

Supplementary information

Technoeconomic analysis of intensified PEGylated biopharmaceutical recombinant protein

production: Alpha antitrypsin as a model case

Ordinary differential equations of Fed-batch production bioreactor

1. Batch phase

$$\frac{dX}{dt} = \mu X \quad (S1)$$

$$X = X_0 e^{\mu t} \quad (S2)$$

$$\Delta m = \int dm = \int q_p V_0 X(t) dt \quad (S3)$$

$$\Delta m = \frac{q_p V_0 X_0}{\mu} [e^{\mu t} - 1] \quad (S4)$$

2. Fed-batch exponential phase

$$\frac{d(XV)}{dt} = \mu XV = X \frac{dV}{dt} + V \frac{dX}{dt} \quad (S5)$$

$$\left(\mu - \frac{F}{V}\right) X = \frac{dX}{dt} \quad (S6)$$

$$\because V = V_0 + \int F dt = V_0(1 + b)^t \quad (S7)$$

$$F = \frac{d}{dt} [V_0(1 + b)^t] = V_0(1 + b)^t \ln(1 + b) \quad (S8)$$

$$\frac{F}{V} = \ln(1 + b) \quad (S9)$$

$$X = X_i e^{[\mu - \ln(1 + b)]t} \quad (S10)$$

$$\Delta m = \int dm = \int q_p V(t) X(t) dt \quad (S11)$$

$$\Delta m = \frac{q_p V_0 X_i}{\mu} [e^{\mu t} - 1] \quad (S12)$$

3. Stationary phase

$$X = X(\text{constant}) \quad (S13)$$

$$\Delta m = \int dm = \int q_p V(t) X dt \quad (S14)$$

$$\Delta m = \int dm = \int q_p V_i (1 + b)^t X(t) dt \quad (S15)$$

$$\Delta m = \frac{q_p V_i X_i}{\ln(1 + b)} [b] \quad (S16)$$

4. Death phase

$$\frac{d(XV)}{dt} = \mu XV = X \frac{dV}{dt} + V \frac{dX}{dt} \quad (S17)$$

$$\left(-k_d - \frac{F}{V}\right) X = \frac{dX}{dt} \quad (S18)$$

$$X = X_i e^{[-k_d - \ln(1+b)]t} \quad (S19)$$

$$\Delta m = \int dm = \int q_p V(t) X(t) dt \quad (S20)$$

$$\Delta m = \frac{q_p V_0 X_i}{-k_d} [e^{-k_d t} - 1] \quad (S21)$$

Ordinary differential equation of the PEGylation reactor

$$-\frac{d}{dt} C_{AAT} = \frac{d}{dt} C_{PEG-AAT} = k C_{AAT} C_{PEG} \quad (S22)$$

$$\frac{d}{dt} C_{PEG} = -k C_{AAT} C_{PEG} - k_d C_{PEG} \quad (S23)$$

Figure S1: Process flow diagram of intensified process B (upstream section).

