Microgravity Environment Interpretation Tutorial

NASA Glenn Research Center

March 2-4, 2004

David M. Klaus

University of Colorado at Boulder

Assistant Professor, Aerospace Engineering Sciences
Associate Director, BioServe Space Technologies

Acronyms and Abbreviations

AA – Amino Acid
ADP - Adenosine Diphosphate
ALARA – As Low As Reasonably Achievable
ALS – Advanced Life Support
ATP - Adenosine Triphosphate
BP – Blood Pressure
CELSS – Closed Ecological Life Support System
CM - Countermeasure
DNA - Deoxyribonucleic Acid
EM – Electromagnetic
EVA – Extravehicular Activity
g – unit gravity (9.8 m/sec^2)

GCRs – Galactic Cosmic Radiation
LBNP – Lower Body Negative Pressure
LEO – Low Earth Orbit
MSL – Mean Sea Level
RAD – Radiation Absorbed Dose
RBC – Red Blood Cell
RBE – Relative Biological Effectiveness
REM – Roentgen Equivalent, Man
RNA - Ribonucleic Acid
SAA – South Atlantic Anomaly
SEPs – Solar Energetic Particles (also SPEs or Solar Particle Events)
SMS –Space Motion Sickness (also SAS - Space Adaptation Syndrome)

Additional Reading:

Churchill, S. (1997) *Fundamentals of Space Life Sciences.* Krieger Publishing Company
Clément, G. (2003) *Fundamentals of Space Medicine*. Microcosm Press / Kluwer Academic Publishers
Nicogossian and Pool (not yet released) *Space Physiology and Medicine, 4th ed*. Lippincott, Williams & Wilkins
Klaus, D.M. (2002): "Space Microbiology: Microgravity and Microorganisms" in *The Encyclopedia of Environmental Microbiology*, G. Britton (ed.), John Wiley & Sons, NY, pp. 2996-3004

Challenges to Life in Space

Vacuum

- ~ ½ of Earth's atmosphere is below 5 km MSL
- Above ~14.4 km, can no longer breathe with the available air
  → *pressure in the lungs = pressure of the atmosphere*
- Above ~60 km, curvature of Earth becomes noticeable and the sky is black
  → *not enough atmosphere to scatter light*

Weightlessness (*freefall*)

Radiation (*electromagnetic and particulate*)

Micrometeroids (*become micrometeorites after they fall to Earth*)

Temperature Extremes

- Spacecraft environment in LEO ranges from approximately -120 to +110°C

Mammals
Plants
Microbes

Research

Vacuum
Weightlessness
Radiation
Micrometeoroids
Thermal extremes

HEALTHY ← **HUMAN** → ALIVE

Research

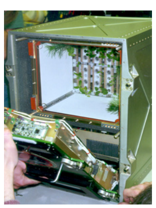
Mammals
Plants
Microbes

Space Life Sciences

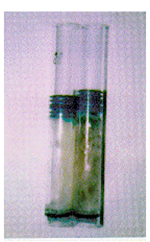
RESEARCH

Spacecraft Life Support and Habitat Design

Oxygen / Pressure Vessel
Water / Food
Radiation Protection
Thermal Control
ALS / CELSS

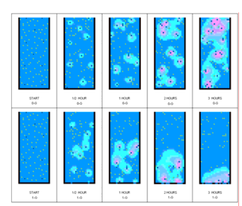


Commercial



Microgravity Sciences

Fluids
Combustion
Materials
Biology



Microbes – prokaryotes, eukaryotes (& viruses)

Plants – gravitropism, growth & seed-to-seed

Animals – cells, tissues & organisms

Similarities

Animals, plants and microbes do not appear to have a lot in common upon superficial examination. At the microscopic level, however, a fundamental unity is observed: a common physical structure – the living cell.

Some common features…

Chemical composition
3 types of complex organic macromolecules

- proteins - polymers of amino acids (AA's)
- deoxyribonucleic acid (DNA)
- ribonucleic acid (RNA)

DNA – carries information to determine properties in coded form
RNA – intermediary that translates the "coded" information into specific patterns of protein synthesis from AA's
Proteins – catalysts or enzymes responsible for cellular operations

Characteristics of microorganisms

Organisms invisible to the unaided human eye
Less than ~ 0.002 inch (50 micron) diameter
Smallest of which are single-celled organisms

Eukaryote – fungi, protozoa and most algae (higher protists)
A single-celled or multicellular organism whose cells have a distinct membrane-bound nucleus containing DNA, ~10's microns

Prokaryote –bacteria and blue-green algae (lower protists)
Organisms whose cells do not have a nucleus in which DNA is housed and which lack many of the organelles found in more advanced cells ~1's microns, highly adaptive to environmental changes

Virus
Acellular, not capable of self-reproduction (requires host), ~ 0.1's microns

