Problem 1

Control volume (C.V.): Liquid volume of the bioreactor

Population species to track: Mass of FGF2 in the liquid solution

Dimensions for each mass balance term: Mass of FGF2 per time

{Accumulation w/in C.V.} = Change of mass of FGF2 in the liquid per unit time

{Mass In} = FGF2 fed into the bioreactor per unit time

{Mass Out} = 0

{Mass produced by reaction} = 0

{Mass consumed by reaction} = Proteolytic degradation of FGF2 or Removal of FGF2 by binding/internalization into stem cells

Change of mass of FGF2 in liquid per time= FGF2 feed rate – FGF2 proteolytic degradation rate – FGF2 cellular uptake

Problem 2

Control volume (C.V.): Intracellular volume of a single cancer cell

Population species to track: Mass of anticancer drug inside the cell

Dimensions for each mass balance term: Mass of drug per time

{Accumulation w/in C.V.} = Change of mass of drug inside the cell per unit time

{Mass In} = Drug entering the cell by passive diffusion

{Mass Out} = Drug leaving the cell by passive diffusion and Drug leaving the cell via membrane transporter

{Mass produced by reaction} = 0

{Mass consumed by reaction} = Drug degraded by endogenous cellular enzymes

Change of intracellular drug mass per time = Passive diffusion into cell – Passive diffusion out of cell – Transporter-mediated efflux – Enzymatic degradation inside cell

Problem 3a

(Eq 1.8) $0 = v_{s,R} - k_{e,R}\,[R]_{ss} + k_r\,[C]_{ss} - k_f\,[R]_{ss}\,[L]_0$

(Eq 1.9) $0 = -k_{e,C}\,[C]_{ss} + k_f\,[R]_{ss}\,[L]_0 - k_r\,[C]_{ss}$

$\implies k_f\,[R]_{ss}\,[L]_0 = (k_r + k_{e,C})[C]_{ss}$

$\implies [C]_{ss} = \frac{k_f[R]_{ss}[L]_0}{k_r + k_{e,C}}$

$\implies 0 = v_{s,R} - k_{e,R}\,[R]_{ss} + k_r\frac{k_f[R]_{ss}[L]_0}{k_r + k_{e,C}} - k_f\,[R]_{ss}\,[L]_0$

$\implies 0 = v_{s,R} - [R]_{ss}(k_{e,R} - \frac{k_r k_f[L]_0}{k_r + k_{e,C}} + k_f\,[L]_0)$

$\implies [R]_{ss} = \frac{v_{s,R}}{(k_{e,R} - \frac{k_r k_f[L]_0}{k_r + k_{e,C}} + k_f[L]_0)}$

$\implies [R]_{ss} = \frac{v_{s,R}(k_{e,C} + k_r)}{(k_{e,C}k_f[l_0] + k_{e,C}k_{e,R} + k_{e,R}k_r)}$

$\implies [R]_{ss} = \frac{\frac{V_{s,r}}{k_{e,R}}(k_{e,C} + k_r)}{k_{e,C} + k_r + \frac{k_{e,C}k_f[L]_0}{k_{e,R}}}$

$\implies [R]_{ss} = [R]_0\frac{(k_{e,C} + k_r)}{k_{e,C} + k_r + \frac{k_{e,C}k_f[L]_0}{k_{e,R}}}$

$\implies [R]_{ss} = [R]_0\frac{\frac{k_{e,c} + k_r}{k_f[L]_0}}{\frac{k_{e,c} + k_r}{k_f[L]_0} + \delta} = \frac{\kappa}{\kappa + \delta}$

$[C]_{ss} = \frac{k_f[R]_{ss}[L]_0}{k_r + k_{e,C}} = \frac{[R]_{ss}}{\kappa}$

$[R]_{ss} + [C]_{ss} = [R]_{ss} + \frac{[R]_{ss}}{\kappa} = [R]_{ss}(1 + \frac{1}{\kappa}) = [R]_0(\frac{\kappa}{\kappa + \delta})(\frac{\kappa + 1}{\kappa})$

$\therefore \frac{[R]_{ss} + [C]_{ss}}{[R]_0} = \frac{\kappa + 1}{\kappa + \delta}$

