Journal of Applied Mathematics & Bioinformatics, vol.3, no.2, 2013, 171-179
ISSN: 1792-6602 (print), 1792-6939 (online)
Scienpress Ltd, 2013

Stochastic Model to Calculate Cell Reproduction

Paolo Rocchi[1]

Abstract

Empirical observations show how the growth of cell population complies with the Gompertz law, however this statistical distribution has not been satisfactory explained in relation to the internal biological kinematics so far.

The description of algorithms and mathematical models that compute the behavior of biosystems is a noteworthy field of research in bioinformatics, and this contribution calculates the growth of cell tissues using the Boltzmann-like entropy function. The parameters of the present mathematical model should enable to examine pathological deviations too, namely the results could be applied to analyze normal tissues and pathological tissues such as tumors.

Mathematics Subject Classification: 60J20, 92B15, 62P10

Keywords: Cell reproduction, Gompertz law

[1] IBM - via Shangai 53, 00144 Roma, Italy,
LUISS University - via Salvini 2, 00198 Roma, Italy, e-mail: procchi@luiss.it

Article Info: *Received* : March 21, 2013. *Revised* : April 25, 2013
Published online : June 30, 2013

1 Focus of Interest

The embryonic and postnatal growth of organs and the growth of the whole organism [1], the regeneration of tails in lizards and newts obey the Gompertz law. As early as 1934 it is observed the Gompertz curve in cancer tissues transplantation; and the current literature confirms the same trend for dozen kinds of tumors [2]. Experimental data bring evidence how apparently different phenomena comply with the same curve. Some attempts to illustrate this trend in mathematical terms emerged during the last decades [3], [4]. These calculations revolve around the speed of the mitosis which although approximates the statistical trend and does not spell out the exact reproduction function. As second the speed does not reveal the reason of the Gompertz curve whose meaning remains rather obscure. In fact it is intriguing that that curve, originally conceived as the `law of human mortality', gives such an accurate description of biological growth.

The present paper tackles this kind of problems through a novel mathematical method. It is introduced the stochastic or Boltzmann-like entropy, which is symmetrical to the function calculated by Boltzmann in thermodynamics, and this function is used for calculating the cell reproduction.

2 Introduction to the Boltzmann-like Entropy

Let the stochastic continuous time system S is finite

$$S = (A_1, A_2, \dots A_m) \tag{1}$$

Where the generic state A_i (i = 1, 2, ... m) depends on the probability P_i

$$A_i = A(P_i) \tag{2}$$

Speaking in general, the system S may be more or less stable in the generic state A_i; in other words, S easily leaves A_i or otherwise rarely abandons A_i. If the system frequently abandons A_i, we tell the state is *reversible*; if the system does not

evolve from A_i, we say this state is *irreversible.* E.g. A patient may be regarded as S in the disease state A_d. If the patient recovers in a few times, the state A_d turns out to be reversible. If the patient does not get better, we say A_d irreversible.

I quantify the ability of the system to evolve from the generic state A_i using the *stochastic* or *Boltzmann-like entropy*

$$H_i = H(A_i) \tag{3}$$

Equation (3) provides the *reversibility and irreversibility* (R/I) of S in the state A_i by means of real numbers (see demonstration in Appendix) [5].

3 Calculation of the Cell Reproduction

3.1 - A cell may be seen as the stochastic system S_C that assumes a certain number of states; for example, the nutrition state A_u, the growing state A_w, the moving state A_v, the decease state A_d, the reproduction state A_r and so forth

$$S_C = (A_u, A_w, A_v, A_d, A_r \quad \ldots) \tag{4}$$

3.2 - The reversibility/ irreversibility of each state specifies the capability/ incapability of the cell S_C to operate in that state. As an example, suppose the nutrition state A_u is irreversible, than the cell S_C is stable in the nutrition state and overfeeds. Conversely A_u reversible means that the cell scarcely feeds itself.

3.3 - The organelles of the cell S_C cooperate; that is to say, each organelle contributes to the effectiveness or to the failure of the states A_u, A_w, A_v,…. Postulate (A.2) holds that one can derive the entropy of the generic state from the entropies of the components. For example, the vibratile cilias make a ciliate protozoon to move. From (A.2) one calculates the capability H_V of the moving state with the entropies H_{Vg} of n cilias

$$H_V = H(A_v) = \sum_{g=1}^{n} H_{Vg} \tag{5}$$

The more the generic cilia g is effective, the more its entropy H_{Vg} is great and the

more the overall cell is able to move.

3.4 - We apply criterion **3.3** to the reproduction state A_r; hence, the greater the entropy H_R of A_r and the more the reproduction process thrives; the smaller H_R and the less the cell is able to reproduce.

