Pennsylvania Department of Health
Final Performance Summary Report
Formula Grants

Overview of the Health Research Project Performance Review Process and Criteria

An applicant that receives a health research grant under Tobacco Settlement Act / Act 77 of 2001, Chapter 9, is subject to a performance review by the Department of Health upon completion of the research project. The performance review is based on requirements specified by Act 77 and criteria developed by the Department in consultation with the Health Research Advisory Committee.

As part of the performance review process, each research project contained in a grant is reviewed by at least three experts who are physicians, scientists or researchers. Reviewers are from the same or similar discipline as the research grant/project under review and are not from Pennsylvania. Reviewers use the applicant's proposed research plan (strategic plan), the annual progress report and final progress reports to conduct the review. A grant that receives an unfavorable performance review by the Department may be subject to a reduction in funding or become ineligible for health research funding in the future. The overall grant evaluation rating is based on the ratings for the individual research projects contained in the grant.

This performance review report contains the outcome of the review for the grant as a whole (outstanding, favorable, or unfavorable), strengths and weaknesses of each research project, as well as recommendations for future improvement.

The following criteria were applied to information submitted by research grant recipients:

- **Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?**
  - Did the project meet the stated objectives?
  - Were the research design and methods adequate in light of the project objectives?
  - Consider these questions about data and empirical results: Were the data developed sufficiently to answer the research questions posed? Were the data developed in line with the original research protocol?
  - If changes were made to the research protocol, was an explanation given, and, if so, is it reasonable?
  - Consider (only for clinical research projects) the extent of laboratory and clinical activities initiated and completed and the number of subjects relative to the target goal.
  - Were sufficient data and information provided to indicate or support the fact that the project met its objectives or made acceptable progress?
  - Were the data and information provided applicable to the project objectives listed in the strategic research plan?

- **Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?**
  - What is the significance of this project for improving health?
  - Consider the value of the research completed towards eventual improvement in health outcomes.
  - Consider any changes in risk factors, services provided, incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of impact and effectiveness of the research being conducted.
  - Consider any major discoveries, new drugs and new approaches for prevention, diagnosis and treatment, which are attributable to the completed research project.
  - What are the future plans for this research project?

- **Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?**
  - If leveraging of funds were expected, did these materialize?
  - Are the researchers planning to apply for additional funding in the future to continue or expand the research?

- **Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted/filed?**
  - If any of the above listed were expected, did these materialize?
  - Are the researchers planning to submit articles to peer-reviewed publications, file for any licenses, or patents or begin any commercial development opportunities in the future?
  - Consider the number/quality of each.

- **Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?**
  - Were there improvements made to infrastructure?
  - Were any new investigators added or were any researchers brought into the institution to help carry out this research?
  - Were funds used to pay for research performed by pre- or post-doctoral students?

- **Criterion 6 - Did the project lead to collaboration with research partners outside the institution, or new involvement with the community?**
  - Are the researchers planning to begin any collaborations as a result of the research?
  - For clinical research only: consider the number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the Commonwealth.

Overall Evaluation Rating

An overall evaluation rating is assigned to each research project. The rating reflects the overall progress the project attained in meeting the stated goals and objectives. The rating is based on a scale of 1–3, with 1 being the highest. An average rating is obtained from all the reviews (minimum of 3) of each project and is the basis for the determination of the final overall rating for each project as follows:

1.00 – 1.33 = *Outstanding*
1.34 – 2.66 = *Favorable*
2.67 – 3.00 = *Unfavorable*

The grant level rating is an average rating from all projects as above. The numerical rating appears in parentheses for the grant and each project in the ***Overall Grant Performance Review Rating*** section of the report.

