Fluid approximation of CTMC with deterministic delays

Jane Hillston
LFCS and SynthSys
University of Edinburgh

19th September 2012

Joint work with Luca Bortolussi, University of Trieste

Outline

Events with delays

- In discrete event modelling a single delay is usually associated with an event (or action leading to the event).

Events with delays

- In discrete event modelling a single delay is usually associated with an event (or action leading to the event).
- The usual interpretation of this delay is the duration of the action or event.

Events with delays

- In discrete event modelling a single delay is usually associated with an event (or action leading to the event).
- The usual interpretation of this delay is the duration of the action or event.
- But if we look at it more closely there can be different delays associated with an event:

Events with delays

- In discrete event modelling a single delay is usually associated with an event (or action leading to the event).
- The usual interpretation of this delay is the duration of the action or event.
- But if we look at it more closely there can be different delays associated with an event:
  - There may be a delay from the time when an event becomes possible (enabled) ;

Events with delays

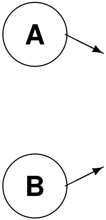
- In discrete event modelling a single delay is usually associated with an event (or action leading to the event).
- The usual interpretation of this delay is the duration of the action or event.
- But if we look at it more closely there can be different delays associated with an event:
  - There may be a delay from the time when an event becomes possible (enabled) ;
  - When an event occurs there may be a delay until the effects of the event become apparent.

Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes

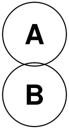
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes



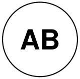
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes



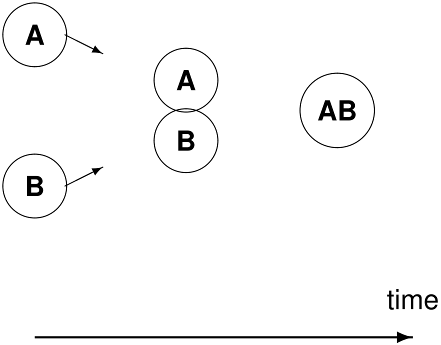
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes



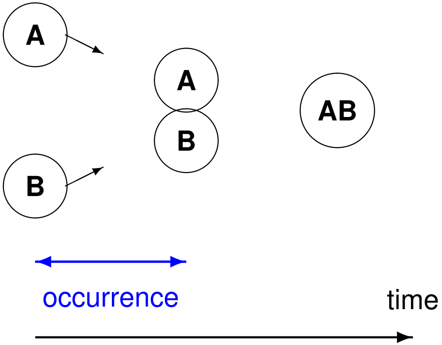
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes



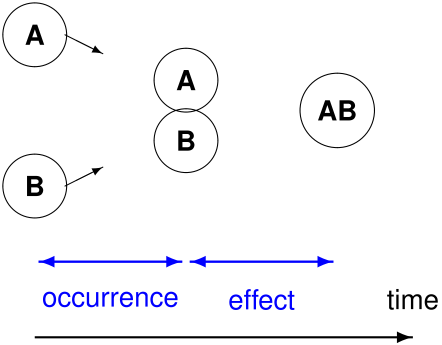
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes



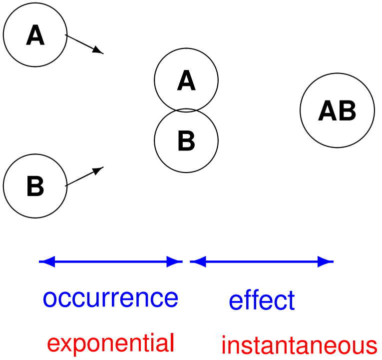
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes



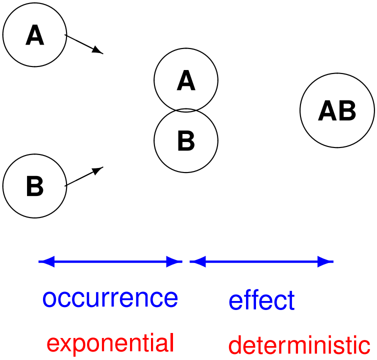
Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes

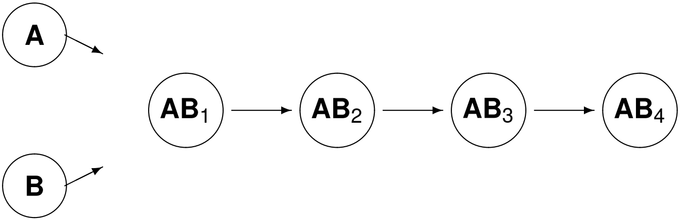


Example: actions with delays in biochemistry

We are interested in modelling intracellular biochemical processes

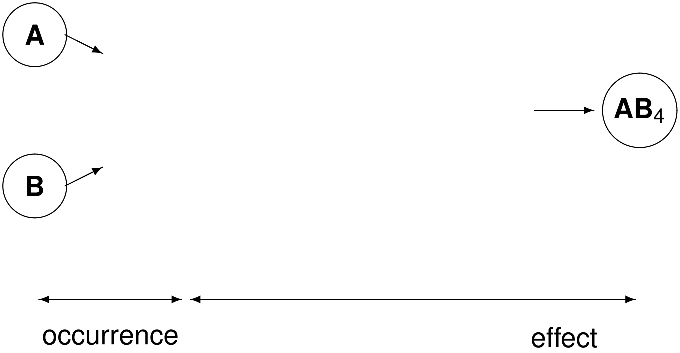


Delays as abstraction

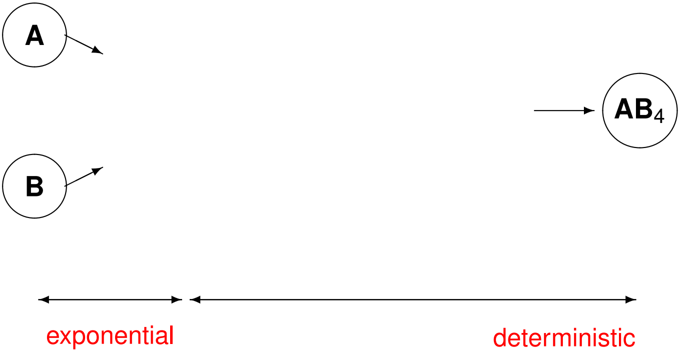


Delays as abstraction

Delays as abstraction



Delays as abstraction



Population Models

The state of the system is a population vector, n, with one entry for each population variable, the entry recording the current value.

Population Models

The state of the system is a population vector, n, with one entry for each population variable, the entry recording the current value.

Each event will update the vector according to the update vector as a single atomic step after an exponentially distributed delay.

Population Models

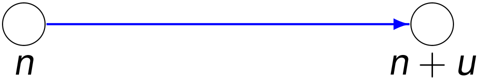
The state of the system is a population vector, n, with one entry for each population variable, the entry recording the current value.

Each event will update the vector according to the update vector as a single atomic step after an exponentially distributed delay.

Population Models

The state of the system is a population vector, n, with one entry for each population variable, the entry recording the current value.

Each event will update the vector according to the update vector as a single atomic step after an exponentially distributed delay.



Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

○ ○ ○

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

As the population N increases the values and the frequency of events both increase.

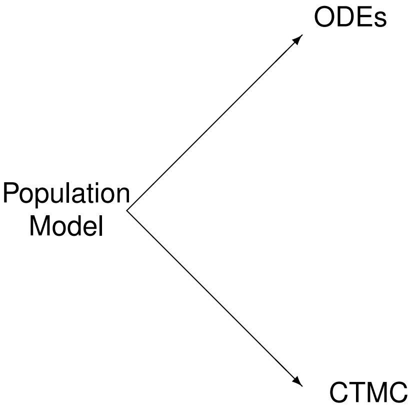
Continuous Approximation

A discrete interpretation (CTMC) is based on discrete events and integer values of variables.

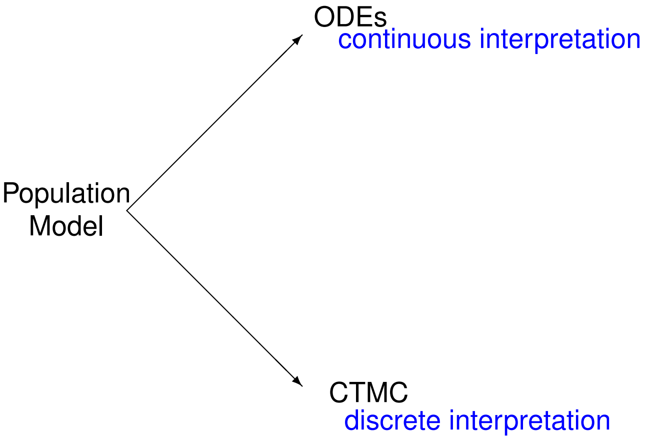
As the population N increases the values and the frequency of events both increase.

Using continuous state variables to approximate the discrete state space and ordinary differential equations to represent the evolution of those variables over time we can make an alternative continuous interpretation.

Alternative Semantics of Population Models

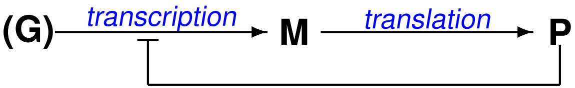


Alternative Semantics of Population Models



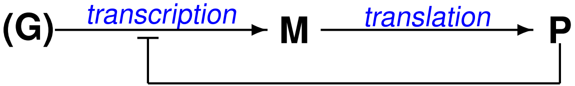
Small Example

Consider a simple genetic network consisting of a single gene expressing a protein which acts as a self-repressor.



Small Example

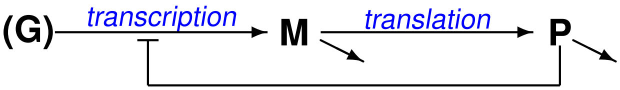
Consider a simple genetic network consisting of a single gene expressing a protein which acts as a self-repressor.



We explicitly model transcription (synthesis of mRNA from the gene), translation (synthesis of protein from mRNA), and degradation.

