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A Competition Model for Tumour Growth

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Abstract

A simple competition model, which couples Gompertz and logistic growth mechanisms, is presented in order to study the growth pattern of two different types of tumour cells growing together. It is shown that the model prediction is in fairly good agreement with the experimental finding.

1. INTRODUCTION

Cancer research has been one of the major areas of medical research for a long time. However, still there are many aspects of tumour growth which are not well understood by medical scientists. In a recent experimental study [9], human tumours were grown as xenografts in nude mice and the differences in the rates of growth at contralateral sites were examined. It was found that the tumour pieces implanted into the dorsal left flanks of the mice grew into significantly larger tumours than the ones implanted into the dorsal right flanks. This was true for the tumour types such as colon carcinoma Colo-205 and gastric carcinoma MKN 45. A somewhat similar finding was noted for mouse tumours too. It was not clear why there should be such anatomical differences in growth rates. But it was hypothesized that it could be due to the effect of morphogenetic gradients as in the case of control differentiation during ontogeny.

In some other experimental investigations controversial results have been reported in regard to the effect of interferons on human myelogeneous cell line (HL-60) established from the peripheral blood of a person with acute promyelocytic leukemia. Certain studies [2,4] find that these cells are insensitive to human alpha and beta interferons. However, there are other studies [10] which show that alpha and beta interferons are effective in the inhibition of HL-60 and do not concur with data in [4]. A convincing explanation either to justify both sets of results or to repudiate one of them is still not available.

Further, most of the research has concentrated on homogeneous tumour growth. It is known that [1] stage A2 prostatic cancer is composed of a heterogeneous group of tumours. But there are not many pathologic studies which investigate this heterogeneity. The question is, can one come up with mathematical models for tumour growth which could be useful for the experimentalists? Since tumour growth experiments can produce lots of quantitative data, it should be possible to construct such models. In this paper,

we look at the problem of heterogeneity in tumour growth and construct a mathematical model. This model is shown to satisfy some of the experimental findings available. We believe that experimentalists could find this simple model very useful.

2. MATHEMATICAL MODEL

One of the growth curves that has been widely used [3, 7, 11] in characterising tumour growth is the S-shaped Gompertzian growth curve. This curve is given by the equation,

$$N(t) = \kappa \exp[-\exp(a - bt)] \tag{1}$$

where $N(t)$ is the total number of tumour cells at time t, κ, the carrying capacity and a, b are appropriate constants. The expression in (1) can be thought of as the solution of the set of differential equations,

$$\frac{dN(t)}{dt} = \gamma(t)N(t) \tag{2}$$

and

$$\frac{d\gamma(t)}{dt} = -\alpha\gamma(t), \tag{3}$$

where α is a positive constant. If the growth curve is a simple exponential growth curve $\gamma(t)$ will be just a positive constant in (2).

It can be argued that there is no particular reason to expect the Gompertz curve to show any wider range of fitting power to a given data set than any other S-shaped curve with three constants. For example, the logistic curve which can be written as,

$$N(t) = \kappa/[1 + \exp(a - bt)] \tag{4}$$

is also S-shaped and has three constants κ (having the same meaning as κ in (1)), a and b. This curve can also be employed to fit any given data. But it should be noted that there is a subtle difference between the Gompertz and the logistic curves. Although, both curves have points of inflection when $t = a/b$, the ordinate that corresponds to Gompertz is κ/e while that corresponds to logistic is $\kappa/2$. This means, that in the cases of Gompertz and logistic the point of inflection occurs when approximately 37% and 50% respectively, of the total growth has been realized. So, it is really up to the experimentalist to decide on the best fitting growth curve for his or her experimental data by determining where the point of inflection should be.

In order to understand the experiments reported in [9] (as mentioned in the previous section), where larger tumours in the left flank were seen than in the right flank, we tried to fit the data obtained for gastric carcinoma MKN 45 by different types of growth curves. It is seen (figures 1 and 2) that Gompertz type curves are the best fitting curves for these data (number of tumour cells are assumed to be proportional to tumour volume). Further, the only difference between the Gompertz expression in the left flank and that of the right

is the constant κ. The values of the constants a and b in both cases do not change. This implies that the left flank has a larger carrying capacity than the right. So, one could argue that the anatomical differences in growth rates of any particular type of tumour cells are essentially due to differing carrying capacities of different regions and nothing else.

