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OPTIMISING mRNA VACCINES MANUFACTURING BY USING MACHINE LEARNING APPROACHES

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New vaccines based on mRNA technology are emerging as alternatives to traditional vaccination to effectively respond to epidemic events due to their inherent advantageous,such as safety, non-inetragtive nature and transient expression. The COVID-19 pandemic has shown a rapid response from vaccine companies, manufacturing and delivering mRNA vaccines in record time. Unlike traditional vaccines, which rely on complex and inflexible manufacturing processes, mRNA vaccines can be produced using standardised manufacturing with reduced footprint. Furthermore, the nature of mRNA vaccines itself enables the manufacturing of different vaccines using the same production platform. These vaccines are produced in an *in vitro* cell-free transcription reaction catalised by RNA polymerase. However, the global demand for COVID-19 vaccines has placed strain upon global manufacturing and supply chain problems are arising. Therefore, optimised processes are necessary to cope with increased demands of these vaccines whilst reducing significantly the vaccine price [1].

In this contribution, we will present results on the use of machine learning approaches, in particular Bayesian optimization, as a form of adaptive data-driven incremental design-of-experiments (DoE) to maximise mRNA production. (Figure 1). We will present for the first time the use of this methodology to optimise mRNA production by varying 12 reaction parameters, and find optimal reaction conditions with solely 60 runs obtaining a maximum of 12 $g.L^{-1}$ total mRNA produced under 2 hours reaction time [2]. This corresponds to a production increase of approximately a factor of four compared to benchmark reaction conditions and productivities [3].

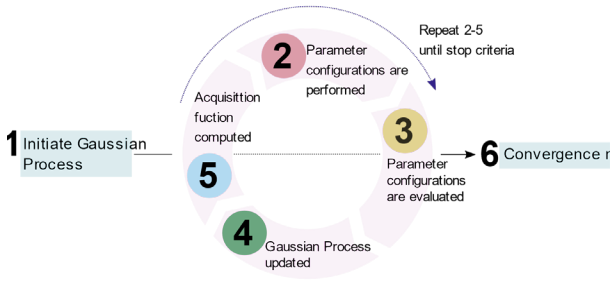

Figure 1 – Overview of Bayesian optimisation workflow.

Downstream processing is also a major bottleneck in the mRNA manufacturing. Traditional purification methods are based on DNA removal by enzymatic digestion with DNAse followed by lithium chloride (LiCl) precipitation. These methods, although simple and well-establish, do not remove impurities that are critical for the mRNA performance. We evaluated new chromatographic operation modes that explore anion exchange, hydrophobic and multimodal interactions as well as affinity chromatography, assessing mRNA recovery yields and product quality (e.g. presence of impurities such as double-strand mRNA, ds-mRNA).

The results will contribute to improve the current state-of-art of mRNA vaccines manufacturing and to contribute to the development of sustainable, flexible and cost-effective mRNA vaccine manufacture that will allow an on-demand response by using continuous manufacturing principles.

References

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