REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
02-12-2019	Final Report	1-Aug-2014 - 31-Jul-2018

4. TITLE AND SUBTITLE

Final Report: Prefrontal brain rhythms and rule-based action (Topic 3.3.3)

5a. CONTRACT NUMBER
W911NF-14-1-0374

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
611102

6. AUTHORS

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES

Boston University
Office of Sponsored Program
881 Commonwealth Avenue
Boston, MA 02215 -1300

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)

U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
65364-MA.37

12. DISTRIBUTION AVAILIBILITY STATEMENT

Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Nancy Kopell
UU	UU	UU	UU		19b. TELEPHONE NUMBER 617-353-5210

RPPR Final Report
as of 06-Jan-2020

Agency Code:

Proposal Number: 65364MA **Agreement Number: W911NF-14-1-0374**
INVESTIGATOR(S):

Name: Nancy Kopell
Email: nk@bu.edu
Phone Number: 6173535210
Principal: Y

Organization: **Boston University**
Address: Office of Sponsored Program, Boston, MA 022151300
Country: USA
DUNS Number: 049435266 EIN: 042103547

Report Date: 31-Oct-2018 Date Received: 02-Dec-2019
Final Report for Period Beginning 01-Aug-2014 and Ending 31-Jul-2018
Title: Prefrontal brain rhythms and rule-based action (Topic 3.3.3)
Begin Performance Period: 01-Aug-2014 **End Performance Period:** 31-Jul-2018
Report Term: 0-Other

Submitted By: Xiaoshi Shi Email: xiaoshi@bu.edu
Phone: (617) 353-4587

Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: 1 **STEM Participants:** 1

Major Goals: Streams of flexible behavior and thought in daily life involve shifts in action-guiding sets of associations previously learned between conditions, responses, and outcomes. For instance, actions performed driving toward a traffic light are guided by a set of associations, called rules, mapping light colors (sensory conditions) to pedal controls (motor responses); after passing the light, other rules guide subsequent actions. This raises the central question: how do the dynamics of the brain affect how rules are carried out? Furthermore, neural oscillations are associated with all facets of cognition and are exhibited by rule-encoding cell assemblies in behaving monkeys; nevertheless, the ways in which such brain dynamics support cognition is only beginning to be addressed. Our goal is to improve our understanding of how rhythmic mechanisms in networks contribute to such cognitively important neural dynamics.

We have implemented computational models of rule-related brain networks in prefrontal cortex (PFC), anterior cingulate cortex (ACC), and striatum in the basal ganglia (BG), constrained by in vivo and in vitro data, investigating the properties of these models by simulation, and applying our findings to better understand how the brain controls the execution of rule-based (i.e., context-dependent) actions. All modeling involves differential equations describing biophysical changes in cellular membrane potentials. Cell models have been constrained by single cell electrophysiology; emergent rhythms in our network models have been constrained by physiological data recorded in isolated rat cortex, intact rat basal ganglia under optogenetic manipulation, and intact monkey cortex recorded during rule-based cognitive tasks. Our simulations investigate the biophysical mechanisms that generate network rhythms; how such rhythms affect cortical dynamics: persistent activity (working memory), combinatorial processing (multi-tasking and multi-modal integration), and selective routing (context-dependent attention and behavior); and how corticostriatal interactions control cognitive and motor action selection processes (i.e., decision making). More particularly, we have constructed two versions of the PFC model that differ in their level of detail. One consists adaptive exponential integrate-and-fire neurons with diversity constrained by experimental data, and the other, more detailed model, consists of conductance-based neurons adapted from the literature. The striatal model of the BG has been extended from previous work in the lab to consider: 1) the two cell types of Spiny Projecting Neurons (D1 and D2 SPNs), 2) the heterogeneous connectivity between them, and 3) physiological properties that differ between D1 and D2 SPNs (maximum conductance and short-term depression of GABAergic connections, and dynamics of Ca-dependent intrinsic currents).

Accomplishments: Heterogeneity, oscillations and routing in ACC and PFC. The ACC is known to be a hub in large-scale brain systems that monitor ongoing activity across the brain and adjust internal rules when present behavior produces unexpected outcomes. Our work has shown that its internal diversity enables its ability to simultaneously process activity from areas producing rhythms at different frequencies, supports parallel processing

(multi-tasking) and downstream (multi-modal) integration. In contrast, less diverse networks like those in PFC exhibit more winner-take-all type dynamics and preferentially respond to inputs at a particular resonant frequency (Adams et al., 2017).
We have found out that firing rate resonance of deep layer pyramidal cells occurred in response to an input oscillating slightly faster than the natural frequency of the PFC network. Surprisingly, the output oscillation frequency has a peak determined by the input frequency maximizing local inhibition. The peak frequency also exceeds the natural network frequency induced by equal-strength noise, and the difference in peak and natural frequencies enables oscillatory inputs to activate target populations in a way that filtered out competing noise-driven responses. We previously demonstrated for the first time that the strength of network resonance (i.e., the maximum output firing rate) increases as population spiking in the input rhythm becomes more synchronous. This implies that any mechanism that dynamically adjusts spike synchrony across projection neurons in an oscillating sender network can simultaneously tune the functional significance of its resonant effect on all downstream networks. These results suggest strategies for optimizing transcranial stimulation and using oscillatory networks in neuromorphic engineering (Sherfey et al., PLoS Comput Biol 2018).

Furthermore, we have explored input frequency- and coherence-based selection mechanisms for flexible routing that conserves rate-coded signals. We have identified a novel resonance-based mechanism for selective frequency-specific biasing among parallel competing pathways. Using this mechanism, a highly- synchronous input rhythm is able to produce greater pathway activation than asynchronous activity with 70% higher firing rates. While signals are encoded in population firing rates, output selection and signal routing can be governed independently by the frequency and coherence of oscillatory inputs and their correspondence with output resonant properties. This resonance-mediated bias could enable PFC beta and gamma oscillations to increase the signal-to-noise ratio of working memory processes, gate working memory read-out, and support context-dependent routing for rule-based action (Sherfey et al., in preparation).

Heterogeneity, oscillations and persistent activity in PFC. We have investigated how cortical oscillations and persistent firing activity in stimulus-driven neurons could be implemented in a highly biologically realistic neural network model of the prefrontal cortex. We have found that the biological details of the model, most importantly the heterogeneity in cell parameters of interneurons, constrain the implementation of these phenomena. While we have found ways to reconcile rhythmic activity with the irregular firing that is considered the baseline state of cortical networks, we have made the surprising finding that the stability of persistent activity is disrupted in this regime. The limiting factor for persistent activity is found in the heterogeneity in the neuron parameters of the inhibitory interneurons and the parameters of short-term synaptic plasticity. Persistent activity is recovered when interneurons are aligned in neural ensembles according to their excitability, which regulates their background input (Hass et al., under revision at PLoS Comput Biol). Physiologically, this could be mediated in PFC via a homeostatic plasticity mechanism.

Our model also predicts that a network exhibiting persistent activity cannot produce intrinsic, in vivo-like, asynchronous-irregular activity (“noise”). The mechanistic explanation for this phenomenon is that the dynamic generation of noise requires substantial heterogeneity in the inhibitory synaptic inputs, which, similarly to the heterogeneity in the excitability of inhibitory interneurons, prevents persistent activity. Therefore, the background noise in a network exhibiting persistent activity must either be produced by external input, or it constitutes an entirely different state of the network, which is brought about by, e.g., neuromodulation (Hass et al., under revision at PLoS Comput Biol).

