

The dynamic evolution of the power exponent in a universal growth model of tumors

Caterina Guiot^{a,b,*}, Pier Paolo Delsanto^{b,c}, Alberto Carpinteri^d, Nicola Pugno^d,
Yuri Mansury^{e,1}, Thomas S. Deisboeck^e

^aDip. Neuroscience, Università di Torino, Italy

^bINFN, Sezioni di Torino Università e Politecnico, Italy

^cDip. Fisica, Politecnico di Torino, Italy

^dDip. Ing. Strutturale e Geotecnica, Politecnico di Torino, Italy

^eComplex Biosystems Modeling Laboratory, Harvard-MIT (HST) Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA 02129, USA

Received 6 February 2005; received in revised form 4 October 2005; accepted 13 October 2005

Available online 1 December 2005

Abstract

We have previously reported that a universal growth law, as proposed by West and collaborators for all living organisms, appears to be able to describe also the growth of tumors in vivo after an initial exponential growth phase. In contrast to the assumption of a fixed power exponent p (assumed by West et al. to be equal to $3/4$), we propose in this paper a dynamic evolution of p , using experimental data from the cancer literature. In analogy with results obtained by applying scaling laws to the study of fragmentation of solids, the dynamic behaviour of p is related to the evolution of the fractal topology of neoplastic vascular systems. Our model might be applied for diagnostic purposes to mark the emergence of an efficient neo-angiogenetic structure if the results of our in silico experiments are confirmed by clinical observations.

© 2005 Elsevier Ltd. All rights reserved.

Keywords: Cancer growth; Scaling laws; Fractal dimension; Angiogenesis

1. Introduction

In former times, tumor growth was simply described as being exponential ('slow' or 'fast', or finally limited by a saturation threshold), without any further attempt for a quantitative description (Retsky et al., 1990). One would, e.g. consider a growth from a few cells up to 1 liter tumor in about 20 doublings and fit it with a Gompertzian curve (Gompertz, 1825) on a pure phenomenological basis. Presently, however, to explain the tumor growth dynamics, one seeks for biological assumptions and/or physical principles (e.g. energy conservation and scaling). In a

previous paper (Guiot et al., 2003), we have proposed to extend the universal growth law for all living organisms (West et al., 2001; West and Brown, 2004) to include neoplasias. West's law conjectures that the incoming rate of energy flow B is related to the mass m by a power law of the type $B \propto m^p$, with $p = 3/4$ as originally proposed by Kleiber (1932). West et al. (1997) justified such a value arguing that the distribution network (i) branches to reach everywhere in any three-dimensional organism (according to a fractal distribution), (ii) has terminal units (e.g. capillaries or terminal xylems) independent of the body size, and (iii) minimizes the total resistance and consequently hence the energy required to distribute nutrients. Also Banavar et al. (1999) approached the problem of determining the exponent for a general distributive system, showing that B is expected to scale as $M^{D/(1+D)}$ if the efficiency of the vascular network is maximized (D is the dimensionality of the embedding space). Thus, in a three-dimensional space, $p = 3/4$ follows from the condition of

*Corresponding author. Dip. Neuroscienze, Università di Torino. 30, C. Raffaello, 10125 Torino, Italy. Tel.: +39 11 670 7710; fax: +39 11 670 7708.

E-mail addresses: caterina.guiot@unito.it (C. Guiot), um10@cornell.edu (Y. Mansury).

¹Current address: Department of City and Regional Planning, Cornell University, 213 W. Sibley Hall, Ithaca, NY 14853, USA.

most efficient space-filling, without having to recur to fractals. In a following paper (Banavar et al., 2002), the value $p = 3/4$ is also obtained by requiring that the mass-specific metabolic demands match the changing delivery capacities of the network at different body sizes.

