Allegra's* Syndrome plays a central Role in bedside clinical Diagnostics.

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"The study of microvessels nowadays shows fortunately its original, essential and favourable influence on the evaluation of all tissues and biological systems, including obviously macro- as micro-circulatory system, under both physiological and pathological conditions"

(August Krogh, Nobel Prize, Dec.11, 1920: "A contribution to physiology of capillary")

Abstract.
In the article, the Authors describe in details, for the first time, Allegra's Syndrome, based on pathological tissue-microcirculatory- unit activation. After having illustrated the fundamental bases of Clinical Microangiology, the presence of deterministic chaos in biological systems and its diagnostic significance are outlined from the diagnostic point of view.
According to the Angiopathy theory, physician can gather at the bedside with a simple stethoscope an awful number of information on biological system structure and function, even in initial stages of disorders.
Finally, Allegra's Syndrome allows physicians to recognize since individual's birth CVD Inherited Real Risk and fully understand Microcirculatory Biophysical Semeiotics Theory of Arteriosclerosis.

Clinical Microangiology Fundamental Bases.

In the medical field, wide and enchanting, of Biophysical Semeiotics, far away from having reached the borders of its domain, *Clinical Microangiology* plays a primary role, from both theoretical and practical view-point, due to its excellent results, collected at the bed-side in original and refined manners (http://www.semeioticabiofisica.it/microangiologia/common_eng.htm).

After 55 years of biophysical semeiotic research and practical performance of this method, one of us have demonstrated that Biophysical Semeiotics is a scientific theory, characterised by multiple values of efficaciousness and beauty, so that it must be considered a scientific progress.

Until now, at the beginning of the first millennium, only a few appointed physicians studied clinical microangiology. However, by Biophysical Semeiotics, it will surely become cultural heritage of every open-minded doctor, which will be able to collect at the bed-side numerous, original and reliable data, obtaining excellent results on diagnosis, differential diagnosis, clinical research and ultimately therapeutic monitoring.

Clinical Microangiology represents the clinical study of deterministic chaos of *vasomotility*, i.e., sphygmicity of small arteries and arterioles, according to Hammersen, and, then, of *vasomotion*, sphygmicity of capillaries and post-capillaries venules, in all biological systems.

This new discipline of Medicine, unavoidable to understand ATS occurrence, according to our Microcirculatory Theory of Arteriosclerosis, we are going to up-date and illustrate in next paper, is based exclusively on clinical evaluation, i.e., using a stethoscope and assessing ureteral reflexes, of autonomous and autoctonus movements of all structures of tissue-microvascular-units, among them Arterio-Venous Anastomoses (AVA), including Endoarteriolar Blocking Devices, that are AVA from the functional viewpoint, of every organ, gland, and tissue (1-3).

Importantly, we are going to describe also an easy method, based on evaluating the gastric aspecific reflex, whose parameters parallel those of more refined, but more difficult, microcirculatory evaluation, in the interest of General Practitioners.

Under basal physiological conditions, tissue-microvascular-unit fluctuations show an high degree of deterministic chaos, i.e. highest *fractal dimension* or *dimensionality* (fD), which is its measure.

The calculation of this parameter, essential in *Clinical Microangiology*, by easy and practical way, can be performed with the aid of evaluation of disappearing time of gastric aspecific reflex: by elegant and refined way doctor quantifies in sec. “differential latency time” of gastric aspecific reflex, which parallels its disappearance, as will be described in details later on.

When a biological system, due to whatever disease, different in origin, evolves slowly to pathological condition, both functional and/or structural, although function and structure must be considered as the poles of the same equation, as states Leuckart, characteristic modifications of deterministic chaos happen in both local *vasomotility* and *vasomotion* and, at macroscopic level, in volume fluctuations of organ, gland, and tissue, where disorder is localized, allowing to draw, even mentally, related diagrams, illustrated in the site pages, dedicated to Biophysical Semeiotics, and, therefore, yet known to reader.

These physiological oscillations (trajectories), in fact, appear modified at microscopic as well as macroscopic level, causing progressive lowering of the *fractal dimension* or *dimensionality*, that from the physiological value, i.e., 3,81, lowers to about 2,57, as in the case of pancreas during Metabolic syndrome, classic or “variant”, we described previously as Reaven’s Syndrome, slowly evolving to diabetes mellitus (4, 5).

