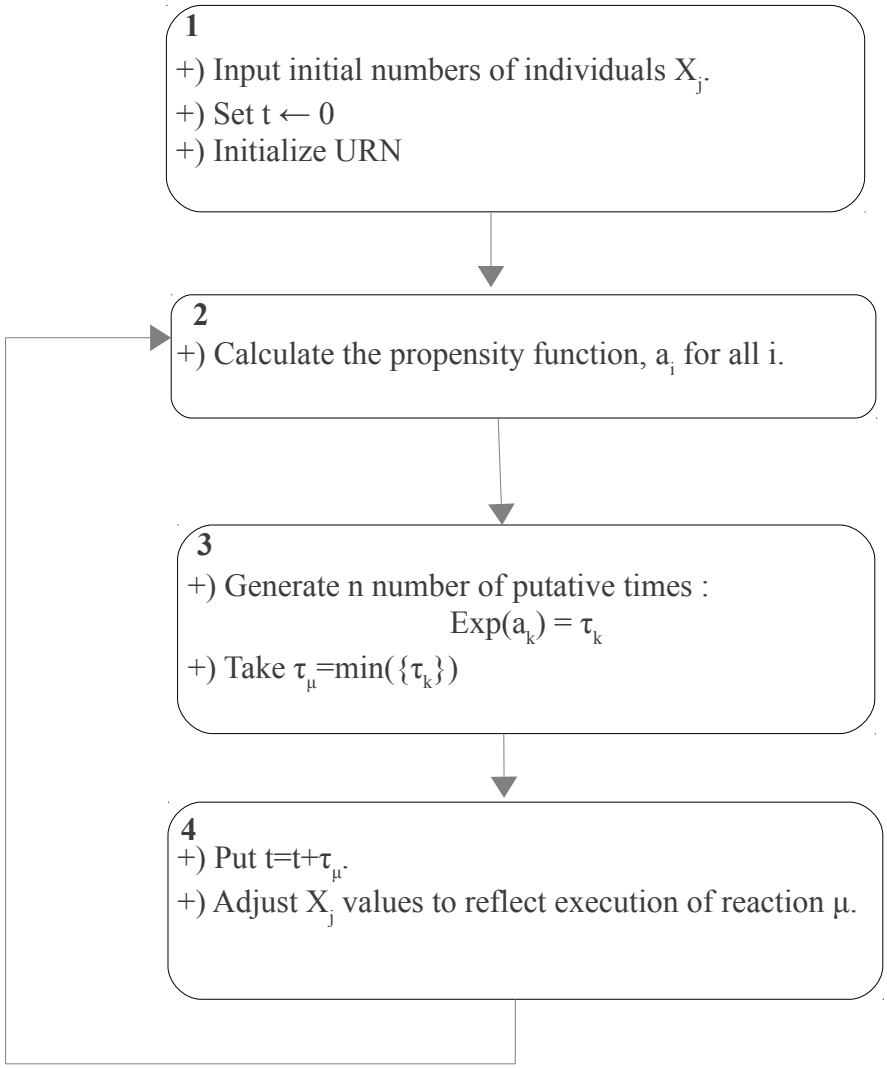
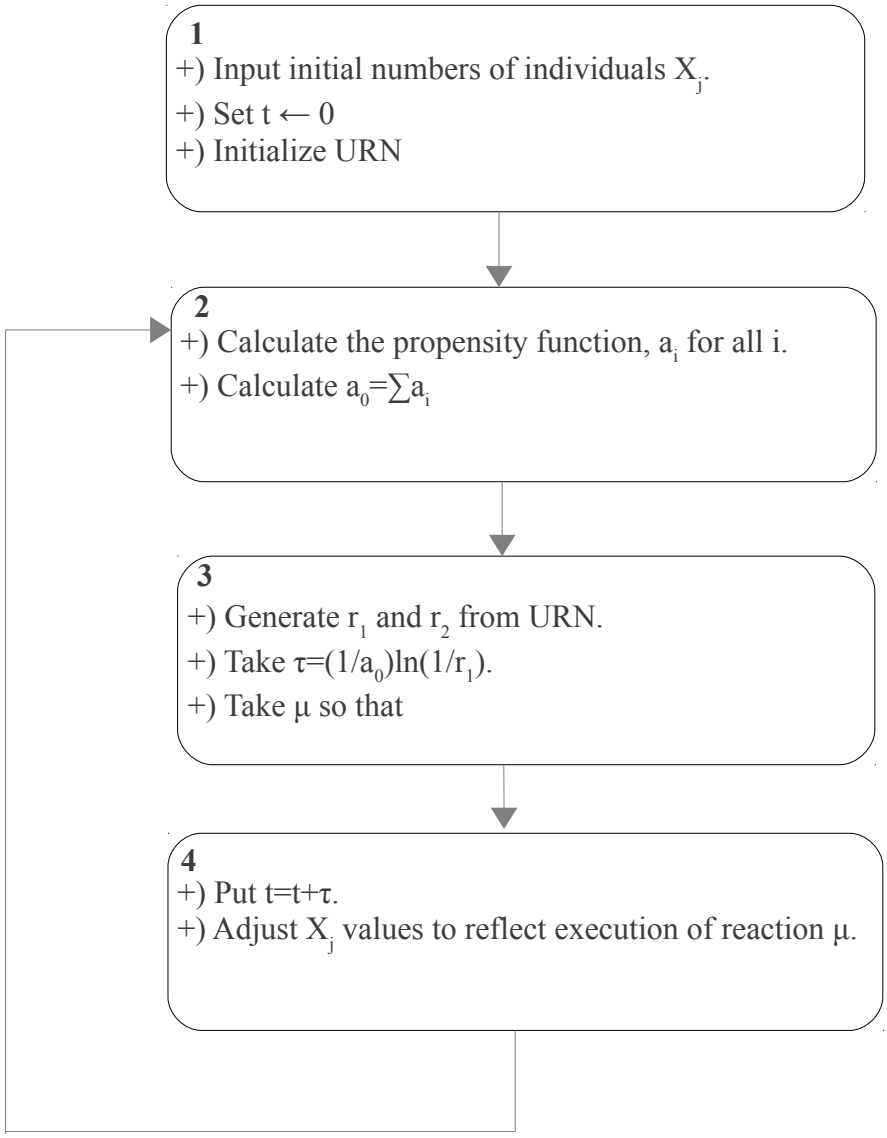
Exact Stochastic Simulation – First Reaction Method (1976) by Gillespie



