Comparing Invasive Species to Metastatic Cancers Inspires New Insights for Modelers

By Mike Martin

They both invade. They both spread. They both grow uncontrollably. So maybe it was only a matter of time before scientists discovered a link between metastatic tumors and invasive species.

Using computer models, high-tech imagery, and aerial photographs that span 40 years in the life of a forest, an international research team has identified a distinct geometrical “signature” that an invasive tree—the English elm—shares with glioma, an aggressive brain tumor. They call their discovery a window on the “ecology of cancer.”

“This is the first work demonstrating that metastasis is indeed an ecological process,” said Argentina National University–Cordoba agricultural biologist and principal investigator Diana Marco, Ph.D.

Uncontrolled cell growth shares a unique “spatiotemporal signature” with species invasion, the researchers discovered. That signature includes a distinct geometry along growth boundaries, a unique patchwork growth pattern, and a comparable distribution of seeds and cells. It indicates that “early spread of individual cancer cells is similar to the spread of individual members of a species,” explained University of Pittsburgh Cancer Institute professor Bo Hu, Ph.D., a study coauthor.

The data “speak for themselves,” said tumor modeling expert Yi Jiang, Ph.D., a researcher at the Los Alamos National Laboratory and Massachusetts General Hospital Center for the Development of a Virtual Tumor. “The paper shows very strong similarities between tumors and invasive species with a rather specific set of measurements,” Jiang explained. The resulting model could affect therapeutic strategies based on assumptions about metastatic spread dynamics, Jiang said.

Cells and Seeds

The invasive species model follows on a hypothesis that Wistar Institute assistant professor Carlo Maley, Ph.D., published in Nature Reviews Cancer. “In 2006, we proposed that ecological theories of dispersal might be usefully applied to the evolution of metastasis” in cancer, Maley said. The new research “suggests that there is a good match between these phenomena and lends further support to the suggestion that this is a fruitful line of research.”

In their article for Nature Precedings, Marco and her colleagues argue that ecology and oncology intersect when cancerous cells disperse like seeds in the wind. Using computer models and growth simulations over long distances and times, they observed that malignant tumors and invasive species proliferate according to a so-called power law.

Power laws are “scale invariant,” meaning that objects or populations of vastly different size can be compared, with nothing lost in translation. “We can compare different processes occurring at very different spatial scales, like kilometers in tree dispersal and microns in cancer dispersal,” Marco said.

Evidence that power laws govern invasive species came from crop pathogen studies and computer simulations reported in such journals as Nature, Science, and Genetics. Marco and fellow authors Marcelo Montemurro, Ph.D., and Sergio Cannas, Ph.D., have studied biological invasions for years and suspected that the same laws govern tumor growth. They confirmed their suspicions by comparing an Argentine forest including invasive species to noninvasive human glioma cells cultured either in live mice or in Matrigel, a patented gelatinous protein mixture secreted by mouse tumors.

“Noninvasive cells from the center of the glioma”—which were used as an experimental control—“were genetically engineered to become invasive by expressing angiopoietin 2, a regulator that promotes tissue infiltration,” Marco explained.

Likewise, aerial black-and-white photographs taken in 1970, 1987, and 1996 revealed the gradual spread of English elm (Ulmus minor), an ornamental European tree that invaded Argentina in the mid-20th century. From 1987 to 1997, 74 elm tree patches became 189 patches scattered across 17 acres. While Marco “would not say that trees native to the forest were a control,” she did identify two noninvasive species—Litreaa ternifolia and Fagara cova—as tantamount to “tissue surrounding a spreading tumor.”

Orderly Disorder

Simulations and observations revealed that malignant cells and invasive seeds grow into colonies that exhibit a “similar patchy pattern characterized by fractal geometry,” a kind of orderly disorder, Pittsburgh’s Hu explained. Appearing first as single patches,
tumors and seedlings reproduce and create new patches that eventually merge, generating a distinct but irregular border. In contrast, the study’s noninvasive control tumors were smooth and clean.

Fractal geometry is both characteristic and predictive of metastatic tumors, said Lisette de Pillis, Ph.D., a tumor modeling expert and mathematics professor at Harvey Mudd College in Pomona, Calif. “Smooth-versus-spiky tumor geometry has been simulated in earlier works,” de Pillis explained.

Marco’s team observed the fractal signature in digital photomicrographs of stained glioma sections at x100 magnification, images de Pillis labeled “a reasonable quantitative representation of the two-dimensional geometry of a metastatic tumor.”

