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Abstract: Endocrine feedback system may not be appreciated by conventional hormone level estimation at a single point of time. Our body also needs to be looked at as a dynamical system, a dissipative structure, a stability outside equilibrium as Ilya Prigogine, the Nobel laureate, called it. Specially, the information processing at neuroendocrine level must be guided by a science that is not random but deterministic. For sustenance of life body environ must always (at present moment) balance itself delicately and relentlessly. In this dynamical system feedback control will essentially be mathematical control that has to be understood in the light of physical control theory. Like, endocrine reaction that will follow Michaelis-Menten-Hill kinetics can be looked at as signal that moves in the phase space of our body and can be plotted in graph that can be digitized and analyzed using nonlinear science. Though image processing and texture screening is done using nonlinear complexity science, or chaos theory, as we call it, this signal of reaction kinetics may be looked as a vector running in phase space and its trajectory can be calculated in an n dimensional context which will require mathematical and statistical manipulation to bring in two dimensional graph. This graph then will be used to detect some fractal dimension after such normalization as is necessary. Whether the same kinetics of two separate body system will coincide or differ can be judged by those dimension. This can be used to differentiate disease state from normal state. Thus positive and negative feedback may be more rationally and mechanically explained and more definitive biochemical knowledge and prediction will be possible. Fractal geometry and nonlinear chaos has proven to be very much useful tool in quantifying the structure of idealized and naturally occurring from pure mathematics, through physics and chemistry, to biology and medicine. Many processes of normalization of data are discussed. A hypothalamo-pituitary ovarian axis and ovarian cancer is taken up as example to use this science for better understanding of cancer aetiopathology

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Role of nonlinear dynamics in endocrine feedback

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ABSTRACT

Endocrine feedback system may not be appreciated by conventional hormone level estimation at a single point of time. Our body also needs to be looked at as a dynamical system, a dissipative structure, a stability outside equilibrium as Ilya Prigogine, the Nobel laureate, called it. Specially, the information processing at neuroendocrine level must be guided by a science that is not random but deterministic. For sustenance of life body environ must always (at present moment) balance itself delicately and relentlessly. In this dynamical system feedback control will essentially be mathematical control that has to be understood in the light of physical control theory. Like, endocrine reaction that will follow Michaelis-Menten-Hill kinetics can be looked at as signal that moves in the phase space of our body and can be plotted in graph that can be digitized and analyzed using nonlinear science. Though image processing and texture screening is done using nonlinear complexity science, or chaos theory, as we call it, this signal of reaction kinetics may be looked as a vector running in phase space and its trajectory can be calculated in an n dimensional context which will require mathematical and statistical manipulation to bring in two dimensional graph. This graph then will be used to detect some fractal dimension after such normalization as is necessary. Whether the same kinetics of two separate body system will coincide or differ can be judged by those dimension. This can be used to differentiate disease state from normal state. Thus positive and negative feedback may be more rationally and mechanically explained and more definitive biochemical knowledge and prediction will be possible. Fractal geometry and nonlinear chaos has proven to be very much useful tool in quantifying the structure of idealized and naturally occurring from pure mathematics, through physics and chemistry, to biology and medicine. Many processes

of normalization of data are discussed. A hypothalamo-pituitary ovarian axis and ovarian cancer is taken up as example to use this science for better understanding of cancer aetiopathology.
(Keywords: dynamical system, nonlinearity, endocrine, feedback)

"It's an experience like no other experience I can describe, the best thing that can happen to a scientist, realizing that something that's happened in his or her mind exactly corresponds to something that happens in nature. It's startling every time it occurs. One is surprised that a construct of one's own mind can actually be realized in the honest-to-goodness world out there. A great shock and great, great joy." - Leo Kadanoff.

"Clouds are not spheres, mountains are not cones, coastlines are not circles, and bark is not smooth, nor does lightening travel in a straight line." –Benoit Mandelbrot

Introduction

Idea of feedback mechanism in endocrine medicine has remained ill conceived specially in the light of modern control theory where energy transfer is understood in a system wise fashion. The idea is showing reductionism (1) i.e. trying to be discrete molecular biologically whilst

visualization is not getting desired accuracy. Text books has even gone with this wind of discreteness, some even drastically cut the subject to bare minimum probably agreeing to the sanctity of its holiness of omnipotence. Roles of end product inhibition, regulatory enzyme, allosteric configuration etc. are described to explain feedback, but confusion in the brain goes round. It is not astonishing that modern control theory with all its mathematical facets has already gained a perceptible entry in our literature (2). What Mr Brincat (3) (1994) thought as philosophical in chaos and found suitable for understanding to gynaecologists and obstetricians was only the beginning. This subject is fast gaining ground and even mathematics, like molecular biology in last decade can not be ignored anymore and be kept in abeyance. The time is coming that a little mathematics, whatever needed for this, is to be learnt and the subject to be introduced now. This is because another paradigm shift has started and is under way like that of molecular biology, which has already immensely influenced medicine including gynaecology and obstetrics. In our endocrine prone discipline diagnostic assessment of hypothalamo-pituitary ovarian axis in varied clinical condition sometimes remains insufficient, inefficient and even obscure. Their laboratory results are influenced by their function as well as by the physiological context of our body. Though they have undoubted value in screening axis disorders, debates over different hormonal manipulations go on, like breast cancer and sex hormone, ovarian cancer and hormone, colonic cancer and contraceptive pill use, understanding of different hypo and hypergonadotrophic state (4), to name a few. Hence, introduction of control theory dynamics of endocrine system is an utter necessity. A brief discussion towards this jump or shift could be worthwhile and rewarding as well.

