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Flexible Nets for the Optimization of IgG Production in CHO cells

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Introduction

Monoclonal antibodies are vital therapeutic tools. Their effectiveness depends on low immunogenicity and proper structural processing [1], which is best achieved using mammalian systems like Chinese Hamster Ovary (CHO) cells. CHO cells are widely-used for antibody production. Though advances have greatly increased yields, large-scale production remains costly. Traditional optimization methods face limitations in capturing metabolic complexity. Computational modeling offers a more efficient path by simulating cell behavior and guiding experiments. Here, we present a new framework to manage multi-scale, uncertain, and nonlinear biological systems.

Flexible Nets: IgG synthesis modeling

Flexible Nets (FNs) [2] consist of two connected subnets, an event net and an intensity net, each having three types of vertices:

- ○ Places (metabolites). In Figure 1: *Ala*, *Arg*,..., and *IgG*.
- ▭ Transitions (reactions). In Figure 1: R_1, R_2, and R_3.
- • Handlers: capture how the a reaction modifies the concentration of metabolites (event handler, e.g., v_1 in Figure 1) and how the concentration of metabolites modulates the reaction rates (intensity handler, e.g., h_s or s_{sout} in Figure 2).

We used the iCHOv1 model which contains the metabolic network of CHO cells [3]. The model was enriched with the reactions:

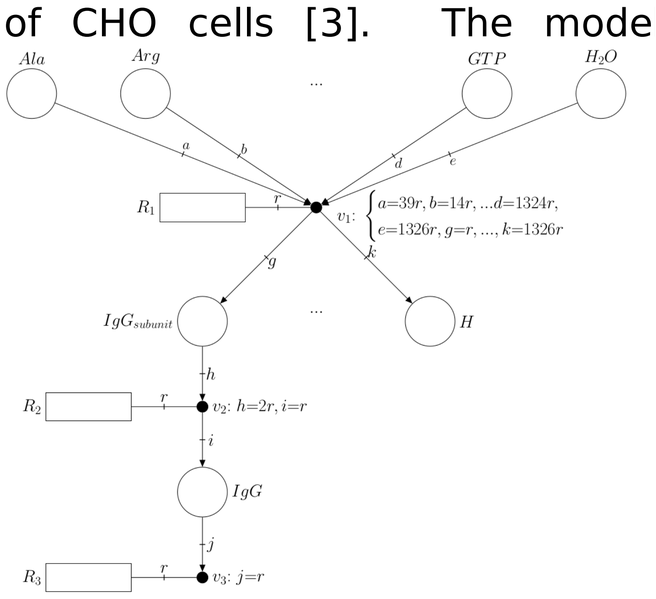


Figure 1. *FN modeling the reactions that produce IgG in the iCHOv1 model.*

R_1: $39Ala + ... + 1326H_2O \rightarrow IgG_{subunit} + ... + 1326H$
R_2: $2\ IgG_{subunit} \rightarrow IgG$
R_3: $IgG \rightarrow \emptyset$

An FN graphical representation of these reactions is shown in Figure 1. The labels a, b, c, etc. model the stoichiometry of each reaction. For instance, $a = 39r$ in reaction R_1 means that 39 moles of the amino acid *Ala* react to produce a mole of the $IgG_{subunit}$.

