

## Appendix C: Stochastic Implementations

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### 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.

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### C2. Stochastic Reactions

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

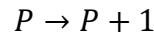
$$(A(t), P(t), M(t), Q(t))$$

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:

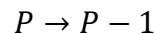
1. Plasmid replication



with propensity:

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

2. Plasmid loss



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.  $P = 0$ ).

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### 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:

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

2. Resistance emergence probability:

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


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### C4. Gillespie Simulation and Pseudocode

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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
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