東北大学 電気通信研究所

研究室外部評価資料

(2013 年度-2018 年度)

Activity Report of Research Laboratory for External Review

April 2013 - March 2019
(FY.2013-2018)

Research Institute of Electrical Communication

Tohoku University

ナノ・バイオ融合分子デバイス研究室

Nano-Bio Hybrid Molecular Devices

A. 研究室名 / Research Laboratory

ナノ・バイオ融合分子デバイス研究室
Nano-Bio Hybrid Molecular Devices

B. 構成員 / Faculty and Research Staff (as of May 1, 2019)

教授 / Professor

氏名 Name	平野　愛弓 Ayumi Hirano-Iwata (RIEC: October 2016-, Tohoku Univ.: October 2006-)
分野名 Research Field	ナノ・バイオ融合分子デバイス研究分野 Nano-Bio Hybrid Molecular Devices

助教 / Assistant Professor

氏名 / Name	山本　英明 / Hideaki Yamamoto (Tohoku Univ.: April 2014-) 馬 騰 / Teng Ma (RIEC: October 2013-March 2017, Tohoku Univ.: October 2013-) 但木　大介 / Daisuke Tadaki (RIEC: April 2017-, Tohoku Univ.: April 2015-) 小宮　麻希 / Maki Komiya (RIEC: April 2018-)

他 / Others

	日本学術振興会特別研究員 PD: 1 名 (2016 - 2018) 日本学術振興会特別研究員 DC: 2 名 (DC1: 2015 – 2017) (DC2: 2017 – 2018) 受託研究員: 1 名 (2017-)

C. 研究目的 / Research Purpose

本研究室では，バイオ素子の持つ高度な機能をナノテクノロジーと融合することにより新しい電子デバイスの開発を行っている。具体的には、人工的に構築した細胞膜構造をベースに新薬候補化合物などの高効率スクリーニング法として応用した研究や、基板加工技術を用いた、生きた神経細胞を原理的素子とした脳のモデル系の創成を目指す研究を進めている。さらに、有機・バイオ材料を用いた新機構を有するデバイスの作製や、その動作機構の評価を通して従来の半導体材料のみに依存しない、新規な電子デバイスの創製を目指している。

Our research group is working on development of novel devices based on the combination of nanotechnology and biomaterials that have highly sophisticated functions. In particular, we are aiming to reconstitute artificial cell membrane structures as a platform for high-throughput screening of new drug candidates, and also aiming to construct a brain model system by utilizing living neuronal cells as fundamental elements, using fabrication technology. In addition, we are developing bio and organic devices with novel functions. Through the evaluation of their working principles, we are aiming to create novel electronic devices that do not solely rely on conventional semiconductor materials.

D. 主な研究テーマ / Research Topics

1. 人工細胞膜に基づくデバイスの開発と応用に関する研究
2. ナノ構造体の構築とバイオセンサ応用に関する研究
3. 培養神経細胞を用いた人工神経回路網に関する研究
4. 生体分子・神経回路網のモデリングに関する研究
5. 二次元バイオ材料に基づく電子・イオンデバイスの創成に関する研究
6. 有機トランジスタを用いたフレキシブルデバイスに関する研究

1. Development of artificial cell membrane sensors and their medical applications
2. Fabrication of nanostructures and their biosensor applications
3. Construction of artificial neuronal networks based on cultured neurons
4. Modelling of biosystems and neuronal circuits
5. Construction of electronic and ionic devices based on biological two-dimensional materials
6. Development of flexible devices using organic transistors

E. 学術論文等の編数 / The Number of Research Papers

	2013	2014	2015	2016	2017	2018	Total
(1) 査読付学術論文 Refereed journal papers	2	2	4	9	11	13	41
(2) 原著論文と同等に扱う 査読付国際会議発表論文 Full papers in refereed conference proceedings equivalent to journal papers				1	2		3
(3) 査読付国際会議 Papers in refereed conference proceedings	2		1	3	1	5	12
(4) 査読なし国際会議・シンポジウム等 Papers in conference proceedings	15	10	5	14	23	51	118
(5) 総説・解説 Review articles		1	2	1		2	6
(6) 査読付国内会議 Refereed proceedings in domestic conferences							
(7) 査読なし国内研究会・講演会 Proceedings in domestic conferences	3	4	28	22	36	53	146
(8) 著書 Books				1			1
(9) 特許 Patents				1	2	1	4
(10) 招待講演 Invited Talks		7	9	4	13	10	43

F. 特筆すべき研究成果 / Significant Research Achievements (FY.2013-2018)

See Ref. 1. "#" mark indicates research carried out at a former organization.

