Inspection of multidimensional phase spaces with an application to the dynamics of hormonal systems

U. Brosa, H.-M. Harms, K. Prank, R.-D. Hesch

Classification
Physics Abstracts
05.40 — 87.00 — 87.25

Short Communication

Inspection of multidimensional phase spaces with an application to the dynamics of hormonal systems

U. Brosa([1]), H.-M. Harms([2]), K. Prank([2]) and R.-D. Hesch([2])

([1]) FB Physik, Philipps-Universität Marburg and Brosa GmbH, Am Brücker Tor 4, D-3572 Amöneburg, Germany

([2]) Abteilung Klinische Endokrinologie im Zentrum Innere Medizin, Medizinische Hochschule Hannover, Konstanty-Gutschow-Straße 8, D-3000 Hannover 61, Germany

(Received 2 January 1991, accepted in final form 15 January 1991)

Abstract. — We look directly into multidimensional phase spaces. This is useful if little is known about suitable observables and underlying laws. The dynamical system we examine is the human body, in particular the secretion of the parathyroid hormone (PTH). Time series of PTH concentrations are transformed to multidimensional data sets. From their representations in phase space we derive a suitable observable: the average lifetime of a PTH fluctuation. It provides a clear-cut discrimination between health and two metabolic bone diseases, viz. osteoporosis and hyperparathyroidism. The derivation is done step by step: First we consider multidimensional displays and observe that it is certain correlation function which plays an important role. Then a single number is taken from that correlation function, and a threshold value is suggested.

Since Boltzmann's time the phase space has been a valuable concept to discuss dynamical systems. The state of any system can be described by a single point in that space, and its evolution by a single trajectory. The advantages of this *conceptual simplicity* have been qualified by *practical difficulties* with the visualization of geometrical objects in high-dimensional spaces. So for a long time just pictures on planes were drawn, and hence only such dynamical properties as singular points and limiting cycles were generally understood. It was not surprising that the discovery of the strange attractors coincided with the widespread use of perspective pictures, so-called 3D graphics. Using modern computer technology we can look into more than three-dimensional spaces. Here we will only present an elementary technique, namely the projection of a high-dimensional space onto three-dimensional subspaces. Already this allows insights which were never achieved before.

The classical approach of statistical physics to phase space is the computation of averages. Variances, covariance matrices, correlation functions, entropies and all the fractal dimensions [1] represent averages. In fact, any observable can be construed as some mean value. This approach, however, is less fruitful if almost nothing is known about the nature of the underlying system. The number of observables is infinite. Which one gives the relevant information?

In such situations direct views into the phase space can be helpful. One obtains at least inklings and can derive from these more specific questions or, in other words, suitable observables. Hence, our approach is preparation rather than replacement of classical methods. For definiteness we present an example from endocrinology, viz. the secretion of the parathyroid hormone (PTH) and its relation to osteoporosis and hyperparathyroidism.

Why is PTH important? In adult mammalian life the structure and function of bone undergoes a permanent plastic adaption, called "remodelling". This concerns hematopoiesis (production of blood) as well as the biomechanical architecture of bone. PTH is the dominant hormone involved in the remodelling. It works by receptor-operated regulation of gene expression in bone cells with subsequent adaption of the structural bone network.

Osteopororis is a disease where the three-dimensional architecture of bone is destroyed and its total mass decreases. In osteoporotic subjects the dynamic pattern of PTH secretion is grossly altered. This leads to increased bone resorption. The bone plates (*ostea*) become perforated, *porotic*, hence the name of the disease. At a certain degree the perforations become irreversible causing biomechanical instability and bone fracture.

Hyperparathyroidism is a disease where the parathyroid glands deliver more PTH than is needed. The bone, in contrast to osteoporosis, exhibits a higher connectivity of plates and an increased bone mass.

We prefer this example because it is not a schematic model (think of all the spin systems) where the most important observables and fundamental laws are known in advance. With PTH concentrations, there is at present no simple criterion to discriminate between health and diseases. Our objective is to find such a criterion and to discuss its relation to systemic (affecting the entire bodily system) processes.

Within the static concepts of endocrinology, *mean values* of PTH concentrations were taken to indicate diseases. Yet this is not sufficiently reliable. Since bone exhibits *prima facie* a chaos-alike structure, we expect a relationship to the dynamic hormonal modulation of this structure which should proceed in a deterministic information-processing system. To say it crudely: The remodelling of bone requires non-stationary dynamics of PTH secretion. Therefore expressions as "not enough PTH" or "too much PTH", which refer to the average PTH production, serve only for first orientation. Healthy PTH secretion is in fact a dynamical process, with large and irregular fluctuations [2]. Healthy secretion has even features of a chaotic evolution as one can show by Grassberger-Procaccia analysis and by Lyapunov exponents [3].

