Modeling Non-Genetic Variability in Drug Response at the Single-Cell Level

April 2, 2025

0.0.1 Modeling TRAIL-Induced Apoptosis with Cell-to-Cell Variability

In this simulation, we model the dynamics of TRAIL-induced apoptosis using a simplified, three-stage ODE system representing the activation of initiator caspases (I), mitochondrial amplification signals (M), and effector caspases (E). Each virtual cell in the population has randomly varied initial conditions and inhibition strength to simulate **non-genetic variability** (e.g., differences in protein levels or Bcl-2 expression).

The model investigates how these differences lead to variations in **apoptosis timing**, **survival outcomes**, and how regulatory mechanisms like **negative feedback** affect overall population behavior. This builds on experimental observations from Spencer et al. (2009) and is grounded in concepts of stochastic gene expression and network dynamics covered in class.

0.0.2 System of Differential Equations

The model consists of three ODEs representing initiator caspase activation, mitochondrial amplification, and effector caspase execution:

$$\frac{dI}{dt} = \frac{k_1}{1 + \alpha E} - \delta_I I$$

$$\frac{dM}{dt} = \frac{k_2 I}{K_d + I} - \delta_M M$$

$$\frac{dE}{dt} = k_3 M - \delta_E E$$

A cell is considered apoptotic when $E \geq$ death threshold.

Variables and Parameters:

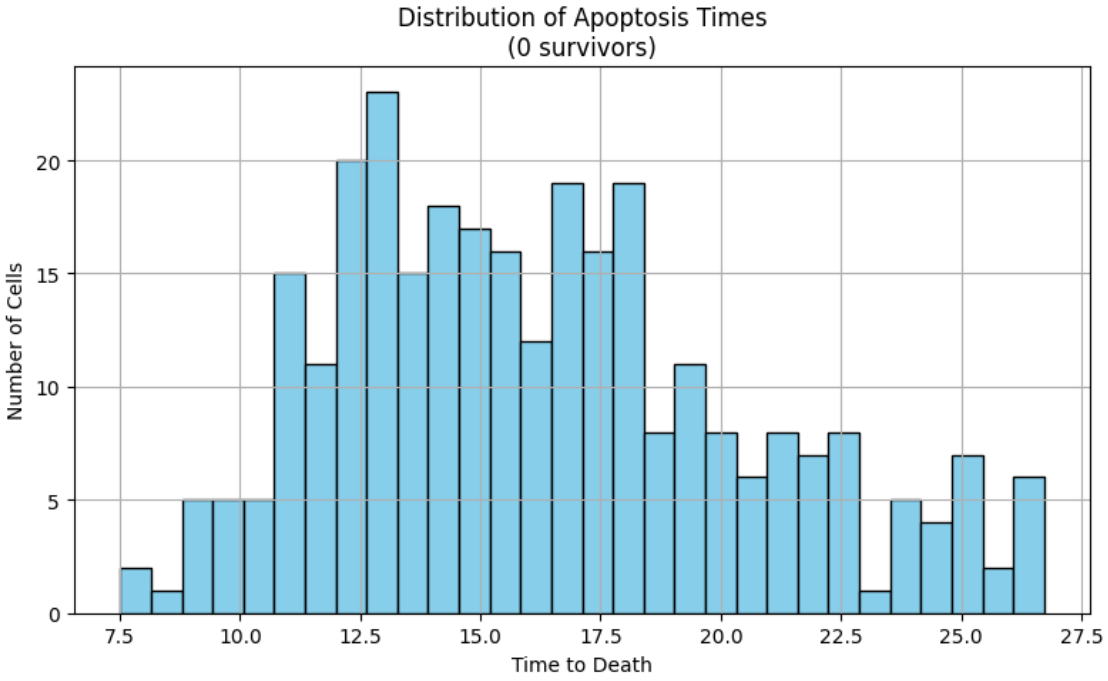
- I — initiator caspase (e.g., Caspase-8)
- M — mitochondrial signal (e.g., cytochrome c)
- E — effector caspase (e.g., Caspase-3)
- k_1, k_2, k_3 — activation rate constants

