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| **PI Name:** | Tavakkoli, Alireza Ph.D. | | |
| **Project Title:** | A Non-intrusive Ocular Monitoring Framework to Model Ocular Structure and Functional Changes due to Long-term Spaceflight | | |
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| **Program/Discipline--Element/Subdiscipline:** | | | |
| **Joint Agency Name:** | | **TechPort:** | Yes |
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| **Contact Monitor:** | Stenger, Michael | **Contact Phone:** | 281-483-1311 |
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**Task Description:**

Unique neuro-ocular structural and functional changes affect a subset of astronauts who have completed prolonged spaceflight missions and due to its unique pathology, a new case definition was proposed and the condition was renamed Spaceflight Associated Neuro-ocular Syndrome (SANS). In this project we investigate two interconnected computational frameworks to develop a diagnostic system as well as a mapping mechanism to assist NASA scientists and clinical experts to more comprehensively study the SANS phenomenon and predict the risk of its development in prolonged spaceflight. Therefore, the first aim (Aim 1) of this project is to develop novel computational tools to establish mappings between the observed ocular structure and visual function, pre-, in-, and post-flight, in order to provide NASA scientists and clinicians with better means to investigate SANS etiology and its progression. The second aim (Aim 2) of this project is to integrate Contrast Sensitivity (CS), Visual Fields (VF), and our novel distortion assessment mechanism into a validated and compact diagnostic tool to better measure ocular function (SANS 301 : Laboratory development of mechanical countermeasures).
We will focus our efforts in each aim on a sub-set of functionalities that allow for the establishment of the interconnected computational framework enabling the pursuit of long-term research to predict the risk of development of SANS and monitor its progression.

Omnibus Aim 1: Structure-Function Mapping

Research Task-1.1: Design a novel mapping between Optical Coherence Tomography (OCT), Magnetic Resonance Imaging (MRI), Contrast Sensitivity (CS), and Visual Fields (VF) perimetry.

Research Task-1.2: Conduct studies on retrospective data from NASA Lifetime Surveillance of Astronaut Health (LSAH) and Life Sciences Data Archive (LSDA) on the three populations (astronauts, head-down-tilt bed rest, and idiopathic intracranial hypertension (IIH)) patient.

These findings will be significant in two ways:

(1) They will allow us to predict measures within a smaller sample set, if a larger analog sample set has known structure-function maps.

(2) They will enable us to design predictive mechanisms to study disease progression both in astronauts and in terrestrial analogs terrestrial analogs.

Expected Outcomes: (1.i) understanding how OCT/MRI correlates with VF, (1.ii) translational parametrization of mappings across cohorts, and (1.iii) ability to predict the risk of development of SANS and monitor its progression by utilizing the proposed mappings.

Omnibus Aim 2: Address SANS 301 Knowledge Gap

Research Task-2.1: Integrate VF and CS assessments into a VR-mediated framework.

Research Task-2.2: Validate VR-based VF/CS on the terrestrial analog populations.

Expected Outcomes: (2.i) a novel Virtual Reality (VR)-based VF/CS assessment and (2.ii) a compact diagnostic tool.

**Rationale for HRP Directed Research:**

**Research Impact/Earth Benefits:**

During the previous year of the project, our team has made contributions on the two aims as follows:
Aim 1- The first aim (Aim 1) of this project is to develop novel computational tools to establish mappings between the observed ocular structure and visual function, pre-, in-, and post-flight, in order to provide NASA scientists and clinicians with better means to investigate SANS etiology and its progression (SANS 1).

Contributions: 1- Design a novel mapping between OCT, MRI, CS, and VF. 2- Conduct studies on retrospective data from NASA Lifetime Surveillance of Astronaut Health (LSAH) and Life Sciences Data Archive (LSDA) on the three populations.

