



C-Trap™ G2

**Optical Tweezers -
Fluorescence Microscopy**

C-Trap | Product Brochure

The C-Trap™ is the world's first instrument that allows simultaneous manipulation and visualization of molecular interactions in real-time. It combines high-resolution optical tweezers, confocal microscopy or STED nanoscopy with an advanced microfluidics system in a truly integrated and correlated solution.

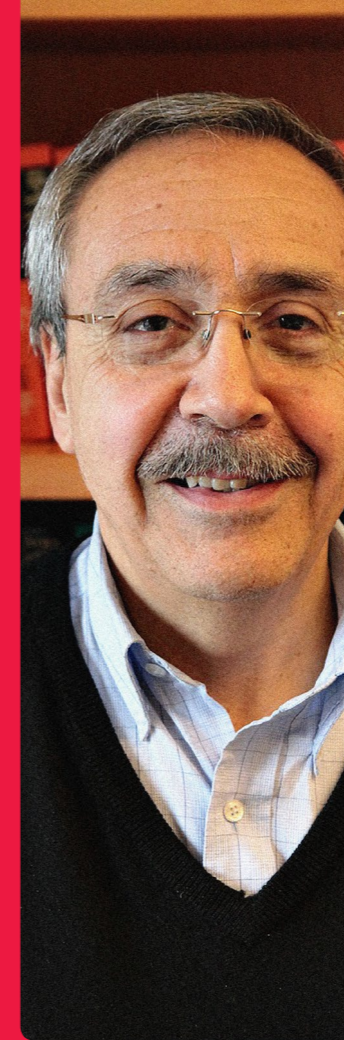
The key to unlocking dynamic single-molecule analysis.

Our dream is to unlock dynamic single-molecule analysis. Understanding the root cause of diseases at the molecular level is one of the greatest scientific challenges of today. Expanding the knowledge of biological processes that are at the basis of disease is key for prevention and the development of future cures. We aim to create the best possible tools for researchers to perform high-quality, high-throughput single-molecule experiments in the most accessible manner.

With this in mind, we bring to you the second generation of the C-Trap™—an evolution of our original optical tweezers–fluorescence microscope, which set the benchmark in high-resolution dynamic single-molecule analysis. We are always looking for ways to advance the technology and to bring new features that enable breakthrough discoveries.

Featuring unmatched force stability, ultra-fast sensors, precise control over temperature, and an entirely new software suite, the **new C-Trap G2** enables you to:

- Sense the smallest molecular conformation changes and the rarest and most transient molecular states.
- Measure under physiological conditions and to investigate temperature-dependent interactions.
- Access scripting, full automation and improved data management for the highest ease-of-use and throughput.



Prof. Carlos Bustamante

HHMI investigator and professor at the University of California, Berkeley

On the importance of single-molecule research.

Adapted from Annu. Rev. Biochem. 2008. 77:45–50

"Combining single-molecule mechanical and fluorescence experiments appears to be the most powerful way to unravel the dynamics and structural transactions that occur during complex biomolecular interactions."

Revealing the complete picture

To decipher complex molecular interactions, scientists need the ability to observe the same biological process from multiple points of view. Using LUMICKS' groundbreaking C-Trap correlated optical tweezers fluorescence microscope, scientists are now—for the first time—able to simultaneously and in real-time visualize individual molecules and measure mechanical properties of biomolecular complexes to reveal

greater detail. With this new ability to perform simultaneous manipulation, force measurements and visualization of these complexes—for example proteins interacting with DNA—scientists can correlate mechanical properties to the number, location and conformational state of the proteins bound to DNA.

This revolutionary single-molecule visualization technology enables the

understanding of life to the smallest detail, which is critical for life science research and drug development. Combining live observation and measurements have proven to be research game changers. Now LUMICKS is making this technology available—as ready-to-use instrumentation—to allow life scientists to focus on their research and enable the next wave of scientific discoveries.

Want to learn more about LUMICKS? Visit www.lumicks.com for more information!



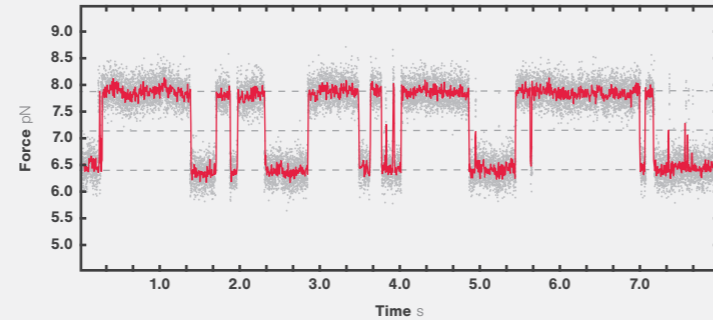
Real-time single-molecule visualization

The kymograph gives unique insights into the dynamic interactions between proteins and filament substrates, such as DNA, and protein–protein interactions. Simultaneous force and extension measurements allow for correlating the **protein activity and binding kinetics** with the **mechanical properties** of the protein–substrate complex.

- ▶ A DNA molecule is tethered between two optically trapped beads and moved into a microfluidic channel containing proteins interacting with the DNA. The position of the fluorescently labeled proteins is visualized over time using a multi-color confocal or STED beam, thus unveiling the position, diffusion, and (un)binding events of the proteins bound along the DNA.

Activity, states, and conformational changes

The C-Trap enables you to detect discrete conformational changes within a protein or DNA molecule. By keeping the traps at fixed position while measuring tension fluctuations caused by intramolecular conformational transitions with ultra-high sensitivity you can detect the **smallest, rarest and most transient states**. Moreover, measuring the **activity and states of molecular motors** over DNA or filaments is achieved with sub-nm resolution, thereby resolving biomolecular processes with extremely high detail.

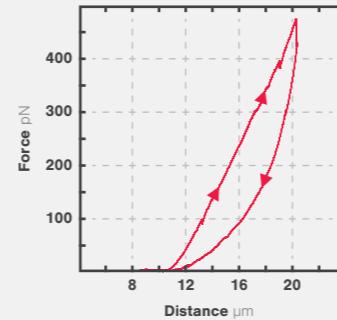
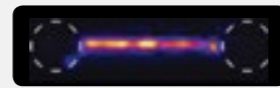


- ▶ By tethering a biomolecule, such as a protein, between two optically trapped beads and measuring force fluctuations, while holding the traps at a fixed distance, equilibrium dynamics are revealed. Observation of transitions between extremely short-lived states within molecules and characterization of conformational transitions during long periods of time is easily achieved.

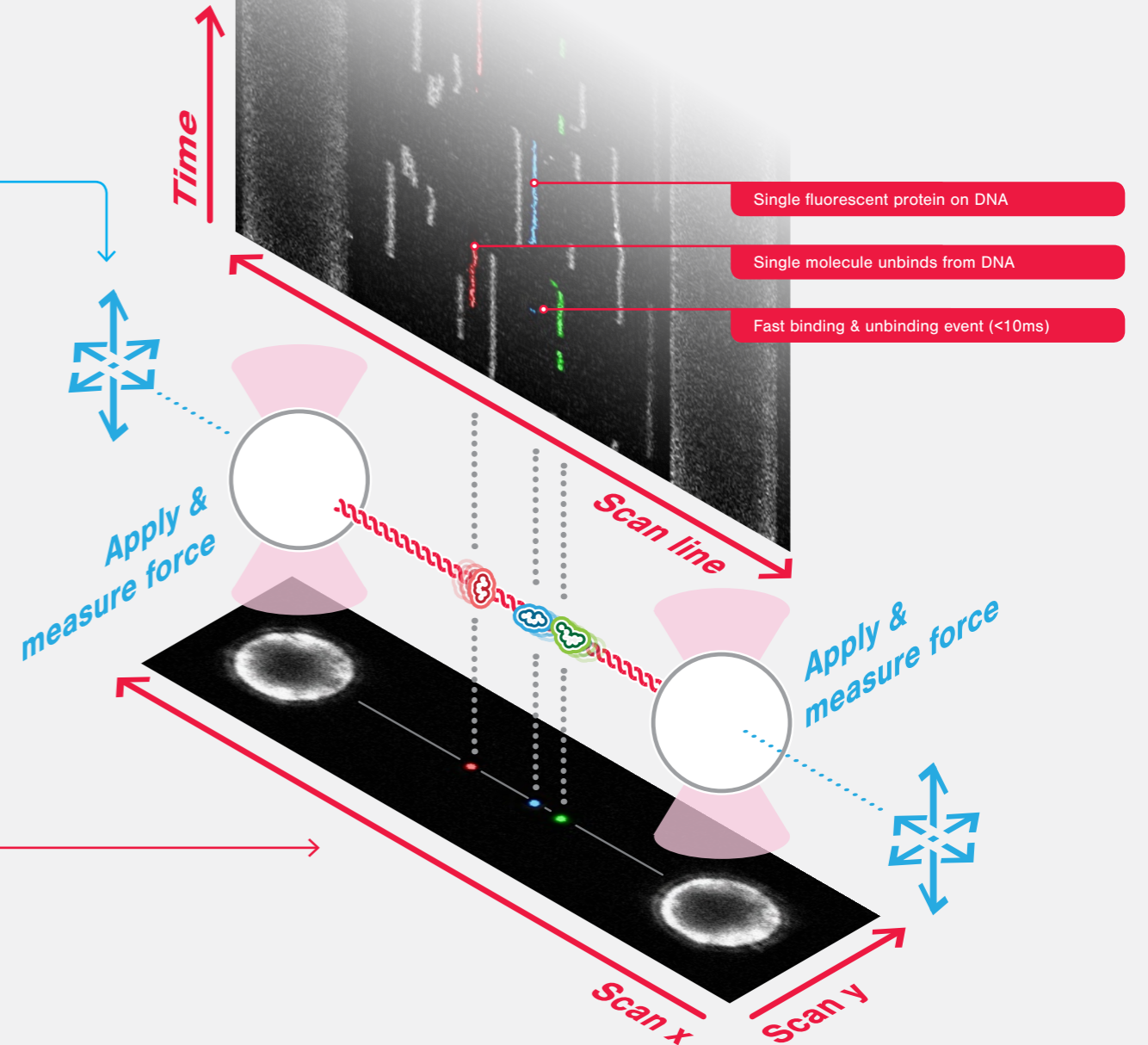
Force extension, manipulation, and visualization of single molecules

Polymers and filaments can be manipulated with the high-resolution optical tweezers while simultaneously measuring force, extension and fluorescence microscopy data. Combining **global mechanistic information** with **local activity** provides important insights on the dynamic function of the substrate under study.

- ▶ A vimentin molecule is tethered between two optically trapped beads. By simultaneously stretching the individual filaments and measuring the force and the extension we obtain the force–extension curve and determine the mechanical properties of the protein filament. Next to the force–distance curve, a confocal fluorescence image is showing the intra-molecular remodeling of a vimentin filament, captured during the same experiment.



Data courtesy of Prof. Sarah Köster at the University of Göttingen.



Applications

Optical Tweezers - Fluorescence Microscopy

With the C-Trap, the correlation of the mechanical and fluorescence measurements is achieved in a controlled and quantitative manner. This enables you to study biological processes at the single-molecule level from multiple angles, providing an unparalleled, wide perspective on biomolecular interactions—quickly and effectively.

[Browse the applications](#) →

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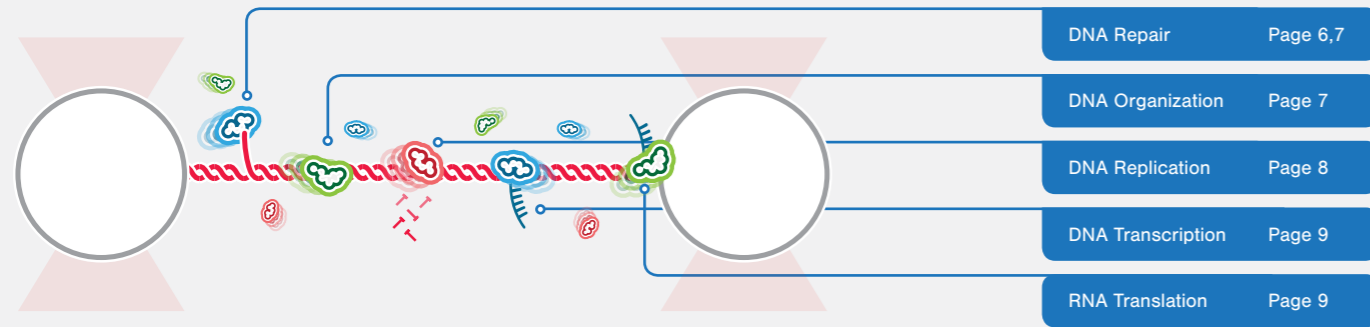
DNA/RNA-Protein Interactions

Study molecular mechanisms involved in DNA repair, replication, transcription, translation, and organization in real-time.

