Symmetric Proliferation:

An Examination of the Fractal Geometry of Tumors

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Sierpinski carpet model of plane fractals

From flowers to faces, nature is abound with symmetry. Most natural objects tend to form according to patterns, a tendency which mathematicians readily exploit in order to create theoretical models of the world around us. The height of a cliff, for instance, is modeled by a one-dimensional line; a snake's path through the sand is modeled across a two-dimensional surface; a block of ice is modeled as a mass extending into three dimensions. But what about objects in between dimensions? In fact, between the 1-D and the 2-D there exist objects known as fractals. These mathematical objects are infinitely self-similar, which means that upon magnification of a certain part of a fractal, one sees the figure of the overall fractal, and so on unto infinity. Self-symmetry allows a fractal to have fractional dimensions because it is not purely linear--the border of a fractal cannot be traced--but this lack of boundedness also means that the fractal never encircles a defined area. Imagine a tree whose branches branch out infinitely, or a snowflake with six tips, each of which looks like the original snowflake, and so on and so forth.

"Picture, for example, water trickling through only the most loosely packed areas of soil in a pot; in the same way, the blood vessels of a tumor grow into the weakest areas of the tissue around it."

Clearly, in fractal models, as in all models of nature, there is a difference between the mathematical and the natural. Natural fractal objects are composed of discrete units and are not infinitely divisible--the fractal pattern must end somewhere, or else, for instance, one might find tiny branches at the cellular level of a tree branch. To correct for this quality, scientists define natural fractal objects as having statistical self-similarity, or when "the statistical properties of the pieces [of an object] are proportional to the statistical properties of the whole" (Grizzi et al., 2008).

In the human body, statistically self-similar models are most commonly applied to branching structures in the lung and in networks of blood vessels. The latter application has had particular importance in medical studies of cancer, as there is evidence that understanding the fractal geometry of tumor vasculature may aid in identification and targeted treatment of cancers.

Tumor vasculature can in fact be described by a fractal model, and is often distinguished from normal vasculature by either an abnormally high or abnormally low fractal dimension (Zook and Iftekharuddin, 2005). An object's fractal dimension is a constant between the integers 1 and 2, and might be described as how 'proliferative' the object looks; i.e., an object with a higher fractal dimension looks more like an object with true area than like a curve. Baish and Jain observed that blood vessels in the tumors of mice had higher fractal dimensions than the mice's normal arteries and veins, claiming that "the fractal dimension quantified the degree of randomness to the vascular distribution, a characteristic not easily captured by the vascular density" (Baish and Jain, 2000). Moreover, the researchers noted that tumor vessels tended to be more twisted than normal vessels, having "many smaller bends upon each larger bend" (Baish and Jain, 2000). They also found that the way tumor vessels grew and branched closely matched a type of statistical growth called invasive percolation. In invasive percolation, a substance moves through a medium which has varying degrees of strength, penetrating the weakest areas of the medium and thus branching out to form a network. Picture, for example, water trickling through only the most loosely packed areas of a pot of soil; in the same way, the blood vessels of a tumor grow into the weakest areas of the tissue around it. On the other hand, normal capillaries are traditionally modeled by the Krogh cylinder model, which assumes that the capillaries are straight, relatively spaced, and only reach a cylindrical volume of tissue immediately

surrounding each linear capillary. Given that the Krogh model idealizes even the most organized vasculature, it is clear that a statistical fractal model is better suited for tumor vasculature, which lacks arterioles, venules and capillaries, and whose irregularly shaped vessels often do not even interconnect (Folkman, 2002).

In the early 1990s, a series of studies concluded that tumor microvessel density (MVD), or the degree to which the cancerous tumor has established its own vasculature, is associated with metastasis of that cancer (Folkman, 2002). Since then, knowledge of tumor vasculature has been applied in attempting antiangiogenesis, or prevention of blood vessel growth, as a proposed way to control tumor growth. However, antiangiogenesis has historically had limited success. Some scientists hypothesize that the irregular geometry of tumor vasculature--given by an abnormal degree of self-symmetry--results in two problems that mirror each other. First, while disorganized vasculature makes it difficult for tumor cells to receive nutrients, it also makes it harder for drugs targeting the tumor to reach a good proportion of the tumor. (Chauhan et al., 2012) Second, if an antiangiogenic drug does succeed in spreading to most of the tumor, the tumor might instead develop relatively normal vasculature that then allows for nutrients to be better transported to tumor cells, speeding up the growth of the tumor.