Small Example

Consider a simple genetic network consisting of a single gene expressing a protein which acts as a self-repressor.



We explicitly model transcription (synthesis of mRNA from the gene), translation (synthesis of protein from mRNA), and degradation.

Small Example

Two variables, M and P, capture the amount of mRNA and protein (as molecule counts) respectively, modified by four transitions:

- $((1,0), \alpha_M \frac{1}{1+(P/P_0)^h})$: transcription of mRNA.
- $((0,1), \alpha_P M)$: translation of mRNA into protein P.
- $((-1,0), \beta_M M)$: degradation of mRNA.
- $((0,-1), \beta_P P)$: degradation of the protein P.

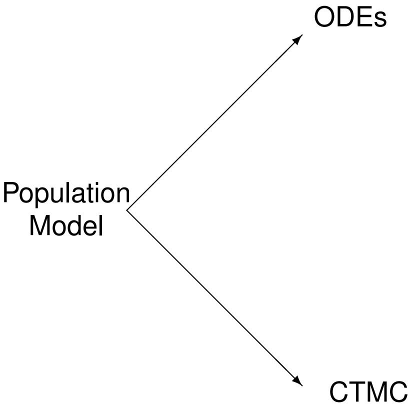
Small Example

For this model we can derive a CTMC and the following system of ODEs:

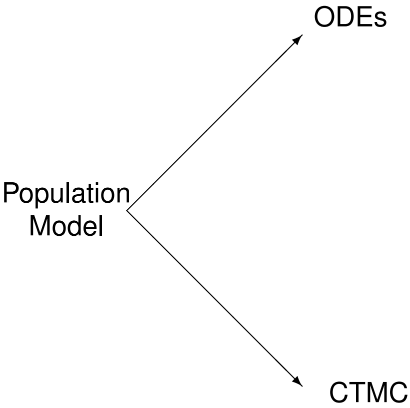
$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1 + (p(t)/P_0)^h} - \beta_m m(t)$$

$$\frac{dp(t)}{dt} = \alpha_p m(t) - \beta_p p(t)$$

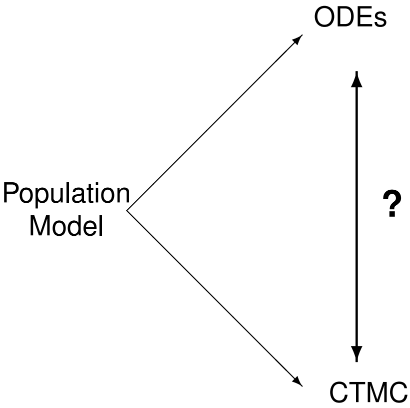
Convergence of Models



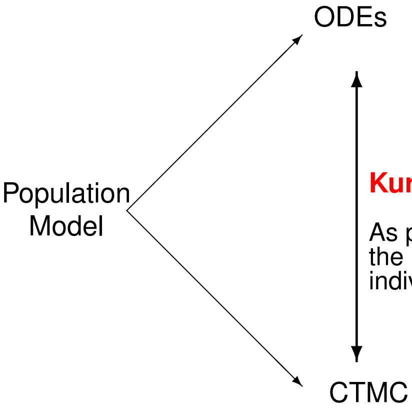
Convergence of Models



Convergence of Models



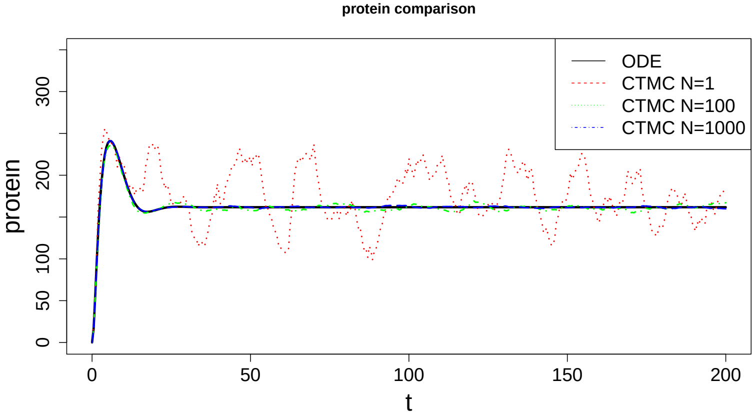
Convergence of Models



Kurtz's Theorem [1970]

As population N grows large (∞), the behaviour of the population and individual models become indistinguishable.

Example Revisited



A trajectory of the ODE model compared with trajectories of the CTMC for protein variable P, for increasing values of N.

Delayed Population Models

As previously the state of the system is a population vector, n, with one entry for each variable.

Delayed Population Models

As previously the state of the system is a population vector, n, with one entry for each variable.

Some events will generate an update after the exponentially distributed occurrence of the event and another update after the deterministically timed delay.

Delayed Population Models

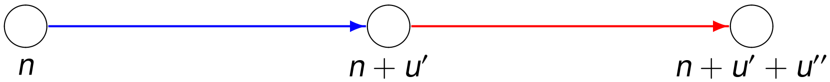
As previously the state of the system is a population vector, n, with one entry for each variable.

