Calibration design for pharmaceutical bioprocesses: A novel approach for knowledge transfer in Design of Experiments

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Abstract

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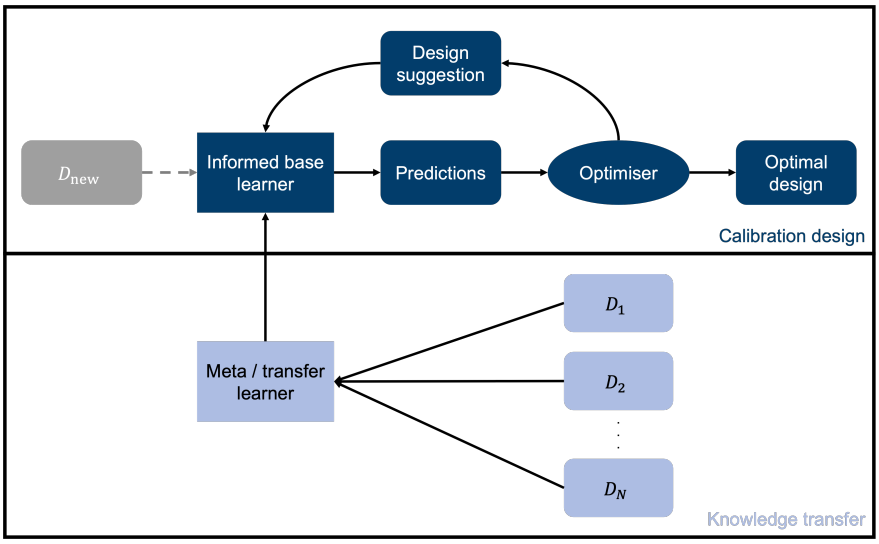

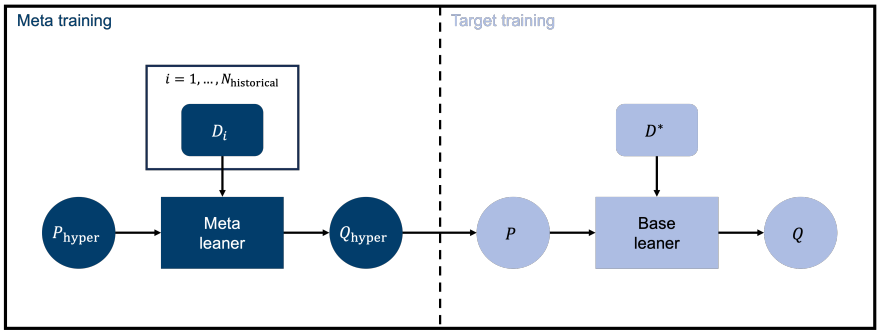

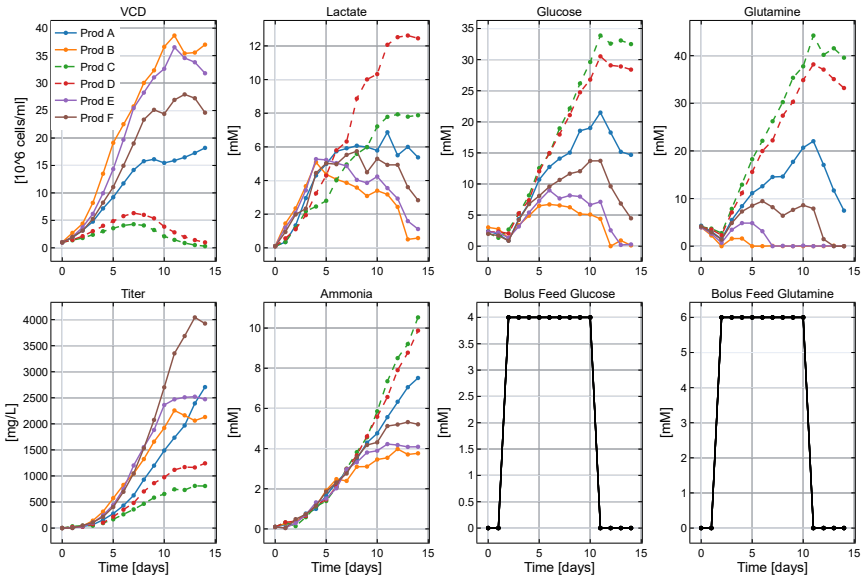

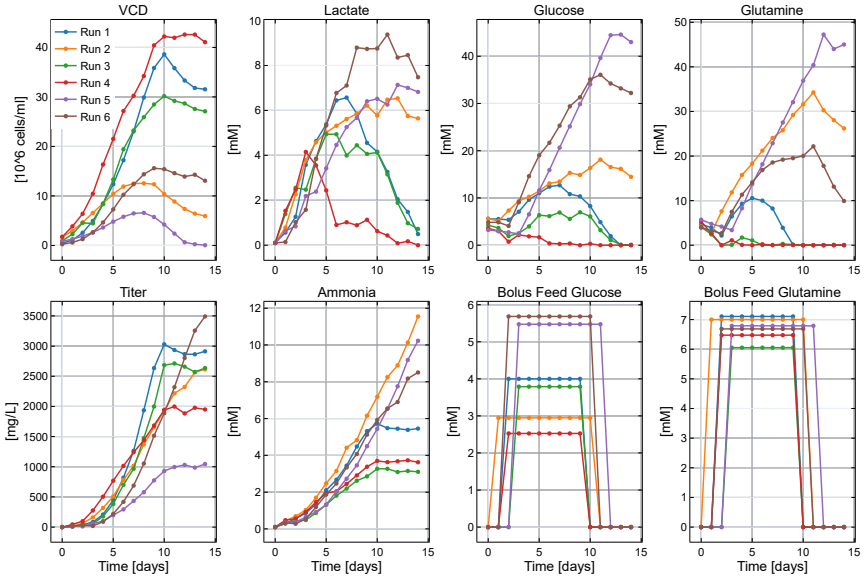

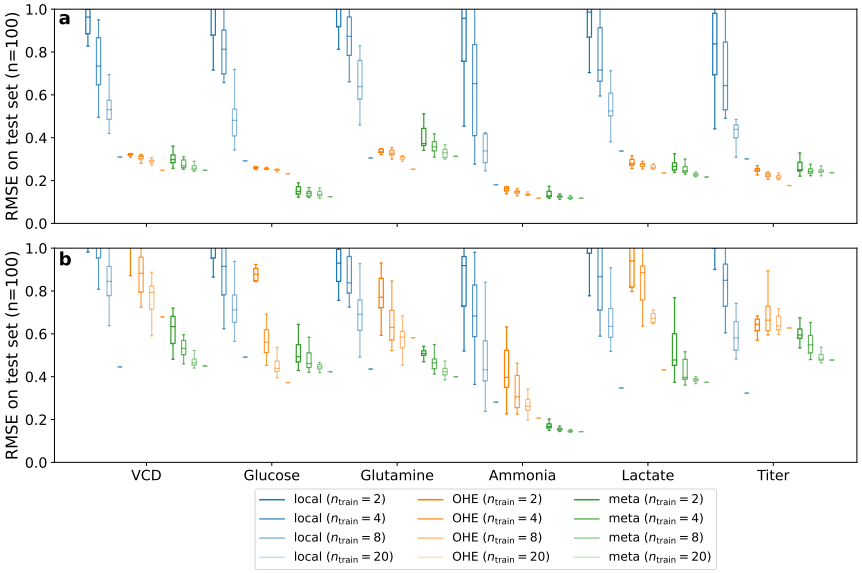

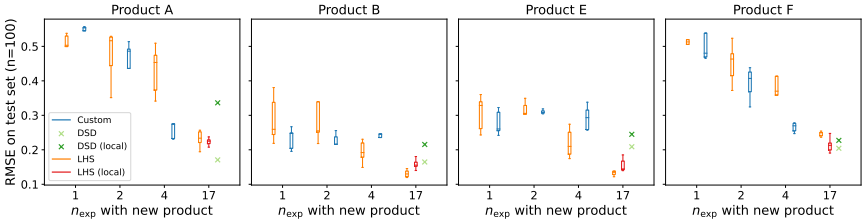

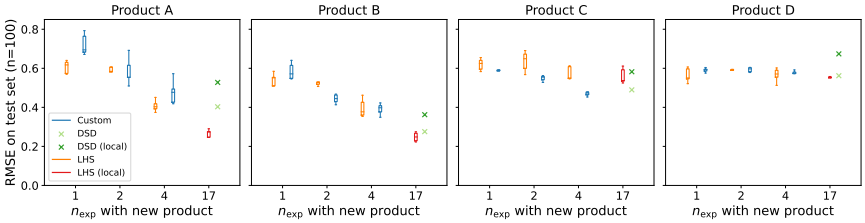

Calibration design for pharmaceutical bioprocesses: A novel approach for knowledge transfer in Design of Experiments

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1 Introduction

Processes for the manufacturing of biopharmaceuticals must consistently deliver the right quality and be economically feasible. The development of these processes needs to be fast, exhibit low technical risk, require limited investment, produce sufficient process understanding, and yield a manufacturing process that is economically viable. Three approaches have been introduced in the past to answer to these needs: platform processes, (miniaturised) high-throughput experimentation and Quality by Design (QbD).