Mechanisms of Biased Competition (BC) under balanced input: predictions from corticostriatal processing. The BC classical mechanism relies on distinct inputs applied to competing neuronal ensembles, otherwise considered identical. How to achieve BC under balanced (i.e., identical) input is unclear. This is especially relevant in the striatum, where GO vs. NO-GO action selection may depend on BC between striatal populations receiving balanced cortical stimulation. Consequently, we built a model based on electrophysiological properties of striatal cells. Instead of focusing on a single mechanism, we have identified the following three distinct BC mechanisms under balanced input (Ardid et al., bioRxiv 258053, under revision at PNAS):

From these three mechanisms, however, only the mechanism based on the close match between the resonant frequency of either D1 or D2 SPNs, and the spectral content of the input, is consistent with current interpretation of PFC rhythmic activity supporting rule-based decisions. In this regime, the striatal circuit is dynamically flexible showing different states, according to cortical stimulation (Ardid et al., bioRxiv 258053, under revision at PNAS): 1) in absence of cortical stimulation, all SPNs show sparse activity, which is weakly oscillatory; 2) when cortical input oscillates at alpha frequencies (reported to emerge in neural ensembles of the PFC encoding dominant information,

when such information is irrelevant), there is increased synchrony in D2 SPNs activity at low beta frequency, in support of inhibitory control; and 3) when cortical input oscillates at high beta frequencies (reported to be stronger for neural ensembles of the PFC encoding the relevant information), there is increased beta synchrony in D1 SPNs activity due to the match with their resonance, which guides action selection.

In the last year, we have focused on non-dominant action selection mediated by inhibitory control mechanisms. Results from our striatal model show that short-term depression between SPNs together with long-term anti-Hebbian plasticity (involved in striatal cell assembly formation) is able to mediate non-dominant action selection under certain circumstances (Ardid and Kopell, in preparation):

First, anti-Hebbian plasticity in inhibitory synapses between SPNs underlies cross-inhibition (which refers to an asymmetrically stronger inhibitory current for SPNs between cell assemblies in comparison to SPNs within a given cell assembly).

Second, experimentally observed alpha rhythmic inputs from PFC before stimulus onset of non-dominant trials specific for dominant cell assemblies activates downstream striatal short-term depression.

Thus, at stimulus onset, synaptic depression from dominant SPNs together with cross-inhibition creates a transient alpha-triggered bias within the striatum in favor of activating non-dominant actions.

However, this mechanism requires that the bias by short-term depression lasts the order of hundreds of milliseconds to be successful (timescale of decision making).

The requirement can be accomplished in two distinct ways: (i) by long-lasting short-term depression in SPNs, or (ii) by slowly raising ramping activity in SPNs in response to cortical stimulation.

Conclusions - more detail in uploaded file.

Training Opportunities: Training Opportunities

Personnel
Sherfey first focused on understanding the implications of heterogeneity in ACC as well as developing DynaSim. Later on, he investigated rhythm-mediated routing in dlPFC.
Ardid studied biased competition under balanced input in a model of corticostriatal processing for action selection and rule-based decisions. During the extension of this grant, he tested the hypothesis that asymmetric rule-based routing (i.e., relative to dominant vs. non-dominant rules) is supported by striatal cell assembly formation and short-term depression.
Hass worked on persistent activity in the presence of cellular and synaptic heterogeneities and the coexistence of oscillatory and asynchronous activity in a biologically detailed PFC model. He was appointed as a professor for statistical methods in psychology at the SRH Hochschule Heidelberg.
Kopell organized and supervised the project.

Collaborations and leveraged funding
Collaborations. The lab of Fiona LeBeau provided data on heterogeneity in the ACC, which was the basis of a joint paper with our group: “Heterogeneity in neuronal intrinsic properties: A possible mechanism for hub-like properties of the rat anterior cingulate cortex during network dynamic activity”.
Helen Barbas and her group provided details of anatomical connections within the PFC and between the PFC and other regions.
Earl Miller, an expert in rule-based decisions and category learning, provided general guidance for our project.
The work we described makes use of other models created within the Kopell group, notably striatal models by Michelle McCarthy and collaborators.
All of this work has been done in the context of the Cognitive Rhythms Collaborative (CRC), a group headed by Kopell and consisting of more than two dozen labs working on topics associated with brain dynamics. This project obtained feedback from other members of the CRC.
Leveraged funding. Over the period of the grant, the William Fairfield Warren Chair of Kopell supported three months salary for Salva Ardid and three months salary for Joachim Hass. In addition, Ardid was supported for two months on a grant from the NSF to Kopell for the Cognitive Rhythms Collaborative. We also obtained travel money for two trips to the Society for Neuroscience meeting from Boston University.

RPPR Final Report
as of 06-Jan-2020

Results Dissemination:
Results Dissemination

Seminars
Jason Sherfey. DynaSim: Neural Modeling in Matlab. 2018 INCF Neuroinformatics Meeting, Montreal, QC, 2018.
Jason Sherfey. Neuroscience Modeling and Data Processing with Community-Authored MATLAB-Based Tools – The DynaSim Toolbox for Neural Modeling. Neuroscience Gateway Workshop at the 2018 Computational Neuroscience Meeting, Seattle, WA, 2018.
Salva Ardid. Brain Mechanisms Supporting Biased Competition under balanced input. University of Texas – Southwestern Medical Center, Dallas TX, 2018.
Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decision Making. Vanderbilt University, Nashville TN, 2017.
Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decision Making. Mount Sinai School of Medicine. New York City NY, 2017.
Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decisions and Inhibitory Control: A Neural Circuit Modeling Approach. Stony Brook University. Stony Brook NY, 2017.
Salva Ardid. Alpha Oscillatory Inputs and Short-Term Depression Underlie Action Inhibitory Control in a Model of the Striatum. 5th Barcelona Computational, Cognitive, and Systems Neuroscience. Barcelona, 2016.
Salva Ardid. Alpha Oscillatory Inputs and Short-Term Depression Underlie Action Inhibitory Control in a Model of the Striatum. Cognitive Rhythms Collaborative: Rhythmic Dynamics and Cognition. Boston MA, 2016.
Jason Sherfey. Competition versus cooperation in the anterior cingulate cortex. 2016 Cognitive Rhythms Collaborative Retreat, Boston, MA, 2016.
Jason Sherfey. Cortical rhythms and interneurons for reading working memory: a computational study of laminar DLPFC. Cognitive Rhythms Collaborative Retreat, Boston, MA, 2014.
Jason Sherfey. Prefrontal brain rhythms for rule-based selection. Gordon Research Seminar., Newry, ME, 2014.
Nancy Kopell. Rhythms, Routing, Resonance and Rule-based Decisions, Neuroscience Colloquium UC San Diego 2017
Nancy Kopell , Rhythms, Routing and Resonance, Oscillations Workshop Princeton University 2016

Posters
Sherfey J, Ardid S, Hass J, Kopell N., Miller, E. K., Hasselmo M. E. Modeling of oscillatory gating for cognitive function. SfN, 2018.
Sherfey J, Ardid S, Hass J, Kopell N., Hasselmo M. E. Prefrontal oscillations bias pathways for thought and action. Computational Neuroscience Meeting, 2018.
Sherfey JS, Soplata AE, Ardid S, Roberts EA, Stanley DA, and Kopell N. DynaSim: A Matlab Toolbox for Neural Modeling and Simulation. INCF Neuroinformatics Meeting, 2018.
Ardid S, Sherfey J, McCarthy MM, Hass J, Pittman?Polletta B, Kopell N. Biased competition in the absence of input bias: predictions from corticostriatal computation, COSYNE Meeting, 2018.
Hass J, Ardid S, Sherfey J, Kopell N: Constraints on Persistent Activity in a Biophysically Detailed Network Model of the Prefrontal Cortex with Heterogeneous Neurons. Bernstein Conference, 2016.
Ardid S, Sherfey J, McCarthty MM, Kopell N. Alpha oscillatory inputs and short-term depression underlie action inhibitory control in a model of the striatum. SfN, 2016.
Sherfey, J., Ardid, S., McCarthy, M., Hass, J., Kopell, N. Oscillations guide rule-based action in a laminar model of prefrontal cortex. SfN, 2016.
Sherfey JS. DynaSim: a Matlab toolbox for rapidly building and exploring neural models. 2016 Janelia conference on Collaborative Development of Data-Driven Models of Neural Systems,, 2016.
Ardid S, Sherfey J, McCarthty MM, Kopell N. Context-dependent action selection mediated by specific temporal coordination between prefrontal cortex and striatum. SfN, 2015.
Sherfey J, Adams N, Kopell N, Whittington M, LeBeau F. Modeling neuronal diversity and fast network oscillations in rat anterior cingulate cortex (ACC). SfN, 2015.
Sherfey J, Kopell N. Dynamic Neural Simulator – a tool for rapidly building neural models. SfN, 2014.

