COURSE 3

ThinkBS

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ADVANCED STATISTICAL METHODS AND ALGORITHMS with applications

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OUTLINE

- ✓ Mathematical models for dynamical systems
- ✓ Deterministic approach
- ✓ Stochastic approach (CTMC)
- ✓ Monte Carlo – based methods for simulations
- ✓ Stochastic modelling for bio-chemical dynamic systems
- ✓ Examples

MATHEMATICAL MODELS FOR DYNAMICAL SYSTEMS

- In 1974, Eykhoff defined a mathematical model as "*a representation of the essential aspects of an existing system […] which presents knowledge of that system in a usable form*".

Mathematical models…

engineering
physics
chemistry
biology
economy
sociology
psychology
political science
….

- The *mathematical model* of a dynamic process *is a representation of the real system through precise mathematical relations* that describe some properties of the studied system.

A model's characteristics depend mostly on the purpose of constructing it. Most of the time, the main purpose is linked to using all the available information about the system to accurately describe the system's elements and the interactions between them.

- *The questions that are essential in designing a mathematical model of a dynamic process are:*
  - *What is the purpose of the study? (for establishing the degree of detail)*
  - *What are the parameters involved and what types are they? (constants, time or state dependent)*
  - *What can be measured experimentally? (to be able to validate the model and determine its degree of predictability)*

- *Depending on the answer to these questions a set of modelling assumptions (hypotheses) can be issued; these assumptions considers:*
  - *the system's variables and parameters*
  - *the system's mechanism (the rules of interaction)*
  - *the workspace (homogenous or non-homogenous)*
  - *the adequate mathematical instruments (algebraic, differential, partially differential or stochastic systems of equations).*

- *For describing the characteristics of a system and for creating an adequate mathematical model, the following aspects should be considered:*
  - *the components and their number;*
  - *the interactions between the system's elements and their configuration (the interaction rules);*
  - *the forming processes, the operating modes and the time scales they take place at;*
  - *diversity and variability;*
  - *the exterior environment and its influence;*
  - *the actions and their finality.*

The evolution of a dynamic system is governed by a set of laws (not necessarily equations) that specify the state of the system for either discreet values or continuous values of the time t.

Dealing with a dynamic system consists of two steps: defining the state and phase spaces and defining the law which allows knowing the state of the system at any moment of time, given the initial state of the system.

The dynamic behaviour of the system represents the sequence of system states over time.

- *Besides the state variables, mathematical models of dynamic systems include parameters which values can be constant (fixed) or can be functions of time.*

  The system's parameters describe the interactions between components and/or with the exterior environment.
  A modification of a parameter's value corresponds to a change of the conditions in the exterior environment or in the system.

- *Depending on the particularity of the characteristics chosen for describing and analysing a dynamic system, the mathematical formalism can be divided into two directions:*

  - *deterministic*
  - *stochastic*

MATHEMATICAL MODELLING OF BIOLOGICAL SYSTEMS – DETERMINISTIC APPROACH

- *The dynamics of the considered systems is described in terms of variation of the quantities of the involved species over time.*

  Each interaction described by a reaction scheme can be characterized by an appropriate mathematical formalism (for example, mass-action or Michaelis-Menten kinetics) and these terms can be combined into a description of the rate of change of the concentration of the various species in the model.

In general, given a network with n *interacting species, we denote the concentration vector by* x *(the vector of state variables) and we denote the rate of change of the concentration of each species by a vector-valued function* $f : \mathbb{R}^n \to \mathbb{R}^n$.

The system dynamics can be described by an (non-linear) ODE system, together with the initial conditions

$$\frac{dx(t)}{dt} = f\left(t, x(t)\right), \; x(t_0) = x_0$$

In terms of biochemical networks, the ODE system is called "a set of rate equations"

and each component of the vector field $f\left(t, x(t)\right)$ *is called a "rate law".*

Finding analytical solutions to nonlinear differential equations systems can be very difficult or impossible, yet often the dynamics of the system can be examined from a qualitative perspective (i.e., without finding the exact solution) to determine types of behaviour of the solutions, which can lead to insight into modelling problems.