Interestingly, dividing *physiological dimensionality and fractal dimension* of Reaven’s syndrome slowly evolving to DM, or other disease, of course, the result oscillates around a 6,18, ϕ, or *golden mean*. In our opinion, such magic numbers, which are really numerous in clinical microangiological evaluation, underline clearly the scientific value of the chaos in Medicine.

In fact, according to many authors, biological, physiological and pathological structure shows its chaotic nature (6). The study of single patient, according to the Single Patient Based Medicine (7-9) has to be performed not by principles valid for the group of individuals, population in general, according to the standards of Evidence Based Medicine (EBM), but to the SPBM, based on the deterministic Chaos (6).

It is nowadays clear that the best knowledge of an individual, under physiological and pathological situations, is acquired by a method based on the sensitivity to initial conditions, on interaction, complexity, standards totally ignored by EBM, as we suggested in a lot of previous articles (10-16).

Data of our researches, performed over the past decades by Biophysical Semeiotics, in a way as easy as possible, aiming to a practical utilization at the bed-side, hopefully demonstrating that phenomena observed in a single individual very often are not identical to those evaluated in the "group" of comparable subjects, on the base of an evidence, which allows to forecast in probabilistic and statistic manner exclusively by great numbers.

Finally, to demonstrate above referred data, it is necessary to say that in the course of chronic disease, *dimensionality* of local tissue-microvascular-units fluctuations and, then, the fractal dimension of macroscopic oscillations of related biological systems, are equal to 1, i.e. topological dimension.

From the above remarks, it results clearly the usefulness and originality of *Clinical Microangiology* in bed-side diagnosis, prevention, research and therapeutic monitoring.

Functional activity, both physiological and pathological, of a biological system is strictly related to its microcirculatory blood-flow pattern. Therefore, it is possible to assess function and structure of the former by evaluating function and structure of the later, according to Angiobiopathy Theroy (17-20). Such study represents the aim of *Clinical Microangiology*, originated with the aid of Biophysical Semeiotics, which is its method or operative tool.

The biological significance of microcirculatory deterministic chaos.

Chaos, a mathematical concept, has been described as "deterministic randomness", meaning that a chaotic system is deterministic, but so complicated that looks random. Chaos theory tells us it is impossible to predict the long term behaviour of very complex systems, because all the conditions are not known with precision at any time and uncertainty increases with time (21) .

It is well known that electrocardiograms, for example, of healthy hearts, constantly vary, however slightly, in an unpredictable way. But in dying patient the intervals between beats (R-R) become practically identical and electrical signals predictably cyclic (22) .

We described in previous papers, for the first time clinically, spleen- (22), liver., kidney- and pancreas- (23, 25) chaotic oscillations, partly due to Autonomic Nervous System activity.

More precisely speaking, organ and tissue oscillations are related to their local microvessels chaotic activity, i.e. the complexity of the dynamism of the firsts corresponds exactly to that of the second.

In addition, the physiologically functioning organ presents complex, chaotic oscillations, constrained to a "strange attractor" in the phase space (See later on).

On the contrary, in a diseased organ there are cyclic, periodic, regular, identical, predictable and low oscillations without *highest spikes* (HS).

In conclusion, the tissue microcirculatory unit and consequently the related organ, as biological dynamic system, lose complexity, it lose its adaptative capacity and ability to respond (25, 26).

Interestingly, biophysical-semeiotic evaluation of the complexity degree is very important as regards prevention, diagnosis and therapeutic monitoring.

As mentioned above, the chaotic volume fluctuations of kidney, pancreas, liver, spleen, aorta, heart (obviously, regardless systo-diastolic movements), a.s.o. are due to their congestion and decongestion (6 cycles per minute) as clinical and experimental evidence suggests.

In facts, organs chaotic oscillations are strictly analogous and synchronous with related microvessels fluctuations, presenting really identical behaviour .

Consequently, we are allowed to state that chaotic behaviour of local nutritional capillaries and venules brings about volume random changing of the related organs, mentioned above. Therefore, it is easy and reliable to assess in a precise manner oscillations of about all organs and tissues by means of the evaluation of corresponding microvessels fluctuations.