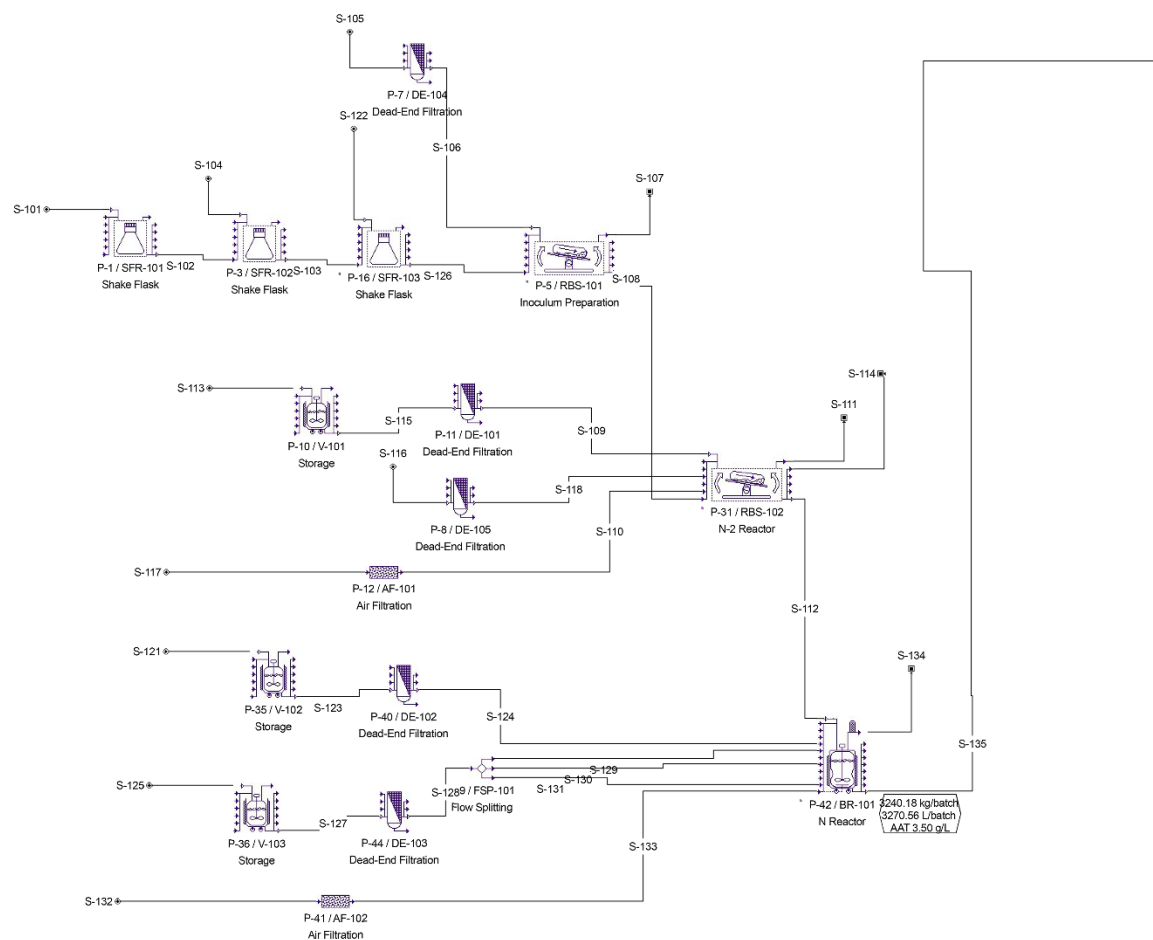


Figure S2: Equipment occupancy chart of the conventional process A.