Overall Grant Performance Review Rating

Grant Rating: Favorable (1.55)

Project Rating:

Project	Title	Average Score
0862701	Mellon Institute Vivarium - Research Infrastructure	Outstanding (1.00)
0862702	Computational and Neural Basis of Visual Inference	Favorable (2.33)
0862703	Memory-Based Neural Activity in the Hippocampus	Outstanding (1.33)

Project Number: 0862701
Project Title: Mellon Institute Vivarium - Research Infrastructure
Investigator: Gilman, Frederick

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The key objective of this proposal was to renovate existing space on the second floor of the Mellon Institute to centralize animal resources. This objective was achieved, and the vivarium space is fully operational. The vivarium has a holding capacity of 2500 rodent cages, with space available for quarantine, imaging, procedure, and behavioral studies. The vivarium accommodates eight investigators currently, and recruitment is underway for two additional faculty who utilize rodent models. The major strength of this project is the centralization of animal holding areas to achieve economy of scale and improve animal welfare standards/regulatory compliance. Another strength is the institutional support equating to ten times the amount of funding provided by grants to ensure project completion. Weaknesses were minor and included an apparent lack of laboratory animal veterinarian involvement in the design process, a one-year delay in project completion, and failure to procure NIH funding to help support the project.

Reviewer 2:
This infrastructure project met its stated objectives successfully.

Reviewer 3:
The completed project appears to have fully accomplished the stated goals.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The significance of this project is tremendously positive. Centralization of animal resources frees up time for investigators to focus on their research, rather than caring for the animals. Animal welfare is positively impacted through employment of laboratory animal care specialists whose main focus is the care of the animals. Regulatory compliance is enhanced by having individuals who focus on the animals first, while accommodating the needs of the research. Although the vivarium has only been operational for just over one year, important research has already been completed and published, with many more discoveries anticipated.

Reviewer 2:
This infrastructure project allowed increased housing and centralization for small animal research.

Reviewer 3:
The likely benefit of this animal facility construction project is highly significant. For scientific purposes, for improving cost efficiencies, and from a compliance perspective, this centralized, up-to-date animal facility is a tremendous improvement over the previous individual laboratory "hodge-podge" of animal facilities at this institution.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:
An NIH G20 facility improvement grant was submitted but not funded. These are extremely competitive grants, so this is not surprising. Additional funding was obtained from Pittsburgh Life Sciences Greenhouse ($467,711), and the institution provided the remaining funds required to complete the project (Carnegie Mellon University $7,352,597). The level of institutional funding and support is a major strength of this project. Additional funding will undoubtedly be pursued by users of this vivarium to pursue research that will be performed within it in the future.

Reviewer 2:
Leveraging of funds directly was not expected. It is anticipated that the new facility will provide space for future increased animal research funding.

Reviewer 3:
The funds ($369,887) from this grant were tremendously leveraged with institutional funds ($7,352,597) and Pittsburgh Life Sciences Greenhouse ($467,711) to build this facility.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:
Since this was a research infrastructure project, these reflections of productivity are not expected. The research that has been and will be performed in the vivarium will undoubtedly result in many publications, licenses, patents, and potentially commercial development opportunities.

Reviewer 2:
The project reporting ended right after animals were moved in. There was one publication reported from the initial move in.

Reviewer 3:
None indicated.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The quality and capacity for research was greatly enhanced through the addition of a centralized vivarium for reasons stated previously. New faculty are being recruited as a result of the increased rodent holding capacity, which is a strength of the project.

Reviewer 2:
The improvements to infrastructure allowed centralization of housing and support services with increased capacity.

Reviewer 3:
This new facility was an important addition to the infrastructure as described above. This facility has helped in recruitment of additional faculty. None of the funds paid for students, since this was not applicable.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution

STRENGTHS AND WEAKNESSES

Reviewer 1:
It is unclear how much collaboration the new vivarium has enabled within the institution or with external entities. The user group consists of a fairly small group of researchers that appear to come from only a few departments, so it is likely they shared great understanding of each other's research prior to this project. The increased capacity afforded by the vivarium has enabled recruitment of new faculty, another strength of the project, which will improve collaboration.

Reviewer 2:
This was an infrastructure project, and collaboration was not an objective.

