nature portfolio

Peer Review File

An ultrasensitive multimodal intracranial pressure biotelemetric system enabled by exceptional point and iontronics

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The manuscript proposed a new intracranial pressure (ICP) sensor that amplified by new technologies including iontronic pressure transducer and exceptional-point (EP) wireless system. The new sensor demonstrated several advantages such as high sensitivity and high resolution. The results were well presented and could be interest to the audience of Nat Commun. I have following questions.

1. Recent studies pointed out that the sensitivity at the EP cannot be enhanced because of the noise at the EP. How much is the sensitivity enhanced? Why the sensitivity can be enhanced in this study? Noise analysis is needed.
2. For an EP circuit with bifurcation effect, the resonance splits and one resonance shifts to a higher frequency and the other one lower. However, as shown in this study (such as Fig. 2c, 4b, et.), the two resonant frequencies shifted to the same direction, and no bifurcation effect cannot be observed. These results are conflicting.
3. The bifurcated frequencies are in the strong coupling regime of parity-time symmetric circuit. However, the high-coupling condition is challenging in the ICP sensor because of the presence of tissue and skull, especially for large animal model and human. How this problem is solved?
4. The heartbeat signal in Fig. 5g are not in well agreement with ECG signals. Seems the fluctuations of resonant frequency are noise. More plots are needed to validate the heartbeat signals.
5. The quality factor defined In theoretical analysis (Line 101) is confusing. Given this definition, the quality factors should be fixed after the circuit's design. Why the quality factors in Fig. 2c are changing?
6. Typo in Line 213, 116. Typo in Line 232, no "quality factors". Typo in Line 235, no "dashed lines".
7. Some important references are missing, including already reported EP biosensors (Dong et al., Nat Electron 2, 335-342 (2019); Li et al., Phy Rev Lett 130, 227201 (2023)) and very recent EP sensors in other fields (Kim et al., eLight 4, 6 (2024); Lee et al., eLight 3, 20 (2023)).

Reviewer #2

(Remarks to the Author)
The noteworthy results from this work can be summarized as follows:
1. Proposed System: Introduction of an exceptional point (EP)-based biotelemetric system for continuous and real-time wireless intracranial pressure (ICP) monitoring using an iontronic capacitive pressure transducer.
2. Enhanced Performance: The system leverages EP degeneracy combined with a highly sensitive iontronic transducer, leading to significant improvements in reliability, resolution, and sensitivity.
3. Sensitivity: Achieved a maximum relative sensitivity of 115.95 kHz/mmHg, which is nearly an order of magnitude higher than current ICP sensing systems.
4. Accuracy: Capable of detecting pressure variations as small as one-thousandth of a millimeter of mercury, greatly surpassing the accuracy of commercial ICP sensors.
5. Validation: In-vivo experiments conducted on a rabbit model validated the practical efficacy of the system, showing its superior sensitivity compared to traditional ICP probes.
6. Multi-modal Detection: The system can accurately identify various degrees of pressure signals and perform multi-modal

detection, including minute ICP fluctuations caused by physiological processes such as respiration and cardiac activity.
7. Comprehensive Monitoring: The system not only monitors ICP but also concurrently tracks respiratory and heart rates, simplifying clinical procedures and enhancing clinical utility by providing a comprehensive monitoring solution in a single device.
8. Healthcare Applications: The integration of this biotelemetry system into bio-implantation practices holds significant promise for healthcare applications, particularly in continuous monitoring of vital signs, potentially transforming patient care and monitoring practices.

Will the work be of significance to the field and related fields? How does it compare to the established literature? If the work is not original, please provide relevant references.
Yes, this work is likely to be significant to the field of biomedical engineering and related fields, particularly in the areas of biotelemetry, intracranial pressure (ICP) monitoring, and patient care technology. Here's how it compares to the established literature and its potential impact:

Significance to the Field:
1. Advancement in ICP Monitoring:
Higher Sensitivity and Accuracy: The proposed system's maximum relative sensitivity of 115.95 kHz/mmHg and the ability to detect pressure variations as small as one-thousandth of a millimeter of mercury are notable advancements over existing ICP monitoring technologies. This could significantly improve patient outcomes by enabling more precise and early detection of abnormal ICP levels.
Wireless Biotelemetry: The continuous and real-time wireless monitoring capability represents a substantial improvement in patient comfort and mobility compared to traditional wired systems.
2. Multi-modal Detection:
The ability to monitor not only ICP but also respiratory and cardiac activity in a single device simplifies clinical procedures and provides a more comprehensive picture of the patient's physiological state, which could be particularly valuable in intensive care settings.
3. Potential Healthcare Applications:
The integration of this system into bio-implantation practices could transform patient care by enabling continuous, real-time monitoring of vital signs, potentially reducing the need for invasive procedures and frequent hospital visits.
Comparison to Established Literature:
1. Current Sensing Systems:
Traditional ICP monitoring systems, such as ventricular catheters and fiber optic transducers, typically have lower sensitivity and resolution compared to the proposed EP-based system. These systems often require invasive procedures and are less capable of detecting minute pressure fluctuations.
2. Wireless and Telemetric Systems:
While there have been advancements in wireless ICP monitoring, such as the use of telemetric sensors, these systems generally do not achieve the same level of sensitivity and resolution as reported in this work.

Originality and Novelty:
The work appears to be original in its application of EP degeneracy with an iontronic capacitive pressure transducer for ICP monitoring, achieving unprecedented sensitivity and accuracy levels. The integration of multi-modal detection capabilities within a single wireless biotelemetric system also represents a novel advancement over current technologies.
Conclusion:
Given the enhancements in sensitivity, accuracy, and the added functionality of concurrent monitoring of respiratory and cardiac activity, this work has the potential to make a significant impact on the field of ICP monitoring and broader healthcare applications. It addresses several limitations of current technologies and introduces innovative solutions that could improve patient care and monitoring practices.

Major concerns:
Within the literature regarding ICP and ICC (intracerebral compliance) there are new advanced system that was not considered and compared with this data regarding the present manuscript. The authors should provide additional literature regarding ICP measurements using Brain4care system, particularly, the robust publications as following:

https://brain4.care/en/home-english/

95
• Article | Characterization of intracranial compliance in healthy subjects using a noninvasive method - results from a multicenter prospective observational study
Gabriela Nagai Ocamoto, Lucas Normando da Silva, Camila da Silva Rocha Tomaz, Matheus Toshio Hisatugu, Gustavo Frigieri, Danilo Cardim, Roberta Lins Gonçalves, Thiago Luiz Russo, Robson Luis Oliveira de Amorim.
DOI: https://doi.org/10.1007/s10877-024-01191-w

94
• Article | Effects of moderate sedation induced by propofol or midazolam on intracranial pressure
Bianca Drewnowski, José Carlos Rebuglio Vellosa, Rafael Nastas Acras, Fábio André dos Santos.
DOI: https://doi.org/10.7322/abcshs.2022098.2164

93
• Article | Methodology for non-invasive monitoring of intracranial pressure waves in dogs with traumatic brain injury using the brain4care® BCMM/2000 monitor
Thyara Weizenmann, Mônica Vicky Bahr Arias.
DOI: https://doi.org/10.35172/rvz.2024.v31.1583

92
• Article | A Comprehensive Perspective on Intracranial Pressure Monitoring and Individualized Management in Neurocritical Care: Results of a Survey with Global Experts
Sérgio Brasil, Daniel Agustín Godoy, Walter Videtta, Andrés Mariano Rubiano, Davi Solla, Fabio Silvio Taccone, Chiara Robba, Frank Rasulo, Marcel Aries, Peter Smielewski, Geert Meyfroidt, Denise Battaglini, Mohammad I. Hirzallah, Robson Amorim, Gisele Sampaio, Fabiano Moulin, Cristian Deana, Edoardo Picetti, Angelos Kolias, Peter Hutchinson, Gregory W. Hawryluk, Marek Czosnyka, Ronney B. Panerai, Lori A. Shutter, Soojin Park, Carla Rynkowski, Jorge Paranhos, Thiago H. S. Silva, Luiz M. S. Malbouisson and Wellingson S. Paiva.
DOI: https://doi.org/10.1007/s12028-024-02008-z

91
• Article | Noninvasive neuromonitoring in acute brain injured patients
Sérgio Brasil, Randall Chesnut, Chiara Robba.
DOI: https://doi.org/10.1007/s00134-024-07406-7

90
• Article | A narrative review on financial challenges and healthcare costs associated with traumatic brain injury in the US
Wander Valentim, Sérgio Brasil, Raphael Bertani.
DOI: https://doi.org/10.1016/j.wneu.2024.03.175

89
• Article | Non-Invasive Study of Intracranial Pressure in Pre- and Post-Chemotherapy Patients for the Treatment of Breast Neoplasia
Lais Daiene Cosmoski, Cristiane Rickli, Danielle Cristyane Kalva Borato, Gustavo Henrique Frigieri, Nicollas Nunes Rabelo, Bruna França Bueno, José Carlos Rebuglio Vellosa .
DOI: https://www.portalnepas.org.br/abcshs/article/view/1971

88
• Case report | Management of shunt dysfunction using noninvasive intracranial pressure waveform monitoring: illustrative case
Raphael Bertani, Caio Perret , Stefan Koester, Paulo Santa Maria, Savio Batista, Sophia de Andrade Cavicchioli, Sany Tomomi de Almeida Rocha Arita, Ruy Monteiro, Gianne Lucchesi, Fernando Augusto Vasconcellos, Matheus Miranda , Wellingson Silva Paiva, Fernando Gomes Pinto.
DOI: https://pubmed.ncbi.nlm.nih.gov/38437677/

87
• Article | Validation of a Non-invasive Method Using Mechanical Extensometer for the Estimation of Intracranial Compliance by Repeated Measures Agreement Analysis
Sanem Pinar Uysal, Hayley G. Williams, Mina Huerta, Nicolas R. Thompson, Catherine E. Hassett
DOI:https://doi.org/10.21203/rs.3.rs-3948331/v1

86
• Case report | Propofol effects over intracranial pressure waveform and cerebral hemodynamics: A case report
Nathália Meneses Neves, Thais Rodrigues Kassahara, Sany Tomomi de Almeida Rocha Arita, Elaine Peixoto, Sérgio Brasil.
DOI: https://doi.org/10.33448/rsd-v13i2.44982

85
• Article | Age as a predictive factor for reduced intracranial compliance in patients with headache
Luiz Gabriel Gonçalves Cherain, Mateus Gonçalves de Sena Barbosa, Ghaspar Gomes de Oliveira Alves Francisco, Luiz Miguel Gonçalves Cherain, Gustavo Frigieri, Nícollas Nunes Rabelo .
DOI: https://doi.org/10.1007/s10877-023-01120-3

84
• Article | ICP wave morphology as a screening test to exclude intracranial hypertension in brain-injured patients: a non-invasive perspective
Fabiano Moulin de Moraes, Sérgio Brasil, Gustavo Frigieri, Chiara Robba, Wellingson Paiva e Gisele Sampaio Silva.
DOI: https://doi.org/10.1007/s10877-023-01120-3

83
• Case report | Astrocytoma Mimicking Herpetic Meningoencephalitis: The Role of Non-Invasive Multimodal Monitoring in Neurointensivism
Uri Adrian Prync Flato, Barbara Cristina de Abreu Pereira, Fernando Alvares Costa, Marcos Cairo Vilela, Gustavo Frigieri,

