Accelerating Epigenetic Research at UPenn's Perelman School of Medicine with Exxact's GPU Workstations

EXXACT

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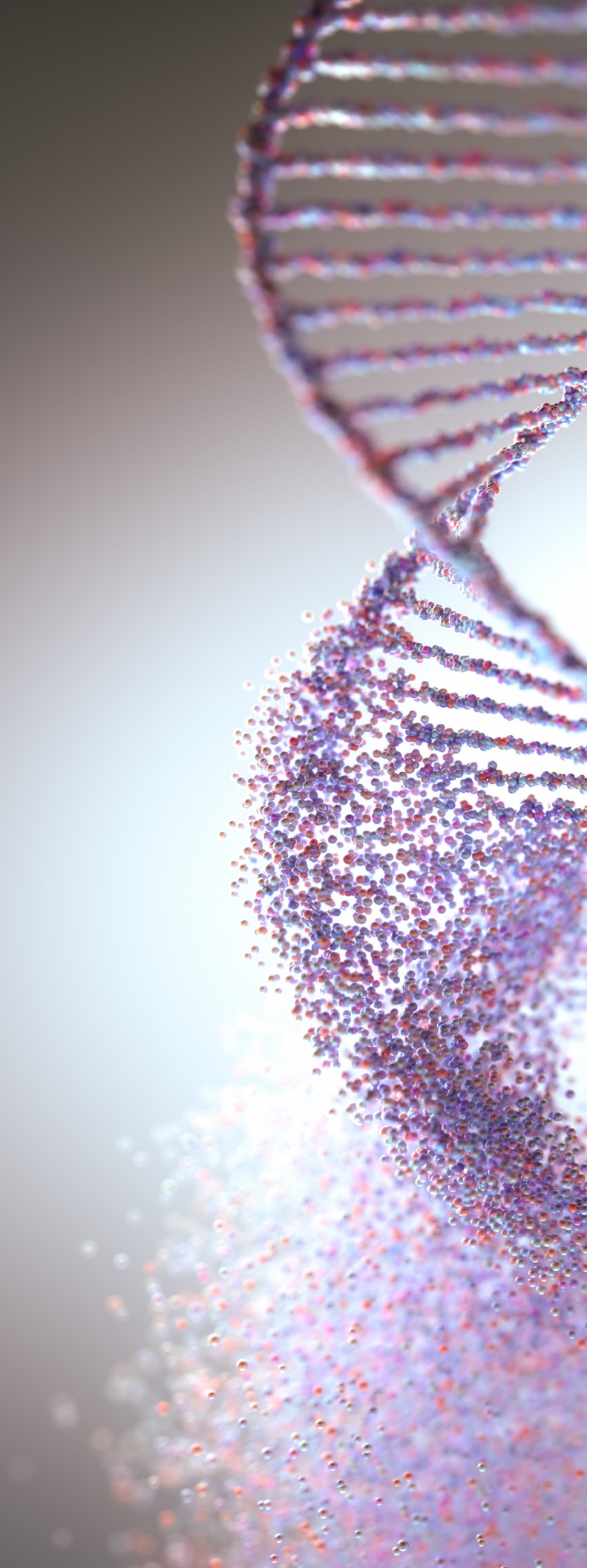
Background

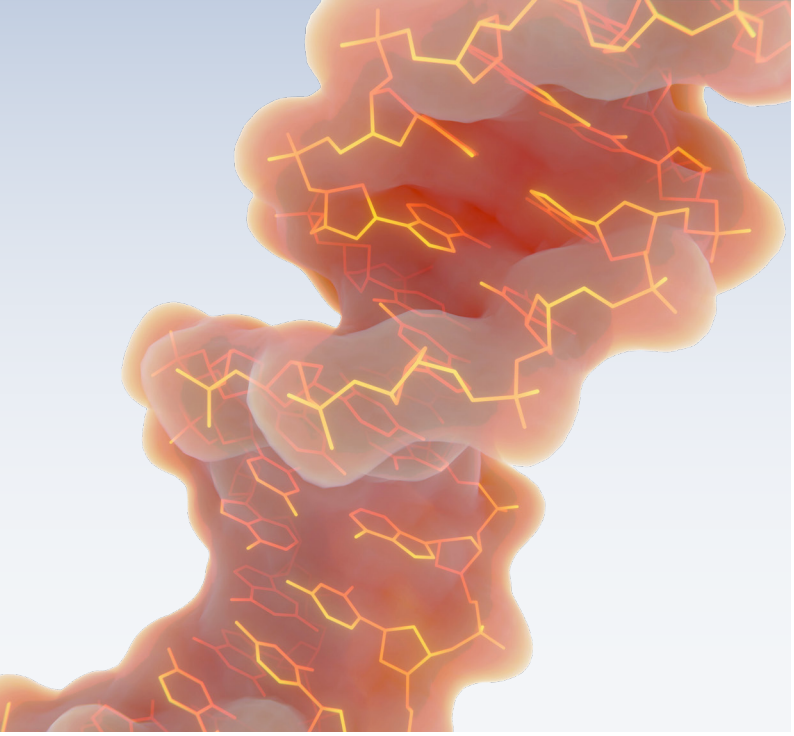
Balint Kacsoh is a postdoctoral research fellow in the Berger Lab of the Epigenetics Institute located at the University of Pennsylvania Perelman School of Medicine. The Berger Lab studies epigenetic regulation in a variety of model systems (S. cerevisiae, DNA tumor virus HSV-1, mouse, and eusocial insects), focusing on chromatin mechanisms underlying aging, gametogenesis, viral infection, cancer (p53 regulation), and animal behavior.