Reviewer 3:
None indicated.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:
Ensure that a qualified laboratory animal veterinarian is involved in the design process of future vivarium renovation or construction. These individuals have thorough knowledge of regulatory requirements and animal needs and are vital to this process.

Reviewer 2:
The proposal, progress, and final reports were well written and complete for an infrastructure project.

Reviewer 3:
None

Project Number: 0862702
Project Title: Computational and Neural Basis of Visual Inference
Investigator: Olson, Carl

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:
It appears that considerable work has been undertaken in the development of computational/statistical models of early vision (Aim 1), object perception (Aim 2), and neuronal responses to objects (Aim 3). For Aim 1, Bayesian networks have been utilized, providing a theoretical framework for Aim 3. For Aim 2, two classes of models were studied, yielding novel empirical results. For Aim 3, new data was collected on monkeys to explore neuronal activity in perception and enabling the testing of models from Aim 1. The design of the three aims seems reasonable, with Aim 1 and 3 being somewhat integrated. The research questions appear to have been addressed, although much of the work for Aims 1 and 2, with publications in 2009, appears to have been well under way prior to the start of this grant in January 2009. Changes to the original proposal appear minimal. No clinical research was undertaken, with the focus being primarily on the development of models of vision and perception, and evaluating such models in simple animal models. Overall, acceptable progress was made, with at least some new work in Aims 1 and 2, and more evident progress in Aim 3, with a number of publications resulting. The results appear to be in line with the strategic research plan.

Reviewer 2:
The objective of the project was to develop computational theories of vision within an analysis by synthesis framework and to test the predictions of such theories in multiple levels of the primate visual system. This was specified in three aims: 1) develop computational models of early vision that combine bottom-up and top-down information; 2) develop computational models of object perception; and, 3) investigate neural responses in monkey V1, V4, and IT during object perception in cluttered scenes.

The objective seems to have been partially met. Strong progress appears to have been made in developing computational models of object recognition, but less development is apparent for early vision. While a strength of the neural recording experiments is that they are highly interesting in themselves, weaknesses include that there seems to be little direct connection with the computational work, they do not evaluate specific analysis-by-synthesis predictions, and they do not integrate measurements from multiple areas of the visual hierarchy. The experiment that was proposed to address such aims does not appear in the reports.

Reviewer 3:

The original project consisted of three aims to investigate the computational basis of figure-ground segmentation (Aim 1), the computational basis of object recognition (Aim 2), and the neurophysiological basis of object representations in multiple visual areas (Aim 3). In the final report, the descriptions of the completed progress were often brief or vague, and in some cases the relationship between the originally proposed work and the final reported work was quite unclear. Overall, many of the original objectives were not met, or the work reported was only tangentially related to the original proposal. These represent major weaknesses.

The accomplishments of Aim 1 consist of a brief statement that "During the first year of the grant we have explored techniques for image denoising…., as well as for inference of shape from shading." A single publication is cited regarding a book chapter by Potetz and Lee (but not included in the separate publications list). This book chapter focuses mostly on reviewing research conducted prior to the grant, rather than on advances in ongoing research. It is unclear exactly what work has been done on developing computational models that can produce scene partitioning based on bottom-up features as well as top-down contextual influence, or in performing figure-ground segmentation, as was originally proposed for Aim 1.

The goal of Aim 2 was to develop a computational model of object recognition. The co-PI cites the publication of two papers that are somewhat related to this aim. The first published paper describes an extension of the Infinite Hidden Markov Model for detecting repeating block-diagonal structures, which could potentially be useful for detecting repeating sequences or motifs in a sequence of data. This work had already been described in the original strategic plan, and the originally stated goal was to apply this model to movies of objects viewed from a dynamically changing vantage point. The final report provides no description of work extending this to multiple object views.

The second cited paper (Li, Lee & Liu, 2011), which was included in the final publications list, involves the development of a hybrid generative-discriminative classification model. This model tries to identify relevant features in data for the purposes of classification, and allows each data sample to influence the model while assessing how well the sample fits the model. This model was applied to tasks of scene categorization and face and non-face classification and generally performed well. This successfully completed work represents one of the strengths of this project.