Feedback mechanism is essentially a physical term, not biochemical, as is evident, and Uvarov and Chapman (6) (1974) understands the theme in 1974 which describes this as " In general, (It

is) the coupling of the output of a process to the input. In negative feedback a rise in the output energy is arranged to cause a decrease in the input energy, as for example, a governor. In positive feedback a rise in the output energy is caused to reinforce the input energy. In particular these terms are applied to electronic amplifiers, in which a portion of the output energy is used to reduce or increase the amplification, by reacting on an earlier stage according the relative phase of the return ". Since this term feedback being used in biology of endocrine system it makes us understand the biochemical phenomenon in two points of two endocrine glands or between gland and target tissue in a homeostasis of our internal milieu which is, so to say, more or less a thermodynamically stable system. But if we consider it as information processing in biological system, phase will mean " a separate part of a heterogeneous body or system as for example a mixture of ice and water is a two phase system while a solution of salt in water is a system of one phase" (5). Feedback can be closed loop like in electric circuit or open loop like environmental biodiversity. Thus in biology it is an open loop system with not only an input and output but also an array of internal variable influencing the outcome.

In case of endocrine glands until now (2,6) at least in thyroid gland milieu TSH patterns were mainly classified comparatively on simple measures like amplitude and rate. This rate of change is data producing and can be appreciated in a statistical system in our hoemeostatis by understanding differential equation i.e. calculus. Only problem here is that the relationship cannot be as simple as one to one, one to two or three or even four relations, we can hardly imagine range of relationships causing a network leading to a successful chaotic system having its influence in any organ system like hypothalamo-pituitary-ovarian (HPO) axis in gynaecology and obstetrics. Chaos theory is however discussed in general here before (3). Visual, tactile, auditory and complex infinite numbers of metabolic phenomena influence this relation. Infinite time

integration of those differential equations of feedback control has become possible by computer only. A small jeopardy in some unnoticeable corner in this homeostatis in one such differential equation will have a butterfly and is capable to give rise to wild oscillation explaining unexplained fallout of disease and treatment including unexplained death. Computer assisted integration of even a few equations assuming other data (2) as much as possible will generate different fractal dimensions and graphic and attracter. We will use those in our known statistical system to evaluate different situations and act likewise. Instead of being single input single output (SISO) it becomes multi output multi input (MIMO) system. Hence, differential linear relation of steady state must break. Frequency domain estimation of simple linear calculation fails and nonlinear calculation in time domain becomes necessary. Nonlinearity and chaos emerges with this idea of time domain. Time domain includes time discrete and time continuous (time series} calculation. Time series may occur in state space with countable variables like in engines and in phase space where it is impossible to find out all variables.

Endocrine & human body Milieu

The value of resultant level of hormone in blood in no way can be underestimated because we have to see it as an outcome of this very complex system. There are scientists who are calculating this feedback in a time discrete multi steady state system and they are not less interesting (8). They are more important in cellular and subcellular mechanism, particularly genomic automanipulations. The Discrete Time (DT) domain is a timed extension of the Synchronous Dataflow (SDF) domain. Although not completely backward compatible with SDF, DT keeps most of the desirable properties of SDF-like static scheduling, regular/periodic execution,

bounded memory usage, and a guarantee that deadlock will never occur. In addition, DT has some desirable temporal properties such as uniformly-timed token flow and causality (9).

In this time domain, continuous state space model helps in protein chemistry (10,11) . But to understand why our dynamical, complex world, our lives, our whether and our experience never repeat but follow a pattern we have to move to nonlinear multivariate model in time series where differential interrelations are repeated (iterated) producing specific patterns in a phase space. It is also like a shape or a system that does never repeat but follow a pattern with different repeating shades and textures like trees, mountains and clouds (12). This 'self similar' feature of a dynamic system having non-integer dimension are described as fractal. Whilst the topological dimension of a line is always 1 and that of a surface always 2, the fractal dimension may be any real number between 1 and 2. The **fractal dimension** *D* is defined by

$$D = \frac{\log (L2 / L1)}{\log (S1 / S2)}$$

where *L*1, *L*2 are the measured lengths of the curves (in units), and *S*1, *S*2 are the sizes of the units (*i.e.* the scales) used in the measurements. Like distance here, change of any vector or its topology like dynamic chemical reaction may give rise to dimension unique to that system. Several other dimensions like capacity dimension, correlation dimensions are described according to the need of the subject or problem. It gives insight to understanding of many biological structure and function. They will have specific dimensions peculiar to a particular system. This direction of understanding, which needs computer to be developed, and which we may call "more sophisticated" approaches is using methods from nonlinear systems to measure the complexities

of the signal patterns. It has been applied to many endocrine control systems, e.g. to the release of PTH in the calcium phosphate homeostasis (13), Growth hormone, prolactin (14), to detect early ovarian cancer based on very low dimensionality adaptive texture feature vectors from cell nuclei from monolayers and histological sections (15). Gough has used fractal dimension in foetal heart rate variability(16). Cerebellar study contains fractal-based analysis (17).