STOCHASTIC APPROACH – general framework

- *(Kolmogorov) – a stochastic processes is a family of random variables defined on a probability space and thereby define a probability law on the set of trajectories of the process. More specifically, stochastic processes generalize the notion of (finite dimensional) vectors of random variables to the case of any family of random variables indexed in a general set "T". Typically, the latter represents "time" and is an interval of $\mathbb{R}$ (in the continuous case) or $\mathbb{N}$ (in the discrete case).*

In this course we shall consider only a special type of stochastic process, namely the continuous-time, discrete space Markov process (referred to as "CTMC").

- CTMC is denoted by $\{X(t): t \geq 0\}$ or simply $X(t)$;
- The states of the process will be denoted by $i, j, k, \ldots\ldots \in E$ and $X(t) = i$ will have the meaning "the system is in state i at time t";
- The *transition probabilities*: $p_{ij}(s,t) = P\left(X(t) = j \middle| X(s) = i\right)$, for $0 \leq s \leq t$, and

$$p_{ij}(t,t) = \begin{cases} 1 & if\ i = j \\ 0 & otherwise \end{cases}$$

- *Transition probability matrix*: $P(s,t) = \left[p_{ij}(s,t)\right]$, at time $t \in T$.
- The *state probabilities* at time t: $P_j(t) = P\left(X(t) = j\right)$, with $\sum_j P_j(t) = 1$ for each time $t \geq 0$. For $t = 0$, we have the *distribution of the initial state* (the probability mass function of $X(0)$);

The transition rates of CTMC

- For $\triangle t \geq 0$ and $i \neq j$ the transition rate is defined as:

$$q_{ij}(t) = \frac{dp_{ij}(t, t+\triangle t)}{dt} = \lim_{\triangle t \to 0} \frac{p_{ij}(t, t+\triangle t) - p_{ij}(t,t)}{\triangle t} = \lim_{\triangle t \to 0} \frac{p_{ij}(t, t+\triangle t)}{\triangle t}$$

so $q_{ij}(t) \geq 0$ and we can write the relation between the transition probabilities and transition rates:

$$p_{ij}(t, t+\triangle t) = P\left(X(t+\triangle t) = j \mid X(t) = i\right) = q_{ij}(t) \cdot \triangle t + o(\triangle t)$$

- For $\triangle t \geq 0$ and $i = j$ the transition rate is defined as:

$$q_{ii}(t) = \frac{dp_{ii}(t, t+\triangle t)}{dt} = \lim_{\triangle t \to 0} \frac{p_{ii}(t, t+\triangle t) - p_{ii}(t,t)}{\triangle t} = -\lim_{\triangle t \to 0} \frac{1 - p_{ii}(t, t+\triangle t)}{\triangle t}$$

so $q_{ii}(t) < 0$ and we can write the relation between the transition probabilities and transition rates:

$$p_{ii}(t, t+\triangle t) = P\left(X(t+\triangle t) = i \mid X(t) = i\right) = 1 + q_{ii}(t) \cdot \triangle t + o(\triangle t)$$

Because $\sum_{j=1} p_{ij}(t, t+\triangle t) = 1$, for any $i \in E$, we obtain:

$$q_{ii}(t) = -q_{ij}(t)$$

A stochastic process $\{X(t): t \geq 0\}$ *is CTMC if it has the Markov property at each time point, that is, for all* $t, s \in T$ *:*

$$P\left(X(t+s) = j \middle| X(s) = i, X(u): 0 \leq u < s\right) = P\left(X(t+s) = j \middle| X(s) = i\right)$$

This is usually called "the memoryless property": the future state depends only on the present state, and not on the previous states.

The CTMC is time homogeneous, if the transition probabilities does not depend on the time moments $s, t \in T$ *,*

but only on the time interval length ($s + t - s = t$ *):*

$$P\left(X(t+s) = j \middle| X(s) = i\right) = P\left(X(t) = j \middle| X(0) = i\right)$$

In a CTMC, the sojourn time in any state $i \in E$ *is a random variable* T_i*, exponentially distributed with parameter* $\lambda(i) = -q_{ii}(t) = \sum_{i \neq j} q_{ij}(t)$ *:*

$$P(T_i \leq t) = 1 - \exp\left(\sum_{i \neq j} q_{ij}(t)\right), \text{ for } \forall t \geq 0$$

MONTE CARLO – BASED METHODS employed in the study of CTMC dynamics

A formal definition of Monte Carlo methods was given, among others, by Halton in 1970. He defined a Monte Carlo method as "*representing the solution of a problem as a parameter of a hypothetical population and using a random sequence of numbers to construct a sample of the population, from which statistical estimates of the parameter can be obtained*".