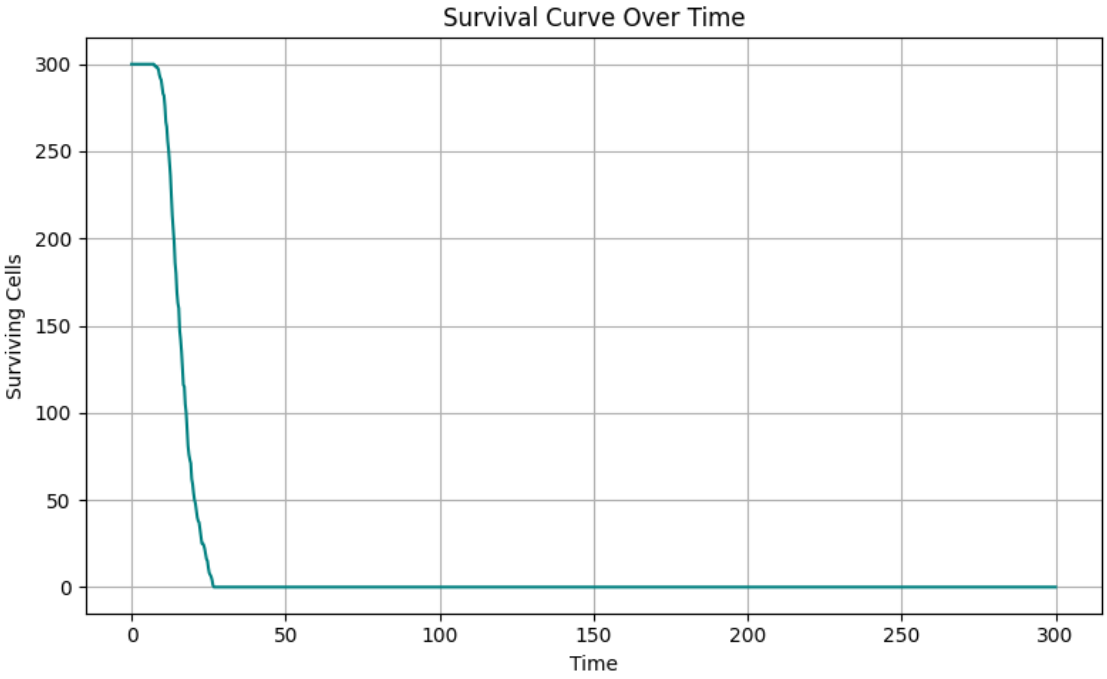
- $\delta_I, \delta_M, \delta_E$ — degradation/inactivation rates
- K_d — inhibition constant (represents Bcl-2 activity)
- α — feedback strength from E to I

