



## Does cancer growth *depend* on surface extension?

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**Summary** We argue that volumetric growth dynamics of a solid cancer *depend* on the tumor system's overall surface extension. While this at first may seem evident, to our knowledge, so far no theoretical argument has been presented explaining this relationship explicitly. In here, we therefore develop a conceptual framework based on the so-called 'universal scaling law' and then support our conjecture through evaluation with experimental data. Our concept suggests not only that cancer tissue invasion operates with relatively few and thin branches of mobile cells but also that this overall tumor surface expansion, and the diffusion of nutrients that it enables, can nourish the tumor prior to the impact of neovascularization.

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### Letter

First, let us consider that from a mechanical perspective any solid malignant tumor grows inside a given organ structure, i.e., is confined to a limited host volume. For instance, in the brain, surrounding bony skull defines this boundary, elsewhere it may be a less rigid organ capsule. Thus, a growing tumor should rapidly induce the build-up of a mechanical

pressure,  $P$ , which, as soon as all 'reserve rooms' have been used up, will increase sharply and may act as a growth constraint for the tumor. Without further adjustment, the tumor's growth curve would saturate at this point. Arguably, this phase coincides with reaching a critical cell density,  $\rho$ , and denotes the time point when tumor cell invasion starts (i) as it offers a way to release 'excess' cells, reduce local cell density ( $\rho$ ) and hence keep  $P$  manageable; (ii) since it reduces the adjacent tissue consistency through the cells' enzymatic activity or proteolysis, meaning that these invasive cells can reduce  $P$  directly [1], and (iii) as it *increases* the total tumor surface  $A$ , in an effort to control  $P$ .

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Secondly, tumor growth depends on nutrient and oxygen availability. As such, when dimensions exceed a few  $\text{mm}^3$  [2], angiogenetic mechanisms are activated to provide the tumor with a nutrient-supply system. Prior and/or in addition to angiogenesis surface-diffusion mechanisms are operating as well. The efficiency of the resulting nutrient-supply system is related to its geometry. Up until now, attention has been devoted only to the dimensionality of the distributive system. Based on the assumption of a fractal vascular network, our extension of West's law [3,4] to tumors conjectures that the rate of input energy,  $B$ , is related to the mass,  $m$ , by a power law of the type  $B \propto m^p$  [5]. While in the case of a spherical tumor nourished only by diffusion, the scaling exponent  $p$  should indeed correspond to  $2/3$ , in the case of a distributive capillary network, however, West argues that  $p = 3/4$ . Correspondingly, Banavar et al. [6] found the same  $p$  value in an effort to solve the problem of determining the exponent for a general distributive system. They claimed 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). Actually, in tumors it has been shown (see e.g. [7]) that the fractal dimension  $\bar{D}$  of the vascularity ranges between 2 and 3 and, correspondingly, the value of  $p = \bar{D}/3$  varies between  $2/3$  and 1. Also, both experimental (e.g., [8,9]) and theoretical considerations [10–12] predict that  $p$  varies at the onset of angiogenesis.

Now, Carpinteri and Pugno [13] have developed universal scaling laws for energy dissipation in a different context, that is during the fragmentation of solids, by assuming a self-similar (i.e., fractal) size 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  $2 < \bar{D} < 3$ . In this case the value of the parameter  $p$  would be related more to the system topology than to the occurrence of a distributive network. Returning then to our initial hypothesis that tumor growth depends on surface extension, we conjecture that such a model could be applied *also* to the case of a non- or pre-vascularized tumor that exhibits cell invasion into the surrounding tissue. In particular, at least in the early phases of dissemination, a multicellular tumor spheroid (MTS) may develop an invasive branching structure nourished by diffusion (see [14,15]). For instance, let us consider a MTS, with radius  $r$ , that starts invading its microenvironment by generating branching structures that are composed of mobile cancer cells. Let each branch's mean radius be  $\varepsilon r$ , with  $\varepsilon$  of the order of magnitude of a few cells, whereas its length,  $l$ , varies in time according to experimental data (for schematic and microscopy example, see Fig. 1).

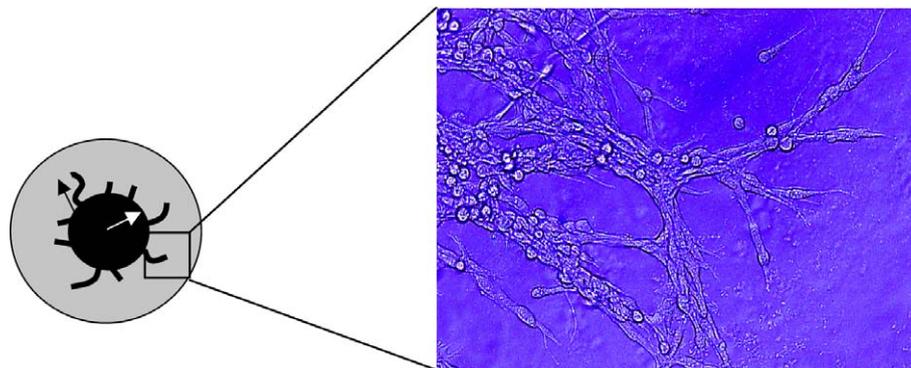
The maximum number of branches is given by  $N_{\max} = \pi r^2 / \varepsilon^2$ . However, in reality only a partial covering of the tumor surface may occur. Therefore we assume that the effective number of tubules is given by  $N = \eta N_{\max}$ , with  $\eta \leq 1$ . It follows, for the total MTS volume:

$$V = 4\pi(r^3/3 + \pi\eta lr^2/4), \quad (1)$$

and for its total surface:

$$S = 4\pi(r^2 + \pi\eta lr/2\varepsilon) \quad (2)$$

Fewer tubules also reduce the occurrence of nutrient depletion at their bases, due to an excessive thickness of the sprouts. In practice,  $\varepsilon$  and  $\eta$  may be used as effective parameters for a more



**Figure 1** Multicellular tumor spheroid (MTS) assay. In the schematic, the *white arrow* marks the radius  $r$  and the *black arrow* the branch length  $l$  used to compute  $V$  and  $S$ . The (right) light microscopy image depicts mobile brain tumor cells forming invasive branches (for experimental details see [14]).