For any implementation of a Monte-Carlo method, we need to be able to reproduce randomness by a computer algorithm. In the following we will assume that independent (pseudo-) random realisations from a uniform distribution are readily available.

Transformation methods

Let X *be a real-valued random variable defined on a probability space* $(\Omega, \Delta_\Omega, P)$.

Let $F(x) = P\{\omega | X(\omega) \le x\}$, $x \in (-\infty, \infty)$, *define the cumulative distribution function (CDF).*

Let $U \sim Unif(0,1)$ *denote a random variable that is uniformly distributed on* $(0,1)$.

The CDF is an increasing function, however it is not necessarily continuous. Thus, we define the generalized inverse $F^- : (0,1) \to (-\infty, \infty)$ *by* $F^-(y) = \inf\{x | F(x) \ge y\}$, *with* $U \sim Unif(0,1)$. *If* F *is continuous, then* $F^-(U) = F^{-1}(U)$.

One of the simplest methods for generating random samples from a distribution with CDF is based on the integral transform theorem, for the generalized inverse.

↓

"Quantile function Theorem" or "Inversion Method" or "Smirnov Transform".

(Integral transform theorem – invertible case):

Let $F:\mathbb{R}\to(0,1)$ *be an invertible CDF (i.e.* $\exists\, F^{-1}:(0,1)\to\mathbb{R}$ *such that* $F^{-1}\left(F\left(x\right)\right)=x,\ \forall x\in\mathbb{R}$ *and* $F\left(F^{-1}\left(a\right)\right)=a,\ \forall a\in(0,1)$*).*

If $U\sim Unif\left(0,1\right)$*, then the random variable* $X=F^{-1}\left(U\right)\sim F$ *(i.e.* $X=F^{-1}\left(U\right)$ *has CDF* F*).*

Exponential distribution

The exponential distribution with rate $\lambda>0$ *has the CDF* $F_\lambda\left(x\right)=1-\exp\left(-\lambda x\right)$*, for* $x\geq 0$*.*

Thus, $F_\lambda^{-}\left(U\right)=F_\lambda^{-1}\left(U\right)=-\frac{1}{\lambda}\ln\left(1-U\right)$*.*

We can generate random samples from an exponential distribution $Expo\left(\lambda\right)$ *by applying the transformation* $-\frac{1}{\lambda}\ln\left(1-U\right)$ *to a uniform random variable* $U\sim Unif\left(0,1\right)$*.*

As U *and* $1-U$*, of course, have the same distribution, we can use* $-\frac{1}{\lambda}\ln\left(U\right)$ *as well.*

Remarks:

The Inversion Method, based on the Integral Transform Theorem is a very efficient tool if the distribution we want to sample from possess a CDF whose (generalized) inverse can be evaluated. An example is the Gaussian distribution, whose CDF is not even available in closed form.

We note that the generalized inverse of the CDF is just one possible transformation and that there are other transformations that yield the desired distribution. An example of such method is the Box-Muller method for generating Gaussian random variables. Another popular transformation methods are the Rejection Sampling or the Importance Sampling.

STOCHASTIC MODELLING OF BIO-CHEMICAL DYNAMIC SYSTEMS

It is considered that, in systems involving low species count, small variations in the number of molecules influence system evolution. Considering the random nature of molecules transformation or collision, kinetic modelling of chemical reactions based on the theory probabilities would be more appropriate.

Consider a system of coupled chemical reactions, represented in a stoichiometric form:

a reaction-specific constant, experimentally deduced

$$(R_\mu): \quad \sum_{i=1}^{N} r_{\mu i} \cdot S_i \xrightarrow{c_\mu} \sum_{i=1}^{N} p_{\mu i} \cdot S_i , \quad \mu = 1, 2, .., M$$

the stoichiometric coefficients for the reactants and products

- *The state-space of the system is given by* $\Omega \subset \mathbb{N}^N$ *and the elements in the state-space are represented by the random vector*

$$X(t) = \left(X_1(t), X_2(t), ..., X_N(t)\right) \in \Omega$$

where $X_i(t)$ *is the number of molecules of type* S_i *present in* V *at time* t.

