

On the Interpretation of Delays in Delay Stochastic Simulation of Biological Systems

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Systems Biology

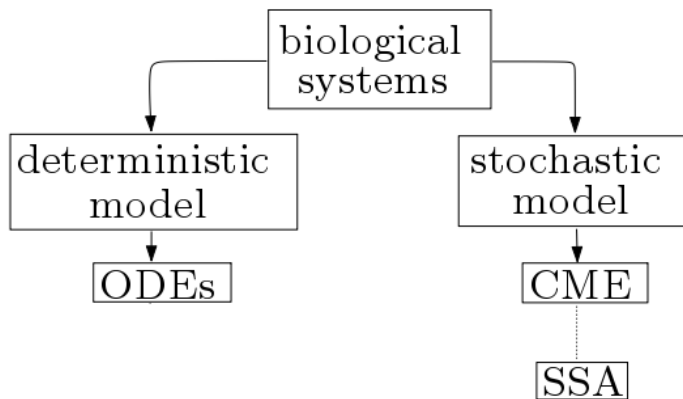
An interdisciplinary field of research regarding:

- the study of the **interactions** between the **components** of *biological systems*, and how these interactions give **rise** to the function and behavior of that system.

i.e.: metabolic pathways, cellular evolution,

- The main aim consists of building **real** models:
 - ▶ via observations / measurements / interactions with experts;
 - ▶ by using specific languages.
- models have to be analyzed:
 - ▶ via **simulation** (deterministic, stochastic);
 - ▶ model checking;

Systems Biology Workflow



The Stochastic Simulation Algorithm [Gillespie, 1977]

Any reaction R_j is associated with a propensity function $a_j(\mathbf{x})$ providing the probability of R_j to fire in state \mathbf{x} .

- 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

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

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

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

The use of delays: a **dual** view

Given a complex dynamics composed by many sub-events (i.e. the cell-cycle). Suppose you know, at least, the average time σ for completion of the whole complex dynamics.

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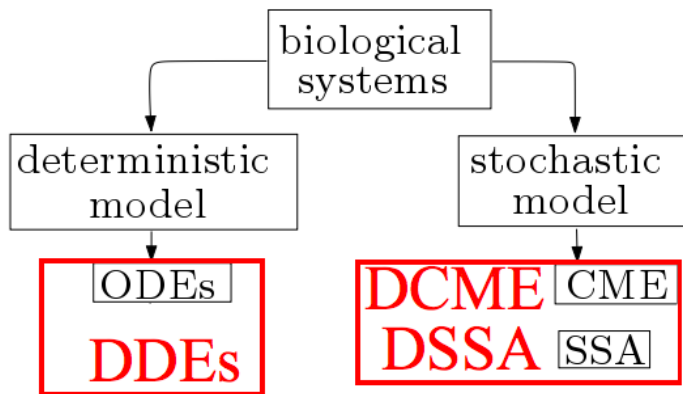
- 1 If the knowledge of the sub-events is incomplete (unobservable, unmeasurable) then the whole dynamics cannot be modeled:
 - ▶ Use σ as an **abstraction**.

The use of delays: a **dual** view

Given a complex dynamics composed by many sub-events (i.e. the cell-cycle). Suppose you know, at least, the average time σ for completion of the whole complex dynamics.

- 1 If the knowledge of the sub-events is incomplete (unobservable, unmeasurable) then the whole dynamics cannot be modeled:
 - ▶ Use σ as an **abstraction**.
- 2 If the whole dynamics is computationally too expensive to be simulated;
 - ▶ Use σ as a **simplification**.

Systems Biology Workflow (extended with delays)



Delay Stochastic Simulation Algorithms (DSSAs)

- extensions of the *Gillespie's* Algorithm;
- related to the Delayed Chemical Master Equation;
- combine delayed and non-delayed reactions;

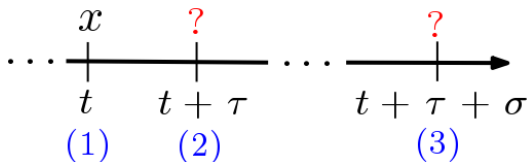
Barrio et al., 2006: DSSA with an interpretation of delays as duration.

