processes

MDPI

Supplementary Materials

mAb Production Modeling and Design Space Evaluation Including Glycosylation Process

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Kinetic model equations [1,2]

The first part is relative to the cell culture which captures viable cell concentration, glucose concentration and mAb concentration.

The mass balances are shown in the following equations.

Volume: $\frac{dV}{dt} = F_{in} - F_{out}$

Viable cell: $\frac{d(V[X_v])}{dt} = F_{in}[X_{v0}] + \mu V[X_v] - \mu_d V[X_v] - F_{out}[X_v]$

Dead cell: $\frac{d(V[X_d])}{dt} = F_{in}[X_{d0}] + \mu_d V[X_v] - F_{out}[X_d]$

mAb production: $\frac{dV[mAb]}{dt} = F_{in}[mAb_0] + q_{mAb}V[X_v] - F_{out}[mAb]$

Glucose concentration: $\frac{d(V[glucose])}{dt} = F_{in}[glucose]_{in} - F_{out}[glucose] + q_{glucose}VX_v$

Cell growth rate, death rate glucose consumption rate and protein productivity are shown below/

Cell growth rate: $\mu = (\frac{\mu_{max}}{T} + a)(\frac{C_{Glc}}{K_{Glc}+C_{Glc}} - \frac{[X_v]}{\alpha_x})$

Cell death rate: $\mu_d = (\frac{\mu_d^{max}}{T} + b)\frac{(\frac{K_{d\mu}}{T}+c)}{(\frac{K_{d\mu}}{T}+c)+\mu}$

Glucose consumption: $\mathrm{q_{Glc}} = -\frac{1}{(\frac{Y_{XGlc}}{T}+d)}\frac{[C_{Glc}]}{[C_{Glc}]+K_{Glc}}$

Protein productivity: $q_{mAb} = \left(\frac{Y_{\frac{mAb}{Glc}}}{T} + e\right) q_{Glc} \exp\left[-\frac{1}{2}\left(\frac{pH_{shift}-pH_{opt}}{w}\right)^2\right]$

The second part of the model is relative to protein glycosylation. Mass balance is shown in the equation below.

$$\frac{\partial[G_m]}{\partial t} = -V_1\frac{\partial[G_m]}{\partial z} + \sum_{n}^{Enzyme} v_{m,n}r_n$$

$$(\mathrm{V_1})(\mathrm{Vol_{Golgi}})[Man9]_{z=0} = \frac{q_p}{MW_{mAb}}(\frac{2umol_{Glyc}}{umol_{mAb}})$$

Three types of reactions exist in the Golgi apparatus that represents the catalytic reactions from different types of enzymes.

$$\mathrm{r_n} = \frac{k_{f,n}[E_n][G_m]}{k_{d,\frac{m}{n}}(1 + \frac{[G_m]}{k_{d,\frac{m}{n}}} + \frac{[G_{m-1}]}{k_{d,m-1/n}})}$$

$$r_n = \frac{k_{f,n}[E_n][NS_k][G_m]}{K_{d,m/n}K_{d,k/n}(1 + \frac{[NS_k]}{K_{d,\,k/n}} + \frac{[NS_k]}{K_{d,\,k/n}}\frac{[G_m]}{K_{d,m/n}} + \frac{[NS_k]}{K_{d,\,k/n}}\sum_{z=1}^{N.C.}\frac{[G_z]}{K_{d,\,z/n}} + \frac{B_k}{K_{i,k/n}}\frac{[G_{m+1}]}{k_{d,\,(m+1)/n}} + \frac{[B_k]}{K_{d,k/n}})}$$

$$r_n = \frac{k_{f,n}[E_n][NS_k][G_m]}{K_{d,\frac{m}{n}}K_{d,\frac{k}{n}}(1 + \frac{[NS_k]}{K_{d,\frac{k}{n}}} + \frac{[G_m]}{K_{d,\frac{m}{n}}} + \sum_{z=1}^{N.C.}\frac{[G_z]}{K_{d,\frac{z}{n}}} + \frac{[NS_k]}{K_{d,\frac{k}{n}}}\frac{[G_m]}{K_{d,\frac{m}{n}}} + \frac{[NS_k]}{K_{d,\frac{k}{n}}}\sum_{z=1}^{N.C.}\frac{[G_z]}{K_{d,\frac{z}{n}}} + \frac{B_k}{K_{i,\frac{k}{n}}}\frac{[G_{m+1}]}{k_{d,\frac{(m+1)}{n}}} + \frac{[G_{m+1}]}{k_{d,\frac{(m+1)}{n}}} + \frac{[B_k]}{K_{d,k/n}})}$$

