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Overview

The Centre for Computational Systems Biology (CCSB) was founded in March 2008. The Centre is affiliated to the Innovation Platform for Science and Technology of Fudan University. Our center focuses its research on Computational Neuroscience and Cellular Biology. The director of the centre is Professor Jianfeng Feng, also professor and head of the Laboratory of Computational Biology in Warwick University, United Kingdom.

The Centre now has around forty+ research members, an administrative assistant and two research assistants. The Centre is divided into two Research Groups, Neuroscience and Cellular Biology.

Prof. Wei Lin leads Cellular Biology group, including
Prof. David Waxman,
Prof. Yunxin Zhang,
Assoc. Prof. Ruoyu Luo,
Assoc. Prof. Shuqin Zhang,
Assoc. Prof. Xiaohong Gong,
Prof. Gunter Schumann,
Prof. Jürgen Kurths,
Prof. Yingcheng Lai,
Prof. Albert Goldbeter,
Prof. Andreas Dress,
Prof. Hong Qian,
Prof. Martin Lascoux,
Prof. Andy Overall,
Dr. Cong Zhou,
PhD student: Yang Pu, Bing Xu, Wenbo Sheng, Xin Chen, Siyang Leng, Lei Zhao, Leiheng Fang, Sixiang Liu, and Pan Li.

Prof. Wenlian Lu is the leader for Computational Neuroscience group, including
Prof. Yuguo Yu,
Assoc. Prof. Jie Zhang,
Prof. Keith Kendrick,
Prof. Edmund T. Rolls,
Prof. Mingzhou Ding,
Assoc. Prof. Shuixia Guo,
Dr. Christophe Ladroue,
Dr. Qiang Luo,
Dr. Wanlu Deng,
Dr. Xinjun Gan,
PhD students: Tian Ge, Xiaoxi, Ji, Yu Wu, Xiangnan He, Ye Yao, Boqiang Fan, Chenyang Tao, jianglong Xu, Hongtao Ruan, Yuankai Ha, Haitao Han.

The members of the centre have various academic backgrounds, ranging from applied mathematics to statistics, from biology physics to molecular biology, and to neuroscience. We have published papers in
Nature (6),
Science (5),
Mol. Psychiatry (1),
Curr. Biol. (3),
PNAS (3),
Mol. Sys. Biol. (1),
J. Neurosci. (4),
PRL (5),
PLoS Comp. Biol. (7),
and others.

The Centre is currently in a growing phase. We welcome applications from colleagues interested in joining us.
Aims and Mission

The Computational Systems Biology Centre applies advances in Mathematics, Statistics and Computer Science to the increasingly challenging applications in biology and medicine. Techniques from diverse areas such as machine learning, image processing and computer vision, data mining, statistical analysis, mathematical modeling/simulations, computation to organize and analyze the vast amount of data generated by biologists and contribute to the understanding of biological systems. Current work focuses on computational neuroscience, computational cell biology, bioimage, proteomics, sociomicrobiology, and applications in medical visualization.

How to Find Us

The Centre for Computational Systems Biology (CCSB) is located in the East Guanhua tower on the Handan Campus of Fudan University, which is located at 220 Handan Road, Shanghai (复旦大学邯郸路校区, 地址：上海市邯郸路220号). If you run into any problems to find us, please feel free to contact the secretary, Qianyi Zhang, at +86-21-55665546 ext. 8001.

Directions From Nearby Airports To Fudan:
- **Hongqiao Airport:**
  1. Take the Metro, Line 10, to Jiangwan Stadium (江湾体育场站), and then walk approximately 15 minutes to the Centre.
  2. Taxi to Fudan University costs roughly CNY 90.

- **Pudong International Airport:**
  1. Take a Shuttle Bus, Line 4 (机场四线), to Wu Jiao Chang (五角场站), which costs CNY 20, and then walk approximately 15 minutes to the Centre.
  2. Taxi to Fudan University costs roughly CNY 120.

Directions From Nearby Train Stations To Fudan:
- **Shanghai Railway Station:**
  1. Take the South Exit of the Railway Station and then go by taxi to Fudan University. This costs roughly CNY 30.
  2. Take the North Exit of the Railway Station and then take a No. 942 Bus to Fudan University Stop (复旦大学站).

- **Shanghai South Railway Station:**
  Take the Metro, Line 3, to Chifeng Road (赤峰路站) and then transfer to No. 139 or 854 or 942 or 991 Bus to Fudan University (复旦大学站).

- **Shanghai Hongqiao Railway Station:**
  Take the Metro, Line 10, to Jiangwan Stadium (江湾体育场站), and then walk approximately 15 minutes to the Centre.
Organisation

Director

Jianfeng FENG received B.Sc., M.Sc., and Ph.D. degrees from the Department of Probability and Statistical, Peking University, China. In 1993, he was Humboldt Fellowship and stayed in Germany for around three years. In 1996, he joined the Babraham Institute, Cambridge, as a Principle Investigator and a project leader and later became the Deputy Head of the Computational Neuroscience Lab. During the period from 2000 to 2004, he was a reader in Sussex University, UK. In 2005--2008, he was awarded a Yangtze Professorship of China. In 2011, he received the Royal Society Wolfson Research Merit Award. Since 2005, he has been professor of the Centre for Scientific Computing and Computer Science, Warwick University, UK. Also, he has been the director of the Centre for Computational Systems Biology, Fudan University, China since 2007. His current research interest focuses on Computational Biology. For his detailed research profiles, please refer to http://www.dcs.warwick.ac.uk/~feng.
Wei LIN was born in Shanghai, China, in 1976. He received B.Sc. and Ph.D. degrees in applied mathematics from Fudan University, Shanghai, China, in July, 1998 and January, 2003, respectively, with specialization in dynamical systems, bifurcation and chaos theory, and chaos control and synchronization. In 2003, Dr. Lin joined the School of Mathematical Sciences, Fudan University, China, where presently, he is a Professor in applied mathematics. From 2004 to 2005, he served as a postdoctoral research fellow at the Department of Mathematics and Statistics, York University, Canada. Currently, he is serving as the Vice Dean of the School of Mathematical Sciences and as the Deputy Dean of the Centre for Computational Systems Biology, Fudan University, China. He is now the Deputy Secretary of the Shanghai Society of Nonlinear Sciences. His current research interests include nonlinear dynamical systems, bifurcation and chaos theory, hybrid systems, stochastic differential and difference equations, chaos control and synchronization, complex networks, and computational systems biology. Dr. Lin received the Second Prize of the Fok-Ying-Tung Education Foundation Award for Young Scientists in Universities from the Ministry of Education of China in 2010 and was selected as the New Century Talent of the Ministry of Education of China in 2011. Dr. Lin serves as the Associate Editor of International Journal of Bifurcation and Chaos from 2012.
Members

David Waxman is a Professor in the Centre for Computational Systems Biology. He has been at Fudan University since 2011. He began his studies in Physics in 1980 at University College London. He then moved to Sussex University and, in 1984, gained a PhD in Theoretical Physics under Professor Tony Leggett. He stayed one year in the USA, at the State University of New York at Stony Brook, as a postdoc of Professor Sudip Chakravarty. He then returned to Sussex University, where he was first Lecturer, and later, Reader in Theoretical Physics. In 1998 he changed subjects and moved to the Biology Department at Sussex and in 2005 was made Professor.

In his research, Professor Waxman develops and analyses mathematical models to answer fundamental questions in evolution, population genetics and related areas, with particular emphasis on the underlying statistical and stochastic aspects of these subjects. His research involves extensive use of mathematics, statistics and computer simulations, and may be described as theoretical or computational or mathematical biology. His current work includes analyses of stochastic processes that occur in populations of finite size (random genetic drift). For more information about his research and access to his publications, please go to http://www.dwaxman.com/

Ruoyu Luo is with the Centre for Computational Systems Biology of Fudan University. He received his Ph.D in Huazong University of Science and Technology in 2006, during which time he modified the optimal objective from the maximization of ATP production to the minimal fluctuation of the profile of metabolite concentration under ischemic conditions, extending the hypothesis of original minimization of metabolic adjustment to create a composite modeling approach called M-DFBA. In 2006, he joined the Key Lab of Systems Biology of Chinese Academy Institution. He studied the robustness of photosynthetic metabolism in the chloroplasts of C3 plants under drought stress and high CO2 concentration conditions by using a MOMA Dynamic flux balance analysis (MDFBA) method and found that highly cooperative regulation assure the robustness of the biological systems that maintains the system’s function under environmental perturbations, resulting in minimizing fluctuations in the profiles of metabolite concentrations, which is the key to maintaining a system’s function. From 2008 to 2010, he worked as a postdoc in Johan elf’s lab in Cell and Molecular Department of Uppsala University in Sweden. His project in the lab is developing a stochastic algorithm (GeneCircuits) for simulating the gene regulation system of E.coli.
Yunxin Zhang is with the School of Mathematical Science at Fudan University. He received B.Sc. in mathematics from East China Normal University in 1994, and M.Sc. and Ph.D. in mathematics from Fudan University in 1997 and 2006, respectively. He had served in army for nine years, and then joined Fudan University in 2006. His research and teaching interests include mathematical modeling, numerical solution of partial differential equation and integral equation, and molecular motors. His recent research interest is biological related mathematical problems, including the mechanism of motor protein kinesin and dynein, the cargo transportation in cells.

Shuqin Zhang is with School of Mathematical Sciences at Fudan University. She received B.Sc. in mathematics from Qufu Normal University in 2000, M.Sc. in operations research and control theory from Beijing Institute of Technology in 2003, and Ph.D. in applied mathematics from The University of Hong Kong in 2007. Then she joined Fudan University. Now she is an associate professor. Her main research interests include the application of optimization techniques, statistics and computational mathematics to bioinformatics and systems biology, and scientific computing.

Xiaohong Gong received her B.S. degree in medicine and Ph.D degree in psychiatry from Peking University Health Science Center in 2000 and 2005, respectively. From 2005 to 2007, she worked as a postdoctoral research fellow in France at the lab of Human Genetics and Cognitive Functions, Pasteur institute. She has been working at school of life sciences, Fudan University since 2007. Her research interests are human molecular genetics, especially focused on psychiatric diseases. Genetic susceptibility to autism, schizophrenia and drug addiction is studied by screening of common SNPs and rare variants of candidate genes or whole genome-wide microarrays.
Visitors:

**Gunter SCHUMANN** received M.D. degree in Medicine from Universities of Tuebingen and Hamburg in 1993 and Ph.D. degree in Medicine from University of Hamburg in 1993. Now he is Professor of Biological Psychiatry and Head of the Section at the Social, Genetic and Developmental Psychiatry Centre (MRC), and Honorary Consultant at South London and Maudsley NHS Foundation Trust (SLaM) where he lead the challenging behaviour programme of the National Psychosis Unit. Before joining the IoP in 2005, he trained (postgraduate) and worked at Harvard University, at the University of Freiburg and at the Central Institute of Mental Health, University of Heidelberg, Germany. His general research interests are in etiological and diagnostic stratification of psychiatric patients to identify neurobehavioural phenotypes, which allow the development of predictive and prognostic biomarkers.

**Jürgen KURTHS** studied mathematics at the University of Rostock and got his Ph.D. in 1983 at the GDR Academy of Sciences and his Dr. habil. in 1990. He was full Professor at the University of Potsdam from 1994-2008 and has been Professor of Nonlinear Dynamics at the Humboldt University, Berlin and chair of the research domain Transdisciplinary Concepts of the Potsdam Institute for Climate Impact Research since 2008 and a 6th century chair at the Institute for Complex Systems and Mathematical Biology at Kings College of the Aberdeen University (UK) since 2009. He is a fellow of the American Physical Society and of the Fraunhofer Society (Germany). He got an Alexander von Humboldt research award from CSIR (India) in 2005 and a Honorary Doctorate in 2008 from the Lobachevsky University Nizhny Novgorod. He has become a member of the Academia Europaea in 2010, Honorary Professor of Potsdam University in 2011 and Honorary Doctorate in 2012 from the State University Saratov. His main research interests are complex synchronization phenomena, complex networks, time series analysis and their applications in climatology, sustainability research, physiology, systems biology and engineering.

**Ying-Cheng LAI** received B.S. and M.S. degrees in Optical Engineering from Zhejiang University in 1982 and 1985, and M.S. and Ph.D. degrees in Physics/Nonlinear Dynamics from University of Maryland at College Park in 1989 and 1992, respectively. He became a Professor of Electrical Engineering in 2001. In 2009, Y.-C. Lai was named the Sixth Century Chair in Electrical Engineering by University of Aberdeen, Scotland, UK. In the past five years, he gave over 50 invited seminars and colloquia all over the world. His papers have received over 7300 scientific citations (according to Google Scholar). His current Google-Scholar based H-index is 44. Y.-C. Lai's current research interests are Chaotic Dynamics, Complex Networks, Quantum Transport in Nanostructures, Biological Physics, and Signal Processing.
**Hong QIAN** received his B.S. in Astrophysics from Peking University. He worked on fluorescence correlation spectroscopy (FCS) and single-particle tracking (SPT) and obtained his Ph.D. in Biochemistry from Washington University (St. Louis). His research interests turned to theoretical biophysical chemistry and mathematical biology when he was a postdoctoral fellow at the University of Oregon and at the California Institute of Technology. Between 1994 and 1997, he was with the Department of Biomathematics at the UCLA School of Medicine, where he worked on the theory of motor proteins and single-molecule biophysics. This work led to his current interest in mesoscopic open chemical systems. He joined the University of Washington (Seattle) in 1997 and is now Professor of Applied Mathematics, and an Adjunct Professor of Bioengineering. His current research is in stochastic analysis and statistical physics of cellular systems. His recent book “Chemical Biophysics: Quantitative Analysis of Cellular Systems”, co-authored with Daniel A. Beard, has been published by the Cambridge University Press.

**Albert GOLDBETER** is a Professor at the Faculty of Sciences of the Free University of Brussels (Université Libre de Bruxelles, ULB, Belgium) where he is Head of the Unit of Theoretical Biology. He is the author of some 200 publications in the field of Theoretical and Computational Systems Biology. His main research interests pertain to the nonlinear dynamics of biological systems, with a focus on modeling cellular rhythms and threshold phenomena in cellular regulatory networks. Albert Goldbeter is the author of the book Biochemical Oscillations and Cellular Rhythms. The molecular bases of periodic and chaotic behavior (Cambridge University Press, Cambridge, UK, 1996). He is member of the Belgian Royal Academy of Sciences.