- *We denote by* $v_\mu = \left(v_{\mu 1}, v_{\mu 2}, ..., v_{\mu N}\right)$ *the stoichiometric vector of each reaction,* $v_\mu \in \mathbb{Z}^N$ *where* $v_{\mu i} = p_{\mu i} - r_{\mu i}$, *for* $i = 1, 2, .., N$.

  After a reaction R_μ *occurs, the state vector* $X(t)$ *changes by* $X(t) + v_\mu$.

To describe the reaction channel R_μ *stochastically, one needs to know the stoichiometric vector* $v_\mu = (v_{\mu 1}, v_{\mu 2}, \ldots, v_{\mu N})$,

and the specific stochastic kinetic law for each reaction channel R_μ.

The key concept of this type of description is the stochastic rate function (propensity function) $a_\mu(x)$ *which is defined by Gillespie as:*

$a_\mu(x)\cdot\triangle t$ = *the probability that exactly one reaction* R_μ *will occur inside the reaction volume* V, *within infinitesimal time interval* $[t, t+\triangle t)$, *given the current state* $X(t) = x$.

The transition rates of CTMC (q_{ij})

(*Theorem 1 Gillespie*). *If* $X(t) = x$, *then the probability that exactly one reaction* R_μ *will occur in the system in the time interval* $[t, t+\triangle t)$ *is equal to* $a_\mu(x)\cdot\triangle t + o(\triangle t)$.

(*Theorem 2 Gillespie*). *If* $X(t) = x$, *then the probability that no reaction will occur in the system in the time interval* $[t, t+\triangle t)$ *is equal to* $1 - \sum_{\mu=1}^{M} a_\mu(x)\cdot\triangle t + o(\triangle t)$.

(*Theorem 3 Gillespie*). *The probability of more than one reaction occurring in the system in the time interval* $[t, t+\triangle t)$ *is* $o(\triangle t)$.

Based on these three theorems and using probability laws, Gillespie deduced the Master Equation (ME) - a time evolution equation for the probability function $P\left(x,t\middle|x_0,t_0\right)$*:*

$$\frac{\partial P\left(x,t\middle|x_0,t_0\right)}{\partial t}=\sum_{\mu=1}^{M}\left[a_\mu\left(x-v_\mu\right)\cdot P\left(x-v_\mu,t\middle|x_0,t_0\right)-a_\mu\left(x\right)\cdot P\left(x,t\middle|x_0,t_0\right)\right]$$

with initial conditions: $P\left(x,t=t_0\middle|x_0,t_0\right)=\begin{cases}1, & x=x_0\\ 0, & x\neq x_0\end{cases}$

REMARKS:

- *The Master Equation fully describes the stochastic behaviour of the chemical system by a (very) large system of linear ODE equations.*
- *Because the Master Equation includes a differential equation for every state that the chemical system can adopt, for most real reaction systems the ME cannot be solved analytically or even numerically.*
- *In order to overcome the computational difficulties of solving the ME, Gillespie proposed in 1976 an alternative method, in two variants: the Direct Method (known as Stochastic Simulation Algorithm (SSA)), and the First Reaction Method. Both methods are based on the same theoretical basis as the ME.*

FIRST REACTION METHOD (Monte-Carlo Method)

- *Given the state of the system $X(t)=x$, the probability density function of the time to first event for each reaction is:*

$$p_\mu(\tau)=a_\mu(x)\cdot\exp\left[-a_\mu(x)\cdot\tau\right],\ \mu=1,2,\ldots,M$$

- *The Monte Carlo inversion method (Integral transform theorem) is used to sample τ from M exponential distributions with parameter $a_\mu(x)$, for $\mu=1,2,\ldots,M$ and the time to the next reaction for each reaction is calculated:*

$$\tau_\mu=\frac{1}{a_\mu}\ln\left(\frac{1}{r_\mu}\right)$$

- *The time to next reaction is: $\tau_{\min}=\min_{\mu=1\ldots M}\{\tau_\mu\}$ and the corresponding reaction will be R_k, with $k=\arg\left\{\min_{\mu=1\ldots M}\{\tau_\mu\}\right\}$*

- *The time is updated: $t\leftarrow t+\tau_{\min}$ and the new state becomes $X(t)\leftarrow X(t)+v_k$.*

- *The simulation is stopped after a predetermined time or if a molecular population becomes zero.*

COMPARATIVE QUALITATIVE ANALYSIS - EXAMPLES

In these examples we shall analyse two biochemical models, using the continuous and the stochastic framework and discuss the relevance of the modelling approach over the model's qualitative behaviour.

