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The Turing Machine, Boolean Networks and the Probabilistic Theory of Error Propagation: What Role in Neurooncogenesis?

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Abstract

Genomics research has incredibly grown, with outstanding results such as the gene technology editing, but to our advice a meditation has to be done to the science within the DNA mechanisms and it's intrinsic significance.

A wise man once said that the truth is like the pyramid of Cheope. Wherever you stand, from the outside you will never be able to see it integrally. The base will be always missed: only from the inside the overall can be seen. The authors hypothesize the deep origin of cancer, an origin written in the physical and mathematical laws of nature. In our society, of the Western world, cancer is thought to be a "wrong" event of our organism due to chemical, physical toxicity. Only recent data indicate that there is an intrinsic predisposition of the patient to favour the development of Brain Tumors. The error in Nature is intrinsic, cancer cells always exists in us but only sometimes develops. Our simulation of the event cancer starts from universal physical and mathematical laws and models, which have already been used to explain phenomena in other scientific branches like astronomy, physics and computer science.

Keywords: *Turing Machine; Boolean Networks; Error Propagation; Neurooncogenesis*

Introduction

The Bible says that it took God 6 days to create this Universe, we could ask ourselves why it took Him so long: is it because of errors? One of the major efforts of mathematicians of this century has been the description of the concept of error. Alan M. Turing has demonstrated that a simple computational model made of a box that moves on two tapes reading an input on one and writing an output on the other tape, is able to do whatever a normal digital programmable calculator is able to do and is subject to the same errors [1-3]. The deduction of this theory is that there is an intrinsic possibility of error for any machine, independently from its perfection, the problem of the sudden arrest is unpredictable [4-10]; there will always exist a case in which it is unpredictable whether a calculation will stop or not (in biology, this could mean that it is unpredictable whether a cell proliferation will stop or not).

A program for the Turing machine is a list of instructions to be done according to the internal state of the box. The output is a list of the numbers that are on the output tape when the calculations are over. This simple machine can execute any algorithm. It is amazing the similarity that the DNA polymerase has with the Turing machine. DNA polymerase is a wonderful nanomachine able to copy a DNA template into a newly synthesised filament.

We built a simulating software in order to demonstrate that the base of error of the DNA polymerase is intrinsic during DNA synthesis, as it for the Turing machine, further more using the simulator described below in its mathematical and Physical laws we simulated the oncogene network and simulated the of wrong configurations of the oncogene-oncosuppressor network thus resulting in genome alteration and instability. A genome is a genetic network system, behaves as a complex calculator for parallel elaboration in which genes regulate each other directly or by means of products of themselves. The coordinated behaviour of this system is essential for the cellular steady state, therefore for genome integrity [11-30].

The mathematical models that we applied to perform a realistic simulation of oncogenesis are the NK autonomous stochastic Boolean networks, where N is the number of genes involved, each one with K inputs. Autonomous because, in our model, none of the inputs arrive from outside the system. If a number of Boolean gates of various sorts are connected from the inputs of each gate to the output of other gates a network is obtained: since the gates are Boolean logic gates, it will be a Boolean Network.

The cell proliferation network system is deterministic and repeats the same succession of states indefinitely unless another signal interrupts this cycle.

We defined N as the number of genes acting in the simulation (virtually could be any number) and K as the number of input to each gate (again could be any number). Amazingly when K ~ 2 the network behaviour changes drastically. The sensitivity to minimal disturbances is low. The mutations originate only slight variations. Few rare mutations may result in drastic changes in the "programs". This is the behaviour at the edge of chaos [24].

It is widely accepted that at K ~ 2 [24], the simulation of the regulatory genetic systems of biological cellular organisms is appropriate. Having the regulatory genetic systems at the edge of chaos will ensure both, necessary stability, and potentiality for progressive evolutionary improvements; for this reason regulation schemes include only a small number of inputs from other genes in accordance with the value K ~ 2.

It is possible, that such kind of regulatory genetic structures were selected at early stages of life, and this made possible the further progressive evolution. The error within the network that rules cell proliferation, is represented by a perturbation.

In order to move the system from one state to the other (i.e. a cell, from quiescence state to proliferation), two types of perturbations were applied: minimal and structural.

Minimal perturbation is when a binary element switches temporarily into its opposite 1 => 0. If this event does not change drastically the state of the network, then, the network sooner or later will go back to the original state. A structural perturbation is a permanent alteration of the links and/or boolean functions of the network which might transform an organized system into a chaotic one and/or vice versa, potentially leading to uncontrolled proliferation.

This mechanism of control of a tissue steady state is the result of a complex genetic expression and its failure is regulated by Boolean stochastic laws. Therefore, it is possible to assign to the primary oncogenic event (caused by a wrong configuration of the network) a probability value that is different than 0.