Nilton José Fernandes Cavalcante, Samantha Longhi Simões de Almeida.
DOI: https://doi.org/10.3390/neurolint15040090

82
• Article | Epidemiological study of pediatric patients with signs and symptoms of intracranial hypertension with non-invasive cerebral compliance
Luana Say, Caroline Mensor Folchini, Guilherme de Rosso Manços, Marinei Campos Ricieri, Fábio de Araújo Motta, Adriano Keijiro Maeda, Simone Carreiro Vieira Karuta.
DOI: https://doi.org/10.33448/rsd-v12i10.43481

81
• Letter | Neuromonitoring-Here, There, and to Every Critically Ill Patient
Juliana Caldas, Sergio Brasil, Rogério Passos.
DOI: 10.1097/CCM.0000000000005926

80
• Article | Intracranial pressure waveform in patients with essential hypertension
Matheus Martins da Costa, Ana Luiza Lima Sousa, Mikaelle Costa Correia, Sayuri Inuzuka, Thiago Oliveira Costa, Priscila Valverde O. Vitorino, Polyana Vulcano de Toledo Piza, Gustavo Frigieri, Antonio Coca, Weimar Kunz Sebba Barroso.
DOI: https://doi.org/10.3389/fcvm.2023.1288080

79
• Article | Non-invasive intracranial pressure waveform analysis in Chiari Malformation type 1: A pilot trial
Eloy Rusafa Neto, Wellingson Silva Paiva, Róger Schimidt Brock, Cintya Yukie Hayashi, Marcia Mitie Nagumo, Maurício Oriente Segurado, Ana Luiza Zaninotto, Róbson Luis Amorim.
DOI: https://doi.org/10.1016/j.wneu.2023.11.067

78
• Article | The influence of hemodialysis on intracranial pressure waveform in patients with chronic kidney disease: an observational study
Mariana Schechtel Koch, Bianca Drewnowski, Cristiane Rickli, Fábio André dos Santos, Gilberto Baroni, José Carlos Rebuglio Vellosa.
DOI: https://doi.org/10.1590/1516-3180.2023.0068.R1.07072023

77
• Article | Multimodal monitoring intracranial pressure by invasive and noninvasive means
Fabiano Moulin de Moraes, Erica Navarro Borba Adissy, Eva Rocha, Felipe Chaves Duarte Barros, Flávio Geraldo Rezende Freitas, Maramelia Miranda, Raul Alberto Valiente, João Brainer Clares de Andrade, Feres Eduardo Aparecido Chaddad-Neto e Gisele Sampaio Silva.
DOI: https://doi.org/10.1038/s41598-023-45834-5

76
• Article | Predicting short-term outcomes in brain-Injured patients: A comprehensive approach with transcranial Doppler and intracranial compliance assessment
Sergio Brasil, Danilo Cardim, Juliana Caldas, Chiara Robba, Fabio Silvio Taccone, Marcelo de-Lima-Oliveira, Márcia Harumy Yoshikawa, Luiz Marcelo Sá Malbouisson, Wellingson Silva Paiva.
DOI: https://doi.org/10.21203/rs.3.rs-3406169/v1

75
• Article | Intracranial pressure changes of cardiac patients that have passed by extracorphorus circulation: A brief literature review
Lais Daiene Cosmoski, Bianca Drewnowski, Bruna França Bueno, Cristiane Rickli, Lisiane Cristine Lopes, Mariana Schechtel Koch, José Carlos Rebuglio Vellosa.
DOI: http://dx.doi.org/10.33448/rsd-v11i15.37512

74
• Editorial | An Unexpected Correlation Between Non-Invasive Intracranial Pressure Waveform Assessment in Hypertensive Patients. Could This Be the Link Between Hypertension and Cerebrovascular Diseases as Well as Cognitive Impairments?
Luciano Brandão Machado, Michele Madeira Brandão, Andre Ferro, Tales Shinji Sawakuchi Minei, Igor José Nogueira Gualberto, Nivaldo Alonso.
DOI: https://doi.org/10.18103/mra.v11i7.2.4166

73
• Experimental | Non-invasive monitoring of intracranial pressure waveforms using Braincare® BCMM 2000 monitor in dogs with myelopathies undergoing myelography
Cardoso GS, Nogueira JF, Arias MVB.
DOI: https://doi.org/10.1590/1678-5150-PVB-7132

72

• Case report | Anesthesia for preoperative non-invasive intracranial pressure measurement in a child with Apert syndrome: a case report
Luciano Brandão Machado, Michele Madeira Brandão, Andre Ferro, Tales Shinji Sawakuchi Minei, Igor José Nogueira Gualberto, Nivaldo Alonso.
DOI: https://doi.org/10.46900/apn.v5i3.190

71
• Article | Comorbities and the occuurence of changes in Intracranial Compliance in elderly
Cristiane Rickli Barbosa, José Carlos Rebuglio Vellosa, Lais Daiene Cosmoski, Mariana Schechtel Koch.
DOI: https://doi.org/10.53660/CLM-1842-23M51

70
• Doing more with less on intracranial pressure monitoring
Daniel A. Godoy, Wellingson S. Paiva. 2023, World Neurosurgery.
DOI: https://doi.org/10.1016/j.wneu.2023.07.055

69
• Article | Analysis of intracranial pressure waveform using a non-invasive method in individuals with craniosynostosis
Michele Madeira Brandão; Cristiano Tonello, Isabella Parizotto; Luciano Brandão Machado; Nivaldo Alonso. 2023, Child´s Nervous System.
DOI: https://doi.org/10.1007/s00381-023-06092-y

68
• Article | The use of noninvasive measurements of intracranial pressure in patients with traumatic brain injury: a narrative review
Luiz Gustavo Guimarães Sacramento, André Vitor Rocha Queiroz, Fernanda de Andrade Dias Leite, Henrique Lacerda Lage Lopes de Oliveira, Thais Yuki Kimura, Rodrigo Moreira Faleiro. 2023, Arquivos de Neuro-Psiquiatria.
DOI: https://doi.org/10.1055/s-0043-1764411

67
• Article | Intracranial compliance and volumetry in patients with traumatic brain injury
Caroline Link, Thomas Markus D´Haese, Gustavo Frigieri, Jose Carlos Rebuglio Vellosa, Leonardo Welling. 2023, Surgical Neurology International.
DOI: 10.25259/SNI_314_2023

66
• Article | A Point-Of-Care Noninvasive Technique For Surrogate ICP Waveforms Application In Neurocritical Care
Sérgio Brasil, Daniel A. Godoy and Gregory W. J. Hawryluk. 2023, Neurocritical Care.
DOI:https://doi.org/10.1007/s12028-023-01786-2

65
• Letter | A new noninvasive method can effectively assess intracranial compliance
Sérgio Brasil e Daniel Agustín Godoy. 2023, Acta Neurochirurgica.
DOI: https://doi.org/10.1007/s00701-023-05644-0

64
• Article | Comparison of Noninvasive Measurements of Intracranial with Tap Test Results in Patients with Idiopathic Normal Pressure Hydrocephalus
Gabriel André da Silva Mendes, Cintya Yukie Hayashi, Gustavo Henrique Frigieri Vilela, Lissa Kido, Manoel Jacobsen Teixeira, Fernando Campos Gomes Pinto. 2023, Neuropsychiatric Disease and Treatment.
DOI: https://doi.org/10.2147/NDT.S402358

63
• Case Report | Noninvasive intracranial pressure involving real-time waveform analysis in a child undergoing general anesthesia: a case report
Gabriela Saba, Thaís Condé, Vinícius Quintão, Gustavo Vilela, Ricardo Carlos, Maria Carmona, 2023, Perioperative Anesthesia Reports.
DOI: http://dx.doi.org/10.4322/par.000223

62
• Article | The intracranial compartmental syndrome: a proposed model for acute brain injury monitoring and management
Daniel Agustín Godoy, Sérgio Brasil, Corrado Iaccarino, Wellingson Paiva, Andres M. Rubiano. 2023, Critical Care.
DOI: 10.1186/s13054-023-04427-4

61
• Case Report | Noninvasive intracranial pressure monitoring throughout brain compliance guiding a ventriculoperitoneal shunt replacement in hydrocephalus—case report
Nelci Zanon, Victor Hugo da Costa Benalia, Thiago Hoesker, Cintya Yukie Hayashi, Gustavo Frigieri, Giselle Coelho. 2023, Child's Nervous System.

DOI: 10.1007/s00381-023-05922-3

60
• Case report | A glimpse into multimodal neuromonitoring in acute liver failure: a case report
Stefano Zorzi, Amanda Ayako Minemura Ordinola, Eduardo Cunha De Souza Lima, Gabriela Martins Teixeira, Michele Salvagno, Elda Diletta Sterchele, Fábio Silvio Taccone.
DOI: http://dx.doi.org/10.1097/MS9.0000000000001519

59
• Article | Qualitative Evaluation of Intracranial Pressure Slopes in Patients Undergoing Brain Death Protocol
Mylena Miki Lopes Ideta, Louise Makarem Oliveira, Daniel Buzaglo Gonçalves, Mylla Christie de Oliveira Paschoalino, Nise Alessandra de Carvalho Sousa, Marcus Vinicius Della Coletta, Wellingson Paiva, Sérgio Brasil and Robson Luís Oliveira de Amorim.
DOI: 10.3390/brainsci13030401

58
• Letter | Application of non-invasive ICP waveform analysis in acute brain injury: Intracranial Compliance Scale
Gustavo Frigieri, Chiara Robba, Fábio Santana Machado, Joao A. Gomes and Sérgio Brasil. 27 January 2023 (27 Janeiro 2023)
DOI: 10.1186/s40635-023-00492-9

57
• Article | Noninvasive intracranial pressure waveforms for estimation of intracranial hypertension and outcome prediction in acute brain injured patients
Brasil, S, et al. 18 Nov. 2022.
DOI: https://doi.org/10.1007/s10877-022-00941-y

56
• Article | Intracranial compliance in type 2 diabetes mellitus and its relationship with the cardiovascular autonomic nervous control
G.A.M. Galdino, et al. Set. 2022
DOI: https://doi.org/10.1590/1414-431X2022e12150

55
• Article | Assessment of Cerebral Autoregulation Using Invasive and Noninvasive Methods of Intracranial Pressure Monitoring
Hassett, C.E., Uysal, S.P., Butler, R. et al. Set. 2022
DOI: doi.org/10.1007/s12028-022-01585-1

54
• Letter | Intracranial pressure pulse morphology: the missing link?
Brasil, S. 29 Ago, 2022
DOI: doi.org/10.1007/s00134-022-06855-2

53
• Article | Noninvasive intracranial pressure in patients with traumatic brain injury
Link C, Botelho AF, Dhaese TM, Frigieri G, Vellosa JCR, Welling LC. 08 Ago. 2022
DOI: doi.org/10.33448/rsd-v11i10.33106

52
• Article | Mechanical Hyperinflation Maneuver and intracranial pressure of critical neurological patients: protocol for a randomized clinical trial
Souza D, Branco MW, Carraro Júnior H, Zocolotti AMD, Takeda SYM, Valderramas S. 13 Jul, 2022
Research Square
Trials

51
• Article | Preliminary assessment of the relationship between blood pressure and intracranial pressure in patients with different stages of chronic kidney disease
Balzer, E.R., Koch, M.S. , Drewnowski, B., Santos, F.A. dos ., Baroni, G., Schuinski , A.F.M. and Vellosa, J.C.R. Jun. 2022.
DOI: doi.org/10.33448/rsd-v11i8.31150.

