

PREDICTIVE MODELS OF COGNITIVE OUTCOMES OF DEVELOPMENTAL INSULTS

Yupo Chan¹, Nidhal Bouaynaya¹, Parimal Chowdhury², Danuta Leszczynska³,
Tucker A. Patterson⁴, and Olga Tarasenko⁵

(1-System Engineering Department, University of Arkansas at Little Rock, Little Rock, Arkansas, USA; 2-Department of Physiology and Biophysics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; 3- Department of Civil and Environmental Engineering and Interdisciplinary Nanotoxicity Center, Jackson State University, Jackson, Mississippi, USA; 4- Division of Neurotoxicology, National Center for Toxicological Research, Jefferson, Arkansas, USA; 5- Department of Biology, University of Arkansas at Little Rock, Little Rock, Arkansas, USA)

ABSTRACT: Representatives of Arkansas medical, research and educational institutions have gathered over the past four years to discuss the relationship between functional developmental perturbations and their neurological consequences. We wish to track the effect on the nervous system by developmental perturbations over time and across species. Except for perturbations, the sequence of events that occur during neural development was found to be remarkably conserved across mammalian species. The tracking includes consequences on anatomical regions and behavioral changes. The ultimate goal is to develop a predictive model of long-term genotypic and phenotypic outcomes that includes developmental insults. Such a model can subsequently be fostered into an educated intervention for therapeutic purposes. Several datasets were identified to test plausible hypotheses, ranging from evoked potential datasets to sleep-disorder datasets. An initial model may be mathematical and conceptual. However, we expect to see rapid progress as large-scale gene expression studies in the mammalian brain permit genome-wide searches to discover genes that are uniquely expressed in brain circuits and regions. These genes ultimately control behavior. By using a validated model we endeavor to make useful predictions.

Keywords: developmental perturbations, neurological consequences, predictive model, evoked potential, mammalian species.

INTRODUCTION

Neuroinformatics has been defined by the Organization for Economic Cooperation and Development (OECD) as "... combining neuroscience and informatics research to develop and apply the advanced tools and approaches that are essential for major advances in understanding the structure and function of the brain." The task of relating the functions of the mind to the regions of the brain is a prerequisite for both basic understanding and progress towards treatments for a range of neurological and psychiatric disorders like Alzheimer's disease.

In the past four years, representatives from the Arkansas Children's Hospital (ACH), National Center for Toxicological Research (NCTR), University of Arkansas for Medical Sciences (UAMS), University of Arkansas at Little Rock (UALR), and University of Central Arkansas (UCA) have met and discussed the relationship between functional developmental perturbations and their neurological consequences. The goal of this multi-institutional collaboration is to develop a predictive model of long-term genotypic and phenotypic outcomes of developmental insults, i.e., to track the genetic makeup and its physical characteristics over

time. The model will be used in prediction of neurological and genetic perturbations and risk assessment. Every model prediction will be validated eventually by conducting laboratory experiments on rodents or other mammalian subjects. An across-species study has shown that research previously conducted in rats and mice can be equated to current and future studies done in humans (Clancy et al., 2009). Understanding the dynamics of genetic and neurological consequences of developmental insults over time and across species forms the basic and crucial steps toward intervention and treatment for a range of neurological ailments - ailments that, if left untreated, often lead to other health complications. For a complete record of the multi-campus team's four-year deliberations, the reader is referred to the project website: <http://bioinformatics.ualr.edu/neuroinformatics>.

METHODOLOGY

It is remarkable that diverse researchers from different backgrounds (Physiology, Neurology, Genomics, and Engineering) have a common interest in the subject of functional developmental perturbations and their neurological consequences. Limited by clinical data on humans, we all agree to perform experiments across mammalian species. Physiologically, we want to track the effects on anatomical regions, and neurologically, we want to track behavioral changes. The empirical data will be used to drive a theoretical model for prediction. Furthermore, we propose to incorporate genetic information in order to study the visible phenotypic characteristics of an organism resulting from the interaction between its genetic makeup and the environment.