2013-2018 年度の研究成果（論文・特許など）のうち，前半（2013-2015 年度）と後半（2016-2018 年度）それぞれで代表的な数件（2-3 件程度ずつ）について，参考資料を引用して，その特徴と学術的意義などを簡単に紹介する．英文のみ，もしくは和文と英文で記載．
要約は 300 字程度．論文誌の要約/Abstract のコピー可．学術面での国際的インパクトならびに社会的影響を 100 字程度で記載．
必ずしも当該期間内に発表・出版したものに限るのではなく，例えば過去に発表したものでもこの期間内に成果が得られたり，評価されるようになったりしたものも含むものとする．
インパクトファクターや被引用件数など，できる限り第三者が定量的に評価できる指標を用いてアピールすること．それらの指標にはそぐわない場合には，その事情とそれに変わる適当な評価指標・尺度を示すこと．

[2013-2015]

1. A. Hirano-Iwata, K. Aoto, A. Oshima, T. Taira, R. Yamaguchi, Y. Kimura, and M. Niwano, "Free-standing lipid bilayers in silicon chips−Membrane stabilization based on microfabricated apertures with a nanometer-scale smoothness", Langmuir, 26, 1949-1952 (2010). #, [IF: 3.683], [Times Cited: 71]

Abstract: In the present study, we propose a method for preparing stable free-standing bilayer lipid membranes (BLMs). The BLMs were prepared in a microfabricated aperture with a smoothly tapered edge, which was prepared in a nanometer-thick Si_3N_4 septum by the wet etching method. Owing to this structure, the stress on lipid bilayers at the contact with the septum was minimized, leading to remarkable membrane stability. The BLMs were not broken by applying a constant voltage of ±1 V. The membrane lifetime was 15−45 h with and without an incorporated gramicidin channel. Gramicidin single-channel currents were recorded from the same BLM preparation when the aqueous solutions surrounding the BLM were repeatedly exchanged, demonstrating the tolerance of the present BLM to repetitive solution exchanges. Such stable membranes enable analysis of channel functions under various solution conditions from the same BLM, which will open up a variety of applications including a high throughput drug screening for ion channels.

International impact on both academic and social aspects: This work demonstrated that stable artificial cell membranes were formed on microfabricated apertures with a smoothly tapered edge. Such membranes provide a novel drug-screening platform for membrane proteins. This study received considerable attention and citations since 2013.

人工細胞膜系の課題であった脆弱性の問題を，膜形成場となる微細孔の縁部ナノ形状制御という独自のアプローチで解決した．2010 年発表の論文であるが，2013 年以降に特に注目されるようになり，第一著者の平野は 2013 年 3 月終了の JST-さきがけ研究の事後評価で「見事な成果」と高い評価を受けた．

2. A. Oshima, A. Hirano-Iwata, H. Mozumi, Y. Ishinari, Y. Kimura, and M. Niwano, "Reconstitution of human ether-a-go-go-related gene channels in microfabricated silicon chips", Anal. Chem., 85, 4363-4369 (2013). #, [IF: 6.35], [Times Cited: 38]

Abstract: This paper reports on the reconstitution of human ether-a-go-go-related gene (hERG) channels in artificial bilayer lipid membranes (BLMs) formed in microapertures fabricated in silicon chips. The hERG channel is a cardiac potassium channel whose relation to arrhythmic side effects following drug treatment is well recognized. The hERG channels were isolated from Chinese hamster ovary cell lines expressing the channels and incorporated into the BLMs formed by a process in which the two lipid monolayers were folded into the apertures. The characteristic features of hERG channels reported by the patch-clamp method, including single-channel conductance, voltage dependence, sensitivity to typical drugs and dependence on the potassium concentration, were

investigated in the BLM reconstitution system. The BLM with hERG channels incorporated exhibited a lifetime of ~65 h and a tolerance to repetitive solution exchanges. Such stable BLMs containing biological channels have the potential for use in a variety of applications, including high-throughput drug screening for various ion-channel proteins.

International impact on both academic and social aspects: This work combined the stable artificial cell membrane system and hERG channel proteins, whose relation to arrhythmic drug side effects is well recognized. The high stability of the membranes enabled blocker assay for the hERG channels, which demonstrates the potentiality of the present system as a high-throughput drug screening for various ion-channel proteins.

上述 1 の論文で安定化した人工細胞膜系と, 薬物副作用の問題で注目を集める心筋のイオンチャネルを融合し, 薬物副作用センサを構築した. 論文1と合わせて, この研究の発展性が評価され, 責任著者の平野は 2014 年度の JST-CREST 研究に採択された.