**Andreas DRESS** studied mathematics in Berlin, Tübingen and Kiel, earned his doctorate in 1962 and obtained his postdoctoral lecture qualification in 1965. He was a member of the Institute for Advanced Studies in Princeton, USA for many years, and has been a professor of mathematics at the University of Bielefeld since 1969. Dress was a visiting scientist at many renowned universities and research institutes worldwide and is co-editor of seven international professional journals. In addition, Dress has been a visiting scientist at the Max Planck Institute for Mathematics in the Sciences in Leipzig since 2003. His current research interests include phylogenetic combinatorics, molecular evolution and the use of topological methods in proteomics and computational chemistry.
Martin LASCOUX received his PhD from Paris-Orsay in 1992. This was followed by a postdoctoral post at the University of Wisconsin-Madison. He then moved to the Evolutionary Biology Centre at Uppsala University in 1997. He has been a Professor of Population Genetics at Uppsala University since 2001. He was an Invited Professor at PICB, Chinese Academy of Sciences in 2010-2011 and has taught courses on population genetics and evolutionary biology at Fudan University in 2011 and 2012. His current work focuses on local adaptation in plants, in particular on clinal variation in phenology. In collaborations with members of the Centre he hopes to gain a better understanding of the architecture of quantitative traits, such as those associated with phenology.

Andy OVERALL received his BSc from University College London (UCL), UK, and his PhD in population genetics from Queen Mary, University of London. In 1998 he worked in the molecular ecology laboratory in Cambridge and in 2001 worked as a NERC postdoctoral researcher at the University of Edinburgh. Since 2004 he has been a senior lecturer at the University of Brighton, UK. His current research interests focus on the use of DNA profiles to infer past and present population dynamics and the consequences of inbreeding for health. For his detailed research profiles, please refer to http://www.brighton.ac.uk/pharmacy/research/groups/dp/population_genetics.php

Cong ZHOU is a research associate in the Paterson Institute for Cancer Research, University of Manchester, UK. He received a B. Eng in computer science from Tianjin University, China in 2001. He later received a M. Res in Artificial Intelligence and a Ph. D degree in Bioinformatics from University of Sussex, UK in 2004 and 2009 respectively. His research interests include applying machine learning approach in proteomics research and exploring cancer biomarker.
Ph.D. Students:

Yang Pu is now Ph.D. student in the School of Mathematical Sciences and the Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2008. He has attended summer school of Applied Mathematics Related to Stochastic Analysis and Statistical Physics in 2008 and The Fourth Shanghai International Symposium on Nonlinear Sciences and Applications in 2010. His research interests include chaotic dynamical system, delay differential equations and microarray data preprocess in systems biology.

Xu Bing is a Ph.D. student in the School of Mathematics Sciences at Fudan University, Shanghai, P.R. China. She received the bachelor degree in Mathematics and Applied Mathematics from Fudan University in 2009. She attended Spring School of Multiscale Methods and Modelling in Biophysics and Systems Biology in Tongji University in 2009.5 and Summer School of Computational Neuroscience and Gene Circuits in Warwick University, UK in 2009.7. Her research interest include parameter identification in nonlinear systems and dynamics in nucleus.
Siyang LENG is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2011. He attended Summer School of Computational Neuroscience and Gene Circuits in Warwick University, UK. His research interests include neuronal network and its properties.

Lei ZHAO is a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He got his bachelor’s degree in Mathematics from Fudan University in 2012. His supervisor is Professor David Waxman. He’s now focusing on dynamical systems and population genetics.

Wenbo SHENG is now a Ph.D. student in the School of Mathematical Sciences and the Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2010. He attended Summer School of Computational Neuroscience and Gene Circuits in Warwick University, UK. His research interests include neuronal network and its properties.

Xin CHEN is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2010. His research interests include random dynamical systems, stochastic differential equations and nonlinear systems.
Leheng Fang is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received bachelor’s degree in Mathematics from Fudan University in 2012. His research interests include functional differential equations and dynamical systems.

Sixiang Liu is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2012. His research interests include semi-tensor product of matrices, systems biology and dynamical systems.

Pan Li is going to be a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He will receive his bachelor’s degree in Mathematics from Fudan University in 2013. His research interests include systems biology and stochastic differential equations.
Neuron Biology Group Leader

Wenlian LU received B.Sc. degree in mathematics and Ph.D. degree in applied mathematics from Fudan University, Shanghai, China, in 2000 and 2005, respectively. He was a postdoc at the Max Planck Institute for Mathematics in Sciences from Aug. 2005 to Oct. 2007 and is currently an Associate Professor with the School of Mathematical Sciences, Fudan University, Shanghai, China. His research interests include neuronal networks, nonlinear dynamical systems, and complex systems. Dr. Wenlian Lu currently serves as an associate editor for Neurocomputing and a guest associate editor for International Journal of Bifurcation and Chaos. He is a member of IEEE and served as PC members for several conferences (ISNN 2006-2010, ICONIP 2006, ICSI2010).
Yuguo Yu is with the Centre for Computational Systems Biology of Fudan University. He received B.Sc and M.S. in Physics from Lanzhou University in 1995 and 1998 respectively, and Ph.D. in Physics from Nanjing University. He was trained in computational/experimental Neuroscience at Carnegie Mellon University as a Postdoctoral Fellow from 2001 to 2004; and then served as a Postdoc Associate and Associate Research Scientist at the Department of Neurobiology, Yale University from 2005 to 2011. Since 2011, he joins the CCSB at Fudan University as a faculty position. His research interests include nonlinear dynamics, systems identification, sensory adaptation and efficient encoding, cortical neuron and circuit reconstruction and modeling, neuroinformatics, and cellular mechanisms of cortical function.

Jie Zhang is with the Centre for Computational Systems Biology of Fudan University. He received B.Sc. in chemical engineering from the China University of Petroleum in 2001, M.S. degree in Electrical Engineering from Shandong University in 2004 and Ph.D. from Hong Kong Polytechnic University in 2007. His research interests include nonlinear time series analysis, computational biology and complex networks. He is a finalist to the 2007 Hong Kong Young Scientist Award. He joins the Centre in 2010.
Postdoctoral Fellows

Qiang Luo is a lecturer with the Department of Management in the National University of Defense Technology. He received B.Sc. in Applied Mathematics and Ph.D in Systems Science from National University of Defense Technology in 2004 and 2010 respectively. He is now working as a post-doc researcher in the Shanghai Center for Mathematical Sciences. His research interests include the theory and applications of soft-computing technology, probabilistic inference, and computational neuroscience.

Wanlu Deng received B.Sc. and Ph.D. degrees from the Department of Probability and Statistical, School of Mathematical Sciences, Peking University, China, in 2007 and 2012, respectively. In 2010, she was supported by Chinese Scholarship Council and stayed at the Department of Biostatistics and Epidemiology, School of Medicine, University of Pennsylvania, United States for one year as a visiting student. In 2009-2012, she was awarded President’s Scholarship of Peking University. Her current research interest focuses on Causal Inference in Biology, such as learning causal networks on time series data, identifying intermediate variables on causal paths, and the comparison of Pearl’s causality with Granger causality.

Xinjun Gan received B.Sc., M.Sc., and Ph.D. degrees from the Department of Mathematics, Shandong University, China. Between 2007-2011, he joined projects about risk control for commercial bank, such as Dongguan bank, Evergrowing bank. In 2009-2012, he did his Ph.D work major in statistics, the topic of the dissertation is the weak duality of Ito diffusion and Monte Carlo simulation of the fundamental solution. Research interests: stochastic process, Monte Carlo method, Schrodinger equation, Green’s function, Multivariate analysis.
Visitors

Keith KENDRICK received a PhD in Psychology from the University of Durham (UK) in 1979. He has held research positions in the University of Durham, Institute of Zoology in London, University of Cambridge and the Babraham Institute in Cambridge where he was Head of Cognitive and Systems Neuroscience prior to moving his current post in the School of Life Science and Technology at the University of Electronic Science and Technology of China in September 2011 as a 1000 Talent Professor. He is a Fellow of the Society of Biology in the UK since 1996 and an Emeritus Professor of Gresham College, London since 2002. He has published over 200 refereed papers, including 8 in Nature, Science and PNAS and received numerous grants from UK, US and China based funding agencies. His current main research work is focussed on establishing how the human brain interprets social and emotional information and also the effects of prosocial peptides using behavioral, brain imaging and pharmacogenetic approaches. He is also investigating functional connectivity and structural changes in the brain associated with psychiatric disorders and the potential therapeutic effects of prosocial peptides.

Edmund T. ROLLS MA, DPhil, DSc, Hon DSc is at the Oxford Centre for Computational Neuroscience, Oxford, UK, and at the Department of Computer Science, University of Warwick, UK, focussing on full-time research, and was Professor of Experimental Psychology at The University of Oxford. Edmund T. Rolls is a neuroscientist with research interests in computational neuroscience, including the operation of real neuronal networks in the brain involved in vision, memory, attention, and decision-making; functional neuroimaging of vision, taste, olfaction, feeding, the control of appetite, memory, and emotion; neurological disorders of emotion; psychiatric disorders including schizophrenia; and the brain processes underlying consciousness. He has published ten books and more than 530 full length research papers on these topics, which are shown, with many .pdfs available, at http://www.oxcns.org.
Mingzhou Ding received his Bachelor of Science degree in astrophysics from Peking University in 1982. From 1982 to 1986 he was a graduate student in the Institute of Theoretical Physics, Chinese Academy of Sciences. He received his PhD degree in physics from the University of Maryland in 1990. From 1990 to 2004 he was assistant, associate and full professor in the Department of Mathematical Sciences and Center for Complex Systems and Brain Sciences, Florida Atlantic University. In 2004 he joined the faculty of the Department of Biomedical Engineering at the University of Florida. Since 2008 he has been the J Crayton Pruitt Family Professor of Biomedical Engineering at the University of Florida. In 2010 and 2012 he was a visiting professor at Centre for Computational Systems Biology, Fudan University. Prof. Ding applies multimodal imaging and related computational methods to study cognitive brain function and its impairments by brain disorders.

Shuixia Guo is with the Mathematics and Computer Science College of Hunan Normal University. She received her Bachelor's degree and Master's degree in 1997 and 2000 respectively in Hunan Normal University. She became a Ph.D. student under the supervisor of Prof. Jianfeng Feng from 2006 and received her Ph.D. degree in 2009. She majors in the statistics and network structure analysis of biological data and fMRI data.

Christophe Ladroue received in PhD from St George's hospital and medical school, University of London, in 2004. His research focuses on machine learning and statistics applied to biological data. He has worked on the development of new techniques for cancer data (Magnetic Resonance Spectroscopy), micro-arrays (plant and fungus), electrophysiology (sheep) and speech recognition. He is also working on molecular simulation, using the theory of rough paths and parallel computing for simulating multiscale systems. He has authored more than 20 papers (PLOS ONE, Annals of Statistics etc.) and taught at international summer schools. He is currently working on the genetic aspects of synthetic biology.
Ph.D. Students

**Tian GE** is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2009. He will be a joint Ph.D. student in the Centre of Scientific Computing at the University of Warwick, United Kingdom from 2010 to 2012 under a scholarship from the State Scholarship Fund. His research interests include computational neuroscience, systems biology and dynamical systems.

**Xiaoxi Ji** is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. She received her bachelor’s degree in Mathematics from East China Normal University in 2009. She attended the Fourth and Fifth Shanghai International Symposium on Nonlinear Sciences and Applications in Xuzhou Normal University in 2010 and Fudan University in 2012 respectively. In 2012, she also attended 18th annual meeting of the Organization for Human Brain Mapping in Beijing, China. Her research interests include statistical analysis and network structure analysis via biological data mining.

**Yu Wu** is a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology of Fudan University. He received his bachelor’s degree in mathematics from Fudan University in 2010. He is a joint Ph.D. student in the Centre of Scientific Computing at the University of Warwick, United Kingdom from 2011 to 2013, sponsored by the China Scholarship Council. His research interests include dynamical model analysis and causal network inference.

**Xiangnan He** received the B.S. degree in the Department of Mathematics from Zhejiang University, Hangzhou, China, in 2007. Now he is with Fudan University as a Ph.D. student in the Centre for Computational Systems Biology. His research interests include neural networks, nonlinear dynamical systems, and complex systems.
Ye Yao is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2011. He will be a joint Ph.D. student in the Centre of Scientific Computing at the University of Warwick, United Kingdom from 2012 to 2014. His research interests include computational neuroscience, systems biology, diffusion MRI and dynamical systems.

Boqiang Fan is now a Ph.D. student in the School of Life Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his master’s degree in Biology from South China Normal University in 2011. His research interests include computational neuroscience, nerve electrophysiology and cognitive neurobiology.

Chenyang Tao is now a PhD student in School of Mathematics and Center for Computational Systems Biology, Fudan University. He got his BS degree from Fudan University in 2011. His research interests include causality inference, nonlinear time series analysis and computational neural science.

Jianglong Xu is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his bachelor’s degree in Mathematics from Fudan University in 2012. His research interests include computational neuroscience, functional magnetic resonance imaging.
Hongtao RUAN is going to be a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He will receive his bachelor’s degree in Mathematics and Applied Mathematics from Fudan University in 2013. His research interests include computational neuroscience, systems biology.

Yuankai HA is going to be a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He will receive his bachelor’s degree in Mathematics and Applied Mathematics from Fudan University in 2013. His research interests include computational neuroscience, systems biology and dynamical systems.

Haitao HAN is now a Ph.D. student in the School of Mathematical Sciences and Centre for Computational Systems Biology at Fudan University, Shanghai, People’s Republic of China. He received his Master’s degree in Mathematics from East China Normal University in 2005, and had worked in Inner Mongolia University until 2011. His research interests include computational neuroscience, statistical physics and dynamic systems.
Advisory Members

**Daqian Li** graduated from the Department of Mathematics, Fudan University in 1957. He is now a Professor of the School of Mathematical Sciences at Fudan University, and an Academician of the Chinese Academy of Sciences. Additionally, he has been a Fellow of the Third World Academy of Sciences (since 1997), a Foreign Member of the French Academy of Sciences (since 2005). Professor Li has received one second prize and one third prize of the National Natural Sciences from the State, one first prize of Scientific and Technological Progress from the State Education Commission, one first prize of Scientific and Technological Progress from Shanghai Municipality, one first National Award and one Exceptional Shanghai Award for Teaching Achievements in Higher Education. Two of his books have been recognised as Excellent University Textbooks by the State. He is accomplished in the theory and application of partial differential equations, and has written 12 monographs, such as 'Mathematical and Physical Equations', 'Application of Preferential Elements in Electrometric'.