Now, we will focus on the problem of two types of tumour cells growing together. In this case, the two cell populations must compete for vital nutrients, growth factors, etc. A study consisting of Ehrlich ascites cells (of different types) proliferating in the peritoneum of mice was carried out in [5]. The types of cells examined were diploid and tetraploid cells. It was found [5, 6, 8] that no matter what the initial distribution of cells were, at the steady state, always, 96% of the total number of cells were diploid and 4% were tetraploid. Can a mathematical model predict this finding? In order to answer this we construct the following competition model:

$$\frac{dN_1}{dt} = rN_1(\ln \kappa - \ln N_1) - \alpha N_1 N_2 \tag{5}$$

$$\frac{dN_2}{dt} = sN_2(L - N_2) - \beta N_1 N_2 \tag{6}$$

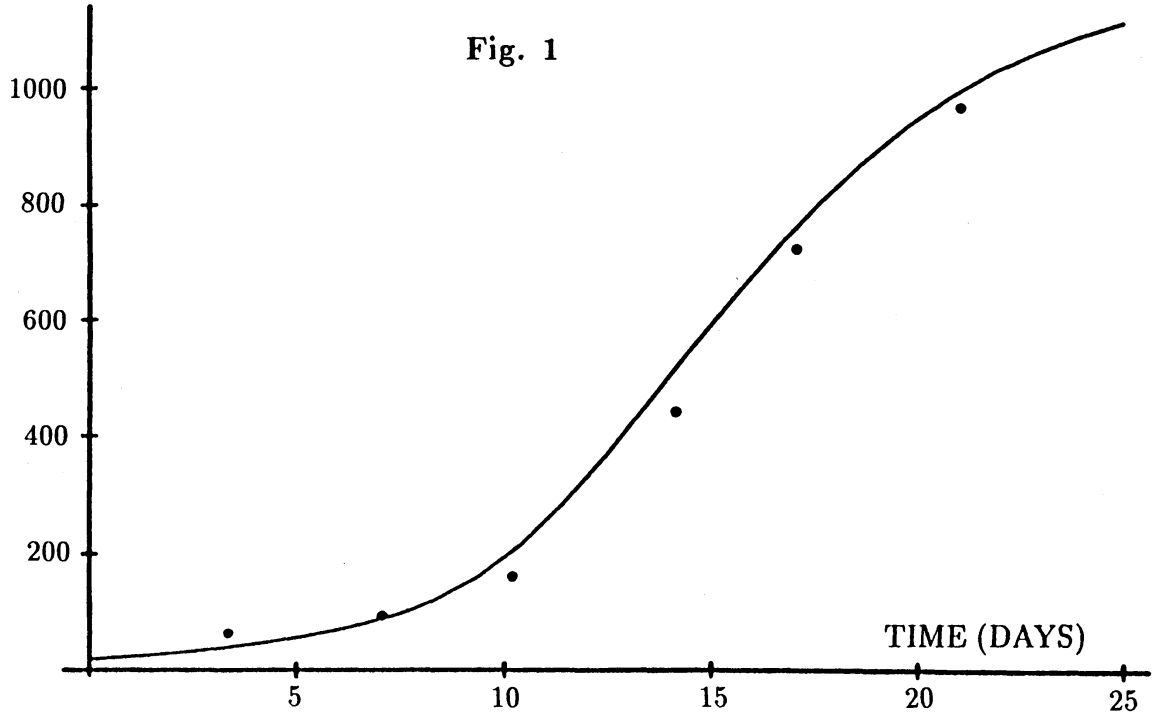
where N_1 and N_2 are the number of diploid cells and tetraploid cells respectively at any given time t. The terms $\alpha N_1 N_2$ and $\beta N_1 N_2$ relate to the competition between the cell populations with α and β being positive constants. As can be noted from equations (5) and (6), we have taken the growth of diploid cells to be Gompertz growth and of tetraploid cells to be logistic growth. This is simply because the growth data of diploid cells growing on their own and of tetraploid cells growing on their own given in [5] were found best fitted by Gompertz and logistic curves, respectively.

In order to analyse the model, let us consider the phase plane diagram for the equations (5) and (6) (figure 3). It is clear that there are four steady states with (0, 0), $(\kappa, 0)$ and $(0, L)$ being the trivial ones. The only non-trivial steady state is given by the point of intersection of the curves,

$$N_2 = \frac{r}{\alpha}\ln(\kappa/N_1) \quad \text{and} \quad N_2 = L - \frac{\beta}{s}N_1$$