Technical Details: In order to establish a comprehensive mapping between different ophthalmic domains we started by designing a conditional generative adversarial network (GAN) to map across the publicly available data we had at our disposal, i.e., fluorescein angiography (FA) and fundus photographs. The GAN comprises of two generator modules and four discriminator modules to take fundus photographs and produce anatomically accurate FA images inferred from the fundus images.

Impact: We have shown novel deep architectures in ophthalmic applications could improve diagnostic accuracy, that attention maps can improve transferability of learned models across datasets, and deep architectures could effectively extract shared feature representations across ophthalmic image modalities to translate from one domain to another. These discoveries have paved the way for our team to tackle the main problem of mapping between the domain of ocular structure to the visual function.

Significance: (1) Understanding how ocular structure correlates with visual function. (2) Parametrization of mappings. (3) Predict the risk of SANS.

Aim 2- The second aim (Aim 2) of this project is to integrate CS, VF, and our novel distortion assessment mechanism into a validated and compact diagnostic tool to better measure ocular function (SANS 3).

Contributions: 1- Integrate VF/CS assessments into a VR-mediated framework. 2- Validate VR-based VF/CS on the terrestrial analog populations.

Technical Details: We present a methodology that comprises a calibration step, four different visual function tests that measure different aspects of user perception, and then a composite pipeline that simulates the modeled deficits for validation. In order to properly utilize the virtual assessment, the environment would need to be calibrated at the beginning of each session. Simple calibrations such as adjusting lens distance, interpupillary distance, and headset adjustments are done at the start. After these adjustments, the fixation and tracking capabilities of the eyes are tested, first binocularly and then monocularly. These performance metrics are saved alongside the user demography information. After the calibration phase, the user's visual assessment can commence. Visual acuity (VA), contrast sensitivity (CS), and visual distortions are assessed through a variety of procedures. For VA, binocular distant VA as

well as dynamic VA is measured under mesopic (natural light) conditions. Instead of using images of conventional charts, we render individual characters in front of the user at predetermined distances and scale it based on user response. The results are reported in logMAR scale among others. The contrast sensitivity is measured using gabor patches as stimuli. In this test, the user gaze follows a gabor patch that alters its contrast and spatial frequency based on user performance. At the end, the contrast sensitivity expressed in logCS among other contrast sensitivity units. The amsler grid test is adapted to VR to measure the perceptual distortions in age-related macular degeneration (AMD) patients. At the start of the exam, the amsler grid is displayed infront of both eyes. While looking at a fixation point in grid, if the straight grid lines appear to be distorted the user emulates the metamorphopsia of the deficient eye on the healthy eye. This grid manipulation is modeled as a gaussian mixture of different scotoma parameters. The results are reported as the image of the altered amsler grid.

Impact: In addition, we have developed a new approach mediated by advances in virtual reality (VR) for better assessment of metamorphopsia to enable remote monitoring of the progression of AMD \cite{zaman2020mixed}. These findings in conjunction with the findings of Aim 1 motivate and inform the objectives of this project, by allowing our team to maintain a correspondence between how the ocular structural changes could impact visual function assessments.

Significance: (1) A novel VR-based VF/CS assessment. (2) A compact diagnostic tool.