However, the “correct” value of p remains a controversial issue as other values have also been proposed in the literature. For instance, a recent paper (Dodds et al., 2001) claims that $p = 3/4$ does not always yield a significantly better fit for all the available data than $p = 2/3$, which is based on a simple geometrical scaling of the body surface area available for heat dissipation. Even the trivial assumption $p = 1$ has been justified as the one leading to the simplest hypothesis of direct proportionality between incoming energy flow and mass.

In our opinion, the controversy reflects the rather ambiguous formulation of the question. Nature is of course more complex than even the most sophisticated mathematical model. Changing the ingredients of the model affects the prediction of the p value and, in turn, may correspond to different phases in the growth of the organism (or tumor). Thus the universality, as defined, e.g. in the framework of a recently proposed ‘black box’ formalism by Hirsekorn and Delsanto (2004), would refer not to a single value of p , but to a suitable range of values. In the present contribution, we suggest that after an initial exponential growth phase, p changes dynamically in the range $2/3$ – 1 , reflecting the different developmental stages of the vascular network and, more specifically, of angiogenesis. Our conjecture is supported by the prediction of similar results by Carpinteri and Pugno (2002a) in a completely different context (see Section 2) and by several instances of observation of evolution of the fractal cancer topology (Section 3). In Section 4, a mathematical model of growth dynamics with variable p is presented and some results are drawn and discussed in Section 5.

2. Correlation between scaling and fractal cancer topology

In a different context, Carpinteri and Pugno (2002a,b) have developed universal scaling laws for energy dissipation during the fragmentation of solids by assuming a self-similar size (i.e. fractal) distribution of fragments. Their assumption implies a power law such as $N \propto r^{-\bar{D}}$, where N is the number of fragments with size larger than r , and $\bar{D}$ is the so-called fractal exponent (a real positive number) of the fragment size distribution. Accordingly, they obtain by integration the total surface S of the fragments, as a function of their total volume V , as $S \propto V^{\bar{D}/3}$, with $2 < \bar{D} < 3$.

Likewise, if the biological clusters (fragments) distribution is fractal by nature, and the energy transportation (dissipation) is proportional to the surface, neglecting the variation of density during growth ($V \propto m$) yields the scaling law $B \propto m^p$, with $p = \bar{D}/3$, with $2/3 < p < 1$, as conjectured in Section 1.

It is interesting to note that, according to the interpretation based on the analysis by Carpinteri and Pugno (2002a), the exponent p should be strongly related to the fractal nature of cancer topology and thus susceptible of independent measurements. The idea of a fractal topology has been proposed in the past by several researchers (see e.g. Baish and Jain, 2000). In particular, Baish et al. (1996) have shown that in vivo estimations of the fractal dimension of planar vascular networks based on the box-counting method (see Bunde and Havlin, 1994) range between 1 and 2. Starting from the 2D observed exponent, stereological methods give an estimate of the corresponding 3D value, close to the 2D fractal exponent plus one, i.e. $\bar{D}$ ranging between 2 and 3. Correspondingly, the value of $p = \bar{D}/3$ is comprised between $2/3$ and 1. In particular, in normal tissues and in four different tumor lines, implanted in the dorsal skinfold chamber in immunodeficient mice, Baish et al. (1996) observed a value of 2 for the 2D fractal exponent (corresponding to $\bar{D} = 2 + 1 = 3$ in three-dimensions and $p = 1$) for normal capillaries, 1.7 ($\bar{D} = 2.7$, $p = 0.9$) for arteries and veins, and 1.88 ($\bar{D} = 2.88$, $p = 0.96$) for tumor vessels, showing that tumor vasculatures are more chaotic and inefficient than normal capillaries (Carmeliet and Jain, 2000), which are almost uniformly distributed. These observations are in agreement with our conjecture and, more specifically, with the prediction of a scaling exponent of 2 for the ‘space-filling’ growth model, 1.71 for the ‘diffusion limited aggregation’ model, and 1.90 for the ‘invasion percolation’ model (Baish et al., 1996). Thus tumor vascularization does not fully satisfy the condition of a ‘space-filling’ network, assumed by West et al. (1997), but could perhaps be better described by an ‘invasion percolation’ model. Accordingly, normal tissues and tumors differ deeply in their vascular structure and metabolism.

