Letter to the Editor

Zooming (a little) out of the M-theory

Roberto Piergentili

Istituto di Biologia e Patologia Molecolari del CNR; Dipartimento di Biologia e Biotecnologie, Sapienza Università di Roma; Rome, Italy

Received on December 5, 2012; Accepted on December 31, 2012; Published on February 20, 2013

Email: roberto.piergentili@uniroma1.it

I've read with much interest the editorial entitled "*An introduction to M-theory and its application in biology"* (Vlachakis & Champeris Tsaniras 2012), and I would like to share some considerations with the readers of your journal.

I do agree with you when writing that, in most fields of knowledge – but particularly in biology – there is a traditional approach to cartesian reductionism, in opposition to holism. Reductionist theories basically imply that every system may be downsized to the sum of its components. Consequently, by stressing this concept in biology, someone concludes that life is just the sum of chemical and physical interactions among molecules. Instead, holistic theories are based on the assumption that the former statement is wrong, and that new, complex qualities may arise in a system, which are unpredictable by simply looking at the system's components; this feature is called *emergence*. This way of considering the problem gave birth to system theories; in this case systems biology (Rosen 1968, von Bertalanffy 1976). Actually, the reductionist approach does not negate the existence of emergent qualities in complex systems, but it explains them as phenomena arising from the processes the system itself is made of. These new features may be then *reduced* to simpler characteristics by studying new variables, previously not identified or insufficiently characterized. In other words, it can be assumed that these new qualities may still be explained with a deeper or different analysis of simpler processes.

An example may be useful to better understand this concept. In *E. coli* the length in microns of the chromosome is known. In optimal laboratory conditions, this organism duplicates its DNA every ~40 minutes. Since the chromosome has only one origin of replication, there are only two replication forks; their speed may be calculated by coupling these data with known DNA helix parameters, resulting in a final speed value of approximately 0.8 Kb/sec per fork. Consequently, it can be easily calculated that, during replication at full speed, the DNA rotates around its major axis at ~4800 rpm, a value similar to a laboratory centrifuge. To our knowledge, nobody ever studied the problem of turbulences creation or heat production by friction around the spinning DNA during its replication, topics that likely would unveil some interesting, new, unexpected characteristics of this process. Certainly, the surrounding water has an high thermal capacity and may also act as a shock-absorber, nonetheless it is unlikely that these effects are negligible at the molecular level, and it would be interesting to understand how the cell copes with these problems. Moreover, this fact also gives us a hint about the speed at which cellular processes usually take place.

Zooming in to the atomic level, an apparently strange feature of the matter is that most of the space seems to be *empty* space. In 1911 Rutherford demonstrated that a gold film is largely unable to stop – or at least to deviate – a straight stream of alpha particles, and concluded that the distance between nuclei and electrons is 10^4-10^5 times the size of the nuclei themselves. For comparison, if a nucleus had the size of a football, the nearest electron would be approximately 1 km away. Even using the Bohr-Sommerfeld model with the Schrödinger's enhancements, large portions of the space surrounding the atomic nucleus are still statistically empty, and if we consider any given, very short instant of time, most of this space contains no matter from a statistical point of view. Indeed, if we look at Figure 1 in the abovementioned manuscript (Vlachakis & Champeris Tsaniras 2012), we may interpret the black zones not only as the probability to find an electron in a certain space in any given instant, but also as a measure of the time spent by the electron at any given position and, consequently, as the spatial distribution over time of the electron, in four dimensions. It is thus tempting to conclude that most of the space inside a cell is devoid of matter, since this space is filled with atoms occupying big volumes with very little masses. But such an assumption would imply that atoms may be compressible, which is clearly false. For example, in the case of water at room temperature, it is

possible to reduce its volume only by 1/1000th by applying a pressure of more than 2.2 MPa; for comparison, at sea level we live at ~0.1 MPa. Moreover, water volume shrinks because different atoms are closer to each other, and not because electrons are closer to their nuclei. Indeed, compression is intimately related to temperature, which in turn is related to molecular dynamics. The latter corresponds to the freedom of movement, which is a function of the molecules' relative distance. What makes atoms not compressible is the energy filling the space between nucleus and electron(s); according to the famous Einstein's equation, energy and matter are basically the same thing, in a different form. This rigidity (coupled, of course, with a long list of physiological adaptations) allowed some barophilic microbes to live in presence of up to 100 MPa pressures at the bottom of the oceans (Pikuta *et al.* 2007). Thus, every cell is filled with molecules which are flexible but not compressible, which continuously hit each other, in a rather crowded environment, filled with similarly rigid water molecules. Somehow, it is similar to children's balloon pools.