In other words, besides kidney, pancreas, heart, spleen, liver, a.s.o., chaotic oscillations assessment, it is practical, useful and reliable to evaluate the "oscillations" of important tissues, organs and glands, such as bone-marrow, prostate, lungs, gall-bladder, breast, urinary-bladder, stomach-duodenum, a.s.o. (27), evaluating *vasomotility* and *vasomotion* of related microcirculatory bed.

As regards bone marrow and breast, for example, digital pressure upon the middle line of breast-bone (and/or hyliac crests) and mammary gland, respectively, in healthy, brings about choledocic "arteriolar", "venular" reflexes as well as ureteral reflex (= nutritional capillaries), which fluctuate in a chaotic manner, as mentioned above.

Interestingly, AP values of marrow- and mamma-oxygenation and CoQlO levels (28) are in perfect relation with chaotic choledocic and ureteral fluctuations.

At this point, it appears relevant to outline that during acute disorder, flogistic in nature, local periodic microvascular oscillations (choledocic and/or low ureteral reflexes) show the most intense degree, almost equal to that of the *highest spikes* (HS), demonstrating clearly the real biological nature of oscillating complexity, namely the adaptative capacity and ability to respond.

In fact, during phlogistic process, the interstitial oedema increases both vasomotility and vasomotion. (29-32). In other words, chaos theory has stimulated some important technical developments in the way we can analyze and interpret medical and other time series data. (33)

As regards the above-mentioned "strange attractors" of chaotic dynamic systems, a key concept is "fractal dimension", very different from the topological one, as demonstrates the generation of Koch's curve (33, 34), which, as the name implies, was developed for fractals, but the practical applications of which has emerged as a byproduct of attempts to prove that certain systems have strange, chaotic, fractal at-tractors, by analyzing time evolution data. (35).

When brain wave data, e.g., in rats are "re-constructed", the attractor for a healthy rat is computed to have a "dimension" of about 5,9 while that for the same rat in epileptic seizure has a dimension of only 2,5. (36). The suggestion is that the "dimension" correlates with the flexibility and adaptability of the organisms: the larger number implies a chaotic system with well developed flexible response to stimuli, whereas the low value associated with the seizure can be regarded as evidence of suppression or malfunction of a number of key elements of the rat's physiology.

A somewhat similar argument can be applied to biophysical-semeiotic data, as regards, e.g., pancreatic oscillations in case of classical or "variant" Reaven's syndrome in diabetic evolution (37) as well as in diabetes mellitus (38). It must also be remembered that fractal dimension (fD) and system complexity are directly correlated.

Clinical evidence demonstrating tissue-microcirculatory-unit deterministic chaos

As above briefly described, there is chaos also in the microvascular system.

In facts, in the healthy subjects the intensity of upper and low ureteral reflexes is really different from the majority of young people born from arteriosclerotic mother. In health, reflex oscillation is varying from 0,5 to 1,5 cm, from biophysical semeiotic stand-point, so that the ratio HS/minimal fluctuations is 3/1 (Fig. 1). These oscillations become less chaotic when an organ is evolving to a pathological state and finally all oscillations are identical and regular in diseased organs: f D decreases from >3 to 1.

Analogously, we observe deterministic chaos in the duration of single cycle; the length of normal period is 10,5 sec in an average, ranging from 9 to 12 sec. In hyper-functioning organs, e.g. in case of a trivial flu, as bone marrow is concerned for example, oscillation intensity is like HS and cycle duration results restricted to 9-11 sec. On the other hand, in diseased organ the duration is fixed at 10 sec. and intensity is 0,5 cm.

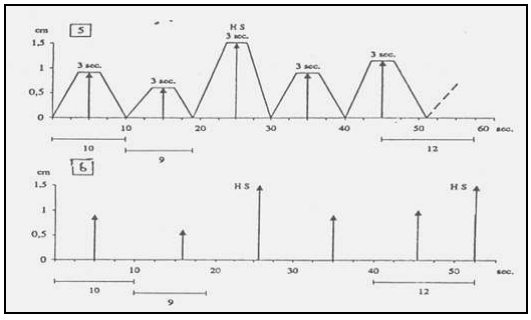


Fig. 1
Physiological microvessel fluctuation. HS indicates Highest Spike

The clinical evidence corroborates biophysical semeiotic theory of the existence of chaos in tissue-microcirculatory-unit, because there is a perfect concordance between chaos and biophysical semeiotic parameters. Our clinical biophysical semeiotic data corroborate actually those of other Authors, (32-34) about random, chaotic activity in the "vasomotion", due to the great number of different in-put in the smooth muscle cells. In diseased organ it is possible that a lot of in-puts decrease and/or disappear and a mechanism becomes dominant. Consequently the tissue present rhythmic "vasomotion", as demonstrated in our tachograms (See later on).

