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Mini Review

Gravity and Telomeres

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Abstract

Telomere shortening is a well-known process that is proposed to influence the pace of aging in every living being. On the other hand, telomere lengthening seems to be restricted to pluripotent cells and adult stem cell population, and it is mainly mediated by the enzyme telomerase. However, how is telomerase activation regulated in these compartments is largely unknown. Telomerase is also aberrantly upregulated in the vast majority of cancer cell where it allows for indefinite cell division. In previous papers, it has been put forth that time asymmetry is important to understand the cellular world, especially stem cells and cancer. This process could also be the cause of the telomerase activation and the corresponding telomere lengthening, but this stress mechanism described in the aforementioned articles could be extended to changes produced by the effects of gravity and the lack of gravity (weightlessness). This paper intends to expand on those previous papers.

Keywords: Asymmetry of time; Cells; Molecular; Gravitation

Introduction

The origin of the arrow of time is still an unsolved problem. Almost all laws of physics are time-symmetrical. The classical and most obvious solution is the thermodynamic arrow of time and, in the field of information theory, entropy, also called information entropy or Shannon entropy [1,2], which measures the uncertainty of a source of information.

Entropy can also be defined as the average amount of information contained in symbols. The least probable symbols carry the most information. The concept of entropy is used in thermodynamics, statistical mechanics and information theory. In any case, entropy is conceived as a measure of disorder or the peculiarity of certain combinations. Entropy can also be considered a measure of uncertainty and the information necessary to limit, reduce or eliminate uncertainty in any process.

The concepts of information and entropy are basically interrelated, although it took years of development in statistical mechanics and information theory before this could become apparent. Entropy in information theory is closely linked with entropy in thermodynamics. In a closed system, interaction among particles tends to increase their diffusion, thus affecting their positions and velocity, and increasing the entropy of the distribution with time until a certain maximum is reached. This is known as the second law of thermodynamics. The difference between the amount of entropy in a system and its potential maximum is called negentropy, and represents the amount of internal organization in the system.

The basic concept of entropy in information theory has much to do with the uncertainty in every random signal or experiment. It is also the amount of noise or disorder contained in or released by a system, which can also be used to determine the amount of information carried by a signal.

Thermodynamics defines the statistical behavior of many entities. Being that the fundamental laws of physics are reversible at any time, it can be argued that irreversibility in thermodynamics must be statistical in nature, which means that it must be very improbable, but not impossible. Both in the universe and in our daily lives, we get the feeling that time flows inexorably from the past into the future, that time has a fixed direction towards a future of increasing entropy and disorder. However, in the microscopic world, this is not necessarily so.

In general, thermodynamics is a branch of physics that studies the effects of temperature, pressure and volume of physical systems on a macroscopic level. The amount of entropy in any thermodynamically closed system tends to increase with time, which would indicate that time flows in one direction, that there is a time asymmetry. As we saw in previous research [3,4], everything seems clear on a macroscopic level, but on a microscopic level, it is harder to assert that entropy is increasing and, thus, time is moving forward.

Developments in nanotechnology have enabled a radically different approach from the previous one, given that today we can manipulate individual molecules. Thus, in biotechnology, it is currently possible to study a single biological molecule or a single virus particle among the billions produced daily in an infected patient.

One of the methods developed for this implies using an instrument called “optical tweezers” or “optical trap”. This method requires the biomolecule under study to be previously joined to another type of molecule or to an artificial nanostructure, so that it’s larger size greatly facilitates the manipulation of the biomolecule in the solution. The high sensitivity of the optical tweezers enables subnanometric movement and rotation.

With this insight, Feng and Crooks [5] created a method to precisely measure time asymmetry on a microscopic level. They used a new method of measurement or evaluation to prove that time moves towards the future even when entropy decreases. For this, they have used experimental data [6,7] to analyze the folding and unfolding of an RNA molecule held by its ends and found out that, for certain intervals, entropy can actually decrease. While the general entropy

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increases on average, time not always has a clear direction.

To study time on this scale, they started researching the increase in energy dispersal in various distributions and proved that, on certain intervals, entropy actually decreases. Thus, we can conclude that, on a macroscopic level, time moves forward, but the direction of time becomes unclear on the scale of a single molecule.

As we said, they analyzed time asymmetry on an experiment with a single RNA molecule. They took a capture with an optic laser trap that could measure the force applied. RNA was initially on thermal equilibrium while being twisted. In the time reversal protocol, RNA was initially on thermal equilibrium during development; then it got shortened and enabled the RNA to fold.

As we can see, they worked with an RNA molecule given its versatility, but other molecules can also be used. They defined time asymmetry as the Jensen-Shannon divergence [1,2] between the probability distributions of the trajectory of an experiment. They analyzed the folding and unfolding of an RNA molecule and used lasers to stretch and compress it. Initially, RNA starts in thermal equilibrium, but as it gets stretched and compressed through the turns, the total entropy of the RNA and its surrounding medium increases on average.

The RNA molecule plays a central role in molecular biology, performing essential tasks in the transcription, translation and replication processes. Recent experiments based on the manipulation of a single molecule generated important information that could not have been produced otherwise. A popular single-molecule manipulation technique is optical tweezer microscopy. With this technique, the mechanical properties of the molecule can be analyzed to get information about the structure, stability and the interactions during the formation of said structure. In these experiments, called stretching experiments, a mechanical force is applied at each end of an RNA molecule.