**Zhiming Ma** received his Ph.D. degree from the Chinese Academy of Sciences (CAS) in 1984. He is now a Professor of the Institute of Applied Mathematics of CAS, the President of the Chinese Mathematical Society, an Academician of the Chinese Academy of Sciences, and a Fellow of the Third World Academy of Sciences. Professor Ma has made important contributions in the theory of Dirichlet forms and Markov processes. Jointly, with co-authors, he found a new framework of quasiregular Dirichlet forms, which correspond to right processes in one-to-one manner. This result completes a twenty year problem in the area. The framework of quasiregular Dirichlet forms has been used in the study of infinite dimensional analysis, quantum field theory, the theory of Markov processes, and in other areas. Professor Ma’s current research interests include probability and stochastic analysis, stochastic topology and stochastic complex networks.

**Li Jin** received Ph.D. degrees in Biomedical Sciences/Genetics from the University of Texas – Houston Health Science Center in 2009. Currently he is a Fudan-Haoqing Professor in the Institute of Genetics, School of Life Sciences, Fudan University. He is serving as the Vice President for Research and Graduate Studies at Fudan University. Professor Li has won many academic awards at home and abroad, and has made distinguished contributions in the life sciences research. Important work of his proposed the theory that modern Chinese man evolved from African ancestors. His current research interests include human and medical genetics, genetic epidemiology, population genetics/genomics, genetic anthropology, computational biology and bioinformatics.
Qianyi Zhang is the Administrative Assistant of the Centre. She joined Fudan University in 2009. If you have any question about the Centre, please contact her. E-mail: zqy@fudan.edu.cn, phone: 86-21-55665546 ext. 8001.

Bing Jia is the Research Assistant of Professor Jianfeng Feng. She joined the Center in 2012. She received M.B. from College of Medicine, Xi’an Jiaotong University, in 2003. During her Ph.D., she majored in cardiovascular pharmacology and neurophysiology from 2004 to 2010. At present, she is engaged in fMRI experiments on psychiatric patients. E-mail: jiabing427@gmail.com, phone: 86-21-55665546 ext. 8003.

Hua Deng joined the Center as the Research Assistant of Professor David Waxman in 2012. She received B.Sc. in Biotechnology from Ningxia University in 2005, and Ph.D. in Botany from Xiamen University in 2012. During her Ph.D., She was trained in Epigenetic and Reproductive Biology at Australian National University as a visiting fellow from 2010 to 2012. Now, she is under the advice of Professor Waxman and does related research on computational biology. E-mail: denghua@fudan.edu.cn, phone: 86-21-55665546 ext. 8002.
Recent Developments

Awards

Royal Society Wolfson Research Merit Award
Prof. Jianfeng Feng, Director of the Centre for Computational Systems Biology at Fudan University, Shanghai, China, is one of the new Royal Society Wolfson Research Merit Award holders. He has received this award for his scientific work, which bridges the gap between fMRI and Genome-wide data, and which has applications to human disease. The scheme provides up to 5 years’ funding, after which the award holder continues with a permanent post at the host university.

Jointly funded by the Wolfson Foundation and the Department for Business, Innovation and Skills (BIS), the scheme aims to provide UK universities with additional support to enable them to attract or retain respected scientists of outstanding achievement and potential in the UK. The focus of the award is a salary enhancement, usually in the range of £10,000 to £30,000 per annum.

The Wolfson Foundation is a grant-making charity established in 1955. Funding is given to support excellence. More information is available from www.wolfson.org.uk

The second prize of the Heng-Yuan-Xiang Award
Ge Tian, a PhD student of the Centre for Computational Systems Biology, has been received the second prize of the Heng-Yuan-Xiang Award. The Award was set up by the Beijing Institute of Life Science, Chinese Academy of Sciences and the Heng-Yuan-Xiang Company. Recipients of the award are young investigators who are working on sensory, psychological or cognitive neuroscience and related areas. These individuals have scientific achievements with potential applications throughout China. In 2012, 4 first prizes and 6 second prizes were awarded.
抑郁症病人不易产生憎恨

来自复旦大学、英国华威大学、湘雅医学院与剑桥巴布拉罕研究所的研究人员组成的团队发现，抑郁症患者大脑中与“憎恨”相关联的功能连接网络存在消失的现象，也就是说抑郁症病人往往难以产生憎恨的情绪。这一研究成果公布在《分子精神病学》（Molecular Psychiatry）杂志上。

抑郁症是一种常见的精神疾病，主要表现为情绪低落，兴趣减低，悲观，思维迟缓，缺乏主动性，自责自罪，饮食、睡眠差，担心自己患有各种疾病，感到全身多处不适，严重者可出现自杀念头和行为。

据报道，英国权威医学杂志《柳叶刀》公布的一份数据表明，中国有高达17.5%的人群患有各种各样的精神障碍，包括心理焦虑、抑郁症等。但国内对这一疾病缺乏重视，患者就医时往往病情已相当严重。

抑郁症病人的一个重要的表现是“恨自己”，大脑中的“憎恨”网络由额上回、杏仁核、壳核等区域组成。当人们看到自己厌恶或者有强烈感情的人或事物时，这些脑区即会被激活。在这篇文章中，研究人员发现抑郁症患者大脑中与“憎恨”相关联的功能连接网络存在消失的现象，更准确地揭示了该人群大脑“憎恨”功能的异常。

研究人员认为，社会个体适度地宣泄其负面“憎恨”情绪，有助于其心理以及精神的调节，“爱憎分明”的人群患抑郁症的概率，可能低于不易产生“憎恨”情绪的人群。

冯建峰教授研究组在生物神经元网络研究方面取得了不少成果，有关工作曾被BBC, 华盛顿邮报, 路透社等世界上数百家新闻社报道。之前其研究组曾揭秘过母亲哺乳的生理机能，他们发现母亲在哺乳过程中，其大脑中下丘脑神经细胞展现出非常有规律的同步发放分泌大量激素的生理现象；母亲大脑中负责细胞之间信号传递的细胞树突通过正反馈也参与到分泌激素的行列之中。
A report by BBC NEWS on the paper “Breastfeeding trust hormone clue” published in “PLoS Computational Biology”
(http://news.bbc.co.uk/2/hi/health/7513267.stm)

Breastfeeding trust hormone clue

Scientists have for the first time shown how a “trust” hormone is released in the brains of breastfeeding mothers. It is further proof that breastfeeding promotes the maternal bond through a biochemical process.
The team at Warwick University said the hormone oxytocin was known to be released during breastfeeding but the mechanism in the brain was unclear.

Oxytocin also produces contractions during labour and causes milk to be “let down” from the mammary glands.
The hormone is produced in the hypothalamus - the part of the brain that controls body temperature, thirst, hunger, anger and tiredness.

It has been shown to promote feelings of trust and confidence and to reduce fear.

"The model gives us a possible explanation of an important event in the brain that could be used to study and explain many other similar brain activities," Professor Jianfeng Feng said.

Co-ordination

The study, published in the journal PLoS Computational Biology, found that in response to a baby suckling, specialised neurons in the mothers' brain start to release the hormone from the nerve endings.

But surprisingly oxytocin is also released from the part of the cell called the dendrite which is usually the part of a neuron which receives, rather than transmits information.

Using a mathematical model, the researchers worked out that this release from the dendrites allows a massive increase in communication between the neurons, co-ordinating a “swarm” of oxytocin factories producing intense bursts of the hormone.

They is an example of an "emergent process", the scientists said - a closely co-ordinated action developing without a single leader, in the same as a flock of birds or insects swarms.

Study leader, Professor Jianfeng Feng said: "We knew that these pulses arise because, during suckling, oxytocin neurons fire together in dramatic synchronised bursts.

"But exactly how these bursts arise has been a major problem that has until now eluded explanation."

"The model gives us a possible explanation of an important event in the brain that could be used to study and explain many other similar brain activities." A spokesperson for the National Childbirth Trust (NCT) said breastfeeding for up to two years can have "significant health benefits" for mother and baby.
Recent Activities

Foreign Experts, including a member of the Centre, were invited to meet General Secretary Xi Jinping

On Dec 5, 2012, at the Great Hall of the People in Beijing, Xi Jinping, the newly selected General Secretary of the Communist Party of China, Central Committee, met a group of Foreign Experts who are working in China. The aim of this meeting was to convey the new leadership’s foreign policy.

Professor David Waxman, a member of the Centre for Computational Systems Biology, was invited to take part in this prestigious meeting, as a representative of Fudan University. He met and communicated, face to face, with Chairman Xi. Professor Waxman, a theoretical biologist, joined our Center in 2011. After his arrival, the academic background and work environment of the Center has become more multi-cultural. Many students in the Centre have now experienced lectures in English from a native speaker; Apart from Professor Waxman’s approach to work influencing members of the Centre, he has learned a lot from Chinese culture as well as learning some Chinese. He can now communicate with Chinese people by means of using simple Chinese words. He continues to learn more about China and the Chinese language and says how stimulating it is to be here.
Conferences in 2012

(I) The Workshop on Unraveling Metal Disorders with Neuroimaging

On June 17, 2012, the Centre for Computational Systems Biology of Fudan University hosted the Workshop on Unraveling Metal Disorders with Neuroimaging. Around 60 leading researchers, from all over the world, gathered at Fudan University and discussed ways that neuroimaging could be used to resolve mental illness questions. During the meeting, Professor Christian Beckmann of Twente University, Holland, Professor Mingzhou Ding of Florida University, America and another 20 scientists gave outstanding presentations on their research.

This symposium was devoted to the modeling of various mental diseases, the related image data processing, and imaging techniques. These approaches have revealed all kinds of causes of mental diseases and have provided new methods and the basis for early diagnosis and treatment. The meeting included discussion of neuroimaging and related areas, the progress in this subject new research directions along with cooperation opportunities for the future. The workshop ended on June 20, 2012. But the participants continue to communicate and collaborate.
The Fifth Shanghai International Symposium on Nonlinear Sciences and Applications (Shanghai NSA’12) was held at Fudan University in Shanghai and on the Yangtze River in a cruise to Chongqing, from June 27 to July 3, 2012. The Shanghai NSA’12 was organized by the Centre for Computational Systems Biology and the School of Mathematical Sciences at Fudan University. It was supported by the Shanghai Society for Nonlinear Science, the LMNS (Fudan University), the Ministry of Education, the Shanghai Centre for Mathematical Sciences, the Natural Science Foundation, and the 863 and 973 programs of China.

Nonlinear science is one of the most active scientific frontiers of recent times, and Shanghai NSA’12 was devoted to this important area of scientific research. The theme of the symposium was intended to be broad enough to cover most directions in nonlinear science, with the aim of promoting wide interactions among researchers from different academic disciplines who are interested in nonlinear science and related technologies.
Recruitment

The Centre for Computational Systems Biology at Fudan University is planning to make 3-5 new PI appointments in Computational Biology this year. Depending on a candidate's experience, the rank is open and salary is negotiable. Applicants using computational or mathematical models and/or data analyzing approaches are encouraged to apply. All areas of biomedical science will be considered. These include but are not limited to bioinformatics and genomics, cellular and molecular biology, computational neuroscience, and a systems approach to cancer/brain diseases. The appointee will be expected to develop a rigorous research program, with some teaching at both graduate and undergraduate levels. The appointment requires a 9 months commitment per year to Fudan University.

Enquiries and applications can be made by email to zqy@fudan.edu.cn. The positions will be open until filled. Applications should include a curriculum vitae (including bibliography), a brief statement of research and teaching interests, and copies of representative scholarly papers. Candidates should also arrange for three letters of reference to be sent.

Fudan University is one of the leading institutions in China and is located in Shanghai, one of the most dynamical cities in the world. With substantial supports from the Chinese government, Fudan University aims to become one of the highest rank universities in the world.
Representative Publications
Depression uncouples brain hate circuit

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It is increasingly recognized that we need a better understanding of how mental disorders such as depression alter the brain’s functional connections to improve both early diagnosis and therapy. A new holistic approach has been used to investigate functional connectivity changes in the brains of patients suffering from major depression using resting-state functional magnetic resonance imaging (fMRI) data. A canonical template of connectivity in 90 different brain regions was constructed from healthy control subjects and this identified a six-community structure with each network corresponding to a different functional system. This template was compared with functional networks derived from fMRI scans of both first-episode and longer-term, drug resistant, patients suffering from severe depression. The greatest change in both groups of depressed patients was uncoupling of the so-called ‘hate circuit’ involving the superior frontal gyrus, insula and putamen. Other major changes occurred in circuits related to risk and action responses, reward and emotion, attention and memory processing. A voxel-based morphometry analysis was also carried out but this revealed no evidence in the depressed patients for altered gray or white matter densities in the regions showing altered functional connectivity. This is the first evidence for the involvement of the ‘hate circuit’ in depression and suggests a potential reappraisal of the key neural circuitry involved. We have hypothesized that this may reflect reduced cognitive control over negative feelings toward both self and others.

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Keywords: fMRI; functional connectivity; hate circuit; major depression; mental disorder; voxel-based morphometry

Introduction

At the brain circuit level, most of what we understand about depression and its biological abnormalities during the resting state comes from functional magnetic resonance imaging (fMRI) studies targeting changes in a small number of the brain regions, as recently reviewed in Raichle\textsuperscript{1} and Zhang and Raichle.\textsuperscript{2} These studies have suggested the involvement of a default mode network including the dorsal anterior cingulate cortex and some subcortical areas such as amygdala and thalamus.\textsuperscript{3–7} However, the conclusions drawn from these studies are based on either seed-based analysis or independent component analysis and are questionable in spite of the wide and successful application of such methods in the analysis of resting-state fMRI data.\textsuperscript{8–13} Seed-based analysis is a hypothesis-driven approach, which means the foci (seeds) of the disorder must be specified \textit{a priori}. It is therefore a biased approach lacking a global and independent view.\textsuperscript{14} With the independent component analysis approach, it is assumed that the human brain is composed of independent components, whereas in reality, different parts of the human brain undoubtedly work in a coordinated manner. Hence, given the complexity and multiple causes of depression together with variability between individuals, a novel, unbiased approach is urgently called for which identifies pathway changes in a holistic manner.