50
• Case Report | Alteration of intracranial compliance in a patient with chronic kidney disease and T1 diabetes mellitus
Koch, M.S., Drewnowski, B., Balzer, E.R., Baroni, G., Schuinski , A.F.M. and Vellosa, J.C.R. Jun. 2022. DOI: doi.org/10.33448/rsd-v11i8.31153.

49
• Article | Relationship Between Dialysis Quality And Brain Compliance In Patients With End-Stage Renal Disease

Mascarenhas S, Rickli C, Frigieri GH, Vellosa JCR, Schuinski, AFM. May 2022. DOI: doi.org/10.1590/1516-3180.2021.0117.R1.14092021

48
• Case Report | Noninvasive Monitoring Of Intracranial Pressure After Cardiac Surgery
Ayres, C., Vellosa, J. C. R. 10 May, 2022. DOI: doi.org/10.33448/rsd-v11i6.29492

47
• Case Report | Use of non-invasive sensor to assess intracranial compliance in the management of migraine patients
Cherain LGG, Barbosa MGS, Souza RLV et al. 22 April 2022 DOI: doi.org/10.21203/rs.3.rs-1162693/v2

46
• Article | Non-invasive monitoring of intracranial pressure in cardiovascular diseases
Ayres, Claudiane. 2022. Collection: Applied biomedical engineering. DOI: doi.org/10.22533/at.ed.896220604

45
• Article | Preliminary evaluation of a non-invasive device for monitoring intracranial pressure waveforms in dogs
Bahr Arias MV, Conceição RT, Guimarães FC, Cardoso GS, Rocha NLFC. J Small Anim Pract. 2022 Mar 4. DOI: doi.org/10.1111/jsap.13460

44
• Article | Photosonic Treatment and Fibromyalgia: The Effect on Brain Compliance - Case Report
Junior AEA, Carbinatto FM, Tomaz CSR, Bagnato VS (2022) J Nov Physiother 12: 510. DOI: doi.org/10.4172/ 2165-7025.1000510

43
• Article | Waveform Morphology as a Surrogate for ICP Monitoring: A Comparison Between an Invasive and a Noninvasive Method
de Moraes FM, Rocha E, Barros FCD, Freitas FGR, Miranda M, Valiente RA, de Andrade JBC, Neto FEAC, Silva GS. 2022: 24:1–9. DOI: doi.org/10.1007/s12028-022-01477-4

42
• Article | From disease to noninvasive intracranial monitoring
Folchini, Caroline Mensor et al. 2022: ISSN 1678-4227. DOI: doi.org/10.1590/0004-282X-ANP-2021-0298

41
• Article | Noninvasive intracranial pressure monitoring in women with migraine
Rossi, D.M., Bevilaqua-Grossi, D., Mascarenhas, S. et al. 2022: Sci Rep 12, 2635. DOI: doi.org/10.1038/s41598-022-06258-9

40
• Article | A novel noninvasive technique for intracranial compliance monitoring in neurocritical care
Brasil, S. Journal of Personalized Medicine. DOI: https://doi.org/10.3390/jpm11121302

39
• Article | The use of a non-invasive intracranial pressure monitoring method in the intensive care unit to improve neuroprotection on postoperative patients following extracorporeal circulation
Salomon, R. RBTI - Revista Brasileira de Terapia Intensiva. DOI: 10.5935/0103-507X.20210066

38
• Article | Intracranial Compliance Concepts and Assessment: A Scoping Review
Ocamoto, G. Frontiers in Neurology. DOI: https://doi.org/10.3389/fneur.2021.756112

37
• Letter | Is It Possible To Monitor The Wave Form With Non-invasive Methods?
Rabelo, N. World neurosurgery. DOI: https://doi.org/10.1016/j.wneu.2021.06.050

36
• Article | Noninvasive intracranial pressure real-time waveform analysis monitor during prostatectomy robotic surgery and Trendelenburg position: case report
Saba, G. Brazilian Journal of Anesthesiology. DOI: https://doi.org/10.1016/j.bjane.2021.09.003

35
• Case Report | Non-invasive intracranial pressure monitoring in idiopathic intracranial hypertension and lumbar puncture in pediatric patient: case report
Dhaese, T. Surgical Neurology International. DOI: 10.25259/SNI_124_2021

34
• Case Report | Effect of hemodialysis on cerebral compliance assessed in a non invasive way
Rickly, C. Brazilian Journal of Development. DOI: doi.org/10.34117/bjdv7n1-689

33
• Case Report | Elderly non invasive intracranial pressure monitorization: a report of waveform morphology and cerebral compliance
Vellosa, J. Brazilian Journal of Development. DOI: doi.org/10.34117/bjdv7n1-470
3
2
• Case report | Untreatable Headache in a Child with Ventriculoperitoneal Shunt Managed by Use of New Non-Invasive ICP Waveform: a Case Report
Paraguassu, G. Frontiers in Neuroscience. DOI: https://doi.org/10.3389/fnins.2021.601945

31
• Chapter | Non-Invasive intracranial pressure monitoring
Welling, L. LIVRO: Neurocritical Care for Neurosurgeons: Principles and Applications. DOI: https://doi.org/10.1007/978-3-030-66572-2

30
• Article | Noninvasive intracranial pressure monitoring in chronic Stroke patients with sedentary behavior-pilot study
Ocamoto, G. Acta Neurochirurgica Supplement. DOI: doi.org/10.1007/978-3-030-59436-7_12

29
• Letter | The Noninvasive Intracranial Pressure in Patients with Intracranial Hypertension
Rabelo, N. Clinics in Surgery. DOI: https://www.clinicsinsurgery.com/pdfs_folder/cis-v6-id3144.pdf

28
• Case report | Non-invasive monitoring of intracranial pressure during midazolam-induced moderate sedation for upper gastro intestinal endoscopy
Drewnoski, B. Brazilian Journal of Development. DOI: https://doi.org/10.34117/bjdv.v7i5.29327

27
• Letter | Neurosurgery and Manned Spaceflight
Rabelo, N. Neurosurgery. DOI: doi.org/10.1093/neuros/nyab133

26
• Article | Intracranial pressure and laboratory parameters in high and low risk pregnant women
Silveira, D. Surgical Neurology International. DOI: doi.org/10.25259/SNI_109_2021

25
• Article | Noninvasive intracranial pressure monitoring methods: a critical review
Moulin, F. 2021. Arquivos de Neuro Psiquiatria. DOI: doi.org/10.1590/0004-282X-ANP-2020-0300

24
• Article | Use of non-invasive intracranial pressure pulse waveform to monitor patients with End-Stage Renal Disease (ESRD)
Rickly, C. PLOS ONE. DOI: doi.org/10.1371/journal.pone.0240570

23
• Article | Comparison of waveforms between non-invasive and invasive ICP monitoring
Gomes, I. Acta Neurochirurgica Supplement. DOI: doi.org/10.1007/978-3-030-59436-7_28
22
• Article | Intracranial compliance assessed by intracranial pressure pulse waveform
Brasil, S. Brainsciences. DOI: doi.org/10.3390/brainsci11080971span>

21
• Article | A nanometer resolution wireless device for non invasive intracranial pressure monitoring
Andrade, R. IEEE Sensors Journal. DOI: doi.org/10.1109/JSEN.2021.3090648

20
• Article | Cerebral Hemodynamics And Intracranial Compliance Impairment In Critically Ill Covid-19 Patients: A Pilot Study
Brasil, S. 2021. Brainsciences. DOI: doi.org/10.3390/brainsci11070874

19
• Article | The historic evolution of intracranial pressure and cerebrospinal fluid pulse pressure concepts: 2 centuries of challenges
Rabelo, N. Surgical Neurology International. DOI: doi.org/10.25259/SNI_53_2021

18
• Article | Obesity and its implications on cerebral circulation and intracranial compliance in severe covid 19
Brasil, S. 2021. Obesity Science & Practice. DOI: doi.org/10.1002/osp4.534

17
• Article | Intracranial Pressure During the Development of Renovascular Hypertension
Fernandes. Hypertension DOI: doi.org/10.1161/HYPERTENSIONAHA.120.16217

16
• Chapter | Intracranial pressure waveform. History, fundamentals and applications in brain injuries
Frigieri, G. LIVRO IntechOpen: Advancement and New Understanding in Brain Injury. DOI: doi.org/10.5772/intechopen.94077

15
• Chapter | Management of patients with brain injury using noninvasive methods
Frigieri, G. LIVRO IntechOpen: Advancement and New Understanding in Brain Injury. DOI: doi.org/10.5772/intechopen.94143

14
• Letter | Use of Intracranial Pressure Monitoring in Patients with Severe Traumatic Brain Injury
Rabelo, N. World Neurosurgery. DOI: doi.org/10.1016/j.wneu.2020.07.222

13
• Letter | Intracranial pressure monitoring: Challenge beyond the threshold numerical value
Rabelo, N. Journal of Neurosurgery. DOI: doi.org/10.3171/2020.9.JNS203395

12
• Article | Use of the Kirkpatrick methodology for training in new non-invasive intracranial pressure monitoring technology for nurses
Barros, T. Brazilian Journal of Health Review. DOI: doi.org/10.34119/bjhrv3n3-098

11
• Article | Intracranial compliance concepts and assessment a scoping review protocol
Russo, T. Research Square. DOI: doi.org/10.21203/rs.3.rs-43616/v1

10
• Article | In-flight analysis of intracranial pressure in pilots undergoing variation in Gz
Bezerra, T. Aeronautics and Aerospace Open Access Journal. 2018;2(3):126–131. DOI: doi: 10.15406/aaoaj.2018.02.00042

09
• Article | Analysis of a minimally invasive intracranial pressure signals during infusion at the subarachnoid spinal space of pigs
Frigieri, G. Acta Neurochirurgica Supplement. 2018;126:75-77. DOI: doi: 10.1007/978-3-319-65798-1_16

08
• Article | Analysis of a non-invasive intracranial pressure monitoring method in patients with traumatic brain injury
Frigieri, G. Acta Neurochirurgica Supplement. 2018;126:107-110. DOI: doi: 10.1007/978-3-319-65798-1_23

07
• Article | Noninvasive intracranial pressure monitoring for HIV-associated cryptococcal meningitis
Bolella, V. Brazilian Journal of Medical and Biological Research. 2017 Aug 7;50(9):e6392. DOI: doi: 10.1590/1414-431X20176392

06
• Article | Prediction of intracranial hypertension through noninvasive intracranial pressure waveform analysis in pediatric hydrocephalus
Ballestero, M. Child’s Nervous System. 2017 Sep;33(9):1517-1524. DOI: doi: 10.1007/s00381-017-3475-1. Epub 2017 Jun 16

05
• Article | Characterization of ICP behavior in an experimental model of hemorrhagic stroke in rats
Cardim, D. Acta Neurochirurgica Supplement. 2016;122:121-4. DOI: doi: 10.1007/978-3-319-22533-3_24

04
• Article | Characterization of intracranial pressure behavior in chronic epileptic animals: a preliminary study
Cardim, D. Acta Neurochirurgica Supplement. 2016; 122:329-333. DOI: doi: 10.1007/978-3-319-22533-3_65

03
• Article | Validation of a new minimally invasive intracranial pressure monitoring method by direct comparison with an invasive technique
Frigieri, G. Acta Neurochirurgica Supplement. 2016;122:97-100. DOI: doi: 10.1007/978-3-319-22533-3_19

02
• Article | Validation of a new noninvasive intracranial pressure monitoring method by direct comparison with an invasive technique
Cabella. B. Acta Neurochirurgica Supplement. 2016;122:93-6. DOI: doi: 10.1007/978-3-319-22533-3_18

01
• Article | The new ICP minimally invasive method shows that the monro-kellie doctrine is not valid.
Mascarenhas, S. Acta Neurochirurgica Supplementum. 2012: 117 – 120. DOI: doi.org/10.1007/978-3-7091-0956-4_21

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This revision has been carefully made, and my major concerns have been addressed. Hence i fully support the publication.