Publications

Sherfey J, Ardid S, Kopell N, Miller EK, Hasselmo ME. Oscillatory gating for cognitive function in circuit models of prefrontal cortex. In preparation.
Ardid S, Kopell N. Short-term depression and long-term anti-Hebbian plasticity mediate non-dominant action selection in a model of the striatum. In preparation.

Hass J, Ardid S, Sherfey J, Kopell N. Constraints on persistent activity in a biophysically detailed network model of the prefrontal cortex with heterogeneous neurons. Under review.
Ardid S, Sherfey J, McCarthy MM, Hass J, Pittman-Polletta BR, Kopell N (2018). Biased competition in the absence of input bias: predictions from corticostriatal computation. biorxiv 258053, doi:10.1101/258053.
Sherfey J, Ardid S, Hass J, Hasselmo M, and Kopell N (2018). Flexible resonance in prefrontal networks with strong feedback inhibition. PLoS Computational Biology, 14(8), e1006357.
Sherfey J, Soplata AE, Ardid S, Roberts EA, Stanley DA, Pittman-Polletta BR and Kopell N (2018). DynaSim: A MATLAB Toolbox for Neural Modeling and Simulation. Front. Neuroinform., 12(10), doi: 10.3389/fninf.2018.00010.
Adams* N, Sherfey* J, Kopell N, Whittington M, LeBeau F (*contributed equally to the work). Heterogeneity in neuronal intrinsic properties: A possible mechanism for hub-like properties of the rat anterior cingulate cortex during network dynamic activity. eNeuro, 4(1), ENEURO-0313, 2017.
Hass J, Durstewitz D: Time at the center, or time at the side? Assessing current models of time perception. Curr Opin Behav Sci.. 8:238-2

Honors and Awards: Honors and Awards

Mathematical Neuroscience Prize 2015 from Israel Brain Technologies to Nancy Kopell.
Kopell published an invited chapter in Vol 9 of History of Neuroscience in Autobiography, Society for Neuroscience.
Kopell was awarded the 2016 Swartz Prize in Theoretical and Computational Neuroscience from Society for Neuroscience.

Protocol Activity Status:

Technology Transfer: Technology Transfer

We have developed and actively maintain DynaSim (https://github.com/DynaSim), an open source freely available Matlab/GNU Octave modeling and simulation Toolbox, to facilitate model building, sharing, and simulation studies (Sherfey et al., Front Neuroinf. 2018). DynaSim shares simplified model building with other modeling tools, such as Brian, NEURON, and XPP. It additionally provides (I) a simple interface for specifying sets of simulations varying model parameters, (II) simulations running in parallel and/or on different cluster nodes, and (III) model sharing. Furthermore, DynaSim is designed to enable future extensions incorporating optimization algorithms (e.g., particle filtering, genetic algorithms) for automatically fitting model parameters constrained by experimental data.
DynaSim has been added to the MathWorks File Exchange. Documentation has been made available online and mailing lists have been created for DynaSim users and developers. Features supporting open-source collaborative development have also been developed. DynaSim facilitates building small to large differential equation models to researchers on their own or in collaboration.
DynaSim was presented in a poster at SfN 2014; a copy of the poster is available online. We demonstrated DynaSim for users at the International Neuroinformatics Coordinating Facility (INCF) booth at SfN 2015, and for developers at the Janelia Research Campus Workshop on Collaborative Development of Data-Driven Models of Neural Systems (2016); We also presented it to MathWorks representatives who have since promoted it at Cosyne (2017) and will be featured on the MathWorks website. We have established a core team of developers to facilitate future development, as well as to be engaged in a community of users.

PARTICIPANTS:

Participant Type: Postdoctoral (scholar, fellow or other postdoctoral position)
Participant: Joan Salvador Ardid Ramirez PhD
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

ARTICLES:

RPPR Final Report
as of 06-Jan-2020

Publication Type: Journal Article Peer Reviewed: **Publication Status:** 0-Other
Journal: NONE
Publication Identifier Type: Publication Identifier:
Volume: Issue: First Page #:
Date Submitted: Date Published:
Publication Location:
Article Title: Oscillatory gating for cognitive function in circuit models of prefrontal cortex.
Authors: Sherfey J, Ardid S, Kopell N, Miller EK, Hasselmo ME.
Keywords: Oscillatory gating for cognitive function in circuit models of prefrontal cortex.
Abstract: Sherfey J, Ardid S, Kopell N, Miller EK, Hasselmo ME. Oscillatory gating for cognitive function in circuit models of prefrontal cortex. In preparation.
Distribution Statement: 1-Approved for public release; distribution is unlimited.
Acknowledged Federal Support: **Y**

CONFERENCE PAPERS:

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Bernstein conference abstract 2016.
Date Received: 17-Oct-2017 Conference Date: 22-Sep-2016 Date Published: 22-Sep-2016
Conference Location: Berlin, Germany
Paper Title: Constraints on Persistent Activity in a Biophysically Detailed Network Model of the Prefrontal Cortex with Heterogeneous Neurons.
Authors: Hass J, Ardid S, Sherfey J, Kopell N:
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Society for Neuroscience Neuroscience 2014
Date Received: 17-Oct-2017 Conference Date: 16-Nov-2014 Date Published: 16-Nov-2014
Conference Location: Washington DC
Paper Title: DynaSim: a MATLAB Toolbox for Neural Modeling and Simulation Dynamic Neural Simulator – a tool for rapidly building neural models.
Authors: Sherfey J, Kopell N.
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Society for Neuroscience Neuroscience 2015
Date Received: 31-Aug-2016 Conference Date: 17-Oct-2015 Date Published: 17-Oct-2015
Conference Location: Chicago
Paper Title: Context-dependent action selection mediated by specific temporal coordination between prefrontal cortex and stria
Authors: Ardid S, Sherfey J, McCarthty MM, Kopell N
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Society for Neuroscience 2015
Date Received: 17-Oct-2017 Conference Date: 17-Oct-2015 Date Published: 17-Oct-2015
Conference Location: Chicago
Paper Title: Context-dependent action selection mediated by specific temporal coordination between prefrontal cortex and striatum.
Authors: Ardid S, Sherfey J, McCarthty MM, Kopell N.
Acknowledged Federal Support: **Y**

RPPR Final Report
as of 06-Jan-2020

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: SfN abstract 2015.
Date Received: 17-Oct-2017 Conference Date: 21-Oct-2015 Date Published: 21-Oct-2015
Conference Location: Chicago, Illinois USA
Paper Title: Neuronal diversity and fast network oscillations in ACC.
Authors: Sherfey J, Adams N, Kopell N, Whittington M, LeBeau F.
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: SfN abstract 2016.
Date Received: 17-Oct-2017 Conference Date: 16-Nov-2016 Date Published: 16-Nov-2016
Conference Location: san diego, CA
Paper Title: Alpha oscillatory inputs and short-term depression underlie action inhibitory control in a model of the striatum.
Authors: Ardid S, Sherfey J, McCarthty MM, Kopell N.
Acknowledged Federal Support: **Y**

DISSERTATIONS:

Publication Type: Thesis or Dissertation
Institution: Boston University
Date Received: 17-Oct-2017 Completion Date: 5/19/17 10:22PM
Title: "PREFRONTAL RHYTHMS FOR COGNITIVE CONTROL"
Authors: Jason Sherfey
Acknowledged Federal Support: **Y**

WEBSITES:

URL: http://cogrhythms.bu.edu/
Date Received: 30-Aug-2016
Title: Cognitive Rhythms Collaborative (CRC)
Description: The Cognitive Rhythms Collaborative (CRC) is a group of scientists in the Boston area who work together to advance our understanding of the brain dynamics underlying cognitive functions such as sensory processing, attention, learning, memory and motor planning. The members of the CRC come from multiple institutions around the Boston area and beyond (see Faculty). We encourage those who are interested in working with us or participating in our events to contact Nancy Kopell (nk at bu.edu). The CRC is supported by the National Science Foundation and the McGovern Center.
URL: https://github.com/DynaSim/DynaSim
Date Received: 30-Aug-2016
Title: DynaSim Toolbox
Description: Open-source repository for the DynaSim modeling and simulation toolbox
URL: http://infinitebrain.org/
Date Received: 30-Aug-2016
Title: InfiniteBrain.org Model Database
Description: A DynaSim-linked model repository to assist collaborative model development

