Systems Information Therapy and the central role of the brain in allostasis

Alberto Foletti* and Settimio Grimaldi°

*Lugano, CH 6900, Switzerland and Institute of Translational Pharmacology, CNR, Rome, Italy,
°Institute of Translational Pharmacology, CNR, Rome, Italy.

E-mail: contact@albertofoletti.ch

Abstract. This work arose from the necessity to update and clarify some basic concepts in contemporary medical practice such as those of health, disease, therapy and prevention. According to this perspective the work starts with a general epistemological review and goes on with an epistemological revision of biology and medicine. The concept of adaptation and the central role of the brain is then analysed and stated as the base to next consideration and deepening from a biophysical perspective. Physio-pathology of adaptation is assumed as a key concept in the definition and in the understanding of health and disease. A huge amount of endogenous and external stimuli has to be processed and response to them may lead to increase, stability or decrease of coherence in agreement with Frohlich’s pioneering ideas. In this framework, the concept of stress, allostasis and allostatic load are outlined. Allostasis is defined as the capability of keeping stability through dynamic changes. A particular attention is paid to the emerging paradigms in biology and medicine especially those of system biology and system medicine trying to integrate the concept of complexity and hierarchical organization of the information flow in living organisms and in humans. In this framework biophysical signalling could play a significant role in modulating endogenous dynamics and in mediating external interactions. Additionally biophysical mechanisms could be involved in biological systems inner communication and could be responsible for the maintenance of systems inner coherence. The integration of the biophysical paradigm into contemporary medical practice is leading from one side to a better understanding of many pathways in physiopathology and from the other side to some new effective clinical applications. System Information Therapy is, for instance, is rising as a suitable and coherent tool in the application of these concept being able to restore the self regulation and self regeneration capabilities both at the local and at the system level operating with endogenous and external electromagnetic signals in the range of the extremely low frequency electromagnetic signals. Some practical applications are described such as the clinical detection and treatment of fluctuating asymmetry by Vega Select 719. Fluctuating asymmetry, as well known, is related to the presence of an allostatic load and its disappearance after a biophysical treatment is a good clinical evidence of restoring of allostasis mediated by the brain at systemic level presumably through a biophysical repatterning in which we assume a key role should be played by membranes, cytoskeleton and especially by microtubules.

1. Introduction.
The living human body achieves his own systems stability, in spite of the continuous fluctuations in its external and internal environment, by an ongoing brain-coordinated process of both systemic and local physiological adjustment called allostasis. In other words the term allostasis describe the process
of maintaining stability through dynamic changes. It is different from the usual term of omeostasis employed so far because it includes the concept of a dynamic process finalized to the aim of maintaining the alive’s dynamic as “a continuous flow of matter, energy and information” [1] as embedded in a biofield.

Being alive means to keep far from the thermodynamic equilibrium and maintain a dissipative dynamic in agreement with Prigogine’s description of the living organisms: in one word being alive means to keep in allostasis.

Adaptation to a current stressor is referred to as allostatic accommodation. The number and the nature of stressors to whom we are exposed at any time during all our life span could be very huge. Any input coming from outside or from inside the organism must be translated from different language, depending on the different channel of the input (sight, hearing, feel, taste, smell, balance, pallaeesthesia,…) into a unique code, the so called organic code [2,3], in order to process these signals as flow of information and translating them into specific meanings. It is a continuous and dynamic process of signals transduction in order to allow the computational process of the different stimuli.

The adaptive process is mainly a computational process aimed to maintain allostasis. It is not allowed not to adapt so it is not allowed not to provide output to any single input coming from the external or from the internal environment (both real or virtual, because the brain only processes its own representation of the world). Nevertheless the outcome is very different in respect to the different kind of output delivery. At this point the difference that makes difference is, uniquely, the kind of output namely the kind of adaptive response delivered. The main criterion to take in account is related to the coherence of the adaptive response to the nature of the adaptive stimulus in order to achieve the allostasis. This criterion was first described as related to biological systems by Herbert Fröhlich [4]. In this framework we can distinguish: Output coherent to the nature of the input: this is the suitable response, delivered at the suitable moment and maintained for the suitable time. This output is defined as the functional adaptive response. And output not coherent to the nature of the input: this is the not suitable response, delivered at the not suitable moment and maintained for the not suitable time. This output is defined as the dysfunctional adaptive response.