With the C-Trap optical tweezers-fluorescence microscope it is possible to visualize and directly measure **DNA-protein and RNA-protein interactions** involved in biological processes. When DNA-protein interactions are visualized and their dynamic behavior is measured at the single-molecule level, the exact mechanisms involved in biological processes can be studied in high-detail—including which proteins interact with each other or with DNA—at every step of the process.

Using optical tweezers, a tethered DNA or RNA template can be probed or manipulated to trigger different structural conformations. The C-Trap allows performing these manipulation steps while simultaneously visualizing nucleic acid-protein interactions and monitoring the mechanical effect generated by proteins involved in DNA processes. This is achieved with the C-Trap's unparalleled basepair and force resolution of <0.1 pN allowing the in-depth investigation of biological processes in unprecedented detail.

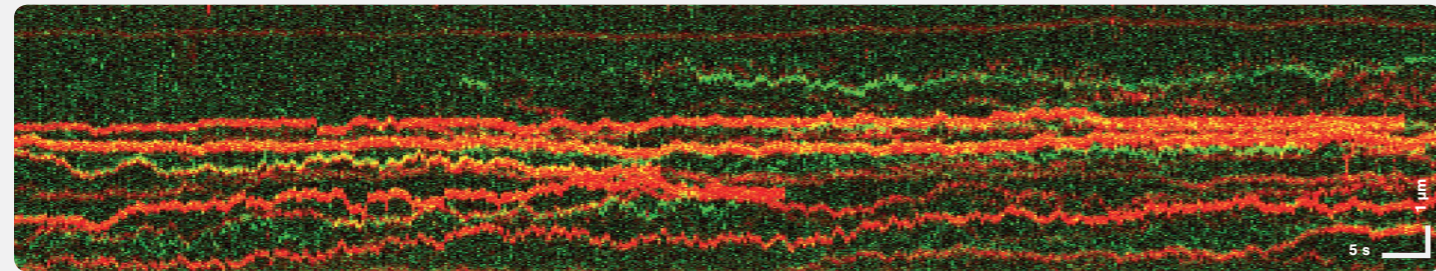
The activity and states of **motor proteins**, such as DNA or RNA polymerase, can be directly measured and readily visualized, thereby extracting novel information on the single stepping of biomolecular motors and their enzymatic mechanisms with basepair resolution and high temporal resolution in the order of μ s.



Visualization of DNA-protein interactions in DNA repair.

DNA Repair

With the C-Trap it is possible to visualize and investigate DNA-protein interactions participating in DNA repair and elucidate the exact mechanisms involved in this process, under biologically relevant conditions and with **high spatial** and **temporal resolution**. In the example presented here, a DNA molecule is tethered between two optically trapped beads while multiple repair proteins are interacting with the DNA. The resulting kymographs provide unique insights into the DNA-protein interactions and protein-protein interactions involved in DNA repair (**Figure 1**).



1 Kymograph showing the binding position of XRCC4 (green, 9% of the total number of events) and XLF (red, 62% of the total number of events), two DNA repair proteins that are involved in the non-homologous end joining repair pathway and can form XRCC4-XLF complexes (yellow, 29% of the total number of events). The X-axis corresponds to time, while the Y-axis corresponds to the positioning of the bound protein along the DNA, giving real-time insights into the DNA-Protein interactions of DNA repair.

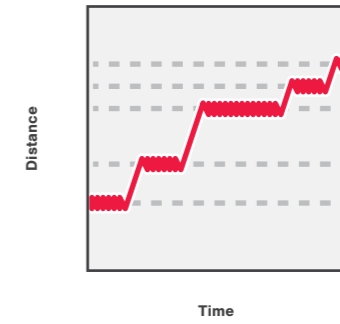
Data courtesy of Prof. Erwin Peterman & Prof. Gijs Wuite at the VU University Amsterdam.

Force-extension, manipulation, and visualization of DNA-DNA interactions.

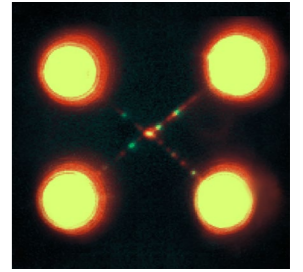
The C-Trap makes it possible to measure interactions between DNA and proteins involved in DNA organization—such as **DNA bridging proteins**—with high-resolution optical tweezers at the single-molecule level. By measuring these interactions at the single-molecule level, the mechanical effect and the target sites of DNA organization mechanisms can be studied in high detail.

A quadruple trap configuration can be used to trap beads and catch biomolecules, such as DNA. The biomolecules can then be manipulated by moving the beads and bringing them into contact, facilitating DNA-DNA interactions. Incubating the two DNA molecules with proteins allows for characterizing DNA-DNA interactions mediated by those proteins. By pulling on one bead using a force ramp, the bridges are disrupted in a controlled manner, resulting in a stepwise length (L) increase between the upper and lower beads, as illustrated in **Figure 3**, which allows measurements of protein-DNA interactions in high detail.

Figure 4 shows an example in which two DNA molecules are trapped using four optical traps. First, the two molecules are held in close proximity in the presence of DNA bridging proteins. Then, the distance between the two trap pairs is increased and the formation of protein bridges (orange), consisting of both XLF (red) and XRCC4 (green), can be visualized. Additionally, by simultaneously applying and measuring force, the strength of these bridges can then be characterized.



3 Stepwise length increase between the upper and lower beads in a quadruple trap configuration, including two DNA molecules and multiple DNA bridging proteins. Length increases are the result of disrupting DNA bridges by pulling on one of the beads.



4 Two DNA molecules trapped using four optical traps. DNA bridging proteins XLF (red) and XRCC4 (green) can be seen both individually and as a DNA bridging complex (orange).

Data courtesy of Prof. Erwin Peterman & Prof. Gijs Wuite at the VU University Amsterdam.

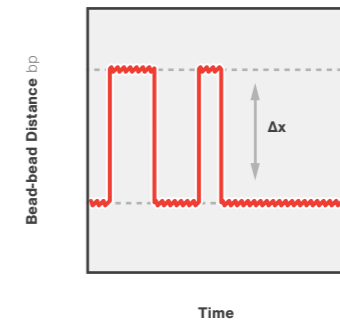
Read more:

Brouwer et al.
Nature (2016)

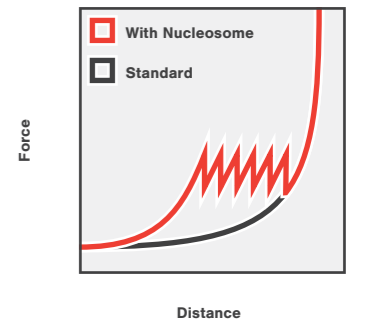
Measurement of conformational changes in DNA organization.

Conformational changes of DNA-protein complexes involved in DNA organization, for example, **nucleosomes**, can be measured with the C-Trap's high-resolution optical tweezers at the single-molecule level.

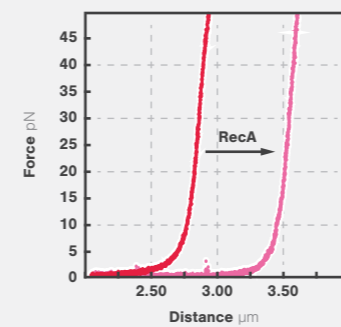
A DNA molecule organized in **DNA-histone complexes** can be tethered between two optically trapped beads. Following the activity of the DNA organization proteins is possible by applying a constant force on the DNA and simultaneously measuring the distance between the two optically trapped beads. The graph in **Figure 5** shows the winding and unwinding of DNA around the histones at the basepair level, measured by end-to-end distance shortening and lengthening bursts and plotted against time. **Figure 6** shows the force-distance curve of the DNA as it unwinds from multiple histone complexes.



5 Winding and unwinding of DNA around histones, measured at a set trap distance.



6 Force-distance curve showing DNA unwinding from histone complexes, as a DNA molecule with multiple DNA-histone complexes is being stretched using the C-Trap.



Force extension, manipulation, and visualization of DNA repair.

Simultaneous force and extension measurements allow for correlating the protein **activity and binding kinetics** with the **mechanical properties** of the protein-DNA complex. With the C-Trap, a single dsDNA molecule can be tethered between two optically trapped beads and subsequently coated with proteins, such as RecA—a class of repair proteins that form helical filaments around DNA. By simultaneously stretching the DNA and measuring the force and extension, it becomes possible to obtain the corresponding **force-distance curve**, which is a signature for the mechanical properties of the molecule (**Figure 2**).

2 Force-extension curves during successive extension and retraction of a RecA-dsDNA complex and a dsDNA molecule. The shift of the force-distance curve is caused by an increased stiffness of the DNA molecule due to the formation of RecA filaments. Less force is necessary to unravel the DNA-RecA complex as the filaments prevent it to coil.



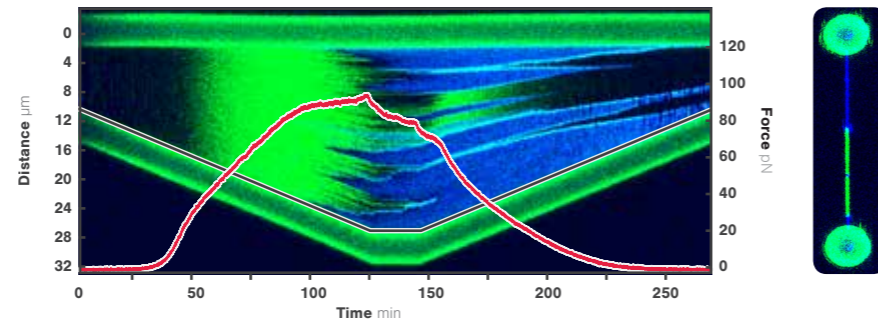
Force-extension, manipulation, and visualization of DNA-Protein interactions in DNA replication.

DNA Replication

When DNA-protein interactions involved in DNA replication are under study, the C-Trap enables the measurement and visualization of DNA-protein complexes to provide information into both the **mechanical effect** and the **target sites** involved in DNA replication mechanisms.

Here, by utilizing the C-Trap's laminar flow microfluidics and the automated in situ assembly procedure, an individual dsDNA molecule was tethered between two optically-trapped microspheres. Then, the tethered construct was transported into a channel containing both Sytox Orange, a dsDNA fluorescent marker, and fluorescently-labeled replication protein A (RPA), a ssDNA binding replication protein.

In **Figure 7** a dsDNA molecule is being stretched with a constant velocity of 140 nm/s while at the same time force, distance and fluorescence signals are continuously recorded. By overlapping all data sets, it can be seen that as the end-to-end distance (grey) increases, Sytox molecules (green) bind between the basepairs of dsDNA. Stretching the DNA even further initiates DNA melting and the formation of single-stranded DNA (ssDNA), which can be seen both **globally**, by a drop in the force (red), and **locally**, by the visualization of the ssDNA binding protein RPA (blue). As soon as RPA began binding, a drop in the force signal was observed, indicating the stabilization of melted DNA, which being coated by RPA cannot be reannealed with its complementary strand to form dsDNA again. This keeps DNA unwound for the polymerase to replicate it in the subsequent stages of the replication process. Finally, relaxing the molecule back under 25 pN, resulted in Sytox Orange dissociation while RPA remained bound.



7 Dual-color fluorescence kymograph corresponding to the extension and retraction of a single molecule of dsDNA. End-to-end distance (grey) and force (red) data sets are overlapped to the fluorescent image showing the true correlation of the data sets.

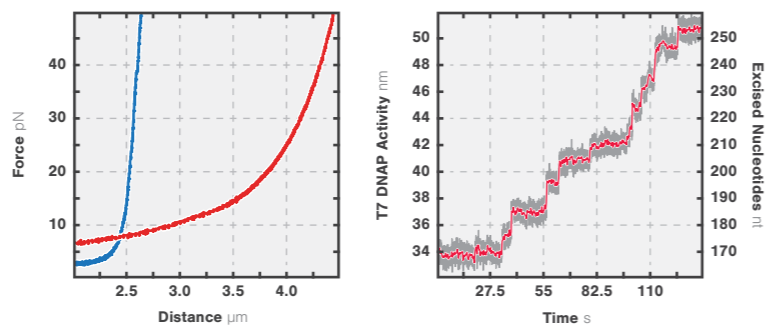
Measurement of DNA replication activity and states with force and fluorescence.

Optical tweezers can be used to measure and visualize the activity and states of motor proteins, such as **RNA or DNA polymerase**. Single-molecule measurements of stepping behavior of biomolecular motors will supply important new information about their enzymatic mechanisms.

A DNA molecule can be caught and stretched at a constant force using the optical tweezers, while a single DNA polymerase protein replicates the DNA. As the DNA polymerase incorporates nucleotides, single-stranded DNA becomes double-stranded; thus, the end-to-end length of the DNA molecule and the distance between the two traps becomes smaller, which can be measured in high resolution. In this way the **activity events of the polymerase** can be measured.

