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Learning-based Control Approach for Nanobody-scorpion Antivenom Optimization

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ABSTRACT

One market scope of bioindustries is the production of recombinant proteins for its application in serotherapy. However, its process's monitoring and optimization present limitations. There are different approaches to optimize bioprocess performance; one is using model-based control strategies such as Model Predictive Control (MPC). Another strategy is learning-based control, such as Reinforcement Learning (RL). In this work, an RL approach was applied to maximize the production of recombinant proteins in *E. coli* at the induction phase using as a control variable the substrate feed flow rate (F_{in}). The RL model was trained using the actor-critic Twin-Delayed Deep Deterministic (TD3) Policy Gradient agent. The reward corresponded to the maximum value of protein productivity. The environment was represented with a dynamic hybrid model. The optimization was evaluated by stages of two hours to check the protein productivity performance. Afterwards, the results were compared with an MPC approach. Finally, the control approaches were trained considering temperature disturbances. The results elucidate that the RL approach could be implemented as a control strategy, reaching values from 0.014 mg/h to 0.079 mg/h through all the optimization stages previously demonstrated to be the optimal ones. Despite exhibiting temperature disturbances, the RL approach demonstrated its robustness by adapting the control action to maintain similar protein productivity values.

Keywords: Model predictive control, Reinforcement Learning, TD3, Protein production, *E.Coli*

INTRODUCTION

Scorpion sting envenoming (scorpionism) is a severe public health issue in developing countries in North Africa, the Middle East, and Central and South America [1,2]. The symptoms associated with scorpion stings are intense local pain, sweating, tachypnea, tachycardia, agitation, pancreatitis, pulmonary edema, hemolysis, necrosis, and, in severe cases, leads to death. The use of antivenom is the only effective treatment against scorpion stings where different types of molecules can neutralize the venom. Those antivenom molecules were commonly obtained from animal origin [1,2].

Advances in serotherapy allowed for the production of recombinant proteins using species such as *E. coli*, becoming one of the critical market scopes of bioindustries [3,4]. Nevertheless, its process's monitoring, control, and optimization are challenging. Different approaches to optimize bioprocess performance exist: model-based control strategies, such as Model Predictive Control (MPC), and learning-based control, like Reinforcement Learning (RL). Dubencovs *et al.* [5] used an MPC to optimize the growth of *E. coli* BL21 (DE3) and the production of two different recombinant proteins, nerve growth factor (NGF) and coat protein of bacteriophage Qβ (Qβ-CP). In their paper, three experiments were conducted: the first focused on finding the optimal "Golden batch" states without any induction, the second considered induction for NGF protein production, and the third considered induction of the bacteriophage Qβ coat protein (Qβ-CP). It was concluded that MPC demonstrates rapid adaptability to various systems, where a meticulous estimation of model parameters could significantly reduce the number of experiments required to optimize the model. The proposed methodology allowed satisfactory control of biomass growth, with deviations between 6-12% compared to the values calculated as the Golden batch. Bonanni *et al.* [6] proposed a deep-learning approach to optimize recombinant protein production using *E. coli*. The authors proposed ML approaches based on a recurrent Neural Network (NN) to predict the optical density (DO) from several process variables such as pH, dissolved oxygen, temperature, etc.

Although the results are prominent, the optimizations were focused on improving cell growth rather than directly maximizing protein production. Additionally, the MPC requires highly detailed knowledge of the process, which must be represented in the model; learning techniques require a large quantity of data [7]. RL appears to be an innovative approach to optimize and control biological processes.

RL refers to mapping situations to actions by maximizing a numerical reward signal. The goal of the RL agent is not to indicate which actions to take; it must discover which actions yield the most reward by associating them with the outcomes they produce [8]. In other words, the goal is to find the best sequence of control actions that generate the optimal outcome by interacting with its environment [9]. In RL, the agent interacts with the environment and learns which actions to take by trial and error. Each interaction implies executing an action over the environment. The agent receives a reward for its actions. In this manner, the agent learns the best control policy that maximizes the total accumulated reward [7,9]. The majority of the RL learners are based on policy gradient methods. This method directly obtains a policy by maximizing a desired performance index [10]. Petsagkourakis *et al.* [10] applied RL over three computational case studies. The first study is a "real" photo-production system; however, the exact model is unknown, and a simplified deterministic model is assumed. In the second case, however, it was assumed that the simplified model is supposed to follow a Wiener stochastic process. The last case was a photoproduction of phycocyanin synthesized by *cyanobacterium Arthrospira platensis*. The results highlight the possibility of obtaining a near-optimal policy for a stochastic system when true dynamics are unknown. However, RL has no applications for recombinant protein production in *E. coli*.