Platform processes seek to provide a template for process development. Typically, a proprietary host cell line, base and feed media as well as process conditions are developed and chosen ones, and process conditions are only adapted slightly to improve quality or titer when changing the product. In this approach, process development is streamlined and fast, a body of knowledge of how the process behaves is acquired and technical risk is reduced. Regardless, early stage (cell line and condition screening) as well as late stage process development (optimisation to reach quality and economic target as well as scale-up) will still require the execution of multiple process runs (Bradl et al., 2016; Rehberger et al., 2013; Xu et al., 2020, 2022). Depending on the product and platform, the average number of process development runs is in the hundreds in early stage and in the dozens for late stage.

(Miniaturised) High-throughput experimentation aims at generating experimental evidence at economically attractive small scales. Experimental results produced with small-scale, high-throughput devices have been shown to be representative of larger scale production process (Bareither & Pollard, 2011; Fink et al., 2021; Hemmerich et al., 2018; Kim et al., 2012). Consequently, these devices have become very popular with industry allowing to execute several runs in parallel, reducing timelines. A component that perhaps contributed to their spreading was the adaptation of the statistical Design of Experiments (DoE) methodology (Politis et al., 2017), which provides a design for several experiments for a planned outcome. Advances in automation such as liquid handling platforms have also fostered the developments in high-throughput experimentation.

Quality by Design (QbD) is defined as 'a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management' in the guidelines Q8/9/10/11 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. QbD found wide attention in industry since its adoption in 2009 (Newcombe, 2014; ter Horst et al., 2021) and DoE was and is seen as one of the central components (Rathore & Winkle, 2009) as it allows to investigate the impact of factors on the process response in a systematic way.

Apart from answering to the process development needs, these three approaches in combination produce data of *sufficient* quantity and quality - significant advances have been made in data gathering and management as well as data science over the last decade (Darmont et al., 2022; Jin et al., 2015; Narayanan et al., 2020; Sarker, 2021) - which seem to render possible a fundamental change in the way that processes are being developed (von Stosch et al., 2021). The main idea is that machine learning (ML) methods allow to use the data produced by processes of different molecules to streamline the design of a process for a new molecule, i.e. horizontal knowledge transfer (Hutter et al., 2021).

An efficient way to address the challenge of horizontal knowledge transfer are transfer and meta learning techniques. In transfer learning, the goal is to exploit knowledge that was gained from one task in a source domain to solve another task in a target domain (Weiss et al., 2016), e.g. by preserving several layers in a pre-trained neural network and only adapting the rest for unseen data. In the context of process development, a task is to find a process model for a specific product, such that the target domain would be a new product that is not explored yet. In contrast, meta learning, often associated with the term *learning to learn*, focuses on solving many source tasks in a joint fashion, usually to learn hyperparameters that can improve the performance of the learning algorithm (Upadhyay et al., 2023).

Regarding the choice of ML models for dynamic systems, Gaussian processs (GPs) gained popularity over the past decades (Deisenroth et al., 2009). GPs are non-parametric, Bayesian ML models; as such, they are simple to set up, work well with noisy and small datasets and naturally incorporate a measurement of uncertainty in the predictions (Kocijan, 2016). These attributes make GPs a valuable tool in biopharma, where they were demonstrated in applications such as modelling of bolus fed-batch cultures for antibodies (Cruz-Bournazou et al., 2022) or process monitoring with spectroscopic data (Tulsyan et al., 2021).

While many specialised transfer and meta learning methods for neural networks exist in the field of ML (e.g. reviewed in Hospedales et al., 2022; Tan et al., 2018), these paradigms are less explored for GPs, particularly in the context of bioprocesses. A simple approach to achieve horizontal knowledge transfer is joint training on historical and new product data using one-hot enconding (OHE) (Ashenden et al., 2021), which means introducing several binary features to represent a categorical feature. Recently, this approach was extended to vector embeddings, where the study showed that transfer learning approaches slightly outperformed models that were trained without historical bioprocess data (Hutter et al., 2021). However, applications of meta learning, where an inductive bias is learned from historical data, remain scarce. Interestingly, meta learning for GPs was recently explored in the work of Rothfuss et al.; in particular, the study found a framework that addresses the challenge of overfitting to the meta-training tasks for small dataset and allows generalisation as well as good scaling (Rothfuss et al., 2021).

Besides these modelling challenges, the related question of how to identify suitable experimental conditions to understand the behaviour of new processes has been addressed in the past. DoE is an old field that goes back to Sir Ronald A. Fisher in the 1920s (Politis et al., 2017). On a high level, the two classical approaches used in bioprocess development are: screening designs, which aim at identifying critical design factors and their main effects, and response surface designs, which aim to optimise these critical factors (Beg & Swain, 2021). Examples for screening designs are fractional factorial designs or definitive screening designs (DSDs), the latter being suitable for screenings with with many design factors that have confounding effects (Jones & Nachtsheim, 2011). The group of response surface designs include central composite, full factorial or Doehlert designs.

Besides classical DoE approaches, Bayesian optimisation became of interest for the field, a concept that was named one of the most important statistical ideas of the past 50 years by Gelman and Vehtari, 2021 in the context of adaptive decision analysis. In experimental designs, Bayesian optimisation has fostered significant improvements in the number of experiments that are required to optimise a process (Greenhill et al., 2020). However, initial designs for new processes, whose data is required to fit an initial model for Bayesian optimisation, are usually chosen by simple, uninformed methods, either by space-filling strategies like latin hypercube sampling (LHS) or by classical DoE methods like factorial designs. As an alternative, we hypothesise that historical data contains information on experimental designs that reveal the underlying

process dynamics more efficiently, thus leading to less required experiments to fit a new process model compared to state-of-the-art methods.

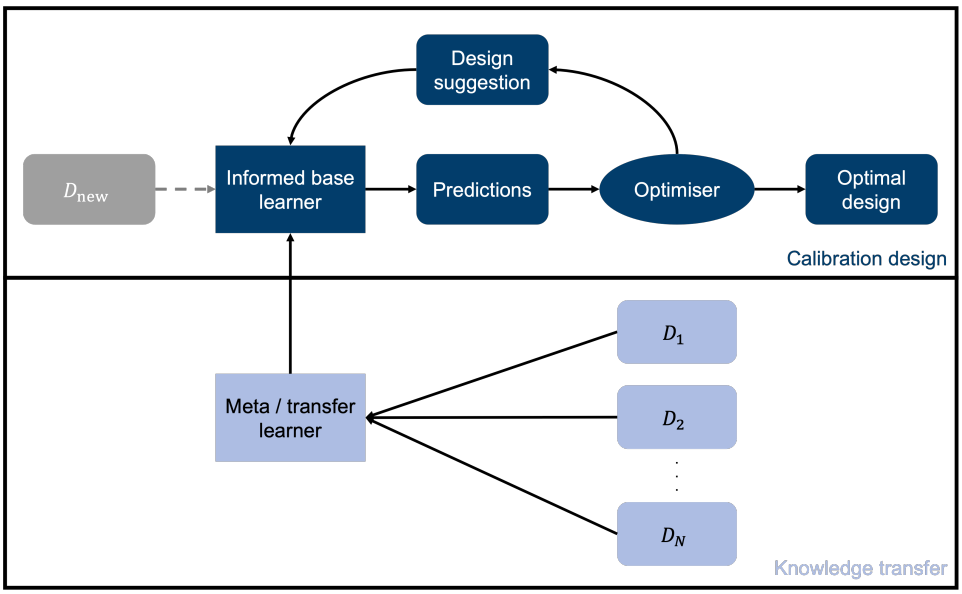

Figure 1: Link between knowledge transfer and calibration design.
In the first part of this work, different strategies for knowledge transfer (light blue) are compared, e.g. meta learning. To identify optimal designs to calibrate a process model, initial data from so-called excitation designs (grey) is usually required. However, meta or transfer learner already informs the base learner as a hyperprior, allowing to suggest optimal designs to calibrate the process model to a new product. This task of generating initial optimal designs for an unseen product is called *calibration design* throughout this work.