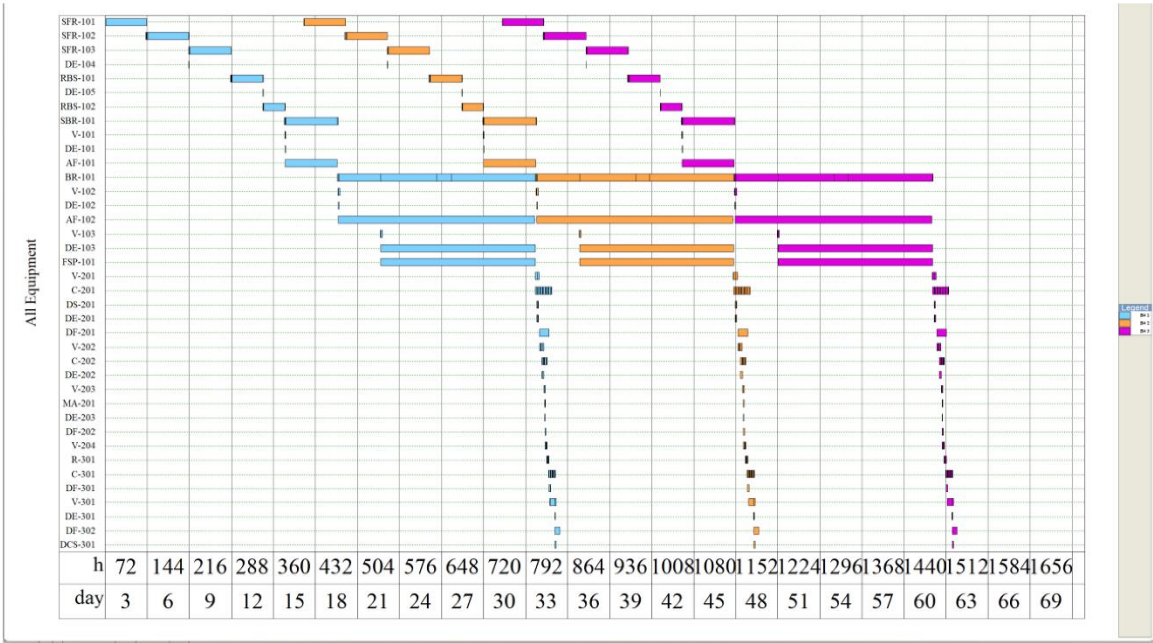


Figure S3: Gantt chart of the conventional process A

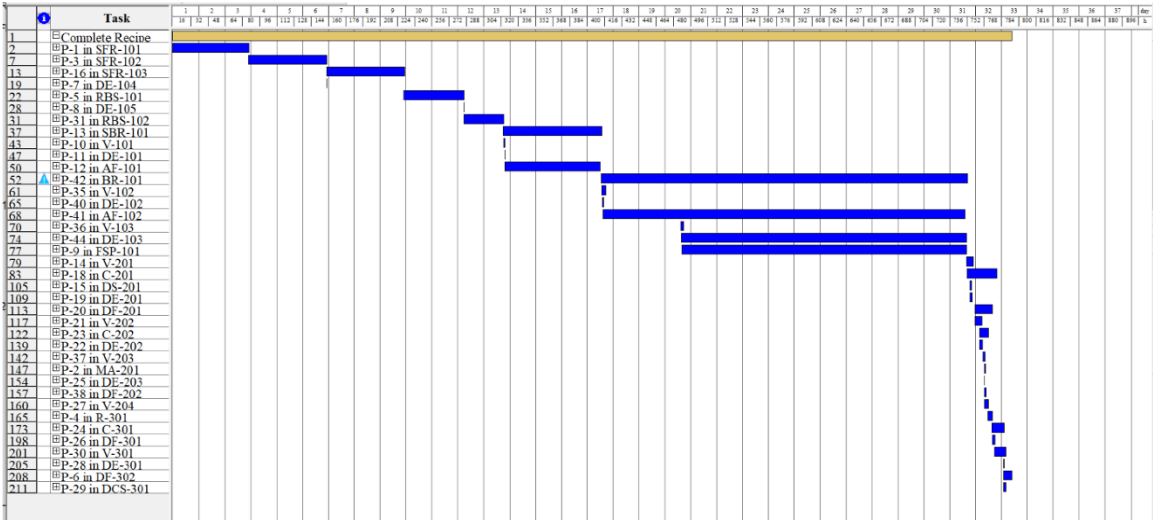


Figure S4: Equipment occupancy chart of intensified process B.

