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MEASURING MOLECULAR MOTIONS:

From Polymer Dynamics to Pocket-Sized Diagnostics



AN INTERVIEW WITH PROFESSOR DANIEL FLETCHER

BY: GRACE ZHOU, ALMA RAZAVILAR, & JUSTIN MAGNO

Daniel A. Fletcher is a Professor of Bioengineering at the University of California, Berkeley, and a Faculty Scientist at Lawrence Berkeley National Laboratory, where he serves as Department Chair and holds the Purnendu Chatterjee Chair in Engineering Biological Systems. He earned his BSE from Princeton University, a DPhil from the University of Oxford, and a PhD from Stanford University, followed by postdoctoral training in biochemistry at Stanford.

His research integrates bioengineering, biophysics, and molecular biology to study how cells move, interact, and respond to disease, with an emphasis on the physical and molecular mechanisms underlying cellular behavior. His lab has contributed to mechanobiology, immunoengineering, and diagnostic technologies, including studies of cytoskeletal dynamics, membrane mechanics, and the glycocalyx in cell-cell interactions and pathogen entry. The group also investigates immune cell recognition and pathogen evasion, while developing portable microscopy platforms to expand access to healthcare.

BSJ: Your lab is highly interdisciplinary, publishing work spanning bioengineering, biophysics, and molecular biology. What initially drew you to these fields, and how did your academic journey lead you to Berkeley?

> *"I could build an instrument, I could take measurements, but I didn't understand how cells are built."*

DF: I can start with the academic journey. My undergraduate training was in mechanical and aerospace engineering, and then I did a public policy certificate as well. The theme that drew me to engineering to begin with was the idea of building things that I really enjoyed, understanding how things were built, and creating new things. There was a creative outlet in engineering where there were design and physical rules, but you could create things like engines and airplanes. This is what initially drew me to engineering.

After undergrad, I was in England for a little while and partaking in more in-depth engineering science, where I worked on gas turbine machinery, studying how the engines that power our airplanes work. Here, I worked on studies, getting into the details of exactly how those things work. A large part of my work was developing methods for measuring temperatures and distributions. This led me into measurement tools, and then, when I came to Stanford for my PhD, I leaned into this. I started asking, "How do we measure small features on surfaces?" I became connected with work on atomic force microscopy and optical microscopy. I was building instruments to make these measurements, and toward the end of my PhD, I began to question what I should be studying with the instruments I had spent so much time building. What are the interesting questions out there?

That is where I ended up veering into biology. I had stayed far from biology ever since a middle school science program where we had done a fetal pig dissection. For me, it was so unpleasant to be cut, and I did not like it at all. This is where I decided soft, squishy things are not for me, and instead, I will work on clean, hard things that do not smell. However, it was at the end of the PhD that I decided these cells and all the things that they can do are fascinating, and I did not understand how they are built. This all comes back to the same theme. I could build an instrument, I could take measurements, but I didn't understand how cells are built. This really drew me into a postdoctorate in biochemistry, where I dived into how cells build and organize themselves. So I got into the cytoskeleton and looked at how structures are assembled in crawling cells.

Then I came to Berkeley after my postdoc, which is where I combined my knowledge of building instruments and understanding how cellular systems are built or organized. Much of the research that my lab does now, 20 years on, is related to those themes: how cells are organized, how we know they are organized that way, and how we build tools to understand that. This has led us toward the immune system and cell-to-cell interactions, where we ask questions such as what the organization of proteins is on cell surfaces, how the actin cytoskeleton makes those proteins available, and what cellular interfaces look like. We have been developing techniques to do that, and in the process, we also became interested in the flip side of the immune system's capabilities, namely, the pathogens that attempt to invade humans and other animals. These pathogens are also incredibly clever, so when our immune system is defeated, we need diagnostics. Through our work in instrumentation, including building microscopes such as mobile phone–based microscopes, we expanded into diagnostics, and the lab now has two main thrusts: developing tools to diagnose disease, including both imaging and molecular diagnostics, and building tools to understand how cells interact with each other, with a primary focus on the immune system.