In this work, we show that horizontal knowledge transfer improves model performance and that the choice of initial experiments to start process optimisation can be improved by using existing knowledge. An overview of the processes and their connection is given in Fig 1. As shown in the lower part of the figure, the first part of this work investigates methods of knowledge transfer. To efficiently handle small datasets, which are present at the start of new product development campaigns, GPs are applied as the model of choice. In a first step, we transfer the meta learning approach by Rothfuss et al., called *PACOH*, to a biopharmaceutical process model based on GPs. In a case study with historical datasets and one novel product, we benchmark the performance of the new algorithm compared to other knowledge transfer models and models that are only trained on data of the novel product. In the second part of this study, we explore how to use transfer learning to calibrate process models to a new, completely unseen product (Fig 1, top). We refer to this novel experimental design as *calibration design* and determine the process conditions based on a new metric that takes the differences in the process evolutions of historical products into account. In contrast to common DoE strategies, the calibration design does not require data from an initial excitation design of the novel product (Fig 1, grey box) to calibrate the base learner, but can leverage information from the knowledge transfer approaches. In the final part of this study, we therefore benchmark the novel calibration design metric to other metrics and designs such as LHS and shed light on potential use-cases as well as future directions for the approach.

2 Material and methods

In this paper, two different methodologies are targeted: knowledge transfer methods and calibration design (identifying optimal initial experimental designs of a new product for model calibration). Both approaches require an underlying process model. GPs are the model of choice in this work due to their efficiency regarding small datasets and their ability to handle noisy experimental data, which is relevant for biopharmaceutical processes. In this chapter, regression using GPs is explained first, followed by an overview of knowledge transfer approaches and introduction of the novel task of calibration design.

2.1 GP regression

GPs are Bayesian machine learning models used throughout various regression problems. In a simple description, consider n m-dimensional input and n scalar output data points. Given some input data $\mathbf{X} \in \mathbb{R}^{n \times m}$ and corresponding output data $\mathbf{y} \in \mathbb{R}^n$ and given a new data point $\mathbf{x}' \in \mathbb{R}^m$, a GP implements the predictive conditional distribution of the output variable y':

$$y' \sim \mathcal{N}(\mathbf{x}'|\mathbf{X}, \mathbf{y}) \equiv \mathcal{N}(m(\mathbf{x}', \mathbf{X}, \mathbf{y}), \sigma^2(\mathbf{x}', \mathbf{X}, \mathbf{y})) \tag{1}$$

where $m(\mathbf{x}', \mathbf{X}, \mathbf{y})$ and $\sigma^2(\mathbf{x}', \mathbf{X}, \mathbf{y})$ describe the predictive mean and variance for a new observation $\mathbf{x}'$, given the data $\mathbf{X}$ and $\mathbf{y}$. A detailed description of GP regression can be found in Rasmussen and Williams, 2006.

To model the time evolution of the process variables, we utilise GP regression in an autoregressive fashion to propagate the process dynamics along the time dimension. To facilitate this, the process is discretised along the time dimension and for all modelled species their generic mass balances are parameterised as follows:

$$\frac{d(c \cdot V)}{dt} = R(x) \cdot V + u_f \tag{2}$$

where c is a vector of concentrations of the modelled process dynamics variables, V the culture volume and u_f a vector of mass feed rates (nonzero only for compounds that are fed). $R(x)$ describes a vector containing the rate of production (or consumption when negative) of the modelled species as a function of all process variables x at a certain time t input to the GP model. The input x is given by a combination of uncontrolled process dynamics variables and controlled process variables (such as pH or temperature). Discretisation of the process in time allows us to utilise the forward-difference formula for the time-derivative of the concentration, where Eq 2 now becomes:

$$\frac{d(c \cdot V)}{dt} = V\frac{dc}{dt} + c\frac{dV}{dt} \cong V\frac{c(t_{i+1}) - c(t_i)}{t_{i+1} - t_i} + c\frac{dV}{dt} = R(x_i)V + u_f \tag{3}$$

where $x_i \equiv x(t_i)$ denotes the vector of all input process variables at time step t_i. Further simplification of Eq 3 allows us to lump the mass balances into a single effective rate of production $\tilde{R}$, as can be seen below in Eq 4.

$$\frac{c(t_{i+1}) - c(t_i)}{t_{i+1} - t_i} \cong R(x_i) + \frac{1}{V}\left(u_f - c\frac{dV}{dt}\right) \stackrel{!}{=} \tilde{R}(x_i, u_f, V) \tag{4}$$

To approximate this effective rate of production $\tilde{R}$ we can utilise any machine learning model. In our case, this approximation is parameterised through the predictive mean of a GP regression model: $GP(x, u_f, V) \approx$

$\tilde{R}(x, u_f, V)$. Here we use the notation $GP(x, u_f, V)$ interchangeably with the predictive mean of the GP. Through this discretisation of the process mass balances in time, as well as the approximation of the effective rate $\tilde{R}$ through the predictive mean of a GP regression model, we can autoregressively propagate the state of the process along discrete steps in time:

$$c(t_{i+1}) \approx GP(x_i, u_f, V) \cdot (t_{i+1} - t_i) + c(t_i). \tag{5}$$

Throughout this work, a squared exponential (SE) kernel with automatic relevance determination (ARD) was used, with the kernel hyperparameters and noise parameters determined from the training data using maximum likelihood estimations. To improve model robustness and predictive performance, a simple mean averaging ensemble approach was chosen with 30 GP models comprising the ensemble, each sub-sampling 50% of the training data experiments. The high number of models in the ensemble, together with the chosen sub-sampling percentage, ensure adequate coverage of the training data while improving the robustness against over-fitting. Further background is given in Pinto et al., 2019.

2.2 Knowledge transfer approaches

In Section 3.2, we compare different models for knowledge transfer with individual-product models as a benchmark. While individual-product models and one-hot encoding were used before, the meta learning framework for GPs was not yet applied to a biopharmaceutical process model to the best of our knowledge. All models are evaluated based on their performance of the predicted effective rate (Eq 4) on a test data set with 100 simulated experiments (Section 2.4). In the following, the methodology of the various models is detailed.

2.2.1 Individual-product models

In the simplest approach, only the data for the product of interest is used to train a GP regression model as described in Section 2.1. This serves as a benchmark for meta learning and one-hot encoding models, which are expected to outperform individual-product models in terms of the test set error (Section 2.3.4) if few experiments are provided. We varied the number of available experiments between one and 20, which were randomly sampled from the available training data generated as described in Section 2.4.

2.2.2 Meta learning for GPs

In the usual training setup of a GP regression model, that is training the *base learner* for a new product (dataset D^*), the training is initialised with pre-defined *prior probabilities* P for the mean and kernel functions, which are usually broad and uninformative if no specific process knowledge is available. In meta learning for GPs, the idea is to obtain informed prior probabilities for a base learner from a *hyperposterior* Q_{hyper}; that is the hyperposterior is learned by a *meta learner* trained on with several historical datasets D_i with $i = 1, ..., N_{\text{historical}}$. This concept is illustrated in Fig 2.

