

## **NO netting and stress**

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### **Abstract**

Why is stress so common in our affluent society, when apparently so many abundant resources are available? And why is stress associated with so many maladies? A hypothesis is presented suggesting that an intercellular communication net coordinates the various bodily functions. Radical gases like nitric oxide (NO) are the signals in this net and its usability affects health and indicates wellness. From a netting point of view, stress is the sense of flow interruption or blockage of this information flow. Vast data from studies on NO signals, on relaxation/stress processes and on health have already been accumulated. Integration of these data supports this novel look of an NO net as a coordinator in the body. The interplay between stress and health is discussed in net perspective and includes some integrative health approaches. Studying the nature of nets and of NO may suggest new ways to reduce stress and approach wellness.

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"The soul grows by subtraction, not addition" - Henry David Thoreau

### **There is order in the mess**

Despite the overflow of information in the 21<sup>st</sup> century, we manage to find our way in this infinite reservoir of knowledge, selecting our relevant routes consciously or subconsciously. How do we choose what to know? Why do we choose it? What affects our selections? The answers to these questions are the basis of the emerging study of patterns of information flow.

In order for us to be able to respond to information and for information to survive in this vast ocean of data, it must be categorized by some laws (of nature?) as well as sustain a relatively unobstructed flow.

It is reasonable to assume that natural patterns will prevail in self-evolving information nets, and with biology becoming the current leading field of informational science, life patterns could constitute the missing clue. An interesting example is the work of Barabasi, who measured the metabolic network patterns of 43 different organisms and demonstrated that they are all strikingly similar [1]. It seems that there are design patterns inherent to all living cells.

### **Biology - an information science**

Our increasing ability to handle complex biological models enabled projects such as the sequencing of the human genome [2] and is causing a shift in attitude toward system biology [3]. Alfred Gilman [4], the 1994 Nobel Prize winner, said: "Scientists have spent the past fifty years taking apart biological systems piece by piece. Now the future of biological research depends on putting them back together."

Understanding the patterns of information flow will help us put biology back together as well as provide the sought-after natural patterns of communication.

Information is crucial to the ability to handle complexity; thus, control mechanisms in the body might be regarded as information processing. This idea was proposed by H. R. Maturana & F. Varela in the concept of Autopoiesis, the process by which systems organize themselves out of disorder, forming a responsive, self-maintaining network characteristic of life [5]. Indeed, BISON (Biology-Inspired techniques for Self-Organization in dynamic Networks) is a major European project which is inspired by complex biological adaptive systems like ants, fireflies and even single cells [5a].

### **Information, Stress and Wellness**

AS information processing is the porthole of this article, stress and wellness are referred to here as the sense of our curability potential, devised from the bodily information. Vast data indeed show that stress is associated with many ailments [6-8], implying that in a way we do feel our health state and/or that the two systems, health and stress, are intertwined. A direct

relationship was recently demonstrated, in that a slower brain's information processing ability was found to be a risk factor for mortality [9]. It is important to note that when considering a net, linear cause and effect association is not necessarily evident.

Feeling stressed could be an indication of ill health and wellness could be a marker of health and potential longevity. Evaluation of the stress or wellness condition requires data input and it is not unreasonable to assume that the body will utilize every available piece of information for the evaluation.

The hypothesis presented here suggests that the body relies on additional potential communication nets to better its maintenance. Besides the major communication tools (nerves, blood, hormones), other inter-cellular communication mechanisms, such as NO signaling, can serve an important role in the wellness data bank. It is suggested that just as on top of television news or cellular phone conversations, the internet can provide additional pathways to help when people face important decisions [10], the body can also benefit from additional communication nets.

If information processing in the body is essential for wellness, a major cause of stress would be the blurring or obstruction of this data flow in our body. Operating under "not enough data" condition is very stressful and enhancement of the relevant information flow can reduce stress and support health. It is suggested that un-obstructing the NO flow, increases the body capabilities to decide where, how and which of its own healing resources to utilize for maintenance and for repairing its maladies. It also suggests that under hectic conditions we are not enjoying our natural potential for cure. This, in different words, is what naturalists/therapists [11] claim - do not obstruct the natural way and just let the body take care of itself.