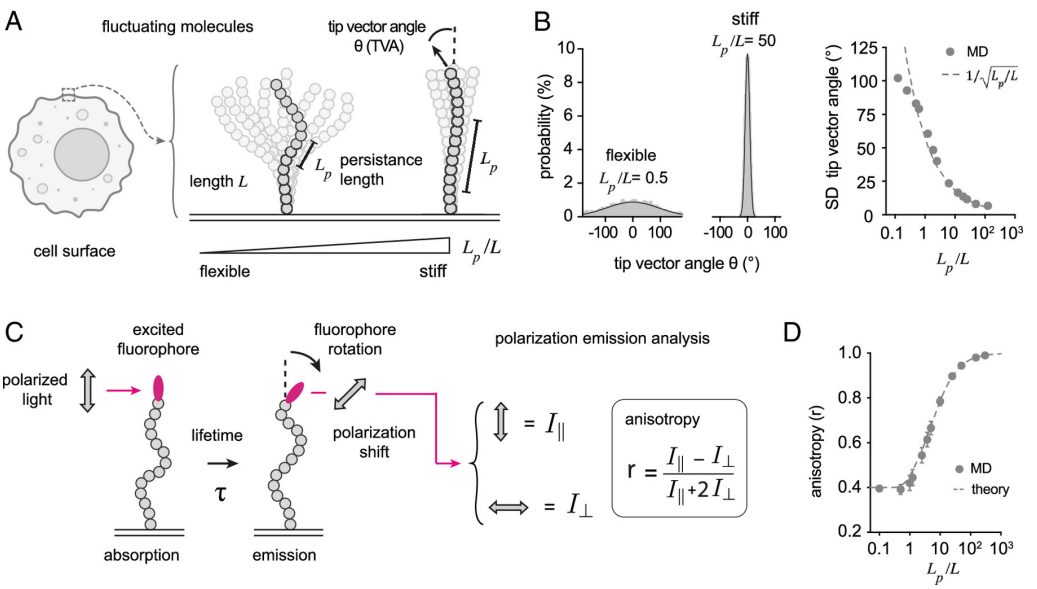


Figure 1. Tip fluctuations of tethered polymers are correlated with molecular flexibility. (A) Tethered molecules on a cell surface fluctuate above the membrane, with stiffer polymers (higher Lp/L) showing narrower angular distributions of their tip orientation (TVA). (B) Coarse-grained MD simulations show tip angle distributions for flexible (Lp/L = 0.5) versus stiff (Lp/L = 50) polymers; standard deviation of the angle decreases with stiffness, matching simple WLC model predictions. (C) Fluorescence anisotropy measures rotational motion of polymer-attached dipoles: more flexible polymers allow greater rotation, increasing perpendicular emission, relative to parallel. (D) Simulated anisotropy values for a 14-unit polymer increase with stiffness, agreeing with theoretical expectations.

BSJ: Your paper uses a worm-like chain model to relate molecular motion to stiffness. For a general audience, could you first explain how this model captures polymer flexibility?

DF: A worm-like chain can be understood with something most are familiar with, like spaghetti, as a model for polymer physics. A polymer of the same length can have different stiffness depending on how it is prepared, like with how long you cook spaghetti. It can be very floppy, medium, or al dente. Before spaghetti is cooked, it is very rigid, with only a bit of flexibility. Similarly, a worm-like chain is a way of describing an ideal polymer composed of multiple subunits, where there is a well-defined energy penalty for bending between those subunits. Although pasta is not typically considered in terms of individual subunits, it can be conceptually divided into segments, each contributing to the overall resistance to bending. In this way, you could define all the properties and all the flexibilities in terms of a bending energy or a persistence length. The persistence length is the distance along a polymer over which the orientation of the chain, as defined by its tangent, becomes uncorrelated. This can be understood as the point along the polymer at which a given segment no longer retains any information about the orientation of another segment. For a relatively rigid polymer, this distance is quite long because if one holds it in a particular direction, the orientation along most of its length can still be predicted with some variability. In contrast, if the polymer is more flexible, such as cooked pasta, holding one end in a particular direction does not strongly constrain the rest of the chain. As one moves along the length, the orientation quickly becomes uncorrelated with the initial direction. This corresponds to a short persistence length. Thus, more flexible molecules have shorter persistence lengths, while less flexible molecules have longer persistence lengths. The underlying idea of the technique is that, by placing a probe at the end of the molecule and observing how the emission of a fluorophore changes over time, specifically, how its orientation fluctuates, it is possible to infer the flexibility of the molecule.

