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Mathematical Modeling of Mutation Rate and Population Size

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ABSTRACT: Assuming F_n to be the probability that the system will fail in the future when it is now at population level n, I had obtained a recurrence relation and solved it completely for all values of n in three different cases. Obtaining the value of $1 - F_n$, I computed F_1 for which I had computed the optimal value. The calculation of F_n and minimum value of F_1 are dealt in detail in this paper. From these calculations, we can understand an important concept regarding the shifting of proliferation to hyper-mutation of cells.

Keywords: Population Level, Relative Rate, Steady Rate, Recurrence Relation, Lagrange Parameters.

I. INTRODUCTION

Beginning with a somewhat impressionistic version of this model, in which exposure to antigen (with T-cell help implied) starts the process by activating a medium affinity B-cell of a population, one mutation away from high affinity. Such a cell proliferates after activation at steady rate λ, while the antigen is killing the infected organism at steady rate r. The population of interest is one mutated site, out of m relevant DNA sites, away from the high-affinity Ab, whose production neutralizes the Ag and so annuls the death rate r; we assume that the mutation rate P_n is controlled by the population size n. We want to choose the repertoire $\{P_n\}$ to minimize the probability F_1 that the initially activated system fails due to death of the host organism before settling into steady high-affinity production.

II. DEVELOPING THE MODEL

Let F_n be the probability that the system will fail in the future when it is now at population level n. The next event can either be death of the host at relative rate r, proliferation at relative rate λn, or mutation of one of the m relevant DNA sites at relative rate mnP_n. But m – 1 of the m mutations produce a still lower affinity cell, which is eliminated from the population and so we have the following recurrence relation

$$F_n = \frac{r}{\lambda n + mnP_n + r} + \frac{\lambda n}{\lambda n + mnP_n + r} F_{n+1} + \frac{(m-1)nP_n}{\lambda n + mnP_n + r} F_{n-1} \quad (2.1)$$

III. SOLUTION TO THE RECURRENCE RELATION

I now choose$\{P_n\}$to minimize F_1 by imposing the "equations of motion" with Lagrange parameters, and since these equations can be written as linear in P_n, optimal strategy will be achieved if either $P_{\min} = 0$ or $P_{\max} = \infty$ (finite $P_{\max}$ gives similar results) at each n. There will then be one—and only one, it can be shown—switch point, say at $n = n_0$, we have

$P_n = 0,\ n \le n_0$ (3.1) and

$P_n = \infty,\ n > n_0$ (3.2).

Now using (3.2) in (2.1) by observing the fact as $P_n = \infty$, the first two terms in the right hand side of (2.1) vanish whereas the doesn't vanish giving

$$F_n = \frac{m-1}{m} F_{n-1},\ n > n_0 \quad (3.3)$$

If $n = n_0$ then from (3.1), we have $P_n = 0$. Using this in (2.1), we get

$$F_{n_0} = \frac{r}{\lambda n_0 + r} + \frac{\lambda n_0}{\lambda n_0 + r} F_{n_0+1},\quad n = n_0 \quad (3.4)$$

Similarly if $n < n_0$ using (3.1) in (2.1), we get

$$F_n = \frac{r}{\lambda n + r} + \frac{\lambda n}{\lambda n + r} F_{n+1},\quad n < n_0 \quad (3.5)$$

Now taking $n = n_0 + 1$ in (3.3), we get

$$F_{n_0+1} = \frac{m-1}{m} F_{n_0} \quad (3.6)$$

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Substituting (3.6) in (3.4), we have $F_{n_0} = \frac{r}{\lambda n_0 + r} + \frac{\lambda n_0}{\lambda n_0 + r} \times \frac{m-1}{m} F_{n_0}$ from which we get $F_{n_0} = \frac{mr}{\lambda n_0 + mr}$ (3.7)

Now from (3.3), we get $F_n = \frac{m-1}{m} F_{n-1} = \left(\frac{m-1}{m}\right)^2 F_{n-2} = \left(\frac{m-1}{m}\right)^3 F_{n-3} = \cdots = \left(\frac{m-1}{m}\right)^{n-n_0} F_{n_0}$ (3.8)

where F_{n_0} is given by (3.7).

Similarly, for $n < n_0$, (3.5) can be written as

$$1 - F_n = 1 - \frac{r}{\lambda n + r} - \frac{\lambda n}{\lambda n + r} F_{n+1} = \frac{\lambda n}{\lambda n + r}\left(1 - F_{n+1}\right) = \frac{n}{n + \frac{r}{\lambda}}\left(1 - F_{n+1}\right) \quad (3.9)$$

Using the pattern obtained in (3.9) for n up to $n_0 - 1$ and using (3.7) we have

$$1 - F_n = \frac{n}{n + \frac{r}{\lambda}} \times \frac{n+1}{\left((n+1) + \frac{r}{\lambda}\right)} \times \frac{n+2}{\left((n+2) + \frac{r}{\lambda}\right)} \times \cdots \times \frac{n_0 - 1}{\left((n_0 - 1) + \frac{r}{\lambda}\right)}\left(1 - F_{n_0}\right)$$

$$= \frac{(n_0 - 1)!}{(n-1)!} \times \frac{\left((n-1) + \frac{r}{\lambda}\right)!}{\left((n_0 - 1) + \frac{r}{\lambda}\right)!} \times \frac{\lambda n_0}{\lambda n_0 + mr}, \; n \le n_0 \quad (3.10)$$

In particular, for n = 1, we have

$$F_1 = 1 - \left(\frac{r}{\lambda}\right)! \frac{(n_0 - 1)! \times \lambda n_0}{\left((n_0 - 1) + \frac{r}{\lambda}\right)! \times (\lambda n_0 + mr)} \quad (3.11)$$

Now in the denominator of (3.11) we find the term $\left((n_0 - 1) + \frac{r}{\lambda}\right)!$

Hence F_1 in (3.11) will attain minimum if $n_0 = m\left(1 - \frac{r}{\lambda}\right)$ (3.12).

Substituting the optimal value of n_0 obtained in (3.12) to (3.7), we find that

$$F_{n_0} = \frac{mr}{\lambda n_0 + mr} = \frac{mr}{m(\lambda - r) + mr} = \frac{r}{\lambda} \quad (3.13)$$

IV. CONCLUSION

In this paper, I had derived the expression for the probability that the system will fail in the future when it is now at population level n. After doing so, I had obtained F_1 and tried to minimize it. From the minimum value of F_1 obtained in (3.13), we see that one doesn't shift from proliferation to hyper-mutation until each of the m closest sequences has had its chance.

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