However, two dimensions may not be adequate, said Fred Hutchinson Cancer Research Center fellow Dennis Chao, Ph.D. “The glioma pictures are just slices of a three-dimensional process, which is hard to compare to the two-dimensional process of an ecological phenomenon,” explained Chao, a member of the Center for the Development of a Virtual Tumor.

Also, to get a true sense of how glioma—an unpredictable and fickle cancer—will progress, mice and Matrigel simply can’t compare with clinical imaging “in real patients, in real time,” said Kristin Swanson, Ph.D., a University of Washington neuro-pathology and mathematics professor. “In vitro glioma invasion patterns also differ dramatically from those observed in vivo,” said Swanson, who specializes in glioma modeling.

**New Dimension**

To generate some hard numbers for comparison, Cannas, a mathematics professor from Argentina National University, and Montemurro, a life sciences professor at the University of Manchester, U.K., calculated the “fractal dimension” of the glioma and elm tree patch borders.

That quantity—about 1.3 for the tumor and 1.6 for the elm tree—yielded “an almost perfect model fit between the dispersal of the invasive elm tree and glioma cells,” said University of Pittsburgh associate pathology professor and Marco team member Shi-Yuan Cheng, Ph.D. Mathematically speaking, the fit is “completely believable,” said de Pillis.

But oncologically speaking, radiation biologist Kedar Prasad, Ph.D., thinks otherwise. “I don’t believe the basic molecular mechanisms involved in cancer metastasis can be modeled by spatiotemporal phenomena,” said Prasad, who studied radiation- and micronutrient-driven brain tumor inhibition when he directed the University of Colorado Center for Vitamins and Cancer Research. “Effective treatment strategies will inevitably need to be based on understanding metastasis at the level of biochemical and genetic mechanisms and only peripherally on spatiotemporal behavior.”

**Telltale Signature**

However, mathematicians researching cancer find ecological models “quite useful,” de Pillis said, citing six published articles, including one she coauthored for Cancer Research that used predator–prey concepts to model how T cells target and kill cancer cells. From such models, Chao of Fred Hutchinson looks for “testable hypotheses or intervention strategies” rather than “analogies between different systems.”

The invasive species analogy is useful because it generates a different ecological model, de Pillis explained. By simulating dispersal of cells and seeds over relatively long times and distances, the model yields a new result, an “underlying set of rules driving the development of tumor geometry,” she said. Marco hopes that imaging technologies will one day use those rules to “enable the direct observation of early spreading cancer cells.” Their geometric signature—that characteristic patchwork pattern and irregular border—shouldn’t be too hard to find.

Cancer’s inherent heterogeneity, however, will always be “a huge challenge to effective treatment” and may preclude searching for anything as simple as a signature, said oncologist Clay Anderson, M.D., a professor at the University of Missouri Ellis Fischel Cancer Center in Columbia. “I like the idea, but I view it as overly simplistic.”

**Invader Versus Invaded**

Years of study have taught Marco that controlling an invasive species is not simple. Suppressing or killing the invader, for instance—the primary tumor or the parent tree—is usually too little, too late. But making the invaded habitat less hospitable has proven effective, at least with invasive plants and animals.

The invasive species cancer model is unique in this aspect, de Pillis said. It shows that “adjusting the rate of metastasis would not be based on the biology or metabolic properties of the particular tumor.” Rather, the model suggests that making metastasis-targeted tissues more “invasion resistant” or less likely to foster drug resistance may be a consequence of ecological pressures selecting for a new genetic trait.

“Cancer cells arriving by metastasis to a new habitat—new tissues—can give rise to a population with a different genetic composition from that of the original population—the primary tumor,” Marco explained. “These genetic differences can include resistance to drugs that were effective with the primary tumor.”

**Out of the Woods**

British physician and virologist John Cairns once quipped that “the characteristics of the cancer cell have been ascribed to some defect in whatever branch of biology happens to be fashionable and exciting.” Then, Cairns said it was “molecular genetics.” Today, it may be ecology.

That’s fine with de Pillis, a strong advocate for interdisciplinary bridge building who sees the invasive species model as “another plank between mathematicians, clinicians, and bench scientists.”

“Although concepts from ecological modeling and tumor modeling have overlapped in the past, I believe it highly beneficial to strengthen ties between those areas of research,” de Pillis said. “Studies such as the one by Marco et al. allow practitioners to see the coarser-grained picture, or step back and look at the forest, not just the trees.”