In this work, an actor-critic agent was selected due to the continuous actions space property. For a determinate observation action, the critic returns an approximation of the policy value. For a determinate observation, the actor returns the action that maximizes the policy value. Overall, the actor learns the best action to take using the feedback from the critic.

This work proposes a learning-based RL approach to optimize the glucose feed flow rate at the induction phase to maximize protein productivity. The contributions of this work are summarized as follows:

- A learning-based RL approach was designed to maximize protein productivity by manipulating the feed flow rate at the induction phase
- An actor-critic Twin-Delayed Deep Deterministic (TD3) policy gradient Agent was used for the first time over a protein production process using *E.coli*
- The impact of temperature disturbances was considered in the training of the TD3 agent
- The results demonstrated that the RL approach produced superior outcomes in comparison to the MPC approach

MATERIALS AND METHODS

Optimization problem statement

The process variables correspond to Glucose (S), Biomass (X), Protein (P), and Volume (V) of the liquid phase in the bioreactor; The Manipulated variables refers to the glucose feed flow rate (F_{in}). The aim is to maximize protein productivity ($Pprod = P \cdot V/t$) through process simulation by finding the optimal F_{in} profile at induction phase ($t \geq 8h$). The optimization strategy was divided into six different control intervals "stages" from the beginning of the induction phase ($t \geq 8h$) until the end of the process ($t = 20h$), as shown in Figure 1.

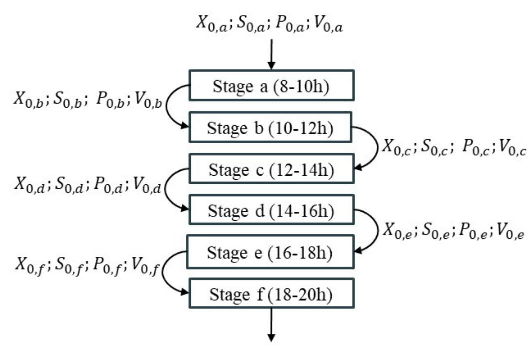

Figure 1. Stages of the optimization strategy. Protein production using *E. coli* CH10-12 with an induction temperature of 28°C.

The in-Silico experiment was conducted for protein production using *E. coli* CH10-12 with an induction temperature of 28°C. In this work, It was considered one of the specific conditions reported in Alonso Villela *et al.* [11]; The simulated conditions were conducted in batch phase at $2L$ and 37°C with an initial glucose concentration of $10 g_{glucose}/L$ ($pO_2 > 15\%$, $pH = 6.8$) for $3.4h$. Then, in the fed-batch phase at 37°C the glucose feed was $300g_{glucose}/L$ with a flowrate $1.0 \times 10^{-3}L/h$ for $8.0h$. Afterwards, the inductor ($1mM$ of isopropyl- thiogalactopyranoside IPTG) was added to start protein production, and temperature was lowered to 28°C.

It is assumed that the optimization stage "a" started at $8h$, considering as inputs the last point of the feed batch process, and successively the output of each optimization stage corresponds to the input of the next stage. This guarantees to check the $Pprod$ performance every two hours until the final process time ($t = 20h$).