- In the FRM, we generate times, $\{\tau\mu\}$, for all M reactions and choose the reaction, k, with the smallest time, τk .
- Only a few species will change population as a result of this reaction--the rest will remain constant.
- For most reactions, the propensity functions will remain constant.
- For these, the times can be reused in the subsequent step to find the next reaction: $\{\tau\mu\} \rightarrow \{\tau\mu - \tau k\}$.
- When there are many different species and reactions, this NRM approach can be done with far fewer random number than the FRM.
- Particularly useful for compartmental or Reaction-Diffusion processes.

Exact Stochastic Simulation – Direct Method (Gllespie) 1977

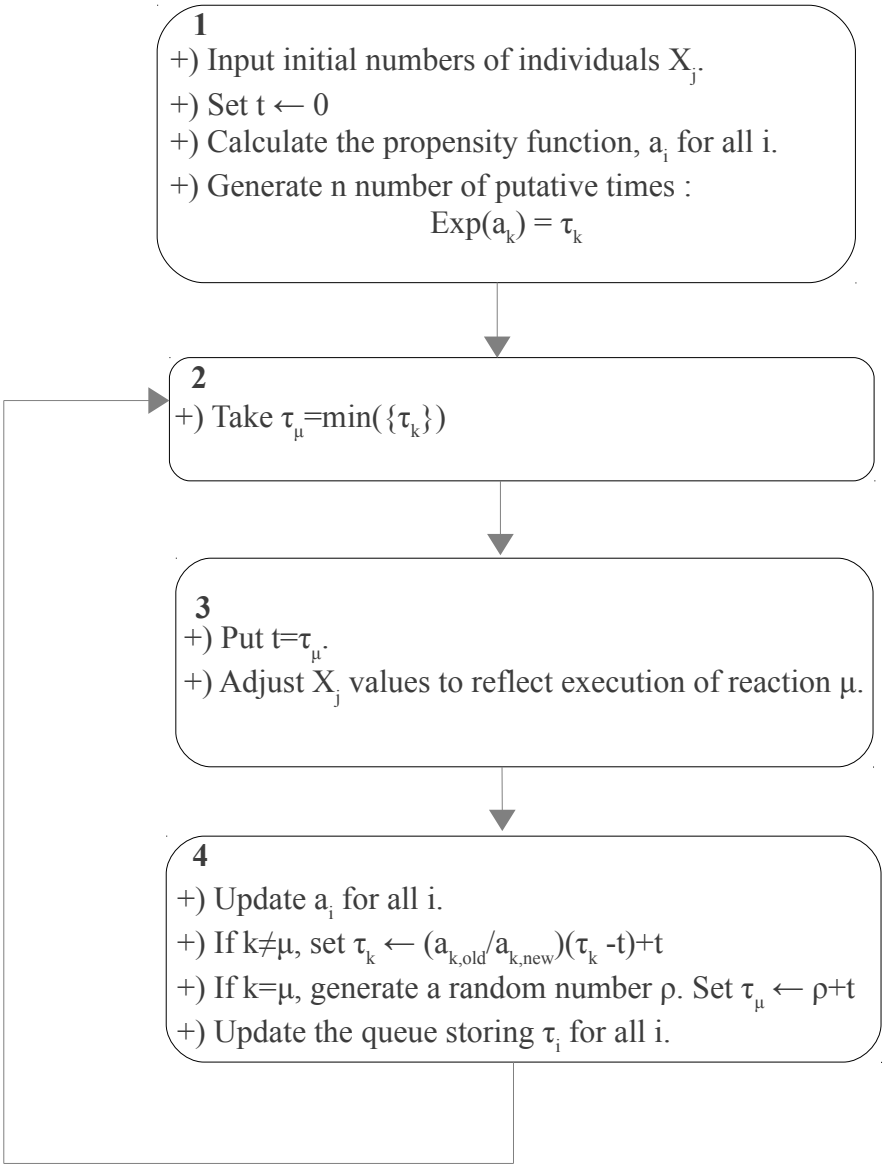


As written, this algorithm uses two random numbers per iteration, takes time proportional to the number of reactions to update the propensity function a_i (chiếm một khoảng thời gian