General information on bacteria

On the order of 1-5 microns

Growth kinetics – lag, exponential growth, stationary

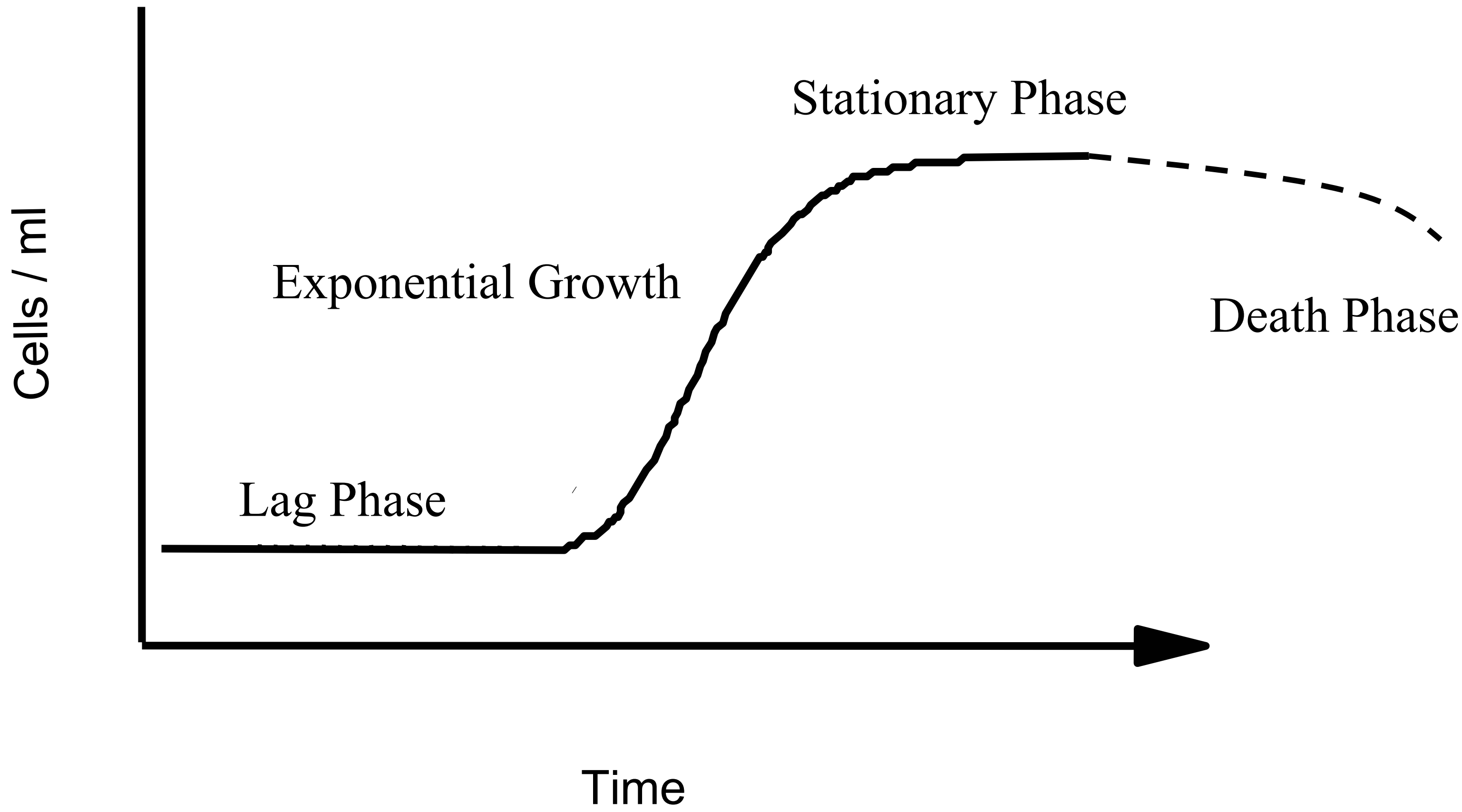
Can be motile or non-motile, aerobic or anaerobic

Uptake nutrients and produce metabolic by-products

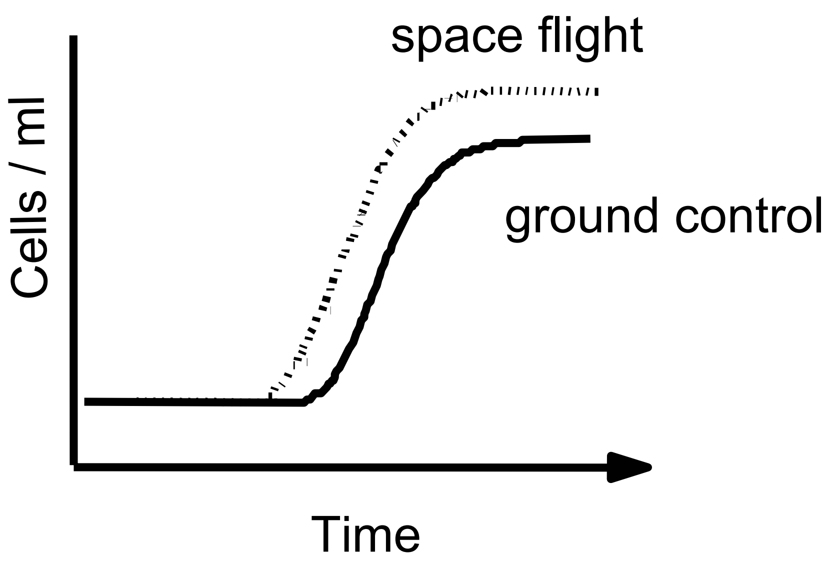
Can produce antimicrobial substances (antibiotics)

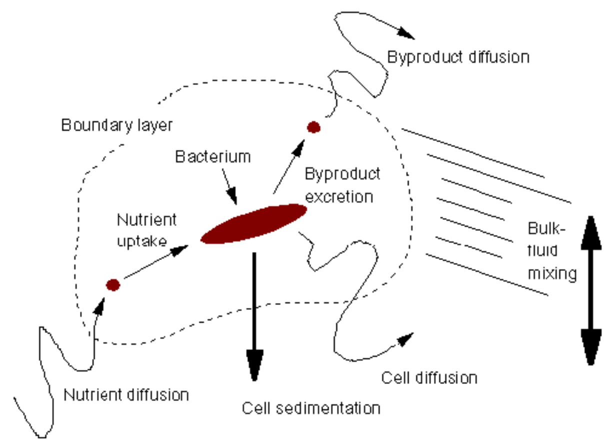
Killed by antibiotics, but can develop resistance

Bacterial Growth Kinetics



Representative Curve Summarizing Differences Between Bacterial Growth Kinetics in 1-g and 0-g





Shortened lag phase
"Possibly" slower growth rate and longer exponential phase
Higher final population concentrations
Higher concentration of antibiotic needed to inhibit growth
Increased specific productivity of antibiotics
More efficient cell mass yield
None of the above…

How can gravity influence any/all of these observations???