In many biological systems, information is transferred by hormonal ligands, and it is assumed that these hormonal signals encode developmental and regulatory programs in mammalian organisms. In contrast to the dogma of endocrine homeostasis, it could be shown that the biological information in hormonal networks is not only present as a constant hormone concentration in the circulation pool. Recently, it has become apparent that hormone pulses contribute to this hormonal pool, which modulates the responsiveness of receptors within the cell membrane by regulation of the receptor synthesis, movement within the membrane layer, coupling to signal transduction proteins and internalization. Phase space analysis of dynamic parathyroid hormone (PTH) secretion allowed the definition of a (in comparison to normal subjects) relatively quiet "low dynamic" secretory pattern in osteoporosis, and a "high dynamic" state in hyperparathyroidism. We now investigate whether this pulsatile secretion of PTH in healthy men exhibits characteristics of nonlinear determinism. Our findings suggest that this is conceivable, although on the basis of presently available data and techniques, no proof can be established. Nevertheless, pulsatile secretion of PTH might be a first example of nonlinear deterministic dynamics in an apparently irregular hormonal rhythm in human physiology.

Feedback control

Feedback control is the basic mechanism by which systems, whether mechanical, electrical, or biological, maintain their equilibrium or homeostasis. In the higher life forms, the conditions under which life can continue are quite narrow. A change in body temperature of half a degree centigrade is generally a sign of illness. The homeostasis of the body is maintained through the use of feedback control (18). A primary contribution of C.R. Darwin during the last century was the theory that feedback over long time periods is responsible for the evolution of species.

Modern control

Modern controls design is fundamentally a time-domain technique. An exact state-space model of the system to be controlled is required. This is a first-order vector differential equation of the form

$dx/dt = Ax + Bu$ $y = Cx$

Where x(t) is a vector of internal variables or system states where infinitesimal data is possible in a biosystem, u(t) is a vector of control inputs, and y(t) is a vector of measured outputs (cybernetic systems).

Our body environ is a place where we cannot think of a closed loop. Everything fluid and solid creates biochemical phases and energy transfer is in open loop system in sub pituitary endocrine system. Closed loop being basic is explained here, but of course anyone interested will start from basic physical here to reach biosystem where number of equations to be understood increase enormously. This fails multivariate estimations (18) and chaos with resultant fractal based statistics intervenes. It helps us with providing different dimensions or constant to realize difference of two situations numerically. The power of modern control has its roots in the fact that the state-space model can as well represent a MIMO system as a SISO system. That is, u(t) and y(t) are generally vectors whose entries are the individual scalar inputs and outputs. Thus, A, B, C are matrices whose elements describe the system's dynamical interconnections.

Modern controls techniques were first firmly established for linear systems. Extensions to nonlinear systems can be made using the Lyapunov (19) (1907) approach, which extends easily to MIMO systems, dynamic programming, and other techniques. Open-loop optimal controls designs can be determined for nonlinear systems by solving nonlinear two-point boundary-value problems.

To achieve suitable closed-loop properties, a feedback control of the form

$u = -Kx$

may be used. The feedback gain K is a matrix whose elements are the individual control gains in the system. Since all the states are used for feedback, this is called state-variable feedback. Multiple feedback gains and large systems are easily handled in this framework. Thus, if there are n state components (where n can be very large in an aerospace or power distribution system) and m scalar controls, so that u(t) is an m-vector, then K is an mxn matrix with mn entries, corresponding to mn control loops. An alternative to static output feedback is to use a dynamic compensator of the form

$dz/dt = Fz + Gy + Eu$

$u = Hz + Dy.$

The inputs of this compensator are the system inputs and outputs. This yields a closed-loop and is called *dynamic output feedback*. The design problem is to select the matrices F, G, E, H, D for good closed-loop performance.

In biochemistry, feedback system is essentially a signal processing mechanism which helps in regulation of genetic and metabolic processes in response to extracellular signal. Regulatory motifs and modules could be of three types,

Switches for logical control, computation, signal integration and memory.

Control elements for continuous adjustment: feedback and feed forward loops

Oscillators for periodic transitions between states: synchronization, carry signal.

We are concerned more with control for continuous adjustment. They depend on signaling network using nonlinear ordinary differential equations as application of mass action or Michaelis Menten kinetics, though Bayesian and Boolean network has role in such case, as specially seen in genetic network.

Simple nonlinear ODEs those are required in feedback signaling are:

-Continuum description $x_i = x_i(t)$

$$dxi/dt = fi(x)$$

-Rate function fi

- Mass action chemical kinetics $f_i(x) = P(x_1, x_2 \ldots\ldots)$

- Michaelis Menten kinetics

$$f_i(x) = \frac{P(x_1, x_2 \ldots\ldots)}{Q(x_1, x_2 \ldots\ldots)}$$

Michaelis constant

Since the substrate concentration at Vmax cannot be measured exactly, enzymes must be characterized by the substrate concentration at which the rate of reaction is half its maximum. This substrate concentration is called the Michaelis-Menten constant (KM) a.k.a. Michaelis constant. This represents (for enzyme reactions exhibiting simple Michaelis-Menten kinetics) the dissociation constant (affinity for substrate) of the enzyme-substrate (ES) complex. Low values indicate that the ES complex is held together very tightly and rarely dissociates without the substrate first reacting to form product.