Cai and Anderson, 2007: improve the performance of Barrio's DSSA.

All based on an interpretation of delays as **duration**.

Delays as duration

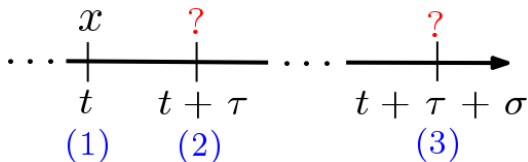
Given the reaction: $A + B \xrightarrow{k, \sigma} C$



- (1) current state: $\mathbf{X}(t) = x$;
- (2) next state: $\mathbf{X}(t + \tau) = x - \{A, B\}$, (i.e. removed reactants);
- (3) scheduled event: $\mathbf{X}(t + \tau + \sigma) = x' + \{C\}$, (i.e. inserted products).

Delays as duration

Given the reaction: $A + B \xrightarrow{k, \sigma} C$



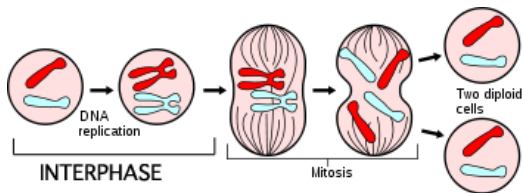
- (1) current state: $\mathbf{X}(t) = x$;
 - (2) next state: $\mathbf{X}(t + \tau) = x - \{A, B\}$, (i.e. removed reactants);
 - (3) scheduled event: $\mathbf{X}(t + \tau + \sigma) = x' + \{C\}$, (i.e. inserted products).
- any scheduled reaction in $[t, t + \tau]$ has priority.
 - reactants **excluded** from **any** event in $[t, t + \tau + \sigma]$;

Delays as duration: the DSSA

- 1 Initialize the time $t = t_0$ and the system state $\mathbf{X}(t_0) = \mathbf{x}_0$.
- 2 Evaluate all the propensity functions;
- 3 Compute time for next reaction, τ ;
- 4 Select next reaction, R_j ;
 - (A) If delayed reaction R_k is scheduled at time $t + \tau_k$ and $\tau_k < \tau$ then update $\mathbf{x} = \mathbf{x} + \nu_k^p$ and $t = t + \tau_k$;
 - (B) else:
 - (B1) If $R_j \in \mathcal{R}_{nd}$ then update $\mathbf{x} = \mathbf{x} + \nu_j$ and $t = t + \tau$;
 - (B2) If $R_j \in \mathcal{R}_c$, schedule R_j at time $t + \sigma_j + \tau$, update $\mathbf{x} = \mathbf{x} + \nu_k^r$ and set time to $t + \tau$;
- 5 go to step 2.

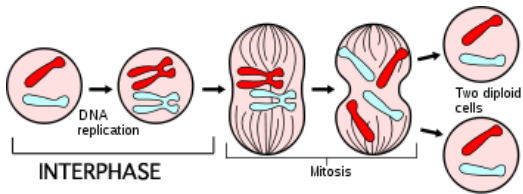
An example: the cell cycle

Four phases: resting (G_1), DNA replication (S), gap (G_2), mitosis (M).



We classify cells in two populations (*Vilassana et al.*):

- T_I : cells in the interphase (G_1 , S and G_2);
- T_M : cells in the mitotic phase (M).



Non-delayed events:

- in any phase a cell may die (i.e. via apoptosis);
- a cell divides (one T_M becomes two T_I).

Delayed events:

- a cell lasts σ time units in the interphase, then starts mitosis (the passage from G_1 to S and from S to G_2 are abstracted by using σ).