Another weakness was the lack of progress in Aim 3. As originally stated, the goal of this aim was to use single and multi-unit recordings to characterize the roles of the primary visual cortex (V1), area V4, and the inferotemporal cortex in figure-ground segmentation and object recognition, with a particular focus on understanding how objects are detected and recognized in cluttered visual scenes. With respect to the issue of visual clutter, their final report contains no mention of such work along these lines. In general, the goals of the original Aim 3 seemed overly ambitious, and there has been little progress to report.

There are two publications cited in this section of the report, though they are not listed in the separate publications section. The co-PI reports the publication of a paper on stereo-depth processing, which does have some potential relevance to understanding figure-ground segmentation; but the specific stimuli and paradigm did not directly address this issue. The PI

reports a very nice Proceedings of the National Academy of Sciences (PNAS) paper on the effects of learning temporal sequences of objects on the response of inferotemporal neurons, showing that greater responses occur to violations of temporal expectation. However, this study has little bearing on the issue of object representation and recognition, or on the perception of objects under conditions of visual clutter.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The work is focused on basic science developments in computational/statistical models of brain function and preliminary evaluation in simple animal models, e.g., monkeys. The value of this work in improving human health outcomes is unclear. As expected, the impact on risk factors, disease, etc. is limited to future developments which might result from the findings of the current grant. No major discoveries are apparent. Future plans involve a continuation of the basic science line of research being pursued in the current grant. The lack of greater focus on translation work which attempts to bring to bear the basic science findings in human populations is not considered. The ultimate benefit of this work is directly connected to such translation work, and it is strongly encouraged in the future.

Reviewer 2:
The outcomes of this project are likely to be important for computer vision and for visual processing in low and high-level visual areas. However, the significance of the project for health-related outcomes is likely to be indirect and distant.

Reviewer 3:
The original proposed work was highly ambitious, with the goal of gaining insight into the computational and neural bases of object recognition in cluttered visual scenes. If the project were successful, its findings would be relevant to understanding the bases of object recognition and enhance current understand of the neural basis of central visual disorders (such as agnosia induced by cortical brain injury). It could also potentially inform the development of better algorithms for performing computer vision tasks.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:
NIH grants (Olson) and National Science Foundation (NSF) and Air Force Office of Scientific Research grants (Lee) were leveraged against the Pennsylvania funding. Future plans for funding include a grant submitted by Lee to NSF-NIH in Collaborative Research in Computational Neuroscience. This seems to be connected to the overarching basic science goals of the researchers, with the translation aspect of the work given limited emphasis in such grants. It is

not clear how critical the current Pennsylvania funding was in this grant submission or the extent to which translational type grants are being contemplated.

Reviewer 2:
Additional funds were obtained to continue the project's research; however, since the submission date was close to the start of the project, it is difficult to determine how influential the outcomes of the current project were for the obtained funds. Further grant submissions arising from the project are described as pending.

Reviewer 3:
Dr. Lee (co-PI) submitted a grant application in 2009 to Air Force Office of Scientific Research to investigate surface representation and has also applied for a CRCNS (Collaborative Research in Computational Neuroscience) grant from NSF-NIH to elucidate the neural encoding of higher order concepts in the visual systems. However, it does not appear that Drs. Olson (PI) and Lee (co-PI) have made any plans to apply jointly for external funds to further the proposed research in this project.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:
A number of publications have resulted, with further publications planned, primarily based on the monkey data collected in Aim 3. The two publications listed in the publications section, Li et al (2010) and Samonds et al (2009), are in high-quality proceedings/journals. The extent to which the 2009 paper was initiated prior to the start of this grant is somewhat of a concern. There are also publications listed in Section 17, but these are not provided in the publications section, and it is not clear whether these are directly connected to the Pennsylvania grant. Overall, the research group has been productive, with many publications resulting, but the direct connection to the current Pennsylvania grant is somewhat unclear, in part because of the formatting of the final report.

