



Research Highlight #2004

Dr. Guy Nir

University of Texas Medical Branch

Exploring genome structure and gene expression using super-resolution microscopy

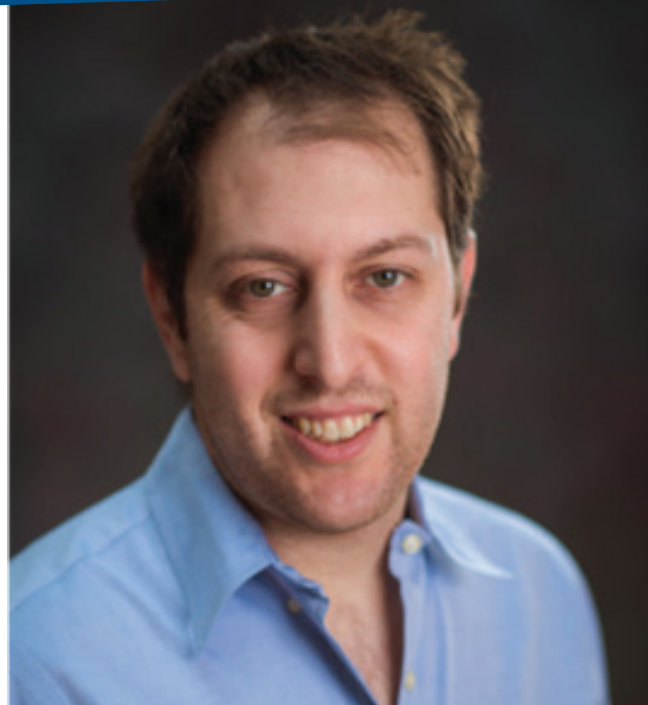
A critical step in the central dogma of biology, the flow of genetic information within a biological system, is the transcription of DNA into RNA. RNA transcripts serve certain functions within a cell, and these functions can be influenced by a variety of factors. Dr. Nir's research program focuses on how genome structures can shape transcriptional regulation in different biological systems, utilizing super-resolution microscopy as a main technology for investigation. His lab studies this phenomenon at the single-cell level, enabling simultaneous detection of gene expression and structure that is critical for determining their relationship. This relationship between genome structure and function can be explored in a variety of biological systems, lending to several interesting research efforts transcending disciplines.

"We have different projects where we have pointed out specific genomic loci that we think that by mutating them with genetic engineering, we can influence transcription. That is basically what we're trying to do now in different aspects and different biological systems, starting from viruses, where we are asking questions about infection rate efficiencies. We also address cancer-related questions, such as translocation and how that influences the structure of chromosomes. We also ask very fundamental questions, like how this transcription then influences the genome organization."

Dr. Nir investigates questions related to structure and gene expression through various different approaches, which vary by project and specific research question. There are some projects in which he is most interested in the function or regulatory elements of specific genes. In this approach, he makes changes to the structure to see whether there will be transcriptional effects, which he has done in key development genes including SOX9. Another approach is analyzing genome organization or gene position and its relationship to transcription and cell fate.

"Through a collaboration with Dr. Michael Robson and Alessa Ringel from Dr. Stefan Mundlos' lab at the Max Plank Institute and Dr. Daniel Ibrahim from the Berlin Institute of Health, using CRISPR, we engineer some of those borders of domains—for instance, for the SOX9 gene—and are asking whether that changes the promoter enhancer communication, which is more specific. But then there's other places where we ask whether the position of some cancer-related gene would influence its likelihood to switch from active to inactive between different cell types."

Regardless of the biological approach or specific question at hand, Bruker's Vutara single-molecule-localization microscope is one of Dr. Nir's main tools of use for exploring genome structure and function for two reasons; one reason is the ability to do high multiplexed imaging of a sample with the microfluidics unit, which is especially important for genome imaging.



ABOUT THE RESEARCHER

Dr. Guy Nir is an assistant professor in the Department of Biochemistry and Molecular Biology at the University of Texas Medical Branch (UTMB). He is also affiliated with the Department of Neuroscience, Cell Biology, and Anatomy, and is a member of the Sealy Center for Structural Biology and Molecular Biophysics at UTMB. Dr. Nir earned his Ph.D. in biophysics from the Department of Physics at Bar Ilan University. Prior to joining UTMB, he was a postdoctoral fellow in the lab of Dr. Ting Wu at Harvard University.