Michaelis-Menten kinetics

The derivation of "Michaelis-Menten" was actually described by Briggs and Haldane (20). It is obtained as follows:

The enzymatic reaction is supposed to be irreversible, and the product does not rebind the enzyme.

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

Because we follow the steady-state approximation:

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

Let's define:

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

Therefore:

$$[ES] = \frac{[E][S]}{K_m}$$

And:

$$[E] = \frac{[ES]K_m}{[S]} \quad (1)$$

The rate (or velocity) of the reaction is:

$$\frac{d[P]}{dt} = k_2[ES] \quad (2)$$

The total concentration of enzyme is:

$[E_0] = [E] + [ES]$

Hence:

$[ES] = [E_0] - [E]$ (3)

Substituting (1) in (3):

$$[ES] = \frac{([E_0] - [ES])[S]}{K_m}$$

$$[ES](1 + \frac{Km}{[S]}) = [Eo]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}} \quad (4)$$

Substituting (4) in (2) and multiplying numerator and denominator by [*S*]:

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

E_0 is the total or starting amount of enzyme. It is not practical to measure the amount of the enzyme substrate complex during the reaction, so the reaction must be written in terms of the total (starting) amount of enzyme, a known quantity.

d[P]/dt a.k.a. V_0 a.k.a. *reaction velocity* a.k.a. *reaction rate* is the rate of production of the product. Note that the term *reaction velocity* is misleading and *reaction rate* is preferred.

$k_2[E_0]$ a.k.a. V_{max} is the *maximum velocity* or *maximum rate*. k_2 is often called k_{cat}.

if [S] is large compared to K_m, $[S]/(K_m + [S])$ approaches 1. Therefore, the rate of product formation is equal to $k_2[E_0]$ in this case.

When [S] equals K_m, $[S]/(K_m + [S])$ equals 0.5. In this case, the rate of product formation is half of the maximum rate (1/2 V_{max}). By plotting V_0 against [S], one can easily determine V_{max} and K_m. Note that this requires a series of experiments at constant E_0 and different substrate concentration [S].

Michaelis-Menten kinetics describe the rate of enzyme mediated reactions for many enzymes. To determine the maximum rate of an enzyme mediated reaction, the substrate concentration ([S]) is

increased until a constant rate of product formation is achieved. This is the maximum velocity (Vmax) of the enzyme. In this state, enzyme active sites are saturated with substrate. Note that at the maximum velocity, the factors that effect the rate of enzyme mediated reactions (ie. pH, temperature, etc) are at optimal values.

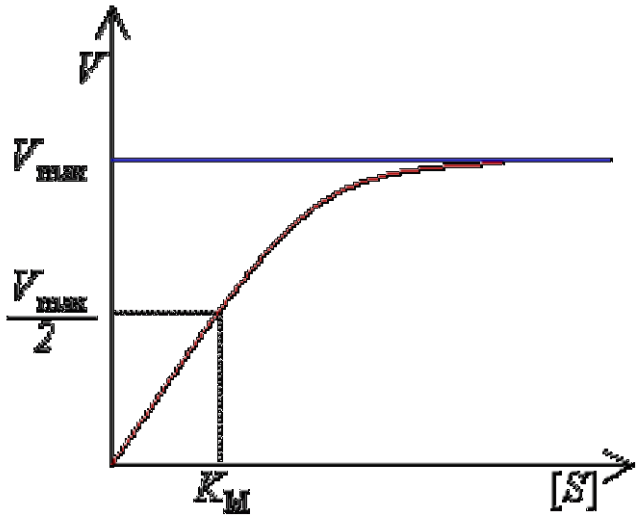

Figure 1. Diagram of reaction speed and Michaelis-Menten constant.

The speed V means the number of reactions per second that are catalyzed by an enzyme. With increasing substrate concentration [S], the enzyme is asymptotically approaching its maximum speed Vmax, but never actually reaching it. Because of that, no [S] for Vmax can be given. Instead, the characteristic value for the enzyme is defined by the substrate concentration at its half-maximum speed (Vmax/2). This KM value is also called Michaelis-Menten constant.

Spatial processes

Spatio-temporal behaviour is modelled by interacting spatial and temporal processes.

Spatial processes are different from temporal processes in that they do not act in a single point but gradually spread influences over space, starting from a boundary between two regions. A spatial process is represented as a field with expanding applicability regions, called expansion regions. The segments of the expansion regions correspond to fronts that move at a certain rate. The path of a spatial process can be guided by defining functional relationships between the rates of the fronts and the values of the regions they move through.

A spatial process can change other fields only indirectly by spreading temporal processes. Each expansion region is associated with a temporal process defined as a local variable within the spatial process. These embedded temporal processes do not themselves select a region to act on, but are applied to the points encountered by the fronts of the expansion region. Once applied, a temporal process is activated and decoupled from the spatial process. It obeys its own stop-conditions, which, however, can refer to the local variables of the spatial process.

A spatial process is defined similarly to a temporal process. The main difference lies in the influences. Since parameters are not directly influenced by spatial processes, I+ and I- are not used. Instead, the expansion regions are defined.