In case of "pathological" oedema, a lot of stimuli, which bring about a random, chaotic "vasomotion", apparently are eliminated, causing a regular vasomotion, as we observed in a long, well established experience (35).

On the contrary, in a jatrogenic oedema, i.e. during digital lymphatic or venous vessels obstruction, after 2 sec vasomotility increases, showing exclusively HS and, thereafter, also vasomotion becomes very intense .

From the above remarks, the vasomotion clearly depends from vasomotility and the two phenomena are really different in nature (35).

Due to a lot of in-puts small arteries and arterioles constrict and dilate autonomously (6 cycles per minute, from biophysical semeiotic stand-point), as arteriolar choledocic reflex demonstrates, because of numerous arteriolar pace-makers. This arteriolar vasomotility, based on sphygmicity, aims at maintaining a physiological "vasomotion" and consequently flow-motion, so that O_2 and metabolites tissue supply persists normal under different conditions. Therefore, vascular tone and vasomotility of healthy people are in perfect relation to tissue request (36, 37, 38).

In an organ or tissue, in other words, arteriolar activity and diameter are generally correlated to a certain extension. Under physiological conditions, arteriolar tone enhancing brings about increasing of blood pressure. In such case, due to secondary hypoxia, the blood pressure should subsequently increase (39).

On the contrary, the increased vasomotility, due to enhanced tone, permits to maintaining a regular flow-motion and fuel supplying, although high blood pressure as well as hematocryt, avoiding a vicious circle.

From a physiological point of view, vasomotility and vasomotion provide to:

1) efficacious and economic tissue blood distribution;
2) reducing peripheral vascular resistance;
3) under some circumstances, permits interstitial fluid to be absorbed (36-39).

Interestingly, **Biophysical Semeiotics** allows the doctor to observe clinical and experimental evidence, which enlights the relation between vasomotility and vasomotion: digital pressure upon radial arteries induces in succession arteriolar dilation with increased vasomotility $\rightarrow$ enhancing of vasomotion $\rightarrow$ occlusion (disactivation) of AVA, functionally speaking, so that 0_2 and metabolites supply to tissues persists in normal ranges to certain extence of digital pressure.

From the above remarks, in case of essential hypertension, e.g., the used drug results really efficacious exclusively in the case fractal dimension of resistence microvessels returnes to physiological values, beside the normalization of blood pressure.

Biophysical-Semeiotic morphological Analysis of Vasomotility and Vasomotion under both physiological and pathological Conditions.

From the practical point of view, it is sufficient and reliable to evaluate periods, as well as intensity of upper and low ureteral reflex oscillation (= vasomotility and respectively vasomotion), as described above, for example during “mean” digital pressure, applied – for instance - upon the middle third of biceps muscle, compressing it between thumb and other fingers, of a supine individual, psychophysically relaxed with open eyes (to reduce melatonin secretion). The muscle pressure allows doctor to examine resistance microvessels dynamics and flow-motion of nutritional capillaries.

Interestingly “small” pressure allows to recognize the microvessel dynamics at rest; “mean” pressure stimulates microvessels, which are working as under stimulation tests; “mean-intense” pressure abolishes microvessel fluctuation: it is particularly useful in investigating arterial wall properties; “intense” pressure allows to assess artery compliance; finally, “most intense” pressure has to be utilize, e.g., in evaluating type I, group 2 AVA, according to Bucciante.

From the above remarks, these adjectives aren’t qualitative at all!

However, the original morphological analysis of vasomotility and vasomotion, i.e the precise evaluation of upper and low ureteral reflex oscillations, reveals interestingly the actual condition of related tissue-micro vascular-units, in a synergetic model.

Interestingly, physicians not skilled in Biophysical Semeiotics have to know that reliable data can be gathered at the bed-side in easier way by assessing the parameter value of gastric aspecific Reflex (Fig. 2, 3).