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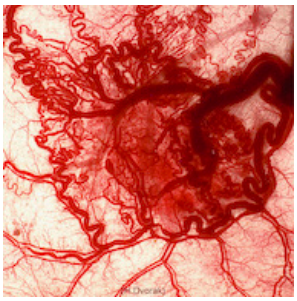
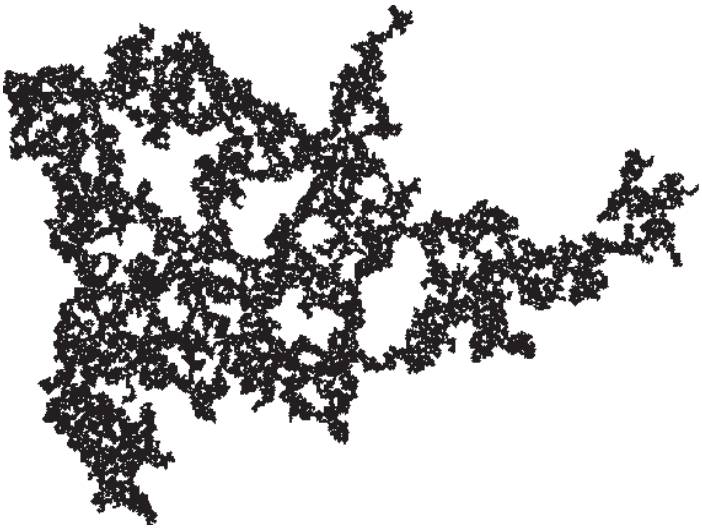


Vascular tumor

Nevertheless, understanding tumor vasculature is still useful since many cancer treatments are affected by drugs which flow through the tumor's blood vessels. Knowing where the tumor vasculature reaches is akin to knowing where in the tumor the treatment can reach. To test this reach, Baish and Jain performed another study in 2012 in which a tracer transport model was coupled to a model of blood flow based on invasive percolation--essentially, the researchers created a fractal model of tracer movement through a tumor, by which the tracer represented a potential drug. This model predicted "highly heterogeneous transport in the tumor," which the researchers deemed "clinically significant because some 'out of the way' regions of tumor may receive low concentrations of [the drug]" (Baish and Jain, 2012). In an article examining medulloblastoma in children, Grizzi, Weber and Di Ieva also support the use of a fractal model for tumor vasculature, and go even further to say that this fractality implies a level of irregularity in blood vessel organization that renders MVD a poor measure of the degree to which the tumor has established its vasculature. The article concludes that greater focus should be placed on modeling tumor vessel networks as fractal objects, so that scientists might better understand where in the tumor the drug cannot reach, and possibly devise drug delivery methods that work around this difficulty.



Dynamic of fluids in porous media and critical percolation phenomenon

Interestingly, Brú et al. used a fractal model to discount antiangiogenesis entirely as a treatment for cancer. These researchers focused their attention on the growth of the tumor as a whole, observing fractal geometry in the way the cells proliferate around the edge, or the contour, of the tumor. According to their article in Biophysical journal, such fractal growth is an indication that the tumor always maintains a layer of actively proliferating tumor cells about its contour. Their article challenges the belief that decreasing vascularization--i.e. antiangiogenesis--to effect cell necrosis could effectively combat tumor growth, on the basis of the idea that it is not poor vascularization that prohibits cell proliferation toward the center of the tumor, but rather "pressure effects" (Brú et al., 2003). Thus, poorly vascularized tumor cells could hypothetically still proliferate actively, as long as they are near the contour of the tumor, where pressure is lower.

In sum, examination of the fractal geometry of tumors reveals a similarity between the way fractals are infinitely proliferated within themselves through self-symmetry, and the way a tumor grows through intense proliferation of its tissue and vasculature. Treatment methods aside, fractal geometry is useful in approximating the pattern and number of blood vessels present around or in a cancerous tumor, and as such is a good way to track tumor progression. Though fully effective drug delivery to tumors remains elusive, fractal models can in the meantime be used to help physicians in predicting the course of a tumor's growth, and thus in forming more accurate prognoses for the health of patients with cancer.

References

Baish, J. W.; and Jain, R. K. Fractals and Cancer. Cancer Res. 2000, 60, 3683

Brú, A.; Albertos S.; Subiza J. L.; García-Asenjo, J. L.; and Brú, I. The Universal Dynamics of Tumor Growth. Biophys J. 2003, 85(5), 2948-2961.

Chauhan. D.; Tian. Z.; Nicholson, B.; Kumar, K. G.; Zhou, B.; Carrasco, R.; McDermott, J. L.; Leach, C. A.; Fulcinniti, M.; Kodrasov, M. P.; Weinstock, J.; Kingsbury, W. D.; Hideshima, T.; Shah, P. K.; Minvielle, S.; Altun, M.; Kessler, B. M.; Orlowski, R.; Richardson, P.; Munshi, N.; Anderson, K. C. A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. Cancer Cell. 2012, 22(3), 354-358.

Folkman, J. Role of angiogenesis in tumor growth and metastasis. Semin. Oncol. 2002, 29(6), 15-18.

Grizzi F., Weber C., and Di Ieva A. Antiangiogenic strategies in medulloblastoma: reality or mystery. Pediatr. Res. 2008, 63(5), 584-590.

Zook, J. M., and Iftekharuddin, K. Statistical analysis of fractal-based brain tumor detection algorithms. Magn. Reson. Imaging. 2005, 23(5), 671-678.

Image Sources

http://mathworld.wolfram.com/images/eps-gif/SierpinskiCarpet_730.gif

http://blogs.uoregon.edu/artofnature/files/2013/12/Blood_vessels_1817314a-2eb9a9f.jpg

http://cvbr.hms.harvard.edu/researchers/images/dvorak1w.jpg

http://www.icp.uni-stuttgart.de/Jahresberichte/97/img18.gif

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