

**Yesim Koca**

**Increasing Biomanufacturing Yield with Bleed-feed**

In cooperation with Tugce Martagan, Ivo Adan, Lisa Maillart, Bram van Ravenstein

Biomanufacturing methods use living organisms (i.e., viruses and bacteria) to generate active ingredients, and this leads to challenges that are different to those incurred by other industries. To address these challenges and improve biomanufacturing efficiency we focus on a novel approach: bleed-feed. Bleed-feed allows biomanufacturers to skip intermediary bioreactor setups. However, the specific time at which the bleed-feed is performed is critical for success. The process is strictly regulated, and its implementation involves unique trade-offs in operational decision-making. In this study we formalize the operational trade-offs of bleed-feed and formulate a Markov decision process model to find optimal bleed-feed policies to maximize the expected biomass obtained from a batch. We analyze the structural characteristics of optimal policies and show that optimal bleed-feed policies have a three-way control-limit structure under mild conditions that were validated with industry data. We perform an industry case study and observe that bleed-feed can bring benefits. Through practically relevant scenarios, we assess the potential impact of implementing bleed-feed on current practice and develop insights for practitioners.