| | | |
|---|---|---|
| PI: **Carney, Laurel H.** | Title: Developing and Testing Models of the Auditory System with and without Hearing Loss | |
| Received: 04/02/2015 | Opportunity: PA-13-302 | Council: 10/2015 |
| Competition ID: FORMS-C | FOA Title: RESEARCH PROJECT GRANT (PARENT R01) | |
| **2R01DC010813-06A1** | Dual: AG | Accession Number: 3808265 |
| IPF: 7047101 | Organization: [redacted] | |
| Former Number: | Department: Biomedical Engineering | |
| IRG/SRG: AUD | AIDS: N | Expedited: N |
| Subtotal Direct Costs (excludes consortium F&A) [redacted] | Animals: Y<br>Humans: Y<br>Clinical Trial: N<br>Current HS Code: 30<br>HESC: N | New Investigator: N<br>Early Stage Investigator: N |
| | | |
| *Senior/Key Personnel:* | *Organization:* | *Role Category:* |
| Laurel Carney Ph.D | [redacted] | PD/PI |

*Additions for Review*

Accepted Publication  Publication Update

APPLICATION FOR FEDERAL ASSISTANCE
**SF 424 (R&R)**

| **3. DATE RECEIVED BY STATE** | **State Application Identifier** |
|---|---|
| | |

**1. TYPE OF SUBMISSION***

❍ Pre-application ● Application ❍ Changed/Corrected Application

**4.a. Federal Identifier**
DC010813

**b. Agency Routing Number**

**2. DATE SUBMITTED**

**Application Identifier**
CarneyR01Models

**c. Previous Grants.gov Tracking Number**

**5. APPLICANT INFORMATION**

**Organizational DUNS*:** 041294109

Legal Name*: [redacted]
Department: ORPA
Division:
Street1*: [redacted]
Street2:
City*: [redacted]
Province:
Country*: USA: UNITED [redacted]

Person to be contacted on matters involving this application

Prefix: Mrs. First Name*: Laurie Middle Name: Last Name*: Naber Suffix:

Position/Title: Research Administrator
Street1*: [redacted]
Street2:
City*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: [redacted] Email: [redacted]

**6. EMPLOYER IDENTIFICATION NUMBER** *(EIN) or (TIN)** [redacted]

**7. TYPE OF APPLICANT*** O: Private Institution of Higher Education

Other (Specify):
**Small Business Organization Type** ❍ Women Owned ❍ Socially and Economically Disadvantaged

**8. TYPE OF APPLICATION***

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

**Is this application being submitted to other agencies?*** ❍Yes ●No What other Agencies?

**9. NAME OF FEDERAL AGENCY***
National Institutes of Health

**10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER**
TITLE:

**11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT***
Developing and Testing Models of the Auditory System with and without Hearing Loss

**12. PROPOSED PROJECT**

Start Date* Ending Date*
04/01/2016 03/31/2021

**13. CONGRESSIONAL DISTRICTS OF APPLICANT**
[redacted]

# SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE



**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: Dr. First Name*: Laurel Middle Name: Last Name*: Carney Suffix: Ph.D

Position/Title: Professor

Organization Name*: [redacted]

Department: Biomedical Engineering

Division: [redacted]

Street2:

City*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: [redacted]

**15. ESTIMATED PROJECT FUNDING**

a. Total Federal Funds Requested* [redacted]

**16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?***

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

**18. SFLLL or OTHER EXPLANATORY DOCUMENTATION** File Name:

**19. AUTHORIZED REPRESENTATIVE**

Prefix: Mrs. First Name*: Laurie Middle Name: Last Name*: Naber Suffix:

Position/Title*: Research Administrator

Organization Name*: [redacted]

Department: ORPA

Division:

Street1*: [redacted]

Street2:

City*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number [redacted] Email*: [redacted]

**Signature of Authorized Representative***

Laurie Naber

**Date Signed***

04/02/2015

**20. PRE-APPLICATION** File Name:

**21. COVER LETTER ATTACHMENT** File Name:1234-Cover_Letter_Letterhead.pdf

# 424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

# Project/Performance Site Location(s)

**Project/Performance Site Primary Location**

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: [redacted]

[redacted]

Street2:

City*: [redacted]

Province:

Country*: USA: UNITED STATES

Zip / Postal Code*: [redacted]

Project/Performance Site Congressional District*: [redacted]

---

File Name

**Additional Location(s)**





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

# RESEARCH & RELATED Other Project Information

**1. Are Human Subjects Involved?*** ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 0000009386

**2. Are Vertebrate Animals Used?*** ● **Yes** ○ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ● No

IACUC Approval Date: 05-20-2014

Animal Welfare Assurance Number A329201

**3. Is proprietary/privileged information included in the application?*** ○ **Yes** ● **No**

**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?*** ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

**5. Is the research performance site designated, or eligible to be designated, as a historic place?*** ○ **Yes** ● **No**

5.a. If yes, please explain:

**6. Does this project involve activities outside the United States or partnership with international collaborators?*** ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

| | Filename |
|---|---|
| **7. Project Summary/Abstract*** | 1235-AbstractFinal.pdf |
| **8. Project Narrative*** | 1236-Project_Narrative_Model.pdf |
| **9. Bibliography & References Cited** | 1237-Bibliography_2015.pdf |
| **10.Facilities & Other Resources** | 1238-LHC_resources.pdf |
| **11.Equipment** | 1239-EQUIPMENT.pdf |





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

This proposal presents plans to develop and test a new model for the processing of acoustic cues in both psychophysical tasks and real-world hearing. Masking paradigms are typically interpreted in the context of two models: The power-spectrum model is based on energy in the responses of one or more band-pass filters that represent peripheral tuning. The envelope-power-spectrum model is based on the responses of a bank of modulation filters. These popular models, however, fail to explain robust performance in a number of psychophysical tasks, especially roving- or equalized-level, and roving- or equalized-envelope-energy tasks. The continued use of these models is largely due to a lack of viable alternatives. Here, we propose a new, alternative model for masked detection and spectral coding that provides a mechanistic explanation for a number of psychophysical results, for listeners with or without hearing loss.

Building upon our recent studies of envelope-related cues in masked detection, our proposal focuses on the role of **neural-fluctuation cues** in the responses of auditory-nerve fibers, and ultimately on how these cues are represented by modulation-tuned neurons in the midbrain. These cues are robust in the healthy ear but, because they are strongly dependent upon peripheral nonlinearities, they are substantially degraded in most common types of hearing loss. We will make detailed measurements on the use of envelope vs. energy cues by individual listeners as a function of frequency and hearing thresholds. These results will provide individualized models that will be used to predict thresholds in specific masking and discrimination tasks.

We will use computational, physiological and psychophysical tools to test a **diotic model of masked detection**, focusing on two classic paradigms: notched-noise and forward-masking tasks. These psychophysical tools have been used extensively to characterize tuning bandwidth, compression, and temporal processing in listeners with and without hearing loss. We will re-examine these tasks with *neural fluctuation-based representations.* Our preliminary results show that the *contrast* in fluctuations across peripheral channels establishes a representation of stimulus features at the level of the midbrain that is robust in noise across a wide range of levels, thus addressing the primary challenges of roving-parameter paradigms. These cues are particularly strong near spectral slopes, and thus warrant consideration for other stimulus features with sharp spectral slopes, such as fricative consonants and pinna cues. We therefore also propose to extend our **dichotic model based on interaural differences in neural fluctuations** to the spectral slopes of pinna cues, which code sound location and externalization. Our preliminary work indicates that neural-fluctuation cues associated with the diotic and dichotic stimuli occur in the modulation frequency range where the majority of midbrain neurons are tuned. Consideration of these tasks and stimuli in the framework of neural-fluctuation cues provides a novel and general understanding for coding stimulus spectra by the normal and impaired ear.

Hearing loss typically involves difficulty understanding complex sounds such as speech, especially in noise. Knowledge of how the healthy brain copes with difficult listening environments will provide new and important insights for aiding listeners with hearing loss. The Public Health Relevance of this project is to develop a better understanding of the difficulties in noisy situations for listeners with hearing loss. We are developing and testing a computational model for the auditory system of listeners with and without sensorineural hearing loss.

## RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

Space dedicated to this project (1150 $ft^2$) is comprised of 2 laboratory rooms containing 3 sound-attenuated booths, plus office space for the PI, grad students and post-docs. We also have the use of an additional sound-attenuated booth in a clinical area of the Department for human psychoacoustic studies.

Clinical:

Not applicable

Animal:

The University of Rochester maintains a full-service AAALAC-approved vivarium facility (~36,000 $ft^2$). Rabbits are housed and cared for on the 6th floor of the medical center in their own room. The Department of Laboratory Animal Medicine (DLAM) at the University of Rochester maintains animal care and has a veterinary staff that provides veterinary care. Surgical procedures are carried out in a core facility of the Department of Neurobiology and Anatomy. However, DLAM also has a fully-equipped necropsy room and animal surgical suite that is available.

Computer:

Several desktop PCs are networked to communicate with other PCs in the laboratory. An HP LaserJet networked printer is available for lab and office use. Computer support is provided by the Department of Information Services at the medical center.

**Center for Research Computing**

An exciting resource at the University [redacted] that will be invaluable for the proposed work is the Center for Research Computing. The University [redacted] recognizes the key role of high-performance computing (HPC) in disciplines spanning all areas of academic scholarship. As a consequence, the University created the Center for Research Computing (CRC) in 2008. This CRC provides researchers across the University with the physical computational resources, software and necessary to fully utilize high-performance computation in their research activities.

The CRC maintains five high-performance computing (HPC) systems totaling more than 23 teraflops of computing power, 200 terabytes of disk storage, and a variety of software applications and tools. All CRC resources are supported and maintained by a professional technology team in the University's state-of-the art data center, which opened Jan 2009. In addition to technology resources, the Center for Research Computing (CRC) at the University [redacted] provides the training, consultation, and support necessary to ensure that scientists have the knowledge base necessary for effective computational research. This support is provided by 3 full-time staff members (Director, HPC Consultant, and HPC System Administrator), a rich set of information sharing and collaboration tools, and an ongoing education and training program. Our students have been able to get up and running very quickly with the help of this staff – currently, we are using this system for some of our simulations and to run some standard speech enhancement algorithms (for comparison to our own, which is not as computationally intense.)

CRC systems include a 14 teraflop BlueGene/P providing 4096 CPU cores, 2.0 TB RAM, and 180TB storage; the 7 teraflop BlueHive cluster, consisting of 84 compute nodes totaling 672 CPU cores, 1.3 TB RAM, and 24 TB storage; the Nova cluster, consisting of 144 CPU cores, 144GB RAM, 1.2 TB storage; and the Nebula cluster consisting of 60 CPU Cores and 120 GB RAM. Supporting software applications and tools include: C/C++ and Fortran compilers from Intel, GNU, and IBM; parallel communication and math libraries; domain-specific scientific applications; and cross-domain scientific applications (e.g. R, MATLAB, and Mathematica).

Office:

Office space for the PI and graduate/post-doctoral students is located near the laboratory space.

Other:

Support is also available through the Department of Neurobiology and Anatomy and the Department of Biomedical Engineering. Each Department provides color printers, copy machines and fax machines.

## EQUIPMENT

[redacted] The PI's lab contains a large sound-attenuated IAC booth that is dedicated to rabbit physiology. We will also have the use of an additional large sound-attenuated booth in a clinical area of the Department for human psychoacoustic studies. A computer-controlled Neuralynx Cheetah system that is interfaced to a TDT Acoustical system is available for rabbit physiological recordings.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

# RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Laurel Middle Name Last Name*: Carney Suffix: Ph.D

Position/Title*: Professor
Organization Name*: [redacted]
Street2:
City*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-[redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: Degree Year:

| | File Name |
|---|---|
| Attach Biographical Sketch*: | 1244-biosketch_Carney_2015_Models.pdf |
| Attach Current & Pending Support: | |





Funding Opportunity Number: PA-13-302 . Received Date: 2015-04-02T14:32:01.000-04:00

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Laurel H. Carney | Professor |
| eRA COMMONS USER NAME (credential, e.g., agency login) [redacted] | |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Massachusetts Institute of Technology, Cambridge, MA | S.B. | 1983 | Electrical Engineering |
| University of Wisconsin, Madison, WI | M.S. | 1985 | Electrical Engineering |
| University of Wisconsin, Madison, WI | Ph.D. | 1989 | Electrical Engineering |

### A. Personal Statement

The project proposed here builds on our recent modeling and experimental work related to masked detection. This work has convinced us that neural-fluctuation cues play a critical role in masked detection, even in tasks such as detection of low-frequency tones, for which fine-structure cues have been the primary focus of previous efforts in the field. The properties of neural fluctuations are sometimes counter-intuitive – they are related to the stimulus envelope *after filtering in the periphery*, including the distortion and/or enhancement by peripheral nonlinearities. The tools that we have developed to visualize neural-fluctuation cues have revealed to us the potentially much broader role of these cues in a variety of masking tasks, as well as in perception of sound localization and speech cues. If our hypothesis is supported - that the primary cues in these tasks are neural-fluctuations - then by providing an alternative to power-spectrum (or energy)-based cues, the project will not only advance hearing science, but will motivate novel approaches for hearing-aid and cochlear implant algorithms (which currently rely in large part on the power-spectrum model). Neural-fluctuation cues change substantially in ears with hearing loss, thus we are motivated to ask whether these differences are key to understanding deficits for these listeners in background noise.

We have a strong team to pursue this project, which requires physiological, audiological, computer programming, linguistics, and psychophysical modeling expertise. I am excited to be leading this team into the next phase of this work. Now that our lab has been established at the University of Rochester for 8 years with a stable technical staff, we are in a strong position to propose an ambitious set of goals for the next 5 years. We will draw new energy from a proposed grad student, whom we will recruit from either the Biomedical Engineering or the Audio and Music Engineering program, which has been a great source of talent for us in the past. We will also support and train a new post-doc to participate in the combined modeling and experimental work proposed here. The scope of the proposed work, though ambitious, was shaped to be consistent with our accomplishments in the first cycle of this grant.

### B. Positions and Honors

#### Positions

1991-1997 Assistant Professor, Boston University, Department of Biomedical Engineering
1997-2001 Associate Professor, Boston University, Department of Biomedical Engineering
1998-2001 Associate Chair for Graduate Studies, BU, Department of Biomedical Engineering
1999-2002 Associate Editor, Physiological Acoustics, *Journal of the Acoustical Society of America*
2001-2007 Professor, Syracuse University, Departments of Biomedical & Chemical Engineering and Electrical Engineering & Computer Science
2001-2009 Associate Editor, *Journal of Neuroscience*

2007-Present Professor, University of Rochester, Department of Biomedical Engineering, Professor, Department of Neurobiology & Anatomy
2010-2013 Associate Editor, *Journal of the Association for Research in Otolaryngology*.
2012-2015 Member, Technical Committee, Psychological and Physiological Acoustics, Acoustical Society of America
2014-Present Member, Editorial Board, Journal of Neurophysiology

**Honors**

2015 - William and Christine Hartmann Prize in Auditory Neuroscience, Acoustical Society of America
2006 - Elected Fellow of the American Institute for Medical and Biological Engineering, "For contributions to the mathematical modeling and empirical characterization of the mammalian auditory system."
2002 - Elected Fellow of the Acoustical Society of America, "For contributions to an integrated understanding of the physiology and psychophysics of hearing."

