Winner of the 2010 $30,000 Lemelson-MIT Student Prize
### *Erez Lieberman-Aiden: Notable Inventions*

Hi-C: 3-D Genome Sequencing

Scientists have known for decades that a few dozen bases of DNA fold up into a double helix, but have not fully understood how the three billion base-pair long genome – 2 meters in length when stretched out – folds to fit into the nucleus of a human cell, which is less than one hundredth of a millimeter in diameter. To answer this question, Erez Lieberman-Aiden developed Hi-C, a technology that enables three-dimensional genome sequencing. Developed together with postdoctoral student Nynke van Berkum, Hi-C uses formaldehyde, acting as a glue-like substance, to link together segments of DNA that are far apart in the linear genome, but adjacent to each other in 3-D. The linked pieces of DNA are marked with biotin, extracted, and mapped onto the reference copy of the human genome, revealing a catalog of loci that neighbor each other in the nucleus. Finally, a computer cross-references gene pairs and assembles a digital 3-D portrait of the genome.
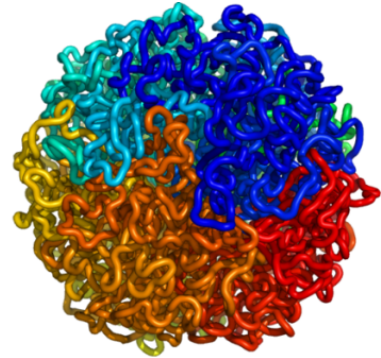
Fractal folding keeps DNA organized in a cell's nucleus. Nearby regions of DNA are depicted in different colors. Photo Credit: Leonid A. Mirny and Maxim Imakaev

Hi-C has resulted in two significant findings. First, it demonstrates that genetic regulation is accompanied by the 3-D movement of genes from an active or "on" compartment within the nucleus to an inactive, or "off" compartment, and vice versa. Hi-C suggests that the spatial arrangement of the genome in a particular nucleus could be a key factor in understanding why skin cells and neurons, despite having identical genomes, can perform entirely different functions. Mastering the ability to regulate genes may lead to scientific breakthroughs, like growing new organs to replace damaged ones, or understanding why certain cells become cancerous.

Secondly, Hi-C enabled the team to observe a never-before-seen macromolecular structure, the fractal globule, which is a polymer state marked by a hierarchical series of folds that enable the genome to pack densely without knotting (contrary to the classical equilibrium globule model). The fractal globule structure sheds light on how cells access genetic material in a tightly confined space without getting hopelessly entangled. Work with computational physicists Leonid Mirny and Maxim Imakaev to simulate the fractal globule has shed new insight on the physical dynamics of the genome inside the cell.

Currently, Hi-C is the only method capable of determining the global folding of an entire genome.

iShoe: Balance Insole

One quarter of senior citizens chronically fall down, leading to over 300,000 broken hips annually in the United States. Tragically, 40 percent of broken hips are followed by death within a year. Although falls

are sudden, they are often the result of a gradual deterioration in the ability to balance. In order to proactively address the issue for senior citizens, Lieberman-Aiden developed the iShoe. This concept is built upon a technology Lieberman-Aiden developed while interning at NASA, where he worked on a project aimed at helping astronauts regain balance after spending time in outer space.
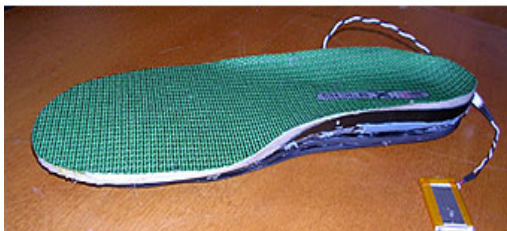
iShoe prototype. Photo Credit: Ricardo Piedrahita

The iShoe is a sensor-loaded insole that measures how pressure is distributed across a person's foot. This information can then be passed on to a computer and analyzed with an algorithm, helping to detect balance problems for a user before an actual fall. The iShoe can be placed inside of any shoe to track the wearer's ability to balance during daily life through a wireless sensor that measures pressure distribution. The insole sends out a signal and records data that the user can give to a doctor to track balance patterns, aiding with early detection and diagnosis of any problems. This technology is the first to systematically address the need for wearable balance diagnostics.
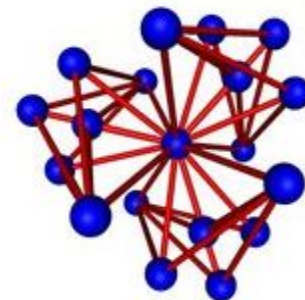
Evolution of Language
Lieberman-Aiden and Jean-Baptiste Michel performed the first study quantifying the evolutionary dynamics of language. They proved that linguistic rules, over time, follow natural selection. By studying the regularization of English verbs over the past 1,200 years, Lieberman-Aiden and Michel showed how modern regular verbs (such as *jump/jumped*) slowly came to dominate. The process was driven by the tendency of uncommon irregular verbs (such as *get/got*) to disappear, because they are less readily learned and more rapidly forgotten.

The pair looked at how the rate of verb regularization depended on the frequency of word usage, and came up with a quantitative analysis of the process by which ancestral word forms gradually yield to an emerging linguistic rule. Using such analyses, linguists can make predictions, such as which irregular verb is likely to regularize next.

Evolutionary Graph Theory
Evolutionary graph theory is a novel approach to studying how topology affects evolution of a population. The theory, developed by Lieberman-Aiden with Harvard mathematics professor Martin Nowak, offers a promising new lead in the effort to understand how population structure affects evolutionary dynamics.

Evolutionary graph theory is a mathematical framework that can be applied to a wide range of evolutionary problems. The theory examines networks and the individuals that reside on them in the context of movement, mutation and influence. One simple question evolutionary graph theory asks is "What is the probability that a different and newly introduced individual generates a lineage that takes over the population?" This fixation probability – the probability that a genetic variant will eventually become fixed in the population – determines the rate of evolution. The higher the correlation between the new individual's fitness and its probability of fixation, the stronger the effect of natural selection; if fixation is largely independent of fitness, genetic drift dominates. Whereas the effects of natural selection cause genetic

The Metafunnel, an evolutionary amplifier arising in evolutionary graph theory. Image credit: Erez Lieberman-Aiden

variants to become more common or less common depending on their reproductive success, it is not the only evolutionary force. Its counterpart, random genetic drift, may cause favorable gene variants to disappear completely.

A biological application of evolutionary graph theory can be found in cancer cells. A crude model of cancer would describe cancer cells as ordinary cells that reproduce slightly faster. While reproduction at the cellular level makes the individual cell more fit, it causes death to the organism as the cancer cells take over. This example shows that natural selection at the cellular level and organismic level are in conflict. By using stem cell architecture, the organism can suppress natural selection at the cellular level and survive long enough to reproduce.

While evolutionary graph theory is most readily applied to biology, it has also been used to examine social networks.

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