ESACT-UK Travel award winner: Marie Dorn (University College London)

Round: June 2023

Conference attended: 14th European Congress of Chemical Engineering and 7th European Congress of Applied Biotechnology (EcceEcab2023), Berlin

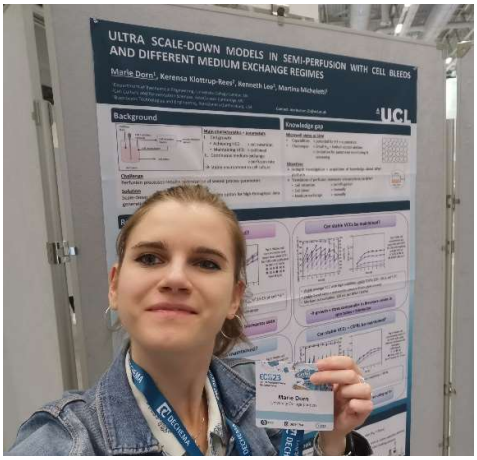
The ESACT-UK Travel award allowed me to attend the 14th European Congress of Chemical Engineering and 7th European Congress of Applied Biotechnology, which was held in Berlin from the 17th to 21st of September 2023.

The conference ran under with the overall motto of "Acting together", which was emphasised throughout as being key for the future of the fields of chemical engineering and biotechnology. Following this approach nine main sections, divided into 1 to 5 subsections, addressed a broad range of topics. These main sections were titled as follows: (A) Green Deal – a common task for chemical and biochemical engineers, (B) Chemical and Biochemical Engineering in Medicine, (C) Acting Together – Biochemical and Chemical Engineering Integration, (D) Matter in Motion, (E) Faster and Move Selective, (F) Solid Matter, (G) Tools and Toolkits for Chemical and Biochemical reactors, (H) Digital transformation and (I) Education. In each section, approaches, and current trends in both chemical engineering as well as applied biotechnology were presented and discussed, which greatly served the overall motto of the conference.
Lectures and discussions in these topics were held in parallel due to the large number of areas covered. Thus, I mainly focused on of section (B) and (C), as my research project is focused on process development in mammalian cell culture and biopharmaceutical production. However, there was no requirement to select a specific stream and delegates could attend any sections that were of interest, which enabled me to listen to several talks in a much broader range and with different focus.

I heard many talks from industry and academia which are of particular interest for my research field. Boehringer Ingelheim presented various interesting approaches on process development of fed-batch processes. One approach discussed the application of intensified design of experiments (iDoE) in comparison to a conventional design of experiments (DoE) scheme to mammalian cell culture processes for the process development. The iDoE allows to parallelise and combine several conditions in such a way that shortens experimental and thus analytical timelines by several weeks ultimately enabling earlier to-clinic and to-market process developments. In the same talk several obstacles encountered and recommendations for future experimentation were mentioned and a few discussed in more depth. Another talk by the same company focused on the optimisation of the manufacturing process at a later larger stage by developing a scale-down model at benchtop bioreactor scale which exactly mimics dynamics observed in the manufacturing scale bioreactor. The motivation for this originated in a massive decrease of viable cell concentration and productivities with increased scale. Through comparably simple changes of certain parameters, for example the gassing and gas flow rate, the dynamics from the manufacturing scale bioreactor could be mirrored in the lab-scale bioreactor. This was a first example that showed me the relevance of our research on scale-up/down of biomanufacturing processes at the Department of Biochemical Engineering at UCL, from another company we (so far) are not collaborating with. Although my research is focused on the intensified perfusion process, I believe that lessons learned as well as inspiration can be drawn from individual experimental designs and concepts.
Another talk also from industry but from a startup based in Berlin, discussed obstacles encountered in development of perfusion processes. It was interesting to hear that the company encounters generally similar problems and what their solution are to overcome these obstacles.

From both industrial presenters and other industrial talks, a general trend emerged towards early application of automation and the use of automated systems ranging from ambr15 or 250 to larger 3, 5 or 10L bioreactors.
Another very interesting lecture focused on the process development of stem cells, where in opposite to the previous discussed lectures not a therapeutic protein produced by the cells, but the cells themselves are the product of interest. As the field of process development is expanding to cell and gene therapy with the expansion of cells in bioreactors, the talk gave a very interesting insight on the current standing and future works planned. Further, the largely similar progression of the process intensification from fed-batch to perfusion was very interesting to see and to hear their motivation of the steps taken.
Since the conference had a great number of sections that were outside my direct research interest but coupled to other areas for professional development, I also attended several lectures and discussion on topics of education in biotech, implementation of new technologies such as virtual reality (VR) in teaching as well as artificial intelligence (AI) in addition to various kinds of mathematical modelling for the development and control of robust processes.

Next to attending talks and discussions, I was able to present a research poster titled: “Ultra scale-down models in semi-perfusion with cell bleeds and different medium exchange regimes”. This enabled me to showcase and discuss my work with a broader community and receive feedback, and suggestions on how to further develop my research. Further, I have connected with many researchers, vendors and industry experts discussing the conference, talks, mine and their research work as well as future developments of the field.
Overall, attending this conference was a very interesting and beneficial experience for me and I am thankful to ESACT-UK for their support.