Klaus (2002) *Encyclopedia of Environmental Microbiology*, 2996-3004

Crew Health Implications

Enhanced microbial growth
Immunosuppression
Microflora exchange in a closed environment (increase in number of resistant strains)
Decreased antibiotic effectiveness
Altered Pharmacokinetics

Rapid enumeration / identification technologies needed onboard spacecraft

Studies required to determine effective pharmaceutical dosage and administration regimen

Health care systems must ultimately address increasingly long duration missions without intervention from Earth

Eukaryotic Cells

Cytoskeleton

3 types of internal support mechanisms help to keep organelles in place

Microtubules – stiff hollow tube, made from tubulin, spiral wound rings formed into a pipe, ~25 nm diameter, intracellular "railway system“

Microfilaments – myosin, actin

Linear and moving elements – use ATP (Ca^{++} pumps)

Tensegrity - tension-integrity (e.g. a self-supporting tent)

· microtubules = compressive
· microfilaments = tensile

Membrane

Separates the physical world from the biological one.

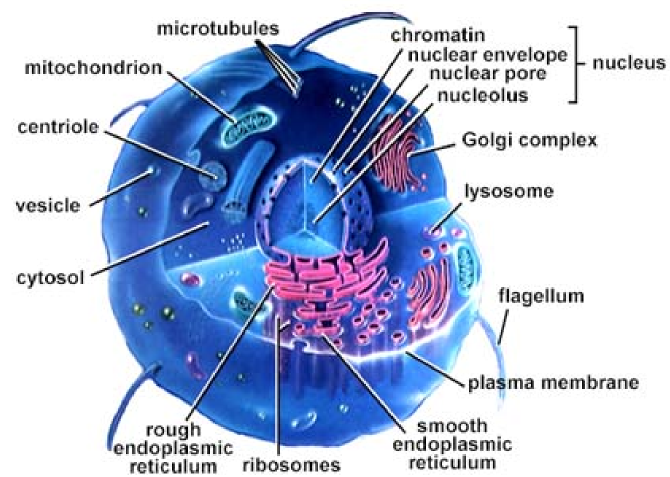
Bi-layered phospho-lipid (phosphates and fatty acids)

Channel specificity for AA's, sugars, Ca^{++}, Na^{+}, K^{+}…

Chemically or electrically gated stimulus gives rise to mechanical deformation or action

Channel deformation - stretch sensitive

Gravity effects?



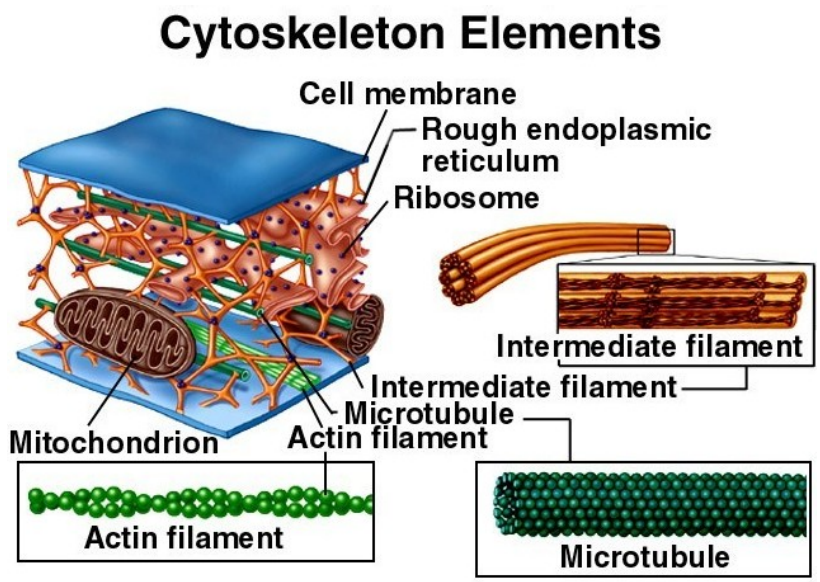
Cytoplasm

Contains most or all of the RNA and protein of the cell

Primary site of synthesis and functional activities

Gelatinous mass – non-Newtonian

Nucleus and other organelles



Density $_{nucleus}$ > Density $_{cytoplasm}$

Contains most or all of the cell's DNA

Supported by cytoskeleton

Mitochondria – "power plants"
Consume oxygen and carbon → ATP
Similarities to prokaryotes (evolutionarily integrated?)
Heart has more mitochondria than any other tissue

Plastids – (chloroplasts in plants) – use energy to make sugars and oxygen, storage granules for starch

Golgi apparatus – membranous vesicles providing lipid return after secreting protein

Ribosomes – RNA "workbenches" (composed of RNA and protein)

Space Flight Effects

Intercellular, transmembrane and/or extracellular phenomena?

