

Innovating Medicine Manufacturing

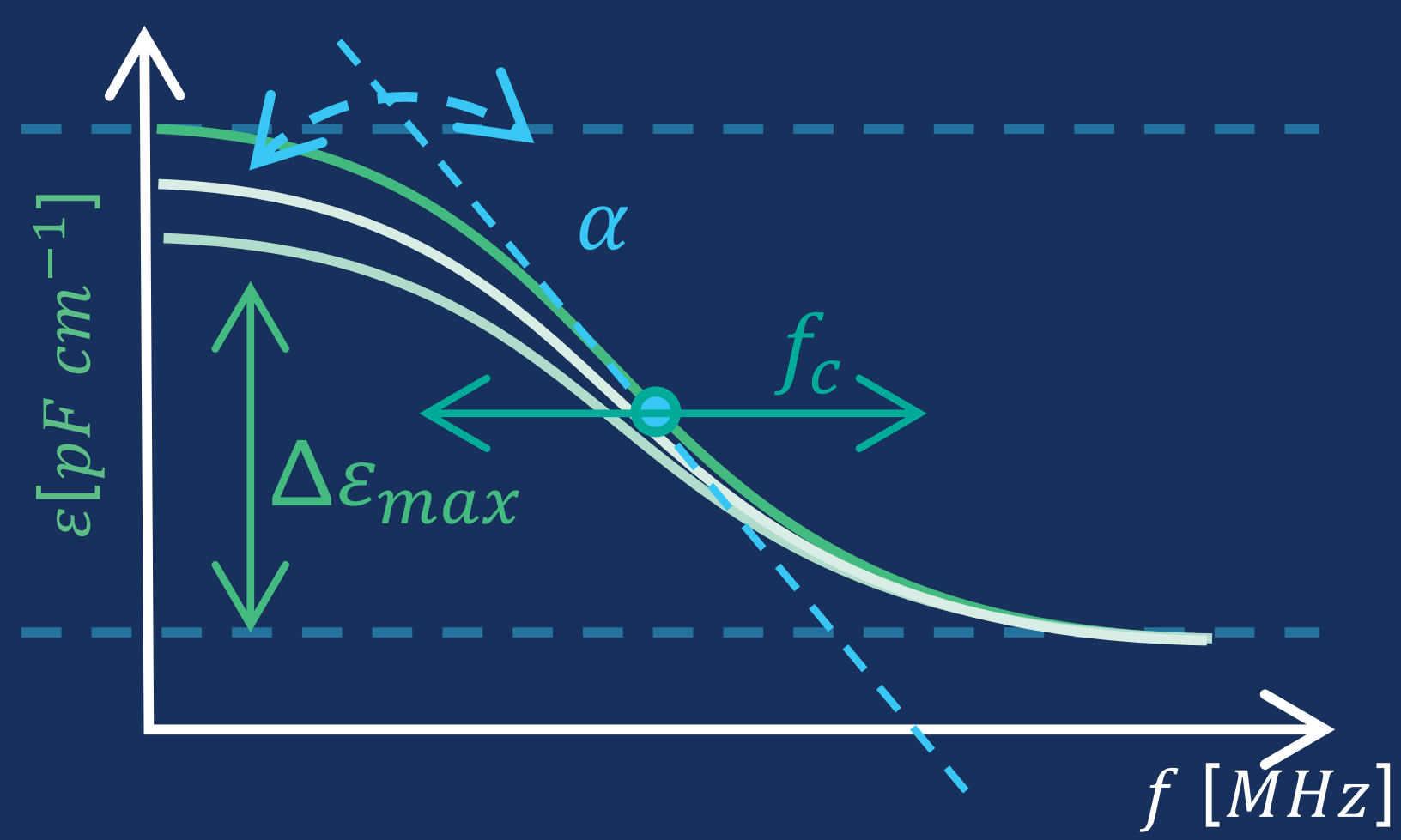
The Future of Process Analytical Technology (PAT) in Single-use Technologies and Expanding Role in Bioprocess Development