In the current paper, we have adopted such a new holistic approach aiming to unambiguously identify the key connections, which are modified in the brains of depressed patients. To achieve this, we have first applied a canonical template constructed for the whole brain based upon data from a large number of healthy individuals. Using a community discovery algorithm we have developed previously,\textsuperscript{15} six discrete interconnected communities were recovered from this template, each corresponding to a functional system in the human brain: a default mode network that has been reported extensively in the...
The efficiency of a random and fast switch in complex dynamical systems

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**Abstract.** In this paper, we show that a fast switch is able to lead a complex dynamical system to being asymptotically stable, although this system is completely unstable in every switch duration and even the associated connection matrices are randomly selected. Importantly, we define some new exponents by which we can figure out the essential patterns that guarantee the stability of fast switching systems, and besides, their calculations need little computational cost. More interestingly, we show the efficiency of some random switches in inducing stability through a comparison of the systems with different switch connection matrices and switch durations, and we give a design method for obtaining higher efficient random switch rules. We also investigate the generalization of the obtained results to a more realistic case where the switch obeys some renewal process.
INVESTIGATION

Population Growth Enhances the Mean Fixation Time of Neutral Mutations and the Persistence of Neutral Variation

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ABSTRACT A fundamental result of population genetics states that a new mutation, at an unlinked neutral locus in a randomly mating diploid population, has a mean time of fixation of \(4N_e\) generations, where \(N_e\) is the effective population size. This result is based on an assumption of fixed population size, which does not universally hold in natural populations. Here, we analyze such neutral fixations in populations of changing size within the framework of the diffusion approximation. General expressions are derived for the mean and variance of the fixation time in changing populations. Some explicit results are given for two cases: (i) the effective population size undergoes a sudden change, representing a sudden population expansion or a sudden bottleneck; (ii) the effective population changes linearly for a limited period of time and then remains constant. Additionally, a lower bound for the mean time of fixation is obtained for an effective population size that increases with time, and this is applied to exponentially growing populations. The results obtained in this work show, among other things, that for populations that increase in size, the mean time of fixation can be enhanced, sometimes substantially so, over \(4N_{e,0}\) generations, where \(N_{e,0}\) is the effective population size at the time the mutation arises. Such an enhancement is associated with (i) an increased probability of neutral polymorphism in a population and (ii) an enhanced persistence of high-frequency neutral variation, which is the variation most likely to be observed.

HOW are properties of mutations at neutral loci, such as the mean time of fixation, modified when population size is not constant? The answer to this question directly influences the persistence of neutral variation in a population and the probability of neutral polymorphism. To put the question in context, we note that the genomes of many organisms contain loci and sites that can be described as neutral, with most substitutions seeming to have a neutral effect on the fitness of the host organism (see, e.g., Kimura 1983; Gillespie 1994, Chap. 6; Nei et al. 2010).

When mutation produces a new allele, its long-term outcome (neglecting additional mutations) is either loss or fixation. Henceforth, we restrict attention to mutations at unlinked neutral loci in randomly mating diploid populations. Typically, a new allele at such a locus does not achieve high relative frequencies and becomes lost in a short time (Kimura and Ohta 1969; Crow and Kimura 1970). A rarer outcome is fixation, which typically takes a relatively long time to occur. With \(N_e\) the (variance) effective population size, alleles that start at low relative frequencies take a mean time to fixation of \(4N_e\) generations (Kimura and Ohta 1969), under the implicit assumption that the effective population size is constant. An allele that fixes generally achieves intermediate and high relative frequencies on the way to fixation and hence contributes to the neutral variation of the population for a time of the order of the mean fixation time. Related to this is neutral polymorphism, which arises from recurrent neutral mutation and random genetic drift. The likelihood of observing neutral polymorphism in a population is governed by the size of the product of mean fixation time and neutral genomic mutation rate (Kimura 1983). Thus there are direct ways the mean fixation time affects a population.

The above ideas form a standard part of our understanding of neutral mutations and connect with a larger body of work describing the effects of random genetic drift at the gene and molecular levels (Crow and Kimura 1970; Kimura 1983). Here we present an analysis of random genetic drift in situations involving neutral fixation in populations of
Key Functional Circuitry Altered in Schizophrenia Involves Parietal Regions Associated with Sense of Self

Shuixia Guo, Keith M. Kendrick, Rongjun Yu, Hsiao-Lan Sharon Wang, and Jianfeng Feng

Abstract: There is still no clear consensus as to which of the many functional and structural changes in the brain in schizophrenia are of most importance, although the main focus to date has been on those in the frontal and cingulate cortices. In the present study, we have used a novel holistic approach to identify brain-wide functional connectivity changes in medicated schizophrenia patients, and functional connectivity changes were analyzed using resting-state fMRI data from 69 medicated schizophrenia patients and 62 healthy controls. As far as we are aware, this is the largest population reported in the literature for a resting-state study. Voxel-based morphometry was also used to investigate gray and white matter volume changes. Changes were correlated with illness duration/symptom severity and a support vector machine analysis assessed predictive validity. A network involving the inferior parietal lobule, superior parietal gyrus, precuneus, superior marginal, and angular gyri was by far the most affected (68% predictive validity compared with 82% using all connections) and different components correlated with illness duration and positive and negative symptom severity. Smaller changes occurred in emotional memory and sensory and motor processing networks along with weak-
Componential Granger causality, and its application to identifying the source and mechanisms of the top–down biased activation that controls attention to affective vs sensory processing

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ABSTRACT

We describe a new measure of Granger causality, componential Granger causality, and show how it can be applied to the identification of the directionality of influences between brain areas with functional neuroimaging data. Componential Granger causality measures the effect of y on x, but allows interaction effects between y and x to be measured. In addition, the terms in componential Granger causality sum to 1, allowing causal effects to be directly compared between systems. We show using componential Granger causality analysis applied to an fMRI investigation that there is a top–down attentional effect from the anterior dorsolateral prefrontal cortex to the orbitofrontal cortex when attention is paid to the pleasantness of a taste, and that this effect depends on the activity in the orbitofrontal cortex as shown by the interaction term. Correspondingly there is a top–down attentional effect from the posterior dorsolateral prefrontal cortex to the insular primary taste cortex when attention is paid to the intensity of a taste, and this effect depends on the activity of the insular primary taste cortex as shown by the interaction term. Componential Granger causality thus not only can reveal the directionality of effects between areas (and these can be bidirectional), but also allows the mechanisms to be understood in terms of whether the causal influence of one system on another depends on the state of the system being causally influenced. Componential Granger causality measures the full effects of second order statistics by including variance and covariance effects between each time series, thus allowing interaction effects to be measured, and also provides a systematic framework within which to measure the effects of cross, self, and noise contributions to causality. The findings reveal some of the mechanisms involved in a biased activation theory of selective attention.

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Increasing power for voxel-wise genome-wide association studies: The random field theory, least square kernel machines and fast permutation procedures

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d Department of Statistics & Warwick Manufacturing Group, The University of Warwick, Coventry, UK

Abstract

Imaging traits are thought to have more direct links to genetic variation than diagnostic measures based on cognitive or clinical assessments and provide a powerful substrate to examine the influence of genetics on human brains. Although imaging genetics has attracted growing attention and interest, most brain-wide genome-wide association studies focus on voxel-wise single-locus approaches, without taking advantage of the spatial information in images or combining the effect of multiple genetic variants. In this paper we present a fast implementation of voxel- and cluster-wise inferences based on the random field theory to fully use the spatial information in images. The approach is combined with a multi-locus model based on least square kernel machines to associate the joint effect of several single nucleotide polymorphisms (SNP) with imaging traits. A fast permutation procedure is also proposed which significantly reduces the number of permutations needed relative to the standard empirical method and provides accurate small p-value estimates based on parametric tail approximation. We explored the relation between 448,294 single nucleotide polymorphisms and 18,043 genes in 31,662 voxels of the entire brain across 740 elderly subjects from the Alzheimer’s Disease Neuroimaging Initiative (ADNI). Structural MRI scans were analyzed using tensor-based morphometry (TBM) to compute 3D maps of regional brain volume differences compared to an average template image based on healthy elderly subjects. We find method to be more sensitive compared with voxel-wise single-locus approaches. A number of genes were identified as having significant associations with volumetric changes. The most associated gene was GRIN2B, which encodes the N-methyl-D-aspartate (NMDA) glutamate receptor NR2B subunit and affects both the parietal and temporal lobes in human brains. Its role in Alzheimer’s disease has been widely acknowledged and studied, suggesting the validity of the approach. The various advantages over existing approaches indicate a great potential offered by this novel framework to detect genetic influences on human brains.

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Introduction

The past decade witnessed tremendous growth in both neuroimaging and genomics. Imaging genetics, as an interdisciplinary field, uses anatomical or functional imaging technologies as phenotypic assays to evaluate genetic variation. Quantitative imaging-derived traits are thought to have more direct links to genetic variation than diagnostic measures based on cognitive or clinical assessments and thus might offer more power to detect the association between specific genes, single nucleotide polymorphisms (SNP) or copy number variations (CNV) and various brain diseases (Cottremans and Gould, 2003). Therefore, a large amount of imaging and genetic data have been collected, such as the Alzheimer’s Disease Neuroimaging Initiative (ADNI), with the hope of speeding up the studies in this area, and ultimately to improve human health care in the future (Aki1 et al., 2010).

In spite of the great investment and efforts poured into this area, imaging genetics is still a very young field. Statistical approaches are rudimentary compared to imaging-only or genetic-only methods. This is partly due to both the ultra-high dimension and complex noise structure of imaging and genetic data. Currently, most of the population-based association studies with neuroimaging phenotypes in the literature can be broadly categorized into candidate-phenotype candidate-SNP/gene association (e.g., Jovner et al., 2009), candidate-phenotype genome-wide association (e.g., Frayling et al., 2007; Potkin et al., 2009), or brain-wide candidate-SNP/gene association (e.g., Braskie et al., 2011; Filippini et al., 2009). All these studies reduce the dimensionality of the data using a priori knowledge, by either selecting specific, well-studied genetic variants that affect brain structure and function, or focusing on a specific brain area or a neuroimaging measure/contrast of interest.

Keywords:
Imaging genetics
Association study
Random field theory
Voxel-wise inference
Cluster size inference
Nonstationarity
Least square kernel machines
Permutation
Pareto distribution
Parametric tail approximation
ADNI
MRI
Tensor-based morphometry
Alzheimer’s disease
GRIN2B

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A Self-Organizing State-Space-Model Approach for Parameter Estimation in Hodgkin-Huxley-Type Models of Single Neurons

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Abstract

Traditional approaches to the problem of parameter estimation in biophysical models of neurons and neural networks usually adopt a global search algorithm (for example, an evolutionary algorithm), often in combination with a local search method (such as gradient descent) in order to minimize the value of a cost function, which measures the discrepancy between various features of the available experimental data and model output. In this study, we approach the problem of parameter estimation in conductance-based models of single neurons from a different perspective. By adopting a hidden-dynamical-systems formalism, we expressed parameter estimation as an inference problem in these systems, which can then be tackled using a range of well-established statistical inference methods. The particular method we used was Kitagawa’s self-organizing state-space model, which was applied on a number of Hodgkin-Huxley-type models using simulated or actual electrophysiological data. We showed that the algorithm can be used to estimate a large number of parameters, including maximal conductances, reversal potentials, kinetics of ionic currents, measurement and intrinsic noise, based on low-dimensional experimental data and sufficiently informative priors in the form of pre-defined constraints imposed on model parameters. The algorithm remained operational even when very noisy experimental data were used. Importantly, by combining the self-organizing state-space model with an adaptive sampling algorithm akin to the Covariance Matrix Adaptation Evolution Strategy, we achieved a significant reduction in the variance of parameter estimates. The algorithm did not require the explicit formulation of a cost function and it was straightforward to apply on compartmental models and multiple data sets. Overall, the proposed methodology is particularly suitable for resolving high-dimensional inference problems based on noisy electrophysiological data and, therefore, a potentially useful tool in the construction of biophysical neuron models.


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Introduction

Among several tools at the disposal of neuroscientists today, data-driven computational models have come to hold an eminent position for studying the electrical activity of single neurons and the significance of this activity for the operation of neural circuits [1–4]. Typically, these models depend on a large number of parameters, such as the maximal conductances and kinetics of gated ion channels. Estimating appropriate values for these parameters based on the available experimental data is an issue of central importance and, at the same time, the most laborious task in single-neuron and circuit modeling.

Ideally, all unknown parameters in a model should be determined directly from experimental data analysis. For example, based on a set of voltage-clamp recordings, the type, kinetics and maximal conductances of the voltage-gated ionic currents flowing through the cell membrane could be determined [5] and, then, combined in a conductance-based model, which replicates the activity of the biological neuron of interest under current-clamp conditions with sufficient accuracy. Unfortunately, this is not always possible, especially for complex compartmental models, which contain a large number of ionic currents.

A first problem arises from the fact that not all parameters can be estimated within an acceptable error margin, especially for small currents and large levels of noise. A second problem arises from the practice of estimating different sets of parameters based on data collected from different neurons of a particular type, instead of estimating all unknown parameters using data collected from a single neuron. Different neurons of the same type may have quite different compositions of ionic currents [6–9] (but, see also [10]). This implies that combining ionic currents measured from different neurons in the same model or even using the average of several parameters calculated over a population of neurons of the same type will not necessarily result in a model that expresses the experimentally recorded patterns of electrical activity under current-clamp conditions. Usually, only some parameters are well characterized, while others are difficult or impossible to measure directly. Thus, most modeling studies rely on a mixture of
Warm Body Temperature Facilitates Energy Efficient Cortical Action Potentials

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Abstract

The energy efficiency of neural signal transmission is important not only as a limiting factor in brain architecture, but it also influences the interpretation of functional brain imaging signals. Action potential generation in mammalian, versus invertebrate, axons is remarkably energy efficient. Here we demonstrate that this increase in energy efficiency is due largely to a warmer body temperature. Increases in temperature result in an exponential increase in energy efficiency for single action potentials by increasing the rate of Na⁺ channel inactivation, resulting in a marked reduction in overlap of the inward Na⁺, and outward K⁺, currents and a shortening of action potential duration. This increase in single spike efficiency is, however, counterbalanced by a temperature-dependent decrease in the amplitude and duration of the spike afterhyperpolarization, resulting in a nonlinear increase in the spike firing rate, particularly at temperatures above approximately 35°C. Interestingly, the total energy cost, as measured by the multiplication of total Na⁺ entry per spike and average firing rate in response to a constant input, reaches a global minimum between 37–42°C. Our results indicate that increases in temperature result in an unexpected increase in energy efficiency, especially near normal body temperature, thus allowing the brain to utilize an energy efficient neural code.

