Basic principles and concept design of a real-time clinical decision support system for autonomous medical care on missions to Mars based on adaptive deep learning

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Abstract

Space agencies and private companies prepare the beginning of the human space exploration for the 2030s with missions to put the first human on the Mars surface. The absence of gravity and radiation, along with distance, isolation and hostile environment are expected to increase medical events with unidentified manifestations along the crewmembers. The current healthcare strategy based on telemedicine and the possibility to stabilise and transport the injured crewmember to a terrestrial definitive medical facility is not applicable in exploration class missions. Therefore, full autonomous capability to solve medical situations will guide design of future healthcare systems onboard.

This study presents the basic principles and concept design of a software suite to bring on-board decision support to help dealing with medical conditions of the crewmembers, with special attention to emergency care situations and critical monitoring. MEDEA is an autonomous clinical decision support system that provides real-time
advice to tertiary interventions on-board in space exploration missions. Its basic principles are 1) to give real-time support for medical decision making, 2) give patient-specific advice for executive problem-solving, 3) take into account available information from life support and monitoring of crewmembers, 4) be full autonomous from remote facilities, 5) continuously adapt predictions to physiological disturbance and changing conditions, 6) optimise medical decision making in terms of mission fundamental priorities, 7) take into account medical supplies and equipment on-board, 8) apply health standards for levels of care V, 9) apply ethical standards for spaceflights, and 10) apply ethical standards for artificial intelligence.

To fulfil these principles, MEDEA is conceptually designed as a software suite consists of four interconnected modules. The main of them is responsible to give direct advice to the crew by means of a deep learning multitask neural network to predict the characters of the medical event (e.g. life-threatening, delayability, ethical dilemma, duration of therapy, and compatible diagnoses), a classifier of the tertiary medical intervention and an optimiser of medical action plans. This module is continuously evaluate and re-trained with changing physiological data from the crew by an adaptive deep learning module, ensuring fairness, interpretability and traceability of decision making during the full operational time of MEDEA. Finally, MEDEA would be semantically interoperable with health information systems on-board by a FIHIR module.

The deployment of MEDEA on-board of future missions to Mars will facilitate the deployment of a comprehensive preventive medical strategy. Moreover, the advance in technology may represent a stepstone of the future quantitative medicine on Earth and on the expansion of humans throughout the solar system.

1 Introduction

On early 2021 three spacecraft, Perseverance, Tianwen-1 and Hope, will hopefully arrive to Mars to study its atmosphere and surface with the potential result of detecting clear signs of life [1]. The three spaceflights are exploration missions based on robotics, but it is not the orbital window for human exploration of Mars yet. NASA, other space agencies and private companies prepare the beginning of the planetary-type missions with humans for the 2030s transfer windows [2], with the objective of putting the first human on
the Mars surface after achieving the moon surface again through its orbital
Gateway station [3]. This new achievement may open a new era of deep
space journeys and planetary design reference missions, including long-term
stays on Mars, Lagrange points and exploitation of near-earth asteroids [4],
opening unseen opportunities to humanity.

Nevertheless, the absence of gravity and radio-protective geomagnetic
fields from Earth, along with distance, isolation and hostile environments
experimented during long duration space travels may increase systematic
effects on the physiology, biology and behaviour of human beings compared
to those measured during short-term experiments performed on International
Space Station (ISS) in the low Earth orbit (LEO) [5]. With that in mind,
NASA applied its continuous risk management platform to identify 30 human
health and performance risks for space exploration including the risks of
adverse outcomes due to *inflight medical conditions* [6].

Many of the consequences of human risks in long spaceflights are not fully
understood yet and technologies for controlling them are still to be invented.
NASA established the Human Resource Programme (HRP) at Johnson Space
Center (JSP) in 2005 for investigating the highest risks to astronaut health
and performance by quantifying the likelihood of occurrence, severity of con-
sequences, and the extent that a risk can be controlled or mitigated both
inflight and post flight for each type of mission. Specifically, the HRP Path
to Risk Reduction for a Planetary Mission estimates that *inflight medical
conditions* with potential high impact [7] will only be partially controlled in
time for a Mars mission in the 2030s.

The accepted approach for the healthcare of the crew on a space mis-
sion follows the occupational medicine prevention strategy [8]. It focuses
on reducing the likelihood and severity of medical events by primary, sec-
dondary and tertiary interventions. With primary interventions, likelihood
of risk factors is reduced by careful selection of crewmembers. Therefore,
priority is currently given to astronauts with low coronary artery calcium
and low Framingham risk scores over those with higher risk levels. Besides,
secondary interventions are also applied as countermeasures of the effects of
environmental factors in space. In LEO missions, countermeasures to the ef-
eft of microgravity and isolations are carried out by routines on treadmills,
resistive devices and cycles. Finally, tertiary interventions are triggered to
treat illness or injury under emergency situations requiring advance life sup-
port, transitional care or ambulatory care. Given the difficulty to provide
full healthcare support to space, current LEO and lunar missions have follow
the paradigm stablize and transport the injured crewmember to a terrestrial
definitive medical care facility (DMCF), that is not applicable to exploration
class missions.

