# Microfluidic-ion mobility-mass spectrometry for assessing cellular response in real time

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***Short Abstract* — A critical endeavor in systems biology research and the associated model specification and validation is the development of rapid measurement strategies for monitoring comprehensive biomolecular responses to changes in chemical environment. The combination of microfluidic cell trapping and electrochemical and optical sensors with high-throughput real-time biomolecular characterization by nanoelectrospray ionization-ion mobility-mass spectrometry (nESI-IM-MS) may help address this challenge. We trap individual cell types in a microfluidic device, expose them to some form of stimulus (*e.g.*, therapeutic, drug, or toxin), and then use nESI-IM-MS to monitor the dynamics of biomolecular responses. Importantly, the use of IM-MS simplifies potentially complicated biomolecular output by performing 2D separations on the basis of both structure and m/z, in near real time.**

***Keywords* — ion mobility-mass spectrometry, microfluidics, cellular response, real time analysis, nanophysiometry**

## I. Purpose

Monitoring cellular responses is a difficult task due to the abundance of secreted biomolecules and the complexity in interpreting their quantitative relevance. Currently work is underway to implement novel cellular response protocols through the use of microfluidics, microsensors, and IM-MS. Because of the complexity of the cellular secretion profile (encompassing many different bimolecular classes), cellular responses to various stimuli have traditionally been characterized by methods to analyze a few specific molecules, often ones that are selectively tagged. However, with the aid of IM-MS, simultaneous sampling of all secreted metabolites and therefore a more complete understanding of cellular mechanisms are potentially within reach. By using a microfluidic multi-trap nanophysiometer [1] to capture cells, one can direct solution over these cells and feed the effluent into an IM-MS instrument to analyze the secreted biomolecules. IM-MS is uniquely suited for accurately and expediently delineating contributions from individual biomolecular classes (*i.e.*, carbohydrates, nucleotides, proteins, and lipids) which may be present in the exudate regardless of isobaric interferences. By these means one can quantify cellular responses based on the biomolecular exudate profile.

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## II. Summary of Results

Preliminary work showed that flow rates for both the microfluidic devices and the nESI source were commensurate. We next demonstrated precise dynamic time resolution by flowing two solutions (one containing bradykinin at 20 μg/mL and a blank containing only acetonitrile (ACN)) through a device. These flows were offset in phase so that only one was flowing through at a time. Time resolution of $< 5$ minutes was achieved, which is limited only by the dead volume of the microfluidic chip and connecting tubing. This temporal accuracy was deemed sufficient based on electrochemical measurements and known metabolic oscillations.

Since these devices were previously used to load and study Jurkat cells, this cellular system was chosen for initial analysis. CD4+ Jurkat cells were loaded into a device and fed a media solution which was deficient of essential metabolic constituents. Through IM-MS analysis the effluent from this experiment was shown to contain a number of identified compounds indicative of a stress response. We are evaluating β-islet cells, which produce extremely high levels of glucose, as a model metabolic system. From the perspective of systems biology, the future utility of such a measurement strategy lies in the rapid testing/validation of models, the possibility of using machine learning for automated model specification, and eventually the external control of cellular biosystems..

## III. Conclusion

Integrative technology such as that outlined here is crucial to advancing prediction and control of cellular regulatory systems. The combination of microfluidics, microsensors, and IM-MS allows for simultaneous measurement of all secreted biomolecules despite interferences or sample complexity which may hinder comparable methods.

## References

[1] Faley S, et al. (2008) Microfluidic platform for real-time signaling analysis of multiple single T cells in parallel. *Lab on a Chip* **8**, 1700-171.