DESIGNING A NEURAL NETWORK FOR TRANSCRIPTION NETWORKS *WITH A SUGGESTIVE REFERENCE TO BIOFLUID DYNAMICS*[1]

Chasing the best topology

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Short View:

Neural Networks have been applied widely to real problem modeling. The applications have been concentrated mainly on image processing, classification of patterns, and function approximation. The best characteristic of neural networks from the point of view for function approximation is the parallel processing power. Besides neural networks by its own are just linear models, their local structure for calculation, named neurons, may be selected properly in order to those behave as a nonlinear model. In the other hand, Transcription Networks has been applied as a gene expression modeling tool. The principle behind those is that nature solves problems in "local machines" termed network motifs. Here is claimed that the theory of neural networks is a powerful tool for transcription network modeling based on experimental data from gene expression.

All the living organism physical state is function in a production and replication level of the genetic code, including all the biological fluids and internal structures. One may use applied genetics to explain biological components, such as the blood cells or different biological liquid separators, which in wrong development or repairing processing may be the cause of significant physical diseases. This justifies the study of genetics in the gene-level.

KEY-WORDS: Neural Networks; Transcription Networks; Gene Expression Estimation; Systems Biology.

NOTE. For a brief look on Artificial Neural Networks, the reader may go to: http://www.dkriesel.com/_media/science/neuronalenetze-en-zeta2-1col-dkrieselcom.pdf. And for a brief look on transcription networks, the reader may go to: http://www.win.tue.nl/~evink/education/2IF35/PDF/2if35-alon2.pdf

1. Introduction

Fluids are between the most important and multi-functional compound in the body. They supports biological function that range from spreading out substance all over the body [10] to substance exchanges ([12]) – inward and outward the body -, or to organ internal structure ([24], [25]). It is interesting to note the covert *synergy* between the *respiratory* and the *cardiovascular* system ([12], [11], [13]).

In spite of the formal separation between mathematics, biology and physics, the laws of nature does have boundaries. This observation was highlighted by *A. Einstein* when he said that physics has to fit the experiments, but the experiments will never fit the laws of physics if it is not correct. The most famous attempt in the direction of understanding the universe in a single set of laws was done by Isaac Newton[4]. In three

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[4] In fact this started with René Descastes. He would like to understand all the universe in a single statement. See (**ABDOUNUR**, Oscar João. *Matemática e Música:o pensamento analógico na construção de siginificados.* Coleção ensaios universais, V.l 3.)

laws he tries to explain from the "tiny bitty" of matter to the giant planets. Unfortunately biological systems are more complicated to be reduced to such laws, if those exist, we still have too much walk. Those set of laws just work for "clock-like organisms", which is not the case for living organisms, see [34] for a warming discussion on the Newtonian picture of reality and its limitations. The problem of reduction of complex systems to simple laws, such as biological systems, was highlighted by Schrödinger's comment, cited by ([14], 5): "…..from all we learnt about the structure of living matter, we must be prepared to find it working in a manner that cannot be reduced to the ordinary laws of physics…".

In [10] , it is presented relations between mathematics and biology and the authors call the mathematicians to understand biology and the biologists to understand the mathematical models. Mathematics and biology have a synergistic relationship. Biology produces interesting problems, mathematics provides models to understand them, and biology returns to test the mathematical models, as claims [10] . *Biofluids Dynamics* is more one attempt in that direction.

All the living-organism physical state is function in a production and replication level of the *genetic* code, including all the biological fluids and internal structures. One may use applied genetics to explain biological components, such as the *blood* cells or different biological liquid separators, which in wrong development or repairing processing may be the cause of significant physical *diseases*. This justifies the study of genetics in the gene-level. As an practical example of the study of a syndrome that is "spread out" by the circulatory system, that is , the blood, see ([15], [16]). In this, it is treated the *Neonatal Jaundice*. This *syndrome* may have many origins, but all of them are spread in the circulatory system, being taking to important and vital point of the body, such as the *brain*, causing irreversible consequences in infants, for the rest of their lives.