Reviewer #2

(Remarks to the Author)
The current version of this manuscript was improved. No additional comments.

Response Letter

An ultrasensitive multimodal intracranial pressure biotelemetric system enabled by exceptional point and iontronics

We would like to express our gratitude to all reviewers for their valuable and constructive comments on our manuscript. In the following, we address each of the issues raised by the reviewers and outline the corresponding changes we have made in our revised manuscript. We believe that implementing the reviewers' suggestions has significantly enhanced the quality of our work. Our aim is to ensure that the revised manuscript meets the criteria of impact, innovation, and interest for publication in *Nature Communications*, as judged by both the reviewers and the editor.

Reviewer #1:

Comment 0

The manuscript proposed a new intracranial pressure (ICP) sensor that amplified by new technologies including iontronic pressure transducer and exceptional-point (EP) wireless system. The new sensor demonstrated several advantages such as high sensitivity and high resolution. The results were well presented and could be interest to the audience of *Nat Commun.*

Our response:

We are thankful to the reviewer for your careful reading of our revised manuscript and the overall positive evaluations.

Comment 1

Recent studies pointed out that the sensitivity at the EP cannot be enhanced because of the noise at the EP. How much is the sensitivity enhanced? Why the sensitivity can be enhanced in this study? Noise analysis is needed.

Our response:

We very much appreciate the reviewer for pointing out this issue. In fact, the exceptional point (EP)-based sensors do enhance the sensitivity but provide no fundamental signal-to-noise ratio (SNR) enhancement[1]. That is said, while the system has enhanced responsivity towards the target perturbations around EP, any unwanted noise existing in the system will also be amplified in the same magnitude. Therefore, the unwanted noise of the sensing system should be suppressed to be sufficiently small compared to the target perturbation, which allows us to benefit from the sensitivity enhancement brought by the EP with minimum noise.

Generally, there are several noise sources in electromagnetic systems, such as shot noise, flicker noise, thermal noise, and quantum noise. Particularly, quantum noise originated from the quantization nature of charged carriers and photons is significant in optical and photonic systems, but can be ignored in our radio-frequency EP sensing system[2]. Shot noise and flicker ($1/f$ noise) exist in solid-state devices and vacuum electronics, which are important only at low frequencies (i.e., 1 Hz to 1 MHz). Consequently, thermal noise (Johnson-Nyquist noise[3]) sourced from the thermal agitation of bounded charges in devices (especially in resistors), which simultaneously introduces the resonance frequency shifts, is considered the dominant noise source in this work.

According to Planck's black body radiation law, the electrons in a real-world resistor are in random motion, whose kinetic energy may produce small and random voltage fluctuations across this resistor with a zero average but a nonzero root mean square (RMS) value, which can be expressed as

$$\overline{V}_{\text{nosie}} = \sqrt{\frac{4hfBR}{e^{hf/kT}-1}}, \tag{1}$$

where h denotes the Planck's constant, k is the Boltzmann's constant, T represents the temperature in kelvin, $f\,(B)$ is the center frequency (bandwidth), and R is the resistance value. In the low frequency range where the approximation $hf = kT$ takes account, the above equation can be simplified to $\overline{V}_{\text{nosie}} = \sqrt{4kTBR}$. This indicates the noise voltage fluctuates between $\pm\sqrt{8kTBR}$. Therefore, the voltage across a non-ideal resistor can be decomposed into $V' = V_R + V_{\text{noise}}$, as seen in Fig. R1a. This model can also be equivalent to the series connection of an ideal resistor (R) and a noisy resistor (R'), as seen in Fig. R1b, such that $V' = I(R+R') = IR + IR' = V_R + V_{\text{noise}}$. Defining a time-fluctuating parameter $\varepsilon_{1,2} = R'/R$ where the subscript 1,2 denotes the deviation occurring to the resistors of gain or loss oscillators, we can analyze the resonance frequency fluctuations due to thermal noise. Here, to simplify our analysis, we assume $\varepsilon_{1,2} \in [-\Delta,\ \Delta]$ where $\Delta \propto \sqrt{8kTB/R}$.

In experiments, the measurement of eigenfrequencies associated with the Hamiltonians is realized by tracking the dips of reflection spectra, which, in this work, is the reflection coefficient (S_{11}) at the gain side (Fig. R1b and R1c). The noise-deviated S_{11}, considering the maximum noise ($\varepsilon_{1,2} \equiv \Delta$), has the form of

$$S_{11} = \frac{\eta(1+\Delta)^2\omega^2 + \eta\gamma^2[1-2\omega^2-(\mu^2-1)\omega^4]}{[(1+\Delta)(\eta+\Delta\eta)-2\omega^2]-2i\gamma\omega(\omega^2-1)+\eta\gamma^2[1-2\omega^2-(\mu^2-1)\omega^4]}, \tag{2}$$

which yields the maximized deviated resonance frequency to be

$$\omega_{1,2}' = \sqrt{\frac{(1+\Delta)^2 - 2\gamma^2 \pm \sqrt{(1+\Delta)^4 - 4\gamma^2(1+\Delta)^2 + 4\gamma^4\mu^2}}{2\gamma^2(\mu^2-1)}}. \tag{3}$$

The frequency fluctuation caused by the noise is $\Delta\omega = \omega_{1,2} - \omega_{1,2}'$. Taking parameters used in our experiments (e.g., $\gamma = 13.56,\ \mu = 0.08$ and the system operates at $f_0 \approx 24.1$ MHz and $T = 290$ K), the above equation yields $\Delta f = 2\pi\Delta\omega \approx 1$ kHz, which agrees well with our noise measurements in Fig. R1d that the measured frequency may have ± 2.5 kHz fluctuation. This noise-introduced frequency fluctuation is indeed ignorable compared to the frequency shift caused by the target pressure variations (~ 10 – ~ 400 kHz), which, therefore, does not negate the implementation of the EP for sensing.

In the revised manuscript, we have included the above discussions in Supplementary Material Note 7.

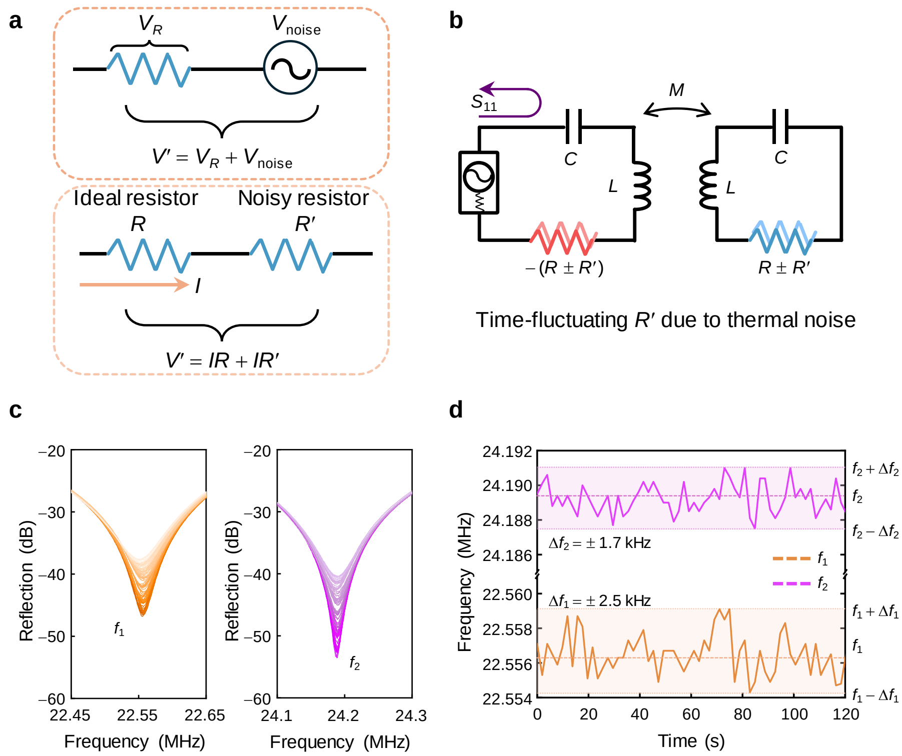

Fig. R1. (a) Circuit equivalent of a non-ideal resistor. (b) Circuit diagram of the EP sensing system considering the presence of thermal noise. (c) Reflection spectra measured within 120 seconds (per 2 seconds) without perturbations applied. (d) Frequency fluctuation caused by the noise.

Comment 2

For an EP circuit with bifurcation effect, the resonance splits and one resonance shifts to a higher frequency and the other one lower. However, as shown in this study (such as Fig. 2c, 4b, et.), the two resonant frequencies shifted to the same direction, and no bifurcation effect cannot be observed. These results are conflicting.

Our response:

This is a good point raised by this reviewer. The reviewer is correct that for normalized eigenfrequencies, i.e., $\omega_{1,2}$ is in the unit of ω_0, the increase of γ ($\gamma = R^{-1}\sqrt{L/C}$) will lead to the bifurcation of $\omega_{1,2}$ to opposite directions. However, we should note here that if the variation of γ is induced due to the change in C, the resonance frequency ($\omega_0 = 1/\sqrt{LC}$) also shifts. This indicates that the non-normalized eigenfrequencies will shift in the same direction in the spectrum. This can be better understood from Fig. R2, where Fig. R2a denotes the normalized eigenfrequency shift and Fig. R2b represents the non-normalized eigenfrequency shift with respect to the change in γ (due to C variation). It can be seen that the non-normalized eigenfrequency will shift in the same direction but at different rates. In the previous manuscript Figs. 2b, 2d, and 2e (theoretical analysis), we exploited the normalized eigenfrequency, and in Fig. 2c and Fig. 4 (experimental measurements), we used the non-normalized eigenfrequency.

In the revised manuscript, we have carefully rephrased the sentences discussing the eigenfrequency bifurcation to avoid ambiguity.

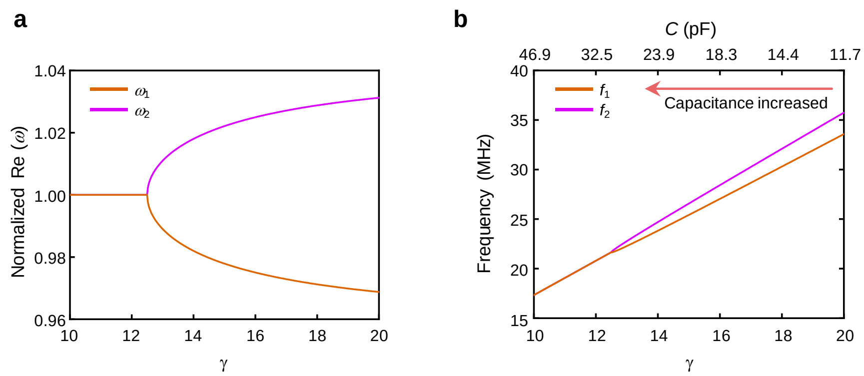

Fig. R2. (a) The real part $\mathrm{Re}(\omega)$ of the eigenfrequencies normalized with respect to $\omega_0 = 1/\sqrt{LC}$ as a function of the non-Hermiticity parameter γ. (b) The non-normalized eigenfrequencies as a function of the non-Hermiticity parameter γ and capacitance C.

