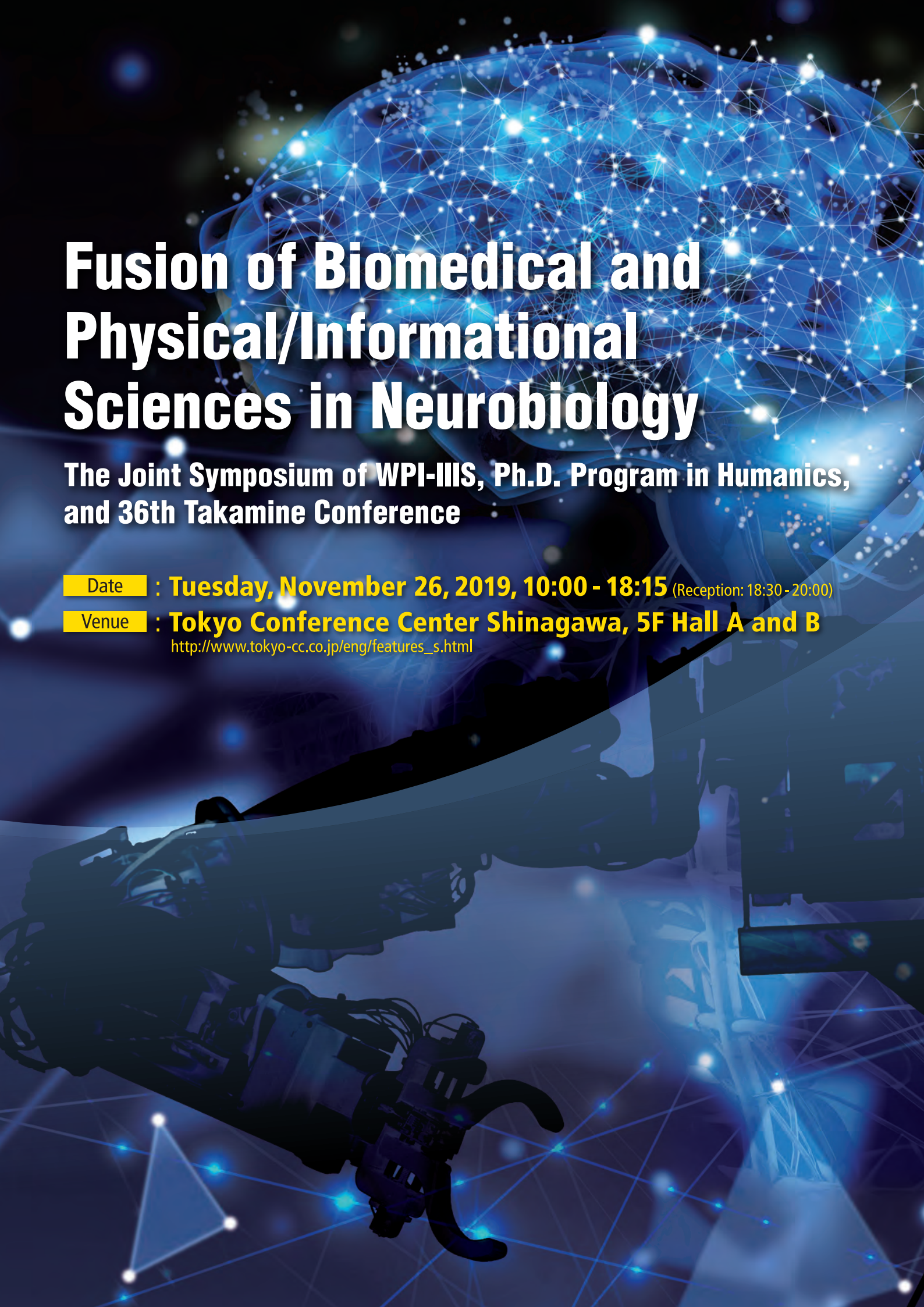

Fusion of Biomedical and Physical/Informational Sciences in Neurobiology

The Joint Symposium of WPI-IIIS, Ph.D. Program in Humanics, and 36th Takamine Conference

