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### Computer Simulation of Survival of Mutants under Non-Selective Condition

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The horizontal transmission of drug resistance (DR) markers from genetically modified foods (GMO) to intestinal bacteria and their persistence are important issues in the recent debate on the safety of GMO-derived food. This paper deals with the latter question, i.e., whether bacteria which once

acquired DR from GMO-derived food (though this event has not been unequivocally demonstrated) can persist in the overwhelming number of resident bacteria in the intestines.

The simulation was performed based on the following premises. The bacterial flora consisted of a single species. The replication rate was the same for the wild type and the mutant, and there was no selection advantage for either. The

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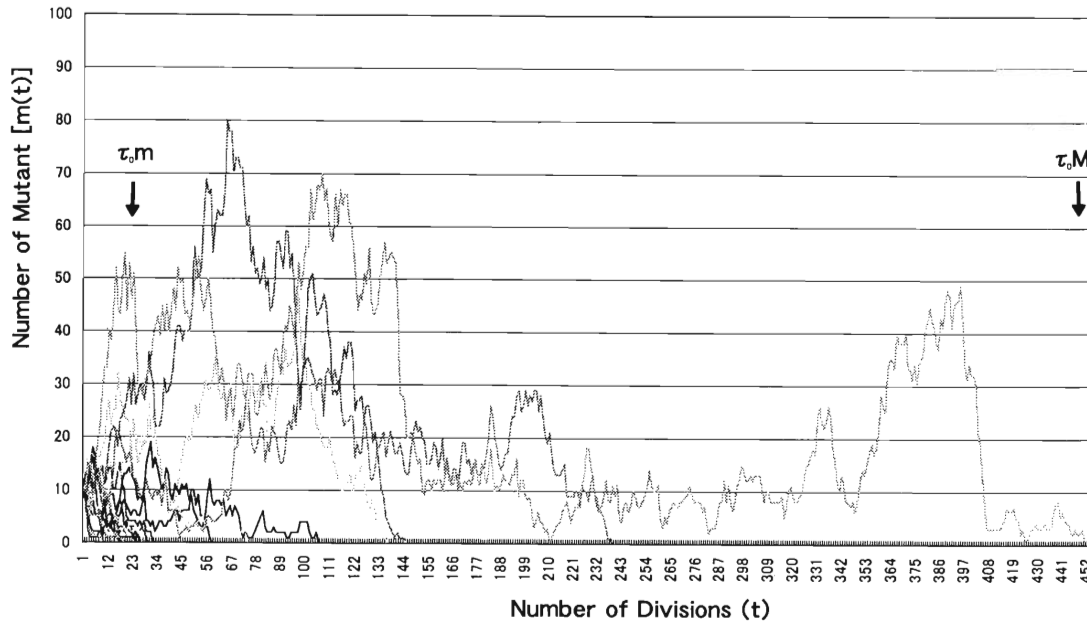


Fig. 1. Simulation of persistence of mutant.  $C = 1,000$ ,  $w(0) = 990$ , and  $m(0) = 10$ . Number of simulations was 50. The  $\tau_{0,m}$  and  $\tau_{0,M}$  values are indicated.

number of bacteria in the flora was constant. The above premises were expressed by using the following four formulae:

$$w(t) + m(t) = w(0) + m(0) = C \quad [1],$$

where  $w(t)$  and  $m(t)$  are numbers of wild type and mutant bacteria at time  $t$ ,

$$w(t+1) = 2w(t) - w_r(t) \quad [2],$$

$$m(t+1) = 2m(t) - m_r(t) \quad [3],$$

where  $w_r(t)$  and  $m_r(t)$  are numbers of wild type or mutant bacteria removed randomly from the flora (mechanically or by death) from time  $t$  to  $t + 1$ , and

$$w_r(t) + m_r(t) = C \quad [4]$$

as the total number of bacteria in the flora is constant.

The simulation was performed by using a Sun Ultra5 computer (Micro Sun, Ltd., Palo Alto, Calif., USA) and C language.

Figure 1 shows 50 simulations performed for a condition in which  $C = 1000$ ,  $w(0) = 990$ , and  $m(0) = 10$ . The time in which complete disappearance of the mutant occurred, i.e.,  $t$  for  $m(t) = 0$ , was called complete disappearance time  $\tau_0$ .  $\tau_0$  was variable from one simulation to another. In one simulation, the mutant did not disappear even after 452 divisions. The mean of  $\tau_0$  values was expressed by  $\tau_{0,m}$ , and the maximum  $\tau_0$  value by  $\tau_{0,M}$  (as expected, this value will increase with the trial number). Figure 2 shows the relation between  $C$  and  $\tau_{0,m}$  (closed triangles) and that between  $C$  and  $\tau_{0,M}$  (open triangles) in the condition where only one mutant bacteria appeared in the flora, i.e.,  $w(0) = C - 1$  and  $m(0) = 1$ . Examined  $C$  values were 100, 300, 600, 800, and 1,000, and number of trials was 100.

The following observations were made.

- (1) The mutant disappears in a finite length of time.
- (2)  $\tau_{0,m}$  is independent of  $C$ .
- (3)  $\tau_{0,M}$  increases with  $C$ .

When a mutant bacteria appears in a flora, it is eliminated within a finite time. The mean of  $\tau_0$  values obtained from multiple trials ( $\tau_{0,m}$ ) is constant irrespective of the size of the flora. However, the longest time ( $\tau_{0,M}$ ), among flora, required for elimination of the mutant increases with the size of the flora.

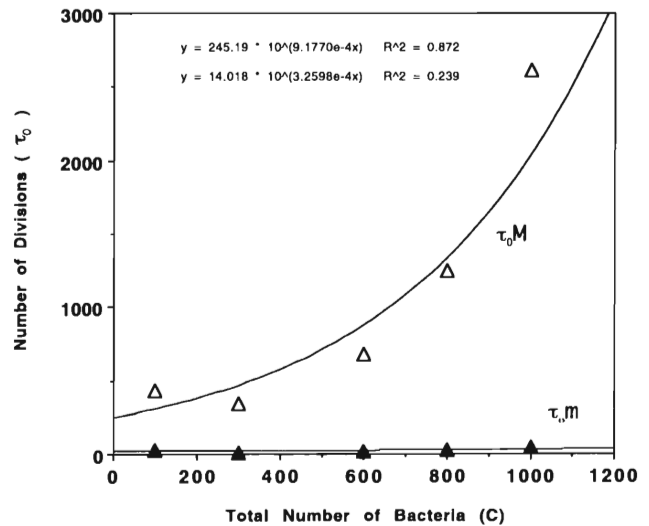


Fig. 2. Relation between size of flora and  $\tau_{0,m}$  and  $\tau_{0,M}$  values. Number of simulations was 100.

Though we used a computer in this report, we can probably solve the problem analytically, because the curves in Fig. 1 suggest that the problem can be reduced to a model of random walk with one outlet. We can make a similar computation for a situation where mutants come up one after another or for a situation where the species in question competes with other species.

Because the problem is simple, the above prediction can be checked experimentally by using a chemostat with a device to keep the total number of bacteria constant.

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