The DDEs model by *Villasana et al.* is:

$$\begin{aligned}\frac{dT_I}{dt} &= 2a_4 T_M - d_2 T_I - a_1 T_I(t - \sigma) & T_I(t) &= \phi_0(t) \text{ for } t \in [-\sigma, 0] \\ \frac{dT_M}{dt} &= a_1 T_I(t - \sigma) - d_3 T_M - a_4 T_M & T_M(t) &= \phi_1(t) \text{ for } t \in [-\sigma, 0]\end{aligned}$$

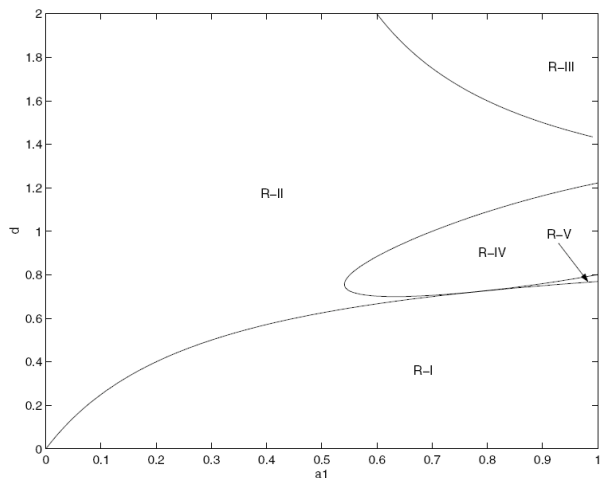
with extended initial conditions in $[-\sigma, 0]$ and explicit number of cells.

- Where are delays?

*The number of cells that enter mitosis at time t depends on the number of cells that entered the interphase σ **time units before**, $T(t - \sigma)$.*

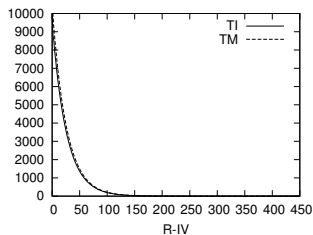
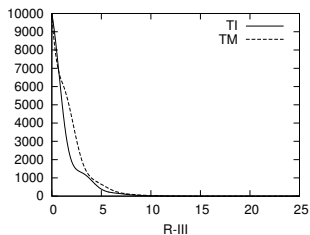
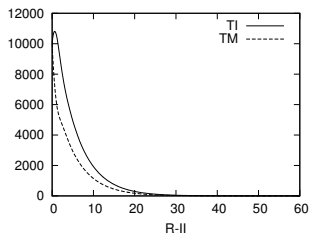
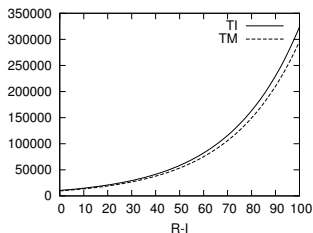
Delays correspond to dependencies to past-states of the system.

Deterministic Simulation



	R-I	R-II	R-III / V	R-IV
$\sigma = 1.0$	∞	$(0, 0)$	$(0, 0)$	$(0, 0)$
$\sigma = 10.0$	∞	osc. $(0, 0)$	osc. ∞	osc. $(0, 0)$

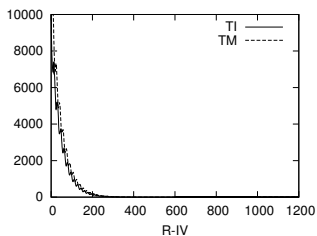
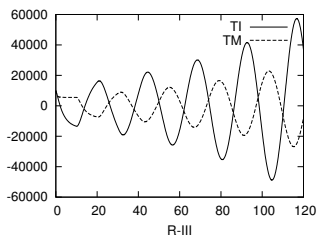
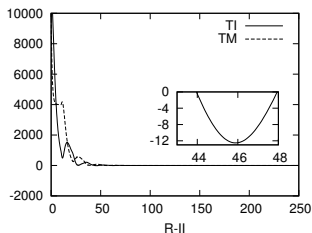
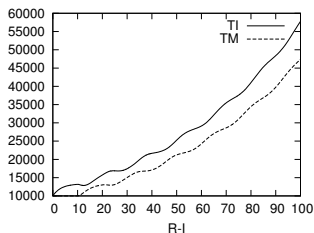
Deterministic Simulation



	R-I	R-II	R-III / V	R-IV
$\sigma = 1.0$	∞	50	15	238

First observable day with $T_I(t)$ and $T_M(t) < 1.0$.