Date : **Tuesday, November 26, 2019, 10:00 - 18:15** (Reception: 18:30 - 20:00)

Venue : **Tokyo Conference Center Shinagawa, 5F Hall A and B**
http://www.tokyo-cc.co.jp/eng/features_s.html

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IIIS
INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

wpi

Ph.D.Program in Humanics

筑波大学
University of Tsukuba

公益財団法人 Daiichi Sankyo Foundation of Life Science
第一三共生命科学研究振興財団

Time Table

Opening				
10:00 - 10:15	Welcome	**Masashi Yanagisawa**	Program Coordinator, Ph.D. Program in Humanics/ Director, WPI-IIIS, University of Tsukuba	
	Opening Address 1	**Akira Ukawa**	WPI Program Director	
	Opening Address 2	**Masaaki Takahashi**	Managing Director, Daiichi Sankyo Foundation of Life Science	
Session for WPI-IIIS | Chair: Arisa Hirano (WPI-IIIS, University of Tsukuba)				
10:15 - 10:50	Neural mechanisms for learning from a small sample	**Mitsuo Kawato**	ATR Brain Information Communication Research Laboratory Group	Page 4
10:50 - 11:25	Searching for Neural Correlates of Sleepiness	**Sakiko Honjoh**	WPI-IIIS, University of Tsukuba	Page 5
36th Takamine Conference				
17th Takamine Memorial Daiichi Sankyo Prize Lecture | Chair: Takao Saruta (Keio University)				
11:25 - 12:10	Toward the Mysteries of Sleep	**Masashi Yanagisawa**	WPI-IIIS, University of Tsukuba	Page 6
12:10 - 12:30	Lunch Preparation			
Part 1 | Chair: Masashi Yanagisawa (WPI-IIIS, University of Tsukuba)				
12:30 - 13:05	An engineering approach to pain	**Ben Seymour**	Center for Information and Neural Networks, National Institute of Information and Communications Technology	Page 7
13:05 - 13:40	Function and connectivity of a visual circuit underlying optic flow processing in zebrafish	**Fumi Kubo**	National Institute of Genetics	Page 8
13:40 - 14:10	Tea Break			
Part 2 | Chair: Masashi Yanagisawa (WPI-IIIS, University of Tsukuba)				
14:10 - 14:55	Sleep: A worm's eye view	**Henrik Bringmann**	Philipps University of Marburg	Page 9
14:55 - 15:30	CryoEM analysis of the GPCR neurotensin receptor 1-G protein complex	**Hideaki Kato**	The University of Tokyo	Page 10
15:30 - 15:40	Break			
Poster Session | Chair: Masayuki Matsumoto (University of Tsukuba)				
15:40 - 16:50	Data Blitz and Poster Presentation			
16:50 - 17:05	Photo / Break			
Session for Ph.D. Program in Humanics | Chair: Jun Izawa (University of Tsukuba)				
17:05 - 17:40	Creating Neurological Rehabilitation with Brain-Machine Interfaces	**Junichi Ushiba**	Keio University	Page 11
17:40 - 18:15	Artificial Intelligence and Brain Science	**Kenji Doya**	Okinawa Institute of Science and Technology Graduate University	Page 12
18:15	Closing			
18:30 - 20:00	Reception			

Information

Precautions

1. No outlets are available nearby audience seats
2. No smoking in symposium venues: please smoke at the designated area on each floor
3. Wireless LAN is available in the foyer.

