MENU

A Delay Chemical Master Equation and a Delay Stochastic Simulation Algorithm

(on request oil, salt and pepper)

G. Caravagna
Ph.D. Lunchtime Seminar

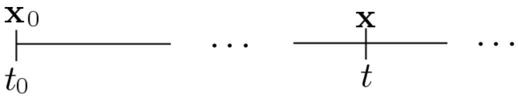
"Il partito dominante, non potendo trasformare apertamente le scuole di stato in scuole di partito, manda in malora le scuole di stato per dare la prevalenza alle scuole private." (P.C.,'50)

Index

Index

The CME ['77]

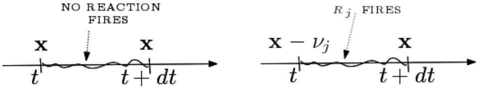
- $\mathbf{X}(t) = \mathbf{x}$ is the vector state at time t;
- $\mathbf{X}(t_0) = \mathbf{x}_0$ is the initial configuration;
- dt so small that at most one reaction fires;
- $P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)$ is the probability that, given the initial configuration, at time t the system is described by the state vector $\mathbf{x}$.



The CME ['77]

Two events:

- at time t the system is already in state $\mathbf{x}$ and in the infinitesimal time $[t; t+dt[$ no reaction fires;
- at time t the system is in state $\mathbf{x}-\nu_j$ and reaction R_j fires.

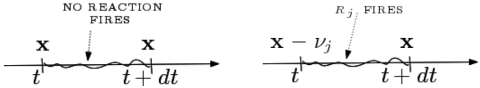


$$P(\mathbf{x}, t+dt \mid \mathbf{x}_0, t_0) = P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)\left(1-\sum_{j=1}^{M} a_j(\mathbf{x})dt\right)$$
$$+\sum_{j=1}^{M} P(\mathbf{x}-\nu_j, t \mid \mathbf{x}_0, t_0)\cdot a_j(\mathbf{x}-\nu_j).$$

The CME ['77]

Two events:

- at time t the system is already in state $\mathbf{x}$ and in the infinitesimal time $[t; t+dt[$ no reaction fires;
- at time t the system is in state $\mathbf{x} - \nu_j$ and reaction R_j fires.



$$P(\mathbf{x}, t+dt \mid \mathbf{x}_0, t_0) = P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)\left(1 - \sum_{j=1}^{M} a_j(\mathbf{x})dt\right)$$

$$+ \sum_{j=1}^{M} P(\mathbf{x}-\nu_j, t \mid \mathbf{x}_0, t_0) \cdot a_j(\mathbf{x}-\nu_j).$$

Index

The SSA ['77]

1. Initialize the time $t = t_0$ and the system state $\mathbf{x} = \mathbf{x}_0$.
2. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(\mathbf{x})$ and their sum $a_0(\mathbf{x}) = \sum_{j=1}^{M} a_j(\mathbf{x})$.
3. Given two random numbers $r_1, r_2 \in U[0;1]$, generate values for τ and j accordingly to

$$\tau = \frac{1}{a_0(\mathbf{x})} \ln(\frac{1}{r_1})$$

$$\sum_{i=1}^{j-1} a_i(\mathbf{x}) < r_2 \cdot a_0(\mathbf{x}) \leq \sum_{i=1}^{j} a_i(\mathbf{x})$$

then update $\mathbf{x} = \mathbf{x} + \nu_j$ and $t = t + \tau$, go to step 2.

Why delays

- application driven in tumor–immune:

  "An immune system is a collection of mechanisms within an organism that protects against disease by identifying and killing pathogens and tumor cells [..]. An antigen or immunogen is a substance that prompts the generation of antibodies and can cause an immune response."
  (Wikipedia)

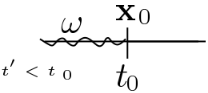
- more detailed modeling;
- mathematically reasonable (DDEs as extensions of ODEs);

A lot of applications for DDEs and, consequently, for delayed stochastic processes.