Reviewer 2:
Two papers are listed as published in good peer-reviewed journals, and the expected publication eventuated and appeared in a high-impact journal. Importantly, the work described in the published manuscripts is of high quality.

Reviewer 3:
Two publications are listed in the publications section, and a few others were mentioned but not uploaded in the other sections of the report. The first listed article consisted of computational modeling work published in an Institute of Electrical and Electronics Engineers (IEEE) conference proceeding, and the second was a neurophysiological study of stereo processing in macaque V1. These two publications represent the strengths of this project. The quality of these publications is very good, though the study of stereo-processing is not so strongly related to the goals of this project.

A major weakness is that most of the contributions to the final report are from the co-PI, and it is not clear what accomplishments have been made by the PI and his lab.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:
Collaboration between Olson and Lee has been strengthened, which has increased capacity in the Center for the Neural Basis of Cognition primate electrophysiology facility at Carnegie Mellon University. Beyond these enhanced interactions, there do not appear to have been real improvements in terms of services offered or enhancements in equipment or facilities. New investigator training involved a number of undergraduate (2), graduate (4), and post-doctoral (2) personnel. It does not appear that any permanent investigators were recruited, with the above mentioned personnel functioning primarily in support of the investigators' high-level research programs, which have been supported by numerous NSF and NIH grants, in addition to the Pennsylvania funds.

Reviewer 2:
The new neural recording technique (multi-electrode array) is a significant infrastructure benefit for the institution, and a good number of students were involved in the project.

Reviewer 3:
The funds were used to provide partial salary support for the PI and co-PI, as well as a departmental business manager and an administrative associate. There were no improvements to infrastructure. No new researchers were brought to the institution to help carry out this research.

This represents a weakness, since the funds could have been better used to attract new talent to the institution.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:
This was quite limited. The only evidence is collaboration with Alan Yuille, a colleague at the University of California Los Angeles, whose R01 was partially based on some of the findings from the current Pennsylvania grant. It does not appear that the investigators have made much effort to identify and cultivate research partners outside the institution or in the community. Such partners would seem important for translating work in primates into human populations, where the ultimate impact is likely to occur.

Reviewer 2:
There was a collaboration with a researcher from the University of California Los Angeles described as resulting from project findings.

Reviewer 3:
A strength is that the co-PI reports that this grant has led to a new collaboration with Professor Alan Yuille at the University of California Los Angeles and has facilitated the development of a new R01 project on the neural representation of higher order visual concepts in the brain, currently pending.

A major weakness of the final report is its failure to convey how this grant has facilitated collaboration between the principal investigator (Dr. Olson) and the co-PI (Lee). In fact, there is little if any evidence of direct collaboration in this report; this represents a major shortcoming.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:
1. Greater emphasis on the translational aspect of the work is recommended, with greater attempts to identify partners who can facilitate translation of the findings into human populations.

2. Emphasis on enhancements in infrastructure is desirable, including leveraging of funds for facilities improvements.

3. Expansion of the research program to include permanent personnel would be desirable, which might require leveraging of Pennsylvania funds with other grant monies.

4. From the point of view of Pennsylvania, community involvement would be desirable in developing lines of work which are of direct interest to the local communities in Pennsylvania. There does not appear to have been thought given to such issues.

5. Greater emphasis on dissemination is recommended, including publications and conference presentations.

Reviewer 2:
1. A weakness is that there is little specific interaction between the computational and neurophysiological branches of the project. The potential to combine such approaches is great, and the research outcomes demonstrate how strong the researchers are in such domains. I recommend that the research team emphasize studies where computational and neurophysiological approaches are combined, or where specific predictions or principles that arise from one domain are directly applied to the other.

2. It is unclear why the proposed neurophysiological study was not undertaken. It appears particularly appropriate to the project objectives.

Reviewer 3:

1. The most major weakness is that very little direct research has been carried out for Aims 1 and 3, and only modest progress has been reported for Aim 2.