**C. Publications Relevant to the Proposed Project (limited to 15)**


1. Heinz, M. G., Zhang, X., Bruce, I. C., and Carney, L. H. (2001) Auditory-nerve model for predicting performance limits of normal and impaired listeners. ARLO 2: 91-96. (No PMID/PMCID available.)
2. Heinz, M.G., Colburn, H.S., and Carney, L.H. (2001) Rate and timing cues associated with the cochlear amplifier: Level discrimination based on Monaural cross-frequency concidence detection. J Acoust Soc Am 110:2065-2084. PMID: 11681385.
3. Nelson, P.C. and Carney, L. H. (2004) A phenomenological model of peripheral and central neural responses to amplitude-modulated tones. J Acoust Soc Am 116:2173-2186. PMCID: PMC1379629.
4. Nelson, P.C., and Carney, L. H. (2006) Cues for masked amplitude-modulation detection. J Acoust Soc Am 120:978-990. PMCID: PMC2572864.
5. Tan, Q., and Carney, L.H. (2006) Predictions of formant-frequency discrimination in noise based on model auditory-nerve responses. J Acoust Soc Am 120:1435-1445. PMCID: PMC2572872.
6. Nelson, P.C. and Carney, L. H. (2007) Neural rate and timing cues for detection and discrimination of amplitude-modulated tones in the awake rabbit inferior colliculus. J Neurophysiol 97:522-539. PMCID: PMC2577033.
7. Zilany, M. S. A., Bruce, I. C., Nelson, P.C., and Carney, L.H. (2009) A phenomenological model of the synapse between the inner hair cell and auditory nerve: Long-term adaptation with power-law dynamics. J Acoust Soc Am 126:2390-2412. PMCID: PMC2787068.
8. Mao, J., Vosoughi, A., and L.H. Carney (2013) Predictions of diotic tone-in-noise detection based on a nonlinear optimal combination of energy, envelope, and fine-structure cues, J Acoust Soc Am 134:396-406. PMCID: PMC3724726.
9. Zilany, M.S.A., Bruce, I.C., and L. H. Carney (2014) Updated parameters and expanded simulation options for a model of the auditory periphery. J Acoust Soc Am 135:283-286. PMCID: PMC3985897.
10. Carney, LH, Zilany, MSA, Huang, NJ, Abrams, KS, Idrobo, F (2014) Sub-optimal use of neural information in a mammalian auditory system, J Neurosci 34:1306-1313. PMCID: PMC3898290.
11. Mao, J. and L.H. Carney (2014) Binaural detection with narrowband and wideband reproducible noise maskers: IV. Models using time, level, and envelope differences. J Acoust Soc Am 135:824-837. PMCID: PMC3985905.
12. Rao, A. and L.H. Carney (2014) Speech Enhancement for Listeners with Hearing Loss Based on a Model for Vowel Coding in the Auditory Midbrain. IEEE Trans Biomed Eng 61:2081-2091. (PMID: 24686228; PMCID not yet assigned).
13. Kim, D.O., Zahorik, P., Carney, L.H. Bishop, B., and S. Kuwada (2015, in press) "Auditory distance coding: rabbit midbrain neurons and human perception," J. Neuroscience. PMCID not yet assigned.
14. Kuwada, S., Kim, D.O., Koch, K.-J., Abrams, K.S., Idrobo, F., Zahorik, P., and L.H. Carney (2015, in press) Near-field discrimination of sound source distance in the rabbit, JARO.
15. Mao, J., and L.H. Carney (2015) Tone-in-Noise Detection Using Envelope Cues: Comparison of Signal-Processing-Based and Physiological Models, JARO 16:121-133. PMCID not yet assigned.

## D. Research Support

ONGOING

"Auditory Processing of Complex Sounds"
PI: Laurel H. Carney
Agency: NIH-NIDCD
Type: R01 DC001641
Period: 12/1/13-11/30/18
The goal of this grant is to test a hypothesis for vowel coding based on the contrast of voiced pitch-related fluctuations in responses across frequency channels. Physiological tests in the midbrain will be conducted in the awake rabbit and in the awake budgerigar. Behavioral tests will be done in humans and budgerigars. Computational models for AM tuning will be expanded to include mode-locking phenomena that have been observed in midbrain responses.

"Developing and Testing Models of the Auditory System with & without Hearing Loss"
PI: Laurel H. Carney
Agency: NIH-NIDCD
Type: R01 DC010813
Period: 12/01/2010-11/30/2015
The central hypothesis of this research is that accurate predictions of detailed performance in psychophysical tasks require an understanding of the physiological transformations of signals and interactions of stimulus features along the auditory pathway. A composite model based on specific physiological mechanisms within the auditory pathway will be developed and tested. The model will be used to predict performance in masked tone detection and masked amplitude-modulation detection tasks for listeners with and without hearing loss. *The current proposal is for a renewal of this project.

"Training in Hearing, Balance, and Spatial Orientation"
PI: Shawn Newlands (Co-Investigator, Carney)
Agency: NIH-NIDCD
Type: T32-DC009974-1
Period: 7/1/2010-6/30/2015

"Speech Enhancement based on Auditory Coding of Voiced Signals"
PI: LH Carney, submitted by OmniSpeech, LLC
Agency: NIH-NIDCD
Type: R41 (STTR)
Period: 12/01/14-11/30/2015
This project focuses on enhancing voiced speech sounds, taking advantage of their harmonic structure. OmniSpeech has developed an algorithm for voice pitch detection in noisy backgrounds and this project will combine our formant identification and enhancement strategy with their algorithm. There is no overlap between the work in this STTR project and the third aim of the current proposal, which focuses on enhancement of modulations associated with spectral slopes, such as pinna cues and fricative speech sounds.

PENDING:

**“**Acoustic Displays and applications to geo-location smart service system”
PI: M Bocko (Co-Investigator, Carney)
Agency: NSF Partnerships for Innovation Proposal Summary
Type PFI-BIC
Period: 8/1/15-7/30/18
There is no scientific or budgetary overlap between this pending project and the current proposal.

“Auditory distance perception: a neural, behavioral and modelling approach”
PIs: Shig Kuwada and Duck Kim, University of Connecticut (Co-Is, L. Carney, and P. Zahorik., Univ. Kentucky)
Agency: NIH-NIDCD
Period: R01 Application revision is in progress
This collaborative effort focuses on physiological, psychophysical, and computational modeling studies of neural coding for sound location, including source distance, in reverberant environments. The modulation tuning properties of midbrain neurons play a critical role in reverberant environments. My role in this project related to modeling IC responses for binaural difference cues involved in azimuthal location and modulation cues for distance. These topics have been omitted from the current proposal to avoid scientific overlap.

“Training in Hearing, Balance, and Spatial Orientation”
PI: Shawn Newlands (Co-Principal Investigator, Carney)
Agency: NIH-NIDCD
Type: T32-DC009974-1
A resubmission of this training grant is in preparation.

# PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

| | |
|---|---|
| Prefix: | Dr. |
| First Name*: | Laurel |
| Middle Name: | |
| Last Name*: | Carney |
| Suffix: | Ph.D |

## 2. Human Subjects

| | | |
|---|---|---|
| Clinical Trial? | ● No | ○ Yes |
| Agency-Defined Phase III Clinical Trial?* | ○ No | ○ Yes |

## 3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

○ Yes ● No

## 4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

| Budget Period* | Anticipated Amount ($)* | Source(s)* |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Cover Page Supplement

## 5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ○ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

## 6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ● Yes ○ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ● Yes ○ No

## 7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:



Tracking Number: GRANT11874440

Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Modular Budget

OMB Number: 0925-0001

## Budget Period: 1

Start Date: 04/01/2016 End Date: 03/31/2017

### A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium F&A* [redacted]

[redacted]

[redacted]

### B. Indirect Costs

| | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | [redacted] | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Arif Kim, [redacted]

Indirect Cost Rate Agreement Date 03/20/2014

Total Indirect Costs [redacted]

### C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) [redacted]





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Modular Budget

Budget Period: 2

Start Date: 04/01/2017 End Date: 03/31/2018

## A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium F&A* [redacted]

Consortium F&A

Total Direct Costs* [redacted]

## B. Indirect Costs

| | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | [redacted] | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Arif Kim, [redacted]

Indirect Cost Rate Agreement Date 03/20/2014

Total Indirect Costs [redacted]

## C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) [redacted]





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Modular Budget

Budget Period: 3

Start Date: 04/01/2018 End Date: 03/31/2019

## A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium F&A* [redacted]

Consortium F&A

Total Direct Costs* [redacted]

## B. Indirect Costs

| | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | [redacted] | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Arif Kim, [redacted]

Indirect Cost Rate Agreement Date 03/20/2014

Total Indirect Costs [redacted]

## C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) [redacted]





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Modular Budget

Budget Period: 4

Start Date: 04/01/2019 End Date: 03/31/2020

## A. Direct Costs

Funds Requested ($)

Direct Cost less Consortium F&A* [redacted]

Consortium F&A

Total Direct Costs* [redacted]

## B. Indirect Costs

| | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | [redacted] | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Arif Kim, [redacted]

Indirect Cost Rate Agreement Date 03/20/2014

Total Indirect Costs [redacted]

## C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) [redacted]





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Modular Budget

| Budget Period: 5 |
|---|
| Start Date: 04/01/2020 End Date: 03/31/2021 |

**A. Direct Costs**

| | Funds Requested ($) |
|---|---|
| Direct Cost less Consortium F&A* | [redacted] |
| Consortium F&A | |
| Total Direct Costs* | [redacted] |

**B. Indirect Costs**

| | Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base ($) | Funds Requested ($) |
|---|---|---|---|---|
| 1. | MTDC | [redacted] | [redacted] | [redacted] |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, Arif Kim, 214.767.3600

Indirect Cost Rate Agreement Date: 03/20/2014

Total Indirect Costs: [redacted]

**C. Total Direct and Indirect Costs (A + B)**

Funds Requested ($): [redacted]





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

# PHS 398 Modular Budget

## Cumulative Budget Information

### 1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium F&A for Entire Project Period ($) [redacted]

[redacted]

### 2. Budget Justifications

| | |
|---|---|
| Personnel Justification | 1245-Budget_Justification.pdf |
| Consortium Justification | |
| Additional Narrative Justification | |





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

**Personnel Justification:**

**NAME # Person months**

Laurel H. Carney, PhD 1.8 Academic year months (20% effort); 0.5 summer months
Role: Principle investigator – Carney will be involved in all psychophysical and physiological testing and in the development and testing of computational models. This role includes running some experiments, training and supervising technicians, and training & mentoring students and postdoctoral fellows who will be engaged in these activities.

[redacted] 12 Calendar months
Role: Lab technician (100%) – This laboratory technician will assist the PI and graduate/post-doc assistants with physiological experiments and testing human subjects.

Post-doctoral Fellow, PhD 12 Calendar months
Role: The Post-Doctoral Fellow will be involved in computational modeling and in the physiological tests proposed here, which include tetrode recordings in the midbrain of the awake rabbit. We will recruit a new post-doc to join this effort.

Graduate Student 12 Calendar months
Role: Grad research assistant – The Graduate assistant will participate in computational modeling and speech-enhancement development. This type of project has been perfect for past students who have used this type of work as the focus of their PhD theses (e.g. [redacted] A new graduate student [redacted], has indicated interest in joining this project.

[redacted] 6 Calendar months (50% effort)
Role: Programmer – The programmer will assist the PI, post-doc and students in the development of modeling & visualization software. The programmer will also assist with the development of specialized software for physiological data collection and analysis.

[redacted] Medical Center 0.6 Calendar months (5% effort)
Role: Audiologist - [redacted] will assist with the detailed audiological testing of listeners, including audiograms, speech-in-noise testing, DPOAEs, and tympanograms.

**Fringe Benefits** are calculated at the University's negotiated rates for faculty and staff. For the Graduate Student, health fees are assessed at the University's standard rate.

**Indirect Costs** are calculated at the University's negotiated rate of 53.5% of MTDC, the latest agreement was dated 3/20/2014.

# PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

| | |
|---|---|
| 1. Introduction to Application (for RESUBMISSION or REVISION only) | 1240-IntroductionFinal.pdf |
| 2. Specific Aims | 1241-Specific_Aims_Resub_Final.pdf |
| 3. Research Strategy* | 1242-Research_Strategy_Rv1.pdf |
| 4. Progress Report Publication List | 1243-PublicationListProgressReport.pdf |
| **Human Subjects Sections** | |
| 5. Protection of Human Subjects | 1246-Prot_Human_Subjects_Model.pdf |
| 6. Inclusion of Women and Minorities | 1247-Inclus_Women_Minorities_Model.pdf |
| 7. Inclusion of Children | 1248-Inclusion_of_Children_Model.pdf |
| **Other Research Plan Sections** | |
| 8. Vertebrate Animals | 1249-Vertebrate_Animals_Model.pdf |
| 9. Select Agent Research | |
| 10. Multiple PD/PI Leadership Plan | |
| 11. Consortium/Contractual Arrangements | |
| 12. Letters of Support | 1250-LettersofSupport.pdf |
| 13. Resource Sharing Plan(s) | 1251-RESOURCE_SHARING.pdf |
| **Appendix (if applicable)** | |
| 14. Appendix | |

The reviewers of the initial submission made a number of helpful suggestions. In response the proposal has been re-focused on developing and testing models for listeners with and without hearing loss, using masking paradigms (Aims 1 & 2) and exploring realistic sounds with steep spectral slopes (Aim 3). Signal-processing applications for which pilot data are not yet available have been removed.

***Testing of sensorineural hearing loss****:* Each subject will be characterized by an audiogram, bone conduction, DPOAEs, tympanograms, and speech testing, as suggested. We will additionally determine whether individuals use energy or envelope cues for masked detection at different frequencies in Aim 1, and will include all of this information in individualized models that will be tested with the experiments in Aims 2 & 3. We have modified the description of our listeners to avoid the use of "categories" for hearing loss.

The ***need to consider individual differences***: Our recent work (Mao et al., JARO, re-submitted, should become available during the course of this review) includes detailed analysis and modeling of the results for each individual, and we will continue this approach. Although a uniform amount of hearing loss is included in the illustrations in the proposal (due to space limits), the amount of inner and/or outer hair cell loss in the auditory periphery model can be customized for each listener and can vary as a function of frequency.

***Learning effects*** will be controlled for by carefully randomizing and interleaving stimuli for different conditions.

***Choice of testing material for speech:*** We have changed our planned test materials to use the fricative consonants from the study of Li et al. (2012), which provides a strong normative dataset.

***Generalization of neural-fluctuation cues across condition:*** It is correct that the "size" of the fluctuation cue varies with notch frequency and with CF and hearing loss, due to changes in peripheral bandwidth. Because our peripheral model captures these effects they can be systematically explored. These effects were included in the predictions of psychophysical thresholds as a function of frequency and notch width made with the model. Our preliminary results (Carney & Varner, 2015) successfully predicted notched-noise detection thresholds, including trends with target frequency and notch width that match human studies. We plan to carefully test the hypothesis by predicting thresholds across several studies that have manipulated various parameters of the notched-noise stimulus. We have clarified the point that indeed, the amplitude of neural fluctuations is relatively robust to level for masking paradigms, but it is sensitive to level in other paradigms (e.g. for pinna cues). These differences, which are due to peripheral response properties, are useful in testing the hypothesis that the neural fluctuations are involved in coding.

**Empirical vs. Modeling Results:** We have made each set of pilot data clear as to whether it is modeled or recorded from neurons. In general, we are not proposing any physiological studies in impaired animals, so all results related to hearing loss in the proposal are from models, and will be tested against listeners' results.

***How will the power-spectrum model be implemented to provide a fair comparison?*** The results of Lentz et al. (1999) definitively rule out the power spectrum model for the notched-noise task. Therefore, the power spectrum model will not be implemented and compared to the neural fluctuation model in the proposed work. Instead, the neural fluctuation–based model will be tested against actual human detection thresholds across many different experimental manipulations, including those in the Lentz et al. study.