Flexible Nets: Bioreactor dynamics

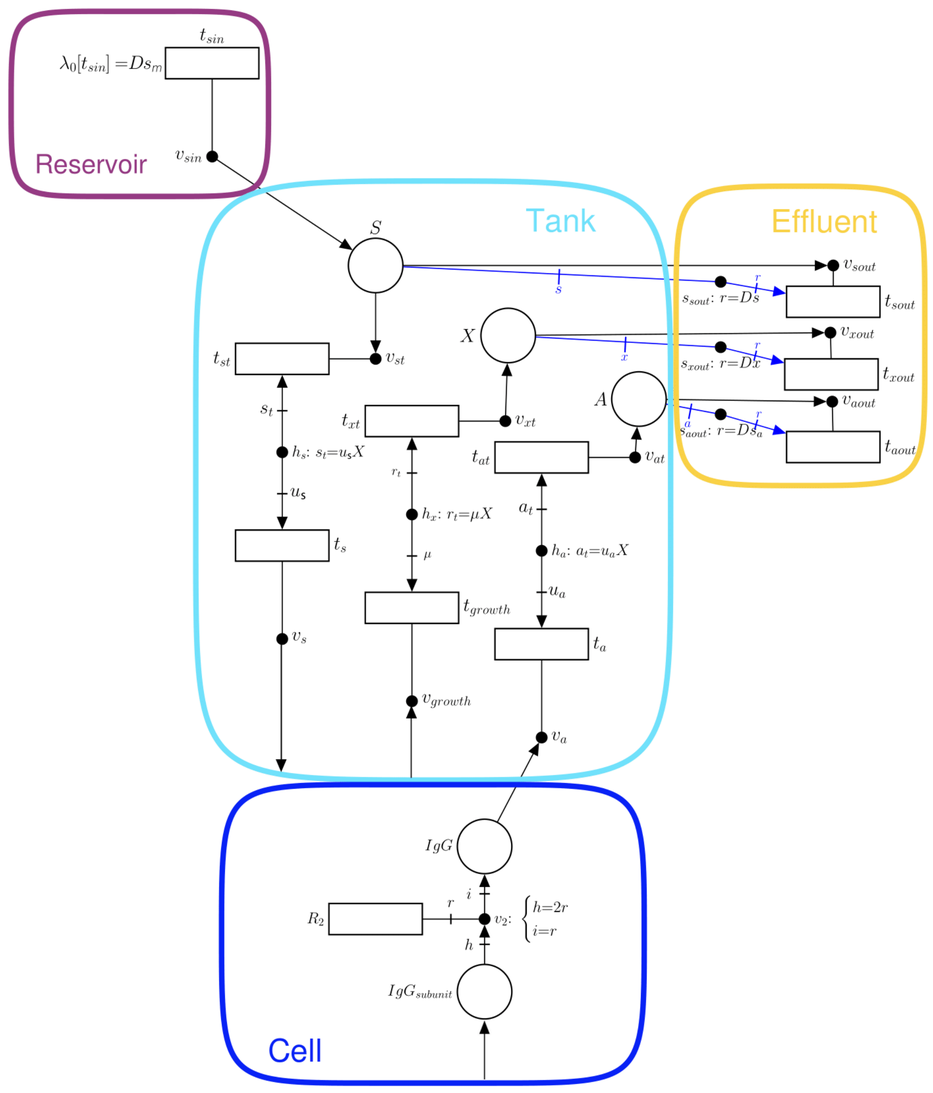
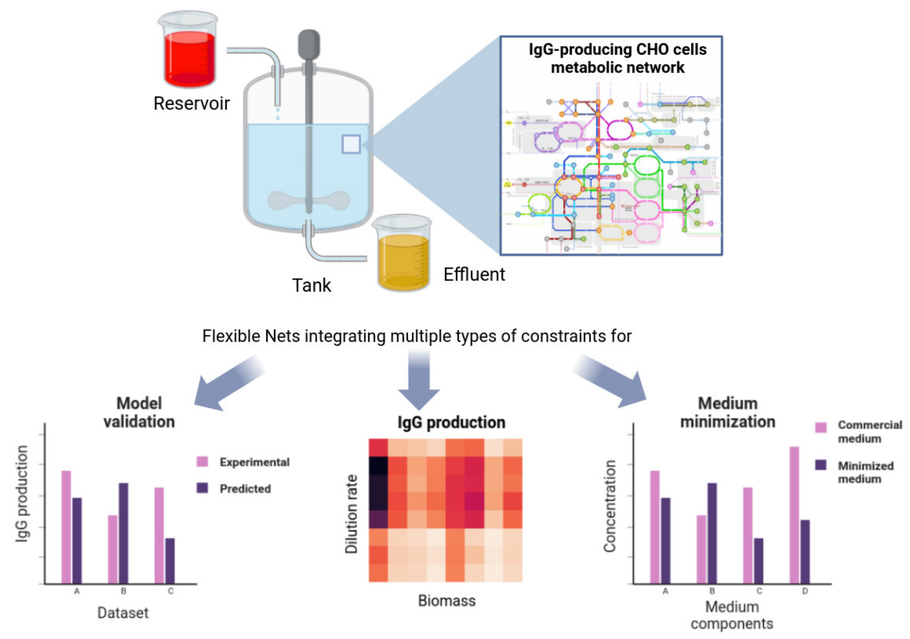


