Constraint-Adaptive Active Learning for Pharmaceutical Particle Size Characterization

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INTRODUCTION

- **Probabilistic modelling** approaches are appropriate to develop **uncertainty-aware predictive machine learning** (ML) models to represent complex chemical processes.
- **Gaussian processes**[1] (GPs) are one of the popular probabilistic modelling approaches.
- The premise of this work is about developing GPs to **autonomously** synthesize **pharmaceutical drug particles** in a desired size range in a continuous flow synthesis process.
- **Closed-loop experimentation** provides an efficient and accelerated approach for the above purpose.
- **Active learning**[2,3] (AL) can be used as the computational method for closed-loop experimentation to develop reliable GP models.
- Mathematically, AL is an **optimization problem** of the form:
  - $\max_{\boldsymbol{u}_{\mathrm{lb}} \le \boldsymbol{u} \le \boldsymbol{u}_{\mathrm{ub}}} \psi(\mathrm{Var}(\hat{\mathbf{y}}))$, where $\mathbf{u}$ is the vector of process inputs; $\hat{y} = f(\mathbf{u})$; $f = \mathrm{GP}(\mathrm{mean}, \mathrm{covariance})$; $\psi(\mathrm{Var}(\cdot))$ represents a scalar function of the posterior predictive GP variance.
- The solution of this optimization problem provides the input conditions corresponding to the **largest uncertainty** in the predictions of the GP model.
- By solving active learning sequentially and updating the GP model by means of closed-loop experimentation, **reliable** GP models can be developed using **limited**, **real-time informative** data.

MOTIVATION

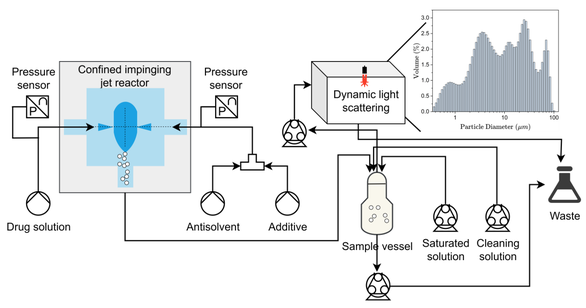


Fig. 1. A simplified schematic of the **NanoAPI** platform for synthesizing drug nanoparticles in continuous flow.

- In the **NanoAPI** platform[4,5], automated flow precipitation experiments in a confined impinging jet reactor[6] were conducted to study how three input variables affect drug particle size and polydispersity.

- The three inputs are:
  1. Total flow rate
  2. Antisolvent to solvent flow ratio
  3. Drug to additive ratio
- The initial goal of the platform was to run automated experiments to develop a reliable GP model that accurately captures the relationship between the inputs and the outputs.
- The platform employed AL for the above purpose.
- The further goal of the platform was to synthesise drugs in a desired size range using the calibrated GP model.

Main challenges were:
- To overcome fouling issues in continuous flow.
- To synthesise drug particles within the size range of dynamic light scattering (DLS) instrument ($< 1\mu\mathrm{m}$).

Operating constraint
- Constraint to bound the operating region that:
  - is non-fouling
  - results in drug particles within the DLS measurement range
- This constraint is unknown and needs to be identified along the development of the GP model.
- Hence the AL can be modified as a **constraint optimization** of the form:

$$\max_{\boldsymbol{u}_{\mathrm{lb}} \le \boldsymbol{u} \le \boldsymbol{u}_{\mathrm{ub}}} \quad \psi(\mathrm{Var}(\hat{\mathbf{y}})) \quad \text{subject to} \quad g(\mathbf{u}) \le 0$$

- with adaptation of the constraint $g(\mathbf{u}) \le 0$.
- For this, we propose:

Constraint-adaptive active learning

METHODOLOGY AND RESULTS

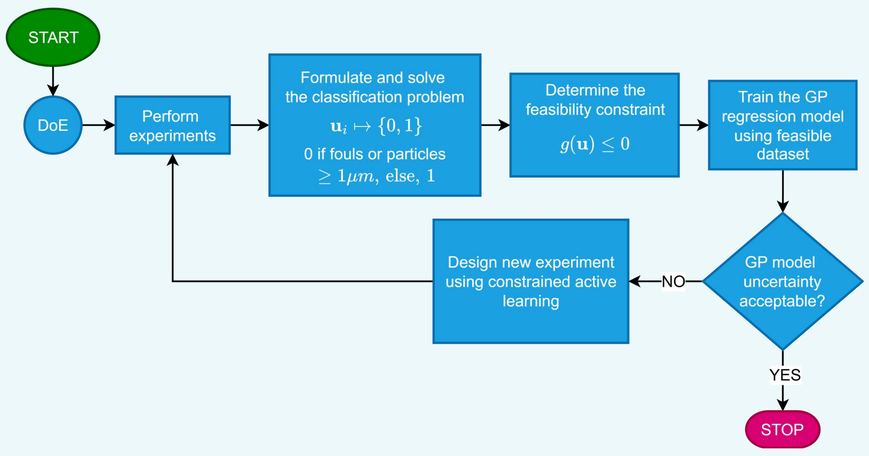


Fig. 2. Flow sheet of the constraint-adaptive active learning for GP model development.