1. Linear birth-and-death process

Consider a single biological or chemical species (for example a bacterial colony) in a unit volume V

We shall denote the number of bacteria at time t *by* $X(t)$ *and assume that the colony size at an initial time* t_0 *is known:* $X(t_0) = x_0$.

It is assumed that each bacterium gives rise to new individuals at a constant rate λ *and dies at rate* μ *(positive rates)*

and that the system obeys the mass-action law (two first order reactions).

- *Modelled as a continuous deterministic process, the dynamic of the bacterial colony is represented by an ODE equation:*

$$\frac{dx(t)}{dt} = (\lambda - \mu)x(t),\ x(t_0) = x_0$$

This can be easily solved analytically and gives the complete dynamics of the system as:

$$x(t) = x_0 \cdot \exp\left[(\lambda - \mu)t\right]$$

The sign of the difference $\lambda - \mu$ *gives the dynamics of the population size*

(exponentially decrease if $\lambda - \mu < 0$ *and exponentially increase if* $\lambda - \mu > 0$*).*

$R_2: X \to 2X$

- *The stochastic version of the model is:*

Reactions	*Intensity rates* a_μ	*State change vector* $v_\mu(X)$
("birth") $R_1: X \xrightarrow{\lambda} 2X$	$a_1 = \lambda X(t)$	$v_1 = (1)$
("death") $R_2: X \xrightarrow{\mu} *$	$a_2 = \mu X(t)$	$v_2 = (-1)$

Comparison between deterministic and stochastic approach

- *In the deterministic approach, there is a lack of identifiability of parameters* λ *and* μ *.*

  The solution $x(t) = x_0 \cdot \exp\left[(\lambda - \mu)t\right]$ *depends only on* $\lambda - \mu$ *and not on the particular values of* λ *and* μ *(for example,* $\lambda = 0,5$ *and* $\mu = 0$ *will lead to exactly the same solution as for* $\lambda = 1$ *and* $\mu = 0,5$*).*

Consequently, using the ODE model and some experimental data, we cannot know if we have a pure birth or death process, or a process involving both births and deaths: any parameter estimation method will lead to an estimated value of $\lambda - \mu$ *.*

- *In the stochastic approach, both parameters λ and μ can be estimated.*

A stochastic model of the linear birth-death process depends explicitly on both λ and μ, and not just on $\lambda - \mu$. The value $\lambda - \mu$ controls the essential shape of the process, but the degree of "noise" or stochastic effects are contained in the value $\lambda + \mu$ (see Figure 1 below). Using a suitable parameter estimation method, both parameters can be determined.

