

Opportunities and Questions for the Fundamental Biological Sciences in Space

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ABSTRACT

With the advent of sophisticated space facilities we discuss the overall nature of some biological questions that can be addressed. We point out the need for broad participation by the biological community, the necessary facilities, and some unique requirements.

INTRODUCTION

Fundamental biological science has many meanings to many people. To us, it means the pursuit of new knowledge about life. With the advent of the space program and the writing of the NASA's charter, access to space suddenly made it possible for the nation's scientists to explore a previously unavailable, but critical (perhaps the most critical) element in the evolution of living systems on Earth. Life has evolved on Earth in the continuous presence of gravity. By going into space, we have been given a glimpse of how gravity may influence biological systems. However, even Soviet achievements of one year in Earth orbit are but a minute fraction of the hundreds of millions of years it has taken life to evolve on Earth. After more than three decades, new knowledge about the physical nature of our solar system, our galaxy, and the cosmos has stimulated, fascinated, thrilled, and dominated scientists involved in the space program, the general public, the young, and the old. On the other hand well over half of NASA's budget has been tied to the manned program and its support. The life sciences program has largely focused on the medical and operational aspects of flying people in space. The basic biological sciences have received but desultory and sporadic attention and support. Why did physical sciences succeed where the biological sciences has lagged so far behind? We are not going to discuss the reasons for the relative paucity of work utilizing the space environment by the community of biological scientists. Rather, we shall focus on the opportunities we see to excite the scientific community into participation.

Unlike the physical sciences, biology is frequently a long, complex, interactive process, not a singular event. Therefore, it requires a continuum of formulation of hypothesis, manipulation, interpretation, reformulation, and replication, which necessitates repeated access to the variables examined. In practical terms, what that means is that in biological sciences, a single flight experiment serves only to whet the appetite and to more accurately point the directions for the next experiment. In other words, a single mission will not answer a biological question. In order to acquire new knowledge in gravitational biology, we need to make this message clearer to NASA and to the public and develop ways to enable long-term commitments between the scientific community and NASA.

The study of biology in space can be divided into four major categories: (a) the study of the origin of life, its distribution, and fate; (b) the utilization of the perspective from space to better understand the complex interactions between the biological and physical, global properties of Earth; (c) the specific exploitation of the microgravity environment to better understand the fundamental properties of life here on Earth; (d) the utilization of spaceflight as a unique form of provocative stimulation to better understand the mechanisms by which living systems respond and adapt. This last approach addresses most closely the acquisition of knowledge in support of space medicine and manned flight. However, it is the pursuit of new knowledge of the effects of gravity and microgravity on living systems that we will dwell on here. Our approach will be to ask and then discuss some first and second order questions about basic issues in biology. These issues include: structure, from cell to organ to organism; function, the regulation of systems such as immunology, neural sciences, and behavior; and reproduction and development. We have selected questions from each of these classical subdivisions of gravitational biology in order to show the depth and profound diversity of disciplines that could actively participate in this relatively new science.

STRUCTURE

Gravity can be envisioned as a load generating physical stress, and as a sensory input. How do individual cells and populations of cells perceive gravity?

Do cells directly perceive and respond to gravity or is gravity's influence upon cells mediated indirectly? Cells have a structural system — the cytoskeleton — that provides them with shape and dimension. In addition to its structural features, the cytoskeleton acts as a sensory organelle. Cells make mechanical connections to the substrate they grow on, to neighboring cells, and to soluble circulating factors like growth factors. These connections can be relayed by the cytoskeleton. They can also be relayed by internal chemical pathways that transmit by cascade action signals that are sensed at the cell membrane and that need to be sent to the cell nucleus where the genetic material, DNA, resides.

From an experimental perspective, what information (stimuli) is passed to a cell living in a three-dimensional body as opposed to one living on a two-dimensional, *in vitro*, cell culture? At the cellular level and in a microgravity environment, what is the relationship between function and structure? If there is a relationship at this level of analysis how does it affect cell differentiation, development, carcinogenesis, or cell senescence?

Autonomous, individual cells suggest other questions. These independent units provide all the functions necessary to life in one compact package. They evolved long before multicellular organisms, like us, with our specialized cell functions. Questions of the role of gravity in evolution, and the adaptability of terrestrial life to altered gravities, surround the study of these types of biological systems.

To go a few steps higher in the living system and its integration: Is gravity necessary for the normal development of a musculoskeletal system? How does the presence or absence of gravity influence the deposition of mineral in matrix? What are the systemic mechanisms involved in the adaptation from Earth gravity to the microgravity of spaceflight? What are the gravity thresholds for proper organ and system development? Do the usual risk factors such as gender, age, nutrition, exercise, species, or strain strongly interact with exposure to altered gravitational forces? How do they interact with the radiations found in deep space or other spaceflight associated factors?

FUNCTION

In animals as well as higher plants there are systems that respond to the acceleration force called gravity. How do they adapt to altered gravitational

environments? Will organisms that mature in microgravity or altered gravitational environments develop phenotypically or functionally different gravity sensors? What are the thresholds and functional dependencies of acceleration for the various gravity sensors? How can the rapid adaptation to microgravity by animals, including humans, be used to understand the plastic nature of the nervous system? Earth's gravity is such that organisms raised on Earth seem to adapt reasonably well to microgravity; is the reverse true?