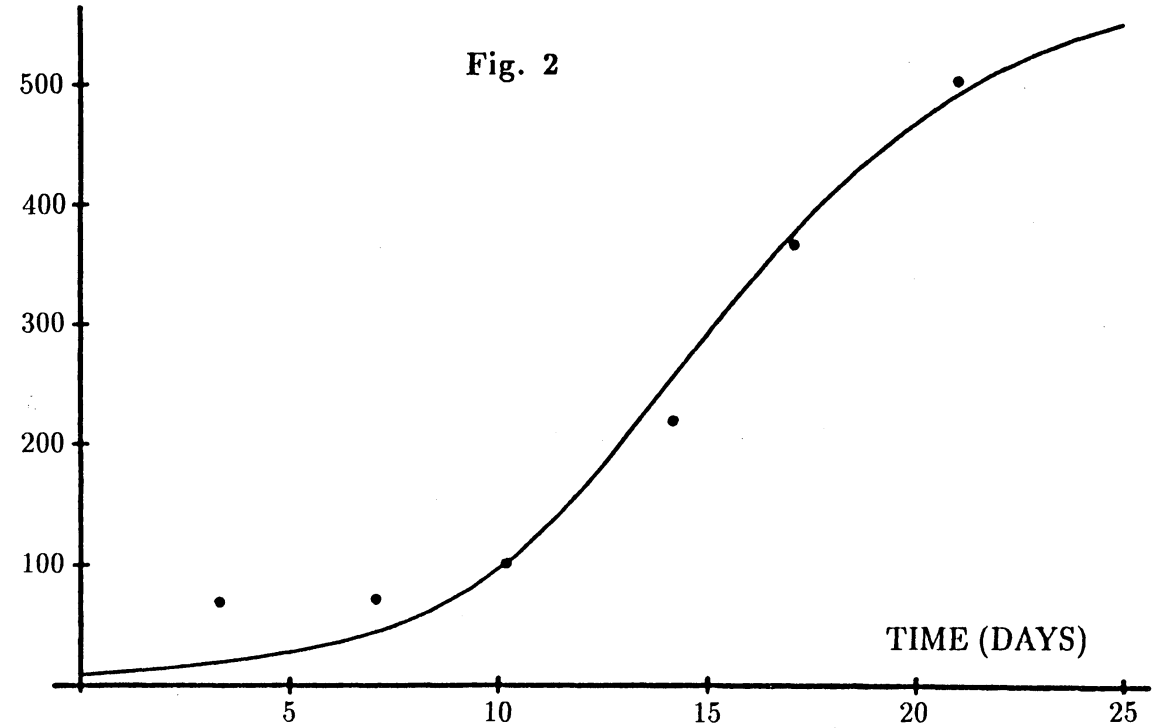
and it can be easily checked that this steady state is asymptotically stable. So, this could be the steady state which relates to 96% to 4%.

Fig. 1



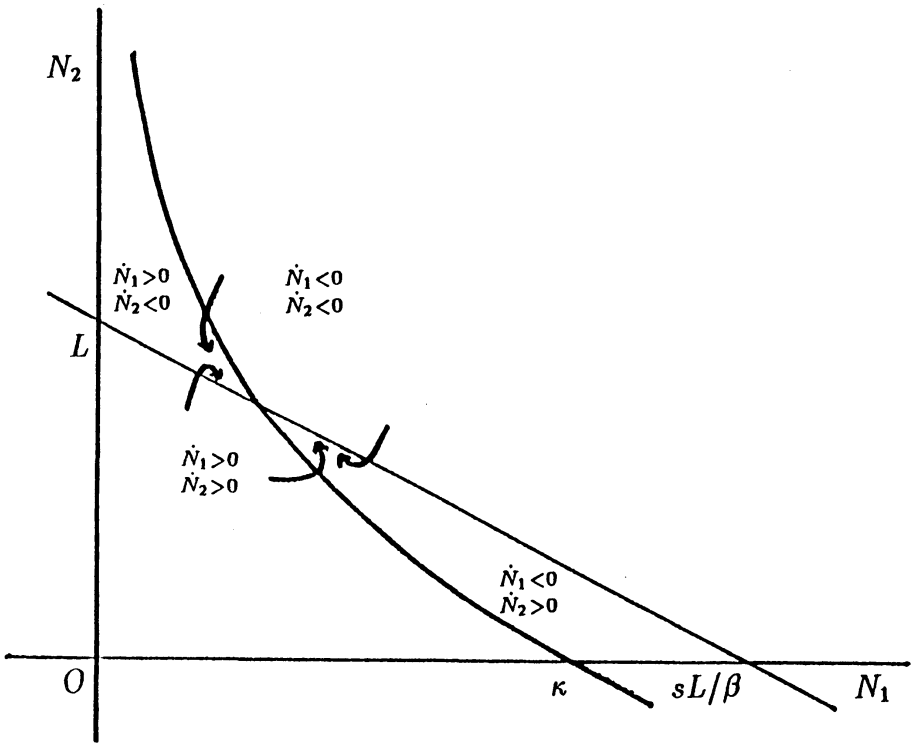
Growth curve of MKN45 tumor xenograft in left flank.