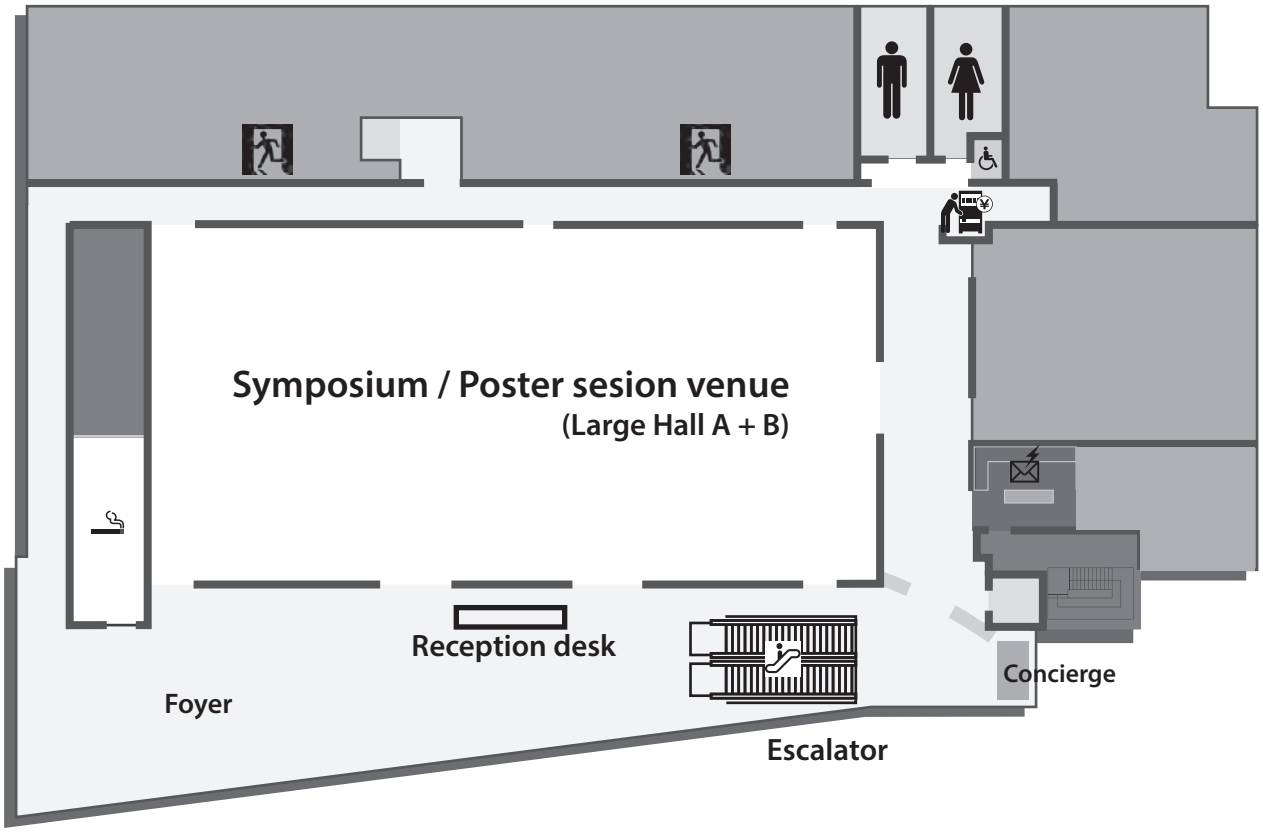
Lunch

Free lunch will be provided for pre-registered participants.