Meta learning in this study was implemented by combining the PACOH framework by Rothfuss et al., 2021 with a stepwise GP described in Section 2.1. Essentially, the mean and kernel functions for the GP are defined as parametric functions, more precisely neural networks, whose parameters are meta-learned in training. As for other ML models, hyperparameter such as the number of layers and neurons in the neural network

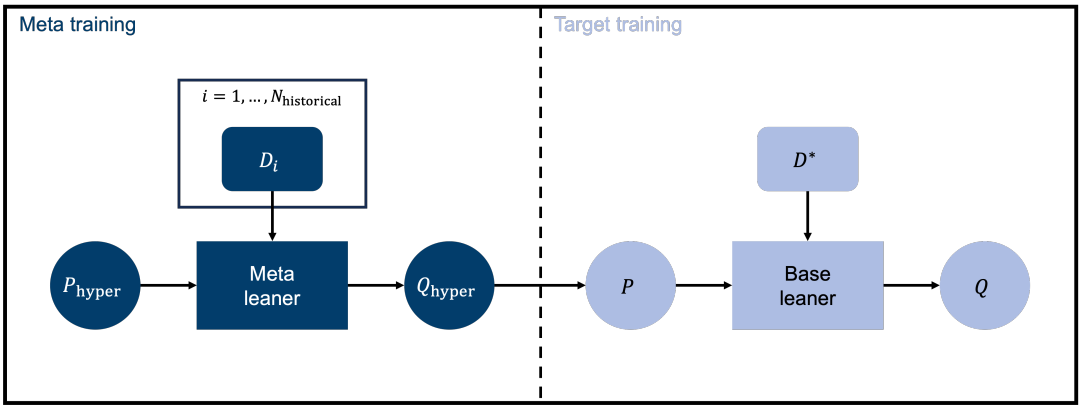

Figure 2: Overview of meta learning concept for GPs.
In a standard GP setup, a base learner is initialised with prior probabilities and the hyperparameters of the GP kernel are learned based on a dataset D^*, resulting in their posterior distribution. The GP, i.e. the posterior distribution Q of the hyperparameters, can then be used for prediction. In meta learning, the prior probabilities are obtained from a hyperposterior Q_{hyper}, which is learned on historical datasets D_i with $i = 1, ..., N_{\text{historical}}$. This plot is a simplified version of Figure 1 presented in Rothfuss et al., 2021.

can determine the predictive output. As done in the original study, we thus performed a hyperparameter optimisation using `Hyperopt` (Bergstra et al., 2013). More details and the optimised parameters can be found in the Supplementary Information. For further details on meta learning and the optimisation guarantees, we refer to Rothfuss et al., 2021. In the case study, we use the six datasets generated as described in Section 2.4 and assume one to be the new product while the other five serve as historical data for meta training. This is benchmarked against a OHE model described in the following subsection.

2.2.3 One-hot encoding models

OHE is a common binary encoding strategy to turn categorical variables into numerical feature vectors. The encoding turns any categorical feature c with N_c potential categories into N_c additional binary features, also referred to as dummy variables, with a 1 denoting the presence of the corresponding category for the data points respectively. Encoding the product information this way, the combined data shared across all products can be utilised to train a model. Keeping the SE kernel with ARD, OHE variables introduce additional similarity conditions to the kernel. A detailed explanation of the effects of binary encoded variables onto the kernel values can be found in Hutter et al., 2021.

2.3 Calibration design of process conditions

The term calibration design refers to the task of identifying a suitable experimental design for a determined number of runs to calibrate an existing model on process data of a new product of interest (in the following, we in short refer to *process data of a new product of interest* as *new product*). In this study, we use different objective functions to identify the best process conditions to calibrate an OHE-GP regression model to the new product, which was initially trained on data of other products. For this, the initial OHE model is trained with 20 experiments of three historical products, designed with LHS over the design space. This is the basis for further generation of experimental designs for the new, completely unseen product, using the objectives described in Section 2.3.2 in an optimisation detailed in Section 2.3.1.

In the simplest case, we designed the conditions for a single experimental run $n_e = 1$, e.g. the setup of a single bioreactor. Here, solely the objective from Section 2.3.2 was optimised. Additionally, designs for parallelised bioreactor setups ($n_e > 1$), which are common for screening, were explored. In this case, the design of the first experiment is identified purely by optimising the respective objective for similarity. Subsequently, the designs of the next experiments are sequentially identified (prior to experimentation) by taking the objective function $f(\mathbf{u})$ with design factors $\mathbf{u}$ (Section 2.3.2), as well as the distance of these factors to the previously suggested design d:

$$f_{\text{parallel}}(\mathbf{u}) = \alpha \cdot f(\mathbf{u}) + (1-\alpha) \cdot \frac{1}{D} \sum_{d}^{D} ||\mathbf{u} - \mathbf{u}_d|| \tag{6}$$

with $\mathbf{u}$ as the vector of design factors that are optimised for the current experiment, D as the total number of experiments that have been optimised so far and the scalar α as the weight of the objective compared to the distance. In equation Eq 6, $||\bullet||$ denotes the euclidean distance over all factors, which are normalised by the boundaries of the design space to yield values between 0 and 1 before calculating the euclidean distance. This approach is iteratively repeated until the desired number of parallel experiments is obtained.

2.3.1 Optimisation framework

Bayesian optimisation of different objective functions was performed with scikit-optimize in version 0.9.2, using the `Optimizer` class with a gradient-boosted regression tree as surrogate model. An LHS with 100 samples was used to initialise the surrogate model and at least 1400 iterations were run for each suggested experiment to ensure convergence. All optimisations were repeated at least five times with different seeds to assess performance.

As an alternative to the distance-based design of parallel experiments (Eq 6), scikit-optimize offers parallel optimisation using the *constant liar* (Chevalier & Ginsbourger, 2013) methodology. In short, the surrogate model, which is an inherent part of the optimiser to approximate the objective function, is first queried for one optimal data point. Subsequently, this data point is added to the observations made so far with a dummy response, assuming either the mean or the minimum so far seen in the surrogate model as the corresponding function value. The surrogate model is then queried for the new optimum and the process is repeated as often as parallel points are to be designed. Afterwards, the true objective function is evaluated at all points in the batch simultaneously and the surrogate model is updated. Further details on the implementation can be found in the scikit-optimize documentation (Shcherbatyi et al., n.d.).

2.3.2 Objective functions

In our customised objective, we reason that data of historical products can inform the choice of new designs that enhance the predictive power of the process model. As a hypothesis, certain experimental designs are better suited to reveal differences in cell line behaviour than others. Using knowledge transfer models, these difference in relevant process parameters such as titer are to be inferred using historical data. For this purpose, a novel metric is introduced, using the same notation as De Luca et al., 2023 for comparability.

In the case study, we chose to optimise based on the predicted interval of final titer $T_i(t_{\text{end}}, \mathbf{u})$ of historical product i, given a set of control variables $\mathbf{u}$. We focus on titer as its optimisation (along with product quality attributes) typically guides the development activities. Let $\tilde{T}_i(t_{\text{end}}, \mathbf{u})$ denote the median prediction and $\sigma_i^2(t_{\text{end}}, \mathbf{u}) = \text{Var}\left[\tilde{T}_i(t_{end}, \mathbf{u})\right]$ the variance of the predicted interval for product i out of N total historical

products. We suggest the following metric that is calculated pairwise between products:

$$f(t_{\text{end}}, \mathbf{u}) = \sum_{i}^{N} \sum_{j,j>i}^{N} \frac{\left| \tilde{T}_i(t_{\text{end}}, \mathbf{u}) \cdot \sigma_j^2(t_{\text{end}}, \mathbf{u}) - \tilde{T}_j(t_{\text{end}}, \mathbf{u}) \cdot \sigma_i^2(t_{\text{end}}, \mathbf{u}) \right|}{\sigma_i^2(t_{\text{end}}, \mathbf{u}) + \sigma_j^2(t_{\text{end}}, \mathbf{u})} \tag{7}$$

where t_{end} represents the end of cultivation and $\mathbf{u}$ a set of control variables, including initial viable cell density (VCD), that can be optimised. In its core, the metric is looking at the pairwise difference in predicted final titer scaled by the width of the predicted interval; it is thus trying to evaluate designs with factors $\mathbf{u}$ that maximise this difference while taking prediction uncertainty into account.

2.3.3 Comparison to further DoE strategies

Further benchmarking of the objectives is done by comparing the modelling performance of the calibration design runs to those stemming from models trained on data generated according to LHS or DSD. For LHS, experiments were generated with different random seeds within the design space, not using center points. DSD is a design strategy widely applied in bio-manufacturing and pharma (Dodds et al., 2022). To generate the design, we used the `definitive-screening-design` package with version 0.4.0 (Ongari, 2023). If not indicated otherwise, the training data of historical products is augmented by the suggested experiments for training a OHE model. The index "local", however, indicates that the models were trained on the experiments of the novel product alone, which is a standard for most DoE methods.