Introduction

Brain signaling is metabolically expensive. Energy expenditure not only constrains the size and architecture of the brain, which limits its computational power, but is critical to the interpretation of functional brain imaging signals through related metabolic mechanisms (e.g. oxygen consumption and blood flow) [1]. Comprising only about 2% of the body’s mass, the mammalian brain consumes about 20% of its energy [2,3,4]. Another unique feature of mammals is their warm body temperature (about 35–39°C). How a warm body temperature affects signaling and energy budget in the brain is largely unknown. Here we address this critical and interesting question through simple Hodgkin-Huxley models as well as recordings from cortical neurons during changes in temperature. Operating neurons is expensive, in part owing to the need to maintain a significantly higher concentration of Na⁺ ions outside, versus inside, nerve cells [5,6,7,8]. Na⁺ entry into neurons, which must be returned to its extracellular location through the operation of the Na⁺/K⁺ ion pump by the expenditure of energy via hydrolysis of ATP, occurs through generation of action potentials [9]. This value of 4 times excess Na⁺ entry has figured prominently in estimates of the distribution of the sources of energy consumption in the mammalian brain [1,5,10,11], as well as in the calculation of the average firing rate of cortical neurons [6]. For example, one classic modeling study of energy consumption in mammalian brains stated “A realistic estimate of the Na⁺ entry needed is obtained for action potential generation by quadrupling [the minimal Na⁺ entry] to take account of simultaneous activation of Na⁺ and K⁺ channels” [5]. Calculations such as these have predicted that up to 50% or more of the energy consumption in mammalian brains is devoted to the reversal of ion exchanges owing to Na⁺ entry (and K⁺ exit) during action potentials [5,10]. Based upon this calculation, it has been proposed that the brain can support an average firing rate of less than 0.2 spikes/second, suggesting that the nervous system operates through a very sparse code [6].

Reconstruction of the inward Na⁺ and outward K⁺ currents occurring during action potential generation in mammalian cortical axons revealed, in contrast to the results predicted, an excess ratio of Na⁺ entry of only 1.5 [12,13], indicating that axons...
In a recent paper by Valleriani et al. [Phys. Rev. E 83, 042903 (2011)], a simple model for the translation of messenger RNA (mRNA) is presented. Using this model, the protein translational ratio \( r \), defined as the ratio of protein translation rate \( \omega_p \) from mRNA to protein degradation rate \( \omega_r \), is obtained. The key point in obtaining the translational ratio \( r \) is to get the protein translation rate \( \omega_p \). In Valleriani et al.’s paper, \( \omega_p \) is obtained as the mean value of the measured translation rate, which is the ratio of the synthesized protein number to the mRNA lifetime. However, in experiments, different methods might be used to obtain the value of \( \omega_p \). Therefore, to apply Valleriani et al.’s model to more general experiments, in this Comment three methods to obtain the translation rate \( \omega_p \), and consequently the translational ratio \( r \), are presented. Based on one of the methods which might be employed in most of the experiments, we find that the translational ratio \( r \) decays exponentially with mRNA length in prokaryotic cells, and decays reciprocally with mRNA length in eukaryotic cells. This result is slightly different from that which was obtained in Valleriani et al.’s paper.

\[
\phi(t) = \omega_p \exp(-\omega_r t). \tag{1}
\]

Meanwhile, the rate of the ribosome entering the coding region of mRNA is assumed to be \( \omega_{r0} \), and the degradation rate of protein is denoted by \( \omega_p \).

To discuss the mRNA length-dependent properties of protein translation, in Ref. [1] the expression of the translational ratio, defined as

\[
r = \frac{\omega_p}{\omega_r}, \tag{2}
\]

is obtained for translations in both prokaryotic and eukaryotic cells, where \( \omega_p \) is the protein translation rate by ribosomes. Since the protein degradation rate \( \omega_r \) is independent of mRNA, the essential point to obtain the translational ratio \( r \) is to get the protein translation rate \( \omega_p \). In experiments, there might be three different methods to obtain the approximated values of \( \omega_p \) (denoted by \( \omega_{p0} \), \( \omega_{p0}^I \), and \( \omega_{p0}^III \), respectively). If there are altogether \( n \) mRNAs which are experimentally measured to get their lifetimes \( T_i \) (\( 1 \leq i \leq n \)) and the corresponding numbers \( N_i \) (\( 1 \leq i \leq n \)) of protein translated from them (here \( T_i \) is the lifetime of the \( i \)th mRNA before its complete degradation), then \( \omega_{p0} \) can be approximated by the average value of \( \omega_{p0} = \frac{\sum_{i=1}^{n} N_i}{\sum_{i=1}^{n} T_i} \). It can be simply approximated by \( \omega_{p0}^I = \frac{\sum_{i=1}^{n} N_i}{\sum_{i=1}^{n} T_i} = \frac{N}{\overline{T}} \), with \( \overline{N} \) and \( \overline{T} \) the average values of \( N_i \) and \( T_i \), respectively. Meanwhile, \( \omega_{p0} \) can also be approximated by the reciprocal of the average time spent to translate one protein, \( \omega_{p0}^II = 1/\overline{T} \) with \( \overline{T} = \frac{\sum_{i=1}^{n} N_i}{n} \). One can easily see that each of the three different outputs is a different measurable property of the system, but they all relate to the standard notion of a translation rate. Theoretically, the definitions of \( \omega_{p0}^I \), \( \omega_{p0}^II \), and \( \omega_{p0}^III \) are as follows.

(1): \( \omega_{p0}^I \) is the mean value of the measured translation rate \( f(t) \) of protein, i.e.,

\[
\omega_{p0}^I = \frac{\langle f(t) \rangle}{\langle T(t) \rangle} = \frac{\int_0^\infty f(t) \phi(t) dt}{\int_0^\infty \phi(t) dt}. \tag{3}
\]

where \( f(t) = N(t)/T(t) \), \( N(t) \) is the mean synthesized protein number if the mRNA degradation occurs at time \( t \), and \( T(t) \) is the lifetime of mRNA before its complete degradation (\( t \) is the lifetime of the intact mRNA).

(II): \( \omega_{p0}^II \) is the ratio of the mean synthesized protein number \( \langle N(t) \rangle \) to the mean lifetime \( \langle T(t) \rangle \) of mRNA, i.e.,

\[
\omega_{p0}^II = \frac{\langle N(t) \rangle}{\langle T(t) \rangle}. \tag{4}
\]

(III): \( \omega_{p0}^III \) is the reciprocal of the mean duration time of translating one protein from mRNA,

\[
\omega_{p0}^III = \frac{1}{\langle 1/f(t) \rangle} = \frac{1}{\langle T(t)/N(t) \rangle} \tag{5}
\]

One can easily show that, for the protein translation problem discussed in Ref. [1], \( T(t) = t, N(t) = \theta(t - t_0^P) \). The results of the experiments for the protein translation rate are as follows.

---

**TABLE I.** Model parameter values of \( \omega_{r0}/\omega_p \) and \( \omega_{r0}/\omega_p^II \) obtained by fitting the theoretical results to experimental data of *E. coli* and *S. cerevisiae*, respectively (see Ref. [1] and references therein for a detailed description of the experimental data).

<table>
<thead>
<tr>
<th>Method</th>
<th><em>E. coli</em></th>
<th><em>S. cerevisiae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \omega_{r0}/\omega_p )</td>
<td>( \omega_{r0}/\omega_p^II )</td>
</tr>
<tr>
<td>Valleriani et al.</td>
<td>708.2</td>
<td>6.79 \times 10^3</td>
</tr>
<tr>
<td>Method II</td>
<td>734</td>
<td>6.34 \times 10^3</td>
</tr>
<tr>
<td>Method III</td>
<td>841.1</td>
<td>6.62 \times 10^3</td>
</tr>
</tbody>
</table>

---

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Community identification in networks with unbalanced structure

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Community (module) structure is a common and important property of many types of networks, such as social networks and biological networks. Several classes of algorithms have been proposed for community structure detection and identification, including clustering techniques, modularity optimization, and other methods. Among these methods, the modularity optimization method has attracted a great deal of attention and much related research has been published. However, the existing modularity optimization method does not perform well in the presence of unbalanced community structures. In this paper, we introduce a metric to characterize the community structure better than other metrics in this situation, and we propose a method to infer the number of communities, which may solve the resolution limit problem. We then develop an algorithm for community structure identification based on eigendecompositions, and we give both simulated and real data examples to illustrate the better performance of our approach.

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1. INTRODUCTION

Network study has attracted a considerable amount of attention in recent years from researchers in different fields, including physics, computer science, statistics, and others. A network can be seen as a synonym for a mathematical graph. It is composed of vertices (nodes) and edges. The vertices represent the members in the network, while the edges represent the pair relations of the vertices. Many complex interaction systems can be described as networks, including biological systems, social systems, and the worldwide web.

Community (module) structure is a common feature of many networks. Since the seminal paper of Girvan and Newman [1], many related papers have been published on network community analysis [2–11]. Intuitively, a community is a subset of a network. The vertices in the same subnetwork are more likely to be connected with each other than those in different subnetworks. In general, members in the same community share some common properties or play similar roles. In a gene coexpression network, the vertices (which correspond to genes) in the same community may belong to the same functional category, such as lipid metabolism and acute-phase response, or they may be involved in the same pathway, such as a metabolic pathway or a ribosome [12,13]. In a collaboration network, the vertices (which correspond to researchers) in the same community likely share some common research interests [8].

There has been a concerted effort in recent years to develop mathematical tools and computer algorithms to identify and quantify community structure in networks [3–9,14]. Several recent review papers provide details of community identification methods [5,8,14]. Reference [14] compares the performance of several existing methods for both computation time and output. Reference [5] is a thorough, more recent discussion. Reference [8] contrasts different perspectives of the methods and sheds light on some important similarities of several methods. These community identification papers are mostly written by computer scientists, statisticians, and physicists, with physicists making the most contributions.

Earlier methods for community identification mainly arose from computer science. The communities are identified using graph partitioning methods or cluster-based methods. Graph partitioning methods require the sizes of the subgraphs as the input for network partitions, but little is known on the sizes in practice [15–18]. Cluster-based methods include hierarchical clustering, partitional clustering, and spectral partitioning. Hierarchical clustering has been shown to be effective since some networks do possess a hierarchical structure and the number of communities can be determined during the clustering process [3]. Partitional clustering is popular in data mining, but it may not be appropriate for community identification since the community structure describes the topological relations of the vertices, which may not be measured by Euclidean distance, correlations, and other distances usually used in partitional clustering. Spectral clustering can be applied to community identification [19], but this method tends to isolate some very small communities from the network instead of dividing the network into reasonably large subnetworks.

Two recent papers by statisticians considered the theoretical aspects of the community identification problem for dense networks [20,21]. In [20], the authors proposed a new modularity definition and provided sufficient conditions so that some modularity can give a consistent estimation of the community structure. Although the proposed modularity was shown to outperform other methods, it is time consuming to solve the optimization problem under this definition. In [21], the authors developed an algorithm for extracting the communities sequentially from a network when some vertices do not fit in with any of the communities. One limitation of the theoretical developments in these two papers is that they...
Abstract

The accurate prediction of general neuropsychiatric disorders, on an individual basis, using resting-state functional magnetic resonance imaging (fMRI) is a challenging task of great clinical significance. Despite the progress to chart the differences between the healthy controls and patients at the group level, the pattern classification of functional brain networks across individuals is still less developed. In this paper we identify two novel neuroimaging measures that prove to be strongly predictive neuroimaging markers in pattern classification between healthy controls and general epileptic patients. These measures characterize two important aspects of the functional brain network in a quantitative manner: (i) coordinated operation among spatially distributed brain regions, and (ii) the asymmetry of bilaterally homologous brain regions, in terms of their global patterns of functional connectivity. This second measure offers a unique understanding of brain asymmetry at the network level, and, to the best of our knowledge, has not been previously in pattern classification of functional brain networks. Using modern pattern-recognition approaches like sparse regression and support vector machine, we have achieved a cross-validated classification accuracy of 83.9% (specificity: 82.5%; sensitivity: 85%) across individuals from a large dataset consisting of 180 healthy controls and epileptic patients. We identified significantly changed functional pathways and subnetworks in epileptic patients that underlie the pathophysiological mechanism of the impaired cognitive functions. Specifically, we find that the asymmetry of brain operation for epileptic patients is markedly enhanced in temporal lobe and limbic system, in comparison with healthy individuals. The present study indicates that with specifically designed informative neuroimaging markers, resting-state fMRI can serve as a most promising tool for clinical diagnosis, and also shed light onto the physiology behind complex neuropsychiatric disorders. The systematic approaches we present here are expected to have wider applications in general neuropsychiatric disorders.


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Introduction

Neuropsychiatric disorders, whose rank in frequency is second only to cardiovascular disease, are widespread all over the world. A large percentage of the population will experience some type of neuropsychiatric disorders at some stage in their life. Traditionally, neuropsychiatric diagnosis is based on a categorical taxonomy arrived at from clinical observations, and questionnaires developed with the aid of rating scales. The results have sometimes been arrived at from clinical observations, and questionnaires developed with the aid of rating scales. The results have sometimes been inconsistent as the questionnaire filled by the subject tends to be subjective. Over the past decade, clinical doctors and researchers have become increasingly interested in finding highly predictive neuroimaging markers that can provide objective ways to predict and evaluate neuropsychiatric conditions [1,2]. With the recent advances in functional magnetic resonance imaging (fMRI), which can provide an unprecedented opportunity to map large scale brain connectivity [3,4,5,6], it remains an important problem to know whether resting state fMRI contains sufficient information to aid the diagnosis of general neuropsychiatric disorders. In practice, the advantage of fMRI is its high spatial resolution, which is beneficial to source location in epilepsy. In comparison, electroencephalogram, which is widely used in clinical diagnosis of epilepsy, has a very high temporal resolution but a limited spatial resolution.

The human brain can be deemed as a large-scale network, with nodes being distinct brain regions and edges representing functional connectivity among them. It has been suggested that many functional brain disorders, such as depression, Alzheimer's...
Bifurcations of Emergent Bursting in a Neuronal Network

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Abstract

Complex neuronal networks are an important tool to help explain paradoxical phenomena observed in biological recordings. Here we present a general approach to mathematically tackle a complex neuronal network so that we can fully understand the underlying mechanisms. Using a previously developed network model of the milk-ejection reflex in oxytocin cells, we show how we can reduce a complex model with many variables and complex network topologies to a tractable model with two variables, while retaining all key qualitative features of the original model. The approach enables us to uncover how emergent synchronous bursting can arise from a neuronal network which embodies known biological features. Surprisingly, the bursting mechanisms are similar to those found in other systems reported in the literature, and illustrate a generic way to exhibit emergent and multiple time scale oscillations at the membrane potential level and the firing rate level.