ULTRA SCALE-DOWN MODELS IN SEMI-PERFUSION WITH CELL BLEEDS AND DIFFERENT MEDIUM EXCHANGE REGIMES

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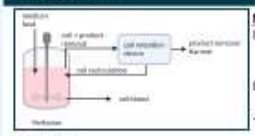
Background



Main characteristics + parameters

I. Cell growth
- Achieving HCD > cell retention
- Maintaining HCD > cell bleed

II. Continuous medium exchange
> perfusion rate

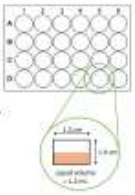
→ Stable environment to cell culture

Challenge
Perfusion processes require optimization of several process parameters

Solution
Scale-down models (SDMs) are the most feasible option for high-throughput data generation + condition screenings

Knowledge gap

Microwell plates as SDM
- Capabilities > potential for HT + automation
- Challenges > Small V_W + limited control abilities
  > Limitation for parameter monitoring & screening



Objectives
- In-depth investigation + acquisition of knowledge about MWP platform
- Translation of perfusion bioreactor characteristics to MWP
  - Cell retention > centrifugation
  - Cell bleed > manually
  - Medium exchange > manually

Results

Can high VCCs be achieved?

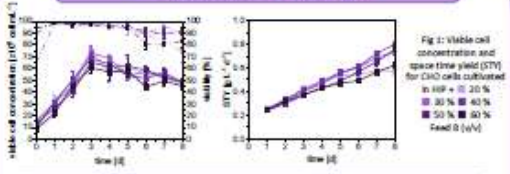


Fig 1: Viable cell concentration and space time yield (STY) for CHO cells cultivated in HIP + 20 % 30 % 40 % 50 % 60 % Feed B (v/v)

- VCC up to 60-74x10⁶ cells mL⁻¹ with high viabilities, $CSPR_{sim}$ of 13-15 pL cell⁻¹ d⁻¹
- Medium consumption: 129 mL per MWP (100%)

→ HIP + 30% Feed B with best growth + production performance

→ VCCs + productivities comparable to bioreactor data in literature

Can stable VCCs be maintained?

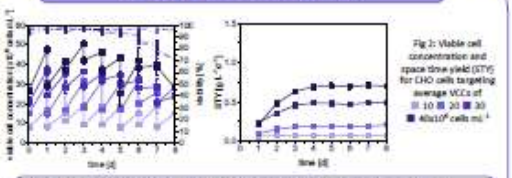


Fig 2: Viable cell concentration and space time yield (STY) for CHO cells targeting average VCCs of 10 20 30 40x10⁶ cells mL⁻¹

- stable average VCC with high viabilities, stable CSPRs (20 – 30 pL cell⁻¹ d⁻¹)
- stable bleed rates + metabolite concentrations (not shown)
- Medium consumption: 129 mL per MWP (100%)

→ growth + titres comparable to literature values in spin tubes + bioreactor

Can stable CSPRs be maintained?

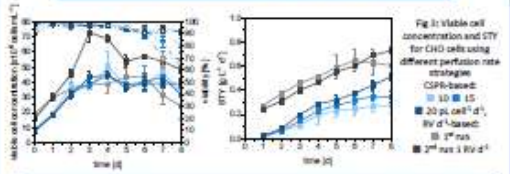


Fig 3: Viable cell concentration and STY for CHO cells using different perfusion rate strategies
CSPR-based: 10 15 20 pL cell⁻¹ d⁻¹, RV d⁻¹-based: 1st run 2nd run 1 RV d⁻¹

- VCCs < 50x10⁶ cells mL⁻¹ for high inoculation concentration with high viability
- stable CSPRs maintained (not shown)
- comparable STYs + improved q_{metA}²

→ Up to 50% less medium consumed for inoculation at high VCC

→ VCC plateaued after reaching VCC_{max} with CSPR-based strategy

Can stable VCCs + CSPRs be maintained?

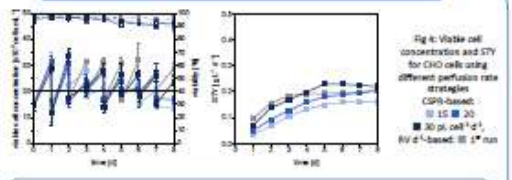


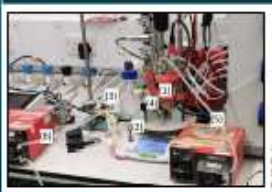
Fig 4: Viable cell concentration and STY for CHO cells using different perfusion rate strategies
CSPR-based: 15 20 30 pL cell⁻¹ d⁻¹, RV d⁻¹-based: 1st run

- stable average VCC at various targeted CSPRs with viabilities > 90 %
- comparable STYs + improved q_{metA}²
- stable CSPRs but lower than targeted (not shown)

→ Up to 50% less medium consumed

→ Similar yields + improved productivities using up to 50% less medium

Approach of application



- MWP as high throughput SDM for cell clone screening
- Taking promising clones in 250mL perfusion bioreactor

250mL perfusion bioreactor
(1) Bioreactor (2) Cell + product removal
(3) Cell retention device (4) Cell recirculation
(5) Medium feed (6) Product removal

Outlook

- Further development of the methodology
  - Scale-up experiments in shaken 6-well deep well plates (V_W = 35mL)
- Automation of methodological workflow + tech transfer
  - Modifications to the methodology to be industrially-relevant i.e. clone selection process
- Apply additional tools such as mathematical modelling in decision making process

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