Dynamic hybrid model

Since the optimization will be conducted through process simulation, it is used the dynamic hybrid model (DHM) for the nanobody-based antivenom (protein) production process proposed by Corrales *et al*. [12]. The model is referred to as dynamic because the estates are represented by differential equations based on the first principles mass balances Eq. (1)-(4), and hybrid due to the integration of machine learning algorithms to estimate kinetics that are not easier to establish, such as the specific productivity of the protein production Eq. (5)-(4).

$$\frac{dX}{dt} = r_X - X\frac{F_{in}}{V} \tag{1}$$

$$\frac{dS}{dt} = \frac{F_{in}}{V}S_{in} - r_S - S\frac{F_{in}}{V} \tag{2}$$

$$\frac{dP}{dt} = r_P \tag{3}$$

$$\frac{dV}{dt} = F_{in} \tag{4}$$

with X and S in g/L; P in mg/L; V in L; F_{in} (L/h) is the glucose feed flow rate, with $S_{in}(g/L)$ as the concentration of glucose; r_X $(g/L/h)$; and r_S $(g/L/h)$ the production rate of biomass and glucose, respectively.

The production rate of proteins $r_P(mg/L/h)$ is defined as Eq. (5).

$$r_P = \begin{cases} 0 & \textit{if there is not induction} \\ q_P X & \textit{if there is an induction} \end{cases} \tag{5}$$

q_P $(mg_{protein}/g_{CDW}/h)$ intended for the specific productivity of the protein production, which was modeled using a Radial Basis Function (RBF) Support Vector Machine (SVM) learner. The SVM was trained with experimental data provided by in Alonso Villela *et al*. [11] as Eq. (6).

$$q_P = SVM_{Model}(\mu, T) \tag{6}$$

with μ $(1/h)$ and $T(°C)$ as the specific growth rate and process temperature. The algorithm was trained using a 5-fold cross-validation using the optimized hyperparameters: $C = 0.4165$, $\varepsilon = 0.0329$, and $\sigma = 0.0825$.

RL DEVELOPMENT

Reinforcement learning training

Figure 2 shows the structure of the learning-based RL training. The actor and critic networks are initialized with random parameters to obtain an initial value of F_{in}. Similarly, the dynamic model is initialized using the final conditions of the fed-batch process (X_0, S_0, P_0, V_0).

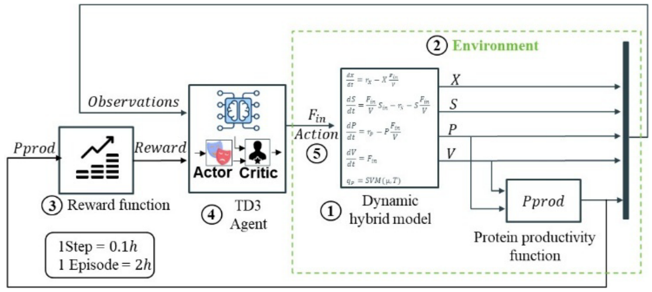

Figure 2. RL structure for protein productivity optimization. Numbers 1-5 in the Figure corresponds to the diagram workflow.

For each episode, *i.e.*, for the subsequent two hours of induction, the environment simulates a single fixed step (0.1h), the observations $(X, S, P, V + Pprod)$ are sent to the TD3 agent, and it is calculated the reward $(Reward)$. Finally, the agent policy (actor-critic interaction) is updated and the new action (optimal F_{in}), subject to $0.001 \leq F_{in} \leq 0.020\ L/h$ and $1.5 \leq V \leq 5.0\ L$, is computed and sent back to the environment. This process is repeated until the maximum number of episodes is reached (max number of episodes=1000). An additionally restriction is imposed to the agent in case of achieve a physical constraint $1.5 \leq V \leq 5.0\ L$.

The workflow is summarized as follows [7]:

```
    1. Initialize the environment (X0,S0,P0,V0)
While stop criterion not satisfied (max number
of episodes):
        for each step in an episode:
    2. Simulate the environment for a single
       step (0.1h)
    3. Provide the observations (X,S,P,V+Pprod)
       to the TD3 agent and calculate the re-
       ward (Reward)
    4. Perform the policy iteration (actor-
       critic interaction)
    5. Provide action to the environment (Fin)
       end for
end while
```

Environment

In learning-based control, the DHM and the computation of $Pprod$ are considered the environment (representation of the process).