Deploying a medical strategy for controlling inflight medical conditions
in exploration class missions will need to deal with limitations imposed by
deep space hazards. Three are the major restrictions affecting healthcare
of mission crewmembers: physiological disturbance, communication latency
and mission length:

- Physiological disturbance includes radiation-induced changes, altered
  nutritional status, neurovestibular deconditioning, cardiovascular de-
  conditioning, bone and muscle loss, renal-stone formation, plasma-
  volume shifts, spaceflight-associated neuro-ocular syndrome (SANS),
  and altered immunity due to microgravity, radiation and isolation,
  among others [9]. Multiple biomedical experiments have been per-
  formed on-board of the ISS [1]. For example, the NASA Twins Study
  identified multiple on-board spaceflight-specific changes, including de-
  creased body mass, telomere elongation, genome instability, carotid
  artery distension and increased intima-media thickness, altered ocular
  structure, transcriptional and metabolic changes, DNA methylation
  changes in immune and oxidative stress-related pathways, and gas-
  trointestinal microbiota alterations [10]. Nevertheless, there are no
evidences of the effects of long distance travels in humans yet. Hence,
healthcare strategies, including clinical decision making, will need to be
full adaptive to continuous changes, to what clinical symptoms will ap-
pear, what new clinical complications will arise and how environmental
conditions will affect the clinical conditions of the crewmembers.

- Communication latency between crew and mission control will increase
  with distance to Earth. From three to six seconds delay for a round
  trip communication from ISS to Earth, any deep space journey to near-
  earth asteroids and planetary missions will take several minutes for a
  full bidirectional communication. This precludes asking immediate in-
  quires to a telemedicine service similar to what ISS uses to consult
  mission surgeon at mission control. Hence, autonomous real-time de-
  cision making based on-board health information system will need to

1https://nebula.esa.int
evaluate non-delayable medical conditions following those ethical and legal rules applicable to long space flights.

- The length of the space missions are going to be extended from a current maximum of months to several years. Given the high cost of medical payload, crewmembers will arrange limited supplies, equipment and resources during mission, so optimisation will be needed on every day-by-day medical decision making. The major condition that mission length implies is the non-return to permanent health facilities in case of requiring advanced healthcare. Therefore, it will be mandatory to provide healthcare autonomy to the mission. Moreover, mission length has a cumulative effect in the physiological disturbance of human beings, increasing probability of health failure and clinical severity with time.

As Hamilton et al. stated on [8], the current tertiary intervention cannot longer draw on a close DMCF at an effective time, so medical design should evolve into an autonomous treat to final resolution capability, which represents a significant challenge to space medicine and mission designers. Given the major restrictions affecting healthcare of mission crewmembers, in this paper we propose a real-time clinical decision support system based on adaptive deep learning as technological solution of tertiary medical interventions for Mars-type missions. Our study establishes ten basic pillars and proposes a concept design based on a software suite composed of the next four modules: autonomous real-time clinical decision making, space adaptive learning, semantic interoperability and ethical & legal functional support. This concept design gives answer to the system-based strategic vision conceived by Williams, Hamilton, Doarn and others [11, 8, 12] by means of the last decade advances in Biomedical Data Science and Artificial Intelligence (AI).

2 State of the art

The routine and emergency medical operations in the human flight missions are currently managed by the flight surgeons from the mission control centre. Crewmembers have an integrated checklist on-board [13] that describes the routine and emergency medical operations procedures and hardware associated with crew health. Nevertheless, these procedures based on telemedicine and prompt evaluation for tertiary medical interventions should change for
exploration and planetary missions. Then, the design of Mars missions includes re-thinking the life support and medical management for remote human risks management. In this way, American and European space programmes have detected unresolved technologies to manage medical interventions on-board of spaceflights in long exploration missions such as Mars-type missions.

The HRP by NASA detected the need of having the capability to provide computed medical decision support during exploration missions as part of the detected gap to identify new capabilities that maximise benefit and/or reduce costs on human system/mission/vehicle resources. By solving this gap, NASA is willing to develop continued monitoring of biomedical signals and images, improve medical capability technology for unique spaceflight needs, provide medical care in a progressively Earth independent fashion and demonstrate the integration of the new procedures and technologies with the on-board processes.