Some events will generate an update after the exponentially distributed occurrence of the event and another update after the deterministically timed delay.

Delayed Population Models

As previously the state of the system is a population vector, n, with one entry for each variable.

Some events will generate an update after the exponentially distributed occurrence of the event and another update after the deterministically timed delay.



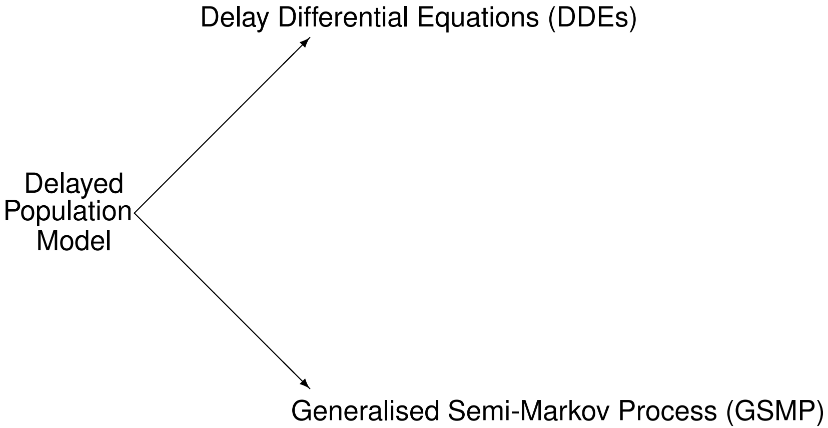
Example as a delayed population model

In our model, we can easily introduce delays by replacing transcription and translation by delayed transitions:

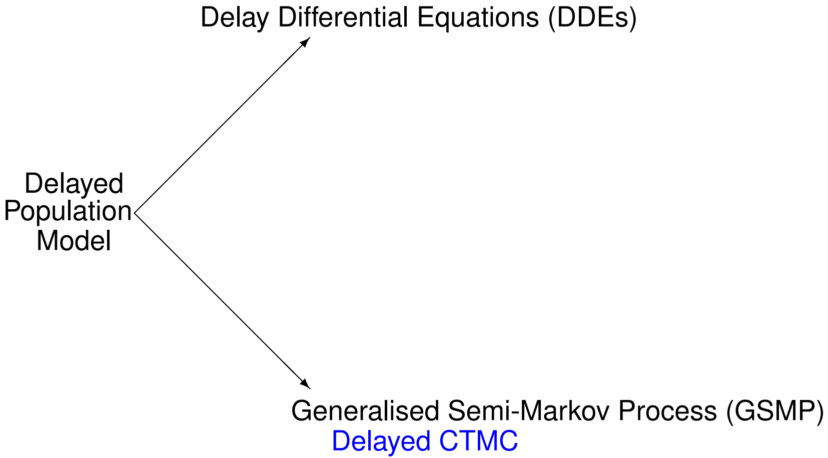
- $((0,0), \alpha_M \frac{1}{1+(P/P_0)^h}, (1,0), \sigma_M)$: delayed transcription;
- $((0,0), \alpha_P M, (0,1), \sigma_P)$: delayed translation.

The degradation transitions remain the same.

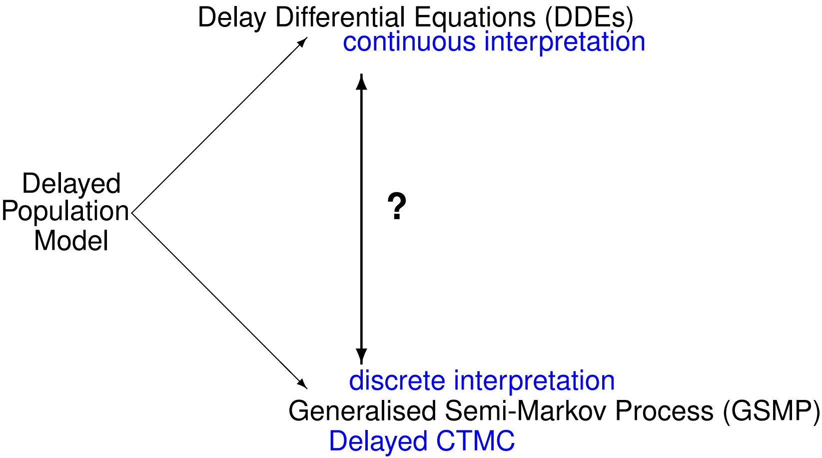
Alternative Semantics of Delayed Population Models



Alternative Semantics of Delayed Population Models



Alternative Semantics of Delayed Population Models



Alternative Semantics of Delayed Population Models

Delay Differential Equations (DDEs)
continuous interpretation

Delayed Population Model

We would like to ensure that:

As population N grows large (∞), the behaviour of two interpretations become indistinguishable.

discrete interpretation
Generalised Semi-Markov Process (GSMP)
Delayed CTMC

Delay Differential Equations

Delay Differential Equations (DDE) are differential equations in which the derivative can depend also on past values of the function

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}_t)$$

Delay Differential Equations

Delay Differential Equations (DDE) are differential equations in which the derivative can depend also on past values of the function

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}_t)$$

The initial condition of a DDE is no longer a single point, but rather a function $\varphi : [-d, 0] \to \mathbb{R}^n$.