3. Evolution of the fractal cancer topology

We report here some instances of observed evolution of the fractal cancer topology. The first work, by Gazit et al. (1997) report changes in the vascular system changes during growth of tumors implanted in mice. Both the fractal dimension $\bar{D}$ and the vessel density were monitored by two-dimensional images during normal development from the 6th to the 12th day, showing an increase from around 1.6 ($\bar{D} = 2.6$ in three-dimensions) to a maximum value of 1.73 ($\bar{D} = 2.73$) on the 10th day, followed by a decrease. Likewise, also the vessel density shows a large increase, reaching its maximum on the 11th day, before it decreases. The authors were able to estimate a nearly linear increase in $\bar{D}$ of 0.06 per day correlated to a nearly linear increase in vessel density of 138 cm^{-2} per day.

In another relevant paper, the extraembryonic vascular network of the chick embryo was investigated by Vico et al. (1998) with similar methods. They found that the vascular fractal dimension increases continuously from about 1.3 ($\bar{D} = 2.3$) by the 60th hour to about 1.68 ($\bar{D} = 2.68$) by the

112th hour, when a plateau is reached and $\bar{D}$ remains stable at approximately 1.7 ($\bar{D} = 2.7$). Provided that the angiogenic process is antagonized with angiostatic factors, the fractal dimensionality of the vascular network has been proven to reflect the observed decrease in branching patterns.

Also Guidolin et al. (2004) showed that after delivering docetaxel to cultured HUVEC cells in Matrigel, the fractal dimension decreases about by 10% from the starting value of 1.20 ($\bar{D} = 2.20$). Finally, a paper by Parsons-Wingerter et al. (1998) shows similar effects after angiostatin delivering in the quail chorioallantoic membrane.

4. A mathematical model

According to the ontogenetic growth law of West et al. (2001) and its extension to neoplastic growths by Guiot et al. (2003), the actual mass $m(t)$ of the tumor and its rate of growth, dm/dt , are non-linearly related:

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

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 considered. We have removed the assumption of $p = 3/4$ replacing it with $p \in (2/3, 1)$, as conjectured in Section 1. An unspecified value of p has also been assumed in a paper by Delsanto et al. (2004), in which the ontogenetic growth model is tested under controlled conditions of malnourishment and applied mechanical stress. From Eq (1), the universal growth law follows:

$$r = (m/M)^{1-p} = 1 - e^{-\tau}, \quad (2)$$

where m_0 and r_0 are the initial values (at $t = 0$) of m and r , respectively, and

$$\tau = (1 - p)bt - \ln(1 - r_0) \quad (3)$$

with

$$b = aM^{p-1}. \quad (4)$$

From Eq. (1), it follows that $m(t)$ exhibits an inflection point at a certain time $t = t'$, corresponding to $m = m'$, which depends on the value of p . The simplest way to determine m' is from the plot of the experimental values of dm/dt vs. m . (see Fig. 1).

As the complex processes involved in angiogenesis presumably take some time to occur and are expected to modify the nutritive delivery system quite slowly, we assume a slow dynamic evolution of the fractal exponent $p = p(t)$, i.e. we neglect dp/dt in the derivatives. It follows that:

$$\frac{d\mu}{dt} = b\mu^p \left(\frac{1}{p} - \mu^{1-p} \right), \quad (5)$$

where $\mu = m/m'$ and

$$m' \cong p^{1/(1-p)} M. \quad (6)$$

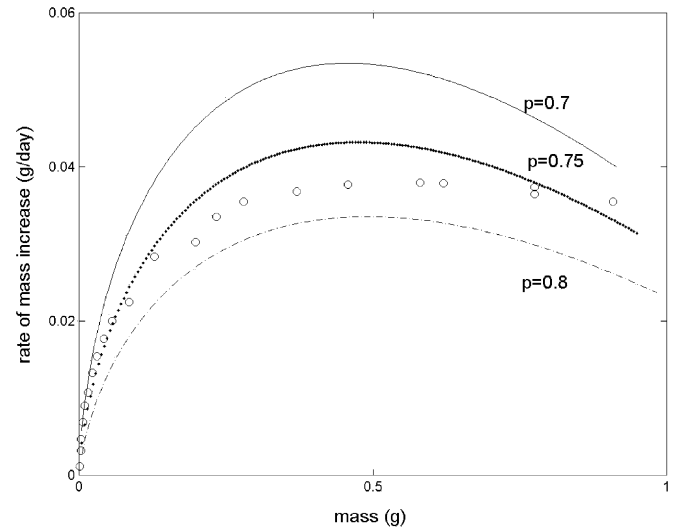


Fig. 1. Plot of dm/dt vs. m based on data on khjj tumors (Steel, 1977). The experimental points cannot be fitted by a single value of p but, according to our assumption of dynamical variation, they can be fitted by different values of p according to the different stages of growth.

From the plot $d\mu/dt$ vs. μ , we obtain the best fitting values of b and p corresponding to the mass m' (and time t'). Then M and a can be immediately computed from Eqs. (6) and (4), respectively. At this point p , can be evaluated in its dynamical evolution (i.e. for each value of m and t) by means of Eq. (4).

There are, however, many other influences that affect a growing tumor, such as the immune system and the interaction between cells and cells of the surrounding tissue. A more comprehensive analysis is therefore needed to confirm the validity of the proposed procedure.

As a first example of application of the procedure, we consider the analysis by Torres et al. (1995), in which a model for the investigation of angiogenesis is presented. It consists in the implantation of a Lewis's lung carcinoma multicellular tumor spheroid into the dorsal skinfold chamber of mice. The authors monitored both the morphometric parameters of tumor growth and the development of the vascular networks around the tumor focus, using intravital microscopy. By applying our procedure to their data, we obtain the results reported in Fig. 2. After an initial decrease to about 0.45, p starts to grow up to a value around 3/4, where the angiogenic process reaches a plateau. According to Parsons-Wingerter et al. (1998) and Vico et al. (1998), p is expected to grow with the vascular density. However, from our plot it appears that p starts growing only when the vascular density has already reached a considerable level. Unfortunately, the latter authors do not consider the evolution from its very beginning, but they show some delay in the relationship between fractal dimension and vascular density. We infer that the initial decrease of p may be due to a combination of adaptation of the implanted cell line to the recipient's microenvironment and to the process of transition from the original (optimal) network to the

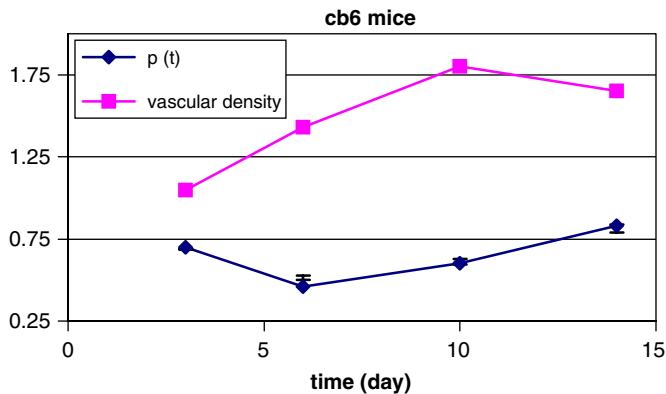


Fig. 2. Predicted values of the scaling exponent p vs. time, based on data from Torres et al. (1995) referring to tumors implanted in CB6 mice. The corresponding values of the vascular density are also reported.

subsequent pre-angiogenic structure. A new vascular network needs to be well established before inducing a local growth in p . As the angiogenic processes occur in a rather inhomogeneous manner, virtually all large tumors assume a ‘mosaic-like’ appearance, with a combination of well oxygenated and necrotic regions (see e.g. Carmeliet and Jain, 2000).

