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Application of neural networks for the recursive identification of the bacterial growth model in the *Escherichia coli* fermentation process.

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Highlights

- Recursive Neural networks have been trained to describe fermentation;
- The predictive model has been validated through several fermentation lots;
- The ability to describe systems with intrinsic variability is demonstrated.

1. Introduction

Biotechnology began to revolutionize the pharmaceutical industry in the 1980s, when the introduction of the insulin-encoding gene in Escherichia coli started the production of the first biotechnology drug that improves the life of diabetics.
Pharmaceutical companies have strengthen their interest in recent years and have invested heavily in the biotech sector, leading to an increase in the production of such drugs. Biotech drugs are estimated to be 50% of those globally under development. They are derived from substances produced by a biological source through various procedures such as: recombinant DNA technologies, controlled expression of biologically active proteins encoding genes in prokaryotes and eukaryotes, hybridoma-based and monoclonal antibody-based methods.

2. Methods

Process studies, such as bacterial fermentations, are very complex because there are many parameters that influence the phenomenon. Since the various deterministic models in the literature are not suitable for such task, the neuro-fuzzy networks approach has been proposed and applied as it takes into account all the parameters and considers the variability of lots. By utilizing experimental data regarding different fermentation campaigns, four goals for the evaluation of the bacterial growth curve have been identified and optimized. The bacterial growth predictive model was subjected to a training phase with different training matrices, obtained from the experimental data collected directly from the production process, and was validated by means of additional data not used during the training phase, in order to identify the most powerful network [1].

Fuzzy logic was introduced by Lotfi Zadeh [2]: a certain degree of truth is assigned to each statement, between 0 (false) and 1 (true); "fuzzy" in fact is well suited to label the type of sets defined by Zadeh, characterized by not clearly defined boundaries. Unlike a normal set, called crisp, where the membership function is a Boolean function that assumes value 1 if the object belongs to the set or 0 if it does not belong to it, in the fuzzy sets there is a degree of membership of each element to the set which can be any real

number between 0 and 1. Therefore, in the fuzzy sets, each data is represented by its similarity to a reference, while in the deterministic representation (singleton) each data corresponds to a numeric value. The degree of membership should not be confused with the concept of probability (frequency), as the membership function provides information on the similarity between a given object and a property defined in a vague way.

The study was developed at the Biotech Production site in L'Aquila, Italy, of Dompé farmaceutici spa and is divided into the following phases:

- Collection of experimental fermentation data, extracted from the control system of fermentation plant;
- Analysis of collected data;
- Interpretation of the influence of operating variables on the process;
- Creation of a recursive neuro-fuzzy network and training of that through appropriate sets of data [3];
- Identification of predictive bacterial growth model;
- Model validation and analysis of results.

3. Results and discussion

In the Conference presentation, the results of recursive network training will be shown and discussed, as well as their ability to describe the growth of the microorganism.

4. Conclusions

The conclusions of this work are encouraging, although based on a few experimental data. By now more data and experimental campaigns are available, so that it is possible to improve the training of the numerical model and to obtain simulations more adherent to real bacterial growth, at the time of the Conference.

References

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Keywords
"Neuro-fuzzy" "Bacterial growth" "Neural network training" "Neural network validation"