2.3.4 Performance metric

A test set of $n_e = 100$ unseen experimental conditions for the new product (Section 2.4) was used to assess the predictive quality of the model after training, which was performed on data from experiments that were simulated according to the conditions planned with the different design strategies. These predictions and the test dataset are used to calculate the relative root-mean-square error (RMSE) of each product:

$$\text{RMSE} = \frac{1}{\sigma_T} \sqrt{\frac{1}{n_e} \frac{1}{n_t} \sum_{j=1}^{n_e} \sum_{t=1}^{n_t} \left(T(t,j) - \tilde{T}(t,j) \right)^2} \tag{8}$$

where n_t is the number of observations of titer made over time, $T(t,j)$ are the measured titer values at time t from the test set experiment j, and $\tilde{T}(t,j)$ the respective predicted median titer. To standardise the error, it is divided by the standard deviation in the actual measurements across the 100 experiments in the test dataset, σ_T. Values of the RMSE well below 1.0 represent a good model performance while values above 1.0 indicate that a constant mean prediction over time would outperform the GP model prediction. For the RMSEs in Section 3.2, titer is substituted by the respective process variables.

2.4 Generation of benchmarking datasets

The *in silico* model used to generate data is based on the macro-kinetic model for a fed-batch chinese hamster ovary (CHO) cell culture as described in Craven et al., 2013 and Xing et al., 2010, with adaptations to impose complex non-linearities in growth rate dependencies and to account for pH and temperature shifts. The *in silico* model has been presented and utilised in past works (e.g. De Luca et al., 2023; Hutter et al.,

2021). We simulated six different cell lines (which are associated with six different products, A-F), using the *in silico* model and varying internal parameters for growth, substrate affinity, pH and temperature tolerance to create different phenotypes.
For each of the six cell lines, the control inputs over a fixed cultivation time of 14 days were determined to follow the subsequently described set point profiles:

Table 1: Overview of process parameters varied for dataset generation and optimisation
For benchmarking of meta learning vs. OHE, 15 parameters were varied as shown in column **Knowledge transfer range**. For calibration design, 7 parameters were varied as shown in column **Optimisation range**. In cases where two ranges are given, the first was used for lactate-consuming products A, B, E and F and the second range for products C and D. The first value in the optimisation range was used for the case study with products A, B, E, F (lactate-consuming only), the second value for the case study with products A, B, C, D.

Process parameter	**Description**	**Knowledge transfer range**	**Optimisation range**	**Unit**
`StirrerSpeed`	constant value	[150 , 250]	[200 , 200]	-
`DissolvedOxygen`	constant value	[30 , 80]	[40 , 40]	% air saturation
`pH-Phase1`	pH profile	[6.5 , 7.5]	[6.5 , 7.5]	-
`pH-TimeSwitch`	(before, switch	[6 , 14]	[7 , 7]	d
`pH-Phase2`	time, after)	[6 , 7]	[6 , 7]	-
`Temp-Phase1`	temp. profile	[36 , 38]	[36 , 38]	°C
`Temp-TimeSwitch`	(before, switch	[6 , 14]	[7 , 7]	d
`Temp-Phase2`	time, after)	[35 , 37]	[35 , 37]	°C
`BolusGlucose`	mass & times of	[2 , 6] / [0.5 , 1]	[2 , 6] / [0.5, 6]	mmol
`BolusGlutamine`	daily bolus feeds	[6 , 8] / [0.5 , 4]	[6 , 8] / [0.5 , 8]	mmol
`FeedStart`	for	[1 , 3]	[3 , 3]	d
`FeedEnd`	glucose/glutamine	[9 , 13]	[13 , 13]	d
`VCD`		[0.2 , 2]	[0.2 , 2]	10^{-3} cells/mL
`Glc`	initial conditions	[2 , 6] / [2 , 5]	[4 , 4]	mM
`Gln`		[4 , 6] / [2 , 4]	[4 , 4]	mM

The variables whose name contains `Phase` represent the value of the set point during the respective phase, those with `TimeSwitch` indicate when the switch from one phase to the other occurred. Initial concentration values of VCD, glucose and glutamine were assumed to be controllable (i.e. they can be optimised), those of lactate, ammonia and titer were fixed. This resulted in total of 15 factors that can be varied for the process data generation and subsequently process optimisation.
The *in silico* model was used to simulate the evolution of six process variables, namely VCD, glucose, glutamine, ammonia, lactate, and titer, where the data is obtained as daily measurements of process variable concentrations c. In the case of noisy measurements of concentrations $\widetilde{c}$, they were corrupted with relative Gaussian noise of 2% and with absolute Gaussian noise applied as follows:

$$\widetilde{c} = c * (1 + 0.02 * \mathcal{N}(0,1)) + \mathcal{N}(0, \sigma_i) \tag{9}$$

In Eq 9, σ_i is corresponding to default standard deviations of the experimental error for different variables (VCD: 0.03×10^6 cells/mL, glucose: 0.5 mM, glutamine: 0.1 mM, ammonia: 0.1 mM, lactate: 0.3 mM, titer: $10\,\mathrm{mg\,L^{-1}}$).

Initial conditions of VCD, glucose, and glutamine were additionally corrupted only in form of an additive, absolute error consisting of Gaussian noise with standard deviations as defined above. Noisy measurements were included in the simulations to facilitate the comparison of different strategies under more realistic conditions. However, run-to-run variation might impact the model performance and the width of the prediction interval, which can be expected to increase with increasing run-to-run variation.

Subsequently, the data were used to fit the stepwise GP model, as detailed in Section 2.1. To generate historical datasets for each product, which can be used for the different knowledge transfer strategies (Section 2.2), LHS was used to vary the 15 process parameters in the ranges described in Table 1. Datasets with 20 experiments for training and 100 experiments for testing were thereby generated, aiming at covering the entire process parameter space. For the calibration design, a subset of 7 parameters was chosen, which are initial VCD, `pH-Phase1`, `pH-Phase2`, `TempPhase1`, `TempPhase2`, `BolusGlucose` and `BolusGlutamine`. The process data for the six products with and without noise is published in an accompanying repository (Helleckes et al., 2024).

3 Results and discussion

3.1 Design of benchmarking dataset

The prerequisite to compare knowledge transfer methods and optimisation procedures for experimental design is the availability of suitable benchmarking datasets. For this study, we simulated process data for six different products A-F with the framework described in Section 2.4. Since the benchmarking datasets should represent the case of different historical process development campaigns, it is important that the different simulated product cases, that is cell lines, show a high degree of inter-product variability. This is shown in Fig 3.

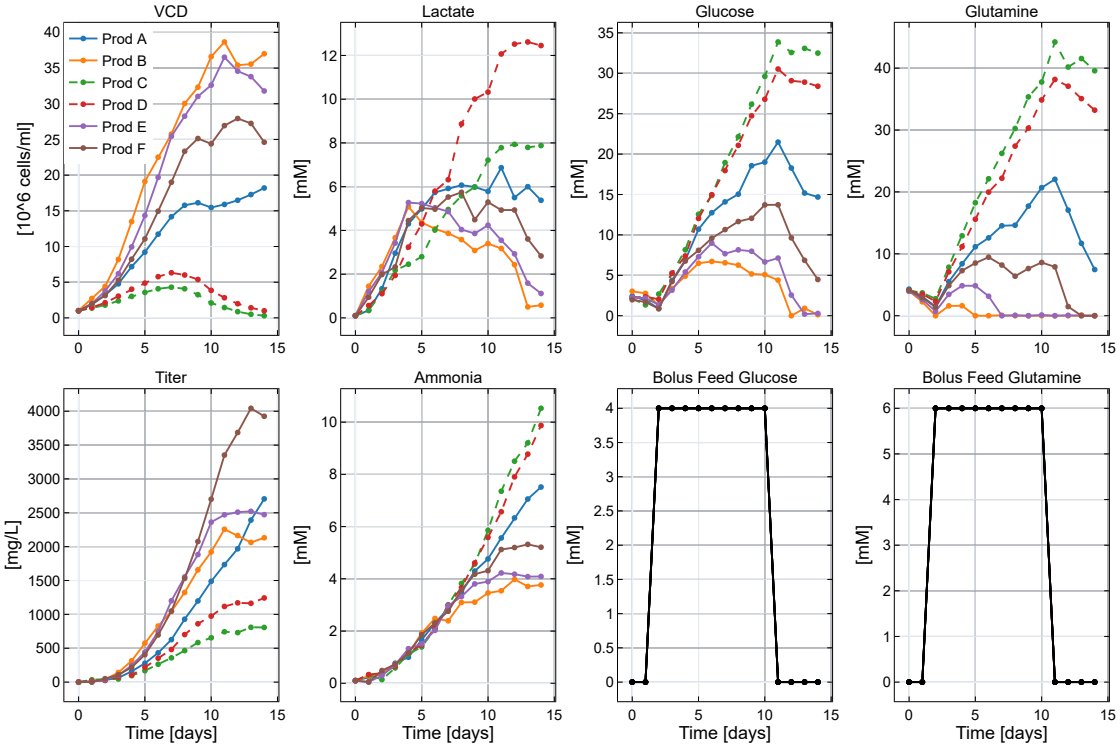

Figure 3: Inter-product variability for identical initial process conditions.
All processes of the six products were simulated using identical initial process conditions and product-specific kinetic parameters (**??**). In particular, processes of products C and D mimic cell lines without lactate consumption (dashed lines). A relative measurement error of 2% along with an absolute error of one standard deviation was added to all simulations. The markers represent the daily measurements, which are used to train the model. It becomes evident that the processes of the six different products have different behaviour when exposed to the same process conditions.

