IS THALASSEMIA A DYNAMICAL DISEASE?

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Abstract

Recently the traditional view of " health " as " regularity" has been challenged, and normality is coinceived as a sort of *constrained randomness* and pathology as a loss of the so called *spectral reserve.Dynamical diseases* would be due to changes in the qualitative dynamics corresponding to bifurcations in the non linear equations describing the system. In this respect, some hematological diseases were modeled in terms of differential-delay equations by assuming a *delayed regulation* of blood cells production. In the present paper the temporal evolution of the hemoglobin destruction rate of 23 thalassemic children is analyzed. The results indicate that these models are to be partialy revised and that Thalassemia can be conceived as a dynamical disease. A relation between the qualitative dynamics of Hb rate of destruction and the clinical evolution is suggested.

1.0 INTRODUCTION

Reiman (1963) described a group of diseases whose symptoms recurred at seven days interval which he called **periodic diseases**. In all of these diseases oscillations appeared in physiological systems not normally characterized by oscillations.

An extension of this concept was introduced by Mackey and Milton (1987) who defined as **dynamical diseases** those diseases occurring in an intact physiological control systems " operating in a range of control parameters that leads to abnormal dynamics".

These authors argued that the qualitative dynamics of a "healthy system " can change due to changes in one or more parameters and that these changes can be conceived as corresponding to bifurcations in the non linear equations describing the system. So, the dynamical diseases may arise because of pathological alteration in underlying control parameters.

From the phenomenological point of view, these diseases occur either when a new periodism appears or when an old " normal" oscillatory pattern is disrupted.

However, Mackey and Milton did not give any interpretation of the concept of "normality": a "normal " or " healthy " system can be either periodical or aperiodical and becomes " abnormal " whenever qualitative changes in its dynamics arise.

On the other hand Goldberg , West et al.(1985) argued that a number of diseases processes and aging itself are characterized by a narrowing of the power

spectrum with a decrease of high frequency components and that this behavior contrasts with the broad inverse power-law spectra seen in normal conditions. They suggested (Golberg and West, 1987) that, although transitions to and from the steady state and periodic behavior may be deleterious " chaos may be the normal state of affairs ": the healthy status is a sort of **organized variability** or of **constrained randomness**.

So, dynamical diseases are characterized by a loss of the physiological variability and by the appearance of pathological usually low frequency periodicities(see also Rensing, 1987).

From a more general and philosophical point of view, **complexity** may be the salient feature shared by all " healthy " systems.

A full discussion of this problem can be found also in Pool (1989).

1.1 Dynamical diseases and blood cell regulation

Several periodical hematological diseases were observed e.g. autoimmune hemolitic anemia (Mackey and Glass 1977), cyclical neutropenia (Mackey 1977), aplastic anemia (Mackey and Milton 1987), cyclic trombocytopenia (Morley 1970). It was also shown that oscillatory dynamics in hematological control systems arise from the application of chemotherapic agents in normal dogs (Kennedy 1970) or of marrow-seeking radioactive compounds in normal mice (Gurney, 1981).

These " diseases" are interesting from the system dynamics point of view because they are susceptible of being modeled in terms of differential-delay equations. For example, Mackey and Milton(1987) suggested a model of hematopoiesis based on the hypothesis of a delayed feedback mechanism, and explained the 30-70 days periodic oscillation of neutrophil counts in some form of mielogenic leukemias by assuming that neutrophil production is a delayed decreasing function of increasing neutrophil density. If time delay is of order of 5 days then the system is stable. If the delay is increased the system becomes unstable and a cascade of bifurcations occurs until chaos is observed at 20-days delay.

Murray (1989) recognized that these results are to be considered rather as a "modelling exercise",and that their practical relevance is not definitely demonstrated.

From the experimental point of view the main difficulty is that the two processes of *destruction* and *production* of blood cells are not directly observable.

In this respect Thalassemia(a genetic disease in which an anomalous and ineffective hemoglobin is produced)can be considered as a sort of natural experimental situation. In fact, thalassemic people are given transfusion therapy in order to maintain the mean exhogenous hemoglobin level above 10 mg/dl. This Hb level is thought to inhibit bone marrow autonomous blood production and to block ineffective hematopoiesis so preventing progressive bone marrow expansion and

other dangerous side effects.So, the spontaneous blood production is blocked and substituted by transfusions, and one can directly observe the time evolution of the destruction rate of exhogenous Hb which in turn is a marker of red blood cells consumption rate.