Empirical Approach. Between the institutions, quite a few datasets were identified to test plausible hypotheses:

- Datasets on the effect of non-competing anesthetic stimulants such as ketamine (which can be obtained across multiple institutions, including UAMS and NCTR)
- Evoked potential datasets as a way to track neurological maturation or degeneration (which are available from UAMS, ACH and Arkansas State University)
- Genomics and proteomic databases (available from NCTR), which offer the promise of understanding the topology, and ultimately the function of the neurological system, opening previously unexplored avenues in Neuroinformatics.
- Methamphetamine exposure datasets (from UAMS)
- Parkinson's disease datasets (including animal databases, such as protein expression in animal subcultures)
- One hundred high-risk mothers from SARA¹ datasets at UAMS (supplemented with hypoxic events, or an inadequacy in the oxygen reaching the body's tissues, to be studied with animals)
- Sleep disorder/development datasets (from the Sleep Lab in the Department of Psychology at UALR)
- Hearing loss data, from ACH (or the Hearing Clinic at UALR)
- Subpopulations of cells, their migratory ability, and how they proliferate (UAMS)

Theoretical Investigation. While the seemingly abundant datasets suggest an experimental approach, researchers at UCA proposed a cyber enabled method to model and predict neural development across mammalian species, based on available developmental datasets that exist in today's rich Internet database (Clancy et al., 2009). Such a modeling approach is possible because the sequence of events that occur during neural development is remarkably conserved across mammalian species. In particular, it was found that brain development in all species occurs in somewhat similar fixed sequences. This allows us to employ statistics to relate across

¹ SQUID Array for Reproductive Assessment

a database constructed from dates of brain development assembled from the vast published literature. A web-based interface provides users with predicted dates of brain development for humans. This is performed in spite of the fact that human data are generally unavailable, because studies have not been, or cannot be, conducted.

Research Implications. Irrespective of an empirical or theoretical approach, we are interested in the common cause of neurological developmental complications and their consequences. Proposed analytical procedures may include classification methods in identifying various patterns of causes and effects. For example, can we separate electroencephalography /magnetoencephalogram (EEG/MEG) signals from different neurological perturbations within the same species? If not, does this mean that they have a common cause? Can we separate brain signals of the same neurological perturbation across species? If not, does that validate the conservation across species theory?

As far as cognitive outcomes, questions may arise regarding which region of the brain we are examining? This means source localization in the brain of the data collected for different neurological perturbations. Are different perturbations emanating from the same source in the brain? Furthermore, one might want to relate the brain source localization study to the EEG/MEG classification and correlation analysis.

Another useful study may be to elucidate the genes and proteins involved in different perturbations within the same species and in one given perturbation across species. If multiple genes are discovered for a given perturbation, we can study their intranet regulatory interactions and then expand to inter-network interactions. A question arises then: Can we relate the genomic study to the phenotypic study above, which used classification, correlation and source localization?

For each of the above studies, we can use the analysis to predict possible outcomes for other species and/or perturbations, which were not considered in the study. This will provide great potential for discovery and new insights into old problems! The potential clinical impact is tremendous as this type of model-based analysis can open up a window on the physiology of an organism and disease progression for humans. This can be fostered into accurate diagnosis, target identification, drug development, and treatment. Let us expand on this point through the consensus that emerged from a panel discussion during the 2009 BioNanoTox Conference held in Little Rock, Arkansas (<http://sites.google.com/site/bionanotox/>).

DISCUSSION

With the excellent resources available from the multidisciplinary panelists as listed in the Appendix, four questions were posed to the panel during the Conference. Here are their thoughtful responses.

Question 1. Coming from different backgrounds, how would the panelists view the problem of “Predictive Models of Cognitive Outcomes of Developmental Insults,” the theme of our panel discussion?

The panelists interpret it as using genetic and chemical perturbations on animals to track neurological development, and then translating the results to humans. Three studies were proposed. The first study controls a group of rats, for example, to examine the maturation of the rat brain. The timing of brain development from the experimental species to humans can then be derived. This conversion, however, might not be straightforward as the time windows between transitions are still not certain.

In a second experiment, a database monitors the lead in paint and other toxic particles. It was shown that such chemicals are harmful to animals. Their exact influence on humans, however, is still unknown. We can try to build a Quantitative Structure-Activity-Relationship/Quantitative-Structure-Property-Relationship (QSAR/QSPR) model, which can be

used for estimating various chemical properties and biological activities. The developed predictive models are based on information available from the animal study. It will be used to validate descriptors against data collected from humans that develop particular diseases associated with lead poisoning.

The third study focuses on nicotine as a risk factor in the development of pancreatic cancer (Chowdhury et al., 2002). The mechanism by which nicotine induces cancer is suspected to be mediated by chemical, environmental, and genetic elements. Therefore, a better understanding of the developmental implications of nicotine should take into account these three aspects.