**Task Progress:**

To achieve the two research aims of this project, we initiated an effort to design a framework to generate mappings between the ocular structure and its function, by developing a computational framework inspired by deep Convolutional Neural Networks (CNNs). We then initiated these novel mappings, trained during research task (RT-1.1). Unlike current classification and segmentation algorithms that merely label test results, the proposed mappings are able to directly connect one domain (function) to the other (physiology). This functionality is significant, as it will enable us to predict progression of changes by cross-validating test results from one domain (function) with the other (structure). Moreover, these deep network models enable the design of cohort studies as a part of research task (RT-1.2) in order to uncover model similarities and differences between Spaceflight Associated Neuro-ocular Syndrome (SANS) and its terrestrial analogs. Below, additional details about the accomplishments in each research task are presented.
1) Mapping Across Domains In order to establish a comprehensive mapping between different ophthalmic domains, we started by designing a conditional generative adversarial network (GAN) to map across the publicly available data we had at our disposal, i.e., fluorescein angiography (FA) and fundus photographs. The GAN comprises a vision-transformer-based generative adversarial network (GAN) consisting of residual, spatial feature fusion, up sampling and down sampling blocks for generators, and transformer encoder blocks for discriminators. We incorporate multiple losses for generating vivid fluorescein angiography images from normal and abnormal fundus photographs for training. Multi-scale Generators: To capture large and fine-scale features to produce realistic vascular images, we combine multi-scale coarse and fine generators. We adopt two generators (fine and coarse). The fine generator synthesizes local features such as arteries and venules. Conversely, the coarse generator translates global features such as large blood vessels, optic disc, and overall contrast and illumination. The generators consist of multiple down sampling, up sampling, spatial feature fusion, residual blocks, and a multi-scale feature summation block between the two generators.

Down Sampling and Up Sampling Blocks: We use, as generators, auto-encoders comprising of multiple down sampling and up sampling blocks for feature extraction. A single down sampling block contains a convolution layer, a batch-norm layer, and a Leaky-ReLU activation function successively. In contrast, an up-sampling block consists of a transposed convolution layer, batch-norm, and Leaky-ReLU activation layer consecutively. We use the down sampling block twice in the fine generator, followed by nine successive residual identity blocks. Finally, the up-sampling blocks are used again to make the spatial output the same as the input. For the coarse generator, we utilize the down sampling once, and after three consecutive residual blocks, a single up sampling block is employed to get the same spatial output as the input. Spatial Feature Fusion Block: The spatial feature fusion (SFF) block consists of two residual units with Convolution, Batch-Norm, Leaky-ReLU layers successively. There are two skip connections, one going from the input and element-wise platform, summed to the first residual unit’s output, and one coming from the input layer and added with the last residual unit’s output. We use spatial feature fusion blocks for combining spatial features from the bottom layers with the topmost layers of the architecture. The fine generator comprises two SFF blocks that connect each of the two down sampling blocks with the two up sampling blocks successively. In contrast, the coarse generator has only one SFF block between the single down sampling and up sampling block. The reason behind incorporating the SFF block is to extract and retain spatial information that is otherwise lost due to consecutive down sampling and up sampling. As a result, we can combine these features with the learned features of the later layers of the network to get an accurate approximation.

VisionTransformers as Discriminators: GAN discriminators require adapting to local and global information changes for differentiating real and fake images. To alleviate this inherent problem, we need a heavy architecture with many parameters. In contrast, convolution with a large receptive field can be employed for obtaining multi-scale features, but can cause overfitting on training data. To resolve this problem, we propose a new Vision Transformer-based Markovian discriminator. We use eight Vision Transformer encoders, consisting of a multi-headed attention layer and multi-layer perceptron (MLP) block. The Layer Normalization layer precedes each block, and a residual skip connection is added to the output from the input. To handle 2D images of 512 x 512, we reshape the images into a sequence of flattened 2D patches with resolution 64 x 64. By doing so, we end up having 64 patches in total. The Transformer uses a constant latent vector size of 64 through all its layers, so we flatten the patches and map to 64 dimensions with a trainable linear projection. The output of this projection is called the patch embedding. Position embeddings are added to the patch embeddings to preserve positional information. We use regular learnable 1D position embeddings. For multi-headed attention, we use 4 heads. For MLP blocks, we use two dense layers with features sized at 128 x 64, each succeeded by a GeLU activation and a dropout of 0.1. Contrarily, our Vision Transformer has two outputs, an MLP head, and a Convolutional layer. The MLP head has two outputs, with hidden units for FA image classification (Abnormal and Normal). In contrast, the convolution layer outputs a feature map of 64 x 64 for classifying each patch in the original image. We use two Vision Transformer-based discriminators that incorporate identical structures but operate at two different scales. The coarse angiograms and fundus are resized to 256 x 256 by a factor of 2 using the Lanczos filter. Both discriminators have identical transformer encoder and output layers. Consequently, we fuse learnable elements from both generators, while training them with their paired Vision Transformer-based discriminators.