3. T. Ma, M. Cagnoni, D. Tadaki, A. Hirano-Iwata, M. Niwano, "Annealing-induced chemical and structural changes in tri-iodide and mixed-halide organometal perovskite layers", J. Mater. Chem. A, 3, 14195-14201 (2015). #, [IF: 10.733], [Times Cited: 20]

Abstract: The annealing process is crucial for obtaining high-quality perovskite layers used in highly efficient planar perovskite solar cells. In this study, we have investigated the annealing-induced chemical and structural changes of tri-iodide (TI) and mixed-halide (MH) organometal perovskite layers using infrared absorption spectroscopy, scanning electron microscopy and X-ray diffraction measurements. For TI layers, the solvent molecules, dimethylformamide (DMF), remained in the form of the PbI_2/DMF compound after drying at room temperature. During annealing, the DMF evaporated to form PbI_2 crystals. When the MH perovskite film was annealed, both $CH_3NH_3PbCl_3$ and $CH_3NH_3PbI_3$ crystals were initially formed from an amorphous phase. With further annealing, the $CH_3NH_3PbI_3$ crystals gradually grew through the incorporation of source materials supplied from the $CH_3NH_3PbCl_3$ crystals and the amorphous phase and the slow evaporation of methylammonium (MA) and chloride ions. The resultant MH perovskite layer after annealing was mainly composed of large $CH_3NH_3PbI_3$ grains with a trace of chloride ions. We suggest that the difference in composition and structure leads to different charge transport properties of the TI and MH perovskite layers.

International impact on both academic and social aspects: This work unveiled structural and chemical changes during the annealing process of perovskite crystals. It provided valuable insights into the crystal formation process and clear guidelines for further research on high-performance perovskite devices. This paper was selected as a 2015 hot paper in J. Mater. Chem. A.

本論文では, 高品質のペロブスカイト結晶を得るアニーリング工程の機構を明らかにし, 高性能ペロブスカイト太陽電池を作製するための指針を導いた. 論文発表直後から高い注目を集め, J. Mater. Chem. A 誌の 2015 年 Hot paper に選出された.

[2016-2018]

1. H. Yamamoto, S. Kubota, Y. Chida, M. Morita, S. Moriya, H. Akima, S. Sato, A. Hirano-Iwata, T. Tanii, M. Niwano, "Size-dependent regulation of synchronized activity in living neuronal networks", Physical Review E 94, 012407 (2016). #, [IF: 2.284], [Times Cited: 10]

Abstract: This paper studied the effect of network size on synchronized activity in living neuronal networks. Using micropatterned surfaces to extrinsically control the size of neuronal networks, the paper showed that synchronized activity can emerge in a network as small as 12 cells. Furthermore, a detailed comparison of small (~20 cells), medium (~100 cells), and large (~400 cells) networks revealed that synchronized activity becomes destabilized in the small networks.

International impact on both academic and social aspects: Spontaneous neural activity plays a critical role in cortical information processing. Present work constructively clarified a fundamental aspect of the structural basis behind this phenomenon.

脳内の情報処理において重要な自発的神経活動について, 神経回路の構造を人工的に制御する構成論的アプローチに基づいて調べ, 回路構造と活動パターンとの関連性を明らかにした. この論文を含む培養神経細胞系の一連の論文が評価され, 第一著者の山本助教が 2018 年度の JST さきがけに採択された.

2. D. Tadaki, D. Yamaura, S. Araki, M. Yoshida, K. Arata, T. Ohori, K. Ishibashi, M. Kato, T. Ma, R. Miyata, Y. Tozawa, H. Yamamoto, M. Niwano, A. Hirano-Iwata, "Mechanically stable solvent-free lipid bilayers in nano- and micro-tapered apertures for reconstruction of cell-free synthesized hERG channels", Sci. Rep., Vol. 7, pp. 17736, 2017. [IF: 4.122], [Times Cited: 10]

Abstract: The self-assembled bilayer lipid membrane (BLM) is the basic component of the cell membrane. The reconstitution of ion channel proteins in artificially formed BLMs represents a well-defined system for the functional analysis of ion channels and screening the effects of drugs that act on them. However, because BLMs are unstable, this limits the experimental throughput of BLM reconstitution systems. Here we report on the formation of mechanically stable solvent-free BLMs in microfabricated apertures with defined nano- and micro-tapered edge structures. The role of such nano- and micro-tapered structures on the stability of the BLMs was also investigated. Finally, this BLM system was combined with a cell-free synthesized human ether-a-go-go-related gene channel, a cardiac potassium channel whose relation to arrhythmic side effects following drug treatment is well recognized. Such stable BLMs as these, when combined with a cell-free system, represent a potential platform for screening the effects of drugs that act on various ion-channel genotypes.