***Spontaneous rates***: The pilot work focuses on high-spontaneous rate AN fibers, which explain a wide range of results, including at supra-threshold levels. We will explicitly add the other spontaneous-rate groups to test their contributions. Adding these fibers may make only small quantitative changes, but this should be tested.

***IC model***: Since the previous submission we have developed a model for the "hybrid" modulation transfer function (Kim et al., ARO 2015b). Our IC models now successfully describe the three major modulation types that are approximately equally represented in the IC. We have clarified the potential role of the DCN model in future work. We have also clarified how neural rate variance will be included. The potential effect of covariance will be tested using model computations; in our experience, it is difficult to empirically assess covariance even with simultaneously recorded neurons on a single tetrode, but this issue can be explored computationally.

**Modulation bands, and IC vs. Cortical modulation tuning:** It is intriguing that at the level of the midbrain, there are relatively few neurons *tuned* to low modulation frequencies. One has to presume that low-frequency *fluctuations* in the midbrain responses drive cortical neurons – this could be a future topic. Note that the plots for pinna cues do show strong modulations at relatively high modulation frequencies (due to broader bandwidths), but the key is the *contrasts* in the modulations at frequencies to which most IC cells are tuned.

**Pinna Cues:** It is true that these spectral cues primarily provide information about the elevation of sounds. This cue must be present binaurally to achieve this effect (monaural cues "collapse" into the head).

**Specific Aims**

This proposal focuses on the role of neural-fluctuation cues in two classic masking paradigms: notched-noise and forward masking. We will also investigate how these cues underlie coding of spectral slopes, which are a key feature of pinna cues (a.k.a. spectral cues) for localization and externalization of sounds, and of fricative consonants. Preliminary modeling and physiological studies suggest that fluctuations of the instantaneous rates in the auditory periphery, and the sensitivity of midbrain neurons to these fluctuations, are critically important in masked detection and spectral coding. Recent experimental results show that these cues are vulnerable to hearing loss. These new results resolve a number of long-standing questions in the field related to masking, and provide a strong alternative to the widely used power-spectrum and envelope power spectrum models for masking.

*Contrasts* in the fluctuations across neural frequency channels and across time provide a code for complex sounds in quiet and noise that is robust across a wide range of sound levels. Models based on this cue outperform models that focus on other diotic or dichotic rate (or energy) and fine-structure timing cues (Mao et al., 2013; Mao and Carney, 2014a). Envelope features have previously been identified as a cue for monaural tone-in-noise detection in narrowband noise at high frequencies (Richards, 1992). We found that envelope-related cues also dominate diotic detection for low-frequency tones in both wideband and narrowband maskers (Mao et al., 2013). Furthermore, this cue predicts diotic 500-Hz detection results for listeners with normal hearing or mild loss, but listeners with greater hearing loss at 500 Hz transition to using energy cues (Mao et al., 2015). In addition, interaural envelope differences are more successful than the classical ITD and ILD cues (or their optimal combination) in explaining binaural detection (Mao and Carney, 2014a,b; Mao et al., 2015). *These results motivate our proposed re-examination of classic masking paradigms and spatial cues in terms of neural-fluctuation cues*. The new models developed here will be tested in three ways: i) by extending the detection results to a wider range of target frequencies, ii) with psychophysical experiments that manipulate the fluctuation cues in masking tasks, and iii) with physiological recordings in the midbrain of awake rabbit.

**Aim 1:** Identify cues used for detection in noise across a range of frequencies, to develop tailored models for individual listeners. **We will test the hypothesis that listeners transition from using envelope to energy cues at frequencies where they have elevated thresholds due to significant inner and/or outer hair cell dysfunction.** In our recent results, we identified listeners who transitioned from using envelope to energy cues for masked detection of a low frequency. Using detection tasks with fixed and roving-level narrowband noise maskers we will determine, in individual listeners, whether they use one cue at all frequencies, or whether they use different cues at different frequencies, depending on hearing threshold in each frequency range. The results will provide the information required to make individualized models for detection and for coding of complex sounds in noise. Our detection model based on neural fluctuation cues will be tested with physiological recordings in awake rabbit using similar tone-in-noise stimuli.

**Aim 2:** Develop and test models for two classic masking tasks used in listeners with and without hearing loss. **We will test the following hypotheses: i) Simultaneous notched-noise masking thresholds can be explained by neural-fluctuation cues, an alternative to the power-spectrum model. ii) Results of forward-masking paradigms are better explained by neural-fluctuation cues than by current temporal processing models.** Extensive psychophysical results available for these tasks, for listeners with and without hearing loss, will be mined to test the model. The role of neural-fluctuation cues will be directly tested by recording responses from midbrain neurons that are sensitive to envelope features. Results for the individuals characterized in Aim 1 and manipulations of fluctuation cues in novel psychophysical tasks will be pursued.

**Aim 3:** Spectral slopes are an important feature of many complex sounds. We have selected two classes of sounds with steeply sloping spectra to extend our study of neural fluctuations to cues for localization and communication. **We will test the hypothesis that the spectral slopes in pinna cues and fricative consonants are represented by the profiles of neural fluctuations set up in the periphery. Further, we hypothesize that interaural differences in neural fluctuations code elevation.** This Aim will include further development of our binaural model based on interaural envelope differences. The model will be tested using existing reports of psychophysical sensitivity to these cues and by physiological recordings in the midbrain.

**Significance**

The goal of our work is to develop models that describe auditory processing of sounds in real-world environments, which often include unwanted noise. Beyond understanding the impressive ability of the normal auditory system to extract information from fleeting signals in noisy environments, we want to better understand how sensorineural hearing loss interferes with this ability.

It is often asserted that the envelopes, or slow amplitude fluctuations, of sounds are essential for carrying information in complex stimuli, such as speech, music, and environmental sounds (review: Joris et al., 2006). Our recent work supports this claim, and highlights the important role of envelope-related cues in basic detection tasks. In general, narrowband noises have large, low-frequency fluctuations that are well coded by the rate fluctuations of auditory-nerve (AN) fibers and brainstem cells. Midbrain neurons are very sensitive to these fluctuations, especially in the ~50-250 Hz range of modulation frequencies (Joris et al., 2006; Nelson & Carney, 2007). Addition of a tone, which has a flat envelope, to a narrowband masker reduces the fluctuations in the stimulus envelope and provides a cue for detection (Richards, 1992). Wideband maskers have a broader modulation spectrum with a flatter envelope. However, an AN fiber's response to a wideband sound is most strongly influenced by a narrow band of frequencies near the fiber's CF. Thus, AN responses, even for wideband stimuli, are narrowband in nature and are associated with large low-frequency fluctuations in instantaneous rate. We have shown that addition of a tone to a wideband masker reduces AN rate fluctuations for fibers tuned near the tone frequency. This reduction provides a cue that explains detection results in reproducible-noise for both diotic and dichotic tasks (Mao et al., 2013; Mao & Carney, 2014, 2015). Interestingly, this *neural-fluctuation* cue for masked detection is particularly strong, much stronger than the more familiar diotic fine-structure cues and dichotic ITD cues, especially at low frequencies where AN tuning is relatively sharp (and where fine-structure cues are typically assumed to dominate.) Also, the most informative changes in neural fluctuations for the masked-detection task occur in the heart of the modulation-tuning range of the midbrain (Mao et al., 2013; Mao & Carney, 2014, 2015).

The CNS does not have direct access to the envelope cues in an acoustic stimulus. Rather it receives neural rate fluctuations that are initially established in the instantaneous-rate responses of AN fibers. These fluctuations are not only influenced by tuning, but also by several nonlinear AN response properties. Ultimately, the amount of rate fluctuation in a given frequency channel (for monaural or diotic tasks), and the amount of fluctuation in the interaural envelope differences (for dichotic tasks), is what "drives" midbrain neurons, which are tuned for amplitude fluctuations (Joris et al., 2006). At the level of the midbrain, the *contrast* in the amount of fluctuations across frequency channels sets up a robust representation of complex sounds across the population. This population response is then the input to higher processing centers.

We refer to the stimulus-evoked changes in the fluctuations of the instantaneous rate of AN fibers as "neural-fluctuation cues." Note that these cues cannot in general be observed in the envelope of the stimulus; rather, they are a result of peripheral filtering (Fig. 1) and are further influenced by nonlinear transformations, such as saturation, synchrony capture, and synaptic adaptation (Fig. 2). These cues are often counter-intuitive, and they play a surprising role in setting up codes at higher stages of the auditory CNS. Figure 2 illustrates a case for which the neural fluctuations cues are "opposite" those that would be expected based on the power-spectrum model. Recent modeling and physiological results suggest that neural-fluctuation cues are important in a number of classical tasks that have generally been analyzed and interpreted in terms of energy-related cues, such as detection in wideband noise and in notched-noise. Furthermore, an established failure of the

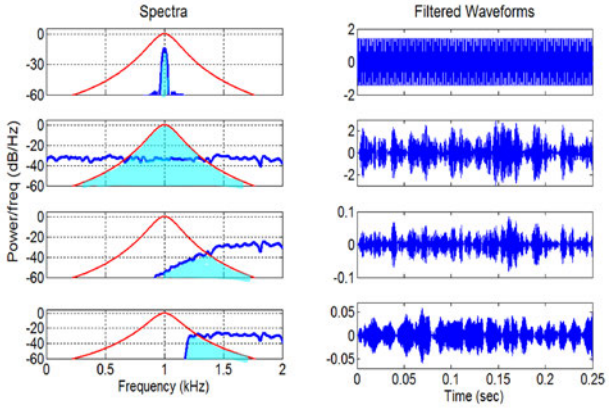


Figure 1 – Schematic illustration of stimulus spectra, simple peripheral filters (red) and the "effective" bandwidth of responses (cyan). Narrow effective bandwidths yield strong low-frequency fluctuations in the filter response. *a*) Responses to pure tones elicit minimal neural fluctuations, except at onset and offset.
*b*) The neural response to wideband noise is determined by the filter bandwidth. *c*) The response of a filter to a sloping spectrum is effectively narrower. *d*) Responses of filters that partially overlap spectral edges can have even narrower bandwidths. Fluctuations in filter responses are further shaped (sometimes dramatically) by peripheral nonlinearities (Fig. 2).

power-spectrum model is that masked-detection thresholds are not affected by either roving- or equalized-level paradigms that render the energy cue unreliable, either for standard noise maskers (*e.g.* Kidd et al., 1989; Richards, 1992; Henning et al., 2005), notched-noise maskers (Lentz et al., 1999), or in forward-masking paradigms (Jesteadt et al., 2005).

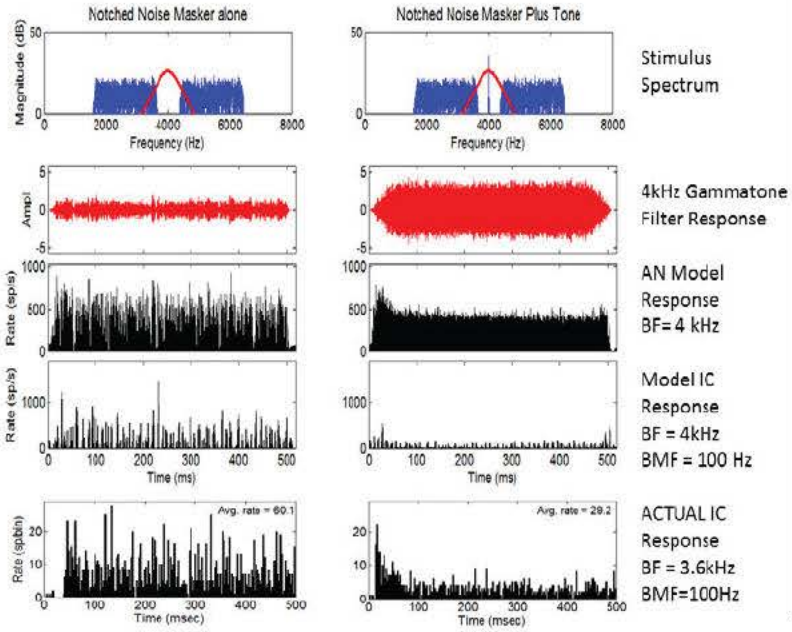


Figure 2 – Schematics and preliminary results for detection in notched-noise. *Top*: Spectra for a notched-noise masker centered at 4 kHz (notch width Δ=0.1; Patterson, 1976). A 4th-order gammatone filter centered at 4 kHz is superimposed; filter responses are shown in red. The power-spectrum model is based on these filter responses, which are clearly larger for the stimulus with added tone (right). Model AN responses illustrate that the difference in amplitude is largely eliminated by peripheral nonlinearities, such as saturation. Importantly the AN response for the masker alone (left) contains strong fluctuations because it is driven by the narrow band(s) of noise near the edges of the notch within the filter skirts (Fig. 1). Most IC cells are sensitive to input fluctuations with best modulation frequencies (BMFs) in the 50-250 Hz range. A model IC neuron's response to the masker alone is brisk, but it is strongly reduced by the added tone. *Bottom*: responses of an *actual* rabbit IC neuron recorded in our lab, with BF near 4 kHz.

In the previous grant cycle, we showed that contrasts in neural-fluctuations, which are robust to the roving-level paradigm, explain a detailed set of simultaneous diotic and dichotic masked-detection data at 500 Hz, for both narrow and wide-band reproducible maskers, in listeners across a range of ages and with normal and mild hearing loss (Mao et al., 2013, in review; Mao & Carney 2015). Listeners with the most hearing loss at 500 Hz shifted from envelope-related cues to energy cues for detection. Here we will determine whether these listeners make a general transition, and use energy-related cues at all frequencies, or whether individual listeners use different cues at different frequencies. The use of envelope vs. energy cues in individuals can be efficiently determined by comparing thresholds for fixed vs. roving-level detection tasks (Mao et al., in review).These results will provide information used to tailor our masking model to individual listeners.

In the proposed work we will also extend this general framework to include a series of tasks that involve steep spectral edges or slopes and/or strong temporal fluctuations. We illustrate below that spectral edges or steep slopes, together with AN tuning, result in strong instantaneous rate fluctuations for neurons tuned near spectral slopes. These neural fluctuations are influenced by addition of tones (in detection tasks) (Figs. 2,3), by the temporal structure of stimuli (in forward-masking tasks), by the spectral slopes of fricative consonants (Fig. 4) and pinna cues (Fig. 5). We will also study tasks that combine these features, such as forward masking with notched-noise (Oxenham & Shera, 2003; Oxenham & Simonson, 2006). These cues are robust across sound level in masking tasks, but can be sensitive to level for spectral coding (see below).

*Although we are pursuing a diverse set of stimuli and tasks, they are all linked by a common neural mechanism and can be explored within a single modeling framework: all of the tasks in this proposal involve generation of strong instantaneous rate fluctuations in the auditory periphery in a frequency range to which midbrain neurons are sensitive.* Performance in all of these tasks is adversely affected in listeners with sensorineural hearing loss. Deficits in these tasks are consistent with our model, which depends upon peripheral nonlinearities such as saturation, cochlear amplification and synchrony capture, all of which are affected by sensorineural hearing loss. Changes in cochlear amplification, driven by the outer hair cells, affects tuning bandwidth, which indirectly affects the neural fluctuation cues. Damage to inner hair cells that results in reduced sensitivity of these cells will reduce synchrony capture (Zilany and Bruce, 2006, 2007), which indirectly affects the neural fluctuation cues. Enhanced envelope coding by AN fibers in ears with sensorineural hearing loss (Henry et al., 2014) also influences these results and is included in our AN model.

Our approach is not only guided by properties of AN responses, but also by population responses at the level of the midbrain (inferior colliculus, IC). Nearly all IC cells show some form of sensitivity to stimulus modulations (*e.g.* Langner & Schreiner, 1989; Krishna & Semple, 2000; Nelson & Carney, 2007, Kim et al.,

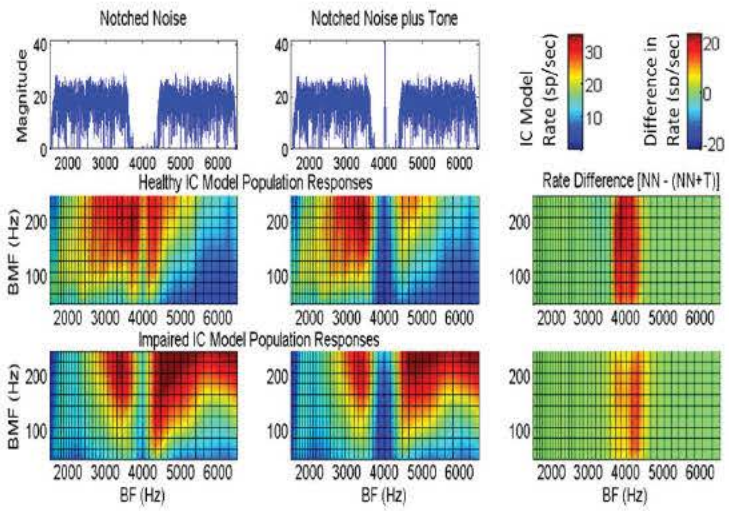


Figure 3 - Model IC Population responses to a notched-noise masker without (*left*) and with (*middle*) an added tone centered in the notch. The average rate of the responses in Fig. 2 is one "pixel" in these images. Healthy (*middle row*, $C_{OHC}$=1 in Zilany et al., 2014) and impaired (*bottom row*, $C_{OHC}$=0.3). *Right*: The difference between responses (spikes/sec) shows that cells with BFs near the tone frequency and with best modulation frequencies (BMFs) in the heart of the IC tuning range are informative for tone detection. The difference is reduced for impaired responses (bottom right). AN model: Zilany et al., 2014; IC model: Nelson & Carney, 2004, with a more flexible modulation filter (Mao et al., 2013). The range of BMFs shown (50-250 Hz) are those most commonly observed in the IC.

2015b). However, these cells are not directly driven by the stimulus envelope, but rather by the neural fluctuations of their inputs. Thus their responses can be counter-intuitive: nonlinear response properties in the auditory periphery, such as saturation, synchrony capture, and adaptation have strong influences on AN rate fluctuations (Fig. 2). These AN properties shape the neural fluctuations that drive the midbrain *via* intermediate brainstem nuclei. Contrasts in the amplitude of rate fluctuations across the AN population set up robust contrasts across the population midbrain response, especially near the spectral edges (Fig. 3). These contrasts are absent from simple filter-based models for auditory processing. This fact motivates our use of computational models to re-examine common test paradigms that have been largely interpreted based on the concept that the *energy* in the response of peripheral filters is what "drives" the CNS. For example, the power-spectrum model (Green & Swets, 1966) and related models, such as the optimum channel model (Durlach et al. 1986), assume that energy in responses of bandpass peripheral filters is the initial representation of stimulus spectra. Addition of different types of channel noise and/or strategies for combining information across channels has dominated work on these models. Several lines of evidence refute the power-spectrum model, including tasks with equalized- or roving-level stimuli (*e.g.* Spiegel & Green, 1982; Kidd et al., 1989; Lentz & Richards, 1997; Lentz et al. 1999; Jesteadt et al., 2005, Henning et al., 2005, and many others). However, no clear alternative to the power-spectrum model has emerged. Alternatives, such as template-matching models, are unable to explain detailed performance for masked detection (*e.g.* Davidson et al., 2009b). We propose that a model based on neural fluctuations provides a successful alternative. Qualitatively, the neural fluctuation model addresses major short-comings of the power-spectrum model, but a thorough and quantitative investigation is required.

In addition to the notched-noise paradigm, we will study forward masking. Straight-forward analyses of AN responses do not explain forward masking (Relkin & Turner 1988). However, physiological responses of IC cells can explain the time course and rate of growth of forward masking (Nelson et al., 2009). Because that work did not directly relate modulation tuning of neurons with their responses to forward-masked stimuli, we will extend our work in that direction. More intriguing, though, is the relation between simultaneous notched-noise masking and forward masking with notched noises. Differences in the filters derived with these two approaches have fueled considerable controversy; however, both sets of data have been interpreted using power-spectrum based approaches. We believe that a fresh approach based on neural-fluctuation cues will resolve this controversy and provide a single framework that explains both sets of results. Our experience with physiological studies of modulation processing and amplitude-modulation forward masking will be an advantage here (Wojtczak et al., 2011). Figure 2 illustrates that a notched-noise masker elicits neural fluctuations similar in nature to responses to an amplitude-modulated signal, and that detection of a tone in notched noise could be considered a neural-fluctuation *suppression* task. Similarly, the notched-noise forward-masking paradigm must be considered as a "modulation" (or neural-fluctuation) forward-masking task. Amplitude-modulation forward masking is a powerful effect with a long time course (Wojtczak & Viemeister, 2005), but it can be explained based on the response properties of IC cells with bandpass modulation transfer functions, followed by a contrast-sensitive mechanism at higher-levels (Wojtczak et al., 2011). Based on our experience with the AM forward-masking paradigm, we are optimistic that we can decipher the role of

fluctuations in the notched-noise forward-masking paradigm. The AN model that will be used here (Zilany et al., 2014) can be “impaired” (Zilany and Bruce 2006, 2007), to include the AN temporal properties important for studying the forward masking task with SNHL (Scheidt et al., 2010).

Another important, related line of work has explored the roles of inherent modulations in maskers of different bandwidths (e.g. Bos & deBoer, 1966; Dau et al., 1996, 1997a,b). More recently, Dau and his colleagues have pursued an envelope power-spectrum model that incorporates the properties of modulation filters (Jorgensen & Dau 2011; Jorgensen et al., 2013). One challenge for this approach is that while roving- or equalized-envelope modulations do affect listener performance, the effects cannot be explained by the envelope power spectrum (Nelson and Carney, 2006). Similar to the power-spectrum and profile-analysis models, the envelope power-spectrum model assumes a relatively simple peripheral filterbank as the first level of processing, followed by adaptation loops that enhance modulation (Dau et al., 1996). However, many stimuli saturate AN responses and reduce the neural fluctuations (see Fig. 2), especially for the *majority* of AN fibers, the high-spontaneous-rate fibers, which in the healthy ear have low thresholds. These saturated AN responses are often omitted from models for spectral coding because of their limited dynamic range, but we show they are critical in developing contrasts in neural fluctuations across the periphery, and ultimately at the level of the midbrain. Inclusion of peripheral nonlinearities and their strong effect on neural fluctuations in the AN population response is a critical component of our new model. Additionally, changes in these properties with SNHL (Henry et al., 2014) are included in the model predictions.

A classical test for computational auditory models is to challenge them to predict psychophysical results (*e.g*. Siebert,1965, 1968; Colburn, 1973, Heinz et al., 2001a,b,2002; Tan & Carney, 2005, 2006; Davidson et al., 2009; Nelson & Carney, 2006, many others). Our recent work follows in this tradition, by testing models for diotic and dichotic detection of low-frequency tones in noise (Mao et al., 2013; Mao & Carney, 2014, 2015). We have also extended the application of computational models to predict detailed masking results for listeners with sensorineural hearing loss (Carney et al., 2013b; Mao et al., in review). The proposed work will push our models much further by attempting to predict a wide range of masking paradigms and other stimuli that elicit interesting neural fluctuations. A goal of this work will be an updated computational AN model appropriate for human that is consistent with a range of masking results. For example, a key challenge for the proposed work is a model that can describe both Glasberg & Moore’s (1990) notched-noise filters and Oxenham & Shera’s (2003) much sharper forward-masked notched-noise filter estimates.

An important aspect of the neural-fluctuation cue described here is that it provides insight into deficits associated with sensorineural hearing loss. Contrasts in the neural rate fluctuations across frequency channels are reduced by changes in tuning and by changes in other nonlinearities that occur in the impaired ear, associated with both inner and outer hair cell dysfunction. Computational models that include peripheral nonlinearities (*e.g*. Zilany et al., 2014) and central models that include sensitivity to individual and/or combined cues (Nelson and Carney, 2004; Mao et al., 2013, Mao and Carney, 2014, 2015) provide tools for better understanding the importance of neural-fluctuation cues in a range of listening tasks. The ability to explicitly impair nonlinearities associated with hair-cell transduction and cochlear amplification in the peripheral model (Zilany and Bruce, 2006, 2007) and then explore the implications for higher-level neural processing is a key tool for this research program (see Figs. 3-5).

Another important test for models based on neural processing is the direct comparison to neural recordings. For several years our system for these comparisons has been the awake rabbit midbrain (Kuwada et al., 1987) which allows the study of responses to controlled diotic and dichotic acoustic stimuli. Our approach for relatively long-term recordings from single neurons using implanted tetrodes enables collection of responses appropriate for comparison to psychophysical paradigms (*e.g*. Carney et al., 2014). Most midbrain neurons are sensitive to envelope features, as characterized by modulation transfer functions (Langner & Schreiner, 1989; Krishna & Semple, 2000; Nelson & Carney, 2007). The *combination* of their frequency tuning and envelope tuning is essential for understanding their responses to complex sounds (e.g. Batra et al., 1989,1993; Carney & McDonough, 2012; Carney et al., 2013a,c). In the proposed work, key model results will be directly tested against recordings from midbrain neurons (see Fig. 2). Recent modeling work has extended our model for bandpass MTFs to include band-reject and ‘hybrid’ MTFs which combine features of bandpass and band-reject MTFs (Kim et al., 2015b), thus all major classes of IC MTFs are now included in our population model.

Finally, we propose to extend this effort to neural-fluctuation cues associated with spectral slopes and

notches. These spectral features occur in many signals, including fricatives, which are characterized by steep spectral slopes (Fig. 4) (Heinz & Stevens, 1961). Consonants with similar modulation spectra are most readily confused (Souza & Gallun, 2010; Gallun & Souza, 2008). Steep spectral slopes are also a hallmark of pinna cues that provide information about elevation and externalization (*e.g.* Hartmann & Wittenberg, 1996; Kulkarni & Colburn 1998). The neural coding of these cues is a mystery: AN tuning is not sharp enough at high CFs to provide a representation of the spectral peaks and notches in terms of discharge rate, and phase-locking is decreased at high frequencies. Modeling results (Fig. 5) and pilot data (below) suggest that responses of IC neurons that are sensitive to neural fluctuations encode the steep spectral slopes in pinna cues.

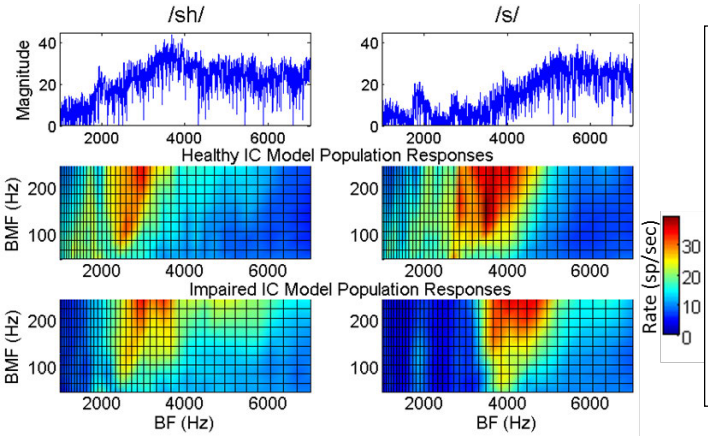


Figure 4 – IC Model responses to two fricative consonants spoken by an adult male. Healthy model responses (*middle*) are strongest near the steepest spectral slopes (cf. Fig. 1). Impaired responses (*bottom*, $C_{OHC}$=0.3, Zilany et al., 2014 AN model) are shifted towards the spectral peaks, and are more similar across the two stimuli. Amplification of the stimuli at the input to the impaired model does not restore the healthy pattern, but instead causes an overall reduction of the population response due to saturation (not shown). Responses here are for IC models with bandpass MTFs.

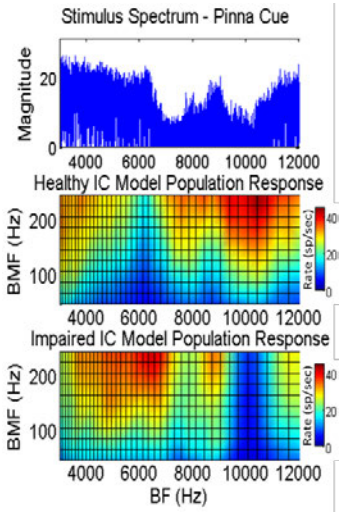


Figure 5 – *Top*: Wideband noise convolved with head-related impulse response (Qu et al., 2009) for the left ear, for a source at 60°az, 10°elev, 40 cm distance, and 45 dB SPL. The healthy IC model (*middle*) has the strongest responses where spectral *slopes* are steepest, and reduced responses near spectral peaks (*e.g.* 6 kHz) due to rate saturation (This simulation is for the low-threshold high-spontaneous-rate AN fibers, which are the majority of AN fibers; dynamic ranges would be extended for medium and low spont fibers, but strongest *fluctuations* would still occur at slopes). The impaired model (*bottom*), with higher thresholds and thus less saturation, has strongest responses near the spectral peaks.

Spectral slope features are not only interesting but are important cues to pursue, especially in the context of SNHL listeners. Many of the spectral slope/notch cues occur at mid to high frequencies, which are most affected by SNHL. Simply amplifying these frequency regions will *not* restore cues that are effected by peripheral tuning and nonlinear response features. Because of the importance of these cues for conveying consonant distinctions and for externalizing and localizing sounds (which is involved in extracting them from noise in real-world settings), we believe this effort is timely and highly significant.

Upon completion of the proposed work we will have a better understanding of the neural coding and processing mechanisms underlying a wide range masking paradigms. This work will provide a new and general framework for interpreting a substantial literature of masking and spectral-shape discrimination results. We believe a critical re-examination of the power-spectrum and related models, given our preliminary modeling and physiological results (together with psychophysical results already in the literature) will provide a significant contribution to hearing science. We will also extend this framework to include coding of dichotic spectral features at high frequencies. *Note: This proposal intentionally omits investigation of low-frequency dichotic cues for sound localization. The models described here are currently being applied to those issues in an independent collaboration directed by Kuwada and Kim (see Biosketch).

**Innovation**

Aim 1 employs classical techniques, but asks a novel question: We now know that listeners with significant hearing loss change strategies in a basic detection task, using energy rather than envelope cues for detection of 500-Hz tones in noise. But when they change strategies, do they do so across all frequencies, or do individual listeners use different strategies at different frequencies, adopting new strategies in different frequency ranges as hearing loss progresses? If so, then signal-processing strategies may also have to vary

across frequencies for an individual listener. We believe that we can not only answer his question, but provide a technique for efficiently characterizing the cues that an individual listener uses across frequencies.

The innovation in Aim 2 is the realization that the structure of stimuli used in classical masking tasks creates neural-fluctuation cues at modulation frequencies that are appropriate for processing in the midbrain (*e.g*. Figs. 2,3). The innovation in Aim 3 the recognition that the spectral slopes of pinna cues and fricative consonants generate neural fluctuations in the range of IC modulation tuning (Figs. 4,5). Also, because pinna cues differ across ears, these stimuli set up unique interaural differences in fluctuations that code sound elevation and perceived externalization of sounds. Thus, the innovations here are mainly conceptual. No new techniques are involved or required in the proposed experiments; classical psychophysical testing procedures, physiological recordings, and computational modeling strategies will be used to test innovative models for auditory coding and processing.

**Progress Report** The goals and progress during the first cycle of this grant are presented below.

**Aim 1.** ***We hypothesized that a phenomenological model could capture the dominant features of IC responses to complex sounds, including the interactions of stimulus features.*** We have created physiologically-based multi-stage models for diotic and dichotic masked detection. We showed that these models perform as well as abstract signal-processing based models in explaining listeners' responses (Mao & Carney, 2015). The proposed 2D display for the model IC population response that includes both audio- and modulation-frequency axes has been developed and was used for the illustrations included in this proposal (*e.g*. Figs. 3-5). Model responses have been compared to IC responses in awake rabbit for tone-in-reproducible-noise stimuli (Zilany et al., ARO 2011) and for modulation-masking stimuli (Zilany et al., ASA 2011). Manuscripts for these studies are currently in preparation.

In related work, the model developed through this grant was applied to the problem of coding the distance of modulated sounds in reverberant and anechoic spaces (Kim et al., 2015a). In collaboration with Kuwada, Kim, & Zahorik (see Biosketch), we are testing the binaural properties of the model with their recent physiological and psychophysical results for modulated stimuli in 3D space. Most recently, we have extended the IC model for sensitivity to AM stimuli to include the three most common MTF types: Band-enhanced, band-suppressed, and combined or 'hybrid' MTFs (Kim et al., ARO 2015b; see model diagram below).

**Aim 2***. Two hypotheses were tested: 1. The physiological representation at the level of the midbrain of both energy and temporal cues in tone-plus-noise stimuli will allow detailed and accurate predictions of the performance of human listeners in diotic (*$\mathbf{N_0S_0}$*) and dichotic (*$\mathbf{N_0S\pi}$*) masked-detection tasks with reproducible noise. 2. The detailed detection performance of listeners with sensorineural hearing loss will differ from that of listeners with normal hearing.*

We created a model that optimally combined energy, fine-structure, and envelope cues and showed that this model could predict essentially all of the predictable variance in diotic detection of low-frequency tones in noise (Mao et al., 2013). *We showed that a model based on interaural envelope-slope differences outperformed the classic ITD and ILD cues*, as well as optimal combinations of these cues, in predicting detailed dichotic detection in noise results (Mao & Carney, 2014). We are also applying these models to related sets of detection results for rabbit and parakeet (Carney et al., in preparation.)

We have completed testing a group of listeners with mild and moderate sensorineural hearing loss, as well as older listeners with normal hearing, for diotic and dichotic detection of 500-Hz tones in narrowband and wideband reproducible-noise maskers. Analyses of these results show that, unlike young listeners with normal hearing, older listeners with or without hearing loss apparently do not use temporal fine-structure information for the diotic masked-detection tasks. Furthermore, the value of ITD and/or ILD cues in explaining their dichotic masking results is minimal. Most of these listeners with normal or mild hearing loss depend upon envelope cues for both diotic and dichotic low-frequency masked-detection tasks. Listeners with the most hearing loss at the 500-Hz target frequency show reduced use of envelope cues and turn instead to energy cues. Analyses were done on a listener by listener basis. These results are currently in re-review at JARO (accepted with minor revisions) (Mao et al., in review).

Physiological responses to 500-Hz tone-in-noise stimuli are currently being analyzed. A challenge for that work is the difficulty of recording from a significant number of neurons tuned very close to 500 Hz. However, we realized that we could take advantage of the result that envelope-related cues dominate our psychophysical detection results. We are thus "shifting" the reproducible noises along the frequency axis to determine the

constancy of the reproducible-noise detection patterns with center frequency. Early results in listeners with normal hearing suggest that the response patterns are conserved. This strategy provides a flexible tool for physiological studies because both target and reproducible maskers envelope cues can be shifted to a cell's BF. In addition, by shifting our stimuli along the frequency axis we can probe the use of envelope vs. energy cues in listeners with SNHL as a function of frequency and hearing loss (Aim 1 of current proposal).

**Aim 3.** ***Hypothesis: Performance in amplitude-modulation detection tasks with frozen AM maskers can be predicted for listeners with and without hearing loss based on model IC responses.***

We have completed both of the proposed experiments of masked modulation detection using reproducible modulation maskers in listeners with sensorineural hearing loss and older listeners with normal hearing. These results are being compared to a companion set of results for young listeners with normal hearing (supported by DC01641). Results suggest that detailed performance across reproducible maskers can be predicted based on neural fluctuation cues using our computational models for peripheral and midbrain tuning. For the first experiment, masked modulation of 4-kHz tone carriers was detected. As hypothesized, these results did not vary significantly as a function of hearing loss because the narrowband stimuli were not affected by changes in peripheral tuning with SNHL. In contrast, results for the 2$^{nd}$ experiment, in which listeners detected SAM modulation of reproducible noises with bandwidths twice the critical band, centered at 4 kHz, varied significantly across listeners. This variability was predicted, as changes in peripheral tuning influence neural fluctuations for stimuli wider than the filter bandwidth. A manuscript describing these results is in preparation.

The results of experiments from the previous grant cycle all contribute to the focus of the current proposal on neural fluctuation cues. Motivated by these results, during the last cycle we began to apply the models developed in this project to a signal-processing strategy that attempts to recreate the contrast in neural envelope cues across the midbrain population (Rao & Carney, 2014, IEEE Transactions in BME; Carney & Schwarz, IHCON 2014). We are currently pursuing that work as part of an STTR project.

**Experimental Design & Approach**

Each Aim below includes Preliminary results, with proposed work that includes 1) Modeling, 2) Physiological and 3) Psychophysical experiments. General methods that apply to all aims are presented first.

**1) Modeling**: Computational models will be used to explore the representation of the stimuli proposed for all tasks. Our current computational model consists of the Zilany et al. (2014) model for AN fibers. The results shown here are for high-spontaneous-rate fibers (a conservative approach with respect to dynamic range), but we will also explore the contributions of medium- and low-spontaneous rate fibers. The AN model is followed by monaural or binaural single-frequency inhibition-excitation (SFIE) models for band-enhanced modulation tuning (aka bandpass; Mao and Carney, 2015). We have recently extended the model to describe band-suppressed MTFs (aka band-reject, Carney et al., 2015; Kim et al., 2015a) and hybrid MTFs, which have both enhanced and suppressed rates at different modulation frequencies (Kim et al., 2015b) (Fig. 6). Inhibitory connections within the IC can explain all three MTF types, which are approximately evenly distributed in the ICC (Kim et al., 2015b).

When comparing model results to normal psychophysical data from the literature, healthy parameter values will be used. When comparing to results of our listeners with hearing loss, the parameters will be tailored for each individual as a function of frequency by varying the status of inner and outer hair cells(Zilany and Bruce, 2006, 2007), based on both audiometric thresholds and information from the presence/amplitude of DPOAEs.

Signal detection theory will be used on model responses to estimate psychophysical thresholds that can be quantitatively compared to psychophysical responses using (Siebert, 1965, 1968; Heinz et al. 2001a,b, 2002, Tan and Carney, 2005, 2006; Carney and McDonough, 2012). The estimated model thresholds can be directly compared to psychophysical results. These calculations involve finding the sensitivity of each model neuron by computing a partial derivative of the response as a function of the stimulus parameter of interest, normalizing the difference by an estimate of variability, and then combining the sensitivity across the population of neurons. Typically Poisson variance is assumed, or variance that is proportional to, but not equal to the mean (e.g. Hancock and Delgutte (2004) showed that a constant of proportionality between the variance and mean rate of approximately 0.8 described the responses of a large set of IC neurons.) The combination of responses across the population can assume statistical independence across the neurons, or the effect of different degrees of covariance across neurons can be tested explicitly. Reponses can be combined across model neurons of one type (e.g. across the bandpass cells in Fig. 3) or across combinations of the three MTF types, which are

represented approximately equally in the IC (Kim et al. 2015b). In general, although there are many variations of the model to explore, it is the trends in model thresholds as a function of stimulus parameters that are of most interest to compare to the psychophysical thresholds. Some model structures or assumptions result in trends that cannot be reconciled with the data; these results exclude these models. Pilot results for predictions of thresholds of a basic model based on bandpass IC neurons have appropriate trends across notch width and target frequency (Carney and Varner, 2015 ARO; model responses were directly comparable to thresholds reported in Patterson 1976), suggesting that this general model structure is worth pursuing further.

The current model for IC responses (Fig. 6) should be adequate and appropriate for the proposed Aims; however, in another project (DC001641) we are exploring nonlinear response properties of IC neurons to stimuli with large modulation depths. As that work develops we will modernize the IC model used here.

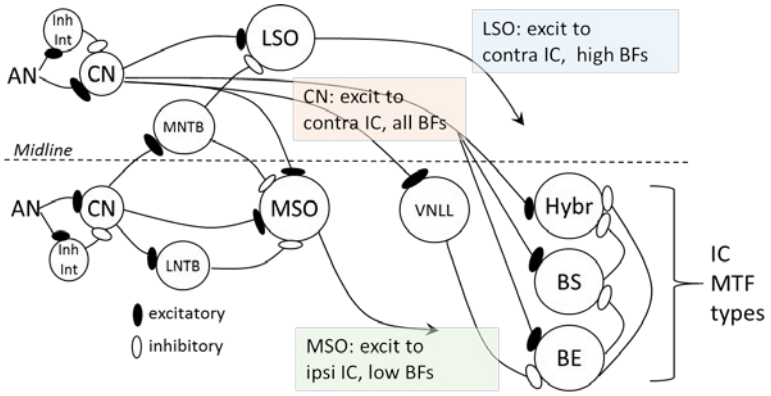


Figure 6 – Schematic of IC model.
Components based on parameters from:
AN: Zilany et al. (2014)
CN/VNLL/IC Band-enhanced (BE) IC MTF is the SFIE model of Nelson & Carney (2004).
MSO – van der Heijden et al (2013); Franken et al. (2014,2015); Gai et al. (2009)
LSO/MNTB/IC – Wang & Colburn (2012); Wang et al. (2014)
IC Band-suppressed (BS) MTF – Carney et al. (2015), Kim et al. (2015a)
IC Hybrid (MTF with both enhanced and suppressed rates) – Kim et al. (2015b)

**2) Physiology**: Recordings will be made using tetrodes in the midbrain of the awake Dutch-belted rabbit (see Carney et al., 2014). Binaural stimuli will be presented using Beyer-Dynamic headphones coupled to the ears with custom-made earmolds (Hal-Hen earmold material). The acoustic system is calibrated at the beginning of each session with an Etymotic ER-7C probe-tube microphone. Daily two-hour recording sessions are conducted; the animal is seated with head fixed, and listens passively during the recordings sessions. The response properties of neurons in the rabbit inferior colliculus are typical of those reported in several other mammalian species, and the rabbit is an outstanding animal model for awake recordings (Kuwada et al., 1987) Neurons will initially be characterized in terms of frequency tuning, response-map type, modulation transfer function and best modulation frequency, and binaural response properties (ITD and ILD sensitivity). Other stimuli will be matched to those used in the modeling and psychophysical studies (see below). Responses will be analyzed to determine neural thresholds for masked detection and forward-masking tasks (*e.g*. Wojtczak et al., 2011; Nelson et al., 2009). Neural thresholds based on rate and/or temporal responses will be directly compared to both model results and human psychophysical thresholds from the literature or from new experiments. (Note: Rabbit behavioral studies will not be included in this project because they have difficulty with complex detection and discrimination tasks (Zheng et al., 2002; Gai et al., 2007), despite the fact that their neural responses have the potential to explain human thresholds (Carney et al., 2014). We will therefore pursue physiological studies in the rabbit but utilize human behavioral studies to assess perceptual responses.

**3) Psychophysics**:

We will test listeners with mild or moderate sensorineural hearing loss, and age-matched listeners with normal hearing. Our consultant, Dr. Karen Doherty from Syracuse University, has been invaluable in guiding our experiments with these listeners. Two groups of listeners will be studied: Control listeners (n=15) and listeners with sensorineural hearing loss (SNHL) (n=30). Control listeners will be age-matched to the SNHL group (because data for the tasks in this proposal are available for young listeners with normal hearing, we do not plan to test that group.) Control listeners will have hearing thresholds less than 20 dB up to 4 kHz. SNHL listeners will have hearing thresholds that must exceed two out of three of the following criteria: >26 dB at 2 kHz, >30 dB at 3 kHz, or >35 dB at 4 kHz. These criteria were selected so that participants' hearing thresholds would be at least > 0.5 standard deviation from the normal hearing thresholds that are reported for these ages in Cruickshanks et al. (1998). In addition, participants' must have an air-bone gap < 10 dB, consistent with a sensorineural hearing loss. Also, hearing thresholds must not exceed 60 dB HL at any audiometric test frequency from 250 Hz through 8000 Hz. All listeners in both groups will have hearing thresholds that do not

differ by more than 15 dB at any test frequency. In their initial session, we will measure audiometric thresholds (250-8kHz), bone-conduction thresholds (to eliminate conductive HL), tympanograms (to assess Eustachian tube function), and DPOAEs (presence/absence, and amplitudes when possible, to assess OHC function), and a standard speech-in-noise test, such as QuickSin. Dr. U-Cheng Leong, an audiologist in the Dept. Of Otolaryngology at UR with experience screening subjects for research studies, will conduct these tests. Based on our ongoing experience with an enthusiastic group of subjects, we do not anticipate any problem with asking listeners to participate in the experiments described below for both Aim 1 and 2, or both Aim 1 and Aim 3. Dr. Joyce McDonough, an expert in phonetics, has agreed to consult on our studies of fricative consonants in Aim 3.

**Aim 1: To test the hypothesis that listeners transition from using envelope to energy cues at frequencies where they have elevated thresholds due to significant inner and/or outer hair cell dysfunction.** Aim 1 will use standard fixed and roving-level masked-detection tasks. One-interval tasks with interleaved fixed and roving-level two-down-one-up tracks (Levitt, 1971) will be used to determine whether thresholds are affected by a 20-dB rove of the overall stimulus level (Kidd et al., 1989; Mao et al., in review). Preliminary results suggest that listeners who depend on energy cues have difficulty in the roving-level task (as expected). By interleaving the two types of tracks we will make them less tiring for these subjects and avoid effects of fatigue on the comparison between conditions. Maskers will be third-octave bands of Gaussian noise centered at target frequencies of 0.5, 1, 2, 4, and 6 kHz (when possible for a listener.) Stimulus levels will be 30 and 60 dB SL, where possible (levels above 100 dB SPL will not be used), to determine whether cues change with level. The first six reversals in each track will be discarded, and threshold will be estimated based on the final 10 reversals. Each track will be repeated four times; if the standard deviation of the final 10 reversals exceeds 5 dB, the track will be repeated. We estimate that these tests will require no more than 3 hours to complete. The results will be used as part of individualizing the model for all listeners.

**Preliminary Results:** A pilot experiment after our tone-in-noise detection study in listeners with hearing loss (Mao et al., in review) explored reproducible-noise detection patterns for masker ensembles that were shifted to different center frequencies, preserving the energy and envelope cues but shifting the detection task to different frequencies. Pilot results suggested that four out of five individual listeners used envelope cues at specific frequencies where their hearing thresholds were better than ~40 dB SPL, and energy cues at frequencies where they had more than 40 dB of loss. However, one listener with a flat audiogram close to 20 dB was better predicted by energy cues across all frequencies tested (0.5, 1, 2, 4 kHz). These results convinced us to add Aim 1 to this proposal. The use of cues will be characterized for individual listeners as a function of frequency, and analyzed with their audiogram and DPOAE results. We realized that a more efficient strategy for this characterization is to use the roving-level paradigm, with 1 ERB maskers and tones at 0.5, 1, 2, 4, (& possibly 6) kHz). Similar thresholds across these conditions imply the use of envelope cues; thresholds elevated by ~25% of the rove range in the roving-level condition imply the use of energy cues (Green, 1988). These results will be combined with the DPOAE measurements and detailed audiograms for each subject to create a tailored model that includes inner and outer hair cell loss that matches all available measures for a given listener across frequency. Individualized models will be used to predict results in Aim 2.

**Aim 2a: To test the hypothesis that simultaneous notched-noise masking thresholds can be better explained by neural-fluctuation cues than by the power-spectrum model.**

**Preliminary results**: Preliminary modeling results in Figs. 2 & 3 illustrate the basic phenomenon of the neural fluctuation cues associated with the notched-noise masker. One example of our preliminary physiological results is also shown to illustrate the robust, yet counter-intuitive, responses of midbrain neurons to these stimuli: Addition of energy at the neuron's CF reduces the neural response as compared to the response to the notched-noise masker alone (Fig. 2). This response is expected when neural fluctuations are considered: the tone increases the response rate in the periphery, but also reduces the fluctuations, which are the driving force for midbrain neurons. The size of this effect varies with notch width, tone level, and also with simulated hearing impairment (Fig. 3). Additional recent physiological data presented at ARO (Carney and Varner, 2015) supports these results, and showed sensitivity to these stimuli for examples of neurons with band-pass, band-reject, and hybrid modulation transfer functions.

MODELING: We will begin by mining the literature for experimental paradigms and data sets. Numerous studies are available; the rationale for selecting a particular subset for our initial work is briefly outlined here:

| | |
|---|---|
| Glasberg & Moore, 1990 | A classic set of filter descriptions based on notched-noise masking thresholds |
| Baker & Rosen, 2002 & 2006 | Results for listeners with and without hearing loss, across a wide range of levels and frequencies |
| Lentz et al., 1999 | Roving-Level notched-noise paradigm |
| Irino et al, 2013 | This recent review summarizes the asymmetrical notch and level paradigms that have been used to fine tune filter estimates |

After replicating the stimuli for a given study, AN and IC model responses will be simulated. To estimate thresholds for the neural model we will apply signal-detection theory techniques to either average rates (as illustrated in Figs. 3-5) or to the instantaneous-rate of model responses (Fig. 2). We have used these techniques in the past to estimate detection and discrimination thresholds in quiet and noise (see above). The goal of these modeling studies is to test the hypothesis that the neural-fluctuation cue, derived from responses of the computational AN models (Zilany et al., 2014), will explain the trends in masked-detection thresholds across stimulus parameters, as well as robust detection in a roving-level paradigm. This modeling work will also be used to identify the most useful stimulus parameters, with respect to a neuron's best frequency, to design a paradigm for testing the model with recordings from individual neurons in physiological studies.

PHYSIOLOGY: Physiological techniques (see above) will be used to test that actual midbrain responses are consistent with model predictions. Each recording session is ~2 hours in duration, and tetrode recordings are typically stable over that entire time period. This timeframe allows systematic variation of a number of parameters, while collecting sufficient repetitions for statistical analyses of the responses. However, we will still need to identify the most informative comparisons and manipulations to make efficient use of recording time. Analyses of neural responses will take advantage of signal-detection theory, including receiver-operating characteristic analysis to estimate thresholds based on neural responses (*e.g*. Nelson and Carney, 2007; Carney et al., 2014). The neural thresholds will be directly compared to model thresholds and psychophysical thresholds from the literature. While recording from single neurons, roving- and equalized-level stimulus sets will be presented for direct comparison to standard fixed-level paradigms.

PSYCHOPHYSICS: It is unnecessary for us to repeat the extensive studies of filter estimates with notched-noise maskers in listeners with normal hearing and sensorineural hearing loss. However, we plan to test our model by manipulating the neural fluctuation cues by introducing controlled amplitude modulations. These manipulations will be fine-tuned using the model population responses. The most effective manipulations will be ones for which the power-spectrum model predicts no effect, or an effect in the "opposite" direction. For example, replacing the 4-kHz tone (Fig. 3) with an equal-energy narrowband noise (Fig. 7) reduces the difference in model rates by approximately 50%. This manipulation qualitatively reduces the salience of the target (although formal threshold estimates have not yet been made.) Other manipulations will be systematically investigated; candidates include substituting a narrowband noise (with inherent fluctuations) for the pure tone target, varying the slopes of the flanking bands, or "filling in" the notch with low-level stimuli with controlled modulations. (Another approach would be to use low-noise noise, however, peripheral filtering distorts the phase spectrum, increasing the fluctuations elicited by this signal.) Effects of all manipulations on detection thresholds will be predicted by the model for comparison to psychophysical results. The effects of the manipulations will be tested in listeners with and without hearing loss (see above). By testing listeners from Aim 1, we will have a detailed description of the use of envelope vs. energy cues across frequency for each listener. Those results will be used to tailor the model used to predict these modified notched-noise masking results for each listener. The listeners will be testing using the standard notched-noise paradigm with tones centered at 0.5, 1, 2, and 4 kHz, with 6 notch widths (Δ=0 to 0.5), presented at 70 dB SPL, and with the modified tasks (see above) centered at 2 kHz.

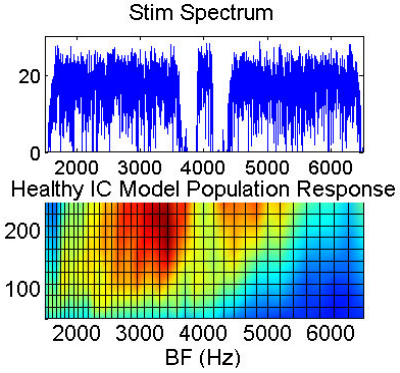


Figure 7 – Response to notched noise with a 200-Hz narrowband (NB) noise centered in the 4 kHz notch. Compare directly to Fig. 3 (color scales are matched across these figures). The energy of the NB noise is matched to that of the 4 kHz tone in Fig. 3. The inherently fluctuating response to the NB noise partially "fills in" the notch in the IC population response.

We plan to follow our empirical and

computational modeling studies with rigorous tests and extensions of theoretical psychoacoustical models to include the nonlinear neural-fluctuation cues. We have thus recruited Dr. Virginia Richards to the project; she has done extensive work in psychoacoustics and theoretical modeling related to masked detection.

**Aim 2b: To test the hypothesis that results of forward-masking paradigms can be explained by neural processing of envelope cues.**

MODELING: We have selected the following subset of studies from the literature to begin our modeling studies. The techniques described above will be used to estimate thresholds for these tasks, based on the responses of model IC neurons that are tuned to amplitude modulations.

| | |
|---|---|
| *Forward Masking* | |
| Oxenham & Plack, 1997, 2000; Plack & Oxenham 1998 | Forward masking, for a range of levels, frequencies and delays; estimates of cochlear nonlinearity. |
| Jesteadt et al., 2005, 2013 | Roving-level forward masking; additivity-of-forward masking paradigms |
| Wojtczak & Oxenham, 2009, 2010 | Examines “pitfalls” in forward masking, using high SPL off-frequency maskers |
| *Notched-Noise Forward Masking* | |
| Oxenham & Shera 2003; Oxenham & Simonson, 2006 | Filter estimates based on notched-noise forward masking, for comparison to simultaneous masking estimates (e.g. Glasberg and Moore, 1990) |
| Lopez-Poveda & Eustaquio-Martin, 2013 | Highlights the debate concerning differences between iso-response and iso-level strategies to estimate filter bandwidth |
| Svec et al. ARO 2015 | Effects of inherent fluctuation in forward maskers: normal and impaired listeners |

PHYSIOLOGY: Forward masking has been demonstrated at the level of the IC in marmoset (Nelson et al., 2009), but that study was not done in the context of modulation tuning. We will test that a neuron’s responses to forward-masked stimuli are consistent with the neural-fluctuation model, given the neuron’s modulation-tuning properties. We will also test selected paradigms from the modeling work, such as the roving-level paradigm and examination of high-SPL off-frequency maskers. We will also test neural responses to the notched-noise forward-masking paradigm. It will be important to understand how a neuron’s modulation tuning influences responses to this stimulus, which has been used in recent studies to estimate peripheral tuning while avoiding the effects of the simultaneous flanking bands in the notched-noise studies. If it is indeed true that this is effectively an amplitude-modulation forward-masking task, then estimates of peripheral tuning cannot be directly inferred using this task (that is, this paradigm yields sharper filter estimates than the simultaneous task, but perhaps not for the reason that is assumed!)

PSYCHOPHYSICS: As above, it is unnecessary for us to repeat the numerous variations of basic forward masking or notched-noise forward masking, but we can use the published results to test the model. During our modeling and physiological studies we will identify key stimulus configurations, or manipulations of them, for testing in the context of the neural-fluctuation model. For example: the model would predict that applying modulation to the masker in the basic forward masking task would increase thresholds, depending upon the relation between the masker modulation frequency and the fluctuations that are inherent in the time course of the gap and probe (Results presented at ARO 2015 support this hypothesis, Svec et al., 2015). The influence of these manipulations on estimates of peripheral compression will be explored. If neural fluctuation cues have a significant effect on these results, it would be impossible to make accurate estimates of peripheral compression with this paradigm. To test the individualized models developed in Aim 1, we will test the listeners from Aim 1 on a notched-noise forward-masking paradigm matched to Oxenham and Simonson (2006). In addition, we will test listeners on the paradigm(s) identified above in the modeling studies that provide the strongest tests of the neural fluctuation model.

**Aim 3: To test the hypothesis that the spectral slopes in pinna cues and fricative consonants are represented by the profiles of neural fluctuations set up in the periphery, and that interaural differences in neural fluctuations code elevation.**

***Pinna Cues*:** MODELING: We will test the role of neural fluctuations in coding spectral notches associated with pinna cues (Shaw and Teranishi, 1968; Hebrank and Wright, 1974; Rice et al., 1995). We will test the ability of the IC population model to predict the results of Kulkarni and Colburn (1998), Wightman and Kistler (1989a,b), and Alves-Pinto et al., (2014). We will test whether a model based on interaural differences of neural fluctuations can explain trends in sensitivity to pinna cues that have been reported for listeners with normal hearing. In the masked detection tasks described above, the neural fluctuation cues are robust across

a wide range of the relatively spectrally flat noise maskers. In contrast, for non-flat spectra, these cues are more level-dependent. In general, the ability to use pinna cues deteriorates as level increases up to 70-80 dB SPL (Hartmann and Rakerd, 1993), which is consistent with our model predictions and preliminary physiological results: as rates saturate, the neural-fluctuation cues decrease (Fig. 8). Alves-Pinto et al. (2014) reported the same decrease in sensitivity up to 80 dB SPL, but then an increase for higher levels. Their study did not use actual pinna cues, however, but rather synthetic (rectangular) spectral notches with very steep sides. We will test whether the trends they observed can be explained by the unusually steep slopes in these stimuli (see Fig. 1). This Aim will lay the groundwork for future study of binaural pinna cues in SNHL listeners.
PHYSIOLOGY: Responses of IC neurons to wideband noise stimuli convolved with head-related impulse responses (HRIRs) will be recorded. HRIRs are available for human (*e.g.* Qu et al., 2009) and rabbit (Kim et al., 2010; Day et al., 2012). AN responses to these cues have not revealed clear representations in rate. A fine-structure-related temporal representation has been proposed, though without a clear mechanism at such high frequencies (Alves-Pinto et al., 2014). Our model suggests a temporal coding mechanism for pinna cues that is specifically based on the low-frequency fluctuations of the AN responses.

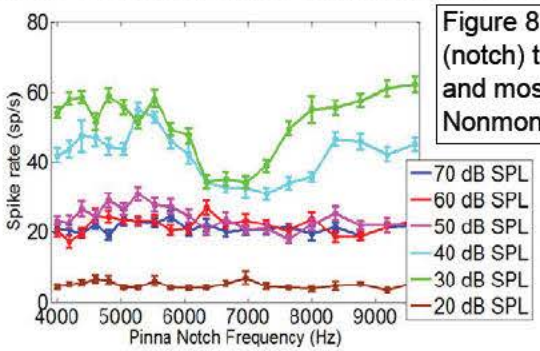


Figure 8 – Responses of a bandpass MTF IC neuron to a synthetic pinna cue (notch) that was shifted across the receptive field (BF ~7kHz). Rates were highest and most sensitive to the notch for intermediate SPLs (30, 40 dB SPL). Nonmonotonic rates illustrate that the cell was not simply driven by energy.

The neural fluctuation model predicts that the representation of these cues at the level of the midbrain is relatively straightforward, based on modulation tuning of IC neurons. We predict that the responses should be relatively insensitive to spectral details (consistent with Kulkarni and Colburn, 1998), but sensitive to level (consistent with Hartmann and Rakerd, 1993). Recordings will also be made with simplified multi-pole filter (IIR) approximations to the HRIRs (Kulkarni & Colburn, 2004). This approach to generating the stimuli is especially attractive for physiological experiments, as it will allow systematic manipulations of the stimuli with respect to a neuron's BF and BMF. Responses will be recorded over a range of SPLs (see above). Responses will also be recorded both monaurally (for both ears) and dichotically. We will test whether neurons are sensitive to interaural differences in fluctuations, as reported by Mao & Carney (2014) for binaural detection.

***Fricative Consonants:***

Physiological and model responses to fricative consonants will test the hypothesis that these sounds are coded at the level of the midbrain by the contrasts in neural fluctuation (Fig. 4) set up by peripheral responses. Changes in these contrasts with hearing loss will be tested with the model and compared to the detailed psychophysical reports of consonant confusion matrices (e.g. Trevino et al., 2013; Li et al. 2012). We will test our individualized models with consonant identification tests in subjects who have been characterized with the masking task in Aim 1, using the stimuli and methods from these two studies.

**PITFALLS and ALTERNATIVE APPROACHES**: We have presented preliminary tests of the proposed model; we don't anticipate problems with feasibility in that component of the study. Working through all stimulus paradigms will simply require time and an organized approach. In contrast, the empirical work is never guaranteed. However, our preliminary studies on several cells with various types of modulation transfer functions, suggest that most IC cells are sensitive to the proposed stimulus features and manipulations.

Our neural-fluctuation framework focuses on responses of AN fibers and of AM-tuned midbrain neurons, with a simplified model for binaural brainstem processing. One brainstem region that may deserve more attention is the dorsal cochlear nucleus, which has been studied extensively in the context of spectral-notch coding (e.g. Nelken and Young, 1997). DCN neurons project directly to the IC, and models for DCN cells are available and can be incorporated in an extended model of the IC. DCN cells have been proposed to be the primary input to "O" type cells in the IC (Davis, 2001). These cells are rare in the awake rabbit preparation, thus the exploration of this population of cells would be based primarily on modeling work.

Another potential pitfall is the current focus on the "amount" of neural fluctuation in each channel. There are also interesting temporal patterns to consider, including sensitivity to envelope phases within and across channels, which will be the subject of future studies.

**Publication List for the last grant cycle – work supported by this grant since initial submission in 2009**
List publications, manuscripts accepted for publication and other printed materials that resulted from the project since last reviewed competitively in the Progress Report Publication List of the Research Plan.

**In Print:**

Mao, J., Vosoughi, A., and L.H. Carney (2013) Predictions of diotic tone-in-noise detection based on a nonlinear optimal combination of energy, envelope, and fine-structure cues, J Acoust Soc Am 134: 396-406. PMCID: PMC3724726.

Mao, J. and L.H. Carney (2014) Binaural detection with narrowband and wideband reproducible noise maskers: IV. Models using time, level, and envelope differences. J. Acoust. Soc. Am., 135: 824-837; PMCID: PMC3985905.

Rao, A, and Carney, LH (2014) Speech Enhancement for Listeners with Hearing Loss Based on a Model for Vowel Coding in the Auditory Midbrain , IEEE Transactions on Bio-medical Engineering. 61:2081-2091.

Mao, J, and Carney, LH (2015) Tone-in-Noise Detection Using Envelope Cues: Comparison of Signal-Processing-Based and Physiological Models, JARO, 16:121-133.

[redacted]

**In Review:**

Mao, J., Koch, K.-J., Doherty, K.A., Carney, L.H. (accepted with minor revisions, re-submitted – should be available to reviewers by time of review) Cues for Diotic and Dichotic Detection of a 500-Hz Tone in Noise Vary with Hearing Loss, JARO.

**Patent:**

A non-provisional patent application was filed on April 16, 2013. [redacted]

**Abstracts for Presentations:**

Axe, D.R., and Carney, L.H. (2009) A neural model of the inferior colliculus with excitatory and inhibitory input from the cochlear nucleus and the superior paraolivary nucleus, Abstract, BMES.

Mao, J., and Carney, L.H. (2009) Detection of Tones in Reproducible Noises: Combining Information across Epochs and across Cues, Abstract, ARO.

Mao, J., A. Vosoughi, L.H. Carney (2011) Stimulus-based Diotic and Dichotic Models that Combined Cues for Detection of Tones in Reproducible Noise. Abstract, Acoustical Society of America.

Zilany, M.S.A., K. Abrams, K.-J. Koch, F. Idrobo, L. H. Carney (2011) Amplitude-Modulation Detection in Reproducible Modulation Maskers: Correlation Between Behavioral and Physiological Responses. Abstract, Acoustical Society of America.

Mao, J., and Carney, L.H. (2013) Physiologically-based Envelope Cues for Diotic and Dichotic Tone-in-noise Detection, Abstract, ARO.

Mao, J., Doherty, K.A., Koch, K.-J., and Carney, L.H. (2013) Effects of sensorineural hearing loss on roving-level tone-in-noise detection, Abstract, American Auditory Society.

Carney LH; Mao J; Koch KJ; Doherty KA (2013) Modeling detection of 500-Hertz tones in reproducible noise for listeners with sensorineural hearing loss. Proceedings, Acoustical Society of America and International Congress on Acoustics, Montreal. JASA.2013;133(5):3559.

[redacted]

Carney, LH, and Schwarz DM – "A Speech Enhancement Strategy based on Midbrain Response Properties" IHCON, August 2014.

Carney, LH, and Varner T (2015) Notched-Noise Revisited: Masked threshold predictions based on modulation-sensitive midbrain neurons, ARO.

**Protection of Human Subjects**

All of the following criteria apply to the primary research site, where all human testing will occur.

*1. Risks to the listeners*

Listeners in this study will be recruited for psychoacoustical tasks associated with the three Aims:
Aim 1) Detection of tones in narrowband noise, using interleaved tracks with fixed- and roving-level paradigms, with target tones at a range of frequencies (0.5, 1, 2, 4, 6 kHz).
Aim 2) Detection of tones masked by notched-noise in simultaneous and forward masking configurations, plus tests with acoustic manipulations designed to influence neural-fluctuation cues.
Aim 3) Consonant identification testing, using the fricative consonant stimuli that were used in Li et al (2012), which were selected from the University of Pennsylvania's Linguistic Data Consortium database (LDC-2005S22, aka the Fletcher AI corpus).

Control listeners and listeners with sensorineural hearing loss (SNHL) will be involved in all three studies. For each study, each listener will spend a total of approximately 12-15 hours over 6-8 weeks. Listeners will sit in a sound-proof booth and listen to acoustic signals over headphones. They will be instructed to respond using a keyboard or mouse. Listeners will be given frequent breaks during test sessions.

A total of 40 listeners will be recruited, as described below. All listeners will complete the relatively brief testing for Aim 1, which along with the initial audiological tests, will be used to individualize the computational model. Listeners will then be tested for Aim 2 and/or Aim 3. We anticipate that some subjects will not be able to complete all three sets of tests, due to travel, moves, or illness. However, if new listeners are recruited for Aim 3, we will have them complete the masked detection tests in Aim 1 in order to develop individualized models for these listeners.

Listeners will be recruited from the students, staff, and community of the University [redacted] Participants will be between 18 and 80 years of age. Before the study, potential listeners' hearing will be tested to characterize their hearing loss. Two groups of listeners will be studied: Control listeners (n=15) and listeners with sensorineural hearing loss (SNHL) (n=30). Control listeners will be age-matched to the SNHL group (because data for the tasks in this proposal are available for young listeners with normal hearing, we do not plan to test that group.) Control listeners will have hearing thresholds less than 20 dB up to 4 kHz. SNHL listeners will have hearing thresholds that must exceed two out of three of the following criteria: >26 dB at 2 kHz, >30 dB at 3 kHz, or >35 dB at 4 kHz. These criteria were selected so that participants' hearing thresholds would be at least > 0.5 standard deviation from the normal hearing thresholds that are reported for these ages in Cruickshanks et al. (1998). In addition, participants' must have an air-bone gap < 10 dB, consistent with a sensorineural hearing loss. Also, hearing thresholds must not exceed 60 dB HL at any audiometric test frequency from 250 Hz through 8000 Hz. All listeners in both groups will have hearing thresholds that do not differ by more than 15 dB at any test frequency. In their initial sessio*n*, we will measure audiometric thresholds (250-8kHz), bone-conduction thresholds (to eliminate conductive HL), tympanograms (to assess Eustachian tube function), and DPOAEs (to test for presence/absence, and amplitudes when possible, to assess OHC function), and a standard speech-in-noise test, such as QuickSin (Niquette et al., 2001). [redacted], an audiologist in the Dept. Of Otolaryngology at [redacted] with experience screening subjects for research studies, will conduct these tests. Audiogram configurations, screening test results, and experimental results will be reviewed with our collaborator, [redacted].

Based on our ongoing experience with an enthusiastic group of subjects, we do not anticipate any problem with asking listeners to participate in the experiments described below for both Aim 1 and 2, or both Aim 1 and Aim 3.

Listeners with normal hearing will be included to provide age-matched controls. These listeners will still be carefully characterized as a function of frequency based on their test results (i.e. listeners will never be assumed to be completely 'normal'.) Based on our experience, we anticipate a range in the degree and configurations of hearing loss, and that there will be variability in both the control and SNHL groups. Variability across listeners is a strength for our approach, as it allows us to test our individualized models in a detailed fashion. Our analyses will not include "grouping" subjects based on categories of hearing loss. Detailed studies of individual listeners can reveal important differences in the performance and cues used between listeners, and within listeners across frequencies (Mao et al., in review).

No special classes of subjects will be involved in this study.

The only significant risk to the listeners in this study is the potential for exposure to loud sounds over the headphones. This risk has been minimized by building in safeguards in the sound-delivery system to prevent the presentation of dangerously loud stimuli.

*2. Adequacy of Protection against Risks*
Recruitment and informed consent: Listeners will be recruited with flyers that have been approved by the University of Rochester RSRB. Informed consent will be solicited using a written informed consent form that has been approved by the University [redacted] RSRB.
Protection against risks: The risk of exposure to loud sounds will be minimized by building safeguards into the software used to deliver stimuli. Listeners will each be assigned an arbitrary identification number and will not be identifiable in reports of their responses.

*3. Potential benefits of the proposed research to subjects or to others.* There are no benefits to the listeners in this study. The potential benefits of this study are in improving our understanding of how the brain processes sounds. Given the minimal risks to the subjects associated with these experiments, and the potential for long-term benefit to others, the risk-benefit ratio is positive.

*4. Importance of the knowledge to be gained.* The knowledge to be gained may improve hearing-aid technology for listeners with hearing loss. The difficulties of listeners with hearing loss in noisy environments are significant and affect a growing percentage of our population, thus the potential benefits are justified in the face of the minimal risks to the subjects in this experiment.

Our planned enrollment is based on the information provided in the following table, which describes the demographics of the population in [redacted] U.S. Census Bureau, estimates for 2013).
[Note: Targeted/Planned Enrollment Table is included separately.]

| | |
|---|---|
| White | 77.7% |
| Black or African American | 16.0% |
| American Indian and Alaska Native | 0.4% |
| Asian | 3.5% |
| Native Hawaiian and Other Pacific Islander | 0.1% |
| Two or More Races | 2.4% |
| Hispanic or Latino | 7.9% |
| White, not Hispanic or Latino | 72.0% |

**Inclusion of Women**

Approximately 50% of the subjects will be women.

**Inclusion of Minorities**

We will continue to pay special attention to the inclusion of minorities in the subject pool. The student, staff, and community populations at the University [redacted] are relatively diverse, thus we do not anticipate difficulty in recruiting minority subjects. To date, we have been successful in recruiting minority subjects by posting flyers around the medical center, which is the largest employer in the [redacted] area. Over the last few years, we have built up a pool of older subjects with and without hearing loss through the Center for Navigation and Communication Sciences. Although the Center grant program was terminated by NIDCD, we will be able to maintain this pool of subjects for at least the near future. We have also established a great relationship with the Hearing Loss Association of America's [redacted] Chapter, and many of their members have already served as subjects or have expressed interest in doing so. The demographics of the University [redacted] are described elsewhere in this application (with the description of Protection of Human Subjects).

OMB Number: 0925-0002

# Planned Enrollment Report

**Study Title:** Developing and Testing Models of the Auditory System with and without Hearing Loss

**Domestic/Foreign:** Domestic

**Comments:**

| Racial Categories | Ethnic Categories | | | | Total |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 | **0** |
| Asian | 2 | 2 | 0 | 0 | **4** |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | **0** |
| Black or African American | 3 | 3 | 1 | 1 | **8** |
| White | 15 | 14 | 2 | 2 | **33** |
| More than One Race | 0 | 0 | 0 | 0 | **0** |
| **Total** | **20** | **19** | **3** | **3** | **45** |

Study 1 of 1





Funding Opportunity Number: PA-13-302. Received Date: 2015-04-02T14:32:01.000-04:00

**Inclusion of Children**

All participants will be at least 18 years of age. The tasks involved in these experiments involve a high level of concentration, and are thus not appropriate for study in young children. For this study, we are specifically recruiting some subjects with mild to moderate sensorineural hearing loss, which is much more common amongst middle-aged or older subjects. If we have an opportunity to include subjects younger than 21 years of age (and thus children according to the NIH criterion) and at least 18 years of age, we will make every effort to do so.

**Vertebrate Animals**

1. Detailed description of the proposed use of animals

The physiological recording sessions will be performed in sound-attenuated chambers located in the Department of Neurobiology & Anatomy in the University [redacted] Each animal will undergo physiological testing for approximately 12-24 months. We expect to use a total of 4 Dutch-belted rabbits over the course of this project (see below). This project, which involves recordings of responses to tone-plus-noise stimuli, will be added to an ongoing protocol that has already been approved by the University [redacted] UCAR committee (UCAR-2007-054R).

**Surgical Procedures for Physiological Studies in Rabbit:**

*Placement of head bar and microdrive positioner:*

Details of the physiological methods are included in Carney et al. (2014). Briefly, in an initial surgery a custom single-piece plastic head bar and microdrive positioner is mounted on the skull to provide access to the auditory midbrain (via a subsequent ~2-3 mm diameter craniotomy) and to provide a means for stabilizing the head during recording sessions. Before surgery, the animal is weighed and anesthetized with a combination of ketamine (66 mg/kg) and xylazine (2 mg/kg) or to effect. Additional doses of anesthesia are given every 30-45 minutes, or as needed, during the surgery to maintain areflexia. The animal is kept on an automated heating pad and covered with blankets to keep it warm during the surgery.

Using blunt dissection techniques, an incision is made in the skin overlying the top of the skull. The opening is large enough to expose the area along the midline where the headbar assembly is attached. Stainless-steel screws are inserted into holes drilled into the skull to either side of the mounting bar. Dental acrylic is used to attach the bar that will hold the animal's head stationary during recording sessions. Part of the head bar assembly (fixed to the posterior end of the headbar) is a plastic cylinder into which the microdrive (Neuralynx 5-Drive) is inserted. The plastic cylinder surrounds the site of the craniotomy, prevents the skin from growing back over the site, and serves as a mount for the microdrive, which holds 4 tetrodes.

After the surgery is complete, the animal is monitored until it completely recovers from anesthesia. An analgesic (flunixin meglumine (Banamine), 1.0 mg/kg, SC, or meloxicam (Metacam), 0.3 mg/kg PO or 0.2 mg/kg SC) is administered at the end of the surgery and every 12-24 hours for up to 48 hours, depending upon the animal's appearance and behavior, to ease the discomfort associated with the surgery. Because these animals are handled daily by the PI and/or colleagues, we are familiar with their usual behavior; behavior that deviates from the normal behavior (e.g. reduced activity and responsiveness) is associated with discomfort due to the surgery, and analgesia is administered. The animal remains in its housing in the [redacted] Vivarium during recovery from the surgery, and will continue to be housed there during the entire course of the experiment. The animal's general health (based on appearance and behavior, food and water intake) is recorded at least daily, and weight is recorded at least twice a week.

*Neurophysiological procedures:*

Before beginning neurophysiological recordings, the animal is gradually conditioned to sit still in a small "chair", with its head held fixed by the mounting bar. Sessions are increased from 15 minutes to 2 hours, in 15-minute increments. The animal is returned to [redacted] Vivarium every day for overnight housing. The animals are also gradually accustomed to the custom-made earmolds (Hal-Hen earmold impression material) and calibration procedures. Calibrations are based on probe-tube measurements of tones presented from 100-20,000 Hz (Er-7C Etymotic probe-tube system.)

A craniotomy is made in the skull to allow access for the recording electrode to the midbrain. Before surgery, the animal is weighed and anesthetized with a combination of ketamine (66 mg/kg) and xylazine (2 mg/kg) or to effect. Additional doses of anesthesia are given every 30-45 minutes, or as needed, during the surgery to maintain areflexia. These surgeries are relatively brief and typically require no more than one additional dose of anesthetic. After the craniotomy, the animal is monitored until it completely recovers from anesthesia. An analgesic (flunixin meglumine, 1.0 mg/kg, SC) is administered by the PI at the end of the surgery and every 12-24 hours for up to 48 hours, depending upon the animal's appearance and behavior, to ease the discomfort associated with the surgery.

The tetrodes are advanced slowly through the IC over the course of several weeks. The microdrive allows 4 tetrodes to be advanced individually using small screws. Typically, tetrodes are advanced at the end of a recording session to allow them to settle into place overnight. Each daily recording session lasts approximately 2 hours. After advancing slowly through the entire dorsal-ventral length of the IC, the tetrodes will be slowly retracted. The microdrive can then be re-mounted in a slightly different position to record from the same IC, or it

can be shifted to the other side of the micro-positioner holder to record from the opposite IC. Under anesthesia (see above), the micro-positioner is removed and a new micro-positioner is mounted. The position of the guide tubes, and thus the location of the tetrode penetration, is varied from penetration to penetration based on the results of the prior penetration.

2. Justify the use of animals, the choice of species, and the numbers to be used.

Each of the 4 rabbits in this study will be used for daily physiological recording sessions for approximately 12-24 months; the duration is limited by the ability to successfully isolate neurons in the brain tissue, which degrades over time due to scarring. This recording time is sufficient to collect responses from approximately 200 neurons for each stimulus condition using single-electrode techniques (2-4 neurons can be studied per day in successful recording sessions). We require large numbers of recordings session to collect sufficient data for statistical tests related to neural encoding and for comparisons to psychophysical data. Because midbrain neurons are tuned to different audio and modulation frequencies and to different binaural cues, a large number of neurons is required to allow statistically significant conclusions to be reached concerning each hypothesis being tested.

We have chosen to use the Dutch-belted rabbit for these studies based on our experience with this strain of rabbit; the Dutch-belted rabbit has been used in a number of other laboratories investigating central auditory function (e.g. the laboratories of Kuwada, Fitzpatrick, Batra, Delgutte). The rabbit adapts well to sitting quietly during recording sessions. The Dutch-belted rabbit is pigmented, which avoids questions related to differences in anatomical structures (especially related to the binaural system) in albino animals. Dutch-belted rabbits also stay relatively small and are easy to house and handle. The anatomy and physiology of the auditory pathways in the rabbit are well characterized.

3. Veterinary Care

The animals are all housed in the [redacted] Vivarium in the School of Medicine & Dentistry. The animals are regularly checked by [redacted] veterinarians, who are available for consultation concerning animal care and surgical procedures.

4. Procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research.

The rabbits are anesthetized for any procedures that involve significant discomfort (i.e., mounting the headbar, craniotomy, molding of ear molds). Analgesia is provided after the headbar surgery and craniotomy. During physiological sessions, animals are seated in a chair that is designed to hold them in a comfortable position.

5. Euthanasia: At the conclusion of studies for each animal, the animal will be anesthetized to a surgical level with Ketamine and Xylazine (Ketamine 66 mg/kg IM and Xylazine 2 mg/kg IM). A euthanizing dose of sodium pentobarbital will then be given either by DLAM or by the PI (Pentobarbital sodium 150mg/kg IV). Some animals will be perfused with a saline solution followed by a formalin solution in order to prepare the brain tissue for histological study required to verify the position of the electrodes used during physiological recordings. In animals that are not perfused, death will be verified by absence of heartbeat, respiration and voluntary reflexes.

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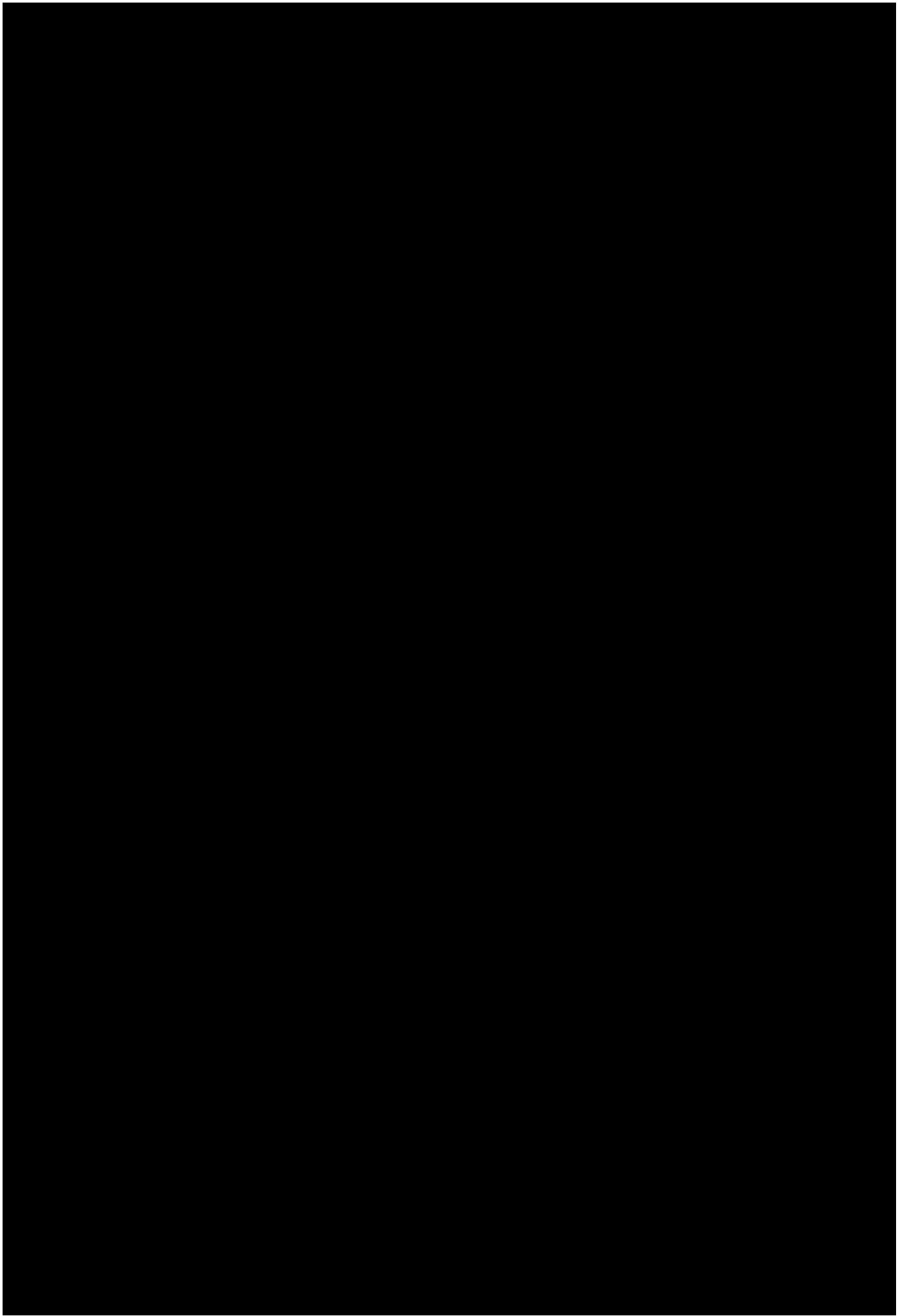

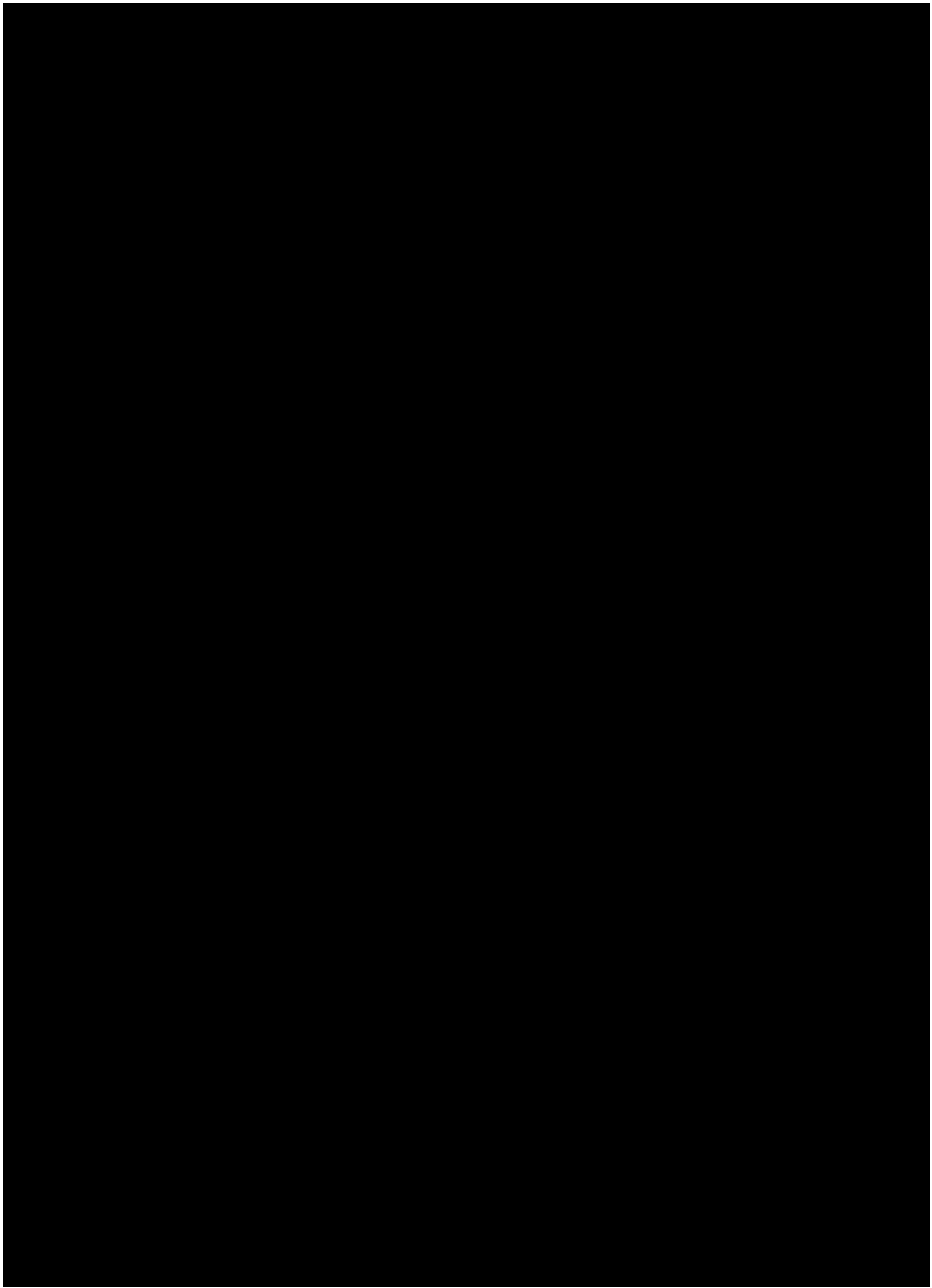

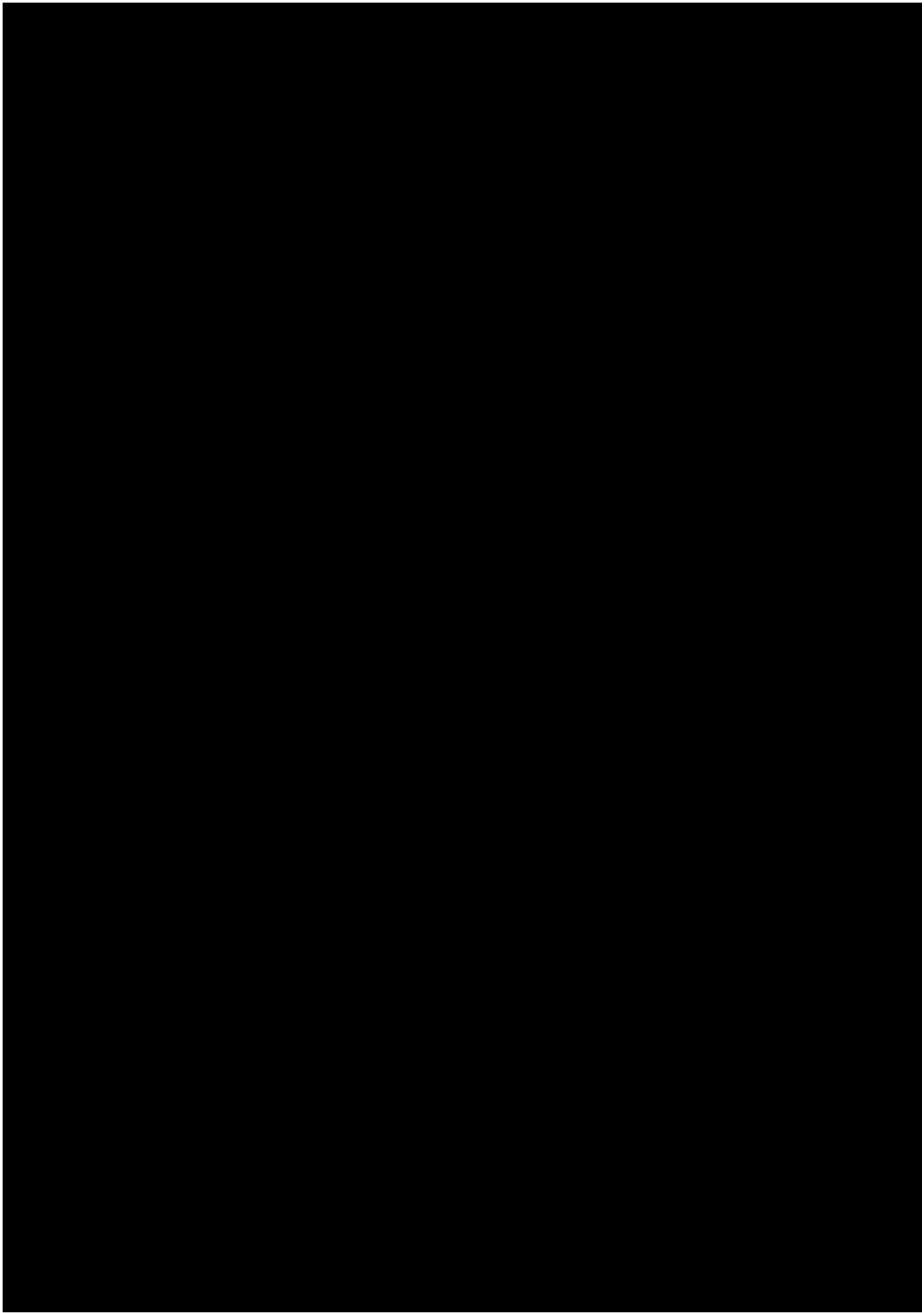

**RESOURCE SHARING: PLAN FOR SHARING MODELS AND SOFTWARE**

Beginning with the first auditory-nerve model that was developed in our lab (Carney, 1993), we have prepared our modeling software with the intention of sharing it with other investigators. Initially, this was done informally by means of e-mail. However, for several years now, we have maintained a lab website where code can be freely downloaded (see www.bme.rochester.edu/carney under the “Carney Lab” & “Auditory Models & Code” links.) The address of this website is mentioned in our publications. [The publications and model software of Zilany and Bruce are also downloadable from our colleague Dr. Ian Bruce’s website at McMaster University, *see* *http://www.ece.mcmaster.ca/~ibruce/zbcatmodel/zbcatmodel.htm)*.] In addition, we have made some of our experimental datasets available either on our lab website, or on the Earlab Website at Boston University. Graduate students who have been involved in model development have all had engineering backgrounds, with formal training in programming, thus the quality of the software has been adequate for the purpose of sharing with other labs. Writing transparent, well-documented code has been an important part of all of our modeling efforts.

*All new models developed and data collected as part of this project will be posted on our lab website so that they can be freely downloaded*. We typically prepare code in Matlab or in C that can be compiled into Matlab functions; compiler commands are also provided. Along with the code, we provide Readme files and simple examples that can be readily executed to quickly get up and running with the software, and then modified by the user for custom purposes (*e.g.*, stimulus waveforms can be modified, or model parameters can be modified, as needed.) Models posted to the website are associated with peer-reviewed publications that describe parameter determination and model validation procedures in detail. We have received excellent feedback from colleagues who have downloaded and used our modeling software, thus we feel that this strategy has been an effective means of sharing our work.