### **The NO net**

The past decade has witnessed an awakening in the interest of biologists in their pioneering research on NO [12]. This highly reactive free radical, first considered only a noxious air pollutant, plays a vital role in many biological events, including regulation of blood flow, immunity and neurotransmission [13].

This awakening was the result of a major change in the understanding of how the body functions due to the realization that some dangerous pollutants, such as nitric oxide or carbon monoxide, are produced and used by the body for its own benefits.

In retrospect, it is not surprising that when NO becomes a signal its toxicity can be a virtue. Applying the "handicap principle" [14] suggests that signals' toxicity can be a reliable way to ensure their credibility.

NO is produced by a family of enzymes, the nitric oxide synthetases (NOS), through enzymatic oxidation of the guanidine group of L-arginine [15]. Generation of NO is intertwined with synthesis, catabolism and transport of arginine, which thus ultimately participates in the regulation of a fine-tuned balance between normal and pathophysiological consequences of NO production.

NO is a small, hydrophobic molecule that can easily pass through membranes. It persists in vivo for a few seconds, and can diffuse only several cell diameters away from its site of synthesis. Molecules containing thiol groups, such as acetylcysteine, albumin and red blood cells, can not only be NO scavengers, but can also protect it from metabolism. They are NO carriers that release active NO or an NO-containing small molecule at a distance from the NO site of production. The reversible addition of NO to Cys-sulfur in proteins, a modification termed S-nitrosylation, has emerged as a ubiquitous signaling mechanism for regulating diverse cellular processes [16, 17]. It has also been suggested that nitrite, which was previously considered to be only an oxidation byproduct of NO, is the largest tissue storage form of NO [18].

NO is implicated in numerous physiological and pathophysiological processes. Its dual-natured activity [19] in almost any physiological system studied, as well as its complex regulation and intricate biochemistry [20], sometimes result in studies without current

conclusive deduction such as "Is the increased NO produced in airway disease good or bad?" [21]. The webby nature of NO may imply that more NO or less NO is not good or bad per se, but rather that it is involved in the regulation.

L-Arginine is the endogenous substrate of NOS. Despite the theoretical saturation of NOS enzymes with intracellular L-arginine, cellular NO production depends on exogenous L-arginine concentration, which is known as the "arginine paradox" [22]. L-Arginine affects many physiological functions [23], at a higher dose it can even replace Viagra [24] in treating erectile dysfunction [25]. A warning against using very high concentrations of L-arginine came after six patients died in a study testing whether L-arginine can improve heart function after a heart attack [26].

As expected from a key signal, many factors can modulate the NO effect on the cells: NO concentration, time course of exposure to NO, type of NO derivative present, thiol status of the cell, glycolytic capacity, NO and NO-independent protective mechanisms, metals such as iron, other free radicals, oxygen, superoxide anion, unsaturated fatty acids and other molecules [27].

Along with NO, a novel type of medication was discovered - sildenafil citrate, Viagra [24]. Its ability to treat erectile dysfunction made it the most famous drug in the world. Sildenafil citrate is a potent inhibitor of phosphodiesterase type 5, and extends the persistence of any elevated scale of NO processed via the guanylate cyclase [20]. If as suggested, increased NO signaling enables better curability, one can expect Viagra to assist not only in treating erectile dysfunction but other maladies as well. Indeed, data are accumulating and indicating that Viagra has other therapeutic use in ailments of the heart [28], lungs [29], and kidneys [30]. Such medication, which enhances the body's own signals, is bound to have fewer side effects than many other drugs as it let the body operate naturally. It is important to note that this does not mean that Viagra has no side effects [31].

### **NO and Stress**

Looking at NO as a major information signal circulating in the body [32] can theoretically explain why we are so stressful and suggest ways to reduce the stress, as well.

NO is a very fragile molecule affected by numerous variables: its information flow depends on its neighboring carriers and many other factors and is thus slow and susceptible. In our times, where our minds as well as our senses are bombarded with stimuli, we can likely assume that many of the NO and the NO-derived reactive species messages do not reach their destination. Operating consciously or subconsciously under missing information conditions is bound to be stressful, especially when considering the centrality of the NO net. Indeed, relaxation response which is associated with NO production [33-35] can help to explain the NO clinical effects in stress.

