Lucky Mice:

Lucky Mice Project Summary:

This project found part of its inspiration in science fiction. In Larry Niven's *Ringworld* series he introduced a fictional alien race called "Pierson's Puppeteers" who carry on secret genetic experiments with human beings for six generations. The purpose of these experiments was to enhance the "good luck" or, what might be called a "propensity for serendipity," through surreptitious breeding of human subjects.

In point of fact, serendipitious phenomena are sufficiently commonplace that almost every human being in the course of an average lifetime is likely to encounter such an experience. These can include highly improbable experiences like winning the lottery, or surviving a plane crash, or more mundane occurrences like being in the right place at the right time, or running into friends in distant places. While serendipity might be ascribed to *chance* in general parlance, a closer examination suggests that true serendipity is *chance* coupled with *coincidence,* in the sense that two or more incidents happen at the same time. Both the judgment to recognize and the ability to accommodate unexpected and unexplained events underlie all episodes of serendipitous discovery.

Louis Pasteur rightly observed "Dan les champs de l'observasion le hazard ne favorise que les esprits prepares" ("In the fields of observation chance favors only the prepared mind"). The history of scientific discovery contains many examples of unexpected accidents that, through some form of enabled reasoning or clever deduction, are newly transformed into opportunity. These have included the discoveries of radioactivity, nuclear fission, the cosmic microwave background, x-rays, electromagnetism, electric current, plastic, penicillin, hallucinogenic properties of lysergic acid and many more.

Serendipity like other, basically intangible qualities (e.g., creativity, love, altruism, grace, patience, charm) may not seem subject to influences of inheritance and genetics, yet there are no reasons to believe that such correlations are absolutely impossible. Investigations of some of these behaviors have been undertaken in terms of psychology, cognitive science, information science and economics, but until now, no serious biological or genetic studies of serendipity have been initiated1. Perhaps this is due to the fact that no precedents for such a relationship have ever been discovered, or that qualities like luck may be considered to be exclusively imaginary. On the other hand, when the probability for success of a given experiment is infinitesimally small, the stakes can be so correspondingly high that experimentation attracts no serious interest. A careless lack of curiosity insults all those actions we do not honor with our attention. In this case, like the mythical *Clue of Ariadne* running through the Labyrinth, artistic avenues of inquiry can provide unexpected advantages for scientific research.

In reality, production of enhanced or desired traits in *Homo sapiens* such as those envisioned in Larry Niven's *Ringworld* would require hundreds of years. By comparison, a single generation of laboratory mice can be produced in only ~12 weeks2. Accordingly, collaborative experiments have been organized to observe serendipitous behaviors and pursue *in vivo* selective breeding of "lucky mice." These experiments investigate a genetic basis for serendipity in laboratory mice and involve mouse-operated apparatus that allow mice to throw dice.

Mouse-driven, dice throwing prototypes have been now been created by Joe Davis and Eswar Iyer at The Wyss Institute and George Church's Laboratory at Harvard Genetics. A further collaboration with Ashley Seifert at University of Kentucky concerns successive generations of mice produced by

selectively breeding pairs according to computational rules for their dice throwing outcomes. Note that analogous (fictional) genetic manipulations described in Niven's *Ringworld* series were carried on with only 6 generations of experimental subjects. Ultimately, we expect to breed at least an F2 (second generation) of "lucky mice" by the time Ars Electronica 2017 opens in September.

Also collaborating is University of Kentucky professor Jeremy Van Cleve, whose specialties include behavior; bioinformatics and computational biology. Jeremy will contribute formal, statistical analysis to our experimental results. Our approaches to these analyses are scientifically rigorous and strictly abide with protocols for both the ethical conduct of research and the humane treatment of laboratory animals. Mice involved in the *Lucky Mice* project are non-recombinant. Our experimental protocols do not call for surgical modifications of mice or administering of performance-enhancing drugs. Since the *Lucky Mice* project involves use of live mice, it inherently highlights dynamics and structures of human-animal relationships in art as well as scientific research. Our presentation will intentionally examine ethical considerations that underlie existing protocols for use and care of laboratory animals.

