# Information on dissertation submitted for the PhD degree of National Research Tomsk State University

**Name of applicant:** Raymond van de Berg

**Title of the thesis:** Biophysics of the Vestibular Implant

**Date of the oral examination:** 14:30, September 15, 2021

**Location of the examination:** Tomsk State University,

<https://us06web.zoom.us/j/82198571221?pwd=eEFDVHRQcDlWYTRFNUw2SUJvLzYvUT09>

**Supervised by:**

* Vladimir Demkin, Doctor of Physical and Mathematical Sciences, Professor, Department of General and Experimental Physics, Physics Faculty, National Research Tomsk State University, Tomsk, Russia
* Herman Kingma, PhD, Professor, Faculty of Health Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands

**Official Opponents**

1. Vincent van Rompaey, PhD, Professor, hoogleraar keel-, neus en oorheelkunde, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
2. Svetlana Valer’evna Gusakova, Doctor of Medical Sciences, devivsion of biophysics and functional diagnostics, Biomedical Department, Siberian State Medical University, Tomsk, Russia

**Chair of PhD Committee**

Yu.V. Kistenev, Doctor of Physical and Mathematical Sciences, Professor, Department of General and Experimental Physics, Physics Faculty, National Research Tomsk State University, Tomsk, Russia, 634050, Lenin, ave., 36, email: yuk@iao.ru

**THESIS ANNOTATION**

**1. Title**

Biophysics of the Vestibular Implant

**2. Problem and relevance**

Each healthy person has two vestibular organs. These organs are located in the temporal bone and are part of the inner ear, and together with the cochlea (hearing organ) form the labyrinth. The vestibular organ is situated in the vestibular part of the labyrinth, the vestibular labyrinth, and contains five sensors: three semicircular canals, which detect mainly angular accelerations, and two otolith organs, which detect mainly linear accelerations, head tilt and (although less sensitive) angular accelerations. The brain calculates head velocity in 3D and head tilts based upon the output of the 10 accelerometers situated in the two balance organs. The vestibular organs are crucial to facilitate gaze stabilization, balance and spatial orientation. Unfortunately, due to different etiologies, their function can decrease, resulting in vestibular hypofunction. Especially in the case of bilateral vestibulopathy (a severe bilateral hypofunction of both vestibular organs), patients often complain of imbalance worsening in darkness or uneven ground, and oscillopsia (the illusory movement of the environment). This latter occurs due to failing gaze stabilization mechanisms. These symptoms results in worse health and a higher risk of falling. Unfortunately, a vestibular hypofunction is difficult to treat. *It is therefore crucial that suited therapeutic options are being developed, especially since vestibular hypofunction happens much more often than previously expected: more than 1% of the population, and more than 32% of the elderly with complaints of dizziness*.

**3. Tasks**

* To get a deep insight of the function of the healthy vestibular system, from a physics and physiological point of view and to describe how the vestibular system works together with vison and somatosensis
* To describe the most commonly used laboratory examinations with a focus on how to perform and analyze them
* To perform experiments using a specifically developed balance belt aimed at reducing imbalance incorporating 300 Hz haptic feedback
* To perform a computational anatomy driven approach based on 3D-reconstructed CT-images of the human semicircular canals, to statistically achieve the most precise electrode placement and optimal number and position of electrical contacts per electrode
* To perform experiments in bilateral vestibulopathy patients using motion-modulated amplitude electrical stimulation by a vestibular implant
* To investigate whether electro-conductivity of the vestibular labyrinth allows electrical stimulation of a semi-circular canal to directly stimulate the nearby inferior vestibular nerve

**4. General aim**

This thesis focuses on the biophysical aspects of the development of the vestibular prosthesis for patients with severe loss of vestibular function.

**5. Propositions for defence**

* Biophysical analysis showed that a simple 3D gyroscope, replacing the complex human vestibular labyrinth, is able to restore major vestibular functions, using a transfer function based on amplitude modulation
* Computer simulation based on our 3D-reconstructed CT-images of the human semicircular canals, allowed to statistically achieve the most precise electrode placement and optimal number and position of electrical contacts per electrode
* Performed calculations and experiments using a specifically developed balance belt aimed at reducing imbalance, incorporating 12 tactors placed around the waist providing 300 Hz haptic stimulation (4 Hz repetition rate and 30% duty cycle), proved that the transfer function has to be characterized by a gain leading to just suprathreshold stimulation. Tactors need to be activated when trunk inclination exceeds 2.5 degrees relative to the gravity vector and deactivated at a tilt angle of 1.5 degrees (1 degree hysteresis, to prevent oscillations).
* It was shown that electro-conductivity in the vestibular labyrinth is such that electrical stimulation of the semi-circular canal is likely to also directly stimulate the nearby inferior vestibular nerve.

**6. Main results of this thesis and their significance**

**Chapter two** showed that when looking at the vestibular system from a biophysics perspective, its function is different than previously described in literature. Especially otolith function is more differentiated than reported in the past. Due to centrifugational forces, otolith organs are also sensitive to angular accelerations, and work complementary to the semicircular canals during these type of movements.

**Chapter three** illustrated that although high-end vestibular testing is available, still many limitations, challenges and pitfalls are involved in each test. This is especially the case, when tests are not properly performed. Since no worldwide diagnostic standard is available about implementation and interpretation of these tests, consensus should be reached about when and how to perform each test. Only by doing so, a worldwide high standard of laboratory testing can be reached. *This will improve the diagnostic pathway of patients with bilateral vestibulopathy, leading in more patients being able to benefit from new emerging therapeutic options like the vibrotactile belt and the vestibular implant*.

