Supplementary Materials

Optimization of Bacteriophage Production in Batch Bioreactors

Gabriel Castro Sahli*, Marina Contreras Lafaury*, Fernanda Santos Astudillo*
Jairo Pinto Sánchez*, José Ricardo Pérez Correa*
*Department of Chemical Engineering and Bioprocesses, Pontificia Universidad Católica de Chile
Emails: gabriel.cs@uc.cl, marina.contreras@uc.cl, fpsantos@uc.cl, jbpinto@uc.cl, jperezc@uc.cl

TABLE S1: Lower and upper bounds for parameter estimation with references

Parameter	Lower bound	Upper bound	Reference
rn	0.1	2.0	[1]
K	10^8	10^{10}	[2]
a	10^{-10}	10^{-2}	[3]
ki	10^{-10}	10^{-5}	[4]
s	0.6	5.0	[4]
rr	0.1	1.0	[5]
b	20	200	[6]
p_decay	10^{-4}	10^{-1}	[7]

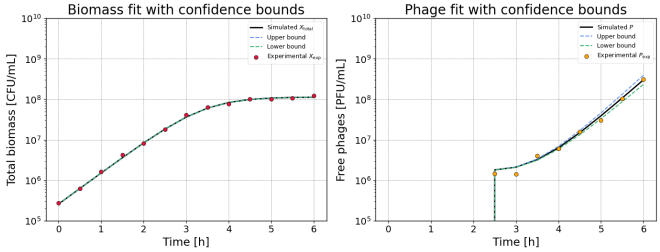


Fig. S1: Model fit and confidence bounds for biomass and phage concentration.

TABLE S2: Comparison of Model Calibration Iterations

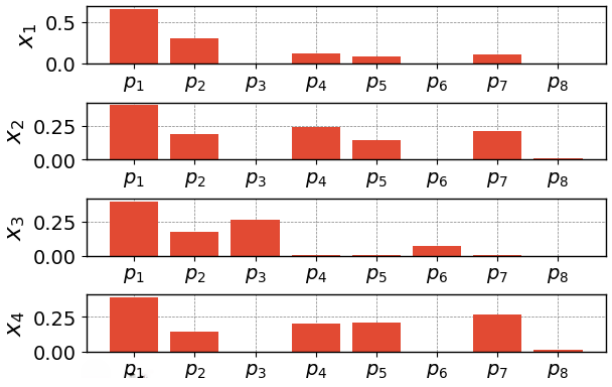
Iteration	R^2	Adj. R^2	AICc	BIC
8p	0.9953	0.9934	827.58	827.65
-decay	0.9926	0.9903	834.37	835.96
-decay -rr	0.9953	0.9941	818.35	820.94
-decay -rr -a	0.9934	0.9921	823.40	826.53
-decay -rr -a -s	0.9962	0.9957	805.59	808.88

TABLE S3: Comparison of t-values across model simplification steps

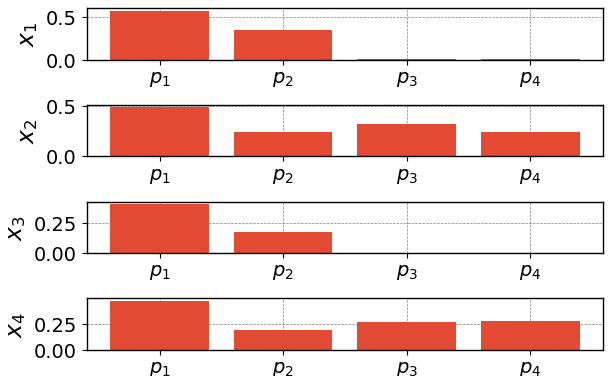
Parameter	8p	-decay	-decay -rr	-decay -rr -a	-decay -rr -a -s
r_n	37.204	47.054	92.512	57.769	86.865
K	19.545	20.013	23.553	31.017	43.244
a	5.646	6.867	0.031	—	—
k_i	10.096	2.959	30.867	3.334	3.212
s	2.885	1.741	6.201	1.889	—
r_r	1.546	1.718	6.529	—	—
b	3.141	1.803	—	1.948	3.253
p_{decay}	0.367	—	—	—	—

TABLE S4: Non-significant parameters in each model iteration ($|t| < 2$)

Iteration	Non-significant parameters
8p	r_r, p_{decay}
-decay	s, r_r,b
-decay -rr	a
-decay -rr -a	s,b
-decay -rr -a -s	—



(a) Sensitivity with 8 calibrated parameters



(b) Sensitivity with 4 calibrated parameters

Fig. S2: Comparison of mean relative sensitivities before and after model reduction.

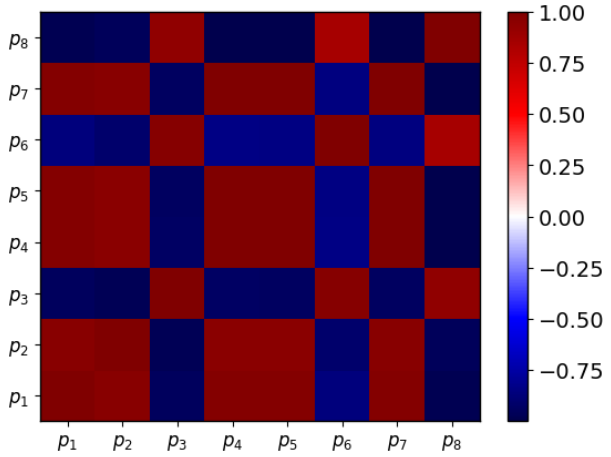


Fig. S3: Correlation matrix between parameters of the full model (8 parameters).