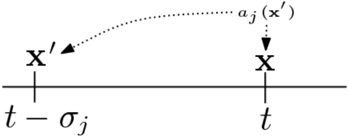
Index

Modifications

- Reactions:
  - R_j has a delay $\sigma_j \geq 0$.
- Propensity functions:
  - a_j depends on the state $\mathbf{X}(t - \sigma_j)$.
- Initial Configuration:
  - $\mathbf{X}(t_0) = \mathbf{x}_0$ as expected;
  - function ω, $\mathbf{X}(t) = \omega(t)$ if $t < t_0$.



INITIAL CONFIGURATION

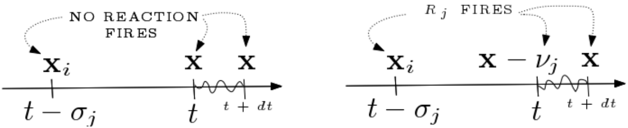


DELAYED PROP. FUN.

Index

Construction of the DCME

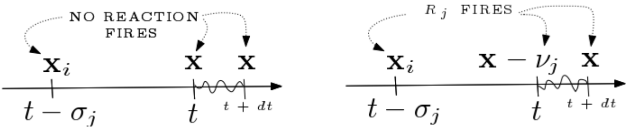
- at time t the system is already in state $\mathbf{x}$ and, at delayed time $t-\sigma_j$, the system was in state $\mathbf{x}_i$, no reactions fire;
- at time t the system is in state $\mathbf{x}-\nu_j$ and, at delayed time $t-\sigma_j$, the system was in state $\mathbf{x}_i$, reaction R_j fires.



$$P(\mathbf{x}, t+dt) = P(\mathbf{x}, t)\left(1 - \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}_i, t-\sigma_j)\cdot a_j(\mathbf{x}_i)dt\right)$$
$$+ \sum_{j=1}^{M} P(\mathbf{x}-\nu_j, t)\left(\sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}_i, t-\sigma_j)\cdot a_j(\mathbf{x}_i)dt\right)$$

Construction of the DCME

- at time t the system is already in state $\mathbf{x}$ and, at delayed time $t-\sigma_j$, the system was in state $\mathbf{x}_i$, no reactions fire;
- at time t the system is in state $\mathbf{x}-\nu_j$ and, at delayed time $t-\sigma_j$, the system was in state $\mathbf{x}_i$, reaction R_j fires.



$$P(\mathbf{x}, t+dt) = P(\mathbf{x}, t)\left(1 - \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}_i, t-\sigma_j)\cdot a_j(\mathbf{x}_i)dt\right)$$

$$+ \sum_{j=1}^{M} P(\mathbf{x}-\nu_j, t)\left(\sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}_i, t-\sigma_j)\cdot a_j(\mathbf{x}_i)dt\right)$$

The DCME

With some tricks we get:

$$\frac{\partial P(\mathbf{x}, t \mid \mathbf{x}_0, t_0; \omega)}{\partial t} = \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x} - \nu_j, t; \mathbf{x}_i, t - \sigma_j \mid \mathbf{x}_0, t_0; \omega) \cdot a_j(\mathbf{x}_i)$$

$$- \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}, t; \mathbf{x}_i, t - \sigma_j \mid \mathbf{x}_0, t_0; \omega) \cdot a_j(\mathbf{x}_i)$$

The DCME

With some tricks we get:

$$\frac{\partial P(\mathbf{x}, t \mid \mathbf{x}_0, t_0; \omega)}{\partial t} = \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x} - \nu_j, t; \mathbf{x}_i, t - \sigma_j \mid \mathbf{x}_0, t_0; \omega) \cdot a_j(\mathbf{x}_i)$$
$$- \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}, t; \mathbf{x}_i, t - \sigma_j \mid \mathbf{x}_0, t_0; \omega) \cdot a_j(\mathbf{x}_i)$$

As expected, if all σ_j's are 0, the DCME is the CME.