Deterministic Simulation

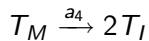


	R-I	R-II	R-III / V	R-IV
$\sigma = 10.0$	∞	59	12	440

First observable day with $T_I(t)$ and $T_M(t) < 1.0$.

Stochastic Simulation

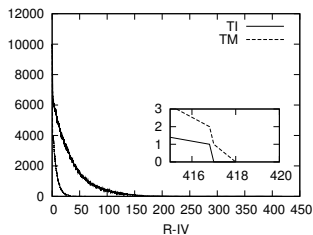
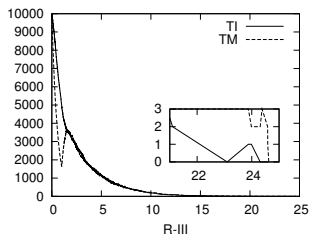
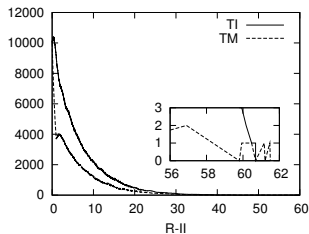
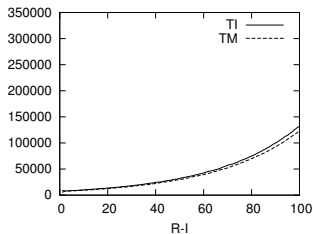
The equivalent stochastic model is given by three non-delayed reaction:



and the delayed reaction:

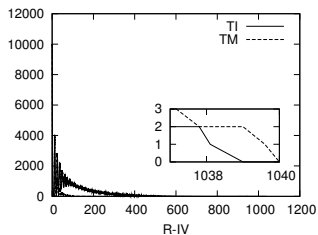
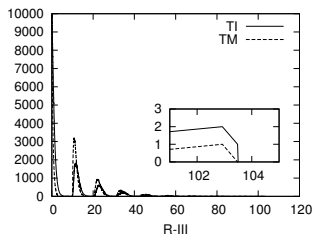
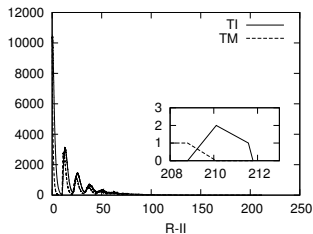
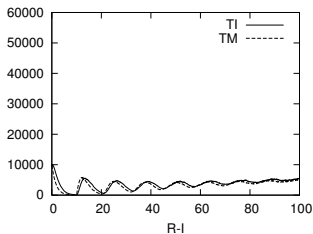


Stochastic Simulation (delays as duration)



	R-I	R-II	R-III / V	R-IV
$\sigma = 1.0$	∞	64	29	302

Stochastic Simulation (delays as duration)



	R-I	R-II	R-III / V	R-IV
$\sigma = 10.0$	∞	224	126	1072

DDEs v.s. Delay as Duration

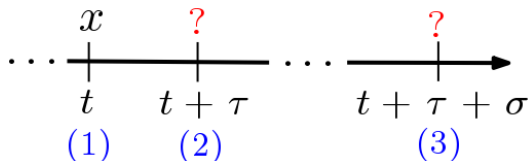
- in general, comparison with DDEs is not necessary meaningful;
- for this simulations, with 10^5 starting cells, we obtain the same **qualitative** behaviour (i.e. growth and eradication);

Is also **quantitatively** equivalent?

	DDEs	DDA Simulation
R-II with $\sigma = 1.0$	50	64
R-II with $\sigma = 10.0$	59	224
R-III with $\sigma = 1.0$	15	29
R-III with $\sigma = 10.0$	12	126
R-IV with $\sigma = 1.0$	238	302
R-IV with $\sigma = 10.0$	440	1072

The purely delayed approach

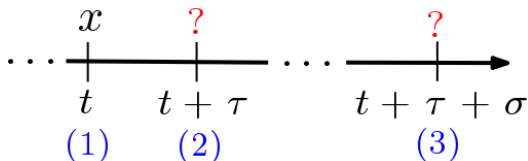
Given the reaction: $A + B \xrightarrow{k, \sigma} C$



- (1) current state: $\mathbf{X}(t) = x$;
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- (3) scheduled event: $\mathbf{X}(t + \tau + \sigma) = x' - \{A, B\} + \{C\}$, (i.e. **application if still possible**, $\{A, B\} \in x'$).

