Charge Detection Mass Spectrometry for Viruses and Particles: Mass Spectrometry into the Gigadalton Regime

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Mass spectrometry (MS) is one of the most powerful analytical techniques, but its reach is limited to masses less than around 1 MDa, and in many cases much smaller. In conventional MS, the quantity measured is the mass to charge (m/z) ratio, and the charge must be deduced to determine the mass. As size and heterogeneity increase it becomes impossible to deduce the charge, and so the m/z ratio cannot be used to determine the mass. This problem can be overcome by charge detection mass spectrometry (CD-MS), a single particle technique where the m/z ratio and charge are measured for each ion, and then multiplied to give the mass for each ion. Measurements are performed for several thousand individual ions and then the masses are binned to give a mass spectrum.

To measure the m/z ratio and charge in CD-MS, the ions pass through a conducting cylinder coupled to a charge sensitive amplifier. When the ion enters the cylinder, it induces a charge that is detected by the amplifier. The cylinder is usually located between the endcaps of an electrostatic linear ion trap (ELIT). The ELIT consists of two opposing ion mirrors that reflect the ions back and forth through the detection cylinder. The resulting periodic signal is analysed using fast Fourier transforms, the oscillation frequency is related to the ion's m/z ratio and the charge is proportional to the signal amplitude (the FFT magnitude). Masses into the gigadalton regime can be measured, opening the door to the measurement of accurate mass distributions for viruses, vaccines, polymers, and nanoparticles.

As an example, Figure 1 shows a CD-MS mass spectrum measured for assembly of the norovirus L1 capsid protein. For the wt virus the L1 protein is expected to assemble into icosahedral *T*=3 capsids with 180 capsid proteins. Instead, we see peaks corresponding to icosahedral *T*=4 (240 capsid proteins) and *T*=7 (420 capsid proteins) in the CD-MS mass distribution. In addition, there are peaks due to capsids with 300, 480, 600, and 700 capsid proteins. These are non-icosahedral structures. The peak at 300 capsid proteins is probably due to an elongated T=4 capsid (supported by cryo-EM). The structures of the capsids with 480, 600, and 700 capsid proteins are not known.

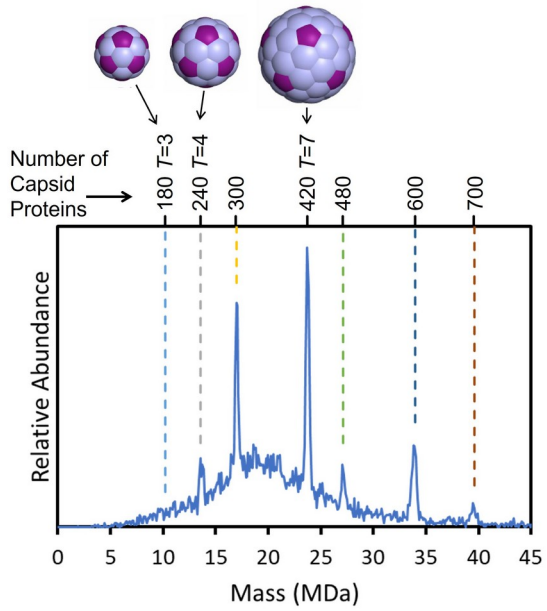

Figure 1. CD-MS mass distribution measured for assembly of the norovirus capsid protein.