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Further Aspects for the Foundation of A Conceptual Framework for Systems Life Science Under Space Conditions

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Introduction

A high impetus for the elaboration of a **conceptual framework** for integrative life science research under space conditions is clearly noticeable.
A group of space-experienced investigators forwarded explicitly a request to the scientific community for such a conceptual framework (1). The EU funded THESEUS project (Towards Human Exploration of Space: a EUropean Strategy, http://www.theseus-eu.org/home.html) favors integrated physiology.
Further high priority issues [beyond the ones in (2)] of a possible conceptual framework should be

- ❑ modeling and model merging
- ❑ meta-analysis alignment* and
- ❑ domain ontology extension.

The investigations of countermeasure (CM) combinations are an appropriate problem area to deliver material for an application scenario. The highlighted CMs (blue) below enable to choose a scenario with an intertwined factor assembly with force/pressure (derived from gravity) and oxygen for bone loss.
**due to space limits of the poster not presented, however see for a relevant meta-analysis (4)*

advanced resistive exercise (ARE)
antioxidant intervention (polyphenols, lycopene, etc.)
artificial gravity based countermeasures (AG-CM)
bicycle ergometer exercise
calcium supplementation
...
resistive exercise + bisphosphonates

Table 1: Term extract „countermeasures"

Levels		Topical issues
Environment		O_2 & phenols (toxic?) produced by algae*
Whole body		body calcium values: ~ 30 mol (1200 g) [textbook]
		gravity/oxygen effects ?
Organ		hydroxyapatite (HA):
		~ 3 kg in bones
Tissue		regional bone loss up to 25% (outlier)
Cell		Cells need oxygen to produce HA, diffusion ?
Subcell. unit		mitochondria produce ROS (electron leaks)
Mol. entity		mitochondria DNA (damage & survival)
Atoms		free radicals interacting

Credits: McCulloch

Fig. 1: System levels (environment to atom)

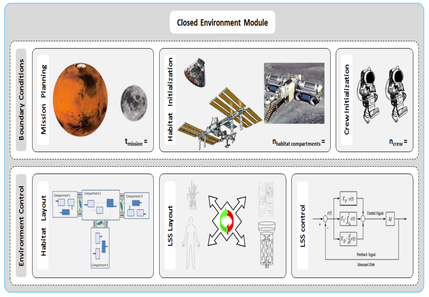


Fig 2: Virtual Habitat Modeling of the TU Munich (5)

Methodology

A central method for setting up a conceptual framework is basically the elaboration of an integrated set of fundamental terms [core concepts]. The approach of Andrew McCulloch (3) for human physiology with six levels for multi-level integration [from the gene to the whole human body level] is extended here by two additional levels.
For human physiology research in the context of space exploitation, a further level beyond the whole human body level is required, namely an environment level.
Furthermore, the division of the molecular level into a molecular and an atomic level is proposed and illustrated by an example, namely electron configurations of free radicals.

Results and Discussion

The proposed core set of elements for the requested conceptual framework are exemplified with application cases: the world of picoNewtons (pN) in the micro-environment of osteocytes and the role of unpaired electrons (free radicals) for microbial control. The applications cases here are interlinked with a recurrent theme: the role of oxygen, reactive species, and antioxidants.
A first in-depth insight into the knowledge domains of systems life science under space conditions is triggering the need of a more rigorous terminology stratification of the countermeasure terms via ontology extensions.

Ontologies	Applicability
Gene Ontology (GO)	master reference for genomics, gene expression and genetic sequence data
Agricultural Gene Ontology (AgriGO) -> algaeBASE	agricultural research, specifically plant genomics, being relevant for gravitropism research
Environ-mental Ontology (ENVO)	newly developed for the environment research community, linking environments and humans
Biomed Ontology (Ricordo)	The Ricordo Ontology group is cooperating with the VPH consortium (virtual physiological human)

Table 2: Selected relevant ontologies (inter-disciplinary domains and fundamentals)

Each term in an ontology depicts a concept. Each relevant concept should be modeled (structure, process, system environment) and placed into the conceptual framework.
Bone cell investigations with a Rotating Wall Vessel for example delivered genetic data showing a secondary signature with regard to antioxidant genes (6), especially interesting being here the upregulation of mitochondrial superoxid dismutase 2 [2.6 fold]. Due to the overwhelming data and the focus of the investigators on lipocalin 2 [8.5 fold] these data were not explicitely interpreted in the original publication.

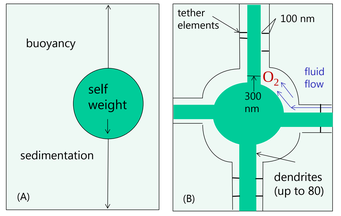
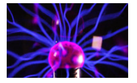


Fig. 3: The osteocyte as system of interest, scales (nm, pN) & microenvironments

(A) Thought model of Stephen C. Cowin (1998), calculating a reaction value of 0.1 pN, denying the self-weight hypothesis (B) simplyfied sketch adopted from the work of Weinstein, Schaffler, Cowin et al., with reaction values of 1-10 pN



Cool atmospheric plasma produces reactive oxygen, free radicals, etc. , alike phagocytes

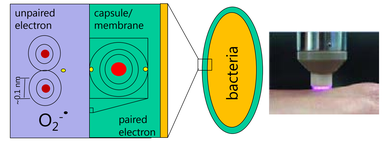


Fig. 4: Free radicals - an example of a simple atomistic level representation (oxygen case)

Starting with the characterization of the electron configuration of oxygen as 1s2 2s2 2p4, modeling the unpaired electron in the valence orbital (atomic/ molecular, electron/ion velocity/density) as reactive and explaining the damaging of the bacteria capsule/membrane, channels, and DNA [explanation model]

Conclusions

Conceptual frameworks shall unify fundamental understanding. The clarification of the relationships between the system of interest and the system environment (micro-environment) is such a fundamental issue.
A further fundamental issue is the relationship between hypothesis-driven und data-driven research. A model and system-based hypothesis may enable to refine and predict a „search space" for data-proven findings and *vice versa*.
A similarity index between inflight and ground-based reference experiments would surely be reasonable in the context of further discussions.

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