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ERGODIC PROBLEMS IN BIOLOGY

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1. Introduction. It is obvious that biological systems are extremely complicated and our methods of measuring biological parameters are far from to be precise. This is the usual explanation of the fact that experimental graphs describing the behavior of biological processes are irregular and chaotic. The purpose of the present lecture is to give another (or rather one more) explanation of this phenomenon. The main idea is to show that in typical biological systems there exists a continuous (non atomic) invariant measure such that the corresponding measure theoretical systems are ergodic, mixing and even exact in the sense of Rohlin.

We start from recalling some recent results concerning the existence of invariant measures. Then we shall apply them to the following biological problems:

- 1) the population growth of a single species,
- 2) the production of blood cells.

We shall study these problems mainly with the discrete time using the technique of difference equations. Only in Section 5 we shall mention some open problems related with a delay differential equation.

2. Existence of invariant measures. Denote by X a topological Hausdorff space. By a measure on X we mean any probabilistic measure defined on the σ -algebra of Borel subsets of X . A measure μ is called continuous if it vanishes on points, that is $\mu(\{x\}) = 0$ for each singleton $\{x\} \subset X$. In [11] and [12] it is proved the following

Theorem 1. Let $T: X \rightarrow X$ be a continuous mapping. Assume that there exist two nonempty compact sets $A, B \subset X$ and an integer $n \geq 1$ such that

$$T^n(A) \cap T^n(B) \supset A \cup B, \quad A \cap B = \emptyset.$$

Then there exists on X a continuous measure μ which is invariant and ergodic with respect to T .

In the special case when $n = 1$ and X is an interval of the real line ($X = \Delta \subset \mathbb{R}$), the measure μ may be chosen in such a way that the dynamical system (Δ, μ, T) is isomorphic to the dyadic transformation $x \rightarrow 2x \pmod{1}$. In this case it is also possible to derive from Theorem 1 the following ([10], [12])

Theorem 2. Let T be a continuous mapping from an interval Δ (bounded or not) into itself. Assume that there exists an integer $n \geq 1$ and a point $x_0 \in \Delta$ such that

$$T^{3n}(x_0) = x_0, \quad T^n(x_0) \neq x_0.$$

Then there exists on Δ a continuous measure μ which is invariant and ergodic with respect to T .

From the Birkhoff ergodic individual theorem it follows, immediately, that under conditions of Theorem 2 there exists an uncountable set S ($\mu(S) = 1$) such that each trajectory starting from a point $x \in S$ is simultaneously "turbulent" and "stationary". We call a trajectory $\{T^n(x)\}$ turbulent if its limit set

$$L(x) = \bigcap_{n=1}^{\infty} \text{cl} \{T^n(x), T^{n+1}(x), \dots\}$$

is infinite (In particular it is not a periodic orbit; cf. [20]). A trajectory $\{T^n(x)\}$ is called stationary if for each bounded continuous function $f: \Delta \rightarrow \mathbb{R}$ there exists the limit

$$\lim_n \frac{1}{n} \sum_{k=0}^{n-1} f(T^k(x)) .$$

Both properties are essential from the biological point of view. The first one is responsible for the irregular character of the process under consideration. The second one enables us to define the time average of each biological parameter related with the process.

Interesting properties of transformations with periodic points of period three were discovered by A.N. Sharkovsky [21] and discussed in several recent papers: [3], [10], [13] and [16]. There remain, however, many open questions. For example, does there exist under assumptions of Theorem 2 a continuous invariant measure μ such that the dynamical system (Δ, μ, T) is exact in the sense of Rohlin [19]? The problem is of some practical value. An affirmative answer would imply a

highly irregular behavior of trajectories starting from an uncountable set $S \subset \Delta$.

3. Population growth of a single species. Consider a population with discrete generations. In ideal conditions, when every individual can mature, the growth of the population is described by the geometrical progression $x_{n+1} = \lambda x_n$ where x_n is the number of individuals in the n -th generation and λ is a constant coefficient larger than 1. In real conditions most of individuals die before they are able to create a new generation. This is due to the limitation of food, existence of competing species, communicable diseases and many other factors which became relevant when x_n is large enough. Thus in the real conditions λ is a decreasing function of x_n . For the sake of simplicity it is often assumed that λ is a linear function, that is: $\lambda = r - qx_n$. This leads to the recurrence equation $x_{n+1} = (r - qx_n)x_n$. After changing the variables $u_n = qx_n/r$ we obtain its simplified form

$$(1) \quad u_{n+1} = ru_n(1 - u_n) .$$

For $0 \leq r \leq 4$ the right hand side $T_r(u) = ru(1 - u)$ maps the unit interval into itself. An easy computation shows that for $r \gg 3.83$ the mapping T_r admits a periodic point of period three. According to Theorem 2 this implies that, for $3.83 \leq r \leq 4$, there exists on $[0,1]$ a continuous measure which is invariant and ergodic with respect to T_r .