Time series data for 14 days was simulated, assuming daily measurements of VCD, glucose, glutamine, ammonia, lactate and the product titer as indicated by the markers (and as common in industry). All products were simulated with the same identical conditions stated at **??**, with a measurement error according to Eq 9. Fig 3 shows the high variance between the different products in simulation, introduced by different parameter settings in the *in silico* model. Most prominently, the ability to consume lactate can be seen for cases A, B, E and F, while lactate is accumulating in cases C and D (dashed lines). Among the lactate-consuming products, the cases of B and E show higher degree of similarity than other products, which can be

seen from the similar trajectories in Fig 3. However, VCD and titer significantly differ for the same process conditions, thus posing a suitable challenge for meta learning.

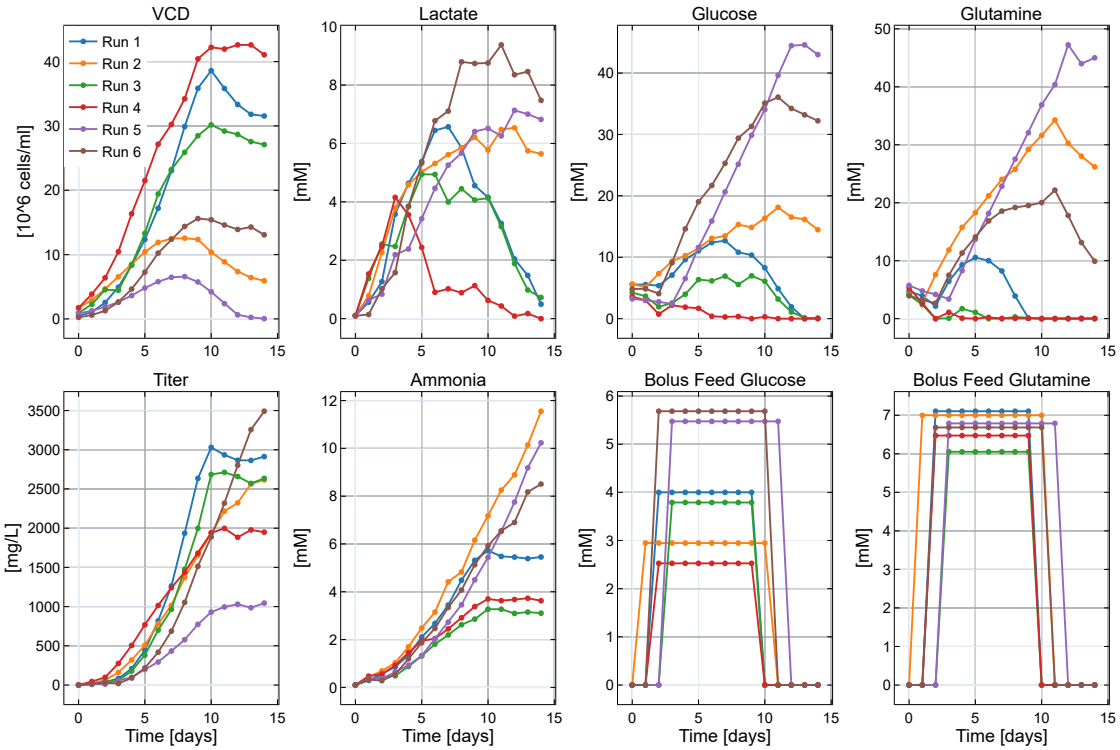

Figure 4: Intra-product variability for product F.
Six exemplary runs are shown to demonstrate the high variability of process conditions within the chosen design space. The datasets thus mimic a process development campaign in which the optimal conditions are investigated in a broad range without prior knowledge. A relative measurement error of 2% along with an absolute error of one standard deviation was added to all simulations. The markers represent the daily measurements, which are used to train the model.

Beside inter-product variability, the dataset used in this paper also shows high intra-product variability when exposed to different process conditions, which is shown in Fig 4 for product F. Similarly to the inter-product variability, this characteristic is important to mimic real-world application scenarios with noisy measurements in bioreactors. Interesting non-linear behaviour can especially be seen for lactate and glutamine. While being used as a challenging benchmark for training of Gaussian processes in this study, the datasets are published in a dedicated Zenodo repository (Helleckes et al., 2024), thus being available for comparison in future methodological papers on knowledge transfer and design of experiments.

3.2 Comparison of models for rate prediction

Three different approaches for knowledge transfer with GPs are compared regarding their performance in predicting the effective production rate $\tilde{R}$ that is used to update concentrations in the stepwise model described in Section 2.1. We shuffle through all possible combinations of the six cell lines, simulating each of them as the new product while utilising the other five as historical datasets, similar to the approach presented

by Hutter et al., 2021. As a first benchmark, the GP is trained on a varying number of experiments of the new cell line alone, also called a local model. In the second approach, we evaluate the OHE model described in Section 2.2.3 and train it on data from the new product plus additional twenty experiments from each of the other five historical products. Finally, we train a meta learning model using the PACOH approach described in Section 2.2.2, which simultaneously uses several GPs as base learners on the historical 20 experiments of each product. After meta training, the hyperposterior of the kernel parameters can be used to initialise a new GP for the novel product. As presented by Rothfuss et al., 2021, hyperparameters influence the meta learning performance for the PACOH approach. Similar to their approach, we thus performed hyperparameter optimisation with the `HyperOpt` Python package and used the determined hyperparameters to train the meta learning model.

Performance is evaluated by calculating the relative RMSEs on a test dataset with 100 experiments, using the predicted and simulated effective rates (Section 2.3.4). The available data from the new product is varied between 2, 4, 8 and 20 experiments. To avoid bias by the choice of subsets in the training data, the selection was shuffled with 10 different seeds. Exemplary results for products A and C are shown as boxplots of RMSEs in Fig 5, the results for the remaining products can be found in **??**. The two examples were chosen since for product A a large amount of similar data is provided in the corresponding training dataset (products B, E and F with lactate consumption). For product C (without lactate consumption), a far smaller body of similar experiments is available in the training dataset with the same size (only product D).