Besides, the European strategy towards human exploration of space developed during the THESEUS FP7 project in 2012 detected insufficient on-board expert systems / decision support systems for medical diagnostics as specific key issue for the space medicine expert group. In 2013, the ASSIST report by ESA/ESTEC encountered a major limitation in the data gathering for remote monitoring by telemedicine. Specifically, they reported the bottleneck of acquiring and transmitting too much data not always immediately and easily available and the difficulty to interpret them, so 75% of validators considered useful to incorporate additional functionalities such as the automatic identification of indicators with high sensitivity and the automatic identification of values for the break-even. Then, CSEM, Airbus and MEDES evaluated in 2016 the benefit of data mining for an autonomous medical monitoring/diagnostic system (AMIGO) in long-term spaceflight and non-space related applications. In their studies, they estimated higher medical risk due to expected human tasks with EVA during asteroid missions for sample extraction and planetary surface exploration for the Mars-type mission. They performed two proof of concept on subjects with de novo cardiac arrhythmia and sleep apnoea, respectively. For their computational experiments, they applied linear classifiers, quadratic classifiers, Gaussian mixture models, hidden Markov models, artificial neural networks, k-nearest neighbours,

2https://humanresearchroadmap.nasa.gov/gaps/gap.aspx?i=642
3https://humanresearchroadmap.nasa.gov/gaps/gap.aspx?i=716
decision trees, Bayes networks, and random forest to biomedical signals from the Physionet open repository \(^4\).

McGregor in 2013 \(^{15}\) proposed a real-time platform call Artemis for on-line health analytics during spaceflight by monitoring the astronauts’ physiological signals on-board as well as sending the signals to mission control for medical support at each stage when communication is available. Prysyazhnyuk et al. in 2017 \(^{16}\) tested by analogs if Artemis was able to support the implementation of the IBMP\(^5\) classification model of health states gravities in four functional states (physiological normal, prenosological, premorbid and pathological) based on the discriminative Heart Rate Variability (HRV). Moreover, in 2017 McGregor and the IBMP \(^{17}\) simulated the integration of the Artemis platform and the Cosmocard device\(^6\) acquiring electrocardiograms from the Russian cosmonauts on ISS. Their results shown limitations for a real-time performance due to deferred transmission from the Cosmocard device.

As well as for medical diagnosis, biomedical signals have been acquired on-board of the ISS to study the effects of microgravity and isolation in human physiology. EveryWear by ESA monitored the ECG, tonometry, and temperature of astronaut Thomas Pesquet from Nov 2016 to May 2017 by wearable sensors connected to an iPad. The Neurolab Spacelab mission on 1996 studied the effects of weightlessness on the brain and nervous system \(^{18}\). Petit et al. in 2019 \(^{19}\) studied the relationship of sleep pressure EEG markers during wakefulness in astronauts throughout 6-month space mission. Gemignani et al. in \(^{20}\) performed what we may consider the first adaptive data-driven decision support system for space medicine. They defined dynamical thresholds on high-density EEG to detect sleep spindles with a false positive rate of 5% to deal with the variability of spindle characteristics as a function of sleep depth and subject. Besides, the Airway Monitoring ISS investigation studied the inflammation and reduced pressure on pulmonary nitric oxide turn-over due to microgravity and other ESA experiments such as DNAm-AGE, ICELAND and IMMUNO have also studied the effect of spaceflights at genomic, microbiome and immunological levels.

Up to now, ultrasonography is the main diagnostic imaging technique

\(^4\)https://physionet.org

\(^5\)Institute of Biomedical Problems (IBMP) of the Russian Academy of Sciences.

\(^6\)https://www.energia.ru/en/iss/researches/human/12.html
on-board. ESA’s Downstream Gateway project\(^7\) and the ECHO experiment tried to solve the operator-dependence by remote controlled ultrasounds operations. Although, this solution is feasible for LEO missions, long latency in exploration and planetary missions will require autonomous operation on-board. Aravindhan et al. proposed in [21] a Raspberry Pi solution for online health diagnosis to operate during space tourism and future Mars colonisation by illustrating its potential application to fundoscopies when suspicion of visual impairment due to intracranial pressure.

HRP have identified 32 physiological, medical, and behavioural risks associated with long-duration spaceflights [22]. Linked to that, Davis et al. presented in [23] a risk management system based on the acceptable levels of risk for each mission type with the goal of guiding research efforts and mission planning through the probability of medical adverse events, uncertainty of outcomes, impacts, costs and benefits of mitigation actions along with related current and future work. More recently, Mindock et al. in [24] defined a connected map of contributing factors and the medical risks, whereas Romero and Francisco in [6] identified 100 hundred probable health problems that may affect mission success and classified the medical risks in five hazards of spaceflight: altered gravity, radiation, distance, isolation and hostile environment. Taking into account that medical care will be limited by mass, volume, and power constraints and that life support will represent the 40% of wet mass in exploration-class spaceflight [25], one of the firsts uses of risk assessments presented above was the list of medical resources on-board. With that objective in mind, Antonsen et al. [26] designed a tradespace analysis tool to score resources, tools, and skillsets required for exploration missions.

As we have seen, current research is focused on identifying adaptation effects to spaceflights. Whereas biomedical signal monitoring is almost routine in astronauts, current solutions are solved by telemedicine but few advances have been made on autonomous decision making. Besides, medical risks, diseases, factors, mitigations and consequences identified in the studies for healthcare management constitutes the key knowledge to plan research directions for designing human spaceflight missions to Mars and asteroids. Hence, our proposal of the clinical decision support system focuses on the specific requirements that crewmembers will have to deploy autonomous tertiary medical interventions and it attends the limitations and state of the art presented above.