Therefore, he is studied biological system – widely termed *system biology* - in a genetic level. It is claimed that *Artificial Neural Networks* (ANN) , shorted called *neural network* or *neural systems* , may be suitable for understanding G*ene Expression Dynamics*. The study of gene expression may be justified bearing in mind that all the components of any living organism, from virus to human being, are constrained to genetic information. Due to this, *ionizing radiation* are so dangerous, they may destroy the genetic code. See ([19], [14], [18]) for a friendly introduction to genetics and its consequences in living beings.

Neural Networks are mathematical models created having the brain as inspiration. The basic components are *neurons* – a *summation* function plus a *transfer* function - and *synapses* – a set of *weights* that connects two neurons and is tuned during the *training* process. Since here is out of scope a survey on neural network theory, See for example ([21], [3], [23] , [22] , [7]) for a first contact with the field.

Here is presented a survey in the application of neural systems to transcription network modeling and claimed that one may apply those to understand biological-physical manifestation in living being. The approach here is similar the one following in statistical mechanics, what matter is the "surface result[5]", but one needs to have at least a minimal notion of the components. As comments [26], Statistical Mechanics is *ideally*

[5] In the case of statistical mechanics, *pressure*, *temperature*…..

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suited to analyzing collective phenomena in a network consisting of very many, relatively simple, constituents.

The next section presents the problem setting.

1.1 Problematic

The *gene expression* may be stated in simple lines as following:

- Given an *external* or *internal stimulus*, the *organism* starts expressing proteins that carry each of them specialized functions of responding to it in an appropriate way. We may say that life boils down to protein production.

Those answers are not given by just one gene, but a network, a "group" response. Those networks are called *transcription networks*[6] and they are complex networks [27]. Above is presented an example of a typical transcription network.

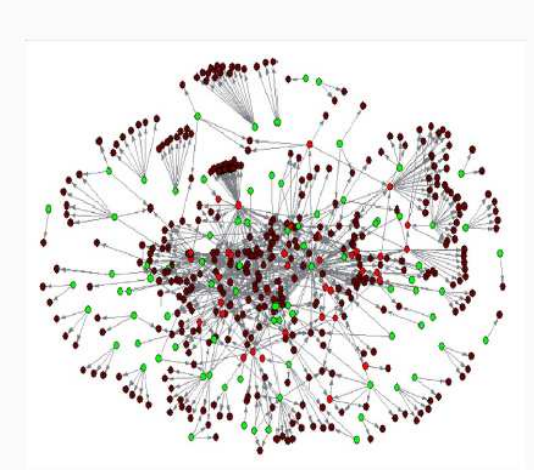

FIGURE 1. *E. Coli* transcription network
Source: from ([8], pp.5).

The problem posed in some application [1] is how to find this network – estimate the main parameters. Here is posed the problem how to find those networks in such a way that it may be represented in a "handful[7]" relation for future simulations.

A biological-mathematical tool applied widely in the modeling of physical phenomena of high-level of nonlinearity is named neural networks. They have similar graphical appeal of the transcription networks, but different origins[8]. The idea is to endow graphs with "specialized"-function placed in *neurons* gathered in layers and connected with each other. Neural networks are linear model, besides its bricks – the neurons – are nonlinear, the neurons "make the trick", the nonlinear and parallel

[6] Besides the name may misguide, those networks does not model only *transcription*. Transcription is the process of creating mRNA in result of DNA stand information – genes. After the transcription, we have the *translation*. But we have some intermediate steps not important for now, such as *splicing.*
[7] Handful in the sense that they may be applied in simulations.
[8] Neural networks connect cells, relatively big bodies compared to genes and proteins, in the case of transcription networks.

