Austin Biochemistry

Open Access

Austin Publishing Group

Short Communication

Temporal Asymmetry in the Molecular World

Aquilano R*
[1]Facultad de Ciencias Exactas, Ingeniería y Agrimensura, Universidad Nacional de Rosario, Argentina
[2]Instituto de Física Rosario (CONICET-UNR), Argentina

***Corresponding author:** Roberto Aquilano, Facultad de Ciencias Exactas, Ingeniería y Agrimensura, Universidad Nacional de Rosario, Av. Pellegrini 250, 2000 Rosario, Argentina

Instituto de Física Rosario (CONICET-UNR), Bv. 27 de Febrero 210 bis, 2000 Rosario, Argentina

Received: July 25, 2017; **Accepted:** August 01, 2017; **Published:** August 08, 2017

Abstract

The asymmetry of time is important to approach the cellular world, especially to understand stem cells and cancer. As the amount of energy involved in microscopic processes is so small, it is more difficult to argue that entropy increases, and therefore the direction of time becomes confusing and undefined at the molecular level. This is an extension of a previous work, where some details are specified and alternatives are proposed.

Keywords: Asymmetry of time; Cells; Molecular

Description

Thermodynamics defines the statistical behavior of many entities. Since the fundamental laws of physics are at all times reversible, it can be argued that the irreversibility of thermodynamics must be statistical in nature, meaning that it must be very unlikely, but not impossible.

Both in the universe and in our daily lives, we get the feeling that time flows inexorably from past to future, that time has a fixed direction, towards a future of increasing entropy and disorder. But is this so in the microscopic world as well?

Broadly speaking, thermodynamics is the branch of physics which studies the effects of temperature, pressure and volume of physical systems on a macroscopic level. The amount of entropy of any thermodynamically isolated system tends to increase with time, which would indicate that time has a direction, that there is a temporal asymmetry.

Ilya Prigogine said that irreversibility and entropy differ from that of traditional physics. In a lecture called The Birth of Time (Rome, 1987) [1], he stated: "Entropy always contains two dialectical elements: an element that creates disorder and an element that creates order. We can see, then, that instability, fluctuations and irreversibility play a part at all levels of nature: chemical, ecological, climatological, biological and cosmological".

Thus, Prigogine argues that the irreversibility is constructive in nature, highlighting the "creative role of time"; at least on a macroscopic level, the universe of non-equilibrium is coherent. Everything seems to be clear at a macroscopic level; however, at a microscopic scale, since the amount of energy involved in processes is so small, it is harder to assert that entropy is increasing and that, as a consequence, time is moving forward.

Current developments in nanotechnology allow us to adopt a radically different approach. Now it is possible to manipulate and move single molecules to understand how each of them works and how they interact with others. This enables bionanotechnology to study a single biological molecule (for instance, a DNA strand or a protein), a single macromolecular addition (for instance, a chromosome or ribosome), or a single virus particle among the thousand millions produced in an infected organism.

One of the methodologies developed for this consists of using "optical tweezers or traps". This method, perfected at Bell Labs in 1970, consists of using a highly focused laser beam that can trap and move non-conductive particles without making contact. For this, the biomolecule under study must have previously been bonded to another type of molecule or to an artificial nanostructure, so that its larger size facilitates the manipulation of the biomolecule in the dilution.

The high sensitivity of optical tweezers enables them to perform sub-nanometric movements and rotations. This has opened the door to a lot of research on biochemical and biophysical processes, on the mechanical properties of nucleic acids and proteins, and on the behavior of different molecular nanomachines and nanomotors that work within the cells. Optical tweezers have been used, for instance, to measure the force needed to stretch, compress or untangle single or double DNA and RNA strands, and to perform a controlled hybridization or dehybridization of both strands of a DNA double helix.

Feng and Crooks [2], feeding on this insight, created a method to accurately measure the time asymmetry at the microscopic level. Using a new measurement and testing method, they sought to prove that time moves forward even when entropy decreases. On a microscopic scale and for some intervals, entropy can actually decrease. To this aim, they employed experimental methods [3,4] to analyze how an RNA molecule folds and unfolds when held by its ends. They discovered that, at certain intervals, entropy can actually decrease; while the general entropy increases on average, time does not always have a clear direction.

To study time at this scale, they started researching the increase of energy dissipation in several distributions and proved that, at certain intervals, entropy actually decreased. While time moves forward in the macroscopic world, the direction of time becomes confusing at the scale of a single molecule. They analyzed temporal asymmetry in an experiment with a single RNA molecule. A capture was taken on an optic laser trap that could measure the force applied. RNA was

Citation: Aquilano R. Temporal Asymmetry in the Molecular World. Austin Biochem. 2017; 2(2): 1011.

initially in thermal equilibrium while folded. In the time-inverted protocol, RNA was initially in thermal equilibrium while unfolded, its extension reducing and allowing RNA to fold. Besides the theoretical implications of this research, the method developed by Feng and Crooks could have other applications, such as computing free energy differences on experiments with non-equilibrium systems.

As I said, Feng and Crooks have been working with just one RNA molecule given its versatility. They defined temporal asymmetry as the Jensen-Shannon divergence between probability distributions of the trajectory of an experiment [5,6]. They analyzed the folding and unfolding of an RNA molecule and used lasers to stretch it and compress it. Initially, RNA starts at thermal equilibrium, but as it is stretched and compressed in turns, the total entropy of RNA and its surrounding medium increases on average. To measure temporal asymmetry in this case, the RNA trajectory is observed to see if it folds and unfolds, and to determine if the trajectory was generated by stretching or compression. This observation can be quantified in terms of the "Jensen-Shannon divergence"; the probability will be "0" if the stretching and compression are identical, "1" if they are distinguishable at every moment, and "some fraction of one" if they occasionally overlap.

The RNA molecule plays a central role in molecular biology, performing essential tasks in the transcription, translation and replication processes. Recent experiments based on single molecule manipulation generated important information that could have not been produced otherwise. A popular single molecule manipulation technique is optical tweezers microscopy. With this technique, the mechanical properties of the molecule can be analyzed to obtain information about the structure, stability and interactions during the formation of such structure. In these experiments, called stretching experiments, a mechanical force is applied at both ends 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 again. The information obtained from these experiments is force as a function of distance from end to end of the system.

This probability can describe the temporal asymmetry more accurately than a simple measurement of average entropy, since average entropy is affected by abnormal events (for example, if RNA is entangled, it will resist unfolding when the tweezers expand). The entangled RNA unrolls really slowly; the process is essentially of temporal asymmetry. It was proven that this process generates a great average dissipation or entropy increase, and a small temporal asymmetry, as it would be intuitively expected due to slow traction.

But they were not the only ones who posited a problem related with this topic. Lorenzo Maccone [7] stated that there can be events run by an arrow of time pointing in the opposite direction, and that we are simply unable to perceive them. In his own words: "sadly, whenever this happens, there's no evidence left of its occurrence, so for lack of the necessary information, we are unable to perceive this".

Can we associate this with stem cells, seeing that the gap of entropy is close to zero or zero? Feng and Crooks [2] contributed to developing a measure of the time-asymmetry of recent single molecule RNA unfolding experiments. They define time asymmetry as the Jensen-Shannon divergence between trajectory probability distributions of an experiment and its time-reversed conjugate. Among other interesting properties, the length of time's arrow bounds the average dissipation and determines the difficulty of accurately estimating free energy differences in non-equilibrium experiments.

Continuing with the previous calculations [8-10], but consistent with low temperatures, we can see that the equations are reduced almost naturally to zero entropy, and this could eventually lead to an inversion in the arrow of time, opening the possibility for this to be an alternative explanation for why some cells could become hypothetically immortal.

The question is if the arrow of time is related with tumor cells and stem cells, and if this relationship could provide an alternative explanation to their mysteries. In them, the "feeling" of time passing is different, because they are awaiting "orders" to start working toward different goals. Could this be the key to the longevity of stem cells, which stay at their prime indefinitely, instead of the non-reception of orders to act? I do not know. But since the time of that question, there have been many breakthroughs on these topics, as we can see, and an interesting space for ideas emerged.

There is a whole body of research assuming that stem cells are involved with cancer, based on the similar behavior of stem cells and tumor cells. They both show an unlimited capacity to split, are very sensitive to the cellular medium where they grow and many of the genes activated on stem cells are also activated on tumor cells.

The fact that many times RNA is seen to stretch and compress without the influence of external forces such as those applied on experiments leads to suspect that the inversion of the arrow of time could be playing an important part. Certain characteristics observed have no accurate explanation, so this theory could be a contribution to find an explanation for lack of other ideas.

In addition, today we have a lot of information on how tumor cells stop the aging process by extending their telomeres [11,12]. Also, we now know that cells that have undergone a transformation usually present telomerase activity (enzyme that promotes telomere extension) and that, if we vary the amount of telomerase for DNA of a certain length, the length of the DNA will vary.

On the other hand, in most of our cells, telomerase levels are too low, but ninety percent of tumors show an elevated level which allows its cells to become immortal and split forever. This is an important part of tumor formation.

Telomerase is repressed in adult cells and, with each division, telomeres are shortened. This could lead to think that cancer cells are younger than the rest of the organism, but this is still undetermined. What we do know is that they find a way to avoid aging with an enzyme formed by an RNA-protein complex present in germ cells, fetal tissue and in certain undifferentiated stem cells, which enables telomere extension. This enzyme is repressed in mature somatic cells after birth, by which telomeres get shortened after each cell division.

All this indicates that telomeres are involved in differentiated cells having a limited number of cell divisions, after which they suffer death by senescence; in other words, the shortening of the telomeres is related with the replicative senescence of differentiated somatic cells lacking in telomerase activity. This indicates that the telomeric shortening acts as a clock that counts the cell divisions remaining on a particular cell.

Modified RNA has been used to transmit instructions from the DNA genes to the protein-making cells. RNA used in some experiments contains a codified sequence of Telomerase reverse transcriptase, the active component that naturally produces the telomerase enzyme, only present in fetal tissue and certain stem cells. This enzyme guarantees that the telomeres on these cells are fully-functioning on the next generation, but it disappears after birth, thus causing telomere shortening and starting the aging process.

When Telomerase reverse transcriptase reappears, the telomeres start growing again; this can be a problem if unchecked. If the cells treated start splitting to infinity, they can become very dangerous, since this process is likely to develop into cancer.

As Renato Dulbecco commented a long time ago [13]: "The abnormal behavior of tumor cells is due, in large part, to genetic alterations and dysfunctional operation". The stretching and compression caused by the arrow of time could be the cause of the "dysfunctional operation" mentioned. Since there is yet no convincing explanation, it is still an open question.

Conclusion

On a microscopic scale, since the amount of energy involved in the processes is very small, it is very difficult to say that entropy is always increasing. Experiments by Feng and Crooks determined that, during some intervals, entropy may decrease, even if overall entropy increases, and became important to explain some behavior. As time has no clear direction in these cases, time asymmetry is not secured. Even if time always moves forward in the macroscopic world, this is unclear at the level of a single molecule.

If we relate this phenomenon to stem cells, as these remain unchanged until receiving instructions, we could say to have found a natural case of a reversal of the arrow of time. We also know that cancer is the result of a gradual loss of cellular self-control, so could this be the cause for this loss of control? There is no clear answer, but, as Albert Einstein once said: "Sometimes the formulation of a problem is more important than its solution".

References

1. Prigogine El nacimiento del tiempo [The Birth of Time], (Barcelona, Tusquets Editores). 1991.
2. Feng EH, Crooks GE. Length of time's arrow. Phys Rev Lett. 2008; 101: 090602.
3. Collin D, Ritort F, Jarzynski C, Smith SB, Tinoco I, Bustamente C. Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies. Nature. 2005; 437: 231.
4. Ritort F. Single-molecule experiments in biological physics: methods and applications. J Phys Condens Matter. 2006; 18: R531.
5. Lin J. Divergence Measures Based on the Shannon Entropy. IEEE Trans Inf Theory. 1991; 37: 145.
6. Majtey A, Lamberti PW, Martin MT. Plastino A. Wootters' distance revisited: a new distinguishability criterium. Eur Phys JD. 2005; 32: 413.
7. Maccone L. Quantum solution to the arrow-of-time dilemma. Phys Rev Lett. 2009; 103: 080401.
8. Aquilano R. The Asymmetry of Time and the Cellular World. Stud Theor Phys. 2010; 4: 907-915.
9. Aquilano R. The asymmetry of time and the cellular world. Is immortality possible? J Biophys Chem. 2011; 2: 49-52.
10. Aquilano R. The Problem of Time at the Molecular Level. Austin Biochem. 2017; 2: 1008.
11. Szostak JW, Blackburn EH. Cloning yeast telomeres on linear plasmid vectors. Cell. 1982; 29: 245-255.
12. Blackburn EH, Szostak JW. The Molecular Structure of Centromeres and Telomeres. A Rev Biochem. 1984; 53: 163-194.
13. Dulbecco R. From the molecular biology of oncogenic DNA viruses to cancer. Science. 1976; 192: 437–440.

Austin Biochem - Volume 2 Issue 2 - 2017
Submit your Manuscript | www.austinpublishinggroup.com

Citation: Aquilano R. Temporal Asymmetry in the Molecular World. Austin Biochem. 2017; 2(2): 1011.