In patients with osteoporosis we could associate the loss of bone mass with a bifurcation from the "normal" dynamic pattern towards "low" dynamics which resembles very much a steady state meaning that cellular receptors are biologically at rest. Generally fluctuations are small in osteoporosis. Therefore the next attempt to establish a suitable criterion would be by *variances*. Unfortunately also this attempt fails, first, because sometimes osteoporotic fluctuations can be as large as healthy ones, and second, because there is this other bone disease, hyperparathyroidism. In patients with hyperparathyroidism we observe large fluctuations which are in most cases larger than in healthy subjects. We have portrayed this as "high" dynamics [4].

Consideration of variances favors another misjudgement, namely with respect to the origin of the diseases. Based on variances one is inclined to think that a too-much is as harmful as a too-small. Yet we will see that hyperparathyroidism and osteoporosis are malfunctions due to qualitatively different causes.

In the measurements blood was drawn from patients every two minutes. One measurement typically lasted 6 hours. From the samples, PTH concentrations are determined by suitable assays. Details can be found in [2]. Let us denote the times of drawing by $\{t_n \,\partial\, n = 1, 2, .. \}$ and by $c(t_n)$ the corresponding concentrations of PTH. Following Takens [5] we rearrange the series $\{c(t_n) \,\partial\, n = 1, 2, \ . \}$ to generate points in a nine-dimensional space:

$$\begin{array}{llllllllll}
\{c(t_1), & c(t_2), & c(t_3), & c(t_4), & c(t_5), & c(t_6), & c(t_7), & c(t_8), & c(t_9) \} \\
\{c(t_2), & c(t_3), & c(t_4), & c(t_5), & c(t_6), & c(t_7), & c(t_8), & c(t_9), & c(t_{10})\} \\
\{c(t_3), & c(t_4), & c(t_5), & c(t_6), & c(t_7), & c(t_8), & c(t_9), & c(t_{10}), & c(t_{11})\} \\
\{ \ .. , & & & & & & & &
\end{array}$$

We call the first variable in these lines x_1, the second x_2, the third x_3 and so forth. To obtain a

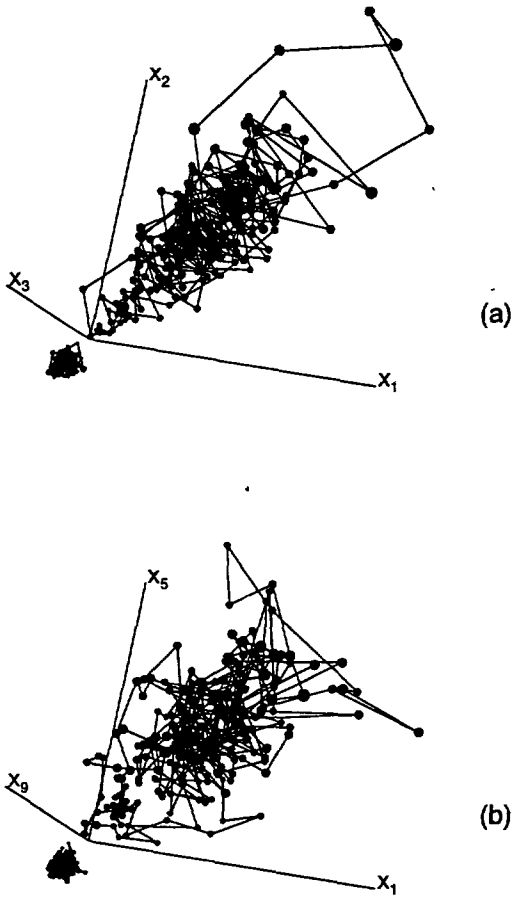

Fig. 1. — Time series of PTH secretion under osteoporosis (small clouds in the lower left) and in a healthy person (big structures) Subsequent points of the series are connected by lines. Part (a) holds if the delay between points is just 1 time unit (2 min). Part (b) describes the behavior for a delay of 4 time units. Between the beginning and end of every axis PTH concentrations vary from 25 to 125 ng/l. This is a figure for people seeing such data for the first time. Generally, data from osteoporotic and healthy subjects are less well separated. Anyway, the shape differences discussed in the text seem always to be present.

representation of the subspace $\{x_1, x_2, x_3\}$, we select the first three columns of the above scheme and display them in a Cartesian coordinate system. An example is shown in Fig.1a.