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processing exhibited by them. This model creates a huge-power for modeling complex phenomena – mapping complex mathematical-relations. Neural networks applied to modeling in applied mathematics may be termed in a simple way as *nonparametric-layered-regression models* – each layer is a nonlinear regressor model itself.

Therefore, one may set the question:

> ***How to use the philosophical-mathematical characteristic from neural networks in synergy with the genetic expression modeling feature of the transcription network aiming to model real genetic expression?***

This is the quest on this work.

1.2 Organization of the work

Since here is presented just the theory, the work has a *suggestive* position, the material is organized in subsections aiming the well-organization of the information. Section 2 is a warming section, one may skip it – it is discussed powerful functions for neurons. Section 3 presents the topologies proposed, organized into sub-section. Section 4 presents a new improvement in *feedforward* neural networks, the addition of *feedbacks*. Section 5 attempts to place the proposed model as a possible feedback judger. Section 6 closes the work with some final consideration.

2. Neural Topology for Transcription Networks: some preliminaries discussions

As an universal function approximator, the feedfoward neural networks are in general designed in one input layer, one hidden layer and one output layer. A typical feedfoward neural network is found sketched below.

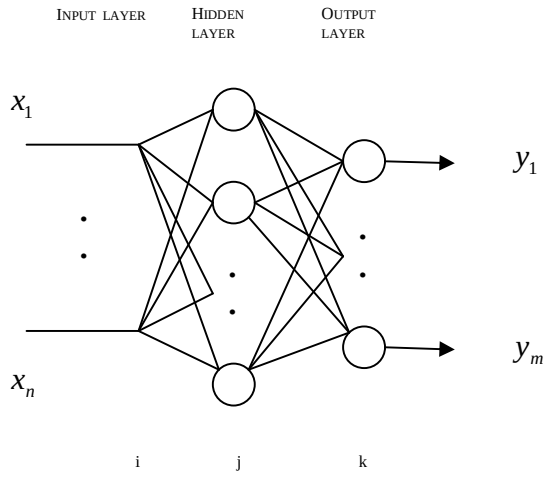

FIGURE 2. A two layer neural network. (*In the sketch, the circles represent neuron and the lines connecting them are the synapses (learning parameters*)
Source: based on ([7], pp. 253).

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Even though, there are not restrictions on the neural network architecture. Montana and Davis [28] cited by [20] designed a neural network to recognize structures in sonar data from underwater acoustic receivers, sometimes called *lofargrams*. The network contained four input neurons, one output neuron, and two hidden layers of seven and ten neuron, respectively, yielding a total of 126 synaptic weights.

In image processing [29], as an example of a well-known of success of the networks, hidden layers is used to extract "hidden" patterns for latter use in classification of image, the idea here is similar, the hidden layers will attempt to find the "identity number" of each transcription networks. Each transcription network has insides parameters that dictate its dynamics, some "hidden laws".

A peculiarity here is that the hidden layers will be fulfilled with *hill* functions (both hill function for *repression* and hill function for *activation*), a mix of *down* and *up* hill functions. In the output, we will have *linear* transfer function.

In *transcription* networks, we have two most important "internal variables": the *production* rate and how it changes in function of time and transcription factor concentration. In other to avoid future complexities, such as having to face *Partial Differential Equations* (PDE) ([31], [30]), one may consider that the production rate is a function only of the transcription factor concentration. Therefore, the hidden layer of the neural network suppose to capture the "shape" of the "transcription-factor-concentration" control while the output layer – *linear transfer* functions – captures the production rate limits – *minimum* and *maximum*.

Now, it is done some discussion on some peculiarity of neural networks as function estimators and hill function in *gene expression*. The discussion on neural networks is postponed to section 3.

2.1 Neural networks as layered regressor models

We may see neural networks in a simple look as *layered-nonlinear* regression model. The difference is that in a nonlinear regression model we just have one layer. In a neural model, we have regression inside regression, which makes the error in a minimization process (*training* step) to travel "deep" inside a "funnel" until the input, making correction on layer by layer. This means that each layer is a nonlinear regression model passing its results to another nonlinear regression model, until the output layer. This endows the neural networks with a powerful and tremendous degree of freedom for approximations.

