

Job Dekker: Hitting the scientific hi-Cs

Dekker investigates the three-dimensional organization of the genome.

Growing up in a small town in the Netherlands, Job Dekker and his twin brother, Martijn, were interested in science and math from a very early age. Whereas Martijn became enthralled with astronomy, Job was more interested in observing wildlife and birds. This avid interest in the natural world, combined with the influence of a chemistry teacher in high school, inspired Dekker to study molecular genetics and biochemistry as an undergraduate at Utrecht University. Remaining at Utrecht University as a postgraduate student in Peter van de Vliet's lab, Dekker used traditional biochemical approaches to probe the architecture and function of the large protein complexes that orchestrate DNA replication and unwinding. But Dekker wanted to see how whole chromosomes fold into higher order chromatin structures and this would require a completely new set of scientific binoculars.

Nancy Kleckner's lab at Harvard University proved to be particularly fertile ground for the seeds of a new technique to be sown during Dekker's postdoctoral studies. Dekker realized that the basic principle of covalent cross-linking to freeze-frame otherwise dynamic protein interactions, which was so useful in his postgraduate studies, could be the basis for pioneering a novel approach of analyzing chromosome structure. Dekker developed a method for capturing a matrix of the pair-wise interactions between different sites of chromatin and inferring the spatial folding of chromosomes from this information. The first iteration of this method Dekker named chromosome conformation capture (3C), and it has revolutionized the way biologists see the genome. The University of Massachusetts Medical School became the base for Dekker's own fledgling lab in 2003, and they started using the 3C technique to answer previously

intractable questions in molecular biology, such as how chromatin folding enables the long range control of gene expression by distant enhancers. We contacted him to find out more.

What first drew you to study the structure of chromosomes?

Chromosomes are among the most important molecules of the cell. We now know they contain our genetic information, but how do they work? I am driven by the idea that when we can determine the structure of chromosomes, we get closer to addressing some of the longest-standing questions in the field of genetics: how are genes regulated by enhancers that are located farther away along the chromosomes? How can incredibly long chromosomes be packed inside the cell nucleus and still function appropriately?

What is your lab actively working on?

Now that we can obtain detailed views of the spatial organization of chromosomes, we need to identify which protein machines build these intricate structures and how; and how these structures in turn influence genes. Recent innovations such as CRISPR/Cas9—

mediated genome editing allow us to alter chromosome structure in very precise ways. We can now go much further than even a few years ago and beyond “simply” observing the structure: we can start to determine the mechanisms by which chromosomes fold. So this is an exciting time for chromosome biology.

What kind of approach do you bring to your work?

I tend to bring a lot of optimism (sometimes too much!), and like to do difficult projects. This can lead to failure, but we always learn something.

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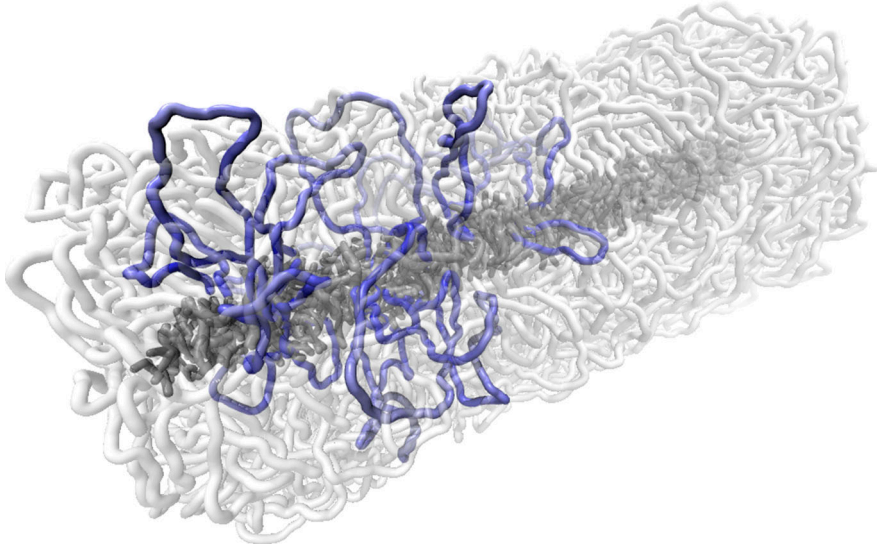
What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

I had very rigorous training during my PhD studies where I learned how to design good experiments, and how to critically interpret data. During my postdoctoral studies, I was challenged to think big, take unconventional approaches and to develop a long-term perspective with goals beyond the immediate horizon. These are all very important skills that have been critical in my own lab for finding my own path. For everything else that running a lab entails, I was less prepared: from working with students and postdocs—one the greatest parts of my job—to the administrative burden of a lab, which is less of a source of inspiration. I think it is hard to prepare for those things; just go for it and ask for advice (and listen!) as you go along.

