Modeling Gene Expression Noise Using a Dual-Reporter System

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This Python script simulates gene expression in single cells using the Gillespie stochastic simulation algorithm. Specifically, it models the dynamics of two synthetic fluorescent reporters—CFP (cyan fluorescent protein) and YFP (yellow fluorescent protein)—under identical expression conditions to analyze noise in gene expression.

Each reporter undergoes:

- Transcription (DNA → mRNA),
- Translation (mRNA → protein),
- mRNA degradation, and
- Protein degradation,

with all kinetic rates shared between CFP and YFP.

The simulation is repeated across a population of virtual cells (n_cells = 500), and for each cell, the final protein counts of CFP and YFP are recorded.

The purpose is to quantify intrinsic and extrinsic noise:

- Intrinsic noise reflects random fluctuations within each gene expression pathway.
- Extrinsic noise captures cell-wide fluctuations that affect both reporters similarly.
- Total noise includes both components and is computed from the average reporter expression.

Finally, the script visualizes the data as a scatter plot comparing CFP and YFP levels in each cell, highlighting the correlation due to extrinsic variability.

This type of simulation and analysis is commonly used in systems biology and synthetic biology to explore how stochastic processes affect gene regulation at the single-cell level.

This code is based on paper "Intrinsic and extrinsic contributions to stochasticity in gene expression" by Elowitz et al. (2002) and the Gillespie algorithm for simulating chemical reactions.