$$[En] = [E_{n,max}]\exp\left[-\frac{1}{2}\left(\frac{z - z_{n,max}}{\omega_n}\right)^2\right]$$

$$[E_{n,max}] = a_n \times T + b_n$$

$k_{f,n}$ is the rate-limiting turnover rate for enzyme n. $[NS_k]$ is nucleotide sugar concentration. $K_{d,\frac{m}{n}}$ is the dissociation constant of the acceptor enzyme complex and $K_{d,\frac{k}{n}}$

is the dissociation constant of the donor enzyme complex. $K_{d,\frac{z}{n}}$ is the dissociation constant of the competitor enzyme complex, $[En]$ is enzyme concentration.

1. Temperature effect under pH = 6.8

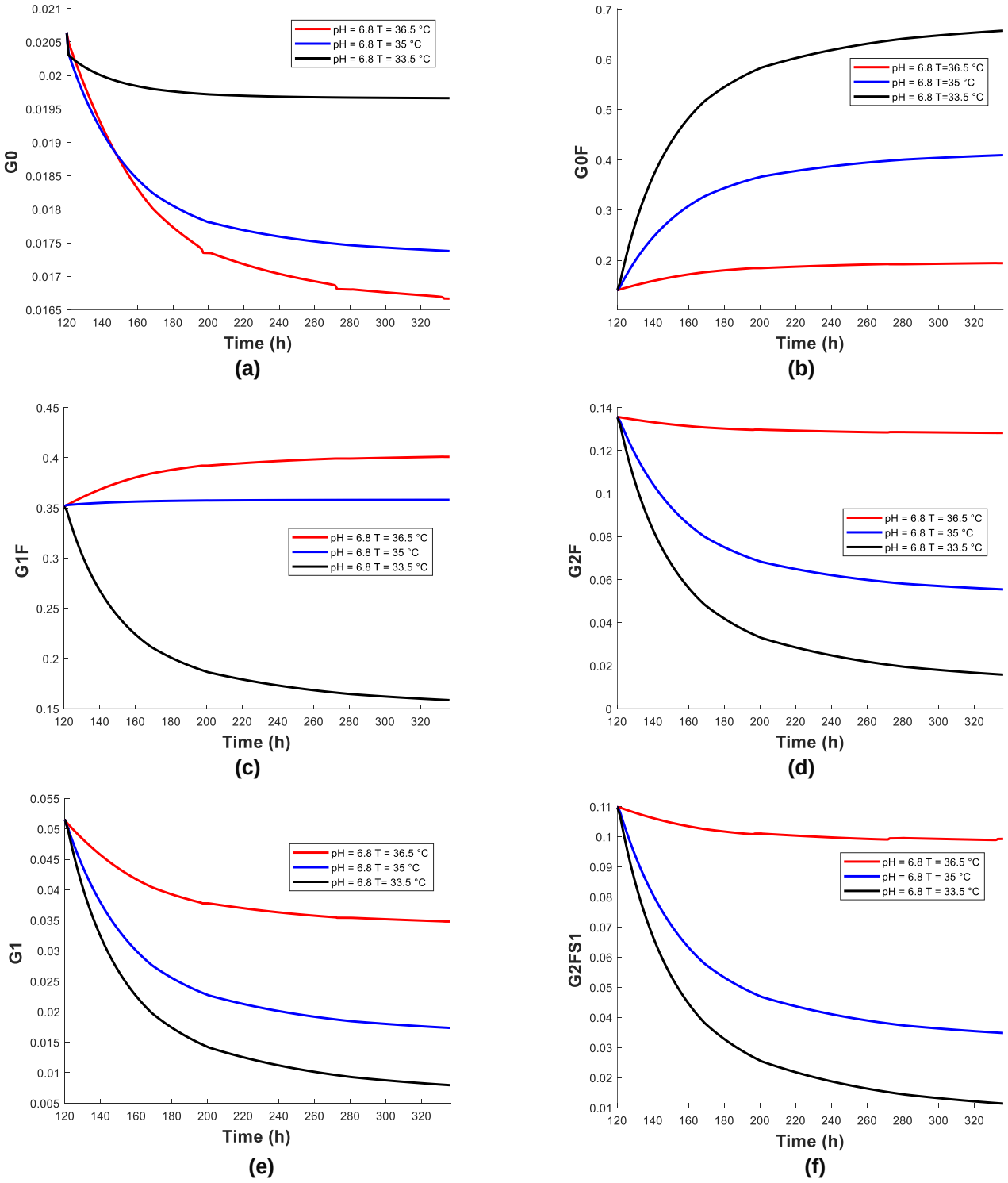

Figure S1. Glycan fractions under different temperature (**a**) G0, (**b**) G0F, (**c**) G1F, (**d**) G2F, (**e**) G1, (**f**) G2FS1 (pH = 6.8).