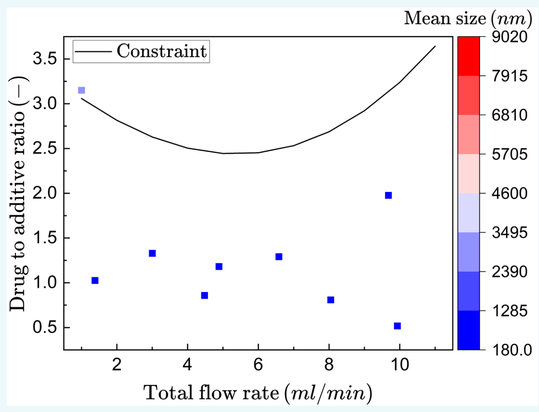


Fig. 3. A feasibility constraint obtained from the classifier model in one of the iterations of the constrained AL.

- Fouling was automatically detected using the pressure sensors provided in Fig. 1.
- An input data point was labelled as 0 if it caused fouling or if it produced drug particles $\ge 1\mu\mathrm{m}$, else it was labelled as 1 (see Fig. 2).
- As shown in Fig. 3, in each AL iteration, a classifier model, trained on the discrete dataset was used to obtain the feasibility constraint $g(\mathbf{u}) \le 0$.
- A **GP regression model** was trained on the size measurements obtained from the **feasible experiments**.
- To generate new training points for the GP regressor, constrained AL was solved sequentially until the model uncertainty was reduced (see Fig. 2).
- The new training points were also utilized to repeatedly modify the feasibility constraint $g(\mathbf{u}) \le 0$.
- Employing gradient-based solvers in PyTorch[7] (trust-region method – minimize_constr) to solve the constrained AL resulted in sub-optimal solutions in some iterations of the AL, as shown in Fig. 4.

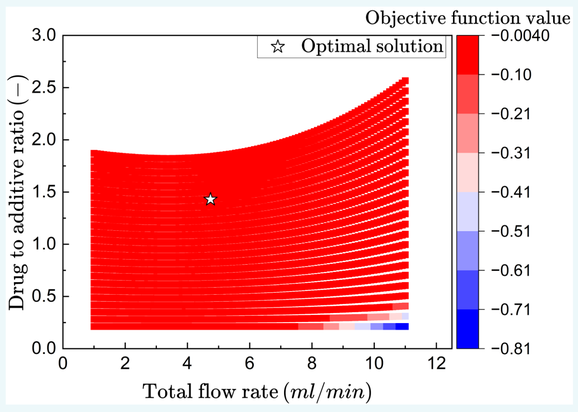
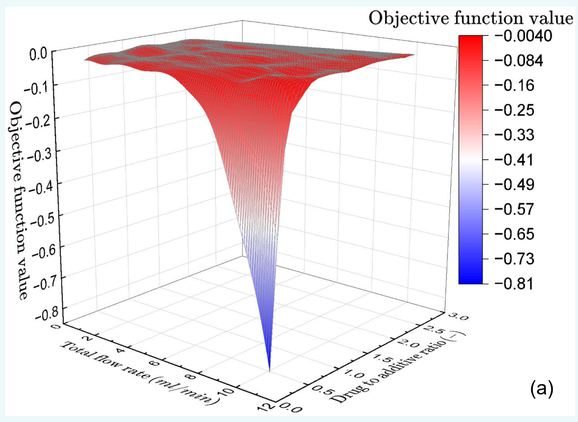


Fig. 4. Gradient-based method leading to a sub-optimal solution in one of the iterations of the constrained AL.