As a second example (Fig. 3), we investigate three out of five cell lines of tumors growing in mice, as reported by Steel (1977). The data from the other two cell lines cannot be used for this purpose as the short duration of the corresponding experimental series does not allow a proper estimate of the tumor mass at the inflection point. Note that, regardless of the cancer type, the power exponent p is observed to change dynamically, i.e. after an initial decrease (related to the implantation process as previously discussed), it eventually rises up to saturation.

5. Discussion and concluding remarks

In this paper, we have studied the correlation between tumor topology and the scaling exponent p , which we have conjectured to vary dynamically in the range $(2/3, 1)$. Consequently, we have modified the ontogenetic growth model of West et al. (2001) and its extension to neoplastic growths by Guiot et al. (2003) in order to develop a model for the prediction of the dynamic behaviour of p . For the application of the model to the analysis of experimental data (tumor masses m), we have considered the plot of dm/dt vs. m , which allows to evaluate p in the simplest way. We found that, in general, after an initial decrease due to the ‘adaptation’ of the implanted tumor to the new environment in the avascular phase, p starts increasing. We conjecture that this point marks the switch in the dominant nutrient-replenishment mechanism from passive diffusion to active perfusion conferred by the extent of vascular density and distinct level of angiogenesis it yields.

This transition occurs in the three cell lines investigated by Steel (1977) at an average tumor diameter of 6.6 mm (± 1.6 STD), clearly beyond the threshold of 2–3 mm

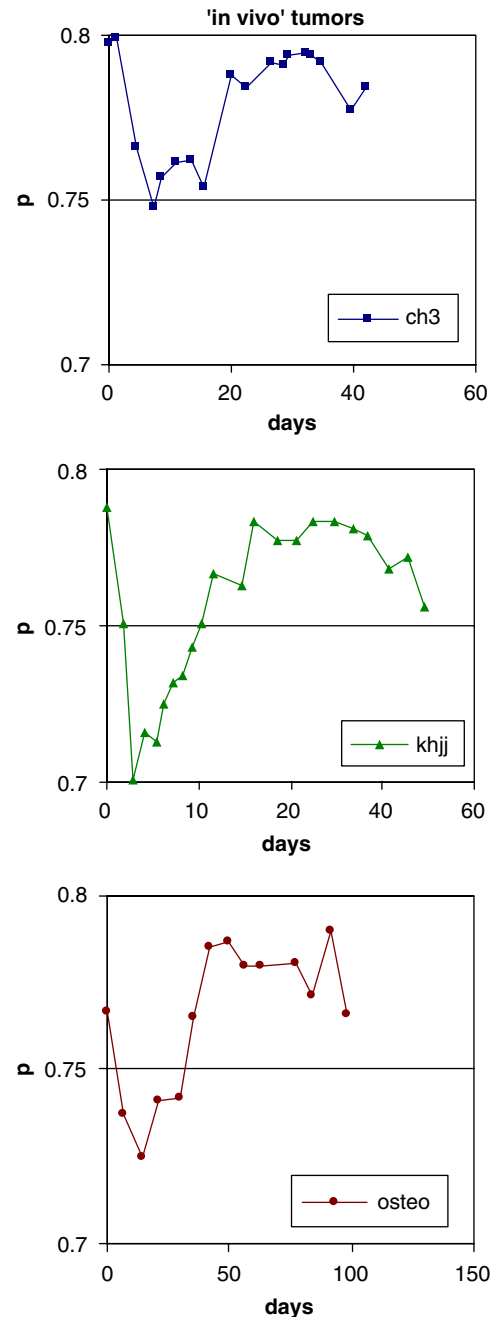


Fig. 3. Predicted values of the scaling exponent p vs. time, based on data from Steel (1977) referring to three different tumor cell lines implanted in mice. Noise in the data may be responsible for the final slight decrease of p observed particularly in the khjj case.

which, according to Folkman (1971), should prompt the onset of angiogenesis.

