COMPUTATIONAL MODELLING AIMS TO PREDICT CELL CULTURE STRATEGIES FOR OPTIMISING GLYCOSYLATION

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Dr Cleo Kontoravdi leads an interdisciplinary group working in the area of Biological Systems Engineering. The group is well known for the development of predictive models for the analysis and optimisation of biological processes involving the culture of cells for the production of therapeutic proteins and other high-value compounds. A unique feature of her research is the integration of engineering principles with biology and biochemistry through mathematical modelling but firmly supported by targeted experiments.

Glycosylation of therapeutic proteins can affect their efficacy and stability, so predicting culture strategies that optimise glycosylation could accelerate process development.

The Kontoravdi group from Imperial College London and the Klymenko group from the University of Surrey worked with MedImmune on building a modelling framework to design optimal cell culture conditions for desired antibody galactosylation.

What methods did we use?

We used a previously developed mathematical model that describes the impact of feeding galactose and uridine to cell culture processes on cell growth, antibody productivity and extent of galactosylation. We also applied a new computational method called constrained global sensitivity analysis.

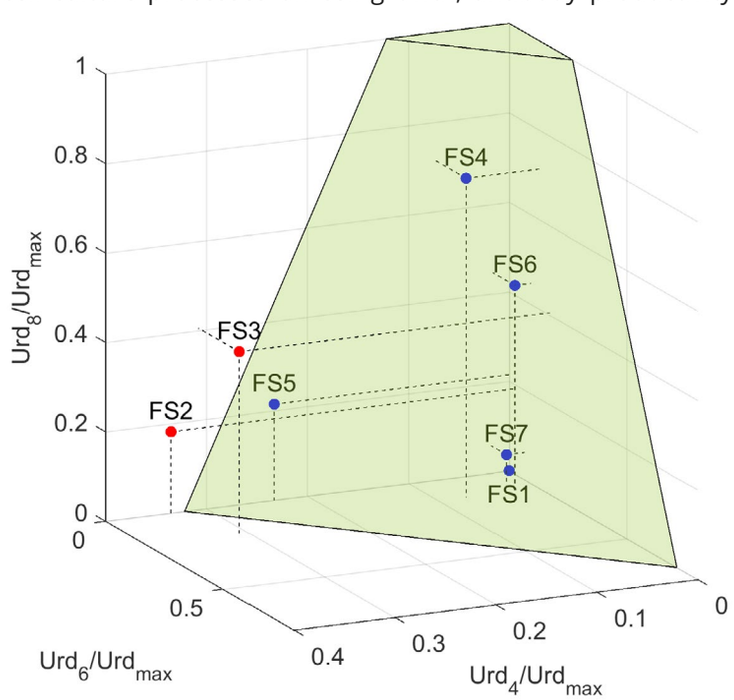

Figure 1

We used these methods together to design cell culture experiments that we anticipated would give rise to higher-quality antibody without being detrimental on cell growth or antibody titre. We had a minimum threshold for both titre and galactosylation that we wanted our cultures to achieve.

Our method identified a subset of 556 out of the 8192 designs that should, according to the model, result in protein with the desired characteristics. We then tested 4 designs and a control experimentally, and compared the experimental results to the model predictions for each set of conditions (Figure 1). We also tested 2 designs that would fail to achieve the constrained targets, as proposed by the model.

What were our main findings?

That the model could successfully describe the culture conditions to achieve protein production with the desired characteristics! The model could predict the viable cell density of cell cultures over time, the concentration of monoclonal antibodies and the glycosylation pattern at the end of culture.

Moreover, the model proved capable of identifying the correct designs that could and that could not lead to the desired product. Hence, following the paradigm of Quality by Design (QbD) the mathematical model is considered capable of identifying the appropriate Design Space.

The proposed concept of use, could reduce the expenses and the time needed for research and development of new biopharmaceutical products or already existing therapeutics.