

## On Microgravity and Biological Process

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### Abstract

Certain biological processes could be directly related to physics, such as telomere shortening and the activation of the telomerase enzyme. Telomere shortening is a well-known process that sets the pace of life in every living being. On the other hand, the reason behind telomere lengthening in some cases is not as well understood. We only know that it is directly linked to the activation of this enzyme. We put forth that time asymmetry is important to understand the cellular world, and microgravity and its variations could partially explain this phenomenon.

**Keywords:** temporal asymmetry; molecular; microgravitation; telomeres; telomerase

### 1. Introduction

The laws of physics are time-symmetrical. Without a doubt, the arrow of time is observed in nature, and the classical and most obvious solution is the thermodynamic arrow of time. In the field of information theory, entropy, also called information entropy or Shannon entropy, measures the uncertainty of a source of information. [1, 2].

The theory of information was developed by Claude Shannon to find the fundamental limits to the reliable compression, storage and communication of data. This has been expanded to find applications in many other areas, including statistical inference, natural language processing, cryptography, other networks

besides communication networks, such as neurobiology, the evolution and function of molecular codes, model selection in ecology, thermal physics, quantum computing, and other forms of data analysis.

A key measure in information theory is known as entropy, which is usually expressed as the average number of bits necessary for storage or communication. Entropy quantifies the uncertainty involved when finding a random variable. For example, a coin toss with two possible outcomes will have less entropy than throwing a dice with 6 equally likely results.

There is a really close relation between entropy and information theory. Let us suppose we have a physical system or other type of system with maximum uncertainty or, in other words, about which we know almost nothing. We then know that the maximum entropy compatible with the information we have is:

$$S_0 = - \sum_i \ln p_i$$

where  $p_i$  is the random probability that a particle in the system will occupy the  $i^{\text{th}}$  state. In the case of non-physical systems, it would be the probability that a certain type of entity is in situation  $i$ . Let us suppose that now we are given certain information about the system. The system must have an internal structure compatible with that information, so now the uncertainty is not at its maximum, but we are forced to comply with certain aspects compatible with the information. Now entropy will be reduced, because we have certain restrictions and we know something about the system. We can say that the maximum entropy compatible with the information available will be:

$$S_f = - \sum_i \bar{p}_i \ln \bar{p}_i \leq S_0$$

Therefore, according to the theory of information, the amount of information can be measured by subtracting the reduction in uncertainty or entropy. This means that the information available about something is equal to the reduction in uncertainty about that topic when accounting for the maximum uncertainty compatible with such information, and the theory of information is based on quantifying the available information as:

$$I_d = - (S_f - S_0) = - \Delta S > 0$$

In fact, the information that increases our knowledge will be positive, while old or inaccurate information increases uncertainty and entropy. Thus, true information available will be reduced.

Entropy can be defined as the average amount of information contained in the symbols used, so 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.

Thermodynamics is the branch of physics that describes the thermodynamic equilibrium states at a macroscopic level. It is the branch of physics that studies the interaction between heat and other manifestations of energy.

In general terms, 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 [3-5], 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.

## **2. Theory**

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 "optic tweezers" or "optic trap". This method requires the biomolecule under

study to be previously joined to another type of molecule or to an artificial nanostructure, so that its larger size greatly facilitates the manipulation of the biomolecule in the solution. The high sensitivity of the optic tweezers enables subnanometric movement and rotation.

With this insight, Feng and Crooks [6] created a method to precisely measure time asymmetry on a microscopic level. Thanks to a new method of measurement or evaluation, they proved that time moves towards the future even when entropy decreases. For this, they used experimental data [7, 8] to analyze the folding and unfolding of an RNA molecule held by its ends and found that, for certain intervals, entropy can actually decrease. While the general entropy increases on average, time not always has a clear direction.

They started by 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.

Thus, 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, and then it was shortened and enabled the RNA to fold.

They worked with an RNA molecule given its versatility, but other molecules could also have been used. Time asymmetry was defined as the Jensen-Shannon divergence [1, 2] between the probability distributions of the trajectory of an experiment [1, 2]. They analyzed the folding and denaturation of an RNA molecule using laser tweezers. Initially, RNA starts in thermal equilibrium, but then the total entropy of the RNA and its surrounding medium increases on average.

In molecular biology, this 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 optic tweezer microscopy. With this technique, the mechanical properties of the molecule can be analyzed to get information about structure, stability and the interactions during the formation of said structure. In these experiments, called stretching experiments, a mechanical force is applied at both ends of the 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 molecules untangle really slowly. This process is essentially of time asymmetry. This process was proved to generate a great average dispersal or increase in entropy and a small temporal asymmetry, as would be expected intuitively due to slow traction.

### **3- Result and discussion**

The contribution by Feng and Crooks [6] to the development of a measure of time asymmetry in a single RNA molecule limits the average dissipation and determines the difficulty of accurately estimating the differences in free energy in non-equilibrium experiments.

The question we ask today is if this same mechanism could be related to what happens to astronauts in space, where variations in microgravity could produce a mechanism equivalent to what Feng & Crooks achieved in the lab, thus causing the activation of the telomerase enzyme which, in turn, produces the stretching of the telomeres, as it happened to astronaut Scott Kelly [9]. This could be an alternative mechanism to explain a phenomenon which remained unexplained until now, the cause of telomere stretching.

Cancer [10] is essentially a disease caused by uncontrolled cell division. Its development and progression are usually linked to a series of changes in cell cycle regulator activity. For instance, cell cycle inhibitors prevent cells from splitting if conditions are not appropriate, thus a reduction in inhibitor activity can promote cancer. Likewise, positive regulators of cell division can lead to cancer if they are too active. In most cases, these changes in activity are caused by gene mutations that codify the cell cycle regulator proteins.

Cancer cells behave differently than normal body cells. Many of those differences are related to cell division behavior. For instance, cancer cells can multiply in culture (outside of the body in a dish) without adding growth factors or protein signals to stimulate growth. This is different from normal cells, which need growth factors to grow in culture. Cancer cells can make their own growth factor, have growth factor pathways that are stuck in the “on” position, or, in the context of the body, even trick neighboring cells into producing growth factors to sustain them.

Cancer cells can split many more times, mainly because they express an enzyme called telomerase, which reverts the wear that normally happens at the ends of chromosomes during each cell division. Cancer cells also differ from normal cells in other ways which are not directly linked to the cell cycle. These differences help them grow, split and form tumors.

Furthermore, we now know a lot about how tumoral cells stop aging, 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 think that cancer cells are younger than the rest of the organism, but this is still not well understood. What is clear is that they find a way to elude aging.

Everything points to the telomeres being implicated in differentiated cells having a limited number of cell divisions, after which they die from aging. Thus, the telomere shortening is related to the replicative senescence of the differentiated somatic cells lacking telomerase activity. This indicates that telomere shortening operates as a clock that counts the number of cell divisions remaining in a specific cell.

Modified ribonucleic acid has been used to transmit instructions from the DNA genes to the cells that produce proteins. The RNA used in some experiments 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 this telomerase returns, the telomeres grow back, which 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, astronaut Scott Kelly, who participated in NASA's Twins Study, 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, but then shortened even more. This finding was completely unexpected.

Telomeres tend to shorten naturally as we age and the rigors of space were supposed to accelerate the shortening, and not the other way round. The most radical and fascinating transformation observed so far in Scott Kelly's body 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.

This research has generated a lot of expectations, since it would be crucial to plan future long-term crewed space travel and also improve the understanding of cancer treatment.

#### **4. Conclusion**

It is very hard to tell if entropy is always increasing on a microscopic scale, so the experiments by Feng and Crooks have become very important, since they indicate that, during certain intervals, entropy can decrease, even if global entropy increases.

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 molecular level.

Comparing these experiments with the conditions that astronauts are submitted to in space, we may suppose that variations in microgravity could act in a similar way in the experiments mentioned. This mechanism may eventually become an explanation for telomerase activation in space.

Today, there are companies and agencies willing to study the effects of variations in microgravity on telomeres to see if they activate the aforementioned enzyme, and there are experiments planned to send humans, mice and plants to space to microgravity platforms and to the International Space Station. This will produce a follow-up paper with the results of these experiments.

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