The model considers the interaction of at least 3 genes; when a gene is active the value of 1 will be attributed. Conversely 0 corresponds to a non-active gene. The second step of the system is to monitor the number of errors occurring in gene replication.

The replication error is calculated on the probability that a certain type of configuration of the network will appear. The system considers which elements fail: oncogenes or oncosuppressors.

The system, when a wrong configuration appears, can react in different ways. For example the system can ignore this state and in this case we will have an non-significant error (minimal perturbation). The second possibility is that the system is sensitive to the configuration and therefore there will be three answers: 1) the system repairs this error with an appropriate repair process in order to remove the error, 2) the system is not able to do anything so it crashes down (structural perturbation, uncontrolled proliferation or cell death), 3) The system crashes down but it has a last defence and suppress itself (apoptosis).

In this simulator the state of the network (Global Index State Figure 1) is generated by two functions one of which is a deterministic function and the second part of the function is a probabilistic function. The evolution of the oncogenic network will not be in function of the winners of a roulette, but rather the fate will also decide which genes will take place to the game and with how many numbers. The fact that two probabilistic functions appear in cascade is very important because it evidences that if P is the probability of failure F is the probability of that gene to be questioned.

$$gobal\_index\_\ state(t1) \square\square\ D[N(t0)]\square\square F[\square(N(t0))]$$

Figure 1: *Global index state.*
D: Deterministic Function; F: Probabilistic Function (Touring); P: Probability of a generic event to take place.

Obviously there will be a sort of critic value beyond which the tissue will be considered tumor.

The frequency of a glial tumour is the percentage fraction of the cell sub populations that after the period of simulation have a neoplastic progeny (Figure 2).

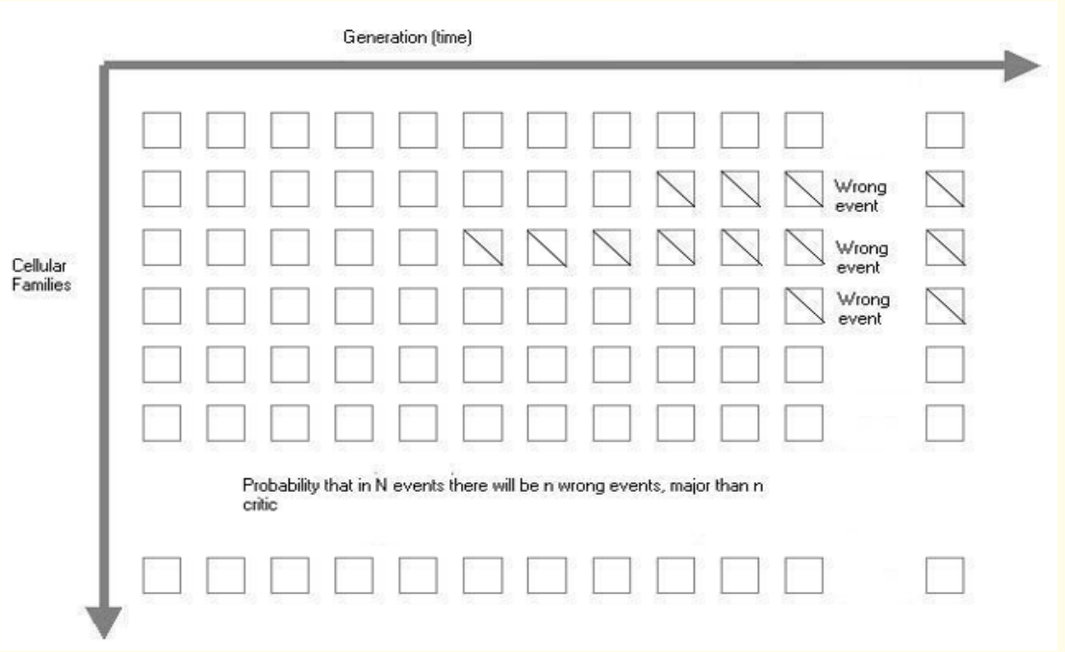

Figure 2: *Schematic representation of error propagation that leads to cancer genesis.*

The simulations built with these simple mathematical rules simulations are very far from the realistic model they provide new insights to the comprehension of physical reasons of genome instability and DNA ageing and so of oncogenesis. Every genetic process involved in oncogenesis is reproducible with a Boolean Stochastic Network; In this view, oncogenesis is only a wrong configuration of the Boolean Network. Most of minimal perturbations do not cause fatal errors.

