NONLINEAR
PHYSICAL
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Meike Wiedemann · Florian P.M. Kohn
Harald Roesner · Wolfgang R.L. Hanke

Self-organization and Pattern-formation in Neuronal Systems Under Conditions of Variable Gravity

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空间条件下的生命科学

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Authors

Meike Wiedemann
Department of Physiology (230)
University of Hohenheim
Membramephysiology
Garbenstrasse 30
70593 Stuttgart, Germany
Email: meike.wiedemann@uni-hohenheim.de

Harald Roesner
Department of Zoology
University of Hohenheim
Garbenstrasse 30
70593 Stuttgart, Germany
Email: roesnerh@uni-hohenheim.de

Florian P.M. Kohn
Department of Physiology (230)
University of Hohenheim
Membramephysiology
Garbenstrasse 30
70593 Stuttgart, Germany
Email: Florian.P.M.kohn@uni-hohenheim.de

Wolfgang R.L. Hanke
Department of Physiology (230)
University of Hohenheim
Membramephysiology
Garbenstrasse 30
70593 Stuttgart, Germany
Email: wolfgang.hanke@uni-hohenheim.de

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Preface

Accepting the statement that man sooner or later should be able to leave the earth and live in space, or at least that this question might be of some basic, possibly just philosophical interest, makes it necessary to recognize that conditions in space are significantly different compared to the earth. For example, radiation is high, atmosphere is not as present and gravity is not given or low. Also, to leave the earth by rockets includes the problem of reasonable high gravity for certain periods at launch and landing. Thus it becomes essential to study "life under space conditions". It might be possible with presently known technologies to minimize some of these problems, such as radiation, or to deliver a proper environment in the atmosphere and nutrition. However, the gravity problem in principle based on our present knowledge remains essential. Thus, to find out how life interacts with low (or high) gravity remains a problem to be studied, especially under the aspect that has been developed under the more or less constant earth gravity of 1*g* for billions of years.

Questions to be answered are, among others, how muscles and the skeleton behave under longer periods of μ-gravity, or how the human sensory system reacts to the changes in gravity. Additionally, the interaction of the human brain itself with μ-gravity is of specific interest, from the system level (the entire brain) down to the level of single molecules. Thus some more biologically basic questions have to be asked, down to the simple one, if single cells or single molecules can interact with gravity on a scale being relevant for living organisms, and what principal mechanisms are involved.

To produce higher than 1*g* gravity, being of interest for launch phases of rockets for example, it is not that difficult on the earth in a centrifuge for longer times and even for bigger volumes, but to produce μ-gravity is by far not trivial. Nevertheless, a variety of platforms have been created, which can be clearly divided by some criteria like whether they are for longer time scale, hours to years, or for shorter periods, seconds to minutes. Practically it has also to be asked if people can be present on board or not.

The most famous presently available platform is by sure the international space station, ISS. Here people can be present, and research can be done on a longer timescale, however, availability is limited and the price is high. These arguments are also hold for other presently available or planned long time scale μ-gravity platforms, one of them might be a Mars mission.

As a consequence, a number of so-called smaller platforms have been developed to do μ-gravity research on the earth, with or without people doing the experiments presented on board. The first half of this book will focus on the platforms and their usage with a detailed discussion of their technology, availability and limitations as well.

After having an idea about the technical basis, it might be asked what to do on these short-term platforms. According mainly to the limited duration of μ-gravity on these platforms, some experiments should be performed with a relevant timescale shorter than the duration of μ-gravity, and these are still a lot to be done. In case of biological questions concerning neuronal systems and even more limited, including the human brain, a number of tempting questions remain under these conditions and limitations, like whether single molecules, for example ionchannels in biological membranes, respond to gravity, or if the active potentials, the basic neuronal processing units, are depending on gravity. It can be also asked whether neurological processes in the connected tissue or the human EEG interact directly with gravity. These are the questions to be addressed in the second half of this book, in which we will demonstrate in details that not only the well-known human sensory apparatus for gravity perception in the vestibular system responds to gravity, but even single molecules, cells and parts of neuronal tissue as the entire brain do as well.

Meike Wiedemann
Florian P.M. Kohn
Harald Roesner
Wolfgang R.L. Hanke

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Finally we would like to thank all those helping us to write this text.

Terms and Abbreviations Used in the Text

Throughout the text as far as possible SI units have been used, as well as the standard chemical abbreviations. These are therefore not listed here. Shortcuts for names are also not listed. The nomenclature for the cell lines used is given in the text only, as well as the names of rarely used chemicals etc.