BERGER LAB

Research Overview

Berger Lab's research focuses on regulation of the nuclear genome in mammals and model organisms. The long strands of nuclear DNA are associated with packaging proteins, called histones, into a structure known as chromatin, akin to the way thread is organized around a spool. They are particularly interested in changes in this chromatin structure via chemical modification of the histone proteins, and how attachment of certain chemical groups onto the histones leads to altered chromatin function. These targeted structural changes are conceptually like the unraveling of the thread to reach specific, buried sections. They are also fascinated by functional changes in chromatin, caused by these histone modifications, that persist through cell division from one cell into two daughter cells; these persistent, or epigenetic, changes are of particular interest because they are key to normal and abnormal growth: they occur during organism development into multicellular tissues and organs, and are typically disrupted during abnormal reversal of tissue specialization and growth control as in cancer, as well as during aging of cells and individuals.

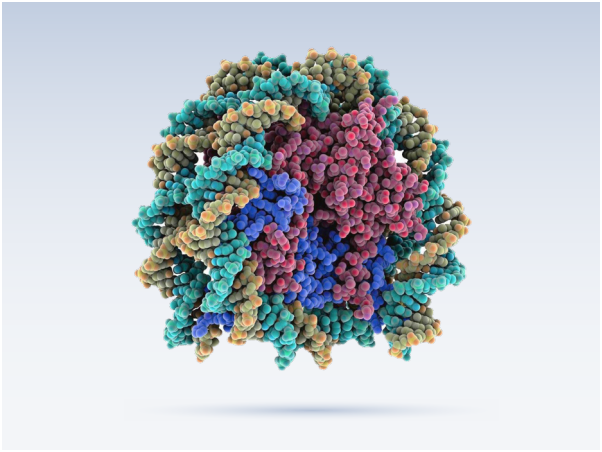


Research Focus

The basis of genome regulation is a fundamental biological question. Past research findings have helped to establish the prevailing view that histone modifications regulate genomic functions, including transcription of genes, DNA replication during cell division, repair of DNA mutations as a result of DNA damage, and other processes. Berger Lab focused on transcription, or the turning on and off of gene expression, and the myriad of histone modifications that occur, such as acetylation, phosphorylation, methylation, among other chemical changes. They identified many new modifications and the enzymes that carry them out, as well as understanding how the enzymes are recruited to certain locations in the genome. There is now an explosion of research in the field of chromatin regulation and how these histone modifications function to regulate the genome. Their research contributed to the current ideas, including how histone PTMs function in combinatorial patterns, and in temporal sequences, to set up the intricate timing and spatial requirements of turning genes on and off. For example, they have extensively studied a pattern on histone H3 consisting of Serine10 phosphorylation and Lysine14 acetylation.

They identified the enzymes that carry out the linked modifications, established the structural and biochemical basis of the cross-talk, and discovered a binding protein that specifically associates with the pattern, rather than the individual modifications. In a second example, they studied the timing of histone H2B ubiquitylation followed by deubiquitylation, identified the deubiquitylating enzyme, and determined the biochemical role of the dynamic switch, i.e. in regulating elongation by RNA polymerase II through transcribed genes.

The work of Berger Lab has also helped to reveal how some of these modifications, first characterized on histone substrates, such as acetylation and methylation, function to regulate non-hist one proteins. In particular, they have identified new modifications on the tumor suppressor and transcription factor, p53. The p53 is key because of its function in regulating growth to prevent cancer, and so they wish to determine how these individual modifications turn p53 function on and off. Recent findings show that methylation and demethylation of p53 at a single lysine residue both activate and repress p53 function. This regulation occurs by promoting or inhibiting, respectively, the binding of a p53 coactivator protein, called 53BP1. The team believes this type of regulation of p53 will prove to be common among non-histone proteins.