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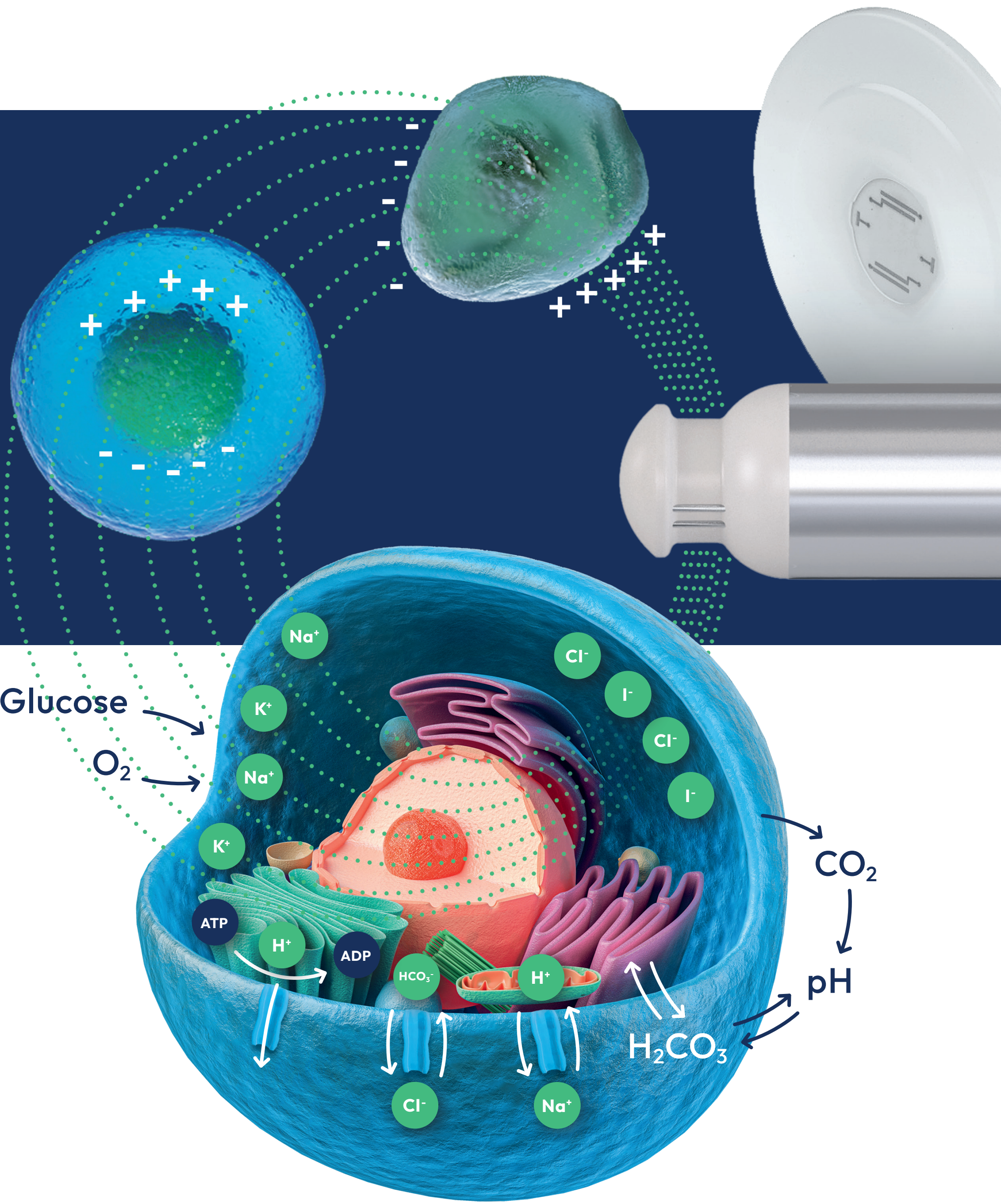
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Delta Epsilon: The permittivity measurement can provide a direct correlation to the cell count and cell size.

alpha: Represents the cell size homogeneity.

fc: Provides information about the cell size and the intra cellular conductivity.