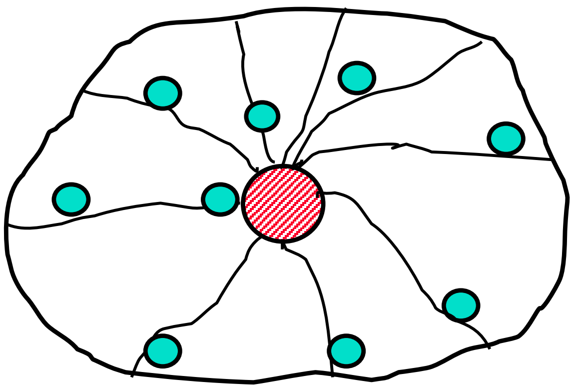
Gravity perception vs. gravity influenced?

Receptor/sensor vs. reaction?

Threshold vs. gradient response?

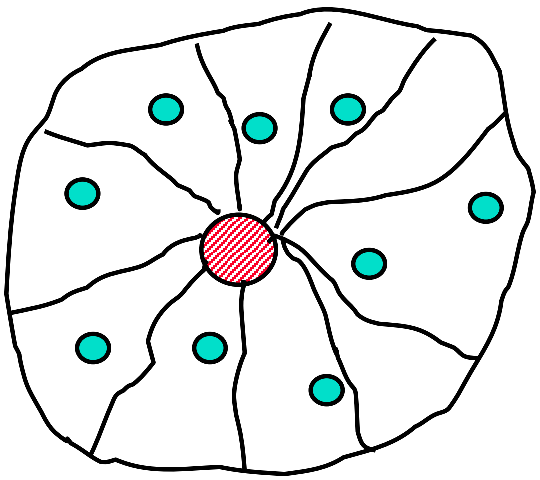
Observed responses vs. mechanistic explanations?

Nutrient diffusion / uptake &
Waste excretion / dispersion



1 g

mitochondria
ribosomes
nucleus
cytoskeleton



0 g

Examples of Cellular Level Responses to Space Flight

Gravity can affect:

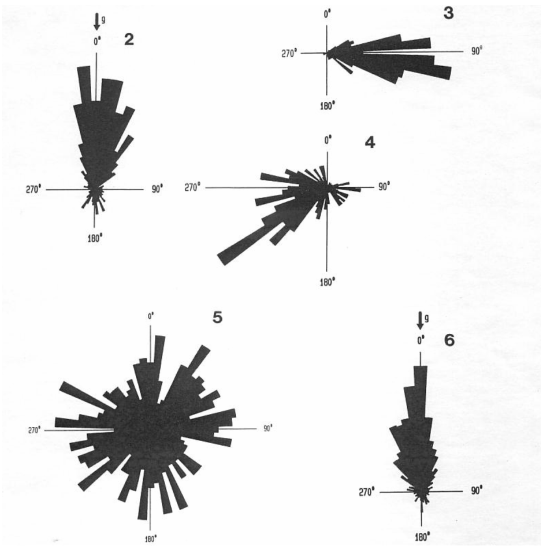
Cell morphology: cytostructure, shape/orientation

Cell function: secretion, extracellular mass transport, metabolism, differentiation, response/behavior, locomotion, cell-to-cell communication, gene expression

Paramecium swimming behavior (Hemmersbach)

Swimming velocity in space (& clinostat) increased 7.5% initially, then normal in ~ 3 min
Swimming orientation onboard 6 minute sounding rocket flight
- first 30 seconds – continued as previous
- next 20 seconds – reversed direction
- remainder – random

Swimming orientation under partial-g
(using the NIZEMI centrifuge microscope)
- 0.16-0.3-g induced gravitaxis
- no post flight adaptation



Physarum slime mold gravity response (Block)

Lowest acceleration sensitivity = 0.1g
Elicited complete response-regulation process
Suggests large/dense organelles likely candidates for g-sensing stimulus
Second messenger model suggests signal transduction chair of events
Density driven intracellular cascade

Immune Cell Function (Pellis; Cogoli)

T-cells (lymphocytes)

in vitro activation suppressed
multiplication impacted
total count reduced
locomotion impeded
cell-cell signaling effectiveness reduced