International impact on both academic and social aspects: This paper demonstrated a successful combination of the stable cell membranes with a cell-free protein synthesis system. Extending this approach to various channel genotypes has the potential to serve as a new screening platform for assessing the potential risks of drug side effects acting on ion channels of patients.

安定化人工細胞膜を無細胞タンパク質合成系と組み合わせることにより，未来の個別化医療のための薬物副作用センサの基礎を構築した．この論文と人工細胞膜の一連の業績が評価され，責任著者の平野は 2018 年より Scientific Reports 誌の Editorial Board に就任した.

3. H. Yamamoto, S. Moriya, K. Ide, T. Hayakawa, H. Akima, S. Sato, S. Kubota, T. Tanii, M. Niwano, S. Teller, J. Soriano, and A. Hirano-Iwata, “Impact of modular organization on dynamical richness in cortical networks,” Science Advances 4, eaau4914 (2018). [IF: 12.804], [Times Cited: 3]

Abstract: As in many naturally formed networks, the brain exhibits an inherent modular architecture that is the basis of its rich operability, robustness, and integration-segregation capacity. However, the mechanisms that allow spatially segregated neuronal assemblies to swiftly change from localized to global activity remain unclear. Here,

we integrated microfabrication technology with in vitro cortical networks to investigate the dynamical repertoire and functional traits of four interconnected neuronal modules. We showed that the coupling among modules is central. The highest dynamical richness of the network emerges at a critical connectivity at the verge of physical disconnection. Stronger coupling leads to a persistently coherent activity among the modules, while weaker coupling precipitates the activity to be localized solely within the modules.

International impact on both academic and social aspects: The work revealed that the advent of coherence is mediated by a trade-off between connectivity and subquorum firing, a mechanism flexible enough to allow for the coexistence of both segregated and integrated activities. Our results unveil a new functional advantage of modular organization in complex networks of nonlinear units.

本論文では, 脳のような複雑なネットワーク系におけるモジュラー構造の機能的優位性を明らかにした. 2018 年 11 月 14 日発表の論文であるが, 翌日にスペインの新聞紙において紹介されるなど発表直後から高い注目を集め, 2019 年 8 月 1 日現在で既に 5 回引用されている.

G. 特筆すべき活動 / Significant Activities (FY.2013-2018)

See Ref. 2-9. "#" mark indicates research carried out at a former organization.

研究室外部評価参考資料の 2 以降を参照しながら，2013-2018 年度のなどの活動の中から特筆すべきものを取り出し，前半（2013-2015 年度）と後半（2016-2018 年度）に分けて簡単に紹介する．英文のみ，もしくは和文と英文で記載.

[2013-2015] (Hirano-Iwata)

Activities in academic societies

・The Surface Science Society of Japan, Division of Soft-Nanotechnology, Vice President (FY. 2013-2016).

・2014 ISSS-7 (The 7th International Symposium on Surface Science), Vice chair of Program committee. #

・The Japan Society for Analytical Chemistry, Tohoku Branch, Committee (Since 2007).

・日本表面科学会ソフトナノテクノロジー研究部会　副部会長（2013−2016 年度).

・日本表面科学会 2014 年 国際会議 ISSS-7, プログラム委員副委員長. #

・日本分析化学会東北支部在仙常任幹事（2007 年以降).

Contributions to society

・Research Area Advisor for JST-PRESTO and JST-CREST "Hyper-nano-space design" (Since 2013).

・Visiting lectures to high school: Aizu Hakuho High School (2013) #, Joshigakuin Senior High School (2013) #.

・Tohoku University, Science Cafe. "Microfabricated Si chips for detecting drug side effects" (2016). #

・JST さきがけ, CREST 領域アドバイザ,「超空間制御と革新的機能創成」領域（2013 年より).

・出前授業:福島県立会津学鳳高等学校（2013 年度) #, 私立女子学院高等学校（2013 年度) #.

・東北大学サイエンスカフェ「薬の副作用を見つける半導体チップ」(2016 年). #

Research Funding

・The Asahi Glass Foundation, Continuation Grants for Outstanding Projects, granted FY. 2013-2015, total ¥14,000,000. (Principal Investigator). #

旭硝子財団ステップアップ助成「人工脂質二分子膜に基づく hERG チャネルアレイの構築と high throughput 副作用評価チップへの応用」, 2013−2015 年度, 14,000 千円（研究代表者）.

