Fed-Batch Bioproduction of Spectinomycin

J. Gomes* and A.S. Menawat**
* Department of Biochemical Engineering & Biotechnology,
  Indian Institute of Technology, Delhi, Hauz Khas, New Delhi 110016, India
** Advanced Solutions & Know-how, 1426, Hidden Creek North, Saline,
  MI-48176, USA

Actinomycetes produce about 67% of the known antibiotics covering a wide range of chemical structures. However, their filamentous growth present several problems during industrial processes. Among these problems oxygen transfer limitation is critical. In this chapter we present the role of oxygen in spectinomycin production by a *Streptomyces* species. Spectinomycin, a broad spectrum antibiotic effective against penicillin resistant gonorrhea, is an aminoglycoside constituted from two glucose moieties. Its bioproduction is strongly influenced by glucose and oxygen. We have shown that for a fixed dissolved oxygen concentration, there are two specific glucose concentrations which give maximum final titers of spectinomycin. The bi-modal maximum indicates the influence of two intermediate metabolites in spectinomycin biosynthesis. We propose a mechanism for spectinomycin biosynthesis and subsequently develop a model based on this mechanism. The proposed mechanism for spectinomycin biosynthesis is validated by successfully reconstructing the air flow rate profiles. A nonlinear systems theory technique termed External Differential Representation, is implemented to reconstruct the spectinomycin bioconversion process which then predicts the spectinomycin concentration from the air flow rate profile. This signifies that spectinomycin titers in industrial fed-batch processes can be controlled if a priori information about the air flow rate profile yielding maximum spectinomycin is available.
List of Symbols and Abbreviations

\( a \) constant for activation term
\( A^* \) saturated dissolved oxygen concentration (g 1\(^{-1}\))
\( A \) dissolved oxygen concentration (g 1\(^{-1}\))
\( b \) constant for activation term
\( C \) cell mass concentration (g 1\(^{-1}\))
\( g \) glucose concentration
\( K_e \) exponential model constant (g 1\(^{-1}\))
\( K_{e1} \) exponential model constant for product 1 (g 1\(^{-1}\))
\( K_{e2} \) exponential model constant for product 2 (g 1\(^{-1}\))
\( K_i \) inhibition constant for Haldane-Monod or exponential structures (g 1\(^{-1}\))
\( K_{i1} \) inhibition constant for product 1 in exponential model (g 1\(^{-1}\))
\( K_{i2} \) inhibition constant for product 2 in exponential model (g 1\(^{-1}\))
\( k_{ta} \) mass transfer coefficient (h\(^{-1}\))
\( K_m \) Monod constant (g 1\(^{-1}\))
\( P \) product concentration (g 1\(^{-1}\))
\( S \) substrate concentration (g 1\(^{-1}\))
\( S_f \) feed concentration (g 1\(^{-1}\))
\( T_{f0} \) time of glucose feed initiation (hr)
\( v \) volumetric air flow rate (1 min\(^{-1}\))
\( V \) volume (l)
\( Y \) yield coefficient \([\text{(cell mass concentration (g 1\(^{-1}\)))/(substrate concentration (g 1\(^{-1}\))}]]\)
\( Y_{CA} \) yield coefficient of cell mass based on oxygen (g cell mass)/(g oxygen)
\( Y_{CS} \) yield coefficient of cell mass from substrate (g cell mass)/(g substrate)
\( Y_{P1A} \) yield coefficient of product 1 based on oxygen (g product 1)/(g oxygen)
\( Y_{P2A} \) yield coefficient of product 2 based on oxygen (g product 2)/(g oxygen)
\( Y_{P1S} \) yield coefficient of product 1 based on substrate (g product 1)/(g substrate)
\( Y_{P2S} \) yield coefficient of product 2 based on substrate (g product 2)/(g substrate)

FIA flow injection analysis
HPLC high pressure liquid chromatography
PHB poly-\(\beta\)-hydroxybutyric
gC gas chromatography
EDR external differential representation
OUR oxygen uptake rate