   Recommendation: A much greater amount of direct work needs to be carried out on each of three original aims to justify this project. If the original aims are now considered overly ambitious or certain difficult/insurmountable problems emerge, then these problems should be openly discussed. A proposal with modified aims would need to provide a clear rationale and justification for any proposed changes to the aims.

2. A second major weakness is the lack of evidence of direct collaboration between the PI and co-PI. Based on the progress report, it appears that the two research groups are pursuing their independent research programs and conducting the types of experiments that they would otherwise carry out in the absence of this collaborative grant.

   Recommendation: Regular meetings (e.g., monthly) between the two researchers and their labs should be implemented to foster a better integrated and interdisciplinary project. A specific set of goals and attainables for improving integration of the experiments, data, and analytic approaches should be clearly spelled out; and progress on attaining those targets should be evaluated throughout the project, if continued funding occurs.

3. Another weakness is that Aim 3 of the project seemed overly ambitious yet vague. There was minimal specification of how specific goals and experiments would be carried out; and there was no description of how data recorded from various levels of the visual hierarchy (V1, V4, IT) would be combined or analyzed to test specific hypotheses, such as feedforward or feedback interactions between these recorded areas. The proposal also lacked a strategic plan for how the experiments and data would be integrated across the two research groups to facilitate the collaborative goals of the proposed research. The lack of specific experiments, designs, and collaborative strategic planning has led to a vague and overly ambitious aim with no clear road map.

   Recommendation: Revise Aim 3 to include a more clearly articulated set of plans and experiments with specific achievable goals.

4. A final weakness is that the current funds have been used to provide partial support for the PI, co-PI and administrative staff. However, these funds could be used to attract new talent to the research institution and to foster the training of pre- and post-doctoral trainees.

   Recommendation: Re-budget the project to enhance the support of new trainees and to attract new talent to the institution.

5. Of note also is that many of the cited publications are only tangentially related to the original aims of the grant proposal.

Generic Recommendations for Carnegie Mellon University

Reviewer 1:
Greater high-level oversight is recommended to ensure aims and objectives are being met and that translational considerations are given appropriate emphasis.

Project Number: 0862703
Project Title: Memory-Based Neural Activity in the Hippocampus
Investigator: Touretzky, David

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The main goal of this project was to determine computational roles played by a major brain structure, the hippocampus, in order to better understand how cognitive processes arise from neural tissues. The input data were obtained from animal (rodent) based experiments performed in collaboration with Dr. Redish's laboratory at the University of Minnesota. The focus on the hippocampus was due to its importance for both memory formation and spatial representation. This project studied trajectory events (as "played" in the hippocampus of a rodent corresponding to travel down one of the two maze arms) in order to arrive at a better understanding of hippocampal information processing. There were two specific aims: 1) to apply statistical analysis techniques to multiunit recording data to reconstruct and characterize trajectories; and, 2) to develop computational models to try to replicate and thus explain the experimental data.

The project has met all its stated objectives. The research design and the methods used were appropriate and state-of-the-art. The investigators adjusted some of their research work in response to comments from reviewers for one of their submitted manuscripts ("Result 2: An attractor model of replay can produce forward, backward, and shortcut trajectories"). This change in research direction by relaxing some of the original assumptions about the underlying process was appropriate and led to more scientific insight. Unfortunately, the investigators have not pursued this manuscript to its completion.

Reviewer 2:
The objective of this project was to study (experimentally and through computational modeling) hippocampal encoding and replay of trajectory events in order to gain a better mechanistic understanding of hippocampal information processing. Specific Aim 1 applied statistical analysis techniques to multiunit recording data from experiments performed in collaboration with the Redish laboratory at the University of Minnesota, to reconstruct and characterize trajectories. Specific Aim 2 developed computational models, which were used to generate plausible mechanisms to explain the experimental data.