$$\frac{\partial P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)}{\partial t} = \sum_{j=1}^{M} P(\mathbf{x} - \nu_j, t \mid \mathbf{x}_0, t_0) \cdot a_j(\mathbf{x} - \nu_j) - \sum_{j=1}^{M} P(\mathbf{x}, t \mid \mathbf{x}_0, t_0) \cdot a_j(\mathbf{x}).$$

The DCME

With some tricks we get:

$$\frac{\partial P(\mathbf{x}, t \mid \mathbf{x}_0, t_0; \omega)}{\partial t} = \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x} - \nu_j, t; \mathbf{x}_i, t - \sigma_j \mid \mathbf{x}_0, t_0; \omega) \cdot a_j(\mathbf{x}_i)$$

$$- \sum_{j=1}^{M} \sum_{\mathbf{x}_i \in \mathbb{I}(\mathbf{x})} P(\mathbf{x}, t; \mathbf{x}_i, t - \sigma_j \mid \mathbf{x}_0, t_0; \omega) \cdot a_j(\mathbf{x}_i)$$

As expected, if all σ_j's are 0, the DCME is the CME.

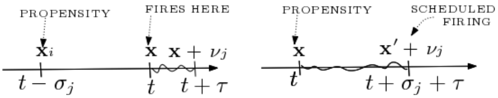
$$\frac{\partial P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)}{\partial t} = \sum_{j=1}^{M} P(\mathbf{x} - \nu_j, t \mid \mathbf{x}_0, t_0) \cdot a_j(\mathbf{x} - \nu_j) - \sum_{j=1}^{M} P(\mathbf{x}, t \mid \mathbf{x}_0, t_0) \cdot a_j(\mathbf{x}).$$

Index

Interpreting delays

Two different interpretations for delays:

1. non–scheduled events:
   - propensities delayed;
   - reactions as in th SSA.
2. scheduled events:
   - propensities non–delayed;
   - reactions scheduled at future time.



Handling Discontinuities

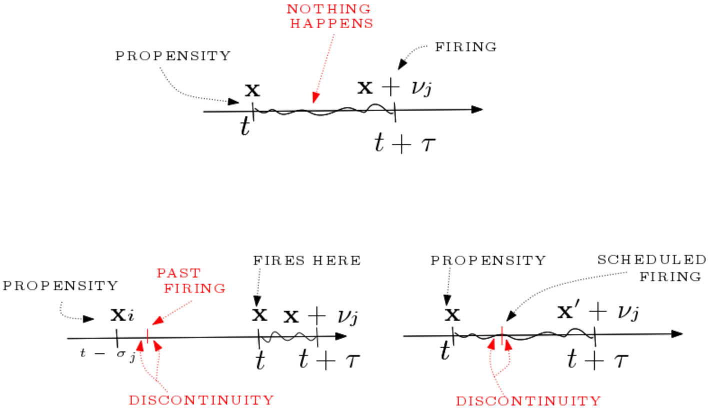
One common problem:

1. given the system at time t;
2. let τ be the time for next reaction;

The propensities have to be **constant** in $[t; t + \tau]$.

1. this always holds in the SSA;
2. *does not always hold here.* :-(

Handling Discontinuities



The DSSA (1)

1. Initialize the time $t = t_0$ and the system state $\mathbf{x} = \mathbf{x}_0$.
2. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(t)$ and their sum $a_0(t) = \sum_{j=1}^{M} a_j(\mathbf{X}(t - \sigma_j))$;
3. Given a random number r_1 uniformally distributed in the interval $[0;1]$, generate values for τ and θ_t accordingly to

$$\tau = \frac{1}{a_0(t)} \ln(\frac{1}{r_1}) \qquad \theta_t = \min\{\theta_{t,j} \mid j = 1, \ldots, M\}$$

   3.1 If $\tau < \theta_t$ then, if r_2 is a random number uniformally distributed in the interval $[0;1]$, select reaction R_j such that

$$\sum_{i=1}^{j-1} a_i(\mathbf{X}(t - \sigma_i)) < r_2 \cdot a_0(t) \leq \sum_{i=1}^{j} a_i(\mathbf{X}(t - \sigma_i))$$

   then update $\mathbf{x} = \mathbf{x} + \nu_j$ and $t = t + \tau$;

   3.2 else $\tau \geq \theta_t$, then $t = t + \theta_t$;
4. go to step 2.