Because a cell activates the states A_u, A_w, A_v,…. at the same time, we can assume that the states A_u, A_w, A_v,…. are equally likely over a large interval of time. The classical theory takes the probability of A_r as the ratio between the favorable cases F_r and the possible cases N

$$P_r = F_r / N \tag{6}$$

Because of the impossibility of counting N, one can calculates the stochastic entropy in function of the favorable cases F_r, hence one can simplify the entropy function H_R that takes the following form

$$H_R = H(F_r) = \ln (F_r) \tag{7}$$

In consequence of this simplification, equation (7) ranges from 0 to $+\infty$, whereas (A.3) [see Appendix] varies between $-\infty$ and 0. The substitution of H_R=$H(P_r)$ with H_R=$H(F_r)$ is clean because the present paper means to investigate the trend of the cell growth rather than to calculate the precise values of H_r. As second, I remind the important precedent of Ludwig Boltzmann who elucidates the third thermodynamic law by means of the absolute number of complexions and does not use the classical probability. In short, I am following the same method of Boltzmann by using (7) instead of (A.3).

3.5 - The reproduction of the cell starts with the preparation of the genetic material until the stage of duplication. The operations of the organelles affect other organelles during this period of time, and these humming activities can be modeled by means of the *mesh*, where the generic component k stimulates a set of components, which in turn affect the next and so on.

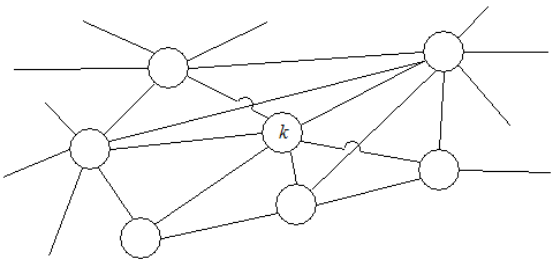

Figure 1

One can calculate the behavior of the mesh through the following steps.

3.6 - The activity of the cell expands from the first stages to the conclusion of the mitosis. I state the activity of the generic organelle *k* spreads out and can quantify its very capability by the entropy H_{Rk} that regularly increases during time

$$H_{Rk}(t) = \lambda_k t \tag{8}$$

3.7 - The organelle *k* interacts with the organelle *h*; their overall capability increases due to this connection, hence the multiplication of H_{Rk} with H_{Rh} provides the effectiveness of this couple

$$H_R(t) = f(H_{Rk}, H_{Rh}) = \left(H_{Rk} \bullet H_{Rh}\right) \tag{9}$$

The accurate demonstration of the multiplication law for entropy may be found in [6].

3.8 - The generic organelle *k* does not influence the other components with a uniform rule, namely the biological reactions are different along the various directions. By way of illustration, *k* works with the component *i* and this in turn influences *s*, and afterward *u*, because the organelles make a mesh.

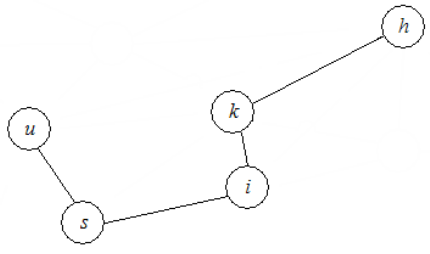

Figure 2

The process stemming from *k* reaches one, or two, or three up to *n* components as in Figure 2. I apply function (9) to every chain and obtain the overall reproductive capability of the cell

$$H_R(t) = \left(H_{Rk} + H_{Rg}H_{Rh} + H_{Rk}H_{Rl}H_{Rd} + H_{Rk}H_{Ri}H_{Rs}H_{Ru} + ...\right) \qquad (10)$$

The entropy of each part varies linearly in time as established in (8), thus (10) becomes

$$H_R(t) = \left|\lambda_1 t + \lambda_2 t^2 + \lambda_3 t^3 + \lambda_4 t^4 + ... + \lambda_n t^n\right| \qquad (11)$$

3.9 - The interactions among the parts are not one-way, hence the product (H_{Rg} H_{Rl} H_{Rd}) regards the combination *gld* and also *gdl*. Symmetrically the chain generated by *l*, which I calculate by (H_{Rl} H_{Rg} H_{Rd}), covers *lgd* and *ldg*. The same discourse should be repeated for *d*. In conclusion the member (H_{Rg} H_{Rl} H_{Rd}) = $\lambda_3 t^3$ quantifies the processes accomplished by 3! configurations, hence I divide each term in (11) by its appropriate factorial

$$H_R(t) = \left|\frac{\lambda_1 t}{1!} + \frac{\lambda_2 t^2}{2!} + \frac{\lambda_3 t^3}{3!} + \frac{\lambda_4 t^4}{4!} ... + \frac{\lambda_n t^n}{n!}\right| \qquad (12)$$

3.10 - For the sake of simplicity, I assume that all the coefficient λ_i (i=1,2...n) be equal, and obtain

$$H_R(t) = \lambda\left|\sum_{k=1}^{n}\frac{t^k}{k!}\right| \qquad (13)$$

As *n* large, $H_R(t)$ approximates the exponential

$$H_R(t) = \lambda e^t \qquad (14)$$

I substitute (14) into (7) and get

$$F_r(t) = ae^{\lambda e^t} \qquad a > 0 \qquad (15)$$

This means that the number of cells increases according the Gompertz law, while the constants a and λ depend on the special kind of tissue. The present approach absolutely provides the exponential-exponential function and gets close the Gompertz curve.