We may choose any combination of three columns. Most important for the present purpose are synopses like $\{x_1, x_3, x_5\}$, $\{x_1, x_4, x_7\}$ and $\{x_1, x_5, x_9\}$ since they reflect the correlations in the series. Consider, for example, Fig.1a. It displays the short-time correlations. The small spherical cloud stems from osteoporosis, while the club-like cloud belongs to health. The centroids of these clouds correspond to the mean values, their extensions to the variances. More significant are their shapes: Sphericity of a cloud tells us that the data are almost uncorrelated. The stretched shape of a club signalizes finite correlation. We may check this by Fig.1b. The data are plotted here in the subspace $\{x_1, x_5, x_9\}$ to indicate medium-time correlations. We see that the small cloud is almost the same as in Fig.1a. Clearly, zero correlations can't be made smaller. The big club, however, became broader. This corresponds to a partial loss of correlations which occurs because there is more delay between the variables x_1, x_5 and x_9 than between x_1, x_2 and x_3.

We may summarize the interpretation of Fig.1 as follows: PTH secretion in osteoporotic subjects resembles a noisy fixed point. In fact, comparison of the same samples using different assays has shown that most osteoporotic fluctuations are artefacts caused by the limited resolution of the immunoradiometric detectors. Healthy PTH secretion, however, occurs in defined pulses. A typical lifetime of such a pulse is 5 time units, i.e. 10 minutes.

In Fig.2 data generated by a person suffering from hyperparathyroidism are juxtaposed to the healthy behavior. That mean value and variance of PTH concentrations are bigger in hyperparathyroidism than in health, is often the case, however not always. More reliable are again the shapes of the clouds: Health maintains some regulation, whereas fluctuations in hyperparathyroidism seem to be uncorrelated.

Hence we propose the familiar correlation function

$$\rho_j = \frac{\langle (c(t_{n+j}) - < c(t_n) >)(c(t_n) - < c(t_n) >) \rangle}{\langle (c(t_n) - < c(t_n) >)^2 \rangle}$$

as a suitable observable. Averages are taken over n. For data from healthy subjects and patients with hyperparathyroidism ρ_j is plotted in Fig.3. We see that the hyperparathyroitic correlation function decays significantly faster than the function of health. Let us define the average lifetime of a fluctuation by that time t_j at which ρ_j takes the value 0.5. From Fig.3 we can derive that the average lifetime of a healthy fluctuation is about 10 minutes whereas that of hyperparathyroidism is at most 4 min. The average lifetime under osteoporosis is even shorter.

Thus we have reduced the complex data from dynamic hormone secretion to a straightforward yes/no decision. We can describe the recipe for the decision between health and disease as follows: Measure the average lifetime of the PTH fluctuations. If this time is longer than 7 minutes, the person does not suffer from osteoporosis or hyperparathyroidism. Among all data sets studied by us, no exception from this rule was found.

The criterion appears simple enough. See however [2] and the papers cited there to understand that its discovery was by no means straightforward.

Now that we found a suitable observable to discriminate between health and disease, we are on safer grounds with hypotheses regarding the mechanisms of PTH modulation.

In healthy conditions, PTH production and secretion is modulated by complex metabolic processes which take place, at least partly, far away from the parathyroid glands. We know this because the average lifetime of PTH fluctuations (10 min) is bigger than the recurrence time of blood circulation (2-4 min).