AC	alternating current
Ach	acetylcholine
AchR	acetylcholine receptor
ADHD	attention deficit hyperactivity disorder
AP	action potential
ATP	adenosine tris phosphate
bpm	beats per minute
BSA	bovine serum albumine
BZ	Belousov-Zhabotinsky
CNS	central nervous system
CPP	Comité pour la protection des personnes
CUMA	Brazilian sounding rocket
HBM	Hepes-buffered medium
DC	direct current
DLR	Deutsches Zentrum für Luft- und Raumfahrt
DNA	Deoxyribonucleic acid
EADS	European Aeronautic Defence and Space Company
EEG	electroencephalogram
EMG	electromyogram
ESA	European Space Agency
ETH	Eidgenössische Hochschule
FCS	heat-inactivated calf serum
FFT	Fast Fourier Transformation
FOTON	Russian orbital satellite
GMO	genetically modified organism
HDT	head down tilt
Hibeta	part of beta frequency band in EEG (22–36 Hz)
HRV	heart rate variability

HUT	head up tilt
IOS	intrinsic optical signal
ISS	International Space Station
JVC	jugular vein compression
LED	light emmiting diode
MAXUS	European sounding rocket
MIKROBA	microgravity with balloons (balloon drop capsule)
MIR	ancient Russian space station
MM	Mueller maneuver
MUSC	Microgravity User Support Center
NASA	National Aeronautics and Space Administration (USA)
NIH	National Institute of Health
NIZEMI	Niedergeschwindigkeits Zentrifugen Mikroskop
PB	phosphate buffer
PFA	paraformaldehyde
PKC	protein kinase C
POM	polyoximethylen
rpm	rounds per minute
SCL	skin conductance level
SCP	slow cortical potential
SD	spreading depression
SEM	standard error of the mean
SMA	scratch migration assay
SMR	low beta part of EEG frequencies (12–15 Hz)
TEA	tetraethylammonium
TEMPUS	German microgravity experiment
TEXUS	European-German sounding rocket
TTX	tetrodotoxin
UPS	uninterruptable power supply
VHS	video home system
VM	Valsalva maneuver
ZARM	Center of Applied Space Technology and Micro Gravity, Germany
$\mu g - 0g$	microgravity

Contents

Chapter 1
Introduction

Life on the earth including neuronal systems and the human brain has developed under the presence of a variety of external parameters including chemicals, light, electromagnetic fields and gravity. Among all these parameters the only one which has been really constant over all the time is gravity, which has been $1g$ since ever. As a consequence, most organisms, from single cells to complex systems, have developed gravity sensing structures or even complex organs. Mainly these structures are used for orientation in an otherwise variable environment.

Presently, for the first time it is possible for living systems to reach an environment in which these conditions do no longer hold, to leave the earth and to live in space (see, for example, Keller and Sahm, 2000; Leao, 1994). Here conditions are significantly different from those on the earth, among others having a zero or low gravity environment. Accordingly, it is necessary to study the influence of such conditions on life and more specifically on neuronal systems and the human brain, and to find out whether and how a low gravity environment influences the function of neuronal systems and the mental capabilities of man.

1.1 Historical remarks

1.1.1 Gravitational research

We have learned in earlier times that gravity and acceleration are identical, and thus technically it has been proven easy to produce higher gravity values than $1g$ for experimental purposes, for example in centrifuges for any relevant biological level and time. As a consequence, experiments and data about the influence of high gravity on living systems are available in sufficient amount. To produce, however, experimentally low gravity, especially over a reasonable time scale, is not that trivial. In this text we will therefore focus first on the present available experimental platforms for producing low or even close to zero gravity. We will separate long time platforms meaning days or more, from short time systems ranging from seconds to minutes. A timescale of seconds to minutes seems to be strange when investigating living systems, and this is by sure true when having in mind the lifetime of man for example or evolutionary processes. However, a significant amount of processes being involved in life, for example the behavior of single molecules, is arranged in sub-second time scales. Thus, even the short experiment on which we will focus in this text, are useful and necessary to understand how gravity interacts with living systems.

Following this idea, in the presented text, after having discussed the technical needs for low gravity experiments we will present a number of results dealing with the interaction of low gravity with neuronal systems on short time scales.

We will start from single molecules and proceed to more and more complex systems up to the human brain itself, always having in mind that the time scale of the process under the investigation will be much shorter than the time of low gravity conditions. To deliver the necessary, controled result, experiments under $1g$ and in case available under higher gravity levels will be presented. On reasons of a more complete overview, additionally some aspects of producing low gravity for longer time will be discussed.

When talking about a low gravity environment, unfortunately it has to be accepted that one is talking about high costs and limited access. Mainly governmentally founded systems are in use presently, and the ISS is the most expensive and famous one. As a result, very often only a strictly limited number of experiments is possible for a specific question, with all the resulting scientific limitations, which will be discussed throughout this book.

