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Model-based strategy for cell culture seed train layout verified at lab scale

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Background

Production of biopharmaceuticals for diagnostic and therapeutic applications with suspension cells in bioreactors requires a seed train up to production scale [1]. For the first steps - the transitions between T-flasks, tubes, roller bottles, shake flasks, stirred bioreactors or single-use reactors - the experimental effort to lay-out these steps is high. At the same time it is known that the first cultivation steps have a significant impact on the success or failure in production scale. A software tool has been developed which provides possibilities for simulation, analysis and design of seed trains [2]. Tool structure:

- A kinetic model. In this case a simple unstructured model where kinetic parameters can be obtained from a few experiments only.
- A Nelder-Mead-algorithm to determine model parameters.
- A developed MATLAB software tool able to determine optimal points in time or viable cell concentrations for transfer into the next scale.

The successful application for the cell line (AGE1. HN_{AAT}, ProBioGen AG) has been shown previously [3]. Here the tool was tested for a suspendable CHO cell line.

Materials and methods

The cell line CHO-K1 has been grown in chemically defined TC-42 medium (TeutoCell AG, Bielefeld, Germany), 4 mmol L-1 glutamine.

Data for parameter identification for the kinetic mode were determined in shake flask cultures. The seed train steps were: 1. culture tube (0.0025 L), 2. shake flask (0.070 L), 3: Labfors 5 Cell (2 L).

Results

For the seed train first different optimization criteria were compared in silico (Fig. 1a). Finally, the average of time at maximal space-time-yield (STY) and time at 90% of maximal growth rate (0.9·μmax) was used as optimization criterion for cell transfer. The concept was tested successfully up to a 2 L scale for 3 scale-up steps (Figure 1b).

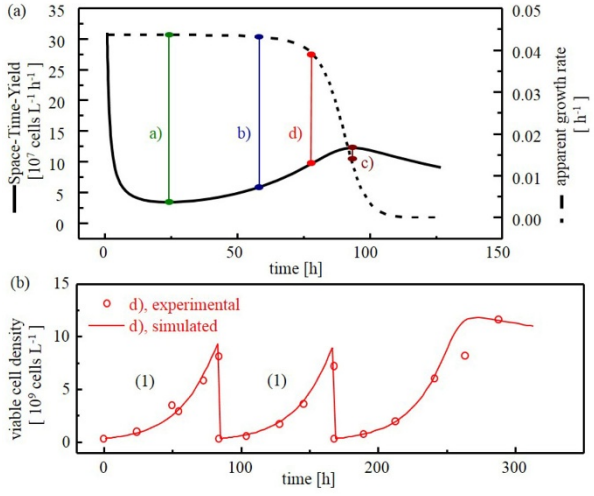

Figure 1 (A) simulated courses of Space-Time-Yield (STY) and apparent growth rateover time exemplarily for one scale: a) point in time of minimal STY, b) average value of a) and c) as a cell passaging criterion, c) point in time of maximal STY as a cell passaging criterion, d) average of time at maximal STY and time at 0.9·μ_{max} as a cell passaging criterion. **(B)** Seed train for CHO-K1 - simulated and experimental courses of viable cell density over time. Passaging of cells at the points in time calculated using average of time at maximal STY and time at 0.9·μ_{max} (criterion d)).The seed train steps were: 1. culture tube (0.0025 L), 2. shake flask (0.070 L), 3: Labfors 5 Cell (2 L)

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Conclusions

The concept offers a simple and inexpensive strategy for design of seed train scale-up steps. The results for the lab scale steps show that the tool was able to perform a seed train optimization only on the basis of two batches, the underlying model and its parameter identification.

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