Fig. 2



Growth curve of MKN45 tumor xenograft in right flank.

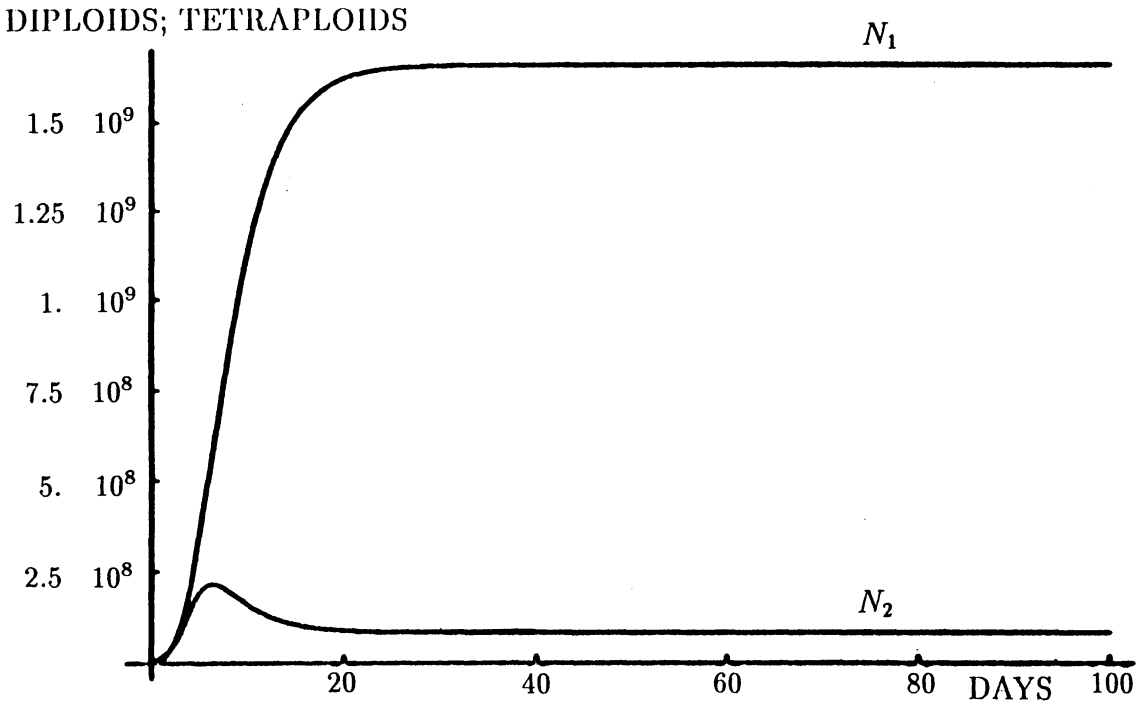
Fig. 3



Phase plane diagram for the Competition model.

In [5], the growth data for diploid and tetraploid cells growing together are also given. Using this data set along with the data set when these cell populations are growing on their own, we are able to estimate the constants κ, L, r, s, α and β. It should be pointed out that for this estimation procedure only data up to **8 days** are used. In the experiments the steady state is reached after **day 20**. This means that our estimation is done at the initial transient phase of the growth process. Is it possible for our model to predict what happens after day 20 using these (up to 8 day) estimates? We obtain the answer to this by numerically solving the coupled ordinary differential equations (5) and (6) using the estimated values for the constants. The result is presented in figure 4 and it is obvious that the steady state is reached after day 20. But, what percentage are the diploid cells of the total cell population at steady state? We find this to be around 91%. Compare it to the value (96%) obtained in experiments. Clearly, the model's prediction is very good, if one makes allowances for the experimental errors, estimation errors and so on.

Fig. 4



Numerically simulated growth curves for diploid and tetraploid cells.

3. CONCLUDING REMARKS

In this short paper, a simple competition model is developed to describe the growth of two different types of tumour cells growing together. We demonstrated that the model can predict the experimental finding fairly well. It should be pointed out that this model can be easily expanded or modified if one needs to have more than two different cell types. For example, if the tetraploid cells springing from diploid cells through endomitotic differentiation are to be considered in a study, one can simply assume them to be a third type of cells. Then, all we need, to modify the mathematical model are an extra growth equation (in differential form) for this third type of cell and a loss term in the growth equation for diploids. Therefore, we feel that the model presented here could be a very valuable quantitative tool to the experimentalists.

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