4 Conclusion

The present paper revolves around two mathematical tools that are the structural model of the cell kinetics and the Boltzmann-like entropy which calculates the elements of that structure. Some researchers use the entropy function in the biological domain, but preferably they calculate the Shannon's entropy [7]

The final outcome matches with a broad statistical inference basis and enlightens the causes of the Gompertzian trend. The present logical frame basically holds that (15) derives from the high number of interconnections of the cell organelles.

Equation (15) does not relay on special constraints, thus it covers normal and pathological cells, embryonic and mature tissues etc. It reunifies the comprehension of different forms of biological development. In particular the overall arrangement of the cell in Figure 1 remains true in the tumor cell when the control of the process misses and the reproduction goes on unchecked [8], [9].

As the Boltzmann entropy is a powerful weapon to grasp the behavior of the thermodynamic system, but does not support specific computational processes, similarly the current work illustrates the reasons for the cell growth while the numerical determination of H_R and F_r does not appear manageable.

Acknowledgements. I would like to thank professor Roberto Chignola for his illuminating assistance and useful discussion.

Appendix

The purpose of the present section is the calculation of the entropy (3), when (1) and (2) are true.

The entropy quantifies the reversibility and irreversibility of S in the generic state A_i under the following conventions:

i) $H(A_i)$ is 'high' if A_i is very irreversible.

ii) $H(A_i)$ is 'low' if A_i is highly reversible.

The demonstration is based on three assumptions; the first pair of assumptions pinpoints the mathematical properties *i* and *ii* just declared. The mechanism of R/I dictates the third and most telling axiom.

1) The stochastic system S has m finite states as in (1).
2) The stochastic entropy $H(A_i)$ is an increasing function of P_i in accordance with *i* and *ii*.
3) Experience shows that the reversibility and irreversibility of a component contributes to R/I of the whole system, namely the entropy of each sub-state influences the entropy of the global state. Take for example the patient who has the diseased organ *x*. If *x* is not very bad, than the patient soon recovers and A_d is rather reversible. If *x* is far-gone unhealthy, than A_d is very irreversible. In conclusion, the entropy of the organ *x* effects on the overall entropy, in particular the more the entropy $H(A_{dx})$ of the organ is great, the more $H(A_d)$ increases. This phenomenon can be translated in the following mathematical axiom.

Let the state A_i consists of n co-operating sub-states

$$A_i = (A_{i1}\ AND\ A_{i2}\ AND\ A_{i3}\ AND \quad ....\ AND\ A_{in}) \qquad \text{(A.1)}$$

The sum of the sub-state entropies provides the entropy H_i if A_i

$$H_i = H(A_i) = H\,(A_{i1}) + H\,(A_{i2}) + ... + H\,(A_{in}) = H_{i1} + H_{i2} + ... + H_{in} \qquad \text{(A.2)}$$

From hypotheses 1), 2) and 3), one can prove that the *stochastic entropy* [5] is the logarithm

$$H_i = H(P_i) = a \ln (P_i) \qquad a > 0 \qquad \text{(A.3)}$$

The form and the significance of (A.3) are symmetrical to the Boltzmann entropy that quantifies I/R for a thermodynamic sample of gas.

References

[1] A.K. Laird, Evolution of the Human Growth Curve, *Growth*, **31**, (1967), 345-355.

[2] S.E. Shackney, *Tumor Growth, Cell Cycle Kinetics and Cancer Treatment*, McGraw Hill,1993.

[3] S.I. Rubinow, *Cell Kinetics*, *Math. Models of Molecular Biology*, L.A. Segel (ed.) Cambridge Univ. Press, 1978.

[4] X.L. Xu, The Biological Foundation of the Gompertz Model, *Intl. Journal of Biomedical Computing*, **20**, (1987), 35-39.

[5] P. Rocchi, Boltzmann-like Entropy in Reliability Theory, *Entropy*, **4**, (2002), 142-150.

[6] P. Rocchi, Calculations of System Aging through the Stochastic Entropy, *Entropy*, **8**, (2006), 134-142.

[7] S. Sieniutycz, Extremum Properties of Entropy to Determine Dynamics of Growth and Evolution in Complex Systems, *Physica A: Statistical Mechanics and its Applications*, **340**(1-3), (2004), 356-363.

[8] N. Bellomo, A. Bellouquid and M. Delitala, Mathematical Topics on the Modelling Complex Multicellular Systems and Tumor Immune Cells Competition, *Math. Models Methods Appl. Sci.*, **14**(11), (2004), 1683-1733.

[9] R.A. Gatenby, T.L. Vincent and R.J. Gillies, Evolutionary Dynamics in Carcinogenesis, *Math. Models Methods Appl. Sci.*, **15**(11), (2005), 1619-1638.