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INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS

EVIDENCE OF CHAOTIC DYNAMICS
DURING THE ONSET OF CANCEROUS GROWTH
OF HEMATOPOIETIC SYSTEM

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EVIDENCE OF CHAOTIC DYNAMICS DURING THE ONSET OF CANCEROUS GROWTH OF HEMATOPOIETIC SYSTEM *

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ABSTRACT

By means of new techniques for time series it is shown that periodic chronic myelogenous leukemia (CML) is in fact not periodic but rather chaotic.

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Chaodynamics [1] is a new branch of modern science which deals with deterministic chaos in non-linear dynamical system. There are now many such systems known in physics, chemistry and biology [2,3].

For a dynamic system to be chaotic the non-linearity is required to guarantee a sensitive dependence on initial conditions and the dissipativity to guarantee a boundedness of trajectories on the attractor. This makes behaviour of solutions very complicated. In what follows it will be established that a malignant growth of formed elements of blood fulfills such conditions.

To this end we exploit new methods developed for the analysis of experimental data obtained from a single variable time series [4,5]. These methods allow one to distinguish between a random or deterministic nature of dynamics in real systems. They also give criteria for the existence of strange attractors as well as information on such quantitative properties of attractors as dimensionality.

Using such techniques the existence of low-dimensional fractal attractors was found from experimental data on hydrodynamic turbulence [6], chemical turbulence [7], climatology [8] and even the activity of the human brain [9].

Hematopoiesis or in other words the blood forming system is the best model system to study normal as well as malignant cell growth, in general [10]. In a normal mammal circulating levels of the formed element of blood (the white and red blood cells, platelets and lymphocytes) are maintained at stationary levels.

It is generally believed that there exists a self-maintaining pluripotential stem cell population (PPSC) in the marrow capable of producing committed cells for the erythroid, myeloid or tromboid lines. These populations are not self-maintained but depend on a cellular flux from the PPSC for their continued integrity. Cells at the committed level undergo four to five divisions before losing their nuclei to enter a maturation phase. Cells are then released from this marrow maturational compartment to enter the blood as a mature white blood cell, red blood cell, or platelets.

In addition to the feedback from circulating blood cells to the PPSC, control mechanisms are believed to exist within the PPSC itself, acting to control cell population numbers [11].

A more detailed discussion as well as scenarios for the onset of leukemic growth of blood forming system are presented elsewhere [12].

There is a number of well documented pathological states characterized by cyclic oscillation of blood components [13-16]. It is interesting to note that one often speaks of periodic oscillations for peripheral lymphocytes, monocytes and platelets number but without precise specification. So it is believed that the CML has a periodic variant with a vague period of 30 to 70 days.

We show using clinical data of white blood cell count (WBC) of a 12 year old girl with the periodic CML [13] that the leukemic growth in that case is a deterministic process with a chaotic dynamics.

Let $X(t)$ be the corresponding time series. Then a multidimensional phase potrait can be constructed by a procedure proposed by Ruelle [17]. The idea which is justified by embedding theorems [4,18] is as follows: For almost every observable $X(t)$ and time delay τ an m-dimensional portrait constructed by the variables

$$X(t),\ X(t+\tau,\ldots,\ x[t + (m-1)\tau]$$

will have the same properties as those constructed from a measurement of N independent variables, if $m \geq 2N + 1$. In Fig.1 a characteristic view of two-dimensional phase potrait of embedding leukemic attractor is presented. This clearly exhibits the complexity of the underlying motion on the attractor.

A power spectrum indicates whether the system is periodic, quasi-periodic or of random nature. The last case is characterized by the broad-band structure of the spectrum. As is shown in Fig.2 the motion on the leukemic attractor is really of random nature.

But a continuous power spectrum with the broad-band structure does not imply in general that such random motion is chaotic in the sense of its deterministic origin. To establish this fact we need to evaluate dimensionality of the underlying leukemic attractor. To do this the integral correlation function $C(r)$ should be calculated [5,8]

$$C(r) = \frac{1}{N^2} \sum_{\substack{i,j=1 \\ i \neq j}}^{N} \theta(r - |\underline{X}_i - \underline{X}_j|) \quad , \qquad (1)$$

where θ is the Heaviside function, $\theta(x) = 0$ if $x < 0$ and $\theta(x) = 1$ if $x > 0$. Vectors $\underline{X}_i(t)$ stand for the points of phase space whose coordinates are $X(t_i),\ldots,X[t_i + (m-1)\tau]$. One shows [5] that for a small r

$$C(r) \cong r^d \qquad (2)$$

the dimensionality d of the attractor is therefore given by the slope of $\log C(r)$ versus $\log r$. This allows to look for a dependence of dimensionality of attractor d on the number of space variables m. In the case of deterministic chaos this dependence is saturated for a finite dimensionality d [8]. And as can be observed Fig.3 shows that this is really the case for the leukemic attractor. For the case of Fig.1 we have $d = 3.04$. But it means that the value m beyond which the saturation is observed will provide the minimum number of variables necessary to model the behaviour represented by the attractor.

A more detailed analysis with some important bilogical consequences as well as other dynamical characteristics of the leukemic attractor for the case presented here, such as Liapunov exponents, Kolmogorov K-entropy will be published elsewhere [19].