\(^7\)http://youbenefit.spaceflight.esa.int/ultrasonography-without-borders/
3 Basic principles and concept design of MEDEA

Primary and secondary can be operated in advance and from mission control as it is currently designed for ISS missions. Nevertheless, long distance in exploration and Mars missions requires autonomy to decide how to react to a medical situation. Here we study how to bring on-board medical decision support to the physician and crewmembers during medical conditions, with special focus on emergency care situations and critical monitoring. Given the limitations imposed by deep space hazards, a clinical decision support system for exploration and Mars missions may fulfil the next ten basic principles:

- Give real-time support for medical decision making
- Give patient-specific and quantitative advice
- Take into account available information from life support and monitoring of crewmembers
- Be fully autonomous from remote facilities
- Continuously adapt predictions to physiological disturbance and changing conditions
- Optimise medical decision making in terms of mission fundamental priorities
- Take into account medical supplies and equipment on-board
- Apply health standards for levels of care
- Apply ethical standards for spaceflights
- Apply ethical standards for artificial intelligence

Therefore, MEDEA is designed as a comprehensive computational suite to deploy personalised Clinical Decision Support for exploration and planetary missions. It should operate continuously to react to emergency and unseen medical situations giving support for clinical decision making by quantitative adapted predictions to individual crewmembers profiles. The suite is composed of four software modules physically distributed on-board or on Earth
facilities to provide four main functionalities of the system: autonomous decision making (on-board), space adaptive deep learning (on Earth), semantic interoperability (on-board) and ethical & legal functional support (on-board and on Earth). Figure 1 shows the details of the four modules that implements the principles enumerated above to support tertiary medical interventions and how the modules are interconnected among them and the information systems on-board.

The module Autonomous real-time CDSS for tertiary medical care is the one that directly interacts with the crewmembers for supporting medical decision making by means of AI-models during medical emergencies and critical monitoring under the paradigm treat to final resolution. To do that, it receives the health status of the crewmembers from the on-board health care system and the medical diagnosis systems through the semantic interoperability module. The AI-models are continuously adapted to the changing space conditions by the Space adaptive deep learning module. Both CDSS and deep learning performances are continuously verified by the Ethical and legal functional support module. In the next four sections, we provide the technological solution of each module of the MEDEA suite.

4 Autonomous real-time CDSS for tertiary medical care

Romero et al. in [6] compiled the most common hundred medical conditions in space derived from the ISS Medical Checklist, scientific research and occupational health statistics. The stratification of this list serves to HRP for planning mitigation actions for the thirty human system risks. Medical conditions in spaceflights may be occupationally-induced conditions or idiopathic illnesses. Crew activities confined in a spacecraft extravehicular activities (EVA) and surface explorations may increase the probability of injuries and trauma, that may derive on emergency medical situations. Although presentations and frequencies of medical conditions during prolonged stays may change for Mars missions, the closest reference given by medical reports from ISS [27] revealed that 46% of crewmembers expressed an event deemed notable, being skin rashes and hypersensitivities (40%, 1.12/flight year) along with upper respiratory symptoms (0.97/flight year), the most reported events. Moreover, artificial life support added to space-specific con-
No return to definitive medical care facility

Tx/Rx latency of several minutes

From 400 days to 3 years mission

Diverse crewmembers

Diverse clinical profiles

Diverse sex & gender

Up to 1 physician in the mission

Medical prevention strategy

Primary prevention

Secondary prevention

Tertiary prevention

Level of care V

Basic life support

First-aid capability

Clinical diagnosis

Ambulatory care

No immediate return to Earth

No RT telemedicine

Advance cardiac life support

Advanced trauma life support

Advanced Life Support

Basic surgical care

Palliative care

Crew selection

LEO: No interventions

"Stabilise and transport" policy

"Treat to final resolution" policy

Countermeasures

Idiopathic illnesses

Subclinical diseases

Occupationally-induced medical events

Disturbed physiology

Mission fundamental priorities & Level of care V

Compatible diagnoses

Optimisation of action plans

Standardised taxonomy of risk factors

Medical operations - procedure library

On-board pharmaeutical supplies

On-board facilities

On Earth facilities

Fairness

Interpretability

Traceability

Ethical & legal functional support

On board & on Earth facilities

Figure 1: Concept design of MEDEA composed of four main subsystems for autonomous decision making, space adaptive deep learning, semantic interoperability and ethical & legal functional support.
ditions and isolation increase the onset of conditions such as space adaptation syndrome, headaches, gastrointestinal distresses, degradation of the immune system, infectious processes, sleeplessness and depression, among others.