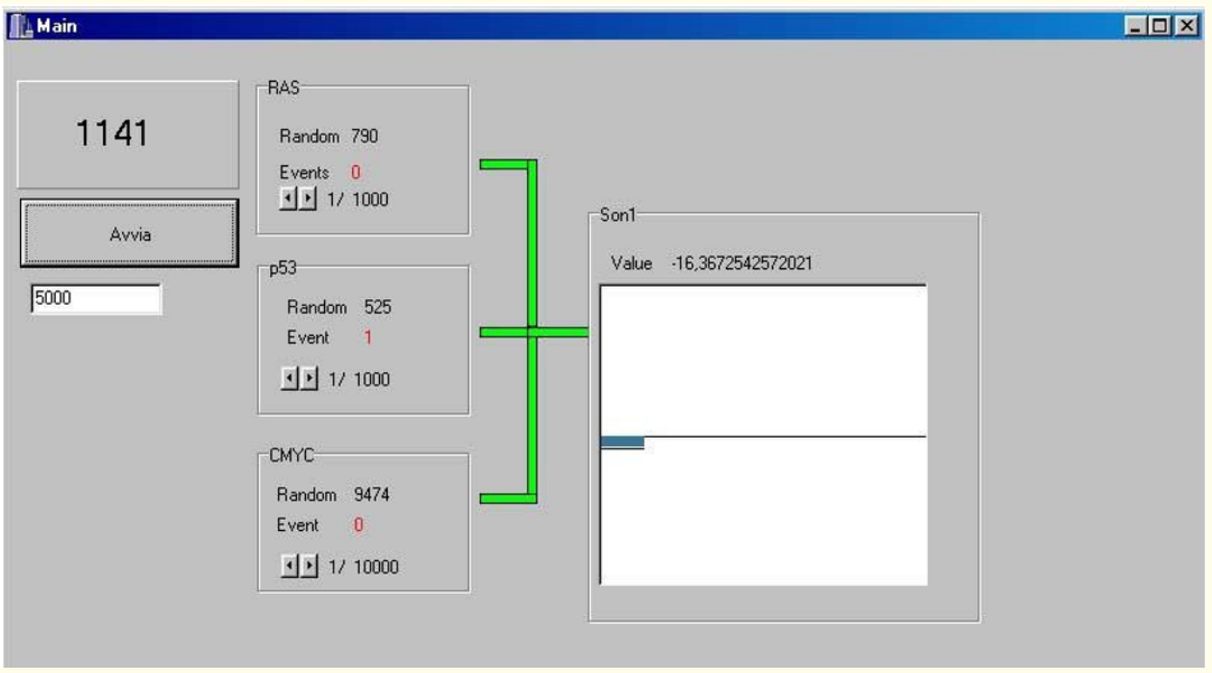

Figure 3: *Screen of the simulation software.*

Once there is a crash due to a structural perturbation the system is not resectable and the" program" is completely different and this may explain the difficulties encountered in gene therapy.

This model explains also the function of some chromosomal regions that influence the speed of transcription as recently described [24].

It gives a clear mathematical explanation of a clinical observation. Nervous system cancers have to be treated the soonest possible because the probability of error accumulates rapidly in crashed systems [17,18].

Conclusion

In the evolving world of genetics it is essential to not forget that the DNA is a biological molecule never the less, it is also a simple but sophisticated computing device. As discussed in the above article the mathematical and physical laws that underlie neurooncogenesis are the laws of the Turing Machine and the NK Autonomous Stochastic Boolean Networks.

Events of sudden arrest of the calculation (for DNA it means transcription), the perturbation of the Networks (Gene Mutation) are intrinsic in DNA and cancer may be an universal side effect of this laws.

What appears a must for DNA is that it has to be sufficiently stable to permit life and sufficiently unstable to permit evolution. In this optic cancer is "necessary" to evolution.

How do we transfer to neuro oncology this theoretical information?

What has been evident running this simulator is that each cell has its cancer within and to avoid the "error propagation" clinicians need to detect altered DNA (crashed systems) as soon as possible. The mutation (network perturbation) may generate a new program (for example a non-purposive or uncontrolled cell proliferation). When the program changes (DNA mutation) the error propagates and the system (DNA of the cell) becomes more and more unstable and different from the original program (the program is completely new) and in biology this means the cell progressively undifferentiated.

In every day practice neuro oncologists know that the diagnosis and treatment of brain tumors specially gliomas has advanced but the overall survival is still poor [35,36]. Clinical studies have already confirmed that overall survival in patients with glioma have better prognosis if surgical treatment is performed as soon as possible [17,18] and with the major extent possible [32] confirming what the simulation has evidenced: the need to reduce probability of error propagation.

In the optic of "error propagation" further genetic studies are needed in order to detect early stages of gliomas even if no lesions are present in the neuro imaging. The results of the simulation indicate that genetic testings and serum markers [33,34,37] should be performed every time there are neurological deficits, epilepsy seizures, speech or motor deficits and unusual headache. In cases that genetic testings are positive, to known genetic alterations, serial MRI screenings are mandatory. Other cancer types have been studied and the John Hopkins group are able to detect in early stages eight types of cancers [38]. These studies demonstrate that DNA mutation are present even if there is still no clinical evidence, once more confirming that all starts in a "little crash" somewhere in the oncogenes.

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