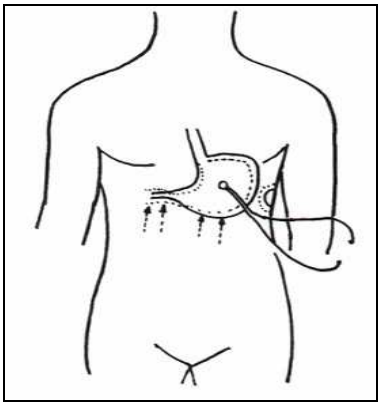
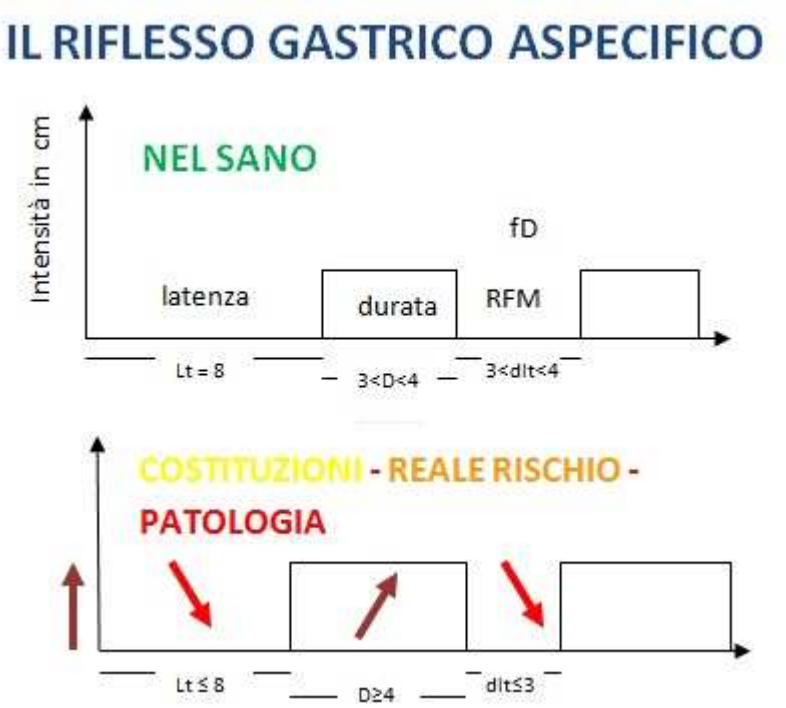


Fig. 2
Figure shows the gastric aspecific Reflex. Physician has to assess Latency Time, Intensity, Duration, and the Duration of Disappearance before the following reflex.



a) Latency Time (in sec.): tissue oxygenation, tissue pH
b) Intensity (in cm.): seriousness of underlying disorder
c) Reflex Duration (in sec.): Microc. Function. Reserve
d) Disappearing Time (in sec.): important parameter value, which parallels fractal Dimension of upper and lower Ureteral Reflex Oscillations, i.e., vasomotility and vasomotion

In order to realize microvessel oscillation analysis it is unavoidable to transfer upon Cartesian coordinates intensity (ordinate, cm) and duration (abscisse, sec.) of three successive fluctuations of low ureteral reflex, observed for example in the above-mentioned situation, during biceps muscle microvascular units stimulation. In healthy subject we observe a characteristic diagram (Fig. 1).

Interestingly, in 2 sec (ascending line: AL) it is reached the highest intensity (NN = 0,5-1,5 cm); the "plateau" line (PL) lasts physiologically 3 sec, then in 1 sec (descending line: DL) the line returns to

basal value (i.e. abscisse), where persists for > 3 sec. < 4 sec. (= fractal Dimension), varying the periods from 9 to 12 seconds under physiological condition.

On the contrary, in pathological situations, e.g. essential hypertension, the diagram results interestingly modified (Fig. 3): AL as well as DL are normal, 3 sec. and 1 sec respectively; intensity is approximately 0,5 cm, in a "predictable" manner; the physiological highest waves, i.e. highest spikes of 1.5 cm intensity (HS), are absent.