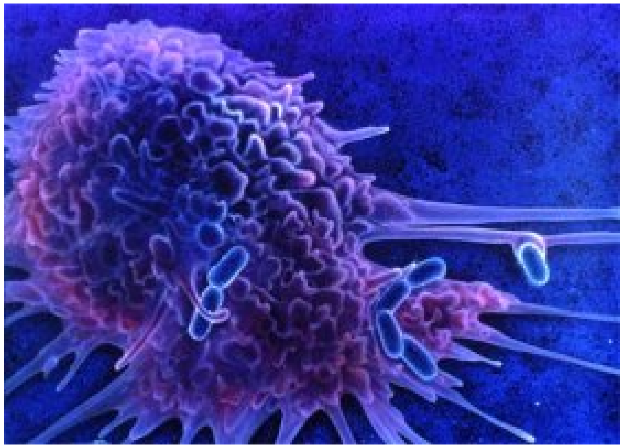


Photo: NASA

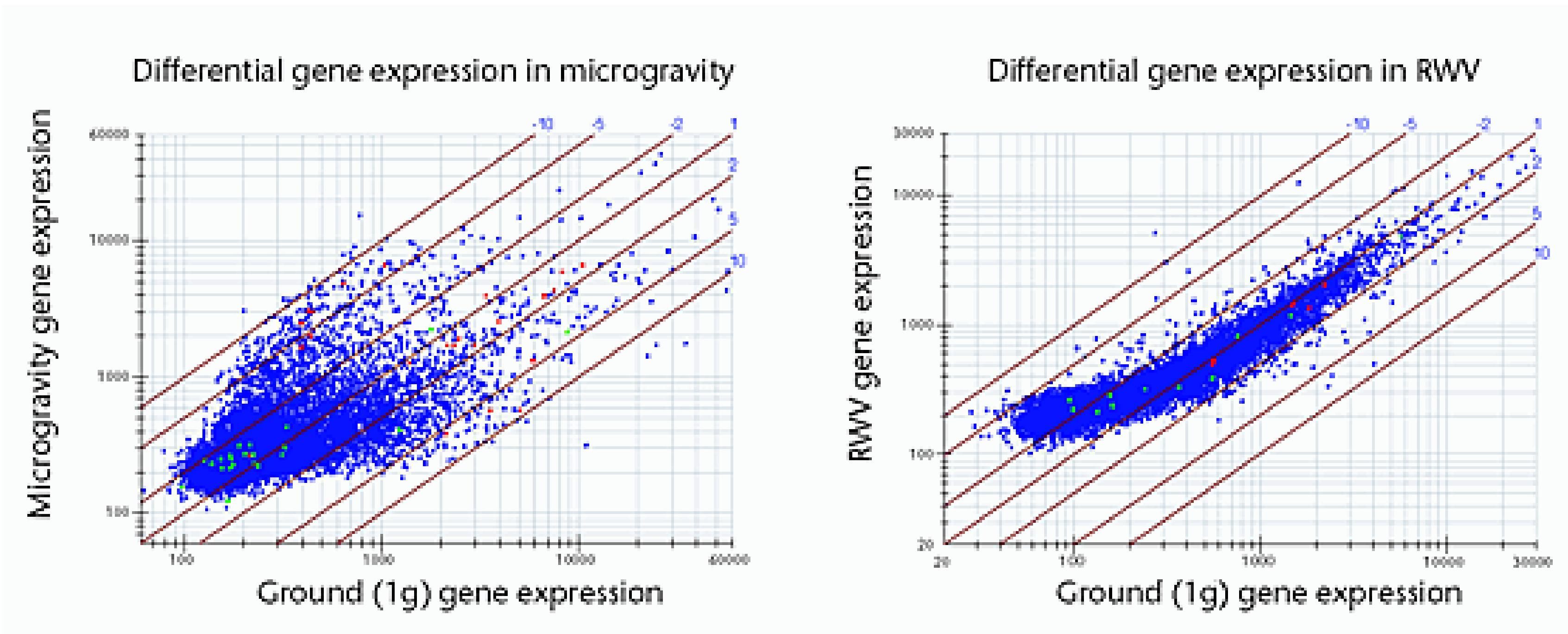
Overall less able to destroy invading antigens

additional online information

http://science.nasa.gov/headlines/y2002/23jan_cellwars.htm
http://www.spacebiol.ethz.ch/research/lymphocytes.htm

Changes in gene expression of human renal cortical cells

Genes with similar expression lie on a line from the origin to the top right corner, Microgravity (left) and rotating wall vessel (right) were compared with a static non-adherent bag culture



T.G. Hammond, F.C. Lewis, T.J. Goodwin, R.M. Linnehan, D.A. Wolf, K.P. Hire, W.C. Campbell, E. Benes, K.C. O'Reilly, R.K. Globus & J.H. Kaysen, Gene expression in space, Nature Medicine, April 1999, Volume 5, Number 4 p 359

Summary of Cellular Level Responses to Space Flight

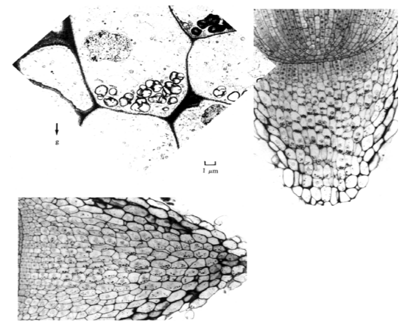
Microgravity affects numerous physical phenomena relevant to biological research, including the hydrostatic pressure in fluid filled vesicles, sedimentation of organelles, and buoyancy-driven convection of flow and heat.

These physical phenomena can in turn directly and indirectly affect cellular morphology, metabolism, locomotion, secretion of extracellular matrix and soluble signals, and assembly into functional tissues.

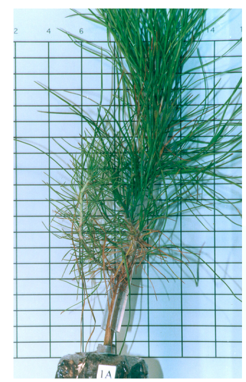
Freed LE, Vunjak-Novakovic G., Spaceflight bioreactor studies of cells and tissues. *Adv Space Biol Med*. 2002;8:177-95.

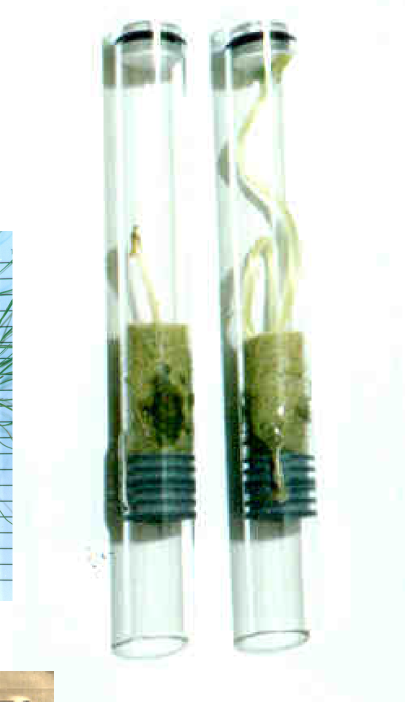
Summary of Plant Responses to Space Flight

Gravitropism *(root/shoot orientation)*
- As low as 1/1000 g can elicit response
- Root can generate a signal from an acceleration in less than 30 seconds