Comment 3

The bifurcated frequencies are in the strong coupling regime of parity-time symmetric circuit. However, the high-coupling condition is challenging in the ICP sensor because of the presence of tissue and skull, especially for large animal model and human. How this problem is solved?

Our response:

We sincerely thank the reviewer for bringing up this valuable question. The reviewer is correct that high-coupling or strong coupling is challenging in the ICP sensor because the strong coupling requires a short distance between the sensor and reader coils, which, due to the presence of tissue and skull, is hard to achieve in reality. In our work, this problem is solved by using a weak coupling-based electronic EP system.

The exact solution of eigenfrequencies in the PT-symmetric electronic system, as a function of γ and the coupling strength μ, has been given by ref. [4], and has the form of

$$\omega_{1,2} = \pm\sqrt{\frac{2\gamma^2 - 1 \pm \sqrt{1 - 4\gamma^2 + 4\gamma^4\mu^2}}{2\gamma^2\left(1-\mu^2\right)}} \tag{4}$$

At the weak coupling regime, i.e., $\mu = \ 1$, the eigenfrequencies can be approximated as

$$\omega_{1,2} = 1 \pm \frac{1}{2\gamma}\sqrt{\mu^2\gamma^2 - 1}. \tag{5}$$

Figure R3a demonstrates that the exact solution and the approximation of eigenfrequencies can have a perfect agreement with each other when $\mu < 0.1$. Figure R3b illustrates that the weaker the coupling strength is, the larger γ should become to ensure the eigenfrequency bifurcation. The red dashed lines in Fig. R3 depict the operating point ($\gamma = 13.96,\ \mu = 0.08$) of the proposed system in this work, which is sufficiently close to the EP for better sensitivity and located in the exact symmetry phase for two real eigenfrequencies.

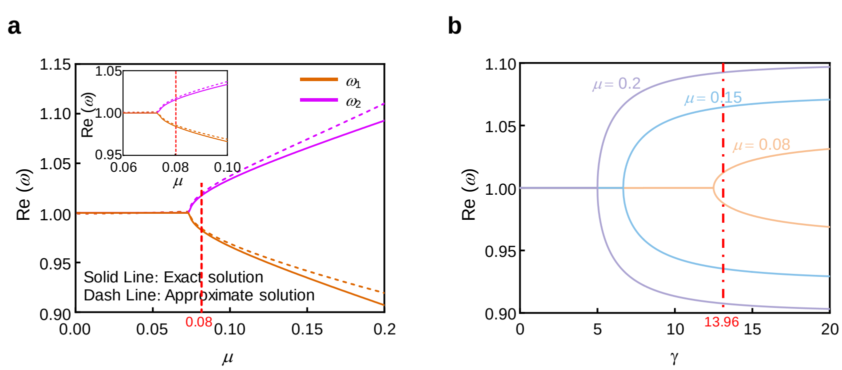

Fig. R3. (a) The exact and approximate solutions of the real part $\mathrm{Re}(\omega)$ of the eigenvalues as a function of coupling coefficient μ. (b) The real part $\mathrm{Re}(\omega)$ of the eigenvalues as a function of the non-Hermiticity parameter γ at coupling coefficient $\mu = 0.2,\ 0.15,\ 0.08$.

Comment 4

The heartbeat signal in Fig. 5g are not in well agreement with ECG signals. Seems the fluctuations of resonant frequency are noise. More plots are needed to validate the heartbeat signals.

Our response:

We sincerely thank the reviewer for pointing out this issue. We believe that addressing this issue will indeed enhance the quality of our manuscript. In the response of comment 1, we have both theoretically and experimentally demonstrated that the noise-induced frequency fluctuations are within ± 2.5 kHz, which can be ignored compared to the eigenfrequency shift caused by the target pressure variations. To demonstrate that the fluctuations in Fig. 5g in the main text are extracted from the heartbeat signal instead of noise, we further perform experiments in the low-pressure range shown in Fig. R4. The results demonstrated that the noise-induced (no pressure applied) frequency fluctuations (marked in Fig. R4a and zoomed-in in Fig. R4b.) are below 2 kHz, while the frequency fluctuations caused by the heartbeat signal (~ 0.05 mmHg, blue area marked in Fig. S9a) are ~ 25 kHz (the grey area marked in Fig. R4a), which is more than one order of magnitude larger than the noise-induced fluctuation (Fig. R4b). In addition, the results in Fig. 4f, which demonstrates clear frequency differentiation under extremely weak pressure perturbations, further support this finding. Figure 5g shows that the frequency fluctuation caused by the heartbeat is about 25 kHz, significantly greater than that caused by noise. The fast Fourier transformation (FFT) analysis (Fig. R3c) of the ICP signal from Fig. 5f reveals two distinct peaks: one for breathing (~ 0.33 Hz) and another for heartbeat (~ 3.76 Hz), which closely matches the ECG results.

In the revised manuscript, we have included the above discussions in Supplementary Material Note 10.

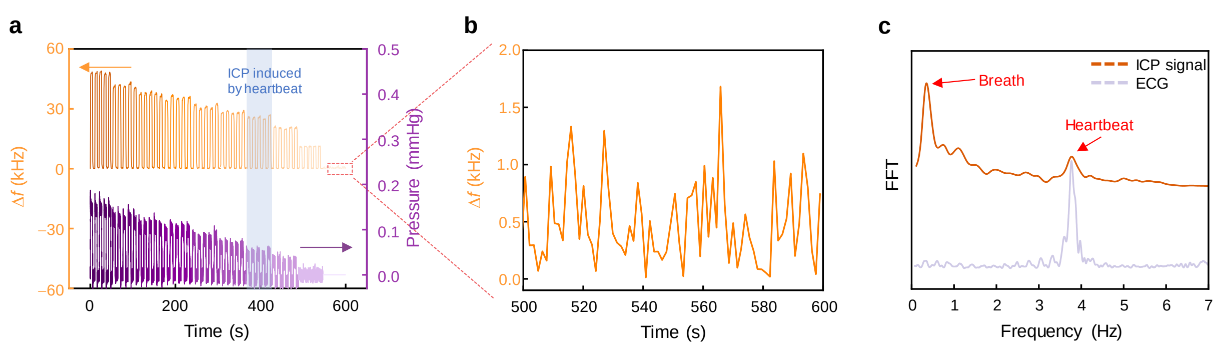

Fig. R4. (a) Frequency shift of ω_2 in response to low applied pressure (~ per 60 seconds). (b) Enlarged view of frequency shift without applied pressure. (c) FFT analysis of ICP signal and ECG.

Comment 5

The quality factor defined in theoretical analysis (Line 101) is confusing. Given this definition, the quality factors should be fixed after the circuit's design. Why the quality factors in Fig. 2c are changing?

Our response:

We very much appreciate the careful reading of this reviewer and pointing out this problem. We apologize that in the previous manuscript, the definition of quality factor was ambiguous. Generally, the quality factor can be categorized as bandpass quality factor, component quality factor, and pole quality factor. Previously, we adopted the component quality factor as the definition of γ but the bandpass quality factor in Fig. 4d in the main context. This explains the changing of quality factor in Fig. 2c.

To avoid the ambiguity, we have revised the definition of γ and only adopt the bandpass quality factor ($Q = f_0 / BW$) in our paper, and the system exhibits its greatest Q-factor in the exact symmetry phase.

Comment 6

Typo in Line 213, 116. Typo in Line 232, no "quality factors". Typo in Line 235, no "dashed lines".

Our response:

We sincerely apologize for the previous oversights in our manuscript, which led to several typographical errors and inaccuracies. We greatly appreciate your meticulous review, which has given us the opportunity to improve the quality of our manuscript. In the revised manuscript, we have addressed each of the issues you highlighted, and conducted a thorough review of the entire text to ensure that similar issues do not persist.

Comment 7

Some important references are missing, including already reported EP biosensors (Dong et al., Nat Electron 2, 335-342 (2019); Li et al., Phy Rev Lett 130, 227201 (2023)) and very recent EP sensors in other fields (Kim et al., eLight 4, 6 (2024); Lee et al., eLight 3, 20 (2023)).

Our response:

We express our gratitude to the reviewer for bringing these valuable references to our attention, which can help us improve the quality of our manuscript. We have now included the references[5–11] (ref. 32 – 38 in the revised main context) to the EP-based sensor in the revised manuscript to provide a more comprehensive context for our study.

Reviewer #2:

Comment 0

The noteworthy results from this work can be summarized as follows:

1. Proposed System: Introduction of an exceptional point (EP)-based biotelemetric system for continuous and real-time wireless intracranial pressure (ICP) monitoring using an iontronic capacitive pressure transducer.

2. Enhanced Performance: The system leverages EP degeneracy combined with a highly sensitive iontronic transducer, leading to significant improvements in reliability, resolution, and sensitivity.

3. Sensitivity: Achieved a maximum relative sensitivity of 115.95 kHz/mmHg, which is nearly an order of magnitude higher than current ICP sensing systems.

4. Accuracy: Capable of detecting pressure variations as small as one-thousandth of a millimeter of mercury, greatly surpassing the accuracy of commercial ICP sensors.

5. Validation: In-vivo experiments conducted on a rabbit model validated the practical efficacy of the system, showing its superior sensitivity compared to traditional ICP probes.

6. Multi-modal Detection: The system can accurately identify various degrees of pressure signals and perform multi-modal detection, including minute ICP fluctuations caused by physiological processes such as respiration and cardiac activity.

7. Comprehensive Monitoring: The system not only monitors ICP but also concurrently tracks respiratory and heart rates, simplifying clinical procedures and enhancing clinical utility by providing a comprehensive monitoring solution in a single device.

8. Healthcare Applications: The integration of this biotelemetry system into bio-implantation practices holds significant promise for healthcare applications, particularly in continuous monitoring of vital signs, potentially transforming patient care and monitoring practices.

Will the work be of significance to the field and related fields? How does it compare to the established literature? If the work is not original, please provide relevant references.

Yes, this work is likely to be significant to the field of biomedical engineering and related fields, particularly in the areas of biotelemetry, intracranial pressure (ICP) monitoring, and patient care technology. Here’s how it compares to the established literature and its potential impact:

Significance to the Field:

1. Advancement in ICP Monitoring:

Higher Sensitivity and Accuracy: The proposed system's maximum relative sensitivity of 115.95 kHz/mmHg and the ability to detect pressure variations as small as one-thousandth of a millimeter of mercury are notable advancements over existing ICP monitoring technologies. This could significantly improve patient outcomes by enabling more precise and early detection of abnormal ICP levels.

Wireless Biotelemetry: The continuous and real-time wireless monitoring capability represents a substantial improvement in patient comfort and mobility compared to traditional wired systems.

2. Multi-modal Detection:

The ability to monitor not only ICP but also respiratory and cardiac activity in a single device simplifies clinical procedures and provides a more comprehensive picture of the patient's physiological state, which could be particularly valuable in intensive care settings.