2.2 The hill function in gene expression modeling

There are two hill function types for modeling promoter activity: hill function for activation and hill for repression [4].

HILL FUNCTION FOR ACTIVATION

The hill function for activation is above.

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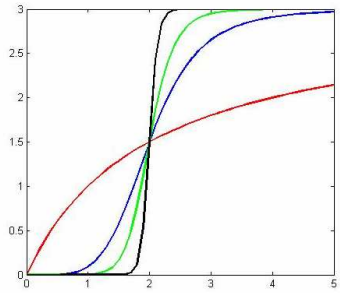
$$f\left(X^*\right)=\left(\frac{X^{*n}}{K^n+X^{*n}}\right)\beta$$

Eq. (1): *Hill function for activation*

Where:

- X^* is the activated form of the transcription factor[9];
- β is the maximum production rate;
- K^n is the threshold. This gives information of the inflection point of the hill function;
- n is the hill function *factor- steepness* factor. The higher it is, the closer the hill function is of the *step function*;

Above is presented some graphs.



GRAPHIC 1. Hill function (activation) for *n* equal 1 (red line), 5 (blue line), 10 (green line), and 30 (black line). The Threshold is "2", beta equal "3" and range from "0" until "5".

In order to capture difficult features from real problems, one may use expansions instead of isolated hill function[10].

$$F\left(X^*\right)=\sum_{i\in\Omega}\alpha_i f_i\left(X^*\right)$$

Where: Ω is the set of hill functions used as the basis expansion. α_i's are the coefficient for the expansion; and $f_i\left(X^*\right)$ are the function from the basis set. Above (GRAF. 2) is an example made up with four activation functions.

It is interesting to highlight the "flexibility" of the expanded curve. This may be used as a *learning machine*: given some real data, one need to train a function for learning those parameters aiming to estimate the real parameters of the real biological network.

[9] One needs to recollect that just the activated form of the transcription factor can bind the *promoters*. The promoters are "short-strand" of DNA that does not encode proteins, just control the gene activity.

[10] Here is following something similar done in *quantum simulations* for approximating molecular orbitals for solving the Schrödinger Equation (SE) dynamics [32]. They name it LCAO (*Linear Combination Of Atomic Orbitals*). All the complex nature of molecular orbitals is reduced to local nonlinear functions such as Gaussian Type of Orbital (GTO) and Slater Type of Orbital (STO). They "pack" them for later to make the linear combination. Then it is optimized under the SE dynamics.

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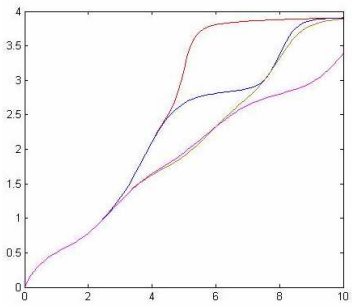


Basis function parameters:

K=[1,3,6,10];
n=[1,5,8,20];
beta =[1,2,5,10];
alfa =[1,1,1,1];

GRAPHIC 2. Hill function as a basis expansion. Here, the notation A=[a,b,c,d] means a vector.

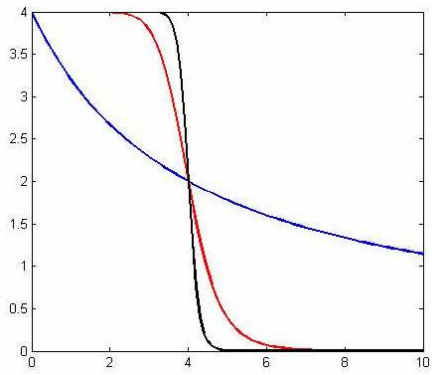
HILL FUNCTION FOR REPRESSION

For repression[11], the hill function may be written as:

$$f\left(X^*\right)=h\left(X^*;K,n\right)\beta \qquad \text{Eq. (2)}$$

Where: $h\left(X^*;K,n\right)=\left(1+\left(\frac{X^*}{K}\right)^n\right)^{-1}$. and $0\le h\left(X^*;K,n\right)\le 1$.