Growth and metabolic pathways
Altered lignin production and gene expression





'Seed-to-seed'
Seed production and viability in space remains a topic of ongoing research

Long Duration Exposure Facility (LDEF)
Postflight germination measurements of ~12 million tomato seeds exposed to space for 6 years indicated that they remained viable

Humans in Space

Launch

Sound
85 dB - threshold of exposure without damage
120 dB - threshold of discomfort
flight deck ~120 dB
Payload Bay ~ 160 dB
CM – Passive attenuation, Active noise cancellation

Vibration
Varying natural frequency of body components
Imperceptible to voluntary tolerance limits
Biomechanical damage (e.g. ultrasonics)
CM – active or passive damage damping (e.g. water suppression system on the pad)

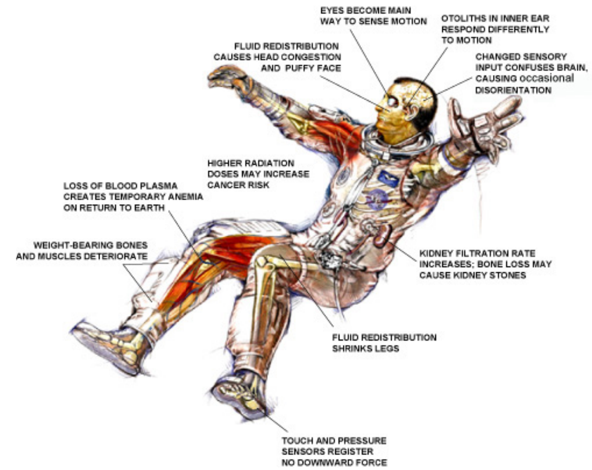
Acceleration
+ Gx (eyeballs in) - up to 40 g's survivable for ~10 seconds
+ Gy (eyeballs left)
+ Gz (eyeballs down) → just 2xg intolerable after ~12 minutes
Countermeasure (CM) – positioning and 3xg throttling on STS

On-orbit

Minor – adaptations occur and reverse rapidly

<ins>Minutes to Hours…</ins>

Height increase ~ 1-2 inches due to biphasic spinal response
Abdominal girth decrease
Internal organ shift
Posture altered (underwater, fetal position)



http://www.sciam.com/1998/0998issue/0998whitebox2.html
'Weightlessness and the Human Body' *Scientific Am.*, Sept. 1998; White

Fluid Shift due to loss of hydrostatic pressure - facial puffiness, stuffy head, suppressed smell -- *actually starts on the pad…*
On average, 60% of body mass is water
- intracellular fluid – in the cells
- blood plasma arteries and veins
- interstitial fluid – between tissues, cells

When standing in 1g:
Blood Pressure (BP) increases by hydrostatic pressure by up to 100mm Hg at the feet
BP drops correspondingly above the heart

Major – more significant physiological effects with correspondingly longer recovery times
(see: http://science.nasa.gov/headlines/y2002/30sept_spacemedicine.htm?list728635)

<u>Hours to Days…</u>
Vestibular system effects –otoliths are g-dependent and tied to other senses
otoloths = static load and acceleration,
semi-circular canals = acceleration, 3-D

Space Motion Sickness (SMS) – signal conflict vs. distortion, 'asymmetry theory'
So far, not predictable
CM – drugs, time, training?

Fluid loss – due to fluid shift (water volume in a 70 kg male is ~ 40 liters)
extracellular fluid decreased ~15% by day 2
~3-4% total body water loss by day 4 or 5
CM – equilibrate to new baseline on orbit, Lower Body Negative Pressure, fluid loading

Leg volume decrease – primarily due to fluid shift initially and later, muscle atrophy

Neuromuscular inhibition (skin pressure and proprioceptive senses)
"Seat of the Pants" sensation

Payload Specialist Chiaki Mukai during a Lower Body Negative Pressure (LBNP) protocol. The sack-like LBNP device is designed to apply negative pressure to the lower extremities of the body. This suction causes a fluid and blood shift from the upper body toward the legs, mimicking a condition that occurs after landing. NASA ID: STS065-16-020

(http://lsda.jsc.nasa.gov/iml2/iml2_lbnp.html)

Days to Weeks…

Blood plasma loss – due to fluid loss
average blood volume ~5 liters, of which, 3 liters = plasma, 2 = RBC mass
blood initially overloaded with RBC's, production stops/slows, destruction increases
compare volume lost to blood donation of 1 pt (0.47 l), or ~10% of total blood volume (plasma + RBC)

RBC mass reduced, perhaps even disproportionately to plasma loss - anemic-like?
post-flight issues?
CM – rehydration, LBNP, time

Muscle atrophy
CM – exercise and stretching, Penguin Suit, electro-stimulation?

Cardiovascular deconditioning (reduced size)
CM – exercise, LBNP

Weeks to Months…

Bone atrophy - lost at rate of up 0.5-2% per month (6-24x osteoporosis) from certain load bearing bones in the lower back and hips (back pain, fatigue, fractures, kidney stones?)
CM – "impact exercise", applied electromotive force (EMF)? pharmaceutics?

Breathing?
Lungs – hypothesis regarding blood and air distribution from top-bottom - gravity dependent or driven by lung geometry/function?