2. Temperature effect under pH = 6.9

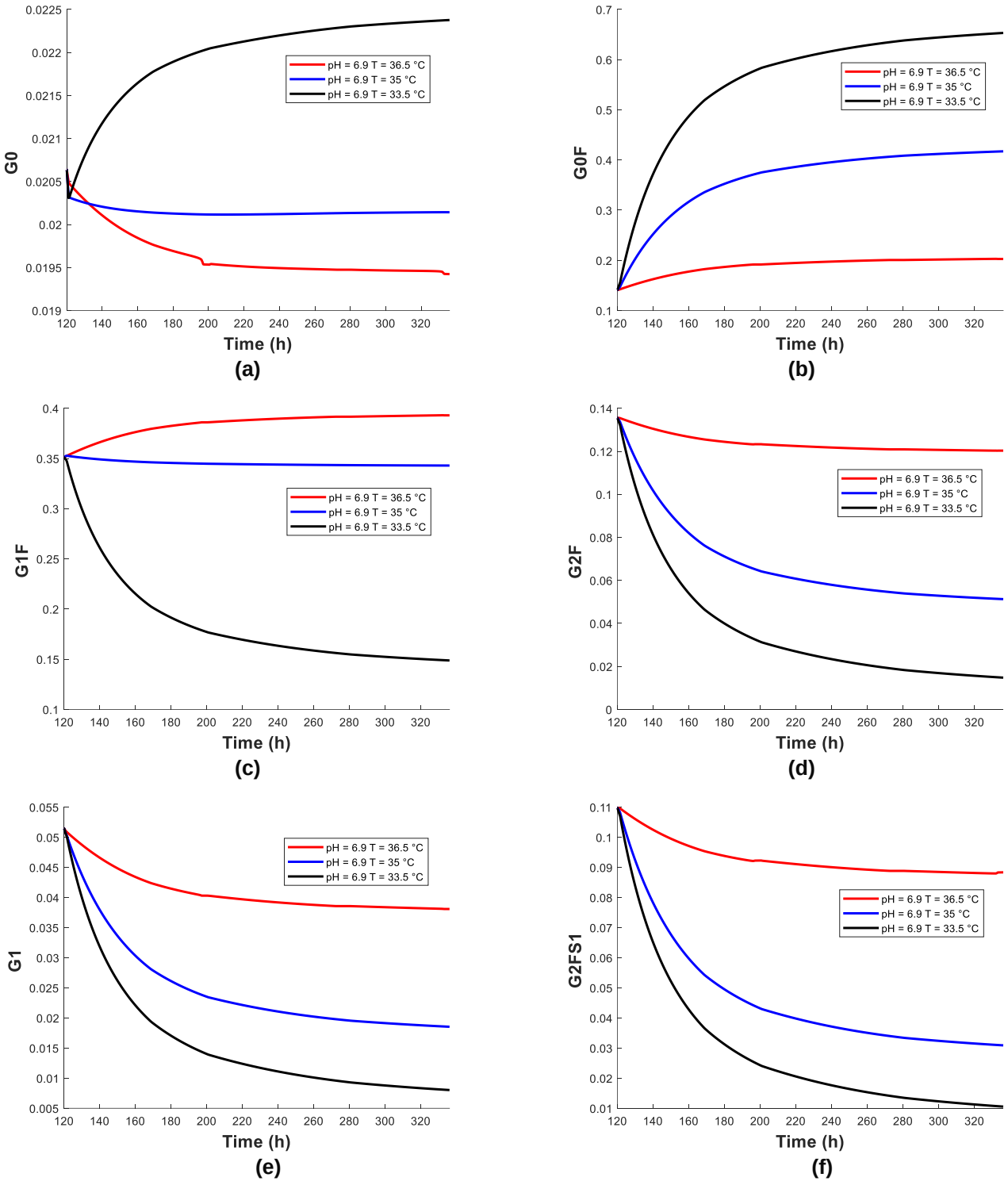

Figure S2. Glycan fractions under different temperature (**a**) G0, (**b**) G0F, (**c**) G1F, (**d**) G2F, (**e**) G1, (**f**) G2FS1 (pH = 6.9).