RPPR Final Report
as of 06-Jan-2020

Contract Number: W911NF1410374

Title: Prefrontal brain rhythms and rule-based action (Topic 3.3.3)

Major Goals:

Streams of flexible behavior and thought in daily life involve shifts in action-guiding sets of associations previously learned between conditions, responses, and outcomes. For instance, actions performed driving toward a traffic light are guided by a set of associations, called rules, mapping light colors (sensory conditions) to pedal controls (motor responses); after passing the light, other rules guide subsequent actions. This raises the central question: how do the dynamics of the brain affect how rules are carried out? Furthermore, neural oscillations are associated with all facets of cognition and are exhibited by rule-encoding cell assemblies in behaving monkeys; nevertheless, the ways in which such brain dynamics support cognition is only beginning to be addressed. Our goal is to improve our understanding of how rhythmic mechanisms in networks contribute to such cognitively important neural dynamics.

We have implemented computational models of rule-related brain networks in prefrontal cortex (PFC), anterior cingulate cortex (ACC), and striatum in the basal ganglia (BG), constrained by in vivo and in vitro data, investigating the properties of these models by simulation, and applying our findings to better understand how the brain controls the execution of rule-based (i.e., context-dependent) actions. All modeling involves differential equations describing biophysical changes in cellular membrane potentials. Cell models have been constrained by single cell electrophysiology; emergent rhythms in our network models have been constrained by physiological data recorded in isolated rat cortex, intact rat basal ganglia under optogenetic manipulation, and intact monkey cortex recorded during rule-based cognitive tasks. Our simulations investigate the biophysical mechanisms that generate network rhythms; how such rhythms affect cortical dynamics: persistent activity (working memory), combinatorial processing (multi-tasking and multi-modal integration), and selective routing (context-dependent attention and behavior); and how corticostriatal interactions control cognitive and motor action selection processes (i.e., decision making). More particularly, we have constructed two versions of the PFC model that differ in their level of detail. One consists adaptive exponential integrate-and-fire neurons with diversity constrained by experimental data, and the other, more detailed model, consists of conductance-based neurons adapted from the literature. The striatal model of the BG has been extended from previous work in the lab to consider: 1) the two cell types of Spiny Projecting Neurons (D1 and D2 SPNs), 2) the heterogeneous connectivity between them, and 3) physiological properties that differ between D1 and D2 SPNs (maximum conductance and short-term depression of GABAergic connections, and dynamics of Ca-dependent intrinsic currents).

Accomplishments Under Goals:

Heterogeneity, oscillations and routing in ACC and PFC. The ACC is known to be a hub in large-scale brain systems that monitor ongoing activity across the brain and adjust internal rules when present behavior produces unexpected outcomes. Our work has shown that its internal diversity enables its ability to simultaneously process activity from areas producing rhythms at different frequencies, supports parallel processing (multi-tasking) and downstream (multi-modal) integration. In contrast, less diverse networks like those in PFC exhibit more winner-take-all type dynamics and preferentially respond to inputs at a particular resonant frequency (Adams et al., 2017).

We have found out that firing rate resonance of deep layer pyramidal cells occurred in response to an input oscillating slightly faster than the natural frequency of the PFC network. Surprisingly, the output oscillation frequency has a peak determined by the input frequency maximizing local inhibition. The peak frequency also exceeds the natural network frequency induced by equal-strength noise, and the difference in peak and natural frequencies enables oscillatory inputs to activate target populations in a way that filtered out competing noise-driven responses. We previously demonstrated for the first time that the strength of network resonance (i.e., the maximum output firing rate) increases as population spiking in the input rhythm becomes more synchronous. This implies that any mechanism that dynamically adjusts spike synchrony across projection neurons in an oscillating sender network can simultaneously tune the functional significance of its resonant effect on all downstream networks. These results suggest strategies for optimizing transcranial stimulation and using oscillatory networks in neuromorphic engineering (Sherfey et al., PLoS Comput Biol 2018).

Furthermore, we have explored input frequency- and coherence-based selection mechanisms for flexible routing that conserves rate-coded signals. We have identified a novel resonance-based mechanism for selective frequency-specific biasing among parallel competing pathways. Using this mechanism, a highly- synchronous input rhythm is able to produce greater pathway activation than asynchronous activity with 70% higher firing rates. While signals are encoded in population firing rates, output selection and signal routing can be governed independently by the frequency and coherence of oscillatory inputs and their correspondence with output resonant properties. This resonance-mediated bias could enable PFC beta and gamma oscillations to increase the signal-to-noise ratio of working memory processes, gate working memory read-out, and support context-dependent routing for rule-based action (Sherfey et al., in preparation).

Heterogeneity, oscillations and persistent activity in PFC. We have investigated how cortical oscillations and persistent firing activity in stimulus-driven neurons could be implemented in a highly biologically realistic neural network model of the prefrontal cortex. We have found that the biological details of the model, most importantly the heterogeneity in cell parameters of interneurons, constrain the implementation of these phenomena. While we have found ways to reconcile rhythmic activity with the irregular firing that is considered the baseline state of cortical networks, we have made the surprising finding that the stability of persistent activity is disrupted in this regime. The limiting factor for persistent activity is found in the heterogeneity in the neuron parameters of the inhibitory interneurons and the parameters of short-term synaptic plasticity. Persistent activity is recovered when interneurons are aligned in neural ensembles according to their excitability, which regulates their background input (Hass et al., under revision at PLoS Comput Biol). Physiologically, this could be mediated in PFC via a homeostatic plasticity mechanism.

Our model also predicts that a network exhibiting persistent activity cannot produce intrinsic, in vivo-like, asynchronous-irregular activity (“noise”). The mechanistic explanation for this phenomenon is that the dynamic generation of noise requires substantial heterogeneity in the inhibitory synaptic inputs, which, similarly to the heterogeneity in the excitability of inhibitory interneurons, prevents persistent activity. Therefore, the background noise in a network exhibiting persistent activity must either be produced by external input, or it constitutes an entirely different state of the network, which is brought about by, e.g., neuromodulation (Hass et al., under revision at PLoS Comput Biol).

Mechanisms of *Biased Competition* (BC) under balanced input: predictions from corticostriatal processing. The BC classical mechanism relies on distinct inputs applied to competing neuronal ensembles, otherwise considered identical. How to achieve BC under balanced (i.e., identical) input is unclear. This is especially relevant in the striatum, where GO vs. NO-GO action selection may depend on BC between striatal populations receiving balanced cortical stimulation. Consequently, we built a model based on

electrophysiological properties of striatal cells. Instead of focusing on a single mechanism, we have identified the following three distinct BC mechanisms under balanced input (Ardid et al., bioRxiv 258053, under revision at PNAS):

From these three mechanisms, however, only the mechanism based on the close match between the resonant frequency of either D1 or D2 SPNs, and the spectral content of the input, is consistent with current interpretation of PFC rhythmic activity supporting rule-based decisions. In this regime, the striatal circuit is dynamically flexible showing different states, according to cortical stimulation (Ardid et al., bioRxiv 258053, under revision at PNAS): 1) in absence of cortical stimulation, all SPNs show sparse activity, which is weakly oscillatory; 2) when cortical input oscillates at alpha frequencies (reported to emerge in neural ensembles of the PFC encoding dominant information, when such information is irrelevant), there is increased synchrony in D2 SPNs activity at low beta frequency, in support of inhibitory control; and 3) when cortical input oscillates at high beta frequencies (reported to be stronger for neural ensembles of the PFC encoding the relevant information), there is increased beta synchrony in D1 SPNs activity due to the match with their resonance, which guides action selection.