Immunosuppression – dependencies on bone marrow, psychological stress, weightlessness, radiation????
(http://science.nasa.gov/headlines/y2002/23jan_cellwars.htm)

Note: In flight exercise and presence of other stressors complicate the study of human adaptation to weightlessness

Reentry

Fluid shift from blood to leg tissue potential for orthostatic intolerance
CM – fluid load (saline) and LBNP
Leads to anemic-like condition following plasma replacement (RBC dilution)
(http://science.nasa.gov/headlines/y2002/25mar_dizzy.htm?list728635)

Loss of coordination – neurovestibular & proprioceptive feedback
Decreased baroreceptor response & hypersensitive reflex reactions
CM – 48-72 hour time course, avoid rapid head movements, slow increase in activities
(http://science.nasa.gov/headlines/y2002/22nov_balance.htm?list728635)

Cardiovascular reconditioning
CM – exercise, dependent on mission duration

Muscle and bone recovery
CM – exercise, dependent on mission duration
and age of astronaut

Dynamic Interaction of Altered Functions and non-g Dependent Parameters

Weightlessness is primary driver of most of the physiological effects addressed, but other factors can complicate the problem

Launch g's and vibration – coupling effect? (shake and spin) on cells during launch?

Closed environment issues and other Physical/Psychological factors
→ Insomnia anxiety, depression, tension and interpersonal issues
→ stress
→ physiological impacts

Workloads

Radiation

Geomagnetic and Electrical fields, Hall Effect?

Other factors?

Radiation

http://dsc.discovery.com/news/briefs/20021125/radiation.html?ct=5760.64302426861

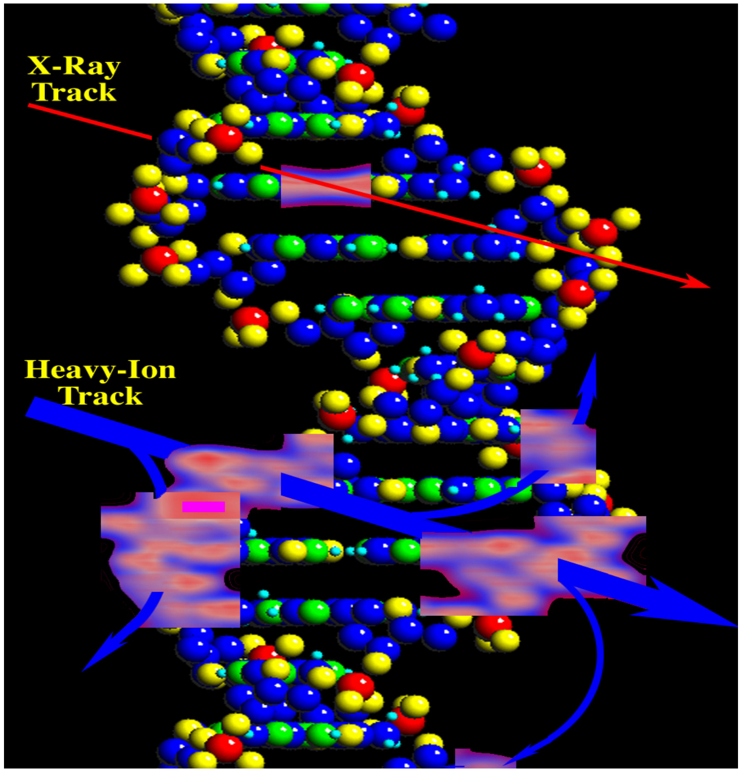
Primary biological risk from space radiation exposure is cancer

When radiation is absorbed in biological material, the energy is deposited along the tracks of radiation.

Neutrons and heavy ions produce much denser pattern of ionization causing more biological effects per unit of absorbed radiation dose.

Dose received is a factor of: Altitude, Attitude, Shielding, Solar Cycle, Time in orbit

Radiation exposure is cumulative



(Some) Units

Roentgen – basic unit for measuring amount of radiation exposure

RAD – Radiation Absorbed Dose (amount of energy absorbed in the body by radiation) (SI Unit), [1 mGray = 0.1 RAD (traditional)]

RBE – Relative Biological Effectiveness (varies dependent on type of radiation)

REM – (Roentgen Equivalent, Man) - measure of biological effect = 1 RAD x Quality Factor, [1 REM = 10 mSievert (SI)]

Quality Factor (or RBE, Relative Biological Effectiveness) depends on specific radiation source and ranges from 1 to ~20

Electromagnetic (EM) Radiation

Waves or streams of massless particles traveling in a wave-like fashion and each carrying energy (photons)

Primary source is the sun (solar wind) Radio, light, X-rays, IR, extreme UV, etc.

Generally non-ionizing

Particulate Radiation

HZE particles (cosmic sources) → High Mass and Energy (Z = atomic number, E = energy)

SEPs – Solar Energetic Particles (also SPEs or Solar Particle Events)

GCRs – Galactic Cosmic Radiation (neutrons, protons & nuclei)
- *electrons, protons, neutrons and nuclei*

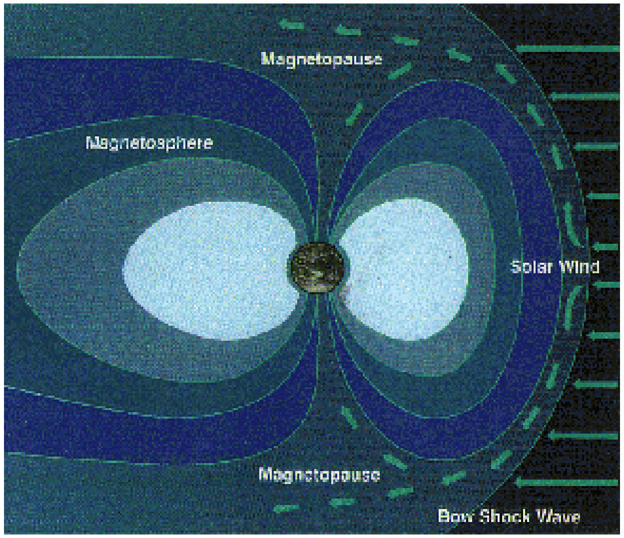
Ionizing radiation – dislodged electron, capable of producing charged atoms (ions) as it passes through matter