Delay Differential Equations

Delay Differential Equations (DDE) are differential equations in which the derivative can depend also on past values of the function

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}_t)$$

The initial condition of a DDE is no longer a single point, but rather a function $\varphi : [-d, 0] \to \mathbb{R}^n$.

Our models give rise to DDEs with constant delays:

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}(t), \mathbf{x}(t - \sigma_1), \ldots, \mathbf{x}(t - \sigma_n)).$$

Example Revisited

The DDEs associated with the transcription/translation example are:

$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1 + (p(t-\sigma_M)/P_0)^h} - \beta_m m(t)$$

$$\frac{dp(t)}{dt} = \alpha_p m(t-\sigma_P) - \beta_p p(t)$$

Eliminating deterministic delays

It is well-known that if you have a sequence of k exponential delays, each with expected duration σ/k, then as $k \to \infty$ then the end-to-end delay tends to a deterministic delay of duration σ.

Eliminating deterministic delays

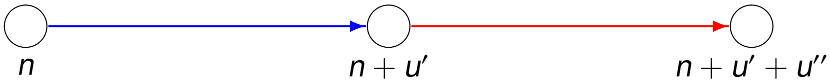
It is well-known that if you have a sequence of k exponential delays, each with expected duration σ/k, then as $k \to \infty$ then the end-to-end delay tends to a deterministic delay of duration σ.

In terms of our models, this means that we can approximate each deterministic delay by a sequence of exponential delays:

Eliminating deterministic delays

It is well-known that if you have a sequence of k exponential delays, each with expected duration σ/k, then as $k \to \infty$ then the end-to-end delay tends to a deterministic delay of duration σ.

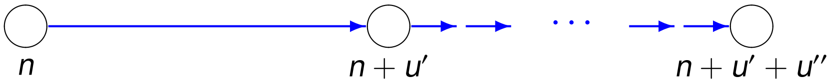
In terms of our models, this means that we can approximate each deterministic delay by a sequence of exponential delays:



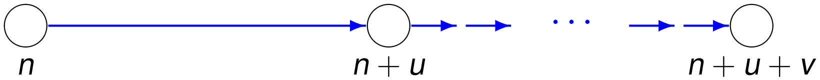
Eliminating deterministic delays

It is well-known that if you have a sequence of k exponential delays, each with expected duration σ/k, then as $k \to \infty$ then the end-to-end delay tends to a deterministic delay of duration σ.

In terms of our models, this means that we can approximate each deterministic delay by a sequence of exponential delays:

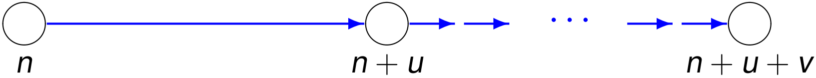


Eliminating deterministic delays



Replacing the deterministic delay by a sequence of exponential delays means that the underlying stochastic process is again a CTMC rather than a delayed CTMC.

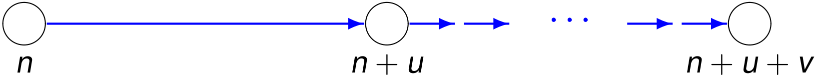
Eliminating deterministic delays



Replacing the deterministic delay by a sequence of exponential delays means that the underlying stochastic process is again a CTMC rather than a delayed CTMC.

That means that we can once again apply Kurtz's Theorem knowing that we have convergence to a set of ODEs.

Eliminating deterministic delays

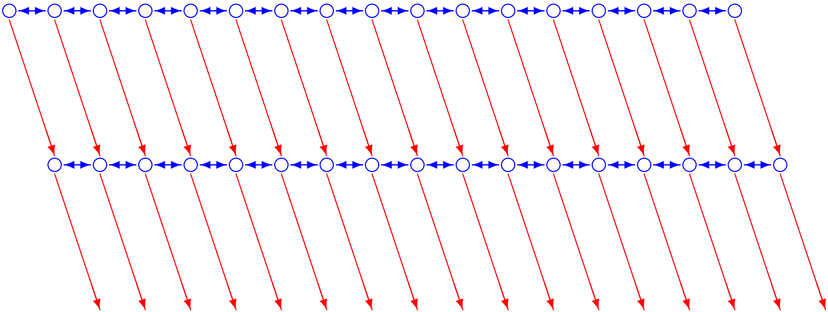


Replacing the deterministic delay by a sequence of exponential delays means that the underlying stochastic process is again a CTMC rather than a delayed CTMC.