tỉ lệ thuận với số lượng các phản ứng, tức là nếu số lượng p/u tăng thì mất càng nhiều thời gian) , and takes time proportional to the number of reactions to calculate total_a_i and to generate a random number according to the probability distribution. The ideas can be used to make the algorithm more efficient, so that the time it takes is proportional to the logarithm of the number of reactions (mất một khoảng thời gian tỉ lệ thuận với log của n với n is number of reactions).

Advantages:

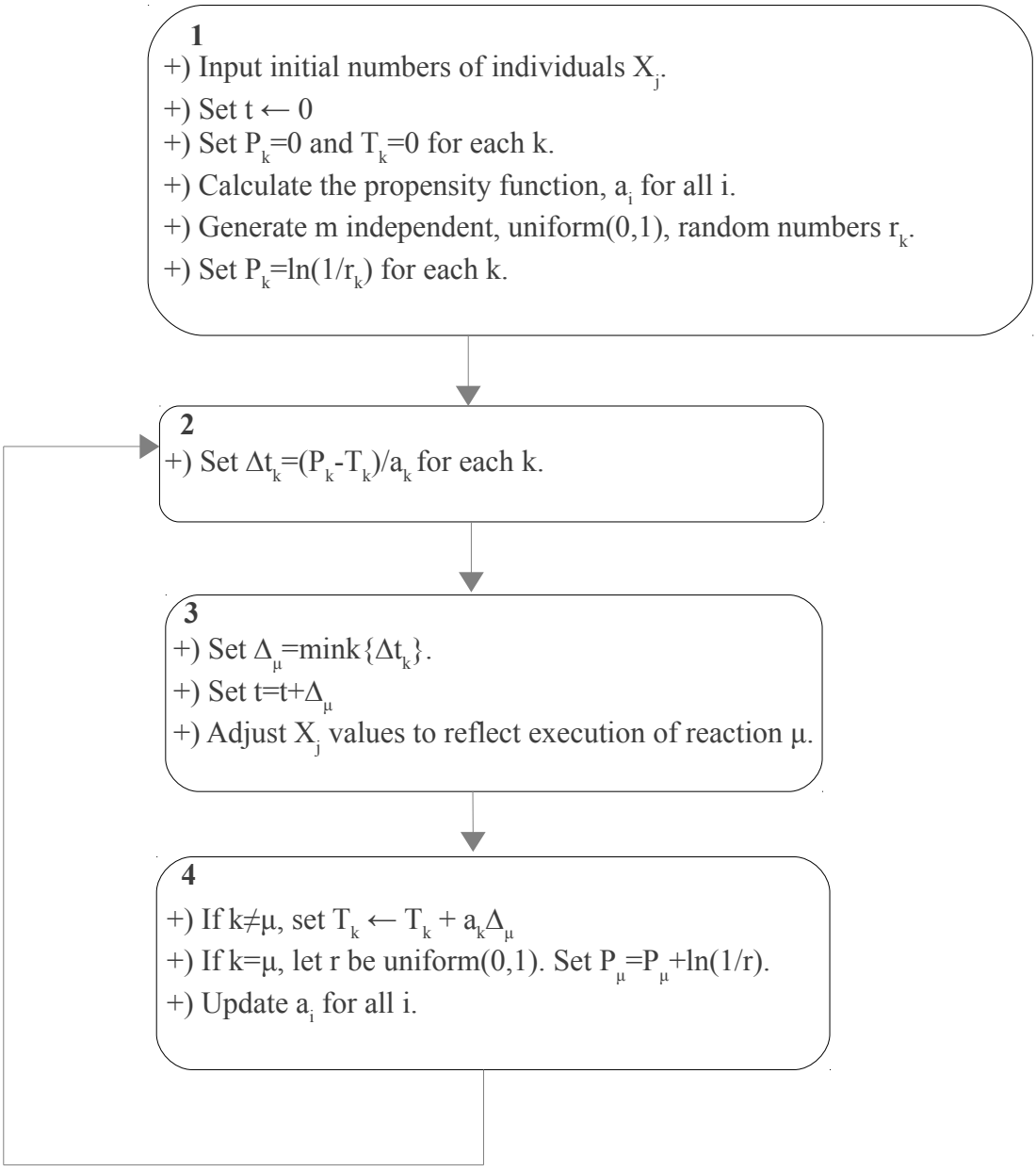
- For time invariant processes, the **Direct is preferable to the First** alg:
  - 1) FIRST is difficult to do the indexing necessary to implement the efficient update aglo.
  - 2) FIRST generates cycle two many random numbers. Since typical computer pseudo-random number generator and should be avoided with extreme prejudice.
  - 3) generating random numbers is relatively slow.