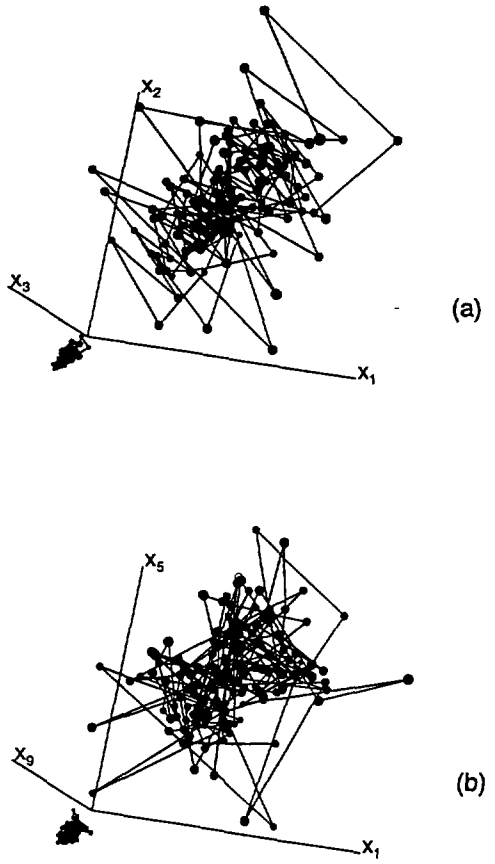

Fig. 2. — Similar to figure 1, but here PTH secretion in hyperparathyroidism is compared with healthy behavior. The data from the healthy subject are the same as in figure 1. Due to the different scale they appear this time in the lower left corner; in this figure PTH concentrations vary from 125 to 913 ng/l. The difference in sizes is not always as spectacular as shown here. Only the correlations seem to be general properties.

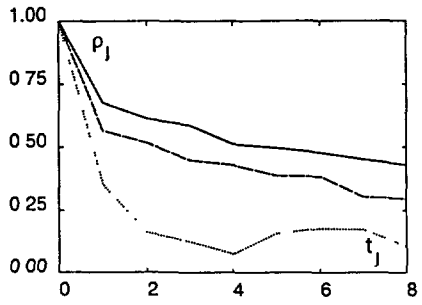

Fig. 3. — Correlations ρ_j of healthy PTH secretion (solid line), secretion in hyperparathyroidism (dashed) and osteoporosis (dotted) as functions of time t_j. One time unit has 2 minutes. This figure was obtained by averaging over data sets described in [2]. The individual correlation functions are quite similar to their average representatives Please notice· The difference between health and disease is much more conspicuous in figure 2.

In osteoporosis, the parathyroid glands have apparently lost their ability to answer external modulation. They just constantly produce some PTH (which might correlate with non-dynamic basal secretion).

Finally in hyperparathyroidism the PTH-producing cells still can respond to modulation, but they are modulated on a different level by different substances. These substances must be produced at a place not far away from the parathyroid glands. One of them probably is chromogranin A [6], a direct inhibitor which is stored in the same secretory granules as PTH. Chromogranin A might play the role of a emergency brake being much faster than the normal modulation, acting however only when a very high level of PTH concentration is transgressed.

In summary, conventional approaches of statistics have failed to analyse data on PTH production [2]. They did not permit systemic interpretations beyond the concept of static reference ranges of variables determined in circulating blood [7]. Our new approach of representing data in multidimensional phase spaces offers a new concept to pathophysiology. We can characterize the dynamics of apparent well being and can portray the evolution of diseases [7]. For physics we find that visualization of objects in high-dimensional spaces eases the very first steps of research.

References

[1] SCHUSTER, H.G., Deterministic Chaos, VCH (Weinheim) 1988.
[2] HARMS, H.-M., KAPTAINA U., KÜLPMANN W.-R., BRABANT G. and HESCH R.-D., *J. Clin. Endocrinology Metabolism* **69** (1989) 843 and the references therein.
[3] PRANK K., HARMS H.-M., KAYSER Ch , BRABANT G., OLSEN L.F. and HESCH R.-D., The dynamic code: information transfer in hormonal systems in: Proceedings of the Advanced NATO Research Workshop on Complex Dynamics and Biological Evolution (Hindsgavl in Denmark 1990) Plenum Press (New York, in press)
[4] DELLING G., DREYER T., HESCH R.-D., SCHULZ W., ZIEGLER R. and BRESSEL M., *Klin. Wochenschr* **65** (1987) 643
[5] TAKENS F., *Lecture Notes in Math.* **898** (Springer, Heidelberg, New York) 1981.
[6] FASCIOTTO B.H., GORR S.-V., DEFRANCO D.J., GREELEY G.H., LEVINE M.A. and COHN D.V. in: Proceedings of the 10th International Conference on Calcium Regulating Hormones and Bone Metabolism (Montreal in Canada 1989), Excerpta Medica (Amsterdam, New York, Oxford) 1990, p. 51.
[7] HESCH R.-D., Hormonlehre in: Endokrinologie, Ed. R.-D. Hesch (Urban und Schwarzenberg, München, Wien, Baltimore) 1989, part A, pp. 1-50.

Cet article a été imprimé avec le Macro Package "Editions de Physique Avril 1990".