2) Non-Intrusive Diagnostics We present a methodology that comprises a calibration step, four different visual function tests that measure different aspects of user perception, and then a composite pipeline that simulates the modeled deficits

for validation.

VR Calibration: In order to properly utilize the virtual assessment, the environment would need to be calibrated at the beginning of each session. Simple calibrations, such as adjusting lens distance, interpupillary distance, and headset adjustments, are done at the start. Additional system specific calibrations, such as color gamut calibration, is done once per each VR device. After these adjustments, the fixation and tracking capabilities of the eyes are tested, first binocularly and then monocularly. These performance metrics are saved alongside the user demography information.

VR Assessment: After the calibration phase, the user's visual assessment can commence. Visual acuity (VA), contrast sensitivity (CS), and visual distortions are assessed through a variety of procedures. For VA, binocular distant VA as well as dynamic VA is measured under mesopic (natural light) conditions. Instead of using images of conventional charts, we render individual characters in front of the user at predetermined distances and scale it based on user response. The results are reported in logMAR scale, among others. The contrast sensitivity is measured using Gabor patches as stimuli. In this test, the user gaze follows a Gabor patch that alters its contrast and spatial frequency based on user performance. At the end, the contrast sensitivity expressed in logCS among other contrast sensitivity units. The Amsler grid test is adapted to VR to measure the perceptual distortions in age-related macular degeneration (AMD) patients. At the start of the exam, the Amsler grid is displayed in front of both eyes. While looking at a fixation point in the grid, if the straight grid lines appear to be distorted the user emulates the metamorphopsia of the deficient eye on the healthy eye. This grid manipulation is modeled as a Gaussian mixture of different scotoma parameters. The results are reported as the image of the altered Amsler grid.

VR Simulation: The collected results for each of the visual assessments are then used to create a simulation of the perception of the user. This pipeline combines results from all of the tests to offer a single visualization. For example, lower visual acuity values would lead to the scene appearing blurry and the existence of scotomas would create distortions in the scene. The saved parameters can be pulled up at any time so that others can experience the perceptual loss measured by all three tests individually and collectively.

2-1) Objectives of Visual Function Assessments Currently, on board the International Space Station (ISS), astronauts undergo many routine functional visual assessments (e.g., visual acuity, Amsler grid test). Contrast sensitivity testing is also available. For optimal monitoring, these visual assessments may benefit from consistent distancing and illumination calibration to reduce the subjectivity of the tests. We achieve these objectives through virtual reality (VR) head-mounted systems. A laptop screen-based test is repurposed for an immersive experience with this technology. Additionally, by delivering all visual function tests using one VR device, it will be possible to make inferences on other tests once a session is recorded. Specifically, for SANS monitoring, it is important to identify any subtle perceptual impact so that countermeasures can be designed. Intelligent delivery of stimuli under various conditions would help identify subtle perceptual loss. Optic disc edema, globe flattening, nerve fiber layer thickening, and choroidal folds are common imaging findings in SANS. While it is important to monitor SANS, frequently repeating these imaging tests would consume a significant portion of mission time. Therefore, quick sessions of different visual function tests are being considered to continually track the different aspects of SANS symptoms. This can be achieved by mapping visual functional data with imaging data using pre-existing astronaut data as well as head-down tilt bed rest, an analog for SANS.

We have conducted several primary tests on this system, including visual acuity, contrast sensitivity, Amsler grid, and visual fields. These assessments can be linked to specific SANS findings that parallel terrestrial ocular relationships, such as contrast sensitivity and retinal nerve fiber layer thickening. In addition, these visual function tests may be able to further characterize any deficiencies in SANS by providing additional visual assessment tests.

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