Figure 8 shows measured data of the activity of T7 DNA polymerase. This protein participates in DNA replication and has 3' to 5' exonuclease activity, which is enhanced in the presence of force. Optical tweezers hold a DNA construct (8.3 kbp), tethered between two beads ($\phi=1.86$ nm) at a constant force of 45 pN to observe force-induced exonucleolysis at the single-molecule level. The length of the DNA increases as more double-stranded DNA becomes single-stranded (**Figure 9**), allowing the measurement of the activity of the polymerase. Short activity bursts ranging between 3 and 10 nucleotides are observed, interspersed by frequent pauses of varying duration.

Additionally, by combining the optical tweezers with simultaneous multi-color fluorescence, measurements allow correlating the **mechanical properties of DNA with the conformational state** of the polymerase (e.g. with FRET) or the location of the enzyme along the DNA.



8 Force-distance curves of double-stranded DNA (blue) and single-stranded DNA (red)

9 Activity bursts of DNA polymerase performing force-induced exonucleolysis on a ssDNA.

Single-molecule visualization of DNA transcription at high protein density.

DNA Transcription

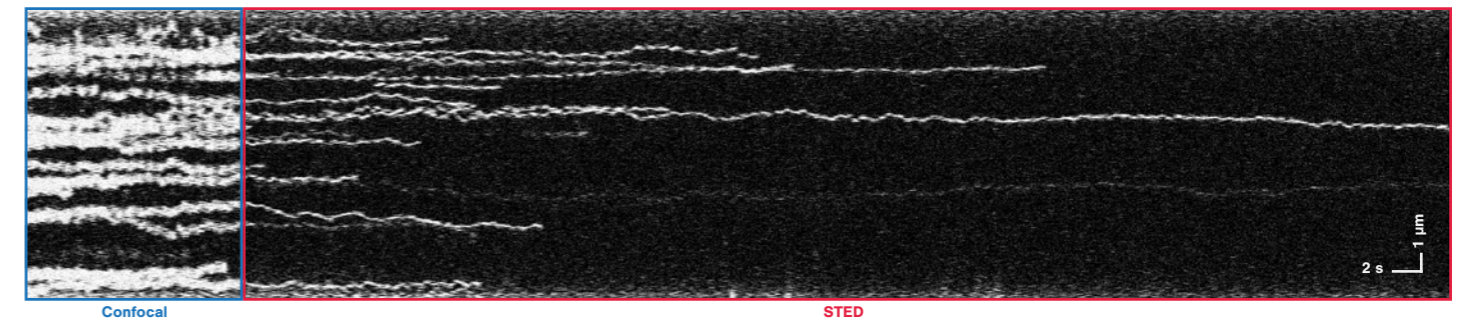
Because biomolecular processes, such as DNA transcription, often occur in highly crowded environments, stimulated emission depletion (STED) microscopy combined with optical tweezers can become an asset to **distinguish between individual labeled proteins**. When *in vitro* experiments are linked with the *in vivo* situation, in which proteins cover the DNA at high protein concentrations, STED is needed when measuring under biologically relevant conditions.

The real-time observation of the fast dynamics of fluorescently labeled mitochondrial transcription factor A (TFAM) on λ -DNA at a high concentration can be seen in **Figure 10**. To study these dynamics, the C-Trap™ SR uses optical tweezers to keep the DNA in place and stretched while 1D STED line-scanning tracks the proteins at high resolution (≤ 35 nm) and high frequency (≤ 200 Hz).

The use of STED enables the tracking of individual protein trajectories, including (un)binding and oligomerization events (Figure 10, right), which cannot always be observed with the diffraction limited resolution of confocal microscopy (**Figure 10, left**)

Read more:

Heller et al.
Nature Methods (2013)



10 Kymograph of the dynamics of human TFAM-Atto 647N at ~ 5 nM on λ -DNA at a constant force of 4 pN using confocal microscopy (left) and STED microscopy (right) coupled with optical tweezers (C-Trap SR). Data courtesy of Prof. Erwin Peterman & Prof. Gijs Wuite at the VU University Amsterdam.

Investigation of protein synthesis at the single-molecule level.

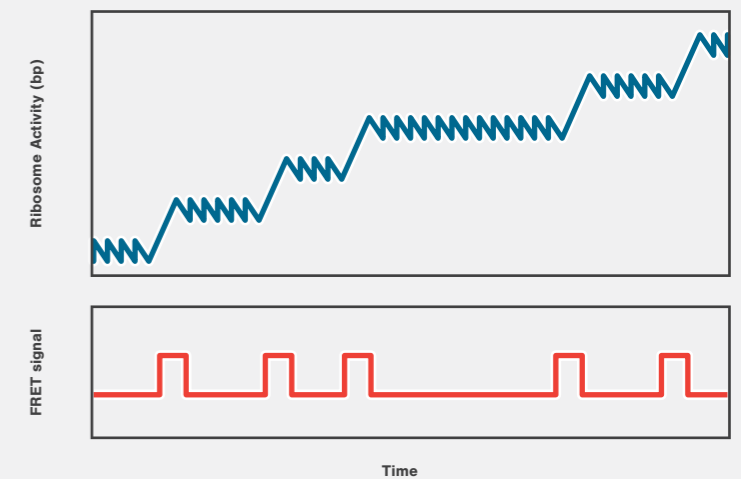
RNA Translation

With the C-Trap, it is possible to measure the activity and states of translation proteins as well as the kinetics and formation of nascent proteins, by using high-resolution optical tweezers.

When RNA-protein interactions are measured at the single-molecule level, the mechanisms involved in mRNA translation can be studied in high detail, including conformational changes of the formed protein.

Optical tweezers can be used to trap beads and tether a biomolecule, such as mRNA, in between the beads, while a single ribosome translates it. By simultaneously stretching the mRNA with a constant force and measuring the distance between the beads, while at the same time, the ribosome translates the RNA template into protein, the tethered RNA fragment becomes smaller, making it possible to measure the **activity events of the ribosome**.

The multicolor fluorescence detection allows quantifying the FRET efficiency changes of a labelled ribosome in time and enables correlating a certain conformational change of the ribosome with activity bursts of the replication protein (**Figure 11**).



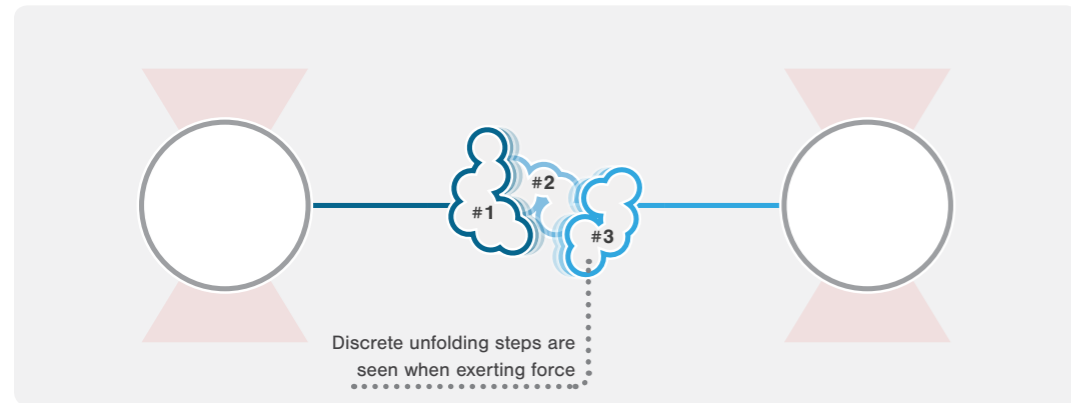
11 Schematic showing the activity of a ribosome across an mRNA molecule and the corresponding FRET signal across time. Combining optical tweezers with FRET measurements allows correlating the mechanical properties of the RNA with the conformational state of the ribosome.

Multi-domain Protein Unfolding

Study protein unfolding steps and visualize domain positions using FRET.

Studying how proteins fold correctly and undergo conformational changes to accomplish their biological function is a valuable method that produces groundbreaking discoveries in the field of biology and biophysics; however, few techniques allow this study in a non-static fashion. Using the C-Trap optical tweezer-fluorescence technology, both unfolding and refolding can be observed, as well as highly detailed equilibrium dynamics. This, in turn, allows scientists to study intermediate states in the unfolding process, **identify the protein (un)folding pathway**, and map its **energy landscape**—providing valuable information of the structure-function of the protein.

The high resolution of the C-Trap, together with the multicolor fluorescence single-molecule FRET capability, enables further characterization of protein conformation by detecting changes in the FRET efficiency signal and force fluctuations simultaneously. This enables **correlating global mechanical properties of the protein with local structural properties**.



Dynamic investigation of protein structure and function at the single-protein level.

Optical tweezers are used to trap beads while a protein is tethered using DNA-handles. The (un)folding of the protein is controlled by moving the beads while the force and distance are measured simultaneously. The resulting force-distance curve (**Figure 1**) of calmodulin—a calcium-binding protein—reveals that the protein unfolds and refolds in two steps which correspond to two separate helix-loop-helix domains.

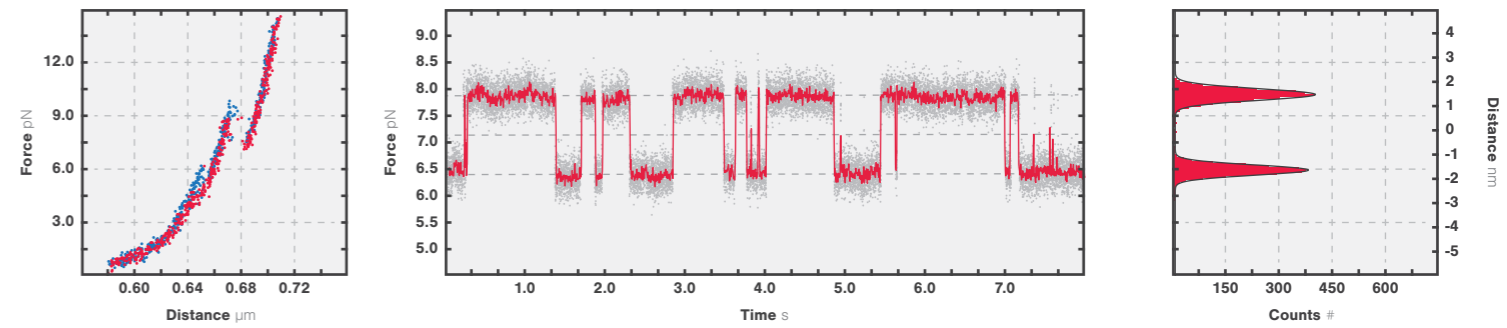
Equilibrium dynamics showing the transition between short-lived intermediate states can be studied because of the intrinsic distance clamp which keeps the traps at a fixed distance, while force fluctuations are measured. When this is applied to calmodulin, the equilibrium fluctuations between the states can be observed with a force resolution of <0.1 pN at 100 Hz. **Figure 2** shows that calmodulin switches between two major states, without a clear preference, and that intermediate steps can be resolved as calmodulin occasionally jumps to a third state for short periods of time, represented by the dashed grey lines.

The C-Trap's ultra-high stability makes it possible to characterize the properties of conformational transitions occurring during protein (un)folding over extremely long periods of time. To demonstrate this, **Figure 3** shows **spontaneous conformational transitions** occurring within a dsDNA molecule at ~56 pN for almost 10 minutes. When looking at a 10 s set of the complete trace, fast transitions between multiple states are clearly visible (**Figure 4**). The histogram analysis for both the complete 520 s trace and two 50 s sections of the main trace (**Figure 5**) show identical features, indicating that the experiment was performed without altering the transition kinetics due to unwanted force drift. When this is applied to protein (un)folding studies, the equilibrium fluctuations and relative probabilities between the states can be observed with a force resolution of <0.1 pN at 100 Hz and a force drift of <0.3 pN over minutes.