Introduction

In neural systems, oscillatory rhythms have essential roles in sensory, cognitive, and motor functioning; in many experimental conditions [1–5], diverse physiological information can be encoded by the oscillatory activity of neuronal ensembles. However, the mechanisms by which rhythmic dynamics are produced vary considerably, from single pacemaker neurons, which can be mathematically described by voltage threshold models such as the integrate-and-fire model [4,5], or the more biophysical Hodgkin-Huxley type model [6], to large cortical networks, where interactions between neurons are responsible for the rhythmic behaviors (see [7–9] and the references therein).

Single neuron oscillation dynamics are often mathematically interpreted as a dynamic bifurcation, where an emission of an action potential is regarded as a cycle of periodic trajectory. Based on this idea, bifurcation theory has been widely employed to investigate neuronal spike dynamics [10]. Conversely, a number of network models have been proposed to realize neuronal oscillation at diverse rhythmic ranges via adapted interactions between inhibition and excitatory neurons [11–13]. Some of these aim to explain the roles of different cortical rhythmic ranges (0 range, 1–4 Hz; β range, 4–8 Hz; α range, 8–13 Hz; β range, 13–30 Hz; and γ range, 30–80 Hz) in cognitive functions such as retrieving memories, attention and motor control.

Thus rhythmic oscillations can be observed and studied at different levels in neural systems, from the single neuron level, to the neuronal population level. Synchronous spikes in a neuronal population, which is a special case of population oscillating dynamics, may play an essential role in neuronal computation in cognition [14], and attention selection [15–18]. Synchronization is a population behavior, and accordingly has to be studied at the network level, and as shown in [19,20], synaptic interactions can be one cause of synchronous dynamics. Synchronous bursting emerges periodically in neuronal networks at a time scale of minutes, much longer than the millisecond time scale of individual neuronal spikes. Synchronous behavior can also be characterized as metastability, i.e. a transmission between different patterns [21,22], rather than attractors.

Some neuronal networks can exhibit rhythmic oscillations at multiple time scales. An interesting example is reported in a recent paper [23], in which a neuronal network model was developed to reproduce paradoxical phenomena observed from recordings of oxytocin-secreting neurons. Oxytocin is a hormone that is released by neuroendocrine neurons into the blood where it can trigger milk let-down in lactation, and it is also released within the brain, where it has powerful behavioral effects. Notably, in humans it is reported that oxytocin can increase the bonding and trust between individuals. These effects have made oxytocin a key drug target for new therapies aimed at mental disorders of social behavior such as autism.

The oxytocin network model in [23] was developed to explain the observed activity of oxytocin neurons in response to suckling. When young suckle, they are rewarded intermittently with a let-down of milk that results from reflex secretion of oxytocin; without oxytocin, newly born young will die unless they are fostered [24].
A Computational Study on Altered Theta-Gamma Coupling during Learning and Phase Coding

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Abstract

There is considerable interest in the role of coupling between theta and gamma oscillations in the brain in the context of learning and memory. Here we have used a neural network model which is capable of producing coupling of theta phase to gamma amplitude firstly to explore its ability to reproduce reported learning changes and secondly to memory-span and phase coding effects. The spiking neural network incorporates two kinetically different GABA_A receptors mediated currents to generate both theta and gamma rhythms and we have found that by selective alteration of both NMDA receptors and GABA_A,subaxons receptors it can reproduce learning-related changes in the strength of coupling between theta and gamma either with or without coincident changes in theta amplitude. When the model was used to explore the relationship between theta and gamma oscillations, working memory capacity and phase coding it showed that the potential storage capacity of short term memories, in terms of nested gamma-subcycles, coincides with the maximal theta power. Increasing theta power is also related to the precision of theta phase which functions as a potential timing clock for neuronal firing in the cortex or hippocampus.

Introduction

The roles of different brain oscillatory rhythms, either alone or in combination, in controlling learning and memory functions have been the subject of extensive investigation and speculation. Local field potential (LFP) recordings in the hippocampus have shown that low frequency theta oscillations (4–8 Hz) are important in carrying information about memory processes [1,2] and function to decreasing reaction times in decision making tasks [3]. Recording studies in the CA1 region of the hippocampus have also shown that both synaptic plasticity and the strength of inputs vary systematically with ongoing theta oscillations [4,5]. On the other hand, high frequency oscillations such as gamma waves (30–80 Hz) can provide tighter co-ordinated control than those in low frequency ranges [6]. EEG and MEG as well as LFP recordings have revealed that synchronous firing of a group of neurons in visual processing is associated with binding problem in which gamma synchronization can combine features in a visual scene to form a coherent percept [7,8]. Modulation of oscillatory synchronisation can also lead to the increase in synaptic gain at postsynaptic target sites thereby potentiating responses to learned stimuli [9,9].

Both low and high frequency oscillations occur in many brain regions [10] and recent interest has focused on how these can be coupled and what the functional consequences of such coupling might be. With the development of mathematical tools such as Bayesian network and Granger causality analysis [10], several cross-frequency interactions have been observed, e.g. n : m amplitude-independent phase coupling [11], and the phase of slow frequency wave interacts with the amplitude of fast rhythm [12,13]. Cross-frequency coupling (CFC) of theta phase with gamma amplitude has recently been shown to strengthen significantly as a function of learning both in the inferior temporal cortex (IT) following a visual face-discrimination task [14] and also in the hippocampus during an item-context association task [15]. The change in coupling strength also correlated positively with behavioral performance. However, while in the IT changes in coupling strength occurred in conjunction with increased theta power [14], although they appeared not to be causally linked, in the hippocampus they occurred without theta power changes [15].

Another potential functional role of theta-gamma coupling may also relate to short term memory and its capacity. In 1956, Miller first provided evidence that people can only hold around 7±2 items in a variety of short-term memory (STM) tasks [16]. It has subsequently been proposed that this capacity limit on STM storage can be explained by a multiplexing mechanism based on coupled theta and gamma oscillations [17]. If individual memory items, for instance a sequence of words, are stored in separate high
Phenomenological Analysis of ATP Dependence of Motor Proteins

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Abstract

In this study, through phenomenological comparison of the velocity-force data of processive motor proteins, including conventional kinesin, cytoplasmic dynein and myosin V, I found that, the ratio between motor velocities of two different ATP concentrations is almost independent of any substall, superstall or negative external loads. Therefore, the velocity of motors can be well approximated by a Michaelis-Menten like formula $V = \frac{[\mathrm{ATP}] k(F) L}{([\mathrm{ATP}]+K_M)}$, with $L$ the step size, and $k(F)$ the external load $F$ dependent rate of one mechanochemical cycle of motor motion in saturated ATP solution. The difference of Michaelis-Menten constant $K_M$ for substall, superstall and negative external load indicates, the configurations at which ATP molecule can bind to motor heads for these three cases might be different, though the expression of $k(F)$ as a function of $F$ might be unchanged for any external load $F$. Verifications of this Michaelis-Menten like formula has also been done by fitting to the recent experimental data.

Introduction

The processive motor proteins, including kinesin, dynein and myosin are essential for biophysical functioning of eukaryotic cells [1,2]. Due to the development of experimental instrument [3,4], much accurate experimental data have been obtained [4–13]. Both conventional kinesin and cytoplasmic dynein move hand-over-hand along microtubules by converting chemical energy stored in ATP molecules into mechanical works [10,14–17]. Myosin (V or VI) also moves hand-over-hand but along actin filament [8,18–20]. The step size of motor proteins is usually a multiple of their track period. So far, there are many biophysical models to understand the mechanism of motor proteins, including the flashing ratchet model [11,21,22], Fokker-Planck equation [23–25]. Meanwhile, more detailed mechanochemical models have also been used to explain the experimental data, and get meaningful biochemical parameters [13,26–31].

In this study, by phenomenological comparison of the velocity-force data of different ATP concentrations, I found that the velocity of processive motor proteins can be described by a Michaelis-Menten like formula $V = \frac{[\mathrm{ATP}] k(F) L}{([\mathrm{ATP}]+K_M)}$, but might with different constant $K_M$ for substall, superstall and negative external loads. The motor velocity in saturated ATP solution is $V_s = k(F)L$, and generally, the velocity of motor can be obtained by multiplying $V_s$ by a constant $\frac{[\mathrm{ATP}]}{([\mathrm{ATP}]+K_M)}$.

Results

For the sake of comparison, the velocity-force data of kinesin, dynein and myosin are plotted in Figs. 1, 2 and 3(a). In Fig. 1(a), the thick dashed line $V_s$ is the velocity-force data of kinesin for $[\mathrm{ATP}] = 1\, \mu\text{M}$ obtained by Nishiyama et al [6], and the solid line $V_s$ is for $[\mathrm{ATP}] = 10\, \mu\text{M}$. One can easily see that there is only little difference between the lines $V_s$ and $V_s/3.3$. Similar phenomena can also be found for the velocity-force data of dynein and myosin obtained in [8,10,32], see Figs. 1(b,c,d). Meanwhile, for negative and superstall force cases, one can find the similar results, but the ratio constants might be different from the positive substall force case, see Figs. 2 and 3(a) for data of kinesin obtained in Refs. [4,7,9]. For the kinesin data in [9], the ratio constant is about 2.6 for $F < 0$, about 7.1 for $0 \leq F \leq 7\, \text{pN}$, and about 2.3 for $F > 7\, \text{pN}$ [see Fig. 2(a)]. For the data in [7], the ratio constant is about 16 for $F < 0$, and about 29 for $0 \leq F \leq 5\, \text{pN}$ [see Fig. 2(b)]. But for the kinesin data measured in [4], the constant 3.6 works well for both substall and negative external load [see Fig. 3(a)].

From the above observations about the experimental data plotted in Figs. 1 and 2, one can see that the velocity-force relation of motor proteins satisfies $V(F,[\mathrm{ATP}]) = f([\mathrm{ATP}]) V_s(F)$. Where $V_s(F) = V_s(F)$ is the velocity-force relation at saturated ATP concentration, and obviously $V_s$ can be written as $V_s(F) = k(F)L$ with $L$ the step size of motor proteins, and $k(F)$ the force dependent rate to complete one ATP hydrolysis cycle (coupled with one mechanical cycle). The function $f([\mathrm{ATP}])$ increases with [ATP], $f(0) = 0$ and $f([\mathrm{ATP}]) \to 1$ with [ATP] $\to \infty$. A reasonable form of $f([\mathrm{ATP}])$ is $f([\mathrm{ATP}]) = [\mathrm{ATP}]/([\mathrm{ATP}]+K_M)$ with a parameter $K_M$ which I called Michaelis-Menten constant [7,33–35]. Finally, the velocity formula can be written as $V(F,[\mathrm{ATP}]) = [\mathrm{ATP}] k(F)L/([\mathrm{ATP}]+K_M)$.

To verify the above velocity-force formula, the force dependent expression of rate $k(F)$ should be given firstly. Usually, the mechanical coupled cycle of ATP hydrolysis includes several internal states, here, as demonstrated in the previous mechanochemical model [27], I assume that, in each cycle, there are two...
Invariance Principles Allowing of Non-Lyapunov Functions for Estimating Attractor of Discrete Dynamical Systems

Tian Ge, Wei Lin, Member, IEEE, and Jianfeng Feng

Abstract—This technical note establishes several versions of invariance principles for describing the eventual dynamical behaviors of discrete dynamical systems. Instead of the requirement of the so-called Lyapunov functions in the classical LaSalle invariance principle, some more relaxed conditions are imported. The established invariance principles thus can be applied to a more general class of discrete dynamical systems for classifying their orbits into two categories based on the eventual dynamical behaviors, and the proposed classification scheme is suitable for theoretically and numerically estimating the local or global attractors produced by the discrete dynamical systems. The practical usefulness of the analytical results is verified by systematically investigating several representative discrete dynamical systems.

Index Terms—Chaotic strange attractor, discrete dynamical system, invariance principle, Omega limit set, synchronization.

I. INTRODUCTION

The invariance principle, originally established by J. P. LaSalle in 1960’s, has elicited a great deal of attention from both the theoretical and the engineering communities. On the one hand, several versions of the invariance principles were consecutively established for both continuous and discrete autonomous dynamical systems [1]–[4]. Also developed were the versions for time-variant systems and the systems with stochastic perturbations [5]–[12]. On the other hand, those established principles have been successfully applied to many natural and artificial systems for analyzing their deterministic or stochastic dynamical behaviors [13]–[21].

It is known that one essential step of applying the LaSalle invariance principle to design a so-called Lyapunov function whose derivative or variation along the system orbits is always semi-definitely negative. The other key is to validate the eventual boundedness of every orbit generated by the considered system. Constructing the Lyapunov function is a kind of subtle work inviting complicated calculations, even though a series of papers have been devoted to developing feasible methods for specific systems [22]–[24]. Meanwhile, the eventual boundedness of the orbit can always follow from the designed Lyapunov function. Therefore, a proper design of the Lyapunov function is essential to the analysis of dynamical systems. Naturally, some questions arise here: “Can the semi-definite negativity of the derivative or variation of the Lyapunov function be relaxed to some extent?” “Can the eventual dynamical behaviors of the system orbits be still classified with the relaxed non-Lyapunov function?” “Are the established conditions for discrete systems different from those for continuous systems, and reflecting the characteristic of the orbits of discrete systems?”

The answer to the first two questions posed above can be found in [25], [26], where two new versions of the invariance principles were developed for continuous systems. So far, as for the third question posed above, there has not been a complete answer yet, to the best of the authors’ knowledge. Indeed, only one version of the invariance principle allowing of non-Lyapunov functions has been established for purely discrete systems [27]. However, this version, which requires intricate set notations, inherits from the versions for continuous dynamical systems [25], [26]. In fact, there is a difference between the orbits produced, respectively, by continuous dynamical systems and discrete dynamical systems. Therefore, more feasible versions of invariance principles with relaxable conditions, that reflect the characteristic of the orbits of discrete dynamical systems, are expected.

The main results of the note are in two folds. On the one hand, inspired by the existing results [25]–[27], we establish several versions of the invariance principles for discrete dynamical systems (see theorems in Section III). All these versions allow the variation of the function along the system orbits to be either positive or negative in some regions, where diverse attractors including the chaotic strange attractors may emerge. On the other hand, the established principles leads to a feasible scheme for classifying the eventual dynamical behaviors, and the scheme is thus applied to several representative nonlinear discrete systems for estimating the attractors (see Section IV). It is noted that the obtained results for these representative systems are even optimal and novel.

The note is finally closed with some comments and remarks.