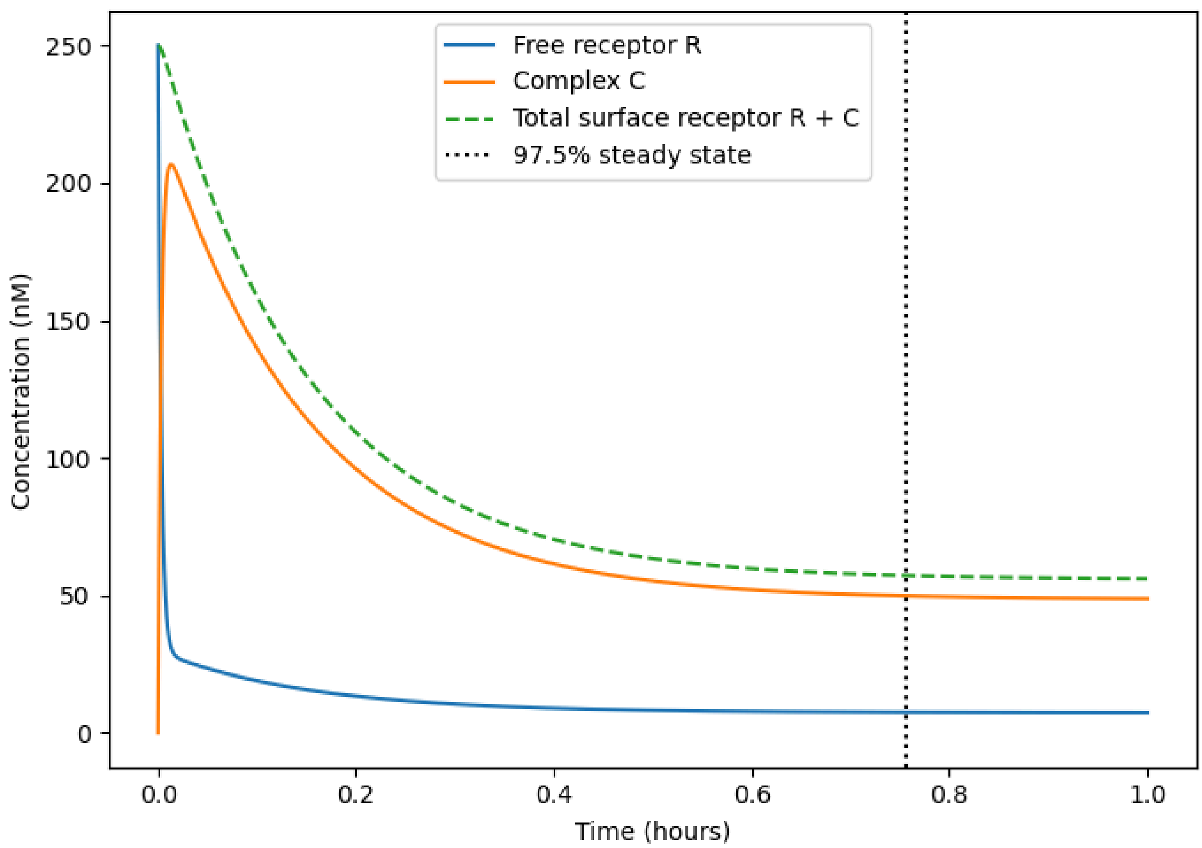
Problem 3b

In [18]:
```
import numpy as np
from scipy.integrate import solve_ivp
import matplotlib.pyplot as plt

k_eC = 2e-3      # s^-1
k_eR = 4e-4      # s^-1
k_r  = 1e-2      # s^-1
k_f  = 8e5 * 1e-9      # nM^-1 s^-1
L0   = 1e-7 * 1e9      # nM
```

```
v_sR = 1e-10 * 1e9     # nM s^-1

def toy_model(t, y, params):
    R, C = y
    k_eC, k_eR, k_r, k_f, L0, v_sR = params

    dRdt = v_sR - k_eR*R + k_r*C - k_f*R*L0
    dCdt = -k_eC*C + k_f*R*L0 - k_r*C

    return [dRdt, dCdt]

R0 = v_sR / k_eR
C0 = 0.0
y0 = [R0, C0]

t_span = (0, (3600*1))  # seconds (~2 hours)
t_eval = np.linspace(t_span[0], t_span[1], 5000)

params = (k_eC, k_eR, k_r, k_f, L0, v_sR)

sol = solve_ivp(
    toy_model,
    t_span,
    y0,
    args=(params,),
    t_eval=t_eval,
    method="LSODA",
)

t = sol.t
R = sol.y[0]
C = sol.y[1]
R_total = R + C

# Calculate steady state values analytically
# From part (a): (R_ss + C_ss)/R0 = (1+kappa)/(delta+kappa)
delta = k_eC / k_eR
kappa = (k_r + k_eC) / (k_f * L0)

R0_threashold = v_sR/k_eR
R_total_ss_analytical = R0_threashold * (1 + kappa) / (delta + kappa)
R_ss_analytical = R0_threashold * kappa / (delta + kappa)
C_ss_analytical = R0_threashold / (delta + kappa)


# Find time to reach 97.5% of steady state
# Define tolerance for “steady state”
tolerance = 0.025 * R_total_ss_analytical  # 2.5%

# Compute difference from steady state
diff = np.abs(R_total - R_total_ss_analytical)

# Find the **last point before steady state**: last index where diff > toler
indices_before_ss = np.where(diff > tolerance)[0]
t_ss_hours = t[indices_before_ss[-1]] / 3600  # convert to hours
```

```
print(f"Time to steady state ≈ {t_ss_hours:.2f} hours")
print(f"Steady state total receptor ≈ {R_total_ss_analytical:.3e} nM")

assert np.isclose(R[-1] + C[-1], R_total_ss_analytical, rtol=tolerance), "Nu
assert np.isclose(R[-1], R_ss_analytical, rtol=0.025*R_ss_analytical), "Nume
assert np.isclose(C[-1], C_ss_analytical, rtol=0.025*C_ss_analytical), "Nume

plt.figure(figsize=(7,5))
plt.plot(t/3600, R, label="Free receptor R")
plt.plot(t/3600, C, label="Complex C")
plt.plot(t/3600, R_total, '--', label="Total surface receptor R + C")

plt.axvline(t_ss_hours, color='k', linestyle=':', label="97.5% steady state"

plt.xlabel("Time (hours)")
plt.ylabel("Concentration (nM)")
plt.legend()
plt.tight_layout()
plt.show()
```

```
Time to steady state ≈ 0.76 hours
Steady state total receptor ≈ 5.583e+01 nM
```



