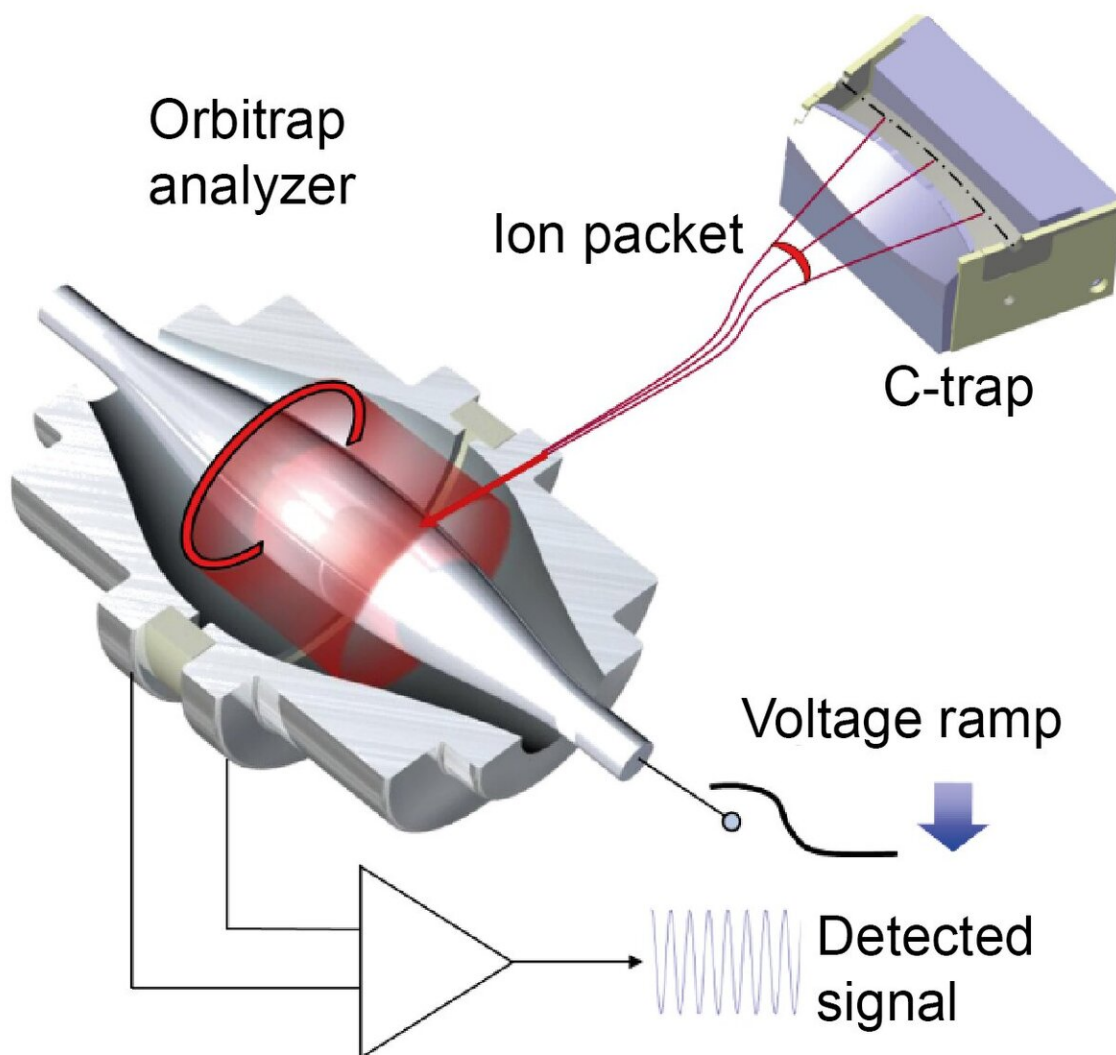


How do you weigh a single molecule?

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The Orbitrap. The ions that pass through it, circle around an electrode, producing an electric current signal. Credit: Utrecht University Faculty of Science

Utrecht scientists have succeeded in measuring the mass of individual molecules. By modifying an existing mass spectrometer and developing special software, the researchers succeeded in making ultra-sensitive measurements. This enables them to measure each particle separately in a mixture of molecules for the first time. This has far-reaching applications in, for example, gene therapy products, in which a precise measurement method is crucial. The researchers will publish their findings on 9 March in *Nature Methods*.

With [mass spectrometry](#), researchers determine the [mass](#) of [molecules](#). But until now, this was not possible in a direct way. Researchers used a [mass spectrometer](#) to deduce the charge of the ions in a molecule ensemble and then calculated back the mass. This works quite well when the molecules and their charges can be identified, but in a mixed protein complex with a high mass that is an almost impossible task.

The research group led by Albert Heck made adjustments to their mass spectrometer in the lab and developed special software allowing them to make single molecule measurements. The mass spectrometer is a large instrument—the size of a copy machine—in the middle of which is a kind of capsule with the size of a thumb: the Orbitrap. The ions that pass through it, circle around an electrode, producing an electric current signal. "Now we can look at each ion in the mass spectrometer separately. This means that we no longer have to look at ion ensembles, but measure the charge directly for each ion," says first author Tobias Wörner. "That makes it possible to determine the mass of things that have an ambiguous mass distribution."

Gene product

Gene therapy is a concrete application in which this new method can make a world of difference. Gene therapy is mostly applied to children with a rare gene defect. Doctors introduce a harmless virus packed with

a healthy version of the gene. Last year, for example, this form of therapy came onto the market for the muscle disease SMA under the name Zolgensma. The cost was \$2.12 million, making the most expensive medicine in the world.

"The challenge is to properly add the gene to the virus. Methods that can measure this are crucial. If the gene is too long, it will not be taken up properly by the virus or will be sliced in pieces. If it is too short, there is a chance that the virus will take up two pieces. It is also possible that the virus particles do not have a gene built in at all. The quality of such a gene product could not be measured until now," says Albert Heck of Utrecht University.

That will change with this new method. "Now, we can measure if and which pieces the [virus](#) has absorbed. We are already being approached by several international pharmaceutical companies, who would like us to do this for them, because [gene therapy](#) is in the middle of a renaissance."

Open software

The new mass analysis can be used for a variety of large complexes, as well: antibodies, ribosomes, protein clots and empty or genome-packed viruses. "This really is a huge breakthrough," Heck says. "This opens up so many possibilities. I don't think we're going to realize how big this breakthrough has been until much later."

Manufacturer Thermo Fisher Scientific has announced that the new application will not be launched on the market for the time being. But the Hecklab software will become available. "We will make the developed software freely accessible," says Joost Snijder, assistant professor involved in the research. "So any lab with an Orbitrap can try it for themselves."

More information: Resolving heterogeneous macromolecular assemblies by Orbitrap-based single particle charge detection mass spectrometry. *Nature Methods*, March 9, 2020. [DOI: 10.1038/s41592-020-0770-7](https://doi.org/10.1038/s41592-020-0770-7).

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