Question 2. If you were to propose new research to solve this problem, what datasets would you need?

One approach focuses on new learning, where puzzles are presented to a control group of subjects to assess their learning process. By pressing levers, children play a prescribed set of games. This experiment assesses learning and visual discrimination for both children and monkeys. Positive reinforcement is used: food for animals and nickels for children (of an early age that their brains are still developing). This research has implications in dispensing anesthetic agents, such as when premature infants are kept sedated in the neonatal intensive-care unit during postnatal care. It is a tough balancing act between saving human lives versus possible permanent damage to the infant's brain.

Another tracking experiment was performed on the administration of drugs. This involves gene expression studies with simultaneous examination of protein alterations. It is known that most ailments are not caused by a single gene mutation but by the complex interaction of multiple genes. Personalized, efficient and proactive medicine, based on individual genome profiles rather than statistically inferred "fit-all" drug models, will become widespread once we successfully understand the dynamics of genes that are linked to diseases (Tarasenko and Kitaev, 2002). Advances in high-throughput gene expression profiling can help identify molecular targets for potential therapeutic intervention. Gene therapy in neurological diseases, however, suffers from many limitations including, mainly, drug delivery and extent of transfection - the infection of a cell with viral DNA leading to production of the virus in the cell.

In a study of the pancreas, the disposal systems among animals are the same. However, the loss of function is different, even though the inflammation of the pancreas is similar between animals. It is suggested that biomarkers (such as particular genes or proteins) could be important. Experimental or quantitative observations that relate insults with outcomes could also be potentially useful for building models. For instance, QSAR/QSPR modeling could search for a relationship between structure-activity and structure-properties.

Question 3. Upon availability of these data, what hypotheses would you like to test or what models would you like to validate?

While one can perform mapping between human and animal time windows, it varies for different regions of the brain. In this regard, models have limitations, since separate models may have to be constructed for discrete areas of the brain. Regarding monitoring toxicity over time, one school of thought is to use cell death as a predictor. Another school of thought is that our brain, and in fact our life, is most influenced by the environment, not necessarily one single factor. Therefore, one must take into account genetic and environmental factors in assessing neurological consequences of developmental insults. For all these hypotheses or theories, validation is difficult; but the gathered evidence by observing the learning process of monkeys looks promising (Paule, 2001). An example is the effects on their short-term memory.

Question 4. Obviously, there are different approaches, namely physiological versus neurological approaches, just to name two. Do you feel that there is common ground between apparently differing techniques to solve this problem?

Datasets exist for known exposures in clinical populations, such as observing attention disorder in a control group versus others not in the group. When supplemented with genomics data, progress can be made. On the one hand we can model the brain function at a molecular level, where there may be molecular level change in energy and isomers, i.e., chemically identical molecule with different structure or energy state. These changes could be permanent or temporary. To mimic the environment, on the other hand, we still need the whole animal or human. An example is autism in children, a disturbance in psychological development in which use of language, reaction to stimuli, interpretation of the world, and the formation of relationships are not fully established and follow unusual patterns. It is not sufficient to make neurological observations in a laboratory setting; a child has to be monitored as he/she interacts with others in a social setting.

From this example, it is clear that in many cases, a neurological approach alone is not sufficient to explain the perturbation. A physiological approach is also necessary. Finally, a question for both approaches is what tests to perform between monitoring, say, a tumor versus one's memory. Another more holistic question is what type of interaction with the environment is cancer prone? This is an area where Physiology, Neurology, and Systems Biology interconnect. Different levels of study provide different pathways of investigation. However, validation remains to be performed irrespective of the approach.

CONCLUSIONS

We are extremely fortunate to have a synergistic group of researchers that pooled their resources together to address the problem of "Predictive Models of Cognitive Outcomes of Developmental Insults." A team of researchers from UCA, UAMS, UALR and Cornell has recently been recognized through a sizable National Science Foundation grant. This grant is to develop tools that will help researchers compare and predict brain development across species (including humans). Many aspects of human brain development are studied in non-human species such as rats or rhesus monkeys. The project "Collaborative Research: A Web-Based System for Modeling and Predicting Neurodevelopment across Mammalian Species" addresses this cross-species conversion problem, employing researchers and students in Neuroscience, Evolutionary Science, Computer Science, Data Mining, Mathematics and Statistics.