Problem 3c

In [1]:

```
def J_func(k_eC, k_eR, k_r, k_f, L0):
    delta = k_eC / k_eR
    kappa = (k_r + k_eC) / (k_f * L0)
    return (1 + kappa) / (delta + kappa)
```

```python
params = {
    'k_eC': 2e-3,
    'k_eR': 4e-4,
    'k_r': 0.01,
    'k_f': 8e5,
    'L0': 1e-7
}

delta_frac = 0.01  # 1% perturbation

S = {}

# Loop over parameters
for p in params:
    p0 = params[p]
    dp = delta_frac * p0
    params_perturbed = params.copy()
    params_perturbed[p] += dp
    J0 = J_func(**params)
    Jp = J_func(**params_perturbed)
    S[p] = (p0 / J0) * ((Jp - J0) / dp)

print(f"Baseline J0 = {J0:.4f}\n")
for p in S:
    print(f"S_{{{p}}} = {S[p]:+.4f}")
```

```
Baseline J0 = 0.2233

S_{k_eC} = -0.9448
S_{k_eR} = +0.9706
S_{k_r} = +0.0844
S_{k_f} = -0.1003
S_{L0} = -0.1003
```

Problem 3d

Objective function is: $f = \frac{[R]_{ss}+[C]_{ss}}{[R]_0} = \frac{1+\kappa}{\delta+\kappa}$

where:

- $\delta = \frac{k_{e,C}}{k_{e,R}}$
- $\kappa = \frac{k_r+k_{e,C}}{k_f[L]_0}$

Normalized local objective function:

$$S_p = \frac{\partial f}{\partial p} \cdot \frac{p}{f}$$

$$\frac{\partial f}{\partial \kappa} = \frac{\delta-1}{(\delta+\kappa)^2}$$

$$\frac{\partial f}{\partial \delta} = -\frac{1+\kappa}{(\delta+\kappa)^2}$$

Sensitivity to $k_{e,C}$

$$\delta = \frac{k_{e,C}}{k_{e,R}} \implies \frac{\partial \delta}{\partial k_{e,C}} = \frac{1}{k_{e,R}}$$

$$\kappa = \frac{k_r + k_{e,C}}{k_f[L]_0} \implies \frac{\partial \kappa}{\partial k_{e,C}} = \frac{1}{k_f[L]_0}$$

$$\implies \frac{\partial f}{\partial k_{e,C}} = \frac{\partial f}{\partial \delta} \cdot \frac{\partial \delta}{\partial k_{e,C}} + \frac{\partial f}{\partial \kappa} \cdot \frac{\partial \kappa}{\partial k_{e,C}} = -\frac{1+\kappa}{(\delta+\kappa)^2} \cdot \frac{1}{k_{e,R}} + \frac{\delta-1}{(\delta+\kappa)^2} \cdot \frac{1}{k_f[L]_0}$$
$$= \frac{1}{(\delta+\kappa)^2}\left[\frac{-(1+\kappa)}{k_{e,R}} + \frac{\delta-1}{k_f[L]_0}\right]$$