The DSSA (1)

1. Initialize the time $t = t_0$ and the system state $\mathbf{x} = \mathbf{x}_0$.
2. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(t)$ and their sum $a_0(t) = \sum_{j=1}^{M} a_j(\mathbf{X}(t - \sigma_j))$;
3. Given a random number r_1 uniformly distributed in the interval $[0;1]$, generate values for τ and θ_t accordingly to

$$\tau = \frac{1}{a_0(t)} \ln\left(\frac{1}{r_1}\right) \qquad \theta_t = \min\{\theta_{t,j} \mid j = 1, \ldots, M\}$$

   3.1 If $\tau < \theta_t$ then, if r_2 is a random number uniformly distributed in the interval $[0;1]$, select reaction R_j such that

$$\sum_{i=1}^{j-1} a_i(\mathbf{X}(t-\sigma_i)) < r_2 \cdot a_0(t) \leq \sum_{i=1}^{j} a_i(\mathbf{X}(t-\sigma_i))$$

   then update $\mathbf{x} = \mathbf{x} + \nu_j$ and $t = t + \tau$;

   3.2 else $\tau \geq \theta_t$, then $t = t + \theta_t$;
4. go to step 2.

The DSSA (1)

1. Initialize the time $t = t_0$ and the system state $\mathbf{x} = \mathbf{x}_0$.
2. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(t)$ and their sum $a_0(t) = \sum_{j=1}^{M} a_j(\mathbf{X}(t - \sigma_j))$;
3. Given a random number r_1 uniformally distributed in the interval $[0;1]$, generate values for τ and θ_t accordingly to

$$\tau = \frac{1}{a_0(t)} \ln(\frac{1}{r_1}) \qquad \theta_t = \min\{\theta_{t,j} \mid j = 1, \ldots, M\}$$

   3.1 If $\tau < \theta_t$ then, if r_2 is a random number uniformally distributed in the interval $[0;1]$, select reaction R_j such that

$$\sum_{i=1}^{j-1} a_i(\mathbf{X}(t - \sigma_i)) < r_2 \cdot a_0(t) \leq \sum_{i=1}^{j} a_i(\mathbf{X}(t - \sigma_i))$$

   then update $\mathbf{x} = \mathbf{x} + \nu_j$ and $t = t + \tau$;

   3.2 else $\tau \geq \theta_t$, then $t = t + \theta_t$;
4. go to step 2.

The DSSA (2)

1. Initialize the time $t = t_0$ and the system state $\mathbf{x} = \mathbf{x}_0$.
2. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(t)$ and their sum $a_0(t) = \sum_{j=1}^{M} a_j(\mathbf{X}(t))$;
3. Given two random numbers r_1, r_2 uniformally distributed in the interval $[0;1]$, generate values for τ and j accordingly to

$$\tau = \frac{1}{a_0(t)} \ln(\frac{1}{r_1}) \qquad \sum_{i=1}^{j-1} a_i(\mathbf{X}(t)) < r_2 \cdot a_0(t) \leq \sum_{i=1}^{j} a_i(\mathbf{X}(t))$$

   3.1 If delayed reaction R_k is scheduled within $[t; t+\tau]$ then update $\mathbf{x} = \mathbf{x} + \nu_k$ and $t = t + \tau_k$;
   3.2 else, schedule R_j at time $t + \sigma_j + \tau$, set time to $t + \sigma_j$;
4. go to step 2.