The proposal presented here suggests that just as our body feels good after physical activity [36] it feels good when its information flow is unobstructed and when signals reach their destinations. Though it is too early at this stage to figure out the mechanism for such data evaluation, it is possible to suggest ways to enhance the information flow and thus to lower stress. The interplay between stress, emotional behavior such as response to anxiety, and NO has been established. It has been demonstrated for example, that much of the mediated effects of the amygdala - the emotional regulatory center, exert their effects coupled to NO release [37]. Both NO and CO exert a stimulatory influence on the acute adrenocorticotrophic hormone (ACTH) response to physico-emotional stressors [38]. NO plays a modulatory role on brain areas related to defensive reactions [39]. NOS inhibitor prevents anxiety-like and depression-like behavior in rats exposed to restraint stress (40). In humans, responses to mental stress test, such as elevation of arterial plasma norepinephrine, were affected by pre-infusion of the NOS inhibitor L-NMMA (41). Other studies, affecting NO in other ways (via L-arginine for example), also demonstrate that NO plays a role in stress and in depression [42-45]. A reduction in stress associated with NO, can give an additional explanation for smoking and nicotine addiction. Inhaled NO from smoke may be able to increase nicotine absorption and NO released through nicotine can reduce symptoms of stress [46].

How does the NO net interact with other stress systems in the body? Due to the multifunctionality of the NO [47], a complex reciprocal relation is expected. The NO net will be both affected and affecting other stress systems and thus netting rather than linear relations models should be looked for.

Data are accumulating establishing the NO interactions with variety of mediators such as acetylcholine and dopamine associated with increased parasympathetic activity [48], morphine [49], ACTH and corticosterone [50], norepinephrin [51], glucocorticoid [52], gamma-aminobutyric acid [53] glutamate or serotonin [39]. To demonstrate just the tip of the NO interactions' iceberg it has been recently shown that sydnapin, a protein previously thought to have no major role in nerve communication, is the molecule that simultaneously works with dynamin to allow the transmission of messages between nerve cells [54]. Dynamin is regulated by NO via S-nitrosylation [55].

#### **How to enable signals to reach their destination or, how to lower stress?**

Considering communication nets, it can be assumed that signals will reach their destination if they are stable enough, distinctive above background noise and their flow is not obstructed. This assumption leads to two main strategies to enhance NO signaling and thus reduce stress: decrease the background noise or increase the signal.

##### A- Lowering the background noise

Living in hectic cities and being excited by so many stimuli can lead to blurring of many central signals and to feelings of anxiety. More is not necessarily better; even the cellular phone use, meant to improve family communication, is associated with increased family distress [56]. This may explain why quieting external stimuli is associated with relaxation and why many alternative therapies are concerned with reducing stimuli: less noise, soft music, less visual mess or simply closing of the eyes. The Zen approach is a good example of attempting minimal stimuli in order to enhance peacefulness [57]. Going out of the city (away from the hectic stimuli) is another popular approach to reduce stress [58].

Lowering the "noise" can be achieved in other areas as well, for example food. Food approaches for healing are numerous, and cutting down on variety, such as the vegan diet [59] or fasting [60] can contribute to the healing power of the body in more ways than one. Leisure-time activities can also diminish noisy interference. A population-based study in Finland showed that leisure participation predicts survival in middle-aged Finnish men. This beneficial effect emphasizes the significance of leisure activities for the promotion of men's health [61].

Regular increase in physical activity is associated with nitric oxide bioavailability and is an example of another aspect of lifestyle that affects health via NO [62]. Thus, as can be expected, NO indeed contributes to the potentially beneficial outcomes of various relaxation approaches [63].

##### B- Enhancing the NO signal

Increasing the effects of NO can be achieved either by increasing NO production or by affecting parameters that influence its behavior.