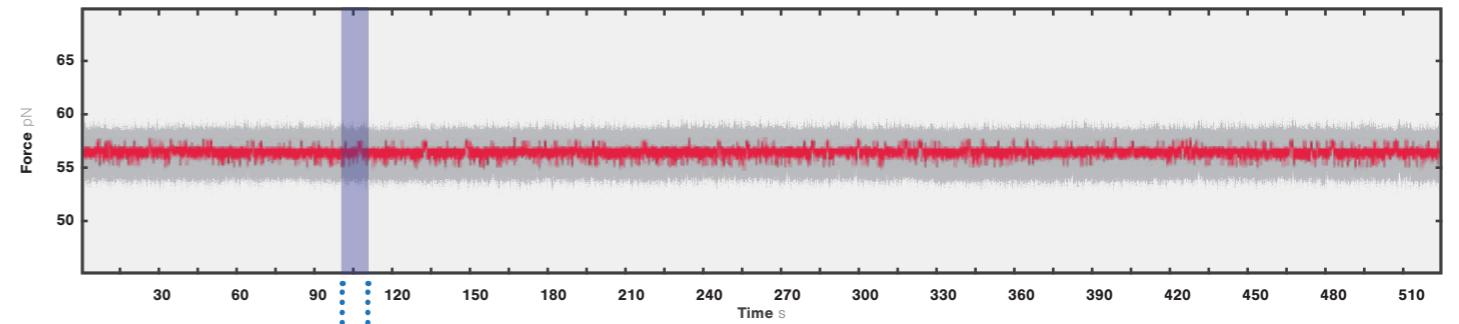


User insights
Prof. Sander Tans
 FOM Institute AMOLF

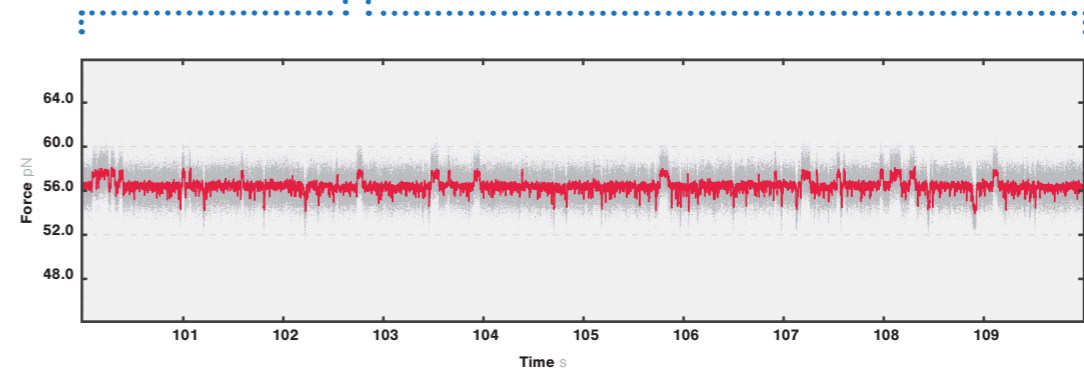
"We use the C-Trap to directly measure the multidimensional effects of mechanical forces in protein (un)folding, enabled by the combination of single-molecule fluorescence with optical tweezers. These findings provide insights into the mechanisms by which chaperones act to control protein conformations and folding to the native state."



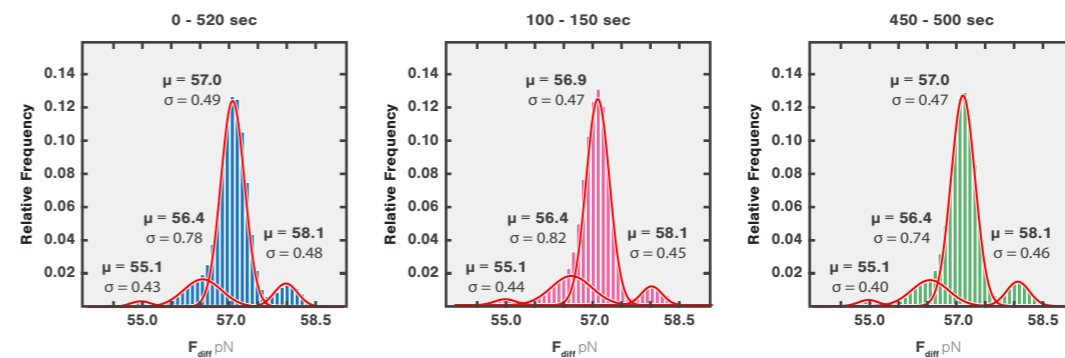
1 Force-extension (blue) and force-retraction (red) curves of a calmodulin protein reveals that the protein unfolds and refolds in two steps. **2** Force trace of equilibrium measurements over 10 seconds displaying the structural fluctuations of a single calmodulin molecule. Grey data is shown at a 2.5 kHz sampling rate while the red line shows raw data decimated to 200 Hz. The histogram on the right shows the two major states, while the third intermediate state becomes negligible due to its transitory existence.



3 Force trace recorded over 520 seconds corresponding to a single dsDNA molecule (8.4 kbp) held at a constant distance using optically-trapped polystyrene beads ($\sigma = 0.8 \mu\text{m}$). The trap stiffness was set at 0.5 pN/nm. Data were recorded at 50 kHz and decimated to 100 Hz (red).



4 Fragment with a duration of 10s of the trace shown within the blue inset in Figure 4.



5 Histograms of the force values collected for the full trace and for values collected during two different fragments of 50 seconds. The mean and sigma values are reported for each peak obtained from a Gaussian fit.

Read more:
 Mashaghi et al. Nature (2016)
 Neupane et al. Science (2016)
 Pelz et al. Nature Communications (2016)



Cellular Structure & Transport

Study the activity and mechanical properties of cellular components.

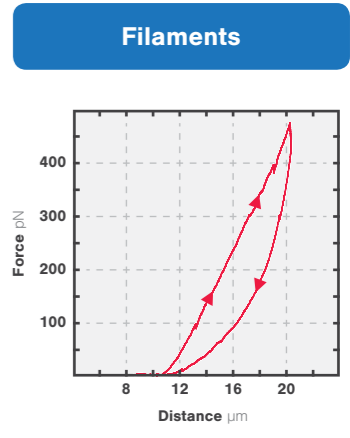
The C-Trap enables measuring the mechanical properties of cytoskeletal filaments and correlating them with local information such as the structural re-arrangement over time. The **kinetics of molecular motor proteins** along cytoskeletal filaments can be visualized and tracked, while their stepping mechanics can be monitored in real-time, allowing one to distinguish **discrete steps** and the subsequent mechanics of motor motion. When these interactions are measured in high resolution at the single-filament and single-molecule level, the exact biological mechanisms involved can be revealed in unprecedented detail. This includes the determination of the **motor protein binding site** to actin or a microtubule and its **diffusive properties**.

Moreover, other processes important to cellular events, such as **protein-mediated membrane fusion**, can be visualized and the dynamics of these processes can be tracked with the combination of optical tweezers and fluorescence microscopy. Such interactions can be studied in high detail by correlating the exchange dynamics within the membrane with the mechanical properties of membrane fusion.

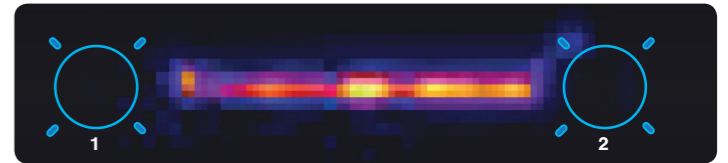
Force extension, manipulation and visualization of polymers and protein filaments.

Polymers and filaments can be manipulated with the high-resolution optical tweezers while simultaneously measuring force, extension and fluorescence microscopy data. Biomolecules can be probed up to the nanoNewton regime because of the extremely high escape force of the C-Trap.

The measured data in **Figure 1** show the extension of vimentin intermediate filament. In this experiment, an individual vimentin filament is held between two optically trapped beads. The **force-distance curve** is measured while stretching and relaxing the intermediate filament at a slow speed, allowing for structural equilibrium. The retraction curve shows clear hysteresis due to the remodeling of the vimentin filament under high tension. Simultaneous confocal fluorescence imaging of the vimentin filament is used to resolve this intra-molecular remodeling.



1 top Force-extension curve of a vimentin filament.
1 bottom Confocal fluorescence image showing the intra-molecular remodeling of a vimentin filament.



Data courtesy of Prof. Sarah Köster at the University of Göttingen.

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Cell Membranes Page 15

3-bead assay immobilized on flow cell surface

User insights

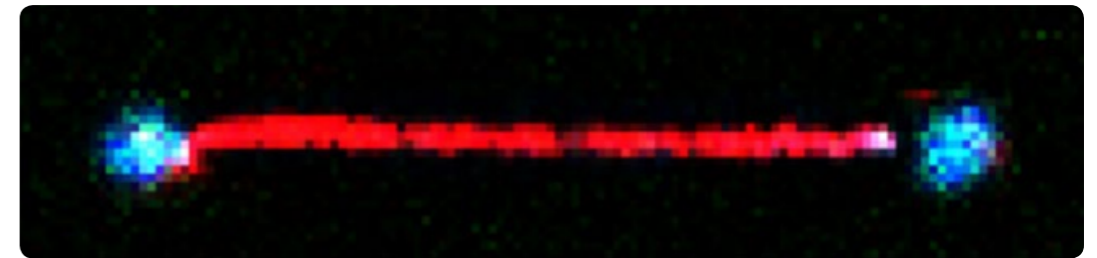
Prof. Tony Hyman & Prof. Stephan Grill
 Max Planck Institute of Molecular Cell Biology & Genetics

"The correlation of force traces with fluorescence observation provides very powerful insights for our research. The team has been fighting over system time!"

Photo copyright of MPI-CBG

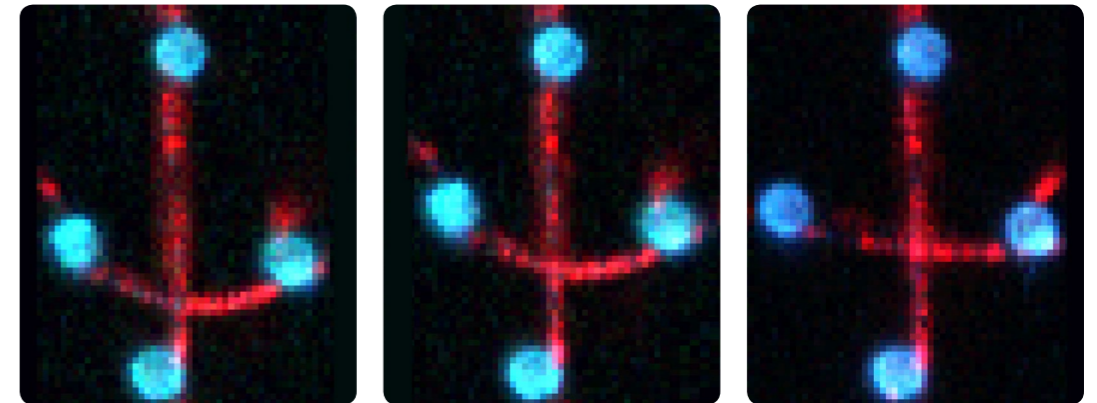
Visualization of filament-filament interactions.

Cytoskeletal filaments interact with other similar and dissimilar filaments. The surface properties of these filaments, their electrostatic and ionic forces and specific interactions, can generate friction when two filaments interact. This friction can be measured using the quadruple trap C-Trap configuration correlated with fluorescence-microscopy to allow for real-time visualization of filament-filament, filament-protein, and filament-protein-filament interactions.



2 A biotinylated fluorescent microtubule held by two avidin coated, optically trapped microspheres, was observed using the C-Trap. The microtubule is fully stretched to be linear. The microspheres on the right can be moved towards the microsphere on the left with a known force causing the microtubule to buckle.

A simple characterization of cellular filaments, such as microtubules, is achieved by holding a microtubule between two trapped microspheres using the dual or quadruple trap optical tweezers-fluorescence microscope. The fluorescently labeled tubulin is visible as a red filament using confocal microscopy, allowing for correlative force and fluorescence spectroscopy (**Figure 2**).



3 Filament interactions studied using quadruple trap optical tweezer-fluorescence microscope. Two fluorescently labelled microtubules held in a crossed pattern. A microtubule is dragged across another microtubule with a known force. A characteristic curve is observed due to the friction force between the two filaments (Left and Middle). After the microspheres are held stationary the microtubule slowly relaxes (Right).

Data courtesy of BIOCEV Prague, Dr. Zdeněk Lánský's group.

Read more:
Block et al.
 Physical Review Letters (2017)
Kurniawan et al.
 Biophysical Journal (2016)

Single-molecule visualization of cytoskeletal motors.

Cellular Transport

Optical tweezers can be used to trap beads and catch a cytoskeletal polymer such as a microtubule in between. Fluorescently-labeled motor proteins can be visualized using fluorescence microscopy which enables studying the binding location, (un)binding events and kinetics of the cytoskeletal motors.

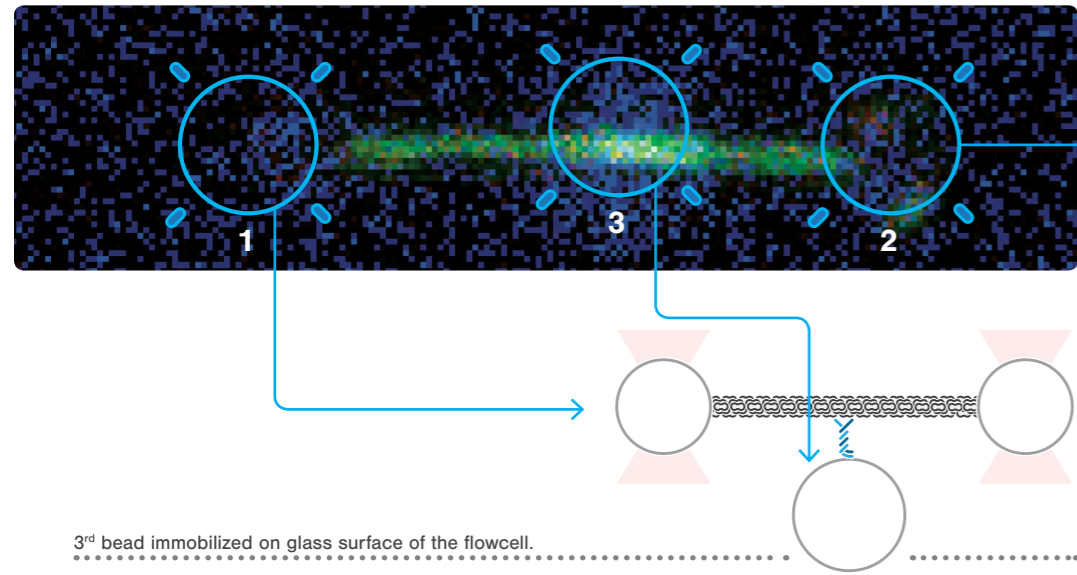
Alternatively, a third bead is immobilized to surface and attached to the motor protein to track the movement and measure the speed of the protein in high resolution.