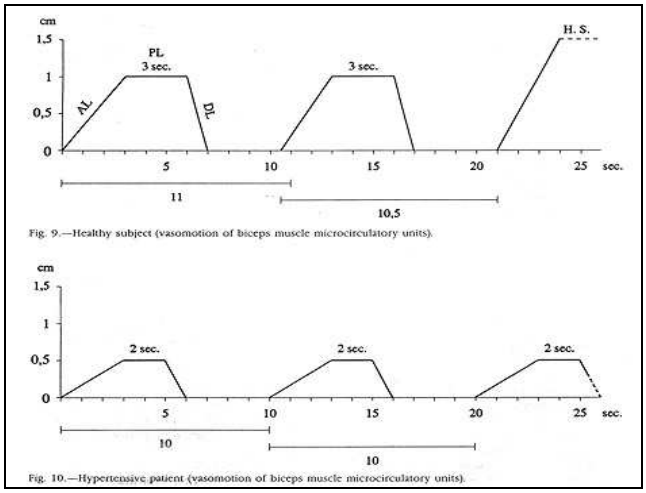


Fig. 3

Figure shows microvessel fluctuations in healthy individual and in hypertensive patient.

Finally, in case of hyperfunctioning tissue, e.g. the bone-marrow during infective disorders of whatever nature, digital pressure upon the middle line of breast bone, brings about low ureteral reflex oscillations, characterized by PL of 5 or more sec, intensity as well as periods practically identical each other (Fig. 4). Intensity and PL of every oscillation are directly correlated: more high the intensity, more prolonged appears PL and consequently more efficacious is the flow-motion of related nutritional capillaries.

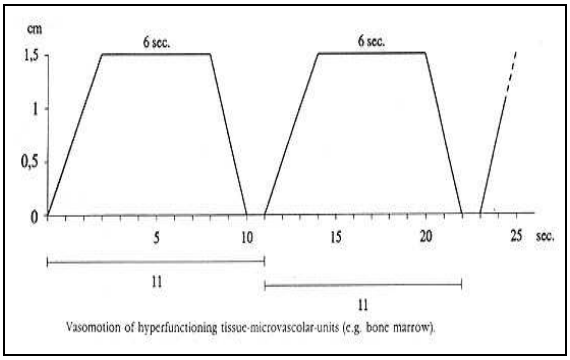


Fig. 4

This clinical evidence underlines the inner consistence of Biophysical Semeiotics.

In addition, superimposing the parameters of three subsequent oscillations of low ureteral reflex, in accordance with the lenght of single period, we realize really interesting figures. In healthy people the obtained area shows a "strange" shape, like a "strange" attractor (Fig. 5: fractal dimension (fD) >3,[1-4] that corresponds to the space occupied by a fractal structure.

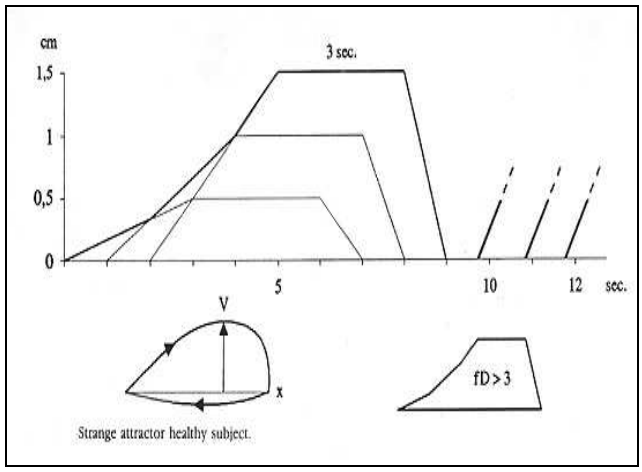


Fig. 5

Strange attractor: healthy subject.

On the contrary, under pathological condition, e.g. essential hypertension as far as biceps muscle microcirculatory bed is concerned, the area obtained in this manner appears quite small, resembling an attractor at fixed point (Fig. 6).

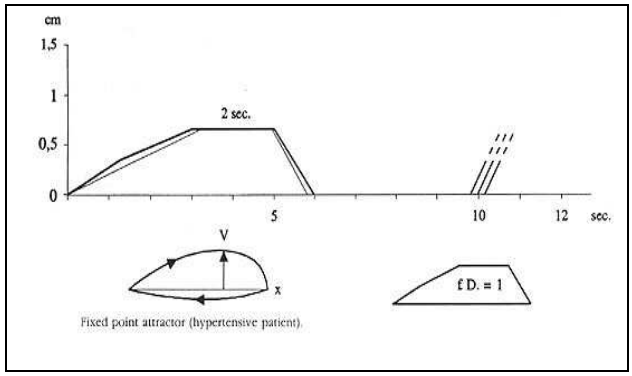


Fig. 6

Fixed point attractor: hypertensive patient

Finally, the area corresponding to hyperfunctioning microcirculatory units results the largest one, due exclusively to its large Euclidean perimeter; its shape, however, resembles clearly a deformed circle, corresponding to a “closed loop” attractor (Fig. 7).

