) that \( m(t) \) exhibits an inflection point at \( t = t' \) corresponding to \( m = m' \), which depends on the value of \( p \). The simplest way to determine \( m' \) is to plot the experimental values of \( m \) and \( dm/dt \) in a cartesian plane with \( m \) as abscissa and \( dm/dt \) as ordinate. In fact the curve \( dm/dt \) vs \( m \) reaches a maximum at \( m = m' \), which can be accurately identified. By assuming a dynamically-changing scaling exponent \( p = p(t) \), but with a slow rate of change in the time interval around \( t' \), it follows that:
\[ \frac{d\mu}{dt} = b\mu^p \left[ \frac{1}{p} - \mu^{1-p} \right], \]

(2)

where \( \mu = \frac{m}{m'} \), \( b = a M^{p-1} \) and

\[ m' \cong p^{1/p} M. \]

(3)

West et al argue that the main mechanism for nutrient supply is related to the fractal-like distribution network, and propose the exponent \( p = 3/4 \) as a universal scaling factor. For tumors, this assumption implies the presence of an angiogenetic network, hence primarily corresponds to active perfusion for tumor growth in vivo. Determining the proper value of the scaling exponent \( p \), however, remains a controversial issue. For example, a recent paper (Dodds et al, 2001) shows that \( p = 3/4 \) does not yield a significantly better fit of all available data than \( p = 2/3 \) (which derives from a simple dimensional analysis).

**Materials and Methods**

To investigate the behaviour of the power exponent \( p \) in experimental in vivo tumors, we examine data reported in Steel (1977). In order to estimate the optimal value of \( p \), instead of assuming it fixed ‘ab initio’, we solve Eq. (2) for \( p \) using the aforementioned data to estimate values of \( \mu \) and \( d\mu/dt \) from the growth curves and then iteratively compute the value of \( p \) for which the difference between the predicted and observed values is smallest. In principle the value of \( b \), which is a biological parameter and is expected to depend on the cell line, should be independently measured.
Since direct measures are not available at the moment, we first assume a tentative constant value for \( b \), and then perform a recursive, autoconsistent procedure to estimate \( p \) at any time. Then the value of \( b \) is changed and the procedure repeated until a satisfactory “best fit” is reached for both \( p \) and \( b \).

**Results**

Using the procedure outlined above, we obtain the \( p(t) \) plots presented in **Fig. 1**. In this study here, we investigate three out of five cell lines of tumors growing in mice as reported in Steel (1977)\(^1\). Note that, regardless of the cancer type, the scaling exponent \( p \) now changes dynamically, i.e., it initially decreases to a minimum before it eventually rises again. From our formalism or, directly from **Fig. 1**, it appears to be possible to predict the time of onset for a perfusion-dominated nutrient mechanism (i.e., angiogenesis). The procedure can be further refined by reformulating the problem in terms of dimensionless rescaled variables, such as \( \tau \) and \( r \) in Eqs. (1) and (2) of Guiot *et al* (2003), respectively, but with \( p \) assumed to vary dynamically as a function of time. In accordance with the results of Guiot *et al* (2003), this should strongly enhance the similarity of the plots of **Fig. 1**. Also the inflection times, which vary in the figure from 5.3 to 14.2 days, should fall once the rescaled time \( \tau \) is confined within a much narrower range (from about 0.21 to 0.39, in a preliminary evaluation). The \( \tau \) range for inflection may be further reduced once more uniform starting times are considered (work in progress).

**Figure 1.**

\(^1\) Data from the remaining two cell lines cannot be used for this procedure since the short duration of these two experimental series does not allow properly estimating the tumor mass at the inflection point.
Discussion

In this study, we report several interesting findings from a tumor biology perspective. We found first that there was an initial decrease in the scaling exponent $p$, likely caused by a rapid onset of volumetric tumor growth ($V_{\text{total}}$) after in vivo implantation. Secondly, we argue that the development of an effective vascular supply network, in agreement with West et al.’s conjecture, does lead to the observed increase of $p$. We thus further hypothesize that the curve’s inflection point signals the switch in the dominant nutrient-replenishment mechanism from passive diffusion to active perfusion conferred by angiogenesis. It therefore fits, that this transition occurs in the three cell lines investigated here at an average tumor diameter of 6.6 mm ($\pm$ 1.6 STD) which is beyond the threshold of 2-3 mm in tumor diameter that Folkman (1971) had argued would prompt the onset of angiogenesis. It is thus less surprising that when fitting the data from Torres Filho et al. (1995), who implanted lewis lung carcinoma cell spheroids into the dorsal skinfold chamber of CB6 mice, we found that the inflection of $p$ occurs at approximately Day 6 post-tumor implantation, i.e., when the vessel density had reportedly reached already 81 percent of its maximum value. Moreover, in this study here, values for $p$ beyond the anticipated 0.75 may suggest that active perfusion ($p = 3/4$) is complemented by another supply mechanisms, likely by passive diffusion, when vascular density approaches its plateau phase. We further argue that such an increased surface diffusion can be explained by the onset of central apoptosis and necrosis, which should reduce the actively metabolizing tumor (cell) volume ($V_a$) while restricting it to the highly proliferating tumor surface, and hence effectively raises the $[S/V_a]$ ratio. In addition, we found, that for the data analyzed here, this dynamic $p$-behaviour appears to be independent of cancer type. It is also noteworthy that the absolute time $\tau$ at which $p$ reaches its minimum turns out to be very similar across the different tumor cell lines. Together, these findings further support our conjecture about the universality of the tumor growth model.
Based on the presented results we argue that the scaling exponent $p$ shows distinct dynamic patterns \textit{in vivo} and that such monitoring of $p$ may be of interest if the angiogenetic switch is to be exploited for diagnostic or therapeutic purposes. More specific experiments are called for in order to test these hypotheses, given their important implications for cancer research.

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Figure Caption

Figure 1. Estimation of the scaling exponent $p$ vs. time. Data from Steel (1977) refer to three different tumor cell lines implanted in mice.