Investigation of stepping mechanics of motor proteins along cytoskeletal filaments.

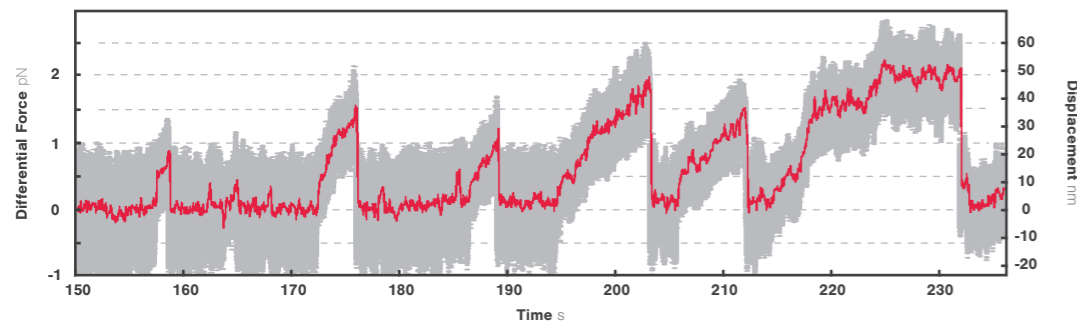
Figure 4 displays a three bead assay utilized to study the stepping behavior of a molecular motor. Two optically-trapped beads hold actin tight, while a myosin-coated bead is immobilized on the glass surface of a flow cell. Fluorescently-tagged actin filaments are visualized using the C-Trap's correlated confocal microscopy capability, while distance measurements are performed simultaneously during imaging.

In this experiment, we used the C-Trap to investigate the displacement of actin with respect to wild-type myosin-VI, by measuring the correlated displacements of the two beads trapped in the dual optical trap. **Figure 5** shows that myosin pulls the actin filament in a unidirectional manner with a measurable force.

With the C-Trap it is possible to track the activity of molecular motors along cytoskeletal proteins and determine their thermodynamic properties at the single-molecule level. The exact kinetics of the motor can be observed by measuring the relative translocation of the filament with respect to the motor and the related forces. From the resulting force-time traces, the speed and processivity of the motor is derived. The processive motion of myosin can be studied with sub-picoNewton force and sub-nanometer distance resolution, owing to the C-Trap's high spatial and temporal resolution.



4 Fluorescent image of a single actin filament tethered between two trapped beads that has been brought into contact with a third bead functionalized with myosin molecules.



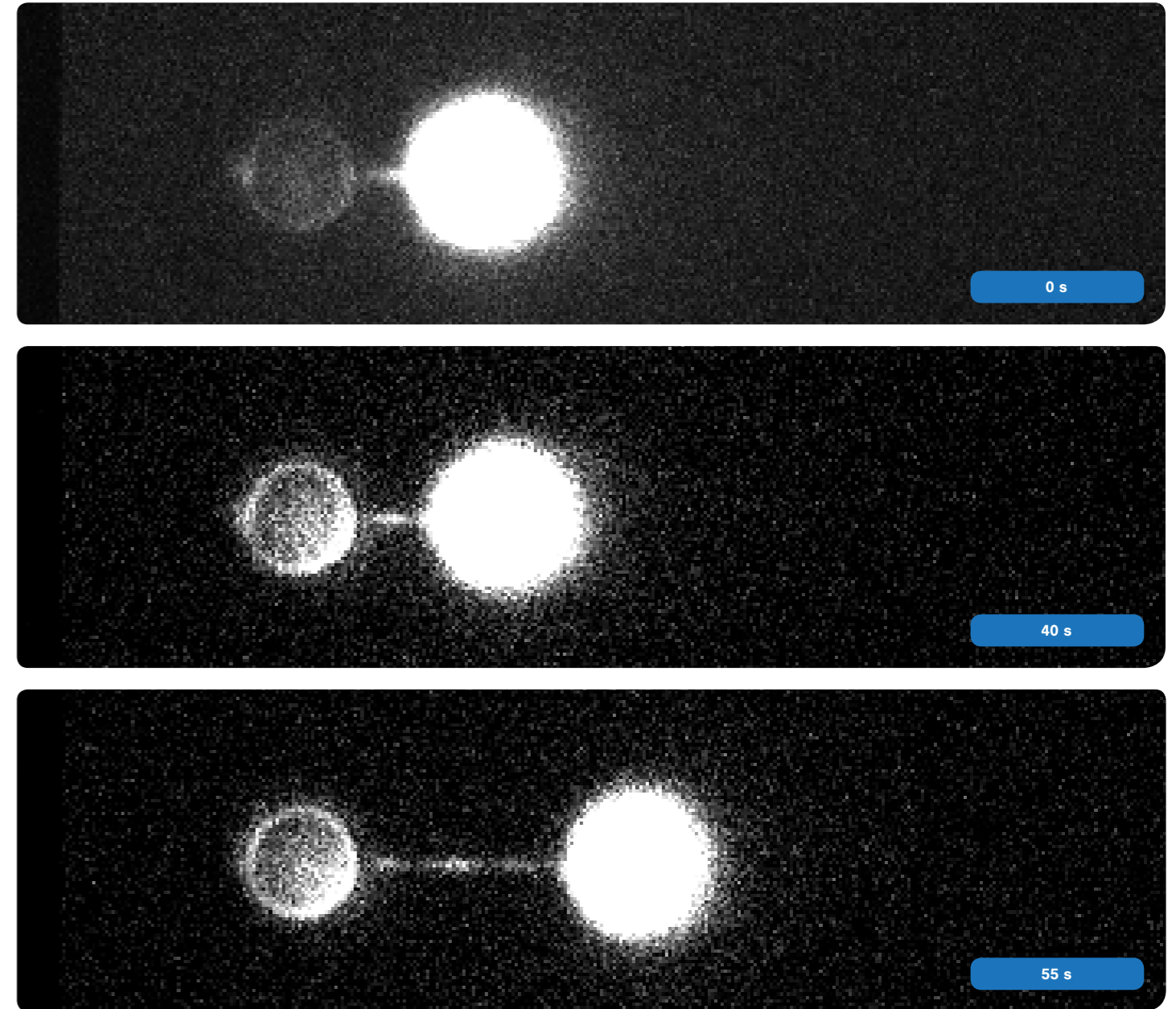
5 Motility of myosin-VI as detected by the three-bead assay. Data acquired shown at 50 kHz (gray) and 20 Hz (red). Sample courtesy of P. Ruijgrok and Z. Bryant, Stanford University.

Measurement of the dynamics and fusion of lipid membranes.

Cell Membranes

With the C-Trap it is possible to perform force-fluorescence membrane fusion experiments. **Lipid-coated beads** can be trapped, and brought into close proximity. By moving the beads apart, the fusion between the membranes can be observed by an increase in force; concurrently, the membrane and stalk formation can be observed in the fluorescent signal.

A proof-of-principle of this correlated force and fluorescent measurements can be seen in **Figure 6**. Two beads covered with a phospholipid bilayer (the right contains fluorescently labeled lipids) are brought together in the presence of Doc2b, a **membrane interacting protein**, and separated sequentially after initial contact. Upon separation of the beads, a micrometer-long membrane stalk is formed in between. High rupture forces (>600 pN) of these stalk complexes are observed, whereas low rupture forces (<25 pN) are measured if no membrane-interacting protein is present. The strong fluorescence increase in the unlabeled membrane and a concurrent decrease in the signal of the labeled membrane indicate that either hemifusion or full membrane fusion occurred.



6 Fluorescent images of two membrane-coated beads at different time-points. As the beads are separated upon initial contact, the formation of a micrometer long stalk is observed. The increase in fluorescent signal of one bead and the concurrent decrease in fluorescent signal of the other bead indicates mixing of the phospholipids by the presence of a lumen, resulting from membrane fusion or hemifusion.

Data courtesy of Prof. Erwin Peterman & Prof. Gijs Wuite at the VU University Amsterdam.

Read more:
Brouwer et al.
Nature Communications (2016)



Small Molecule-Protein Interactions

Study how small molecules interact with proteins or DNA to modulate enzymatic activity.

Small molecule inhibitors are widely used in the **pharmaceutical industry**. Intercalation of small molecules within the DNA template, or binding to the active binding sites of various enzymes, are broadly used as drug treatments to compromise DNA-associated processes that progress in an abnormal fashion; therefore, small molecule inhibitors are often used in cancer therapy and they still remain one of the most effective agents in clinical use.

By using correlated high-resolution optical tweezers and fluorescence microscopy, not only can the **binding properties** of small molecules be studied (e.g. kinetics or diffusive features) but also their **effect in the inhibition of the activity** of DNA-processing motors. These processes can be grouped into two main categories: those in which small molecules interact with the DNA template, resulting in roadblocks that hamper the motion of the proteins, and those in which small molecules interact with the active binding site of the enzymes, thereby reducing or altering their performance.

Visualization and characterization of small molecule-protein interactions.

With the C-Trap it is possible to visualize interactions between small molecules and biomolecules, such as motor proteins and DNA, at the single-molecule level. Small molecules can inhibit DNA-associated processes such as DNA replication, transcription, and repair, and are therefore widely used for drug screening and discovery.

The C-Trap's optical tweezers can be used to catch a DNA molecule tethered between two beads, while a motor protein and differently labeled small molecules can be visualized by correlative fluorescence microscopy. The illustration at the left shows how small molecules interact with the motor protein, thereby **reducing or altering its activity**. Alternatively, the small molecules can interact with the DNA template, resulting in barriers that restrict the movement of the proteins.

Figure 1 shows the results of an experiment in which initially, the DNA template (8.3 kbp) was fully coated by SYTOX Orange, a small molecule that fluoresces when intercalated between the base pairs of double-stranded DNA. A single bound DNA polymerase proofreading the nucleotides by removing them from the template can be monitored via fluorescence microscopy, by the appearance of an increasing dark region over time. Simultaneously, by maintaining a constant tension, a clear increase of the end-to-end DNA distance is observed, due to the generation of single-stranded DNA. The presence of small molecules, in this case, compromises the motility of the motor protein, by drastically reducing its velocity by increasing the frequency and duration of pauses during its performance.