Example of hypothalamus pituitary ovarian (HPO) axis

As we propose to elucidate the unknown mechanism of pulsatile FSH release in three distinct different phase of postmenopausal, premenopausal proliferative and premenopausal secretary phase we have to construct a number of physiologically consistent model with empirically determined input-output relation. All models must be having parametrically isomorphic basis. Dynamical property of pituitary being largely unknown some modification may be needed at that level. First

the equation is to be solved analytically to obtain instant solution of of the mean equifinal hormone levels and the computer simulation has to be generated to obtain time series of the respective hormone levels. Biological information transfer will be base on Michaelis-Menten kinetics and feedback equation as in (1) supplemented by several loops for binding hormone to receptor and plasma protein.

The concept of "complexity," derived from the field of nonlinear dynamics, can be adapted to measure the output of physiologic processes that generate highly variable fluctuations resembling "chaos." We review data suggesting that physiologic aging is associated with a generalized loss of such complexity in the dynamics of healthy organ system function and hypothesize that such loss of complexity leads to an impaired ability to adapt to physiologic stress. This hypothesis (21) is supported by observations showing an age-related loss of complex variability in multiple physiologic processes including cardiovascular control, pulsatile hormone release, and electroencephalographic potentials. If further research supports this hypothesis, measures of complexity based on chaos theory and the related geometric concept of fractals may provide new ways to monitor senescence and test the efficacy of specific interventions to modify the age-related decline in adaptive capacity.

Michaelis-Menten kinetics which is known to deduct not only enzymatic conversion but receptor mediated signal transduction can be written as a subsystem as follows

$$y_e = \frac{Gx_e}{D + x_e}$$

Input signal being xe where G is the maximum possible response of the transduction element and D is the input signal yielding half of the maximum response G.

The temporal behaviour of the system's variable as described in a can be written as below which is done (as in a model ASIA element in case of thyroid study) and essentially consisting of a variable stimulating its own degradation

$$\frac{dy}{dt} = \alpha x(t) - \beta y(t)$$

in a first order feedback loop y denotes the output signal α the input gain factor and β a gain factor for output extinction. In the equifinal stage the subsystem will converge to

$$y_{\infty} = \alpha x(t) - \beta y(t)$$

with a first order time constant of

$$\tau_1 = 1/\beta$$

Oestrogen binds sex hormone binding protein (SHBG) or FSH binds its receptor can be simulated in a 0^{th} order linear feedback loop as per law of mass action with

$[H_F] = [H_T] - K[P][H_F]$,

where $[H_F]$ denotes the concentration of the free hormone , $[H_T]$ the total hormone leve, K binding constant and P concentration of respective plasma protein or receptor. In equilibrium

$$[H_F] = \frac{[H_T]}{1 + K[P]}$$

will be obtained.

For each level of signal transfer the respective equation is to be mapped to values taken from empirical studies.

As processing of information occurs in a much more complex way in pituitary gonadotrophin releasing hormone (GnRH) will have differing temporal pattern of release into the hypothalamic pituitary portal vessels. Ultra-short feedback loop connecting FSH to pituitary is also taken into account. Non competitive inhibition of FSH release by receptor bound oestrogen ($[E]_R$) could be expressed as

$$\frac{d[FSH]}{dt} = \frac{\alpha_S G_h [GnRH]_0}{(D_H + [GnRH]_0)(1 + L_S[E]_R)} - ß_S[FSH]$$

$[GnRH]_0$ is the GnRH level in the pituitary stalk vessel and with ultra short feedback loop of FSH in the pituitary $[FSH]_Z$ effects its own release according to

$$\frac{d[FSH]}{dt} = \frac{\alpha_S G_h [GnRH]_0}{(D_H + [GnRH]_0)(1 + L_S[E]_R) Z} - ß_S[FSH]$$

where $Z = \left(1 + \frac{S_S[FSH]_Z}{D_S + [FSH]_Z}\right)$

Where G_h = Secretion capacity of pituitary

D_H = Damping constant of GnRH in pituitary

D_S = Damping constant of FSH in pituitary

α_S = Dilution factor of FSH

$ß_S$ = clearance exponent of FSH

S_S = Brake constant of FSH ultra short feedback

L_S = Damping constant of FSH in ovary

Fractal character of biochemical signal data

How to predict that data is deterministic?

This is a very tricky problem. It is difficult because in practice no time series consists of pure 'signal.' There will always be some form of corrupting noise, even if it is present as round-off or truncation error or as a result of finite arithmetic or quantization. Thus any real time series, even if mostly deterministic, will be a stochastic process.

All methods for distinguishing deterministic and stochastic processes rely on the fact that a deterministic system will always evolve in the same way from a given starting point. Thus given a time series that we are testing for determinism we

(1) pick a test state

(2) search the time series for a similar or 'nearby' state and

(3) compare their respective time evolution.

Define the error as the difference between the time evolution of the 'test' state and the time evolution of the nearby state. A deterministic system will have an error that either remains small (stable, regular solution) or increase exponentially with time (chaotic solution). A stochastic system will have a randomly distributed error. Essentially all measures of determinism taken from time series rely upon finding the closest states to a given 'test' state (i.e., correlation dimension,

Lyapunov exponents, etc.). To define the state of a system one typically relies on phase space embedding methods.

Typically one chooses an embedding dimension, and investigates the propagation of the error between two nearby states. If the error looks random, one increases the dimension. If you can increase the dimension to obtain a deterministic looking error, then you are done. Though it may sound simple it is not really! One complication is that as the dimension increases the search for a nearby state requires a lot more computation time and a lot of data (the amount of data required increases exponentially with embedding dimension) to find a suitably close candidate. If the embedding dimension (number of measures per state) is chosen too small (less than the 'true' value) deterministic data can appear to be random but in theory there is no problem choosing the dimension too large--the method will work. Practically, anything approaching about 10 dimensions is considered so large that a stochastic description is probably more suitable and convenient anyway.