Reception

18:30 - 20:00 at Foyer on 5th floor

Floor Map (5th floor) | Tokyo Conference Center Shinagawa



Neural mechanisms for learning from a small sample

Mitsuo Kawato

ATR Brain Information Communication Research Laboratory Group

ABSTRACT

Deep neural networks have been remarkably useful for image classification. Combined with reinforcement learning algorithms, deep neural networks have outperformed human experts in “Go”. To achieve such successes, millions of images, and tens of millions of games have been utilized as training data sets in the supervised learning or training trials in the reinforcement learning. Meanwhile, in the 2015 DARPA robotics challenge final competition, many humanoid robots fell while walking on sand, going up stairs, turning bulbs, or getting out of a car. A small number of humanoids completed all the tasks, but they were extremely slower than humans. By age 5, human infants are able to execute all of the above tasks more quickly and reliably than humanoid robots developed by world premier researchers. What could be the reasons of this dramatic contrast between success and failure for simulated versus real-world tasks by artificial intelligence? In the simulated video games and “Go”, the degrees of freedom of the controlled system were relatively small, there were no hidden variables, and state transitions were deterministic without noise and perfectly described by simple rules. Thus, the computer simulations were exactly correct without errors. For the final reason, tens of millions of simulated games are generated by software players, and they can be used efficiently for DeepQ learning. In contrast, for a humanoid robot in the real world, many physical processes, including contact and friction, are difficult to model. Thus, a large number of training sample is unavailable. Brains resolve this difficult issue of learning from a small sample. I show a persuasive example of this without genetic prewiring. I propose that synchronization of neural firing, information communication between different areas, and metacognition are useful neural mechanisms for this characteristics.

Session for WPI-IIIS | **10:50 - 11:25**

Searching for neural correlates of sleepiness

Sakiko Honjoh

WPI-IIIS, University of Tsukuba

ABSTRACT

Sleep is a tightly regulated biological process as shown by the fact that humans spend one-third of their lives asleep. As we stay awake longer, a "sleep need" accumulates in the brain and we feel sleepier and sleepier, resulting in a marked decline in our cognitive ability. Since accumulated "sleep need" subsequently promotes deep NREM sleep, slow wave, NREM sleep-specific brain waves are currently the best marker for sleep need. However, the molecular identities of "sleep need" and how it promotes deep NREM sleep remain unclear. Therefore, to better understand the neural mechanisms underlying prolonged, wakefulness-induced sleepiness, we recorded neural activities in multiple brain regions across sleep/wake cycles in freely behaving mice. We quantified firing rates of each neuron, slow wave activity during NREM sleep, and estimated "sleep need" at an individual level based on previous wake/sleep history. Our analyses revealed that thalamic neurons show a consistent switch-like behavior, with the highest and the lowest firing in wake and in NREM sleep, respectively. In contrast, cortical neuron activity was heterogeneous and the cortex possesses a diverse population of wake-active, NREM sleep–active, and REM sleep-active neurons. Not all neurons showed a vigilance state-dependent firing rate and our analyses also revealed that a minor cortical neuron population shows significant correlation between firing rate and estimated sleep need.

Toward the Mysteries of Sleep

Masashi Yanagisawa

WPI-IIIS, University of Tsukuba

ABSTRACT

Although sleep is a ubiquitous behavior in animal species with well-developed central nervous systems, many aspects in the neurobiology of sleep remain mysterious. Our discovery of orexin, a hypothalamic neuropeptide involved in the maintenance of wakefulness, has triggered an intensive research examining the exact role of the orexinergic and other neural pathways in the regulation of sleep/wakefulness. The orexin receptor antagonist suvorexant, which specifically block the endogenous waking system, has been approved as a new drug to treat insomnia. Also, since the sleep disorder narcolepsy-cataplexy is caused by orexin deficiency, orexin receptor agonists are expected to provide mechanistic therapy for narcolepsy; they will likely be also useful for treating excessive sleepiness due to other etiologies.

Despite the fact that the executive neurocircuitry and neurochemistry for sleep/wake switching has been increasingly revealed in recent years, the mechanism for homeostatic regulation of sleep, as well as the neural substrate for "sleepiness" (sleep need), remains unknown. To crack open this black box, we have initiated a large-scale forward genetic screen of sleep/wake phenotype in mice based on true somnographic (EEG/EMG) measurements. We have so far screened >8,000 heterozygous ENU-mutagenized founders and established a number of pedigrees exhibiting heritable and specific sleep/wake abnormalities. By combining linkage analysis and the next-generation whole exome sequencing, we have molecularly identified and verified the causal mutation in several of these pedigrees. Biochemical and neurophysiological analyses of these mutations are underway. Since these dominant mutations cause strong phenotypic traits, we expect that the mutated genes will provide new insights into the elusive pathway regulating sleep/wakefulness. Indeed, through a systematic cross-comparison of the Sleepy mutants and sleep-deprived mice, we have recently found that the cumulative phosphorylation state of a specific set of mostly synaptic proteins may be the molecular substrate of sleep need.