Added to that, idiopathic illnesses during 3-4 years of a Mars-type mission are willing to appear more than in a LEO mission due to: prolonged stays of the same crewmembers, variability of tasks during exploration missions [28], completely absence of gravity, exposure to radiation, and increase in the number of astronauts from private and public space programmes and higher variability of medical profiling [9].

Current design of exploration-type and Mars-type missions plans to book one seat of the spacecraft for a physician acting as Chief Medical Officer (CMO) in every spaceflight crew [29,8]. Although this may enhance mission safety, long latency to communicate from mission control involves isolation on medical decision making to solve emergency situations. A real-time clinical decision support system may give processed knowledge related to patients’ conditions to CMO during on-board emergency situations. Moreover, the result of the system may assist crewmembers in the critical case CMO is unavailable.

Furthermore, current design of clinical decision support systems should follow the next four caveats by Shortliffe and Sepulveda [30]:

- Black boxes are unacceptable
- Complexity and lack of usability thwart use
- Delivery of knowledge and information must be respectful
- Scientific foundation must be strong

This module performs three sequential functionalities to give a complete support for dealing with medical situations: multitask prediction modelling, classification of type of tertiary medical intervention and optimisation of the action plan. Each functionality and its design are described below.

4.1 Multitask prediction modelling

When a medical emergency arises, a prompt prediction should be carried out to decide #1 if it is a life-threatening situation, #2 its delayability, #3 if it represents an ethical dilemma for the mission fundamental priorities, and to
estimate #4 duration of therapy and #5 compatible diagnoses. A positive prediction of a life-threatening situation should activate emergency protocols on-board that depending of the delayability may wait advice from mission control or not. Moreover, when a situation is considered an ethical dilemma, specific constraints may be contemplated from the very beginning of the action plan, taking into account the potential duration of the treatments. Besides, the ordered list of compatible diagnoses may guide the specific set of medical operations to restore health and performance of the crew.

From the five prediction tasks, #1 life-threatening situation and #3 ethical dilemma are classification tasks (i.e. yes/no), #2 delayability and #4 duration are regression tasks (i.e. positive numbers in a limited range), and #5 is a recommendation task (i.e. ordered list of diagnoses). For the Task #5 compatible diagnoses, the list of potential diagnoses may be large. A total of 71932 codes of diagnoses are included in the 2019 version 10 of the International Statistical Classification of Diseases and Related Health Problems (ICD) by the World Health organisation (WHO). From them, 135 conditions (including several ICD-10 codes each) were considered as should plan to treat in the draft list of the medical conditions for Mars missions presented by Nusbaum et al. in 2019 [31]. Additional 22 conditions were plan to treat with conditions and 34 of them should not plan to treat. Given that large amount of prediction values and varying conditions in deep space, the best configuration for the Task #5 is a recommendation system [32].

Given the shared input and context of the five predictions to carry out and the our previous deep learning technology for emergency medicine [33], we propose a deep multitask learning network with hard parameter sharing approach [34, 35] to exploit the dependences among tasks. The proposed architecture will ensemble four task-specific subnetworks with specific parameters for tasks #1 to #4 and a task-shared subnetwork sharing a set of parameters for all prediction tasks. The task-shared subnetwork is basically a dense block composed of fully connected layers, a batch normalisation layer, a leaky ReLU [36] activation function and a dropout layer. The output of the task-shared subnetwork is the input of the five task specific subnetworks, all of them configured as dense blocks, but with different output layers. Softmax functions are used for classification tasks #1 and #3 whereas linear functions are used for regression tasks #2 and #4. Following the multi-view deep learning approach by [37], we obtain a latent space for task #5 recommendation system from the fully connected layers of the task-shared
subnetwork. Then, an ordered list of diagnoses is obtained by the votes of the nearest neighbours (training cases) of the test case in the latent space.

The input of this module will be the paramount of biomedical data from crewmembers and situation awareness. Structured information from electronic health records may be combined with free-text reports and speech notes of the emergency scenario. Previous conditions and patient evolution may be extracted from longitudinal signals acquired from wearable monitoring sensors, such as electrocardiogram (ECG), electroencephalography (EEG), blood pressure signals and respiratory signals. In short, all possible input data may be classified on structured stationary data (e.g. clinical symptoms), structured sequential data (e.g. ECG) and unstructured sequential data (e.g. clinical notes in free text). Our proposed deep multitask learning network includes three subnetworks to extract the relevant information from each data type. The structured stationary data is processed by a multi-layer perceptron (MLP) composed of dense and output blocks. Besides, the structured sequential data is processed by a stack of multiple bidirectional long short-term memory (BLSTM) [38] units, multiple skip connections across the BLSTM units, a concatenation block of the skip connections and a MLP, consisting of dense and output blocks. Finally, the unstructured sequential data is processed by a bidirectional encoding representation obtained by a transformer (BERT) [39] block and a MLP module. All outputs of the three subnetworks are concatenated as input to the task-shared subnetwork described in the previous paragraph.