Above follows an example.



Color	k	n	beta
Blue	4	1	4
red	4	10	4
black	4	30	4

GRAPHIC 3. Hill function for repression.

2.3 Feedbacks in feedfoward networks

A new feature that one needs to introduce in the feedforward networks for capturing the peculiarities of the transcription networks is *feedbacks*. Feedbacks are quite powerful biological option in transcription networks. What makes us – human being – so complex is not the number of genes, but the biological-controlling devises ([4], [19]). This is possible that we have more feedbacks than the other species. A single feedback introduces a huge number of new *combinatorial* features.

[11] Repression is when a gene is "asked to stopped" producing by a external proteins, this might be its own protein, called *auto-regulation* [4] .

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3. Neural Topology for Transcription Networks: most interesting topologies

We may identify two possible topologies for the neural network. The choice is a matter of training procedure. Two problems may happen in the training procedure: a) slow convergence for the minimal error due to the high-dimensionality of the neural network as a function under optimization [33]; b) not convergence due to insufficient number of neurons or training data.

3.1 Topology one: one-hidden layer neural network

It is possible to find in the literature that a *Multilayer neural network* composed of one input layer, one hidden layer and one output layer may approximate any function ([3]).

Following this idea, one may use a three layer neural network as a first attempt to model transcription networks. The advantage of this neural network is that the less is the number of layer, the easier it is to train. This network is the lowest layered neural network. Above is presented a sketch.

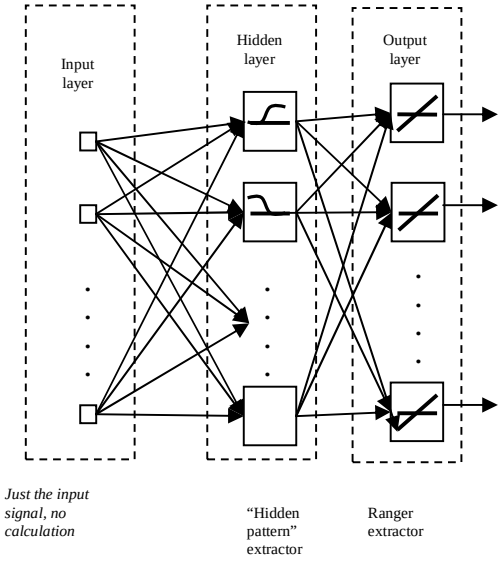

FIGURE 3. First possible layout for the neural network. (*The blank box means a general neuron, one may choose any neuron for placing in this blank neurons*).

In summary, the input layer reads the data, the hidden layer learn the controlling shape and the output learn the range of the control (Maximum- Minimum limits).

3.2 Topology two: two-hidden layer neural network

A new topology is got just by separating the neurons type in layers, as done below (FIG.4).

One topology may be better than other in particular cases. But, it is easier to train a one-hidden layer neural network than a N-hidden layer neural network.

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3.3 Some insights into the training procedures for supervised training type

Two different training styles may be applied to training a supervised neural network as an unconstrained optimization problem [7]: a) training by layers or b) training by global treatment. In the former, the corrections in the weights are done by "waves", the error starts in the output layer and it travels *backward*, the most well-know method is as the *backpropagation* algorithm, it is based on the *steepest* descent algorithm borrowed from *optimization* theory; whereas the latter used *global* optimization. The most applied procedure is the *backpropagation* algorithm.