References

1.Funato et al. Forward-genetics analysis of sleep in randomly mutagenized mice. Nature 539: 378-383, 2016
2.Wang et al. Quantitative phosphoproteomic analysis of the molecular substrates of sleep need. Nature, 558: 435–439, 2018

An engineering approach to pain

Ben Seymour

Center for Information and Neural Networks, National Institute of Information and Communications Technology

ABSTRACT

Abstract: Pain is often considered intangibly subjective, and neuroscience theory has so far failed to capture the core essence of pain as a sensory and emotional percept. Since noxious stimulation usually leads to the perception of pain, pain has traditionally been thought of as sensory nociception, but its variability and sensitivity to a broad array of cognitive and motivational factors have led to a common view that it is inherently imprecise and intangibly subjective. However the core function of pain is motivational - to direct both short and long-term behaviour away from harm. Here I will show how an engineering approach allows us to reframe pain in terms of signal processing and control theory, and present a reinforcement learning model of pain. This offers a mechanistic understanding of how the brain supports pain perception and behaviour, illustrating the underlying computational architecture of the pain system in the brain. Importantly, it provides an explanation as to why pain is tuned by multiple factors and necessarily supported by a distributed network of brain regions, and so recasts pain as a precise and objectifiable control signal.

Bio: Ben Seymour is Principal Investigator at the Center for Information and Neural Networks (National institute of Information and Communications Technology) and the Computational and Biological Learning Lab at Cambridge University Department of Engineering. He received his undergraduate degrees in molecular biology and medicine at Manchester University, and PhD in neuroscience at UCL. He does interdisciplinary research at the interface of neuroscience and engineering, focusing on the systems and computational neuroscience of pain and learning, and applied research in clinical neuroengineering.

Function and connectivity of a visual circuit underlying optic flow processing in zebrafish

Fumi Kubo

National Institute of Genetics

ABSTRACT

A wide range of animals use global image motion to actively stabilize their position or gaze by compensatory movements, such as the optomotor or optokinetic responses. In zebrafish, the main visual area that process optic flow information is the pretectum. Previous studies have shown that pretectal neurons distinguish different optic flow patterns, such as rotation and translation, to drive appropriate compensatory behaviors. To elucidate critical neuroanatomical features that underlie this sensorimotor transformation, we have combined functional imaging and morphological reconstruction of single cells. Using a function-guided inducible morphological analysis (FuGIMA) that we developed, we identified a feed forward pretectum-premotor circuit in which “simple” direction selective information is combined to produce “complex” functional responses and transmitted to premotor centers in the hindbrain. Furthermore, using a whole-brain electron microscopy stack of larval zebrafish from which we recorded the responses of pretectal neurons, we are determining the interconnectivity of pretectal neurons made by their direct synaptic connections. These approaches will directly test and refine our circuit model for the binocular optic flow computation in the pretectum.

References:
Kramer A, Wu Y, Baier H, Kubo F. (2019) Neuronal architecture of a visual center that processes optic flow. *Neuron* 103, 118-132.

Kubo F, Hablitzel B, Dal Maschio M, Driever W, Baier H, Arrenberg AB. (2014) Functional architecture of an optic flow responsive area that drives horizontal eye movements in zebrafish. *Neuron* 81, 1344-59.