The DSSA (2)

1. Initialize the time $t = t_0$ and the system state $\mathbf{x} = \mathbf{x}_0$.
2. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(t)$ and their sum $a_0(t) = \sum_{j=1}^{M} a_j(\mathbf{X}(t))$;
3. Given two random numbers r_1, r_2 uniformally distributed in the interval $[0; 1]$, generate values for τ and j accordingly to

$$\tau = \frac{1}{a_0(t)} \ln(\frac{1}{r_1}) \qquad \sum_{i=1}^{j-1} a_i(\mathbf{X}(t)) < r_2 \cdot a_0(t) \leq \sum_{i=1}^{j} a_i(\mathbf{X}(t))$$

   3.1 If delayed reaction R_k is scheduled within $[t; t+\tau]$ then update $\mathbf{x} = \mathbf{x} + \nu_k$ and $t = t + \tau_k$;
   3.2 else, schedule R_j at time $t + \sigma_j + \tau$, set time to $t + \sigma_j$;
4. go to step 2.

Index

Starters

The Chemical Master Equation

The Stochastic Simulation Algorithm

Soup of the day

Scenario

The Delayed Chemical Master Equation

The Delayed Stochastic Simulation Algorithms

Dessert

Examples

What to do

Predator–prey model with harvesting

$$\frac{dx}{dt} = r_1 x(t)\left(1 - \frac{1}{K}x(t)\right) - bx(t)y(t) - H$$
$$\frac{dy}{dt} = -r_2 y(t) + cx(t-\tau)y(t-\tau)$$

- logistic growth of the preys;
- non–linear predation;
- linear death of the predators;
- constant harvesting;

Predator–prey model with harvesting

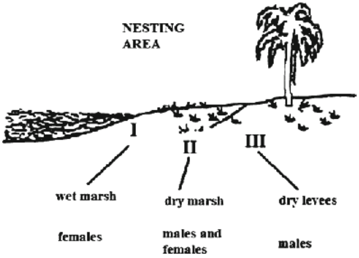
$$\frac{dx}{dt} = r_1 x(t)\left(1 - \frac{1}{K}x(t)\right) - bx(t)y(t) - H$$
$$\frac{dy}{dt} = -r_2 y(t) + cx(t-\tau)y(t-\tau)$$

- logistic growth of the preys;
- non–linear predation;
- linear death of the predators;
- constant harvesting;
- delayed effect of predation.

$$X + Y \overset{c}{\mapsto} X + 2Y \quad \text{with delay } \tau$$

Crocodilian population

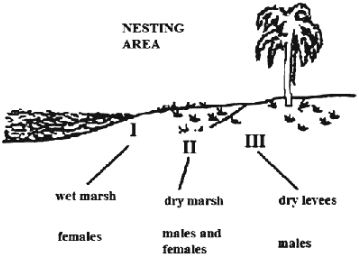
"In crocodilian populations, the choice of nesting site determines the sex of hatchlings. In the wet marsh, cool temperatures primarily produce female hatchlings. The hot temperatures of the dry levees result in primarily male hatchlings. The dry marsh has an intermediate temperature profile, resulting in hatchlings of both sexes."



- two populations: juvenile and adults;
- three regions: wet/dry marsh and levees;

Crocodilian population

"In crocodilian populations, the choice of nesting site determines the sex of hatchlings. In the wet marsh, cool temperatures primarily produce female hatchlings. The hot temperatures of the dry levees result in primarily male hatchlings. The dry marsh has an intermediate temperature profile, resulting in hatchlings of both sexes."



- two populations: juvenile and adults;
- three regions: wet/dry marsh and levees;
- delays: at any time t, the juvenile females born at time $t-\tau$ years ago who have survived τ years enter the adult female population.

Index

Future works

- Extending delays:
  - time–dependent delays;
  - stochastic delays;
  - ...
- Implementation issues delay–dependent;
- DSSA and formal methods:
  - PT Nets with time;
  - Timed/History–dependent Automata;
  - ...

References

P. Calamandrei. **Discorso al III Congresso ADSN**. *Scuola Democratica* (2:iv), pp. 1–5, 1950.

R. Schlicht et al., **A Delay Stochastic Process with Applications in Molecular Biology**, *Journal of Mathematical Biology* 57(5) (2008), 613–648.

G.Caravagna et al., **??**, *Journal on My Desk*.

A. Martin et al., **Predator-prey Models with Delay and Prey Harvesting**, *Journal of Mathematical Biology* 43(3) (2001), 247–267.