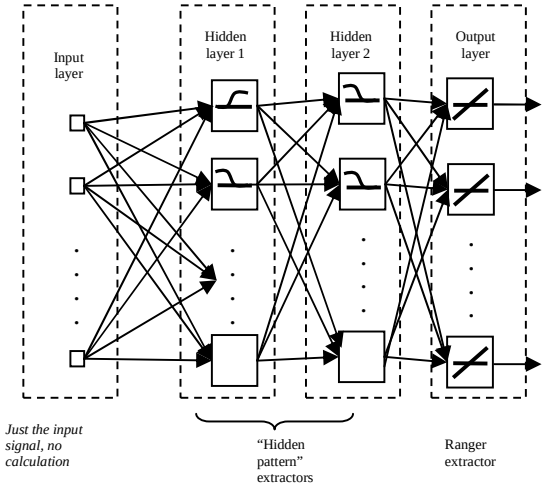

FIGURE 4. Second possible layout for the neural network. (*The blank box means a general neuron, one may choose any neuron for placing in this blank neurons*).

The backpropagation algorithm is a *local* optimization procedure. As so, it has as drawback the "traps" done by local minimum. See scheme below (FIG.5).

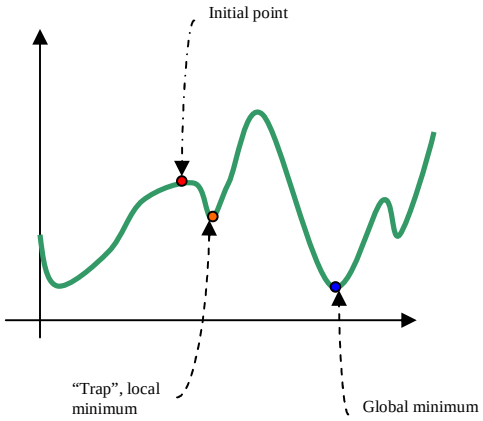

FIGURE 5. A hypothetical function with some "traps" (local minima).

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The drawback of global search is the high number of "solution" required for each iteration. Some authors include *simulating annealing* as global search. It does not require many solutions for each iteration. Also some authors include *Nelder-Mead Simplex Algorithm* as global search, it use "N+1" solutions for each iterations. The bad side of using too much solution per *epoch* is the high-dimension of the neural networks for real applications, but it may be "paid" by a fast convergence – what cannot be guaranteed.

4. Feedforward-*feedback* neural networks

Besides the proposed topology before, one may add a new feature: feedbacks in *feedforward* neural networks. This goes against the common sense of feedforward neural networks.

Above is drawn a *feedforward-feedback* neural network FIG.6. As one may note easily, this network allows the neuron to send signal to its own input, by this way, each neuron is endowed with the power of influencing its decision by means of its previous decision: this is a *memory* effect. This makes the network a *dynamical system*. The biggest impact is in the training procedure.

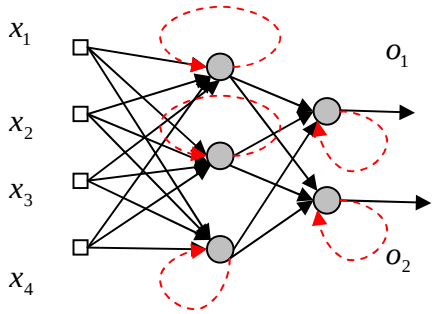

FIGURE 6. A feedforward Neural Network with four inputs, two outputs, and one hidden layer (three neurons) *with feedbacks*.

One may introduce *dummy* neurons in order to get rid of the *autoregulation* and turning the feedforward-feedback neural network into a simple and classical feedforward neural network. This is a great deal, once it is not necessary to worry about effective new training procedure; feedforward neural networks are already well-developed. Above is presented the network with dummy neurons.