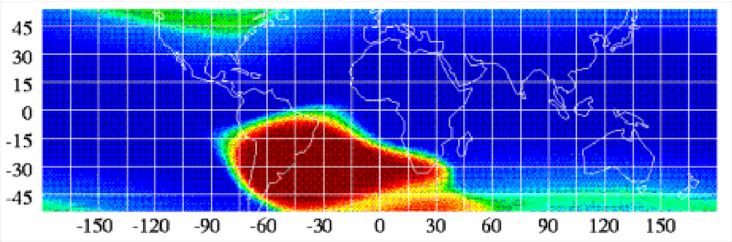
Trapped Belt Radiation

Van Allen Belts (inner 1-3x Earth Radii, outer 4.5-10x)

South Atlantic Anomaly – cusp in VA Belts

90% of exposure in LEO occurs in the SAA region





Solar Flares

EM waves reach Earth in ~8.5 min

Magnetic cloud (particulates) reaches Earth 2-3 days later

Solar Max moderates GCRs but increases SEPs

Different types of radiation produce different amounts of damage
Rate of energy loss per length of track, or Linear Energy Transfer (LET)

Two general categories: somatic (exposed individual) and genetic (hereditary effects)
Effects are acute (early) or chronic (late)
-tissue damage, loss of fertility, lens opacification, cancer induction, heritable effects

Tissue effects = thermal, chemical, cellular and genetic
Carcinogenic effects are of great concern

Sensitivity proportional to biological complexity e.g. eyes > skin > bone

Proliferating cells of renewing tissue & organs are most sensitive - bone marrow, lymph, intestine and reproductive organs

Younger people and women are more susceptible to radiation damage in general

- Youth have longer for potential damage to develop
- Women have 2 radiation sensitive organs (breasts and ovaries) and longer expected life span than men

Ave exposure in the US: ~40 mREM / year (from soil, rocks, wood, etc.)
(East coast ~20 mREM / year and Rocky Mtn area ~90 mREM / year)
Cosmic Rays: add ~40 mREM / year (~160 mREM high in the Rocky Mtns)
Food and water: add ~ 20-50 mREM / year
NY to Paris flight: add ~4 mREM

→ ~ 100 mREM / year compared to ~65 – 195 mREM / typical shuttle flight

Acute Dose Effects on Humans

Dose (Rads)	Probable Effect
0–50	No obvious effects, blood changes
80–120	10% chance of vomiting/nausea for 1 day
130–170	25% chance of nausea, other symptoms
180–220	50% chance of nausea, other symptoms
270–330	20% deaths in 2–6 weeks, or 3 mo. recovery
400–500	50% deaths in 1 mo., or 6 mo. recovery
550–750	Nausea within 4 hours, few survivors
1000	Nausea in 1–2 hours, no survivors
5000	Immediate incapacitation, death within 1 week

Of all the risks encountered by astronauts during space flight, cancer induction from radiation exposure is one of the few that persists after landing

Low (equatorial) orbits are considerably less hazardous than polar orbits or beyond LEO and Timing of exposure when radiation is least intense (e.g. no scheduled EVAs over SAA)

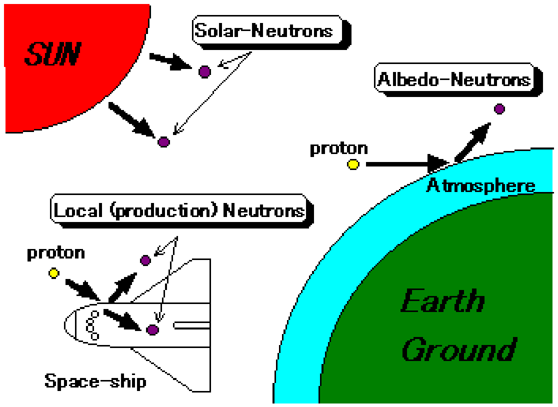
Shielding to stop or alter the trajectory of high energy particles before they reach humans (but secondary effects…) evaluation of effectiveness is complex and depends on actual composition of the impacting radiation

Protection against non-ionizing radiation is relatively simple, but ionizing sources create secondary and tertiary particles, some of which produce gamma rays

Pharmaceutical treatment and body’s natural DNA repair mechanisms (although some concern exists over synergistic effects of radiation and microgravity)

Issues for Mars Mission include: monitor and forecast, storm shelter, effects on humans, evaluation of risk, pharmaceutical intervention and/or shielding (Liquid Hydrogen is likely the best shielding candidate)

Current Research



EVA Radiation Monitoring Experiment on ISS
http://spaceresearch.nasa.gov/research_projects/ros/evarm.html

Bonner Ball Neutron Detector (BBND)
http://spaceresearch.nasa.gov/research_projects/ros/bbnd.html
http://sees.tksc.nasda.go.jp/English/WhatsSEES/bbnd.html

Dosimetric Mapping (DOSMAP)
http://spaceresearch.nasa.gov/research_projects/ros/dosmap.html

Phantom Torso (TORSO)
http://spaceresearch.nasa.gov/research_projects/ros/ptorso.html

Summary

Biological responses in space are primarily attributed to reduced gravity

Consider gravity as a 'physical trigger' and evaluate downstream responses

- direct, indirect, altered gene expression, etc.

Radiation factors increase with longer duration and further distance

- exposure goal: ALARA

Synergistic effects of microgravity and radiation alter cellular repair mechanisms?

Common underlying mass transport-related events?

Many observations, few explanations, even fewer validated countermeasures…