BSJ: Short single-stranded DNA sequences can exhibit sequence-dependent bending and transient base-stacking interactions. How well does the worm-like chain framework capture flexibility in these cases, and what are its limitations when the assumption of uniform bending is not strictly valid?

DF: The idea of a persistence length is a very useful mental tool for thinking about the overall behavior of a single-stranded DNA. One of the observations in the study was that this sequence dependence matters. Meaning, ideally and theoretically, a worm-like chain would have identical subunits. So a persistence length would really be capturing the bending penalty between each of the subunits, all of which are equal. What we are showing with that sequence dependence is that when we have all the same nucleotides, then we get different properties. When heterogeneity is introduced, such as when different bases are present, additional interactions can arise within the polymer. These self-interactions can create the appearance of a lower bending penalty, as there may be energetic advantages to different parts of the polymer interacting with one another. If you were treating it like a worm-like chain, then that would appear to be like the behavior of a polymer that was softer or more flexible. However, in reality, it is not more flexible. It is just that it has this other interaction that is not like the ideal worm-like chain. The polymer is therefore engaging in additional interactions, and the goal is not to force a worm-like chain description onto a system where it may not be appropriate. Rather, the ideal model serves as a reference: we assess whether the behavior matches that expected of a worm-like chain, and if it does not, we then investigate the factors driving those deviations. This sort of focuses our attention on the alternative behavior of these polymers, and I think that helps us think in more nuanced ways about DNA or RNA. When it bends, the bending is in part because of resistance, because it is a worm-like chain, but it can be promoted because there are these self-interactions.

BSJ: Since SurFlex measurements average over many molecules in each pixel, how might the method reflect heterogeneous populations of conformations, particularly in sequences where transient structures form intermittently? Does that signal represent a weighted mixture of different conformational states?

DF: This provides good insight into how the measurements are made, since this is an average over a certain area in a given region. There are two directions we are thinking about to address this. First is increasing the spatial precision of the measurement. Right now, we are averaging over fluctuations spatially, and some of our newer probe development efforts are aimed at allowing us to look more locally. As we apply this to cells that are crawling and moving, we want to understand, for example, whether at the leading edge of a crawling cell, there is more or less crowding, or more or less flexibility in the receptors.

To do that, we need to measure different polarizations at a specific point. Right now, we are averaging because of how we excite the system. If we hold all excitation parameters (i.e. intensity, wavelength, etc.) fixed except for polarization, we can access different fluctuation spectra at a single point. Because molecular orientation affects how fluorescence responds to the polarized light, changing the polarization allows us to probe different aspects of that motion. That would require hardware changes to the microscope, but it would also allow us to obtain more complete local information without relying on spatial averaging.

The second approach is more specific labeling. If we want to understand what an individual molecule is doing, we should label fewer molecules. Borrowing from super-resolution microscopy, we can use a low labeling density so that, although many molecules are present, we are primarily detecting one at a time. If we can increase sensitivity while reducing labeling, we may begin to resolve different conformational states. This also requires improved time resolution. I have focused

on spatial resolution, but increasing temporal resolution will also be important, which again involves additional hardware improvements. So there are paths forward on both fronts: improving spatial precision and control, and reducing averaging through more selective labeling and better time resolution.

BSJ: In the red blood cell experiments, enzymatic removal of surface proteins altered glycan fluctuations. Could similar measurements reveal disease-associated glycocalyx remodeling, such as during malaria infection or inflammation? In the future, do you see SurFlex serving as a biophysical diagnostic tool to detect changes in glycoprotein organization or flexibility?

DF: Our initial motivation in developing the technique with DNA was to validate it using a known polymer. As we found, there are nuances: it is not a perfect worm-like chain, but we are still able to extract properties that are consistent and interpretable. That helped establish how to apply the technique in more complex scenarios.

At this stage, the focus is less on defining a specific persistence length and more on using it as a measure of flexibility. A longer persistence length corresponds to higher flexibility. This framework allows us to observe changes when we manipulate the surface. A key aspect of the method is the probe being used, since we are ultimately measuring the fluctuations of that probe. In the case of the red blood cell, we used lectin, a sugar-binding molecule, to assess how it fluctuates.

The broader goal is to develop a new way of asking questions about surface flexibility and how it changes in disease states. A graduate student in my lab, Lena Blackmon, who is now focusing on red blood cells and the effects of malaria infection, has observed significant changes in the glycocalyx, or at least in the flexibility of the surface, using this technique. We therefore see this as a potential new approach for studying cells.