3. pH effect under T = 33.5 °C

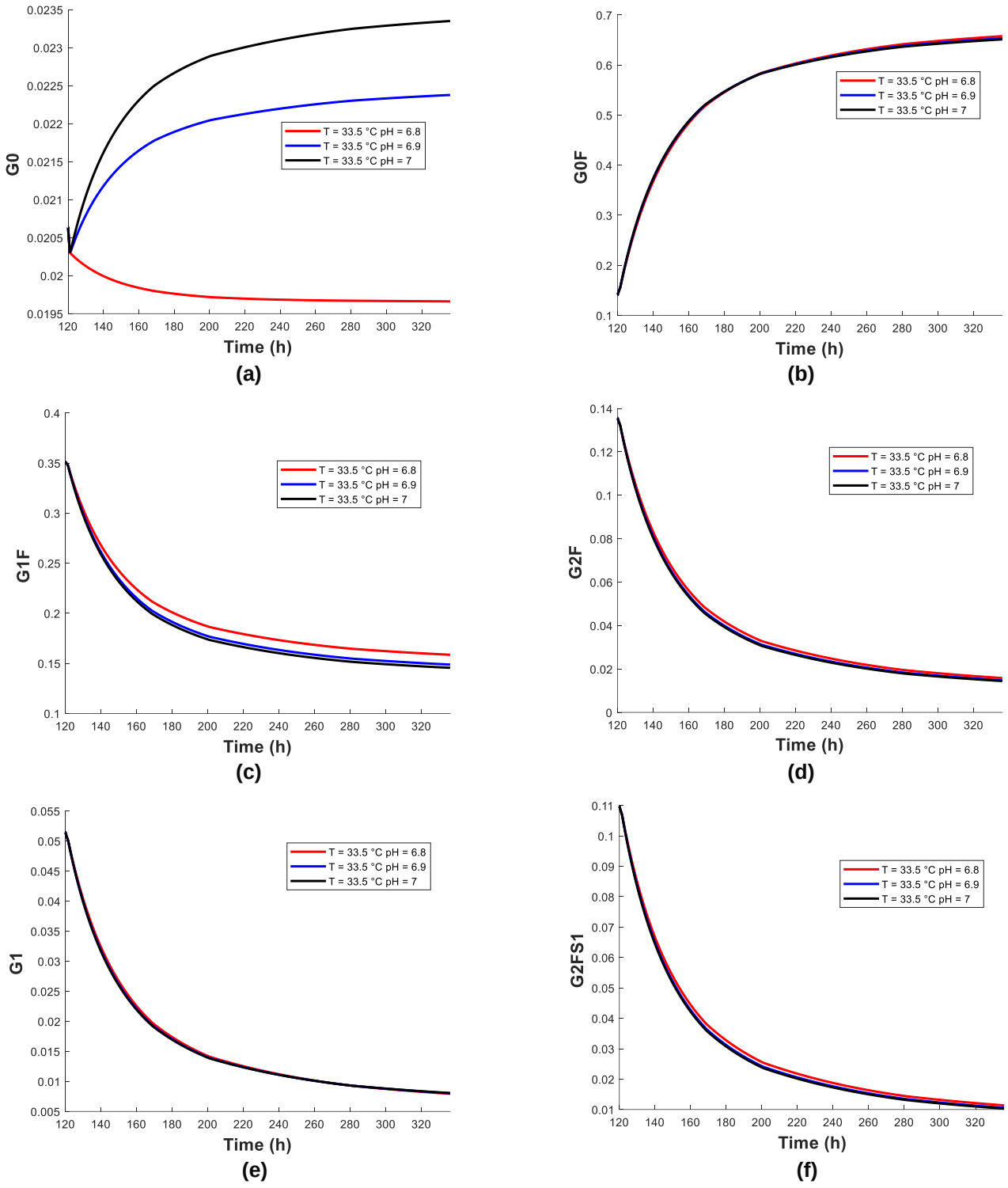

Figure S3. Glycan fractions under different pH (**a**) G0, (**b**) G0F, (**c**) G1F, (**d**) G2F, (**e**) G1, (**f**) G2FS1 (T = 33.5 °C).

