Environmental Hormones and Nonlinear Science

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As my area of expertise is nonlinear science, I am a complete amateur when it comes to so called "environmental hormones." The research themes I am involved in, however, include for example metabolism and gene/protein networks, and creation of mathematical models for them. These may be related to problems of environmental hormones. Today I would like to comment on environmental hormones from the standpoint of nonlinear science. Show the first slide, please.

Let me begin by saying I have devoted a great deal of energy to preparing various topics. It would take about two hours to talk about all of these, so today I will not talk about most of them. First of all, I thought I would take advantage of a recently published book, "Hormone Chaos." I thought I would just read the book and talk about the contents of the book, but I finally came to the conclusion that the "chaos" discussed in the book had almost nothing to do with the concept of "deterministic chaos" used in nonlinear science. The book was therefore no relation to my field although it were quite interesting , so I had to wing it on my own.

Gene networks and metabolism networks are extremely important when considering life systems, especially the effect of hormones. These life systems have extremely strong nonlinearity. In this sense, the concept of nonlinearity is an extremely important subject. In relation to this, later on today I will briefly talk about bifurcation theory and somewhat complexity and uncertainty.

First of all, "nonlinear" means "not linear." You may then want to know what "linear" means. If you think in terms of Ohm's Law, input and output of an electric circuit would have a "linear" relationship. If we distort this relationship, it then becomes "nonlinear."

Generally speaking, in nonlinear systems, one plus one may not equal two. This may seem a bit strange, but if you really think about it, it is not unnatural. Take for example a case where two people perform a task together, the result of the joint effort would be greater than the sum of two individual efforts. This is the rationale behind teamwork. If the two workers on the other hand did not get along well together and began to argue and fight, the result of the joint effort would be much less than the sum of two individual efforts. In either case, the accomplished work of the joint effort is different from the sum of individual efforts.

The concept of nonlinearity is a generalized version of this concept. Nonlinearity for example plays an important role in brain and genome systems.

Today we have with us the distinguished brain scientist Prof. Yoro, so I would like to begin with examples of the brain. This figure is called an "ambiguous figure." Although it is a single illustration, our brains can interpret it in two ways. One would be the face of a young woman. You can see the jaw, the nose, the eyelashes -- here are the ears. She's wearing a necklace and is facing that way. At the same time however, you could interpret the whole thing as the face of an old woman. Here is the nose, the eyes, the jaw and the mouth. Can you make out both of them? The fact that both interpretations coexist is proof that our cognitive system is nonlinear. With a linear system, when input is fixed, the system will only act in a certain way. The existence of two occurs because it is nonlinear.

We can create lots of illustrations such as this. With this one, the man's face changes gradually into the figure of a woman. Ambiguity is similarly formed in the center. Let's say for example you first see the man's face. When you move the illustration to the right, you notice at this stage a woman. On the other hand, you might first notice the figure of the woman, and when you move the picture to the left, you see the face of the man at this stage. This kind of histeretic phenomena occur in lots of nonlinear systems such as magnetic properties.

If we arrange these properties to fit the concept, this is what you get: being able to see the man's face is here. Being able to see the figure of the woman is here. Once you see the man's face, you can not recognize the figure of the woman until here. If you however next see the figure of the woman, you can then see the man's face here. With two interpretations existing for this part, we decide which it is based on past recognition. This is called "hysteresis." This occurs on the cognitive level of the brain. It also occurs in gene networks.

Research of genes has progressed and we have recently learned a lot about genes. Particularly important is the fact that some genes may be simply interpreted by the 1:1 causality, but not always. They generally create networks. The type of network they create is one whereby protein actually controls switching of other genes. This kind of protein is called "transcription factor." In other words, transcription factor proteins produced when a certain gene is switched on either promote or suppress emergence of other genes, thereby creating a network of genes and proteins. This invites various phenomena to occur by the system if there is also nonlinearity.

Let me introduce an example. Prof. Collins of Boston University conducted research on creating a toggle switch by gene networks.

The principle is very simple. Take for example two genes. Consider a network whereby the genes suppress each other. With such as network, the same phenomenon where there are two interpretations, a man's face and the figure of a woman, occurs.

The horizontal axis adopts the amount of external stimulus. The vertical axis adopts the amount of manifestation of either gene. When external stimulus is changed, this is like the gene being "off." Almost none is manifested. Here the switch is toggled, changing discontinuously, with the gene being "on."

Once the gene is on, it remains high just like before, even if external stimulus is reduced. Here is off. In other words there are switches where you raise or lower the knob. This indicates that this type of switch can actually be easily created by a gene network. I do not know very much about the problem of environmental hormones, but if a switch were located somewhere in a gene network, when the amount of environmental hormone changes, even if the amount subsequently drops, for example, the switch remains on for a while. This can be easily obtained.

What we are doing in our laboratory now is studying under what conditions such switching occur with a more generalized gene network, and we have obtained several mathematical theorems. In Prof. Collins' example, the main point is that basically an even number of suppressions exist in a loop. Suppression and suppression have a positive effect. If all loops have such positive feedback, no matter how complex it may be, the stable condition of this system can mathematically and rigorously prove that the switch is either on or off without for example any ascillations.

This example was a switch, but with a different gene network, a rhythm may be produced for example. In mathematical terminology, this is related to "Hopf bifurcation." Circadian rhythm for example is well known. Concerning recent studies on circadian rhythms, we know quite a bit about the mechanism on the gene level, and are becoming capable of advancing mathematical analysis of this. In this sense, we have learned a great deal about nonlinearity through analysis of metabolism and gene networks. Be conducting such research, we might be able to contribute to solving the problem of environmental hormones.

Finally I would like to comment on another example from the standpoint of nonlinear science. Let us consider for example a case where there is a combination effect when there are two chemical substances. You may think of it as investigating low-concentration additive effect.

The basic purpose is to clarify that the effect of environmental hormones is toxic in a certain range of concentration and nontoxic when outside that range. With certain types of nonlinear systems, however, the nonlinear dynamics could easily prevent such a black-and-white decision.

Here is an example of this. This has nothing to do with gene networks, but is rather purely a mathematical model. If we start from the black, we converge on a certain state. If we start from white on the other hand, we converge on a chaotic state. The initial values for converging on a certain state and the initial values for converging on a chaotic state can be intermixed. This for instance appears white, so let's magnify it. It appears white, but when we magnify it, these black parts appear one after another. Thinking this white part, when we enlarge it, we see black spots in the magnified image. Concerning this system, we can clearly demonstrate the fact that black and white cannot be clearly decided. In other words, the systems of the world cannot necessarily clearly decide black and white. Such things can easily occur in a nonlinear system.

In a certain sense, this guarantees that experiments cannot be reproduced. In other words, when an experiment is conducted, we establish a certain initial condition. The initial condition we can establish however naturally possesses a small error. Thus within the range of error, initial conditions that converge on a certain state and initial conditions that converge on the state of chaos always coexist. This means that experiments cannot be essentially reproduced.

I have just touched on a few examples today, but we are conducting research in hope of perhaps being able to contribute to solving the problem of environmental hormones particularly through mathematical analysis of gene and metabolism networks. Thank you very much.