However, we could not largely measure rotation. For molecules that are fixed and not diffusing, their ability to move, specifically their rotational freedom, can significantly influence their capacity to interact and bind. This is particularly relevant at surfaces such as the red blood cell. If polymers on the surface are fluctuating, they can obscure underlying binding sites, or if they are more rigid, those sites may remain accessible. In this sense, we have been largely unable to assess where fluctuations occur in anchored polymers, how large those fluctuations are, and how the surrounding environment constrains them. This technique provides a way to probe those properties directly.

At present, we anticipate that this will primarily serve as a research tool. However, if flexibility proves to be a strong biomarker in specific contexts, it could eventually have diagnostic applications.

BSJ: What do you see as the biggest barriers to deploying the NTDscope at scale in real-world clinical settings, particularly in low-resource regions? How has your lab accounted for these translational challenges during the design process?

DF: There are a few different layers to the challenges of translating a tool like this. First, it has to be low-cost. We have tried to take advantage of mobile phone-based technologies (i.e., the processor, cameras, and lenses) to build a compact, low-cost imaging system.

Second is simplicity. Even if a device is low-cost, translation becomes difficult if it is complicated to use or if the sample preparation is complex, as this can introduce more errors. The system is highly automated, and we have benefited from advances in AI-based imaging, which enables rapid analysis without requiring a clinician to review each case. Beyond that, the device must fit within the healthcare system where it will be used.

The central challenge is sustainability. Academia is well-suited to developing and validating new technologies, but long-term deployment (i.e., manufacturing, distribution, and continued access) requires a different set of capabilities.

> *"Even if a device is low-cost, translation becomes difficult if it is complicated to use or if the sample preparation is complex..."*

At the moment, support from the Bill and Melinda Gates Foundation has enabled pilot studies and early device production, and now we are working toward scalable manufacturing. Foundations are not designed to sustain these efforts indefinitely, so long-term success will depend on partners with both the public and private sectors. This is particularly important in applications like onchocerciasis, where treatment depends on detecting Loa loa, a filarid nematode. Our device can quantify microfilariae in blood samples, allowing safer treatment decisions. In regions such as Cameroon, where the absence of reliable screening has limited mass drug administration, this creates an opportunity to resume those programs.

There has been strong support from Ministries of Health. For example, the Minister of Health in Cameroon publicly took the test on television to demonstrate that it was safe and acceptable, which was a powerful way to build trust. At the same time, seeing the technology used in a real-world setting is both exciting and somewhat daunting. Unlike a laboratory experiment, which may only work under controlled conditions, a diagnostic tool like this had to perform reliably and consistently.

As implementations expand, questions around funding and long-term responsibility become more pressing. From a technical standpoint, the system also has to be highly robust and needs to perform reliably in real-world conditions.

BSJ: Your lab reports that the NTDscope detected microfilariae in 20 patients, who were classified as negative using the gold-standard thick smear method. Do you think this suggests that current definitions of a "negative" infection might need to be re-evaluated in disease elimination programs? How might this increased sensitivity affect decisions about when it is safe to stop treatment campaigns?

DF: I believe it raises an important issue that comes up with almost any new diagnostic technology. There is a kind of chicken-and-egg problem: to validate a new technology, you have to compare it to the gold standard, the method currently used to diagnose the disease. While the gold standard is not always perfect, it has its own limitations and may fail to detect disease in certain situations. If a new technology detects something that the gold standard does not, all you can initially say is that the results are different. One interpretation is that the new result is a false positive.

In this case, we would argue that we are seeing something real. We can observe movement, which is different from what you get with a fixed smear. We strongly believe that this new approach does a better job of quantifying microfilariae than the older method. At the same time, because the older method is still considered the gold standard, we still have to compare our results to it. That creates a larger question: at what point do you decide that the gold standard is no longer the most accurate method?

I think this is always a challenge with new diagnostics. When you see a difference between a new technology and the gold standard, the question becomes whether the new test made a mistake or whether it detected something the older method missed. That is what we need to investigate more deeply—when did you actually make a mistake versus when did you catch something the gold standard did not? Examining this helps identify the limitations of the existing approach. If it can be confirmed that the parasite is indeed present and the previous method failed to detect it, that provides strong motivation to change how measurements are made.