Website: [Nir Lab Website](#)

Recent Publications

Nir G, et al. Walking along chromosomes with super-resolution imaging, contact maps, and integrative modeling. *PLoS Genet* 14(12), e1007872 (2018). <https://doi.org/10.1371/journal.pgen.1007872>

Nguyen, H.Q., et al. 3D mapping and accelerated super-resolution imaging of the human genome using in situ sequencing. *Nat Methods* 17, 822–832 (2020). <https://doi.org/10.1038/s41592-020-0890-0>

Nussinov, R., Jang, H., Nir, G. et al. A new precision medicine initiative at the dawn of exascale computing. *Sig Transduct Target Ther* 6, 3 (2021). <https://doi.org/10.1038/s41392-020-00420-3>

“Standard microscopy is limited by the spectral resolution, so usually you can do about four different targets. With the Vutara fluidic system, we can do tens, hundreds, or thousands of different loads, and we can do the RNA and the DNA of the same cells. So that really makes it incredible, we can now look at genome-wide interactions in single cells and directly connect the RNA expression to the DNA structure. That’s why Vutara is really important for us, because it allows us to do easy multiplexing.”

The second reason super-resolution is critical for his research is its ability to image beyond the traditional optical diffraction limit. Traditional microscopy methods are limited to a lateral resolution of ~200-300 nanometers. With super-resolution microscopy, and more specifically the single-molecule localization method of the Vutara, a lateral resolution of ~20 nanometers is achievable.

“With a diffraction-limited spot, there’s so much information being missed, like there could be chromatin loops within that one spot. When you want to go down to that level of resolution and understand how chromatin looping helps with promotor interactions, and a lot of other biological functions, that’s where you need super-resolution microscopy. With this you can actually find the physical properties of the folding of the DNA, and you can directly relate a structure with the function. We are looking for chromatin signatures, and that’s why we need super resolution microscopy.”

In addition to the super-resolution microscopy with the microfluidics accessory, Dr. Nir utilizes Bruker’s SRX software for data analysis. Localization analysis is necessary to turn data into information and is made easy with the software.

“You have your single-molecule localization dots, but then you have to understand what’s noise and what’s your actual sample. SRX helps a lot with that. After cluster analysis, you can do more sophisticated analysis on the physical properties of each of those clusters, asking about surface area and volume and density. You can also ask more complicated questions, such as how much is one target overlapping with the other, and how close are they together? There is a lot of that in SRX, which is very useful for us. This is how you know whether you have two different structures, and then you can ask whether also if the function is different between those, which is what we find often and what makes it so interesting.”

Dr. Nir has enjoyed applying his interests in physics to answering important biological questions with single-molecule localization. He has had many exciting moments and findings using super-resolution microscopy, including imaging an instance of cell replication, and achieving views of entire chromosomal landscapes.

“It’s hard to pick the favorites. But maybe when we were looking at some specific chromosomal loci, and we saw that they were duplicated. This was a human cell, and the other homolog was somewhere else in the nucleus, so we knew it wasn’t the other homolog. We realized this was a cell that was replicating in that very moment, so we were able to see that it replicates in a way that some of those loci come together, and others were already separated from one another. It was really nice to see that, it was kind of unexpected. Another thing that we’ve seen with the microscope that was also exciting was seeing chromosomal loci that are mega-basepairs apart from one another, and you can see them in the 3D coming together and colocalizing with one another. So, it’s really amazing to have an image to actually see the chromatin. I’m always excited when I get to see something new, I can spend hours just looking at each image.”

By using super-resolution microscopy, Dr. Nir can effectively investigate the relationship between genome structure and transcriptional regulation through the lens of a variety of biological systems. Understanding this relationship can lend to an understanding of influences on cell fates, disease development, and more.

Learn more

To learn more about Bruker’s comprehensive suite of super-resolution microscopy solutions visit, www.bruker.com/Vutara

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