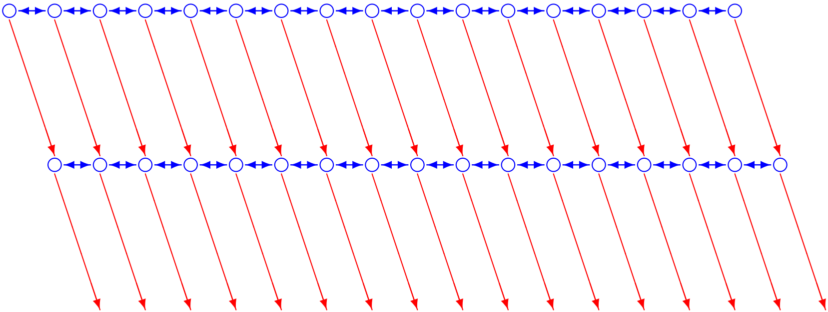
That means that we can once again apply Kurtz's Theorem knowing that we have convergence to a set of ODEs.

Unfortunately this does not immediately tell us anything about the relationship with the set of DDEs generated from the delay population model.

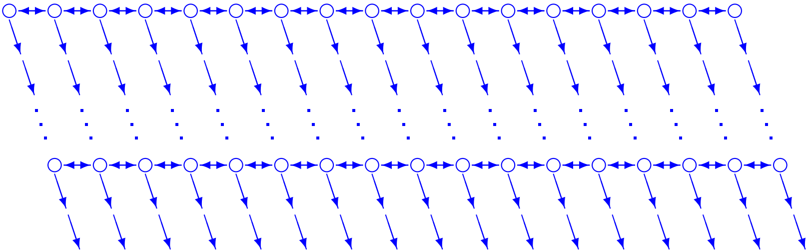
Erlang Approximation



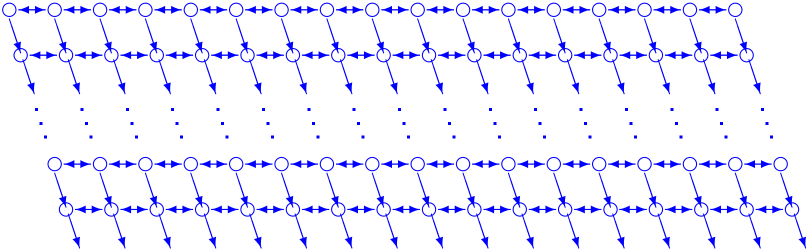
Erlang Approximation



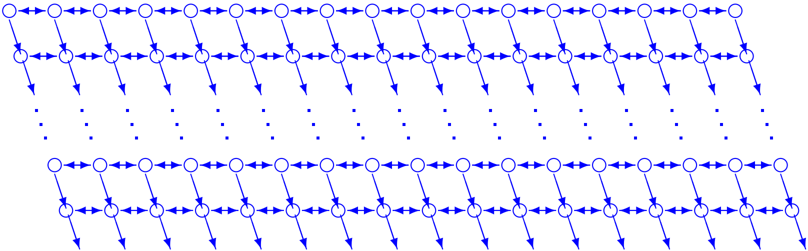
Erlang Approximation



Erlang Approximation

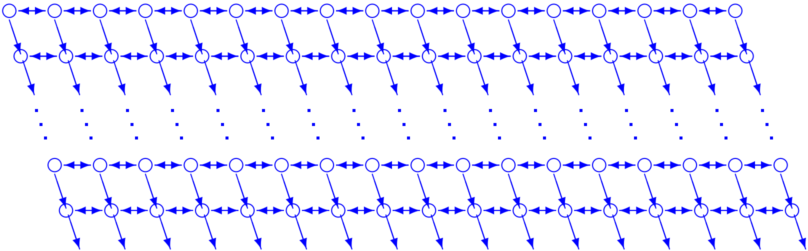


Erlang Approximation



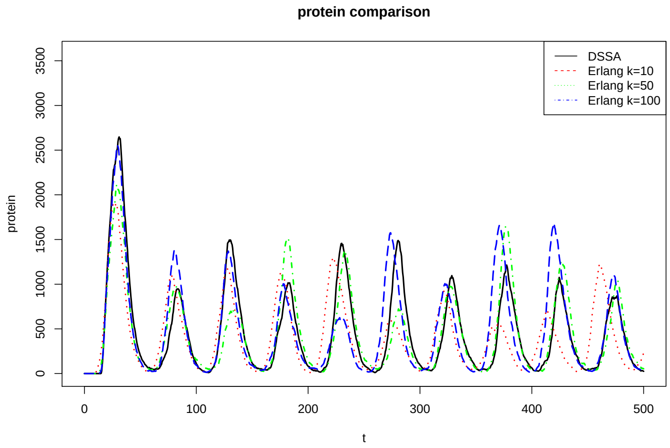
This expanded CTMC has more states as we now need to keep track of the phase of the delays as well as the original variables.

Erlang Approximation



We are able to prove that, as N tends to infinity, the behaviour of the delayed CTMC and the expanded CTMC are the same.

Convergence in the Example



As k increases the expanded CTMC has better agreement with the delayed CTMC.

Erlang Approximation for DDE

We can make the same "Erlang approximation" with the deterministic delays in the DDEs.