II. PRELIMINARIES

Consider a discrete system described by the following $\mathbb{R}^n$-dimensional difference equation:

\[
\mathbf{x}(k+1) = \mathbf{f}(\mathbf{x}(k)), \quad \mathbf{x} \in \mathbb{R}^n
\]  

(1)

with the initial value $\mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}^n$. Here, $\mathbf{f}(\mathbf{x}) = (f_1(\mathbf{x}), \ldots, f_n(\mathbf{x}))$ is the state variable at the $k$-th iteration starting from $\mathbf{x}_0 \in \mathbb{R}^n$, and $\mathbb{R}^n$-valued and continuous mapping defined on the space $\mathbb{R}^n$, denotes the vector field of the system (1), and $f_i$ represents the family of all positive integers. Denote by $\mathcal{L} = \{f_1, \ldots, f_n\}$ an $\mathbb{R}^n$-valued and continuous mapping defined on the space $\mathbb{R}^n$. The positive orbit of the system (1). Define the distance between $\mathbf{r} \in \mathbb{R}^n$ and $\mathbb{S} \subseteq \mathbb{R}^n$ by $d_i[\mathbf{r}, \mathbb{S}] = \inf \left\{ \| \mathbf{r} - \mathbf{s} \| : \mathbf{s} \in \mathbb{S} \right\}$, where $\| \cdot \|$ is the Euclidean norm. With this setting, $\mathbf{r} \in \mathbb{R}^n$ is positive if $\mathbf{r} = f_1(\mathbf{r}), \ldots, f_n(\mathbf{r})$ as $\mathbf{r} \rightarrow +\infty$ can be interpreted as $d_i[\mathbf{r}, \mathbb{S}] \rightarrow 0$ as $\mathbf{r} \rightarrow +\infty$. The following theorem (refer to Theorem 4.2.3 in [2]) will be useful later.

Theorem 2.1: Every Omega limit set $\Omega$ of the discrete dynamical system (1) is closed and invariant. Furthermore, assume that $\mathcal{L}$ is a bounded. Then $\Omega$ is nonempty, compact, invariant, and invariantly connected.

Define the variation of a function $V: \mathbb{R}^n \rightarrow \mathbb{R} \cup \{0\}$ along the system (1) by $\Delta V(\mathbf{r}, \mathbf{s}) = V(\mathbf{r}) - V(\mathbf{s})$. If $\mathbf{r} \rightarrow \mathbf{s}$ is a positive orbit of the system (1), this variation can be written as $\Delta V(\mathbf{r}, \mathbf{s}) = \sum_{i=1}^{n} f_i(\mathbf{r}) \Delta r_i - \sum_{i=1}^{n} r_i \Delta f_i$. Let $\mathbb{P}$ be a set contained in $\Omega$. The function $\mathbf{V}: \mathbb{P} \rightarrow \mathbb{R}$ is said to be a Lyapunov function of the system (1) on the set
On the Spectral Characterization and Scalable Mining of Network Communities

Bo Yang, Jiming Liu, and Jianfeng Feng

Abstract—Network communities refer to groups of vertices within which their connecting links are dense but between which they are sparse. A network community mining problem (or NCMP for short) is concerned with the problem of finding all such communities from a given network. A wide variety of applications can be formulated as NCMPs, ranging from social and/or biological network analysis to web mining and searching. So far, many algorithms addressing NCMPs have been developed and most of them fall into the categories of either optimization based or heuristic methods. Distinct from the existing studies, the work presented in this paper explores the notion of network communities and their properties based on the dynamics of a stochastic model naturally introduced. In the paper, a relationship between the hierarchical community structure of a network and the local mixing properties of such a stochastic model has been established with the large-deviation theory. Topological information regarding to the community structures hidden in networks can be inferred from their spectral signatures. Based on the above-mentioned relationship, this work proposes a general framework for characterizing, analyzing, and mining network communities. Utilizing the two basic properties of metastability, i.e., being locally uniform and temporarily fixed, an efficient implementation of the framework, called the LM algorithm, has been developed that can scalably mine communities hidden in large-scale networks. The effectiveness and efficiency of the LM algorithm have been theoretically analyzed as well as experimentally validated.

Index Terms—Social network, community structure, Markov chain, local mixing, large-deviation theory.

1 INTRODUCTION

Currently, online social communities are the most popular applications provided by Web 2.0 portals, in which people with common interests join anytime anywhere to freely share information, experiences, opinions, services, and other useful resources. Techniques that can automatically discover such virtual communities will provide huge help in building and managing personalized smart web portals or intelligent recommender systems through analyzing and predicting the collective behaviors of users by mining their underlying community structures. Formally, this task can be formulated as a network community mining problem (NCMP), which aims to discover all communities from a given network.

A network community generally refers to a group of vertices within which the connecting links are dense but between which they are sparse. Particularly, network communities in different contexts may be circles of a society within which people share common interests and keep more contacts, groups of proteins with similar functions, or clusters of webpages related to common topics. Besides online social community discovering, a wide variety of applications can be represented as NCMPs, ranging from social network analysis [1], [2], [3], [4], biological network analysis [10], [11], [12], [13], [14], [15] to web mining and web searching [16], [17], [18], [19]. Thus, how to effectively and efficiently solve such NCMPs is of fundamental importance for both theoretical research and practical applications.

1.1 Related Work

Many methods addressing NCMPs have been developed. In view of the fact that the NCMP is an application-oriented problem, i.e., what structure should be mined will depend on specific applications, it can be stated that all the proposed methods for NCMPs have been heuristic in nature. That is to say, their methodologies would rely more or less on human intuitive observations. So far, most of the existing methods can be classified into two main categories, in terms of whether or not explicit optimization objectives are being used.

The methods with explicit optimization objectives solve an NCMP by transforming it into an optimization problem and trying to find an optimal solution for a predefined objective function, such as different kinds of cut criteria adopted by different spectral methods [5], [6], [7], [8], [9], the energy function of a Potts model with multiple states employed in several algorithms [7], [11], [15], the Q function proposed by Newman [21] and employed in several algorithms [7], [11], the energy function of a Potts model with multiple states [24], and the likelihood of a hierarchical random graph [25].

On the other hand, the methods without using explicit optimization objectives solve the NCMP based on predefined assumptions or heuristic rules. For example, the heuristic rule used in the maximum flow community (MFC) algorithm [16] is that the “flows” through intercommunity
Synchronization in Complex Networks With Stochastically Switching Coupling Structures

Bo Liu, Wenlian Lu, and Tianping Chen, Senior Member, IEEE

Abstract—Synchronization in complex networks with time dependent coupling and stochastically switching coupling structure is discussed. A novel approach investigating synchronization based on the scramblingness property of the coupling matrix is proposed. Some sufficient condition for a network with general time-varying coupling structure to reach complete synchronization is provided. Based on the general theorem, networks with stochastically switching coupling structures is investigated. In particular, two kinds of stochastic switching coupling networks are addressed: (a) independent and identically distributed switching processes and (b) Markov jump processes. In both cases, some sufficient condition for almost sure synchronization of the networks is given. Also, numerical simulations are provided to illustrate the theoretical results.

Index Terms—Coupled system, stochastic systems, switched systems, synchronization, time-varying.

I. INTRODUCTION

Today, the study of synchronization in complex dynamical systems has become a subject of great interest due to its applications and potential applications in a variety of fields, such as communication [1], seismology [2], and neural networks [3]. Till now, many works are available engaging in the study of synchronization of complex networks. For example, in the pioneering work [4], Master Stability Function (MSF) method to study the local synchronization of coupled chaotic systems was proposed. In [5]–[7], the distance to the synchronization manifold was defined, and some sufficient conditions for an array of linearly coupled systems to synchronize were proposed. Most of the works on synchronization are focused on static networks, i.e., the coupling structure and coupling strength is constant in time. In such cases, the criteria for synchronization have been well-established by analyzing the eigen-structure of the coupling matrix. Besides, there are also some papers concerning synchronization in dynamic networks, i.e., the network coupling structure and coupling strength is dynamically changing along with time. Here, we list some (not all) relating papers [9]–[13], [15], [20], etc. In [9], the authors studied global synchronization in a blinking network model. They used the connection graph stability method developed in [8]. In [20], the authors investigated synchronization in networks of coupled Kuramoto oscillators with switching topologies and time delays. This model also can be viewed as nonlinear consensus (see [25]). In [12], sufficient conditions for fast switching synchronization in networks with time-varying topologies were given. In [15], the authors studied synchronization in networks with random switching topologies and gave sufficient conditions for almost sure local synchronization. Both [12] and [15] indicate that under the assumption of fast switching, the synchronization of the time-varying network can be deduced from their time-average system. Another topic closely relating to synchronization problem is consensus problem in networks of multiagents. [16]–[19], [21]–[30] are a few among them.

Though consensus problem is a special case of synchronization problem, some efficient approach used in the consensus problem can still be applied to investigation of synchronization problem.

It is also known that if the networks are time-varying or with switching topologies, the synchronization or consensus becomes complicated [10], [14], [28]. Because it is difficult to construct a Lyapunov function when the coupling matrices are time varying, except the switching occurs among several strongly connected and balanced graphs. In such case, it is proved that for arbitrary switching, average consensus can be reached exponentially (see [16]). Instead, if the graph is not node balanced, it is difficult to find a common Lyapunov function so that this approach can not apply.

Another efficient approach comes from the theory of nonhomogeneous Markov chains by reducing the convergence of consensus algorithm to the ergodicity of infinite products of stochastic matrices. This method is widely used in [21]–[23], [27] and others. It was based on the work of Hajnal back to the 1950’s [31]. Hajnal investigated the weak ergodicity of non-homogenous Markov chains and proposed scrambling matrix, which plays an important role in the convergence of products of stochastic matrices. Similar method has also been used to study consensus problem in continuous time networks in [17], [18], [26], etc. This method was also used to discuss synchronization in [13].

It is natural to ask if this method can be further extended to more general cases in synchronization analysis. This is the aim of this technical note.

In the following, we first address global synchronization in networks with a general time-varying topology and sufficient condition for global synchronization is given. To this purpose, we extend the concept of Hajnal’s scrambling property from stochastic matrices to matrices with nonnegative off-diagonal entries. Then we will turn to stochastic switching networks. Particularly, we will study synchronization for networks with two kinds of stochastically switching topologies. That is: (a) the switching sequence are independent and identically distributed; (b) the switching sequence forms a Markov chain. In both cases, we give sufficient conditions for the network to synchronize almost surely.

In previous works, the authors considered either special node dynamics such as Kuramoto model in [20], or linear dynamics such as in [13], or local synchronization as in [15]. Instead, in this note, we consider global synchronization for continuous-time networks with general nonlinear node dynamics and general time varying topologies. In case the stochastic switching topologies, we don’t require the network to switch fast enough, while this requirement is assumed in [9], [12]. We also point out that if there is a nonzero probability of a scrambling coupling matrix, then the network will synchronize almost surely if the coupling strength is strong enough.

The rest of the technical note is organized as follows. In Section II, we study networks with general time-varying topologies and provide a sufficient condition for such networks to achieve synchronization. In Section III, we study stochastic network and give sufficient conditions for almost sure synchronization. An example with numerical simulations are provided in Section IV, and the technical note is concluded in Section V.

II. GENERAL THEORY

In this section, we discuss synchronization in networks with general time dependent coupling.

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Individual classification of ADHD patients by integrating multiscale neuroimaging markers and advanced pattern recognition techniques

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is characterized by clinical symptoms of inattention, impulsivity, and hyperactivity. It is one of the most common brain and behavioral disorders among children, which affects 5–8% school age children. ADHD can frequently persist into adolescence and adulthood (Biederman, 2004; Barkley, 2006), which can cause significant functional impairments in the brain (Frances, 1994). A number of neuroimaging studies have demonstrated the abnormalities in both structure and function of the brain for ADHD patients (Seidman et al., 2005; Bassett et al., 2006). Structural abnormalities involve reduced volume and cortical thickness found in frontal, parieto-temporal, cingulate regions, cerebellum, and corpus callosum (Krain and Castellanos, 2006; Shaw et al., 2006; Mackie et al., 2007; Carmona et al., 2009; Batty et al., 2010; Rubia, 2011). Functional connectivity alterations of ADHD patients include fronto-parietal (Dickstein et al., 2006), fronto-striatal (Castellanos et al., 2006), and frontotemporal-parietal network (Smith et al., 2006), and also anterior cingulate (Tian et al., 2006). Although there have been extensive studies of ADHD in terms of widespread brain regions and the connectivity patterns, relatively less attention are focused on the pattern classification based on the neuroimaging data of individual ADHD patients, which is crucial for subjective and accurate clinical diagnosis of ADHD (Zhu et al., 2008). Compared with identifying differences at the group level, pattern classification on the individual level proves to be a more difficult task. It should be approached with highly sensitive neuroimaging markers, and efficient feature-selection/pattern recognition approaches (Zhang et al., 2012). As a specific example, consider the hippocampal volume measurements for individuals in two samples. Suppose a two sample t-test comparison of the two samples resulted in a significantly small p-value. Generally, it will be hard to accurately distinguish (e.g., with 90% accuracy) which sample an individual is drawn from, because the hippocampal volume of these two samples may have substantially overlapping distributions. In other words, finding group difference only requires a p value that is less than a threshold, while accurately distinguishing the two samples, at the...
Technical Note

Granger causality with signal-dependent noise

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ABSTRACT

It is generally believed that the noise variance in in vivo neuronal data exhibits time-varying volatility, particularly signal-dependent noise. Despite a widely used and powerful tool to detect causal influences in various data sources, Granger causality has not been well tailored for time-varying volatility models. In this technical note, a unified treatment of the causal influences in both mean and variance is naturally proposed on models with signal-dependent noise in both time and frequency domains. The approach is first systematically validated on toy models, and then applied to the physiological data collected from Parkinson patients, where a clear advantage over the classical Granger causality is demonstrated.

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A Unified Treatment of the Probability of Fixation when Population Size and the Strength of Selection Change Over Time

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ABSTRACT

The fixation probability is determined when population size and selection change over time and differs from Kimura’s result, with long-term implications for a population. It is found that changes in population size are not equivalent to the corresponding changes in selection and can result in less drift than anticipated.

A new mutation in a finite population is subject to genetic drift and its ultimate fate is random: it may be either extinction (loss) or complete establishment (fixation). In a randomly mating population, the typical outcome for a new mutation is its loss, with fixation occurring only with small probability. Under static conditions (constant population size and constant strength of selection) a new beneficial mutation with small selective advantage, s, in a randomly mating population with discrete generations, has only a small probability of fixation: \( \sim 2s \) when reproduction is treated as a branching process and the number of offspring has a Poisson distribution (Haldane 1927). A deleterious mutation has a yet smaller probability of fixation that is not calculable under a branching process. However, despite the relative rarity of fixation among the fates of all mutations, attention is largely focused on this outcome because the fixation of beneficial mutations plays a central role in the long-term adaptation of populations, and the fixation of deleterious mutations, in the absence of recombination, plays an important role in the long-term survival of populations (Muller 1964; Felsenstein 1974). Our understanding of the rate of such phenomena depends sensitively on the probability of fixation, and deviations from its static value, due to time-dependent conditions, are of particular significance.