Normalize Sensitivity to $k_{e,C}$

$$S_{k_{e,C}} = \frac{\partial f}{\partial k_{e,C}} \cdot \frac{k_{e,C}}{f} = k_{e,C} \cdot \frac{\delta+\kappa}{1+\kappa} \cdot \frac{1}{(\delta+\kappa)^2}\left[\frac{-(1+\kappa)}{k_{e,R}} + \frac{\delta-1}{k_f[L]_0}\right]$$
$$= \frac{k_{e,C}}{(1+\kappa)(\delta+\kappa)}\left[\frac{-(1+\kappa)}{k_{e,R}} + \frac{\delta-1}{k_f[L]_0}\right]$$

Sensitivity to $k_{e,R}$

$$\delta = \frac{k_{e,C}}{k_{e,R}} \implies \frac{\partial \delta}{\partial k_{e,R}} = \frac{-k_{e,C}}{k_{e,R}^2}$$

$$\frac{\partial f}{\partial k_{e,R}} = \frac{\partial f}{\partial \delta} \cdot \frac{\partial \delta}{\partial k_{e,R}} = -\frac{1+\kappa}{(\delta+\kappa)^2} \cdot \frac{-k_{e,C}}{k_{e,R}^2} = \frac{\delta(1+\kappa)}{k_{e,R}(\delta+\kappa)^2}$$

Normalize Sensitivity to $k_{e,R}$

$$S_{k_{e,R}} = \frac{\partial f}{\partial k_{e,R}} \cdot \frac{k_{e,R}}{f} = \frac{\delta(1+\kappa)}{k_{e,R}(\delta+\kappa)^2} \cdot k_{e,R} \cdot \frac{\delta+\kappa}{1+\kappa} = \frac{\delta}{\delta+\kappa}$$

Sensitivity to k_r

$$\kappa = \frac{k_r + k_{e,C}}{k_f[L]_0} \implies \frac{\partial \kappa}{\partial k_r} = \frac{1}{k_f[L]_0}$$

$$\implies \frac{\partial f}{\partial k_r} = \frac{\partial f}{\partial \kappa} \cdot \frac{\partial \kappa}{\partial k_r} = \frac{\delta-1}{(\delta+\kappa)^2} \cdot \frac{1}{k_f[L]_0}$$

Normalized Sensitivity to k_r

$$S_{k_r} = \frac{\partial f}{\partial k_r} \cdot \frac{k_r}{f} = \frac{\delta-1}{(\delta+\kappa)^2} \cdot \frac{1}{k_f[L]_0} \cdot k_r \cdot \frac{\delta+\kappa}{1+\kappa} = \frac{(\delta-1)\cdot k_r}{(\delta+\kappa)\cdot k_f \cdot [L]_0 \cdot (1+\kappa)}$$

Sensitivity to k_f

$$\kappa = \frac{k_r+k_{e,C}}{k_f[L]_0} \implies \frac{\partial\kappa}{\partial k_f} = \frac{-(k_r+k_{e,C})}{k_f^2[L]_0} = -\kappa \cdot k_f^{-1}$$

$$\frac{\partial f}{\partial k_f} = \frac{\partial f}{\partial\kappa} \cdot \frac{\partial\kappa}{\partial k_f} = \frac{\delta-1}{(\delta+\kappa)^2} \cdot -\kappa \cdot k_f^{-1}$$

Normalize Sensitivity to k_f

$$S_{k_f} = \frac{\partial f}{\partial k_f} \cdot \frac{k_f}{f} = \frac{\delta-1}{(\delta+\kappa)^2} \cdot -\kappa \cdot k_f^{-1} \cdot k_f \cdot \frac{\delta+\kappa}{1+\kappa} = \frac{-(\delta-1)\kappa}{(\delta+\kappa)(1+\kappa)}$$

Sensitivity to $[L]_0$

$$\kappa = \frac{k_r+k_{e,C}}{k_f[L]_0} \implies \frac{\partial\kappa}{\partial[L]_0} = \frac{-(k_r+k_{e,C})}{k_f[L]_0^2} = -\kappa \cdot [L]_0^{-1}$$

$$\frac{\partial f}{\partial[L]_0} = \frac{\partial f}{\partial\kappa} \cdot \frac{\partial\kappa}{\partial[L]_0} = \frac{\delta-1}{(\delta+\kappa)^2} \cdot -\kappa \cdot [L]_0^{-1}$$