Let's now zoom out again, at the molecular level. In 2010 an interesting review was published, dealing with the rigidity of some biological molecules involved in cell division (Bloom & Yeh 2010). The authors clearly explain that, at the cellular level, viscosity is far more important than gravity, mass and inertia. This means that, for example, if a chromosome detaches for any reason from the microtubule spindle during mitosis, it is not supposed to float away like a boat from the pier, but it will remain in place, likely for a lot of time – a lot of time in cellular terms, of course. Similarly, a microtubule is structurally as rigid as Plexiglas, and if we consider globular kinetochore proteins, their rigidity is on the scale of GPa. Instead, mitotic chromatin is deeply different: contrarily to naked DNA (which has a rigidity comparable to tubulin), chromatin is *soft*, thus it is not only highly flexible, but also highly compressible. A balance of forces between these molecules (chromatin on one side, proteins of the spindle and the kinetochore on the other side) is the foundation for a proper metaphase plate formation and provides the basis for a subsequent correct chromosome segregation. In another section of their work, the authors also underline that most biophysical studies are made using diluted solutions of salt water, a condition that is very far from the average intracellular environment; an example of how reductionism is used in some biological studies.

In conclusion, the reductionist approach has been, and still is, a very good approach to *start* the study of complex systems, but it is unable to give us the full picture of a process. Bioinformatics and mathematical models will surely help, in the near future, to reach a better understanding of complex systems by integrating large amounts of data from diverse, reductionist sources (Ishii *et al.* 2007, Buescher *et al.* 2012, Nicolas *et al.* 2012).

Conflicts of Interest

The author declares no conflicts of interest.

References

Bloom K & Yeh E 2010 Tension management in the kinetochore. *Curr Biol* **20** R1040-1048

Buescher JM, Liebermeister W, Jules M, Uhr M, Muntel J, Botella E, Hessling B, Kleijn RJ, Le Chat L, Lecointe F, Mäder U, Nicolas P, Piersma S, Rügheimer F, Becher D, Bessieres P, Bidnenko E, Denham EL, Dervyn E, Devine KM, Doherty G, Drulhe S, Felicori L, Fogg MJ, Goelzer A, Hansen A, Harwood CR, Hecker M, Hubner S, Hultschig C, Jarmer H, Klipp E, Leduc A, Lewis P, Molina F, Noirot P, Peres S, Pigeonneau N, Pohl S, Rasmussen S, Rinn B, Schaffer M, Schnidder J, Schwikowski B, Van Dijl JM, Veiga P, Walsh S, Wilkinson AJ, Stelling J, Aymerich S & Sauer U 2012 Global network reorganization during dynamic adaptations of *Bacillus subtilis* metabolism. *Science* **335** 1099-1103

Ishii N, Nakahigashi K, Baba T, Robert M, Soga T, Kanai A, Hirasawa T, Naba M, Hirai K, Hoque A, Ho PY, Kakazu Y, Sugawara K, Igarashi S, Harada S, Masuda T, Sugiyama N, Togashi T, Hasegawa M, Takai Y, Yugi K, Arakawa K, Iwata N, Toya Y, Nakayama Y, Nishioka T, Shimizu K, Mori H & Tomita M 2007 Multiple high-throughput analyses monitor the response of *E. coli* to perturbations. *Science* **316** 593-597

Nicolas P, Mäder U, Dervyn E, Rochat T, Leduc A, Pigeonneau N, Bidnenko E, Marchadier E, Hoebeke M, Aymerich S, Becher D, Bisicchia P, Botella E, Delumeau O, Doherty G, Denham EL, Fogg MJ, Fromion V, Goelzer A, Hansen A, Härtig E, Harwood CR, Homuth G, Jarmer H, Jules M, Klipp E, Le Chat L, Lecointe F, Lewis P, Liebermeister W, March A, Mars RA, Nannapaneni P, Noone D, Pohl S, Rinn B, Rügheimer F, Sappa PK, Samson F, Schaffer M, Schwikowski B, Steil L, Stülke J, Wiegert T, Devine KM, Wilkinson AJ, van Dijl JM, Hecker M, Völker U, Bessières P & Noirot P 2012 Condition-dependent transcriptome reveals high-level regulatory architecture in *Bacillus subtilis*. *Science* **335** 1103-1106

Pikuta EV, Hoover RB & Tang J 2007 Microbial extremophiles at the limits of life. *Crit Rev Microbiol*

33 183-209
Rosen R 1968 A Means Toward a New Holism. *Science* **161** 34-35
Vlachakis D & Champeris Tsaniras S 2012 An introduction to M-theory and its application in biology. *J Mol Biochem* **1** 65-67
von Bertalanffy L 1976 General System theory: Foundations, Development, Applications, pp. 295. New York: George Braziller Inc.