Stochastic Simulation – Next Reaction Method by Gibson and Bruck 2000



- O(log(r)), r is number of reactions
- The Next Reaction Method words even if k is large, but will achieve more of speedup if k is small, relative to the number of reactions. (k is number of edges)
- **Advantages:**
  The **Direct/ NEXT method**:
  - NEXT uses just a single random number per iteration. So as not to regenerate any other random number. Always find a sure random number.

Exact Stochastic Simulation – Modified Next Reaction Method
by Anderson 2007



Approximative Stochastic Simulation – Tau leaping

SSA/Tau-Leaping Methods

- SSA must proceed one reaction at a time, it is much too slow for most practical problems.
- **Tau-Leaping asks the question**: How many times does each action channel fire in each subinterval? In each step, the tau-leaping method can proceed with many reactions?.
- **Stiffness** reflects the presence of multiple timescales, the fastest of which are stable. Stiffness is a well-known challenge in the deterministic simulation of chemically reacting systems.
  - For stiff systems, the stepsize of explicit methods must be restricted to maintain numerical stability. In the case of discrete stochastic simulation using the explicit tau-leaping method, which limits to the explicit Euler method as the population of each chemical species becomes very large, the stepsize must be similarly restricted to maintain numerical stability. Implicit tau-leaping methods have been proposed to solve this problem, in particular the implicit tau method and the trapezoidal tau method.

- **Leap Condition**: Require to be small enough that the change in the state during [t; t+ τ) will be so small that no propensity function will suffer an appreciable change in its value.
- **The basic (explicit) tau-leaping method** proceeds as follows: Choose a value for that satisfies the Leap Condition. Generate for each j = 1, …, M a sample value kj of the Poisson random variable P(aj(x)), and update the state.
  - the explicit Euler formula ~ explicit tau-leaping is known to be inefficient when applied to stiff problems.
- **The implicit tau formula is proposed to handle the stiffness.**
  - the implicit tau formula allows much larger stepsizes than the explicit tau formula, when applied to stiff stochastic systems.
- If a problem is known to be stiff, the implicit tau-leaping methods can be applied along with the stiff tau -selection formula. If a problem is non stiff, it is better to use explicit tau-leaping because it is cheaper per step.
- **Problem:** What if we do not have this knowledge before the simulation? Or what if the system presents dynamical behavior such that in one time period it is stiff but in another time period it is nonstiff?
- **Adaptive Tau-Leaping algo** arise as follows:
- dfds
-

1

+) Given state x at time t

+) Define the set of indices of critical reactions:
(the maximum number of times C_j that R_j can fire before exhauting one of its reactants)

$$\mathscr{C} := \left\{ m \in \{1,\ldots,M\} : \alpha_m(x) > 0 \wedge \min_{i:\nu_{im}<0} \left\lfloor \frac{x_i}{|\nu_{im}|} \right\rfloor < n_c \right\}$$

2

+) Compute candidate step sizes $\tau^{(expl)}$, $\tau^{(impl)}$ for explicit and implicit tau-leaping.

3

+) If $\tau^{(expl)} < n_a/\alpha_0(x) \Lambda \tau^{(impl)} < n_a/\alpha_0(x)$
Then simulate n_b single reactions, update t and x, and goto 1.

4

+) Compute candidate step size T as expected time to next critical reaction:
Generate $T \sim \text{Exponential}(\Sigma\alpha_m(x))$

5

+)If $\tau^{(expl)} > \min(\tau^{(impl)}/n_d; T)$
then use explicit tau-leaping with $\tau := \min(\tau^{(expl)}; T)$;
else use implicit tau-leaping with $\tau := \min(\tau^{(impl)}; T)$;

6

+)If $x+\Sigma k_m v_m$ has negative components
then reduce $\tau^{(expl)}$ and $\tau^{(impl)}$; and goto 3.

Exact Stochastic Simulation – Direct Method (Gllespie) 1977 for multipopulation