Strengths: Generally speaking, the project met the stated objectives. The collaboration with the Redish lab resulted in some interesting findings and a publication in a respected journal (*Neuron*). The most important finding was that hippocampal "replay" can produce "short-cut"

trajectories the animal never actually experienced in real life. With respect to Specific Aim 2, the PI and collaborators developed a computational model that has undergone several revisions (still unpublished at the time of the project report). The model deployed is of the "attractor" type, which was shown to produce forward, backward, and "shortcut" trajectories that were observed experimentally. This model, however, was found to have some problematic issues concerning the connectivity of hippocampal neurons required to learn "backward" replay. A second model was built to account for other characteristics of hippocampal function associated with hippocampal theta sequences exhibiting segmentation of spatial experience.

Reviewer 3:
The project had two distinct objectives, each of which I will review separately.

1) To apply statistical analysis techniques to multi-unit recording data obtained from other laboratories to reconstruct and characterize trajectories.

Strengths: This objective was accomplished very successfully. The resulting collaboration between Dr. Touretzky's laboratory and Dr. Redish's laboratory produced two high-profile papers. The first paper demonstrated that the hippocampus can replay sequences that represent trajectories that had never before been experienced, providing a possible neural substrate for mental exploration of new routes through space. That paper also provided a strong replication of work carried out simultaneously (and published just previously to the Gupta *et al* paper from the Touretzky and Redish groups) in two other laboratories demonstrating replay of local and remote spatial sequences. This work has substantial importance to the field and to our understanding of the role of replay in memory and navigation processes.

The second paper described sequences in the context of the theta rhythm and explored their structure, showing that these sequences tended to represent contiguous sections of a maze reminiscent of psychological "chunking."

The first of these papers developed a novel sequence detection algorithm which seeks to identify specific neuronal sequences in hippocampal place cell data. The second paper used a more robust Bayesian decoding approach to sequence analyses, but both represent a successful application of statistical techniques to understanding the hippocampal representation of space.

2) To develop computational models to try to replicate and thus explain the experimental data.

Strengths: This objective was partially accomplished. The investigators developed a model of the hippocampus that could encode and then replay sequences that relied on a specific gradient of connections from one end of the hippocampus to another. The authors submitted a manuscript detailing this model for review.

Based on feedback from that review the authors also considered alternative mechanisms for learning in the hippocampus that could support the same sequence learning phenomenon.

Weaknesses: As the authors note in their progress reports, the first model's predictions are incompatible with the available data, in that the model predicted that sequences would only be

seen in recordings that included a substantial cross-section of the longitudinal axis of the hippocampus.

The model also makes the common assumption that plasticity in the relevant circuits is governed by precise spike timing (STDP). It is important to note that this rule, which was derived from cultured neurons, may not accurately describe synaptic plasticity in the hippocampus *in vivo* (see, for example, Lisman and Spruston, 2010). The absence of a deep understanding of the actual learning rules *in vivo* makes developing well-constrained and testable models very difficult.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The ultimate benefit of this line of research would be in gaining better understanding of how the brain processes information and memory. The major brain structure that was studied, the hippocampus, is important in diseases such as Alzheimer's, since "hippocampal deterioration is also a major factor in Alzheimer's disease." The hippocampus is among the first brain regions that would be affected due to temporary loss of oxygen supply as a result of a major event such as stroke, heart stoppage, or drowning. Even though this research is mainly statistical and computational in nature and also based on data from rodent studies, it has the potential of inspiring similar studies in humans and shaping clinical and/or public health practice. There are no clear plans for next steps articulated in the final progress report.

Reviewer 2:
This project will impact our understanding of hippocampal function, which may lead to the development of intervention procedures for disorders of memory. It has also produced some computational models that can be used to generate predictions that can be tested in future experiments.

Reviewer 3:
This project aimed to futher our understanding of the hippocampus using basic research approaches. Hippocampal dysfunction is implicated in many disorders, including depression, schizophrenia and Alzheimer's disease; but we lack even a basic understanding of how the hippocampus works, making it difficult if not impossible to treat the brain-level manifestation of these diseases. Thus, research that helps us understand what the hippocampus does and how it does it has great potential for long-term improvements in mental health.