An additional problem is the high level of safety being required in most of the platforms. By this very often technical and experimental limitations have to be accepted, again reducing among others the access to scientific questions and the number of the experiments which can be done.

Nevertheless, general data about the interaction of gravity with living systems are available at a big amount. A lot has been done to understand, for example, how plants grow at variable gravity. A lot is also known about human physiology under such conditions, and presently the investigation of molecular and cellular processes under variable gravity is an important area of research. In this book, in each experimental chapter some historical remarks will be thus given about the presented subject.

1.2 Excitable media and their control by small external forces

There is another aspect of this text, which is pointing out towards a direction discussing neuronal systems under the aspect of nonlinear systems and excitable media (Epstein and Poiman, 1998; Sagues and Epstein, 2003; Tabony, 2006). An excitable medium is defined to fulfill a variety of conditions:

- it must be thermodynamically open
- mass and / or energy transfer through the system should be present
- the system should be far away from equilibrium
- feedback must be present within it

Such a system then will show a variety of things like self-organization, pattern formation, oscillations, travelling waves and others.

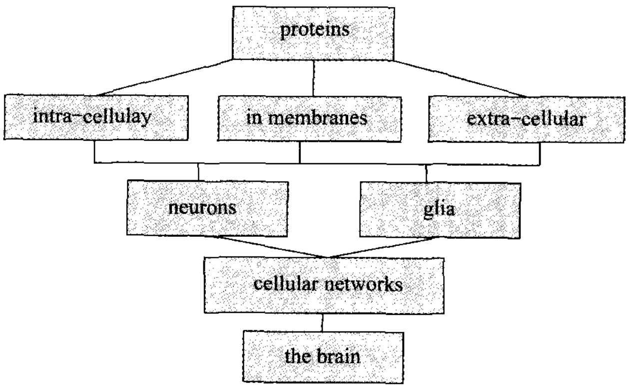

Fig. 1.1 Principal organization of the central nervous system.

When having in mind the structure of neuronal systems, see Fig. 1.1, it is obvious that they are hierarchically organized structures of excitable media at least from membranes over single cells and neuronal networks up to the entire human brain. Most of the processes requested for such systems indeed meanwhile have been found in all levels of neuronal structures and the human brains.

An additional aspect of this point of view is that such systems are strictly dependent on the influence of small external forces. One of these small external forces, following our above discussion, must be gravity, being physically a small force, but being present all the time on earth at $1g$.

1.3 Waves and oscillations in biological systems

In the excitable media, propagating excitation waves and oscillations are known to occur. As already said that the neuronal system is an excitable medium, thus waves and oscillations will be presented here, and have been investigated to any extent. These processes, which the action potential of excitable cells belongs to, which is the central electrical event for information transfer in neuronal systems.

Another example is the spreading depression, a slowly propagating wave of a transient suppression of neuronal activity, which is, among others, related to migraine, transient global amnesia, and epilepsy. Oscillations in biological systems are important for example for biological clocks, for biorhythms and for memory. Accordingly, it is a major aspect of this text to understand the interaction of gravity with wave propagation and oscillations in excitable media under the influence of variable gravity.

1.4 Book layout

The rational of this text will be consequently as follows. Neuronal systems are excitable media which can be controlled by small external forces. Gravity is a small, physically given force which is always present on the earth at $1g$ and thus here will permanently interfere with neuronal systems. This interaction can happen on all levels of the organization of neuronal systems. The understanding of how gravity interacts with neuronal systems, and what the absence of gravity will cause, is a prerequisite for long lasting missions in a low gravity environment, meaning manned space missions.

In this context it must be understood that the interaction of gravity with neuronal systems is not necessary coupled to the sensation of gravity by specialized organs or structures, but that gravity can interact with the system itself due to the properties of an excitable medium. Thus, in this text gravity sensing structures and specialized organs are not the point of interest, but indeed the system itself.

Following this introduction, a few words will be said about gravity in next Chapter. Then, in Chapter 3, the necessary details about the structure of neuronal systems will be delivered. In Chapter 4 the technical needs for gravitational research will be discussed, mainly delivering information about the platforms available for micro gravity research. The focus will be on short term systems and only for these, later in Chapter 6, experiments will be shown, but also some more general remarks about long-term systems will be included. Accordingly Chapter 4 is one of the main chapters of this book. In Chapter 5 as a short insert, an interesting model system for research in excitable media will be discussed in its gravitational dependence, the Belousov-Zhabotinsky reaction (Belousov, 1958). This can deliver useful general information about how gravity interacts with such media. In Chapters 6 to 11, being the core of the text, a variety of experiments will be presented, dealing with gravitational research at neuronal systems from the level of single molecules up to the entire human brain. The text will be finished by a discussion and an outlook on possible future research in the field.

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