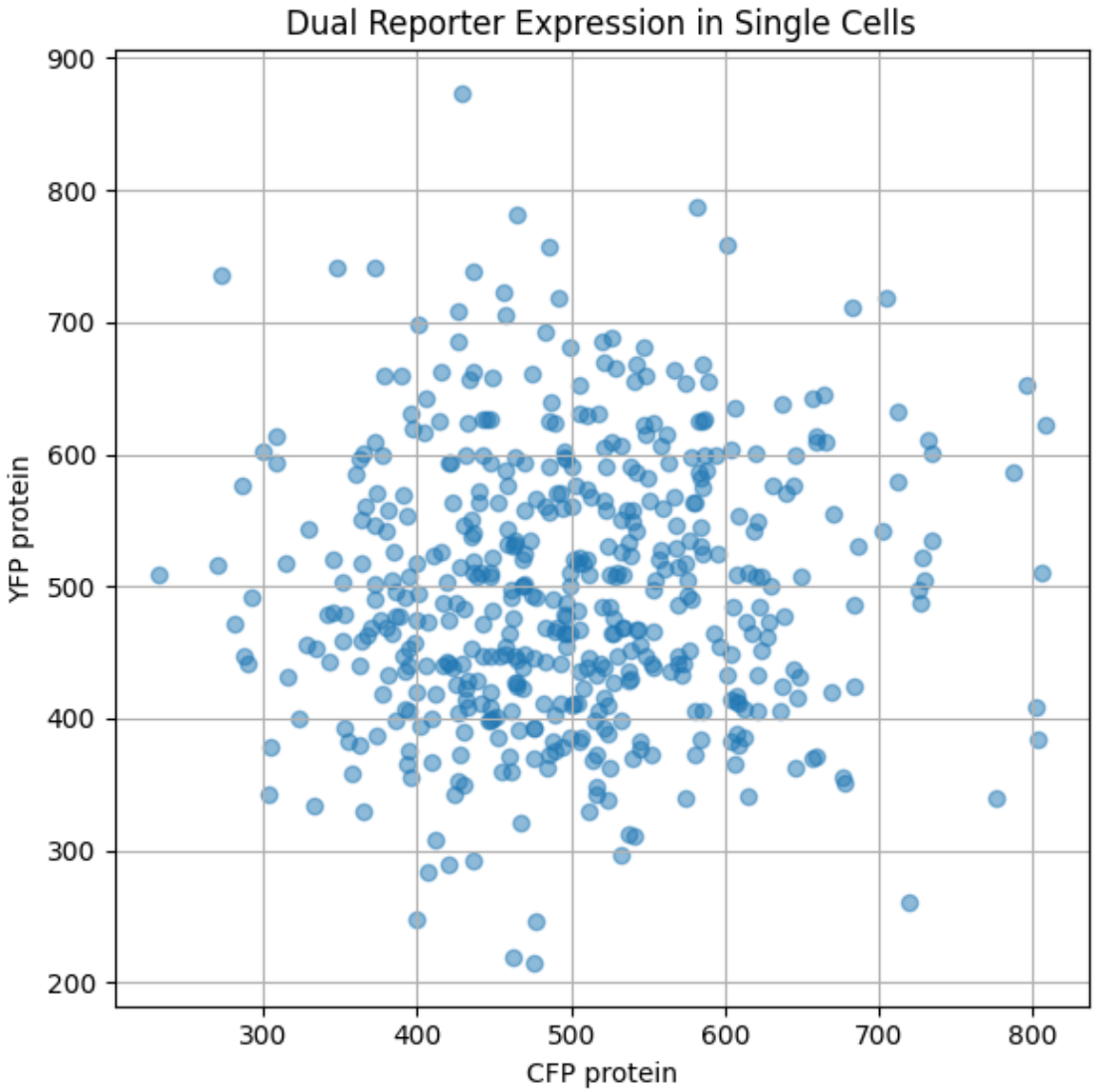
[2]:
```
import numpy as np
import matplotlib.pyplot as plt
from tqdm import tqdm

# Set model parameters
k_tx = 1.0      # transcription rate (DNA → mRNA)
k_tl = 5.0      # translation rate (mRNA → protein)
gamma_m = 0.2   # mRNA degradation rate
```

```
gamma_p = 0.05  # protein degradation rate

# Simulation parameters
T = 500         # simulation time
n_cells = 500   # number of cells to simulate

# Store final protein levels for each cell
cfp_data = []
yfp_data = []

def gillespie_simulate():
    # Initial counts: [mRNA_CFP, Protein_CFP, mRNA_YFP, Protein_YFP]
    state = np.array([0, 0, 0, 0])
    t = 0

    while t < T:
        mC, pC, mY, pY = state

        # Propensities
        a = [
            k_tx,            # transcribe CFP
            k_tl * mC,       # translate CFP
            gamma_m * mC,    # degrade CFP mRNA
            gamma_p * pC,    # degrade CFP protein

            k_tx,            # transcribe YFP
            k_tl * mY,       # translate YFP
            gamma_m * mY,    # degrade YFP mRNA
            gamma_p * pY     # degrade YFP protein
        ]

        a0 = sum(a)
        if a0 == 0:
            break

        # Time until next reaction
        r1, r2 = np.random.random(2)
        tau = -np.log(r1) / a0
        t += tau

        # Choose reaction
        r = r2 * a0
        cum_sum = np.cumsum(a)
        reaction_index = np.searchsorted(cum_sum, r)

        # Reaction update vectors
        updates = [
```

```
            [1, 0, 0, 0],   # transcribe CFP
            [0, 1, 0, 0],   # translate CFP
            [-1, 0, 0, 0],  # degrade CFP mRNA
            [0, -1, 0, 0],  # degrade CFP protein
            [0, 0, 1, 0],   # transcribe YFP
            [0, 0, 0, 1],   # translate YFP
            [0, 0, -1, 0],  # degrade YFP mRNA
            [0, 0, 0, -1],  # degrade YFP protein
        ]

        state += updates[reaction_index]

    return state[1], state[3]  # return final protein levels: [CFP, YFP]

# Run simulations
for _ in tqdm(range(n_cells), desc="Simulating cells"):
    cfp, yfp = gillespie_simulate()
    cfp_data.append(cfp)
    yfp_data.append(yfp)

cfp_data = np.array(cfp_data)
yfp_data = np.array(yfp_data)

# Compute intrinsic and extrinsic noise
mean_cfp = np.mean(cfp_data)
mean_yfp = np.mean(yfp_data)

# Total noise
total_var = np.var((cfp_data + yfp_data) / 2)
total_noise = total_var / ((mean_cfp + mean_yfp)/2)**2

# Intrinsic noise (variance of difference)
int_noise = np.var(cfp_data - yfp_data) / (2 * ((mean_cfp + mean_yfp)/2)**2)

# Extrinsic noise
ext_noise = total_noise - int_noise

print(f"Intrinsic noise: {int_noise:.4f}")
print(f"Extrinsic noise: {ext_noise:.4f}")
print(f"Total noise:     {total_noise:.4f}")

# Plot
plt.figure(figsize=(6,6))
plt.scatter(cfp_data, yfp_data, alpha=0.5)
plt.xlabel("CFP protein")
plt.ylabel("YFP protein")
plt.title("Dual Reporter Expression in Single Cells")
```

```
plt.grid(True)
plt.tight_layout()
plt.show()
```

```
Simulating cells: 100%|      | 500/500 [04:29<00:00,  1.85it/s]

Intrinsic noise: 0.0391
Extrinsic noise: -0.0173
Total noise:     0.0218
```



0.0.1 Interpretation of the Scatter Plot

The scatter plot above shows the simulated final protein levels of CFP and YFP for 500 individual cells, modeled using the stochastic Gillespie algorithm. Both proteins are produced independently under identical promoters, mimicking the experimental setup from Elowitz et al. (2002).

Each point represents a single cell. If gene expression were entirely deterministic and identical across cells, all points would fall on a single spot. However, due to the stochastic nature of gene expression, we observe a cloud of points centered roughly around the mean expression level for each reporter.

There is clear spread along the diagonal (bottom-left to top-right), which indicates extrinsic noise — shared fluctuations that affect both genes equally, such as variability in RNA polymerase or ribosome levels from cell to cell.

There is also spread perpendicular to the diagonal, which reflects intrinsic noise — random fluctuations in the expression of each gene independently, even within the same cell.

Together, this distribution shows that both intrinsic and extrinsic noise contribute to gene expression variability in this system. This matches the findings of Elowitz et al., validating the simulation and providing a foundation to explore how noise might be affected by other regulatory mechanisms (such as feedback or different promoter strengths).