Development of a self-optimizing platform for flow-based peptide synthesis

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Despite improvements in data analysis techniques, data- and ML-based optimization is not yet widespread in chemistry due to the need to collect data of adequate quality and quantity. Automated fast-flow peptide synthesis (AFPS), with its rapid reaction rates and already integrated analytical tools (in line UV-Vis), would be well suited to explore this toolbox. Although reaction conditions for solid-phase peptide synthesis (SPPS) were optimized over decades, SPPS is sequence-dependent, and events such as often-observed aggregation can lead to a decreased synthesis outcome. The occurrence of aggregation is thus a major remaining challenge in batch- and flow-SPPS, and the impact of various parameters, such as protecting groups, the sequence itself, and linkers, needs to be better understood. We therefore developed improved data-based methods to exploit the generated in-line UV data in multiple ways to reduce aggregation: We developed a new approach to identify aggregation from UV data, which enables the recovery of lost or low-quality data while simplifying the prediction for future machine learning applications. Furthermore, we developed a real-time self-optimizing algorithm allowing quick intervention upon aggregation detection. These two methods serve as the initial steps in creating a more complex machine learning-based system that aims to eliminate sequence dependence in SPPS.