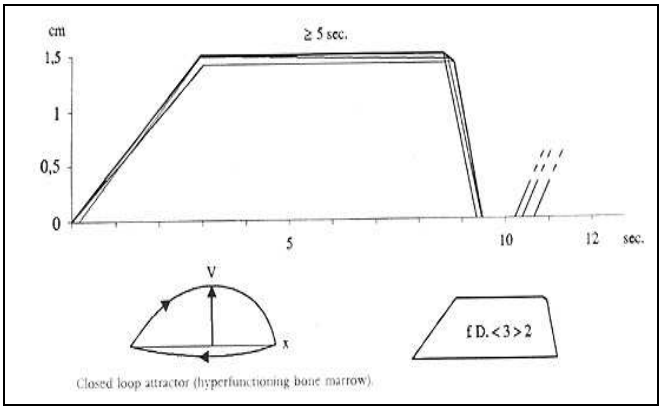


Fig. 7

Closed loop attractor in hyperfunctioning bone-marrow.

From the above remarks it results that morphological analysis of vasomotion, by means of **Biophysical Semeiotics**, in physiological as well as in pathological conditions, represents an original, reliable and useful tool in both clinics and research, as allows us to state a long, well established experience.

Allegra's Syndrome*: Pathological Dissociated Microcirculatory Activation type II and III.

In health, at rest, both vasomotility and vasomotion parameter values are identical, so that the blood-flow along the diverse AVA types is not abundant: middle third ureter oscillates slightly, showing an intensity about 0,5 cm.; tissue oxygenation is normal, thus pH is about 7,4.

Really, physicians observe more easily these data with the aid of gastric aspecific Reflex parameter values, showing a latency time during "small intense" digital pressure applied upon, for instance, the phemoral artery at groin level: 8 sec. (NN = 8 sec.), reflex duration > 3 sec. < 4 sec., i.e., normal value, since Microcirculatory Functional Reserve is physiological, and finally reflex disappearing time before the following oscillation is > 3 sec. < 4 sec.: fractal Dimension = 3,81.

During microcirculatory activation, e.g., under stress tests, physician can gather really interesting data, illustrated in Tab.1

MICROCIRCULATORY ACTIVATION.

Type I , "associated", physiological, e.g., in working parenchyma: both vasomotility and vasomotion are activated in the same manner, showing identical parameter values. AVA is slightingly open. Tissue pH about 7,4.

Type II, "dissociated", intermediate, e.g., in localised diseased organ in initial stage: at rest, vasomotility is more or less activated, but vasomotion shows normal fluctuation, indicating the beginning of every disorder. AVA appear more open than under physiological condition: > 0,5 cm. to 1 cm. Tissue pH is still about 7,4.

Type III, "dissociated", pathological, wherein *vasomotility* is intensively activated, while *vasomotion* shows a decreasing activity, i.e., below the normal one. As a consequence, AVA are pathologically open and hyper-functioning :more than 1 cm. , i.e., AVA hyperstomie. Tissue Acidosis.

Tab. 1

At this point, it is easy to understand the real nature and diagnostic significance of Allegra's Syndrome.
For instance, in the virus hepatitis, even initial, firstly is present type 2, intermediate, dissociated, and secondly type III pathologically dissociated microcirculatory activation.
In case of Inherited Real Risk of type 2 Diabetes Mellitus, small stimulation of VI thoracic dermatomere (= the skin immediately below the costal arch, along middle clavicular line) shows type II, dissociated, intermediate microcirculatory activation, but in overt DM, even in the I-II Biophysical Semeiotic Stages (41- 47), we observe worsening type III dissociated microcirculatory activation.
Analogously, in case of Inherited Real Risk of prostatic cancer, in initial stage, physician observes type II dissociated microcirculatory activation in the precise site of cancer can occur, demonstrating the diagnostic importance of microcirculatory changes (48).

Allegra’s Syndrome proved to be particularly useful in studying and structuring Biophysical Semeiotic Microcirculatory Theory of Arteriosclerosis (49) to which we shall dedicate an up-dated article in next future.

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