Agent

The actor-critic Twin-Delayed Deep Deterministic (TD3) Policy Gradient Agent was used due to the continuous action-space property of the environment, and NN's were used as function approximators for the actor and critic. The critic NN presented an Observation/Action path comprising three layers with 64/32/32 nodes per layer and 2 ReLU activation functions. The actor NN presented an Observation patch consisting of one layer with 32 nodes and a Tanh activation function. The training options are reported in Table 1.

Table 1: Training options for the TD3 RL agent.

Optimizer	Adam
Max Episode Number	1000
Simulation time (h)	2
Agent sample time (h)	0.1
Episode Steps	20
Total Agent Steps	20000
Experience Buffer Length	1×10^{6}
Mini batch size	100
Standard deviation	0.3
Standard deviation decay rate	1×10^{-5}
TargetSmoothFactor	1×10^{-3}
DiscountFactor	0.9
LearnRate	Critic= 1×10^{-3}; Actor= 1×10^{-4}
GradientThreshold	Critic= Actor= 1.0
Total Agent Steps	20000

Reward Function

The TD3 RL agent learns the optimal policies by maximizing the reward function. In this case it corresponds to the final value of $Pprod$, which is calculated as in Eq (7)

Model Predictive Control

The results of the learning-based control approach were compared with a model-based control approach in terms of an MPC; the open loop optimization problem is represented in Eq. (7).

$$\max_{\{F_{in}\}} (Pprod = P \cdot V/t) \tag{7}$$

$$Subject\ to \begin{cases} Equations\ 1-4 \\ 0.001 \leq F_{in} \leq 0.020\ L/h \\ 1.5 \leq V \leq 5.0\ L \end{cases} \tag{8}$$

To maintain conditions similar to the RL approach, in the MPC, the goal was to optimize the $Pprod$ every $2\ h$ with a prediction horizon of $2\ h$ as a manipulated variable the F_{in} and subject to the constraints of Eq. (8). In this work, the time step (solver step) of the DHM was fixed at $0.1h$ to allow the comparison between the two approaches.

RESULTS AND DISCUSSION

All simulations were run using a 13th Gen Intel® Core(TM) i7-13800H 2.50 GHz, 32 GB RAM computer. The *fmincon* function from MATLAB® was used to obtain optimal feed flow rate performance to develop the MPC control. The TD3 RL agent from the reinforcement learning toolbox from MATLAB® was used to develop the RF.

RL training results

Figure 3 shows the results of the training using the TD3 RL agent. In the optimization stage "a" (Figure 3a), the episode reward ($Ep\ rew$) and the average reward ($Av\ rew$) started at approximately 0.13 until episode 280, where it converged to 0.14. In the following stages, the $Ep\ rew$ and $Av\ rew$ increased to 0.45 (stage b), 0.78 (stage c), 1.10 (stage d), 1.36 (stage e), and 1.57 (stage f). This is expected since $Pprod$ depends on protein concentration and process time, increasing $Av\ rew$. The average rewards showing the highest variability occurred in stage "a", while the other stages stabilized during the first episodes. This is due to the learning limitation given by the nature of the optimization; each starting point depends on the previous output conditions. A statistical evaluation ($Ev\ Stat$) was performed with a frequency of 100 episodes considering a number of 50 episodes. In all optimization stages, the $Ev\ Stat$ (red squares in Figure 3) fits with the average reward, indicating that the agent's training is appropriately done.