1. The cognitive neuroscience of creativity, Arne Dietrich
Psychonomic Bulletin & Review; Dec 2004; 11, 6; ProQuest Psychology Journals pg. 1011
http://econweb.ucsd.edu/~jandreon/Publications/PalgraveAltruism.pdf
https://www.omicsgroup.org/journals/is-ugly-the-new-beautiful-an-investigation-of-perceptions-of-beauty-by-young-female-viewers-of-ugly-betty-in-the-us-2165-7912.1000155.php?aid=15281
Investigating Serendipity: How it Unfolds and What may Influence it, Lori McCay-Peet, Elaine G. Toms, Journal of the Association for Information Science and Technology Jul 2015; 66(7):1463–1476
2. Laboratory mouse generation = 3 week gestation + 21-day weaning + 5-6 weeks until sexual maturity

Lay Summary

Luck, like other intangible qualities (e.g., creativity, love, altruism, grace, patience, charm) may not seem subject to influences of inheritance and genetics, yet there is no reason to believe that such correlations are absolutely impossible. Investigations of such behaviours have been undertaken in the fields of psychology, cognitive science, information science and economics, but until now, no biological or genetic studies of luck have been initiated. Perhaps this is because no precedents for such a relationship have ever been discovered, or that qualities such as luck might be considered exclusively imaginary. When the probability for success of a given experiment is infinitesimally small, the stakes can be so correspondingly high that experimentation attracts no serious interest. And yet, such artistic pursuits of inquiry can provide unexpected advantages for scientific research. In the study proposed here, we will test for a genetic basis of luck utilizing a novel mouse-driven device consisting of a standard mouse running wheel attached to an Archimedes screw that is pre-loaded with dice. Using the running wheel, individual mice will cause the Archimedes screw to turn, which "tosses" dice; the number of each die will then be recorded for a fixed number of tosses. Lucky male and female mice will determined based on their ability to throw matched die (i.e., doubles) more times than would be predicted by chance and will be bred and their offspring tested in a similar manner to determine if there is a genetic basis to luck.

Objectives

The “Lucky Mice” project is a collaborative endeavor between artist-scientists at the University of Kentucky (Ashley Seifert, Jeremey Van Cleve), Harvard University (Joe Davis, Eswar Iyer,) and freelance artists Dana dal Bo and Larissa Belcic. A primary objective of the proposed project is an attempt to relay how artistic motivation can drive scientific investigation and in doing so, inform the public at large about the application of scientific practice. Through these efforts, this project develops new forms of instrumentation and research with applications for both art and science. We have created simple tools to investigate hitherto unknown relationships of universal biological principles with transcendental, fleeting qualities that enrich life with substance and meaning. It is artistic expression that touches on the long-standing association of the operations of biology with mathematics and it accomplishes these rather lofty goals with practices and implements that are accessible and easily understood by a large public.

Larry Niven’s “Ringworld” serves as inspiration for the project where humans enrich for desired complex traits through selective breeding. Although in reality selective breeding in Homo sapiens as envisioned by Larry Niven would require hundreds of years, the genetic manipulations he describes were carried on with only 6 generations of experimental subjects. By comparison, a single generation of laboratory mice can be produced in only ~12 weeks. This project will use selective breeding to perform a pilot experiment to test if luck can be bred in outbred laboratory mice (Swiss Webster). To accomplish this objective, we will use a mouse-operated apparatus that allows mice to “toss” dice. The mouse-driven, dice throwing prototype was created by Joe Davis and Eswar Iyer at The Wyss Institute and in George Church’s Laboratory at Harvard Genetics.

Briefly, a standard free-running wheel was attached to an Archimedes screw such that turning of the running wheel powers the Archimedes screw to turn in unison. The Archimedes screw is contained in a closed tube. The bottom end is pre-loaded with dice that get carried towards the top end as the screw turns. At the top end there is an opening out of which the dice are tossed. This apparatus will be placed in one of Dr. Seifert’s custom spiny mouse cages (specs = 24” x 18” x 16”). A single mouse will be placed in a cage with free access to the running wheel. Mice will be placed in the cage in the morning to acclimate to the cage. Wheel running occurs in the evening.