In the last year, we have focused on non-dominant action selection mediated by inhibitory control mechanisms. Results from our striatal model show that short-term depression between SPNs together with long-term anti-Hebbian plasticity (involved in striatal cell assembly formation) is able to mediate non-dominant action selection under certain circumstances (Ardid and Kopell, in preparation):

- First, anti-Hebbian plasticity in inhibitory synapses between SPNs underlies cross-inhibition (which refers to an asymmetrically stronger inhibitory current for SPNs between cell assemblies in comparison to SPNs within a given cell assembly).

- Second, experimentally observed alpha rhythmic inputs from PFC before stimulus onset of non-dominant trials specific for dominant cell assemblies activates downstream striatal short-term depression.

- Thus, at stimulus onset, synaptic depression from dominant SPNs together with cross-inhibition creates a transient alpha-triggered bias within the striatum in favor of activating non-dominant actions.

- However, this mechanism requires that the bias by short-term depression lasts the order of hundreds of milliseconds to be successful (timescale of decision making).

- The requirement can be accomplished in two distinct ways: (i) by long-lasting short-term depression in SPNs, or (ii) by slowly raising ramping activity in SPNs in response to cortical stimulation.

Conclusions

We have met the milestones that were set in our grant application. More specifically, we have constructed basic models of PFC and striatum, and have investigated the implications of network dynamics in these models for rule-based decision making. The major conclusions from our current work are:

- Physiological heterogeneity in ACC supports its role as a higher-order hub in combining multi-modal inputs at different frequencies, an important operation for monitoring activity throughout the brain.
- Network resonance enables beta and gamma rhythms in PFC to govern the selection and gating of rate- coded signals for downstream read-out in service of working memory and rule-based decision making.

- Heterogeneity in PFC interneurons is a barrier to persistent activity, which can be overcome by plasticity- dependent formation of homogeneous cell assemblies.
- There are three distinct mechanisms by which balanced input can differentially bias D1 and D2 SPNs, hence biasing GO vs. NO-GO action selection.
- Only the match between the spectral content of the input and one, or another, SPN resonance, is consistent with the proposed functional role of PFC rhythms in rule-based decisions.
- Long-lasting and/or slowly raising short-term depression between SPNs supports non-dominant action selection if acting upon striatal cell assemblies mediated by anti-Hebbian plasticity.

Training Opportunities:

Personnel

Sherfey first focused on understanding the implications of heterogeneity in ACC as well as developing DynaSim. Later on, he investigated rhythm-mediated routing in dlPFC.

Ardid studied biased competition under balanced input in a model of corticostriatal processing for action selection and rule-based decisions. During the extension of this grant, he tested the hypothesis that asymmetric rule-based routing (i.e., relative to dominant vs. non-dominant rules) is supported by striatal cell assembly formation and short-term depression.

Hass worked on persistent activity in the presence of cellular and synaptic heterogeneities and the coexistence of oscillatory and asynchronous activity in a biologically detailed PFC model. He was appointed as a professor for statistical methods in psychology at the SRH Hochschule Heidelberg.

Kopell organized and supervised the project.

Collaborations and leveraged funding

Collaborations. The lab of Fiona LeBeau provided data on heterogeneity in the ACC, which was the basis of a joint paper with our group: “Heterogeneity in neuronal intrinsic properties: A possible mechanism for hub-like properties of the rat anterior cingulate cortex during network dynamic activity”.
Helen Barbas and her group provided details of anatomical connections within the PFC and between the PFC and other regions.

Earl Miller, an expert in rule-based decisions and category learning, provided general guidance for our project.

The work we described makes use of other models created within the Kopell group, notably striatal models by Michelle McCarthy and collaborators.

All of this work has been done in the context of the Cognitive Rhythms Collaborative (CRC), a group headed by Kopell and consisting of more than two dozen labs working on topics associated with brain dynamics. This project obtained feedback from other members of the CRC.

Leveraged funding. Over the period of the grant, the William Fairfield Warren Chair of Kopell supported three months salary for Salva Ardid and three months salary for Joachim Hass. In addition, Ardid was supported for two months on a grant from the NSF to Kopell for the Cognitive Rhythms Collaborative. We also obtained travel money for two trips to the Society for Neuroscience meeting from Boston University.

Results Dissemination

Seminars

Jason Sherfey. DynaSim: Neural Modeling in Matlab. 2018 INCF Neuroinformatics Meeting, Montreal, QC, 2018.

Jason Sherfey. Neuroscience Modeling and Data Processing with Community-Authored MATLAB-Based Tools – The DynaSim Toolbox for Neural Modeling. Neuroscience Gateway Workshop at the 2018 Computational Neuroscience Meeting, Seattle, WA, 2018.

Salva Ardid. Brain Mechanisms Supporting Biased Competition under balanced input. University of Texas – Southwestern Medical Center, Dallas TX, 2018.

Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decision Making. Vanderbilt University, Nashville TN, 2017.

Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decision Making. Mount Sinai School of Medicine. New York City NY, 2017.

Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decisions and Inhibitory Control: A Neural Circuit Modeling Approach. Stony Brook University. Stony Brook NY, 2017.

Salva Ardid. Alpha Oscillatory Inputs and Short-Term Depression Underlie Action Inhibitory Control in a Model of the Striatum. 5th Barcelona Computational, Cognitive, and Systems Neuroscience. Barcelona, 2016.

Salva Ardid. Alpha Oscillatory Inputs and Short-Term Depression Underlie Action Inhibitory Control in a Model of the Striatum. Cognitive Rhythms Collaborative: Rhythmic Dynamics and Cognition. Boston MA, 2016.

Jason Sherfey. Competition versus cooperation in the anterior cingulate cortex. 2016 Cognitive Rhythms Collaborative Retreat, Boston, MA, 2016.

Jason Sherfey. Cortical rhythms and interneurons for reading working memory: a computational study of laminar DLPFC. Cognitive Rhythms Collaborative Retreat, Boston, MA, 2014.

Jason Sherfey. Prefrontal brain rhythms for rule-based selection. Gordon Research Seminar., Newry, ME, 2014.

Nancy Kopell. Rhythms, Routing, Resonance and Rule-based Decisions, Neuroscience Colloquium UC San Diego 2017

Nancy Kopell , Rhythms, Routing and Resonance, Oscillations Workshop Princeton University 2016

Posters

Sherfey J, Ardid S, Hass J, Kopell N., Miller, E. K., Hasselmo M. E. Modeling of oscillatory gating for cognitive function. SfN, 2018.

Sherfey J, Ardid S, Hass J, Kopell N., Hasselmo M. E. Prefrontal oscillations bias pathways for thought and action. Computational Neuroscience Meeting, 2018.

Sherfey JS, Soplata AE, Ardid S, Roberts EA, Stanley DA, and Kopell N. DynaSim: A Matlab Toolbox for Neural Modeling and Simulation. INCF Neuroinformatics Meeting, 2018.

Ardid S, Sherfey J, McCarthy MM, Hass J, Pittman-Polletta B, Kopell N. Biased competition in the absence of input bias: predictions from corticostriatal computation, COSYNE Meeting, 2018.

Hass J, Ardid S, Sherfey J, Kopell N: Constraints on Persistent Activity in a Biophysically Detailed Network Model of the Prefrontal Cortex with Heterogeneous Neurons. Bernstein Conference, 2016.

Ardid S, Sherfey J, McCarthty MM, Kopell N. Alpha oscillatory inputs and short-term depression underlie action inhibitory control in a model of the striatum. SfN, 2016.

Sherfey, J., Ardid, S., McCarthy, M., Hass, J., Kopell, N. Oscillations guide rule-based action in a laminar model of prefrontal cortex. SfN, 2016.

Sherfey JS. DynaSim: a Matlab toolbox for rapidly building and exploring neural models. 2016 Janelia conference on Collaborative Development of Data-Driven Models of Neural Systems,, 2016.

Ardid S, Sherfey J, McCarthty MM, Kopell N. Context-dependent action selection mediated by specific temporal coordination between prefrontal cortex and striatum. SfN, 2015.