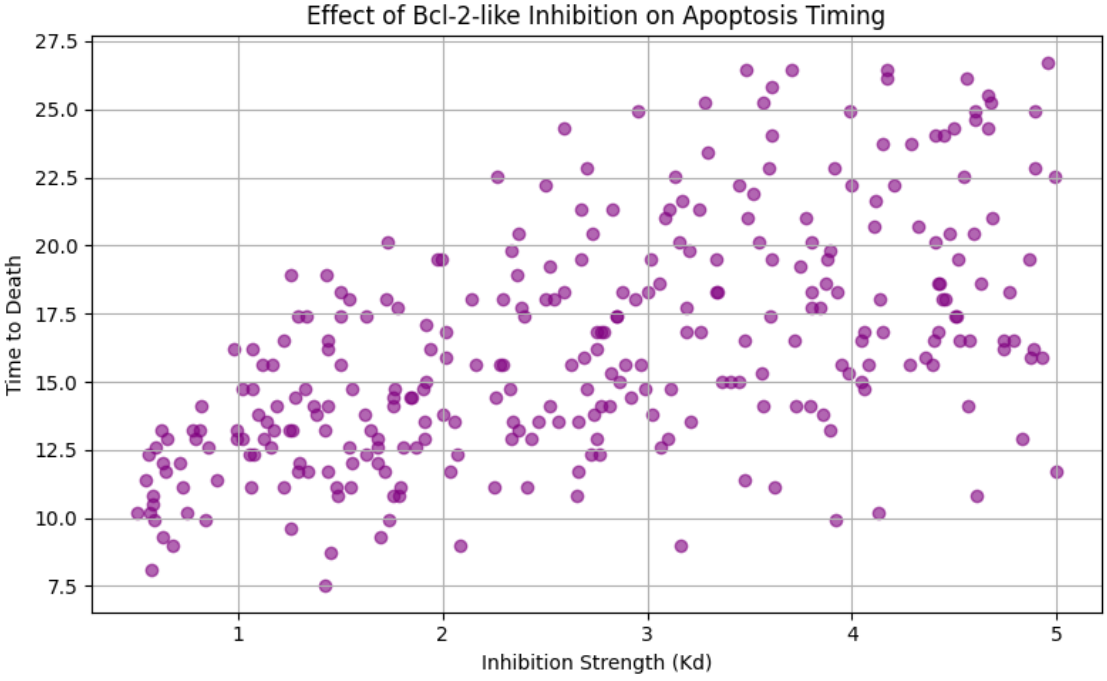
[6]:
```
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import solve_ivp

# --------------------------------
# Parameters (Adjusted)
# --------------------------------
k1 = 0.2      # Increased TRAIL signal strength
k2 = 1.0
k3 = 0.5

delta_I = 0.01
delta_M = 0.05
delta_E = 0.1

death_threshold = 20  # Lowered threshold for clearer outputs
use_feedback = True

n_cells = 300
t_max = 300
t_eval = np.linspace(0, t_max, 1000)

# --------------------------------
# ODE System
# --------------------------------
def apoptosis_model(t, y, k1, k2, k3, kd, feedback):
    I, M, E = y
    k1_eff = k1 / (1 + 0.01 * E) if feedback else k1
    dI_dt = k1_eff - delta_I * I
    dM_dt = (k2 * I) / (kd + I + 1e-6) - delta_M * M
    dE_dt = k3 * M - delta_E * E
    return [dI_dt, dM_dt, dE_dt]

# --------------------------------
# Simulate One Cell
# --------------------------------
def simulate_cell(kd, feedback):
    I0 = np.abs(np.random.normal(0, 3))
    M0 = np.abs(np.random.normal(0, 2))
    E0 = np.abs(np.random.normal(0, 2))
```

```
    sol = solve_ivp(apoptosis_model, [0, t_max], [I0, M0, E0],
                    args=(k1, k2, k3, kd, feedback), t_eval=t_eval)

    for t, e in zip(sol.t, sol.y[2]):
        if e >= death_threshold:
            return t
    return np.inf

# ------------------------------
# Run Simulation
# ------------------------------
death_times = []
kd_values = []

for _ in range(n_cells):
    kd = np.random.uniform(0.5, 5)  # Reduced inhibition range
    kd_values.append(kd)
    death_times.append(simulate_cell(kd, feedback=use_feedback))

death_times = np.array(death_times)
kd_values = np.array(kd_values)

# ------------------------------
# Visualization
# ------------------------------
# Histogram of death times
plt.figure(figsize=(8, 5))
plt.hist(death_times[death_times != np.inf], bins=30, color='skyblue',␣
 ↪edgecolor='black')
plt.xlabel("Time to Death")
plt.ylabel("Number of Cells")
plt.title(f"Distribution of Apoptosis Times\n({np.sum(death_times == np.inf)}␣
 ↪survivors)")
plt.grid(True)
plt.tight_layout()
plt.show()

# Survival Curve
survival_curve = [(death_times > t).sum() for t in t_eval]
plt.figure(figsize=(8, 5))
plt.plot(t_eval, survival_curve, color='teal')
plt.xlabel("Time")
plt.ylabel("Surviving Cells")
plt.title("Survival Curve Over Time")
plt.grid(True)
plt.tight_layout()
plt.show()
```

```
# Scatter plot: Kd vs. Time to Death
plt.figure(figsize=(8, 5))
plt.scatter(kd_values[death_times != np.inf], death_times[death_times != np.
  ↪inf], alpha=0.6, color='purple')
plt.xlabel("Inhibition Strength (Kd)")
plt.ylabel("Time to Death")
plt.title("Effect of Bcl-2-like Inhibition on Apoptosis Timing")
plt.grid(True)
plt.tight_layout()
plt.show()
```




Survival Curve Over Time
Surviving Cells
Time
0
50
100
150
200
250
300


Effect of Bcl-2-like Inhibition on Apoptosis Timing
Time to Death
Inhibition Strength (Kd)
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
1
2
3
4
5

0.0.3 Interpretation

The simulation captures how cell-to-cell variability in protein levels and inhibitory signaling leads to heterogeneous responses to TRAIL-induced apoptosis.

- **Histogram**: Shows a wide distribution of death times, indicating that even with the same drug dose, some cells die quickly while others delay or survive entirely.
- **Survival Curve**: Demonstrates how the population gradually undergoes apoptosis over time, instead of an all-at-once response.
- **Scatter Plot (Kd vs. Time to Death)**: Reveals a clear trend where higher inhibition strength (simulating Bcl-2 levels) delays or prevents apoptosis. This supports the idea that **non-genetic resistance** to therapy can arise purely from differences in protein abundance or signaling strength.

These results align with experimental observations and emphasize the importance of considering biological variability when designing and evaluating cancer treatments.