One easy way to accomplish this is via nutrition. Foods like honey [64], garlic [65], olives [66] or nutrients containing the NO precursor – L-arginine (e.g. peanuts [67] or L-arginine itself) will enhance NO production. Here again is a suggestion for food contribution to relaxation and not necessarily via lowered calories.

Another approach to influence the NO effect was mentioned earlier, the use of medication like Viagra [24]. It can enhance the NO resultant cGMP by lowering its breakup rate. The advantage of this approach is that it does not automatically increase the level of NO in the body, but rather allows the body to choose where and when to utilize the NO.

A well established technique is to use NO directly. Inhaled NO has been used for treatment of acute respiratory failure and pulmonary hypertension both in adult patients [68] and in newborns [69].

Gene therapy is another potential way to exert the diverse NO functions. All three NOS isoforms have been used in cardiovascular gene transfer studies with encouraging results in cardiovascular biology and pathobiology in various animal models [70].

An additional approach to increasing the level of NO is to increase its carriers' availability by burning processes such as candle lighting or therapies like Moxa. Moxa, the Chinese heat/burn therapy, uses the ground up leaves of the plant Mugwort (*Artemisia vulgaris*) [71]. If indeed they enhance the NO signalling then it is no wonder that lighting candles is an essential part of so many healing, romantic or spiritual ceremonies. Heat can also enhance NO and may suggest another perspective for understanding the relaxing effect of a sauna [72].

#### **Focusing while overlooking non-relevant signals**

A whole range of alternative therapies and arts is concerned with focusing attention and ignoring or "letting go" of disturbing information signals. Attention to breathing is a major tool in many of these techniques, as it assists guided imagery [73], meditation and relaxation. Is it related to the role of NO in signal transduction affecting oxygen transfer in the body [74]? NO has a very complex role in respiration [75] and despite the accumulated data its integrated role is not yet elucidated. It is proposed that holistic terms like the Buddhist term "within us" [76] or the Chinese term "qi" [77] may be related to the integrative role of NO netting information.

Focusing attention will result in quieting of all other areas and thus can exert well-being by enabling NO signals to reach their destinations undisturbed. Biological studies in this field are starting to accumulate; for example, three different studies on meditation demonstrated that meditation is associated with happiness [78], health [79] and increased levels of NO [80]. It seems that the good feeling that accompanies meditation is really associated with significant better health and is not just a non-relevant feel. Another study on directed focusing showed that concentrating on the fMRI image of the brain region responsible for pain perception allowed the participants to increase or lower their pain while holding a very hot metal cube [81].

It is interesting to note that the whole range of concentration and "letting go" practices is associated with apparent time waste. Overly busy people usually do not have the time and/or the patience required to achieve the needed attention and perhaps this is an additional reason for stress in our western society, where "time is money."

Does this mean that enabling ("listening to") the inner NO disposition, or any communication system, requires time and space? Probably yes, but considering the recent study

demonstrating that success follows happiness [82], it might be beneficial to invest in enabling NO moves and reducing stress. As teachers in many cultures try to impart, happiness/wellness does not depend on the next success - wellness is the here and now.

#### **A general note on netting**

Studying wellness from a net perspective will enable applying novel approaches to therapy. Besides decreasing the background noise and enhancing the signal (suggested in this article), the universal patterns of netting can be applied to maximize therapeutic potential. One good example is timing. A recent study demonstrated a universal dynamic nature of net traffic, characterized by a pattern of bursts of rapidly occurring events separated by long periods of inactivity [83]. Therapy might be more efficient if applied at the optimal burst time.

#### **Final words**

Scientists in the west now appreciate the idea that information alone is sufficient to handle complex organization. This in fact was fundamental to the Chinese philosopher Lau-Tsu, who wrote in The Tao te Ching more than two thousand years ago that the world is ruled by letting things take their course, and cannot be controlled through interference [84]. Furthermore, documents (Dunhuang scrolls) dating to approximately 800 AD suggest that nitrite and nitrate were used by the Chinese to relieve heart pains and cold in the hands [18].

Perhaps we can learn from the Chinese philosophers that trying to control information flow is hazardous, but aiding its unobstructed flow will bring us joy.

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"Life is too short to be in a hurry"