Erlang Approximation for DDE

We can make the same "Erlang approximation" with the deterministic delays in the DDEs.

Recall a DDE has the form

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}(t), \mathbf{x}(t-\sigma_1), \ldots, \mathbf{x}(t-\sigma_n)).$$

Erlang Approximation for DDE

We can make the same "Erlang approximation" with the deterministic delays in the DDEs.

Recall a DDE has the form

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}(t), \mathbf{x}(t - \sigma_1), \ldots, \mathbf{x}(t - \sigma_n)).$$

We can approximate each of the σ_i by a sequence of small steps.

Erlang Approximation for DDE

Consider the DDE: $\frac{dx(t)}{dt} = f(x(t-\sigma))$.

Erlang Approximation for DDE

Consider the DDE: $\frac{dx(t)}{dt} = f(x(t-\sigma))$.

We introduce k variables $z_1, \ldots, z_k$, representing k intermediate steps, with

$$z_1(t + \sigma/k) = f(x(t))$$

and

$$z_{j+1}(t + \sigma/k) = z_j(t), \qquad j = 1, \ldots, k-1.$$

Erlang Approximation for DDE

Noting $\frac{dz_{j+1}(t)}{dt} = \frac{k}{\sigma}\left(z_j(t) - z_{j+1}(t)\right)$ we obtain the following set of ODEs:

$$\begin{cases} \frac{dz_1(t)}{dt} & = & \frac{k}{\sigma}\left(f(x(t)) - z_1(t)\right) \\ & \vdots & \\ \frac{dz_{j+1}(t)}{dt} & = & \frac{k}{\sigma}\left(z_j(t) - z_{j+1}(t)\right) \\ & \vdots & \\ \frac{dx(t)}{dt} & = & z_k(t) \end{cases}$$

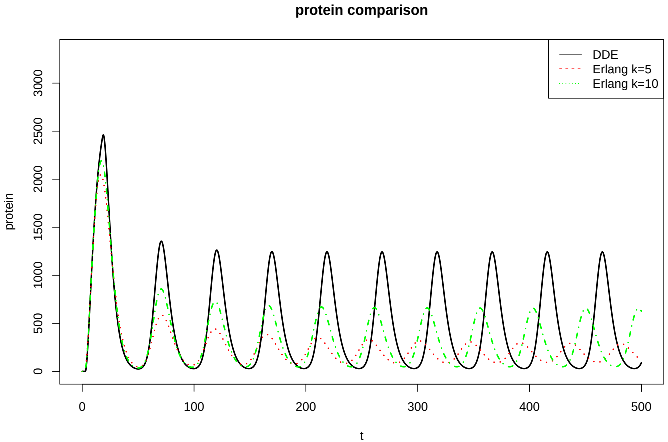
Erlang Approximation for DDE

Noting $\frac{dz_{j+1}(t)}{dt} = \frac{k}{\sigma}\left(z_j(t) - z_{j+1}(t)\right)$ we obtain the following set of ODEs:

$$\begin{cases} \frac{dz_1(t)}{dt} & = & \frac{k}{\sigma}\left(f(x(t)) - z_1(t)\right) \\ & \vdots & \\ \frac{dz_{j+1}(t)}{dt} & = & \frac{k}{\sigma}\left(z_j(t) - z_{j+1}(t)\right) \\ & \vdots & \\ \frac{dx(t)}{dt} & = & z_k(t) \end{cases}$$

We can show that as $k \longrightarrow \infty$ the DDEs and the ODEs exhibit the same behaviour.

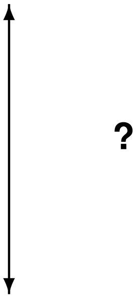
DDE Convergence in the Example



Increasing k improves agreement between the ODE and the DDE.

Convergence Result

Delay Differential Equations (DDEs)



Delay Continuous Time Markov Chain

Convergence Result

Delay Differential Equations (DDEs)

?