Basically, the value of the force applied grows linearly until the molecule unfolds. If the process is reversed, relaxing the tension applied on the system, the molecule folds back on itself again. The information obtained from these experiments is the force as a function of the distance from end to end of the system.

This probability can describe the time asymmetry with greater accuracy than a simple measurement of the average entropy, since the average entropy is affected by abnormal events (for instance, if the RNA is entangled, it will resist unfolding when the tweezers expand. Entangled RNA untangles really slowly. This process is essentially of time asymmetry. It was proven that this process generates a great average dispersal or increase in entropy and a small temporal asymmetry, as would be expected intuitively due to slow traction.

Feng and Crooks [5], as we have seen, have contributed to the development of a measure of time asymmetry in a single RNA molecule, and, among other interesting properties, we can see that time asymmetry limits the average dissipation and determines the difficulty of accurately estimating the differences in free energy in non-equilibrium experiments.

The fact that, many times, RNA also folds and unfolds without the influence of external forces such as those applied in the aforementioned experiments leads us to suspect that the reversal of the arrow of time could really play an important role. Certain characteristics observed have no clear explanation, therefore this hypothesis could be the trigger to find an explanation for this unexplained phenomenon.

Scientific Objectives

The question we ask now is if this same mechanism could be related to what happens to astronauts in space, where the gravitational effect or lack there of (i. e., weightlessness) could produce a mechanism equivalent to what Feng & Crooks achieved in the lab, thus causing potentially resulting in activation of the telomerase enzyme and lengthening of telomeres as observed in NASA astronaut Scott Kelly, who spent almost a year in space. This may represent an alternative mechanism for explaining such a phenomenon.

Furthermore, we now know a lot about how tumoral cells stop the aging process by the telomeres elongation [8], and that cells that have suffered a transformation usually present telomerase activity which is repressed in adult cells and with every division the telomeres shorten. We could then consider that cancer cells are younger than the rest of the organism, at least in terms of being able to keep dividing without any time limitation, but this is still not well understood. What is clear is that by maintaining their telomeres they find a way to elude senescence and become immortal, while normal cells are mortal, among other things because their shorten their telomeres with time.

Everything points to the telomeres implicated in differentiated cells having a limited number of cellular divisions, after which they die or stop dividing in a process known as cellular senescence. The shortening of the telomeres is related to the replicative senescence of the differentiated somatic cells lacking telomerase activity. This indicates that the telomeric shortening operates as a clock that counts the number of cellular divisions remaining in certain cell.

Modified ribonucleic acid has been used to transmit instructions from the DNA genes to the cells that produce proteins. The RNA contains a codified sequence of the reverse telomerase transcriptase, the active component naturally produced by the telomerase enzyme. This enzyme makes sure that the telomeres on these cells remain in prime condition in the next generation, but disappears after birth, causing telomeres to shorten and the aging process to start.

When the reverse transcriptase telomerase returns, the telomeres grow back and can become a problem if the process is left unchecked. If the treated cells start splitting, they can become very dangerous because it is very likely for a cancer to develop in the process.

After spending 340 days in space in the International Space Station (ISS), the astronaut Scott Kelly presented changes in his gene expression, in the DNA methylation and in other biomarkers. As identical twins, Scott and Mark Kelly are very similar genetically. However, it was found that while Scott was in orbit, the ends of his chromosomes grew until they became longer than his brother's, although they quickly recovered their original length shortly after returning to Earth. This is a completely unexpected discovery.

Telomeres tend to shorten naturally as we age and the rigors of space, including increased exposure to radiation-induced DNA damage, were supposed to accelerate the shortening, and not the other way round. The most radical and fascinating transformation observed so far in the body of Scott Kelly is in his DNA, specifically in his telomeres, the ends of the chromosomes whose main functions are structural stability for eukaryote cells, cell division and the lifespan of cellular lineage, which against all odds became longer. This could be either due to telomerase activation as the consequence of the space travel and associated environmental variables, such as exposure to low radiation doses, or absence of gravity. Alternatively, telomeres may be protected from shortening in the space owing to lower rates of cell division.

Clarifying the molecular mechanisms underlying these observations, will be of interest to understand how space affects telomere length and therefore, the regenerative capacity of the organism, to plan future crewed space travel.

Conclusion and Future Perspective

We know that, on a microscopic scale, it is very hard to tell if entropy is always increasing, so the experiments by Feng and Crooks have become very important, since they indicate that, during certain intervals, entropy can even decrease, even if global entropy does not. In these cases, time has no clear direction. Time asymmetry is not certain, so even if time always moves forward in the macroscopic world, this would not be so clear at the level of a single molecule.

Assimilating these experiments with the situations that astronauts are submitted to in space, we may suppose that it is a possibility that gravitation or lack thereof could be similar to the experiments mentioned. Perhaps studying the variations of the levels of estrogen in the organism of the astronauts, it could be known if this mechanism could be the explanation of the lengthening of the telomeres in the space, being in this case possibly the cause of the activation of the telomerase, and in this direction we are analyzing the future experiments to be carried out.

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