At the same time, this has important implications for public health decisions. If these results are interpreted as false positives, that could lead to unnecessary treatment. If they represent true infections that were previously missed, then increased sensitivity could change how we define a "negative" case and influence when it is considered safe to stop treatment campaigns. Ultimately, resolving this requires careful, in-depth study to determine whether these signals represent true positives and to guide how diagnostic standards should evolve.

"That is what we need to investigate more deeply—when did you actually make a mistake versus when did you catch something the gold standard did not?"

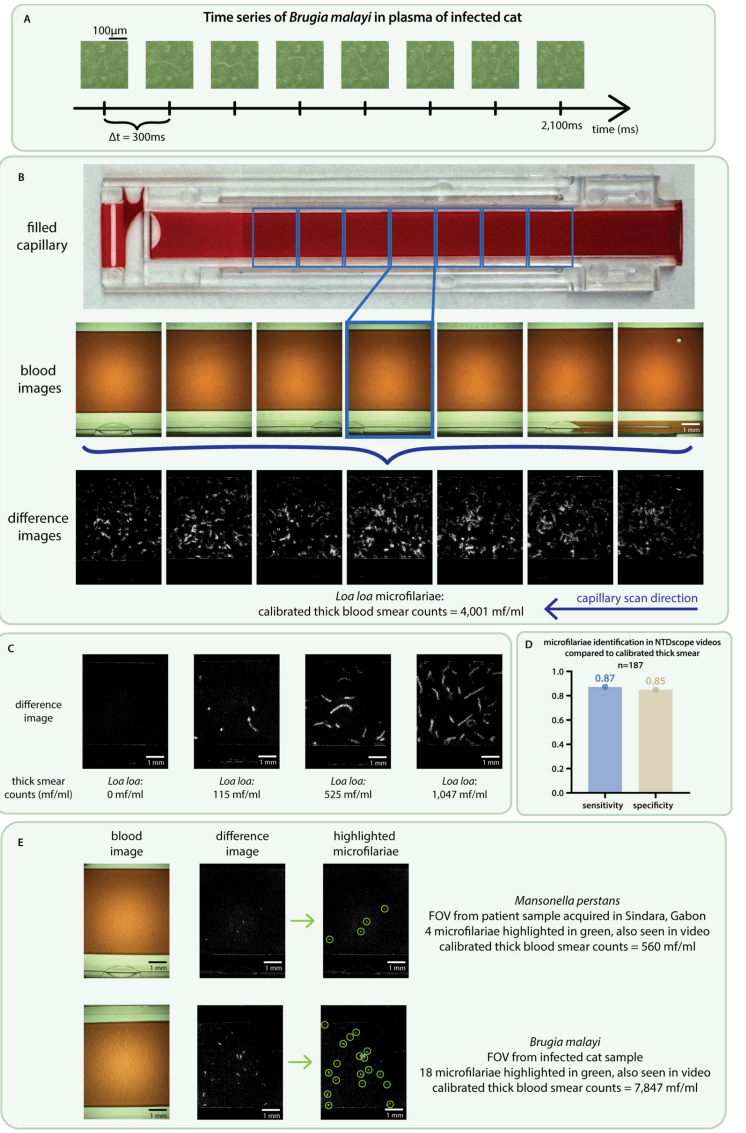


Figure 2. NTDscore for live imaging of microfilariae in blood and plasma samples by leveraging motion-based imaging.

BSJ: It is noted that some very small pathogens were difficult to fully resolve with NTDScope's current system. What optical or computational improvements do you believe could allow the NTDscope to detect smaller pathogens like malaria, leishmania, or even viruses in the future?

DF: There are a couple of possible approaches. One is to make changes in the lenses to achieve higher magnification. The trade-off there is that if you increase magnification, you decrease your field of view. If you decrease your field of view, you are seeing less of the sample, so you have to move the sample more or potentially miss parasites if you are not imaging enough of it.

The alternative approach is something called dithering, where the optical information collected by the lenses is actually greater than what the CMOS (digital image sensor) can capture, because those sensors were not designed for the specific microscope application we are using them for. The lenses have a higher numerical aperture and collect more

spatial information. In any imaging system, the lens gathers spatial information, and the sensor samples it. If you do not sample enough, you miss information that is present. If you make the pixels smaller and smaller, at some point, you are not capturing more information; you just have more pixels. If you do not have enough pixels, then you are not capturing all the available information.