Figure 2. *Bioreactor consisting of three compartments: reservoir, tank and effluent. The blue rectangle "Cell" at the bottom contains the whole metabolic network of iCHOv1.*

Graphical abstract



Flexible Nets integrating multiple types of constraints for

Results

1. Model Validation

	HP
Experimental	$2.02 \cdot 10^{-5}$
Model	$2.04 \cdot 10^{-5}$
Relative error	$9.9 \cdot 10^{-3}$

Table 1. *Antibody production in mmol $g_{DW}^{-1}\ h^{-1}$.*

2. IgG synthesis Optimization

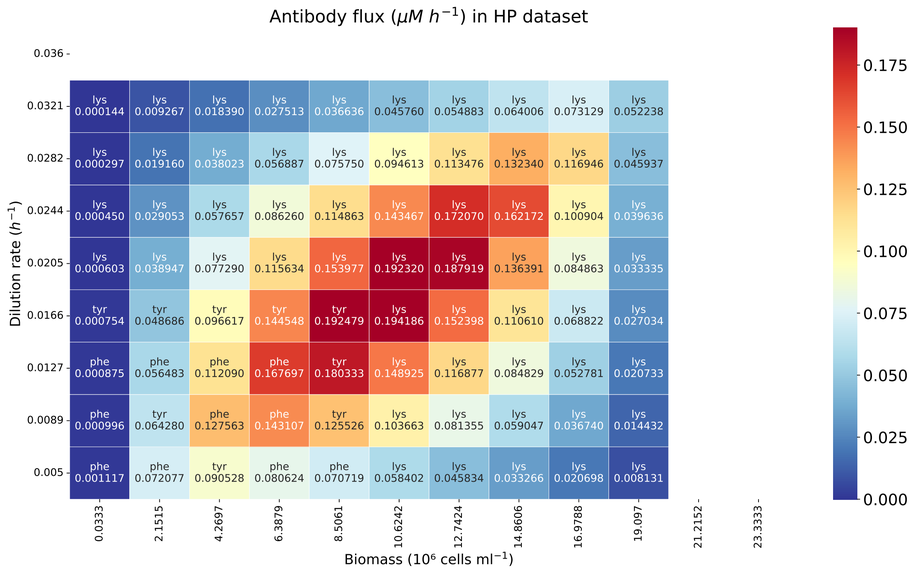


Figure 3. *IgG synthesis reaction flux depending on the dilution rate and biomass [3].*

3. Medium minimization

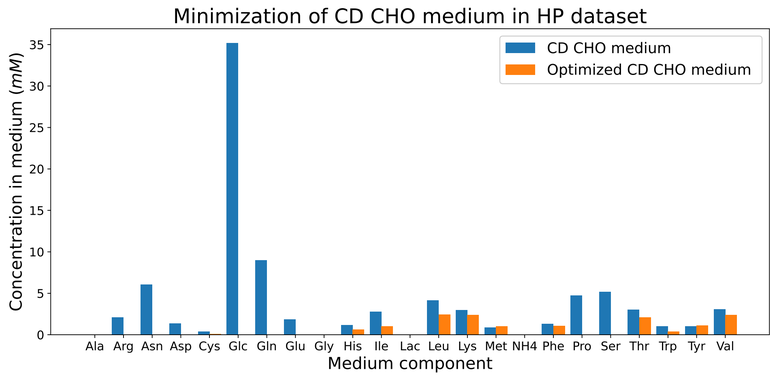


Figure 4. *Bar plot representing the concentrations of each nutrient in the original CD CHO medium (blue bars) and in the optimized medium according to the FN-based model (orange bars).*

Conclusions

Flexible Nets can integrate intracellular metabolic fluxes with macroscopic bioreactor dynamics under a multi-scale modeling framework, enabling simulation of complex, dynamic, and nonlinear systems. The developed FN model successfully predicted IgG antibody production and medium optimization.

References

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