The dysfunctional response may be temporary without leading to damages or lead to a progressive biological damage leading in that case to the so called pathologic adaptive response. In this case we can register and measure the damages at the biological level evaluating the possibility to stop and reverse the process or otherwise the progressive lose of the function with no possibility to restore allostasis.

The cumulative amount of wear and tear, the continuous effort, coming from the continuous allostatic mechanism could represent the concept of allostatic load [5, 6, 7]. This process is spread over all our lifespan beginning from the conception till to the death. As allostatic load accumulates, the body’s capability for effective allostatic adaptation decreases, leading to a downward spiral of increased vulnerability to new stressors, and ultimately to impaired global health both in biological mechanisms (immune system, hormonal system, autonomic nervous system, postural response) and in psycho neuro emotional behavioural mechanism. From the above description the following consideration seem to be of interest.

The possibility to estimate the presence of the allostatic load during a clinical examination could not be neglected in the light of the recent finding related to ill health dynamics [8]. The possibility of managing allostatic load in the clinical activity is consequently one of the main aims of any therapeutic intervention.

Moreover reducing allostatic load is the greatest deal of any preventive hints in medicine because of the evidence still available regarding the reduction of all risk of mortality by reducing allostatic load [9, 10].

At this point the following question has to be answered:

- Is it available some clinical method to detect the presence of the allostatic load at first as a general feature and secondly as detailed feature?
- Is it available a clinical method to manage allostatic load in order to restore allostasis?
Some papers showed a relationship between the presence of the allostatic load and the presence of fluctuating asymmetry [11, 12, 13, 14, 15]. Fluctuating asymmetry is defined as the asymmetric activation of symmetric group of muscles due to a loose of coherence into the inter hemispheric synchrony at the brain level. As recently established optimal information transfer in the brain is related to synchronization [16]. Evolutionistic and behavioural biological sciences have extensively proved that human beings develop forms of “Fluctuating Asymmetry” in response to environmental stress. Fluctuating Asymmetry has been defined as the loss of perfect symmetry, which also involve symmetric body segments, induced by stressful environmental factors and is the expression of the presence of allostatic load. Fluctuating asymmetry is most probably related to the lose of synchronization between the two brain hemiphere due to allostatic load.

It is well established that the brain is the key organ in managing stress coping and in keeping allostasis through activation of self regulation and self recovery properties of the system [17, 18] both in event of general adaptation(GAS) syndrome and in local adaptation syndrome(LAS) according to Selye’s former description [19]. Therefore the clinical detection of a fluctuating asymmetry through semeiotic evaluation is a good model to asses the presence of allostatic load as referred to a general reaction of the whole organism like in case of General Adaptation Syndrome mediated through the brain. Clinical evaluation of fluctuating asymmetry is reliable and objective, quick to learn and easy to perform, it is also not invasive and comfortable to the patient. Clinical evaluation of fluctuating asymmetry can be integrated in the current clinical evaluation so resulting even time saving and cost effective. Clinical evaluation of fluctuating asymmetry is a very good tool to detect allostatic load and to follow its evolution at different time.