Thus using only time series record of spontaneous oscillations of WBC count we were able to deduce some intrinsic properties of the leukemic growth. This paper represents the first attempt to treat a cancerous growth as the dynamical system represented by time series and possessing a chaotic behaviour [20]. To proceed further, a new quality of experimental and clinical data will be required. In the case of leukemia it means that new techniques should be developed to observe blood component oscillation counts for a long enough time. This will probably bring not only the possibility of detecting cancer early but can make even a prevention possible.

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[20] See also [12] where the Lorenz plot for data presented here was constructed and a simple tent-like model possessing a chaotic dynamics was proposed.

Figure captions:

Fig. 1. Two dimensional phase portraits constructed from time series of a 12 year old girl with the CML [13]. The time delay is $\tau = 4T$ respectively $\tau = 6T$, where T = 1 week.

Fig.2. The power spectrum of the same time series as in Fig. 1.

Fig. 3. The dependence of dimensionality d on the number of phase space variables m = 2, ..., 10 with the saturation at $d=3.04$. This value determines the dimension of the leukemic attractor in Fig.1.

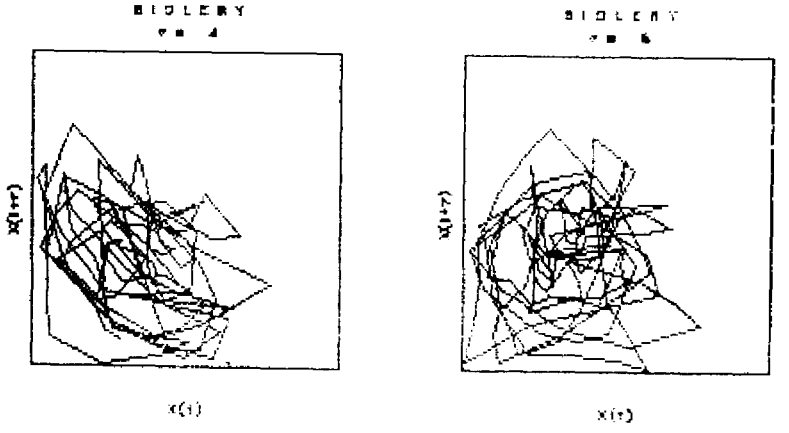

Fig.1

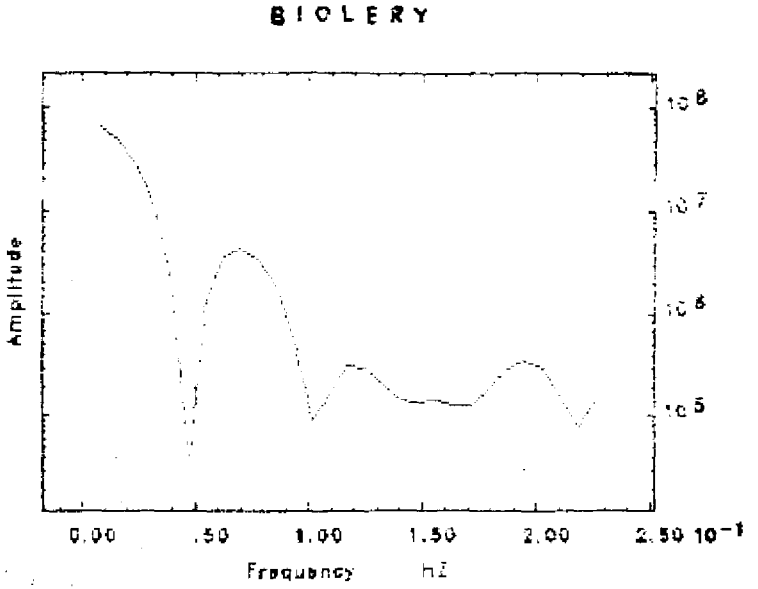

Fig.2

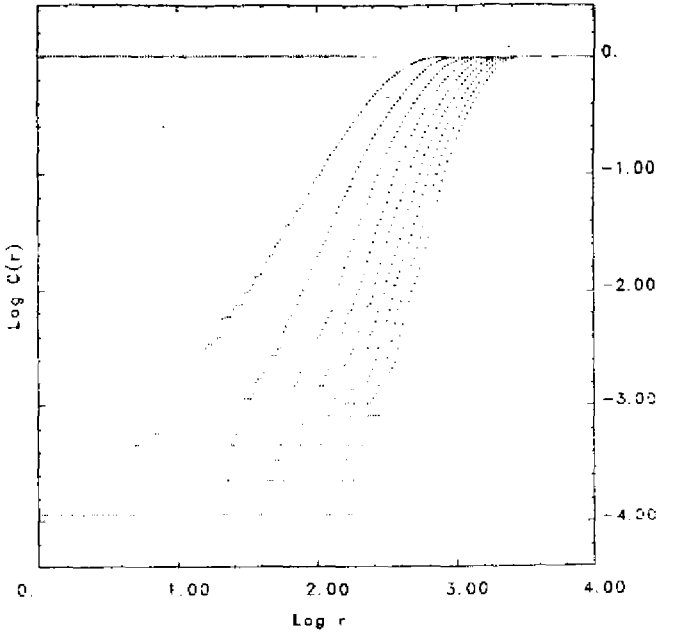

Fig.3