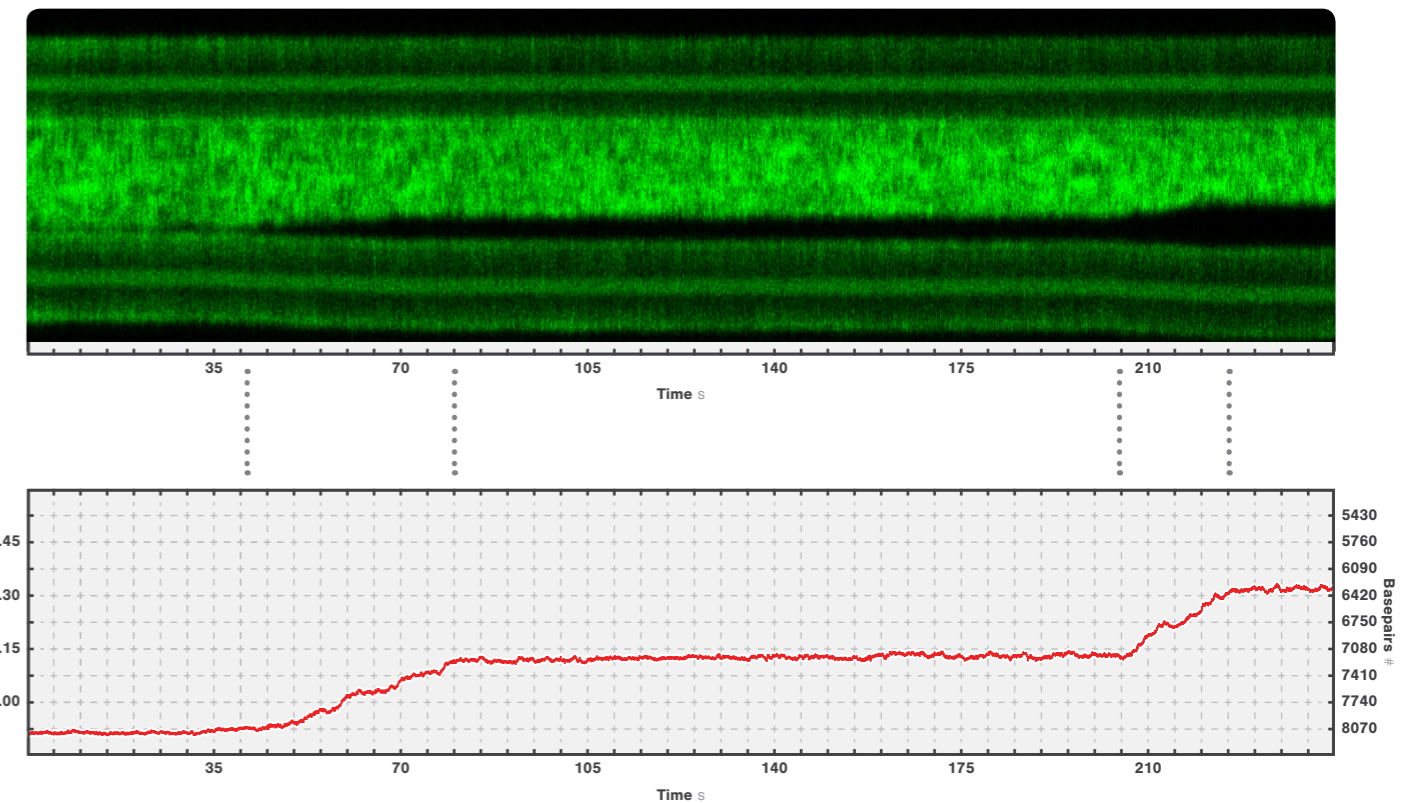
A correlative solution

The C-Trap's optical tweezers can be used to catch a DNA molecule tethered between two beads, while a motor protein and differently labeled small molecules can be visualized by correlative fluorescence microscopy. The illustration above shows how small molecules interact with the motor protein, thereby reducing or altering its activity. Alternatively, the small molecules can interact with the DNA template, resulting in barriers that restrict the movement of the proteins.

Why use single-molecule techniques for drug discovery?

Identification of the most potent drug candidates with single-molecule methods has enormous potential in the future of drug-discovery, offering major benefits over conventional assays used for screening. The ability of single-molecule tools to characterize new properties and specific transient steps in complex biochemical pathways, which are otherwise obscured in ensemble-average systems, allows you to look for **inhibition of specific steps**. Given that most biochemical pathways usually consist of multiple steps, the total number of potential drug targets is considerably increased. Because of the C-Trap's ability to directly visualize multi-step processes (even the most transient ones), it is extremely straightforward to observe at which step inhibition occurs and how it works. This, in turn, allows the development of **more precise drugs** while requiring significantly fewer secondary targets, and thus reducing the probability of side effects.

Common concerns such as long experimental time and high costs completely diminish when using the C-Trap. Bulk assays are often indirect methods of screening and require many experiments to reveal the molecular mechanism in question. Moreover, since only single molecules are required for the C-Trap experiments, the material consumption is several orders of magnitude lower. The intuitive software, the integrated microfluidics, and the automation capabilities guarantee an unprecedentedly quick workflow. The C-Trap gives access to novel information and ensures the **precise screening of small molecules, quickly and effectively**.



1 (Top) Kymograph showing SYTOX Orange bound to double-stranded DNA, thus indirectly visualizing the position and activity of DNA polymerase. (Bottom) Simultaneous measurement of the end-to-end DNA distance shows activity steps of DNA polymerase with high-resolution as single-stranded DNA is generated.

Read more:

Manosas et al.
Nature Communications (2017)
Almaqwashi et al.
Nucleic Acid Research (2016)



User insights

Prof. Sarah Köster

Georg August University

"Using our C-Trap we manipulate cellular components and study their dynamic behavior while visualizing them in real-time. Moreover, we are new users to optical tweezers, which makes it even more impressive that with this instrument we have been able to really start from scratch and go to 100% and perform experiments within a day."

Inside C-Trap G2

Features & options.

With the ever-increasing pressure on researchers to perform breakthrough discoveries in the least amount of time, you need an instrument that brings unprecedented insights with high precision, accuracy, reliability and the shortest time-to-result.

With the latest evolution of our C-Trap system you gain access to a variety of enabling features and state-of-the-art performance.



The challenge in measuring small, transient, and rare conformational changes

A discussion on resolution, stiffness & drift

Due to water molecules that continuously bombard the object that is measured with the optical trap, there is an intrinsic force noise floor on the measurement. In order to still be able to measure the smallest conformational changes, you need **extremely stiff** optical traps to quench the motion of the trapped bead, so that the smallest displacements are revealed by the **high-resolution** optical trap measurement.

Very low force drift is required to enable long measurements to average out the Brownian noise, to reveal small steps and/or rare states. Additionally, in a typical case of a multi-state biological system, **extremely low drift** is also required to avoid change in tension on the molecule, which would skew the populations of the different states.

The LUMICKS solution

Unlike microscopy bolt-on tweezers, the C-Trap's purpose-built body has been fully optimized to provide extreme force stability and resolution. With drift below 0.3 pN over minutes and a trap distance resolution of less than 3 Å (at 100 Hz), we achieve the highest combination of force/bandwidth resolution.

3 Microfluidics

Flip to the next page to get an understanding of our full microfluidic workflow.

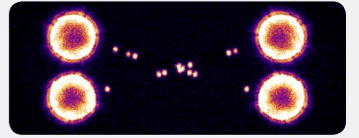
5 Sample Control

A high-resolution piezo-controlled nanostage enables the repeatable and absolute positioning of the sample in x, y and z and can be used for surface measurements with sub-nanometer accuracy.

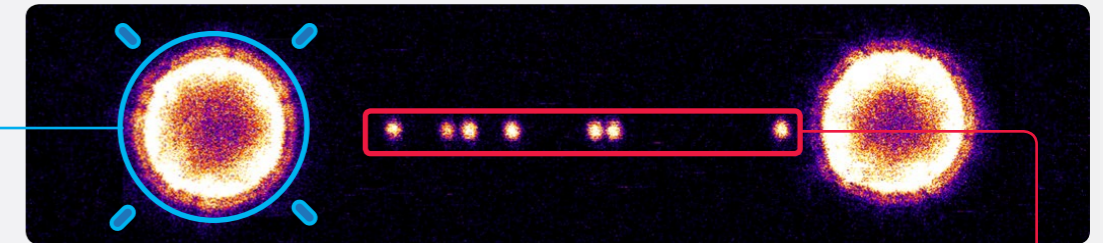
1 Manipulation

The C-Trap includes two optical traps for manipulating either a single biomolecule or four traps for manipulating multiple biomolecules while measuring the interactions between them. The C-Trap's continuous, non-time-shared optical traps can be operated both individually and in pairs. The high escape force ensures that a wide range of biological systems can be investigated.

The purpose-built C-Trap enables **extremely long acquisitions** at a constant distance or constant force—with drift below 0.3 pN over minutes—revealing even the rarest states and smallest conformational changes, otherwise hidden by Brownian motion or instrumental drift.

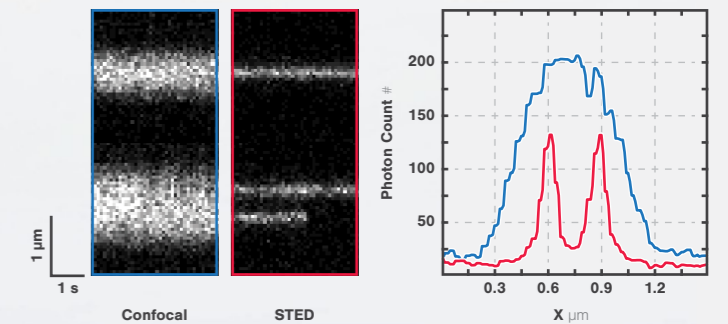


Quadruple trap configuration, allowing for complex DNA-DNA experiments.



2 Visualization

The multi-color (up to 3) confocal fluorescence imaging allows the visualization of biological processes such as protein kinetics and (un) binding events on DNA. It is also possible to measure conformational changes of proteins by combining the C-Trap with FRET.



A comparison of confocal (left) and STED (right) images of Atto 647N-labeled restriction enzymes bound to optically stretched DNA.

Intensity profiles of two proteins located close to each other by using confocal (blue) and STED microscopy (red).

Data courtesy of Prof. Erwin Peterman & Prof. Gijs Wuite at the VU University Amsterdam.

C-Trap™ SR

Upgrade to **C-Trap SR** for stimulated emission depletion (STED) nanoscopy to better distinguish individual DNA-binding proteins on densely covered DNA with unprecedented resolution (<35 nm).

4 Force Detection

The force on the sample is measured with sub-picoNewton resolution on two traps through ultra-sensitive position sensing detectors. Tension values ranging from a few tenths of pNs to the nN level and beyond can be applied and measured. This allows for monitoring extremely small steps on a broad regime, relevant for example in protein unfolding experiments.

New The C-Trap G2 can be delivered with the option for **ultra-fast sensors**. Capable of detecting extremely short-lived states, the ultra-fast sensors allow the user to study biomolecular processes that occur on the microsecond timescale.

6 Temperature Control

The C-Trap G2 temperature control option enables the user to measure molecular interactions at the physiological temperature and investigate temperature-dependent interactions in single-molecule experiments. The temperature can be controlled with an absolute accuracy of **0.2°C** and a stability of **0.05°C**, without compromising on other specifications of the C-Trap.

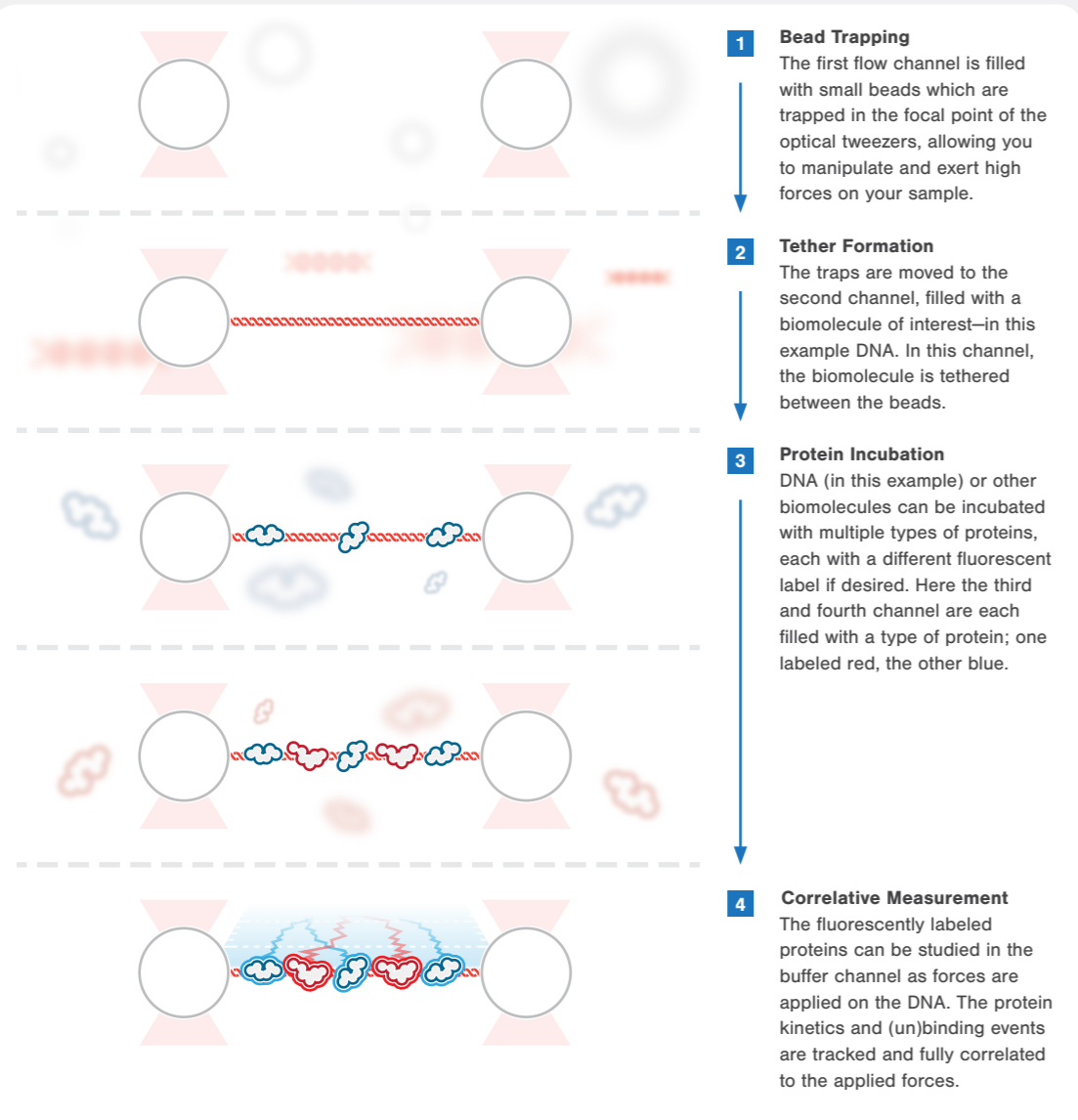
7 Stabilization

The C-Trap is delivered with a pressure-stabilized optical table. Depending on your requirements, LUMICKS can find the optimal solution for ultra-stable experiments with minimal noise.

u-Flux Microfluidics

A highly stable microfluidic system for single-molecule experiments.

u-Flux has been developed as an easy-to-use high throughput solution dedicated for single-molecule applications. The microfluidic flow cell provides multiple adjacent laminar flow channels that do not mix (no physical barriers are involved). Flow channels can be independently switched on and off through automated fluidic valves.



