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Mutations & Math

BY TOM SIEGFRIED

Calculating whether the enemy has allies.

Cancer has always been one of humankind's most devilish adversaries, waging a relentless war with dismaying success against the defensive strategies of both the body and modern medicine.

In their arsenal of strategic defenses, though, medical scientists may soon be adding a new weapon: math. Clues to fighting cancer have begun to emerge from game theory—the mathematics used for analyzing strategic interactions.

As a branch of mathematics, game theory has a misleading name. It was partly inspired by poker, but actually was developed in the 1940s for use in economics, where the prize for "winners" is money. At first, economists mostly ignored it, and game theory made its initial splash in biology. Scientists studying the history of life found the math useful in explaining features of evolution, where the "winners" are those who survive and reproduce.

Game theory proved especially helpful in explaining how cooperation, rather than pure competition, sometimes emerges among animals. (Animals that cooperate in finding food sometimes stand a better chance of surviving than animals that fight over food, game theory analyses show.)

Lately, some game theory experts have turned their attention to cancer, which can also be viewed as an evolutionary game. Cancer cells, after all, battle the body for supremacy, adapting and evolving to outwit counterattacks from the immune system.

Cancer cells may seem supremely selfish, but game theory shows that cancer's growth may stem in part from the ability of precancerous cells to cooperate. Such cooperation could explain why cancers sometimes develop rapidly, and may even imply new strategies for bringing cancer under control, say Robert Axelrod, PhD, and Kenneth Pienta, MD, of the University of Michigan, and David Axelrod, PhD, of Rutgers University.

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Researchers long ago established that a healthy cell does not turn cancerous

overnight. Rather, it accumulates mutations over time, each providing some of the many necessary hallmarks that transform a precancerous cell mass into a full-fledged malignancy. Only cells with such a “full deck” of mutations can multiply uncontrollably, invade their host tissue, and then spread to other tissues in the body, defying the body’s defenses.

Precancerous cells within a young tumor are not all alike, and they compete for space and nutrients, not unlike animals fighting over food and turf in the jungle. But with cells, as with animals, sometimes it’s the best cooperators, not the best fighters, who survive.

Suppose, for instance, that a cell with almost all the mutations it needs to be cancerous still requires two distinct chemical signals in order to proliferate without restraint. Call those signals Growth Factors A and B. Our cell is able on its own to produce only Growth Factor A. Someday a new mutation may confer the ability to produce Growth Factor B, but that might take a long time.

Among our cell’s millions of neighbors, though, at least one might develop the ability to secrete Growth Factor B sooner, providing the ingredient our original cell needs to start dividing rapidly. If our cell had to wait to acquire a full deck of cancer-causing mutations on its own, the potential cancer might never appear. But with help from a neighbor, the cell could become cancerous more quickly.

Identifying such non-obvious pathways to cancer, using insights from game theory, could suggest clues for new strategies to interfere with cancer’s progress.

“The hypothesis of cooperation among tumor cells … provides a new framework for therapeutic design,” the Axelrods and Pienta wrote recently in the *Proceedings of the National Academy of Sciences.*

Other researchers have also begun to investigate the cancer-game theory connection. French scientists, writing recently in the journal *Biosystems,* outline a game theory approach to analyzing the chemistry of cancer cell migration, for example. So just as game theory has provided a better understanding of the evolution of life, it may help doctors improve the prospects for defeating one of life’s greatest enemies.