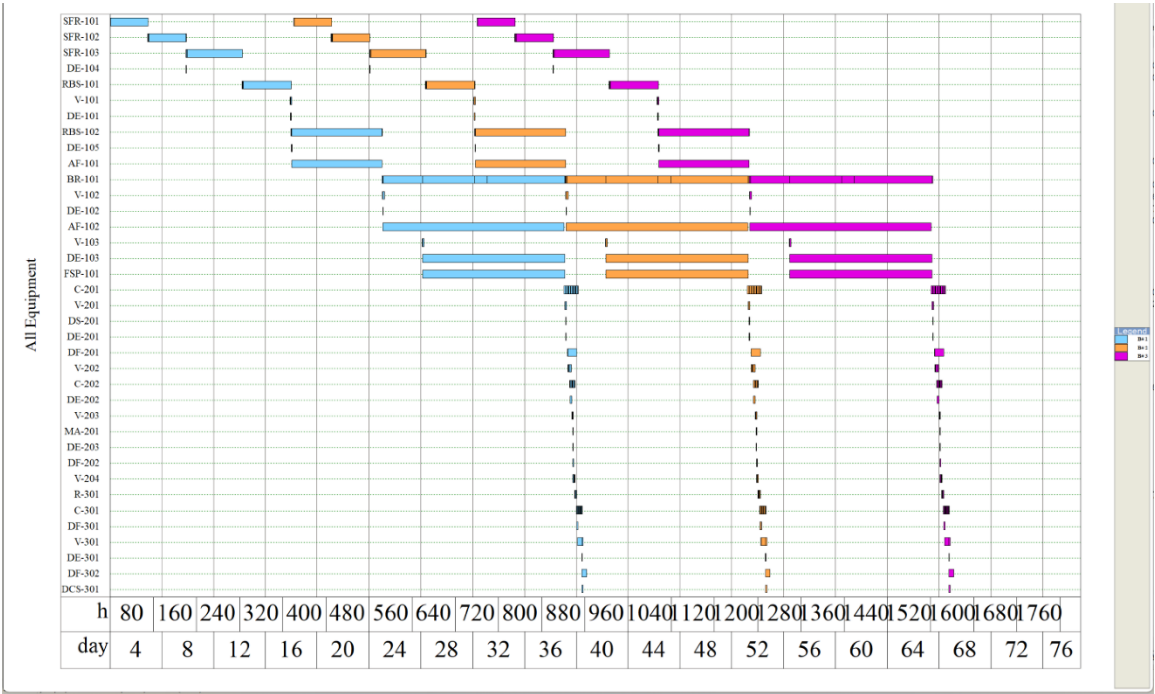


Figure S5: Gantt chart of intensified process B.

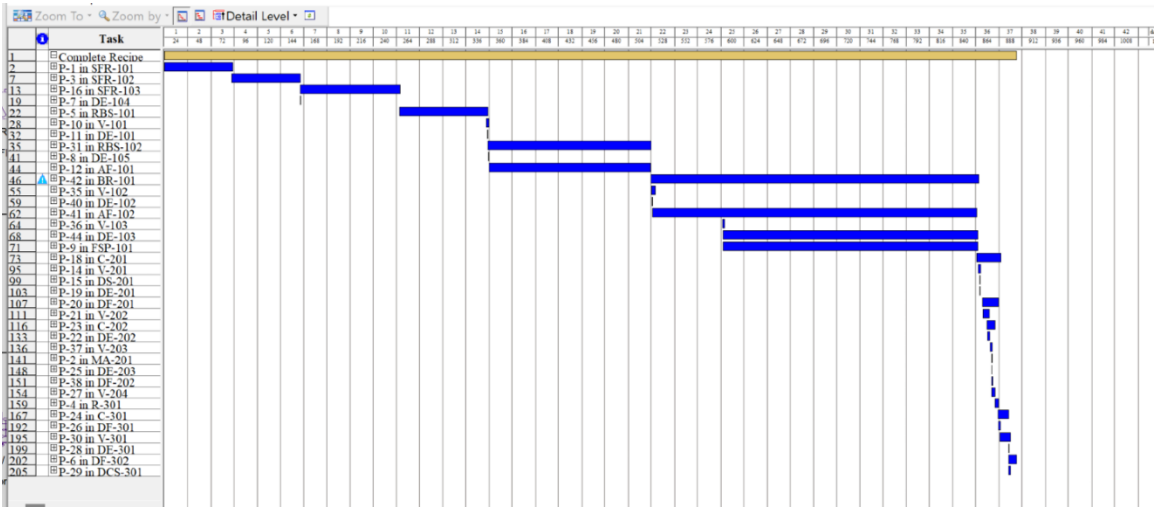


Table S1: Main assumptions of production N-bioreactor in the conventional process A and intensified process B.

	Traditional	Intensified
Seed cell density (10^6 cell/mL)	0.2	8
Peak cell density (10^6 cell/mL)	7.0	13.6
Day peak cell density achieved	7	3
Growth rate (day^{-1})	0.37	0.2
Death constant (day^{-1})	0.02	0.04
Cell-specific productivity (pg/cell/day)	30	30
Titer (g/L)	1.5	3.5

Table S2: Downstream and PEGylation unit operation yield.

	AAT				PEG-AAT
-	Clarification	Primary capture	Downstream IEX column	Downstream HIC Membrane	PEG IEX
Process A	99%	90%	90%	95%	88%
Process B	99%	90%	90%	95%	88%
Process C	99%	90%	90%	95%	88%