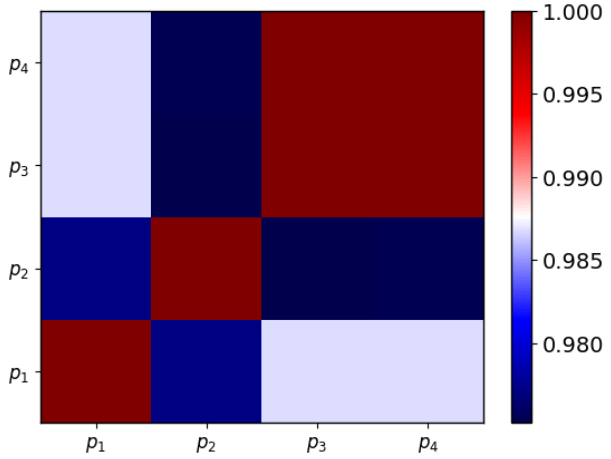


Fig. S4: Correlation matrix between parameters of the reduced model (4 parameters)

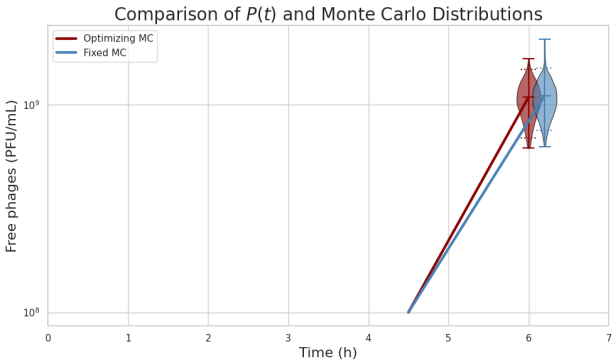


Fig. S5: Comparison of final phage titer distributions in Monte Carlo simulations

TABLE S5: Parameter Values Across Model Calibration Iterations (Split View)

Parameter	8p	-decay	-decay -rr
r_n	1.81872	1.77619	1.82063
K	1.06399×10^8	1.16129×10^8	1.06356×10^8
a	4.99278×10^{-6}	0.00954×10^{-3}	4.99642×10^{-6}
k_i	5.96398×10^{-9}	1.61681×10^{-9}	5.99062×10^{-9}
s	0.600012	2.77948	0.600012
r_r	0.582558	0.582064	—
b	20.4265	23.1149	20.3955
p_{decay}	0.0996885	—	—

TABLE S6: Parameter Values Across Model Calibration Iterations (Split View)

Parameter	-decay -rr -a	-decay-rr-
r_n	1.77024	1.77408
K	1.1562×10^8	1.14137×10^8
a	—	—
k_i	1.5734×10^{-9}	1.86483×10^{-10}
s	2.47758	—
r_r	—	—
b	24.6669	194.213
p_{decay}	—	—

REFERENCES

[1] Z. Yu, T. Luong, S. Banuelos, A. Sue, H. Ryu, R. Segal, D. R. Roach, and Q. Huang, "Leveraging mathematical modeling framework to guide regimen strategy for phage therapy," *PLOS Complex Systems*, vol. 1, no. 3, pp. e0000015–e0000015, 2024.

[2] L. K. Strawn and M. D. Danyluk, "Fate of *Escherichia coli* o157:h7 and salmonella spp. on fresh and frozen cut mangoes and papayas," *International Journal of Food Microbiology*, vol. 134, no. 3, pp. 169–177, 2009.

[3] J. Pan, W. Li, J. Ni, K. Wu, I. Konigsberg, C. E. Rivera, C. Tincher, C. Gregory, X. Zhou, T. G. Doak, H. Lee, Y. Wang, X. Gao, M. Lynch, and H. Long, "Rates of mutations and transcript errors in the foodborne pathogen *Salmonella enterica* subsp. *enterica*," *Molecular Biology and Evolution*, vol. 39, no. 4, p. msac081, 2022.

[4] Y. Shao and I. Wang, "Bacteriophage adsorption rate and optimal lysis time," *Genetics*, vol. 180, no. 1, pp. 471–482, 2008.

[5] L. Zeng, M. Hu, C. Zheng, Q. Zhou, Z. Wang, X. Zhang, F. Liu, and Y. Sun, "Fitness trade-offs in phage cocktail-resistant *Salmonella enterica*," *Microbiology Spectrum*, vol. 10, no. 37, pp. e02914–22, 2022.

[6] S. B. Santos, E. E. Fernandes, C. M. Carvalho, S. Sillankorva, and V. N. Krylov, "Selection and characterization of a multivalent salmonella phage and its production in a non-pathogenic *escherichia coli* strain," *Applied and Environmental Microbiology*, vol. 76, no. 18, pp. 6926–6933, 2010.

[7] J. J. Bull, B. R. Levin, and I. J. Molineux, "Growth-dependent predation and generalized transduction of bacteriophages," *mBio*, vol. 13, no. e9040582, 2022. Report decay rates between 10^{-3} and 10^{-1}h^{-1}.