Research Future Directions

The current focus of the team is to continue to discover novel chromatin and factor modifications and their mechanisms of action. However they are now endeavoring to elucidate the role and importance of these modifications in normal and abnormal cellular function. In particular, they are keen to determine whether these modifications are important in persistent or epigenetic cellular states, as mentioned above. Thus, the emphasis is more biological in the sense of investigating how physical changes in chromatin impact biological processes such as gametogenesis and viral latency, as well as broader phenomenon such as aging, behavior and cancer. As one recent example, their lab initiated a study of chromatin changes during replicative aging in the model S. cerevisiae. They discovered that telomeric changes in chromatin are centrally involved. Specifically in old cells there is a reduction in the level of the histone deacetylase Sir2, which is crucial in maintaining compact chromatin in sub-telomeric regions, leading to an increase in histone H4 K16 acetylation by the acetylase Sas2. The result of this is decompaction of the teleomeric chromatin in the old cells.

Epigenetics is still an emerging field in biology, and is exerting an increasingly profound impact on medicine because of its potential explanatory power in development and disease. In spite of the broad interest, there is no clear consensus on a definition of epigenetics in chromatin research. To help to provide a framework for the field and beyond into the wider research community, their team recently published a short proposal defining epigenetics, encompassing both established ideas in the chromatin field and providing some operational concepts.

Situation

The lab is using a model to perform deep learning on ant behaviors. They're studying the epigenetics behind caste determination, so they need a very powerful computer to train the behavioral networks to analyze their data. The goal is to analyze behavior in an unbiased way, and they use high speed videography and deep learning to analyze the videos. Ants are almost genetically identical. Yet, their castes vary as well as their behavior. Using video with deep learning, the Berger Lab is looking to determine how behavior is regulated on an epigenetic level.

Challenge

Balint recognized the importance of having a powerful GPU to run their software on. Using only a CPU based laptop required a huge amount of time to run several thousand iterations of training. For example, it would take their laptop over 36 hours to run 2,000 iterations of training. Running his own research analysis, along with research training models for 10 other people in the lab, the performance of the current system was woefully inadequate to turn out results quickly.

Solution

The Berger Lab knew they needed a very powerful GPU and Exxact was the only place they found that could run a dual NVIDIA Titan RTX configuration. Exxact's resources were very good at demonstrating the deep learning ability of their workstations and servers, and the laboratory chose an Exxact Valence Deep Learning DevBox to replace their outdated laptop. An additional configuration request was to have the Titan RTX GPUs connected with NVLink in order to optimize the speed and power they required from the system.

When the lab received the system, the results were everything they expected and more, with the performance proving "amazing for our research speed". Instead of taking 36 hours to run 2,000 iterations of training, the new Exxact Valence system allowed them to run 200,000 iterations of training in only 5 hours. **A whopping 9900% speed increase!** They plan on using the Exxact workstation for years in analyzing video research as they hope to further the study of epigenetics and how it regulates behavior and health.

> "The Exxact workstation has revolutionized our research lab's work on behavior.

A special thanks to our contributor, Balint Kacsoh.

From Balint Kacsoh
Research Interest

I believe that the interplay of neurobiology and the social sciences is a critical region of study, termed "sociogenetics." With more and more precise molecular and neurogenetic tools, we are to better understand and define the relevant differences between a variety of social orders.

In 1975, E.O. Wilson accurately predicted that a split in these two disciplines would occur primarily based on mechanistic/molecular approaches and evolution/ecological approaches. Sociality exists across many branches of the tree of life and is thought to encompass a spectrum of behaviors. But is there a single criterion that is truly suggestive of all forms of sociality? E.O Wilson suggested that the common denominator of sociality is the ability to communicate, stating: "the terms society and social must be defined quite broadly in order to prevent arbitrary exclusion of many interesting phenomenon" (Wilson 1971). In particular, I view sociality as the degree to which individuals tend be gregarious, or associate in social settings, and form cooperative groups that ultimately increase the survival and fitness of the individuals. But what influences these behaviors on the molecular level? How do experiences shape our genetic information? This remains unknown and my long-term goal is to answer these questions using the more fluid reproductive plasticity present in ponerine ants such as Harpegnathos saltator, where I am studying the epigenetic effects of caste identity as a function of social environment. In ants, bees, wasps, Drosophila, and other insects, we are privileged to not only see how complex societies evolve independently of humans, but also to dissect, with ever increasing clarity, the relationship between advanced social order, the forces of natural selection that shaped them, and the underlying neuro-genetic, epigenetic, and genetic mechanisms that guide these behaviors.

We have only just arrived at the boundary between insect behavioral neuro-genetics, evolution and ecology, and sociobiology. These findings and studies could have fruitful vertical integration to humans when asking about the genetics of sociality.

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