Figure 1 shows that this rate is not constant but varies almost unpredictably both within and between subjects.

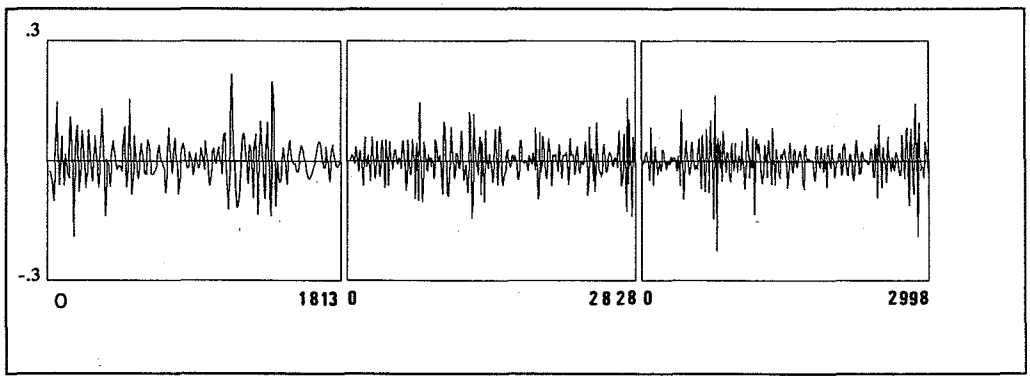

Figure 1 : three typical time series of Hb rate of destruction(for details see the text)

Despite this, one can notice that physicians ,in order to scheduling the time of the next transfusion, usually formulate a raw prediction of the rate of Hb destruction in the days after the transfusion. So, at the n-th transfusion setting, they compute the future daily consuption of Hb by taking the difference between the level reached after the previous transfusion and the actual pretransfusional level and by dividing it by the interval between the last and the actual transfusion. This figure is then projected into the near future and the time of the next transfusion is scheduled so that the Hb level will not, hopefully, fall below 10 mg/dl.

This procedure, which is well radicated in medical practice, may be a cue that physicians, albeit unconsciuosly, perceive that at least a short term prediction is sound. This means that they implicitly assume that the rate of Hb destruction is not merely random.

So, in the present work the temporal evolution of Hb destruction rate of a set of thalassemic children is analyzed in order to:

1. estabilish whether fluctuations in the rate of Hb destruction are to be considered as random or as chaotic,

2. verify whether the Mackey's and Milton's hypothesis of delayed regulation can be applied to red blood cells,

3. judge whether there is sufficient evidence for considering Thalassemia as a

3. judge whether there is sufficient evidence for considering Thalassemia as a dynamical disease,

4. suggest some relationships between typologies of temporal evolutions of Hb destruction and the clinical evolution,

5. help physicians to rationalize their therapeutic behavior.

2. METHODS AND RESULTS

An analysis of the temporal series of Hb daily consumption of 23 thalassemic children was carried out. Table 1 summarizes the salient features of each case.

CASE	SEX	AGE (years)	RECORD LENGHT (days)	TOTAL NUMBER OF TRANSFUSIONS	AVERAGE INTERVAL BETWEEN TRANSFUSIONS
1	M	16.5	1813	116	15.62
2	F	18.3	2828	172	16.44
3	F	15.7	2918	172	16.96
4	M	15.1	2933	163	17.99
5	M	14.0	3194	193	16.54
6	F	10.7	2046	108	18.94
7	M	13.0	2937	183	16.04
8	F	11.1	2068	104	19.88
9	F	12.2	2056	140	14.68
10	M	17.0	2099	136	15.43
11	M	12.0	2060	102	20.19
12	M	11.6	2037	91	22.38
13	F	14.2	2203	161	13.68
14	M	12.2	2114	149	14.18
15	F	12.5	1823	109	16.72
16	F	12.6	1943	92	21.11
17	F	11.1	1996	115	17.35
18	F	10.0	1964	106	18.52
19	M	9.6	1861	108	17.23
20	F	11.6	2101	98	21.43
21	F	13.2	2282	118	19.33
22	M	12.0	2162	124	17.43
23	M	14.5	2199	135	16.28

Table 1

Since lags between transfusions were not fixed each time series was interpolated by a cubic spline function (de Boor, 1978), and the Hb destruction rate at 10 days intervals was, so, " estimated". Each series was tranformed into a zero mean time

series by subtracting the mean value .