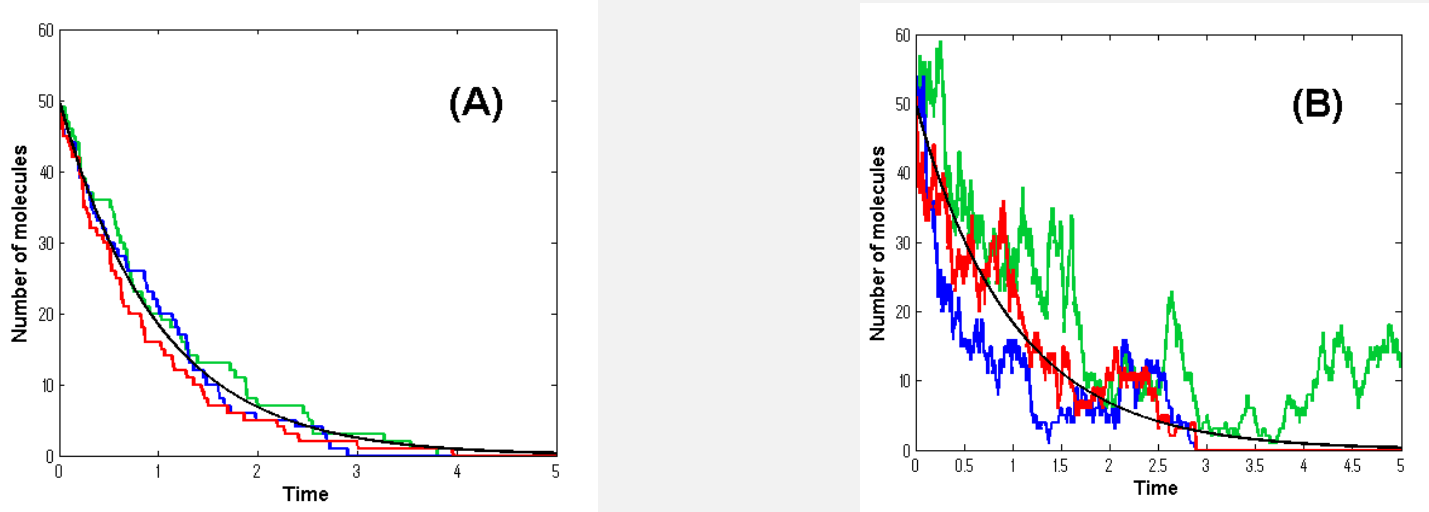

Figure 1. *Linear birth-death model. Three realizations of the stochastic model (in colours) and ODE solution (black solid line). Parameter values for both cases: $\lambda - \mu = -1$, $x_0 = 50$; Case* **(A)** *$\lambda + \mu = 1$; Case* **(B)** *$\lambda + \mu = 15$;*

- *The deterministic and stochastic model can exhibit different qualitative behaviour, for the same value of* $\lambda - \mu > 0$

Under the deterministic model, the solution $x(t)$ *never reaches zero (tends to infinity at* $t \to \infty$*).*

Using a stochastic model, the population of bacteria do go extinct and there is considerable randomness associated with the time that it occurs (Figure 2, blue line).

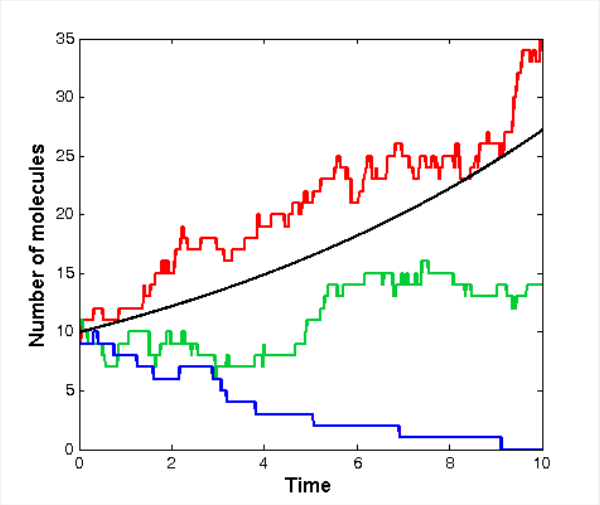

Figure 2. *Linear birth-death model. Three realizations of the stochastic model (in colours) and ODE solution (black solid line). Parameter values:* $x_0 = 10$, $\lambda = 0.3$ *and* $\mu = 0.2$.

Even if these realizations of the stochastic model are rare events, in some cases there is a special research interest associated with the rare event, and therefore a stochastic modelling approach must be chosen.

2. Noise-induced oscillator

This is an original model for a circadian oscillator. The state variables are the activator and repressor proteins and the inactivated complex formed by the two proteins.

- *The noise-induced oscillator has the ODE model representation:*

$$\begin{cases} \dfrac{dx}{dt} = a_1 \dfrac{b+x}{1+x} - c \cdot x \cdot y - d_1 \cdot x \\ \dfrac{dy}{dt} = a_2 \dfrac{x}{1+x} - c \cdot x \cdot y + d_1 \cdot z - d_2 \cdot y \\ \dfrac{dz}{dt} = c \cdot x \cdot y - d_1 \cdot z \end{cases}$$

where x is the concentration of the activator, y is the concentration of the repressor and z is the concentration of the complex.

The synthesis rates of the activator and repressor are Michaelis-Menten type.

For a comparison with the stochastic version of the model, we are interested in finding a difference in the qualitative behaviour, for the same set of parameters, knowing, from the experimental data, that the system dynamic is oscillatory.

Qualitative analysis:

Because the ODE system is a model for a biochemical system, all analysis will be conducted for biologically relevant values of the state variables (i.e. $x \geq 0$, $y \geq 0$ *and* $z \geq 0$*) and parameters. From the experimentally data, we have* $a_1 >> d_1$.