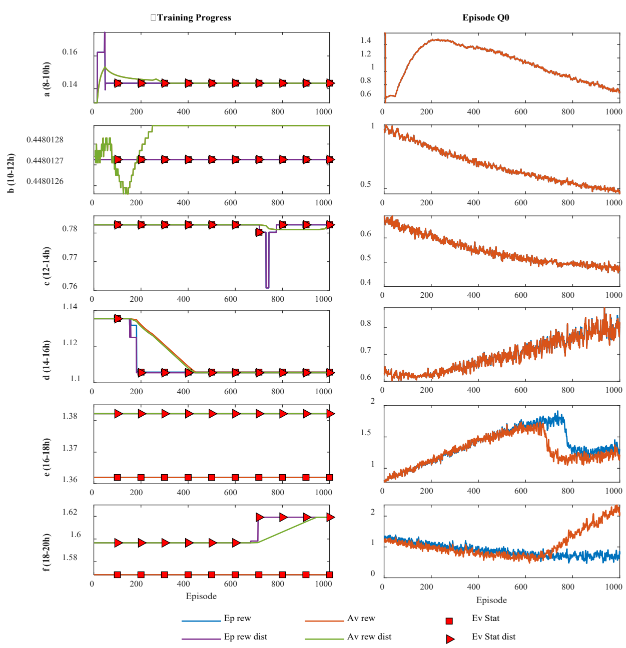

Figure 3. RL training progresses every 2 hours at the induction stage. The episode reward (Ep rew), Average reward (Av rew), and Statistical evaluation (Ev Stat). The variables with temperature disturbances are indicated as dist.

RL and MPC test

Figure 4 displays the results of evaluating the MPC and RL optimizations. It is observed how the dynamics of variables S, X, and V changes over the bath, fed-batch, and induction phases. Additionally, it is displayed the optimized F_{in} and the $Pprop$ respond to these actions. Temperature disturbance at induction phase is presented to relate it with the pair F_{in} action – $Pprod$ response.

The dynamic variables S, X, V, and P presents different behaviors with both approaches. Table 2 summarizes the main results. The RL approach suggests maintaining a $F_{in} = 0.02\ L/h$ in the optimization stages "a"-"c" and then changing to $F_{in} = 0.001$ L/h in optimization stages "d"-"f". In contrast, the MPC approach suggests maintaining a $F_{in} = 0.02\ L/h$ in stages "a", "d"- "f", and reducing to $F_{in} = 0.0014$ L/h and $F_{in} = 0.019\ L/h$ in stages "b" and "c", respectively. Those changes represent a $Pprod$ difference between the MPC and RL of 0.016mg/h, 0.009mg/h, 0.006mg/h, 0.009mg/h, and 0.012mg/h thought stages "b", "c", "d", "e", and "f" (see Table 2).

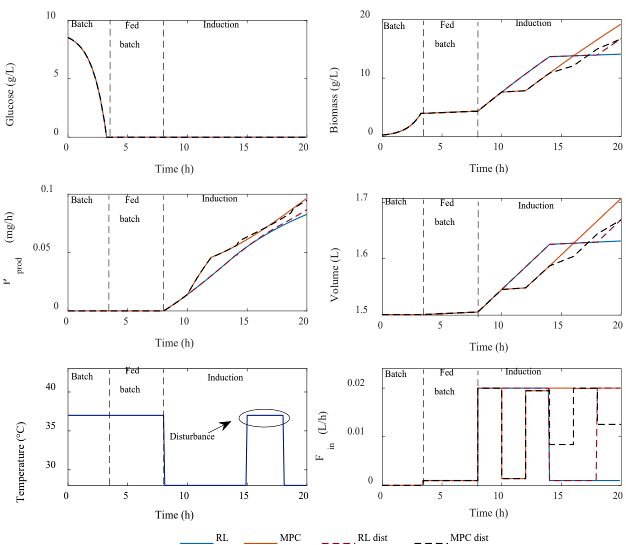

Figure 4. Dynamic behavior results with the MPC and TD3 RL at induction temperatures of 28°C. States: Glucose (S), Biomass (X), Protein (P), and Volume (V); Manipulated variable: glucose feed flow rate (F_{in}); Optimized variable: protein productivity ($Pprod$).

Given the variability in the results obtained from both approaches, the protein yield ($Pyield$) was calculated at the end of each optimization stage, Eq. (9). The $Pyield$ accounts for the relation between the protein produced and the quantity of substrate added in each optimization step.

$$Pyield = \frac{P \cdot V - P_0 \cdot V_0}{Glu_0 \cdot V_0 + Glu_{in} \cdot F_{in} \cdot t_{induction}} \quad (9)$$

P_0, Glu_0, and V_0 refers to the protein and glucose concentrations, and volume at the beginning of each optimization stage. $t_{induction}$ is the duration of the optimization stage.