Twist-lock syringes

Sample loading is easily performed by directly pipetting your sample(s) into the syringes. The twist-lock syringe adaptor with bayonet fitting allows for quick and easy refilling of individual syringes.

Remote control

Automated flow control and valve switching allow for an optimal remote operation to perform robust measurements with high throughput. Using the software, you are able to regulate the pressure and control each of the channels with simple clicks or with a scripting plugin for automation.

Reliable & precise

The pressure driven flow in combination with the monolithic glass flow cell provides an extremely stable and repeatable experimental environment. The laminar flow permits the sequential assembly of single-molecule assays and the controlled triggering of biochemical reactions by exposing the molecule of interest to different buffer environments at specific time-points.

Repeated use

The monolithic glass design allows for re-use. Even highly-concentrated chemical solutions can be cleaned quickly and effectively.



User insights

Dr.
Zdeněk Lánský
BIOCEV

"We are now able to construct and investigate complex macromolecular assemblies because of the microfluidics system integrated in our setup."

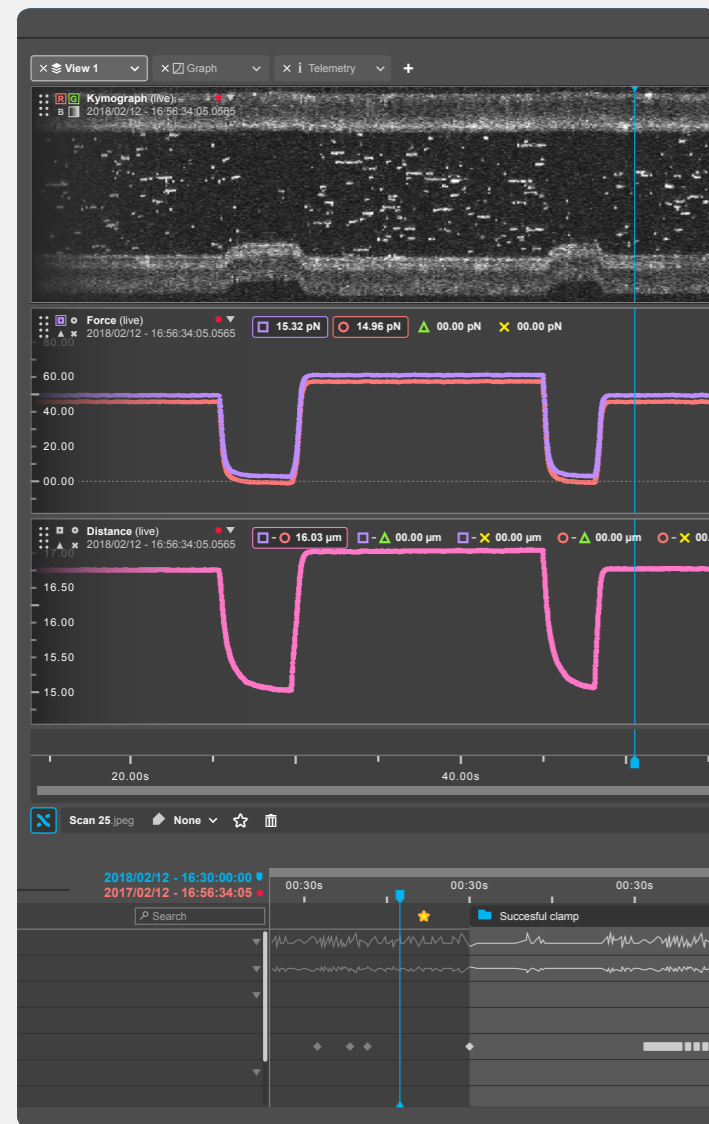
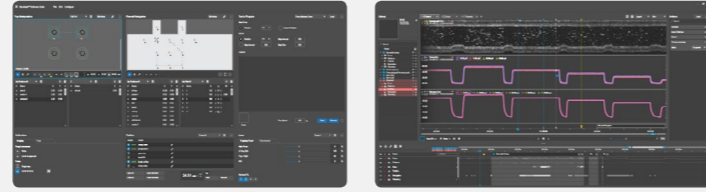
Introducing:

Bluelake

An intuitive single-molecule software suite for high throughput correlated experiments.

Designed from the ground up, our brand new software suite **Bluelake** provides intuitive controls that bring you closer to your experiment and enable the **highest experimental throughput**. Manipulate your sample directly with simple mouse and joystick movements, and **fully automate your measurement** with our powerful Python scripting engine.

With a click of a button, you perform complex single-molecule experiments and gather simultaneous force, fluorescence, bright-field, and instrument status data streams. The new timeline feature ensures you can focus on the data that matters, and never lose anything of value.



True correlation

Bluelake was designed to control all aspects of the C-Trap from a **single interface**. The trap positions, force data, bright-field and fluorescence images are acquired using the same software package, making the experiments truly correlative. All data streams are saved in the same single data file and synchronized using the same hardware clock.

High performance

By focusing on the ultimate performance of the software, we ensure that the user interface remains smooth and responsive, even when performing **the most demanding experiments**. Because of the unique GPU rendering technique of Bluelake, it provides fast, quick and smooth data navigation through extremely large datasets. Visualize your data in real-time, even at acquisition frequencies up to **2.5 MHz**.

Auto-save functionality

Our intuitive timeline interface for data storage automatically generates a structured overview of the state of your experiments, allowing for **fast & smooth navigation** through **multiple days of typical measurements**. The fully correlated data streams can be viewed, compared and exported during—or after your experiment. In addition, the extensive list of metadata is always streamed to disk, ensuring that you will never miss anything of value and will always be able to reproduce your experiments.

An open data standard and open source initiative

Data integrity is a key aspect of scientific instrumentation. All data of the C-Trap is stored in the standardized HDF5 open data format, which ensures that data can be accessed by anybody independent of LUMICKS software. Besides that, it is our philosophy that the user has direct access to the raw data and all data processing algorithms within the software (e.g. power spectrum fitting). This gives you **full flexibility** to understand, inspect, adapt, share and publish the data algorithms used within the instrument for online and offline data analysis. By storing extensive metadata about your experiments and saving the data in an open file format, ensures better reproducibility of your experiments and raw data that are easily accessible.

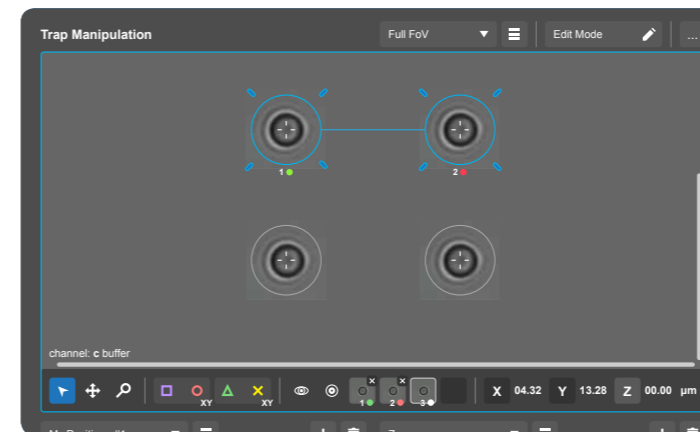
User insights

Prof. Ben Schuler
University of Zurich

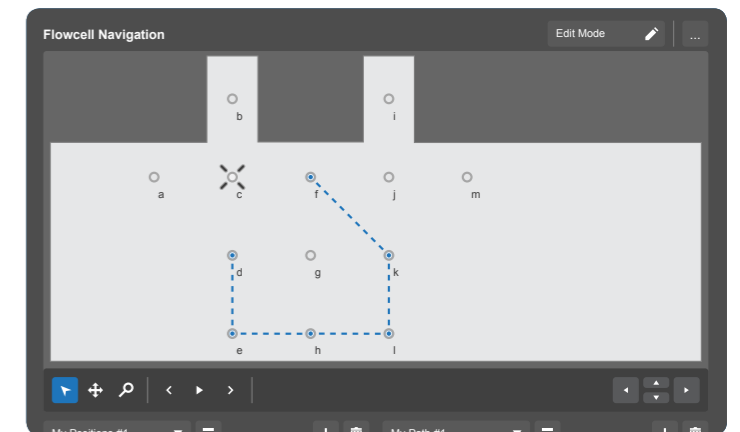
"The user-friendly software combined with the high-throughput experimental workflow and the dedicated training we received from LUMICKS, has fully equipped us to perform state-of-the-art single molecule force spectroscopy experiments in no time."



Bead trapping



Flow cell navigation



Ease of use

Bluelake provides intuitive controls that bring you closer to your experiment. The software is developed in such a way that it gives you all the controls you need in an easy and intuitive manner. Whether you are visually navigating through the laminar flow cell on screen, or selecting the area you wish to scan in the bright-field camera tab, our user-entered approach provides you with an intuitive experience that is accessible for anyone.

Automation & scripting with Python

Repeatable experiments are key for gathering statistically relevant quantities of data and publishable results. The C-Trap software allows for automation through the implementation of:

Programmable controls that automate basic procedures, such as predefined trap calibration, force-extension measurements, force-clamp experiments and predefined sample-stage trajectories, making measurements faster and less prone to human or random errors.

Scripting with full access to all relevant system parameters and data streams to allow the user to fully automate any kind of repeated experimental procedure, enabling to perform experiments autonomously.

```
1 trap.clear() # to get rid of any existing bead
2 stage.move_to("beads")
3 fluidics.open(1, 2, 3, 6) # depends on experiment
4
5 while trap.match_score < 30:
6     if 0 < trap.match_score < 30:
7         trap.clear() # bad bead, BAAAD bead! >:(
8         pause(1) # second
9
10 stage.move_to("buffer")
11 fluidics.close(1, 2, 3, 6)
```

Catching beads with 11 lines of code

Here we show the power of **Bluelake's** scripting features; **automated bead catching**. The software moves the traps into the bead channel, and selectively catches beads that fit the user's set criteria. The moment the perfect beads are trapped, the flow is stopped and the sample is automatically moved to the buffer channel, ready for you to start the next step of your experiment.

Spec Sheet

Unique & enabling features of C-Trap G2.

Optical Tweezers	
Force resolution	< 0.1 pN at 100 Hz (1 μ m beads at 0.3 pN/nm trap stiffness)
Maximum escape force	> 1000 pN using 4.5 μ m polystyrene beads
Force stability	< 0.3 pN over 2 minutes
Minimal incremental step size	2 Å Absolute position
Force acquisition frequency	Up to 2.5 MHz
Trap distance resolution	< 3 Å at 100 Hz
Live bead tracking accuracy	< 3 nm at 100 Hz using video analysis , simultaneous with force and fluorescence detection
Maximum corner frequency	15 KHz
Field of movement (FoM)	50 μ m x 50 μ m x 35 μ m (X, Y, Z)
Trap type	Continuous wave for unparalleled stiffness, stability and precision
Number of independent traps	1 - 4
Trap positioning capability	All traps independently movable in X, Y. Trap 1 + 2 & 3 + 4 moveable in X, Y, Z (pairs)

Dual/quadruple continuous optical tweezers; for manipulating single or multiple biomolecules with high stability and precision.

New Force detection; with an extremely high escape force (> 1000 pN), **superior force stability** (< 0.3 pN over minutes) and force resolution (< 0.1 pN at 100 Hz) for probing different biological systems with a large dynamic range while measuring very small force steps.