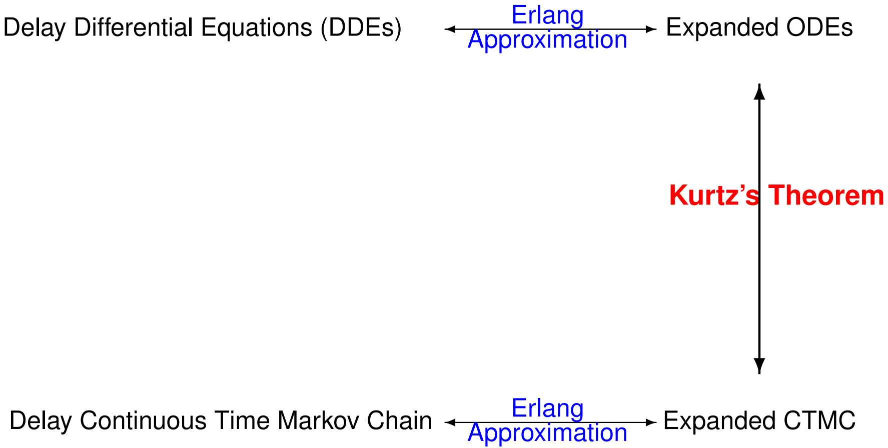
Delay Continuous Time Markov Chain

Convergence Result

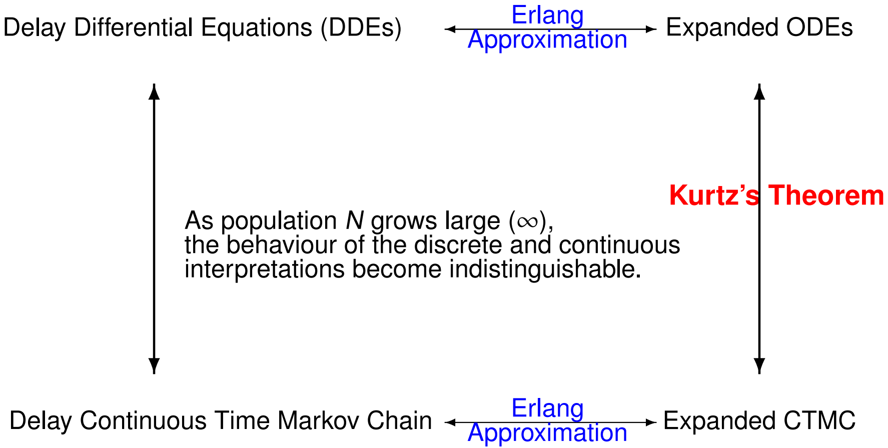
Delay Differential Equations (DDEs) ⟷ Erlang Approximation ⟷ Expanded ODEs

Delay Continuous Time Markov Chain ⟷ Erlang Approximation ⟷ Expanded CTMC

Convergence Result



Convergence Result

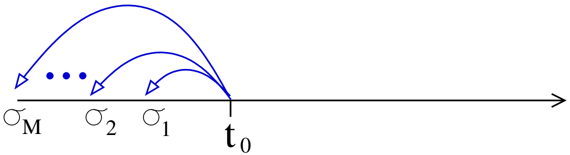


Initial Conditions

Recall that the initial conditions of a DDE are a function in the time interval $[t_0 - \sigma_M, t_0]$, where σ_M is the largest delay.

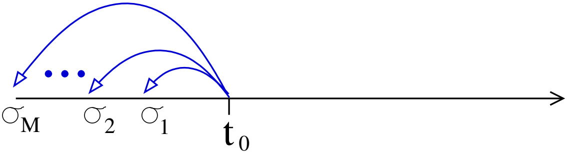
Initial Conditions

Recall that the initial conditions of a DDE are a function in the time interval $[t_0 - \sigma_M, t_0]$, where σ_M is the largest delay.



Initial Conditions

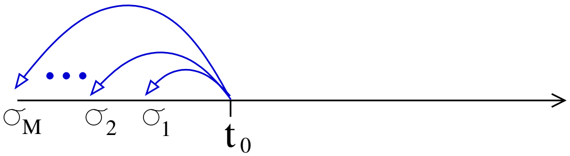
Recall that the initial conditions of a DDE are a function in the time interval $[t_0 - \sigma_M, t_0]$, where σ_M is the largest delay.



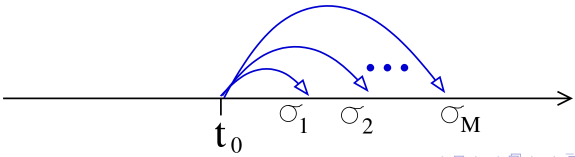
In contrast, in the CTMC approximation of the delayed CTMC the newly added variables are set to zero, and the effects of delays take place in the future with no effect from the past.

Initial Conditions

Recall that the initial conditions of a DDE are a function in the time interval $[t_0 - \sigma_M, t_0]$, where σ_M is the largest delay.

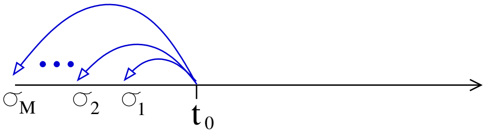


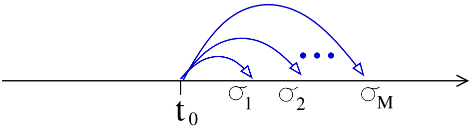
In contrast, in the CTMC approximation of the delayed CTMC the newly added variables are set to zero, and the effects of delays take place in the future with no effect from the past.



Initial Conditions

Therefore, we consider the solution of the DDE starting not from time t_0, but from time $t_0 + \sigma_M$, and construct the initial condition for the DDE from the behaviour of the delayed CTMC in $[t_0, t_0 + \sigma_M]$.





Conclusions

- We have defined a class of population models in which some events may have delayed effects.

Conclusions

- We have defined a class of population models in which some events may have delayed effects.
- We have shown that the continuous semantics, given in terms of DDEs, and the discrete semantics, given in terms of a delayed CTMC, converge as populations grow.

Thank you!

Thank you!

This work was supported by funding from the BBSRC and the Royal Society.