3. Potential Healthcare Applications:

The integration of this system into bio-implantation practices could transform patient care by enabling continuous, real-time monitoring of vital signs, potentially reducing the need for invasive procedures and frequent hospital visits.

Comparison to Established Literature:

1. Current Sensing Systems:

Traditional ICP monitoring systems, such as ventricular catheters and fiber optic transducers, typically have lower sensitivity and resolution compared to the proposed EP-based system. These systems often require invasive procedures and are less capable of detecting minute pressure fluctuations.

2. Wireless and Telemetric Systems:

While there have been advancements in wireless ICP monitoring, such as the use of telemetric sensors, these systems generally do not achieve the same level of sensitivity and resolution as reported in this work.

Originality and Novelty:

The work appears to be original in its application of EP degeneracy with an iontronic capacitive pressure transducer for ICP monitoring, achieving unprecedented sensitivity and accuracy levels. The integration of multi-modal detection capabilities within a single wireless biotelemetric system also represents a novel advancement over current technologies.

Conclusion:

Given the enhancements in sensitivity, accuracy, and the added functionality of concurrent monitoring of respiratory and cardiac activity, this work has the potential to make a significant impact on the field of ICP monitoring and broader healthcare applications. It addresses several limitations of current technologies and introduces innovative solutions that could improve patient care and monitoring practices.

Our response:

We greatly appreciate the reviewer for your positive comments on our work.

Comment 1

Within the literature regarding ICP and ICC (intracerebral compliance) there are new advanced system that was not considered and compared with this data regarding the present manuscript. The authors should provide additional literature regarding ICP measurements using Brain4care system, particularly, the robust publications as following: https://brain4.care/en/home-english/

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• Article | Characterization of intracranial compliance in healthy subjects using a noninvasive method - results from a multicenter prospective observational study

Gabriela Nagai Ocamoto, Lucas Normando da Silva, Camila da Silva Rocha Tomaz, Matheus Toshio Hisatugu, Gustavo Frigieri, Danilo Cardim, Roberta Lins Gonçalves, Thiago Luiz Russo, Robson Luis Oliveira de Amorim.

DOI: https://doi.org/10.1007/s10877-024-01191-w

94

• Article | Effects of moderate sedation induced by propofol or midazolam on intracranial pressure

Bianca Drewnowski, José Carlos Rebuglio Vellosa, Rafael Nastas Acras, Fábio André dos Santos.

DOI: https://doi.org/10.7322/abcshs.2022098.2164

93

• Article | Methodology for non-invasive monitoring of intracranial pressure waves in dogs with traumatic brain injury using the brain4care® BCMM/2000 monitor

Thyara Weizenmann, Mônica Vicky Bahr Arias.

DOI: https://doi.org/10.35172/rvz.2024.v31.1583

92

• Article | A Comprehensive Perspective on Intracranial Pressure Monitoring and Individualized Management in Neurocritical Care: Results of a Survey with Global Experts

Sérgio Brasil, Daniel Agustín Godoy, Walter Videtta, Andrés Mariano Rubiano, Davi Solla, Fabio Silvio Taccone, Chiara Robba, Frank Rasulo, Marcel Aries, Peter Smielewski, Geert Meyfroidt, Denise Battaglini, Mohammad I. Hirzallah, Robson Amorim, Gisele Sampaio, Fabiano Moulin, Cristian Deana, Edoardo Picetti, Angelos Kolias, Peter Hutchinson, Gregory W. Hawryluk, Marek Czosnyka, Ronney B. Panerai, Lori A. Shutter, Soojin Park, Carla Rynkowski, Jorge Paranhos, Thiago H. S. Silva, Luiz M. S. Malbouisson and Wellingson S. Paiva.

DOI: https://doi.org/10.1007/s12028-024-02008-z

91

• Article | Noninvasive neuromonitoring in acute brain injured patients

Sérgio Brasil, Randall Chesnut, Chiara Robba.

DOI: https://doi.org/10.1007/s00134-024-07406-7

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• Article | A narrative review on financial challenges and healthcare costs associated with traumatic brain injury in the US

Wander Valentim, Sérgio Brasil, Raphael Bertani.

DOI: https://doi.org/10.1016/j.wneu.2024.03.175

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• Article | Non-Invasive Study of Intracranial Pressure in Pre- and Post-Chemotherapy Patients for the Treatment of Breast Neoplasia

Lais Daiene Cosmoski, Cristiane Rickli, Danielle Cristyane Kalva Borato, Gustavo Henrique Frigieri, Nicollas Nunes Rabelo, Bruna França Bueno, José Carlos Rebuglio Vellosa .

DOI: https://www.portalnepas.org.br/abcshs/article/view/1971

88

• Case report | Management of shunt dysfunction using noninvasive intracranial pressure waveform monitoring: illustrative case

Raphael Bertani, Caio Perret , Stefan Koester, Paulo Santa Maria, Savio Batista, Sophia de Andrade Cavicchioli, Sany Tomomi de Almeida Rocha Arita, Ruy Monteiro, Gianne Lucchesi, Fernando Augusto Vasconcellos, Matheus Miranda , Wellingson Silva Paiva, Fernando Gomes Pinto.

DOI: https://pubmed.ncbi.nlm.nih.gov/38437677/

87

• Article | Validation of a Non-invasive Method Using Mechanical Extensometer for the Estimation of Intracranial Compliance by Repeated Measures Agreement Analysis

Sanem Pinar Uysal, Hayley G. Williams, Mina Huerta, Nicolas R. Thompson, Catherine E. Hassett

DOI:https://doi.org/10.21203/rs.3.rs-3948331/v1

86

• Case report | Propofol effects over intracranial pressure waveform and cerebral hemodynamics: A case report

Nathália Meneses Neves, Thais Rodrigues Kassahara, Sany Tomomi de Almeida Rocha Arita, Elaine Peixoto, Sérgio Brasil.

DOI: https://doi.org/10.33448/rsd-v13i2.44982

85

• Article | Age as a predictive factor for reduced intracranial compliance in patients with headache

Luiz Gabriel Gonçalves Cherain, Mateus Gonçalves de Sena Barbosa, Ghaspar Gomes de Oliveira Alves Francisco, Luiz Miguel Gonçalves Cherain, Gustavo Frigieri, Nicollas Nunes Rabelo .

DOI: https://doi.org/10.1007/s10877-023-01120-3

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• Article | ICP wave morphology as a screening test to exclude intracranial hypertension in brain-injured patients: a non-invasive perspective

Fabiano Moulin de Moraes, Sérgio Brasil, Gustavo Frigieri, Chiara Robba, Wellingson Paiva e Gisele Sampaio Silva.

DOI: https://doi.org/10.1007/s10877-023-01120-3

83

• Case report | Astrocytoma Mimicking Herpetic Meningoencephalitis: The Role of Non-Invasive Multimodal Monitoring in Neurointensivism

Uri Adrian Prync Flato, Barbara Cristina de Abreu Pereira, Fernando Alvares Costa, Marcos Cairo Vilela, Gustavo Frigieri, Nilton José Fernandes Cavalcante, Samantha Longhi Simões de Almeida.

DOI: https://doi.org/10.3390/neurolint15040090

82

• Article | Epidemiological study of pediatric patients with signs and symptoms of intracranial hypertension with non-invasive cerebral compliance
Luana Say, Caroline Mensor Folchini, Guilherme de Rosso Manços, Marinei Campos Ricieri, Fábio de Araújo Motta, Adriano Keijiro Maeda, Simone Carreiro Vieira Karuta.
DOI: https://doi.org/10.33448/rsd-v12i10.43481

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• Letter | Neuromonitoring-Here, There, and to Every Critically Ill Patient
Juliana Caldas, Sergio Brasil, Rogério Passos.
DOI: 10.1097/CCM.0000000000005926

80
• Article | Intracranial pressure waveform in patients with essential hypertension
Matheus Martins da Costa, Ana Luiza Lima Sousa, Mikaelle Costa Correia, Sayuri Inuzuka, Thiago Oliveira Costa, Priscila Valverde O. Vitorino, Polyana Vulcano de Toledo Piza, Gustavo Frigieri, Antonio Coca, Weimar Kunz Sebba Barroso.
DOI: https://doi.org/10.3389/fcvm.2023.1288080

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• Article | Non-invasive intracranial pressure waveform analysis in Chiari Malformation type 1: A pilot trial
Eloy Rusafa Neto, Wellingson Silva Paiva, Róger Schimidt Brock, Cintya Yukie Hayashi, Marcia Mitie Nagumo, Maurício Oriente Segurado, Ana Luiza Zaninotto, Róbson Luis Amorim.
DOI: https://doi.org/10.1016/j.wneu.2023.11.067

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• Article | The influence of hemodialysis on intracranial pressure waveform in patients with chronic kidney disease: an observational study
Mariana Schechtel Koch, Bianca Drewnowski, Cristiane Rickli, Fábio André dos Santos, Gilberto Baroni, José Carlos Rebuglio Vellosa.
DOI: https://doi.org/10.1590/1516-3180.2023.0068.R1.07072023

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• Article | Multimodal monitoring intracranial pressure by invasive and noninvasive means
Fabiano Moulin de Moraes, Erica Navarro Borba Adissy, Eva Rocha, Felipe Chaves Duarte Barros, Flávio Geraldo Rezende Freitas, Maramelia Miranda, Raul Alberto Valiente, João Brainer Clares de Andrade, Feres Eduardo Aparecido Chaddad-Neto e Gisele Sampaio Silva.
DOI: https://doi.org/10.1038/s41598-023-45834-5

76
• Article | Predicting short-term outcomes in brain-Injured patients: A comprehensive approach with transcranial Doppler and intracranial compliance assessment
Sergio Brasil, Danilo Cardim, Juliana Caldas, Chiara Robba, Fabio Silvio Taccone, Marcelo de-Lima-Oliveira, Márcia Harumy Yoshikawa, Luiz Marcelo Sá Malbouisson, Wellingson Silva Paiva.
DOI: https://doi.org/10.21203/rs.3.rs-3406169/v1

75
• Article | Intracranial pressure changes of cardiac patients that have passed by extracorphorus circulation: A brief literature review
Lais Daiene Cosmoski, Bianca Drewnowski, Bruna França Bueno, Cristiane Rickli, Lisiane Cristine Lopes, Mariana Schechtel Koch, José Carlos Rebuglio Vellosa.
DOI: http://dx.doi.org/10.33448/rsd-v11i15.37512

74
• Editorial | An Unexpected Correlation Between Non-Invasive Intracranial Pressure Waveform Assessment in Hypertensive Patients. Could This Be the Link Between Hypertension and Cerebrovascular Diseases as Well as Cognitive Impairments?
Luciano Brandão Machado, Michele Madeira Brandão, Andre Ferro, Tales Shinji Sawakuchi Minei, Igor José Nogueira Gualberto, Nivaldo Alonso.
DOI: https://doi.org/10.18103/mra.v11i7.2.4166

73
• Experimental | Non-invasive monitoring of intracranial pressure waveforms using Braincare® BCMM 2000 monitor in dogs with myelopathies undergoing myelography
Cardoso GS, Nogueira JF, Arias MVB.
DOI: https://doi.org/10.1590/1678-5150-PVB-7132