The purely delayed approach

Given the reaction: $A + B \xrightarrow{k, \sigma} C$



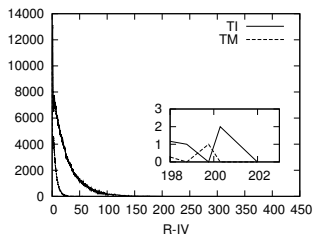
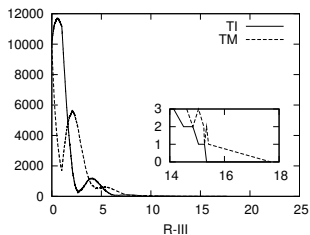
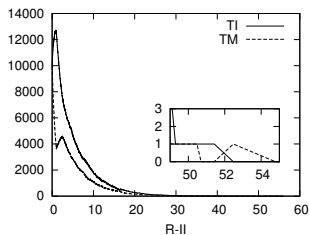
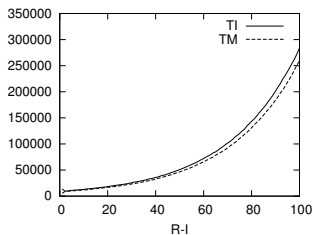
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- any scheduled reaction in $[t, t + \tau]$ has priority;
- reactants **can participate** in reactions firing in $[t, t + \tau + \sigma]$ (i.e. cell death);

The purely delayed approach: the DSSA

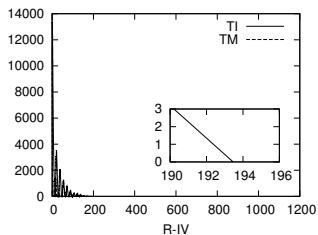
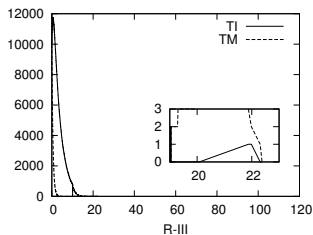
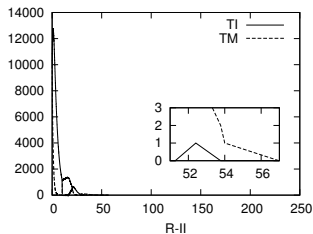
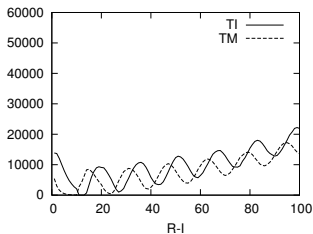
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- 5 go to step 2.

Stochastic Simulation (purely delayed)



	R-I	R-II	R-III / V	R-IV
$\sigma = 1.0$	∞	51	17	214

Stochastic Simulation (purely delayed)



	R-I	R-II	R-III / V	R-IV
$\sigma = 10.0$	∞	67	20	248

	DDEs	DDA Simulation	PDA Simulation
R-II with $\sigma = 1.0$	50	64	51
R-II with $\sigma = 10.0$	59	224	67
R-III with $\sigma = 1.0$	15	29	17
R-III with $\sigma = 10.0$	12	126	20
R-IV with $\sigma = 1.0$	238	302	214
R-IV with $\sigma = 10.0$	440	1072	248

Table: Average eradication times given in *days* for DDE model, DDA and PDA stochastic models. For the stochastic models the entries represent the sample of 100 simulations.

Conclusions and Future Work

Our approach has to be improved:

- it may schedule multiple times the same reactants;
- hard checking applicability (fresh reactants);

Possible solution is a **marking procedure** (\neq removal) of the reactants.

It is also of interest the combination of **both** the approaches.

All these simulation algorithms must be embedded in the semantics of languages for the specification of models.

We could inherit advices from already existing languages (i.e. **Petri Nets** have got similar notions of reaction firing with delays).