For $a_1 > d_1$*, the system has an unique hyperbolic equilibrium point* (x_e, y_e, z_e)

$$x_e = \frac{a_1 - d_1 + \sqrt{(d_1 - a_1)^2 + 4a_1 b\left(\frac{c \cdot a_2}{d_2} + d_1\right)}}{2\left(\frac{c \cdot a_2}{d_2} + d_1\right)} \qquad y_e = \frac{a_2}{d_2} \cdot \frac{x_e}{1 + x_e} \qquad z_e = \frac{c \cdot a_2}{d_1 \cdot d_2} \cdot \frac{x_e^2}{1 + x_e^2}$$

Stability analysis:

Using the experimental data, we calculate the following set of parameters for our model:

$$a_1 = 250,\ b = 0.05,\ c = 200,\ d_1 = 1,\ a_2 = 50 \text{ and } d_2 = 0.1.$$

For this parameter set we used numerical analysis in order to study the stability near the equilibrium point.

The equilibrium point for this data set is $(x_e, y_e, z_e) = (0.017, 6.1701, 15.607)$.

The Jacobian matrix of the linearized system has one real, negative eigenvalue and two complex eigenvalues with negative real part. Therefore, the equilibrium point is a stable focus-node.

Using the hypothesis that the reaction volume is scaled to unity, we construct the stochastic version of the model, for the parameter set that give rise to a stable focus node in the ODE model.

- *The stochastic version of the model is:*

Reactions		Intensity rate a_μ	State change vector $v_\mu(X,Y,Z)$
(activator synthesis)	$R_1: \ * \to k_1 \cdot X$	$a_{R_1} = \frac{a_1}{k_1} \cdot \frac{b + N_X}{1 + N_X}$	$v_1 = (k_1, 0, 0)$
(repressor synthesis)	$R_2: \ * \to k_2 \cdot Y$	$a_{R_2} = \frac{a_2}{k_2} \cdot \frac{N_X}{1 + N_X}$	$v_2 = (0, k_2, 0)$
(activator decay)	$R_3: \ X \to *$	$a_{R_3} = d_1 N_X$	$v_3 = (-1, 0, 0)$
(repressor decay)	$R_4: \ Y \to *$	$a_{R_4} = d_2 N_Y$	$v_4 = (0, -1, 0)$
(complex formation)	$R_5: \ X + Y \to Z$	$a_{R_5} = c N_X N_Y$	$v_5 = (-1, -1, 1)$
(dissociation, decay)	$R_6: \ Z \to Y$	$a_{R_6} = d_1 N_Z$	$v_6 = (0, 1, -1)$

We denoted by N_X, N_Y and N_Z the molecular counts for the activator, repressor and activator-repressor complex.

The parameters k_1 and k_2 compensate for the burst size expression of the ODE model.

For the stochastic model, we have used the same parameters as in the stability analysis of the ODE model and we set $k_1 = 5,\ k_2 = 10$.

The initial molecular counts are set to $(N_X, N_Y, N_Z) = (0, 10, 35)$.

We have run the stochastic simulation (FRM) for $t = 200$ (and 600 runs) and the system exhibits oscillations, showing no signs of stability (Figure 1, Figure 2 and Figure 3).