In 3-D living bodies are also made of fractals and the pulmonary system is the best example. Trachea breaks into smaller and smaller tube creating fractal canopie giving alveolar area of 80 sq m and 140 sq m in electron microscopy and measured fractal dimension is very close to 3 whereas in brain its 2.73 to 2.79, highest among all animals and in arteries it is 2.7. Like wise in 2D fractal this will be image analysis like x-ray or sonography film in medical imaging or histological texture of tumour.

In ovarian cancer context while 3-D fractal texture analysis will define inticrate papillary or mucinous growth of ovarian cancer as in vivo, 2-D image will be from ultrasonography or magnetic resonance image and in 1-D biochemical signaling in hypothalamo-pituitary-ovarian axis can be analyses.`

It should be emphasized that D is a descriptive, quantitaive measure: it is a statistics, in the sense that it represents an attempt to estimate a single valued number for property (complexity) of an object with a sample of data from the object. One can, for example, view D in much the same way that thermodynamics might view intense measures such as temperature. That is, as a measure of a property of some object or material, even though unlike in the case of temperature not much is known about the underlying mechanisms leading to this value. But it not unique as two object may appear visually very different and yet have the same fractal dimension (22,23).

Fractal calculation of different dimensions i.e. 1-D, 2-D and 3-D can effectively establish signal patterns in varied circumstance of body system. 1-D fractal and biomedical signal analysis are generated by complex self-regulating systems. That is why physiological time series may have fractal or multifractal temporal structure, while being extremely inhomogenous and non-stationary. A characteristic feature of nonlinear process is the interaction (coupling) of different modes leading to nonrandom signal phase structure, properties of which cannot be detected by linear spectral method. In phase space biochemical signalling will be a curve that may take course following apperantly stochastic process in increased dimension. Hence, further calculation will be needed to first have its topology in 2-D (by correlation, embedding dimension or other methods) and then calculating its D.

Fractal dimensioning in HPO axis

In recent studies, serum follicle stimulating hormone (FSH) levels in postmenopausal epithelial ovarian cancer patients were found to be significantly lower (24,25,26), even in preclinical phase of the disease (27). Levels of luteinizing hormone (LH) were found unchanged in those studies. Since ovulation is intrinsically linked to gonadotrophin stimulation, regulation of gonadotrophin

stimulation and gonadotrophin receptors (FSHR & LHR) may be important in such cancers. By repeated experiments cause of lowering of FSH level could not be ascertained. As a result gonadotrophin theory itself suffers a setback . Gonadotrophin releasing hormone (GnRH) agonist, triptorelin, has failed earlier to produce any relevant beneficial effect in patients with advanced ovarian cancer who received standard surgical cytoreduction and cytotoxic chemotherapy in a fairly large prospective double blind randomized trial (28). While evidence is conflicting, a critical role for gonadotrophins in the genesis and progression of ovarian cancer cannot be ruled out specially in a position where we are getting high FSHR expression in abnormal, though most relevant, place of ovarian surface epithelium and low level of FSH in blood. It seems lucrative to think that these two phenomenon has a common and important relation in causation of such cancer. However, it is not possible to comment on it before both FSH and FSHR are tested in same set of experiment. There are a few studies of the receptors in epithelial ovarian cancer (29,30,31,32). Basic issue of role of receptors other than the receptors of GnRH, gonadotrophin and sexteroids in endocrine feedback if even set aside, searching for the cause of aberrated expression of FSHR in epithelial cells seems worthwhile.

Hence, simulated and real time series of HPO axis hormone as described in biochemical reaction kinetics can be digitized and processed by two programs for calculating fractal dimensions of the signal patterns.

The first measure of complexity used is the fractal capacity dimension D_{cap}. This approach cover the graphical representation of the time series with squares of successively varied border length e using mesh counting theorem. For each length it countss the number N(e) of squares covering the curve. With

$$D_{cap} = \lim_{e \to 0} \frac{\log(N(e))}{\log(1/e)}.$$

The capacity dimension can be calculated and compared for real (premenopausal proliferative, premenopausal secretary, postmenopausal normal and postmenopausal epithelial ovarian cancer cases) and simulated time series.

By means of second approach to determine the data's complexity the so-called correlation dimension, D_2 will be calculated.

After embedding the time series x1,x2.x3……xn into the m-dimensional vector

$$\mathbf{y_i} = (x_i, x_{i+r}, x_{i+2r}, \ldots, x_{i+(m-1)r}), \quad i = 1, 2, \ldots .$$

the local density

$$n_i(e) = \frac{1}{n} \sum_{j=1}^{n} u_0(\varepsilon - |y_i - y_j|)$$

as relative number of neighbour points of an attractor point y_i whose distance is smaller than ε could be calculated with heaviside function

$$u_0(x) = \begin{cases} 0, x < 0 \\ 1, x > 0 \end{cases}$$

Subsequently by averaging over several reference points the correlation integral

$$C(\epsilon) = \lim_{n\to\infty} \frac{1}{n^2} \sum_{i,j=1}^{n} H(\epsilon - |\mathbf{y_i} - \mathbf{y_j}|),$$

as the number of correlated vectors normalized over the number of possible vector pairs n^2 can be calculated.

