Question 3.7.3

a.

Let e_T denote the total enzyme concentration: $e_T = e(t) + c(t)$

$$
\begin{aligned}
\frac{d}{dt}s(t) &= k_{-1}c(t) - k_1 s(t)e(t) = k_{-1}c(t) - k_1 s(t)(e_T - c(t)) \\
\frac{d}{dt}c(t) &= k_1 s(t)e(t) + k_{-2}p(t)e(t) - k_{-1}c(t) - k_2 c(t) = k_1 s(t)(e_T - c(t)) + k_{-2}p(t)(e_T - c(t)) - k_{-1}c(t) - k_2 c(t) \\
\frac{d}{dt}p(t) &= k_2 c(t) - k_{-2}p(t)e(t) = k_2 c(t) - k_{-2}p(t)(e_T - c(t))
\end{aligned}
$$

Apply a quasi-steady-state assumption to the complex C, where $\frac{d}{dt}c^{qss}(t) = 0$, and the goal is to arrive the description of $c^{qss} = \frac{k_1 e_T s + k_{-2} e_T p}{k_1 s + k_{-2} p + k_{-1} + k_2}$

$$
\begin{aligned}
&0 = k_1 s(t)[e_T - c^{qss}] + k_{-2}p(t)[e_T - c^{qss}] - k_{-1}c^{qss} - k_2 c^{qss} \\
&\Rightarrow (k_{-1} + k_2)c^{qss} = [k_1 s(t) + k_{-2}p(t)][e_T - c^{qss}] \\
&\Rightarrow (k_{-1} + k_2)c^{qss} + [k_1 s(t) + k_{-2}p(t)]c^{qss} = [k_1 s(t) + k_{-2}p(t)]e_T \\
&\Rightarrow [k_{-1} + k_2 + k_1 s(t) + k_{-2}p(t)]c^{qss} = [k_1 s(t) + k_{-2}p(t)]e_T \\
&\Rightarrow c^{qss} = \frac{k_1 e_T s(t) + k_{-2} e_T p(t)}{k_1 s(t) + k_{-2}p(t) + k_{-1} + k_2}
\end{aligned}
$$

$$
\frac{d}{dt}p(t) = k_2\, c(t) - k_{-2}\, p(t)\Big(e_T - c(t)\Big)
$$

Substitute $c(t)$ with c^{qss} and simplify:

$$
\begin{aligned}
&= k_2\, \frac{k_1 e_T s(t) + k_{-2} e_T p(t)}{k_1 s(t) + k_{-2}p(t) + k_{-1} + k_2} \\
&\quad - k_{-2}\, p(t) \left(e_T - \frac{k_1 e_T s(t) + k_{-2} e_T p(t)}{k_1 s(t) + k_{-2}p(t) + k_{-1} + k_2} \right) \\
&= \frac{k_1 k_2 e_T s(t) + k_2 k_{-2} e_T p(t)}{k_1 s(t) + k_{-2}p(t) + k_{-1} + k_2} \\
&\quad - \frac{k_1 k_{-2} e_T s(t)p(t) + k_{-2}^2 e_T [p(t)]^2 + k_{-1}k_{-2}e_T p(t) + k_2 k_{-2} e_T p(t) - k_1 k_{-2} e_T s(t)p(t) - k_{-2}^2 e_T [p(t)]^2}{k_1 s(t) + k_{-2}p(t) + k_{-1} + k_2} \\
&= \frac{k_1 k_2 e_T s(t) - k_{-1}k_{-2} e_T p(t)}{k_1 s(t) + k_{-2}p(t) + k_{-1} + k_2}\,.
\end{aligned}
$$

Done.

b.

Assuming the complex C is in quasi-steady-state with respect to S and P,

$$
\begin{aligned}
\text{Net rates } S \to P &= \frac{V_f \frac{s}{K_S} - V_r \frac{p}{K_P}}{1 + \frac{s}{K_S} + \frac{p}{K_P}} \\
&= \frac{k_1 k_2 e_T s(t) - k_{-1} k_{-2} e_T p(t)}{k_1 s(t) + k_{-2} p(t) + k_{-1} + k_2} \\
&\text{divide by } k_{-1} + k_2 \Rightarrow \frac{\frac{k_1 k_2 e_T s(t) - k_{-1} k_{-2} e_T p(t)}{k_{-1}+k_2}}{\frac{k_1 s(t) + k_{-2} p(t) + k_{-1} + k_2}{k_{-1}+k_2}} \\
&= \frac{\frac{k_1 k_2 e_T s}{k_{-1}+k_2} + \frac{k_{-1} k_{-2} e_T p}{k_{-1}+k_2}}{\frac{k_1}{k_{-1}+k_2} s + \frac{k_{-2}}{k_{-1}+k_2} p + \frac{k_{-1}+k_2}{k_{-1}+k_2}} \\
&\text{Substitute } \frac{k_{-1}+k_2}{k_1} \text{ with } K_S, \frac{k_{-1}+k_2}{k_{-2}} \text{ with } K_P \\
&\Rightarrow \frac{\frac{k_2 e_T s}{K_S} + \frac{k_{-1} e_T p}{K_P}}{\frac{s}{K_S} + \frac{p}{K_P} + 1} \\
&\text{Substitute } k_2 e^T \text{ with } V_f, k_{-1} e^T \text{ with } V_r \\
&\Rightarrow \frac{V_f \frac{s}{K_S} + V_r \frac{p}{K_P}}{\frac{s}{K_S} + \frac{p}{K_P} + 1}
\end{aligned}
$$

$$
V_f = k_2 e^T, V_r = k_{-1} e^T, K_S = \frac{k_{-1}+k_2}{k_1}, K_P = \frac{k_{-1}+k_2}{k_{-2}}
$$

Done.

c.

$$
\begin{aligned}
v = \frac{d}{dt} p(t) &= \frac{k_1 k_2 e_T s(t) - k_{-1} k_{-2} e_T p(t)}{k_1 s(t) + k_{-2} p(t) + k_{-1} + k_2} \\
&\text{when } k_{-2} = 0 \\
&= \frac{k_1 k_2 e_T s(t)}{k_1 s(t) + k_{-1} + k_2} \\
&= \frac{k_1 k_2 e_T s(t)}{k_1 \left(s(t) + \frac{k_{-1}+k_2}{k_1} \right)} \\
&\text{Define } \textit{Michaelis} \text{ constant } K_M = \frac{k_{-1}+k_2}{k_1}, V_{\max} = k_2 e_T \\
&\Rightarrow \frac{V_{\max} s(t)}{s(t) + K_M}, \text{which is the form of the irreversible Michaelis-Menten rate law}
\end{aligned}
$$

Done.