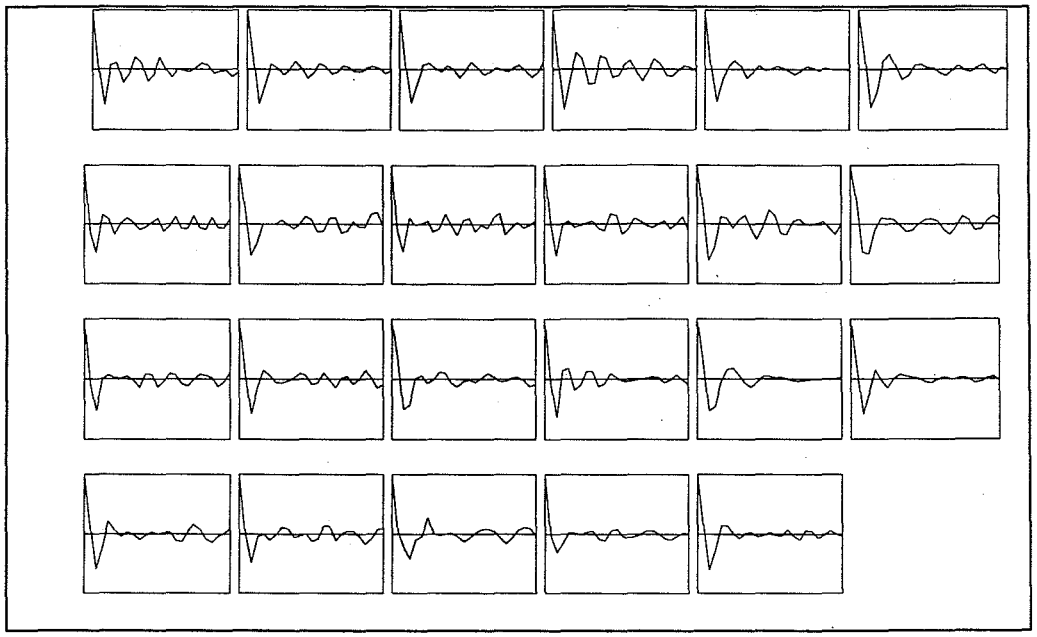

Figure 2. Autocorrelograms (maximum lag = 24)

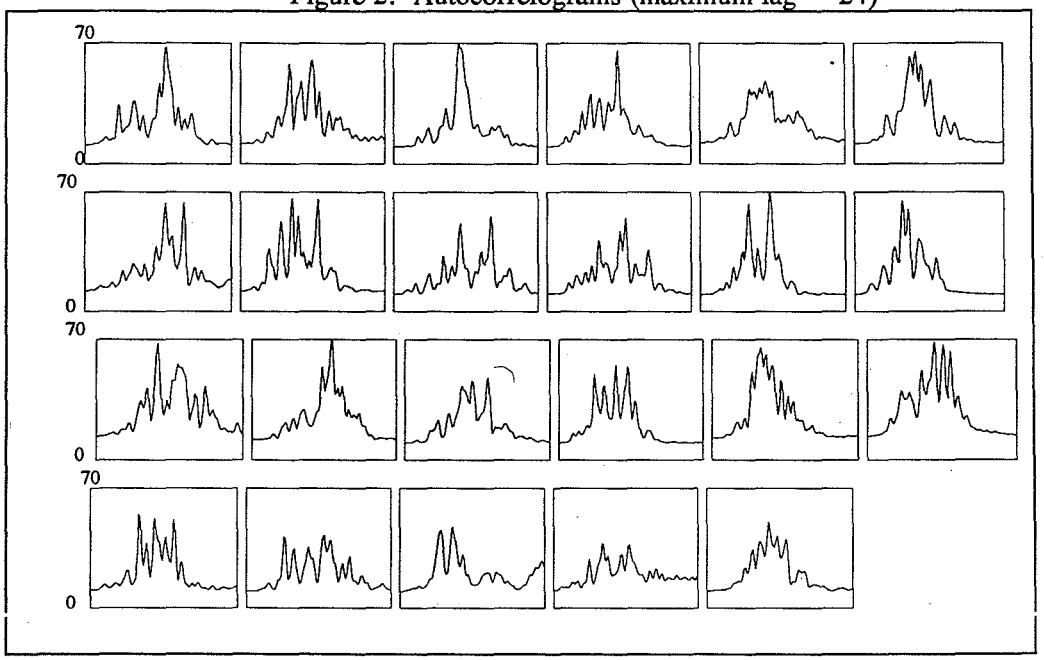

Figure 3: Power spectra

CASE	AR(1)	AR(2)	CONSTANT	RESIDUAL STANDARD DEVIATION	CORRELATION DIMENSION
1	.0189	-.573	-.00086	.04823	2.57
2	.0116	-.553	-.00024	.03819	2.55
3	.0711	-.662	-.00003	.03395	2.20
4	.30434	-.618	-.00003	.03115	2.21
5	.08448	-.532	-.00129	.04432	2.72
6	.36683	-.700	.00207	.04504	0.91
7	-.20618	-.508	.00670	.0374	2.76
8	.4363	-.650	.00040	.0024	1.03
9	-.15533	-.467	.00064	.0576	2.91
10	.0587	-.520	.00067	.0333	2.75
11	.4622	-.750	.00016	.0160	2.11
12	.6675	-.721	.00320	.0124	1.77
13	-.1148	-.572	.00170	.0474	2.77
14	..0976	-.630	.00006	.0380	2.85
15	.12767	-.593	.00004	.0370	1.71
16	.5830	-.697	.00017	.0131	2.24
17	.4575	-.655	.00008	.0355	2.15
18	.2151	-.617	.00156	.0317	2.26
19	.0143	-.480	.00145	.0495	1.74
20	.0582	-.223	.00005	.0381	2.27
21	.29416	-.630	.00014	.0316	2.13
22	-.0564	-.304	.00107	.0473	2.03
23	.22813	-.636	.00065	.0335	2.55

Table 2

3. DISCUSSION

The main result of this work is that the temporal evolution of the destruction rate of Hb in thalassemic people has a narrow-band power spectrum with a maximum peak corresponding to a characteristic oscillation with a period of about fourty days.

This is at variance with what one would expect if only unpredictable random factors such as, for example, intercurrent deseases, stressfull events, fever, exercises and so forth affected Hb consumption.

The analysis of correlation dimensions seems to indicate that the time evolutions are in reality chaotic. But, table 3 shows that they can also be modeled as second order stochastic autoregressive processes.

We are not able at the moment to disambiguate among these two competing hypotheses since it is known that stochastic processes different from white noise can show a correlation dimension lower than the embedding one.

However, the problem arises of whether the observed quasi-periodic fluctuations are physiological findings which are normally obscured by the

mechanism of Hb production, which is blocked in transfused thalassemic people, or are they a peculiar feature of blood consumption in thalassemic people.

At the present state of the analysis we can only be conservative and merely say that the observed narrow-band spectra are consistent with the hypothesis that Talassemia is a dynamical disease, and that other analyses are needed in order to exclude that also the temporal evolution of Hb destruction rate in normal people is quasi-periodical.

From the system dynamics point of view, the narrow-band power spectrum is probably a cue of the existence of a control mechanism of the number of circulating red blood cells which is more complex than the one postulated by Mackey and Milton. In fact, Machey's and Glass's model is based upon the assumption of a delayed blood cell production with a constant rate of cell destruction, whereas our data indicate that the rate of Hb destruction itself is quasi-periodical. So, other more complex models are needed.

Another possible hypothesis is that the oscillations are caused by the transfusions themselves which in fact substitute the normal blood production mechanism, the main difference being that this artificial blood production is not continuous.

Against this conjecture one can argue that the rate of Hb destruction is not significantly crosscorrelated at any time displacement with Hb level attained at the previous transfusion since this level, due to the therapeutical objectives, is kept practically constant.

However, one cannot exclude that the artificial "discretization" of blood production may induce oscillations in the Hb desctruction rate.

Nor oscillations can be thought as generated by a sort of physician dependent feedback since physicians can control only the timing of transfusions but not the rate of hemoglobin destruction.

Moreover, from table 2 one can notice that all of the second order autoregressive coefficients are significantly negative, whereas the first order ones can be zero, slightly positive or slightly negative. This leads to different types of power spectra. Whether or not these different typologies correspond to different clinical pictures and/or to different genetic structures is the object of an ongoing analysis.

Finally, from the pragmatical point of view, one must notice that autocorrelograms indicate that the physicians' rule of thumb of projecting the past rate of Hb destruction into the near future must be partially revised because of the inverse relationship at 20 days lag and of the different values of the second order autoregressive coefficient.

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