For each embedding dimension, formally similar to the definition of the capacity dimension, a specific local correlation dimension D_2 can be obtained from

$$D_2 = \lim_{\varepsilon\to 0} \frac{\log C(\varepsilon)}{\log \varepsilon}$$

The first maximum of the local correlation dimensions D_2 arranged by increasing embedding dimension m, can be regarded as global correlation dimension of the time series.

Real time series of four conditions as mentioned above can thus be compared among themselves and with that generated from models. Both capacity dimension and correlation dimension can now be calculated different available calculators found in web.

By this approach not only we can guess what could be the reason of aberrant expression of FSHR in epithelial ovarian cancer, if we use processes as described for differentiating this real time series we can compare which of them is most sensitive as was done before in case of multivariate analysis (33). There, we could show that discriminant function, Z was superior to Mahalanabis Distance in differentiating cancer from normal cases.

Further deduction (function of function of function etc.) takes us to the end of modern physical control and by repeating (iterating) function infinitesimally we get fractal dimensions and graphics.

A conjecture

We can demodulate the above theme very easily in nonlinear area from a little absolute perspective. It's also a link between input and output. By the quality of working link at that moment, i.e. whether serial, parallel, negative feedback, positive feedback, behaviour of the system is determined at random. Here, the control is, of course, nonlinear (Poincaré). Comparing with linear system, here, we can't get a cross-section of the system at our will, having some values to work with; rather we have to have a picturesque overview of the whole system (in phase space – of dimension depending on number of variables controlling) as a categorical object for

qualitative study to understand the dynamism, as like the study of other chaotic system (34). It is comparable with the study of a system from the dynamic shape of its shadow (Homeomorphism). This is practically feasible in case of a thermodynamically stable system like the biological system within us. Like every physical system it is undergoing entropy, perpetuating disorderly state. It is obvious also because in our probabilistic existence the chances of getting disorderly states completely outweigh the chance of encountering orderly state in our future. What in our biological system is responsible to give feedback, go opposite to the direction of thermodynamical time i.e. direction of entropy. Information theory says us that only our complex biological pattern (relics of investment of energy) is the basis of that order which appears to negates the entropy (called negentropy) and eventuates, what we call, feedback.

All biological functions are executions of the subsystem in face of changing space-time (35). Macroscopic quantum systems (MCQs) equipped with memory functions are self-organisations in associative phase space. Here, the sub-system may be either in non-stimulated or in stimulated (volitional) status. As endocrine feedback is supported on autonomic control this execution is primarily a ready show as cosmology is the reflection of one's own biology. MCQs are highly sophisticated sensitive system that reads and adapts aperiodic changes of space-time i.e. entropy-negentropy, the only essentials of information system. Any system study without the consideration of involved space-time complexity in account always remains futile.

Proper time of any event is universal to all individual existences irrespective of their coordinates. It is '0'-symmetry. Möbius strip topology of ½ spin and 3/2 spin supports the absolute display of space-time in two and three dimension respectively (35). Time can only start in both ways: forward, as space or Classical entropy (Prime field on real number) of the subsystem reflecting its own design of entropy in context of other systems at that moment and backward, as time or quantum

negentropy (Antiprime field on imaginary number). Proper time satisfies their conjugate validity along ascending series of aperiodic discretes on '0'-symmetry or Null. This ascending series of Prime-Antiprimes is the common base of all subsystems as absolute grid where all has to concur in Classico-quantum measurement. Thus, space-time becomes fractal. One who is closer to the event perceives it while younger. So subsystem always adjusts itself with space-time even by time dilation in the direction of journey!

All quasi-random subsystems along Monte Carlo path originate from Parent system of pure randomness or Null. At birth of the subsystem, in its condensate phase of zygote, a segment of Null gets incorporated across Bosonic Null of infinite motor wing as discrete stations. Infinite motor wing is infinite twistor arm (Wallace-half) that obeys Pauli's spin algebra (35) in continuous phase space. In its spinor space these stations are the above said ascending series of Prime-Antiprime conjugates. Thus path of Null disposition is being paved within the subsystem in advance. As both entropy and negentropy increases with time every MCQ is infallibly a thermodynamically stable system. And, the finite part that holds the heredity is carried along sensory wing. The sensory wing that obeys quarternion algebra in the context of discrete Classico-quantum measurements is based on infinite untwistor arm (Darwin-half). The wings with central fulcrum define the identity of the subsystem as the basis of feedback mechanism. Input in sensory wing is recorded as self-similar untwist of weak and strong untwistors. Twistor and untwistors are trinary elements, homologous to genomes, along subsystem's space-time journey including that of its inheritance. If analogy is drawn in between genetic algorithm and structure of sensory wing it will be found that four sub-elements, $+^{Q}$, $-^{C}$, $+^{C}$ & $-^{Q}$, represent nitrogenous bases. They along null operation of central commutating function of $+^{C}\text{--}^{Q}$, Prime-antiprime or Clasical entropy-quantum negentropy conjugate of present moment, with the anticommutating functions, $0^{C}\text{-}+^{Q}$ & $-^{C}\text{-}0^{Q}$, in its symmetric arms

forms a semantic untwisted triplet structure in gravity wing if antisymmetry exists simultaneously in energy wing. So, the above untwist, as a record of space-time, are encoded in untwists and folds of gene and, along its journey, of DNA-string. And they when gets decoded in absolute churn with motor wing eventuates exact feedback as output. Here, one may note that in genetic transmission by haploid cell division memory pages that eventuates on joint participation of two wings get lost but prominent twists and folds of DNA-string of sensory wing, adapted in lifetime of the species, are carried up the hierarchy.