72
• Case report | Anesthesia for preoperative non-invasive intracranial pressure measurement in a child with Apert syndrome: a case report
Luciano Brandão Machado, Michele Madeira Brandão, Andre Ferro, Tales Shinji Sawakuchi Minei, Igor José Nogueira Gualberto, Nivaldo Alonso.
DOI: https://doi.org/10.46900/apn.v5i3.190

71
• Article | Comorbities and the occuurence of changes in Intracranial Compliance in elderly
Cristiane Rickli Barbosa, José Carlos Rebuglio Vellosa, Lais Daiene Cosmoski, Mariana Schechtel Koch.
DOI: https://doi.org/10.53660/CLM-1842-23M51

70
• Doing more with less on intracranial pressure monitoring
Daniel A. Godoy, Wellingson S. Paiva. 2023, World Neurosurgery.
DOI: https://doi.org/10.1016/j.wneu.2023.07.055

69
• Article | Analysis of intracranial pressure waveform using a non-invasive method in individuals with craniosynostosis
Michele Madeira Brandão; Cristiano Tonello, Isabella Parizotto; Luciano Brandão Machado; Nivaldo Alonso. 2023, Child´s Nervous System.
DOI: https://doi.org/10.1007/s00381-023-06092-y

68
• Article | The use of noninvasive measurements of intracranial pressure in patients with traumatic brain injury: a narrative review
Luiz Gustavo Guimarães Sacramento, André Vitor Rocha Queiroz, Fernanda de Andrade Dias Leite, Henrique Lacerda Lage Lopes de Oliveira, Thais Yuki Kimura, Rodrigo Moreira Faleiro. 2023, Arquivos de Neuro-Psiquiatria.
DOI: https://doi.org/10.1055/s-0043-1764411

67
• Article | Intracranial compliance and volumetry in patients with traumatic brain injury
Caroline Link, Thomas Markus D'Haese, Gustavo Frigieri, Jose Carlos Rebuglio Vellosa, Leonardo Welling. 2023, Surgical Neurology International.
DOI: 10.25259/SNI_314_2023

66
• Article | A Point-Of-Care Noninvasive Technique For Surrogate ICP Waveforms Application In Neurocritical Care
Sérgio Brasil, Daniel A. Godoy and Gregory W. J. Hawryluk. 2023, Neurocritical Care.
DOI:https://doi.org/10.1007/s12028-023-01786-2

65
• Letter | A new noninvasive method can effectively assess intracranial compliance
Sérgio Brasil e Daniel Agustín Godoy. 2023, Acta Neurochirurgica.
DOI: https://doi.org/10.1007/s00701-023-05644-0

64
• Article | Comparison of Noninvasive Measurements of Intracranial with Tap Test Results in Patients with Idiopathic Normal Pressure Hydrocephalus
Gabriel André da Silva Mendes, Cintya Yukie Hayashi, Gustavo Henrique Frigieri Vilela, Lissa Kido, Manoel Jacobsen Teixeira, Fernando Campos Gomes Pinto. 2023, Neuropsychiatric Disease and Treatment.
DOI: https://doi.org/10.2147/NDT.S402358

63
• Case Report | Noninvasive intracranial pressure involving real-time waveform analysis in a child undergoing general anesthesia: a case report
Gabriela Saba, Thaís Condé, Vinícius Quintão, Gustavo Vilela, Ricardo Carlos, Maria Carmona, 2023, Perioperative Anesthesia Reports.
DOI: http://dx.doi.org/10.4322/par.000223

62
• Article | The intracranial compartmental syndrome: a proposed model for acute brain injury monitoring and management
Daniel Agustín Godoy, Sérgio Brasil, Corrado Iaccarino, Wellingson Paiva, Andres M. Rubiano. 2023, Critical Care.
DOI: 10.1186/s13054-023-04427-4

61
• Case Report | Noninvasive intracranial pressure monitoring throughout brain compliance guiding a ventriculoperitoneal shunt replacement in hydrocephalus—case report
Nelci Zanon, Victor Hugo da Costa Benalia, Thiago Hoesker, Cintya Yukie Hayashi, Gustavo Frigieri, Giselle Coelho. 2023, Child's Nervous System.
DOI: 10.1007/s00381-023-05922-3

60
• Case report | A glimpse into multimodal neuromonitoring in acute liver failure: a case report
Stefano Zorzi, Amanda Ayako Minemura Ordinola, Eduardo Cunha De Souza Lima, Gabriela Martins Teixeira, Michele Salvagno, Elda Diletta Sterchele, Fá bio Silvio Taccone.
DOI: http://dx.doi.org/10.1097/MS9.0000000000001519

59
• Article | Qualitative Evaluation of Intracranial Pressure Slopes in Patients Undergoing Brain Death Protocol
Mylena Miki Lopes Ideta, Louise Makarem Oliveira, Daniel Buzaglo Gonçalves, Mylla Christie de Oliveira Paschoalino, Nise Alessandra de Carvalho Sousa, Marcus Vinicius Della Coletta, Wellingson Paiva, Sérgio Brasil and Robson Luis Oliveira de Amorim.
DOI: 10.3390/brainsci13030401

58
• Letter | Application of non-invasive ICP waveform analysis in acute brain injury: Intracranial Compliance Scale
Gustavo Frigieri, Chiara Robba, Fábio Santana Machado, Joao A. Gomes and S érgio Brasil. 27 January 2023 (27 Janeiro 2023)
DOI: 10.1186/s40635-023-00492-9

57
• Article | Noninvasive intracranial pressure waveforms for estimation of intracranial hypertension and outcome prediction in acute brain injured patients
Brasil, S, et al. 18 Nov. 2022.
DOI: https://doi.org/10.1007/s10877-022-00941-y

56
• Article | Intracranial compliance in type 2 diabetes mellitus and its relationship with the cardiovascular autonomic nervous control
G.A.M. Galdino, et al. Set. 2022
DOI: https://doi.org/10.1590/1414-431X2022e12150

55
• Article | Assessment of Cerebral Autoregulation Using Invasive and Noninvasive Methods of Intracranial Pressure Monitoring
Hassett, C.E., Uysal, S.P., Butler, R. et al. Set. 2022
DOI: doi.org/10.1007/s12028-022-01585-1

54
• Letter | Intracranial pressure pulse morphology: the missing link?
Brasil, S. 29 Ago, 2022
DOI: doi.org/10.1007/s00134-022-06855-2

53

• Article | Noninvasive intracranial pressure in patients with traumatic brain injury

Link C, Botelho AF, Dhaese TM, Frigieri G, Vellosa JCR, Welling LC. 08 Ago. 2022

DOI: doi.org/10.33448/rsd-v11i10.33106

52

• Article | Mechanical Hyperinflation Maneuver and intracranial pressure of critical neurological patients: protocol for a randomized clinical trial

Souza D, Branco MW, Carraro Júnior H, Zocolotti AMD, Takeda SYM, Valderramas S. 13 Jul, 2022

Research Square

Trials

51

• Article | Preliminary assessment of the relationship between blood pressure and intracranial pressure in patients with different stages of chronic kidney disease

Balzer, E.R., Koch, M.S. , Drewnowski, B., Santos, F.A. dos ., Baroni, G., Schuinski , A.F.M. and Vellosa, J.C.R. Jun. 2022. DOI: doi.org/10.33448/rsd-v11i8.31150.

50

• Case Report | Alteration of intracranial compliance in a patient with chronic kidney disease and T1 diabetes mellitus

Koch, M.S., Drewnowski, B., Balzer, E.R., Baroni, G., Schuinski , A.F.M. and Vellosa, J.C.R. Jun. 2022. DOI: doi.org/10.33448/rsd-v11i8.31153.

49

• Article | Relationship Between Dialysis Quality And Brain Compliance In Patients With End-Stage Renal Disease

Mascarenhas S, Rickli C, Frigieri GH, Vellosa JCR, Schuinski, AFM. May 2022. DOI: doi.org/10.1590/1516-3180.2021.0117.R1.14092021

48

• Case Report | Noninvasive Monitoring Of Intracranial Pressure After Cardiac Surgery

Ayres, C., Vellosa, J. C. R. 10 May, 2022. DOI: doi.org/10.33448/rsd-v11i6.29492

47

• Case Report | Use of non-invasive sensor to assess intracranial compliance in the management of migraine patients

Cherain LGG, Barbosa MGS, Souza RLV et al. 22 April 2022 DOI: doi.org/10.21203/rs.3.rs-1162693/v2

46

• Article | Non-invasive monitoring of intracranial pressure in cardiovascular diseases

Ayres, Claudiane. 2022. Collection: Applied biomedical engineering. DOI: doi.org/10.22533/at.ed.896220604

45

• Article | Preliminary evaluation of a non-invasive device for monitoring intracranial pressure waveforms in dogs

Bahr Arias MV, Conceição RT, Guimarães FC, Cardoso GS, Rocha NLFC. J Small Anim Pract. 2022 Mar 4. DOI: doi.org/10.1111/jsap.13460

44

• Article | Photosonic Treatment and Fibromyalgia: The Effect on Brain Compliance - Case Report

Junior AEA, Carbinatto FM, Tomaz CSR, Bagnato VS (2022) J Nov Physiother 12: 510. DOI: doi.org/10.4172/ 2165-7025.1000510

43

• Article | Waveform Morphology as a Surrogate for ICP Monitoring: A Comparison Between an Invasive and a Noninvasive Method

de Moraes FM, Rocha E, Barros FCD, Freitas FGR, Miranda M, Valiente RA, de Andrade JBC, Neto FEAC, Silva GS. 2022: 24:1–9. DOI: doi.org/10.1007/s12028-022-01477-4

42

• Article | From disease to noninvasive intracranial monitoring

Folchini, Caroline Mensor et al. 2022: ISSN 1678-4227. DOI: doi.org/10.1590/0004-282X-ANP-2021-0298

41

• Article | Noninvasive intracranial pressure monitoring in women with migraine

Rossi, D.M., Bevilaqua-Grossi, D., Mascarenhas, S. et al. 2022: Sci Rep 12, 2635. DOI: doi.org/10.1038/s41598-022-06258-9

40

• Article | A novel noninvasive technique for intracranial compliance monitoring in neurocritical care

Brasil, S. Journal of Personalized Medicine.

DOI: https://doi.org/10.3390/jpm11121302

39

• Article | The use of a non-invasive intracranial pressure monitoring method in the intensive care unit to improve neuroprotection on postoperative patients following extracorporeal circulation

Salomon, R. RBTI - Revista Brasileira de Terapia Intensiva. DOI: 10.5935/0103-507X.20210066

38

• Article | Intracranial Compliance Concepts and Assessment: A Scoping Review

Ocamoto, G. Frontiers in Neurology.

DOI: https://doi.org/10.3389/fneur.2021.756112

37

• Letter | Is It Possible To Monitor The Wave Form With Non-invasive Methods?

Rabelo, N. World neurosurgery.

DOI: https://doi.org/10.1016/j.wneu.2021.06.050

36

• Article | Noninvasive intracranial pressure real-time waveform analysis monitor during prostatectomy robotic surgery and Trendelenburg position: case report

Saba, G. Brazilian Journal of Anesthesiology.

