First Reaction Method (exact 1976)

- 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:

$$\{\tau\mu\} \rightarrow \{\tau\mu - \tau k\}.$$

N événements

a_k fonction de propensité avec k={1,N}

1. N tirages τ_k=Exp(a_k)

2. T_μ=min({τ_k})

3. Mise à jour→ des **Vector Event**

→ des **a_k**.

Direct Method
(exact 1977 by Gillespie) - monopopulation

Advantages:

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 too many random numbers.

3) generating random numbers is relatively slow.

N événements

a_k fonctions de propensités avec k={1,N}

1. 01 tirage $\tau=Exp(\Sigma a_k)$

2. **01 tirage** pour choisir l'événement μ selon la formule

$$\sum_{\nu=1}^{\mu-1} a_\nu < r_2 a_0 \leq \sum_{\nu=1}^{\mu} a_\nu$$

3. Mise à jour → des **Vector Event**

→ des $\mathbf{a_k}$.

Next Reaction Method (exact 2000 by Gibson and Bruck)

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.

N événements

a_k fonctions de propensités avec k={1,N}

1. N tirages $\tau_k = Exp(a_k)$
2. **$T_\mu = min(\{\tau_k\})$**
3. Mise à jour → des **Vector Event**
   → des **a_k**.
4. Mise à jour des τ_α ($\alpha \neq \mu$) selon la formule

$$\tau_\alpha \leftarrow (a_{\alpha,old}/a_{\alpha,new})(\tau_\alpha - t) + t$$

5. **01 tirage pour τ_α ($\alpha = \mu$)**

Modified Next Reaction Method (exact 2007 by Anderson)

- **NEXT/Modified NEXT** have the same simulation speeds.
- The two are equivalent.
- Modified NEXT extends itself to systems with time dependent rate constants in a smooth way whereas NEXT does not (ex: systems with delays)

N événements

a_k fonctions de propensités avec k={1,N}

τ_k=0 avec k={1,N}

1. N tirages pour T_k=Exp(a_k)
2. **T_μ=min({τ_k})**
3. Mise à jour → des **Vector Event**.
4. Mise à jour des τ_k($k\neq\mu$) selon une formule
5. 01 tirage pour τ_k ($k=\mu$) pour mettre à jour P_μ
6. **Mise à jour → des a_k.**

Adaptive Tau-leaping Method (approx 2007 by Yang Cao et al.)

- **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. 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.

Adaptive Tau-leaping Method (approx 2007 by Yang Cao et al.)

- **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.
  - **Disadvantage**: to be inefficient when applied to stiff problems.
- The implicit tau-leaping method: allows much larger stepsizes than the explicit tau formula, when applied to stiff stochastic systems.
- **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:

Adaptive Tau-leaping Method (approx 2007 by Yang Cao et al.)

- **2001:** D.Gillespie. Approximate accelerated stochastic simulation of chemically reacting systems.
- **2004:** Y.Cao, H.Li and L.Petzold. Ecient formulation of the stochastic simulation algorithm for chemically reacting systems.
- **2007:** Y.Cao, D.Gillespie and Linda R. Petzold. The Adaptive Explicit-Implicit Tau-Leaping Method with Automatic Tau Selection.

Adaptive Tau-leaping Method (approx 2007 by Yang Cao et al.)

While(t<tmax){

0. State **x** at time **t** avec **N** événements

a_k fonctions de propensités avec k={1,N}

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

2. Compute step size $\mathcal{T}$: $\boldsymbol{\mathcal{T} \sim Exp(\Sigma \alpha_m(x))}$

3. If $\boldsymbol{\tau^{(expl)} > \min(\tau^{(impl)}/n_d; \mathcal{T})}$

then use explicit tau-leaping with $\tau := \min(\tau^{(expl)}; \mathcal{T})$;

else use implicit tau-leaping with $\tau := \min(\tau^{(impl)}; \mathcal{T})$;

4. Update $\boldsymbol{x+\Sigma k_m v_m}$ **and** $\boldsymbol{t \leftarrow t+\mathcal{T}}$

}

Direct Method
(exact 1977 by Gillespie) - multipopulation

m villes, chaque ville a **N** événements

a_k fonctions de propensités avec k={1,N}

1. 01 tirages $\tau=Exp(\Sigma a_k)$

2. **01 tirage** pour chosir quelle ville où l'événement se produit.

3. **01 itrage** pour choisir l'événement μ à la ville choisir.

4. Mise à jour → des **Vector Event**

→ des $\mathbf{a_k}$.