Sherfey J, Adams N, Kopell N, Whittington M, LeBeau F. Modeling neuronal diversity and fast network oscillations in rat anterior cingulate cortex (ACC). SfN, 2015.

Sherfey J, Kopell N. Dynamic Neural Simulator – a tool for rapidly building neural models. SfN, 2014.

Honors and Awards

Mathematical Neuroscience Prize 2015 from Israel Brain Technologies to Nancy Kopell.

Kopell published an invited chapter in Vol 9 of History of Neuroscience in Autobiography, Society for Neuroscience.

Kopell was awarded the 2016 Swartz Prize in Theoretical and Computational Neuroscience from Society for Neuroscience.

Technology Transfer

We have developed and actively maintain DynaSim (https://github.com/DynaSim), an open source freely available Matlab/GNU Octave modeling and simulation Toolbox, to facilitate model building, sharing, and simulation studies (Sherfey et al., Front Neuroinf. 2018). DynaSim shares simplified model building with other modeling tools, such as Brian, NEURON, and XPP. It additionally provides (I) a simple interface for specifying sets of simulations varying model parameters, (II) simulations running in parallel and/or on different cluster nodes, and (III) model sharing. Furthermore, DynaSim is designed to enable future extensions incorporating optimization algorithms (e.g., particle filtering, genetic algorithms) for automatically fitting model parameters constrained by experimental data.

DynaSim has been added to the MathWorks File Exchange. Documentation has been made available online and mailing lists have been created for DynaSim users and developers. Features supporting open-source collaborative development have also been developed. DynaSim facilitates building small to large differential equation models to researchers on their own or in collaboration.

DynaSim was presented in a poster at SfN 2014; a copy of the poster is available online. We demonstrated DynaSim for users at the International Neuroinformatics Coordinating Facility (INCF) booth at SfN 2015, and for developers at the Janelia Research Campus Workshop on Collaborative Development of Data-Driven Models of Neural Systems (2016); We also presented it to MathWorks representatives who have since promoted it at Cosyne (2017) and will be featured on the MathWorks website. We have established a core team of developers to facilitate future development, as well as to be engaged in a community of users.

Participants

First Name: Nancy **Last Name:** Kopell

Project Role: PD/PI

National Academy Member: Y **Months Worked:** 0

Countries of Collaboration

First Name: Joachim **Last Name:** Hass

Project Role: Postdoctoral (scholar, fellow or other postdoctoral position)

National Academy Member: N **Months Worked:** 0

Countries of Collaboration

First Name: Joan Salvador **Last Name:** Ardid Ramirez

Project Role: Postdoctoral (scholar, fellow or other postdoctoral position)

National Academy Member: N **Months Worked:** 12

Countries of Collaboration

First Name: Jason **Last Name:** Sherfey

Project Role: Graduate Student (research assistant)

National Academy Member: N **Months Worked:** 0

Countries of Collaboration

Distribution Statement

Award Information

Title: Prefrontal brain rhythms and rule-based action (Topic 3.3.3)
Contract Number: W911NF1410374
Grantee Proposal Number:

Period of Performance (Reporting Period for this report)
Start: Sep, 01 2017 End: Aug, 31 2018

Recipient of Award

Organization
TRUSTEES OF BOSTON UNIVERSITY
Boston, 022151300, USA
Investigators:

Prof. Kopell, Nancy
Principal: Yes
Submitter

Abstract

Neural oscillations are associated with facets of cognition, including rule encoding in cell assemblies; nevertheless, how oscillatory dynamics support cognition is unknown. Our goal is to improve our understanding of rhythmic mechanisms contributing to cognitively-relevant neural dynamics. To address this question we constrained biophysical models by physiological data recorded in prefrontal cortex (PFC), anterior cingulate cortex (ACC), and striatum in the basal ganglia (BG). We then investigated the properties of these models with simulations, so our findings help to understand how the brain performs rule-based decisions. Our results show that heterogeneity observed in ACC pyramidal cells enables multi-modal integration of inputs at different frequencies, whereas simulations with homogeneous populations show lack of integration; this feature of ACC may serve rule updating in PFC. In the simulated PFC, interneuron heterogeneity is a barrier to rule-encoding persistent activity, which can be overcome by plasticity-dependent formation of homogeneous cell assemblies. Also in PFC, network resonance enables beta and gamma oscillations to bias pathways in service of gating outputs and selecting rule-based actions. Downstream in the BG, spectral properties of balanced PFC input are able to differentially activate D1 and D2 SPNs, hence biasing the direct vs. the indirect pathway. During the last year, we have investigated the biophysical and network properties that govern inhibitory control and routing of non-dominant information in the context of flexible, rule-based decisions. Results from our striatal model show that short-term depression between SPNs together with long-term anti-Hebbian plasticity (involved in striatal cell assembly formation) are capable of mediating non-dominant action selection.

Keywords

Rule-based decisions, context-dependent routing, inhibitory control, dominant vs. non-dominant processing, neural rhythms, frontal cortex, basal ganglia, heterogeneity

Major Goals

Streams of flexible behavior and thought in daily life involve shifts in action-guiding sets of associations previously learned between conditions, responses, and outcomes. For instance, actions performed driving toward a traffic light are guided by a set of associations, called rules, mapping light colors (sensory conditions) to pedal controls (motor responses); after passing the light, other rules guide subsequent actions. This raises the central question: how do the dynamics of the brain affect how rules are carried out? Furthermore, neural oscillations are associated with all facets of cognition and are exhibited by rule-encoding cell assemblies in behaving monkeys; nevertheless, the ways in which such brain dynamics support cognition is only beginning to be addressed. Our goal is to improve our understanding of how rhythmic mechanisms in networks contribute to such cognitively important neural dynamics.

We have implemented computational models of rule-related brain networks in prefrontal cortex (PFC), anterior cingulate cortex (ACC), and striatum in the basal ganglia (BG), constrained by in vivo and in vitro data, investigating the properties of these models by simulation, and applying our findings to better understand how the brain controls the execution of rule-based (i.e., context-dependent) actions. All modeling involves differential equations describing biophysical changes in cellular membrane potentials. Cell models have been constrained by single cell electrophysiology; emergent rhythms in our network models have been constrained by physiological data recorded in isolated rat cortex, intact rat basal ganglia under optogenetic manipulation, and intact monkey cortex recorded during rule-based cognitive tasks. Our simulations investigate the biophysical mechanisms that generate network rhythms; how such rhythms affect cortical dynamics: persistent activity (working memory), combinatorial processing (multi-tasking and multi-modal integration), and selective routing (context-dependent attention and behavior); and how corticostriatal interactions control cognitive and motor action selection processes (i.e., decision making). More particularly, we have constructed two versions of the PFC model that differ in their level of detail. One consists adaptive exponential integrate-and-fire neurons with diversity constrained by experimental data, and the other, more detailed model, consists of conductance-based neurons adapted from the literature. The striatal model of the BG has been extended from previous work in the lab to consider: 1) the two cell types of Spiny Projecting Neurons (D1 and D2 SPNs), 2) the heterogeneous connectivity between them, and 3) physiological properties that differ between D1 and D2 SPNs (maximum conductance and short-term depression of GABAergic connections, and dynamics of Ca-dependent intrinsic currents).

Accomplished under Goals

Heterogeneity, oscillations and routing in ACC and PFC. The ACC is known to be a hub in large-scale brain systems that monitor ongoing activity across the brain and adjust internal rules when present behavior produces unexpected outcomes. Our work has shown that its internal diversity enables its ability to simultaneously process activity from areas producing rhythms at different frequencies, supports parallel processing (multi-tasking) and downstream (multi-modal) integration. In contrast, less diverse networks like those in PFC exhibit more winner-take-all type dynamics and preferentially respond to inputs at a particular resonant frequency (Adams et al., 2017).
We have found out that firing rate resonance of deep layer pyramidal cells occurred in response to an input oscillating slightly faster than the natural frequency of the PFC network. Surprisingly, the output oscillation frequency has a peak determined by the input frequency maximizing local inhibition. The peak frequency also exceeds the natural network frequency induced by equal-strength noise, and the difference in peak and natural frequencies enables oscillatory inputs to activate target populations in a way that filtered out competing noise-driven responses. We previously demonstrated for the first time that the strength of network resonance (i.e., the maximum output firing rate) increases as population spiking in the input rhythm becomes more synchronous. This implies that any mechanism that dynamically adjusts spike synchrony across projection

neurons in an oscillating sender network can simultaneously tune the functional significance of its resonant effect on all downstream networks. These results suggest strategies for optimizing transcranial stimulation and using oscillatory networks in neuromorphic engineering (Sherfey et al., PLoS Comput Biol 2018).