Another, more realistic assumption concerning λ is the

"logistic" formula $\lambda = re^{-qx_n}$. This leads to the equation $x_{n+1} = rx_n e^{-qx_n}$ which after substitution $u_n = qx_n$ may be written as

$$(2) \quad u_{n+1} = ru_n e^{-u_n}.$$

The right hand side $S_r(u) = ru e^{-u}$ maps the half line $[0, \infty)$ into itself and has a periodic point of period three for $r \gg 42.8$. Thus for such r 's there exists on $[0, \infty)$ a continuous measure which is ergodic and invariant under S_r .

Summarizing our results we conclude that, for r sufficiently large, both systems (1) and (2) describing the population growth of a single species admit an uncountable family of stationary turbulent trajectories. In both cases the biological meaning of the parameter r is the same; it is equal to the maximal (net) reproductive rate. An experimental proof of the chaotic behavior of the size of a population with the high net reproductive rate (insects: *Lucilla cuprima*) was given by A. Nicholson [17].

Periodic and "chaotic" trajectories of difference equations (1) and (2) have been studied by many authors; see for example [4], [5], [7], [8], [14], [15] and [22]. In comparison with the previous results which require rather complicated and deep technique, Theorem 2 enables us to predict "stationary turbulence" by solving a simple numerical problem: equation $T^3(u) = u$.

4. Production of blood cells. The major blood forming organ is the bone marrow. From the bone marrow the blood

cells pass to the blood vascular system. Here they carry oxygen from the lungs to the body tissues (red cells) protect the body against infections (white cells) and participate in the process of blood clotting (platelets). The blood cells are not everlasting. After a time they are destroyed either by the natural aging process or by some accidental factors (blood diseases, infections,...). An important property of the bone marrow is the ability to change the production when the number of blood cells changes.

Denote by x_n the number of blood cells of fixed type (for example red cells) at time n . We have

$$(3) \quad x_{n+1} - x_n = -d_n + p_n$$

where d_n is the number of cells which are destroyed in the time interval $[n, n+1]$ and p_n is the number of cells which are produced during the same period. We shall assume that both d_n and p_n are functions of x_n , namely

$$(4) \quad d_n = \sigma x_n, \quad p_n = (kx_n)^s e^{-qx}$$

where k, q, s are positive constants and $0 < \sigma < 1$. The first assumption is quite natural (constant destruction rate) and the second coincides with recent experimental results due to Dr. M. Ważewska-Czyżewska. Setting $u_n = qx_n$ and substituting (4) into (3) we obtain

$$(5) \quad u_{n+1} = (1 - \sigma)u_n + (cu_n)^s e^{-u} \quad (c = kq^{\frac{1-s}{s}}) .$$

This simple difference equation enables us to model the behavior of the blood cell population in many clinical cases. We shall show some typical examples without going into biological details. Fix $c = 0.47$, $s = 8$ and consider (5) for a few values of σ .

(a) Normal conditions: $\sigma = 0.1$. Each trajectory $\{u_n\}$ starting with $u_0 \geq 2.5$ converges to the stationary solution $\bar{u} = 15.4 \dots$. If $u_0 \leq 2.4$, then $\lim_n u_n = 0$. These facts have a simple biological meaning. In normal conditions the number of blood cells is stable. However, when it is too small (for example after a heavy haemorrhage) the organism must die.