Sleep: A worm's eye view

Henrik Bringmann

Philipps University of Marburg, Germany

ABSTRACT

Sleep is conserved from jellyfish to humans and can thus be studied in simple model systems. Perhaps the simplest yet molecularly accessible model system that sleeps is C. elegans. How and why does a simple animal such as "the worm" sleep? The answers to this question can shed light on the fundamental reasons for how and why we sleep. We are applying a combination of genetics, functional imaging, optogenetics, and physiological analysis to find out how and why C. elegans sleeps. We showed that C. elegans requires a single sleep-active neuron called RIS to induce sleep. RIS is controlled by upstream circuits that measure and translate wakefulness into sleep. Cellular stress activates RIS through EGFR signaling and through the stress-sensing ALA neuron, thus increasing sleep. Without sleep, larvae show an increased progression of aging phenotypes, that decreases the rate of survival. Thus, sleep in C. elegans is ultimately simplified: It requires a single sleep-active neuron that is controlled by upstream circuits and responds to sleep need. Sleep appears to serve basic functions that include counteracting the progression of aging phenotypes.

CryoEM analysis of the GPCR neurotensin receptor 1-G protein complex

Hideaki Kato

The University of Tokyo

ABSTRACT

G protein-coupled receptor (GPCR) family is one of the largest membrane receptor protein families in human, and they are involved in almost every physiological process. The neurotensin receptor 1 (NTSR1) is a GPCR involved in regulation of blood pressure, body temperature, weight, and response to pain. NTSR1 couples to multiple G-protein subtypes (i.e. Gs, Gi/o, Gq/11, and G12/13), but the molecular details of G-protein activation remain unknown. In this symposium, I will present 3E structures of the human NTSR1 in complex with the heterotrimeric Gi1 protein in two distinct conformations (C and NC state). While the C-state complex is similar to recently reported GPCR-Gi/o complexes, the G protein in the NC state is rotated by ~45 degrees relative to the receptor. NTSR1 in the NC state exhibits features of both active and inactive conformations, suggesting that the structure represents an intermediate along the G-protein activation pathway. This structural information, complemented by molecular dynamics simulations and functional studies, provide insights into the complex process of G-protein activation.

Creating Neurological Rehabilitation with Brain-Machine Interfaces

Junichi Ushiba

Keio University

ABSTRACT

Stroke is a major disease in aging societies. Annually, 5 million people worldwide are left permanently disabled by strokes, placing a burden on family and community. According to WHO, stroke burden DALY is set to increase by 160% between 1990 and 2020. Under such circumstances, how will technology support our lives and livelihood? It had been believed that the brain cannot recover once it sustains a structural stroke injury, but recent treatment aided by advanced technologies with a brain-computer interface (BCI), electrical/magnetic cortical stimulation, and robotics has succeeded in guiding functional reorganization of brains damaged by stroke. After the reorganization, brains gain the neural activity of the spared cortico-spinal-muscular pathways, and reanimates paralyzed limbs. A recent challenge with data-driven approach identifies optimal brain regions of care to maximize therapeutic effects in these treatments. Data-driven approach is also used to select and adopt the most efficient therapeutics for each individual patient. In these senses, computational approaches for describing neural dynamics and recovery process are becoming important to bridge the gaps between fundamental sciences and real-world clinics. Creating computational syntax as a common language will help understanding brain function and neurological rehabilitation entirely. In this talk, I will discuss the present state and the future prospects of technology-aided neurological rehabilitation in an aging society.

Artificial Intelligence and Brain Science

Kenji Doya

Okinawa Institute of Science and Technology Graduate University

ABSTRACT

Human brain functions have long served as the targets of development of artificial intelligent systems. Findings in neuroscience have provided guidance at multiple levels in the designs of machine learning architectures and algorithms. Today's neuroscience, in turn, necessitates applications of artificial intelligence and machine learning algorithms for making sense of huge datasets.
This lecture reviews examples of co-evolution of AI and brain science and consider how they can help each other for further progress.

MEMO

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