4.2 Classification of tertiary medical interventions

We can distinguish among five different types of tertiary medical interventions on spaceflight: advance life support care, transitional care, ambulatory care, palliative care and emergency care. The classification of the medical intervention for any medical situation can be directly mapped from the five predictions carried out by the multitask prediction modelling. Given that space medicine shares many attributes with extreme conditions and environments where emergency medicine operates, we propose following the approach applied by Ferri et al. [33] for classifying emergency medical call incidents. Hence, the mapping can be defined by a panel of over 20 physicians and mission designers using a Delphi methodology [40].
4.3 optimisation of action plans

Once a compatible diagnosis and the type of tertiary intervention have been assigned, it is time to apply a set of medical action to restore the health and performance of the crewmembers. They should be compatible with the Level of Care V, that entails basic and advanced life support, first aid, clinical diagnosis, imaging, ambulatory care, telemedicine, sustainable advanced cardiac life support, advanced trauma life support, basic surgical care and palliative care without immediate return to earth capability [8]. Therefore, the medical actions available in exploration and planetary missions would be an upgraded version of the routine and emergency medical operations included in the ISS Integrated Medical Group Medical Checklist [13].

Then, a complete medical action plan should be tailored to the medical situation trying to optimise the mission fundamental priorities (i.e. 1: vehicle survival, 2: health & safety of the crew, 3: mission success, and 4: payload success) under the constraints imposed by the restricted medical equipment for diagnoses and a limited amount of medical supplies for treatment. For this functionality, we intend to optimise the sequence of actions using a reinforcement learning approach [41] continuously checked by a real-time alert when the action plan diverts from the mission fundamental priorities.

Emergency events are the situations where an on-board clinical decision support may be more needed by the crew. Nevertheless, it cannot be isolated from the full tertiary interventions deployed for the medical prevention strategy. Of most interest is to evaluate if multitask prediction models developed for medical emergencies on Earth [33] can be transferred to on-board decision making with high rates of accuracy. Doing that, the development of clinical decision support systems to help on-board medical interventions may take advantage of massive biomedical data analysis performed on Earth.

5 Space adaptive learning

Deep learning [42] is the novel technology with more success for mimicking human decision making [43] from complex types of data, such as involving high dimensional and multimodal data [44], sequences [45] and unstructured data [46]. Given the modular architecture proposed in 4.1, we suggest performing an independent learning process of each task-independent sub-network by the Adam stochastic optimisation algorithm [47] with a weigh decay
term to promote regularisation [48] followed by their ensemble as loosely coupled models [49]. Moreover, to evaluate the model performance and tune hyperparameters without biases maximising available re-use data we follow the robust methodology proposed by Kohavi [50].

Nevertheless, the main potential limitation to design prediction models for medical decision-making during exploration missions is the continuous medical dataset shift [51] of the on-board cases produced by the physiological disturbance. Dataset shift was first described in [52] and defined by Moreno-Torres et al. [51] as the situation in which the training and test data follow joint distributions that are different. Dataset shift occurs when the data experience a phenomenon that leads to a change in the distribution of a single feature, a combination of features or the output boundaries.

In medical prediction problems, where the output (e.g. the disease) causally determines the values of the features (e.g. symptoms), there are two types of dataset shift that may appear independently or at the same time. First, prior probability shift refers to changes in the distribution of the output variable. In space medicine it is observed how the prevalence of some medical conditions increase due to the specific environment and activities of the crewmembers. Then, the frequencies of arrhythmia, headache, dermatitis, respiratory infection, and renal stone formation, among other medical events, are increased in space with respect to on Earth. We can expect that probability shift of medical conditions in space will continuously change given the cumulative effect of space influence in the physiological disturbance and the non-stationary environment of exploration missions. Second, concept drift (a.k.a. concept shift) happens when the representation of the inputs conditioned to the outputs of a predictive model changes in test cases with regard to training cases. In medical applications, this may happen when the observation of symptoms manifesting diseases changes during operations with respect to the data distributions learned during the design of the prediction model. Given the effect of microgravity, radiation and isolation in human bodies, we can expect a major concept drift in the biomedical data generated in long-term space missions.

Moreover, designing an effective data-driven decision support system for space exploration missions will require a continual update of prediction models to the lastest registered data. That can be solved by several alternative approaches: a) perform retraining using the complete historical dataset, b) perform continual learning of models’ parameters including periodically the
new test cases \cite{53}, c) select the most robust models adapted to imprecise environments \cite{54}. Given that currently there are no registries of biomedical data of humans from space exploration missions, our choice is the continual deep learning approach that avoids access to historical multisource data, allows using data from ISS and Earth at present time and produces prediction models continuously adapted by cases which features are conditioned by the disturbance physiology effects of space.

Moreover, a careful monitor of biases affecting data representation should be carried out to ensure quality and performance of updated models \cite{55}. The methodology developed in \cite{56} based on non-parametric statistical manifolds may be useful to calculate the dynamics of temporal variability of biomedical data from crewmembers, including continuous temporal trends, seasonal behaviours and abrupt changes produced by dataset shift effects.