(b) Disease: $\sigma = 0.4$. Now there exists the unique periodic solution of period two:

$$\dots, \quad u_n = 15.5\dots, \quad u_{n+1} = 10.7\dots, \quad u_{n+2} = 15.5\dots,$$

and any trajectory starting with $u_0 \geq 3.4$ is asymptotically periodic. Exceptions are trajectories which finish in the unstable fixed point $\bar{u} = 12.6\dots$. If $u_0 \leq 3.3$, then $\lim_n u_n = 0$. This behavior of trajectories explains several biological facts first of all the existence of stable oscillations in blood cell population. It is also worthwhile to observe the adaptation of the "ill" system to the new destruction coefficient which now is four times as large. In the case (a) the time average of the number of blood cells was equal to 15.4... and now we have

$$\lim_n \frac{1}{n} \sum_{k=0}^{n-1} u_k = \frac{1}{2} (15.5 + 10.7) = 13.1\dots$$

which is not much worse.

(c) Severe disease: $\sigma = 0.8$. With this value of σ the right hand side of equation (5)

$$S(u) = (1 - \sigma)u + (cu)^8 e^{-u}$$

maps the interval $[4.2, 15.1]$ into itself and admits a periodic point of period three. Thus there exists on this interval a continuous measure which is ergodic and invariant with respect to S . This implies the existence of an uncountable family of stationary turbulent trajectories which remain in the interval $[4.2, 15.1]$. When $u_0 \leq 4.1$, we have $\lim_n u_n = 0$. There is an experimental evidence of chaotic oscillations in blood cell populations; see for example [18]. Equation (5) gives a simple mathematical explanation of this phenomenon.

It is necessary to remark that the model of blood cell population given by equation (5) is far from to be correct. The weakness lies in the discretization of time. There is no biological reason for assuming that the blood is produced in portions. We can obtain much more realistic model replacing the difference equation (5) by a similar delay differential equation. Such equation will be discussed in the next Section.

5. Invariant measures for delay differential equations.

Let C_h be the space of continuous functions $v: [-h, 0] \rightarrow \mathbb{R}$ with the supremum norm topology. Consider a functional differential equation (see: [6])

$$(6) \quad u'(t) = f(u_t) \quad 0 \leq t < \infty$$

where $f: C_h \rightarrow R$ is a given function and u_t denotes the restriction of the unknown function $u: [-h, \infty) \rightarrow R$ to the interval $[t-h, t]$. We shall suppose that f is sufficiently regular, for example Lipschitzean

$$|f(v) - f(w)| \leq L \|v - w\|_{C_h} \quad v, w \in C_h.$$

Then, for each $v \in C_h$. equation (6) admits exactly one solution $u: [-h, \infty) \rightarrow R$ which is continuous on $[-h, \infty)$ differentiable on $[0, \infty)$ and satisfies the initial value condition

$$(7) \quad u(t) = v(t), \quad -h \leq t \leq 0.$$

Given f , consider the mapping $T_f: C_h \rightarrow C_h$ defined by the formula

$$(T_f v)(t) = u(t + h), \quad -h \leq t \leq 0$$

where u is the solution of (6), (7). If f is Lipschitzean, the mapping T_f is not only uniquely determined on C_h but also continuous and we can describe the properties of equation (6) in terms of T_f . Namely, we say that a measure μ on C_h is invariant (ergodic) with respect to equation (6) if it is invariant (ergodic) under T_f .

Now we shall show an example of a delay differential equation for which, as we conjecture, there exists a continuous ergodic invariant measure. Let us turn back to the problem of the production of blood cells. Denote by $x(t)$

the number of cells (of fixed type) at time t . We have

$$(8) \quad x'(t) = -d(t) + p(t)$$

where $p(t)$ and $d(t)$ denote the instantaneous production and instantaneous destruction at time t respectively. Since the bone marrow needs several days to product a blood cell it is natural to admit that $p(t)$ is a function of $x(t-h)$. Thus instead of (4) we assume that

$$(9) \quad d(t) = -\sigma x(t), \quad p(t) = (kx(t-h))^s e^{-qx(t-h)}.$$

Setting $u = qx$ and substituting (9) into (8) we obtain

$$(10) \quad u'(t) = -\sigma u(t) + (cu(t-h))^s e^{-u(t-h)}.$$

Equation (10) with $s = 0$ was proposed in [23] as a red cell model. In this case ($s = 0$), according to the recent results of S. N. Chow, J. Mallet-Paret [1],[2] J. Kaplan and J. Yorke [9] it admits periodic solutions for certain values of the parameters h and σ . In the case $s > 0$ we have the following

Conjecture. For some positive values of the parameters c , h , s and σ there exists on C_h a continuous measure which is ergodic and invariant with respect to equation (10).