Energy Dynamical System and Gravity Dynamical System handle entropy and negentropy counter-complimentarily. One is inverse in function and direction (in time) the other. Basic difficulty of dealing with infinite systems is its normalization. But two infinite functions, real and imaginary becomes orthonormal iff these number systems form a counter-complementary ring system where real number system ascends towards '∞' and imaginary number system ascends towards '0' in 2D topology (36). Möbius group of complex functions, while satisfying fundamental Lorentz invariance, conserves orthonormality of infinite functions. MQSs are open systems. In spite of having boundaries they are infinite systems (infinite within its finite frame). So, deterministic study of such system should include whole history of space-time. To thrive intelligently it has to understand and deal with sophisticated group operations i.e. addition, multiplication with their inverse ones in associative discrete tangential space.. In this case while executing the above operation the subsystem bases itself on null operator. So, unaltered core makes itself an eigenfunction. This is not the case when one studies on a subsystem from outside. Notwithstanding, in all cases where the above operations become very fast and get transformed into basic exponential operations of entropy-negentropy i.e. integration (addition to multiplication to positive exponentiation) or differentiation (additive inverse to multiplicative inverse to negative exponentiation) the eigenfunction remain unaltered! And, in this exponential phase MQS can only

function automatically and deterministically, yet absolutely sharing with others. This happens in continuous phase space where all information glues into a non-sharable soup. Here observer gets merged with the observed.

So, to study a system in deterministic way on discrete data conventional reach towards entropy should always be supported with simultaneous reach towards negentropy. And it is only possible if there is no energy waste while collecting working data. Thus, Lorenz's modeling is the ideal fit in this context. It represents not formally as information from one sectional data but the phenomenon itself. So, it includes not only entropy and negentropy but also null operation into consideration as it represents itself as Möbius topology in phase space. It is truly a homomorphic study of not only a chaotic system but also a living system as MQSs. The strength of Lorenz's parameters to study the convection within a system directly is its unending periodicity (or aperiodicity). But, in study of biological system, how much influence its status of entropy or negentropy will have on parameters to study biological phenomena is still undecided. Or, to reveal whether equations relating the function of other variables (more than three) end in zeros is highly difficult. At best we can sort out a phenomenon that is dependent on three independent variables. And Calcium homeostasis is an ideal example of that as it is dependent primarily on serum levels of Parathormone, Calcitonin and Vitamin D_3. Their differentials on time series in the above model whether behaves periodically or not is our present interest. Moreover in our context we have observed another relation in the above classical (37) model, commonly called the Lorenz system. Here, first equation is of different kind from second and third one because the later hold mixed terms like 'xz' or 'xy'.

$$dx/dt = 10(y-x)$$

$$dy/dt = xz + 28x - y$$

$$dz/dt = xy - (8/3)z$$

Parathormone and Calcitonin are functionally more or less antisymmetric. But, functional status of Vitamin D_3 is different from the above two. In physiological doses (produced in body depending on geo-ethnic factors like skin pigmentation) it helps deposition of calcium in bone but in high doses its action becomes Parathormone like. Here, it helps mobilization of calcium out of bone.

Möbius complex functions are analogous to Geometric algebra. So, if a strange attractor begins to emerge in analogue study of Calcium homeostasis it can be placed under complex analysis along the Clifford algebra for strict verification and further improvisation. This will help to decode the attractor, label the normalcy or exact pathology from its different appearances and gestures in phase space.

Conclusion

Calculation of endocrine function in system of chaos and fractal will generate new dimension in nonlinear system like fractal dimension, in single or multiple time series giving us scope to differentiate and evaluate self similar features or Poincaré c section indicating fractal attractor.

But it has to sustain test of time to come out as an efficacious method. Other processes like time discrete, state space model, Markov chain, Monte Carlo path (38), are already being tried alongside. Markov chain Monte Carlo statistics are more used in assessing cost effectiveness and relative efficacy of different hospitals (38) where as random walk technique is used in researches on gait (39), cerebellar function, ophthalmology (40) etc. But, undoubtedly, fractal based statistical calculations are more modern and very much useful in indicated cases.

Previous behaviorally isomorphic way using different classes of equations (linear, logarithmic, exponential or polynomial) though deliver probable ways in which the system might be realized, this approach also exposes the models to charges of being arbitrary (41,42). Neuroendocrinal hierarchy of pituitary thyroid axis has already disproved theory of pulsatility of input of TRH at the pituitary yielding corresponding TSH pulse (43,44) where as mechanism of causing the fast oscillations is also unknown.

Pituitary ovarian axis as yet unexplained by this new system, attracts concentration. People will speculate how accurate it will be to have the glimpses of this complex calculation and some will doubt its efficacy. However trial run with many different systems with this new mathematics serving as statistics at hand will go on unhindered revealing more accurate picture with more approximate differential reach. It will eventually endow human hands with more power and edge leading to lesser sufferings of the humanity; we hope.

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