The RL shows the highest $Pyield$ increase from stage "c" to "f" (Table 2), which indicates that the F_{in} profile exhibited with the RL approach could be a better alternative to optimize the protein production, *i.e.*, the optimal control policy the training of the TD3 agent and the use of the DHM as environment permits to find the optimal F_{in} actions to maximize the $Pprod$. In summary, it can be concluded that although MPC achieves higher $Pprod$ than RL, it requires significantly more F_{in}. RL can achieve competitive $Pprod$ with MPC while using less F_{in}.

Table 2: Optimization results with MPC and RL approaches.

Stage	Fin (L/h)	$Pprod$ (mg/h)	$Pyield$ (mg/g)	Average optimization time (s)*
MPC				
a	0.020	0.014	1.173×10^{-2}	0.2490 0.2821
b	0.001	0.046	4.890×10^{-1}	0.4084 0.5051
c	0.019	0.056	1.929×10^{-2}	0.7140 0.8661
d	0.020	0.068	2.541×10^{-2}	0.1021 0.3133
e	0.020	0.082	3.227×10^{-2}	0.2684 0.3115
f	0.020	0.091	3.880×10^{-2}	0.2046 0.5431
RL				
a	0.020	0.014	1.173×10^{-2}	0.8534 3.8471
b	0.020	0.030	1.843×10^{-2}	0.1512 0.5540
c	0.020	0.047	2.579×10^{-2}	0.1884 0.4821
d	0.001	0.062	5.437×10^{-1}	0.1968 0.5925
e	0.001	0.073	5.506×10^{-1}	0.6449 0.3126
f	0.001	0.079	5.576×10^{-1}	0.3794 0.4553
$Pprod$ difference+	Stage a= 0.000; Stage b= 0.000; Stage c= 0.016; Stage d= 0.009; Stage e= 0.006; Stage f= 0.009			

*Without (first line) and with (second line) temperature disturbance. +It corresponds to the difference MPC $Pprod$-RL $Pprod$.

Temperature Disturbance analysis

A temperature disturbance is simulated between 15 and $18h$, *i.e.*, the temperature increased from 28 to 37°C between the optimization stages "d" and "e" (see temperature in Figure 4). Figure 3 displays the training results for optimization stages "a" to "d". The $Ep\ rew$ and $Av\ rew$ were the same as the process without disturbances. In the optimization stages "e"-"f", the $Ep\ rew$ and $Av\ rew$ differ, which is related to the citric episode $Q0$. This means the critic expected different cumulative $Q0$ values for each step episode with and without temperature disturbance. Figure 4 presents the behavior of dynamic variables considering the temperature disturbances. Until $14h$, both control approaches followed the same behavior, with and without disturbance.

The RL follows the same behavior with and without temperature disturbance. In the subsequent optimization stages, both approaches optimized F_{in} to maintain the $Pprod$ differences $< 0.016 mg/h$, *e.g.*, the RL approach suggest to change F_{in} from 0.001L/h to 0.02L/h in the last optimization stage "f" to maintain similar productivities with and without temperature disturbances. This implies that the optimal control policy can adapt the control actions (optimal F_{in}), including temperature disturbances. Although the MPC approach presented the lowest average optimization time (see Table 2) concerning the RL approach, the latest is preferred due to its performance.

CONCLUSIONS

Model Predictive Control and Reinforcement Learning approaches were explored to optimize protein production in *E. coli*. The optimization was evaluated by stages of two hours to check the protein productivity performance at the induction phase. Protein productivity values of $0.091 mg/h$ and $0.079 mg/h$ were reached with the MPC and RL approaches after $20h$ of process. Nevertheless, the latest exhibited the highest $Pyield$ increase through the optimization stages "c" to "f", indicating that this approach produces a higher quantity of protein per hour by applying a lower F_{in} concerning the MPC approach. The results suggest that the RL approach yields an optimal control policy by interacting with the environment (dynamic hybrid model) and can adapt the control action during the optimization process, accounting for temperature disturbances. In future work, rewards that include protein productivity and yield can be studied, enabling a better understanding of the process. Additionally, the integration of two Critic NNs in the training of the TD3 agent can be applied, allowing for enhanced process optimization through the learning-based strategy.

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