

## Systems Biology and Microgravity Effects on Living Organisms

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### Editorial

Gravity has constantly influenced biological phenomena throughout all the Earth's history. The gravitational field has probably played a major role in shaping evolution when life moved from water to land, even if, for a while, it has been generally deemed to influence natural selection only by limiting the range of acceptable body sizes, according to Galilei's principle. Indeed, to counteract gravity, living organisms would need to develop systems to provide cell membrane rigidity, fluid flow regulation, and appropriate structural support and locomotion. However, gravity may influence in a more deep and subtle fashion the way the cells behave and build themselves [1]. Cells exposed to microgravity (both in outer space as in simulated weightless condition) undergo dramatic changes, involving cytoskeleton architecture, cell shape, molecular pathways, gene expression and many others [2,3]. Over time, those effects on cells and tissues may lead to severe physiological and medical problems, such as osteoporosis, muscle atrophy, cardiac failure, changes in metabolism and immune functions, among others [4].

During the last decades, microgravity research has been focused in searching for the direct (i.e., mediated by gravity-sensor-like structures) and indirect mechanisms through which cells could "sense" the gravitational field [5]. Yet, despite some data have been gathered supporting both hypotheses, it seems quite evident that field's effects may be understood only by looking at the system as a "whole", that is to say by adopting a Systems Biology approach. Indeed, too many functions and cell's property are changing in concert after microgravity exposure, thus it would be pointless trying to locate a single master, triggering mechanism, as pivotal it might be.

Complex living systems are governed by non-equilibrium dynamics and are therefore sensitive to changes occurring in field's force. Even very "weak" forces, such as those displayed by electromagnetic and gravitational fields, can be "amplified" when the system encounter a bifurcation point from which it is driven in experiencing a "phase transition" leading to new, different attractor states. Those states are equally accessible when the field is absent, whereas the superimposition of an external field may break the system's symmetry, bestowing a preferential directionality according to which the system preferentially evolve into a specific attractor state [6]. In other words, the 'weak' force dramatically influences the system in selecting one of the two possible configurations. Indeed, recent studies gave compelling evidence that such processes actually occur in cells exposed to a microgravity field [7,8]. It is very unlikely that such phase-transitions could be grasped by only looking to selected molecular pathways, as the transition involves the overall system, and induces a dramatic rewiring of gene-expression pattern, cytoskeleton structure, enzyme dynamics and so forth. A systems biology approach is indeed mandatory in order to understand how changes in the non-equilibrium dynamics may lead to concomitant modification of such

different processes. As a matter of fact, several biochemical mechanisms within the cell are true dissipative processes (microtubule assembly, cytoskeleton arrangement, cyclins kinetics) and as such they could be described as non-linear reactions occurring far from the equilibrium [9]. These kinds of reactions are highly sensitive to changes in field's strength and may undergo a transition at the bifurcation point, after experiencing a symmetry breaking, leading hence to novel self-organized configurations.

According to that framework, gravity may be considered an 'inescapable' constraint that obliges living beings to adopt only a few configurations among many others. In turn, by 'removing' the gravitational field, living structures are free to recover more degrees of freedom, thus acquiring new phenotypes and new functions/properties. Those configurations may be explored in dept only through a systems biology framework. That statement raises several crucial questions. Some of these entail fundamentals of theoretical biology, as they cast on doubt the gene-centered paradigm, according to which biological behavior can be explained by solely genetic mechanism [10]. Indeed, influence of physical cues in biology (and, in particular, on gene expression) is still now largely overlooked. This is why it has been argued that the ultimate reason for human space exploration is precisely to enable us to discover ourselves [11].

Undoubtedly, the microgravitational space field presents an unlimited horizon for investigation and discovery. Controlled studies conducted in microgravity can advance our knowledge, providing amazing insights into the biological mechanism underlying physiology as well as many relevant diseases, like cancer. Thereby, space-based investigations coupled to systems biology may serve as a novel paradigm for innovation in basic and applied science.

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