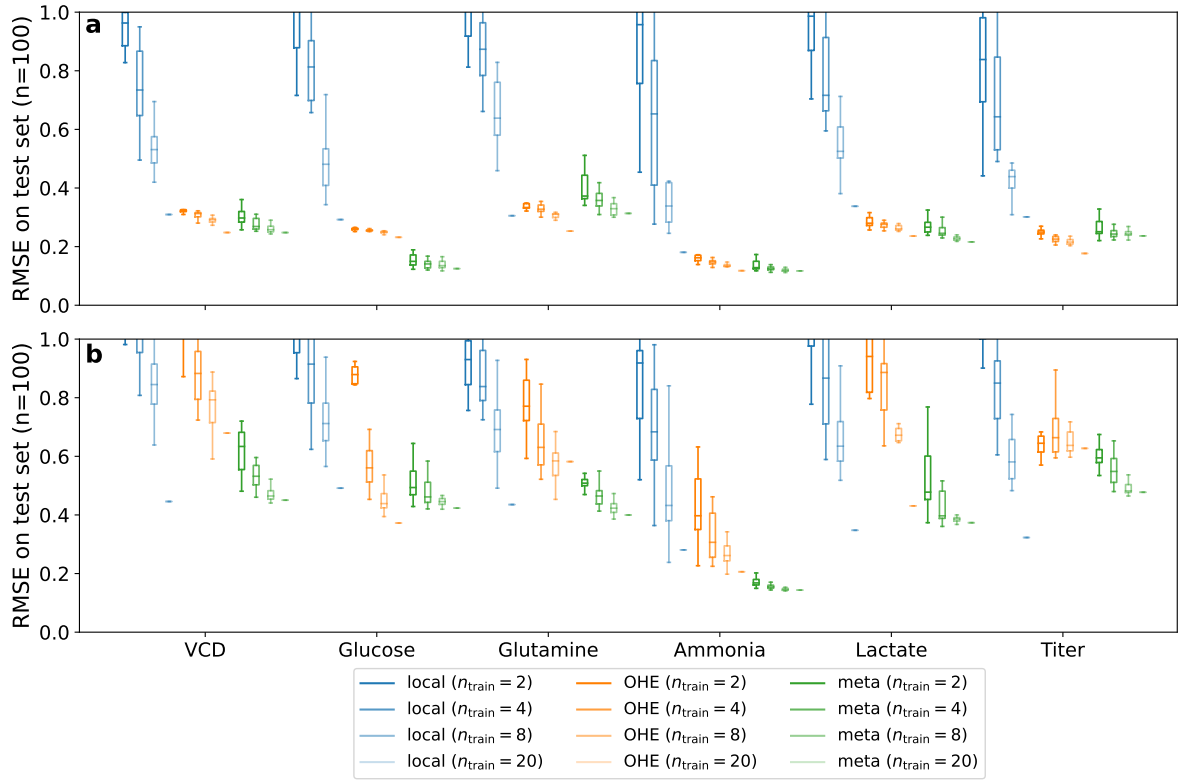

Figure 5: Prediction of rates for **a**: product A and **b**: product C. Local models (blue) are compared to OHE models (orange) and meta learning models (green), i.e. two different kinds of knowledge transfer models. Single GP instead of ensembles are compared to compare predictive performance on the learning problem directly.

For product A (upper plot), it can be seen that both knowledge transfer approaches clearly outperform the local model (blue) trained only on the data from the new product. As expected, using an increasing number of experiments from the new product in training is enhancing the predictive performance of the respective models, which can be seen by the improved relative RMSEs for the predicted effective rates across various features. While for some variables such as VCD, or titer, OHE (orange) outperforms the meta learning (green), the opposite is true for glucose and lactate. Overall, the RMSEs are well below 0.4, indicating a good performance for both OHE and meta learning. Interestingly, while a local model with 20 experiments also leads to decently low RMSE, the knowledge transfer approaches still outperform it, indicating that similarities from historical products strongly enhance the predictive performance.
Regarding product C, which is a case where a cell line without the lactate consumption was simulated, the results change. Here, meta learning is outperforming OHE for VCD, glutamine, ammonium, lactate and titer predictions. For this case, the local model with 20 experiments performs equally well as meta learning for VCD and significantly better for titer, indicating that the prediction quality for this product does not benefit as much from the historical data. Since only products C and D simulate the case of missing lactate consumption in the cell line, these results indicate that knowledge transfer works best when similarity is high, which is to be expected. For heterogeneous datasets, meta learning outperforms OHE, indicating a promising direction to improve GP regression models. Due to the comparable performance and lower computation time compared to meta learning, the OHE model was used as a benchmark for the following case studies of calibration design.

3.3 Calibration design for parallel experiments

When starting with model-assisted process development for a new product, the underlying process model needs to be trained with initial data, sometimes referred to as excitation design (De Luca et al., 2023; Ferreira et al., 2014; Huang et al., 2023). Traditionally, this design is either determined by methods of DoE such as a full or fractional factorial design (Freier et al., 2016) or space-filling designs such as LHS (Bader et al., 2023), Doehlert Designs (Pinto et al., 2019) and Sobol sequences (Siedentop et al., 2023). However, industrial process development campaigns might share certain similarities, for example a closely related cell line for protein production, or exploration of similar design spaces during optimisation. Related to the previously explored methods for knowledge transfer, it thus becomes evident that these models might also be used to obtain experimental designs to calibrate knowledge transfer models to data of a new product in a systematic way. We refer to this task as *calibration design*, which has the potential to reduce the number of experiments required for process model calibration.
In this study, a novel metric for calibration design is introduced (Section 2.3.2), which is based on the process dynamics observed for historical products. By optimising this metric, the resulting suggestions in experimental design points maximise the dissimilarity in the final titer among the historical datasets. The reasoning is that certain experimental designs are better suited to reveal differences in cell line behaviour than others. As a hypothesis, choosing these experimental designs, together with knowledge transfer models, leads to model calibration requiring less experiments and resulting in better predictive performance compared to standard DoE approaches, thus aiding process understanding.
The design of parallel experiments with Bayesian optimisation is an ongoing field of research (González & Zavala, 2023), in which popular strategies include the *constant liar* method (Ginsbourger et al., 2010) or a distance-based optimisation of points (De Luca et al., 2023). In the distance-based approach, the first

experiment is determined by Bayesian optimisation, which inherently uses a surrogate model to approximate the objective function over the design space. In the first step, the surrogate model is first queried to identify the maximum of the objective of choice during optimisation. For further experiments, the objective function for the first experiment is augmented by a term that is regulating the distance between suggested designs, thus jointly optimising the objective and the distance (Section 2.3). The constant liar technique as implemented in `skopt`, which is further explained in Section 2.3.1, led to locally clustered suggestions for parallel experiments (supporting information), wherefore the distance-based approach was chosen for calibration design.
In the following, the novel metric is demonstrated in two case studies, using different combinations of similar and dissimilar historical datasets to evaluate calibration design. For benchmarking, we compare the results to a process model that was trained on designs sampled by LHS, which was previously evaluated by Stosch, 2018 to be a well-suited excitation design for hybrid models. To obtain a feasible subset for optimisation, we chose four of our six simulated products and a subset of 7 design factors that determine the calibration design (Section 2.4). In the first case study, all four products A, B, E and F represent lactate-consuming cell lines. Within this case, the processes of products B and E were designed to be similar to each other while A and B differ stronger in their dynamics (see also Section 3.1). Since all products were simulated as cell lines with lactate consumption, we chose a OHE model as the knowledge transfer model for calibration design, which is in line with the findings in Section 3.2 that OHE and meta learning perform equally well on these products.

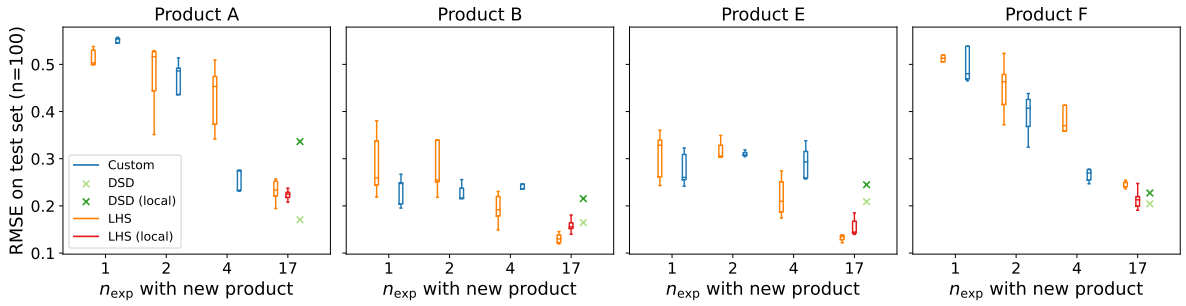

Figure 6: First case study. Relative RMSEs on test set for titer utilising a OHE model trained on new data obtained through various design paradigms: calibration design with custom metric (blue), definitive screening designs (green) and LHS designs (orange, red). OHE models were initially trained on historical 20 experiments from the other three products. Calibration and LHS designs were then performed to identify experiments to retrain the model to the novel product using 1, 2 and 4 new experiments. All four chosen products mimic cell lines that can consume lactate. For 17 experiments, which is the number of experiments required for DSD with 7 factors, we also trained local GP model on data from the new product alone. The weight between distance and metric in Eq 6 was chosen to be $\alpha = 0.0001$ so that both terms are in the same order of magnitude and have approximately equal weight.