4. pH effect under T = 35 °C

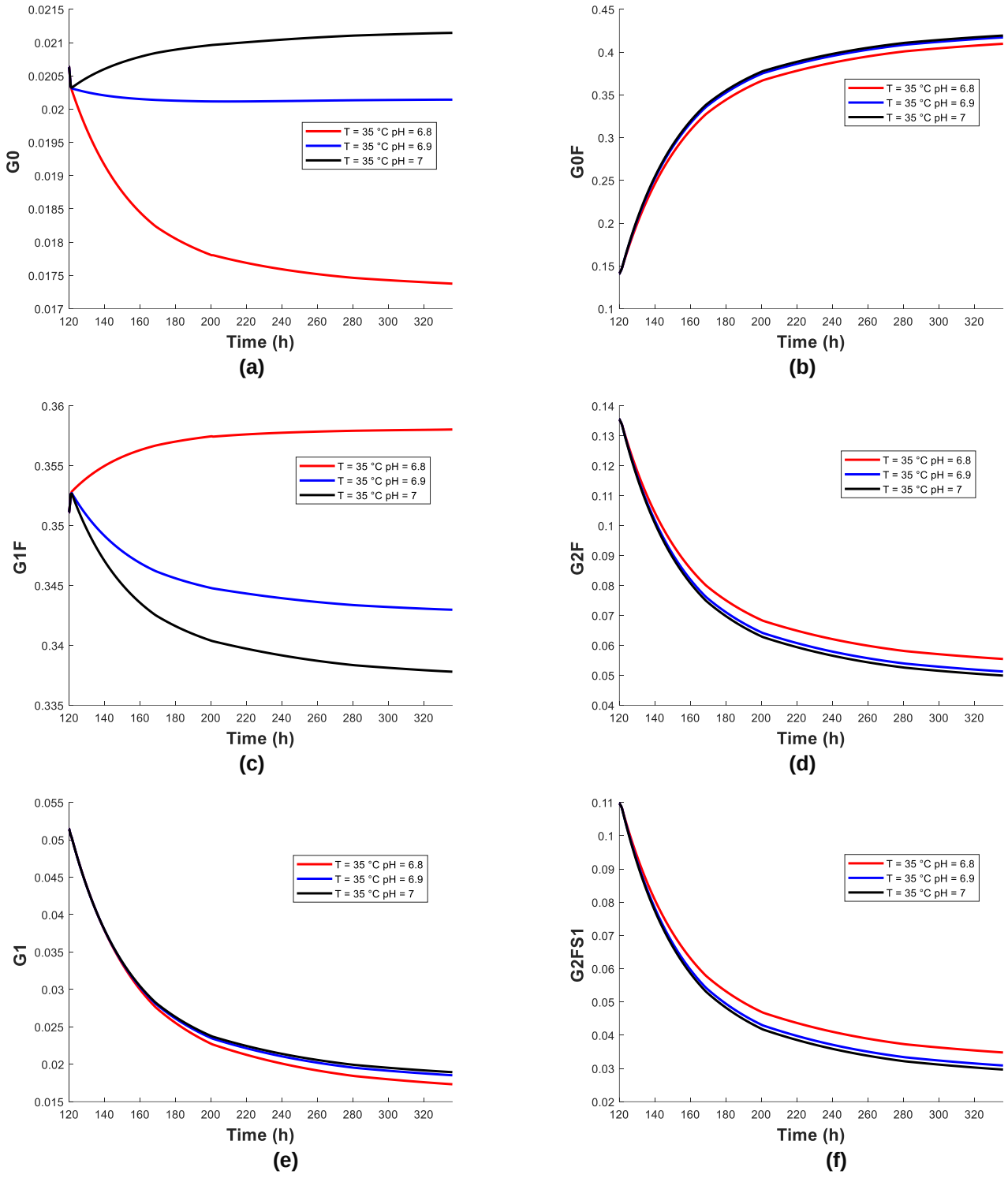

Figure S4. Glycan fractions under different pH (**a**) G0, (**b**) G0F, (**c**) G1F, (**d**) G2F, (**e**) G1, (**f**) G2FS1 (T = 35 °C).