In the last decays a true change of paradigm as began involving at first biology and later on medicine. The progressive fall of reductionism has lead to the rise of the concept of systems biology and only very recently to the concept of systems medicine. In the framework of systems medicine it is clear that some features and behaviour of the system as a whole are not the sum of the single parts but arises from emergent characteristics due to the complexity of the human organism. All the adaptive dynamics we described earlier considering the brain as the central switchboard has therefore to be understood within the System Medicine approach [20, 21, 22]. As a consequence biology and medicine has to deal nowadays from one side with the need to understanding biological complexity and from the other side with the need to manage biological complexity with new and appropriate tools both in experimental biology and in clinical practice. The comprehension of complexity of biological systems is a challenge that requires any effort to build bridges between different sciences such as chemistry, biochemistry, molecular biology, genetics, epigenetic, physics, biophysics, information theory, signals theory, networks theory, bioinformatics, and communication theory, physiopathology of adaptation, evolution theory, and epistemology. Many evidences has accumulated on how cells, tissues and organisms usually generate electromagnetic signals in different frequency ranges and on how living organisms could use electromagnetic signals as an additional mechanism to synchronize specific physiological activities especially at the level of brain, nerves, hearth, muscles and most probably at any level of cell and tissue function both in adaptive allostatic response leading to resilience and in maladaptive adaptive response leading to defiance through allostatic load.

The managing of complexity in clinical medical practice at the light of these new biophysical knowledge is still at is beginning nevertheless thanks to the bridging between Systems Medicine, biophysics, electronics we can useful employ some electro-medical devices that allow to manage different symptoms and diseases especially those of dysfunctional origin coherently with the aim of improving quality of life and reducing allostatic load. This new clinical approach is called Systems Information Therapy (SIT). Systems Information Therapy is based on the concepts of a bio-informational effects of physical factors (pattern of endogenous or exogenous signals within specific range) and assume the physiopathology of adaptation as a basis for the comprehension of the dynamics that underlay to health and disease. The restore of the coherence of response to internal or external stimuli and the restoring of the self regulation and self regeneration abilities locked by appearance of a dysfunction in the biophysical pathways is the main aim of Systems Information
Therapy by biophysical means. In one word the activation of the built in self-recovery ability. We previously demonstrated that electromagnetic signals in the extremely low frequency range generated by a commercially available electro-medical device (Vegaselect 719) were able to transfer specific information pattern to living cells triggering stem cells differentiation [23], epithelial cell [24] and neuronal cell differentiation [25, 26] as well as human neuroblasoma cell differentiation toward a normal cell type by electrically transferring the molecular signals of retinoic acid [27].

And now the answer to the question if a clinical method to manage allostatic load in order to restore allostasis is available. According to our previous experimental finding at cellular level especially those regarding the effect of extremely low frequency electromagnetic signals on neuronal cells [26] we decide to employ the same commercially available electro-medical device (Vega Select 719) in order to asses if it was able to induce clinical effect in managing fluctuating asymmetry. We found out that a Systems Information Therapy approach is effective in erasing the clinical patterns of fluctuating asymmetry leading therefore to the clinical possibility of a useful management of allostatic load.

2. Materials and methods
A total of 300 patients clinically assessed in search for evidence of fluctuating asymmetry were found positive. Patients with evidence of fluctuating asymmetry whit previous history of congenital anomalies, major traumas, fractures or surgical procedures performed at the hips or legs levels was not included into the trial in order to select homogeneous parameters of evaluation. These selective criteria lead to exclusion of 12 patients. As inclusion criteria only patients showing a fluctuating asymmetry of at least one centimetre, or more, was enrolled in order to increase the reliability of the differential evaluation. At the end 288 of them was enrolled and dived into two groups. The first group of 144 patients was treated by Vega Select 719 and the second of 144 was enrolled as control group. The treatment was delivered according to the following experimental design distinguishing treated and non treated group:

- **Treated group**: patients were lying on a usual clinical bed and the electro medical device placed at the left side. Input electrode was placed bilaterally at the level of the forehead by an adhesive while output electrode was placed at the level of the ears and hold in place by the patient. The setting of the device’s parameters was as follow. Currying wave swinging from 4.0 to 10.0 Hz, modulating waves fixed 7.0 Hz, intensity of the delivered electromagnetic field was 35% of the maximum of 5 μT available. The entire procedure lasted 10 minutes.

- **Control group**: patients were lying on a usual clinical bed and the electro medical device placed at the left side as for the treated group. Input and output electrodes were placed as for the treated group. The device was simply switched on but started therefore not running. The entire procedure lasted 10 minutes as well.

Each patient of both treated and control groups were asked to walk in the examination room for 10 minutes after the end of the experimental procedure. At this time a new clinical examination was carried out focused on fluctuating asymmetry with the same criteria of first one.