Normalize Sensitivity to $[L]_0$

$$S_{[L]_0} = \frac{\partial f}{\partial[L]_0} \cdot \frac{[L]_0}{f} = \frac{\delta-1}{(\delta+\kappa)^2} \cdot -\kappa \cdot [L]_0^{-1} \cdot [L]_0 \cdot \frac{\delta+\kappa}{1+\kappa} = \frac{-(\delta-1)\kappa}{(\delta+\kappa)(1+\kappa)}$$

Parameter	**Sensitivity Parameter Eq**	**Normalized Sensitivity Parameter Eq**
$k_{e,R}$	$\frac{\partial f}{\partial k_{e,R}} = \frac{\delta(1+\kappa)}{k_{e,R}(\delta+\kappa)^2}$	$S_{k_{e,R}} = \frac{\delta}{\delta+\kappa}$
$k_{e,C}$	$\frac{\partial f}{\partial k_{e,C}} = \frac{1}{(\delta+\kappa)^2}\left[\frac{-(1+\kappa)}{k_{e,R}} + \frac{\delta-1}{k_f[L]_0}\right]$	$S_{k_{e,C}} = \frac{k_{e,C}}{(1+\kappa)(\delta+\kappa)}\left[\frac{-(1+\kappa)}{k_{e,R}} + \frac{\delta-1}{k_f[L]_0}\right]$
k_r	$\frac{\partial f}{\partial k_r} = \frac{\delta-1}{(\delta+\kappa)^2 k_f[L]_0}$	$S_{k_r} = \frac{(\delta-1)k_r}{(\delta+\kappa)k_f[L]_0(1+\kappa)}$
k_f	$\frac{\partial f}{\partial k_f} = \frac{-\kappa(\delta-1)}{k_f(\delta+\kappa)^2}$	$S_{k_f} = \frac{-\kappa(\delta-1)}{(\delta+\kappa)(1+\kappa)}$
$[L]_0$	$\frac{\partial f}{\partial[L]_0} = \frac{-\kappa(\delta-1)}{[L]_0(\delta+\kappa)^2}$	$S_{[L]_0} = \frac{-\kappa(\delta-1)}{(\delta+\kappa)(1+\kappa)}$

Symbol	Value
$k_{e,C}$	2×10^{-3}
$k_{e,R}$	4×10^{-4}
k_r	0.01
k_f	8×10^{5}
$[L]_0$	1×10^{-7}
s_R	1×10^{-10}
δ	$\delta = \frac{k_{e,C}}{k_{e,R}} = \frac{2 \times 10^{-3}}{4 \times 10^{-4}} = 5$
κ	$\kappa = \frac{k_r + k_{e,C}}{k_f [L]_0} = \frac{0.01 + 2 \times 10^{-3}}{8 \times 10^5 \cdot 1 \times 10^{-7}} = 0.15$

Parameter	Normalized Sensitivity Equation	Numerical Substitution
$k_{e,R}$	$S_{k_{e,R}} = \frac{\delta}{\delta+\kappa}$	$S_{k_{e,R}} = \frac{5}{5+0.15}$
$k_{e,C}$	$S_{k_{e,C}} = \frac{k_{e,C}}{(1+\kappa)(\delta+\kappa)}\left[\frac{-(1+\kappa)}{k_{e,R}} + \frac{\delta-1}{k_f[L]_0}\right]$	$\left[\frac{-1.15}{4\times10^{-4}} + \frac{4}{8\times10^5\times10^{-7}}\right]$
k_r	$S_{k_r} = \frac{(\delta-1)k_r}{(\delta+\kappa)k_f[L]_0(1+\kappa)}$	$S_{k_r} = \frac{(5-1)(0.01)}{(5.15)(8\times10^5)(10^{-7})(1.15)}$
k_f	$S_{k_f} = \frac{-\kappa(\delta-1)}{(\delta+\kappa)(1+\kappa)}$	$S_{k_f} = \frac{-(0.15)(5-1)}{(5.15)(1.15)}$
$[L]_0$	$S_{[L]_0} = \frac{-\kappa(\delta-1)}{(\delta+\kappa)(1+\kappa)}$	$S_{[L]_0} = \frac{-(0.15)(5-1)}{(5.15)(1.15)}$

Analytical Value	Computational Value
$S_{k_{e,R}} = 0.971$	$S_{k_{e,R}} = 0.9706$
$S_{k_{e,C}} = \frac{2 \times 10^{-3}}{(1.15)(5.15)}\left	
$S_{k_{e,C}} = -0.945$	$S_{k_eC} = -0.9448$
$S_{k_r} = 0.084$	$S_{k_r} = 0.0844$
$S_{k_f} = -0.101$	$S_{k_f} = -0.1003$
$S_{[L]_0} = -0.101$	$S_{L0} = -0.1003$

In [ ]: