Appendix C: Stochastic Implementations

C1. Stochastic Integration for Plasmid Dynamics

A hybrid modelling approach is adopted, in which plasmid copy-number $P(t)$ is treated as a discrete, stochastic variable:

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

While intracellular antimicrobial concentration $A(t)$, plasmid-encoded mRNA $M(t)$, and efflux protein $Q(t)$, are treated as continuous, deterministic variables evolving between stochastic events.

This defines a piecewise-deterministic Markov process (PDMP), combining stochastic jumps in P and deterministic ODE evolution of the remaining state variables.

C2. Stochastic Reactions

At any simulation step t, the system state is given by:

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

where:

- $P(t) \in \mathbb{N}_0$ is stochastic.
- $A(t), M(t), Q(t) \in \mathbb{R}_{\geq 0}$ is deterministic.

At a given state, the following reactions are possible:

1. Plasmid replication

$$P \to P + 1$$

   with propensity:

$$a_1(P, A) = r_P G(A) P$$

2. Plasmid loss

$$P \to P - 1$$

   with propensity:

$$a_2(P) = (c_P + \gamma P) P$$

Total propensity:

$$a_0 = a_1 + a_2$$

If $a_0 > 0$, the time to the next stochastic event is sampled from an exponential distribution:

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

where $u_1 \approx \; Uniform(0,1)$

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

- If $u_2 < a_1/a_0$, replication occurs.

- Otherwise, plasmid loss occurs.

If $a_0 = 0$, no further stochastic events are possible (i.e. $P = 0$).

C3. Quantitative Analysis and Probabilities

The stochastic formulation enables measurement of biologically meaningful quantities that cannot be obtained from the deterministic model alone. Particularly:

1. Plasmid extinction probability:

$$\mathbb{P}_{ext} = \frac{1}{N}\sum_{i=1}^{N} I_i^{ext} \begin{cases} 1, if\ extinct \\ 0\ otherwise \end{cases}$$

2. Resistance emergence probability:

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

C4. Gillespie Simulation and Pseudocode

```
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)
    Sample next reaction time: 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
```