3. Results
In the treated group, 144 patients, behaved as follow:

- complete disappearance of fluctuating asymmetry was reported in 116 patients, 81,25%,

- partial reduction of fluctuating asymmetry was reported in 24 patients, 15,97%,

- same amount of fluctuating asymmetry was reported in 4 patients, 2,78%,
In the control group, 144 patients, behaved as follow:

- complete disappearance of fluctuating asymmetry was reported in 0 patients, 0%,
- partial reduction of fluctuating asymmetry was reported in 17 patients, 11.8%,
- same amount of fluctuating asymmetry was reported in 127 patients, 88.2%,

None of the patients reported side effects during or after the therapeutic procedure. Patients of both group reported a significant increase of feeling of relaxation.

Fig. 1 shows a clear demonstration of the presence of fluctuating asymmetry according to the picture taken at the first clinical evaluation and comparatively, in the same patient, the positive effect of System Information Therapy (S.I.T.) in re-establish completely the symmetry at the level of the ankles.

4. Discussion
A first astonishing consideration comes from this preliminary, but systematic, clinical assessment of the presence of fluctuating asymmetry: fluctuating asymmetry is almost ubiquitous even if it shows a different amount in its measure. These data are consistent with the framework of allostasis and allostatic load that propose that both allostasis and allostatic load are a direct, and someway, unavoidable consequence of being alive. In this perspective live mean be under a number of stressors, coming both from outside and from inside the organism. Each input stressor is traduced into signals suitable to be processed and translated to the brain. The brain has a central role in processing each signals referring to inner or external inputs [28, 29, 30]. This computational process done by the brain allows to translate this flow information into different meaning according to specific codes [2, 3] and give rise to signals able to deliver the adaptive response as final output. Most of these process are out of the level of consciousness, only a very few amount of these continuous adaptive process occur at the conscious level. Adaptive response involves at once, both the neurological psycho-emotional behavioural side and the biological side including hormonal system, immune system, autonomic nervous system and muscle-skeletal system. Actually any adaptive response is a true complex pattern
involving in different time and in different blended amount each of the above mentioned system. In this framework when an input stressor appears two possible outcomes are outlined as possible: functional, namely adaptive responses, or dysfunctional, namely maladaptive responses.

While, on one side, functional adaptive response sustains allostasis and improves resilience increasing health and, by an upward spiral, salutogenesis. On the other side, dysfunctional maladaptive response sustain allostatic load and improve defiance increasing disease potential and, by a downward spiral, pathogenesis. As a consequence health and disease could now be considered as the two side of the same life-lasting adaptive effort and could not be longer considered separately but rather as a dynamic process aimed to survival and personal evolution.

According to the literature evidence of fluctuating asymmetry has to be considered a as a clinical marker of allostatic load due to impairment of the physiologic inter hemispheric synchronization leading to the lose of symmetry between the two side of the body that, as well known, are controlled each one from the opposite side of the brain hemisphere. This impairment in keeping lateral symmetry is the effect of the dysfunctional adaptive response involving muscle-skeletal system at the body level as peripheral expression of the central control output delivered at the brain level. Therefore the clinical evaluation of fluctuating asymmetry is as easy and reliable tool to evaluate the presence of allostatic load involving the brain. Consistently with these considerations it does not so astonish the ubiquitous presence of fluctuating asymmetry because allostatic load, even if in different amount, is someway underpinning any life process. Moreover it is of interest focus on the great clinical utility of a first, even if general, criterion of assessment and monitoring of allostatic load also in the growing field of preventive medicine. Disappearance of fluctuating asymmetry could be a marker of a disappearance or at least of a not negligible decrease of the amount of the allostatic load of the examined subject. That is the reason for which in this preliminary study we assume significant reduction or disappearance of fluctuating asymmetry as a good clinical response as well as expression of an effective management of allostatic load. The Systems Information Therapy approach was performed in this study by a commercial available electro medical device (Vega Select 719) of which the authors have reported some interesting evidence of effect at cellular level on different cell culture especially differentiation of human pituitary neurons in vitro [26]. These evidences lead to the clinical application of the same device in order to asses any possible useful effect in humans in agreement with some previous report of similar devices operating in the extremely low frequency range of the electromagnetic signals by means of a resonance effect [31, 32, 33, 34, 35, 36] by external signal. We integrated the use of endogenous signals recorded at the level of the forehead bilaterally. We settled the currying wave at 7 Hz, in agreement with our previous finding on neurons [26], and set the modulating frequency within the range from 4 to 10 Hz swinging very slowly from 4 up to 10 Hz and backward in agreement with the usual range of functioning of the brain during rest and deep relaxation. Finally the magnetic field delivered was settled at 35% of the 5 μT (micro Tesla) available. We speculate that these setting could trigger the self-regulation and self-regeneration capability at the level of neurons and promote the inter hemispheric synchronization leading to the fast recovery of central symmetric activation of symmetric muscles chains thus restoring symmetry at any peripheral level as at the knees and at the ankles.

