Mathematics of Cellular Evolution and Some Biomedical Applications

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Background: Two Types of Genes

There are two types of genes whose evolution we would like to understand because of these genes' important role in cancer. *Tumor suppressor genes* protect cells from acquiring malignant properties. If a genetic mutation inactivates one of the copies of such a gene, the other copy will still protect the cell from becoming malignant. Therefore, in the context of this pathway, it takes two independent genetic "hits" to transform a cell. *Oncogenes* work differently. A specific mutation in any of the two copies of such a gene can turn on a malignant function, making the cell cancerous. It takes only a single genetic hit to turn on this mechanism of cancerous transformation.

Many cancers evolve as a chain of several events that can include mutations in one or both of these types of genes. In this talk we will look at the mathematical methods to study the evolution of cancerous populations and concentrate on these two gene types as building blocks of cancer.

The Moran Process of Cellular Turnover

Cellular populations are sometimes described by means of the so-called Moran process. Assume that there are N cells that undergo discrete rounds of divisions and deaths. In each round, one division and one death occur. There are two types of cells, which we will refer to as "wild type" (type A) and "mutant" (type B) cells. All wild type cells are characterized with a constant division rate, r_A , and a constant death rate, d_A . Similarly, mutants have a constant division rate, r_B , and a constant death rate, d_B , where in general, $r_A \neq r_B$ and/or $d_A \neq d_B$. For each update, a cell is selected for division with a probability that is proportional to its division rate. For example, if there are m mutants and $N - m$ wild type cells in the system, the probability that a mutant cell will divide is given by

$$P(\text{mut. div.}) = \frac{mr_B}{(N - m)r_A + mr_B},$$

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and the probability that a wild type cell will divide is given by $P(\text{w.t. div.}) = 1 - P(\text{mut. div.})$. A division is followed by a death, with probabilities proportional to cells' death rates (formulated similarly). The newly produced offspring of the cell that divided then replaces the dead cell, and the total population remains at N . In the simplest case, the progeny cell retains the type of the parent cells. If mutations are included, the progeny cell may be of a different type compared to the parent cell.

If we are interested in oncogenes (or, more generally, the production of one-hit mutants), we can study the statistics and dynamics of mutant generation and spread; we can assume that the mutants can be advantageous (e.g. $r_B > r_A, d_B = d_A$), neutral ($r_B = r_A, d_B = d_A$), or disadvantageous (e.g. $r_B < r_A, d_B = d_A$). In the context of tumor suppressor genes (two consecutive mutations) we can study the timing of the generation of two-hit mutants.

This basic process is as well understood as it is unrealistic [4, 7]. Adding more complexities leads to interesting mathematical problems and opens up possibilities to answer some biologically relevant questions.

Spatial Moran Process

One important modification is to include a network of interactions. A reproducing cell can only replace a dying cell if they are connected by an edge of a network. In particular, a geometric network can be used to describe 1D, 2D (Figure 1), or 3D spatial systems. Do such spatial interactions speed up or slow down evolution? In the context of tumor-suppressor genes, the result is that under geometric networks, double-hit mutants are produced faster (and this can be explained intuitively) [1, 5]. When it comes to one-hit mutants (such as mutations in oncogenes), the answer is less straightforward: spatial systems may have fewer or more mutants compared to nonspatial systems of the same size.

Figure 1. Nonspatial (a) and spatial (b) Moran process.

Cellular Hierarchies

Even if we don't consider mutations, not all cells are created equal. In real tissues, we can distinguish the so-called stem cells (SCs) and differentiated cells (DCs). Oversimplifying, we can say that SCs can divide into two SCs, two DCs, or one of each. Differentiated cells do not divide at all. What happens if we add cellular hierarchies to the basic Moran process (so, in the presence of a single type of mutation, there are now four types of cells)? Does this hierarchical structure change the speed of evolution? It turns out that it has an effect that is opposite of that described above. Cellular hierarchies slow down evolution considerably [6]. Perhaps this is one of the reasons the organs of multicellular organisms often have a hierarchical structure: this is a type of protection against cancer.

Cooperation and Defection

Cells in organs can cooperate. For example, suppose two consecutive mutations that occur in the same cell make this cell very advantageous. It could happen that two cells with complementary mutations, if they are found in each other's proximity, can share the products of the mutated genes, and both act as a very advantageous cell. Does cooperation speed up evolution? Yes, absolutely [3]. But cheating (defection) can speed up evolution even more!

Random Environments

So far, all the properties conferred by genetic mutations were fixed. For example, a disadvantageous mutant would always have a reduced division rate. This is a simplification which does not take into account the randomness of the environment. Depending on time and/or space, a mutant could have a higher or lower division rate compared to the wild type. What consequences does this have for the evolutionary process? Some very counterintuitive results can be found in this area [2], which will be presented in the lecture.

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Credits

Figure 1 is from [5].

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