Indeed, there are a variety of reasons, both abiotic and biotic, why population size and the strength of selection do not generally remain constant over time.

Temporal changes, such as systematic trends in the composition or temperature of the atmosphere or oceans over time, although abiotic in nature, often have major implications for biological systems and may force biotic change. For example, atmospheric temperature changes may affect various biological processes within an organism, but also affect the vegetation on which an organism feeds, thereby affecting both selection and carrying capacity. Thus the general situation is complex, with selection fluctuating for multiple reasons; indeed, “... natural selection is very complicated, it is unlikely that the selection coefficient stays constant” (Ohta 1972, p. 307). Additionally, changes in, for example, resource/habitat availability or the density of parasites or predators will generally change the strength of selection as well as the size of a population. Thus generally we should expect variation in population size and the strength of selection.

The Soay sheep provide an illustration of the interplay of the various factors that affect population size and the strength of selection and the interrelation of these two quantities. The Soay sheep are an intensively studied wild mammalian population and their survival is density dependent and closely tied in with the availability of vegetation, whose quality and abundance are highly variable (Clutton-Brock and Pemberton 2003). Parasite population dynamics have been shown to regulate vertebrate populations and, in the Soay sheep, over-winter survival has been...
A Dynamical Model Reveals Gene Co-Localizations in Nucleus

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Abstract

Co-localization of networks of genes in the nucleus is thought to play an important role in determining gene expression patterns. Based upon experimental data, we built a dynamical model to test whether pure diffusion could account for the observed co-localization of genes within a defined subnuclear region. A simple standard Brownian motion model in two and three dimensions shows that preferential co-localization is possible for co-regulated genes without any direct interaction, and suggests the occurrence may be due to a limitation in the number of available transcription factors. Experimental data of chromatin movements demonstrates that fractional rather than standard Brownian motion is more appropriate to model gene mobilizations, and we tested our dynamical model against recent static experimental data, using a sub-diffusion process by which the genes tend to colocalize more easily. Moreover, in order to compare our model with recently obtained experimental data, we studied the association level between genes and factors, and presented data supporting the validation of this dynamic model. As further applications of our model, we applied it to test against more biological observations. We found that increasing transcription factor number, rather than factory number and nucleus size, might be the reason for decreasing gene co-localization. In the scenario of frequency- or amplitude-modulation of transcription factors, our model predicted that frequency-modulation may increase the co-localization between its targeted genes.

Introduction

A central theme in the regulation of transcription is the binding of transcription factor proteins to specific sites along the DNA. Though these sites can be several tens or hundreds of kilobases from a target gene promoter, regulation is achieved by the formation of chromatin loops that bring the sites together to form transcriptional hubs. It is thought that proximity between distal regulatory elements and their target genes increases the local concentration of specific regulatory factors to affect transcriptional control. Recent studies have also shown that active genes co-localize in the nuclear space at focal concentrations of the active form of RNA Polymerase II (RNAPII) called transcription factories [1,2,3,4,5,6]. A genome-wide enhanced 4C (e4C) screen demonstrated that specific combinations of genes from different chromosomes share factories with a high frequency, suggesting that active genes have preferred transcription partners. Co-localization of these spatial gene networks at transcription factories was found to be dependent on the transcription factor Klf1, which co-regulates many of the partners [7]. Just as distal regulatory elements are thought to affect gene regulation by spatial clustering, intra- and inter-chromosomal associations between co-regulated genes may affect expression by creating specialized microenvironments that are optimized for their transcription. Thus, the transcriptional program of a cell may be reflected by, or may even be dependent upon, the spatial organization of the genome. The appreciation that a very large proportion of the genome is transcribed with relatively few transcription sites suggests that the organization of the transcriptional machinery plays a major role in shaping the nuclear organization of the genome. The positioning of genes, regulatory sequences and transcription factors in relation to each other and to landmarks in the nucleus, such as nuclear bodies and lamina, are important determinants in gene expression [8].

How specific subgroups of active genes and transcription factors come to be positioned at factories is still unknown. Gaining an understanding of the emergence of complex spatiotemporal patterns of behavior from the interactions between genes in a regulatory network poses a huge scientific challenge with potentially high industrial pay-offs [4,9,10,11,12]. Experimental techniques to dissect regulatory interactions on the molecular level are critical to this end. In addition to experimental tools, mathematical modeling and computer tools will be indispensable. As most genetic regulatory systems of interest involve many genes connected through interlocking feedback loops, an intuitive understanding of their behavior is hard to obtain. By explicating hypotheses on the topology of a regulatory network in the form of a computer model, the behavior of possibly large and complex systems can be predicted and compared against experimental data.
Suprathreshold stochastic resonance in neural processing tuned by correlation

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Suprathreshold stochastic resonance (SSR) is examined in the context of integrate-and-fire neurons, with an emphasis on the role of correlation in the neuronal firing. We employed a model based on a network of spiking neurons which received synaptic inputs modeled by Poisson processes stimulated by a stepped input signal. The smoothed ensemble firing rate provided an output signal, and the mutual information between this signal and the input was calculated for networks with different noise levels and different numbers of neurons. It was found that an SSR effect was present in this context. We then examined a more biophysically plausible scenario where the noise was not controlled directly, but instead was tuned by the correlation between the inputs. The SSR effect remained present in this scenario with nonzero noise providing improved information transmission, and it was found that negative correlation between the inputs was optimal. Finally, an examination of SSR in the context of this model revealed its connection with more traditional stochastic resonance and showed a trade-off between suprathreshold and subthreshold components. We discuss these results in the context of existing empirical evidence concerning correlations in neuronal firing.

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I. INTRODUCTION

One of the more striking facts about neural processing is that neurons in vitro fire with considerable regularity in response to a constant stimulus, while neurons in vivo exhibit much greater irregularity in response to the same stimulus [1]. This irregularity has often been characterized as noise without this necessarily implying a lack of functional utility [2]. A number of possible sources for neuronal noise in vivo have been proposed, including intrinsic channel noise [3] and Johnson electrical noise [4], and one of the most important sources, especially in view of the clear difference between the in vivo and in vitro cases, is network noise. This argues that noise can arise from the pattern of spiking inputs arriving at synapses to a given neuron, which itself may arise due to the presynaptic neurons themselves having irregular firing patterns, or by their having a particular pattern of connectivity. The presence of this irregularity has led to neural spike trains being treated as stochastic processes, and in particular Poisson processes.

Given the prominence of neuronal noise in vivo, it is natural to question what the functional role of such noise might be, especially in neural coding where the map from stimuli to neural response is explored. Two frequently used coding schemes are rate coding, which concerns the average number of spikes per unit time and contains information about the stimuli in the firing rate of the neuron, and temporal coding, which focuses on the precise timing of single spikes or the high-frequency firing-rate fluctuations which may carry information [5]. For many years, there has been a debate on the significance of temporal coding vs rate coding within the neuroscience community. Some suggestions, such as coincidence detection, posit the existence of a precise temporal code in neural spike trains [6,7], arguing that the variability in neural spike trains is directly useful in capturing features of the presynaptic input. Others reject these claims [8–10] and argue for a rate code in which it is the number of spikes occurring in a given short time period that is the principal carrier of information, regardless of the precise timing of the spikes within that period. Although the debate about temporal and rate coding continues [2,11,12], both temporal and rate coding allow for the possibility that neuronal noise is beneficial in neural information processing.

One well-documented example of the benefits of noisy coding is stochastic resonance (SR) [13,14], in which an appropriate amount of noise can help to reveal the temporal structure in a predominantly subthreshold signal. Neurophysiological experiments have suggested that the mechanism could be used by sensory systems [15] and motor systems [16] in enhancing the perception and transfer of information. In neural systems this has also been demonstrated in the context of both temporal coding [17], including specifically coincidence detection [18], and rate coding [19]. However, in general, traditional SR suffers from the problem that neural systems are adaptive in a number of ways, including a limited ability to independently...
Hierarchical organization of brain functional networks during visual tasks

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The functional network of the brain is known to demonstrate modular structure over different hierarchical scales. In this paper, we systematically investigated the hierarchical modular organizations of the brain functional networks that are derived from the extent of phase synchronization among high-resolution EEG time series during a visual task. In particular, we compare the modular structure of the functional network from EEG channels with that of the anatomical parcellation of the brain cortex. Our results show that the modular architectures of brain functional networks correspond well to those from the anatomical structures over different levels of hierarchy. Most importantly, we find that the consistency between the modular structures of the functional network and the anatomical network becomes more pronounced in terms of vision, sensory, vision-temporal, motor cortices during the visual task, which implies that the strong modularity in these areas forms the functional basis for the visual task. The structure-function relationship further reveals that the phase synchronization of EEG time series in the same anatomical group is much stronger than that of EEG time series from different anatomical groups during the task and that the hierarchical organization of functional brain network may be a consequence of functional segmentation of the brain cortex.

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I. INTRODUCTION

The human brain, which consists of ten thousand million neurons and even more synapses, is perhaps the most complex system ever known. Benefiting from the development of brain anatomy since the 19th century, we now know that the neuronal elements of the brain constitute an extremely complex structural network, which subserves a wide variety of cognitive functions and neural activities [1–3]. Recently, it has gained great interests among scientists to investigate the functional connectivity of brain based on complex network theory in which the brain can naturally be abstracted as a functional network. A brain functional network can be extracted based on functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), or multielectrode array (MEA) data, which record electric, magnetic, or other signals representing cortical activities of the brain [4]. Vertices of brain functional network derived from fMRI data describe anatomically localized regions of interest (ROIs) or voxels of fMRI image, whereas the vertices of those derived from EEG, MEG, or MEA data denote surface electrodes or sensors. The functional connectivity (or edge) between pairs of vertices is usually estimated using correlation between time series recordings of the vertices.

It has been widely observed that the brain functional networks demonstrate properties such as small-worldness [5] and power-law degree distribution [6], which distinguish themselves from regular and random networks [7–12]. However, the small-worldness and power-law degree distribution represent only the global properties of brain functional networks. To understand brain functional networks imposed by structural and functional constraints more comprehensively, the hierarchical modular organization, which can reflect both local and global organization of brain functional network, should be fully investigated.

Hierarchical organization, also called community structure and modular architecture, describes the fact that some nodes in a network are densely connected as groups, and these groups are only sparsely connected among themselves, which is a common phenomenon in diverse networks such as World Wide Web, scientist collaboration networks, genetic networks, protein-protein interaction networks, and financial networks [13–16]. A large number of algorithms have been developed to detect the hierarchical organizations of real networks [13,17–23] (also see the review in Ref. [24]). Interestingly, several recent works have also found the hierarchical organization of the brain functional networks derived from resting-state fMRI data [25,26] and epileptic MEG signals [27], respectively.

Although there are many works devoted to the hierarchical organization of the brain functional networks, most of them are confined to the “resting state.” The study of this organization in the “task state” and the investigation of its functional implications are rare. In this paper, we analyzed the brain functional networks of the subjects during the visual task which involves visual, sensory, and motor functions of the brain cortex. In our work, the brain functional networks are derived from high-resolution synchronous EEG time series, which consist of 238 channels and are recorded during the visual task. In the functional network, the vertices correspond to surface electrodes (i.e., channels), while edges are determined by the extent of phase synchronization of EEG time series from pairs of channels, and we first analyze the community structure of the brain functional networks by the fast Girvan-Newman (GN) algorithm (i.e., functional cluster). On the other hand, these electrodes can also be assigned into the same group by their spatial positions on scalp and a priori

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Learning alters theta amplitude, theta-gamma coupling and neuronal synchronization in inferotemporal cortex

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Abstract

Background: How oscillatory brain rhythms alone, or in combination, influence cortical information processing to support learning has yet to be fully established. Local field potential and multi-unit neuronal activity recordings were made from 64-electrode arrays in the inferotemporal cortex of conscious sheep during and after visual discrimination learning of face or object pairs. A neural network model has been developed to simulate and aid functional interpretation of learning-evoked changes.

Results: Following learning the amplitude of theta (4-8 Hz), but not gamma (30-70 Hz) oscillations was increased, as was the ratio of theta to gamma. Over 75% of electrodes showed significant coupling between theta phase and gamma amplitude (theta-nested gamma). The strength of this coupling was also increased following learning and this was not simply a consequence of increased theta amplitude. Actual discrimination performance was significantly correlated with theta and theta-gamma coupling changes. Neuronal activity was phase-locked with theta but learning had no effect on firing rates or the magnitude or latencies of visual evoked potentials during stimuli. The neural network model developed showed that a combination of fast and slow inhibitory interneurons could generate theta-nested gamma. By increasing N-methyl-D-aspartate receptor sensitivity in the model similar changes were produced as in inferotemporal cortex after learning. The model showed that these changes could potentiate the firing of downstream neurons by a temporal desynchronization of excitatory neuron output without increasing the firing frequencies of the latter. This desynchronization effect was confirmed in IT neuronal activity following learning and its magnitude was correlated with discrimination performance.

Conclusions: Face discrimination learning produces significant increases in both theta amplitude and the strength of theta-gamma coupling in the inferotemporal cortex which are correlated with behavioral performance. A network model which can reproduce these changes suggests that a key function of such learning-evoked alterations in theta and theta-nested gamma activity may be increased temporal desynchronization in neuronal firing leading to optimal timing of inputs to downstream neural networks potentiating their responses. In this way learning can produce potentiation in neural networks simply through altering the temporal pattern of their inputs.

Background

The functions of both low and high frequency oscillations in the brain are the subject of considerable speculation [1]. Low frequency theta oscillations (4-8 Hz) have been observed to increase in terms of power during working memory tasks [2,3] and in power and phase-locked discharge of single neurons in a visual memory task [4]. In hippocampus the phase of theta functions as the clock signal for timing of pyramidal neurons and long-term potentiation (theta peaks) and depotentiation (theta troughs) [5]. These findings may reflect the patterns of synaptic plasticity and maintenance of the memory for a stimulus. Fast frequency gamma oscillations (30-70 Hz) can provide tighter control and coordination than lower frequency ones [6] and are hypothesized to be responsible for higher cognitive functions such as perceptual binding of visual features [7]. Human electroencephalographic (EEG) recordings