Rather than a theoretical investigation, some prefer an empirical approach. As surfaced during the panel discussion, however, there is a handicap in experimentally identifying these neurological developmental time windows. Some researchers argue that they cannot be distinctly observed, owing to a familiar phenomenon in experimental science, where the observation procedure changes the state of that being observed. In our case, there might be underlying behavioral changes due to chemical imbalances or other factors, making it difficult to precisely define these windows. Non-invasive techniques such as EEG and MEG signals makes it possible to record a developing brain's evoked response due to both auditory and visual stimulation. An ongoing study at UAMS includes Magneto-cardiogram (MCG) to jointly track fetal neurological development. By correlating the MEG signals with the MCG signals, one begins to verify (and eventually validate) observations. To assess the accuracy of an empirical approach based on signal measurements, we can apply the latest spatial signal-processing techniques to detect intervention on these datasets. Spatial signal processing employs multiple sensors to monitor different parts of the subject, including different areas of the brain. Recent experiments with spatial signal processing have yielded promising results, including source localization (Soni et al., 2007).

Another recent advancement is in genomics and proteomics. Tremendous progress has been made the past few years in generating large-scale datasets for gene-gene interactions,

protein–protein interactions, organelle composition, protein activity patterns and protein profiles in cancer patients. Aside from the cellular (molecular) level, computational systems biology is being undertaken to better understand the interaction of an organism with the environment. We need more computational research and other holistic models that can predict toxicity and prevent unwanted developmental effects, which ultimately lead toward disease prevention. To the extent that human development is influenced not only by a single factor, but a multitude of factors that exist in the environment, this approach is worthy of closer examination.

Regarding the debate between a physiological versus neurological approach to address the problem of “Predictive Models of Cognitive Outcomes of Developmental Insults,” the panel discussion suggests that the debate may be ill conceived. The body is made up of the mind and organs, which are inseparable. One influences the other. The branch of Chinese medicine, acupuncture, is a good example. It demonstrates the close interaction between the nervous system and the organs. It is certainly advantageous to have physiologists, neurologists, psychologists, environmentalists and engineers (just to name a few) working side-by-side to address this important subject problem. The success of multi-campus and multi-institutional collaboration to date speaks to the power of synergism. One goal of the panel and this accompanying paper is to facilitate additional collaboration in the future.

APPENDIX – LIST OF PANELISTS

Nidhal Bouaynaya, Ph.D. is assistant professor in the Dept. of Systems Engineering at UALR. Her research interests are signal, image, and video processing, genomic signal processing, and mathematical morphology.

Yupo Chan, Ph.D. is Professor and Founding Chair of the Dept. of Systems Engineering at UALR. His interests include telecommunications, networks and combinatorial optimization, multi-criteria decision-making and spatial-temporal information. He spent five years with the UAMS SARA project performing spatial signal-processing.

Parimal Chowdhury, Ph.D. is Professor of Physiology and Biophysics and Associate Professor of Pharmacology and Toxicology at UAMS. His research focuses on nicotine-induced patho-physiological changes of the exocrine pancreas.

Danuta Leszczynska, Ph.D. is a Professor in the Dept. of Civil and Environmental Engineering and a member of the Interdisciplinary Nanotoxicity Center at Jackson State University. Her latest research includes nano-particles and their biological applications.

Tucker A. Patterson, Ph.D. is a Senior Research Biologist in the Division of Neurotoxicology at NCTR and Adjunct Assistant Professor in the Dept. of Pharmacology & Toxicology at UAMS. He is interested in predicting neurotoxicity by measuring neurotoxic compounds and their metabolites in the blood and brain.

Merle G. Paule, Ph.D. is Director of the Division of Neurotoxicology at NCTR and Adjunct Professor in the Dept. of Pharmacology & Toxicology at UAMS. He has developed an automated system for monitoring multiple complex brain functions using similar behavioral tasks across species to determine how exposure data can be used for risk assessment.

Olga Tarasenko, MD is an Assistant Professor in the Dept. of Biology at UALR. Her research focuses on how to enhance resistance macrophages and/or immune cells to spores, capsule, and, parasites, and toxins during phagocytosis. These studies are meaningful for pathogen-host interaction studies involving different genes, receptors; for the development of detection methods; establishment of a ligands library; vaccine and/or immunomodulators and/or decontamination methods development.

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