The results for the calibration design of 1, 2 and 4 experiments using our metric (Section 2.3.2) or LHS are shown in Fig 6. More precisely, initial OHE models were retrained with experiments of calibration design to improve the predictive performance, which is benchmarked by the relative RMSEs of titer on test datasets of the new product. This measure was chosen since accurate prediction of process variables increases process understanding and is important for process characterisation, e.g. in the context of regulatory demands and QbD. We shuffle through all possible combination of historical datasets within the the case study for better

generalisation.

First, Fig 6 shows that the relative RMSEs of titer on a test dataset with 100 experiments is lower for products B and E as compared to products A and F. Since the OHE model used to evaluate the metric for calibration design is based on the other three products and B and E share a greater similarity, this lower RMSE values are to be expected. The proposed metric based on dissimilarities of historical products outperforms a LHS calibration design for the dissimilar products A and F, especially when four experiments are designed. This indicates that the combination of the proposed metric and the distance works well to spread experiments across the design space, but at the same time optimise for those designs which reveal differences in process dynamics well. For product B and E, RMSE values lower than 0.4 can already be observed when using only one experiment for calibration design, which shows that the initial OHE has a high predictive performance due to the high similarity of historical products.

In a second case study, we tested the proposed calibration design strategy on four products, this time choosing two with lactate consumption (A and B) and two without (C and D). The results are shown in Fig 7.

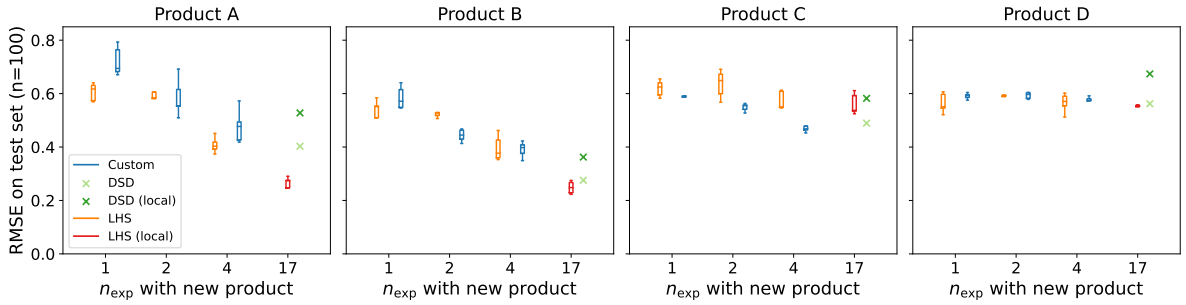

Figure 7: Second case study. Relative RMSEs on test set for titer of a OHE model utilising calibration design with custom metric (blue) and LHS designs (orange). OHE models were initially trained on historical 20 experiments from the other three products. In this case study, two products with lactate consumption (A and B) and two without lactate consumption (C and D) were chose. Calibration design was performed to identify experiments to calibrate the model to the novel product. For 1, 2 and 4 experiments, all data shows the result for OHE models, i.e. knowledge transfer approaches. For 17 experiments, which is the number of experiments required for DSD with 7 factors, we also trained a local model on data from the new product alone, both for LHS (red) and DSD (dark green). The weight between distance and metric in Eq 6 was chosen to be $\alpha = 0.0001$ so that both terms are in the same order of magnitude and have approximately equal weight.

It can be seen that the relative RMSEs are generally greater than observed for the previous case study, which is explained by the fact that a OHE model works better if data is more similar. Furthermore, it can be observed that LHS and the proposed metric for calibration design perform similarly. Compared to a DSD, a well-established strategy for design of experiments during early process development, a similar or even better predictive performance is achieved already with 4 experiments. For a DSD with 7 design factors, 17 experiments are required. First, it can be seen that even with 17 experiments in the training data, a OHE model with DSD (light green) outperforms a local model (dark green), showing the benefit of knowledge transfer models. However, LHS is superior to DSD for sampling 17 experiment, since a local LHS model without data from the historical datasets outperforms even the OHE DSD model in three out of four cases and performs similarly well for the fourth case (product C). Most interestingly, the proposed metric for calibration

design leads to similar or better performance compared to local DSD, which is one of the most chosen designs in early process parameter screening. Compared to LHS for 1, 2 or 4 experiments, the test set performance for the customised metric is similar in most cases and better for product C. In conclusion, calibration design is particularly useful for homogeneous datasets as shown in the first case study, but still performs well in case of heterogeneous historical datasets. This highlights the potential to exploit knowledge transfer in calibration design for process campaigns, even if historical training data is more dissimilar to the product of interest.

3.4 Limitations and future work

In this work, we explored the use of knowledge transfer models to improve prediction of pharmaceutical processes and suggest calibration designs to adapt the process for a new product. While meta learning showed comparable performance for those products which exhibit similarity in the training data, it showed significant potential for cases with few similar products in the historical training data, where the test set RMSEs could be reduced compared to OHE and local models. This should be further investigated with heterogeneous datasets from industrial applications to assess the benefit for real-world applications. Moreover, approaches for similarity assessment between datasets might be exploited to further understand for which use-cases meta learning can be beneficial.

Regarding the calibration design, this study showed high potential of process models utilising knowledge transfer to characterise pharmaceutical processes. However, some aspects of this novel procedure should still be addressed. First, local optimisers were used throughout this study, thus not guaranteeing convergence to a global optimum. In addition to the proposed metric, further objectives for calibration design based on dissimilarity could be investigated, for example by varying the weight of uncertainty in the prediction of historical datasets or introducing weights for individual historical datasets based on their similarity to the new product. Moreover, we focused on final titer as an important performance indicator of a process and work could thus be extended to account for the entire evolution and other variables. In the future, the proposed metric could also be extended to a combination of various features, most importantly including VCD as an relevant influence.

4 Conclusion

In this work, we compared two knowledge transfer modelling methods with local models developed on data of one product only, by using data of a simulated mammalian cell cultivation process, typically used for monoclonal antibody production in the pharmaceutical industry. In a case study with six simulated products, both knowledge transfer methods, i.e. meta learning and OHE models, outperformed local models, especially if only few experiments of the new product were available. Further, we observed that meta learning boosts the predictive performance of GP hybrid models for heterogeneous datasets. For future benchmarking and comparison to methods proposed by others, we provide the simulated datasets in a dedicated repository.

Subsequently, we adopted the OHE knowledge transfer model to identify process conditions that are particularly suited to calibrate the model to data from a new product. For achieving the task, which we coined *calibration design*, we proposed a customised metric. The metric favours those process conditions that lead to the most dissimilar predicted titers in the historical datasets, reasoning that those conditions are most informative to train a knowledge transfer model. We observed that the OHE models trained on experiments obtained through LHS or calibration design with the new customised optimisation metric yield similar test

set RMSEs in the final predicted titer when compared to common approaches such as DSDs. However, much fewer experiments are needed for calibration designs utilising the LHS or customised metric paradigms, making them a promising alternative. The customised metric performs similarly or better than LHS on different homogeneous and heterogeneous datasets, thus presenting an interesting alternative with low risk for inferior model performance. While further studies on industrial data are needed to evaluate the practical application of this novel approach, it shows a new direction for process development workflows.
In the future, our metric could be further extended to more features than only titer. In addition, the combination of meta learning and calibration design to boost the predictive performance should be investigated further. It could also be tested in scenarios where more process knowledge is integrated, i.e. using hybrid GP models that consider first principles. Since calibration design and knowledge transfer approaches seem to be able to reduce the number of experiments for process development significantly, they are of high research interest and could possibly lead to significant savings in biopharma and perhaps other bioprocess industries.

Abbreviations

ARD automatic relevance determination

CHO chinese hamster ovary

DoE Design of Experiments

DSD definitive screening design

GP Gaussian process

LHS latin hypercube sampling

ML machine learning

OHE one-hot enconding

QbD Quality by Design

RMSE root-mean-square error

SE squared exponential

VCD viable cell density

Author's contributions

LH performed data analyses, prepared the figures and wrote the manuscript, with contributions from CW, JP and MVS. CW, JP, GG, AB and MVS contributed to project administration and supervision. All authors were involved in regular project discussions, read and approved the final manuscript.

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Data availability

The data that was used for benchmarking throughout this study is available on Zenodo (DOI: 10.5281/zenodo.10630629).

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Conflict of interest

CW, JP, AB and MVS were employees of DataHow AG at the time of the study.

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