What has been the biggest accomplishment in your career so far?

When I set out to develop 3C in 1998, my goal was to solve the structure of mitotic and meiotic chromosomes. I always thought mitotic chromosomes were the most beautiful cellular structures and the real material of genetics. After our initial yeast 3C studies—which my twin brother, Martijn, now a mathematician, used to calculate a model of a chromosome—(1), our work over the last 15 years or so has been focused on developing a range of high-throughput 3C related technologies and methods for analyzing chromatin interaction data, and applying these to determining higher order chromosome structures and how they relate to gene regulation. But I continued to think about mitotic chromosomes, and in 2010

IMAGE COURTESY OF MAXIM IMAKAEV, GEOFF FUDENBERG, AND LEONID MIRNY



A model of the structure of a human mitotic chromosome based on 5C and Hi-C data (2). Chromatin is shown as a transparent chain. Anchors of the loops, forming the scaffold of the chromosome, are shown in dark gray. Several loops are highlighted in blue.

or so, we finally had all the tools, including genome-wide 3C methods, modeling approaches and synchronous cell systems, in hand to start making maps of the human genome folded inside mitotic chromosomes. With my friend and long-time collaborator Leonid Mirny and his team, we obtained 5C and Hi-C data and applied polymer simulations to obtain a coherent model for the organization of mitotic chromosomes. This model, published in 2013 (2), shows that each chromosome is folded in a universal pattern as an array of chromatin loops, each around 80–100 Kb in size. Although we are still a long way from a complete molecular view of how the genome is organized inside mitotic chromosomes, this work has been particularly rewarding for me because I had wanted to do this for so long, and because the resulting model was so satisfying. The model makes a lot of sense, suggests mechanisms of how mitotic chromosomes are formed, and is closely related to models proposed many years ago by Uli Laemmli and coworkers (3). Laemmli had used entirely different methods to probe

the organization of mitotic chromosomes and had originally proposed the radial loop model that we now found to closely describe the structure we observed. It was wonderful to see such convergence!

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many years to answer. Her courage to take such a long view and her creativity in her approach continues to be an inspiration.

What is the best advice you have been given?

Work with people you like. Science can be hard, and in any project there will be struggles, differences of opinion and dis-

What has been the biggest challenge in your career so far?

To overcome insecurity: am I doing the right things? Having good mentors and people around you who believe in you is very important.

Who were your key influences early in your career?

The key influence on my career is without a doubt my postdoctoral advisor, Nancy Kleckner. She thinks intuitively and pursues big questions that typically take

appointments. When you work with people you get along with well, you will get through these challenges and enjoy the successes together even more. I have been very lucky that I have been able to do much of my science with friends.

What hobbies do you have?

I am an avid birder. I combine many of my work-related travels, such as giving seminars and attending conferences, with going out and finding birds. I consider this one of the perks of being a scientist: you have opportunities to travel quite a bit, and thus I have been birding in many places around the world.

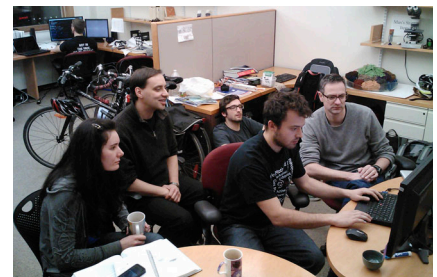
What do you think you would be if you were not a scientist?

Difficult to know, but I would be quite happy being a field ornithologist!

Any tips for a successful research career?

Pursue a question you are really interested in. This may not be the one that is the most fashionable or timely. But given that science is hard, with many ups and downs, I believe that only studying a topic of your heart will give you the motivation to persevere and ultimately succeed. Another very important tip is to identify strong collaborators from different disciplines. This will broaden your research. Together, you can do much more.

1. Dekker, J., et al. 2002. *Science*. 295:1306–1311.
2. Naumova, N., et al. 2013. *Science*. 342:948–953.
3. Earnshaw, W.C., and U.K. Laemmli. 1983. *J. Cell Biol.* 96:84–93.



Dekker (far right) with his collaborators (left to right) Natasha Naumova, Leonid Mirny, Geoff Fudenberg, and Max Imakaev.

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