What is the consequence of altered gravity perception on musculoskeletal function? On smooth muscle? How are these translated into altered motor behavior and autonomic functions? Similarly, what is the consequence of altered perception on endocrine feedback regulating systems? How is that translated into altered metabolism, arousal, sensory thresholds, and reproduction? What is the consequence of altered perception on the regulation of circadian rhythmicity? Is gravity a major *zeitgeber*?

REPLICATION, REPRODUCTION, AND DEVELOPMENT

Mammalian cells, in certain growth stages, present particular questions with respect to gravity-mediated effects. During fetal development, spatial orientations and associations with certain substrates are critical in the proper execution of programmed development, differentiation, and growth. This occurs in the buoyant environment of the womb akin to the marine environment where life evolved, and where gravity is perceived quite differently than after birth. The activated, dividing behavior of fetal cells is partially recapitulated in adult life during the processes of healing and repair and, in the case of cancer cells, where normal growth controls are bypassed. The relationship between structural forces provided by or enforced by gravity in these growth states can be determined only by studying the effects of altered gravity on these processes (Grymes, 1991).

Mammalian reproduction and reproductive behavior are particularly sensitive to perturbations. It will be particularly challenging to isolate the effects of gravity on these functions, since numerous spaceflight associated conditions are well known to interfere with this process. However controlled these experiments might be, it may not be for several generations, following adequate adaptation to these conditions, that the true effects of microgravity on reproduction and reproductive behavior may become evident.

In both plant and animal systems, the concept of critical periods in development, wherein experimental intervention can irreversibly alter neural circuitry,

adult sexual behavior, or endocrine responses (Vernikos, 1972), suggests that gravity may also exert its most profound effects at these times.

Furthermore, the effects of gravity and microgravity on life span as well as seed-to-seed and generation-to-generation morphological and functional evolution need to be addressed.

THE NEED FOR CONTROLS

Biological research is complex since, at all levels, from a single cell to entire organisms, there are so many interacting, mutually dependent subsystems. Such research depends heavily on the elimination of interfering variables by conducting appropriate controls. This is particularly and overwhelmingly true in the spaceflight scenario. Delay between loading and experiment and inflight access, lift-off forces, need for remotely controlled manipulation, re-entry forces, and delay in accessing experimental specimens post-flight are all unique and difficult to control variables. For example, microgravity-induced alterations of the immune system have been reported. However, inflight samples from animal species have yet to be obtained or analyzed. It is now increasingly evident that acute immune responses can be measured in humans following postural change or exercise so that differences in pre- and postflight data may be accounted for by re-entry and landing events. Similarly, inflight human evidence may be due to microgravity or to the confinement of spaceflight or some other environmental variable, which, so far, has not been controlled.

The requirement for an onboard centrifuge to provide a 1 g simultaneous control could reduce much of the ambiguity present in many past studies. Of course, centrifugation may well introduce new and unexpected variables. The validity of a conclusion that a particular biological phenomenon is, indeed, due to gravity or its absence is one not only where all possible other explanations have been systematically eliminated, but also where the phenomenon can be demonstrated in multiple species, including humans.

FACILITIES

What do we need to conduct such research? At the very least, continuity and the ability to conduct repeated experiments in the same laboratory are required. The Soviet Cosmos unmanned biological satellite program, which launched multispecies experiments approximately every two years since 1972, has proven the value of such an approach. As we become more sophisticated in the use of artificial intelligence for inflight, remotely controlled manipulation of payloads, an unmanned, recoverable, free-

floating untended platform that exposes specimens to prolonged periods of microgravity (e.g., greater than 60 days) could form the bread and butter of a biological sciences program. It is clear, however, that such an unmanned satellite could never replace the need for a human-tended, permanent, Earth orbiting laboratory. Such a laboratory should make it possible to study, on orbit, significant numbers and varieties of experimental specimens, with appropriate 1 g controls and the capability for observation, intervention, and testing. It does not have to be elaborate, but it is essential if gravitational biology is to move forward — away from simple parametric observations.

CONCLUDING REMARKS

The history of biological science (as well as all science, for that matter) is replete with examples of discovering deep and profound new knowledge upon gaining control of a primary physical variable, viz. light, momentum, sound, chemistry, and radiation, to mention but a few. There is every expectation the same will be true for gravity since now, for the first time in history, we can "control" or manipulate accelerations to less than the equivalent of 1 g.

The questions raised in this paper are but a few examples. It is up to the biological scientific community to harness their creativity towards this exciting research frontier. The facilities to conduct the research are expensive and complicated, yet some are already available to our nation's scientists; better ones will become available in the not-too-distant future. Support for biological research in space will happen only if the scientific community strongly believes, as we do, in its value and potential. Together we can capture the imagination of the public and persuade them of the benefits. The laboratories in space will always be a scarce and expensive commodity; we must make sure that as scientists we are selective and apply the highest scientific rigor to experimental design and data interpretation. On our part, we at NASA must develop a way to simplify procedures for enabling science to be conducted in space. A broad foundation of ground research, addressing specifically these questions, needs to be developed and nurtured before the jump to flight is made.

Ground and flight scientific programs are inexorably intertwined and although ground facilities exist, the community to support a space laboratory is inadequately small.

The reality of experimental control of gravity is within the reach of biologists; using this opportunity properly, we will reap new and exciting insights into life. With such insights we will be able to make intelligent and efficient advances as humankind con-

tinues to personally explore the limitless frontiers of space. We can only speculate about findings that will permeate our understanding of Earthly biology . . . life as we know it. The entire history of science indicates it is certain that the new knowledge will be important to furthering our understanding of biology: our personal origins and fate!

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