The most challenging step in the design of the MEDEA system is indeed the space adaptive learning. Added to the lack of data from deep space, continual learning is nowadays an open topic still to be solved for terrestrial scenarios. Nevertheless, space exploration missions involve a dynamism difficult to compare with other situations. Hence obtaining a successful continual learning of on-board data-driven clinical decision making is the most salience hypothesis of the MEDEA concept design. With this approach we expect that the evidence of tomorrow will help us further develop and build smart medical systems to address those yet undiscovered challenges of long-duration, long-distance spaceflight \cite{57}.

6 Semantic interoperability

This module is in charge of exchanging unambiguous information with the computer systems for the health maintenance of the crewmembers. Space agencies have addressed exchange of data in multiple vendors environments by definition of interoperability protocols, such as STEP-SPE. Whereas space agencies were focused on the exchange of information among space environment analysis tools \cite{58}, medical informatics has focused the attention on deploying semantic interoperability in healthcare organisations, that goes some steps further in the exchange of information among heterogeneous systems. Specifically, semantic interoperability is defined as the transmission of data along with the required knowledge to understand it, by sharing clinical concepts described in a reference model using a binding medical terminology.
shared vocabulary \[59\]. This may allow sending information to buses of data without assuming that every receptor needs to know in advance its semantic.

Then, we propose to adopt the Fast Healthcare Interoperability Resources (FHIR) to exchange medical data on-board between our clinical decision support system and the on-board healthcare systems and medical diagnosis systems. FHIR was designed for exchanging electronic health records (EHR) by the Health Level Seven International (HL7) organisation and it is supported by the American Medical Informatics Association. The idea is to organize entities, such as patients, observations, measurements and diagnoses, as FHIR resources specified by profiles (clinical concepts) with U.S. Core Data for Interoperability (USCDI) elements written in SNOMED Clinical Terms. In that way, medical records of the astronauts will be consistent with the with the international standards followed by the providers of medical information technologies.

Although a FHIR-based system would provide a full semantic interoperability with health information systems, given that current on-board computer systems do not follow interoperable standards yet or they are based on industrial standards from aeronautics, the semantic operability module may also include connectors to the specific on-board systems with adapters to their data structures.

7 Ethical & legal functional support

Several ethical and legal concerns must be addressed correctly for a proper day-by-day operation of MEDEA as on-board clinical decision support system. First, the massive use of biomedical data of the crewmembers in the context of a unique environment of deep space requires the correct management of regulation for data protection and privacy. Emphasis on the confidentiality of astronaut clinical data has resulted in missed opportunities to understand human physiological adaptations to space \[60\]. Laws adopted to take into account the digital era, such as the General Data Protection Regulation (GDPR) \[61\] implemented by the European Union on 2018, give control of data to the individual. Our premise is that the new regulations for data protection may be a mechanism to avoid the loss of valuable biomedical information from deep space environments.

Another relevant issue is the application of ethical criteria when giving real-time decision support for solving medical events. To this, mission fun-
damental priorities and available resources for Level of Care V may guide the optimisation of the medical action plan.

More generally, given that we are proposing a data-driven decision support system, independently of the medical certificates requested to the crew medical officers [9], our proposal may also adopt solutions for the next additional issues:

- Fairness to avoid reproducing any pattern of discrimination due to prejudices or bias [62]
- Interpretability to enable a correct explanation of medical predictions and decisions by human experts [63]
- Traceability to achieve a comprehensive examination of responsibilities of any medical decision making at any time, ensuring the currency of the knowledge base and that it is safe to use [30]

The inclusion of an ethical and legal framework as a module of MEDEA may ensure the practical implementation of solutions for the five issues described above. A careful validation of its performance through computational simulations and analogues may guarantee the correct functionality of the MEDEA system with respect to the human well-being.

8 Discussion

Our approach may give real-time decision support for continuously changing medical situations in a way that can be managed in long-duration spaceflight, with special attention to emergency medicine and critical monitoring. Stewart et al. [22] identified traumatic injury as one of the most relevant emergency situations in space exploration given the expected incidence and consequences to the mission fundamental priorities. Additionally, it is largely unknown the cardiovascular and immunological effects of long-duration spaceflight on wider spectra of medical profiles of astronauts. Kuypers et al. in [29] include two lists of health concerns due to specific space conditions and medical emergencies, respectively. The first list identifies medical aspects such as cancer, cataracts, immunologic changes, decreased red blood cell mass, bone and mineral loss, muscle atrophy/loss of strength, vestibular/sensorimotor changes, cardiovascular changes, hyperopic vision shifts, mental health problems, bacterial growth, water and air contamination or
degradation, and other deficiencies. The second list includes wounds, burns, contusions, sprains, fractures, cardiac dysrhythmias, orthostatic intolerance, pneumonitis, persistent latent viral reactivation, anaphylactic reactions, dermatologic cellulitis, dermatitis, space motion sickness, gastroenteritis, constipation, renal stones, urinary tract infections, acute urinary retention, crown fracture, dental infections, abscess corneal abrasion, corneal infection, foreign bodies, depression, anxiety, exposure to toxins, acute radiation illness and decompression sickness. Besides, Stewart et al. in [22] and Komoroski and Fleming in [64] focused on the medical emergency procedures of the critically ill and injured on extreme conditions and environments. Nevertheless, we are not aware of any scientific paper or experiment report about information technology specialised in emergency medicine in space, being this study the first that propose basic principles and a concept design of a clinical decision support systems to tackle autonomous tertiary medical interventions.