5. Conclusions

Coherence of the adaptive response to the nature of the external or internal stimuli is the suggested criterion to take in account defining health and disease dynamics in the emerging framework of Systems Information Therapy that arises from bridging Systems Medicine and physio-pathology of adaptation. The central role of the brain could be taken in account also from a biophysical and computational perspective in which microtubules are assumed to play an important role [37, 38]. Adaptive dynamics are assumed as a key concept in definition and understanding of health and disease including the evolutionary perspective [39]. Lots of endogenous and external stimuli, namely stressors, have to be processed and the adaptive response given to them may lead to increase, stability or decrease of coherence in agreement with Frohlich’s description [4]. In this framework, the concept
of stress, allostasis and allostatic load has been outlined until to the definition of a true “price of adaptation” [40] referred to the consequences of allostatic load.

The emerging paradigms in biology and medicine especially those of system biology and system medicine try to integrate the concept of complexity and hierarchical organization of the information flow in living organisms and in humans stating the brain as the interface between inner and external stressors. In this framework biophysical signalling could play a significant role in modulating endogenous dynamics and in mediating external interactions through brain’s computational activity. Biophysical mechanisms are involved in biological systems inner communication including brain function and could be responsible for the maintenance of systems inner coherence. I particular some evidence tribute to microtubules a role in the maintenance of synchronicity [41]. This preliminary report leads us to some interesting closing remarks.

Systems Information Therapy showed a very significant effect in reducing or erasing fluctuating asymmetry. In the control group none of the patient showed a complete recovery, only 11.8% showed some partial reduction of the previous amount of fluctuating asymmetry and 88.2% showed no variation from the initial record. Surprising in the treated group a complete recovery was reported in 81.25% with a complete restore of symmetry, partial reduction was reported in 15.97% and no variation only in 2.78%. It is a well stated and current opinion that fluctuating asymmetry is a clinical correlate of allostatic load. Therefore we could argue that the disappearance of fluctuating asymmetry has to be considered as a clinical evidence of a significant reduction of allostatic load achieved through a restore of coherence at the brain level involving peripheral changes.

These preliminary results are very promising and indicate a Systems Information Therapy approach as an effective and safe tool suitable to manage allostatic load in clinical practice. Future studies should be designed in order to expand the number of patients, to study which other clinical parameters should undergo some significant useful modification and in order to achieve a better definition of the possible use in managing allostatic load and in contributing to management of dysfunctional disease and to improve health quality moreover contributing to successful aging.