Numerical simulations indicate that this is true for $c = 0.47$, $h = 10$, $s = 8$ and $\sigma = 0.8$.

For other interesting models of blood cell kinetics and references to the literature consult [18], [23], [24], [25] and [26] .

References

- [1] S.N.Chow, Existence of periodic solutions of autonomous functional differential equations, *J.Differential Equations* 15(1974), 350-378.
- [2] S.N.Chow and J.Mallet-Paret, Integral averaging and Hopf's bifurcation, preprint, Lefschetz Center for Dynamical Systems.
- [3] J.Guckenheimer, On the bifurcation of maps of the interval, *Invent. Math.* 39(1977), 165-178.
- [4] J.Guckenheimer, G.Oster and A.Ipaktchi, The dynamics of density dependent population models, *J. Math. Biology* 4(1977), 101-147.
- [5] I.Gumowski and C.Mira, Accumulations de bifurcations dans une récurrence, *C.R.Acad.Sci.Paris, Sér A-B* 281(1975), 45-48.
- [6] J.Hale, *Functional Differential Equations*, Springer Verlag New York 1971.
- [7] F.C.Hoppensteadt and J.M.Hyman, Periodic solutions of a logistic difference equation, *SIAM J.Appl.Math.* 32(1977), 73-81.
- [8] M.V.Jacobson, On the properties of the one parameter family of dynamical systems $x \rightarrow Axe^{-x}$, *Uspehi Mat. Nauk* 31(1976), 239-240.
- [9] J.Kaplan and J.Yorke, On the nonlinear differential delay equation $x'(t) = -f(t, x(t-1))$, *J.Differential Equations* 23(1977), 293-314.
- [10] A.Lasota, On mappings isomorphic to r -adic transformations, *Ann.Polon.Math.* (to appear).
- [11] A.Lasota and G.Pianigiani, Invariant measures on topological spaces, *Boll.Un.Mat.Ital.* 18-B(1977).
- [12] A.Lasota and J.Yorke, On the existence of invariant measures for transformations with strictly turbulent trajectories, *Bull.Acad.Polon.Sci.Sér.Sci.Math.Astronom.Phys.* 25(1977), 233-238.

- [13] T.Y.Li and J.Yorke, Period three implies chaos, *Amer.Math. Monthly* 82(1975), 985-992.
- [14] R.May and G.Oster, Bifurcations and dynamic complexity in simple ecological models, *Am.Naturalist* 110(1976)573-599.
- [15] P.J.Myrberg, Iteration der reellen Polynome zweiten Grades III, *Ann.Acad.Sci.Fenn.Ser.A I*, 366(1963), 1-18.
- [16] M.B.Nathanson, Permutations, periodicity and chaos, *J.Combinatorial Theory Ser.A* 22(1977), 61-68.
- [17] A.J.Nicholson, An outline of the dynamic of animal populations, *Austr.J.Zool.* 2(1954), 9-65.
- [18] J.S.Orr, J.Kirk, K.G.Gray and J.R.Anderson, A study of the interdependence of red cell and bone marrow stem cell populations, *Brit.J.Haemat.* 15(1968), 23-34.
- [19] V.A.Rohlin, Exact endomorphisms of Lebesgue spaces, *Izv. Akad.Nauk SSSR Ser.Mat.* 25(1961), 499-530.
- [20] D.Ruelle and F.Takens, On the nature of turbulence, *Comm. Math.Phys.* 20(1971), 167-192.
- [21] A.N.Sharkovsky, Co-existence of the cycles of continuous mapping of the line into itself, *Ukrain.Mat.Z.* 16(1964), 61-71.
- [22] S.Smale and R.F.Williams, The qualitative analysis of a difference equation of population growth, *J.Math.Biology* 3(1976), 1-5.
- [23] M.Ważewska-Czyżewska and A.Lasota, Mathematical models of the red cell system (Polish), *Matematyka Stosowana* 6(1976), 25-40.
- [24] G.H.Weiss and G.Zajicek, Kinetics of red blood cells following hemolysis, *J.Theoret.Biol.* 23(1969), 475-491.
- [25] T.E.Wheldon, Mathematical models of oscillatory blood cell production, *Math.Biosciences* 24(1975), 289-305.
- [26] T.E.Wheldon, J.Kirk and H.M.Finlay, Cyclical granulopoiesis in chronic granulocytic leukemia: a simulation study, *Blood* 43(1974), 379-387.

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