5. Dynamic kriging fitting results

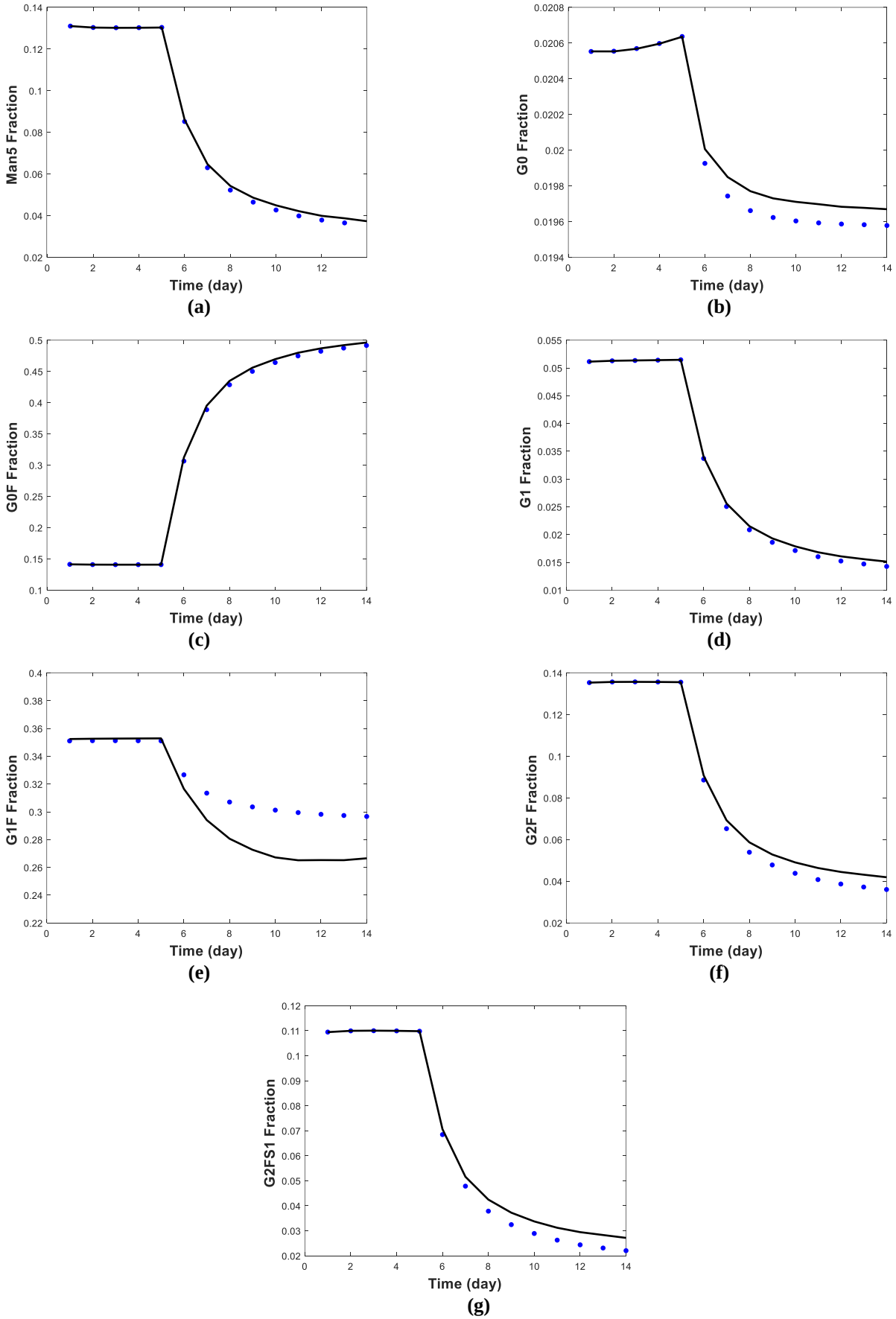

Figure S5. Glycan fractions fitting from day 1 by using dynamic kriging.

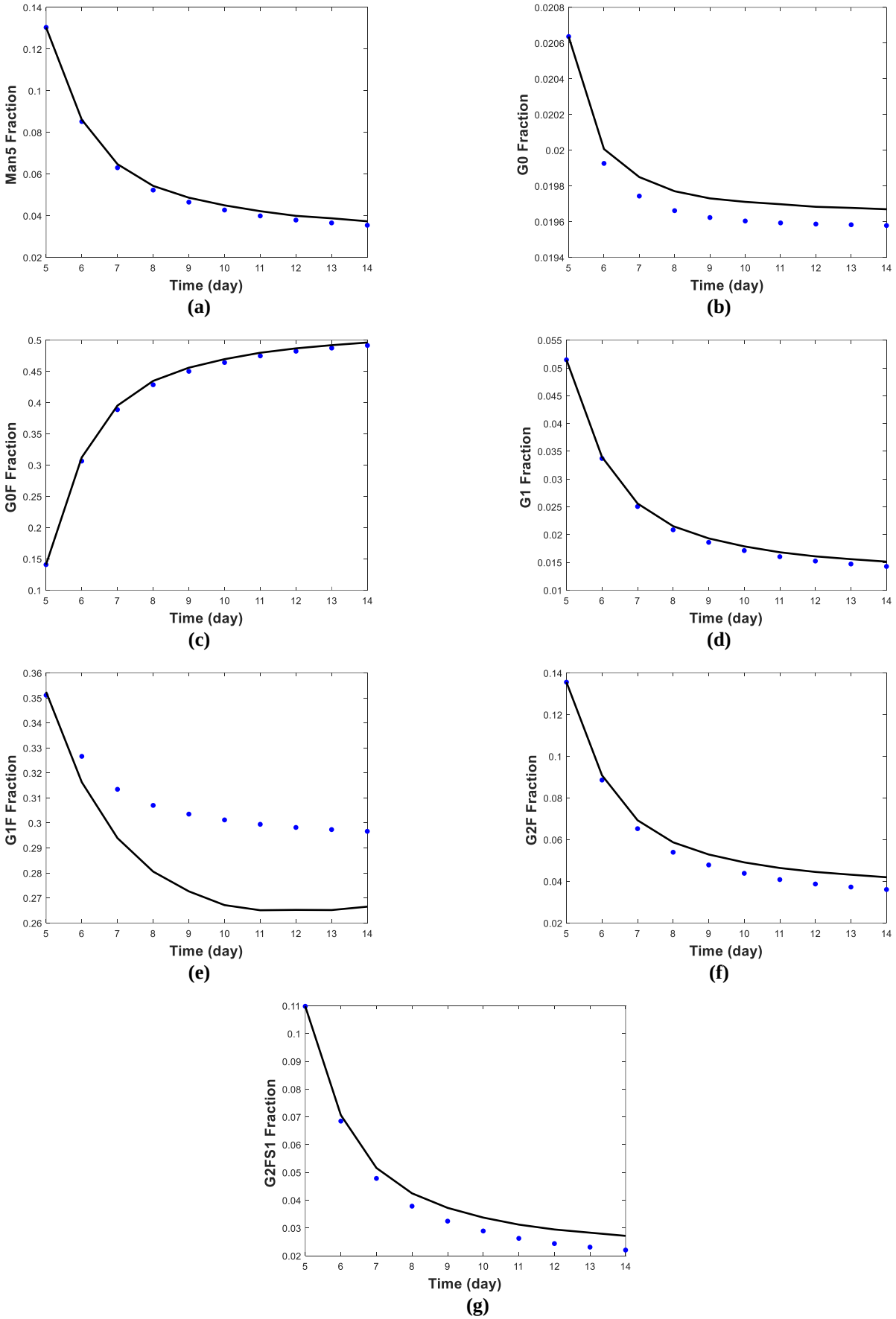

Figure S6. Glycan fraction fitting from day 5 by using dynamic kriging.

References

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2. Jimenez Del Val, I.; Fan, Y.; Weilguny, D., Dynamics of immature mAb glycoform secretion during CHO cell culture: An integrated modelling framework. *Biotechnol J* **2016,** *11* (5), 610-23.