Introduction

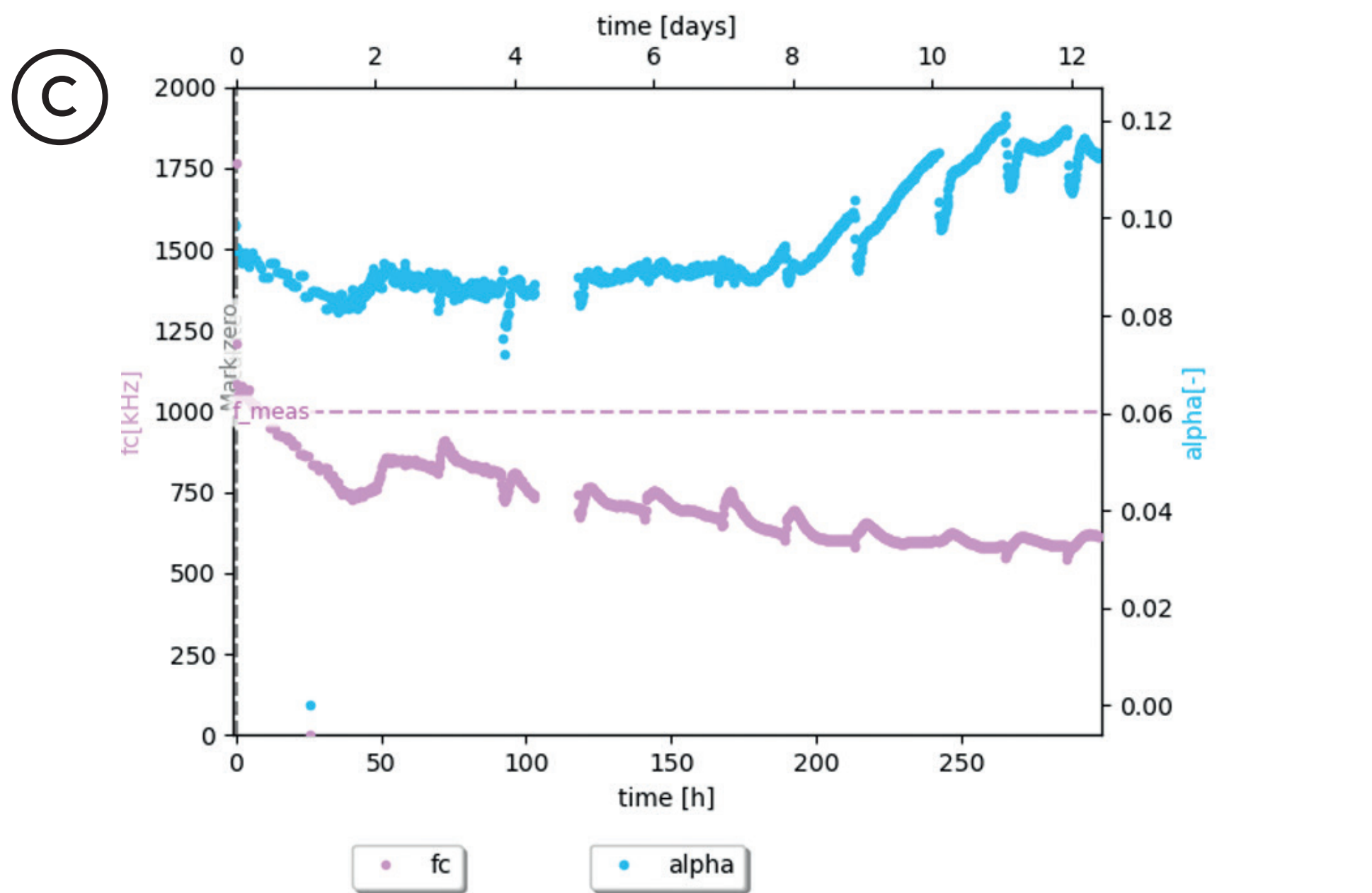
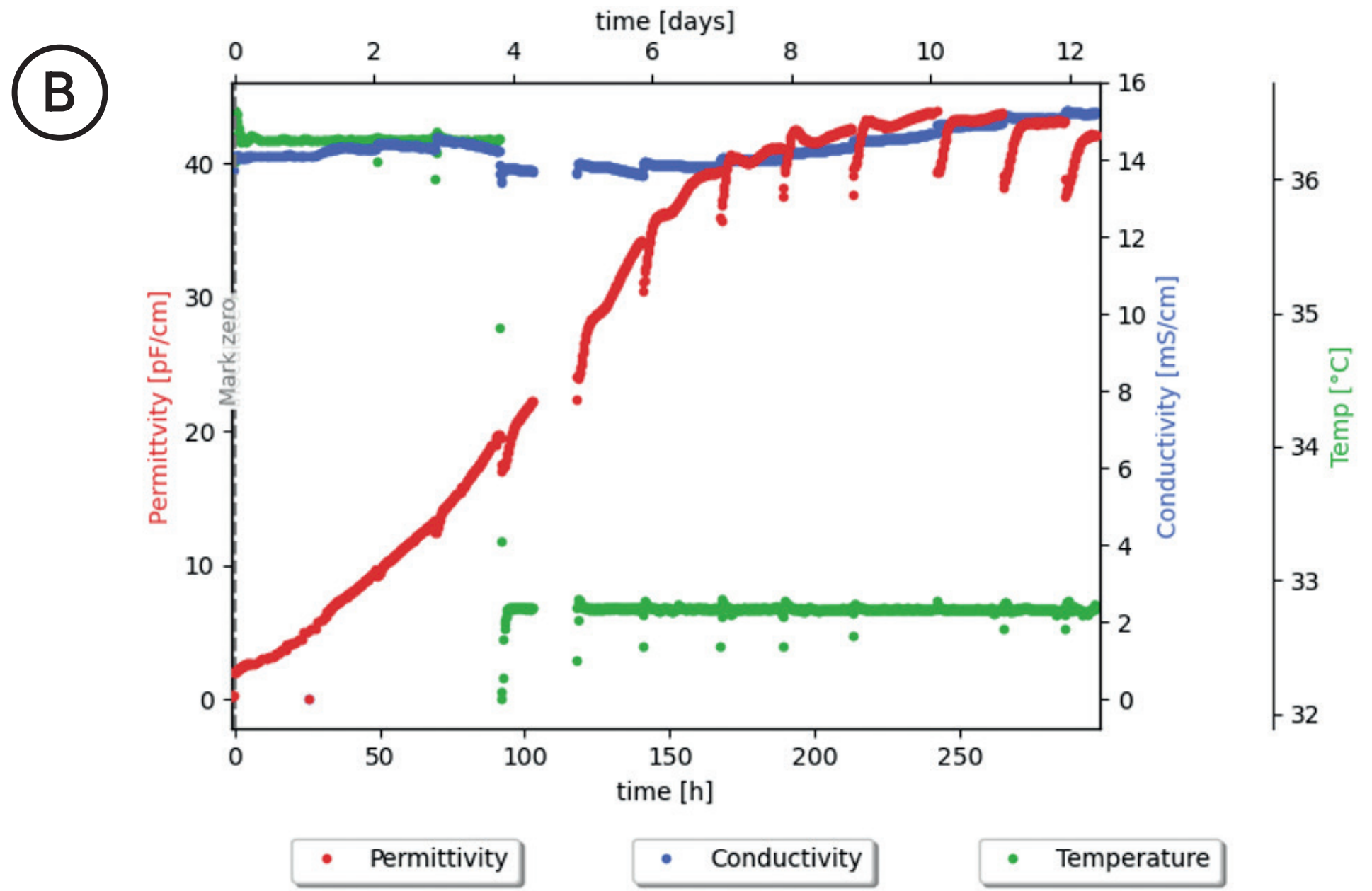
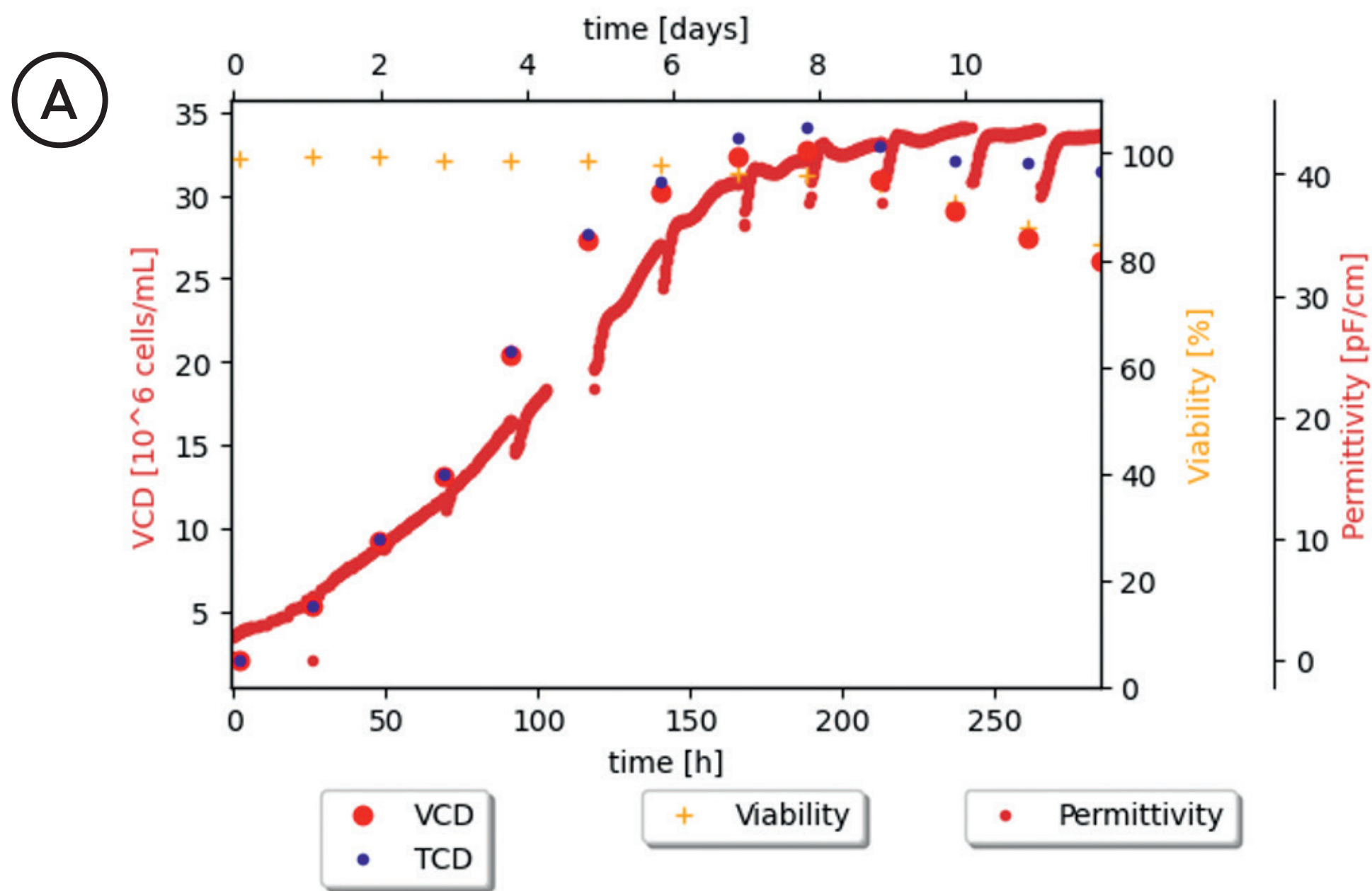
Process development is under constant time pressure. With the help of platform approaches, efforts are constantly being made to reduce the number of factors that influence a process in order to bring a finished process to the pharmaceutical market more quickly. The more known about the process, the easier it is to define influencing factors and evaluate the response of the cells to derive the highest yield production strategy. Impedance spectroscopy not only shows the viable cell volume, but also provides information on intracellular conductivity and the cell size distribution, which provides valuable information about the response of the cells to the process control. In combination with a real-time CO₂ measurement, challenges such as CO₂ accumulation from 500 L in the bottom of the reactor are observed at a new level.

Results

Process control in the small reactor is relatively easy to implement. Even here, the aim is to follow simple protocols that can then be transferred to production scale. In most cases, viability and viable cell density are indicators of a successful process. How active or what osmotic state a cell in is often ignored, as this cannot be seen in offline samples.

The data from KBI Biopharma shows an increasing trend in permittivity, which represents the living biovolume. The cells are induced by a temperature shift, the conductivity trend indicates the feeding points (see graph B).

Changing trends of alpha and fc represent the lag-phase for the first 45 hours. Thereafter, the fc trend indicates a response of the cells to the feed. The current theory is that the cells use their ion channels to adapt to the new conditions. Towards the end of the process, the development of the cells to an apoptotic state can be observed in the alpha trend (see graph C).



Conclusion

- Changes in the cell at the intracellular level and in the cell size distribution offer opportunities for process development and for production.
- New approach such as changing the feeding strategy with different time, volume, concentration, and feed media can enhance/improve: change of the feeding strategy with different time, volume, concentration and feed media.

Potential improvements:

- Shortening the time to market by implementing feeding strategies that enable higher yields in a shorter time can improve the productivity of the process.

Data is kindly provided by 