In **Chapter four**, the performed calculations and experiments using a specifically developed balance belt aimed at reducing imbalance, incorporating 12 tactors placed around the waist providing 300 Hz haptic stimulation (4 Hz repetition rate and 30% duty cycle), proved that the transfer function has to be characterized by a gain leading to just suprathreshold stimulation and a hysteresis of 1.5 degree tilt. This vibrotactile belt, which makes use of sensory substitution, can provide a clear benefit in preselected patients beyond the placebo effect. Most patients wanted to keep the belt and use it permanently. *These results show that the balance belt seems to be a promising option to non-invasively improve the functionality of patients with bilateral vestibulopathy*. It would especially be interesting for patients in which vestibular implantation is not (yet) indicated, or as a complementary tool next to the vestibular implant. Meanwhile the device has been redesigned into a lightweight comfortable belt and will be evaluated in multi-center international clinical trials.

**Chapter five** presented that inner ear structures can be visualized with very high detail in 2D and 3D, using a combination of micro-CT scanning (up to 5.5. µm voxel resolution) with OsO4 contrast staining, and specific image processing techniques. *This has provided new insights in the 3D anatomy of especially the neural inner ear structures, which are very relevant when developing electrodes and stimulation strategies for neural prostheses, like the vestibular implant*. These results demonstrated that in case electrodes need to be close to the sensory epithelium, they should be implanted in the ampullae of the semicircular canals, but each with their main contact directed to a different wall of the ampullae.

**Chapter six** showed that a computational anatomy driven approach based on 3D-reconstructed CT-images of the human semicircular canals, allows to statistically achieve the most precise electrode placement and optimal number and position of electrical contacts per electrode. It was demonstrated that when using surgical landmarks and an electrode lead with one contact, less than the initially aimed 95% of all electrodes will successfully reach their intended target within 1 mm. However, when modifying the electrode lead design by incorporating three electrodes per lead, it is more likely each lead will have one electrode contact reaching the intended target. This should still be validated in a “real life setting” using e.g. temporal bones. *Nevertheless, it was obvious that current electrode designs and surgical approaches are not yet fully optimized for reliable semicircular canal implantation*.

Biophysical analysis in **Chapter seven** demonstrated that a simple 3D gyroscope, replacing the complex human vestibular labyrinth, is able to restore major vestibular functions with motion-modulated electrical stimulation in patients with bilateral vestibulopathy. The used stimulus involved a biphasic pulse with a fixed frequency, which was modulated in amplitude around a baseline. A frequency-dependency of the vestibulo-ocular reflex was shown, as present in the “natural” vestibular system. Also, the vestibular-ocular reflex gain increased with increasing modulation strength. *These results imply that the vestibular implant, using a transfer function based on amplitude modulation, can become a clinically useful device in the near future*.

**Chapter eight** illustrated that vestibular evoked myogenic potentials (VEMPS) and postural responses, which are believed to be mainly of otolith origin, can be elicited by electrical semicircular canal stimulation from a vestibular implant. This implies that electro-conductivity in the vestibular labyrinth is such that electrical stimulation of the semi-circular canal is likely to also directly stimulate the nearby inferior vestibular nerve. cVEMPs were successfully evoked in five out of eight patients and the amplitudes of the N-P complex varied from 44 to 120 μV, similar to air conduction VEMPs in normal subjects. Latency of electrically elicited cVEMPs were shorter than expected in normal controls: N waves: 9.71(± 1.17) ms; P waves: 17.24 ms (± 1.74), instead of around 13 ms and 23 ms respectively. This might probably reflect the shorter stimulus pathway, since the electrodes are closer to the otolith organs than an air conduction stimulus. Furthermore, consistent whole-body postural responses were obtained by rapid changes in “baseline” (constant rate and amplitude) electrical stimulation delivered by the vestibular implant in two out of three tested subjects. The amplitude and direction of body rotations were significantly correlated with the intensity of stimulation and side of delivered stimulus respectively. *These results suggest that electrical stimulation of semicircular canals by a vestibular implant might also be able to improve postural responses in patients with bilateral vestibulopathy.*

**Main publications** (1-7)

1. Kingma H, van de Berg R. Anatomy, physiology, and physics of the peripheral vestibular system. Handb Clin Neurol. 2016;137:1-16.

2. van de Berg R, Rosengren S, Kingma H. Laboratory examinations for the vestibular system. Current opinion in neurology. 2018;31(1):111-6.

3. Kingma H, Felipe L, Gerards MC, Gerits P, Guinand N, Perez-Fornos A, et al. Vibrotactile feedback improves balance and mobility in patients with severe bilateral vestibular loss. Journal of neurology. 2018.

4. van den Boogert T, van Hoof M, Handschuh S, Glueckert R, Guinand N, Guyot JP, et al. Optimization of 3D-Visualization of Micro-Anatomical Structures of the Human Inner Ear in Osmium Tetroxide Contrast Enhanced Micro-CT Scans. Front Neuroanat. 2018;12:41.

5. Seppen BF, van Hoof M, Stultiens JJA, van den Boogert T, Guinand N, Guyot JP, et al. Drafting a Surgical Procedure Using a Computational Anatomy Driven Approach for Precise, Robust, and Safe Vestibular Neuroprosthesis Placement-When One Size Does Not Fit All. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2019;40(5S Suppl 1):S51-S8.

6. Perez Fornos A, Guinand N, van de Berg R, Stokroos R, Micera S, Kingma H, et al. Artificial balance: restoration of the vestibulo-ocular reflex in humans with a prototype vestibular neuroprosthesis. Frontiers in neurology. 2014;5:66.

7. Fornos AP, van de Berg R, Armand S, Cavuscens S, Ranieri M, Cretallaz C, et al. Cervical myogenic potentials and controlled postural responses elicited by a prototype vestibular implant. Journal of neurology. 2019;266(Suppl 1):33-41.