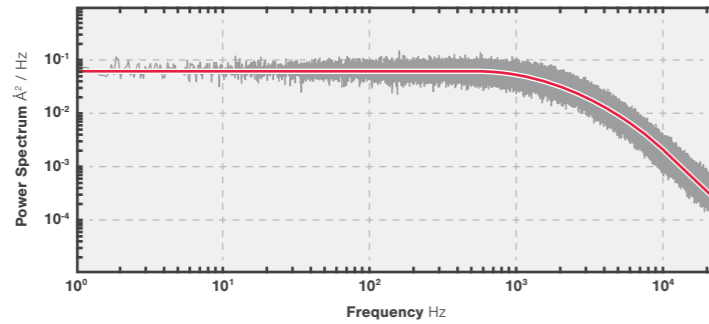
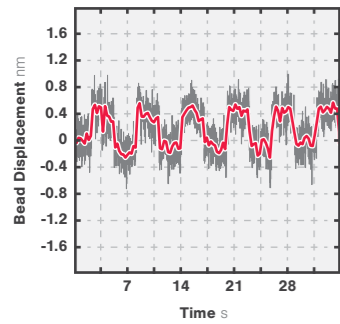
Tandem scanner for simultaneous dual optical trap movement; for identical movement of two optical traps so that the tethered sample can be moved at a constant force and extension.

Ultra-stable trap steering; providing 2 Å positioning accuracy accessible over a large range; for providing trap movement over a large field-of-view with base-pair precision.

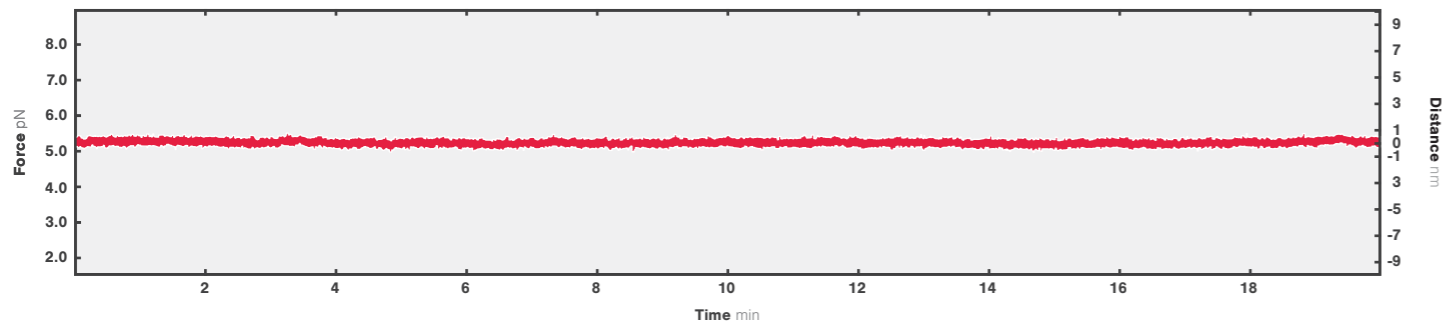
New Option for Ultra-fast Sensor; for the detection of extremely short-lived states and the mapping of high-resolution energy landscape of molecules with a sampling frequency of up to 2.5 MHz.

Video based bead-tracking; with an accuracy of <3nm at 100Hz for independent distance tracking.

Software regulated force clamp with high temporal resolutions; for applying a constant force to the biomolecule under study throughout the whole duration of the experiment.



◀ Bead displacement steps of 4 Å can be resolved with the high-resolution optical tweezers.
 ◀ Power spectrum (acquisition time of 5 minutes) of the Brownian motion in the X-direction of an optically-trapped 1.00 μ m polystyrene bead. Raw data was binned in 20 points bins (grey), which were then used for performing a 2-step fit (red).
 ▼ Force trace recorded over 20 minutes to a single dsDNA molecule (8.4 kbp) held at a constant distance using optically-trapped polystyrene beads ($\sigma = 1.0 \mu$ m). Data is shown at 100 Hz.



LUMICKS is committed to standing by you to ensure your instrument performs to specification throughout its lifetime, provide you with access to our experts for application support and service to facilitate the fastest time to result for your experiments.

*C-Trap SR exclusive

Fluorescence Microscopy	
Confocal resolution	Diffraction limited
C-Trap SR STED resolution*	< 35 nm
Spot position accuracy	< 5 nm
Localization accuracy	< 5 nm
Scanning speed	Up to 200 Hz
Sensitivity	Optimized for single fluorophore detection
Dark counts	< 0.25 photons per pixel dwell time (=100 μ s)
Background rejection limit	100 nM at 1 ms integration time
Field of view (FoV)	50 μ m x 35 μ m (X, Y)
Number of confocal colors	Up to 3, to choose between 10 different wavelengths (488 nm to 647 nm)
Other notable features	Full integration with optical tweezers for correlative measurement and user interactions, ALEX-FRET ready

One/two/three-color confocal fluorescence microscopy; for simultaneous and correlative visualization of differently labeled biomolecules in real-time with high accuracy.

C-Trap SR STED super-resolution nanoscopy; for higher imaging resolution, and localization accuracy of fluorophores.

Microfluidics

New Option for precise temperature control; for measuring samples in varying temperatures ranging from room temperature up to 45°C, with an accuracy of 0.2°C. Because of the closed-loop nature of the system, the temperature is highly stable, with fluctuations of only 0.05°C.

Multi-channel laminar flow microfluidics system; without physical barriers between the channels; for introducing precious reagents in a controlled manner and *in-situ* assembly of a wide range of complex, multi-step single-molecule assays.

Remote fluidics valve control; for programming the software user interface for high data throughput applications.

Software

New Bluelake software suite with optimized workflow; for high throughput single-molecule experimentation by trapping microspheres, tethering and subsequent manipulation and imaging of biomolecules within minutes.

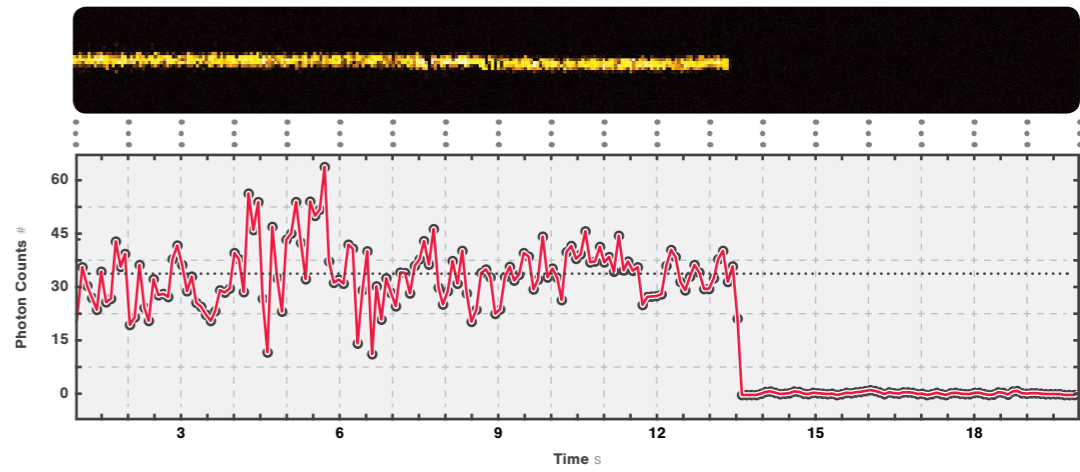
Software support; at LUMICKS, we have a software team working relentlessly to continuously optimize and adapt the C-Trap software for novel applications. We work with our users to implement features that help them improve their research capabilities, enhancing the possibilities of the system with every release

General

High-resolution piezo-controlled nanostage; for surface assays and repeatable and absolute positioning of the sample.

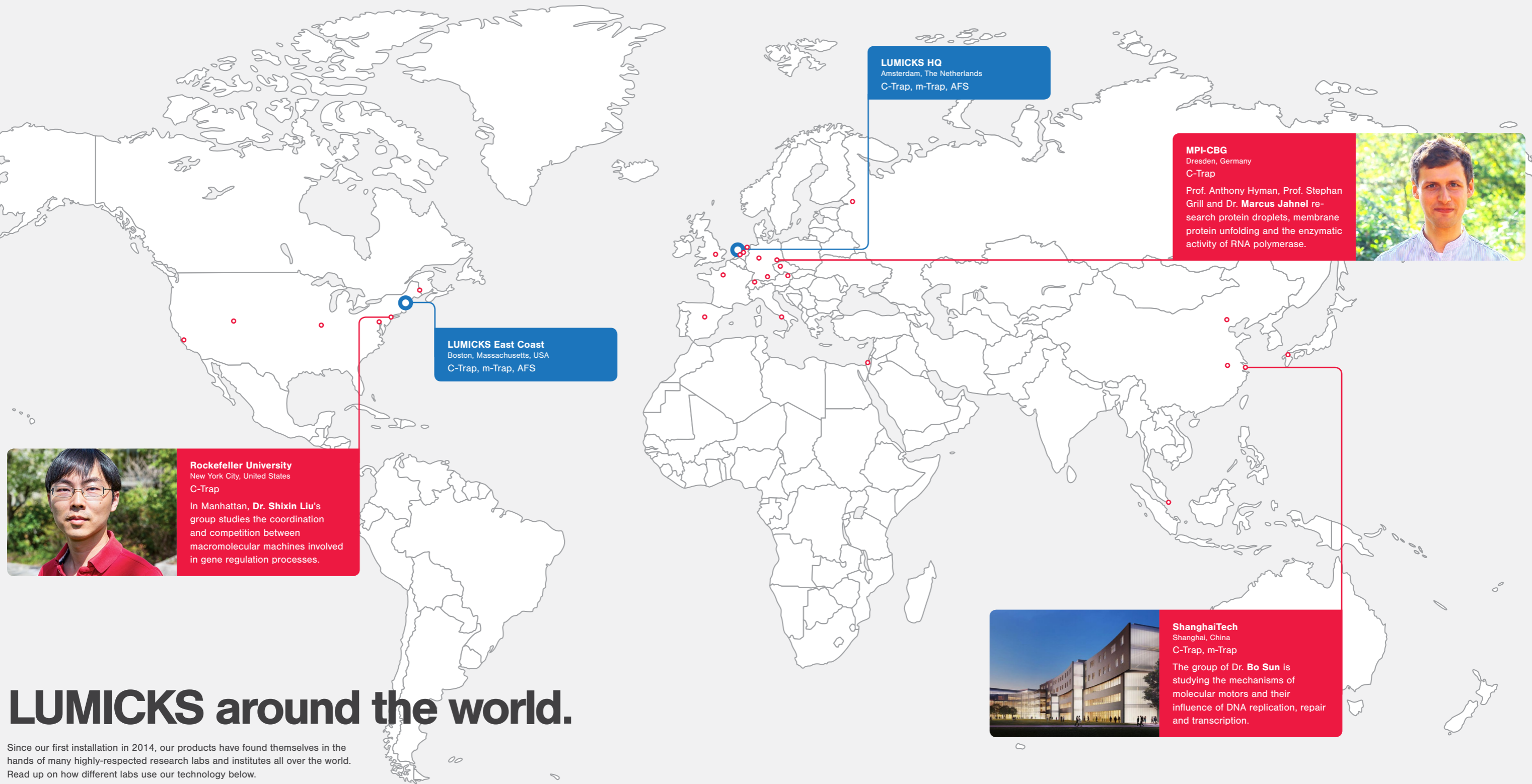
On-site application and scripting training; for expert support from our specialists dedicated to the customer's scientific application.

Remote and automated condenser positioning; for ensuring quick and perfect intrinsic z-alignment of the system.



▶ The photobleaching step of a single fluorophore can be detected with the C-Trap.





LUMICKS around the world.

Since our first installation in 2014, our products have found themselves in the hands of many highly-respected research labs and institutes all over the world. Read up on how different labs use our technology below.

- | | | | |
|---|--|---|---|
| <p>UC Berkeley
Berkeley, California, USA
C-Trap SR, u-Flux</p> | <p>Imperial College London
London, United Kingdom
C-Trap, AFS</p> | <p>Johns Hopkins University
Baltimore, Maryland, USA
C-Trap, AFS</p> | <p>University of Zürich
Zürich, Switzerland
C-Trap</p> |
| <p>Göttingen University
Göttingen, Germany
C-Trap</p> | <p>FOM Institute AMOLF
Amsterdam, The Netherlands
C-Trap</p> | <p>VU University
Amsterdam, The Netherlands
C-Trap, AFS, u-Flux</p> | <p>University of Groningen
Groningen, The Netherlands
C-Trap</p> |
| <p>BIOCEV
Prague, Czech Republic
C-Trap</p> | <p>Pasteur Institute
Paris, France
AFS</p> | <p>Kyushu University
Kyushu, Japan
AFS</p> | <p>Hefei University of Technology
Heifei, China
AFS</p> |
| <p>Ludwig Maximilian University
Munich, Germany
AFS</p> | <p>Max F. Perutz Laboratories
Vienna, Austria
AFS</p> | <p>Colorado State University
Fort Collins Colorado, US
AFS</p> | <p>CSIC Madrid
Madrid, Spain
AFS</p> |

LUMICKS Support

Our application scientists constantly travel around the globe to conferences and institutes to perform demonstrations, jobs, training and hands-on workshops. The whole LUMICKS team focuses on offering the best possible support for your research needs. Interested in how C-Trap works and what it can do for your research? Reach out to us to experience the possibilities yourself!



LUMICKS - Capture Molecular Interactions

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