Furthermore, we have explored input frequency- and coherence-based selection mechanisms for flexible routing that conserves rate-coded signals. We have identified a novel resonance-based mechanism for selective frequency-specific biasing among parallel competing pathways. Using this mechanism, a highly- synchronous input rhythm is able to produce greater pathway activation than asynchronous activity with 70% higher firing rates. While signals are encoded in population firing rates, output selection and signal routing can be governed independently by the frequency and coherence of oscillatory inputs and their correspondence with output resonant properties. This resonance-mediated bias could enable PFC beta and gamma oscillations to increase the signal-to-noise ratio of working memory processes, gate working memory read-out, and support context-dependent routing for rule-based action (Sherfey et al., in preparation).

Heterogeneity, oscillations and persistent activity in PFC. We have investigated how cortical oscillations and persistent firing activity in stimulus-driven neurons could be implemented in a highly biologically realistic neural network model of the prefrontal cortex. We have found that the biological details of the model, most importantly the heterogeneity in cell parameters of interneurons, constrain the implementation of these phenomena. While we have found ways to reconcile rhythmic activity with the irregular firing that is considered the baseline state of cortical networks, we have made the surprising finding that the stability of persistent activity is disrupted in this regime. The limiting factor for persistent activity is found in the heterogeneity in the neuron parameters of the inhibitory interneurons and the parameters of short-term synaptic plasticity. Persistent activity is recovered when interneurons are aligned in neural ensembles according to their excitability, which regulates their background input (Hass et al., under revision at PLoS Comput Biol). Physiologically, this could be mediated in PFC via a homeostatic plasticity mechanism.

Our model also predicts that a network exhibiting persistent activity cannot produce intrinsic, in vivo-like, asynchronous-irregular activity (“noise”). The mechanistic explanation for this phenomenon is that the dynamic generation of noise requires substantial heterogeneity in the inhibitory synaptic inputs, which, similarly to the heterogeneity in the excitability of inhibitory interneurons, prevents persistent activity. Therefore, the background noise in a network exhibiting persistent activity must either be produced by external input, or it constitutes an entirely different state of the network, which is brought about by, e.g., neuromodulation (Hass et al., under revision at PLoS Comput Biol).

Mechanisms of *Biased Competition* (BC) under balanced input: predictions from corticostriatal processing. The BC classical mechanism relies on distinct inputs applied to competing neuronal ensembles, otherwise considered identical. How to achieve BC under balanced (i.e., identical) input is unclear. This is especially relevant in the striatum, where GO vs. NO-GO action selection may depend on BC between striatal populations receiving balanced cortical stimulation. Consequently, we built a model based on electrophysiological properties of striatal cells. Instead of focusing on a single mechanism, we have identified the following three distinct BC mechanisms under balanced input (Ardid et al., bioRxiv 258053, under revision at PNAS):

From these three mechanisms, however, only the mechanism based on the close match between the resonant frequency of either D1 or D2 SPNs, and the spectral content of the input, is consistent with current interpretation of PFC rhythmic activity supporting rule-based decisions. In this regime, the striatal circuit is dynamically flexible showing different states, according to cortical stimulation (Ardid et al., bioRxiv 258053, under revision at PNAS): 1) in absence of cortical stimulation, all SPNs show sparse activity,

which is weakly oscillatory; 2) when cortical input oscillates at alpha frequencies (reported to emerge in neural ensembles of the PFC encoding dominant information, when such information is irrelevant), there is increased synchrony in D2 SPNs activity at low beta frequency, in support of inhibitory control; and 3) when cortical input oscillates at high beta frequencies (reported to be stronger for neural ensembles of the PFC encoding the relevant information), there is increased beta synchrony in D1 SPNs activity due to the match with their resonance, which guides action selection.

In the last year, we have focused on non-dominant action selection mediated by inhibitory control mechanisms. Results from our striatal model show that short-term depression between SPNs together with long-term anti-Hebbian plasticity (involved in striatal cell assembly formation) is able to mediate non-dominant action selection under certain circumstances (Ardid and Kopell, in preparation):

- First, anti-Hebbian plasticity in inhibitory synapses between SPNs underlies cross-inhibition (which refers to an asymmetrically stronger inhibitory current for SPNs between cell assemblies in comparison to SPNs within a given cell assembly).

- Second, experimentally observed alpha rhythmic inputs from PFC before stimulus onset of non-dominant trials specific for dominant cell assemblies activates downstream striatal short-term depression.

- Thus, at stimulus onset, synaptic depression from dominant SPNs together with cross-inhibition creates a transient alpha-triggered bias within the striatum in favor of activating non-dominant actions.

- However, this mechanism requires that the bias by short-term depression lasts the order of hundreds of milliseconds to be successful (timescale of decision making).

- The requirement can be accomplished in two distinct ways: (i) by long-lasting short-term depression in SPNs, or (ii) by slowly raising ramping activity in SPNs in response to cortical stimulation.

Conclusions

We have met the milestones that were set in our grant application. More specifically, we have constructed basic models of PFC and striatum, and have investigated the implications of network dynamics in these models for rule-based decision making. The major conclusions from our current work are:

- Physiological heterogeneity in ACC supports its role as a higher-order hub in combining multi-modal inputs at different frequencies, an important operation for monitoring activity throughout the brain.
- Network resonance enables beta and gamma rhythms in PFC to govern the selection and gating of rate- coded signals for downstream read-out in service of working memory and rule-based decision making.
- Heterogeneity in PFC interneurons is a barrier to persistent activity, which can be overcome by plasticity- dependent formation of homogeneous cell assemblies.
- There are three distinct mechanisms by which balanced input can differentially bias D1 and D2 SPNs, hence biasing GO vs. NO-GO action selection.
- Only the match between the spectral content of the input and one, or another, SPN resonance, is consistent with the proposed functional role of PFC rhythms in rule-based decisions.
- Long-lasting and/or slowly raising short-term depression between SPNs supports non-dominant action selection if acting upon striatal cell assemblies mediated by anti-Hebbian plasticity.

Training Opportunities

Personnel

Sherfey first focused on understanding the implications of heterogeneity in ACC as well as developing DynaSim. Later on, he investigated rhythm-mediated routing in dlPFC.

Ardid studied biased competition under balanced input in a model of corticostriatal processing for action selection and rule-based decisions. During the extension of this grant, he tested the hypothesis that asymmetric rule-based routing (i.e., relative to dominant vs. non-dominant rules) is supported by striatal cell assembly formation and short-term depression.

Hass worked on persistent activity in the presence of cellular and synaptic heterogeneities and the coexistence of oscillatory and asynchronous activity in a biologically detailed PFC model. He was appointed as a professor for statistical methods in psychology at the SRH Hochschule Heidelberg.

Kopell organized and supervised the project.

Collaborations and leveraged funding

Collaborations. The lab of Fiona LeBeau provided data on heterogeneity in the ACC, which was the basis of a joint paper with our group: “Heterogeneity in neuronal intrinsic properties: A possible mechanism for hub-like properties of the rat anterior cingulate cortex during network dynamic activity”.
Helen Barbas and her group provided details of anatomical connections within the PFC and between the PFC and other regions.

Earl Miller, an expert in rule-based decisions and category learning, provided general guidance for our project.

The work we described makes use of other models created within the Kopell group, notably striatal models by Michelle McCarthy and collaborators.

All of this work has been done in the context of the Cognitive Rhythms Collaborative (CRC), a group headed by Kopell and consisting of more than two dozen labs working on topics associated with brain dynamics. This project obtained feedback from other members of the CRC.