References
[1] Brizhik L S, Del Giudice E, Popp F-A, Marie-Oeler W, Schlebusch K P 2009 Electromagn. Biol. Med. 28 28
[2] Barbieri M 2003 Hist. Philos Life Sci. 25 243
[3] Barbieri M 2004 Riv. Biol. 97 91
[4] Fröhlich H, editor 1988 Biological coherence in response to external stimuli (Berlin: Springer Verlag)
[5] McEwen B S, Stellar E 1993 Arch. Intern. Med. 153 2093
[6] McEwen B S 1998 Ann. N.Y. Acad. Sci. 840 33
[7] McEwen B S, Wingfield J C 2003 Horm. Behav. 43 2
[8] Fava G A, Guidi J, Semproni F, Tomba E, Sonino N 2010 Psychother. Psychosom. 79 280
[9] Karlamangla A S , Singer B H , McEwen B S , Rowe J W, Seeman T E 2002 J. Clin. Epidemiol. 55 696
[10] Karlamangla A S , Singer B H , Seeman T E 2006 Psychosomatic Med. 68 500
[11] Parson P A 1990 Biol. Rev. Camb. Philos. Soc. 65 131
[12] Livshits G ,Kobyliansky E 1991 Hum Biol. 63 441
[13] Kownner R 2001 Br. J. Psychol. 92 447
[14] Al-Elisa E, Egan D, Wassersung R 2004 Evolution and Human Behavior. 25 31
[15] Brown W M, Price M E, Kang J, Pound N, Zhao Y, Yu H 2008 Proc. Natl. Acad. Sci. USA 105 12938
[16] Buehlmann A, Deco G 2010 PloS Comput. Biol. 6 e1000934.
[17] McEwen B S 2007 Physiol. Rev. 87 873
[18] McEwen B S, Gianaros P J 2010 Ann. N.Y. Acad. Sci. 1186 190
[19] Selye H 1956 The stress of life (New York: McGraw-Hill Book Co.)
[20] Dhar P K, Zhu H, Mishra S K 2004 IEEE Trans. Nanobioscience 3 144
[21] Bateson P 2005 J. Biosci. 30 31
[22] Federoff H G, Gostin L O 2009 J.A.M.A. 302 994
[23] Lisi A, Ledda M, De Carlo F, Pozzi D, Messina E, Gaetani R, Chimenti I, Barile L, Giacomello A, D’Emilia E, Giuliani L, Foletti A, Patti A, Vulcano A, Grimaldi S 2008 Electromagn. Biol. Med. 27 127
[24] Lisi A, Ledda M, De Carlo F, Foletti A, Giuliani L, D’Emilia E, Grimaldi S 2008 Electromagn. Biol. Med. 27 230
[25] Foletti A, Lisi A, Ledda M, De Carlo F, Grimaldi S 2009 Electromagn. Biol. Med. 28 71
[26] Foletti A, Ledda M, De Carlo F, Grimaldi S, Lisi A 2010 Electromagn. Biol. Med. 29 63
[27] Foletti A, Ledda M, D’Emilia E, Grimaldi S, Lisi A 2011 J. Altern. Complement. Med. 17 701
[28] Goldstein D S, McEwen B S 2002 Stress 5 55
[29] Goldstein D S 2007 Stress 10 109
[30] Goldstein D S 2008 Ann. N. Y. Acad. Sci. 1148 223
[31] Rossi E, Corsetti M T, Sukkar S, Poggi C 2007 Electromagn. Biol. Med. 26 277
[32] Vallesi G, Raggi F, Rufini S, Gizzi S, Ercoleani E, Rossi R 2007 Electromagn. Biol. Med. 26 283
[33] Ciafaloni A 2007 Electromagn. Biol. Med. 26 299
[34] Crescentini F 2007 Electromagn. Biol. Med. 26 305
[35] Mancuso M, Ghezzi V, Di Fede G 2007 Electromagn. Biol. Med. 26 311
[36] Raggi F, Vallesi G, Rufini S, Gizzi S, Ercoleani E, Rossi R 2008 Electromagn. Biol. Med. 27 325
[37] Hameroff S R, Watt R C 1982 J. Theor. Biol. 98 549
[38] Dayhoff J, Hameroff S, Beltra R L, Swenberg C 1994 Eur. Biophys. J. 23 79
[39] Nesse R M, Williams G C 1998 Scientific American 279 86
[40] Seeman T E, Singer B H, Rowe J W, Horwitz R I, McEwen B S 1997 Arch. Intern. Med. 157 2259
[41] Insinna E M 1992 Nanobiology 1 191