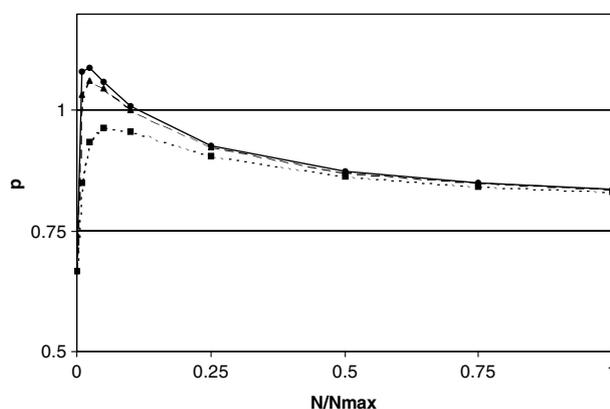
realistic fitting. For this purpose we have investigated for a large number of pairs of  $\varepsilon$  and  $\eta$ , kept constant for each run, and for different experimental values of  $r$  and  $l$  (up to the sixth day of in vitro culture, see Table 1 in Ref. [14]), the following relationship :

$$\ln(S) = k + p \ln(V), \quad (3)$$

in order to obtain the best fitting values of  $p$  (see Fig. 2).

In the case of  $\eta = 0$ , (i.e. no invasive sprouts on the MTS surface), obviously  $p = 2/3$  (see Fig. 2). Note that the smaller  $\varepsilon$  is, the thinner are the tubules sprouting from the MTS and the higher is the predicted value for  $p$ . However,  $p$  is much more sensitive to the variation of  $\eta$ , which describes the covering of the MTS surface by invasive branches. In fact, its value increases from 0.83 in the case of full coverage to about 1 when the number of sprouts is reduced to 10% of  $N_{\max}$ . This increase in  $p$  may reflect a better 'efficiency' in providing nutrients to the invading MTS when its branches are relatively few and thin, thus reducing the aforementioned nutrient depletion at their bases.

In conclusion, a branch-inducing MTS may indeed yield  $p$  values in the range (2/3; 1), depending on the length or extent of its invasive architecture – even in the absence of angiogenesis (which by itself has been credited for moving  $p$  to 3/4). This point is rather critical since it argues that invasion-mediated tumor surface expansion, and thus surface-diffusion nourishment can and should precede neovascularization, which may take more time in order to become effective.



**Figure 2** Plot of the parameter ' $p$ ' defined in Eq. (3) vs. the parameter  $\eta$ , expressing the ratio between the actual number  $N$  of branches and its maximum possible number  $N_{\max}$ . Experimental data for MTS [14,15] were used for estimating  $r$  and  $l$ , while the radius  $\varepsilon$  of the branches was assumed to be 5  $\mu\text{m}$  (solid line), 10  $\mu\text{m}$  (dashed line) and 50  $\mu\text{m}$  (dotted line), respectively. As expected, in the absence of sprouts  $p = 2/3$ .

In summary, as an amendment to a recent paper of ours [11], which claims that a transition occurs for  $p$  from 2/3 to 1 for an angiogenesis-dominant nutrition-supply mechanism, we argue here that, even before the onset of angiogenesis, i.e. in the early phase of tumor cell invasion, the parameter  $p$  can vary according to changes in the topological configuration. Therefore, we conjecture that cancer system growth, at least in its early stages, does critically depend on surface extension and thus on rapid tissue infiltration. Cautiously extrapolated to the experimental research side, our conjecture may yield intriguing insights into the sequence of events involved in the molecular progression pathways. For instance, one could hypothesize that genetic and epigenetic profiles which increase the tumor's invasive fitness are selected for at a relatively early stage – a process that would have implications both for diagnostics and therapeutics alike. Furthermore, we argue that this surface expansion due to nourishment requirements complements the cell density– and thus largely mechanically-driven trigger, described in detail in Deisboeck et al. [1].

Lastly, in the presence of vasculature, the aforementioned mechanism may be responsible for regional heterogeneities in the prevailing nourishment process at the same time point, in that wherever the surface to volume ratio is favorably high, a diffusion-dominant supply mechanisms is sufficient (i.e., in the regions that show extensive cell invasion branching), whereas for tightly packed volumetric objects such as the main tumor growth core, for microsatellites and metastases, angiogenesis, and therefore  $p = 3/4$ , is the desired, necessary nutrient-supply mechanism. Even the occurrence of  $p$  values larger than 3/4, as observed by Guiot et al. [12] can then be explained by such a mechanism.

This letter therefore presents further evidence that many different tumor growth conditions can be described with a relatively simple law such as the one proposed by West et al., provided the scaling parameter  $p$  is kept variable in space and time to account for different nourishment conditions.

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