DOI: https://doi.org/10.1016/j.bjane.2021.09.003

35

• Case Report | Non-invasive intracranial pressure monitoring in idiopathic intracranial hypertension and lumbar puncture in pediatric patient: case report

Dhaese, T. Surgical Neurology International. DOI: 10.25259/SNI_124_2021

34

• Case Report | Effect of hemodialysis on cerebral compliance assessed in a non invasive way

Rickly, C. Brazilian Journal of Development. DOI: doi.org/10.34117/bjdv7n1-689

33

• Case Report | Elderly non invasive intracranial pressure monitorization: a report of waveform morphology and cerebral compliance

Vellosa, J. Brazilian Journal of Development. DOI: doi.org/10.34117/bjdv7n1-470

3

2

• Case report | Untreatable Headache in a Child with Ventriculoperitoneal Shunt Managed by Use of New Non-Invasive ICP Waveform: a Case Report

Paraguassu, G. Frontiers in Neuroscience.

DOI: https://doi.org/10.3389/fnins.2021.601945

31

• Chapter | Non-Invasive intracranial pressure monitoring

Welling, L. LIVRO: Neurocritical Care for Neurosurgeons: Principles and Applications. DOI: https://doi.org/10.1007/978-3-030-66572-2

30

• Article | Noninvasive intracranial pressure monitoring in chronic Stroke patients with sedentary behavior-pilot study

Ocamoto, G. Acta Neurochirurgica Supplement. DOI: doi.org/10.1007/978-3-030-59436-7_12

29

• Letter | The Noninvasive Intracranial Pressure in Patients with Intracranial Hypertension

Rabelo, N. Clinics in Surgery. DOI: https://www.clinicsinsurgery.com/pdfs_folder/cis-v6-id3144.pdf

28

• Case report | Non-invasive monitoring of intracranial pressure during midazolam-induced moderate sedation for upper gastro intestinal endoscopy

Drewnoski, B. Brazilian Journal of Development.

DOI: https://doi.org/10.34117/bjdv.v7i5.29327

27

• Letter | Neurosurgery and Manned Spaceflight

Rabelo, N. Neurosurgery. DOI: doi.org/10.1093/neuros/nyab133

26

• Article | Intracranial pressure and laboratory parameters in high and low risk pregnant women

Silveira, D. Surgical Neurology International. DOI: doi.org/10.25259/SNI_109_2021

25

• Article | Noninvasive intracranial pressure monitoring methods: a critical review

Moulin, F. 2021. Arquivos de Neuro Psiquiatria. DOI: doi.org/10.1590/0004-282X-ANP-2020-0300

24

• Article | Use of non-invasive intracranial pressure pulse waveform to monitor patients with End-Stage Renal Disease (ESRD)

Rickly, C. PLOS ONE. DOI: doi.org/10.1371/journal.pone.0240570

23

• Article | Comparison of waveforms between non-invasive and invasive ICP monitoring

Gomes, I. Acta Neurochirurgica Supplement. DOI: doi.org/10.1007/978-3-030-59436-7_28

22

• Article | Intracranial compliance assessed by intracranial pressure pulse waveform

Brasil, S. Brainsciences. DOI: doi.org/10.3390/brainsci11080971span>

21

• Article | A nanometer resolution wireless device for non invasive intracranial pressure monitoring

Andrade, R. IEEE Sensors Journal. DOI: doi.org/10.1109/JSEN.2021.3090648

20

• Article | Cerebral Hemodynamics And Intracranial Compliance Impairment In Critically Ill Covid-19 Patients: A Pilot Study

Brasil, S. 2021. Brainsciences. DOI: doi.org/10.3390/brainsci11070874

19

• Article | The historic evolution of intracranial pressure and cerebrospinal fluid pulse pressure concepts: 2 centuries of challenges

Rabelo, N. Surgical Neurology International. DOI: doi.org/10.25259/SNI_53_2021

18

• Article | Obesity and its implications on cerebral circulation and intracranial compliance in severe covid 19

Brasil, S. 2021. Obesity Science & Practice. DOI: doi.org/10.1002/osp4.534

17

• Article | Intracranial Pressure During the Development of Renovascular Hypertension

Fernandes. Hypertension DOI: doi.org/10.1161/HYPERTENSIONAHA.120.16217

16

• Chapter | Intracranial pressure waveform. History, fundamentals and applications in brain injuries

Frigieri, G. LIVRO IntechOpen: Advancement and New Understanding in Brain Injury. DOI: doi.org/10.5772/intechopen.94077

15

• Chapter | Management of patients with brain injury using noninvasive methods

Frigieri, G. LIVRO IntechOpen: Advancement and New Understanding in Brain Injury. DOI: doi.org/10.5772/intechopen.94143

14

• Letter | Use of Intracranial Pressure Monitoring in Patients with Severe Traumatic Brain Injury

Rabelo, N. World Neurosurgery. DOI: doi.org/10.1016/j.wneu.2020.07.222

13

• Letter | Intracranial pressure monitoring: Challenge beyond the threshold numerical value

Rabelo, N. Journal of Neurosurgery. DOI: doi.org/10.3171/2020.9.JNS203395

12

• Article | Use of the Kirkpatrick methodology for training in new non-invasive intracranial pressure monitoring technology for nurses

Barros, T. Brazilian Journal of Health Review. DOI: doi.org/10.34119/bjhrv3n3-098

11

• Article | Intracranial compliance concepts and assessment a scoping review protocol

Russo, T. Research Square. DOI: doi.org/10.21203/rs.3.rs-43616/v1

10

• Article | In-flight analysis of intracranial pressure in pilots undergoing variation in Gz

Bezerra, T. Aeronautics and Aerospace Open Access Journal. 2018;2(3):126–131. DOI: doi: 10.15406/aaoaj.2018.02.00042

09

• Article | Analysis of a minimally invasive intracranial pressure signals during infusion at the subarachnoid spinal space of pigs

Frigieri, G. Acta Neurochirurgica Supplement. 2018;126:75-77. DOI: doi: 10.1007/978-3-319-65798-1_16

08

• Article | Analysis of a non-invasive intracranial pressure monitoring method in patients with traumatic brain injury

Frigieri, G. Acta Neurochirurgica Supplement. 2018;126:107-110. DOI: doi: 10.1007/978-3-319-65798-1_23

07

• Article | Noninvasive intracranial pressure monitoring for HIV-associated cryptococcal meningitis

Bolella, V. Brazilian Journal of Medical and Biological Research. 2017 Aug 7;50(9):e6392. DOI: doi: 10.1590/1414-431X20176392

06

• Article | Prediction of intracranial hypertension through noninvasive intracranial pressure waveform analysis in pediatric hydrocephalus

Ballestero, M. Child's Nervous System. 2017 Sep;33(9):1517-1524. DOI: doi: 10.1007/s00381-017-3475-1. Epub 2017 Jun 16

05

• Article | Characterization of ICP behavior in an experimental model of hemorrhagic stroke in rats

Cardim, D. Acta Neurochirurgica Supplement. 2016;122:121-4. DOI: doi: 10.1007/978-3-319-22533-3_24

04

• Article | Characterization of intracranial pressure behavior in chronic epileptic animals: a preliminary study

Cardim, D. Acta Neurochirurgica Supplement. 2016; 122:329-333. DOI: doi: 10.1007/978-3-319-22533-3_65

03

• Article | Validation of a new minimally invasive intracranial pressure monitoring method by direct comparison with an invasive technique

Frigieri, G. Acta Neurochirurgica Supplement. 2016;122:97-100. DOI: doi: 10.1007/978-3-319-22533-3_19

02

• Article | Validation of a new noninvasive intracranial pressure monitoring method by direct comparison with an invasive technique

Cabella. B. Acta Neurochirurgica Supplement. 2016;122:93-6. DOI: doi: 10.1007/978-3-319-22533-3_18

01

• Article | The new ICP minimally invasive method shows that the monro-kellie doctrine is not valid.

Mascarenhas, S. Acta Neurochirurgica Supplementum. 2012: 117 – 120. DOI: doi.org/10.1007/978-3-7091-0956-4_21

Our response:

We thank the reviewer for bringing these valuable references to our attention.

We recognize the importance of including comprehensive and current references to accurately reflect the state of research in this field. In response to your suggestion, we have reviewed the recent literature on ICP measurements using the Brain4care system. We have incorporated several publications[12–17] (ref. 8 – 13 in the revised main context) into the revised manuscript for comparison.

REFERENCE

1. Loughlin, H. & Sudhir, V. Exceptional-Point Sensors Offer No Fundamental Signal-to-Noise Ratio Enhancement. *Phys. Rev. Lett.* **132**, 243601 (2024).

2. Xiao, Z., Li, H., Kottos, T. & Alù, A. Enhanced Sensing and Nondegraded Thermal Noise Performance Based on PT-Symmetric Electronic Circuits with a Sixth-Order Exceptional Point. *Phys. Rev. Lett.* **123**, 213901 (2019).

3. Nyquist, B. H. Thermal agitation of electric charge in conductors. *Phys. Rev.* **32**, 110 (1928).

4. Chen, P.-Y. *et al.* Generalized parity–time symmetry condition for enhanced sensor telemetry. *Nat. Electron.* **1**, 297–304 (2018).

5. Dong, Z., Li, Z., Yang, F., Qiu, C. W. & Ho, J. S. Sensitive readout of implantable microsensors using a wireless system locked to an exceptional point. *Nat. Electron.* **2**, 335–342 (2019).

6. Zeng, C. *et al.* Enhanced sensitivity at high-order exceptional points in a passive wireless sensing system. *Opt. Express* **27**, 27562 (2019).

7. Lee, H. *et al.* Chiral exceptional point and coherent suppression of backscattering in silicon microring with low loss Mie scatterer. *eLight* **3**, 20 (2023).

8. Kim, C. *et al.* Parity-time symmetry enabled ultra-efficient nonlinear optical signal processing. *eLight* **4**, 6 (2024).

9. Kononchuk, R., Cai, J., Ellis, F., Thevamaran, R. & Kottos, T. Exceptional-point-based accelerometers with enhanced signal-to-noise ratio. *Nature* **607**, 697–702 (2022).

10. Chen, W., Özdemir, Ş. K., Zhao, G., Wiersig, J. & Yang, L. Exceptional points enhance sensing in an optical microcavity. *Nature* **548**, 192–195 (2017).

11. Hodaei, H. *et al.* Enhanced sensitivity at higher-order exceptional points. *Nature* **548**, 187–191 (2017).

12. Dixon, B. *et al.* Assessment of a Non-Invasive Brain Pulse Monitor to Measure Intra-Cranial Pressure Following Acute Brain Injury. *Med. Devices Evid. Res.* **16**, 15–26 (2023).

13. Ocamoto, G. N. *et al.* Characterization of intracranial compliance in healthy subjects using a noninvasive method - results from a multicenter prospective observational study. *J. Clin. Monit. Comput.* 1-13 (2024).

14. Hassett, C. E. *et al.* Assessment of Cerebral Autoregulation Using Invasive and Noninvasive Methods of Intracranial Pressure Monitoring. *Neurocrit. Care* **38**, 591–599 (2023).

15. Aspide, R., Moneti, M. & Castioni, C. A. Are Intracranial Pressure Waveforms the New Frontier for Noninvasive Assessment of Intracranial Pressure? *Neurocrit. Care* **40** 48–50 (2024).

16. Ballestero, M. *et al.* Can a new noninvasive method for assessment of intracranial pressure predict intracranial hypertension and prognosis? *Acta Neurochir.* **165**, 1495–1503 (2023).

17. Brasil, S. *et al.* A novel noninvasive technique for intracranial pressure waveform monitoring in critical care. *J. Pers. Med.* **11**, 1302 (2021).