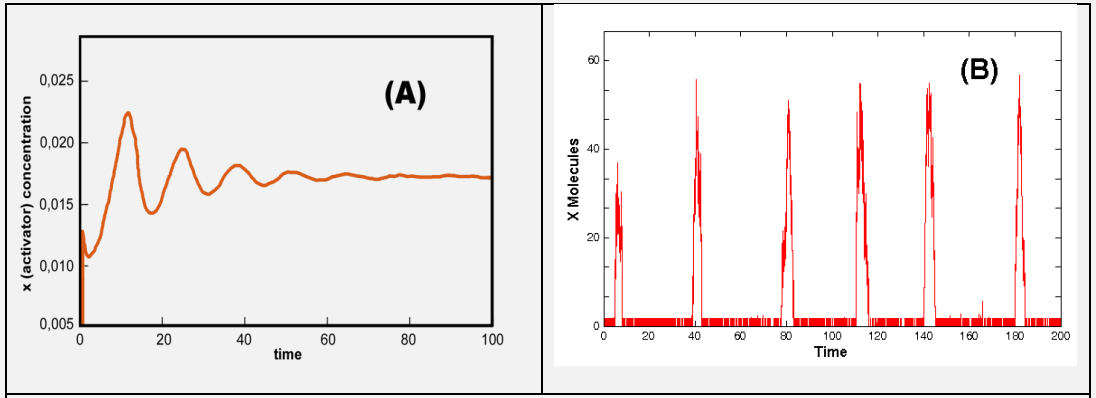

Figure 1. *Comparison of the time evolution of the activator X, in the deterministic ODE model (panel **A**) and the stochastic model (panel **B**), for the same parameters values. In the deterministic model, the concentration of X tends to the equilibrium value $x_e = 0.017$.*

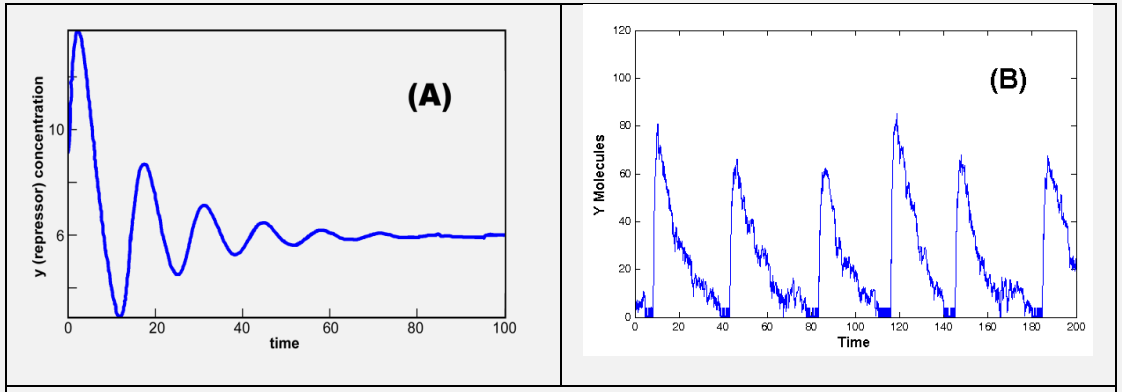

Figure 2. *Comparison of the time evolution of the repressor Y, in the deterministic ODE model (panel **A**) and the stochastic model (panel **B**), for the same parameters values. In the deterministic model, the concentration of Y tends to the equilibrium value $y_e = 6.1701$.*

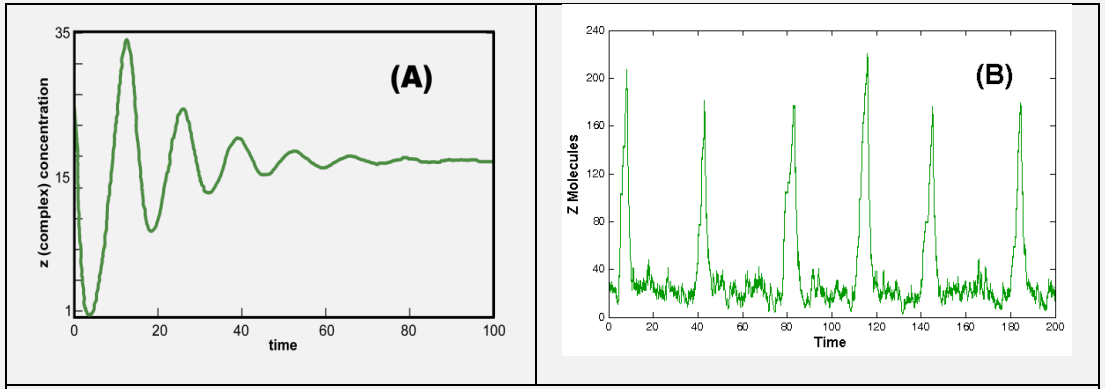

Figure 3. *Comparison of the time evolution of the complex Z, in the deterministic ODE model (panel **A**) and the stochastic model (panel **B**), for the same parameters values. In the deterministic model, the concentration of Z tends to the equilibrium value $z_e = 15.607$*

For the parameter set corresponding to the experimental data, the stochastic model reproduces the real dynamic of the system (oscillatory behaviour).