Awards

・2014 Award for Tohoku Researchers in Analytical Chemistry (March, 2015). #

・2015 RIEC Award for Tohoku University Researchers (November, 2015) . #

・2015 Minoru Ishida Award (November, 2015) . #

・2014 年度東北分析化学賞受賞（2015 年 3 月). #

・平成 27 年度 RIEC Award 東北大学研究者賞受賞（2015 年 11 月) . #

・平成 27 年度石田實記念財団研究奨励賞受賞（2015 年 11 月) . #

[2016-2018]

Activities in academic societies (Hirano-Iwata)

・Editorial Board of Scientific Reports (Since 2018).

・The Japan Society of Vacuum and Surface Science, Division of Soft-Nanotechnology, President (Since FY. 2017).

・The Japan Society of Applied Physics, Division of Molecular Electronics and Bioelectronics (JSAP-M&BE), executive committee (FY. 2017-2018).

・Scientific Reports 誌 Editorial Board (2018 年より).

・日本表面真空学会ソフトナノテクノロジー研究部会　部会長（2017 年度より).

・応用物理学会 有機分子・バイオエレクトロニクス分科会(M&BE) 常任幹事（2017−2018 年度).

Contributions to society (Hirano-Iwata)

・Ministry of Internal Affairs and Communications, JAPAN
Information and Communications Council Committee, and Information and Communication Technology Committee (Since 2017).

・Visiting lectures to high school, Yamagata Nishi High School (2016), #, Utsunomiya Girl's High School (2019).

・Organizing Public Lecture of JSAP-M&BE, "The Future Brought by AI×Advanced Sensors" (2018).

・総務省情報通信審議会委員 および 同情報通信技術分科会委員（2017 年より).

・出前授業: 山形西高等学校（2016 年度）#, 宇都宮女子高等学校（2018 年度）.

・応用物理学会 M&BE 部会常任幹事として市民講座の開催「AI×最先端センサーがもたらす未来」（2018 年).

Research Funding (Hirano-Iwata and Yamamoto)

・Hirano-Iwata: JST-CREST, granted FY. 2014-2019, total ¥293,730,000. (Principal Investigator).
"Construction of ion and electron nano-channels in super-resistive lipid bilayers"

・Hirano-Iwata: Scientific Research (B), granted FY. 2015-2017, total ¥13,400,000. (Principal Investigator).
"Expression of an artifical action potential and its application to biosensors for drug side effects"

・Yamamoto: JST-PRESTO, granted FY. 2018-2021, total ¥39,500,000. (Principal Investigator).
"Artificial reconstruction of a bionic information processing system"

・Tadaki: JST-A-STEP, granted FY. 2018-2019, total ¥2,308,000. (Principal Investigator).
"Array chips containing microapertures as a high-throughput screening for drug side effects"

・平野: JST-CREST, 2014-2019 年度, 293,730 千円（研究代表者).
"二次元機能性原子・分子薄膜の創製と利用に資する基盤技術の創出"

・平野: 科研費基盤研究(B), 2015-2017 年度, 13,400 千円（研究代表者).
"チャネル包埋脂質二分子膜に基づく人工活動電位の発現と薬物副作用評価チップへの応用"

・山本: JST-さきがけ, 2018-2021 年度, 39,500 千円（研究代表者).
"バイオニック情報処理システムの人工再構成"

・但木: JST-A-STEP, 2018-2019 年度, 2,308 千円.（研究代表者).
"高効率薬物副作用評価のための微細孔アレイ型チップの開発"

Awards (Yamamoto)

・Tokin Foundation, Research Award for Young Scientist (March, 2017).

・Aoba Foundation for the Promotion of Engineering, 23rd Research Award for Young Scientist (December, 2017).

・山本:トーキン財団奨励賞受賞（2017 年 3 月）.

・山本:第 23 回青葉工学研究奨励賞受賞（2017 年 12 月）.

International Joint Research

・Prof. Jordi Soriano, Universitat de Barcelona, Spain (Since 2015)

・Prof. Theoden I. Netoff, Universidad of Minnesota, USA (Since 2016)

・Prof. Bernhard Wolfrum, Technische Universität München, Germany (Since 2017)

Research Supervision (Hirano-Iwata)

・"Advanced Graduate Program for AI Electronics" was adopted as a WISE Program (Doctoral Program for World-leading Innovative & Smart Education), MEXT, Japan. Hirano-Iwata joins as a core-member of this program.

・文部科学省卓越大学院プログラムに「人工知能エレクトロニクス」プログラムが採択された. 平野は, このプログラムにコアメンバーとして参画している.