Values of p beyond 0.75 may suggest that active perfusion is complemented by other supply mechanisms, such as passive diffusion, when vascular density approaches its plateau. For the analysed data, this dynamic p behaviour appears to be independent of the in vivo cancer type. It is also interesting to note that the time at which p starts growing, supposedly following the onset of efficient angiogenesis, ranges between 5.3 and 14.2 days after implantation. By rescaling it to the dimensionless time

τ defined in Eq. (2), this temporal interval falls into a much narrower range (from about 0.21–0.39). The τ range might be further reduced with a proper analysis of the implantation mechanism.

Based on the presented results, we argue that the scaling exponent p shows distinct dynamic patterns in vivo and that a monitoring of p may be of interest for diagnostic or therapeutic purposes if the correspondence of the minimum of p with the emergence of a neoangiogenetic structure is confirmed (although currently, most of the clinical tumors are detected long after the onset of angiogenesis). For instance, in an effort to gain clinical input data for specific cancer types such as brain tumors, one could imagine to measure both tumor volume and its perfusion with distinct magnetic resonance imaging (MRI) techniques (see e.g. Cha, 2003).

In conclusion, from a merely computational point of view, many of the current models for tumor growth could fit the observational data satisfactorily by assuming that one or more of their parameters might evolve in time. In our case, however, to the variation of p can be given a direct physical meaning, i.e. it can be related to the occurrence of a variation in the topology of the nutrient supply system, which can be measured independently.

To validate the model, in vivo experiments should monitor, in parallel, the evolution of the fractal dimension of the neovascular network and the tumor growth rate. The estimation of the tumor volume should be very accurate, giving a definite error bar, which allows a correct estimation of the changing p values and of the sensitivity of the above variation. Current contrast-enhanced in vivo MR-imaging techniques are capable to study both volumetric tumor growth and vessel architecture in parallel, dynamically and at a relatively high spatial resolution based on the MR-setting available and the animal model chosen. The control experiment would use standard histopathological methods and assess vascular density and tumor diameter through a process of selective labeling and image-analyses of tissue sections. Contrary to the aforementioned non-invasive imaging methods, the latter would be an endpoint assessment, hence require multiple experiments terminated at consecutive time points.

Acknowledgments

This work was supported in part by the National Institutes of Health (CA 085139 and CA 113004) and by the Harvard-MIT (HST) Athinoula A. Martinos Center for Biomedical Imaging and the Department of Radiology at Massachusetts General Hospital. We also thank Drs. M. Griffo and P.G. Degiorgis for useful discussions.