Upon entering and using the wheel, the mouse will thus power the machine and toss dice. The number of pre-loaded die is fixed. As a die is thrown, the number shown will be recorded. For the pilot, we will define a “lucky roll” as two or more die rolling the same number. This occurs by chance 1/6 of the time and if each mouse rolls a pair of dice 10 times, it will have at least one lucky roll on average. We will use a form of “truncation selection” for choosing who will breed where the three mice with the most lucky rolls will get to breed. The offspring of these crosses will then be tested in an identical manner and subsequently bred to determine if there is a genetic basis to luck. As a pilot experiment, we will conduct breeding for six generations.

Our approaches to these analyses are scientifically rigorous and strictly abide with protocols for both the ethical conduct of research and the humane treatment of laboratory animals. Outbred mice (Swiss Webster) involved in the “Lucky Mice” project are outbred, will experience no pain or distress, and operate running wheels on their own terms. Our experimental protocols do not call for surgical modifications of mice or the administration of performance-enhancing drugs. Importantly, mice used for this project will be made available to transfer to any other protocol at

the University of Kentucky, in addition to Dr. Seifert's protocols. Since the "Lucky Mice" project involves use of live mice, it inherently highlights dynamics and structures of human-animal relationships in art as well as scientific research. We will intentionally examine ethical considerations that underlie existing protocols for use and care of laboratory animals and will consider the design and presentation of physical environments, mouse habitats and dice throwing apparatus as a means to enhance public understanding of ethical contexts relating to the work.

We plan to analyse the data from our pilot experiment in two ways. First, we will estimate the heritability of rolling lucky die rolls using the "animal model" of quantitative genetics (Lynch and Walsh, 1998). The animal model tends to produce less biased results than other approaches (e.g., parent-offspring regression and sibling analysis using ANOVA; Kruuk and Hadfield, 2007) and also allows the analysis of arbitrary pedigrees, which will permit a full analysis of the pilot experiment instead of isolating parent-offspring families. The improved accuracy of the animal model trades off with increasing computational complexity. Thus, we will estimate our false positive rate using instead estimates from parent-offspring regression. This estimate suggests that 60 families (10 families per generation of breeding) will generate a false positive rate of less than 5% for heritability values of 0.5 and higher (see equation 17.11a in Lynch and Walsh, 1998). For the purposes of a pilot study, this should allow us to detect a strong genetic component of lucky die rolling, if one exists. Our second analysis method will estimate the strength of selection in terms of standardized selection coefficients and the response to selection on the luckiness of the mice in the experiment over the six generations using a standard approach developed by Lande and Arnold (1983).

Kruuk, L. E. B., and J. D. Hadfield. (2007). How to separate genetic and environmental causes of similarity between relatives. Journal of evolutionary biology 20.5: 1890-1903.
Lande, Russell, and Stevan J. Arnold. (1983). The measurement of selection on correlated characters. Evolution 37.6: 1210-1226.
Lynch, Michael, and Bruce Walsh. (1998). Genetics and analysis of quantitative traits. Vol. 1. Sunderland, MA: Sinauer.
Niven, Larry. (1970). Ringworld. Ballantine Books.

Choice/Justification for Species

Mice are a model organism for genetic research. The Mus musculus genome has been completely sequenced and annotated. Mus breed well in captivity and readily use running wheels when placed in their cages. Swiss webster mice are frequently used in research by Dr. Seifert and other University of Kentucky researchers and mice will be made available to other researchers on campus after use. Our animal numbers are based on our a priori statistical approach and are requesting to use 135 animals total. This number is calculated as follows:

We will begin with 15 male and 15 female mice. All will be run through the experiment and the top 3 from each sex selected for breeding. We will setup 3 breeding pairs. Expecting an average litter size of 9 for this strain, we will then run ~27 mice from the F1 generation through the experiment. We will again, choose the top 3 male and female and breed these animals to produce ~27 F2. We will repeat this for 6 generations. Therefore: Initial 30 animals + 27*6 = 192

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Total mice requested = 192 C