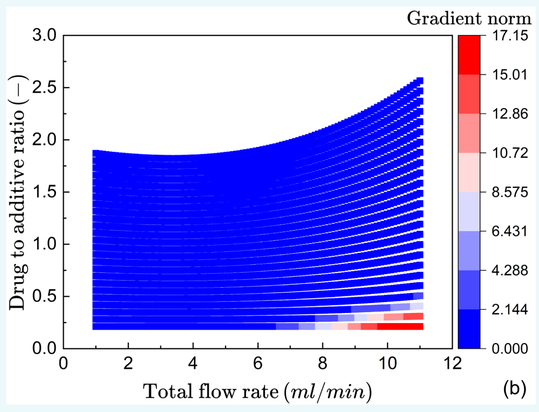


Fig. 5. Causes for the sub-optimal behaviour of the gradient-based methods in the constrained AL. (a) non-smooth objective function surface, (b) large gradient-norm at the optimal point.

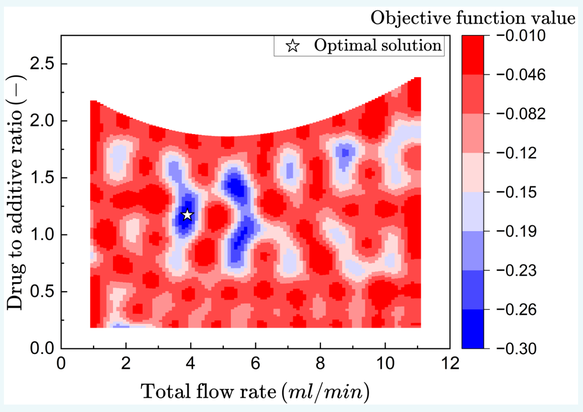


Fig. 6. A combination of derivative-free and gradient-based methods resulted in good performance of the constrained AL.

- Potential causes for the sub-optimal behaviour of the gradient-based solver such as **non-smooth objective function surface** leading to **large values of gradient norm** (L2 norm of the gradient of the objective function with respect to the decision variables) are illustrated in Fig. 5.
- Coupling derivative-free methods along with the gradient-based methods helped to effectively solve the constrained AL problem (see Fig. 6).
- Ultimately, the NanoAPI platform executed the constraint-adaptive AL method to autonomously develop a reliable GP model that maps the relationship between the inputs and the mean size of drug particles in the feasible operating space.
- The predictions of the final GP model, at the end of the constraint-adaptive active learning is provided in Fig. 7. The predictions are pretty much aligned with the measurements.
- Thus, combining constrained AL with automated experiments enabled closed-loop experimentation to **autonomously eliminate undesirable operating regions** and to **autonomously develop reliable predictive models within a narrow desirable region of utility**.

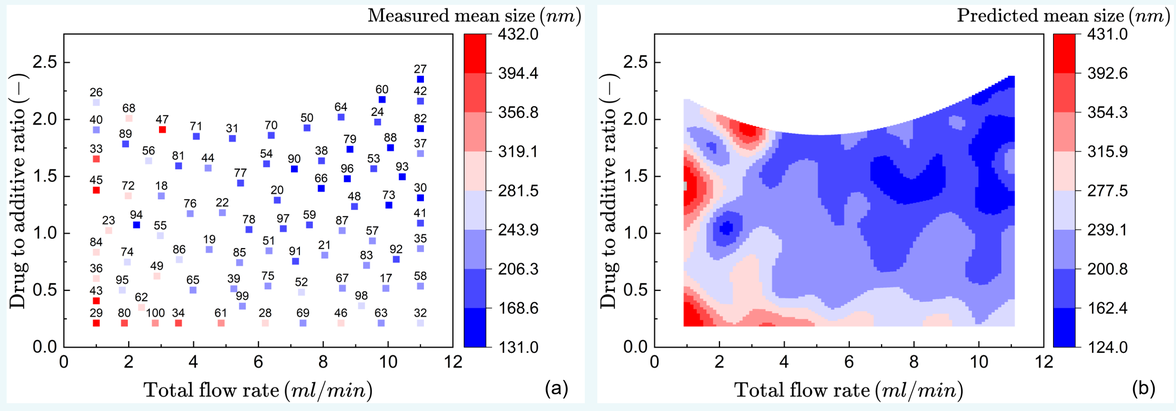


Fig. 7. The outcome of the autonomous GP model development using constraint-adaptive AL. (a) measured drug particle size (labels represent the experiment number), (b) predictions of the final GP model obtained at the end of the AL iterations.

CONCLUSION AND FUTURE WORK

- We developed and applied constraint-adaptive active learning in a flow platform to autonomously synthesise drug particles in desired size ranges.
- Gradient-based solvers produced sub-optimal solutions in active learning.
- Coupling derivative-free methods and gradient-based methods allowed to solve active learning problems effectively.
- Future work will evaluate the platform across a range of drug systems.

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