References

- Baish, J.W., Jain, R.K., 2000. Fractals and cancer. *Cancer Res.* 60, 3683–3688.
- Baish, J.W., Gazit, Y., Berk, D.A., Nozue, M., Baxter, L.T., Jain, R.K., 1996. Role of tumor vascular architecture in nutrient and drug delivery: an invasion percolation-based network model. *Microvasc. Res.* 51, 327–346.
- Banavar, J.R., Maritan, A., Rinaldo, A., 1999. Size and form in efficient transportation networks. *Nature* 399, 130–132.
- Banavar, J.R., Damuth, J., Maritan, A., Rinaldo, A., 2002. Supply demand balance and metabolic scaling. *PNAS* 99, 10506–10509.
- Bunde, A., Havlin, S., 1994. A brief introduction to fractal geometry. In: *Fractals in Science*. Springer, Berlin, pp. 1–25.
- Carmeliet, P., Jain, R.K., 2000. Angiogenesis in cancer and other diseases. *Nature* 407, 249–257.
- Carpinteri, A., Pugno, N., 2002a. One- two and three-dimensional universal laws for fragmentation due to impact and explosion. *J. Appl. Mech.* 69, 854–856.
- Carpinteri, A., Pugno, N., 2002b. A fractal comminution approach to evaluate the drilling energy dissipation. *Int. J. Numer. Anal. Methods Geomech.* 26, 499–513.
- Cha, S., 2003. Perfusion MR imaging: basic principles and clinical applications. *Magn. Reson. Imaging Clin. North Am.* 11, 403–413.
- Delsanto, P.P., Guiot, C., Degiorgis, P.G., Condat, A.C., Mansury, Y., Desiboeck, T.S., 2004. Growth model for multicellular tumor spheroids. *Appl. Phys. Lett.* 85, 4225–4227.
- Dodds, P.S., Rothman, D.H., Weitz, J.S., 2001. Re-examination of the “3/4-law” of metabolism. *J. Theor. Biol.* 209, 9–27.
- Folkman, J., 1971. Tumor angiogenesis: therapeutic implications. *N. Engl. J. Med.* 285, 1182–1186.
- Gazit, Y., Baish, J.W., Safabakhsh, N., Leunig, M., Baxter, L.T., Jain, R.K., 1997. Fractal characteristics of tumor vascular architecture during tumor growth and regression. *Microcirculation* 4, 395–402.
- Gompertz, B., 1825. On the nature of the function expressive of the law of human mortality and on a new mode of determining the value of life contingencies. *Philos. Trans. R. Soc. London* 115, 513–585.
- Guidolin, D., Vacca, A., Nussdorfer, G.G., Ribatti, D., 2004. A new image analysis method based on topological and fractal parameters to evaluate the angiostatic activity of docetaxel by using the Matrigel assay in vitro. *Microvasc. Res.* 67, 117–124.
- Guiot, C., Degiorgis, P.G., Delsanto, P.P., Gabriele, P., Deisboeck, T.S., 2003. Does tumor growth follow a “universal law”? *J. Theor. Biol.* 225, 147–283.
- Hirsekorn, S., Delsanto, P.P., 2004. On the universality of nonclassical nonlinear phenomena and their classification. *Appl. Phys. Lett.* 84, 1413–1415.
- Kleiber, M., 1932. Body size and metabolism. *Hilgardia* 6, 315–353.
- Parsons-Wingerter, P., Lwai, B., Yang, M.C., Elliott, K.E., Milaninin, A., Redlitz, A., Clark, J.L., Sage, E.H., 1998. A novel assay of angiogenesis in the quail chorioallantoic membrane: simulation by bFGF and inhibition by angiostatin according to fractal dimension and grid intersection. *Microvasc. Res.* 55, 201–214.
- Retsky, M.W., Wartzendruber, D.E., Wardwell, R.H., et al., 1990. Is gompertzian or exponential kinetics a valid description of individual human cancer growth. *Med. Hypotheses* 33, 95–106.
- Steel, G.G., 1977. *Growth Kinetics of Tumours*. Oxford, Clarendon Press.
- Torres, F.I.P., Hartley-Asp, B., Borgstrom, P., 1995. Quantitative angiogenesis in a syngeneic tumor spheroid model. *Microvasc. Res.* 49, 212–226.
- Vico, P.G., Kyriacos, S., Heymans, O., Loutyans, S., Cartilier, L., 1998. Dynamic study of the extraembryonic vascular network of the chick embryo by fractal analysis. *J. Theor. Biol.* 195, 525–532.
- West, G.B., Brown, J.H., 2004. Life’s universal scaling laws. *Phys. Today* 57, 36–43.
- West, G.B., Brown, J.H., Enquist, B.J., 1997. A general model for the origin of allometric scaling laws in biology. *Science* 276, 122–126.
- West, G.B., Brown, J.H., Enquist, B.J., 2001. A general model for ontogenetic growth. *Nature* 413, 628–631.