Appendix C: Stochastic Implementations

C1. Hybrid Stochastic–Deterministic Framework

To capture stochastic effects arising at low plasmid copy number, a hybrid modeling framework is employed. Plasmid copy number $P(t)$ is treated as a discrete stochastic variable,

$$P(t) \in [0, 1, 2, \dots]$$

while intracellular antimicrobial concentration $A(t)$, efflux pump mRNA $M(t)$, and efflux pump protein $Q(t)$, are treated as continuous deterministic variables.

Between stochastic events in $P(t)$, the continuous variables evolve according to the deterministic ODE system defined in Appendix A. This formulation defines a piecewise-deterministic Markov process (PDMP).
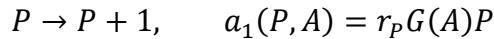
C2. Stochastic Reaction Channels

Plasmid copy-number dynamics are modeled as a continuous-time Markov jump process, with replication and loss events occurring as Poisson processes with state-dependent propensities.
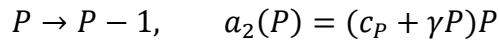
At time t, the system state is:

$$\big(A(t), P(t), M(t), Q(t)\big)$$

The following stochastic reactions are permitted:

Plasmid replication

$$P \rightarrow P + 1, \qquad a_1(P, A) = r_P G(A) P$$

Plasmid loss

$$P \rightarrow P - 1, \qquad a_2(P) = (c_P + \gamma P) P$$

The total propensity is:

$$a_0 = a_1 + a_2$$

C3. Event Timing and Selection

When $a_0 > 0$, the waiting time τ until the next stochastic event is exponentially distributed:

$$\tau = -\frac{1}{a_0} \ln (u_1)$$

where $u_1 \sim Uniform(0,1)$

The type of event is determined by a second independent uniform random variable u_2:

- If $u_2 < a_1/a_0$, a replication event occurs.
- Otherwise, a plasmid loss event occurs.

If $a_0 = 0$ (i.e. $P = 0$), no further stochastic events are possible and the system remains plasmid-free.

C4. Quantitative Outcome Measures

The stochastic formulation allows estimation of biologically meaningful quantities not accessible in the deterministic model. In particular:

Plasmid extinction probability:

$$\mathbb{P}_{ext} = \frac{1}{N} \sum_{i=1}^{N} I_i^{ext}$$

where $I_i^{ext} = 1$ if extinction occurs in realization i, and 0 otherwise.

Resistance emergence probability:

$$\mathbb{P}_{rescue} = 1 - \mathbb{P}_{ext}$$

C5. Gillespie-Type Simulation Algorithm

```
t = 0
A = A0, P = P0, M = 0, Q = 0

while t < TMAX:

    if P == 0:
        record extinction
        break

    compute a1 = rP * G(A) * P
    compute a2 = (cP + gamma * P) * P
    a0 = a1 + a2

    if a0 == 0:
        record extinction
        break

    draw u1, u2 ~ Uniform(0,1)
    tau = -(1/a0) * ln(u1)

    integrate ODEs for A, M, Q from t to t + tau with P fixed

    if u2 < a1 / a0:
        P = P + 1
    else:
        P = P - 1

    t = t + tau
```