Strengths: The results presented in the two papers published as a result of this work are important contributions to the field. The first paper highlights the importance of hippocampal replay events in the exploration of an internal cognitive map, which is likely a central function of the hippocampus. Thus, treatments aimed at improving these replay events could have major benefits in the future. The second paper provides a new understanding of how sequences are

organized in the hippocampus, which also highlights the importance of the storage and replay of these sequences in behavior.

Overall, the budget for this project was quite small (~$100K), and the resulting discoveries are significant, indicating good value for the funds spent.

Weaknesses: The computational models developed are likely less significant than the physiological results. In addition, the future plans are somewhat vague. It is not clear whether this collaboration will continue, in part because the student is returning to medical school to finish his M.D. training.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:
A National Science Foundation (NSF) Integrative Graduate Education and Research Traineeship (IGERT) fellowship was used to leverage funding for a graduate student, Anoopum Gupta. In 2009, an NIH F30 training grant funding was also successfully obtained for Anoopum Gupta as a result of this project, entitled "Cognitive Maps and Novel Behavioral Sequences in the Hippocampus." No additional grant proposals are planned as a follow-up to this study.

Reviewer 2:
Anoopum Gupta has completed his Ph.D. and returned to medical school to complete his M.D. training. There are some plans to pursue some additional analyses of the data collected together with the PI, David Touretzky. Dr. Gupta secured an NIH F30 training grant ($231,900). No further grant applications will be made.

Reviewer 3:
Strengths: The project leveraged funds from a training grant to Dr. Gupta which paid his salary.

Weaknesses: No other grants or plans to write grants were listed, although I would assume that these results would be used to support grant applications in the future.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:
One peer-reviewed publication has been published already (Gupta *et al*., 2010), with one additional paper submitted and revised. No patents and/or commercial development opportunities have been pursued, since this line of research is not suitable for such initiatives. The research output and quality from this study is appropriate and satisfactory.

Reviewer 2:
One peer-reviewed manuscript was published in *Neuron*. This is a Tier 1 journal with high visibility. They have additional data that can also be published, but no further comments are made by the PI in this regard.

Reviewer 3:
Strengths: The project contributed to two high-profile, high-quality manuscripts, both of which have been published as of the date of this review.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:
A doctoral student, Anoopum Gupta, was supported and trained through this research program. Dr. Gupta has now completed his Ph.D. studies and has gone back to medical school to complete his M.D. There were no immediate improvements to infrastructure at Carnegie Mellon University, and no other investigators were brought to Carnegie Mellon University to carry out the research, aside from the collaboration with Dr. Redish from the University of Minnesota.

Reviewer 2:
One pre-doctoral student completed degree requirements through work on this project.

Reviewer 3:
There were no improvements made to infrastructure.

Strengths: The project supported a pre-doctoral student.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:
The study involved an outside collaborator, Dr. Redish from the Department of Neurosciences, University of Minnesota. The future for the entire research program, and hence the fate of the collaboration with Dr. Redish, is not immediately clear. Despite the excellent progress and research output from this study, the lack of clear next steps to build on this work is a weakness.

Reviewer 2:
The project led to a research collaboration with outside partners (Professor Redish, University of Minnesota).

Reviewer 3:
Strengths: The project supported a collaboration between Dr. Touretzky's laboratory and Dr. Redish's laboratory at the University of Minnesota.

Weakness: The future plans for this collaboration are not made clear.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:
1. They need to publish findings from Result 2.

2. They needed to articulate clear next steps as a follow-up to their interesting work.

Reviewer 2:
Excellent training program and facilities.

Reviewer 3:
Overall I think this was a small amount of money spent for a substantial amount of scientific progress.

Although the overall progress made was excellent, the modeling component was less successful than it could have been. I would encourage Dr. Touretzky to consider all of the assumptions made in the models to identify broader classes of models that could explain the data.