The way we are addressing this challenge is by taking multiple images that are slightly offset and then computationally combining them into a higher-resolution image. This approach appears to be effective for improving the resolution of the system.

BSJ: What do you consider to be the most significant breakthroughs in bioengineering, and how have those advances shaped the direction you envision for your lab's future research?

DF: That is a big question. The most significant breakthrough in bioengineering, I think, is viewing biology as something that can be engineered. If you look over the broader arc of history, biology was originally something you observed. Early biologists were collecting and drawing different organisms, trying to understand why our flora and fauna are the way they are. As medicine developed, people began to realize they could intervene–washing hands before surgery or removing infected tissue, for example–so there was some ability to manipulate biological systems, but mostly at a macroscopic level. Bioengineering has truly expanded from its early roots in building better clinical tools, like improved X-rays or medical imaging devices, to a much deeper idea: that cells, tissues, and molecules themselves can be engineered. We can apply design principles to biology. What originally drew me to engineering was the idea that you could build things, and now the exciting frontier in bioengineering is the realization that we can build within biological systems. Whether it is designing therapeutic molecules with specific properties or organizing cell-cell interfaces in precise ways, we can now control how cells interact by changing molecular crowding on the cell surface or altering molecular flexibility. These approaches allow us to create new interactions and build biological systems with intention. I think this shift, seeing biology as something that can be engineered, has opened an entirely new frontier for research.

"What originally drew me to engineering was the idea that you could build things, and now the exciting frontier in bioengineering is the realization that we can build within biological systems."

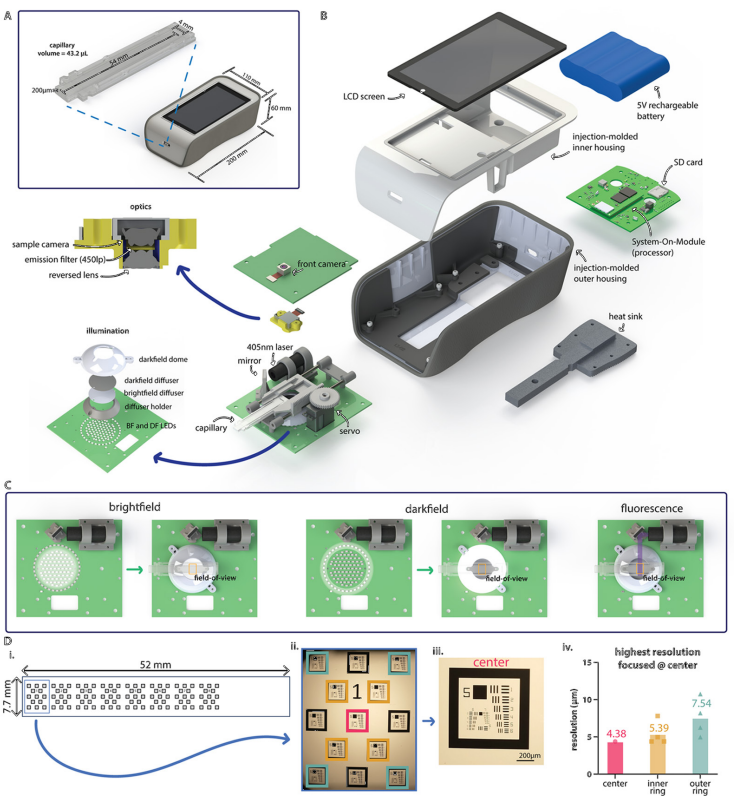


Figure 3. NTDscope design, illumination, and resolution. (A) Diagram showing NTDscope and straight channel capillary external dimensions. (B) Exploded view of NTDscope and main components. (C) NTDscope illumination modes, showing brightfield, darkfield, and fluorescence illumination. (D) NTDscope resolution measurements, showing design of custom slide with USAF resolution targets (D.i.), image of USAF resolution target array acquired on NTDscope used to measure resolution, with the resolution targets used in calculations color coded with pink (center), yellow (inner ring) and green (outer ring) (D.ii.), close-up of center resolution target (D.iii.), and resolution measurements at each target location, showing root mean square of horizontal and vertical resolution measurements (D.iv.).

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