Estimated in 2010 and 2019 the cost of their first mission to Mars at 6 Billion USD and 10 Billion USD, respectively. Added to the loss of a life, a health problem in the crew may put in danger the rest of the crewmembers, jeopardise the mission and loss of the vehicle and payload. History has shown that during the exploration of frontiers on Earth, human physiologic maladaptation, illness, and injury have accounted for more failures of expeditions than any single technical or environmental factor [65]. Therefore, it is critical to rely on robust fault-tolerant solutions to deploy tertiary medical interventions in the most autonomous fashion during space exploration missions, where evacuation and synchronous communication to mission control is not a reliable option.

Clinical decision support systems may provide real-time advice tailored to the health problem and optimised in terms of the mission fundamental priorities and in compliance of the highest ethical and legal conditions. The support for a wide set of medical conditions must be deployed to deal with medical emergency events and nominal health issues as well, in light of the expected increase of astronauts profiles and civilian spaceflight [9]. Moreover, adaptive learning must guarantee predictive models updated to the cumulative and variable disturbance of space effects in human physiology.

The autonomous clinical decision support system developed in MEDEA may be directly transfer to medical applications on Earth. Specific scenarios may have specific requirements similar to space exploration missions. Isolation and extreme conditions may appear on deep sea exploration, Artic and
Antarctic missions, and isolated communities on desserts and forests. The global market of clinical decision support systems for general and specialised medicine for the year 2028 has been estimated at 3.5 Billion USD. The development of quantitative medicine will go hand-in-hand with the design of this technology, so robustness and adaptation required for operating in space will speed up this process.

Sooner or later humans will expand along solar systems so spaceflight among planets, asteroids and space stations will become frequent. Developing adaptive clinical decision support systems will be a keystone for delivering medical care on-board, opening the career of healthcare in space. It is not possible to estimate the economic impact of healthcare after humans expand but we can grossly understand its dimension by the size of the current global healthcare market calculated at 12 Trillion USD.

Getting MEDEA on-board of a spacecraft is not going to be easy. Initially, the four modules will have to be designed at the same time as the missions to Mars are designed for the launch windows by 2030s. Therefore, real-time integration with health information systems on-board may represent a challenge on its own. Moreover, the initial versions of predictive models will not be able to be trained from any real data acquired during previous planetary missions, so we will have to use medical data from Earth and ISS relying on the continual adaptive learning to get relevant knowledge from the physiological conditions that astronauts will experiment on-board. Stakeholders and public opinion will only trust MEDEA if we guarantee its ethical and legal compliance shown by a clear fairness, interpretability and traceability capabilities. The principles and concept design described in this study may serve as the basis to implement a complete and qualified clinical decision support system to operate in space exploration missions before 2030s.

9 Conclusion

In less than two decades space missions for human exploration of Mars will be designed and launched. A key element for their success will be the capability to provide autonomous healthcare adapted to the dynamic space conditions. On-board healthcare may be fully redesigned taking into account that low-latency telemedicine and prompt evacuation to Earth will not be feasible
in that new type of human missions. Therefore, autonomy for real-time decision making will be mandatory to solve medical emergency situations and necessary to monitor medical status for space induced health conditions.

In this study we have introduced the basic principles and concept design of MEDEA, a clinical decision support system to provide real-time advice to tertiary interventions on-board of space exploration missions. The presented design applies the current Biomedical Data Science and AI technology to fulfil the fundamental priorities and the level V of healthcare in spaceflights. The design consists of four dependent modules, being the main one the responsible for giving direct advice to the crew by means of a deep learning multitask network to predict the character of the medical event, a classifier of the tertiary medical intervention and an optimiser of the medical action plan. The adaptation of prediction model to the changing physiology on space will be solved by a continual deep learning module and both modules will be integrated with health information systems on-board by means of a semantic interoperability FHIR module. Fairness, interpretability and traceability provided by the ethical and legal module is expected to ensure best practices and trust during the full operational time of MEDEA.

The clinical decision support system implementing the MEDEA concept design is expected to give autonomous decision making for the next human missions to Mars. Besides, it will represent a stepstone for the future of quantitative medicine on Earth and a potential healthcare device for the expansion of humankind throughout the solar system.

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Competing interests statement

The author has no competing interests to declare.

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