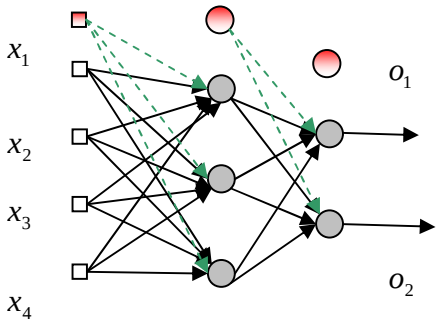

FIGURE 7. A feedforward neural network with some dummy neurons, (feedforward feedback neural networks).

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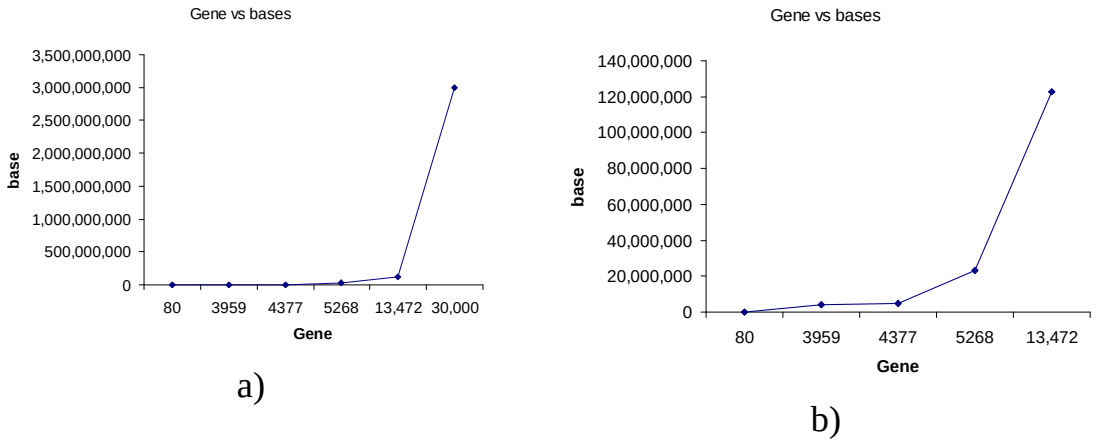
5. Feedforward-*feedback* neural networks as *feedback* level judger

It was an unexpectedly discovered that the number of gene in human being and other species does not change too much in number as one may expect bearing in mind the "superior" biological system exhibited by us [19]. See a graph (GRAF.4) below for a base-gene number relation between different species.

In the current state of the art, they associate the differences between us – *Homos Sapiens* - and the other species to our genetic controlling system. Feedback is a powerful "tool" and it would be interesting to chase it. Hence, system that could measure in an indirect way the "level" of feedback in a transcription network could be of quite practical system.

The feedback in the neural system supposes in theory to learn feedbacks and gives a methodology for measuring feedbacks in transcription networks.



GRAPHIC 4. The Genome size for different species. a) complete and b) without the human in order to show the exponential growth.
Source: data from *([9], pp. 18).*

Here follows the table used to generate the graphs.

Table 1. The genome size for different species

Organism	Description	Bases	Genes
Epstein barr virus	Virus	170,000	80
Mycobacterium tuberculosis	Bacteria	4,400,000	3959
E. Coli	Bacteria	4,600,000	4377
Plasmodium falciparum	Malarie parasite	23,000,000	5268
Drosophila melanogaster	Fruit Fly	123,000,000	13,472
Human		3,000,000,000	30,000

Source: ([9], pp. 18).

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6. Final notes

Here was introduced the idea for gathering the power of transcription network for modeling gene expression and the mathematical-philosophical principles of neural networks as *learning* machine. Besides the huge number of existing types of neural networks, it is necessary to introduce new features for well-capture the ways of transcription networks. One of the most important features to introduce is feedbacks, once in real biological networks those are present and quite important.

Here is claimed that the well-understanding of transcription network may turn into a theoretical source of insights into the biofluid dynamics, once what gives the peculiarity of the biofluids are the cells. Organelles, and bio-molecules.

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