Leveraged funding. Over the period of the grant, the William Fairfield Warren Chair of Kopell supported three months salary for Salva Ardid and three months salary for Joachim Hass. In addition, Ardid was supported for two months on a grant from the NSF to Kopell for the Cognitive Rhythms Collaborative. We also obtained travel money for two trips to the Society for Neuroscience meeting from Boston University.

Results Dissemination

Seminars

Jason Sherfey. DynaSim: Neural Modeling in Matlab. 2018 INCF Neuroinformatics Meeting, Montreal, QC, 2018.

Jason Sherfey. Neuroscience Modeling and Data Processing with Community-Authored MATLAB-Based Tools – The DynaSim Toolbox for Neural Modeling. Neuroscience Gateway Workshop at the 2018 Computational Neuroscience Meeting, Seattle, WA, 2018.

Salva Ardid. Brain Mechanisms Supporting Biased Competition under balanced input. University of Texas – Southwestern Medical Center, Dallas TX, 2018.

Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decision Making. Vanderbilt University, Nashville TN, 2017.

Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decision Making. Mount Sinai School of Medicine. New York City NY, 2017.

Salva Ardid. Brain Mechanisms Supporting Context-Dependent Decisions and Inhibitory Control: A Neural Circuit Modeling Approach. Stony Brook University. Stony Brook NY, 2017.

Salva Ardid. Alpha Oscillatory Inputs and Short-Term Depression Underlie Action Inhibitory Control in a Model of the Striatum. 5th Barcelona Computational, Cognitive, and Systems Neuroscience. Barcelona, 2016.

Salva Ardid. Alpha Oscillatory Inputs and Short-Term Depression Underlie Action Inhibitory Control in a Model of the Striatum. Cognitive Rhythms Collaborative: Rhythmic Dynamics and Cognition. Boston MA, 2016.

Jason Sherfey. Competition versus cooperation in the anterior cingulate cortex. 2016 Cognitive Rhythms Collaborative Retreat, Boston, MA, 2016.

Jason Sherfey. Cortical rhythms and interneurons for reading working memory: a computational study of laminar DLPFC. Cognitive Rhythms Collaborative Retreat, Boston, MA, 2014.

Jason Sherfey. Prefrontal brain rhythms for rule-based selection. Gordon Research Seminar., Newry, ME, 2014.

Nancy Kopell. Rhythms, Routing, Resonance and Rule-based Decisions, Neuroscience Colloquium UC San Diego 2017

Nancy Kopell , Rhythms, Routing and Resonance, Oscillations Workshop Princeton University 2016

Posters

Sherfey J, Ardid S, Hass J, Kopell N., Miller, E. K., Hasselmo M. E. Modeling of oscillatory gating for cognitive function. SfN, 2018.

Sherfey J, Ardid S, Hass J, Kopell N., Hasselmo M. E. Prefrontal oscillations bias pathways for thought and action. Computational Neuroscience Meeting, 2018.

Sherfey JS, Soplata AE, Ardid S, Roberts EA, Stanley DA, and Kopell N. DynaSim: A Matlab Toolbox for Neural Modeling and Simulation. INCF Neuroinformatics Meeting, 2018.

Ardid S, Sherfey J, McCarthy MM, Hass J, Pittman-Polletta B, Kopell N. Biased competition in the absence of input bias: predictions from corticostriatal computation, COSYNE Meeting, 2018.

Hass J, Ardid S, Sherfey J, Kopell N: Constraints on Persistent Activity in a Biophysically Detailed Network Model of the Prefrontal Cortex with Heterogeneous Neurons. Bernstein Conference, 2016.

Ardid S, Sherfey J, McCarthty MM, Kopell N. Alpha oscillatory inputs and short-term depression underlie action inhibitory control in a model of the striatum. SfN, 2016.

Sherfey, J., Ardid, S., McCarthy, M., Hass, J., Kopell, N. Oscillations guide rule-based action in a laminar model of prefrontal cortex. SfN, 2016.

Sherfey JS. DynaSim: a Matlab toolbox for rapidly building and exploring neural models. 2016 Janelia conference on Collaborative Development of Data-Driven Models of Neural Systems,, 2016.

Ardid S, Sherfey J, McCarthty MM, Kopell N. Context-dependent action selection mediated by specific temporal coordination between prefrontal cortex and striatum. SfN, 2015.

Sherfey J, Adams N, Kopell N, Whittington M, LeBeau F. Modeling neuronal diversity and fast network oscillations in rat anterior cingulate cortex (ACC). SfN, 2015.

Sherfey J, Kopell N. Dynamic Neural Simulator – a tool for rapidly building neural models. SfN, 2014.

Honors and Awards

Mathematical Neuroscience Prize 2015 from Israel Brain Technologies to Nancy Kopell.

Kopell published an invited chapter in Vol 9 of History of Neuroscience in Autobiography, Society for Neuroscience.

Kopell was awarded the 2016 Swartz Prize in Theoretical and Computational Neuroscience from Society for Neuroscience.

Technology Transfer

We have developed and actively maintain DynaSim (https://github.com/DynaSim), an open source freely available Matlab/GNU Octave modeling and simulation Toolbox, to facilitate model building, sharing, and simulation studies (Sherfey et al., Front Neuroinf. 2018). DynaSim shares simplified model building with other modeling tools, such as Brian, NEURON, and XPP. It additionally provides (I) a simple interface for specifying sets of simulations varying model parameters, (II) simulations running in parallel and/or on different cluster nodes, and (III) model sharing. Furthermore, DynaSim is designed to enable future extensions incorporating optimization algorithms (e.g., particle filtering, genetic algorithms) for automatically fitting model parameters constrained by experimental data.

DynaSim has been added to the MathWorks File Exchange. Documentation has been made available online and mailing lists have been created for DynaSim users and developers. Features supporting open-source collaborative development have also been developed. DynaSim facilitates building small to large differential equation models to researchers on their own or in collaboration.

DynaSim was presented in a poster at SfN 2014; a copy of the poster is available online. We demonstrated DynaSim for users at the International Neuroinformatics Coordinating Facility (INCF) booth at SfN 2015, and for developers at the Janelia Research Campus Workshop on Collaborative Development of Data-Driven Models of Neural Systems (2016); We also presented it to MathWorks representatives who have since promoted it at Cosyne (2017) and will be featured on the MathWorks website. We have established a core team of developers to facilitate future development, as well as to be engaged in a community of users.

Publications

Sherfey J, Ardid S, Kopell N, Miller EK, Hasselmo ME. Oscillatory gating for cognitive function in circuit models of prefrontal cortex. In preparation.

Ardid S, Kopell N. Short-term depression and long-term anti-Hebbian plasticity mediate non-dominant action selection in a model of the striatum. In preparation.

Hass J, Ardid S, Sherfey J, Kopell N. Constraints on persistent activity in a biophysically detailed network model of the prefrontal cortex with heterogeneous neurons. Under review.

Ardid S, Sherfey J, McCarthy MM, Hass J, Pittman-Polletta BR, Kopell N (2018). Biased competition in the absence of input bias: predictions from corticostriatal computation. biorxiv 258053, doi:10.1101/258053.

Sherfey J, Ardid S, Hass J, Hasselmo M, and Kopell N (2018). Flexible resonance in prefrontal networks with strong feedback inhibition. PLoS Computational Biology, 14(8), e1006357.

Sherfey J, Soplata AE, Ardid S, Roberts EA, Stanley DA, Pittman-Polletta BR and Kopell N (2018). DynaSim: A MATLAB Toolbox for Neural Modeling and Simulation. Front. Neuroinform., 12(10), doi: 10.3389/fninf.2018.00010.

Adams* N, Sherfey* J, Kopell N, Whittington M, LeBeau F (*contributed equally to the work). Heterogeneity in neuronal intrinsic properties: A possible mechanism for hub-like properties of the rat anterior cingulate cortex during network dynamic activity. eNeuro, 4(1), ENEURO-0313, 2017.

Hass J, Durstewitz D: Time at the center, or time at the side? Assessing current models of time perception. Curr Opin Behav Sci.. 8:238-244, 2016.